

The Synthesis of Azetidine and Piperidine Iminosugars from Monosaccharides

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Abstract

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Iminosugars are polyhydroxylated alkaloids, and can be generally defined as sugar mimetics in which the endocyclic oxygen atom has been replaced with a basic nitrogen. A common affect of this atomic substitution is to bestow these compounds with the ability to inhibit various sugar-processing enzymes; most significantly the glycosidases (glycoside hydrolases) which are intimately involved in a huge array of biological functions. Compounds which inhibit these enzymes concordantly possess much potential as medicinal agents for the treatment of a variety of diseases. Several iminosugars have already achieved market approval as drugs, and many more are promising candidates in the late stages of clinical development. As such there remains considerable interest in this class of compound, both in terms of the exploration of novel iminosugar structures, as well as the continual development of more efficient general methodology for their synthesis. The densely-packed functionality and stereochemical information present in iminosugars makes them challenging targets for asymmetric chemical synthesis, whereas carbohydrates are clearly very attractive as chiral-pool starting materials for this purpose. Indeed, the majority of the most successful syntheses of iminosugars use the latter approach, and such is the focus of this thesis.

Chapter 1 presents a relatively brief introduction to iminosugars, including their types of structure, natural occurrence and biological mode of action. The rationale behind their use as therapeutic agents for the treatment of some significant disease targets is also discussed.

Chapter 2 is concerned with the preparation of a number of novel polyhydroxylated azetidines, and their evaluation as glycosidase inhibitors. Such compounds represent an almost entirely neglected class of iminosugars within the literature. An overview of natural and synthetic products incorporating an azetidine motif is given, as well as a brief review of preparative methods and known azetidine iminosugars. A highly efficient and flexible method for the key azetidine ring formation is demonstrated by the cyclisations of 3,5-di-*O*-triflates of pentoses and hexoses, and of a 2,4-di-*O*-triflate of glucose, with various primary amines. In this manner, many azetidine triols and tetrols were prepared in good yield. Furthermore, this process is readily adaptable to the installation of added functionality to the azetidine scaffold, as demonstrated by the preparation of 1-acetamido analogues. The initial biological screening of these compounds showed a promising array of glycosidase inhibition, including that of selective inhibition of fungal enzymes.

Chapter 3 describes a strategy with which to prepare all sixteen stereoisomers of a known piperidine iminosugar, α -homonojirimycin (α -HNJ), in a highly divergent manner from just four of the possible thirty-two 6-azidoheptitols using traditional chemical synthesis in tandem with biotechnological transformations. One half of the execution of this strategy is described in this thesis. Two 6-azidoheptitols were prepared from D-mannose, thereby providing access to four 6-azidoketoheptoses through a combination of microbial oxidation and enzymatic epimerisation. Catalytic hydrogenation of these 6-azidoketoheptoses furnished four diastereomeric mixtures of 2,6-iminoheptitols, with varying degrees of stereoselectivity. Purification of these mixtures allowed six 2,6-iminoheptitols to be isolated, two of which have never previously been tested for glycosidase inhibition. Significantly, one of them was found to be a potent and highly selective inhibitor of α -galactosidases, and may therefore be of interest in the treatment of Fabry disease.

For Cecilia:

*The moment of the rose and the moment of the yew-tree
Are of equal duration*

- T.S. Eliot

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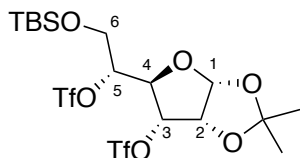
Contents

Concerning nomenclature	i
List of Abbreviations	ii
1. General Introduction to Iminosugars	1
1.1 Natural occurrence and bioactivity of iminosugars	2
1.2 Mode of action	6
1.3 Anti-diabetic drugs	10
1.4 Therapeutics for lysosomal storage disorders	11
1.5 Anti-cancer therapeutics	16
1.6 References	20
2. Azetidine Iminosugars	24
2.1 Introduction	24
2.1.1 Natural products and synthetic drugs	25
2.1.2 Methods of preparation	34
2.1.2.1 Cyclisations <i>via</i> nucleophilic substitution by amines	34
2.1.2.2 Reduction of azetidin-2-ones	38
2.1.2.3 Cyclisations <i>via</i> C-C bond formation	39
2.1.2.4 [2 + 2] Cycloadditions	40
2.1.2.5 Ring rearrangements	41
2.1.3 Known azetidine iminosugars	42
2.2 Synthesis and biological evaluation of azetidine iminosugars	48
2.2.1 Azetidine triols from aldopentofuranoses (3,5-displacement)	50
2.2.2 Azetidine tetrols from aldohexofuranoses (3,5-displacement)	68
2.2.3 D- <i>Talo</i> azetidine tetrol from glucopyranoside (2,4-displacement)	78
2.2.4 1-Acetamido L- <i>ido</i> azetidine triols (3,5-displacement)	84
2.3 Conclusions and future work	90
2.4 Experimental	92
2.4.1 <i>Arabino</i> azetidine triols from arabinose	93
2.4.2 <i>Xylo</i> azetidine triols from ribose	112
2.4.3 <i>Ido</i> and <i>gulo</i> azetidine tetrols from allose and talose	124
2.4.4 <i>Talo</i> azetidine tetrol from glucose	145
2.4.5 <i>Ido</i> 1-acetamido azetidine triols from allose	156
2.5 References	168

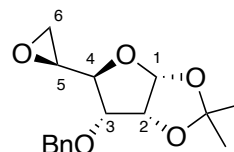
3. Homonojirimycin Diastereomers	176
3.1 Introduction	176
3.1.1 Biotechnological transformations of monosaccharides	177
3.1.1.1 Epimerisation of ketoses	178
3.1.1.2 The interconversion of polyols and ketoses	179
3.1.1.3 Isomerisation of ketoses and aldoses	181
3.1.1.4 The complete Izumoring picture	182
3.1.2 Strategy for the preparation of HNJ diastereomers	184
3.2 Syntheses of the 6-azidoheptitols AP-1 and AP-17	188
3.3 Preparation and analysis of the 6-azidoketoheptoses	197
3.4 Preparation and biological evaluation of the 2,6-iminoheptitols	202
3.5 Conclusions and future work	209
3.6 Experimental	211
3.6.1 Preparation of the 6-azidoheptitols	212
3.6.2 Izumoring procedures and preparation of the 2,6-iminoheptitols	222
3.7 References	229
 Appendix A - Deviations from IUPAC nomenclature	 232
 Appendix B - Publications arising from work within this thesis	 233

Concerning nomenclature

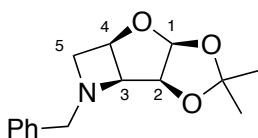
Unless otherwise noted, the naming and numbering conventions used for carbohydrate derivatives throughout this thesis are consistent with the guidelines provided by IUPAC.* Representative examples are given below:



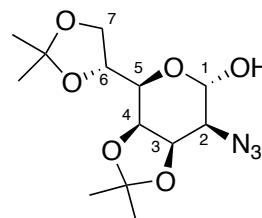
6-*O*-*tert*-Butyldimethylsilyl-1,2-*O*-isopropylidene-3,5-di-*O*-trifluoromethanesulfonyl- α -D-allofuranose



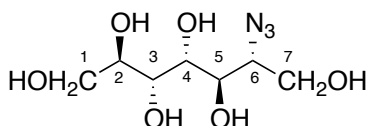
5,6-Anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene- β -L-talofuranose



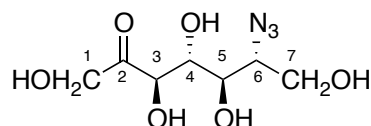
N-Benzyl-3,5-dideoxy-3,5-imino-1,2-*O*-isopropylidene- β -D-lyxofuranose



2-Azido-2-deoxy-3,4:6,7-di-*O*-isopropylidene- α -D-*glycero*-D-*talo*-heptopyranose



6-Azido-6-deoxy-D-*glycero*-D-*manno*-heptitol



6-Azido-6-deoxy-D-*allo*-hept-2-ulose

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

List of Abbreviations

-ve	Negative (in MS data)
+ve	Positive (in MS data)
a-	Apparent (in NMR data)
Ac	Acetyl
ACE	Angiotensin-converting enzyme
ADHD	Attention deficit hyperactivity disorder
AK	Azidoketose
AKI	Azidoketose-derived iminoheptitol
AON	Antisense oligonucleotide
AP	Azidopolyol
APCI	Atmospheric pressure chemical ionisation
aq	Aqueous
Ar	Aromatic moiety
ASSC	Active site-specific chaperone
ATP	Adenosine triphosphate
BMT	Bone marrow transplantation
Bn	Benzyl
br	Broad (in NMR and IR data)
Bu	Butyl
Bz	Benzoyl
<i>c</i>	Concentration (in optical rotation data)
CAN	Ammonium cerium(IV) nitrate
Cbz	Carboxybenzyl
CGT	Ceramide glucosyltransferase
CI	Chemical ionisation
CMT	Chaperone-mediated therapy
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
COSY	Correlation spectroscopy
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
d	Doublet/double (in NMR data)
DAB	1,4-Dideoxy-1,4-imino-D-arabinitol
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano- <i>para</i> -benzoquinone
DGDP	2,5-Dideoxy-2,5-imino-D-glucitol
DGJ	1-Deoxygalactonojirimycin
DGJNAc	2-Acetamido-1,2-dideoxy-D- <i>galacto</i> -nojirimycin
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMDP	2,5-Dideoxy-2,5-imino-D-mannitol
DMF	<i>N,N</i> -Dimethylformamide
DMJ	1-Deoxymannojirimycin
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
DNJ	1-Deoxynojirimycin
dr	Diastereomeric ratio

DTE	D-Tagatose-3-epimerase
E2	Bimolecular elimination
EBV	Epstein-Barr virus
EBV-EA	Epstein-Barr virus early antigen
ECM	Extracellular matrix
ER	Endoplasmic reticulum
ERAD	Endoplasmic reticulum-associated degradation
ERT	Enzyme replacement therapy
ESI	Electrospray ionisation
Et	Ethyl
EWG	Electron withdrawing group
FDA	Food and Drug Administration
FG	Fagomine
fod	6,6,7,7,8,8,8-Heptafluoro-2,2-dimethyl-3,5-octanedionato
GABA	γ -Aminobutyric acid
GalNAc	N-Acetylgalactosamine
GalNAcT	N-Acetylgalactosaminyltransferase
GalT	Galactosyltransferase
Gc	Human group-specific component
GcMAF	Gc protein-derived macrophage activating factor
Glc	Glucosyl
GlcNAc	N-Acetylglucosaminyl
GSL	Glycosphingolipid
h	Hours
HCMV	Human cytomegalovirus
HMBC	Heteronuclear multiple bond coherence
HNJ	Homonojirimycin
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
IC ₅₀	The half maximal inhibitory concentration
IFG	Isofagomine
imid.	Imidazole
IUPAC	International Union of Pure and Applied Chemistry
KHMDS	Potassium hexamethyldisilazide [potassium <i>bis</i> (trimethylsilyl)amide]
K _i	Inhibition constant
L-Aze	L-Azetidine-2-carboxylic acid
L.A.	Lewis acid
LDA	Lithium diisopropylamide
Lit.	Literature value
LSD	Lysosomal storage disorder
M	Molar
m	Multiplet (in NMR data)
m.p.	Melting point
Man	Mannosyl
Me	Methyl
Mesylate	Methanesulfonate
min	Minutes
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MS	Mass spectrometry
Ms	Methanesulfonyl
NAc	N-Acetyl

nAChR	Neuronal nicotinic acetylcholine receptor
NaGalase	α -N-Acetyl-galactosaminidase
NB-DNJ	N-Butyl-1-deoxynojirimycin
NIS	N-iodosuccinimide
NJ	Nojirimycin
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NRI	Noradrenaline reuptake inhibitor
Nu	Nucleophile
OD	Optical density
P	Protecting group
PCC	Pyridinium chlorochromate
PDE4	Phosphodiesterase-4
PDH	Polyol dehydrogenase
Ph	Phenyl
Piv	Pivaloyl
PKC	Protein kinase C
PMB	<i>para</i> -Methoxybenzyl
PNP	Purine nucleoside phosphorylase
Pr	Propyl
PTK	Protein tyrosine kinase
pyr.	Pyridine
q	Quartet (in NMR data)
R _f	Retention factor
RNase H	Ribonuclease H
ROE	Rotating frame nuclear Overhauser effect
ROESY	Rotating frame nuclear Overhauser effect spectroscopy
rt	Room temperature
s	Singlet (in NMR data); strong intensity (in IR data)
SA	Sialic acid
SRT	Substrate reduction therapy
t	Triplet/triple (in NMR data)
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TBDPS	<i>tert</i> -Butyldiphenylsilyl
TBS	<i>tert</i> -Butyldimethylsilyl
TEA	Triethylamine
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TOCSY	Total correlation spectroscopy
Tosylate	<i>para</i> -Toluenesulfonate
TPA	12- <i>O</i> -Tetradecanoylphorbol-13-acetate
Tr	Trityl
Triflate	Trifluoromethanesulfonate
Ts	<i>para</i> -Toluenesulfonyl
U	Enzyme unit
UDP	Uridine diphosphate
VLA-4	Very late activating antigen-4

Chapter 1. General Introduction to Iminosugars

Broadly speaking, iminosugars[†] are a class of sugar analogue in which the endocyclic oxygen atom is replaced by a basic nitrogen. This single atomic substitution renders these resulting polyhydroxylated alkaloids metabolically inert, and yet bestows many of them with the ability to inhibit or otherwise modulate the activity of various carbohydrate processing enzymes (chiefly glycosidases and glycosyltransferases) by virtue of their electronic character and structural mimicry of the natural substrates. These affected carbohydrate processing enzymes play a vital role in a host of biological functions,^{1,2} including: intestinal digestion; catabolism of glycoconjugates; the post-translational modification, maturation and transport of glycoproteins; in cellular signalling and recognition processes; and the immune response. As a result iminosugars have been, and remain, of great interest³⁻⁸ as potential therapeutic agents for the treatment of various diseases, including type II diabetes, lysosomal storage disorders and cancer. Concordantly these compounds are the targets of much current synthetic endeavour,⁹⁻¹² for the purposes of preparation and biological evaluation of novel iminosugars, as well as for the development of improved methodology towards the access of known examples. The absolute stereochemistries of these glycomimetics are of course a crucial factor for their biological activity, but preparation of iminosugars in stereochemically pure form remains a considerable challenge posed to the synthetic organic chemist. Carbohydrates, with their dense array of “built in” functionality and stereochemical information, are clearly of great merit as enantiopure chiral pool starting materials in the syntheses of these targets, and such is the focus of this thesis. A comprehensive review of iminosugars is beyond the scope of this chapter, however presented here is a brief overview of their natural occurrence and history – including discussion of some iconic examples – as well as their typical mode of action and the mechanistic rationale behind the principle therapeutic targets mentioned above.

[†] Sometimes called azasugars, although this is strictly incorrect as “aza” denotes substitution of a carbon for nitrogen.

1.1 Natural occurrence and bioactivity of iminosugars

Iminosugars are widely found in nature, with currently more than 100 having been isolated from a variety of plants and microorganisms,^{3,5,6} and their use as therapeutic agents goes back to antiquity and traditional Chinese herbal medicines; the extracts and leaves of the white mulberry tree (a rich source of iminosugars)^{7,13} were used to treat various ailments, including diabetes. Broadly speaking, naturally occurring iminosugars fall into one of five structural categories: polyhydroxylated pyrrolidines **1.1**, piperidines **1.2**, indolizidines **1.3**, pyrrolizidines **1.4** and nortropenes **1.5** (Figure 1.1). Some significant examples of each class are discussed below.

The piperidine nojirimycin (NJ **1.6**, Figure 1.2) was the first naturally occurring iminosugar to be identified, being isolated by Inouye and co-workers in 1966 from *Streptomyces roseochromogenes* and *S. lavendulae* and described as an antibiotic.^{14,15} Its *gluco* configuration confers potent inhibitory activity against α - and β -glucosidases from various sources, but due to its hemiaminal functionality it is quite unstable and is thus usually stored as a bisulfite adduct. The reduced analogue of NJ, 1-deoxynojirimycin (DNJ **1.7**), is a stable compound and was synthesised

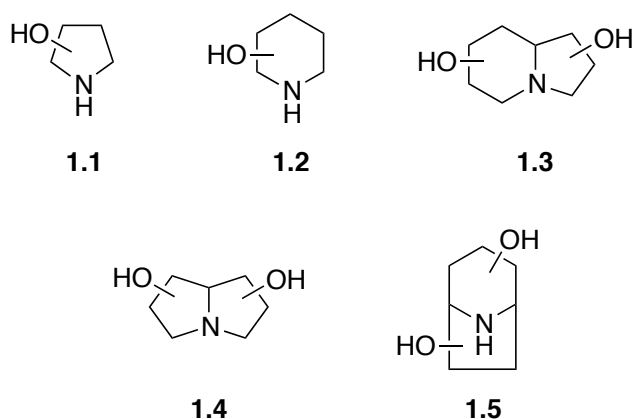


Figure 1.1: Structural classes of naturally occurring iminosugars

both from the reduction of NJ¹⁵ and from L-sorbofuranose¹⁶ well before its later isolation as a natural product from the roots of mulberry trees¹⁷ and from various bacterial cultures,¹⁸⁻²⁰ and it

exhibits potent inhibition of a broad range of α -glucosidases.³ The extension of this trivial nomenclature lends convenient description to 1-deoxy analogues of other sugars, such as the mannose equivalent deoxymannojirimycin (DMJ **1.8**) first isolated from the seeds of the legume *Lonchocarpus sericeus*,²¹ and which is a potent inhibitor of Golgi α -mannosidase I (IC_{50} 1-2 μ M)²² as well as α -L-fucosidase (IC_{50} 22 μ M).²³ The 1,2-dideoxy equivalent of nojirimycin, better known as fagomine (FG **1.9**), was originally isolated from the Japanese buckwheat *Fagopyrum esculentum*,²⁴ and displays some inhibition towards α -glucosidases,²⁵ albeit considerably less potent than that of DNJ. α -Homonojirimycin (α -HNJ **1.10**) was isolated from *Omphalea diandra* in 1988 as the first known example of a naturally occurring C-glycoside of an iminosugar,²⁶ and was found to be a potent inhibitor of various α -glucosidases (α -HNJ and its isomers are discussed in more detail in Chapter 3). Curiously enough, its 7-O- β -D-glucoside (MDL 25637) had been conceived of

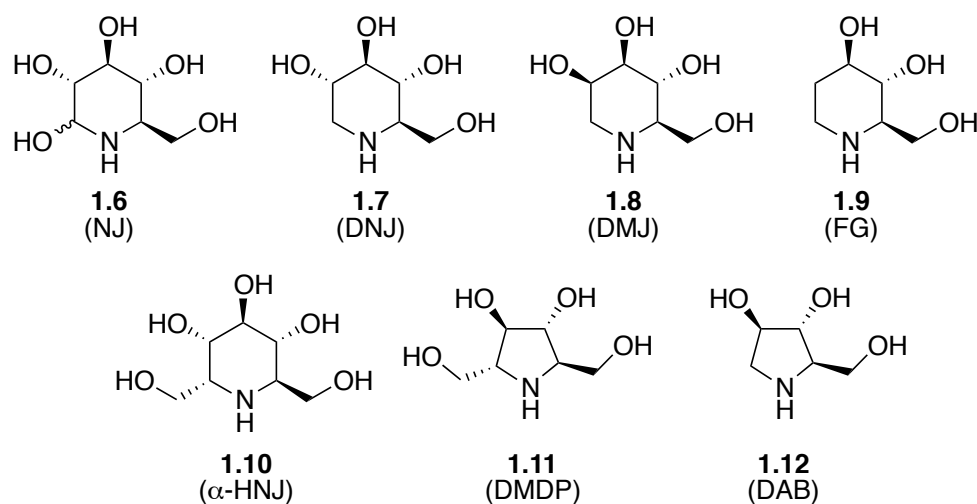


Figure 1.2: Some piperidine and pyrrolidine iminosugar natural products

and synthesised the previous year²⁷ as a potential drug for the treatment of diabetes. The pyrrolidine 2,5-dideoxy-2,5-imino-D-mannitol (DMDP **1.11**) – a mimic of β -D-fructofuranose – is one of the most widely found iminosugars in nature,⁵ and was originally isolated from the legume *Derris elliptica* in the mid-seventies.²⁸ It is a moderate inhibitor of α -glucosidases, but a powerful inhibitor of both β -glucosidases and β -galactosidases;²⁹ inhibitors of these latter enzymes are targets of

interest as potential medicinal agents for the treatment of certain lysosomal storage diseases.³ The structurally related 1,4-dideoxy-1,4-imino-D-arabinitol (DAB **1.12**) was first isolated almost a decade later from *Angylocalyx boutiqueanus*,³⁰ and is another compound of interest in the treatment of type II diabetes due to its inhibition of hepatic glycogen phosphorylase.³¹⁻³³

The observation that the legumes *Swainsona canescens* and *Castanospermum australe* were toxic to grazing livestock led to the isolation of the indolizidines swainsonine³⁴ **1.13** and castanospermine³⁵ **1.14** (Figure 1.3) respectively as the principle causative agents, and this discovery served to stimulate much of the early research into iminosugars and their potential applications. Swainsonine is a potent inhibitor of both lysosomal α -mannosidase³⁶ and Golgi α -mannosidase II,³⁷ and castanospermine is a potent inhibitor of lysosomal α -glucosidase,³⁸ and they thus give rise to phenocopies of the lysosomal storage disorders Mannosidosis and Pompe's

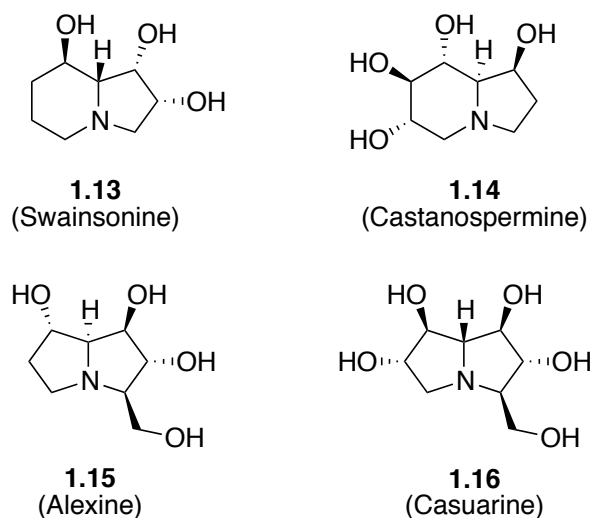


Figure 1.3: Indolizidine and pyrrolizidine iminosugar natural products

disease respectively; the former syndrome has been termed “pea struck” and “locoism” in animals which have consumed swainsonine-containing species of flora.^{6,39} Alexine **1.15** was the first example of a pyrrolizidine iminosugar to be isolated from nature, being found in the legume *Alexia leiopetala* in 1988,⁴⁰ but showed only poor inhibition of glycosidases. In contrast, the highly hydroxylated casuarine **1.16** and its 6-*O*- α -D-glucoside, isolated from the bark of *Casuarina*

equisetifolia (Casuarinaceae) in the mid-nineties,^{41,42} are both highly potent inhibitors of α -glucosidases with IC₅₀ values in the nM range;⁴³ in India and Western Samoa the bark has been prescribed as a traditional medicine for gastrointestinal disorders as well as breast cancer.

Finally, the most recently discovered class of naturally occurring iminosugars are the polyhydroxylated nortropenes known as the calystegines. There are 14 known members of this family,⁴⁴ all sharing the common structural features of three to five hydroxyl groups of differing position and stereochemistry, as well as an aminoketal functionality at the C1 bridgehead (with the exception of calystegine N₁ which bears an NH₂ group at C1 instead), but some of the most commonly encountered in nature are calystegines A₃, B₁, B₂ and C₁ (**1.17-1.20**, Figure 1.4). The family name derives from their first isolation from the roots of *Calystegia sepium*,⁴⁵ but they have

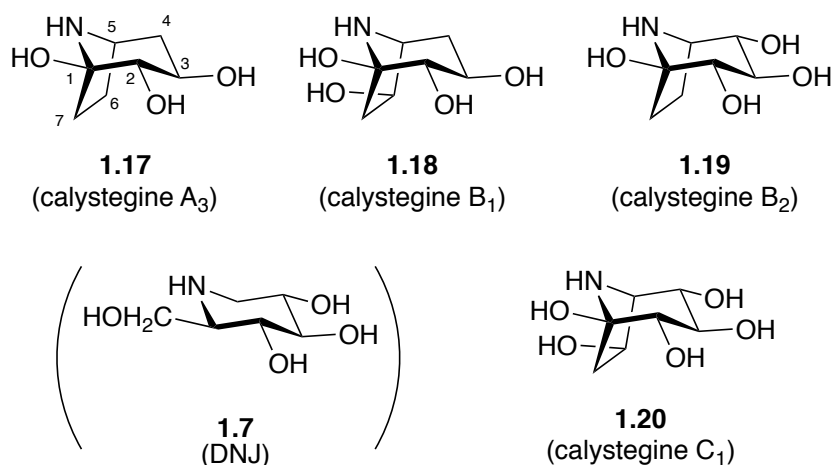


Figure 1.4: Some naturally occurring nortropene iminosugars

since been discovered in many species of Convolvulaceae, Moraceae and Solanaceae,⁵ including edible fruits and vegetables such as peppers, potatoes, aubergines, tomatoes and mulberries.⁴⁶ The calystegines A₃, B₁, B₂ and C₁ collectively display potent, competitive inhibition of various α - and β -glucosidases and galactosidases (*cf.* the structural similarity of DNJ **1.7**),⁶ and this activity has thus raised some concern over the safety of the above foods in the human diet, although to date no compelling argument for their toxicity has been presented. Despite their powerful glycosidase inhibition, the calystegines have seen very limited application as medicinal agents when compared

to the other structural classes of iminosugars, perhaps due to their comparative novelty and limited availability.

1.2 Mode of action

As the previous section amply demonstrates, the most significant biological mode of action of iminosugars is that of inhibition of glycosidases (glycoside hydrolases), and the exploitation of this activity underpins the therapeutic rationale behind the treatments of most disease targets with iminosugars, those mentioned later in this chapter being no exception. As such, the discussions herein will be limited to a simple overview of these enzymes.

Glycosidases are enzymes which catalyse the cleavage of the glycosidic bonds within all manner of glycans and glycoconjugates. These bonds are normally extraordinarily stable; the half life for the spontaneous hydrolysis of a glycosidic bond within cellulose has been estimated⁴⁷ to be 4.7 million years, for example. Glycosidases can accelerate this reaction by a factor of up to 10^{17} , making them one of the most efficient enzyme catalysts known.⁴⁸ The hydrolysis of the glycosidic

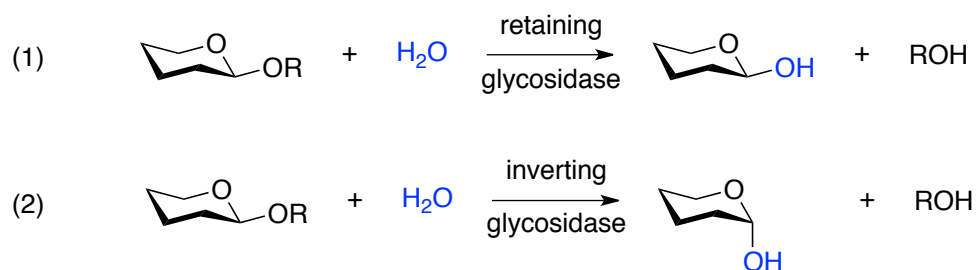


Figure 1.5: Overall action of retaining and inverting glycosidases

bond can occur with either retention or inversion of configuration at the anomeric centre, and these outcomes serve to distinguish glycosidases into the mechanistically distinct classes of “retaining” or “inverting” enzymes (Eqn. 1 and Eqn. 2 respectively, Figure 1.5); the reactions shown are for the hydrolysis of β -glycosides but the principle applies equally to α -glycosides. The mechanisms

involved in both classes of glycosidases have historically been the subject of much study, and their exact natures are now well established,⁴⁸⁻⁵⁰ generally conforming to the remarkably prescient hypotheses concerning glycoside hydrolysis put forth by Koshland almost 60 years ago.⁵¹

Inverting glycosidases act through a concerted mechanism involving two active site carboxylic acid residues (either glutamate or aspartate) as general acid and base catalysts (Figure 1.6). A single molecule of water is positioned in line with the substrate such that deprotonation by the basic residue occurs simultaneously to attack on the anomeric centre and the departure of the

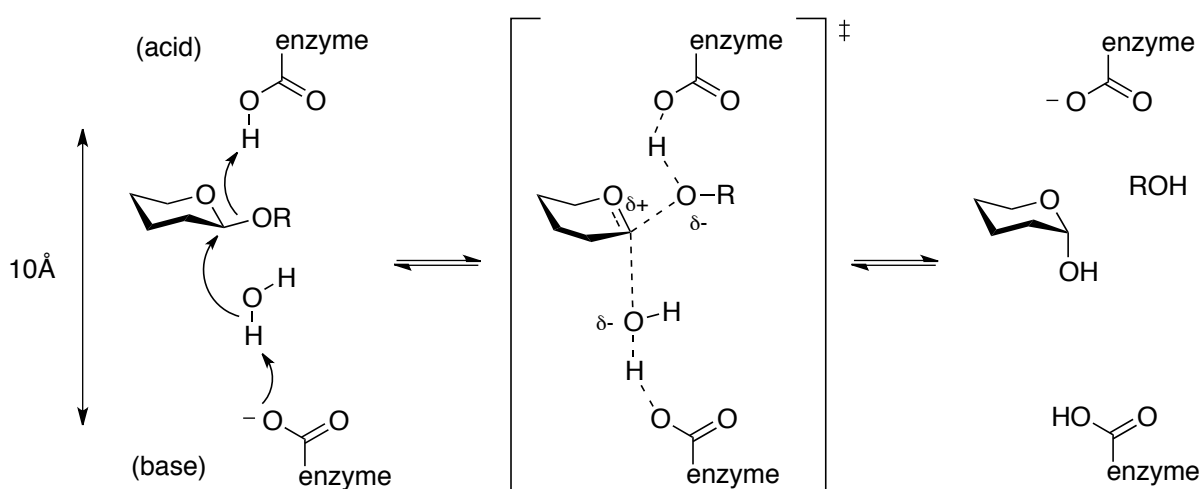


Figure 1.6: Mechanism of inverting glycosidases

aglycon fragment, facilitated by protonation *via* the acid residue. In contrast, the more common retaining glycosidases act through a two-step mechanism involving two sequential inversions of the anomeric centre, resulting in a net retention of configuration (Figure 1.7). The initial step involves acid assisted nucleophilic displacement of the aglycon with inversion of configuration, forming a glycosyl-enzyme intermediate. The paradigmatic nucleophile is a carboxylic acid residue as depicted, although other examples do exist such as in glycosidases which utilise a tyrosine residue,⁵² or those which use the anchimeric assistance of a substrate-borne 2-acetamido group, such as chitinases⁵³ or *N*-acetylhexosaminidases.^{54,55} Once the aglycon has departed, the carboxylate residue now behaves as a base in the second step, deprotonating a molecule of water

which simultaneously displaces the enzyme fragment with inversion of configuration, leading to the products. A key feature of retaining glycosidases is the reduced spacing between the catalytic residues when compared to inverting glycosidases, reflecting the closer approach of the nucleophile necessary for the formation of the glycosyl-enzyme covalent intermediate.

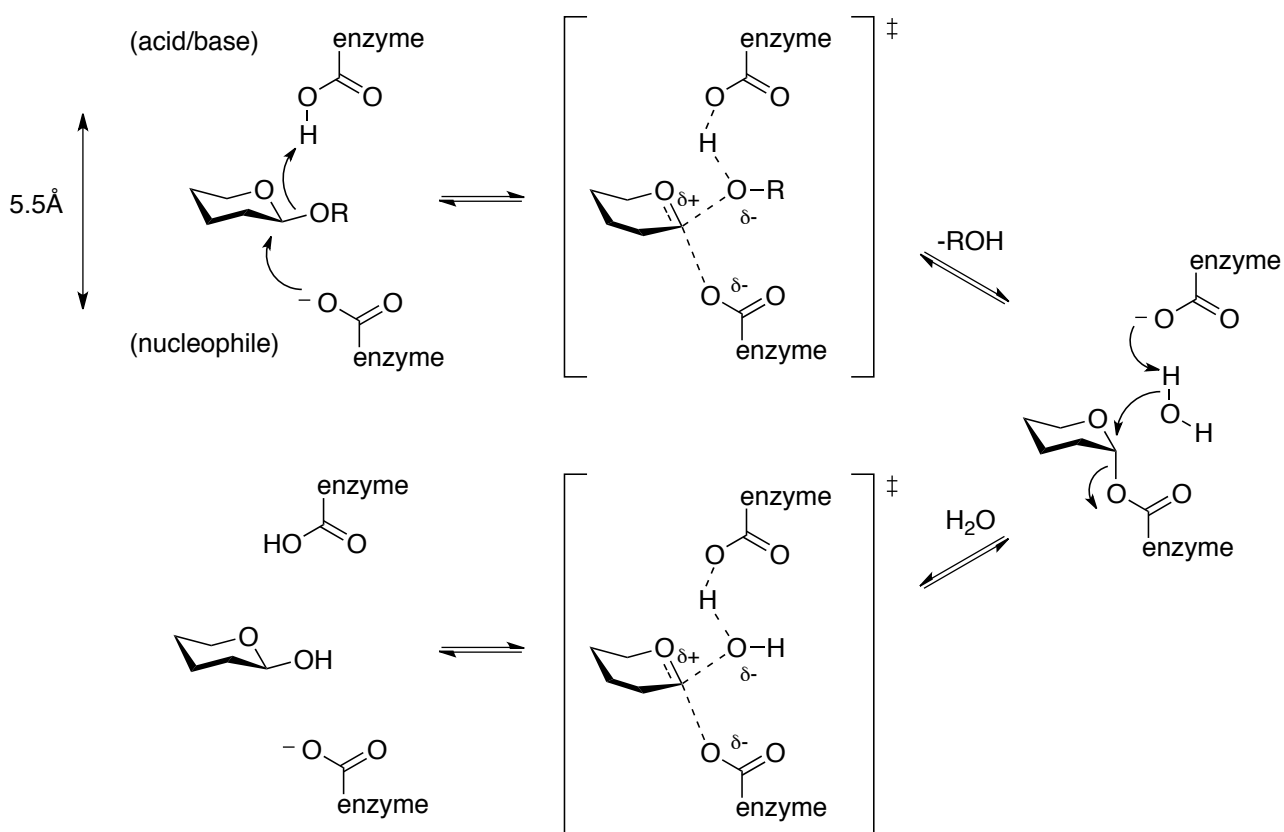


Figure 1.7: Mechanism of retaining glycosidases

The transition states involved in the mechanisms of both retaining and inverting glycosidases all possess significant oxocarbenium ion character. Iminosugars are protonated at physiological pH, and it is these ammonium forms which thus act as competitive inhibitors of these enzymes *via* mimicry of the oxocarbenium transition states of the natural substrates (shown in Figure 1.8 for a pyranose substrate/piperidine iminosugar); non-competitive inhibition of glycosidases by iminosugars is also known (for example by the L-enantiomers of natural D-iminosugars),⁵⁶ however the mechanism is not well understood. As one would expect, when considering competitive inhibition by iminosugars, the ring size, configuration of hydroxyl groups, and presence of any ring

substituents can have a profound impact on its inhibition profile, and generally those iminosugars which closely mimic the structures of the natural substrates are found to be good inhibitors of the relevant processing enzymes (for example DNJ and its inhibition of α -glucosidases).

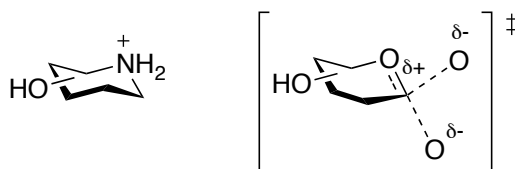


Figure 1.8: Protonated iminosugars as transition state mimics

Finally, the position of the endocyclic nitrogen (and hence the resulting ammonium ion) within the ring can have an affect on the selectivity of inhibition towards retaining α - or β -glycosidases, due to the differing charge distribution of the oxocarbenium ions associated with each enzyme during the formation of the glycosyl-enzyme intermediate. An emblematic example of this is provided by the differing inhibition of α - and β -glucosidases by DNJ and the synthetic iminosugar isofagomine,³ or IFG (Figure 1.9). With α -glucosidases, the approaching nucleophilic residue takes part in a *syn* interaction with the endocyclic oxygen, therefore favouring distribution of the positive charge onto the oxygen within the oxocarbenium ion. Concordantly, DNJ is a more powerful inhibitor of retaining α -glucosidases than β -glucosidases, as its protonated ring nitrogen occupies the same relative position to the endocyclic oxygen of glucose. In the contrasting β -glucosidase case, the nucleophile must approach in such a way as to render interaction with the endocyclic oxygen impossible, and instead a *syn* interaction with the 2-hydroxyl of glucose takes place. This situation favours distribution of the positive charge onto the anomeric carbon rather than the endocyclic oxygen. As a result, IFG is a much more potent inhibitor of β -glucosidases than α -glucosidases, as its protonated ring nitrogen occupies the same relative position as the anomeric carbon within glucose.

