
# The Synthesis and Biology of Iminosugars and their Precursors

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2013

A thesis submitted in partial fulfilment of the requirement for the degree of Doctor of Philosophy (D. Phil.)

# Abstract

## The Synthesis and Biology of Iminosugars and their Precursors

Benjamin J. Ayers, Lincoln College, University of Oxford
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Iminosugars are carbohydrate mimics, where the endocyclic ring oxygen has been replaced by nitrogen. This substitution affords these compounds their inhibitory activity towards sugar-processing enzymes (glycosidases) and, as a consequence, their chemotherapeutic potential in the treatment of a broad range of diseases. Several iminosugars are currently in clinical trials or have entered the market as approved drugs. This has consequently led to increasing levels of research into their synthesis and application, both in terms of the development of efficient methodology to access naturally occurring examples, and also to elaborate novel scaffolds. The presence of multiple chiral centres within iminosugars provides a considerable challenge in accessing these targets by asymmetric means, whereas carbohydrates pose a more attractive chiral pool. As such the majority of literature methods have employed this latter method.

The focus of the thesis is on the elaboration of robust methodologies to access both naturally occurring and novel iminosugars, and their precursors, from readily available carbohydrate starting materials.

**Chapter 1** presents an introduction to iminosugars, including an overview of glycosidase inhibition by this class of sugar-mimic, their historical medical usage and the basis for their potential employment in treating diabetes, lysosomal storage disorders (LSDs) and cancer. This chapter also gives a general review of the methods employed in the literature for the assembly of iminosugar scaffolds.

**Chapter 2** is concerned with the synthesis of iminosugars from the carbohydrate glucuronolactone. This versatile chiron has previously allowed for access to many homochiral targets, and in this thesis is used to access DGJNAc on a gram-scale. This iminosugar has been shown to be a potent α-*N*-acetylgalactosaminidase inhibitor and is potentially extremely valuable in the treatment of late-stage cancer. Both enantiomers of glucuronolactone are also utilised in the divergent synthesis of every stereoisomer of two classes of five-membered iminosugars; the pyrrolidines (including DMDP), and the proline amides. These compounds demonstrate remarkable biological activity against a panel of glycosidases and hexosaminidases, allowing for the analysis of the structure-activity relationship between these compounds and the target enzymes.

**Chapter 3** describes the development of a novel, one-pot methodology - a tandem Strecker reaction and iminocyclisation - for the assembly of trihydroxy piperidine α-iminonitriles from a range of unbranched and branched pentose monosaccharides. These piperidine α-iminonitriles are precursors to pipecolic acids which may also be potentially valuable targets in the treatment of cancer.

## Acknowledgements

Firstly I would like to thank George not only for giving me the opportunity to work within his group, but also for his endless enthusiasm, patience, encouragement and inspiration. There have been great times and tough times, but overall it has been an amazing and rewarding experience. The people within the Fleet group have contributed immeasurably to my research. I'm not sure where I would be without Sarah, from getting me going with my very first reaction, to proof reading my posters, reports, summaries, manuscripts, abstracts and finally this thesis. I am indebted to her for finding the time for all this (especially in the rapid turn-around of extremely lengthy thesis chapters!). There are so many more people to thank from the group. My thanks go to all those who participated on the glucuronolactone projects with me: Dan, Sarah, Fernando, Nigel and Andreas. A special thank you to Andreas for drafting and finally getting the DGJNAc paper submitted. Thank you to everyone else who has made my time here so enjoyable; Noelia, Gabe, James, Mike, Scott, Loren, Elizabeth and Thibault. It would have been a lot duller without you all, I'm already missing working in Oxford! My thanks also go to Professor Atsushi Kato for his incredibly speedy and efficient return of assay results.

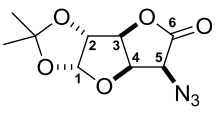
I would like to thank my family for their love and support through all of this. Not just during my doctorate, but throughout, and also before, my time in Oxford. I owe you more than I can ever repay.

Finally, thank you to my fiancée Jolene, you've been there for me literally from day one, and it has been an incredible journey. I feel that this small paragraph barely does justice to the enormity of your contribution. I will never be able to thank you enough for all that you have done and all the support you have given me during both the research and the writing of this thesis. You have encouraged, supported and lent me your strength during the low points, and you have been there to celebrate the highs. I would not be where I am today without you, thank you.

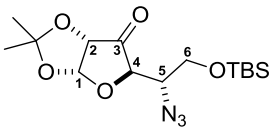
# Contents

## Concerning nomenclature

Throughout this thesis the naming and numbering conventions used for carbohydrate derivatives are consistent with the guidelines provided by IUPAC.[1] Below are representative examples of this:



5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-glucurono-3,6-lactone



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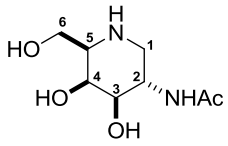
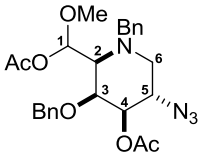
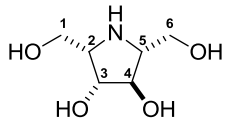


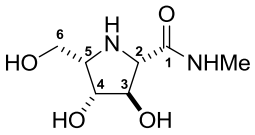
2-acetamido-1,2,5-trideoxy-1,5-imino-D-galactitol



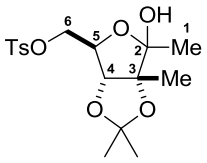
4-*O*-acetyl-5-azido-2-*N*,3-*O*-dibenzyl-2,5,6-trideoxy-2,6-imino-L-galactose acetyl methyl acetal



2,5-dideoxy-2,5-imino-D-glucitol



methyl 2,5-dideoxy-2,5-imino-L-gulonamide



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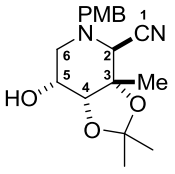


2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-2-*N*-(4-methoxybenzyl)-3-*C*-methyl-D-allononitrile

[1] McNaught, A. D. *Carbohydr. Res.* **1997**, *297*, 1-92.

# Abbreviations

## Abbreviations

| | |
|---|---|
| +ve | positive |
| –ve | negative |
| $[\alpha]_D^T$ | specific optical rotation (at temperature $T$ °C) |
| α-GalNAcase | α-*N*-acetylgalactosaminidase |
| α-NAGALase | α-*N*-acetylgalactosaminidase |
| a | apparent (NMR) |
| Ac | acetyl |
| Ar | aryl |
| ASSC | active site specific chaperone |
| β-GlcNAcase | β-*N*-acetylglucosaminidase |
| Bn | benzyl |
| Boc | *tert*-butyloxycarbonyl |
| br. | broad (IR), broad (NMR) |
| BR-1 | 2,6-dideoxy-2,6-imino-L-gulonic acid |
| brsm | based on recovered starting material |
| Bu | butyl |
| Bz | benzyloxy |
| Bzh | benzhydryl |
| *c* | concentration (optical rotation) |
| CAN | cerium ammonium nitrate |
| Cer | ceramide |
| CMT | chaperone-mediated therapy |
| CPT-11 | camptothecin-11 |
| δ | chemical shift (ppm) |
| d | day(s), doublet (NMR), double- (NMR) |
| DAB-1 | 1,4-dideoxy-1,4-imino-D-arabinitol |
| DADP | 2,5-dideoxy-2,5-imino-D-altritol |
| DCM | dichloromethane |
| DEAD | *N*,*N*-diethylazodicarboxylate |
| DGADP | 2,5-dideoxy-2,5-imino-galactitol |
| DGDP | 2,5-dideoxy-2,5-imino-D-glucitol |
| DGJ | 1-deoxygalactonojirimycin |
| DGJNAc | 2-acetamido-1,2,5-trideoxy-2,5-imino-D-galactitol |
| $(DHQD)_2PHAL$ | hydroquinidine 1,4-phthalazinediyl diether |
| DIBAL-H | diisobutylaluminium hydride |
| DIDP | 2,5-dideoxy-2,5-imino-D-iditol |
| DIPEA | *N*,*N*-diisopropylethylamine |
| DMDP | 2,5-dideoxy-2,5-imino-D-mannitol |
| DMF | *N*,*N*-dimethylformamide |
| DMJ | 1-deoxymannonojirimycin |
| DMJNAc | 2-acetamido-1,2,5-trideoxy-2,5-imino-D-mannitol |
| DMP | Dess-Martin periodinane |
| DMSO | dimethylsulfoxide |
| DNJ | 1-deoxynojirimycin |
| DNJNAc | 2-acetamido-1,2,5-trideoxy-2,5-imino-D-glucitol |
| DTJ | 1-deoxytalonojirimycin |
| EC | enzyme commission number |
| ECM | extracellular matrix |
| ER | endoplasmic reticulum |
| ERAD | endoplasmic reticulum-associated degradation |
| ERT | enzyme replacement therapy |
| ESI | electrospray ionisation |
| Et | ethyl |
| FG | fagomine |
| FOS | free oligosaccharide |

| | |
|---|---|
| Gal | galactose |
| GalNAc | 2-acetamido-2-deoxy-D-galactose (*N*-acetylgalactosamine) |
| GalT | galactosyl tranferase |
| GcMAF | macrophage activating factor |
| gem | geminal (NMR) |
| Glc | glucose |
| GlcNAc | 2-acetamido-2-deoxy-D-glucose (*N*-acetylglucosamine) |
| GlcT | glucosyl transferase |
| GM1 | monosialotetrahexosylganglioside |
| GSL | glycosphingolipid |
| h | hour(s) |
| Hex | hexosaminidase |
| HexT | hexosaminidyl transferase |
| HL60 | human promyelocytic leukemia cells |
| HMBC | heteronuclear multiple-bond correlation spectroscopy |
| HPLC | high-performance liquid chromatography |
| HRMS | high resolution mass spectrometry (accurate mass) |
| *I* | inversion |
| $IC_{50}$ | half maximal inhibitory concentration |
| IFG | isofagomine |
| Imid | imidazole |
| *J* | coupling constant (Hz, NMR) |
| $K_i$ | enzyme-inhibitor complex dissociation constant |
| LA | Lewis acid |
| LAB-1 | 1,4-dideoxy-1,4-imino-L-arabinitol |
| LG | leaving group |
| Lit. | literature |
| LRMS | low resolution mass spectrometry |
| LSD | lysosomal storage disorder |
| µ | micro |
| m | multiplet (NMR), medium (IR) |
| M | mass (in mass spectrometry) |
| M | molar |
| MAF | macrophage activating factor |
| Me | methyl |
| min | minute(s) |
| min. | mineral |
| mol | mole |
| m.p. | melting point |
| Ms | methanesulfonyl |
| MS | molecular sieves |
| $\nu_{max}$ | infrared absorption frequency ($cm^{-1}$) |
| n | nano |
| NAG | *N*-acetylglucose |
| *N*B-DNJ | *N*-butyl-deoxynojirimycin |
| ND | not determined |
| NeuAc | *N*-acetylneuraminic acid (sialic acid) |
| NeuAcT | *N*-acetylneuraminic acid transferase |
| NI | no inhibition |
| NJ | nojirimycin |
| NMO | *N*-methylmorpholine *N*-oxide |
| NMR | nuclear magnetic resonance |
| NOESY | nuclear Overhauser effect spectroscopy |
| Non | nonyl |
| PCC | pyridinium chlorochromate |
| Pf | phenylfluorene |
| Ph | phenyl |
| PMB | 4-methoxybenzyl |
| ppm | parts per million (NMR) |
| *p*TSA | *para*-toluenesulfonic acid |

| | |
|---|---|
| pyr | pyridine |
| q | quartet (NMR) |
| quant. | quantitative |
| quin. | quintet (NMR) |
| *R* | retention |
| RCM | ring-closing metathesis |
| RER | rough endoplasmic reticulum |
| $R_f$ | retention factor (thin layer chromatography) |
| RT | room temperature |
| s | strong (IR), singlet (NMR) |
| SER | smooth endoplasmic reticulum |
| sext. | sextet (NMR) |
| $S_N2$ | bimolecular nucleophilic substitution |
| SRT | substrate reduction therapy |
| t | triplet (NMR), triple- (NMR) |
| TBAF | *tetra*-*n*-butylammonium fluoride |
| TBDPS | *tert*-butyldiphenylsilyl |
| TBS | *tert*-butyldimethylsilyl |
| Tf | trifluoromethanesulfonyl |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| Ts | *para*-toluenesulfonyl |
| TSRI | tandem Strecker reaction and iminocyclisation |
| v | volume |
| vitamin $D_3$-BP | vitamin $D_3$ binding protein |
| w | weight, weak (IR) |
| XRD | X-ray diffraction |
| Z | benzyloxycarbonyl |

# Chapter 1: Introduction

## 1.1 General overview

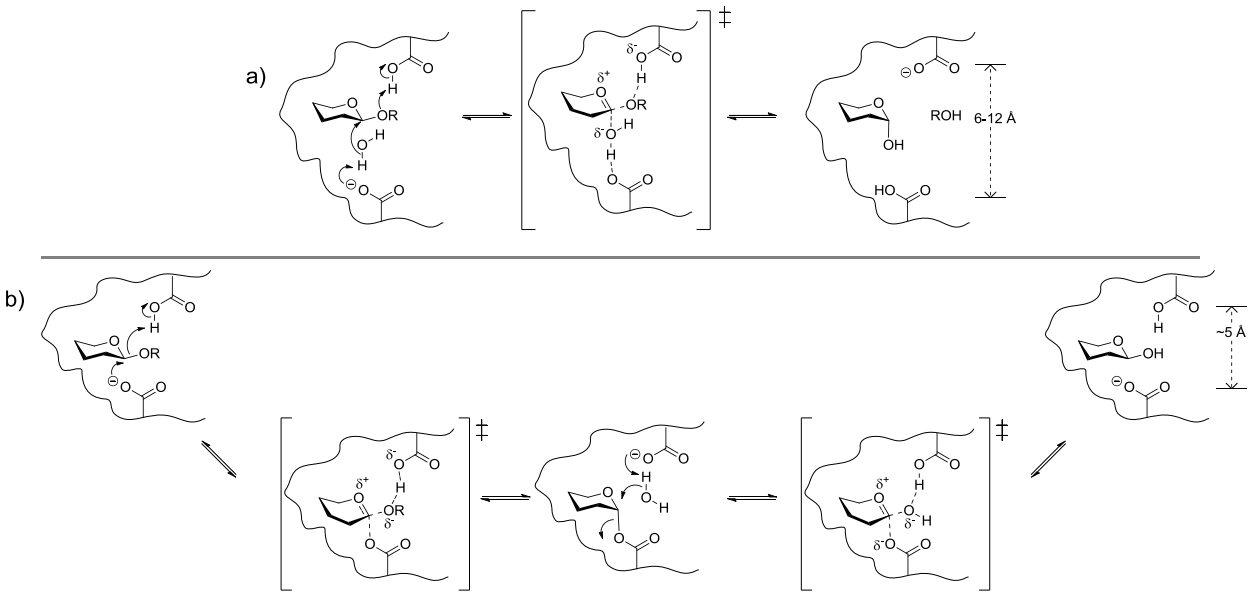
Iminosugars, also known as azasugars, can be defined as carbohydrate analogues in which the endocyclic oxygen atom has been replaced with nitrogen. These polyhydroxylated alkaloids are abundant in nature, with a plethora of examples isolated from a broad range of plant species and also from a variety of bacterial sources. Iminosugars closely resemble the transition-state of glycoside hydrolysis, both structurally and electronically,[1,2] and due to this many are biologically active. Their glycosidase transition-state mimicry leads to iminosugars generally acting as competitive inhibitors, however there are some that demonstrate non-competitive behaviour.[3] Glycosidase enzymes are involved in a wide array of crucial biological processes. Over- or under-expression of these enzymes, through genetic mutations or disease, leads to a range of serious medical conditions, including; cancer, diabetes, cystic fibrosis, osteoarthritis and lysosomal storage disorders (LSDs). This makes glycosidase enzymes important and valuable therapeutic targets.[4] The inherent structural complexity of iminosugars leads to challenging syntheses, but the potential for their medical application makes them ultimately rewarding targets.

This introductory chapter will describe the journey from the discovery of iminosugars, to their modern medical applications, and to their future in the treatment of diseases. Also, the motivation for, and the fundamental synthetic methodology of, turning carbohydrates into iminosugars will be overviewed - leading to the description of my work in the design and synthesis of biologically active iminosugars in the succeeding chapters.

## 1.2 Glycosidase inhibition

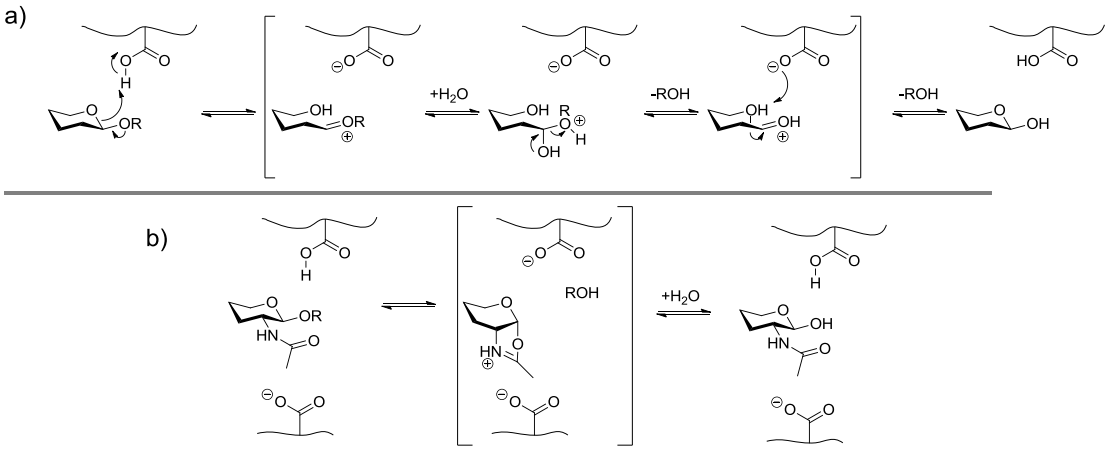
Glycosidases, or glycoside hydrolase enzymes, are essential to all living organisms, allowing the essential processing of carbohydrates. Consequently they are widely abundant and critical in a multitude of biological pathways, catalysing the degradation of polysaccharides such as starch, glycogen, cellulose and chitin, as well as being employed in complex glycosylation and deglycosylation sequences. Therefore, aberrant expression of glycosidase enzymes leads to the manifestation of a swathe of biological disorders and afflictions - from diabetes to cancer, osteoarthritis and lysosomal storage disorders (LSDs). Thus, the selective inhibition and suppression of overexpressed glycosidases, or the enhancement of the level of underexpressed enzymes, would pose ideal strategies for the therapeutic treatment of these diseases. This has formed a powerful incentive to classify and understand the modes-of-action of glycosidase enzymes - and has led to decades of experimental work to this end.

Glycosidase enzymes may be categorised into two classes; those that cleave *O*- and *S*-glycosides (class EC 3.2.1) and those that cleave *N*-glycosidic bonds (EC 3.2.2). They may also be further classified based on configuration, anomeric specificity and the stereochemical outcome of the reaction. The latter case consists of two distinct classes; a) inverting glycosidases, and b) retaining glycosidases - with the key structural difference between them being the spatial separation between the general acid and base units of the active site. For inverting glycosides this is typically 6-12 Å and in the case of retaining glycosides is about 5 Å. Inverting glycoside active sites are larger due to the reaction proceeding *via* a single transition state, with the active site accommodating both the substrate, the incoming nucleophilic water molecule and the exiting aglycon. Whereas retaining glycosides have two transition states and consequently a smaller spatial requirement (**Scheme 1.1**).[1,5,6]




**Scheme 1.1**. Mechanisms of; a) inverting, and b) retaining glycosidases.[1,6]

In an extension to these two mechanisms an alternative route has been suggested whereby the ring oxygen is protonated instead of the anomeric hydroxyl group - leading to an open-chain transition state.[7,8] Additionally, some retaining *N*-acetylhexosaminidases are hydrolysed by a pathway involving neighbouring-group participation, forming an α-oxazoline intermediate with subsequent hydrolysis occurring selectively at the β-face (**Scheme 1.2**).[9]




**Scheme 1.2**. Mechanisms of; a) hydrolysis involving ring-oxygen protonation,[7,8] and b) hydrolysis of retaining *N*-acetylhexosaminidases.[9]

Rate comparisons of enzymatic and spontaneous glycoside hydrolysis have led to the conclusion that the glycosidase transition state is the most stabilised species in the reaction pathway.[6,10,11]

From this it may be inferred that potentially the most successful and effective competitive inhibitors of glycosidases would be those that mimic the transition state. Thus the inhibitor must be rationally designed to satisfy two criteria: firstly, the inhibitor must mimic the transition state structure of the natural substrate *structurally*, and secondly, it must mimic the transition state structure *electronically*. Satisfying these conditions fully would allow for the maximisation of the interaction, and therefore inhibition. The simplest method of fulfilling the former criterion is for the inhibitor to possess a polyhydroxylated scaffold with an identical, or near-identical, spatial arrangement to the natural substrate. In terms of the latter, formation of an analogous positive charge is required at physiological pH, giving an ersatz transition state electrostatic interaction with the general base of the active site, akin to that of the oxocarbenium cation generated by the natural substrate.

There are many different classes of competitive glycosidase inhibitors based on carbohydrate-scaffolds, including carbocyclic systems - where the ring-oxygen is replaced by a carbon atom, thiosugars - replacement by sulfur, and aza- or iminosugars - replacement by nitrogen.[12,13] While there are excellent inhibitory examples from the first two classes, it is within the iminosugar class that the most extensive research has been conducted. This is a direct result of the synthetic availability of iminosugars, their structural variability, inhibitory properties and their ability to be made into virtually any configuration, ring-size and substitution pattern. This structural variety fulfils the first requirement - *structural* mimicry of natural substrates. The second requirement, *electronic* mimicry is satisfied by the protonation of the endocyclic ring-nitrogen at physiological pH - this positive charge then being analogous to the oxocarbenium cation of the substrate in the glycosidase transition state (**Figure 1.1**).

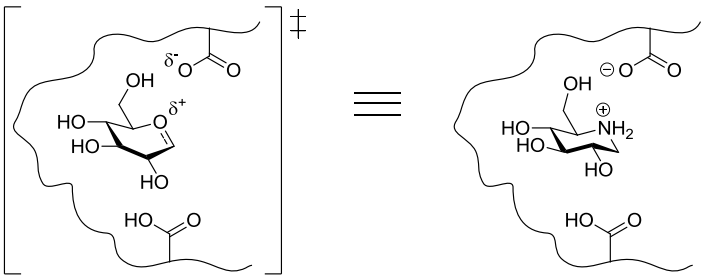



**Figure 1.1**. Structural and electronic mimicry of glycosidase transition states by iminosugars.

The possible structural variation is important as the selectivity of an iminosugar for a particular glycosidase arises through the configuration of the hydroxyl groups and other exocyclic substituents, and as would be expected an iminosugar bearing an identical, or near-identical, disposition of hydroxyl groups to a natural sugar is often a specific inhibitor of the enzymes which process that sugar. Two prime examples of this are DNJ **1.1** and DGJ **1.2** (**Figure 1.2**). DNJ **1.1** is *gluco*-configured and is evidently a structural mimic of D-glucose **1.3** and as such is a potent inhibitor of α-glucosidases (human lysosomal: $IC_{50}$ 40 nM[14]). Similarly, epimeric DGJ (1,5-dideoxy-1,5-imino-D-galactitol) **1.2** is *galacto* configured and resembles natural D-galactose **1.4** and is a potent inhibitor of α-galactosidases (human lysosomal: $IC_{50}$ 70 nM[14]).

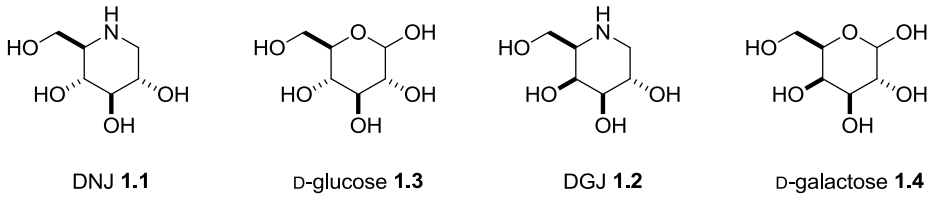
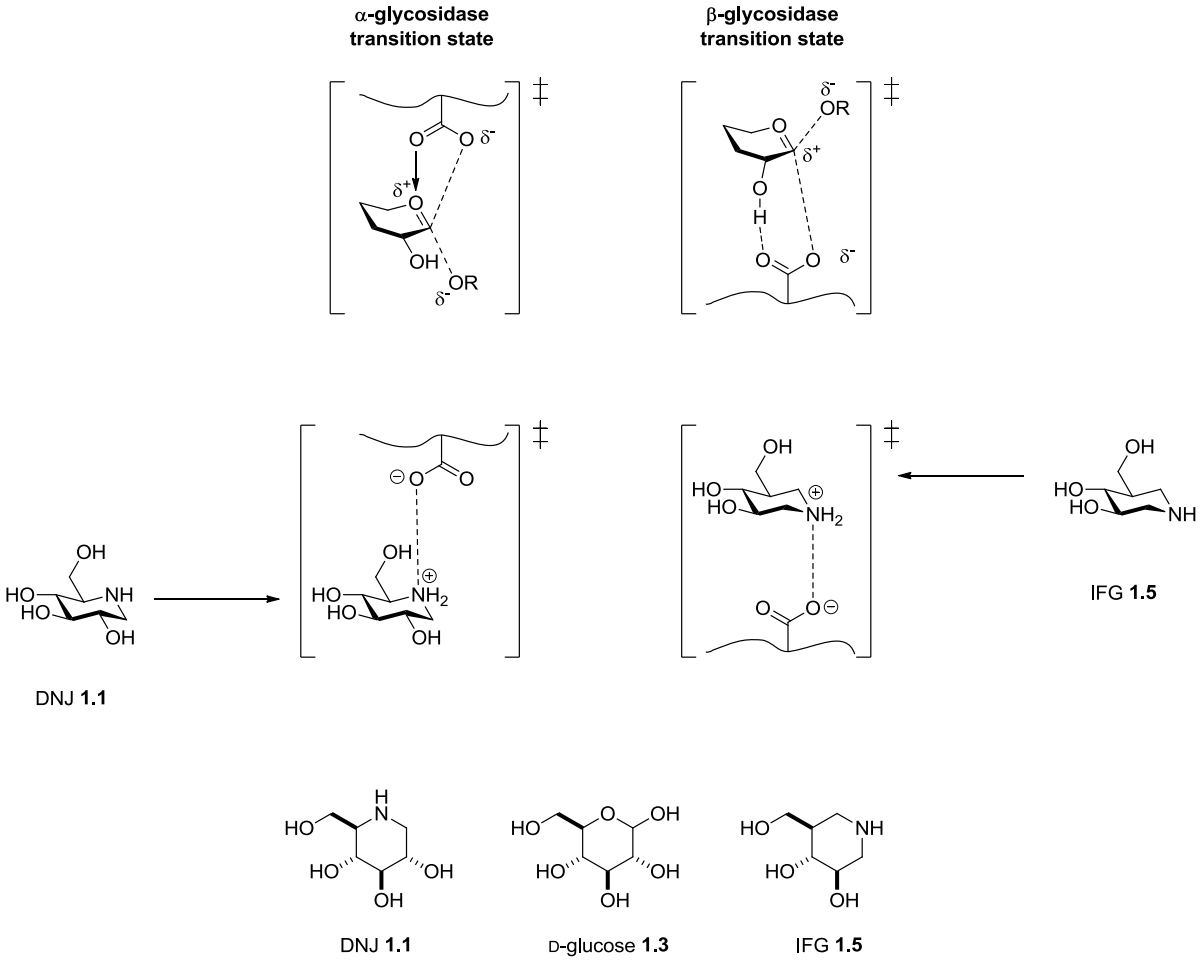



**Figure 1.2**. Iminosugars as carbohydrate mimics.

DNJ **1.1** and DGJ **1.2** are selective inhibitors of α-glycosidases, displaying markedly less activity against β-glycosidases, despite their structural resemblance to the natural substrates of these enzymes (human lysosomal: β-glucosidase $IC_{50}$ 240 μM and β-galactosidase $IC_{50}$ 90 μM, respectively).[14] If the structural-mimicry requirement is fulfilled by these iminosugars, then it can be surmised that this selectivity is due to an electronic effect - and this is indeed the case.

The selectivity in inhibition arises in the catalytic mechanism of α- and β-glycosidases, which culminates in a difference in charge distribution of the transition state. Taking retaining glycosidases as an example, it has been indicated that the reactions of α- and β- proceed *via* the same pathway, and that the difference lies in a subtle variation in the oxocarbenium ion of the transition state.[1] The *syn* interaction of the nucleophilic carboxyl oxygens with the anomeric centre and the 2-hydroxyl group in β-glycosidases leads to greater positive charge build-up on the anomeric carbon atom (**Scheme 1.3**). Whereas, in α-glycosidases this *syn* interaction is with the anomeric centre and the endocyclic ring-oxygen - this favours positive charge build-up on the ring-oxygen.[1,15] So, replacement of the endocyclic ring-oxygen with an ammonium cation results in α-glycosidase inhibition - as can be seen with in DNJ **1.1**. Alternatively, locating the ammonium cation at the anomeric centre, exemplified by isofagomine (IFG) **1.4**, results in selective β-glucosidase inhibition (almond: $IC_{50}$ 110 nM).[16,17] Similarly the *galacto* analogue of IFG **1.4** is a potent and selective β-inhibitor (*Aspergillus oryzae*: $IC_{50}$ 40 nM).[18,19]

These principles in the variation of structure and ring-nitrogen position afford the ability to design selective inhibitors for differently configured natural sugars and their processing-enzymes and to then select between α- and β-glycosides. Selective inhibition is necessary to optimise the therapeutic application of iminosugars, limiting off-target effects. The potential pharmacological targets and implementation of iminosugars will be discussed in the next section.




**Scheme 1.3**. Differing transition-state interactions of retaining α- and β-glycosidases with iminosugars.[1]

## 1.3 Iminosugars - natural occurrence and historical discovery

Naturally occurring iminosugars can be broadly categorised into five structural subclasses; monocyclic five-membered pyrrolidines, six-membered piperidines, bicyclic [3.3.0] pyrrolizidines, [4.3.0] indolizidines and [3.2.1] nortropanes (**Figure 1.3**).[20]

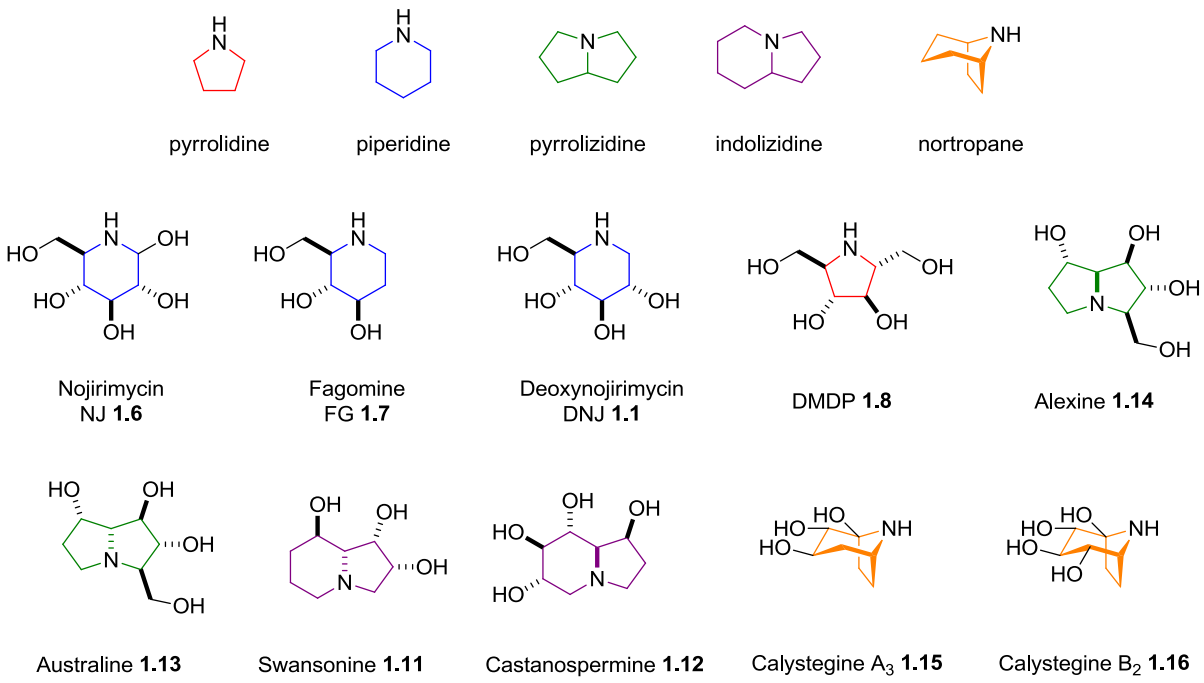
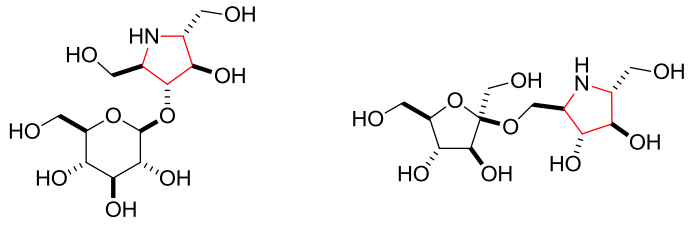



**Figure 1.3**. Iminosugar structural subclasses and naturally occurring examples of each.

The first iminosugar isolated from Nature was the piperidine 5-amino-5-deoxy-D-glucopyranose, or nojirimycin (NJ) **1.6**.[21] This compound was discovered in a *Streptomyces* culture in 1966 by Inouye and co-workers and constituted the first natural glucose mimic. It took until 1973 for the first iminosugar to be isolated from plants, with Koyama *et al*. isolating 1,2-dideoxynojirimycin (fagomine, FG) **1.7** from Buckwheat seeds (*Fagopyrum escelentum*).[22] FG **1.7** was the first 1,2-dideoxy iminosugar isolated, and was shortly followed by the discovery of the first 1-deoxy example - 1-deoxynojirimycin (DNJ) **1.1** - extracted from mulberry trees (*Morus alba*) in 1976.[23] DNJ **1.1** was also later isolated from a bacterial culture,[24] but had in fact been made synthetically a decade earlier following the discovery of NJ **1.6**.[25] Also in 1976, 2,5-dideoxy-2,5-imino-D-

mannitol (DMDP) **1.8** constituted the first pyrrolidine iminosugar to be discovered, isolated from the leaves of *Derris eliptica*. Since then DMDP **1.8** has been found to occur in a wide range of natural sources, including; bacteria,[26,27] plants[20,28-30] - for example the Thai traditional crude medicine "Non tai yak" (*Stemona tuberosa*),[31] the neotropical moth *Urania fulgens* and its larval foodplant *Omphalea diandra*,[32] to name but a few. This makes DMDP **1.8** by far the most abundant iminosugar in Nature.

Iminosugars possessing an hemiaminal functionality, such as NJ **1.6**, have an inherent metabolic instability arising from this moiety, whereas 1-deoxy iminosugars, also called iminoalditols or iminocyclitols, such as FG **1.7**, DNJ **1.1** and DMDP **1.8**, lack this group affording significantly increased stability both *in vitro* and *in vivo*. Inevitably the focus of the iminosugar field of research is biased towards the synthesis of iminocyclitols due to their greater potential in treating diseases *in vivo*. The early discoveries described above began an explosion in the isolation of naturally occurring iminosugars, including examples of glycosylated DMDP (**1.9** & **1.10**, **Figure 1.4**) and the pyrrolidine-containing bicyclic systems – pyrrolizidines, indolizidines and calystegines. The indolizidine swansonine **1.11** was the first bicyclic iminosugar to be isolated from the Australian legume *Swainsona canescens*,[33] and this was quickly followed by another indolizidine castanospermine **1.12** - discovered in the Australian legume *Castanospermum australe*.[34]

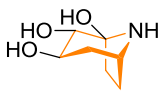



3-*O*-β-D-glucopyranosyl DMDP **1.9**

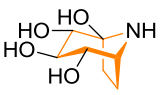
1-*O*-β-D-fructofuranosyl DMDP **1.10**

**Figure 1.4**. Examples of naturally occurring iminosugar-glycosides.

The next bicyclic subclass to be discovered was the pyrrolizidines, with the isolation of alexine **1.13** from *Alexa leiopetala*[35] and australine **1.14** from *C. australe*.[36] The calystegines were the final bicyclic class to be discovered, with the first examples found in *Calystegia sepium*.[37] With interest in the isolation of iminosugars increasing, more common plants were subject to screening - with focus being especially applied to those plants known to have adverse effects on grazing cattle. Taking calystegines as an example, Nash and co-workers discovered calystegine $A_3$ **1.15** and calystegine $B_2$ **1.16** in the tubers and leaves of potatoes (*Solanum tuberosum*, **Figure 1.5**). These natural products were also isolated in aubergines (*S. melongena*), in leaf fragments of other *Solanum* species known to cause a degenerative neurological disorder in cattle, and in a variety of other sources.[38] Other plant species containing high concentrations of iminosugars, such as the United Kingdom's common bluebell (*Hyacinthoides non-scripta*), have also been known to be harmful to livestock and as such are fenced off to prevent grazing.[39] Also, the Australian legumes *Swainsona canescens* and *Castanospermum australe*, the eponymous sources of the indolizidines swansonine **1.11** and castanospermine **1.12**, described above, had been known to be toxic in people and animals for a long time prior to the iminosugar discoveries.




Calystegine $A_3$ **1.15**




Calystegine $B_2$ **1.16**

**Figure 1.5**. Nortropane iminosugars found in potatoes (*S. tuberosum*).[38]

Despite these effects in cattle and livestock, many insect species tolerate persisting levels of iminosugars ingested from their foodplants. One example has been mentioned earlier, that of the Swallowtail moth (*U. fulgens*). The pupa of this insect feed on iminosugar-rich plants, storing the alkaloids into maturity – even the eggs subsequently laid contain iminosugars.[32] The reason for this is not fully understood, but the consequent toxicity of this insect and its eggs towards

predators may afford an evolutionary advantage. Another example is the Death's head hawkmoth (*Acherontia atropus*) which stores calystegines, including $A_3$ **1.15** and $B_2$ **1.16** (**Figure 1.5**), consumed during the consumption of potatoes by the pupa.[38] Bees can also accumulate iminosugars, leading to iminosugar-containing nectars, with some African varieties possessing relatively high levels.[40] With the isolation of iminosugars expanding exponentially in an ever-increasing pool of plants, attention was drawn naturally towards the examination of the possible iminosugar content of both traditional and modern herbal therapeutic remedies.

## 1.4 Medicine and iminosugars

The consumption of plants containing iminosugars is not always detrimental, in fact many human food plants contain high levels of iminosugars - these have even been shown to be stable to typical cooking conditions.[38] The examination of many traditional and herbal medicines has shown that they can possess relatively high levels of iminosugars, an example mentioned earlier mentioned previously was the Thai crude drug "Non tai yak" which is a source of DMDP **1.8** among others.[31] This, and other examples, indicates a long history in the therapeutic use of iminosugars, dominated especially by Chinese phytomedicines. In the seventeenth century Haarlem oil was the first medication to be produced industrially, and was recommended for the treatment of diabetes and for whitening the skin. One of the major components of this medication was *Morus alba*, the white mulberry, an extremely rich source of iminosugars - especially DNJ **1.1** - and traditionally used in Chinese medicine to treat 糖尿病 (táng niào bìng), or type II diabetes.[20] In terms of modern applications this has led to the development and licensing of the drug Miglitol, or *N*-hydroxyethyl-DNJ **1.17**, a derivative of DNJ **1.1** and a modern chemotherapeutic agent in the treatment of diabetes (**Figure 1.6**). This then formed the first modern pharmaceutical application of iminosugars, and an explosion in research to discover and expand their therapeutic applications.

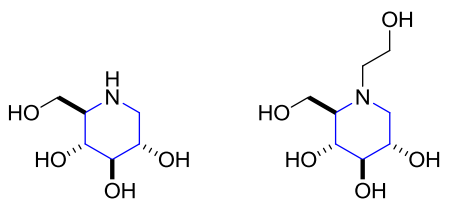



**Figure 1.6**. DNJ **1.1**, isolated from *Morus alba*,[20] and Miglitol **1.17**.

## 1.5 Therapeutic applications of glycosidase inhibition by iminosugars

### 1.5.1 Type II diabetes

As highlighted at the end of the preceding section, the first and foremost application of iminosugars has been in the treatment of type II diabetes. This disease is caused by cellular resistance to insulin - the hormonal signal for cellular uptake and storage of glucose. Resistance leads to this signal being ignored and resultant hyperglycaemia, with long term increased risk of heart-attacks, strokes and kidney failure. *N*-Hydroxyethyl-DNJ **1.17** (**Figure 1.7**), or Miglitol (Glyset - Pfizer), was developed as an intestinal α-glucosidase inhibitor. The inhibition of intestinal glucosidases limits the uptake of glucose into the bloodstream, decreasing postprandial blood-glucose levels thus preventing hyperglycaemia and chemotherapeutically managing the symptoms and effects of type II diabetes.[41] Miglitol **1.17** has an additional mode-of-action - acting as an inhibitor of glycogenolysis,[42] a process that is also responsible for the control of blood-glucose levels. Glucagon-induced and spontaneous glycogenolysis leads to hyperglycaemia due to the lack of homeostatic feedback normally provided by the release of insulin - thus Miglitol **1.17** offers a two-pronged approach in the treatment of diabetes. Besides Miglitol, 1,4-dideoxy-1,4-imino-D-arabinitol, DAB-1 **1.18** (**Figure 1.7**), has also demonstrated an ability to decrease glycogenolysis and presents an additional drug candidate for the chemotherapeutic treatment of type II diabetes.[43]

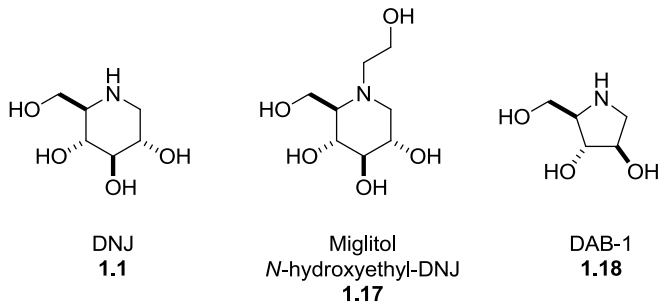
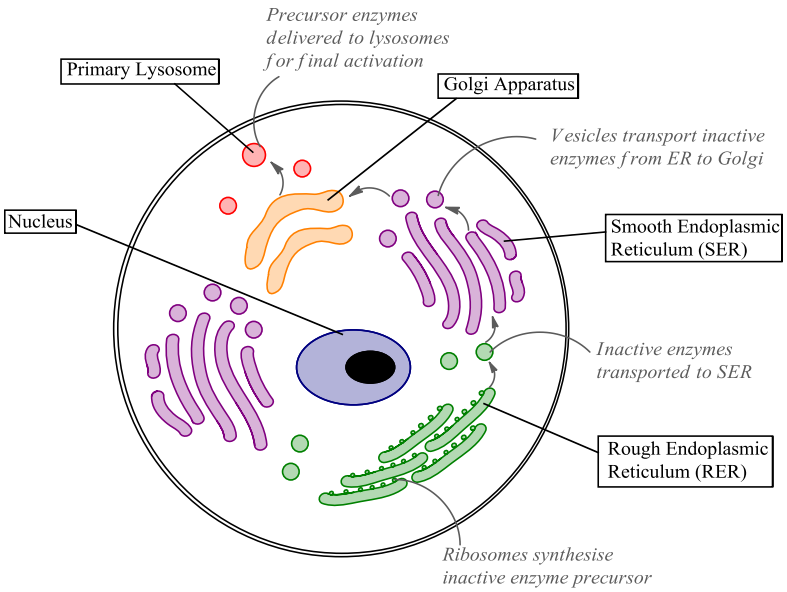



**Figure 1.7**. Iminosugars deployed in the historical and modern treatment of type II diabetes.

### 1.5.2 Lysosomal storage disorders

Lysosomal storage disorders (LSDs) form a disease class of which there are more than fifty distinct forms, and their potential treatment has proven to be the major breakthrough in the therapeutic utilisation of iminosugars. These disorders arise from the aberrant metabolism of carbohydrates and glycoconjugates by defective lysosomal glycosidases. The result of this is the accumulation and storage of unmetabolised substrate within lysosomes of a variety of cell types, leading to cell damage and tissue inflammation. To date there are more than fifty distinct LSDs, many of which have common neuronopathic effects, involving neurological degeneration and subsequent developmental retardation.[44] The degree to which the symptoms are expressed is determined by the residual enzyme activity, and hence level of substrate accumulation where, in the most severe infantile cases patients do not survive the first year of life. At the other end of the spectrum, patients can be asymptomatic during childhood with the onset occurring in later life, ultimately leading to a reduced life expectancy.

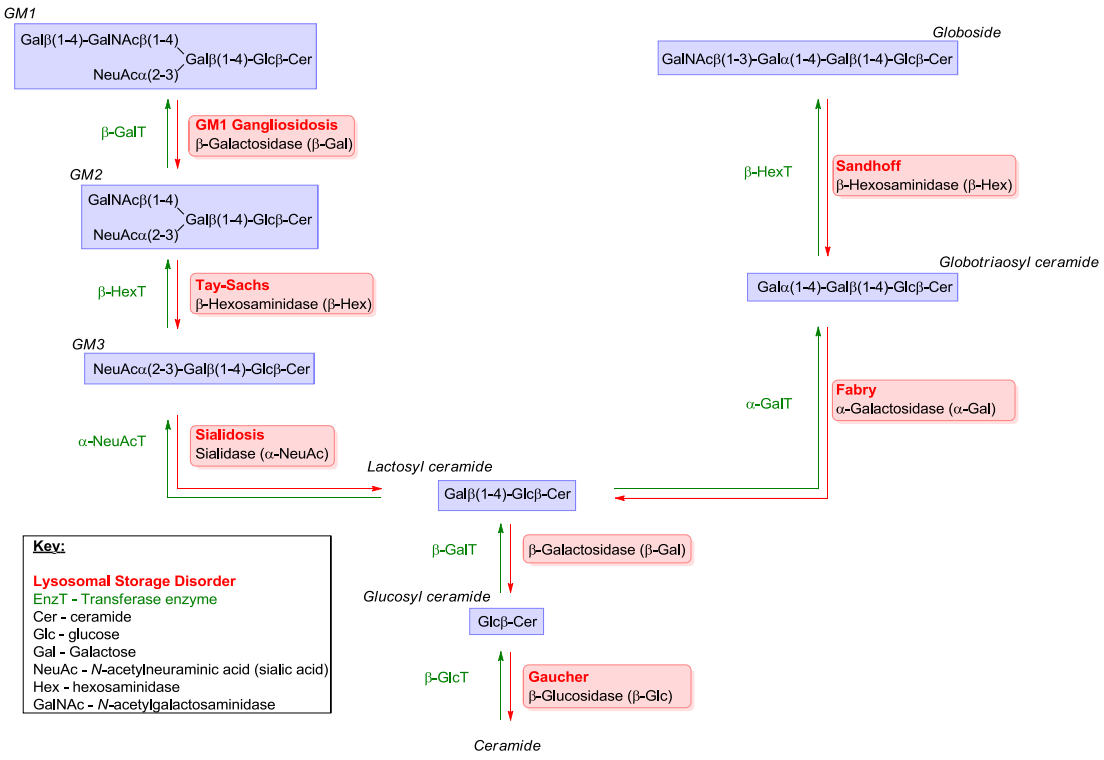



**Scheme 1.4**. Cellular synthesis and trafficking of lysosomal enzymes.

LSDs are autosomal, recessive, largely monogenetic disorders where mutations in a gene encoding for one of the estimated 50-60 soluble glycosidases found in lysosomes causes an LSD.[45] This mutation is then translated by the ribosomes of the endoplasmic reticulum (ER) into

the protein structure of the enzyme (**Scheme 1.4**). Altering a single amino acid residue in a protein sequence of an enzyme may result in misfolded conformations being adopted. The ER-associated degradation (ERAD) machinery detects such misfolded proteins, which undergo catabolism - a process that critically maintains cellular integrity.[46,47]

LSDs were first identified in the late nineteenth century, initially with the description of Tay-Sachs and Gaucher disease.[45] But it wasn't until 1975 that de Duve detailed the isolation of the lysosome and identified it as the structure responsible for intracellular digestion and macromolecule recycling.[48] Following this Brady and co-workers were the first to demonstrate that substrate accumulation in Gaucher disease was due to a specific, defective lysosomal enzyme - β-glucocerebrosidase, or β-glucosidase.[49] This glycosidase enzyme is one of many required in the sequential, step-wise cleavage of terminal sugar residues in the degradation of glycosphingolipids (GSLs), where one faulty enzyme results in a 'bottle-neck' in the pathway and accumulation of substrate (**Scheme 1.5**).

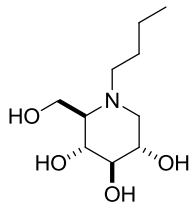



**Scheme 1.5**. Lysosomal biosynthesis and metabolism of glycosphingolipids.

With this knowledge, the basic therapeutic concept of replacing the defective enzymes and removing the 'bottle-neck' was conceived. Enzyme replacement therapy (ERT) was approved in the 1990s and has subsequently been utilised in the treatment of thousands of patients displaying a range of LSDs.[45] Although ERT has been successfully utilised in the treatment of some LSDs, the ultimate problem is in the targeting of defective cells and, more critically, crossing the blood-brain barrier. The former can be overcome, but the latter is not possible by the enzymes used in ERT. This limits the efficacy of ERT, given that the more severe forms of the disease are neuronopathic, ultimately finding a treatment that is able to cross the blood-brain barrier is essential. This is where iminosugars have found a major breakthrough, leading to the immergence of two promising therapies that hinge on the idea that, however limited, the mutant enzymes still possess some residual activity.

The first strategy to be developed was termed substrate reduction therapy (SRT). The principle of this strategy lies in the prevention of substrate build-up by inhibiting GSL biosynthesis, thereby reducing it to a level that can be managed by the defective enzyme. This has been successfully deployed in the treatment of Gaucher disease, where *N*-butyl-DNJ (*N*B-DNJ) **1.19** (**Figure 1.8**), marketed as Zavesca, has been approved as a clinical treatment of type I Gaucher disease. The mode of action of *N*B-DNJ **1.19** is as a competitive inhibitor of glucosyl-ceramide transferase (β-GlcT, **Scheme 1.5**), decreasing the rate of glucose ceramide substrate accumulation to a level manageable by the defective β-glucosidase enzyme (β-Glc). This leads to a reduction in the phenotype of the LSD. Gaucher disease is the commonest LSD, especially within the Askenazi-Jewish community where this disorder occurs in 0.1% of the population.[50] Although, to date this therapy has only been applied to non-neuronopathic Gaucher disease (type I), it has been indicated that *N*B-DNJ **1.19** has the capability to cross the blood-brain barrier which may lead to this iminosugar being therapeutically beneficial in the more severe

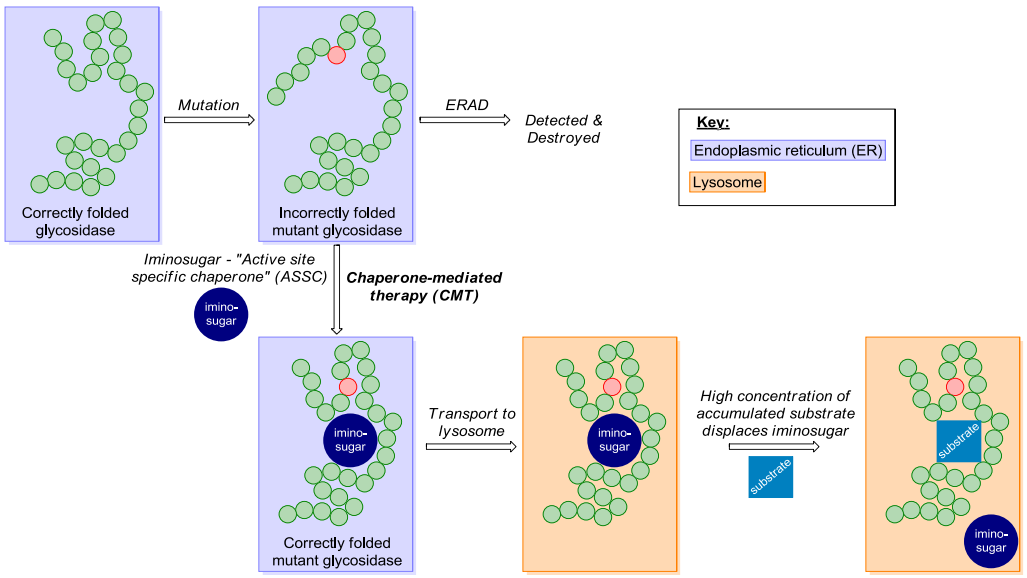
type II and type III forms of this LSD.[51] Thus SRT forms a valuable and general therapy that could potentially be applied to a wide range of LSDs and patients.




Zavesca
*N*-butyl-DNJ
**1.19**

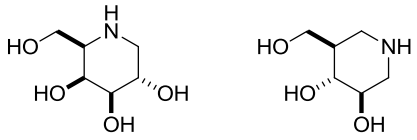
**Figure 1.8:** *N*-butyl-DNJ **1.19** a chemotherapeutic agent in the SRT of Gaucher disease.

The second of the two iminosugar-based strategies is called chaperone-mediated therapy (CMT) and concerns the ERAD mechanism. As mentioned earlier this process maintains the intracellular integrity by catabolising misfolded proteins, regardless of the fact that mutant enzymes still possess some residual function.[43] The principal concept behind this strategy is the facilitated trafficking of mutant glycosidases out of the ER, bypassing ERAD, and eventually into the lysosomes, where the residual enzyme activity can have an impact on the level of the accumulated substrate. In the case of Gaucher disease reduction in the storage of glucosyl ceramide is observed when β-glucosidase activity is greater than 11-15% of normal function,[52] and for the majority of other LSDs 5-10% of normal activity is required.[44] CMT is a fascinating and counter-intuitive process where iminosugars can be utilised as templates, or scaffolds, around which the mutant enzyme can be induced to correctly fold inside the ER (**Scheme 1.6**). This results in the mutant enzyme-iminosugar complex avoiding ERAD and being successfully transported to the lysosomes, where the high-concentration of accumulated substrate competitively displaces the iminosugar template. Thus the mutant enzyme concentration is increased leading to a reduction of substrate within the lysosome.




**Scheme 1.6**. Chaperone-mediated therapy (CMT) in the treatment of LSDs.

Fan[53] and Asano[54] demonstrated the very first active site specific chaperone (ASSC) study targeting the CMT of Fabry disease (α-galactosidase, **Scheme 1.5**) and from this ASSCs have so far been identified for Gaucher (β-glucosidase),[55-57] GM1-gangliosidosis (β-galactosidase),[58] Pompe (α-glucosidase),[59-61] Schindler/Kanzaki (α-*N*-acetylgalactosaminidase),[62] Tay-Sachs and Sandhoff diseases (β-hexosaminidases, or more specifically β-*N*-acetylglucosaminidases)[63-66] - resulting in the establishment of several clinical trials. DGJ **1.2** (Amigal™, **Figure 1.9**) is currently in phase III clinical trials for the CMT of Fabry disease,[67,68] and IFG **1.5** (Plicera™) is in phase II trials for the CMT of Gaucher disease.[69] Currently an investigation is also in phase II trials for the treatment of Tay-Sachs and Sandhoff diseases.[70] Thus it can be seen that iminosugars have great potential in the future treatment of LSDs.




Amigal
DGJ **1.2**

Plicera
IFG **1.5**

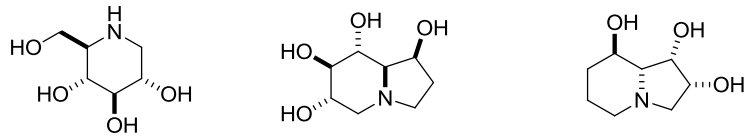
**Figure 1.9**. Pharmacological chaperones (ASSCs) for the treatment of LSDs by CMT.

1.5.3 Cancer

As the majority of human cancers develop the primary tumour releases pioneer cells that colonise distant tissues establishing secondary tumour colonies.[71] This culminates in the ultimate shortcoming of modern cancer therapy, where the undetected and more difficult to treat distant secondary tumours account for an estimated 90% of mortality in cancer patients.[72] Primarily this is because surgery is not possible for these secondary tumours and the toxicity of chemotherapy agents limits their usage. This then presents a profound need for tools in the prevention of the invasive, metastatic phase of cancer development, allowing for a reduction in overall cancer mortality.

Although metastasis and tissue invasion are extremely complex processes, glycosidase inhibition offers several approaches in the chemotherapeutic treatment of cancer. The first, and most widely studied, stems from the association of *N*-linked glycoconjugates with malignancy and metastasis in tumours. The overexpression of these cancer cell-surface glycans is known to contribute to a cancer cell's ability to grow and metastasise, due to an insensitivity to anti-growth signals and a decrease in intercellular adhesion. Metastasis begins with this lack of adhesion which causes the detachment of cells from the tumour's leading edge, with subsequent invasion of new tissues forming new tumour colonies. The assembly of the glycoconjugates involves the cleavage of glucose and mannose residues, by α-glucosidases and α-mannosidases, creating a core scaffold which then undergoes further elaboration and subsequent cell-surface expression. As a result this first anti-cancer strategy pivots around the inhibition of these enzymes, thereby either directly preventing glycan overexpression, or indirectly provoking an immune response.[40] Despite both normal cells and cancer cells sharing the same pathways, disruption of these has a more pronounced effect of the hyperactivity of cancer cells. Iminosugars that inhibit α-glucosidases and α-mannosidases have therefore undergone investigation for their potential in

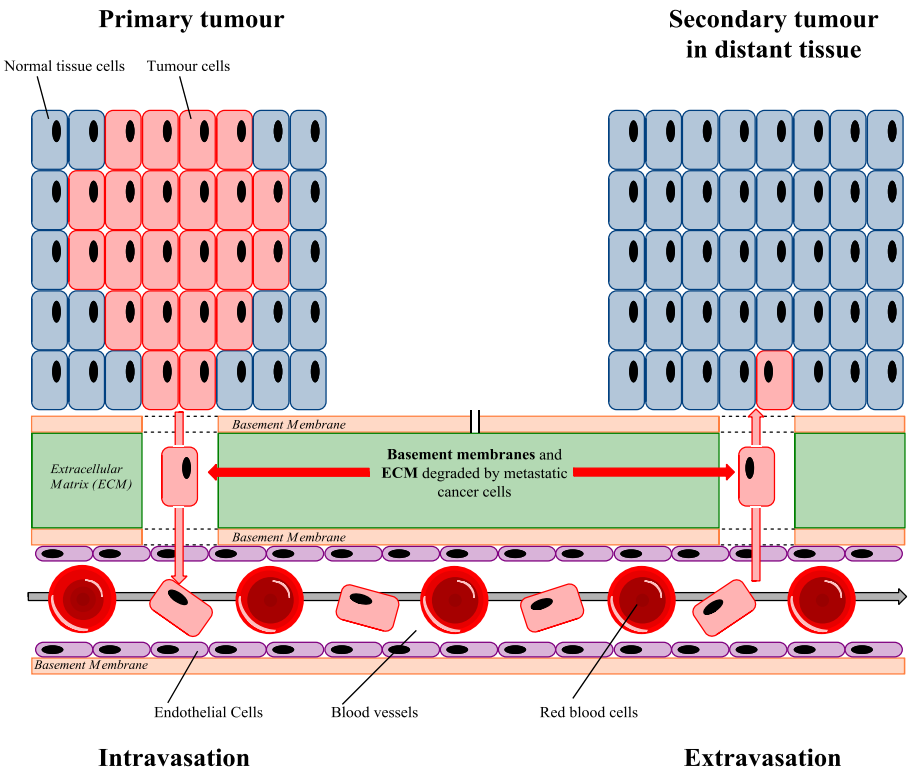
this therapeutic strategy. The α-glucosidase inhibitors DNJ **1.1** and castanospermine **1.12** have exhibited some anticancer activity (**Figure 1.10**). The iminosugar swansonine **1.11**, a potent α-mannosidase inhibitor, has been studied the most extensively - with clinical trials extending to phase II[73] - however, swansonine **1.11** failed to demonstrate significant anticancer activity, but did reduce the incidence of lung colonies implying it reduced metastatic capabilities.[74]




DNJ **1.1** | Castanospermine **1.12** | Swansonine **1.11**

**Figure 1.10**. Iminosugar α-glucosidase and α-mannosidase inhibitors.

Taking a different approach to the preventation of metastasis by glycosidase inhibition, two further potential strategies have recently been identified involving hexosaminidase enzymes. In order to achieve metastasis, a cancer cell must be able to break through a number of barriers. The first is that a cancer cell must be able to move through basement membranes, and the second to be able to move through the extracellular matrix (ECM). This is known as 'intravasation', the process by which a metastatic cancer cell enters the bloodstream. From here these cancer cell pioneers are carried to distant areas in the body, commonly deposited in pulmonary and hepatic tissues. Utilising the same mechanisms as before the cancer cell is then able to move through basement membranes and the ECM to penetrate and invade tissues causing the formation of a new colony, or a secondary, satellite tumour - this process then being called 'extravasation' (**Scheme 1.7**).[75]




**Scheme 1.7**. Mechanism of secondary tumour formation by metastatic cancer cells - demonstrating the destruction of the basement membranes and the extracellular matrix (ECM) by the leading cell edge of the tumour, and the colonisation of distant tissues by cancer cells.[75]

The process of intra- and extravastion is no easy task and requires the use of specialised degradative proteinases, matrix metalloproteinases and glycosidases to cut through the dense, fibrous proteins (collagen and elastin), proteoglycans (heparan, chondroitin and keratan sulfates) and cross-linked polysaccharides of the ECM. Specifically the carbohydrate elements of the ECM include hyaluronic acid (hyaluronan) and glycosaminoglycans. The former is a polymer consisting of alternating glucuronic acid and *N*-acetylglucosamine (GlcNAc) units (**Figure 1.11**),[76] and the glycosaminoglycans are attached to the densely glycosylated proteoglycans, possessing similar composition to hyaluronic acid. GlcNAc residues are therefore extremely abundant in the ECM; a fact demonstrated by the release of this residue at rapid rates during cancer cell-based degradation of the ECM.[77] Elevated levels of extracellular β-*N*-acetylglucosaminidase (β-GlcNAcase) are also present in advanced stages of malignant cancer development.[78] The inhibition of β-GlcNAcase then affords a potential approach to the

reduction of cancer metastasis, by preventing ECM degradation and decreasing both intra- and extravastion - a complementary approach to methods aimed at destroying the primary tumour.

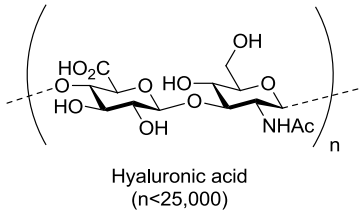
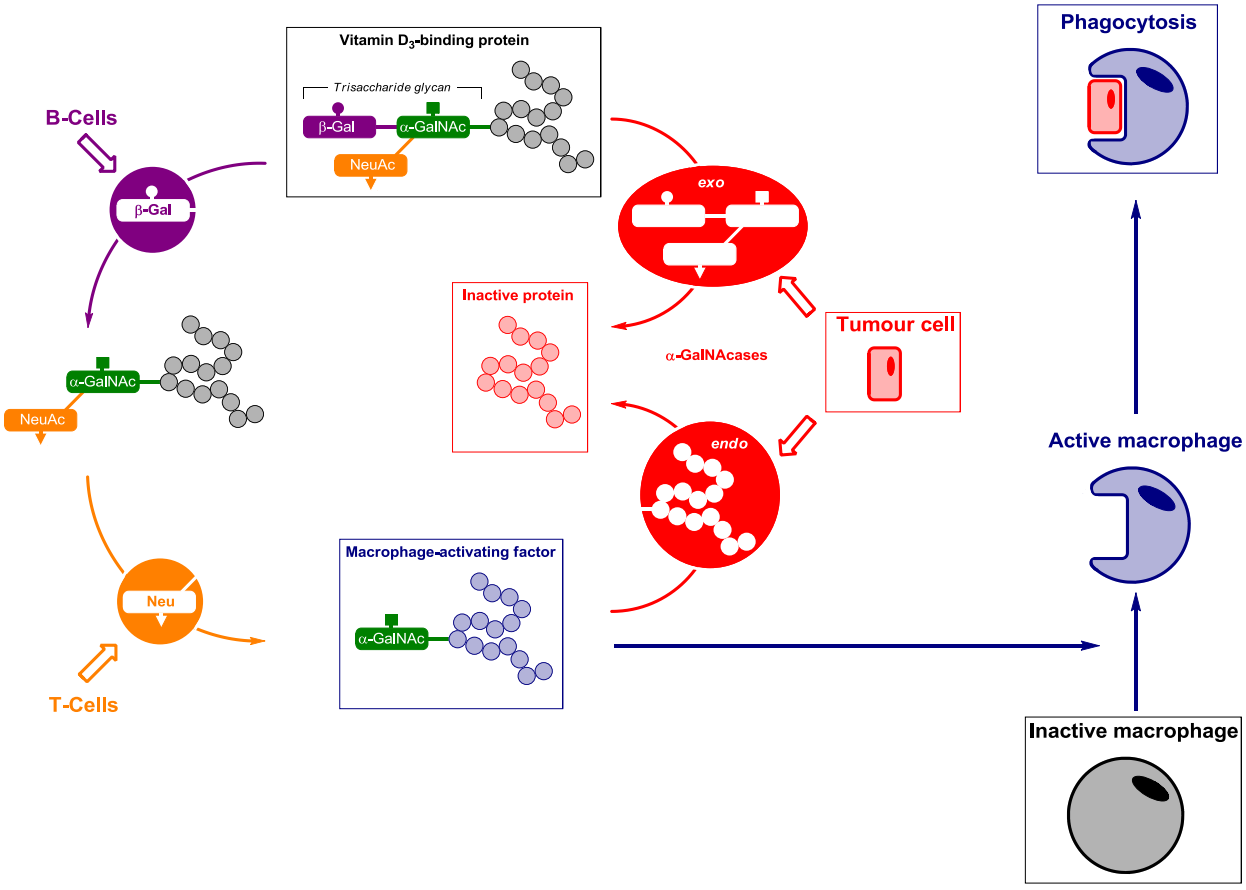



**Figure 1.11**. Structure of hyaluronic acid, a component of the ECM.[76]

The second potential approach to cancer therapy utilising hexosaminidase inhibition focuses on α-*N*-acetylgalactosaminidase (α-GalNAcase, α-NAGALase). In addition to β-GlcNAcase this enzyme has also been strongly indicated in the advancement of cancers,[79] acting extracellularly as an immunosuppressant.[80] α-GalNAcase achieves this by being key in the degradation of the macrophage-activating factor (MAF, GcMAF) to an inactive form, thereby preventing macrophage activation and phagocytosis of aberrantly developing cancer cells. This allows for the sustained growth of a malignant tumour (**Scheme 1.8**). MAF is normally produced by the action of the immune system's B- and T-cells. B-Cells release β-galactosidase and T-cells release neuraminidase which sequentially cleave β-galactose and *N*-acetylneuraminidase residues from a trisaccharide glycan of the vitamin $D_3$-binding protein (vitamin $D_3$-BP, Gc protein) - this forms the activated MAF with an exposed α-*N*-acetylgalactosaminidase residue, which in turn leads to the normal immune response.[80] Cancer cells secrete both extracellular *exo*- and *endo*-α-GalNAcase enzymes. The *exo*-form cleaves the trisaccharide glycan from the Gc protein,[81] whereas the *endo*-form deglycosylates the protein itself from the α-GalNAc residue.[82] The specificity and ratio of the enzymes produced varies greatly between cancers and cell-lines, but the net effect is identical for both α-GalNAcases: deactivation of the MAF and resulting immunosuppression in the locale of the tumour. So, a strategy involving extracellular α-

GalNAcase inhibition would ultimately lead to a decrease in the MAF deactivation and a restoration of normal immune system function.[83]




**Scheme 1.8**. Action of B- and T-cells to form the MAF, leading to cancer cell phagocytosis; also deactivation of the MAF by *exo*- and *endo*-α-GalNAcase enzymes secreted extracellularly by cancer cells.

Thus, hexosaminidase enzymes (β-GlcNAcase and α-GalNAcase) afford potentially valuable targets in the future treatment of metastatic cancers. The design and synthesis of iminosugar hexosaminidase inhibitors will be discussed later in this thesis.

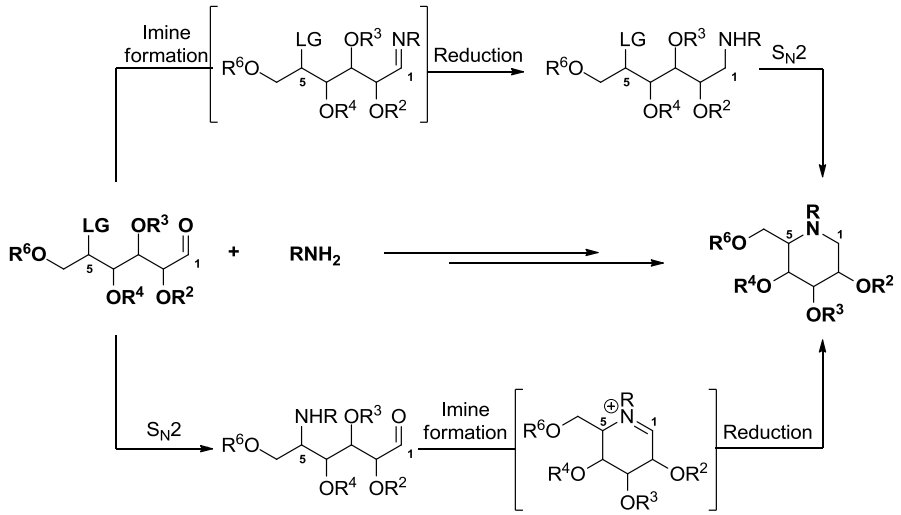
## 1.6 General methods of iminosugar synthesis

There are two core principles for the assembly of an iminosugar ring - asymmetric synthesis and chiral pool. Asymmetric methods involve the creation of new chiral centres utilising chiral catalysts or auxiliaries, whereas chiral pool reagents allow the use of enantiomerically pure starting materials with rich, predefined stereochemistry. The most diverse group of optically-active chiral pool materials are carbohydrates - which possess several contiguous, hydroxyl-bearing chiral centres. Because of this they are ideal starting materials for the synthesis of iminosugars, which also bear several asymmetric centres on their carbon skeleton. However, carbohydrates have a drawback: until recently only a handful of sugars were cheap and readily available. From the sixteen possible aldohexoses, only three are viable starting materials due to their availability and cost; D-glucose, D-mannose and D-galactose. Similarly only three ketohexoses (D-fructose, D-tagatose and L-sorbose) and only four of the eight aldopentoses (D-arabinose, L-arabinose, D-ribose and D-xylose) are readily available. Although, some additional monosaccharides are easily accessible from those listed above over short synthetic routes. The reason for this limitation is natural abundance - if a monosaccharide is not employed widely in Nature it cannot be isolated on a large scale. But now, modern chemical techniques and use of biotechnological advances have led to the possible formation of unprecedented, and previously unobtainable, quantities of rare and "unnatural" monosaccharides.[84,85] Research in this field has led to the diversification and expansion of the carbohydrate chiral pool, and hence a vast reduction in the cost of some rare and "unnatural" monosaccharide precursors. This has allowed for the synthesis of both novel and known iminosugars over cheaper or shorter synthetic routes.

In order to access a desired iminosugar from a monosaccharide the researcher typically conducts a number of staple, core modifications - which are given here in the order of importance - firstly, and most essentially, nitrogen must be introduced to the scaffold, and the iminosugar ring subsequently formed. Secondly, the modification of specific hydroxyl groups may be required to achieve a specific stereochemistry or functionality. And thirdly, carbon-chain homologation, truncation or branching may be required in order to access the desired target. This following subsection will present an overview, and highlight examples, of the methods utilised to perform these necessary transformations.

1.6.1 Nitrogen: introduction and iminosugar ring formation

The formation of an iminosugar requires two fundamental steps; introduction of nitrogen, and subsequent closure to another centre forming the ring. The two main methods employed are $S_N2$-displacement reactions of a leaving group with a nitrogen-based nucleophile, and reductive amination of an imine formed *in situ* (**Scheme 1.9**).

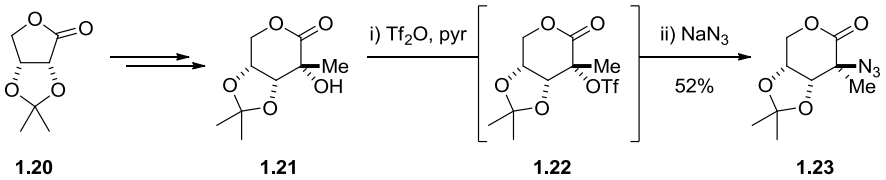



**Scheme 1.9**. Introduction of nitrogen and ring formation by $S_N2$-displacement or reductive amination.

Nucleophilic attack is the more widely employed and preferred method - and has been achieved with a range of nitrogen-based nucleophiles. Commonly utilised nitrogen-sources range from

simple ammonia to amines, such as benzylamine, hydroxylamine, hydrazine, and also to phthalamide. Azide, a 'masked' amine source, has proven to be one of the most successful methods for introducing nitrogen to a monosaccharide. It is a powerful nucleophile, and in combination with active leaving groups, displacements have even been conducted at tertiary and neopentyl centres.[87] And furthermore, once azide is installed it is robust to a wide range of reaction conditions and can be efficiently reduced to the 'unmasked' primary amine. Reductive aminations have also been widely employed, with the only synthetic difficulty arising in ketose sugars. The reaction of a ketose with an amine forms a prochiral imine, with an unselective reduction ultimately forming a diastereoisomeric mixture - although these reactions have in certain cases been found to be quite selective.[86]

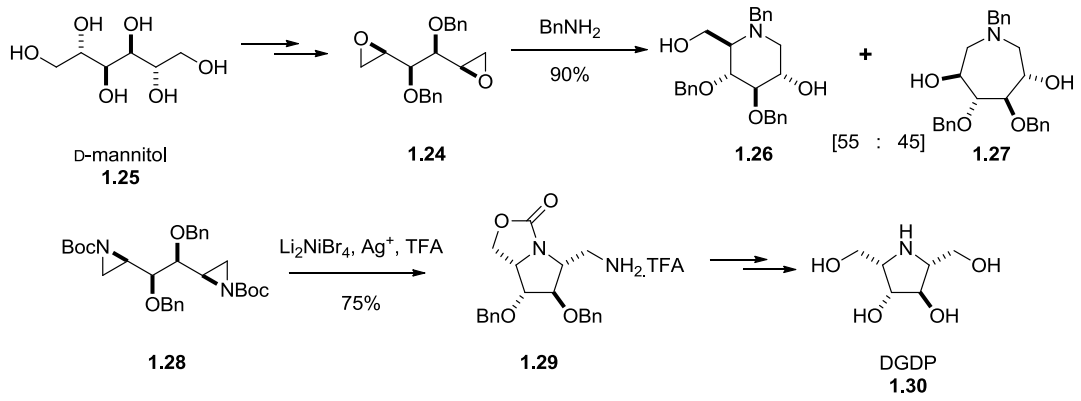
In terms of leaving groups, commonly used systems include halides, sulfonates and the opening of reactive three-membered rings. Classically in early iminosugar syntheses, halides were predominately and successfully used - especially in displacements at primary centres. However, limitations are found in more hindered systems with more reactive sulfonates such as methanesulfonate (mesylate) and *para*-toluenesulfonate (tosylate) now being more widely employed, due to their ease of formation and their greater reactivity towards $S_N2$-displacements at more hindered positions. Trifluoromethanesulfonates (triflates) are exceptionally more reactive, with azide being shown to displace tertiary triflate **1.22** - presumably by a highly selective, $S_N2$ process - forming azido-lactone **1.23** with inversion of configuration (**Scheme 1.10**).[87]




**1.20** **1.21** **1.22** **1.23**

**Scheme 1.10**. $S_N2$ displacement of a tertiary triflate by azide nucleophile.[87]

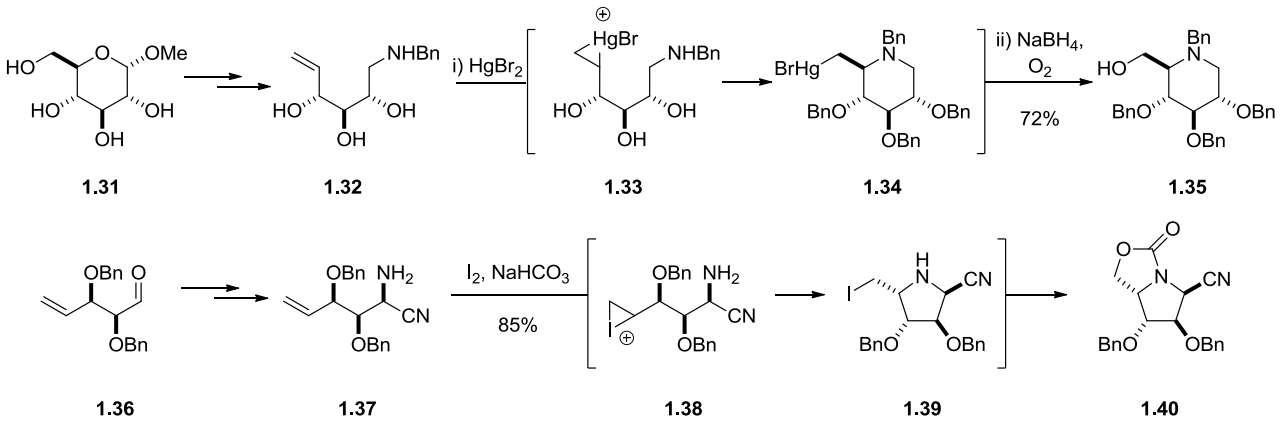
Another widely-used strategy involves the opening of three-membered ring systems, including; epoxides, aziridines and also *in situ* species formed by the activation of an alkene with iodine or mercury(II) salts. The $C_2$-symmetric diepoxide **1.24** can be readily accessed from commercially available D-mannitol **1.25**, and then can undergo cyclisation with benzylamine to give an inseparable mixture of the six-ring piperidine **1.26** (a protected version of DNJ **1.1**) and seven-ring azepane **1.27** products (**Scheme 1.11**).[88] This reaction proceeds with favoured opening at C1, followed by either a 6-*exo*-tet or 7-*exo*-tet cyclisation to afford piperidine **1.26** and azepane **1.27** respectively - albeit without the preference for **1.26** that would be expected. Similarly, the bis-aziridine **1.28** undergoes a similar C1 regioselective opening with $Li_2NiBr_4$ - a bromide source - followed by fast 5-*exo*-tet cyclisation and silver(I) promoted carbamate formation, affording pyrrolidine **1.29** and ultimately the target D-*gluco* pyrrolidine natural product **1.30** (DGDP, **Scheme 1.11**).[89,90]




**Scheme 1.11**. Iminosugars formed by the opening of three-membered rings.[88-90]

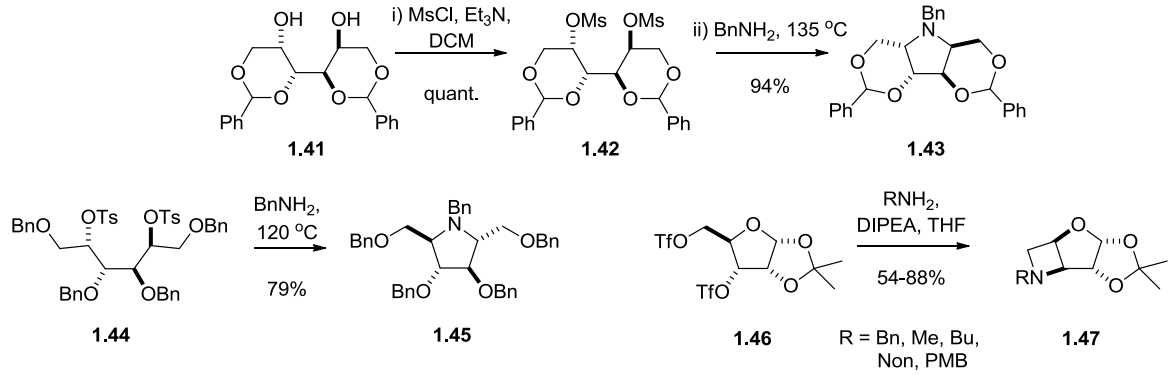
Conditions of alkene activation by oxymercuration or by the action of iodine lead to the *in situ* formation of reactive three-membered intermediates, which may undergo intramolecular cyclisation with an internal nitrogen-nucleophile. For example the reaction of the amino-alkene **1.32** with mercury(II) bromide leads to the formation of the intermediate **1.33**, which cyclises and is reduced to form the piperidine **1.35** (**Scheme 1.12**).[91] In a similar fashion, the reaction of

the α-aminonitrile-containing alkene **1.37** with iodine forms the carbamate-protected pyrrolidine product **1.40** *via* the intermediate iodonium **1.38**.[92]



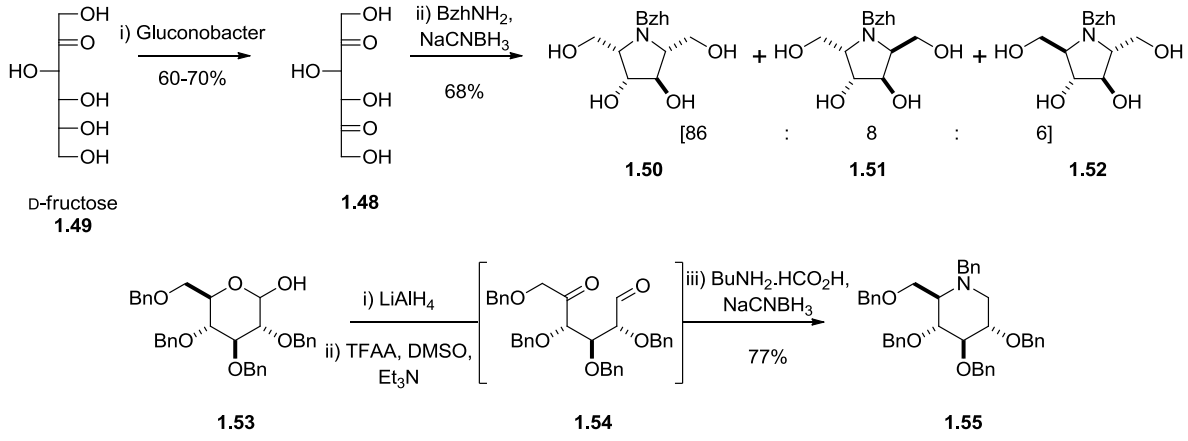

**Scheme 1.12**. Iminosugars formed by the opening of three-membered rings formed *in situ*.[91,92]

As can be seen, the methods utilised for the introduction of nitrogen and subsequent cyclisation may be similar, or even identical. Strategically this may be exploited so that they can be performed in a single synthetic reaction. Conducting these two steps simultaneously has allowed for the elaboration of some particularly elegant and note-worthy syntheses - demonstrated above by the reaction of the diepoxide **1.24** with benzylamine (**Scheme 1.11**, page 27). The efficacy of double $S_N2$-displacements has been demonstrated in numerous synthetic routes, allowing for the formation of six-, five- and even four-membered iminosugars. Masaki and co-workers showed that the dimesylate **1.42** cyclises efficiently with benzylamine to afford the pyrrolidine **1.43** in high yield (94%, **Scheme 1.13**),[93] this followed an earlier cyclisation by Shing of an identically protected ditriflate substrate with hydrazine.[94] Durealt and colleagues also showed that the ditosylate **1.44** would similarly cyclise to the pyrrolidine **1.45**, also in good yield.[95] Recently Fleet and co-workers have produced multiple examples of ditriflate and dimesylate displacements forming iminosugars - of which the formation of four-membered azetidines is particularly note-worthy:[96,97] for example, the ditriflate **1.46** was treated with a range of amines forming the azetidines **1.47**.[96]




**Scheme 1.13**. Examples of double-displacements forming iminosugars.[93,95,96]

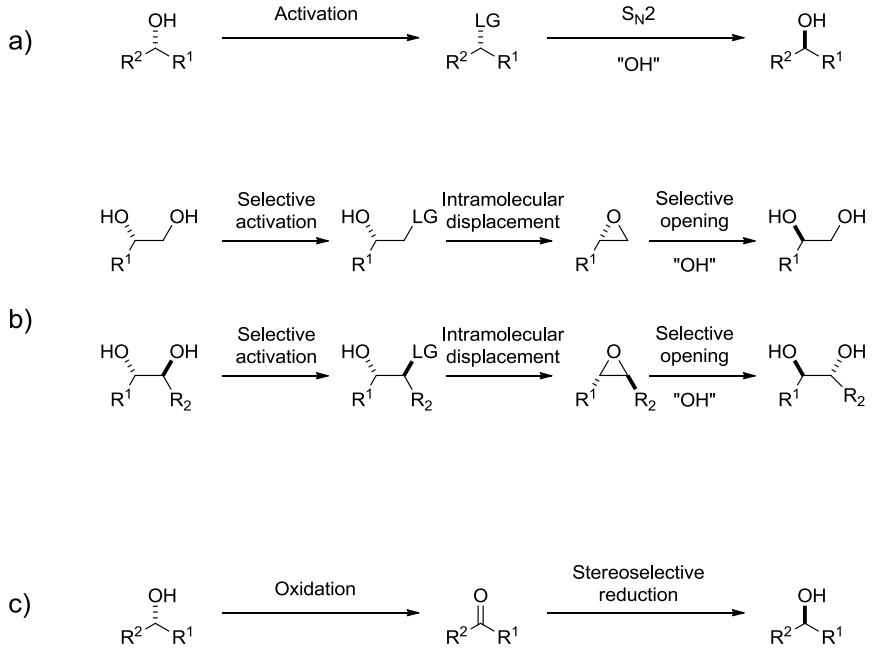
Aside from double-displacements, double-reductive aminations have also been used in the synthesis of iminosugars. 5-Keto-D-fructose **1.48**, derived from D-fructose **1.49**,[98] has undergone double-reductive amination with benzyhydrylamine and sodium cyanoborohydride, forming a mixture of three benzhydryl-protected pyrrolidine products; D-*gluco* **1.50**, L-*ido* **1.51** and D-*manno* **1.52** (**Scheme 1.14**).[99] And similarly Matos *et al* demonstrated that the 5-keto-aldose **1.53**, formed by reduction and then Swern oxidation of suitably protected D-glucose **1.54**, would form the piperidine **1.55** selectively and in good yield.[100]




**Scheme 1.14**. Examples of double-reductive aminations forming iminosugars.[99,100]

1.6.2 Oxygen: manipulation of hydroxyl group stereochemistry

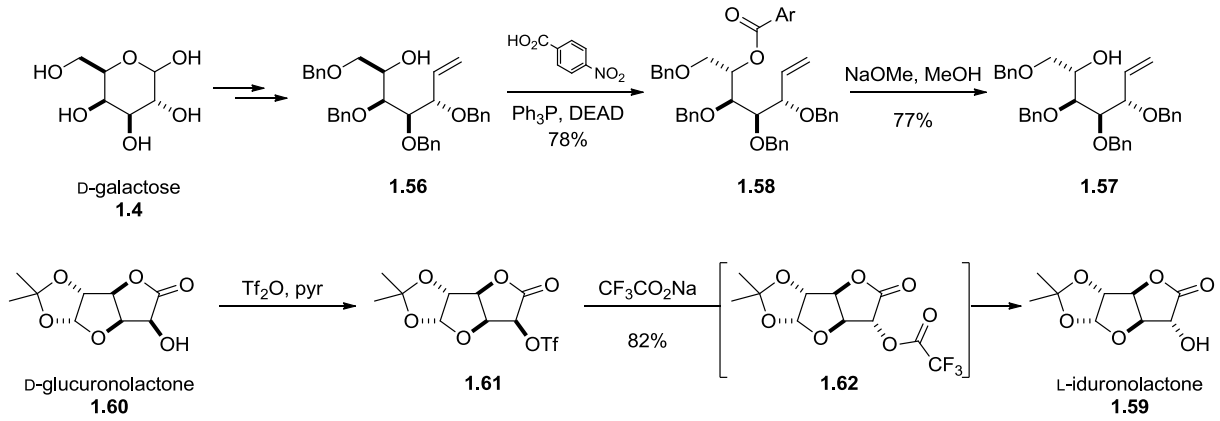
With the essential methods of ring formation established, the next stage is in planning the stereochemical disposition of the hydroxyl groups borne by the iminosugar ring. It may be that this arrangement needs no modification from that of a readily available starting monosaccharide. On the other hand, the required target may possess an unnatural functionality akin to that of an unnatural, and hence potentially expensive precursor. So, processes by which the stereochemistry of individual hydroxyl groups may be modified are crucial to accessing a diverse range of target materials from cheap and readily available starting carbohydrates. To that end, three efficient methods for inverting hydroxyl groups have come to prominence: the first is the $S_N2$-displacement of a leaving group by a nucleophilic oxygen source, the second is the formation and ring opening of an epoxide, and the third is the two-stage oxidation and stereoselective reduction of a prochiral ketone (**Scheme 1.15**). These methods are described and illustrated below.




**Scheme 1.15**. Overview of the processes used to invert alcohol stereochemistry on carbohydrate rings.

*1.6.2.1 $S_N2$-inversion of hydroxyl configuration*

Activation and subsequent displacement of a hydroxyl group provides the best, and most routinely, used method for access to an inverted hydroxyl configuration. Mitsunobu conditions have proven useful in this regard, providing access to the inverted configuration in a single synthetic step. Albeit with an extra step required to hydrolyse the ester that is formed. The L-*Altro* heptenitol **1.56**, derived from D-galactose **1.4**, was converted to the inverted alcohol target **1.57** by reaction with *para*-nitrobenzoic acid, triphenylphosphine and diethyl azodicarboxylate - and subsequent basic hydrolysis of the resultant benzoate ester **1.58** proceeded in good yield over two steps (**Scheme 1.16**).[101]

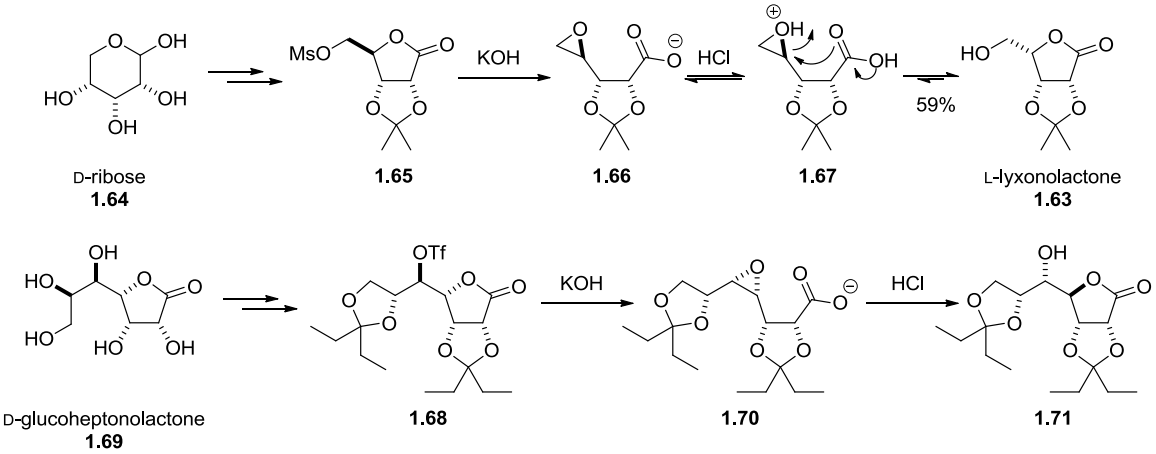



**Scheme 1.16**. Inversion of a secondary alcohol by Mitsunobu conditions,[101] and by trifluoroacetate displacement.[102]

It has been found that better yields may be obtained by the displacement of a triflate leaving group by trifluoroacetate - with the resultant ester being hydrolysed under basic work-up conditions. Csuk and co-workers demonstrated this method in the synthesis of iduronolactone **1.59** from glucuronolactone **1.60**. Reaction of the triflate **1.61** with sodium trifluoroacetate afforded iduronolactone **1.59** in excellent yield (**Scheme 1.16**).[102] It has been shown more recently that enhanced yields may be obtained by employing a caesium, rather than sodium, counter-cation.[103]

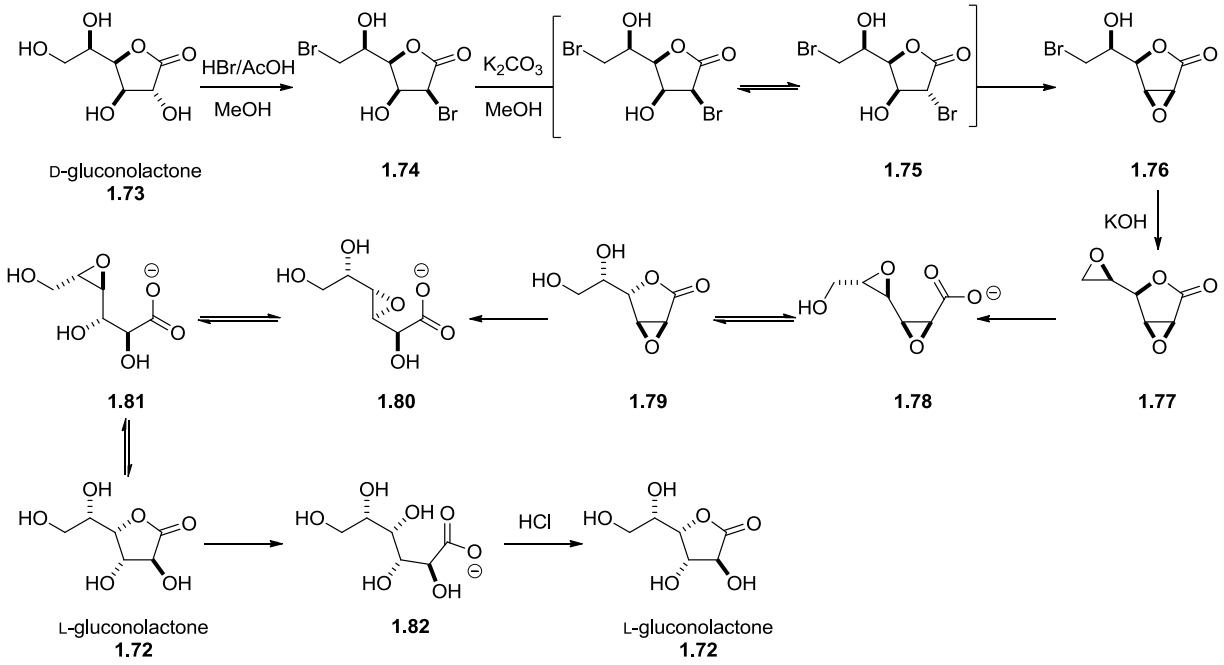
*1.6.2.2 Inversion by epoxide-ring opening*

Another commonly utilised method by which $S_N2$-displacement may be used to access inverted hydroxyl configurations is that of epoxide formation and subsequent ring opening. Activation of an hydroxyl as a leaving group, and subsequent intramolecular epoxide formation results in the inversion of that position. Regioselective opening at the internal position of a terminal epoxide formed in this manner, will elicit the overall inversion of a single centre, whereas for an internal epoxide opening the result will be the inversion of both stereocentres (**Scheme 1.15**, page 30). This makes the use of epoxides a very powerful tool in the derivitisation of commercially available monosaccharides. For example L-lyxonolactone **1.63**, a costly starting material, may be formed from cheap and readily available D-ribose **1.64** on a large scale *via* an intermediate epoxide (**Scheme 1.17**). The D-*ribo* mesylate **1.65** was treated with potassium hydroxide, which led to opening of the lactone ring and $S_N2$-displacement of the C5-mesylate by the C4-hydroxyl, forming the terminal epoxide **1.66**. Acidification resulted in rapid epoxide ring-opening by the carboxyl group of **1.67** affording the desired L-lyxonolactone **1.63** in good yield over a short synthetic sequence, with the overall inversion of a single hydroxyl group.[104,105] Likewise the triflate **1.68**, formed from D-glucoheptonolactone **1.69**, led to the internal epoxide **1.70** - with acidification and closure of the lactone ring yielding the lactone **1.71**, and the overall inversion of two chiral centres.[106,107]




**Scheme 1.17**. Epoxide intermediates in the synthesis of five-membered lactones.[104-107]

More expeditiously, it could be envisaged that the formation of two internal epoxides, with regioselective opening, would lead to the inversion of a total of four stereocentres. For a hexose monosaccharide this would cause the formation of the enantiomer from the starting material - a very useful synthetic procedure. This concept was successfully employed by Lundt *et al* in the synthesis of L-gluconolactone **1.72** from enantiomeric D-gluconolactone **1.73** (**Scheme 1.18**).[108,109]



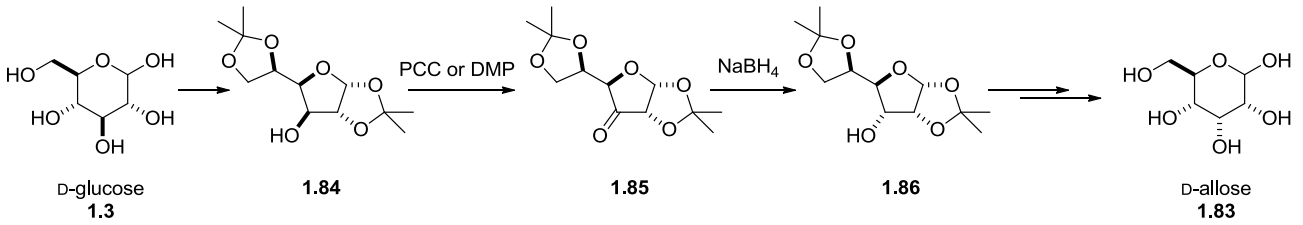

**Scheme 1.18**. Formation of a diepoxide allowing inversion of every stereocentre.[108,109]

To achieve this D-gluconolactone **1.73** was reacted with HBr, which formed dibromolactone **1.74**. This lactone **1.74** was treated with potassium carbonate leading to the 2,3-epoxy lactone **1.76** - with base-catalysed epimerisation of C2 affording the required 2,3-*trans* disposition in the intermediate **1.75** required for the $S_N2$-displacement to occur. From here treatment with potassium hydroxide led to the product-forming cascade. The proposed mechanism proceeds *via* initial formation of the diepoxide **1.77**, and opening of the lactone ring by hydroxide giving the diepoxy-carboxylate **1.78**. This intermediate would reasonably undergo an intramolecular 5-*exo*-tet cyclisation forming the five-membered lactone **1.79**. The basic conditions lead to opening of

the lactone ring and a succeeding Payne rearrangement to give the 3,4-epoxide **1.80**. This epoxide is in equilibrium with the 4,5-epoxide **1.81** by another Payne rearrangement, and it is this epoxide which may then cyclise, according to Baldwin's rules,[110] to form L-gluconolactone **1.72**. This lactone is irreversibly hydrolysed under the basic reaction conditions and subsequently reformed by final acidic work-up. This reaction proceeds by a complex mechanism, but ultimately allows access of the fully inverted product in just three synthetic steps.

*1.6.2.3 Inversion by oxidation and selective reduction*

The last of the three methods for inverting the stereochemistry of a hydroxyl group is that of oxidation and reduction (**Scheme 1.15**, page 30). Oxidising a hydroxyl to a prochiral ketone allows for a subsequent selective reduction to an inverted configuration, where the resultant stereochemistry is induced by the chirality of the carbohydrate scaffold. This approach is typified by the conversion of D-glucose **1.3** to unnatural, and consequently expensive, D-allose **1.83** (**Scheme 1.19**). [96,111] Acetonide protection of D-glucose **1.3** may be achieved in high-yield, forming the diacetonide **1.84**. Subsequent oxidation of the free C3-hydroxyl with either pyridinium chlorochromate[111] (PCC) or Dess-Martin periodinane[96] (DMP) affords the stable ketone **1.85** which then may undergo facially-selective reduction with sodium borohydride - induced by the neighbouring, bulky 1,2-acetonide - forming the D-*allo* inverted alcohol **1.86** in good yield.

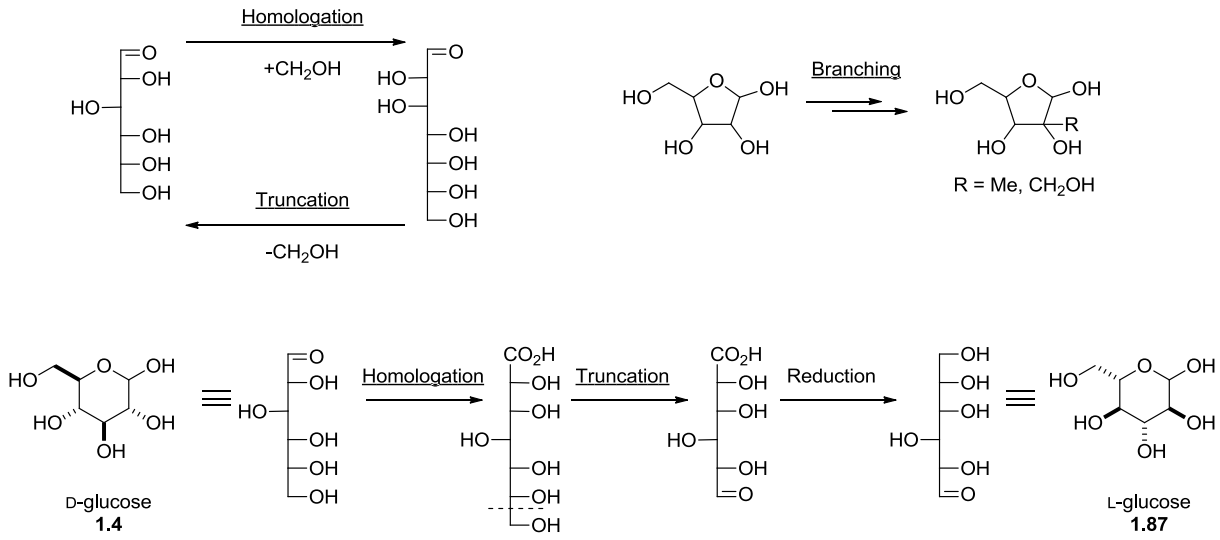



**Scheme 1.19**. Oxidation/reduction strategy used to access D-allose from D-glucose.[96,111]

As can be seen, the necessity of great steric bulk to induce selective reduction becomes the major limitation of this strategy, which reduces the applicability of this method to many synthetic routes, however it still remains a valuable and useful tool in many syntheses.

### 1.6.3 Carbon: homologation, truncation and branching

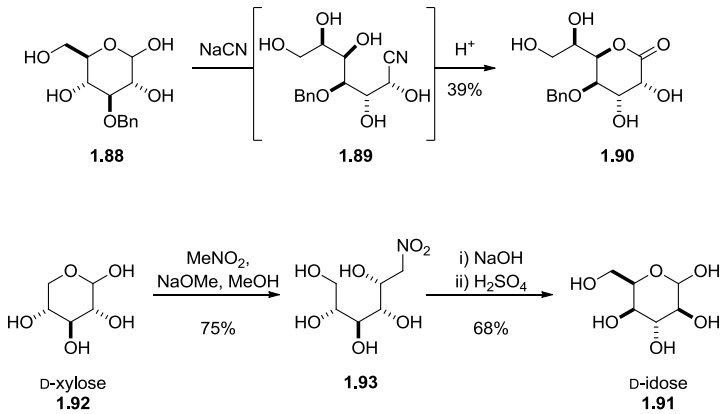
The final, general modification that may be utilised in carbohydrate diversification involves processes that modify the carbon skeleton itself. This may be divided into three processes: firstly, homologation (or chain-extension); secondly, truncation (chain-reduction); and thirdly, branching (**Scheme 1.20**). These methods can not only be used to derivitise a monosaccharide, but have been utilised to access rare and "unnatural" sugars and therefore have great synthetic utility. One example, which will be examined in more depth in **Chapter 2** (pages 86-87), is the use of homologation and truncation to access rare and expensive L-glucose **1.87** from abundant and cheap D-glucose **1.3**.




**Scheme 1.20**. General methods of carbon-chain derivitisation;
and the use of homologation and truncation to access L-glucose from D-glucose.

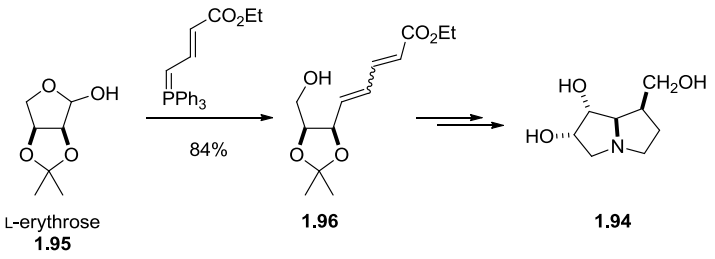
*1.6.3.1 Homologation*

A number of synthetically important methods have been developed since the beginning of carbohydrate chemistry for their chain-extension and the access of higher sugars. One of the most fundamental and famous of these is the Kiliani-Fischer cyanohydrin synthesis,[112,113] also known as the Kiliani ascension. This method allows an aldehyde sugar to be taken, for example benzyl-protected glucose **1.88** (**Scheme 1.21**),[114] treated with a cyanide source which reversibly forms a cyanohydrin **1.89**. Subsequent acidic or basic hydrolysis then allows irreversible formation of a chain-extended carboxylic acid **1.90**. The drawback of Kiliani reactions is that although they can work well in some instances, but typically they produce low-yielding complex mixtures that necessitate extensive separation. The Fischer-Sowden reaction,[115] or Sowden homologation, uses nitromethane under basic conditions to afford a stereoselective[116] nitro-aldol condensation (Henry reaction) - chain-extending an aldehyde sugar. A subsequent Nef decomposition yields the target sugar. Dromowicz and colleagues have recently improved the classical reaction to produce a moderate yielding synthesis of the "unnatural" monosaccharide D-idose **1.91** from cheap and readily available D-xylose **1.92** (**Scheme 1.21**).[117] Comparing the Kiliani and Sowden methods, it is the former that is usually preferred, but the Sowden homologation is useful in cases where the Kiliani ascension is impeded by difficult separation or where it has not successfully given the desired product configuration.[118]




**Scheme 1.21**. Kiliani and Sowden ascensions.[114,117]

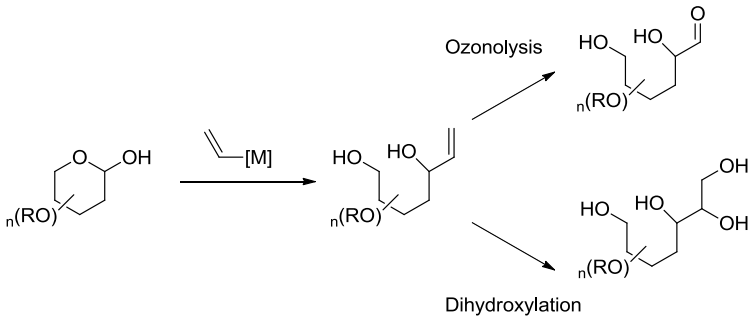
Beyond these two fundamental ascension protocols there are three other simple and important methods that are widely employed; these are the Strecker α-aminonitrile synthesis, Wittig olefination and organometallic additions. Classically the Strecker synthesis is used convert an aldehyde into an α-amino acid, *via* an α-aminonitrile. This method is analogous to the Kiliani ascension where cyanide is used as a carbon-based nucleophile, however in the Strecker reaction cyanide attacks an imine which is formed by reaction of an aldehyde with an amine.[119] As shown earlier in **Scheme 1.12** (Section 1.6.1, page 28) this is an extremely useful method for iminosugar chemists, as it gives not only chain homologation, but also introduction of nitrogen in the same step.[92] Wittig olefination has been used extensively on unprotected and protected monosaccharides for almost fifty years,[120] with the resultant alkene possessing the potential to be further derivatised. For example Hudlicky *et al* used a Wittig homologation to establish the scaffold required for the assembly of bicyclic pyrrolizidine (+)-trihydroxyheliotridane **1.94** from L-erythrose **1.95** (**Scheme 1.22**).[121]




**Scheme 1.22**. The use of a Wittig olefination in carbohydrate chain extension[121]

Lastly, the addition of organometallic reagents to carbohydrates is one of the most extensively researched areas of sugar homologation,[122] where the product of the addition follows, in most cases, the Felkin-Ahn or Cram-chelate models of asymmetric induction during nucleophilic attack.[123-125] The addition of methyllithium or methyl grignard reagents is the simplest case - where the chain is extended by a single carbon atom forming a deoxy centre. More significantly, addition of vinylic reagents offers similar potential to Wittig olefinations for further

derivitisation - for example ozonolysis and dihydroxylation are just two examples of reactions that have been widely applied to access fully hydroxylated higher carbon sugars (**Scheme 1.23**).[126-129]



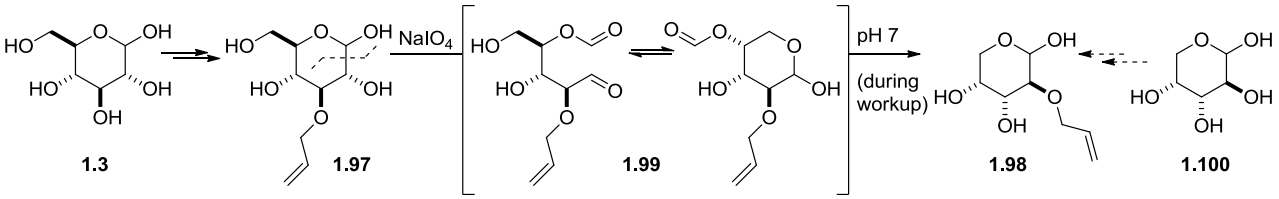

**Scheme 1.23**. Vinyl organometallic addition to protected monosaccharides, and subsequent derivitisation.

*1.6.3.2 Truncation*

In comparison to chain-lengthening techniques, processes for chain-reduction, or truncation, are somewhat sparse. Radical processes, such as the Ruff degradation have been utilised - but far more applicable and wide-spread is the use of lead(IV) acetate, and also of periodate, for the cleavage of vicinal diols and α-hydroxy aldehydes. The Ruff degradation is a reaction performed most efficiently with hydrogen peroxide in the presence of iron(III) or copper(II) salts,[130,131] but this procedure has drawbacks both in terms of the large quantity of metal salts required, and also in the modest yields obtained. Despite this, the methodology and has undergone a considerable recent revival especially in the industrial synthesis of pentose sugars, including xylitol.[132]

Cleavage of 1,2-diols or α-hydroxy aldehydes with periodates, or lead(IV) acetate, yields the corresponding, chain-shortened aldehydes. It is generally a very successful procedure and is widely employed in carbohydrate syntheses.[133-136] Oxidative cleavage is almost always performed on protected sugars, as over-oxidation of unprotected sugars is extremely difficult to

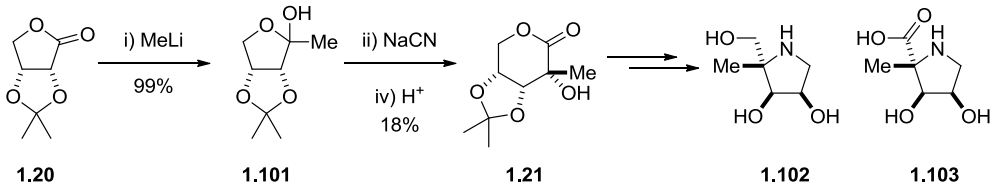
control. However there are examples of the successful deployment of periodate on unprotected sugars. Storz *et al* recently demonstrated that sodium periodate cleavage could be efficiently utilised on 3-*O*-allyl protected D-glucose **1.97** to form 2-*O*-allyl-D-arabinose **1.98**, *via* the formyl ester **1.99**. This allowed access to an extremely useful chiron in fewer synthetic steps and higher yield than previously reported from the parent sugar D-arabinose **1.100** (**Scheme 1.24**).[137]




**Scheme 1.24**. Synthesis of 2-*O*-allyl protected D-arabinose **1.98** from D-glucose **1.3** by periodate cleavage.[137]

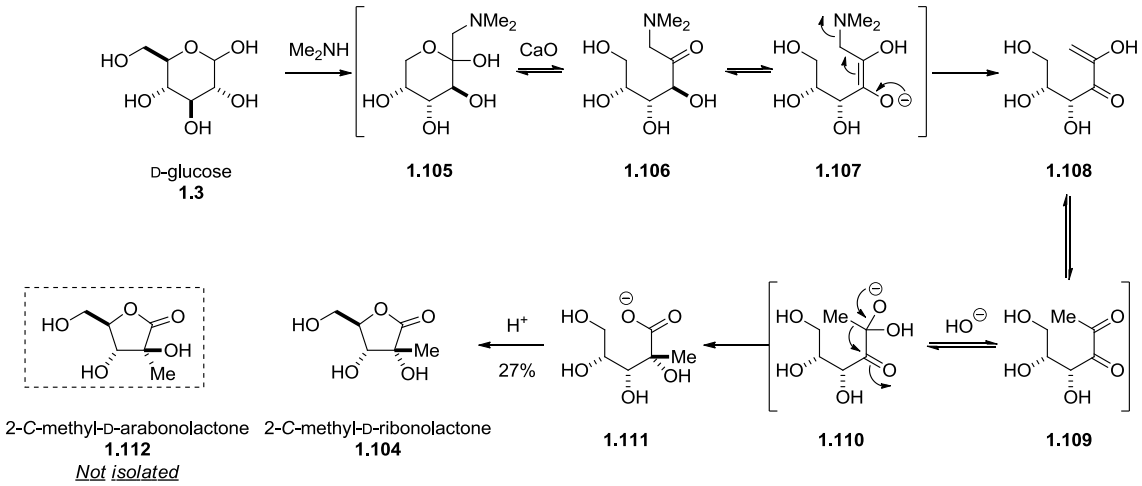
*1.6.3.3 Branching*

In addition to homologation and cleavage, branching offers a final strategy in carbon-chain derivitisation, with processes that lead to branching of the carbohydrate scaffold providing an additional tool in improving the structural mimicry of carbohydrates by iminosugars. The simplest form of branching involves the replacement of a ring hydrogen atom with a methyl group, an example of which has been indicated previously in **Scheme 1.10** (Section 1.6.1, page 26) where the 2-*C*-methyl-branched lactone **1.21** could be accessed from D-erythronolactone **1.20** (**Scheme 1.25**). This 2-*C*-methyl branching was achieved by combining two chain-homologation methods; firstly, methyllithium addition to the lactone **1.20** forms 1-deoxy-ketose **1.101**; and secondly, Kiliani ascension of this ketose **1.101** affords 2-*C*-methyl-branched D-arabinonolactone **1.21**.[138] This branched lactone **1.21** was subsequently utilised in the synthesis of branched pyrrolidine iminosugars, including **1.102** and **1.103**.[87]



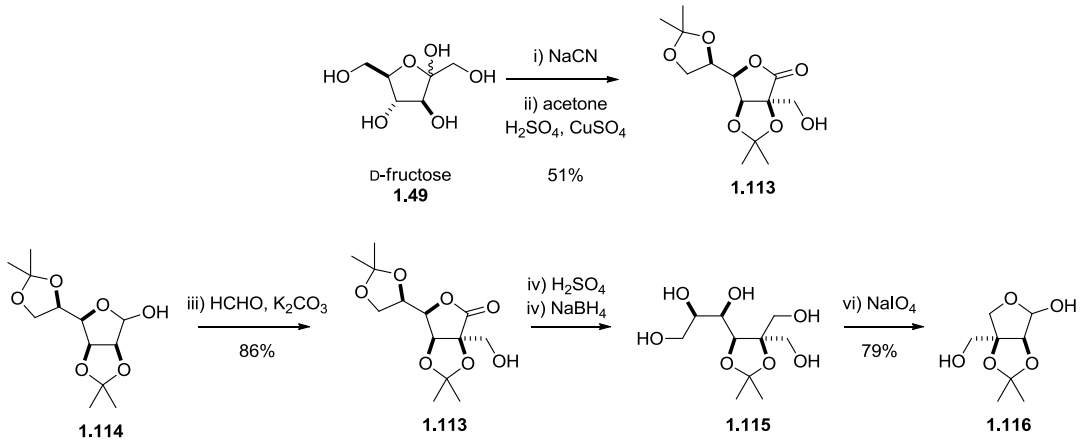

**Scheme 1.25**. Carbon chain homologation leading to chain-branching.[87,138]

Methyl-branching may also be introduced by alternative methods. The most straightforward of all is the addition of methyl organometallics to a prochiral ketone, with selectivity conferred by the chirality of the monosaccharide in an identical fashion to that discussed for the reduction of a prochiral ketone in Section 1.6.2.3 (**Scheme 1.19**, page 34). Alternatively, methyl-branched sugars may be accessed by the Amadori rearrangement of Amadori ketoses (**Scheme 1.26**). The result of this reaction is that the carbon backbone is shortened by one carbon, so, for example, a hexose is converted to a pentose, and a methyl branch is created at C2. One important and illustrative example of this is the conversion of D-glucose **1.3** to 2-*C*-methyl-D-ribonolactone **1.104**. D-Glucose **1.3** is converted to the Amadori ketose **1.105** with a dialkylamine, and subsequent Amadori rearrangement is afforded in the presence of calcium oxide. The mechanism of the rearrangement is complex,[139] and it is suggested that the reaction proceeds by formation of the ene-diol **1.108** by elimination of dimethylamine from ketose **1.107**. This ene-diol **1.108** is in tautomeric equilibrium with the diketone **1.109**, which may undergo a benzilic acid rearrangement *via* a chelated Felkin-Ahn transition state - mediated by a calcium cation - irreversibly giving the carboxylate **1.111**. Formation of the lactone ring during acidic work-up conditions then affords the product 2-*C*-methyl-D-ribonolactone **1.104**, without any of the *arabino*-epimer **1.112** being isolated - demonstrating the selectivity of the benzilic acid rearrangement.[138,140,141] Despite the low yield over the two reaction steps this reaction uses an extremely cheap and abundant starting material and can be conducted on a large-scale, this enhances the synthetic utility of this sequence.[141]




**Scheme 1.26**. Amadori rearrangement of glucose.[138,140,141]

Aside from methyl-branching, another important example is that of hydroxymethyl-branching. These branches can be used to dramatically alter the disposition of hydroxyl groups within an iminosugar carbohydrate-mimic. Two main methods are used to introduce hydroxymethyl branches; the first is by the Kiliani ascension of ketose sugars, and the second is by the Ho aldol reaction of aldoses. Despite being an ascension reaction, the former method does not result in formal homologation, instead leading to the formation of a hydroxymethyl branch. A prime example of this is the Kiliani ascension of D-fructose **1.49** which forms 2-*C*-hydroxymethyl-branched mannose **1.113** in a 51% yield (**Scheme 1.27**).[142] Similar treatment of D-tagatose, L-sorbose and D-psicose has also afforded access to 2-*C*-hydroxymethyl branched lactones.[142,143] In contrast the Ho aldol reaction consists of treating protected aldose monosaccharides with formaldehyde under basic conditions. For example D-mannose **1.114** under these conditions affords 2-*C*-hydroxymethyl-branched D-mannose **1.113**, with the selectivity being enforced by the presence of the acetonide ring. This branched sugar was key in the synthesis of D-apiose **1.116** by further reduction and periodate truncation.[144]




**Scheme 1.27**. Kiliani ascension of D-fructose **1.49**;[142] and Ho aldol reaction of D-mannose **1.114**.[144]

## 1.7 Summary

This introductory chapter has laid out a summary of the discovery and evolution of research in the field of iminosugars, identifying their historical, current and potential future applications in treating a broad range of diseases. Derivatives of DNJ **1.1** are current chemotherapeutics, with many other iminosugars are at various stages of clinical investigation and development. Despite theoretical and elucidatory works towards determination of the mode-of-action of iminosugars as glycosidase inhibitors, iminosugars possess many more interactions at the protein level - including huge recent developments in glycosyltranferase inhibition. The development of novel iminosugars and the study of their biological activity has the potential to aid in the understanding of these less well understood enzymatic pathways, and elucidate novel therapeutic strategies. With the potential of iminosugars being so great, this chapter has also highlighted general tools which may be utilised in the derivitisation of readily available carbohydrate-based chiral pool reagents. In the next two chapters this thesis will demonstrate the employment of some of these invaluable methods in the strategic synthesis of natural and unnatural biologically active iminosugars.

## 1.8 References


1. Zechel, D. L.; Withers, S. G. *Acc. Chem. Res.* **2000**, *33*, 11-18.
2. Heightman, T. D.; Vasella, A. T. *Angew. Chem. Intl. Ed.* **1999**, *38*, 750-770.
3. D'Alonzo, D.; Guaragna, A.; Palumbo, G. *Curr. Med. Chem.* **2009**, *16*, 473-505.
4. Horne, G.; Wilson, F. X.; Tinsley, J.; Williams, D. H.; Storer, R. *Drug Discov. Today*, **2011**, *16*, 107-118.
5. Yip, V. L. Y.; Withers, S. G. *Org. Biomol. Chem.* **2004**, *2*, 2707-2713.
6. Stuetz, A. E.; Wrodnigg, T. M. *Adv. Carbohydr. Chem. Biochem.* **2011**, *66*, 187-298.
7. Fleet, G. W. J. *Tetrahedron Lett.* **1985**, *26*, 5073-5076.
8. Post, C. B.; Karplus, M. *J. Am. Chem. Soc.* **1986**, *108*, 1317-1319.
9. Knapp, S.; Vocadlo, D.; Gao, Z.; Kirk, B.; Lou, J.; Withers, S. G. *J. Am. Chem. Soc.* **1996**, *118*, 6804-6805.
10. Wolfenden, R.; Lu, X.; Young, G. *J. Am. Chem. Soc.* **1998**, *120*, 6814-6815.
11. Withers, S. G.; Namchuk, M.; Mosi, R. *Iminosugars as Glycosidase Inhibitors*, **1999**, 188-206.
12. Borges de Melo, E.; Gomes, A. d. S.; Carvalho, I. *Tetrahedron*, **2006**, *62*, 10277-10302.
13. Compain, P.; Martin, O. R. *From Synthesis Iminosugars to Therapeutic Applications*, John Wiley & Sons Ltd. **2007**.
14. Kato, A.; Kato, N.; Kano, E.; Adachi, I.; Ikeda, K.; Yu, L.; Okamoto, T.; Banba, Y.; Ouchi, H.; Takahata, H.; Asano, N. *J. Med. Chem.* **2005**, *48*, 2036-2044.
15. Uitdehaag, J. C. M.; Mosi, R.; Kalk, K. H.; Van Der Veen, B. A.; Dijkhuizen, L.; Withers, S. G.; Dijkstra, B. W. *Nat. Struct. Biol.* **1999**, *6*, 432-436.
16. Jespersen, T. M.; Bols, M.; Sierks, M. R.; Skrydstrup, T. *Tetrahedron*, **1994**, *50*, 13449-13460.
17. Jespersen, T. M.; Dong, W.; Sierks, M. R.; Skrydstrup, T.; Lundt, I.; Bols, M. *Angew. Chem. Intl. Ed.* **1994,** *33*, 1778-1779.
18. Jensen, H. H.; Bols, M. *J. Chem. Soc. Perkin Trans. 1*, **2001**, *8*, 905-909.
19. Liu, H.; Liang, X.; Sohoel, H.; Buelow, A.; Bols, M. *J. Am. Chem. Soc.* **2001**, *123*, 5116-5117.
20. Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry*, **2000**, *11*, 1645-1680.
21. Inouye, S.; Tsuruoka, T.; Niida, T. *J. Antibiot. Ser. A*, **1966**, *19*, 288-292.
22. Koyama, M.; Sakamura, S. *Agr. Biol. Chem.* **1974**, *38*, 1111-1112.
23. Yagi, M.; Kouno, T.; Aoyagi, Y.; Murai, H. *Nippon Nogei Kagaku Kaishi*, **1976**, *50*, 571-572.
24. Schmidt, D. D.; Frommer, W.; Mueller, L.; Truscheit, E. *Naturwissenschaften*, **1979**, *66*, 584-585.
25. Paulsen, H. *Angew. Chem., Intl. Ed.* **1966**, *5*, 495-511.
26. Watanabe, S.; Kato, H.; Nagayama, K.; Abe, H. *Biosci., Biotechnol. Biochem.* **1995**, *59*, 936-937.
27. Juettner, F.; Wessel, H. P. *J. Phycol.* **2003**, *39*, 26-32.
28. Asano, N.; Kato, A.; Miyauchi, M.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *J. Nat. Prod.* **1998**, *61*, 625-628.
29. Kim, H. S.; Kim, Y. H.; Hong, Y. S.; Paek, N. S.; Lee, H. S.; Kim, T. H.; Kim, K. W.; Lee, J. J. *Planta Med.* **1999**, *65*, 437-439.
30. Ueda, H.; Kawanishi, K.; Ayala, F.; Moriyasu, M. *Nat. Med.* **2004**, *58*, 85.
31. Asano, N.; Yamauchi, T.; Kagamifuchi, K.; Shimizu, N.; Takahashi, S.; Takatsuka, H.; Ikeda, K.; Kizu, H.; Chuakul, W.; Kettawan, A.; Okamoto, T. *J. Nat. Prod.* **2005**, *68*, 1238-1242.
32. Kite, G. C.; Horn, J. M.; Romeo, J. T.; Fellows, L. E.; Lees, D. C.; Scofield, A. M.; Smith, N. G. *Phytochemistry*, **1990**, *29*, 103-105.
33. Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1979**, *32*, 2257-2264.
34. Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, D. P.; Pryce, R. J.; Arnold, E.; Clardy, J. *Phytochemistry*, **1981**, *20*, 811-814.
35. Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Derome, A. E.; Hamor, T. A.; Scofield, A. M.; Watkin, D. J. *Tetrahedron Lett.* **1988**, *29*, 2487-2490.
36. Molyneux, R. J.; Benson, M.; Wong, R. Y.; Tropea, J. E.; Elbein, A. D. *J. Nat. Prod.* **1988**, *51*, 1198-1206.
37. Tepfer, D.; Goldmann, A.; Pamboukdjian, N.; Maille, M.; Lepingle, A.; Chevalier, D.; Denarie, J.; Rosenberg, C. *J. Bacteriol.* **1988**, *170*, 1153-1161.
38. Nash, R. J.; Rothschild, M.; Porter, E. A.; Watson, A. A.; Waigh, R. D.; Waterman, P. G. *Phytochemistry*, **1993**, *34*, 1281-1283.
39. Watson, A. A.; Nash, R. J.; Wormald, M. R.; Harvey, D. J.; Dealler, S.; Lees, E.; Asano, N.; Kizu, H.; Kato, A.; Griffiths, R. C.; Cairns, A. J.; Fleet, G. W. J. *Phytochemistry*, **1997**, *46*, 255-259.
40. Nash, R. J. *MNL Pharma Limited*, UK. **2006**, 40.
41. Sels, J.-P. J. E.; Huijberts, M. S. P.; Wolffenbuttel, B. H. R. *Expert Opin. Pharmaco.* **1999**, *1*, 149-156.
42. Wang, N.; Minatoguchi, S.; Chen, X.; Uno, Y.; Arai, M.; Lu, C.; Takemura, G.; Fujiwara, T.; Fujiwara, H. *Br. J. Pharmacol.* **2004**, *142*, 983-990.
43. Winchester, B. G. *Tetrahedron: Asymmetry*, **2009**, *20*, 645-651.
44. Fan, J.-Q. *Biol. Chem.* **2007**, *389*, 1-11.

45. Futerman, A. H.; van Meer, G. *Nat. Rev. Mol. Cell Biol.* **2004**, *5*, 554-565.
46. Hartl, F. U.; Hayer-Hart, M. *Science*, **2002**, *295*, 1852-1858.
47. Ellgaard, L.; Helenius, A. *Nat. Rev. Mol. Cell Biol.* **2003**, *4*, 181-191.
48. Duve, C. *Science* **1975**, *189*, 186-194.
49. Brady, R. O. *Bailliere. Clin. Haem.* **1997**, *10*, 621-634.
50. Guggenbuhl, P.; Grosbois, B.; Chales, G. *Joint Bone Spine*, **2008**, *75*, 116-124.
51. Capablo, J. L.; Franco, R.; Saenz de Cabezon, A.; Alfonso, P.; Pocovi, M.; Giraldo, P. *Epilepsia*, **2007**, *48*, 1406-1408.
52. Schueler, U. H.; Kolter, T.; Kaneski, C. R.; Zirzow, G. C.; Sandhoff, K.; Brady, R. O. *J. Inherit. Metab. Dis.* **2004**, *27*, 649-658.
53. Fan, J.-Q.; Ishii, S.; Asano, N.; Suzuki, Y. *Nat. Med.* **1999**, *5*, 112-115.
54. Asano, N.; Ishii, S.; Kizu, H.; Ikeda, K.; Yasuda, K.; Kato, A.; Martin, O. R.; Fan, J.-Q. *Eur. J. Biochem.* **2000,** *267*, 4179-4186.
55. Ogawa, S.; Kobayashi, Y.; Kabayama, K.; Jimbo, M.; Inokuchi, J.-I. *Bioorg. Med. Chem.* **1998**, *6*, 1955-1962.
56. Zhu, X.; Sheth, K. A.; Li, S.; Chang, H. H.; Fan, J.-Q. *Angew. Chem. Intl. Ed.* **2005**, *44*, 7450-7453.
57. Chang, H.-H.; Asano, N.; Ishii, S.; Ichikawa, Y.; Fan, J.-Q. *FEBS J.* **2006**, *273*, 4082-4092.
58. Fan, J.-Q.; Ishii, S. *Method. Enzymol.* **2003**, *363*, 412-420.
59. Asano, N.; Oseki, K.; Tomioka, E.; Kizu, H.; Matsui, K. *Carbohydr. Res.* **1994**, *259*, 243-255.
60. Pili, R.; Chang, J.; Partis, R. A.; Mueller, R. A.; Chrest, F. J.; Passaniti, A. *Cancer Res.* **1995**, *55*, 2920-2926.
61. Asano, N.; Nishida, M.; Kizu, H.; Matsui, K.; Watson, A. A.; Nash, R. J. *J. Nat. Prod.* **1997**, *60*, 98-101.
62. Clark, N. E.; Metcalf, M. C.; Best, D.; Fleet, G. W. J.; Garman, S. C. *P. Natl. Acad. Sci. USA*, **2012**, *109*, 17400-17405.
63. Aoyama, T.; Naganawa, H.; Suda, H.; Uotani, K.; Aoyagi, T.; Takeuchi, T. *J. Antibiot.* **1992**, *45*, 1557-1558.
64. Tatsuta, K.; Miura, S.; Ohta, S.; Gunji, H. *J. Antibiot.* **1995**, *48*, 286-288.
65. Ichikawa, Y.; Igarashi, Y.; Ichikawa, M.; Suhara, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3007-3018.
66. Asano, N.; Yasuda, K.; Kizu, H.; Kato, A.; Fan, J.-Q.; Nash, R. J.; Fleet, G. W. J.; Molyneux, R. J. *Eur. J. Biochem.* **2001**, *268*, 35-41.
67. Fan, J.-Q. *Biol Chem* **2008**, *389*, 1-11.
68. Benjamin, E. R.; Flanagan, J. J.; Schilling, A.; Chang, H. H.; Agarwal, L.; Katz, E.; Wu, X.; Pine, C.; Wustman, B.; Desnick, R. J.; Lockhart, D. J.; Valenzano, K. J. *J. Inherit. Metab. Dis.* **2009**, *32*, 424-440.
69. Dulsat, C.; Mealy, N. *Drug. Future*, **2009**, *34*, 23-25.
70. http://www.exsar.com/drug-development/therapeutic-areas-of-interest/tay-sachs-disease
71. Hanahan, D.; Weinberg, R. A. *Cell*, **2000**, *100*, 57-70.
72. Sporn, M. B. *Lancet*, **1996**, *347*, 1377-1381.
73. Shaheen, P. E.; Stadler, W.; Elson, P.; Knox, J.; Winquist, E.; Bukowski, R. M. *Invest. New Drugs*, **2005**, *23*, 577-581.
74. Dennis, J. W.; Laferte, S. *Cancer Metast. Rev.* **1987**, *5*, 185-204.
75. Dimitroff, C. J.; Sharma, A.; Bernacki, R. J. *Cancer Invest.* **1998**, *16*, 279-290.
76. Meyer, K.; Hobby, G. L.; Chaffee, E.; Dawson, M. H. *J. Exp. Med.* **1940**, *71*, 137-146.
77. Niedbala, M. J.; Madiyalakan, R.; Matta, K.; Crickard, K.; Sharma, M.; Bernacki, R. J. *Cancer Res.* **198**7, *47*, 4634-4641.
78. Plucinsky, M. C.; Prorok, J. J.; Alhadeff, J. A. *Cancer*, **1986**, *58*, 1484-1487.
79. Reddi, A. L.; Sankaranarayanan, K.; Arulraj, H. S.; Devaraj, N.; Devaraj, H. *Cancer Lett.* **2000**, *158*, 61-64.
80. Yamamoto, N.; Suyama, H.; Yamamoto, N.; Ushijima, N. *Int. J. Cancer*, **2007**, *122*, 461-467.
81. Yamamoto, N.; Naraparaju, V. R.; Asbell, S. O. *Cancer Res.* **1996,** *56*, 2827-2831.
82. Mohamad, S. B.; Nagasawa, H.; Uto, Y.; Hori, H. *Comp. Biochem. Physiol. A*, **2002**, *132*, 1-8.
83. Greco, M.; De Mitri, M.; Chiriacò, F.; Leo, G.; Brienza, E.; Maffia, M. *Cancer Lett.* **2009**, *283*, 222-229.
84. Izumori, K. *J. Biotechnol.* **2006**, *124*, 717-722.
85. Beerens, K.; Desmet, T.; Soetaert, W. *J. Ind. Microbiol. Biotechnol.* **2012**, *39*, 823-834.
86. Card, P. J.; Hitz, W. D. *J. Org. Chem.* **1985**, *50*, 891-893.
87. da Cruz, F. P.; Horne, G.; Fleet, G. W. J. *Tetrahedron Lett.* **2008**, *49*, 6812-6815.
88. Poitout, L.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron Lett.* **1994**, *35*, 3293-3296.
89. McCort, I.; Duréault, A.; Depezay, J.-C. *Tetrahedron Lett.* **1996**, *37*, 7717-7720.
90. Campanini, L.; Duréault, A.; Depezay, J.-C. *Tetrahedron Lett.* **1995**, *36*, 8015-8018.
91. Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 4981-4982.
92. Win-Mason, A. L.; Dangerfield, E. M.; Tyler, P. C.; Stocker, B. L.; Timmer, M. S. M. *Eur. J. Org. Chem.* **2011**, 4008-4014.

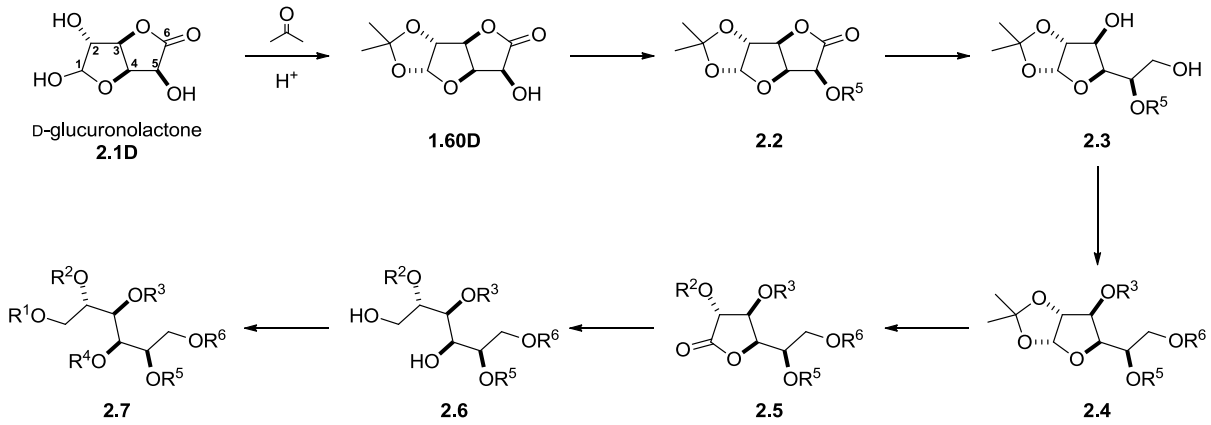
93. Masaki, Y.; Oda, H.; Kazuta, K.; Usui, A.; Itoh, A.; Xu, F. *Tetrahedron Lett.* **1992**, *33*, 5089-5092.
94. Shing, T. K. M. *J. Chem. Soc. Chem. Commun.* **1987,** 262-263.
95. Duréault, A.; Portal, M.; Depezay, J.-C. *Synlett*, **1991**, 225-226.
96. Lenagh-Snow, G. M. J.; Araujo, N.; Jenkinson, S. F.; Rutherford, C.; Nakagawa, S.; Kato, A.; Yu, C.-Y.; Weymouth-Wilson, A. C.; Fleet, G. W. J. *Org. Lett.* **2011**, *13*, 5834-5837.
97. Lenagh-Snow, G. M. J.; Araujo, N.; Jenkinson, S. F.; Martínez, R. F.; Shimada, Y.; Yu, C.-Y.; Kato, A.; Fleet, G. W. J. *Org. Lett.* **2012**, *14*, 2142-2145.
98. Avigad, G.; Englard, S. *Meth. Enzymol.* **1975**, *41*, 84-90.
99. Reitz, A. B.; Baxter, E. W. *Tetrahedron Lett.* **1990**, *31*, 6777-6780.
100. Matos, C. R. R.; Lopes, R. S. C.; Lopes, C. C. *Synthesis*, **1999**, 571-573.
101. Martin, O. R.; Saavedra, O. M.; Xie, F.; Liu, L.; Picasso, S.; Vogel, P.; Kizu, H.; Asano, N. *Bioorg. Med. Chem.* **2001**, *9*, 1269-1278.
102. Csuk, R.; Hoenig, H.; Nimpf, J.; Weidmann, H. *Tetrahedron Lett.* **1980**, *21*, 2135-2136.
103. Bell, A. A.; Pickering, L.; Finn, M.; De la Fuente, C.; Krulle, T. M.; Davis, B. G.; Fleet, G. W. J. *Synlett*, **1997**, *9*, 1077-1078.
104. Godskesen, M.; Lundt, I.; Madsen, R.; Winchester, B. *Bioorg. Med. Chem.* **1996**, *4*, 1857-1865.
105. Batra, H.; Moriarty, R. M.; Penmasta, R.; Sharma, V.; Stanciuc, G.; Staszewski, J. P.; Tuladhar, S. M.; Walsh, D. A.; Datla, S.; Krishnaswamy, S. *Org. Process Res. Dev.* **2006**, *10*, 484-486.
106. Håkansson, A. E.; van Ameijde, J.; Guglielmini, L.; Horne, G.; Nash, R. J.; Evinson, E. L.; Kato, A.; Fleet, G. W. J. *Tetrahedron: Asymmetry*, **2007**, *18*, 282-289.
107. Håkansson, A. E.; van Ameijde, J.; Horne, G.; Nash, R. J.; Wormald, M. R.; Kato, A.; Besra, G. S.; Gurcha, S.; Fleet, G. W. J. *Tetrahedron Lett.* **2008**, *49*, 179-184.
108. Lundt, I.; Pedersen, C. *Synthesis*, **1992**, *7*, 669-672.
109. Lundt, I.; Madsen, R. *Top. Curr. Chem.* **2001**, *215*, 177-191.
110. Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976,** 734-736.
111. Fleet, G. W. J.; Ramsden, N. G.; Dwek, R. A.; Rademacher, T. W.; Fellows, L. E.; Nash, R. J.; Green, D. St. C.; Winchester, B. *J. Chem. Soc. Chem. Commun.* **1988,** 483-485.
112. Fischer, E. *Liebigs Ann. Chem.* **1906**, *270*, 64-107.
113. Kiliani, H. *Chemische Berichte* **1885**, *18*, 3066.
114. Bichard, C. J. F.; Wheatley, J. R.; Fleet, G. W. J. *Tetrahedron: Asymmetry*, **1994**, *5*, 431-440.
115. Sowden, J. C.; Fischer, H. O. L. *J. Am. Chem. Soc.* **1944**, *66*, 1312-1314.
116. Koell, P.; Stenns, C.; Seelhorst, W.; Brandenburg, H. *Liebigs Ann. Chem.* **1991,** 201-206.
117. Dromowicz, M.; Koell, P. *Carbohydr. Res.* **1998**, *308*, 169-171.
118. Györgydeák, Z.; Pelyvás, I. F. *Monosaccharide Sugars: Chemical Synthesis by Chain Elongation, Degradation, and Epimerization*; Academic Press: San Diego, **1998**.
119. Strecker, A. *Liebigs Ann. Chem.* **1850,** *75*, 27-45.
120. Kochetkov, N. K.; Dmitriev, B. A. *Tetrahedron*, **1965**, *21*, 803-815.
121. Hudlicky, T.; Luna, H.; Price, J. D.; Rulin, F. *J. Org. Chem.* **1990**, *55*, 4683-4687.
122. Pelyvas, I. F.; Gyorgydeak, Z. *Glycoscience*, **2001**, *1*, 305-364.
123. Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968,** *18*, 2199-2204.
124. Anh, N. Springer Berlin / Heidelberg, 1980; pp. 145-162.
125. Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828-5835.
126. Jiang, S.; Rycroft, A. D.; Singh, G.; Wang, X.-Z.; Wu, Y.-L. *Tetrahedron Lett.* **1998**, *39*, 3809-3812.
127. Lubineau, A.; Gavard, O.; Alais, J.; Bonnaffé, D. *Tetrahedron Lett.* **2000**, *41*, 307-311.
128. Behr, J.-B.; Guillerm, G. *Tetrahedron Lett.* **2007**, *48*, 2369-2372.
129. Kosma, P. *Curr. Org. Chem.* **2008**, *12*, 1021-1039.
130. Ruff, O. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 1573-1577.
131. Stapley, J. A.; BeMiller, J. N. *Carbohydr. Res.* **2007**, *342*, 407-418.
132. Hourdin, G.; Germain, A.; Moreau, C.; Fajula, F. *Catal. Lett.* **2000**, *69*, 241-244.
133. Gautam, D.; Kumar, D. N.; Rao, B. V. *Tetrahedron: Asymmetry*, **2006**, *17*, 819-821.
134. Wu, W.-L.; Wu, Y.-L. *J. Org. Chem.* **1993**, *58*, 3586-3588.
135. Lee, J. A.; Moon, H. R.; Kim, H. O.; Kim, K. R.; Lee, K. M.; Kim, B. T.; Hwang, K. J.; Chun, M. W.; Jacobson, K. A.; Jeong, L. S. *J. Org. Chem.* **2005**, *70*, 5006-5013.
136. Freiría, M.; Whitehead, A. J.; Motherwell, W. B. *Synthesis*, **200**5, *18*, 3079-3084.
137. Storz, T.; Vasella, A. *Synthesis*, **2006**, *9*, 1461-1464.
138. Hotchkiss, D. J.; Jenkinson, S. F.; Storer, R.; Heinz, T.; Fleet, G. W. J. *Tetrahedron Lett.* **2006**, *47*, 315-318.
139. Yang, B. Y.; Montgomery, R. *Carbohydr. Res.* **1996**, *280*, 27-45.
140. Hotchkiss, D. J.; Soengas, R.; Booth, K. V.; Weymouth-Wilson, A. C.; Eastwick-Field, V.; Fleet, G. W. J. *Tetrahedron Lett.* **2007**, *48*, 517-520.

141. Booth, K. V.; da Cruz, F. P.; Hotchkiss, D. J.; Jenkinson, S. F.; Jones, N. A.; Weymouth-Wilson, A. C.; Clarkson, R.; Heinz, T.; Fleet, G. W. J. *Tetrahedron: Asymmetry*, **2008**, *19*, 2417-2424.
142. Hotchkiss, D.; Soengas, R.; Simone, M. I.; van Ameijde, J.; Hunter, S.; Cowley, A. R.; Fleet, G. W. J. *Tetrahedron Lett.* **2004**, *45*, 9461-9464.
143. Soengas, R.; Izumori, K.; Simone, M. I.; Watkin, D. J.; Skytte, U. P.; Soetaert, W.; Fleet, G. W. J. *Tetrahedron Lett.* **2005**, *46*, 5755-5759.
144. Ho, P.-T. *Can. J. Chem.* **1979**, *57*, 381-383.

# Chapter 2: Iminosugars from glucuronolactone

## 2.1 Introduction

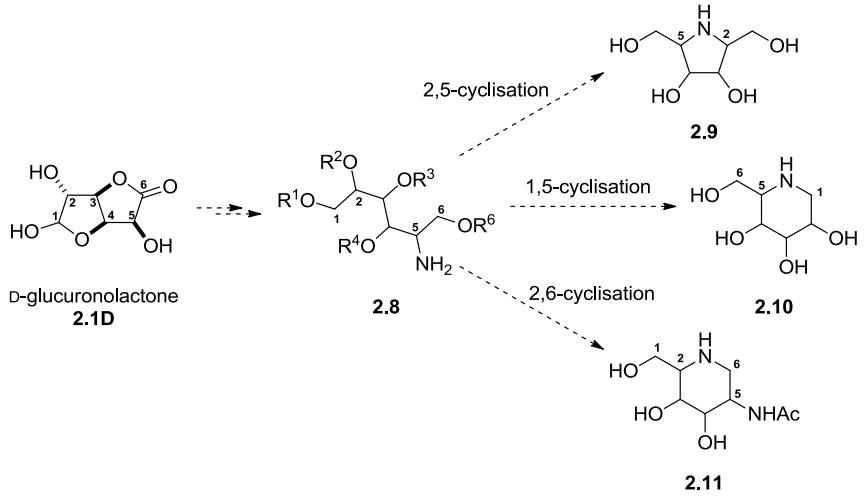
The previous chapter outlined the great utility of carbohydrates as synthetically flexible starting materials in the synthesis of iminosugars. This chapter demonstrates this by presenting two projects showing the development and elaboration of simple and efficient syntheses of biologically active iminosugars from the two enantiomers of glucuronolactone. This monosaccharide presents as an ideal starting material for two main reasons; firstly, both enantiomers are readily available and enantiomerically pure; and secondly, glucuronolactone affords an exceptionally versatile synthetic scaffold.




**Scheme 2.1**. Potential synthetic elaboration of D-glucuronolactone.

The "natural" enantiomer D-glucuronolactone **2.1D** is inexpensive, commercially available and may be protected as the 1,2-acetonide **1.60D** (**Scheme 2.1**), which, with a single hydroxyl at C5 remaining unprotected, is an ideal carbohydrate starting material. Conceptually, this hydroxyl may be protected to form the fully protected lactone **2.2**. The 3,6-lactone moiety of lactone **2.2** may be regarded as a protected diol, and hence would afford the diol **2.3**. Chemoselective

protection would permit the differentiation of the C3- and C6-hydroxyl groups giving the protected triol **2.4**. Subsequent hydrolysis of the 1,2-acetonide, chemoselective anomeric oxidation and protection of the free C2-hydroxyl would give the protected 1,4-lactone **2.5**. Finally, reduction to the diol **2.6** and selective protection of the C1- and C4-hydroxyls would allow access to the fully protected D-*gluco* scaffold **2.7**. It is evident that with this strategy the chiral hydroxyls C2, C3, C4 and C5 can be accessed independently, which would allow for derivitisation and elaboration of the scaffold. This demonstrates why glucuronolactone presents such a flexible starting material and possesses great synthetic potential, which may be exploited to assemble a variety of monocyclic iminosugar classes (**Scheme 2.2**), including; pyrrolidines **2.9** (by 2,5 cyclisation), piperidines **2.10** (by 1,5 cyclisation) and acetamido-piperidines **2.11** (by 2,6 cyclisation). These strategies arise from the ability to stereoselectively introduce nitrogen at C5 of glucuronolactone;[1,2] with cyclisation of the C5-nitrogen onto C2 affording pyrrolidines **2.9**, and onto C1 giving DNJ-piperidines **2.10**. Alternatively the C5-nitrogen may be used to develop an *exo*-cyclic acetamide moiety, with 2,6-cyclisation from a second nitrogen-source forming a piperidine ring and the 2-acetamido-piperidine class **2.11**.




**Scheme 2.2**. Simple strategies of iminosugar formation.
(carbon atoms numbered according to starting material)

The piperidine class **2.10** possesses sixteen possible stereoisomers, five of which are naturally occurring iminosugars: DNJ **1.1**,[3] 1,5-dideoxy-1,5-imino-D-mannitol or 1-deoxymannonojirimycin (DMJ) **2.12**,[4] 1,5-dideoxy-1,5-imino-D-altritol (*altro*-DNJ) **2.13**,[5] 1,5-dideoxy-1,5-imino-L-gulitol (*gulo*-DNJ) **2.14**,[5] and 1,5-dideoxy-1,5-imino-D-allitol (*allo*-DNJ) **2.15** (**Figure 2.1**).[6] All sixteen isomers of DNJ have been synthetically produced, with all but 1,5-dideoxy-1,5-imino-D-talitol (DTJ) **2.16** having been examined for activity against glycosidase enzymes.[6-10]

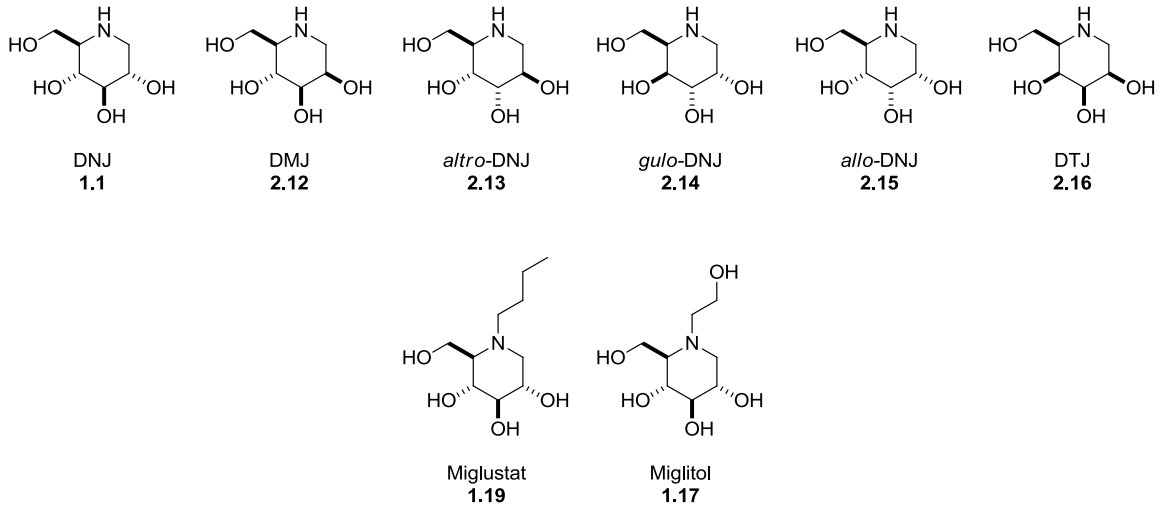



**Figure 2.1**. 1,5-Dideoxy-1,5-imino-hexitols.

Given the natural occurrence and structural similarity of the 1,5-dideoxy-1,5-imino-hexitols to sugar pyranosides - mammalian glycosidases' natural substrates - much of the iminosugar research effort has been expended in the synthesis of these molecules and the study of their derivatives. As detailed in **Chapter 1** (Section 1.5.1-1.5.2, pages 13-18) this has been pharmaceutically productive with the successful licensing of miglustat **1.19** (Zavesca) and miglitol **1.17** (Glyset). In contrast, pyrrolidines **2.9** have received far less scientific attention despite being naturally abundant and displaying excellent biological activity against glycosidase enzymes. Research has been even scarcer in the case of the 2-acetamido-piperidine class **2.11** despite their structural mimicry of the biologically relevant *N*-acetylhexosamine residues:

*N*-acetylglucosaminidase (GlcNAc) **2.17** and *N*-acetylgalactosaminidase (GalNAc) **2.18** (**Figure 2.2**). These acetamido-containing sugars are abundant in the extracellular matrix (ECM) and are part of an important trisaccharide motif on the vitamin-$D_3$ binding protein, a precursor to the macrophage activating factor (MAF) (Section 1.5.3, pages 19-23). In an analogous fashion to the mimicry of D-glucose **1.3** and D-galactose **1.4** by DNJ **1.1** and DGJ **1.2**, respectively, it may be postulated that at least structurally if not electronically, the 2-acetamido-equivalents of these iminosugars - DNJNAc **2.19** and DGJNAc **2.20** - would mimic GlcNAc **2.17** and GalNAc **2.18**. Thus, it can be seen that these compounds would be ideal candidates for the two novel strategies in the treatment of metastatic cancers, as well as in the therapy of LSDs.

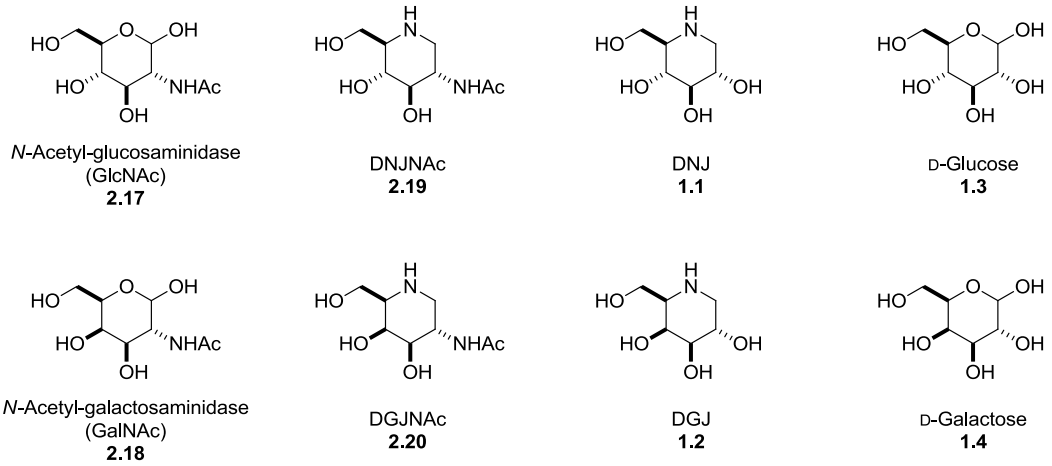



**Figure 2.2**. 2-Acetamido piperidines as potential glycosidase inhibitors.

Thus, with the desired starting material, biological motivation, and iminosugar targets identified (the pyrrolidine **2.9** and 2-acetamido-piperidine **2.11** classes), the following sections will highlight previous work and establish a divergent synthetic methodology to the target compounds from glucuronolactone.

## 2.2 Synthesis of DGJNAc from D-glucuronolactone

### 2.2.1 History of DGJNAc and hexosaminidase inhibitors

The 2-acetamido piperidine class **2.11** of iminosugars structurally resembles the biologically important *N*-acetylhexosamine residues GlcNAc **2.17** and GalNAc **2.18** - the mimicry of which has the potential to lead to the inhibition of the hexosaminidases β-GlcNAcase and α-GalNAcase, respectively. As discussed in **Chapter 1** this affords two new targets in the chemotherapeutic treatment of metastatic cancer and the LSDs Schindler/Kanzaki, Tay Sachs and Sandhoff. The selective inhibition of β-hexosaminidases (β-GlcNAcase & β-GalNAcase) also possesses potential in the study of osteoarthritis,[11] allergy,[12] and Alzheimer's disease.[13] To date there have only been a few reported potent iminosugar inhibitors of β-GlcNAcase in the literature (**Figure 2.3** & **Figure 2.4**).

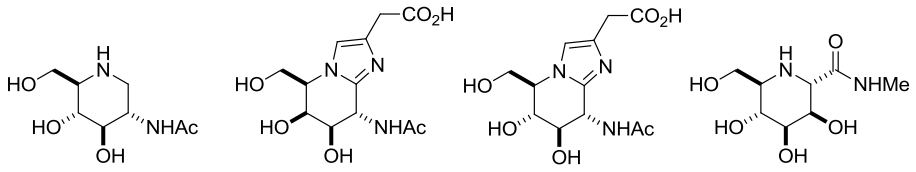



**Figure 2.3**. Piperidine-based iminosugar examples of potent β-hexosaminidase inhibitors.

Given the structural similarity between DNJNAc **2.19** and the natural substrate GlcNAc **2.17**, this compound was the first to receive attention and was synthesised by Fleet *et al*. The biological evaluation was as anticipated - DNJNAc **2.19** demonstrated potent, and selective activity against β-GlcNAcase (jack beans: $IC_{50}$ 0.34 μM).[14-16] Although DNJNAc **2.19** has not yet been discovered in Nature, in fact neither have any stereoisomers of this molecule, a derivative nagstatin **2.21** has been isolated by Aoyama and co-workers,[17] and later synthesised.[18] This fused piperidine-imidazole compound was shown to be an extremely potent β-GlcNAcase

inhibitor (bovine kidney: $IC_{50}$ 13 nM), and also exhibited some α-GalNAcase activity (chicken liver: $IC_{50}$ 63 μM) - but overall a surprising selectivity given the *galacto* configuration of nagstatin **2.21**. Tatsuta *et al* synthesised the *gluco*-derivative **2.22** which was a more potent and specific inhibitor of β-GlcNAcase (bovine kidney: $IC_{50}$ 5.6 nM; chicken liver α-GalNAcase: $IC_{50}$ >330 μM).[18,19] Shilvock and colleagues synthesised the 1-amide derivative **2.23**, and again despite the molecule possessing a *manno*-configuration this molecule demonstrated excellent and specific activity against β-GlcNAcase (human placenta: $IC_{50}$ 90 nM).[20] This result combined with that of nagstatin **2.21** indicates that despite the expectation of β-GlcNAcase enzymes to be inhibited most potently by *gluco*-configured iminosugars, this is not necessarily the case - and additionally the amide functionality maybe located elsewhere on the ring and the inhibition remains strong.

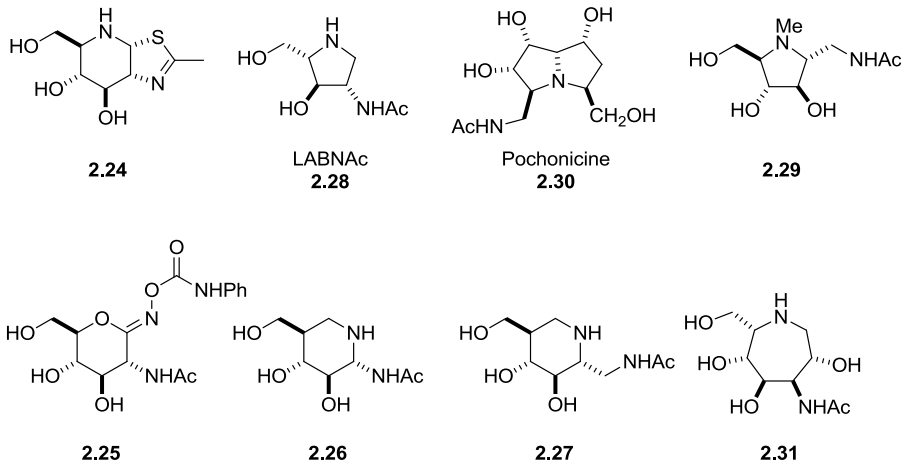
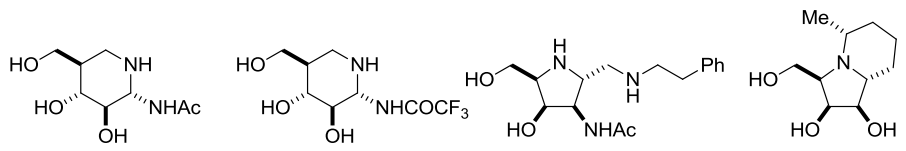



**Figure 2.4**. Other iminosugar examples of potent β-hexosaminidase inhibitors.

This structural tolerance has been further extended to molecules with amide isosteres (**Figure 2.4**), such as NAG-thiazoline[21] **2.24** (jack bean: $K_i$ 280 nM) and PUBNAc[22] **2.25** (*Bacteroides thetaiotaomicron*: $K_i$ 10 nM). The 1-*N*-iminosugar DNJNAc derivative **2.26** was shown to present good and selective activity (bovine epididymis: $IC_{50}$ 3.2 μM),[23] although the geminal diamine motif resulted in inhibitor instability. Van der Berg *et al* improved on this with

the more stable homologated version **2.27** which demonstrated similar activity (human lysosomal: $IC_{50}$ 3.0 μM).[24] There are a few rare examples of iminosugars containing five-membered rings also displaying potent inhibition, including; LABNAc[25] **2.28** (jack bean: $IC_{50}$ 3.4 μM), the 1-acetamido analogue[26] **2.29** (human placenta: $K_i$ 24 nM) and the natural product pochonicine[27] **2.30** (jack bean: $IC_{50}$ 0.3 nM) - the first pyrrolizidine β-GlcNAcase inhibitor. Recently seven-ring azepanes have also been shown to inhibit β-hexosaminidases - with azepane **2.31** demonstrated excellent activity (jack bean: $IC_{50}$ 50 nM).[28]

These examples demonstrate the scope and range of research to date towards iminosugar inhibitors of β-GlcNAcases. However, compared to this α-GalNAcase inhibitors are even sparser and have received little attention (**Figure 2.5**). One β-GlcNAcase inhibitor discussed above, the 1-*N* iminosugar amide **2.26** also inhibited α-GalNAcase (chicken liver: $IC_{50}$ 390 nM). The poor enzyme selectivity was improved by installing a trifluoroacetamide group in derivative **2.32** which gave α-GalNAcase inhibitory specificity (chicken liver: $IC_{50}$ 2.5 μM) with no β-GlcNAcase inhibition observed.[23,29] The two remaining examples of iminosugar α-GalNAcase inhibitors are the pyrrolidine[30] **2.33** and the bicyclic indolizidine (-)-steviamine[31] **2.34** (chicken liver: $IC_{50}$ 100 nM and 814 μM respectively) - interestingly, neither of which possess an amide functionality, or amide isostere.



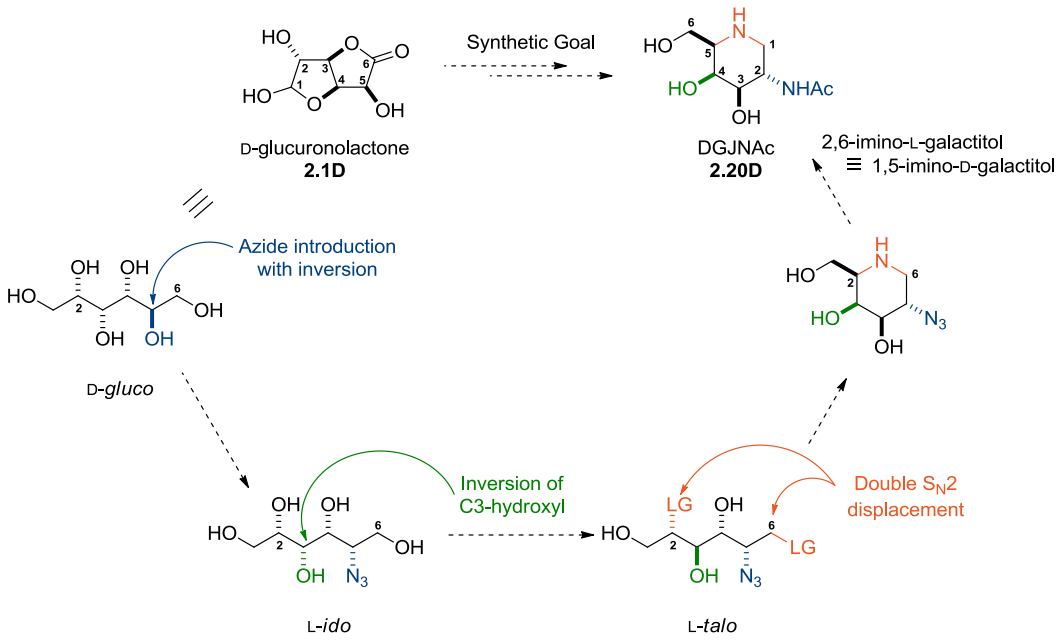

**2.26** **2.32** **2.33** **2.34**

**Figure 2.5**. Known iminosugar α-*N*-acetylgalactosaminidase (α-GalNAcase) inhibitors.

It is evident from this limited range of α-GalNAcase inhibitors, and from the potential therapeutic applications, that there is a distinct need for further examples in the study of this enzyme. Most importantly this starts with DGJNAc **2.20**, the structural mimic of GalNAc **2.18**. Despite the obvious potential this molecule has received less attention that it's *gluco*-configured counterpart DNJNAc **2.19** which after the original synthesis from D-glucose,[14-16] was also synthesised from DNJ **1.1**,[16,32] GlcNAc **2.17**,[33,34] sucrose,[35] and chemoenzymatically.[36] In contrast DGJNAc **2.20** has only been synthesised three times. The original synthesis by Schueller *et al* in 1990 started with DNJ **1.1**,[37] and a year later Kiso and co-workers published an alternative route from the same starting material.[32] These syntheses are far from ideal, not only are the overall yields below 5%, but the starting material is expensive and hence not amenable to larger scale syntheses. In addition to this no biological evaluation of DGJNAc **2.20** was reported. The third and most recently published route utilised a more convenient starting material, but the synthesis itself was racemic.[38]

It can be seen from this work that to further the field of research in α-GalNAcase inhibition by iminosugars the critical starting point is to develop a new synthetic method for convenient access to DGJNAc **2.20**, and to conduct a biological evaluation of this compound. This would provide a starting point for future research and development of inhibitors of α-GalNAcases, and the potential study and treatment of LSDs and metastatic cancer. The following section details research into the development of a new route to DGJNAc **2.20** from the cheap and readily available carbohydrate D-glucuronolactone **2.1D**. In addition the biological activity of this potential inhibitor is also assessed.

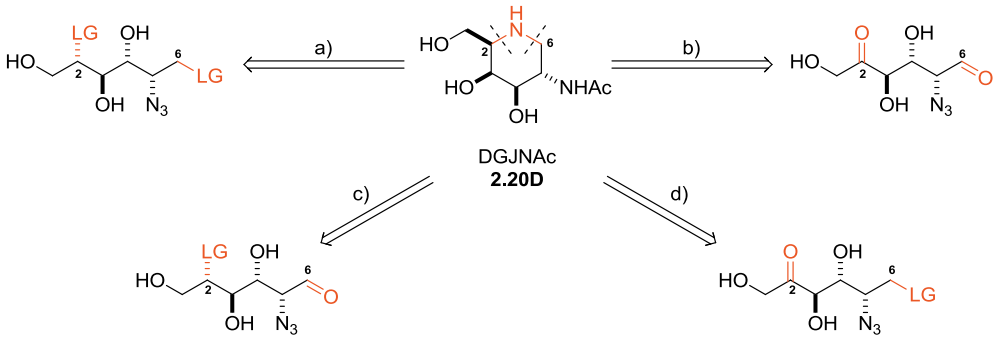
## 2.2.2 Synthetic strategy




**Scheme 2.3**. Synthetic goal.

The first goal of this project was to develop a strategy by which DGJNAc **2.20D** may be accessed from D-glucuronolactone **2.1D** (**Scheme 2.3**). This would necessitate the introduction of two nitrogen atoms; the first to form the exocyclic 2-acetamido group, and the second to form the 1,5-piperidine ring. As indicated previously (**Scheme 2.2**) azide may be used to introduce nitrogen reliably at C5 of D-glucuronolactone **2.1D**, which with subsequent 2,6-cyclisation would form the desired 2-acetamido piperidine scaffold of DGJNAc **2.20D**. In order to reduce the overall number of steps required, this cyclisation would be best accomplished in a single reaction, i.e. by introducing nitrogen to both C2 and C6 simultaneously with a primary amine (**Scheme 2.4**). This could be afforded by, either: a) double $S_N2$-displacement, b) double reductive amination, or c) and d) a combination of these methods. For the sake of simplicity potential routes b) and d) were disregarded at this stage due to the need to induce the selective reduction of the C2 prochiral ketone. From the two remaining possibilities, route a) was selected as having the best potential, as the two leaving groups at C2 & C6 may be formed from a

suitably protected diol. The only other modification to the scaffold that is required is the selective inversion of the C3-hydroxyl - this would then afford the required D-*galacto* configuration of the product. This produces the straightforward synthetic strategy displayed in **Scheme 2.3** (page 55).



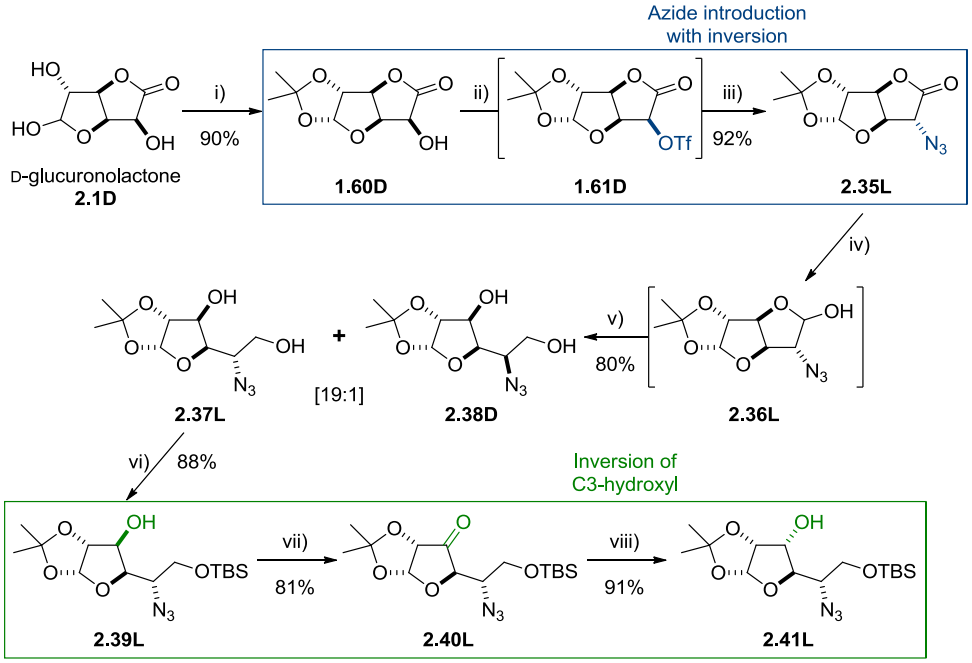

**Scheme 2.4**. Examples of 2,6-cyclisations which may afford DGJNAc **2.4**.
(DGJNAc numbered according to starting material)

This strategy was successfully employed in the synthesis DGJNAc **2.20D** from D-glucuronolactone **2.1D** in 20% yield over 18 steps.[39] With a strategy elucidated, the goal of this section of this thesis was to then develop this into a robust and scalable synthesis which would ultimately afford DGJNAc **2.20D** on a gram-scale - both demonstrating the utility of this new methodology, and providing material for further derivitisation and biological study.

### 2.2.3 Scale-up of the synthesis of DGJNAc

Protection of D-glucuronolactone **2.1D** with acetone in the presence of sulfuric acid afforded the acetonide **1.60D** in 90% overall yield after recrystallisation (**Scheme 2.5**). This molecule possessed the necessary protection required for the introduction of azide at C5. Esterification of the acetonide **1.60D** with trifluoromethanesulfonic anhydride in the presence of pyridine at -40 $^{o}$C gave the intermediate triflate **1.61D**. $S_N2$-displacement of this leaving group with sodium azide in DMF at low temperature (-30 $^{o}$C) proceeded smoothly to give the inverted

*ido*-azide **2.35L** in a 92% yield over two steps.[1,40] Following successful installation of the azide group at C5 with inversion of configuration, attention was turned to the reduction of the 3,6-lactone functionality. A careful approach was required in this process due to the base sensitivity of the *ido*-azide **2.35L**. Treatment of this lactone **2.35L** with sodium or lithium borohydride met with difficulty, and only complex mixtures resulted. The acidity of the α-proton gave rise to epimerisation of C5 as well as potential eliminations.[1,40] So, an alternative two-step protocol was employed; whereby the lactone **2.35L** was reduced by the Lewis-acidic reagent diisobutylaluminium hydride (DIBAL-H) at -78 °C to the lactol **2.36L**. This lactol was less base-sensitive and was fully reduced by sodium borohydride at -10 °C, with care, to the desired diol **2.37L**. The epimerisation which formed the *gluco*-diol **2.38D** was minimal under this protocol (5%), and the overall yield was 80% over the two steps.

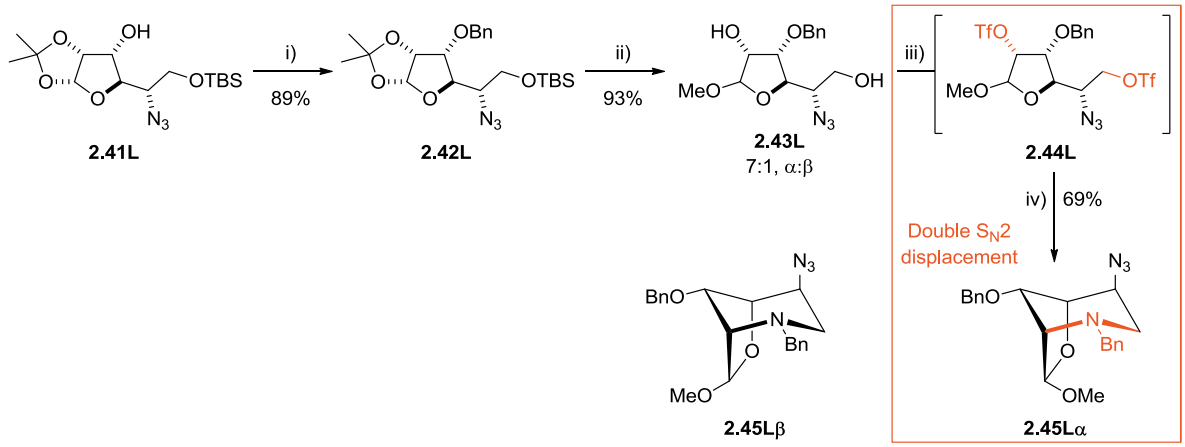



**Reagents & conditions**: i) acetone, $H_2SO_4$, RT, 4 h; ii) $Tf_2O$, pyr, DCM, -30 °C, 1 h; iii) $NaN_3$, DMF, -30 °C, 1.5 h; iv) DIBAL-H, DCM, -78 °C, 1.5 h; v) $NaBH_4$, MeOH, -10 °C, 1.5 h; vi) TBSCl, pyr, RT, 18 h; vii) PCC, DCM, 3 Å MS, 18 h; viii) $NaBH_4$, EtOH, $H_2O$, 0 °C to RT, 1.5 h.

**Scheme 2.5**. Introduction of nitrogen at C5 with inversion; reduction of 3,6-lactone; and inversion of C3.

With the azide group installed and the lactone ring reduced, the next stage was to address the required inversion of the C3 hydroxyl. It was envisaged that this could be accomplished by a two-step oxidation and reduction protocol: oxidation would form a prochiral ketone at C3, and facially selective reduction, induced by the neighbouring 1,2-acetonide, would favour the formation of the 'inverted' configuration of the C3-hydroxyl. To this end the primary C6-hydroxyl in the diol **2.37L** was selectively protected by reaction with *tert*-butyldimethylsilyl chloride (TBSCl) in pyridine to afford the silyl ether **2.39L** in 88% yield. This reaction was chemoselective and no disilylation was observed. This silyl ether **2.39L** was treated with pyridinium chlorochromate (PCC) in the presence of molecular sieves to afford the ketone **2.40L** (81%). This molecule was a perfectly stable intermediate and amenable to purification. Due to the toxicity and problematic handling of PCC on large scales, subsequent repetition of this reaction has been conducted with the oxidant Dess-Martin periodinane (DMP) in place of PCC (see Section 2.3.5.4.1, page 96). Reaction of this ketone **2.40L** with sodium borohydride gave the 'inverted' *talo*-alcohol **2.41L** diastereoselectively in an excellent 91% yield, without observation of any 'retained' alcohol **2.39L** being formed.