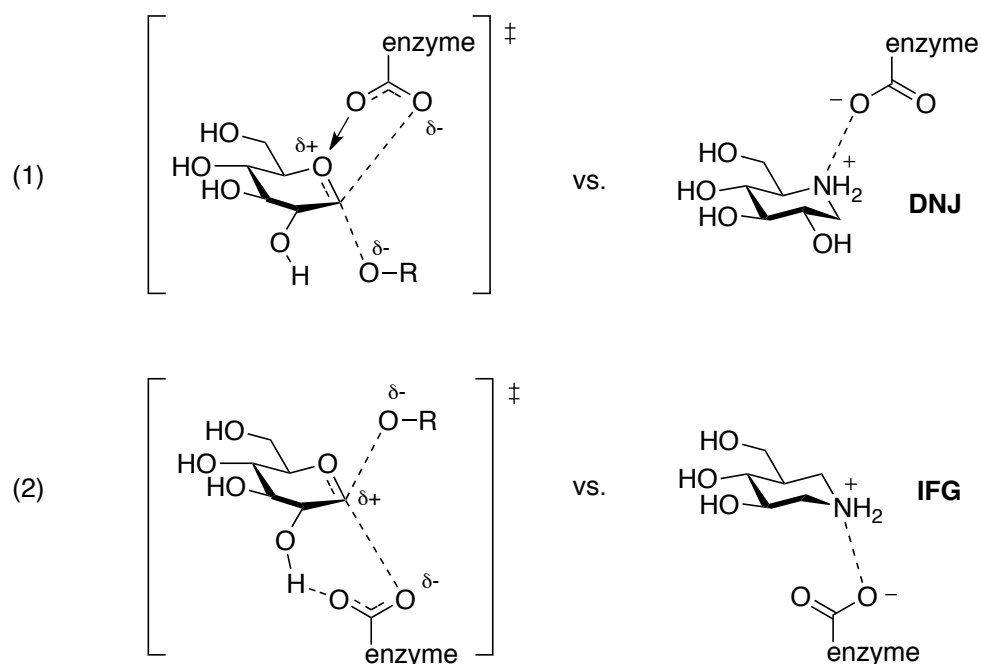


Figure 1.9: Transition states for retaining α - and β -glucosidases vs DNJ and IFG

1.3 Anti-diabetic agents

Non-insulin-dependant (type II) diabetes mellitus is a chronic metabolic disorder which is primarily characterised by high levels of blood glucose (hyperglycaemia), the cause being a deficiency in levels of insulin and/or resistance to the insulin produced, and the long term effects of untreated diabetes can include cardiovascular disease, stroke, kidney failure and blindness. Diabetes is a disease which is fast approaching epidemic proportions in the western world, due in large part to the rising levels of obesity; the World Health Organisation currently estimate that 346 million people worldwide are sufferers, with type II diabetes comprising 90% of those cases.⁵⁷

Many iminosugars are potent inhibitors of the α -glucoside-specific oligo- and disaccharidases (sucrase, maltase, isomaltase, trehalase etc) which are components of the cell membranes of the brush border region of the small intestine. These glycosidases play a crucial role in mammalian digestion, breaking down the dietary carbohydrates to monosaccharides which can then be absorbed into the bloodstream. It was thus realised in the late 1970s that inhibitors of these enzymes could be

used as orally-administered therapeutics to treat type II diabetes,¹⁸ by slowing the breakdown of carbohydrates and therefore mitigating postprandial hyperglycaemia. This interest ultimately led to the development of the highly potent α -glucosidase inhibitor *N*-hydroxyethyl-DNJ, otherwise known as Miglitol⁵⁸ (Figure 1.10); in 1996 Miglitol was granted market clearance by the FDA and in 1999 went on sale under the trade name GLYSET[®] as a treatment for type II diabetes. More recently, interest has emerged over a possible alternative approach to the control of blood glucose levels through modulation of glycogen phosphorylase. In type II diabetes the activity of hepatic glycogen phosphorylase is elevated compared to the non-diabetic phenotype, leading to a rise in blood glucose, and therefore inhibitors of this enzyme are viewed as potential alternative anti-diabetic drugs.⁵⁹ As previously mentioned in Section 1.1, the pyrrolidine iminosugar DAB is a potent inhibitor of hepatic glycogen phosphorylase, and as such is of much current interest as a potential novel anti-hyperglycaemic agent.

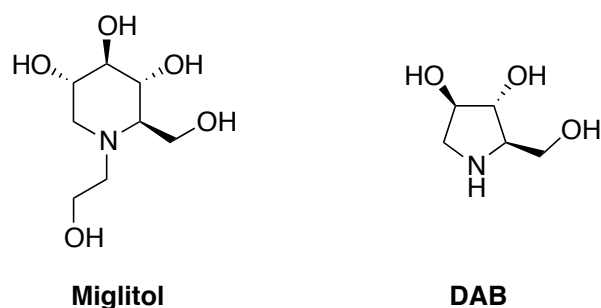
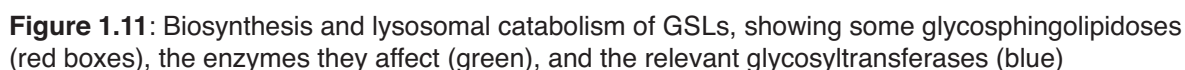


Figure 1.10: Iminosugars with antidiabetic activity

1.4 Therapeutics for lysosomal storage disorders

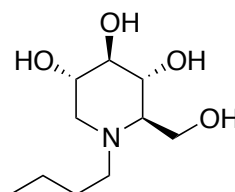
Lysosomes are acidic, membranous organelles which contain an array of degradative enzymes, and they are responsible for the catabolism of a broad range of macromolecules, including glycoproteins, mucopolysaccharides and glycolipids, thus enabling the recycling of their constituent fragments within the cell. The lysosomal storage disorders (LSDs) are a group of more than 50 genetic diseases which give rise to mutations of these metabolic enzymes (or their necessary co-



Therapeutic strategies for the treatment of glycosphingolipidoses have been the subject of several recent reviews,⁶¹⁻⁶³ and broadly speaking fall into two categories: the augmentation of the defective enzymes, or a reduction in the concentration of substrates on which they act. Methods for enzyme augmentation include enzyme replacement therapy (ERT), bone marrow transplantation (BMT), gene therapy, and chaperone-mediated therapy (CMT). Intravenous ERT is limited by its extreme cost and the fact that the administered enzymes are not able to pass the blood-brain barrier, thus limiting this approach to treatment of the minority of glycosphingolipidoses with no central nervous system (CNS) pathology. BMT is also problematic, due to the generally low efficiency of enzyme delivery to the brain, the difficulty of finding suitable donors and the considerable risks associated with the procedure, and gene therapy is a long way from being a clinical reality. The use of iminosugars as medicinal agents for chaperone-mediated therapy (CMT) and substrate reduction therapy (SRT) overcomes many of the problems associated with the alternative approaches, not least by virtue of their ability to cross the blood-brain barrier and access cells of the CNS, and they have thus been the targets of much interest in these roles.^{3,64,65}

The principle behind SRT is reducing the influx of the GSL substrates into the lysosomes by inhibiting their biosynthesis; in this way the rate of uptake of the substrates can be regulated to be in balance with the reduced turnover by the mutant enzymes, thus avoiding lysosomal storage. A pivotal enzyme in the biosynthesis of all the GSLs is ceramide glucosyltransferase (CGT), whose action results in the glucosylceramide from which, courtesy of various glycosyltransferases, the other GSLs are derived (Figure 1.11). *N*-alkylated piperidine iminosugars were found to inhibit GSL biosynthesis *via* reversible, competitive inhibition of CGT;^{66,67} *N*-butyl-DNJ (NB-DNJ, Figure 1.12), also known as miglustat, is a particularly potent inhibitor of CGT, with a K_i of 7 μM .⁶⁵ Gaucher disease is the most common of the glycosphingolipidoses, and results in the expression of a less active form of β -glucocerebrosidase, leading to an accumulation of lysosomal glucosylceramide. Depending on the severity of the disease, the variable affects can include enlargement of the liver and spleen, haematological disturbance and bone destruction caused by the

build up of glucosylceramide in macrophages. NB-DNJ has been granted approval in Europe, the USA and Israel for the treatment of type I Gaucher disease (under the trade name Zavesca[®]), but it also shows promise as a more general drug for the SRT of other glycosphingolipidoses.^{64,65}



NB-DNJ

Figure 1.12: *N*-butyl-DNJ (Miglustat), a drug for the treatment of Gaucher disease

CMT (sometimes referred to as pharmacological chaperone therapy) is a relatively novel strategy for the treatment of LSDs,^{68,69} and involves lessening the retention and destruction of the mutant lysosomal enzymes by the quality-control systems of the endoplasmic reticulum (ER). During the biosynthesis of these enzymes (Figure 1.13) the constituent proteins are synthesised in the cytosol and translocated to the lumen of the ER, where they bind to the lectins Calnexin and Calreticulin, which act as chaperones to facilitate correct folding and assembly in the normal case. The lectins then dissociate from the correctly formed enzyme, which is transported to the Golgi apparatus for further processing and targeting to the lysosome. Many of the genetic mutations giving rise to LSDs encode for enzymes which cannot correctly fold or assemble, or that become aggregated in the ER; these are ultimately destroyed by a quality-control process known as ER-associated degradation (ERAD). However, some of the disease forms give rise to mutant enzymes which are less stable relative to the wild type, but in which the conformation of the active site is unaffected. As a result these mutant enzymes are able to retain some residual activity, provided they can be successfully trafficked to the lysosome. Active site-specific chaperones (ASSCs) are potent competitive inhibitors of the enzymes, and at sub-inhibitory concentrations are able to either induce or stabilise the correct folding of the enzyme *via* binding to its active site, thereby promoting its maturation and

transportation to the lysosome. As the ASSC is a competitive inhibitor, once the complex reaches the lysosome the ASSC is displaced by the higher concentration of GSL substrate, which can then be hydrolysed. Thus, with carefully controlled dosing the net enzyme activity within the lysosomes can be increased.

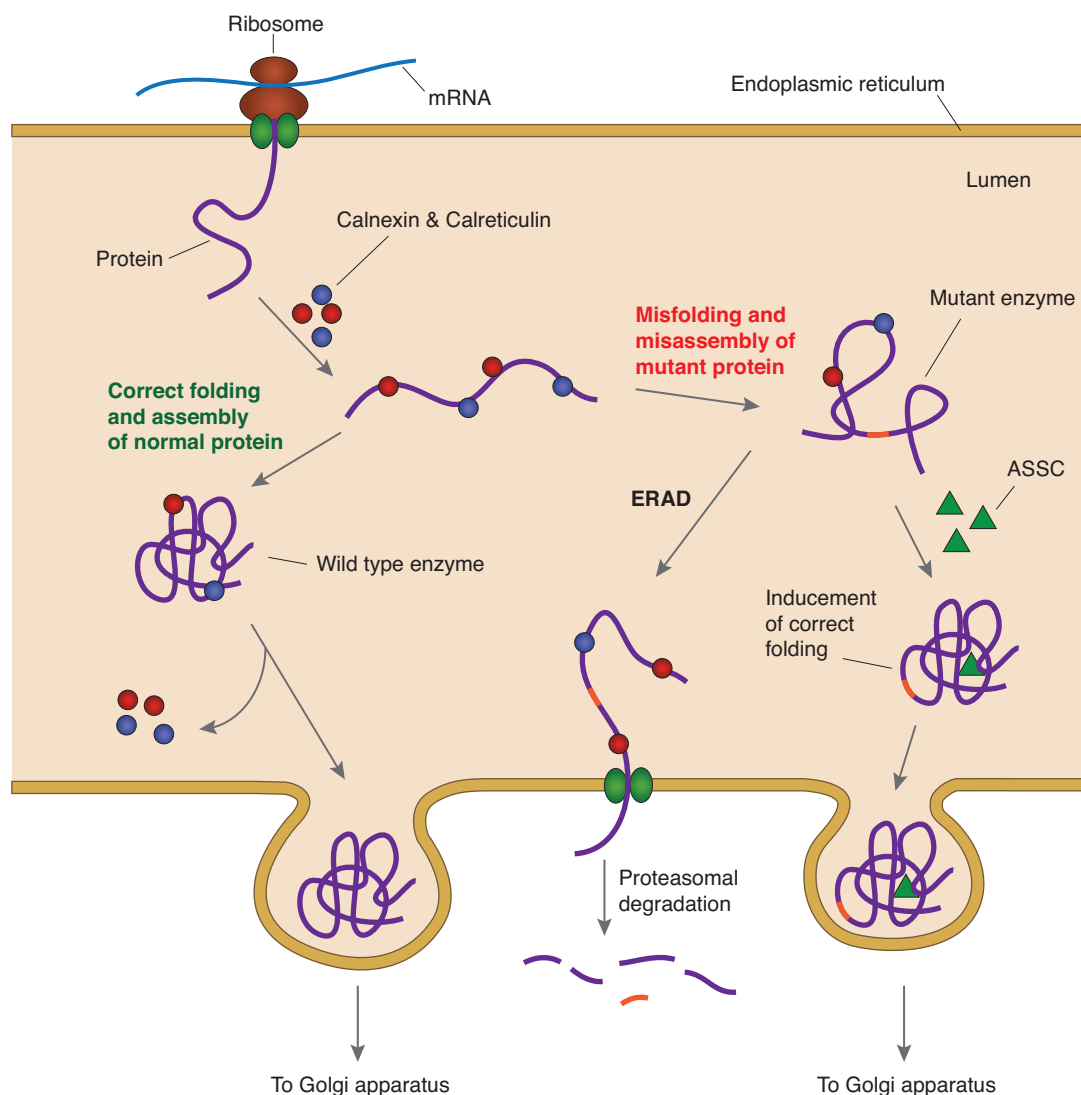


Figure 1.13: The quality-control system for protein folding and assembly within the endoplasmic reticulum, and the principle of Active Site-Specific Chaperone (ASSC) mediated therapy

The use of iminosugars as ASSCs was first demonstrated by Fan and co-workers^{70,71} for the treatment of Fabry disease, which is characterised by a deficiency in α -galactosidase A (α -Gal A) and subsequent storage of globotriaosylceramide. They found that the mutant α -Gal A enzymes could be rescued by various iminosugar inhibitors of α -Gal A, including 1-deoxygalactonojirimycin

(DGJ, Figure 1.14); DGJ is a particularly potent inhibitor of α -Gal A, with an IC_{50} value of 40 nM, and is currently undergoing phase III clinical trials under the trade name Amigal[®] for the treatment of Fabry disease.⁷² Additionally, other iminosugar ASSCs have subsequently been identified as potential treatments for Gaucher disease,^{73,74} G_{M1} -gangliosidosis,⁷⁵ and Tay-Sachs and Sandhoff diseases.⁷⁶

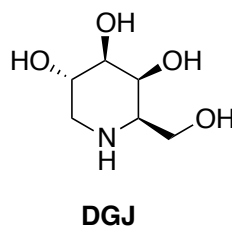


Figure 1.14: DGJ (Amigal), an ASSC for the treatment of Fabry disease

1.5 Anti-cancer therapeutics

The historical focus of much of the research into iminosugars as anti-cancer agents has been concerned with their role as inhibitors of the biosynthesis and processing of the *N*-linked oligosaccharide (glycan) components of cell-surface glycoconjugates.^{3,5,6} These glycoconjugates – such as glycoproteins, glycolipids and proteoglycans – play a significant role in many important biological functions, including transport, growth, differentiation, cell-cell communication and immune response, and the enzymes which metabolise the glycan components are key to the regulation of these functions. Malignant transformation of healthy cells into tumour cells gives rise to the expression of abnormal and highly distinct cell-surface glycans,^{77,78} being typically larger with a high degree of branching and possessing sialylated chain termini, and these glycans have been shown to play an important part in tumour growth and metastasis. The synthesis of *N*-linked glycans occurs in the ER and Golgi apparatus *via* the action of various glycosidases and glycosyltransferases.⁷⁹ Although the types of glycan structures thus produced are many and varied

their syntheses all share a common set of precursory steps within the ER, in which the *N*-linked tetradecasaccharide core of GlcNAc₂Man₉Glc₃ is successively trimmed by the actions of α -glucosidase I, α -glucosidase II and ER α -1,2-mannosidase I to afford a GlcNAc₂Man₈ core. Furthermore, the subsequent diversification of this deca-saccharide core very commonly entails the trimming of more mannose residues *via* the actions of Golgi α -mannosidase I and Golgi α -mannosidase II. Thus, by inhibiting these processing glucosidases and mannosidases by iminosugars⁸⁰ the synthesis of these abnormal glycans can potentially be hindered, thereby curbing tumour proliferation. In this regard, the α -glucosidase I inhibitors NJ (**1.6**, Figure 1.2) and castanospermine (**1.14**, Figure 1.3) have received some interest in studies of mouse melanoma^{81,82} and lymphoma⁸³ models respectively. However, greater research efforts have been invested into the potent Golgi α -mannosidase II inhibitor swainsonine (**1.13**, Figure 1.3), which showed promise in Phase I clinical trials.⁸⁴⁻⁸⁶ Unfortunately, one subsequent Phase II study into patients with metastatic renal cell carcinoma was less encouraging, with no anti-tumour activity being noted.⁸⁷

Two alternative approaches towards anti-cancer therapy are of current interest within the Fleet group, both involving the use of iminosugars to inhibit hexosaminidases. The first strategy is concerned with preventing or curtailing tumour metastasis – the establishment of discrete, secondary colonies, and the process which is ultimately responsible for 90% of cancer-related deaths⁸⁸ – by protecting the extracellular matrix (ECM). Metastasis is a complex, multi-step process^{89,90} (Figure 1.15) initiated by metastatic cells detaching from the primary tumour, followed by their invasion of basement membranes and degradation of the ECM to allow entry to a blood vessel; an overall process known as intravasation. The reverse process of extravasation begins with tumour cell aggregation and adhesion at a distant, downstream site, followed by invasion of basement membranes and degradation of the ECM to allow the foundation of secondary tumours. Preventing the degradation of the ECM therefore represents an attractive therapeutic strategy with which to arrest tumour metastasis, thereby allowing an increased window for treatment of the disease.

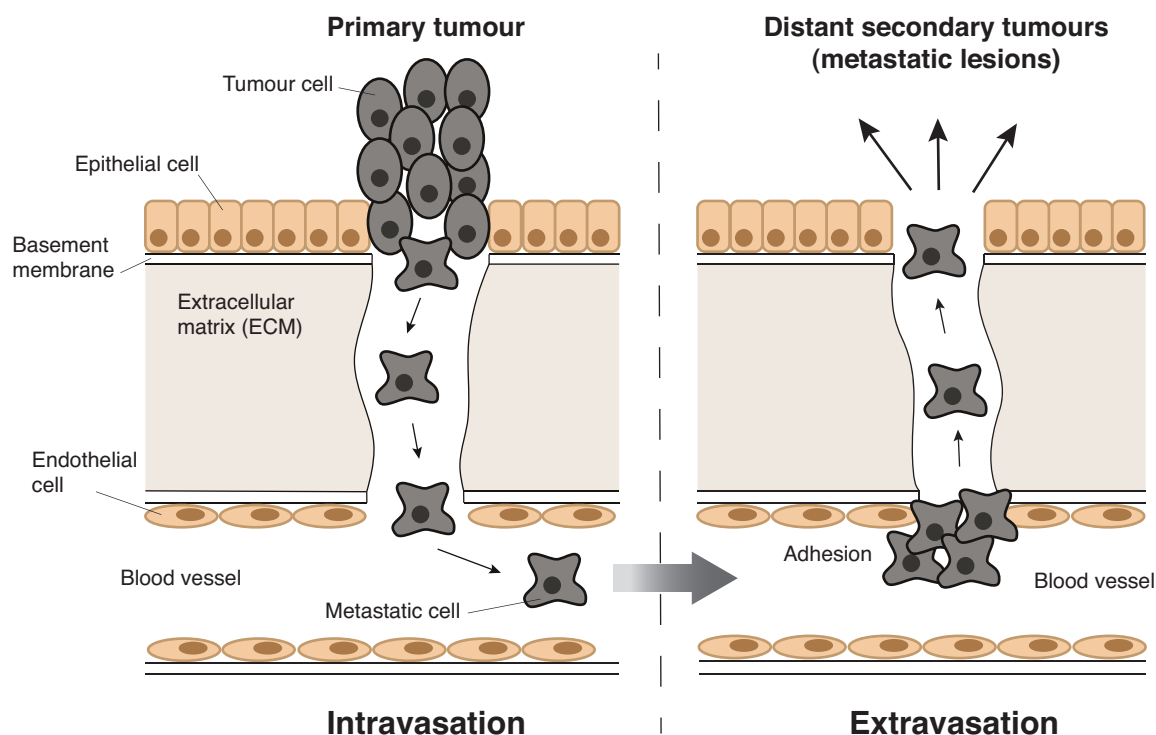


Figure 1.15: The process of tumour metastasis

The ECM is comprised of a mixture of macromolecules, including fibrous proteins, proteoglycans, and glycosaminoglycans. One of these glycosaminoglycans, and a chief component of the ECM, is hyaluranan (hyaluronic acid), a polysaccharide consisting of alternating D-glucuronic acid and *N*-acetylglucosamine residues. Concordantly, in order to degrade the ECM tumour cells secrete a cocktail of enzymes such as cysteine/serine proteinases, matrix metalloproteinases and glycosidases, including β -*N*-acetyl-glucosaminidase; tumour cells have been shown to secrete far greater levels of this enzyme than healthy tissue,⁹¹ and its level in blood serum has been proposed as a biomarker of malignancy.⁹² Thus, if a suitable iminosugar could be designed which inhibits β -*N*-acetyl-glucosaminidase it may prove to be a valuable anti-metastatic agent for the treatment of cancer.

The second potential approach to using hexosaminidase inhibitors as anti-cancer agents involves the strengthening of the patient's immune system *via* the activation of macrophages. Specifically, the strategy is concerned with the preservation of the Gc protein-derived macrophage activating factor (GcMAF).⁹³ The production of GcMAF (Figure 1.16) occurs *via* the step-wise modification of vitamin D-binding protein (Gc protein);⁹⁴ a threonine-borne trisaccharide unit is sequentially

trimmed by the actions of membrane-bound β -galactosidase and sialidase on B-Cells and T-Cells respectively, leaving a lone GalNAc residue on the protein. The GcMAF then serves to activate macrophages, which are able to destroy cancerous cells by phagocytosis; the administration of GcMAF has shown much promise in the treatment of cancers in both mouse models and human trials.⁹⁵⁻⁹⁹

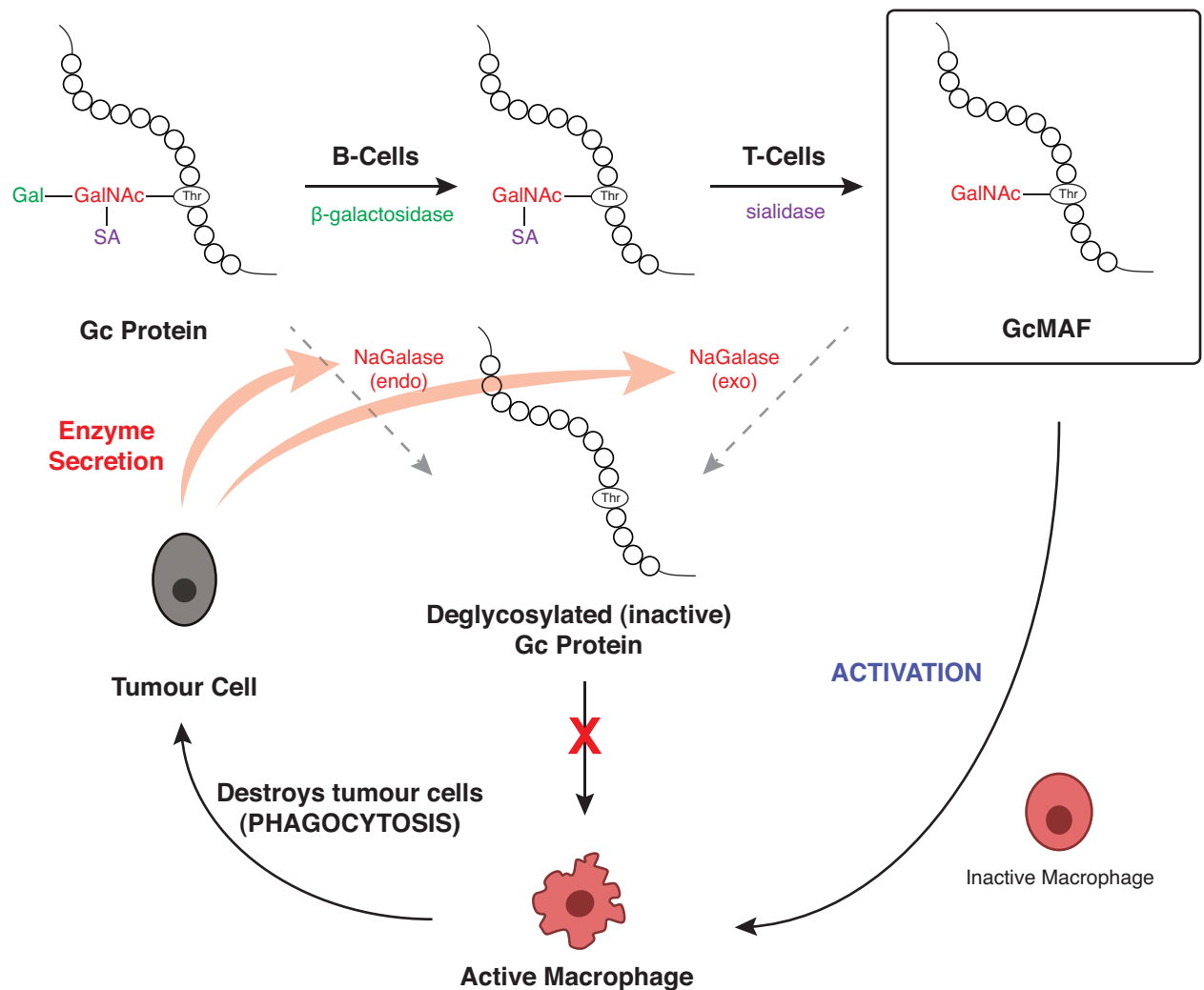


Figure 1.16: The macrophage activation cascade from Gc protein, and the immunosuppressive activity of α -N-acetyl-galactosaminidases (NaGalases) secreted by tumour cells

Tumour cells secrete α -N-acetyl-galactosaminidases (or “NaGalases”) into the host’s serum;¹⁰⁰ either the endo form which cleaves off the entire trisaccharide unit of Gc protein, or the exo form which cleaves the GalNAc residue from GcMAF. The actions of either produces the same result of a deglycosylated form of the Gc protein which is unable to stimulate macrophages, and therefore

leads to immunosuppression.¹⁰¹ The application of a suitable iminosugar inhibitor of α -N-acetyl-galactosaminidases could therefore prove to be an effective method of protecting the production of GcMAF, thereby bolstering the patient's immune system and promoting the destruction of tumours.

Clearly iminosugars possess huge potential not only as effective therapeutic agents in their own right, but also as chemical tools for unravelling the many biochemical mechanisms involved in the burgeoning field of glycobiology, and as such they remain targets of considerable interest to the synthetic organic chemist. Their diverse structure and biological activity have bestowed them with varied and widespread success over the past 40 years, due in large part to their ability to inhibit glycosidases; several iminosugars are already of prominent clinical interest in this role, either as marketed products or as candidates in the late stages of drug development. Such a track record no doubt belies fertile ground of form and function yet to be uncovered, and provides great impetus for the exploration of novel iminosugar structures, as well as the development of improved methodology for their synthesis. The following two chapters are concerned with the synthesis and preliminary biological evaluation of a number of novel azetidine iminosugars, as well as the utilisation of biotechnological transformations of monosaccharides in tandem with traditional synthesis to deliver rapid and efficient access to a known family of piperidine iminosugars.

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Chapter 2. Azetidine Iminosugars

2.1 Introduction

Azetidines are a class of four-membered, saturated aza-heterocycles containing a single nitrogen atom within the ring. Compared with their homologous heterocycles (aziridines, pyrrolidines, piperidines and azepanes), azetidines have enjoyed the least attention in the literature over the years.¹⁻³ This is in stark contrast with the wealth of publications regarding azetidin-2-ones (β -lactams); obvious targets of interest due to their key role as antibacterial agents. This comparative lack of interest in azetidines appears to be due to three principle reasons: the relative rarity with which the azetidine motif is encountered in nature, and thus less inherent incentive for its exploration; the general synthetic difficulty of forming the strained four-membered ring;³ and a lack of methods for preparing enantiopure azetidines.⁴ Nonetheless, they remain an important class of aza-heterocycle, being encountered in several highly bioactive natural products, and further they have more recently found diverse use as structural motifs in pharmacological tools for medicinal chemistry studies, as non-natural amino acids in conformationally-constrained peptidomimetics, as ligands for metal-catalysed reactions or chiral auxiliaries, and even as explosives. Despite the high degree of ring strain present in these compounds they are generally highly stable, being amenable to purification *via* chromatographic methods as well as distillation, and can be stored for extended periods at room temperature without any issue.

In comparison with the ubiquity of reports on 5-, 6- and 7-membered ring iminosugars and corresponding studies into their biological activities (see Chapter 1), polyhydroxylated azetidines (or azetidine iminosugars) are to date a virtually unexplored class of compounds, and will be discussed in due course.

2.1.1 Natural products and synthetic drugs

L-Azetidine-2-carboxylic acid **2.1**,⁵ also commonly referred to as L-Aze, is the simplest naturally occurring example of an azetidine, and can be considered as a ring-contracted homologue of L-proline (Figure 2.1). It was the first known azetidine to be isolated from nature, being extracted from the liliaceae *Convallaria majalis* by Fowden in 1955.⁶ Virtanen and Linko independently discovered L-Aze in the same year,⁷ but their initially reported structure was wrong and they later acknowledged their mistake,⁸ crediting Fowden's structure as correct. It has since been discovered to be present in various other species of plant.⁵ It is an example of a non-proteinogenic amino acid, and is thus toxic to predators, exhibiting a range of biological effects; its incorporation into proteins in place of proline has been shown to affect their folding, altering the structures of collagen, keratin and haemoglobin and to give rise to teratogenic effects in animals.^{5,9} It is also known to act as a growth inhibitor towards competitor species of vegetation.¹⁰

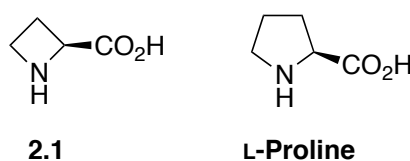


Figure 2.1: Structures of L-Aze and L-proline

Subsequent to the discovery of L-Aze **2.1**, several natural products containing this moiety have been isolated. The most prominent class of these derivatives is perhaps the phytosiderophores mugineic acid **2.2**,¹¹ 2'-deoxymugineic acid **2.3**,¹² isomugeneic acid **2.4**¹³ and nicotianamine **2.5**¹⁴⁻¹⁶ (Figure 2.2). The mugineic acids are found in gramineous plants such as oats, wheat and barley, whereas nicotianamine has been isolated from tobacco leaves, alfalfa and sugar beet. These compounds act as iron-chelating agents, thus performing a vital role in the sequestering, uptake and transport of the iron needed for the biosynthesis of chlorophyll.

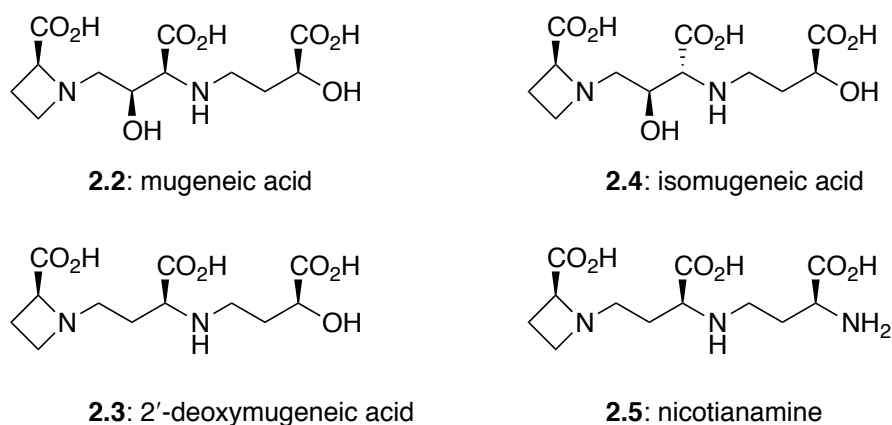


Figure 2.2: Structures of L-Aze-based phytosiderophores

The polyoxins are a class of fifteen related nucleoside peptide antibiotics isolated from *Streptomyces cacaoi* var. *asoensis* by Isono and co-workers.¹⁷⁻²⁰ Four of them – polyoxins A, F, H and K (2.6, 2.7, 2.8 and 2.9 respectively) – contain a 3-*cis*-ethylidene functionalised L-Aze motif within their structure (Figure 2.3),^{20,21} varying only in the substitution at C5 of the nucleosidic base. The compounds of this family are potent competitive inhibitors of chitin synthetase, making them highly active antifungal agents; they have been used commercially in Japan as agricultural fungicides.

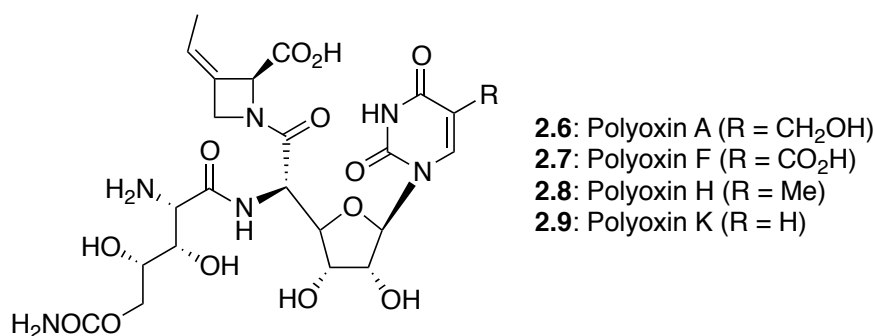


Figure 2.3: Structures of the azetidine-containing polyoxins

Two enantiomeric, branched azetidine dicarboxylic acids were recently isolated by Akihisa and co-workers;²² (+)- and (-)-monascumic acids (2.10 and 2.11, Figure 2.4) were found in the 70% ethanol extract of red-mold rice fermented with *Monascus pilosus*. Compound 2.11 was found to be

a potent inhibitor of 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation in mice, and both **2.10** and **2.11** were found to be potent inhibitors of the induction of Epstein-Barr virus early antigen (EBV-EA) by TPA.²³ These compounds are thus of interest as potential anticancer agents, as active EBV has been associated with the development of various kinds of cancer, particularly lymphomas.²⁴

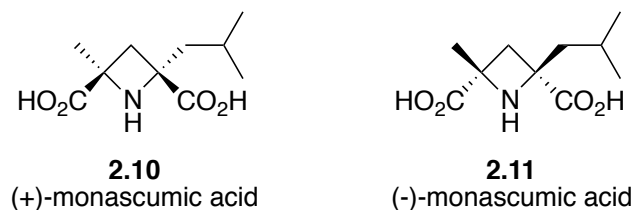


Figure 2.4: The monascumic acids

The vioprolides A (**2.12**) and C (**2.13**) are two of a family of four macrocyclic peptolides isolated by Schummer and co-workers from *Cystobacter violaceus* strain Cb vi35,²⁵ and both contain what can be considered as a reduced L-Aze peptide unit within the ring (Figure 2.5). They all exhibit cytotoxicity towards mammalian cells and show a broad range of antifungal activities.