With the crucial C3 hydroxyl inverted the protecting group pattern could be suitably arranged for the required 2,6-iminocyclisation (**Scheme 2.6**). Overall this would require the protection of the free C3 hydroxyl and the unmasking of the protected C2 & C6 hydroxyls. To achieve this, the alcohol **2.41L** was treated with benzyl bromide and sodium hydride to afford the benzyl ether **2.42L** (89%). Acidic methanolysis cleaved both the C6-silyl and 1,2-acetonide protecting groups of the dibenzyl ether **2.42L**, and also led to the reprotection of the C1 anomeric centre as the methyl glycoside **2.43L**, in a 7:1 (α:β) anomeric mixture (93%). With only the C2 & C6 hydroxyls now free, in furanosides **2.43L**, suitable protection had thus been installed in order for the 2,6-cyclisation to take place.

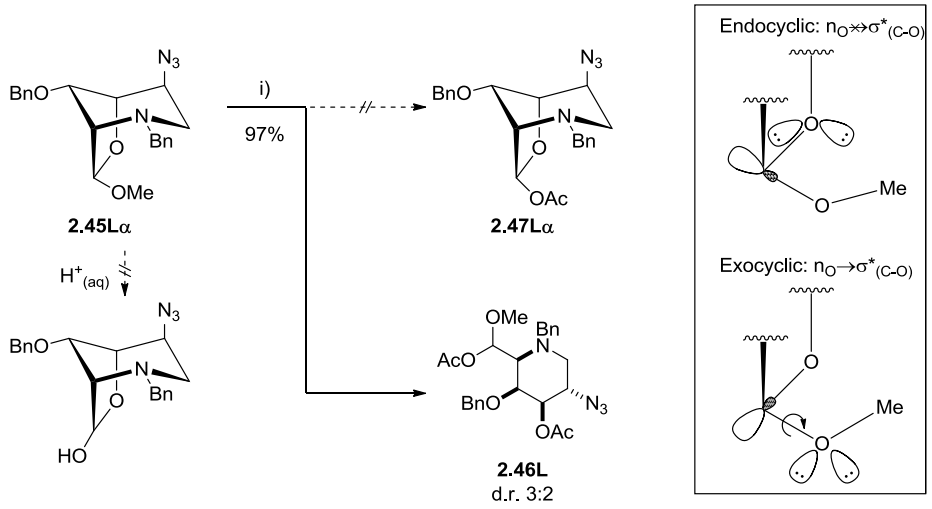



**Reagents & conditions**: i) NaH, BnBr, DMF, 0 °C to RT, 1 h; ii) MeOH, AcCl, 55 °C, 2 h; iii) $Tf_2O$, pyr, DCM, -40 °C, 1 h; iv) $BnNH_2$, THF, -30 °C to RT, 2 h; *then* 60 °C, 16 h.

**Scheme 2.6**. 2,6-Iminocyclisation.

The 2,6-cyclisation strategy chosen in the conception of this synthesis was that of a double $S_N2$-displacement of two leavings groups with benzylamine. This was proven to be effective in the original methodology, which utilised two triflate leaving groups. This is an elegant approach, albeit the lowest yield step of the synthetic route (61%).[39] It should be noted that there are no literature examples of a ditriflate cyclisation forming a hydroxylated piperidine ring. Here, the low yield observed reflected that only the α-anomer of the ditriflates **2.44L** underwent cyclisation to form the iminobicycle **2.45Lα**. The anomer **2.45Lβ** was not formed, presumably due to unfavourable steric interactions between the C1-methyl and C3-benzyl groups. If this low yield is framed in the context of the anomeric ratio of the methyl glycosides **2.43L**, which at 5:1 (α:β) would then give a maximum possible yield of 83% - and a relative yield of 73% for this step. When this methodology was deployed in the larger scale, a higher 7:1 (α:β) anomeric ratio of the methyl glycosides **2.43L** was obtained, giving an increased potential yield for the cyclisation. Triflation of the glycosides **2.43L** was conducted in the usual manner, and the crude ditriflates **2.44L** reacted with benzylamine in THF. The displacement of the C6-primary triflate occurred readily at -30 °C, with the reaction warmed to 55 °C to allow the intramolecular displacement of the C2-secondary triflate. Formation of the iminobicycle **2.45Lα** was observed

in an increased yield of 69% (79% relative to anomeric ratio of **2.43L**). Thus, with the key 2,6-cyclisation complete and every stereocentre in the required configuration, the next stage was the hydrolysis and reduction of the furanoside ring to afford the monocyclic scaffold of the target (**Scheme 2.7**). It was anticipated that this was to be a relatively straightforward process, but ultimately proved contrary to this. Attempts at hydrolysis with aqueous protic acids were unfruitful, with ultimately the most successful approach being with Lewis acid-catalysed acetolysis. The reaction of iminobicycle **2.45Lα** with boron trifluoride diethyl etherate in acetic anhydride permitted the opening of the furanoside ring and formation of the monocyclic mixed acetals **2.46L** (97%).

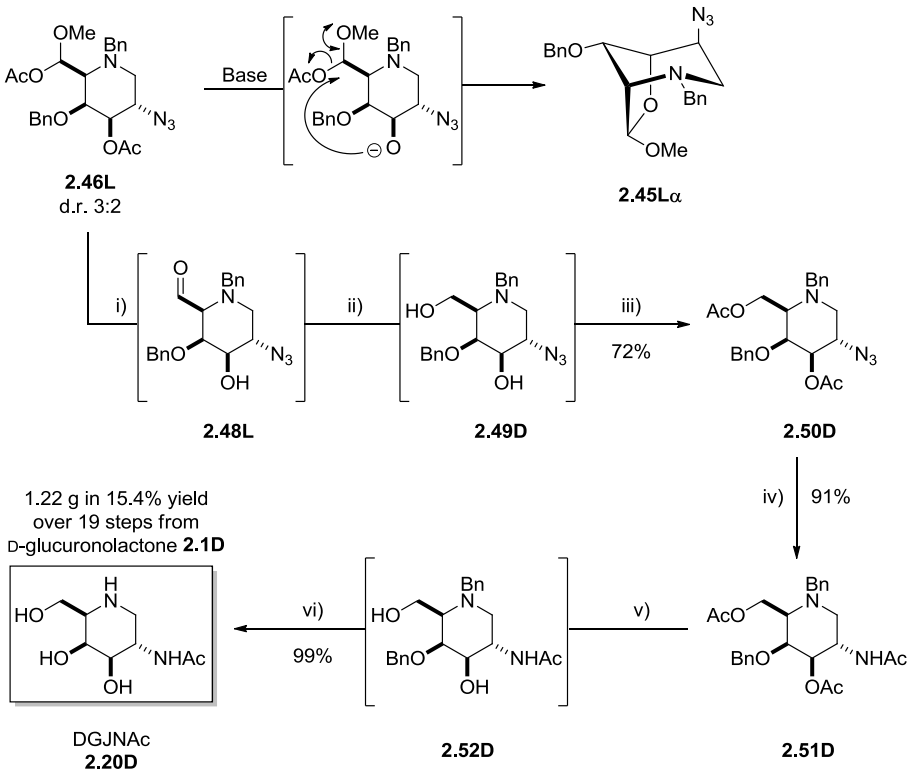



**Reagents & conditions**: i) $BF_3 \cdot OEt_2$, $Ac_2O$, -30 °C to RT, 2.5 h.

**Scheme 2.7**. Lewis acid acetolysis of bicyclic glycoside **2.45Lα**, and orbital rationale for endocyclic C-O cleavage.

Interestingly, in order for this mixed acetal to form it must be concluded that it was the endocyclic C-O bond which underwent cleavage, rather than the expected exocyclic C-O bond. This observation may be explained by the lack of endocyclic oxygen lone-pair overlap with the σ*-orbital of the C-OMe bond, thus preventing exocyclic cleavage. The rotational freedom of the C-OMe bond allows the overlap of the lone pair of the exocyclic oxygen atom to develop with

the σ*-orbital of the endocyclic C-OMe bond, thereby leading to the observed cleavage (**Scheme 2.7**).




**Reagents & conditions**: i) DIBAL-H, DCM, -78 °C, 45 min; ii) $NaBH_4$, MeOH, 0 °C to RT, 3 h; iii) $Ac_2O$, pyr, RT, 16 h; iv) $CuSO_4$(aq), Zn, THF, AcOH, $Ac_2O$, RT, 30 min; v) NaOMe, MeOH, RT, 16 h; vi) $H_2$, Pd/C (10%), $H_2O$, 2 M HCl, 1,4-dioxane, RT, 24 h.

**Scheme 2.8**. Final stages in the synthesis of DGJNAc **2.20D**.

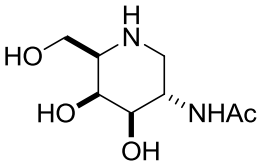
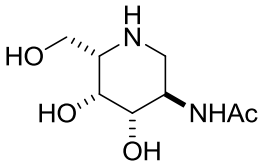
Prior attempts at the direct reduction of the mixed acetals **2.46L** with sodium borohydride were only marginally successful, with reformation of the iminobicycle **2.45Lα** being the predominant reaction (**Scheme 2.8**). So a strategy was developed that employed a two-stage reduction in order to afford the desired diol **2.49D**, with final acetylation permitting purification by column chromatography. This process was achieved by initial reduction of the mixed acetals **2.46L** with excess DIBAL-H which led to formation of the intermediate aldehyde **2.48L**. Reduction with sodium borohydride gave the intermediate diol **2.49L**, which was acetylated with acetic anhydride in the presence of pyridine to afford the diacetate **2.50D** in a yield of 72% over the three steps. With the monocyclic piperidine scaffold accessed, the penultimate step involved the

reductive acetylation of the azide group to form an acetamide functionality. This was completed by the copper(II)-initiated zinc reduction of the azide **2.50D** in the presence of acetic anhydride to form the acetamide **2.51D** (91%).[41,42]

All that remained was the final, global deprotection. Cleavage of the acetate groups was achieved by basic methanolysis to form the intermediate diol **2.52D**. Acidic hydrogenolysis in the presence of palladium (10% on carbon) produced the target compound DGJNAc **2.20D** in 99% yield over two steps.[43] Thus this nineteen step methodology was shown to be extremely amenable to scaling, with 1.22 g of DGJNAc **2.20D** easily accessed from D-glucuronolactone **2.1D** in a highly efficient 15.4% overall yield.[43] This represented only a minor decrease from that achieved in the initial pilot, small scale (17.2%).[39]

## 2.2.4 Biological evaluation

With a successful, scalable and robust synthesis of DGJNAc **2.20D** established from D-glucuronolactone **2.20D**, the next phase of the project was the biological evaluation of this iminosugar. This was done in collaboration with Prof. Atsushi Kato (University of Toyama, Japan) (**Table 2.1**). As well as elucidating the initial strategy in this project Dr. Dan Best also synthesised L-DGJNAc **2.20L** from L-glucuronolactone **2.1L**, the data for which is shown here for comparison.[39]

| | **$IC_{50}$ (μM)** | |
|---|---|---|
| |  |  |
| **Enzyme** | DGJNAc **2.20D** | L-DGJNAc **2.20L** |
| α-Galactosidase | | |
| Coffee beans | 64 | NI[a] (17.3)[b] |
| β-*N*-Acetylglucosaminidase | | |
| Human placenta | 8.3 [2.2][c] | 830 [1100] |
| Bovine kidney | 4.2 | NI (46.8) |
| *Aspergillus oryzae* | NI (8.8) | NI (0.8) |
| HL60 | 7.1 | NI (31.3) |
| Jack beans | 1.8 | NI (46.3) |
| α-*N*-Acetylglucosaminidase | | |
| Chicken liver | 0.32 [0.081] | NI (22.6) |
| *Charonia lampas* | [0.136] | ND |
| β-*N*-Acetylgalactosaminidase | | |
| *Aspergillus oryzae* | NI (9.6) | NI (0) |
| HL60 | 23 | NI (12.9) |

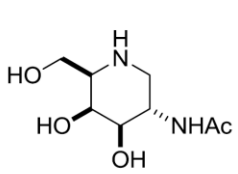
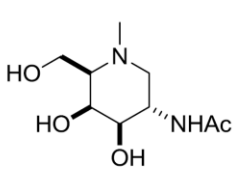
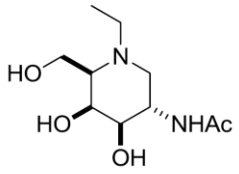
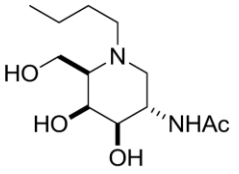
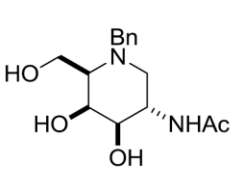
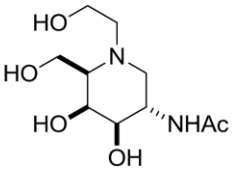
*[a]NI: no inhibition (less that 50% inhibition at 1000 μM); [b]( ): inhibition % at 1000 μM; [c] $K_i$ values are given in square parentheses.*

**Table 2.1**. Concentration of iminosugars giving 50% inhibition of various glycosidases.

[No inhibition (less than 50% inhibition at 1000 μM) was observed in both enantiomers for: α-glucosidase (rice, yeast), β-glucosidase (almond, bovine liver), β-galactosidase (bovine liver), α-mannosidase (Jack beans), β-mannosidase (snail), α-L-rhamnosidase (*Pandanus decumbens*), α-L-fucosidase (bovine epididymis) and β-glucuronidase (*E. coli*, bovine liver)]

As originally anticipated DGJNAc **2.20D** was shown to be a highly competitive inhibitor of α-GalNAcase (chicken liver: $IC_{50}$ 320 nM), with moderate selectivity over β-hexosaminidases (β-GlcNAc & β-GalNAc). The "unnatural" enantiomer L-DGJNAc **2.20L** only demonstrated very weak inhibition of β-hexosaminidases (human placenta: $IC_{50}$ 830 μM - compared with 8.3 μM for DGJNAc **2.20D**). Importantly it should be noted that the inhibition displayed by L-DGJNAc **2.20L** was non-competitive; an observation which is in accord with previous observations by Asano and others, where "unnatural" enantiomers show non-competitive inhibition in contrast to "natural" enantiomers.[6,44] DGJNAc **2.20L** also displayed modest inhibition of α-galactosidase (coffee beans: $IC_{50}$ 64 μM).

Although DGJNAc **2.20D** only demonstrated selectivity for α-GalNAcases over β-hexosaminidases by one order of magnitude, this was an encouraging result due to the scarcity of molecules which demonstrate such selectivity and potency. In order to increase the degree of enzyme specificity *N*-alkylated derivatives (*N*-methyl **2.53D**, *N*-ethyl **2.54D**, *N*-butyl **2.55D**, *N*-benzyl **2.56D** & *N*-(2-hydroxylethyl) **2.57D**) were prepared by the reductive amination of DGJNAc **2.20D** with the relevant aldehyde. This work was conducted by Andreas Glawar (**Table 2.2**). All the derivatives were found to be good inhibitors of β-GlcNAcases (except for *A. oryzae*), although *N*-benzyl **2.56D** was significantly weaker (HL60: $IC_{50}$ 52 μM). The *N*-ethyl **2.54D**, *N*-benzyl **2.56D** and *N*-(2-hydroxylethyl) **2.57D** compounds were all good inhibitors of α-GalNAcase (chicken liver: $IC_{50}$ 5.6-11.0 μM), however *N*-methyl **2.53D** and *N*-butyl **2.55D** appear to be less well tolerated by this enzyme (chicken liver: $IC_{50}$ 107 & 166 μM respectively). With such comparable HL60 β-GlcNAcase inhibition, free oligosaccharide (FOS) analysis was used to determine the intracellular lysosomal β-GlcNAcase inhibition exhibited by these iminosugars.

| | $IC_{50}$ (μM) | | | | | |
|---|---|---|---|---|---|---|
| |  |  |  |  |  |  |
| **Enzyme** | DGJNAc **2.20D** | *N*-methyl **2.53D** | *N*-ethyl **2.54D** | *N*-butyl **2.55D** | *N*-benzyl **2.56D** | *N*-(2-hydroxyethyl) **2.57D** |
| β-*N*-Acetyl-glucosaminidase | | | | | | |
| Human placenta | 8.3 | 5.7 | 7.3 | 2.7 | 45 | 8.2 |
| Bovine kidney | 4.2 | 2.1 | 3.1 | 1.2 | 40 | 3.7 |
| *Aspergillus oryzae* | NI (8.8) | NI (22.1) | NI (26.5) | NI (22.6) | NI (11.4) | NI (46.9) |
| HL60 | 7.1 | 5,4 | 7.9 | 1.7 | 52 | 8.3 |
| Jack beans | 1.8 | 1.5 | 3.4 | 2.7 | 22 | 1.9 |
| α-*N*-Acetyl-glucosaminidase | | | | | | |
| Chicken liver | 0.32 | 107 | 5.6 | 166 | 11 | 6.3 |
| *Charonia lampas* | [0.17][c] | [0.97] | [7.9] | [148] | [14] | [3.9] |
| β-*N*-Acetyl-galactosaminidase | | | | | | |
| *Aspergillus oryzae* | NI (9.6) | NI (29.4) | NI (26.3) | NI (29.8) | NI (5.8) | 926 |
| HL60 | 23 | 26 | 44 | 14 | 187 | 35 |

*[a] NI: no inhibition (less that 50% inhibition at 1000 μM); [b] ( ): inhibition % at 1000 μM; [c] $K_i$ values are given in square parentheses.*

**Table 2.2**. Concentration of iminosugars giving 50% inhibition of various glycosidases.

This FOS analysis indicated that despite similar β-GlcNAcase inhibition there was a range of intracellular effects, with the maximum cellular interference displayed by the *N*-butyl derivative of DGJNAc **2.55D**, and the minimum by *N*-(2-hydroxylethyl) **2.57D**. There was a five-fold difference between the two derivatives,[43] which may be ascribed to the difference in their cellular penetration of the cells and organelles. This would indicate that a polar, hydrophilic hydroxyethyl branch confines the derivative **2.57D** to the extracellular space, decreasing the observed level of intracellular interference. Therefore it can be seen that the addition of a polar branch to the potent iminosugar DGJNAc **2.20D** would allow for the preferential targeting of extracellular enzymes. This dramatically enhances the potential of this class of molecule in the treatment of metastatic cancer by preferential inhibition of extracellular enzymes. Further study of these polar-branched DGJNAc derivatives will afford an optimisation of both the inhibitory activity and also extracellular enzyme selectivity for the future treatment of cancer by this strategy.

## 2.3 Pyrrolidines: all stereoisomers of two compound classes divergently from glucuronolactone

### 2.3.1 Introduction

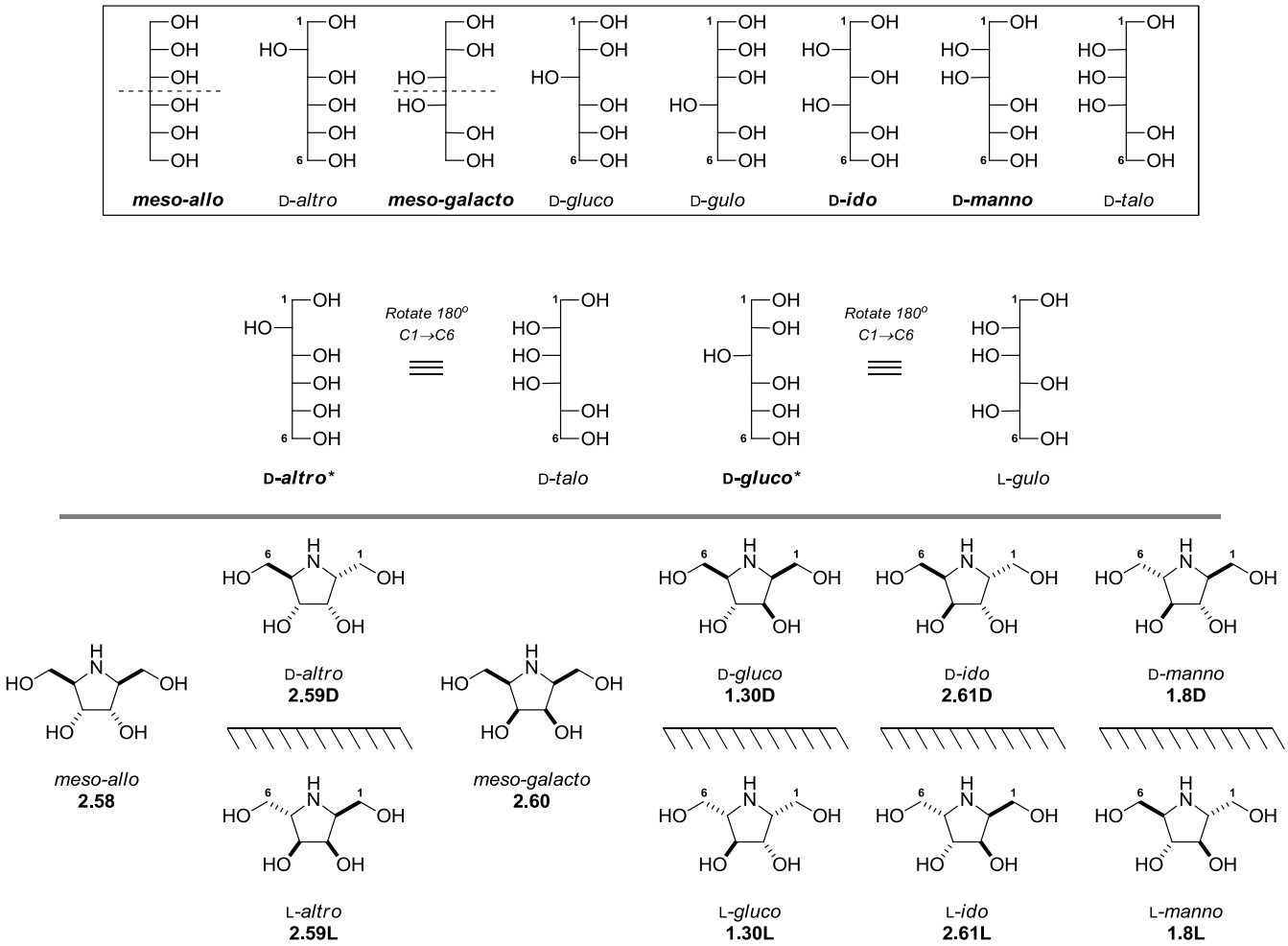



**Figure 2.6**. Fischer projections demonstrating the degeneracy of alditol structures;[45] and the resultant ten stereoisomeric pyrrolidines.
[**In the case of alditol degeneracy the nomenclature is derived from alphabetical precedence*]

The 2,5-iminohexitol, or pyrrolidine, iminosugar scaffold possesses four stereogenic centres which would give sixteen possible stereoisomeric configurations. Employing standard carbohydrate nomenclature these can be described as either D- or L-enantiomers of *allo*, *altro*, *galacto*, *gluco*, *gulo*, *ido*, *manno* and *talo* configurations (**Figure 2.6**). However, due to the degeneracy of the alditol scaffold of these sixteen possible configurations there are six

degenerate pairs, comprising two *meso* forms (*allo* and *galacto*) and four equivalent configurations (D-*gluco* = L-*gluco*, L-*gluco* = D-*gluco*, D-*altro* = D-*talo* and L-*altro* = L-*talo*). This leads to there being only ten possible pyrrolidine configurations: *meso-allo* **2.58**, D-*altro* (DADP) **2.59D**, L-*altro* (L-DADP) **2.59L**, *meso-galacto* (DGADP) **2.60**, D-*gluco* (DGDP) **1.30D**, L-*gluco* (L-DGDP) **1.30L**, D-*ido* (DIDP) **2.61D**, L-*ido* (L-DIDP) **2.61L**, D-*manno* (DMDP) **1.8D** and L-*manno* (L-DMDP) **1.8L**. Of these pyrrolidines three are naturally occurring; D-*manno*-configured DMDP **1.8D** was the first to be discovered,[46] and as discussed earlier (Section 1.3, page 9) is the most widely abundant iminosugar in Nature. DMDP **1.8D** has displayed both potent β-glucosidase (bovine liver: $IC_{50}$ 9.7 μM) and β-galactosidase inhibition (bovine liver: $IC_{50}$ 3.3 μM).[47] D-*Gluco*-configured DGDP **1.30D** was discovered recently in a Thai traditional medicine and has been shown to be a weak α- and β-glucosidase inhibitor.[48] Finally, D-*altro* (DADP) **2.59D** was discovered by Kato *et al* in 2010 in the roots of *Adenophora triphylla* and was shown to be a powerful and competitive α-galactosidase inhibitor (human lysosome: $IC_{50}$ 69 μM). This degree of inhibition led the authors to suggest that the pyrrolidine **2.59D** would pose an ideal candidate for the chaperone-mediated therapy (CMT) of Fabry's disease - an LSD.[49] These naturally occurring examples have led to the increasing interest in the pharmacological potential of this class of iminosugar. The remaining seven stereoisomers, which have not been isolated from natural sources, have all received some degree of synthetic attention. However, those that are naturally occurring have received the greatest research effort. The past syntheses of these pyrrolidines will be summarised below in Section 2.3.2 (page 69).

In other pyrrolidine-based systems the powerful inhibition of "unnatural" enantiomers has been observed, highlighting the need to synthesise these compounds in addition to their "natural" counterparts. One example of this was shown earlier with DGJNAc **2.20D** (Section 2.2.4, pages 63-64). Another prime example of this is the naturally occurring compound DAB-1 **1.18D**

(**Figure 2.7**). This iminosugar displays potent and competitive inhibition of α-glucosidases (rat intestinal maltase; $IC_{50}$ 5.8 μM), whereas it's "unnatural" enantiomer, LAB-1 **1.18L**, is a far more potent and also non-competitive inhibitor of the same enzyme ($IC_{50}$ 80 nM).[50] The enantiomer of DMDP **1.8D**, L-*manno* **1.8L**, has also been shown to exhibit greater and more specific inhibition of α-glucosidases (rat intestinal sucrase; $IC_{50}$ 40 μM versus 0.62 μM, respectively).[47] This therefore illustrates the importance of determining the biological profile of all pyrrolidine iminosugars, not just those with 'natural' configurations.

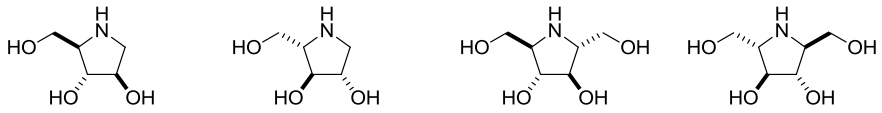


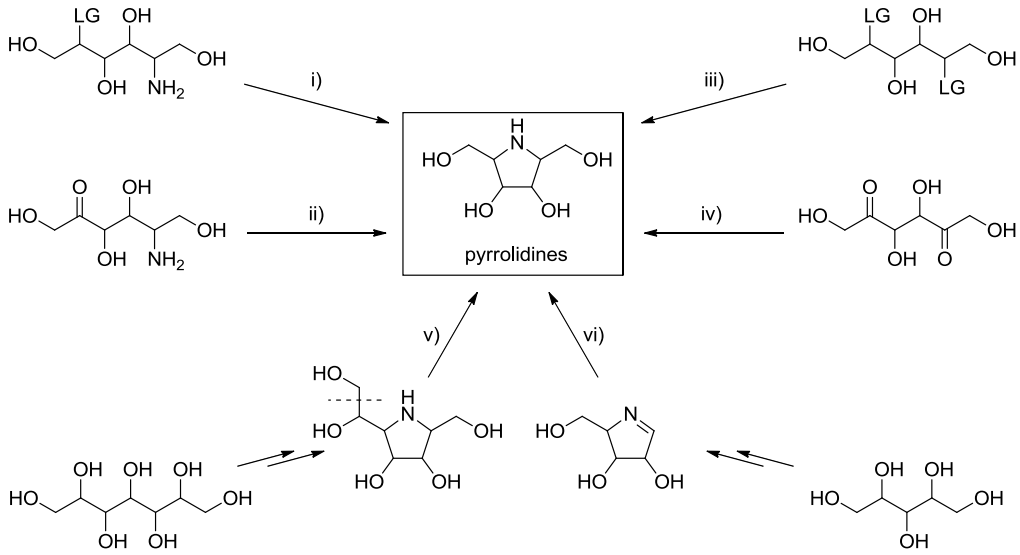

**Figure 2.7**. Biologically active pyrrolidine iminosugars

2.3.2 Previous syntheses of 2,5-iminohexitol (pyrrolidine) iminosugars

Since the discovery of DMDP **1.8D** in 1976[46] there have been many reported syntheses of this compound and other 2,5-iminohexitols. However, these have primarily focussed on elaborating routes to access both this iminosugar and the naturally occurring diastereoisomer DGDP **1.30D**. The remaining stereoisomers have subsequently all received some attention, but this has been inevitably limited.

The general principles employed in the assembly of iminosugars were reviewed in Section 1.6 (pages 24-42). The syntheses of pyrrolidines which have been conducted to date may be categorised according to the method by which the iminosugar scaffold was constructed (**Scheme 2.9**): (i) intramolecular displacement of a leaving group; (ii) intramolecular reductive amination; (iii) double-displacement of two leaving groups by the same nitrogen source; and

(iv) double reductive amination of two carbonyl groups with the same nitrogen source. Additionally, the carbon skeleton may undergo (v) truncation or (vi) elongation to achieve the target compound (combined with a cyclisation method (i-iv)). Each method will be discussed and illustrated in the following section.

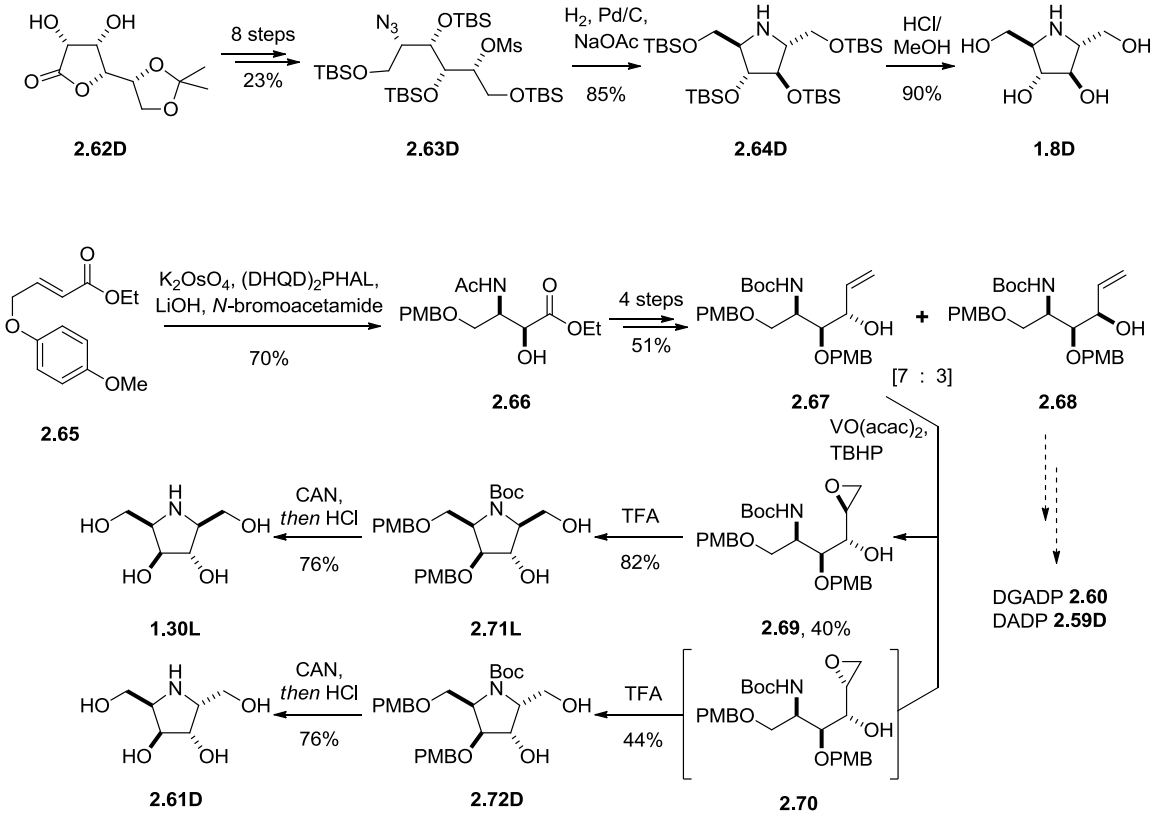



**Scheme 2.9**. General methods of pyrrolidine assembly.

2.3.2.1 Assembly of the pyrrolidine scaffold

The most straightforward method for the formation of a pyrrolidine is the intramolecular iminocyclisation of an amine with a leaving group. As detailed in Section 1.6.1 (page 25), the nature of the leaving group may vary; from halides[51] and sulfonate esters - such as triflates,[52,53] mesylates,[54-58] and tosylates[57] - to Mitsunobu conditions,[59] epoxides[60,61] and also alkenes activated by iodine[62] or by mercury(II) salts.[63-65] These methods of iminocyclisation have been successfully utilised in the synthesis of DMDP **1.8D**,[54,61-64] L-DMDP **1.8L**,[55] DGDP **1.30D**,[51,53,56-59] L-DGDP **1.30L**,[52,60] DADP **2.59D**,[60,65] DGADP **2.60**,[57,60,65] D-DIDP **2.61D**,[60] and L-DIDP **2.61L**.[59] Two prime examples of the utilisation of this methodology are in the synthesis of L-DMDP **1.8L** by Yu *et al*[55] and L-DGDP **1.30L** by Singh and co-workers[60] (**Scheme 2.10**).

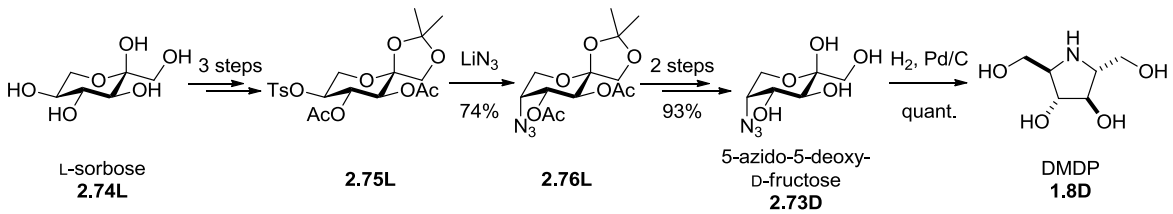
The former synthesis of L-DMDP **1.8L** demonstrates the intramolecular $S_N2$-displacement of a mesylate leaving group in order to obtain the pyrrolidine in good overall yield from protected D-gulonolactone **2.62D**.[55] The latter asymmetric synthesis of L-DGDP **1.30L** from achiral alkene **2.65** demonstrates the great utility of divergency within synthetic methodology, whereby multiple targets may be accessed from a single starting material (for further discussion see Section 2.3.2.2, page 80).




**Scheme 2.10**. $S_N2$-displacement forming pyrrolidines from chiral pool and asymmetric syntheses.[55,60]

Asymmetric aminohydroxylation afforded the ester **2.66**, with the creation of two chiral centres. Subsequently, two further centres are established with separation of the four epoxide diastereoisomers (including **2.69** and **2.70**). Removal of the Boc amino protecting group then led to intramolecular 5-*exo*-tet epoxide ring-opening and formation of the pyrrolidine rings. This divergent sequence gave access to the four pyrrolidines L-DGDP **1.30L**, D-DIDP **2.61D**, DGADP **2.60** and DADP **2.59D** from the achiral alkene **2.65**.[60]

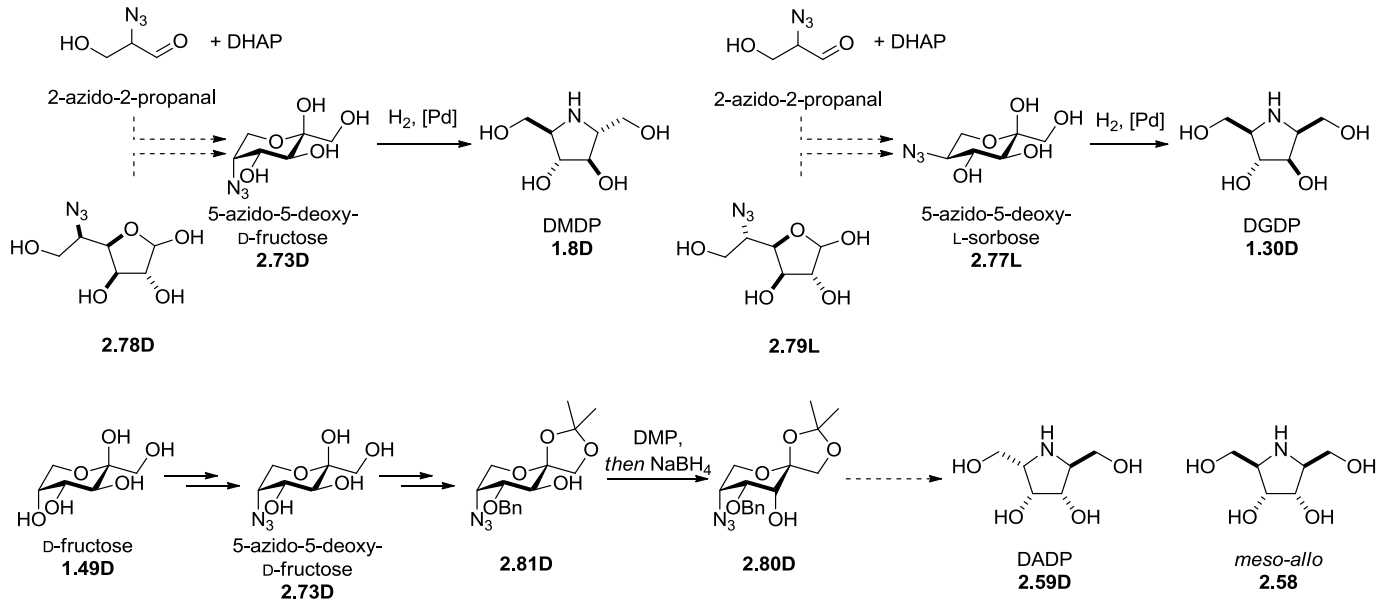
As can be seen, cyclisations of this type are stereospecific and generally high-yielding. This has led to intramolecular $S_N2$-displacement being the most widely employed cyclisation method in the access of pyrrolidine iminosugars. Intramolecular reductive amination of an amino group and a ketone is the next most commonly used method for pyrrolidine ring formation. These reactions are chemoselective, and as such can be performed in the absence of protecting groups - an advantage over the previous methodology in that shorter synthetic sequences may be possible. However, this class of reaction proceeds *via* a prochiral imine and therefore the selectivity of the reduction needs to be addressed in order to access the desired target selectively. The pyrrolidines DMDP **1.8D**,[66-70] L-DMDP **1.8L**,[71] DGDP **1.30D**,[68,69,72-75] L-DGDP **1.30L**,[71] DGADP **2.60**,[76-78] DADP **2.59D**[79] and *meso-allo* **2.58**[79] have been formed using this methodology. In addition L-DADP **2.59L** has also been accessed, albeit as a mixture with DGADP **2.60**.[80] The syntheses previously conducted require the preparation of a 5-azido-5-deoxy-ketose, invariably from either carbohydrate starting materials or asymmetrically from 2-azido-propanal and dihydroxyacetone phosphate (DHAP). Subsequent intramolecular reductive amination of the 5-azido-5-deoxy-ketose forms the pyrrolidine scaffold. In 1985 Card *et al* employed this methodology to access DMDP **1.8D**, this entailed the six-step synthesis of 5-azido-5-deoxy-D-fructose **2.73D** from L-sorbose **2.74L**, with hydrogenolysis giving DMDP **1.8D** stereoselectively. (**Scheme 2.11**).[66]




**Scheme 2.11**. Synthesis of DMDP **1.8D** by intramolecular reductive amination.[66]

Hung and co-workers have also prepared 5-azido-5-deoxy-D-fructose **2.73D** enzymatically and asymmetrically from 2-azido-propanal and DHAP in order to access DMDP **1.8D**.[67] This methodology was also employed in the synthesis of DGDP **1.30D** by accessing the epimeric

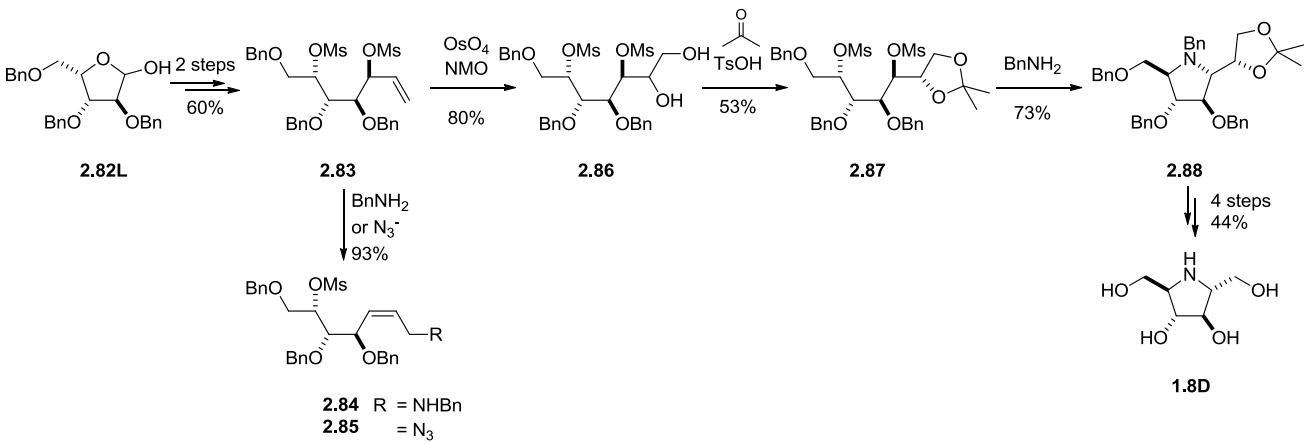
5-azido-5-deoxy-L-sorbose **2.77L** (**Scheme 2.12**).[73] The enantiomers of these pyrrolidines, L-DMDP **1.8L** and L-DGDP **1.30L**, have been afforded by the enantiomeric methodology.[71] DGADP **2.60** has also been synthesised by an analogous process.[76] Legler *et al* demonstrated access to 5-azido-5-deoxy-D-fructose **2.73D** and L-sorbose **2.77L** enzymatically from 5-azido-5-deoxy-D-glucose **2.78D** and L-idose **2.79L**, respectively.[68] Appropriate protection and subsequent C3-epimerisation of 5-azido-5-deoxy-D-fructose **2.73D** by Izquierdo and colleagues gave 5-azido-5-deoxy-D-psicose **2.80D** which was used to form the pyrrolidines DADP **2.59D** and *meso-allo* **2.58**.[79] Syntheses of pyrrolidines utilising an intramolecular reductive amination have proven very successful, however, as mentioned above, the applicability of the methodology towards other pyrrolidine stereoisomers is limited due to the inherent selectivity in the reduction of a prochiral imine intermediate.




**Scheme 2.12**. Enzymatic syntheses of pyrrolidines *via* 5-azido-5-deoxy-ketoses.[67,68,73,79]

These two main methods of synthesising the pyrrolidine core - intramolecular displacement and reductive amination - have also been expanded further to incorporate the process of nitrogen introduction to the scaffold. Thus the double-displacement of two leaving groups with the same

source of nitrogen has proved an attractive and successful method for the facile construction of the pyrrolidine iminosugars DMDP **1.8D**,[81,82] L-DMDP **1.8L**[83] and L-DIDP **2.61L**.[81,84-86] Commonly syntheses of this type have relied on the use of $C_2$-symmetric starting materials, such as D-mannitol[81,84-86] or L-(+)-tartrate[83] to permit a strategy of symmetrical protection, C2/C5-di-activation and subsequent cyclisation to a $C_2$-symmetrical product. Given that there are only four $C_2$-symmetric pyrrolidines (DMDP **1.8D**¸ L-DMDP **1.8L**, DIDP **2.61D** and L-DIDP **2.61L**) this has limited the application of this methodology. Examples of the synthesis of both DMDP **1.8D** and L-DIDP **2.61L** have been previously illustrated in **Scheme 1.13** (page 29).[81,84] Behr and co-workers recently published one exception to this, whereby DMDP **1.8D** was synthesised from L-xylose (**Scheme 2.13**).[82]

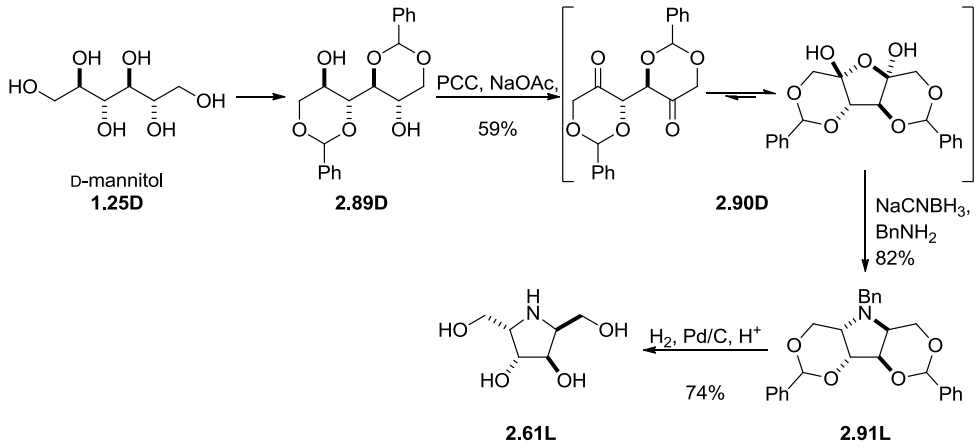



**Scheme 2.13**. Synthesis of DMDP **1.8D** from L-xylose by double $S_N2$-displacement.[82]

L-Xylose was converted to the dimesylate **2.83**, which upon reaction with both amine and azide exclusively gave the $S_N2'$ products **2.84** and **2.85**, respectively, and in the case of the amine, gave no desired cyclised product at all. To circumvent this problem, the terminal alkene was dihydroxylated with osmium tetraoxide and *N*-methylmorpholine *N*-oxide (NMO) to give a mixture of diols **2.86**. Subsequent acetonation of this mixture permitted separation to give the desired acetonide-protected dimesylate **2.87**. Treatment with benzylamine afforded the desired

cyclisation and the homopyrrolidine **2.88**. Deprotection and truncation then afforded the target iminosugar DMDP **1.8D**.[82]

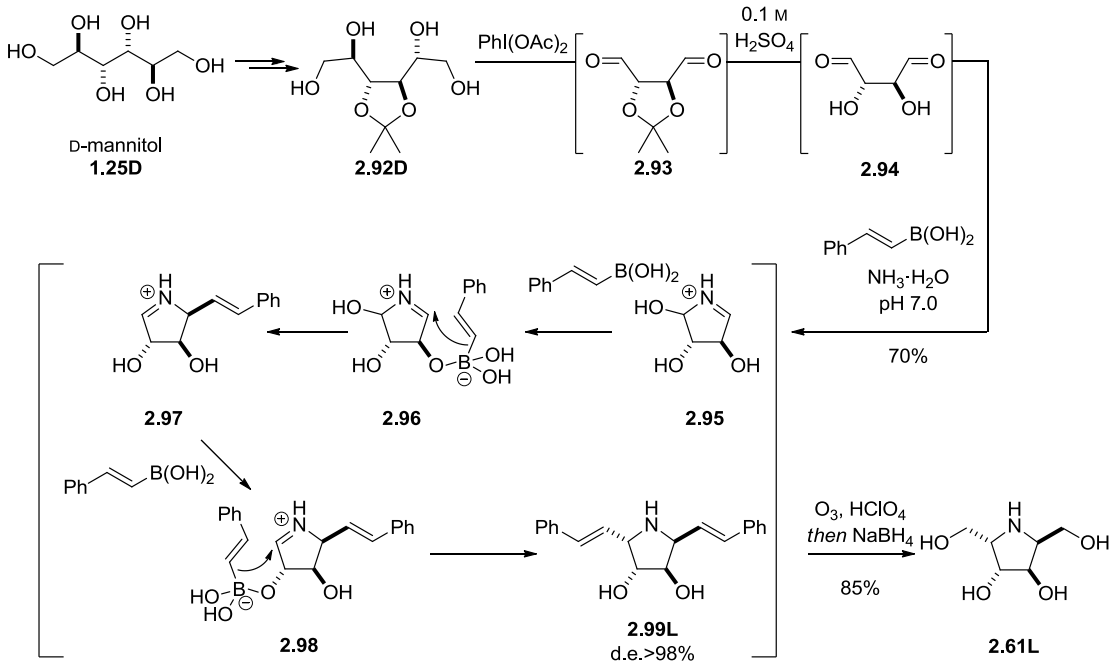
Similarly to double-displacement, double-reductive amination has also provided access to the pyrrolidines DGDP **1.30D**,[87,88] L-DIDP **2.61L**,[89,90] D-DIDP **2.61**[90] and DGADP **2.60**.[90] The first synthesis of this type was conducted by Reitz *et al* in 1990, and has been described earlier in **Chapter 1** (**Scheme 1.14**, page 29).[87] Reductive amination of 5-keto-D-fructose **1.48** (accessible by *Gluconobacter* oxidation of D-fructose **1.49**) with sodium cyanoborohydride and benzhydrylamine gave a mixture of benzhydryl-protecting pyrrolidines of D-*gluco*-, L-*ido*- and D-*manno*-configuration in a 43:4:3 ratio. This was the best selectivity observed.




**Scheme 2.14**. Synthesis of L-DIDP **2.61L** by double-reductive amination.[89]

This reaction was improved upon by Zou and colleagues in 1993, by the hypothesis that a protected and therefore rigid starting material, would lead to a greater degree of selectivity in the double-reductive amination step (**Scheme 2.14**).[89] Thus protection of D-mannitol **1.25D** as the 1,3;4,6-dibenzylidene-acetal **2.89D** and subsequent oxidation to the diketone **2.90D** gave the starting material for the double-reductive amination. Reaction with sodium cyanoborohydride and benzylamine then gave the pyrrolidine **2.91L** stereoselectively. Final deprotection afforded the L-*ido*-configured pyrrolidine **2.61L**.

Finally, the most recent example of the utilisation of a dicarbonyl starting material was demonstrated by Hong and co-workers in 2009.[90] However, this work is not a formal reductive amination, but involves a double aminohomologation of a four-carbon dialdehyde *via* a Petasis-type aminocyclisation (**Scheme 2.15**) - but the similarity in the type of starting material leads to its mention here.

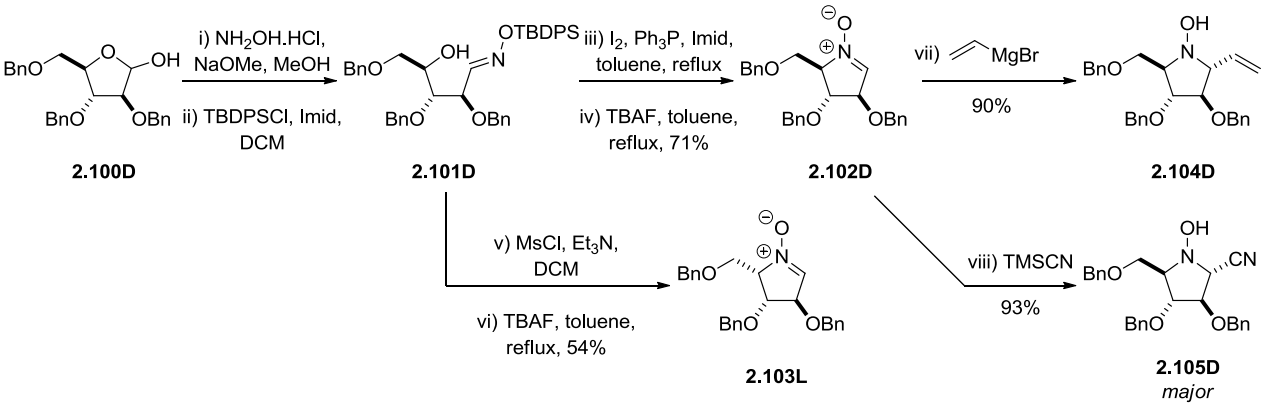



**Scheme 2.15**. Double aminohomologation of a four-carbon dialdehyde.[90]

As is demonstrated in this synthesis, the employment of homologation reactions to afford pyrrolidines allows a diversification of the pool of potential starting materials. This makes access to a six-carbon monosaccharide starting material no longer crucial in a synthetic strategy. And similarly, the final general method of pyrrolidine access - truncation - would also access six-carbon pyrrolidines from higher sugars as starting materials.

Despite only limited synthetic attention homologation has allowed access to a wide range of the pyrrolidines, including *meso-allo* **2.58**,[91-93] D-DADP **2.59D**,[91] DGDP **1.30D**,[92-96] L-DIDP **2.61L**,[94] DMDP **1.8D**,[92,93,95] L-DMDP **1.8L**,[92] and L-DADP **2.59L**.[92,93] Homologation, or

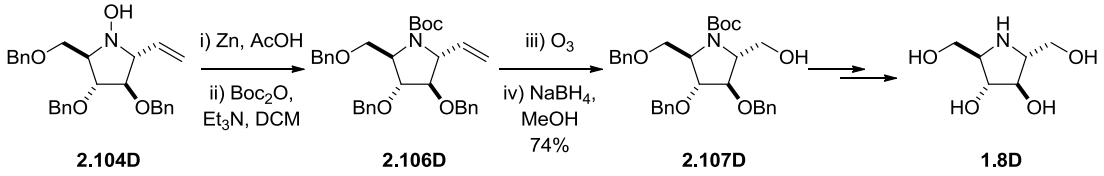
specifically in this case aminohomologation, involves the addition of a carbon-based nucleophile to a carbon-nitrogen double bond, which may occur before or after the iminosugar ring has been formed. In order to formally add an hydroxymethyl-group the typical carbon nucleophiles utilised are either cyanide[92,95] or organometallic reagents - of which vinylmagnesium bromide is the most common,[91,92,94] however hydroxymethyllithium[95] and thiazolinyllithium[93,96] have also been employed. Tsou *et al* demonstrated the use of both trimethylsilyl cyanide (TMSCN) and vinylmagnesium bromide in the addition to five-carbon cyclic nitrones (**Scheme 2.16**).[92]




**Scheme 2.16**. Cyclic nitrone syntheses, and subsequent homologation with TMSCN or vinylmagnesium bromide.[92]

Formation of the protected open-chain nitrone intermediate **2.101D** was achieved from tribenzylated D-arabinose **2.100D**. This intermediate could then either undergo: (i) cyclisation by mesylation and subsequent intramolecular $S_N2$-displacement to form the nitrone **2.103L** with inversion of configuration at C4; or (ii) a double inversion with iodine and triphenylphosphine - *via* a C4-iodo-intermediate - to form the C4-epimeric nitrone **2.102D** with overall retention of configuration. Thus two nitrones were formed from one starting material. This paper demonstrates another example of the possible divergent synthesis of multiple pyrrolidine targets from a single starting material, where nitrone **2.102D** could be utilised to synthesise both the pyrrolidine DMDP **1.8D** and also DGDP **1.30D**. If all eight stereoisomeric nitrones were accessed from the four pentoses - D-arabinose, D-lyxose, D-ribose and D-xylose - this would then give potential access to every pyrrolidine stereoisomer. This paper also aptly demonstrates the

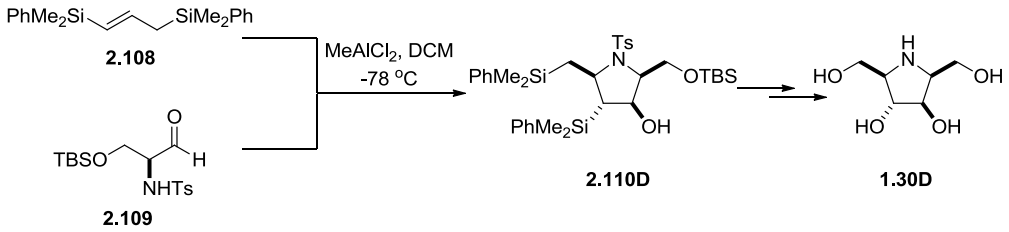
use of truncation in order to access pyrrolidine targets (**Scheme 2.17**). The alkene **2.104D** gained by addition of vinylmagnesium bromide to the cyclic nitrone **2.102D** underwent reduction in order to cleave the hydroxyamine functionality, with Boc protection giving the protected seven-carbon alkene **2.106D**. Truncation was afforded by ozonolysis with subsequent sodium borohydride reduction, with global deprotection giving the six-carbon pyrrolidine DMDP **1.8D**.[92] Truncation has been employed in very few cases of pyrrolidine formation, with this being the sole case of the use of ozonolysis to afford this transformation. Typically, vicinal diol cleavage is used to truncate a seven-carbon sugar backbone. For example, lead(IV) tetraacetate has been utilised in the synthesis of DADP **2.59D** by Saotome *et al*,[97] but more commonly sodium periodate is used for this purpose, such as in the synthesis of L-DMDP **1.8L**,[98] DGADP **2.60**[99] and DGDP **1.30D**.[52]




**Scheme 2.17**. The employment of truncation to access a pyrrolidine iminosugar.[92]

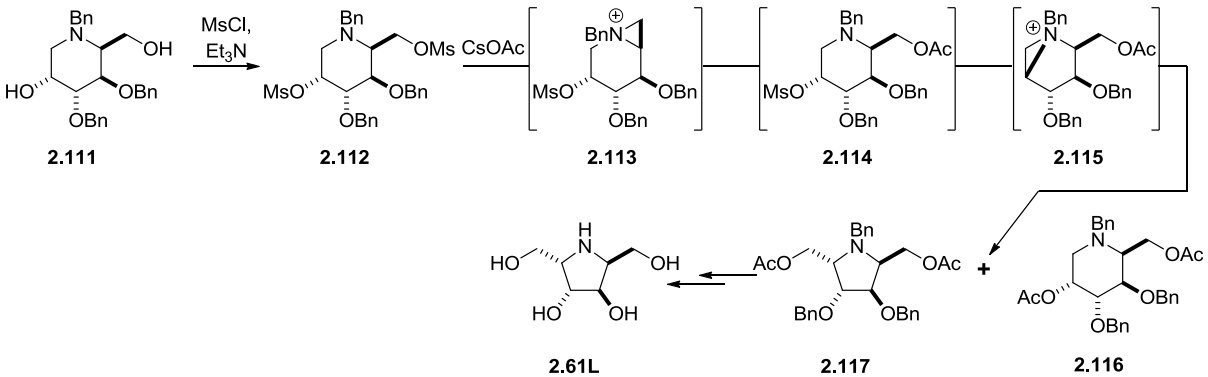
Beyond the more common and general six methods discussed above, pyrrolidines have also been accessed by a range of other miscellaneous methods. One such method employed by Wang *et al* relied on the simple interconversion of one pyrrolidine into another by chemical means. Here DGDP **1.30D** was converted to DGADP **2.60**.[76] The majority of the remaining miscellaneous syntheses have all been asymmetric in nature. Donohoe and co-workers used stereoselective reductions and hydroxylations in order to access DMDP **1.8D**, *meso-allo* **2.60** and DGDP **1.30D** from a pyrrole diester derivative.[100,101] Ring-closing metathesis (RCM) followed by selective *trans*-dihydroxylation was employed by Trost *et al* in order to access DMDP **1.8D**.[102] And finally, Restorp and colleagues formed DGDP **1.30D** by a stereoselective [3+2]-annulation of

silane **2.108** with *N*-tosyl-α-aminoaldehyde **2.109** to form the five-membered ring **2.110D**, with final deprotection affording DGDP **1.30D** (**Scheme 2.18**).[103,104]




**Scheme 2.18**. [3+2] Annulation affording DGDP **1.30D** stereoselectively.[103,104]

One final and interesting synthesis of pyrrolidines concerns the isomerisation of six-membered piperidines to form DMDP **1.8D** and L-DIDP **2.61L**.[105,106] For example, in the case of L-DIDP **2.61L**, a suitably protected piperidine **2.111** is taken and treated with mesyl chloride in the presence of triethylamine to afford the dimesylate **2.112** (**Scheme 2.19**). Subsequent treatment with caesium acetate leads to intramolecular displacement of the primary triflate, forming a bicyclic aziridine intermediate **2.113**, which is opened by an acetate nucleophile to form the mono-mesylate **2.114**. Subsequent and slower intramolecular displacement of the secondary mesylate forms a bicyclic aziridine intermediate **2.115**, which either undergoes opening with acetate at C2 to form the piperidine **2.116**, or at C1, which leads to the formation of the ring-contracted pyrrolidine **2.117**. Final deprotection then yields the target L-DIDP **2.61L**.




**Scheme 2.19**. Isomerisation of piperidine **2.111** to form L-DIDP **2.61L**.[105,106]

It can be seen from the summary of previous syntheses that every stereoisomeric pyrrolidine has been accessed synthetically during the last forty years. However, there has never been a single definitive method that has been applied to the access of every stereoisomer. This is due to the fact that the majority of syntheses focus on accessing a single pyrrolidine, commonly either DMDP **1.8D** or DGDP **1.30D**, from a single starting material. Given the excellent biological activity demonstrated by the three natural stereoisomers (Section 2.3.1, page 68) there is a distinct need to compare the activity of the remaining pyrrolidines. Therefore, it is evident from this that there is also a requirement to develop a robust methodology that permits access to every stereoisomer from readily available starting materials - and if the optimum starting material were utilised, this may indeed be possible *divergently* from a single starting material.

2.3.2.2 Divergency: one starting material to ten pyrrolidine targets

Divergency in the synthesis of target compounds makes for a powerful strategy. The use of methods to epimerise, or induce opposing chirality at different stereocentres allows the utilisation of common starting materials which has three main benefits: (i) access to a wider range of isomeric compounds allows the analysis of a greater range of biological data and the derivation of a structure-activity relationship; (ii) divergency bypasses the potential limitation of expensive "unnatural" starting materials in synthesis; (iii) very often syntheses which are developed may be applied to an epimeric system without a great degree of optimisation or alteration. So, by a divergent route, a greater number of epimeric targets may be accessed in a shorter time frame. The effectiveness of divergency has not however been exploited to its full potential in synthesis of the pyrrolidines. Only two examples stand-out, and these were published by Singh *et al* in 2004 (**Scheme 2.10**, page 71),[60] and by Tsou and co-workers in 2009 (**Schemes 2.16** & **2.17**, pages 77-78).[92] The former synthesised four pyrrolidine stereoisomers asymmetrically from a single achiral olefin, and reasonably proposed that the synthesis of the

remaining targets would also be accessible from this starting material. The latter uses four starting pentoses - D-arabinose, D-lyxose, D-ribose and D-xylose - to access eight cyclic nitrones, which may then be utilised to afford the ten pyrrolidines. These papers show the possible efficacy of a divergent methodology, however in the former case the synthesis remains uncompleted, and in the latter, four starting materials are employed rather than an ideal one. Therefore there is indeed motivation to devise a definitive synthesis leading divergently to these targets from a single starting material, which would also lead to the first and definitive side-by-side biological evaluation.

2.3.2.3 Divergency: two classes of targets

When considering the concept of divergency in synthesis it has two applications: the first discussed above, which allows access to multiple stereoisomeric targets from common intermediates; and the second which permits access to different functionalities - a more widely employed technique. This latter consideration allows for potential pharmacological activity against different biological targets. In the context of this thesis **Chapter 1** (Section 1.5, pages 13-23) identified two classes of glycosidase targets - simple glycosidases, and hexosaminidases - and the differing biological motivation for developing novel inhibitors of them. The naturally occurring pyrrolidines have already demonstrated inhibition of the former class of enzymes, but as highlighted earlier in this chapter (Section 2.2.1, pages 51-54) there are very few known examples of the potent and selective inhibition of the latter class - the hexosaminidases. In this section three known pyrrolidine-based inhibitors were identified, all of which contained an acetamido-moiety as a mimic of that contained by GlcNAc **2.17** and GalNAc **2.18** residues (**Figure 2.8**). It is evident then that divergent access to a second class of inhibitors would be worthwhile given that hexosaminidase enzymes may be important biological targets.

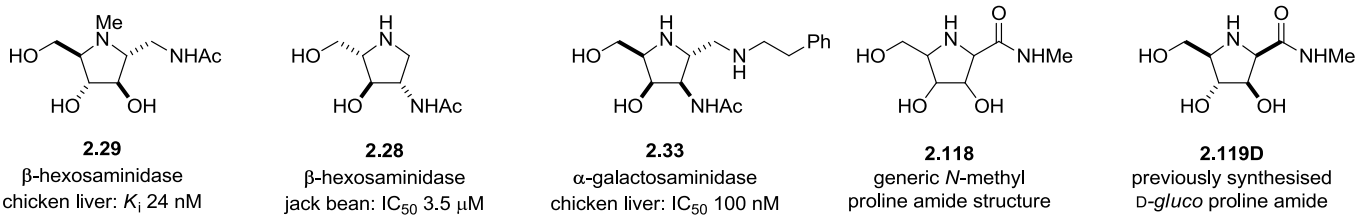
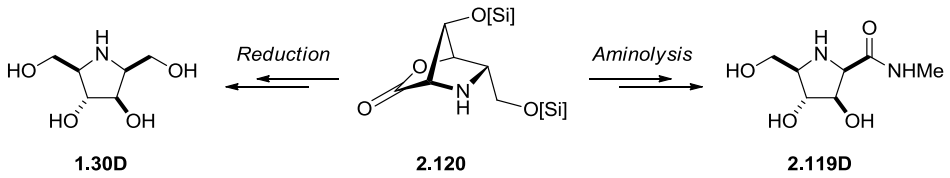



**Figure 2.8**. Known pyrrolidine hexosaminidase inhibitors;[25,26,30] the target amide structure **2.118**; and the only known *N*-methyl proline amide **2.119D**.

In terms of the structure of the target selected for this project, the *N*-methyl proline amide structure **2.118** (**Figure 2.8**) was chosen for two reasons. Firstly, hydroxyl and amide functionalities may be simply and divergently obtained from a common ester intermediate by reduction or aminolysis, respectively. This was demonstrated in the synthesis of the only known compound of this class, the D-*gluco*-configured proline amide **2.119D** (**Scheme 2.20**). Long *et al* utilised a late-stage divergent lactone intermediate **2.120** to access both the pyrrolidine DGDP **1.30D**, and also the proline amide **2.119D**.[53] However, the biological profile of this amide was not obtained. Secondly, it is envisaged that this amide functionality would resemble the 1-acetamido group of the inhibitor **2.29**, which has demonstrated very potent inhibition.



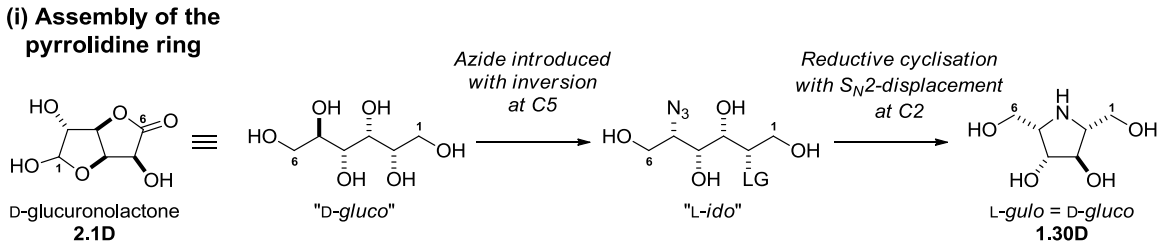

**Scheme 2.20**. The synthesis of a pyrrolidine and a proline amide *via* a divergent lactone intermediate.[53]

## 2.3.3 Project Aims

The preceding sections have identified both the motives for and the targets to be accessed divergently from a single starting material. The following sections will detail the synthetic strategy, the synthesis conducted to obtain the targets, and the subsequent biological evaluation of both target classes against a panel of glycosidases and hexosaminidases.

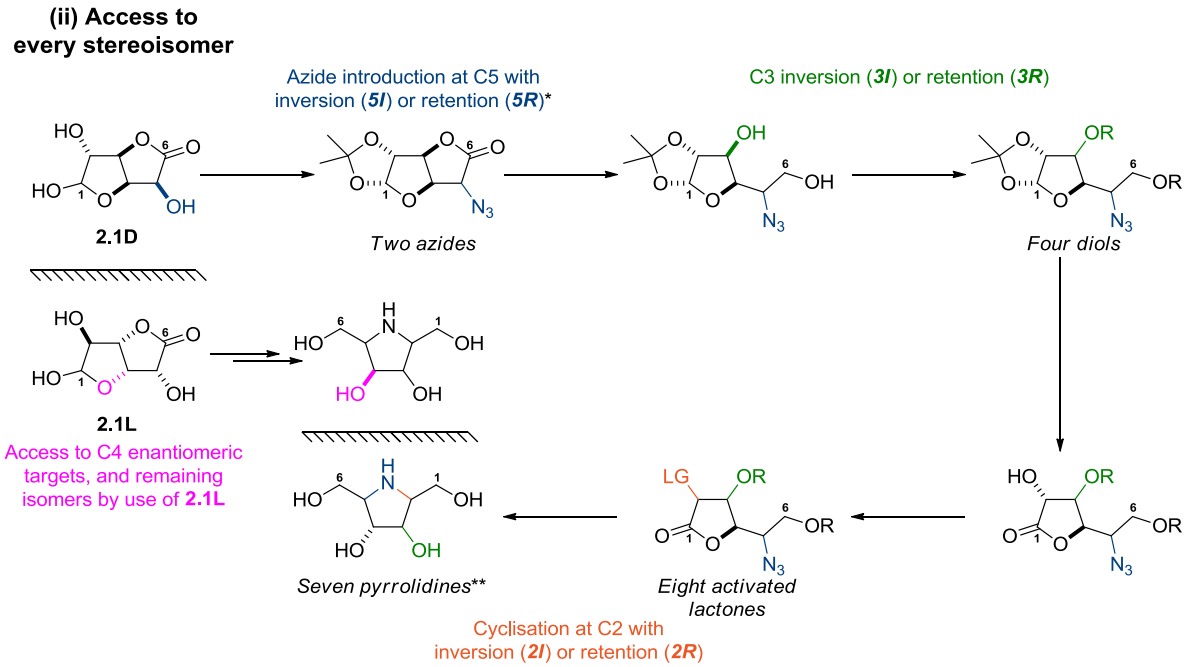
2.3.4 Synthetic Strategy

With the motivation for developing a robust and divergent synthetic pathway to the pyrrolidines from a single starting material identified, this section of the thesis describes the strategy envisaged to achieve this from glucuronolactone. It was also anticipated that the use of a late-stage intermediate would permit divergent access to an additional class of molecule - the proline amides. With this aim in mind there were three main considerations: (i) the method for assembly of the 2,5-iminohexitol scaffold from glucuronolactone (**Scheme 2.21**); (ii) the processes for manipulating hydroxyl-configurations in order to access every stereoisomer (**Scheme 2.22**); (iii) the utilisation of a late-stage divergent intermediate to allow access to both the pyrrolidine and proline amide classes (**Scheme 2.23**).




**Scheme 2.21**. Assembly of the pyrrolidine ring from D-glucuronolactone.

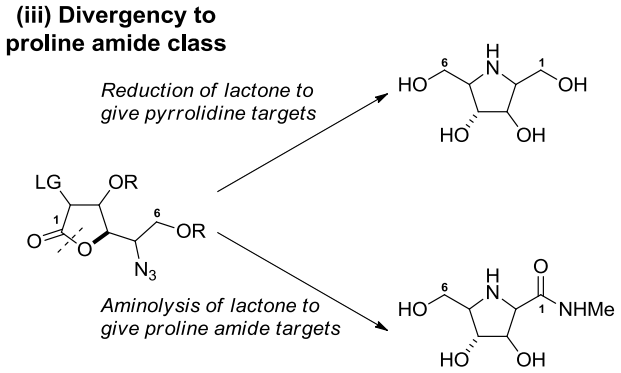
The simplest method for formation of the pyrrolidine ring with complete and reliable stereocontrol is by two $S_N2$-displacements at C2 and C5 by nitrogen. It was proposed that this would be accomplished by utilising similar intermediates to those from in the synthesis of DGJNAc **2.20D** (Section 2.2.3, page 56-62). This synthesis demonstrated that azide may be introduced efficiently and stereospecifically at C5 by $S_N2$-displacement. From here simple protecting group manipulation could be used to enable the selective activation of the C2-hydroxyl, allowing a second $S_N2$-displacement upon azide reduction and the formation of the desired iminosugar ring to occur (**Scheme 2.21**).




**Scheme 2.22**. Manipulation of hydroxyl-configuration to access every stereoisomer.
[*In this chapter the 'inversion' or 'retention' of each of the C2, C3 and C5 stereocentres will be described by the shorthand '**I**' or '**R**'; **the degeneracy of D-gluco/L-gulo configurations result in seven pyrrolidines being accessed from eight activated lactones]*

In order to access every stereoisomer, manipulation of each stereocentre of D-glucuronolactone **2.1D** would be required. It was proposed that this could be achieved by the sequential and selective manipulation of each of the C2, C3 and C5 hydroxyls, and by utilisation of L-glucuronolactone **2.1L** which would give access to both C4 configurations (**Scheme 2.22**). The synthesis of DGJNAc **2.20D** had already demonstrated the introduction of azide at C5 with inversion of the C5-configuration (herewith abbreviated as ***5I***), introduction with retention (***5R***) would access the required C5-epimeric configurations. The previous synthesis of DGJNAc **2.20D** also showed that the stereospecific reduction of a prochiral C3-ketone allows for inversion of the C3-hydroxyl (***3I***), while omitting this process affords retention (***3R***). From here it is proposed that C1 should be oxidised to a lactone functionality for three main reasons; (i) this would act as a protecting group for C1 during the activation of the C2-hydroxyl; (ii) this establishes a carbonyl moiety α to the leaving group at C2 - stabilising the transition state of the $S_N2$-displacement (***2I***). Given the similarity between this position and C5 earlier in the synthesis

(both α to a lactone) identical manipulation could be potentially employed to give an overall retention of C2 (***2R***); (iii) the reduction or aminolysis of this lactone moiety would permit the divergent access to the desired pyrrolidine and proline amide classes respectively (**Scheme 2.23**).




**Scheme 2.23**. Divergent lactone intermediate.

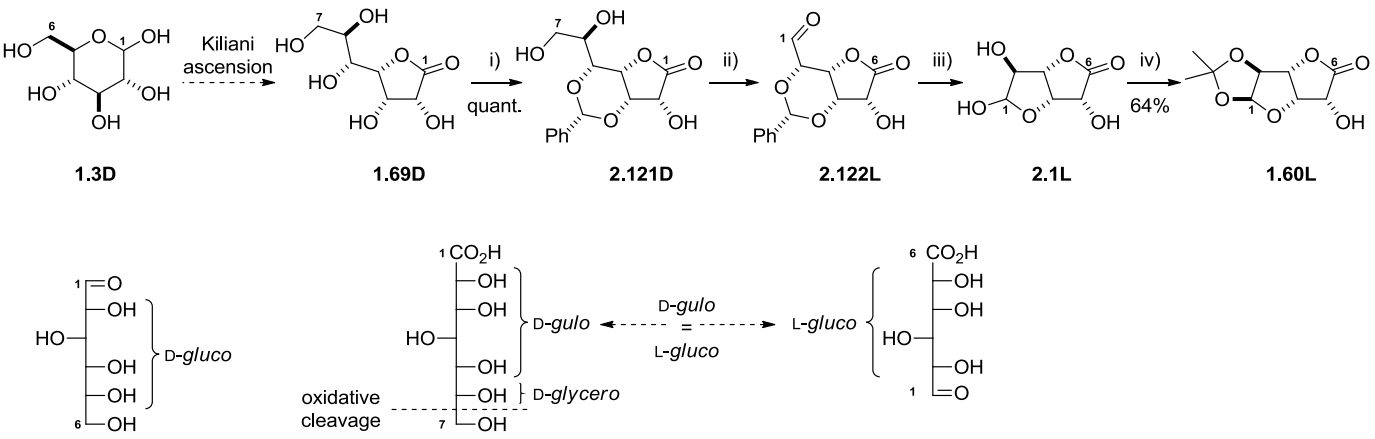
With the general strategy outlined, successful development of the synthetic methodology would thus give access to every stereoisomer of both the pyrrolidine and proline amide iminosugar classes. This would ultimately furnish the first methodology for the global access to these classes of molecule from a single pair of readily available starting materials - both derived from D-glucose (Section 2.3.5.1, pages 86-87) - and allow for a definitive and comparative side-by-side investigation into their biological profiles.

2.3.5 Synthesis

The work in this project, and hence this section of the thesis, can be divided into five distinct subsections; (i) the necessary large-scale synthesis of the "unnatural" enantiomeric starting material L-glucuronolactone **2.1L** (Section 2.3.5.1); (ii) the synthesis of the *gulo*-configured (***2I-3R-5I***) iminosugar targets - the simplest route from glucuronolactone (Section 2.3.5.2, page 88); (iii) the expansion of the methodology to the C5-epimeric system, *manno* (***2I-3R-5R***) (Section 2.3.5.3, page 91); (iv) C3-inversion leading to *galacto* (***2I-3I-5I***) and *altro* (***2I-3I-5R***) systems (Section 2.3.5.4, page 95); (v) the extension of these four previous routes by the net retention of the C2-configuration in order to access the remaining configurations - *ido* (***2R-3R-5I***), *gluco* (***2R-3R-5R***), *talo* (***2R-3I-5I***) and *allo* (***2R-3I-5R***) (Section 2.3.5.5, page 105).

*2.3.5.1 Synthesis of L-glucuronolactone **2.1L***

Access to L-glucuronolactone **2.1L** was afforded by the utilisation of a procedure initially published by Sowa,[107] but developed more recently into a large-scale process by Weymouth-Wilson *et al* of Dextra Laboratories Ltd.[108] This synthesis makes use of the cheap starting material D-glucoheptonolactone **1.69D** - which is itself produced by the highly Felkin-Ahn diastereoselective Kiliani ascension of D-glucose **1.3L** (**Scheme 2.24**).[109] D-glucoheptonolactone **1.69D** may be less ambiguously and more systematically named D-*glycero*-D-*gulo*-heptono-1,4-lactone, and it is within this name that the approach of this strategy can be seen. This molecule possesses a D-*gulo* structural motif within the seven-carbon structure, which as indicated in Section 2.3.1 (page 67), when viewed in reverse, is equivalent to the desired L-*gluco* configuration. So, conceptually, cleavage of C7 would ultimately give rise to the L-*gluco*-configured L-glucuronolactone **2.1L**.

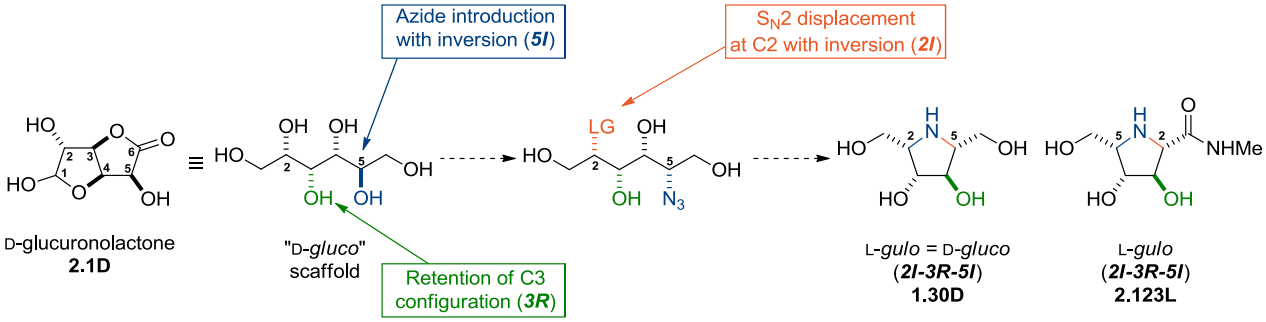



**Reagents & conditions**: i) PhCHO, HCl, RT, 3 h; ii) $NaIO_4$, $THF/H_2O$, 40 °C, 90 min; iii) $TFA/H_2O$, 45 °C, 80 min; iv) acetone, $H_2SO_4$, RT, 3 h.

**Scheme 2.24**. Synthesis of L-glucuronolactone.

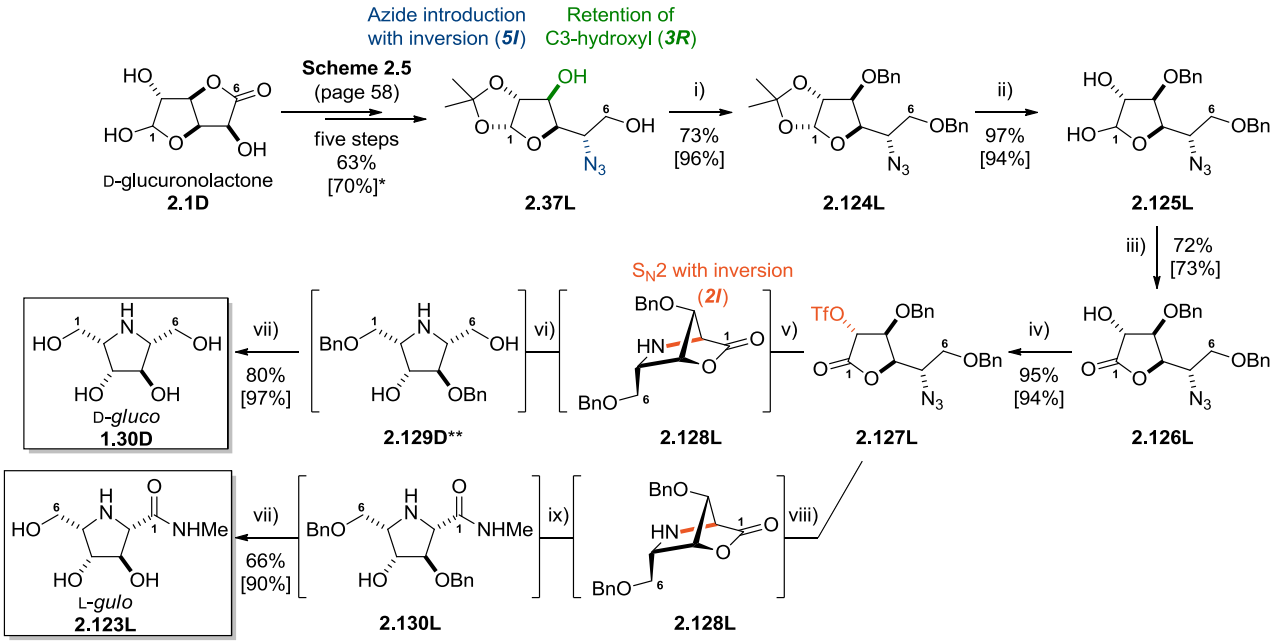
D-glucoheptonolactone **1.69D** was protected as the 3,6-benzylidene acetal **2.121D** by reaction with benzaldehyde and sulfuric acid in a mechanically-stirred reactor, which afforded the benzylidene **2.121D** quantitatively.[110] Subsequent cleavage between C6 and C7 was achieved with sodium periodate, with the internal temperature carefully maintained below 40 °C by use of a cooled reactor vessel. This afforded the truncated aldehyde intermediate - benzylidene-protected L-glucuronolactone **2.122L**, which now possessed the desired L-*gluco*-configuration.[107] The benzylidene group was removed by heating aldehyde **2.122L** in aqueous trifluoroacetic acid, which afforded crude L-glucuronolactone **2.1L**. Recrystallisation at this stage proved unsuccessful, so the crude lactone **2.1L** was protected as the acetonide **1.60L** in order to purify the product by chromatography. Reaction of the crude lactone **2.1L** with acetone in the presence of sulfuric acid gave the desired 1,2-acetonide **1.60L**, which with medium-pressure chromatography afforded the pure 1,2-acetonide **1.60L** in 64% yield over four steps from D-glucoheptonolactone **1.69D**. This efficient synthesis allowed access to 125 grams of protected L-glucuronolactone **1.60L**, with only a single purification step at the end of the sequence. With this enantiomeric starting material in hand synthetic work towards the iminosugar targets could proceed.

### *2.3.5.2 Synthesis of gulo-configured iminosugars (**2I-3R-5I**)*




**Scheme 2.25**. Conceptual strategy to the iminosugars *via* the "*gulo*-" synthetic route.

The synthetic route to the *gulo*-configured pyrrolidine and proline amide targets constitutes the shortest potential sequence to these classes of iminosugar from glucuronolactone. This is due to the fact that the only changes in stereocentre configuration arise from the two $S_N2$-displacements at C2 and C5 required to form the iminosugar ring (**Scheme 2.25**).




**Reagents & conditions**: i) NaH, BnBr, DMF, -10 °C to RT, 17 h; ii) *p*TSA, 1,4-dioxane/water, 80 °C, 2.5 h; iii) $I_2$, $K_2CO_3$, $^t$BuOH, 100 °C, 2 h; iv) $Tf_2O$, pyr, DCM, -40 °C, 1 h; v) $H_2$, Pd/C, EtOH, RT, 1 h; vi) *then* add $NaBH_4$, RT, 16 h; vii) *then* add 2 M HCl(aq), $H_2$, Pd/C, RT, 18-20 h; viii) $H_2$, Pd/C, 1,4-dioxane, RT, 1.5 h; ix) *then* add $MeNH_2$, RT, 16 h.

**Scheme 2.26**. Synthesis of iminosugar targets by the "*gulo*-" route.

* The enantiomeric syntheses will not be discussed directly in this chapter - the reactions were conducted under similar reaction conditions on similar scales - the yields are quoted in parentheses ([%]) in this chapter and the appropriate enantiomeric data quoted in the experimental section.

** Alditol degeneracy leads to this compound systematically being D-*gluco* in configuration rather than L-*gulo*.

The synthesis of DGJNAc **2.20D** (Section 2.2.3, pages 56-62) demonstrated the stereospecific introduction of azide at C5 of the glucuronolactone scaffold with inversion of configuration (***5I***), and subsequent, careful, reduction of the lactone ring affording the *ido*-diol **2.37L** in excellent yield over five steps (63%, [70% for the enantiomeric system from L-glucuronolactone **2.1L]**). The *ido*-diol **2.37L** possessed the required 'retained' C3-hydroxyl configuration (***3R***) and therefore could undergo suitable protecting group manipulation prior to the iminocyclisation step. Thus, the diol motif was protected as the dibenzyl ether by reaction of the diol **2.37L** with excess benzyl bromide and sodium hydride, affording the fully protected acetonide **2.124L** in good yield (73%, [96%]). In order to convert fully protected **2.124L** into the desired lactone **2.126L**, the 1,2-acetonide was hydrolysed with *para*-toluenesulfonic acid (*p*TSA) which gave a mixture of the lactols **2.125L** (97%, [94%]). Subsequent chemoselective oxidation was achieved with iodine in the presence of potassium carbonate to give the lactone **2.126L** (72%, [73%]). The oxidation protocol of iodine/potassium carbonate[111] was used here in place of the more typical bromine/barium carbonate[112,113] for two main reasons; the first is that the bromine could lead to substantial benzyl ether cleavage,[114] with non-trivial optimisation of these conditions required.[115] Secondly, the solvent for bromine oxidations is typically water, whereas the *tert*-butanol employed in the iodine case was far more preferable for the substrate of this reaction given its solubility.

The lactone functionality was thus installed at C1 - which would afford both the necessary protection of C1 during C2-activation, and also the divergent access to both desired classes of iminosugar targets. So, triflate was chosen as the most suitable, and reactive, leaving group for C2 - akin to the azide displacement at the C5-triflate conducted earlier in the synthetic sequence. The lactone **2.126L** underwent esterification with trifluoromethanesulfonic anhydride and

pyridine in DCM at -40 $^{o}$C to afford the triflate **2.127L**. The compound proved quite stable and amenable to isolation by column chromatography (95%, [94%]).

In order to access the first target, pyrrolidine **1.30D**, the triflate **2.127L** was reduced in the presence of hydrogen and palladium on carbon (10%), with spontaneous cyclisation *via* $S_N2$-displacement of the C2-triflate (***2I***) forming the intermediate iminobicycle **2.128L**. The crude iminobicycle **2.128L** was highly-strained ($\nu_{max}$ 1822 cm$^{-1}$) and hence not amenable to purification, however the crude material was characterised by NMR and IR spectroscopy. The crude reaction mixture was filtered and sodium borohydride added to the filtrate to facilitate the reduction of the lactone ring. This resulted in successful formation of the monocyclic dibenzyl intermediate **2.129D**, which due to the degeneracy of alditol structures is now systematically of D-*gluco*-configuration despite being produced by this L-*gulo* synthetic route.[45] Aqueous hydrochloric acid, palladium on carbon and an atmosphere of hydrogen were added to the reaction mixture to affect the acidic hydrogenolysis of the benzyl ethers. This afforded the target D-*gluco* pyrrolidine (DGDP) **1.30D** in good yield (80%, [97%]). Overall, DGDP **1.30D** was accessed in 24% yield over twelve steps from D-glucuronolactone **2.1D** [42%].*

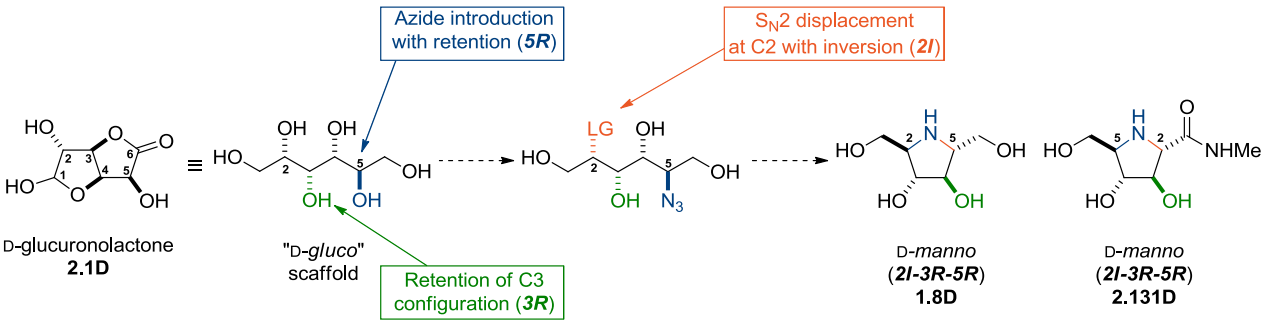
The second target, the L-*gulo* proline amide **2.123L**, was accessed in a similar fashion. The iminobicycle **2.128L** was formed by hydrogenolysis - with the use of 1,4-dioxane as the solvent. Ethanol was used previously due to it being preferable in the formation of the dibenzylated piperidine **2.129D** by reduction. Filtration of the crude reaction mixture removed the palladium on carbon, and methylamine was added to elicit aminolysis of the lactone ring. This formed the crude monocyclic amide **2.130L** which underwent acidic hydrogenolysis, as previously

* The synthesis from triflate **2.127L** to D-*gluco* pyrrolidine **1.30D**, and to L-*gulo* proline amide **2.123L** was conducted by Nigel Ngo (Part II student, 2010/11) and is included here for comparison.

described, to afford the desired L-*gulo* proline amide **2.123L** (66%, [90%]) in 20% over twelve steps from D-glucuronolactone **2.1D** [39%].

With the successful isolation of both desired pyrrolidine and proline amide targets by the "*gulo*-" route (***2I-3R-5I***), the core methodology for this project was established. The following section presents the extension of this methodology to the "*manno*-" route (***2I-3R-5R***) by retention of configuration at C5 (***5R***).

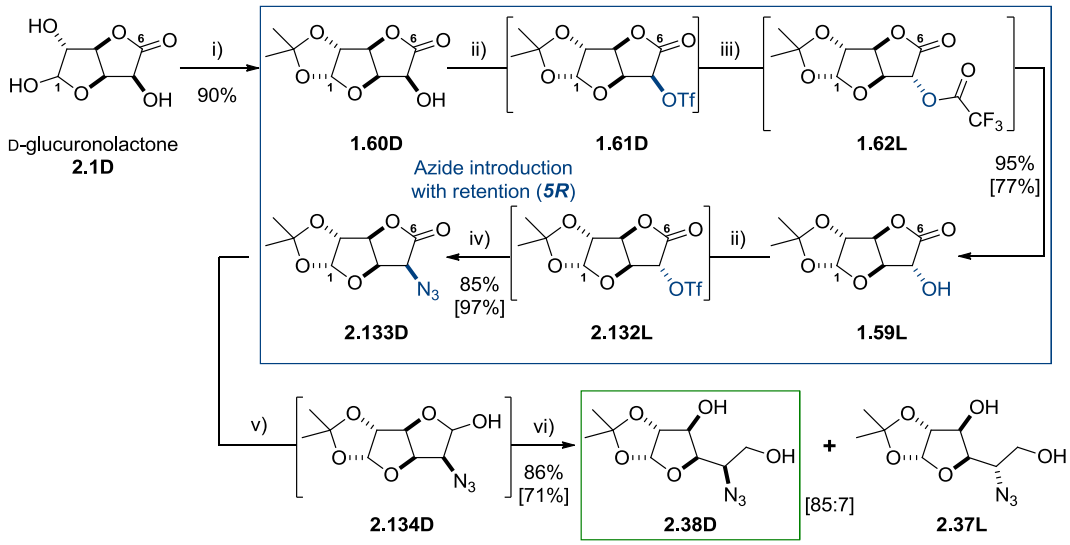
### *2.3.5.3 Retention of C5 (**5R**): the extension to manno-configured iminosugars (**2I-3R-5R**)*




**Scheme 2.27**. Conceptual strategy to the iminosugars *via* the "*manno*-" synthetic route.

With the establishment of the basic methodology in the preceding route, this project could then undergo the expansion required to access the remaining iminosugars targets. The first such extension to be examined was in the 'retention' of the configuration at C5 (***5R***). This would give access to *manno*-configured targets (**Scheme 2.27**). It was envisaged that this would entail minor modification of the "*gulo*-" methodology in order to access a retained configuration of C5 (***5R***). Due to the ease with which $S_N2$-displacement had been utilised to access the C5-inverted azide **2.35L** (***5I***) it was proposed that two sequential inversions, firstly with an oxygen-based nucleophile[116] (Section 1.6.2.1, page 31) and secondly with azide would furnish the net-retained configuration of C5 (***5R***).[2]

So, as conducted previously D-glucuronolactone **2.1D** was protected as the 1,2-acetonide and activated by triflation at C5 (Section 2.2.3, page 57). The crude triflate **1.61D** was treated with sodium trifluoroacetate forming the intermediate trifluoroacetic ester **1.62L** (**Scheme 2.28**). On basic work-up this labile ester was hydrolysed, forming the C5-inverted L-iduronolactone **1.59L** (95% [77%]).[116] This lactone **1.59L** underwent C5-activation, again by triflation under the usual conditions, and this intermediate triflate **2.132L** was treated with sodium azide to afford the net-retained (***5R***) azido-lactone **2.133D** in excellent yield (85% [97%]).[2]

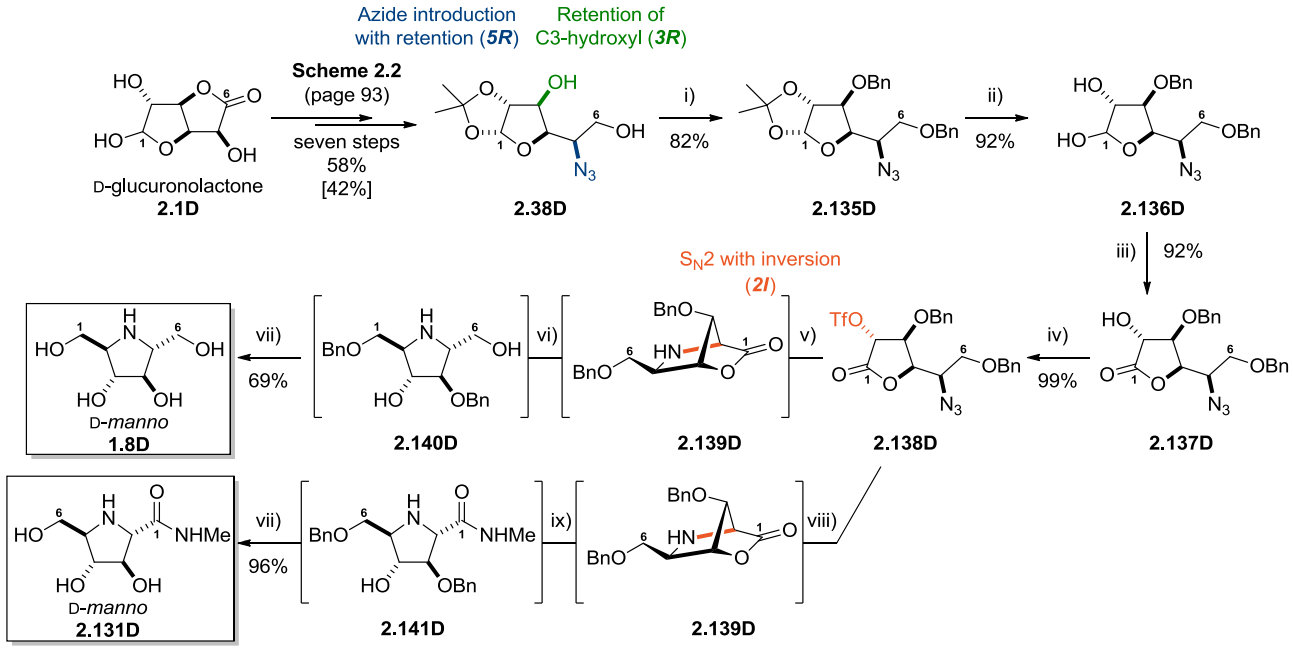



**Reagents & conditions**: i) acetone, $H_2SO_4$, RT, 4 h; ii) $Tf_2O$, pyr, DCM, -40 °C, 1 h; iii) $NaCO_2CF_3$, DMF, RT, 2 h; iv) $NaN_3$, DMF, -30 °C, 2 h; v) DIBAL-H, DCM, -78 °C, 1.5 h; vi) $NaBH_4$, MeOH, -30 °C, 2 h.

**Scheme 2.28**. Introduction of nitrogen at C5 with net-retention (***5R***) by two $S_N2$-displacements.

The use of the sequential $S_N2$-displacements to afford net-retention was found to be the optimal strategy. Alternatively base-catalysed equilibration of the inverted azide **2.35L** would potentially afford the retained azide **2.133D**, especially as this latter compound is the thermodynamically favoured one. It would appear that this method would present a shorter and more efficient route, however in this case base-catalysed epimerisation has previously only returned a 65% yield in a 6:1 ratio in favour of the thermodynamic azide **2.133D**,[117] and as such is lower yielding than the double-$S_N2$ strategy utilised in this project.

The *gluco*-azide **2.133D** was taken, and in an analogous fashion to the C5-epimeric azide, was reduced to the desired diol **2.38D** with a careful two-step protocol *via* the lactols **2.134D**. Initial DIBAL-H reduction of the azide **2.133D** at -78 °C afforded the crude lactols **2.134D**, which were treated with sodium borohydride at -30 °C to afford the diol **2.38D** in a 79% yield over two steps [63%]. This diol possessed the required 'retained' configuration of C3 (***3R***) and thus could undergo final protecting group manipulation prior to iminocyclisation.




**Reagents & conditions**: i) NaH, BnBr, DMF, -10 °C to RT, 1.5 h; ii) *p*TSA, 1,4-dioxane/water, 90 °C, 2.5 h; iii) $I_2$, $K_2CO_3$, $^t$BuOH, 100 °C, 4 h; iv) $Tf_2O$, pyr, DCM, -40 °C, 1 h; v) $H_2$, Pd/C, EtOH, RT, 1 h; vi) *then* add $NaBH_4$, RT, 16 h; vii) *then* add 2 M HCl(aq), $H_2$, Pd/C, RT, 16 h; viii) $H_2$, Pd/C, 1,4-dioxane, RT, 1.5 h; ix) *then* add $MeNH_2$, RT, 16 h.

**Scheme 2.29**. Synthesis of the *manno* targets.[47]

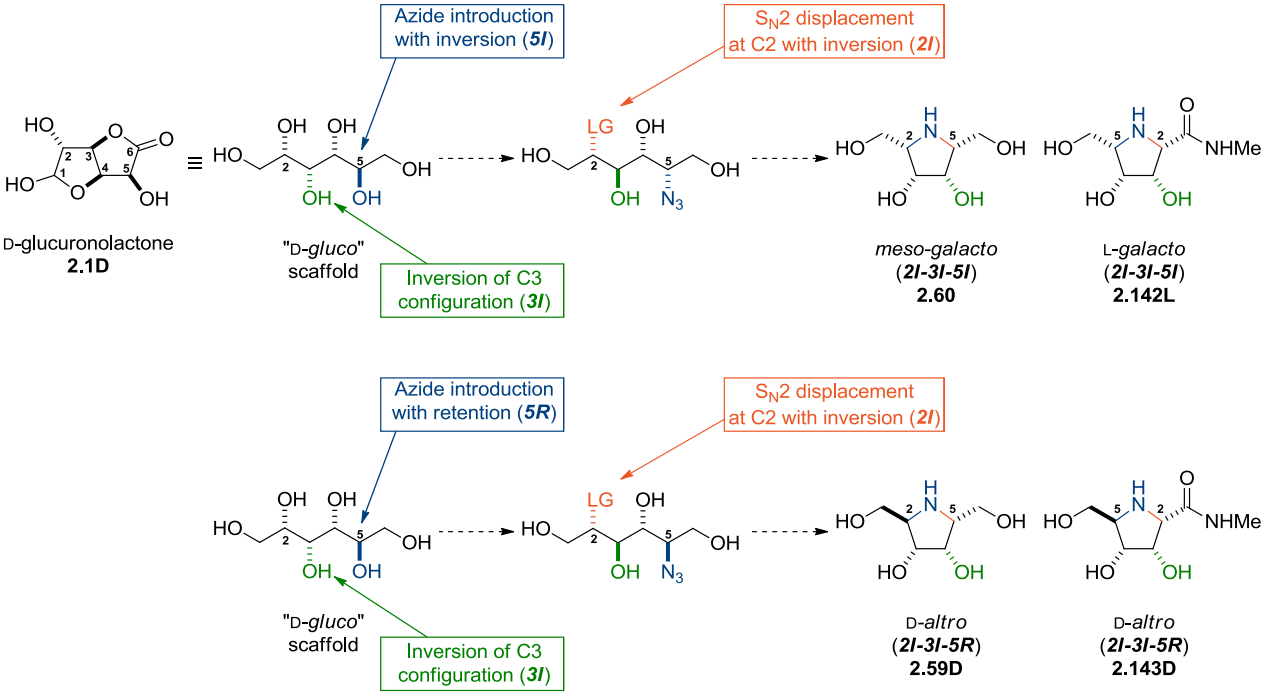
Further work from this diol **2.38D** to the targets was conducted by Dr. Dan Best and Dr. Sarah Jenkinson, and the synthetic work is described here for the purpose of comparison.

In an identical fashion to the previous "*gulo*-" route, the diol **2.38D** was taken and treated with benzyl bromide and sodium hydride to afford the dibenzyl ether **2.135D** (82%) (**Scheme 2.29**). This fully protected compound was hydrolysed in order to remove the 1,2-acetonide -

accomplished with *p*TSA in 1,4-dioxane/water at 90 $^{o}$C. This gave the lactols **2.136D** (92%). This mixture of anomers was chemoselectively oxidised with iodine in the presence of potassium carbonate to the lactone **2.137D** in a 92% yield, with this lactone now possessing the protecting pattern compatible with the desired iminocyclisation. The free C2-hydroxyl was activated by esterification with trifluoromethanesulfonic anhydride in the usual fashion to afford triflate **2.138D** (99%). In order to access the pyrrolidine DMDP **1.8D** the triflate **2.138D** was taken and reduced by hydrogenolysis in the presence of palladium on carbon (10%), with spontaneous cyclisation by $S_N2$-displacement of the C2-triflate leaving group forming the iminobicyclic intermediate **2.139D**. The reaction mixture was filtered and sodium borohydride added to the filtrate in order to reduce the lactone ring and afford the monocyclic dibenzylated intermediate **2.140D**. Acidic hydrogenolysis afforded the target DMDP **1.8D** (69% over three steps) in an overall yield of 27% over fourteen steps from D-glucuronolactone **2.1D**. In an identical reaction sequence the D-*manno* proline amide **2.131D** was formed from the triflate **2.138D** in 96% yield over three steps. Thus the target amide **2.131D** was afforded in 38% yield over fourteen steps from D-glucuronolactone **2.1D**. The L-*manno* pyrrolidine, L-DMDP, **1.8L** and proline amide **2.131L** were also accessed from L-glucuronolactone **2.1L** in similar overall yields.

With the "*manno*-" (***2I-3R-5R***) configured targets successfully accessed by expanding the initial methodology to a "retained" configuration at the C5 centre (***5R***), the next section presents the further extension of the methodology with the "inversion" of the C3-hydroxyl (***3I***).

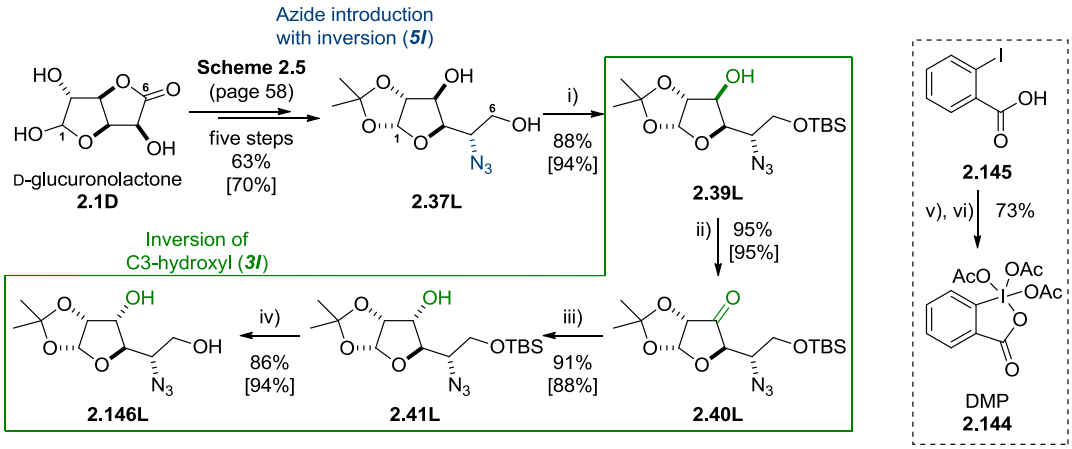
*2.3.5.4 Inversion of C3 (**3I**): expansion to the galacto- (**2I-3I-5I**) & altro-configurations (**2I-3I-5R**)*




**Scheme 2.30**. Conceptual strategy to iminosugars *via* the "*galacto*-" and "*altro*-" synthetic routes.

With both "*gulo*-" (***2I-3R-5I***) and "*manno*-" (***2I-3R-5R***) routes completed by utilisation of both inverted and retained configurations of C5 (***5I*** & ***5R***), the methodology was ready to be further expanded to the "*galacto*-" (***2I-3I-5I***) and "*altro*-" (***2I-3I-5R***) systems by inversion of the C3-hydroxyl (***3I***) (**Scheme 2.30**).

*2.3.5.4.1 The route to galacto- configured targets (**2I-3I-5I**)*

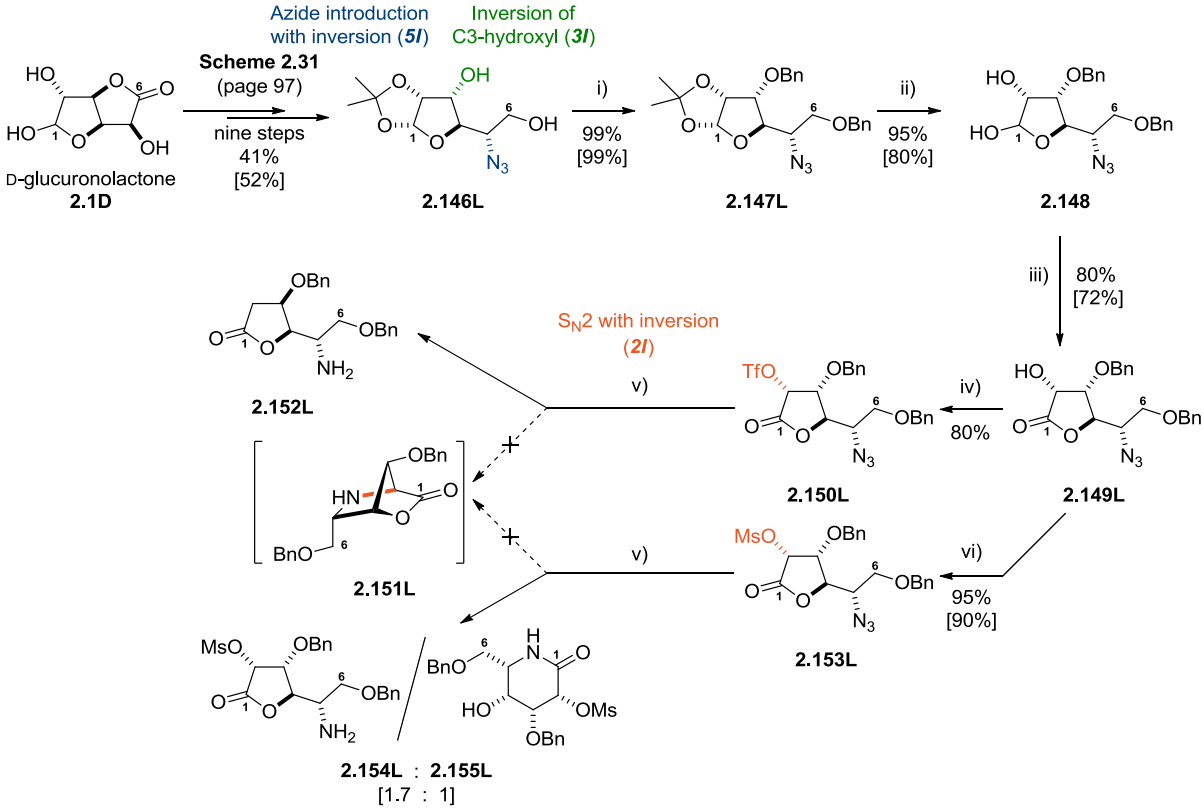



**Reagents & conditions**: i) TBSCl, pyr, RT, 18 h; ii) DMP **2.144**, DCM, 0 $^{o}$C to RT, 4 h; iii) $NaBH_4$(aq), EtOH, 0 $^{o}$C to RT, 1.5 h; iv) TBAF, THF, RT, 2 h; v) Oxone®, $H_2O$, 80 $^{o}$C, 3.5 h, *then* to 0 $^{o}$C, 1.5 h; vi) *p*TSA, $Ac_2O$, 80 $^{o}$C, 3 h, *then* 0 $^{o}$C, 1 h.

**Scheme 2.31**. Towards *galacto*-configured iminosugars.

Previous work in the synthesis of piperidine iminosugar DGJNAc **2.20D** (Section 2.2.3, page 57) demonstrated that the inversion of the C3-hydroxyl of the D-glucuronolactone **2.1D** scaffold may be accomplished by facially selective reduction of a prochiral C3-ketone. Thus, as before, the diol **2.37L**, accessed from D-glucuronolactone **2.1D** in five steps (63%, [70%]), was taken and the primary C6-hydroxyl chemoselectively protected by reaction with TBSCl in pyridine to afford the silyl ether **2.39L** (**Scheme 2.31**). The previous procedure was amended here as it requires a large quantity of hazardous PCC. It was decided that Dess-Martin periodinane (DMP) **2.144**, readily and cheaply accessed from 2-iodobenzoic acid **2.145** by treatment with Oxone® followed by acetic anhydride and *p*TSA (73% over two steps), would serve as a less hazardous oxidant. Thus, alcohol **2.39L** was treated with DMP **2.144** which formed the prochiral ketone **2.40L** (95%, [95%]) in greater yield than previously with PCC. This prochiral ketone **2.40L** underwent facially selective reduction with sodium borohydride forming the inverted C3-alcohol **2.41L** (***3I***) in 91% yield [88%]. Now, diverging from the DGJNAc **2.20D** synthetic pathway, the silyl ether group of compound **2.41L** was removed with tetra-*n*-butylammonium fluoride (TBAF)

in THF forming the diol **2.146L** (86%, [94%]). This diol now possessed the required stereoconfiguration to undergo final protecting group manipulation prior to iminocyclisation.




**Reagents & conditions**: i) NaH, BnBr, DMF, 0 $^{o}$C to RT, 19 h; ii) *p*TSA, 1,4-dioxane/water, 50 $^{o}$C, 2 h; iii) $I_2$, $K_2CO_3$, $^{t}$BuOH, 100 $^{o}$C, 1.5 h; iv) $Tf_2O$, pyr, DCM, -40 $^{o}$C, 1.5 h; v) $H_2$, Pd/C, 1,4-dioxane, RT, 2.5 h; vi) MsCl, pyr, 0 $^{o}$C to RT, 1.5 h.

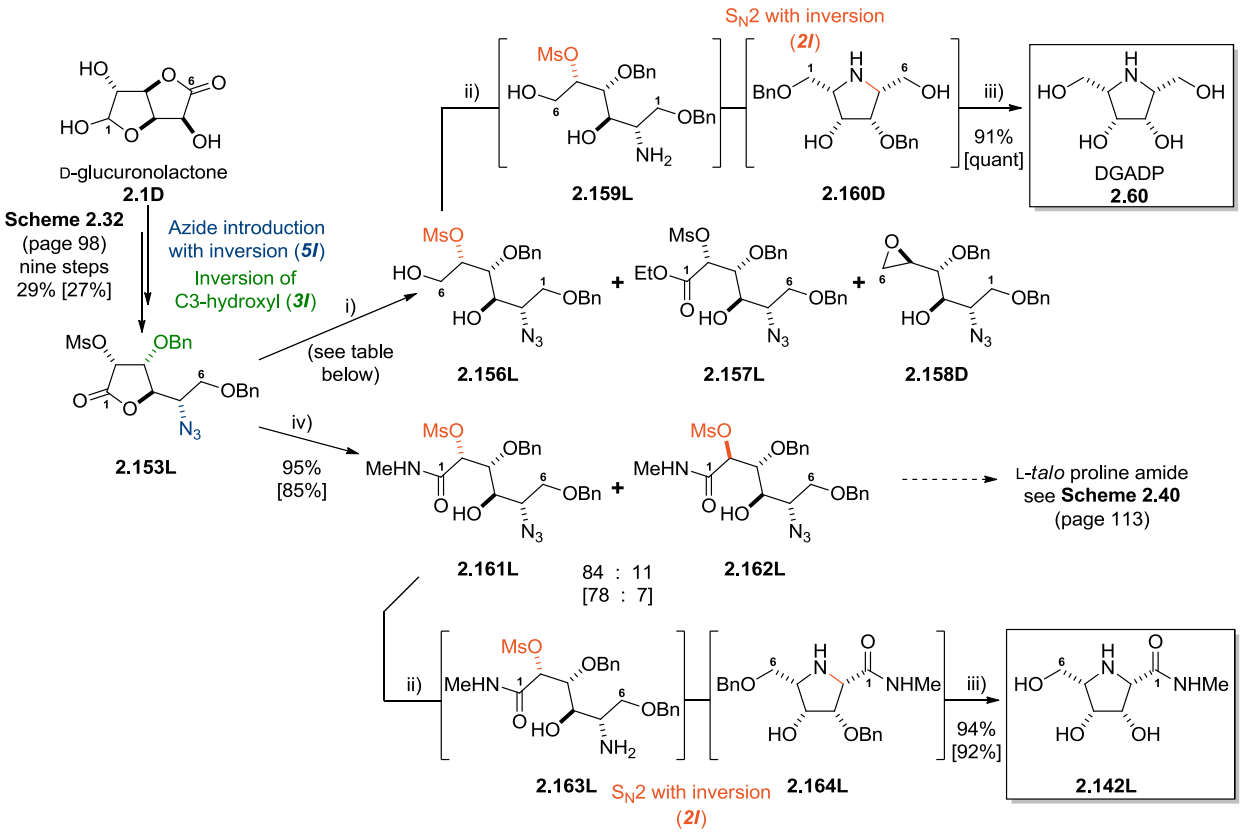
**Scheme 2.32**. Synthesis towards *galacto* targets.

The diol **2.146L** was protected as the dibenzyl ether **2.147L** by reaction with benzyl bromide and sodium hydride in an excellent 99% yield [99%] (**Scheme 2.32**). Hydrolysis with *p*TSA at 50 $^{o}$C afforded the lactols **2.148L** (95%, [80%]) which were oxidised to the lactone **2.149L** by treatment with iodine and potassium carbonate in refluxing *tert*-butanol (80% [72%]). This lactone **2.149L** was activated as the triflate **2.150L** under the usual conditions (80%). It was anticipated that the same reaction conditions that led to the formation of the iminobicycles **2.128L** and **2.139D** in the "*gulo*-" and "*manno*-" routes (**Schemes 2.26** & **2.29**, pages 88 & 93, respectively) would also lead to the formation of the desired iminobicycle **2.151L** for this route. However, this was found not to be the case.

Reduction of the azide **2.150L** led to the rapid formation of the 2-deoxy amine **2.152L**, which was detected as the major component of a complex mixture of products. It is likely that this compound arose from the elimination of trifluoromethanesulfonic acid (TfOH) in preference to the formation of the iminobicycle **2.151L**, with reduction of the resultant 2,3-alkene occurring under the reaction conditions. Interestingly, this reduction demonstrated facial selectivity opposing that displayed earlier in the reduction of the prochiral ketone **2.40L** by sodium borohydride. Despite further attempts the iminobicycle **2.151L** was not detected. An alternative and less reactive mesylate (methanesulfonate) leaving group at C2 was therefore tested. Esterification of lactone **2.149L** with methanesulfonyl chloride in pyridine gave the mesylate **2.153L** in good yield (95% [90%]). This mesylate **2.153L** was submitted to the same reduction conditions as the previous C2-triflates, and although it did not prove to be prone to elimination, cyclisation to the desired iminobicycle **2.151L** did not occur - instead a mixture of the amino-lactone **2.154L** and mesylate-lactam **2.155L** resulted. Thus a redesign of the strategy was required for this "*galacto*-" route. The current methodology developed had relied on conducting the *iminocyclisation* and *lactone-opening* steps in this sequence, so it was proposed that reversing the order of these two steps might mitigate the complications in this reaction by removing the necessitated formation of an unfavoured and strained bicyclic intermediate.

So, in order to reverse the *cyclisation* and *lactone ring-opening* steps, and permit access to the *meso-galacto*-configured pyrrolidine **2.60**, the reduction of mesylate **2.153L** with sodium borohydride was attempted (**Scheme 2.33**). This reaction did not prove to be devoid of difficulty, but proved to be amenable to optimisation. In the first attempted reduction of mesylate **2.153L** with sodium borohydride at -30 $^{o}$C (entry 1) it was observed that in just over an hour a major product had been formed, which upon isolation was identified as the lactone-ring opened ethyl ester **2.157L** (55%). Subsequent treatment of mesylate **2.153L** with a greater excess of sodium

borohydride and a prolonged reaction time (8 h) in which the reaction was permitted to slowly warm to RT (entry 2), led to no ethyl ester **2.157L** being isolated. These conditions did lead to the formation of the desired diol **2.156L** (45%), however substantial formation of the 5,6-epoxide **2.158D** was observed (20%). This arose from intramolecular displacement at elevated reaction temperatures. The ideal reaction conditions were subsequently found to involve a reaction temperature between -15 °C and -30 °C (entry 3). Reaction of the mesylate **2.153L** with excess sodium borohydride (~10 equivalents) below -15 °C led to a good yield of the diol **2.156L** (65%, [66%]) whilst keeping epoxide **2.157L** (5%, [7%]) formation to a minimum.




**Reagents & conditions**: i) see Table below; ii) $H_2$, Pd/C, NaOAc, 1,4-dioxane, RT, 5 h; iii) *then* add 2 M HCl(aq), 16 h; iv) $MeNH_2$, 1,4-dioxane, RT, 16 h.

| | | Product Yield (%) | | |
|---|---|---|---|---|
| Entry | Conditions | **2.156L** | **2.157L** | **2.158D** |
| *1* | $NaBH_4$ (2.2 eq), EtOH, -30 °C, 1.5 h | - | 55 | - |
| *2* | $NaBH_4$ (8 eq), EtOH, -30 °C to RT, 8 h | 45 | - | 20 |
| *3* | $NaBH_4$ (10 eq), EtOH, -30 °C to -15 °C, 4.5 h | 65 [66] | - | 5 [7] |

**Scheme 2.33**. Synthesis of *galacto* targets.

Following this, the diol **2.156L** underwent hydrogenation in the presence of palladium on carbon in order to reduce the azide moiety to an intermediate amine **2.159L**. The reaction was conducted in the presence of sodium acetate in order to induce the iminocyclisation of this mesylate-amine **2.159L** to the pyrrolidine intermediate **2.160D**. The reaction was monitored by LRMS (low-resolution mass spectrometry) which allowed the qualitative assessment of the progress of the reaction. After the first hour the major assignable compound present was the uncyclised amine intermediate **2.159L**, and after a further four hours this was replaced by the cyclised pyrrolidine intermediate **2.160D**. At this time aqueous hydrochloric acid was added to increase the rate of benzyl ether hydrogenolysis, which afforded the *meso-galacto* pyrrolidine DGADP **2.60** in 91% yield from the diol **2.156L**, and in 17% yield from the starting material D-glucuronolactone **2.1D** over eleven steps [18%].

With access to DGADP **2.60** achieved, attention was then turned towards the L-*galacto* proline amide **2.142L**. Similarly to the pyrrolidine, it was envisaged that initial opening of the lactone ring with methylamine, followed by iminocyclisation would afford the target iminosugar. So, the mesylate **2.153L** was treated with an ethanolic solution of methylamine which afforded a mixture of the desired open-chain amide **2.161L** and the C2-epimeric amide **2.162L**, arising from the base-catalysed epimerisation of this C2-centre (95%, 84:11; [85%, 78:7]). Despite attempts to optimise this reaction the degree of epimerisation could not be reduced further - however, this C2-epimeric amide **2.162L** is required in the upcoming synthesis of the L-*talo* proline amide (Section 2.3.5.5.3, pages 111-112) and could be utilised here. The desired amide **2.161L** was taken, and under identical conditions employed in the synthesis of DGADP **2.60**, the L-*galacto* amide **2.142L** was synthesised in 94% yield [92%], and in a yield of 23% [19%] over eleven steps from D-glucuronolactone **2.1D**. The D-*galacto* amide **2.142D** was recrystallised form isopropanol (**Figure 2.9**). Thus the *galacto*-configured targets were successfully isolated

with minor alterations to the experimental protocol. Attention was now turned towards accessing the *altro*-configured targets (***2I-3I-5R***). This required expanding the methodology used in the "*manno*-" route (***2I-3R-5R***) by employing the C3-inversion (***3I***) procedure.

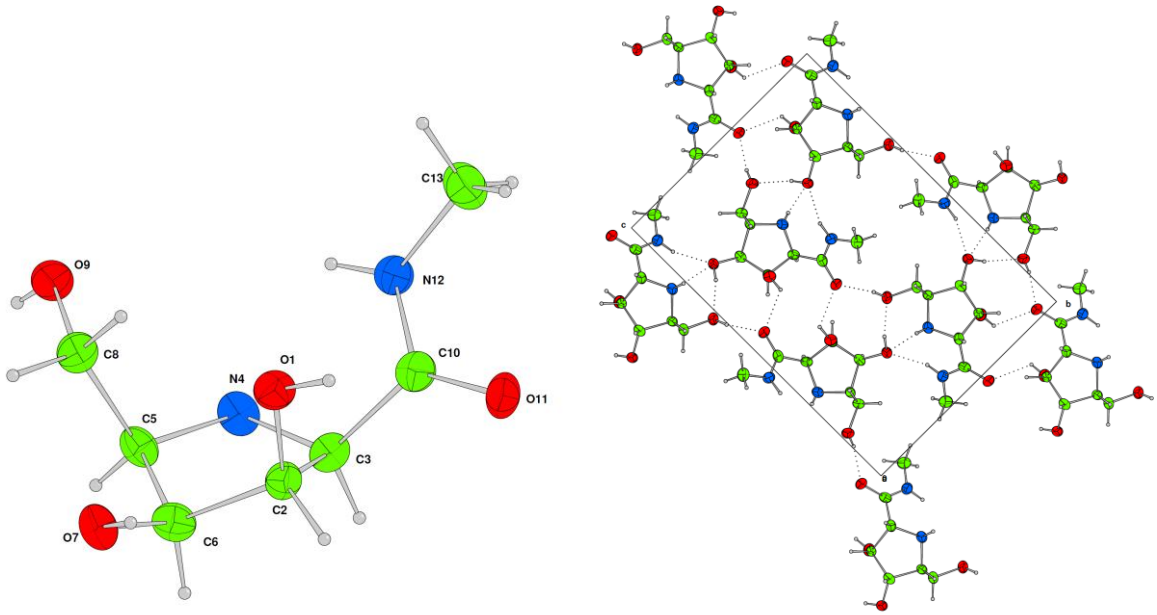
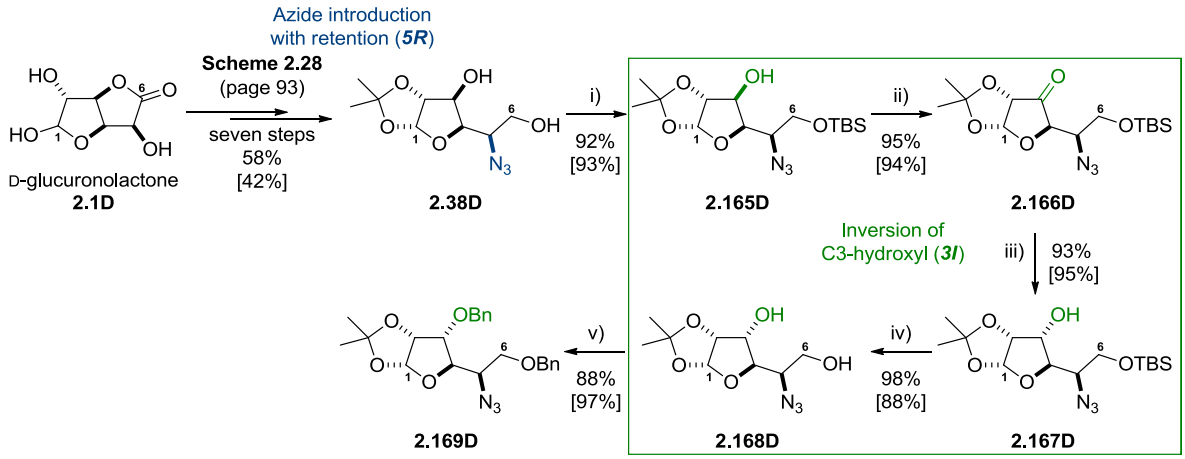



**Figure 2.9**. The crystal structure of the D-*galacto* amide **2.142D**.

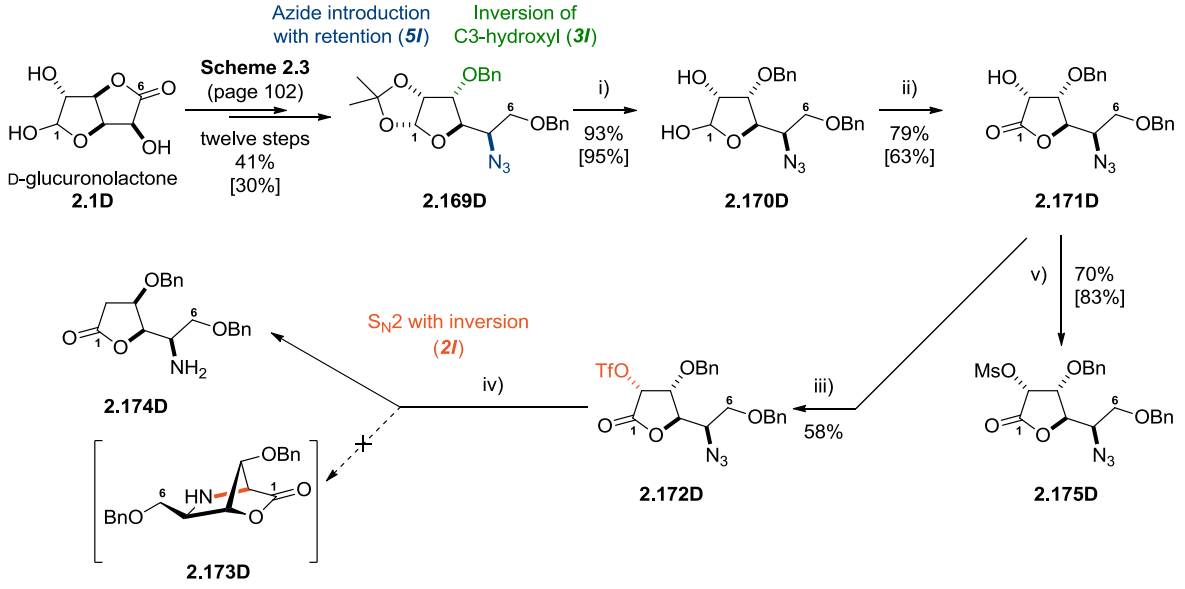
### *2.3.5.4.2 The route to altro-configured targets (**2I-3I-5R**)*




**Reagents & conditions**: i) TBSCl, pyr, RT, 20 h; ii) DMP **2.144**, DCM, 0 °C to RT, 18 h; iii) $NaBH_4$(aq), EtOH, 0 °C to RT, 2 h; iv) TBAF, THF, RT, 1 h; v) NaH, BnBr, DMF, 0 °C to RT, 18 h.

**Scheme 2.34**. Towards *altro*-configured iminosugars by inversion of C3 (***3I***).

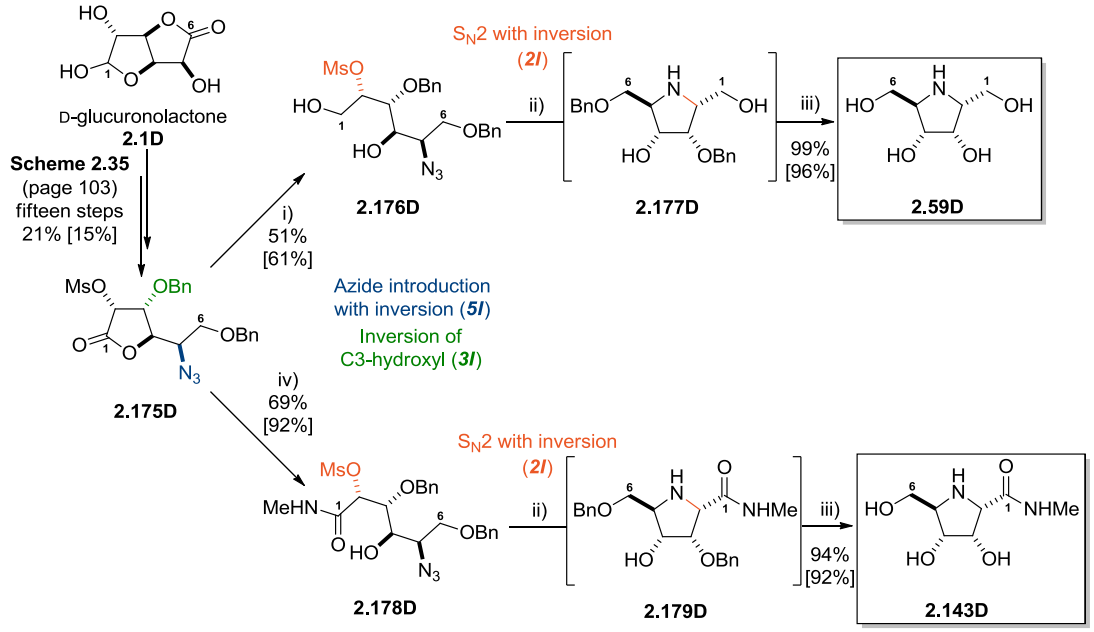
In order to access *altro*-configured (***2I-3I-5R***) iminosugars the "*manno*-" route (***2I-3R-5R***) utilised in Section 2.3.5.3 (pages 90-91) required modification by inversion of the C3-hydroxyl (***3I***). To achieve this, the diol **2.38D**, accessed from D-glucuronolactone **2.1D** in seven steps (58%, [42%]), was taken and the primary C6-hydroxyl selectively protected by reaction with TBSCl in pyridine affording the silyl ether **2.165D** in 92% yield [93%] (**Scheme 2.34**). This silyl ether **2.165D** was oxidised with DMP **2.144**, leading to the formation of the prochiral ketone **2.166D** (95%, [94%]). The subsequent facially selective reduction with sodium borohydride afforded the inverted C3-alcohol **2.167D** (93%, [95%]). With the C3-hydroxyl inverted, this compound **2.167D** now possessed the correct stereochemical disposition to undergo final protecting group manipulation prior to iminocyclisation. Reaction of this silyl ether **2.167D** with TBAF in THF afforded cleavage of the silyl moiety, forming the diol **2.168D** (98%, [88%]). Treatment of this diol **2.168D** with benzyl bromide and sodium hydride afforded the fully protected dibenzyl ether **2.169D** (88%, [97%]).




**Reagents & conditions**: i) *p*TSA, 1,4-dioxane/water, 80 °C, 2 h; ii) $I_2$, $K_2CO_3$, $^t$BuOH, 100 °C, 2 h; iii) $Tf_2O$, pyr, DCM, -40 °C, 1 h; iv) $H_2$, Pd/C, 1,4-dioxane, RT, 2 h; v) MsCl, pyr, 0 °C to RT, 2 h.

**Scheme 2.35**. Synthesis towards *altro* targets.

As before, dibenzyl ether **2.169D** was reacted with *p*TSA at 80 °C affording hydrolysis of the 1,2-acetonide and formation of the lactols **2.170D** (93%, [95%]) (**Scheme 2.35**). This anomeric mixture underwent oxidation with iodine in the presence of potassium carbonate, giving chemoselective oxidation and the lactone **2.171D** in good yield (79%, [63%]). As with previous routes this lactone **2.171D**, with the C2-hydroxyl free, was activated as the triflate **2.172D** under the usual conditions (58%). This triflate **2.172D** was reduced by hydrogenation, and unfortunately, as in the case of the "*galacto*-" route (<u>Section 2.3.5.4.1</u>, page 97), the iminobicyclic intermediate **2.173D** was not observed. Instead TfOH was eliminated and the resultant olefin reduced under the reaction conditions giving a mixture of which the 2-deoxy compound **2.174D** was the major component. Again facial selectivity under hydrogenation was observed. With the failure of this route the modified procedure developed in the previous section for the "*galacto*-" route was employed, starting with the generation of mesylate **2.175D** by reaction of lactone **2.171D** with mesyl chloride in pyridine (70%, [83%]).




**Reagents & conditions**: i) $NaBH_4$, EtOH, -30 °C to -20 °C, 6 h; ii) $H_2$, Pd/C, NaOAc, 1,4-dioxane, RT, 4 h; iii) *then* add 2 M HCl(aq), 19 h; iv) $MeNH_2$, 1,4-dioxane, RT, 17 h.

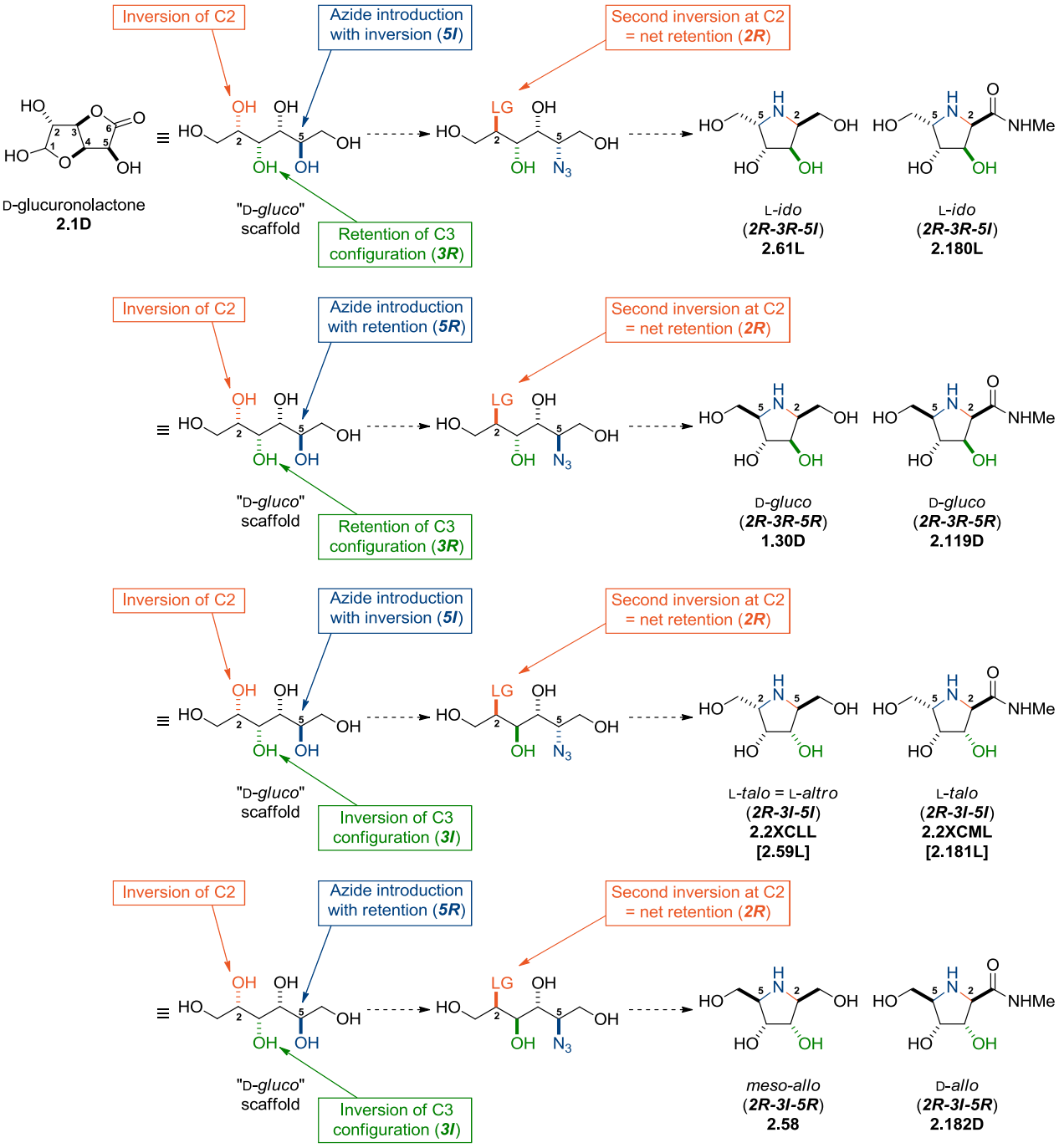
**Scheme 2.36**. Synthesis of *altro* targets.

To access the desired D-*altro* pyrrolidine target DADP **2.59D**, the mesylate **2.175D** was taken and the careful reduction conditions previously utilised were employed here again. Reaction with excess sodium borohydride over six hours at a temperature maintained between -20 $^{o}$C and -30 $^{o}$C afforded the diol **2.176D** in 51% yield [61%], without isolation of an epoxide by-product. This diol **2.176D** was treated under the same hydrogenolysis conditions as before in the presence of palladium on carbon, and sodium acetate. The reaction was monitored by LRMS which indicated the formation of the cyclised pyrrolidine intermediate **2.177D** after four hours. Aqueous hydrochloric acid was added to facilitate an increased rate of benzyl ether hydrogenolysis, affording DAPD **2.59D** in a 99% yield [96%], and 10% over seventeen steps from D-glucuronolactone **2.1D** [9%].

Similarly, in work conducted by Nigel Ngo, the lactone ring of the mesylate **2.175D** underwent aminolysis with an ethanolic solution of methylamine to afford the open-chain amide **2.178D** (69%, [92%]). Unlike the previous "*galacto*-" system no base-catalysed C2-epimerisation was observed - and only the desired amide **2.178D** was isolated. This amide **2.178D** was subjected to identical cyclisation reaction conditions to that of the diol **2.176D**, which afforded the D-*altro* proline amide **2.143D** in 94% yield [92%], and in 14% yield over seventeen steps from D-glucuronolactone **2.1D** [13%].

With the successful expansion and adaptation of the initial methodology to the C3-inverted systems - "*galacto*-" (***2I-3I-5I***) and "*altro*-" (***2I-3I-5R***) - the following section moves onto accessing the final iminosugars obtainable by the overall retention of the configuration at C2 (***2R***).

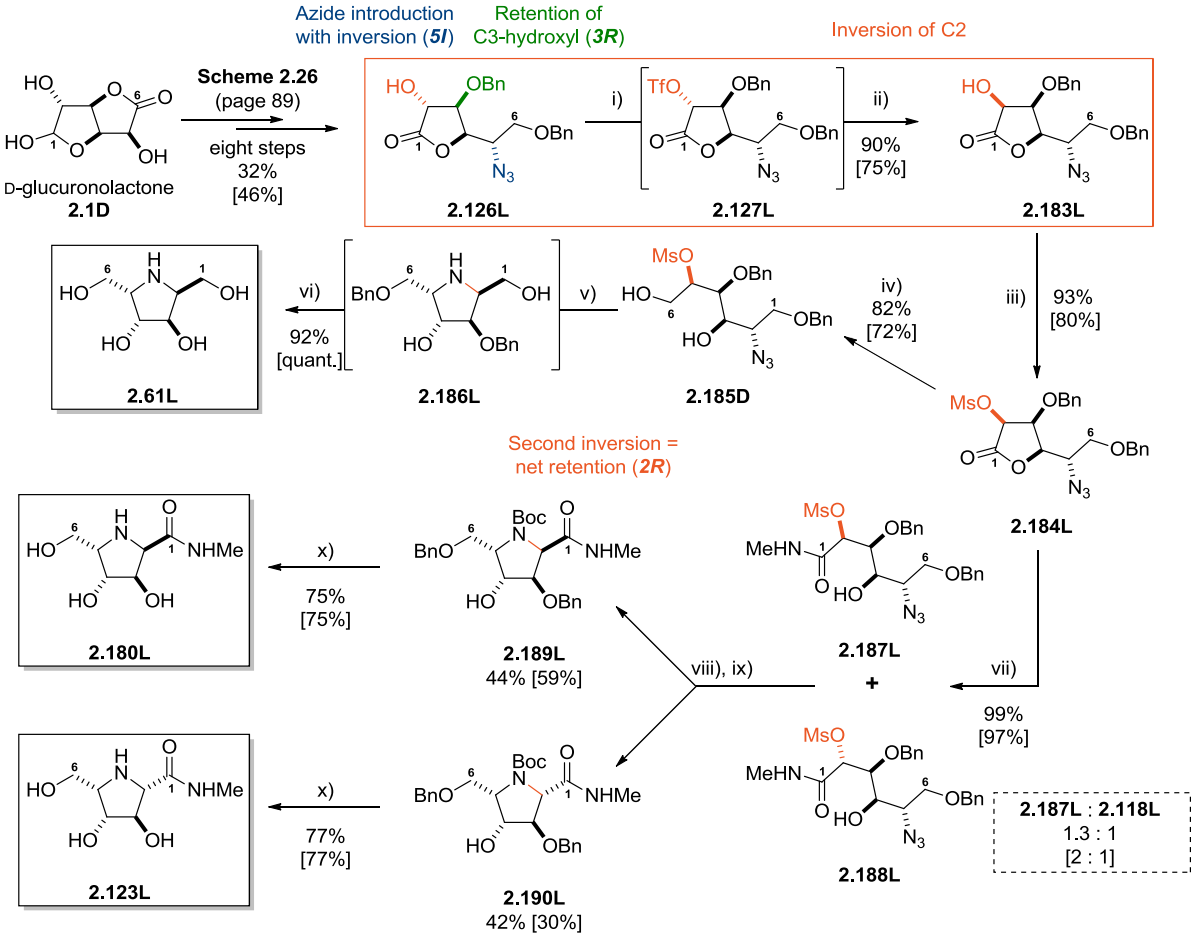
### 2.3.5.5 C2 epimerisation: gluco- (**2R-3R-5R**), ido- (**2R-3R-5I**), talo- (**2R-3I-5I**) & allo-configurations (**2R-3I-5R**)




**Scheme 2.37**. Conceptual strategy to iminosugars *via* the "*ido*-", "*gluco*-", "*talo*-" and "*allo*-" synthetic routes.

With the "*gulo*-" (***2I-3R-5I***), "*manno*-" (***2I-3R-5R***), "*galacto*-" (***2I-3I-5I***) and "*altro*-" (***2I-3I-5R***) routes completed by utilisation of both inverted and retained configurations of C5 (***5I*** & ***5R***) and C3 (***3I*** & ***3R***), the methodology was ready to be finally expanded to the "*ido*-" (***2R-3R-5I***), "*gluco*-" (***2R-3R-5R***), "*talo*-" (***2R-3I-5I***) and "*allo*-" (***2R-3I-5R***) routes by the net retention of the C2-hydroxyl configuration (**Scheme 2.37**).

### *2.3.5.5.1 The route to ido-configured targets (**2R-3R-5I**)*




**Reagents & conditions**: i) $Tf_2O$, pyr, DCM, -40 °C, 1 h; ii) $NaCO_2CF_3$, DMF, RT, 2 h; iii) MsCl, pyr, 0 °C to RT, 2 h; iv) $NaBH_4$, 1,4-dioxane/EtOH, -30 °C to -15 °C, 6 h; v) $H_2$, Pd/C, NaOAc 1,4-dioxane, RT, 24 h; vi) *then* add 2 M HCl(aq), 16 h; vii) $MeNH_2$, 1,4-dioxane, RT, 16 h; viii) $H_2$, Pd/C, NaOAc, 1,4-dioxane, RT, 3 h; ix) *then* filter and add $Boc_2O$, RT, 16 h; x) $H_2$, Pd/C, 1,4-dioxane/2 M HCl, RT, 16 h.

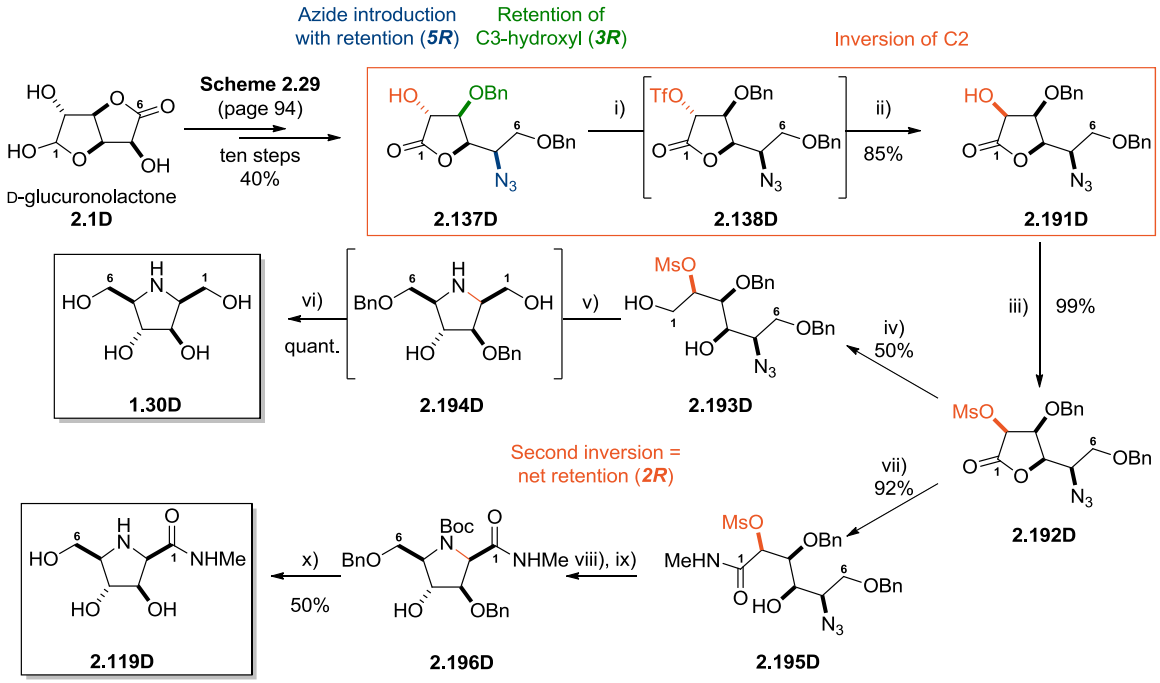
**Scheme 2.38**. Synthesis of *ido* targets.

In order to access the *ido*-configured iminosugar targets (***2R-3R-5I***) modification of the original "*gulo*-" route (***2I-3R-5I***) was required, with the net retention of the C2-stereocentre (***2R***) on formation of the five-membered iminosugar ring. As the ring in the methods so far has been formed by an intramolecular $S_N2$-displacement giving inversion (***2I***), an extra inversion preceding this with an oxygen-based nucleophile would result in the desired net-retention (***2R***). It can be seen that the lactone **2.126L** from the "*gulo*-" route (**Scheme 2.26**, page 88), has the C2-hydroxyl α to the carbonyl moiety of C1 (**Scheme 2.38**). So it was envisaged that this centre could undergo a similar double-inversion strategy to that employed in the earlier case of the C5-stereocentre. In order to achieve this, the lactone **2.126L** was taken and the C2-hydroxyl activated by triflation - forming the crude triflate **2.127L**. Reaction with sodium trifluoroacetate, which as in the C5 case, successfully gave the lactone **2.183L** with inversion of configuration at C2 (90%, [75%]). With this inversion complete, the lactone **2.183L** now possessed the correct stereochemical disposition to undergo final protecting group manipulation prior to iminocyclisation.

One important point to discuss at this stage regards the required cyclisation of these C2-retained (***2R***) compounds to form iminosugars. The initial methodology employed in the "*gulo*-" (***2I-3R-5I***) and "*manno*-" (***2I-3R-5R***) systems, whereby a C2-triflate was reduced and formed an iminobicyclic intermediate with inversion (***2I***), is no longer feasible for these remaining routes. This is due to the fact that these molecules no longer possess the required stereochemistry for this iminocyclisation to occur - the C5-amino group derived by reduction of the azide will be on the opposing face of the molecule to the C2-triflate σ* C-O antibonding orbital. Thus the C2-retained routes (***2R***) must utilise the methodology adapted for the "*galacto*-" (***2I-3I-5I***) and "*altro*-" (***2I-3I-5R***) routes, *via* open-chain intermediates which would enable the iminocyclisation to be possible.

Thus, as previously described, the lactone **2.183L** underwent C2-activation by mesylation - with mesyl chloride in pyridine - forming the mesylate **2.184L** (93%, [80%]). Careful reduction of the mesylate lactone **2.184L** with sodium borohydride yielded the desired diol **2.185D** in an excellent 82% yield [72%]. Hydrogenolysis of diol **2.185D** under the usual conditions of palladium on carbon and sodium acetate led to the formation of the dibenzyl pyrrolidine intermediate **2.186L**. Subsequent acidic hydrogenolysis gave the desired L-*ido* pyrrolidine L-DIDP **2.61L** in an excellent 92% yield [quant.], and in 20% yield over thirteen steps from D-glucuronolactone **2.1D** [20%]. In order to access the desired proline amide target the mesylate lactone **2.184L** was reacted with ethanolic methylamine which unfortunately, much like the "*galacto*-" route (Section 2.3.5.4.1, page 99), gave a mixture of C2-epimeric open-chain amides **2.187L** and **2.188L** (99%, 1.3:1; [97%, 2:1]) which were not separable at this stage. In order to afford the necessary separation of these epimers the synthetic methodology underwent a slight modification. The mixture of amides **2.187L** and **2.188L** were reduced by hydrogenolysis under the usual conditions, and after three hours, when cyclisation was judged to be complete, the reaction mixture was filtered and di-*tert*-butyldicarbonate ($Boc_2O$, Boc anhydride) was added. This afforded the now separable and Boc-protected proline amides **2.189L** (44%, [59%]) and **2.190L** (42%, [30%]). These amides underwent acidic hydrogenolysis removing both benzyl ether and Boc-protecting groups to afford the L-*ido* proline amide **2.180L** (75%, [75%]) and the L-*gulo* proline amide **2.123L** (77%, [77%]), respectively. The latter having been synthesised earlier in Section 2.3.5.2 (page 88). Thus, the L-*ido* proline amide **2.180L** was obtained in a 9% yield over fifteen steps [12%], and the L-*gulo* proline amide **2.123L** in a 9% yield over fifteen steps [6%]. With the successful isolation of the desired *ido*-configured targets by the employment of the double-inversion strategy to afford net-retention of the C2-configuration (***2R***), attention was now turned toward the next configuration - the "*gluco*-" route (***2R-3R-5R***).

*2.3.5.5.2 The route to "gluco-" configured targets (**2R-3R-5R**)*




**Reagents & conditions**: i) $Tf_2O$, pyr, DCM, -30 °C, 2 h; ii) $NaCO_2CF_3$, DMF, RT, 17 h; iii) MsCl, pyr, 0 °C to RT, 2 h; iv) $NaBH_4$, 1,4-dioxane/EtOH, -30 °C to -20 °C, 4 h; v) $H_2$, Pd/C, NaOAc 1,4-dioxane, RT, 16 h; vi) *then* add 2 M HCl(aq), 24 h; vii) $MeNH_2$, 1,4-dioxane, RT, 16 h;viii) $H_2$, Pd/C, NaOAc, 1,4-dioxane, RT, 4 h; ix) *then* filter and add $Boc_2O$, RT, 16 h; x) $H_2$, Pd/C, 1,4-dioxane/2 M HCl, RT, 20 h.

**Scheme 2.39**. Synthesis of *gluco* targets.

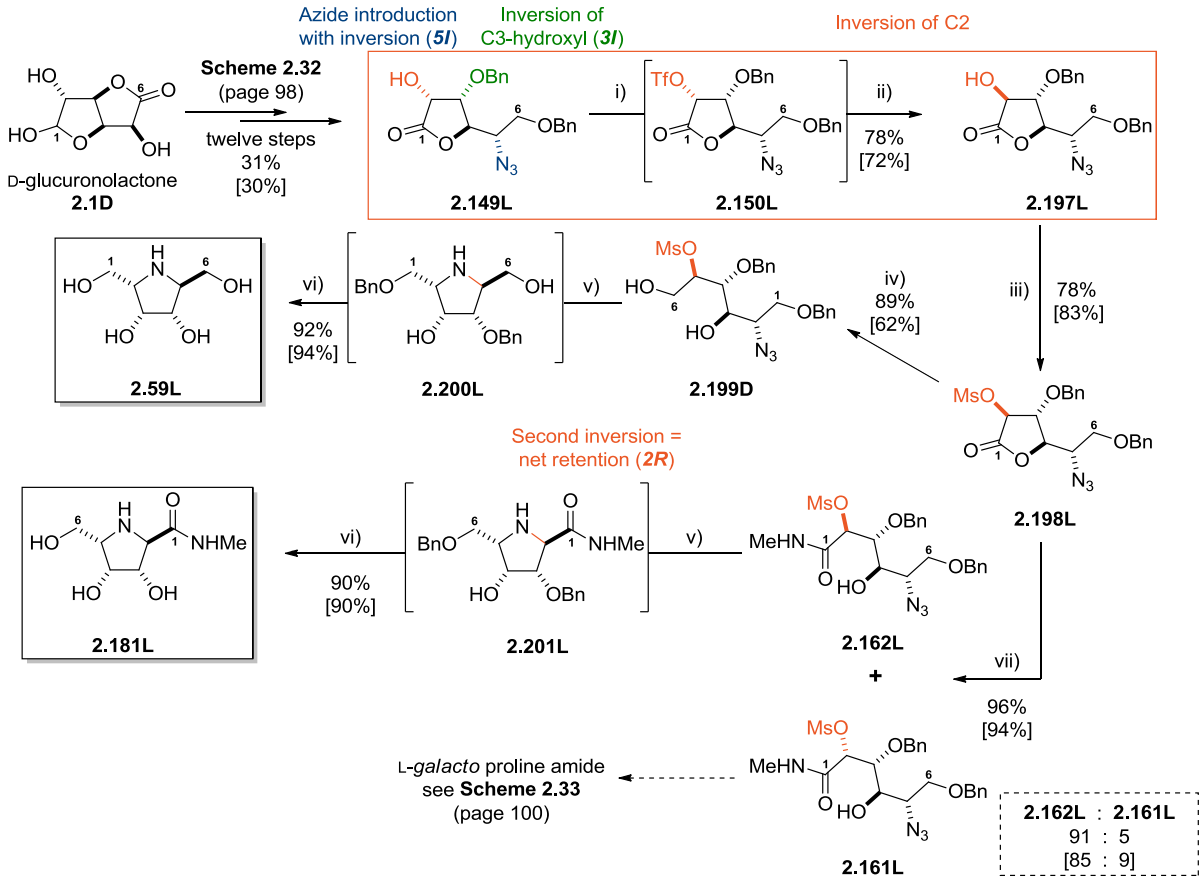
Taking the preceding methodology that afforded the net-retention of the C2-configuration (***2R***) and applying it to the "*manno*-" route (***2I-3R-5R***) would afford access to the *gluco*-configured targets (***2R-3R-5R***). In work conducted by Dr. Fernando Martinez, the lactone **2.137D** underwent C2-activation by triflation in the usual manner (**Scheme 2.39**), affording the intermediate triflate **2.138D.** Treatment with sodium trifluoroacetate gave the C2-inverted lactone **2.191D** (85%). Reaction of this lactone **2.191D** with mesyl chloride gave the divergent mesylate **2.192D** in excellent yield (99%). In order to access the pyrrolidine target **1.30D** the mesylate **2.192D** was taken and carefully reduced with sodium borohydride to give the open-chain diol **2.193D** (50%). This diol **2.193D** underwent cyclisation and cleavage of the benzyl ether groups with the usual hydrogenolysis conditions to form the desired D-*gluco* pyrrolidine DGDP **1.30D** in quantitative yield, and in 17% over sixteen steps from

D-glucuronolactone **2.1D**. DGDP **1.30D** was also previously accessed by the "*gulo*-" route (**Scheme 2.26**, page 88) in 24% over twelve steps [42%]. The enantiomeric pyrrolidine L-DGDP **1.30L** was accessed from L-glucuronolactone **2.1L** in a similar yield.

The divergent mesylate **2.192D** was also reacted with ethanolic methylamine to afford the open-chain amide **2.195D** (92%) with no epimerisation of C2 observed. This amide **2.195D** was reduced and cyclised under the standard hydrogenolysis conditions, however on the first attempt this reaction did not prove to be successful and gave a mixture of products. So, this procedure was adapted, with Boc-protection after cyclisation affording the isolable intermediate **2.196D** which could be purified. Acidic hydrogenolysis cleaved the benzyl ether and Boc-protecting groups to afford the clean D-*gluco* amide **2.119D** (50%) - this yield was much lower than expected by previous results, and did not improve in the enantiomeric series or with successive attempts. The target D-*gluco* amide **2.119D** was thus isolated in 15% yield over seventeen steps from D-glucuronolactone **2.1D**. The enantiomeric L-*gluco* amide **2.119L** was accessed from L-glucuronolactone **2.1L** in a similar yield.

With the targets of the "*gluco*-" route (***2R-3R-5R***) thus isolated, attention was turned to the penultimate system of *talo*-configured iminosugars (***2R-3I-5I***).

*2.3.5.5.3 The route to "talo-" configured targets (**2R-3I-5I**)*




**Reagents & conditions**: i) $Tf_2O$, pyr, DCM, -40 °C, 1.5 h; ii) $NaCO_2CF_3$, DMF, -30 °C to RT, 20 h; iii) MsCl, pyr, 0 °C to RT, 1.5 h; iv) $NaBH_4$, 1,4-dioxane/EtOH, -30 °C to -15 °C, 5.5 h; v) $H_2$, Pd/C, NaOAc 1,4-dioxane, RT, 5-6 h; vi) *then* add 2 M HCl(aq), 16 h; vii) $MeNH_2$, 1,4-dioxane, RT, 16 h.

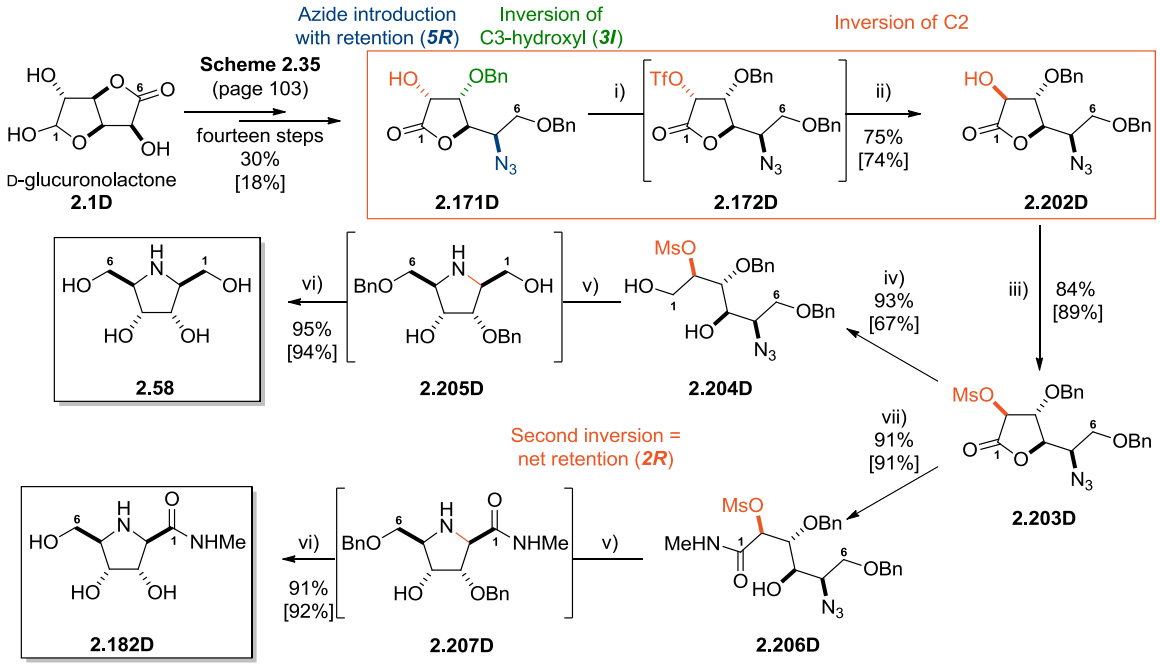
**Scheme 2.40**. Synthesis of *talo* targets.

Expansion of the "*galacto*-" route (***2I-3I-5I***) by the net-retention of the configuration of C2 (***2R***) would afford access to the *talo*-configured iminosugar targets (***2R-3I-5I***). So, implementing the methodology established in the preceding sections, the lactone **2.149L** was taken and the C2-hydroxyl inverted by activation as the intermediate triflate **2.150L** (**Scheme 2.40**). Subsequent $S_N2$-displacement with sodium trifluoroacetate afforded the inverted lactone **2.197L** (78%, [72%]). The C2-hydroxyl of lactone **2.197L** was activated by mesylation under the usual conditions of mesyl chloride in pyridine, giving the mesylate lactone **2.198L** (78%, [83%]). Reduction with sodium borohydride between -30 °C and -15 °C afforded the open-chain diol **2.199L** in good yield (89%, [62%]). Finally, the hydrogenolysis conditions previously developed

efficiently gave the desired L-*altro* pyrrolidine L-DADP **2.59L** (92%, [94%]). The degeneracy of alditol structures is again demonstrated here, with the L-*talo* and L-*altro* configurations being equivalent. The L-*altro* nomenclature takes alphabetical precedence.[45] Thus, this pyrrolidine **2.59L** has been previously accessed by the "*altro*-" route (***2I-3I-5R***) in 9% yield over seventeen steps from L-glucuronolactone **2.1L** (10% for **2.59D** from **2.1D**, Section 2.3.5.4.2, pages-101-104). Here, in this "*talo*-" route L-DADP **2.59L** was accessed in 15% overall yield over eighteen steps from D-glucuronolactone **2.1D** [10%].

As with the diastereomeric "*galacto*-" route, the methylamine opening of the lactone ring of mesylate **2.198L** led to a degree epimerisation at C2, giving a separable mixture of open-chain amides **2.162L** and **2.161L** (96%; 91:5; [94%; 85:9]). The open-chain amide **2.161L** was used in the previous synthesis of the L-*galacto* amide **2.142L** (**Scheme 2.33**, page 99). The open-chain amide **2.162L** was reduced and cyclised under the usual conditions to afford the L-*talo* proline amide **2.181L** in an excellent 90% yield [90%], and in 15% yield over eighteen steps from D-glucuronolactone **2.1D** [14%]. With the developed methodology successfully deployed in the synthesis of *talo*-configured targets (***2R-3I-5I***), attention was turned to the final route - "*allo*-" (***2R-3I-5R***).

*2.3.5.5.4 The route to "allo-" configured targets (**2R-3I-5R**)*




**Reagents & conditions**: i) $Tf_2O$, pyr, DCM, -40 °C, 1 h; ii) $NaCO_2CF_3$, DMF, -30 °C to RT, 16 h; iii) MsCl, pyr, 0 °C to RT, 2 h; iv) $NaBH_4$, 1,4-dioxane/EtOH, -30 °C to -15 °C, 4 h; v) $H_2$, Pd/C, NaOAc 1,4-dioxane, RT, 4 h; vi) *then* add 2 M HCl(aq), 16-24 h; vii) $MeNH_2$, 1,4-dioxane, RT, 18 h.

**Scheme 2.41**. Synthesis of *allo* targets.

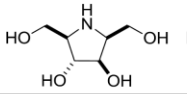
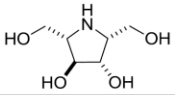
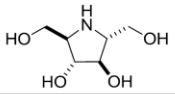
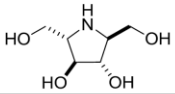
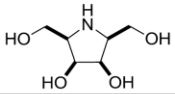
The final targets possess an *allo*-configuration (***2R-3I-5R***) and were to be accessed by expansion of the "*altro*-" route (***2I-3I-5R***) by the net-retention of the C2-configuration (***2R***). Following the methodology developed and honed in the previous routes, the C2-hydroxyl of lactone **2.171D** was inverted by activation as the triflate **2.172D** and subsequent displacement with sodium trifluoroacetate to give the lactone **2.202D** (75%, [74%]). This inverted lactone **2.202D** was activated as the mesylate **2.203D** (84%, [89%]), which was then reduced carefully with sodium borohydride to afford the open-chain diol **2.204D** (93%, [67%]). Hydrogenolysis of the diol **2.204D** led initially to the dibenzylated intermediate **2.205D**, with final acidic hydrogenolysis cleaving the benzyl groups and forming the desired *meso-allo* pyrrolidine **2.58** in good yield (95%, [94%]). This pyrrolidine **2.58** was thus formed in 17% overall yield over twenty steps

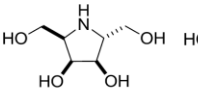
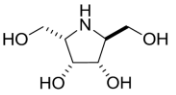
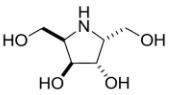
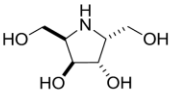
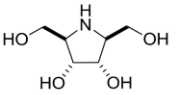
from D-glucuronolactone **2.1D**, and also in 7% by the enantiomeric route from L-glucuronolactone **2.1L**. The mesylate lactone **2.203D** was also treated with ethanolic methylamine to afford the open-chain amide **2.206D** (91%, [91%]), and like the previous C2-diastereomeric "*altro*-" route there was no detection of any base-catalysed C2-epimerisation. This amide **2.206D** was then subjected to the reductive iminocyclisation conditions with formed the desired D-*allo* proline amide **2.182D** *via* the dibenzylated intermediate **2.207D** (91%, [92%]). This amide **2.182D** was thus afforded in 16% yield over twenty steps from D-glucuronolactone **2.1D** [10%].

With all ten pyrrolidine and all sixteen proline amide targets successfully synthesised from D- and L-glucuronolactone, the robustness of the initially developed methodology was aptly demonstrated. This presents the first truly universal methodology by which these two classes of iminosugar may be accessed readily and affordably on a convenient scale. The final synthetic route, *allo*- (***2R-3I-5R***), which possesses the largest number of overall steps, successfully gave over one-gram of target proline amide **2.182D** from just nine-grams of D-glucuronolactone **2.1D**, thereby demonstrating the scalability, efficiency and extreme utility of this methodology. And, with this the synthesis section of the project was completed and the thesis now moves on to the biological evaluation and comparison of these iminosugar targets.

## 2.3.6 Biological Activity

### *2.3.6.1 Pyrrolidines*

| | $IC_{50}$ (μM) | | | | |
|---|---|---|---|---|---|
| |  |  |  |  |  |
| | D-*gluco* (DGDP) | L-*gluco* | D-*manno* (DMDP) | L-*manno* | *meso-galacto* |
| Enzyme | **1.30D** | **1.30L** | **1.8D** | **1.8L** | **2.60** |
| α-Glucosidase | | | | | |
| Rice | 131 | **60** | 214 | **5.8** | NI (38.9%) |
| Yeast | 167 | NI (16.0%) | NI (15.6%) | NI (34.9%) | NI (0%) |
| Rat intestinal maltase | 138 | **48** | 290 | **1.2** | NI (44.2%) |
| β-Glucosidase | | | | | |
| Almond | 256 | NI (32.4%) | **10** | NI (12.1%) | 597 |
| Bovine liver | 523 | NI (5.4%) | **9.7** | NI (4.6%) | NI (44.5%) |
| α-Galactosidase | | | | | |
| Coffee beans | NI[a] (38.4%)[b] | 216 | NI (10.5%) | NI (13.78%) | **0.19** |
| β-Galactosidase | | | | | |
| Bovine liver | 361 | NI (12.0%) | **3.3** | NI (0%) | NI (48.2%) |
| α-Mannosidase | | | | | |
| Jack beans | NI (13.3%) | NI (0%) | NI (31.5%) | NI (17.3%) | NI (10.2%) |
| β-Mannosidase | | | | | |
| Snail | NI (14.6%) | NI (0%) | 721 | NI (12.6%) | NI (0%) |
| α-L-Rhamnosidase | | | | | |
| *Penicillium decumber* | NI (3.3%) | NI (16.1%) | NI (24.1%) | NI (45.6%) | 550 |
| α-L-Fucosidase | | | | | |
| Bovine kidney | NI (37.2%) | NI (0.3%) | NI (37.2%) | NI (0%) | **41** |
| β-Glucuronidase | | | | | |
| *E. coli* | NI (5.1%) | NI (1.4%) | NI (0.4%) | NI (0.8%) | NI (21.3%) |
| Trehalase | | | | | |
| Porcine kidney | 379 | NI (40.1%) | 200 | **48** | NI (8.4%) |

| | $IC_{50}$ (μM) | | | | |
|---|---|---|---|---|---|
| |  |  |  |  |  |
| | D-*altro* (DADP) | L-*altro* | D-*ido* | L-*ido* | *meso-allo* |
| Enzyme | **2.59D** | **2.59L** | **2.61D** | **2.61L** | **2.58** |
| α-Glucosidase | | | | | |
| Rice | NI (24.1%) | NI (35.7%) | 792 | NI (36.7%) | NI (30.5%) |
| Yeast | NI (26.5%) | NI (35.1%) | NI (4.1%) | NI (29.4%) | NI (33.4%) |
| Rat intestinal maltase | NI (31.8%) | 754 | 654 | NI (37.6%) | NI (45.0%) |
| β-Glucosidase | | | | | |
| Almond | 126 | NI (15.9%) | NI (44.4%) | 650 | 463 |
| Bovine liver | 759 | NI (10.3%) | NI (41.2%) | NI (34.7%) | NI (32.9%) |
| α-Galactosidase | | | | | |
| Coffee beans | **5.2** | 120 | 419 | 229 | **51** |
| β-Galactosidase | | | | | |
| Bovine liver | 358 | NI (5.9%) | 655 | NI (43.1%) | 610 |
| α-Mannosidase | | | | | |
| Jack beans | 421 | NI (37.6%) | NI (0%) | NI (22.3%) | NI (34.3%) |
| β-Mannosidase | | | | | |
| Snail | NI (0%) | NI (3.7%) | NI (9.5%) | NI (0.5%) | NI (3.7%) |
| α-L-Rhamnosidase | | | | | |
| *Penicillium decumber* | NI (13.4%) | **91** | NI (12.2%) | NI (9.8%) | NI (32.3%) |
| α-L-Fucosidase | | | | | |
| Bovine kidney | NI (38.0%) | 205 | NI (10.1%) | NI (15.8%) | NI (28.1%) |
| β-Glucuronidase | | | | | |
| *E. coli* | NI (6.3%) | NI (2.0%) | NI (3.6%) | NI (2.1%) | NI (1.0%) |
| Trehalase | | | | | |
| Porcine kidney | NI (4.3%) | 1000 | NI (13.1%) | NI (30.5%) | 1000 |

[a] *NI : No inhibition (less than 50% inhibition at 1000 μM).*

[b] *( ) : inhibition % at 1000 μM*

**Table 2.3**. Concentration of pyrrolidines giving 50% inhibition ($IC_{50}$) of various glycosidases.

In collaboration with Professor Atsushi Kato (University of Toyama, Japan) the biological profiles of the ten stereoisomeric pyrrolidines were examined against a range of glycosidases (**Table 2.3**).[118] The biological data for the DMDP **1.8D** and L-DMDP **1.8L** enantiomers has also been published previously.[47] Although there have been syntheses of every stereoisomer, very few of these have undergone extensive biological examination. Indeed DMDP **1.8D** has been the most extensively studied towards a number of biological targets;[119-126] DGDP **1.30D** has also received some attention,[94,127,128] as has the last naturally occurring stereoisomer DAPD **2.59D**.[49] Moreover, there has also been little comparison of pyrrolidine structures against their biological profile, and none between the different stereoisomers - save those that are naturally occuring. This is very important due to the difficulty in predicting the inhibition of glycosidases by five-membered iminosugars. In the contrasting case of the piperidine pyranoside mimics, such as DNJ **1.1** and DGJ **1.2**, there is often a good correlation between the structures of the glycoside and the inhibtion by the iminosugar structural mimic.[129] Given this difficulty in prediction, the data gathered in this thesis becomes a real asset, as for the first time a side-by-side comparison of every pyrrolidine is possible allowing the assessment of the structure-activity relationship between these compounds and glycosidases.

In Section 1.2 (page 4), it was outlined that both *structural* and *electronic* mimicry was required in order for potent inhibition to occur - particularly with regard to the transition state of the glycosidase. Here, the biological evaluation (**Table 2.3**) shows that both the natural products DGDP **1.30D** and DMPD **1.8D** are modest α-glucosidase inhibitors (rat intestinal maltase: $IC_{50}$ 138 μM and 290 μM respectively). This can be ascribed to their structural similarity of the α-glucosidase transition state (**Figure 2.10**). The "unnatural" enantiomers of these pyrrolidines, L-DGDP **1.30L** and L-DMDP **1.8L** are more potent and specific inhibitors of the same enzyme ($IC_{50}$ 48 μM and 1.2 μM, respectively).[47] This is a result which has been frequently observed for other iminosugars, whereby the "unnatural" enantiomers of natural iminosugars demonstrate

more potent and specific inhibition of the same enzyme (Section 2.3.1, page 69). It has been suggested that this may be due to non-competitive allosteric inhibition.[6,44,130-133] L-DMDP **1.8L** was also shown to be a potent trehalase inhibitor (porcine kidney: $IC_{50}$ 48 μM).