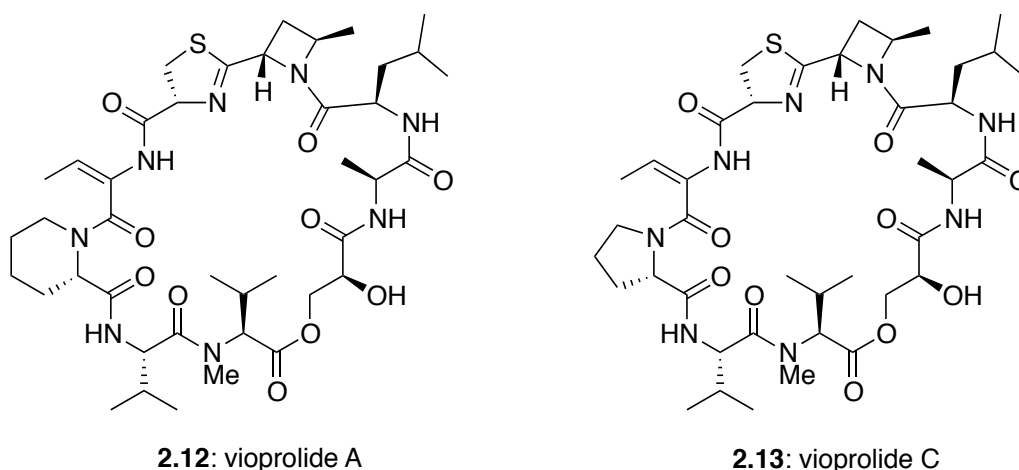


Figure 2.5: Azetidine-containing vioprolides

In recent decades, L-Aze **2.1** has been incorporated into the design and formulation of numerous compounds with a broad range of biological activities, some of which are shown in Figure 2.6. The mercaptoacyl derivative **2.14** was prepared by Petrillo and co-workers, and was found to be an inhibitor of angiotensin-converting enzyme (ACE),²⁶ making it a potential agent for the treatment of hypertension, heart failure and type II diabetes. Suto and co-workers at Parke-Davis prepared the acid **2.15** and ester **2.16** amongst a series of compounds designed for the treatment of cancers; they found them to be efficient radiosensitisers, as well as selectively cytotoxic towards hypoxic cells.²⁷ An L-Aze adduct of geldanamycin, **2.17**, was prepared by Schnur and co-workers and was found to inhibit the p185 phosphotyrosine kinase in the human breast cancer SKBR-3 cell line.²⁸ The most well known examples of drugs containing an L-Aze motif are the thrombin inhibitors **2.18** and **2.19**,²⁹ marketed by Astra-Zeneca under the trade names Melagatran and Ximelagatran (or Exanta) respectively. Ximelagatran is the prodrug form of Melagatran, being readily metabolised to the latter *in vivo*. They had been investigated as possible replacements for traditional anticoagulants such as warfarin and heparin, with the aim of mitigating the problems associated with therapy involving those agents, and showed very promising results.^{30,31} However, application for their approval was eventually withdrawn due to later discovery of hepatotoxicity in patients undergoing more prolonged trials.³² Kamenecka and co-workers from Merck have reported the synthesis and biological evaluation of the L-Aze ester **2.20** and the amide **2.21**,³³ both highly potent (IC₅₀ pM to low nM range) antagonists of VLA-4 (very late activating antigen-4), a key cell surface integrin which plays an important role in inflammation. As a result, they show potential as drugs for the treatment or prevention of diseases such as asthma, rheumatoid arthritis and multiple sclerosis. Deaton and co-workers at GlaxoSmithKline designed the ester **2.22**, containing a highly active azetidine cyanamide “warhead”, as an extremely potent (IC₅₀ 48 pM) inhibitor of cathepsin K (a cysteine protease target for the treatment of osteoporosis).³⁴ O’Dowd and co-workers synthesised a series of novel antibacterial azetidine lincosamides **2.23**,³⁵ several of which showed equal or better activity than clindamycin, the currently most commonly used lincosamide antibiotic. Finally,

González-Muñiz and co-workers have reported the preparation of the ester **2.24** and various dipeptides **2.25**, which show anti-HCMV (human cytomegalovirus) activity *via* the inhibition of HCMV serine protease.^{36,37}

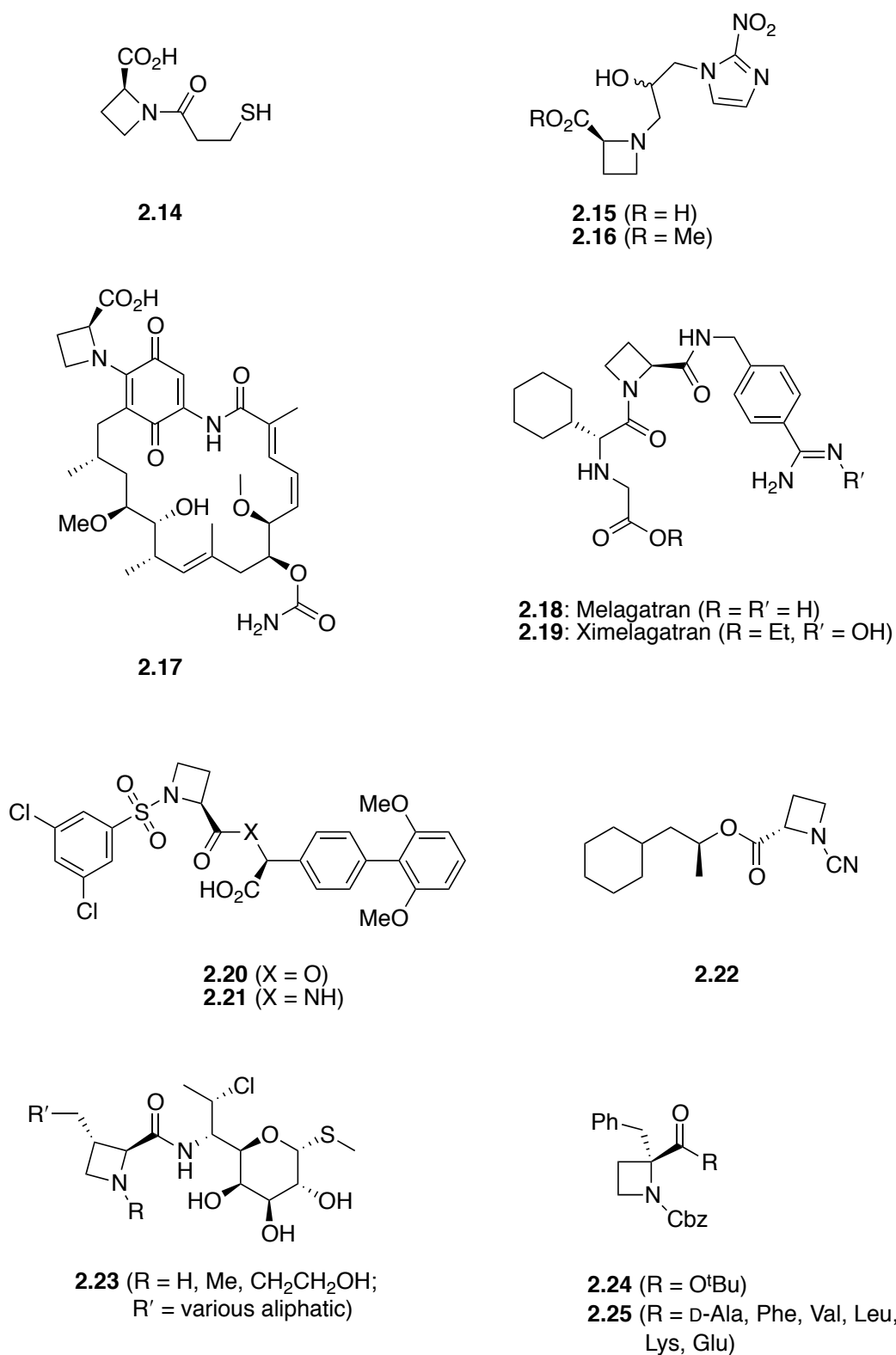


Figure 2.6: Structures of some L-Aze derived synthetic drugs

Although as yet less numerous, there also exist other examples of azetidine-containing natural products which are discrete from L-Aze in origin. Penaresidins A (**2.26**) and B (**2.27**), two sphingosine-like alkaloids containing a dihydroxylated azetidine moiety, were isolated as a mixture from the Okinawan marine sea sponge *Penares* sp. by Kobayashi and co-workers (Figure 2.7).^{38,39} When tested as a mixture they were found to act as potent actomyosin ATPase activators, elevating the activity of ATPase in myofibrils from rabbit skeletal muscle to 181% of the control at a concentration of 30 μ M. They therefore represent potentially useful chemical probes for the study of molecular mechanisms in actin-myosin muscular contractile systems, as they are one of only a very few substances which exhibit such activity.

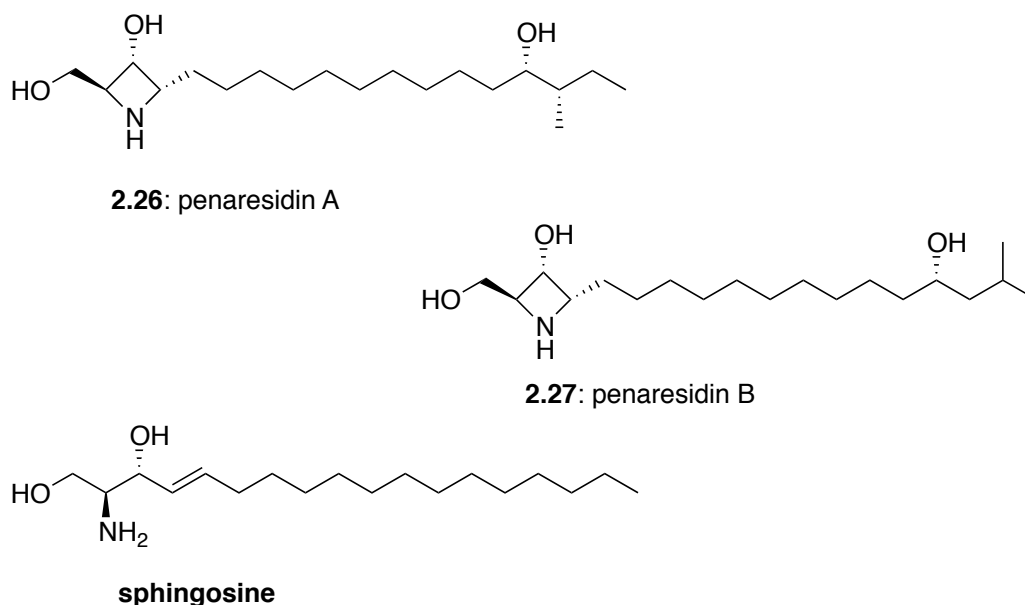


Figure 2.7: Comparison of the structures of sphingosine and the penaresidins

A closely related compound is penazetidine A (**2.28**, Figure 2.8), isolated from the Indo-Pacific marine sponge *Penares sollasi* by Crews and co-workers shortly after the discovery of the penaresidins.⁴⁰ They found **2.28** to be a potent inhibitor of protein kinase C (PKC), whilst being inactive towards protein tyrosine kinase (PTK). PKC inhibitors are of interest as potential leads in the development of new anticancer therapeutics, as PKC is involved in protein synthesis, gene

expression, cell proliferation, differentiation and tumorigenesis, and is often overexpressed in cancers.^{41,42}

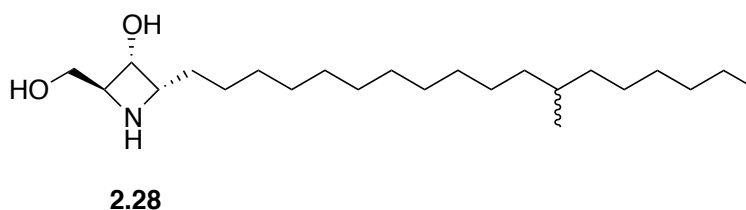


Figure 2.8: Penazetidine A

Finally, two further natural products most recently reported are the monoterpenoid indole alkaloid gelsemoxonine **2.29**, and the hexacyclic alkaloid calydaphinone **2.30**, featuring a unique 4-azatricyclo[5.2.2.0^{1,4}]undecan ring system (Figure 2.9). **2.29** was originally isolated by Lin and co-workers from *Gelsemium elegans*,⁴³ but their reported structure was wrong and was later re-assigned by Aimi and co-workers by way of X-ray crystallography and NMR studies.⁴⁴ **2.30** was isolated by Hao and co-workers from the leaves and twigs of *Daphniphyllum calycillum*.⁴⁵ To date, no biological studies of either **2.29** or **2.30** have been reported, but due to their unique structures they remain challenging targets of interest for total synthesis, as well as testing grounds for biogenetic studies.

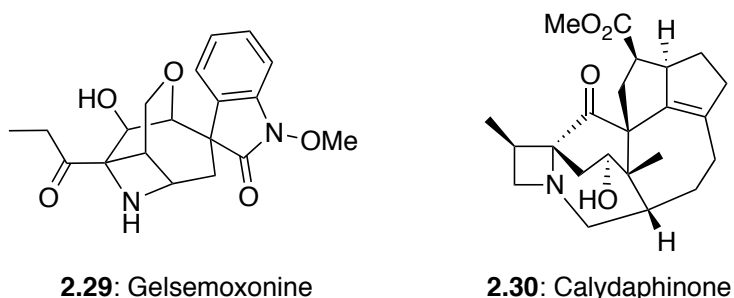


Figure 2.9: Gelsemoxonine and Calydaphinone alkaloids

There are numerous examples of synthetic drug candidates reported in the last 15 years which incorporate an azetidine motif, some of which are shown below (Figure 2.10).

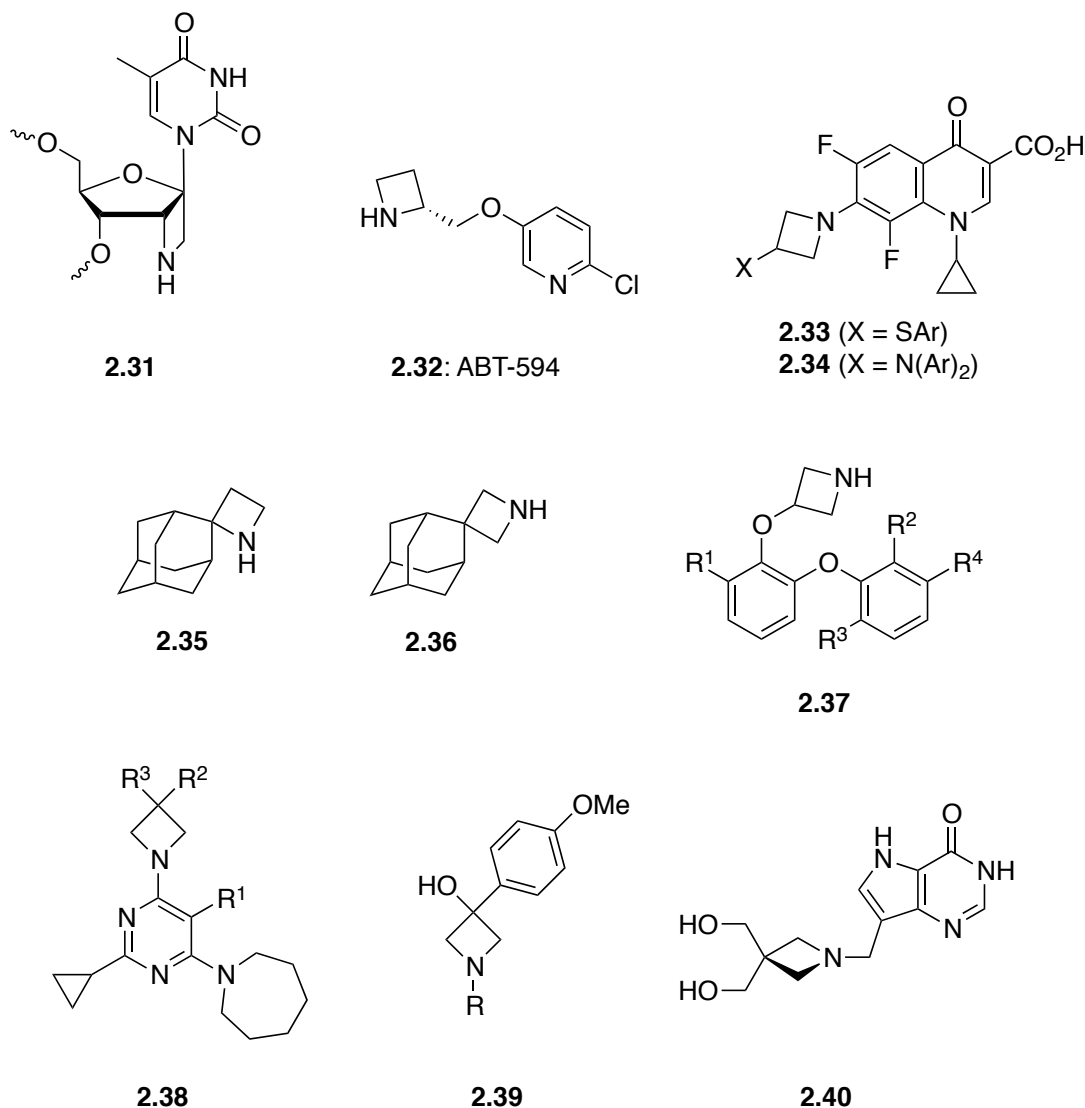


Figure 2.10: Some synthetic drugs containing an azetidine motif

Chattopadhyaya and co-workers reported the synthesis of an antisense oligonucleotide (AON) containing the *North-East* conformationally constrained azetidine-bridged nucleoside **2.31** as an RNase H activator; a common enzymatic target for the regulation of gene expression.⁴⁶ ABT-594⁴⁷ (**2.32**) is a very effective non-opioid analgesic, being an extremely potent (K_i 37 pM) neuronal nicotinic acetylcholine receptor (nAChR) inhibitor; it shows equal efficacy of severe pain relief to that of morphine, whilst avoiding the inducement of opioid-like withdrawal or physical dependency.⁴⁸ Nagao and co-workers reported the synthesis of a series of fluoroquinolones **2.33** and

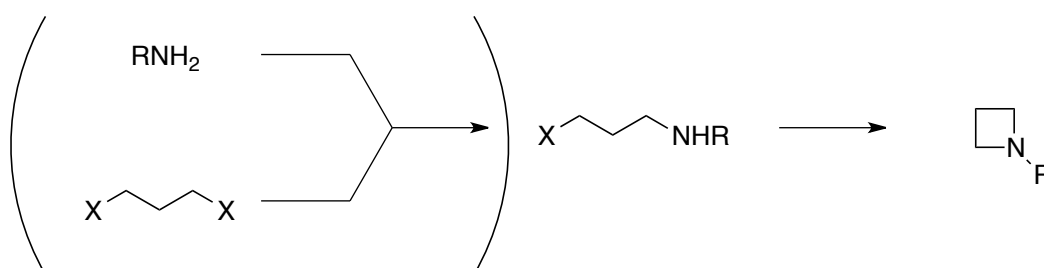
2.34 as potent antibacterial agents,^{49,50} some of which showed a greater activity against methicillin-resistant *Staphylococcus aureus* (MRSA) than that of clinically used fluoroquinolones, such as levofloxacin. Kolocouris and co-workers have reported the preparation of the azetidine adamantane spiro heterocycles **2.35** and **2.36**, which were found to exhibit potent anti-influenza A (H3N2) activity.⁵¹ Pettersson and co-workers recently designed and prepared a series of variously-functionalised azetidine aryl ethers **2.37** with combined noradrenaline reuptake inhibitor (NRI) and serotonin 1A (5-HT_{1A}) partial agonist activity,⁵² which may offer a novel therapeutic approach to the treatment of neuropsychiatric disorders such as ADHD, depression and anxiety. A series of *N*-aryl azetidines **2.38** which possess potent dual muscarinic M₃ antagonist and PDE4 (phosphodiesterase 4) inhibitory activities have been prepared by Provins and co-workers.⁵³ Compounds with such activity are a relatively new class of drug which combine bronchodilating and anti-inflammatory properties as a potential treatment for COPD (chronic obstructive pulmonary disease). Wanner and co-workers reported the synthesis of the 3-branched azetidines **2.39** amongst a series designed as γ -aminobutyric acid (GABA) reuptake inhibitors;⁵⁴ drugs used in the treatment of various CNS disorders such as epilepsy, migraine, Parkinson's disease, Huntington's chorea and depression. Finally, Evans and co-workers have reported the synthesis of the *N*-linked nucleoside analogue **2.40** amongst a series of azetidine based transition state analogue inhibitors of *N*-ribosyl hydrolases.⁵⁵ They found **2.40** to be a very potent (K_i 229 pM) inhibitor of purine nucleoside phosphorylase (PNP). Due to its crucial role in purine nucleoside metabolism and in T-cell function, PNP has been an enzyme target of great interest over the last few decades for several potential applications, such as the treatment of T-cell leukemias and lymphomas, for the suppression of tissue rejection in organ transplant patients, and in the treatment of autoimmune diseases.⁵⁶

2.1.2 Methods of preparation

Broadly speaking, the reported strategies for synthesising azetidine rings generally fall into one of five categories: i) cyclisations *via* nucleophilic substitution by an amine nucleophile, i.e. C-N bond formation; ii) reduction of an existing azetidine-2-one motif; iii) cyclisations *via* C-C bond formation; iv) [2 + 2] cycloadditions; and v) ring rearrangements. These methods are briefly outlined below.

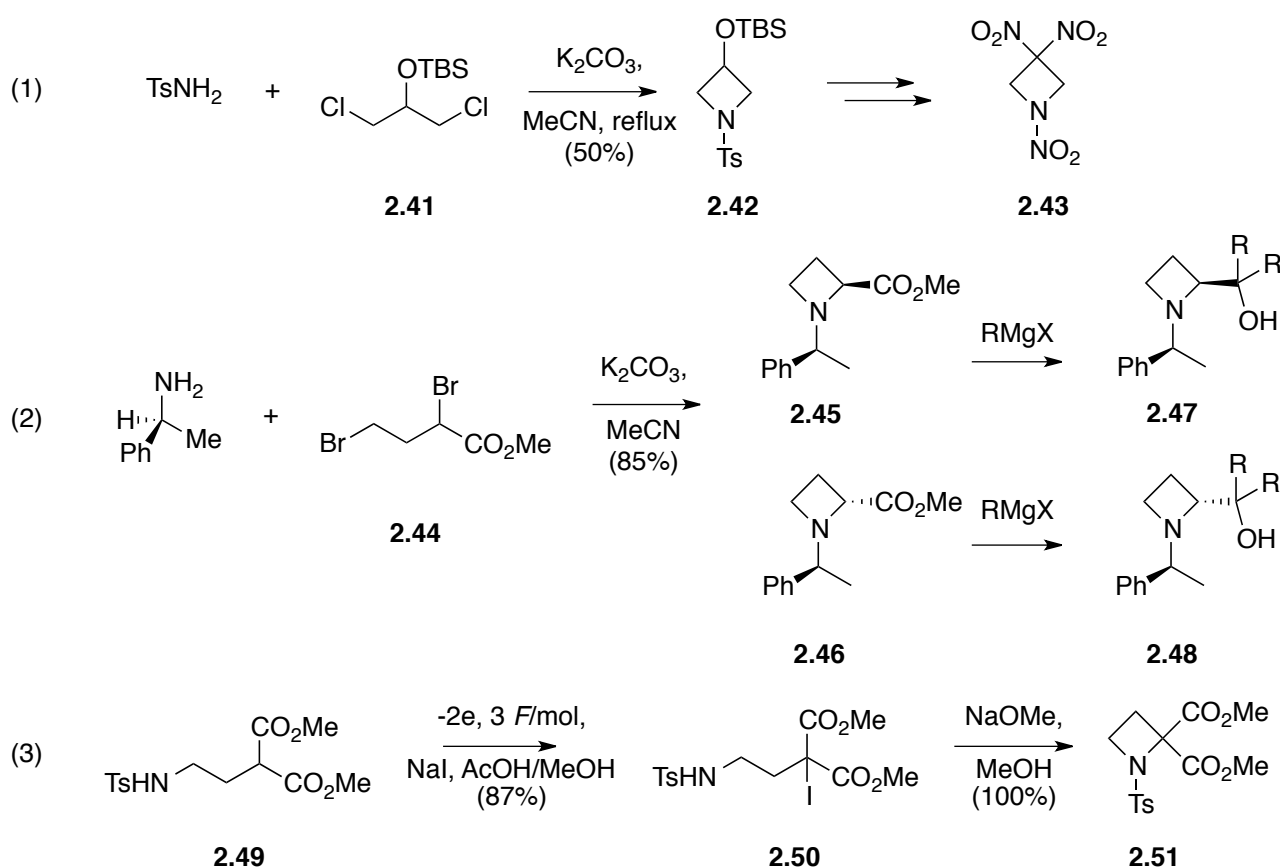
2.1.2.1 Cyclisations *via* nucleophilic substitution by amines

This is the most commonly employed strategy for the formation of azetidine rings,² no doubt due to its inherent flexibility and the high yields generally obtained. The reaction can be considered in its most general form as shown in Scheme 2.1: a 1,3-cyclisation of an internal amine onto an appropriate leaving group X, either from a preformed chain (a mono-displacement) or *via* the generation of the cyclisation substrate *in situ* from the intermolecular nucleophilic substitution of an amine on an intermediate bearing two leaving groups (an overall di-displacement). The main drawback of this method is the sometimes appreciable amounts of elimination of HX which can compete with the difficult cyclisation to the strained four membered ring.



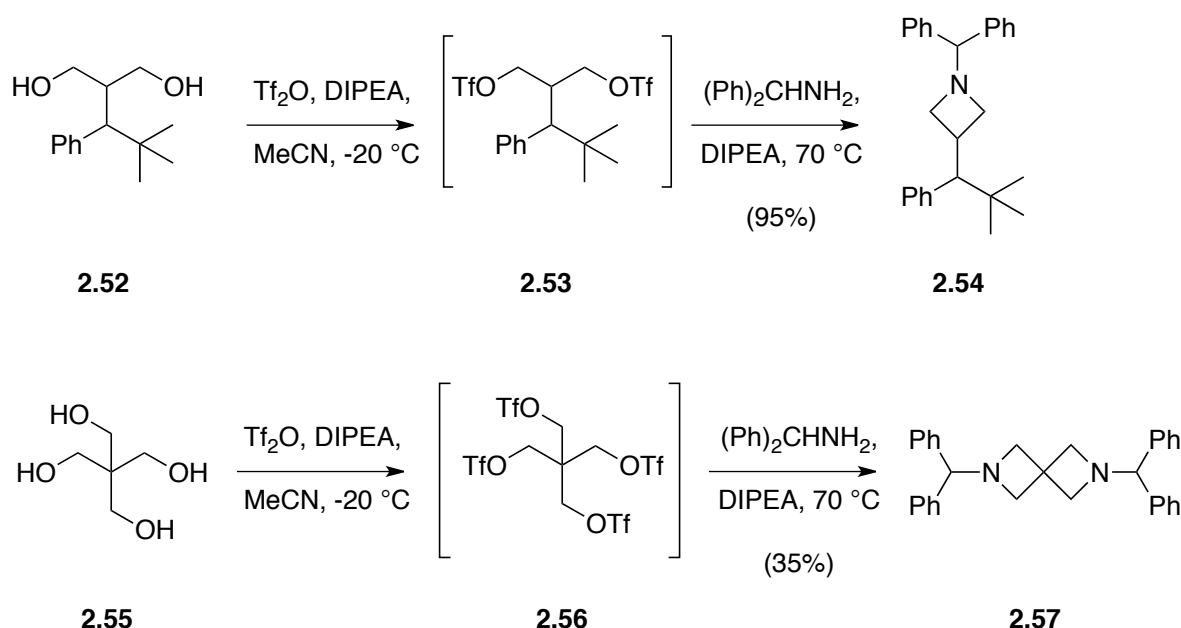
Scheme 2.1: General cyclisation *via* C-N bond formation

The leaving groups X are commonly halides; most often chloride⁵⁷⁻⁶⁷ or bromide^{65,68-81} due to their ease of access and stability with comparison to iodides, although the latter have also been employed.⁸²⁻⁸⁶ Representative examples of the use of chloride (Eq. 1), bromide (Eq. 2) and iodide (Eq. 3) leaving groups are illustrated below (Scheme 2.2). Axenrod and co-workers reported the cyclisation of *p*-toluenesulfonamide with the 1,3-dichloropropyl derivative **2.41** under basic conditions in refluxing acetonitrile to generate the *N*-tosyl azetidine **2.42**, which was ultimately converted into the explosive trinitroazetidine **2.43**.⁶⁵ Zwanenberg and co-workers prepared the azetidine carbinol auxiliaries **2.47** and **2.48** as ligands for the boron-catalysed Diels-Alder reaction: reaction of (*S*)- α -methylbenzylamine with methyl 2,4-dibromobutanoate **2.44** and potassium carbonate furnished the diastereomeric azetidine esters **2.45** and **2.46**, which were then converted into **2.47** and **2.48** by reaction with various Grignard reagents.⁷⁴ Shono and co-workers reported the anodic oxidation of tosylsulfonamide derivative **2.49** to give the iodide **2.50**, which on treatment with sodium methoxide underwent quantitative cyclisation to the azetidine **2.51**.⁸²



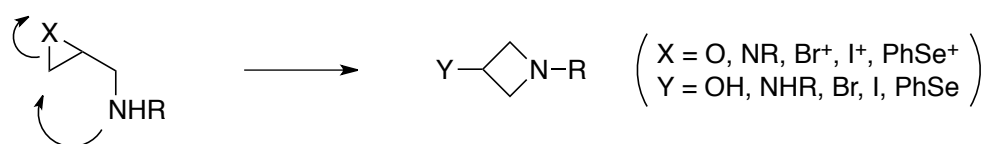
Scheme 2.2: Uses of halide leaving groups in C-N bond forming cyclisations

Another highly popular approach, and a variant on the above theme, is the use of sulfonic esters as leaving groups, *via* their corresponding alcoholic precursors. Mesylates are the most commonly employed,⁸⁷⁻¹⁰³ followed by tosylates,¹⁰⁴⁻¹¹¹ and least frequently with triflates.^{55,112-114} In light of the difficulty of these cyclisations, the fact that triflates are so rarely used is somewhat surprising given their greatly enhanced reactivity with respect to the other sulfonic esters, especially in cyclisations involving bulky substituents. This is illustrated nicely by the examples shown in Scheme 2.3 below, reported by Hillier and co-workers.¹¹³ The branched diol **2.52** was converted to its di-triflate ester **2.53** with trifluoromethanesulfonic anhydride and DIPEA in acetonitrile, and without isolation was cyclised to the sterically bulky azetidine **2.54** in excellent yield *via* reaction with benzhydrylamine and DIPEA at elevated temperature. This same approach was even successfully applied to pentaerythritol **2.55** in a *bis*-cyclisation strategy, furnishing the spiro-fused *bis*-azetidine **2.57** on reaction with benzhydrylamine *via* a tetra-triflate intermediate **2.56**.

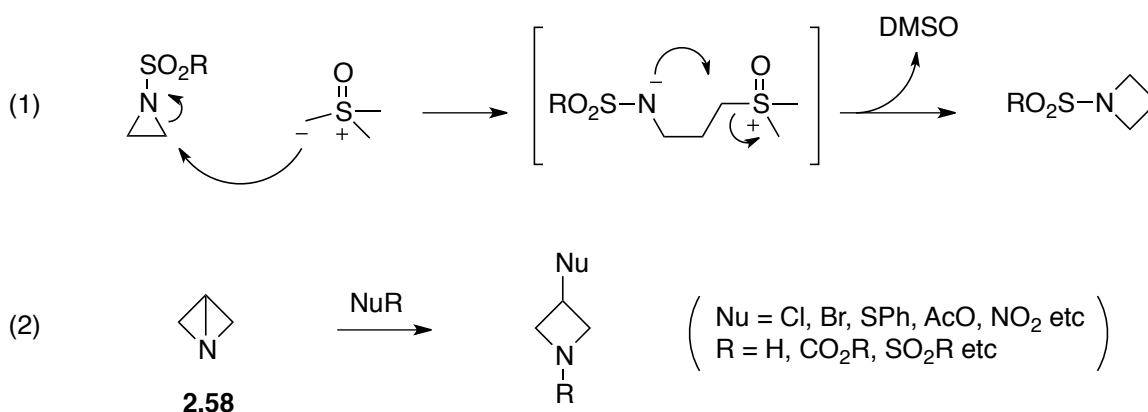


Scheme 2.3: Use of triflates as leaving groups during cyclisation

Another less commonly used variant of the strategy involves cyclisation *via* the opening of a three membered ring. The general reaction takes one of two forms: Type I and Type II. Type I reactions involve the opening of a pendant three membered ring with an internal amine to furnish the azetidine ring (Scheme 2.4); this has been observed for the opening of epoxides,¹¹⁵⁻¹²⁰ aziridines,¹²¹ bromonium,¹²²⁻¹²⁴ iodonium¹²⁵⁻¹²⁷ and seleniranium^{128,129} intermediates. Type II reactions are less common, and involve the opening of an aziridine ring with a non-amine nucleophile (Scheme 2.5). Reported examples involve either opening of a sulfonamide derivative with dimethylsulfoxonium methylide, followed by 4-*exo-tet* cyclisation of the resulting amide with concomitant expulsion of DMSO (Eqn. 1),^{130,131} or the generation of the highly reactive 1-azabicyclo[1.1.0]butane moiety **2.58**, followed by activation of the nitrogen and trapping with an appropriate nucleophile (Eqn. 2).^{49,50,132-134}



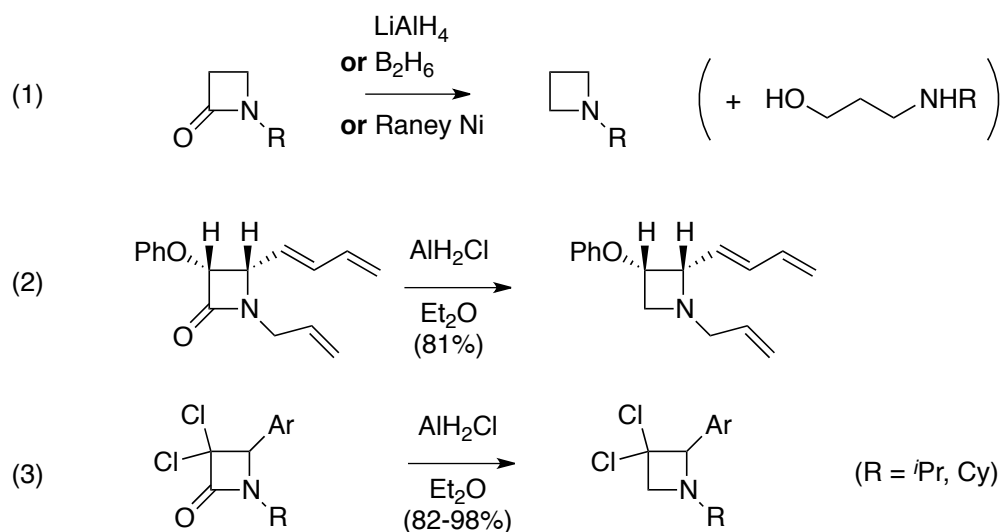
Scheme 2.4: Type I three membered ring opening



Scheme 2.5: Type II three membered ring openings

2.1.2.2 Reduction of azetidin-2-ones

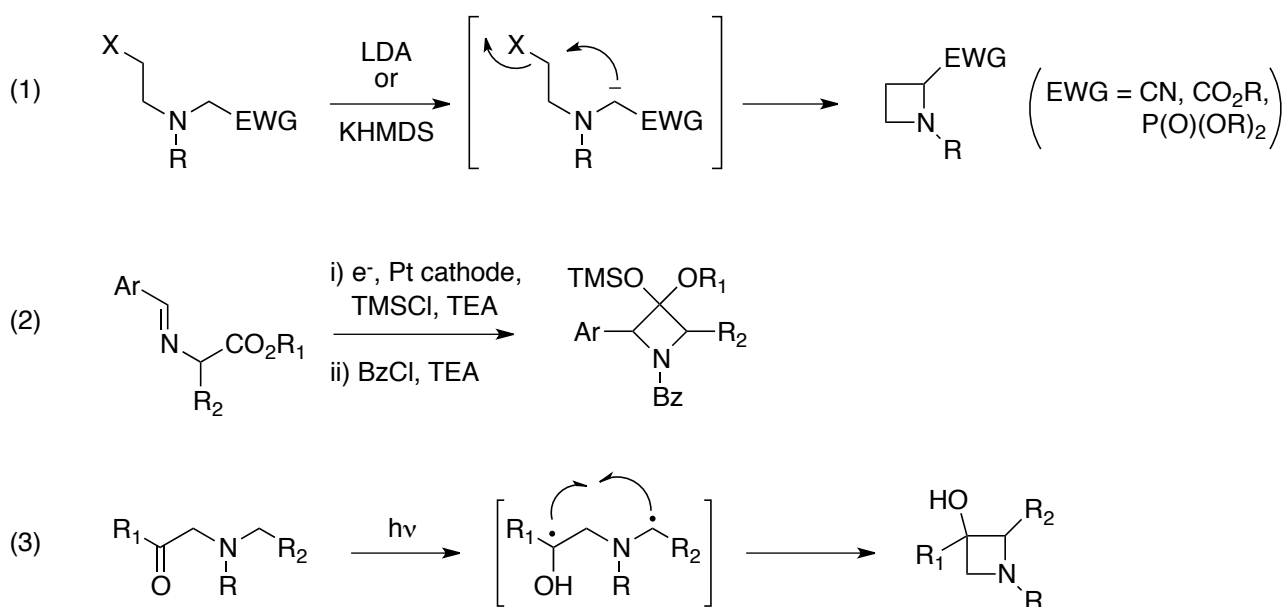
The preparation of azetidines from the reduction of an azetidin-2-one (β -lactam) precursor is another very commonly used approach found in the literature. This is perhaps unsurprising given the various well-established methods² that exist for the synthesis of azetidin-2-ones (fuelled by the great interest in their bioactivity), and the generally facile reduction process. Efficient and rapid reduction is typically predicated upon an *N*-substituted azetidin-2-one substrate, thus furnishing an *N*-substituted azetidine. Generally good yields have been reported with the use of lithium aluminium hydride,^{47,135-138} diborane in tetrahydrofuran,¹³⁹ diisobutylaluminium hydride¹⁴⁰ and Raney nickel,¹⁴¹ but by far the most commonly employed reagents are alanes in ether.^{135,136,142-154} This is primarily due to their greater efficacy, milder reaction conditions and tolerance of many other functional groups, but also because reductions involving LiAlH_4 , diborane or Raney nickel can give rise to 3-aminopropanol derivatives as side products from reductive ring cleavage of the hemiaminal intermediate (Eqn. 1, Scheme 2.6); an annoyance which is avoided with the use of alanes. Reported examples of their use are shown in Scheme 2.6 (Eqn. 2¹⁴⁸ and Eqn. 3¹⁴⁹), showing the good yields and chemoselectivity of the reduction.