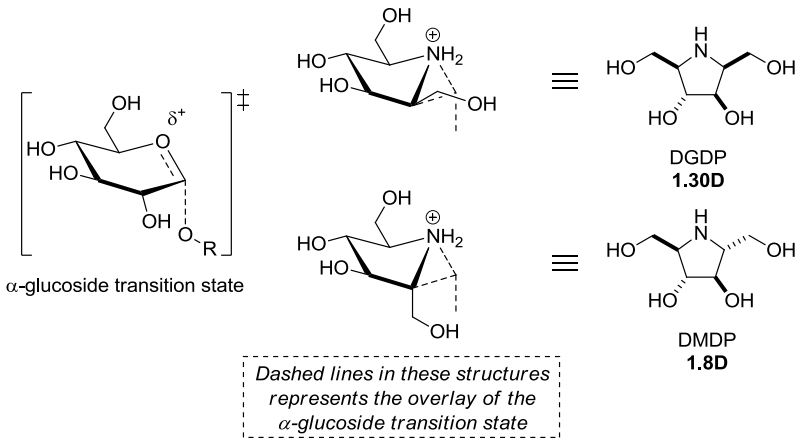



**Figure 2.10**. Structural correlation between the transition state of the α-glucosidase transition state and the iminosugars DGDP **1.30D** and DMDP **1.8D**.

DMDP **1.8D** also demonstrated far more potent inhibition of β-glucosidases and β-galactosidases than its C2/C5-epimer DGDP **1.30D** (β-glucosidase, almond: $IC_{50}$ 10 μM and 256 μM; β-galactosidase, bovine liver: $IC_{50}$ 3.3 μM and 361 μM, respectively). Legler *et al* suggested that, in the case of β-glucosidase, this difference would be due to the fact that the disposition of hydroxyls in DMDP **1.8D** is analogous to that of DNJ **1.1** and hence to D-glucose **1.3**; whereas this cannot be achieved by DGDP **1.30D**.[68] However, in this comparison DNJ **1.1** is in a chair-conformation rather than the boat- of the glucosidase transition state. The C2/C4-epimer of DMDP **1.8D**, the pyrrolidine DADP **2.59D**, also showed reasonable inhibition of these enzymes (β-glucosidase, almond: $IC_{50}$ 126 μM; β-galactosidase, bovine liver: $IC_{50}$ 358 μM). This indicates that changing a single stereocentre of DMDP **1.8D** is reasonably well tolerated by both β-glucosidases and β-galactosidases.

The enzyme α-galactosidase (coffee beans) was inhibited extremely well by DGADP **2.60** ($IC_{50}$ 190 nM). This is in accord with the previous observations by Wang and co-workers in

1994.[76] DGADP **2.60** can be seen to have a good structural correlation with the α-galactosidase transition state (**Figure 2.11**). DGADP **2.60** also displayed good inhibition against α-L-fucosidase (bovine kidney: $IC_{50}$ 41 μM). This is due to the pyrrolidine and the substrate, α-L-fucosides, possessing L-*galacto* stereochemistry. The equivalence of α-L-fucosidase and α-galactosidase inhibition has been previously well established.[134,135] The C2-epimer of DGADP **2.60**, DADP **2.59D** showed twenty-fold worse inhibition ($IC_{50}$ 5.2 μM), but again the change in a single stereocentre was reasonably well tolerated. Even changing two stereocentres, C3 and C4, which leads to the *meso-allo* pyrrolidine **2.58**, still presented good inhibition ($IC_{50}$ 51 μM). Kato *et al* proposed that the inhibition and selectivity demonstrated by DADP **2.59D** towards the enzyme would make it an ideal candidate for the pharmacological chaperone-mediated therapy (CMT) of Fabry disease - an LSD.[49] However, this work demonstrates that the DGADP isomer **2.60** is far more potent and slightly more selective, and would pose a superior candidate for further clinical study.

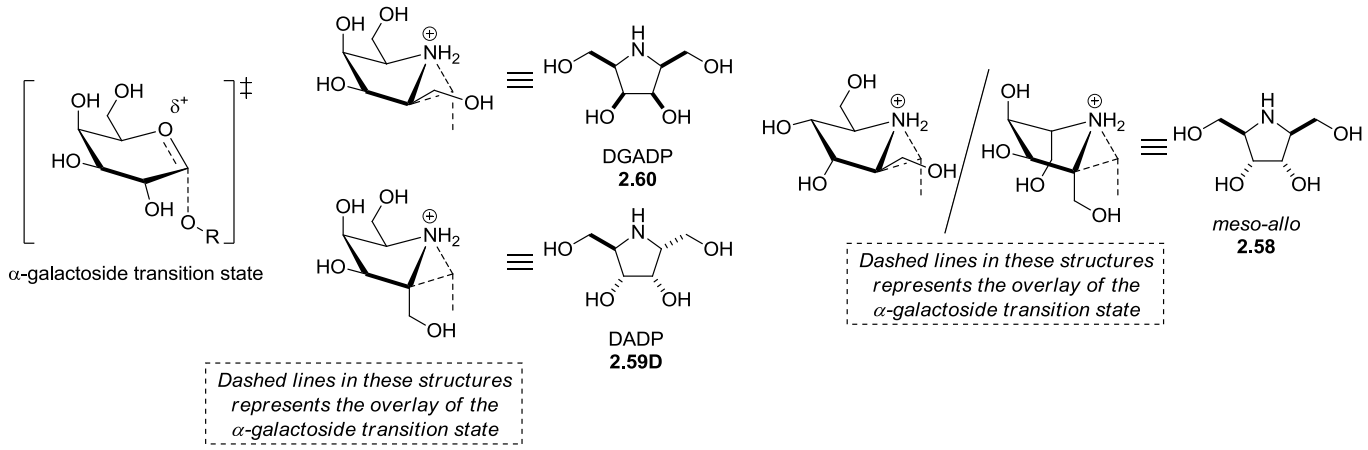
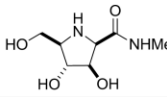
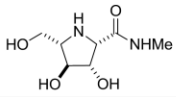
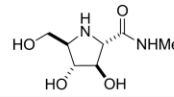
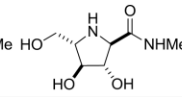
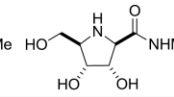
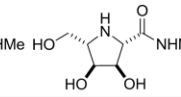
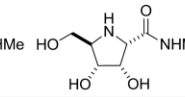
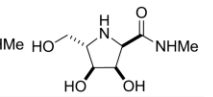



**Figure 2.11**. Structural correlation between the transition state of the α-galactosidase transition state and the iminosugars DGADP **2.60**,[76] DADP **2.59D** and *meso-allo* **2.58**.

The only enzymes for which no significant inhibition was observed for any iminosugar, were the α- and β-mannosidases, and β-glucuronidase. Also, the only two iminosugars that failed to significantly inhibit any enzyme were the *ido*-enantiomers; DIDP **2.61D** and L-DIDP **2.61L**.

2.3.6.2 *Proline amides*

| | $IC_{50}$ (μM) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| |  |  |  |  |  |  |  |  |
| | D-*gluco* | L-*gluco* | D-*manno* | L-*manno* | D-allo | L-allo | D-*altro* | L-*altro* |
| Enzyme | **2.119D** | **2.119L** | **2.131D** | **2.131L** | **2.182D** | **2.182L** | **2.143D** | **2.143L** |
| β-*N*-Acetylglucosaminidase | | | | | | | | |
| Human placenta | **2.6** | NI (13.0%) | **0.20** | **41** | 914 | **0.72** | NI (43.6%) | **11** |
| Bovine kidney | **3.1** | NI (18.1%) | **0.22** | **32** | NI (44.6%) | **0.32** | NI (44.1%) | **4.0** |
| Jack beans | **0.46** | NI (39.9%) | **0.033** | **7.3** | 219 | **0.41** | 249 | **7.7** |
| HL60 | **2.8** | NI (18.7%) | **0.20** | **50** | NI (42.9%) | **0.93** | NI (34.9%) | **14** |
| *Aspergillus oryzae* | **3.6** | NI (3.4%) | **0.30** | **53** | NI (29.8%) | **12** | NI (24.4%) | 115 |
| α-*N*-Acetylgalactosaminidase | | | | | | | | |
| Chicken liver | NI[a] (5.5%)[b] | NI (0%) | NI (0%) | NI (9.6%) | NI (1.3%) | NI (16.0%) | NI (0.6%) | NI (0%) |
| β-*N*-Acetylgalactosaminidase | | | | | | | | |
| HL60 | **11** | NI (1.8%) | **1.0** | 206 | NI (22.4%) | **2.8** | NI (18.8%) | 133 |
| *Aspergillus oryzae* | **5.4** | NI (0%) | **0.35** | **84** | NI (28.0%) | **9.5** | NI (21.0%) | 103 |
| β-Glucuronidase | | | | | | | | |
| *E. coli* | NI (0.8%) | NI (0%) | NI (25.1%) | NI (26.9%) | NI (1.2%) | NI (10.0%) | NI (0%) | NI (1.5%) |
| Bovine liver | NI (12.5%) | NI (10.3%) | NI (0%) | NI (3.6%) | NI (1.4%) | NI (0%) | NI (0.1%) | NI (0%) |

| | $IC_{50}$ (μM) | | | | | | | |
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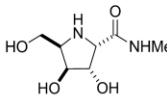
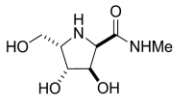
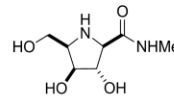
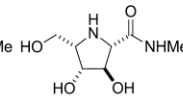
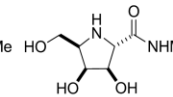
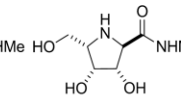
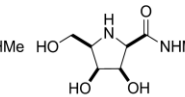
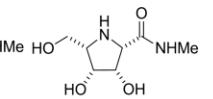
| |  |  |  |  |  |  |  |  |
| | D-*ido* | L-*ido* | D-*gulo* | L-*gulo* | D-talo | L-talo | D-*galacto* | L-*galacto* |
| Enzyme | **2.180D** | **2.180L** | **2.123D** | **2.123L** | **2.181D** | **2.181L** | **2.142D** | **2.142L** |
| β-*N*-Acetylglucosaminidase | | | | | | | | |
| Human placenta | 351 | **38** | 584 | **5.3** | **0.92** | NI (34.6%) | **54** | NI (37.4%) |
| Bovine kidney | 250 | **34** | 566 | **4.8** | **0.69** | NI (33.5%) | **60** | NI (34.0%) |
| Jack beans | **38** | **4.5** | 119 | **1.2** | **0.15** | 409 | **9.0** | 588 |
| HL60 | 329 | **88** | 849.00 | **6.1** | **0.96** | NI (32.6%) | **24** | NI (31.5%) |
| *Aspergillus oryzae* | NI (1.3%) | **87** | NI (9.3%) | **6.6** | **32** | NI (11.0%) | NI (37.4%) | NI (11.7%) |
| α-*N*-Acetylgalactosaminidase | | | | | | | | |
| Chicken liver | NI (6.7%) | NI (31.1%) | NI (10.0%) | NI (0%) | 312 | NI (2.9%) | **99** | NI (23.2%) |
| β-*N*-Acetylgalactosaminidase | | | | | | | | |
| HL60 | NI (41.8%) | 269 | NI (30.2%) | **26** | **3.6** | NI (12.7%) | **83** | NI (15.5%) |
| *Aspergillus oryzae* | NI (2.8%) | **83** | NI (9.6%) | **7.3** | **25** | NI (11.0%) | NI (37.4%) | NI (17.5%) |
| β-Glucuronidase | | | | | | | | |
| *E. coli* | NI (2.6%) | NI (3.5%) | NI (1..9%) | NI (0%) | NI (0%) | NI (16.1%) | NI (0%) | NI (10.0%) |
| Bovine liver | NI (6.6%) | NI (16.5%) | NI (2.6%) | NI (8.5%) | NI (2.6%) | NI (3.2%) | NI (0%) | NI (9.8%) |

[a] *NI : No inhibition (less than 50% inhibition at 1000 μM).*

**Table 2.4**. Concentration of pyrrolidines giving 50% inhibition ($IC_{50}$) of various glycosidases.

There are relatively few examples of potent hexosaminidase inhibitors within the literature (Section 2.2.1, pages 51-54), and despite this it can be seen that the *N*-methyl proline amide class represents a significant family of such inhibitors (**Table 2.4**). None of the proline amides were found to inhibit β-glucuronidase enzymes, and only two presented activity against the α-*N*-acetylgalactosaminidase enzyme (chicken liver). The D-*galacto*-configured amide **2.142D** showed good inhibition ($IC_{50}$ 99 μM) and the C2-epimeric amide, D-*talo* **2.181D** gave moderate inhibition that was approximately three-fold weaker ($IC_{50}$ 312 μM). The inhibition displayed by these compounds is due to the orientation of the C3, C4 and C5 stereocentres. In both inhibitors the structural correlation of this motif with the α-*N*-acetylgalactosaminidase transition state affords the activity (**Figure 2.12**). The magnitude of that inhibition is related to the orientation of the C2-amide moiety. The correlation between the C2-amide functionality of the more potent D-*galacto* inhibitor **2.142D** and the transition state is not comparable - it would appear that the D-*talo* amide **2.181D** would be a better fit. This result may indicate additional interactions between the amide group of the iminosugar **2.142D** and the α-*N*-acetylgalactosaminidase enzyme active site.

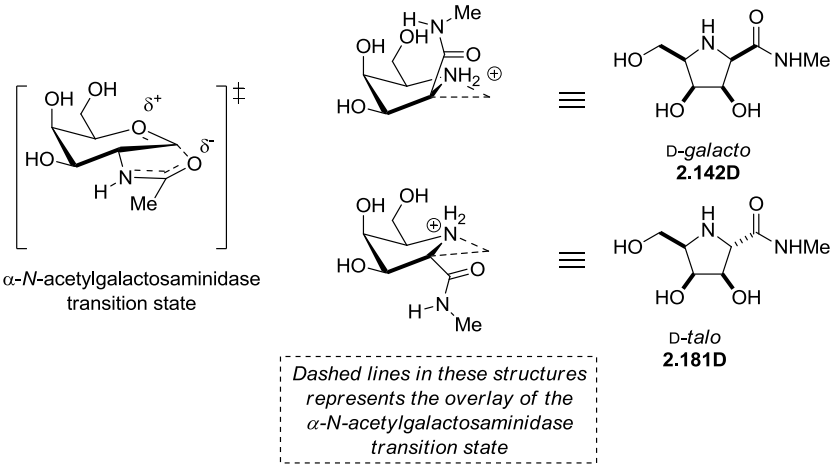



**Figure 2.12**. Structural correlation between the transition state of the α-*N*-acetylgalactosaminidase transition state and the proline amides D-*galacto* **2.142D** and D-*talo* **2.181D**.

At least one of each pair of enantiomers demonstrates excellent inhibition of β-hexosaminidases (β-*N*-acetylglucosaminidases and β-*N*-acetylgalactosaminidases). D-*Manno* **2.131D** possesses the

strongest inhibition (jack bean: $IC_{50}$ 33 nM), and its C4-epimer, D-*talo* **2.181D** is a close second (jack bean: $IC_{50}$ 150 nM). Structural comparison of these compounds reveals that the best inhibitor of each pair of enantiomers possesses a (*R*)-configured hydroxyl at C3. This C3-hydroxyl thus appears to convey biological activity in this class. For example, taking D-*manno* **2.131D** and inverting C3-hydroxyl leads to the (3*S*)-configured D-*altro* amide **2.143D** (**Figure 2.13**). This amide shows extremely weak inhibition (jack bean: $IC_{50}$ 249 μM) - approximately a 10,000-fold decrease in activity. In the eight amides which possess a (3*R*)-configuration, better inhibition is displayed by those with a 2,3-*trans* arrangement, or (2*R*,3*R*)-configuration. Again, taking D-*manno* **2.131D** as the example, this amide has a 2,3-*trans* disposition; changing this to 2,3-*cis*, or (2*S*,3*R*), leads to the amide D-*gluco* **2.119D** and a 10-fold reduction in activity (jack bean: $IC_{50}$ 460 nM). Any changes in the remaining two stereocentres are similarly well tolerated. Altering C4 of D-*manno* **2.131D** gives D-*talo* **2.181D** and a five-fold reduction in activity. L-*Gulo* **2.123L** (jack bean: $IC_{50}$ 1.2 μM) is given by a change in C5 of D-*manno* **2.131D**, and a more significant fifty-fold reduction is observed. However if both C4 and C5 are simultaneously changed this affords L-*allo* **2.182L** and only a ten-fold drop (jack bean: $IC_{50}$ 430 nM). Thus it can be seen that β-hexosaminidase enzymes are fairly tolerant towards the structural diversity of the (3*R*)-configured proline amides.

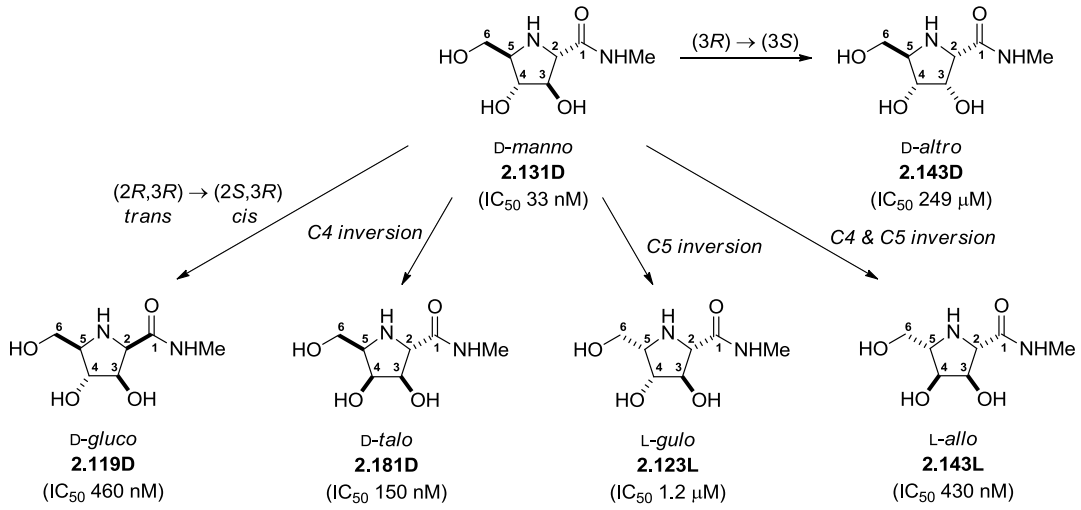



**Figure 2.13**. The effect of changing the stereoconfiguration on β-*N*-acetylglucosaminidase (jack bean) inhibition.

The best inhibitors are D-*manno* **2.131D** and D-*talo* **2.181D**, and the reason for this can be seen in their structural similarity to the β-*N*-acetylglucosaminidase and β-*N*-acetylgalactosaminidase transition states, respectively (**Figure 2.14**). The (2*R*,3*R*)-trans disposition is present in the transition states of the natural substrates GlcNAc **2.17** and GalNAc **2.18**, evidently accounting for the inhibitory activity observed in the (2*R*,3*R*)-proline amides. D-*Manno* **2.131D** possesses the same spatial arrangement of C4- and C6-hydroxyls as GlcNAc **2.17**; and D-*talo* **2.181D** possesses an equivalent configuration to GalNAc **2.18**. This accounts for the greater inhibition shown by these two proline amides compared to the remaining (3*R*)-configured proline amides. This mode of inhibition has been recently supported in a publication by Sumida *et al*.[136]

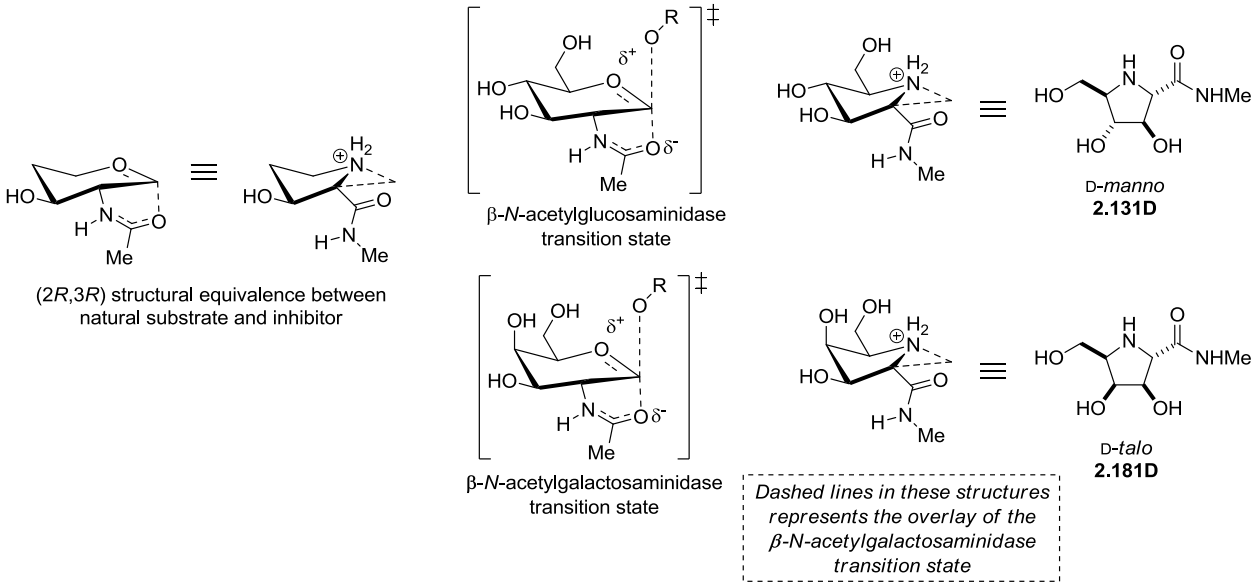
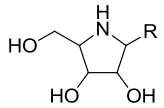



**Figure 2.14**. Reasoning for the inhibitory properties of the (2*R*,3*R*)-motif; and structural correlation between the transition state of the β-hexosaminidase transition states,[136] and the proline amides D-*manno* **2.131D** and D-*talo* **2.181D**.

The inhibition profiles of the proline amides are found to be in good agreement with a similar class of pyrrolidine-containing 1-acetamido-iminosugars (**Table 2.5**). Eight of these compounds have been synthesised, however the biological evaluation of these is incomplete, with the equivalent L-*ido* configured acetamide having not been tested against β-hexosaminidase. In addition, none of these compounds have been assayed for α-*N*-acetylgalactosaminidase inhibition.

|  | **β-hexosaminidase inhibition - $IC_{50}$ (μM)** Relative Configuration | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | D-*manno* | L-*manno* | D-*gluco* | D-*talo* | L-*talo* | D-*altro* | L-*galacto* | L-*ido* |
| **1-acetamide** (R = $CH_2NHAc$) | 0.022-0.10[92,137] ($K_i$ 0.22-40)[26,27,138,139] | 27[92] | 3.6[27,138] ($K_i$ 240)[26] | 0.2[92] | 500[140] | NI[140] | 500[140] | ND[b] |
| **proline amide**[a] (R = CONHMe) | 0.033 | 7.3 | 0.46 | 0.15 | 409 | 249 | 588 | 4.5 |

[a]β-*N*-acetylglucosaminidase (jack bean); [b]ND = no data.

**Table 2.5**. Correlation in biological profiles for β-hexosaminidase inhibition between 1-acetamide pyrrolidines and the equivalent proline amides

## 2.3.7 Conclusion and future work

The research presented in this chapter has shown the versatility of glucuronolactone as a starting material. In Section 2.2 (pages 51-66) the synthetic methodology previously established to access DGJNAc **2.20D** was shown to be both robust and scalable; affording in excess of one-gram of target material. From there Section 2.3 (pages 67-123) demonstrated that independent epimerisation of three stereocentres of a readily accessible, enantiomeric-pair of starting materials, could lead to every possible stereoisomer of two pyrrolidine-based iminosugar classes. Overall two different categories of iminocyclisation were employed on the glucuronolactone scaffold: double-displacement of a ditriflate leading to DGJNAc **2.20D** and the intramolecular $S_N2$-displacement leading to the pyrrolidines and proline amides. All of the target iminosugars were synthesised with high efficiency, and in addition Section 2.3 presents the first methodology to be completed for the global access to every pyrrolidine and proline amide stereoisomer. This work has permitted, for the first time, a side-by-side comparison of the biological profile of every pyrrolidine and also every proline amide. This has allowed the qualitative analysis of the structure-activity relationships between these inhibitors and a range of glycosidases. Given the potent and selective inhibition that is displayed by a remarkable quantity of these iminosugars, many deserve further study for potential clinical applications. One such

example being the *meso-galacto*-configured pyrrolidine DGAPD **2.60**; this compound demonstrated more potent inhibition that the C2-epimer D-DADP **2.59D**, which has been suggested to be a possible pharmacological chaperone for the treatment of Fabry disease, a lysosomal storage disorder (LSD).[49] The biological evaluation of DGJNAc **2.20D** and its *N*-alkyl derivatives has shown that extracellular enzymes may be targeted in preference, which in future may be extended and studied for to the D-*galacto* proline amide **2.142D**. This compound may prove useful in developing a new cancer treatment strategy by the preservative of the macrophage-activating factor (MAF).

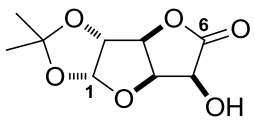
## 2.4 Experimental

### 2.4.1 General Experimental

All commercial reagents were used as supplied. THF and DMF were purchased dry from the Aldrich chemical company in sure-seal bottles. Methanol and pyridine were purchased dry from the Fluka chemical company in sure-seal bottles over molecular sieves. All other solvents were used as supplied (Analytical or HPLC grade), without prior purification. Thin layer chromatography (TLC) was performed on aluminium sheets coated with 60 $F_{254}$ silica. Plates were visualised using a spray of 0.2% w/v cerium (IV) sulfate and 5% ammonium molybdate solution in 2 M sulfuric acid. Flash chromatography was performed on Sorbsil C60 40/60 silica. Melting points were recorded on a Kofler hot block and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g.100 $mL^{-1}$. Equilibrium values are quoted for all anomeric mixtures. Infrared spectra were recorded on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer using neat samples or thin films on NaCl plates unless otherwise stated. Only the characteristic peaks are quoted. Low resolution mass spectra (LRMS *m*/*z*) were recorded on a VG MassLab 20-250, Micromass BIOQ-II, Micromass Platform 1, Micromass TofSpec 2E, or Micromass Autospec 500 OAT spectrometers, and high resolution mass spectra (HRMS *m*/*z*) on a Micromass Autospec 500 OAT. Techniques used were electrospray (ESI), chemical ionization (CI $NH_3$) or atmospheric pressure chemical ionization (ACPI). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AMX 500 ($^1$H: 500 MHz and $^{13}$C: 125.7 MHz) and Bruker DPX 400 and DQX 400 spectrometers ($^1$H: 400 MHz and $^{13}$C: 100.6 MHz) in the deuterated solvent stated. All chemical shifts ($\delta$) are quoted in ppm and coupling constants ($J$) in Hz. Residual signals from the solvents were used as an internal reference, except in the case of deuterium oxide, where acetonitrile was used as the reference. Salt solutions used during work-up procedures are saturated unless otherwise stated. All reactions are performed under argon or nitrogen.

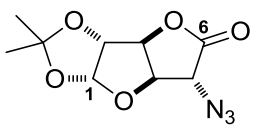
2.4.2 Synthesis of DGJNAc

**1,2-*O*-Isopropylidene-α-D-glucurono-3,6-lactone 1.60D**



D-Glucurono-3,6-lactone **2.1D** (30.0 g, 170 mmol) was dissolved in a solution of acetone (250 mL) and concentrated sulfuric acid (8.3 mL) at RT. The reaction mixture was stirred for 4 h, after which TLC analysis (ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.40→baseline) and the formation of a major product ($R_f$ 0.88). The reaction mixture was neutralized by the addition of solid sodium bicarbonate, filtered and concentrated *in vacuo*. The crude residue was recrystallised (toluene) to afford the acetonide **1.60D** as a white crystalline solid (33.0 g, 90%); HRMS (ESI +ve): found 239.0526 [M+$Na^+$]; $C_9H_{12}NaO_6$ requires 239.0526; m.p. 118-120 °C (toluene) [Lit.[2] m.p. 120.5-121.5 °C (toluene)]; $[\alpha]_D^{25}$ +59.2 (*c* 2.00, $CHCl_3$) [Lit.[2] $[\alpha]_D^{20}$ +52.5 (*c* 1.95, $CHCl_3$)]; $\nu_{max}$ (thin film): 1790 (s, C=O), 3441 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.36, 1.53 (2 x 3H, s, $C(CH_3)_2$), 3.02 (1H, s, OH5), 4.53 (1H, d, H5, $J_{5,4}$ 4.4), 4.83 (1H, d, H2, $J_{2,1}$ 3.4), 4.84 (1H, d, H3, $J_{3,4}$ 2.9), 4.95 (1H, dd, H4, $J_{4,3}$ 2.9, $J_{4,5}$ 4.4), 6.00 (1H, d, H1, $J_{1,2}$ 3.4); $\delta_C$ ($CDCl_3$, 100 MHz): 26.5, 26.9 ($C(\underline{C}H_3)_2$), 70.6 (C5), 78.1 (C4), 81.3 (C3), 82.9 (C2), 106.6 (C1), 113.6 ($\underline{C}(CH_3)_2$), 173.7 (C6); LRMS (ESI +ve): 239 (54%, M+$Na^+$), 271 (30%, M+MeOH+$Na^+$), 455 (100%, 2M+$Na^+$).

**5-Azido-5-deoxy-1,2-*O*-isopropylidene-β-L-idurono-3,6-lactone 2.35L**



Trifluoromethanesulfonic anhydride (39.1 mL, 232 mmol) was added dropwise to a solution of the lactone **1.60D** (38.7 g, 179 mmol) and pyridine (43.4 mL, 536 mmol) in dichloromethane

(400 mL) at -40 °C. The reaction mixture was stirred for 1 h, with an internal temperature maintained between -35 °C and -25 °C, after which TLC analysis (1:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.32) and the formation of a major product ($R_f$ 0.80). The reaction was diluted with dichloromethane (150 mL) and washed with 2 M aqueous hydrochloric acid (3 x 600 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude triflate **1.61D**.

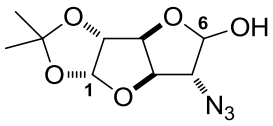
Partial data for crude triflate **1.61D**: m.p. 160-162 °C [Lit.[2] m.p. 160 °C (ethanol)]; $[\alpha]_D^{25}$ +55.1 (*c* 1.01, $CHCl_3$) [Lit.[2] $[\alpha]_D^{20}$ +49.2 (*c* 1.28, $CHCl_3$)]; $\delta_H$ ($CDCl_3$, 400 MHz): 1.37, 1.54 (2 x 3H, s, $C(CH_3)_2$), 4.87 (1H, d, H2, $J_{2,1}$ 3.6), 4.94 (1H, d, H3, $J_{3,4}$ 2.8), 5.08 (1H, dd, H4, $J_{4,3}$ 2.8, $J_{4,5}$ 4.3), 5.42 (1H, d, H5, $J_{5,4}$ 4.3), 6.06 (1H, d, H1, $J_{1,2}$ 3.6).

Sodium azide (15.2 g, 232 mmol) was added in one portion to a solution of the crude triflate **1.61D** in DMF (400 mL) at -30 °C. The reaction mixture was stirred for 90 min, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.58) and formation of a major product ($R_f$ 0.72). The reaction was diluted with ethyl acetate (600 mL) and washed with a 4:1 water/brine solution (3 x 300 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (5:1, cyclohexane/ethyl acetate) to afford the azide **2.35L** as a white crystalline solid (39.7 g, 92%); HRMS (ESI +ve): found 296.0855 [M+MeOH+$Na^+$]; $C_{10}H_{15}N_3NaO_6$ requires 296.0853; m.p. 110-112 °C [Lit.[2] m.p. 114-116 °C]; $[\alpha]_D^{25}$ +240.1 (*c* 1.00, $CHCl_3$) [Lit.[2] $[\alpha]_D^{20}$ +243 (*c* 1.1, $CHCl_3$)]; $\nu_{max}$ (thin film): 1792 (s, C=O), 2124 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz): 1.35, 1.51 (2 x 3H, s, $C(CH_3)_2$), 4.24 (1H, s, H5), 4.66 (1H, d, H4, $J_{4,3}$ 3.1), 4.84 (1H, d, H2, $J_{2,1}$ 3.8), 4.95 (1H, d, H3, $J_{3,4}$ 3.1), 5.94 (1H, d, H1, $J_{1,2}$ 3.8); $\delta_C$ ($CDCl_3$, 100 MHz): 26.5, 27.0 ($C(\underline{C}H_3)_2$), 61.2 (C5), 81.1 (C4), 81.8 (C2), 84.9 (C3), 106.2 (C1), 113.4

($\underline{C}(CH_3)_2$), 170.7 (C6); LRMS (ESI +ve): 264 (25%, $M+Na^+$), 296 (100%, $M+MeOH+Na^+$), 328 (15%, $M+2MeOH+Na^+$), 569 (85%, $2M+2MeOH+Na^+$); (ESI –ve): 276 (100%, $M+^{35}Cl^-$), 278 (40%, $M+^{37}Cl^-$).

Similar treatment of **1,2-*O*-isopropylidene-α-L-glucurono-3,6-lactone 1.60L** (10.0 g, 46.3 mmol) in a suitably scaled procedure afforded **1,2-*O*-isopropylidene-5-*O*-trifluoromethanesulfonyl-α-L-glucurono-3,6-lactone 1.61L** (16.1 g, quant.) as a white crystalline solid; m.p. 159-161°C; $[\alpha]_D^{25}$ -53.3 (*c* 0.93, $CHCl_3$). Subsequent treatment of **1,2-*O*-isopropylidene-5-*O*-trifluoromethanesulfonyl-α-L-glucurono-3,6-lactone 1.61L** (16.1 g, 46.3 mmol) in a suitably scaled procedure afforded **5-azido-5-deoxy-1,2-*O*-isopropylidene-β-D-idurono-3,6-lactone 2.35D** (10.9 g, 97% over two steps) as a white crystalline solid; m.p. 111-113°C; $[\alpha]_D^{25}$ -213.5 (*c* 0.96, $CHCl_3$).

**5-Azido-5-deoxy-1,2-*O*-isopropylidene-β-L-*ido*-hexodialdo-1,4:3,6-difuranose 2.36L**



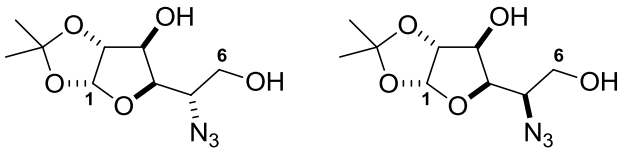

Diisobutylaluminium hydride (1.5 M in toluene, 91.0 mL, 137 mmol) was added dropwise to a solution of the azide **2.35L** (21.9 g, 90.8 mmol) in dichloromethane (200 mL) at -78 °C. The reaction mixture was stirred at this temperature for 90 min, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.72) and formation of two products (major $R_f$ 0.40, minor $R_f$ 0.39). The reaction was diluted with dichloromethane (600 mL) and saturated aqueous sodium potassium tartrate (500 mL) added. The biphasic mixture was stirred vigorously for 18 h, after which the phases were separated and the aqueous layer extracted with dichloromethane (8 x 300 mL). The organic fractions were

combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude lactols **2.36L** as a pale-yellow crystalline solid (18.6 g, 84%), in a 2:3 (A:B) ratio of anomers. This crude product was reacted on without further purification. HRMS (ESI +ve): found 298.10110 [M+MeOH+$Na^+$]; $C_{10}H_{17}N_3NaO_6$ requires 298.1010; m.p. 53-55 $^oC$; $[\alpha]_D^{25}$ -21.4 (*c* 1.10, $CHCl_3$); $\nu_{max}$ (thin film): 2113 (s, $N_3$), 3425 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.33 (3H, s, $CH_3^B$), 1.35 (3H, s, $CH_3^A$), 1.51 (6H, s, $CH_3^A$, $CH_3^B$), 3.28 (1H, d, $OH6^A$, $J_{OH,6}$ 7.2), 3.46 (1H, br. s, $OH6^B$), 4.08 (1H, s, $H5^A$), 4.09 (1H, d, $H5^B$, $J_{5,6}$ 4.1), 4.64 (1H, d, $H2^B$, $J_{2,1}$ 3.8), 4.72 (1H, d, $H3^B$ or $H4^B$, $J_{3,4}$ 3.6), 4.76 (2H, a-t, $H2^A$, $H3^A$ or $H4^A$, *J* 3.1), 4.79 (1H, d, $H3^B$ or $H4^B$, $J_{3,4}$ 3.6), 4.81 (1H, d, $H3^A$ or $H4^A$, $J_{3,4}$ 4.1), 5.35 (1H, d, $H6^A$, $J_{6,OH}$ 6.8), 5.52 (1H, dd, $H6^B$, $J_{5,6}$ 4.1, $J_{6,OH}$ 8.0), 5.89 (1H, d, $H1^B$, $J_{1,2}$ 3.4), 6.01 (1H, d, $H1^A$, $J_{1,2}$ 3.8); $\delta_C$ ($CDCl_3$, 100 MHz): 26.5, 27.2 ($C(\underline{C}H_3)_2^B$), 26.7, 27.3 ($C(\underline{C}H_3)_2^A$), 66.4 ($C5^B$), 69.1 ($C5^A$), 83.5 ($C2^B$), 83.6, 85.0 ($C3^B$, $C4^B$), 84.7, 85.2, 86.9 ($C2^A$, $C3^A$, $C4^A$), 98.9 ($C6^B$), 102.5 ($C6^A$), 106.5 ($C1^B$), 106.9 ($C1^A$), 112.7 ($\underline{C}(CH_3)_2^B$), 113.0 ($\underline{C}(CH_3)_2^A$); LRMS (ESI +ve): 298 (100%, M+MeOH+$Na^+$), 573 (83%, 2M+2MeOH+$Na^+$), 589 (48%, 2M+2MeOH+$K^+$).

Similar treatment of **5-azido-5-deoxy-1,2-*O*-isopropylidene-β-D-idurono-3,6-lactone 2.35D** (10.7 g, 44.4 mmol) in a suitably scaled procedure afforded **5-azido-5-deoxy-1,2-*O*-isopropylidene-β-D-*ido*-hexodialdo-1,4:3,6-difuranose 2.36D** (10.0 g, 93%) as a white crystalline solid, in a 1.8:1 (A:B) anomeric mixture; m.p. 57-59 $^oC$; $[\alpha]_D^{25}$ +27.4 (*c* 1.05, $CHCl_3$).

**5-Azido-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose 2.37L /**

**5-Azido-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose 2.38L**



**2.37L** **2.38D**

Sodium borohydride (1.16 g, 30.6 mmol) was added portion-wise to a solution of the lactols **2.36L** (18.6 g, 76.5 mmol) in methanol (200 mL) at -30 °C. The reaction mixture was stirred for 90 min, with an internal temperature maintained between -20 °C and -10 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the consumption of the starting material (major $R_f$ 0.40, minor $R_f$ 0.39) and the formation of a major ($R_f$ 0.15) and a minor product ($R_f$ 0.17). The reaction was neutralized with glacial acetic acid and concentrated *in vacuo*. The crude residue was dissolved in ethyl acetate (600 mL), washed with aqueous sodium bicarbonate (600 mL) and the aqueous phase extracted with ethyl acetate (2 x 800 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (2:1 to 1:9, cyclohexane/ethyl acetate) to afford the *ido*-diol **2.37L** as a white crystalline solid (16.9 g, 90%) and the *gluco*-diol **2.38D** as a clear oil (940 mg, 5%).

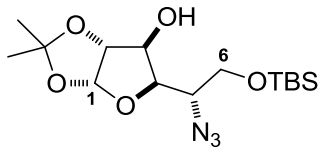
Data for *ido*-diol **2.37L**: HRMS (ESI +ve): found 268.0903 [M+$Na^+$]; $C_9H_{15}N_3NaO_5$ requires 268.0904; m.p. 122-124 °C [Lit.[47] m.p. 119-121 °C]; $[\alpha]_D^{25}$ -75.4 (*c* 1.00, $CHCl_3$) [Lit.[47] $[\alpha]_D^{25}$ -77.0 (*c* 1.04, methanol)]; $\nu_{max}$ (thin film): 2108 (s, $N_3$), 3335 (br. s, OH); $\delta_H$ ($(CD_3)_2CO$, 400 MHz): 1.27, 1.41 (2 x 3H, s, $C(CH_3)_2$), 3.66 (1H, a-dt, H6, $J_{6,5} = J_{6,OH}$ 5.8, $J_{6,6'}$ 10.6), 3.70-3.75 (1H, m, H5), 3.78 (1H, ddd, H6', $J_{6',5}$ 3.4, $J_{6',OH}$ 5.1, $J_{6',6}$ 10.6), 4.16-4.18 (2H, m, H3, H4), 4.27 (1H, a-t, OH6, $J_{OH,6} = J_{OH,6'}$ 5.5), 4.52 (1H, d, OH3, $J_{OH,3}$ 4.8), 4.54 (1H, d, H2, $J_{2,1}$ 3.8), 5.91 (1H, d, H1, $J_{1,2}$ 3.8); $\delta_C$ ($(CD_3)_2CO$, 100 MHz): 26.8, 27.4 ($C(\underline{C}H_3)_2$), 62.8

(C6), 65.0 (C5), 75.5, 81.9 (C3, C4), 87.0 (C2), 105.9 (C1), 112.3 ($\underline{C}(CH_3)_2$); LRMS (ESI +ve): 268 (93%, $M+Na^+$), 513 (100%, $2M+Na^+$); (ESI –ve): 244 (25%, $[M-H]^-$), 280 (100%, $M+^{35}Cl^-$), 282 (70%, $M+^{37}Cl^-$), 489 (55%, $[2M-H]^-$).

Data for *gluco*-diol **2.38D**: HRMS (ESI +ve): found 268.0902 [M+Na+]; $C_9H_{15}N_3NaO_5$ requires 268.0904; $[\alpha]_D^{25}$ -11.2 (*c* 1.42, $CHCl_3$) [Lit.[141] $[\alpha]_D^{25}$ -10.55 (*c* 2.18, $CHCl_3$)]; $\nu_{max}$ (thin film): 2111 (s, $N_3$), 3424 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.32, 1.49 (2 x 3H, s, $C(CH_3)_2$), 2.91 (2H, br. s, OH3, OH6), 3.81 (1H, dd, H6, $J_{6,5}$ 5.6, $J_{6,6'}$ 11.4), 3.87 (1H, ddd, H5, $J_{5,6'}$ 3.4, $J_{5,6}$ 5.6, $J_{5,4}$ 8.5), 3.98 (1H, dd, H6', $J_{6',5}$ 3.4, $J_{6',6}$ 11.4), 4.12 (1H, dd, H4, $J_{4,3}$ 2.7, $J_{4,5}$ 8.5), 4.32 (1H, d, H3, $J_{3,4}$ 2.7), 4.54 (1H, d, H2, $J_{2,1}$ 3.8), 5.94 (1H, d, H1, $J_{1,2}$ 3.8); $\delta_C$ ($CDCl_3$, 100 MHz): 26.1, 26.7 ($C(\underline{C}H_3)_2$), 60.8 (C5), 63.0 (C6), 74.9 (C3), 79.2 (C4), 85.0 (C2), 104.8 (C1), 112.1 ($\underline{C}(CH_3)_2$); LRMS (ESI +ve): 268 (100%, $M+Na^+$), 300 (15%, $M+MeOH+Na^+$), 513 (100%, $2M+Na^+$); (ESI –ve): 244 (91%, $[M-H]^-$), 280 (30%, $M+^{35}Cl^-$), 282 (9%, $M+^{37}Cl^-$), 489 (100%, $[2M-H]^-$).

Similar treatment of **5-azido-5-deoxy-1,2-*O*-isopropylidene-β-D-*ido*-hexodialdo-1,4:3,6-difuranose 2.36D** (10.0g, 41.1 mmol) in a suitably scaled procedure afforded **5-azido-5-deoxy-1,2-*O*-isopropylidene-β-D-idofuranose 2.37D** (8.7 g, 86%) as a white crystalline solid and **5-azido-5-deoxy-1,2-*O*-isopropylidene-α-L-glucofuranose 2.38L** (201 mg, 2%) as a yellow oil; **2.37D**: m.p. 119-120°C (toluene); $[\alpha]_D^{25}$ +63.1 (*c* 1.15, $CHCl_3$). **2.38D**: $[\alpha]_D^{25}$ +13.2 (*c* 1.41, $CHCl_3$).

**5-Azido-6-*O*-*tert*-butyldimethylsilyl-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose 2.39L**

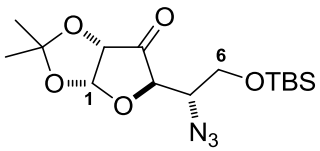



*tert*-Butyldimethylsilyl chloride (19.5 g, 129 mmol) was added to a solution of the diol **2.37L** (21.1 g, 86.0 mmol) in pyridine (210 mL) at RT. The reaction mixture was stirred for 18 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.15) and the formation of a major product ($R_f$ 0.60). The reaction was quenched with methanol (4 mL) and concentrated *in vacuo*. The crude residue was dissolved in ethyl acetate (750 mL) and washed with 2 M aqueous hydrochloric acid (3 x 450 mL). The organic phase was dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash chromatography (20:1 to 3:1, cyclohexane/ethyl acetate) to afford the silyl ether **2.39L** as a colourless oil (27.2 g, 88%); HRMS (ESI +ve): found 382.1769 [M+$Na^+$]; $C_{15}H_{29}N_3NaO_5Si$ requires 382.1769; $[\alpha]_D^{25}$ -13.9 (*c* 1.40, $CHCl_3$); $\nu_{max}$ (thin film): 2099 (s, $N_3$), 3464 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 0.13 (6H, s, $Si(CH_3)_2$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.32, 1.50 (2 x 3H, s, $C(CH_3)_2$), 3.22 (1H, d, OH3, $J_{OH,3}$ 3.5), 3.64-3.69 (1H, m, H5), 3.77-3.82 (2H, m, H6, H6'), 4.12 (1H, dd, H4, $J_{4,3}$ 2.5, $J_{4,5}$ 7.8), 4.21 (1H, a-t, H3, $J_{3,4} = J_{3,OH}$ 3.0), 4.55 (1H, d, H2, $J_{2,1}$ 3.5), 5.97 (1H, d, H1, $J_{1,2}$ 3.5); $\delta_C$ ($CDCl_3$, 100 MHz): -5.7, -5.7 ($Si(\underline{C}H_3)_2$), 18.1 ($Si\underline{C}(CH_3)_3$), 25.7 ($SiC(\underline{C}H_3)_3$), 26.2, 26.8 ($C(\underline{C}H_3)_2$), 61.9 (C5), 63.3 (C6), 75.2 (C3), 82.4 (C4), 85.0 (C2), 104.5 (C1), 111.7 ($\underline{C}(CH_3)_2$); LRMS (ESI +ve): 382 (100%, M+$Na^+$), 741 (98%, 2M+$Na^+$); (ESI –ve): 358 (76%, [M-H]$^-$), 394 (100%, M+$^{35}Cl^-$), 396 (74%, M+$^{37}Cl^-$), 404 (80%, M+$HCOO^-$), 717 (98%, [2M-H]$^-$).

Similar treatment of **5-azido-5-deoxy-1,2-*O*-isopropylidene-β-D-idofuranose 2.37D** (5.07 g, 60.7 mmol) in a suitably scaled procedure afforded **5-azido-6-*O*-*tert*-butyldimethylsilyl-5-**

**deoxy-1,2-*O*-isopropylidene-β-D-idofuranose 2.39D** (7.00 g, 94%) as a clear oil; $[\alpha]_D^{25}$ +15.1 (*c* 1.20, $CHCl_3$).

**5-Azido-6-*O*-*tert*-butyldimethylsilyl-5-deoxy-1,2-*O*-isopropylidene-β-L-*lyxo*-hexofuranos-3-ulose 2.40L**



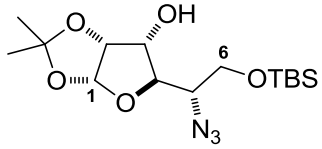

Method A (PCC): Pyridinium chlorochromate (110 g, 511 mmol) was added to a solution of the alcohol **2.39L** (30.6 g, 85.1 mmol) in dichloromethane (450 mL) over 3 Å molecular sieves at RT. The reaction mixture was stirred for 18 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.60) and the formation of a product ($R_f$ 0.80→0.30). The reaction was filtered through Celite®, concentrated *in vacuo* and purified by flash chromatography (5:1 to 3:1, cyclohexane/ethyl acetate) to afford the ketone **2.40L** as a clear oil (24.6 g, 81%).

Method B (DMP): Dess-Martin periodinane **2.144** (2.5 g, 5.89 mmol) was added to a solution of the alcohol **2.39L** (1.41 g, 3.92 mmol) in dichloromethane (20 mL) at 0 °C. The reaction was allowed to warm to RT and stirred for 4 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.60) and the formation of a single product ($R_f$ 0.80→0.30). The reaction mixture was diluted with ethyl acetate (100 mL) and a saturated solution of sodium bicarbonate and sodium thiosulfate added (125 mL). The biphasic mixture was stirred vigorously, separated and the organic layer washed with a saturated solution of sodium bicarbonate and sodium thiosulfate (2 x 100 mL). The organic phase was dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash chromatography (5:1 to 3:1,

cyclohexane/ethyl acetate) to affording the ketone **2.40L** as a clear oil (1.33 g, 95%); HRMS (ESI +ve): found 412.1878 [M+MeOH+$Na^+$]; $C_{16}H_{31}N_3NaO_6Si$ requires: 412.1880; $[\alpha]_D^{25}$ +130.8 (*c* 1.09, $CHCl_3$); $\nu_{max}$ (thin film): 1777 (s, C=O), 2111 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz): 0.10, 0.11 (2 x 3H, s, $Si(CH_3)_2$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.43, 1.46 (2 x 3H, s, $C(CH_3)_2$), 3.80 (1H, ddd, H5, $J_{5,4}$ 2.0, $J_{5,6}$ 5.5, $J_{5,6'}$ 7.9), 3.87 (1H, dd, H6, $J_{6,5}$ 5.5, $J_{6,6'}$ 10.2), 3.94 (1H, dd, H6', $J_{6',5}$ 7.9, $J_{6',6}$ 10.2), 4.39 (1H, dd, H2, $J_{2,4}$ 1.0, $J_{2,1}$ 4.3), 4.41 (1H, d, H4, $J_{4,2}$ 1.0, $J_{4,5}$ 2.0), 6.10 (1H, d, H1, $J_{1,2}$ 4.3); $\delta_C$ ($CDCl_3$, 100 MHz): -5.6, -5.6 ($Si(\underline{C}H_3)_2$), 18.2 ($Si\underline{C}(CH_3)_3$), 25.7 ($SiC(\underline{C}H_3)_3$), 27.1, 27.5 ($C(\underline{C}H_3)_2$), 62.8 (C6), 63.4 (C5), 76.4 (C2), 77.9 (C4), 103.6 (C1), 114.6 ($\underline{C}(CH_3)_2$), 208.9 (C3); LRMS (ESI +ve): 380 (100%, M+$Na^+$), 412 (95%, M+MeOH+$Na^+$), 737 (15%, 2M+$Na^+$); (ESI –ve): 424 (100%, M+MeOH+$^{35}Cl^-$), 426 (40%, M+MeOH+$^{37}Cl^-$).

Similar treatment of **5-azido-6-*O*-*tert*-butyldimethylsilyl-5-deoxy-1,2-*O*-isopropylidene-β-D-idofuranose 2.39D** (6.95 g, 19.3 mmol) in a suitably scaled procedure afforded **5-azido-6-*O*-*tert*-butyldimethylsilyl-5-deoxy-1,2-*O*-isopropylidene-β-D-*lyxo*-hexofuranos-3-ulose 2.40D** (6.59 g, 95%) as a clear oil; $[\alpha]_D^{25}$ -140.1 (*c* 1.11, $CHCl_3$).

**5-Azido-6-*O*-*tert*-butyldimethylsilyl-5-deoxy-1,2-*O*-isopropylidene-β-L-talofuranose 2.41L**

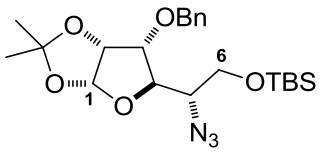



A solution of sodium borohydride (2.59 g, 68.4 mmol) in water (50 mL) was added dropwise to a solution of the ketone **2.40L** (24.6 g, 68.4 mmol) in ethanol (200 mL) at 0 °C. The reaction mixture was allowed to warm to RT and stirred for 90 min, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material

($R_f$ 0.80→0.30) and the formation of a single product ($R_f$ 0.58). The reaction was neutralised with glacial acetic acid and concentrated *in vacuo*. The crude residue was dissolved in ethyl acetate (400 mL), washed with aqueous sodium bicarbonate (2 x 400 mL) and brine (400 mL). The organic phase was dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash chromatography (50:1 to 3:1, cyclohexane/ethyl acetate) to afford the alcohol **2.41L** as a clear oil (22.4 g, 91%); HRMS (ESI +ve): found 382.1768 [M+$Na^+$]; $C_{15}H_{29}N_3NaO_5Si$ requires 382.1769; $[\alpha]_D^{25}$ +65.3 (*c* 1.30, $CHCl_3$); $\nu_{max}$ (thin film): 2099 (s, $N_3$), 3473 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 0.11 (6H, s, $Si(CH_3)_2$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.37, 1.56 (2 x 3H, s, $C(CH_3)_2$), 2.58 (1H, d, OH3, $J_{OH,3}$ 9.9), 3.64 (1H, dd, H5, $J_{5,4}$ 3.4, $J_{5,6}$ 5.5, $J_{5,6'}$ 7.9), 3.81 (1H, dd, H4, $J_{4,5}$ 3.4, $J_{4,3}$ 8.7), 3.87 (1H, dd, H6, $J_{6,5}$ 5.5, $J_{6,6'}$ 10.6), 3.91 (1H, dd, H6', $J_{6',5}$ 7.9, $J_{6',6}$ 10.6), 4.06 (1H, ddd, H3, $J_{3,2}$ 5.1, $J_{3,4}$ 8.7, $J_{3,OH}$ 9.9), 4.59 (1H, dd, H2, $J_{2,1}$ 3.8, $J_{2,3}$ 5.1), 5.82 (1H, dd, H1, $J_{1,2}$ 3.8); $\delta_C$ ($CDCl_3$, 100 MHz): -5.5, -5.5 ($Si(\underline{C}H_3)_2$), 18.1 ($Si\underline{C}(CH_3)_3$), 25.7 ($SiC(\underline{C}H_3)_3$), 26.5, 26.5 ($C(\underline{C}H_3)_2$), 62.4 (C5), 63.9 (C6), 72.2 (C3), 78.4 (C2), 79.3 (C4), 104.1 (C1), 112.9 ($\underline{C}(CH_3)_2$); LRMS (ESI +ve): 382 (100%, M+$Na^+$), 741 (70%, 2M+$Na^+$); (ESI –ve): 358 (100%, [M-H]$^-$), 394 (48%, M+$^{35}Cl^-$), 396 (15%, M+$^{37}Cl^-$), 717 (64%, [2M-H]$^-$).

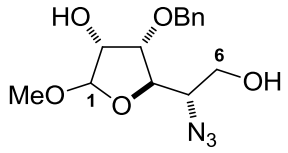
Similar treatment of **5-azido-6-*O*-*tert*-butyldimethylsilyl-5-deoxy-1,2-*O*-isopropylidene-β-D-*lyxo*-hexofuranos-3-ulose 2.40D** (6.50 g, 18.2 mmol) in a suitably scaled procedure afforded **5-azido-6-*O*-*tert*-butyldimethylsilyl-5-deoxy-1,2-*O*-isopropylidene-β-D-talofuranose 2.41D** (5.62 g, 88%) as a clear oil; $[\alpha]_D^{25}$ -70.7 (*c* 1.08, $CHCl_3$).

**5-Azido-3-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-5-deoxy-1,2-*O*-isopropylidene-β-L-talofuranose 2.42L**



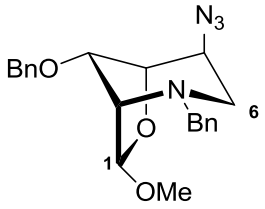

Sodium hydride (60% min. oil suspension, 3.74 g, 93.4 mmol) was added portion-wise to a solution of the alcohol **2.41L** (22.4 g, 62.2 mmol) and benzyl bromide (11.1 mL, 93.4 mmol) in DMF (200 mL) at 0 $^{o}$C. The reaction mixture was allowed to warm to RT and stirred for 1 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.58) and the formation of a major product ($R_f$ 0.72). The reaction mixture was quenched with methanol (2 mL) at 0 $^{o}$C and concentrated *in vacuo*. The crude residue was dissolved in ethyl acetate (500 mL) and washed with a 1:1 water/brine solution (3 x 200 mL). The organic phase was dried ($MgSO_4$), filtered, concentrated *in vacuo* and the crude residue was purified by flash chromatography (50:1 to 20:1, cyclohexane/ethyl acetate) to afford the benzyl ether **2.42L** as a colourless oil (24.9 g, 89%); HRMS (ESI +ve): found 472.2239 [M+Na$^+$]; $C_{22}H_{35}N_3NaO_5Si$ requires 472.2238; $[\alpha]_D^{25}$ +110.0 (*c* 0.90, $CHCl_3$); $\nu_{max}$ (thin film): 2098 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz): 0.09, 0.10 (2 x 3H, s, $Si(CH_3)_2$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.36, 1.58 (2 x 3H, s, $C(CH_3)_2$), 3.58 (1H, ddd, H5, $J_{5,4}$ 2.1, $J_{5,6}$ 4.6, $J_{5,6'}$ 8.9), 3.85 (1H, dd, H6, $J_{6,5}$ 4.6, $J_{6,6'}$ 10.6), 3.88 (1H, dd, H3, $J_{3,2}$ 5.1, $J_{3,4}$ 8.9), 3.90 (1H, dd, H6', $J_{6',5}$ 8.9, $J_{6',6}$ 10.6), 4.04 (1H, dd, H4, $J_{4,5}$ 2.1, $J_{4,3}$ 8.9), 4.56 (1H, a-t, H2, $J_{2,1} = J_{2,3}$ 4.1), 4.57 (1H, d, $OC\underline{H}_2Ph$, $J_{gem}$ 12.1), 4.80 (1H, d, $OC\underline{H}_2Ph$, $J_{gem}$ 12.1), 5.72 (1H, d, H1, $J_{1,2}$ 3.4), 7.34-7.40 (5H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): -5.5, -5.5 ($Si(\underline{C}H_3)_2$), 18.1 ($Si\underline{C}(CH_3)_3$), 25.8 ($SiC(\underline{C}H_3)_3$), 26.5, 26.8 ($C(\underline{C}H_3)_2$), 62.1 (C5), 64.4 (C6), 72.3 ($O\underline{C}H_2Ph$), 76.9 (C2), 76.9 (C4), 77.8 (C3), 104.3 (C1), 113.1 ($\underline{C}(CH_3)_2$), 128.0, 128.2, 128.5 (Ar$\underline{C}$H), 137.3 (Ar$\underline{C}$C); LRMS (ESI +ve): 472 (97%, M+Na$^+$), 921 (100%, 2M+Na$^+$).

**Methyl 5-azido-3-*O*-benzyl-5-deoxy-L-talofuranoside 2.43L**




Benzyl ether **2.42L** (19.2 g, 42.7 mmol) was dissolved in a mixture of methanol (200 mL) and acetyl chloride (20 mL) at RT. The reaction mixture was heated to 55 $^{o}$C and stirred for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.72) and the formation of a major product ($R_f$ 0.20). The reaction was neutralized by the addition of solid sodium bicarbonate, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1 to 2:3, cyclohexane/ethyl acetate) to afford the methyl talofuranosides **2.43L** as a pale yellow oil (12.3 g, 93%), in a 7:1 (α:β) ratio of anomers; HRMS (ESI +ve): found 332.1217 [M+$Na^+$]; $C_{14}H_{19}N_3NaO_5$ requires 332.1217; $\nu_{max}$ (thin film): 2116 (s, $N_3$), 3427 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz, *major anomer only*): 2.19 (1H, dd, OH6, $J_{OH,6}$ 5.2, $J_{OH,6'}$ 7.6), 2.54 (1H, d, OH2, $J_{OH,2}$ 2.6), 3.39 (3H, s, $OCH_3$), 3.43 (1H, td, H5, $J_{5,6'}$ 4.3, $J_{5,4}$ = $J_{5,6}$ 6.1), 3.71 (1H, ddd, H6, $J_{6,OH}$ 5.2, $J_{6,5}$ 6.1, $J_{6,6'}$ 12.0), 3.77 (1H, ddd, H6', $J_{6',5}$ 4.3, $J_{6',OH}$ 7.6, $J_{6',6}$ 12.0), 4.04 (1H, dd, H2, $J_{2,OH}$ 2.6, $J_{2,3}$ 4.3), 4.13 (1H, dd, H4, $J_{4,5}$ 6.1, $J_{4,3}$ 7.5), 4.20 (1H, dd, H3, $J_{3,2}$ 4.3, $J_{3,4}$ 7.5), 4.55 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.4), 4.62 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.4), 4.89 (1H, s, H1), 7.32-7.42 (5H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz, *major anomer only*): 55.6 ($OCH_3$), 62.5 (C6), 65.4 (C5), 72.5 (C2), 73.1 (O$\underline{C}H_2$Ph), 79.6 (C3), 81.0 (C4), 108.6 (C1) 128.2, 128.7, 128.7, 128.8 (Ar$\underline{C}$H), 136.4 (Ar$\underline{C}$C); LRMS (ESI +ve): 332 (100%, M+$Na^+$), 641 (41%, 2M+$Na^+$).

**Methyl 5-azido-2-*N*,3-*O*-dibenzyl-2,5,6-trideoxy-2,6-imino-L-galactofuranoside 2.45Lα**

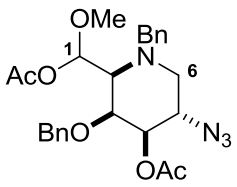



Trifluoromethanesulfonic anhydride (10.6 mL, 62.8 mmol) was added dropwise were added to a solution of the diols **2.43L** (7.2 g, 23 mmol) and pyridine (10.2 mL, 126 mmol) in dichloromethane (75 mL) at -40 $^{o}$C. The reaction mixture was stirred for 1 h, with the internal temperature maintained between -30 $^{o}$C and -20 $^{o}$C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.20) and the formation of two products (major $R_f$ 0.77, minor $R_f$ 0.65), thought to be a mixture of anomeric ditriflates. The reaction mixture was diluted with dichloromethane (100 mL) and washed with 2 M aqueous hydrochloric acid (3 x 60 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude ditriflates **2.44L**.

Benzylamine (7.6 mL, 70 mmol) was added dropwise to a solution of the crude ditriflates **2.44L** in THF (75 mL) at -30 $^{o}$C. The reaction mixture was allowed to warm to RT and stirred for 2 h, after which TLC analysis (79:20:1, cyclohexane/ethyl acetate/triethylamine) indicated the complete consumption of the ditriflates and the formation of two products (major $R_f$ 0.42, minor $R_f$ 0.30), thought to be the two anomeric mono-substituted triflates. The reaction mixture was heated to 60 $^{o}$C for 16 h, after which TLC analysis (79:20:1, cyclohexane/ethyl acetate/triethylamine) indicated the complete consumption of the major component ($R_f$ 0.42), a new major product ($R_f$ 0.67) and the persistence of the minor starting component ($R_f$ 0.30). The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (99:0:1 to 96:3:1, cyclohexane/ethyl acetate/triethylamine) to afford the α-iminobicycle **2.45Lα** as a pale yellow oil (6.12 g, 69%) and as a single anomer; HRMS (ESI +ve): found 381.1920 [M+H$^+$];

$C_{21}H_{25}N_4O_3$ requires 381.1921; $[\alpha]_D^{25}$ +16.2 (*c* 1.1, $CHCl_3$); $\nu_{max}$ (thin film): 2109 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz): 2.74 (1H, d, H6, $J_{6,6'}$ 12.8), 3.21 (1H, br. s, H2), 3.52 (1H, dd, H6', $J_{6',5}$ 4.1, $J_{6',6}$ 12.8), 3.54 (3H, s, $OCH_3$), 3.87 (1H, a-t, H5, $J_{5,4} = J_{5,6'}$ 4.4), 3.90 (1H, d, $NC\underline{H}_2Ph$, $J_{gem}$ 13.8), 4.01 (1H, d, $NC\underline{H}_2Ph$, $J_{gem}$ 13.8), 4.11 (1H, d, H3, $J_{3,2}$ 1.0), 4.30 (1H, d, H4, $J_{4,5}$ 5.1), 4.52 (1H, d, $OC\underline{H}_2Ph$, $J_{gem}$ 11.8), 4.58 (1H, d, $OC\underline{H}_2Ph$, $J_{gem}$ 11.8), 5.32 (1H, d, H1, $J_{1,2}$ 2.7), 7.26-7.37 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 48.6 (C6), 57.6 ($OCH_3$), 59.7 (C5), 59.9 ($N\underline{C}H_2Ph$), 61.4 (C2), 71.0 ($O\underline{C}H_2Ph$), 78.7 (C4), 81.5 (C3), 109.7 (C1), 127.0, 127.7, 127.8, 128.3, 128.4 (Ar<u>C</u>H), 137.7, 139.1 (Ar<u>C</u>C); LRMS (ESI +ve): 381 (100%, $M+H^+$), 403 (80%, $M+Na^+$).

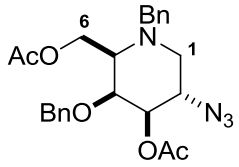
**4-*O*-Acetyl-5-azido-2-*N*,3-*O*-dibenzyl-2,5,6-trideoxy-2,6-imino-L-galactose acetyl methyl acetal 2.46L**




Boron trifluoride diethyl etherate (5.1 mL, 40 mmol) was added dropwise to a solution of the bicyclic acetal **2.45Lα** (6.12 g, 16.1 mmol) in acetic anhydride (60 mL) at -30 °C. The reaction mixture was allowed to warm to RT and stirred for 2.5 h, after which TLC analysis (69:30:1, cyclohexane/ethyl acetate/triethylamine) indicated the complete consumption of the starting material ($R_f$ 0.72) and the formation of two products ($R_f$ 0.56, 0.47). The reaction was concentrated *in vacuo*, the crude residue dissolved in ethyl acetate (200 mL) and washed with an aqueous sodium bicarbonate solution (3 x 100 mL). The organic phase was dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash chromatography (97:2:1 to 79:20:1, cyclohexane/ethyl acetate/triethylamine) to afford the monocyclic mixed-acetals **2.46L** as a pale

yellow oil (7.54 g, 97%), in a 3:2 (A:B) mixture of diastereoisomers; HRMS (ESI +ve): found 505.2058 [M+$Na^+$]; $C_{25}H_{30}N_4NaO_6$ requires 505.2058; $\nu_{max}$ (thin film): 1743 (s, C=O), 2106 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz): 2.05 (3H, s, $COCH_3^B$), 2.10 (3H, s, $COCH_3^A$), 2.13 (3H, s, $COCH_3^B$), 2.14 (3H, s, $COCH_3^A$), 2.38 (1H, dd, $H6^A$, $J_{6,5}$ 10.6, $J_{6,6'}$ 13.8), 2.41 (1H, dd, $H6^B$, $J_{6,5}$ 10.8, $J_{6,6'}$ 14.0), 3.04 (1H, dd, $H2^B$, $J_{2,3}$ 1.5, $J_{2,1}$ 7.9), 3.05 (1H, dd, $H6'^B$, $J_{6',5}$ 4.6, $J_{6',6}$ 14.0), 3.07 (1H, dd, $H2^A$, $J_{2,3}$ 1.8, $J_{2,1}$ 7.5), 3.10 (1H, dd, $H6'^A$, $J_{6',5}$ 4.6, $J_{6',6}$ 13.8), 3.31 (3H, s, $OCH_3^B$), 3.48 (3H, s, $OCH_3^A$), 3.90 (2H, s, $NC\underline{H}_2Ph^A$), 3.94 (2H, s, $NC\underline{H}_2Ph^B$), 4.05 (1H, dd, $H3^A$, $J_{3,2}$ 1.8, $J_{3,4}$ 2.9), 4.11 (1H, ddd, $H5^B$, $J_{5,6'}$ 4.6, $J_{5,4}$ 10.1, $J_{5,6}$ 10.8), 4.13 (1H, ddd, $H5^A$, $J_{5,6'}$ 4.6, $J_{5,4}$ 10.0, $J_{5,6}$ 10.6), 4.29 (1H, dd, $H3^B$, $J_{3,2}$ 1.5, $J_{3,4}$ 2.9), 4.50 (1H, d, $OC\underline{H}_2Ph^A$, $J_{gem}$ 11.0), 4.59 (1H, d, $OC\underline{H}_2Ph^B$, $J_{gem}$ 11.6), 4.67 (1H, d, $OC\underline{H}_2Ph^A$, $J_{gem}$ 11.0), 4.80 (1H, d, $OC\underline{H}_2Ph^B$, $J_{gem}$ 11.6), 4.86 (1H, dd, $H4^B$, $J_{4,3}$ 2.9, $J_{4,5}$ 10.1), 4.88 (1H, dd, $H4^A$, $J_{4,3}$ 2.9, $J_{4,5}$ 10.0), 6.16 (1H, d, $H1^B$, $J_{1,2}$ 7.9), 6.31 (1H, d, $H1^A$, $J_{1,2}$ 7.5), 7.22-7.43 (20H, m, $ArH^A$, $ArH^B$); $\delta_C$ ($CDCl_3$, 100 MHz): 20.9, 21.0 ($CO\underline{C}H_3^B$), 20.0, 21.1 ($CO\underline{C}H_3^A$), 51.6 ($C6^B$), 51.9 ($C6^A$), 53.9 ($N\underline{C}H_2Ph^B$), 53.9 ($C5^B$), 54.4 ($C5^A$), 54.7 ($N\underline{C}H_2Ph^A$), 56.4 ($OCH_3^A$), 56.9 ($OCH_3^B$), 63.2 ($C2^A$), 64.2 ($C2^B$), 74.9 ($O\underline{C}H_2Ph^A$), 75.2 ($O\underline{C}H_2Ph^B$), 76.0 ($C3^A$), 76.8 ($C3^B$), 77.2 ($C4^B$), 77.6 ($C4^A$), 95.1 ($C1^A$, $C1^B$), 126.7, 127.0, 127.1, 127.4, 127.5, 127.7, 127.8, 128.3, 128.4, 128.5, 128.6 ($Ar\underline{C}H^A$, $Ar\underline{C}H^B$), 138.0, 138.2, 139.3, 139.6 ($Ar\underline{C}C^A$, $Ar\underline{C}C^B$), 170.2, 170.2, 170.6, 171.0 ($\underline{C}OCH_3^A$, $\underline{C}OCH_3^B$); LRMS (ESI +ve): 423, (95%, $[M\text{-}OAc]^+$), 483 (98%, $M+H^+$), 505 (100%, $M+Na^+$), 521 (83%, $M+K^+$), 955 (20%, $2M+H^+$), 987 (95%, $2M+Na^+$).

**3,6-Di-*O*-acetyl-2-azido-1-*N*,4-*O*-dibenzyl-1,2,5-trideoxy-1,5-imino-D-galactitol 2.50D**



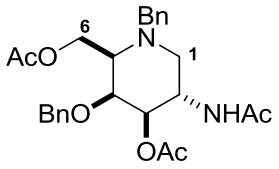

Diisobutylaluminium hydride (1.5 M in toluene, 52.0 mL, 78.0 mmol) was added dropwise to a solution of the mixed acetals **2.46L** (7.54 g, 15.6 mmol) in dichloromethane (75 mL) at -78 $^{o}$C. The reaction mixture was stirred for 45 min, after which TLC analysis (59:40:1, cyclohexane/ethyl acetate/triethylamine) indicated the complete consumption of the starting material ($R_f$ 0.70, 0.73) and the formation of three products ($R_f$ 0.20, 0.60, 0.80). The reaction was quenched and diluted with ethyl acetate (400 mL) and aqueous sodium potassium tartrate (400 mL) added. The biphasic mixture was stirred vigorously for 90 min, after which the phases were separated and the aqueous layer extracted with ethyl acetate (3 x 300 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude intermediate aldehyde **2.48L**. After which TLC analysis (59:40:1, cyclohexane/ethyl acetate/triethylamine) indicated the disappearance of one product ($R_f$ 0.80).

Sodium borohydride (590 mg, 15.6 mmol) was added portion-wise to a solution of the crude intermediate aldehyde **2.48L** in methanol (100 mL) at 0 $^{o}$C. The reaction mixture was allowed to warm to RT and stirred for 3 h, after which TLC analysis (59:40:1, cyclohexane/ethyl acetate/triethylamine) indicated the complete consumption of the intermediate products ($R_f$ 0.60, 0.20) and the formation of a major product ($R_f$ 0.25). The reaction was concentrated *in vacuo* and co-evaporated with methanol (3 x 50 mL) to afford the crude intermediate diol **2.49D**.

The crude intermediate diol **2.49D** was dissolved in a 1:1 pyridine/acetic anhydride solution (150 mL) at RT. The reaction mixture was stirred for 16 h, after which TLC analysis (59:40:1,

cyclohexane/ethyl acetate/triethylamine) indicated the complete consumption of the intermediate ($R_f$ 0.25) and the formation of a major product ($R_f$ 0.65). The reaction was concentrated *in vacuo* and purified by flash chromatography (97:2:1 to 89:10:1, cyclohexane/ethyl acetate/triethylamine) to afford the diacetyl piperidine **2.50D** as a light yellow oil (5.08 g, 72% over 3 steps); HRMS (ESI +ve): found 475.1950 [M+$Na^+$]; $C_{24}H_{28}N_4NaO_5$ requires 475.1952; $[\alpha]_D^{25}$ +65.7 (*c* 0.60, $CHCl_3$); $\nu_{max}$ (thin film): 1740 (s, C=O), 2108 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz): 2.04, 2.14 (2 x 3H, s, $COCH_3$), 2.26 (1H, dd, H1, $J_{1,2}$ 8.9, $J_{1,1'}$ 12.6), 2.95-3.00 (1H, m, H5), 3.02 (1H, dd, H1', $J_{1',2}$ 4.4, $J_{1',1}$ 12.7), 3.64 (1H, d, $NCH_2Ph$, $J_{gem}$ 14.1), 3.88 (1H, d, $NCH_2Ph$, $J_{gem}$ 14.1), 3.96 (1H, a-td, H2, $J_{2,1'}$ 4.1, $J_{2,1}$ = $J_{2,3}$ 8.5), 4.04 (1H, a-t, H4, $J_{4,3}$ = $J_{4,5}$ 2.7), 4.23 (1H, dd, H6, $J_{6,5}$ 6.1, $J_{6,6'}$ 11.6), 4.55 (1H, dd, H6', $J_{6',5}$ 6.1, $J_{6',6}$ 11.6), 4.57 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.4), 4.75 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.4), 4.90 (1H, dd, H3, $J_{3,4}$ 2.7, $J_{3,2}$ 8.5), 7.26-7.40 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 21.0, 21.0 ($COCH_3$), 51.4 (C1), 56.5 (C2), 56.9 ($NCH_2Ph$), 60.7 (C5), 61.9 (C6), 74.3 ($OCH_2Ph$), 74.8 (C4), 75.1 (C3), 127.3, 127.8, 127.9, 128.4, 128.5, 128.7 (ArCH), 137.8, 138.0 (ArCC), 170.1, 170.6 ($COCH_3$); LRMS (ESI +ve): 475 (100%, M+$Na^+$).

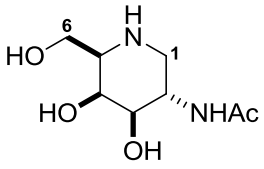
**2-Acetamido-3,6-di-*O*-acetyl-1-*N*,4-*O*-dibenzyl-1,2,5-trideoxy-1,5-imino-D-galactitol 2.51D**




Powdered zinc (9.0 g, 130 mmol) was added to a solution of the azide **2.50D** (3.0 g, 6.6 mmol) in a mixture of 3:2:1 THF/glacial acetic acid/acetic anhydride (72 mL) and stirred vigorously before the dropwise addition of a saturated copper(II) sulfate solution (9 mL) to initiate the reaction. The reaction was stirred for 30 min, after which TLC analysis (49:50:1, cyclohexane/ethyl acetate/triethylamine) indicated the complete consumption of the starting

material ($R_f$ 0.78) and the formation of a major product ($R_f$ 0.15). The reaction was filtered (GF/A, glass microfibre), concentrated *in vacuo* and the crude residue purified by flash chromatography (94:5:1 to 29:70:1, cyclohexane/ethyl acetate/triethylamine) to afford the acetamide **2.51D** as a white crystalline solid (2.83 g, 91%); HRMS (ESI +ve): found 491.2151 [M+$Na^+$]; $C_{26}H_{32}N_2NaO_6$ requires 491.2153; m.p. 112-114 $^oC$; $[\alpha]_D^{25}$ +20.3 (*c* 1.02, acetone); $\nu_{max}$ (thin film): 1541 (br. s, amide II), 1655 (s, amide I), 1739 (s, C=O); $\delta_H$ ($CDCl_3$, 500 MHz): 1.87 (3H, s, NHCOC<u>H</u>$_3$), 2.05, 2.11 (2 x 3H, s, COC$H_3$), 2.20 (1H, dd, H1, $J_{1,2}$ 5.2, $J_{1,1'}$ 12.6), 3.04 (1H, dd, H1', $J_{1',2}$ 3.1, $J_{1',1}$ 12.6), 3.33 (1H, br. s, H5), 3.72 (1H, d, NC<u>H</u>$_2$Ph, $J_{gem}$ 13.8), 3.82 (1H, d, NC<u>H</u>$_2$Ph, $J_{gem}$ 13.8), 3.86 (1H, dd, H4, *J* 2.9, *J* 4.3), 4.20 (1H, br. s, H2), 4.31 (1H, dd, H6, $J_{6,5}$ 3.6, $J_{6,6'}$ 11.9), 4.54 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 11.8), 4.66 (1H, dd, H6', $J_{6',5}$ 7.6, $J_{6',6}$ 11.9), 4.76 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 11.8), 5.19 (1H, br. s, H3), 5.70 (1H, d, N<u>H</u>COC$H_3$, $J_{NH,2}$ 8.0), 7.25-7.38 (10H, m, ArH); $\delta_C$ ($(CD_3)_2CO$, 126 MHz): 21.0, 21.0 (CO<u>C</u>$H_3$), 22.9 (NHCO<u>C</u>$H_3$), 46.6 (C2), 50.1 (C1), 58.2 (N<u>C</u>$H_2$Ph), 61.5 (C5), 61.6 (C6), 72.5 (C3), 73.4 (O<u>C</u>$H_2$Ph), 75.5 (C4), 127.6, 128.1, 128.2, 128.9, 128.9, 129.3 (Ar<u>C</u>H), 139.4, 140.1 (Ar<u>C</u>C), 169.6, 170.2, 170.7 (<u>C</u>OC$H_3$, NH<u>C</u>OC$H_3$); LRMS (ESI +ve): 469 (100%, M+$H^+$), 491 (55%, M+$Na^+$); (ESI –ve): 503 (55%, M+$^{35}Cl^-$), 505 (15%, M+$^{37}Cl^-$), 513 (100%, M+$HCOO^-$);

**2-Acetamido-1,2,5-trideoxy-1,5-imino-D-galactitol (DGJNAc) 2.20D**




Sodium methoxide (10 mg, cat.) was added to a solution of the piperidine **2.51D** (2.83 g, 6.03 mmol) in methanol (40 mL) at RT. The reaction mixture was stirred for 16 h, after which TLC analysis (99:1, ethyl acetate/triethylamine) indicated the complete consumption of the

starting material ($R_f$ 0.50) and the formation of a major product ($R_f$ 0.14→0.0). The reaction mixture was neutralised with glacial acetic acid and concentrated *in vacuo* to afford the crude diol **2.52D**.

Palladium (10% on carbon, 600 mg) was added to a solution of the crude diol **2.52D** in a 10:2:1 water/2 M aqueous hydrochloric acid/1,4-dioxane mixture (78 mL). The vessel was evacuated and flushed with hydrogen. The reaction mixture stirred for 24 h, after which LRMS and $^1$H NMR indicated that a single product had been formed, with no trace of benzylated intermediates. The reaction was filtered (GF/A, glass microfibre) and concentrated *in vacuo* to afford crude DGJNAc **2.20D** as the hydrochloride salt.

Selected data for DGJNAc.HCl **2.20D**: $\delta_H$ ($D_2O$, 400 MHz): 1.96 (3H, s, NHCOC<u>H</u>$_3$), 2.82 (1H, a-t, H1, $J_{1,1'} = J_{1,2}$ 12.5), 3.34 (1H, br. s, H5), 3.41 (1H, dd, H1', $J_{1',2}$ 5.0, $J_{1',1}$ 12.9), 3.72 (1H, dd, H3, $J_{3,4}$ 2.6, $J_{3,2}$ 10.9), 3.75 (1H, dd, H6, $J_{6,5}$ 7.5, $J_{6,6'}$ 12.3), 3.82 (1H, dd, H6', $J_{6',5}$ 5.5, $J_{6',6}$ 12.3), 4.11 (1H, dd, H4, $J_{4,5}$ 1.0, $J_{4,3}$ 2.6), 4.26 (1H, ddd, H2, $J_{2,1'}$ 5.0, $J_{2,3}$ 10.9, $J_{2,1}$ 11.9); LRMS (ESI +ve): 205 (100%, $M+H^+$), 409 (35%, $2M+H^+$); (ESI –ve): 203 (100%, $[M-H]^-$).

The crude salt of DGJNAc **2.20D** was loaded onto a short column of Dowex® (50W-X8, $H^+$) and the resin washed with water. The product was liberated with 2 M aqueous ammonia and the ammoniacal fractions concentrated *in vacuo*. The product was recrystallised (ethanol) to afford DGJNAc **2.20D** as a pale yellow crystalline solid (1.22 g, 99%); HRMS (ESI +ve): found 205.1184 [$M+H^+$]; $C_8H_{17}N_2O_4$ requires 205.1183; m.p. 153-156 °C (ethanol); $[\alpha]_D^{25}$ +49.3 (*c* 0.65, $H_2O$); $\nu_{max}$ (neat): 1563 (s, amide II), 1638 (s, amide I), 3285 (br. s, OH/NH); $\delta_H$ ($D_2O$, 400 MHz): 1.88 (3H, s, NHCOC<u>H</u>$_3$), 2.24 (1H, a-t, H1, $J_{1,1'} = J_{1,2}$ 12.2), 2.63 (1H, a-t, H5, $J_{5,6} = J_{5,6'}$ 6.5), 2.96 (1H, dd, H1', $J_{1',2}$ 4.9, $J_{1',1}$ 13.1), 3.45-3.53 (3H, m, H3, H6, H6'), 3.83 (1H,

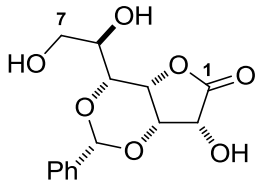
a-td, H2, $J_{2,1'}$ 4.9, $J_{2,1} = J_{2,3}$ 10.9), 3.89 (1H, s, H4); $\delta_C$ ($D_2O$, 100 MHz): 22.6 ($NHCO\underline{C}H_3$), 47.7 (C1), 49.1 (C2), 59.3 (C5), 61.8 (C6), 68.9 (C4), 73.2 (C3), 175.1 ($NH\underline{C}OCH_3$); LRMS (ESI +ve): 205 (100%, $M+H^+$), 409 (30%, $2M+H^+$); (ESI –ve): 203 (100%, $[M-H]^-$); Found: C, 46.88; H, 7.86; N, 13.55; $C_8H_{16}N_2O_4$ requires: C, 47.05; H, 7.90; N, 13.72.

2.4.3 Synthesis of pyrrolidines

*2.4.3.1 Synthesis of L-glucuronolactone*

**3,5-(*R*)-*O*-Benzylidene-D-glucoheptono-1,4-lactone 2.121D**

**(3,5-(*R*)-*O*-Benzylidene-D-*glycero*-D-*gulo*-heptono-1,4-lactone)**

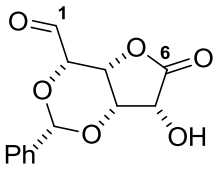



D-Glucoheptono-1,4-lactone **1.69D** (200 g, 962 mmol) was added to a mixture of benzaldehyde (600 mL) and concentrated hydrochloric acid (32%, 60 mL) in a 2 L-jacketed glass reactor fitted with a mechanical overhead stirrer. The reaction mixture was stirred at RT for 3 h, after which TLC analysis (45:5:1, ethyl acetate/ethanol/water) indicated the complete consumption of the starting material ($R_f$ 0.05) and the formation of a major product ($R_f$ 0.45). Petroleum ether (40-60, 1600 mL) was added to the reaction mixture and the crystalline suspension stirred for 30 min. The suspension was filtered, the filter cake suspended in diethyl ether (700 mL) and stirred for 15 min to achieve a fine suspension. This suspension was filtered and the filter cake washed with diethyl ether (2 x 150 mL). The solid was collected and dried under vacuum for 24 h to afford the benzylidene **2.121D** (285 g, quant.). The product was reacted on without further purification.

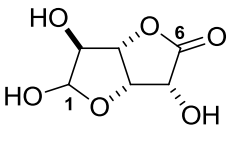
Selected data for benzylidene **2.121D**: m.p. 201-205 $^{o}$C [Lit.[108] 202-206 $^{o}$C]; $[\alpha]_D^{25}$ -46.3 (*c* 1.00, methanol) [Lit.[108] $[\alpha]_D^{25}$ -57.0 (*c* 1.01, methanol)]; $\nu_{max}$ (thin film): 1788 (s, C=O), 3345 (br. s, OH); $\delta_H$ ($(CD_3)_2SO$, 400 MHz): 3.65 (1H, dd, H7, $J_{7,6}$ 4.6, $J_{7,7'}$ 11.9), 3.77 (1H, dd, H7', $J_{7',6}$ 2.5, $J_{7',7}$ 11.9), 3.92 (1H, ddd, H6, $J_{6,7'}$ 2.5, $J_{6,7}$ 4.6, $J_{6,5}$ 9.1), 4.10 (1H, dd, H5, $J_{5,4}$ 1.9, $J_{5,6}$ 9.1), 4.59 (1H, t, H4, $J_{4,3} = J_{4,5}$ 1.9), 4.72 (1H, d, H2, $J_{2,3}$ 4.3), 4.78 (1H, dd, H3, $J_{3,4}$ 1.9, $J_{3,2}$ 4.3), 5.74 (1H, s, C<u>H</u>Ph), 7.30-7.34 (2H, m, ArH), 7.45-7.50 (3H, m, ArH); $\delta_C$ ($(CD_3)_2SO$, 100 MHz): 63.1 (C7), 69.7, 70.6, 72.1, 75.8, 76.0, 99.8 (<u>C</u>HPh), 127.1, 127.4, 128.7, 128.9, 129.6 (Ar<u>C</u>H), 139.5

(ArCC), 178.2 (C1); LRMS (ESI +ve): 319 (55%, $M+Na^+$), 351 (65%, $M+MeOH+Na^+$), 615 (100%, $2M+Na^+$), 647 (25%, $2M+MeOH+Na^+$); (ESI –ve): 295 (100%, $[M-H]^-$).

**L-Glucurono-3,6-lactone 2.1L**




**2.122L**




**2.1L**

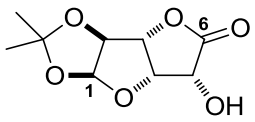
Benzylidene-protected **2.121D** was suspended in a 10:1 THF/water mixture (2200 mL) in a 2 L-jacketed glass reactor and heated to 40 $^oC$. After 40 min the starting material had dissolved and sodium periodate (226 g, 1060 mmol) was added portion-wise over 1 h, maintaining the internal temperature below 45 $^oC$. After 30 min, a yellow suspension formed and TLC analysis (45:5:1, ethyl acetate/ethanol/water) indicated the complete consumption of the starting material ($R_f$ 0.45) and the formation of a major product ($R_f$ 0.76). The suspension was removed from the reactor and filtered (GF/A, glass microfibre), the filter cake washed with a 10:1 THF/$H_2O$ mixture (550 mL) and the filtrate concentrated in vacuo to give a yellowish, crystalline crude aldehyde **2.122L**.

The crude aldehyde **2.122L** was dissolved in a 9:1 TFA/water mixture (600 mL) and stirred at 45 $^oC$ for 80 min. At this time an orange suspension had formed and TLC analysis (45:5:1, ethyl acetate/ethanol/water) indicated the consumption of the starting material ($R_f$ 0.76) and the formation of a major product ($R_f$ 0.51). This suspension was concentrated *in vacuo* at 50 $^oC$, to afford a crude solid which was co-evaporated with toluene (3 x 500 mL, 1 x 250 mL). The residue was dissolved in ethyl acetate (300 mL) and water (1250 mL), the phases separated and the organic layer extracted with water (100 mL). The combined aqueous fractions were washed

with ethyl acetate (250 mL) and concentrated *in vacuo*. The crude solid was dried for 72 h, after which L-glucurono-3,6-lactone **2.1L** (168 g, 99%) was obtained as a light pinkish solid. This material was reacted on without any further purification

Selected data for L-glucurono-3,6-lactone **2.1L**: m.p. 164-168 °C [Lit.[108] 165-167 °C]; $[\alpha]_D^{25}$ initial: -16.2, equilibrium: -23.4 (*c* 1.00, water) [Lit.[108] $[\alpha]_D^{25}$ initial: -17.8, equilibrium: -21.5 (*c* 1.05, water)]; $\nu_{max}$ (thin film): 1791 (s, C=O), 3230 (br. s, OH).

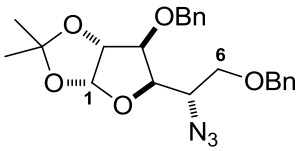
**1,2-*O*-Isopropylidene-L-glucurono-3,6-lactone 1.60L**




L-Glucurono-3,6-lactone **2.1L** (168 g, 953 mmol) was dissolved in acetone (1500 mL) and concentrated sulphuric acid (50 mL). This mixture was stirred at RT for 3 h, after which TLC analysis (7:3, pet. ether 40-60/acetone) indicated the complete consumption of the starting material (baseline) and the formation of a major product ($R_f$ 0.28). The reaction mixture was neutralised with solid sodium bicarbonate (~1200 g), filtered and concentrated *in vacuo*. The crude residue was purified by medium-pressure chromatography (7:3, pet. ether 40-60/acetone) to give the acetonide **1.60L** (132.5 g, 64%) as a yellow crystalline solid. Recrystallisation (toluene) afforded the acetonide **1.60L** (125 g, 61%) as a white crystalline solid; *refer to page 126 for enantiomeric data*; m.p. 117-119 °C (toluene) [Lit.[108] 118-120 °C]; $[\alpha]_D^{25}$ -62.3 (*c* 2.00, $CHCl_3$) [Lit.[108] -56.9 (*c* 1.09, $CHCl_3$)].

*2.4.3.2 Synthesis of gulo-configured Iminosugars*

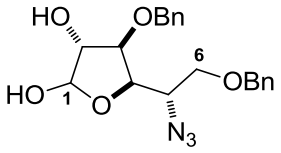
**5-Azido-3,6-di-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose 2.124L**




Sodium hydride (60% min. oil suspension, 118 mg, 4.89 mmol) was added portion-wise to a solution of the diol **2.37L** (410 mg, 1.67 mmol) and benzyl bromide (0.60 mL, 4.89 mmol) in DMF (5 mL) at -10 °C. The reaction mixture was allowed to warm to RT and stirred for 17 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.15) and the formation of a major product ($R_f$ 0.68). The reaction mixture was quenched with methanol (0.5 mL), diluted with ethyl acetate (60 mL) and washed with a 1:1 brine/water solution (5 x 60 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (24:1 to 1:1, cyclohexane/ethyl acetate) to afford the dibenzyl ether **2.124L** (519 mg, 73%) as a yellow oil; HRMS (ESI +ve): found 448.1837 [M+$Na^+$]; $C_{23}H_{27}N_3NaO_5$ requires 448.1843; $[\alpha]_D^{25}$ -30.7 (*c* 0.93, $CHCl_3$); $\nu_{max}$ (thin film): 2097 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz): 1.34, 1.51 (2 x 3H, s, $C(CH_3)_2$), 3.38 (1H, dd, H6, $J_{6,5}$ 5.8, $J_{6,6'}$ 10.0), 3.45 (1H, dd, H6', $J_{6',5}$ 3.3, $J_{6',6}$ 10.0), 3.81 (1H, d, H3, $J_{3,4}$ 3.3), 3.92 (1H, ddd, H5, $J_{5,6'}$ 3.3, $J_{5,6}$ 5.8, $J_{5,4}$ 8.9), 4.25 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 4.27 (1H, dd, H4, $J_{4,3}$ 3.3, $J_{4,5}$ 8.9), 4.39 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 12.1), 4.51 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.9), 4.60 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.9), 4.62 (1H, d, H2, $J_{2,1}$ 3.8), 5.97 (1H, d, H1, $J_{1,2}$ 3.8), 7.24-7.38 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 26.3, 26.8 (C($\underline{C}H_3)_2$), 60.8 (C5), 69.2 (C6), 71.6, 73.4 (O$\underline{C}H_2$Ph), 79.9 (C4), 81.5 (C3), 81.9 (C2), 104.8 (C1), 112.0 ($\underline{C}(CH_3)_2$), 127.8, 127.9, 128.0, 128.2, 128.5, 128.6 (Ar$\underline{C}$H), 136.8, 137.6 (Ar$\underline{C}$C); LRMS (ESI +ve): 448 (34%, M+$Na^+$), 873 (100%, 2M+$Na^+$).

Similar treatment of **5-azido-5-deoxy-1,2-*O*-isopropylidene-β-D-idofuranose 2.37D** (1.47 g, 5.99 mmol) in a suitably scaled procedure afforded **5-azido-3,6-di-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-D-idofuranose 2.124D** (2.50 g, 96%) as a pale yellow oil; $[\alpha]_D^{25}$ +38.2 (*c* 1.00, $CHCl_3$).

**5-Azido-3,6-di-*O*-benzyl-5-deoxy-L-idofuranose 2.125L**

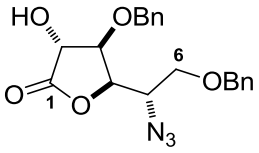



*para*-Toluenesulfonic acid (1.04 g, 5.5 mmol) was added to a solution of the acetonide **2.124L** (1.05 g, 2.5 mmol) in a 7:1 1,4-dioxane/water mixture (6.4 mL) at 80 °C. Water (2 mL) was added over 30 min to maintain a homogeneous reaction mixture. The reaction was stirred for 2.5 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.68) and the formation of a major product ($R_f$ 0.07). The reaction mixture was allowed to cool to RT, quenched with an aqueous sodium bicarbonate solution (32 mL) and extracted with ethyl acetate (3 x 32 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the lactols **2.125L** (917 mg, 97%) as a yellow oil, and as an anomeric mixture (A:B, 3:1). The lactols **2.125L** were reacted on without further purification; HRMS (ESI +ve): found 408.1528 [M+$Na^+$]; $C_{20}H_{23}N_3NaO_5$ requires 408.1530; $[\alpha]_D^{25}$ +23.2 (*c* 0.83, $CHCl_3$); $\nu_{max}$ (thin film): 2101 (s, $N_3$), 3417 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 3.48 (1H, dd, $H6^A$, $J_{6,5}$ 6.6, $J_{6,6'}$ 10.1), 3.51-3.56 (3H, m, $H6^B$, $H6'^A$, $H6'^B$), 3.84 (1H, td, $H5^A$, $J_{5,6'}$ 4.2, $J_{5,6} = J_{5,4}$ 6.6), 3.88-3.91 (2H, m, $H3^B$, $H5^B$), 3.93 (1H, dd, $H3^A$, $J_{3,2}$ 3.3, $J_{3,4}$ 5.0), 4.30 (1H, dd, $H2^A$, $J_{2,3}$ 3.3, $J_{2,1}$ 4.9), 4.33-4.35 (2H, m, $H2^B$, $H4^B$), 4.36 (1H, d, $OC\underline{H}_2Ph^B$, $J_{gem}$ 11.6), 4.38 (1H, dd, $H4^A$, $J_{4,3}$ 5.0, $J_{4,5}$ 6.6), 4.38 (1H, d, $OC\underline{H}_2Ph^A$, $J_{gem}$ 11.6), 4.45 (1H, d, $OC\underline{H}_2Ph^A$, $J_{gem}$ 11.9), 4.46 (1H, d, $OC\underline{H}_2Ph^B$, $J_{gem}$ 11.9), 4.52 (1H, d,

$OC\underline{H}_2Ph^A$, $J_{gem}$ 11.9), 4.54 (1H, d, $OC\underline{H}_2Ph^B$, $J_{gem}$ 11.9), 4.62 (1H, d, $OC\underline{H}_2Ph^B$, $J_{gem}$ 11.6), 4.70 (1H, d, $OC\underline{H}_2Ph^A$, $J_{gem}$ 11.6), 5.15 (1H, d, $H1^B$, $J_{1,2}$ 10.6), 5.53 (1H, d, $H1^A$, $J_{1,2}$ 4.8), 7.28-7.39 (20H, m, $ArH^A$, $ArH^B$); $\delta_C$ ($CDCl_3$, 100 MHz): 60.9 ($C5^A$), 61.8 ($C5^B$), 69.4 ($C6^B$), 69.8 ($C6^A$), 71.9, 73.4 ($O\underline{C}H_2Ph^A$), 72.6, 73.5 ($O\underline{C}H_2Ph^B$), 75.4 ($C2^A$), 77.6 ($C4^A$), 78.5 ($C2^B$), 80.4 ($C4^B$), 82.4 ($C3^B$), 82.9 ($C3^A$), 95.7 ($C1^A$), 103.5 ($C1^B$), 127.8, 127.9, 128.0, 128.0, 128.2, 128.5, 128.5, 128.7 ($Ar\underline{C}H^A$, $Ar\underline{C}H^B$), 137.2 ($Ar\underline{C}C^B$), 137.6 ($Ar\underline{C}C^A$); LRMS (ESI +ve): 403 (59%, $M+NH_4^+$), 408 (73%, $M+Na^+$), 739 (100%, $2M+Na^+$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-D-idofuranose 2.124D** (2.46 g, 5.78 mmol) in a suitably scaled procedure afforded **5-azido-3,6-di-*O*-benzyl-5-deoxy-β-D-idofuranose 2.125D** (2.08 g, 94%) as a yellow oil, as an anomeric mixture (A:B, 3:1); $[\alpha]_D^{25}$ -34.6 (*c* 0.95, $CHCl_3$).

**5-Azido-3,6-di-*O*-benzyl-5-deoxy-L-idono-1,4-lactone 2.126L**

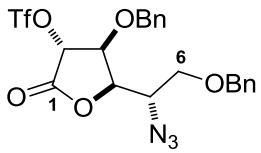



Potassium carbonate (337 mg, 2.44 mmol) and iodine (620 mg, 2.44 mmol) were added to a solution of the lactols **2.125L** (464 mg, 1.20 mmol) in *tert*-butanol (5 mL) at 100 °C. The reaction was stirred for 2 h, after which TLC analysis (1:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.33) and the formation of a major product ($R_f$ 0.60). The reaction mixture was allowed to cool to RT and diluted with ethyl acetate (35 mL). Saturated aqueous sodium thiosulfate (15 mL) was added slowly and the biphasic mixture stirred until the iodine was visibly quenched. The phases were separated and the aqueous layer extracted with ethyl acetate (3 x 35 mL). The organic fractions were combined, dried ($MgSO_4$), filtered

and concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1 to 1:1, cyclohexane/ethyl acetate) to afford the lactone **2.126L** (317 mg, 72%) as a yellow oil; HRMS (ESI +ve): found 406.1370 [M+$Na^+$]; $C_{20}H_{21}N_3NaO_5$ requires 406.1373; $[\alpha]_D^{25}$ +39.1 (*c* 1.26, $CHCl_3$); $\nu_{max}$ (thin film): 1794 (s, C=O), 2116 (s, $N_3$), 3424 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 3.21 (1H, br. s, OH2), 3.62 (1H, dd, H6, $J_{6,5}$ 6.6, $J_{6,6'}$ 9.5), 3.69 (1H, dd, H6', $J_{6',5}$ 7.6, $J_{6',6}$ 9.5), 4.07 (1H, ddd, H5, $J_{5,4}$ 1.5, $J_{5,6}$ 6.6, $J_{5,6'}$ 7.6), 4.41 (1H, dd, H3, $J_{3,2}$ 7.8, $J_{3,4}$ 8.2), 4.55 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.9), 4.59 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.9), 4.65 (1H, dd, H4, $J_{4,5}$ 1.5, $J_{4,3}$ 8.2), 4.67 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.9), 4.84 (1H, dd, H2, $J_{2,OH}$ 2.5, $J_{2,3}$ 7.8), 4.88 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.9), 7.32-7.39 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 59.4 (C5), 69.4 (C6), 72.0 (C2), 72.8, 73.6 (O$\underline{C}H_2$Ph), 76.1 (C4), 79.7 (C3), 127.7, 128.0, 128.2, 128.5, 128.6 (Ar$\underline{C}$H), 136.8, 137.3 (Ar$\underline{C}$C), 174.8 (C1); LRMS (ESI +ve): 401 (15%, M+$NH_4^+$), 406 (100%, M+$Na^+$), 438 (28%, M+MeOH+$Na^+$), 789 (74%, 2M+$Na^+$); (ESI –ve): 418 (100%, M+$^{35}Cl^-$), 420 (39%, M+$^{37}Cl^-$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-β-D-idofuranose 2.125D** (1.46 g, 3.78 mmol) in a suitably scaled procedure afforded **5-azido-3,6-di-*O*-benzyl-5-deoxy-D-idono-1,4-lactone 2.126D** (1.06 g, 73%) as a pale yellow oil; $[\alpha]_D^{25}$ -35.2 (*c* 1.15, $CHCl_3$).

**5-Azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-trifluoromethanesulfonyl-L-idono-1,4-lactone 2.127L**

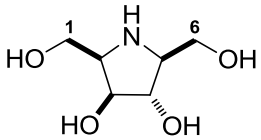



Trifluoromethanesulfonic anhydride (0.13 mL, 0.76 mmol) was added dropwise to a solution of the lactone **2.126L** (220 mg, 0.58 mmol) and pyridine (0.14 ml, 1.74 mmol) in dichloromethane (2.5 mL) at -40 °C. The reaction was stirred for 1 h, after which TLC analysis (2:1,

cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.39) and the formation of a major product ($R_f$ 0.59). The reaction was diluted with dichloromethane (11 mL) and washed with 2 M aqueous hydrochloric acid (3 x 11 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (19:1 to 4:1, cyclohexane/ethyl acetate) to afford the triflate **2.127L** (280 mg, 95%) as a yellow oil; HRMS (ESI +ve): found 538.0862 [M+$Na^+$]; $C_{21}H_{20}F_3N_3NaO_7S$ requires 538.0866; $[\alpha]_D^{25}$ +56.9 (*c* 0.84, $CHCl_3$); $\nu_{max}$ (thin film): 1813 (s, C=O), 2119 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz): 3.60 (1H, dd, H6, $J_{6,5}$ 6.7, $J_{6,6'}$ 9.5), 3.69 (1H, dd, H6', $J_{6',5}$ 7.4, $J_{6',6}$ 9.5), 4.01 (1H, dd, H5, $J_{5,6}$ 6.7, $J_{5,6'}$ 7.4), 4.53 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 11.8), 4.57 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 11.3), 4.58 (1H, d, H3, $J_{3,2}$ 8.0), 4.59 (1H, d, H4, $J_{4,2}$ 5.3), 4.60 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 11.6), 4.84 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 11.8), 5.82 (1H, dd, H2, $J_{2,4}$ 5.3, $J_{2,3}$ 8.0), 7.30-7.42 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 58.9 (C5), 68.9 (C6), 73.8, 73.8 (O<u>C</u>H$_2$Ph), 76.2 (C3), 76.7 (C4), 81.4 (C2), 127.8, 128.1, 128.2, 128.6, 128.9 (Ar<u>C</u>H), 135.5, 137.0 (Ar<u>C</u>C), 165.7 (C1); LRMS (ESI +ve): 538 (100%, M+$Na^+$), 570 (54%, M+MeOH+$Na^+$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-D-idono-1,4-lactone 2.126D** (100 mg, 0.26 mmol) in a suitably scaled procedure afforded **5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-trifluoromethanesulfonyl-D-idono-1,4-lactone 2.127D** (126 mg, 94%) as a pale yellow oil; $[\alpha]_D^{25}$ -63.4 (*c* 0.98, $CHCl_3$).

**2,5-Dideoxy-2,5-imino-L-glucitol (L-DGDP) 1.30L**



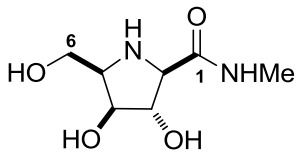

Palladium (10% on carbon, 30 mg) was added to a solution of the triflate **2.127D** (108 mg, 0.21 mmol) in ethanol (1.2 mL). The reaction vessel was evacuated and flushed with hydrogen and stirred for 1 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of starting material ($R_f$ 0.59) and the formation of a major product ($R_f$ 0.19). The reaction mixture was filtered (GF/B, glass microfibre) to afford the bicyclic lactone **2.128D**. LRMS indicated the absence of a peak corresponding to the triflate **2.127D** (*m/z* 538 [M+$Na^+$]) and the presence of a peak corresponding to the bicyclic lactone **2.128D** (*m/z* 340 [M+$H^+$]). The crude bicyclic lactone **2.128D** was reacted on without further purification.

Partial data for the bicyclic lactone **2.128D**: $\nu_{max}$ (thin film): 1822 (s, C=O); $\delta_H$ ($CDCl_3$, 500 MHz): 3.78 (1H, dd, H6, $J_{6,5}$ 7.6, $J_{6,6'}$ 10.1), 3.85 (1H, dd, H6', $J_{6',5}$ 7.0, $J_{6',6}$ 10.1), 4.36 (1H, d, H3 or H4, *J* 2.2), 4.39 (1H, dd, H5, $J_{5,6'}$ 7.0, $J_{5,6}$ 7.6), 4.51 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 12.0), 4.54 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 12.0), 4.58 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.7), 4.78 (2H, m, H2, H3 or H4), 4.84 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 12.0), 7.25-7.37 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 125 MHz): 59.4 (C5), 60.3 (C2), 63.9 (C6), 72.9, 73.7 (O$\underline{C}H_2$Ph), 79.1, 79.5 (C3,C4), 127.9, 128.0, 128.2, 128.3, 128.4, 128.5, 128.7, 128.8 (Ar$\underline{C}$H), 135.4, 136.9 (Ar$\underline{C}$C), 165.5 (C1); LRMS (ESI +ve): 362 (60%, M+$Na^+$), 394 (100%, M+MeOH+$Na^+$), 701 (24%, 2M+$Na^+$).

Sodium borohydride (50 mg, 1.31 mmol) was added portion-wise to a solution of the bicyclic lactone **2.128D** in ethanol (2 mL) and the reaction stirred at RT for 16 h. 2 M Aqueous hydrochloric acid (1.5 mL) and palladium (10% on carbon, 50 mg) were added to the reaction mixture. The reaction vessel was evacuated and flushed with hydrogen and stirred for 20 h. The

reaction mixture was filtered through glass microfibre (GF/B) and the filtrate concentrated *in vacuo*. The crude residue was loaded onto a short column of Dowex® (50W-X8, $H^+$) and washed with water. The L-*gluco* pyrrolidine L-DGDP **1.30L** was liberated with 2 M aqueous ammonia and the ammoniacal fractions concentrated *in vacuo* to afford the L-*gluco* pyrrolidine L-DGDP **1.30L** (36 mg, 97% over three steps) as a yellow oil; HRMS (ESI +ve): $C_6H_{13}NNaO_4$ found 186.0738; ($M+Na^+$) requires 186.0737; $[\alpha]_D^{25}$ -19.1 (*c* 1.8, $H_2O$) [Lit.[52] $[\alpha]_D^{22}$ -23.6 (*c* 2.0, $H_2O$)]; $\nu_{max}$ (thin film): 3332 (br. s, NH/OH); $\delta_H$ ($D_2O$, 400 MHz): 3.52 (1H, ddd, H5, $J_{5,4}$ 3.5, $J_{5,6'}$ 4.8, $J_{5,6}$ 8.3), 3.82 (1H, dd, H6, $J_{6,5}$ 8.3, $J_{6,6'}$ 12.1), 3.87 (1H, dd, H2, $J_{2,3}$ 3.7, *J* 7.6), 3.88 (1H, dd, H6', $J_{6',5}$ 4.8, $J_{6',6}$ 12.1), 3.85-3.93 (2H, m, H1, H1'), 4.07 (1H, dd, H4, $J_{4,3}$ 2.3, $J_{4,5}$ 3.5), 4.24 (1H, dd, H3, $J_{3,4}$ 2.3, $J_{3,2}$ 3.7); $\delta_C$ ($D_2O$, 100 MHz): 57.4 (C1), 59.8 (C6), 63.7 (C2), 67.3 (C5), 75.0 (C3), 76.5 (C4); LRMS (ESI +ve): 164 (100%, $M+H^+$); (ESI –ve): 162 (100%, $[M-H]^-$), 325 (25%, $[2M-H]^-$).

**Methyl 2,5-dideoxy-2,5-imino-D-gulonamide 2.123D**




Method A (from triflate **2.127D**): Palladium (10% on carbon, 30 mg) was added to a solution of the triflate **2.127D** (108 mg, 0.21 mmol) in ethanol (1.2 mL). The reaction vessel was evacuated and flushed with hydrogen and stirred for 1 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of starting material ($R_f$ 0.59) and the formation of a major product ($R_f$ 0.19). The reaction mixture was filtered through (GF/B, glass microfibre) to afford the bicyclic lactone **2.128D**. Methylamine (33 wt.% in ethanol, 0.01 mL, 0.23 mmol) was added to the filtrate and the reaction mixture stirred at RT for 16 h, after which TLC analysis (ethyl acetate) indicated the complete consumption of the intermediate bicyclic lactone **2.128D**

($R_f$ 0.29) and the formation of a single product ($R_f$ 0.02). The reaction mixture was concentrated *in vacuo* to afford the crude dibenzyl amide **2.130D**, which was reacted on without further purification.

Partial data for **2.130D**: HRMS (ESI +ve): found 371.1962 [$M+H^+$]; $C_{21}H_{27}N_2O_4$ requires 371.1965; $\delta_C$ ($CD_3OD$, 100 MHz): 26.8 ($NCH_3$), 62.2 (C5), 66.7 (C6), 72.6 (C4), 74.5 (C2), 75.4 (C3), 128.9, 128.9, 129.1, 129.5, 129.5, 129.6, 129.7 (Ar<u>C</u>H), 139.5, 139.7 (Ar<u>C</u>C), 174.7 (C1); LRMS (ESI +ve): 371 (80%, $M+H^+$), 393 (85%, $M+Na^+$), 741 (100%, $2M+H^+$), 763 (96%, $2M+Na^+$).

Palladium (10% on carbon, 25 mg) was added to a solution of the crude dibenzyl amide **2.130D** in a 5:1 1,4-dioxane/2 M aqueous hydrochloric acid mixture (6 mL). The flask was evacuated and flushed with hydrogen and stirred for 16 h, after which the reaction mixture was filtered (GF/B, glass microfibre) and concentrated *in vacuo*. The crude residue was dissolved in 2 M aqueous hydrochloric acid, loaded onto a short column of Dowex® (50W-X8, $H^+$) and the resin washed with water. The D-*gulo* amide **2.123D** was liberated with 2 M aqueous ammonia and the ammoniacal fractions concentrated *in vacuo* to afford the D-*gulo* amide **2.123D** (34 mg, 90%) as a yellow oil.

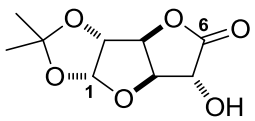
<u>Method B (from Boc protected **2.190L**):</u> Palladium (10% on carbon, 24 mg) was added to a solution of the dibenzyl ether **2.190L** (61 mg, 0.13 mmol) in a 1:1 1,4-dioxane/2 M aqueous hydrochloric acid mixture (2.5 mL). The reaction vessel was evacuated and flushed with hydrogen and stirred for 16 h. The reaction mixture was filtered, the filtrate stirred at 50 °C for 2 h and concentrated *in vacuo*. $^1H$ NMR indicated the removal of the benzyl ether and Boc protecting groups. The crude residue was loaded onto a short column of Dowex® (5W-80, $H^+$)

and the resin washed with water. The L-*gulo* amide **2.123L** was liberated with 2 M aqueous ammonia and the ammoniacal fractions concentrated *in vacuo* to afford the L-*gulo* amide **2.123L** (19 mg, 77%) as a pale-yellow oil; HRMS (ESI +ve): found 213.0855 [$M+Na^+$]; $C_7H_{14}N_2NaO_4$ requires: 213.0846; $[\alpha]_D^{25}$ -9.0 (*c* 0.32, $H_2O$) [Lit.[53] $[\alpha]_D^{25}$ -4.3 (*c* 0.8, $H_2O$); $\nu_{max}$ (thin film): 1562 (s, C=O), 1648 (s, C=O), 3325 (br. s, NH/OH); $\delta_H$ ($D_2O$, 400 MHz): 2.63 (3H, s, $NCH_3$), 3.40 (1H, a-q, H5, $J_{5,4} = J_{5,6} = J_{5,6'}$ 5.6), 3.50 (1H, d, H2, $J_{2,3}$ 2.5), 3.56 (1H, dd, H6, $J_{6,5}$ 6.8, $J_{6,6'}$ 11.2), 3.68 (1H, dd, H6', $J_{6',5}$ 6.1, $J_{6',6}$ 11.2), 3.98 (1H, dd, H4, $J_{4,3}$ 2.6, $J_{4,5}$ 4.8), 4.06 (1H, a-t, H3, $J_{3,2} = J_{3,4}$ 2.6); $\delta_C$ ($D_2O$, 100 MHz): 26.2 ($NCH_3$), 61.2 (C5), 61.5 (C6), 66.5 (C2), 76.6 (C4), 80.8 (C3), 175.6 (C1); LRMS (ESI +ve): 191 (100%, $M+H^+$).

Similar treatment of **methyl 2-*N*-(tert-butoxycarbonyl)-3,6-di-*O*-benzyl-2,5-dideoxy-2,5-imino-D-gulonamide 2.190D** (93 mg, 0.198 mmol) in a suitably scaled procedure afforded **methyl 2,5-dideoxy-2,5-imino-D-gulonamide 2.123D** (29 mg, 77%) as a yellow oil; $[\alpha]_D^{25}$ +7.9 (*c* 0.30, $H_2O$);

*2.4.3.3 Synthesis of manno-configured iminosugars*

**1,2-*O*-Isopropylidene-β-L-idurono-3,6-lactone 1.59L**



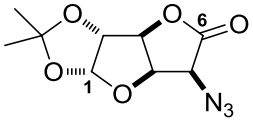

Trifluoromethanesulfonic anhydride (9.0 mL, 53.5 mmol) was added dropwise to a solution of the lactone **1.60D** (8.90 g, 41.2 mmol) and pyridine (11.2 mL, 139 mmol) in anhydrous dichloromethane (90 mL) at -40 °C. The reaction was stirred for 1 h, with the internal temperature rising to -30 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of starting material ($R_f$ 0.13) and the formation of a major product ($R_f$ 0.52). The reaction mixture was diluted with dichloromethane (200 mL) and washed with 2 M aqueous hydrochloric acid (3 x 150 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude triflate **1.61D**, which was reacted on without further purification.

Sodium trifluoroacetate (10.2 g, 74.1 mmol) was added portion-wise to a solution of the triflate **1.61D** in DMF (100 mL). The reaction was stirred at RT for 2 h, after which TLC analysis indicated the complete consumption of starting material ($R_f$ 0.52) and the formation of a major product ($R_f$ 0.31). The reaction mixture was diluted with ethyl acetate (200 mL) and washed with an aqueous sodium bicarbonate solution (200 mL). The aqueous phase was extracted with ethyl acetate (2 x 200 mL), the organic fractions combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Recrystallisation of the crude residue (toluene) afforded the lactone **1.59L** (8.46 g, 95%) as a white crystalline solid; HRMS (ESI +ve): found 271.0791 [M+MeOH+$Na^+$]; $C_{10}H_{16}NaO_7$ requires 271.0788; m.p. 134-136 °C [Lit.[142] m.p. 128-130 °C]; $[\alpha]_D^{25}$ +97.2 (*c* 1.50, acetone) [Lit.[142] $[\alpha]_D^{25}$ +101.8 (*c* 0.5, acetone)]; $\nu_{max}$ (thin film): 1764 (s, C=O), 3399 (br. s, OH); $\delta_H$ ($CD_3CN$, 400 MHz): 1.30, 1.47 (2 × 3H, s, $C(C\underline{H}_3)_2$), 4.16 (1H, d, H5, $J_{5,OH}$ 5.3), 4.39 (1H, d,

OH5, $J_{OH,5}$ 5.3), 4.69 (1H, d, H4, $J_{4,3}$ 3.3), 4.82 (1H, d, H2, $J_{2,1}$ 3.7), 5.01 (1H, d, H3, $J_{3,4}$ 3.3), 5.91 (1H, d, H1, $J_{1,2}$ 3.7); $\delta_C$ ($CD_3CN$, 100 MHz): 26.8, 27.2 ($C(\underline{C}H_3)_2$), 72.3 (C5), 83.1 (C2), 83.7 (C4), 85.7 (C3), 107.2 (C1), 113.7 ($\underline{C}(CH_3)_2$), 175.4 (C6); LRMS (ESI +ve): 239 (60%, $M+Na^+$), 271 (100%, $M+MeOH+Na^+$).

Similar treatment of **1,2-*O*-isopropylidene-α-L-glucurono-3,6-lactone 1.60L** (9.0 g, 41.6 mmol) in a suitably scaled procedure afforded **1,2-*O*-isopropylidene-β-D-idurono-3,6-lactone 1.59L** (6.86 g, 77%) as a white crystalline solid: m.p. 134-136 °C [Lit.[142] m.p. 132-134 °C]; $[\alpha]_D^{25}$ -103.2 (*c* 1.04, acetone) [Lit.[142] $[\alpha]_D^{25}$ -105.6 (*c* 1.0, acetone)].

**5-Azido-5-deoxy-1,2-*O*-isopropylidene-α-D-glucurono-3,6-lactone 2.133D**



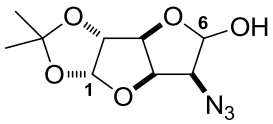

Trifluoromethanesulfonic anhydride (9.0 mL, 53.5 mmol) was added dropwise to a solution of the lactone **1.59L** (8.46 g, 39.1 mmol) and pyridine (11.2 mL, 138.5 mmol) in anhydrous dichloromethane (90 mL) at -40 °C. The reaction was stirred at for 1 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of starting material ($R_f$ 0.31) and the formation of a major product ($R_f$ 0.62). The reaction mixture was diluted with dichloromethane (200 mL) and washed with 2 M aqueous hydrochloric acid (3 x 200 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude triflate **2.132L** which was reacted on without further purification.

Sodium azide (3.50 g, 53.5 mmol) was added in one-portion to a solution of the crude triflate **2.132L** in DMF (100 mL) at -30 °C. The reaction was stirred for 2 h, with the internal

temperature rising to -20 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the triflate ($R_f$ 0.62) and the formation of a major product ($R_f$ 0.43). The reaction mixture was diluted with ethyl acetate (500 mL), washed with a 3:1 water/brine solution (3 x 150 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash chromatography (5:1 to 1:1, cyclohexane/ethyl acetate) to afford the azide **2.133D** (8.00 g, 85%) as a white crystalline solid; HRMS (ESI +ve): found 296.0854 [M+MeOH+$Na^+$]; $C_{10}H_{15}N_3NaO_6$ requires 296.0853; m.p. 88-90 °C [Lit.[117] m.p. 89 °C]; $[\alpha]_D^{25}$ +24.6 (*c* 1.90, $CHCl_3$) [Lit.[117] $[\alpha]_D^{25}$ +25.1 (*c* 0.56, $CHCl_3$)]; $\nu_{max}$ (thin film): 1791 (s, C=O), 2116 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz): 1.36, 1.53 (2 × 3H, s, $C(C\underline{H}_3)_2$), 4.11 (1H, d, H5, $J_{5,4}$ 4.3), 4.82-4.87 (2H, m, H2, H3), 5.02 (1H, dd, H4, $J_{4,3}$ 2.7, $J_{4,5}$ 4.3), 6.02 (1H, d, H1, $J_{1,2}$ 3.5); $\delta_C$ ($CDCl_3$, 100 MHz): 26.4, 26.8 ($C(\underline{C}H_3)_2$), 60.4 (C5), 79.0 (C4), 82.4, 82.5 (C2, C3), 106.7 (C1), 113.6 ($\underline{C}(CH_3)_2$), 169.7 (C6); LRMS (ESI +ve): 264 (66%, M+$Na^+$), 296 (100%, M+MeOH+$Na^+$), 505 (45%, 2M+$Na^+$); (ESI –ve): 276 (100%, M+$^{35}Cl^-$), 278 (35%, M+$^{37}Cl^-$).

Similar treatment of **1,2-*O*-isopropylidene-β-D-idurono-3,6-lactone 1.59D** (6.86 g, 31.7 mmol) in a suitably scaled procedure afforded **5-azido-5-deoxy-1,2-*O*-isopropylidene-α-L-glucurono-3,6-lactone 2.133L** (7.50 g, 97%) as a white crystalline solid: m.p. 78-80 °C [Lit.[47] m.p. 82-84 °C]; $[\alpha]_D^{25}$ -21.4 (*c* 1.00, $CHCl_3$) [Lit.[47] $[\alpha]_D^{25}$ -24.2 (*c* 1.00, $CHCl_3$)].

**5-Azido-5-deoxy-1,2-*O*-isopropylidene-α-D-*gluco*-hexodialdo-1,4:3,6-difuranose 2.143D**




Diisobutylaluminium hydride (1.5 M in toluene, 42 mL, 62.8 mmol) was added dropwise to a solution of the lactone **2.133D** (8.00 g, 33.2 mmol) in anhydrous dichloromethane (100 mL)

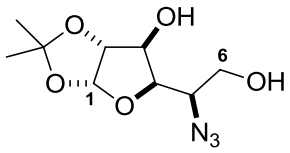
at -78 °C. The reaction was stirred for 90 min, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of starting material ($R_f$ 0.43) and the formation of a major product ($R_f$ 0.33). The reaction mixture was diluted with dichloromethane (400 mL) and a 1:3 water/saturated potassium tartrate solution (400 mL) added. The biphasic mixture was stirred vigorously at RT for 18 h, after which the phases were separated and the aqueous layer extracted with dichloromethane (8 × 100 mL). The organic fractions were combined, filtered, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was co-evaporated with dichloromethane (3 x 50 mL) to afford the crude lactols **2.134D** (7.50 g, 93%) as a yellow oil, in a 4:3 (A:B) ratio of anomers. The lactols **2.134D** were reacted on without further purification.

HRMS (ESI +ve): found 266.0750 [M+$Na^+$]; $C_9H_{13}N_3NaO_5$ requires 266.0747; $[\alpha]_D^{25}$ +17.1 (*c* 1.75, $CHCl_3$); $\nu_{max}$ (thin film): 2117 (s, $N_3$), 3429 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.35 (3H, s, C$\underline{H}_3^B$), 1.36 (3H, s, C$\underline{H}_3^A$), 1.50 (6H, s, C$\underline{H}_3^A$, C$\underline{H}_3^B$), 3.45 (1H, a-t, H5$^A$, $J_{5,4}$ = $J_{5,6}$ 4.8), 3.66 (2H, br. s, $OH^A$, $OH^B$), 3.75 (1H, a-t, H5$^B$, $J_{5,4}$ = $J_{5,6}$ 4.4), 4.64-4.65 (2H, m, H2$^B$, H3$^B$), 4.76 (2H, a-d, H2$^A$, H3$^A$, *J* 3.5), 4.98-5.01 (2H, m, H4$^A$, H4$^B$), 5.38 (1H, d, H6$^B$, $J_{6,5}$ 4.0), 5.41 (1H, d, H6$^A$, $J_{6,5}$ 4.3), 5.98 (1H, d, H1$^B$, $J_{1,2}$ 3.5), 6.10 (1H, d, H1$^A$, $J_{1,2}$ 3.5); $\delta_C$ ($CDCl_3$, 100 MHz): 26.7, 27.2 (C($\underline{C}H_3)_2^B$), 26.8, 27.4 (C($\underline{C}H_3)_2^A$), 62.7 (C5$^A$), 67.5 (C5$^B$), 81.8 (C4$^A$), 82.5 (C4$^B$), 84.1, 84.5 (C2$^B$, C3$^B$), 85.3, 85.8 (C2$^A$, C3$^A$), 97.7 (C6$^A$), 101.2 (C6$^B$), 107.1 (C1$^B$), 107.2 (C1$^A$), 113.0 ($\underline{C}(CH_3)_2^B$), 113.3 ($\underline{C}(CH_3)_2^A$); LRMS (ESI +ve): 266 (100%, M+$Na^+$), 509 (45%, 2M+$Na^+$).

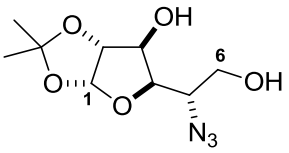
Similar treatment of **5-azido-5-deoxy-1,2-*O*-isopropylidene-α-L-glucurono-3,6-lactone 2.133L** (7.50 g, 31.1 mmol) in a suitably scaled procedure afforded **5-azido-5-deoxy-1,2-*O*-isopropylidene-α-L-*gluco*-hexodialdo-1,4:3,6-difuranose 2.134L** (6.84 g, 90%) as a yellow oil, as an anomeric mixture (A:B = 4:3): $[\alpha]_D^{25}$ -29.2 (*c* 1.34, $CHCl_3$).

**5-Azido-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose 2.38D** /

**5-Azido-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose 2.37L**




**2.38D**



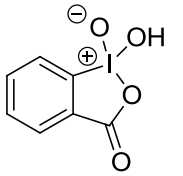

**2.37L**

Sodium borohydride (625 mg, 16.5 mmol) was added portion-wise to a solution of the lactols **2.134D** (7.40 g, 30.4 mmol) in methanol (100 mL) at -30 °C. The reaction stirred for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.33) and the formation of a major ($R_f$ 0.17) and a minor product ($R_f$ 0.15). The reaction was neutralised with glacial acetic acid and concentrated *in vacuo*. The crude residue was dissolved in ethyl acetate (250 mL), washed with an aqueous sodium bicarbonate solution (150 mL) and the aqueous layer extracted with ethyl acetate (5 x 200 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1 to 1:1, cyclohexane/ethyl acetate) to afford the *gluco*-diol **2.38D** (6.30 g, 85%) as a yellow oil, and the *ido*-diol **2.37L** (500 mg, 7%) as a white crystalline solid. *These compounds were previously synthesised from lactols **2.36L**, refer to pages 130-131 for experimental data.*

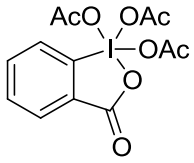
Similar treatment of **5-azido-5-deoxy-1,2-*O*-isopropylidene-α-L-*gluco*-hexodialdo-1,4:3,6-difuranose 2.134L** (5.90 g, 24.3 mmol) in a suitably scaled procedure afforded **5-azido-5-deoxy-1,2-*O*-isopropylidene-α-L-glucofuranose 2.38L** (4.10 g, 70%) as a yellow oil and **5-azido-5-deoxy-1,2-*O*-isopropylidene-β-D-idofuranose 2.37D** (517 mg, 9%) as a white crystalline solid.

*2.4.3.4 Synthesis of galacto-configured iminosugars*

**2-Iodoxybenzoic acid (IBX) & 1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one, Dess-Martin Periodinane 2.144**



**IBX**



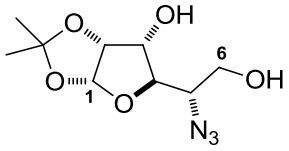
**DMP**
**2.144**

2-Iodobenzoic acid **2.145** (50 g, 202 mmol) was added in one-portion to a solution of Oxone® (181 g, 294 mmol) in water (650 mL). A mechanical overhead-stirrer was attached and the suspension heated to 80 $^{o}$C for 3.5 h, after which the suspension had become more granular in appearance. The suspension was cooled to 0 $^{o}$C for 1.5 h, after which the suspension was filtered and washed with water (6 x 100 mL) and acetone (2 x 100 mL). The filter cake was dried overnight to afford **IBX** (46.6 g, 83%) as a white granular crystalline solid.

**IBX** (46.6 g, 166 mmol), *para*-toluenesulfonic acid (253 mg, 1.33 mmol) and acetic anhydride (190 mL) were added to a dried flask. A reflux condenser and drying tube were attached and the suspension stirred at 80 $^{o}$C for 3 h, after which the pale yellow suspension was cooled to 0 $^{o}$C for 1 h and then filtered. The filter cake was washed with diethyl ether (4 x 50 mL) and dried overnight to afford DMP **2.144** (61.9 g, 88%, 73% over two steps) as a fine white powder.

Partial data for DMP **2.144**: m.p. 208-210$^{o}$C; $\nu_{max}$ (neat): 1707 (s, endocyclic C=O), 1730 (s, acetyl C=O); $\delta_H$ ($(CD_3)_2SO$, 400 MHz): 1.90 (9H, s, $OCOCH_3$), 7.84 (1H, td, *J* 1.0, *J* 7.4, *J* 7.4), 8.00 (1H, td, *J* 1.3, *J* 7.7, *J* 7.7), 8.04 (1H, dd, *J* 1.3, *J* 7.7), 8.14 (1H, d, *J* 7.7); $\delta_C$ ($(CD_3)_2SO$, 100 MHz): 21.9 ($OCO\underline{C}H_3$), 125.8 (Ar$\underline{C}$I), 132.0 (Ar$\underline{C}$C), 131.0, 133.9, 134.4, 147.3 (Ar$\underline{C}$H), 168.7 (Ph$\underline{C}$O), 173.1 ($O\underline{C}OCH_3$).

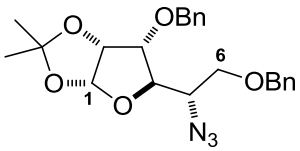
**5-Azido-5-deoxy-1,2-*O*-isopropylidene-β-L-talofuranose 2.146L**




Tetra-*n*-butylammonium fluoride (1 M in THF, 24 mL, 24.0) was added to a solution of the silyl ether **2.41L** (7.83 g, 21.8 mmol) in THF (80 mL) at RT. The reaction was stirred for 2 h, after which TLC analysis (1:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.70) and the formation of a major product ($R_f$ 0.25). The reaction mixture was concentrated *in vacuo* and the crude residue purified by flash chromatography (1:1:0 to 0:9:1, cyclohexane/ethyl acetate/methanol) to afford the diol **2.146L** as a white crystalline solid (4.6 g, 86%); HRMS (ESI +ve): found 268.0908 [M+$Na^+$]; $C_9H_{15}N_3NaO_5$ requires 268.0904; m.p. 100-102 $^oC$ (acetone) [Lit.[143] m.p. 98-100 $^oC$ (methanol)]; $[\alpha]_D^{25}$ +32.4 (*c* 2.9, acetone) [Lit.[143] $[\alpha]_D^{22}$ +43.3 (*c* 0.9, methanol)]; $\nu_{max}$ (thin film): 2111 (s, $N_3$), 3381 (br. s, OH); $\delta_H$ ($(CD_3)_2CO$, 400 MHz): 1.30, 1.46 (2 x 3H, s, $C(CH_3)_2$), 3.52 (1H, a-dt, H5, $J_{5,4} = J_{5,6'}$ 4.5, $J_{5,6}$ 7.6), 3.79 (1H, ddd, H6, $J_{6,OH}$ 5.8, $J_{6,5}$ 7.6, $J_{6,6'}$ 11.4), 3.85 (1H, ddd, H6', $J_{6',5}$ 4.5, $J_{6',OH}$ 5.8, $J_{6',6}$ 11.4), 3.92 (1H, dd, H4, $J_{4,5}$ 4.3, $J_{4,3}$ 8.8), 4.00 (1H, a-td, H3, $J_{3,2}$ 4.5, $J_{3,OH} = J_{3,4}$ 9.0), 4.13 (1H, d, OH3, $J_{OH,3}$ 9.1), 4.25 (1H, t, OH6, $J_{OH,6} = J_{OH,6'}$ 5.8), 4.62 (1H, a-t, H2, $J_{2,1} = J_{2,3}$ 4.3), 5.77 (1H, d, H1, $J_{1,2}$ 3.8); $\delta_C$ ($(CD_3)_2CO$, 100 MHz): 26.3, 26.4 ($C(\underline{C}H_3)_2$), 62.4 (C6), 64.1 (C5), 73.0 (C3), 79.6 (C2), 79.6 (C4), 104.4 (C1), 112.5 ($\underline{C}(CH_3)_2$); LRMS (ESI +ve): 268 (94%, M+$Na^+$), 513 (100%, 2M+$Na^+$); (ESI –ve): 244 (87%, $[M-H]^-$), 489 (100%, $[2M-H]^-$).

Similar treatment of **5-azido-6-*O*-*tert*-butyldimethylsilyl-5-deoxy-1,2-*O*-isopropylidene-β-D-talofuranose 2.41D** (5.50 g, 15.3 mmol) in a suitably scaled procedure afforded **5-azido-5-deoxy-1,2-*O*-isopropylidene-β-D-talofuranose 2.146D** (3.53 g, 94%) as a white crystalline solid; m.p. 101-103 $^oC$ (acetone); $[\alpha]_D^{25}$ -38.4 (*c* 2.5, acetone).

**5-Azido-3,6-di-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-L-talofuranose 2.147L**

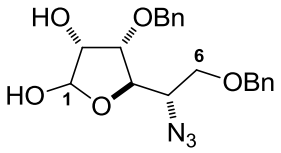



Sodium hydride (60% min. oil suspension, 2.2 g, 55.1 mmol) was added portion-wise to a solution of the diol **2.146L** (4.50 g, 18.4 mmol) and benzyl bromide (6.55 mL, 55.1 mmol) in DMF (70 mL) at 0 $^{o}$C. The reaction mixture was allowed to warm to RT and stirred for 19 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.13) and the formation of a major product ($R_f$ 0.73). The reaction was quenched with methanol (2 mL), diluted with ethyl acetate (200 mL) and washed with a 1:1 brine/water solution (3 x 100 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (20:1 to 10:1, cyclohexane/ethyl acetate) to afford the dibenzyl ether **2.147L** (7.73 g, 99%) as a colourless oil; HRMS (ESI +ve): found 448.1841 [M+Na$^+$]; $C_{23}H_{27}N_3NaO_5$ requires 448.1843; $[\alpha]_D^{25}$ +122.0 (*c* 1.5, $CHCl_3$); $\nu_{max}$ (thin film): 2098 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz): 1.37, 1.58 (2 x 3H, s, $C(CH_3)_2$), 3.70 (1H, ddd, H5, $J_{5,4}$ 2.3, $J_{5,6}$ 3.8, $J_{5,6'}$ 9.1), 3.75 (1H, dd, H6, $J_{6,5}$ 3.8, $J_{6,6'}$ 10.1), 3.80 (1H, dd, H6', $J_{6',5}$ 9.1, $J_{6',6}$ 10.1), 3.90 (1H, dd, H3, $J_{3,2}$ 4.3, $J_{3,4}$ 8.8), 4.08 (1H, dd, H4, $J_{4,5}$ 2.3, $J_{4,3}$ 8.8), 4.56 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 4.57-4.59 (1H, m, H2), 4.57 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.7), 4.62 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.9), 4.79 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.9), 5.74 (1H, d, H1, $J_{1,2}$ 3.5), 7.29-7.42 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 26.4, 26.8 (C($\underline{C}H_3)_2$), 60.0 (C5), 70.8 (C6), 72.3, 73.4 (O$\underline{C}H_2$Ph), 77.0 (C2), 77.6 (C4), 77.9 (C3), 104.3 (C1), 113.3 ($\underline{C}(CH_3)_2$), 127.7, 127.8, 128.1, 128.3, 128.5, 128.6 (Ar$\underline{C}$H), 137.2, 137.7 (Ar$\underline{C}$C); LRMS (ESI +ve): 448 (100%, M+Na$^+$), 464 (25%, M+K$^+$), 873 (100%, 2M+Na$^+$);

Similar treatment of **5-azido-5-deoxy-1,2-*O*-isopropylidene-β-D-talofuranose 2.146D** (3.44 g, 14.03 mmol) in a suitably scaled procedure afforded **5-azido-3,6-di-*O*-benzyl-5-deoxy-1,2-*O*-**

**isopropylidene-β-D-talofuranose 2.147D** (5.91 g, 99%) as a clear oil; $[\alpha]_D^{25}$ -138.4 (*c* 1.60, $CHCl_3$).

**5-Azido-3,6-di-*O*-benzyl-5-deoxy-L-talofuranose 2.148L**

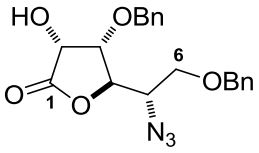



*para*-Toluenesulfonic acid (6.0 g, 36.7 mmol) was added to a solution of the acetonide **2.147L** (7.1 g, 16.7 mmol) in a 7:1 1,4-dioxane/water mixture (40 mL). The reaction mixture was heated to 50 $^oC$ and stirred for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.73) and the formation of a major product ($R_f$ 0.24). The reaction mixture was allowed to cool to RT, quenched with an aqueous sodium bicarbonate solution (350 mL) and extracted with ethyl acetate (3 x 350 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (7:3 to 1:1, cyclohexane/ethyl acetate) to afford the lactols **2.148L** (6.0 g, 95%) as a colourless oil, in a 3:2 (A:B) anomeric mixture; HRMS (ESI +ve): found 408.1528 $[M+Na^+]$; $C_{20}H_{23}N_3NaO_5$ requires 408.1530; $[\alpha]_D^{25}$ +66.8 (*c* 2.4, $CHCl_3$); $\nu_{max}$ (thin film): 2100 (s, $N_3$), 3422 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 2.59 (1H, br. s, $OH2^B$), 2.93 (1H, br. s, $OH2^A$), 3.13 (1H, br. s, $OH1^B$), 3.49 (1H, ddd, $H5^A$, $J_{5,4}$ 2.8, $J_{5,6}$ 4.4, $J_{5,6'}$ 8.2), 3.58 (1H, adt, $H5^B$, $J_{5,4} = J_{5,6}$ 4.0, $J_{5,6'}$ 8.0), 3.68 (1H, dd, $H6^B$, $J_{6,5}$ 4.4, $J_{6,6'}$ 10.1), 3.68 (1H, dd, $H6^A$, $J_{6,5}$ 4.4, $J_{6,6'}$ 9.9), 3.72 (1H, dd, $H6'^B$, $J_{6',5}$ 8.0, $J_{6',6}$ 10.1), 3.74 (1H, dd, $H6'^A$, $J_{6',5}$ 8.2, $J_{6',6}$ 9.9), 3.88 (1H, br. s, $OH1^A$), 4.01 (1H, a-t, $H3^A$, $J_{3,2} = J_{3,4}$ 5.6), 4.03 (1H, d, $H2^B$, $J_{2,3}$ 3.9), 4.05 (1H, dd, $H4^B$, $J_{4,5}$ 3.5, $J_{4,3}$ 7.1), 4.11 (1H, dd, $H4^A$, $J_{4,5}$ 2.8, $J_{4,3}$ 5.3), 4.11-4.13 (1H, m, $H2^A$), 4.29 (1H, dd, $H3^B$, $J_{3,2}$ 4.0, $J_{3,4}$ 7.1), 4.53 (1H, d, $OC\underline{H}_2Ph^B$, $J_{gem}$ 11.5), 4.62 (1H, d, $OC\underline{H}_2Ph^B$, $J_{gem}$ 11.5), 4.54 (1H, d, $OC\underline{H}_2Ph^A$, $J_{gem}$ 11.7), 4.56 (1H, d, $OC\underline{H}_2Ph^A$, $J_{gem}$ 11.7), 4.59 (1H, d,

OC<u>H</u>$_2$Ph$^B$, $J_{gem}$ 11.6), 4.65 (1H, d, OC<u>H</u>$_2$Ph$^B$, $J_{gem}$ 11.6), 4.60 (1H, d, OC<u>H</u>$_2$Ph$^A$, $J_{gem}$ 11.6), 4.68 (1H, d, OC<u>H</u>$_2$Ph$^A$, $J_{gem}$ 11.6), 5.27 (1H, s, H1$^B$), 5.30 (1H, br. s, H1$^A$), 7.29-7.43 (20H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 61.1 (C5$^A$), 62.0 (C5$^B$), 69.7 (C2$^A$), 70.1 (C6$^A$), 70.5 (C6$^B$), 73.1, 73.5 (O<u>C</u>H$_2$Ph$^B$), 73.4, 73.6 (O<u>C</u>H$_2$Ph$^A$), 73.4 (C2$^B$), 78.1 (C3$^A$), 78.8 (C3$^B$), 79.7 (C4$^A$), 80.4 (C4$^B$), 97.3 (C1$^A$), 102.3 (C1$^B$), 127.7, 127.8, 127.9, 127.9, 128.2, 128.5, 128.6, 128.7, 128.8 (Ar<u>C</u>H), 136.7, 136.7, 137.5, 137.5 (Ar<u>C</u>C); LRMS (ESI +ve): 408 (100%, M+Na$^+$), 793 (73%, 2M+Na$^+$); (ESI –ve): 384 (20%, [M-H]$^-$), 420 (25%, M+$^{35}$Cl$^-$), 422 (10%, M+$^{37}$Cl$^-$), 769 (100%, [2M-H]$^-$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-β-D-talofuranose 2.147D** (5.83 g, 13.7 mmol) in a suitably scaled procedure afforded **5-azido-3,6-di-*O*-benzyl-5-deoxy-D-talofuranose 2.148D** (4.22 g, 80%) as a yellow oil, in a 1.7:1 (A:B) anomeric mixture; $[\alpha]_D^{25}$ -80.8 (*c* 2.00, $CHCl_3$).

**5-Azido-3,6-di-*O*-benzyl-5-deoxy-L-talono-1,4-lactone 2.149L**

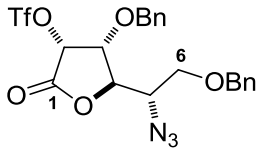



Potassium carbonate (1.98 g, 14.33 mmol) and iodine (3.64 g, 14.33 mmol) were added to a warm solution of the lactols **2.148L** (2.76 g, 7.17 mmol) in *tert*-butanol (30 mL) at 100 $^o$C. The reaction was stirred for 90 min, after which TLC analysis (1:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.40) and the formation of a major product ($R_f$ 0.68). The reaction was allowed to cool to RT and diluted with ethyl acetate (200 mL). Saturated aqueous sodium thiosulfate (100 mL) was added slowly and the biphasic mixture stirred until the iodine was visibly quenched. The phases were separated and the aqueous layer extracted with ethyl acetate (2 x 200 mL). The organic fractions were combined, dried

($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (17:3 to 1:1, cyclohexane/ethyl acetate) to afford the lactone **2.149L** (2.20 g, 80%) as a clear oil; HRMS (ESI +ve): found 406.1365 [$M+Na^+$]; $C_{20}H_{21}N_3NaO_5$ requires 406.1373; $[\alpha]_D^{25}$ +110.3 (*c* 1.25, $CHCl_3$); $\nu_{max}$ (thin film): 1790 (s, C=O), 2112 (s, $N_3$), 3447 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 3.04 (1H, br. s, OH2), 3.68-3.78 (3H, m, H5, H6, H6'), 4.15 (1H, dd, H3, $J_{3,4}$ 0.9, $J_{3,2}$ 6.2), 4.45 (1H, br. s, H4), 4.54 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 11.9), 4.59 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 11.9), 4.66 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 11.6), 4.67 (1H, d, H2, $J_{2,3}$ 6.2), 4.72 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 11.9), 7.31-7.41 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 61.1 (C5), 67.8 (C2), 69.5 (C6), 73.1, 73.8 (O<u>C</u>H$_2$Ph), 75.9 (C3), 80.9 (C4), 127.9, 128.1, 128.1, 128.6, 128.6, 128.8 (Ar<u>C</u>H), 136.3, 137.0 (Ar<u>C</u>C), 174.7 (C1); LRMS (ESI +ve): 406 (45%, $M+Na^+$), 438 (40%, $M+MeOH+Na^+$), 789 (60%, $2M+Na^+$), 821 (63%, $2M+MeOH+Na^+$), 853 (100%, $2M+2MeOH+Na^+$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-D-talofuranose 2.148D** (3.53 g, 9.17 mmol) in a suitably scaled procedure afforded **5-azido-3,6-di-*O*-benzyl-5-deoxy-D-talono-1,4-lactone 2.149D** (2.52 g, 72%) as a pale yellow oil; $[\alpha]_D^{25}$ -102.2 (*c* 1.30, $CHCl_3$).

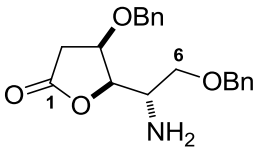
**5-Azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-trifluoromethanesulfonyl-L-talono-1,4-lactone 2.150L**




Trifluoromethanesulfonic anhydride (0.14 mL, 0.85 mmol) was added dropwise to a solution of the alcohol **2.149L** (250 mg, 0.65 mmol) and pyridine (0.16 mL, 1.96 mmol) in dichloromethane (3 mL) at -40 °C. The reaction was stirred for 90 min, with the internal temperature rising to -25 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete

consumption of the starting material ($R_f$ 0.38) and the formation of a major product ($R_f$ 0.71). The reaction was diluted with dichloromethane (20 mL), washed with 2 M aqueous hydrochloric acid (3 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (49:1 to 9:1, cyclohexane/ethyl acetate) to afford the triflate **2.150L** (270 mg, 80%) as a pale yellow oil; HRMS (ESI +ve): found 570.1112 [M+MeOH+$Na^+$]; $C_{22}H_{24}F_3N_3NaO_8S$ requires 570.1128; $[\alpha]_D^{25}$ +63.2 (*c* 1.25, $CHCl_3$); $\nu_{max}$ (thin film): 1808 (s, C=O), 2115 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz): 3.69-3.78 (3H, m, H5, H6, H6'), 4.32 (1H, dd, H3, $J_{3,4}$ 1.8, $J_{3,2}$ 6.1), 4.52-4.53 (1H, m, H4), 4.54 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 4.59 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 4.60 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 4.79 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 5.56 (1H, d, H2, $J_{2,3}$ 6.1), 7.32-7.43 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 60.2 (C5), 69.1 (C6), 73.5, 73.8 (O$\underline{C}H_2$Ph), 74.6 (C3), 76.3 (C2), 81.8 (C4), 127.9, 128.2, 128.3, 128.6, 128.9 (Ar$\underline{C}$H), 135.6, 136.8 (Ar$\underline{C}$C), 166.6 (C1); LRMS (ESI +ve): 554 (95%, M+$K^+$), 570 (100%, M+MeOH+$Na^+$).

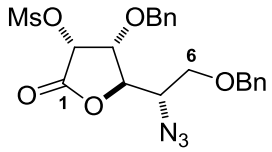
**5-Amino-3,6-di-*O*-benzyl-2,5-dideoxy-L-gulono-1,4-lactone 2.152L**




Palladium (10% on carbon, 22 mg) was added to a solution of the triflate **2.150L** (110 mg, 0.21 mmol) in 1,4-dioxane (2.5 mL). The flask was evacuated and flushed with hydrogen and stirred for 2.5 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.71) and the formation of a major product ($R_f$ 0.29). The reaction mixture was filtered (GF/A, glass microfibre) and concentrated *in vacuo* to afford the crude amine **2.152L** as a yellow oil (73 mg, quant.); HRMS (ESI +ve): found 342.1696 [M+$H^+$]; $C_{20}H_{24}NO_4$ requires 342.1700; $[\alpha]_D^{25}$ +15.1 (*c* 1.1, $CHCl_3$); $\nu_{max}$ (thin film): 1791 (s, C=O), 3064 (br. s, $NH_2$); $\delta_H$ ($CDCl_3$, 400 MHz): 2.52 (1H, dd, H2, $J_{2,3}$ 4.0, $J_{2,2'}$ 18.3),

2.89 (1H, dd, H2', $J_{2',3}$ 7.1, $J_{2',2}$ 18.3), 3.61 (1H, dd, H6, $J_{6,5}$ 4.0, $J_{6,6'}$ 10.4), 3.65-3.69 (1H, m, H5), 3.73 (1H, dd, H6', $J_{6',5}$ 3.0, $J_{6',6}$ 10.4), 4.15 (1H, a-dt, H3, $J_{3,2} = J_{3,4} = 3.7$, $J_{3,2'}$ 7.2), 4.34 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 12.1), 4.38 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 12.1), 4.45 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 12.1), 4.57 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 12.1), 4.75 (1H, dd, H4, $J_{4,3}$ 3.5, $J_{4,5}$ 9.6), 7.17-7.37 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 34.9 (C2), 53.1 (C5), 65.0 (C6), 71.6, 73.6 (O$\underline{C}$H$_2$Ph), 75.0 (C3), 81.3 (C4), 127.9, 127.9, 128.0, 128.1, 128,1, 128.3, 128.5, 128.5, 128.6, 128.7 (Ar$\underline{C}$H), 136.4, 136.6 (Ar$\underline{C}$C), 175.5 (C1); LRMS (ESI +ve): 342 (100%, M+H$^+$), 683 (92%, 2M+H$^+$), 705 (33%, 2M+Na$^+$).

**5-Azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-talono-1,4-lactone 2.153L**

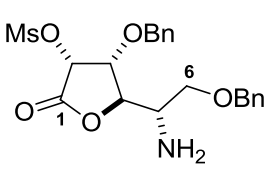



Methanesulfonyl chloride (90 μL, 1.06 mmol) was added to a solution of the alcohol **2.149L** (340 mg, 0.89 mmol) in pyridine (3.5 mL) at 0 $^oC$. After 10 min the reaction was allowed to warm to RT and stirred for a further 90 min, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.38) and the formation of a major product ($R_f$ 0.60). The reaction mixture was concentrated *in vacuo* and co-evaporated with toluene (2 x 5 mL). The crude residue was purified by flash chromatography (47:3 to 3:1, cyclohexane/ethyl acetate) to afford the mesylate **2.153L** (390 mg, 95%) as a clear oil; HRMS (ESI +ve): found 516.1408 [M+MeOH+Na$^+$]; $C_{22}H_{27}N_3NaO_8S$ requires 516.1411; $[\alpha]_D^{25}$ +106.6 (*c* 1.27, $CHCl_3$); $\nu_{max}$ (thin film): 1180 (s, $SO_2$), 1455 (s, $SO_2$), 1801 (s, C=O), 2117 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz): 3.30 (3H, s, $SO_2CH_3$), 3.71 (1H, dd, H6, $J_{6,5}$ 6.5, $J_{6,6'}$ 9.7), 3.74 (1H, dd, H6', $J_{6',5}$ 6.5, $J_{6',6}$ 9.7), 3.82 (1H, td, H5, $J_{5,4}$ 1.9, $J_{5,6} = J_{5,6'}$ 6.5), 4.30 (1H, dd, H3, $J_{3,4}$ 1.4, $J_{3,2}$ 6.0), 4.55 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.8), 4.55 (1H, a-t, H4, $J_{4,3} = J_{4,5}$ 1.7), 4.59 (1H, d, OC$\underline{H}_2$Ph,

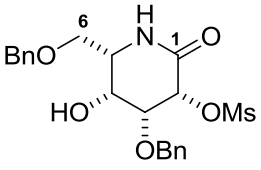
$J_{gem}$ 11.8), 4.60 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.8), 4.86 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.8), 5.57 (1H, d, H2, $J_{2,3}$ 6.0), 7.32-7.41 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 39.7 ($SO_2\underline{C}H_3$), 60.6 (C5), 69.4 (C6), 72.9 (C2), 73.6, 73.8 (O$\underline{C}H_2$Ph), 75.1 (C3), 82.5 (C4), 127.8, 128.2, 128.2, 128.5, 128.6, 128.7 (Ar$\underline{C}$H), 136.3, 136.9 (Ar$\underline{C}$C), 169.8 (C1); LRMS (ESI +ve): 484 (27%, $M+Na^+$), 516 (100%, $M+MeOH+Na^+$), 945 (25%, $2M+Na^+$), 977 (34%, $2M+MeOH+Na^+$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-D-talono-1,4-lactone 2.149L** (300 mg, 0.78 mmol) in a suitably scaled procedure afforded **5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-talono-1,4-lactone 2.153D** (336 mg, 90%) as a pale yellow oil; $[\alpha]_D^{25}$ -96.3 (*c* 1.25, $CHCl_3$).

**5-Amino-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-talono-1,4-lactone 2.154L & 5-Amino-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-talono-1,5-lactam 2.155L**




**2.154L**




**2.155L**

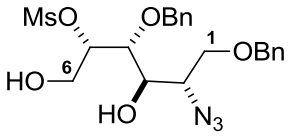
Palladium (10% on carbon, 10 mg) was added to a solution of the azide **2.153L** (46 mg, 0.10 mmol) in 1,4-dioxane (1.5 mL). The flask was evacuated and flushed with hydrogen and stirred for 75 min, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.60) and the formation of two products ($R_f$ 0.12, 0.05). The reaction mixture was filtered (GF/A, glass microfibre) and concentrated *in vacuo* to afford a crude 1.7:1 (A:B) mixture of lactone **2.154L** and lactam **2.155L** (40 mg). Partial data for **2.154L**/**2.155L** mixture: $\nu_{max}$ (thin film): 1177 (s, $SO_2$), 1455 (s, $SO_2$), 1684 (s, $C=O^A$), 1792 (s, $C=O^B$), 3450 (br. s, $OH^A$, $NH_2^B$); $\delta_H$ ($(CD_3)_2CO$, 500 MHz): 3.27 (3H, s,

$SO_2CH_3^A$), 3.32 (3H, s, $SO_2CH_3^B$), 3.38 (1H, dd, H6$^B$, $J_{6,5}$ 7.0, $J_{6,6'}$ 9.3), 3.64 (1H, dd, H6'$^B$, $J_{6',5}$ 7.0, $J_{6',6}$ 9.3), 3.77-3.85 (2H, m, H5$^A$, H6$^A$), 3.93-3.95 (1H, m, H6'$^A$), 4.10 (1H, td, H5$^B$, $J_{5,4}$ 2.6, $J_{5,6} = J_{5,6'}$ 7.0), 4.25 (1H, dd, H3$^A$, $J_{3,4}$ 2.1, $J_{3,2}$ 4.4), 4.32 (1H, d, H3$^B$, $J_{3,2}$ 5.5), 4.49 (1H, dd, H4$^A$, $J_{4,3}$ 2.1, $J_{4,5}$ 4.6), 4.72-4.86 (8H, m, OC$\underline{H}_2$Ph$^A$, OC$\underline{H}_2$Ph$^B$), 4.99 (1H, d, H4$^B$, $J_{4,5}$ 2.6), 5.27 (1H, d, H2$^A$, $J_{2,3}$ 4.4), 5.82 (1H, d, H2$^B$, $J_{2,3}$ 5.5), 7.28-7.48 (20H, m, ArH); $\delta_C$ ($(CD_3)_2CO$, 125 MHz): 39.5 ($SO_2CH_3^A$, $SO_2CH_3^B$), 55.6 (C5$^A$), 61.4 (C5$^B$), 66.6 (C4$^A$), 69.7 (C6$^B$), 71.9 (C6$^A$), 73.3, 73.8 (O$\underline{C}$H$_2$Ph$^B$), 73.7, 74.2 (O$\underline{C}$H$_2$Ph$^A$), 74.8 (C2$^B$), 76.5 (C2$^A$), 77.7 (C3$^B$), 79.2 (C3$^A$), 84.7 (C4$^B$), 128.4, 128.6, 128.7, 128.8, 129.1, 129.1, 129.2, 129.3, 129.3, 129.4 (Ar$\underline{C}$H$^A$, Ar$\underline{C}$H$^B$), 138.6, 139.4 (Ar$\underline{C}$C$^B$), 139.3, 139.5 (Ar$\underline{C}$C$^A$), 166.2 (C1$^A$), 171.9 (C1$^B$); LRMS (ESI +ve): 468 (100%, M+Na$^+$), 903 (63%, 2M+Na$^+$), 935 (60%, 2M+MeOH+Na$^+$).

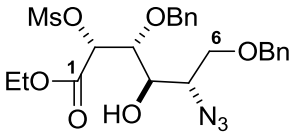
**2-Azido-1,4-di-*O*-benzyl-2-deoxy-5-*O*-methanesulfonyl-L-altritol 2.156L /**

**Ethyl 5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-talonate 2.157L /**

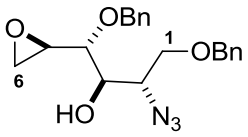
**5,6-Anhydro-2-azido-3,6-di-*O*-benzyl-2-deoxy-D-galactitol 2.158D**




**2.156L**




**2.157L**




**2.158D**

Method A: A solution of sodium borohydride (8.6 mg, 0.227 mmol) in ethanol (0.5 mL) was added drop-wise to a solution of the lactone **2.153L** (46 mg, 0.100 mmol) in ethanol (4 mL) at -30 $^o$C. The reaction was stirred for 90 min, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.60) and the formation of a major product ($R_f$ 0.52). The reaction was neutralised with glacial acetic acid and concentrated *in vacuo*. The crude residue was dissolved with ethyl acetate (5 mL), washed with saturated aqueous sodium bicarbonate (3 mL) and the aqueous layer extracted with ethyl acetate

(2 x 5 mL). The organic fractions were combined, washed with brine (3 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (23:2 to 3:7, cyclohexane/ethyl acetate) to afford the ethyl ester **2.157L** as a clear oil (30 mg, 55%).

Method B: Sodium borohydride (36 mg, 0.95 mmol) was added portion-wise to a solution of the lactone **2.153L** (66 mg, 0.14 mmol) in ethanol (4 mL) at -30 $^{o}$C. The reaction was stirred for 4 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.60) and the formation of the ethyl ester **2.157L** ($R_f$ 0.52) and a minor product ($R_f$ 0.11). Additional sodium borohydride was added (27 mg, 0.72 mmol) at -30 $^{o}$C, the reaction stirred for 22 h and allowed to warm to RT, after which TLC analysis indicated the complete consumption of the ethyl ester **2.157L** ($R_f$ 0.52) and the presence of a major ($R_f$ 0.11) and a minor product ($R_f$ 0.43). The reaction was neutralised with glacial acetic acid and concentrated *in vacuo*. The crude residue was dissolved with ethyl acetate (10 mL), washed with an aqueous sodium bicarbonate solution (3 mL) and the aqueous layer extracted with ethyl acetate (2 x 6 mL). The organic fractions were combined, washed with brine (3 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1 to 3:7, cyclohexane/ethyl acetate) to afford the diol **2.156L** ($R_f$ 0.11, 30 mg, 45%) and the epoxide **2.158D** ($R_f$ 0.43, 7.4 mg, 20%), as clear oils.

Method C: Sodium borohydride (41 mg, 1.08 mmol) was added portion-wise to a solution of the lactone **2.153L** (100 mg, 0.217 mmol) in ethanol (9 mL) at -30 $^{o}$C. The reaction was stirred for 2.5 h, with the internal temperature maintained between -30 $^{o}$C and -15 $^{o}$C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.60), the formation of the ethyl ester ($R_f$ 0.52) and the diol ($R_f$ 0.11). Additional

sodium borohydride was added (41 mg, 1.08 mmol) at -30 $^{o}$C and the reaction allowed to warm to -15 $^{o}$C over 4.5 h, after which TLC analysis indicated the almost complete consumption of the ethyl ester ($R_f$ 0.52) and the presence of the diol ($R_f$ 0.11) and the epoxide products ($R_f$ 0.43). The reaction was neutralised with glacial acetic acid and concentrated *in vacuo*. The crude residue was dissolved with ethyl acetate (20 mL), washed with an aqueous sodium bicarbonate solution (6 mL) and the aqueous phase extracted with ethyl acetate (2 x 20 mL). The organic fractions were combined, washed with brine (6 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1 to 0:1, cyclohexane/ethyl acetate) to afford the diol **2.156L** ($R_f$ 0.11, 65 mg, 65%), and the epoxide **2.158D** ($R_f$ 0.43, 5.5 mg, 5%), as clear oils.

Data for diol **2.156L**: HRMS (ESI +ve): found 488.1458 [M+Na$^+$]; $C_{21}H_{27}N_3NaO_7S$ requires 488.1462; $[\alpha]_D^{25}$ +63.5 (*c* 1.25, $CHCl_3$); $\nu_{max}$ (thin film): 1173 (s, $SO_2$), 1337 (s, $SO_2$), 2104 (s, $N_3$), 3484 (br. s, OH); $\delta_H$ ($CD_3CN$, 400 MHz): 3.09 (3H, s, $SO_2CH_3$), 3.27 (1H, t, OH1, $J_{OH,1} = J_{OH,1'}$ 5.7), 3.58 (1H, d, OH4, $J_{OH,4}$ 6.8), 3.73-3.77 (4H, m, H2, H4, H6, H6'), 3.82-3.85 (3H, m, H1, H1', H3), 4.54 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.9), 4.56 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.0), 4.58 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.9), 4.80 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.0), 5.06 (1H, ddd, H5, *J* 1.5, *J* 4.8, *J* 6.3), 7.28-7.39 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz): 39.0 ($SO_2CH_3$), 61.4 (C6), 62.0 (C2), 70.8 (C3), 71.5 (C1), 74.0, 74.5 (OC$\underline{H}_2$Ph), 80.6 (C4), 85.7 (C5), 128.8, 128.8, 129.0, 129.4, 129.5 (Ar$\underline{C}$H), 139.0, 139.3 (Ar$\underline{C}$C); LRMS (ESI +ve): 488 (45%, M+Na$^+$), 504 (100%, M+K$^+$), 953 (15%, 2M+Na$^+$), 969 (10%, 2M+K$^+$); (ESI –ve): 464 (10%, [M-H]$^-$), 500 (50%, M+$^{35}$Cl$^-$), 502 (22%, M+$^{37}$Cl$^-$), 510, (100%, M+HCOO$^-$), 929 (41%, [2M-H]$^-$).

Data for ethyl ester **2.157L**: HRMS (ESI +ve): found 530.1568 [M+Na$^+$]; $C_{23}H_{29}N_3NaO_8S$ requires 530.1568; $[\alpha]_D^{25}$ +81.2 (*c* 1.28, $CHCl_3$); $\nu_{max}$ (thin film): 1178 (s, $SO_2$), 1363 (s, $SO_2$),

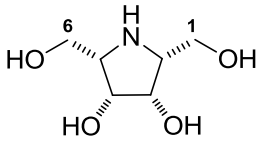
1756 (s, C=O), 2105 (s, $N_3$), 3504 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.31 (3H, t, $CH_2C\underline{H}_3$, *J* 7.1), 2.65 (1H, d, OH4, $J_{OH,4}$ 6.3), 3.17 (3H, s, $SO_2CH_3$), 3.75 (1H, ddd, H5, $J_{5,4}$ 0.9, $J_{5,6'}$ 4.5, $J_{5,6}$ 5.3), 3.81 (1H, dd, H6, $J_{6,5}$ 5.3, $J_{6,6'}$ 10.0), 3.84 (1H, dd, H6', $J_{6',5}$ 4.5, $J_{6',6}$ 10.1), 4.02 (1H, ddd, H4, $J_{4,5}$ 0.9, $J_{4,OH}$ 6.3, $J_{4,3}$ 9.4), 4.15 (1H, dd, H3, $J_{3,2}$ 1.6, $J_{3,4}$ 9.3), 4.25 (1H, dq, C$\underline{H}$H'$CH_3$, *J* 7.1, $J_{gem}$ 10.6), 4.30 (1H, dq, CH$\underline{H}$'$CH_3$, *J* 7.1, $J_{gem}$ 10.6), 4.54 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 10.9), 4.55 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.9), 4.59 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 12.1), 4.82 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 10.9), 5.50 (1H, d, H2, $J_{2,3}$ 1.6), 7.30-7.41 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 14.0 ($CH_2\underline{C}H_3$), 39.3 ($SO_2CH_3$), 59.6 (C5), 62.2 ($\underline{C}H_2CH_3$), 70.9 (C4), 71.8 (C6), 72.9, 73.8 (O$\underline{C}H_2$Ph), 76.7 (C2), 78.7 (C3), 127.8, 128.1, 128.4, 128.6, 128.6, 128.7 (Ar$\underline{C}$H), 136.5, 137.0 (Ar$\underline{C}$C), 167.2 (C1); LRMS (ESI +ve): 530 (100%, $M+Na^+$).

Data for epoxide **2.158D**: HRMS (ESI +ve): found 392.1567 [$M+Na^+$]; $C_{20}H_{23}N_3NaO_4$ requires 392.1581; $[\alpha]_D^{25}$ +61.0 (*c* 0.48, $CHCl_3$); $\nu_{max}$ (thin film): 2102 (s, $N_3$), 3450 (br. s, OH); $\delta_H$ ($CD_3CN$, 400 MHz): 2.63 (1H, dd, H6, $J_{6,5}$ 2.8, $J_{6,6'}$ 5.1), 2.79 (1H, dd, H6', $J_{6',5}$ 4.3, $J_{6',6}$ 5.1), 3.08 (1H, ddd, H5, $J_{5,6}$ 2.8, $J_{5,6'}$ 4,3, $J_{5,4}$ 6.7), 3.19 (1H, dd, H4, $J_{4,5}$ 6.7, $J_{4,3}$ 8.4), 3.30 (1H, d, OH3, $J_{OH,3}$ 7.2), 3.73 (1H, dd, H1, $J_{1,2}$ 5.3, $J_{1,1'}$ 11.4), 3.75 (1H, ddd, H3, $J_{3,2}$ 2.0, $J_{3,OH}$ 7.2, $J_{3,4}$ 8.4), 3.76 (1H, dd, H1', $J_{1',2}$ 7.2, $J_{1',1}$ 11.4), 3.83 (1H, ddd, H2, $J_{2,3}$ 2.0, $J_{2,1}$ 5.3, $J_{2,1'}$ 7.2), 4.54-4.74 (3H, m, OC$\underline{H}_2$Ph), 4.79 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.4), 7.28-7.37 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz): 44.1 (C6), 53.4 (C5), 61.6 (C2), 70.7 (C1), 71.1 (C3), 72.5, 73.3 (O$\underline{C}H_2$Ph), 80.5 (C4), 128.1, 128.1, 128.1, 128.4, 128.7, 128.8 (Ar$\underline{C}$H), 138.7, 138.8 (Ar$\underline{C}$C); LRMS (ESI +ve): 392 (93%, $M+Na^+$), 761 (100%, $2M+Na^+$); (ESI –ve): 404 (96%, $M+^{35}Cl^-$), 406 (34%, $M+^{37}Cl^-$), 428 (44%, $M+AcO^-$), 737 (100%, $[2M-H]^-$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-talono-1,4-lactone 2.153D** (197 mg, 0.43 mmol) in a suitably scaled procedure afforded **2-azido-1,4-di-*O*-**

**benzyl-2-deoxy-5-*O*-methanesulfonyl-D-altritol 2.156D** (131 mg, 66%) and **5,6-anhydro-2-azido-3,6-di-*O*-benzyl-2-deoxy-L-galactitol 2.158L** (11 mg, 7%) as a clear oils; **2.156D**: $[\alpha]_D^{25}$ -60.7 (*c* 1.20, $CHCl_3$). **2.158L**: $[\alpha]_D^{25}$ -61.0 (*c* 0.48, $CHCl_3$).

**2,5-Dideoxy-2,5-imino-galactitol (DGADP) 2.60**



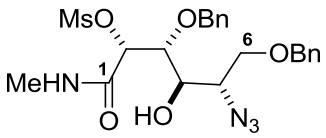

Palladium (10% on carbon, 6 mg) and sodium acetate (11 mg, 0.13 mmol) were added to a solution of the diol **2.156L** (30 mg, 0.06 mmol) in 1,4-dioxane (2 mL). The reaction vessel was evacuated and flushed with hydrogen and stirred for 1 h, after which TLC analysis (99:1, ethyl acetate/triethylamine) indicated the complete consumption of the starting material ($R_f$ 0.88) and the formation of a major product ($R_f$ 0.08). LRMS also indicated the absence of a peak corresponding to the starting material (*m/z* 488 [M+$Na^+$]) and the formation of a peak corresponding to the amino intermediate **2.159L** (*m/z* 440 [M+$H^+$]). After a further 4 h, LRMS indicated the absence of the amino intermediate **2.159L** (*m/z* 440 [M+$H^+$]) and the presence of a peak corresponding to the cyclised dibenzylated intermediate **2.160D** (*m/z* 344 [M+$H^+$]). 2 M Aqueous hydrochloric acid (0.4 mL) was added, the reaction vessel evacuated and flushed with hydrogen and stirred for 16 h, after which LRMS indicated the absence of the cyclised dibenzylated intermediate (*m/z* 344 [M+$H^+$]) and presence of a peak corresponding to the *meso-galacto* pyrrolidine DGADP **2.60** (*m/z* 164 [M+$H^+$]). The reaction mixture was filtered (GF/A, glass microfibre), concentrated *in vacuo* and loaded onto a short column of Dowex® (50W-X8, $H^+$). The resin was washed with water, the product liberated with 2 M aqueous ammonia and the ammoniacal fractions combined and concentrated *in vacuo* to afford the *meso-galacto* pyrrolidine DGADP **1.60D** (9.5 mg, 91%) as a yellow oil; HRMS (ESI +ve): found 186.0743

[M+Na$^+$]; $C_6H_{13}NNaO_4$ requires 186.0737; $[\alpha]_D^{25}$ 0.0 (*c* 1.50, $H_2O$); $\nu_{max}$ (thin film): 3319 (br. s, OH, NH); $\delta_H$ ($D_2O$, 500 MHz): 3.25 (1H, q, H2, $J_{2,1} = J_{2,1'} = J_{2,3}$ 5.7), 3.59 (1H, dd, H1, $J_{1,2}$ 5.7, $J_{1,1'}$ 11.4), 3.70 (1H, dd, H1', $J_{1',2}$ 5.7, $J_{1',1}$ 11.4), 4.21 (1H, d, H3, $J_{3,2}$ 5.7); $\delta_C$ ($D_2O$, 125 MHz): 60.4 (C1), 60.5 (C2), 71.9 (C3); LRMS (ESI +ve): 164 (55%, M+H$^+$), 186 (85%, M+Na$^+$), 327 (100%, 2M+H$^+$); (ESI –ve): 162 (100%, [M-H]$^-$).

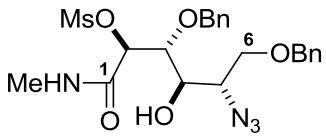
Similar treatment of **2-azido-1,4-di-*O*-benzyl-2-deoxy-5-*O*-methanesulfonyl-D-altritol 2.156D** (121 mg, 0.26 mmol) in a suitably scaled procedure afforded **2,5-dideoxy-2,5-imino-galactitol** (DGADP) **2.60** (42 mg, quant.) as a yellow oil: $[\alpha]_D^{25}$ +0.0 (*c* 0.50, MeOH).

**Methyl 5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-talonamide 2.161L /**

**Methyl 5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-galactonamide 2.162L**




**2.161L**




**2.162L**

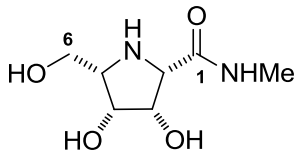
Methylamine (33% in ethanol, 90 μL, 2.13 mmol) was added to a solution of the lactone **2.153L** (197 mg, 0.426 mmol) in 1,4-dioxane (10 mL). The reaction was stirred for 16 h, after which TLC analysis (3:7, cyclohexane/ethyl acetate) indicated the almost complete consumption of the starting material ($R_f$ 0.61), the formation of a major ($R_f$ 0.35) and a minor product ($R_f$ 0.52). The reaction mixture was concentrated *in vacuo* and the crude residue purified by flash chromatography (7:3 to 1:4, cyclohexane/ethyl acetate) to afford returned starting material **2.153L** (14 mg), the L-*talo* amide **2.161L** ($R_f$ 0.35, 165 mg, 84%) as a clear, viscous oil and the minor L-*galacto* amide **2.162L** ($R_f$ 0.52, 22 mg, 11%) as a clear oil which crystallised on standing.

Data for L-*talo* amide **2.161L**: HRMS (ESI +ve): found 515.1568 [M+$Na^+$]; $C_{22}H_{28}N_4NaO_7S$ requires 515.1571; $[\alpha]_D^{25}$ +66.6 (*c* 2.01, $CHCl_3$); $\nu_{max}$ (thin film): 1179 (s, $SO_2$), 1455 (s, $SO_2$), 1560 (s, C=O), 1666 (s, C=O), 2105 (s, $N_3$), 3418 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 2.71 (1H, d, OH4, $J_{OH,4}$ 8.8), 2.83 (3H, d, NHC<u>H</u>$_3$, $J_{H,NH}$ 5.1), 3.06 (3H, s, $SO_2CH_3$), 3.77 (1H, dd, H6, $J_{6,5}$ 5.1, $J_{6,6'}$ 9.9), 3.78 (1H, dd, H6', $J_{6',5}$ 6.6, $J_{6',6}$ 9.9), 3.82 (1H, ddd, H4, $J_{4,5}$ 1.3, $J_{4,OH}$ 8.8, $J_{4,3}$ 9.3), 3.86 (1H, ddd, H5, $J_{5,4}$ 1.3, $J_{5,6}$ 5.1, $J_{5,6'}$ 6.6), 4.24 (1H, dd, H3, $J_{3,2}$ 1.4, $J_{3,4}$ 9.3), 4.55 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 11.9), 4.57 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 10.9), 4.59 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 11.9), 4.78 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 10.9), 5.47 (1H, d, H2, $J_{2,3}$ 1.4), 6.48 (1H, q, N<u>H</u>$CH_3$, $J_{NH,H}$ 4.5), 7.26-7.39 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 26.2 ($NHCH_3$), 38.9 ($SO_2CH_3$), 60.6 (C5), 70.1 (C4), 71.2 (C6), 73.3, 73.7 (O<u>C</u>$H_2$Ph), 79.0 (C3), 79.3 (C2), 127.8, 128.0, 128.5, 128.5, 128.7, 128.7 (Ar<u>C</u>H), 136.4, 137.3 (Ar<u>C</u>C), 167.3 (C1); LRMS (ESI +ve): 515 (100%, M+$Na^+$); (ESI –ve): 491 (64%, [M-H]$^-$), 527 (52%, M+$^{35}Cl^-$), 529 (18%, M+$^{37}Cl^-$), 983 (100%, [2M-H]$^-$).