Scheme 2.6: Examples of reduction of azetidin-2-ones

2.1.2.3 Cyclisations *via* C-C bond formation

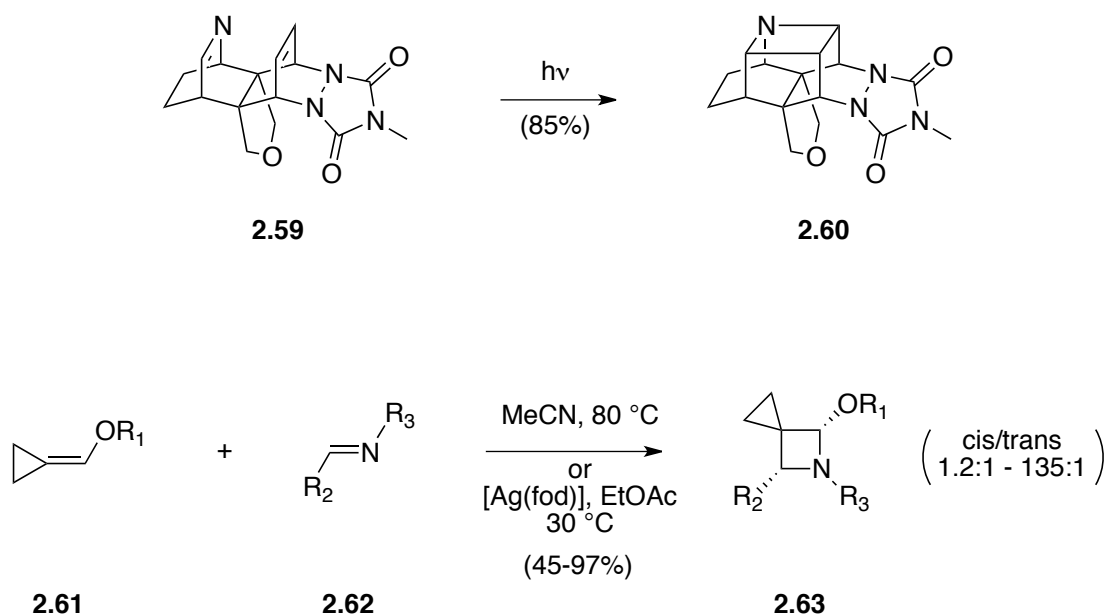
This approach invariably involves the cyclisation of an appropriately functionalised secondary or tertiary amine, or secondary imine. One method is the generation of a stabilised carbanion α to an amine, which then undergoes cyclisation by nucleophilic attack on an internal leaving group (most typically a halide,¹⁵⁵⁻¹⁶² but alternate use of a Michael acceptor has also been reported¹⁶³). This is illustrated in general terms in Scheme 2.7 below (Eqn. 1); the stabilising electron withdrawing groups used include carboxylic acids, esters, phosphonates and nitriles. Another related method is that of cyclisations involving carbonyl groups: either *via* TMSCl promoted electroreductive intramolecular cross-coupling of aryl imines with esters (Eqn. 2, Scheme 2.7);¹⁶⁴⁻¹⁶⁶ or *via* photochemical activation of α -aminoketones, leading to a radical coupling known as the Yang cyclisation¹⁶⁷⁻¹⁷⁵ (Eqn. 3, Scheme 2.7).



Scheme 2.7: Types of cyclisation involving C-C bond formation

2.1.2.4 [2 + 2] Cycloadditions

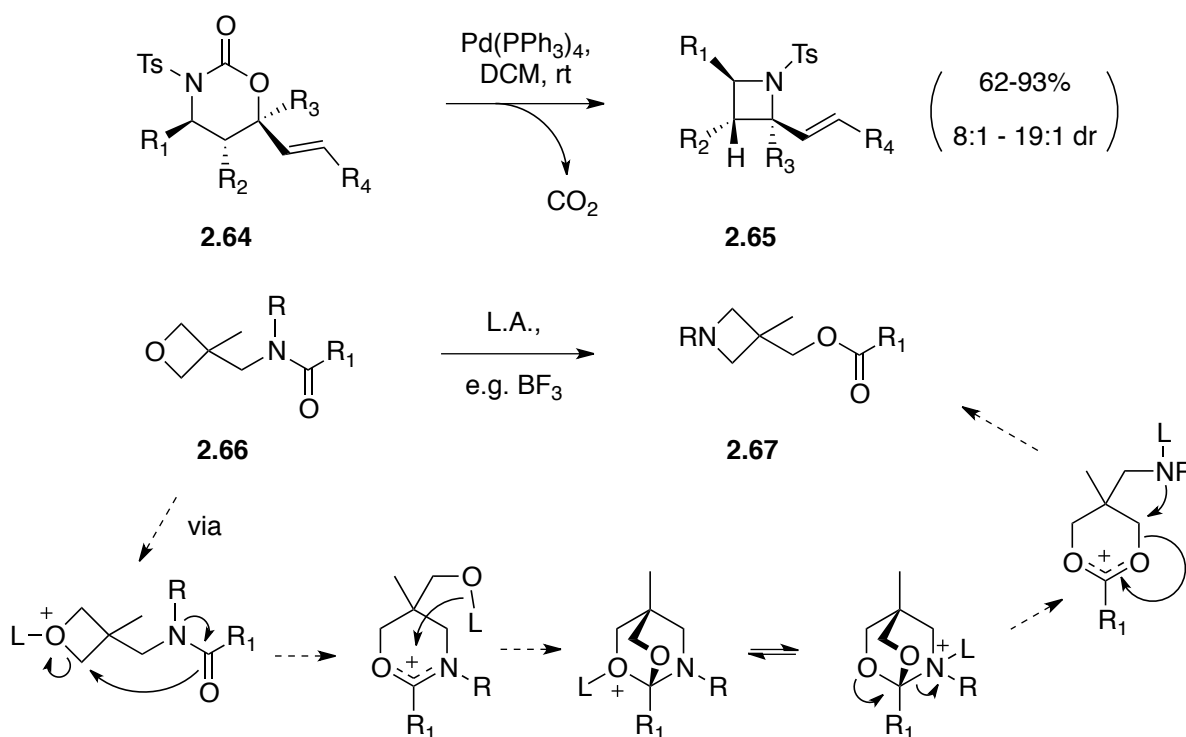
Azetidines are most commonly prepared by [2 + 2] cycloadditions only indirectly, *via* initial preparation of the analogous β -lactam from a Staudinger synthesis (the [2 + 2] cycloaddition of imines and ketenes), followed by reduction. Nonetheless, direct formation of the azetidine ring moiety has been reported by [2 + 2] cycloaddition of imines with alkenes or enol ethers,¹⁷⁶⁻¹⁷⁸ as illustrated by the examples below (Scheme 2.8). Prinzbach and co-workers reported the photocycloaddition of the rigid polycyclic substrate **2.59**, affording the caged compound **2.60**.¹⁷⁷ In contrast, [2 + 2] cycloadditions of imines with enol ethers are rarely employed due to the typically high energy barrier of the reaction; Sheeren and co-workers reported requirements of 12 kbar internal pressure, for example.¹⁷⁶ However, alkoxymethylene-functionalised cyclopropanes, such as **2.61**, are very good substrates for these reactions due to their high ring strain. Nakamura and co-workers reported the reaction of **2.61** with various imines **2.62** to give the spirocyclopropane azetidines **2.63**,¹⁷⁸ either under thermal activation or *via* the use of a silver catalyst, which improved diastereoselectivity.



Scheme 2.8: Azetidine formation *via* [2 + 2] cycloadditions

2.1.2.5 Ring rearrangements

Although often possessing quite specific substrate requirements, the following approaches are nonetheless valuable as they can furnish azetidines with unusual structures or patterns of functionality not easily accessed by other methods. Ring contractions represent the most commonly used type of rearrangement to furnish azetidines. Reported examples include contraction of dihydropyridines,¹⁷⁹⁻¹⁸² azabicyclohexanes,¹⁸³ oxazinanones,¹⁸⁴⁻¹⁸⁶ isoquinolines,¹⁸⁷ pyrroles,^{188,189} pyrrolidine-fused oxaziridines,^{190,191} and oxathiazines.¹⁹² An illustrative example is that reported by Tunge and Wang (Scheme 2.9),¹⁸⁶ which found that under palladium catalysis a series of 6-vinyl oxazinanones **2.64** underwent diastereoselective, decarboxylative ring contraction to form vinyl azetidines **2.65**. Rearrangements of existing four membered rings are also known; both from oxetanes^{193,194} and azetidin-2-ones.¹⁹⁵ For example, Kanoh and co-workers reported the Lewis acid catalysed isomerisation of tertiary oxetane amides **2.66** to azetidine esters **2.67**, with a proposed mechanism as shown (Scheme 2.9).¹⁹³

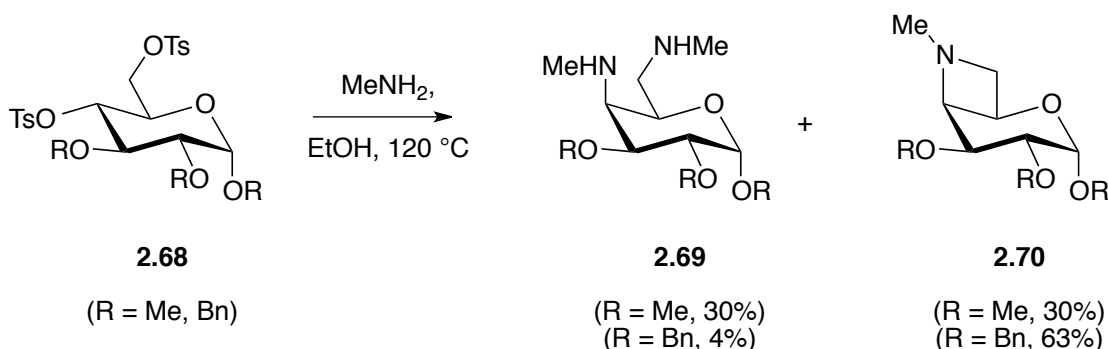


Scheme 2.9: Example ring rearrangements

2.1.3 Known azetidine iminosugars

To date there exist only a handful of azetidine analogues of iminosugars reported in the literature, and at the onset of this project only one reported study into the biological activity of these compounds; a study which, albeit limited in scope, yielded very interesting and promising results. These findings will be briefly discussed herein.

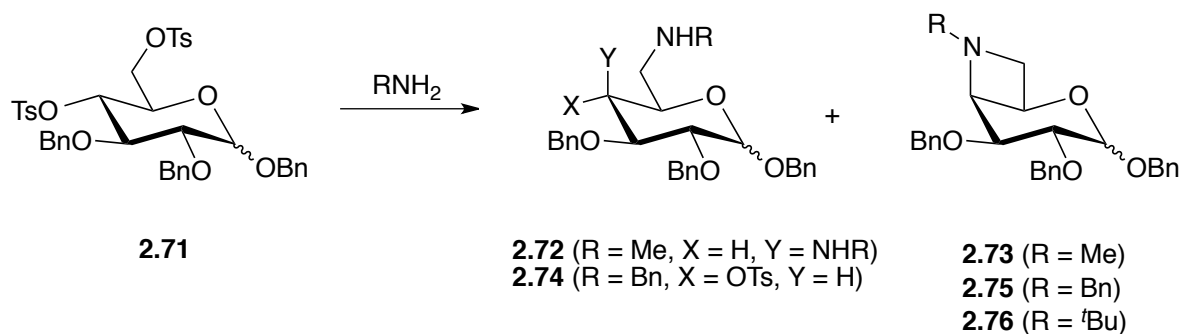
Hall and Inch were the first to report the preparation of an azetidine derivative of a monosaccharide.¹⁰⁴ During their attempts to prepare the 4,6-*bis*-amino galactose derivatives **2.69** from the corresponding glucose 4,6-di-tosylates **2.68** by treatment with ethanolic methylamine, they also observed the unexpected formation of the fused galactose azetidines **2.70** (Scheme 2.10). They did not attempt any further manipulations of **2.70**, however.



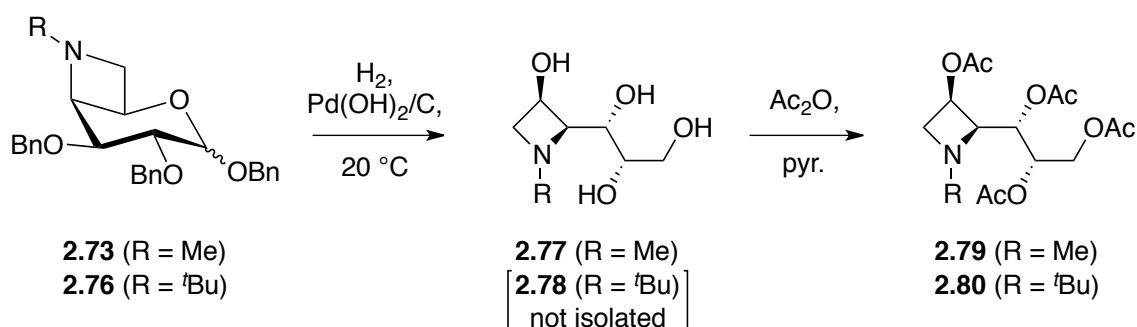
Scheme 2.10: D-Galacto azetidine derivatives from D-glucose

This strategy of cyclisation *via* 4,6-di-tosylates of hexopyranoses was expanded by Michaud and co-workers (Scheme 2.11).¹⁰⁶ On reaction of the anomeric mixture of 4,6-di-tosylates **2.71** with methylamine, they observed a similar outcome to Hall and Inch; namely a mixture of the *bis*-aminated product **2.72** and the corresponding azetidine **2.73**. In contrast, reaction of **2.71** with benzylamine furnished a mixture of the 6-amino-4-*O*-tosyl intermediate **2.74** and the desired azetidine **2.75**. Finally, reaction of **2.71** with *tert*-butylamine gave only the azetidine product **2.76**. In a follow-up publication,¹⁹⁶ they described the one-pot debenzylation and reduction of the *N*-

methyl and *N*-*tert*-butyl fused products **2.73** and **2.76** by hydrogenation with Pearlman's catalyst (Scheme 2.12), to afford the azetidine tetrols **2.77** and **2.78** respectively. Both were then acetylated to afford their respective per-acetates **2.79** and **2.80**, ostensibly for ease of purification.

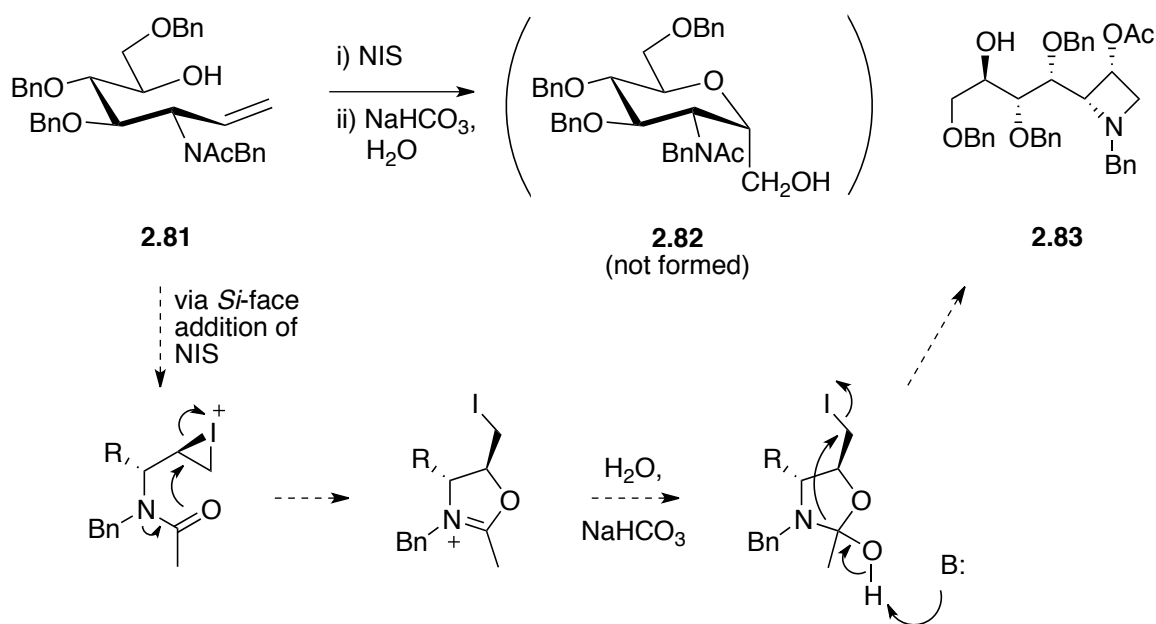


Scheme 2.11: Reaction of 4,6-di-tosylates with various amines

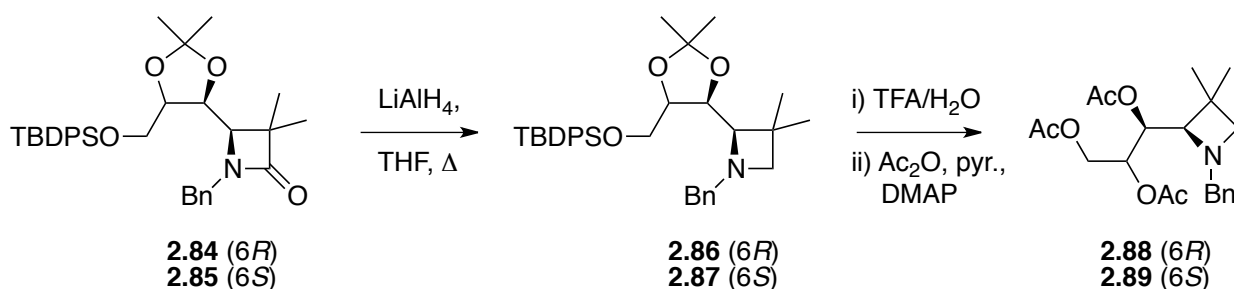


Scheme 2.12: Conversion of fused azetidines to azetidine tetrols

Martin and Eniade reported the unexpected formation of the azetidine pentitol **2.83** during their attempts at generating the α -C-glycosyl GlcNAc derivative **2.82** as a potential precursor to a homo analogue of UDP-GlcNAc (Scheme 2.13).¹²⁵ On treatment of the *D*-gluco-hept-1-enitol derivative **2.81** with *N*-iodosuccinimide they found that iodocyclisation involving the adjacent amide occurred rather than that with the expected 6-hydroxyl, furnishing **2.83** rather than **2.82**. They postulated a mechanism involving attack of the amide on the iodonium ring, followed by hydrolysis of the intermediate and base-induced collapse of the resulting orthoamide with concomitant C-N bond migration.

Scheme 2.13: Formation of azetidine pentitol *via* iodocyclisation

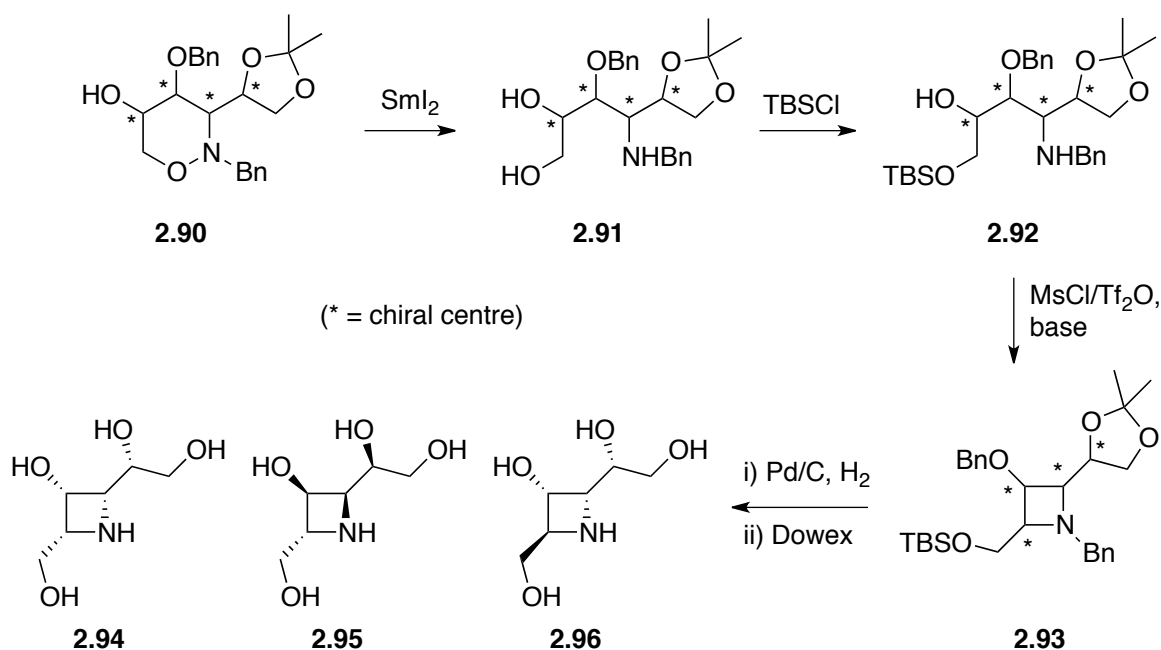
Soengas and co-workers have reported the preparation of two 3,3-dimethyl azetidine tri-acetates as an aside to their preparation of various polyhydroxylated β -lactams (Scheme 2.14).¹⁹⁷ Reduction of the protected β -lactams **2.84** and **2.85** with lithium aluminium hydride gave the azetidines **2.86** and **2.87**. Subsequent hydrolysis of the acetone and silyl protecting groups with aqueous trifluoroacetic acid, followed by per-acetylation afforded the azetidine tri-acetates **2.88** and **2.89**.



Scheme 2.14: Preparation of 3,3-dimethyl azetidine iminosugars

Reissig and Dekaris have prepared a series of enantiopure azetidine tetrols which differ from the previously reported examples in that they possess an additional hydroxymethylene group opposite the carbon chain on the azetidine ring, and thus more closely resemble well known pyrrolidine

iminosugars such as DMDP and its stereoisomers (Scheme 2.15).¹⁹⁸ Their strategy involved the reductive ring-opening of a series of polyhydroxylated 1,2-oxazines **2.90** with samarium iodide, to give the diols **2.91**. Protection of the primary alcohol as the TBS ethers **2.92**, sulfonylation of the remaining unprotected secondary alcohol and cyclisation gave the protected azetidines **2.93**. Subsequent debenzoylation and acid hydrolysis of the acetonide and silyl groups afforded the azetidine tetrols **2.94-2.96**.

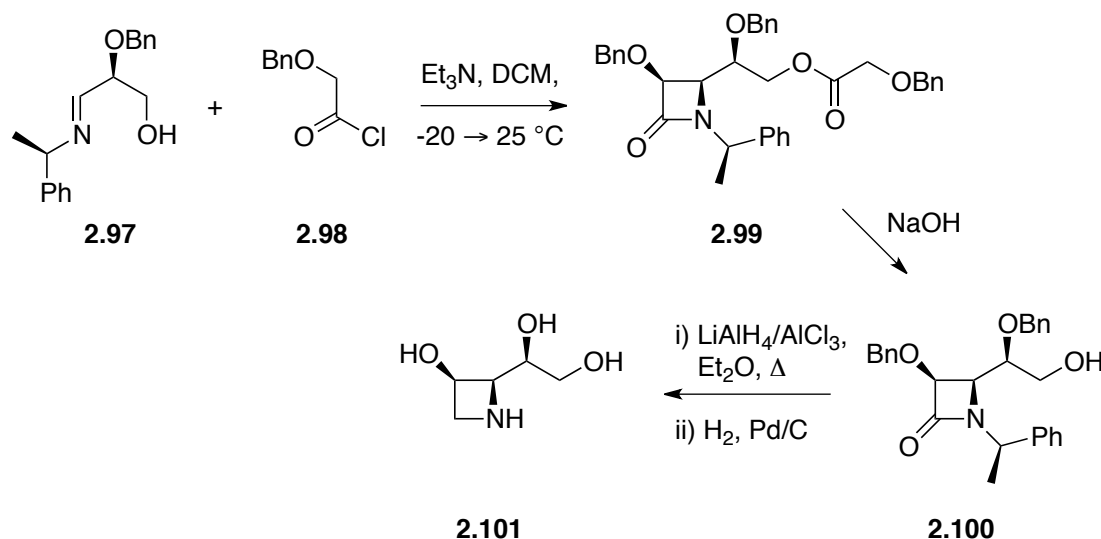


Scheme 2.15: Preparation of azetidine tetrols *via* 1,2-oxazines

Jäger and co-workers reported the preparation of the *L-xylo* configured azetidine triol **2.101** (Scheme 2.16).¹³⁶ The [2 + 2] cycloaddition of the chiral imine **2.97** with the ketene generated *in-situ* from benzyloxyacetyl chloride **2.98** gave the β -lactam **2.99**. Hydrolysis of the terminal α -alkoxy ester gave the alcohol **2.100**, and reduction of the β -lactam and global deprotection then furnished **2.101**. They found **2.101** to be a potent inhibitor of glucoamylases: EC 3.2.1.3[†] *Aspergillus niger* IC₅₀ 30.9, K_i 41.7 μ M; *Rhizopus mold* IC₅₀ 4.0, K_i 7.6 μ M. Furthermore, they also

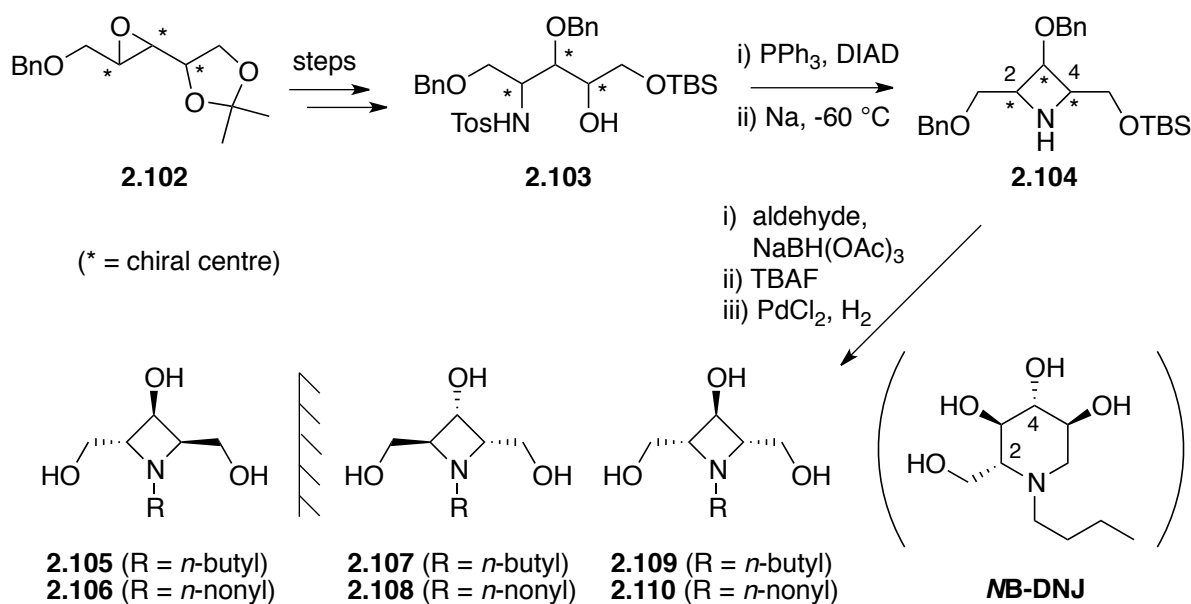
[†] International Union of Biochemistry and Molecular Biology (IUBMB) nomenclature for glucan 1,4- α -glucosidases.

found it to be a highly selective inhibitor, as it exhibited no activity towards any of the other screened glycosidases.



Scheme 2.16: Preparation of biologically active L-xylo azetidine triol

Finally, Lee and co-workers very recently reported the preparation of a number of *N*-alkylated azetidine triols **2.105-2.110** (Scheme 2.17) as analogues of *N*-butyl-deoxynojirimycin (NB-DNJ), with the aim of developing potential new leads for non-hormonal male contraceptive agents.¹⁹⁹ Their syntheses involved the derivatisation of the epoxides **2.102**, furnishing the tosylsulfonamides **2.103**. Ring formation was then accomplished *via* an internal Mitsunobu reaction, and reductive cleavage of the tosyl group gave the protected azetidines **2.104**. Reductive amination with butyraldehyde or nonyl aldehyde followed by deprotection then afforded the target compounds. They found **2.108** to be a selective inhibitor of rat-derived β-glucosidase 2 (IC₅₀ 70 μM), and **2.110** to be a selective inhibitor of both mouse- and rat-derived ceramide-specific glucosyltransferases (IC₅₀ 44 and 91 μM respectively). Furthermore, **2.110** was also found to be a potent inhibitor of α-glucosidase (*Saccharomyces cerevisiae*, IC₅₀ 600 nM) and of β-glucosidase (almond, IC₅₀ 20 μM).

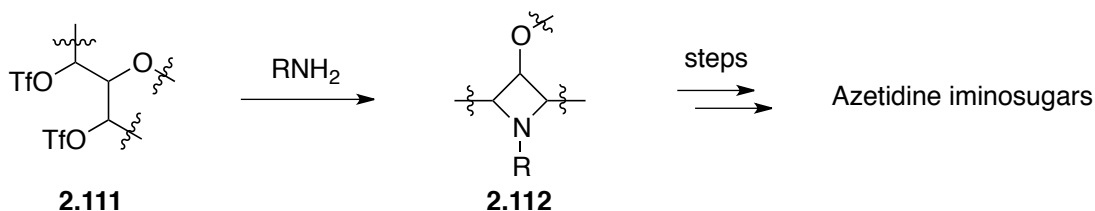


Scheme 2.17: Preparation of 2,4-imino-pentitol azetidines

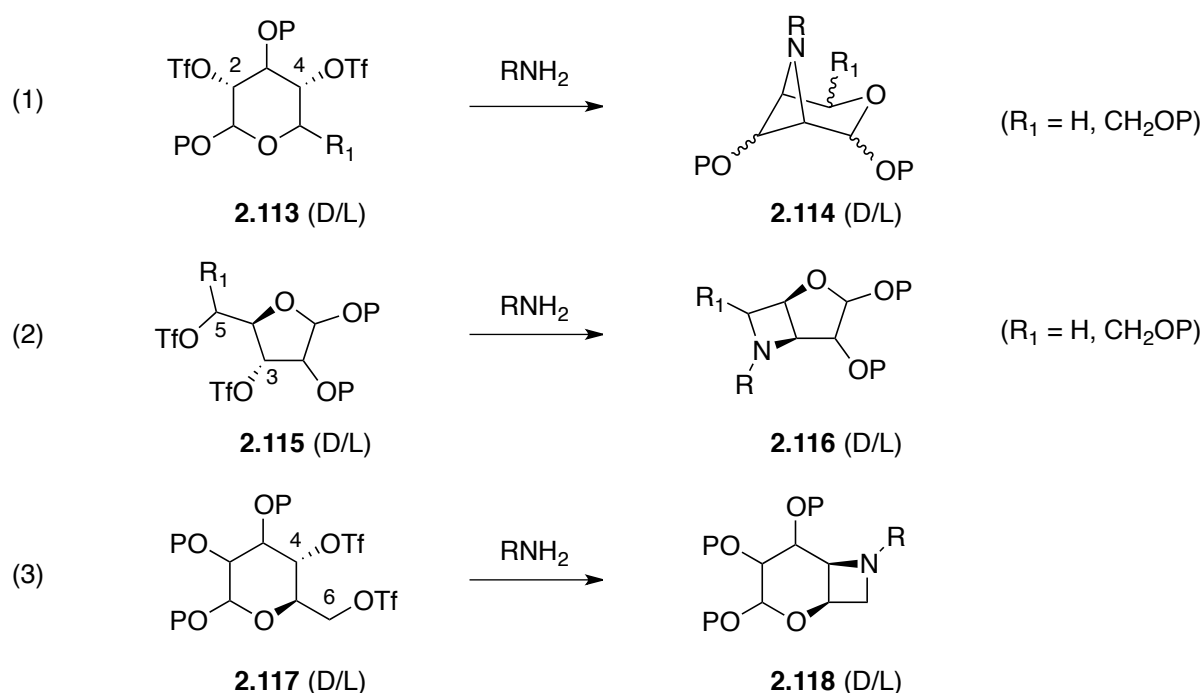
Clearly there is a growing interest in this class of compounds in the field of iminosugar research, and these last findings in particular are very encouraging, hinting at the possibility of an almost entirely untapped family of novel iminosugars with potentially highly interesting biological activities. We therefore wished to investigate both the scope and feasibility of a general synthetic approach towards preparing azetidine iminosugars from monosaccharide precursors, and if successful to utilise such methodology for the preparation of a range of these compounds in order to investigate their biological activity.

2.2 Synthesis and biological evaluation of azetidine iminosugars

Although very rare, there is precedent for the preparation of iminosugars *via* cyclisations of ditriflate derivatives of monosaccharides with amines. Only two such examples of this strategy have been previously reported: those involving the syntheses of a pyrrolidine^{200,201} and a piperidine²⁰² iminosugar. In light of this, and the fact that simple azetidines have also been efficiently prepared from ditriflate precursors, we envisaged the application of the same general approach towards the preparation of azetidine iminosugars from monosaccharides. Thus, the key ring-forming step would hopefully be achieved by treatment of a generic sugar-derived ditriflate **2.111** with amines to afford the general azetidine **2.112** (Scheme 2.18), which could then undergo further manipulation towards the desired azetidine iminosugars. Consequently, when considering aldopentoses and aldohexoses as substrates, the required relative 1,3-configuration of the ditriflate dictates the adoption of one of three possible general approaches: (i) that of displacement of a 2,4-ditriflate **2.113** of a pentose or hexose, affording the [1.1.3] bicyclic intermediate **2.114** (Eqn. 1, Scheme 2.19); (ii) displacement of a 3,5-ditriflate **2.115** of a pentose or hexose, affording the fused 4-5 bicycle **2.116** (Eqn. 2); and (iii) displacement of a 4,6-ditriflate **2.117** of a hexose, affording the fused 4-6 bicycle **2.118** (Eqn. 3). The use of a 1,3-ditriflate of an aldose is clearly less feasible in this scenario, as not only would it require the preparation of a labile anomeric triflate intermediate, but the azetidine ring if formed would be part of a fused, bicyclic hemiaminal, and likely to be highly unstable. This approach was therefore not considered.

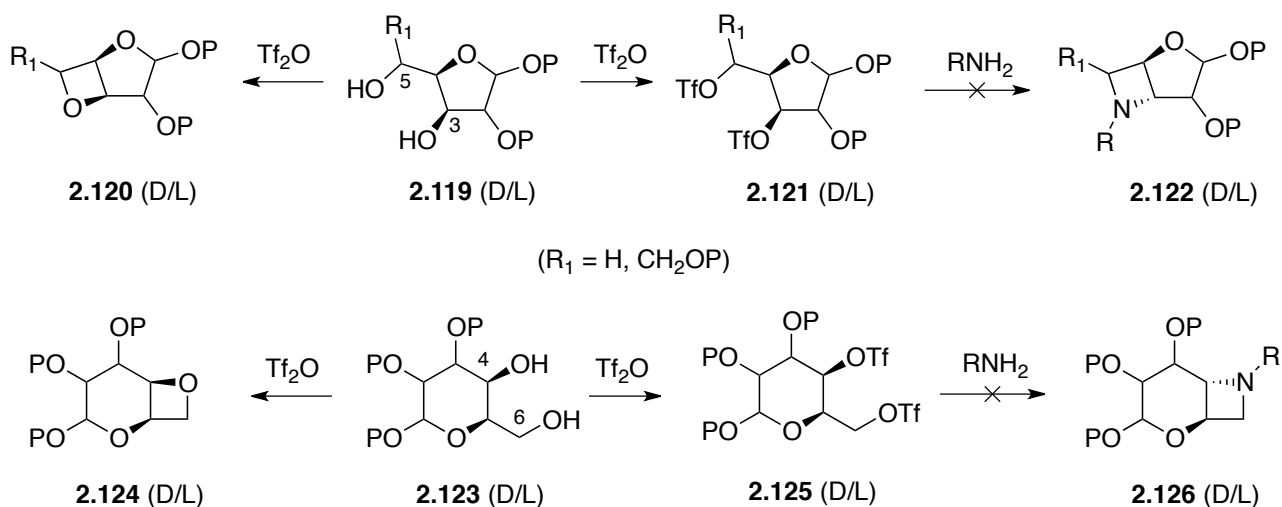


Scheme 2.18: Generic ditriflate displacement strategy



Scheme 2.19: Possible dinitrile displacement strategies (only relevant stereochemistry shown for clarity)

The stereochemical requirement for a *cis*-configured substrate in the 2,4-displacement strategy is self-explanatory. In the 3,5- and 4,6-displacement strategies, the requirement that the substrate have a *trans* relationship at C3/C4 with respect to the adjacent side chain can be rationalised when one considers the respective *cis*-configuration (Scheme 2.20). Firstly, triflation of the diols **2.119/2.123** could lead to unwanted formation of the oxetanes **2.120/2.124** by rapid cyclisation of the mono-



Scheme 2.20: Highly disfavoured *cis*-configured substrates

triflate intermediates. Secondly, and more importantly, if the ditriflates **2.121/2.125** could even be prepared efficiently, subsequent cyclisation with amines would clearly be extremely disfavoured as it would involve the formation of products **2.122/2.126** containing a *trans*-fused azetidine ring. Clearly, these considerations limit the pool of sugars which may be used to those of stereochemistry appropriate for the desired strategy.

2.2.1 Azetidine triols from aldopentofuranoses (3,5-displacement)²⁰³

The cyclisation of suitably protected 3,5-ditriflates of aldopentose furanosides was considered to be the most appropriate initial testing ground for the general strategy, as it represents the simplest case and the one in which we envisaged the least potential problems and greatest chance of success. The stereochemical considerations discussed above preclude the use of the *cis*-configured lyxose or xylose, therefore limiting the available starting materials to arabinose and ribose (Figure 2.11).

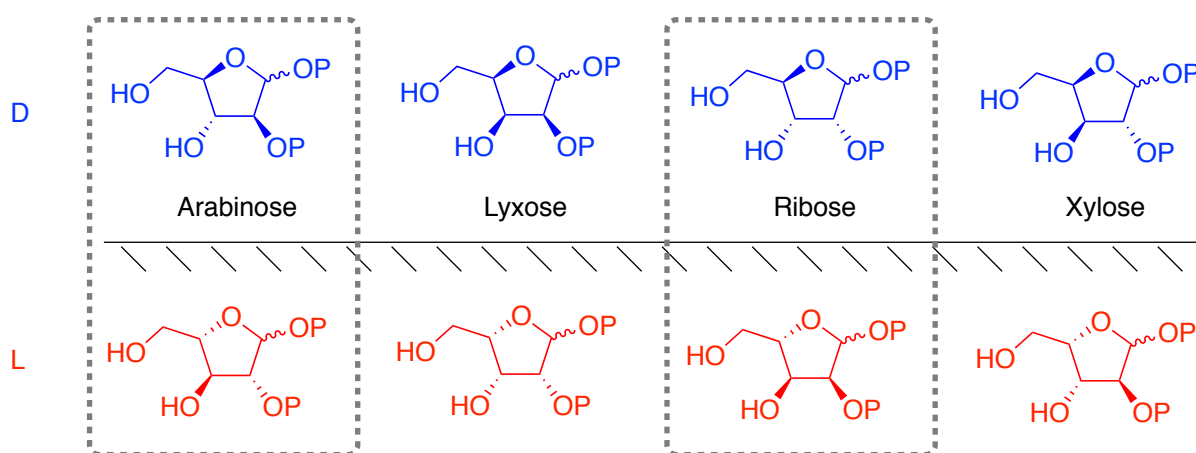
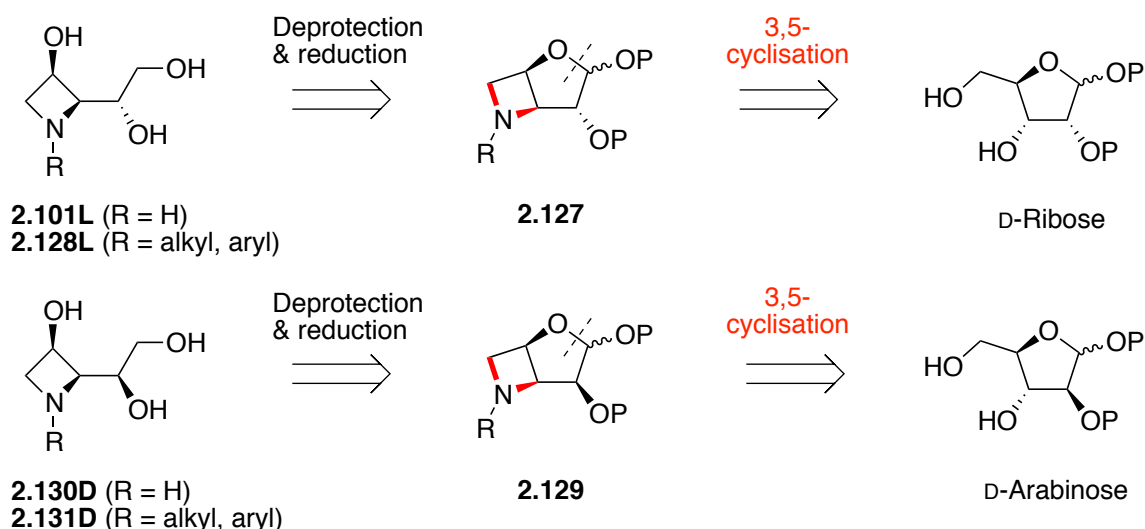


Figure 2.11: Aldopentose furanosides, showing those suitable for the 3,5-strategy (dashed boxes)

In a retrosynthetic sense, the known 1,3-dideoxy-1,3-imino-L-xylitol[‡] **2.101L** and its various *N*-substituted analogues **2.128L** arise from deprotection and reduction of the D-*xylo* fused bicycles

[‡] IUPAC guidelines for nomenclature in this instance gives a 3,5-dideoxy-3,5-imino-D-xylitol, but for the sake of consistency a naming convention according to lowest numbering of substitution is used for the azetidine iminosugars throughout this thesis (see Appendix A).

2.127, which in turn are formed *via* triflation and cyclisation of D-ribose (Scheme 2.21). This enables confirmation of the previously reported¹³⁶ biological activity of **2.101L**, as well as probing of the effects of *N*-substitution on glycosidase inhibition. Similarly, the 1,3-dideoxy-1,3-imino-D-arabinitol series **2.130D/2.131D** arises from the D-*lyxo* intermediates **2.129**, in turn formed from D-arabinose. Thus, the affects of C4-epimerisation on the biological activity will be explored.



Scheme 2.21: Retrosyntheses of D-arabinitol and L-xylitol azetidines

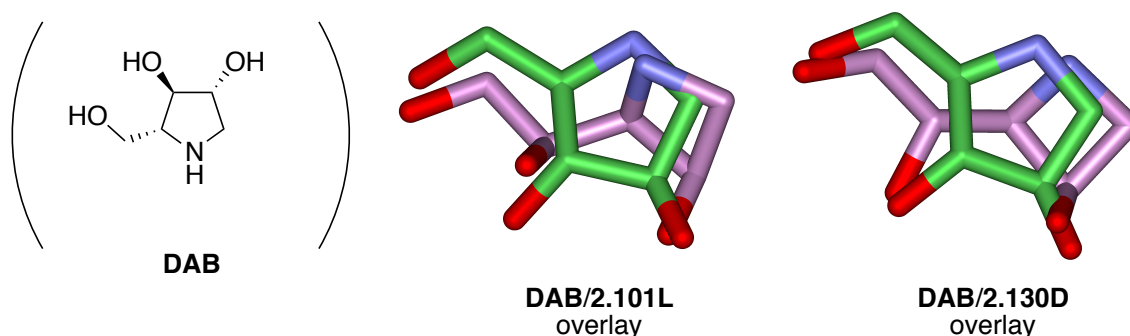
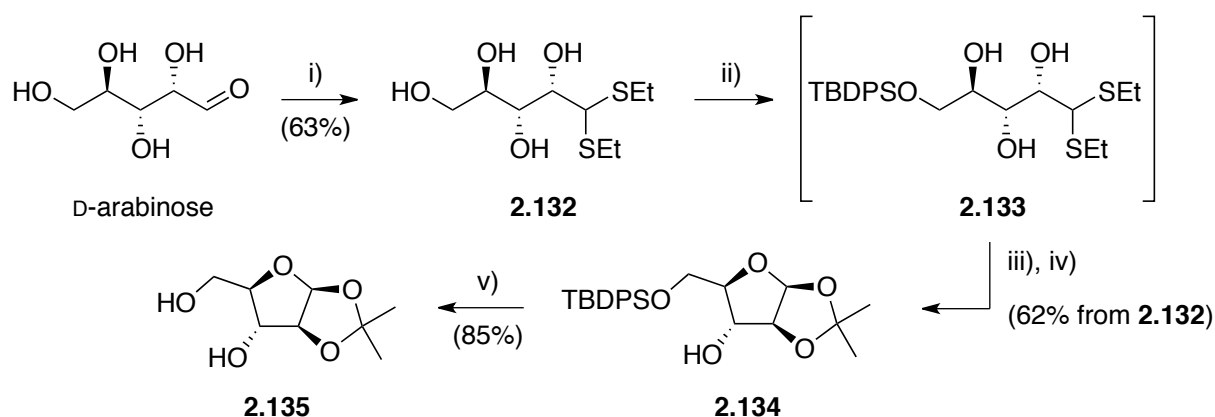


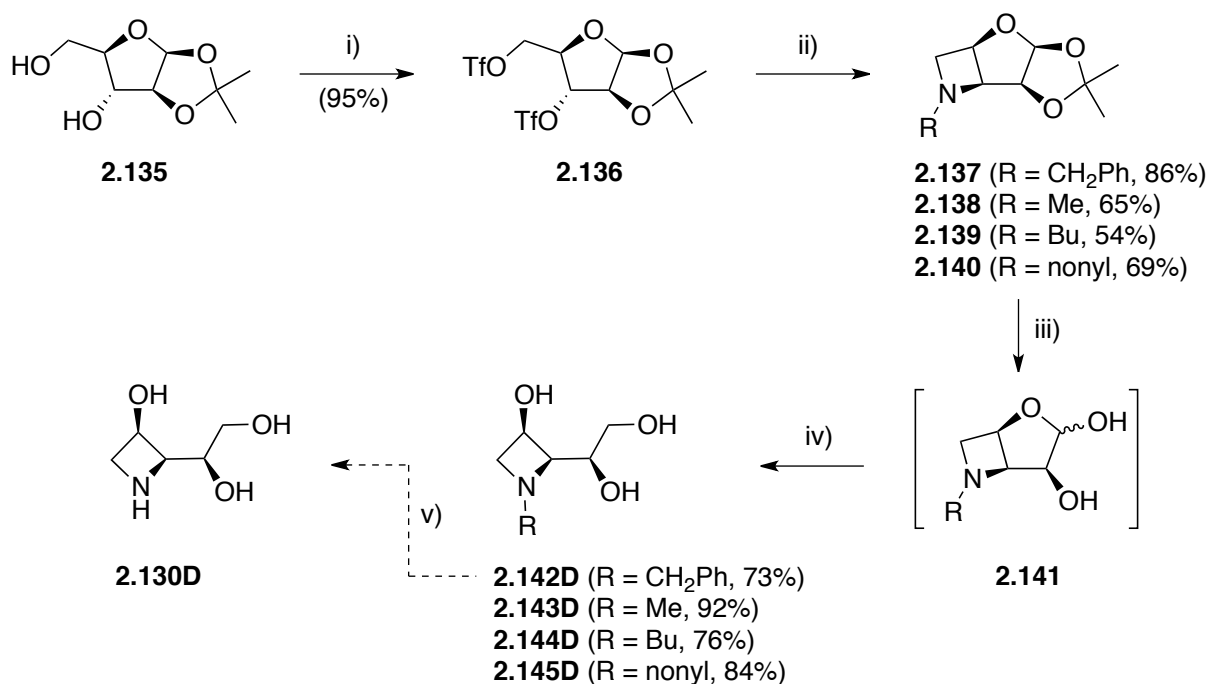
Figure 2.12: Structural overlays of DAB with L-*xylo* and D-*arabino* azetidines

The well known pyrrolidine iminosugar 1,4-dideoxy-1,4-imino-D-arabinitol (DAB, Figure 2.12) is a potent, competitive inhibitor of various glycosidases (including α -D-glucosidases)²⁰⁴ and of glycogen phosphorylase.²⁰⁵⁻²⁰⁷ The structural similarities of DAB with the respective L-*xylo* and D-*arabino* azetidines **2.101L** and **2.130D** are illustrated by the molecular overlays of their minimum

energy conformations (Figure 2.12). The reasonable degrees of overlap shown may be indicative of the biological activity reported for **2.101L**, and gave us reason to hope that **2.130D** would also exhibit glycosidase inhibition.

The synthesis from arabinose was the first to be attempted, as both enantiomers are cheap and readily available, and moreover the 1,2-protected intermediate is easier to prepare than the ribose equivalent. The following chemistry was later repeated by a colleague (Catherine Rutherford) for the mirror-image *L-arabino* series,²⁰⁸ but only the author's original work is presented here for brevity. D-Arabinose was first converted to its 1,1-diethyl-dithioacetal **2.132** on large scale (> 50 g) and in 63% yield by reaction with ethanethiol in aqueous hydrochloric acid (Scheme 2.22). Selective protection of the terminal alcohol was then achieved with *tert*-butyldiphenylsilyl chloride and imidazole in anhydrous *N,N*-dimethylformamide, affording the corresponding silyl ether **2.133**. Without purification, **2.133** was then treated to a one-pot desulfurisation/reprotection protocol; stirring with mercury(II) oxide and mercury(II) chloride in aqueous acetone induced cleavage of the thioacetal, and subsequent treatment with anhydrous copper(II) sulfate and camphorsulfonic acid in acetone resulted in selective 1,2-protection, affording the acetonide **2.134** in 62% yield over three steps. Finally, treatment with tetra-*n*-butylammonium fluoride in tetrahydrofuran effected desilylation in 85% yield, allowing ready access to multi-gram quantities of the key diol **2.135**.





Reagents and conditions: i) Tf₂O, pyr., DCM, -30 °C, 1 h; ii) either RNH₂ (3.5 eq., for butylamine and nonylamine), MeCN, rt, **or** RNH₂ (1.1 eq., for benzylamine and methylamine), DIPEA (2.5 eq.), MeCN, rt, 12-21 h; iii) 1:1 TFA/H₂O, rt, 18-24 h; iv) NaBH₄, H₂O (5:2:1 water/ethanol/1,4-dioxane for **2.145D**), rt, 19-24 h; v) various

Scheme 2.23: Syntheses of 1,3-imino-D-arabinitol azetidines

With **2.135** in hand, highly efficient sulfonylation was achieved by treatment with trifluoromethanesulfonic anhydride and pyridine in dichloromethane at -30 °C, affording the crystalline 3,5-ditriflate **2.136** in 95% isolated yield after column chromatography (Scheme 2.23). This intermediate was quite stable, and could be stored at low temperature (-20 °C) for months without incident. We were very pleased to find that cyclisation readily occurred on subsequent treatment of **2.136** with various primary amines in acetonitrile at room temperature – either using an excess of the amine alone, or with the addition of diisopropylethylamine as a co-base – affording the *N*-benzyl, -methyl, -butyl and -nonyl fused azetidines **2.137-2.140** in good yields (the structure of **2.137** was later confirmed by X-ray crystallographic analysis of its enantiomer).²⁰⁹ It is worth noting, however, that these are unoptimised results; with the exception of the reaction with benzylamine all cyclisations were only performed once under the stated conditions, and the *N*-methyl and -butyl products are somewhat volatile, implying that the isolated yields do not reflect the real yields in those cases. Also remarkable was the lack of any detectable products of competing

elimination, which was gratifying considering the difficulty of such a cyclisation. After some initial experimentation with both Brønsted and Lewis acid catalysed conditions for the hydrolysis of the acetonide functionality, successful deprotection was found to be best achieved by treatment with a 1:1 mixture of trifluoroacetic acid and water, giving the lactol intermediates **2.141**, which without isolation were then reduced with sodium borohydride, affording the *N*-benzyl, -methyl, -butyl and -nonyl 1,3-imino-D-arabinitol azetidine iminosugars **2.142D-2.145D** in good yields.

Initially, we conceived that general access to all of the parent N-H azetidines may be readily achieved *via* cleavage of their *N*-benzyl analogues under standard hydrogenation conditions. However, efforts at generating the N-H azetidine **2.130D** from **2.142D** by palladium catalysed debenzylation with molecular hydrogen proved problematic under a range of conditions (Table 2.1).

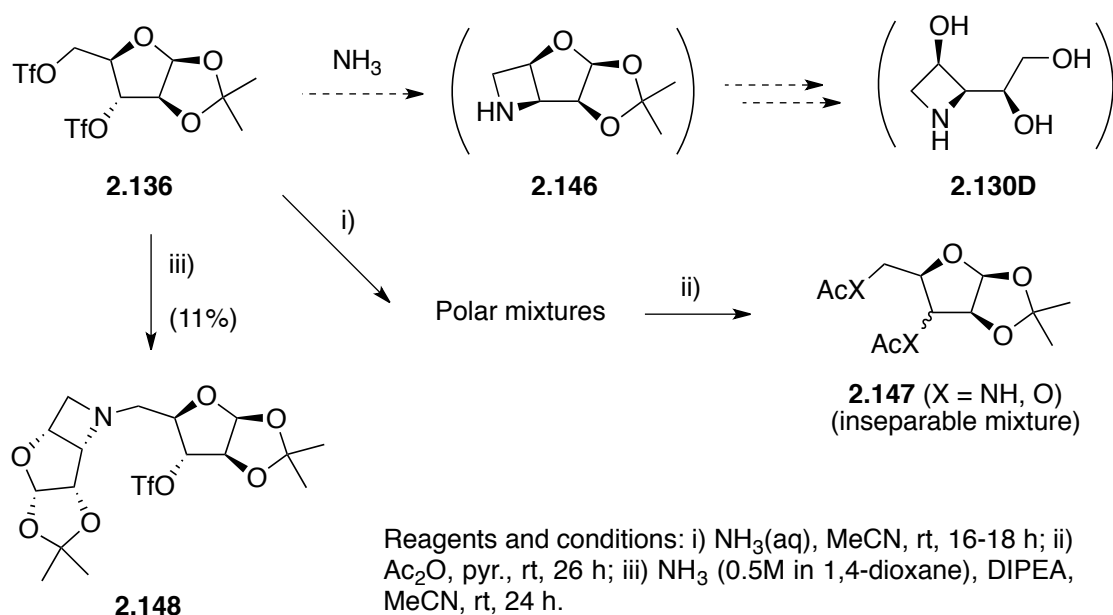
Reaction conditions	Result
Pd/C (10 mol. %), H ₂ , water, HCl, 24 h	No reaction
Pd/C (10 mol. %), H ₂ , water, HCl, 44 h	No reaction
Pd/C (10 mol. %), H ₂ , 1:1 EtOH/water, HCl, 42 h	No reaction
Pd black (50 mol. %), H ₂ , water, HCl, 48 h	2.130D (60%)
Pd black (30 mol. %), H ₂ , water, HCl, 23 h	No reaction
Pd black (50 mol. %), H ₂ , 10:1 water/dioxane, HCl, 20 h	No reaction
Pd(OH) ₂ /C (15 mol. %), 4:1 water/THF, HCl, 43 h	~ 80:20 mixture of 2.130D and side products (54%)

Table 2.1: Attempts at debenzylation of **2.142D**

The use of palladium on carbon under acidic conditions in either water or a mixture of ethanol and water resulted in no reaction at all (entries 1-3). One treatment with palladium black in aqueous acidic conditions was successful, affording **2.130D** in 60% yield (entry 4), but repeat attempts under very similar conditions gave no reaction whatsoever (entries 5 and 6). This capricious behaviour is presumably due to the varying effect of catalyst poisoning by the amine functionality.^{210,211} Pearlman's catalyst (palladium hydroxide on carbon) is known to be more effective than palladium

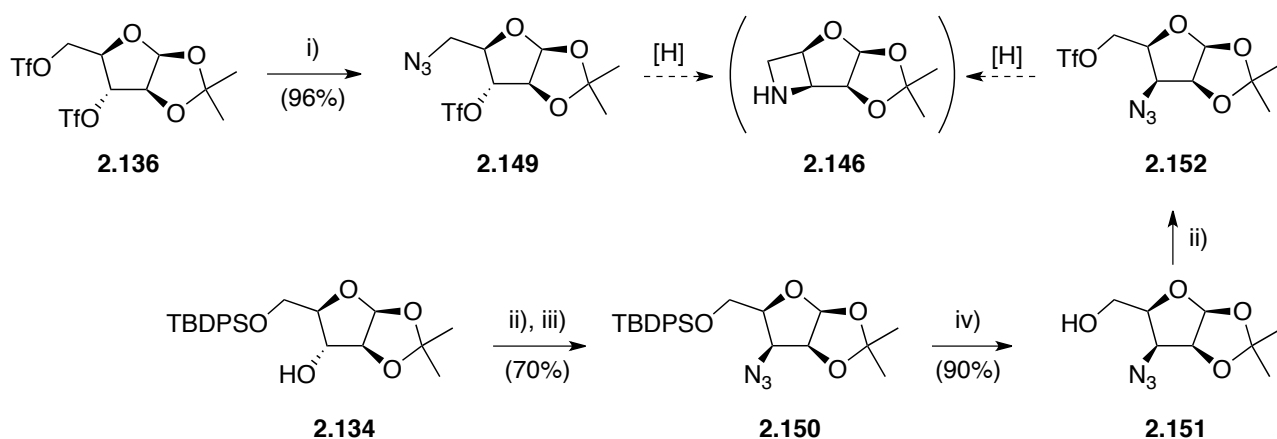
for the removal of *O*- and *N*-benzyl groups,²¹² and indeed substitution of the catalyst did result in successful deprotection in an acidified mixture of water and tetrahydrofuran (entry 7). However, these more forceful conditions also resulted in the unavoidable formation of two minor, inseparable impurities which appeared to be products of reductive cleavage of the azetidine ring; such an observation has been previously reported for the hydrogenolysis of an azetidine with Pearlman's catalyst.²¹³

These discouraging results led to attempts at various alternative methodologies towards general access of the N-H compounds. First, the use of ammonia in the di-displacement of ditriflate **2.136** was trialled with the aim of preparing the unsubstituted azetidine intermediate **2.146** directly, from which **2.130D** could potentially then be accessed (Scheme 2.24). However, reaction with aqueous ammonia in acetonitrile led to messy, highly polar unidentified mixtures. Acetylation of these crude mixtures led only to what appeared to be complex, inseparable mixtures of diacetates **2.147**. Reaction with anhydrous ammonia and DIPEA in acetonitrile also led to a complex mixture, of which the unstable, dimerised material **2.148** was the sole isolatable product in poor yield. This approach was not pursued further.



Scheme 2.24: Attempted cyclisations with ammonia

A potential alternative approach towards generating the protected N-H azetidine **2.146** directly was that of one-pot reduction and cyclisation of an azido-triflate precursor; there is precedent for the formation of an azetidine ring in this fashion from both azido-mesylate⁹⁶ and azido-tosylate¹⁰⁸ substrates. Thus, the regioisomeric *arabino* and *lyxo* azido-triflates **2.149** and **2.152** respectively both represent potential precursors to **2.146** in this strategy (Scheme 2.25). Highly efficient, selective displacement of the primary triflate in **2.136** was achieved by utilising the sparing solubility of sodium azide in acetone, affording the *arabino* substrate **2.149** in 96% yield. For the preparation of the *lyxo* substrate **2.152**, the TBDPS ether **2.134** was first converted to its 3-*O*-triflate ester by treatment with trifluoromethanesulfonic anhydride and pyridine in dichloromethane at low temperature, which without isolation was then heated with sodium azide in DMF, leading to introduction of azide with inversion of configuration to afford the D-*lyxo* silyl azide **2.150** in 70% yield over two steps. Cleavage of the silyl ether was then achieved with tetra-*n*-butylammonium fluoride, affording the alcohol **2.151** in 90% yield, and subsequent triflation gave the *lyxo* substrate **2.152**, which was used without purification for the subsequent reactions.



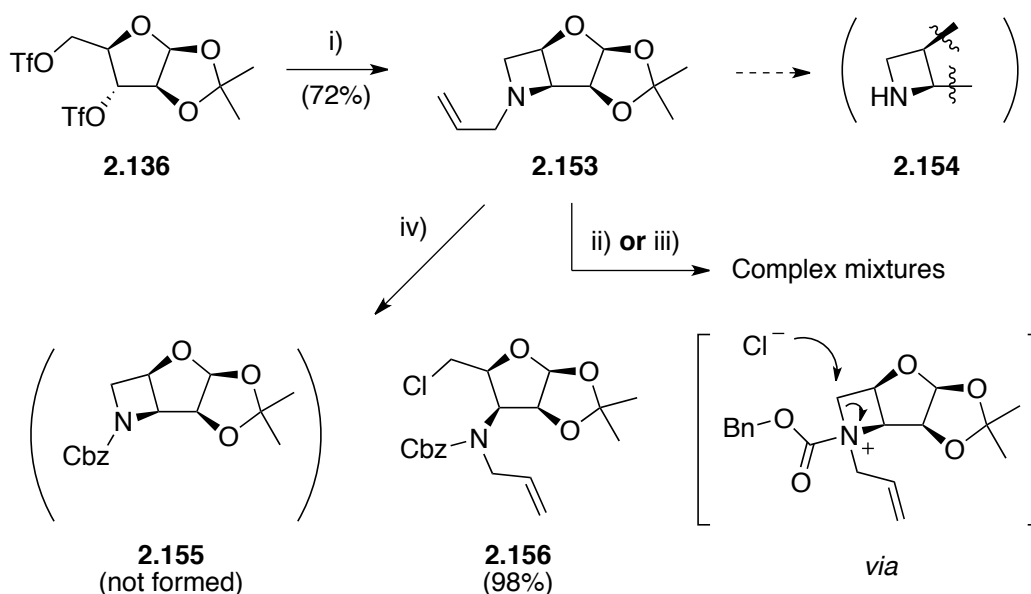
Reagents and conditions: i) NaN_3 , acetone, rt, 24 h; ii) Tf_2O , pyr., DCM, -30°C , 30 min.; iii) NaN_3 , DMF, 60°C , 19 h; iv) TBAF, THF, rt, 1 h.

Scheme 2.25: Preparation of azido-triflate precursors

Many conditions were trialled for the reduction/cyclisation of both **2.149** and **2.152**: various palladium catalysed hydrogenations in different solvents, with or without the addition of base, and

with or without heating of the reduced intermediates; reduction with ethanolic sodium hydrogen telluride (Suzuki-Takaoka reduction),^{214,215} or reduction with zinc and ammonium chloride²¹⁶ in refluxing aqueous ethanol, but all resulted in the formation of complex, intractable polar mixtures. Attempts at facilitating purification of these mixtures *via* conversion to their acetates or carbamates also proved fruitless.

In light of the difficulties with *N*-debenzylation, the preparation of azetidines bearing alternative, labile *N*-substituents was next considered, with the hope that their subsequent removal would prove easier than the *N*-benzyl case. Allylamines may be cleaved under a variety of conditions,^{217,218} but three methods commonly encountered involve either (i) rhodium- or (ii) palladium-assisted isomerisation of the allyl group with concomitant hydrolysis of the resulting enamine, or (iii) treatment with a chloroformate to form an intermediate carbamate with expulsion of allyl chloride, followed by hydrolysis of the carbamate.

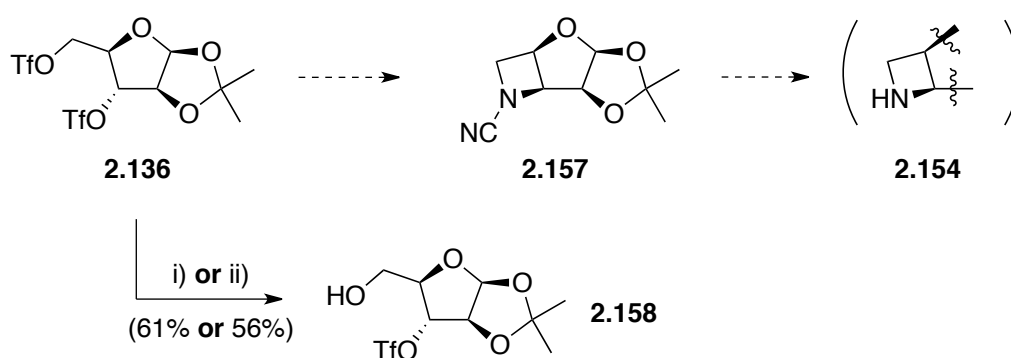


Reagents and conditions: i) allylamine (3.5 eq.), MeCN, rt, 18 h; ii) RhCl(PPh₃)₃ (5 mol. %), 5:1 MeCN/H₂O, reflux, 4 h; iii) Pd/C (10 mol. %), TFA/H₂O, 50 °C, 21 h; iv) ClCO₂CH₂Ph, 1,2-dichloroethane, rt, 1.5 h

Scheme 2.26: Attempts towards *N*-allyl cleavage

Treatment of the ditriflate **2.136** with allylamine in acetonitrile at room temperature resulted in successful cyclisation, forming the *N*-allyl azetidine **2.153** in 72% yield (Scheme 2.26). The three common methodologies for allyl cleavage discussed above were then tried in an attempt to generate the intermediate(s) **2.154**. Treatment of **2.153** with Wilkinson's catalyst in refluxing aqueous acetonitrile, or with palladium on carbon in aqueous trifluoroacetic acid at 50 °C, both resulted in the formation of complex mixtures which were not investigated further. Conversely, reaction of **2.153** with benzyl chloroformate in 1,2-dichloroethane did not lead to the expected *N*-Cbz azetidine **2.155**, but rather to the almost quantitative formation of the 5-chloro compound **2.156**; clearly a product of attack by the liberated chloride on the highly labile ring of the quaternary azetidine intermediate. This approach was therefore abandoned.

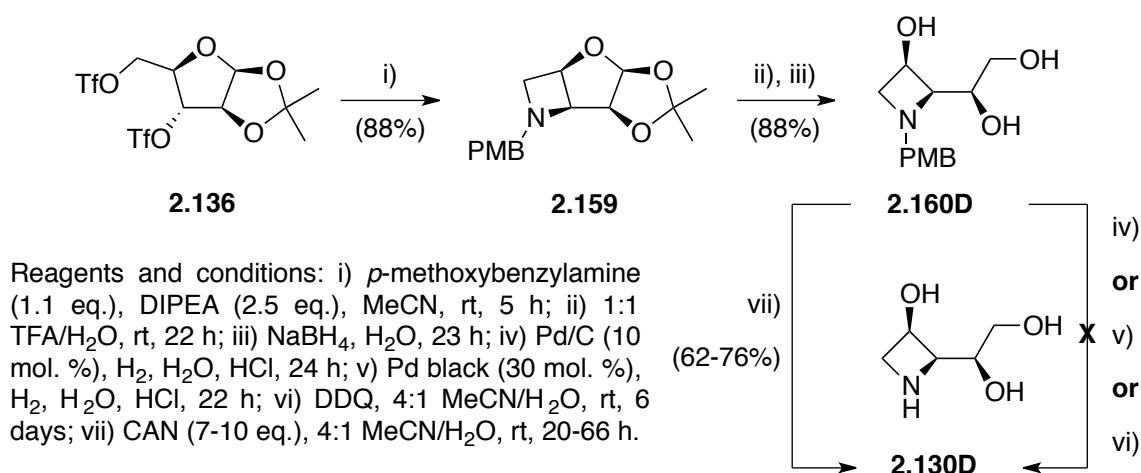
Brief attempts were made at generating the *N*-cyano azetidine **2.157**, with the aim of subsequent hydrolysis of the nitrile and the resulting carbamic acid to access **2.154** (Scheme 2.27). However, clearly cyanamide is too poor a nucleophile to react in this case, as attempted displacements of ditriflate **2.136** with cyanamide failed – even at temperatures as high as 90 °C – affording instead only the 3-*O*-triflate **2.158**. This outcome is presumably a result of selective displacement of the primary triflate by the water present in the solvent and/or the hygroscopic cyanamide reagent itself.



Reagents and conditions: i) cyanamide (1.1 eq.), DIPEA (2.5 eq.), 5:1 MeCN/water, reflux, 1.5 h; ii) cyanamide (2 eq.) DIPEA (2.5 eq.), DMF, 90 °C, 1 h.

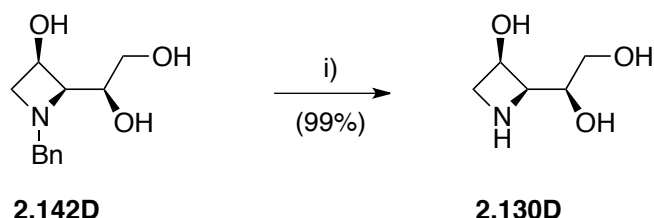
Scheme 2.27: Attempts towards preparing *N*-cyano azetidine

Finally, *p*-methoxybenzyl (PMB) *N*-substitution was examined as an alternative to benzyl, as *N*-PMB groups can also be cleaved by hydrogenolysis, but crucially they are also more susceptible to oxidative cleavage than their benzyl analogues.²¹⁸ The 3,5-displacement of ditriflate **2.136** with *p*-methoxybenzylamine and DIPEA occurred readily in acetonitrile at room temperature, affording the protected *N*-PMB azetidine **2.159** in 88% yield (Scheme 2.28). Subsequent hydrolysis with aqueous trifluoroacetic acid followed by reduction of the resulting lactol with sodium borohydride furnished the *N*-PMB *arabino* azetidine **2.160D** in 88% yield over two steps. This product proved similarly resistant to hydrogenolysis as the benzyl analogue; treatment with molecular hydrogen under catalysis by either palladium on carbon or palladium black in acidified aqueous solution gave no reaction whatsoever. Attention was then turned to oxidative cleavage methods: stirring with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in aqueous acetonitrile gave no cleavage even after prolonged reaction time, but substitution of DDQ for the more powerful ammonium cerium(IV) nitrate (CAN) did result in successful deprotection. However, despite various efforts with differing reaction times and reagent stoichiometry, the desired product **2.130D** was always accompanied by varying amounts (~ 15-20%) of inseparable, unidentified by-products; presumably as a result of over-oxidation. These observations suggest that CAN is too harsh an oxidant to reliably generate clean N-H azetidines using this methodology, and this approach was therefore also abandoned.



Scheme 2.28: Preparation of *N*-PMB azetidine and attempts at deprotection

These frustrating setbacks ultimately motivated a re-examination of the debenzylation protocol for **2.130D**, with an eye towards the use of catalytic transfer hydrogenation conditions rather than those utilising molecular hydrogen. Of particular interest was a report by Ram and Spicer on the efficient debenzylation of various *N*-benzyl compounds *via* catalytic transfer hydrogenation under neutral conditions using ammonium formate as the hydrogen donor.²¹⁹ To our relief and delight, it was found that refluxing the *N*-benzyl compounds **2.142D/2.142L** with ammonium formate and palladium on carbon in anhydrous methanol under an atmosphere of argon effected reliable, clean and highly efficient debenzylation, affording the N-H azetidines **2.130D/2.130L** in near-quantitative yields (Scheme 2.29).

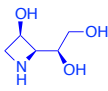
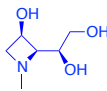
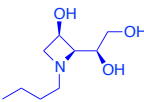
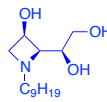
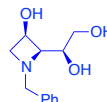
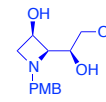


Reagents and conditions: i) Pd/C (10-20 mol. %), HCO_2NH_4 (10 eq.), dry MeOH, argon, reflux, 20-30 min (yield for enantiomer **2.130L** = 97%).

Scheme 2.29: Clean and efficient debenzylation using catalytic transfer hydrogenation

Both the D- and L-arabinitol azetidines **2.130D/2.130L** and their *N*-substituted analogues were assayed for their inhibitory activity against a panel of glycosidases (Tables 2.2 and 2.3 respectively), courtesy of Professor Atsushi Kato (University of Toyama, Japan).

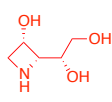
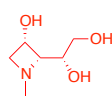
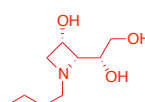
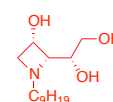
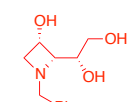
Concentration of 1,3-dideoxy-1,3-imino-D-arabinitol (**2.130D**) and its derivatives giving 50 % inhibition of various glycosidases

	IC ₅₀ (μM)					
						
Enzyme	2.130D	2.143D	2.144D	2.145D	2.142D	2.160D
α-Glucosidase						
Rice	NI ^a (11.9 %) ^b	NI (9.0 %)	NI (7.2 %)	NI (15.1 %)	NI (8.1 %)	NI (3.4 %)
Yeast	NI (0 %)	NI (0 %)	NI (9.7 %)	NI (0.3 %)	NI (0 %)	NI (1.9 %)
Rat intestinal maltase	NI (20.9 %)	NI (0 %)	NI (1.3 %)	NI (4.9 %)	NI (0 %)	NI (9.7 %)
<i>A. niger</i>	NI (6.4 %)	NI (10.9 %)	NI (2.3 %)	NI (0 %)	NI (0 %)	NI (0.7 %)
β-Glucosidase						
Almond	755	NI (45.6 %)	NI (24.8 %)	NI (44.4 %)	69	NI (37.5 %)
Bovine liver	NI (40.7 %)	NI (7.4 %)	NI (0 %)	178	NI (0 %)	NI (11.5 %)
α-Galactosidase						
Coffee beans	NI (37.0 %)	NI (8.4 %)	NI (0 %)	NI (5.3 %)	NI (7.2 %)	NI (5.7 %)
β-Galactosidase						
Bovine liver	NI (27.5 %)	NI (8.8 %)	NI (16.2 %)	74	NI (8.5 %)	NI (22.9 %)
Rat intestinal lactase	241	391	NI (7.7 %)	NI (0 %)	NI (19.7 %)	NI (5.0 %)
α-Mannosidase						
Jack beans	713	110	798	365	NI (16.0 %)	NI (20.2 %)
β-Mannosidase						
Snail	NI (0 %)	NI (0 %)	NI (0 %)	NI (0 %)	NI (3.3 %)	NI (1.0 %)
α-L-Rhamnosidase						
<i>P. decumbens</i>	NI (3.8 %)	NI (14.8 %)	NI (7.9 %)	NI (4.8 %)	NI (3.5 %)	NI (5.0 %)
α-L-Fucosidase						
Bovine epididymis	NI (8.5 %)	NI (17.3 %)	NI (1.9 %)	NI (4.2 %)	NI (2.8 %)	NI (5.8 %)
Trehalase						
Rat intestinal trehalase	NI (17.3 %)	NI (4.0 %)	NI (7.3 %)	NI (6.3 %)	NI (4.9 %)	NI (8.8 %)
Amyloglucosidase						
<i>A. niger</i>	NI (8.4 %)	NI (4.4 %)	NI (2.2 %)	NI (0 %)	NI (3.5 %)	NI (1.5 %)
<i>Rhizopus sp</i>	NI (0 %)	NI (0 %)	NI (2.1 %)	NI (16.1 %)	NI (1.6 %)	NI (0.8 %)

^a NI : No inhibition (less than 50% inhibition at 1000 μM).^b () : Inhibition % at 1000 μM.**Table 2.2:** Assays of D-arabinitol azetidine iminosugars

None of the D-arabinitol azetidines displayed any inhibition of fungal (*A. niger* or *Rhizopus* sp.) glycosidases, indicating that the stereochemistry at C4 is crucial for such activity (*cf.* the biological assay of the C4 epimer **2.101L** as reported by Jäger¹³⁶). The parent N-H compound **2.130D** showed fairly broad, yet moderate to weak inhibition of a number of enzymes. *N*-Methylation caused an increased specificity and potency towards α-mannosidase, whereas *N*-butylation gave rise to completely specific, but weaker, inhibition of α-mannosidase, and *N*-nonylation gave increased potency but no increase in specificity. Interestingly, *N*-benzylation gave rise to potent and completely specific inhibition of β-glucosidase, whereas *N*-PMB substitution destroyed all activity.