Data for L-*galacto* amide **2.162L**: HRMS (ESI +ve): found 515.1575 [M+$Na^+$]; $C_{22}H_{28}N_4NaO_7S$ requires 515.1571; m.p. 114-116 $^oC$; $[\alpha]_D^{25}$ +33.9 (*c* 1.08, $CHCl_3$); $\nu_{max}$ (thin film): 1178 (s, $SO_2$), 1455 (s, $SO_2$), 1555 (s, C=O), 1668 (s, C=O), 2105 (s, $N_3$), 3407 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 2.89 (3H, d, NHC<u>H</u>$_3$, $J_{H,NH}$ 4.5), 3.07 (1H, br. s, OH4), 3.13 (3H, s, $SO_2CH_3$), 3.70 (1H, dd, H4, $J_{4,5}$ 1.3, $J_{4,3}$ 9.3), 3.75 (1H, ddd, H5, $J_{5,4}$ 1.3, $J_{5,6}$ 4.3, $J_{5,6'}$ 6.6), 3.84 (1H, dd, H6, $J_{6,5}$ 4.3, $J_{6,6'}$ 10.4), 3.87 (1H, dd, H6', $J_{6',5}$ 6.6, $J_{6',6}$ 10.4), 4.31 (1H, dd, H3, $J_{3,2}$ 1.7, $J_{3,4}$ 9.3), 4.53 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 11.1), 4.60 (3H, a-d, 3 x OC<u>H</u>$_2$Ph, *J* 11.4), 5.33 (1H, d, H2, $J_{2,3}$ 1.7), 6.61 (1H, q, N<u>H</u>$CH_3$, $J_{NH,H}$ 4.5), 7.26-7.39 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 26.5 ($NHCH_3$), 38.2 ($SO_2CH_3$), 59.7 (C5), 70.3 (C4), 71.4 (C6), 73.7, 75.1 (O<u>C</u>$H_2$Ph), 78.6 (C3), 79.0 (C2), 127.8, 128.0, 128.3, 128.6, 128.6 (Ar<u>C</u>H), 137.0, 137.2 (Ar<u>C</u>C), 168.2 (C1); LRMS (ESI +ve): 515 (100%, M+$Na^+$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-talono-1,4-lactone 2.153D** (310 mg, 0.67 mmol) in a suitably scaled procedure afforded **methyl 5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-talonamide 2.161D** (259 mg, 78%) as a clear viscous oil and **methyl 5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-galactonamide 2.162D** (24 mg, 7%) as a clear oil which crystallised on standing; **2.161D**: $[\alpha]_D^{25}$ -71.1 (*c* 2.05, $CHCl_3$). **2.162D**: m.p. 114-116 $^oC$; $[\alpha]_D^{25}$ -36.1 (*c* 1.10, $CHCl_3$).

**Methyl 2,5-dideoxy-2,5-imino-L-galactonamide 2.142L**




Method A: Palladium (10% on carbon, 15 mg) was added to a solution of the L-*talo* azide **2.161L** (37 mg, 0.08 mmol) and sodium acetate (25 mg, 0.30 mmol) in 1,4-dioxane (2 mL). The flask was evacuated and flushed with hydrogen and stirred for 2 h, after which TLC analysis (99:1, ethyl acetate/triethylamine) indicated the complete consumption of the starting material ($R_f$ 0.72) and the formation of a major product ($R_f$ 0.08). LRMS also indicated the consumption of the starting material (*m/z* 515 $[M+Na^+]$) and the formation of the amino intermediate **2.163L** (*m/z* 467 $[M+H^+]$). The reaction mixture was filtered (GF/A, glass microfibre), an additional portion of sodium acetate was added (25 mg, 0.30 mmol) and the reaction mixture stirred for 16 h, after which LRMS indicated the absence of a peak corresponding to the amino intermediate **2.163L** (*m/z* 467 $[M+H^+]$) and the formation of the cyclised dibenzylated intermediate **2.164L** (*m/z* 371 $[M+H^+]$). The reaction was filtered and concentrated *in vacuo*. The cyclised dibenzylated intermediate **2.164L** (28 mg) was reacted on without further purification.

Data for cyclised dibenzylated intermediate **2.164L**: HRMS (ESI +ve): found 371.1965 [M+H$^+$]; $C_{21}H_{27}N_2O_4$ requires 371.1960; $[\alpha]_D^{25}$ +16.4 (*c* 0.20, MeOH); $\nu_{max}$ (thin film): 1552 (s, C=O), 1654 (s, C=O), 3350 (br. s, NH, OH); $\delta_H$ ($CD_3OD$, 400 MHz): 2.80 (3H, a-s, NHC<u>H</u>$_3$), 3.47 (1H, a-q, H5, $J_{5,4} = J_{5,6} = J_{5,6'}$ 6.4), 3.62 (1H, dd, H6, $J_{6,5}$ 6.4, $J_{6,6'}$ 11.5), 3.74 (1H, dd, H6', $J_{6',5}$ 6.6, $J_{6',6}$ 11.5), 3.80 (1H, d, H2, $J_{2,3}$ 5.8), 4.34 (1H, dd, H4, $J_{4,3}$ 4.8, $J_{4,5}$ 6.2), 4.37 (1H, dd, H3, $J_{3,4}$ 4.8, $J_{3,2}$ 5.8), 7.24-7.42 (10H, m, ArH); $\delta_C$ ($CD_3OD$, 100 MHz): 26.0 ($NHCH_3$), 59.7 (C5), 68.6 (C6), 72.3 (C4), 75.4 (C2), 77.5 (C3), 127.9, 128.0, 128.5, 128.8, 128.9 (Ar<u>C</u>H), 137.4, 138.3 (Ar<u>C</u>C), 169.4 (C1); LRMS (ESI +ve): 371 (73%, M+H$^+$), 393 (58%, M+Na$^+$), 741 (100%, 2M+H$^+$); (ESI −ve): 369 (100%, [M-H]$^-$).

Palladium (10% on carbon, 5 mg) was added to a solution of the pyrrolidine **2.164L** (25 mg, 0.07 mmol) in a 17:3 1,4-dioxane/2 M aqueous hydrochloric acid mixture (2 mL, 17:3). The flask was evacuated and flushed with hydrogen and stirred for 18 h, after which TLC analysis (99:1, ethyl acetate/triethylamine) indicated the complete consumption of the starting material ($R_f$ 0.08) and the formation of a major product (baseline). LRMS also indicated the absence of a peak corresponding to the cyclised dibenzylated intermediate **2.164L** (*m/z* 371 [M+H$^+$]) and the formation of the L-*galacto* amide **2.142L** (*m/z* 191 [M+H$^+$]). The reaction mixture was filtered (GF/A, glass microfibre) and concentrated *in vacuo*. The crude residue was loaded onto a short column of Dowex® (50W-X8, H$^+$) and washed with water. The product was liberated with 2 M aqueous ammonia and the ammoniacal fractions were combined and concentrated *in vacuo* to afford the L-*galacto* amide **2.142L** (8 mg, 63%) as a yellow oil.

<u>Method B:</u> Palladium (10% on carbon, 75 mg) was added to a solution of the L-*talo* amide **2.161L** (165 mg, 0.34 mmol) and sodium acetate (72 mg, 0.88 mmol) in 1,4-dioxane (8 mL). The flask was evacuated and flushed with hydrogen and stirred for 2 h, after which TLC analysis

(99:1, ethyl acetate/triethylamine) indicated the complete consumption of the starting material ($R_f$ 0.72) and the formation of a major product ($R_f$ 0.08). LRMS also indicated the absence of a peak corresponding to the starting material (*m/z* 515 [M+$Na^+$]) and the formation of the amino intermediate **2.163L** (*m/z* 467 [M+$H^+$]). After a further 4 h LRMS indicated the absence of a peak corresponding to the amino intermediate **2.163L** (*m/z* 467 [M+$H^+$]) and the formation of the cyclised dibenzylated intermediate **2.164L** (*m/z* 371 [M+$H^+$]). 2 M Aqueous hydrochloric acid (1.4 mL) was added, the reaction vessel evacuated and flushed with hydrogen and the reaction stirred for 16 h, after which LRMS indicated the absence of a peak corresponding to the cyclised dibenzylated intermediate **2.164L** (*m/z* 371 [M+$H^+$]) and the formation of the L-*galacto* amide **2.142L** (*m/z* 191 [M+$H^+$]). The reaction mixture was filtered (GF/A, glass microfibre) and concentrated *in vacuo*. The crude residue was loaded onto a short column of Dowex® (50W-X8, $H^+$) and the resin washed with water. The product was liberated with 2 M aqueous ammonia and the ammoniacal fractions were combined and concentrated *in vacuo* to afford the L-*galacto* amide **2.142L** (60 mg, 94%) as a yellow oil; HRMS (ESI +ve): found 191.1025 [M+$H^+$]; $C_7H_{15}N_2O_4$ requires 191.1026; $[\alpha]_D^{25}$ -41.1 (*c* 0.24, $H_2O$); $\nu_{max}$ (thin film): 1554 (s, C=O), 1645 (s, C=O), 3332 (br. s, OH, NH); $\delta_H$ ($D_2O$, 500 MHz): 2.74 (3H, a-s, NHC$\underline{H}_3$), 3.43 (1H, a-q, H5, $J_{5,4} = J_{5,6} = J_{5,6'}$ 5.8), 3.61 (1H, dd, H6, $J_{6,5}$ 6.3, $J_{6,6'}$ 11.5), 3.69 (1H, dd, H6', $J_{6',5}$ 4.8, $J_{6',6}$ 11.5), 3.89 (1H, d, H2, $J_{2,3}$ 6.1), 4.31 (1H, dd, H4, $J_{4,3}$ 5.5, $J_{4,5}$ 6.2), 4.35 (1H, a-t, H3, $J_{3,2} = J_{3,4}$ 5.5); $\delta_C$ ($D_2O$, 125 MHz): 25.6 ($NHCH_3$), 59.9 (C5), 60.1 (C6), 61.7 (C2), 71.5 (C4), 72.0 (C3), 172.0 (C1); LRMS (ESI +ve): 191 (100%, M+$H^+$), 213 (68%, M+$Na^+$).

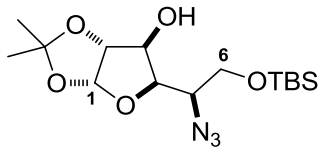
Similar treatment of **methyl 5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-talonamide 2.161D** (259 mg, 0.53 mmol) in a suitably scaled procedure afforded **methyl 2,5-dideoxy-2,5-imino-D-galactonamide 2.142D** (92 mg, 92%) as a yellow oil. The D-*galacto*

amide **2.142D** was recrystallized (isopropanol) to afford a white crystalline solid: m.p. 85-87 $^{o}$C (isopropanol); $[\alpha]_D^{25}$ +46.6 (*c* 0.26, $H_2O$).

*2.4.3.5 Synthesis of altro-configured iminosugars*

**5-Azido-6-*O*-*tert*-butyldimethylsilyl-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose**

**2.165D**

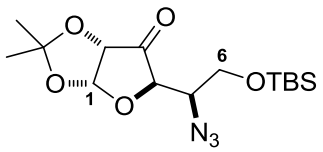



*tert*-Butyldimethylsilyl chloride (5.90 g, 38.5 mmol) was added to a solution of the diol **2.38D** (6.30 g, 25.7 mmol) in pyridine (60 mL) at RT. The reaction was stirred for 20 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.15) and the formation of a major product ($R_f$ 0.52). The reaction was diluted with ethyl acetate (500 mL), washed with 2 M aqueous hydrochloric acid (3 x 150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (39:1 to 4:1, cyclohexane/ethyl acetate) to afford the silyl ether **2.165D** (8.50 g, 92%) as a colourless oil; HRMS (ESI +ve): found 382.1767 [M+$Na^+$]; $C_{15}H_{29}N_3NaO_5Si$ requires 382.1769; $[\alpha]_D^{25}$ -23.1 (*c* 1.30, $CHCl_3$); $\nu_{max}$ (thin film): 2099 (s, $N_3$), 3458 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 0.11, 0.11 (2 x 3H, s, Si(C$\underline{H}_3$)$_2$), 0.92 (9H, s, SiC(C$\underline{H}_3$)$_3$), 1.32, 1.49 (2 × 3H, s, C(C$\underline{H}_3$)$_2$), 2.42 (1H, d, OH3, $J_{OH,3}$ 4.3), 3.74 (1H, ddd, H5, $J_{5,6'}$ 3.2, $J_{5,6}$ 5.8, $J_{5,4}$ 8.1), 3.84 (1H, dd, H6, $J_{6,5}$ 5.8, $J_{6,6'}$ 10.6), 4.03 (1H, dd, H6', $J_{6',5}$ 3.2, $J_{6',6}$ 10.6), 4.14 (1H, dd, H4, $J_{4,3}$ 2.8, $J_{4,5}$ 8.1), 4.31 (1H, dd, H3, $J_{3,4}$ 2.8, $J_{3,OH}$ 4.3), 4.53 (1H, d, H2, $J_{2,1}$ 3.7), 5.94 (1H, d, H1, $J_{1,2}$ 3.7); $\delta_C$ ($CDCl_3$, 100 MHz): -5.6 (Si(C$\underline{H}_3$)$_2$), 18.2 (SiC(CH$_3$)$_3$), 25.7 (SiC(C$\underline{H}_3$)$_3$), 26.2, 26.7 (C(C$\underline{H}_3$)$_2$), 60.9 (C5), 63.8 (C6), 75.2 (C3), 78.4 (C4), 84.9 (C2), 104.9 (C1), 111.9 (C(CH$_3$)$_2$);

LRMS (ESI +ve): 382 (95%, M+$Na^+$), 741 (100%, 2M+$Na^+$); (ESI −ve): 358 (10%, $[M-H]^-$), 394 (25%, M+$^{35}Cl^-$), 396 (10%, M+$^{37}Cl^-$), 717 (100%, $[2M-H]^-$).

Similar treatment of **5-azido-5-deoxy-1,2-*O*-isopropylidene-α-L-glucofuranose 2.38L** (2.52 g, 10.3 mmol) in a suitably scaled procedure afforded **5-azido-6-*O*-*tert*-butyldimethylsilyl-5-deoxy-1,2-*O*-isopropylidene-α-L-glucofuranose 2.165L** (3.44 g, 93%) as a yellow oil: $[\alpha]_D^{25}$ +29.9 (*c* 0.90, $CHCl_3$).

**5-Azido-6-*O*-*tert*-butyldimethylsilyl-5-deoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose 2.166D**

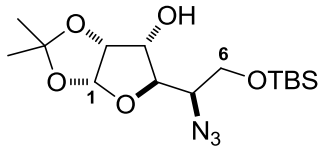



Dess-Martin periodinane **2.144** (15.1 g, 35.5 mmol) was added to a solution of the alcohol **2.165D** (8.50 g, 23.6 mmol) in dichloromethane (90 mL) at 0 °C. The reaction was stirred for 18 h and allowed to warm to RT, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.52) and the formation of a major product ($R_f$ 0.67→0.23). The reaction mixture was diluted with ethyl acetate (450 mL) and washed with an aqueous sodium bicarbonate/sodium thiosulfate solution (400 mL, 2 x 100 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (83:17 to 5:1, cyclohexane/ethyl acetate) to afford the ketone **2.166D** (8.00 g, 95%) as a clear oil; HRMS (ESI +ve): found 412.1870 [M+MeOH+$Na^+$]; $C_{16}H_{31}N_3NaO_6Si$ requires 412.1874; $[\alpha]_D^{25}$ +93.5 (*c* 1.40, $CHCl_3$); $\nu_{max}$ (thin film): 1775 (s, C=O), 2106 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz): 0.08 (6H, s, Si(C$\underline{H}_3$)$_2$), 0.89 (9H, s, SiC(C$\underline{H}_3$)$_3$), 1.44, 1.48 (2 × 3H, s, C(C$\underline{H}_3$)$_2$), 3.78-3.83 (3H, m, H5, H6, H6'), 4.41 (1H, dd, H2, *J* 1.0, $J_{2,1}$ 4.3), 4.52 (1H,

br. s, H4), 6.10 (1H, d, H1, $J_{1,2}$ 4.3); $\delta_C$ ($CDCl_3$, 100 MHz): -5.5, -5.5 (Si($\underline{C}H_3)_2$), 18.3 (Si$\underline{C}(CH_3)_3$), 25.8 (SiC($\underline{C}H_3)_3$), 27.2, 27.5 (C($\underline{C}H_3)_2$), 60.7 (C6), 64.2 (C5), 76.7 (C2), 78.7 (C4), 103.7 (C1), 114.4 ($\underline{C}(CH_3)_2$), 207.5 (C3); LRMS (ESI +ve): 412 (75%, M+MeOH+$Na^+$), 801 (100%, M+2MeOH+$Na^+$).

Similar treatment of **5-azido-6-*O*-*tert*-butyldimethylsilyl-5-deoxy-1,2-*O*-isopropylidene-α-L-glucofuranose 2.165L** (3.44 g, 9.57 mmol) in a suitably scaled procedure afforded **5-azido-6-*O*-*tert*-butyldimethylsilyl-5-deoxy-1,2-*O*-isopropylidene-α-L-*ribo*-hexofuranos-3-ulose 2.166L** (3.20 g, 94%) as a yellow oil: $[\alpha]_D^{25}$ -96.9 (*c* 0.92, $CHCl_3$).

**5-Azido-6-*O*-*tert*-butyldimethylsilyl-5-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose 2.167D**

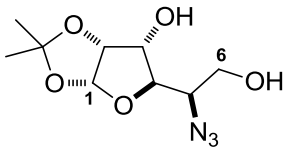



Sodium borohydride (847 mg, 22.4 mmol) was added portion-wise to a solution of the ketone **2.166D** (8.00 g, 22.4 mmol) in ethanol (80 mL) at 0 °C. The reaction was stirred at 0 °C for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.67→0.23) and the formation of a major product ($R_f$ 0.47). The reaction was neutralised with glacial acetic acid and concentrated *in vacuo*. The crude residue was dissolved with ethyl acetate (500 mL) and washed with an aqueous sodium bicarbonate solution (3 x 100 mL) and brine (100 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (19:1 to 3:2, cyclohexane/ethyl acetate) to afford the alcohol **2.167D** (7.48 g, 93%) as a clear oil; HRMS (ESI +ve): found 382.1769 [M+$Na^+$]; $C_{15}H_{29}N_3NaO_5Si$ requires 382.1769; $[\alpha]_D^{25}$ +19.9 (*c* 1.05, $CHCl_3$); $\nu_{max}$ (thin film): 2099 (s, $N_3$), 3479 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 0.11 (6H, s,

$Si(C\underline{H}_3)_2$), 0.91 (9H, s, $SiC(C\underline{H}_3)_3$), 1.37, 1.58 (2 × 3H, s, $C(C\underline{H}_3)_2$), 3.14 (1H, d, OH3, $J_{OH,3}$ 7.3), 3.80-3.83 (2H, m, H5, H6), 3.87-3.92 (1H, m, H6'), 3.96 (1H, dd, H4, $J_{4,5}$ 3.7, $J_{4,3}$ 8.4), 4.09 (1H, ddd, H3, $J_{3,2}$ 4.9, $J_{3,OH}$ 7.3, $J_{3,4}$ 8.4), 4.63 (1H, dd, H2, $J_{2,1}$ 3.6, $J_{2,3}$ 4.9), 5.81 (1H, d, H1, $J_{1,2}$ 3.6); $\delta_C$ ($CDCl_3$, 100 MHz): -5.6, -5.6 ($Si(\underline{C}H_3)_2$), 18.2 ($Si\underline{C}(CH_3)_3$), 25.7 ($SiC(\underline{C}H_3)_3$), 26.4, 26.6 ($C(\underline{C}H_3)_2$), 63.2 (C6), 63.5 (C5), 71.4 (C3), 79.2 (C2), 79.9 (C4), 103.8 (C1), 113.0 ($\underline{C}(CH_3)_2$); LRMS (ESI +ve): 382 (85%, $M+Na^+$), 741 (100%, $2M+Na^+$); (ESI –ve): 358 (45%, $[M-H]^-$), 394 (30%, $M+^{35}Cl^-$), 396 (10%, $M+^{37}Cl^-$), 717 (100%, $[2M-H]^-$).

Similar treatment of **5-azido-6-*O*-*tert*-butyldimethylsilyl-5-deoxy-1,2-*O*-isopropylidene-α-L-*ribo*-hexofuranos-3-ulose 2.166D** (3.20 g, 8.95 mmol) in a suitably scaled procedure afforded **5-azido-6-*O*-*tert*-butyldimethylsilyl-5-deoxy-1,2-*O*-isopropylidene-α-L-allofuranose 2.167L** (3.03 g, 95%) as a yellow oil: $[\alpha]_D^{25}$ -21.7 (*c* 1.34, $CHCl_3$).

**5-Azido-5-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose 2.168D**

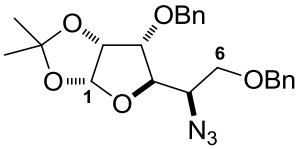



Tetra-*n*-butylammonium fluoride (1 M in THF, 26 mL, 26.0 mmol) was added to a solution of the silyl ether **2.167D** (7.48 g, 20.8 mmol) in THF (75 mL) at RT. The reaction was stirred for 1 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.47) and the formation of a major product ($R_f$ 0.19). The reaction was concentrated *in vacuo* and purified by flash chromatography (1:1:0 to 0:9:1, cyclohexane/ethyl acetate/methanol) to afford the diol **2.168D** (5.00 g, 98%) as a white crystalline solid; HRMS (ESI +ve): found 268.0901 $[M+Na^+]$; $C_9H_{15}N_3NaO_5$ requires 268.0904; m.p. 82-84 °C [Lit.[144] m.p. 82-83 °C]; $[\alpha]_D^{25}$ +50.1 (*c* 1.20, acetone) [Lit.[144] $[\alpha]_D^{25}$ +47.6 (*c* 1.0,

$CHCl_3$)]; $\nu_{max}$ (thin film): 2098 (s, $N_3$), 3382 (br. s, OH); $\delta_H$ ($(CD_3)_2CO$, 400 MHz): 1.31, 1.47 (2 x 3H, s, $C(CH_3)_2$), 3.71 (1H, dd, H6, $J_{6,5}$ 7.3, $J_{6,6'}$ 11.9), 3.80 (1H, dd, H6', $J_{6',5}$ 3.8, $J_{6',6}$ 11.9), 3.87 (1H, a-dt, H5, $J_{5,4} = J_{5,6'}$ 3.8, $J_{5,6}$ 7.3), 4.00 (1H, dd, H4, $J_{4,5}$ 3.2, $J_{4,3}$ 8.6), 4.05 (1H, dd, H3, $J_{3,2}$ 4.3, $J_{3,4}$ 8.6), 4.61 (1H, a-t, H2, $J_{2,1} = J_{2,3}$ 3.9), 5.78 (1H, d, H1, $J_{1,2}$ 3.5); $\delta_C$ ($(CD_3)_2CO$, 100 MHz): 26.8, 27.0 ($C(\underline{C}H_3)_2$), 62.3 (C6), 65.8 (C5), 72.4 (C3), 80.4 (C2), 80.5 (C4), 104.9 (C1), 113.1 ($\underline{C}(CH_3)_2$); LRMS (ESI –ve): 244 (100%, $[M-H]^-$), 489 (82%, $[2M-H]^-$).

Similar treatment of **5-azido-6-*O*-*tert*-butyldimethylsilyl-5-deoxy-1,2-*O*-isopropylidene-α-L-allofuranose 2.167L** (3.0 g, 8.35 mmol) in a suitably scaled procedure afforded **5-azido-5-deoxy-1,2-*O*-isopropylidene-α-L-allofuranose 2.168L** (1.81 g, 88%) as a white crystalline solid: m.p. 84-86 °C; $[\alpha]_D^{25}$ -55.3 (*c* 1.12, acetone).

**5-Azido-3,6-di-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose 2.169D**

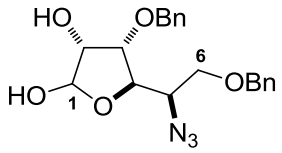



Sodium hydride (60% min. oil suspension, 2.50 g, 61.2 mmol) was added portion-wise to a solution of the diol **2.168D** (5.00 g, 20.4 mmol) and benzyl bromide (7.30 mL, 61.2 mmol) in DMF (75 mL) at 0 °C. The reaction mixture was allowed to warm to RT and stirred for 18 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.19) and the formation of a major product ($R_f$ 0.68). The reaction was quenched with methanol (10 mL), diluted with ethyl acetate (600 mL) and washed with a 1:1 brine/water solution (3 x 150 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (99:1 to 1:1, cyclohexane/ethyl acetate) to afford the dibenzyl ether **2.169D** (7.61 g, 88%) as a colourless oil;

HRMS (ESI +ve): found 448.1838 [M+$Na^+$]; $C_{23}H_{27}N_3NaO_5$ requires 448.1843; $[\alpha]_D^{25}$ +58.3 (*c* 1.25, $CHCl_3$); $\nu_{max}$ (thin film): 2099 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz): 1.37, 1.59 (2 x 3H, s, C(C$\underline{H}_3$)$_2$), 3.52 (1H, dd, H6, $J_{6,5}$ 9.1, $J_{6,6'}$ 10.1), 3.62 (1H, dd, H6', $J_{6',5}$ 4.0, $J_{6',6}$ 10.1), 3.90 (1H, dd, H3, $J_{3,2}$ 4.3, $J_{3,4}$ 8.6), 4.03 (1H, a-dt, H5, $J_{5,4}$ = $J_{5,6'}$ 3.5, $J_{5,6}$ 8.6), 4.17 (1H, dd, H4, $J_{4,5}$ 3.0, $J_{4,3}$ 8.6), 4.53 (2H, a-d, 2 x OC$\underline{H}_2$Ph, *J* 11.6), 4.55 (1H, a-t, H2, $J_{2,1}$ = $J_{2,3}$ 4.1), 4.56 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.9), 4.72 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 5.75 (1H, d, H1, $J_{1,2}$ 3.8), 7.31-7.39 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 26.5, 26.8 (C($\underline{C}H_3$)$_2$), 62.1 (C5), 69.4 (C6), 72.1, 73.3 (O$\underline{C}H_2$Ph), 77.4 (C2), 77.5 (C3), 77.8 (C4), 104.1 (C1), 113.2 ($\underline{C}(CH_3)_2$), 127.7, 127.7, 128.1, 128.1, 128.4, 128.4 (Ar$\underline{C}$H), 137.1, 137.6 (Ar$\underline{C}$C); LRMS (ESI +ve): 443 (25%, M+$NH_4^+$), 448 (70%, M+$Na^+$), 873 (100%, 2M+$Na^+$).

Similar treatment of **5-azido-5-deoxy-1,2-*O*-isopropylidene-α-L-allofuranose 2.168L** (1.60 g, 6.53 mmol) in a suitably scaled procedure afforded **5-azido-3,6-di-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-*α*-L-allofuranose 2.169L** (2.65 g, 97%) as a yellow oil: $[\alpha]_D^{25}$ -63.4 (*c* 1.23, $CHCl_3$).

**5-Azido-3,6-di-*O*-benzyl-5-deoxy-D-allofuranose 2.170D**

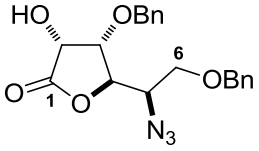



*para*-Toluenesulfonic acid (7.30 g, 39.3 mmol) was added to a solution of the acetonide **2.169D** (7.60 g, 17.9 mmol) in a 7:1 1,4-dioxane/water mixture (40 mL). The reaction was heated to 80 °C and stirred for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.68) and the formation of a major product ($R_f$ 0.16). The reaction mixture was allowed to cool to RT, diluted with ethyl acetate (600 mL)

and washed with an aqueous sodium bicarbonate solution (250 mL). The phases were separated and the aqueous layer extracted with ethyl acetate (2 x 350 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the lactols **2.170D** (6.39 g, 93%) as a yellow oil, in a 2:1 (A:B) anomeric mixture. The lactols **2.170D** was reacted on without further purification; HRMS (ESI +ve): found 408.1526 [M+$Na^+$]; $C_{20}H_{23}N_3NaO_5$ requires 408.1530; $[\alpha]_D^{25}$ +12.0 (*c* 1.50, $CHCl_3$); $\nu_{max}$ (thin film): 2099 (s, $N_3$), 3411 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 3.47 (1H, dd, $H6^A$, $J_{6,5}$ 7.3, $J_{6,6'}$ 10.0), 3.53 (1H, dd, $H6^B$, $J_{6,5}$ 8.2, $J_{6,6'}$ 10.1), 3.61 (1H, dd, $H6'^A$, $J_{6',5}$ 4.0, $J_{6',6}$ 10.1), 3.68-3.74 (2H, m, $H5^A$, $H6'^B$), 3.81 (1H, ddd, $H5^B$, $J_{5,6'}$ 3.3, $J_{5,4}$ 6.3, $J_{5,6}$ 8.2), 3.99 (1H, dd, $H3^A$, $J_{3,2}$ 3.9, $J_{3,4}$ 5.7), 4.02 (1H, br. d, $H3^B$, $J_{3,4}$ 4.5), 4.07-4.11 (2H, m, $H2^A$, $H2^B$), 4.19 (1H, a-t, $H4^A$, $J_{4,3} = J_{4,5}$ 4.0), 4.29 (1H, a-t, $H4^B$, $J_{4,5} = J_{4,3}$ 5.3), 4.52 (2H, a-d, 2 x $OC\underline{H}_2Ph^B$, *J* 12.1), 4.54-4.57 (2H, m, 2 x $OC\underline{H}_2Ph^A$), 4.58 (2H, a-d, 2 x $OC\underline{H}_2Ph^A$, *J* 11.9), 4.62 (2H, a-d, 2 x $OC\underline{H}_2Ph^B$, *J* 11.7), 5.26-5.27 (2H, m, $H1^A$, $H1^B$), 7.30-7.39 (20H, m, $ArH^A$, $ArH^B$); $\delta_C$ ($CDCl_3$, 100 MHz): 62.5 ($C5^A$), 63.3 ($C5^B$), 67.0 ($C6^A$), 69.7 ($C6^B$), 70.6 ($C2^A$), 73.0, 73.5 ($O\underline{C}H_2Ph^B$), 73.0, 73.5 ($O\underline{C}H_2Ph^A$), 73.7 ($C3^B$), 77.5 ($C3^A$), 79.0 ($C4^B$), 80.2 ($C2^B$), 80.4 ($C4^A$), 97.0 ($C1^A$), 102.3 ($C1^B$), 127.6, 127.8, 127.9, 128.2, 128.2, 128.4, 128.5, 128.5, 128.7 ($Ar\underline{C}H^A$, $Ar\underline{C}H^B$), 136.6, 136.6, 137.4, 137.5 ($Ar\underline{C}C^A$, $Ar\underline{C}C^B$); LRMS (ESI +ve): 408 (60%, M+$Na^+$), 793 (100%, 2M+$Na^+$); (ESI –ve): 769 (100%, [2M-H]$^-$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-L-allofuranose 2.169L** (1.90 g, 4.47 mmol) in a suitably scaled procedure afforded **5-azido-3,6-di-*O*-benzyl-5-deoxy-L-allofuranose 2.170L** (1.63 mg, 95%) as a yellow oil, as a 2:1 (A:B) anomeric mixture: $[\alpha]_D^{25}$ -11.5 (*c* 1.20, $CHCl_3$).

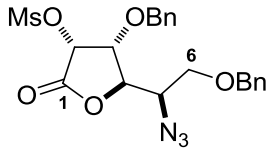
**5-Azido-3,6-di-*O*-benzyl-5-deoxy-D-allono-1,4-lactone 2.171D**




Potassium carbonate (4.94 mg, 35.7 mmol) and iodine (9.07 g, 35.7 mmol) were added to a solution of the lactols **2.170D** (6.39 g, 16.7 mmol) in *tert*-butanol (80 mL) at 100 °C. The reaction was stirred for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.16) and the formation of a major product ($R_f$ 0.32). The reaction mixture was allowed to cool to RT and diluted with ethyl acetate (500 mL). Saturated aqueous sodium thiosulfate (250 mL) was added slowly and the biphasic mixture stirred until the iodine was visibly quenched. The phases were separated and the aqueous layer extracted with ethyl acetate (2 x 200 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1 to 1:1, cyclohexane/ethyl acetate) to afford the lactone **2.171D** (5.1 g, 79%) as a colourless oil; HRMS (ESI +ve): found 406.1369 [M+$Na^+$]; $C_{20}H_{21}N_3NaO_5$ requires 406.1373; $[\alpha]_D^{25}$ -20.3 (*c* 1.50, $CHCl_3$); $\nu_{max}$ (thin film): 1789 (s, C=O), 2104 (s, $N_3$), 3434 (br. s, OH); $\delta_H$ ($CD_3CN$, 400 MHz): 3.62 (1H, dd, H6, $J_{6,5}$ 7.1, $J_{6,6'}$ 10.4), 3.71 (1H, dd, H6', $J_{6',5}$ 4.0, $J_{6',6}$ 10.4) 3.77 (1H, d, OH2, $J_{OH,2}$ 8.6), 3.94 (1H, ddd, H5, $J_{5,6'}$ 4.0, $J_{5,4}$ 6.0, $J_{5,6}$ 7.1), 4.19 (1H, dd, H3, $J_{3,4}$ 0.8, $J_{3,2}$ 5.8), 4.45 (1H, dd, H4, $J_{4,3}$ 0.8, $J_{4,5}$ 6.0), 4.54 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 12.1), 4.57 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 12.1), 4.59 (1H, dd, H2, $J_{2,3}$ 5.8, $J_{2,OH}$ 8.6), 4.61 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 4.65 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 7.30-7.39 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz): 61.9 (C5), 69.0 (C2), 70.3 (C6), 73.1, 74.1 (O$\underline{C}H_2$Ph), 75.9 (C3), 81.8 (C4), 128.8, 128.8, 129.0, 129.1, 129.5 (Ar$\underline{C}$H), 138.6, 139.0 (Ar$\underline{C}$C), 175.8 (C1); LRMS (ESI +ve): 789 (100%, 2M+$Na^+$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-L-allofuranose 2.170L** (1.63 g, 4.23 mmol) in a suitably scaled procedure afforded **5-azido-3,6-di-*O*-benzyl-5-deoxy-L-allono-1,4-lactone 2.171L** (1.02 g, 63%) as a yellow oil: $[\alpha]_D^{25}$ +20.5 (*c* 1.40, $CHCl_3$).

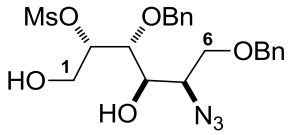
**5-Azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-allono-1,4-lactone 2.175D**




Methanesulfonyl chloride (29 μL, 0.37 mmol) was added dropwise to a solution of the alcohol **2.171D** (90 mg, 0.24 mmol) in pyridine (1.0 mL) at 0 °C. The reaction was allowed to warm to RT and stirred for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.32) and the formation of a major product ($R_f$ 0.52). The reaction mixture was concentrated *in vacuo* and co-evaporated with toluene (3 x 3 mL). The crude residue was purified by flash chromatography (19:1 to 3:1, cyclohexane/ethyl acetate) to afford the mesylate **2.175D** (76 mg, 70%) as a colourless oil; HRMS (ESI +ve): found 516.1407 [M+MeOH+$Na^+$]; $C_{22}H_{27}N_3NaO_8S$ requires 516.1411; $[\alpha]_D^{25}$ +26.2 (*c* 1.00, $CHCl_3$); $\nu_{max}$ (thin film): 1178 (s, $SO_2$), 1365 (s, $SO_2$), 1801 (s, C=O), 2109 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz): 3.31 (3H, s, $SO_2CH_3$), 3.47 (1H, dd, H6, $J_{6,5}$ 6.6, $J_{6,6'}$ 10.1), 3.52 (1H, dd, H6', $J_{6',5}$ 4.9, $J_{6',6}$ 10.1), 3.92 (1H, ddd, H5, $J_{5,4}$ 3.5, $J_{5,6'}$ 4.9, $J_{5,6}$ 6.6), 4.30 (1H, d, H3, $J_{3,2}$ 6.1), 4.51-4.55 (3H, m, 3 x OC$\underline{H}_2$Ph), 4.58 (1H, d, H4, $J_{4,5}$ 3.5), 4.76 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.9), 5.50 (1H, d, H2, $J_{2,3}$ 6.1), 7.30-7.40 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 39.8 ($SO_2CH_3$), 61.3 (C5), 68.6 (C6), 73.1 (C2) 73.1, (C3), 73.3, 73.7 (O$\underline{C}H_2$Ph), 83.3 (C4), 127.8, 128.2, 128.3, 128.4, 128.6, 128.7 (Ar$\underline{C}$H), 136.4, 136.7 (Ar$\underline{C}$C), 169.8 (C1); LRMS (ESI +ve): 484 (24%, M+$Na^+$), 516 (21%, M+MeOH+$Na^+$), 945 (100%, 2M+$Na^+$); (ESI –ve): 352 (100%), 496 (76%, M+$^{35}Cl^-$), 498 (32%, M+$^{37}Cl^-$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-L-allono-1,4-lactone 2.171L** (360 mg, 0.94 mmol) in a suitably scaled procedure afforded **5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-allono-1,4-lactone 2.175L** (363 mg, 83%) as a yellow oil: $[\alpha]_D^{25}$ -22.7 (*c* 1.15, $CHCl_3$).

**5-Azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-allitol 2.176D**

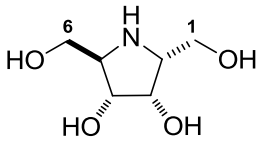



Sodium borohydride (90 mg, 2.40 mmol) was added portion-wise to a solution of the lactone **2.175D** (101 mg, 0.22 mmol) in a 8:1 ethanol/1,4-dioxane mixture (6 mL) at -30 °C. The reaction was stirred for 6 h, with the internal temperature rising to -20 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.52) and the formation of a major product ($R_f$ 0.05). The reaction was neutralised with glacial acetic acid and concentrated *in vacuo*. The crude residue was dissolved with ethyl acetate (40 mL), washed with an aqueous sodium bicarbonate solution (25 mL) and the aqueous layer extracted with ethyl acetate (2 x 40 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1 to 1:1, cyclohexane/ethyl acetate) to afford the diol **2.176D** (52 mg, 51%) as a yellow oil; HRMS (ESI +ve): found 488.1460 $[M+Na^+]$; $C_{21}H_{27}N_3NaO_7S$ requires 488.1462; $[\alpha]_D^{25}$ +12.1 (*c* 0.90, $CHCl_3$); $\nu_{max}$ (thin film): 1173 (s, $SO_2$), 1339 (s, $SO_2$), 2102 (s, $N_3$), 3449 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 3.08 (3H, s, $SO_2CH_3$), 3.58 (1H, dd, H6, $J_{6,5}$ 5.7, $J_{6,6'}$ 10.1), 3.66 (1H, dd, H6', $J_{6',5}$ 3.4, $J_{6',6}$ 10.1), 3.75 (1H, ddd, H5, $J_{5,6'}$ 3.4, $J_{5,4}$ 4.5, $J_{5,6}$ 5.7), 3.83 (1H, dd, H3, $J_{3,2}$ 2.3, $J_{3,4}$ 7.7), 3.92 (1H, dd, H4, $J_{4,5}$ 4.5, $J_{4,3}$ 7.7), 3.96 (1H, dd, H1, $J_{1,2}$ 6.5, $J_{1,1'}$ 12.9), 4.01 (1H, dd, H1', $J_{1',2}$ 4.1, $J_{1',1}$ 12.9), 4.46 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.9), 4.47 (1H, d, OC$\underline{H}_2$Ph,

$J_{gem}$ 11.1), 4.53 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 11.9), 4.75 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 11.1), 5.14 (1H, ddd, H2, $J_{2,3}$ 2.3, $J_{2,1'}$ 4.1, $J_{2,1}$ 6.5), 7.29-7.39 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 38.5 ($SO_2CH_3$), 61.3 (C1), 61.4 (C5), 69.4 (C6), 71.4 (C4), 73.4, 73.7 (O<u>C</u>H$_2$Ph), 79.2 (C3), 82.8 (C2), 127.9, 128.1, 128.3, 128.5, 128.6, 128.6 (Ar<u>C</u>H), 136.8, 137.0 (Ar<u>C</u>C); LRMS (ESI +ve): 953 (100%, 2M+$Na^+$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-allono-1,4-lactone 2.175L** (363 mg, 0.79 mmol) in a suitably scaled procedure afforded **2-azido-1,4-di-*O*-benzyl-2-deoxy-5-*O*-methanesulfonyl-D-allitol 2.176L** (223 mg, 61%) as a pale-yellow oil: $[\alpha]_D^{25}$ -8.5 (*c* 1.00, $CHCl_3$).

**2,5-Dideoxy-2,5-imino-D-altritol (D-DADP) 2.59D**



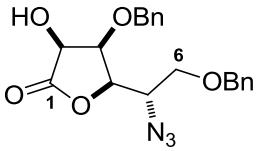

Palladium (10% on carbon, 60 mg) and sodium acetate (54 mg, 0.65 mmol) were added to a solution of the diol **2.176D** (152 mg, 0.33 mmol) in 1,4-dioxane (10 mL). The reaction vessel was evacuated and flushed with hydrogen and the reaction stirred for 4 h, after which TLC analysis (3:7, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.64) and the formation of a major product ($R_f$ 0.02). LRMS indicated the absence of a peak corresponding to the starting material (*m/z* 488 [M+$Na^+$]) and the presence of a peak corresponding to the cyclised dibenzylated intermediate **2.177D** (*m/z* 344 [M+$H^+$]). 2 M Aqueous hydrochloric acid (0.5 mL) was added, the reaction vessel evacuated and flushed with hydrogen and the reaction stirred for 19 h, after which LRMS indicated the absence of a peak corresponding to cyclised dibenzylated intermediate **2.177D** (*m/z* 344 [M+$H^+$]) and the presence

of a peak corresponding to the D-*altro* pyrrolidine DADP **2.59D** (*m/z* 164 [M+H$^+$]). The reaction was filtered (GF/B, glass microfibre), concentrated *in vacuo*, loaded onto a short column of Dowex® (50W-X8, H$^+$) and the resin washed with water. The product was liberated with 2 M aqueous ammonia and the ammoniacal fractions combined and concentrated *in vacuo* to afford the D-*altro* pyrrolidine DADP **2.59D** (53 mg, 99%) as a colourless oil; HRMS (ESI +ve): found 186.0736 [M+Na$^+$]; $C_6H_{13}NNaO_4$ requires 186.0737; $[\alpha]_D^{25}$ +31.0 (*c* 1.10, $H_2O$) [Lit.[49] $[\alpha]_D^{25}$ +34.2 (*c* 0.83, $H_2O$)]; $\nu_{max}$ (thin film): 3283 (br. s, NH/OH); $\delta_H$ ($D_2O$, 400 MHz): 3.57 (1H, ddd, H5, $J_{5,6'}$ 3.5, $J_{5,6}$ 5.8, $J_{5,4}$ 9.1), 3.68 (1H, ddd, H2, $J_{2,3}$ 3.3, $J_{2,1'}$ 5.3, $J_{2,1}$ 8.1), 3.77 (1H, dd, H6, $J_{6,5}$ 5.8, $J_{6,6'}$ 12.6), 3.82 (1H, dd, H1, $J_{1,2}$ 8.1, $J_{1,1'}$ 12.1), 3.89 (1H, dd, H6', $J_{6',5}$ 3.5, $J_{6',6}$ 12.6), 3.92 (1H, dd, H1', $J_{1',2}$ 5.3, $J_{1',1}$ 12.1), 4.19 (1H, dd, H4, $J_{4,3}$ 3.8, $J_{4,5}$ 9.1), 4.26 (1H, dd, H3, $J_{3,2}$ 3.3, $J_{3,4}$ 3.8); $\delta_C$ ($D_2O$, 100 MHz): 58.0 (C1), 58.6 (C6), 62.2 (C5), 62.8 (C2), 70.6 (C3), 71.7 (C4); LRMS (ESI +ve): 164 (100%, M+Na$^+$), 250 (38%, M+2MeOH+Na$^+$).

Similar treatment of **2-azido-1,4-di-*O*-benzyl-2-deoxy-5-*O*-methanesulfonyl-D-allitol 2.176L** (223 mg, 0.48 mmol) in a suitably scaled procedure afforded **2,5-dideoxy-2,5-imino-L-altritol 2.59L** (75 mg, 96%) as a yellow oil; $[\alpha]_D^{25}$ -25.5 (*c* 0.90, $H_2O$)

*2.4.3.6 Synthesis of ido-configured iminosugars*

**5-Azido-3,6-di-*O*-benzyl-5-deoxy-L-gulono-1,4-lactone 2.183L**



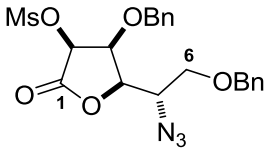

Trifluoromethanesulfonic anhydride (0.35 mL, 2.07 mmol) was added dropwise to a solution of the lactone **2.126L** (610 mg, 1.59 mmol) and pyridine (0.39 mL, 4.77 mmol) in dichloromethane (6 mL) at -40 °C. The reaction was stirred for 1 h, after which TLC analysis (2:1,

cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.39) and the formation of a major product ($R_f$ 0.59). The reaction mixture was diluted with dichloromethane (8 mL), washed with 2 M aqueous hydrochloric acid (3 x 8 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude triflate **2.183L** as a yellow oil. The crude triflate **2.183L** was reacted on without further purification.

Sodium trifluoroacetate (362 mg, 2.66 mmol) was added to a solution of the crude triflate **2.183L** in DMF (3 mL) at RT. The reaction was stirred for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.59) and the formation of a major product ($R_f$ 0.27). The reaction mixture was diluted with ethyl acetate (30 mL) and washed with an aqueous sodium bicarbonate solution (30 mL). The aqueous phase was extracted with ethyl acetate (2 x 30 mL), the organic fractions combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1 to 2:1, cyclohexane/ethyl acetate) to afford the lactone **2.183L** (444 mg, 90%) as a yellow oil; HRMS (ESI +ve): found 406.1362 [M+$Na^+$]; $C_{20}H_{21}N_3NaO_5$ requires 406.1373; $[\alpha]_D^{25}$ +11.7 (*c* 0.81, $CHCl_3$); $\upsilon_{max}$ (thin film): 1785 (s, C=O), 2099 (s, $N_3$), 3410 (br. s, OH); $\delta_H$ ($CD_3CN$, 400 MHz): 3.42 (1H, dd, H6, $J_{6,5}$ 5.6, $J_{6,6'}$ 10.4), 3.54 (1H, dd, H6', $J_{6',5}$ 2.9, $J_{6',6}$ 10.4), 3.94 (1H, ddd, H5, $J_{5,6'}$ 2.9, $J_{5,6}$ 5.6, $J_{5,4}$ 9.1), 4.09 (1H, br. d, OH2, $J_{OH,2}$ 6.1), 4.20 (1H, dd, H3, $J_{3,4}$ 3.3, $J_{3,2}$ 4.6), 4.37 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 4.39 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 4.44 (1H, dd, H4, $J_{4,3}$ 3.3, $J_{4,5}$ 9.1), 4.47 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 4.63 (1H, br. dd, H2, $J_{2,3}$ 4.6, $J_{2,OH}$ 6.1), 4.88 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 7.30-7.39 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz): 61.8 (C5), 69.2 (C6), 72.9 (C2), 74.0, 74.9 (O$\underline{C}H_2$Ph), 77.3 (C3), 79.3 (C4), 128.9, 129.0, 129.2, 129.5 (Ar$\underline{C}$H), 138.8, 139.0 (Ar$\underline{C}$C), 175.5 (C1); LRMS (ESI +ve): 406 (70 %, $[M+Na]^+$), 789 (100 %, $[2M+Na]^+$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-D-idono-1,4-lactone 2.126D** (100 mg, 0.26 mmol) in a suitably scaled procedure afforded **5-azido-3,6-di-*O*-benzyl-5-deoxy-D-gulono-1,4-lactone 2.183D** (75 mg, 75% over two steps) as a yellow oil; $[\alpha]_D^{25}$ -11.2 (*c* 0.95, $CHCl_3$).

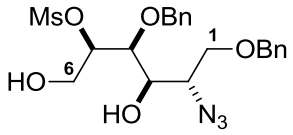
**5-Azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-gulono-1,4-lactone 2.184L**




Methanesulfonyl chloride (133 μL, 1.72 mmol) was added drop-wise to a solution of the lactone **2.183L** (444 mg, 1.15 mmol) in pyridine (2 mL) at 0 $^oC$. The reaction was allowed to warm to RT and stirred for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.27) and the formation of a major product ($R_f$ 0.55). The reaction mixture was concentrated *in vacuo* and co-evaporated with toluene (3 x 5 mL). The crude residue was purified by flash chromatography (9:1 to 2:1, cyclohexane/ethyl acetate) to afford the mesylate **2.184L** (494 mg, 93%) as a yellow oil; HRMS (ESI +ve): found 484.1144 [M+$Na^+$]; $C_{21}H_{23}N_3NaO_7S$ requires 484.1149; $[\alpha]_D^{25}$ +2.52 (*c* 0.45, $CHCl_3$); $\upsilon_{max}$ (thin film): 1178 (s, $SO_2$), 1361 (s, $SO_2$), 1801 (s, C=O), 2102 (s, $N_3$); $\delta_H$ ($CD_3CN$, 400 MHz): 3.30 (3H, s, $SO_2CH_3$), 3.44 (1H, dd, H6, $J_{6,5}$ 5.2, $J_{6,6'}$ 10.5), 3.55 (1H, dd, H6', $J_{6',5}$ 2.8, $J_{6',6}$ 10.5), 3.99 (1H, ddd, H5, $J_{5,6'}$ 3.3, $J_{5,6}$ 5.3, $J_{5,4}$ 8.8), 4.40 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 4.42 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 4.47 (1H, dd, H3, $J_{3,4}$ 3.3, $J_{3,2}$ 4.6), 4.49 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 4.61 (1H, dd, H4, $J_{4,3}$ 3.0, $J_{4,5}$ 9.1), 4.78 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 5.58 (1H, d, H2, $J_{2,3}$ 4.6), 7.30-7.40 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz); 39.7 ($SO_2CH_3$), 61.3 (C5), 69.1 (C6), 74.0, 75.1 (O$\underline{C}H_2$Ph), 76.5 (C3), 77.1 (C2), 80.4 (C4), 129.0, 129.1, 129.3, 129.4, 129.5, 129.6 (Ar$\underline{C}$H), 138.0, 138.9 (Ar$\underline{C}$C), 170.7 (C1); LRMS (ESI +ve): 484 (38%, M+$Na^+$), 516 (100%, M+MeOH+$Na^+$), 945 (70 %, [2M+Na]$^+$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-D-gulono-1,4-lactone 2.183D** (272 mg, 0.71 mmol) in a suitably scaled procedure afforded **5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-gulono-1,4-lactone 2.184D** (288 mg, 88%) as a pale yellow oil; $[\alpha]_D^{25}$ -1.54 (*c* 0.65, $CHCl_3$).

**2-Azido-1,4-di-*O*-benzyl-2-deoxy-5-*O*-methanesulfonyl-D-glucitol 2.185D**

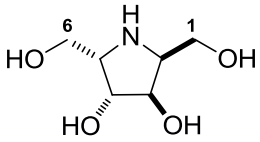



Sodium borohydride (41 mg, 1.08 mmol) was added portion-wise to a solution of the lactone **2.184L** (100 mg, 0.22 mmol) in a 8:1 ethanol/1,4-dioxane mixture (5 mL) at -30 $^oC$. The reaction was stirred for 4 h, with the internal temperature rising to -15 $^oC$, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the partial consumption of the starting material ($R_f$ 0.55) and the formation of a major product ($R_f$ 0.42). Additional sodium borohydride (41 mg, 1.08 mmol) was added at -30 $^oC$ and the reaction allowed to warm to -15 $^oC$. After 6 h TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.55) and the major product ($R_f$ 0.42). The reaction mixture was neutralised with glacial acetic acid and concentrated *in vacuo*. The crude residue was dissolved with ethyl acetate (30 mL) and washed with an aqueous sodium bicarbonate solution (20 mL). The aqueous phase was extracted with ethyl acetate (2 x 30 mL), the organic fractions combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1 to 1:4, cyclohexane/ethyl acetate) to afford the diol **2.185D** (83 mg, 82%) as a yellow oil; HRMS (ESI +ve): found 488.1458 [M+$Na^+$]; $C_{21}H_{27}N_3NaO_7S$ requires 488.1462; $[\alpha]_D^{25}$ +4.76 (*c* 0.48, $CHCl_3$); $\upsilon_{max}$ (thin film): 1172 (s, $SO_2$), 1336 (s, $SO_2$), 2098 (s, $N_3$), 3490 (br. s, OH); $\delta_H$ ($CD_3OD$, 400 MHz): 3.13 (3H, s, $SO_2CH_3$), 3.43 (1H, dd, H1, $J_{1,2}$ 6.6, $J_{1,1'}$ 10.4), 3.55 (1H, dd,

H1', $J_{1',2}$ 3.5, $J_{1',1}$ 10.4), 3.63 (1H, ddd, H2, $J_{2,1'}$ 3.5, $J_{2,3}$ 6.3, $J_{2,1}$ 6.6), 3.84 (1H, dd, H3, $J_{3,4}$ 3.8, $J_{3,2}$ 6.3), 3.84 (1H, dd, H6, $J_{6,5}$ 6.8, $J_{6,6'}$ 12.7), 3.92 (1H, t, H4, $J_{4,3} = J_{4,5}$ 3.8), 4.05 (1H, dd, H6', $J_{6',5}$ 3.0, $J_{6',6}$ 12.7), 4.45 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 4.52 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 9.5), 4.55 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 9.5), 4.76 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 4.85 (1H, m, H5), 7.30-7.36 (10H, m, ArH); $\delta_C$ ($CD_3OD$, 100 MHz): 38.6 ($SO_2\underline{C}H_3$), 61.8 (C6), 65.0 (C2), 70.1 (C1), 72.2 (C3), 74.5, 75.3 (O$\underline{C}H_2$Ph), 80.1 (C4), 85.9 (C5), 129.0, 129.1, 129.2, 129.6, 129.6 (Ar$\underline{C}$H), 139.3, 139.3 (Ar$\underline{C}$C); LRMS (ESI +ve): 488 (60 %, $M+Na^+$), 953 (100 %, $2M+Na^+$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-gulono-1,4-lactone 2.184D** (109 mg, 0.236 mmol) in a suitably scaled procedure afforded **2-azido-1,4-di-*O*-benzyl-2-deoxy-5-*O*-methanesulfonyl-L-glucitol 2.185L** (72 mg, 72%) as a clear oil; $[\alpha]_D^{25}$ -4.54 (*c* 0.50, $CHCl_3$).

**2,5-Dideoxy-2,5-imino-L-iditol 2.61L**

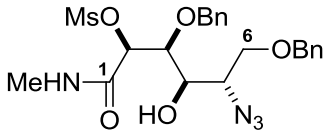



Palladium (10% on carbon, 32 mg) and sodium acetate (29 mg, 0.35 mmol) were added to a solution of the mesylate **2.185D** (81 mg, 0.17 mmol) in 1,4-dioxane (4 mL). The reaction vessel was evacuated and flushed with hydrogen and stirred for 24 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.42) and the formation of a major product (baseline). 2 M Aqueous hydrochloric acid (1 mL) was added, the reaction vessel evacuated and flushed with hydrogen and the reaction stirred for 16 h. The reaction mixture was filtered (GF/A, glass microfibre), concentrated *in vacuo*, loaded onto a short column of Dowex® (50W-X8, $H^+$) and the resin washed with water. The product was

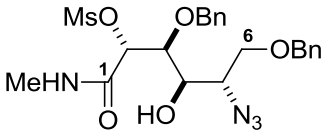
liberated with 2 M aqueous ammonia and the ammoniacal fractions combined and concentrated *in vacuo* to afford the L-*ido* pyrrolidine L-DIDP **2.61L** (26 mg, 92%) as a yellow oil; HRMS (ESI +ve): found 164.0912 [M+H$^+$]; $C_6H_{14}NO_4$ requires 164.0917; $[\alpha]_D^{25}$ +7.25 (*c* 0.30, $H_2O$) [Lit.[90] $[\alpha]_D^{25}$ +14.0 (*c* 1.0, $H_2O$)]; $\nu_{max}$ (thin film): 3347 (br. s, NH/OH); $\delta_H$ ($D_2O$, 400 MHz): 3.79 (1H, dd, H1, $J_{1,2}$ 6.6, $J_{1,1'}$ 10.4), 3.80-3.84 (1H, m, H2), 3.89 (1H, dd, H1', $J_{1',2}$ 6.8, $J_{1',1}$ 10.4), 4.10 (1H, d, H3, $J_{3,2}$ 2.5); $\delta_C$ ($D_2O$, 100 MHz): 57.9 (C1), 63.4 (C2), 75.1 (C3); LRMS (ESI +ve): 164 (100 %, M+Na$^+$);

Similar treatment of **2-azido-1,4-di-*O*-benzyl-2-deoxy-5-*O*-methanesulfonyl-L-glucitol 2.185L** (72 mg, 0.155 mmol) in a suitably scaled procedure afforded **2,5-dideoxy-2,5-imino-D-iditol 2.61D** (25 mg, 100%) as a yellow oil; $[\alpha]_D^{25}$ -8.11 (*c* 0.45, $H_2O$).

**Methyl 5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-gulonamide 2.187L** & **methyl 5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-idonamide 2.188L**




**2.187L**




**2.188L**

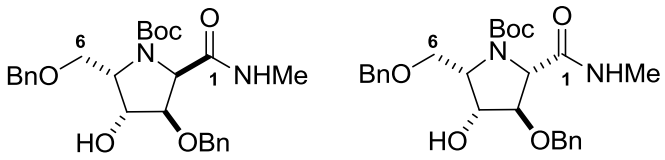
Methylamine (33% in ethanol, 0.11 mL, 0.86 mmol) was added to a solution of the lactone **2.184L** (132 mg, 0.29 mmol) in 1,4-dioxane (6 mL) at RT. The reaction mixture was stirred for 16 h, after which t.l.c. analysis (3:7, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.72) and the formation of two major, co-spotting products ($R_f$ 0.60). The reaction mixture was concentrated *in vacuo*, co-evaporated with dichloromethane (3 x 10 mL) and the residue purified by flash chromatography (9:1 to 1:1, cyclohexane/ethyl acetate) to afford an inseparable 1.3:1 (A:B) epimeric mixture of the L-*gulo*

amide **2.187L** and the L-*ido* amide **2.188L** (140 mg, 99%) as a yellow oil; HRMS (ESI +ve): found 515.1567 [M+$Na^+$]; $C_{22}H_{28}N_4NaO_7S$ requires 515.1571; $\nu_{max}$ (thin film): 1176 (s, $SO_2$), 1358 (s, $SO_2$), 1558 (s, C=O), 1668 (s, C=O), 2100 (s, $N_3$), 3405 (br. s, OH); $\delta_H$ ($CD_3OD$, 400 MHz): 2.75 (3H, s, NHC$\underline{H}_3^B$), 2.76 (3H, s, NHC$\underline{H}_3^A$), 3.14 (3H, s, $SO_2CH_3^B$), 3.14 (3H, s, $SO_2CH_3^A$), 3.52-3.56 (2H, m, $H6^A$, $H6^B$), 3.61-3.67 (2H, m, $H6'^A$, $H6'^B$), 3.75 (1H, ddd, $H5^A$ or $H5^B$, *J* 3.7, *J* 5.6, *J* 6.9), 3.77-3.80 (1H, m, $H5^A$ or $H5^B$), 3.82 (1H, dd, $H4^B$, $J_{4,5}$ 4.5, $J_{4,3}$ 5.3), 3.90 (1H, dd, $H4^A$, $J_{4,3}$ 4.3, $J_{4,5}$ 5.6), 3.96 (1H, dd, $H3^A$, $J_{3,4}$ 4.3, $J_{3,2}$ 5.1), 4.05 (1H, dd, $H3^B$, $J_{3,2}$ 4.3, $J_{3,4}$ 5.6), 4.49 (1H, d, O$\underline{C}H_2$Ph, $J_{gem}$ 11.9), 4.50 (1H, d, O$\underline{C}H_2$Ph, $J_{gem}$ 12.1), 4.53 (1H, d, O$\underline{C}H_2$Ph, $J_{gem}$ 11.6), 4.54 (1H, d, O$\underline{C}H_2$Ph, $J_{gem}$ 11.9), 4.56 (1H, d, O$\underline{C}H_2$Ph, $J_{gem}$ 12.1), 4.62 (1H, d, O$\underline{C}H_2$Ph, $J_{gem}$ 10.9), 4.64 (1H, d, O$\underline{C}H_2$Ph, $J_{gem}$ 10.9), 4.70 (1H, d, O$\underline{C}H_2$Ph, $J_{gem}$ 10.9), 5.13 (1H, d, $H2^B$, $J_{2,3}$ 4.3), 5.18 (1H, d, $H2^A$, $J_{2,3}$ 5.1), 7.25-7.37 (20H, m, $ArH^A$, $ArH^B$); $\delta_C$ ($CD_3OD$, 100 MHz): 26.6, 26.6 ($NHCH_3^A$, $NHCH_3^B$), 38.6, 38.7 ($SO_2CH_3^A$, $SO_2CH_3^B$), 63.2, 64.5 ($C5^A$, $C5^B$), 71.2, 71.3 ($C6^A$, $C6^B$), 71.7 ($C4^B$), 72.0 ($C4^A$), 74.3, 74.4, 75.4, 76.9 (O$\underline{C}H_2Ph^A$, O$\underline{C}H_2Ph^B$), 79.1 ($C2^A$), 79.9 ($C2^B$), 80.7, 80.8 ($C3^A$, $C3^B$), 128.9, 129.0, 129.1, 129.1, 129.2, 129.5, 129.5, 129.6, 129.6 (Ar$\underline{C}H^A$, Ar$\underline{C}H^B$), 139.1, 139.1, 139.4, 139.4 (Ar$\underline{C}C^A$, Ar$\underline{C}C^B$), 169.8 ($C1^A$, $C1^B$); LRMS (ESI +ve): 515 (18%, M+$Na^+$), 1007 (100%, 2M+$Na^+$); (ESI –ve): 491 (65%, $[M-H]^-$), 983 (100%, $[2M-H]^-$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-gulono-1,4-lactone 2.184D** (179 mg, 0.388 mmol) in a suitably scaled procedure afforded an inseparable, 2:1 (A:B) mixture of **methyl 5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-gulonamide 2.187D** and **methyl 5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-idonamide 2.188D** (186 mg, 97%) as a clear, viscous oil.

**Methyl 2-*N*-(*tert*-butoxycarbonyl)-3,6-di-*O*-benzyl-2,5-dideoxy-2,5-imino-L-idonamide 2.189L /**

**Methyl 2-*N*-(*tert*-butoxycarbonyl)-3,6-di-*O*-benzyl-2,5-dideoxy-2,5-imino-L-gulonamide 2.190L**




**2.189L** **2.190L**

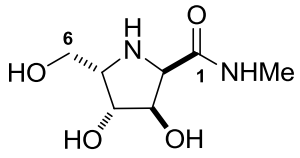
Palladium (10% on carbon, 54 mg) and sodium acetate (45 mg, 0.46 mmol) were added to a solution of the inseparable L-*gulo* and L-*ido* amides **2.187L**/**2.188L** (1.3:1 mixture, 134 mg, 0.27 mmol) in 1,4-dioxane (5 mL). The reaction vessel was evacuated and flushed with hydrogen and stirred for 3 h, after which TLC analysis (2:1, toluene/acetone) indicated the complete consumption of the starting materials ($R_f$ 0.54) and the presence of a major product ($R_f$ 0.07). The reaction was filtered (GF/A, glass microfibre) and di-*tert*-butyldicarbonate (Boc anhydride, $Boc_2O$, 45 mg, 0.46 mmol) was added portion-wise to the filtrate. This reaction mixture was stirred for 16 h, after which TLC analysis (2:1, toluene/acetone) indicated the complete consumption of the intermediate product ($R_f$ 0.07) and the formation of two products ($R_f$ 0.54, 0.36). The reaction mixture was concentrated *in vacuo* and the crude residue purified by flash chromatography (1:0 to 3:2, toluene/acetone) to afford the cyclized Boc-protected amides, L-*ido* **2.189L** ($R_f$ 0.36, 56 mg, 44%) and L-*gulo* **2.190L** ($R_f$ 0.54, 54 mg, 42%) as clear oils.

Partial data for L-*ido* amide **2.189L** ($R_f$ 0.36): HRMS (ESI +ve): found 493.2310 [$M+Na^+$]; $C_{26}H_{34}N_2NaO_6$ requires 493.2309; $[\alpha]_D^{25}$ -21.7 (*c* 1.17, $CHCl_3$); $\nu_{max}$ (thin film): 1550 (s, C=O), 1657 (s, C=O), 3326 (br. s, OH); LRMS (ESI +ve): 493 (25%, $M+Na^+$), 963 (100%, $2M+Na^+$);

Partial data for L-*gulo* amide **2.190L** ($R_f$ 0.54): HRMS (ESI +ve): found 493.2304 [M+$Na^+$]; $C_{26}H_{34}N_2NaO_6$ requires 493.2309; $[\alpha]_D^{25}$ -10.0 (*c* 0.58, $CHCl_3$); $\nu_{max}$ (thin film): 1552 (s, C=O), 1666 (s, C=O), 3321 (br. s, OH); LRMS (ESI +ve): 493 (30%, M+$Na^+$), 963 (100%, 2M+$Na^+$);

Similar treatment of an inseparable, 2:1 mixture of **methyl 5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-gulonamide 2.187D** and **methyl 5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-idonamide 2.188D** (186 mg, 0.378 mmol) in a suitably scaled procedure afforded **methyl 2-*N*-(*tert*-butoxycarbonyl)-3,6-di-*O*-benzyl-2,5-dideoxy-2,5-imino-D-idonamide 2.189D** (103 mg, 59%) and **methyl 2-*N*-(*tert*-butoxycarbonyl)-3,6-di-*O*-benzyl-2,5-dideoxy-2,5-imino-D-gulonamide 2.190D** (53 mg, 30%) as clear oils; **2.189D** ($R_f$ 0.36): $[\alpha]_D^{25}$ +15.8 (*c* 0.96, $CHCl_3$). **2.190D** ($R_f$ 0.54): $[\alpha]_D^{25}$ +2.9 (*c* 1.0, $CHCl_3$).

**Methyl 2,5-dideoxy-2,5-imino-L-idonamide 2.180L**



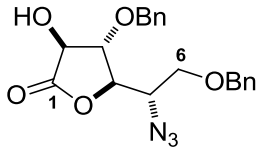

Palladium (10% on carbon, 20 mg) was added to a solution of the Boc-protected amide **2.189L** (48 mg, 0.102 mmol) in a 1:1 1,4-dioxane/2 M aqueous hydrochloric acid mixture (4 mL). The reaction vessel was evacuated and flushed with hydrogen and stirred for 16 h. The reaction mixture was filtered, the filtrate stirred at 45 °C for 2 h and concentrated *in vacuo*. $^1$H NMR indicated the removal of the benzyl ether and Boc-protecting groups. The crude residue was loaded onto a short column of Dowex® (50W-X8, $H^+$) and the resin washed with water. The product was liberated with 2 M aqueous ammonia and the ammoniacal fractions combined and concentrated *in vacuo* to afford the L-*ido* amide **2.180L** as a pale-yellow oil (14.5 mg, 75%); HRMS (ESI +ve): found 213.0843 [M+$Na^+$]; $C_7H_{14}N_2NaO_4$ requires 213.0846; $[\alpha]_D^{25}$ +44.3

(*c* 0.92, $CHCl_3$); $\nu_{max}$ (thin film): 1560 (s, C=O), 1646 (C=O), 3450 (br. s, NH/OH); $\delta_H$ ($D_2O$, 500 MHz): 2.66 (3H, s, $NHC\underline{H}_3$), 3.50 (1H, ddd, H5, $J_{5,4}$ 3.3, $J_{5,6'}$ 6.1, $J_{5,6}$ 6.8), 3.63 (1H, dd, H6, $J_{6,5}$ 6.8, $J_{6,6'}$ 11.4), 3.73 (1H, dd, H6', $J_{6',5}$ 6.1, $J_{6',6}$ 11.4), 4.06 (1H, d, H2, $J_{2,3}$ 4.5), 4.10 (1H, dd, H4, $J_{4,3}$ 1.0, $J_{4,5}$ 3.3), 4.26 (1H, dd, H3, $J_{3,4}$ 1.0, $J_{3,2}$ 4.5); $\delta_C$ ($D_2O$, 125 MHz): 26.2 ($NHCH_3$), 60.1 (C6), 62.0 (C5), 63.9 (C2), 77.0 (C4), 77.8 (C3), 172.6 (C1); LRMS (ESI +ve): 191 (100%, $M+H^+$).

Similar treatment of **methyl 2-*N*-(*tert*-butoxycarbonyl)-3,6-di-*O*-benzyl-2,5-dideoxy-2,5-imino-D-idonamide 2.189D** (36 mg, 0.08 mmol) in a suitably scaled procedure afforded **methyl 2,5-dideoxy-2,5-imino-D-idonamide 2.180D** (11 mg, 75%) as a yellow oil; $[\alpha]_D^{25}$ -46.7 (*c* 0.95, $H_2O$).

*2.4.3.7 Synthesis of talo-configured iminosugars*

**5-Azido-3,6-di-*O*-benzyl-5-deoxy-L-galactono-1,4-lactone 2.197L**




Trifluoromethanesulfonic anhydride (0.30 mL, 1.75 mmol) was added dropwise to a solution of the lactone **2.149L** (517 mg, 1.35 mmol) and pyridine (0.33 mL, 4.05 mmol) in dichloromethane (5 mL) at -40 °C. The reaction was stirred for 90 min, with the internal temperature rising to -25 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.38) and the formation of a major product ($R_f$ 0.71). The reaction was diluted with dichloromethane (150 mL), washed with 2 M aqueous hydrochloric acid (3 x 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the

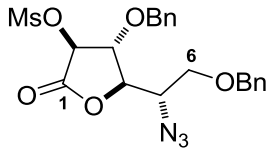
crude triflate **2.150L** as a yellow oil. The crude triflate **2.150L** was reacted on without further purification.

Sodium trifluoroacetate (370 mg, 2.70 mmol) was added portion-wise to a solution of the crude triflate **2.150L** in DMF (10 mL) at -30 $^{o}$C. The reaction was allowed to warm to RT and stirred for 20 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.71) and the formation of a major product ($R_f$ 0.50). The reaction mixture was diluted with ethyl acetate (150 mL), washed with an aqueous sodium bicarbonate solution (50 mL) and the aqueous phase extracted with ethyl acetate (3 x 80 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (49:1 to 1:1, cyclohexane/ethyl acetate) to afford the lactone **2.197L** (403 mg, 78% over two steps) as a pale yellow oil, which crystallised on standing to form a white solid; HRMS (ESI +ve): found 406.1364 [M+Na$^+$]; $C_{20}H_{21}N_3NaO_5$ requires 406.1373; m.p. 62-64 $^{o}$C; $[\alpha]_D^{25}$ +99.8 (*c* 1.25, $CH_3Cl$); $\nu_{max}$ (thin film): 1793 (s, C=O), 2104 (s, $N_3$), 3423 (br. s, OH); $\delta_H$ ($CD_3CN$, 400 MHz): 3.70 (1H, dd, H6, $J_{6,5}$ 8.3, $J_{6,6'}$ 10.1), 3.76 (1H, dd, H6', $J_{6',5}$ 4.3, $J_{6',6}$ 10.1), 3.83 (1H, a-dt, H5, $J_{5,4} = J_{5,6'}$ 3.8, $J_{5,6}$ 8.0), 4.19 (1H, a-t, H3, $J_{3,2} = J_{3,4}$ 7.6), 4.22 (1H, d, OH2, $J_{OH,2}$ 5.6), 4.25 (1H, dd, H4, $J_{4,5}$ 3.5, $J_{4,3}$ 7.8), 4.53 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 12.1), 4.56 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 12.1), 4.57 (1H, dd, H2, $J_{2,OH}$ 5.6, $J_{2,3}$ 7.6), 4.64 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 4.82 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 7.29-7.41 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz): 61.9 (C5), 70.5 (C6), 73.1, 74.0 (O$\underline{C}H_2$Ph), 74.8 (C2), 78.3 (C4), 81.8 (C3), 128.8, 129.1, 129.2, 129.5, 129.5 (Ar$\underline{C}$H), 138.8, 139.1 (Ar$\underline{C}$C), 174.2 (C1); LRMS (ESI +ve): 484 (18%, M+Na$^+$), 516 (100%, M+MeOH+Na$^+$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-D-talono-1,4-lactone 2.149D** (394 mg, 1.03 mmol) in a suitably scaled procedure afforded **5-azido-3,6-di-*O*-benzyl-5-deoxy-D-**

**galactono-1,4-lactone 2.197D** (284 mg, 72% over 2 steps) as a yellow oil: m.p. 62-64 °C; $[\alpha]_D^{25}$ -104.0 (*c* 1.40, $CHCl_3$).

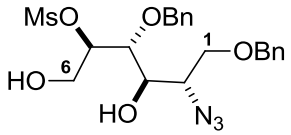
**5-Azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-galactono-1,4-lactone 2.198L**




Methanesulfonyl chloride (0.10 mL, 1.29 mmol) was added dropwise to a solution of the alcohol **2.197L** (330 mg, 0.861 mmol) in pyridine (4 mL) at 0 °C. The reaction mixture was allowed to warm to RT and stirred for 90 min, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.50) and the formation of a major product ($R_f$ 0.65). The reaction mixture was concentrated *in vacuo*, co-evaporated with toluene (3 x 10 mL) and the crude residue purified by flash chromatography (47:3 to 4:1, cyclohexane/ethyl acetate) to afford the mesylate **2.198L** (310 mg, 78%) as a clear oil; HRMS (ESI +ve): found 516.1414 [M+MeOH+$Na^+$]; $C_{22}H_{27}N_3NaO_8S$ requires 516.1411; $[\alpha]_D^{25}$ -99.9 (*c* 1.35, $CHCl_3$); $\nu_{max}$ (thin film): 1173 (s, $SO_2$), 1363 (s, $SO_2$), 1801 (s, C=O), 2107 (s, $N_3$); $\delta_H$ ($CD_3CN$, 400 MHz): 3.27 (3H, s, $SO_2CH_3$), 3.71 (1H, dd, H6, $J_{6,5}$ 8.1, $J_{6,6'}$ 10.1), 3.77 (1H, dd, H6', $J_{6',5}$ 4.3, $J_{6',6}$ 10.1), 3.86 (1H, ddd, H5, $J_{5,4}$ 3.3, $J_{5,6'}$ 4.3, $J_{5,6}$ 8.1), 4.43 (1H, dd, H4, $J_{4,5}$ 3.3, $J_{4,3}$ 7.6), 4.54 (1H, a-t, H3, $J_{3,2} = J_{3,4}$ 7.7), 4.55 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 12.1), 4.56 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 12.1), 4.65 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.4), 4.81 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.4), 5.56 (1H, d, H2, $J_{2,3}$ 7.8), 7.30-7.41 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz): 40.2 ($SO_2CH_3$), 61.2 (C5), 69.8 (C6), 70.3, 73.6 (O$\underline{C}H_2$Ph), 79.3 (C4), 79.4 (C3), 80.5 (C2), 128.8, 128.8, 129.4, 129.5, 129.6 (Ar$\underline{C}$H), 138.0, 139.0 (Ar$\underline{C}$C), 169.4 (C1); LRMS (ESI +ve): 484 (100%, M+$Na^+$), 516 (73%, M+MeOH+$Na^+$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-D-galactono-1,4-lactone 2.197D** (200 mg, 0.52 mmol) in a suitably scaled procedure afforded **5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-galactono-1,4-lactone 2.198D** (200 mg, 83%) as a pale yellow oil: $[\alpha]_D^{25}$ +105.8 (*c* 1.32, $CHCl_3$).

**2-Azido-1,4-di-*O*-benzyl-2-deoxy-5-*O*-methanesulfonyl-D-galactitol 2.199D**

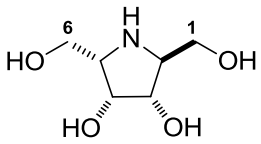



Sodium borohydride (80 mg, 2.11 mmol) was added portion-wise to a solution of the lactone **2.198L** (150 mg 0.325 mmol) in a 8:1 ethanol/1,4-dioxane mixture (4 mL) at -30 °C. The reaction was stirred for 90 min, with the internal temperature rising to -15 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the incomplete consumption of the starting material ($R_f$ 0.65) and the formation of a major product ($R_f$ 0.24). Additional sodium borohydride (80 mg, 2.11 mmol) was added at -30 °C and the reaction allowed to warm to -15 °C. After 4 h TLC analysis indicated the complete consumption of the starting material ($R_f$ 0.65) and the presence of the major product ($R_f$ 0.24). The reaction was neutralised with glacial acetic acid and concentrated *in vacuo*. The crude residue was dissolved with ethyl acetate (80 mL) and washed with an aqueous sodium bicarbonate solution (40 mL). The aqueous phase was extracted with ethyl acetate (2 x 80 mL), the organic fractions combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1 to 3:7, cyclohexane/ethyl acetate) to afford the diol **2.199D** (134 mg, 89%) as a white, crystalline solid; HRMS (ESI +ve): found 488.1461 [M+$Na^+$]; $C_{21}H_{27}N_3NaO_7S$ requires 488.1462; m.p. 80-81 °C; $[\alpha]_D^{25}$ +44.5 (*c* 0.97, $CHCl_3$); $\nu_{max}$ (thin film): 1169 (s, $SO_2$), 1333 (s, $SO_2$), 2102 (s, $N_3$), 3484 (br. s, OH); $\delta_H$ ($CD_3CN$, 400 MHz): 3.10 (3H, s, $SO_2CH_3$), 3.28 (1H, t, OH6, $J_{OH,6} = J_{OH,6'}$ 5.8),

3.42 (1H, d, OH4, $J_{OH,4}$ 6.3), 3.75-3.91 (7H, m, H1, H1', H2, H3, H4, H6, H6'), 4.55 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.9), 4.59 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.9), 4.62 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.1), 4.69 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.1), 4.89 (1H, ddd, H5, *J* 2.0, *J* 6.1, *J* 6.8), 7.29-7.39 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz): 38.9 ($SO_2\underline{C}H_3$), 61.5 (C2), 61.8 (C1), 70.7, 78.3 (C3, C4), 71.5 (C6), 73.9, 75.8 (O$\underline{C}H_2$Ph), 83.2 (C5), 128.8, 128.8, 129.0, 129.2, 129.5, 129.5 (Ar$\underline{C}$H), 139.0, 139.3 (Ar$\underline{C}$C); LRMS (ESI +ve): 488 (45%, M+$Na^+$), 953 (100%, 2M+$Na^+$); (ESI –ve): 929 (100%, [2M-H]$^-$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-galactono-1,4-lactone 2.198D** (100 mg, 0.22 mmol) in a suitably scaled procedure afforded **2-azido-1,4-di-*O*-benzyl-2-deoxy-5-*O*-methanesulfonyl-L-galactitol 2.199L** (64 mg, 62%) as a white crystalline solid: m.p. 80-81 $^oC$; $[\alpha]_D^{25}$ -52.2 (*c* 1.00, $CHCl_3$).

**2,5-Dideoxy-2,5-imino-L-altritol (L-DADP) 2.59L**



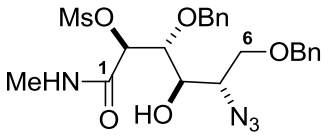

Palladium (10% on carbon, 54 mg) and sodium acetate (48 mg, 0.576 mmol) were added to a solution of the diol **2.199D** (134 mg, 0.29 mmol) in 1,4-dioxane (5 mL). The reaction flask was evacuated and flushed with hydrogen and the reaction stirred for 5 h, after which TLC analysis (99:1, ethyl acetate/triethylamine) indicated the complete consumption of the starting material ($R_f$ 0.24) and the formation of a major product ($R_f$ 0.08). LRMS also indicated the absence of a peak corresponding to the starting material (*m/z* 488 [M+$Na^+$]) and the formation of a peak corresponding to the cyclised dibenzylated intermediate **2.200L** (*m/z* 344 [M+$H^+$]). 2 M Aqueous hydrochloric acid (1.0 mL) was added, the reaction vessel evacuated and flushed with hydrogen

and the reaction stirred for 16 h. After which LRMS indicated the absence of the cyclised dibenzylated intermediate **2.200L** (*m/z* 344 [M+H$^+$]) and the formation a peak corresponding to the L-*altro* pyrrolidine L-DAPD **2.59L** (*m/z* 164 [M+H$^+$]). The reaction mixture was filtered (GF/B, glass microfibre) and concentrated *in vacuo*. The crude residue was loaded onto a short column of Dowex® (50W-X8, H$^+$) and the resin washed with water. The product was liberated with 2 M aqueous ammonia and the ammoniacal fractions combined and concentrated *in vacuo* to afford the L-*altro* pyrrolidine L-DADP **2.59L** (43 mg, 92%) as a yellowish oil; *this compound was previously synthesised from the diol **2.176L**, refer to pages 192-193 for experimental data.*

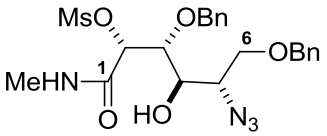
Similar treatment of **2-azido-1,4-di-*O*-benzyl-2-deoxy-5-*O*-methanesulfonyl-L-galactitol 2.199L** (50 mg, 0.11 mmol) in a suitably scaled procedure afforded **2,5-dideoxy-2,5-imino-D-altritol 2.59D** (16 mg, 94%) as a yellow oil; *refer to pages 192-193 for experimental data.*

**Methyl 5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-galactonamide 2.162L /**

**Methyl 5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-talonamide 2.161L**




**2.162L**



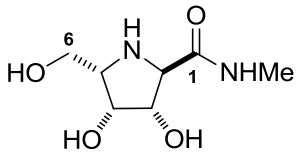

**2.161L**

Methylamine (33% in EtOH, 0.11 mL, 0.89 mmol) was added to a solution of the lactone **2.198L** (137 mg, 0.297 mmol) in 1,4-dioxane (2.5 mL) under argon. The reaction mixture was stirred for 16 h, after which TLC analysis (3:7, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.96) and the formation of a major ($R_f$ 0.64) and a minor product ($R_f$ 0.35). The reaction was concentrated *in vacuo* and the crude residue was purified by flash chromatography (7:3 to 11:9, cyclohexane/ethyl acetate) to afford the L-*galacto* amide

**2.162L** ($R_f$ 0.64, 133 mg, 91%) as a white crystalline solid, and the L-*talo* amide **2.161L** ($R_f$ 0.35, 7 mg, 5%) as a clear oil; *these compounds were previously synthesised from the lactone **2.153L**, refer to pages 177-178 for experimental data.*

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-galactono-1,4-lactone 2.198D** (80 mg, 0.17 mmol) in a suitably scaled procedure afforded **methyl 5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-galactonamide 2.162D** (72 mg, 85%) as a white crystalline solid and **methyl 5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-talonamide 2.161D** (8 mg, 9%) as a pale yellow oil; *refer to pages 177-178 for experimental data.*

**Methyl 2,5-dideoxy-2,5-imino-L-talonamide 2.181L**



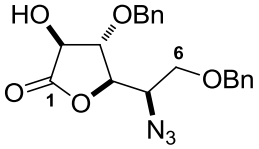

Palladium (10% on carbon, 10 mg) was added to a solution of the azide **2.162L** (22 mg, 0.04 mmol) and sodium acetate (16 mg, 0.20 mmol) in 1,4-dioxane (2 mL). The flask was evacuated and flushed with hydrogen and stirred for 6 h, after which TLC analysis (99:1, ethyl acetate/triethylamine) indicated the complete consumption of the starting material ($R_f$ 0.82) and the formation of a major product ($R_f$ 0.18). LRMS also indicated the absence of a peak corresponding to the starting material (*m/z* 515 [M+$Na^+$]) and the formation of the cyclised dibenzylated intermediate **2.201L** (*m/z* 371 [M+$H^+$]). 2 M Aqueous hydrochloric acid (0.4 mL) was added, the reaction vessel evacuated and flushed with hydrogen and the reaction stirred for 16 h, after which LRMS indicated the absence of the cyclised dibenzylated intermediate **2.201L** (*m/z* 371 [M+$H^+$]) and the formation of the L-*talo* amide **2.181L** (*m/z* 191 [M+$H^+$]). The reaction

mixture was filtered (GF/A, glass microfibre) and concentrated *in vacuo*. The crude residue loaded onto a short column of Dowex® (50W-X8, $H^+$) and the resin washed with water. The product was liberated with 2 M aqueous ammonia and the ammoniacal fractions combined and concentrated *in vacuo* to afford the L-*talo* amide **2.181L** (5.5 mg, 90%) as a yellow oil; HRMS (ESI +ve): found 191.1028 [M+$H^+$]; $C_7H_{15}N_2O_4$ requires 191.1026; $[\alpha]_D^{25}$ -5.0 (*c* 0.28, $H_2O$); $\nu_{max}$ (thin film): 1558 (s, C=O), 1648 (s, C=O), 3335 (br. s, OH, NH); $\delta_H$ ($D_2O$, 500 MHz): 2.66 (3H, s, NHC$\underline{H}_3$), 3.30 (1H, a-td, H5, $J_{5,4}$ 4.1, $J_{5,6} = J_{5,6'}$ 6.6), 3.44 (1H, d. H2, $J_{2,3}$ 8.2), 3.52 (1H, dd, H6, $J_{6,5}$ 6.6, $J_{6,6'}$ 11.0), 3.67 (1H, dd, H6', $J_{6',5}$ 6.6, $J_{6',6}$ 11.0), 4.05 (1H, dd, H3, $J_{3,4}$ 4.1, $J_{3,2}$ 8.2), 4.08 (1H, a-t, H4, $J_{4,3} = J_{4,5}$ 4.1); $\delta_C$ ($D_2O$, 125 MHz): 26.4 ($NHCH_3$), 61.0 (C5), 61.0 (C6), 63.9 (C2), 72.9 (C4), 77.1 (C3), 175.6 (C1); LRMS (ESI +ve): 191 (100%, M+$H^+$), 213 (55%, M+$Na^+$).

Similar treatment of **methyl 5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-galactonamide 2.162D** (23 mg, 0.05 mmol) in a suitably scaled procedure afforded **methyl 2,5-dideoxy-2,5-imino-D-talonamide 2.181D** (8 mg, 90%) as a white crystalline solid: $[\alpha]_D^{25}$ +6.9 (*c* 0.30, $H_2O$).

*2.4.3.8 Synthesis of allo-configured iminosugars*

**5-Azido-3,6-di-*O*-benzyl-5-deoxy-D-altrono-1,4-lactone 2.202D**



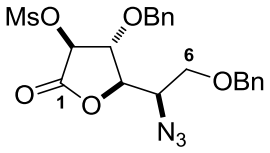

Trifluoromethanesulfonic anhydride (2.9 mL, 17.3 mmol) was added dropwise to a solution of the lactone **2.171D** (5.1 g, 13.3 mmol) and pyridine (3.2 mL, 39.9 mmol) in dichloromethane (60 mL) at -40 °C. The reaction was stirred for 1 h, with the internal temperature rising to -25 °C,

after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.32) and the formation of a major product ($R_f$ 0.63). The reaction was diluted with dichloromethane (250 mL), washed with 2 M aqueous hydrochloric acid (3 x 250 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude triflate **2.172D**. The crude triflate **2.172D** was reacted on without further purification.

Sodium trifluoroacetate (3.62 g, 26.6 mmol) was added portion-wise to a solution of the crude triflate **2.172D** in DMF (30 mL) at -30 $^oC$. The reaction was allowed to warm to RT and stirred for 16 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.63) and the formation of a major product ($R_f$ 0.45). The reaction mixture was diluted with ethyl acetate (250 mL) and washed with an aqueous sodium bicarbonate solution (150 mL). The aqueous phase was extracted with ethyl acetate (3 x 250 mL), the organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (49:1 to 1:1, cyclohexane/ethyl acetate) to afford the lactone **2.202D** (3.80 g, 75%) as a white crystalline solid; HRMS (ESI +ve): found 406.1369 [M+$Na^+$]; $C_{20}H_{21}N_3NaO_5$ requires 406.1373; m.p. 121-123 °C; $[\alpha]_D^{25}$ +37.1 (*c* 1.97, $CHCl_3$); $\nu_{max}$ (thin film): 1799 (s, C=O), 2115 (s, $N_3$), 3175 (br. s, OH); $\delta_H$ ($CD_3CN$, 400 MHz): 3.54 (1H, dd, H6, $J_{6,5}$ 8.1, $J_{6,6'}$ 10.2), 3.65 (1H, dd, H6', $J_{6',5}$ 4.0, $J_{6',6}$ 10.2), 4.09 (1H, a-dt, H5, $J_{5,4} = J_{5,6'}$ 4.0, $J_{5,6}$ 8.1), 4.19 (1H, a-t, H3, $J_{3,2} = J_{3,4}$ 7.6), 4.24 (1H, br. d, OH2, $J_{OH,2}$ 6.1), 4.33 (1H, dd, H4, $J_{4,5}$ 4.2, $J_{4,3}$ 7.5), 4.51 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 12.1), 4.54 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 12.1), 4.59 (1H, dd, H2, $J_{2,OH}$ 6.1, $J_{2,3}$ 7.6), 4.61 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 4.79 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.6), 7.29-7.38 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz): 62.7 (C5), 69.8 (C6), 72.9, 73.9 (O$\underline{C}H_2$Ph), 75.1 (C2), 78.1 (C4), 81.2 (C3), 128.8, 129.0, 129.3, 129.5 (Ar$\underline{C}$H), 138.6, 139.1 (Ar$\underline{C}$C), 174.4 (C1); LRMS (ESI +ve): 406 (100%, M+$Na^+$), 789 (60%, 2M+$Na^+$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-L-altrono-1,4-lactone 2.171L** (1.02 g, 2.66 mmol) in a suitably scaled procedure afforded **5-azido-3,6-di-*O*-benzyl-5-deoxy-L-altrono-1,4-lactone 2.202L** (750 mg, 74%) as a yellow crystalline solid; m.p. 120-122 $^{o}$C; $[\alpha]_D^{25}$ -31.9 (*c* 2.00, $CHCl_3$).

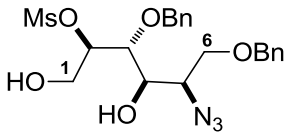
**5-Azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-altrono-1,4-lactone 2.203D**




Methanesulfonyl chloride (1.2 mL, 15.6 mmol) was added dropwise to a solution of the lactone **2.202D** (3.99 g, 10.4 mmol) in pyridine (40 mL) at 0 $^{o}$C. The reaction was allowed to warm to RT and stirred for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.45) and the formation of a major product ($R_f$ 0.60). The reaction mixture was concentrated *in vacuo* and co-evaporated with toluene (2 x 25 mL) and dichloromethane (2 x 25 mL). The crude residue was purified by flash chromatography (47:3 to 3:2, cyclohexane/ethyl acetate) to afford the mesylate **2.203D** (4.04 g, 84%) as a clear oil; HRMS (ESI +ve): found 516.1406 [M+MeOH+$Na^+$]; $C_{22}H_{27}N_3NaO_8S$ requires 516.1411; $[\alpha]_D^{25}$ +40.5 (*c* 2.40, $CHCl_3$); $\nu_{max}$ (thin film): 1178 (s, $SO_2$), 1369 (s, $SO_2$), 1803 (s, C=O), 2110 (s, $N_3$); $\delta_H$ ($CD_3CN$, 400 MHz): 3.29 (3H, s, $SO_2CH_3$), 3.56 (1H, dd, H6, $J_{6,5}$ 7.8, $J_{6,6'}$ 10.2), 3.67 (1H, dd, H6', $J_{6',5}$ 4.5, $J_{6',6}$ 10.2), 4.10 (1H, a-dt, H5, $J_{5,4} = J_{5,6'}$ 4.0, $J_{5,6}$ 7.8), 4.48-4.56 (4H, m, H3, H4, 2 x O<u>C</u>$H_2$Ph), 4.61 (1H, d, O<u>C</u>$H_2$Ph, $J_{gem}$ 11.0), 4.78 (1H, d, O<u>C</u>$H_2$Ph, $J_{gem}$ 11.0), 5.59 (1H, d, H2, $J_{2,3}$ 6.8), 7.31-7.40 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz): 40.3 ($SO_2CH_3$), 62.2 (C5), 69.6 (C6), 73.4, 74.0 (O<u>C</u>$H_2$Ph), 79.0, 79.2 (C3, C4), 81.0 (C2), 128.8, 128.8, 129.3, 129.5, 129.5, 129.6 (Ar<u>C</u>H), 137.8, 139.0 (Ar<u>C</u>C), 169.6 (C1); LRMS (ESI +ve): 484 (56%, M+$Na^+$), 516 (100%, M+MeOH+$Na^+$), 945 (48%, 2M+$Na^+$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-L-altrono-1,4-lactone 2.202L** (620 mg, 1.62 mmol) in a suitably scaled procedure afforded **5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-altrono-1,4-lactone 2.203L** (664 mg, 89%) as a clear oil: $[\alpha]_D^{25}$ -35.6 (*c* 2.05, $CHCl_3$).

**5-Azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-altritol 2.204D**

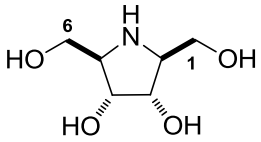



Sodium borohydride (205 mg, 5.42 mmol) was added portion-wise to a solution of the mesylate **2.203D** (500 mg, 1.08 mmol) in a 8:1 ethanol/1,4-dioxane mixture (24 mL) at -30 °C. The reaction was stirred for 1 h, with the internal temperature rising to -25 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the incomplete consumption of the starting material ($R_f$ 0.60) and the formation of a major product ($R_f$ 0.18). Additional sodium borohydride (205 mg, 5.42 mmol) was added at -30 °C and the reaction allowed to warm to -15 °C. After 3 h TLC analysis indicated the complete consumption of the starting material ($R_f$ 0.60) and the presence of the major product ($R_f$ 0.18). The reaction was neutralised with glacial acetic acid and concentrated *in vacuo*. The crude residue was dissolved with ethyl acetate (200 mL) and washed with an aqueous sodium bicarbonate solution (75 mL). The aqueous phase was extracted with ethyl acetate (2 × 100 mL), the organic fractions combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1 to 7:3, cyclohexane/ethyl acetate) to afford the diol **2.204D** (468 mg, 93%) as a pale yellow oil; HRMS (ESI +ve): found 488.1463 [M+$Na^+$]; $C_{21}H_{27}N_3NaO_7S$ requires 488.1462; $[\alpha]_D^{25}$ +5.7 (*c* 0.91, $CHCl_3$); $\nu_{max}$ (thin film): 1171 (s, $SO_2$), 1334 (s, $SO_2$), 2100 (s, $N_3$), 3500 (br. s, OH); $\delta_H$ ($CD_3CN$, 400 MHz): 3.07 (3H, s, $SO_2CH_3$), 3.67 (1H, dd, H1 or H6, *J* 7.7, *J* 10.2), 3.77-3.89

(8H, m, H1 or H6, H1', H3, H4, H5, H6', OH1, OH4), 4.50 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 12.1), 4.54 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 12.1), 4.60 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.1), 4.64 (1H, d, OC$\underline{H}_2$Ph, $J_{gem}$ 11.1), 4.85 (1H, td, H2, *J* 3.4, *J* 5.5, *J* 5.5), 7.29-7.38 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz): 38.9 ($SO_2CH_3$), 61.8 (C1 or C6), 64.0 (C5), 70.7 (C1 or C6), 71.5 (C3 or C4), 73.9 , 75.0 (O$\underline{C}H_2$Ph), 78.8 (C3 or C4), 83.7 (C2), 128.7, 128.8, 128.9, 129.2, 129.4, 129.4 (Ar$\underline{C}$H), 139.0, 139.3 (Ar$\underline{C}$C); LRMS (ESI +ve): 488 (85%, M+$Na^+$), 953 (100%, 2M+$Na^+$); (ESI –ve): 929 (100%, $[2M-H]^-$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-altrono-1,4-lactone 2.203L** (310 mg, 0.67 mmol) in a suitably scaled procedure afforded **5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-altritol 2.204L** (210 mg, 67%) as a pale yellow oil; $[\alpha]_D^{25}$ –7.1 (*c* 1.05, $CHCl_3$).

**2,5-Dideoxy-2,5-imino-allitol 2.58**

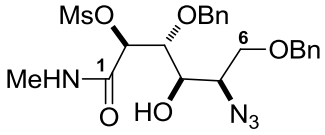



Palladium (10% on carbon, 180 mg) and sodium acetate (160 mg, 1.94 mmol) were added to a solution of the diol **2.204D** (450 mg, 0.97 mmol) in 1,4-dioxane (16 mL). The reaction vessel was evacuated and flushed with hydrogen. The reaction was stirred at RT for 4 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.38) and the formation of a single product (baseline). LRMS also indicated the absence of a peak corresponding to the starting material (*m/z* 488 [M+$Na^+$]) and the presence of a peak corresponding to the cyclised dibenzylated intermediate **2.205D** (*m/z* 344 [M+$H^+$]). 2 M Aqueous hydrochloric acid (4 mL) was added, the reaction vessel evacuated and flushed with

hydrogen and the reaction mixture stirred for 16 h, after which LRMS indicated the absence of a peak corresponding to the cyclised dibenzylated intermediate **2.205D** (*m/z* 344 [M+H$^+$]) and the presence of a peak corresponding to the pyrrolidine **2.58** (*m/z* 164 [M+H$^+$]). The reaction was filtered (GF/B, glass microfibre) and concentrated *in vacuo*. The crude residue was loaded onto a short column of Dowex® (50W-X8, H$^+$) and the resin washed with waster. The product was liberated with 2 M aqueous ammonia and the ammoniacal fractions were combined and concentrated *in vacuo* to afford the *meso-allo* pyrrolidine **2.58** (150 mg, 95%) as a colourless oil; HRMS (ESI +ve): found 164.0919 [M+H$^+$]; $C_6H_{14}NO_4$ requires 164.0917; $[\alpha]_D^{25}$ 0.0 (*c* 1.00, $H_2O$) [Lit.[92] $[\alpha]_D^{20}$ +39.2 (*c* 2.0, $H_2O$)]; $\nu_{max}$ (thin film): 3450 (br. s, OH/NH); $\delta_H$ ($D_2O$, 400 MHz): 3.61 (1H, a-q, H2, $J_{2,1} = J_{2,1'} = J_{2,3}$ 4.9), 3.73 (1H, dd, H1, $J_{1,2}$ 5.8, $J_{1,1'}$ 12.4), 3.82 (1H, dd, H1', $J_{1',2}$ 4.0, $J_{1',1}$ 12.4), 4.11 (1H, d, H3, $J_{3,2}$ 4.0); $\delta_C$ ($D_2O$, 100 MHz): 58.5 (C1), 64.5 (C2), 71.0 (C3); LRMS (ESI +ve): 164 (100%, M+H$^+$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-altritol 2.204L** (190 mg, 0.41 mmol) in a suitably scaled procedure afforded **2,5-dideoxy-2,5-imino-allitol 2.58** (63 mg, 94%) as a clear oil; $[\alpha]_D^{25}$ 0.0 (*c* 1.00, $H_2O$).

**Methyl 5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-D-altronamide 2.206D**

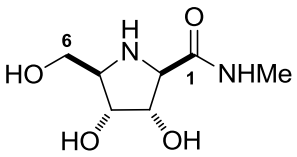



Methylamine (33% in ethanol, 2.75 mL, 22.3 mmol) was added to a solution of the lactone **2.203D** (3.43 g, 7.43 mmol) in 1,4-dioxane (75 mL) at RT. The reaction was stirred for 18 h, after which TLC analysis (3:1, toluene/acetone) indicated complete consumption of the starting material ($R_f$ 0.80) and the formation of a major product ($R_f$ 0.37). The reaction mixture was

concentrated *in vacuo* and the residue purified by flash chromatography (7:3 to 13:7, cyclohexane/ethyl acetate) to afford the amide **2.206D** (3.31 g, 91%) as a white crystalline solid; HRMS (ESI +ve): found 515.1570 [M+$Na^+$]; $C_{22}H_{28}N_4NaO_7S$ requires 515.1571; m.p. 86-88 °C; $[\alpha]_D^{25}$ -1.50 (*c* 1.72, $CHCl_3$); $\nu_{max}$ (thin film): 1176 (s, $SO_2$), 1360 (s, $SO_2$), 1544 (s, C=O), 1666 (s, C=O), 2101 (s, $N_3$), 3402 (br. s, OH); $\delta_H$ ($CD_3CN$, 400 MHz): 2.77 (3H, d, NHC<u>H</u>$_3$, $J_{H,NH}$ 4.8), 3.16 (3H, s, $SO_2CH_3$), 3.63 (1H, dd, H6, $J_{6,5}$ 7.7, $J_{6,6'}$ 10.4), 3.69 (1H, dd, H6', $J_{6',5}$ 3.8, $J_{6',6}$ 10.4), 3.71 (1H, d, OH4, $J_{OH,4}$ 6.6), 3.80 (1H, ddd, H4, $J_{4,5}$ 3.0, $J_{4,OH}$ 6.6, $J_{4,3}$ 9.3), 3.87 (1H, a-dt, H5, $J_{5,4} = J_{5,6'}$ 3.5, $J_{5,6}$ 7.7), 4.05 (1H, dd, H3, $J_{3,2}$ 1.8, $J_{3,4}$ 9.3), 4.43 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 11.1), 4.46 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 11.1), 4.48 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 12.0), 4.51 (1H, d, OC<u>H</u>$_2$Ph, $J_{gem}$ 12.0), 5.12 (1H, d, H2, $J_{2,3}$ 1.8), 7.05 (1H, br. q, N<u>H</u>$CH_3$, $J_{NH,H}$ 4.8), 7.24-7.38 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz): 26.5 ($NHCH_3$), 38.8 ($SO_2CH_3$), 64.6 (C5), 70.4 (C6), 71.0 (C4), 73.9, 74.9 (O<u>C</u>$H_2$Ph), 79.2 (C2), 80.0 (C3), 128.8, 128.8, 129.0, 129.4, 129.5 (Ar<u>C</u>H), 138.5, 139.2 (Ar<u>C</u>C), 169.0 (C1); LRMS (ESI +ve): 493 (16%, M+$H^+$), 515 (100%, M+$Na^+$); (ESI –ve): 491 (100%, [M-H]$^-$), 427 (65%, M+$^{35}Cl^-$), 429 (25%, M+$^{37}Cl^-$), 983 (45%, [2M-H]$^-$).

Similar treatment of **5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-altrono-1,4-lactone 2.203L** (320 mg, 0.69 mmol) in a suitably scaled procedure afforded **methyl 5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-altronamide 2.206L** (310 mg, 91%) as a white crystalline solid; m.p. 85-87 °C; $[\alpha]_D^{25}$ +2.4 (*c* 1.60, $CHCl_3$).

**Methyl 2,5-dideoxy-2,5-imino-D-allonamide 2.182D**




Palladium (10% on carbon, 650 mg) and sodium acetate (1.08 g, 13.21 mmol) were added to a solution of the amide **2.206D** (3.25 g, 6.61 mmol) in 1,4-dioxane (65 mL) at RT. The flask was evacuated and flushed with hydrogen and stirred for 3.5 h, after which TLC analysis (1:1, toluene/ethyl acetate) indicated the complete consumption of starting material ($R_f$ 0.70) and the formation of a major product ($R_f$ 0.28). 2 M Aqueous hydrochloric acid (13 mL) was added to the reaction mixture and the flask evacuated and flushed with hydrogen. The reaction mixture was stirred for 24 h, after which LRMS indicated the absence of a peak corresponding to cyclised dibenzylated intermediate **2.207D** (*m/z* 371 [M+H$^+$]) and the presence of a peak corresponding to the D-*allo* amide **2.182D** (*m/z* 191 [M+H$^+$]). The reaction was filtered (GF/B, glass microfibre) and the filtrate concentrated *in vacuo*. The crude residue was loaded onto a short column of Dowex® (50W-X8, H$^+$) and the resin washed with water. The product was liberated with 2 M aqueous ammonia and the ammoniacal fractions were combined and concentrated *in vacuo* to afford the D-*allo* amide **2.182D** (1.15 g, 91%) as a yellow oil; HRMS (ESI +ve): found 213.0842 [M+Na$^+$]; $C_7H_{14}N_2NaO_4$ requires 213.0846; $[\alpha]_D^{25}$ +14.6 (*c* 0.27, $H_2O$); $\nu_{max}$ (thin film): 1543 (s, C=O), 1643 (s, C=O), 3272 (br. s, OH/NH); $\delta_H$ ($D_2O$, 400 MHz): 2.66 (3H, s, NHC$\underline{H}_3$), 3.31 (1H, a-td, H5, $J_{5,6'}$ 4.0, $J_{5,4} = J_{5,6}$ 6.1), 3.58 (1H, dd, H6, $J_{6,5}$ 5.6, $J_{6,6'}$ 12.1), 3.69 (1H, dd, H6', $J_{6',5}$ 4.0, $J_{6',6}$ 12.1), 3.74 (1H, d, H2, $J_{2,3}$ 4.3), 3.84 (1H, dd, H4, $J_{4,3}$ 4.7, $J_{4,5}$ 6.7), 4.07 (1H, a-t, H3, $J_{3,2} = J_{3,4}$ 4.5); $\delta_C$ ($D_2O$, 100 MHz): 26.4 (NHC$\underline{H}_3$), 61.2 (C6), 63.3 (C5), 64.9 (C2), 72.0 (C4), 75.1 (C3), 172.9 (C1); LRMS (ESI +ve): 191 (100%, M+H$^+$).

Similar treatment of **methyl 5-azido-3,6-di-*O*-benzyl-5-deoxy-2-*O*-methanesulfonyl-L-altronamide 2.206L** (286 mg, 0.58 mmol) in a suitably scaled procedure afforded

**methyl 2,5-dideoxy-2,5-imino-L-allonamide 2.182L** (101 mg, 92%) as a pale yellow oil; $[\alpha]_D^{25}$ -17.3 (*c* 0.33, $H_2O$).

## 2.5 References


1. Bashyal, B. P.; Chow, H. F.; Fleet, G. W. J. *Tetrahedron Lett.* **1986**, *27*, 3205-3208.
2. Bashyal, B. P.; Chow, H. F.; Fellows, L. E.; Fleet, G. W. J. *Tetrahedron*, **1987**, *43*, 415-22.
3. Yagi, M.; Kouno, T.; Aoyagi, Y.; Murai, H. *J. Agr. Chem. Soc. Jpn*. **1976**, *50*, 571-572.
4. Fellows, L. E.; Bell, E. A.; Lynn, D. G.; Pilkiewicz, F.; Miura, I.; Nakanishi, K. *J. Chem. Soc. Chem. Commun.* **1979**, *22*, 977-978.
5. Asano, N.; Yasuda, K.; Kizu, H.; Kato, A.; Fan, J.-Q.; Nash, R. J.; Fleet, G. W. J.; Molyneux, R. J. *Eur. J. Biochem.* **2001**, *268*, 35-41.
6. Asano, N.; Ikeda, K.; Yu, L.; Kato, A.; Takebayashi, K.; Adachi, I.; Kato, I.; Ouchi, H.; Takahata, H.; Fleet, G. W. J. *Tetrahedron: Asymmetry*, **2005**, *16*, 223-229.
7. Takahata, H.; Banba, Y.; Ouchi, H.; Nemoto, H. *Org. Lett.* **2003**, *5*, 2527-2529.
8. Takahata, H.; Banba, Y.; Sasatani, M.; Nemoto, H.; Kato, A.; Adachi, I. *Tetrahedron* **2004**, *60*, 8199-8205.
9. Hashimoto, H.; Hayakawa, M. *Chem. Lett.* **1989**, 1881-1884.
10. van den Nieuwendijk, A. M. C. H.; van den Berg, R. J. B. H. N.; Ruben, M.; Witte, M. D.; Brussee, J.; Boot, R. G.; van der Marel, G. A.; Aerts, J. M. F. G.; Overkleeft, H. S. *Eur. J. Org. Chem.* **2012**, 3437-3446.
11. Liu, J.; Numa, M. M. D.; Liu, H.; Huang, S.-J.; Sears, P.; Shikhman, A. R.; Wong, C.-H. *J. Org. Chem.* **2004**, *69*, 6273-6283.
12. Reese, T. A.; Liang, H.-E.; Tager, A. M.; Luster, A. D.; Van Rooijen, N.; Voehringer, D.; Locksley, R. M. *Nature*, **2007**, *447*, 92-96.
13. Liu, F.; Iqbal, K.; Grundke-Iqbal, I.; Hart, G. W.; Gong, C.-X. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 10804-10809.
14. Fleet, G. W. J.; Smith, P. W.; Nash, R. J.; Fellows, L. E.; Parekh, R. B.; Rademacher, T. W. *Chem. Lett.* **1986**, 1051-1054.
15. Fleet, G. W. J.; Fellows, L. E.; Smith, P. W. *Tetrahedron* **1987**, *43*, 979-990.
16. Boeshagen, H.; Heiker, F.-R.; Schueller, A. M. *Carbohydr. Res.* **1987**, *164*, 141-148.
17. Aoyama, T.; Naganawa, H.; Suda, H.; Uotani, K.; Aoyagi, T.; Takeuchi, T. *J. Antibiot.* **1992**, *45*, 1557-1558.
18. Tatsuta, K.; Miura, S.; Ohta, S.; Gunji, H. *J. Antibiot.* **1995**, *48*, 286-288.
19. Dorfmueller, H. C.; Borodkin, V. S.; Schimpl, M.; van Aalten, D. M. F. *Biochem. J.* **2009**, *420*, 221-227.
20. Shilvock, J. P.; Nash, R. J.; Lloyd, J. D.; Winters, A. L.; Asano, N.; Fleet, G. W. J. *Tetrahedron: Asymmetry*, **1998**, *9*, 3505-3516.
21. Shanmugasundaram, B.; Debowski, A. W.; Dennis, R. J.; Davies, G. J.; Vocadlo, D. J.; Vasella, A. *Chem. Commun.* **2006**, 4372-4374.
22. Knapp, S.; Vocadlo, D.; Gao, Z.; Kirk, B.; Lou, J.; Withers, S. G. *J. Am. Chem. Soc.* **1996**, *118*, 6804-6805.
23. Shitara, E.; Nishimura, Y.; Kojima, F.; Takeuchi, T. *J. Antibiot.* **1999**, *52*, 348-350.
24. van den Berg, R. J. B. H. N.; Donker-Koopman, W.; van Boom, J. H.; Aerts, H. M. F. G.; Noort, D. *Bioorg. Med. Chem.* **2004**, *12*, 891-902.
25. Rountree, J. S. S.; Butters, T. D.; Wormald, M. R.; Dwek, R. A.; Asano, N.; Ikeda, K.; Evinson, E. L.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron Lett.* **2007**, *48*, 4287-4291.
26. Liu, J.; Shikhman, A. R.; Lotz, M. K.; Wong, C. H. *Chem. Biol.* **2001**, *8*, 701-711.
27. Usuki, H.; Toyo-oka, M.; Kanzaki, H.; Okuda, T.; Nitoda, T. *Bioorg. Med. Chem.* **2009**, *17*, 7248-7253.
28. Li, H.; Marcelo, F.; Bello, C.; Vogel, P.; Butters, T. D.; Rauter, A. P.; Zhang, Y.; Sollogoub, M.; Bleriot, Y. *Bioorg. Med. Chem.* **2009**, *17*, 5598-5604.
29. Nishimura, Y.; Satoh, T.; Kudo, T.; Kondo, S.; Takeuchi, T. *Bioorg. Med. Chem.* **1996**, *4*, 91-96.
30. Saotome, C.; Wong, C.-H.; Kanie, O. *Chem. Biol.* **2001**, *8*, 1061-1070.
31. Hu, X.-G.; Bartholomew, B.; Nash, R. J.; Wilson, F. X.; Fleet, G. W. J.; Nakagawa, S.; Kato, A.; Jia, Y.-M.; van Well, R.; Yu, C.-Y. *Org. Lett.* **2010**, *12*, 2562-2565.
32. Kiso, M.; Kitagawa, M.; Ishida, H.; Hasegawa, A. *J. Carbohydr. Chem.* **1991**, *10*, 25-45.
33. Kappes, E.; Legler, G. *J. Carbohydr. Chem.* **1989**, *8*, 371-378.

34. Ho, C.-W.; Popat, S. D.; Liu, T.-W.; Tsai, K.-C.; Ho, M.-J.; Chen, W.-H.; Yang, A.-S.; Lin, C.-H. *ACS Chem. Biol.* **2010**, *5*, 489-497.
35. Gradnig, G.; Legler, G.; Stuetz, A. E. *Carbohydr. Res.* **1996**, *287*, 49-57.
36. Kajimoto, T.; Liu, K. K.-C.; Pederson, R. L.; Zhong, Z.; Ichikawa, Y.; Porco Jr., J. A.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6187-6196.
37. Schueller, A. M.; Heiker, F. R. *Carbohydr. Res.* **1990**, *203*, 308-313.
38. Kang, S. H.; Ryu, D. H. *Tetrahedron Lett.* **1997**, *38*, 607-610.
39. Best, D.; Chairatana, P.; Glawar, A. F. G.; Crabtree, E.; Butters, T. D.; Wilson, F. X.; Yu, C.-Y.; Wang, W.-B.; Jia, Y.-M.; Adachi, I.; Kato, A.; Fleet, G. W. J. *Tetrahedron Lett.* **2010**, *51*, 2222-2224.
40. Bashyal, B. P.; Chow, H.-F.; Fleet, G. W. J. *Tetrahedron* **1987**, *43*, 423-430.
41. Winans, K. A.; King, D. S.; Rao, V. R.; Bertozzi, C. R. *Biochemistry*, **1999**, *38*, 11700-11710.
42. Campo, V. L.; Carvalho, I.; Allman, S.; Davis, B. G.; Field, R. A. *Org. Biomol. Chem.* **2007**, *5*, 2645-2657.
43. Glawar, A. F. G.; Best, D.; Ayers, B. J.; Miyauchi, S.; Nakagawa, S.; Aguilar-Moncayo, M.; García Fernández, J. M.; Ortiz Mellet, C.; Crabtree, E. V.; Butters, T. D.; Wilson, F. X.; Kato, A.; Fleet, G. W. J. *Chem. Eur. J.* **2012**, *18*, 9341-9359.
44. Kato, A.; Kato, N.; Kano, E.; Adachi, I.; Ikeda, K.; Yu, L.; Okamoto, T.; Banba, Y.; Ouchi, H.; Takahata, H.; Asano, N. *J. Med. Chem.* **2005**, *48*, 2036-2044.
45. McNaught, A. D. *Pure Appl. Chem.* **1996**, *68*, 1919-2008.
46. Welter, A.; Jadot, J.; Dardenne, G.; Marlier, M.; Casimir, J. *Phytochemistry*, **1976**, *15*, 747-749.
47. Best, D.; Wang, C.; Weymouth-Wilson, A. C.; Clarkson, R. A.; Wilson, F. X.; Nash, R. J.; Miyauchi, S.; Kato, A.; Fleet, G. W. J. *Tetrahedron: Asymmetry*, **2010**, *21*, 311-319.
48. Asano, N.; Yamauchi, T.; Kagamifuchi, K.; Shimizu, N.; Takahashi, S.; Takatsuka, H.; Ikeda, K.; Kizu, H.; Chuakul, W.; Kettawan, A.; Okamoto, T. *J. Nat. Prod.* **2005**, *68*, 1238-1242.
49. Kato, A.; Yamashita, Y.; Nakagawa, S.; Koike, Y.; Adachi, I.; Hollinshead, J.; Nash, R. J.; Ikeda, K.; Asano, N. *Bioorg. Med. Chem.* **2010**, *18*, 3790-3794.
50. Minami, Y.; Kuriyama, C.; Ikeda, K.; Kato, A.; Takebayashi, K.; Adachi, I.; Fleet, G. W. J.; Kettawan, A.; Okamoto, T.; Asano, N. *Bioorg. Med. Chem.* **2008**, *16*, 2734-2740.
51. Malle, B. M.; Lundt, I.; Wrodnigg, T. M. *Org. Biomol. Chem.* **2008**, *6*, 1779-1786.
52. Lee, R. E.; Smith, M. D.; Nash, R. J.; Griffiths, R. C.; McNeil, M.; Grewal, R. K.; Yan, W.; Besra, G. S.; Brennan, P. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1997**, *38*, 6733-6736.
53. Long, D. D.; Frederiksen, S. M.; Marquess, D. G.; Lane, A. L.; Watkin, D. J.; Winkler, D. A.; Fleet, G. W. J. *Tetrahedron Lett.* **1998**, *39*, 6091-6094.
54. Park, K. H.; Yoon, Y. J.; Lee, S. G. *Tetrahedron Lett.* **1994**, *35*, 9737-9740.
55. Yu, C.-Y.; Asano, N.; Ikeda, K.; Wang, M.-X.; Butters, T. D.; Wormald, M. R.; Dwek, R. A.; Winters, A. L.; Nash, R. J.; Fleet, G. W. J. *Chem Commun.* **2004,** 1936-1937.
56. Kim, I. S.; Kim, S. J.; Lee, J. K.; Li, Q. R.; Jung, Y. H. *Carbohydr. Res.* **2007**, *342*, 1502-1509.
57. Blanco, O.; Pato, C.; Ruiz, M.; Ojea, V. *Org. Biomol. Chem.* **2009**, *7*, 2310-2321.
58. Blanco, O.; Pato, C.; Ruiz, M.; Ojea, V. *Org. Biomol. Chem.* **2008**, *6*, 3967-3969.
59. Kumar, V.; Ramesh, N. G. *Tetrahedron*, **2006**, *62*, 1877-1885.
60. Singh, S.; Han, H. *Tetrahedron Lett.* **2004**, *45*, 6349-6352.
61. Fleet, G. W. J.; Smith, P. W. *Tetrahedron*, **1987**, *43*, 971-978.
62. Kondo, Y.; Suzuki, N.; Takahashi, M.; Kumamoto, T.; Masu, H.; Ishikawa, T. *J. Org. Chem.* **2012**, *77*, 7988-7999.
63. Chorghade, M. S.; Cseke, C. *Pure Appl. Chem.* **1994**, *66*, 2211-2214.
64. Chorghade, M. S.; Cseke, C. T.; Liu, P. S. *Tetrahedron: Asymmetry*, **1994**, *5*, 2251-2254.
65. Chikkanna, D.; Han, H. *Synlett*, **2004**, *13*, 2311-2314.
66. Card, P. J.; Hitz, W. D. *J. Org. Chem.* **1985**, *50*, 891-893.
67. Hung, R. R.; Straub, J. A.; Whitesides, G. M. *J. Org. Chem.* **1991**, *56*, 3849-3855.
68. Legler, G.; Korth, A.; Berger, A.; Ekhart, C.; Gradnig, G.; Stuetz, A. E. *Carbohydr. Res.* **1993**, *250*, 67-77.
69. García-Moreno, M. I.; Aguilar, M.; Mellet, C. O.; García Fernández, J. M. *Org. Lett.* **2006**, *8*, 297-299.
70. Tatibouët, A.; Lefoix, M.; Nadolny, J.; Martin, O. R.; Rollin, P.; Yang, J.; Holman, G. D. *Carbohydr. Res.* **2001**, *333*, 327-334.
71. Sugiyama, M.; Hong, Z.; Whalen, L. J.; Greenberg, W. A.; Wong, C.-H. *Adv. Synth. Catal.* **2006**, *348*, 2555-2559.
72. Kajimoto, T.; Chen, L.; Liu, K. K.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6678-6680.
73. Liu, K. K.-C.; Kajimoto, T.; Chen, L.; Zhong, Z.; Ichikawa, Y.; Wong, C.-H. *J. Org. Chem.* **1991**, *56*, 6280-6289.
74. Takayama, S.; Martin, R.; Wu, J.; Laslo, K.; Siuzdak, G.; Wong, C.-H. *J. Am. Chem. Soc.* **1997**, *119*, 8146-8151.
75. Izquierdo, I.; Plaza, M. T.; Yáñez, V. *Tetrahedron*, **2007**, *63*, 1440-1447.

76. Wang, Y.-F.; Takaoka, Y.; Wong, C.-H. *Angew. Chem. Intl. Ed.* **1994**, *106*, 1343-1345.
77. Doyagüez, E. G.; Calderón, F.; Sánchez, F.; Fernández-Mayoralas, A. *J. Org. Chem.* **2007**, *72*, 9353-9356.
78. Calderón, F.; Doyagüez, E. G.; Cheong, P. H.-Y.; Fernández-Mayoralas, A.; Houk, K. N. *J. Org. Chem.* **2008**, *73*, 7916-7920.
79. Izquierdo, I.; Plaza, M. T.; Rodríguez, M.; Franco, F.; Martos, A. *Tetrahedron*, **2005**, *61*, 11697-11704.
80. Fechter, M. H.; Stuetz, A. E. *Carbohydr. Res.* **1999**, *319*, 55-62.
81. Dureault, A.; Portal, M.; Depezay, J. C. *Synlett*, **1991**, *4*, 225-226.
82. Behr, J.-B.; Guillerm, G. *Tetrahedron Lett.* **2007**, *48*, 2369-2372.
83. Colobert, F.; Tito, A.; Khiar, N.; Denni, D.; Medina, M. A.; Martin-Lomas, M.; Ruano, J.-L. G.; Solladié, G. *J. Org. Chem.* **1998**, *63*, 8918-8921.
84. Masaki, Y.; Oda, H.; Kazuta, K.; Usui, A.; Itoh, A.; Xu, F. *Tetrahedron Lett.* **1992**, *33*, 5089-5092.
85. Shing, T. K. M. *J. Chem. Soc., Chem. Commun.* **1987**, 262-263.
86. Shing, T. K. M. *Tetrahedron*, **1988**, *44*, 7261-7264.
87. Reitz, A. B.; Baxter, E. W. *Tetrahedron Lett.* **1990**, *31*, 6777-6780.
88. Baxter, E. W.; Reitz, A. B. *J. Org. Chem.* **1994**, *59*, 3175-3185.
89. Zou, W.; Szarek, W. A. *Carbohydr. Res.* **1993**, *242*, 311-314.
90. Hong, Z.; Liu, L.; Sugiyama, M.; Fu, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 8352-8353.
91. Ikota, N. *Tetrahedron Lett.* **1992**, *33*, 2553-2556.
92. Tsou, E.-L.; Yeh, Y.-T.; Liang, P.-H.; Cheng, W.-C. *Tetrahedron*, **2009,** *65*, 93-100.
93. Dondoni, A.; Giovannini, P. P.; Perrone, D. *J. Org. Chem.* **2002**, *67*, 7203-7214.
94. Gautier-Lefebvre, I.; Behr, J.-B.; Guillerm, G.; Muzard, M. *Eur. J. Med. Chem.* **2005**, *40*, 1255-1261.
95. Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Marradi, M.; Faggi, E.; Parmeggiani, C.; Goti, A. *Eur. J. Org. Chem.* **2008,** 2929-2947.
96. Dondoni, A.; Perrone, D. *Tetrahedron Lett.* **1999**, *40*, 9375-9378.
97. Saotome, C.; Kanie, Y.; Kanie, O.; Wong, C.-H. *Bioorg. Med. Chem.* **2000**, *8*, 2249-2261.
98. Li, Y.-X.; Huang, M.-H.; Yamashita, Y.; Kato, A.; Jia, Y.-M.; Wang, W.-B.; Fleet, G. W. J.; Nash, R. J.; Yu, C.-Y. *Org. Biomol. Chem.* **2011**, *9*, 3405-3414.
99. Vyavahare, V. P.; Chattopadhyay, S.; Puranik, V. G.; Dhavale, D. D. *Synlett*, **2007**, *4*, 559-562.
100. Donohoe, T. J.; Headley, C. E.; Cousins, R. P. C.; Cowley, A. *Org. Lett.* **2003**, *5*, 999-1002.
101. Donohoe, T. J.; Cheeseman, M. D.; O'Riordan, T. J. C.; Kershaw, J. A. *Org. Biomol. Chem.* **2008**, *6*, 3896-3898.
102. Trost, B. M.; Horne, D. B.; Woltering, M. J. *Chem. Eur. J.* **2006,** *12*, 6607-6620.
103. Restorp, P.; Fischer, A.; Somfai, P. *J. Am. Chem. Soc.* **2006**, *128*, 12646-12647.
104. Restorp, P.; Dressel, M.; Somfai, P. *Synthesis*, **2007**, *10*, 1576-1583.
105. Poitout, L.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron Lett.* **1996**, *37*, 1609-1612.
106. Le Merrer, Y.; Poitout, L.; Depezay, J.-C.; Dosbaa, I.; Geoffroy, S.; Foglietti, M.-J. *Bioorg. Med. Chem.* **1997**, *5*, 519-533.
107. Sowa, W. *Can. J. Chem.* **1969**, *47*, 3931-3934.
108. Weymouth-Wilson, A. C.; Clarkson, R. A.; Jones, N. A.; Best, D.; Wilson, F. X.; Pino-González, M.-S.; Fleet, G. W. J. *Tetrahedron Lett.* **2009**, *50*, 6307-6310.
109. Kiliani, H. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 767-772.
110. Bichard, C. J. F.; Bruce, I.; Hughes, D. J.; Girdhar, A.; Fleet, G. W. J.; Watkin, D. J. *Tetrahedron: Asymmetry*, **1993**, *4*, 1579-1589.
111. Mori, N.; Togo, H. *Tetrahedron*, **2005**, *61*, 5915-5925.
112. Ho, P.-T. *Can. J. Chem.* **1979**, *57*, 381-383.
113. Booth, V. K.; Jenkinson, S. F.; Best, D.; Nieto, F. F.; Estevez, R. J.; Wormald, M. R.; Weymouth-Wilson, A. C.; Fleet, G. W. J. *Tetrahedron Lett.* **2009**, *50*, 5088-5093.
114. Deno, N. C.; Potter, N. H. *J. Am. Chem. Soc.* **1967**, *89*, 3550-3554.
115. Fleet, G. W. J.; Carpenter, N. M.; Petursson, S.; Ramsden, N. G. *Tetrahedron Lett.* **1990**, *31*, 409-412.
116. Csuk, R.; Hönig, H.; Nimpf, J.; Weidmann, H. *Tetrahedron Lett.* **1980**, *21*, 2135-2136.
117. Krulle, T. M.; Davis, B.; Ardron, H.; Long, D. D.; Hindle, N. A.; Smith, C.; Brown, D.; Lane, A. L.; Watkin, D. J.; Marquess, D. G.; Fleet, G. W. J. *Chem. Commun.* **1996,** *11*, 1271-1272.
118. Ayers, B. J.; Ngo, N.; Jenkinson, S. F.; Martínez, R. F.; Shimada, Y.; Adachi, I.; Weymouth-Wilson, A. C.; Kato, A.; Fleet, G. W. J. *J. Org. Chem.* **2012**, *77*, 7777-7792.
119. Romero, P. A.; Friedlander, P.; Fellows, L.; Evans, S. V.; Herscovics, A. *FEBS Lett.* **1985**, *184*, 197-201.
120. Scofield, A. M.; Fellows, L. E.; Nash, R. J.; Fleet, G. W. *Life Sci.* **1986**, *39*, 645-650.
121. Fleet, G. W. J.; Karpas, A.; Dwek, R. A.; Fellows, L. E.; Tyms, A. S.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Smith, P. W.; Son, J. C.; Wilson, F.; Witty, D. R.; Jacob, G. S.; Rademacher, T. W. *FEBS Lett.* **1988**, *237*, 128-132.
122. Simmonds, M. S. J.; Blaney, W. M.; Fellows, L. E. *J. Chem. Ecol.* **1990**, *16*, 3167-3196.

123. Birch, A. N. E.; Robertson, W. M.; Geoghegan, I. E.; McGavin, W. J.; Alphey, T. J. W.; Fellows, L. E.; Watson, A. A.; Simmonds, M. S. J.; Porter, E. A. *Brighton Crop Prot. Conf. Pests Dis.* **1992,** *1*, 67-72.
124. Asano, N.; Kizu, H.; Oseki, K.; Tomioka, E.; Matsui, K.; Okamoto, M.; Baba, M. *J. Med. Chem.* **1995**, *38*, 2349-2356.
125. Nojima, H.; Kimura, I.; Chen, F.-J.; Sugihara, Y.; Haruno, M.; Kato, A.; Asano, N. *J. Nat. Prod.* **1998**, *61*, 397-400.
126. Chang, H.-H.; Asano, N.; Ishii, S.; Ichikawa, Y.; Fan, J.-Q. *FEBS J.* **2006**, *273*, 4082-4092.
127. Maddry, J. A.; Bansal, N.; Bermudez, L. E.; Comber, R. N.; Orme, I. M.; Suling, W. J.; Wilson, L. N.; Reynolds, R. C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 237-242.
128. Yu, Z.; Sawkar, A. R.; Whalen, L. J.; Wong, C.-H.; Kelly, J. W. *J. Med. Chem.* **2007**, *50*, 94-100.
129. Davis, B. G.; Hull, A.; Smith, C.; Nash, R. J.; Watson, A. A.; Winkler, D. A.; Griffiths, R. C.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2947-2960.
130. Rountree, J. S. S.; Butters, T. D.; Wormald, M. R.; Boomkamp, S. D.; Dwek, R. A.; Asano, N.; Ikeda, K.; Evinson, E. L.; Nash, R. J.; Fleet, G. W. J. *ChemMedChem*, **2009**, *4*, 378-392.
131. D'Alonzo, D.; Guaragna, A.; Palumbo, G. *Curr. Med. Chem.* **2009**, *16*, 473-505.
132. Jenkinson, S. F.; Fleet, G. W. J.; Nash, R. J.; Koike, Y.; Adachi, I.; Yoshihara, A.; Morimoto, K.; Izumori, K.; Kato, A. *Org. Lett.* **2011**, *13*, 4064-4067.
133. Clinch, K.; Evans, G. B.; Fleet, G. W. J.; Furneaux, R. H.; Johnson, S. W.; Lenz, D. H.; Mee, S. P. H.; Rands, P. R.; Schramm, V. L.; Taylor, R. E. A.; Tyler, P. C. *Org. Biomol. Chem.* **2006**, *4*, 1131-1139.
134. Bleriot, Y.; Gretzke, D.; Kruelle, T. M.; Butters, T. D.; Dwek, R. A.; Nash, R. J.; Asano, N.; Fleet, G. W. J. *Carbohydr. Res.* **2005**, *340*, 2713-2718.
135. Winchester, B.; Barker, C.; Baines, S.; Jacob, G. S.; Namgoong, S. K.; Fleet, G. W. J. *Biochem. J.* **1990**, *265*, 277-282.
136. Sumida, T.; Stubbs, K. A.; Ito, M.; Yokoyama, S. *Org. Biomol. Chem.* **2012**, *10*, 2607-2612.
137. Liang, P.-H.; Cheng, W.-C.; Lee, Y.-L.; Yu, H.-P.; Wu, Y.-T.; Lin, Y.-L.; Wong, C.-H. *ChemBioChem*, **2006**, *7*, 165-173.
138. Takaoka, Y.; Kajimoto, T.; Wong, C.-H. *J. Org. Chem.* **1993**, *58*, 4809-4812.
139. Takebayashi, M.; Hiranuma, S.; Kanie, Y.; Kajimoto, T.; Kanie, O.; Wong, C.-H. *J. Org. Chem.* **1999**, *64*, 5280-5291.
140. Win-Mason, A. L.; Jongkees, S. A. K.; Withers, S. G.; Tyler, P. C.; Timmer, M. S. M.; Stocker, B. L. *J. Org. Chem.* **2011**, *76*, 9611-9621.
141. Nayak, U. G.; Whistler, R. L. *J. Org. Chem.* **1968**, *33*, 3582-3585.
142. Horton, D.; Tsai, J.-H. *Carbohydr. Res.* **1977**, *58*, 89-108.
143. Garcia-Moreno, M. I.; Mellet, C. O.; Fernandez, J. M. G. *Eur. J. Org. Chem.* **2004,** *8*, 1803-1819.
144. Lee, C.-K.; Jiang, H. *J. Carbohydr. Chem.* **1995**, *14*, 407-416.

# Chapter 3: Piperidine α-iminonitriles - precursors to pipecolic acids

## 3.1 Introduction

### 3.1.1 Glucuronidase - a biological target

In **Chapter 1** (Section 1.5.3, pages 21-22), it was shown that the prevention of the catabolism of the hyaluronan by hexosaminidase enzymes affords a novel and attractive strategy in the treatment of late-stage metastatic cancers.[1] In an analogous fashion it has been suggested that the inhibition of β-glucuronidase, a lysosomal glycosidase responsible for the degradation of the glycosaminoglycans (such as the hyaluronan and heparan sulfate),[2] would provide a similar therapeutic strategy for reducing metastasis.[3-6] Heparan sulfate is a sulfated, heterogeneous polysaccharide chain (**Figure 3.1**) and like the hyaluronan is an important structural component of both the basement membranes and the extracellular matrix (ECM).[7-9] Heparanase, an *endo*-β-glucuronidase, is responsible for the degradation of heparan sulfate and has been observed to be over-expressed in certain tumours, possibly playing an important role in cellular invasion through basement membranes.[10] It can thus be seen that the development of inhibitors for, and the inhibition of, this enzyme provides an extremely attractive target for the future treatment of metastatic cancer. This potential application furnishes the primary motivation for the synthesis of β-glucuronidase inhibitors.

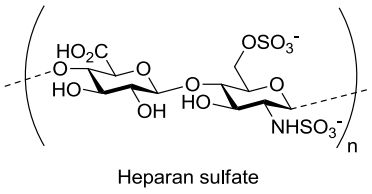



**Figure 3.1**. Structure of heparan sulfate, a component of the ECM.[11]

The second motivation arises from the potentially valuable strategy of alleviating the harmful side-effects of cancer chemotherapy. D-Glucuronic acid plays an important role in drug metabolism by a process termed "glucuronic acid conjugation", or glucuronidation, whereby the addition of glucuronic acid to xenobiotics and other harmful substances permits safe excretion from the human body.[12] β-Glucuronidase is responsible for the hydrolysis of these glucuronide conjugates, contributing to the potentially toxic build up of unwanted substances - such as drug metabolites. This is especially relevant in the field of cancer chemotherapy, where the toxicity of metabolites limits the dosage and efficacy of treatment. Here the inhibition of β-glucuronidase has been shown to be clinically important.[13-15] Wallace *et al* demonstrated that the selective inhibition of *E. coli* β-glucuronidase in the gastrointestinal tract decreased the concentration of toxic metabolites arising from antitumour camptotecin derivative CPT-11.[13] Methods by which the toxic and harmful side-effects of chemotherapy may be reduced forms an extremely attractive target, and ultimately the second motivation towards the development of β-glucuronidase inhibitors.

The third motivation arises from the fact that β-glucuronidase is a lysosomal glycosidase, which means that a mutation in the encoding gene results in the lysosomal storage disorder (LSD) Sly disease, also known as Sly syndrome or mucopolysaccharidosis VII. As outlined in **Chapter 1** (Section 1.5.2, pages 14-18), active site specific chaperones (ASSCs) of β-glucuronidase would afford a potential therapeutic strategy for treating this disease and a valuable motivation for developing inhibitors of this enzyme.[16,17] It can be seen from these three pharmacological goals that there is a distinct need for developing selective inhibitors of β-glucuronidase. However, despite being an attractive target, there has been scarce attention towards accessing inhibitors of this enzyme.

3.1.2 Pipecolic acids and glucuronidase inhibitors

With such an attractive biological target, the research into iminosugar-based inhibitors of β-glucuronidase has been surprisingly scarce, if not scarcer, than that for α-*N*-acetylgalactosaminidase in the preceding Chapter. Only a handful of iminosugar-based inhibitors of β-glucuronidase have been developed. The direct iminocyclitol analogue of D-glucuronic acid **3.1** is the trihydroxypipecolic acid BR-1 **3.2** (**Figure 3.2**) - a uronic acid derivative of DNJ. This compound has been isolated in Nature from both *Baphia racemosa*[18] and *Baphiopsis parviflora*,[19] and has shown good inhibition of β-glucuronidase (bovine liver: $IC_{50}$ 70 μM).[20] In additional studies BR-1 **3.2** also demonstrated promising antimetastatic properties.[21] The synthetic C3-epimer, *epi*-BR-1 **3.3**, has also been shown to possess a similar level of potency (bovine liver: $IC_{50}$ 86 μM).[20]

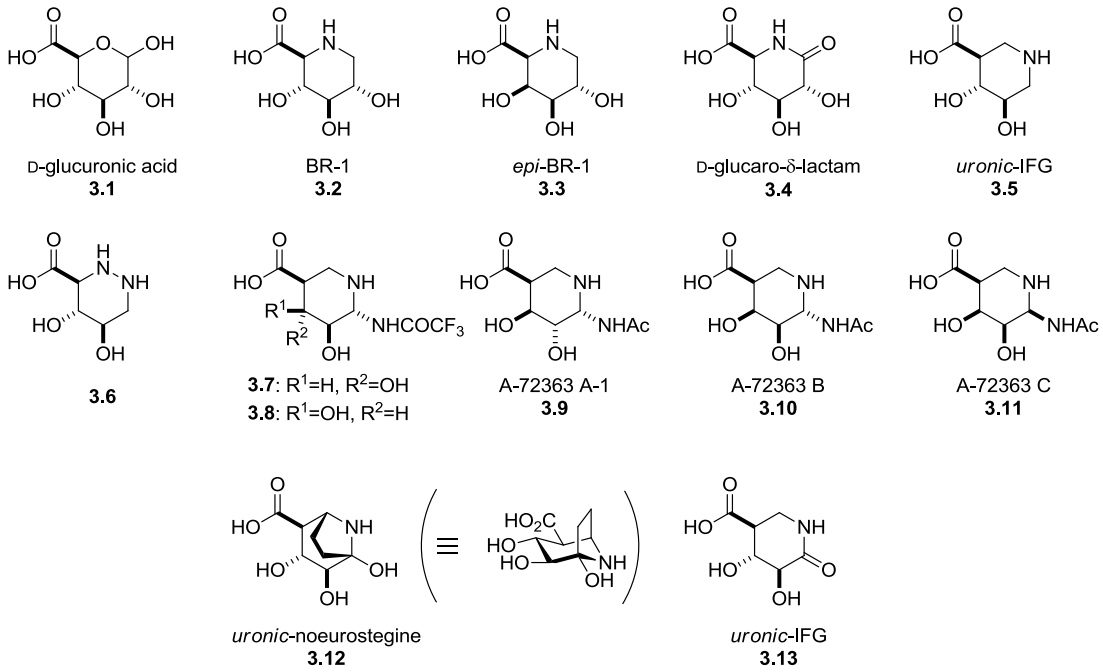



**Figure 3.2**. Iminosugar examples of β-glucuronidase inhibitors.

The related compound D-glucaro-δ-lactam **3.4** has been shown to be a powerful inhibitor (bovine liver: $IC_{50}$ 180 nM),[22] and Igarashi *et al* showed that an isofagomine-like 1-*N*-analogue of BR-1,

*uronic*-isofagomine (*uronic*-IFG) **3.5** was a similarly potent inhibitor (bovine liver: $K_i$ 79 nM),[23] while Jensen and co-workers demonstrated that the diamine **3.6** had a much weaker level of inhibition (bovine liver: $K_i$ 1 μM).[24] The trifluoroacetyl *gem*-diamine **3.7** derivative of *uronic*-IFG and the *galacto*-configured epimer **3.8** were shown to be potent inhibitors and demonstrated identical activity (bovine liver: $K_i$ 65 nM).[25] These 1-*N*-iminosugars are related to a class of naturally occurring compounds which demonstrate good activity against β-glucuronidase. Takatsu and colleagues isolated three *gem*-diamine acetamides; A-72363 A-1 **3.9**, A-72363 B (siastatin B) **3.10** and A-72363 C **3.11**, among others, from a *Streptomyces* fermentation broth.[26] Both A-72363 A-1 **3.9** and A-72363 B **3.10** proved to be moderate β-glucuronidase inhibitors ($IC_{50}$ 50 μM & 39 μM, respectively), but were poor inhibitors of *endo*-β-glucuronidase (heparanse: both $IC_{50}$ >350 μM). However, A-72363 C **3.11** proved to be an excellent inhibitor of both enzymes ($IC_{50}$ 1.6 μM & 12 μM).[27] Recently the very interesting calystegine-like *uronic*-noeurostegine **3.12** has been reported.[28] Although this molecule possessed weaker inhibition against bovine liver β-glucuronidase compared to the parent *uronic*-IFG **3.5** compound ($K_i$ 2.3 μM), remarkable selectively was demonstrated for the *E. coli* enzyme with a thirty-fold difference in inhibitory activity ($K_i$ 60 nM). Finally, in 2012 Lindback *et al* reported the potent inhibition of β-glucuronidase by the lactam-derivative of *uronic*-IFG **3.13** (bovine liver: $K_i$ 36 nM).[15]

It can be seen from this range of known inhibitors that the structural requirement for good to excellent inhibition varies greatly for β-glucuronidase. All the inhibitors possess a primary carboxylate group which electronically mimics that of D-glucuronic acid **3.1**, but the location and nature of the ring nitrogen differs, from a traditional α-imino group in the natural product BR-1 **3.2** to the 1-*N*-isofagamine-type inhibitors and lactams which make up the majority of examples shown here.

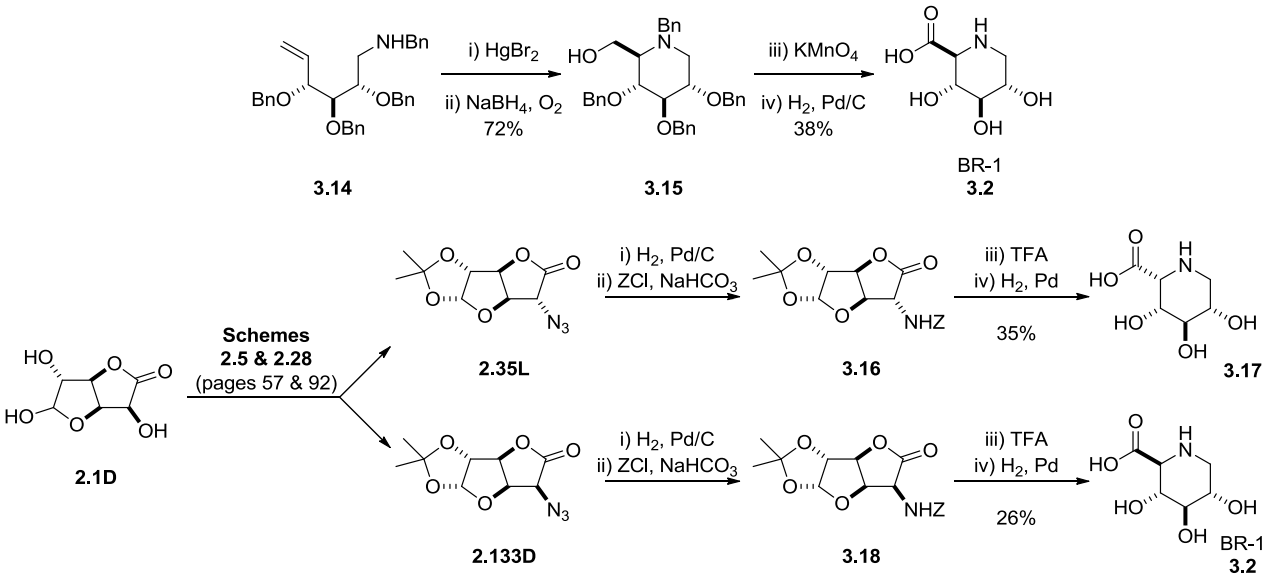
Given the chemotherapeutic potential, the activity displayed by these β-glucuronidase inhibitors and the limited research to date, it can be seen that pursuing this target could be extremely rewarding in both accessing novel inhibitors, and in further analysing the structure-activity relationship of β-glucuronidase enzymes towards pipecolic acid inhibitors. With this in mind the following sections will outline the synthetic goals of this chapter of the thesis, highlight previous synthetic work within the field and describe the research that was conducted.

## 3.2 Pipecolic acids and piperidine α-iminonitriles

### 3.2.1 Previous synthetic work towards trihydroxypipecolic acids

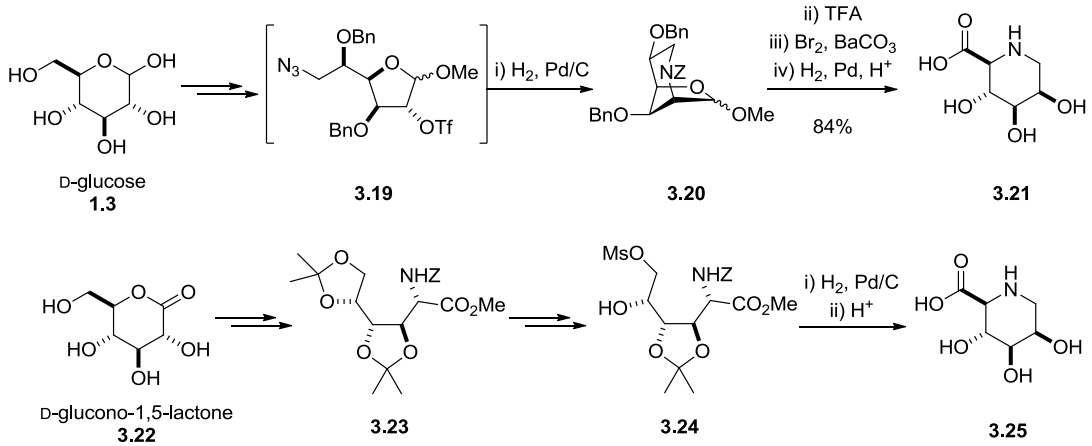
The general principles employed in the synthesis of iminosugars were reviewed in **Chapter 1** (Section 1.6, pages 24-42), and this section illustrates these with specific examples in the synthesis of pipecolic acids.

Following the discovery of the natural product BR-1 **3.2** in 1984,[18,29] the first published synthetic route to this trihydroxypipecolic acid was conducted by Bernotas *et al* in 1985 (**Scheme 3.1**).[2] BR-1 **3.2** was synthesised from suitably protected DNJ **3.15** by oxidation with permanganate. The protected starting material **3.15** itself arose from an intramolecular cyclisation promoted by mercury(II) bromide. This cyclisation approach by oxymercuration was also employed by Tong and co-workers to access *epi*-BR-1 **3.3**,[30] and by Le Merrer and colleagues who also produced BR-1 **3.2** by oxidation of a protected form of DNJ.[31] The initial synthesis of BR-1 **3.2** was followed in 1986 by a route from D-glucuronolactone **2.1D**, which also permitted access to the C2-epimeric pipecolic acid **3.17**.[32,33] These pipecolic acids were formed by intramolecular reductive amination, followed by hydrolysis and the opening of the lactone ring.



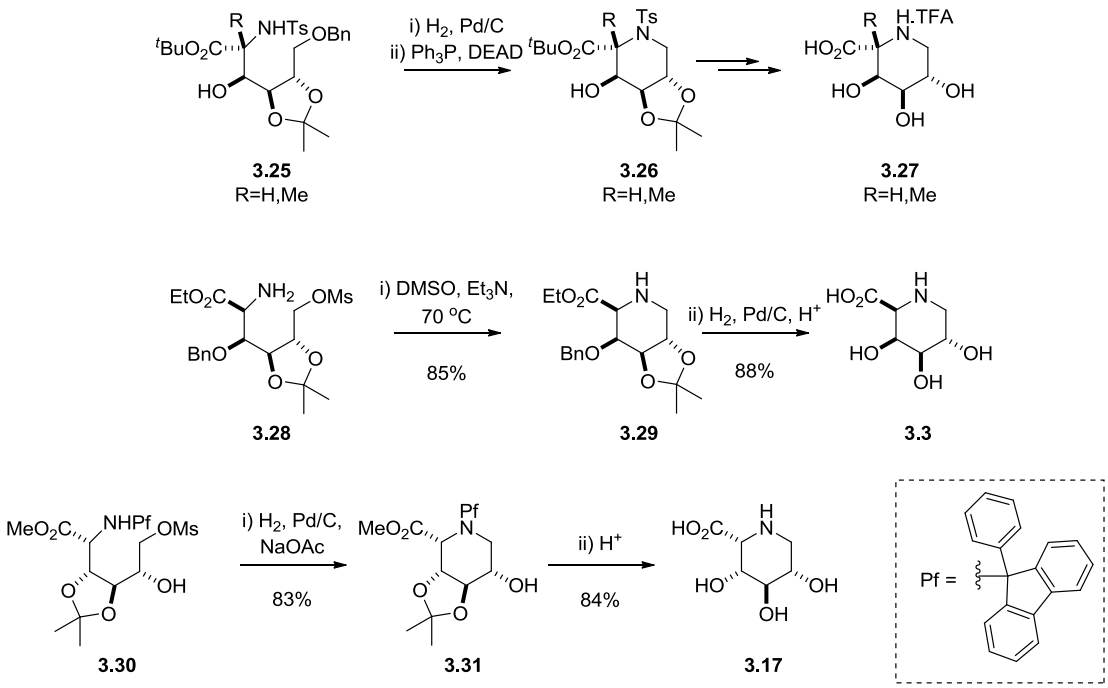

**Scheme 3.1**. The first syntheses of trihydroxy pipecolic acids.[2,32,33]

D-Glucose **1.3** was successfully utilised in two routes by Fleet *et al* which allowed access to both BR-1 **3.2**,[34] and the *manno*-configured C5-epimeric pipecolic acid **3.20** (**Scheme 3.2**).[35] The iminosugar rings of these targets were produced by intramolecular $S_N2$-displacement, with subsequent methyl glycoside hydrolysis, oxidation and ring opening forming the pipecolic acids. An intramolecular $S_N2$-displacement was also utilised by Park and colleagues later in 1994 to access the same target **3.20**, although a starting material with the same oxidation level as the product was utilised here.[36]



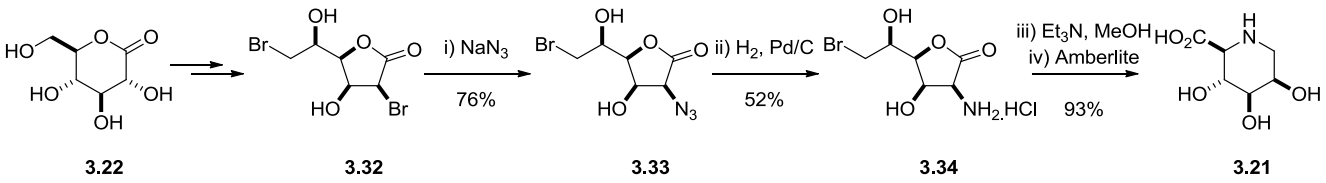

**Scheme 3.2**. The synthesis of the C5-epimer of BR-1.[34-36]

The cyclisation of an α-amino ester has also been employed by other researchers to access pipecolic acid targets. Grandel *et al* accessed the C2-methyl-branched pipecolic acids **3.27** by Mitsunobu-based cyclisation of the α-amino ester **3.25** (**Scheme 3.3**),[37-40] while Ruiz and co-workers utilised the $S_N2$-displacement of a mesylate on a similarly protected substrate **3.28** to afford *epi*-BR-1 **3.3**.[41] This latter methodology was also adopted by Lee *et al* to synthesise the pipecolic acid **3.17**, albeit with a phenylfluorene (Pf) amino-protecting group.[42]




**Scheme 3.3**. The synthesis of pipecolic acids *via* Mitsunobu cyclisation,[37-40] and mesylate displacement.[41,42]

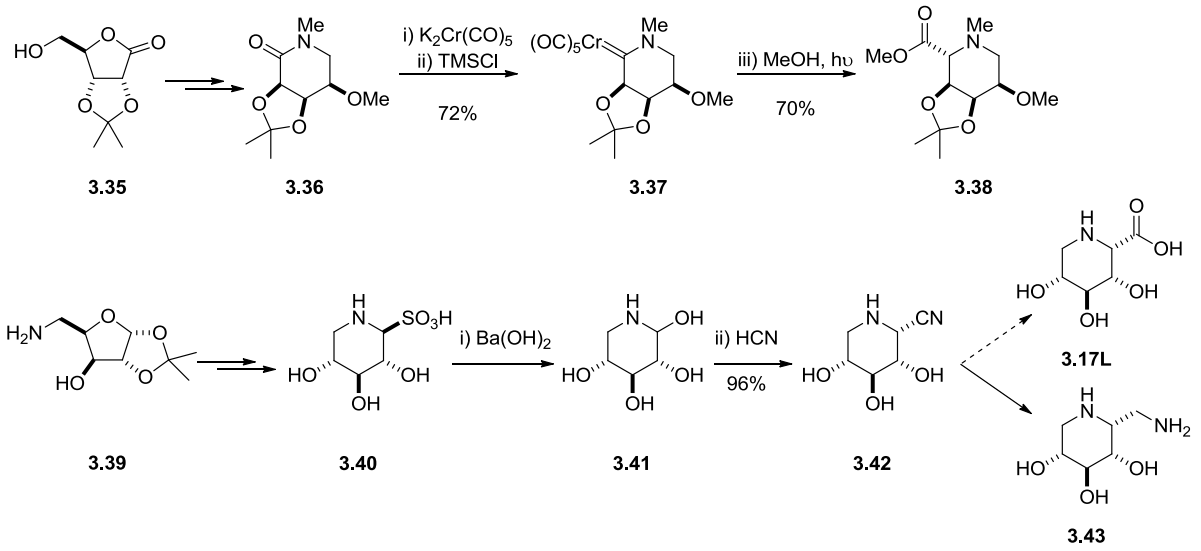
The use of two identical leaving groups proved extremely effective in a short and efficient route developed by Malle *et al* (**Scheme 3.4**).[43] The dibromolactone **3.32** was readily accessed from D-glucono-1,4-lactone **3.22**, and azide substitution at C2 gave the azido-lactone **3.33** with overall retention of the configuration at C2. Acidic hydrogenolysis afforded the amine **3.34**, and subsequent addition of base resulted in cyclisation and formation of the pipecolic acid **3.21**.




**3.22** **3.32** **3.33** **3.34** **3.21**

**Scheme 3.4**. The synthesis of the pipecolic acid **3.21**.[43]

As discussed in **Chapter 1** (Section 1.6.3.1, pages 36-38) carbon chain homologation provides extremely useful methods for accessing a diverse range of carbohydrate scaffolds. One interesting example has been developed by Klumpe *et al* whereby the trapping of a Fischer-type carbene complex **3.37** (**Scheme 3.5**), derived from methyl lactam **3.36** - itself accessed from protected D-ribono-1,4-lactone **3.35** - with methanol allowed for the stereoselective access to the pipecolic acid precursor **3.38**.[44,45]



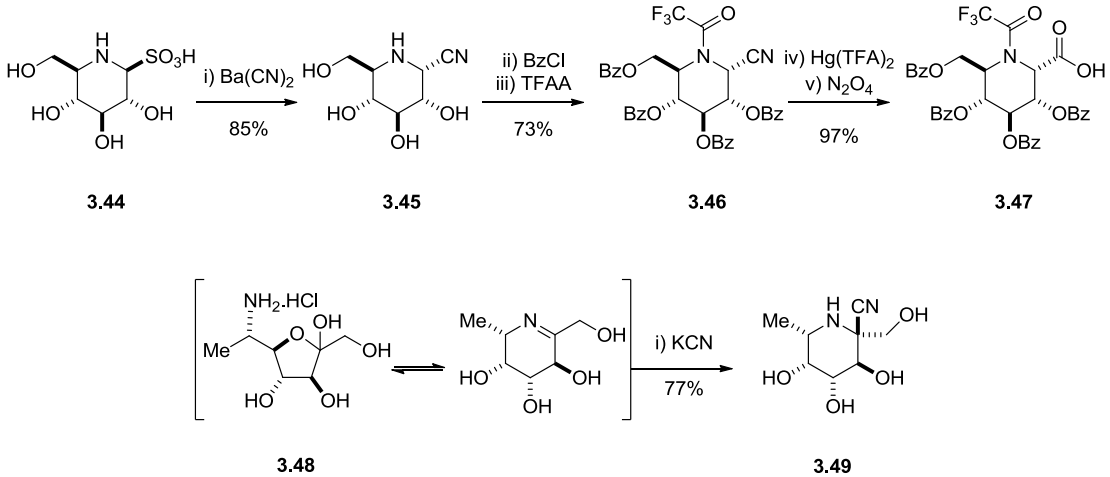

**3.35** **3.36** **3.37** **3.38**

**3.39** **3.40** **3.41** **3.42** **3.17L** **3.43**

**Scheme 3.5**. The use of carbon-chain homologation to access pipecolic acids and their precursors *via* a Fischer-type carbene complex,[44,45] and by a piperidine α-iminonitrile.[46-49]

A more widely employed method of homologation concerns the use of nucleophilic cyanide, with the resultant nitrile being a flexible chiron for the synthesis of a carboxylic acid as well as other functionalities. The first work of this kind was conducted by Paulsen and co-workers in 1967, and concerned the addition of hydrogen cyanide to an hemiacetal centre of a piperidine iminosugar ring (**Scheme 3.5**).[46-49] This reaction involved the synthesis of a stable bisulfite

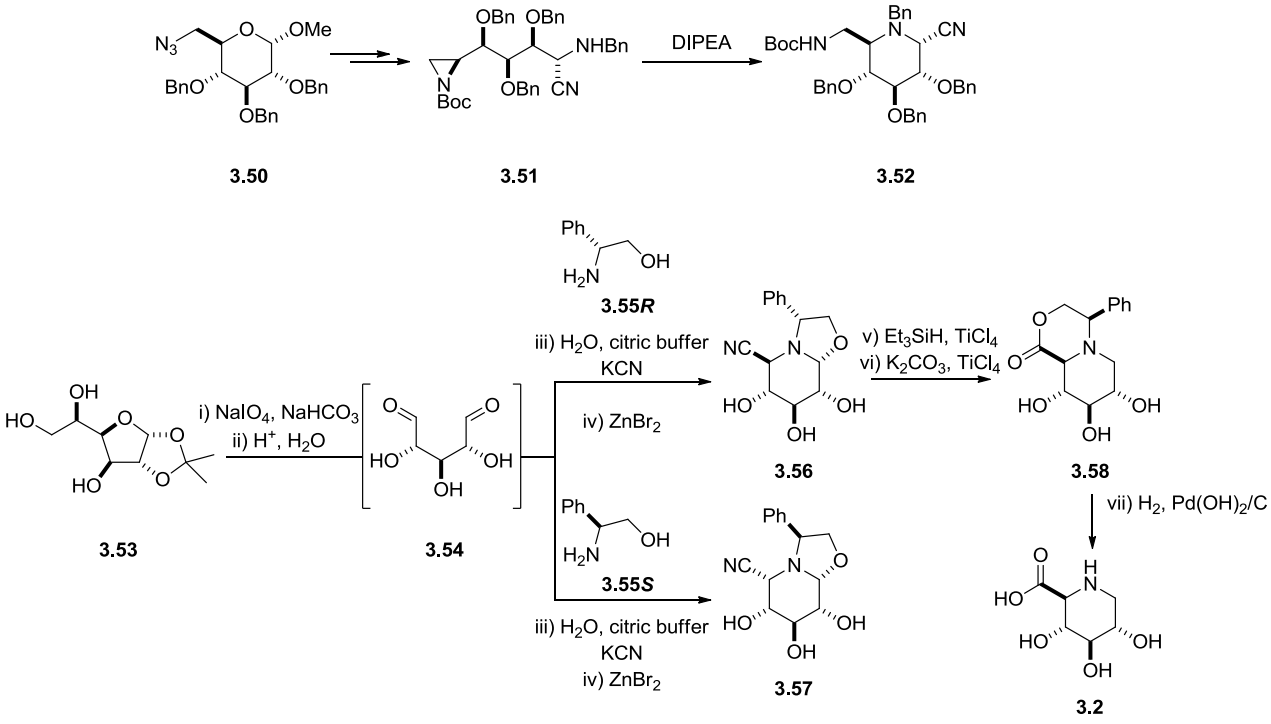
iminosugar intermediate **3.40** from 5-amino D-xylose **3.39**. Treatment of the bisulfite **3.40** with barium hydroxide gave the hemiaminal **3.41**, which on treatment with hydrogen cyanide gave the piperidine α-iminonitrile **3.42**. Despite this nitrile **3.42** serving as an ideal precursor to the pipecolic acid **3.17L**, this was not the aim of this publication - instead the desired target accessed was the reduced primary amine **3.43**. The tactic of adding cyanide to an existing iminosugar scaffold has been the predominant method utilised to date.[50-52] Following the work of Paulsen *et al* in 1966, Anzeveno and colleagues used barium cyanide to access the α-iminonitrile **3.45** selectively from bisulfite **3.44** (**Scheme 3.6**) in a single step.[53] This nitrile **3.45** was subsequently hydrolysed to the protected pipecolic acid **3.47** by treatment with mercury(II) trifluoroacetate, then nitrogen dioxide. Wong and co-workers later synthesised the same α-iminonitrile **3.45** and extended the methodology to afford the C3-epimeric α-iminonitrile by reaction with barium hydroxide and potassium cyanide in the presence of hydrochloric acid.[54] This research group also demonstrated that this methodology was applicable to the formation of quaternary centres; where the quaternary α-iminonitrile **3.49** was formed when amino-ketose **3.48** was treated with potassium cyanide.[55]




**Scheme 3.6**. Formation of α-iminonitriles.[53,55]

In an alternative approach to these methods, cyanide may be added prior to iminocyclisation. This entails a traditional Strecker α-aminonitrile synthesis - by reaction of a carbonyl with an

amine and hydrogen cyanide - with subsequent iminosugar ring formation. There are only a handful of examples of this approach being utilised in the synthesis of piperidine α-iminonitriles. The first was conducted by Chakraborty *et al* and involved the formation of the open-chain α-iminonitrile aziridine **3.51** from the azido-glycoside **3.50** (**Scheme 3.7**), which under basic conditions led to intramolecular aziridine ring opening and formation of the piperidine α-iminonitrile **3.52**.[56]

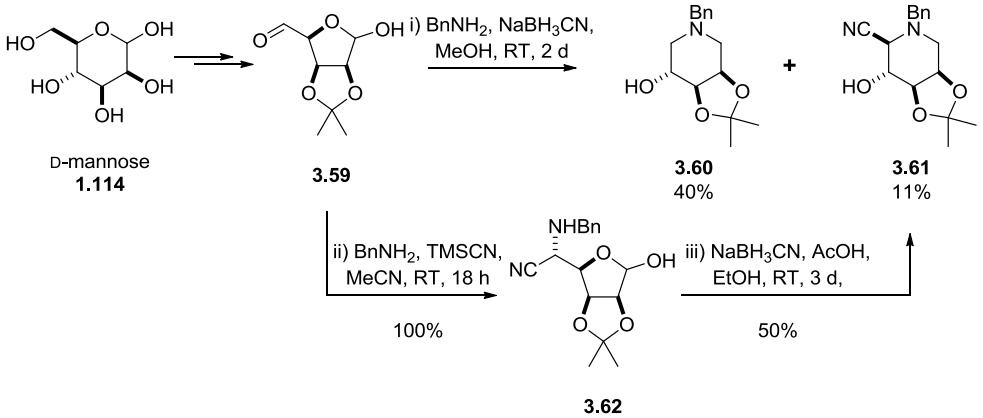



**Scheme 3.7**. Synthesis of an α-iminonitrile by a Strecker reaction and subsequent iminocyclisation;[56] also by use of a dialdehyde starting material.[57-60]

The remaining two examples by Husson *et al* and Matassini *et al* utilise dicarbonyl starting materials with assembly of the iminosugar ring and cyanide addition conducted in tandem. These interesting reactions permit facile assembly of the target piperidine α-iminonitriles. The method by Husson *et al* involves the use of a chiral phenylglycinol **3.55** as the amine nucleophile, and potassium cyanide - followed by treatment of the crude product with zinc bromide. The use of the chiral amine allows access to the epimeric α-iminonitrile products, as can be seen in

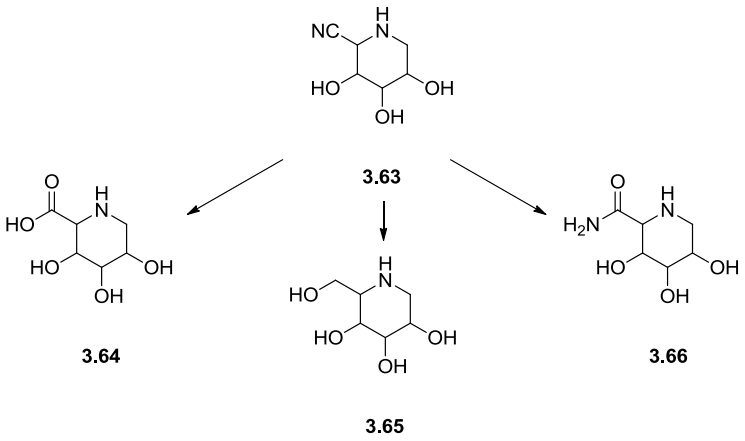
**Scheme 3.7**. Reaction of the dialdehyde **3.53** with the (*R*)-phenylglycinol **3.55*R*** affords the α-iminonitrile **3.56**, whereas use of the (*S*)-phenylglycinol **3.55*S*** affords the α-iminonitrile **3.57**.[57-59] A publication by this research group also showed that the α-iminonitrile **3.56** could be converted to the pipecolic acid BR-1 **3.2** *via* the bicyclic lactone **3.58** (**Scheme 3.7**).[60] An additional paper also demonstrated an important synthetic feature of the nitrile functional group - it's potential as a flexible chiron - whereby it may be converted to a range of other functionalities, including; hydroxymethyl, aldehyde and primary amide groups, as well as others.[61] The potential of divergency in a synthesis of this type was discussed previously in **Chapter 2** (Section 2.3.2.3, pages 81-82) where producing a range of functionalities may lead to the targeting of multiple biological targets from a common, late-stage intermediate. This makes producing these piperidine α-iminonitrile precursors potentially very rewarding.

The second method of this class, published by Matassini *et al*, involves the reductive amination of a dialdehyde **3.59** with benzylamine and sodium cyanoborohydride (**Scheme 3.8**). The intended product of the reaction was the isofagomine-type precursor **3.60**, however significant amounts of the piperidine α-iminonitrile **3.61** were also isolated as a by-product stereoselectively. It was found that the yield of the α-iminonitrile **3.61** could be increased to 50% with an alternative two-step protocol *via* the isolated Strecker product **3.62**.[62]



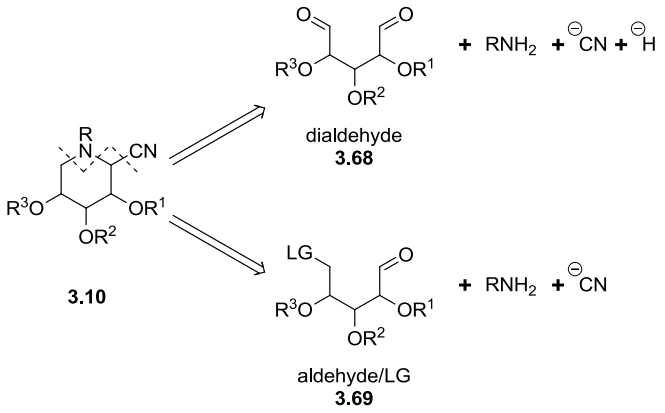

**Scheme 3.8**. Synthesis of an α-iminonitrile by a tandem Strecker reaction and iminocyclisation.[62]

These examples of tandem Strecker reactions and iminocyclisations (TSRIs) exhibit excellent stereoselectivity and afford possible methods to access piperidine α-iminonitriles **3.63** in a single synthetic step from dialdehyde starting materials (**Scheme 3.9**). These piperidine α-iminonitriles **3.63** are potential precursors not only to the biologically relevant pipecolic acids **3.64** (Section 3.1.2, pages 223-224), but also to the DNJ-class of iminosugar **3.65** - potential glycosidase inhibitors, as well as the pipecolic amides **3.66** - potential hexosaminidase inhibitors. Thus, it can be seen that developing novel synthetic methodologies towards these piperidine α-iminonitriles **3.63** could be highly rewarding in allowing synthetic access to existing and novel classes of iminosugar in relatively short synthetic sequences. This opportunity proffers the aim of this chapter of the thesis - the development of a novel tandem Strecker reaction and iminocyclisation (TSRI) methodology; and the following sections outline the strategy and research towards this goal.




**Scheme 3.9**. Pipecolic acids, amides and DNJs from piperidine α-iminonitriles.

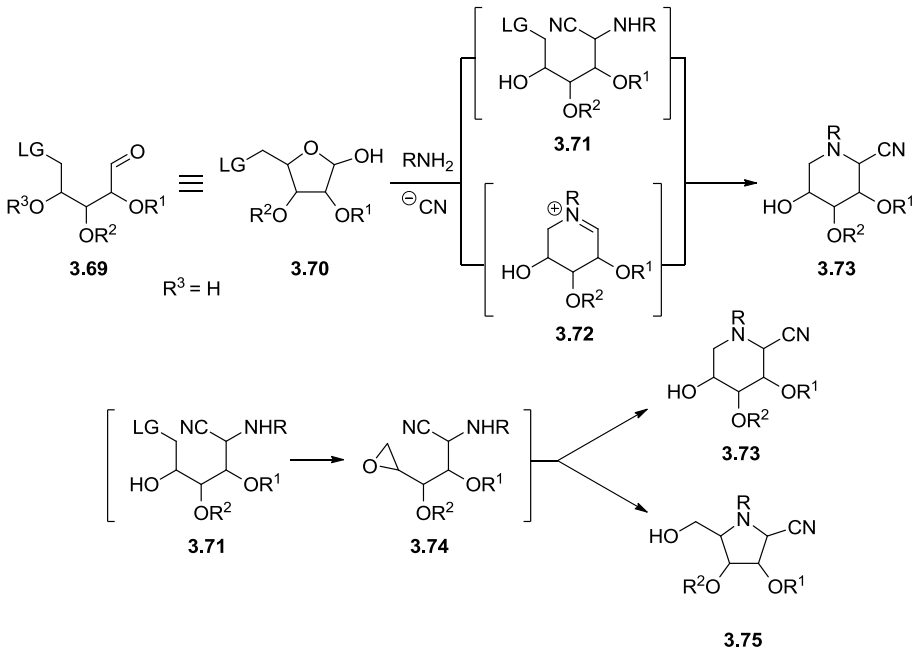
*3.2.2 Tandem Strecker reaction and iminocyclisation (TSRI) synthetic strategy*




**Scheme 3.10**. Possible tandem Strecker reaction and iminocyclisation (TSRI) strategies.

In order to assemble a piperidine α-iminonitrile **3.67** by a tandem Strecker reaction and iminocyclisation (TSRI) two synthetic routes are feasible (**Scheme 3.10**). The first, employed by Husson *et al* and Matassini *et al*,[57-62] relied on the reaction of a dialdehyde starting material **3.68** with a primary amine, a source of cyanide and the formal reduction of one of the aldehyde centres. This adds a degree of complexity to the methodology with observed yields having a maximum of 11-50%. In the case of Husson *et al* (**Scheme 3.7**, page 231) this reduction was accomplished by reaction of intermediate hemiaminals (**3.56** & **3.57**) with triethylsilane in an additional synthetic step, whereas for Matassini *et al* this was achieved during the reaction by utilising sodium cyanoborohydride as both the reducing agent and the cyanide source (**Scheme 3.8**, page 240). In the latter case the use of the reducing agent during the reaction led to poor isolated yields of the piperidine α-iminonitrile. In contrast to these methods a simpler approach would be to utilise a starting material of the correct oxidation level, possessing both a primary leaving group (LG) and an aldehyde moiety (**3.69**). Addition of a primary amine and cyanide would thus lead to the desired TSRI. From this comparison it can be seen that this is the more preferential strategy, and also constitutes a novel approach.

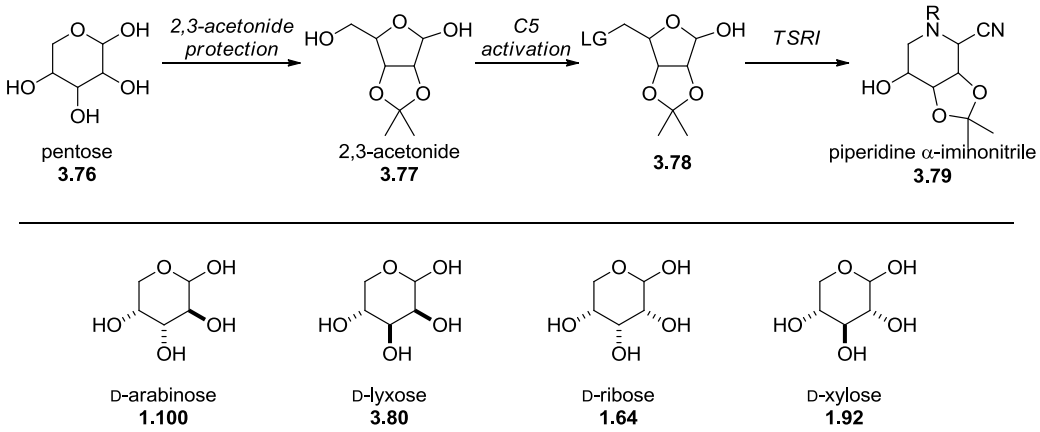
On examination of the proposed mixed aldehyde/leaving group starting material **3.69**, it may be envisaged that if the C4-hydroxyl were unprotected ($R^3$ = H) then the starting material would be a conveniently accessible furanose **3.70** (**Scheme 3.11**). Reaction of which with a primary amine and cyanide would proceed *via* either initial Strecker reaction to an α-aminonitrile **3.71**, with subsequent iminocyclisation, or by initial iminocyclisation of the furanose **3.70** to the iminium **3.72** and ensuing cyanide addition. Either route would result in the same piperidine α-iminonitrile target **3.73** by an overall TSRI. However this strategy may present some complication. With a free C4-hydroxyl adjacent to the primary leaving group in the intermediate **3.71** there arises the possibility for intramolecular displacement and epoxide **3.74** formation. The epoxide **3.74** could then undergo iminocyclisation to form either the desired piperidine **3.73**, or the undesired pyrrolidine **3.75** α-iminonitriles. If this were to arise it is envisaged that this pyrrolidine formation could be minimised by controlling the nature and reactivity of the leaving group. Thus with a proposed strategy in mind, the succeeding sections of the thesis describe the research conducted to elaborate this novel methodology.




**Scheme 3.11**. Tandem Strecker reaction and iminocyclisation (TSRI) pathway, and potential formation of a pyrrolidine α-iminonitrile arising from epoxide by-product formation.

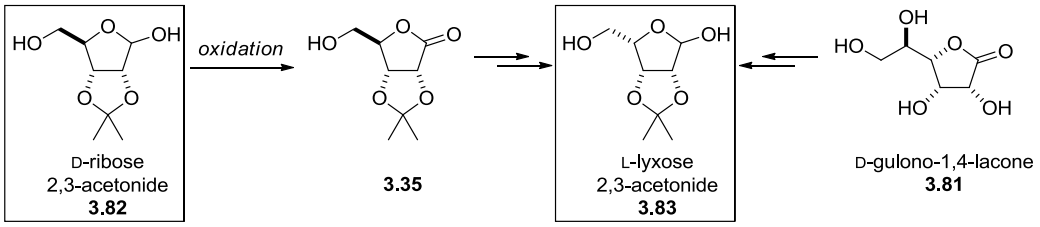
## 3.3 TSRI methodology and the synthesis of piperidine α-iminonitriles

The first consideration in developing this methodology was in selecting the most readily accessible 5-activated protected furanose system as the initial starting material. It was envisaged that the pentose sugar **3.76** would be simply protected as the 2,3-acetonide **3.77** and activated with a leaving group at C5 **3.78** (**Scheme 3.12**). There are eight pentoses; D-arabinose **1.100**, D-lyxose **3.80**, D-ribose **1.64** and D-xylose **1.92**, and their enantiomers. Given that we require acetonide protection of the C2 and C3 vicinal hydroxyls, the starting material must possess a *cis*-arrangement between these positions. Thus only ribose and lyxose may be protected in this fashion, and hence these are the initial candidate starting materials for this project.




**Scheme 3.12**.The proposed synthetic route and the four D-pentoses.

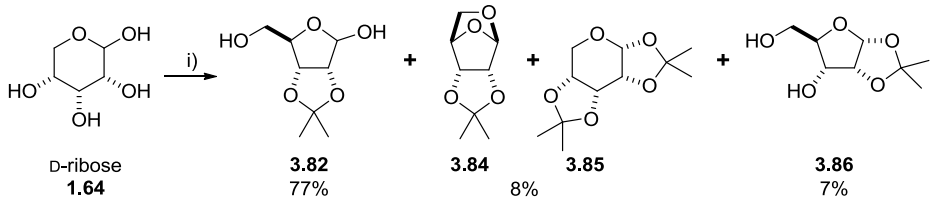
D-Ribose **1.64** is naturally abundant and therefore cheap and commercially available, whereas L-lyxose **3.80L** occurs only rarely in Nature and as a result is not. However, L-lyxose **3.80L** may be accessed from either D-ribose **1.64**[63,64] (**Scheme 1.17**, page 32) or D-gulono-1,4-lactone **3.81**,[65] in relatively short synthetic sequences (**Scheme 3.13**). From this it can be seen that the simplest and hence initial system should be that of D-ribose **1.64**.