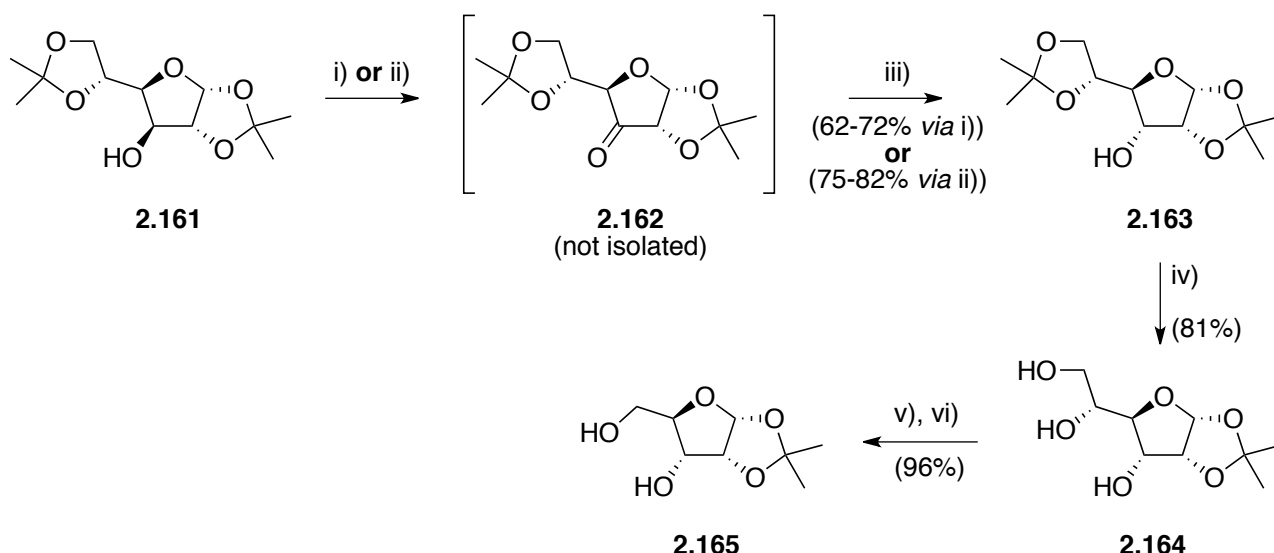
Concentration of 1,3-dideoxy-1,3-imino-L-arabinitol (**2.130L**) and its derivatives giving 50 % inhibition of various glycosidases

Enzyme	IC ₅₀ (μM)				
					
	2.130L	2.143L	2.144L	2.145L	2.142L
α-Glucosidase					
Rice	NI ^a (12.1 %) ^b	NI (7.6 %)	NI (12.1 %)	NI (17.6 %)	NI (13.5 %)
Yeast	NI (16.0 %)	NI (19.2 %)	NI (0 %)	NI (1.5 %)	NI (0 %)
Rat intestinal maltase	607	NI (35.5 %)	NI (27.0 %)	NI (44.4 %)	NI (14.8 %)
<i>A. niger</i>	39	21	NI (45.9 %)	52	419
β-Glucosidase					
Almond	347	NI (3.6 %)	NI (5.0 %)	NI (0 %)	NI (14.9 %)
Bovine liver	997	NI (0 %)	NI (0.3 %)	NI (35.0 %)	NI (1.0 %)
α-Galactosidase					
Coffee beans	NI (7.6 %)	NI (9.7 %)	NI (33.3 %)	NI (8.1 %)	NI (7.0 %)
β-Galactosidase					
Bovine liver	NI (25.2 %)	NI (2.6 %)	NI (0 %)	357	988
Rat intestinal lactase	70	NI (46.8 %)	NI (6.8 %)	NI (0%)	NI (25.0 %)
α-Mannosidase					
Jack beans	NI (2.4 %)	NI (13.8 %)	NI (19.7 %)	NI (18.9 %)	NI (2.5 %)
β-Mannosidase					
Snail	NI (0 %)	NI (32.2 %)	NI (20.0 %)	NI (0 %)	NI (0 %)
α-L-Rhamnosidase					
<i>P. decumbens</i>	634	NI (10.4 %)	NI (10.1 %)	NI (1.1 %)	NI (27.1 %)
α-L-Fucosidase					
Bovine epididymis	NI (4.6 %)	NI (1.3 %)	NI (0.9 %)	NI (3.1 %)	NI (3.8 %)
Trehalase					
Rat intestinal trehalase	NI (11.7 %)	NI (12.8 %)	NI (48.9 %)	54	NI (3.6 %)
Amyloglucosidase					
<i>A. niger</i>	105	140	232	206	NI (41.3 %)
<i>Rhizopus sp</i>	19	50	96	125	424

^a NI : No inhibition (less than 50% inhibition at 1000 μM).^b () : Inhibition % at 1000 μM.**Table 2.3:** Assays of L-arabinitol azetidine iminosugars

In contrast with the D-series, the L-arabinitol azetidines showed generally potent and selective inhibition of fungal glucosidases over those from plant or mammalian sources, although the parent N-H compound **2.130L** showed the broadest spectrum of activity, with activity against α-glucosidase (rat intestinal maltase), β-glucosidase (almond), β-galactosidase and α-L-rhamnosidase (607, 347, 70 and 634 μM respectively). Furthermore, N-substitution resulted in a general trend of decreasing potency of inhibition with increasing size of the lipophilic substituent. Of noteworthy exception was the N-nonyl compound **2.145L**, which additionally exhibited potent inhibition of rat intestinal trehalase (54 μM).

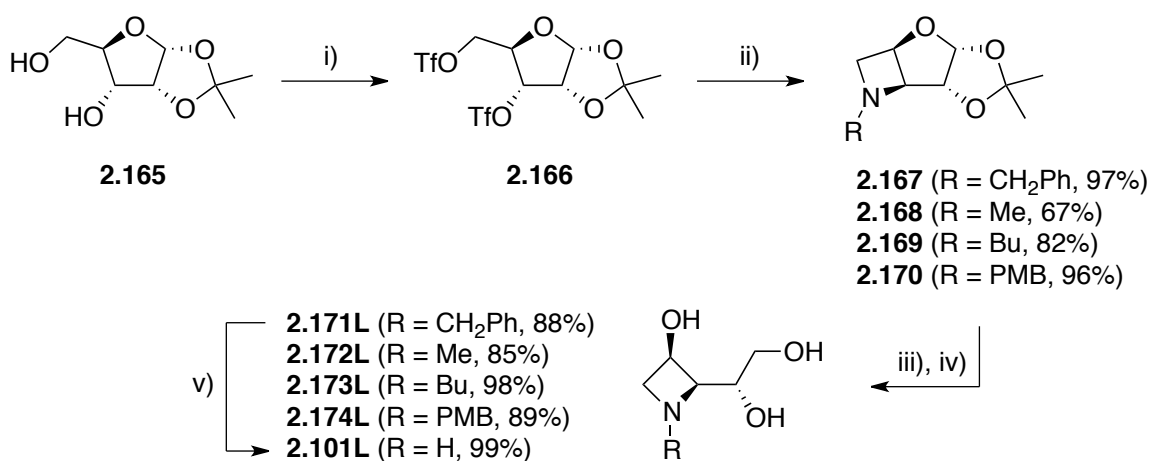
With the successful completion of the syntheses from arabinose, attention was then turned towards the analogous ribose route. What follows is a discussion of the original work from D-ribose; the work on the enantiomeric series was later carried out by a colleague (Noelia Araújo). Following a known procedure,²²⁰ diacetone-D-glucose **2.161** was converted into diacetone-D-allose **2.163** via a two step oxidation-reduction protocol (Scheme 2.30). Oxidation with pyridinium chlorochromate (PCC) in DCM over powdered 3 Å molecular sieves furnished the intermediate ketone **2.162**, which without isolation was then treated with sodium borohydride in aqueous ethanol, effecting stereoselective reduction from the least hindered face, thus affording the epimeric *allo* compound **2.163** in reasonable yield. However, the extreme sensitivity of PCC to moisture proved problematic, as the desired *allo* compound was always accompanied by varying proportions (as high as 30%) of the inseparable *gluco* contaminant resulting from incomplete oxidation. The use of PCC was therefore ultimately eschewed, and Dess-Martin periodinane (DMP) employed as an alternative oxidant. This resulted in the reliable formation of diastereomerically pure **2.163** in higher yield, and with the ancillary benefits of easier purification and reduced toxicity. Efficient and selective acid hydrolysis of the terminal acetonide of **2.163** to form the mono-acetonide **2.164** proved more difficult than anticipated, as over-hydrolysis was found to occur easily during either the reaction itself or the ensuing workup and isolation, depending on the conditions employed. However, after lengthy optimisation the most effective procedure was found to be treatment with a 7:3 mixture of glacial acetic acid and water, followed by careful evaporation of the solvent at 25 °C to remove all traces of acid before column chromatography; in this manner **2.164** was isolated in 81% yield. Oxidative cleavage of the terminal diol moiety in **2.164** was readily achieved with sodium *meta*-periodate in aqueous solution, and reduction of the intermediate aldehyde with sodium borohydride in aqueous ethanol then afforded the key D-*ribo* diol **2.165** in an excellent yield of 96% over two steps.



Reagents and conditions: i) PCC, DCM, 3 Å molecular sieves, rt, 19-26 h; ii) Dess-Martin periodinane, DCM, 0 °C → rt, 18-21 h; iii) NaBH₄, EtOH/H₂O, 0 °C → rt, 1 h; iv) 7:3 AcOH/H₂O, rt, 18 h; v) NaIO₄, H₂O, rt, 1 h; vi) NaBH₄, 3:1 EtOH/H₂O, rt, 3 h.

Scheme 2.30: Preparation of the key *ribo* diol

Treatment with triflic anhydride and pyridine in DCM then effected triflation of the unmasked hydroxyls in **2.165**, furnishing the *ribo* 3,5-ditriflate **2.166** in 88% yield (Scheme 2.31). Subsequent treatment of this ditriflate with the appropriate amine and DIPEA in acetonitrile at room temperature then allowed access to the D-*xylo* *N*-benzyl, -methyl, -butyl and -*p*-methoxybenzyl fused azetidines **2.167-2.170** in good to excellent yields, further demonstrating the general efficiency and utility of this methodology. Hydrolysis of the acetonide functionality with aqueous trifluoroacetic acid followed by reduction of the resulting lactols with sodium borohydride afforded the *N*-benzyl, -methyl, -butyl and -*p*-methoxybenzyl 1,3-dideoxy-1,3-imino-L-xylitol iminosugars **2.171L-2.174L** in excellent yields over two steps. Finally, debenzylation of **2.171L** *via* transfer hydrogenation with ammonium formate and palladium on carbon afforded the parent N-H compound **2.101L** in 99% yield. The *N*-benzyl compound **2.171L** proved to be highly crystalline, allowing its X-ray structure to be obtained (Figure 2.13).²²¹



Reagents and conditions: i) Tf₂O, pyr., DCM, -30 °C, 1 h; ii) RNH₂ (1.1 eq.), DIPEA (2.5 eq.), MeCN, rt, 18-22 h; iii) 1:1 TFA/H₂O, rt, 20-42 h; iv) NaBH₄, H₂O, rt, 16-45 h; v) Pd/C (20 mol. %), HCO₂NH₄, dry MeOH, reflux, argon, 20 min.

Scheme 2.31: Syntheses of 1,3-imino-L-xylitol iminosugars

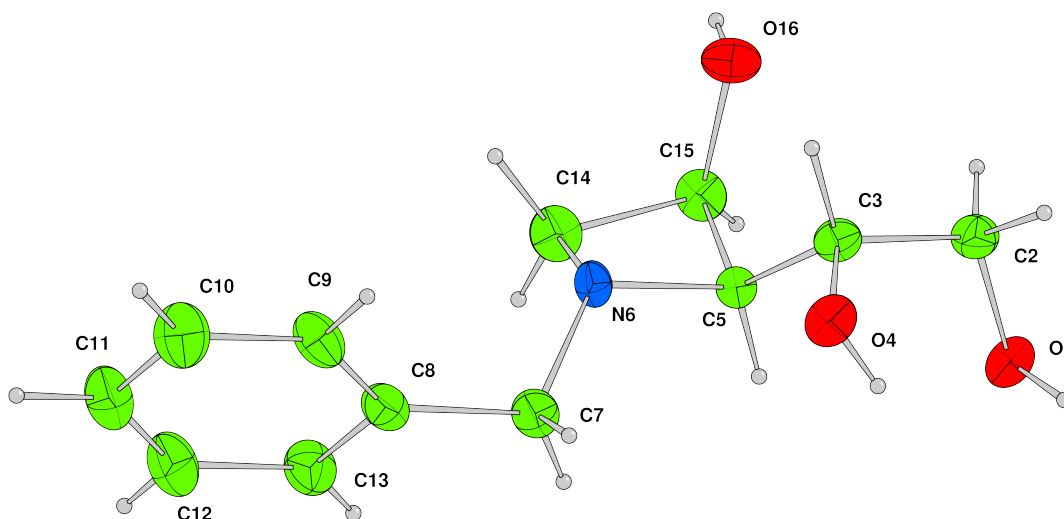
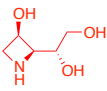
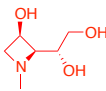
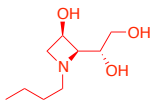
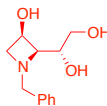
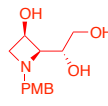


Figure 2.13: Single crystal X-ray structure of **2.171L**

The L- and D-xylitol azetidine iminosugars and their respective *N*-substituted analogues were assayed in the same manner as for the arabinitol azetidines (Atsushi Kato). The results are shown in Tables 2.4 and 2.5 respectively.

Concentration of 1,3-dideoxy-1,3-imino-L-xylitol (2.101L) and its derivatives giving 50 % inhibition of various glycosidases					
	IC ₅₀ (μM)				
					
Enzyme	2.101L	2.172L	2.173L	2.171L	2.174L
α-Glucosidase					
Rice	NI ^a (0 %) ^b	NI (6.8 %)	NI (0 %)	NI (5.6 %)	NI (3.9 %)
Yeast	NI (6.7 %)	NI (1.6 %)	NI (0.8 %)	NI (1.9 %)	NI (1.1 %)
Rat intestinal maltase	NI (21.7 %)	NI (15.8 %)	NI (9.7 %)	NI (8.8 %)	NI (6.0 %)
<i>A. niger</i>	175	163	NI (5.1 %)	NI (6.4 %)	NI (6.0 %)
β-Glucosidase					
Almond	NI (9.3 %)	NI (29.8 %)	NI (5.5 %)	NI (14.0 %)	NI (0.8 %)
Bovine liver	NI (20.5 %)	NI (3.2 %)	NI (16.6 %)	NI (16.3 %)	NI (10.4 %)
α-Galactosidase					
Coffee beans	NI (14.1 %)	NI (13.5 %)	NI (11.0 %)	NI (7.4 %)	NI (6.7 %)
β-Galactosidase					
Bovine liver	NI (0 %)	NI (5.1 %)	NI (0 %)	NI (28.5 %)	NI (22.2 %)
Rat intestinal lactase	NI (0 %)	NI (44.3 %)	NI (0 %)	NI (15.2 %)	NI (13.7 %)
α-Mannosidase					
Jack beans	NI (1.7 %)	NI (1.7 %)	NI (1.2 %)	NI (0 %)	NI (2.4 %)
β-Mannosidase					
Snail	NI (4.9 %)	NI (4.0 %)	NI (2.1 %)	NI (0 %)	NI (0 %)
α-L-Rhamnosidase					
<i>P. decumbens</i>	NI (2.3 %)	NI (0 %)	NI (0.7 %)	NI (13.3 %)	NI (6.8 %)
α-L-Fucosidase					
Bovine epididymis	NI (4.6 %)	NI (0 %)	NI (5.7 %)	NI (3.1 %)	NI (3.6 %)
Trehalase					
Rat intestinal trehalase	NI (0 %)	NI (7.6 %)	NI (6.0 %)	NI (0.5 %)	NI (6.0 %)
Amyloglucosidase					
<i>A. niger</i>	414	630	NI (1.2 %)	NI (1.4 %)	NI (2.6 %)
<i>Rhizopus sp</i>	25	58	NI (6.9 %)	NI (7.7 %)	NI (8.8 %)

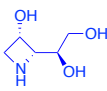
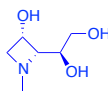
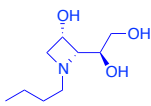
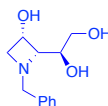
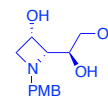
^a NI : No inhibition (less than 50% inhibition at 1000 μM).

^b () : Inhibition % at 1000 μM.

Table 2.4: Assays of L-xylitol azetidine iminosugars

These results are in good agreement with those of Jäger *et al.*,¹³⁶ namely in the selective inhibition of amyloglucosidases by the N-H compound **2.101L**, although our measured IC₅₀ values were higher than those they reported. In addition, **2.101L** also showed moderate inhibition of fungal (*A. niger*) α-glucosidase (175 μM). Unfortunately all N-substitutions led to a complete loss of activity, with the exception of N-methylated **2.172L**, which retained similar but weaker inhibition to **2.101L**. The sharply contrasting tolerance of N-substitution between these L-xylitols and the L-arabinitols with respect to fungal glycosidase inhibition is interesting, and may suggest a differing mode of inhibition (competitive or non-competitive) between the two.

Concentration of 1,3-dideoxy-1,3-imino-D-xylitol (**2.101D**) and its derivatives giving 50 % inhibition of various glycosidases

Enzyme	IC ₅₀ (μM)				
					
	2.101D	2.172D	2.173D	2.171D	2.174D
α-Glucosidase					
Rice	NI ^a (4.8 %) ^b	NI (0 %)	NI (0.6 %)	NI (4.7 %)	NI (1.0 %)
Yeast	NI (6.0 %)	NI (3.8 %)	NI (1.6 %)	NI (1.2 %)	NI (2.2 %)
Rat intestinal maltase	NI (17.8 %)	NI (14.7 %)	NI (7.6 %)	NI (3.1 %)	NI (5.5 %)
<i>A. niger</i>	NI (6.3 %)	NI (0.7 %)	NI (7.6 %)	NI (19.9 %)	NI (0 %)
β-Glucosidase					
Almond	NI (9.6 %)	NI (3.5 %)	NI (1.8 %)	NI (29.0 %)	NI (12.2 %)
Bovine liver	NI (4.7 %)	NI (0 %)	NI (5.0 %)	NI (17.7 %)	NI (25.0 %)
α-Galactosidase					
Coffee beans	NI (0.2 %)	NI (0.2 %)	NI (4.3 %)	NI (6.1 %)	NI (0 %)
β-Galactosidase					
Bovine liver	NI (2.1 %)	NI (1.7 %)	NI (13.5 %)	NI (29.3 %)	NI (43.0 %)
Rat intestinal lactase	NI (0 %)	NI (19.1 %)	NI (0 %)	NI (8.0 %)	NI (16.7 %)
α-Mannosidase					
Jack beans	NI (0.6 %)	NI (1.4 %)	NI (2.7 %)	NI (0 %)	NI (0 %)
β-Mannosidase					
Snail	NI (0 %)	NI (1.5 %)	NI (4.6 %)	NI (5.6 %)	NI (0 %)
α-L-Rhamnosidase					
<i>P. decumbens</i>	NI (5.7 %)	NI (0 %)	NI (4.3 %)	NI (3.7 %)	NI (0 %)
α-L-Fucosidase					
Bovine epididymis	NI (0 %)	NI (28.7 %)	NI (5.1 %)	NI (0 %)	NI (0 %)
Trehalase					
Rat intestinal trehalase	NI (6.4 %)	NI (2.9 %)	NI (5.6 %)	NI (0.2 %)	NI (0 %)
Amyloglucosidase					
<i>A. niger</i>	NI (5.7 %)	NI (0 %)	NI (2.6 %)	NI (4.2 %)	NI (9.7 %)
<i>Rhizopus sp</i>	NI (1.2 %)	NI (0 %)	NI (0 %)	NI (20.8 %)	NI (3.5 %)

^a NI : No inhibition (less than 50% inhibition at 1000 μM).^b () : Inhibition % at 1000 μM.**Table 2.5:** Assays of D-xylitol azetidine iminosugars

Unfortunately, the D-xylitol azetidines lacked any inhibitory activity towards the glycosidases tested. Nonetheless these results represent an interesting contrast to the arabinitol azetidines, in which both enantiomers exhibited unique patterns of inhibition.

2.2.2 Azetidine tetrols from aldohexofuranoses (3,5-displacement)²²²

The conceptually more challenging extension of the 3,5-displacement strategy to the use of aldohexose furanosides as substrates was next considered. The stereochemical prerequisite for a *trans*-configuration in the furanose substrate (as discussed in Section 2.2) limits the pool of suitable aldohexoses to allose, altrose, galactose and talose (Figure 2.14).

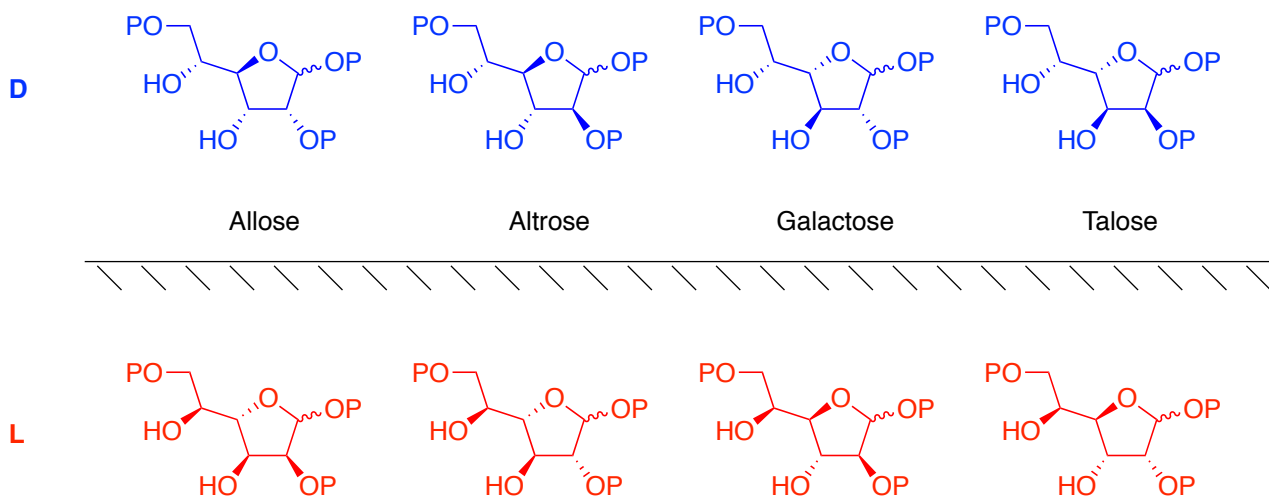
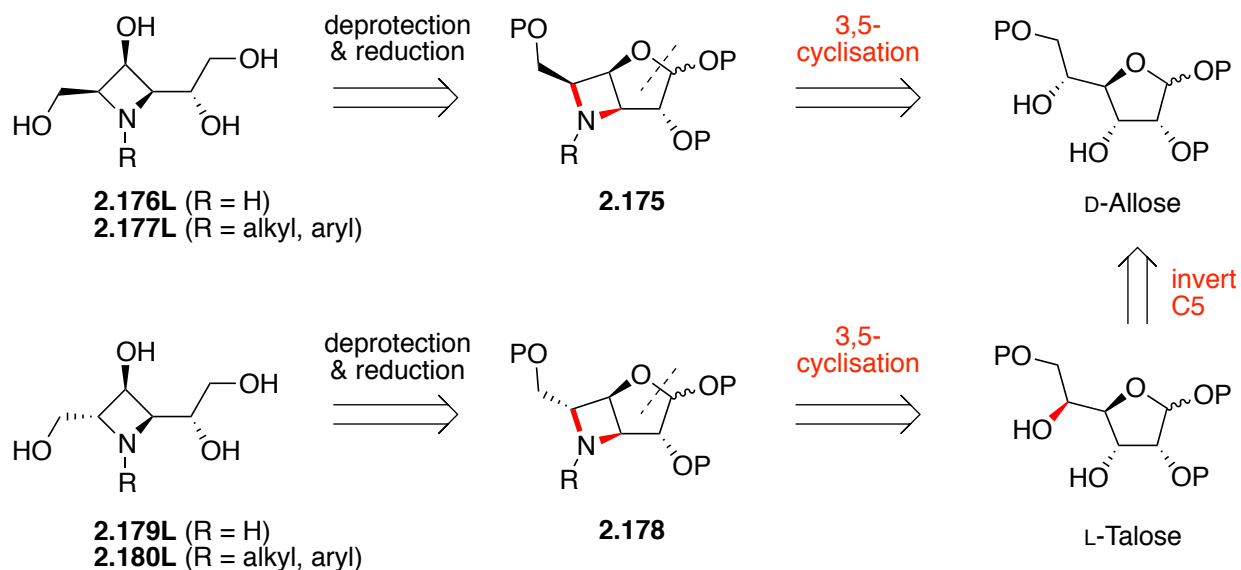


Figure 2.14: Aldohexose furanosides suitable for the 3,5-displacement strategy

Altrose is not simple to prepare from other sugars, and is only available from suppliers at prohibitive expense. D-Galactose is cheaply available, but preparing a *galacto* furanoside substrate with the appropriate pattern of protecting groups is also not straightforward. The *altro* and *galacto* substrates were therefore disregarded in favour of the *D-allo* system, as not only was this already in hand from the synthesis of the L-xylitol azetidines, but epimerisation at C5 would also allow ready access to the corresponding *L-talo* substrate. Thus, retrosynthetically the 2,4-dideoxy-2,4-imino-L-*iditol* **2.176L** and its *N*-substituted analogues **2.177L** would arise from deprotection and reduction of the *L-ido* fused azetidines **2.175**, which would in turn be formed from triflation and 3,5-displacement of a masked D-allofuranose (Scheme 2.32). Concordantly, the 2,4-dideoxy-2,4-imino-

L-gulitol **2.179L** and its *N*-substituted analogues **2.180L** would similarly arise from the *D*-gluco intermediates **2.178**, in turn formed from L-talose.



Scheme 2.32: Retrosyntheses of L-iditol and L-gulitol azetidine iminosugars

These azetidine tetrols can be considered as ring-contracted analogues of the pyrrolidine iminosugars 2,5-dideoxy-2,5-imino-D-mannitol (DMDP), its enantiomer L-DMDP, and the C2-epimeric 2,5-dideoxy-2,5-imino-D-glucitol (DGDP); compounds with well established and potent glycosidase inhibitory activities. DMDP is a potent and competitive inhibitor of various α -glucosidases and L-DMDP has been shown to be an even more potent, but non-competitive, inhibitor of the same enzymes,²⁰⁴ whereas DGDP is a potent inhibitor of both α - and β -glucosidases as well as α -galactosidase.²²³ The molecular superimpositions (Figure 2.15) of both L-iditol and L-gulitol azetidines **2.176L** and **2.179L** respectively with DMDP, L-DMDP and DGDP show reasonable to good degrees of overlap – particularly in the cases of **DMDP/2.179L**, **L-DMDP/2.176L** and **DGDP/2.176L** – which gave us plausible reason to hope they would also exhibit similar activity.

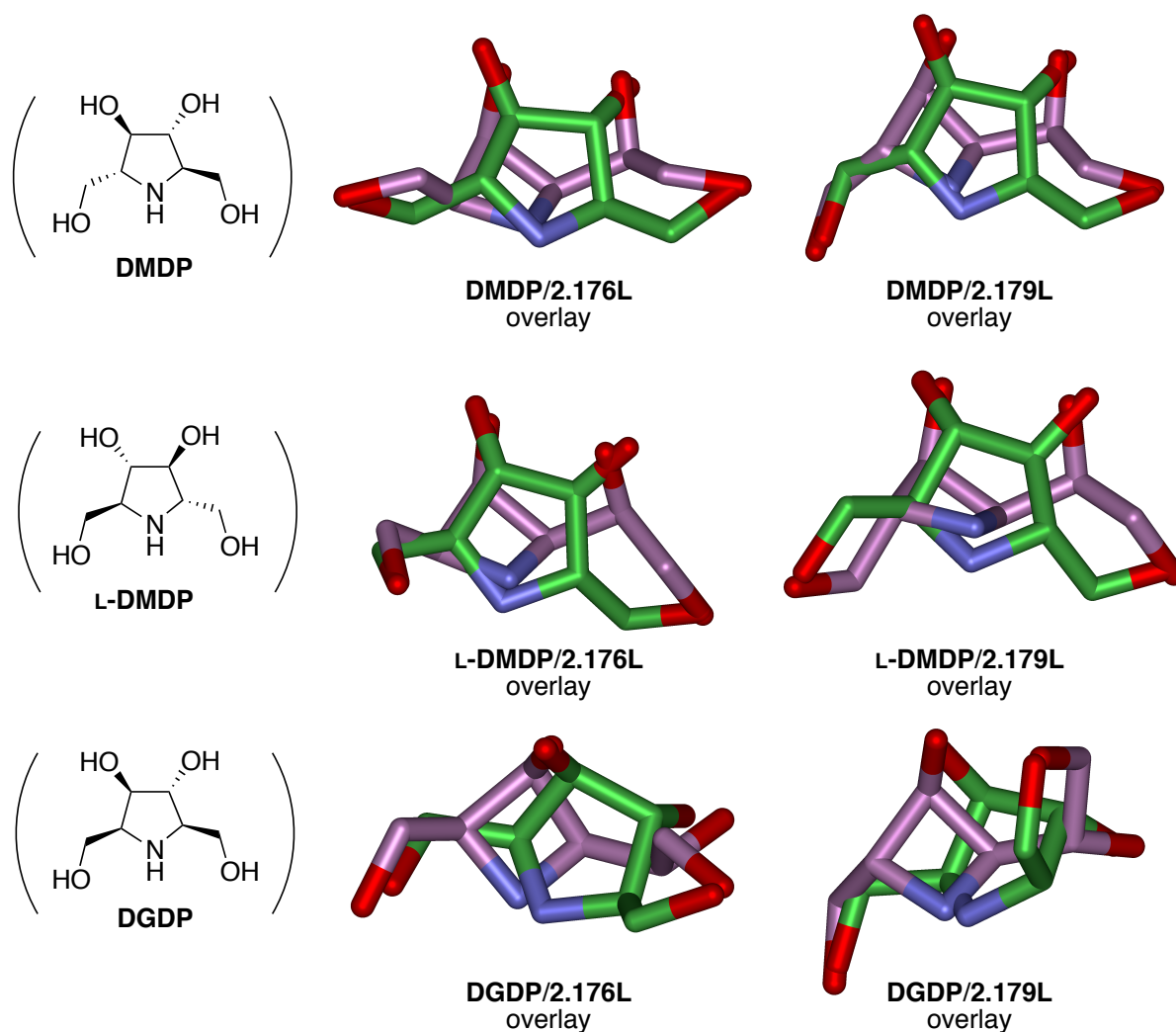
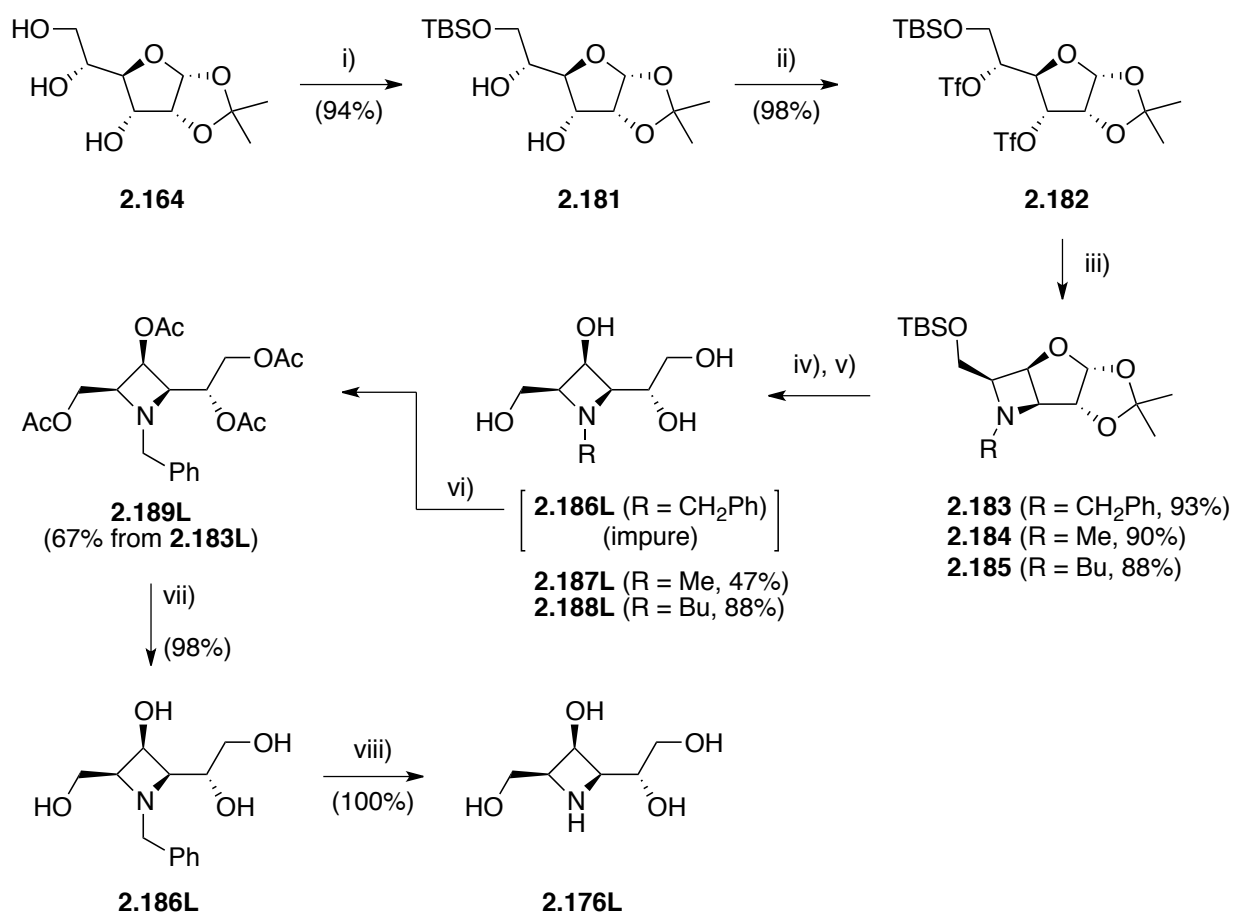


Figure 2.15: Molecular overlays of L-iditol and L-gulitol azetidines with DMDP, L-DMDP and DGDP

The selective protection of the terminal alcohol in the D-allofuranose 1,2-acetonide **2.164** was achieved with *tert*-butyldimethylsilyl chloride and imidazole in anhydrous DMF at low temperature, affording the corresponding 6-*O*-silyl ether **2.181** in 94% yield (Scheme 2.33). Subsequent treatment with triflic anhydride and pyridine in DCM at low temperature afforded the 3,5-ditriflate **2.182** in almost quantitative yield. The CH₂OTBS moiety in **2.182** represents an appreciable additional steric demand during 3,5-cyclisation in comparison to the aldopentose systems, yet highly efficient cyclisation was maintained on treatment with several amines and DIPEA in acetonitrile – albeit at slightly elevated temperature – affording the corresponding fused L-*ido* azetidines **2.183-2.185** in very good yields. Hydrolysis of both the acetonide and TBS ether functionalities with aqueous TFA afforded the intermediate lactols, which without purification were

reduced with aqueous sodium borohydride to afford the corresponding L-iditol azetidine tetrols **2.186L-2.188L**. However, hydrolysis with equal proportions of TFA and water was found to be sluggish (apparently due to issues of solubility), with concomitantly long reaction times. More efficient hydrolysis was effected by the use of 9:1 TFA/water (as with the *N*-benzyl intermediate), but the target compound **2.186L** was isolated along with various trace impurities after ion exchange chromatography, requiring derivatisation to completely purify; treatment with acetic anhydride and pyridine thus afforded the per-acetate **2.189L** in 67% yield over three steps. De-acetylation of **2.189L** under Zemplén conditions afforded pure **2.186L** in 98% yield, and subsequent debenzylation under catalytic transfer hydrogenation conditions with ammonium formate effected quantitative formation of the parent N-H azetidine **2.176L**.

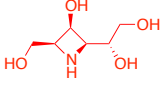
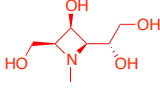
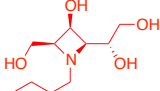
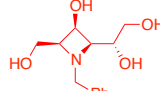


Reagents and conditions: i) TBSCl, imid., DMF, -20 $\rightarrow$ -10 $^{\circ}\text{C}$, 1.5 h; ii) Tf₂O, pyr., DCM, -30 $\rightarrow$ -10 $^{\circ}\text{C}$, 2 h; iii) RNH₂ (1.1 eq.), DIPEA (2.5 eq.), MeCN, 40-50 $^{\circ}\text{C}$, 15-25 h; iv) either 1:1 TFA/H₂O, rt, 3 days (for **2.184/2.185**) or 9:1 TFA/H₂O, rt, 3 h (for **2.183**); v) NaBH₄, H₂O, rt, 18-24 h; vi) Ac₂O, pyr., rt, 23 h; vii) NaOMe, MeOH, rt, 21 h; viii) Pd/C (20 mol. %), HCO₂NH₄, dry MeOH, reflux, argon, 30 min.

Scheme 2.33: Preparation of L-iditol azetidine iminosugars

The enantiomeric D-iditol series was later prepared in a similar fashion from L-allose by a colleague (Noelia Araújo). Both L- and D-series were assayed against the usual panel of glycosidases (Atsushi Kato), and the results are displayed in Tables 2.6 and 2.7 respectively for comparison.

Concentration of 2,4-dideoxy-2,4-imino-L-iditol (**2.176L**) and its derivatives giving 50 % inhibition of various glycosidases

	IC ₅₀ (μM)			
				
Enzyme	2.176L	2.177L	2.188L	2.186L
α-Glucosidase				
Rice	NI ^a (3.5%) ^b	NI (6.5%)	NI (9.2%)	NI (2.9%)
Yeast	NI (3.8%)	NI (0.9%)	NI (0%)	NI (0%)
Rat intestinal maltase	NI (17.8%)	NI (13.9%)	NI (3.3%)	NI (14.0%)
<i>A. niger</i>	NI (0%)	NI (1.4%)	NI (0%)	NI (5.8%)
β-Glucosidase				
Almond	NI (21.6%)	NI (0.4%)	NI (6.8%)	NI (26.2%)
Bovine liver	NI (2.6%)	NI (9.4%)	NI (6.5%)	NI (6.5%)
α-Galactosidase				
Coffee beans	416	NI (25.1%)	NI (28.2%)	NI (35.5%)
β-Galactosidase				
Bovine liver	NI (3.8%)	NI (0%)	NI (22.9%)	NI (18.5%)
α-Mannosidase				
Jack beans	NI (2.2%)	NI (1.7 %)	NI (0%)	NI (0 %)
β-Mannosidase				
Snail	NI (0%)	NI (0.9%)	NI (0.2%)	NI (0 %)
α-L-Rhamnosidase				
<i>P. decumbens</i>	NI (0.4%)	NI (1.3%)	NI (2.1%)	NI (0 %)
α-L-Fucosidase				
Bovine kidney	NI (0%)	NI (0%)	NI (5.7 %)	NI (9.2%)
Trehalase				
Porcine kidney	NI (0%)	NI (0%)	NI (1.9%)	NI (0%)
Amyloglucosidase				
<i>A. niger</i>	NI (0.1%)	NI (5.4%)	NI (1.4%)	NI (0%)
<i>Rhizopus sp</i>	NI (9.7%)	NI (0%)	NI (0%)	NI (0%)

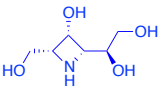
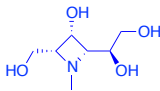
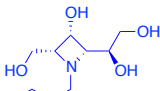
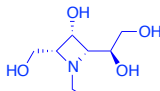
^a NI : No inhibition (less than 50% inhibition at 1000 μM).
^b () : Inhibition % at 1000 μM.

Table 2.6: Assays of L-iditol azetidine iminosugars

Of the L-iditols, only the N-H compound **2.176L** showed any activity, with weak but selective inhibition of α-galactosidase (416 μM). Conversely, of the D-iditols the N-H compound **2.176D** showed no activity towards the screened glycosidases, but its *N*-benzyl analogue **2.186D** showed

potent inhibition of α -glucosidases (rice 27 μ M, rat intestinal maltase 71 μ M), as well as weak inhibition of β -galactosidase (635 μ M).

Concentration of 2,4-dideoxy-2,4-imino-D-iditol (**2.176D**) and its derivatives giving 50 % inhibition of various glycosidases

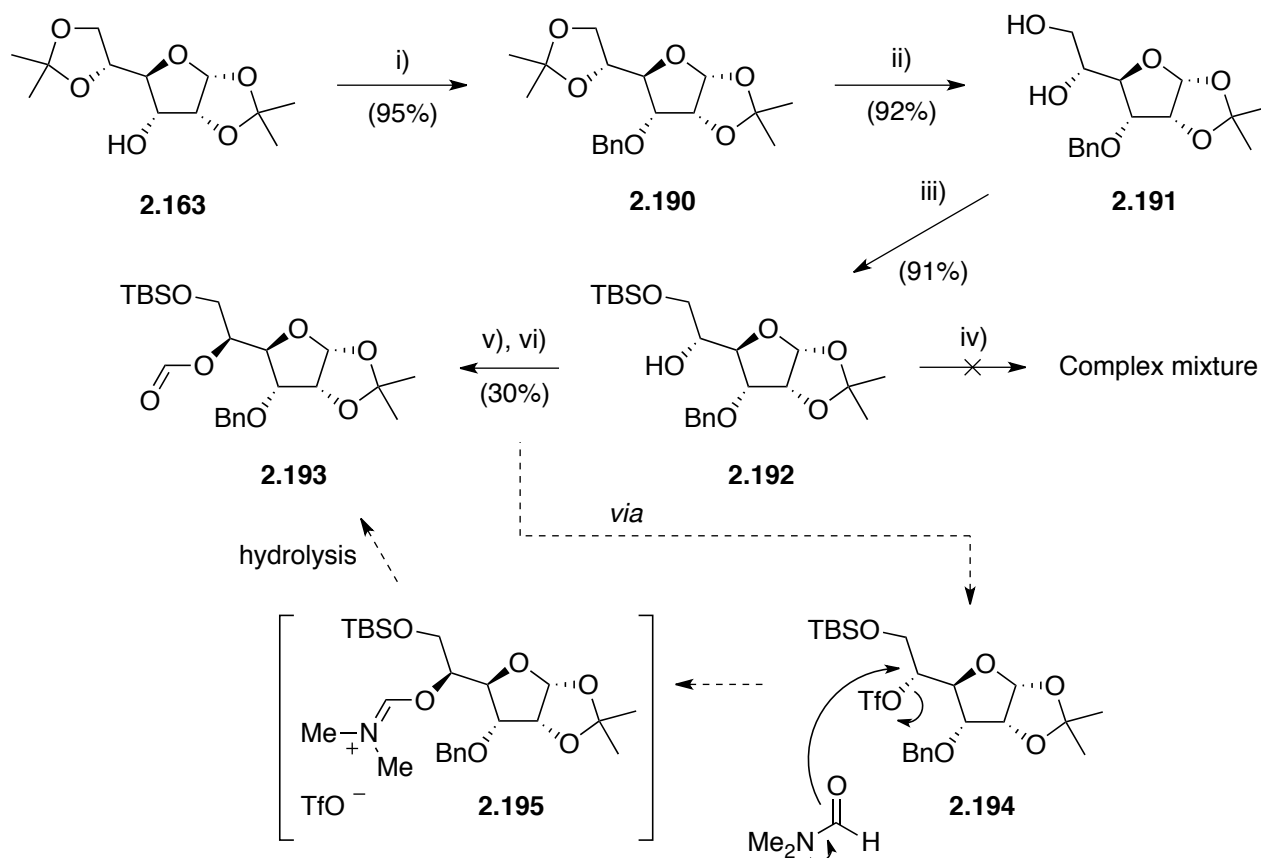
	IC ₅₀ (μ M)			
				
Enzyme	2.176D	2.187D	2.188D	2.186D
α -Glucosidase				
Rice	NI ^a (0%) ^b	NI (10.2%)	NI (7.4%)	27
Yeast	NI (2.0%)	NI (0%)	NI (1.6%)	NI (34.5%)
Rat intestinal maltase	NI (4.6%)	NI (9.3%)	NI (0%)	71
<i>A. niger</i>	NI (1.4%)	NI (2.7%)	NI (3.2%)	NI (23.7%)
β -Glucosidase				
Almond	NI (8.4%)	NI (17.5%)	NI (1.4%)	NI (26.2%)
Bovine liver	NI (0%)	NI (5.5%)	NI (16.8%)	NI (33.9%)
α -Galactosidase				
Coffee beans	NI (10.8%)	NI (2.4%)	NI (8.9%)	NI (6.1%)
β -Galactosidase				
Bovine liver	NI (6.3%)	NI (11.7%)	NI (25.2%)	635
α -Mannosidase				
Jack beans	NI (3.1%)	NI (0%)	NI (0%)	NI (0.1%)
β -Mannosidase				
Snail	NI (0%)	NI (2.4%)	NI (0%)	NI (1.7%)
α -L-Rhamnosidase				
<i>P. decumbens</i>	NI (1.0%)	NI (0.5%)	NI (0%)	NI (5.4%)
α -L-Fucosidase				
Bovine kidney	NI (0%)	NI (9.5%)	NI (0%)	NI (6.4%)
Trehalase				
Porcine kidney	NI (0.5%)	NI (7.2%)	NI (0.2%)	NI (9.8%)
Amyloglucosidase				
<i>A. niger</i>	NI (0%)	NI (4.7%)	NI (1.4%)	NI (9.7%)
<i>Rhizopus sp</i>	NI (0%)	NI (5.2%)	NI (2.4%)	NI (15.2%)

^a NI : No inhibition (less than 50% inhibition at 1000 μ M).
^b () : Inhibition % at 1000 μ M.

Table 2.7: Assays of D-iditol azetidine iminosugars

Efforts were next focused on the preparation of the C2-epimeric azetidine series, which would arise from 3,5-displacement of the *L-talo* substrate. Initially, epimerisation was envisaged as taking place on a suitable *D-allo* substrate with only the C5-OH unmasked, either directly under Mitsunobu conditions, or *via* typical trifluoroacetate displacement of its C5-triflate, with concurrent hydrolysis of the resulting trifluoroacetate ester. Thus, benzylation of di-acetone-D-allose **2.163**

with benzyl bromide and sodium hydride in anhydrous DMF afforded the 3-*O*-benzyl ether **2.190** in 95% yield (Scheme 2.34). Selective hydrolysis of the terminal acetonide with aqueous acetic acid then furnished the diol **2.191** in 92% yield, and subsequent selective protection of the terminal alcohol with *tert*-butyldimethylsilyl trifluoromethanesulfonate and 2,6-lutidine in DCM at -78 °C allowed ready access to the TBS ether **2.192** in 91% yield. The attempted inversion of C5 by a



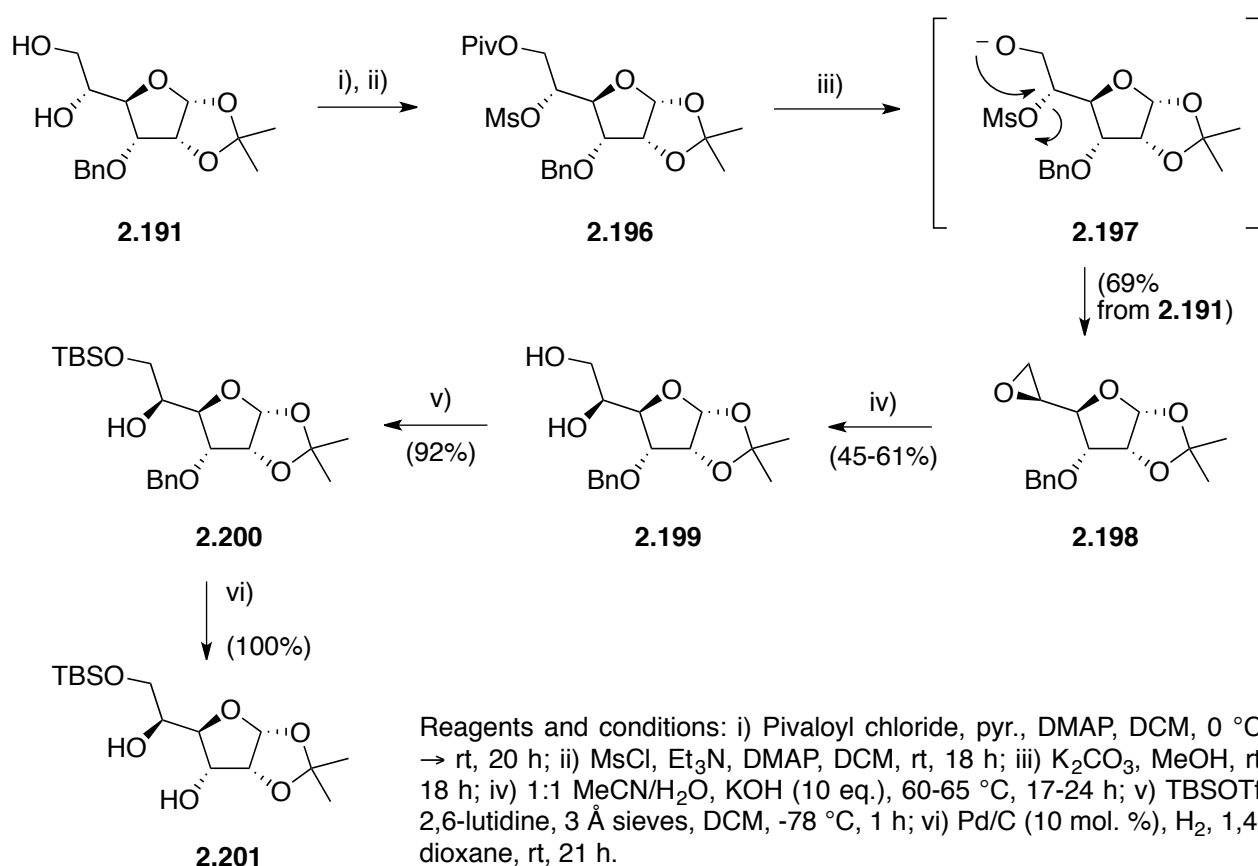
Reagents and conditions: i) BnBr, NaH, 3 Å sieves, DMF, rt, 2 h; ii) 4:1 AcOH/H₂O, rt, 24 h; iii) TBSOTf, 2,6-lutidine, 3 Å sieves, DCM, -78 °C, 30 min; iv) PPh₃, DIAD, *p*-NO₂-C₆H₄-CO₂H, PhMe, rt; v) Tf₂O, pyr., DCM, -30 °C, 45 min; vi) CF₃CO₂Na, DMF, 40 °C, 20 h.

Scheme 2.34: First approach towards C5 epimerisation

Mitsunobu reaction with triphenylphosphine, diisopropyl azodicarboxylate and 4-nitrobenzoic acid in toluene led to the formation of a complex, unidentified mixture of products which was not investigated further. The alternative approach to inversion *via* triflation of **2.192** followed by treatment with sodium trifluoroacetate at elevated temperature was thus attempted. However, rather

than the desired *L-talo* alcohol, the sole isolated product from this sequence was the corresponding formate ester **2.193** in poor yield. This somewhat surprising outcome is presumably a result of the preferential nucleophilic attack by DMF – rather than trifluoroacetate – on the triflate **2.194**, followed by the hydrolysis of the intermediate imidate ester salt **2.195** as shown.²²⁴

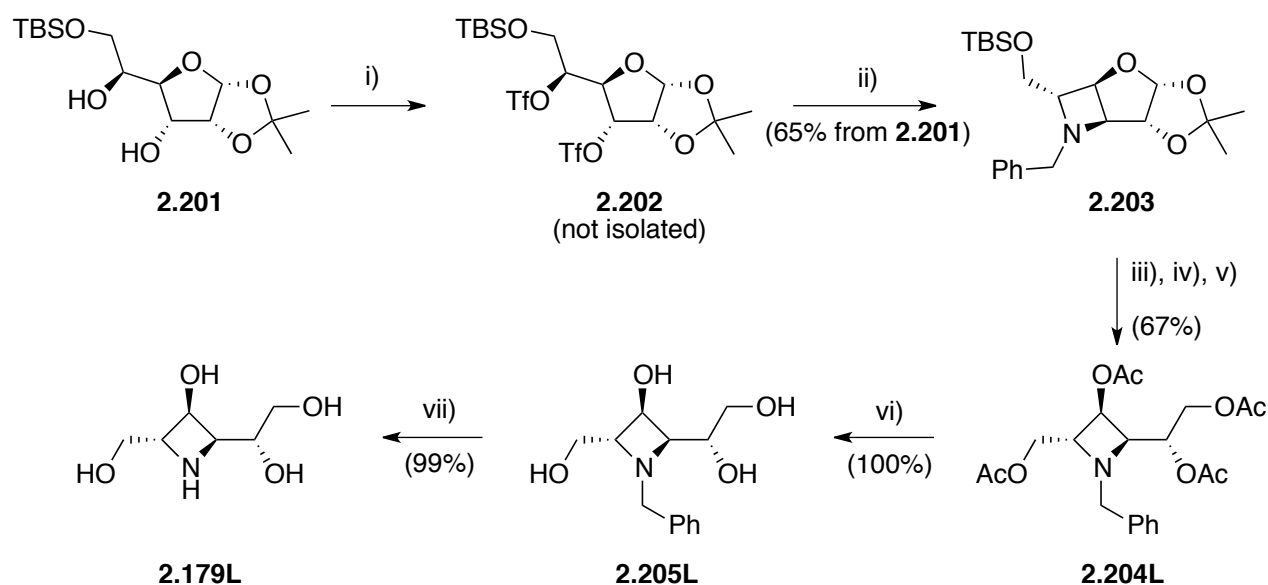
An alternative, divergent route towards the *L-talo* alcohol was therefore devised involving the corresponding epoxide precursor. Thus, the 5,6-anhydro *L-talo*furanose **2.198** was prepared using a known procedure (Scheme 2.35).²²⁵ Treatment of the diol **2.191** with pivaloyl chloride, pyridine



Scheme 2.35: Second approach towards C5 epimerisation

and catalytic 4-dimethylaminopyridine (DMAP) in DCM effected selective protection of the terminal alcohol as its pivaloyl ester, and subsequent sulfonylation of the free remaining alcohol with mesyl chloride, triethylamine and catalytic DMAP in DCM furnished the mesylate **2.196**. Basic hydrolysis of the pivaloyl ester of **2.196** with methanolic potassium carbonate, followed by

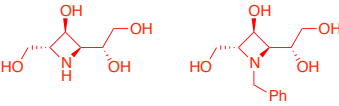
nucleophilic ring closure of the liberated alkoxide **2.197** afforded the epoxide **2.198** in 69% over three steps. The subsequent regioselective ring opening of the epoxide of **2.198** with potassium hydroxide in aqueous acetonitrile proved more troublesome than expected. No reaction occurred at room temperature, but successful ring opening was achieved at elevated temperatures. However, under these conditions only moderate yields of the desired *L-talo* diol **2.199** were isolated, with the remaining material comprising inseparable mixtures of polar, unidentified side products. None of these products were the *D-allo* diol **2.191** however, which could arise from competing ring opening at the C5 side of the epoxide, and the exact nature of these side reactions therefore remains unclear. Nonetheless, this method allowed access to reasonable amounts of **2.199**. Efficient, selective protection of the terminal alcohol in **2.199** was next achieved with *tert*-butyldimethylsilyl trifluoromethanesulfonate and 2,6-lutidine in DCM at -78 °C, affording the TBS ether **2.200** in 92% yield. Finally, hydrogenolysis of the benzyl ether with palladium on carbon and molecular hydrogen in 1,4-dioxane afforded the 3,5-diol **2.201** in quantitative yield.



Reagents and conditions: i) TiF_2O , pyr., DCM, -30 °C, 1 h; ii) BnNH_2 (1.1 eq.), DIPEA (2.5 eq.), MeCN, 50 °C, 19 h; iii) 9:1 TFA/ H_2O , rt, 24 h; iv) NaBH_4 , H_2O , rt, 66 h; v) Ac_2O , pyr., rt, 2.5 h; vi) NaOMe , MeOH, rt, 14 h; vii) Pd/C, HCO_2NH_4 , MeOH, argon, reflux, 10 min.

Scheme 2.36: Preparation of *L*-gulitol azetidine iminosugars

With the diol **2.201** in hand, treatment with triflic anhydride and pyridine in DCM at low temperature afforded the ditriflate **2.202**, which without isolation was cyclised with benzylamine and DIPEA in acetonitrile at 50 °C, affording the D-*gluco* fused azetidine **2.203** in 65% yield over two steps (Scheme 2.36). Hydrolysis of the TBS ether and acetonide was achieved with 9:1 TFA/water, and reduction of the resulting lactol with aqueous sodium borohydride followed by treatment with acetic anhydride and pyridine furnished the per-acetate **2.204L** in 67% yield over three steps. Zemplén conditions then effected quantitative de-acetylation to the *N*-benzyl L-gulitol azetidine **2.205L**, and debenzylation under the established transfer hydrogenation conditions afforded the parent N-H compound **2.179L** in 99% yield.

Concentration of 2,4-dideoxy-2,4-imino-L-gulitols giving 50 % inhibition of various glycosidases		
	IC ₅₀ (μM)	
		
Enzyme	2.179L	2.205L
α-Glucosidase		
Rice	NI (17.2%)	NI (7.3%)
Yeast	NI (21.7%)	NI (8.0%)
Rat intestinal maltase	NI (20.2%)	NI (0%)
<i>A. niger</i>	NI (9.2%)	NI (1.8%)
β-Glucosidase		
Almond	NI (27.0%)	NI (4.8%)
Bovine liver	NI (15.4%)	NI (32.4%)
α-Galactosidase		
Coffee beans	NI (37.0%)	NI (11.8%)
β-Galactosidase		
Bovine liver	NI (7.9%)	530
α-Mannosidase		
Jack beans	NI (3.3%)	NI (10.2%)
β-Mannosidase		
Snail	NI (4.4%)	NI (1.7%)
α-L-Rhamnosidase		
<i>P. decumbens</i>	NI (0%)	NI (3.6%)
α-L-Fucosidase		
Bovine kidney	NI (0%)	NI (1.5%)
Trehalase		
Porcine kidney	NI (9.9%)	NI (3.3%)
Amyloglucosidase		
<i>A. niger</i>	NI (1.6%)	NI (2.7%)

^a NI : No inhibition (less than 50% inhibition at 1000 μM).

^b () : Inhibition % at 1000 μM.

The L-gulitol azetidines **2.179L** and **2.205L** were assayed in the same manner as before (Atsushi Kato), and the results are shown to the left (Table 2.8). Unfortunately the N-H azetidine **2.179L** showed no activity at all, but the *N*-benzyl azetidine **2.205L** showed selective, albeit weak, inhibition of β-galactosidase (IC₅₀ 530 μM). Further investigations into the effects of alternative *N*-substitutions, as well as the biological activity of the mirror image D-series, are currently underway within the Fleet group.

Table 2.8: Assays of L-gulitol azetidines

2.2.3 *D-Talo* azetidine tetrol from glucopyranoside (2,4-displacement)²²²

With the validation of the 3,5-displacement strategies on both pento- and hexofuranosides, the cyclisation onto a 2,4-ditriflate of a hexopyranoside was the final general strategy to be tackled. In light of the high amount of ring strain inherent in the [1.1.3] bicyclic type products **2.114** (Scheme 2.19, Section 2.2), successful cyclisation to such targets would appear a considerably more challenging prospect than that of the analogous 3,5- or 4,6-displacements. The stereochemical requirement for a *cis*-ditriflate in the substrate limits the suitable hexoses to glucose, allose, idose and talose (Figure 2.16). Glucopyranoside was chosen as the test substrate for the strategy, as amongst those shown it is unique in being able to adopt a conformation in which all potentially disfavourable 1,3-diaxial interactions – either in the substrate itself or the intermediate(s) of the reaction – are avoided. As such it was considered the system likely to be most favourable towards ring formation. Thus, the *D-talo* azetidine tetrol resulting from the following work was not designed with any particular targeted function in mind, but rather represents a synthetic proof-of-principle for the general 2,4-displacement strategy.

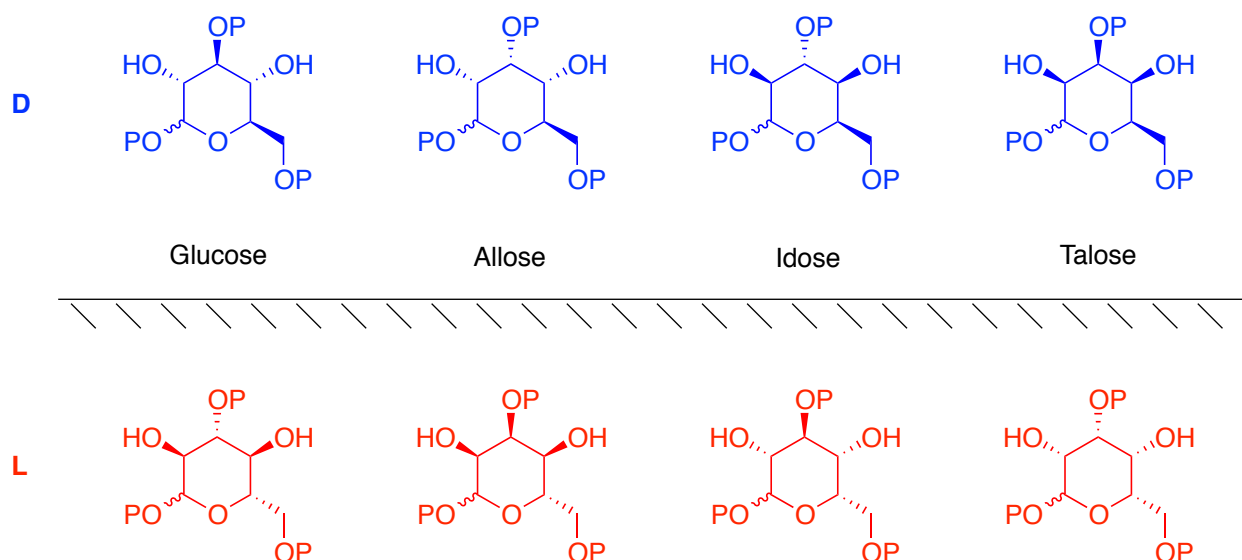
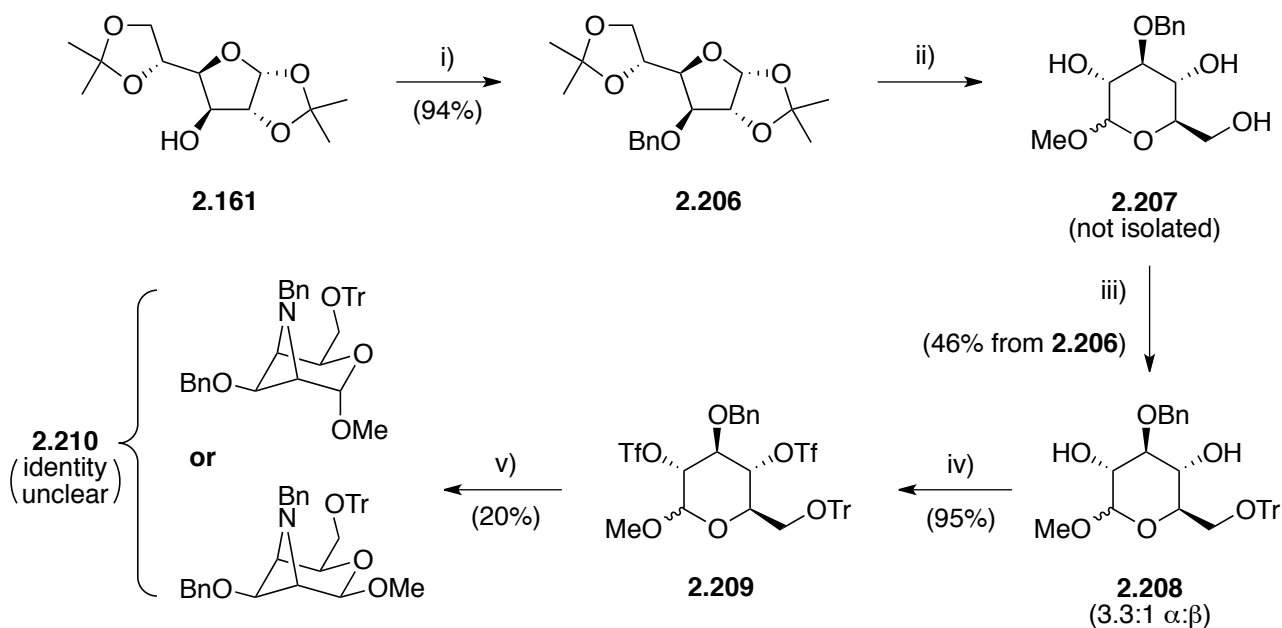


Figure 2.16: Aldohexose pyranosides suitable for 2,4-displacement strategy

The initial approach towards preparing a suitable substrate for 2,4-cyclisation involved an acid catalysed Fischer glycosidation as the key pyranoside-forming step (Scheme 2.37). Protection of diacetone-D-glucose **2.161** as its 3-*O*-benzyl ether **2.206** was achieved in 94% yield with the use of sodium hydride and benzyl bromide in anhydrous DMF. One-pot hydrolysis of the acetonide groups in **2.206** with concomitant Fischer glycosylation was then carried out *via* reflux with anhydrous hydrochloric acid generated *in situ* from methanolysis of acetyl chloride, furnishing the crude mixture of methyl pyranosides **2.207**. Without isolation, selective protection of the primary alcohol in **2.207** with trityl chloride and pyridine at 100 °C afforded the anomeric mixture of trityl ethers **2.208** in 46% yield over two steps, and subsequent triflation of the free alcohols afforded the unstable 2,4-ditriflates **2.209** in 95% yield. Attempts at cyclisation of **2.209** with benzylamine in

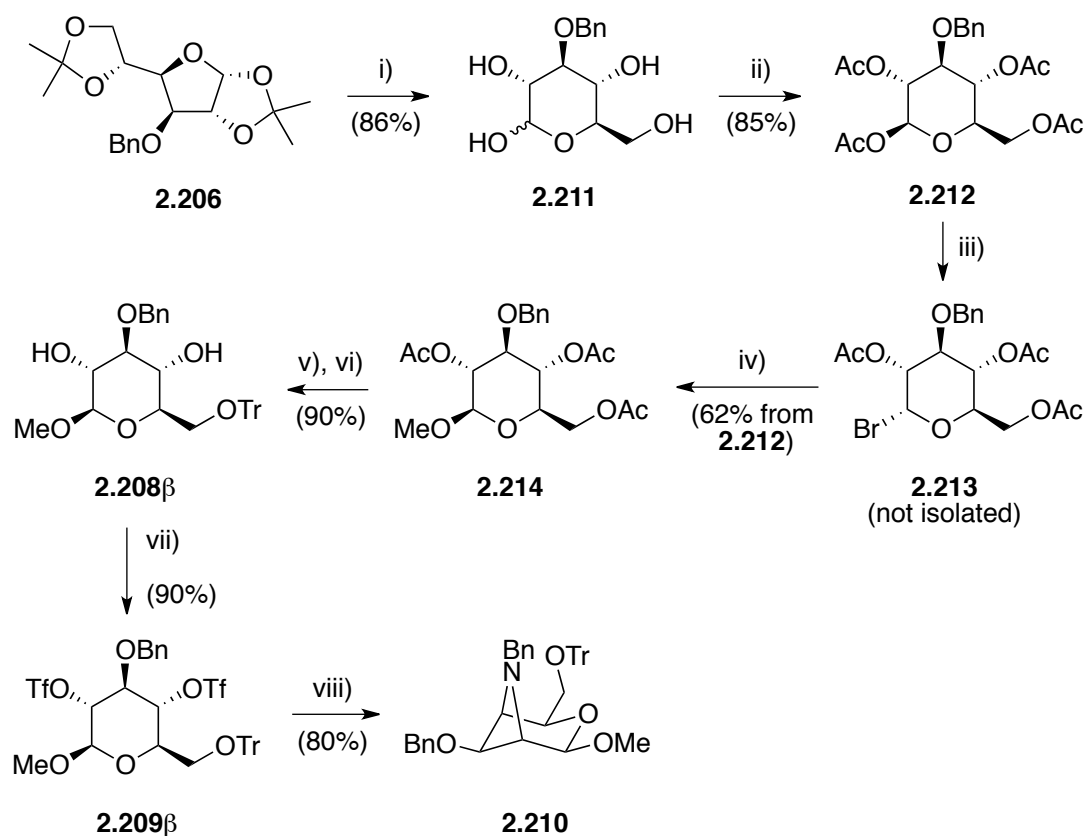


Scheme 2.37: Initial approach towards 2,4-cyclisation

acetonitrile at either room temperature or 50 °C resulted in no reaction, whereas raising the temperature to 80 °C gave successful cyclisation, generating the fused bicycle **2.210** in 20% yield. This product was formed as a single anomer, the identity (α or β) of which could not be reliably

discerned through NMR studies, and its amorphous consistency foiled attempts at growing a crystal suitable for X-ray analysis. Nonetheless the fact that only a single product was being formed, coupled with the low yield obtained, led to a suspicion that only the minor β -anomer of the precursor mixture was reacting successfully. Indeed, careful column chromatography of the anomeric mixture **2.209** allowed some of the α -ditriflate **2.209 α** to be isolated, and subsequent subjection of this single anomer to the same cyclisation conditions as for the mixture led only to decomposition rather than any discernable formation of the bicyclic product **2.210**. An alternative route was therefore devised involving the β -pyranoside as the sole intermediate, in order to definitively confirm the issue of reactivity as well as the identity of the bicycle **2.210**.

3-*O*-Benzyl-di-acetone-D-glucose **2.206** was hydrolysed *via* treatment with aqueous trifluoroacetic acid, affording 3-*O*-benzyl glucopyranose **2.211** in 86% yield (Scheme 2.38). Subsequent peracetylation with acetic anhydride and pyridine furnished the β -acetate **2.212** as the sole product in 85% yield after re-crystallisation. Bromination of **2.212** was then achieved with hydrobromic acid in acetic acid and DCM at 5 °C, affording the α -bromide **2.213**, which was used without purification in a Koenigs-Knorr glycosidation by treatment with silver carbonate in methanol with exclusion of light, affording the methyl β -pyranoside tri-acetate **2.214** as the sole anomer in 62% yield over two steps. Next, Zemplén de-acetylation with sodium methoxide in methanol at a slightly elevated temperature of 40 °C afforded the corresponding triol, and selective re-protection of the 6-hydroxyl as its trityl ether with trityl chloride, pyridine and catalytic DMAP afforded the diol **2.208 β** in 90% yield over two steps. Sulfonylation with triflic anhydride and pyridine in DCM at -10 °C then furnished the 2,4-ditriflate **2.209 β** in 90% yield. Finally, it was found that treatment of **2.209 β** with benzylamine in acetonitrile at 70 °C effected remarkably efficient cyclisation, and the bicyclic product thus formed in 80% yield was **2.210**: the same as that afforded from similar treatment of the anomeric mixture **2.209** (Scheme 2.37). The hypothesis of differing anomeric reactivity was therefore vindicated, and the identity of **2.210** confirmed as the β -glycoside.



Reagents and conditions: i) 1:1 TFA/H₂O, rt, 23 h; ii) 1:1 Ac₂O/pyr., rt, 14 h; iii) HBr, AcOH, DCM, 5 °C, 4 h; iv) Ag₂CO₃, MeOH, dark, rt, 17 h; v) NaOMe, MeOH, rt → 40 °C, 36 h; vi) TrCl, pyr., DMAP, rt, 50 h; vii) Tf₂O, pyr., DCM, -10 °C, 4 h; viii) BnNH₂ (5 eq.), MeCN, 70 °C, 2 h.

Scheme 2.38: Second approach towards 2,4-cyclisation

The reason behind the inability of the ditriflate **2.209a** to successfully give rise to a bicyclic product is not clear. Figure 2.17 shows the possible conformations of the bicyclic product **2.210** (^oC₃ and B_{O,3}), along with its salient measured Nuclear Overhauser Effect (NOE) enhancements. The complete lack of NOE enhancement between the methyl protons and H₂, between H₆/H_{6'} and H₄, or most crucially between H₁ and H₅, indicates that **2.210** adopts the B_{O,3} conformation – or something close to it – in solution over that of ^oC₃. Presumably the stabilising anomeric effect present in B_{O,3} must overcome the added steric demand of the axial OMe and C6 groups when compared to the ^oC₃ case. There does not appear to be a compelling reason why the formation of the α -glycoside analogue of **2.210** would be so much less favourable in terms of the comparative stability of the products. On the other hand, one possible explanation for the differing reactivity of the α - and β -ditriflate substrates **2.209a** and **2.209b** could be their contrasting potential for

competing E2 elimination (Figure 2.18); **2.209 α** possesses two conformers (${}^1,4\text{B}$ and ${}^1\text{C}_4$, shown in red) in which there is an antiperiplanar arrangement of a proton and triflate necessary for E2 elimination, whereas **2.209 β** possesses none. The glucal product of such an elimination would then be capable of undergoing any number of side reactions or rearrangements, and could thus account for the observed decomposition. Such a hypothesis would seem plausible in light of the high temperature and excess base necessary for cyclisation, but nevertheless the exact nature of the problem remains unknown.