**Scheme 3.13**. Two synthetic routes to L-lyxose.[63-65]

3.3.1 From D-ribose

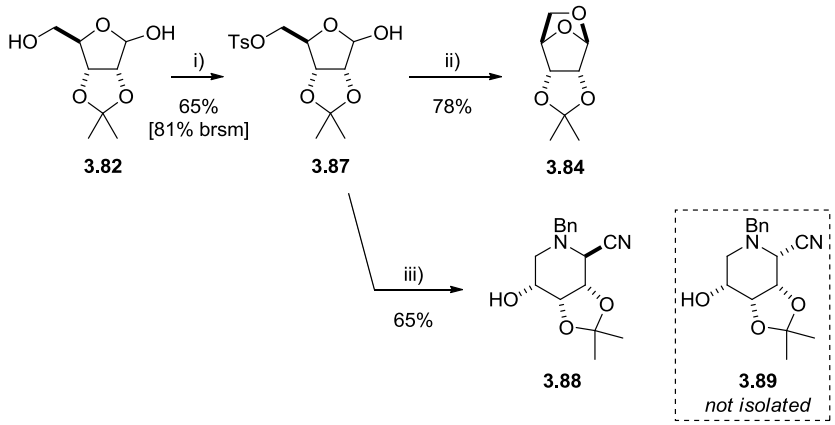
The first stage in this synthetic route was the acetonide protection of D-ribose **1.64**,[66] the reaction of which with acetone and anhydrous copper(II) sulfate at 45 °C gave a mixture of products (**Scheme 3.14**). The major separable product was found to be the desired 2,3-acetonide **3.82**, obtained in a good 77% yield, with the minor 1,5-anhydro-compound **3.84** and the diacetonide **3.85** isolated as an inseparable mixture (8%), and the 1,2-acetonide **3.86** found as the major component of a complex mixture (7%).




**Reagents & conditions**: i) acetone, $CuSO_4$, 45 °C, 17 h.

**Scheme 3.14**. Acetonide protection of D-ribose.[66]

With the 2,3-acetonide **3.82** isolated, chemoselective activation of the C5-hydroxyl was required. Esterification with *para*-toluenesulfonyl chloride (tosyl chloride, TsCl) in pyridine was chosen for this purpose as it had been previously found to be selective.[67] The 2,3-acetonide **3.82** underwent selective esterification at C5 by careful treatment with tosyl chloride in pyridine at -30 °C (**Scheme 3.15**).[67] The reaction was slowly warmed to room temperature which afforded the desired tosylate **3.87** in 65% yield (81% based on recovered starting material [brsm]).




**Reagents & conditions**: i) TsCl, pyr, -30 $^{o}$C to RT, 4 h; ii) KCN, $BnNH_2$, MeOH, RT, 4 h; iii) KCN, $BnNH_2$, AcOH, MeOH, RT, 16 h.

**Scheme 3.15**. Synthesis of the tosylate **3.87**,[67] and access to the first α-iminonitrile.

The tosylate **3.87** was treated with benzylamine and potassium cyanide in order to achieve the first tandem Strecker reaction and iminocyclisation (TSRI). Within four hours the reaction was complete with a single product formed (78%). However, this product was revealed to be the 1,5-anydro-compound **3.84**, rather than an intended piperidine α-iminonitrile. This reaction arose from the inherent basicity of the reaction mixture, which promoted an intramolecular displacement. In order to prevent this in subsequent reactions, acetic acid was added to neutralise the reaction mixture.[*] This modification was successful and the addition of acetic acid to the reaction led to no detectable formation of the 1,5-anhydro-compound **3.84**, with sole, stereoselective formation of the piperidine α-iminonitrile **3.88** (65%). This α-iminonitrile **3.88** was recrystallised and the relative configuration determined by both nuclear Overhauser effect spectroscopy (NOESY) and by single crystal X-ray diffraction (XRD) (**Figure 3.3**).

[*] Neutralisation of both the amine and also potassium cyanide was required.

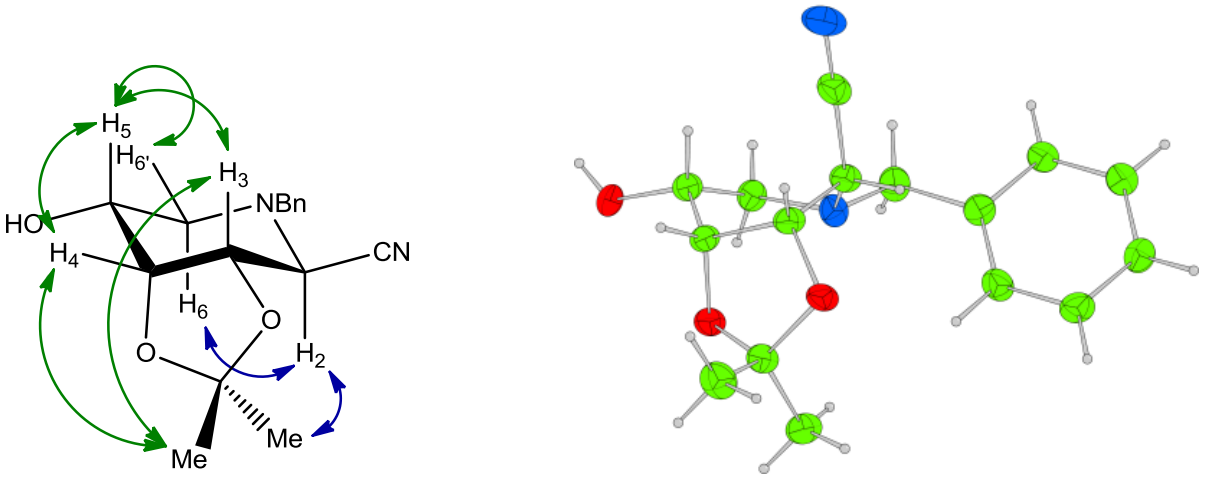
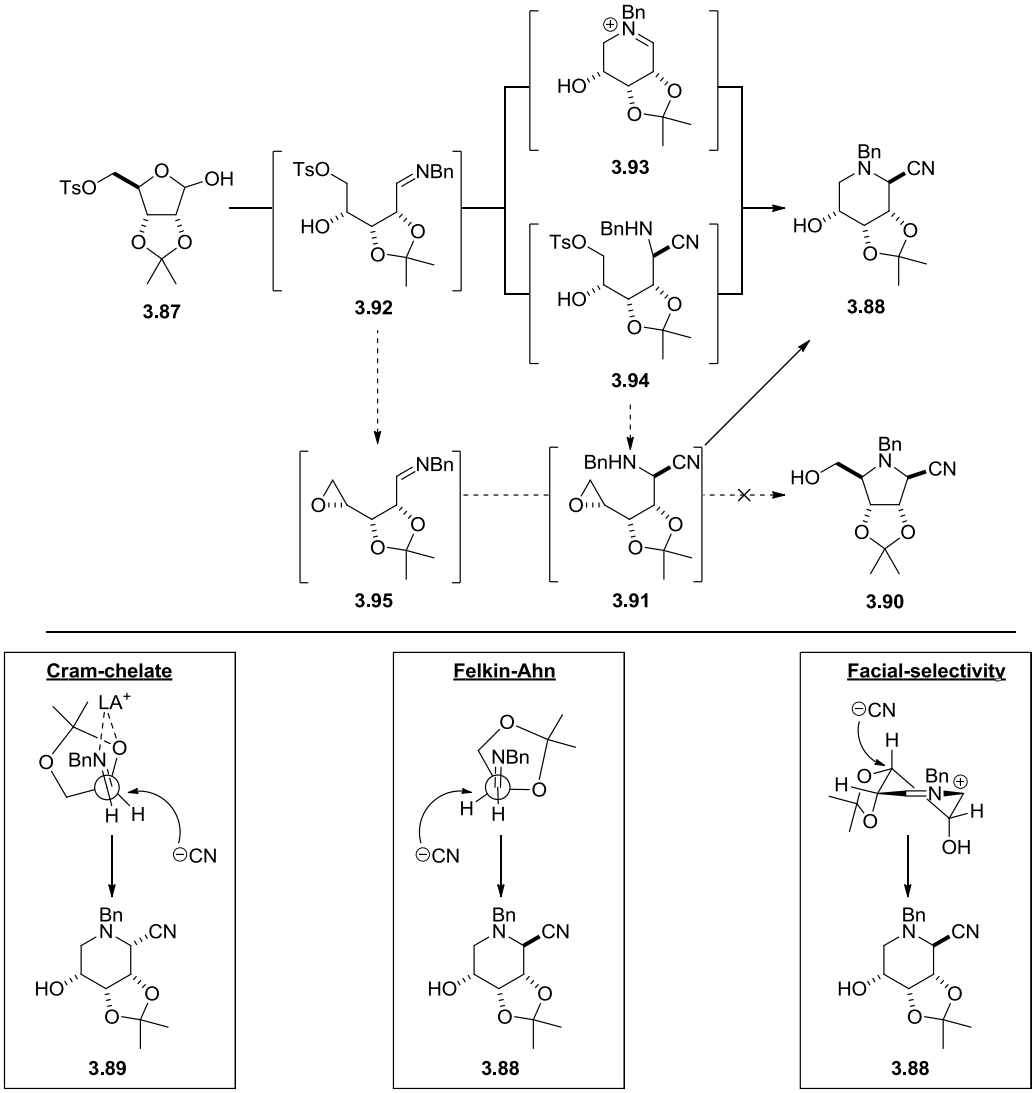



**Figure 3.3**. The relative configuration of the α-iminonitrile **3.88** as confirmed by NOESY and XRD. [see Appendix 1.2 for XRD data ]

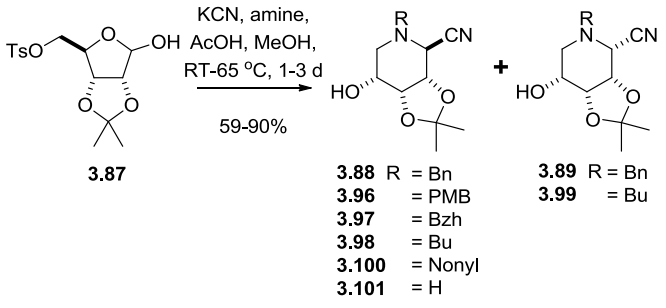
The selectivity of this reaction was remarkable for two reasons: the first being that none of the possible pyrrolidine nitrile by-product **3.90**, arising from epoxide (**3.91**) formation, was observed (**Scheme 3.16**). The second was that no trace of the epimeric α-iminonitrile **3.89** was isolated. This magnitude of selectivity has been previously observed in similar Strecker reactions of carbohydrates,[56,57,62,68] however the product observed in these cases varies. It has been suggested that reactions of this type conform to a Cram-chelate model,[62,68] but this pathway would in this reaction lead to the unobserved product **3.89**. Thus, if selectivity is determined by the addition of the cyanide to the open-chain imine **3.92** it is the Felkin-Ahn model of attack that dominates - this is in accordance with a previously reported precedent.[56] There may also be two further explanations for the selectivity displayed in this reaction: (i) it has been suggested that an axial-conformation of the nitrile is stabilised by a pseudo-anomeric effect, whereby the nitrogen lone-pair of electrons is in antiperiplanar alignment with the σ* C-CN antibonding orbital.[57,69,70,62] Indeed in the crystal structure of the α-iminonitrile **3.88** it can be seen that the nitrile group does adopt an axial conformation; (ii) if instead of considering addition to the open-chain imine **3.92**, we consider addition to the cyclised iminium species **3.93** - where iminocyclisation precedes attack by cyanide - then the selectivity of the reaction may be simply regarded as a facially-selective addition determined by the neighbouring bulky acetonide group.

There are multiple explanations as to the remarkable selectivity observed here, but the predominating influence cannot be deduced as the exact reaction pathway is unknown. However, it was envisaged that varying the reaction conditions may allow the accumulation of more information and potential elucidation of the governing force of selectivity in this novel TSRI method. To affect this three components were examined; (i) the temperature of reaction; (ii) the nature of the amine nucleophile; and (iii) the nature of the substrate (this last point will be examined in later sections of this chapter).




**Scheme 3.16**. Reaction pathways and models for selectivity.

Firstly, the influence of temperature on the TSRI conditions was examined (**Scheme 3.17**, **Table 3.1**, entries 1-3). Increasing the temperature of the reaction to 40 °C led to a dramatic increase in the overall yield over the same duration (90%). This also led to the appearance of a new, and inseparable* minor product of identical molecular weight and similar spectroscopic character to the α-iminonitrile **3.88**. This product constituted less that 5% of the recovered material and was judged to be the previously unobserved epimeric product **3.89**. Increasing the temperature to 65 °C gave a slight decrease in yield, owing to some decomposition, but also led to a marked decrease in the selectivity of the reaction - where over one third of the recovered material was the inseparable epimeric α-iminonitrile **3.89**. To assess whether the result observed at high temperature was of kinetic origin during the reaction, or thermodynamic by equilibration of the α-iminonitrile **3.88**, the pure α-iminonitrile **3.88** was subjected to the reaction conditions at 65 °C, where after sixteen hours no epimerisation was observed.




| | Amine | *T* (°C) | Yield (%) | Ratio |
|---|---|---|---|---|
| *1* | $BnNH_2$ | RT | 65 | 1:0 |
| *2* | $BnNH_2$ | 40 | 90 | >19:1[a] |
| *3* | $BnNH_2$ | 65 | 82 | 1.7:1[a] |
| *4* | $PMBNH_2$ | RT | 90 | 1:0 |
| *5* | $PMBNH_2$[b] | RT | 73 | 1:0 |
| *6* | $BzhNH_2$ | RT | 79[c] | 1:0 |
| *7* | $BuNH_2$ | RT | 60 | 4.8:1[a] |
| *8* | $NonylNH_2$ | RT | 65 | 1:0 |
| *9* | $NH_4OAc$ | 35 | 59 | 1:0 |

[a] Inseparable, ascertained by $^1H$ NMR integration; [b] TMSCN used as cyanide source; [c] based on recovered starting material

**Scheme 3.17** & **Table 3.1**. The effect of changing the reaction temperature and the amine nucleophile.

With the variance in temperature examined the second investigation into the influence of the amine nucleophile was probed. 4-Methoxybenzylamine ($PMBNH_2$, entries 4-5) proved to be a superior nucleophile when compared to unsubstituted benzylamine (entry 1). Over a similar

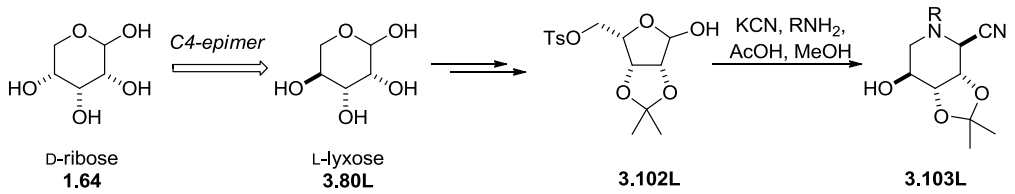
* The α-iminonitriles **3.88** and **3.89** proved to be inseparable in a wide range of solvent systems, as a result **3.89** was characterised from the mixture of these two epimeric products.

reaction time $PMBNH_2$ gave a higher yield of the α-iminonitrile **3.96** (90%, comparable to benzylamine at 40 °C [entry 2]) and equal selectivity - the epimeric α-iminonitrile product was never observed. At this point a different source of cyanide was briefly assessed with the use of trimethylsilylcyanide (TMSCN, entry 5). This gave identical selectivity but a lower overall yield, so this was not pursued further. The more hindered secondary-alkyl amine, benzhydrylamine (entry 6), required a substantially longer reaction time (3 d) but did result in the same specific selectivity giving the α-iminonitrile **3.97** in a good yield (68%, 79% brsm). Surprisingly butylamine (entry 7) gave reduced selectivity and an inseparable mixture of the α-iminonitriles **3.98** & **3.99** (4.8:1) in a moderate yield (60%). The longer chain nonylamine (entry 8) gave the α-iminonitrile **3.100** in the expected specific selectivity (65%), and treatment of the tosylate **3.87** with an excess of ammonium acetate[62,68,71] gave selectively the NH-free α-iminonitrile **3.101** albeit with a low 59% yield and an elevated reaction temperature required.

These changes demonstrated that in this D-ribose system, increases in the reaction temperature led to a decrease in the selectivity of the reaction; but also that a range of amine nucleophiles are well tolerated and do not significantly alter the observed selectivity. In addition the utilisation of a different cyanide source did not alter the results significantly. With this system investigated and a novel TSRI methodology established the following sections will examine the effect of altering the substrate, beginning with the other accessible pentose 2,3-acetonide, L-lyxose **3.83** (page 236).

3.3.2 From D-/L-lyxose

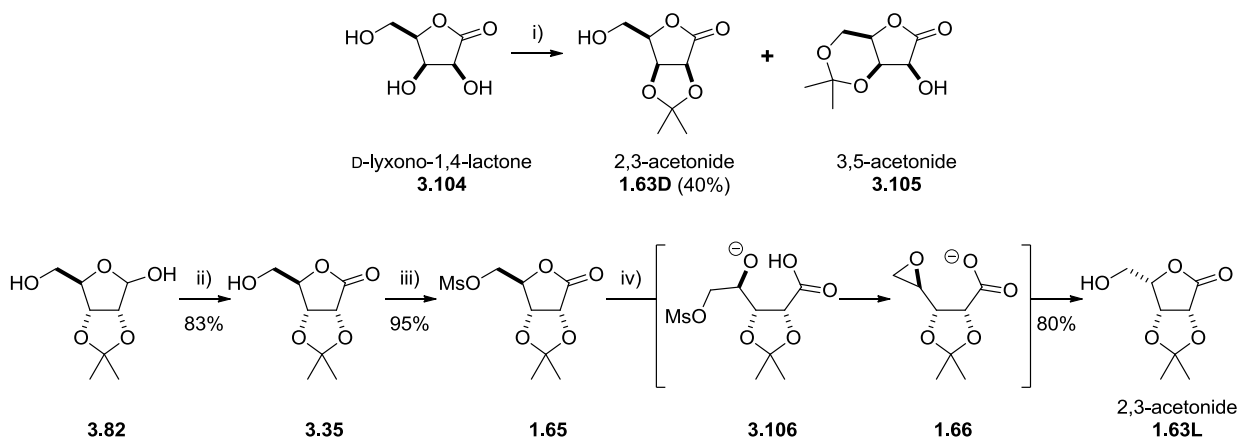
L-Lyxose **3.80L** is the C4-epimer of D-ribose **1.64**, and it was anticipated that the methodology developed in the preceding D-ribose system (Section 3.3.1) could be expanded to accommodate this starting material (**Scheme 3.18**). It was also expected that given the Felkin-Ahn or iminium-facial selectivity postulated in the previous cyanide addition (**Scheme 3.16**, page 239), the outcome of the reaction in this system would demonstrate similar stereoselectivity.




**Scheme 3.18**. Expansion to an L-lyxose substrate.

Of the two enantiomers of lyxose **3.80**, L-lyxose **3.80L** is the naturally occurring enantiomer, however this monosaccharide is not abundant and this scarcity leads to a lack of its availability. The L-*lyxo* configuration, however, may be accessed in short synthetic routes from protected D-ribono-1,4-lactone **3.82**[63,64] or from D-gulono-1,4-lactone **3.81**[65] as previously highlighted (**Scheme 3.13**, page 236). Alternatively the "unnatural" enantiomer D-lyxose is commercially available in the lactone form (D-lyxono-1,4-lactone **3.104**), and is comparatively cheaper. It was envisaged that the oxidised anomeric centre of lyxonolactone would afford protection during the esterification of the C5-hydroxyl with tosyl chloride, with simple DIBAL-H reduction then forming the desired tosylate lactol **3.102**. For the D-lyxose system acetonide protection of D-lyxono-1,4-lactone **3.104** with acetone and anhydrous copper(II) sulfate allowed access to the 2,3-acetonide **1.63D** in a low 40% yield (**Scheme 3.19**). The poor separability of the 2,3- **1.63D** and 3,5-acetonides **3.105** accounts for this low return of product (56% a mixture of these acetonides). The enantiomeric protected L-lyxono-1,4-lactone **1.63L** was accessed from 2,3-acetonide protected D-ribose **3.82** *via* a literature procedure previously described in

**Scheme 1.17** (page 32).[63,64] The D-ribose acetonide **3.82** was oxidised to the lactone **3.35** by reaction with bromine in the presence of barium carbonate (83%). The C5-hydroxyl was then activated as the mesylate **1.65** by esterification with mesyl chloride and triethylamine in DCM (95%). Treatment of mesylate **1.65** with aqueous potassium hydroxide led to opening of the lactone ring (of **3.106**) and intramolecular mesylate displacement forming the epoxide-carbonate **1.66**. Acidification of the reaction mixture with glacial acetic acid facilitated 5-*exo*-tet cyclisation and formation of the desired L-lyxono-1,4-lactone acetonide **1.63L** in an excellent 80% yield.

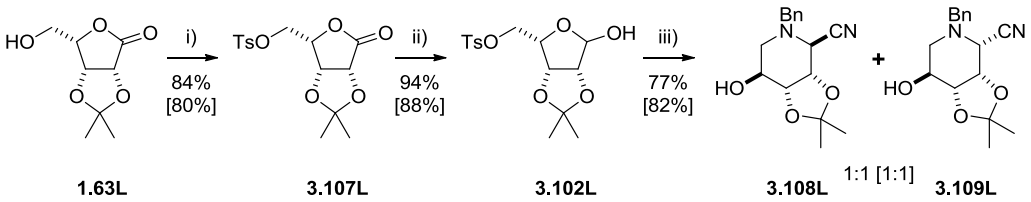



**Reagents & conditions**: i) acetone, $CuSO_4$, RT, 17 h; ii) $Br_2$, $BaCO_3$, $H_2O$, 0 °C to 10 °C, 2.5 h; iii) MsCl, $Et_3N$, DCM, 0 °C, 2 h; iv) KOH, $H_2O$/1,4-dioxane, RT, 1 h; *then* AcOH, 17 h.

**Scheme 3.19**. Synthesis of the enantiomeric lyxono-1,4-lactones **1.63**.[63,64]

With the enantiomeric lactones **1.63** in hand their subsequent treatment was identical (**Scheme 3.20**). Esterification of the L-enantiomer with tosyl chloride and pyridine gave the tosylate **3.107L** (84%, [80%]*), and reduction with DIBAL-H afforded the desired lactol **3.102L** (94%, [88%]). Subsequent treatment of the lactol **3.102L** under the TSRI conditions with benzylamine, led to the formation of equal proportions of the both the expected **3.108L** and the epimeric α-iminonitriles **3.109L** (77%, [82%]).

* Square parentheses denote the yield for the enantiomeric system [%], or the ratio of enantiomeric products [A:B].

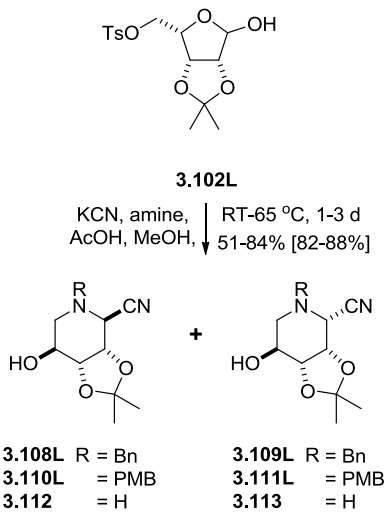



**1.63L** **3.107L** **3.102L** **3.108L** **3.109L**

**Reagents & conditions**: i) TsCl, pyr, 0 °C to RT, 4 h; ii) DIBAL-H, DCM, -78 °C, 1.5 h; iii) KCN, $BnNH_2$, AcOH, MeOH, RT, 3 d.

**Scheme 3.20**. Synthesis of the *lyxo*-configured tosylate-lactols **3.102**.

This result is at odds with that expected from the original D-ribose system, the reaction itself was relatively sluggish - taking three days to reach completion - and there was a complete absence of any stereoselectivity in cyanide addition. After this result, the effect of temperature and amine nucleophile was briefly examined (**Scheme 3.21** & **Table 3.2**). Changing the amine nucleophile from benzylamine to $PMBNH_2$ (entry 2) led to the formation of the α-iminonitriles **3.110L** and **3.111L**, with a small increase in yield (82%, [84%] from 77%, [82%]), a slight decrease in reaction time (2 d from 3 d) and no observable difference in the ratio of the α-iminonitriles formed. Increasing the temperature of the reaction to 40 °C (entry 3) led to an increase in selectivity (**3.110L**:**3.111L**; 1.4:1, [2:1]), and increasing further to 65 °C (entry 4) gave a greater increase (2:1, [2.3:1]). The observed trend of increasing Felkin-Ahn product selectivity with increasing reaction temperature is the opposite of that demonstrated by the preceding D-ribose system. However this increase is small and does not amount to stereospecificity. Finally, the L-*lyxo* tosylate **3.102L** was reacted with an excess of ammonium acetate at 40 °C which gave a low yield (51%) of an inseparable mixture (1.8:1) of the NH-free α-iminonitriles **3.112** and **3.113**.




| | Amine | *T* (°C) | Yield (%) | Ratio |
|---|---|---|---|---|
| *1* | $BnNH_2$ | RT | 77 [82][a] | 1:1 [1.1] |
| *2* | $PMBNH_2$ | RT | 82 [84] | 1:1 [1:1] |
| *3* | $PMBNH_2$ | 40 | 84 [85] | 1.4:1 [2:1] |
| *4* | $PMBNH_2$ | 65 | 83 [88] | 2:1 [2.3:1] |
| *5* | $NH_4OAc$ | 40 | 51[b] | 1.8:1[c] |

[a] [ ] denotes yield for enantiomeric system; [b] reaction not performed on enantiomeric system; [c] Inseparable - ascertained by $^1$H NMR integration.

**Scheme 3.21** & **Table 3.2**. The effect of changing the reaction temperature and the amine nucleophile.

Unlike the mixture of α-iminonitriles **3.88** and **3.89** that arose in the D-ribose system, the mixtures of the PMB- and benzyl-protected α-iminonitriles obtained here (**3.108L** & **3.109L**, and **3.110L** & **3.111L**) were separable, but unfortunately it was not possible to obtain X-ray crystal structures of these α-iminonitriles. The structure of each was instead elucidated by the use of heteronuclear multiple-bond correlation (HMBC) spectroscopy and NOESY NMR experiments (**Figure 3.4**). The former experiment establishes the proton-carbon atom connectivity over three-bonds and from this the ring-size of the product can be inferred. Correlations between C6-H2 and between C2-H6/6' indicates the formation of a piperidine ring, whereas a correlation between C5-H2 and between C2-H5 would demonstrate a pyrrolidine ring. The latter experiment allows for the elucidation of the nitrile stereochemistry by determining on which face of the molecule the H2 proton lies. In the previous D-ribose system (**Figure 3.3**, page 238) the α-iminonitrile **3.88** adopted a chair/twisted-chair conformation, allowing for a pseudo-anomeric overlap between the lone-pair of the endocyclic nitrogen atom and the antibonding orbital of the axial carbon-nitrile bond to develop. In the case of the α-iminonitriles **3.110L** and **3.111L** generated in this L-lyxose system, the determination of the structure was considerably more difficult. The NOESY spectrum of each indicated that neither α-iminonitrile possessed a

correlation between the H2 proton and an H6 proton. A correlation of this type would be expected in a chair/twisted-chair conformation due to the proximity of the axial H2 and H6 protons in space. This indicated that one or both of these α-iminonitriles did not adopt a chair conformation. Supporting this is the lack of correlation between the H5 and H6/6' protons, which is also expected in chair-like conformations. From this it was inferred that both α-iminonitrile epimers arising from this lyxose system may adopt boat/twisted-boat conformations - a particularly surprising result given the high level of strain that would exist in these molecules, especially in **3.110L** with two flagpole substituents. However, in the absence of X-ray crystal structures, it is impossible to confirm this structural supposition, as it is based solely on comparison to the α-iminonitrile **3.88** arising from the original D-ribose system. As a result it is only the correlation between the H2 proton and an acetonide methyl-group that determines the configuration of each epimer, with this being present in the case of **3.110L** and absent for **3.111L**.

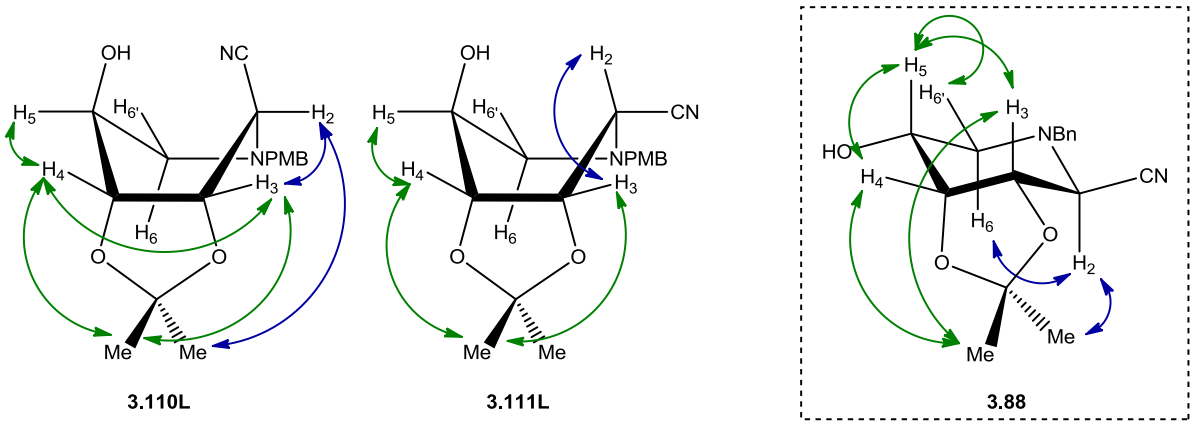
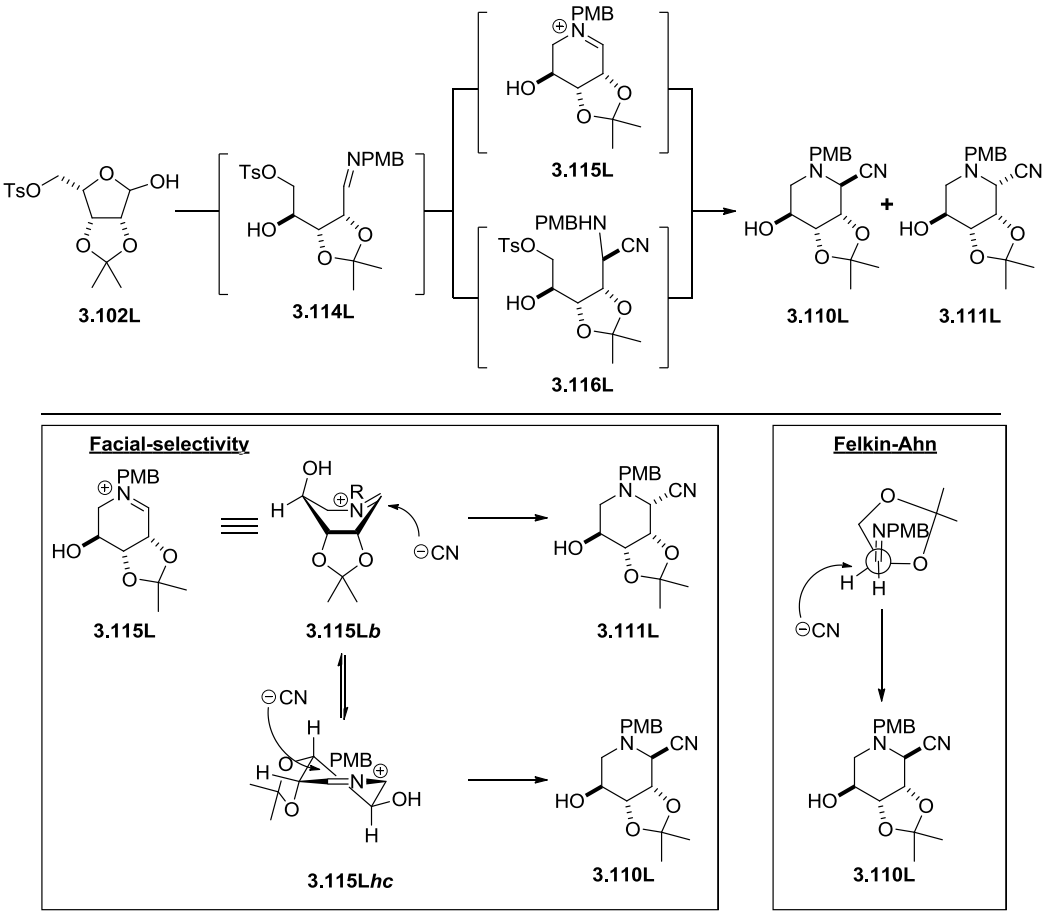



**Figure 3.4**. The relative configuration of the α-iminonitriles **3.110L** and **3.111L** confirmed by NOESY; the NOESY correlation of the α-iminonitrile **3.88** is also included for comparison.

In terms of the selectivity demonstrated in cyanide addition, as mentioned earlier, this was the inverse of that observed for the original D-ribose route. Based on the assumption that the reaction pathways for both systems should theoretically be similar, it cannot be said that the outcome of the reaction is determined by the Felkin-Ahn type addition of cyanide to the open-chain

imine **3.114L** (**Scheme 3.22**), as the only change in the substrate is the C4-hydroxyl configuration - too distant to affect the Felkin-Ahn model.




**Scheme 3.22**. Selectivity rationale for cyanide addition in the *lyxo*-configured system.

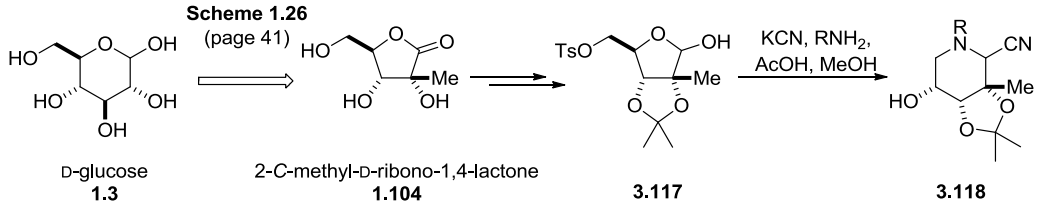
From the original reasoning for selectivity in the D-ribose system there are two other potential causes, either; (i) a stabilising pseudo-anomeric effect, or (ii) a feature of facial-selectivity in addition of cyanide to the iminium-intermediate **3.115L**. The former reason is unlikely as the α-iminonitrile **3.111L** would be expected to adopt a twisted-chair conformation, much like that of the earlier α-iminonitrile **3.88**. The outcome of the latter would be expected to be identical to the Felkin-Ahn product, unless the conformation of the iminium-intermediate **3.115L** is not that of a half-chair **3.115L*hc***. This may prove a plausible and indeed reasonable explanation. The adoption of a boat-like conformation by the iminium intermediate **3.115L*b*** would promote

equatorial attack by cyanide, rather than that of axial expected for the half-chair **3.115L*hc***, due to the sterically hindering flag-pole interactions of the C4-hydroxyl. Cyanide attack in an equilibrium of both iminium structures thus accounts for the product distribution, and the increase in temperature leads to a bias in the equilibrium for the half-chair state **3.115L*hc*** which would give an increase in the α-iminonitrile **3.110L**, contrary to the observed reduction in selectivity with increasing temperature observed for the D-ribose products. In the case of the D-ribose system it can be inferred that an increase in temperature leads to possible adoption of a similar boat-like iminium intermediate conformation and a degree of equatorial attack. Although in this case there would be no flag-pole C4-hydroxyl steric hindrance to axial attack by cyanide.

With these observed results, and a rationale developed with regards to the selectivity obtained, this chapter moves on to the utilisation of methyl-branched starting material equivalents of D-ribose and L-lyxose. The reason for testing this kind of structural variation is three-fold: (i) in some cases methyl-branched iminosugars have been shown to increase the level of specificity for particular glycosidases;[72,73] (ii) methyl-branching allows further potential for insight into the structure-activity relationship between certain iminosugar scaffolds and glycosidases; and most importantly (iii) the potential enantioselective assembly of quaternary centres poses an important synthetic challenge - these could be assembled by applying this methodology to anomerically methyl-branched sugars, or 1-deoxy-ketoses, of which there is only one known example (**Scheme 3.6**, page 229).[55] Alternatively the presence of sterically hindering quaternary centres in the reaction substrate also allows for the probing of the limitations of this novel TSRI methodology. With this in mind the next section of the thesis describes the research conducted towards methyl-branched α-iminonitriles.

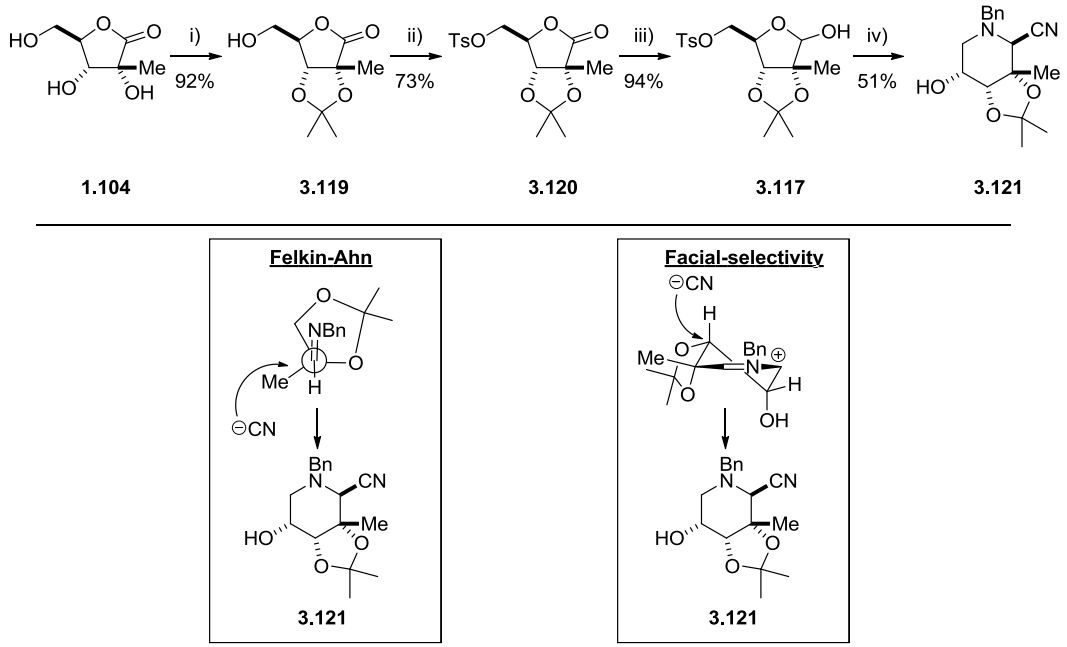
3.3.3 From 2-*C*-methyl-D-ribono-1,4-lactone

In **Chapter 1** (Section 1.6.3.3, pages 39-42) the general methods for accessing branched sugars were introduced. In particular **Scheme 1.26** (page 41) demonstrated access to the 2-*C*-methyl-branched analogue of D-ribono-1,4-lactone, 2-*C*-methyl-D-ribono-1,4-lactone **1.104**, afforded by the Amadori and subsequent benzilic acid rearrangement of D-glucose **1.3**.[74-77] This branched-sugar presents a readily accessible starting material and also would lead to the incorporation of a quaternary centre in the target piperidine α-iminonitriles **3.118** (**Scheme 3.23**).




**Scheme 3.23**. Expansion to a 2-*C*-methyl-D-ribose substrate.

In order to access the desired TSRI starting material, tosylate **3.117**, 2-*C*-methyl-D-ribono-1,4-lactone **1.104** was treated in an analogous fashion to D-lyxono-1,4-lactone **1.63D** in the preceding route. First, the 2,3-hydroxyl moiety was protected as the 2,3-acetonide **3.119** (**Scheme 3.24**), by reaction with acetone, sulfuric acid and anhydrous copper(II) sulfate (92%).[78] Second, the free, primary C5-hydroxyl was esterified with tosyl chloride in pyridine to form the tosylate lactone **3.120** (73%),[79] and finally DIBAL-H reduction gave the desired tosylate lactol **3.117** in an excellent 94% yield. With the desired tosylate **3.117** accessed, the first TSRI was attempted under the standard conditions with benzylamine as the amine nucleophile.




**Reagents & conditions**: i) acetone, $CuSO_4$, $H_2SO_4$, RT, 1 d; ii) TsCl, pyr, 0 °C to RT, 1 d; ii) DIBAL-H, DCM, -78 °C, 1 h; iv) KCN, $BnNH_2$, AcOH, MeOH, RT, 4 d.

**Scheme 3.24**. Accessing a piperidine α-iminonitrile from 2-*C*-methyl-D-ribonolactone; and the Felkin-Ahn/facially-selective addition rationales.

In comparison with the original D-ribose system this reaction was sluggish, accessing the piperidine α-iminonitrile **3.121** in over four days and only achieving a relatively poor 51% yield. However this methyl-branched system did display identical stereoselectivity to that of the parent system despite the presence of the bulky 2-*C*-methyl-group disfavouring the Felkin-Ahn, or facially selective attack of the imine/iminium intermediates by cyanide. This piperidine α-iminonitrile **3.121** was also extremely crystalline, allowing the relative structure to be determined by X-ray crystallography (**Figure 3.5**).[80]

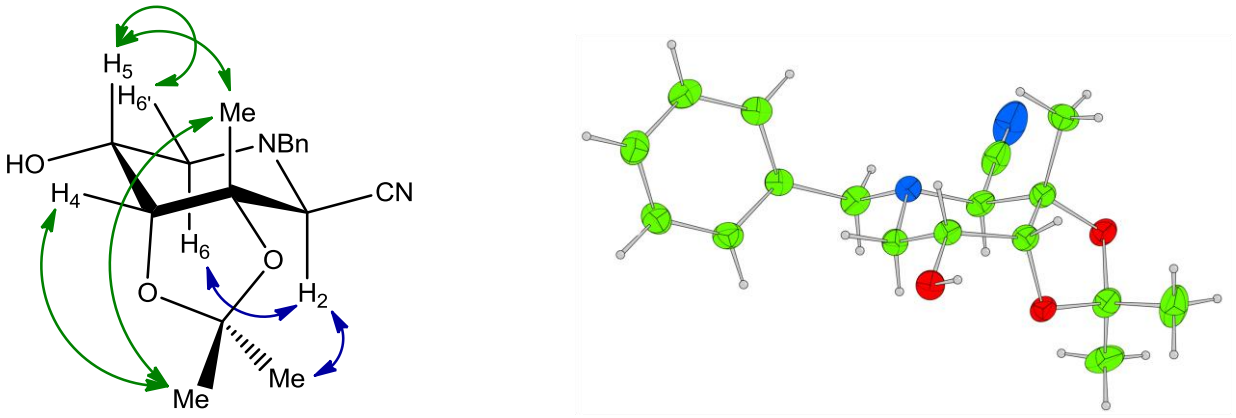
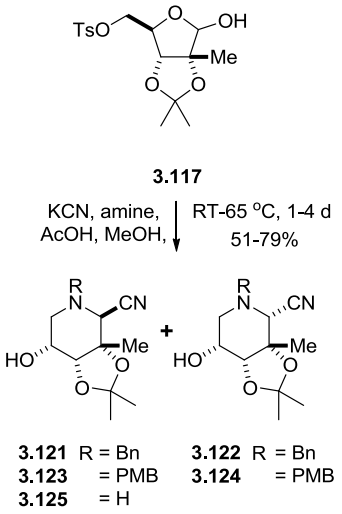



**Figure 3.5**. The relative configuration of the α-iminonitrile **3.121** confirmed by NOESY and by XRD.[80] [see Appendix 2 for XRD data]

Despite the similarity in selectivity of the reaction there is a interesting contrast between the crystal structures of the piperidine α-iminonitriles arising from the D-ribose and 2-*C*-methyl-D-ribono-1,4-lactone systems. In the former, parent route the piperidine α-iminonitrile **3.88** (**Figure 3.3**, page 238) possessed an axial nitrile disposition and it was suggested that this molecule in a half-chair configuration was stabilised by a pseudo-anomeric effect whereby the endocyclic-nitrogen lone pair was delocalised with the σ* C-CN antibonding orbital. However, it can be seen that in the latter case, the neighbouring bulky methyl-branch in the piperidine α-iminonitrile **3.121** (**Figure 3.5**, page 250) leads to the adoption of a chair conformation and no pseudo-anomeric overlap being possible, accommodating instead the steric demands of this more hindered system.

As with the two previous systems the effect of changing the reaction temperature and amine nucleophile was briefly assessed (**Scheme 3.25 & Table 3.3**).




| | Amine | *T* (°C) | Yield (%) | Ratio |
|---|---|---|---|---|
| *1* | $BnNH_2$ | RT | 51 | 1:0 |
| *2* | $BnNH_2$ | 40 | 79 | 15:1[a] |
| *3* | $BnNH_2$ | 65 | 73 | 4.4:1[a] |
| *4* | $PMBNH_2$ | RT | 68 | 1:0 |
| *5* | $PMBNH_2$ | 40 | 79 | >19:1[a] |
| *6* | $NH_4OAc$ | 40 | 71 | 1:0 |

[a] Inseparable - ascertained by $^1$H NMR integration.

**Scheme 3.25** & **Table 3.3**. The effect of changing the reaction temperature and the amine nucleophile.

Increasing the temperature of the reaction (entry 2) led to a dramatic rise in the overall yield (from 51% to 79%) and a reduction in the reaction time (from 4 d to 2 d), but was associated with a drop in the selectivity of the cyanide addition (**3.121**:**3.122**, 15:1).

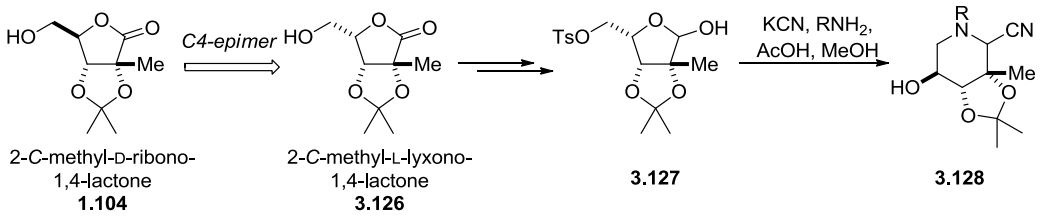
Compared with the parent D-ribose system at this temperature, the ratio of piperidine α-iminonitrile products was still >19:1. Raising the temperature further (entry 3) led to the reaction time reducing to one day, a slight drop in yield (73%) - due to some decomposition - and as could be expected, a reduction in selectivity (4.4:1). The comparative drop in selectivity at 65 $^{o}$C for the parent D-ribose system was greater (1.7:1). Again $PMBNH_2$ proved to be a superior nucleophile (entry 4), with a greater yield of the piperidine α-iminonitrile **3.123** being obtained at RT over a similar duration of reaction (3 d, 68%). The reaction conducted at 40 $^{o}$C (entry 5) demonstrated an expected increase in yield (79%), gratifyingly without the loss of selectivity (>19:1). Unfortunately, both the mixtures of the benzyl- and PMB-protected piperidine α-iminonitriles (**3.121**/**3.122** and **3.123**/**3.124**) proved not to be amenable to chromatographic separation.[*] Finally, reaction with an excess of ammonium acetate (entry 6) gave the NH-free piperidine α-iminonitrile **3.125** in a good 71% yield over four days at 40 $^{o}$C. The results of these variations in the reaction conditions of the system demonstrated a close correlation with that of the parent D-ribose system. They also show that the reactions conditions for TSRI may be expanded successfully to a more sterically hindered substrate.

The following section will assess whether these conditions may be applied to the C4-epimeric 2-*C*-methyl-L-lyxono-1,4-lactone system, and whether this is similarly related to its parent, unbranched lyxose route

[*] As a result the α-iminonitrile **3.122** was characterised from the inseparable mixture of **3.121**/**3.122**. The minor component of the >19:1 mixture of **3.123** was assumed to be **3.124** although could not be thoroughly assigned.

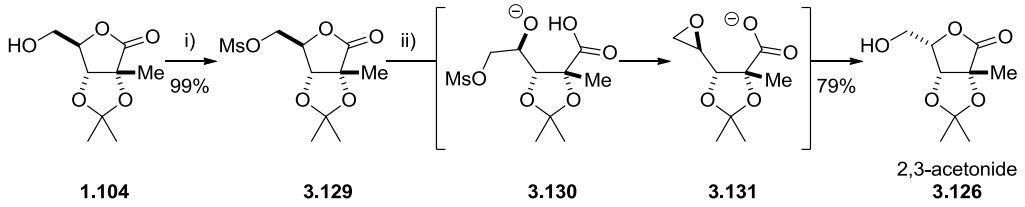
3.3.4 From 2-*C*-methyl-L-lyxono-1,4-lactone

In the unbranched L-lyxose system (Section 3.3.2, pages 242-248) it was shown that L-lyxono-1,4-lactone **1.63L** may be accessed in a short synthetic sequence from 2,3-acetonide protected D-ribono-1,4-lactone **3.35** (**Scheme 3.19**, page 243),[63,64] and this methodology has also been applied to the access of 2-*C*-methyl-L-lyxono-1,4-lactone **3.126** (**Scheme 3.26**).[78] From here it was envisaged that the tosylate lactol **3.127** would be accessed in an identical fashion to that of the preceding, epimeric system. It is also expected, given the observations of the parent lyxose system, that the TSRI of this system will be both sluggish, even at increased temperatures, and demonstrate poor overall selectivity in cyanide addition.




**Scheme 3.26**. Expansion to a 2-*C*-methyl-L-lyxose substrate.

In order to access 2-*C*-methyl-L-lyxono-1,4-lactone **3.126** (**Scheme 3.28**) the free C5-hydroxyl of 2-*C*-methyl-D-ribono-1,4-lactone **1.104** was esterified with methanesulfonyl chloride and pyridine to afford the mesylate **3.129** almost quantitatively (99%). This mesylate **3.129** was treated with aqueous potassium hydroxide which, under the proposed reaction mechanism, elicited the opening of the lactone ring to the open-chain intermediate **3.130** and subsequent intramolecular mesylate displacement forming the epoxide carboxylate **3.131**. Acidification of the reaction mixture gave selective intramolecular epoxide-opening and formation of the desired 2-*C*-methyl-L-lyxono-1,4-lactone **3.126** in an excellent 79% yield.

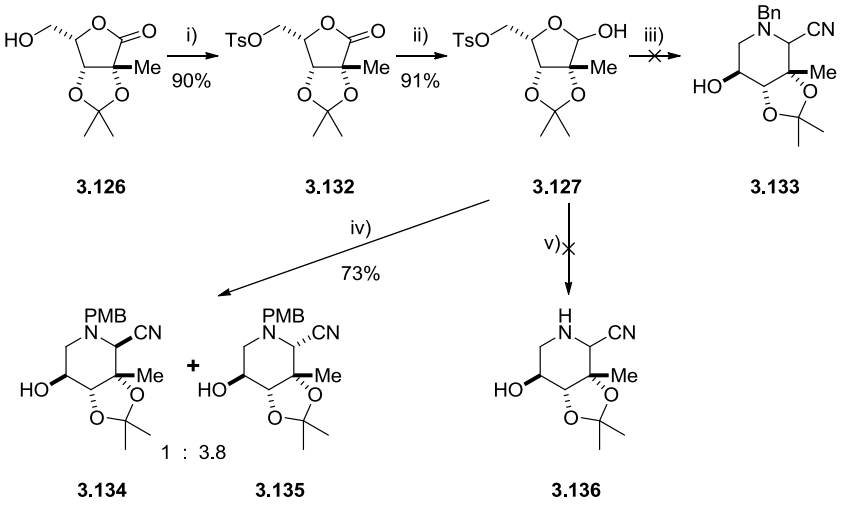



**1.104** **3.129** **3.130** **3.131** **3.126**

**Reagents & conditions**: i) MsCl, pyr, DCM, 0 °C to RT, 3 h;
ii) KOH, $H_2O$/1,4-dioxane, RT, 1.5 h; *then* 2 M AcOH, 1 h.

**Scheme 3.27**. Synthesis of 2-*C*-methyl-L-lyxono-1,4-lactone **3.126**.[78]

Following this the free C5-hydroxyl of the lactone **3.126** then underwent esterification with tosyl chloride in pyridine to afford the tosylate lactone **3.132** (90%), which was reduced with DIBAL-H to give the tosylate lactol **3.127** in a 91% yield (**Scheme 3.28**). This tosylate lactol **3.127** was reacted under the TSRI conditions with benzylamine at RT in order to access the desired piperidine α-iminonitrile **3.133**. The reaction was expected to be sluggish at RT, but the additional steric hindrance of the 2-*C*-methyl group prevented the reaction from occurring, with no reaction detectable under these conditions.



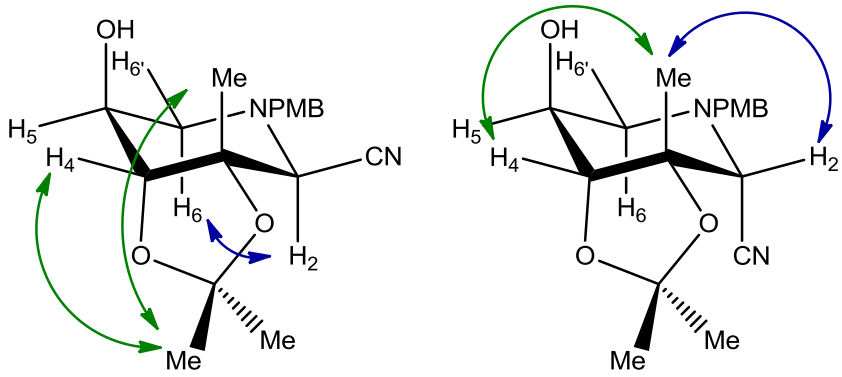

**3.126** **3.132** **3.127** **3.133**

**3.134** **3.135** **3.136**

**Reagents & conditions**: i) TsCl, pyr, 0 °C to RT, 14 h;
ii) DIBAL-H, DCM, -78 °C, 2 h; iii) KCN, $BnNH_2$, AcOH, MeOH, RT, 7 d;
iv) KCN, $PMBNH_2$, AcOH, MeOH, 50 °C, 2 d; v) KCN, $NH_4OAc$, AcOH, MeOH, 50 °C, 7 d.

**Scheme 3.28**. Accessing piperidine α-iminonitriles from 2-*C*-methyl-L-lyxonolactone.

As $PMBNH_2$ had proved to be a better nucleophile in preceding systems, it was used in a subsequent reaction at 50 °C which gratifyingly gave a TSRI and forming an inseparable 1:3.8 mixture of the piperidine α-iminonitriles **3.134** & **3.135** (73%). Similarly to the unbranched parent, and separable, piperidine α-iminonitriles **3.110L** and **3.111L** (pages 246-247) the structural assignment of this inseparable mixture was difficult, but could be determined by NOESY (**Figure 3.6**). The major component was the α-iminonitrile **3.135** and the minor component α-iminonitrile **3.134**, both judged to exist in a chair-like conformation. Reaction of the tosylate lactol **3.127** with an excess of ammonium acetate also proved to be unsuccessful over a prolonged reaction period (7 d) at 50 °C and the free-NH piperidine α-iminonitriles **3.136** were not detected or isolated. The reactions of the 2-*C*-methyl-L-lyxono-1,4-lactone system began to show the limitations of the TSRI methodology towards sterically hindered substrates, as they were sluggish and ultimately proved to be unsuccessful at RT.




**3.134** *minor*

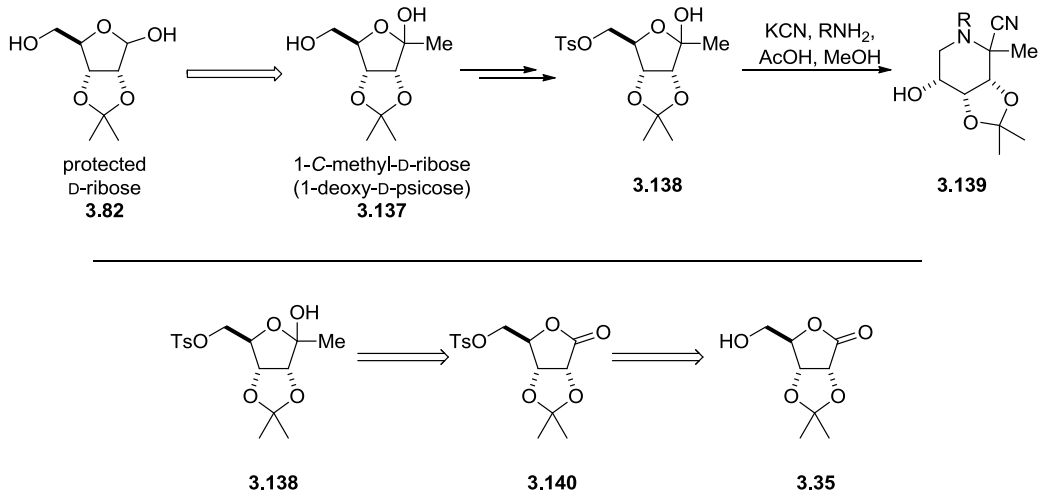
**3.135** *major*

**Figure 3.6**. The relative configuration of the α-iminonitriles **3.134** & **3.135** determined by NOESY.

With the effect of 2-*C*-methyl-branching assessed for both the D-ribose and L-lyxose configurations, the next stage was in determining the possibility of assembling a quaternary nitrile centre under the TSRI conditions from a 1-*C*-methyl branched substrate. The following sections describe the research conducted towards this goal for both D-*ribo*- and L-*lyxo*-configurations.

3.3.5 From 1-*C*-methyl-D-ribose (1-deoxy-D-psicose)

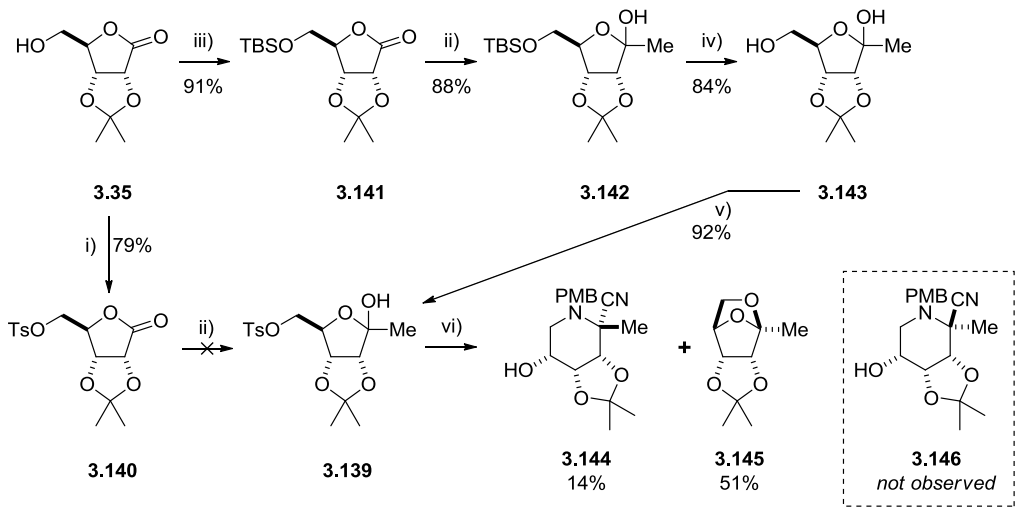
The application of the TSRI methodology towards a 1-*C*-methyl-branched system (formally a 1-deoxy-ketose) would allow for the assembly of a quaternary centre during the reaction, and access to a quaternary piperidine α-iminonitrile. For the D-*ribo*-configuration this would entail accessing 1-*C*-methyl-D-ribose **3.137** (**Scheme 3.29**), systematically named 1-deoxy-D-psicose. From here the 5-*O*-tosylate **3.138** could be accessed chemoselectively and the TSRI methodology applied to this system. It was envisaged that methyllithium addition to the tosylate lactone **3.140** would afford the tosylate ketose **3.138**. The tosylate group would act here as both a protecting group for the C5-hydroxyl during the methyllithium addition and the desired leaving group in the following TSRI. The tosylate lactone **3.140** itself would then arise from tosylation of acetonide-protected D-ribono-1,4-lactone **3.35**.




**Scheme 3.29**. Expansion to a 1-*C*-methyl-D-ribose (1-deoxy-D-psicose) substrate and proposed route from D-ribono-1,4-lactone.

Acetonide-protected D-ribono-1,4-lactone **3.35** was taken and esterified with tosyl chloride and pyridine to afford the tosylate lactone **3.140** in a 79% yield (**Scheme 3.30**).[81] The treatment of this tosylate lactone **3.140** with methyllithium did not meet with success and a complex mixture of non-isolable products resulted. In an alternative route to the desired tosylate ketose **3.138**, the

free C5-hydroxyl of lactone **3.35** was protected as the silyl ether **3.141** by reaction with TBSCl in pyridine (91%). Treatment of the protected lactone **3.141** with methyllithium proceeded smoothly this time to afford the lactol **3.142** as a single anomer (88%). Cleavage of the silyl ether protecting group with TBAF gave the diol **3.144** (84%), and selective tosylation at low temperature afforded the desired tosylate ketose **3.138** in an excellent 92% yield.[82-84] From here formation of a piperidine α-iminonitrile proved troublesome. Under the developed TSRI reaction conditions with $PMBNH_2$ at room temperature the reaction did not yield a product, and at elevated temperature the presence of the methyl-branch promoted formation of the 2,6-anhydro-compound **3.145** (51% at 40 °C) with the reaction being sluggish and taking two days for isolable levels of the piperidine α-iminonitrile **3.144** to be formed (14%).




**Reagents & conditions**: i) TsCl, pyr, 0 °C to RT, 5 h; ii) MeLi, THF, -78 °C, 2 h; iii) TBSCl, pyr, RT, 15 h; iv) TBAF, THF, RT, 4 h; v) TsCl, pyr, -30 °C to RT, 6 h; vi) KCN, $PMBNH_2$, AcOH, MeOH, 40 °C, 2 d.

**Scheme 3.30**. Accessing a quaternary piperidine α-iminonitrile.

Despite a difficult reaction and preferential formation of an undesired by-product, the piperidine α-iminonitrile **3.144** was formed stereoselectively, and the relative configuration confirmed by HMBC and NOESY spectroscopy (**Figure 3.7**), although this was not the selectivity that was anticipated. From the preceding D-ribose and 2-*C*-methyl-D-ribono-1,4-lactone routes

(Sections 3.3.1 & 3.3.3, pages 236-241 & 249-252, respectively) it was expected that the C2-epimer **3.146** would predominate - however this piperidine α-iminonitrile was never observed. It was not possible to gather further data to establish a rationale for this observed selectivity as increased reaction temperature led to the sole formation of the anhydro-compound **3.145**, and a decrease in temperature led to no reaction being detected. However, with the first quaternary piperidine α-iminonitrile isolated, it could be assessed whether it was possible to form another from an equivalent L-*lyxo*-configured system.

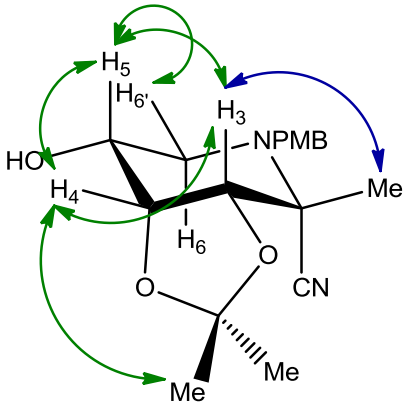
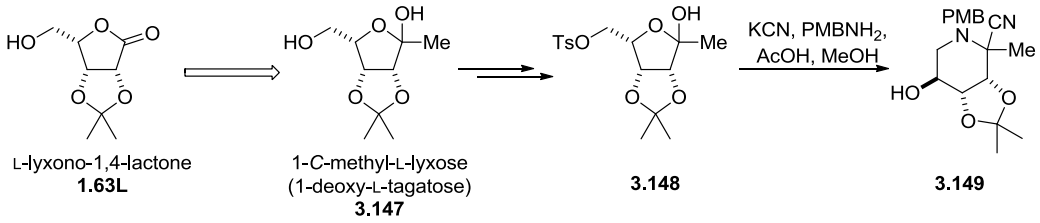


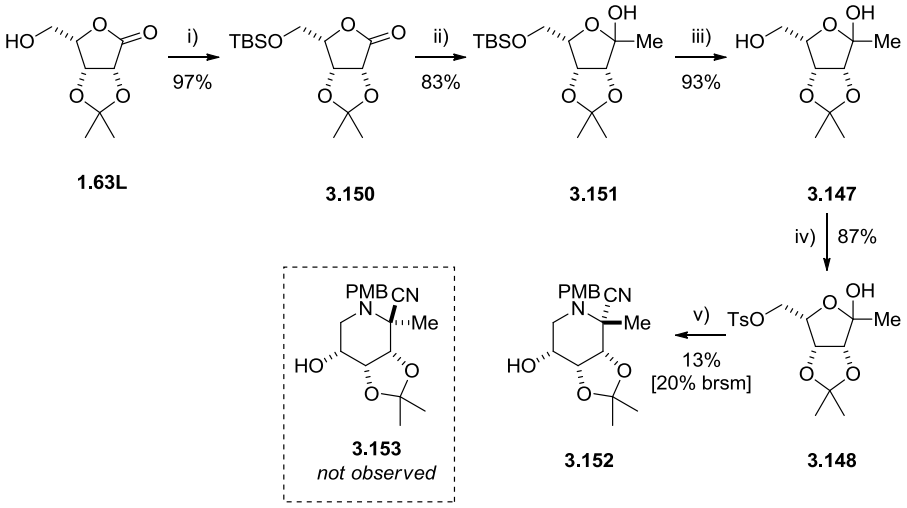

**Figure 3.7**. The relative configuration of α-iminonitrile **3.145** confirmed by NOESY.

### *3.3.6 From 1-C-methyl-L-lyxose (1-deoxy-L-tagatose)*




**Scheme 3.31**. Expansion to a 1-*C*-methyl-L-lyxose (1-deoxy-L-tagatose) substrate.

It was envisaged that the required tosylate hemiacetal **3.148** could be accessed from the protected L-lyxono-1,4-lactone **1.63L**, in an identical fashion to the preceding system, *via* the protected 1-*C*-methyl-L-lyxose compound (1-deoxy-L-tagatose) **3.147** (**Scheme 3.31**). In order to affect this, L-lyxono-1,4-lactone **1.63L** was protected as the silyl ether **3.150** by reaction with TBSCl and pyridine (97%) (**Scheme 3.32**). Treatment of this silyl ether **3.150** with methyllithium at -78 $^{o}$C afforded the protected lactol **3.151** in good yield (83%), and subsequent use of TBAF efficiently cleaved the silyl protecting group. This gave the lactol **3.147** (93%), and with this lactol in hand the required selective tosylation proceeded smoothly and chemoselectively to afford the tosylate hemiacetal **3.148** in an excellent 87% yield.



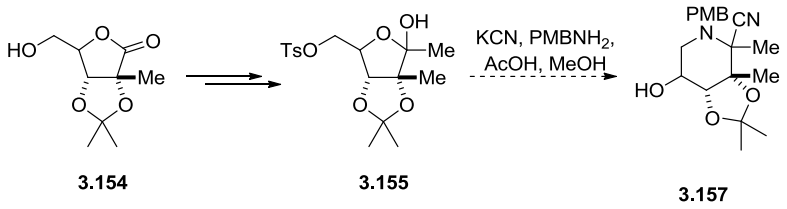

**Reagents & conditions**: i) TBSCl, pyr, RT, 16 h; ii) MeLi, THF, -78 $^{o}$C, 4 h;
iii) TBAF, THF, RT, 4 h; iv) TsCl, pyr, -30 $^{o}$C to RT, 17 h;
v) KCN, $PMBNH_2$, AcOH, MeOH, 50-65 $^{o}$C, 2 d.

.

**Scheme 3.32**. Accessing a quaternary piperidine α-iminonitrile.

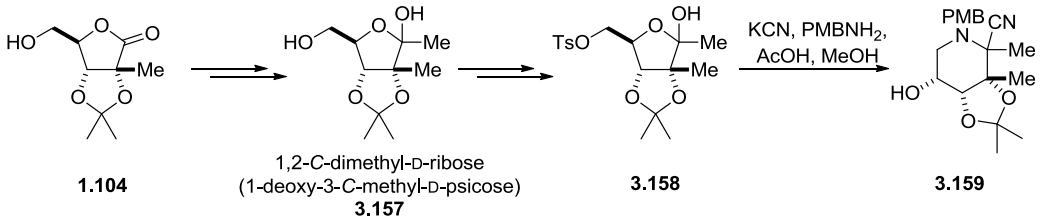
With the tosylate hemiacetal **3.148** accessed the TSRI conditions could be applied. As with the preceding D-*ribo*-configured ketose the reaction proved extremely sluggish. Two days were required and a high reaction temperature. Unlike the D-*ribo* system the formation of an 2,6-anhydro species was not possible, but the substrate was susceptible to decomposition. The slow reaction rate also led to considerable unreacted starting material being recovered (34%). These factors aside, the TSRI conditions with $PMBNH_2$ as the amine nucleophile did give the piperidine α-iminonitrile **3.152** selectively (13%, 20% brsm) without the epimer **3.153** being isolated.

With the TSRI expanded to accomplish access to quaternary piperidine α-iminonitriles, albeit in low yields, it was decided that the next stage would be to ambitiously combine both the 2-*C*-methyl- and 1-*C*-methyl-modifications to assess whether it is possible to assemble piperidine α-iminonitriles **3.156** with vicinal quaternary centres (**Scheme 3.33**).




**Scheme 3.33**. Ambitious assembly of piperidine α-iminonitriles with vicinal dimethyl-branching.

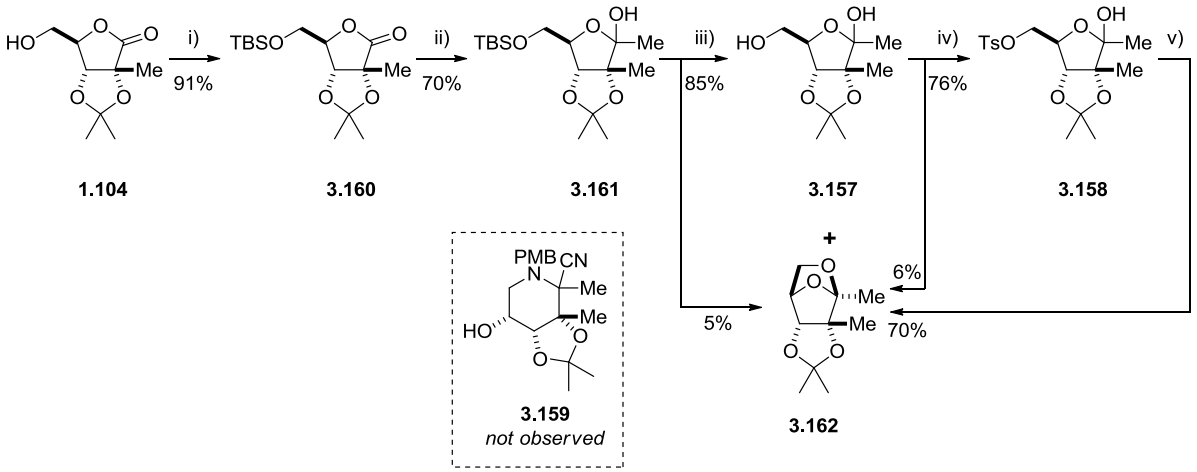
*3.3.7 From 1,2-C-dimethyl-D-ribose (1-deoxy-3-C-methyl-D-psicose)*




**Scheme 3.34**. Expansion to a 1,2-*C*-dimethyl-D-ribose substrate.

It was envisaged that the previously developed methods for accessing D-*ribo*-configured tosylate hemiacetals with a 1-*C*-methyl- or a 2-*C*-methyl-branch could be easily combined to give the 1,2-*C*-dimethyl-branched tosylate hemiacetal **3.158** from 2-*C*-methyl-D-ribono-1,4-lactone **1.104** (**Scheme 3.34**), by adding a 1-*C*-methyl-branch. Starting with the lactone **1.104**, treatment with TBSCl in pyridine afforded the fully protected silyl ether **3.160** in good yield (91%) (**Scheme 3.35**). Methyllithium was utilised again to introduce a methyl-branch to the lactone moiety of this silyl ether **3.160**, giving the protected lactol **3.161** (70%). Cleavage of the silyl protecting group was affected with TBAF, which gave the deprotected lactol **3.157** (85%), however this was accompanied by the surprising formation of a small quantity of the 2,6-anhydro-compound **3.162** (5%). Tosylation of the lactol **3.157** with tosyl chloride in pyridine also gave formation of some of the 2,6-anhydro-compound **3.162** (6%) as well as the expected tosylate hemiacetal **3.158** (76%). The application of the developed TSRI conditions to this system proved unsuccessful with the sole isolable product being that of the dimethyl-branched 2,6-anhydro species **3.162** (70%). The propensity of the D-*ribo* configuration to form an anhydro-species has been previously observed in this thesis with the acetonide protection of D-ribose **1.64** (**Scheme 3.14**, page 236) and in the TSRI of the 1-*C*-methyl-branched system (**Scheme 3.30**, page 257). Also the acetonide protection of 1-deoxy-D-psicose has been previously shown to yield only the 2,6-anhydro-acetonide **3.145**.[85] The introduction of the additional 2-*C*-methyl branch appears to have significantly increased the tendency of

*ribo*-configured systems towards forming anhydro-species, with both the silyl deprotection and tosylation steps in the dimethyl-branched case yielding a small amount of the 2,6-anhydro-compound **3.162**. Attempts to modify this procedure and reduce anhydro-formation did not meet with success and unfortunately the desired vicinal dimethyl-branched piperidine α-iminonitrile **3.159** was never observed.

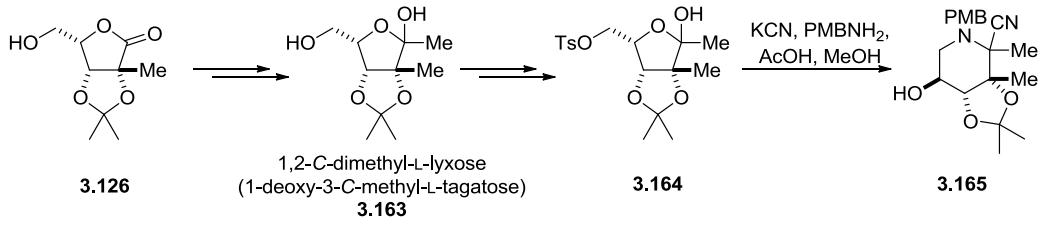



**Reagents & conditions**: i) TBSCl, pyr, RT, 16 h; ii) MeLi, THF, -78 °C, 4 h;
iii) TBAF, THF, RT, 4 h; iv) TsCl, pyr, -30 °C to RT, 17 h; v) KCN, $PMBNH_2$, AcOH, MeOH, 50-65 °C, 2 d.

**Scheme 3.35**. Towards accessing a vicinal dimethyl branched piperidine α-iminonitrile.

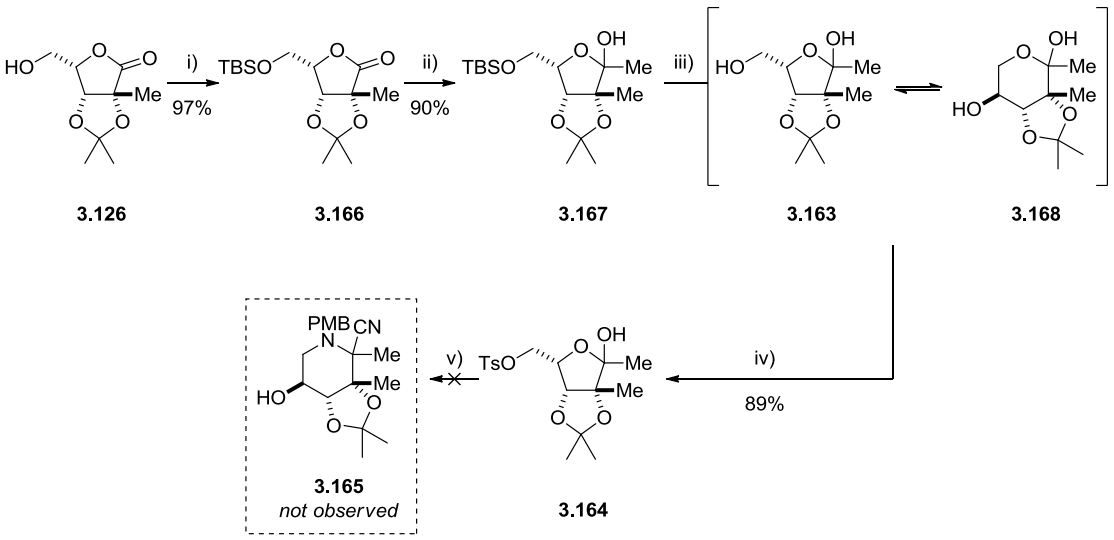
*3.3.8 From 1,2-C-dimethyl-L-lyxose (1-deoxy-3-C-methyl-L-tagatose)*

It was hoped that with the analogous *lyxo*-system lacking the required configuration to form a 2,6-anhydro-species, the accessing of a vicinal dimethyl-branched piperidine α-iminonitrile **3.165** would be achievable (**Scheme 3.36**).




**Scheme 3.36**. Expansion to a 1,2-*C*-dimethyl-L-lyxose substrate.

As with previous systems the lactone **3.126** was protected as the silyl ether **3.166** by reaction with TBSCl in pyridine (97%) (**Scheme 3.37**). Treatment with methyllithium at -78 $^{o}$C gave the silyl ether protected lactol **3.167** in a good yield (90%), and subsequent TBAF deprotection of the silyl ether moiety affording a mixture of the furanose and pyranose forms of the lactol (**3.163** & **3.168**). Surprisingly this equilibration of forms was not observed previously in the other systems. The mixture of the lactols **3.163** and **3.168** was treated with tosyl chloride and pyridine and the chemoselective reaction resulted in the sole formation of the primary tosylate lactol **3.164** in an excellent 89% yield over two steps from the silyl ether **3.167**. The tosylate hemiacetal **3.164** was subsequently treated under the TSRI conditions and although it was expected that a side product could not form, the reaction yielded no detectable products with only decomposition being observed. Despite successive reaction attempts the piperidine α-iminonitrile **3.165** was not observed. Unfortunately, this demonstrated the limitations of the methodology where the ambitious vicinal dimethyl branched piperidine α-iminonitriles could not be isolated for both the *ribo*- and *lyxo*-configured systems.




**Reagents & conditions**: i) TBSCl, pyr, RT, 16 h; ii) MeLi, THF, -78 $^{o}$C, 2.5 h;
iii) TBAF, THF, RT, 2.5 h; iv) TsCl, pyr, -30 $^{o}$C to RT, 22 h; v) KCN, $PMBNH_2$, AcOH, MeOH, 65 $^{o}$C, 4 d.

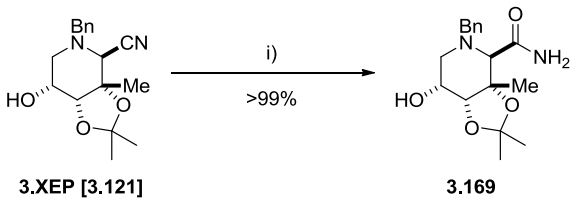
**Scheme 3.37**. Towards a vicinal dimethyl-branched quaternary piperidine α-iminonitrile.

*3.3.9 Summary and future work*

This chapter has demonstrated the development of a novel methodology towards accessing trihydroxy piperidine α-iminonitriles, precursors to biological relevant trihydroxy pipecolic acids. This route combines both a Strecker reaction and an iminocyclisation in a single tandem step (**TSRI**) to furnish the piperidine α-iminonitriles from readily accessible 5-*O*-tosyl-pentoses.The initial work was conducted from **D-ribose** with the TSRI conditions being shown to accommodate a range of amine nucleophiles and produce piperidine α-iminonitriles in good yields with remarkable stereoselectivity in cyanide addition. These reactions were not just remarkable for this, but also for the sole formation of a piperidine ring when there was a potential route to a pyrrolidine by-product. With increasing reaction temperature it was observed that the stereoselectivity of cyanide addition was diminished, a trend which was reversed in the second system of the C4-epimeric pentose **L-lyxose**. This led to the hypothesis that it was attack by cyanide on a cyclic iminium intermediate, and hence its conformation, that governed the selectivity expressed by these systems. Moving on from these simple systems, **2-*C*-methyl-branched** TSRI substrates of *ribo*- and *lyxo*-configuration were used to assess the effect of steric hindrance on the TSRI methodology. Similar selectivities were observed in comparison with their parent, unbranched routes, but the reactions required mild heating to avoid lower yields being obtained. With these systems tested the application of the methodology moved to the examination of **1-deoxy-ketoses** (1-*C*-methyl-pentoses), with a view to forming a quaternary α-iminonitrile centre. These reactions were sluggish and low yielding, with the unexpected epimer isolated stereoselectively in both *ribo*- and *lyxo*-configurations. Finally, to test the limits of the TSRI conditions these 1-*C*- and 2-*C*-methyl-branching techniques were combined in an attempt to form **vicinal dimethyl-branched** piperidine α-iminonitriles. Unfortunately this is where the limits were found to lie with the reactions being too disfavoured even at high temperatures, or forming a by-product in preference to the desired target. This aside, the novel

TSRI methodology established here has given successful access to a range of trihydroxy piperidine α-iminonitriles.

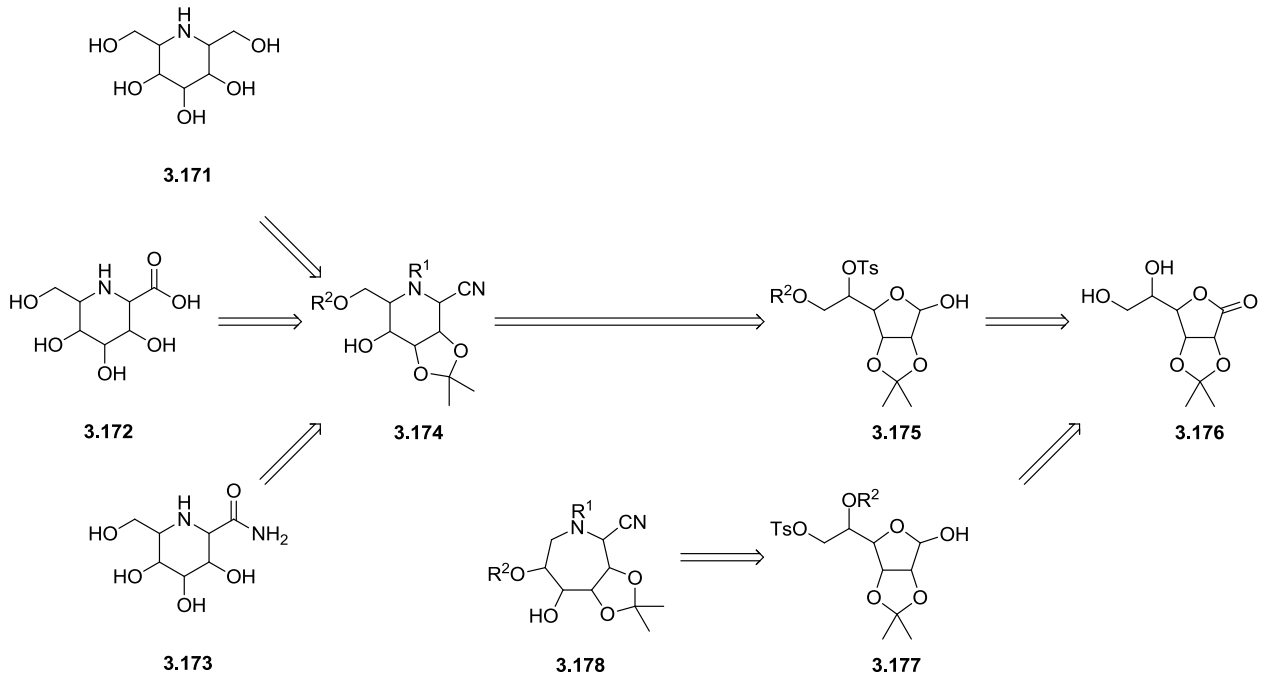
Given that nitriles may be converted to a wide array of functionalities including carboxylic acids, primary amide, primary amines, hydroxymethyl and aldehydes, these piperidine α-iminonitriles may be utilised divergently to develop a range of carbohydrate-processing enzyme inhibitors, targeting β-glucuronidase (carboxylic acid), hexosaminidases (primary amides) and simple glycosidases (hydroxymethyl). Thus the future work of this chapter lies here, in the accessing of iminosugar inhibitor derivatives, as well as in expanding the range of substrates that are accommodated by this TSRI methodology. One primary amide **3.169** was successfully synthesised from the 3-*C*-methyl-branched piperidine α-iminonitrile **3.121** (**Scheme 3.38**) quantitatively by utilisation of hydrogen peroxide and sodium hydroxide.[86,87]




**3.XEP [3.121]** **3.169**

**Scheme 3.38**. Hydrolysis of a piperidine α-iminonitrile with basic peroxide to form a primary amide.

It is envisaged that the scope of this TSRI methodology could be further expanded to encompass substrates with a secondary leaving group **3.170** (**Scheme 3.39**), this would permit possible access to biologically relevant homonojirmycins **3.171**, homopipecolic acids **3.172** and homopipecolic amides **3.173**, from suitably protected and activated hexofuranoses **3.175**. This proposed route would begin with the selective primary protection of a 2,3-acetonide of hexono-1,4-lactone in order to install a leaving group at C5 of the TSRI substrate, lactol **3.174**. Instead, if a leaving group were chemoselectively installed at C6 (**3.177**) the result would be potential access to a seven-membered class of homopiperidine, or azepane α-iminonitriles **3.17**8.




**Scheme 3.39**. Possible route to hydroxymethyl-branched piperidine α-iminonitriles and their targets, as well as to homopiperidine (azepane) α-iminonitriles from hexono-1,4-lactones.

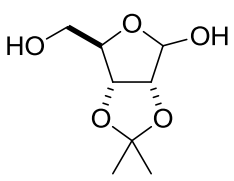
With a range of piperidine α-iminonitriles accessed in this chapter, panels of target compounds may in future be developed to inhibit a range of glycosidases, furthering the understanding of the structure-activity relationship between these enzymes and iminosugars, and hopefully, ultimately contribute to the future treatment of diseases highlighted in the outset of this thesis.

## 3.4 Experimental

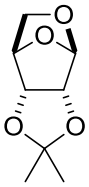
*Refer to **Chapter 2** (page 125) for the general experimental.*

### 3.4.1 D-Ribose route

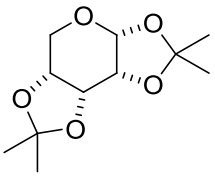
**2,3-*O*-Isopropylidene-D-ribose 3.82 / 1,5-Anhydro-2,3-*O*-isopropylidene-D-ribose 3.84 / 1,2:3,4-Di-*O*-isopropylidene-D-ribose 3.85 / 1,2-*O*-Isopropylidene-D-ribopyranose 3.86**



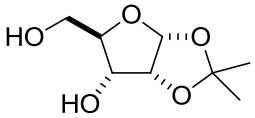

**3.82**




**3.84**




**3.85**




**3.86**

Anhydrous copper(II) sulfate (34.0 g, 213 mmol) was added to a stirring suspension of D-ribose **1.64** (20.0 g, 133 mmol) in acetone (700 mL). The reaction mixture was heated at 45 $^{o}$C for 17 h, after which TLC analysis (ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.14) and the formation of one major product ($R_f$ 0.69) and two minor products ($R_f$ 0.33, 0.92). The reaction mixture was filtered through Celite®, the filter pad washed with acetone (2 x 100 mL) and the filtrate concentrated *in vacuo*. The crude residue was purified by flash chromatography (4:1 to 0:1, cyclohexane/ethyl acetate) to separate the major and minor products. The major product, acetonides **3.82** ($R_f$ 0.69, 19.6 g, 77%) were afforded as a pale yellow oil and in a 11:1 (A:B) anomeric mixture. A co-spotting mixture of minor by-products was isolated; anhydro-acetonide **3.84** and diacetonide ribopyranose **3.85** ($R_f$ 0.92, 1.95 g, 8%) as fine white needles in a 2.3:1 (A:B) mixture. Also isolated was a complex, co-spotting mixture of compounds ($R_f$ 0.33, 1.78 g, 7%) as a clear oil, of which the 1,2-acetonide **3.86** was the major component.

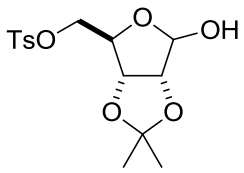
Data for the acetonides **3.84** ($R_f$ 0.69): HRMS (ESI +ve): found 213.0727 [M+$Na^+$]; $C_8H_{14}NaO_5$ requires 213.0733; $[\alpha]_D^{25}$ -34.3 (*c* 1.0, $CHCl_3$) [Lit.[88] $[\alpha]_D^{25}$ -24.7 (*c* 1.1, $CHCl_3$)]; $\nu_{max}$ (thin film): 3374 (br. s, OH); $\delta_H$ ($CD_3CN$, 400 MHz): 1.27, 1.40 (2 x 3H, s, $C(CH_3)_2^A$), 1.34, 1.49 (2 x 3H, s, $C(CH_3)_2^B$), 3.49-3.56 (2H, m, $H5^A$, $H5^B$), 3.58-3.64 (4H, m, $H5'^A$, $H5'^B$, $OH5^A$, $OH5^B$), 3.97 (1H, a-td, $H4^B$, $J_{4,3}$ 1.5, $J_{4,5} = J_{4,5'}$ 4.0), 4.04 (1H, d, $OH1^B$, $J_{OH,1}$ 10.7), 4.20 (1H, a-t, $H4^A$, $J_{4,5} = J_{4,5'}$ 3.3), 4.47 (1H, dd, $H2^A$, $J_{2,3}$ 6.1, $J_{2,1}$ 7.2), 4.55 (1H, dd, $H2^B$, $J_{2,1}$ 4.7, $J_{2,3}$ 6.4), 4.67 (1H, dd, $H3^B$, $J_{3,4}$ 1.5, $J_{3,2}$ 6.4), 4.74 (1H, d, $H3^A$, $J_{3,2}$ 6.1), 4.96 (1H, d, $OH1^A$, $J_{OH,1}$ 7.2), 5.20 (1H, d, $H1^A$, $J_{1,2}$ 7.2), 5.27 (1H, dd, $H1^B$, $J_{1,2}$ 4.7, $J_{1,OH}$ 10.7); $\delta_C$ ($CD_3CN$, 100 MHz), *major anomer only*: 25.0, 26.8 ($C(\underline{C}H_3)_2^A$), 64.0 ($C5^A$), 83.0 ($C3^A$), 88.0 ($C2^A$), 88.3 ($C4^A$), 103.7 ($C1^A$), 112.5 ($\underline{C}(CH_3)_2^A$); LRMS (ESI -ve): 189 (100%, $[M-H]^-$), 379 (65%, $[2M-H]^-$).

Selected data for the anhydro/diacetonide mixture **3.84**$^A$/**3.85**$^B$ ($R_f$ 0.92): m.p. 57-59 °C; $\delta_H$ ($CD_3CN$, 400 MHz): 1.24, 1.36 (2 x 3H, s, $C(CH_3)_2^A$), 1.29, 1.32, 1.44, 1.51 (4 x 3H, s, $C(CH_3)_2^B$), 3.27 (1H, dd, $H5^A$, $J_{5,4}$ 0.8, $J_{5,5'}$ 7.3), 3.29 (1H, dd, $H5'^A$, $J_{5',4}$ 3.3, $J_{5',5}$ 7.3), 3.74 (1H, dd, $H5^B$, $J_{5,4}$ 8.8, $J_{5,5'}$ 11.1), 3.92 (1H, dd, $H5'^B$, $J_{5',4}$ 7.3, $J_{5',5}$ 11.1), 4.21 (1H, d, $H3^A$, $J_{3,2}$ 5.6), 4.22 (1H, d, $H3^B$, $J_{3,2}$ 4.3), 4.35 (1H, d, $H2^A$, $J_{2,3}$ 5.3), 4.38 (1H, a-t, $H2^B$, $J_{2,1} = J_{2,3}$ 4.4), 4.44 (1H, dd, $H4^B$, $J_{4,5'}$ 7.3, $J_{4,5}$ 8.8), 4.63 (1H, dd, $H4^A$, $J_{4,5}$ 0.8, $J_{4,5'}$ 3.3), 5.33 (1H, s, $H1^A$), 5.36 (1H, d, $H1^B$, $J_{1,2}$ 4.5); $\delta_C$ ($CD_3CN$, 100 MHz): 25.3, 25.7, 26.6, 26.8 ($C(\underline{C}H_3)_2^B$), 25.4, 26.3 ($CC(\underline{C}H_3)_2^A$), 62.0 ($C5^B$), 63.7 ($C5^A$), 70.5 ($C4^B$), 72.9 ($C3^B$), 73.2 ($C2^B$), 78.5 ($C4^A$), 80.1 ($C2^A$), 82.2 ($C3^A$), 97.5 ($C1^B$), 100.6 ($C1^A$), 109.8, 111.3 ($\underline{C}(CH_3)_2^B$), 112.4 ($\underline{C}(CH_3)_2^A$).

Selected data for the mixture containing the 1,2-acetonide **3.86** ($R_f$ 0.33): $\nu_{max}$ (thin film): 3420 (br. s, OH); $\delta_H$ ($CD_3CN$, 400 MHz) *major component only*: 1.31, 1.49 (2 x 3H, s, $C(CH_3)_2$), 2.74 (1H, dd, OH5, *J* 5.1, *J* 6.8), 3.20 (1H, d, OH3, $J_{OH,3}$ 6.3), 3.44-3.55 (1H, m, H5), 3.70-3.82 (3H, m, H3, H4, H5'), 4.50 (1H, a-t, H2, $J_{2,1} = J_{2,3}$ 4.0), 5.70 (1H, d, H1, $J_{1,2}$ 3.8); $\delta_C$ ($CD_3CN$, 100

MHz) *major component only*: 26.8, 26.9 (C($\underline{C}H_3)_2$), 61.6 (C5), 72.1 (C3), 80.1 (C2), 81.6 (C4), 105.1 (C1), 113.0 ($\underline{C}(CH_3)_2$).

**2,3-*O*-Isopropylidene-5-*O*-*para*-toluenesulfonyl-D-ribose 3.87**

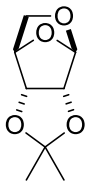



A solution of *para*-toluenesulfonylchloride (3.27 g, 17.2 mmol) in pyridine (12 mL) was added dropwise to a stirring solution of the acetonides **3.82** (2.95 g, 15.5 mmol) in pyridine (12 mL) at -30 $^oC$. The reaction was stirred at 0 $^oC$ for 1 h, and at RT for 4 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the persistence of a small amount of starting materials ($R_f$ 0.18) and the formation of a major products ($R_f$ 0.39). The reaction was diluted with ethyl acetate (100 mL) and washed with a 10% aqueous $H_2SO_4$ solution (4 x 12 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1 to 3:2, cyclohexane/ethyl acetate) to afford the major products, lactols **3.87** ($R_f$ 0.39, 3.48 g, 65%, 81% brsm), in a 8:1 (A:B) anomeric ratio, as a clear oil which slowly crystallised on standing, and returned starting material **3.82** (590 mg, 20%).

Data for the tosylates **3.87**: HRMS (ESI +ve): found 367.0825 [M+$Na^+$]; $C_{15}H_{20}NaO_7S$ requires 367.0822; $[\alpha]_D^{25}$ +8.7 (*c* 1.0, $CHCl_3$) [Lit.[89] $[\alpha]_D^{25}$ +1.5 (*c* 1.00, MeOH)]; m.p. 91-93 $^oC$ [Lit.[89] m.p. 92.5-94 $^oC$]; $\nu_{max}$ (thin film): 1176 (s, $SO_2$), 1361 (s, $SO_2$), 3399 (br. s, OH); $\delta_H$ ($CD_3CN$, 400 MHz): *major anomer only*; 1.24, 1.38 (2 x 3H, s, $C(CH_3)_2$), 2.45 (3H, s, $ArCH_3$), 4.00 (1H, dd, H5, $J_{5,4}$ 7.1, $J_{5,5'}$ 10.1), 4.05 (1H, dd, H5', $J_{5',4}$ 7.1, $J_{5',5}$ 10.1), 4.17 (1H, td, H4, $J_{4,3}$ 0.9, $J_{4,5} = J_{4,5'}$ 7.1), 4.31 (1H, d, OH1, $J_{OH,1}$ 3.8), 4.46 (1H, d, H2, $J_{2,3}$ 5.8), 4.57 (1H, dd, H3,

$J_{3,4}$ 0.9, $J_{3,2}$ 5.8), 5.26 (1H, d, H1, $J_{1,OH}$ 3.8), 7.45 (1H, d, ArH, $J_{H,H}$ 8.1), 7.79 (1H, d, ArH, $J_{H,H}$ 8.1); $\delta_C$ ($CD_3CN$, 100 MHz) *major anomer only*: 21.7 ($ArCH_3$), 25.0, 26.7 ($C(\underline{C}H_3)_2$), 71.7 (C5), 82.4 (C3), 84.3 (C4), 87.0 (C2), 103.5 (C1), 113.2 ($\underline{C}(CH_3)_2$), 128.9 (ArCH), 131.2 (ArCH), 133.6 ($Ar\underline{C}CH_3$), 146.7 ($Ar\underline{C}SO_2$); LRMS (ESI +ve): 362 (52%, $M+NH_4^+$), 367 (81%, $M+Na^+$), 383 (78%, $M+K^+$), 711 (100%, $2M+Na^+$), 727 (31%, $2M+K^+$); (ESI –ve): 379 (100%, $M+^{35}Cl^-$), 381 (40%, $M+^{37}Cl^-$).

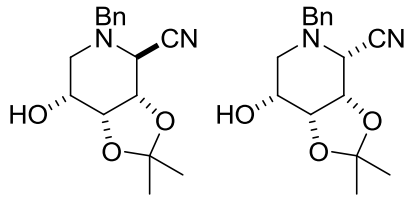
**1,5-Anhydro-2,3-*O*-isopropylidene-D-ribose 3.84**



Benzylamine (70 μL, 0.64 mmol) and potassium cyanide (23 mg, 0.35 mmol) were added to a solution of the tosylates **3.87** (100 mg, 0.29 mmol) in anhydrous methanol (2 mL) at RT. After 30 min the previously clear reaction mixture had become a suspension of a white solid. After 4 h TLC analysis (49:10:1, toluene/acetone/triethylamine) indicated the complete consumption of the starting materials ($R_f$ 0.45) and the formation of a single product ($R_f$ 0.62). The reaction mixture was filtered through glass-fibre (GF/B) and concentrated *in vacuo*. The crude residue was purified by flash chromatography (49:1 to 47:3, toluene/acetone) to afford the 2,3-anhydro-compound **3.84** (39 mg, 78%) as a white crystalline solid; selected data for the 2,3-anhydro-compound **3.84**: $[\alpha]_D^{25}$ -72.1 (*c* 1.0, acetone) [Lit.[90] $[\alpha]_D^{25}$ -64.7 (*c* 1.00, acetone)]; m.p. 62-63 °C [Lit.[90] 60-61 °C]; $\delta_H$ ($(CD_3)_2CO$, 400 MHz): 1.23, 1.34 (2 x 3H, s, $C(CH_3)_2$), 3.28 (1H, dd, H5, $J_{5,4}$ 3.5, $J_{5,5'}$ 7.2), 3.32 (1H, d, H5', $J_{5',5}$ 7.2), 4.21 (1H, d, H3, $J_{3,2}$ 5.6), 4.41 (1H, d, H2, $J_{2,3}$ 5.6), 4.66 (1H, d, H4, $J_{4,5}$ 3.5), 5.32 (1H, s, H1); $\delta_C$ ($(CD_3)_2CO$, 100 MHz): 25.5, 26.4 ($C(\underline{C}H_3)_2$), 63.5 (C5), 78.4 (C4), 80.2 (C2), 82.2 (C3), 100.5 (C1), 112.3 ($\underline{C}(CH_3)_2$).

**2-*N*-Benzyl-2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-D-allononitrile 3.88 /**

**2-*N*-Benzyl-2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-D-altrononitrile 3.89**




**3.88** **3.89**

Method A (RT): A solution of benzylamine (0.21 mL, 1.92 mmol), potassium cyanide (68 mg, 1.05 mmol) and the tosylates **3.87** (300 mg, 0.87 mmol) in anhydrous methanol (6 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.2 mL, 3.48 mmol). The reaction mixture was stirred at RT for 16 h, after which TLC analysis (49:10:1, cyclohexane/ethyl acetate/triethylamine) indicated the complete consumption of the starting materials ($R_f$ 0.45) and the formation of a major product ($R_f$ 0.39). The resulting suspension was filtered through glass-fibre (GF/B) and concentrated *in vacuo*. The crude residue was purified by flash chromatography (19:1 to 37:3, cyclohexane/ethyl acetate) to afford the α-iminonitrile **3.88** (164 mg, 65%) as a pale-yellow crystalline solid.

Method B (40 $^{o}$C): A solution of benzylamine (0.24 μL, 2.20 mmol), potassium cyanide (76 mg, 1.17 mmol) and the tosylates **3.87** (335 mg, 0.97 mmol) in anhydrous methanol (6 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.3 mL, 3.78 mmol). The reaction mixture was stirred at 40 $^{o}$C for 17 h, after which TLC analysis (5:1, toluene/acetone) indicated the complete consumption of the starting materials ($R_f$ 0.38) and the formation of a major product ($R_f$ 0.36). The reaction was allowed to cool to RT and the resulting suspension was filtered through glass-fibre (GF/B) and concentrated *in vacuo*. The crude residue was purified by flash chromatography (49:1 to 9:1, toluene/acetone) to afford a >19:1 (A:B)

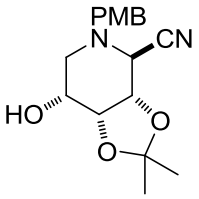
inseparable mixture of the α-iminonitriles **3.88/3.89** (238 mg, 68%) as a pale-yellow oil, which crystallised on standing.

Method C (65 $^{o}$C): A solution of benzylamine (0.22 μL, 2.01 mmol), potassium cyanide (72 mg, 1.11 mmol) and the tosylates **3.87** (315 mg, 0.92 mmol) in anhydrous methanol (6 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.2 mL, 3.48 mmol). The reaction mixture was stirred at 65 $^{o}$C for 17 h, after which TLC analysis (5:1, toluene/acetone) indicated the complete consumption of the starting materials ($R_f$ 0.38) and the formation of a major product ($R_f$ 0.36). The reaction was allowed to cool to RT and the resulting suspension was filtered through glass-fibre (GF/B) and concentrated *in vacuo*. The crude residue was purified by flash chromatography (49:1 to 9:1, toluene/acetone) to afford a 1.7:1 (A:B) inseparable mixture of the α-iminonitriles **3.88/3.89** (237 mg, 82%) as a pale-yellow oil, which crystallised on standing.

Data for the α-iminonitrile **3.88**: HRMS (ESI +ve): found 311.1365 [M+$Na^+$]; $C_{16}H_{20}N_2NaO_3$ requires 311.1366; m.p. 69-71 $^{o}$C; $[\alpha]_D^{20}$ +20.3 (*c* 1.75, MeOH); $\nu_{max}$ (thin film): 2234 (w, CN), 3461 (br. s, OH); $\delta_H$ ($(CD_3)_2CO$, 500 MHz): 1.33, 1.50 (2 x 3H, s, $C(CH_3)_2$), 2.40 (1H, a-t, H6, $J_{6,5} = J_{6,6'}$ 10.2), 2.70 (1H, dd, H6', $J_{6',5}$ 4.8, $J_{6',6}$ 11.1), 3.52 (1H, d, H2, $J_{2,3}$ 6.1), 3.59 (1H, d, NC$\underline{H}_2$Ph, $J_{gem}$ 13.2), 3.92-3.98 (1H, m, H5), 4.06 (1H, d, NC$\underline{H}_2$Ph, $J_{gem}$ 13.2), 4.44 (1H, a-t, H3, $J_{3,2} = J_{3,4}$ 5.8), 4.48 (1H, dd, H4, $J_{4,5}$ 3.3, $J_{4,3}$ 5.3), 7.18-7.38 (5H, m, ArH); $\delta_C$ ($(CD_3)_2CO$, 125 MHz): 26.1, 27.8 ($C(\underline{C}H_3)_2$), 52.2 (C6), 56.9 (C2), 60.0 (N$\underline{C}H_2$Ph), 65.7 (C5), 75.9 (C4), 76.5 (C3), 111.0 ($\underline{C}(CH_3)_2$), 118.8 (CN), 128.5, 129.4, 129.9 (Ar$\underline{C}$H), 137.8 (Ar$\underline{C}$C); LRMS (ESI +ve): 311 (100%, M+$Na^+$), 599 (35%, 2M+$Na^+$).

Partial data for the inseparable **3.88**$^{A}$/**3.89**$^{B}$ mixtures: $\delta_H$ ($(CD_3)_2CO$, 400 MHz): 1.34 (3H, s, $C(CH_3)^A$), 1.50 (6H, s, $C(CH_3)^A$, $C(CH_3)^B$), 1.68 (3H, s, $C(CH_3)^B$), 2.40 (1H, a-t, H6$^A$, $J_{6,5} = J_{6,6'}$ 10.2), 2.57 (1H, a-t, H6$^B$, $J_{6,5} = J_{6,6'}$ 10.4), 2.70 (2H, add, H6'$^A$, H6'$^B$, $J$ 4.8, $J$ 11.1), 3.52 (1H, d, H2$^A$, $J_{2,3}$ 6.1), 3.59 (1H, d, NC$\underline{H}_2$Ph$^A$, $J_{gem}$ 13.2), 3.70 (1H, d, NC$\underline{H}_2$Ph$^B$, $J_{gem}$ 13.4), 3.73 (1H, d, NC$\underline{H}_2$Ph$^B$, $J_{gem}$ 13.4), 3.91-3.99 (2H, m, H5$^A$, H5$^B$), 4.06 (1H, d, NC$\underline{H}_2$Ph$^A$, $J_{gem}$ 13.2), 4.20 (1H, br. d, H2$^B$, $J_{2,3}$ 7.9), 4.40 (1H, dd, H3$^B$, $J_{3,4}$ 5.4, $J_{3,2}$ 7.9), 4.44 (1H, a-t, H3$^A$, $J_{3,2} = J_{3,4}$ 5.8), 4.48 (1H, dd, H4$^A$, $J_{4,5}$ 3.3, $J_{4,3}$ 5.3), 4.57 (1H, a-t, H4$^B$, $J_{4,3} = J_{4,5}$ 4.8), 7.11-7.37 (10H, m, ArH$^A$, ArH$^B$); $\delta_C$ ($(CD_3)_2CO$, 100 MHz): 25.9 ($C(\underline{C}H_3)_2^B$), 26.1 ($C(\underline{C}H_3)_2^A$), 26.5 ($C(\underline{C}H_3)_2^B$), 27.8 ($C(\underline{C}H_3)_2^A$), 49.9 (C6$^B$), 52.2 (C6$^A$), 56.9 (C2$^A$), 57.1 (C2$^B$), 60.0 (N$\underline{C}H_2$Ph$^A$), 60.1 (N$\underline{C}H_2$Ph$^B$), 65.7 (C5$^A$), 66.7 (C5$^B$), 72.9 (C3$^B$), 75.2 (C4$^B$), 75.9 (C4$^A$), 76.5 (C3$^A$), 111.0 ($\underline{C}(CH_3)_2^A$), 111.2 ($\underline{C}(CH_3)_2^B$), 118.8 (CN$^A$, CN$^B$), 128.5, 128.5, 129.1, 129.4, 129.5, 129.6, 129.8, 129.9 (Ar$\underline{C}$H$^A$, Ar$\underline{C}$H$^B$), 137.8 (Ar$\underline{C}$C$^A$), 138.3 (Ar$\underline{C}$C$^B$).

**2,6-Dideoxy-2,6-imino-3,4-*O*-isopropylidene-2-*N*-(4-methoxybenzyl)-D-allononitrile 3.96**



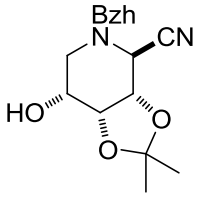

Method A (KCN): A solution of 4-methoxybenzylamine (0.25 mL, 1.92 mmol), potassium cyanide (85 mg, 1.31 mmol) and the tosylates **3.87** (300 mg, 0.87 mmol) in anhydrous methanol (6 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.2 mL, 3.49 mmol). The reaction mixture was stirred at RT for 19 h, after which TLC analysis (5:1, toluene/acetone) indicated the complete consumption of the starting materials ($R_f$ 0.38) and the formation of a major product ($R_f$ 0.50). The suspension was concentrated *in vacuo*, dissolved in ethyl acetate (40 mL) and washed with a saturated aqueous sodium bicarbonate solution

(3 x 10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (49:1 to 9:1, toluene/acetone) to afford the α-iminonitrile **3.96** (250 mg, 90%) as a white crystalline solid.

Method B (TMSCN): A solution of 4-methoxybenzylamine (0.19 mL, 1.45 mmol), trimethylsilyl cyanide (0.18 mL, 1.45 mmol) and the tosylates **3.87** (200 mg, 0.58 mmol) in anhydrous methanol (4 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 0.5 mL, 1.46 mmol). The reaction mixture was stirred at RT for 24 h, after which TLC analysis (5:1, toluene/acetone) indicated the complete consumption of the starting materials ($R_f$ 0.38) and the formation of a major product ($R_f$ 0.50). The suspension was concentrated *in vacuo*, dissolved in ethyl acetate (100 mL) and washed with a saturated aqueous sodium bicarbonate solution (3 x 25 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (49:1 to 9:1, toluene/acetone) to afford the α-iminonitrile **3.96** (136 mg, 73%) as a white crystalline solid.

Data for the α-iminonitrile **3.96**: HRMS (ESI +ve): found 341.1461 [$M+Na^+$]; $C_{17}H_{22}N_2NaO_4$ requires 341.1472; $[\alpha]_D^{20}$ +36.1 (*c* 2.41, $CHCl_3$); m.p. 142-144 $^oC$; $\nu_{max}$ (thin film): 2221 (w, CN), 3482 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.39, 1.58 (2 x 3H, s, $C(CH_3)_2$), 2.39 (1H, d, OH5, $J_{OH,5}$ 9.9), 2.61 (1H, dd, H6, $J_{6,5}$ 7.1, $J_{6,6'}$ 12.0), 2.79 (1H, dd, H6', $J_{6',5}$ 3.5, $J_{6',6}$ 12.0), 3.58 (1H, d, $NC\underline{H}_2Ar$, $J_{gem}$ 13.1), 3.72 (1H, d, H2, $J_{2,3}$ 4.0), 3.82 (3H, s, $OCH_3$), 3.87-3.92 (1H, m, H5), 3.93 (1H, d, $NC\underline{H}_2Ar$, $J_{gem}$ 13.1), 4.32 (1H, a-t, H4, $J_{4,3} = J_{4,5}$ 4.8), 4.40 (1H, a-t, H3, $J_{3,2} = J_{3,4}$ 4.8), 6.90 (2H, d, ArH, *J* 8.3), 7.26 (2H, d, ArH, *J* 8.6); $\delta_C$ ($CDCl_3$, 100 MHz): 25.8, 26.6 ($C(\underline{C}H_3)_2$), 51.7 (C6), 54.5 (C2), 55.3 ($OCH_3$), 58.8 ($N\underline{C}H_2Ar$), 65.2 (C5), 73.4 (C4), 74.3 (C3), 110.6 ($\underline{C}(CH_3)_2$), 114.1 (Ar$\underline{C}$H), 116.1 (CN), 127.5 (Ar$\underline{C}$C), 130.3 (Ar$\underline{C}$H), 159.3 (Ar$\underline{C}OCH_3$); LRMS (ESI +ve): 307 (100%, $M+H^+$), 329 (92%, $M+Na^+$).

**2-*N*-Benzhydryl-2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-D-allononitrile 3.97**



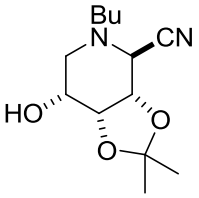

A solution of benzhydrylamine (0.14 mL, 0.79 mmol), potassium cyanide (52 mg, 0.79 mmol) and the tosylates **3.87** (109 mg, 0.32 mmol) in anhydrous methanol (10 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 0.6 mL, 1.75 mmol). The reaction mixture was stirred at RT for 3 d, after which TLC analysis (9:1, dichloromethane/diethyl ether) indicated the almost complete consumption of the starting materials ($R_f$ 0.60) and the formation of a major product ($R_f$ 0.75). The suspension was concentrated *in vacuo*, dissolved in ethyl acetate (50 mL) and washed with 2 M aqueous hydrochloric acid (20 mL). The aqueous phase was extracted with ethyl acetate (4 x 25 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (99:1 to 9:1, dichloromethane/diethyl ether) to afford the α-iminonitrile **3.97** (78 mg, 68%, 79% brsm) as a white crystalline solid, and recovered starting materials **3.87** (15 mg, 14%).

Data for the α-iminonitrile **3.97**: HRMS (ESI +ve): found 387.1683 [M+$Na^+$]; $C_{22}H_{24}N_2NaO_3$ requires 387.1679; $[\alpha]_D^{20}$ +5.6 (*c* 1.05, $CHCl_3$); m.p. 152-154 $^oC$; $\nu_{max}$ (thin film): 2251 (w, CN), 3461 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.39, 1.71 (2 x 3H, s, $C(CH_3)_2$), 2.50 (1H, br. s, OH), 2.64 (1H, dd, H6, $J_{6,5}$ 4.0, $J_{6,6'}$ 12.2), 2.92 (1H, dd, H6', $J_{6',5}$ 6.4, $J_{6',6}$ 12.2), 4.00 (1H, br. s, H5), 4.04 (1H, br. s, H2), 4.35 (1H, dd, H4, $J_{4,5}$ 4.3, $J_{4,3}$ 6.1), 4.40 (1H, dd, H3, $J_{3,2}$ 1.8, $J_{3,4}$ 6.1), 4.75 (1H, s, $Ph_2C\underline{H}$), 7.22-7.28 (2H, m, ArH), 7.31-7.36 (4H, m, ArH), 7.46-7.49 (4H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 25.5, 26.2 ($C(\underline{C}H_3)_2$), 49.7 (C6), 52.3 (C2), 65.0 (C5), 72.8 ($Ph_2\underline{C}H$), 73.2

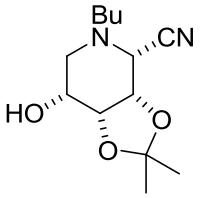
(C4), 74.2 (C3), 110.6 (<u>C</u>($CH_3$)$_2$), 115.4 (<u>C</u>N), 127.6, 128.0, 128.0, 128.8, 129.2 (Ar<u>C</u>H), 139.5, 140.6 (Ar<u>C</u>C); LRMS (ESI +ve): 387 (100%, M+$Na^+$).

**2-*N*-Butyl-2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-D-allononitrile 3.98 /**

**2-*N*-Butyl-2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-D-altrononitrile 3.99**




**3.98**

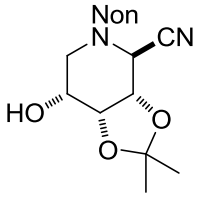



**3.99**

A solution of butylamine (0.13 mL, 1.31 mmol), potassium cyanide (86 mg, 1.31 mmol) and the tosylates **3.87** (180 mg, 0.52 mmol) in anhydrous methanol (1 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.1 mL, 3.20 mmol). The reaction mixture was stirred at RT for 2 d, after which TLC analysis (9:1, dichloromethane/diethyl ether) indicated the almost complete consumption of the starting materials ($R_f$ 0.60) and the formation of a major product ($R_f$ 0.53). The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (100 mL) and washed with 2 M aqueous hydrochloric acid (20 mL). The aqueous phase was extracted with ethyl acetate (4 x 25 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (49:1 to 9:1, dichloromethane/diethyl ether) to afford a 4.8:1 (A:B) mixture of α-iminonitriles **3.98**$^A$/**3.99**$^B$ (80 mg, 60%) as a pale-yellow oil; HRMS (ESI +ve): found 277.1520 [M+$Na^+$]; $C_{13}H_{22}N_2NaO_3$ requires 277.1523; $\nu_{max}$ (thin film): 2241 (w, CN); $\delta_H$ ($CDCl_3$, 400 MHz): 0.89 (3H, t, $NCH_2CH_2CH_2C\underline{H}_3^B$, *J* 7.3), 0.91 (3H, t, $NCH_2CH_2CH_2C\underline{H}_3^A$, *J* 7.3), 1.33 (4H, a-sext, $NCH_2CH_2C\underline{H}_2CH_3^A$, $NCH_2CH_2C\underline{H}_2CH_3^B$, *J* 7.3), 1.37, 1.55 (2 x 3H, s, $C(CH_3)_2^A$), 1.38, 1.73 (2 x 3H, s, $C(CH_3)_2^B$), 1.47 (4H, a-quin, $NCH_2C\underline{H}_2CH_2CH_3^A$, $NCH_2C\underline{H}_2CH_2CH_3^A$,

*J* 7.3), 2.43-2.62 (2H, m, NC<u>H</u>H'$^{B}$, H6$^{B}$), 2.52 (1H, dt, NC<u>H</u>H'$^{A}$, *J* 7.8, *J* 7.8, $J_{gem}$ 12.7), 2.59 (1H, dd, H6$^{A}$, $J_{6,5}$ 7.3, $J_{6,6'}$ 11.9), 2.66-2.72 (1H, m, NCH<u>H</u>'$^{B}$), 2.70 (1H, dt, NCH<u>H</u>'$^{A}$, *J* 7.8, *J* 7.8, $J_{gem}$ 12.7), 2.75 (1H, dd, H6'$^{A}$, $J_{6',5}$ 3.8, $J_{6',6}$ 11.9), 2.79 (1H, dd, H6'$^{B}$, $J_{6',5}$ 6.6, $J_{6',6}$ 11.9), 3.72 (1H, d, H2$^{A}$, $J_{2,3}$ 4.3), 3.90 (2H, br. s, H5$^{A}$, H5$^{B}$), 4.03 (1H, d, H2$^{B}$, $J_{2,3}$ 8.1), 4.29 (1H, a-t, H4$^{A}$, $J_{4,3} = J_{4,5}$ 5.0), 4.32 (1H, dd, H3$^{B}$, $J_{3,4}$ 5.2, $J_{3,2}$ 8.1), 4.35 (1H, a-t, H3$^{A}$, $J_{3,2} = J_{3,4}$ 5.1), 4.48 (1H, t, H4$^{B}$, $J_{4,3} = J_{4,5}$ 5.2); $\delta_C$ ($CDCl_3$, 100 MHz): 13.7 ($NCH_2CH_2CH_2\underline{C}H_3{}^{A}$, $NCH_2CH_2CH_2\underline{C}H_3{}^{B}$), 20.0 ($NCH_2CH_2\underline{C}H_2CH_3{}^{A}$, $NCH_2CH_2\underline{C}H_2CH_3{}^{B}$), 25.5, 25.7 ($C(\underline{C}H_3)_2{}^{B}$), 25.8, 26.6 ($C(\underline{C}H_3)_2{}^{A}$), 28.4 ($NCH_2\underline{C}H_2CH_2CH_3{}^{A}$), 29.1 ($NCH_2\underline{C}H_2CH_2CH_3{}^{B}$), 49.6 (C6$^{B}$), 51.6 (C6$^{A}$), 54.7 ($N\underline{C}H_2CH_2CH_2CH_3{}^{A}$), 54.9 ($N\underline{C}H_2CH_2CH_2CH_3{}^{B}$), 55.3 (C2$^{A}$), 56.6 (C2$^{B}$), 65.0 (C5$^{A}$), 65.8 (C5$^{B}$), 71.7 (C3$^{B}$), 73.5 (C3$^{A}$), 73.6 (C4$^{A}$), 74.4 (C4$^{B}$), 110.5 ($\underline{C}(CH_3)_2{}^{A}$), 111.6, ($\underline{C}(CH_3)_2{}^{B}$), 116.1 (CN$^{B}$), 116.2 (CN$^{A}$); LRMS (ESI +ve): 255 (65%, M+H$^+$), 277 (100%, M+Na$^+$), 290 (15%, M+K$^+$).

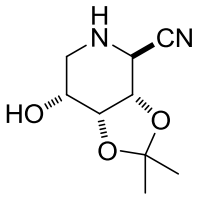
**2,6-Dideoxy-2,6-imino-3,4-*O*-isopropylidene-2-*N*-nonyl-D-allononitrile 3.100**




A solution of nonylamine (0.21 mL, 1.15 mmol), potassium cyanide (75 mg, 1.15 mmol) and the tosylates **3.87** (158 mg, 0.46 mmol) in anhydrous methanol (2 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 0.8 mL, 2.33 mmol). The reaction mixture was stirred at RT for 2 d, after which TLC analysis (5:1, toluene/acetone) indicated the almost complete consumption of the starting materials ($R_f$ 0.38) and the formation of a major product ($R_f$ 0.48). The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (100 mL) and washed with 2 M aqueous hydrochloric acid (20 mL). The aqueous phase was extracted with

ethyl acetate (4 x 25 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (99:1 to 97:3, dichloromethane/diethyl ether) to afford the α-iminonitrile **3.100** (55 mg, 65%) as a pale-yellow oil; HRMS (ESI +ve): found 347.2298 [M+$Na^+$]; $C_{18}H_{32}N_2NaO_3$ requires 347.2305; $[\alpha]_D^{20}$ -10.1 (*c* 1.11, $CHCl_3$); $\nu_{max}$ (thin film): 2247 (w, CN), 3448 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 0.87 (3H, s, $N(CH_2)_8C\underline{H}_3$), 1.23-1.31 (12H, m, $NCH_2CH_2(C\underline{H}_2)_6CH_3$), 1.39, 1.57 (2 x 3H, s, $C(CH_3)_2$), 1.49 (2H, quin., $NCH_2C\underline{H}_2(CH_2)_6CH_3$, *J* 7.1), 2.53 (1H, dt, $NC\underline{H}H'CH_2(CH_2)_6CH_3$, *J* = *J* 7.2, $J_{gem}$ 12.6), 2.61 (1H, dd, H6, $J_{6,5}$ 7.2, $J_{6,6'}$ 12.0), 2.70 (1H, dt, $NCH\underline{H}'CH_2(CH_2)_6CH_3$, *J* = *J* 7.2, $J_{gem}$ 12.6), 2.76 (1H, dd, H6', $J_{6',5}$ 3.7, $J_{6',6}$ 12.0), 3.76 (1H, d, H2, $J_{2,3}$ 4.0), 3.91 (1H, a-dt, H5, $J_{5,4} = J_{5,6'}$ 3.8, $J_{5,6}$ 7.0), 4.29 (1H, dd, H4, $J_{4,5}$ 4.0, $J_{4,3}$ 5.3), 4.36 (1H, dd, H3, $J_{3,2}$ 4.0, $J_{3,4}$ 5.3); $\delta_C$ ($CDCl_3$, 100 MHz): 14.0 ($N(CH_2)_8\underline{C}H_3$), 22.6, 26.4, 26.9, 29.2, 29.3, 29.4, 31.8 ($NCH_2(\underline{C}H_2)_7CH_3$), 25.8, 26.6 ($C(\underline{C}H_3)_2$), 51.7 (C6), 55.1 ($N\underline{C}H_2(CH_2)_7CH_3$), 55.3 (C2), 65.1 (C5), 73.6 (C3), 74.4 (C4), 110.6 ($\underline{C}(CH_3)_2$), 116.2 (CN); LRMS (ESI +ve): 325 (55%, M+$H^+$), 347 (100%, M+$Na^+$), 360 (45%, M+$K^+$)

**2,6-Dideoxy-2,6-imino-3,4-*O*-isopropylidene-D-allononitrile 3.101**



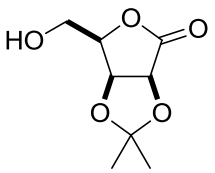

A solution of ammonium acetate (356 mg, 4.62 mmol), potassium cyanide (76 mg, 1.15 mmol) and the tosylates **3.87** (159 mg, 0.46 mmol) in anhydrous methanol (2 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.2 mL, 3.49 mmol). The reaction mixture was stirred at RT for 1 d, then at 35 °C for 1 d, after which TLC analysis (9:1, dichloromethane/diethyl ether) indicated the almost complete consumption of the starting

materials ($R_f$ 0.60) and the formation of a major product ($R_f$ 0.14). The reaction mixture was concentrated *in vacuo* and co-evaporated with ethyl acetate (3 x 10 mL). The crude residue was purified by flash chromatography (3:1:0 to 9:0:1, dichloromethane/diethyl ether/methanol) to afford the α-iminonitrile **3.101** (54 mg, 59%) as a pale-yellow oil; HRMS (ESI +ve): found 221.0904 [M+$Na^+$]; $C_9H_{14}N_2NaO_3$ requires 221.0897; $[\alpha]_D^{20}$ -32.1 (*c* 2.77, $CHCl_3$); $\nu_{max}$ (thin film): 2249 (w, CN), 3292 (br. s, OH, NH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.39, 1.55 (2 x 3H, s, $C(CH_3)_2$), 2.77 (1H, dd, H6, $J_{6,5}$ 8.7, $J_{6,6'}$ 12.5), 3.04 (1H, dd, H6', $J_{6',5}$ 4.7, $J_{6',6}$ 12.5), 3.73 (1H, d, H2, $J_{2,3}$ 6.8), 3.90 (1H, a-dt, $J_{5,4} = J_{5,6'}$ 4.4, $J_{5,6}$ 8.7 ), 4.26 (1H, dd, H3, $J_{3,2}$ 6.8, $J_{3,4}$ 5.1), 4.41 (1H, a-t, H4, $J_{4,3} = J_{4,5}$ 4.7); $\delta_C$ ($CDCl_3$, 100 MHz): 25.8, 27.5 ($C(\underline{C}H_3)_2$), 46.1 (C6), 49.4 (C2), 65.2 (C5), 74.3 (C3), 74.3 (C4), 110.5 ($\underline{C}(CH_3)_2$), 118.6 (CN); LRMS (ESI +ve): 199 (10%, M+$H^+$), 221 (25%, M+$Na^+$), 370 (100%, [M+(M-$CN^-$)]$^+$).

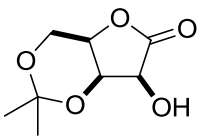
3.4.2 D-/L-Lyxose routes

**2,3-*O*-Isopropylidene-D-lyxono-1,4-lactone 1.63D /**

**3,5-*O*-Isopropylidene-D-lyxono-1,4-lactone 3.105**



**1.63D**

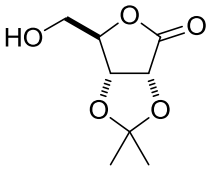


**3.105**

Anhydrous copper(II) sulfate (22 g, 135 mmol) and a few drops of concentrated sulfuric acid were added to a suspension of D-lyxono-1,4-lactone **3.104** (10.0 g, 67.5 mmol) in acetone (200 mL). The reaction was stirred at RT for 17 h, after which TLC analysis (1:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material (baseline)

and the formation of a major ($R_f$ 0.21) and a minor product ($R_f$ 0.14). The suspension was filtered through Celite®, the filter pad washed with acetone (100 mL) and the filtrate neutralised with excess solid sodium bicarbonate. The mixture was filtered, concentrated *in vacuo* and the crude residue purified by flash chromatography (4:1 to 0:1, cyclohexane/ethyl acetate) to afford the major 2,3-acetonide **1.63D** (2.0 g, 16%) as a white crystalline solid and a mixture of the 2,3-**1.63D** and 3,5-acetonides **3.105** (10.2 g, 80%). The latter mixture was purified by further flash chromatography (13:7 to 0:1, cyclohexane/ethyl acetate) to afford the 2,3-acetal **1.63D** (3.0 g, 24% [40% combined yield]) as a white crystalline solid; HRMS (ESI +ve): found 211.0580 [M+$Na^+$]; $C_8H_{12}NaO_5$ requires 211.0577; m.p. 95-97 °C [Lit.[91] m.p. 97-99 °C]; $[\alpha]_D^{20}$ +94.4 (*c* 1.1, acetone) [Lit.[91] $[\alpha]_D^{20}$ +88.5 (*c* 1.0, acetone)]; $\nu_{max}$ (thin film): 1778 (s, C=O), 3444 (br. s, OH); $\delta_H$ ($CD_3CN$, 400 MHz): 1.34, 1.38 (2 x 3H, s, $C(CH_3)_2$), 3.09 (1H, t, OH5, $J_{OH,5} = J_{OH,5'}$ 5.9), 3.78 (1H, ddd, H5, $J_{5,OH}$ 5.9, $J_{5,4}$ 7.1, $J_{5,5'}$ 12.1), 3.82 (1H, a-dt, H5', $J_{5',OH} = J_{5',4}$ 6.0, $J_{5',5}$ 12.1), 4.51-4.55 (1H, m, H4), 4.84-4.87 (2H, m, H2, H3); $\delta_C$ ($CD_3CN$, 100 MHz): 25.9, 27.1 ($C(\underline{C}H_3)_2$), 61.0 (C5), 77.3 (C2), 77.3 (C3), 80.8 (C4), 114.5 ($\underline{C}(CH_3)_2$), 175.3 (C1); LRMS (ESI +ve): 211 (100%, M+$Na^+$), 243 (95%, M+MeOH+$Na^+$).

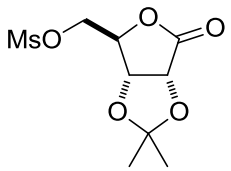
**2,3-*O*-Isopropylidene-D-ribono-1,4-lactone 3.35**




Bromine (8.5 mL, 165 mmol) was added dropwise to a suspension of barium carbonate (33.0 g, 165 mmol) and the lactols **3.82** (10 g, 52.6 mmol) in water (750 mL) at 0 °C. The reaction mixture was stirred for 2.5 h, with the internal temperature rising to 10 °C, after which TLC analysis (ethyl acetate) indicated the complete consumption of the starting materials ($R_f$ 0.69)

and the formation of a major product ($R_f$ 0.80). A saturated aqueous sodium thiosulfate solution (~10 mL) was added dropwise until the bromine was visibly quenched. The reaction mixture was filtered through Celite® and concentrated *in vacuo*. The crude residue was extracted with ethyl acetate (4 x 250 mL) and the organic fractions combined and concentrated *in vacuo* to afford the crude lactone **3.35** (8.2 g, 83%) as an off-white crystalline solid; HRMS (ESI +ve): found 211.0577 [M+$Na^+$]; $C_8H_{12}NaO_5$ requires 211.0577; $[\alpha]_D^{20}$ -80.1 (*c* 1.20, acetone) [Lit.[92] $[\alpha]_D^{20}$ -74 (*c* 1.0, $CHCl_3$)]; m.p. 132-133 °C [Lit.[92] 139 °C (*tert*-butylmethylether)]; $\nu_{max}$ (thin film): 1770 (s, C=O), 3447 (br. s, OH); $\delta_H$ ($CD_3CN$, 400 MHz): 1.34, 1.40 (2 x 3H, s, ($C(CH_3)_2$), 3.27 (1H, t, OH5, $J_{OH,5} = J_{OH,5'}$ 5.1), 3.70 (1H, ddd, H5, $J_{5,4}$ 2.0, $J_{5,OH}$ 5.1, $J_{5,5'}$ 12.1), 3.74 (1H, ddd, H5', $J_{5',4}$ 2.5, $J_{5',OH}$ 5.1, $J_{5',5}$ 12.1), 4.56 (1H, a-t, H4, $J_{4,5} = J_{4,5'}$ 2.3), 4.75 (1H, d, H3, $J_{3,2}$ 5.6), 4.77 (1H, d, H2, $J_{2,3}$ 5.6); $\delta_C$ ($CD_3CN$, 100 MHz): 25.6, 27.1 ($C(\underline{C}H_3)_2$), 62.0 (C5), 76.5 (C2), 79.4 (C3), 83.6 (C4), 113.4 ($\underline{C}(CH_3)_2$), 175.7 (C1); LRMS (ESI +ve): 211 (62%, M+$Na^+$), 243 (73%, M+MeOH+$Na^+$), 399 (100%, 2M+$Na^+$).

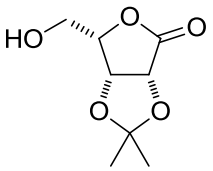
**2,3-*O*-Isopropylidene-5-*O*-methanesulfonyl-D-ribono-1,4-lactone 1.65**




Methanesulfonyl chloride (3.0 mL, 39.1 mmol) was added dropwise to a solution of the lactone **3.35** (4.9 g, 26.0 mmol) and triethylamine (5.5 mL, 39.1 mmol) in anhydrous dichloromethane (75 mL) at 0 °C. The reaction was stirred for 2 h, after which TLC analysis (2:3, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.57) and the formation of a major product ($R_f$ 0.64). The reaction mixture was diluted with dichloromethane (150 mL) and washed with water (150 mL). The aqueous phase was extracted

with dichloromethane (3 x 100 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1 to 1:1, cyclohexane/ethyl acetate) to afford the mesylate **1.65** (6.58 g, 95%) as a clear oil, which crystallised on standing; HRMS (ESI +ve): found 289.0347 [$M+Na^+$]; $C_9H_{14}NaO_7S$ requires 289.0352; $[\alpha]_D^{20}$ -56.3 (*c* 1.0, $CHCl_3$) [Lit.[92] $[\alpha]_D^{20}$ -52 (*c* 1.0, $CHCl_3$)]; m.p. 44-46 °C [Lit.[92] 43-44 °C (ether/ethanol)]; $\nu_{max}$ (thin film): 1172, (s, $SO_2$), 1354 (s, $SO_2$), 1788 (s, C=O); $\delta_H$ ($CD_3CN$, 400 MHz): 1.36, 1.42 (2 x 3H, s, $C(CH_3)_2$), 3.08 (3H, s, $SO_2CH_3$), 4.42 (1H, dd, H5, $J_{5,4}$ 3.0, $J_{5,5'}$ 11.4), 4.46 (1H, dd, H5', $J_{5',4}$ 2.5, $J_{5',5}$ 11.4), 4.80-4.85 (3H, m, H2, H3, H4); $\delta_C$ ($CD_3CN$, 100 MHz): 25.6, 27.0 ($C(\underline{C}H_3)_2$), 37.8 ($SO_2CH_3$), 70.0 (C5), 75.9, 78.4, 80.5 (C2, C3, C4), 114.3 ($\underline{C}(CH_3)_2$; LRMS (ESI +ve): 289, (32%, $M+Na^+$), 321 (81%, $M+MeOH+Na^+$), 555 (24%, $2M+Na^+$), 587 (44%, $2M+MeOH+Na^+$), 619 (100%, $2M+2MeOH+Na^+$); (ESI –ve): 265 (94%, $[M-H]^-$), 333 (100%, $M+^{35}Cl^-$), 335 (34%, $M+^{37}Cl^-$).

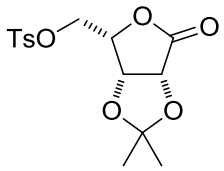
**2,3-*O*-Isopropylidene-L-lyxono-1,4-lactone 1.63L**




A solution of potassium hydroxide (3.93 g, 70 mmol, in water 120 mL) was added to a solution of the mesylate **1.65** in 1,4-dioxane (120 mL). The reaction was stirred at RT for 1 h, after which TLC analysis (ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.90) and the formation of baseline material. Glacial acetic acid (28 mL) was added and TLC analysis (5:3:2, *n*-BuOH/EtOH/$H_2O$) indicated an intermediate ($R_f$ 0.40) which was consumed after 17 h to form a major product ($R_f$ 0.80). The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (100 mL) and washed with water (100 mL). The aqueous layer was extracted with

ethyl acetate (3 x 100 mL), the organic fractions combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash chromatography (4:1 to 3:7, cyclohexane/ethyl acetate) to afford the lactone **1.63L** (3.61 g, 80%) as a white crystalline solid; *refer to page 280 for enantiomeric data*; m.p. 92-94 °C [Lit.[64] 98-99 °C (isopropanol)]; $[\alpha]_D^{25}$ -82.3 (*c* 1.01, acetone) [Lit.[64] $[\alpha]_D^{25}$ -89 (*c* 1.0, acetone)].

**2,3-*O*-Isopropylidene-5-*O*-*para*-toluenesulfonyl-L-lyxonolactone 3.107L**

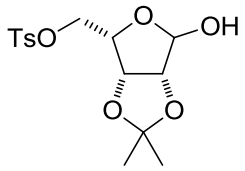



A solution of *para*-toluenesulfonyl chloride (3.8 g, 19.9 mmol) in pyridine (5 mL) was added dropwise to a solution of the lactone **1.63L** (1.50 g, 7.97 mmol) in pyridine (15 mL) at 0 °C. The reaction was allowed to warm to RT and stirred for 4 h, after which TLC analysis (2:3, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.30) and the formation of a major product ($R_f$ 0.74). The reaction was diluted with ethyl acetate (150 mL) and washed with 2 M aqueous hydrochloric acid (3 x 30 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1 to 1:3, cyclohexane/ethyl acetate) to afford the tosylate **3.107L** (2.3 g, 84%) as a white crystalline solid; HRMS (ESI +ve): found 365.0658 [$M+Na^+$]; $C_{15}H_{18}NaO_7S$ requires 365.0665; $[\alpha]_D^{20}$ -60.5 (*c* 0.82, $CHCl_3$) [Lit.[65] $[\alpha]_D^{20}$ -66.8 (*c* 0.4, $CHCl_3$)]; m.p. 116-118 °C [Lit.[65] 121-123 °C (ethanol)]; $\nu_{max}$ (thin film): 1174 (s, $SO_2$), 1360 (s, $SO_2$), 1790 (s, C=O); $\delta_H$ ($CDCl_3$, 400 MHz): 1.34, 1.37 (2 x 3H, s, $C(CH_3)_2$), 2.46 (3H, s, Ar$C\underline{H}_3$), 4.25 (1H, dd, H5, $J_{5,4}$ 7.2, $J_{5,5'}$ 11.2), 4.39 (1H, dd, H5', $J_{5',4}$ 4.8, $J_{5',5}$ 11.2), 4.70-4.72 (1H, m, H4), 4.81-4.84 (2H, m, H2, H3), 7.37 (2H, d, ArH, *J* 8.2), 7.81 (2H, d, ArH, *J* 8.2); $\delta_C$ ($CDCl_3$, 100 MHz): 21.6

(Ar<u>C</u>$H_3$), 25.7, 26.5 (C(<u>C</u>$H_3$)$_2$), 66.8 (C5), 75.3, 75.7 (C2, C3), 75.9 (C4), 114.6 (<u>C</u>($CH_3$)$_2$), 128.1, 130.0 (Ar<u>C</u>H), 132.1 (Ar<u>C</u>$CH_3$), 145.4 (Ar<u>C</u>$SO_2$), 172.7 (C1); LRMS (ESI +ve): 360 (30%, M+$NH_4^+$), 365 (45%, M+$Na^+$), 392 (10%, M+MeOH+$NH_4^+$), 397 (90%, M+MeOH+$Na^+$), 707 (35%, 2M+$Na^+$), 739 (75%, 2M+MeOH+$Na^+$), 771 (100%, 2M+2MeOH+$Na^+$).

Similar treatment of **2,3-*O*-isopropylidene-D-lyxono-1,4-lactone 1.63D** (4.80 g, 25.5 mmol) in a suitably scaled procedure afforded **2,3-*O*-isopropylidene-5-*O*-*para*-toluenesulfonyl-D-lyxono-1,4-lactone 3.107D** (6.99 g, 80%) as a white crystalline solid; m.p. 118-120 $^oC$; $[\alpha]_D^{20}$ +60.1 (*c* 0.70, $CHCl_3$).

**2,3-*O*-Isopropylidene-5-*O*-*para*-toluenesulfonyl-L-lyxofuranose 3.102L**



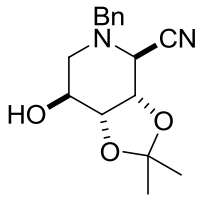

Diisobutylaluminium hydride (1.5 M in toluene, 5.4 mL, 8.06 mmol) was added dropwise over 15 min to a solution of the lactone **3.107L** (2.3 g, 6.71 mmol) in anhydrous dichloromethane (25 mL) at -78 $^oC$. The reaction mixture was stirred for 1.5 h, after which TLC analysis (5:1, toluene/acetone) indicated the complete consumption of the starting material ($R_f$ 0.47) and the formation of a major product ($R_f$ 0.56). The reaction was diluted with ethyl acetate (100 mL), allowed to warm to RT and a 1:3 water/saturated sodium potassium tartrate solution (100 mL) was added. The biphasic mixture was stirred vigorously for 1.5 h, after which the phases were separated and the aqueous layer extracted with ethyl acetate (6 x 25 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (3:1 to 1:4, cyclohexane/ethyl acetate) to afford the lactols **3.102L**

(2.17 g, 94%) as a white crystalline solid, in a 5.6:1 (A:B) mixture of anomers; HRMS (ESI +ve): found 367.0826 [M+$Na^+$]; $C_{15}H_{20}NaO_7S$ requires 367.0822; m.p. 116-118 $^oC$ [Lit.[65] 121-123 $^oC$ (ethanol)]; $[\alpha]_D^{20}$ -7.0 (*c* 1.11, $CHCl_3$); $\nu_{max}$ (thin film): 1175 (s, $SO_2$), 1359 (s, $SO_2$), 3459 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.25, 1.34 (2 x 3H, s, $C(CH_3)_2^A$), 1.31, 1.41 (2 x 3H, s, $C(CH_3)_2^B$), 2.45 (6H, s, $ArCH_3^A$, $ArCH_3^B$), 3.81 (1H, td, $H4^B$, $J_{4,3}$ 3.5, $J_{4,5} = J_{4,5'}$ 6.1), 4.17 (1H, dd, $H5^A$, $J_{5,4}$ 7.6, $J_{5,5'}$ 10.6), 4.19 (1H, dd, $H5^B$, $J_{5,4}$ 6.1, $J_{5,5'}$ 10.6), 4.31 (2H, a-dd, $H5'^A$, $H5'^B$, *J* 4.3, *J* 10.6), 4.38 (1H, a-q, $H4^A$, *J* 4.0), 4.21 (1H, dd, $H2^B$, $J_{2,1}$ 3.4, $J_{2,3}$ 6.3), 4.59 (1H, d, $H2^A$, $J_{2,3}$ 5.8), 4.68 (1H, dd, $H3^B$, $J_{3,4}$ 3.5, $J_{3,2}$ 6.3), 4.73 (1H, dd, $H3^A$, $J_{3,4}$ 3.6, $J_{3,2}$ 5.8), 5.00 (1H, d, $H1^B$, $J_{1,2}$ 3.3), 5.37 (1H, s, $H1^A$), 7.35 (4H, d, $ArH^A$, $ArH^B$, *J* 8.1), 7.81 (4H, d, $ArH^A$, $ArH^B$, *J* 8.3); $\delta_C$ ($CDCl_3$, 100 MHz): 21.6 ($Ar\underline{C}H_3^A$, $Ar\underline{C}H_3^B$), 24.6, 25.8 ($C(\underline{C}H_3)_2^A$), 24.7, 25.6 ($C(\underline{C}H_3)_2^B$), 67.1 ($C5^B$), 68.1 ($C5^A$), 73.2 ($C4^B$), 77.5 ($C4^A$), 78.4 ($C2^B$), 79.0 ($C3^B$), 79.5 ($C3^A$), 85.3 ($C2^A$), 97.0 ($C1^B$), 101.2 ($C1^A$), 112.9 ($\underline{C}(CH_3)_2^A$), 113.5 ($\underline{C}(CH_3)_2^B$), 128.1 ($Ar\underline{C}H^A$, $Ar\underline{C}H^B$), 129.8 ($Ar\underline{C}H^B$), 129.8 ($Ar\underline{C}H^A$), 132.6 ($Ar\underline{C}CH_3^A$, $Ar\underline{C}CH_3^B$), 144.9 ($Ar\underline{C}SO_2^A$, $Ar\underline{C}SO_2^B$); LRMS (ESI +ve): 367 (100%, M+$Na^+$).

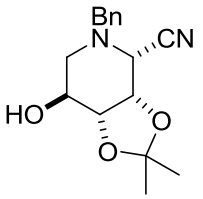
Similar treatment of **2,3-*O*-isopropylidene-5-*O*-*para*-toluenesulfonyl-D-lyxono-1,4-lactone 3.XDZD 3.107D** (6.8 g, 19.8 mmol) in a suitably scaled procedure afforded **2,3-*O*-isopropylidene-5-*O*-*para*-toluenesulfonyl-D-lyxofuranose 3.102D** (6.01 g, 88%) as a white crystalline solid; m.p. 116-118 $^oC$; $[\alpha]_D^{20}$ +6.1 (*c* 2.39, $CHCl_3$).

**2-*N*-Benzyl-2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-L-talononitrile 3.108L /**

**2-*N*-Benzyl-2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-L-galactononitrile 3.109L**




**3.108L**




**3.109L**

A solution of benzylamine (0.14 mL, 1.31 mmol), potassium cyanide (85 mg, 1.31 mmol) and the tosylates **3.102L** (180 mg, 0.52 mmol) in anhydrous methanol (1 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.0 mL, 2.91 mmol). The reaction mixture was stirred at RT for 3 d, after which TLC analysis (9:1, dichloromethane/diethyl ether) indicated the complete consumption of the starting materials ($R_f$ 0.40) and the formation of two products ($R_f$ 0.50, $R_f$ 0.35). The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (50 mL) and washed with 2 M aqueous hydrochloric acid (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 20 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (99:1 to 19:1, dichloromethane/diethyl ether) to afford the separable α-iminonitriles **3.108L** ($R_f$ 0.35, 56 mg, 37%) and **3.109L** ($R_f$ 0.50, 60 mg, 40%) as clear oils.

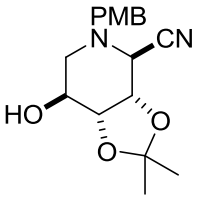
Data for the α-iminonitrile **3.108L** ($R_f$ 0.35): HRMS (ESI +ve): found 311.1368 [M+$Na^+$]; $C_{16}H_{20}N_2NaO_3$ requires 311.1366; $[\alpha]_D^{20}$ +3.1 (*c* 1.20, $CHCl_3$); $\nu_{max}$ (thin film): 2251 (w, CN), 3476 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.37, 1.53 (2 x 3H, s, $C(CH_3)_2$), 2.54 (1H, dd, H6, $J_{6,5}$ 8.2, $J_{6,6'}$ 12.3), 2.74 (1H, dd, H6', $J_{6',5}$ 4.1, $J_{6',6}$ 12.3), 3.66 (1H, d, $NC\underline{H}_2Ph$, $J_{gem}$ 13.1), 3.88-3.91 (2H, m, H2, H5), 3.93 (1H, d, $NC\underline{H}_2Ph$, $J_{gem}$ 13.1), 4.11 (1H, a-t, H4, $J_{4,3} = J_{4,5}$ 5.7), 4.41 (1H, dd, H3, $J_{3,2}$ 3.6, $J_{3,4}$ 5.2), 7.29-7.37 (5H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 26.2, 28.0 ($C(\underline{C}H_3)_2$), 51.6 (C6), 55.0 (C2), 59.2 ($N\underline{C}H_2Ph$), 68.7 (C5), 74.3 (C3), 77.8 (C4), 110.5

($\underline{C}(CH_3)_2$), 115.4 (CN), 127.9, 128.7, 128.9 (Ar$\underline{C}$H), 125.8 (Ar$\underline{C}$C); LRMS (ESI +ve): 289 (50%, $M+H^+$), 311 (100%, $M+Na^+$).

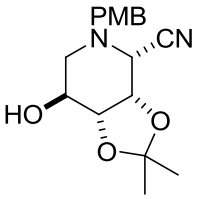
Data for α-iminonitrile **3.109L** ($R_f$ 0.50): HRMS (ESI +ve): found 311.1367 [$M+Na^+$]; $C_{16}H_{20}N_2NaO_3$ requires 311.1366; $[\alpha]_D^{20}$ +13.5 (*c* 1.15, $CHCl_3$); $\nu_{max}$ (thin film): 2252 (w, CN), 3461 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.37, 1.71 (2 x 3H, s, $C(CH_3)_2$), 2.77 (1H, br. d, H6, $J_{6,6'}$ 13.2), 3.05 (1H, br. dd, H6', $J_{6',5}$ 2.2, $J_{6',6}$ 12.9), 3.69 (1H, d, NC$\underline{H}_2$Ph, $J_{gem}$ 12.9), 3.77 (1H, d, NC$\underline{H}_2$Ph, $J_{gem}$ 12.9), 4.03 (1H, dd, H2, $J_{2,6'}$ 0.9, $J_{2,3}$ 7.8), 4.07 (1H, a-q, H5, $J_{5,4} = J_{5,6} = J_{5,6'}$ 2.5), 4.28 (1H, dd, H4, $J_{4,5}$ 2.2, $J_{4,3}$ 5.7), 4.35 (1H, dd, H3, $J_{3,4}$ 5.8, $J_{3,2}$ 7.8), 7.31-7.38 (5H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 25.4, 25.8 ($C(\underline{C}H_3)_2$), 50.5 (C6), 55.9 (C2), 59.7 (N$\underline{C}H_2$Ph), 65.4 (C5), 69.6 (C3), 75.4 (C4), 110.9 ($\underline{C}(CH_3)_2$), 115.6 (CN), 128.2, 128.8, 129.0 (Ar$\underline{C}$H), 135.8 (Ar$\underline{C}$C); LRMS (ESI +ve): 289 (45%, $M+H^+$), 311 (100%, $M+Na^+$).

Similar treatment of **2,3-*O*-isopropylidene-5-*O*-*para*-toluenesulfonyl-D-lyxofuranose 3.102D** (200 mg, 0.58 mmol) in a suitably scaled procedure afforded **2-*N*-benzyl-2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-D-talononitrile 3.108D** (67 mg, 40%) and **2-*N*-benzyl-2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-D-galactononitrile 3.109D** (59 mg, 42%) as clear oils; **3.108D**: $[\alpha]_D^{20}$ -5.7 (*c* 1.39, $CHCl_3$); **3.109D**: $[\alpha]_D^{20}$ -17.2 (*c* 1.24, $CHCl_3$).

**2,6-Dideoxy-2,6-imino-3,4-*O*-isopropylidene-2-*N*-(4-methoxybenzyl)-L-talononitrile 3.110L / 2,6-Dideoxy-2,6-imino-3,4-*O*-isopropylidene-2-*N*-(4-methoxybenzyl)-L-galactononitrile 3.111L**




**3.110L**




**3.111L**

Method A (RT): A solution of 4-methoxybenzylamine (0.31 mL, 2.40 mmol), potassium cyanide (156 mg, 2.40 mmol) and the tosylates **3.102L** (331 mg, 0.96 mmol) in anhydrous methanol (6 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.9 mL, 5.5 mmol). The reaction mixture was stirred at RT for 2 d, after which TLC analysis (9:1, dichloromethane/diethyl ether) indicated the complete consumption of the starting materials ($R_f$ 0.40) and the formation of two products ($R_f$ 0.67, 0.51). The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (75 mL) and washed with 2 M aqueous hydrochloric acid (15 mL). The aqueous phase was extracted with ethyl acetate (3 x 30 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (49:1 to 5:1, dichloromethane/diethyl ether) to afford the α-iminonitriles **3.110L** ($R_f$ 0.51, 124 mg, 41%) and **3.111L** ($R_f$ 0.67, 126 mg, 41%) as pale-yellow oils. The α-iminonitrile **3.111L** crystallised on standing to form a white crystalline solid.

Similar treatment of **2,3-*O*-isopropylidene-5-*O*-*para*-toluenesulfonyl-D-lyxofuranose 3.102D** (250 mg, 0.73 mmol) in a suitably scaled procedure afforded **2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-2-*N*-(4-methoxybenzyl)-D-talononitrile 3.110D** (100 mg, 43% as a clear oil, and **2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-2-*N*-(4-methoxybenzyl)-D-galactononitrile 3.111D** (95 mg, 41%) as a white crystalline solid.

Method B (40 °C): A solution of 4-methoxybenzylamine (0.31 mL, 2.40 mmol), potassium cyanide (156 mg, 2.40 mmol) and the tosylates **3.102L** (330 mg, 0.96 mmol) in anhydrous methanol (6 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.9 mL, 5.53 mmol). The reaction mixture was stirred at 40 °C for 30 h, after which TLC analysis (9:1, dichloromethane/diethyl ether) indicated the complete consumption of the starting materials ($R_f$ 0.40) and the formation of two products ($R_f$ 0.67, 0.51). The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (75 mL) and washed with 2 M aqueous hydrochloric acid (15 mL). The aqueous phase was extracted with ethyl acetate (3 x 30 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (49:1 to 5:1, dichloromethane/diethyl ether) to afford the α-iminonitriles **3.110L** ($R_f$ 0.51, 150 mg, 49%) and **3.111L** ($R_f$ 0.67, 107 mg, 35%) as pale-yellow oils. The α-iminonitrile **3.111L** crystallised on standing to form a white crystalline solid.

Similar treatment of **2,3-*O*-isopropylidene-5-*O*-*para*-toluenesulfonyl-D-lyxofuranose 3.102D** (220 mg, 0.64 mmol) in a suitably scaled procedure afforded **2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-2-*N*-(4-methoxybenzyl)-D-talononitrile 3.110D** (104 mg, 51%) as a clear oil, and **2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-2-*N*-(4-methoxybenzyl)-D-galactononitrile 3.111D** (69 mg, 34%) as a white crystalline solid.

Method C (65 °C): A solution of 4-methoxybenzylamine (0.34 mL, 2.62 mmol), potassium cyanide (171 mg, 2.62 mmol) and the tosylates **3.102L** (361 mg, 1.05 mmol) in anhydrous methanol (6 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.9 mL, 1.53 mmol). The reaction mixture was stirred at 65 °C for 1 d, after which TLC analysis (9:1, dichloromethane/diethyl ether) indicated the complete consumption of the starting materials

($R_f$ 0.40) and the formation of two products ($R_f$ 0.67, 0.51). The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (75 mL) and washed with 2 M aqueous hydrochloric acid (15 mL). The aqueous phase was extracted with ethyl acetate (3 x 30 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (49:1 to 5:1, dichloromethane/diethyl ether) to afford the α-iminonitriles **3.110L** ($R_f$ 0.51, 187 mg, 56%) and **3.111L** ($R_f$ 0.67, 90 mg, 27%) as pale-yellow oils. The α-iminonitrile **3.111L** crystallised on standing to form a white crystalline solid.

Similar treatment of **2,3-*O*-isopropylidene-5-*O*-*para*-toluenesulfonyl-D-lyxofuranose 3.102D** (300 mg, 0.87 mmol) in a suitably scaled procedure afforded **2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-2-*N*-(4-methoxybenzyl)-D-talononitrile 3.110D** (169 mg, 61%) as a clear oil, and **2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-2-*N*-(4-methoxybenzyl)-D-galactononitrile 3.111D** (75 mg, 27%) as a white crystalline solid.

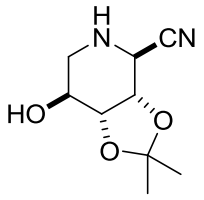
Data for the α-iminonitrile **3.110L** ($R_f$ 0.51): HRMS (ESI +ve): found 341.1474 [$M+Na^+$]; $C_{17}H_{22}N_2NaO_4$ requires 341.1472; $[\alpha]_D^{20}$ +37.6 (*c* 1.95, $CHCl_3$); $\nu_{max}$ (thin film): 2260 (w, CN), 3483 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.36, 1.52 (2 x 3H, s, $C(CH_3)_2$), 2.49 (1H, dd, H6, $J_{6,5}$ 8.7, $J_{6,6'}$ 12.2), 2.74 (1H, dd, H6', $J_{6',5}$ 4.3, $J_{6',6}$ 12.2), 3.02 (1H, br. s, OH5), 3.59 (1H, d, $NC\underline{H}_2Ar$, $J_{gem}$ 13.1), 3.80 (3H, s, $OCH_3$), 3.84 (1H, d, $NC\underline{H}_2Ar$, $J_{gem}$ 13.1), 3.87 (1H, br. s, H5), 3.90 (1H, d, H2, $J_{2,3}$ 3.3), 4.09 (1H, a-t, H4, $J_{4,3} = J_{4,5}$ 5.6), 4.39 (1H, dd, H3, $J_{3,2}$ 3.3, $J_{3,4}$ 5.3), 6.88 (2H, d, ArH, *J* 8.6), 7.26 (2H, d, ArH, *J* 8.6); $\delta_C$ ($CDCl_3$, 100 MHz): 26.1, 27.9 ($C(\underline{C}H_3)_2$), 51.5 (C6), 54.5 (C2), 55.1 ($OCH_3$), 58.4 ($N\underline{C}H_2Ar$), 68.7 (C5), 74.1 (C3), 77.9 (C4), 110.3 ($\underline{C}(CH_3)_2$), 113.9 (Ar$\underline{C}$H), 115.3 (CN), 127.6 (Ar$\underline{C}$C), 130.0 (Ar$\underline{C}$H), 159.1 (Ar$\underline{C}OCH_3$); LRMS (ESI +ve): 319 (15%, $M+H^+$), 341 (100%, $M+Na^+$).

Data for the α-iminonitrile **3.111D** ($R_f$ 0.67): HRMS (ESI +ve): found 341.1458 [M+$Na^+$]; $C_{17}H_{22}N_2NaO_4$ requires 341.1472; m.p. 84-86 °C; $[\alpha]_D^{20}$ -72.4 (*c* 1.73, $CHCl_3$); $\nu_{max}$ (thin film): 2230 (w, CN), 3488 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.37, 1.71 (2 x 3H, s, $C(CH_3)_2$), 2.69 (1H, br. s, OH5), 2.77 (1H, br. d, H6, $J_{6,6'}$ 12.9), 3.03 (1H, dd, H6', $J_{6',2}$ 1.0, $J_{6',6}$ 12.9), 3.61 (1H, d, $NCH_2Ar$, $J_{gem}$ 12.6), 3.70 (1H, d, $NCH_2Ar$, $J_{gem}$ 12.6), 3.81 (3H, s, $OCH_3$), 4.02 (1H, dd, H2, $J_{2,6'}$ 1.0, $J_{2,3}$ 7.8), 4.06 (1H, br. s, H5), 4.27 (1H, dd, H4, $J_{4,5}$ 2.0, $J_{4,3}$ 5.6), 4.32 (1H, dd, H3, $J_{3,4}$ 5.8, $J_{3,2}$ 7.8), 6.89 (2H, d, ArH, *J* 8.6), 7.23 (2H, d, ArH, *J* 8.6); $\delta_C$ ($CDCl_3$, 100 MHz): 25.4, 25.8 ($C(CH_3)_2$), 50.3 (C6), 55.3 ($OCH_3$), 55.8 (C2), 59.1 ($NCH_2Ar$), 65.3 (C5), 69.6 (C3), 75.4 (C4), 110.9 ($C(CH_3)_2$), 114.2 (ArCH), 115.7 (CN), 127.7 (ArCC), 130.3 (ArCH), 159.5 ($ArCOCH_3$); LRMS (ESI +ve): 319 (20%, M+$H^+$), 341 (100%, M+$Na^+$).

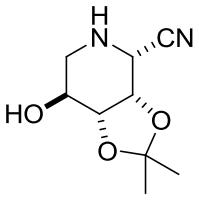
Data for the enantiomers: **3.110D**: $[\alpha]_D^{20}$ -38.2 (*c* 1.84, $CHCl_3$); **3.111D**: m.p. 84-86 °C; $[\alpha]_D^{20}$ +70.1 (*c* 1.65, $CHCl_3$).

**2,6-Dideoxy-2,6-imino-3,4-*O*-isopropylidene-L-talononitrile 3.112 /**

**2,6-Dideoxy-2,6-imino-3,4-*O*-isopropylidene-L-galactononitrile 3.113**




**3.112**



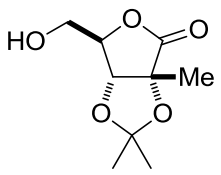

**3.113**

A solution of ammonium acetate (546 mg, 7.09 mmol), potassium cyanide (115 mg, 1.77 mmol) and the tosylates **3.102L** (244 mg, 0.71 mmol) in anhydrous methanol (4 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.8 mL, 5.24 mmol). The reaction mixture was stirred at 40 °C for 3 d, after which TLC analysis (9:1, dichloromethane/diethyl

ether) indicated the almost complete consumption of the starting materials ($R_f$ 0.40) and the formation of a major product ($R_f$ 0.11). The reaction mixture was concentrated *in vacuo* and co-evaporated with ethyl acetate (3 x 10 mL). The crude residue was purified by flash chromatography (3:1:0 to 9:0:1, dichloromethane/diethyl ether/methanol) to afford an inseparable 1.8:1 (A:B) mixture of the α-iminonitriles **3.112**$^A$/**3.113**$^B$ (71 mg, 51%) as a pale-yellow oil; HRMS (ESI +ve): found 221.0891 [M+Na$^+$]; $C_9H_{14}N_2NaO_3$ requires 221.0897; $\nu_{max}$ (thin film): 2234 (w, CN), 3488 (br. s, OH, NH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.36, 1.50 (2 x 3H, s, C(CH$_3$)$_2^A$), 1.37, 1.62 (2 x 3H, s, C(CH$_3$)$_2^B$), 2.79 (1H, dd, H6$^B$, $J_{6,5}$ 4.5, $J_{6,6'}$ 13.4), 2.89 (1H, dd, H6$^A$, $J_{6,5}$ 4.5, $J_{6,6'}$ 13.6), 2.94 (1H, dd, H6'$^A$, $J_{6',5}$ 3.3, $J_{6',6}$ 13.6), 3.24 (1H, dd, H6'$^B$, $J_{6',5}$ 3.3, $J_{6',6}$ 13.4), 3.73 (1H, d, H2$^A$, $J_{2,3}$ 7.0), 3.92-3.97 (2H, m, H5$^A$, H5$^B$), 4.18-4.21 (2H, m, H4$^A$, H4$^B$), 4.28 (1H, d, H2$^B$, $J_{2,3}$ 5.3), 4.31 (1H, dd, H3$^A$, $J_{3,4}$ 5.1, $J_{3,2}$ 7.0), 4.35 (1H, a-t, H3$^B$, $J_{3,2} = J_{3,4}$ 5.6); $\delta_C$ ($CDCl_3$, 100 MHz): 25.3, 26.4 (C(<u>C</u>H$_3$)$_2^B$), 26.1, 28.0 (C(<u>C</u>H$_3$)$_2^A$), 44.9 (C6$^B$), 46.7 (C6$^A$), 48.3 (C2$^B$), 49.7 (C2$^A$), 66.0 (C5$^A$, C5$^B$), 70.3 (C3$^B$), 72.7 (C3$^A$), 76.0 (C4$^B$), 76.4 (C4$^A$), 110.3 (<u>C</u>(CH$_3$)$_2^A$), 110.6 (<u>C</u>(CH$_3$)$_2^B$), 118.2 (CN$^B$), 118.4 (CN$^A$); LRMS (ESI +ve): 199 (85%, M+H$^+$), 221 (100%, M+Na$^+$).

<u>3.4.3 2-*C*-Methyl-D-ribose route</u>

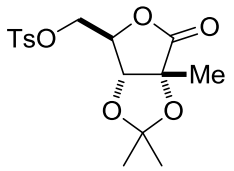
**2,3-*O*-Isopropylidene-2-*C*-methyl-D-ribono-1,4-lactone 3.119**




Anhydrous copper(II) sulfate (78.8 g, 493 mmol) and concentrated sulfuric acid (1.4 mL) were added to a suspension of the lactone **1.104** (40.0 g, 247 mmol) in acetone (700 mL). The reaction

was stirred for 24 h, after which TLC analysis (ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.27) and the formation of a single product ($R_f$ 0.67). The reaction mixture was neutralised with solid sodium bicarbonate, filtered through Celite® and concentrated *in vacuo*. The crude residue was purified by flash chromatography (1:1, cyclohexane/ethyl acetate) to afford the acetonide **3.119** as a white crystalline solid (42.7 g, 92%); HRMS (ESI +ve): found 225.0733 [M+$Na^+$]; $C_9H_{14}NaO_5$ requires 225.0733; m.p. 54-56 °C (acetone) [Lit.[78] 52-54 °C (acetone)]; $[\alpha]_D^{20}$ -45.0 (*c* 1.5, acetone) [Lit.[78] $[\alpha]_D^{19}$ -35.6 (*c* 1.4, acetone)]; $\nu_{max}$ (thin film): 1701 (s, C=O), 3490 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.42, 1.44 (2 x 3H, s, $C(CH_3)_2$), 1.65 (3H, s, 2-$CH_3$), 3.82 (1H, dd, H5, $J_{5,4}$ 2.0, $J_{5,5'}$ 12.1), 3.99 (1H, dd, H5', $J_{5',4}$ 2.8, $J_{5',5}$ 12.1), 4.52-4.57 (2H, m, H3, H4); $\delta_C$ ($CDCl_3$, 100 MHz): 19.8 (2-$CH_3$), 26.7, 26.8 ($C(\underline{C}H_3)_2$), 62.2 (C5), 82.6, 83.5 (C3, C4), 82.8 (C2), 112.9 ($\underline{C}(CH_3)_2$), 176.9 (C1); LRMS (ESI +ve): 225 (58%, M+$Na^+$), 427 (100%, 2M+$Na^+$); (ESI –ve): 201 (37%, $[M-H]^-$), 403 (100%, $[2M-H]^-$).

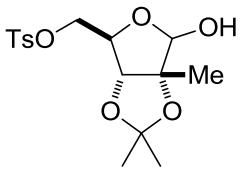
**2,3-*O*-Isopropylidene-2-*C*-methyl-5-*O*-*para*-toluenesulfonyl-D-ribono-1,4-lactone 3.120**




*para*-Toluenesulfonyl chloride (9.43 g, 49.5 mmol) was added portion-wise to a solution of the lactone **3.119** (5 g, 24.7 mmol) in pyridine (10 mL) at 0 °C. After 10 min the reaction was allowed to warm to RT and stirred for a further 3 d, after which TLC analysis (2:3, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.18) and the formation of a single product ($R_f$ 0.82). The reaction mixture was diluted with ethyl acetate (200 mL) and washed with 2 M hydrochloric acid (4 x 25 mL). The organic phase was

dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (19:1 to 1:1, cyclohexane/ethyl acetate) to afford the tosylate **3.120** (6.4 g, 73%) as a white crystalline solid; HRMS (ESI +ve): found 379.0820 [M+$Na^+$]; $C_{16}H_{20}NaO_7S$ requires 379.0822; m.p. 90-91 $^oC$ [Lit.[79] 93-94$^oC$ (petroleum ether/ether)]; $[\alpha]_D^{20}$ +2.6 (*c* 1.50, $CHCl_3$) [Lit.[79] $[\alpha]_D^{22}$ +3.5 (*c* 2.2, $CHCl_3$)]; $\nu_{max}$ (thin film): 1177 (s, $SO_2$), 1364 (s, $SO_2$), 1789 (s, C=O); $\delta_H$ ($CD_3CN$, 400 MHz): 1.35, 1.36 (2 x 3H, s, $C(CH_3)_2$), 1.53 (3H, s, 2-$CH_3$), 2.45 (3H, s, Ar$CH_3$), 4.24 (1H, dd, H5, $J_{5,4}$ 3.3, $J_{5,5'}$ 11.6), 4.27 (1H, dd, H5', $J_{5',4}$ 3.3, $J_{6',6}$ 11.6), 4.49 (1H, s, H3), 4.62 (1H, t, H4, $J_{4,5} = J_{4,5'}$ 3.3), 7.46 (2H, br. d, ArCH, *J* 8.2), 7.78 (2H, br. d, ArCH, *J* 8.2); $\delta_C$ ($CD_3CN$, 100 MHz): 20.2 (2-$CH_3$), 21.8 (Ar$\underline{C}H_3$), 26.8, 27.1 ($C(\underline{C}H_3)_2$), 69.9 (C5), 80.7 (C4), 82.6 (C3), 83.2 (C2), 113.9 ($\underline{C}(CH_3)_2$), 129.0, 131.3 (Ar$\underline{C}$H), 132.8 (Ar$\underline{C}CH_3$), 147.2 (Ar$\underline{C}SO_2$), 176.6 (C1); LRMS (ESI +ve): 374 (57%, M+$NH_4^+$), 379 (83%, M+$Na^+$), 395 (25%, M+$K^+$), 735 (100%, 2M+$Na^+$).

**2,3-*O*-Isopropylidene-2-*C*-methyl-5-*O*-*para*-toluenesulfonyl-D-ribofuranose 3.117**

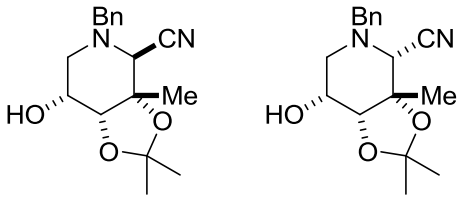



Diisobutylaluminium hydride (1.5 M in toluene, 12.0 mL, 17.5 mmol) was added dropwise over 15 min to a solution of the lactone **3.120** (5.2 g, 14.6 mmol) in anhydrous dichloromethane (50 mL) at -78 $^oC$. The reaction mixture was stirred for 1 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the incomplete consumption of the starting material ($R_f$ 0.54) and the formation of a major product ($R_f$ 0.50). The reaction was diluted with ethyl acetate (200 mL), allowed to warm to RT and a 1:3 water/saturated sodium potassium tartrate solution (200 mL) was added. The biphasic mixture was stirred vigorously for 2.5 h, after which the

phases were separated and the aqueous layer extracted with ethyl acetate (6 x 50 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (19:1 to 1:1, cyclohexane/ethyl acetate) to afford the lactols **3.117** (4.9 g, 94%) as a yellow oil, as a 2:1 mixture of anomers (A:B); HRMS (ESI +ve): found 381.0971 [M+$Na^+$]; $C_{16}H_{22}NaO_7S$ requires 381.0978; $[\alpha]_D^{20}$ +6.4 (*c* 1.52, $CHCl_3$); $\nu_{max}$ (thin film): 1177 (s, $SO_2$), 1363 (s, $SO_2$), 3485 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.40, 1.43 (2 x 3H, s, $C(CH_3)_2{}^B$), 1.41 (3H, s, 2-$CH_3{}^B$), 1.44, 1.52 (2 x 3H, s, $C(CH_3)_2{}^A$), 1.50 (3H, s, 2-$CH_3{}^A$), 2.46 (6H, s, Ar$C\underline{H}_3{}^A$, Ar$C\underline{H}_3{}^B$), 2.94 (1H, d, OH1$^B$, $J_{OH,1}$ 4.3), 3.84 (1H, d, OH1$^A$, $J_{OH,1}$ 10.1), 4.05 (1H, dd, H5$^A$, $J_{5,4}$ 3.5, $J_{5,5'}$ 10.6), 4.06-4.10 (1H, m, H5$^B$), 4.12-4.16 (1H, m, H5'$^B$), 4.15 (1H, dd, H5'$^A$, $J_{5',4}$ 2.5, $J_{5',5}$ 10.6), 4.22-4.26 (3H, m, H3$^B$, H4$^A$, H4$^B$), 4.41 (1H, d, H3$^A$, $J_{3,4}$ 1.0), 4.94 (1H, d, H1$^A$, $J_{1,OH}$ 10.1), 5.25 (1H, d, H1$^B$, $J_{1,OH}$ 4.3), 7.37 (4H, a-d, ArH$^A$, ArH$^B$, *J* 8.3), 7.80 (4H, a-t, ArH$^A$, ArH$^B$, *J* 8.6); $\delta_C$ ($CDCl_3$, 100 MHz): 20.1 (2-$CH_3{}^B$), 21.6 (Ar$CH_3{}^A$, Ar$CH_3{}^B$), 21.7 (2-$CH_3{}^A$), 26.8, 27.1 ($C(\underline{C}H_3)_2{}^A$), 27.6, 28.0 ($C(\underline{C}H_3)_2{}^B$), 69.8 (C5$^B$), 70.3 (C5$^A$), 79.2 (C4$^A$), 82.8 (C4$^B$), 86.4 (C3$^A$), 87.3 (C3$^B$), 87.8 (C2$^A$), 91.6 (C2$^B$), 102.3 (C1$^A$), 104.6 (C1$^B$), 113.1 ($\underline{C}(CH_3)_2{}^A$), 113.9 ($\underline{C}(CH_3)_2{}^B$), 127.9 (Ar$\underline{C}H^A$), 128.0 (Ar$\underline{C}H^B$), 129.9 (Ar$\underline{C}H^B$), 130.0 (Ar$\underline{C}H^A$), 132.1 (Ar$\underline{C}CH_3{}^A$), 132.5 (Ar$\underline{C}CH_3{}^B$), 145.2 (Ar$\underline{C}SO_2{}^B$), 145.4 (Ar$\underline{C}SO_2{}^A$); LRMS (ESI +ve): 381 (22%, M+$Na^+$), 739 (100%, 2M+$Na^+$).

**2-*N*-Benzyl-2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-3-*C*-methyl-D-allononitrile 3.121 /**

**2-*N*-Benzyl-2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-3-*C*-methyl-D-altrononitrile 3.122**




**3.121** **3.122**

Method A (RT): A solution of benzylamine (0.20 mL, 1.84 mmol), potassium cyanide (70 mg, 1.07 mmol) and the tosylates **3.117** (300 mg, 0.84 mmol) in anhydrous methanol (6 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.1 mL, 3.20 mmol). The reaction mixture was stirred at RT for 4 d, after which TLC analysis (5:1, toluene/acetone) indicated the complete consumption of the starting materials ($R_f$ 0.48) and the formation of a major product ($R_f$ 0.41). The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (75 mL) and washed with 2 M aqueous hydrochloric acid (15 mL). The aqueous phase was extracted with ethyl acetate (3 x 30 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (49:1 to 23:2, toluene/acetone) to afford the α-iminonitrile **3.121** (130 mg, 51%) as a pale-yellow oil, which crystallised on standing.

Method B (40 $^oC$): A solution of benzylamine (0.20 mL, 1.84 mmol), potassium cyanide (70 mg, 1.07 mmol) and the tosylates **3.117** (300 mg, 0.84 mmol) in anhydrous methanol (6 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.1 mL, 3.20 mmol). The reaction mixture was stirred at 40 $^oC$ for 2 d, after which TLC analysis (5:1, toluene/acetone) indicated the complete consumption of the starting materials ($R_f$ 0.48) and the formation of a major product ($R_f$ 0.41). The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (75 mL) and washed with 2 M aqueous hydrochloric acid (15 mL). The aqueous phase

was extracted with ethyl acetate (3 x 30 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (49:1 to 23:2, toluene/acetone) to afford a 15:1 (A:B) mixture of the α-iminonitriles **3.121**$^A$/**3.122**$^B$ (201 mg, 79%) as a pale-yellow oil, which crystallised on standing.

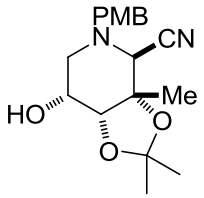
Method C (65 $^oC$): A solution of benzylamine (0.20 mL, 1.84 mmol), potassium cyanide (70 mg, 1.07 mmol) and the tosylates **3.117** (300 mg, 0.84 mmol) in anhydrous methanol (6 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.1 mL, 3.20 mmol). The reaction mixture was stirred at 65 $^oC$ for 1 d, after which TLC analysis (5:1, toluene/acetone) indicated the complete consumption of the starting materials ($R_f$ 0.48) and the formation of a major product ($R_f$ 0.41). The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (75 mL) and washed with 2 M aqueous hydrochloric acid (15 mL). The aqueous phase was extracted with ethyl acetate (3 x 30 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (49:1 to 23:2, toluene/acetone) to afford a 4.4:1 (A:B) mixture of the α-iminonitriles **3.121**$^A$/**3.122**$^B$ (185 mg, 73%) as a pale-yellow oil, which crystallised on standing.

Data for the α-iminonitrile **3.121**: HRMS (ESI +ve): found 325.1512 [M+$Na^+$]; $C_{17}H_{22}N_2NaO_3$ requires 325.1523; m.p. 121-122 $^oC$ (ethyl acetate/cyclohexane); $[\alpha]_D^{20}$ +39.7 (*c* 5.5, MeOH); $\nu_{max}$ (thin film): 2239 (w, CN), 3427 (br. s, OH); $\delta_H$ ($(CD_3)_2CO$, 400 MHz): 1.35, 1.48 (2 x 3H, s, $C(CH_3)_2$), 1.57 (3H, s, 3-$CH_3$), 2.28 (1H, a-t, H6, $J_{6,5} = J_{6,6'}$ 10.9), 2.72 (1H, dd, H6', $J_{6',5}$ 5.7, $J_{6',6}$ 10.7), 3.52 (1H, d, NC$\underline{H}_2$Ph, $J_{gem}$ 13.2), 3.56 (1H, s, H2), 3.84-3.88 (1H, m, H5), 4.05 (1H, br. s, OH5), 4.16 (1H, d, NC$\underline{H}_2$Ph, $J_{gem}$ 13.2), 4.18 (1H, d, H4, $J_{4,5}$ 3.2), 7.28-7.38 (5H, m, ArH); $\delta_C$ ($(CD_3)_2CO$, 100 MHz): 20.5 (3-$CH_3$), 26.8, 28.3 ($C(\underline{C}H_3)_2$), 53.3 (C6), 60.0 (N$\underline{C}H_2$Ph), 62.0 (C2), 65.5 (C5), 80.6 (C3), 81.4 (C4), 110.1 ($\underline{C}(CH_3)_2$), 118.2 (CN), 128.4,

129.3, 129.8, 129.8 (Ar<u>C</u>H), 137.9 (Ar<u>C</u>C); LRMS (ESI +ve): 303 (32%, $M+H^+$), 325 (87%, $M+Na^+$), 627 (100%, $2M+Na^+$).

Data for the mixture of α-iminonitriles **3.121**$^A$/**3.122**$^B$: HRMS (ESI +ve): found 325.1510 [$M+Na^+$]; $C_{17}H_{22}N_2NaO_3$ requires 325.1523; $\nu_{max}$ (thin film): 2241 (w, CN), 3441 (br. s, OH); $\delta_H$ ($(CD_3)_2CO$, 400 MHz): 1.35, 1.48 (2 x 3H, s, $C(CH_3)_2{}^A$), 1.37, 1.42 (2 x 3H, s, $C(CH_3)_2{}^B$) 1.58 (3H, s, 3-$CH_3{}^A$), 1.68 (3H, s, 3-$CH_3{}^B$), 2.27 (1H, a-t, H6$^B$, $J_{6,5} = J_{6,6'}$ 11.1), 2.29 (1H, a-t, H6$^A$, $J_{6,5} = J_{6,6'}$ 11.4), 2.70 (1H, dd, H6'$^B$, $J_{6',5}$ 5.0, $J_{6',6}$ 10.6), 2.72 (1H, dd, H6'$^A$, $J_{6',5}$ 5.7, $J_{6',6}$ 10.7), 3.52 (1H, d, NC<u>H</u>$_2$Ph$^A$, $J_{gem}$ 13.2), 3.55 (1H, d, NC<u>H</u>$_2$Ph$^B$, $J_{gem}$ 12.5), 3.56 (1H, s, H2$^A$), 3.71 (1H, s, H2$^B$), 3.82-3.90 (1H, m, H5$^A$), 3.94-4.01 (1H, m, H5$^B$) 4.07 (2H, m, OH5$^A$, OH5$^B$), 4.12 (1H, d, NC<u>H</u>$_2$Ph$^B$, $J_{gem}$ 12.5), 4.16 (1H, d, NC<u>H</u>$_2$Ph$^A$, $J_{gem}$ 13.2), 4.18 (1H, d, H4$^A$, $J_{4,5}$ 3.2), 4.24 (1H, d, H4$^B$, $J_{4,5}$ 4.5), 7.12-7.38 (10H, m, ArH$^A$, ArH$^B$); $\delta_C$ ($(CD_3)_2CO$, 100 MHz): 20.4 (3-$CH_3{}^A$), 21.5 (3-$CH_3{}^B$), 26.1, 26.5 ($C(\underline{C}H_3)_2{}^B$) 26.8, 28.3 ($C(\underline{C}H_3)_2{}^A$), 50.4 (C6$^B$), 53.3 (C6$^A$), 60.0 (N<u>C</u>H$_2$Ph), 62.0 (C2$^A$), 62.5 (C2$^B$), 65.5 (C5$^A$), 66.3 (C5$^B$), 79.9 (C3$^B$), 80.6 (C3$^A$), 81.4 (C4$^A$, C4$^B$), 110.1 ($\underline{C}(CH_3)_2{}^A$), 110.6 ($\underline{C}(CH_3)_2{}^B$), 117.3 (CN$^B$), 118.2 (CN$^A$), 128.4, 128.5, 129.1, 129.3, 129.4, 129.6, 129.8 (Ar<u>C</u>H$^A$, Ar<u>C</u>H$^B$), 137.9 (Ar<u>C</u>C$^A$), 138.2 (Ar<u>C</u>C$^B$); LRMS (ESI +ve): 303 (40%, $M+H^+$), 325 (100%, $M+Na^+$), 627 (85%, $2M+Na^+$).

**2,6-Dideoxy-2,6-imino-3,4-*O*-isopropylidene-2-*N*-(4-methoxybenzyl)-3-*C*-methyl-D-allononitrile 3.123**



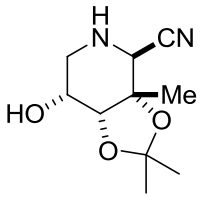

Method A (RT): A solution of 4-methoxybenzylamine (0.28 mL, 2.14 mmol), potassium cyanide (75 mg, 1.15 mmol) and the tosylates **3.117** (340 mg, 0.95 mmol) in anhydrous methanol (6 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.4 mL, 4.07 mmol). The reaction mixture was stirred at RT for 3 d, after which TLC analysis (5:1, toluene/acetone) indicated the complete consumption of the starting materials ($R_f$ 0.48) and the formation of a major product ($R_f$ 0.40). The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (75 mL) and washed with 2 M aqueous hydrochloric acid (15 mL). The aqueous phase was extracted with ethyl acetate (3 x 30 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (49:1 to 23:2, toluene/acetone) to afford the α-iminonitrile **3.123** (208 mg, 68%) as a white crystalline solid.

Method B (40 $^oC$): A solution of 4-methoxybenzylamine (0.28 mL, 2.14 mmol), potassium cyanide (75 mg, 1.15 mmol) and the tosylates **3.117** (340 mg, 0.95 mmol) in anhydrous methanol (6 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.4 mL, 4.07 mmol). The reaction mixture was stirred at 40 $^oC$ for 2 d, after which TLC analysis (5:1, toluene/acetone) indicated the complete consumption of the starting materials ($R_f$ 0.40) and the formation of a major product ($R_f$ 0.41). The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (75 mL) and washed with 2 M aqueous hydrochloric acid (15 mL). The aqueous phase was extracted with ethyl acetate (3 x 30 mL). The organic fractions were

combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (49:1 to 23:2, toluene/acetone) to afford the α-iminonitrile **3.123** (250 mg, 79%, >95% brsm) as white crystalline solid.

Data for the α-iminonitrile **3.123**: HRMS (ESI +ve): found 355.1618 [M+$Na^+$]; $C_{18}H_{24}N_2NaO_4$ requires 355.1628; m.p. 150-152 $^oC$; $[\alpha]_D^{20}$ +35.6 (*c* 0.99, $CHCl_3$); $\nu_{max}$ (thin film): 2230 (w, CN), 3384 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.40, 1.52 (2 x 3H, s, $C(CH_3)_2$), 1.61 (3H, s, 3-$CH_3$), 2.18 (1H, a-t, H6, $J_{6,5} = J_{6,6'}$ 10.9), 2.86 (1H, dd, H6', $J_{6',5}$ 5.9, $J_{6',6}$ 11.0), 3.37 (1H, s, H2), 3.44 (1H, d, NC$\underline{H}_2$Ar, $J_{gem}$ 12.8), 3.81 (3H, s, $OCH_3$), 3.84-3.90 (1H, m, H5), 4.13 (1H, d, NC$\underline{H}_2$Ar, $J_{gem}$ 12.8), 4.14 (1H, d, H4, $J_{4,5}$ 3.9), 6.86-6.89 (2H, m, ArH), 7.20-7.24 (2H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 20.3 (3-$CH_3$), 26.6, 28.0 ($C(\underline{C}H_3)_2$), 52.6 (C6), 55.3 ($OCH_3$), 58.9 (N$\underline{C}H_2$Ar), 60.9 (C2), 65.1 (C5), 79.9 (C3), 80.1 (C4), 110.0 ($\underline{C}(CH_3)_2$), 113.9 (Ar$\underline{C}$H), 116.9 (CN), 127.8 (Ar$\underline{C}$C), 130.4 (Ar$\underline{C}$H), 159.2 (Ar$\underline{C}$OMe); LRMS (ESI +ve): 333 (45%, M+$H^+$), 355 (100%, M+$Na^+$).

**2,6-Dideoxy-2,6-imino-3,4-isopropylidene-3-*C*-methyl-D-allononitrile 3.125**

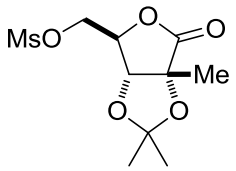



A solution of ammonium acetate (508 mg, 6.59 mmol), potassium cyanide (107 mg, 1.65 mmol) and the tosylates **3.117** (236 mg, 0.66 mmol) in anhydrous methanol (2 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.7 mL, 4.95 mmol). The reaction mixture was stirred at 40 $^oC$ for 4 d, after which TLC analysis (9:1, dichloromethane/diethyl ether) indicated the almost complete consumption of the starting materials ($R_f$ 0.69) and the

formation of a major product ($R_f$ 0.14). The reaction mixture was concentrated *in vacuo* and co-evaporated with ethyl acetate (3 x 10 mL). The crude residue was purified by flash chromatography (3:1:0 to 9:0:1, dichloromethane/diethyl ether/methanol) to afford the α-iminonitrile **3.125** (93 mg, 71%) as a pale-yellow oil; HRMS (ESI +ve): found 235.1058 [M+$Na^+$]; $C_{10}H_{16}N_2NaO_3$ requires 235.1053; $[\alpha]_D^{20}$ -19.1 (*c* 1.52, $CHCl_3$); $\nu_{max}$ (thin film): 2240 (w, CN), 3321 (br. s, OH, NH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.39, 1.53 (2 x 3H, s, $C(CH_3)_2$), 1.52 (3H, s, 3-$CH_3$), 2.69 (1H, a-t, H6, $J_{6,5} = J_{6,6'}$ 11.5), 3.07 (1H, dd, H6', $J_{6',5}$ 5.7, $J_{6',6}$ 11.7), 3.71 (1H, s, H2), 3.84 (1H, ddd, H5, $J_{5,4}$ 3.8, $J_{5,6'}$ 5.7, $J_{5,6}$ 10.7), 4.12 (1H, br. s, OH5), 4.16 (1H, d, H4, $J_{4,5}$ 3.8); $\delta_C$ ($CDCl_3$, 100 MHz): 18.5 (3-$CH_3$), 26.6, 28.2 ($C(\underline{C}H_3)_2$), 47.5 (C6), 54.3 (C2), 65.8 (C5), 79.1 (C3), 80.4 (C4), 109.9 ($\underline{C}(CH_3)_2$), 117.7 (CN); LRMS (ESI +ve): 213 (82%, M+$H^+$), 235 (100%, M+$Na^+$).

3.4.4 2-*C*-Methyl-L-lyxose route

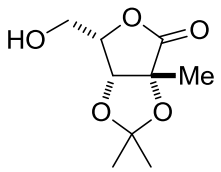
**2,3-*O*-Isopropylidene-5-*O*-methanesulfonyl-2-*C*-methyl-D-ribono-1,4-lactone 3.129**




Methanesulfonyl chloride (1.4 mL, 17.8 mmol) was added drop-wise to a solution of the lactone **1.104** (3.0 g, 14.8 mmol) in pyridine (20 mL) at 0 °C. The reaction was allowed to warm to RT and stirred for 3 h, after which TLC analysis (1:2, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.40) and the formation of a major product ($R_f$ 0.51). The reaction mixture was concentrated *in vacuo* and purified by flash chromatography (3:1, cyclohexane/ethyl acetate) to afford the mesylate **3.129** as a pale yellow oil (4.12 g, 99%);

HRMS (ESI +ve): found 303.0515 [M+$Na^+$]; $C_{10}H_{16}NaO_7S$ requires 303.0512; $[\alpha]_D^{25}$ -35.1 (*c* 1.00, $CHCl_3$) [Lit.[78] $[\alpha]_D^{24}$ -24.7 (*c* 1.0, $CHCl_3$)]; $\nu_{max}$ (thin film): 1172 (s, $SO_2$), 1459 (s, $SO_2$), 1781 (s, C=O); $\delta_H$ ($CDCl_3$, 400 MHz): 1.44, 1.46 (2 x 3H, s, $C(CH_3)_2$), 1.67 (3H, s, 2-$CH_3$), 3.07 (3H, s, $SO_2CH_3$), 4.45 (2H, a-d, H5, H5', *J* 3.1), 4.53 (1H, s, H3), 4.71 (1H, a-t, H4, *J* 3.2); $\delta_C$ ($CDCl_3$, 100 MHz): 20.0 (2-$CH_3$), 26.7, 26.8 ($C(\underline{C}H_3)_2$), 37.6 ($SO_2CH_3$), 68.0 (C5), 79.7 (C4), 81.8 (C3), 82.3 (C2), 113.6 ($\underline{C}(CH_3)_2$), 175.3 (C1); LRMS (ESI +ve): 298 (20%, M+$NH_4^+$), 303 (25%, M+$Na^+$), 583 (100%, 2M+$Na^+$).

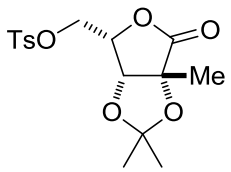
**2,3-*O*-Isopropylidene-2-*C*-methyl-L-lyxono-1,4-lactone 3.126**




A solution of potassium hydroxide (1.31 g, 23.3 mmol) in water (37 mL) was added to a solution of the mesylate **3.129** (2.18 g, 7.78 mmol) in 1,4-dioxane (44 mL) at RT. The reaction was stirred for 80 min, after which TLC analysis (2:3, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.67) and the formation of baseline material. 2 M Aqueous hydrochloric acid (~8 mL) was added and the reaction stirred vigorously for 1 h, after which TLC analysis (ethyl acetate) indicated the complete conversion of the baseline material to a major product ($R_f$ 0.71). The reaction was diluted with dichloromethane (150 mL) and the resultant biphasic mixture separated. The aqueous layer was exhaustively extracted (dichloromethane: 5 x 150 mL; ethyl acetate: 5 x 100 mL, 5 x 50 mL) until no detectable organic material remained. The combined organic fractions were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (1:1 to 0:1, cyclohexane/ethyl acetate) to afford the lactone **3.126** (1.24 g, 79%) as a clear oil which

crystallised on standing; HRMS (ESI +ve): found 225.0740 [M+$Na^+$]; $C_9H_{11}NaO_5$ requires 225.0733; m.p. 65-67 °C [Lit.[78] 64-66 °C]; $[\alpha]_D^{25}$ -86.3 (*c* 1.1, acetone) [Lit.[78] -74.1 (*c* 0.6, acetone)]; $\nu_{max}$ (thin film): 1777 (s, C=O), 3437 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.41, 1.44 (2 x 3H, s, $C(CH_3)_2$), 1.58 (3H, s, 2-$CH_3$), 3.96 (1H, dd, H5, $J_{5,4}$ 4.8, $J_{5,5'}$ 12.2), 4.03 (1H, dd, H5', $J_{5',4}$ 6.6, $J_{5',5}$ 12.2), 4.47 (1H, d, H3, $J_{3,4}$ 3.3), 4.52 (1H, ddd, H4, $J_{4,3}$ 3.3, $J_{4,5}$ 4.8, $J_{4,5'}$ 6.6); $\delta_C$ ($CDCl_3$, 100 MHz): 18.2 (2-$CH_3$), 26.6, 26.8 ($C(\underline{C}H_3)_2$), 60.7 (C5), 78.0 (C4), 80.8 (C3), 83.1 (C2), 113.5 ($\underline{C}(CH_3)_2$), 176.2 (C1); LRMS (ESI +ve): 225 (100%, M+$Na^+$).

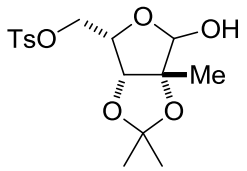
**2,3-*O*-Isopropylidene-2-*C*-methyl-5-*O*-*para*-toluenesulfonyl-L-lyxono-1,4-lactone 3.132**




*para*-Toluenesulfonyl chloride (2.8 g, 14.8 mmol) was added in one portion to a solution of the lactone **3.126** (1.2 g, 5.93 mmol) in pyridine (6 mL) at 0 °C. The reaction mixture was allowed to warm to RT and stirred for 14 h, after which TLC analysis (2:3, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.43) and the formation of a major product ($R_f$ 0.86). The reaction was diluted with ethyl acetate (100 mL) and washed with 2 M aqueous hydrochloric acid (3 x 20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (19:1 to 7:3, cyclohexane/ethyl acetate) to afford the tosylate **3.132** (1.91 g, 90%) as a clear, viscous gel; HRMS (ESI +ve): found 379.0816 [M+$Na^+$]; $C_{16}H_{20}NaO_7S$ requires 379.0822; $[\alpha]_D^{25}$ -41.6 (*c* 2.87, $CHCl_3$); $\nu_{max}$ (thin film): 1190 (s, $SO_2$), 1364 (s, $SO_2$), 1792 (s, C=O); $\delta_H$ ($CDCl_3$, 400 MHz): 1.33, 1.35 (2 x 3H, s, $C(CH_3)_2$), 1.54 (3H, s, 2-$CH_3$), 2.46 (3H, s, Ar$C\underline{H}_3$), 4.26 (1H, dd, H5, $J_{5,4}$ 7.3, $J_{5,5'}$ 11.1), 4.37 (1H, dd, H5', $J_{5',4}$ 5.1, $J_{5',5}$ 11.1), 4.42 (1H, d, H3, $J_{3,4}$ 3.3), 4.63

(1H, ddd, H4, $J_{4,3}$ 3.3, $J_{4,5'}$ 5.1, $J_{4,5}$ 7.3), 7.37 (2H, d, ArH, *J* 8.2), 7.82 (2H, d, ArH, *J* 8.2); $\delta_C$ ($CDCl_3$, 100 MHz): 18.0 (2-$CH_3$), 21.6 (Ar$\underline{C}H_3$), 26.6, 26.7 (C($\underline{C}H_3)_3$), 66.7 (C5), 74.9 (C4), 79.9 (C3), 82.7 (C2), 113.6 ($\underline{C}(CH_3)_2$), 128.1, 129.9 (Ar$\underline{C}$H), 132.1 (Ar$\underline{C}CH_3$), 145.4 (Ar$\underline{C}SO_2$), 175.3 (C1); LRMS (ESI +ve): 379 (100%, M+$Na^+$), 395 (48%, M+$K^+$).

**2,3-*O*-Isopropylidene-2-*C*-methyl-5-*O*-*para*-toluenesulfonyl-L-lyxofuranose 3.127**

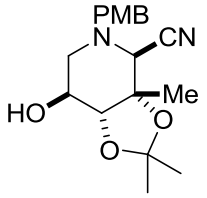



Diisobutylaluminium hydride (1.5 M in toluene, 4.3 mL, 6.33 mmol) was added dropwise over 10 min to a solution of the lactone **3.132** (1.88 g, 5.28 mmol) in dichloromethane (20 mL) at -78 $^oC$. The reaction was stirred for 2 h, after which TLC analysis (5:1, toluene/acetone) indicated the complete consumption of the starting material ($R_f$ 0.60) and the formation of a major product ($R_f$ 0.49). The reaction mixture was diluted with ethyl acetate (100 mL) and allowed to warm to RT. A 1:3 water/sodium potassium tartrate solution (100 mL) was added and the biphasic mixture was vigorously stirred for 2.5 h. The phases were separated and the aqueous layer extracted with ethyl acetate (6 x 30 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (19:1 to 7:3, cyclohexane/ethyl acetate) to afford the lactols **3.127** (1.73 g, 91%), in a 2:1 (A:B) anomeric mixture, as a white crystalline solid; HRMS (ESI +ve): found 381.0970 [M+$Na^+$]; $C_{16}H_{22}NaO_7S$ requires 381.0978; m.p. 112-114 $^oC$; $[\alpha]_D^{25}$ +4.9 (*c* 2.6, $CHCl_3$); $\nu_{max}$ (thin film): 1190 (s, $SO_2$), 1361 (s, $SO_2$), 3493 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.32, 1.35 (2 x 3H, s, $C(CH_3)_2{}^B$), 1.39, 1.40 (2 x 3H, s, $C(CH_3)_2{}^A$), 1.44 (3H, s, 2-$CH_3{}^A$), 1.47 (3H, s, 2-$CH_3{}^B$), 2.45 (6H, s, Ar$C\underline{H}_3{}^A$, Ar$C\underline{H}_3{}^B$), 3.83 (2H, a-td, H4$^A$, H3$^B$, *J* 3.3, *J* 6.1, *J* 6.1), 4.18 (1H,

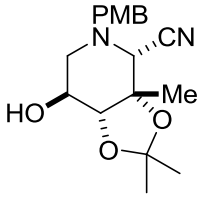
dd, $H5^A$, $J_{5,4}$ 6.3, $J_{5,5'}$ 10.4), 4.19 (1H, dd, $H5^B$, $J_{5,4}$ 7.6, $J_{5,5'}$ 10.4), 4.27-4.31 (3H, m, $H3^A$, $H5'^A$, $H5'^B$), 4.38 (1H, ddd, $H4^B$, *J* 3.3, *J* 4.0, $J_{4,5}$ 7.6), 4.64 (1H, br. s, $H1^A$), 5.20 (1H, s, $H1^B$), 7.35 (4H, d, ArH, *J* 8.1), 7.79-7.83 (4H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 21.4 ($Ar\underline{C}H_3^B$), 21.6 ($Ar\underline{C}H_3^A$), 26.6, 26.7 ($C(\underline{C}H_3)_2^A$), 27.2, 27.5 ($C(\underline{C}H_3)_2^B$), 67.0 ($C5^A$), 67.9 ($C5^B$), 72.6 ($C4^A$), 77.2 ($C4^B$), 84.3 ($C3^A$), 85.8 ($C3^B$), 86.5 ($C2^A$), 92.2 ($C2^B$), 101.1 ($C1^A$), 103.1 ($C1^B$), 113.2 ($\underline{C}(CH_3)_2^B$), 113.4 ($\underline{C}(CH_3)_2^A$), 128.1, 129.8 ($Ar\underline{C}H^A$, $Ar\underline{C}H^B$), 132.5 ($Ar\underline{C}CH_3^A$), 132.7 ($Ar\underline{C}CH_3^B$), 144.9 ($Ar\underline{C}SO_2^B$), 144.9 ($Ar\underline{C}SO_2^A$); LRMS (ESI +ve): 381 (100%, $M+Na^+$), 397 (50%, $M+K^+$).

**2,6-Dideoxy-2,6-imino-3,4-*O*-isopropylidene-2-*N*-(4-methoxybenzyl)-3-*C*-methyl-L-talononitrile 3.134 /**

**2,6-Dideoxy-2,6-imino-3,4-*O*-isopropylidene-2-*N*-(4-methoxybenzyl)-3-*C*-methyl-L-galactononitrile 3.135**




**3.134**



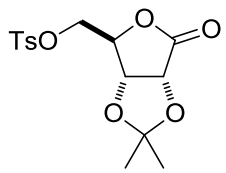

**3.136**

A solution of 4-methoxybenzylamine (0.18 mL, 1.40 mmol), potassium cyanide (91 mg, 1.40 mmol) and the tosylates **3.127** (200 mg, 0.59 mmol) in anhydrous methanol (6 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.0 mL, 2.91 mmol). The reaction mixture was stirred at 50 °C for 2 d, after which TLC analysis (5:1, toluene/acetone) indicated the complete consumption of the starting materials ($R_f$ 0.49) and the formation of a major product ($R_f$ 0.46). The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (50 mL) and washed with 2 M aqueous hydrochloric acid (10 mL). The aqueous phase

was extracted with ethyl acetate (3 x 20 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (99:1 to 39:1, dichloromethane/diethyl ether) to afford an inseparable 3.8:1 (A:B) mixture of the α-iminonitriles **3.135**$^A$/**3.134**$^B$ (142 mg, 73%) as a yellow oil; HRMS (ESI +ve): found 355.1625 [M+$Na^+$]; $C_{18}H_{24}N_2NaO_4$ requires 355.1628; $\nu_{max}$ (thin film): 2239 (w, CN), 3389 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.39 (6H, s, $C(CH_3)^A$, $C(CH_3)^B$), 1.42 (3H, s, $C(CH_3)^A$), 1.47 (3H, s, $C(CH_3)^B$), 1.69 (3H, s, 3-$CH_3^B$), 1.69 (3H, s, 3-$CH_3^A$), 2.41 (1H, br. d, OH5$^A$, $J_{OH,5}$ 6.8), 2.45 (1H, dd, H6$^B$, $J_{6,5}$ 1.8, $J_{6,6'}$ 12.4), 2.79 (1H, br. d, H6$^A$, $J_{6,6'}$ 13.1), 2.82 (1H, dd, H6'$^B$, $J_{6',5}$ 2.5, $J_{6',6}$ 12.4), 3.07 (1H, dd, H6'$^A$, $J_{6',5}$ 1.5, $J_{6',6}$ 13.1), 3.38 (1H, s, H2$^B$), 3.49 (1H, d, NC$\underline{H}_2$Ar$^B$, $J_{gem}$ 13.1), 3.59 (1H, d, NC$\underline{H}_2$Ar$^A$, $J_{gem}$ 12.8), 3.63 (1H, s, H2$^A$), 3.72 (1H, d, NC$\underline{H}_2$Ar$^A$, $J_{gem}$ 12.8), 3.82 (6H, s, $OCH_3^A$, $OCH_3^B$), 3.93-3.97 (1H, m, H5$^B$), 3.98-4.00 (2H, m, H4$^A$, H4$^B$), 4.06 (1H, br. d, H5$^A$, $J_{5,OH}$ 6.8), 4.20 (1H, d, NC$\underline{H}_2$Ar$^B$, $J_{gem}$ 13.1), 6.89 (4H, d, ArH, *J* 8.6), 7.23 (4H, d, ArH, *J* 8.6); $\delta_C$ ($CDCl_3$, 100 MHz): 21.7 (3-$CH_3^B$), 25.6, 26.1 ($C(\underline{C}H_3)_2^A$), 26.3 (3-$CH_3^A$), 26.6, 28.1 ($C(\underline{C}H_3)_2^B$), 50.4 (C6$^A$), 53.2 (C6$^B$), 55.3 ($OCH_3^A$, $OCH_3^B$), 58.9 (N$\underline{C}H_2Ar^B$), 59.2 (N$\underline{C}H_2Ar^A$), 61.8 (C2$^A$), 62.2 (C2$^B$), 64.7 (C5$^B$), 65.2 (C5$^A$), 76.7 (C3$^A$), 78.2 (C3$^B$), 80.0 (C4$^B$), 80.4 (C4$^A$), 109.4 ($\underline{C}(CH_3)_2^B$), 110.0 ($\underline{C}(CH_3)_2^A$), 114.1 (Ar$\underline{C}H^B$), 114.2 (Ar$\underline{C}H^A$), 115.9 (CN$^A$, CN$^B$), 127.4 (Ar$\underline{C}C^B$), 127.9 (Ar$\underline{C}C^A$), 130.2 (Ar$\underline{C}H^A$), 130.5 (Ar$\underline{C}H^B$), 159.3 (Ar$\underline{C}OCH_3^B$), 159.4 (Ar$\underline{C}OCH_3^A$); LRMS (ESI +ve): 333 (55%, M+$H^+$), 355 (100%, M+$Na^+$), 371 (25%, M+$K^+$).

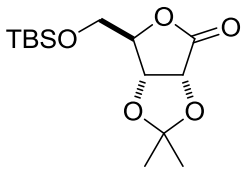
3.4.5 1-*C*-Methyl- D-ribose (1-deoxy-D-psicose) route

**2,3-*O*-Isopropylidene-5-*O*-*para*-toluenesulfonyl-D-ribono-1,4-lactone 3.140**



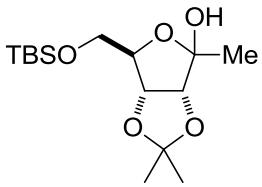

A solution of *para*-toluenesulfonyl chloride (4.6 g, 23.9 mmol) in pyridine (6 mL) was added dropwise to a solution of the lactone **3.35** (1.5 g, 7.97 mmol) in pyridine (8 mL) at 0 $^{o}$C. The reaction was allowed to warm to RT and stirred for 5 h, after which TLC analysis (2:3, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.56) and the formation of a major product ($R_f$ 0.80). The reaction was diluted with ethyl acetate (150 mL) and washed with 2 M aqueous hydrochloric acid (3 x 30 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (19:1 to 1:1, cyclohexane/ethyl acetate) to afford the tosylate **3.140** (2.17 g, 79%) as a white crystalline solid; HRMS (ESI +ve): found 365.0653 [M+Na$^+$]; $C_{15}H_{18}NaO_7S$ requires 365.0665; m.p. 112-116 $^{o}$C [Lit.[65] m.p. 116-118 $^{o}$C]; $[\alpha]_D^{20}$ -18.2 (*c* 1.20, acetone) [Lit.[65] $[\alpha]_D^{24}$ -15.5 (*c* 2.4, acetone)]; $\nu_{max}$ (thin film): 1180 (s, $SO_2$), 1369 (s, $SO_2$), 1793 (s, C=O); $\delta_H$ ($CD_3CN$, 400 MHz): 1.32, 1.38 (2 x 3H, s, $C(CH_3)_2$), 2.45 (3H, s, Ar$CH_3$), 4.25 (1H, dd, H5, $J_{5,4}$ 3.6, $J_{5,5'}$ 12.4), 4.38 (1H, dd, $J_{5',4}$ 3.0, $J_{5',5}$ 12.4), 4.69 (1H, a-t, H4, $J_{4,5} = J_{4,5'}$ 3.3), 4.81 (1H, d, H3, $J_{3,2}$ 5.8), 4.89 (1H, d, H2, $J_{2,3}$ 5.8); $\delta_C$ ($CD_3CN$, 100 MHz): 21.8 (Ar$CH_3$), 25.5, 26.9 ($C(CH_3)_2$), 70.1 (C5), 75.9 (C2), 78.3 (C4), 80.3 (C3), 114.3 ($C(CH_3)_2$), 128.9, 131.3 (ArCH), 132.9 (Ar$C$CH$_3$), 147.1 (Ar$C$SO$_2$), 174.5 (C1); LRMS (ESI +ve): 360 (35%, M+$NH_4^+$), 365 (100%, M+$Na^+$), 397 (47%, M+MeOH+$Na^+$).

**5-*O*-*tert*-Butyldimethylsilyl-2,3-*O*-isopropylidene-D-ribono-1,4-lactone 3.141**



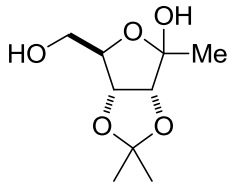

*tert*-Butyldimethylsilyl chloride (1.8 g, 12.0 mmol) was added to a solution of the lactone **3.35** (1.5 g, 7.97 mmol) in pyridine (15 mL) at RT. The reaction was stirred for 15 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.24) and the formation of a major product ($R_f$ 0.83). The reaction mixture was diluted with ethyl acetate (100 mL) and washed with 2 M aqueous hydrochloric acid (3 x 25 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (19:1 to 9:1, cyclohexane/ethyl acetate) to afford silyl ether **3.141** (2.2 g, 91%) as a white crystalline solid; HRMS (ESI +ve): found 325.1431 [$M+Na^+$]; $C_{14}H_{26}NaO_5Si$ requires 325.1442; m.p. 68-70 $^oC$ [Lit.[93] m.p. 70-71 $^oC$]; $[\alpha]_D^{20}$ -51.7 (*c* 1.1, $CHCl_3$) [Lit.[93] $[\alpha]_D^{23}$ -49.0 (*c* 1.16, $CHCl_3$)]; $\nu_{max}$ (thin film): 1775 (s, C=O); $\delta_H$ ($CDCl_3$, 400 MHz): 0.06, 0.07 (2 x 3H, s, $Si(CH_3)_2$), 0.88 (9H, s, $SiC(CH_3)_3$), 1.39, 1.48 (2 x 3H, s, $C(CH_3)_2$), 3.80 (1H, br. d, H5, $J_{5,5'}$ 11.4), 3.89 (1H, dd, H5', $J_{5',4}$ 1.5, $J_{5',5}$ 11.4), 4.60 (1H, br. s, H4), 4.71 (1H, d, H3, $J_{3,2}$ 5.8), 4.73 (1H, d, H2, $J_{2,3}$ 5.8); $\delta_C$ ($CDCl_3$, 100 MHz): -5.8, -5.7 ($Si(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 25.6, 26.8 ($C(CH_3)_2$), 25.7 ($SiC(CH_3)_3$), 62.9 (C5), 75.8 (C2), 78.4 (C3), 82.3 (C4), 113.0 ($C(CH_3)_2$), 174. 2 (C1); LRMS (ESI +ve): 320 (78%, $M+NH_4^+$), 325 (100%, $M+Na^+$).

**6-*O*-*tert*-Butyldimethylsilyl-1-deoxy-3,4-*O*-isopropylidene-D-psicofuranose 3.142**



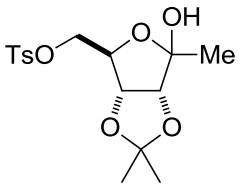

Methyllithium (1.6 M in $Et_2O$, 4.75 mL, 7.56 mmol) was added dropwise over 15 min to a solution of the lactone **3.141** (2.2 g, 6.87 mmol) in THF (20 mL) at -78 $^oC$. The reaction was stirred for 2 h, after which TLC analysis (5:1, cyclohexane/ethyl acetate) indicated the consumption of the starting material ($R_f$ 0.71) and the formation of a major product ($R_f$ 0.62). Water (20 mL) was added dropwise to the reaction, the biphasic mixture allowed to warm to RT and stirred for a further 15 min. Ethyl acetate was added (50 mL), the phases separated and the aqueous layer extracted with ethyl acetate (3 x 50 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (39:1 to 4:1, cyclohexane/ethyl acetate) to afford the lactol **3.142** (2.04 g, 88%) as a white crystalline solid, and as a single anomer; HRMS (ESI +ve): found 341.1750 [M+$Na^+$]; $C_{15}H_{30}NaO_5Si$ requires 341.1755; m.p. 42-44 $^oC$; $[\alpha]_D^{20}$ -21.0 (*c* 1.15, $CHCl_3$) [Lit.[93] $[\alpha]_D^{21}$ -13.1 (*c* 0.99, $CHCl_3$)]; $\nu_{max}$ (thin film): 3445 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 0.14, 0.15 (2 x 3H, s, $Si(CH_3)_2$), 0.93, (9H, s, $SiC(CH_3)_3$), 1.35 (3H, s, H1), 1.50, 1.52 (2 x 3H, s, $C(CH_3)_2$), 3.76 (1H, dd, H6, $J_{6,5}$ 2.0, $J_{6,6'}$ 11.1), 3.80 (1H, dd, H6', $J_{6',5}$ 1.8, $J_{6',6}$ 11.1), 4.26 (1H, br. s, H5), 4.44 (1H, d, H3, $J_{3,4}$ 5.8), 4.80 (1H, br. d, H4, $J_{4,3}$ 5.8), 5.16 (1H, s, OH2); $\delta_C$ ($CDCl_3$, 100 MHz): -5.8, -5.7 ($Si(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 21.2 (C1), 25.1, 26.6 ($C(CH_3)_2$), 25.7 ($SiC(CH_3)_3$), 64.9 (C6), 82.0 (C4), 85.8 (C5), 88.0 (C3), 106.5 (C2), 112.4 ($C(CH_3)_2$); LRMS (ESI +ve): 341 (100%, M+$Na^+$); (ESI –ve): 317 (100%, [M-H]$^-$).

**1-Deoxy-3,4-*O*-isopropylidene-D-psicofuranose 3.143**




*tetra*-*n*-Butylammonium fluoride (1 M in THF, 8.2 mL, 8.2 mmol) was added dropwise to a solution of the silyl ether **3.142** (2 g, 6.28 mmol) in THF (20 mL) at RT. The reaction was stirred for 4 h, after which TLC analysis (1:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.93) and the formation of a major product ($R_f$ 0.30). The reaction was concentrated *in vacuo* and the crude residue purified by flash chromatography (3:1:0 to 0:9:1, cyclohexane/ethyl acetate/methanol) to afford the lactol **3.143** (1.08 g, 84%) as a clear oil, which crystallised on standing to form a white solid; HRMS (ESI +ve): found 227.0890 [M+$Na^+$]; $C_9H_{16}NaO_5$ requires 227.0890; m.p. 73-75 °C [Lit.[93] m.p. 72-74 °C]; $[\alpha]_D^{20}$ -11.1 (*c* 0.95, $CHCl_3$) [Lit.[93] $[\alpha]_D^{21}$ -15.0 (*c* 1.11, $CHCl_3$)]; $\nu_{max}$ (thin film): 3388 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.33 (3H, s, H1), 1.50, 1.54 (2 x 3H, s, $C(CH_3)_2$), 3.68-3.80 (2H, m, H6, H6'), 4.29 (1H, br. s, H5), 4.47 (1H, d, H3, $J_{3,4}$ 5.9), 4.89 (1H, d, H4, $J_{4,3}$ 5.9); $\delta_C$ ($CDCl_3$, 100 MHz): 22.3 (C1), 24.9, 26.5 ($C(\underline{C}H_3)_2$), 63.7 (C6), 82.0 (C4), 86.2 (C5), 87.0 (C3), 106.7 (C2), 112.4 ($\underline{C}(CH_3)_2$); LRMS (ESI +ve): 227 (100%, M+$Na^+$); (ESI –ve): 203 (100%, $[M-H]^-$).

**1-Deoxy-3,4-*O*-isopropylidene-6-*O*-*para*-toluenesulfonyl-D-psicofuranose 3.138**

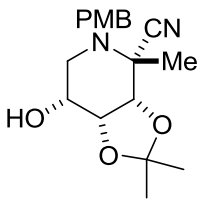



A solution of *para*-toluenesulfonyl chloride (583 mg, 3.06 mmol) in pyridine (1 mL) was added dropwise to a solution of the lactol **3.143** (500 mg, 2.45 mmol) in pyridine (4 mL) at -30 °C. The

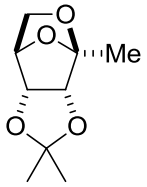
reaction was allowed to warm to 0 °C after 1 h, and after a further 1 h was allowed to warm to RT. After 6 h at RT, TLC analysis (1:1, cyclohexane/ethyl acetate) indicated the partial consumption of the starting material ($R_f$ 0.30) and the formation of a major product ($R_f$ 0.66). The reaction was cooled to 0 °C and an additional portion of *para*-toluenesulfonyl chloride was added (230 mg, 1.21 mmol). After 15 min the reaction was allowed to warm to RT and stirred for 17 h. After which, TLC analysis indicated the complete consumption of the starting material and the presence of the major product. The reaction was diluted with ethyl acetate (100 mL) and washed with 2 M aqueous hydrochloric acid (3 x 20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1 to 7:3, cyclohexane/ethyl acetate) to afford the tosylate **3.138** (812 mg, 92%) as a pale yellow oil, which crystallised on standing to give a white crystalline solid, in a 2.6:1 (A:B) ratio of anomers; HRMS (ESI +ve): found 381.0972 [M+$Na^+$]; $C_{16}H_{22}NaO_7S$ requires 381.0978; m.p. 80-82 °C; $[\alpha]_D^{20}$ -63.7 (*c* 4.08, $CHCl_3$); $\nu_{max}$ (thin film): 1177 (s, $SO_2$), 1365 (s, $SO_2$), 3500 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.31, 1.46 (2 x 3H, s, $C(CH_3)_2^A$), 1.38 (3H, s, $H1^B$), 1.41, 1.58 (2 x 3H, s, $C(CH_3)_2^B$), 1.49 (3H, s, $H1^A$), 2.46 (6H, s, $ArC\underline{H}_3^A$, $ArC\underline{H}_3^B$), 4.04-4.20 (5H, m, $H5^B$, $H6^A$, $H6^B$, $H6'^A$, $H6'^B$), 4.25 (1H, br. a-t, $H5^A$, $J_{5,6} = J_{5,6'}$ 6.6), 4.42 (1H, d, $H3^B$, $J_{3,4}$ 6.7), 4.43 (1H, d, $H3^A$, $J_{3,4}$ 5.7), 4.65 (1H, br. d, $H4^A$, $J_{4,3}$ 5.7), 4.69 (1H, dd, $H4^B$, $J_{4,5}$ 4.0, $J_{4,3}$ 6.7), 7.32-7.37 (4H, m, $ArH^A$, $ArH^B$), 7.76-7.82 (4H, m, $ArH^A$, $ArH^B$); $\delta_C$ ($CDCl_3$, 100 MHz): 21.6 ($Ar\underline{C}H_3^A$, $Ar\underline{C}H_3^B$), 22.8 ($C1^A$), 24.9 ($C1^B$), 25.1, 26.5 ($C(\underline{C}H_3)_2^A$), 25.8, 26.4 ($C(\underline{C}H_3)_2^B$), 68.9 ($C6^B$), 70.2 ($C6^A$), 78.8 ($C5^B$), 80.9 ($C4^B$), 82.3 ($C4^A$), 82.9 ($C5^A$), 83.7 ($C3^B$), 85.6 ($C3^A$), 102.2 ($C2^B$), 107.5 ($C2^A$), 113.0 ($\underline{C}(CH_3)_2^A$), 116.0 ($\underline{C}(CH_3)_2^B$), 128.0, 129.9 ($Ar\underline{C}H^A$, $Ar\underline{C}H^B$), 132.4 ($Ar\underline{C}CH_3^B$), 132.8 ($Ar\underline{C}CH_3^A$), 145.1 ($Ar\underline{C}SO_2^A$. $Ar\underline{C}SO_2^B$); LRMS (ESI +ve): 381 (100%, M+$Na^+$).

**2,6-Dideoxy-2,6-imino-3,4-*O*-isopropylidene-2-*N*-(4-methoxybenzyl)-2-*C*-methyl-D-altrononitrile 3.144 /**

**2,6-Anhydro-1-deoxy-3,4-*O*-isopropylidene-D-psicofuranose 3.145**




**3.144**




**3.145**

A solution of 4-methoxybenzylamine (0.18 mL, 1.40 mmol), potassium cyanide (91 mg, 1.40 mmol) and the tosylates **3.138** (200 mg, 0.56 mmol) in anhydrous methanol (4 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.0 mL, 2.91 mmol). The reaction mixture was stirred at RT for 1 d, and at 40 $^{o}$C for 2 d, after which TLC analysis (5:1, toluene/acetone) indicated the complete consumption of the starting materials ($R_f$ 0.56) and the formation of a major product ($R_f$ 0.68) and a minor product ($R_f$ 0.47). The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (50 mL) and washed with 2 M aqueous hydrochloric acid (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 20 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (99:1 to 9:1, toluene/acetone) to afford the α-iminonitrile **3.144** ($R_f$ 0.47, 26 mg, 14%) as a yellow oil, and the anhydro-compound **3.145** ($R_f$ 0.68, 54 mg, 51%) as a volatile, white crystalline solid.

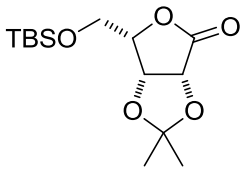
Data for the α-iminonitrile **3.144**: HRMS (ESI +ve): found 355.1619 [M+$Na^+$]; $C_{18}H_{24}N_2NaO_4$ requires 355.1628; $[\alpha]_D^{20}$ -12.9 (*c* 0.89, $CHCl_3$); $\nu_{max}$ (thin film): 2221 (w, CN), 3460 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.42, 1.79 (2 x 3H, s, $C(CH_3)_2$), 1.69 (3H, s, 2-$CH_3$), 2.50 (1H, a-t, H6, $J_{6,5} = J_{6,6'}$ 11.7), 2.80 (1H, dd, H6', $J_{6',5}$ 6.0, $J_{6',6}$ 11.9), 3.18 (1H, d, NC$\underline{H}_2$Ar, $J_{gem}$ 13.2), 3.80-3.86 (1H, m, H5), 3.81 (3H, s, $OCH_3$), 3.89 (1H, d, H3, $J_{3,4}$ 5.7), 4.00 (1H, d, NC$\underline{H}_2$Ar,

$J_{gem}$ 13.2), 4.51 (1H, a-t, H4, $J_{4,3} = J_{4,5}$ 5.2), 6.87 (2H, d, ArH, *J* 8.5), 7.19 (2H, d, ArH, *J* 8.5); $\delta_C$ ($CDCl_3$, 100 MHz): 25.3, 25.9 ($C(\underline{C}H_3)_2$), 25.6 (2-$CH_3$), 49.1 (C6), 53.2 ($N\underline{C}H_2Ar$), 55.3 ($OCH_3$), 62.7 (C2), 65.5 (C5), 74.0 (C4), 80.2 (C3), 111.3 ($\underline{C}(CH_3)_2$), 114.0 ($Ar\underline{C}H$), 119.1 (CN), 127.4 ($Ar\underline{C}C$), 129.7 ($Ar\underline{C}H$), 159.0 ($Ar\underline{C}OCH_3$); LRMS (ESI +ve): 355 (100%, $M+Na^+$), 371 (12%, $M+K^+$).

Selected data for **3.145**: m.p. 102-104 °C [Lit.[85] m.p. 105-106 °C (hexane)]; $[\alpha]_D^{20}$ -65.4 (*c* 1.13, $CHCl_3$) [Lit.[85] $[\alpha]_D$ -78.1 (*c* 1.1, $CHCl_3$)]; $\delta_H$ ($CDCl_3$, 400 MHz): 1.30, 1.46 (2 x 3H, s, $C(CH_3)_2$), 1.60 (3H, s, H1), 3.36 (1H, d, H6, $J_{6,6'}$ 7.1), 3.54 (1H, dd, H6', $J_{6',5}$ 4.0, $J_{6',6}$ 7.1), 4.11 (1H, d, H3, $J_{3,4}$ 5.5), 4.38 (1H, d, H4, $J_{4,3}$ 5.5), 4.60 (1H, d, H5, $J_{5,6'}$ 4.0); $\delta_C$ ($CDCl_3$, 100 MHz): 13.9 (C1), 25.4, 26.0 ($C(\underline{C}H_3)_2$), 64.4 (C6), 78.0 (C5), 80.6 (C4), 82.6 (C3), 107.2 (C2), 112.0 ($\underline{C}(CH_3)_2$).

3.4.6 1-*C*-Methyl-L-lyxose (1-deoxy-L-tagatose) route

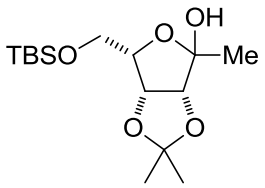
**5-*O*-*tert*-Butyldimethylsilyl-2,3-*O*-isopropylidene-L-lyxono-1,4-lactone 3.150**




*tert*-Butyldimethylsilyl chloride (2.4 g, 15.9 mmol) was added to a solution of the lactone **1.63L** (2.0 g, 10.6 mmol) in pyridine (20 mL) at RT. The reaction was stirred for 16 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.11) and the formation of a major product ($R_f$ 0.71). The reaction mixture was diluted with ethyl acetate (150 mL) and washed with 2 M aqueous hydrochloric acid (3 x 40 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was

purified by flash chromatography (49:1 to 9:1, cyclohexane/ethyl acetate) to afford the silyl ether **3.150** (3.13 g, 97%) as a white crystalline solid; HRMS (ESI +ve): found 325.1433 [M+$Na^+$]; $C_{14}H_{26}NaO_5Si$ requires 325.1442; m.p. 85-87 $^oC$ [Lit.[94] m.p. 90-91 $^oC$[*]]; $[\alpha]_D^{20}$ -39.6 (*c* 1.37, $CHCl_3$) [Lit.[94] $[\alpha]_D^{20}$ +54.9 (*c* 1.03, $CHCl_3$)[*]]; $\nu_{max}$ (thin film): 1773 (s, C=O); $\delta_H$ ($CDCl_3$, 400 MHz): 0.10 (6H, s, $Si(CH_3)_2$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.39, 1.47 (2 x 3H, s, $C(CH_3)_2$), 3.94 (1H, dd, H5, $J_{5,4}$ 7.3, $J_{5,5'}$ 10.6), 3.99 (1H, dd, H5', $J_{5',4}$ 6.3, $J_{5',5}$ 10.6), 4.53 (1H, a-t, H4, $J_{4,5} = J_{4,5'}$ 6.8), 4.81 (2H, br. s, H2, H3); $\delta_C$ ($CDCl_3$, 100 MHz): -5.6, -5.4 ($Si(CH_3)_2$), 18.3 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 25.9, 26.8 ($C(CH_3)_2$), 60.8 (C5), 75.7, 76.0 (C2, C3), 79.4 (C4), 114.0 ($C(CH_3)_2$), 173.8 (C1); LRMS (ESI +ve): 325 (10%, M+$Na^+$), 357 (100%, M+MeOH+$Na^+$).

**6-*O*-*tert*-Butyldimethylsilyl-1-deoxy-3,4-*O*-isopropylidene-L-tagatofuranose 3.151**

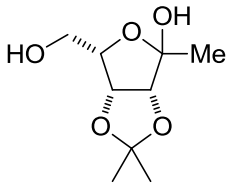



Methyllithium (1.6 M in $Et_2O$, 7.8 mL, 12.4 mmol) was added dropwise to a solution of lactone **3.150** (3.13 g, 10.4 mmol) in THF (40 mL) at -78 $^oC$. The reaction mixture was stirred for 4 h, after which TLC analysis (5:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.40) and the formation of a major product ($R_f$ 0.38). Water (30 mL) and ethyl acetate (200 mL) were added slowly and the reaction mixture stirred vigorously at RT. The phases were separated and the aqueous layer extracted with ethyl acetate (3 x 100 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (49:1 to 9:1, cyclohexane/ethyl acetate) to afford

[*] Literature data for the enantiomeric product.

the lactols **3.151** (2.73 g, 83%) as a white crystalline solid, in a 4.1:1 (A:B) anomeric mixture; HRMS (ESI +ve): found 341.1755 [M+$Na^+$]; $C_{15}H_{30}NaO_5Si$ requires 341.1755; m.p. 66-72 $^oC$; $[\alpha]_D^{20}$ -8.1 (*c* 1.32, $CHCl_3$); $\nu_{max}$ (thin film): 3430 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 0.08 (6H, s, $Si(CH_3)_2^B$), 0.09 (6H, s, $Si(CH_3)_2^A$), 0.90 (9H, s, $SiC(CH_3)_3^B$), 0.91 (9H, s, $SiC(CH_3)_3^A$), 1.31, 1.45 (2 x 3H, s, $C(CH_3)_2^A$), 1.36, 1.53 (2 x 3H, s, $C(CH_3)_2^B$), 1.39 (3H, s, $H1^B$), 1.52 (3H, s, $H1^A$), 3.67 (1H, ddd, $H5^B$, $J_{5,4}$ 3.8, $J_{5,6}$ 5.3, $J_{5,6'}$ 7.1), 3.80 (2H, a-dd, $H6^A$, $H6^B$, *J* 6.6, *J* 10.6), 3.90 (1H, dd, $H6'^B$, $J_{6',5}$ 7.1, $J_{6',6}$ 10.6), 3.93 (1H, dd, $H6'^A$, $J_{6',5}$ 5.6, $J_{6',6}$ 10.6), 4.17 (1H, a-td, $H5^A$, $J_{5,4}$ 4.0, $J_{5,6} = J_{5,6'}$ 6.8), 4.26 (1H, d, $H3^B$, $J_{3,4}$ 6.1), 4.43 (1H, d, $H3^A$, $J_{3,4}$ 5.8), 4.73 (1H, dd, $H4^B$, $J_{4,5}$ 3.5, $J_{4,3}$ 6.1), 4.78 (1H, dd, $H4^A$, $J_{4,5}$ 3.8, $J_{4,3}$ 5.8); $\delta_C$ ($CDCl_3$, 100 MHz): -5.5 ($SiCH_3^B$), -5.3 ($SiCH_3^A$, $SiCH_3^B$), -5.2 ($SiCH_3^A$), 18.4 ($Si\underline{C}(CH_3)_3^B$), 18.5 ($Si\underline{C}(CH_3)_3^A$), 22.1 ($C1^B$), 25.9 ($C1^A$), 25.7, 26.1 ($C(\underline{C}H_3)_2^B$), 25.9, 26.0 ($C(\underline{C}H_3)_2^A$), 26.0 ($SiC(\underline{C}H_3)_3^A$), 26.1 ($SiC(\underline{C}H_3)_3^B$), 60.8 ($C6^B$), 61.4 ($C6^A$), 76.8 ($C5^B$), 79.7 ($C4^B$), 79.8 ($C5^A$), 80.6 ($C4^A$), 82.2 ($C3^B$), 85.4 ($C3^A$), 102.2 ($C2^B$), 105.1 ($C2^A$), 112.4 ($\underline{C}(CH_3)_2^A$), 112.7 ($\underline{C}(CH_3)_2^B$); LRMS (ESI +ve): 341 (100%, M+$Na^+$); (ESI –ve): 317 (100%, $[M-H]^-$).

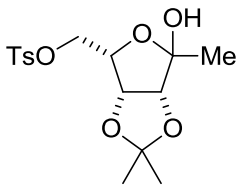
**1-Deoxy-3,4-*O*-isopropylidene-L-tagatofuranose 3.147**




*tetra-n*-Butylammonium fluoride (1 M in THF, 11.0 mL, 11.0 mmol) was added dropwise to a solution of the silyl ethers **3.151** (2.68 g, 8.41 mmol) at RT. The reaction was stirred for 18 h, after which TLC analysis (5:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting materials ($R_f$ 0.38) and the formation of a major product (baseline). The reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash chromatography

(3:1:0 to 0:9:1, cyclohexane/ethyl acetate/methanol) to afford the lactol **3.147** (1.60 g, 93%) as a white crystalline solid, and as a single anomer; HRMS (ESI +ve): found 227.0898 [M+$Na^+$]; $C_9H_{16}NaO_5$ requires 227.0890; m.p. 130-131 $^oC$; $[\alpha]_D^{20}$ -19.0 (*c* 1.55, $CHCl_3$); $\nu_{max}$ (thin film): 3359 (br. s, OH); $\delta_H$ ($CD_3OD$, 400 MHz): 1.30, 1.41 (2 x 3H, s, $C(CH_3)_2$), 1.42 (3H, s, H1), 3.68 (1H, dd, H6, $J_{6,5}$ 6.8, $J_{6,6'}$ 11.4), 3.80 (1H, dd, H6', $J_{6',5}$ 5.1, $J_{6',6}$ 11.4), 4.12 (1H, ddd, H5, $J_{5,4}$ 3.9, $J_{5,6'}$ 5.1, $J_{5,6}$ 6.8), 4.36 (1H, d, H3, $J_{3,4}$ 5.8), 4.79 (1H, dd, H4, $J_{4,5}$ 3.9, $J_{4,3}$ 5.8); $\delta_C$ ($CD_3OD$, 100 MHz): 22.3 (C1), 25.1, 26.6 ($C(\underline{C}H_3)_2$), 61.4 (C6), 80.6 (C5), 82.2 (C4), 87.4 (C3), 105.9 (C2), 113.7 ($\underline{C}(CH_3)_2$); LRMS (ESI +ve): 227 (100%, M+$Na^+$); (ESI –ve): 203 (100%, $[M-H]^-$).

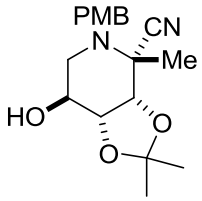
**1-Deoxy-3,4-*O*-isopropylidene-6-*O*-*para*-toluenesulfonyl-L-tagatofuranose 3.148**




A solution of *para*-toluenesulfonyl chloride (1.5 g, 7.84 mmol) in pyridine (2 mL) was added dropwise to a solution of the lactol **3.147** (800 mg, 3.92 mmol) in pyridine (8 mL) at 0 $^oC$. After 30 min the reaction was allowed to warm to RT and stirred for a further 16 h, after which TLC analysis (5:1, toluene/acetone) indicated the complete consumption of the starting material ($R_f$ 0.09) and the formation of a major product ($R_f$ 0.56). The reaction was diluted with ethyl acetate (200 mL) and washed with 2 M aqueous hydrochloric acid (3 x 30 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (19:1 to 7:3, cyclohexane/ethyl acetate) to afford the tosylate **3.148** (1.22 g, 87%) as a white crystalline solid, and as a single anomer; HRMS (ESI +ve): found 381.0975 [M+$Na^+$]; $C_{16}H_{22}NaO_7S$ requires 381.0978; m.p. 90-92 $^oC$; $[\alpha]_D^{20}$ -4.6 (*c* 2.05, $CHCl_3$); $\nu_{max}$ (thin film): 1177 (s, $SO_2$), 1364 (s, $SO_2$), 3489 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.26, 1.35 (2 x 3H,

s, $C(CH_3)_2$), 1.47 (3H, s, H1), 2.45 (3H, s, $ArC\underline{H}_3$), 4.15 (1H, dd, H6, $J_{6,5}$ 8.3, $J_{6,6'}$ 11.4), 4.28 (1H, dt, H5, $J_{5,4} = J_{5,6'}$ 3.8, $J_{5,6}$ 8.3), 4.29 (1H, dd, H6', $J_{6',5}$ 3.8, $J_{6',6}$ 11.4), 4.41 (1H, d, H3, $J_{3,4}$ 5.8), 4.75 (1H, dd, H4, $J_{4,5}$ 3.8, $J_{4,3}$ 5.8), 7.34 (2H, d, ArH), 7.81 (2H, d, ArH); $\delta_C$ ($CDCl_3$, 100 MHz): 21.6 ($Ar\underline{C}H_3$), 22.2 (C1), 24.7, 25.9 ($C(\underline{C}H_3)_2$), 68.2 (C6), 73.7 (C5), 80.3 (C4), 85.2 (C3), 105.5 (C2), 112.9 ($\underline{C}(CH_3)_2$), 128.1 ($Ar\underline{C}H$), 129.7 ($Ar\underline{C}H$), 132.7 ($Ar\underline{C}CH_3$), 144.8 ($Ar\underline{C}SO_2$); LRMS (ESI +ve): 381 (100%, $M+Na^+$).

**2,6-Dideoxy-2,6-imino-3,4-*O*-isopropylidene-2-*N*-(4-methoxybenzyl)-2-*C*-methyl-L-galactononitrile 3.152**

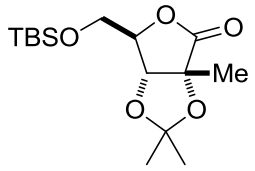



A solution of 4-methoxybenzylamine (0.18 mL, 1.40 mmol), potassium cyanide (91 mg, 1.40 mmol) and the tosylate **3.148** (201 mg, 0.56 mmol) in anhydrous methanol (4 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.0 mL, 2.91 mmol). The reaction mixture was stirred at 65 $^oC$ for 2 d, after which the reaction was stopped due to visible decomposition. TLC analysis (9:1, dichloromethane/diethyl ether) indicated the partial consumption of the starting material ($R_f$ 0.57) and the formation of a major product ($R_f$ 0.45). The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (50 mL) and washed with 2 M aqueous hydrochloric acid (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 20 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (99:1 to 24:1, dichloromethane/diethyl ether) to afford returned starting material **3.148** (69 mg, 34%) and the α-iminonitrile **3.152** (25 mg, 13%, 20% brsm) as a yellow oil; HRMS (ESI +ve): found 355.1622

[M+$Na^+$]; $C_{18}H_{24}N_2NaO_4$ requires 355.1628; $[\alpha]_D^{20}$ +34.1 (*c* 1.13, $CHCl_3$); $\nu_{max}$ (thin film): 2230 (w, CN), 3478 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.39, 1.75 (2 x 3H, s, $C(CH_3)_2$), 1.74 (3H, s, 2-$CH_3$), 2.26 (1H, br. d, OH5, $J_{OH,5}$ 7.3), 2.75 (1H, dd, H6, $J_{6,5}$ 2.4, $J_{6,6'}$ 13.5), 2.90 (1H, dd, H6', $J_{6',5}$ 1.8, $J_{6',6}$ 13.5), 3.19 (1H, d, NC$\underline{H}_2$Ar, $J_{gem}$ 12.6), 3.81 (3H, s, $OCH_3$), 3.93 (1H, br. s, H5), 3.97 (1H, d, H3, $J_{3,4}$ 5.6), 4.06 (1H, d, NC$\underline{H}_2$Ar, $J_{gem}$ 12.6), 4.27 (1H, dd, H4, $J_{4,5}$ 1.3, $J_{4,3}$ 5.6), 6.89 (2H, d, ArH, *J* 8.6), 7.20 (2H, d, ArH, *J* 8.6); $\delta_C$ ($CDCl_3$, 100 MHz): 25.4 (2-$CH_3$, C($\underline{C}H)_3$), 25.9 (C($\underline{C}H_3$)), 49.3 (C6), 53.1 (N$\underline{C}H_2$Ar), 55.3 ($OCH_3$), 63.2 (C2), 64.5 (C5), 75.8 (C4), 78.0 (C3), 110.9 ($\underline{C}(CH_3)_2$), 114.3 (Ar$\underline{C}$H), 118.8 (CN), 129.1 (Ar$\underline{C}$C), 130.0 (Ar$\underline{C}$H), 159.2 (Ar$\underline{C}OCH_3$); LRMS (ESI +ve): 355 (100%, M+$Na^+$), 371 (25%, M+$K^+$).

3.4.7 1,2-*C*-Dimethyl-D-ribose (1-deoxy-3-*C*-methyl-D-psicose) route

**5-*O*-*tert*-Butyldimethylsilyl-2,3-*O*-isopropylidene-2-*C*-methyl-D-ribono-1,4-lactone 3.160**

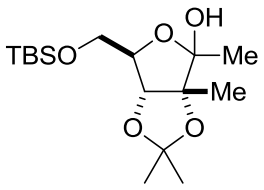



*tert*-Butyldimethylsilyl chloride (2.8 g, 18.5 mmol) was added in one portion to a solution of the lactone **1.104** (2.5 g, 12.4 mmol) at RT. The reaction was stirred for 17 h, after which TLC analysis (1:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.53) and the formation of a major product ($R_f$ 0.91). The reaction was diluted with ethyl acetate (150 mL) and washed with 2 M aqueous hydrochloric acid (3 x 50 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (19:1 to 9:1, cyclohexane/ethyl acetate) to afford the silyl ether **3.160** (3.56 g, 91%) as a white crystalline solid; HRMS (ESI +ve): found 339.1588 [M+$Na^+$];

$C_{15}H_{28}NaO_5Si$ requires 339.1598; m.p. 50-52 $^oC$; $[\alpha]_D^{25}$ -19.5 (*c* 1.49, $CHCl_3$); $\nu_{max}$ (thin film): 1787 (s, C=O); $\delta_H$ ($CDCl_3$, 400 MHz): 0.08, 0.09 (2 x 3H, s, $Si(CH_3)_2$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.43, 1.45 (2 x 3H, s, $C(CH_3)_2$), 1.64 (3H, s, 2-$CH_3$), 3.85 (1H, dd, H5, $J_{5,4}$ 1.8, $J_{5,5'}$ 11.6), 3.92 (1H, dd, H5', $J_{5',4}$ 3.0, $J_{5',5}$ 11.6), 4.49 (1H, a-t, H4, $J_{4,5} = J_{4,5'}$ 2.3), 4.51 (1H, s, H3); $\delta_C$ ($CDCl_3$, 100 MHz): -5.6, -5.4 ($Si(CH_3)_2$), 18.6 ($SiC(CH_3)_3$), 20.0 (2-$CH_3$), 25.9 ($SiC(CH_3)_3$), 26.8, 26.8 ($C(CH_3)_2$), 63.3 (C5), 82.6 (C3), 82.7 (C2), 83.1 (C4), 112.9 ($C(CH_3)_2$), 176.2 (C1); LRMS (ESI +ve): 334 (75%, $M+NH_4^+$), 339 (100%, $M+Na^+$).

**6-*O*-*tert*-Butyldimethylsilyl-1-deoxy-3,4-*O*-isopropylidene-3-*C*-methyl-D-psicofuranose**

**3.161**

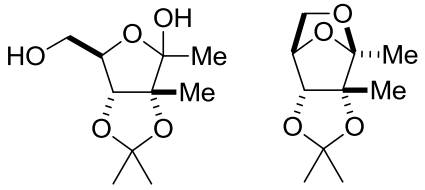



Methyllithium (1.6 M in $Et_2O$, 6.5 mL, 10.4 mmol) was added dropwise to a solution of the lactone **3.160** (3.0 g, 9.48 mmol) in THF (30 mL) at -78 $^oC$. The reaction mixture was stirred for 4 h, after which TLC analysis (5:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.73) and the formation of a major product ($R_f$ 0.81). Water (30 mL) and ethyl acetate (75 mL) were added slowly and the biphasic mixture allowed to warm to RT. The phases were separated and the aqueous layer extracted with ethyl acetate (3 x 75 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (19:1 to 9:1, cyclohexane/ethyl acetate) to afford the lactol **3.162** (2.20 g, 70%) as a clear oil, and as a single anomer; HRMS (ESI +ve): found 355.1911 [$M+Na^+$]; $C_{16}H_{32}NaO_5Si$ requires 355.1911; $[\alpha]_D^{25}$ +4.5 (*c* 3.79, $CHCl_3$); $\nu_{max}$ (thin film): 3398 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 0.14 (6H, s, $Si(CH_3)_2$), 0.93

(9H, s, $SiC(CH_3)_3$), 1.43 (3H, s, 3-$CH_3$), 1.44, 1.46 (2 x 3H, s, $C(CH_3)_2$), 1.48 (3H, s, H1), 3.74 (1H, dd, H6, $J_{6,5}$ 1.8, $J_{6,6'}$ 11.1), 3.80 (1H, dd, H6', $J_{6',5}$ 1.5, $J_{6',6}$ 11.1), 4.16 (1H, a-q, H5, $J_{5,4} = J_{5,6} = J_{5,6'}$ 1.5), 4.49 (1H, d, H4, $J_{4,5}$ 1.3), 4.98 (1H, s, H3); $\delta_C$ ($CDCl_3$, 100 MHz): -5.8, -5.8 ($Si(CH_3)_2$), 18.3 ($SiC(CH_3)_3$), 20.4 (3-$CH_3$), 20.6 (C1), 25.8 ($SiC(CH_3)_3$), 27.8, 28.9 ($C(CH_3)_2$), 65.0 (C6), 84.8 (C5), 87.4 (C4), 93.3 (C3), 107.4 (C2), 112.8 ($C(CH_3)_2$); LRMS (ESI +ve): 355 (100%, $M+Na^+$); (ESI –ve): 331 (100%, $[M-H]^-$).

**1-Deoxy-3,4-*O*-isopropylidene-3-*C*-methyl-D-psicofuranose 3.157 /**

**2,6-Anhydro-1-deoxy-3,4-*O*-isopropylidene-3-*C*-methyl-D-psicofuranose 3.162**




**3.157** **3.162**

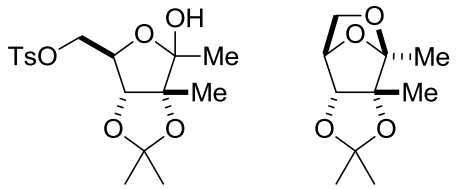
*tetra-n*-Butylammonium fluoride (1 M in THF, 7.2 mL, 7.2 mmol) was added dropwise to a solution of the lactol **3.161** (1.82 g, 5.47 mmol) at RT. The reaction was stirred for 2 h, after which TLC analysis (1:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.91), the formation of a major product ($R_f$ 0.34) and a minor product ($R_f$ 0.95). The reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash chromatography (3:1:0 to 0:9:1, cyclohexane/ethyl acetate/methanol) to afford the lactols **3.157** ($R_f$ 0.34, 1.02 g, 85%) as a clear oil, in a 1:1 (A:B) mixture of anomers, and the 2,6-anhydro-compound **3.162** ($R_f$ 0.95, 55 mg, 5%) as a volatile, white crystalline solid.

Data for the lactols **3.157**: HRMS (ESI +ve): found 241.1041 $[M+Na^+]$; $C_{10}H_{18}NaO_5$ requires 241.1046; $[\alpha]_D^{25}$ -53.1 (*c* 1.92, $CHCl_3$); $\nu_{max}$ (thin film): 3286 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz):

1.34 (3H, s, $H1^A$), 1.37 (3H, s, $C(CH_3)^A$), 1.41 (3H, s, $C(CH_3)^B$), 1.44 (9H, s, $H1^B$, $C(CH_3)^A$, $C(CH_3)^B$), 1.46 (3H, s, $C(CH_3)^B$), 1.51 (3H, s, $3\text{-}CH_3{}^A$), 1.53 (3H, s, $3\text{-}CH_3{}^B$), 3.34 (1H, d, $H6^A$, $J_{6,6'}$ 9.8), 3.57 (1H, dd, $H6'^A$, $J_{6',5}$ 4.3, $J_{6',6}$ 9.8), 3.71-3.80 (2H, m, $H6^B$, $H6'^B$), 4.02 (1H, br. s, $H4^A$), 4.17-4.20 (1H, m, $H5^B$), 4.49 (1H, br. d, $H5^A$, $J_{5,6'}$ 4.0), 4.58 (1H, d, $H4^B$, $J_{4,5}$ 1.2); $\delta_C$ ($CDCl_3$, 100 MHz): 19.7 ($C1^A$), 20.2 ($C1^B$), 21.8 ($3\text{-}CH_3{}^A$), 22.7 ($3\text{-}CH_3{}^B$), 27.0, 27.7 ($C(\underline{C}H_3)_2{}^A$), 27.6, 28.6 ($C(\underline{C}H_3)_2{}^B$), 63.6 ($C6^B$), 63.7 ($C6^A$), 78.3 ($C5^A$), 85.2 ($C5^B$), 85.9 ($C4^A$), 87.5 ($C4^B$), 89.6 ($C3^B$), 92.8 ($C3^A$), 107.5 ($C2^A$), 109.2 ($C2^B$), 112.3 ($\underline{C}(CH_3)_2{}^B$), 112.7 ($\underline{C}(CH_3)_2{}^A$); LRMS (ESI -ve): 217 (100%, $[M\text{-}H]^-$).

Selected data for the 2,6-anhydro-compound **3.162**: m.p. 44-46 °C (sublimes); $[\alpha]_D^{25}$ -15.1 (*c* 1.1, $CHCl_3$); $\delta_H$ ($CDCl_3$, 400 MHz): 1.37, 1.43 (2 x 3H, s, $C(CH_3)_2$), 1.40 (3H, s, $3\text{-}CH_3$), 1.52 (3H, s, H1), 3.33 (1H, d, H6, $J_{6,6'}$ 7.3), 3.55 (1H, dd, H6', $J_{6',5}$ 4.3, $J_{6',6}$ 7.3), 4.01 (1H, s, H4), 4.47 (1H, d, H5, $J_{5,6'}$ 4.3); $\delta_C$ ($CDCl_3$, 100 MHz): 12.2 (C1), 19.7 ($3\text{-}CH_3$), 27.0, 27.7 ($C(\underline{C}H_3)_2$), 63.7 (C6), 78.4 (C5), 85.9 (C4), 89.6 (C3), 109.1 (C2), 112.2 ($\underline{C}(CH_3)_2$).

**1-Deoxy-3,4-*O*-isopropylidene-3-*C*-methyl-6-*O*-*para*-toluenesulfonyl-D-psicofuranose 3.158 / 2,6-Anhydro-1-deoxy-3,4-*O*-isopropylidenee-3-*C*-methyl-D-psicofuranose 3.162**



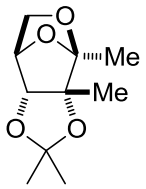

**3.158** **3.162**

A solution of *para*-toluenesulfonyl chloride (890 mg, 4.67 mmol) in pyridine (2 mL) was added dropwise to a solution of the lactols **3.157** (510 mg, 2.34 mmol) in pyridine (4 mL) at -30 °C. After 30 min the reaction was allowed to warm to 0 °C and after a further 1 h was allowed to

warm to RT. After 19 h at RT, TLC analysis (5:1, toluene/acetone) indicated the complete consumption of the starting materials ($R_f$ 0.20) and the formation of a major product ($R_f$ 0.60) and a minor product ($R_f$ 0.64). The reaction was diluted with ethyl acetate (100 mL) and washed with 2 M aqueous hydrochloric acid (3 x 25 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (99:1 to 9:1, toluene/acetone) to afford the tosylates **3.158** (660 mg, 76%) as a white, waxy solid, in a 2:1 (A:B) ratio of anomers, and the 2,6-anhydro-compound **3.162** (28 mg, 6%) as a volatile, white crystalline solid.

Data for the tosylates **3.158**: HRMS (ESI +ve): found 395.1121 [M+$Na^+$]; $C_{17}H_{24}NaO_7S$ requires 395.1135; m.p. 92-94 $^oC$; $[\alpha]_D^{25}$ +13.7 (*c* 3.12, $CHCl_3$); $\nu_{max}$ (thin film): 1190 (s, $SO_2$), 1369 (s, $SO_2$), 3487 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.29 (3H, s, $CH_3^B$), 1.36-1.46 (18H m, $CH_3$), 1.55 (3H, s, $CH_3^B$), 2.46 (6H, s, Ar$C\underline{H}_3^A$, Ar$C\underline{H}_3^B$), 4.09-4.23 (6H, m, $H5^A$, $H5^B$, $H6^A$, $H6^B$, $H6'^A$, $H6'^B$), 4.26-4.29 (1H, m, $H4^A$), 4.31-4.34 (1H, m, $H4^B$), 7.34-7.38 (4H, m, $ArH^A$, $ArH^B$), 7.77-7.83 (4H, m, $ArH^A$, $ArH^B$); $\delta_C$ ($CDCl_3$, 100 MHz): 20.3 (3-$CH_3^A$), 21.2 (3-$CH_3^B$), 21.6 (Ar$CH_3^A$, Ar$CH_3^B$), 22.4 ($C1^A$), 22.6 ($C1^B$), 26.1, 26.9 ($C(\underline{C}H_3)_2^B$), 27.6, 28.7 ($C(\underline{C}H_3)_2^A$), 68.9 ($C6^B$), 70.5 ($C6^A$), 77.5 ($C5^B$), 81.4 ($C5^A$), 86.5 ($C4^B$), 88.0 ($C4^A$), 89.7 ($C3^B$), 91.9 ($C3^A$), 104.1 ($C2^B$), 108.3 ($C2^A$), 113.3 ($\underline{C}(CH_3)_2^A$), 115.6 ($\underline{C}(CH_3)_2^B$), 128.0 (Ar$\underline{C}H^B$), 128.1 (Ar$\underline{C}H^A$), 129.9 (Ar$\underline{C}H^A$), 129.9 (Ar$\underline{C}H^B$), 132.5 (Ar$\underline{C}CH_3^B$), 132.8 (Ar$\underline{C}CH_3^A$), 145.0 (Ar$\underline{C}SO_2^A$), 145.1 (Ar$\underline{C}SO_2^B$); LRMS (ESI +ve): 395 (100%, M+$Na^+$).

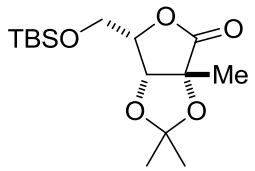
**2,6-Anhydro-1-deoxy-3,4-*O*-isopropylidenee-3-*C*-methyl-D-psicofuranose 3.162**




A solution of 4-methoxybenzylamine (0.17 mL, 1.32 mmol), potassium cyanide (86 mg, 1.32 mmol) and the tosylates **3.158** (197 mg, 0.53 mmol) in anhydrous methanol (1 mL) was neutralised with a solution of acetic acid/anhydrous methanol (1:5, v:v, 1.0 mL, 2.91 mmol). The reaction mixture was stirred at 45 $^{o}$C for 2 d, after which TLC analysis (5:1, toluene/acetone) indicated the complete consumption of the starting materials ($R_f$ 0.50) and the formation of a major product ($R_f$ 0.64). The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (50 mL) and washed with 2 M aqueous hydrochloric acid (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 20 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (99:1 to 39:1, dichloromethane/diethyl ether) to afford the anhydro-compound **3.162** (74 mg, 70%) as a volatile, white crystalline solid.

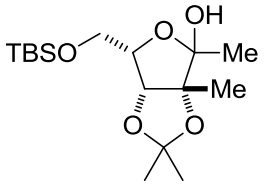
3.4.8 1,2-*C*-Dimethyl-L-lyxose (1-deoxy-3-*C*-methyl-L-tagatose) route

**5-*O*-*tert*-Butyldimethylsilyl-2,3-*O*-isopropylidene-3-*C*-methyl-L-lyxono-1,4-lactone 3.165**




*tert*-Butyldimethylsilyl chloride (1.32 g, 8.75 mmol) was added to a solution of the lactone **3.126** (1.18 g, 5.84 mmol) in pyridine (6 mL) at RT. The reaction was stirred for 16 h, after which TLC analysis (1:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.20) and the formation of a major product ($R_f$ 0.88). The reaction mixture was diluted with ethyl acetate (150 mL) and washed with 2 M aqueous hydrochloric acid (40 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (39:1 to 9:1, cyclohexane/ethyl acetate) to afford the silyl ether **3.165** (1.78 g, 97%) as a white crystalline solid; HRMS (ESI +ve): found 339.1590 [M+$Na^+$]; $C_{15}H_{28}NaO_5Si$ requires 339.1598; m.p. 46-48 $^oC$; $[\alpha]_D^{20}$ -41.1 (*c* 2.38, $CHCl_3$); $\nu_{max}$ (thin film): 1789 (s, C=O); $\delta_H$ ($CDCl_3$, 400 MHz): 0.10 (6H, s, $Si(CH_3)_2$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.39, 1.43 (2 x 3H, s, $C(CH_3)_2$), 1.55 (3H, s, 2-$CH_3$), 3.93 (1H, dd, H5, $J_{5,4}$ 6.6, $J_{5,5'}$10.9), 3.97 (1H, dd, H5, $J_{5',4}$ 5.8, $J_{5',5}$ 10.9), 4.40 (1H, d, H3, $J_{3,4}$ 3.3), 4.43 (1H, a-td, H4, $J_{4,3}$ 3.3, $J_{4,5} = J_{4,5'}$ 6.2); $\delta_C$ ($CDCl_3$, 100 MHz): -5.6, -5.4 ($Si(CH_3)_2$), 18.0 (2-$CH_3$), 18.3 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 26.7, 26.8 ($C(CH_3)_2$), 60.8 (C5), 78.4 (C4), 80.4 (C3), 82.8 (C2), 113.0 ($C(CH_3)_2$), 176.4 (C1); LRMS (ESI +ve): 339 (100%, M+$Na^+$).

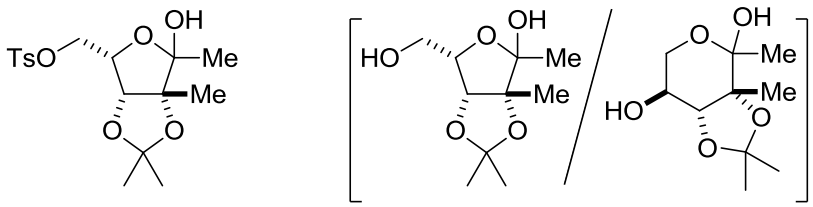
**6-*O*-*tert*-Butyldimethylsilyl-1-deoxy-3,4-*O*-isopropylidene-3-*C*-methyl-L-tagatofuranose 3.166**




Methyllithium (1.6 M in $Et_2O$, 4.1 mL, 6.52 mmol) was added dropwise to a solution of the lactone **3.165** (1.72 g, 5.43 mmol) in THF (17 mL) at -78 $^oC$. The reaction mixture was stirred for 2.5 h, after which TLC analysis (5:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.48) and the formation of a major product ($R_f$ 0.47). Water (15 mL) and ethyl acetate (100 mL) were added slowly and the vigorously stirring, biphasic mixture allowed to warm to RT. The phases were separated and the aqueous layer extracted with ethyl acetate (3 x 75 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (39:1 to 9:1, cyclohexane/ethyl acetate) to afford the lactols **3.166** (1.62 g, 90%) as a white crystalline solid, and in a 2.4:1 (A:B) mixture of anomers; HRMS (ESI +ve): found 355.1906 [M+$Na^+$]; $C_{16}H_{32}NaO_5Si$ requires 355.1911; m.p. 78-80 $^oC$; $[\alpha]_D^{20}$ +1.9 (*c* 1.35, $CHCl_3$); $\nu_{max}$ (thin film): 3455 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 0.07 (6H, s, $Si(CH_3)_2^B$), 0.09 (6H, s, $Si(CH_3)_2^A$), 0.90 (9H, s, $SiC(CH_3)_3^B$), 0.91 (9H, s, $SiC(CH_3)_3^A$), 1.35 (3H, s, $H1^B$), 1.41, 1.43 (2 x 3H, s, $C(CH_3)_2^A$), 1.44 (3H, s, $H1^A$), 1.45, 1.51 (2 x 3H, s, $C(CH_3)_2^B$), 1.48 (6H, s, 3-$CH_3^A$, 3-$CH_3^B$), 3.64 (1H, ddd, $H5^B$, $J_{5,4}$ 3.3, $J_{5,6}$ 5.3, $J_{5,6'}$ 7.3), 3.79 (1H, dd, $H6^B$, $J_{6,5}$ 5.3, $J_{6,6'}$ 9.8), 3.80 (1H, dd, $H6^A$, $J_{6,5}$ 6.3, $J_{6,6'}$ 10.4), 3.90 (1H, dd, $H6'^B$, $J_{6',5}$ 7.3, $J_{6',6}$ 9.8), 3.93 (1H, dd, $H6'^A$, $J_{6',5}$ 5.7, $J_{6',6}$ 10.4), 4.15 (1H, a-td, $H5^A$, $J_{5,4}$ 3.5, $J_{5,6} = J_{5,6'}$ 6.0), 4.36 (1H, d, $H4^B$, $J_{4,5}$ 3.3), 4.39 (1H, d, $H4^A$, $J_{4,5}$ 3.5); $\delta_C$ ($CDCl_3$, 100 MHz): -5.4, -5.3 ($Si(CH_3)_2^B$), -5.3, -5.2 ($Si(CH_3)_2^A$), 18.4, ($SiC(CH_3)_3^B$), 18.5 ($SiC(CH_3)_3^A$), 20.2 ($C1^B$), 20.5 ($C1^A$), 20.9 (3-$CH_3^B$), 22.6 (3-$CH_3^A$), 25.8, 27.1 ($C(CH_3)_2^B$), 25.9 ($SiC(CH_3)_3^B$), 26.0 ($SiC(CH_3)_3^A$), 27.2, 27.8 ($C(CH_3)_2^A$), 60.8 ($C6^B$), 61.3 ($C6^A$), 76.0 ($C5^B$), 78.8 ($C5^A$), 85.7 ($C4^B$), 86.7 ($C4^A$), 88.8 ($C3^B$), 92.1 ($C3^A$), 104.1 ($C2^B$),

106.2 ($C2^A$), 112.7 ($\underline{C}(CH_3)_2^A$), 112.8 ($\underline{C}(CH_3)_2^B$); LRMS (ESI +ve): 355 (100%, $M+Na^+$); (ESI –ve): 331 (100%, $[M-H]^-$).

**1-Deoxy-3,4-*O*-isopropylidene-3-*C*-methyl-6-*O*-*para*-toluenesulfonyl-L-tagatofuranose 3.164 / [1-Deoxy-3,4-*O*-isopropylidene-3-*C*-methyl-L-tagatofuranose 3.163 / 1-Deoxy-3,4-*O*-isopropylidene-3-*C*-methyl-L-tagatopyranose 3.168]**




**3.164** **3.163** **3.168**

*tetra-n*-Butylammonium fluoride (1 M in THF, 6.2 mL, 6.2 mmol) was added dropwise to a solution of the lactols **3.160** (1.59 g, 4.78 mmol) at RT. The reaction was stirred for 2.5 h, after which TLC analysis (5:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting materials ($R_f$ 0.52) and the formation of a major product (baseline). The reaction mixture was concentrated *in vacuo* to afford the crude lactols **3.163** and **3.168** as a white crystalline solid, which was reacted on without further purification.

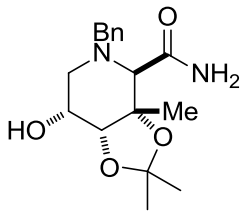
Partial data for the mixture of the lactols **3.163** and **3.16**8: HRMS (ESI +ve): found 241.1051 $[M+Na^+]$; $C_{10}H_{18}NaO_5S$ requires 241.1046; m.p. 100-102 $^oC$; $[\alpha]_D^{20}$ -16.8 (*c* 1.33, $CHCl_3$); $\nu_{max}$ (thin film): 3448 (br. s, OH); LRMS (ESI +ve): 241 (100%, $M+Na^+$); (ESI –ve): 217 (100%, $[M-H]^-$).

A solution of *para*-toluenesulfonyl chloride (699 mg, 3.67 mmol) in pyridine (1 mL) was added dropwise to a solution of the crude lactols **3.163** and **3.168** (400 mg, 1.83 mmol) in pyridine

(4 mL) at -30 °C. After 30 min the reaction was allowed to warm to 0 °C and stirred for 1 h, before warming to RT. The reaction was stirred for a further 22 h, after which TLC analysis (5:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting materials (baseline) and the formation of a major product ($R_f$ 0.30). The reaction was diluted with ethyl acetate (50 mL) and washed with 2 M aqueous hydrochloric acid (15 mL). The aqueous phase was extracted with ethyl acetate (3 x 30 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (9:1 to 7:3, cyclohexane/ethyl acetate) to afford the tosylates **3.164** (678 mg, 89% over two steps) as a clear, viscous oil, in a 3.3:1 (A:B) ratio of anomers; HRMS (ESI +ve): found 395.1134 [M+$Na^+$]; $C_{17}H_{24}NaO_7S$ requires 395.1135; $[\alpha]_D^{20}$ -1.3 (*c* 1.24, $CHCl_3$); $\nu_{max}$ (thin film): 1176 (s, $SO_2$), 1364 (s, $SO_2$), 3500 (br. s, OH); $\delta_H$ ($CDCl_3$, 400 MHz): 1.31 (6H, s, 3-$CH_3^B$, C($CH_3$)$^A$), 1.35 (3 H, s, C($CH_3$)$^A$), 1.39 (6H, s, H1$^B$, C($CH_3$)$^B$), 1.42 (3H, s, C($CH_3$)$^B$), 1.43 (3H, s, H1$^A$), 1.45 (3H, s, 3-$CH_3^A$), 2.45 (6H, s, Ar$CH_3^A$, Ar$CH_3^B$), 3.83 (1H, a-td, H5$^B$, $J_{5,6}$ 3,5, $J_{5,4} = J_{5,6'}$ 6.1), 4.15 (1H, dd, H6$^B$, $J_{6,5}$ 3.5, $J_{6,6'}$ 11.6), 4.17 (1H, dd, H6$^A$, $J_{6,5}$ 8.3, $J_{6,6'}$ 11.6), 4.25-4.31 (3H, m, H5$^A$, H6'$^A$, H6'$^B$), 4.36-4.37 (2H, m, H4$^A$, H4$^B$), 7.35 (4H, d, ArH, *J* 8.3), 7.81 (4H, d, ArH, *J* 8.3); $\delta_C$ ($CDCl_3$, 100 MHz): 20.1 (3-$CH_3^B$), 20.3 (3-$CH_3^A$), 20.7 (C1$^B$), 21.6 (O$CH_3^A$, O$CH_3^B$), 22.2 (C1$^A$), 26.9, 27.0 (C(<u>C</u>$H_3$)$_2^B$), 27.1, 27.7 (C(<u>C</u>$H_3$)$_2^A$), 67.5 (C6$^B$), 68.1 (C6$^A$), 72.9 (C5$^B$), 75.5 (C5$^A$), 85.4 (C4$^B$), 86.3 (C4$^A$), 88.9 (C3$^B$), 92.2 (C3$^A$), 104.8 (C2$^B$), 106.6 (C2$^A$), 113.2 (<u>C</u>(CH$_3$)$_2^A$), 113.4 (<u>C</u>(CH$_3$)$_2^B$), 128.1 (Ar<u>C</u>H$^A$, Ar<u>C</u>H$^B$), 129.7 (Ar<u>C</u>H$^A$, Ar<u>C</u>H$^B$), 132.6 (Ar<u>C</u>C$^B$), 132.8 (Ar<u>C</u>C$^A$), 144.8 (Ar<u>C</u>S$O_2^A$, Ar<u>C</u>S$O_2^B$); LRMS (ESI +ve): 395 (100%, M+$Na^+$).

*3.4.9 Access to a pipecolic primary amide*

**2-*N*-Benzyl-2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-3-*C*-methyl-D-allonamide 3.169**




Aqueous hydrogen peroxide (30%, 0.5 mL) was added to a solution of the α-iminonitrile **3.121** (25 mg, 0.08 mmol) in 1 M aqueous sodium hydroxide (0.75 mL) and methanol (0.5 mL) at 0 $^{o}$C. The reaction was allowed to warm to RT and stirred for 4.5 h, after which TLC analysis (1:1, toluene/acetone) indicated the complete consumption of the starting material ($R_f$ 0.71) and the formation of a major product ($R_f$ 0.36). The reaction mixture was diluted with brine (4 mL) and extracted with dichloromethane (10 x 10 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (19:1 to 3:7, toluene/acetone) to afford the pipecolic primary amide **3.169** (25 mg, quant.) as a white crystalline solid; HRMS (ESI +ve): found 343.1624 [M+$Na^+$]; $C_{17}H_{24}N_2NaO_4$ requires 343.1628; $[\alpha]_D^{20}$ +39.7 (*c* 1.31, $CHCl_3$); m.p. 158-160 $^{o}$C; $\nu_{max}$ (thin film): 1580 (s, C=O), 1678 (s, C=O), 3350 (br. s, OH/NH); $\delta_H$ ($CD_3OD$, 500 MHz): 1.37, 1.56 (2 x 3H, s, $C(CH_3)_2$), 1.40 (3H, s, 3-$CH_3$), 2.25 (1H, a-t, H6, $J_{6,5} = J_{6,6'}$ 11.0), 2.71 (1H, dd, H6', $J_{6',5}$ 5.0, $J_{6',6}$ 10.8), 3.03 (1H, s, H2), 3.22 (1H, d, NC$\underline{H}_2$Ph, $J_{gem}$ 12.9), 3.81 (1H, ddd, H5, $J_{5,4}$ 3.8, $J_{5,6'}$ 5.0, $J_{5,6}$ 11.2), 4.02 (1H, d, NC$\underline{H}_2$Ph, $J_{gem}$ 12.9), 4.05 (1H, d, H4, $J_{gem}$ 3.8), 7.23-7.38 (5H, m, ArH); $\delta_C$ ($CD_3OD$, 125 MHz): 21.2 (3-$CH_3$), 27.2, 28.6 (C($\underline{C}H_3)_2$), 53.3 (C6), 60.5 (N$\underline{C}H_2$Ph), 66.1 (C5), 73.2 (C2), 81.5 (C3), 83.1 (C4), 110.7 ($\underline{C}(CH_3)_2$), 128.5, 129.4, 130.7 (Ar$\underline{C}$H), 138.8 (Ar$\underline{C}$C), 175.2 (C1); LRMS (ESI +ve): 321 (100%, M+$H^+$), 343 (75%, M+$Na^+$), 663 (100%, 2M+$Na^+$); (ESI –ve): 319 (100%, [M-H]$^-$).

## 3.5 References

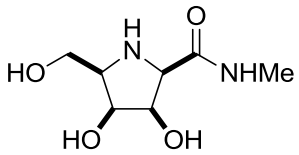

1. Meyer, K.; Hobby, G. L.; Chaffee, E.; Dawson, M. H. *J. Exp. Med.* **1940**, *71*, 137-146.
2. Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 4981-4982.
3. Ferro, V.; Hammond, E.; Fairweather, J. K. *Mini-Rev. Med. Chem.* **2004**, *4*, 693-702.
4. Simizu, S.; Ishida, K.; Osada, H. *Cancer Sci.* **2004**, *95*, 553-558.
5. Csíki, Z.; Fuegedi, P. *Tetrahedron*, **2010**, *66*, 7821-7837.
6. Csíki, Z.; Fuegedi, P. *Tetrahedron Lett.* **2010**, *51*, 391-395.
7. Fugedi, P. *Mini-Rev. Med. Chem.* **2003**, *3*, 659-667.
8. Velleman, S. G.; Liu, C. In *Chemistry and Biology of Heparin and Heparan Sulfate;* Garg, H. G.; Lindhart, R. J.; Hales, C. A. Elseveir: The Netherlands, **2005**, 29-54.
9. Nakajima, M.; Irimura, T.; Di Ferrante, N.; Nicolson, G. L. *J. Biol. Chem.* **1984**, *259*, 2283-2290.
10. Rohloff, J.; Zinke, J.; Schoppmeyer, K.; Tannapfel, A.; Witzigmann, H.; Messner, J.; Wittekind, C.; Caca, K. *Br. J. Cancer*, **2002**, *86*, 1270-1275.
11. Casu, B.; Lindahl, U. *Adv. Carbohydr. Chem. Biochem.* **2001**, *57*, 159-206.
12. Kaspersen, F. M.; Van Boeckel, C. A. A. *Xenobiotica*, **1987**, *17*, 1451-1471.
13. Wallace, B. D.; Wang, H.; Lane, K. T.; Scott, J. E.; Orans, J.; Koo, J. S.; Venkatesh, M.; Jobin, C.; Yeh, L.-A.; Mani, S.; Redinbo, M. R. *Science*, **2010**, *330*, 831-835.
14. Mori, K.; Kondo, T.; Kamiyama, Y.; Kano, Y.; Tominaga, K. *Cancer Chemoth. Pharm.* **2003**, *51*, 403-406.
15. Lindback, E.; Zhou, Y.; Lopez, O.; Fernandez-Bolanos, J. G.; Pedersen, C. M.; Bols, M. *Tetrahedron Lett.* **2012**, *53*, 2045-2047.
16. Fan, J.-Q.; Ishii, S.; Asano, N.; Suzuki, Y. *Nat. Med.* **1999**, *5*, 112-115.
17. Asano, N.; Ishii, S.; Kizu, H.; Ikeda, K.; Yasuda, K.; Kato, A.; Martin, O. R.; Fan, J.-Q. *Eur. J. Biochem.* **2000**, *267*, 4179-4186.
18. Cenci di Bello, I.; Dorling, P.; Fellows, L.; Winchester, B. *FEBS Lett.* **1984**, *176*, 61-64.
19. Kite, G. C. *Biochem. Syst. Ecol.* **2003**, *31*, 45-50.
20. Yoshimura, Y.; Ohara, C.; Imahori, T.; Saito, Y.; Kato, A.; Miyauchi, S.; Adachi, I.; Takahata, H. *Bioorg. Med. Chem.* **2008**, *16*, 8273-8286.
21. Tsuruoka, T.; Fukuyasu, H.; Ishii, M.; Usui, T.; Shibahara, S.; Inouye, S. *J. Antibiot.* **1996**, *49*, 155-161.
22. Niwa, T.; Tsuruoka, T.; Inouye, S.; Naito, Y.; Koeda, T.; Niida, T. *J. Biochem.* **1972**, *72*, 207-211.
23. Igarashi, Y.; Ichikawa, M.; Ichikawa, Y. *Tetrahedron Lett.* **1996**, *37*, 2707-2708.
24. Jensen, H. H.; Jensen, A.; Hazell, R. G.; Bols, M. *J. Chem. Soc. Perkin Trans. 1*, **2002**, *9*, 1190-1198.
25. Nishimura, Y.; Shitara, E.; Adachi, H.; Toyoshima, M.; Nakajima, M.; Okami, Y.; Takeuchi, T. *J. Org. Chem.* **2000**, *65*, 2-11.
26. Takatsu, T.; Takahashi, M.; Kawase, Y.; Enokita, R.; Okazaki, T.; Matsukawa, H.; Ogawa, K.; Sakaida, Y.; Kagasaski, T.; Kinoshita, T.; Nakajima, M.; Tanzawa, K. *J. Antibiot.* **1996**, *49*, 54-60.
27. Kawase, Y.; Takahashi, M.; Toshio, T.; Arai, M.; Nakajima, M.; Tanzawa, K. *J. Antibiot.* **1996**, *49*, 61-64.
28. Rasmussen, T. S.; Koldso, H.; Nakagawa, S.; Kato, A.; Schiott, B.; Jensen, H. H. *Org. Biomol. Chem.* **2011**, *9*, 7807-7813.
29. Manning, K. S.; Lynn, D. G.; Shabanowitz, J.; Fellows, L. E.; Singh, M.; Schrire, B. D. *J. Chem. Soc. Chem. Commun.* **1985**, 127-129.
30. Tong, M. K.; Blumenthal, E. M.; Ganem, B. *Tetrahedron Lett.* **1990**, *31*, 1683-1684.
31. Le Merrer, Y.; Poitout, L.; Depezay, J. C.; Dosbaa, I.; Geoffroy, S.; Foglietti, M. J. *Bioorg. Med. Chem.* **1997**, *5*, 519-533.
32. Bashyal, B. P.; Chow, H. F.; Fleet, G. W. J. *Tetrahedron Lett.* **1986**, *27*, 3205-3208.
33. Bashyal, B. P.; Chow, H. F.; Fellows, L. E.; Fleet, G. W. J. *Tetrahedron*, **1987**, *43*, 415-422.
34. Fleet, G. W. J.; Smith, P. W. *Tetrahedron*, **1987**, *43*, 971-978.
35. Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron*, **1989**, *45*, 327-336.
36. Park, K. H.; Yoon, Y. J.; Lee, S. G. *J. Chem. Soc. Perkin Trans. 1*, **1994**, *18*, 2621-2623.
37. Grandel, R.; Kazmaier, U. *Tetrahedron Lett.* **1997**, *38*, 8009-8012.
38. Grandel, R.; Kazmaier, U.; Rominger, F. *J. Org. Chem.* **1998**, *63*, 4524-4528.
39. Kazmaier, U.; Grandel, R. *Eur. J. Org. Chem.* **1998**, *9*, 1833-1840.
40. Kummeter, M.; Kazmaier, U. *Eur. J. Org. Chem.* **2003**, *17*, 3330-3334.
41. Ruiz, M.; Ruanova, T. M.; Ojea, V.; Quintela, J. M. *Tetrahedron Lett.* **1999**, *40*, 2021-2024.
42. Lee, B. W.; Jeong, I.-Y.; Yang, M. S.; Choi, S. U.; Park, K. H. *Synthesis*, **2000**, *9*, 1305-1309.
43. Malle, B. M.; Lundt, I.; Wrodnigg, T. M. *Org. Biomol. Chem.* **2008**, *6*, 1779-1786.
44. Klumpe, M.; Dotz, K. H. *Tetrahedron Lett.* **1998**, *39*, 3683-3684.
45. Dotz, K. H.; Klumpe, M.; Nieger, M. *Chem. Eur. J.* **1999**, *5*, 691-699.
46. Paulsen, H.; Leupold, F.; Todt, K. *Liebigs Ann. Chem.* **1966**, *692*, 200-214.
47. Paulsen, H.; Steinert, G. *Chem. Ber.* **1967**, *100*, 2467-2473.

48. Paulsen, H.; Leupold, F. *Chem. Ber.* **1969**, *102*, 2822-2834.
49. Paulsen, H.; Maeckel, E. *Chem. Ber.* **1969**, *102*, 3844-3853.
50. Shankar, B. B.; Kirkup, M. P.; McCombie, S. W.; Ganguly, A. K. *Tetrahedron Lett.* **1993**, *34*, 7171-7179.
51. Granier, T.; Vasella, A. *Helv. Chim. Acta*, **1998**, *81*, 865-880.
52. Peer, A.; Vasella, A. *Helv. Chim. Acta*, **1999**, *82*, 1044-1065.
53. Anzeveno, P. B.; Creemer, L. J.; Daniel, J. K.; King, C. H. R.; Liu, P. S. *J. Org. Chem.* **1989**, *54*, 2539-2542.
54. Wong, C.-H.; Provencher, L.; Porco, J. A.; Jung, S.-H.; Wang, Y.-F.; Chen, L.; Wang, R.; Steensma, D. H. *J. Org. Chem.* **1995**, *60*, 1492-1501.
55. Takayama, S.; Martin, R.; Wu, J.; Laslo, K.; Siuzdak, G.; Wong, C.-H. *J. Am. Chem. Soc.* **1997**, *119*, 8146-8151.
56. Chakraborty, T. K.; Jayaprakash, S. *Tetrahedron Lett.* **1997**, *38*, 8899-8902.
57. Poupon, E.; Luong, B.-X.; Chiaroni, A.; Kunesch, N.; Husson, H.-P. *J. Org. Chem.* **2000**, *65*, 7208-7210.
58. Tite, T.; Lallemand, M.-C.; Poupon, E.; Kunesch, N.; Tillequin, F.; Gravier-Pelletier, C.; Le Merrer, Y.; Husson, H.-P. *Bioorg. Med. Chem.* **2004**, *12*, 5091-5097.
59. Tite, T.; Tsimilaza, A.; Lallemand, M.-C.; Tillequin, F.; Leproux, P.; Libot, F.; Husson, H.-P. *Eur. J. Org. Chem.* **2006**, *4*, 863-868.
60. Tsimilaza, A.; Tite, T.; Boutefnouchet, S.; Lallemand, M.-C.; Tillequin, F.; Husson, H.-P. *Tetrahedron: Asymmetry*, **2007**, *18*, 1585-1588.
61. Francois, D.; Poupon, E.; Kunesch, N.; Husson, H.-P. *Eur. J. Org. Chem.* **2004**, *23*, 4823-4829.
62. Matassini, C.; Mirabella, S.; Goti, A.; Cardona, F. *Eur. J. Org. Chem.* **2012**, *2012*, 3920-3924.
63. Godskesen, M.; Lundt, I.; Madsen, R.; Winchester, B. *Bioorg. Med. Chem.* **1996**, *4*, 1857-1865.
64. Batra, H.; Moriarty, R. M.; Penmasta, R.; Sharma, V.; Stanciuc, G.; Staszewski, J. P.; Tuladhar, S. M.; Walsh, D. A.; Datla, S.; Krishnaswamy, S. *Org. Process Res. Dev.* **2006**, *10*, 484-486.
65. Varela, O.; Zunszain, P. A. *J. Org. Chem.* **1993**, *58*, 7860-7864.
66. Hughes, N. A.; Speakman, P. R. H. *Carbohydr. Res.* **1965**, *1*, 171-175.
67. Attia, M. I.; Timmermann, M.; Hoegger, P.; Herdeis, C. *Eur. J. Org. Chem.* **2007**, *22*, 3669-3675.
68. Win-Mason, A. L.; Dangerfield, E. M.; Tyler, P. C.; Stocker, B. L.; Timmer, M. S. M. *Eur. J. Org. Chem.* **2011**, *2011*, 4008-4014.
69. Bonin, M.; Chiaroni, A.; Riche, C.; Beloeil, J. C.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* **1987**, *52*, 382-385.
70. Takahashi, K.; Mikajiri, T.; Kurita, H.; Ogura, K.; Iida, H. *J. Org. Chem.* **1985**, *50*, 4372-4375.
71. Win-Mason, A. L.; Jongkees, S. A. K.; Withers, S. G.; Tyler, P. C.; Timmer, M. S. M.; Stocker, B. L. *J. Org. Chem.* **2011**, *76*, 9611-9621.
72. Håkansson, A. E.; van Ameijde. J.; Horne, G.; Nash, R. J.; Wormald, M. R.; Kato, A.; Besra, G. S.; Gurcha, S.; Fleet, G. W. J. *Tetrahedron Lett.* **2008**, *49*, 179-184.
73. da Cruz, F. P.; Newberry, S.; Jenkinson, S. F.; Wormald, M. R.; Butters, T. D.; Alonzi, D. S.; Nakagawa, S.; Becq, F.; Norez, C.; Nash, R. J.; Kato, A.; Fleet, G. W. J. *Tetrahedron Lett.* **2011**, *52*, 219-223.
74. Hotchkiss, D. J.; Jenkinson, S. F.; Storer, R.; Heinz, T.; Fleet, G. W. J. *Tetrahedron Lett.* **2006**, *47*, 315-318.
75. Hotchkiss, D. J.; Soengas, R.; Booth, K. V.; Weymouth-Wilson, A. C.; Eastwick-Field, V.; Fleet, G. W. J. *Tetrahedron Lett.* **2007**, *48*, 517-520.
76. Booth, K. V.; da Cruz, F. P.; Hotchkiss, D. J.; Jenkinson, S. F.; Jones, N. A.; Weymouth-Wilson, A. C.; Clarkson, R.; Heinz, T.; Fleet, G. W. J. *Tetrahedron: Asymmetry*, **2008**, *19*, 2417-2424.
77. Yang, B. Y.; Montgomery, R. *Carbohydr. Res.* **1996**, *280*, 27-45.
78. Hotchkiss, D. J.; Kato, A.; Odell, B.; Claridge, T. D. W.; Fleet, G. W. J. *Tetrahedron: Asymmetry*, **2007**, *18*, 500-512.
79. Sowden, J. C.; Strobach, D. R. *J. Am. Chem. Soc.* **1960**, *82*, 3707-3708.
80. Ayers, B. J.; Jenkinson, S. F.; Fleet, G. W. J.; Thompson, A. L. *Acta Crystallogr. E*, **2012**, *68*, o1474.
81. Wang, C.; Sim, L.; Rose, D. R.; Pinto, B. M. *Carbohydr. Res.* **2007**, *342*, 1661-1667.
82. Wilcox, C. S.; Cowart, M. D. *Carbohydr. Res.* **1987**, *171*, 141-160.
83. Haytakawa, H.; Miyazawa, M.; Tanaka, H.; Miyasaka, T. *Nucleos. Nucleot.* **1994**, *13*, 297-308.
84. Ciuffreda, P.; Buzzi, B.; Alessandrini, L.; Santaniello, E. *Eur. J. Org. Chem.* **2004**, *21*, 4405-4409.
85. Izquierdo, C. I.; Garcia, P. D. *Carbohydr. Res.* **1985**, *138*, 139-142.
86. Tsou, E.-L.; Yeh, Y.-T.; Liang, P.-H.; Cheng, W.-C. *Tetrahedron*, **2008,** *65*, 93-100.
87. Katritzky, A. R.; Pilarski, B.; Urogdi, L. *Synthesis*, **1989**, *12*, 949-950.
88. Pedatella, S.; Guaragna, A.; D'Alonzo, D.; De Nisco, M.; Palumbo, G. *Synthesis*, **2006,** *2*, 305-308.
89. Chan, M. F.; Hsiao, C. N. *Tetrahedron Lett.* **1992**, *33*, 3567-3570.
90. Fleetwood, A.; Hughes, N. A. *Carbohydr. Res.* **1999**, *317*, 204-209.
91. Fan, A.; Jaenicke, S.; Chuah, G.-K. *Org. Biomol. Chem.* **2011**, *9*, 7720-7726.
92. Herdeis, C.; Waibel, D. *Arch. Pharm.* **1991**, *324*, 269-274.

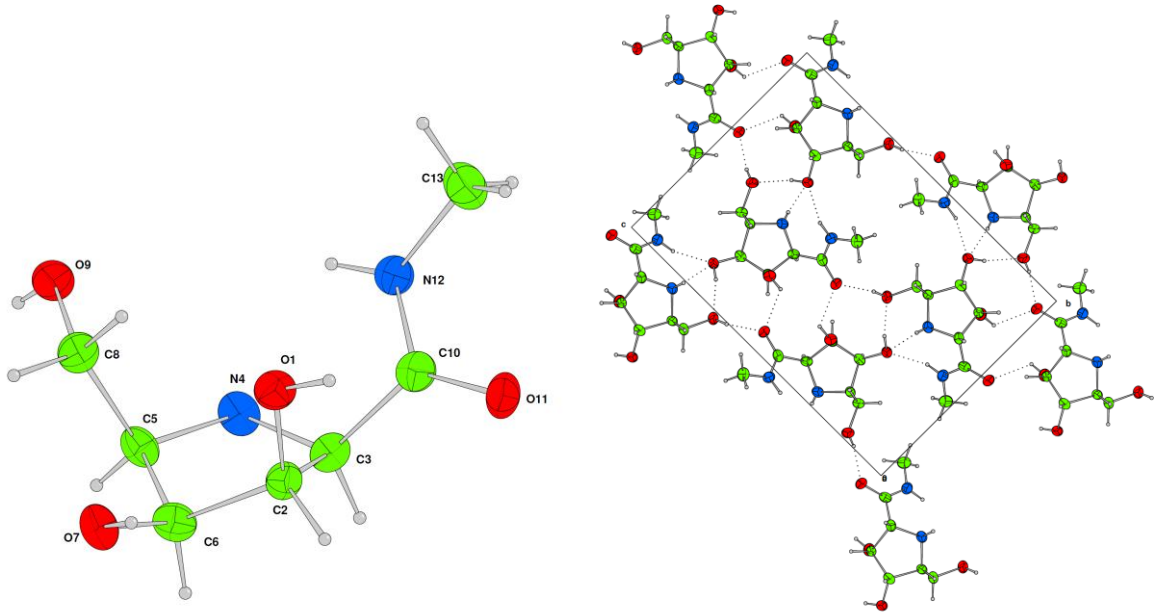
93. Jones, N. A.; Jenkinson, S. F.; Soengas, R.; Fanefjord, M.; Wormald, M. R.; Dwek, R. A.; Kiran, G. P.; Devendar, R.; Takata, G.; Morimoto, K.; Izumori, K.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2007**, *18*, 774-786.
94. Clinch, K.; Evans, G. B.; Fleet, G. W. J.; Furneaux, R. H.; Johnson, S. W.; Lenz, D. H.; Mee, S. P. H.; Rands, P. R.; Schramm, V. L.; Taylor, R. E. A.; Tyler, P. C. *Org. Biomol. Chem.* **2006**, *4*, 1131-1139.

# Appendix 1: XRD data

## Appendix 1.1: D-*galacto* proline amide




**2.142D**




The crystal was placed in the cold stream of an Oxford Cryosystems open-flow nitrogen cryostat (Cosier & Glazer, 1986) with a nominal stability of 0.1 K

*Crystal data*

| | |
|---|---|
| $C_7H_{14}N_2O_4$ | $D_x$ = 1.444 Mg m$^{-3}$ |
| $M_r$ = 190.20 | Melting point: ? K |
| Orthorhombic, $P2_12_12_1$ | Mo $K\alpha$ radiation<br>λ = 0.71073 Å |
| Hall symbol: P 2ac 2ab | Cell parameters from 1187 reflections |
| $a$ = 5.0007 (4) Å | θ = 5–27° |

| | |
|---|---|
| $b$ = 11.0903 (8) Å | μ = 0.12 $mm^{-1}$ |
| $c$ = 15.7758 (14) Å | $T$ = 150 K |
| $V$ = 874.91 (12) $Å^3$ | Cell measurement pressure: ? kPa |
| $Z$ = 4 | Block, colourless |
| $F_{000}$ = 408 | 0.25 × 0.15 × 0.10 mm |

*Data collection*

| | |
|---|---|
| Nonius KappaCCD diffractometer | 7173 measured reflections |
| Radiation source: ? | 1191 independent reflections |
| Monochromator: graphite | 614 reflections with $I > 2.0\sigma(I)$ |
| Detector resolution: ? pixels $mm^{-1}$ | $R_{int}$ = 0.118 |
| $T$ = 150 K | $\theta_{max}$ = 27.5° |
| $P$ = ? kPa | $\theta_{min}$ = 5.2° |
| ω scans | $h$ = −6 6 |
| Absorption correction: multi-scan (DENZO/SCALEPACK; Otwinowski & Minor, 1997) | $k$ = −14 14 |
| $T_{min}$ = 0.94, $T_{max}$ = 0.99 | $l$ = −20 20 |

*Refinement*

| | |
|---|---|
| Refinement on $F^2$ | Hydrogen site location: inferred from neighbouring sites |
| Least-squares matrix: full | ? |
| $R[F^2 > 2\sigma(F^2)]$ = 0.041 | Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.07P)^2 + 0.03P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$ |
| $wR(F^2)$ = 0.098 | $(\Delta/\sigma)_{max}$ = 0.001 |
| $S$ = 0.89 | $\Delta\rho_{max}$ = 0.41 e $Å^{-3}$ |
| 830 reflections | $\Delta\rho_{min}$ = −0.43 e $Å^{-3}$ |
| 118 parameters | Extinction correction: None |
| ? constraints | Absolute structure: ? |

| | |
|---|---|
| Primary atom site location: structure-invariant direct methods | Flack parameter: ? |
| Secondary atom site location: ? | Rogers parameter: ? |

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å$^2$)

| | *x* | *y* | *z* | $U_{iso}$*/$U_{eq}$ |
|---|---|---|---|---|
| O1 | 0.0212 (5) | −0.7454 (2) | −0.37497 (15) | 0.0267 |
| C2 | −0.2609 (8) | −0.7445 (3) | −0.3680 (2) | 0.0228 |
| C3 | −0.3717 (8) | −0.6151 (3) | −0.3793 (2) | 0.0239 |
| N4 | −0.3400 (7) | −0.5591 (3) | −0.29536 (18) | 0.0262 |
| C5 | −0.3016 (8) | −0.6520 (3) | −0.2300 (2) | 0.0233 |
| C6 | −0.3494 (9) | −0.7715 (3) | −0.2768 (2) | 0.0266 |
| O7 | −0.2153 (5) | −0.8698 (2) | −0.23692 (15) | 0.0267 |
| C8 | −0.0268 (8) | −0.6434 (3) | −0.1904 (2) | 0.0272 |
| O9 | 0.0184 (6) | −0.5282 (2) | −0.15247 (15) | 0.0309 |
| C10 | −0.2197 (8) | −0.5502 (3) | −0.4477 (2) | 0.0244 |
| O11 | −0.2477 (5) | −0.5788 (2) | −0.52407 (15) | 0.0308 |
| N12 | −0.0591 (7) | −0.4621 (3) | −0.4228 (2) | 0.0274 |
| C13 | 0.1182 (9) | −0.3974 (4) | −0.4799 (2) | 0.0366 |
| H21 | −0.3511 | −0.8002 | −0.4072 | 0.0270* |
| H31 | −0.5631 | −0.6218 | −0.3956 | 0.0284* |
| H51 | −0.4355 | −0.6422 | −0.1854 | 0.0267* |
| H61 | −0.5395 | −0.7893 | −0.2785 | 0.0322* |
| H81 | −0.0021 | −0.7065 | −0.1481 | 0.0337* |
| H82 | 0.1043 | −0.6554 | −0.2352 | 0.0326* |
| H131 | 0.2687 | −0.3704 | −0.4472 | 0.0553* |
| H133 | 0.1805 | −0.4486 | −0.5254 | 0.0553* |
| H132 | 0.0266 | −0.3281 | −0.5027 | 0.0553* |
| H121 | −0.0479 | −0.4478 | −0.3688 | 0.0332* |
| H41 | −0.4589 | −0.5080 | −0.2833 | 0.0325* |

| | | | | |
|---|---|---|---|---|
| H91 | −0.0871 | −0.5088 | −0.1145 | 0.0468* |
| H71 | −0.1352 | −0.9072 | −0.2739 | 0.0400* |
| H11 | 0.0653 | −0.7771 | −0.4189 | 0.0409* |

Atomic displacement parameters (Å$^2$)

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{12}$ | $U^{13}$ | $U^{23}$ |
|---|---|---|---|---|---|---|
| O1 | 0.0229 (17) | 0.0287 (15) | 0.0285 (14) | 0.0018 (14) | 0.0022 (13) | −0.0058 (13) |
| C2 | 0.027 (2) | 0.018 (2) | 0.0234 (18) | −0.0013 (19) | −0.0039 (18) | −0.0010 (17) |
| C3 | 0.022 (2) | 0.022 (2) | 0.027 (2) | 0.0035 (18) | −0.0018 (18) | −0.0045 (18) |
| N4 | 0.030 (2) | 0.0215 (17) | 0.0268 (18) | 0.0057 (17) | 0.0057 (16) | −0.0019 (14) |
| C5 | 0.030 (2) | 0.0178 (19) | 0.022 (2) | 0.0002 (18) | 0.0058 (18) | 0.0017 (17) |
| C6 | 0.030 (2) | 0.0180 (19) | 0.032 (2) | −0.0005 (19) | 0.001 (2) | 0.0018 (18) |
| O7 | 0.0334 (16) | 0.0218 (12) | 0.0248 (13) | 0.0062 (13) | 0.0050 (13) | 0.0008 (12) |
| C8 | 0.033 (2) | 0.023 (2) | 0.026 (2) | −0.002 (2) | 0.000 (2) | −0.0048 (18) |
| O9 | 0.041 (2) | 0.0265 (15) | 0.0254 (14) | −0.0088 (14) | 0.0016 (15) | −0.0050 (12) |
| C10 | 0.019 (2) | 0.021 (2) | 0.032 (2) | 0.006 (2) | −0.0027 (18) | 0.0057 (19) |
| O11 | 0.0417 (19) | 0.0310 (16) | 0.0197 (16) | −0.0023 (15) | −0.0055 (15) | 0.0004 (12) |
| N12 | 0.029 (2) | 0.0285 (18) | 0.0243 (17) | −0.0036 (18) | 0.0014 (15) | −0.0015 (16) |
| C13 | 0.044 (3) | 0.035 (2) | 0.030 (2) | −0.005 (2) | 0.004 (2) | 0.006 (2) |

Geometric parameters (Å, °)

| | | | |
|---|---|---|---|
| O1—C2 | 1.415 (5) | C6—H61 | 0.971 |
| O1—H11 | 0.807 | O7—H71 | 0.820 |
| C2—C3 | 1.549 (5) | C8—O9 | 1.429 (4) |
| C2—C6 | 1.534 (5) | C8—H81 | 0.974 |
| C2—H21 | 0.984 | C8—H82 | 0.973 |
| C3—N4 | 1.471 (4) | O9—H91 | 0.827 |
| C3—C10 | 1.504 (5) | C10—O11 | 1.253 (4) |
| C3—H31 | 0.994 | C10—N12 | 1.325 (5) |

| | | | |
|---|---|---|---|
| N4—C5 | 1.470 (4) | N12—C13 | 1.454 (5) |
| N4—H41 | 0.843 | N12—H121 | 0.867 |
| C5—C6 | 1.537 (5) | C13—H131 | 0.961 |
| C5—C8 | 1.512 (6) | C13—H133 | 0.966 |
| C5—H51 | 0.977 | C13—H132 | 0.965 |
| C6—O7 | 1.426 (4) | | |
| C2—O1—H11 | 110.1 | C2—C6—O7 | 115.3 (3) |
| O1—C2—C3 | 110.7 (3) | C5—C6—H61 | 109.9 |
| O1—C2—C6 | 111.1 (3) | C2—C6—H61 | 107.3 |
| C3—C2—C6 | 100.7 (3) | O7—C6—H61 | 108.5 |
| O1—C2—H21 | 113.8 | C6—O7—H71 | 107.6 |
| C3—C2—H21 | 110.2 | C5—C8—O9 | 111.9 (3) |
| C6—C2—H21 | 109.6 | C5—C8—H81 | 110.7 |
| C2—C3—N4 | 104.4 (3) | O9—C8—H81 | 109.5 |
| C2—C3—C10 | 110.2 (3) | C5—C8—H82 | 107.7 |
| N4—C3—C10 | 112.9 (3) | O9—C8—H82 | 108.6 |
| C2—C3—H31 | 107.8 | H81—C8—H82 | 108.3 |
| N4—C3—H31 | 111.6 | C8—O9—H91 | 115.9 |
| C10—C3—H31 | 109.6 | C3—C10—O11 | 120.8 (3) |
| C3—N4—C5 | 110.5 (3) | C3—C10—N12 | 116.5 (3) |
| C3—N4—H41 | 114.3 | O11—C10—N12 | 122.7 (4) |
| C5—N4—H41 | 113.8 | C10—N12—C13 | 123.3 (3) |
| N4—C5—C6 | 104.3 (3) | C10—N12—H121 | 117.7 |
| N4—C5—C8 | 111.4 (3) | C13—N12—H121 | 118.6 |
| C6—C5—C8 | 113.2 (3) | N12—C13—H131 | 107.3 |
| N4—C5—H51 | 109.7 | N12—C13—H133 | 111.5 |
| C6—C5—H51 | 109.6 | H131—C13—H133 | 109.3 |
| C8—C5—H51 | 108.6 | N12—C13—H132 | 109.5 |
| C5—C6—C2 | 103.7 (3) | H131—C13—H132 | 108.9 |
| C5—C6—O7 | 111.9 (3) | H133—C13—H132 | 110.2 |

Hydrogen-bond geometry (Å, °)

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| C3—H31···O1$^{i}$ | 0.99 (1) | 2.51 (1) | 3.363 (5) | 144 (1) |
| C8—H82···O1 | 0.97 (1) | 2.46 (1) | 3.132 (5) | 126 (1) |
| C13—H133···O9$^{ii}$ | 0.97 (1) | 2.52 (1) | 3.375 (5) | 147 (1) |
| N12—H121···O7$^{iii}$ | 0.87 (1) | 2.30 (1) | 3.046 (5) | 145 (1) |
| N4—H41···O7$^{iv}$ | 0.84 | 2.26 | 3.100 (5) | 175 |
| O9—H91···O11$^{v}$ | 0.83 | 1.91 | 2.710 (5) | 161 |
| O7—H71···O9$^{vi}$ | 0.82 | 1.87 | 2.665 (5) | 163 |
| O1—H11···O11$^{vii}$ | 0.81 (1) | 2.06 (1) | 2.770 (5) | 147 (1) |

Symmetry codes: (i) *x*−1, *y*, *z*; (ii) −*x*+1/2, −*y*−1, *z*−1/2; (iii) −*x*, *y*+1/2, −*z*−1/2; (iv) −*x*−1, *y*+1/2, −*z*−1/2; (v) −*x*−1/2, −*y*−1, *z*+1/2; (vi) −*x*, *y*−1/2, −*z*−1/2; (vii) *x*+1/2, −*y*−3/2, −*z*−1.

## Refinement

In the absence of significant anomalous scattering, Friedel pairs were merged and the absolute configuration was arbitrarily assigned.

The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C—H in the range 0.93–0.98, N—H in the range 0.86–0.89 N—H to 0.86 O—H = 0.82 Å) and $U_{iso}$(H) (in the range 1.2–1.5 times $U_{eq}$ of the parent atom), after which the positions were refined with riding constraints (Cooper *et al.*, 2010).

## Computing details

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: DENZO/SCALEPACK Otwinowski & Minor, 1997); program(s) used to solve structure: SIR92 (Altomare *et al.*, 1994); program(s) used to refine structure: CRYSTALS (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: CRYSTALS (Betteridge *et al.*, 2003).

## References

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435–435.

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl.*

*Cryst.* **36**, 1487–1487.

Cooper, *R*. I., Thompson, A. *L*. & Watkin, D. J. (2010). J. Appl. Cryst. 43, 1100–1107.

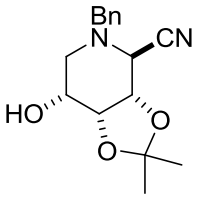
Cosier, J. & Glazer, A·*M*., 1986. J. Appl. Cryst. 105 107.

Nonius (2001). *COLLECT*. Nonius BV, Delft, The Netherlands.

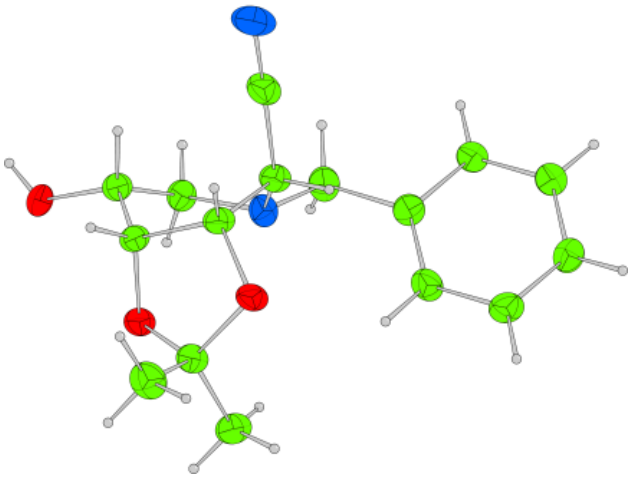
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.

Watkin, D. J., Prout, C. K. & Pearce, L. J. (1996). *CAMERON*, Chemical Crystallography Laboratory, Oxford, UK.

## Appendix 1.2: D-*ribo* piperidine α-iminonitrile




**3.88**



The crystal was placed in the cold stream of an Oxford Cryosystems open-flow nitrogen cryostat (Cosier & Glazer, 1986) with a nominal stability of 0.1 K.

*Crystal data*

| | |
|---|---|
| $C_{16}H_{20}N_2O_3$ | $D_x$ = 1.271 Mg m$^{-3}$ |
| $M_r$ = 288.35 | Melting point: ? K |
| Orthorhombic, $P2_12_12_1$ | Mo $K\alpha$ radiation<br>λ = 0.71073 Å |
| Hall symbol: P 2ac 2ab | Cell parameters from 1934 reflections |
| *a* = 8.3978 (3) Å | θ = 5–27° |
| *b* = 11.2689 (4) Å | μ = 0.09 mm$^{-1}$ |
| *c* = 15.9210 (6) Å | *T* = 150 K |
| *V* = 1506.67 (9) Å$^3$ | Cell measurement pressure: ? kPa |
| *Z* = 4 | Plate, colourless |
| $F_{000}$ = 616 | 0.40 × 0.40 × 0.20 mm |

*Data collection*

| | |
|---|---|
| Nonius KappaCCD diffractometer | 1970 measured reflections |
| Radiation source: ? | 1970 independent reflections |
| Monochromator: graphite | 1403 reflections with $I > 2.0\sigma(I)$ |
| Detector resolution: ? pixels $mm^{-1}$ | $R_{int}$ = 0.047 |
| $T$ = 150 K | $\theta_{max}$ = 27.5° |
| $P$ = ? kPa | $\theta_{min}$ = 5.1° |
| ω scans | $h$ = 0 10 |
| Absorption correction: multi-scan (DENZO/SCALEPACK;Otwinowski & Minor, 1997) | $k$ = 0 14 |
| $T_{min}$ = 0.97, $T_{max}$ = 0.98 | $l$ = 0 20 |

*Refinement*

| | |
|---|---|
| Refinement on $F^2$ | Hydrogen site location: difference Fourier map |
| Least-squares matrix: full | H-atom parameters constrained |
| $R[F^2 > 2\sigma(F^2)]$ = 0.042 | Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = $1.0/[A_0*T_0(x) + A_1*T_1(x) \cdots + A_{n-1}]*T_{n-1}(x)]$ where $A_i$ are the Chebychev coefficients listed below and x = $F$ /$F$max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta$F$/6*sigma$F$)$^2$]$^2$ $A_i$ are: 8.95 12.8 6.44 1.73 |
| $wR(F^2)$ = 0.123 | $(\Delta/\sigma)_{max}$ = 0.0001 |
| $S$ = 0.93 | $\Delta\rho_{max}$ = 0.45 e Å$^{-3}$ |
| 1970 reflections | $\Delta\rho_{min}$ = −0.42 e Å$^{-3}$ |
| 190 parameters | Extinction correction: None |
| ? constraints | Absolute structure: ? |
| Primary atom site location: structure-invariant direct methods | Flack parameter: ? |

| Secondary atom site location: ? | Rogers parameter: ? |
|---|---|

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å$^2$)

| | *x* | *y* | *z* | $U_{iso}$*/$U_{eq}$ |
|---|---|---|---|---|
| O1 | 0.6465 (3) | 0.0633 (2) | 0.37775 (14) | 0.0304 |
| C2 | 0.5963 (4) | 0.1833 (3) | 0.37196 (19) | 0.0257 |
| C3 | 0.6543 (4) | 0.2450 (3) | 0.29345 (19) | 0.0244 |
| O4 | 0.5816 (3) | 0.19580 (19) | 0.21980 (13) | 0.0271 |
| C5 | 0.5778 (4) | 0.2890 (3) | 0.15879 (19) | 0.0261 |
| O6 | 0.5489 (3) | 0.39519 (19) | 0.20739 (13) | 0.0269 |
| C7 | 0.6006 (4) | 0.3758 (3) | 0.29153 (19) | 0.0255 |
| C8 | 0.4595 (4) | 0.4018 (3) | 0.3505 (2) | 0.0264 |
| N9 | 0.3478 (3) | 0.3035 (2) | 0.34961 (17) | 0.0261 |
| C10 | 0.4159 (4) | 0.1919 (3) | 0.3825 (2) | 0.0270 |
| C11 | 0.1968 (4) | 0.3292 (3) | 0.3921 (2) | 0.0315 |
| C12 | 0.1021 (4) | 0.4285 (3) | 0.3531 (2) | 0.0275 |
| C13 | 0.0910 (5) | 0.4450 (3) | 0.2669 (2) | 0.0315 |
| C14 | −0.0032 (5) | 0.5344 (3) | 0.2333 (2) | 0.0321 |
| C15 | −0.0878 (5) | 0.6088 (3) | 0.2859 (2) | 0.0308 |
| C16 | −0.0756 (5) | 0.5947 (3) | 0.3725 (2) | 0.0341 |
| C17 | 0.0182 (4) | 0.5058 (3) | 0.4056 (2) | 0.0290 |
| C18 | 0.5178 (5) | 0.4307 (3) | 0.4371 (2) | 0.0329 |
| N19 | 0.5612 (5) | 0.4487 (3) | 0.50422 (19) | 0.0469 |
| C20 | 0.4377 (5) | 0.2689 (3) | 0.1017 (2) | 0.0327 |
| C21 | 0.7353 (5) | 0.3003 (4) | 0.1128 (2) | 0.0385 |
| H21 | 0.6479 | 0.2257 | 0.4198 | 0.0309* |
| H31 | 0.7714 | 0.2399 | 0.2898 | 0.0293* |
| H71 | 0.6920 | 0.4289 | 0.3036 | 0.0311* |
| H81 | 0.4053 | 0.4725 | 0.3288 | 0.0320* |
| H101 | 0.3908 | 0.1840 | 0.4426 | 0.0319* |

| | | | | |
|---|---|---|---|---|
| H102 | 0.3694 | 0.1263 | 0.3501 | 0.0317* |
| H111 | 0.2187 | 0.3475 | 0.4519 | 0.0372* |
| H112 | 0.1312 | 0.2572 | 0.3896 | 0.0371* |
| H131 | 0.1500 | 0.3963 | 0.2301 | 0.0381* |
| H141 | −0.0097 | 0.5444 | 0.1754 | 0.0379* |
| H151 | −0.1540 | 0.6689 | 0.2633 | 0.0372* |
| H161 | −0.1333 | 0.6461 | 0.4083 | 0.0410* |
| H171 | 0.0256 | 0.4954 | 0.4641 | 0.0353* |
| H201 | 0.4271 | 0.3351 | 0.0636 | 0.0490* |
| H202 | 0.3402 | 0.2633 | 0.1345 | 0.0491* |
| H203 | 0.4541 | 0.1973 | 0.0696 | 0.0488* |
| H212 | 0.7325 | 0.3686 | 0.0752 | 0.0575* |
| H213 | 0.8228 | 0.3103 | 0.1520 | 0.0582* |
| H211 | 0.7535 | 0.2277 | 0.0799 | 0.0582* |
| H11 | 0.5998 | 0.0249 | 0.3380 | 0.0464* |

Atomic displacement parameters (Å$^2$)

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{12}$ | $U^{13}$ | $U^{23}$ |
|---|---|---|---|---|---|---|
| O1 | 0.0390 (13) | 0.0234 (11) | 0.0287 (11) | 0.0065 (11) | −0.0064 (11) | 0.0010 (10) |
| C2 | 0.0334 (17) | 0.0204 (15) | 0.0232 (14) | 0.0016 (14) | −0.0038 (14) | 0.0001 (12) |
| C3 | 0.0304 (16) | 0.0221 (14) | 0.0207 (14) | 0.0005 (14) | −0.0048 (14) | 0.0002 (12) |
| O4 | 0.0383 (13) | 0.0206 (10) | 0.0226 (10) | −0.0005 (11) | −0.0022 (10) | 0.0006 (9) |
| C5 | 0.0359 (18) | 0.0200 (13) | 0.0223 (14) | −0.0022 (14) | 0.0009 (15) | 0.0011 (12) |
| O6 | 0.0407 (14) | 0.0195 (10) | 0.0207 (10) | −0.0006 (10) | −0.0012 (10) | −0.0007 (9) |
| C7 | 0.0326 (17) | 0.0228 (14) | 0.0211 (14) | −0.0035 (14) | −0.0039 (14) | 0.0008 (12) |
| C8 | 0.0356 (19) | 0.0216 (14) | 0.0219 (14) | −0.0012 (14) | −0.0010 (14) | 0.0007 (12) |
| N9 | 0.0292 (14) | 0.0201 (12) | 0.0289 (13) | 0.0012 (12) | 0.0032 (12) | 0.0036 (11) |
| C10 | 0.0358 (17) | 0.0202 (14) | 0.0250 (15) | 0.0011 (15) | 0.0009 (15) | 0.0062 (13) |
| C11 | 0.0355 (19) | 0.0311 (18) | 0.0280 (16) | 0.0046 (15) | 0.0085 (15) | 0.0054 (15) |
| C12 | 0.0304 (17) | 0.0267 (16) | 0.0255 (14) | 0.0001 (15) | 0.0027 (14) | 0.0034 (13) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C13 | 0.041 (2) | 0.0281 (16) | 0.0257 (15) | 0.0047 (16) | 0.0065 (16) | 0.0009 (14) |
| C14 | 0.042 (2) | 0.0310 (17) | 0.0237 (16) | 0.0000 (16) | −0.0005 (16) | 0.0043 (14) |
| C15 | 0.0306 (17) | 0.0282 (15) | 0.0335 (17) | 0.0004 (15) | −0.0040 (16) | 0.0032 (15) |
| C16 | 0.0337 (19) | 0.0363 (18) | 0.0322 (17) | 0.0070 (17) | −0.0012 (15) | −0.0041 (15) |
| C17 | 0.0297 (18) | 0.0314 (17) | 0.0259 (16) | 0.0026 (14) | 0.0005 (14) | −0.0021 (13) |
| C18 | 0.046 (2) | 0.0235 (16) | 0.0296 (17) | 0.0003 (16) | 0.0013 (16) | −0.0017 (13) |
| N19 | 0.072 (3) | 0.0401 (17) | 0.0286 (15) | −0.002 (2) | −0.0035 (17) | −0.0078 (14) |
| C20 | 0.039 (2) | 0.0302 (17) | 0.0288 (17) | −0.0044 (16) | −0.0058 (16) | 0.0015 (14) |
| C21 | 0.040 (2) | 0.041 (2) | 0.0349 (19) | 0.0007 (18) | 0.0094 (17) | 0.0005 (19) |

Geometric parameters (Å, °)

| | | | |
|---|---|---|---|
| O1—C2 | 1.419 (4) | C11—C12 | 1.507 (5) |
| O1—H11 | 0.861 | C11—H111 | 0.992 |
| C2—C3 | 1.511 (4) | C11—H112 | 0.982 |
| C2—C10 | 1.527 (5) | C12—C13 | 1.389 (4) |
| C2—H21 | 0.999 | C12—C17 | 1.397 (5) |
| C3—O4 | 1.433 (4) | C13—C14 | 1.388 (5) |
| C3—C7 | 1.542 (4) | C13—H131 | 0.943 |
| C3—H31 | 0.987 | C14—C15 | 1.381 (5) |
| O4—C5 | 1.431 (4) | C14—H141 | 0.930 |
| C5—O6 | 1.445 (4) | C15—C16 | 1.393 (5) |
| C5—C20 | 1.504 (5) | C15—H151 | 0.947 |
| C5—C21 | 1.517 (5) | C16—C17 | 1.379 (5) |
| O6—C7 | 1.425 (4) | C16—H161 | 0.946 |
| C7—C8 | 1.540 (5) | C17—H171 | 0.941 |
| C7—H71 | 0.992 | C18—N19 | 1.147 (5) |
| C8—N9 | 1.452 (4) | C20—H201 | 0.965 |
| C8—C18 | 1.499 (5) | C20—H202 | 0.973 |
| C8—H81 | 0.980 | C20—H203 | 0.965 |
| N9—C10 | 1.477 (4) | C21—H212 | 0.975 |

| | | | |
|---|---|---|---|
| N9—C11 | 1.465 (4) | C21—H213 | 0.971 |
| C10—H101 | 0.984 | C21—H211 | 0.983 |
| C10—H102 | 0.982 | | |
| C2—O1—H11 | 107.2 | N9—C10—H102 | 107.6 |
| O1—C2—C3 | 113.3 (3) | H101—C10—H102 | 110.9 |
| O1—C2—C10 | 110.4 (3) | N9—C11—C12 | 114.4 (3) |
| C3—C2—C10 | 112.4 (3) | N9—C11—H111 | 108.9 |
| O1—C2—H21 | 106.1 | C12—C11—H111 | 109.8 |
| C3—C2—H21 | 105.7 | N9—C11—H112 | 107.7 |
| C10—C2—H21 | 108.5 | C12—C11—H112 | 107.5 |
| C2—C3—O4 | 111.2 (3) | H111—C11—H112 | 108.3 |
| C2—C3—C7 | 111.2 (3) | C11—C12—C13 | 122.8 (3) |
| O4—C3—C7 | 103.2 (2) | C11—C12—C17 | 118.9 (3) |
| C2—C3—H31 | 110.1 | C13—C12—C17 | 118.3 (3) |
| O4—C3—H31 | 110.8 | C12—C13—C14 | 121.0 (3) |
| C7—C3—H31 | 110.2 | C12—C13—H131 | 120.0 |
| C3—O4—C5 | 106.3 (2) | C14—C13—H131 | 119.0 |
| O4—C5—O6 | 104.4 (2) | C13—C14—C15 | 120.1 (3) |
| O4—C5—C20 | 108.5 (3) | C13—C14—H141 | 120.1 |
| O6—C5—C20 | 108.5 (3) | C15—C14—H141 | 119.8 |
| O4—C5—C21 | 111.7 (3) | C14—C15—C16 | 119.5 (3) |
| O6—C5—C21 | 109.6 (3) | C14—C15—H151 | 120.5 |
| C20—C5—C21 | 113.7 (3) | C16—C15—H151 | 120.0 |
| C5—O6—C7 | 109.0 (2) | C15—C16—C17 | 120.2 (3) |
| C3—C7—O6 | 104.7 (2) | C15—C16—H161 | 119.3 |
| C3—C7—C8 | 113.3 (3) | C17—C16—H161 | 120.5 |
| O6—C7—C8 | 108.0 (3) | C12—C17—C16 | 120.8 (3) |
| C3—C7—H71 | 110.3 | C12—C17—H171 | 118.8 |
| O6—C7—H71 | 109.0 | C16—C17—H171 | 120.4 |
| C8—C7—H71 | 111.2 | C8—C18—N19 | 177.5 (4) |

| | | | |
|---|---|---|---|
| C7—C8—N9 | 110.3 (3) | C5—C20—H201 | 109.6 |
| C7—C8—C18 | 110.5 (3) | C5—C20—H202 | 110.1 |
| N9—C8—C18 | 112.7 (3) | H201—C20—H202 | 108.1 |
| C7—C8—H81 | 107.3 | C5—C20—H203 | 109.5 |
| N9—C8—H81 | 108.5 | H201—C20—H203 | 109.0 |
| C18—C8—H81 | 107.4 | H202—C20—H203 | 110.5 |
| C8—N9—C10 | 113.3 (3) | C5—C21—H212 | 110.0 |
| C8—N9—C11 | 113.8 (3) | C5—C21—H213 | 111.0 |
| C10—N9—C11 | 109.9 (2) | H212—C21—H213 | 108.7 |
| C2—C10—N9 | 113.6 (3) | C5—C21—H211 | 108.9 |
| C2—C10—H101 | 108.2 | H212—C21—H211 | 109.5 |
| N9—C10—H101 | 109.8 | H213—C21—H211 | 108.8 |
| C2—C10—H102 | 106.8 | | |

Hydrogen-bond geometry (Å, °)

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| O1—H11···O6$^{i}$ | 0.86 | 2.05 | 2.850 (5) | 153 (1) |

Symmetry codes: (i) −*x*+1, *y*−1/2, −*z*+1/2.

## Refinement

In the absence of significant anomalous scattering, Friedel pairs were merged and the absolute configuration was arbitrarily assigned from the starting material.

The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C—H in the range 0.93–0.98, O—H = 0.82 Å) and $U_{iso}$(H) (in the range 1.2–1.5 times $U_{eq}$ of the parent atom), after which the positions were refined with riding constraints (Cooper *et al.*, 2010).

## Computing details

Data collection: COLLECT (Nonius, 2001).; cell refinement: DENZO/SCALEPACK (Otwinowski & Minor, 1997); data reduction: DENZO/SCALEPACK (Otwinowski & Minor, 1997); program(s) used to solve structure: SIR92 (Altomare *et al.*, 1994); program(s) used to refine structure: CRYSTALS (Betteridge *et al.*, 2003); molecular graphics: CAMERON (Watkin *et al.*, 1996); software used to prepare material for publication: CRYSTALS.

## References

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435-435.

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487–1487.

Cooper, *R*. I., Thompson, A. *L*. & Watkin, D. J. (2010). J. Appl. Cryst. 43, 1100–1107.

Cosier, J. & Glazer, A·*M*., 1986. J. Appl. Cryst. 105–107.

Nonius (2001). *COLLECT*. Nonius BV, Delft, The Netherlands.

Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.

Prince, E. Mathematical Techniques in Crystallography and Materials Science Springer-Verlag, New York, 1982.

Watkin, D. J. (1994). *Acta Cryst.* A**50**, 411–437.

Watkin, D. J., Prout, C. K. & Pearce, L. J. (1996). *CAMERON*, Chemical Crystallography Laboratory, Oxford, UK.

# Appendix 2: publications arising from this thesis

## Chapter 2

Glawar, A. F. G.; Best, D.; Ayers, B. J.; Miyauchi, S.; Nakagawa, S.; Aguilar-Moncayo, M.; García Fernández, J. M.; Ortiz Mellet, C.; Crabtree, E. V.; Butters, T. D.; Wilson, F. X.; Kato, A.; Fleet, G. W. J. *Chem. Eur J.* **2012**, *18*, 9341-9359.

Ayers, B. J.; Ngo, N.; Jenkinson, S. F.; Martínez, R. F.; Shimada, Y.; Adachi, I.; Weymouth-Wilson, A. C.; Kato, A.; Fleet, G. W. J. *J. Org. Chem*. **2012**, *7777*, 7777-7792.

## Chapter 3

Ayers, B. J.; Jenkinson, S. F.; Fleet, G. W. J.; Thompson, A. L. *Acta Cryst. E*, **2012**, *68*, o1474.

CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201200110

# Scalable Syntheses of Both Enantiomers of DNJNAc and DGJNAc from Glucuronolactone: The Effect of *N*-Alkylation on Hexosaminidase Inhibition

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**Abstract:** The efficient scalable syntheses of 2-acetamido-1,2-dideoxy-D-*galacto*-nojirimycin (DGJNAc) and 2-acetamido-1,2-dideoxy-D-*gluco*-nojirimycin (DNJNAc) from D-glucuronolactone, as well as of their enantiomers from L-glucuronolactone, are reported. The evaluation of both enantiomers of DNJNAc and DGJNAc, along with their *N*-alkyl derivatives, as glycosidase inhibitors showed that DGJNAc and its *N*-alkyl derivatives were all inhibitors of α-GalNAcase but that none of the epimeric DNJNAc derivatives inhibited this enzyme. In contrast, both DGJNAc and DNJNAc, as well as their alkyl derivatives, were potent inhibitors of β-GlcNAcases and β-GalNAcases. Neither of the L-enantiomers showed any significant inhibition of any of the enzymes tested. Correlation of the in vitro inhibition with the cellular data, by using a free oligosaccharide analysis of the lysosomal enzyme inhibition, revealed the following structure–property relationship: hydrophobic side-chains preferentially promoted the intracellular access of iminosugars to those inhibitors with more-hydrophilic side-chain characteristics.

**Keywords:** carbohydrates · cell penetration · inhibitors · iminosugars · oligosaccharides

## Introduction

Although there are many naturally occurring hydroxylated piperidines that are related to sugars in which the oxygen atom of the pyranose ring has been replaced by a nitrogen atom,[1] neither DGJNAc (2-acetamido-1,2-dideoxy-D-*galacto*-nojirimycin, **1D**) nor DNJNAc (2-acetamido-1,2-dideoxy-D-*gluco*-nojirimycin, **2D**), which are analogues of GalNAc and GlcNAc, respectively, have yet been isolated as natural products (Figure 1). Nagstatin (**3**),[2] which is isolated from the fermentation broth of *Streptomyces amakusaensis* MG846-fF3,[3] and pochonicine (**4**),[4] which is isolated from *Pochonia suchlasporia* var. *suchlasporia* TAMA 87, are potent inhibitors of β-hexosaminidases but show no inhibition of α-GalNAcases. Although synthetic piperidines are common,[5] LABNAc (2-acetamido-1,4-imino-1,2,4-trideoxy-

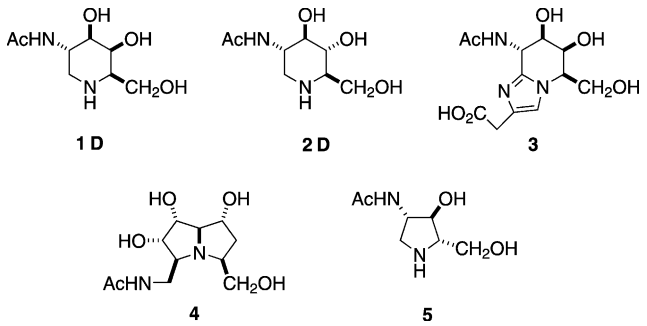


Figure 1. Hexosaminidase inhibitors.

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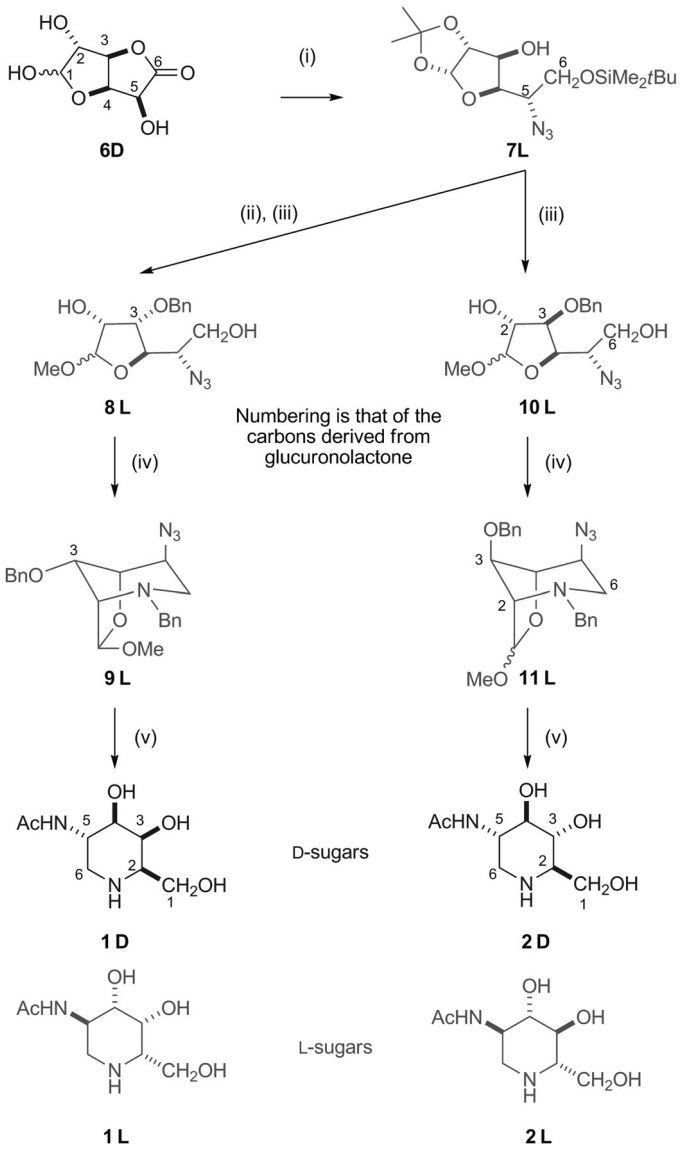
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201200110.

L-arabinitol, **5**) is a rare example of a pyrrolidine hexosaminidase inhibitor[6] that has promise as a chaperone in Sandhoff[7] and Tay–Sachs diseases.[8] The interest in selective inhibitors of hexosaminidases is due to their potential use in the chemotherapy of a wide range of diseases,[9] including *O*-GlcNAcase inhibition[10] and cancer metastasis.[11] DGJNAc is rare example of a potent inhibitor of α-GalNAcases.[12] Specific α-GalNAcase inhibition is of interest in the studies of Schindler–Kanzaki disease,[13] the treatment of cancer by the protection of macrophage-activating factor,[14] and the modification of a number of pathogens by the inhibition of *endo*-GalNAcases.[15] DNJNAc[16] and its *N*-alkyl derivatives[17] are highly potent and specific inhibitors of β-hexosaminidases but show no significant inhibition of α-GalNAcases. Herein, we report scalable syntheses of DGJNAc (**1D**) and DNJNAc (**2D**) from D-glucuronolactone (**6D**), as well as of their enantiomers (**1L** and **2L**, respectively) from L-glucuronolactone (**6L**), which is readily available from D-glucoheptonolactone.[18] A comparison of the inhibition profiles of both enantiomers of compounds **1** and **2**, together with a number of *N*-alkyl derivatives, is reported; the alkylation of DGJNAc (**1D**) decreases the inhibition of α-GalNAcases but not of β-hexosaminidases. The cellular lysosomal inhibition of β-hexosaminidases by compounds **1D**, **1Da**–**1Dc**, and **1De** by using protein-derived carbohydrate analysis was performed, thereby revealing enhanced cellular penetration of hydrophobic side-chain derivatives.

## Results and Discussion

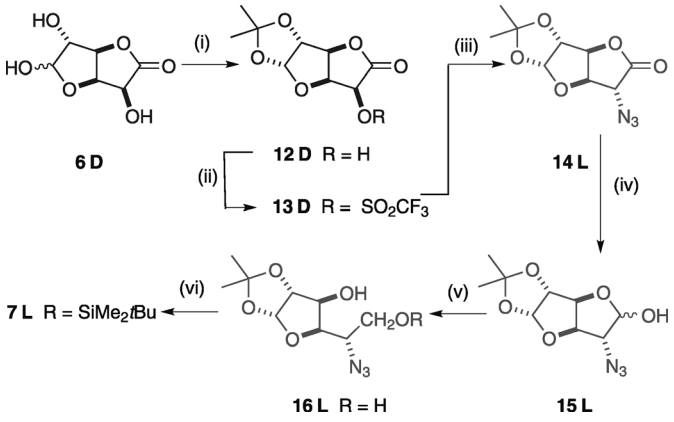
**Synthesis**: D-Glucuronolactone (**6D**) has been used for the efficient synthesis of many iminosugars and amino acids, wherein a nitrogen moiety is introduced at the C5 position and then joined to the C1 atom to form the nitrogen center in the piperidine ring.[19] For the preparation of both DGJNAc (**1D**) and DNJNAc (**2D**) from D-glucuronolactone (**6D**, Scheme 1): i) an azide group was introduced with inversion of the configuration at the C5 position as a precursor to the exocyclic acetamido group. Sequential reduction of the lactone at the C6 position and protection of the C6 primary alcohol gave silyl ether **7L** as a divergent intermediate. For the synthesis of DGJNAc (**1D**): ii) inversion of the configuration at the C3 position was necessary. iii) Protection as the benzyl ether and subsequent change in the protecting groups gave diol **8L**. iv) Activation of diol **8L** allowed double nucleophilic displacement of the leaving groups on the C2 and C6 positions by benzylamine to form the bicyclic piperidine (**9L**). v) Subsequent functional-group manipulation gave DGJNAc (**1D**). Performing analogous transformations (iii), (iv), and (v) without inversion of the C3 OH group in compound **7L** afforded access to DNJNAc (**2D**). The enantiomers (**1L** and **2L**, respectively) were prepared in an identical manner from L-glucuronolactone (**6L**); L-enantiomers of many iminosugars have surprising biological activities compared to their D-natural analogues.[8,20]



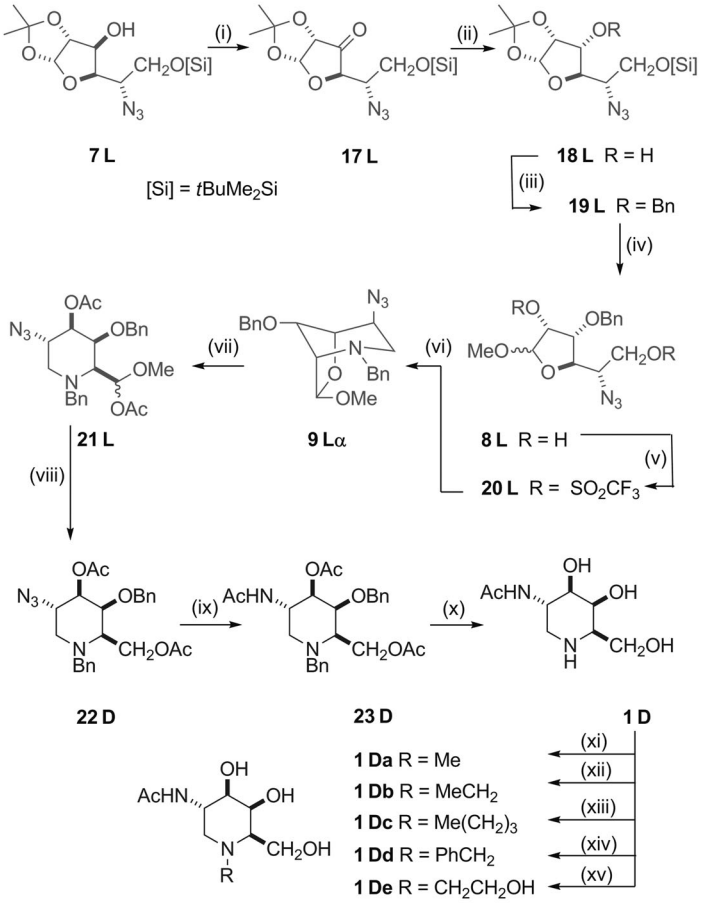

Scheme 1. (i) Introduction of a N atom with inversion of the stereochemistry at the C5 position and reduction of the C6 atom; (ii) inversion of the stereochemistry at the C3 position; (iii) protection of the oxygen atom at the C3 position; (iv) ring-closure between the C2 and C6 positions; (v) functional-group manipulation.

The synthesis of the divergent silyl ether in the D-series (**7L**) is shown in Scheme 2. D-Glucuronolactone (**6D**) was condensed with acetone in the presence of concentrated sulfuric acid to give the known acetonide (**12D**) in 90% yield. Esterification of the free alcohol group at the C5 position in compound **12D** with trifluoromethanesulfonic (triflic) anhydride in $CH_2Cl_2$ in the presence of pyridine gave the corresponding triflate (**13D**), which, on treatment with sodium azide in DMF, afforded azide **14L** with inversion of the configuration at the C5 position (92% yield). Compound **14L** was very sensitive to base, such that direct reduction with sodium borohydride gave a very low yield of the required diol (**16L**). A two-step procedure was much more efficient: initial reduction of lactone **14L** with diisobutylaluminum hy-




Scheme 2. (i) $Me_2CO$, conc. $H_2SO_4$, 90%; (ii) $(CF_3SO_2)_2O$, $CH_2Cl_2$, pyridine; (iii) $NaN_3$, DMF, 92% over two steps; (iv) DIBAL-H, $CH_2Cl_2$, 84%; (v) $NaBH_4$, MeOH, 90%; (vi) *t*$BuMe_2SiCl$, pyridine, 88%.




Scheme 3. (i) PCC, $CH_2Cl_2$, molecular sieves, 81%; (ii) $NaBH_4$, EtOH, $H_2O$, 91%; (iii) $PhCH_2Br$, NaH, DMF, 89%; (iv) AcCl, MeOH, 93%; (v) $(CF_3SO_2)_2O$, $CH_2Cl_2$, pyridine; (vi) $PhCH_2NH_2$, THF, 69% from **8L**; (vii) $Et_2O{\cdot}BF_3$, $Ac_2O$, 97%; (viii) DIBAL-H, $CH_2Cl_2$; then $NaBH_4$, MeOH; then $Ac_2O$, pyridine, 72% from **21L**; (ix) Zn, $CuSO_4$ (aq), THF/AcOH/$Ac_2O$ 3:2:1, 91%; (x) MeONa, MeOH; then $H_2$, Pd/C (10%), HCl, 1,4-dioxane, $H_2O$, 99%; (xi) HCHO, $H_2$, Pd/C (10%), 1,4-dioxane, $H_2O$, 100%; (xii) MeCHO, $H_2$, Pd/C (10%), EtOH, 100%; (xiii) $MeCH_2CH_2CHO$, $NaBH_3CN$, AcOH, EtOH, 100%; (xiv) PhCHO, $NaBH_3CN$, AcOH, EtOH, 68%; (xv) $HOCH_2CHO$, $H_2$, Pd/C (10%), 1,4-dioxane, $H_2O$, 95%.

dride (DIBAL-H) in $CH_2Cl_2$ gave lactol **15L** (84% yield), which, on treatment with sodium borohydride in MeOH, provided compound **16L** in 90% yield. Selective protection of the primary alcohol in compound **16L** with *tert*-butyldimethylsilyl chloride in pyridine afforded silyl ether **7L** (88% yield). Over 30 g of this key intermediate was prepared in one batch and 55% overall yield from D-glucuronolactone. The corresponding enantiomer (**7D**) was also prepared in an identical manner starting from L-glucuronolactone (**6L**).

The synthesis of DGJNAc (**1D**) required the inversion of the configuration of the alcohol at the C3 position in compound **7L**. Oxidation of compound **7L** with pyridinium chlorochromate (PCC) in $CH_2Cl_2$ in the presence of molecular sieves gave ketone **17L** (81% yield), which, on treatment with sodium borohydride in aqueous EtOH, underwent a highly diastereoselective reduction to give the more-hindered alcohol (**18L**) in 91% yield (Scheme 3). Treatment of compound **18L** with benzyl bromide and sodium hydride in DMF afforded the completely protected azide (**19L**, 89%). Treatment of compound **19L** with HCl in MeOH caused the concomitant removal of the silyl ether and the acetonide protecting groups to form an anomeric mixture of methyl furanosides **8L** (93% yield; α/β ratio: 7:1), which contained unprotected alcohol functionalities at the C2 and C6 positions. Esterification of both OH groups in compounds **8L** with triflic anhydride in $CH_2Cl_2$ in the presence of pyridine gave stable ditriflate **20L**. Reaction of ditriflate **20L** with benzylamine in THF proceeded in a stepwise manner (as inferred by monitoring the reaction by TLC) that probably involved initial nucleophilic substitution of the more reactive primary triflate group. Only the major α-anomer underwent subsequent displacement of the secondary triflate group at the C2 position to afford bicyclic piperidine **9Lα** (69% from **8L**), whilst the minor anomer remained unreacted.

All attempts to hydrolyze methyl furanoside **9Lα** by acid treatment were unsuccessful, instead leading to complex mixtures. Alternatively, acetolysis of compound **9Lα** could be achieved by conducting the reaction with over one equivalent of boron trifluoride etherate in acetic anhydride, thereby leading to a mixture of the acetylated hemiacetals (**21L**, 97% yield); the first equivalent of the Lewis acid was needed to complex the amine, thereby allowing subsequent catalytic acetolysis of the glycosidic bond. A two-step reduction of compound **21L** by sequential treatment with DIBAL-H and sodium borohydride in MeOH gave the corresponding diol, which was transformed into diacetate **22D** by conventional acetylation with acetic anhydride in pyridine (72% yield). Reduction of azide **22D** with zinc in a mixture of THF/acetic-acid/acetic-anhydride in the presence of aqueous copper(II) sulfate[21] produced di-*O*-acetylated acetamide **23D** in 91% yield. Selective removal of the acetate esters in compound **23D** with sodium methoxide in MeOH, followed by hydrogenolysis of the benzyl protecting groups in the presence of 10% palladium/HCl, gave the

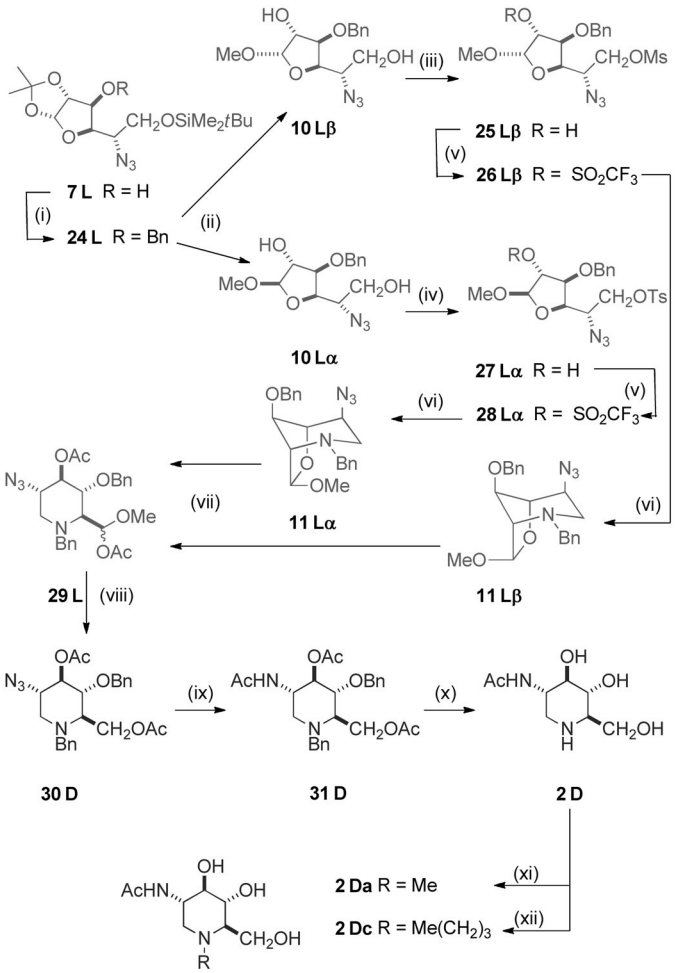
target iminosugar DGJNAc (**1D**) in 99% yield, which corresponded to an overall yield of 27% from silyl ether **7L**. This procedure was suitable for the synthesis of DGJNAc (**1D**) on a multigram scale in 15% yield from D-glucuronolactone (**6D**); the enantiomer L-DGJNAc (**1L**) was made by a similar sequence from L-glucuronolactone (**6L**, Scheme 3).

A series of *N*-alkylated derivatives of compound **1D** was prepared to determine the effect on hexosaminidase inhibition. Reductive amination of compound **1D** by hydrogenation with formaldehyde and glycoaldehyde in 1,4-dioxane/$H_2O$ (1:1) in the presence of palladium gave *N*-methyl-DGJNAc (**1Da**) and *N*-(2-hydroxyethyl)-DGJNAc (**1De**) in yields of 100% and 95%, respectively. Hydrogenation of compound **1D** in EtOH in the presence of ethanal and palladium formed *N*-ethyl-DGJNAc (**1Db**) in 100% yield. Treatment of compound **1D** in EtOH with butyraldehyde and benzaldehyde in the presence of sodium cyanoborohydride gave the *N*-butyl- (**1Dc**) and *N*-benzyl analogues (**1Dd**) in yields of 100% and 68%, respectively.

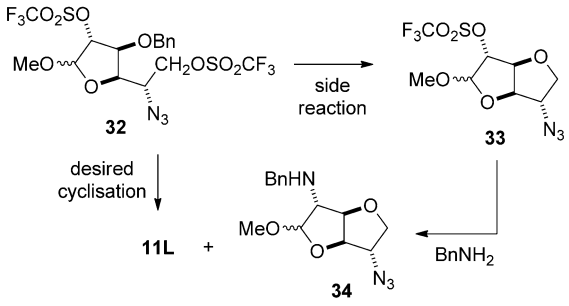
For the synthesis of DNJNAc (**2D**), silyl ether **7L** was first treated with benzyl bromide and sodium hydride in DMF to give the benzyl ether derivative (**24L**, 100%), which, on treatment with HCl in MeOH, afforded an easily separable mixture of approximately equal amounts of furanoside anomers **10Lβ** (48%) and **10Lα** (43%, Scheme 4).

Treatment of anomers **10Lα** or **10Lβ** with triflic anhydride in $CH_2Cl_2$ in the presence of pyridine gave ditriflate **32**, which was found to be much less stable than its C3 epimer (**20L**). The benzyl ether at the C3 position, which was in a *cis* disposition with respect to the primary triflate at the C6 position in compound **32**, spontaneously began to form 3,6-anhydro derivative **33** (Scheme 5); subsequent treatment with benzylamine in the next step gave monoamine **34**, which was not readily separable from the required bicycle (**11L**). All attempts to generate the 2,6-di-*O*-trifyl ester and react it in situ with benzylamine for the isolation of compound **11L** in good yield were unsuccessful. Replacing the triflyl groups by methanesulfonyl (mesyl) groups led to a stable disulfonate ester; however, following displacement at the C6 position with benzylamine, the compound was insufficiently reactive at the C2 position to allow ring closure. Therefore, it was necessary to introduce a less-reactive leaving group at the C6 position to suppress the formation of a 3,6-anhydro derivative whilst keeping a reactive triflate at the C2 position to facilitate ring closure.

In the case of the β-anomer (**10Lβ**), reaction with mesyl chloride in $CH_2Cl_2$ in the presence of 2,4,6-collidine allowed selective esterification of the primary alcohol group to produce the corresponding monomesylate (**25Lβ**, 86% yield; Scheme 4). Subsequent activation of the secondary alcohol in compound **25Lβ** by reaction with triflic anhydride formed mixed disulfonate **26Lβ**, which, on treatment with benzylamine, gave the bicyclic piperidine (**11Lβ**) in 70% yield. The α-anomer (**10Lα**) did not undergo selective mesylation under the above conditions. However, the reaction of compound **10Lα** with *p*-toluenesulfonyl (tosyl) chloride afforded the primary tosylate (**27Lα**) in satisfactory yield (74%).




Scheme 4. (i) $PhCH_2Br$, NaH, DMF, 100%; (ii) AcCl, MeOH, 48% **10Lβ**, 43% **10Lα**; (iii) $MeSO_2Cl$, 2,4,6-collidine, $CH_2Cl_2$, 86%; (iv) TsCl, 2,4,6-collidine, $CH_2Cl_2$, 74%; Ts = 4-toluenesulfonyl; (v) $(CF_3SO_2)_2O$, $CH_2Cl_2$, pyridine; (vi) $PhCH_2NH_2$, THF, 70% from **25Lβ**, 68% from **27Lα**; (vii) $Et_2O{\cdot}BF_3$, $Ac_2O$, 75% from **11Lβ**, 71% from **11Lα**; (viii) DIBAL-H, $CH_2Cl_2$, pyridine; then $NaBH_4$, MeOH; then $Ac_2O$, pyridine, 78%; (ix) Zn, $CuSO_4$ (aq), THF/AcOH/$Ac_2O$ 3:2:1, 79%; (x) MeONa, MeOH; then $H_2$, Pd/C (10%), HCl, 1,4-dioxane, $H_2O$, 94%; (xi) HCHO, $H_2$, Pd/C (10%), $H_2O$, 94%; (xii) $MeCH_2CH_2CHO$, $H_2$, Pd/C (10%), 1,4-dioxane, $H_2O$, 96%.




Scheme 5. Unwanted formation of THF.

Esterification of compound **27Lα** with triflic anhydride formed the triflate (**28Lα**), which underwent double nucleo-

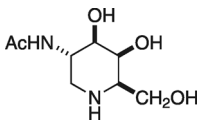
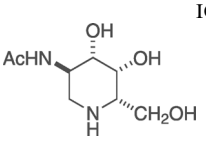
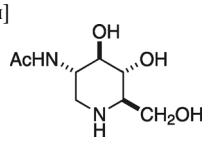
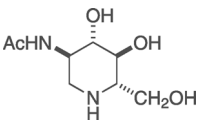
philic displacement with benzylamine to give the fully protected piperidine (**11Lα**, 68%). Acetolysis of bicyclic amines **11Lα** and **11Lβ** with boron trifluoride etherate in acetic anhydride led to the same epimeric mixture of the diacetates (**29L**) in 71% and 75% yield, respectively. A two-step reduction of compound **29L** by sequential treatment with DIBAL-H and sodium borohydride in MeOH, followed by acetylation with acetic anhydride in pyridine, gave the diacetate (**30D**) in 78% yield. Reductive acetylation of the azide group in compound **30D** with zinc/copper-sulfate in THF/acetic-acid/acetic-anhydride provided amide **31D** (79% yield), which, on deprotection by conventional catalytic transesterification and hydrogenolysis, formed DNJNAc (**2D**) in 94% yield. Enantiomer L-DNJNAc (**2L**) was prepared in a similar sequence from L-glucuronolactone (**6L**). Reductive alkylation of compound **2D** by hydrogenation with formaldehyde in water and butyraldehyde in aqueous 1,4-dioxane gave *N*-methyl-DNJNAc (**2Da**, 94%) and *N*-butyl-DNJNAc (**2Dc**, 96%), respectively.

**Biological evaluation**: Both enantiomers of DGJNAc and DNJNAc, as well as their *N*-alkyl derivatives, were tested in vitro for their glycosidase-inhibiting potential against the following enzymes: β-*N*-acetyl-glucosaminidase (β-GlcNAcase), β-*N*-acetyl-galactosaminidase (β-GalNAcase), and α-*N*-acetyl-galactosaminidase (α-GalNAcase; Tables 1–3); the influence of DGJNAc (**1D**) and its derivatives **1Da**, **1Db**, **1Dc**, and **1De** on lysosomal glycosidase inhibition was investigated by using a free oligosaccharide (FOS) analysis in HL60 cells (Figure 2, Table 4). This set of glycosidases has been implicated in a range of pathological disorders. In cancer patients that carry pancreatic adenocarcinoma[22] or gliomas,[23] β-HexNAcase activity is elevated in the blood in comparison to healthy individuals. α-GalNAcase activity was identified as a biomarker for patients that suffer from melanoma.[14a] Furthermore, inhibitors of these enzymes could be employed to treat lysosomal-storage disorders, such as Tay–Sachs, Sandhoff, and Schindler–Kanzaki diseases, by improving mutant-enzyme activity through a chaperone-mediated pathway.[24] *N*-Butyl deoxynorjirimycin (*N*Bu-DNJ, Zavesca), which is structurally related to *N*-butyl-DGJNAc (**1Dc**), has been approved for the treatment of the lysosomal-storage disorder Type 1 Gaucher disease by substrate-reduction therapy. The *N*-hydroxyethyl derivative of DNJ (Glyset, Miglitol), which is analogous to compound **1De**, is used for the treatment of non-insulin-dependent diabetes mellitus.

**Comparison of DGJNAc (1D) versus DNJNAc (2D)**: Table 1 shows the inhibitory data of the enantiomers of DGJNAc (**1**) and DNJNAc (**2**); the L-enantiomers of D-iminosugar competitive glycosidase inhibitors are often non-competitive inhibitors of the same enzyme.[25] The syntheses reported herein from the enantiomers of glucuronolactone ensured the enantiomeric purity of inhibitors **1** and **2**. Neither of the L-enantiomers (**1L** and **2L**) significantly inhibited any of the glycosidases at the highest concentration tested; L-DGJNAc (**1L**) showed very weak inhibition ($IC_{50}=830$ μM) of human placenta β-GlcNAcase. In contrast, both compounds **1D** and **2D** were good inhibitors of β-GlcNAcases, with the exception of enzyme from *Aspergillus oryzae*. Therefore, β-GlcNAcases were inhibited by both epimers at the C4 position with either gluco- or galacto-stereochemistry; the same was true for β-GalNAcase inhibition against the enzyme that was derived from HL60 cell lysate. These results suggested that the stereochemistry at the C4 OH group was not strictly distinguished by β-GalNAcases and β-GlcNAcases.

DGJNAc (**1D**) was a potent inhibitor of α-GalNAcase with an $IC_{50}$ value of 0.32 μM against chicken liver and a $K_i$ value of 0.17 μM against *Charonia lampas*.[12] None of the other three NH iminosugars (compounds **1L**, **2D**, or **2L**) significantly inhibited α-GalNAcase from chicken liver (Table 1).

Table 1. Concentrations of the iminosugars that give 50% inhibition of various glycosidases.

| | $IC_{50}$ [μM] | | | |
|---|---|---|---|---|
| |  |  |  |  |
| Enzyme<br>β-*N*-acetyl-glucosaminidase | DGJNAc (**1D**) | L-DGJNAc (**1L**) | DNJNAc (**2D**) | L-DNJNAc (**2L**) |
| human placenta | 8.3 | 830 | 7.0 | NI (31.2) |
| bovine kidney | 4.2 | NI (46.8) | 7.4 | NI (24.4) |
| *Aspergillus oryzae* | NI[a] (8.8)[b] | NI (0.8) | 891 | NI (0.7) |
| HL60 | 7.1 | NI (31.3) | 9.8 | NI (25.9) |
| jack beans | 1.8 | NI (46.3) | 2.9 | NI (28.8) |
| α-*N*-acetyl-galactosaminidase | | | | |
| chicken liver | 0.32 | NI (22.6) | NI (5.0) | NI (36.9) |
| β-*N*-acetyl-galactosaminidase | | | | |
| *Aspergillus oryzae* | NI (9.6) | NI (0) | 998 | NI (0) |
| HL60 | 23 | NI (12.9) | 17 | NI (14.8) |

[a] NI = No inhibition (less than 50% inhibition at 1000 μM). [b] Inhibition (%) at 1000 μM are given in parentheses.

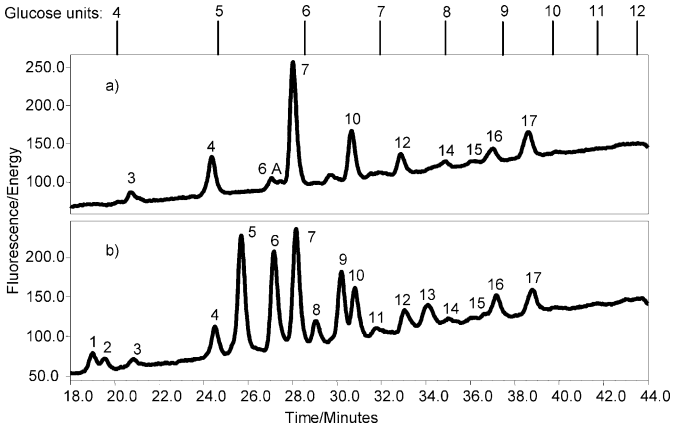



Figure 2. HL60 cells were homogenized and the FOS was extracted as described in the Experimental Section. After labeling with 2-AA, the FOS were separated by using HPLC. a) Control cells; b) cells that were treated with DGJNAc (**1D**, 500 μM). The peaks are numbered and their corresponding structures are given in Table 4.

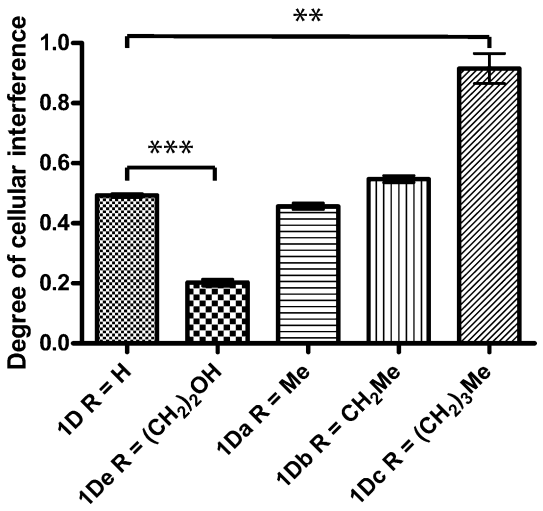


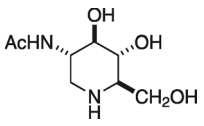
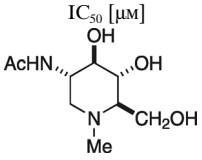
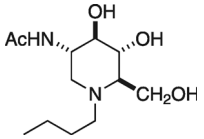

Figure 3. Ratio of the integration of peak 5 to the control peak 7 is shown for the derivatives of compound **1D** (50 μM). Because all of the derivatives have very comparable in vitro inhibition, the variation can be attributed to the differences in cell- and organelle penetration. To test for significance, a student t-test was performed (99% confidence interval).

***N*-Alkyl derivatives of DNJNAc (2D)**: The *N*-alkylated derivatives of DNJNAc **2D** (**2Da** and **2Dc**) showed similar inhibition of β-GlcNAcase or β-GalNAcase to that of the NH parent compound (Table 2). In general, *N*-alkylation of compound **2D** had little effect on enzyme inhibition, in contrast to the observed increased inhibition for the L-lysine-linked dansyl derivatives of DNJNAc that were generated by Steiner et al.;[17b] however, inhibition of the *Aspergillus oryzae* enzyme was significantly increased by alkylation, notably for *N*-methyl-DNJNAc (**2Da**). None of the derivatives of compound **2D** inhibited α-GalNAcase.

***N*-Alkyl derivatives of DGJNAc (1D)**: All of the derivatives of DGJNAc (**1D**) were good inhibitors of β-GlcNAcases (except for *Aspergillus oryzae*, Table 3), although *N*-benzyl-DGJNAc (**1Dd**) was significantly weaker. *N*-Ethyl- (**1Db**), *N*-benzyl- (**1Dd**), and *N*-hydroxyethyl-DGJNAc (**1De**) were all good inhibitors of α-GalNAcase that was derived from chicken liver. However, the methyl and butyl groups seemed to be less-well-tolerated by the same enzyme. This trend was reflected in the $K_i$ values against the enzyme that was derived from *Charonia lampas*, with the exception of the *N*-methyl derivative.

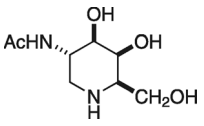
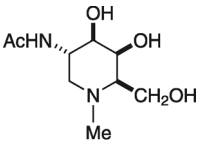
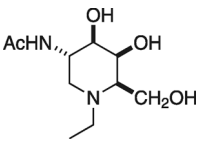
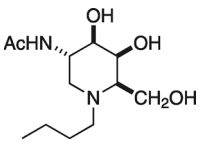
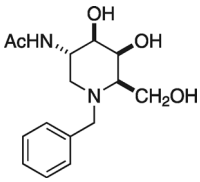
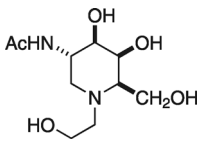
Free oligosaccharide (FOS) analysis[26] was performed on HL60 cells after treatment for 24 h with the *N*-alkyl derivatives of DGJNAc (**1Da**, **1Db**, **1Dc**, and **1De**), which gave additional free glycans (FOS) in the HPLC profiles that were derived from HL60 homogenates (Figure 2b) in comparison to the untreated control reactions (Figure 2a). Subsequent treatment of these FOSs with jack bean β-GlcNAcase identified the newly produced glycans as non-reducing

Table 2. Concentrations of DNJNAc and its *N*-alkyl derivatives that give 50% inhibition of various glycosidases.

| | | $IC_{50}$ [μM] | |
|---|---|---|---|
| |  |  |  |
| Enzyme | DNJNAc (**2D**) | *N*-Me-DNJNAc (**2Da**) | *N*-Bu-DNJNAc (**2Dc**) |
| β-*N*-acetyl-glucosaminidase | | | |
| human placenta | 7.0 | 18 | 10 |
| bovine kidney | 7.4 | 12 | 8.1 |
| *Aspergillus oryzae* | 891 | 225 | 478 |
| HL60 | 9.8 | 22 | 16 |
| jack beans | 2.9 | 17 | 24 |
| α-*N*-acetyl-galactosaminidase | | | |
| chicken liver | NI[a] (5.0)[b] | NI (0.8) | NI (9.6) |
| β-*N*-acetyl-galactosaminidase | | | |
| *Aspergillus oryzae* | 998 | 167 | 381 |
| HL60 | 17 | 74 | 62 |

[a] NI = No inhibition (less than 50% inhibition at 1000 μM). [b] Inhibition (%) at 1000 μM are given in parentheses.

Table 3. Concentrations of DGJNAc and its *N*-alkyl derivatives that give 50% inhibition of various glycosidases.

| | $IC_{50}$ [μM] | | | | | |
|---|---|---|---|---|---|---|
| |  |  |  |  |  |  |
| Enzyme | DGJNAc (**1D**) | *N*-Me-DGJNAc (**1Da**) | *N*-Et-DGJNAc (**1Db**) | *N*-Bu-DGJNAc (**1Dc**) | *N*-Bn-DGJNAc (**1Dd**) | *N*-(2-Hydroxyethyl)-DGJNAc (**1De**) |
| β-*N*-acetyl-glucosaminidase | | | | | | |
| human placenta | 8.3 | 5.7 | 7.3 | 2.7 | 45 | 8.2 |
| bovine kidney | 4.2 | 2.1 | 3.1 | 1.2 | 40 | 3.7 |
| *Aspergillus oryzae* | NI[a] (8.8)[b] | NI (22.1) | NI (26.5) | NI (22.6) | NI (11.4) | NI (46.9) |
| HL60 | 7.1 | 5.4 | 7.9 | 1.7 | 52 | 8.3 |
| jack beans | 1.8 | 1.5 | 3.4 | 2.7 | 22 | 1.9 |
| α-*N*-acetyl-galactosaminidase | | | | | | |
| chicken liver | 0.32 | 107 | 5.6 | 166 | 11 | 6.3 |
| *Charonia lampas* | [0.17][c] | [0.97] | [7.9] | [148] | [14] | [3.9] |
| β-*N*-acetyl-galactosaminidase | | | | | | |
| *Aspergillus oryzae* | NI (9.6) | NI (29.4) | NI (26.3) | NI (29.8) | NI (5.8) | 926 |
| HL60 | 23 | 26 | 44 | 14 | 187 | 35 |

[a] NI = No inhibition (less than 50% inhibition at 1000 μM). [b] Inhibition (%) at 1000 μM are given in parentheses. [c] $K_i$ values are given in square brackets.

terminal GlcNAc-containing species; their identity was verified by comparison with the retention times in glucose units (GUs) reported by Boomkamp et al. (Table 4).[26] A structure of the glycans (peaks 8, 11, and 13) was proposed based on their retention times and the β-GlcNAcase-digestion results. The appearance of non-reducing terminal GlcNAc-containing glycans was dose-dependent for all of the inhibitors tested over the range 500 μM, 100 μM, and 50 μM; moreover, their appearance was due to inhibition of lysosomal β-HexNAcase, thus leading to incomplete degradation of the glycans.

Quantitative comparison of glycan 5 ($GlcNAc_2Man_3GlcNAc_1$) with control glycan 7 ($Man_5GlcNAc_1$) allowed an estimation of the degree of lysosomal β-GlcNAcase inhibition. At a concentration of 50 μM, the levels of inhibition that were displayed by the derivatives showed strong differences depending on the side-chain that was present on the inhibitor. Increasing the length of the alkyl side-chain in comparison to parent compound **1D** led to stronger inhibition in this cell-based assay, whilst the hydroxyethyl variant showed lower levels of inhibition (Figure 3). With the in vitro inhibition activity against β-GlcNAcase of all of the inhibitors being of comparable strength (HL60 data, Table 3), the apparent differences between the inhibition of lysosomal β-GlcNAcase in the cells could be attributed to differential penetration of the cells or organelles by the inhibitors. Accordingly, the *N*-butyl derivative (**1Dc**) was approximately 5-fold more-effective at inhibiting lysosomal β-GlcNAcase than the *N*-hydroxyethyl derivative (**1De**). This result correlated with the bio-distribution of two iminosugar inhibitors of DNJ that are already used clinically. Miglustat (Zavesca), the *N*-butyl derivative of DNJ, shows a volume of distribution ($V_D$) of 1.04–1.31 $L\,kg^{-1}$ (calculated for an 80 kg individual),[27] whilst Miglitol (Glyset), which is the *N*-hydroxyethyl derivative of DNJ, has a value of $V_D = 0.18\,L\,kg^{-1}$, which is 5.7–7.3-fold lower.[28] Therefore, whilst Miglustat is able to penetrate tissues beyond the bloodstream, Miglitol is primarily restricted to the extracellular fluid. Previous results have also demonstrated that the *N*-alk(en)yl derivatives ($C_4$, $C_9$, $C_{18}$) of DNJ are taken up by cells in less than 1 min.[29]

In the design of a potential therapeutic agent, a polar *N*-alkyl group, such as *N*-hydroxyethyl **1De**, on the ring nitrogen atom could restrict the iminosugar to the extracellular space, whilst a hydrophobic side-chain derivative, such as *N*-butyl, would assist in the cell-membrane-penetration of the inhibitor. Therefore, the correlation of the in vitro data with those in cells could be used to estimate how well the inhibitor is able to reach an intracellular therapeutic target. If the target is secreted into extracellular space, this method could be used to estimate the side-effects of intracellular enzyme inhibition. The iminosugar derivatives presented herein all showed this inhibition to some degree, albeit only at very non-physiological high concentrations of 50 μM (the maximum plasma concentration of Miglustat in a multiple dose regime is 12.7 μM; the maximum plasma concentration of Miglitol in a 100 mg oral dose is 8.4 μM).[30,31]

Table 4. Structures, number of glucose units (GUs), and percentage proportion of isolated FOS peaks from the control experiment and 500 μM DGJNAc-treated HL60 cells.[a]

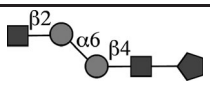
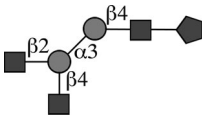
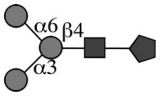
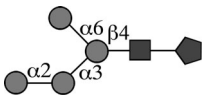
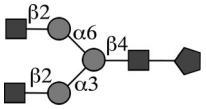
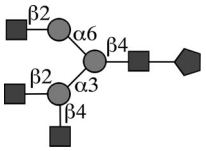
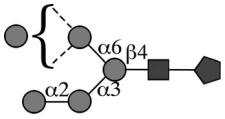
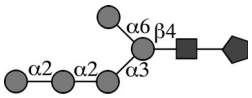
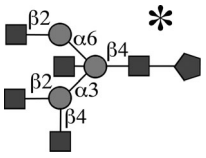
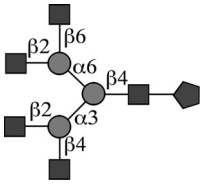
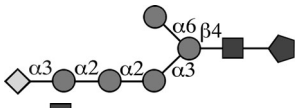
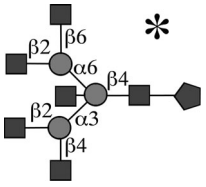
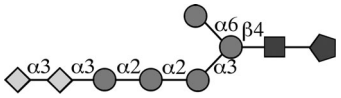
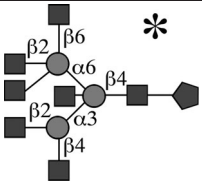
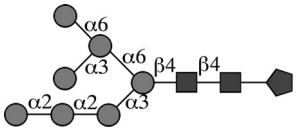
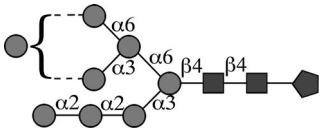
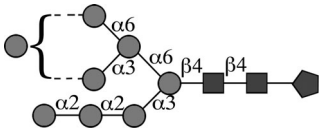
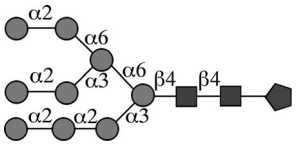
| ID | Untreated GUs | Treated GUs | Structure name | Structure | In control cells [%] | In treated cells [%] |
|---|---|---|---|---|---|---|
| 1 | – | 3.77 | $GlcNAc_1Man_2GlcNAc_1$ |  | – | 2.45(±0.10) |
| 2 | – | 3.88 | $GlcNAc_2Man_2GlcNAc_1$ |  | – | 1.62(±0.21) |
| 3 | 4.13 | 4.16 | $Man_3GlcNAc_1$ |  | 3.44(±1.16) | 1.66(±0.88) |
| 4 | 4.95 | 4.99 | $Man_4GlcNAc_1$ |  | 14.37(±1.67) | 5.20(±0.93) |
| 5 | – | 5.28 | $GlcNAc_2Man_3GlcNAc_1$ |  | – | 17.98(±0.68) |
| 6 | – | 5.65 | $GlcNAc_3Man_3GlcNAc_1$ |  | – | 15.08(±0.11) |
| 6A | 5.62 | – | $Man_5GlcNAc_1$ |  | 4.22(±0.45) | – |
| 7 | 5.87 | 5.91 | $Man_5GlcNAc_1$ |  | 38.76(±1.06) | 16.81(±0.37) |
| 8 | – | 6.16 | $GlcNAc_4Man_3GlcNAc_1$ |  | – | 2.92(±0.29) |
| 9 | – | 6.49 | $GlcNAc_4Man_3GlcNAc_1$ |  | – | 10.00(±0.24) |
| 10 | 6.62 | 6.67 | $Glc_1Man_5GlcNAc_1$ |  | 14.92(±0.13) | 7.37(±0.36) |
| 11 | – | 6.96 | $GlcNAc_5Man_3GlcNAc_1$ |  | – | 1.35(±0.16) |
| 12 | 7.31 | 7.37 | $Glc_2Man_5GlcNAc_1$ |  | 6.17(±0.35) | 3.24(±0.57) |

Table 4. (Continued)

| ID | Untreated GUs | Treated GUs | Structure name | Structure | In control cells [%] | In treated cells [%] |
|---|---|---|---|---|---|---|
| 13 | – | 7.73 | $GlcNAc_6Man_3GlcNAc_1$ |  | – | 4.51(±0.12) |
| 14 | 7.99 | 8.04 | $Man_7GlcNAc_2$ |  | 2.25(±0.81) | 0.88(±0.20) |
| 15 | 8.47 | 8.42 | $Man_8GlcNAc_2$ |  | 1.25(±0.12) | 1.03(±0.60) |
| 16 | 8.79 | 8.87 | $Man_8GlcNAc_2$ |  | 5.39(±0.58) | 3.88(±0.29) |
| 17 | 9.46 | 9.55 | $Man_9GlcNAc_2$ |  | 9.24(±0.54) | 4.05(±0.23) |

[a] The peak IDs correspond to the labels in Figure 2. The mean values were each taken from three independent measurements (±S.D.). The species were assigned in reference to the GU units in ref. [26]. The labels are as follows:

◇ Glucose ● Mannose ⬟ 2-aminobenzoic acid ■ *N*-acetylglucosamine ✻ Proposed structure

## Conclusion

This paper describes efficient scalable syntheses of both enantiomers of DGJNAc (**1**) and DNJNAc (**2**) from glucuronolactone, thereby allowing easy access to this class of hexosaminidase inhibitor. DGJNAc (**1D**) and its *N*-alkyl derivatives (**1Da**–**1De**) were all inhibitors of α-GalNAcase but none of the epimeric DNJNAc (**2**) derivatives inhibited the same enzyme. In contrast, both DGJNAc (**1D**) and DNJNAc (**2D**), as well as their alkyl derivatives, were potent inhibitors of β-hexosaminidases. Neither of their enantiomers (**1L** and **2L**, respectively) showed any significant inhibition against this enzyme. The correlation of the in vitro inhibition data against β-GlcNAcase with the cellular lysosomal inhibition data of this enzyme by using protein-derived carbohydrate analysis revealed a side-chain-dependent variation in cell- and organelle penetration. Hydrophobic side-chains of increasing length promote cellular uptake whilst hydrophilic variants restrict access of the inhibitor to intracellular organelles.

## Experimental Section

All commercial reagents were used as supplied. Dry pyridine and DMF were purchased from Aldrich in Sure-Seal™ bottles. All other solvents were used as supplied (analytical or HPLC grade). The reactions that were performed under an atmosphere of argon or hydrogen were maintained by an inflated balloon. All water sensitive reactions were performed under an inert atmosphere of argon/nitrogen unless otherwise stated. All solutions are saturated unless otherwise stated. Thin layer chromatography (TLC) analysis was performed on aluminum sheets (Merck) that were coated with 60 $F_{254}$ silica. The sheets were either visualized by using a dip of 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid or potassium permanganate (0.5% in 1 M NaOH). Flash chromatography was either performed on Sorbsil C60 40/60 silica or Merck grade 9385, 230–400 mesh, 60 Å. Where chromatographic techniques that involve triethylamine-containing mobile phases were employed, silica was doped with triethylamine before use. Melting points were recorded on a Kofler hot block and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g 100 $mL^{-1}$. IR spectra were recorded on a Bruker Tensor 27 FTIR spectrophotometer by using thin films on either NaCl or Ge plates. Only the characteristic peaks are quoted. NMR spectra were record on a Bruker AMX500 ($^1H$: 500 MHz and $^{13}C$: 125.7 MHz) or on a Bruker AV400 spectrometer ($^1H$: 400.2 MHz and $^{13}C$: 100.6 MHz) in the stated deuterated solvent. Chemical shifts ($\delta$) are quoted in ppm and coupling constants ($J$) are given in Hz. Residual signals from the solvents were used as an internal reference. MeCN or MeOH were used as an internal reference when $D_2O$ was used as the solvent. MS (ESI) was recorded on a Micromass LCT spectrometer. HRMS (ESI) was performed on a Bruker MicroTof (resolution = 10000 FWHM). Assays for the inhibition of glycosidases were performed according to literature procedures.[32]

**Synthesis of divergent protected silyl ether 7**

*1,2-O-Isopropylidene-α-D-glucurono-3,6-lactone* (***12D***): D-Glucurono-3,6-lactone (**6D**, 30.0 g, 170 mmol) was dissolved in acetone (250 mL) and

concentrated sulfuric acid (8.3 mL). The mixture was stirred at RT for 4 h, after which time TLC analysis (EtOAc) indicated the complete consumption of the starting material ($R_f$ = 0.40, streaks to baseline) and the formation of a major product ($R_f$ = 0.88). The reaction mixture was neutralized by the addition of solid sodium bicarbonate, filtered, and concentrated in vacuo. The crude residue was recrystallized (toluene) to afford acetonide **12D** as a white crystalline solid (33.0 g, 90%). M.p. 118–120°C (toluene) [lit. 120.5–121.5°C[19c] (toluene)]; $[\alpha]_D^{25}$ = +59.2 (*c* 2.00, $CHCl_3$) [lit. $[\alpha]_D^{20}$ = +52.5[19c] (*c* 1.95, $CHCl_3$)]; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 1.36, 1.53 (s, 2×3H; $C(CH_3)_2$), 3.02 (s, 1H; OH5), 4.53 (d, *J*(5,4) = 4.4 Hz, 1H; H5), 4.83 (d, *J*(2,1) = 3.4 Hz, 1H; H2), 4.84 (d, *J*(3,4) = 2.7 Hz, 1H; H3), 4.95 (dd, *J*(4,3) = 3.1 Hz, *J*(4,5) = 4.4 Hz, 1H; H4), 6.00 ppm (d, *J*(1,2) = 3.4 Hz, 1H; H1); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 26.5, 26.9 ($C(CH_3)_2$), 70.6 (C5), 78.1 (C4), 81.3 (C3), 82.9 (C2), 106.6 (C1), 113.6 ($C(CH_3)_2$), 173.7 ppm (C6); IR (thin film): $\tilde{\nu}$ = 1790 (s; C=O), 3441 $cm^{-1}$ (s; OH); LRMS (ESI+): *m*/*z* (%): 239 (54) $[M+Na]^+$, 271 (30) $[M+MeOH+Na]^+$, 455 $cm^{-1}$ (100) $[2M+Na]^+$; HRMS (ESI+): *m*/*z* calcd for $C_9H_{12}NaO_6$: 239.0526 $[M+Na]^+$; found: 239.0526.

For enantiomer **12L**: M.p. 117–119°C (toluene); $[\alpha]_D^{25}$ = −62.3 (*c* 2.00, $CHCl_3$).

*5-Azido-5-deoxy-1,2-O-isopropylidene-β-*L*-idurono-3,6-lactone* (***14L***): Trifluoromethanesulfonic anhydride (39.1 mL, 232 mmol) was added dropwise to a solution of lactone **12D** (38.65 g, 178.8 mmol) in $CH_2Cl_2$ (400 mL) and pyridine (43.4 mL, 536 mmol) at −40°C. The reaction mixture was stirred for 1 h at between −35°C and −25°C. After this time, TLC analysis (cyclohexane/EtOAc, 1:1) indicated the complete consumption of the starting material ($R_f$ = 0.32) and the formation of a major product ($R_f$ = 0.80). The reaction mixture was diluted with $CH_2Cl_2$ (150 mL), washed with 2M HCl (3×600 mL), and the organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford crude triflate **13D**. M.p. 160–162°C [lit. 160°C[19c] (EtOH)]; $[\alpha]_D^{25}$ = +55.1 (*c* 1.01, $CHCl_3$) [lit. $[\alpha]_D^{20}$ = +49.2[19c] (*c* 1.28, $CHCl_3$)]; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 1.37, 1.54 (s, 2×3H; $C(CH_3)_2$), 4.87 (d, *J*(2,1) = 3.6 Hz, 1H; H2), 4.94 (d, *J*(3,4) = 2.7 Hz, 1H; H3), 5.08 (dd, *J*(4,3) = 2.9 Hz, *J*(4,5) = 4.3 Hz, 1H; H4), 5.42 (d, *J*(5,4) = 4.3 Hz, 1H; H5), 6.06 ppm (d, *J*(1,2) = 3.6 Hz, 1H; H1).

Sodium azide (15.20 g, 232.4 mmol) was added in one portion to a solution of crude triflate **13D** in DMF (400 mL) at −30°C. After 90 min, TLC analysis (cyclohexane/EtOAc, 2:1) indicated the complete consumption of the starting material ($R_f$ = 0.58) and formation of a major product ($R_f$ = 0.72). The reaction mixture was partitioned between EtOAc (600 mL) and a water/sat. brine (4:1) solution (300 mL), separated, and the organic phase was washed with water/sat. brine (4:1, 2×300 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (cyclohexane/EtOAc, 5:1) to afford the azide (**14L**) as a white crystalline solid (39.7 g, 92%). M.p. 110–112°C [lit. 114–116°C];[19c] $[\alpha]_D^{25}$ = +240.1 (*c* 1.00, $CHCl_3$) [lit. $[\alpha]_D^{20}$ = +243[19c] (*c* 1.1, $CHCl_3$)]; $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 1.35, 1.51 (s, 2×3H; $C(CH_3)_2$), 4.24 (s, 1H; H5), 4.66 (d, *J*(4,3) = 3.1 Hz, 1H; H4), 4.84 (d, *J*(2,1) = 3.8 Hz, 1H; H2), 4.95 (d, *J*(3,4) = 3.1 Hz, 1H; H3), 5.94 ppm (d, *J*(1,2) = 3.8 Hz, 1H; H1); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 26.5, 27.0 ($C(CH_3)_2$), 61.2 (C5), 81.1 (C4), 81.8 (C2), 84.9 (C3), 106.2 (C1), 113.4 ($C(CH_3)_2$), 170.7 ppm (C6); IR (thin film): $\tilde{\nu}$ = 1792 (s; C=O), 2124 $cm^{-1}$ (s; $N_3$); LRMS (ESI+): *m*/*z* (%): 264 (25) $[M+Na]^+$, 296 (100) $[M+MeOH+Na]^+$, 328 (15) $[M+2MeOH+Na]^+$, 569 (85) $[2M+2MeOH+Na]^+$; (ESI−): 276 (100) $[M+^{35}Cl]^-$, 278 (40) $[M+^{37}Cl]^-$; HRMS (ESI+): *m*/*z* calcd for $C_{10}H_{15}N_3NaO_6$: 296.0853 $[M+MeOH+Na]^+$; found: 296.0855.

For enantiomer **14D**: M.p. 111–113°C; $[\alpha]_D^{25}$ = −213.5 (*c* 0.96, $CHCl_3$).

*5-Azido-5-deoxy-1,2-O-isopropylidene-β-*L*-ido-hexodialdo-1,4:3,6-difuranose* (***15L***): Diisobutylaluminum hydride (1.5M in toluene, 91.0 mL, 137 mmol) was added dropwise to a solution of azide **14L** (21.9 g, 90.8 mmol) in $CH_2Cl_2$ (200 mL) under an argon atmosphere at −78°C. The reaction mixture was stirred at this temperature for 90 min. After this time, TLC analysis (cyclohexane/EtOAc, 2:1) indicated the complete consumption of the starting material ($R_f$ = 0.72) and formation of two products (major $R_f$ = 0.40, minor $R_f$ = 0.39). A saturated solution of sodium potassium tartrate (500 mL) and $CH_2Cl_2$ (600 mL) were added and the reaction mixture was stirred vigorously at RT for 18 h. The organic phase was collected and the aqueous layer was extracted with $CH_2Cl_2$ (8×300 mL). The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford crude lactol **15L** as a pale-yellow crystalline solid (18.6 g, 84%) in a 2:3 (A/B) ratio of the anomers. This crude product was reacted on without further purification. M.p. 53–55°C; $[\alpha]_D^{25}$ = −21.4 (*c* 1.10, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 1.33 (s, 3H; $CH_3^B$), 1.35 (s, 3H; $CH_3^A$), 1.50 (s, 6H; $CH_3^A$ and $CH_3^B$), 3.45 (br s, 1H; $OH6^B$), 4.08 (s, 1H; $H5^A$), 4.08 (d, *J*(5,6) = 4.1 Hz, 1H; $H5^B$), 4.64 (d, *J*(2,1) = 3.8 Hz, 1H; $H2^B$), 4.72 (d, *J*(3,4) = 3.4 Hz, 1H; $H3^B$ or $H4^B$), 4.75 (app t, *J* = 3.1 Hz, 2H; $H2^A$, $H3^A$ or $H4^A$), 4.79 (d, *J*(3,4) = 3.8 Hz, 1H; $H3^B$ or $H4^B$), 4.81 (d, *J*(3,4) = 4.1 Hz, 1H; $H3^A$ or $H4^A$), 5.34 (s, 1H; $H6^A$), 5.52 (d, *J*(5,6) = 4.1 Hz, 1H; $H6^B$), 5.88 (d, *J*(1,2) = 3.4 Hz, 1H; $H1^B$), 6.00 ppm (d, *J*(1,2) = 3.8 Hz, 1H; $H1^A$); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 26.5, 27.2 ($C(CH_3)_2{}^B$), 26.7, 27.3 ($C(CH_3)_2{}^A$), 66.4 ($C5^B$), 69.1 ($C5^A$), 83.5 ($C2^B$), 83.6, 85.0 (2C; $C3^B$ and $C4^B$), 84.7, 85.2, 86.9 (3C; $C2^A$, $C3^A$, and $C4^A$), 98.9 ($C6^B$), 102.5 ($C6^A$), 106.5 ($C1^B$), 106.8 ($C1^A$), 112.7 ($C(CH_3)_2{}^B$), 113.0 ppm ($C(CH_3)_2{}^A$); IR (thin film): $\tilde{\nu}$ = 2113 (s, $N_3$), 3425 $cm^{-1}$ (br s; OH); LRMS (ESI+): *m*/*z* (%): 298 (100) $[M+MeOH+Na]^+$, 573 (83) $[2M+2MeOH+Na]^+$, 589 (48) $[2M+2MeOH+K]^+$; HRMS (ESI+): *m*/*z* calcd for $C_{10}H_{17}N_3NaO_6$: 298.1010 $[M+MeOH+Na]^+$; found: 298.1010.

For enantiomer **15D**: M.p. 57–59°C; $[\alpha]_D^{25}$ = +27.4 (*c* 1.05, $CHCl_3$).

*5-Azido-5-deoxy-1,2-O-isopropylidene-β-*L*-idofuranose* (***16L***): Sodium borohydride (1.16 g, 30.6 mmol) was added slowly to a solution of lactol **15L** (18.6 g, 76.5 mmol) in MeOH (200 mL) at −30°C. The reaction mixture was stirred for 90 min, with an internal temperature maintained between −20°C and −10°C; after which time, TLC analysis (cyclohexane/EtOAc, 2:1) indicated the consumption of the starting material (major $R_f$ = 0.40, minor $R_f$ = 0.39) and the formation of a major product ($R_f$ = 0.15). The reaction was neutralized with glacial acetic acid and concentrated in vacuo. The crude residue was dissolved in EtOAc (600 mL), washed with a saturated solution of sodium bicarbonate (600 mL), and the aqueous phase was extracted with EtOAc (2×800 mL). The organic fractions were combined, dried ($MgSO_4$), filtered, concentrated in vacuo, and purified by column chromatography on silica gel (cyclohexane/EtOAc, 2:1 to 1:9) to afford diol **16L** as a white crystalline solid (16.9 g, 90%); M.p. 122–124°C [lit. 120–122°C];[12] $[\alpha]_D^{25}$ = −75.4 (*c* 1.00, $CHCl_3$) [lit. $[\alpha]_D^{25}$ = −69.6[12] (*c* 0.94, $CHCl_3$)]; $^1$H NMR ([$D_6$]acetone, 400 MHz): $\delta$ = 1.27, 1.41 (s, 2×3H; $C(CH_3)_2$), 3.66 (app dt, *J*(6,5) = *J*(6,OH6) = 5.8 Hz, *J*(6,6′) = 10.6 Hz, 1H; H6), 3.70–3.75 (1H, m; H5), 3.78 (ddd, *J*(6′,5) = 3.4 Hz, *J*(6′,OH6) = 5.1 Hz, *J*(6′,6) = 10.6 Hz, 1H; H6′), 4.16–4.18 (m, 2H; H3 and H4), 4.27 (app t, *J*(OH6,6) = *J*(OH6,6′) = 5.5 Hz, 1H; OH6), 4.52 (d, *J*(OH3,3) = 4.8 Hz, 1H; OH3), 4.54 (d, *J*(2,1) = 3.8 Hz, 1H; H2), 5.91 ppm (d, *J*(1,2) = 3.8 Hz, 1H; H1); $^{13}$C NMR ([$D_6$]acetone, 100 MHz): $\delta$ = 26.8, 27.4 ($C(CH_3)_2$), 62.8 (C6), 65.0 (C5), 75.5, 81.9 (C3, C4), 87.0 (C2), 105.9 (C1), 112.3 ppm ($C(CH_3)_2$); IR (thin film): $\tilde{\nu}$ = 2108 (s; $N_3$), 3335 $cm^{-1}$ (br s; OH); LRMS (ESI+): *m*/*z* (%): 268 (93) $[M+Na]^+$, 513 $cm^{-1}$ (100) $[2M+Na]^+$; (ESI−): 244 (25) $[M-H]^-$, 280 (100) $[M+^{35}Cl]^-$, 282 (70) $[M+^{37}Cl]^-$, 489 (55) $[2M-H]^-$; HRMS (ESI+): *m*/*z* calcd for $C_9H_{15}N_3NaO_5$: 268.0904 $[M+Na]^+$; found: 268.0903.

For enantiomer **16D**: M.p. 119–120°C; $[\alpha]_D^{25}$ = +63.1 (*c* 1.15, MeOH).

*5-Azido-6-O-tert-butyldimethylsilyl-5-deoxy-1,2-O-isopropylidene-β-*L*-idofuranose* (***7L***): *tert*-Butyldimethylsilyl chloride (19.5 g, 129 mmol) was added to a solution of diol **16L** (21.1 g, 86.0 mmol) in pyridine (210 mL). The reaction mixture was stirred at RT for 18 h, after which time TLC analysis (cyclohexane/EtOAc, 2:1) indicated the complete consumption of the starting material ($R_f$ = 0.15) and the formation of a major product ($R_f$ = 0.60). The reaction was quenched by the addition of MeOH (4 mL) and concentrated in vacuo. The crude residue was dissolved in EtOAc (750 mL), washed with 2M HCl (3×450 mL), dried ($MgSO_4$), filtered, concentrated in vacuo, and purified by column chromatography on silica gel (cyclohexane/EtOAc, 20:1 to 3:1) to afford the silyl ether **7L** as a colorless oil (27.2 g, 88%); $[\alpha]_D^{25}$ = −13.9 (*c* 1.40, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 0.13 (s, 6H; $Si(CH_3)_2$), 0.91 (s, 9H; $SiC(CH_3)_3$), 1.32, 1.50 (s, 2×3H; $C(CH_3)_2$), 3.22 (d, *J*(OH3,3) = 3.5 Hz, 1H; OH3), 3.64–3.67 (m, 1H; H5), 3.77–3.82 (m, 2H; H6 and H6′), 4.12 (dd, *J*(4,3) = 2.5 Hz, *J*-

(4,5) = 7.8 Hz, 1H; H4), 4.21 (app t, $J(3,4)=J(3,OH3)=3.0$ Hz, 1H; H3), 4.55 (d, $J(2,1)=3.5$ Hz, 1H; H2), 5.97 ppm (d, $J(1,2)=3.5$ Hz, 1H; H1); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta=-5.7$, $-5.7$ (Si($CH_3$)$_2$), 18.1 (Si$C$(CH$_3$)$_3$), 25.7 (SiC($CH_3$)$_3$), 26.2, 26.8 (C($CH_3$)$_2$), 61.9 (C5), 63.3 (C6), 75.2 (C3), 82.4 (C4), 85.0 (C2), 104.5 (C1), 111.7 ppm ($C$(CH$_3$)$_2$); IR (thin film): $\tilde{\nu}=$ 2099 (s; $N_3$), 3464 cm$^{-1}$ (br s; OH); LRMS (ESI+): $m/z$ (%): 382 (100) [$M$+Na]$^+$, 741 (98) [2$M$+Na]$^+$; (ESI−): 358 (76) [$M$−H]$^-$, 394 (100) [$M$+$^{35}$Cl]$^-$, 396 (74) [$M$+$^{37}$Cl]$^-$, 404 (80) [$M$+HCOO]$^-$, 717 (98) [2$M$−H]$^-$; HRMS (ESI+): $m/z$ calcd for $C_{15}H_{29}N_3NaO_5Si$: 382.1769 [$M$+Na]$^+$; found: 382.1769.

For enantiomer **7D**: $[\alpha]_D^{25}=+15.1$ ($c$ 1.2, $CHCl_3$).

**Synthesis of DGJNAc and derivatives**

*5-Azido-6-O-tert-butyldimethylsilyl-5-deoxy-1,2-O-isopropylidene-β-*L*-lyxo-hexofuranos-3-ulose* (***17L***): Pyridinium chlorochromate (110.1 g, 510.7 mmol) was added to a solution of alcohol **7L** (30.6 g, 85.1 mmol) in $CH_2Cl_2$ (450 mL) over 3 Å molecular sieves. The reaction mixture was stirred under a nitrogen atmosphere at RT for 18 h, after which time TLC analysis (cyclohexane/EtOAc, 2:1) indicated almost complete consumption of the starting material ($R_f=0.60$) and the formation of a major product ($R_f=0.30$ streaking to 0.80). The reaction mixture was filtered through Celite and concentrated in vacuo. The residue was purified by column chromatography on silica gel (cyclohexane/EtOAc, 5:1 to 3:1) to afford the ketone (**17L**) as a colorless oil (24.6 g, 81%); $[\alpha]_D^{25}=+130.8$ ($c$ 1.09, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta=0.10$, 0.11 (s, 2×3H; Si-(CH$_3$)$_2$), 0.91 (s, 9H; SiC(CH$_3$)$_3$), 1.43, 1.46 (s, 2×3H; C(CH$_3$)$_2$), 3.80 (ddd, $J(5,4)=2.0$ Hz, $J(5,6)=5.5$ Hz, $J(5,6')=7.7$ Hz, 1H; H5), 3.87 (dd, $J(6,5)=5.5$ Hz, $J(6,6')=10.2$ Hz, 1H; H6), 3.94 (dd, $J(6',5)=8.0$ Hz, $J$-(6′,6) = 10.2 Hz, 1H; H6′), 4.39 (dd, $J(2,4)=1.0$ Hz, $J(2,1)=4.3$ Hz, 1H; H2), 4.41 (d, $J(4,2)=1.0$ Hz, $J(4,5)=2.0$ Hz, 1H; H4), 6.10 ppm (d, $J$-(1,2) = 4.3 Hz, 1H; H1); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta=-5.6$, $-5.6$ (Si-($CH_3$)$_2$), 18.2 (Si$C$(CH$_3$)$_3$), 25.7 (SiC($CH_3$)$_3$), 27.1, 27.5 (C($CH_3$)$_2$), 62.8 (C6), 63.4 (C5), 76.4 (C2), 77.9 (C4), 103.6 (C1), 114.6 ($C$(CH$_3$)$_2$), 208.9 ppm (C3); IR (thin film): $\tilde{\nu}=1777$ (s; C=O), 2111 cm$^{-1}$ (s; $N_3$); LRMS (ESI+): $m/z$ (%): 380 (100) [$M$+Na]$^+$, 412 (95) [$M$+MeOH+Na]$^+$, 737 (15) [2$M$+Na]$^+$; (ESI−): 424 (100) [$M$+MeOH+$^{35}$Cl]$^-$, 426 (40) [$M$+MeOH+$^{37}$Cl]$^-$; HRMS (ESI+): $m/z$ calcd for $C_{16}H_{31}N_3NaO_6Si$: 412.1874 [$M$+MeOH+Na]$^+$; found: 412.1873.

For enantiomer **17D**: $[\alpha]_D^{25}=-140.1$ ($c$ 1.11, $CHCl_3$).

*5-Azido-6-O-tert-butyldimethylsilyl-5-deoxy-1,2-O-isopropylidene-β-*L*-talofuranose* (***18L***): A solution of sodium borohydride (2.59 g, 68.4 mmol) in water (50 mL) was added dropwise to a solution of ketone **17L** (24.6 g, 68.4 mmol) in EtOH (200 mL) at 0°C. The reaction mixture was allowed to warm to RT and stirred for 90 min. After this time, TLC analysis (cyclohexane/EtOAc, 2:1) indicated the complete consumption of the starting material ($R_f=0.30$ streaking to 0.80) and the formation of a major product ($R_f=0.59$). The reaction was neutralized with glacial acetic acid, concentrated in vacuo, dissolved in EtOAc (400 mL), and washed with saturated solutions of sodium bicarbonate (2×400 mL) and brine (400 mL). The organic phase was dried ($MgSO_4$), filtered, concentrated in vacuo, and purified by column chromatography on silica gel (cyclohexane/EtOAc, 50:1 to 3:1) to afford alcohol **18L** as a colorless oil (22.4 g, 91%); $[\alpha]_D^{25}=+65.3$ ($c$ 1.30, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta=0.11$ (s, 6H; Si(CH$_3$)$_2$), 0.92 (s, 9H; SiC(CH$_3$)$_3$), 1.37, 1.56 (s, 2×3H; C(CH$_3$)$_2$), 2.58 (d, $J$(OH3,3) = 9.9 Hz, 1H; OH3), 3.64 (ddd, $J$-(5,4) = 3.4 Hz, $J(5,6)=5.5$ Hz, $J(5,6')=7.9$ Hz, 1H; H5), 3.81 (dd, $J(4,5)=$ 3.4 Hz, $J(4,3)=8.5$ Hz, 1H; H4), 3.87 (dd, $J(6,5)=5.5$ Hz, $J(6,6')=$ 10.6 Hz, 1H; H6), 3.91 (dd, $J(6',5)=7.9$ Hz, $J(6',6)=10.6$ Hz, 1H; H6′), 4.06 (ddd, $J(3,2)=5.1$ Hz, $J(3,4)=8.9$ Hz, $J$(3,OH3) = 9.9 Hz, 1H; H3), 4.59 (dd, $J(2,1)=3.8$ Hz, $J(2,3)=5.1$ Hz, 1H; H2), 5.82 ppm (dd, $J(1,2)=$ 3.8 Hz, 1H; H1); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta=-5.5$, $-5.5$ (Si(CH$_3$)$_2$), 18.1 (Si$C$(CH$_3$)$_3$), 25.7 (SiC($CH_3$)$_3$), 26.5, 26.5 (C($CH_3$)$_2$), 62.4 (C5), 63.9 (C6), 72.2 (C3), 78.4 (C2), 79.3 (C4), 104.1 (C1), 112.9 ppm ($C$(CH$_3$)$_2$); IR (thin film): $\tilde{\nu}=2099$ (s; $N_3$), 3473 cm$^{-1}$ (br s; OH); LRMS (ESI+): $m/z$ (%): 382 (100) [$M$+Na]$^+$, 741 (70) [2M+Na]$^+$; (ESI−): 358 (100) [$M$−H]$^-$, 394 (48) [$M$+$^{35}$Cl]$^-$, 396 (15) [$M$+$^{37}$Cl]$^-$, 717 (64) [2M−H]$^-$; HRMS (ESI+): $m/z$ calcd for $C_{15}H_{29}N_3NaO_5Si$: 382.1769 [$M$+Na]$^+$;found: 382.1768.

For enantiomer **18D**: $[\alpha]_D^{25}=-70.7$ ($c$ 1.08, $CHCl_3$).

*5-Azido-3-O-benzyl-6-O-tert-butyldimethylsilyl-5-deoxy-1,2-O-isopropylidene-β-*L*-talofuranose* (***19L***): Sodium hydride (60% min. oil suspension, 3.74 g, 93.4 mmol) was added to a solution of alcohol **18L** (22.4 g, 62.2 mmol) and benzyl bromide (11.1 mL, 93.4 mmol) in DMF (200 mL) at 0°C. The reaction mixture was allowed to warm to RT and stirred for 1 h. TLC analysis (cyclohexane/EtOAc, 2:1) indicated the complete consumption of the starting material ($R_f=0.58$) and the formation of a major product ($R_f=0.70$). The reaction mixture was quenched with MeOH (2 mL) at 0°C, diluted with EtOAc (500 mL), washed with water/sat. brine (1:1) solution (3×200 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (cyclohexane/EtOAc, 50:1 to 20:1) to afford the benzyl ether (**19L**) as a colorless oil (24.9 g, 89%); $[\alpha]_D^{25}=+110.0$ ($c$ 0.90, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta=0.09$, 0.10 (s, 2×3H; Si(CH$_3$)$_2$), 0.92 (s, 9H; SiC(CH$_3$)$_3$), 1.36, 1.58 (s, 2×3H; C(CH$_3$)$_2$), 3.58 (ddd, $J(5,4)=$ 2.0 Hz, $J(5,6)=4.8$ Hz, $J(5,6')=8.9$ Hz, 1H; H5), 3.85 (dd, $J(6,5)=4.4$ Hz, $J(6,6')=10.6$ Hz, 1H; H6), 3.88 (dd, $J(3,2)=5.1$ Hz, $J(3,4)=8.9$ Hz, 1H; H3), 3.90 (dd, $J(6',5)=8.9$ Hz, $J(6',6)=10.6$ Hz, 1H; H6′), 4.04 (dd, $J$-(4,5) = 2.1 Hz, $J(4,3)=8.9$ Hz, 1H; H4), 4.56 (app t, $J(2,1)=J(2,3)=$ 4.1 Hz, 1H; H2), 4.57 (d, $J_{gem}=12.1$ Hz, 1H; OC$H_2$Ph), 4.80 (d, $J_{gem}=$ 12.1 Hz, 1H; OC$H_2$Ph), 5.72 (d, $J(1,2)=3.4$ Hz, 1H; H1), 7.34–7.40 ppm (5H, m; ArH); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta=-5.5$, $-5.5$ (Si($CH_3$)$_2$), 18.1 (Si$C$(CH$_3$)$_3$), 25.8 (SiC($CH_3$)$_3$), 26.5, 26.8 (C($CH_3$)$_2$), 62.1 (C5), 64.4 (C6), 72.3 (OC$H_2$Ph), 76.9 (C2), 76.9 (C4), 77.8 (C3), 104.3 (C1), 113.1 ($C$(CH$_3$)$_2$), 128.0, 128.2, 128.5 (ArCH), 137.3 ppm (Ar$C$C); IR (thin film): $\tilde{\nu}=2098$ cm$^{-1}$ (s; $N_3$); LRMS (ESI+): $m/z$ (%): 472 (97) [$M$+Na]$^+$, 921 (100) [2$M$+Na]$^+$; HRMS (ESI+): $m/z$ calcd for $C_{22}H_{35}N_3NaO_5Si$: 472.2238 [$M$+Na]$^+$; found: 472.2239.

For enantiomer **19D**: $[\alpha]_D^{25}=-95.2$ ($c$ 0.59, $CHCl_3$).

*Methyl-5-azido-3-O-benzyl-5-deoxy-*L*-talofuranoside* (***8L***): A solution of benzyl ether **19L** (19.2 g, 42.7 mmol) in a mixture of MeOH (200 mL) and acetyl chloride (20 mL) was stirred at 55°C for 2 h. TLC analysis (cyclohexane/EtOAc, 2:1) indicated the complete consumption of the starting material ($R_f=0.72$) and the formation of a major product ($R_f=0.20$). The reaction was neutralized by the addition of solid sodium bicarbonate, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (cyclohexane/EtOAc, 9:1 to 2:3) to afford the methyl talofuranoside (**8L**) as a pale-yellow oil (12.3 g, 93%) as a 7:1 ratio of the anomers; $^1$H NMR ($CDCl_3$, 400 MHz, major anomer only): 2.19 (dd, $J$(OH6,6) = 5.2 Hz, $J$(OH6,6′) = 7.6 Hz, 1H; OH6), 2.54 (d, $J$(OH2,2) = 2.6 Hz, 1H; OH2), 3.39 (s, 3H; OCH$_3$), 3.43 (td, $J(5,6')=$ 4.3 Hz, $J(5,4)=J(5,6)=6.1$ Hz, 1H; H5), 3.71 (ddd, $J$(6,OH6) = 5.2 Hz, $J$-(6,5) = 6.1 Hz, $J(6,6')=12.0$ Hz, 1H; H6), 3.77 (ddd, $J(6',5)=4.3$ Hz, $J$-(6′,OH6) = 7.6 Hz, $J(6',6)=12.0$ Hz, 1H; H6′), 4.04 (dd, $J$(2,OH2) = 2.6 Hz, $J(2,3)=4.3$ Hz, 1H; H2), 4.13 (dd, $J(4,5)=6.1$ Hz, $J(4,3)=7.5$ Hz, 1H; H4), 4.20 (dd, $J(3,2)=4.3$ Hz, $J(3,4)=7.5$ Hz, 1H; H3), 4.55 (d, $J_{gem}=11.4$ Hz, 1H; OC$H_2$Ph), 4.62 (d, $J_{gem}=11.4$ Hz, 1H; OC$H_2$Ph), 4.89 (s, 1H; H1), 7.32–7.42 ppm (m, 5H; ArH); $^{13}$C NMR ($CDCl_3$, 100 MHz, major anomer only): $\delta=55.6$ (OCH$_3$), 62.5 (C6), 65.4 (C5), 72.5 (C2), 73.1 (OC$H_2$Ph), 79.6 (C3), 81.0 (C4), 108.6 (C1), 128.2, 128.7, 128.7, 128.8 (Ar$C$H), 136.4 ppm (Ar$C$C); IR (thin film): $\tilde{\nu}=2116$ (s; $N_3$), 3427 cm$^{-1}$ (br s; OH); LRMS (ESI+): $m/z$ (%): 332 (100) [$M$+Na]$^+$, 641 (41) [2$M$+Na]$^+$; HRMS (ESI+): $m/z$ calcd for $C_{14}H_{19}N_3NaO_5$: 332.1217 [$M$+Na]$^+$; found: 332.1217.

*Methyl-5-azido-2-N,3-O-dibenzyl-2,5,6-trideoxy-2,6-imino-*L*-galactofuranoside* (***9Lα***): Trifluoromethanesulfonic anhydride (10.6 mL, 62.8 mmol) and pyridine (10.2 mL, 126 mmol) were added to a solution of diol **8L** (7.2 g, 23 mmol) in $CH_2Cl_2$ (75 mL) at −40°C under an argon atmosphere. After 1 h, with the internal temperature rising to −20°C, TLC analysis (cyclohexane/EtOAc, 2:1) indicated the complete consumption of the starting material ($R_f=0.19$) and the formation of two products (major $R_f=0.77$, minor $R_f=0.65$), which were thought to be a mixture of anomeric ditriflates. The reaction mixture was diluted with $CH_2Cl_2$ (100 mL), washed with 2M HCl (3×60 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude ditriflate (**20L**) was dissolved in THF (75 mL), cooled to −30°C under an argon atmosphere, and benzylamine (7.6 mL, 70 mmol) was added dropwise. The reaction mixture was allowed to warm to RT and stirred for 2 h, after which time TLC analysis

(cyclohexane/EtOAc/triethylamine, 79:20:1) indicated the consumption of both ditriflates and the formation of the two anomeric monosubstituted triflates (major $R_f=0.42$, minor $R_f=0.30$). The reaction was heated to 60 °C for 16 h. TLC analysis indicated the complete consumption of the major component ($R_f=0.42$), the formation of a new major product ($R_f=0.67$), and the persistence of the minor component ($R_f=0.30$). The reaction mixture was concentrated in vacuo and purified by column chromatography on silica gel (cyclohexane/EtOAc/triethylamine, 99:0:1 to 96:3:1) to afford the bicyclic compound (**9Lα**) as a pale-yellow oil and a single anomer (6.12 g, 69%). $[\alpha]_D^{25}=+16.2$ (*c* 1.1, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta=2.74$ (d, $J(6,6')=12.8$ Hz, 1H; H6), 3.21 (br s, 1H; H2), 3.52 (dd, $J(6',5)=4.1$ Hz, $J(6',6)=12.8$ Hz, 1H; H6′), 3.54 (s, 3H; $OCH_3$), 3.87 (app t, $J(5,4)=J(5,6')=4.4$ Hz, 1H; H5), 3.90 (d, $J_{gem}=13.8$ Hz, 1H; NC$H_2$Ph), 4.01 (d, $J_{gem}=13.8$ Hz, 1H; NC$H_2$Ph), 4.11 (d, $J(3,2)=1.0$ Hz, 1H; H3), 4.30 (d, $J(4,5)=5.1$ Hz, 1H; H4), 4.52 (d, $J_{gem}=11.8$ Hz, 1H; OC$H_2$Ph), 4.58 (d, $J_{gem}=11.8$ Hz, 1H; OC$H_2$Ph), 5.32 (d, $J(1,2)=2.7$ Hz, 1H; H1), 7.26–7.37 ppm (m, 10H; ArH); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta=48.6$ (C6), 57.6 ($OCH_3$), 59.7 (C5), 59.9 (N*C*$H_2$Ph), 61.4 (C2), 71.0 (O*C*$H_2$Ph), 78.7 (C4), 81.5 (C3), 109.7 (C1), 127.0, 127.7, 127.8, 128.3, 128.4 (Ar*C*H), 137.7, 139.1 ppm (Ar*C*C); IR (thin film): $\tilde{\nu}=2109$ cm$^{-1}$ (s; $N_3$); LRMS (ESI+): *m*/*z* (%): 381 (100) $[M+H]^+$, 403 (80) $[M+Na]^+$; HRMS (ESI+): *m*/*z* calcd for $C_{21}H_{24}N_4NaO_3$: 381.1921 $[M+H]^+$; found: 381.1920.

For enantiomer **9Dα**: $[\alpha]_D^{25}=-21.4$ (*c* 1.20, $CHCl_3$).

*4-O-Acetyl-5-azido-2-N,3-O-dibenzyl-2,5,6-trideoxy-2,6-imino-*L*-galactose acetyl methyl acetal* (***21L***): Boron trifluoride diethyl etherate (5.1 mL, 40 mmol) was added dropwise to a solution of bicyclic acetal **9Lα** (6.12 g, 16.1 mmol) in acetic anhydride (60 mL) at −30 °C. The reaction was allowed to warm to RT and stirred for 2.5 h, after which time TLC analysis (cyclohexane/EtOAc/triethylamine, 69:30:1) indicated the complete consumption of the starting material ($R_f=0.72$) and the formation of major products ($R_f=0.47$, 0.56). The reaction mixture was concentrated in vacuo and the residue was dissolved in EtOAc (200 mL), washed with a saturated solution of sodium bicarbonate (3×100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (cyclohexane/EtOAc/triethylamine, 97:2:1 to 79:20:1) to afford the mixed-acetal piperidine (**21L**) as a pale-yellow oil (7.54 g, 97%), in a 3:2 (A/B) mixture of diastereoisomers. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta=2.05$ (s, 3H; $COCH_3^B$), 2.10 (s, 3H; $COCH_3^A$), 2.13 (s, 3H; $COCH_3^B$), 2.14 (s, 3H; $COCH_3^A$), 2.38 (dd, $J(6,5)=10.6$ Hz, $J(6,6')=13.8$ Hz, 1H; H6$^A$), 2.41 (dd, $J(6,5)=10.8$ Hz, $J(6,6')=14.0$ Hz, 1H; H6$^B$), 3.04 (dd, $J(2,3)=1.5$ Hz, $J(2,1)=7.9$ Hz, 1H; H2$^B$), 3.05 (dd, $J(6',5)=4.6$ Hz, $J(6',6)=14.0$ Hz, 1H; H6′$^B$), 3.07 (dd, $J(2,3)=1.8$ Hz, $J(2,1)=7.5$ Hz, 1H; H2$^A$), 3.10 (dd, $J(6',5)=4.6$ Hz, $J(6',6)=13.8$ Hz, 1H; H6′$^A$), 3.31 (s, 3H; $OCH_3^B$), 3.48 (s, 3H; $OCH_3^A$), 3.90 (s, 2H; NC$H_2$Ph$^A$), 3.94 (s, 2H; NC$H_2$Ph$^B$), 4.05 (dd, $J(3,2)=1.8$ Hz, $J(3,4)=2.9$ Hz, 1H; H3$^A$), 4.11 (ddd, $J(5,6')=4.6$ Hz, $J(5,4)=9.9$ Hz, $J(5,6)=10.8$ Hz, 1H; H5$^B$), 4.13 (ddd, $J(5,6')=4.6$ Hz, $J(5,4)=10.0$ Hz, $J(5,6)=10.6$ Hz, 1H; H5$^A$), 4.29 (dd, $J(3,2)=1.5$ Hz, $J(3,4)=2.9$ Hz, 1H; H3$^B$), 4.50 (d, $J_{gem}=11.0$ Hz, 1H; OC$H_2$Ph$^A$), 4.59 (d, $J_{gem}=11.6$ Hz, 1H; OC$H_2$Ph$^B$), 4.67 (d, $J_{gem}=11.0$ Hz, 1H; OC$H_2$Ph$^A$), 4.80 (d, $J_{gem}=11.6$ Hz, 1H; OC$H_2$Ph$^B$), 4.86 (dd, $J(4,3)=2.9$ Hz, $J(4,5)=10.2$ Hz, 1H; H4$^B$), 4.88 (dd, $J(4,3)=2.9$ Hz, $J(4,5)=10.0$ Hz, 1H; H4$^A$), 6.16 (d, $J(1,2)=7.9$ Hz, 1H; H1$^B$), 6.31 (d, $J(1,2)=7.5$ Hz, 1H; H1$^A$), 7.22–7.43 ppm (m, 20H; ArH$^A$ and ArH$^B$); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta=$ 20.9, 21.0 ($COCH_3^B$), 20.0, 21.1 ($COCH_3^A$), 51.6 (C6$^B$), 51.9 (C6$^A$), 53.9 (N*C*$H_2$Ph$^B$), 53.9 (C5$^B$), 54.4 (C5$^A$), 54.7 (N*C*$H_2$Ph$^A$), 56.4 ($OCH_3^A$), 56.9 ($OCH_3^B$), 63.2 (C2$^A$), 64.2 (C2$^B$), 74.9 (O*C*$H_2$Ph$^A$), 75.2 (O*C*$H_2$Ph$^B$), 76.0 (C3$^A$), 76.8 (C3$^B$), 77.2 (C4$^B$), 77.6 (C4$^A$), 95.1 (C1$^A$, C1$^B$), 126.7, 127.0, 127.1, 127.4, 127.5, 127.7, 127.8, 128.3, 128.4, 128.5, 128.6 (Ar*C*H$^A$ and Ar*C*H$^B$), 138.0, 138.2, 139.3, 139.6 (Ar*C*C$^A$ and Ar*C*C$^B$), 170.2, 170.2, 170.6, 171.0 ppm ($COCH_3^A$ and $COCH_3^B$); IR (thin film): $\tilde{\nu}=1743$ (s; C=O), 2106 cm$^{-1}$ (s; $N_3$); LRMS (ESI+): *m*/*z* (%): 423, (95) $[M-OAc]^+$, 483 (98) $[M+H]^+$, 505 (100) $[M+Na]^+$, 521 (83) $[M+K]^+$, 955 (20) $[2M+H]^+$, 987 (95) $[2M+Na]^+$; HRMS (ESI+): *m*/*z* calcd for $C_{25}H_{30}N_4NaO_6$: 505.2058 $[M+Na]^+$; found: 505.2058.

*3,6-Di-O-acetyl-2-azido-1-N,4-O-dibenzyl-1,2,5-trideoxy-1,5-imino-*D*-galactitol* (***22D***): Diisobutylaluminium hydride (1.5 M in toluene, 52.0 mL, 78.0 mmol) was added dropwise to a solution of mixed acetal **21L** (7.54 g, 15.6 mmol) in $CH_2Cl_2$ (75 mL) at −78 °C. After 45 min, TLC analysis (cyclohexane/EtOAc/triethylamine, 59:40:1) indicated the consumption of the starting material ($R_f=0.70$, 0.73) and the appearance of three new spots ($R_f=0.20$, 0.60, and 0.80). The reaction mixture was quenched and diluted with EtOAc (400 mL) and allowed to warm to RT. A saturated solution of sodium potassium tartrate (400 mL) was added and the biphasic mixture was stirred vigorously for 90 min. The organic layer was collected and the aqueous layer was extracted with EtOAc (3× 300 mL). The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. TLC analysis (cyclohexane/EtOAc/triethylamine, 59:40:1) indicated the disappearance of the spot at $R_f=0.80$ during the work-up procedure. The crude residue was dissolved in MeOH (100 mL) and sodium borohydride (590 mg, 15.6 mmol) was added at 0 °C. The reaction mixture was allowed to warm to RT and stirred for 3 h, after which time, TLC analysis (cyclohexane/EtOAc/triethylamine, 59:40:1) indicated the formation of one major product ($R_f=0.25$) with the disappearance of all previous spots. The reaction mixture was concentrated in vacuo, co-evaporated with MeOH (3×50 mL), and dissolved in pyridine (75 mL) and acetic anhydride (75 mL). The reaction mixture was stirred at RT for 16 h, after which time, TLC analysis (cyclohexane/EtOAc/triethylamine, 59:40:1) indicated the consumption of the starting material ($R_f=0.25$) and the formation of a major product ($R_f=0.65$). The reaction mixture was concentrated in vacuo and purified by column chromatography on silica gel (cyclohexane/EtOAc/triethylamine, 97:2:1 to 89:10:1) to afford the diacetyl piperidine (**22D**) as a light-yellow oil (5.08 g, 72% over 3 steps). $[\alpha]_D^{25}=+65.7$ (*c* 0.60, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta=2.04$, 2.14 (s, 2×3H; $COCH_3$), 2.26 (dd, $J(1,2)=8.9$ Hz, $J(1,1')=12.6$ Hz, 1H; H1), 2.95–3.00 (m, 1H; H5), 3.02 (dd, $J(1',2)=4.4$ Hz, $J(1',1)=12.7$ Hz, 1H; H1′), 3.64 (d, $J_{gem}=14.1$ Hz, 1H; NC$H_2$Ph), 3.88 (d, $J_{gem}=14.1$ Hz, 1H; NC$H_2$Ph), 3.96 (app td, $J(2,1')=4.1$ Hz, $J(2,1)=J(2,3)=8.5$ Hz, 1H; H2), 4.04 (app t, $J(4,3)=J(4,5)=2.7$ Hz, 1H; H4), 4.23 (dd, $J(6,5)=6.1$ Hz, $J(6,6')=11.6$ Hz, 1H; H6), 4.55 (dd, $J(6',5)=6.1$ Hz, $J(6',6)=11.6$ Hz, 1H; H6′), 4.57 (d, $J_{gem}=11.4$ Hz, 1H; OC$H_2$Ph), 4.75 (d, $J_{gem}=11.4$ Hz, 1H; OC$H_2$Ph), 4.90 (dd, $J(3,4)=2.7$ Hz, $J(3,2)=8.5$ Hz, 1H; H3), 7.26–7.40 ppm (m, 10H; ArH); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta=21.0$, 21.0 ($CO*C*H_3$), 51.4 (C1), 56.5 (C2), 56.9 (N*C*$H_2$Ph), 60.7 (C5), 61.9 (C6), 74.3 (O*C*$H_2$Ph), 74.8 (C4), 75.1 (C3), 127.3, 127.8, 127.9, 128.4, 128.5, 128.7 (Ar*C*H), 137.8, 138.0 (Ar*C*C), 170.1, 170.6 ppm (*C*OCH$_3$); IR (thin film): $\tilde{\nu}=1740$ (s; C=O), 2108 cm$^{-1}$ (s; $N_3$); LRMS (ESI+): *m*/*z* (%): 475 (100) $[M+Na]^+$; HRMS (ESI+): *m*/*z* calcd for $C_{24}H_{28}N_4NaO_5$: 475.1952 $[M+Na]^+$; found: 475.1950.

For enantiomer **22L**: $[\alpha]_D^{25}=-75.6$ (*c* 0.87, $CHCl_3$).

*2-Acetamido-3,6-di-O-acetyl-1-N,4-O-dibenzyl-1,2,5-trideoxy-1,5-imino-*D*-galactitol* (***23D***): Powdered zinc (9.0 g, 130 mmol) was added to a solution of azide **22D** (3.0 g, 6.6 mmol) in THF/glacial-acetic-acid/acetic-anhydride (3:2:1, 72 mL) and the mixture was stirred vigorously before the dropwise addition of a saturated copper(II) sulfate solution (9 mL) to initiate the reaction. After 30 min, TLC analysis (cyclohexane/EtOAc/triethylamine, 49:50:1) indicated the complete consumption of the starting material ($R_f=0.78$) and the formation of a major product ($R_f=0.15$). The reaction mixture was filtered (GF/A glass microfiber), concentrated in vacuo, and the crude residue was purified by column chromatography on silica gel (cyclohexane/EtOAc/triethylamine, 94:5:1 to 29:70:1) to afford the acetamide (**23D**) as a white crystalline solid (2.83 g, 91%). M.p. 112–114 °C; $[\alpha]_D^{25}=+20.3$ (*c* 1.02, acetone); $^1$H NMR ($CDCl_3$, 500 MHz): $\delta=$ 1.87 (s, 3H; NHCOC$H_3$), 2.05, 2.11 (s, 2×3H; $COCH_3$), 2.20 (dd, $J(1,2)=5.2$ Hz, $J(1,1')=12.6$ Hz, 1H; H1), 3.04 (dd, $J(1',2)=3.1$ Hz, $J(1',1)=12.6$ Hz, 1H; H1′), 3.33 (br s, 1H; H5), 3.72 (d, $J_{gem}=13.8$ Hz, 1H; NC$H_2$Ph), 3.82 (d, $J_{gem}=13.8$ Hz, 1H; NC$H_2$Ph), 3.86 (dd, $J=2.9$ Hz, $J=4.3$ Hz, 1H; H4), 4.20 (br s, 1H; H2), 4.31 (dd, $J(6,5)=3.6$ Hz, $J(6,6')=11.9$ Hz, 1H; H6), 4.54 (d, $J_{gem}=11.8$ Hz, 1H; OC$H_2$Ph), 4.66 (dd, $J(6',5)=7.6$ Hz, $J(6',6)=11.9$ Hz, 1H; H6′), 4.76 (d, $J_{gem}=11.8$ Hz, 1H; OC$H_2$Ph), 5.19 (br s, 1H; H3), 5.70 (d, $J$(NH,2)=8.0 Hz, 1H; N*H*COCH$_3$), 7.25–7.38 ppm (m, 10H; ArH); $^{13}$C NMR ([D$_6$]acetone, 126 MHz): $\delta=21.0$, 21.0 ($CO*C*H_3$), 22.9 (NHCO*C*H$_3$), 46.6 (C2), 50.1 (C1), 58.2 (N*C*$H_2$Ph), 61.5 (C5), 61.6 (C6), 72.5 (C3), 73.4 (O*C*$H_2$Ph), 75.5 (C4), 127.6, 128.1, 128.2, 128.9, 128.9, 129.3 (Ar*C*H), 139.4, 140.1

(Ar*C*C), 169.6, 170.2, 170.7 ppm (*C*OCH$_3$; NH*C*OCH$_3$); IR (thin film): $\tilde{\nu}$=1541 (br s; amide II), 1655 (s; amide I), 1739 (s; C=O), 3296 cm$^{-1}$ (br s; OH); LRMS (ESI+): *m*/*z* (%): 469 (100) [*M*+H]$^+$, 491 (55) [*M*+Na]$^+$; (ESI−): 503 (55) [*M*+$^{35}$Cl]$^-$, 505 (15) [*M*+$^{37}$Cl]$^-$, 513 (100) [*M*+HCOO]$^-$; HRMS (ESI+): *m*/*z* calcd for $C_{26}H_{33}N_2O_6$: 491.2153 [*M*+H]$^+$; found: 491.2151.

For enantiomer **23L**: M.p. 113–115 °C; $[\alpha]_D^{25}=-28.6$ (*c* 1.06, $CHCl_3$).

*2-Acetamido-1,2,5-trideoxy-1,5-imino*-D-*galactitol* (*DGJNAc,* ***1D***): Sodium methoxide (10 mg, cat.) was added to a solution of the protected piperidine (**23D**, 2.83 g, 6.03 mmol) in MeOH (40 mL) at RT and the mixture was stirred for 16 h. TLC analysis (EtOAc/triethylamine, 99:1) indicated the complete consumption of the starting material ($R_f$=0.50) and the formation of a major product ($R_f$=0.14 streaking to 0.0). The reaction mixture was neutralized with glacial acetic acid and concentrated in vacuo. The crude residue was dissolved in water/2 M HCl/1,4-dioxane (10:2:1, 78 mL) and palladium (10% on carbon, 600 mg) was added. The vessel was degassed, charged with hydrogen, and the reaction mixture was stirred at RT for 24 h. LRMS and $^1$H NMR indicated that a single product had been formed, with no trace of any benzylated intermediates observed. The reaction mixture was filtered (GF/A glass microfiber) and concentrated in vacuo to afford crude DGJNAc (**1D**) as its hydrochloride salt.

Selected data for DGJNAc·HCl (**1D**): $^1$H NMR ($D_2O$, 400 MHz): $\delta$= 1.96 (s, 3H; NHCOC$H_3$), 2.82 (app t, *J*(1,1′)=*J*(1,2)=12.5 Hz, 1H; H1), 3.34 (br s, 1H; H5), 3.41 (dd, *J*(1′,2)=5.0 Hz, *J*(1′,1)=12.9 Hz, 1H; H1′), 3.72 (dd, *J*(3,4)=2.6 Hz, *J*(3,2)=10.7 Hz, 1H; H3), 3.75 (dd, *J*(6,5)= 7.5 Hz, *J*(6,6′)=12.3 Hz, 1H; H6), 3.82 (dd, *J*(6′,5)=5.5 Hz, *J*(6′,6)= 12.3 Hz, 1H; H6′), 4.11 (dd, *J*(4,5)=1.0 Hz, *J*(4,3)=2.6 Hz, 1H; H4), 4.26 ppm (ddd, *J*(2,1′)=5.1 Hz, *J*(2,3)=11.0 Hz, *J*(2,1)=11.9 Hz, 1H; H2); LRMS (ESI+): *m*/*z* (%): 205 (100) [*M*+H]$^+$, 409 (35) [2*M*+H]$^+$; (ESI−): 203 (100) [*M*−H]$^-$.

The crude salt of compound **1D** was loaded onto a short column of Dowex (50W-X8, H$^+$) and the resin was washed with water until neutral fractions were obtained. The product was liberated with aqueous ammonia (2 M) and the ammoniacal fractions were concentrated in vacuo. The residue was co-evaporated with EtOH (3×50 mL) to give DGJNAc (**1D**) as a pale-yellow crystalline solid (1.22 g, 99%). M.p. 153–156 °C (EtOH); $[\alpha]_D^{25}=+49.3$ (*c* 0.65, $H_2O$); $^1$H NMR ($D_2O$, 400 MHz): $\delta$=1.88 (s, 3H; NHCOC$H_3$), 2.24 (app t, *J*(1,1′)=*J*(1,2)=12.2 Hz, 1H; H1), 2.63 (app t, *J*(5,6)=*J*(5,6′)=6.5 Hz, 1H; H5), 2.96 (dd, *J*(1′,2)=4.9 Hz, *J*(1′,1)= 13.1 Hz, 1H; H1′), 3.45–3.53 (m, 3H; H3, H6, and H6′), 3.83 (app td, *J*-(2,1′)=4.9 Hz, *J*(2,1)=*J*(2,3)=10.9 Hz, 1H; H2), 3.89 ppm (s, 1H; H4); $^{13}$C NMR ($D_2O$, 100 MHz): $\delta$=22.6 (NHCO*C*H$_3$), 47.7 (C1), 49.1 (C2), 59.3 (C5), 61.8 (C6), 68.9 (C4), 73.2 (C3), 175.1 ppm (NH*C*OCH$_3$); IR (thin film, Ge): $\tilde{\nu}$=1563 (s; amide II), 1638 (s; amide I), 3285 cm$^{-1}$ (br s; OH/NH); LRMS (ESI+): *m*/*z* (%): 205 (100) [*M*+H]$^+$, 409 (30) [2*M*+H]$^+$; (ESI−): 203 (100) [*M*−H]$^-$; HRMS (ESI+): *m*/*z* calcd for $C_8H_{17}N_2O_4$: 205.1183 [*M*+H]$^+$; found: 205.1184; elemental analysis calcd (%) for $C_8H_{16}N_2O_4$: C 47.05, H 7.90, N 13.72; found: C 46.88, H 7.86, N 13.55.

For enantiomer **1L**: M.p. 152–156 °C (EtOH); $[\alpha]_D^{25}=-46.6$ (*c* 0.73, $H_2O$).*2-Acetamido-1,2,5-trideoxy-1,5-imino-1-N-methyl*-D-*galactitol,* (*N-methyl-DGJNAc,* ***1Da***): Formaldehyde (37% in water, 0.03 mL, 0.3 mmol) and palladium (10% on carbon, 6 mg) were added to a solution of DGJNAc (**1D**, 30 mg, 0.15 mmol) in 1,4-dioxane/water (1:1, 2 mL). The vessel was degassed, charged with hydrogen, and the reaction mixture was stirred at RT for 18 h. The reaction mixture was filtered (GF/A glass microfiber) and concentrated in vacuo. The residue was loaded onto a short column of Dowex (50W-X8, H$^+$) and the resin washed with water until neutral fractions were obtained. The product was liberated with aqueous ammonia (2 M) and the ammoniacal fractions were concentrated in vacuo to afford *N*-methyl-DGJNAc (**1Da**) as a brown, crystalline solid (35 mg, quant.). M.p. 203–206 °C; $[\alpha]_D^{22}=+23.6$ (*c* 0.65, $H_2O$); $^1$H NMR ($D_2O$, 400 MHz): $\delta$=1.88 (s, 3H; NHCOC$H_3$), 2.04 (app t, *J*-(1,1′)=*J*(1,2)=11.6 Hz, 1H; H1), 2.20 (app s, 4H; NC$H_3$, H5), 2.81 (dd, *J*(1′,2)=4.5 Hz, *J*(1′,1)=11.7 Hz, 1H; H1′), 3.41 (dd, *J*(3,2)=2.1 Hz, *J*-(3,4)=10.6 Hz, 1H; H3), 3.68 (dd, *J*(6,5)=6.1 Hz, *J*(6,6′)=11.6 Hz, 1H; H6), 3.74 (dd, *J*(6′,5)=4.5 Hz, *J*(6′,6)=11.6 Hz, 1H; H6′), 3.92–4.10 ppm (m, 2H; H2 and H4); $^{13}$C NMR ($D_2O$, 126 MHz): $\delta$=22.6 (NHCO*C*H$_3$), 41.5 (NCH$_3$), 47.8 (C2), 58.4 (C1), 61.3 (C6), 65.9, 70.0, 73.1 (C3, C4 and C5), 174.9 ppm (NH*C*OCH$_3$); IR (thin film): $\tilde{\nu}$=1561 (s; amide II), 1639 (s; amide I), 3289 cm$^{-1}$ (br s; OH); LRMS (ESI+): *m*/*z* (%): 459 (100) [2*M*+Na]$^+$; HRMS (ESI+): *m*/*z* calcd for $C_9H_{18}N_2NaO_4$: 241.1159 [*M*+Na]$^+$; found: 241.1158.

*2-Acetamido-1,2,5-trideoxy-1-N-ethyl-1,5-imino*-D-*galactitol,* (*N-ethyl-DGJNAc,* ***1Db***): Ethanal (0.01 mL, 0.2 mmol) and palladium (10% on carbon, 8 mg) were added to a solution of DGJNAc (**1D**, 20.9 mg, 0.10 mmol) in EtOH (1 mL). The vessel was degassed, charged with hydrogen, and the reaction mixture was stirred at RT for 4.5 h, after which LRMS indicated the absence of the starting material. The reaction mixture was filtered (GF/A glass microfiber) and concentrated in vacuo. The residue was loaded onto a short column of Dowex (50W-X8, H$^+$) and the resin was washed with water. The product was liberated with aqueous ammonia (2 M) and the ammoniacal fractions were concentrated in vacuo to afford *N*-ethyl-DGJNAc (**1Db**) as a colorless oil (24 mg, quant.); $[\alpha]_D^{25}=+18.1$ (*c* 1.00, MeOH); $^1$H NMR ($D_2O$, 400 MHz): $\delta$=1.02 (t, *J*= 6.9 Hz, 3H; NCH$_2$C$H_3$), 2.01 (s, 3H; NHCOC$H_3$), 2.23 (app t, *J*(1,1′)=*J*-(1,2)=11.4 Hz, 1H; H1), 2.58 (app s, 1H; H5), 2.63 (dd, *J*=7.0 Hz, $J_{gem}$= 13.6 Hz, 1H; NC*H*H′CH$_3$), 2.85 (dd, *J*=6.9 Hz, $J_{gem}$=13.6 Hz, 1H; NCH*H*′CH$_3$), 2.98 (dd, *J*(1′,2)=4.0 Hz, *J*(1′,1)=11.5 Hz, 1H; H1′), 3.51 (br d, *J*=10.3 Hz, 1H; H3), 3.80 (dd, *J*(6,5)=6.4 Hz, *J*(6,6′)=11.4 Hz, 1H; H6), 3.87 (dd, *J*(6′,5)=3.9 Hz, *J*(6′,6)=11.4 Hz, 1H; H6′), 4.04–4.20 ppm (m, 2H; H2 and H4); $^{13}$C NMR ($D_2O$, 100 MHz): $\delta$=8.6 (NCH$_2$*C*H$_3$), 22.7 (NHCO*C*H$_3$), 46.6 (N*C*H$_2$CH$_3$), 47.8 (C2), 53.3 (C1), 60.8 (C6), 62.8 (C5), 70.0 (C4), 73.0 (C3), 175.0 ppm (NH*C*OCH$_3$); IR (thin film): $\tilde{\nu}$=1560 (s; amide II), 1637 (s; amide I), 3317 cm$^{-1}$ (br s; OH); LRMS (ESI+): *m*/*z* (%): 487 (100) [2*M*+Na]$^+$; HRMS (ESI+): *m*/*z* calcd for $C_{10}H_{21}N_2O_4$: 233.1496 [*M*+H]$^+$; found: 233.1495.

*2-Acetamido-1-N-butyl-1,2,5-trideoxy-1,5-imino*-D-*galactitol,* (*N-butyl-DGJNAc,* ***1Dc***): Butyraldehyde (0.01 mL, 0.1 mmol) and sodium cyanoborohydride (6 mg, 0.1 mmol) were added to a solution of DGJNAc (**1D**, 22.4 mg, 0.110 mmol) in EtOH/acetic-acid (200:1, 10 mL). The mixture was stirred at RT for 2.5 h after which LRMS indicated the absence of the starting material. The reaction mixture was concentrated in vacuo and the crude residue was purified by cation-exchange chromatography (Bond Elut SCX 1 cc cartridge, residue loaded in 50 mM HCl and eluted with 3.5% ammonium hydroxide in MeOH/water 9:1) and reverse-phase chromatography (SepPak $C_{18}$ 1 cc cartridge, residue loaded in water and eluted with MeOH) to afford *N*-butyl-DGJNAc (**1Dc**) as a white crystalline solid (32 mg, quant.). M.p. 180–184 °C; $[\alpha]_D^{25}=+$ 14.4 (*c* 0.62 in MeOH); $^1$H NMR ($D_2O$, 400 MHz): $\delta$=0.89 (t, *J*=7.3 Hz, 3H; NCH$_2$CH$_2$CH$_2$C$H_3$), 1.20–1.32 (m, 2H; NCH$_2$CH$_2$C$H_2$CH$_3$), 1.35–1.52 (m, 2H; NCH$_2$C$H_2$CH$_2$CH$_3$), 2.01 (s, 3H; NHCOC$H_3$), 2.18 (app t, *J*-(1,1′)=*J*(1,2)=11.5 Hz, 1H; H1), 2.43–2.52 (m, 2H; H5 and NC*H*H′CH$_2$CH$_2$CH$_3$), 2.67 (ddd, *J*=6.8 Hz, *J*=9.7 Hz, $J_{gem}$=13.5 Hz, 1H; NCH*H*′CH$_2$CH$_2$CH$_3$), 2.95 (dd, *J*(1′,2)=4.6 Hz, *J*(1′,1)=11.7 Hz, 1H; H1′), 3.49 (dd, *J*(3,4)=3.7 Hz, *J*(3,2)=10.8 Hz, 1H; H3), 3.78 (dd, *J*-(6,5)=6.7 Hz, *J*(6,6′)=11.4 Hz, 1H; H6), 3.86 (dd, *J*(6′,5)=4.6 Hz, *J*-(6′,6)=11.4 Hz, 1H; H6′), 4.07 (dd, *J*(4,3)=3.7 Hz, *J*(4,5)=5.7 Hz, 1H; H4), 4.07–4.13 ppm (m, 1H; H2); $^{13}$C NMR ($D_2O$, 126 MHz): $\delta$=13.8 (NCH$_2$CH$_2$CH$_2$*C*H$_3$), 20.7 (NCH$_2$CH$_2$*C*H$_2$CH$_3$), 22.7 (NHCO*C*H$_3$), 25.9 (NCH$_2$CH$_2$CH$_2$CH$_3$), 48.0 (C2), 52.4 (NCH$_2$CH$_2$CH$_2$CH$_3$), 54.4 (C1), 61.0 (C6), 63.1 (C5), 70.1 (C4), 73.4 (C3), 175.0 ppm (NH*C*OCH$_3$); IR (thin film, Ge): $\tilde{\nu}$=1559 (s; amide II), 1644 (s; amide I), 3286 cm$^{-1}$ (br s; OH); LRMS (ESI+): *m*/*z* (%): 261 (100) [*M*+H]$^+$; HRMS (ESI+): *m*/*z* calcd for $C_{12}H_{25}N_2O_4$: 261.1809 [*M*+H]$^+$; found: 260.1809.

Data for the HCl salt: $^1$H NMR ($D_2O$, 400 MHz): $\delta$=0.93 (t, *J*=7.4 Hz, 3H; NCH$_2$CH$_2$CH$_2$C$H_3$), 1.31–1.45 (m, 2H; NCH$_2$CH$_2$C$H_2$CH$_3$), 1.58–1.81 (m, 2H; NCH$_2$C$H_2$CH$_2$CH$_3$), 2.03 (s, 3H; NHCOC$H_3$), 3.01 (app t, *J*(1,2)=*J*(1,1′)=11.9 Hz, 1H; H1), 3.16–3.38 (m, 2H; NC$H_2$CH$_2$CH$_2$CH$_3$), 3.45–3.57 (m, 2H; H1′ and H5), 3.78 (dd, *J*(3,4)= 2.8 Hz, *J*(3,2)=10.8 Hz, 1H; H3), 4.01 (app d, *J*=4.3 Hz, 2H; H6 and H6′), 4.31 (app s, 1H; H4), 4.37 ppm (td, *J*(2,1)=4.8 Hz, *J*(2,1′)=*J*(2,3)= 11.9 Hz, 1H; H2); $^{13}$C NMR ($D_2O$, 100 MHz): $\delta$=13.4 (NCH$_2$CH$_2$CH$_2$*C*H$_3$), 19.9 (NCH$_2$CH$_2$*C*H$_2$CH$_3$), 22.6 (NHCO*C*H$_3$), 24.4

($NCH_2CH_2CH_2CH_3$), 46.0 (C2), 52.1 (C1), 53.8 ($NCH_2CH_2CH_2CH_3$), 59.8 (C6), 64.5 (C5), 70.1 (C4), 70.6 (C3), 175.3 ppm ($NHCOCH_3$).

*2-Acetamido-1-N-benzyl-1,2,5-trideoxy-1,5-imino-*D*-galactitol,* (*N-benzyl-DGJNAc,* ***1Dd***): Benzaldehyde (0.01 mL, 0.1 mmol) and sodium cyanoborohydride (6 mg, 0.1 mmol) were added to a solution of DGJNAc (**1D**, 20 mg, 0.10 mmol) in EtOH/acetic-acid (200:1, 10 mL). The reaction was stirred at RT for 3 h, after which time LRMS indicated the absence of the starting material. The reaction mixture was concentrated in vacuo and the crude residue was purified by cation-exchange chromatography (Bond Elut SCX 1 cc cartridge, residue loaded in 50 mM HCl and eluted with 3.5% ammonium hydroxide in MeOH/water 9:1). A large proportion of the product was eluted during the wash fractions, which were concentrated and purified by column chromatography on Dowex (50W-X8, $H^+$, washed with water). The product was liberated with aqueous ammonia (2 M) and the ammoniacal fractions were concentrated in vacuo. The products of both columns were combined to afford *N*-benzyl-DGJNAc (**1Dd**) as a colorless oil (20 mg, 68%); $[\alpha]_D^{25} = +17.6$ (*c* 0.25, MeOH); $^1$H NMR ($D_2O$, 400 MHz): $\delta = 1.95$ (s, 3H; $NHCOCH_3$), 2.30 (app t, $J(1,1') = J(1,2) = 11.7$ Hz, 1H; H1), 2.96 (app s, 1H; H5), 3.02 (dd, $J(1',2) = 4.2$ Hz, $J(1',1) = 11.7$ Hz, 1H; H1′), 3.58 (dd, $J = 2.9$ Hz, $J = 10.7$ Hz, 1H; H3), 3.83 (d, $J_{gem} = 13.1$ Hz, 1H; $NCHH'Ph$), 4.06 (dd, $J(5,6') = 5.9$ Hz, $J(6,6') = 12.1$ Hz, 1H; H6), 4.11–4.25 (m, 3H; H2, H4 and H6′), 4.30 (d, $J_{gem} = 13.1$ Hz, 1H; $NCHH'Ph$), 7.41–7.48 ppm (m, 5H; ArH); $^{13}$C NMR ($D_2O$, 126 MHz): $\delta = 22.5$ ($NHCOCH_3$), 46.5 (C2), 52.7 (C1), 56.7 ($NCH_2Ph$), 60.5 (C6), 64.6 (C5), 70.2 (C4), 72.3 (C3), 128.9, 129.4, 131.3, 131.8 (ArCH), 136.8 (ArCC), 175.0 ppm ($NHCOCH_3$); IR (thin film, Ge): $\tilde{\nu} = 1558$ (s; amide II), 1635 (s; amide I), 3385 $cm^{-1}$ (br s; OH); LRMS (ESI+): *m*/*z* (%): 295 (100) $[M+H]^+$, 317 (75) $[M+Na]^+$; HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{23}N_2O_4$: 295.1652 $[M+H]^+$; found: 295.1648.

*2-Acetamido-1,2,5-trideoxy-1-N-hydroxyethyl-1,5-imino-*D*-galactitol,* (*N-hydroxyethyl-DGJNAc,* ***1De***): Glycoaldehyde dimer (180 mg, 1.50 mmol) and palladium (10% on carbon, 12 mg) were added to a solution of DGJNAc (**1D**, 30 mg, 0.15 mmol) in 1,4-dioxane/water (1:1, 4 mL). The vessel was degassed, charged with hydrogen, and the reaction mixture was stirred at RT for 16 h. The reaction mixture was filtered (GF/A glass microfiber) and concentrated in vacuo. The residue was loaded onto a short column of Dowex (50W-X8, $H^+$) and the resin was washed with water. The product was liberated with aqueous ammonia (2 M) and the ammoniacal fractions were concentrated in vacuo to afford *N*-hydroxyethyl-DGJNAc (**1De**) as an off-white, viscous gum (35 mg, 95%); $[\alpha]_D^{25} = +14.2$ (*c* 0.96, MeOH); $^1$H NMR ($D_2O$, 400 MHz): $\delta = 2.00$ (s, 3H; $NHCOCH_3$), 2.21 (app t, $J(1,1') = J(1,2) = 11.4$ Hz, 1H; H1), 2.52–2.71 (m, 2H; H5 and $NCHH'CH_2OH$), 2.85–2.96 (m, 1H; $NCHH'CH_2OH$), 3.02 (dd, $J(1',2) = 4.5$ Hz, $J(1',1) = 11.8$ Hz, 1H; H1′), 3.50 (dd, $J = 2.8$ Hz, $J = 10.5$ Hz, 1H; H3), 3.68 (app dt, $J = 5.7$ Hz, $J_{gem} = 11.8$ Hz, 2H; $NCH_2CH_2OH$), 3.79 (dd, $J(6,5) = 5.9$ Hz, $J(6,6') = 11.5$ Hz, 1H; H6), 3.85 (dd, $J(6',5) = 5.1$ Hz, $J(6',6) = 11.5$ Hz, 1H; H6′), 3.96–4.12 ppm (m, 2H; H2 and H4); $^{13}$C NMR ($D_2O$, 100 MHz): $\delta = 22.6$ ($NHCOCH_3$), 48.2 (C2), 53.5 ($NCH_2CH_2OH$), 54.8 (C1), 58.7 ($NCH_2CH_2OH$), 61.4 (C6), 64.1 (C5), 70.6 (C4), 73.2 (C3), 175.0 ppm ($NHCOCH_3$); IR (thin film, Ge): $\tilde{\nu} = 1561$ (s; amide II), 1638 (s; amide I), 3318 $cm^{-1}$ (br s; OH); LRMS (ESI+): *m*/*z* (%): 249 (27) $[M+H]^+$, 271 (66) $[M+Na]^+$, 519 (100) $[2M+Na]^+$; HRMS (ESI+): *m*/*z* calcd for $C_{10}H_{20}N_2NaO_5$: 271.1264 $[M+Na]^+$; found: 271.1260.

**Synthesis of DNJNAc and derivatives**

*5-Azido-3-O-benzyl-6-O-tert-butyldimethylsilyl-5-deoxy-1,2-O-isopropylidene-β-*L*-idofuranose* (***24L***): Sodium hydride (60% min. oil suspension, 1.00 g, 25.0 mmol) was added to a solution of alcohol **7L** (5.90 g, 16.4 mmol) and benzyl bromide (3.0 mL, 25 mmol) in DMF (50 mL) at 0°C. The reaction mixture was allowed to warm to RT and stirred for 1 h. TLC analysis (cyclohexane/EtOAc, 3:1) indicated the complete consumption of the starting material ($R_f = 0.30$) and the formation of a single product ($R_f = 0.60$). The reaction mixture was diluted with EtOAc (150 mL), washed with a water/sat. brine solution (1:1, 3×150 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (cyclohexane/EtOAc, 49:1 to 9:1) to afford benzyl ether **24L** as a colorless oil (7.36 g, 100%). $[\alpha]_D^{25} = -39.4$ (*c* 1.78, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta = 0.01$, 0.03 (s, 2×3H; $Si(CH_3)_2$), 0.87 (s, 9H; $SiC(CH_3)_3$), 1.33, 1.49 (s, 2×3H; $C(CH_3)_2$), 3.53 (dd, $J(6,5) = 6.3$ Hz, $J(6,6') = 11.4$ Hz, 1H; H6), 3.68–3.72 (m, 2H; H5 and H6′), 3.89 (d, $J(3,4) = 3.0$ Hz, 1H; H3), 4.28 (dd, $J(4,3) = 3.0$ Hz, $J(4,5) = 8.3$ Hz, 1H; H4), 4.44 (d, $J_{gem} = 11.9$ Hz, 1H; $OCH_2Ph$), 4.67 (d, $J(2,1) = 3.8$ Hz, 1H; H2), 4.71 (d, $J_{gem} = 11.9$ Hz, 1H; $OCH_2Ph$), 5.97 (d, $J(1,2) = 3.8$ Hz, 1H; H1), 7.30–7.39 ppm (m, 5H; ArH); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta = -5.7$, $-5.6$ ($Si(CH_3)_2$), 18.1 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 26.4, 26.7 ($C(CH_3)_2$), 61.9 (C5), 63.1 (C6), 71.5 ($OCH_2Ph$), 78.8 (C4), 81.3 (C3), 81.8 (C2), 104.7 (C1), 111.9 ($C(CH_3)_2$), 128.0, 128.2, 128.6 (ArCH), 136.8 ppm (ArCC); IR (thin film): $\tilde{\nu} = 2100$ (s; $N_3$); LRMS (ESI+): *m*/*z* (%): 472 (67) $[M+Na]^+$, 551 (56), 916 (93) $[2M+NH_4]^+$, 921 (100) $[2M+Na]^+$; HRMS (ESI+): *m*/*z* calcd for $C_{22}H_{35}N_3NaO_5Si$: 472.2238 $[M+Na]^+$; found: 472.2235.

For enantiomer **24D**: $[\alpha]_D^{25} = +30.1$ (*c* 1.21, $CHCl_3$).

*Methyl 5-azido-3-O-benzyl-5-deoxy-*L*-idofuranosides* (***10L***): A solution of benzyl ether **24L** (7.36 g, 16.4 mmol) in a mixture of MeOH (50 mL) and acetyl chloride (2.5 mL) was stirred at 50°C for 1 h. TLC analysis (cyclohexane/EtOAc, 3:1) indicated the complete consumption of the starting material ($R_f = 0.60$) and the formation of two products ($R_f = 0.00$; toluene/acetone (4:1): $R_f = 0.25$, 0.35). The reaction mixture was neutralized by the addition of solid sodium bicarbonate, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (toluene/acetone, 49:1 to 3:1) to afford anomeric methyl furanoside **10Lβ** as a white crystalline solid ($R_f = 0.35$, 2.42 g, 48%) and **10Lα** as a colorless oil ($R_f = 0.25$, 2.19 g, 43%).

Data for compound **10Lβ**: M.p. 46–50°C; $[\alpha]_D^{25} = +79.1$ (*c* 1.39, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta = 2.04$ (t, $J(OH6,6) = J(OH6,6') = 6.3$ Hz, 1H; OH6), 2.85 (d, $J(OH2,2) = 6.8$ Hz, 1H; OH2), 3.51 (s, 3H; $OCH_3$), 3.57 (app dt, $J(6,5) = J(6,OH6) = 6.1$ Hz, $J(6,6') = 11.6$ Hz, 1H; H6), 3.66 (ddd, $J(6',5) = 4.0$ Hz, $J(6',OH6) = 6.6$ Hz, $J(6',6) = 11.6$ Hz, 1H; H6′), 3.82 (app dt, $J(5,6') = 4.0$ Hz, $J(5,4) = J(5,6) = 6.4$ Hz, 1H; H5), 3.99 (dd, $J(3,2) = 3.8$ Hz, $J(3,4) = 5.6$ Hz, 1H; H3), 4.28 (app t, $J(4,3) = J(4,5) = 6.0$ Hz, 1H; H4), 4.37 (ddd, $J(2,3) = 3.8$ Hz, $J(2,1) = 4.5$ Hz, $J(2,OH2) = 7.1$ Hz, 1H; H2), 4.55 (d, $J_{gem} = 11.9$ Hz, 1H; $OCH_2Ph$), 4.81 (d, $J_{gem} = 11.9$ Hz, 1H; $OCH_2Ph$), 5.05 (d, $J(1,2) = 4.8$ Hz, 1H; H1), 7.30–7.39 ppm (m, 5H; ArH); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta = 55.8$ ($OCH_3$), 62.4 (C6), 62.9 (C5), 71.7 ($OCH_2Ph$), 76.4 (C2), 77.9 (C4), 83.1 (C3), 101.6 (C1), 127.9, 128.0, 129.5 (ArCH), 137.2 ppm (ArCC); IR (thin film): $\tilde{\nu} = 2105$ (s; $N_3$), 3424 (br s; OH); LRMS (ESI+): *m*/*z* (%): 332 (91) $[M+Na]^+$, 348 (78) $[M+K]^+$, 641 (100) $[2M+Na]^+$; HRMS (ESI+): *m*/*z* calcd for $C_{14}H_{19}N_3NaO_5$: 332.1217 $[M+Na]^+$; found: 332.1215.

For enantiomer **10Dβ**: M.p. 43–44°C; $[\alpha]_D^{25} = -73.2$ (*c* 1.32, $CHCl_3$).

Data for compound **10Lα**: $[\alpha]_D^{25} = -41.4$ (*c* 0.92, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta = 2.20$ (t, $J(OH6,6) = J(OH6,6') = 6.5$ Hz, 1H; OH6), 2.51 (d, $J(OH2,2) = 4.3$ Hz, 1H; OH2), 3.47 (s, 3H; $OCH_3$), 3.50 (app dt, $J(6,5) = J(6,OH6) = 6.1$ Hz, $J(6,6') = 11.6$ Hz, 1H; H6), 3.65 (ddd, $J(6',5) = 3.5$ Hz, $J(6',OH6) = 6.1$ Hz, $J(6',6) = 11.6$ Hz, 1H; H6′), 3.91 (ddd, $J(5,6') = 3.8$ Hz, $J(5,6) = 5.8$ Hz, $J(5,4) = 8.1$ Hz, 1H; H5), 3.94 (dd, $J(3,2) = 2.3$ Hz, $J(3,4) = 5.6$ Hz, 1H; H3), 4.33 (app dt, $J(2,1) = J(2,3) = 2.0$ Hz, $J(2,OH2) = 4.0$ Hz, 1H; H2), 4.35 (dd, $J(4,3) = 5.6$ Hz, $J(4,5) = 8.3$ Hz, 1H; H4), 4.49 (d, $J_{gem} = 11.9$ Hz, 1H; $OCH_2Ph$), 4.73 (d, $J_{gem} = 11.9$ Hz, 1H; $OCH_2Ph$), 4.86 (d, $J(1,2) = 1.5$ Hz, 1H; H1), 7.30–7.39 ppm (m, 5H; ArH); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta = 56.2$ ($OCH_3$), 62.2 (C6), 64.2 (C5), 72.1 ($OCH_2Ph$), 78.3 (C2), 80.7 (C4), 82.3 (C3), 109.6 (C1), 128.1, 128.1, 129.6 (ArCH), 137.0 ppm (ArCC); IR (thin film): $\tilde{\nu} = 2106$ (s; $N_3$), 3417 (br s; OH); LRMS (ESI+): *m*/*z* (%): 332 (74) $[M+Na]^+$, 348 (57), $[M+K]^+$, 641 (100) $[2M+Na]^+$; HRMS (ESI+): *m*/*z* calcd for $C_{14}H_{19}N_3NaO_5$: 332.1217 $[M+Na]^+$; found: 332.1214.

For enantiomer **10Dα**: $[\alpha]_D^{25} = +33.6$ (*c* 1.03, $CHCl_3$).

*Methyl-5-azido-3-O-benzyl-5-deoxy-6-O-methanesulfonyl-β-*L*-idofuranoside* (***25Lβ***): Methanesulfonyl chloride (0.29 mL, 3.8 mmol) was added dropwise to a solution of diol **10Lβ** (982 mg, 3.17 mmol) and pyridine (0.61 mL, 7.6 mmol) in $CH_2Cl_2$ (9 mL) at 0°C. After 3 h, TLC analysis (toluene/acetone, 4:1) indicated the complete consumption of the starting material ($R_f = 0.35$) and the formation of a major product ($R_f = 0.45$) and a minor product ($R_f = 0.50$). The reaction mixture was diluted with $CH_2Cl_2$ (15 mL), washed with 2 M HCl (3×20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by

column chromatography on silica gel ($CH_2Cl_2$/MeOH, 60:1) to afford the primary mesylate (**25Lβ**) as a colorless oil (582 mg, 86%); $[\alpha]_D^{25}=+72.6$ (*c* 0.97, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta=2.74$ (d, $J$(OH2,2)= 7.6 Hz, 1H; OH2), 3.02 (s, 3H; $SO_2CH_3$), 3.49 (s, 3H; $OCH_3$), 3.95 (app dt, $J(5,6')=4.3$ Hz, $J(5,4)=J(5,6)=6.3$ Hz, 1H; H5), 4.05 (dd, $J(3,2)=$ 4.3 Hz, $J(3,4)=6.1$ Hz, 1H; H3), 4.20 (dd, $J(6,5)=6.7$ Hz, $J(6,6')=$ 10.6 Hz, 1H; H6), 4.25 (dd, $J(6',5)=4.3$ Hz, $J(6',6)=10.6$ Hz, 1H; H6′), 4.26 (app t, $J(4,3)=J(4,5)=6.0$ Hz, 1H; H4), 4.37 (app dt, $J(2,1)=J$-(2,3)=4.5 Hz, $J$(2,OH2)=7.6 Hz, 1H; H2), 4.57 (d, $J_{gem}=11.6$ Hz, 1H; $OCH_2Ph$), 4.83 (d, $J_{gem}=11.6$ Hz, 1H; $OCH_2Ph$), 5.01 (d, $J(1,2)=4.8$ Hz, 1H; H1), 7.30–7.40 ppm (m, 5H; ArH); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta=37.5$ ($SO_2CH_3$), 55.9 ($OCH_3$), 60.0 (C5), 68.5 (C6), 71.9 ($OCH_2Ph$), 76.6 (C2), 76.7 (C4), 82.8 (C3), 101.7 (C1), 128.1, 128.6 (Ar*C*H), 137.1 ppm (Ar*C*C); IR (thin film): $\tilde{\nu}=2110$ (s; $N_3$), 3518 (br s; OH); LRMS (ESI+): *m*/*z* (%): 410 (100) $[M+Na]^+$; HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{21}N_3NaO_7S$: 410.0992 $[M+Na]^+$; found: 410.0991.

For enantiomer **25Dβ**: $[\alpha]_D^{25}=-65.5$ (*c* 0.87, $CHCl_3$)

*Methyl-5-azido-2-N-benzyl-3-O-benzyl-2,6-imino-2,5,6-trideoxy-β-*L*-gulofuranoside* (***11Lβ***): Trifluoromethanesulfonic anhydride (0.69 mL, 4.2 mmol) and pyridine (0.68 mL, 8.4 mmol) were added to a solution of mesylate **25Lβ** (1.28 g, 3.38 mmol) in $CH_2Cl_2$ (14 mL) at −40°C. After 1 h, with the internal temperature rising to −30°C, TLC analysis ($CH_2Cl_2$/MeOH, 30:1) indicated the complete consumption of the starting material ($R_f=0.45$) and the formation of a single product ($R_f=0.65$). The reaction mixture was diluted with $CH_2Cl_2$ (25 mL), washed with 2M HCl (3×20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude triflate (**26Lβ**) was dissolved in benzylamine (5.8 mL) and stirred at 100°C for 18 h. TLC analysis (cyclohexane/EtOAc/triethylamine, 66:33:1) indicated the complete consumption of the triflate ($R_f=0.30$) and the formation of a major product ($R_f=0.70$). The reaction mixture was pre-adsorbed onto silica gel and purified by column chromatography on silica gel (cyclohexane/EtOAc/triethylamine, 99:0:1 to 94:5:1) to afford the bicyclic piperidine (**11Lβ**) as a pale-yellow crystalline solid (1.09 g, 70%). M.p. 50–54°C; $[\alpha]_D^{25}=+120.3$ (*c* 0.46, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta=3.02$ (dd, $J(6,5)=4.3$ Hz, $J(6,6')=13.1$ Hz, 1H; H6), 3.06 (d, $J(6',6)=13.1$ Hz, 1H; H6′), 3.18 (d, $J(2,3)=4.3$ Hz, 1H; H2), 3.35 (s, 3H; $OCH_3$), 3.49–3.52 (m, 1H; H5), 3.73 (s, 2H; $NCH_2Ph$), 4.16 (app t, $J(3,2)=J(3,4)=4.6$ Hz, 1H; H3), 4.26 (t, $J(4,3)=J(4,5)=$ 4.6 Hz, 1H; H4), 4.51 (d, $J_{gem}=11.9$ Hz, 1H; $OCH_2Ph$), 4.63 (d, $J_{gem}=$ 11.9 Hz, 1H; $OCH_2Ph$), 4.94 (s, 1H; H1), 7.28–7.47 ppm (m, 10H; ArH); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta=49.4$ (C6), 55.4 ($OCH_3$), 56.3 (C5), 60.1 ($NCH_2Ph$), 61.5 (C2), 70.7 ($OCH_2Ph$), 72.2 (C4), 73.1 (C3), 101.4 (C1), 127.5, 127.6, 127.7, 128.3, 128.4, 129.1 (Ar*C*H), 137.5, 137.9 ppm (Ar*C*C); IR (thin film): $\tilde{\nu}=2114$ (s; $N_3$); LRMS (ESI+): *m*/*z* (%): 381 (75) $[M+H]^+$, 403 (77) $[M+Na]^+$, 783 (100) $[M+Na]^+$; HRMS (ESI+): *m*/*z* calcd for $C_{21}H_{24}N_4NaO_3$: 403.1741 $[M+Na]^+$; found: 403.1737.

For enantiomer **11Dβ**: M.p. 48–50°C; $[\alpha]_D^{25}=-109.2$ (*c* 0.67, $CHCl_3$).

*Methyl-5-azido-3-O-benzyl-5-deoxy-6-O-p-toluenesulfonyl-α-*L*-idofuranoside* (***27Lα***): *p*-Toluenesulfonyl chloride (450 mg, 2.36 mmol) was added to a solution of diol **10Lα** (358 mg, 1.16 mmol) and 2,4,6-collidine (0.60 mL, 4.5 mmol) in $CH_2Cl_2$ (5 mL) at RT. After 24 h, TLC analysis (toluene/acetone, 4:1) indicated a trace of starting material ($R_f=0.25$), as well as the formation of a major product ($R_f=0.50$) and a minor product ($R_f=0.75$). The reaction mixture was diluted with $CH_2Cl_2$ (10 mL), washed with 2M HCl (3×10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (toluene/acetone, 99:1 to 19:1) to afford the primary tosylate (**27Lα**) as a colorless oil (397 mg, 74%). $[\alpha]_D^{25}=-7.0$ (*c* 1.32, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta=2.07$ (br s, 1H; OH2), 2.44 (s, 3H; $SO_2C_6H_4CH_3$), 3.40 (s, 3H; $OCH_3$), 3.90–3.95 (m, 2H; H3 and H5), 4.05 (dd, $J(6,5)=$ 5.8 Hz, $J(6,6')=10.4$ Hz, 1H; H6), 4.09 (dd, $J(6',5)=3.8$ Hz, $J(6',6)=$ 10.4 Hz, 1H; H6′), 4.28–4.29 (m, 1H; H2), 4.30 (dd, $J=6.1$ Hz, $J=$ 7.6 Hz, 1H; H4), 4.46 (d, $J_{gem}=11.6$ Hz, 1H; $OCH_2Ph$), 4.67 (d, $J_{gem}=$ 11.6 Hz, 1H; $OCH_2Ph$), 4.81 (d, $J(1,2)=1.5$ Hz, 1H; H1), 7.30–7.39 (m, 7H; ArH), 7.74–7.77 ppm (m, 2H; ArH); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta=21.7$ ($SO_2C_6H_4CH_3$), 56.1 ($OCH_3$), 60.8 (C5), 68.9 (C6), 72.3 ($OCH_2Ph$), 78.3 (C2), 79.7 (C4), 82.5 (C3), 109.6 (C1), 128.0, 128.1, 128.2, 128.6, 129.9 (Ar*C*H), 132.5, 137.0, 145.1 ppm (Ar*C*C); IR (thin film): $\tilde{\nu}=$ 2105 (s; $N_3$), 3443 (br s; OH); LRMS (ESI+): *m*/*z* (%): 486 (100) $[M+Na]^+$; HRMS (ESI+): *m*/*z* calcd for $C_{21}H_{25}N_3NaO_7S$: 486.1305 $[M+Na]^+$; found: 486.1303.

For enantiomer **27Dα**: $[\alpha]_D^{25}=+11.0$ (*c* 1.15, $CHCl_3$).

*Methyl-5-azido-2-N,3-O-dibenzyl-2,5,6-trideoxy-2,6-imino-α-*L*-gulofuranoside* (***11Lα***): Trifluoromethanesulfonic anhydride (0.20 mL, 1.2 mmol) and pyridine (0.20 mL, 2.5 mmol) were added to a solution of tosylate **27Lα** (483 mg, 1.04 mmol) in $CH_2Cl_2$ (5 mL) at −40°C. After 1 h, with the internal temperature rising to −30°C, TLC analysis (cyclohexane/EtOAc, 2:1) indicated the complete consumption of the starting material ($R_f=0.15$) and the formation of a single product ($R_f=0.55$). The reaction mixture was diluted with $CH_2Cl_2$ (15 mL), washed with 2M HCl (3× 20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude triflate (**28Lα**) was dissolved in benzylamine (2.5 mL) and the mixture was stirred at 100°C for 18 h. TLC analysis (cyclohexane/EtOAc, 80:19:1) indicated the complete consumption of the triflate ($R_f=0.35$) and the formation of a major product ($R_f=0.60$). The reaction mixture was preadsorbed onto silica gel and purified by column chromatography on silica gel (cyclohexane/EtOAc/triethylamine, 99:0:1 to 94:5:1) to afford the bicyclic piperidine (**11Lα**) as a pale-yellow oil (267 mg, 68%). $[\alpha]_D^{25}=+39.2$ (*c* 1.05, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta=3.00$ (d, $J$-(6,6′)=12.9 Hz, 1H; H6), 3.27 (app t, $J(2,1)=J(2,3)=3.7$ Hz, 1H; H2), 3.50 (s, 3H; $OCH_3$), 3.56 (app t, $J(5,4)=J(5,6')=4.7$ Hz, 1H; H5), 3.77 (dd, $J(6',5)=5.6$ Hz, $J(6',6)=12.9$ Hz, 1H; H6′), 3.83 (app t, $J(3,2)=J$-(3,4)=4.5 Hz, 1H; H3), 3.92 (d, $J_{gem}=13.4$ Hz, 1H; $NCH_2Ph$), 4.06 (d, $J_{gem}=13.4$ Hz, 1H; $NCH_2Ph$), 4.24 (app t, $J(4,3)=J(4,5)=4.5$ Hz, 1H; H4), 4.47 (d, $J_{gem}=12.1$ Hz, 1H; $OCH_2Ph$), 4.64 (d, $J_{gem}=12.1$ Hz, 1H; $OCH_2Ph$), 5.02 (d, $J(1,2)=2.8$ Hz, 1H; H1), 7.25–7.37 ppm (m, 10H; ArH); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta=49.0$ (C6), 56.4 (C5), 56.8 ($OCH_3$), 57.6 (C2), 60.1 ($NCH_2Ph$), 71.5 ($OCH_2Ph$), 74.9 (C4), 75.1 (C3), 107.3 (C1), 127.1, 127.6, 127.7, 128.2, 128.3, 129.1 (Ar*C*H), 137.7, 138.4 ppm (Ar*C*C); IR (thin film): $\tilde{\nu}=2114$ (s; $N_3$); LRMS (ESI+): *m*/*z* (%): 381 (97) $[M+H]^+$, 403 (100) $[M+Na]^+$; HRMS (ESI+): *m*/*z* calcd for $C_{21}H_{25}N_4O_3$: 381.1921 $[M+H]^+$; found: 381.1921.

For enantiomer **11Dα**: $[\alpha]_D^{25}=-40.0$ (*c* 1.58, $CHCl_3$).

*4-O-Acetyl-5-azido-2-N,3-O-dibenzyl-2,5,6-trideoxy-2,6-imino-*L*-gulose acetyl methyl acetal* (***29L***): Boron trifluoride diethyl etherate (0.82 mL, 6.6 mmol) was added dropwise to a solution of bicyclic acetal **11Lβ** (797 mg, 2.09 mmol) in acetic anhydride (8 mL) at 0°C. The reaction mixture was allowed to warm to RT and stirred for 36 h, after which time TLC analysis (cyclohexane/EtOAc/triethylamine, 80:19:1) indicated the complete consumption of the starting material ($R_f=0.60$) and the formation of a major product ($R_f=0.50$). The reaction mixture was concentrated in vacuo and the residue was dissolved in EtOAc (40 mL), washed with a saturated solution of sodium bicarbonate (3×20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (cyclohexane/EtOAc/triethylamine, 99:0:1 to 90:9:1) to afford the mixed-acetal piperidine (**29L**) as a pale-yellow oil (951 mg, 94%), in a 2:1 (A/B) ratio of diastereoisomers.

Similar treatment of the epimer (**11Lα**, 96 mg, 0.25 mmol, $R_f=0.55$ in cyclohexane/EtOAc/triethylamine, 80:19:1) with boron trifluoride etherate for 3 h afforded compound **29L** as a pale-yellow oil (86 mg, 71%), as a 2:1 (A/B) ratio of diastereoisomers.

Data for compound **29L**: $^1$H NMR ($CDCl_3$, 400 MHz): $\delta=2.06$ (s, 3H; $COCH_3^B$), 2.07, 2.09 (s, 2×3H; $COCH_3^A$), 2.14 (s, 3H; $COCH_3^B$), 2.16–2.23 (m, 2H; H6$^A$ and H6$^B$), 2.82–2.85 (m, 2H; H2$^A$ and H2$^B$), 2.96 (dd, $J(6',5)=4.8$ Hz, $J(6',6)=12.4$ Hz, 1H; H6′$^A$), 2.96 (dd, $J(6',5)=4.5$ Hz, $J$-(6′,6)=11.9 Hz, 1H; H6′$^B$), 3.35 (s, 3H; $OCH_3^B$), 3.39 (s, 3H; $OCH_3^A$), 3.42 (d, $J_{gem}=14.1$ Hz, 1H; $NCH_2Ph^B$), 3.45–3.52 (m, 2H; H5$^A$ and H5$^B$), 3.57 (d, $J_{gem}=13.4$ Hz, 1H; $NCH_2Ph^A$), 3.64 (t, $J(3,2)=J(3,4)=8.1$ Hz, 1H; H3$^B$), 3.70 (t, $J(3,2)=J(3,4)=8.8$ Hz, 1H; H3$^A$), 4.29 (d, $J_{gem}=$ 13.4 Hz, 1H; $NCH_2Ph^A$), 4.38 (d, $J_{gem}=14.1$ Hz, 1H; $NCH_2Ph^B$), 4.63 (d, $J_{gem}=11.1$ Hz, 1H; $OCH_2Ph^A$), 4.64 (d, $J_{gem}=10.9$ Hz, 1H; $OCH_2Ph^B$), 4.68 (d, $J_{gem}=11.1$ Hz, 1H; $OCH_2Ph^A$), 4.73 (d, $J_{gem}=10.9$ Hz, 1H; $OCH_2Ph^B$), 5.08–5.13 (m, 2H; H4$^A$ and H4$^B$), 6.14 (d, $J(1,2)=1.8$ Hz, 1H; H1$^B$), 6.23 (d, $J(1,2)=2.3$ Hz, 1H; H1$^A$), 7.24–7.39 ppm (m, 20H; ArH); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta=21.0$, 21.0 ($COCH_3^A$), 21.1, 21.1

($CO\mathit{C}H_3^B$), 52.0 ($C6^A$), 52.4 ($C6^B$), 57.0 ($N\mathit{C}H_2Ph^A$), 57.2 ($OCH_3^B$), 57.6 ($OCH_3^A$), 58.3 ($N\mathit{C}H_2Ph^B$), 58.7 ($C5^A$), 58.9 ($C5^B$), 66.2 ($C2^A$), 66.8 ($C2^B$), 74.2 ($O\mathit{C}H_2Ph^A$), 74.3 ($O\mathit{C}H_2Ph^B$), 76.6, 76.8, 76.9, 76.9 ($C3^A$, $C3^B$, $C4^A$, $C4^B$), 96.9 ($C1^A$), 97.2 ($C1^B$), 127.1, 127.2, 127.5, 127.7, 127.7, 127.7, 128.0, 128.1, 128.4, 128.4, 128.6, 128.9 (Ar*C*H), 137.9, 138.7, 138.7, 139.0 (Ar*C*C), 170.0, 170.2, 170.2, 171.0 ppm ($\mathit{C}OCH_3$); IR (thin film): $\tilde{\nu}$ = 1746 (s, C=O), 2104 (s, $N_3$); LRMS (ESI+): *m/z* (%): 483 (97) $[M+H]^+$, 505 (100) $[M+Na]^+$, 987 (92) $[2M+Na]^+$; HRMS (ESI+): *m/z* calcd for $C_{25}H_{31}N_4O_6$: 483.2238 $[M+H]^+$; found: 483.2242.

*3,6-Di-O-acetyl-2-azido-1-N,4-O-dibenzyl-1,2,5-trideoxy-1,5-imino*-D-*glucitol* (***30D***): Diisobutylaluminium hydride (16.8 mL, 16.8 mmol) was added dropwise to a solution of mixed acetal **29L** (1.6 g, 3.3 mmol) in $CH_2Cl_2$ (13 mL) at −78 °C. After 40 min, TLC analysis (cyclohexane/EtOAc/triethylamine, 79:20:1) indicated the complete consumption of the starting material ($R_f$ = 0.40) and the formation of a major product ($R_f$ = 0.25). The reaction mixture was quenched and diluted with EtOAc (88 mL) and allowed to warm to RT. A saturated solution of sodium potassium tartrate (88 mL) was added and the biphasic mixture was stirred vigorously for 1 h. The organic layer was collected and the aqueous layer was extracted with EtOAc (3 × 20 mL). The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was dissolved in MeOH (18 mL) and sodium borohydride (125 mg, 3.30 mmol) was added at −10 °C. After 2 h, TLC analysis (cyclohexane/EtOAc/triethylamine, 59:40:1) indicated the complete consumption of the intermediate ($R_f$ = 0.55) and the formation of a major product ($R_f$ = 0.25). The reaction mixture was neutralized with glacial acetic acid, concentrated in vacuo, and dissolved in pyridine (9 mL) and acetic anhydride (9 mL). The reaction was stirred at RT for 16 h, after which time TLC analysis (cyclohexane/EtOAc/triethylamine, 59:40:1) indicated the complete consumption of the starting material ($R_f$ = 0.25) and the formation of a major product ($R_f$ = 0.40). The reaction mixture was concentrated in vacuo and purified by column chromatography on silica gel (cyclohexane/EtOAc/triethylamine, 96:3:1 to 84:15:1) to afford the diacetyl piperidine (**30D**) as a white crystalline solid (1.315 g, 88 % over 3 steps). M.p. 89–91 °C; $[\alpha]_D^{22}$ = +3.3 (*c* 1.20, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 2.06 (app t, $J(1,1')=J(1,2)$ = 11.4 Hz, 1H; H1), 2.07, 2.08 (s, 2 × 3H; $COCH_3$), 2.55 (app dt, $J(5,6)=J(5,6')$ = 2.7 Hz, $J(5,4)$ = 9.6 Hz, 1H; H5), 2.98 (dd, $J(1',2)$ = 4.8 Hz, $J(1',1)$ = 11.6 Hz, 1H; H1′), 3.27 (d, $J_{gem}$ = 13.3 Hz, 1H; $NC\mathit{H}_2Ph$), 3.47 (app dt, $J(2,1')$ = 4.8 Hz, $J(2,1)=J(2,3)$ = 10.4 Hz, 1H; H2), 3.66 (app t, $J(4,3)=J(4,5)$ = 9.4 Hz, 1H; H4), 4.09 (d, $J_{gem}$ = 13.3 Hz, 1H; $NC\mathit{H}_2Ph$), 4.31 (dd, $J(6,5)$ = 2.7 Hz, $J(6,6')$ = 12.6 Hz, 1H; H6), 4.59 (d, $J_{gem}$ = 10.9 Hz, 1H; $OC\mathit{H}_2Ph$), 4.64 (dd, $J(6',5)$ = 2.4 Hz, $J(6',6)$ = 12.8 Hz, 1H; H6′), 4.66 (d, $J_{gem}$ = 10.9 Hz, 1H; $OC\mathit{H}_2Ph$), 5.08 (app t, $J(3,2)=J(3,4)$ = 9.6 Hz, 1H; H3), 7.26–7.38 ppm (m, 10H; ArH); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 20.9, 20.9 ($CO\mathit{C}H_3$), 53.6 (C1), 56.5 ($N\mathit{C}H_2Ph$), 59.3 (C2), 59.9 (C6), 63.9 (C5), 75.0 ($O\mathit{C}H_2Ph$), 76.9 (C4), 77.4 (C3), 127.4, 128.0, 128.0, 128.5, 128.5, 128.7 (Ar*C*H), 137.3, 137.6 (Ar*C*C), 170.0, 170.6 ppm ($\mathit{C}OCH_3$); IR (thin film): $\tilde{\nu}$ = 1743 (s, C=O), 2104 (s, $N_3$); LRMS (ESI+): *m/z* (%): 453 (94) $[M+H]^+$, 475 (100) $[M+Na]^+$, 927 (99) $[2M+Na]^+$; HRMS (ESI+): *m/z* calcd for $C_{24}H_{28}N_4NaO_5$: 475.1952 $[M+H]^+$; found: 475.1954.

For enantiomer **30L**: M.p. 90–92 °C; $[\alpha]_D^{25}$ = −4.3 (*c* 2.2, $CHCl_3$).

*2-Acetamido-3,6-di-O-acetyl-1-N,4-O-dibenzyl-1,2,5-trideoxy-1,5-imino*-D-*glucitol* (***31D***): Powdered zinc (3.8 g, 58 mmol) was added to a solution of azide **30D** (1.31 g, 2.91 mmol) in THF/glacial-acetic-acid/acetic-anhydride (3:2:1, 35 mL) and the mixture was stirred vigorously before the dropwise addition of a saturated solution of copper(II) sulfate (9.2 mL) to initiate the reaction. After 20 min, TLC analysis (cyclohexane/EtOAc/triethylamine, 79:20:1) indicated the complete consumption of the starting material ($R_f$ = 0.50) and the formation of a major product ($R_f$ = 0.10). The reaction mixture was filtered through Celite, concentrated in vacuo, and the crude residue was purified by column chromatography on silica gel ($CH_2Cl_2$/MeOH, 40:1) to afford the acetamide (**31D**) as a white crystalline solid (1.11 g, 81 %). M.p. 149–151 °C; $[\alpha]_D^{25}$ = +0.9 (*c* 0.92, acetone); $^1$H NMR ([$D_6$]acetone), 400 MHz): $\delta$ = 1.74 (s, 3H; $NHCOC\mathit{H}_3$), 1.98, 2.06 (s, 2 × 3H; $COCH_3$), 2.14 (dd, $J(1,2)$ = 10.4 Hz, $J(1,1')$ = 11.6 Hz, 1H; H1), 2.63 (app dt, $J(5,6)=J(5,6')$ = 3.0 Hz, $J(5,4)$ = 8.8 Hz, 1H; H5), 2.85 (dd, $J(1',2)$ = 4.5 Hz, $J(1',1)$ = 11.6 Hz, 1H; H1′), 3.34 (d, $J_{gem}$ = 13.6 Hz, 1H; $NC\mathit{H}_2Ph$), 3.72 (app t, $J(4,3)=J(4,5)$ = 8.8 Hz, 1H; H4), 4.05 (app dq, $J(2,1')$ = 4.5 Hz, $J(2,1)=J(2,3)=J(2,NH)$ = 9.9 Hz, 1H; H2), 4.13 (d, $J_{gem}$ = 13.6 Hz, 1H; $NC\mathit{H}_2Ph$), 4.35 (dd, $J(6,5)$ = 3.3 Hz, $J(6,6')$ = 12.6 Hz, 1H; H6), 4.64 (dd, $J(6',5)$ = 2.8 Hz, $J(6',6)$ = 12.6 Hz, 1H; H6), 4.65 (d, $J_{gem}$ = 11.1 Hz, 1H; $OC\mathit{H}_2Ph$), 4.72 (d, $J_{gem}$ = 11.1 Hz, 1H; $OC\mathit{H}_2Ph$), 4.90 (dd, $J(3,4)$ = 8.6 Hz, $J(3,2)$ = 9.6 Hz, 1H; H3), 6.77 (d, $J(NH,2)$ = 9.3 Hz, 1H; $N\mathit{H}COCH_3$), 7.21–7.37 ppm (m, 10H; ArH); $^{13}$C NMR ([$D_6$]acetone), 100 MHz): $\delta$ = 20.8, 21.0 ($CO\mathit{C}H_3$), 22.9 ($NHCO\mathit{C}H_3$), 49.0 (C2), 54.6 (C1), 57.3 ($N\mathit{C}H_2Ph$), 60.6 (C6), 64.7 (C5), 75.2 ($O\mathit{C}H_2Ph$), 77.7 (C3), 77.9 (C4), 127.8, 128.4, 128.7, 128.1, 128.1, 128.5 (Ar*C*H), 139.3, 140.0 (Ar*C*C), 169.5, 170.9, 170.9 ppm ($\mathit{C}OCH_3$; $NHC\mathit{O}CH_3$); IR (thin film, Ge): $\tilde{\nu}$ = 1546 (s; amide II), 1660 (s; amide I), 1739 (s; C=O); LRMS (ESI+): *m/z* (%): 469 (100) $[M+H]^+$, 491 (64) $[M+Na]^+$; HRMS (ESI+): *m/z* calcd for $C_{26}H_{33}N_2O_6$: 469.2333 $[M+H]^+$; found: 469.2334.

For enantiomer **31L**: M.p. 144–148 °C; $[\alpha]_D^{25}$ = −2.6 (*c* 1.18, acetone).

*2-Acetamido-1,2,5-trideoxy-1,5-imino*-D-*glucitol* (*DNJNAc,* ***2D***). Sodium methoxide (60 mg, cat.) was added to a solution of the protected piperidine (**31D**, 1.11 g, 2.63 mmol) in MeOH (25 mL) at RT and the mixture was stirred for 16 h. TLC analysis (EtOAc/triethylamine, 99:1) indicated the complete consumption of the starting material ($R_f$ = 0.70) and the formation of a major product ($R_f$ = 0.25). The reaction mixture was neutralized with solid $CO_2$, concentrated in vacuo, and purified by column chromatography on silica gel ($CH_2Cl_2$/MeOH, 20:1 to 9:1). The crude residue was dissolved in water/2 M HCl/1,4-dioxane (13:3:4, 35 mL) and palladium (10 % on carbon, 408 mg) was added. The vessel was degassed, charged with hydrogen, and the reaction mixture was stirred at RT for 22 h. LRMS and $^1$H NMR spectroscopy indicated that a single product had been formed, with no trace of benzylated intermediates observed. The reaction mixture was filtered through Celite and concentrated in vacuo to afford crude DNJNAc (**2D**) as its hydrochloride salt.

Selected data for DNJNAc·HCl (**2D**): $^1$H NMR ($D_2O$, 400 MHz): $\delta$ = 2.03 (s, 3H; $NHCOC\mathit{H}_3$), 2.99 (app t, 1H, $J(1,2)=J(1,1')$ = 12.5 Hz; H1), 3.23 (ddd, $J(5,6')$ = 3.2 Hz, $J(5,6)$ = 5.0 Hz, $J(5,4)$ = 10.1 Hz, 1H; H5), 3.50 (dd, $J(1',2)$ = 5.0 Hz, $J(1',1)$ = 12.6 Hz, 1H; H1′), 3.63 (app t, $J(3,2)=J(3,4)$ = 9.6 Hz, 1H; H3), 3.67 (dd, $J(4,3)$ = 9.1 Hz, $J(4,5)$ = 10.2 Hz, 1H; H4), 3.90 (dd, $J(6,5)$ = 5.1 Hz, $J(6,6')$ = 12.8 Hz, 1H; H6), 3.96 (dd, $J(6',5)$ = 3.2 Hz, $J(6',6)$ = 12.8 Hz, 1H; H6′), 3.72 ppm (ddd, $J(2,1')$ = 5.0 Hz, $J(2,3)$ = 10.1 Hz, $J(2,1)$ = 12.3 Hz, 1H; H2).

The crude salt of compound **2D** was loaded onto a short column of Dowex (50W-X8, $H^+$) and the resin washed with water until neutral fractions were obtained. The product was liberated with aqueous ammonia (2 M) and the ammoniacal fractions were concentrated in vacuo to afford DNJNAc (**2D**) as a white crystalline solid (510 mg, 95 %). M.p. 224–226 °C [lit. 227–228 °C];[16c] $[\alpha]_D^{25}$ = +14.6 (*c* 0.86, $H_2O$) [lit. $[\alpha]_D^{20}$ = +16.4[16c] (*c* 1.00, $H_2O$)]; $^1$H NMR ($D_2O$, 400 MHz): $\delta$ = 2.00 (s, 3H; $NHCOC\mathit{H}_3$), 2.43 (dd, $J(1,2)$ = 11.5 Hz, $J(1,1')$ = 12.6 Hz, 1H; H1), 2.54 (ddd, $J(5,6')$ = 3.0 Hz, $J(5,6)$ = 6.1 Hz, $J(5,4)$ = 9.7 Hz, 1H; H5), 3.06 (dd, $J(1',2)$ = 4.9 Hz, $J(1',1)$ = 12.6 Hz, 1H; H1′), 3.30 (app t, $J(3,2)=J(3,4)$ = 9.7 Hz, 1H; H3), 3.39 (dd, $J(4,3)$ = 9.1 Hz, $J(4,5)$ = 10.0 Hz, 1H; H4), 3.66 (dd, $J(6,5)$ = 6.1 Hz, $J(6,6')$ = 11.6 Hz, 1H; H6), 3.72 (ddd, $J(2,1')$ = 4.9 Hz, $J(2,3)$ = 10.2 Hz, $J(2,1)$ = 11.4 Hz, 1H; H2), 3.82 ppm (dd, $J(6',5)$ = 2.9 Hz, $J(6',6)$ = 11.6 Hz, 1H; H6′); $^{13}$C NMR ($D_2O$, 100 MHz): $\delta$ = 22.6 ($NHCOC\mathit{H}_3$), 47.5 (C1), 52.8 (C2), 61.0 (C5), 61.8 (C6), 72.5 (C3), 76.4 (C4), 174.9 ppm ($NHC\mathit{O}CH_3$); IR (thin film, Ge): $\tilde{\nu}$ = 1561 (s, amide II), 1638 (s, amide I), 3286 (br s; OH/NH); LRMS (ESI+): *m/z* (%): 205 (100) $[M+H]^+$, 227 (90) $[M+Na]^+$, 431 (91) $[2M+Na]^+$; HRMS (ESI+): *m/z* calcd for $C_8H_{17}N_2O_4$: 205.1183 $[M+H]^+$; found: 205.1183.

For enantiomer **2L**: M.p. 220 °C (dec.); $[\alpha]_D^{25}$ = −18.8 (*c* 0.57, $H_2O$).

*2-Acetamido-1,2,5-trideoxy-1,5-imino-1-N-methyl*-D-*glucitol,* (*N-methyl-DNJNAc,* ***2Da***): Formaldehyde (37 % in water, 0.10 mL) and palladium (10 % on carbon, 5 mg) were added to a solution of DNJNAc (**2D**, 11.5 mg, 56.9 μmol) in water (1 mL). The vessel was degassed, charged with hydrogen, and the reaction mixture was stirred at RT for 24 h. The reaction mixture was filtered (GF/A glass microfiber) and concentrated in vacuo. The residue was loaded onto a short column of Dowex (50W-X8, $H^+$) and the resin washed with water until neutral fractions were obtained. The product was liberated with aqueous ammonia (2 M) and the

ammoniacal fractions were concentrated in vacuo to afford *N*-methyl-DNJNAc (**2Da**) as a white crystalline solid (11.6 mg, 94%). M.p. 248°C (dec.); $[\alpha]_D^{25}=+20.3$ (*c* 0.53, $H_2O$); $^1H$ NMR ($D_2O$, 400 MHz): $\delta=1.99$ (app dt, $J(5,6)=J(5,6')=2.8$ Hz, $J(5,4)=9.9$ Hz, 1H; H5), 2.01 (s, 3H; $NHCOCH_3$), 2.17 (t, $J(1,1')=J(1,2)=11.6$ Hz, 1H; H1), 2.33 (s, 3H; $NCH_3$), 2.89 (dd, $J(1',2)=4.8$ Hz, $J(1',1)=11.6$ Hz, 1H; H1′), 3.34 (dd, $J(3,4)=9.3$ Hz, $J(3,2)=10.1$ Hz, 1H; H3), 3.46 (app t, $J(4,3)=J(4,5)=9.6$ Hz, 1H; H4), 3.78–3.85 (m, 2H; H2 and H6), 3.82 ppm (dd, $J(6',5)=2.5$ Hz, $J(6',6)=12.9$ Hz, 1H; H6′); $^{13}C$ NMR ($D_2O$, 100 MHz): $\delta=22.6$ ($NHCOCH_3$), 41.3 ($NCH_3$), 50.5 (C2), 58.1 (C1), 58.1 (C6), 68.5 (C5), 70.9 (C4), 76.3 (C3), 174.9 ppm ($NHCOCH_3$); IR (thin film, Ge): $\tilde{\nu}=1565$ (s; amide II), 1635 (s; amide I), 3300 (br s; OH); LRMS (ESI+): *m/z* (%): 219 (70) $[M+H]^+$, 459 (100) $[2M+Na]^+$; HRMS (ESI+): *m/z* calcd for $C_9H_{19}N_2O_4$: 219.1339 $[M+H]^+$; found: 219.1340.

*2-Acetamido-1-N-butyl-1,2,5-trideoxy-1,5-imino-*D*-glucitol,* (*N-Butyl-DNJNAc,* ***2Dc***): Butyraldehyde (0.10 mL, 1.1 mmol) and palladium (10% on carbon, 5 mg) were added to a solution of DNJNAc (**2D**, 11.0 mg, 53.9 μmol) in water/1,4-dioxane (1:1, 2 mL). The vessel was degassed, charged with hydrogen, and the reaction mixture was stirred for 24 h. The reaction mixture was filtered (GF/A glass microfiber) and concentrated in vacuo. The residue was loaded onto a short column of Dowex (50W-X8, $H^+$) and the resin washed with water until neutral fractions were obtained. The product was liberated with 25% aqueous ammonia/MeOH (3:17) and the ammoniacal fractions were concentrated in vacuo to afford *N*-butyl-DNJNAc (**2Dc**) as a white crystalline solid (13.4 mg, 96%). M.p. 192–196°C; $[\alpha]_D^{25}=+13.3$ (*c* 0.56, $H_2O$); $^1H$ NMR ($D_2O$, 400 MHz): $\delta=0.89$ (t, $J=7.3$ Hz, 3H; $NCH_2CH_2CH_2CH_3$), 1.27 (sext, $J=7.3$ Hz, 2H; $NCH_2CH_2CH_2CH_3$), 1.40–1.48 (m, 2H; $NCH_2CH_2CH_2CH_3$), 2.01 (s, 3H; $NHCOCH_3$), 2.25 (app t, $J(1,1')=J(1,2)=11.6$ Hz, 1H; H1), 2.25 (app dt, $J(5,6)=J(5,6')=2.5$ Hz, $J(5,4)=9.6$ Hz, 1H; H5), 2.55–2.62 (m, 1H; $NCHH'CH_2CH_2CH_3$), 2.71–2.79 (m, 1H; $NCHH'CH_2CH_2CH_3$), 2.98 (dd, $J(1',2)=4.5$ Hz, $J(1',1)=11.9$ Hz, 1H; H1′), 3.32 (dd, $J(3,4)=9.3$ Hz, $J(3,2)=10.1$ Hz, 1H; H3), 3.45 (app t, $J(4,3)=J(4,5)=9.3$ Hz, 1H; H4), 3.79 (app dt, $J(2,1')=4.5$ Hz, $J(2,1)=J(2,3)=10.9$ Hz, 1H; H2), 3.84 (dd, $J(6,5)=2.8$ Hz, $J(6,6')=12.6$ Hz, 1H; H6), 3.92 ppm (dd, $J(6',5)=2.3$ Hz, $J(6',6)=12.6$ Hz, 1H; H6′); $^{13}C$ NMR ($D_2O$, 100 MHz): $\delta=13.8$ ($NCH_2CH_2CH_2CH_3$), 20.8 ($NCH_2CH_2CH_2CH_3$), 22.6 ($NHCOCH_3$), 25.9 ($NCH_2CH_2CH_2CH_3$), 50.6 (C2), 52.2 ($NCH_2CH_2CH_2CH_3$), 53.9 (C1), 58.2 (C6), 65.7 (C5), 71.2 (C4), 76.4 (C3), 174.9 ppm ($NHCOCH_3$); IR (thin film, Ge): $\tilde{\nu}=1562$ (s; amide II), 1640 (s; amide I), 3296 (br s; OH); LRMS (ESI+): *m/z* (%): 261 (94) $[M+H]^+$, 331 (74) $[M+MeOH+K]^+$, 543 (100) $[2M+Na]^+$; HRMS (ESI+): *m/z* calcd for $C_{12}H_{25}N_2O_4$: 261.1809 $[M+H]^+$; found: 261.1816.

**Biological experiments**

*In vitro enzyme inhibition, $IC_{50}$ determination*: The β-*N*-acetyl-glucosaminidases (from human placenta, bovine kidney, *Aspergillus oryzae*, and jack beans), α-*N*-acetyl-galactosaminidase (from chicken liver), β-*N*-acetyl-galactosaminidase (from *Aspergillus oryzae*), and *p*-nitrophenyl glycosides were purchased from Sigma–Aldrich. The cell lysate of the human acute amyloid leukemia cell-line HL60 (RBRC), which was cultured in RPMI 1640 medium that contained 10% fetal calf serum, 100 units $mL^{-1}$ of penicillin, and 100 μg $mL^{-1}$ streptomycin (Invitrogen) at 37°C under 5% $CO_2$, was used as the source of β-*N*-acetyl-glucosaminidase and β-*N*-acetyl-galactosaminidase. The glycosidase activities were determined by using an appropriate *p*-nitrophenyl glycoside as the substrate at the optimum pH value of each enzyme. The reaction mixture (1 mL) contained 2 mM of the substrate and the appropriate amount of enzyme. The reaction was stopped by adding of 400 mM $Na_2CO_3$ (2 mL). The released *p*-nitrophenol was measured spectrometrically at 400 nm.

*α-N-Acetyl-*D*-galactosaminidase assay, $K_i$ determination*: Before use, the enzyme solutions were thawed at RT then put on ice. The solutions were stored at −20°C. The inhibitors were dissolved in deionized $H_2O$ to a stock concentration of 50 mM. These solutions were stored at RT. The enzyme substrate solutions were 4 mM in 50 mM citrate/citric acid buffer, pH 5.0. These solutions were stored at 4°C. Assays were carried out in triplicate/duplicate by using $H_2O$ in place of the inhibitor as a positive control; replacing both the enzyme and inhibitor with $H_2O$ was used as a blank to determine the background of the experiment. Linearity over the time course of the reaction was confirmed by using a series of incubation times.

*Materials*: Enzyme α-*N*-acetyl-D-galactosaminidase (*Charonia lampas*) was purified from the natural sources (Oxford Glycobiology Institute) in 50 mM citrate-phosphate buffer at pH 5 that contained 1 mg $mL^{-1}$ bovine serum albumin (BSA) and 0.02% $NaN_3$. Substrate: *p*-nitrophenyl-2-acetamido-2-deoxy-α-D-galactopyranoside (Koch-Light Ltd.). Method: Solutions of the enzyme (5 μL) and the inhibitor (5 μL) were added separately to a 96-well microtitre plate that was pre-incubated at 37°C for 5 min before starting the reaction by addition of the substrate solution (40 μL). After a further 40 min of incubation at 37°C, the reaction was quenched by the addition of 0.5 M aq. $Na_2CO_3$ (200 μL). Absorbance at 405 nm was measured immediately by using a microtitre plate reader (Molecular Devices UVmax kinetic microplate reader and SOFTmax 2.35 software).

**Data analysis**

*$K_i$ values*: Data sets were analyzed on Prism 4.0a by using a Lineweaver–Burk plot (1/rate versus 1/[substrate concentration]) for 4–7 different substrate concentrations that were selected from a suitable range (4, 2, 1, 0.75, 0.5, 0.2, 0.1 mM) and 3–5 inhibitor concentrations. The slopes were plotted against the inhibitor concentration and the $K_i$ value was obtained from the intercept on the *x* axis.

**Free oligosaccharide assay**

*Materials*: Tissue culture media and supplies were purchased from PAA (Pashing, Austria); sodium cyanoborohydride, bicinchoninic acid/copper(-II) sulfate reagent, sodium acetate trihydrate, and anthranilic acid (2-AA) were purchased from Sigma–Aldrich (Dorset, UK); water was Milli-Q™ grade; MeCN (HPLC grade) was purchased from Merk (Darmstadt, Germany); boric acid was purchased from BDH; MeOH was purchased from VWR (Lutterworth, Leicestershire, UK); ion-exchange resins AG50-X12 and AG4-X4 were purchased from Biorad (Hemel Hampstead, Hertfordshire, UK), Spe-ed amide 2 was purchased from Applied Separations (Allentown, Pennsylvania, U.S.); an Amicon Ultra centrifugal filter was purchased from Millipore (Croxley, Watford, UK).

*Cell culture HL60*: The human acute amyloid leukemia cell-line HL60 (ATCC) was cultured in RPMI 1640 medium that contained 10% fetal calf serum, 100 units $mL^{-1}$ of penicillin, and 100 μg $mL^{-1}$ streptomycin (PAA) at 37°C and 5% $CO_2$. Cell viability was checked by using Trypan Blue (Sigma Aldrich).

*Inhibition treatment of HL60 cells and FOS isolation*: Having been propagated at a higher density, HL60 cells were seeded in a 6 well plate at a concentration of $5\times10^5$ cells $mL^{-1}$ and treated with a fresh medium (2 mL) that contained the derivatives of DGJNAc (**1D**) at a concentration of 500 μM, 100 μM, and 50 μM for 24 h. NB-DNJ (500 μM) and untreated wells were used as controls. Following incubation, the cells were centrifuged at 350 g, 10°C, for 7 min and the pellet was washed three times with PBS. The washed cell pellets were stored at −20°C until use. Following thawing at RT, the samples were resuspended in water (650 μL) and Dounce homogenized. An aliquot (50 μL) was removed and treated with 0.25 M NaOH solution for 16 h prior to determination of the protein concentration in comparison to a standard by using bicinchoninic acid/copper(II) sulfate reagent (Sigma Aldrich). For desalting and deproteination, the homogenate (500 μL) was subjected to a mixed-bed ion-exchange column [AG50-X12 (0.2 mL), ($H^+$, 100–200 mesh), AG4-X4 (0.4 mL), ($OH^-$, 100–200 mesh)], which had been preequilibrated with water (5×1 mL). The homogenate was added to the column and eluted with water (4×1 mL). The eluent that contained the free oligosaccharides (FOS) was collected and dried by lyophilization.

*Carbohydrate fluorescent labeling*: The lyophilized samples were resuspended in water (300 μL), transferred to an Eppendorf tube, and evaporated to dryness by using a Thermo Savant (SPD121P) SpeedVac system. As previously described,[33] anthranilic acid (2-AA) was dissolved at a concentration of 30 mg $mL^{-1}$ in a MeOH solution that contained 4% sodium acetate trihydrate (w/v) and 2% boric acid (w/v). To this mixture was added sodium cyanoborohydride to a final concentration of 45 mg $mL^{-1}$ (labeling buffer). The dried samples were dissolved in water

(30 μL) and 2-AA labeling buffer (80 μL) was added, followed by incubation at 80 °C for 1 h.

*Purification of fluorescently labeled FOS*: After cooling, MeCN/water (97:3, 1 mL) was added to the labeled FOS samples and the samples were vortexed and added to a spe-ed amide-2 column that had been pre-equilibrated as follows: MeCN (1 mL), water (2 mL), MeCN (2 mL). The eluent was discarded and the column was washed with MeCN/water (95:5, 2 mL) and discarded. The purified 2-AA-labeled FOS was eluted by gravity by using water (2× 0.75 mL). The samples were stored at −20 °C until they were analyzed by using HPLC.

*Carbohydrate analysis by normal-phase HPLC*: As previously described, the chromatography system that was used consisted of a Water Alliance 2695 separations module and an in-line Waters 474 fluorescence detector that was set at $Ex_\lambda$ 360 nm and $Em_\lambda$ 425 nm.[34] The gain for the detector was set to 1000 and the emission bandwidth was set to 40 nm. Chromatography was performed at 30 °C. Solvent A was MeCN; solvent B was water; solvent C consisted of ammonium hydroxide (800 mM) that was titrated to pH 3.85 with acetic acid in water and was prepared by using a standard 5 M ammonium hydroxide solution (Sigma Aldrich). Data collection and -processing were performed by using Waters Empower software. Glucose units were derived by comparison to a 2-AA-labeled glucose oligomer ladder (which was obtained by the partial digestion of dextran) as an external standard. A sample/MeCN mixture (1:1, 50 μL) was injected for each run. Separation was performed on a 4.6×250 mm TSK gel-Amide 80 column (5 μM; Anachem, Luton, UK) and the following gradient conditions were used for the analysis of the FOS samples: time = 0 min ($t$=0), 71.6% A, 25.9% B, 2.5% C (0.8 mL min$^{-1}$); $t$=6, 71.6% A, 25.9% B, 2.5% C (0.8 mL min$^{-1}$); $t$=45, 46.2% A, 51.3% B, 2.5% C (0.8 mL min$^{-1}$); $t$=46, 35% A, 62.5% B, 2.5% C (0.8 mL min$^{-1}$); $t$=48, 35% A, 62.5% B, 2.5% C (0.8 mL min$^{-1}$); $t$=49, 71.6% A, 25.9% B, 2.5% C (0.8 mL min$^{-1}$); $t$=51, 71.6% A, 25.9% B, 2.5% C (1.2 mL min$^{-1}$); $t$=64, 71.6% A, 25.9% B, 2.5% C (1.2 mL min$^{-1}$); $t$=65, 71.6% A, 25.9% B, 2.5% C (0.8 mL min$^{-1}$).

*Enzyme* (*jack bean β-HexNAcase) digest*: Glycosidase digest using jack bean β-HexNAcase (10 μL of 6 U mL$^{-1}$ in 50 mM citrate buffer (pH 5.0) that contained 1 mg mL$^{-1}$ BSA and 0.02% sodium azide, purified in house) was performed on a representative sample (100 μL) of the complete FOS population from 500 μM DGJNAc-treated HL60 cells. After 16 h incubation at 37 °C, the enzyme digest was diluted with water (90 μL). An Amicon Ultra centrifugal filter (Millipore, 10000 MWCO) was pretreated with water (150 μL) and used to remove proteins following centrifugation at 13000 g for 15 min at 4 °C. The filter was washed with water (100 μL) and the combined eluate was evaporated to dryness before being reconstituted in MeCN/water (1:1, 100 μL) for HPLC analysis.

*Statistical analysis*: Experiments were performed in triplicate. To test for significance, Prism 4.0a software was used to perform a student t-test by using a 99% confidence interval.

## Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research (C) (23590127) from the Japanese Society for the Promotion of Science (JSPS), by the Spanish Ministerio de Ciencia e Innovación (contract no.: SAF2010-15670), and by the Fundación Ramón Areces. A.G. was supported by the Medicinal Chemistry for Cancer Graduate Programme from Cancer Research UK (CRUK). B.A. was supported by the Newton Abraham Research Fund.

[1] a) N. Asano, *Cell. Mol. Life Sci.* **2009**, *66*, 1479–1492; b) B. Winchester, G. W. J. Fleet, *Glycobiology* **1992**, *2*, 199–210; c) N. Asano, R. J. Nash, R. J. Molyneux, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; d) A. A. Watson, G. W. J. Fleet, N. Asano, R. J. Molyneux, R. J. Nash, *Phytochemistry* **2001**, *56*, 265–295.

[2] T. Aoyama, H. Naganawa, H. Suda, K. Uotani, T. Aoyagi, T. Takeuchi, *J. Antibiot.* **1992**, *45*, 1557–1558.

[3] T. Aoyagi, H. Suda, K. Uotani, F. Kojima, T. Aoyama, K. Horiguchi, M. Hamada, T. Takeuchi, *J. Antibiot.* **1992**, *45*, 1404–1408.

[4] H. Usuki, M. Toyo-oka, H. Kanzaki, T. Okuda, T. Nitoda, *Bioorg. Med. Chem.* **2009**, *17*, 7248–7253.

[5] a) S. Knapp, D. Fash, M. Abdo, T. J. Emge, P. R. Rablen, *Bioorg. Med. Chem.* **2009**, *17*, 1831–1836; b) S. Knapp, D. Vocadlo, Z. N. Gao, B. Kirk, J. P. Lou, S. G. Withers, *J. Am. Chem. Soc.* **1996**, *118*, 6804–6805; c) B. Shanmugasundaram, A. W. Debowski, R. J. Dennis, G. J. Davies, D. J. Vocadlo, A. Vasella, *Chem. Commun.* **2006**, 4372–4374; d) Y. Yang, T. A. Liu, Y. L. Yang, Q. Y. Wu, Q. Yang, B. A. Yu, *ChemBioChem* **2011**, *12*, 457–467.

[6] a) J. S. S. Rountree, T. D. Butters, R. A. Dwek, N. Asano, K. Ikeda, E. L. Evinson, R. J. Nash, G. W. J. Fleet, *Tetrahedron Lett.* **2007**, *48*, 4287–4291; b) J. S. S. Rountree, T. D. Butters, R. A. Dwek, G. W. J. Fleet, *Comptes Rendus Chimie* **2011**, *14*, 126–133.

[7] a) T. Kolter, K. Sandhoff, *Biochem. Biophys. Acta* **2006**, *1758*, 2057–2079; b) T. Kolter, K. Sandhoff, *Angew. Chem.* **1999**, *111*, 1632–1670; *Angew. Chem. Int. Ed.* **1999**, *38*, 1532–1568.

[8] J. S. S. Rountree, T. D. Butters, M. R. Wormald, S. D. Boomkamp, R. A. Dwek, N. Asano, K. Ikeda, E. L. Evinson, R. J. Nash, G. W. J. Fleet, *ChemMedChem* **2009**, *4*, 378–392.

[9] a) J. Liu, M. M. D. Numa, S.-J. Huang, P. Sears, A. R. Shikhman, C.-H. Wong, *J. Org. Chem.* **2004**, *69*, 6273–6283; b) T. A. Reese, H.-E. Liang, A. M. Tager, A. D. Luster, N. van Roojen, D. Voehringer, R. M. Locksley, *Nature* **2007**, *447*, 92–96; c) F. Liu, K. Iqbal, I. Grundje-Iqbal, G. W. Hart, C.-X. Gong, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 10804–10809.

[10] a) T. H. Li, L. N. Guo, Z. H. Li, J. J. Wang, J. Li, W. Zhao, *Progress Chem.* **2011**, *23*, 1657–1664; b) M. S. Macauley, Y. A. He, T. M. Gloster, K. A. Stubbs, G. J. Davies, D. J. Vocadlo, *Chem. Biol.* **2010**, *17*, 937–948; c) B. Laczy, S. A. Marsh, C. A. Brocks, I. Wittmann, J. C. Chatham, *Am. J. Physiol. Heart. Circ. Physiol.* **2010**, *299*, 1715–1727; d) K. Slamova, P. Bojarova, L. Petraskova, V. Kren, *Biotechnol. Adv.* **2010**, *28*, 682–693.

[11] a) B. Woynarowska, H. Wikiel, M. Sharma, G. W. J. Fleet, R. J. Bernacki, *Proc. Amer. Assoc. Cancer Res.* **1989**, *30*, 91; b) B. Woynarowska, H. Wikiel, M. Sharma, N. Carpenter, G. W. J. Fleet, R. J. Bernacki, *Anticancer Res.* **1992**, *12*, 161–166.

[12] D. Best, P. Chairatana, A. F. G. Glawar, E. Crabtree, T. D. Butters, F. X. Wilson, C.-Y. Yu, W.-B. Wang, Y.-M. Jia, I. Adachi, A. Kato, G. W. J. Fleet, *Tetrahedron Lett.* **2010**, *51*, 2222–2224.

[13] a) I. B. Tomasic, M. C. Metcalf, A. I. Guce, N. E. Clark, S. C. Garman, *J. Biol. Chem.* **2010**, *285*, 21560–21566; b) A. I. Guce, N. E. Clark, E. N. Salgado, D. R. Ivanen, A. A. Kulminskaya, H. Brumer, S. C. Garman, *J. Biol. Chem.* **2010**, *285*, 3625–3632; c) N. E. Clark, S. C. Garman, *J. Mol. Biol.* **2009**, *393*, 435–447; d) T. Kanekura, H. Sakuraba, F. Matsuzawa, S. Aikawa, H. Doi, Y. Hirabayashi, N. Yoshii, T. Fukushige, T. Kanzaki, *J. Dermatol. Sci.* **2005**, *37*, 15–20; e) O. Staretz-Chacham, T. C. Lang, M. E. LaMarca, D. Krasnewich, E. Sidransky, *Pediatrics* **2009**, *123*, 1191–1207; f) B. Asfaw, J. Ledinova, R. Dobrovolny, H. D. Bakker, R. J. Desnick, O. P. van Diggelen, J. G. N. de Jong, T. Kanzaki, A. Chabas, I. Maire, E. Conzelmann, D. Schindler, *J. Lipid Res.* **2002**, *43*, 1096–1104.

[14] a) M. Greco, M. De Mitri, F. Chiriaco, G. Leo, E. Brienza, M. Maffia, *Cancer Lett.* **2009**, *283*, 222–229; b) D. S. Yin, Z. Q. Ge, W. Y. Yang, C. X. Liu, Y. J. Yuan, *Cancer Lett.* **2006**, *243*, 71–79.

[15] a) L. M. Willis, R. Zhang, A. Reid, S. G. Withers, W. W. Wakarchuk, *Biochemistry* **2009**, *48*, 10334–10341; b) R. Suzuki, T. Katayama, M. Kitaoka, H. Kumagai, T. Wakagi, H. Shoun, H. Ashida, K. Yamamoto, S. Fushinobu, *J. Biochemistry* **2009**, *146*, 389–398; c) C. Marion, D. H. Limoli, G. S. Bobulsky, J. L. Abraham, A. M. Burnaugh, S. King, *J. Infect. Immun.* **2009**, *77*, 1389–1396; d) H. M. Goda, K. Ushigusa, H. Ito, N. Okino, H. Narimatsu, M. Ito, *Biochem. Biophys. Res. Commun.* **2008**, *375*, 541–546; e) D. Koutsioulis, D. Landry, E. P. Guthrie, *Glycobiology* **2008**, *18*, 799–805; f) H. Ashida, R. Maki, H. Ozawa, Y. Tani, M. Kiyohara, M. Fujita, A. Imamura, H. Ishida, M. Kiso, K. Yamamoto, *Glycobiology* **2008**, *18*, 727–734.

[16] a) G. W. J. Fleet, L. E. Fellows, P. W. Smith, *Tetrahedron* **1987**, *43*, 979–990; b) G. W. J. Fleet, P. W. Smith, R. J. Nash, L. E. Fellows, R. B. Parekh, T. W. Rademacher, *Chem. Lett.* **1986**, 1051–1054; c) H. Boshagen, F.-R. Heiker, A. M. Schueller, *Carbohydr. Res.* **1987**, *164*, 141–148.

[17] a) C.-W. Ho, S. D. Popat, T. A. Liu, K.-C. Tsai, M. J. Ho, W.-H. Chen, A.-S. Yang, C.-H. Lin, *ACS Chem. Biol.* **2010**, *5*, 489–497; b) A. J. Steiner, G. Schitter, A. E. Stutz, T. M. Wrodnigg, C. A. Tarling, S. G. Withers, D. J. Mahuran, M. B. Tropak, *Tetrahedron: Asymmetry* **2009**, *20*, 832–835.

[18] A. C. Weymouth-Wilson, R. Clarkson, D. Best, M.-S. Pino-Gonzalez, F. X. Wilson, G. W. J. Fleet, *Tetrahedron Lett.* **2009**, *50*, 6307–6310.

[19] a) B. P. Bashyal, H.-F. Chow, L. E. Fellows, G. W. J. Fleet, *Tetrahedron* **1987**, *43*, 423–430; b) B. P. Bashyal, H.-F. Chow, G. W. J. Fleet, *Tetrahedron Lett.* **1986**, *27*, 3205–3208; c) B. P. Bashyal, H.-F. Chow, G. W. J. Fleet, *Tetrahedron* **1987**, *43*, 415–422; d) D. Best, C. Wang, A. C. Weymouth-Wilson, R. A. Clarkson, F. X. Wilson, R. J. Nash, S. Miyauchi, A. Kato, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2010**, *21*, 311–319; e) V. M. Díaz Pérez, M. I. García Moreno, C. Ortiz Mellet, J. Fuentes, J. C. Díaz Arribas, F. J. Cañada, J. M. García Fernández, *J. Org. Chem.* **2000**, *65*, 136–143; f) M. I. García Moreno, J. M. Benito, C. Ortiz Mellet, J. M. García Fernández, *J. Org. Chem.* **2001**, *66*, 7604–7614; g) M. Aguilar, P. Díaz Pérez, M. I. García Moreno, C. Ortiz Mellet, J. M. García Fernández, *J. Org. Chem.* **2008**, *73*, 1995–1998.

[20] a) D. D′Alonzo, A. Guaragna, G. Palumbo, *Curr. Med. Chem.* **2009**, *16*, 473–505; b) K. Clinch, G. B. Evans, G. W. J. Fleet, R. H. Furneaux, S. W. Johnson, D. Lenz, S. Mee, P. R. Rands, V. L. Schramm, E. A. T. Ringia, P. C. Tyler, *Org. Biomol. Chem.* **2006**, *4*, 1131–1139; c) S. S. Smith, *Toxicol. Sci.* **2009**, *110*, 4–30; d) T. B. Mercer, S. F. Jenkinson, R. J. Nash, S. Miyauchi, A. Kato, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2009**, *20*, 2368–2373; e) F. P. da Cruz, S. Newberry, S. F. Jenkinson, M. R. Wormald, T. D. Butters, D. S. Alonzi, S. Nakagawa, F. Becq, C. Norez, R. J. Nash, A. Kato, G. W. J. Fleet, *Tetrahedron Lett.* **2011**, *52*, 219–223.

[21] V. L. Campo, I. Carvalho, S. Allman, B. G. Davis, R. A. Field, *Org. Biomol. Chem.* **2007**, *5*, 2645–2657.

[22] S. D. Szajda, N. Waszkiewicz, A. Stypulkowska, J. Dadan, K. Zwierz, *Folia Histochem. Cytochem.* **2010**, *48*, 351–357.

[23] P. Wielgat, U. Walczuk, S. Szadjda, M. Bien, L. Zimnoch, Z. Mariak, K. Zwierz, *J. Neurooncol.* **2006**, *80*, 243–249.

[24] T. D. Butters, R. A. Dwek, F. M. Platt, *Glycobiology* **2005**, *15*, 43–52.

[25] N. Asano, K. Ikeda, L. Yu, A. Kato, K. Takebayashi, I. Adachi, I. Kato, H. Ouchi, H. Takahata, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2005**, *16*, 223–229.

[26] S. D. Boomkamp, J. S. S. Rountree, D. C. A. Neville, R. A. Dwek, G. W. J. Fleet, T. D. Butters, *Glycoconjugate J.* **2010**, *27*, 297–308.

[27] Package insert Zavesca: http://www.zavesca.com/pdf/Zavesca_miglustat_Prescribing_Information.pdf.

[28] Package insert Glyset: http://labeling.pfizer.com/ShowLabeling.aspx?id=581.

[29] H. R. Mellor, D. C. A. Neville, D. J. Harvey, F. M. Platt, R. A. Dwek, T. D. Butters, *Biochem. J.* **2004**, *381*, 861–866.

[30] G. H. B. Maegawa, P. L. M. Giersgergen, S. Yang, B. Banwell, C. P. Morgan, J. Dingemanse, C. J. Tifft, J. T. R. Clarke, *Mol. Genet. Metab.* **2009**, *97*, 284–291.

[31] N. V. S. Ramakrishna, K. N. Vishwottam, S. Manoj, M. Koteshwara, M. Santosh, B. Ravikumar, Y. Anjaneyulu, *Arzneim.-Forsch.* **2006**, *56*, 328–336.

[32] A. E. Hakansson, J. van Ameijde, L. Guglielmini, G. Horne, R. J. Nash, E. L. Evinson, A. Kato, G. W. J. Fleet, *Tetrahedron: Asymmetry* **2007**, *18*, 282–289.

[33] D. Neville, V. Coquard, D. Priestman, D. te Vruchte, D. Sillence, R. Dwek, F. Platt, T. Butters, *Anal. Biochem.* **2004**, *331*, 275–282.

[34] D. S. Alonzi, D. C. A. Neville, R. H. Lachmann, R. A. Dwek, T. D. Butters, *Biochem. J.* **2008**, *409*, 571–580.

Received: January 11, 2012
Published online: June 26, 2012

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# Glycosidase Inhibition by All 10 Stereoisomeric 2,5-Dideoxy-2,5-iminohexitols Prepared from the Enantiomers of Glucuronolactone

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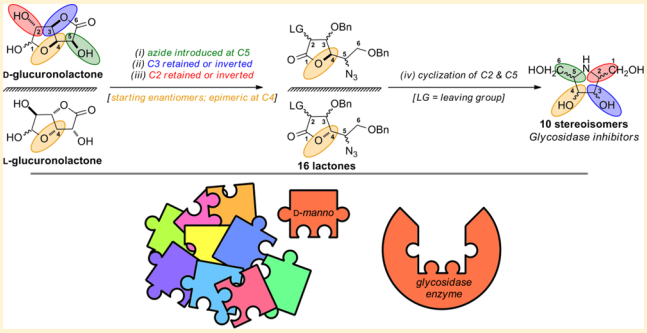
Supporting Information

**ABSTRACT:** The enantiomers of glucuronolactone are excellent chirons for the synthesis of the 10 stereoisomeric 2,5-dideoxy-2,5-iminohexitols by formation of the pyrrolidine ring by nitrogen substitution at C2 and C5, with either retention or inversion of configuration; the stereochemistry at C3 may be adjusted during the synthesis to give seven stereoisomers from each enantiomer. A definitive side-by-side comparison of the glycosidase inhibition of a panel of 13 glycosidases showed that 8 of the 10 stereoisomers showed significant inhibition of at least one glycosidase.




## INTRODUCTION

The chemotherapeutic potential of iminosugars is due to the inhibition of glycosidases and interaction with other sugar receptors and metabolizing enzymes.[1−4] Glucuronolactone **1D** has been used as the starting material for many homochiral targets,[5−12] including iminosugars.[13] This paper reports the synthesis from the enantiomers of glucuronolactone of all 10 stereoisomeric 2,5-dideoxy-2,5-iminohexitols, three of which have been isolated from plants. Intermediates in the syntheses also allow access to any of 16 stereoisomeric lactones as precursors to a wide range of hydroxylated prolines and their derivatives. A side-by-side comparison showed that 8 of the 10 stereoisomers gave significant inhibition of varying glycosidases.

The strategy for the synthesis of the 10 stereoisomeric 2,5-dideoxy-2,5-iminohexitols is shown in Figure 1. There are four pairs of enantiomers and two *meso* forms. For all of them, the exocyclic primary alcohols result from reduction of C1 and C6 of glucuronolactone. The acetonide **1D** has a single unprotected hydroxyl group at C5 that allows introduction of nitrogen by azide at C5 with either inversion (***I5***) or retention (***R5***) of configuration. The stereochemistry at C3 (***R3***, ***I3***) and C2 can be adjusted, with subsequent nucleophilic displacement of leaving groups at C2 (***R2***, ***I2***), by nitrogen derived from the azide at C5 forming the pyrrolidine ring. Access to C4 is not possible; however, identical sequences starting from the acetonide of L-glucuronolactone **1L** allow access to epimers at C4.

Since the ring is formed by nucleophilic displacements at C2 and C5, the shortest synthesis is that of the D-*gluco* isomer (DGDP) **2D** with ***I5−R3−I2*** from the D-glucuronolactone **1D**. DGDP **2D** can also be formed by a longer sequence ***R5−R3−R2*** from the *same* acetonide, **1D**. This pyrrolidine is not available from the L-enantiomer **1L**. Similarly, the L-*gluco* enantiomer **2L** is accessible *via* identical sequences from the readily available acetonide of L-glucuronolactone **1L**.[14] In contrast, there is a single sequence for the syntheses from the acetonide **1D** of the two $C_2$-symmetric stereoisomers, D-*manno* (DMDP) **3D** [by ***R5−R3−I2***] and L-*ido* **4L** [***I5−R3−R2***]. The enantiomers L-*manno* (L-DMDP) **3L** [by ***R5−R3−I2***] and D-*ido* **4D** [***I5−R3−R2***] are thus identically available from the acetonide **1L**. The D-*altro* isomer **5D** is obtained in the same number of steps from either **1D** [***R5−I3−I2***] or from **1L** [***I5−I3−R2***]; the L-*altro* isomer **5L** is similarly accessible from both **1L** and **1D**. The *meso*-diastereomer *galacto* **6** [***I5−I3−I2***] was obtained in identical sequences from **1D** and **1L**. *meso-allo* **7** [***R5−I3−R2***] was similarly accessed from both enantiomers of acetonide **1**. Thus, the D-acetonide **1D** forms seven stereoisomers, whereas another seven are formed with the epimeric configuration at C4 from the L-enantiomer **1L**.

## RESULTS AND DISCUSSION

The diols **8L** and **9D** are the key intermediates in the synthesis of all 2,5-dideoxy-2,5-iminohexitol stereoisomers. Compounds **8L** and **9D** are formed by the introduction of nitrogen as azide at C5 with inversion (***I5***) or retention (***R5***) of configuration,

**Received:** June 15, 2012
**Published:** August 28, 2012

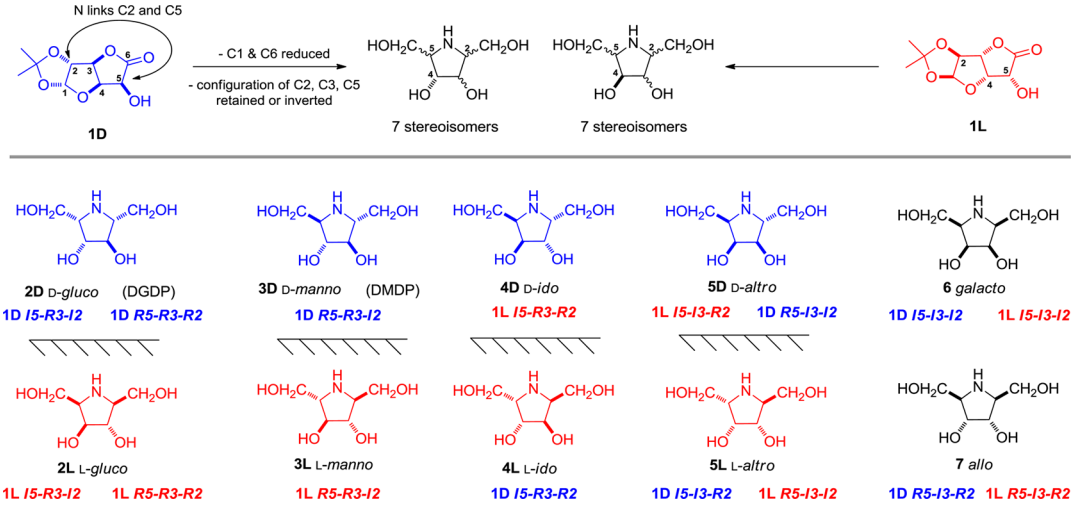
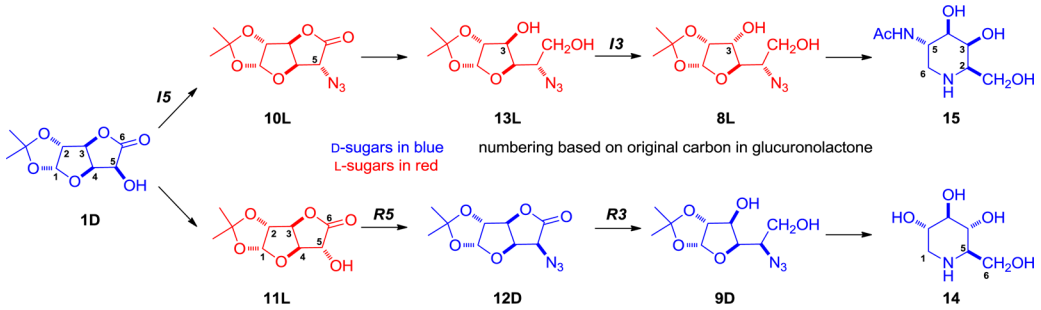



**Figure 1.** Ten stereoisomeric 2,5-dideoxy-2,5-iminohexitols showing the configurational changes *R* (retention) or *I* (inversion) required at C5−C3−C2 of the enantiomers of glucuronolactone acetonide **1D** and **1L**.

**Scheme 1. Synthesis of Diols 8L and 9D as Key Intermediates for All 10 Stereoisomers of 2,5-Dideoxy-2,5-iminohexitols**




reduction of C6 to a primary alcohol, and inversion (*I3*) or retention (*R3*) of the hydroxyl group at C3 (Scheme 1). The acetonide **1D**, with only the C5 OH group unprotected, is formed in 96% yield from D-glucuronolactone. Nucleophilic substitution $\alpha$ to a carbonyl group, even when $\beta$-oxygens are present, generally proceeds in high yield; thus, esterification of the free alcohol in **1D** with trifluoromethanesulfonic (triflic) anhydride affords the corresponding triflate ester, which on treatment with sodium azide in DMF forms the azido-lactone **10L** in 92% yield with inversion of configuration at C5 (*I5*).[15]

Reaction of the triflate of **1D** with trifluoroacetate as an oxygen nucleophile gives the epimeric *ido*-acetonide **11L** with inversion of configuration at C5.[16] Triflation of **11L** followed by azide displacement affords the azide **12D** with overall retention of configuration at C5 from **1D** (*R5*) in an overall yield of 84%.[17] Both of the epimeric azido-lactones **10L** and **12D** are stable, but highly base sensitive. Nonetheless, efficient two-step reductions of **10L** and **12D** by DIBALH followed by sodium borohydride afford the epimeric diols **13L** and **9D** in overall 70% and 71% yields, respectively, from D-glucurono-lactone acetonide **1D** on a multigram scale. The piperidine ring in a large scale synthesis of DNJ **14** was formed from reduction of the azide at C5 in the diol **9D** followed by intramolecular reductive amination with an aldehyde at C1.[17] The configuration at C3 in **13L** may be inverted by oxidation of C3 to the corresponding ketone followed by reduction with sodium borohydride to afford diol **8L** (*I3*).[18] Diol **8L** is a key intermediate in the scalable synthesis of the potent $\alpha$-galactosaminidase inhibitor DGJNAc **15**,[19] in which the nitrogen at C5 forms the exocyclic NHAc group and the piperidine ring is formed by linking with nitrogen between C2 and C6.

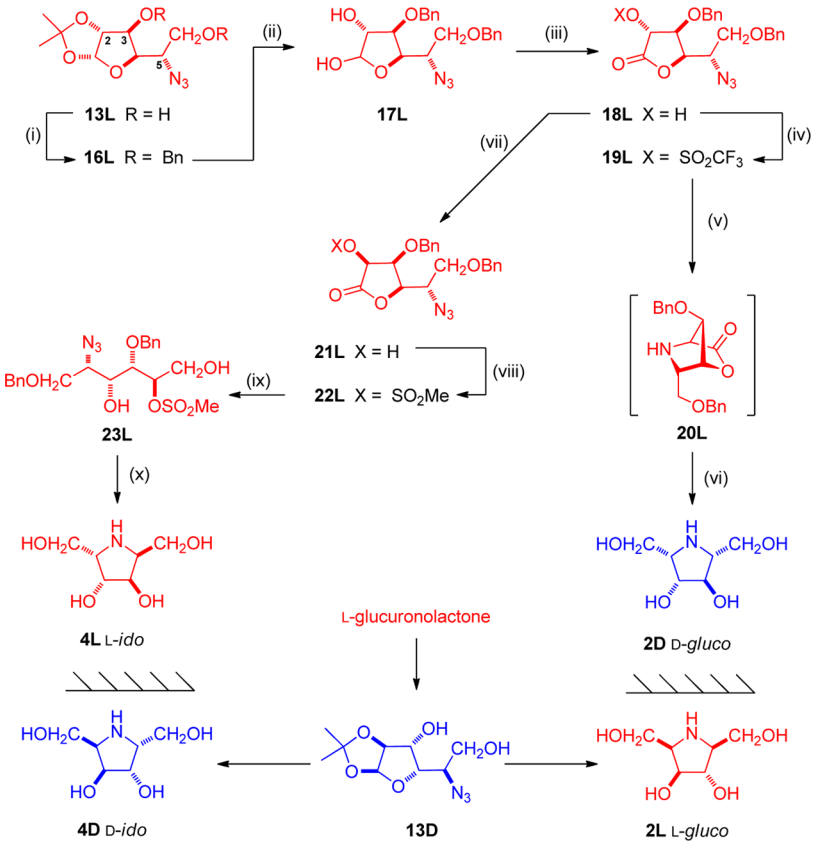
The diol **13L**, formed from **1D** in 70% yield by *I5*-*R3*, was converted into the triflate **19L** as a common intermediate for the synthesis of D-*gluco* (DGDP) **2D** and L-*ido* **4L** isomers (Scheme 2). Reaction of **13L** with benzyl bromide and sodium hydride in DMF gave the dibenzyl ether **16L** (73%). Hydrolysis of the acetonide **16L** with tosic acid in aqueous dioxane afforded the lactols **17L** (97%) which on oxidation with iodine in 2-methyl-2-propanol in the presence of potassium carbonate formed the lactone **18L** (72%). Esterification of the only free hydroxyl group in **18L** with triflic anhydride in the presence of pyridine in dichloromethane gave the stable triflate **19L** (95%). The overall yield of **19L** from **13L** was 48%.

The triflate $\alpha$ to the carbonyl group in **19L** is susceptible to easy intra- or intermolecular nucleophilic substitution. Thus, catalytic hydrogenation of the azide **19L** in ethanol in the presence of 10% palladium on charcoal gave the corresponding amine which spontaneously cyclized to the unstable bicyclic lactone **20L**; reduction of **20L** by sodium borohydride in ethanol, followed by further hydrogenation in the presence of hydrochloric acid, gave DGDP[20] **2D** in 80% yield [39% from diol **13L**, 27% from **1D**].

For the L-*ido* isomer **4L**, treatment of the triflate with sodium trifluoroacetate gave the inverted alcohol **21L** in 90% yield. Mesylation of **21L** with methanesulfonyl chloride in pyridine formed the mesylate **22L** (93%) which with sodium borohydride in ethanol/dioxane gave the open chain azido-


dx.doi.org/10.1021/jo301243s | J. Org. Chem. 2012, 77, 7777−7792

**Scheme 2. Synthesis of *ido*- and *gluco*-2,5-Dideoxy-2,5-iminohexitols from Diols 13 Derived from Glucuronolactone by *I5−R3*[a]**




[a]Reagents and conditions: (i) NaH, $PhCH_2Br$, DMF, 73%; (ii) TsOH, dioxane/water, 7:1, 97%; (iii) $I_2$, $K_2CO_3$, *t*-BuOH, 72%; (iv) $(CF_3SO_2)_2O$, pyridine, $CH_2Cl_2$, 95%; (v) 10% Pd/C, $H_2$, EtOH; (vi) $NaBH_4$, EtOH, then 10% Pd/C, $H_2$, HCl, EtOH, 80% from **19L**; (vii) $(CF_3SO_2)_2O$, pyridine, $CH_2Cl_2$, then $CF_3CO_2Na$, DMF, 90%; (viii) MsCl, pyridine, 93%; (ix) $NaBH_4$, EtOH/dioxane, 8:1, 82%; (x) 10% Pd/C, $H_2$, $CH_3CO_2Na$, dioxane, then add HCl, 92%

mesylate **23L** (82%). Initial hydrogenation of **23L** in ethanol in the presence of 10% palladium and sodium acetate caused reduction to the amine, cyclization to the pyrrolidine, and partial removal of the benzyl groups; further hydrogenation with the addition of hydrochloric acid gave the L-*ido*[27] isomer **4L** (92%) in 32% overall yield from **13L** (23% from **1D**). The L-*gluco* **2L** and D-*ido* **4D** isomers were prepared by identical sequences from L-glucuronolactone **1L**.

The synthesis of DGDP **2D** from **13L** in Scheme 2 required ***I5−R3−I2***. An alternative approach to **2D** from diol **9D**, with ***R5−R3−R2***, is shown in Scheme 3. The diol **9D** was first converted to the lactone **24D** as previously described in an overall yield of 70%.[17] Esterification of the C2 hydroxyl group $\alpha$ to the lactone carbonyl in **24D** gave the corresponding triflate which underwent a clean $S_N2$ reaction with sodium trifluoroacetate in DMF to afford the epimeric alcohol **26D** (85%). Treatment of **26D** with mesyl chloride formed the mesylate **27D** (99%) which on reduction with sodium borohydride in methanol gave the diol **28D** (50%). Catalytic hydrogenation of the azido-mesylate **28D** with 10% palladium in dioxane, initially in the presence of sodium acetate to ensure facile cyclization to the pyrrolidine, and subsequently in the presence of hydrochloric acid to hydrogenolyze the benzyl protecting groups, gave D-*gluco* **2D** (100%). The overall yield of **2D** was 29% from the diol **9D** and 21% from glucuronolactone **1D**.

The lactone **24D** was a divergent intermediate for both the synthesis of DGDP **2D** and DMDP[32] **3D**. **24D** was converted to DMDP **3D** via the relatively stable bicyclic lactone **25D** as previously reported[17] in an overall yield of 56% from the diol **9D** [40% from glucuronolactone **1D**]. The enantiomeric L-*gluco* **2L** and L-*manno* **3L** were similarly prepared from L-glucuronolactone **1L**.

An inversion of configuration at C3 of **9D** was required for the synthesis of the lactone **35D** as a divergent intermediate in the synthesis of the D-*altro*[38] **5D** and *meso-allo*[41] **7** isomers (Scheme 4). Nucleophilic substitution of the secondary triflate from **29D**, which lacks an $\alpha$-carbonyl group, was not efficient due to the steric hindrance of the isopropylidene protecting group being on the same side as the incoming nucleophile. Accordingly, the primary alcohol group in **9D** was selectively protected by reaction with *tert*-butyldimethylsilyl (TBDMS) chloride in pyridine to give the silyl ether **29D** (92%) which, on oxidation with Dess−Martin periodinane, gave the ketone **30D** (95%). Reduction of **30D** by sodium borohydride in ethanol was completely stereoselective, with hydride attack from the less hindered side, to give the epimeric silyl ether **31D** (93%). Removal of the silyl protecting group in **31D** with tetrabutylammonium fluoride (TBAF) in THF gave **32D** (98%); subsequent protection of both the C3 and C6 hydroxyl groups with benzyl bromide and sodium hydride in DMF afforded the dibenzyl ether **33D** (88%). Hydrolysis of the isopropylidene protecting group in **33D** by tosic acid in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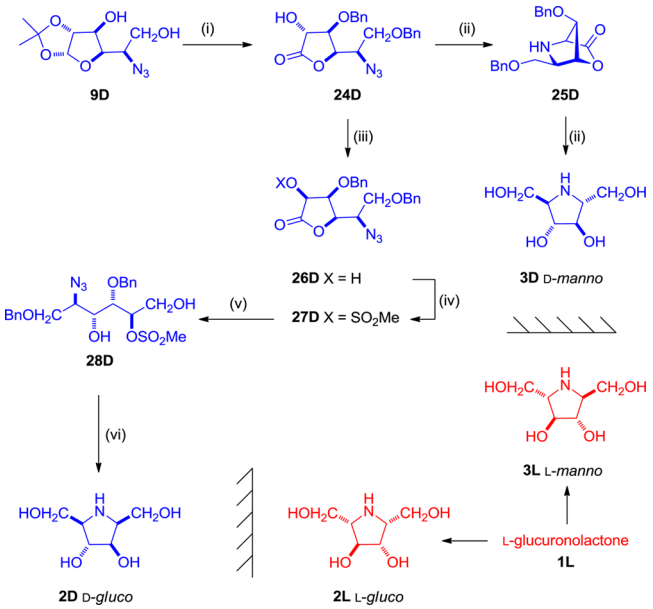
**Scheme 3. Synthesis of *gluco*- and *manno*-2,5-Dideoxy-2,5-iminohexitols from Diols 9 Derived from Glucuronolactone by *R5*−*R3*[a]**




[a]Reagents and conditions: (i) **24D** from **9D**, 70%;[17] (ii) **3D** from **9D**, 56%;[17] (iii) $(CF_3SO_2)_2O$, pyridine, $CH_2Cl_2$, then $CF_3CO_2Na$, DMF, 85% from **24D**; (iv) $MeSO_2Cl$, pyridine, 99%; (v) $NaBH_4$, EtOH/dioxane, 8:1, 50%; (vi) 10% Pd/C, $H_2$, $CH_3CO_2Na$, dioxane, then add HCl, 100%.

aqueous dioxane afforded the lactols **34D** (93%); C1 was then protected by oxidation with iodine in 2-methyl-2-propanol in the presence of potassium carbonate to give the lactone **35D** (79%); **35D**, a common intermediate for the synthesis of both targets **5D** and **7**, was prepared in overall yield of 52% from **9D**.

For the synthesis of D-*altro* **5D**, initial conversion of **35D** to the triflate **38D** (80%), followed by reduction of the azide to the amine, produced a complex mixture. Accordingly, esterification of **35D** by mesyl chloride in pyridine gave **36D** (70%); subsequent reduction with sodium borohydride in ethanol/dioxane formed **37D** (51%). Hydrogenation of **37D** in ethanol in the presence of 10% palladium and sodium acetate, followed by addition of hydrochloric acid to the hydrogenation mixture, produced the D-*altro* analogue **5D** (99%) in 18% overall yield from **9D** (13% from **1D**). Inversion of configuration at C2 of the lactone **35D** was necessary for access to the *meso-allo* isomer **7**. The triflate **38D**, formed by esterification with triflic anhydride, with sodium trifluoroacetate in DMF, gave the epimeric alcohol **39D** (75%). Mesylation of **39D** to give **40D** (84%) was followed by reduction by sodium borohydride to afford **41D** (93%); catalytic hydrogenation of **41D** formed *meso-allo* **7** (95%); the overall yield of **7** was 29% from the diol **9D** and 21% from **1D**. The L-*altro* **5L** and *meso-allo* **7** isomers were prepared by identical sequences from L-glucuronolactone **1L**.

The preceding synthesis of D-*altro* **5D** from **9D**, and of L-*altro* **5L** from **9L**, involves *R5*−*I3*−*I2*. An alternative strategy of *I5*−*I3*−*R2* leads to D-*altro* **5D** from **13D** and of L-*altro*-**5L** from **13L** and also to the *meso-galacto* analogue **6** from both enantiomers of **13** (Scheme 5).

For the synthesis of the lactone **44L**, a divergent intermediate in the synthesis of the L-*altro* **5L** and *meso-galacto*[45] **6** isomer, diol **13L** was converted to the C3 epimer **8L** in 66% yield as previously reported (*I5*−*I3*) (Scheme 5).[18] The diol **8L** with benzyl bromide and sodium hydride in DMF gave the dibenzyl ether **42L** (99%). Hydrolysis of the isopropylidene protecting group in **42L** by tosic acid in aqueous dioxane afforded the lactols **43L** (95%) in which C1 was protected by oxidation with iodine in 2-methyl-2-propanol in the presence of potassium carbonate to give the lactone **44L** (80%); **44L**, a common intermediate for the synthesis of both targets **5L** and **6**, was prepared in overall yield of 50% from **13L**.

For the synthesis of the *meso-galacto* isomer **6**, initial conversion of **44L** to the triflate **47L** (80%) followed by reduction of the azide to the amine produced a complex mixture. Accordingly, conversion of **44L** by mesyl chloride in pyridine to the mesylate **45L** (95%), followed by reduction with sodium borohydride in ethanol/dioxane formed **46L** (65%). Hydrogenation of **46L** in dioxane in the presence of 10% palladium and sodium acetate, followed by addition of hydrochloric acid to the hydrogenation mixture, gave the *meso-galacto* analogue **6** (91%) in 28% overall yield from **13L** (20% from **1D**). Inversion of configuration at C2 of the lactone **44L** was necessary for access to the L-*altro* isomer **5L**. The triflate **47L**, formed by esterification with triflic anhydride, with sodium trifluoroacetate in DMF gave the epimeric alcohol **48L** (72%). Mesylation of **48L** to give **49L** (78%), followed by reduction by sodium borohydride, afforded **50L** (89%) which on catalytic hydrogenation formed L-*altro* **5L** (92%); the overall yield of **5L** from the diol **13L** was 23% (16% from **1D**). The D-*altro* **5D** and *meso-galacto* **6** isomers were also prepared by identical sequences from L-glucuronolactone **1L**.

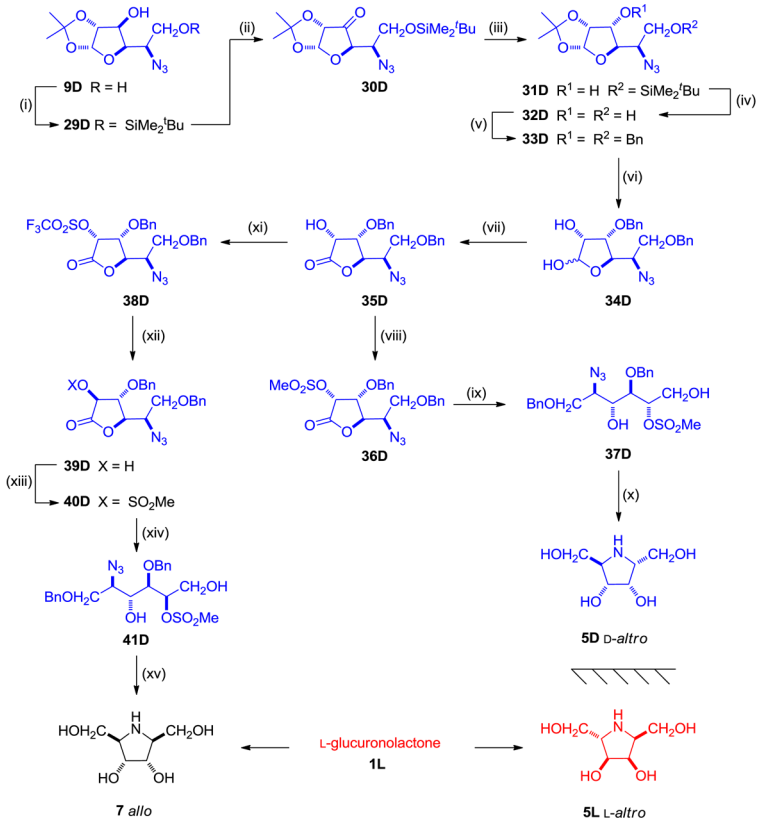
The overall number of steps and yields for the syntheses of seven DMDP stereoisomers from the azido-diols are summarized in Table 1; the epimeric diols **13L** and **9D** were prepared in overall 70% and 72% yields, respectively, from D-glucuronolactone acetonide **1D** on a multigram scale. The stereochemistry required (*R* or *I*) at C5, C3, and C2 for the individual synthetic routes are shown. The general procedures are scalable, robust and reliable for the synthesis of all the stereoisomers. While the yields for the different steps after the formation of diols **13L** and **9D** have not been optimized, the overall yields indicate that these are practicable sources of any stereoisomer. Both the $^{13}C$ NMR shifts and the specific rotations $[\alpha]_D$ of each diastereomer are also compared in Table 1; of the six diastereoisomers **2**−**7** only two (*gluco* **2** and *altro* **5**) have six nonequivalent $^{13}C$ signals. Full NMR analysis of each diastereomer is given in the experimental procedures.

**Glycosidase inhibition.** In piperidine pyranoside mimics (such as DNJ and DGJ), there is usually, but not always,[49] a good overlap between the structure of the glycoside and inhibition by the corresponding iminosugar mimic. Prediction of glycosidase inhibition by pyrrolidine analogues is far less reliable. A comparison of inhibition of a panel of glycosidases by all 10 stereoisomeric 2,5-dideoxy-2,5-iminohexitols was obtained by assays as previously described (Table 2).[50] Three of the stereoisomers are natural products. DGDP **2D** was isolated from the Thai traditional crude drug "Non tai yak" (*Stemona tuberosa*),[51] D-*altro* **5D** was extracted from the roots of *Adenophora triphylla*[52] and DMDP **3D** is the most widely naturally occurring iminosugar.[53]

Both DGDP **2D** and DMDP **3D** are modest $\alpha$-glucosidase inhibitors; DMDP is a much more potent inhibitor of $\beta$-glucosidase[54,55] and $\beta$-galactosidase. DGDP **2D**, but not DMDP **3D**, is an inhibitor of xylose isomerase.[56] Enantiomers


dx.doi.org/10.1021/jo301243s | J. Org. Chem. 2012, 77, 7777−7792

**Scheme 4. Synthesis of *meso-allo-* and *altro*-2,5-Dideoxy-2,5-iminohexitols from Diols 9 Derived from Glucuronolactone by *R5*–*I3*[a]**




[a]Reagents and conditions: (i) *t*-BuMe$_2$SiCl, pyridine, 92%; (ii) Dess–Martin periodinane, $CH_2Cl_2$, 95%; (iii) $NaBH_4$, EtOH, 93%; (iv) TBAF, THF, 98%; (v) NaH, $PhCH_2Br$, DMF, 88%; (vi) TsOH, dioxane/water, 7:1, 93%; (vii) $I_2$, $K_2CO_3$, *t*-BuOH, 79%; (viii) $MeSO_2Cl$, pyridine, 70%; (ix) $NaBH_4$, EtOH/dioxane, 8:1, 51%; (x) 10% Pd/C, $H_2$, $CH_3CO_2Na$, EtOH, then add HCl, 99%; (xi) $(CF_3SO_2)_2O$, pyridine, $CH_2Cl_2$, 80%; (xii) $CF_3CO_2Na$, DMF, 75% from **35D**; (xiii) $MeSO_2Cl$, pyridine, 84%; (xiv) $NaBH_4$, EtOH/dioxane, 8:1, 93%; (xv) 10% Pd/C, $H_2$, $CH_3CO_2Na$, dioxane, then add HCl, 95%.

of iminosugars frequently inhibit the *same* enzymes as the natural product.[57−62] Thus, L-*gluco* **2L** is a better, and more specific, α-glucosidase inhibitor than the natural product DGDP **2D**. L-*manno* **3L** shows potent α-glucosidase and trehalase inhibition. The *meso-galacto* **6** is an excellent inhibitor of both α-D-galactosidase and α-L-fucosidase; **6** contains both D-*galacto* and L-*fuco* motifs (Figure 2); the equivalence of α-D-galactosidase and α-L-fucosidase inhibition is well established.[63,64] The natural product D-*altro* **5D** is a good inhibitor of α-galactosidase and a weak inhibitor of β-glucosidase; **5D** has shown promise as a pharmacological chaperone alternative to DGJ for the treatment of Fabry's disease. The L-*altro* enantiomer **5L** is a moderate inhibitor of both α-galactosidase and α-L-rhamnosidase and a weak inhibitor of α-L-fucosidase (Table 2). *meso-allo* **7** is also good inhibitor of α-galactosidase. Neither of the *ido* **4** enantiomers showed any significant inhibition of any glycosidase. None of the stereoisomers showed any significant inhibition of β-mannosidase or of β-glucuronidases.

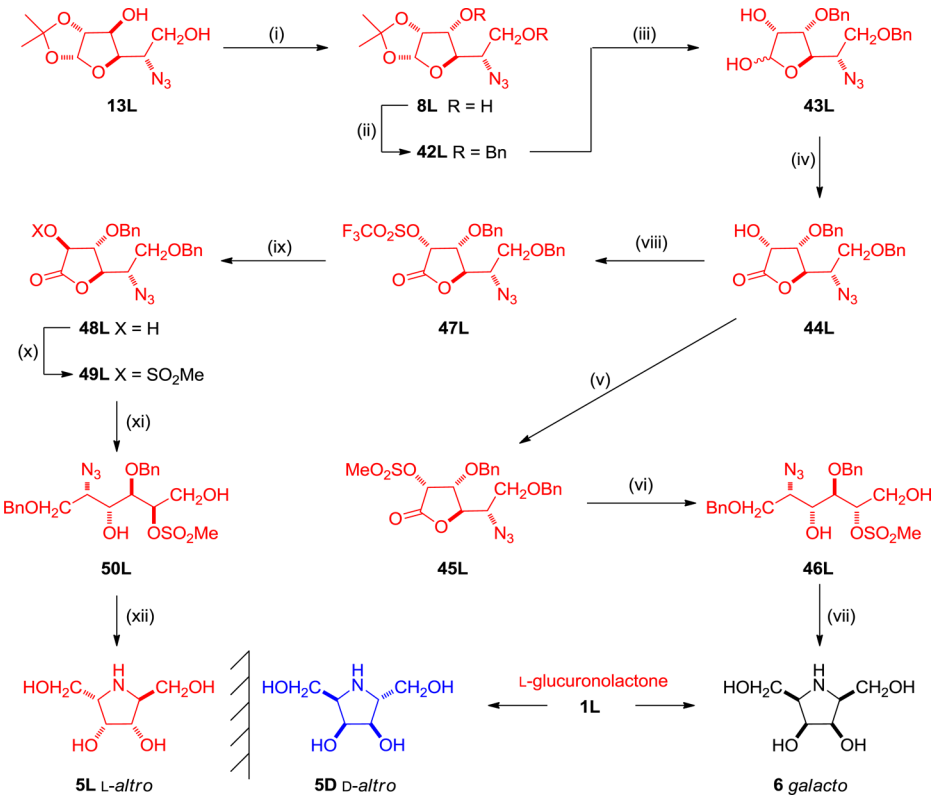
A recent paper reported that L-*gluco* **2L**, L-*manno* **3L**, L-*altro* **5L**, and *meso-allo* **7**, synthesized from chiral tri-*O*-benzyl cyclic nitrones,[33] are all good inhibitors of Jack bean α-mannosidase with $IC_{50}$ values of 98, 88, 94, and 52 μM, respectively. In our present study, none of these stereoisomers caused 50% inhibition for the same Jack bean α-mannosidase even at concentrations as high as 1000 μM. Of all 10 iminohexitols, only D-*altro* **5D** showed modest inhibition against α-mannosidase with $IC_{50}$ value of 421 μM (Table 2), whereas its enantiomer L-*altro* **5L** gave good inhibition of α-L-rhamnosidase ($IC_{50}$ 91 μM) but *no* inhibition of Jack bean α-mannosidase; pyrrolidine mimics of D-mannofuranose inhibit α-mannosidase,[65,66] whereas pyrrolidine mimics of L-mannofuranose inhibit α-L-rhamnosidase.[67]

## CONCLUSION

The synthesis of all 10 stereoisomers of 2,5-dideoxy-2,5-iminohexitols from the enantiomers of glucuronolactone shows the versatility of the acetonides **1D** and **1L** as chirons. Of the 10 2,5-dideoxy-2,5-iminohexitol stereoisomers, eight are good inhibitors of varying glycosidases, with only the *ido* enantiomers **4D** and **4L** failing to significantly inhibit at least one glycosidase ($IC_{50}$ >100 μM). The main features of the inhibition are as follows. (a) The natural products DGDP **2D** and DMDP **3D** are weak—and their enantiomers **2L** and L-DMDP **3L** more specific and potent—inhibitors of α-glucosidases; the other six stereoisomers show no inhibition of α-glucosidases; (b) both *meso* isomers (*meso-galacto* **6** and *meso-allo* **7**) and D-*altro* **5D** are excellent inhibitors of α-galactosidase; (c) DMDP **3D** is the only isomer that exhibits good inhibition of β-glucosidases; (d) none of the stereoisomers show any significant inhibition of α-mannosidase. Biological properties, including glycosidase


dx.doi.org/10.1021/jo301243s | J. Org. Chem. 2012, 77, 7777−7792

**Scheme 5. Synthesis of *altro*- and *meso-galacto*-2,5-Dideoxy-2,5-iminohexitols from Diols 13 Derived from Glucuronolactone by *I5−I3*[a]**




[a]Reagents and conditions: (i) **8L** from **13L**, 66%;[18] (ii) NaH, $PhCH_2Br$, DMF, 99%; (iii) TsOH, dioxane/water, 7:1, 95%; (iv) $I_2$, $K_2CO_3$, *t*-BuOH, 80%; (v) $MeSO_2Cl$, pyridine, 95%; (vi) $NaBH_4$, EtOH/dioxane, 8:1, 65%; (vii) 10% Pd/C, $H_2$, $CH_3CO_2Na$, dioxane, then add HCl, 91%; (viii) $(CF_3SO_2)_2O$, pyridine, $CH_2Cl_2$, 80%; (ix) $CF_3CO_2Na$, DMF, 72% from **44L**; (x) $MeSO_2Cl$, pyridine, 78%; (xi) $NaBH_4$, EtOH/dioxane, 8:1, 89%; (xii) 10% Pd/C, $H_2$, $CH_3CO_2Na$, dioxane, then add HCl, 92%.

**Table 1. $^{13}C$ NMR, $[\alpha]^{25}_D$, Overall Yields, and Number of Steps from Diols 9D and 13L Derived from D-Glucuronolactone Acetonide 1D for 2,5-Dideoxy-2,5-iminohexitols**

| | | | | | $\delta_C$ (ppm) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2,5-dideoxy-2,5-iminohexitol | | from diol | steps | yield (%) | C1 | C2 | C3 | C4 | C5 | C6 | $[\alpha]^{25}_D$ ($H_2O$) |
| D-*gluco* **2D** | ***I5−R3−I2*** | **13L** | 6 | 39 | 57.4 | 63.7 | 75.0 | 76.5 | 67.3 | 59.8 | +22.2 (*c* 1.2) |
| D-*gluco* **2D** | ***R5−R3−R2*** | **9D** | 8 | 29 | | | | | | | |
| D-*manno* **3D** | ***R5−R3−I2*** | **9D** | 6 | 56 | 62.5 | 62.2 | 78.3 | | | | +50.4[a] (c 0.9) |
| L-*ido* **4L** | ***I5−R3−R2*** | **13L** | 8 | 32 | 57.9 | 63.4 | 75.1 | | | | +7.25 (*c* 0.3) |
| D-*altro* **5D** | ***R5−I3−I2*** | **9D** | 10 | 18 | 58.0 | 62.8 | 70.6 | 71.7 | 62.2 | 58.6 | +31.0 (*c* 1.1) |
| L-*altro* **5L** | ***I5−I3−R2*** | **13L** | 12 | 23 | | | | | | | −25.5 (*c* 0.9) |
| *meso-galacto* **6** | ***I5−I3−I2*** | **13L** | 10 | 28 | 60.4 | 60.5 | 71.9 | | | | 0 (*c* 1.5) |
| *meso-allo* **7** | ***R5−I3−R2*** | **9D** | 12 | 29 | 58.5 | 64.5 | 71.0 | | | | 0 (*c* 1.0) |

[a]$[\alpha]^{21}_D$.

inhibition, are likely to lead to commercial exploitation of stereoisomers of DMDP.

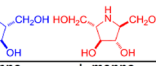
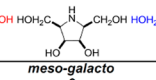
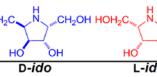
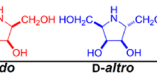
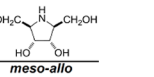
## EXPERIMENTAL SECTION

**General Experimental Procedures.** All commercial reagents were used as supplied. Thin-layer chromatography (TLC) was performed on aluminum sheets coated with 60 $F_{254}$ silica. Plates were visualized using a spray of 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate solution in 2 M aqueous sulfuric acid. Flash chromatography was performed on Sorbsil C60 40/60 silica. Melting points were recorded on a Kofler hot block and are uncorrected. Optical rotation concentrations are quoted in g·100 $mL^{-1}$. $^1H$ and $^{13}C$ NMR spectra were assigned by utilizing 2D COSY and HSQC spectra. All chemical shifts ($\delta$) are quoted in ppm and coupling constants ($J$) in Hz. Residual signals from the solvents were used as an internal reference, except in the case of deuterium oxide, where acetonitrile was used as the reference. HRMS measurements were made using a time-of-flight (TOF) mass analyzer.

*5-Azido-3,6-di-O-benzyl-5-deoxy-1,2-O-isopropylidene-β-L-ido-furanose (**16L**).* Sodium hydride (60% min oil suspension, 118 mg, 4.89 mmol) was added portionwise to a solution of diol **13L** (410 mg, 1.67 mmol) and benzyl bromide (0.60 mL, 4.89 mmol) in DMF (5 mL) at −10 °C under argon. The reaction mixture was allowed to warm to rt and stirred for 17 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.07) and the formation of a major product ($R_f$ 0.68). The reaction was quenched with methanol (0.5 mL), diluted with ethyl acetate (60 mL), and washed with a 1:1 brine/water


dx.doi.org/10.1021/jo301243s | J. Org. Chem. 2012, 77, 7777−7792

**Table 2. Concentration of 2,5-Dideoxy-2,5-iminohexitols Giving 50% Inhibition ($IC_{50}$) of Various Glycosidases**

| | $IC_{50}$ (μM) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| |  |  |  |  |  |  |  |  |  |  |
| Enzyme | D-*gluco* **2D** (DGDP) | L-*gluco* **2L** | D-*manno* **3D** (DMDP) | L-*manno* **3L** | *meso-galacto* **6** | D-*ido* **4D** | L-*ido* **4L** | D-*altro* **5D** | L-*altro* **5L** | *meso-allo* **7** |
| α-Glucosidase | | | | | | | | | | |
| Rice | 131 | **60** | 214 | **5.8** | NI (38.9%) | 792 | NI (36.7%) | NI (24.1%) | NI (35.7%) | NI (30.5%) |
| Yeast | 167 | NI (16.0%) | NI (15.6%) | NI (34.9%) | NI (0%) | NI (4.1%) | NI (29.4%) | NI (26.5%) | NI (35.1%) | NI (33.4%) |
| Rat intestinal maltase | 138 | **48** | 290 | **1.2** | NI (44.2%) | 654 | NI (37.6%) | NI (31.8%) | 754 | NI (45.0%) |
| β-Glucosidase | | | | | | | | | | |
| Almond | 256 | NI (32.4%) | **10** | NI (12.1%) | 597 | NI (44.4%) | 650 | 126 | NI (15.9%) | 463 |
| Bovine liver | 523 | NI (5.4%) | **9.7** | NI (4.6%) | NI (44.5%) | NI (41.2%) | NI (34.7%) | 759 | NI (10.3%) | NI (32.9%) |
| α-Galactosidase | | | | | | | | | | |
| Coffee beans | NI[a] (38.4%)[b] | 216 | NI (10.5%) | NI (13.78%) | **0.19** | 419 | 229 | **5.2** | 120 | **51** |
| β-Galactosidase | | | | | | | | | | |
| Bovine liver | 361 | NI (12.0%) | **3.3** | NI (0%) | NI (48.2%) | 655 | NI (43.1%) | 358 | NI (5.9%) | 610 |
| α-Mannosidase | | | | | | | | | | |
| Jack beans | NI (13.3%) | NI (0%) | NI (31.5%) | NI (17.3%) | NI (10.2%) | NI (0%) | NI (22.3%) | 421 | NI (37.6%) | NI (34.3%) |
| β-Mannosidase | | | | | | | | | | |
| Snail | NI (14.6%) | NI (0%) | 721 | NI (12.6%) | NI (0%) | NI (9.5%) | NI (0.5%) | NI (0%) | NI (3.7%) | NI (3.7%) |
| α-L-Rhamnosidase | | | | | | | | | | |
| *Penicillium decumbens* | NI (3.3%) | NI (16.1%) | NI (24.1%) | NI (45.6%) | 550 | NI (12.2%) | NI (9.8%) | NI (13.4%) | **91** | NI (32.3%) |
| α-L-Fucosidase | | | | | | | | | | |
| Bovine kidney | NI (37.2%) | NI (0.3%) | NI (37.2%) | NI (0%) | **41** | NI (10.1%) | NI (15.8%) | NI (38.0%) | 205 | NI (28.1%) |
| β-Glucuronidase | | | | | | | | | | |
| *E. coli* | NI (5.1%) | NI (1.4%) | NI (0.4%) | NI (0.8%) | NI (21.3%) | NI (3.6%) | NI (2.1%) | NI (6.3%) | NI (2.0%) | NI (1.0%) |
| Trehalase | | | | | | | | | | |
| Porcine kidney | 379 | NI (40.1%) | 200 | **48** | NI (8.4%) | NI (13.1%) | NI (30.5%) | NI (4.3%) | 1000 | 1000 |

[a] *NI : No inhibition (less than 50% inhibition at 1000 μM).*
[b] *( ) : inhibition % at 1000 μM*

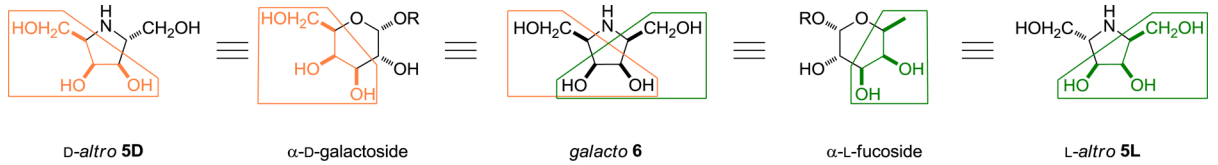



**Figure 2.** D-*galacto*- and L-*fuco*-stereochemical motifs in *altro*-**5D** and **5L** and in *meso-galacto* **6**.

solution (5 × 60 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (24:1 to 1:1, cyclohexane/ethyl acetate) to afford the dibenzyl ether **16L** (519 mg, 73%) as a yellow oil: $[\alpha]^{25}_D$ −30.7 (*c* 0.93, $CHCl_3$); $\nu_{max}$ (thin film) 2097 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz) 1.34, 1.51 (2 × 3H, s, $C(CH_3)_2$), 3.38 (1H, dd, H6, $J_{6,5}$ 5.8, $J_{6,6'}$ 10.0), 3.45 (1H, dd, H6′, $J_{6',5}$ 3.3, $J_{6',6}$ 10.0), 3.81 (1H, d, H3, $J_{3,4}$ 3.3), 3.92 (1H, ddd, H5, $J_{5,6'}$ 3.3, $J_{5,6}$ 5.8, $J_{5,4}$ 8.9), 4.25 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 4.27 (1H, dd, H4, $J_{4,3}$ 3.3, $J_{4,5}$ 8.9), 4.39 (1H, d, $OCH_2Ph$, $J_{gem}$ 12.1), 4.51 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 4.60 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 4.62 (1H, d, H2, $J_{2,1}$ 3.8), 5.97 (1H, d, H1, $J_{1,2}$ 3.8), 7.24−7.38 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz) 26.3, 26.8 ($C(CH_3)_2$), 60.8 (C5), 69.2 (C6), 71.6, 73.4 ($OCH_2Ph$), 79.9 (C4), 81.5 (C3), 81.9 (C2), 104.8 (C1), 112.0 ($C(CH_3)_2$), 127.8, 127.9, 128.0, 128.2, 128.5, 128.6 (ArCH), 136.8, 137.6 (ArCC); LRMS (ESI +ve) 448 (34, M + $Na^+$), 873 (100, 2M + $Na^+$); HRMS (ESI +ve) found 448.1827 [M + $Na^+$], $C_{23}H_{27}N_3NaO_5$ requires 448.1843.

For the enantiomer **16D**: $[\alpha]^{25}_D$ +38.2 (*c* 1.00, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-*L*-idofuranose (**17L**).* *p*-Toluenesulfonic acid (1.04 g, 5.5 mmol) was added to a solution of isopropylidene-protected **16L** (1.05 g, 2.5 mmol) in 7:1 1,4-dioxane/water (6.4 mL) at 80 °C. Water (2 mL) was added over 30 min to maintain a homogeneous reaction mixture. The reaction was stirred for 2.5 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.68) and the formation of a major product ($R_f$ 0.07). The reaction mixture was allowed to cool to rt, quenched with saturated aqueous sodium bicarbonate (32 mL), and extracted with ethyl acetate (3 × 32 mL). The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford lactol **17L** (917 mg, 97%) as a yellow oil, in an anomeric mixture (A:B, 3:1). Lactol **17L** was reacted without further purification: $[\alpha]^{25}_D$ +23.2 (*c* 0.83, $CHCl_3$); $\nu_{max}$ (thin film) 2101 (s, $N_3$), 3417 (br s, OH); $\delta_H$ ($CDCl_3$, 400 MHz) 3.48 (1H, dd, $H6^A$, $J_{6,5}$ 6.6, $J_{6,6'}$ 10.1), 3.51−3.56 (3H, m, $H6^B$, $H6'^A$, $H6'^B$), 3.84 (1H, td, $H5^A$, $J_{5,6'}$ 4.2, $J_{5,6}$ = $J_{5,4}$ 6.6), 3.88−3.91 (2H, m, $H3^B$, $H5^B$), 3.93 (1H, dd, $H3^A$, $J_{3,2}$ 3.3, $J_{3,4}$ 5.0), 4.30 (1H, dd, $H2^A$, $J_{2,3}$ 3.3, $J_{2,1}$ 4.9), 4.33−4.35 (2H, m, $H2^B$, $H4^B$), 4.36 (1H, d, $OCH_2Ph^B$, $J_{gem}$ 11.6), 4.38 (1H, dd, $H4^A$, $J_{4,3}$ 5.0, $J_{4,5}$ 6.6), 4.38 (1H, d, $OCH_2Ph^A$, $J_{gem}$ 11.6), 4.45 (1H, d, $OCH_2Ph^A$, $J_{gem}$ 11.9), 4.46 (1H, d, $OCH_2Ph^B$, $J_{gem}$ 11.9), 4.52 (1H, d, $OCH_2Ph^A$, $J_{gem}$ 11.9), 4.54 (1H, d, $OCH_2Ph^B$, $J_{gem}$ 11.9), 4.62 (1H, d, $OCH_2Ph^B$, $J_{gem}$ 11.6), 4.70 (1H, d, $OCH_2Ph^A$, $J_{gem}$ 11.6), 5.15 (1H, d, $H1^B$, $J_{1,2}$ 10.6), 5.53 (1H, d, $H1^A$, $J_{1,2}$ 4.6), 7.28−7.39 (20H, m, $ArH^A$, $ArH^B$); $\delta_C$ ($CDCl_3$, 100 MHz) 60.9 ($C5^A$), 61.8 ($C5^B$), 69.4 ($C6^B$), 69.8 ($C6^A$), 71.9, 73.4 ($OCH_2Ph^A$), 72.6, 73.5 ($OCH_2Ph^B$), 75.4 ($C2^A$), 77.6 ($C4^A$), 78.5 ($C2^B$), 80.4 ($C4^B$), 82.4 ($C3^B$), 82.9 ($C3^A$), 95.7 ($C1^A$), 103.5 ($C1^B$), 127.8, 127.9, 128.0, 128.0, 128.2, 128.5, 128.5, 128.7 ($ArCH^A$, $ArCH^B$), 137.2 ($ArCC^B$), 137.6 ($ArCC^A$); LRMS (ESI +ve) 403 (59, M + $NH_4^+$), 408 (73, M + $Na^+$), 739 (100, 2M + $Na^+$); HRMS (ESI +ve) found 408.1520 [M + $Na^+$], $C_{20}H_{23}N_3NaO_5$ requires 408.1530.

For the enantiomer **17D**: $[\alpha]^{25}_D$ −34.6 (*c* 0.95, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-*L*-idono-1,4-lactone (**18L**).* Potassium carbonate (337 mg, 2.44 mmol) and iodine (620 mg, 2.44 mmol) were added to a solution of lactol **17L** (464 mg, 1.20 mmol) in 2-methyl-2-propanol (5 mL) at 100 °C. The reaction was stirred for 2 h, after which TLC analysis (1:1, cyclohexane/ethyl acetate) indicated complete consumption of the starting material ($R_f$ 0.33) and the formation of a major product ($R_f$ 0.60). The reaction mixture was allowed to cool to rt and diluted with ethyl acetate (35 mL). Saturated aqueous sodium thiosulfate (15 mL) was added slowly and the biphasic mixture stirred until the iodine was visibly quenched. The phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 35 mL). The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (9:1 to 1:1, cyclohexane/ethyl acetate) to afford the lactone **18L** (317 mg, 72%) as a yellow oil: $[\alpha]^{25}_D$ +39.1 (*c* 1.26, $CHCl_3$); $\nu_{max}$ (thin film) 1794 (s, C═O), 2116 (s, $N_3$), 3424 (br s, OH); $\delta_H$ ($CDCl_3$, 400 MHz) 3.21 (1H, br s, OH2), 3.62 (1H, dd, H6, $J_{6,5}$ 6.6, $J_{6,6'}$ 9.5), 3.69 (1H, dd, H6′, $J_{6',5}$ 7.6, $J_{6',6}$ 9.5), 4.07 (1H, ddd, H5, $J_{5,4}$ 1.5, $J_{5,6}$ 6.6, $J_{5,6'}$ 7.6), 4.41 (1H, dd, H3, $J_{3,2}$ 7.8, $J_{3,4}$ 8.2), 4.55 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 4.59 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 4.65 (1H, dd, H4, $J_{4,5}$ 1.5, $J_{4,3}$ 8.2), 4.67 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 4.84 (1H, dd, H2, $J_{2,OH}$ 2.5, $J_{2,3}$ 7.8), 4.88 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 7.32−7.39 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100


dx.doi.org/10.1021/jo301243s | *J. Org. Chem.* 2012, 77, 7777−7792

MHz) 59.4 (C5), 69.4 (C6), 72.0 (C2), 72.8, 73.6 ($OCH_2Ph$), 76.1 (C4), 79.7 (C3), 127.7, 128.0, 128.2, 128.5, 128.6 (ArCH), 136.8, 137.3 (ArCC), 174.8 (C1); LRMS (ESI +ve) 401 (15, M + $NH_4^+$), 406 (100, M + $Na^+$), 438 (28, M + MeOH + $Na^+$), 789 (74, 2M + $Na^+$); (ESI −ve) 418 (100, M + $^{35}Cl^-$), 420 (39, M + $^{37}Cl^-$); HRMS (ESI +ve) found 406.1360 [M + $Na^+$], $C_{20}H_{21}N_3NaO_5$ requires 406.1373.

For the enantiomer **18D**: $[\alpha]^{25}_D$ −35.2 (*c* 1.15, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-trifluoromethanesulfonyl-L-idono-1,4-lactone (19L).* Trifluoromethanesulfonic anhydride (0.13 mL, 0.76 mmol) was added dropwise to a solution of lactone **18L** (220 mg, 0.58 mmol) and pyridine (0.14 mL, 1.74 mmol) in dichloromethane (2.5 mL) at −40 °C under argon. The reaction was stirred for 1 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated complete consumption of the starting material ($R_f$ 0.39) and the formation of a major product ($R_f$ 0.59). The reaction was diluted with dichloromethane (11 mL), washed with 2 M aqueous hydrochloric acid (3 × 11 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (19:1 to 4:1, cyclohexane/ethyl acetate) to afford the triflate **19L** (280 mg, 95%) as a yellow oil: $[\alpha]^{25}_D$ +56.9 (*c* 0.84, $CHCl_3$); $\nu_{max}$ (thin film) 1813 (s, C═O), 2119 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz) 3.60 (1H, dd, H6, $J_{6,5}$ 6.7, $J_{6,6'}$ 9.5), 3.69 (1H, dd, H6′, $J_{6',5}$ 7.4, $J_{6',6}$ 9.5), 4.01 (1H, dd, H5, $J_{5,6}$ 6.7, $J_{5,6'}$ 7.4), 4.53 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.8), 4.57 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.3), 4.58 (1H, d, H3, $J_{3,2}$ 8.0), 4.59 (1H, d, H4, $J_{4,2}$ 5.3), 4.60 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 4.84 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.8), 5.82 (1H, dd, H2, $J_{2,4}$ 5.3, $J_{2,3}$ 8.0), 7.30−7.42 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz) 58.9 (C5), 68.9 (C6), 73.8, 73.8 ($OCH_2Ph$), 76.2 (C3), 76.7 (C4), 81.4 (C2), 127.8, 128.1, 128.2, 128.6, 128.9 (ArCH), 135.5, 137.0 (ArCC), 165.7 (C1); LRMS (ESI +ve) 456 (100), 538 (18, M + $Na^+$), 570 (54, M + MeOH + $Na^+$); HRMS (ESI +ve) found 538.0858 [M + $Na^+$], $C_{21}H_{20}F_3N_3NaO_7S$ requires 538.0866.

For the enantiomer **19D**: $[\alpha]^{25}_D$ −63.4 (*c* 0.98, $CHCl_3$).

*2,5-Dideoxy-2,5-imino-D-glucitol (2D).* Palladium (10% on C, 28 mg) was added to a solution of triflate **19L** (106 mg, 0.21 mmol) in ethanol (1.2 mL). The reaction vessel was evacuated and flushed with hydrogen and stirred for 1 h. TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of starting material ($R_f$ 0.59) and the formation of a major product ($R_f$ 0.19). The reaction mixture was filtered through glass microfiber (GF/B) to afford the bicyclic lactone **20L**. LRMS indicated the absence of a peak corresponding to the triflate **19L** (*m*/*z* 538 [M + $Na^+$]) and the presence of a peak corresponding to the bicyclic lactone **20L** (*m*/*z* 340 [M + $H^+$]). The crude bicyclic lactone **20L** was reacted without further purification.

Partial data for bicyclic lactone **20L**: $\nu_{max}$ (thin film) 1822 (s, C═O); $\delta_H$ ($CDCl_3$, 500 MHz) 3.78 (1H, dd, H6, $J_{6,5}$ 7.6, $J_{6,6'}$ 10.1), 3.85 (1H, dd, H6′, $J_{6',5}$ 7.0, $J_{6',6}$ 10.1), 4.36 (1H, d, H3 or H4, *J* 2.2), 4.39 (1H, dd, H5, $J_{5,6'}$ 7.0, $J_{5,6}$ 7.6), 4.51 (1H, d, $OCH_2Ph$, $J_{gem}$ 12.0), 4.54 (1H, d, $OCH_2Ph$, $J_{gem}$ 12.0), 4.58 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.7), 4.78 (2H, m, H2, H3 or H4), 4.84 (1H, d, $OCH_2Ph$, $J_{gem}$ 12.0), 7.25−7.37 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 125 MHz) 59.4 (C5), 60.3 (C2), 63.9 (C6), 72.9, 73.7 ($OCH_2Ph$), 79.1, 79.5 (C3 or C4), 127.9, 128.0, 128.2, 128.3, 128.4, 128.5, 128.7, 128.8 (ArCH), 135.4, 136.9 (ArCC), 165.5 (C1); LRMS (ESI +ve) 362 (60, M + $Na^+$), 394 (100, M + MeOH + $Na^+$), 701 (24, 2M + $Na^+$).

Sodium borohydride (50 mg, 1.31 mmol) was added portionwise to a solution of the bicyclic lactone **20L** in ethanol (2 mL) and the reaction stirred at rt for 16 h. Aqueous hydrochloric acid (2 M, 1.5 mL) and palladium (10% on C, 50 mg) were added to the reaction mixture. The reaction vessel was evacuated and flushed with hydrogen and stirred for 20 h. The reaction mixture was filtered through glass microfiber (GF/B) and the filtrate concentrated to approximately 1 mL. This was loaded onto a short column of Dowex 50W-X8 ($H^+$ form) and the pyrrolidine **2D** liberated with 2 M aqueous ammonia. The ammoniacal fractions were concentrated in vacuo to afford pyrrolidine **2D** (26 mg, 80% over three steps) as a yellow oil: $[\alpha]^{25}_D$ +22.2 (*c* 1.18, $H_2O$) [lit.[68] $[\alpha]^{25}_D$ +26.1 (*c* 1.2, $H_2O$)]; $\nu_{max}$ (thin film) 3332 (br s, NH/OH); $\delta_H$ ($D_2O$, 400 MHz) 3.52 (1H, ddd, H5, $J_{5,4}$ 3.5, $J_{5,6'}$ 4.8, $J_{5,6}$ 8.3), 3.82 (1H, dd, H6, $J_{6,5}$ 8.3, $J_{6,6'}$ 12.1), 3.87 (1H, dd, H2, $J_{2,3}$ 3.7, *J* 7.6), 3.88 (1H, dd, H6′, $J_{6',5}$ 4.8, $J_{6',6}$ 12.1), 3.85−3.93 (2H, m, H1, H1′), 4.07 (1H, dd, H4, $J_{4,3}$ 2.3, $J_{4,5}$ 3.5), 4.24 (1H, dd, H3, $J_{3,4}$ 2.3, $J_{3,2}$ 3.7); $\delta_C$ ($D_2O$, 100 MHz) 57.4 (C1), 59.8 (C6), 63.7 (C2), 67.3 (C5), 75.0 (C3), 76.5 (C4); LRMS (ESI +ve) 164 (100, M + $H^+$); (ESI −ve) 162 (100, [M − H]$^-$), 325 (57, [2M − H]$^-$); HRMS (ESI +ve) found 162.0765 [M − H]$^-$, $C_6H_{12}NO_4$ requires 162.0772.

For the enantiomer **2L**: $[\alpha]^{25}_D$ −19.1 (*c* 1.80, $H_2O$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-L-gulono-1,4-lactone (21L).* Trifluoromethanesulfonic anhydride (0.35 mL, 2.07 mmol) was added dropwise to a solution of lactone **18L** (610 mg, 1.59 mmol) and pyridine (0.39 mL, 4.77 mmol) in dichloromethane (6 mL) at −40 °C under argon. The reaction was stirred for 1 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.39) and the formation of a major product ($R_f$ 0.59). The reaction mixture was diluted with dichloromethane (8 mL), washed with 2 M aqueous hydrochloric acid (3 × 8 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford crude triflate **19L** as a yellow oil. The crude triflate **19L** was reacted on without further purification.

Sodium trifluoroacetate (362 mg, 2.66 mmol) was added to a solution of crude triflate **19L** in DMF (3 mL) at rt under argon. The reaction was stirred for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.59) and the formation of a major product ($R_f$ 0.27). The reaction mixture was diluted with ethyl acetate (30 mL) and washed with saturated aqueous sodium bicarbonate (30 mL). The aqueous phase was extracted with ethyl acetate (2 × 30 mL), and the organic fractions were combined, dried ($MgSO_4$), and concentrated in vacuo. The crude residue was purified by flash chromatography (9:1 to 2:1, cyclohexane/ethyl acetate) to afford lactone **21L** (444 mg, 90%) as a yellow oil: $[\alpha]^{25}_D$ +11.7 (*c* 0.81, $CHCl_3$); $\nu_{max}$ (thin film) 1785 (s, C═O), 2099 (s, $N_3$), 3410 (br s, OH); $\delta_H$ ($CD_3CN$, 400 MHz) 3.42 (1H, dd, H6, $J_{6,5}$ 5.6, $J_{6,6'}$ 10.4), 3.54 (1H, dd, H6′, $J_{6',5}$ 2.9, $J_{6',6}$ 10.4), 3.94 (1H, ddd, H5, $J_{5,6'}$ 2.9, $J_{5,6}$ 5.6, $J_{5,4}$ 9.1), 4.09 (1H, br d, OH2, $J_{OH,2}$ 6.1), 4.20 (1H, dd, H3, $J_{3,4}$ 3.3, $J_{3,2}$ 4.4), 4.37 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 4.39 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 4.44 (1H, dd, H4, $J_{4,3}$ 3.3, $J_{4,5}$ 9.1), 4.47 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 4.63 (1H, br dd, H2, $J_{2,3}$ 4.8, $J_{2,OH}$ 6.1), 4.88 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.4), 7.30−7.39 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz) 61.8 (C5), 69.2 (C6), 72.9 (C2), 74.0, 74.9 ($OCH_2Ph$), 77.3 (C3), 79.3 (C4), 128.9, 129.0, 129.2, 129.5 (ArCH), 138.8, 139.0 (ArCC), 175.5 (C1); LRMS (ESI +ve) 406 (70, [M + Na]$^+$), 789 (100, [2M + Na]$^+$); HRMS (ESI +ve) found 406.1362 [M + $Na^+$], $C_{20}H_{21}N_3NaO_5$ requires 406.1373.

For the enantiomer **21D**: $[\alpha]^{25}_D$ −11.2 (*c* 0.95, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-L-gulono-1,4-lactone (22L).* Methanesulfonyl chloride (133 μL, 1.72 mmol) was added dropwise to a solution of lactone **21L** (444 mg, 1.15 mmol) in pyridine (2 mL) at 0 °C under argon. The reaction was allowed to warm to rt and stirred for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.27) and the formation of a major product ($R_f$ 0.55). The reaction mixture was concentrated in vacuo and coevaporated with toluene (3 × 5 mL). The crude residue was purified by flash chromatography (9:1 to 2:1, cyclohexane/ethyl acetate) to afford mesylate **22L** (494 mg, 93%) as a yellow oil: $[\alpha]^{25}_D$ +2.52 (*c* 0.45, $CHCl_3$); $\nu_{max}$ (thin film) 1178 (s, $SO_2$), 1361 (s, $SO_2$), 1801 (s, C═O), 2102 (s, $N_3$); $\delta_H$ ($CD_3CN$, 400 MHz) 3.30 (3H, s, $SO_2CH_3$), 3.44 (1H, dd, H6, $J_{6,5}$ 5.2, $J_{6,6'}$ 10.5), 3.55 (1H, dd, H6′, $J_{6',5}$ 2.8, $J_{6',6}$ 10.5), 3.99 (1H, ddd, H5, $J_{5,6'}$ 3.3, $J_{5,6}$ 5.3, $J_{5,4}$ 8.3), 4.40 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 4.42 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 4.47 (1H, dd, H3, $J_{3,4}$ 3.3, $J_{3,2}$ 4.6), 4.49 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 4.61 (1H, dd, H4, $J_{4,3}$ 3.0, $J_{4,5}$ 9.1), 4.78 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 5.58 (1H, d, H2, $J_{2,3}$ 4.6), 7.30−7.40 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz); 39.7 ($SO_2CH_3$), 61.3 (C5), 69.1 (C6), 74.0, 75.1 ($OCH_2Ph$), 76.5 (C3), 77.1 (C2), 80.4 (C4), 129.0, 129.1, 129.3, 129.4, 129.5, 129.6 (ArCH), 138.0, 138.9 (ArCC), 170.7 (C1); LRMS (ESI +ve) 484 (38, M + $Na^+$), 516 (100, M + MeOH + $Na^+$), 945 (70, [2M + Na]$^+$); HRMS


dx.doi.org/10.1021/jo301243s | J. Org. Chem. 2012, 77, 7777−7792

(ESI +ve) found 484.1144 [M + $Na^+$], $C_{21}H_{23}N_3NaO_7S$ requires 484.1149.

For the enantiomer **22D**: $[\alpha]^{25}_D$ −1.54 (*c* 0.65, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-L-gulitol (23L).* Sodium borohydride (41 mg, 1.08 mmol) was added portionwise to a solution of lactone **22L** (100 mg, 0.22 mmol) in 8:1 ethanol/1,4-dioxane (5 mL) at −30 °C under argon. The reaction was stirred for 4 h, with the internal temperature rising to −15 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the partial consumption of the starting material ($R_f$ 0.55) and the formation of a major product ($R_f$ 0.42). Further sodium borohydride (41 mg, 1.08 mmol) was added at −30 °C and the reaction allowed to warm to −15 °C. After 6 h, TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.55) and the major product ($R_f$ 0.42). The reaction mixture was neutralized with glacial acetic acid and concentrated in vacuo. The crude residue was dissolved in ethyl acetate (30 mL) and washed with saturated aqueous sodium bicarbonate (20 mL). The aqueous phase was extracted with ethyl acetate (2 × 30 mL), and the organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (9:1 to 1:4, cyclohexane/ethyl acetate) to afford diol **23L** (83 mg, 82%) as a yellow oil: $[\alpha]^{25}_D$ +4.76 (*c* 0.48, $CHCl_3$); $\nu_{max}$ (thin film) 1172 (s, $SO_2$), 1336 (s, $SO_2$), 2098 (s, $N_3$), 3490 (br s, OH); $\delta_H$ ($CD_3OD$, 400 MHz) 3.13 (3H, s, $SO_2CH_3$), 3.43 (1H, dd, H6, $J_{6,5}$ 6.6, $J_{6,6'}$ 10.4), 3.55 (1H, dd, H6′, $J_{6',5}$ 3.5, $J_{6',6}$ 10.4), 3.63 (1H, ddd, H5, $J_{5,6'}$ 3.5, $J_{5,4}$ 6.3, $J_{5,6}$ 6.6), 3.84 (1H, dd, H4, $J_{4,3}$ 3.8, $J_{4,5}$ 6.3), 3.84 (1H, dd, H1, $J_{1,2}$ 6.8, $J_{1,1'}$ 12.7), 3.92 (1H, t, H3, $J_{3,4}$ = $J_{3,2}$ 3.8), 4.05 (1H, dd, H1′, $J_{1',2}$ 3.0, $J_{1',1}$ 12.7), 4.45 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 4.52 (1H, d, $OCH_2Ph$, $J_{gem}$ 9.5), 4.55 (1H, d, $OCH_2Ph$, $J_{gem}$ 9.5), 4.76 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 4.85 (1H, m, H2), 7.30−7.36 (10H, m, ArH); $\delta_C$ ($CD_3OD$, 100 MHz) 38.6 ($SO_2CH_3$), 61.8 (C1), 65.0 (C5), 70.1 (C6), 72.2 (C4), 74.5, 75.3 ($OCH_2Ph$), 80.1 (C3), 85.9 (C2), 129.0, 129.1, 129.2, 129.6, 129.6 (ArCH), 139.3, 139.3 (ArCC); LRMS (ESI +ve) 488 (60, M + $Na^+$), 953 (100, 2M + $Na^+$); HRMS (ESI +ve) found 488.1462 [M + $Na^+$], $C_{21}H_{27}N_3NaO_7S$ requires 488.1448.

For the enantiomer **23D**: $[\alpha]^{25}_D$ −4.54 (*c* 0.50, $CHCl_3$).

*2,5-Dideoxy-2,5-imino-L-iditol (4L).* Palladium (10% on carbon, 32 mg) and sodium acetate (29 mg, 0.35 mmol) were added to a solution of mesylate **23L** (81 mg, 0.17 mmol) in 1,4-dioxane (4 mL). The reaction vessel was evacuated, flushed with hydrogen, and stirred for 24 h. TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.42) and the formation of a major product (baseline). Aqueous hydrochloric acid (2 M, 1 mL) was added and the reaction vessel evacuated and flushed with hydrogen and the reaction stirred for 16 h. The reaction mixture was filtered through glass microfiber (GF/A), concentrated in vacuo, dissolved in 2 M aqueous hydrochloric acid (4 mL), and loaded onto a short column of Dowex 50W-X8 ($H^+$ form). The product was liberated with 2 M aqueous ammonia, and the ammoniacal fractions were combined and concentrated in vacuo to afford the pyrrolidine **4L** (26 mg, 92%) as a yellow oil: $[\alpha]^{25}_D$ +7.25 (*c* 0.30, $H_2O$) [lit.[28] $[\alpha]^{25}_D$ +14.0 (*c* 1.0, $H_2O$)]; $\nu_{max}$ (thin film) 3347 (br s, NH/OH); $\delta_H$ ($D_2O$, 400 MHz) 3.79 (1H, dd, H1, $J_{1,2}$ 6.6, $J_{1,1'}$ 10.4), 3.80−3.84 (1H, m, H2), 3.89 (1H, dd, H1′, $J_{1',2}$ 6.8, $J_{1',1}$ 10.4), 4.10 (1H, d, H3, $J_{3,2}$ 2.5); $\delta_C$ ($D_2O$, 100 MHz) 57.9 (C1), 63.4 (C2), 75.1 (C3); LRMS (ESI +ve) 164 (100, M + $Na^+$); HRMS (ESI +ve) found 164.0912 [M + $H^+$], $C_6H_{14}NO_4$ requires 164.0917.

For the enantiomer **4D**: $[\alpha]^{25}_D$ −8.11 (*c* 0.45, $H_2O$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-D-mannono-1,4-lactone (26D).* Trifluoromethanesulfonic anhydride (0.21 mL, 1.27 mmol) was added dropwise to a solution of lactone **24D** (0.405 g, 1.06 mmol) and pyridine (0.21 mL, 2.64 mmol) in dichloromethane (4 mL) at −30 °C under argon. The reaction was stirred for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.40) and the formation of a major product ($R_f$ 0.55). The reaction was diluted with dichloromethane (20 mL), washed with 2 M aqueous hydrochloric acid (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford crude triflate as a yellow oil. The crude triflate was reacted on without further purification.

Sodium trifluoroacetate (0.29 g, 2.11 mmol) was added portionwise to a solution of crude triflate in DMF (6 mL) at rt under argon. The reaction was stirred for 17 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.55) and the formation of a major product ($R_f$ 0.29). The reaction mixture was partitioned between ethyl acetate (10 mL) and saturated aqueous sodium bicarbonate (10 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic fractions were washed with a 1:1 brine/water solution (2 × 20 mL), dried ($MgSO_4$), and concentrated . The crude residue was purified by flash chromatography (4:1, cyclohexane/ethyl acetate) to afford the lactone **26D** (344 mg, 85%) as a white solid: $[\alpha]^{25}_D$ −41.2 (*c* 0.89, $CHCl_3$) [lit.[69] $[\alpha]^{25}_D$ −42.0 (*c* 0.5, $CH_2Cl_2$)]; mp 115−117 °C; $\nu_{max}$ (thin film) 1790 (s, C═O), 2102 (s, $N_3$) 3424 (br s, OH); $\delta_H$ ($CDCl_3$, 400 MHz) 2.85 (1H, d, OH2, $J_{OH,2}$ 7.6), 3.79 (1H, dd, H6′, $J_{6,5}$ 5.6, $J_{6,6'}$ 10.4), 3.93 (1H, br d, H6′, $J_{6',6}$ 10.4), 3.98 (1H, m, H5), 4.38 (2H, m, H3, H4), 4.50 (1H, m, H2), 4.61 (2H, a-s, 2 × $OCH_2Ph$), 4.78 (1H, d, $OCH_2Ph$, $J_{gem}$ 10.8), 4.87 (1H, d, $OCH_2Ph$, $J_{gem}$ 10.8), 7.32 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz) 57.9 (C5), 69.1 (C6), 71.4 (C2), 73.6, 75.0 ($OCH_2Ph$), 76.1 (C3), 76.4 (C4), 127.7, 127.9, 128.2, 128.4, 128.5, 128.6 (ArCH), 136.8, 137.4 (ArCC), 174.5 (C1); LRMS (ESI +ve) 406 (100, M + $Na^+$), 789 (83, 2M + $Na^+$); HRMS (ESI +ve) found 406.1362 [M + $Na^+$], $C_{20}H_{21}N_3NaO_5$ requires 406.1373.

For the enantiomer **26L**: $[\alpha]^{20}_D$ +44.9 (*c* 0.52, $CHCl_3$); mp 114−116 °C.

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-D-mannono-1,4-lactone (27D).* Methanesulfonyl chloride (0.09 mL, 1.17 mmol) was added dropwise to a solution of alcohol **26D** (300 mg, 0.78 mmol) in pyridine (3 mL) at 0 °C under argon. The reaction was stirred for 2 h, after which TLC analysis (1:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.67) and the formation of a major product ($R_f$ 0.83). The reaction was mixture was concentrated in vacuo, and the crude residue was purified by flash chromatography (3:1, cyclohexane/ethyl acetate) to afford the mesylate **27D** (358 mg, 99%) as a colorless oil: $[\alpha]^{25}_D$ −40.0 (*c* 1.3, $CHCl_3$); $\nu_{max}$ (thin film) 1178 (s, $SO_2$), 1362 (s, $SO_2$), 1802 (s, C═O), 2103 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz) 3.33 (3H, s, $SO_2CH_3$), 3.76 (1H, dd, H6, $J_{6,5}$ 5.2, $J_{6,6'}$ 10.4), 3.90 (1H, dd, H6′, $J_{6',5}$ 2.2, $J_{6',6}$ 10.4), 4.00 (1H, ddd, H5, $J_{5,6'}$ 2.2, $J_{5,6}$ 5.2, $J_{5,4}$ 11.0), 4.44 (1H, dd, H4, $J_{4,3}$ 3.0, $J_{4,5}$ 11.0), 4.52 (1H, dd, H3, $J_{3,4}$ 3.0, $J_{3,2}$ 4.5), 4.60 (2H, a-s, $OCH_2Ph$), 4.70 (1H, d, $OCH_2Ph$ $J_{gem}$ 10.8), 4.94 (1H, d, $OCH_2Ph$, $J_{gem}$ 10.8), 5.40 (1H, d, H2, $J_{2,3}$ 4.5), 7.36 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz) 39.9 ($SO_2CH_3$), 57.7 (C5), 68.8 (C6), 73.6, 74.9 ($OCH_2Ph$), 75.1 (C3), 75.7 (C2), 76.7 (C4), 127.8, 127.9, 128.4, 128.4, 128.5, 128.5 (ArCH), 136.4, 137.3 (ArCC), 169.2 (C1); LRMS (ESI +ve) 484 (50, M + $Na^+$), 516 (71, M + MeOH + $Na^+$), 945 (100, 2M + $Na^+$); HRMS (ESI +ve) found 516.1413 [M + MeOH + $Na^+$], $C_{22}H_{27}N_3NaO_8S$ requires 516.1411.

For the enantiomer **27L**: $[\alpha]^{20}_D$ +29.8 (*c* 0.90, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-D-mannitol (28D).* Sodium borohydride (52 mg, 1.37 mmol) was added portionwise to a solution of lactone **27D** (0.13 g, 0.27 mmol) in 8:1 ethanol/1,4-dioxane (6 mL) at −30 °C under argon. The reaction mixture was stirred for 4 h, with the internal temperature rising to −20 °C, after which TLC analysis (1:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.83) and the formation of a major product ($R_f$ 0.43). The reaction mixture was neutralized with glacial acetic acid and concentrated in vacuo. The crude residue was dissolved with ethyl acetate (30 mL) and washed with saturated aqueous sodium bicarbonate (30 mL). The aqueous phase was extracted with ethyl acetate (2 × 30 mL), and the organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (3:1, cyclohexane/ethyl acetate) to afford the diol **28D** (63 mg, 50%) as a pale yellow oil: $[\alpha]^{25}_D$ −45.4 (*c* 0.55, methanol); $\nu_{max}$ (thin film) 2106 (s, $N_3$), 3375 (br s, OH); $\delta_H$ ($CD_3OD$, 400 MHz) 3.14 (3H, s, $SO_2CH_3$), 3.64 (2H, m, H4, H5),

3.75 (1H, dd, H6, $J_{6,5}$ 6.4, $J_{6,6'}$ 10.4), 3.87 (1H, dd, H1, $J_{1,2}$ 5.6, $J_{1,1'}$ 12.8), 3.96 (1H, dd, H6′, $J_{6',5}$ 2.2, $J_{6',6}$ 10.4), 4.10 (2H, m, H1′, H3), 4.58 (2H, a-s, 2 × $OCH_2Ph$), 4.66 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.2), 4.83 (2H, m, $OCH_2Ph$, H2), 7.34 (10H, m, ArH); $\delta_C$ ($CD_3OD$, 100 MHz) 38.7 ($SO_2CH_3$), 61.9 (C1), 63.1 (C5), 70.6 (C4), 71.8 (C6), 74.5, 75.9 ($OCH_2Ph$), 78.4 (C3), 84.8 (C2), 128.9, 128.9, 129.2, 129.5, 129.6 (ArCH), 139.4, 139.6 (ArCC); LRMS (ESI +ve) 488 (67, M + $Na^+$), 953 (100, 2M + $Na^+$); HRMS (ESI +ve) found 488.1455 [M + $Na^+$], $C_{21}H_{27}N_3NaO_7S$ requires 488.1462.

For the enantiomer **28L**: $[\alpha]^{20}_D$ +42.6 (*c* 0.63, MeOH).

*2,5-Dideoxy-2,5-imino-D-glucitol (**2D**).* Palladium (10% on C, 25 mg) and sodium acetate (17 mg, 0.20 mmol) were added to a solution of diol **28D** (63 mg, 0.14 mmol) in 1,4-dioxane (2 mL). The reaction vessel was evacuated and flushed with hydrogen and stirred for 16 h. TLC analysis (1:1, cyclohexane/ethyl acetate) indicated the complete consumption of starting material ($R_f$ 0.43) and the formation of a major product (baseline). Aqueous hydrochloric acid (2 M, 0.4 mL) was added, and the reaction vessel was evacuated and flushed with hydrogen and the reaction stirred for 24 h. The reaction mixture was filtered through glass microfiber (GF/B) and concentrated in vacuo. The crude residue was dissolved in 2 M aqueous hydrochloric acid and loaded onto a short column of Dowex 5W-X80 ($H^+$ form). The product was liberated with 2 M aqueous ammonia, the ammoniacal fractions combined and concentrated in vacuo to afford the pyrrolidine **2D** (22.1 mg, quant) as a yellow oil.[70]

*5-Azido-6-O-tert-butyldimethylsilyl-5-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (**29D**).* *tert*-Butyldimethylsilyl chloride (5.90 g, 38.5 mmol) was added to a solution of diol **9D** (6.30 g, 25.7 mmol) in pyridine (60 mL) at rt under argon. The reaction was stirred for 20 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.19) and the formation of a major product ($R_f$ 0.52). The reaction was diluted with ethyl acetate (500 mL), washed with 2 M aqueous hydrochloric acid (3 × 150 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (39:1 to 4:1, cyclohexane/ethyl acetate) to afford silyl ether **29D** (8.50 g, 92%) as a colorless oil: $[\alpha]^{25}_D$ −23.1 (*c* 1.30, $CHCl_3$); $\nu_{max}$ (thin film) 2099 (s, $N_3$), 3458 (br s, OH); $\delta_H$ ($CDCl_3$, 400 MHz) 0.11, 0.11 (2 × 3H, s, $Si(CH_3)_2$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.32, 1.49 (2 × 3H, s, $C(CH_3)_2$), 2.42 (1H, d, OH3, $J_{3,OH}$ 4.3), 3.74 (1H, ddd, H5, $J_{5,6'}$ 3.2, $J_{5,6}$ 5.8, $J_{5,4}$ 8.1), 3.84 (1H, dd, H6, $J_{6,5}$ 5.8, $J_{6,6'}$ 10.6), 4.03 (1H, dd, H6′, $J_{6',5}$ 3.2, $J_{6',6}$ 10.6), 4.14 (1H, dd, H4, $J_{4,3}$ 2.8, $J_{4,5}$ 8.1), 4.31 (1H, dd, H3, $J_{3,4}$ 2.8, $J_{3,OH}$ 4.3), 4.53 (1H, d, H2, $J_{2,1}$ 3.7), 5.94 (1H, d, H1, $J_{1,2}$ 3.7); $\delta_C$ ($CDCl_3$, 100 MHz) −5.6 ($Si(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 26.2, 26.7 ($C(CH_3)_2$), 60.9 (C5), 63.8 (C6), 75.2 (C3), 78.4 (C4), 84.9 (C2), 104.9 (C1), 111.9 ($C(CH_3)_2$); LRMS (ESI +ve) 382 (95, M + $Na^+$), 741 (100, 2M + $Na^+$); (ESI −ve) 358 (10, [M − H]$^-$), 394 (25, M + $^{35}Cl^-$), 396 (10, M + $^{37}Cl^-$), 717 (100, [2M − H]$^-$); HRMS (ESI +ve) found 382.1767 [M + $Na^+$], $C_{15}H_{29}N_3NaO_5Si$ requires 382.1769.

For the enantiomer **29L**: $[\alpha]^{25}_D$ +29.9 (*c* 0.90, $CHCl_3$).

*5-Azido-6-O-tert-butyldimethylsilyl-5-deoxy-1,2-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose (**30D**).* Dess−Martin periodinane (15.1 g, 35.5 mmol) was added to a solution of alcohol **29D** (8.50 g, 23.6 mmol) in dichloromethane (90 mL) at 0 °C under argon. After 15 min, the reaction was allowed to warm to rt. After 18 h, TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.52) and the formation of a major product ($R_f$ 0.23 streaking to $R_f$ 0.67). The reaction mixture was diluted with ethyl acetate (450 mL) and washed with a saturated aqueous sodium bicarbonate/sodium thiosulfate solution (400 mL, 2 × 100 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (83:17 to 5:1, cyclohexane/ethyl acetate) to afford ketone **30D** (8.00 g, 95%) as a clear oil: $[\alpha]^{25}_D$ +93.5 (*c* 1.40, $CHCl_3$); $\nu_{max}$ (thin film) 1775 (s, C═O), 2106 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz) 0.08 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.44, 1.48 (2 × 3H, s, $SiC(CH_3)_2$), 3.78−3.83 (3H, m, H5, H6, H6′), 4.41 (1H, dd, H2, *J* 1.0, $J_{2,1}$ 4.3), 4.52 (1H, br s, H4), 6.10 (1H, d, H1, $J_{1,2}$ 4.3); $\delta_C$ ($CDCl_3$, 100 MHz) −5.5, −5.5 ($Si(CH_3)_2$), 18.3 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 27.2, 27.5 ($C(CH_3)_2$), 60.7 (C6), 64.2 (C5), 76.7 (C2), 78.7 (C4), 103.7 (C1), 114.4 ($C(CH_3)_2$), 207.5 (C3); LRMS (ESI +ve) 412 (75, M + MeOH + $Na^+$), 801 (100, M + 2MeOH + $Na^+$); HRMS (ESI +ve) found 412.1870 [M + MeOH + $Na^+$], $C_{16}H_{31}N_3NaO_6Si$ requires 412.1874.

For the enantiomer **30L**: $[\alpha]^{25}_D$ −96.9 (*c* 0.92, $CHCl_3$).

*5-Azido-6-O-tert-butyldimethylsilyl-5-deoxy-1,2-O-isopropylidene-α-D-allofuranose (**31D**).* Sodium borohydride (847 mg, 22.4 mmol) was added portionwise to a solution of ketone **30D** (8.00 g, 22.4 mmol) in ethanol (80 mL) at 0 °C under argon. The reaction was stirred at 0 °C for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.23 streaking to $R_f$ 0.67) and the formation of a major product ($R_f$ 0.47). The reaction was neutralized with glacial acetic acid and concentrated in vacuo. The crude residue was dissolved with ethyl acetate (500 mL) and washed with saturated aqueous sodium bicarbonate (3 × 100 mL) and brine (100 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (19:1 to 3:2, cyclohexane/ethyl acetate) to afford alcohol **31D** (7.48 g, 93%) as a clear oil: $[\alpha]^{25}_D$ +19.9 (*c* 1.05, $CHCl_3$); $\nu_{max}$ (thin film) 2099 (s, $N_3$), 3479 (br s, OH); $\delta_H$ ($CDCl_3$, 400 MHz) 0.11 (6H, s, $Si(CH_3)_2$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.37, 1.58 (2 × 3H, s, $C(CH_3)_2$), 3.14 (1H, d, OH3, $J_{OH,3}$ 7.3), 3.80−3.83 (2H, m, H5, H6), 3.87−3.92 (1H, m, H6′), 3.96 (1H, dd, H4, $J_{4,5}$ 3.7, $J_{4,3}$ 8.4), 4.09 (1H, ddd, H3, $J_{3,2}$ 4.9, $J_{3,OH}$ 7.3, $J_{3,4}$ 8.4), 4.63 (1H, dd, H2, $J_{2,1}$ 3.6, $J_{2,3}$ 4.9), 5.81 (1H, d, H1, $J_{1,2}$ 3.6); $\delta_C$ ($CDCl_3$, 100 MHz) −5.6, −5.6 ($Si(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 26.4, 26.6 ($C(CH_3)_2$), 63.2 (C6), 63.5 (C5), 71.4 (C3), 79.2 (C2), 79.9 (C4), 103.8 (C1), 113.0 ($C(CH_3)_2$); LRMS (ESI +ve) 382 (85, M + $Na^+$), 741 (100, 2M + $Na^+$); (ESI −ve) 358 (45, [M − H]$^-$), 394 (30, M + $^{35}Cl^-$), 396 (10, M + $^{37}Cl^-$), 717 (100, [2M − H]$^-$); HRMS (ESI +ve) found 382.1769 [M + $Na^+$], $C_{15}H_{29}N_3NaO_5Si$ requires 382.1769.

For the enantiomer **31L**: $[\alpha]^{25}_D$ −21.7 (*c* 1.34, $CHCl_3$).

*5-Azido-5-deoxy-1,2-O-isopropylidene-α-D-allofuranose (**32D**).* Tetrabutylammonium fluoride (1 M in THF, 26 mL, 26.0 mmol) was added to a solution of silyl ether **31D** (7.48 g, 20.8 mmol) in THF (75 mL) under argon. The reaction was stirred at rt for 1 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.47) and the formation of a major product ($R_f$ 0.19). The reaction was concentrated in vacuo and purified by flash chromatography (1:1:0 to 0:9:1, cyclohexane/ethyl acetate/methanol) to afford diol **32D** (5.0 g, 98%) as a white crystalline solid: $[\alpha]^{25}_D$ +50.1 (*c* 1.20, acetone) [lit.[71] $[\alpha]^{25}_D$ +47.6 (*c* 1.0, $CHCl_3$)]; mp 82−84 °C [lit.[71] mp 82−83 °C]; $\nu_{max}$ (thin film) 2098 (s, $N_3$), 3382 (br s, OH); $\delta_H$ (($CD_3)_2CO$, 400 MHz) 1.31, 1.47 (2 × 3H, s, $C(CH_3)_2$), 3.71 (1H, dd, H6, $J_{6,5}$ 7.3, $J_{6,6'}$ 11.9), 3.80 (1H, dd, H6′, $J_{6',5}$ 3.8, $J_{6',6}$ 11.9), 3.87 (1H, a-dt, H5, $J_{5,4} = J_{5,6'}$ 3.8, $J_{5,6}$ 7.3), 4.00 (1H, dd, H4, $J_{4,5}$ 3.2, $J_{4,3}$ 8.6), 4.05 (1H, dd, H3, $J_{3,2}$ 4.3, $J_{3,4}$ 8.6), 4.61 (1H, a-t, H2, $J_{2,1} = J_{2,3}$ 3.9), 5.78 (1H, d, H1, $J_{1,2}$ 3.5); $\delta_C$ (($CD_3)_2CO$, 100 MHz) 26.8, 27.0 ($C(CH_3)_2$), 62.3 (C6), 65.8 (C5), 72.4 (C3), 80.4 (C2), 80.5 (C4), 104.9 (C1), 113.1 ($C(CH_3)_2$); LRMS (ESI −ve) 244 (100, [M − H]$^-$), 489 (82, [2M − H]$^-$); HRMS (ESI +ve) found 268.0901 [M + $Na^+$], $C_9H_{15}N_3NaO_5$ requires 268.0904.

For the enantiomer **32L**: $[\alpha]^{25}_D$ −55.3 (*c* 1.12, acetone), mp 84−86 °C.

*5-Azido-3,6-di-O-benzyl-5-deoxy-1,2-O-isopropylidene-α-D-allofuranose (**33D**).* Sodium hydride (60% min oil suspension, 2.50 g, 61.2 mmol) was added portionwise to a solution of diol **32D** (5.00 g, 20.4 mmol) and benzyl bromide (7.30 mL, 61.2 mmol) in DMF (75 mL) at 0 °C under argon. The reaction mixture was allowed to warm to rt and stirred for 18 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.19) and the formation of a major product ($R_f$ 0.68). The reaction was quenched with methanol (10 mL), diluted with ethyl acetate (600 mL), and washed with a 1:1 brine/water solution (3 × 150 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (99:1 to 1:1, cyclohexane/ethyl acetate) to afford

dibenzyl ether **33D** (7.61 g, 88%) as a colorless oil: $[\alpha]^{25}_{D}$ +58.3 (*c* 1.25, $CHCl_3$); $\nu_{max}$ (thin film) 2099 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz) 1.37, 1.59 (2 × 3H, s, $C(CH_3)_2$), 3.52 (1H, dd, H6, $J_{6,5}$ 9.1, $J_{6,6'}$ 10.1), 3.62 (1H, dd, H6′, $J_{6',5}$ 4.0, $J_{6',6}$ 10.1), 3.90 (1H, dd, H3, $J_{3,2}$ 4.3, $J_{3,4}$ 8.6), 4.03 (1H, a-dt, H5, $J_{5,4} = J_{5,6'}$ 3.5, $J_{5,6}$ 8.6), 4.17 (1H, dd, H4, $J_{4,5}$ 3.0, $J_{4,3}$ 8.6), 4.53 (2H, a-d, 2 × $OCH_2Ph$, *J* 11.6), 4.55 (1H, a-t, H2, $J_{2,1} = J_{2,3}$ 4.1), 4.56 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 4.72 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 5.75 (1H, d, H1, $J_{1,2}$ 3.8), 7.31−7.39 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz) 26.5, 26.8 ($C(CH_3)_2$), 62.1 (C5), 69.4 (C6), 72.1, 73.3 ($OCH_2Ph$), 77.4 (C2), 77.5 (C3), 77.8 (C4), 104.1 (C1), 113.2 ($C(CH_3)_2$), 127.7, 127.7, 128.1, 128.1, 128.4, 128.4 (ArCH), 137.1, 137.6 (ArCC); LRMS (ESI +ve) 443 (25, M + $NH_4^+$), 448 (70, M + $Na^+$), 873 (100, 2M + $Na^+$); HRMS (ESI +ve) found 448.1838 [M + $Na^+$], $C_{23}H_{27}N_3NaO_5$ requires 448.1843.

For the enantiomer **33L**: $[\alpha]^{25}_{D}$ −63.4 (*c* 1.23, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-D-allofuranose (**34D**).* *p*-Toluenesulfonic acid (7.30 g, 39.3 mmol) was added to a solution of isopropylidene-protected **33D** (7.60 g, 17.9 mmol) in 7:1 1,4-dioxane/water (40 mL) and heated to 80 °C. The reaction was stirred for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.68) and the formation of a major product ($R_f$ 0.16). The reaction mixture was allowed to cool to rt, diluted with ethyl acetate (600 mL) and quenched with saturated aqueous sodium bicarbonate (250 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (2 × 350 mL). The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford lactol **34D** (6.39 g, 93%) as a yellow oil, in an anomeric mixture (A:B, 2:1). Lactol **34D** was reacted without further purification: $[\alpha]^{25}_{D}$ +12.0 (*c* 1.50, $CHCl_3$); $\nu_{max}$ (thin film) 2099 (s, $N_3$), 3411 (br s, OH); $\delta_H$ ($CDCl_3$, 400 MHz) 3.47 (1H, dd, $H6^A$, $J_{6,5}$ 7.3, $J_{6,6'}$ 10.0), 3.53 (1H, dd, $H6^B$, $J_{6,5}$ 8.2, $J_{6,6'}$ 10.1), 3.61 (1H, dd, $H6'^A$, $J_{6',5}$ 4.0, $J_{6',6}$ 10.1), 3.68−3.74 (2H, m, $H5^A$, $H6'^B$), 3.81 (1H, ddd, $H5^B$, $J_{5,6'}$ 3.3, $J_{5,4}$ 6.3, $J_{5,6}$ 8.2), 3.99 (1H, dd, $H3^A$, $J_{3,4}$ 3.9, $J_{3,2}$ 5.7), 4.02 (1H, br d, $H3^B$, $J_{3,4}$ 4.7), 4.07−4.11 (2H, m, $H2^A$, $H2^B$), 4.19 (1H, a-t, $H4^A$, $J_{4,3} = J_{4,5}$ 4.0), 4.29 (1H, a-t, $H4^B$, $J_{4,5} = J_{4,3}$ 5.0), 4.52 (2H, a-d, 2 × $OCH_2Ph^B$, *J* 12.1), 4.54−4.57 (2H, m, 2 × $OCH_2Ph^A$), 4.58 (2H, a-d, 2 × $OCH_2Ph^A$, *J* 11.9), 4.62 (2H, a-d, 2 × $OCH_2Ph^B$, *J* 11.7), 5.26−5.27 (2H, m, $H1^A$, $H1^B$), 7.30−7.39 (20H, m, $ArH^A$, $ArH^B$); $\delta_C$ ($CDCl_3$, 100 MHz) 62.5 ($C5^A$), 63.3 ($C5^B$), 67.0 ($C6^A$), 69.7 ($C6^B$), 70.6 ($C2^A$), 73.0, 73.5 ($OCH_2Ph^B$), 73.0, 73.5 ($OCH_2Ph^A$), 73.7 ($C3^B$), 77.5 ($C3^A$), 79.0 ($C4^B$), 80.2 ($C2^B$), 80.4 ($C4^A$), 97.0 ($C1^A$), 102.3 ($C1^B$), 127.6, 127.8, 127.9, 128.2, 128.2, 128.4, 128.5, 128.5, 128.7 ($ArCH^A$, $ArCH^B$), 136.6, 136.6, 137.4, 137.5 ($ArCC^A$, $ArCC^B$); LRMS (ESI +ve) 408 (60, M + $Na^+$), 793 (100, 2M + $Na^+$); (ESI −ve) 769 (100, $[2M - H]^-$), HRMS (ESI +ve) found 408.1526 [M + $Na^+$]; $C_{20}H_{23}N_3NaO_5$ requires 408.1530.

For the enantiomer **34L**: $[\alpha]^{25}_{D}$ −11.5 (*c* 1.20, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-D-allono-1,4-lactone (**35D**).* Potassium carbonate (4.94 mg, 35.7 mmol) and iodine (9.07 g, 35.7 mmol) were added to a solution of lactol **34D** (6.39 g, 16.7 mmol) in 2-methyl-2-propanol (80 mL) at 100 °C. The reaction was stirred for 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.16) and the formation of a major product ($R_f$ 0.32). The reaction mixture was allowed to cool to rt and diluted with ethyl acetate (500 mL). Saturated aqueous sodium thiosulfate (250 mL) was added slowly and the biphasic mixture stirred until the iodine was visibly quenched. The phases were separated, and the aqueous layer was extracted with ethyl acetate (2 × 200 mL). The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (9:1 to 1:1, cyclohexane/ethyl acetate) to afford lactone **35D** (5.1 g, 79%) as a colorless oil: $[\alpha]^{25}_{D}$ −20.3 (*c* 1.50, $CHCl_3$); $\nu_{max}$ (thin film) 1789 (s, C═O), 2104 (s, $N_3$), 3434 (br s, OH); $\delta_H$ ($CD_3CN$, 400 MHz) 3.62 (1H, dd, H6, $J_{6,5}$ 7.1, $J_{6,6'}$ 10.4), 3.71 (1H, dd, H6′, $J_{6',5}$ 4.0, $J_{6',6}$ 10.4) 3.77 (1H, d, OH2, $J_{OH,2}$ 8.6), 3.94 (1H, ddd, H5, $J_{5,6'}$ 4.0, $J_{5,4}$ 6.0, $J_{5,6}$ 7.1), 4.19 (1H, dd, H3, $J_{3,4}$ 0.8, $J_{3,2}$ 5.8), 4.45 (1H, dd, H4, $J_{4,3}$ 0.8, $J_{4,5}$ 6.0), 4.54 (1H, d, $OCH_2Ph$, $J_{gem}$ 12.1), 4.57 (1H, d, $OCH_2Ph$, $J_{gem}$ 12.1), 4.59 (1H, dd, H2, $J_{2,3}$ 5.8, $J_{2,OH}$ 8.6), 4.61 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 4.65 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 7.30−7.39 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz) 61.9 (C5), 69.0 (C2), 70.3 (C6), 73.1, 74.1 ($OCH_2Ph$), 75.9 (C3), 81.8 (C4), 128.8, 128.8, 129.0, 129.1, 129.5 (ArCH), 138.6, 139.0 (ArCC), 175.8 (C1); LRMS (ESI +ve) 789 (100, 2M + $Na^+$); HRMS (ESI +ve) found 406.1369 [M + $Na^+$], $C_{20}H_{21}N_3NaO_5$ requires 406.1373.

For the enantiomer **35L**: $[\alpha]^{25}_{D}$ +20.5 (*c* 1.40, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-trifluoromethanesulfonyl-D-allono-1,4-lactone (**38D**).* Trifluoromethanesulfonic anhydride (0.06 mL, 0.35 mmol) was added dropwise to a solution of lactone **35D** (100 mg, 0.27 mmol) and pyridine (0.07 mL, 0.81 mmol) in dichloromethane (1.0 mL) at −40 °C under argon. The reaction was stirred for 1 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.32) and the formation of a major product ($R_f$ 0.63). The reaction was diluted with dichloromethane (5 mL), washed with 2 M aqueous hydrochloric acid (3 × 5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (19:1 to 4:1, cyclohexane/ethyl acetate) to afford triflate **38D** (108 mg, 80%) as a yellow oil, which crystallized on standing: $[\alpha]^{25}_{D}$ −5.7 (*c* 1.06, $CHCl_3$); mp 66−68 °C; $\nu_{max}$ (thin film) 1808 (s, C═O), 2125 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz) 3.53−3.54 (2H, m, H6, H6′), 3.94 (1H, ddd, H5, *J* 5.8, *J* 5.6, $J_{5,4}$ 3.0), 4.35 (1H, d, H3, $J_{3,2}$ 5.7), 4.51 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 4.52 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 4.55 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 4.62 (1H, d, H4, $J_{4,5}$ 3.0), 4.66 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 5.52 (1H, d, H2, $J_{2,3}$ 5.7), 7.26−7.42 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz) 61.2 (C5), 68.4 (C6), 73.0 (C3), 73.2, 73.9 ($OCH_2Ph$), 76.5 (C2), 82.9 (C4), 127.8, 128.2, 128.4, 128.6, 128.7, 128.7 (ArCH), 135.8, 136.6 (ArCC), 166.7 (C1); LRMS (ESI +ve) 565 (38, M + MeOH + $NH_4^+$), 570 (100, M + MeOH + $Na^+$); HRMS (ESI +ve) found 570.1127 [M + MeOH + $Na^+$], $C_{22}H_{24}F_3N_3NaO_8S$ requires 570.1128.

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-D-allono-1,4-lactone (**36D**).* Methanesulfonyl chloride (29 μL, 0.37 mmol) was added dropwise to a solution of alcohol **35D** (90 mg, 0.24 mmol) in pyridine (1.0 mL) at 0 °C under argon. The reaction was stirred at 0 °C for 15 min, allowed to warm to rt, and stirred for a further 2 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.32) and the formation of a major product ($R_f$ 0.52). The reaction mixture was concentrated in vacuo and coevaporated with toluene (3 × 3 mL). The crude residue was purified by flash chromatography (19:1 to 3:1, cyclohexane/ethyl acetate) to afford mesylate **36D** (76 mg, 70%) as a colorless oil: $[\alpha]^{25}_{D}$ +26.2 (*c* 1.00, $CHCl_3$); $\nu_{max}$ (thin film) 1178 (s, $SO_2$), 1365 (s, $SO_2$), 1801 (s, C═O), 2109 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz) 3.31 (3H, s, $SO_2CH_3$), 3.47 (1H, dd, H6, $J_{6,5}$ 6.6, $J_{6,6'}$ 10.1), 3.52 (1H, dd, H6′, $J_{6',5}$ 4.9, $J_{6',6}$ 10.1), 3.92 (1H, ddd, H5, $J_{5,4}$ 3.5, $J_{5,6'}$ 4.9, $J_{5,6}$ 6.6), 4.30 (1H, d, H3, $J_{3,2}$ 6.1), 4.51−4.55 (3H, m, 3 × $OCH_2Ph$), 4.58 (1H, d, H4, $J_{4,5}$ 3.5), 4.76 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 5.50 (1H, d, H2, $J_{2,3}$ 6.1), 7.30−7.40 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz) 39.8 ($SO_2CH_3$), 61.3 (C5), 68.6 (C6), 73.1 (C2) 73.1, (C3), 73.3, 73.7 ($OCH_2Ph$), 83.3 (C4), 127.8, 128.2, 128.3, 128.4, 128.6, 128.7 (ArCH), 136.4, 136.7 (ArCC), 169.8 (C1); LRMS (ESI +ve) 484 (24, M + $Na^+$), 516 (21, M + MeOH + $Na^+$), 945 (100, 2M + $Na^+$); (ESI −ve) 352 (100), 496 (76, M + $^{35}Cl^-$), 498 (32, M + $^{37}Cl^-$); HRMS (ESI +ve) found 516.1407 [M + MeOH + $Na^+$], $C_{22}H_{27}N_3NaO_8S$ requires 516.1411.

For the enantiomer **36L**: $[\alpha]^{25}_{D}$ −22.7 (*c* 1.15, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-D-allitol (**37D**).* Sodium borohydride (90 mg, 2.40 mmol) was added portionwise to a solution of lactone **36D** (101 mg, 0.22 mmol) in 8:1 ethanol/1,4-dioxane (6 mL) at −30 °C under argon. The reaction was stirred for 6 h, with the internal temperature rising to −20 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.52) and the formation of a major product ($R_f$ 0.05). The reaction was neutralized with glacial acetic acid and concentrated in vacuo. The crude residue was dissolved with ethyl acetate (40 mL) and washed with saturated aqueous sodium bicarbonate (25 mL) and the aqueous layer extracted with ethyl acetate (2 × 40 mL). The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue


dx.doi.org/10.1021/jo301243s | J. Org. Chem. 2012, 77, 7777−7792

was purified by flash chromatography (9:1 to 1:1, cyclohexane/ethyl acetate) to afford diol **37D** (52 mg, 51%) as a yellow oil: $[\alpha]^{25}_{D}$ +12.1 (*c* 0.90, $CHCl_3$); $\nu_{max}$ (thin film) 1173 (s, $SO_2$), 1339 (s, $SO_2$), 2102 (s, $N_3$), 3449 (br s, OH); $\delta_H$ ($CDCl_3$, 400 MHz) 3.08 (3H, s, $SO_2CH_3$), 3.58 (1H, dd, H6, $J_{6,5}$ 5.7, $J_{6,6'}$ 10.1), 3.66 (1H, dd, H6′, $J_{6',5}$ 3.4, $J_{6',6}$ 10.1), 3.75 (1H, ddd, H5, $J_{5,6'}$ 3.4, $J_{5,4}$ 4.5, $J_{5,6}$ 5.7), 3.83 (1H, dd, H3, $J_{3,2}$ 2.3, $J_{3,4}$ 7.7), 3.92 (1H, dd, H4, $J_{4,5}$ 4.5, $J_{4,3}$ 7.7), 3.96 (1H, dd, H1, $J_{1,2}$ 6.5, $J_{1,1'}$ 12.9), 4.01 (1H, dd, H1′, $J_{1',2}$ 4.1, $J_{1',1}$ 12.9), 4.46 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 4.47 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.1), 4.53 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 4.75 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.1), 5.14 (1H, ddd, H2, $J_{2,3}$ 2.3, $J_{2,1'}$ 4.1, $J_{2,1}$ 6.5), 7.29–7.39 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz) 38.5 ($SO_2CH_3$), 61.3 (C1), 61.4 (C5), 69.4 (C6), 71.4 (C4), 73.4, 73.7 ($OCH_2Ph$), 79.2 (C3), 82.8 (C2), 127.9, 128.1, 128.3, 128.5, 128.6, 128.6 (ArCH), 136.8, 137.0 (ArCC); LRMS (ESI +ve) 953 (100, 2M + $Na^+$); HRMS (ESI +ve) found 488.1460 [M + $Na^+$], $C_{21}H_{27}N_3NaO_7S$ requires 488.1462.

For the enantiomer **37L**: $[\alpha]^{25}_{D}$ −8.5 (*c* 1.00, $CHCl_3$).

*2,5-Dideoxy-2,5-imino-D-altritol (**5D**).* Palladium (10% on C, 60 mg) and sodium acetate (54 mg, 0.65 mmol) were added to a solution of diol **37D** (152 mg, 0.33 mmol) in 1,4-dioxane (10 mL). The reaction vessel was evacuated and flushed with hydrogen and the reaction stirred for 4 h. TLC analysis (3:7, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.64) and the formation of a major product ($R_f$ 0.02). LRMS indicated the absence of a peak corresponding to the diol **37D** (*m*/*z* 488 [M + $Na^+$]) and the presence of a peak corresponding to the dibenzyl pyrrolidine intermediate (*m*/*z* 344 [M + $H^+$]). Aqueous hydrochloric acid (2 M, 0.5 mL) was added, the reaction vessel evacuated and flushed with hydrogen, and the reaction stirred for 19 h. LRMS indicated the absence of a peak corresponding to dibenzylpyrrolidine intermediate (*m*/*z* 344 [M + $H^+$]) and the presence of a peak corresponding to the pyrrolidine **5D** (*m*/*z* 164 [M + $H^+$]). The reaction was filtered through glass microfiber (GF/B), concentrated in vacuo, dissolved in 2 M aqueous hydrochloric acid (1 mL), and loaded onto a short column of Dowex 50W-X8 ($H^+$ form). The product was liberated with 2 M aqueous ammonia. The ammoniacal fractions were combined and concentrated in vacuo to afford the pyrrolidine **5D** (53 mg, 99%) as a colorless oil: $[\alpha]^{25}_{D}$ +31.0 (*c* 1.10, $H_2O$) [lit.[52] $[\alpha]^{25}_{D}$ +34.2 (*c* 0.83, $H_2O$)]; $\nu_{max}$ (thin film) 3283 (br s, NH/OH); $\delta_H$ ($D_2O$, 400 MHz) 3.57 (1H, ddd, H5, $J_{5,6'}$ 3.5, $J_{5,6}$ 5.8, $J_{5,4}$ 9.1), 3.68 (1H, ddd, H2, $J_{2,3}$ 3.3, $J_{2,1'}$ 5.3, $J_{2,1}$ 8.1), 3.77 (1H, dd, H6, $J_{6,5}$ 5.8, $J_{6,6'}$ 12.6), 3.82 (1H, dd, H1, $J_{1,2}$ 8.1, $J_{1,1'}$ 12.1), 3.89 (1H, dd, H6′, $J_{6',5}$ 3.5, $J_{6',6}$ 12.6), 3.92 (1H, dd, H1′, $J_{1',2}$ 5.3, $J_{1',1}$ 12.1), 4.19 (1H, dd, H4, $J_{4,3}$ 3.8, $J_{4,5}$ 9.1), 4.26 (1H, dd, H3, $J_{3,2}$ 3.3, $J_{3,4}$ 3.8); $\delta_C$ ($D_2O$, 100 MHz) 58.0 (C1), 58.6 (C6), 62.2 (C5), 62.8 (C2), 70.6 (C3), 71.7 (C4); LRMS (ESI +ve) 164 (100, M + $Na^+$), 250 (38, M + 2MeOH + $Na^+$); HRMS (ESI +ve) found 186.0736 [M + $Na^+$], $C_6H_{13}NNaO_4$ requires 186.0737.

For the enantiomer **5L**: $[\alpha]^{25}_{D}$ −25.5 (*c* 0.90, $H_2O$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-D-altrono-1,4-lactone (**39D**).* Trifluoromethanesulfonic anhydride (2.9 mL, 17.3 mmol) was added dropwise to a solution of lactone **35D** (5.1 g, 13.3 mmol) and pyridine (3.2 mL, 39.9 mmol) in dichloromethane (60 mL) at −40 °C under argon. The reaction was stirred for 1 h, with the internal temperature rising to −25 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.32) and the formation of a major product ($R_f$ 0.63). The reaction was diluted with dichloromethane (250 mL), washed with 2 M aqueous hydrochloric acid (3 × 250 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford crude triflate **38D**. The crude triflate **38D** was reacted on without further purification.

Sodium trifluoroacetate (3.62 g, 26.6 mmol) was added portionwise to a solution of the crude triflate **38D** in DMF (30 mL) at −30 °C under argon. The reaction was allowed to warm to rt and stirred for 16 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.63) and the formation of a major product ($R_f$ 0.45). The reaction mixture was partitioned between ethyl acetate (250 mL) and saturated aqueous sodium bicarbonate (150 mL). The phases were separated and the aqueous layer extracted with ethyl acetate (3 × 250 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified by flash chromatography (49:1 to 1:1, cyclohexane/ethyl acetate) to afford the lactone **39D** (3.80 g, 75%) as a white crystalline solid: $[\alpha]^{25}_{D}$ +37.1 (*c* 1.97, $CHCl_3$); mp 121–123 °C; $\nu_{max}$ (thin film) 1799 (s, C═O), 2115 (s, $N_3$), 3175 (br s, OH); $\delta_H$ ($CD_3CN$, 400 MHz) 3.54 (1H, dd, H6, $J_{6,5}$ 8.1, $J_{6,6'}$ 10.2), 3.65 (1H, dd, H6′, $J_{6',5}$ 4.0, $J_{6',6}$ 10.2), 4.09 (1H, a-dt, H5, $J_{5,4} = J_{5,6'}$ 4.0, $J_{5,6}$ 8.1), 4.19 (1H, a-t, H3, $J_{3,2} = J_{3,4}$ 7.6), 4.24 (1H, br d, OH2, $J_{OH,2}$ 6.1), 4.33 (1H, dd, H4, $J_{4,5}$ 4.2, $J_{4,3}$ 7.5), 4.51 (1H, d, $OCH_2Ph$, $J_{gem}$ 12.1), 4.54 (1H, d, $OCH_2Ph$, $J_{gem}$ 12.1), 4.59 (1H, dd, H2, $J_{2,OH}$ 6.1, $J_{2,3}$ 7.6), 4.61 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 4.79 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 7.29–7.38 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz) 62.7 (C5), 69.8 (C6), 72.9, 73.9 ($OCH_2Ph$), 75.1 (C2), 78.1 (C4), 81.2 (C3), 128.8, 129.0, 129.3, 129.5 (ArCH), 138.6, 139.1 (ArCC), 174.4 (C1); LRMS (ESI +ve) 406 (100, M + $Na^+$), 789 (60, 2M + $Na^+$); HRMS (ESI +ve) found 406.1369 [M + $Na^+$], $C_{20}H_{21}N_3NaO_5$ requires 406.1373.

For the enantiomer **39L**: $[\alpha]^{25}_{D}$ −31.9 (*c* 2.00, $CHCl_3$), mp 120–122 °C.

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-D-altrono-1,4-lactone (**40D**).* Methanesulfonyl chloride (1.20 mL, 15.6 mmol) was added dropwise to a solution of alcohol **39D** (3.99 g, 10.4 mmol) in pyridine (40 mL) at 0 °C under argon. After 10 min, the reaction was allowed to warm to rt and stirred for a further 2 h. After which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.45) and the formation of a major product ($R_f$ 0.60). The reaction mixture was concentrated in vacuo and coevaporated with toluene (2 × 25 mL) and dichloromethane (2 × 25 mL). The crude residue was purified by flash chromatography (47:3 to 3:2, cyclohexane/ethyl acetate) to afford the mesylate **40D** (4.04 g, 84%) as a clear oil: $[\alpha]^{25}_{D}$ +40.5 (*c* 2.40, $CHCl_3$); $\nu_{max}$ (thin film) 1178 (s, $SO_2$), 1369 (s, $SO_2$), 1803 (s, C═O), 2110 (s, $N_3$); $\delta_H$ ($CD_3CN$, 400 MHz) 3.29 (3H, s, $SO_2CH_3$), 3.56 (1H, dd, H6, $J_{6,5}$ 7.8, $J_{6,6'}$ 10.2), 3.67 (1H, dd, H6′, $J_{6',5}$ 4.5, $J_{6',6}$ 10.2), 4.10 (1H, a-dt, H5, $J_{5,4} = J_{5,6'}$ 4.0, $J_{5,6}$ 7.8), 4.48–4.56 (4H, m, H3, H4, $OCH_2Ph$ × 2), 4.61 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.0), 4.78 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.0), 5.59 (1H, d, H2, $J_{2,3}$ 6.8), 7.31–7.40 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz) 40.3 ($SO_2CH_3$), 62.2 (C5), 69.6 (C6), 73.4, 74.0 ($OCH_2Ph$), 79.0, 79.2 (C3, C4), 81.0 (C2), 128.8, 128.8, 129.3, 129.5, 129.5, 129.6 (ArCH), 137.8, 139.0 (ArCC), 169.6 (C1); LRMS (ESI +ve) 484 (56, M + $Na^+$), 516 (100, M + MeOH + $Na^+$), 945 (48, 2M + $Na^+$); HRMS (ESI +ve) found 516.1406 [M + MeOH + $Na^+$], $C_{22}H_{27}N_3NaO_8S$ requires 516.1411.

For the enantiomer **40L**: $[\alpha]^{25}_{D}$ −35.6 (*c* 2.05, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-D-altritol (**41D**).* Sodium borohydride (205 mg, 5.42 mmol) was added portionwise to a solution of mesylate **40D** (500 mg, 1.08 mmol) in 8:1 ethanol/1,4-dioxane (24 mL) at −30 °C under argon. The reaction was stirred for 1 h, with the internal temperature rising to −25 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the incomplete consumption of the starting material ($R_f$ 0.60) and the formation of a major product ($R_f$ 0.18). Further sodium borohydride (205 mg, 5.42 mmol) was added at −30 °C and the reaction allowed to warm to −15 °C. After 3 h, TLC analysis indicated the complete consumption of the starting material ($R_f$ 0.60) and the major product ($R_f$ 0.18). The reaction was neutralized with glacial acetic acid and concentrated in vacuo. The crude residue was dissolved with ethyl acetate (200 mL) and washed with saturated aqueous sodium bicarbonate (75 mL). The aqueous layer was extracted with ethyl acetate (2 × 100 mL), and the organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (9:1 to 7:3, cyclohexane/ethyl acetate) to afford the diol **41D** (468 mg, 93%) as a pale yellow oil: $[\alpha]^{25}_{D}$ +5.7 (*c* 0.91, $CHCl_3$); $\nu_{max}$ (thin film) 1171 (s, $SO_2$), 1334 (s, $SO_2$), 2100 (s, $N_3$), 3500 (br s, OH); $\delta_H$ ($CD_3CN$, 400 MHz) 3.07 (3H, s, $SO_2CH_3$), 3.67 (1H, dd, H1 or H6, *J* 7.7, *J* 10.2), 3.77–3.89 (8H, m, H1 or H6, H1′, H3, H4, H5, H6′, OH1, OH4), 4.50 (1H, d, $OCH_2Ph$, $J_{gem}$ 12.1), 4.54 (1H, d, $OCH_2Ph$, $J_{gem}$ 12.1), 4.60 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.1), 4.64 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.1), 4.85 (1H, td, H2, *J* 3.4, *J* 5.5, *J* 5.5), 7.29–7.38 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100

MHz) 38.9 ($SO_2CH_3$), 61.8 (C1 or C6), 64.0, 70.7 (C1 or C6), 71.5, 73.9 ($OCH_2Ph$), 75.0 ($OCH_2Ph$), 78.8, 83.7 (C2), 128.7, 128.8, 128.9, 129.2, 129.4, 129.4 (ArCH), 139.0, 139.3 (ArCC); LRMS (ESI +ve) 488 (85, M + $Na^+$), 953 (100, 2M + $Na^+$); (ESI −ve) 929 (100, [2M − H]$^-$); HRMS (ESI +ve) found 488.1463 [M + $Na^+$], $C_{21}H_{27}N_3NaO_7S$ requires 488.1462.

For the enantiomer **41L**: $[\alpha]^{25}_D$ −7.1 (*c* 1.05, $CHCl_3$).

*2,5-Dideoxy-2,5-iminoallitol (7).* Palladium (10% on C, 180 mg) and sodium acetate (160 mg, 1.94 mmol) were added to a solution of diol **41D** (450 mg, 0.97 mmol) in 1,4-dioxane (16 mL). The reaction vessel was evacuated and flushed with hydrogen. The reaction was stirred at rt for 4 h under hydrogen, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.38) and the formation of a single product (baseline). LRMS indicated the absence of a peak corresponding to the diol **41D** (*m*/*z* 488 [M + $Na^+$]) and the presence of a peak corresponding to the dibenzyl pyrrolidine intermediate (*m*/*z* 344 [M + $H^+$]). Aqueous hydrochloric acid (2 M, 4 mL) was added, the reaction vessel evacuated and flushed with hydrogen, and the reaction stirred for 16 h. LRMS indicated the absence of a peak corresponding to the dibenzylpyrrolidine intermediate (*m*/*z* 344 [M + $H^+$]) and the presence of a peak corresponding to the pyrrolidine 7 (*m*/*z* 164 [M + $H^+$]). The reaction was filtered through glass microfiber (GF/B), concentrated in vacuo, dissolved in 2 M aqueous hydrochloric acid (1 mL), and loaded onto a short column of Dowex 50W-X8 ($H^+$ form). The product was liberated with 2 M aqueous ammonia, and the ammoniacal fractions were combined and concentrated in vacuo to afford the pyrrolidine 7 (150 mg, 95%) as a colorless oil: HRMS (ESI +ve) found 164.0919 [M + $H^+$]; $C_6H_{14}NO_4$ requires 164.0917; $[\alpha]^{25}_D$ 0.0 (*c* 1.00, $H_2O$); $\nu_{max}$ (thin film) 3450 (br s, OH/NH); $\delta_H$ ($D_2O$, 400 MHz) 3.61 (1H, a-q, H2, $J_{2,1} = J_{2,1'} = J_{2,3}$ 4.9), 3.73 (1H, dd, H1, $J_{1,2}$ 5.8, $J_{1,1'}$ 12.4), 3.82 (1H, dd, H1′, $J_{1',2}$ 4.0, $J_{1',1}$ 12.4), 4.11 (1H, d, H3, $J_{3,2}$ 4.0); $\delta_C$ ($D_2O$, 100 MHz) 58.5 (C1), 64.5 (C2), 71.0 (C3); LRMS (ESI +ve) 164 (100, M + $H^+$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-1,2-O-isopropylidene-β-L-talofuranose (42L).* Sodium hydride (60% mineral oil suspension, 2.2 g, 55.1 mmol) was added portionwise to a solution of diol **8L** (4.50 g, 18.4 mmol) and benzyl bromide (6.55 mL, 55.1 mmol) in DMF (70 mL) at 0 °C under argon. The reaction mixture was allowed to warm to rt and stirred for 19 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.13) and the formation of a major product ($R_f$ 0.73). The reaction was quenched with methanol (2 mL), diluted in ethyl acetate (200 mL) and washed with a 1:1 brine/water solution (3 × 100 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (20:1 to 10:1, cyclohexane/ethyl acetate) to afford the dibenzyl ether **42L** (7.73 g, 99%) as a colorless oil: $[\alpha]^{25}_D$ +122.0 (*c* 1.5, $CHCl_3$); $\nu_{max}$ (thin film) 2098 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz) 1.37, 1.58 (2 × 3H, s, $C(CH_3)_2$), 3.70 (1H, ddd, H5, $J_{5,4}$ 2.3, $J_{5,6}$ 3.8, $J_{5,6'}$ 9.1), 3.75 (1H, dd, H6, $J_{6,5}$ 3.8, $J_{6,6'}$ 10.1), 3.80 (1H, dd, H6′, $J_{6',5}$ 9.1, $J_{6',6}$ 10.1), 3.90 (1H, dd, H3, $J_{3,2}$ 4.3, $J_{3,4}$ 8.8), 4.08 (1H, dd, H4, $J_{4,5}$ 2.3, $J_{4,3}$ 8.8), 4.56 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 4.57−4.59 (1H, m, H2), 4.57 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.7), 4.62 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 4.79 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 5.74 (1H, d, H1, $J_{1,2}$ 3.5), 7.29−7.42 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz) 26.4, 26.8 ($C(CH_3)_2$), 60.0 (C5), 70.8 (C6), 72.3, 73.4 ($OCH_2Ph$), 77.0 (C2), 77.6 (C4), 77.9 (C3), 104.3 (C1), 113.3 ($C(CH_3)_2$), 127.7, 127.8, 128.1, 128.3, 128.5, 128.6 (ArCH), 137.2, 137.7 (ArCC); LRMS (ESI +ve) 448 (100, M + $Na^+$), 464 (25, M + $K^+$), 873 (100, 2M + $Na^+$); HRMS (ESI +ve) found 448.1831 [M + $Na^+$], $C_{23}H_{27}N_3NaO_5$ requires 448.1843.

For the enantiomer **42D**: $[\alpha]^{25}_D$ −138.4 (*c* 1.60, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-L-talofuranose (43L).* *p*-Toluenesulfonic acid (6.0 g, 36.7 mmol) was added to a solution of isopropylidene-protected **42L** (7.1 g, 16.7 mmol) in 7:1 1,4-dioxane/water (40 mL) and heated to 50 °C for 2 h. TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.73) and the formation of a major product ($R_f$ 0.24). The reaction mixture was allowed to cool to rt, quenched with saturated aqueous sodium bicarbonate (350 mL), and extracted with ethyl acetate (3 × 350 mL). The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (7:3 to 1:1, cyclohexane/ethyl acetate) to afford lactol **43L** (6.0 g, 95%) as a colorless oil, in an anomeric mixture (A:B, 3:2): $[\alpha]^{25}_D$ +66.8 (*c* 2.4, $CHCl_3$); $\nu_{max}$ (thin film) 2100 (s, $N_3$), 3422 (br s, OH); $\delta_H$ ($CDCl_3$, 400 MHz) 2.59 (1H, br s, $OH2^B$), 2.93 (1H, br s, $OH2^A$), 3.13 (1H, br s, $OH1^B$), 3.49 (1H, ddd, $H5^A$, $J_{5,4}$ 2.8, $J_{5,6}$ 4.4, $J_{5,6'}$ 8.2), 3.58 (1H, a-dt, $H5^B$, $J_{5,4} = J_{5,6}$ 4.0, $J_{5,6'}$ 8.0), 3.68 (1H, dd, $H6^B$, $J_{6,5}$ 4.4, $J_{6,6'}$ 10.1), 3.68 (1H, dd, $H6^A$, $J_{6,5}$ 4.4, $J_{6,6'}$ 9.9), 3.72 (1H, dd, $H6'^B$, $J_{6',5}$ 8.0, $J_{6',6}$ 10.1), 3.74 (1H, dd, $H6'^A$, $J_{6',5}$ 8.2, $J_{6',6}$ 9.9), 3.88 (1H, br s, $OH1^A$), 4.01 (1H, a-t, $H3^A$, $J_{3,2} = J_{3,4}$ 5.6), 4.03 (1H, d, $H2^B$, $J_{2,3}$ 3.9), 4.05 (1H, dd, $H4^B$, $J_{4,5}$ 3.5, $J_{4,3}$ 7.1), 4.11 (1H, dd, $H4^A$, $J_{4,5}$ 2.8, $J_{4,3}$ 5.3), 4.11−4.13 (1H, m, $H2^A$), 4.29 (1H, dd, $H3^B$, $J_{3,2}$ 4.0, $J_{3,4}$ 7.1), 4.53 (1H, d, $OCH_2Ph^B$, $J_{gem}$ 11.5), 4.62 (1H, d, $OCH_2Ph^B$, $J_{gem}$ 11.5), 4.54 (1H, d, $OCH_2Ph^A$, $J_{gem}$ 11.7), 4.56 (1H, d, $OCH_2Ph^A$, $J_{gem}$ 11.7), 4.59 (1H, d, $OCH_2Ph^B$, $J_{gem}$ 11.6), 4.65 (1H, d, $OCH_2Ph^B$, $J_{gem}$ 11.6), 4.60 (1H, d, $OCH_2Ph^A$, $J_{gem}$ 11.6), 4.68 (1H, d, $OCH_2Ph^A$, $J_{gem}$ 11.6), 5.27 (1H, s, $H1^B$), 5.30 (1H, br s, $H1^A$), 7.29−7.43 (20H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz) 61.1 ($C5^A$), 62.0 ($C5^B$), 69.7 ($C2^A$), 70.1 ($C6^A$), 70.5 ($C6^B$), 73.1, 73.5 ($OCH_2Ph^B$), 73.4, 73.6 ($OCH_2Ph^A$), 73.4 ($C2^B$), 78.1 ($C3^A$), 78.8 ($C3^B$), 79.7 ($C4^A$), 80.4 ($C4^B$), 97.3 ($C1^A$), 102.3 ($C1^B$), 127.7, 127.8, 127.9, 127.9, 128.2, 128.5, 128.6, 128.7, 128.8 (ArCH), 136.7, 136.7, 137.5, 137.5 (ArCC); LRMS (ESI +ve) 408 (100, M + $Na^+$), 793 (73, 2M + $Na^+$); (ESI −ve) 384 (20, [M − H]$^-$), 420 (25, M + $^{35}Cl^-$), 422 (10, M + $^{37}Cl^-$), 769 (100, [2M − H]$^-$); HRMS (ESI +ve) found 408.1528 [M + $Na^+$], $C_{20}H_{23}N_3NaO_5$ requires 408.1530.

For the enantiomer **43D**: $[\alpha]^{25}_D$ −80.8 (*c* 2.00, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-L-talono-1,4-lactone (44L).* Potassium carbonate (1.98 g, 14.33 mmol) and iodine (3.64 g, 14.33 mmol) were added to a warm solution of lactol **43L** (2.76 g, 7.17 mmol) in 2-methyl-2-propanol (30 mL) at 100 °C. The reaction was stirred for 90 min, after which TLC analysis (1:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.40) and the formation of a major product ($R_f$ 0.68). The reaction was allowed to cool to rt and diluted with ethyl acetate (200 mL). Saturated aqueous sodium thiosulfate (100 mL) was added slowly and the biphasic mixture stirred until the iodine was visibly quenched. The phases were separated, and the aqueous phase was extracted with ethyl acetate (2 × 200 mL). The organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (17:3 to 1:1, cyclohexane/ethyl acetate) to afford lactone **44L** (2.20 g, 80%) as a clear oil: $[\alpha]^{25}_D$ +110.3 (*c* 1.25, $CHCl_3$); $\nu_{max}$ (thin film) 1790 (s, C═O), 2112 (s, $N_3$), 3447 (br s, OH); $\delta_H$ ($CDCl_3$, 400 MHz) 3.04 (1H, br s, OH2), 3.68−3.78 (3H, m, H5, H6, H6′), 4.15 (1H, dd, H3, $J_{3,4}$ 0.9, $J_{3,2}$ 6.2), 4.45 (1H, br s, H4), 4.54 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 4.59 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 4.66 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 4.67 (1H, d, H2, $J_{2,3}$ 6.2), 4.72 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 7.31−7.41 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz) 61.1 (C5), 67.8 (C2), 69.5 (C6), 73.1, 73.8 ($OCH_2Ph$), 75.9 (C3), 80.9 (C4), 127.9, 128.1, 128.1, 128.6, 128.6, 128.8 (ArCH), 136.3, 137.0 (ArCC), 174.7 (C1); LRMS (ESI +ve) 406 (45, M + $Na^+$), 438 (40, M + MeOH + $Na^+$), 789 (60, 2M + $Na^+$), 821 (63, 2M + MeOH + $Na^+$), 853 (100, 2M + 2MeOH + $Na^+$); HRMS (ESI +ve) found 406.1365 [M + $Na^+$], $C_{20}H_{21}N_3NaO_5$ requires 406.1373.

For the enantiomer **44D**; $[\alpha]^{25}_D$ −102.2 (*c* 1.30, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-trifluoromethanesulfonyl-L-talono-1,4-lactone (47L).* Trifluoromethanesulfonic anhydride (0.14 mL, 0.85 mmol) was added dropwise to a solution of alcohol **44L** (250 mg, 0.65 mmol) and pyridine (0.16 mL, 1.96 mmol) in dichloromethane (3 mL) at −40 °C under argon. The reaction was stirred for 90 min, with the internal temperature rising to −25 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.38) and the formation of a major product ($R_f$ 0.71). The reaction was diluted with dichloromethane (20 mL), washed with 2 M aqueous hydrochloric acid (3 × 20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (49:1 to 9:1, cyclohexane/ethyl acetate) to afford triflate **47L** (270 mg, 80%) as a


dx.doi.org/10.1021/jo301243s | J. Org. Chem. 2012, 77, 7777−7792

pale yellow oil: $[\alpha]^{25}_{D}$ +63.2 (*c* 1.25, $CHCl_3$); $\nu_{max}$ (thin film) 1808 (s, C═O), 2115 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz) 3.69−3.78 (3H, m, H5, H6, H6′), 4.32 (1H, dd, H3, $J_{3,4}$ 1.8, $J_{3,2}$ 6.1), 4.52−4.53 (1H, m, H4), 4.54 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 4.59 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 4.60 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 4.79 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 5.56 (1H, d, H2, $J_{2,3}$ 6.1), 7.32−7.43 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz) 60.2 (C5), 69.1 (C6), 73.5, 73.8 ($OCH_2Ph$), 74.6 (C3), 76.3 (C2), 81.8 (C4), 127.9, 128.2, 128.3, 128.6, 128.9 (ArCH), 135.6, 136.8 (ArCC), 166.6 (C1); LRMS (ESI +ve) 554 (95, M + $K^+$), 570 (100, M + MeOH + $Na^+$); HRMS (ESI +ve) found 570.1112 [M + MeOH + $Na^+$], $C_{22}H_{24}F_3N_3NaO_8S$ requires 570.1128.

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-L-talono-1,4-lactone (**45L**).* Methanesulfonyl chloride (90 μL, 1.06 mmol) was added to a solution of alcohol **44L** (340 mg, 0.89 mmol) in pyridine (3.5 mL) at 0 °C under argon. After 10 min, the reaction was allowed to warm to rt and stirred for a further 90 min. TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.38) and the formation of a major product ($R_f$ 0.50). The reaction mixture was concentrated in vacuo and coevaporated with toluene (2 × 5 mL). The crude residue was purified by flash chromatography (47:3 to 3:1, cyclohexane/ethyl acetate) to afford mesylate **45L** (390 mg, 95%) as a clear oil: $[\alpha]^{25}_{D}$ +106.6 (*c* 1.27, $CHCl_3$); $\nu_{max}$ (thin film) 1180 (s, $SO_2$), 1455 (s, $SO_2$), 1801 (s, C═O), 2117 (s, $N_3$); $\delta_H$ ($CDCl_3$, 400 MHz) 3.30 (3H, s, $SO_2CH_3$), 3.71 (1H, dd, H6, $J_{6,5}$ 6.5, $J_{6,6'}$ 9.7), 3.74 (1H, dd, H6′, $J_{6',5}$ 6.5, $J_{6',6}$ 9.7), 3.82 (1H, td, H5, $J_{5,4}$ 1.9, $J_{5,6}$ = $J_{5,6'}$ 6.5), 4.30 (1H, dd, H3, $J_{3,4}$ 1.4, $J_{3,2}$ 6.0), 4.55 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.8), 4.55 (1H, a-t, H4, $J_{4,3}$ = $J_{4,5}$ 1.7), 4.59 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.8), 4.60 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.8), 4.86 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.8), 5.57 (1H, d, H2, $J_{2,3}$ 6.0), 7.32−7.41 (10H, m, ArH); $\delta_C$ ($CDCl_3$, 100 MHz) 39.7 ($SO_2CH_3$), 60.6 (C5), 69.4 (C6), 72.9 (C2), 73.6, 73.8 ($OCH_2Ph$), 75.1 (C3), 82.5 (C4), 127.8, 128.2, 128.2, 128.5, 128.6, 128.7 (ArCH), 136.3, 136.9 (ArCC), 169.8 (C1); LRMS (ESI +ve) 484 (27, M + $Na^+$), 516 (100, M + MeOH + $Na^+$), 945 (25, 2M + $Na^+$), 977 (34, 2M + MeOH + $Na^+$); HRMS (ESI +ve) found 516.1408 [M + MeOH + $Na^+$], $C_{22}H_{27}N_3NaO_8S$ requires 516.1411.

For the enantiomer **45D**: $[\alpha]^{25}_{D}$ −96.3 (*c* 1.25, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-L-talitol (**46L**).* Sodium borohydride (41 mg, 1.08 mmol) was added portionwise to a solution of lactone **45L** (100 mg, 0.217 mmol) in 8:1 ethanol/1,4-dioxane (9 mL) at −30 °C under argon. The reaction was stirred for 2.5 h, with the internal temperature rising to −15 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the partial consumption of the starting material ($R_f$ 0.50) and the formation of a major product ($R_f$ 0.11). Further sodium borohydride (41 mg, 1.08 mmol) was added at −30 °C and the reaction allowed to warm to −15 °C. After 2 h, TLC analysis indicated the complete consumption of the starting material $R_f$ 0.50) and the major product ($R_f$ 0.11). The reaction was neutralized with glacial acetic acid and concentrated in vacuo. The crude residue was dissolved in ethyl acetate (20 mL) and washed with saturated aqueous sodium bicarbonate (6 mL) and the aqueous phase extracted with ethyl acetate (2 × 20 mL). The organic fractions were combined, washed with brine (6 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (9:1 to 0:1, cyclohexane/ethyl acetate) to afford the diol **46L** (65 mg, 65%) as a clear oil: $[\alpha]^{25}_{D}$ +63.5 (*c* 1.25, $CHCl_3$); $\nu_{max}$ (thin film) 1173 (s, $SO_2$), 1337 (s, $SO_2$), 2104 (s, $N_3$), 3484 (br s, OH); $\delta_H$ ($CD_3CN$, 400 MHz) 3.09 (3H, s, $SO_2CH_3$), 3.27 (1H, t, OH6, $J_{OH,6}$ = $J_{OH,6'}$ 5.7), 3.58 (1H, d, OH3, $J_{OH,3}$ 6.8), 3.73−3.77 (4H, m, H1, H1′, H5, H3), 3.82−3.85 (3H, m, H4, H6, H6′), 4.54 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 4.56 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.0), 4.58 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 4.80 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.0), 5.06 (1H, ddd, H2, *J* 1.5, *J* 4.8, *J* 6.3), 7.28−7.39 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz) 39.0 ($SO_2CH_3$), 61.4 (C1), 62.0, 70.8 (C4, C5), 71.5 (C6), 74.0, 74.5 ($OCH_2Ph$), 80.6 (C3), 85.7 (C2), 128.8, 128.8, 129.0, 129.4, 129.5 (ArCH), 139.0, 139.3 (ArCC); LRMS (ESI +ve) 488 (45, M + $Na^+$), 504 (100, M + $K^+$), 953 (15, 2M + $Na^+$), 969 (10, 2M + $K^+$); (ESI −ve) 464 (10, [M − H]$^-$), 500 (50, M + $^{35}Cl^-$), 502 (22, M + $^{37}Cl^-$), 510, (100, M + $HCOO^-$), 929 (41, [2M − H]$^-$); HRMS (ESI +ve) found 488.1445 [M + $Na^+$], $C_{21}H_{27}N_3NaO_7S$ requires 488.1462.

For the enantiomer **46D**: $[\alpha]^{25}_{D}$ −60.7 (*c* 1.20, $CHCl_3$).

*2,5-Dideoxy-2,5-iminogalactitol (**6**).* Palladium (10% on carbon, 6 mg) and sodium acetate (11 mg, 0.13 mmol) were added to a solution of diol **46L** (30 mg, 0.06 mmol) in 1,4-dioxane (2 mL). The reaction vessel was evacuated and flushed with hydrogen and stirred for 1 h. TLC analysis (99:1, ethyl acetate/triethylamine) indicated the complete consumption of the starting material ($R_f$ 0.88) and the formation of a major product ($R_f$ 0.08). LRMS also indicated the absence of a peak corresponding to the starting material **46L** (*m*/*z* 488 [M + $Na^+$]) and the formation of a peak corresponding to the amino intermediate (*m*/*z* 440 [M + $H^+$]). After a further 4 h, LRMS indicated the absence of the amino diol intermediate (*m*/*z* 440 [M + $H^+$]) and the presence of a peak corresponding to the dibenzylated pyrrolidine intermediate (*m*/*z* 344 [M + $H^+$]). Aqueous hydrochloric acid (2 M, 0.4 mL) was added and the reaction vessel evacuated, flushed with hydrogen and stirred for 16 h. LRMS indicated the absence of the dibenzylated pyrrolidine intermediate (*m*/*z* 344 [M + $H^+$]) and presence of a peak corresponding to the fully deprotected pyrrolidine **6** (*m*/*z* 164 [M + $H^+$]). The reaction mixture was filtered through a glass microfiber (GF/A), concentrated in vacuo, dissolved in 2 M aqueous hydrochloric acid (1 mL), and loaded onto a short column of Dowex 50W-X8 ($H^+$ form). The product was liberated with 2 M aqueous ammonia and the ammoniacal fractions combined and concentrated in vacuo to afford the pyrrolidine **6** (9.5 mg, 91%) as a yellow oil: $[\alpha]^{25}_{D}$ 0.0 (*c* 1.50, $H_2O$); $\nu_{max}$ (thin film) 3319 (br s, OH, NH); $\delta_H$ ($D_2O$, 500 MHz) 3.25 (1H, q, H2, $J_{2,1}$ = $J_{2,1'}$ = $J_{2,3}$ 5.7), 3.59 (1H, dd, H1, $J_{1,2}$ 5.7, $J_{1,1'}$ 11.4), 3.70 (1H, dd, H1′, $J_{1',2}$ 5.7, $J_{1',1}$ 11.4), 4.21 (1H, d, H3, $J_{3,2}$ 5.7); $\delta_C$ ($D_2O$, 125 MHz) 60.4 (C1), 60.5 (C2), 71.9 (C3); LRMS (ESI +ve) 164 (55, M + $H^+$), 186 (85, M + $Na^+$), 327 (100, 2M + $H^+$); (ESI −ve) 162 (100, [M − H]$^-$); HRMS (ESI +ve) found 186.0743 [M + $Na^+$], $C_6H_{13}NNaO_4$ requires 186.0737.

*5-Azido-3,6-di-O-benzyl-5-deoxy-L-galactono-1,4-lactone (**48L**).* Trifluoromethanesulfonic anhydride (0.30 mL, 1.75 mmol) and pyridine (0.33 mL, 4.05 mmol) were added to a solution of lactone **44L** (517 mg, 1.35 mmol) in dichloromethane (5 mL) at −40 °C under argon. The reaction was stirred for 90 min, with the internal temperature rising to −25 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.38) and the formation of a major product ($R_f$ 0.71). The reaction was diluted with dichloromethane (150 mL), washed with 2 M aqueous hydrochloric acid (3 × 50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the crude triflate **47L** as a yellow oil. The crude triflate **47L** was reacted on without further purification.

Sodium trifluoroacetate (370 mg, 2.70 mmol) was added portionwise to a solution of the crude triflate **47L** in DMF (10 mL) at −30 °C under argon. The reaction was allowed to warm to rt and stirred for 20 h, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.71) and the formation of a major product ($R_f$ 0.50). The reaction mixture was partitioned between ethyl acetate (150 mL) and saturated aqueous sodium bicarbonate (50 mL). The phases were separated, and the aqueous layer was extracted with ethyl acetate (3 × 80 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude residue was purified by flash chromatography (49:1 to 1:1, cyclohexane/ethyl acetate) to afford the lactone **48L** (403 mg, 78% over two steps) as a pale yellow oil, which crystallized on standing to form a white crystalline solid: $[\alpha]^{25}_{D}$ +99.8 (*c* 1.25, $CH_3Cl$); mp 62−64 °C; $\nu_{max}$ (thin film) 1793 (s, C═O), 2104 (s, $N_3$), 3423 (br s, OH); $\delta_H$ ($CD_3CN$, 400 MHz) 3.70 (1H, dd, H6, $J_{6,5}$ 8.3, $J_{6,6'}$ 10.1), 3.76 (1H, dd, H6′, $J_{6',5}$ 4.3, $J_{6',6}$ 10.1), 3.83 (1H, a-dt, H5, $J_{5,4}$ = $J_{5,6'}$ 3.8, $J_{5,6}$ 8.0), 4.19 (1H, a-t, H3, $J_{3,2}$ = $J_{3,4}$ 7.6), 4.22 (1H, d, OH2, $J_{OH,2}$ 5.6), 4.25 (1H, dd, H4, $J_{4,5}$ 3.5, $J_{4,3}$ 7.8), 4.53 (1H, d, $OCH_2Ph$, $J_{gem}$ 12.1), 4.56 (1H, d, $OCH_2Ph$, $J_{gem}$ 12.1), 4.57 (1H, dd, H2, $J_{2,OH}$ 5.6, $J_{2,3}$ 7.6), 4.64 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 4.82 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.6), 7.29−7.41 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz) 61.9 (C5), 70.5 (C6), 73.1, 74.0 ($OCH_2Ph$), 74.8 (C2), 78.3 (C4), 81.8 (C3), 128.8, 129.1, 129.2, 129.5, 129.5 (ArCH), 138.8,


dx.doi.org/10.1021/jo301243s | J. Org. Chem. 2012, 77, 7777−7792

139.1 (ArCC), 174.2 (C1); LRMS (ESI +ve) 484 (18, M + $Na^+$), 516 (100, M + MeOH + $Na^+$); HRMS (ESI +ve) found 406.1364 [M + $Na^+$], $C_{20}H_{21}N_3NaO_5$ requires 406.1373.

For the enantiomer **48D**: $[\alpha]^{25}_D$ −104.0 (*c* 1.40, $CHCl_3$), mp 62−64 °C.

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-L-galactono-1,4-lactone (**49L**).* Methanesulfonyl chloride (0.10 mL, 1.29 mmol) was added dropwise to a solution of alcohol **48L** (330 mg, 0.861 mmol) in pyridine (4 mL) at 0 °C under argon. After 10 min, the reaction mixture was allowed to warm to rt and stirred for 90 min. TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the complete consumption of the starting material ($R_f$ 0.50) and the formation of a major product ($R_f$ 0.65). The reaction mixture was concentrated in vacuo, coevaporated with toluene (3 × 10 mL) and the crude residue purified by flash chromatography (47:3 to 4:1, cyclohexane/ethyl acetate) to afford the mesylate **49L** (310 mg, 78%) as a clear oil: $[\alpha]^{25}_D$ −99.9 (*c* 1.35, $CHCl_3$); $\nu_{max}$ (thin film) 1173 (s, $SO_2$), 1363 (s, $SO_2$), 1801 (s, C═O), 2107 (s, $N_3$); $\delta_H$ ($CD_3CN$, 400 MHz) 3.27 (3H, s, $SO_2CH_3$), 3.71 (1H, dd, H6, $J_{6,5}$ 8.1, $J_{6,6'}$ 10.1), 3.77 (1H, dd, H6′, $J_{6',5}$ 4.3, $J_{6',6}$ 10.1), 3.86 (1H, ddd, H5, $J_{5,4}$ 3.3, $J_{5,6'}$ 4.3, $J_{5,6}$ 8.1), 4.43 (1H, dd, H4, $J_{4,5}$ 3.3, $J_{4,3}$ 7.6), 4.54 (1H, a-t, H3, $J_{3,2} = J_{3,4}$ 7.7), 4.55 (1H, d, $OCH_2Ph$, $J_{gem}$ 12.1), 4.56 (1H, d, $OCH_2Ph$, $J_{gem}$ 12.1), 4.65 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.4), 4.81 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.4), 5.56 (1H, d, H2, $J_{2,3}$ 7.8), 7.30−7.41 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz) 40.2 ($SO_2CH_3$), 61.2 (C5), 70.3, 73.6 ($OCH_2Ph$), 79.3 (C4), 79.4 (C3), 80.5 (C2), 128.8, 128.8, 129.4, 129.5, 129.6 (ArCH), 138.0, 139.0 (ArCC), 169.4 (C1); LRMS (ESI +ve) 484 (100, M + $Na^+$), 516 (73, M + MeOH + $Na^+$); HRMS (ESI +ve) found 516.1414 [M + MeOH + $Na^+$], $C_{22}H_{27}N_3NaO_8S$ requires 516.1411.

For the enantiomer **49D**: $[\alpha]^{25}_D$ +105.8 (*c* 1.32, $CHCl_3$).

*5-Azido-3,6-di-O-benzyl-5-deoxy-2-O-methanesulfonyl-L-galactitol (**50L**).* Sodium borohydride (80 mg, 2.11 mmol) was added portionwise to a solution of lactone **49L** (150 mg 0.325 mmol) in 8:1 ethanol/1,4-dioxane (4 mL) at −30 °C under argon. The reaction was stirred for 90 min, with the internal temperature rising to −15 °C, after which TLC analysis (2:1, cyclohexane/ethyl acetate) indicated the incomplete consumption of the starting material ($R_f$ 0.65) and the formation of a major product ($R_f$ 0.24). Further sodium borohydride (80 mg, 2.11 mmol) was added at −30 °C and the reaction allowed to warm to −15 °C. After 4 h, TLC analysis indicated the complete consumption of the starting material ($R_f$ 0.65) and the major product ($R_f$ 0.24). The reaction was neutralized with glacial acetic acid and concentrated in vacuo. The crude residue was dissolved in ethyl acetate (80 mL) and washed with saturated aqueous sodium bicarbonate (40 mL). The aqueous phase was extracted with ethyl acetate (2 × 80 mL), and the organic fractions were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (9:1 to 3:7, cyclohexane/ethyl acetate) to afford the diol **50L** (134 mg, 89%) as a white, crystalline solid: $[\alpha]^{25}_D$ +44.5 (*c* 0.97, $CHCl_3$); mp 80−81 °C; $\nu_{max}$ (thin film) 1169 (s, $SO_2$), 1333 (s, $SO_2$), 2102 (s, $N_3$), 3484 (br s, OH); $\delta_H$ ($CD_3CN$, 400 MHz) 3.10 (3H, s, $SO_2CH_3$), 3.28 (1H, t, OH1, $J_{OH,1} = J_{OH,1'}$ 5.8), 3.42 (1H, d, OH4, $J_{OH,4}$ 6.3), 3.75−3.91 (7H, m, H1, H1′, H3, H4, H5, H6, H6′), 4.55 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 4.59 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.9), 4.62 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.1), 4.69 (1H, d, $OCH_2Ph$, $J_{gem}$ 11.1), 4.89 (1H, ddd, H2, *J* 2.0, *J* 6.1, *J* 6.8), 7.29−7.39 (10H, m, ArH); $\delta_C$ ($CD_3CN$, 100 MHz) 38.9 ($SO_2CH_3$), 61.5 (C5), 61.8 (C6), 70.7, 78.3 (C3, C4), 71.5 (C1), 73.9, 75.8 ($OCH_2Ph$), 83.2 (C2), 128.8, 128.8, 129.0, 129.2, 129.5, 129.5 (ArCH), 139.0, 139.3 (ArCC); LRMS (ESI +ve) 488 (45, M + $Na^+$), 953 (100, 2M + $Na^+$); (ESI −ve) 929 (100, [2M − H]$^-$); HRMS (ESI +ve) found 488.1461 [M + $Na^+$], $C_{21}H_{27}N_3NaO_7S$ requires 488.1462.

For the enantiomer **50D**: $[\alpha]^{25}_D$ −52.2 (*c* 1.00, $CHCl_3$); mp 80−81 °C.

*2,5-Dideoxy-2,5-imino-L-altritol (**5L**).* Palladium (10% on carbon, 54 mg) and sodium acetate (48 mg, 0.576 mmol) were added to a solution of diol **50L** (134 mg, 0.29 mmol) in 1,4-dioxane (5 mL). The reaction flask was evacuated and flushed with hydrogen and the reaction stirred for 1 h. After which TLC analysis (99:1, ethyl acetate/triethylamine) indicated the complete consumption of the starting material ($R_f$ 0.24) and the formation of a major product ($R_f$ 0.08). LRMS indicated the absence of a peak corresponding to the starting material **50L** (*m*/*z* 488 [M + $Na^+$]) and the formation of a peak corresponding to the amino intermediate (*m*/*z* 440 [M + $H^+$]). After a further 4 h, LRMS indicated the absence of the amino intermediate (*m*/*z* 440 [M + $H^+$]) and the formation of peak corresponding to the dibenzylated pyrrolidine intermediate (*m*/*z* 344 [M + $H^+$]). Aqueous hydrochloric acid (2 M, 1.0 mL) was added, the reaction vessel evacuated and flushed with hydrogen, and the reaction stirred for 16 h. LRMS indicated the absence of the dibenzylated pyrrolidine intermediate (*m*/*z* 344 [M + $H^+$]) and the formation a peak corresponding to the fully deprotected pyrrolidine **5L** (*m*/*z* 164 [M + $H^+$]). The reaction mixture was filtered through glass microfiber (GF/B) and concentrated in vacuo, and the residue dissolved in 2 M aqueous hydrochloric acid (1 mL) and loaded onto a short column of Dowex 50W-X8 ($H^+$ form). The product was liberated with 2 M aqueous ammonia, and the ammoniacal fractions were combined and concentrated in vacuo to afford the pyrrolidine **5L** (43 mg, 92%) as a yellowish oil.[72]

## ■ ASSOCIATED CONTENT

### Supporting Information

$^1H$ and $^{13}C$ NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by the Newton Abraham Research Fund (B.J.A.), Fundación Ramón Areces (R.F.M.), and a Grant-in-Aid for Scientific Research (C) (No. 23590127) (A.K.) from the Japanese Society for the Promotion of Science (JSPS).

## ■ REFERENCES


(1) Horne, G.; Wilson, F. X.; Tinsley, J.; Williams, D. H.; Storer, R. *Drug Discovery Today* **2011**, *16*, 107−118.

(2) Winchester, B. G. *Tetrahedron: Asymmetry* **2009**, *20*, 645−651.

(3) Compain, P.; Martin, O. R. *Iminosugars From Synthesis to Therapeutic Applications*; Wiley-VCH: New York, 2007.

(4) Martinez-Montero, S.; Fernandez, S.; Sanghvi, Y. S.; Chattopadhyaya, J.; Ganesan, M.; Ramesh, N. G.; Gotor, V.; Ferrero, M. *J. Org. Chem.* **2012**, *77*, 4671−4678.

(5) Rauter, A. P.; Figueiredo, J.; Ismael, M.; Canda, T.; Font, J.; Figueredo, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1131−1146.

(6) Goddard-Borger, E. D.; Ghisalberti, E. L.; Stick, R. V. *Eur. J. Org. Chem.* **2007**, 3925−3934.

(7) Matsuura, D.; Mitsui, T.; Sengoku, T.; Takahashi, M.; Yoda, H. *Tetrahedron* **2008**, *64*, 11686−11696.

(8) Xu, D. D.; Waykole, L.; Calienni, J. V.; Ciszewski, L.; Lee, G. T.; Liu, W.; Szewczyk, J.; Vargas, K.; Prasad, K.; Repic, O.; Blacklock, T. J. *Org. Process Res. Dev.* **2003**, *7*, 856−865.

(9) Ke, W.; Whitfield, D. M.; Gill, M.; Larocque, S.; Yu, S.-H. *Tetrahedron Lett.* **2003**, *44*, 7767−7770.

(10) Le Manach, C.; Baron, A.; Guillot, R.; Vauzeilles, B.; Beau, J.-M. *Tetrahedron Lett.* **2011**, *52*, 1462−1465.

(11) Shing, T. K. M.; Tsui, H.-C.; Zhou, Z.-H. *J. Org. Chem.* **1995**, *60*, 3121−3130.

(12) Kitahara, T.; Ogawa, T.; Naganuma, T.; Matsui, M. *Agric. Biol. Chem.* **1974**, *38*, 2189−2190.

(13) Kalamkar, N. B.; Kasture, V. M.; Chavan, S. T.; Sabharwal, S. G.; Dhavale, D. D. *Tetrahedron* **2010**, *66*, 8522−8526.

(14) Weymouth-Wilson, A. C.; Clarkson, R. A.; Jones, N. A.; Best, D.; Wilson, F. X.; Pino-González, M.-S.; Fleet, G. W. J. *Tetrahedron Lett.* **2009**, *50*, 6307−6310.
(15) Bashyal, B. P.; Chow, H. F.; Fleet, G. W. J. *Tetrahedron Lett.* **1986**, *27*, 3205−3208.
(16) Bell, A. A.; Pickering, L.; Finn, M.; de la Fuente, C.; Krulle, T. M.; Davis, B. G.; Fleet, G. W. J. *Synlett* **1997**, 1077−1078.
(17) Best, D.; Wang, C.; Weymouth-Wilson, A. C.; Clarkson, R. A.; Wilson, F. X.; Nash, R. J.; Miyauchi, S.; Kato, A.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2010**, *21*, 311−319.
(18) Best, D.; Chairatana, P.; Glawar, A. F. G.; Crabtree, E.; Butters, T. D.; Wilson, F. X.; Yu, C.-Y.; Wang, W.-B.; Jia, Y.-M.; Adachi, I.; Kato, A.; Fleet, G. W. J. *Tetrahedron Lett.* **2010**, *51*, 2222−2224.
(19) Glawar, A. F. G.; Best, D.; Ayers, B. J.; Miyauchi, S.; Nakagawa, S.; Aguilar-Moncayo, M.; García Fernández, J. M.; Mellet, C. O.; Crabtree, E. V.; Butters, T. D.; Wilson, F. X.; Kato, A.; Fleet, G. W. J. *Chem.—Eur. J.* **2012**, *18*, 9341−9359.
(20) Example syntheses of the enantiomers of *gluco* **2**.[21−26]
(21) Blanco, O.; Pato, C.; Ruiz, M.; Ojea, V. *Org. Biomol. Chem.* **2009**, *7*, 2310−2321.
(22) Malle, B. M.; Lundt, I.; Wrodnigg, T. M. *Org. Biomol. Chem.* **2008**, *6*, 1779−1786.
(23) Donohoe, T. J.; Cheeseman, M. D.; O'Riordan, T. J. C.; Kershaw, J. A. *Org. Biomol. Chem.* **2008**, *6*, 3896−3898.
(24) Izquierdo, I.; Plaza, M. T.; Yáñez, V. *Tetrahedron* **2006**, *63*, 1440−1447.
(25) García-Moreno, M. I.; Aguilar, M.; Mellet, C. O.; Fernandez, J. M. G. *Org. Lett.* **2006**, *8*, 297−299.
(26) Dondoni, A.; Giovannini, P. P.; Perrone, D. *J. Org. Chem.* **2002**, *67*, 7203−7214.
(27) Example syntheses of the enantiomers of *ido* **4**.[28−31]
(28) Hong, Z.; Liu, L.; Sugiyama, M.; Fu, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 8352−8353.
(29) Kumar, V.; Ramesh, N. G. *Tetrahedron* **2006**, *62*, 1877−1885.
(30) Gautier-Lefebvre, I.; Behr, J.-B.; Guillerm, G.; Muzard, M. *Eur. J. Med. Chem.* **2005**, *40*, 1255−1261.
(31) Singh, S.; Han, H. *Tetrahedron Lett.* **2004**, *45*, 6349−6352.
(32) Example syntheses of the enantiomers of *manno* **3**.[25,26,33−37]
(33) Tsou, E.-L.; Yeh, Y.-T.; Liang, P.-H.; Cheng, W.-C. *Tetrahedron* **2009**, *65*, 93−100.
(34) Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Marradi, M.; Faggi, E.; Parmeggiani, C.; Goti, A. *Eur. J. Org. Chem.* **2008**, 2929−2947.
(35) Behr, J.-B.; Guillerm, G. *Tetrahedron Lett.* **2007**, *48*, 2369−2372.
(36) Shing, T. K. M. *Tetrahedron* **1988**, 7261−7264.
(37) Card, P. J.; Hitz, W. D. *J. Org. Chem.* **1985**, *50*, 891−893.
(38) Example syntheses of the enantiomers of *altro*-**5**.[26,31,39,40]
(39) Chikkanna, D.; Han, H. *Synlett* **2004**, 2311−2314.
(40) Saotome, C.; Kanie, Y.; Kanie, O.; Wong, C. H. *Bioorg. Med. Chem.* **2000**, *8*, 2249−2261.
(41) Example syntheses of *meso-allo* **7**.[26,42−44]
(42) Izquierdo, I.; Plaza, M. T.; Rodriguez, M.; Franco, F.; Martos, A. *Tetrahedron* **2005**, *61*, 11697−11704.
(43) Moreno-Vargas, A. J.; Robina, I.; Petricci, E.; Vogel, P. *J. Org. Chem.* **2004**, *69*, 4487−4491.
(44) Donohoe, T. J.; Headley, C. E.; Cousins, R. P. C.; Cowley, A. *Org. Lett.* **2003**, *5*, 999−1002.
(45) Example syntheses of *meso-galacto* **6**.[21,28,31,33,46−48]
(46) Calderón, F.; Doyagüez, E. G.; Cheong, P. H.-Y.; Férnandez-Mayoralas, A.; Houk, K. N. *J. Org. Chem.* **2008**, *73*, 7916−7920.
(47) Izquierdo, I.; Plaza, M. T.; Rodríguez, M.; Tamayo, J. A.; Martos, A. *Tetrahedron* **2006**, *62*, 2693−2697.
(48) Wang, Y.-F.; Takaoka, Y.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1994**, *33*, 1242−1244.
(49) Davis, B. G.; Hull, A.; Smith, C.; Nash, R. J.; Watson, A. A.; Winkler, D. A.; Griffiths, R. C.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2947−2960.
(50) Hakansson, A. E.; van Ameijde, J.; Guglielmini, L.; Horne, G.; Nash, R. J.; Evinson, E. L.; Kato, A.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2007**, *18*, 282−289.
(51) Asano, N.; Yamauchi, T.; Kagamifuchi, K.; Shimizu, N.; Takahashi, S.; Takatsuka, H.; Ikeda, K.; Kizu, H.; Chuakul, W.; Kettawan, A.; Okamoto, T. *J. Nat. Prod.* **2005**, *68*, 1238−1242.
(52) Kato, A.; Yamashita, Y.; Nakagawa, S.; Koike, Y.; Adachi, I.; Hollinshead, J.; Nash, R. J.; Ikeda, K.; Asano, N. *Bioorg. Med. Chem.* **2010**, *18*, 3790−3794.
(53) Wrodnigg, T. M. *Monatsh. Chem.* **2002**, *133*, 393−426.
(54) Wrodnigg, T. M.; Stuetz, A. E.; Tarling, C. A.; Withers, S. G. *Carbohydr. Res.* **2006**, *341*, 1717−1722.
(55) Wrodnigg, T. M.; Withers, S. G.; Stuetz, A. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1063−1064.
(56) Collyer, C. A.; Goldberg, J. D.; Viehmann, H.; Blow, D. M.; Ramsden, N. G.; Fleet, G. W. J.; Montgomery, F. J.; Grice, P. *Biochemistry* **1992**, *31*, 12211−12218.
(57) D'Alonzo, D.; Guaragna, A.; Palumbo, G. *Curr. Med. Chem.* **2009**, *16*, 473−505.
(58) Jenkinson, S. F.; Fleet, G. W. J.; Nash, R. J.; Koike, Y.; Adachi, I.; Yoshihara, A.; Morimoto, K.; Izumori, K.; Kato, A. *Org. Lett.* **2011**, *13*, 4064−4067.
(59) Rountree, J. S. S.; Butters, T. D.; Wormald, M. R.; Boomkamp, S. D.; Dwek, R. A.; Asano, N.; Ikeda, K.; Evinson, E. L.; Nash, R. J.; Fleet, G. W. J. *ChemMedChem* **2009**, *4*, 378−392.
(60) Kato, A.; Kato, N.; Kano, E.; Adachi, I.; Ikeda, K.; Yu, L.; Okamoto, T.; Banba, Y.; Ouchi, H.; Takahata, H.; Asano, N. *J. Med. Chem.* **2005**, *48*, 2036−2044.
(61) Asano, N.; Ikeda, K.; Yu, L.; Kato, A.; Takebayashi, K.; Adachi, I.; Kato, I.; Ouchi, H.; Takahata, H.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2005**, *16*, 223−229.
(62) Clinch, K.; Evans, G. B.; Fleet, G. W. J.; Furneaux, R. H.; Johnson, S. W.; Lenz, D. H.; Mee, S. P. H.; Rands, P. R.; Schramm, V. L.; Taylor, R. E. A.; Tyler, P. C. *Org. Biomol. Chem.* **2006**, *4*, 1131−1139.
(63) Blériot, Y.; Gretzke, D.; Kruelle, T. M.; Butters, T. D.; Dwek, R. A.; Nash, R. J.; Asano, N.; Fleet, G. W. J. *Carbohydr. Res.* **2005**, *340*, 2713−2718.
(64) Winchester, B.; Barker, C.; Baines, S.; Jacob, G. S.; Namgoong, S. K.; Fleet, G. W. J. F. *Biochem. J.* **1990**, *265*, 277−282.
(65) Winchester, B.; Al-Daher, S. S.; Carpenter, N. C.; Dibello, I. C.; Choi, S. S.; Fairbanks, A. J.; Fleet, G. W. J. *Biochem. J.* **1993**, *290*, 743−749.
(66) Myerscough, P. M.; Fairbanks, A. J.; Jones, A. H.; Bruce, I.; Choi, S. S.; Fleet, G. W. J.; Al-Daher, S. S.; Dibello, I. C.; Winchester, B. *Tetrahedron* **1992**, *48*, 10177−10190.
(67) Mercer, T. B.; Jenkinson, S. F.; Bartholomew, B.; Nash, R. J.; Miyauchi, S.; Kato, A.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2009**, *20*, 2368−2373.
(68) Legler, G.; Korth, A.; Berger, A.; Ekhart, C.; Gradnig, G.; Stuetz, A. E. *Carbohydr. Res.* **1993**, *250*, 67−77.
(69) Berger, A.; Ebner, M.; Stuetz, A. E. *Tetrahedron Lett.* **1995**, *36*, 4989−4990.
(70) Data for D-*gluco* **2D** is quoted earlier in the experimental procedures.
(71) Lee, C. K.; Jiang, H. *J. Carbohydr. Chem.* **1995**, *14*, 407−416.
(72) Data for L-*altro* **5L** is quoted earlier in the experimental procedures.

## NOTE ADDED AFTER ASAP PUBLICATION

Table 2 contained errors in the version published ASAP September 6, 2012; the correct version reposted September 10, 2012.

Acta Crystallographica Section E
**Structure Reports Online**
ISSN 1600-5368

# 2-*N*-Benzyl-2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-3-*C*-methyl-D-allononitrile

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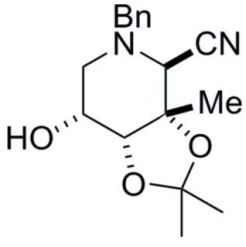
Received 12 April 2012; accepted 14 April 2012

Key indicators: single-crystal X-ray study; $T$ = 150 K; mean $\sigma$(C–C) = 0.003 Å; $R$ factor = 0.041; $wR$ factor = 0.106; data-to-parameter ratio = 10.4.

X-ray crystallography firmly established the relative stereochemistry of the title compound, $C_{17}H_{22}N_2O_3$. The absolute configuration was determined by use of 2-*C*-methyl-D-ribonolactone as the starting material. The compound exists as O—H···N hydrogen-bonded chains of molecules running parallel to the *a*-axis.

## Related literature

For 2-*C*-methyl sugar lactones and their use in synthesis, see: da Cruz *et al.* (2011); Best *et al.* (2010); da Cruz & Horne (20086); Booth *et al.* (2008); Hotchkiss, Soengas *et al.* (2007); Hotchkiss, Kato *et al.* (2007); Hotchkiss *et al.* (2006); Sowden & Strobach (1960). For the biological activity of polyhydroxylated piperidines, see: Nash *et al.* (2011); Watson *et al.* (2001). For the extinction correction, see: Larson (1970). For the temperature controller, see: Cosier & Glazer (1986).




## Experimental

### Crystal data

$C_{17}H_{22}N_2O_3$
$M_r$ = 302.37
Orthorhombic, $P2_12_12_1$
$a$ = 8.5647 (3) Å
$b$ = 10.0019 (4) Å
$c$ = 18.7031 (7) Å
$V$ = 1602.17 (10) Å$^3$
$Z$ = 4
Mo $K\alpha$ radiation
$\mu$ = 0.09 mm$^{-1}$
$T$ = 150 K
0.25 × 0.25 × 0.20 mm

### Data collection

Nonius KappaCCD diffractometer
Absorption correction: multi-scan (*DENZO/SCALEPACK*; Otwinowski & Minor, 1997)
$T_{min}$ = 0.96, $T_{max}$ = 0.98
7953 measured reflections
2082 independent reflections
1808 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.042

### Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.106
$S$ = 0.97
2082 reflections
200 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.22 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.22 e Å$^{-3}$

**Table 1**
Hydrogen-bond geometry (Å, °).

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| O1—H11···N4$^{i}$ | 0.88 | 2.15 | 2.997 (3) | 161 |

Symmetry code: (i) $x-\frac{1}{2}, -y+\frac{3}{2}, -z+1$.

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS*.

Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: LH5456).

## References

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). *J. Appl. Cryst.* **27**, 435.
Best, D., Jenkinson, S. F., Saville, A. W., Alonzi, D. S., Wormald, M. R., Butters, T. D., Norez, C., Becq, F., Bleriot, Y., Adachi, I., Kato, A. & Fleet, G. W. J. (2010). *Tetrahedron Lett.* **51**, 4170–4174.
Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). *J. Appl. Cryst.* **36**, 1487.
Booth, K. V., da Cruz, F. P., Hotchkiss, D. J., Jenkinson, S. F., Jones, N. A., Weymouth-Wilson, A. C., Clarkson, R., Heinz, T. & Fleet, G. W. J. (2008). *Tetrahedron Asymmetry*, **19**, 2417–2424.
Cosier, J. & Glazer, A. M. (1986). *J. Appl. Cryst.* **19**, 105–107.
Cruz, F. P. da & Horne, G. (2008). *Tetrahedron Lett.* **49**, 6812–6815.
Cruz, F. P. da, Newberry, S., Jenkinson, S. F., Wormald, M. R., Butters, T. D., Alonzi, D. S., Nakagawa, S., Becq, F., Norez, C., Nash, R. J., Kato, A. & Fleet, G. W. J. (2011). *Tetrahedron Lett.* **52**, 219–223.
Hotchkiss, D. J., Jenkinson, S. F., Storer, R., Heinz, T. & Fleet, G. W. J. (2006). *Tetrahedron Lett.* **47**, 315–318.
Hotchkiss, D. J., Kato, A., Odell, B., Claridge, T. D. W. & Fleet, G. W. J. (2007). *Tetrahedron Asymmetry*, **18**, 500–512.
Hotchkiss, D. J., Soengas, R., Booth, K. V., Weymouth-Wilson, A. C., Eastwick-Field, V. & Fleet, G. W. J. (2007). *Tetrahedron Lett.* **48**, 517–520.
Larson, A. C. (1970). *Crystallographic Computing*, edited by F. R. Ahmed, S. R. Hall & C. P. Huber, pp. 291–294. Copenhagen: Munksgaard.
Nash, R. J., Kato, A., Yu, C.-Y. & Fleet, G. W. J. (2011). *Future Med. Chem.* **3**, 1513–1521.
Nonius (2001). *COLLECT*. Nonius BV, Delft, The Netherlands.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
Sowden, J. C. & Strobach, D. R. (1960). *J. Am. Chem. Soc.* **82**, 3707–3708.
Watkin, D. J., Prout, C. K. & Pearce, L. J. (1996). *CAMERON*. Chemical Crystallography Laboratory, Oxford, England.
Watson, A. A., Fleet, G. W. J., Asano, N., Molyneux, R. J. & Nash, R. J. (2001). *Phytochemistry*, **56**, 265–295.

# supplementary materials

*Acta Cryst.* (2012). E**68**, o1474 [doi:10.1107/S1600536812016273]

## 2-*N*-Benzyl-2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-3-*C*-methyl-D-allononitrile

**Benjamin J. Ayers, Sarah F. Jenkinson, George W. J. Fleet and Amber L. Thompson**

### Comment

Many polyhydroxylated piperidines have been found to display interesting biological properties (Nash *et al.*, 2011; Watson *et al.*, 2001). 2-*C*-Methyl lactones, derived from sugars (Hotchkiss, Soengas *et al.*, 2007; Sowden & Strobach, 1960; Hotchkiss *et al.*, 2006), have been used for the synthesis of iminosugars bearing a carbon branch (da Cruz *et al.*, 2011; Best *et al.*, 2010; da Cruz *et al.*, 2008; Hotchkiss, Kato *et al.*, 2007). In a new one-pot approach to carbon-branched piperidines, the *α*-iminonitrile **4** was prepared from the lactol tosylate **3**, itself readily available in two steps from 2-*C*-methyl-D-ribonolactone **1** (Booth *et al.*, 2008), by Strecker *α*-aminonitrile formation and concomitant intramolecular tosylate displacement (Fig. 1).

X-ray crystallography firmly established the relative stereochemistry of the title compound **4**. The absolute configuration was determined by the use of 2-*C*-methyl-D-ribonolactone **1** as the starting material. The acetonide ring adopts an envelope conformation with C16 out of the plane and the piperidine ring adopts a chair conformation (Fig. 2). The compound exists as O—H···N hydrogen-bonded chains of molecules running parallel to the *a*-axis (Fig. 3). Only classical hydrogen-bonding was considered.

### Experimental

*α*-Iminonitrile **4** was recrystallized by diffusion from a mixture of ethyl acetate and cyclohexane: m.p. 394–395 K; $[\alpha]_D^{20}$ +39.7 (*c* 5.5, methanol).

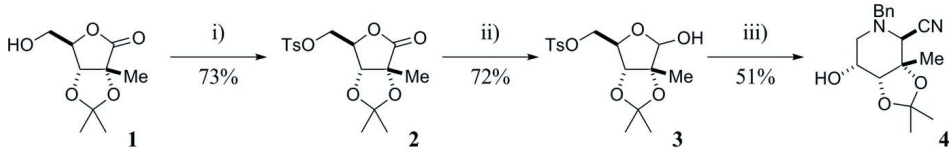
### Refinement

In the absence of significant anomalous scattering, Friedel pairs were merged and the absolute configuration was assigned from the starting material.

The H atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C—H in the range 0.93–0.98, O—H = 0.82 Å) and $U_{iso}$(H) (in the range 1.2–1.5 times $U_{eq}$ of the parent atom), after which the positions were refined with riding constraints.

### Computing details

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).




Reagents and conditions: i) TsCl, pyridine, 16 h, RT; ii) DIBALH, DCM, 1 h, -78 °C;
iii) $BnNH_2$, AcOH, KCN, MeOH, 3 d, RT.

**Figure 1**

Synthetic Scheme

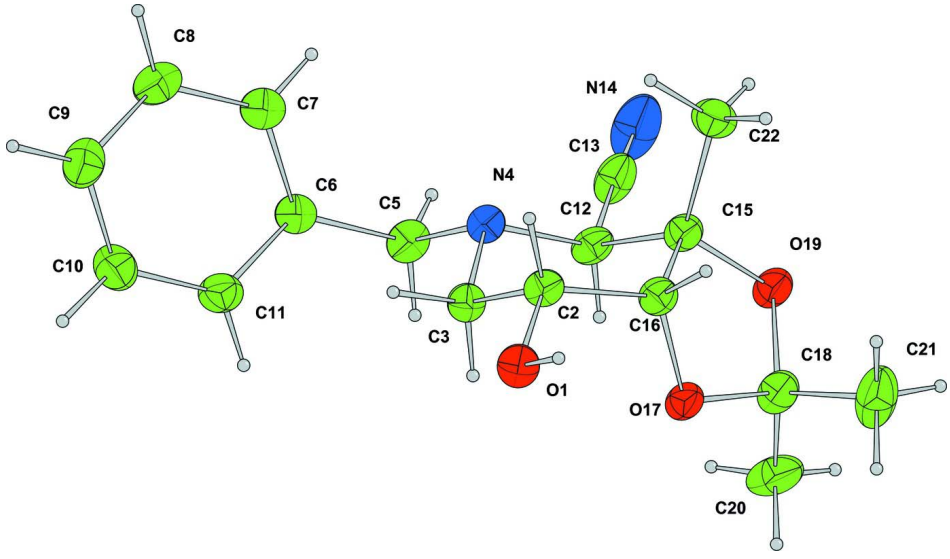



**Figure 2**

The title compound with displacement ellipsoids drawn at the 50% probability level. H atoms are shown as spheres of arbitary radius.

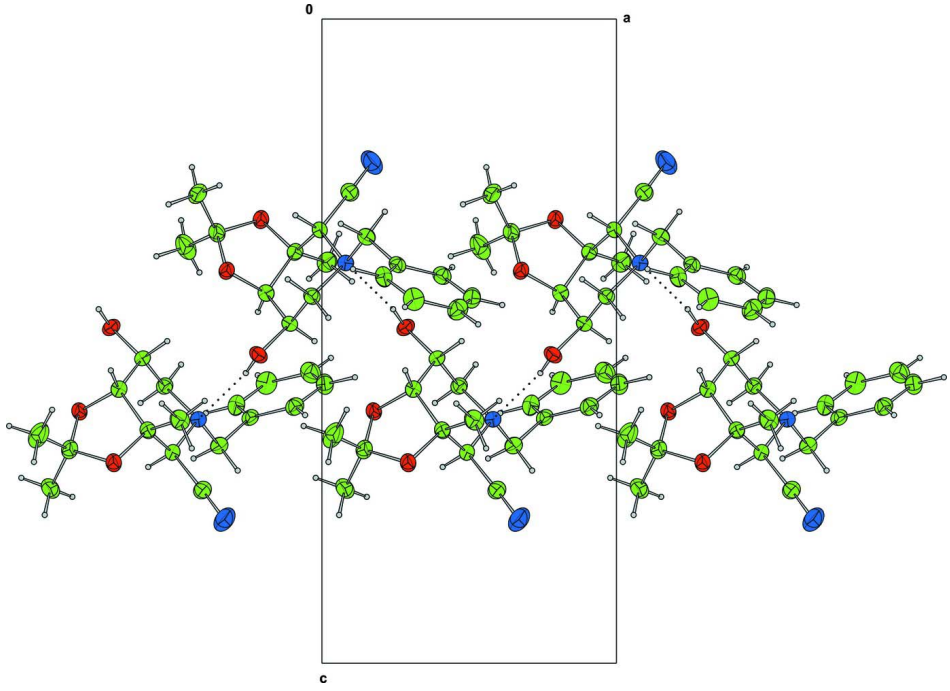



**Figure 3**

Packing diagram for the crystal projected along the *b*-axis. Hydrogen bonds are shown as dotted lines.

### 2-*N*-Benzyl-2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene- 3-*C*-methyl-*D*-allononitrile

*Crystal data*

$C_{17}H_{22}N_2O_3$
$M_r = 302.37$
Orthorhombic, $P2_12_12_1$
Hall symbol: P 2ac 2ab
$a = 8.5647$ (3) Å
$b = 10.0019$ (4) Å
$c = 18.7031$ (7) Å
$V = 1602.17$ (10) Å$^3$
$Z = 4$
$F(000) = 648$
$D_x = 1.253$ Mg m$^{-3}$
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 1959 reflections
$\theta = 5$–27°
$\mu = 0.09$ mm$^{-1}$
$T = 150$ K
Block, colourless
0.25 × 0.25 × 0.20 mm

*Data collection*

Nonius KappaCCD diffractometer
Graphite monochromator
$\omega$ scans
Absorption correction: multi-scan (*DENZO*/*SCALEPACK*; Otwinowski & Minor, 1997)
$T_{min} = 0.96$, $T_{max} = 0.98$
7953 measured reflections
2082 independent reflections
1808 reflections with $I > 2\sigma(I)$
$R_{int} = 0.042$
$\theta_{max} = 27.5°$, $\theta_{min} = 5.2°$
$h = -11 \rightarrow 11$
$k = -12 \rightarrow 12$
$l = -24 \rightarrow 24$

*Refinement*

Refinement on $F^2$
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.041$
$wR(F^2) = 0.106$
$S = 0.97$
2082 reflections
200 parameters
0 restraints
Primary atom site location: structure-invariant direct methods

Hydrogen site location: inferred from neighbouring sites
H-atom parameters constrained
Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.07P)^2 + 0.23P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.0002994$
$\Delta\rho_{max} = 0.22$ e Å$^{-3}$
$\Delta\rho_{min} = -0.22$ e Å$^{-3}$
Extinction correction: Larson (1970), Equation 22
Extinction coefficient: 280 (110)

*Special details*

**Experimental**. The crystal was placed in the cold stream of an Oxford Cryosystems open-flow nitrogen cryostat (Cosier & Glazer, 1986) with a nominal stability of 0.1 K.

*Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å$^2$)*

| | *x* | *y* | *z* | $U_{iso}$*/$U_{eq}$ |
|---|---|---|---|---|
| O1 | 0.28415 (17) | 0.66972 (14) | 0.47877 (7) | 0.0285 |
| C2 | 0.3904 (2) | 0.7319 (2) | 0.52685 (10) | 0.0240 |
| C3 | 0.4656 (2) | 0.62006 (19) | 0.56970 (10) | 0.0245 |
| N4 | 0.58010 (19) | 0.67473 (16) | 0.62140 (8) | 0.0237 |
| C5 | 0.6509 (2) | 0.5619 (2) | 0.66204 (10) | 0.0290 |
| C6 | 0.7562 (2) | 0.47284 (19) | 0.61857 (10) | 0.0252 |
| C7 | 0.9075 (2) | 0.5134 (2) | 0.60165 (11) | 0.0298 |
| C8 | 1.0092 (3) | 0.4276 (2) | 0.56690 (11) | 0.0356 |
| C9 | 0.9612 (3) | 0.2999 (2) | 0.54895 (12) | 0.0377 |
| C10 | 0.8116 (3) | 0.2586 (2) | 0.56503 (13) | 0.0377 |
| C11 | 0.7094 (3) | 0.3444 (2) | 0.59975 (12) | 0.0317 |
| C12 | 0.4923 (2) | 0.7579 (2) | 0.67274 (10) | 0.0258 |
| C13 | 0.5940 (3) | 0.8056 (2) | 0.73119 (12) | 0.0349 |
| N14 | 0.6690 (3) | 0.8455 (3) | 0.77702 (12) | 0.0563 |
| C15 | 0.4085 (2) | 0.8802 (2) | 0.63836 (10) | 0.0258 |
| C16 | 0.3102 (2) | 0.8340 (2) | 0.57458 (10) | 0.0251 |
| O17 | 0.17610 (16) | 0.77936 (14) | 0.60920 (7) | 0.0267 |
| C18 | 0.1432 (2) | 0.8661 (2) | 0.66828 (11) | 0.0322 |
| O19 | 0.29237 (16) | 0.92224 (14) | 0.68874 (8) | 0.0293 |
| C20 | 0.0777 (3) | 0.7836 (3) | 0.72865 (12) | 0.0435 |
| C21 | 0.0377 (3) | 0.9798 (3) | 0.64619 (15) | 0.0503 |
| C22 | 0.5170 (3) | 0.9967 (2) | 0.62255 (12) | 0.0337 |
| H21 | 0.4744 | 0.7726 | 0.4999 | 0.0256* |
| H31 | 0.5218 | 0.5592 | 0.5364 | 0.0293* |
| H32 | 0.3838 | 0.5684 | 0.5958 | 0.0277* |
| H51 | 0.5641 | 0.5120 | 0.6821 | 0.0339* |
| H52 | 0.7138 | 0.6041 | 0.7009 | 0.0357* |
| H71 | 0.9426 | 0.5985 | 0.6148 | 0.0359* |
| H81 | 1.1119 | 0.4591 | 0.5562 | 0.0416* |
| H91 | 1.0304 | 0.2415 | 0.5259 | 0.0458* |
| H101 | 0.7821 | 0.1690 | 0.5530 | 0.0463* |
| H111 | 0.6056 | 0.3166 | 0.6118 | 0.0379* |
| H121 | 0.4100 | 0.7095 | 0.6953 | 0.0311* |
| H161 | 0.2829 | 0.9145 | 0.5454 | 0.0290* |
| H203 | 0.0584 | 0.8381 | 0.7698 | 0.0637* |
| H202 | −0.0209 | 0.7457 | 0.7123 | 0.0635* |

| | | | | |
|---|---|---|---|---|
| H201 | 0.1521 | 0.7143 | 0.7417 | 0.0639* |
| H211 | 0.0220 | 1.0417 | 0.6876 | 0.0718* |
| H212 | −0.0621 | 0.9372 | 0.6318 | 0.0712* |
| H213 | 0.0838 | 1.0319 | 0.6067 | 0.0702* |
| H223 | 0.4563 | 1.0631 | 0.5969 | 0.0499* |
| H222 | 0.6019 | 0.9635 | 0.5928 | 0.0502* |
| H221 | 0.5578 | 1.0406 | 0.6665 | 0.0511* |
| H11 | 0.2417 | 0.7301 | 0.4504 | 0.0457* |

*Atomic displacement parameters (Å²)*

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{12}$ | $U^{13}$ | $U^{23}$ |
|---|---|---|---|---|---|---|
| O1 | 0.0278 (7) | 0.0332 (7) | 0.0244 (6) | 0.0012 (7) | −0.0070 (6) | −0.0039 (6) |
| C2 | 0.0225 (10) | 0.0293 (10) | 0.0201 (8) | −0.0011 (8) | −0.0021 (8) | −0.0007 (8) |
| C3 | 0.0242 (9) | 0.0254 (9) | 0.0239 (9) | 0.0009 (8) | −0.0016 (8) | 0.0003 (8) |
| N4 | 0.0231 (8) | 0.0267 (8) | 0.0215 (7) | 0.0005 (7) | −0.0002 (7) | −0.0002 (7) |
| C5 | 0.0277 (10) | 0.0346 (11) | 0.0249 (9) | 0.0025 (9) | −0.0021 (8) | 0.0032 (9) |
| C6 | 0.0253 (9) | 0.0272 (10) | 0.0233 (9) | 0.0004 (8) | −0.0041 (8) | 0.0050 (8) |
| C7 | 0.0295 (10) | 0.0318 (10) | 0.0281 (10) | −0.0015 (9) | −0.0036 (9) | 0.0040 (9) |
| C8 | 0.0264 (11) | 0.0433 (12) | 0.0370 (11) | 0.0009 (10) | 0.0014 (9) | 0.0064 (10) |
| C9 | 0.0368 (12) | 0.0367 (12) | 0.0397 (12) | 0.0081 (10) | 0.0054 (10) | 0.0025 (10) |
| C10 | 0.0386 (12) | 0.0288 (10) | 0.0457 (12) | 0.0000 (10) | −0.0020 (11) | −0.0007 (10) |
| C11 | 0.0254 (10) | 0.0320 (10) | 0.0377 (11) | −0.0020 (10) | −0.0031 (9) | 0.0022 (9) |
| C12 | 0.0202 (9) | 0.0347 (10) | 0.0226 (8) | −0.0004 (9) | −0.0014 (8) | −0.0006 (8) |
| C13 | 0.0287 (10) | 0.0480 (13) | 0.0280 (10) | 0.0089 (10) | −0.0025 (9) | −0.0087 (10) |
| N14 | 0.0397 (12) | 0.0796 (16) | 0.0496 (13) | 0.0170 (13) | −0.0156 (10) | −0.0290 (13) |
| C15 | 0.0225 (9) | 0.0295 (10) | 0.0254 (9) | −0.0005 (9) | 0.0015 (8) | −0.0028 (8) |
| C16 | 0.0233 (9) | 0.0274 (9) | 0.0246 (9) | 0.0006 (8) | −0.0010 (7) | 0.0000 (8) |
| O17 | 0.0214 (7) | 0.0322 (7) | 0.0266 (7) | −0.0012 (6) | 0.0021 (6) | −0.0085 (6) |
| C18 | 0.0240 (10) | 0.0411 (12) | 0.0314 (11) | 0.0006 (9) | −0.0023 (9) | −0.0138 (9) |
| O19 | 0.0219 (7) | 0.0362 (8) | 0.0297 (7) | −0.0004 (6) | 0.0010 (6) | −0.0104 (6) |
| C20 | 0.0300 (12) | 0.0660 (16) | 0.0346 (11) | −0.0147 (12) | 0.0082 (10) | −0.0152 (12) |
| C21 | 0.0372 (13) | 0.0574 (16) | 0.0563 (15) | 0.0182 (13) | −0.0146 (12) | −0.0231 (13) |
| C22 | 0.0346 (11) | 0.0305 (10) | 0.0362 (11) | −0.0075 (10) | 0.0036 (10) | −0.0040 (9) |

*Geometric parameters (Å, º)*

| | | | |
|---|---|---|---|
| O1—C2 | 1.422 (2) | C11—H111 | 0.958 |
| O1—H11 | 0.882 | C12—C13 | 1.477 (3) |
| C2—C3 | 1.519 (3) | C12—C15 | 1.557 (3) |
| C2—C16 | 1.521 (3) | C12—H121 | 0.954 |
| C2—H21 | 0.968 | C13—N14 | 1.143 (3) |
| C3—N4 | 1.482 (2) | C15—C16 | 1.531 (3) |
| C3—H31 | 0.994 | C15—O19 | 1.433 (2) |
| C3—H32 | 0.998 | C15—C22 | 1.519 (3) |
| N4—C5 | 1.490 (2) | C16—O17 | 1.427 (2) |
| N4—C12 | 1.477 (2) | C16—H161 | 0.999 |
| C5—C6 | 1.506 (3) | O17—C18 | 1.433 (2) |
| C5—H51 | 0.971 | C18—O19 | 1.447 (2) |
| C5—H52 | 0.998 | C18—C20 | 1.507 (3) |

| | | | |
|---|---|---|---|
| C6—C7 | 1.394 (3) | C18—C21 | 1.510 (3) |
| C6—C11 | 1.391 (3) | C20—H203 | 0.958 |
| C7—C8 | 1.385 (3) | C20—H202 | 0.975 |
| C7—H71 | 0.935 | C20—H201 | 0.972 |
| C8—C9 | 1.383 (3) | C21—H211 | 1.000 |
| C8—H81 | 0.956 | C21—H212 | 0.992 |
| C9—C10 | 1.380 (4) | C21—H213 | 0.987 |
| C9—H91 | 0.937 | C22—H223 | 0.971 |
| C10—C11 | 1.387 (3) | C22—H222 | 0.974 |
| C10—H101 | 0.958 | C22—H221 | 0.995 |

| | | | |
|---|---|---|---|
| C2—O1—H11 | 110.2 | N4—C12—H121 | 112.2 |
| O1—C2—C3 | 106.45 (16) | C13—C12—H121 | 105.8 |
| O1—C2—C16 | 112.06 (16) | C15—C12—H121 | 103.9 |
| C3—C2—C16 | 112.12 (15) | C12—C13—N14 | 177.7 (2) |
| O1—C2—H21 | 109.3 | C12—C15—C16 | 109.79 (16) |
| C3—C2—H21 | 105.6 | C12—C15—O19 | 106.20 (15) |
| C16—C2—H21 | 111.0 | C16—C15—O19 | 102.67 (15) |
| C2—C3—N4 | 110.68 (15) | C12—C15—C22 | 113.61 (16) |
| C2—C3—H31 | 109.0 | C16—C15—C22 | 114.56 (16) |
| N4—C3—H31 | 108.3 | O19—C15—C22 | 109.11 (16) |
| C2—C3—H32 | 110.0 | C15—C16—C2 | 114.30 (16) |
| N4—C3—H32 | 109.6 | C15—C16—O17 | 101.79 (14) |
| H31—C3—H32 | 109.2 | C2—C16—O17 | 111.85 (16) |
| C3—N4—C5 | 108.84 (15) | C15—C16—H161 | 108.1 |
| C3—N4—C12 | 107.17 (15) | C2—C16—H161 | 109.1 |
| C5—N4—C12 | 107.60 (14) | O17—C16—H161 | 111.5 |
| N4—C5—C6 | 114.61 (15) | C16—O17—C18 | 106.03 (14) |
| N4—C5—H51 | 105.9 | O17—C18—O19 | 105.37 (15) |
| C6—C5—H51 | 111.3 | O17—C18—C20 | 108.63 (18) |
| N4—C5—H52 | 105.7 | O19—C18—C20 | 110.04 (17) |
| C6—C5—H52 | 108.7 | O17—C18—C21 | 111.28 (18) |
| H51—C5—H52 | 110.5 | O19—C18—C21 | 107.97 (18) |
| C5—C6—C7 | 120.47 (18) | C20—C18—C21 | 113.3 (2) |
| C5—C6—C11 | 120.68 (19) | C18—O19—C15 | 108.96 (14) |
| C7—C6—C11 | 118.6 (2) | C18—C20—H203 | 110.8 |
| C6—C7—C8 | 120.7 (2) | C18—C20—H202 | 107.5 |
| C6—C7—H71 | 120.2 | H203—C20—H202 | 108.8 |
| C8—C7—H71 | 119.0 | C18—C20—H201 | 109.6 |
| C7—C8—C9 | 120.0 (2) | H203—C20—H201 | 108.5 |
| C7—C8—H81 | 118.2 | H202—C20—H201 | 111.7 |
| C9—C8—H81 | 121.8 | C18—C21—H211 | 109.6 |
| C8—C9—C10 | 120.0 (2) | C18—C21—H212 | 105.4 |
| C8—C9—H91 | 120.0 | H211—C21—H212 | 111.2 |
| C10—C9—H91 | 120.1 | C18—C21—H213 | 111.3 |
| C9—C10—C11 | 120.2 (2) | H211—C21—H213 | 107.9 |
| C9—C10—H101 | 118.3 | H212—C21—H213 | 111.6 |
| C11—C10—H101 | 121.5 | C15—C22—H223 | 107.1 |
| C6—C11—C10 | 120.5 (2) | C15—C22—H222 | 107.8 |

| | | | |
|---|---|---|---|
| C6—C11—H111 | 118.4 | H223—C22—H222 | 110.5 |
| C10—C11—H111 | 121.1 | C15—C22—H221 | 113.1 |
| N4—C12—C13 | 111.28 (16) | H223—C22—H221 | 107.1 |
| N4—C12—C15 | 114.13 (15) | H222—C22—H221 | 111.1 |
| C13—C12—C15 | 108.91 (17) | | |

*Hydrogen-bond geometry (Å, º)*

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| C22—H222···O1$^{i}$ | 0.97 | 2.45 | 3.405 (3) | 167 |
| O1—H11···N4$^{ii}$ | 0.88 | 2.15 | 2.997 (3) | 161 |

Symmetry codes: (i) $x+1/2, -y+3/2, -z+1$; (ii) $x-1/2, -y+3/2, -z+1$.