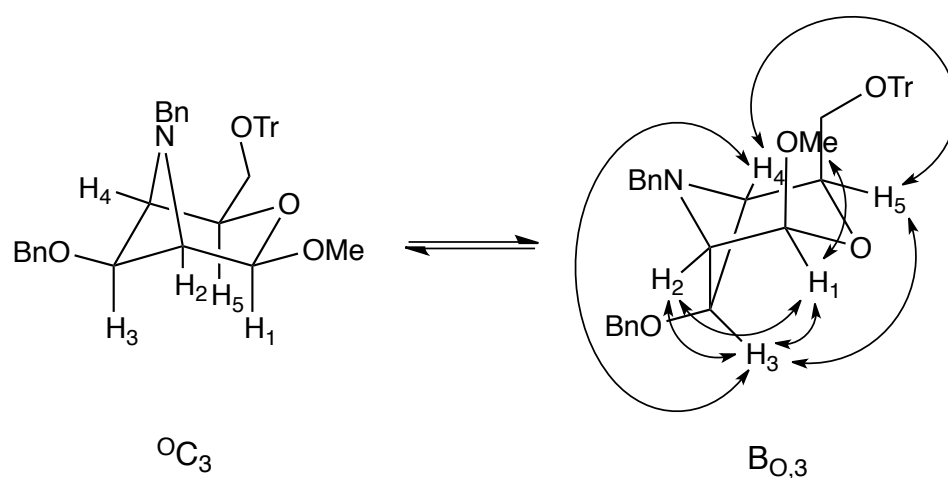


Figure 2.17: Possible conformations of bicycle **2.210** along with its NOE enhancements

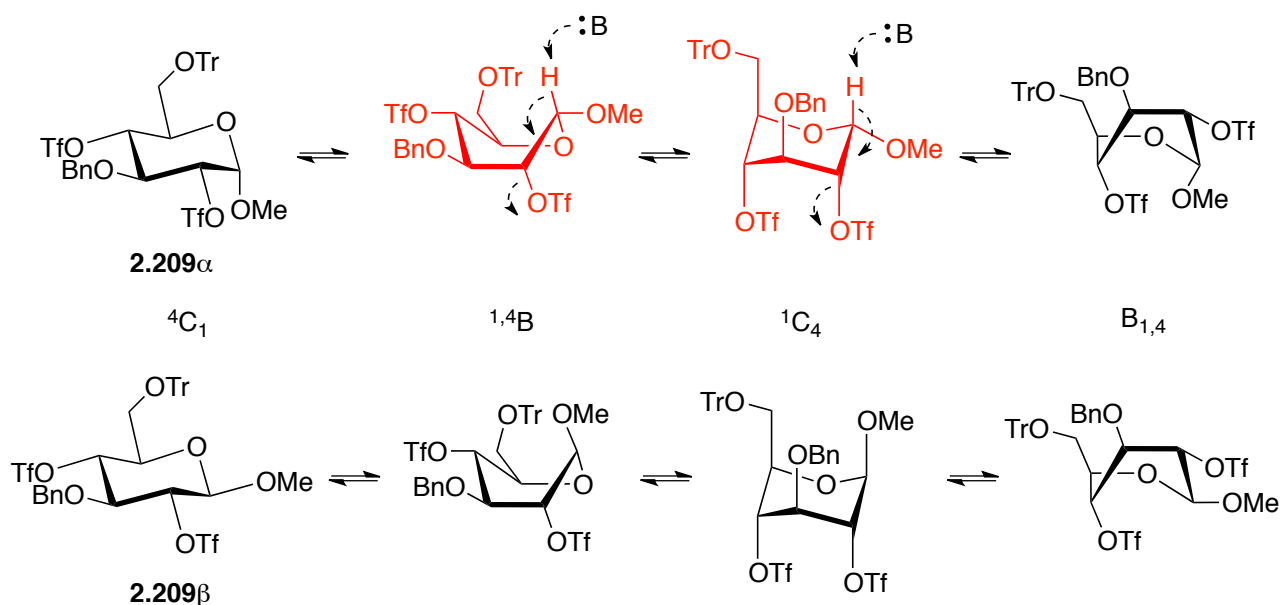
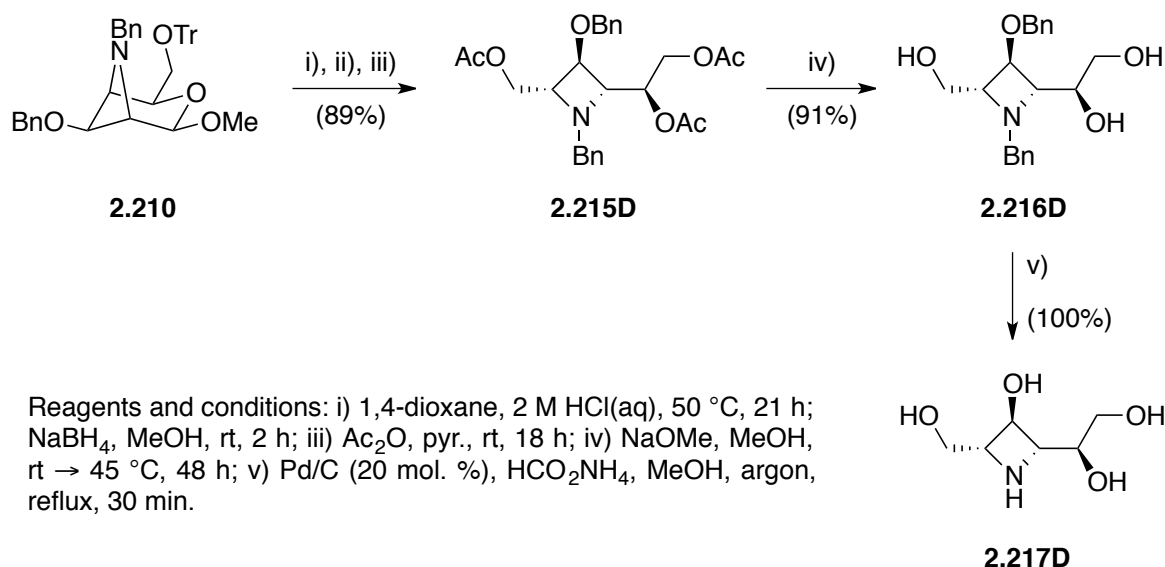


Figure 2.18: Ditriflate conformers and potential E2 eliminations

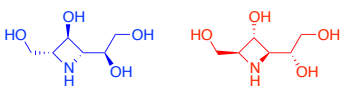
For the completion of the synthesis (Scheme 2.39), hydrolysis of both the trityl ether and methyl glycoside functionality of the bicycle **2.210** was achieved in a mixture of 1,4-dioxane and 2 M aqueous hydrochloric acid at 50 °C. Reduction of the intermediate aldehyde with methanolic sodium borohydride and re-protection of the resulting triol with acetic anhydride and pyridine facilitated purification as its corresponding tri-acetate **2.215D**. Zemplén de-acetylation at 45 °C then furnished the triol **2.216D**, and subsequent cleavage of both the *O*- and *N*-benzyl groups under the established transfer hydrogenation conditions afforded the N-H D-talitol azetidine **2.217D** in quantitative yield.



Scheme 2.39: Preparation of D-talitol azetidine iminosugar

There was insufficient time or material within the project to prepare any *N*-substituted analogues of **2.217D**. However the successful synthesis thus developed was later repeated by a colleague (Noelia Araújo) for the preparation of the mirror image L-talitol **2.217L** from L-glucose. Both compounds were assayed against the usual panel of glycosidases (Atsushi Kato), and the results are shown in Table 2.9.

Concentration of 2,4-dideoxy-2,4-imino-talitols giving 50 % inhibition of various glycosidases

IC ₅₀ (μM)		
		
Enzyme	2.217D	2.217L
α-Glucosidase		
Rice	NI ^a (14.5%) ^b	481
Yeast	NI (40.6%)	NI (8.3%)
Rat intestinal maltase	NI (11.6%)	176
<i>A. niger</i>	NI (5.2%)	NI (6.4%)
β-Glucosidase		
Almond	NI (7.1%)	NI (2.0%)
Bovine liver	NI (17.7%)	NI (18.8%)
α-Galactosidase		
Coffee beans	NI (10.1%)	NI (24.3%)
β-Galactosidase		
Bovine liver	NI (11.4%)	NI (8.2%)
α-Mannosidase		
Jack beans	NI (1.4%)	NI (7.2%)
β-Mannosidase		
Snail	NI (5.7%)	NI (0%)
α-L-Rhamnosidase		
<i>P. decumbens</i>	NI (2.3%)	NI (3.9%)
α-L-Fucosidase		
Bovine kidney	NI (0%)	NI (0%)
Trehalase		
Porcine kidney	NI (21.1%)	NI (0%)
Amyloglucosidase		
<i>A. niger</i>	NI (3.7%)	NI (2.4%)
<i>Rhizopus sp</i>	NI (5.4%)	NI (1.1%)

^a NI : No inhibition (less than 50% inhibition at 1000 μM).^b () : Inhibition % at 1000 μM.**Table 2.9:** Assays of talitol azetidines

The D-talitol azetidine **2.217D** prepared herein unfortunately showed no activity against any of the screened glycosidases. In contrast, the L-enantiomer **2.217L** did show selective, albeit weak, inhibition of plant (rice) and mammalian (rat intestinal maltase) α-glycosidases, with IC₅₀ values of 481 and 176 μM respectively.

2.2.4 1-Acetamido L-ido azetidine triols (3,5-displacement)

Hexosaminidase inhibitors are targets of ongoing interest within the Fleet group, primarily due to their potential as anti-cancer therapeutics (see Chapter 1). DGJNAc (Figure 2.19) is a highly potent and competitive inhibitor of α-N-acetylgalactosaminidases²⁰² (chicken liver IC₅₀ 320 nM, K_i 81 nM; *Charonia lampas* K_i 136 nM), as well as a potent inhibitor of β-N-acetylglucosaminidases (jack beans IC₅₀ 1.8 μM; bovine kidney IC₅₀ 4.2 μM; human placenta IC₅₀ 8.3 μM). N-substituted

analogues of DGJNAc have also been prepared,²²⁶ and were found to exhibit similar potency of inhibition towards β -*N*-acetylglucosaminidases at the expense of reduced potency towards α -*N*-acetylgalactosaminidases by 1-2 orders of magnitude. Furthermore, various pipecolic acid amide and proline amide analogues have also been prepared as part of ongoing projects within the Fleet group, and a number (for example **AG301**, **AG337**, **SFJ8-758**, **BA4/335**, Figure 2.19) exhibit potent inhibition of hexosaminidases.²²⁷ It was therefore desired to extend the established azetidine ring-forming methodology towards the preparation of ring-contracted analogues of these 5- and 6-ring amide and NAc compounds in order to investigate their potential as hexosaminidase inhibitors; presented herein is the author's work on the syntheses of the first of these NAc azetidines.

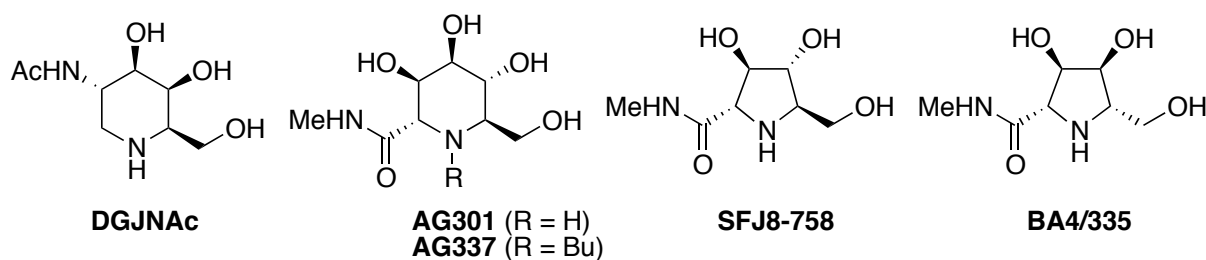
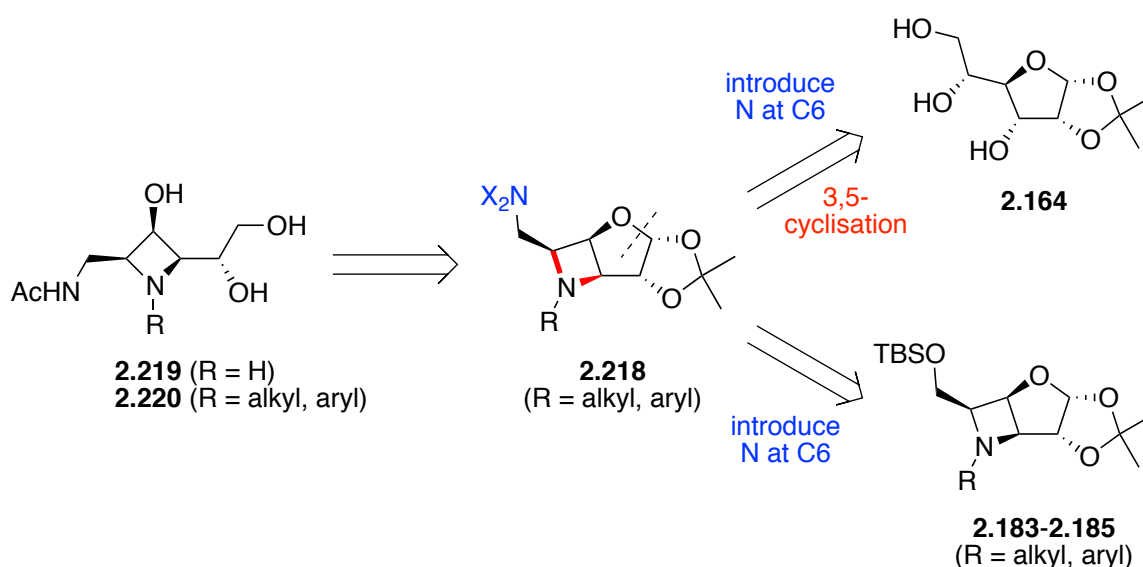


Figure 2.19: Structures of some hexosaminidase inhibitors

The 1-acetamido L-iditol azetidine **2.219** and its *N*-substituted analogues **2.220** were chosen as appropriate initial targets (Scheme 2.40), as retrosynthetically the common fused intermediate **2.218** could potentially be accessed in a divergent manner from the precursors **2.164** or **2.183-2.185** already prepared; either from introduction of a masked nitrogen before or after azetidine ring formation respectively. Furthermore, the molecular superimposition of **2.219** with DGJNAc (Figure 2.20) shows a good degree of overlap, implying that this particular stereoisomer and its *N*-substituted analogues may exhibit similar hexosaminidase inhibition to that of the DGJNAc series.



Scheme 2.40: Retrosynthesis of 1-acetamido L-iditol azetidine iminosugars

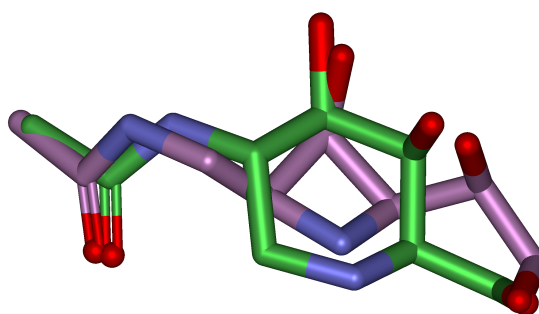
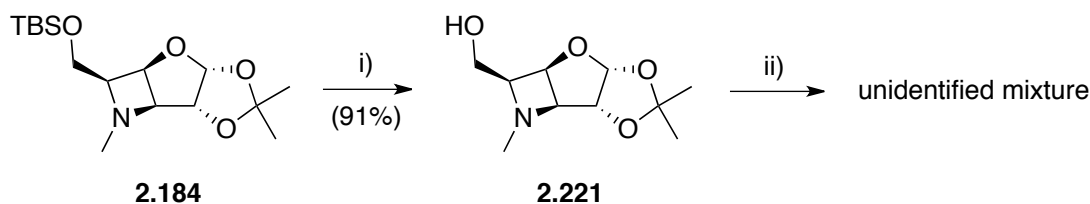


Figure 2.20: Molecular superimposition of DGJNAc with **2.219**

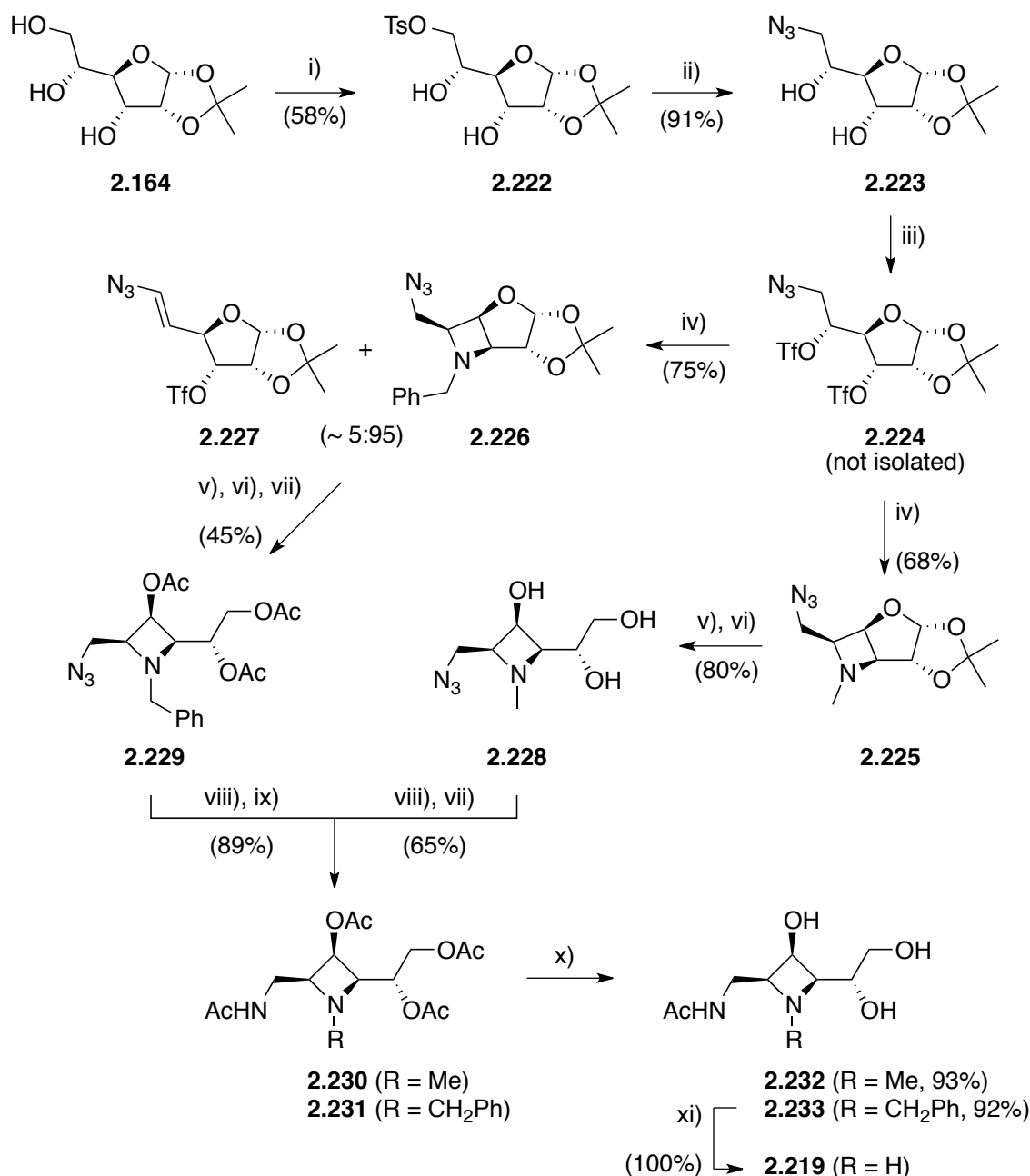
Initially, the introduction of nitrogen at C6 post azetidine ring formation was planned by way of sodium azide displacement of the parent triflate precursor (Scheme 2.41). Thus, desilylation of the TBS ether **2.184** with TBAF in THF afforded the corresponding terminal alcohol **2.221** in 91% yield. However subsequent attempts at generating the 6-*O*-triflate by treatment of **2.221** with triflic anhydride and pyridine in DCM at -30 °C failed, instead resulting in a mixture of at least three unidentified products; presumably as a consequence of the various possible ring rearrangements of the triflate intermediate. This approach was therefore deemed unsuitable and was not pursued any further; an alternative route *via* introduction of nitrogen prior to ring formation was therefore devised.



Reagents and conditions: i) TBAF, THF, rt, 6.5 h; ii) Tf₂O, pyr., DCM, -30 °C, 30 min.

Scheme 2.41: Attempted introduction of nitrogen post ring formation

Selective sulfonylation of the primary alcohol of the previously prepared D-*allo* triol **2.164** was achieved with *p*-toluenesulfonyl chloride and pyridine, affording the 6-*O*-tosylate **2.222**, albeit in a yield of only 58% (Scheme 2.42). Although this is a relatively modest result, the stated conditions were the most optimal found; the desired product was always accompanied by mixtures of recovered starting material and di-tosylated products. Numerous attempts with differing reaction temperatures or with the use of more sterically hindered reagents (2,6-lutidine, 2,4,6-collidine, mesitylenesulfonyl chloride) gave no improvement in the yield of the desired 6-*O*-sulfonyl products. Nonetheless, with the tosylate **2.222** in hand, subsequent heating with sodium azide in DMF gave slow but efficient nucleophilic displacement, affording the corresponding azide **2.223** in 91% yield. Triflation of the free alcohols in **2.223** then afforded the 3,5-ditriflate **2.224**, which was used without purification for the subsequent reactions. Treatment of this ditriflate with methylamine and DIPEA in acetonitrile at room temperature resulted in clean formation of the fused *N*-methyl azetidine azide **2.225** in 68% yield over two steps. However, similar treatment of **2.224** with benzylamine and DIPEA in acetonitrile at 40 °C afforded a 75% yield of an inseparable mixture of the expected azetidine azide **2.226** and the *trans*-alkene **2.227** in an approximate ratio of 95:5. This result constituted the first observable formation of an elimination product during a 3,5-displacement. Nonetheless, hydrolysis of this mixture with aqueous TFA followed by reduction with sodium borohydride afforded a crude mixture which was passed through a column of acidic ion exchange



Reagents and conditions: i) TsCl, pyr., 3 Å sieves, -20 °C → rt; ii) NaN₃, DMF, 50-75 °C, 6 days; iii) Tf₂O, pyr., DCM, -30 °C, 1 h; iv) RNH₂, DIPEA, MeCN, rt (R = Me) or 40 °C (R = CH₂Ph), 21-23 h; v) 1:1 TFA/H₂O, rt, 27-48 h; vi) NaBH₄, H₂O (for **2.228**) or 2:1 H₂O/1,4-dioxane (for **2.229**), rt, 16-20 h; vii) Ac₂O, pyr., rt, 15-20 h; viii) Pd/C (5-10 mol. %), H₂, H₂O (R = Me) or EtOH (R = CH₂Ph), rt, 2 h; ix) Ac₂O, pyr., DCM, DMAP, 68 h; x) NaOMe, MeOH, rt, 18 h; xi) Pd/C (20 mol. %), HCO₂NH₄, MeOH, argon, reflux, 1.5 h.

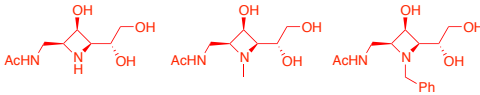
Scheme 2.42: Preparation of 1-acetamido L-iditols *via* introduction of nitrogen prior to ring formation

resin, thus facilitating the removal of the non-basic side products. Subsequent acetylation of this semi-purified material then afforded the pure tri-acetate **2.229** in 45% yield over three steps. Similarly, hydrolysis of the *N*-methyl fused azetidine azide **2.225** with aqueous TFA and reduction

of the resulting lactol with sodium borohydride furnished the azetidine azide triol **2.228** in 80% yield; no further purification *via* acetylation was required in this case. Reduction of the azide functionality in **2.228** and **2.229** was then achieved with palladium on carbon and molecular hydrogen, and subsequent acetylation of the resulting amines afforded the 1-acetamido 2-*N*-methyl and -benzyl tri-acetates **2.230** and **2.231** in yields of 65% and 89% respectively over two steps. Finally, Zemplén de-acetylation of **2.230** and **2.231** afforded the corresponding 1-acetamido L-idoitol azetidines **2.232** and **2.233** in respective yields of 92% and 93%, and subsequent debenzylation of **2.233** under catalytic transfer hydrogenation with ammonium formate afforded the parent N-H compound **2.219** in quantitative yield. The successful syntheses of these 1-acetamido azetidines further demonstrates the utility and flexibility of this general ring-forming strategy, with the allowance for divergent installation of added functionality to the azetidine scaffold. Such methodology should therefore allow access to many different amine- or NAc-functionalised azetidine targets *via* the 3,5-, 2,4- or indeed 4,6-displacement strategies.

Biological screening of the 1-acetamido L-idoitols **2.219**, **2.232** and **2.233** for activity against a panel of relevant glucosidases was performed by Professor Atsushi Kato, and the results are displayed in Table 2.10. Unfortunately only the *N*-methyl compound **2.232** displayed any activity, with weak inhibition of both β -*N*-acetylglucosaminidase (jack bean, IC₅₀ 721 μ M) and α -*N*-acetylgalactosaminidase (chicken liver, IC₅₀ 682 μ M). However, a number of similar analogues have very recently been prepared by a colleague,²²⁸ and they show more promising biological results. These analogues differ from the 1-acetamido L-idoitols prepared herein in that they possess different stereochemistries, a one-carbon – rather than two-carbon – side chain and primary amides in place of the *N*-acetyl group (amides are well known to be effective bioisosteres of *N*-acetyl moieties). Some of them have displayed quite potent inhibition of β -*N*-acetylglucosaminidase, with IC₅₀ values in the low μ M range. Such results clearly demonstrate that these azetidine scaffolds merit further examination as potential hexosaminidase inhibitors; in particular the relative

significance of their differing structural factors to the discrepancy in the displayed inhibition profiles is something that will require elucidation.

Concentration of 1-acetamido L-iditols giving 50 % inhibition of various glycosidases			
IC ₅₀ (μM)			
			
Enzyme	2.219	2.232	2.233
β-N-Acetylglucosaminidase			
Human placenta	NI (12.2%)	NI (27.8%)	NI (1.9%)
Bovine kidney	NI (21.2%)	NI (39.9%)	NI (9.4%)
Jack beans	NI (27.6%)	721	NI (19.0%)
HL60	NI (12.9%)	NI (36.4%)	NI (7.5%)
<i>Aspergillus oryzae</i>	NI (0%)	NI (12.6%)	NI (25.6%)
α-N-Acetylgalactosaminidase			
Chicken liver	NI (6.5%)	682	NI (30.4%)
β-N-Acetylgalactosaminidase			
HL60	NI (4.9%)	NI (12.6%)	NI (0.4%)
<i>Aspergillus oryzae</i>	NI (4.8%)	NI (10.6%)	NI (8.3%)
β-glucuronidase			
E.coli	NI (2.3%)	NI (1.0%)	NI (21.0%)
Bovine liver	NI (2.4%)	NI (4.2%)	NI (26.0%)

^a NI : No inhibition (less than 50% inhibition at 1000 μM).

^b () : inhibition % at 1000 μM

Table 2.10: Assays of 1-acetamido L-iditol azetidines

2.3 Conclusions and future work

The utilisation of nucleophilic displacements of ditriflates of monosaccharides by amines as a key general methodology for the preparation of polyhydroxylated azetidines as four-membered ring iminosugar analogues has been firmly established. The use of this highly efficient, general approach to ring-formation – in the guise of 3,5- and 2,4-ditriflate displacement strategies – has thus enabled the preparation of a number of enantiopure target azetidine iminosugars in relatively brief fashion from either pentoses or hexoses: *arabino* and *xylo* azetidine triols from arabinose and ribose respectively; *ido*, *gulo* and *talo* azetidine tetrols from allose, talose and glucose respectively; and finally 1-acetamido *ido* azetidine triols from allose. Although the biological assays thus far

performed on these first few compounds have not revealed any particularly potent activity, they nevertheless do exhibit an array of glycosidase inhibition, including that of selective inhibition of fungal enzymes. Such results are clearly encouraging, and indicate that with further exploration and refined target design, future examples of this neglected class of compound may well prove valuable additions to the available arsenal of iminosugars used to treat relevant diseases.

The flexible methodology developed herein clearly has broader potential applications: for example in the preparation of any number of bicyclic, ring-contracted analogues of well-known indolizidine and pyrrolizidine iminosugars such as swainsonine, castanospermine and casuarine (see Chapter 1); a purpose for which the 4,6-displacement strategy – if similarly successful – would seem particularly well suited. The ready possibility of preparing NAc derivatives has been demonstrated with the syntheses of the 1-acetamido L-iditol azetidines, but alternative modifications to the chemistry should also readily allow for the introduction of other functionality to the azetidine scaffold, such as carboxylic acids or their amide analogues. All these targets described above – and their potential applications – are the subject of ongoing research within the Fleet group.

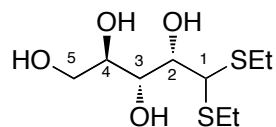
2.4 Experimental

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 F₂₅₄ silica. Plates were visualised using a spray of 1% w/v potassium permanganate in 1M sodium hydroxide, or a 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate solution in 2M sulfuric acid. Flash column 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. Infrared spectra were recorded on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer using thin films on NaCl plates (thin film) unless otherwise stated. Only the characteristic peaks are quoted. Low resolution mass spectra (*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 NH₃) or atmospheric pressure chemical ionization (APCI). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AMX 500 (¹H: 500 MHz and ¹³C: 125.7 MHz) and Bruker DPX 400 and DQX 400 spectrometers (¹H: 400 MHz and ¹³C: 100.6 MHz) in the deuterated solvent stated. All chemical shifts (δ) 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. Chemical shifts of reference peaks were calibrated according to literature values.²²⁹

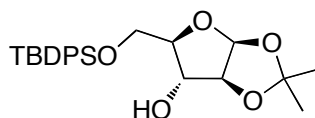
2.4.1 *Arabino* azetidine triols from arabinose

D-Arabinose-1,1-diethyl-dithioacetal **2.132**



Ethanethiol (49.3 mL, 666 mmol) was added to a stirred solution of D-arabinose (50.00 g, 333 mmol) in 3M hydrochloric acid (85 mL) at rt under nitrogen atmosphere. After 16 h the resulting suspension was filtered, and the cake washed sequentially with water (200 mL), cold ethanol (100 mL) and finally diethyl ether (500 mL) to afford the title compound as a white crystalline solid (53.90 g, 63%); $[\alpha]_D^{25}$ -12.6 (c 1.08 in MeOH) [lit.²³⁰ $[\alpha]_D^{25}$ -11.2 (c 3.67 in MeOH)]; $\nu_{\max}$ (thin film): 3262 (s, br, OH); m.p. 121-124 °C [lit.²³⁰ m.p. 126-127 °C]; δ_H (CD₃OD, 400 MHz): 1.24-1.27, 1.26-1.29 (2 x 3H, 2 x dd, J 4.3, J 7.4 Hz, 2 x SCH₂CH₃), 2.63-2.80 (2 x 2H, m, 2 x SCH₂CH₃), 3.60-3.64 (1H, dd, H5, $J_{5,4}$ 6.0, J_{gem} 11.1), 3.67-3.72 (1H, ddd, H4, $J_{4,5'}$ 3.2, $J_{4,5}$ 6.0, $J_{4,3}$ 8.5), 3.79-3.82 (1H, dd, H5', $J_{5',4}$ 3.2, J_{gem} 11.1), 3.84-3.87 (1H, dd, H2, $J_{2,3}$ 1.4, $J_{2,1}$ 9.2), 3.98-4.00 (1H, dd, H3, $J_{3,2}$ 1.4, $J_{3,4}$ 8.5), 4.06-4.08 (1H, d, H1, $J_{1,2}$ 9.2); δ_C (CD₃OD, 100 MHz): 14.8, 14.8 (2 x SCH₂CH₃), 25.4 (2 x SCH₂CH₃), 56.2 (C1), 65.1 (C5), 72.0 (C3), 72.8 (C2), 73.1 ppm (C4); m/z (ESI+ve): 279 ([M + Na]⁺, 100%), 535 ([2M + Na]⁺, 16%); HRMS m/z (ESI+ve): found 279.0693 ([M + Na]⁺); C₉H₂₀NaO₄S₂ requires 279.0695.

5-*O*-*tert*-Butyldiphenylsilyl-1,2-*O*-isopropylidene-β-D-arabinofuranose **2.134**

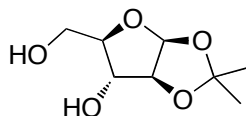


tert-Butyldiphenylsilyl chloride (5.58 mL, 21.45 mmol) was added to a stirred solution of dithioacetal **2.132** (5.00 g, 19.50 mmol) and imidazole (2.66 g, 39.00 mmol) in anhydrous dimethylformamide (25 mL) at 0 °C, and the mixture allowed to slowly warm to rt. TLC analysis

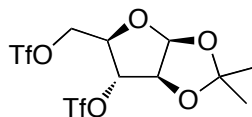
(1:1 cyclohexane/ethyl acetate) after 20 h showed no starting material (R_f 0.00) and formation of a single major product (R_f 0.57). The mixture was concentrated *in vacuo* and the resulting syrup partitioned between ethyl acetate (100 mL) and 20% brine (60 mL). The organic layer was washed with more 20% brine (2 x 60 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude 5-*O*-*tert*-butyldiphenylsilyl-D-arabinose-1,1-diethyl-dithioacetal as a clear oil. This was re-dissolved in 10% aqueous acetone (80 mL), yellow mercuric oxide (8.31 g, 38.4 mmol) and mercury(II) chloride (13.02 g, 48.0 mmol) added and the mixture stirred vigorously at rt. TLC analysis (1:1 cyclohexane/ethyl acetate) after 15 h showed no starting material and formation of a single product (R_f 0.20). The mixture was filtered through Celite, the pad washed with acetone and the filtrate concentrated *in vacuo*. The resulting yellow residue was purified through a silica gel plug (1:1 to 7:3 ethyl acetate/cyclohexane) to afford a clear oil (6.51 g). This oil was re-dissolved in acetone (80 mL), anhydrous copper(II) sulfate (9.80 g, 61.4 mmol) added, followed by DL-camphorsulfonic acid until pH 1 was obtained, and the mixture stirred at rt with exclusion of moisture. TLC analysis (1:1 cyclohexane/ethyl acetate) after 16 h showed formation of one major product (R_f 0.68). The mixture was quenched with solid sodium bicarbonate until pH 7, filtered through Celite and the filtrate concentrated *in vacuo* to afford a pale green oil. This oil was partitioned between chloroform (80 mL) and water (80 mL), the aqueous layer washed with chloroform (80 mL) and the organic layers dried ($MgSO_4$) and concentrated *in vacuo* to afford a clear oil (6.58 g). Purification *via* flash column chromatography on silica gel (30:1 to 1:1 cyclohexane/ethyl acetate) afforded the title compound as a clear oil (5.06 g, 62%); R_f 0.34 (3:1 cyclohexane/ethyl acetate); $[\alpha]_D^{24} +5.9$ (c 1.01 in $CHCl_3$) [lit.²³¹ $[\alpha]_D^{24} +5.6$ (c 3.2 in $CHCl_3$)]; ν_{max} (neat): 3455 (s, br, OH); δ_H ($CDCl_3$, 400 MHz): 1.07 (9H, s, $SiC(CH_3)_3$), 1.29, 1.33 (6H, 2 x s, $C(CH_3)_2$), 2.02-2.03 (1H, d, 3-OH, $J_{OH,3}$ 4.3), 3.79-3.83 (1H, dd, H5, $J_{5,4}$ 6.1, J_{gem} 10.3), 3.82-3.87 (1H, dd, H5', $J_{5',4}$ 7.5, J_{gem} 10.3), 4.04-4.08 (1H, m, H4), 4.43-4.44 (1H, m, H3), 4.54-4.55 (1H, d, H2, $J_{2,1}$ 4.0), 5.88-5.89 (1H, d, H1, $J_{1,2}$ 4.0), 7.36-7.45, 7.66-7.68 (10H, 2 x m, 10 x ArH); δ_C ($CDCl_3$, 100 MHz): 19.3 ($SiC(CH_3)_3$), 26.3 27.0 ($C(CH_3)_2$) 27.0 ($SiC(CH_3)_3$), 63.8 (C5), 76.5 (C3), 87.2 (C4), 87.5 (C2), 105.7 (C1), 112.7

($\underline{\text{C}}(\text{CH}_3)_2$), 129.9, 130.0 (2 x $p\text{-Ar}\underline{\text{C}}\text{H}$), 133.3, 133.3 (2 x $ipso\text{-Ar}\underline{\text{C}}\text{H}$), 127.9, 127.9, 135.7, 135.7 ppm (2 x $o\text{-Ar}\underline{\text{C}}\text{H}$ and 2 x $m\text{-Ar}\underline{\text{C}}\text{H}$); m/z (ESI+ve): 451 ($[\text{M} + \text{Na}]^+$, 97%), 467 ($[\text{M} + \text{K}]^+$, 100%), 879 ($[\text{2M} + \text{Na}]^+$, 34%); HRMS m/z (ESI+ve): found 451.1904 ($[\text{M} + \text{Na}]^+$); $\text{C}_{24}\text{H}_{32}\text{NaO}_5\text{Si}$ requires 451.1911.

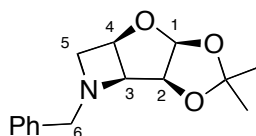
1,2-*O*-Isopropylidene- β -D-arabinofuranose **2.135**



A 1M solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (110.4 mL, 110.4 mmol) was added over a period of 20 mins to a stirred solution of silyl ether **2.134** (31.55 g, 73.6 mmol) in tetrahydrofuran (200 mL) at rt. TLC analysis (1:1 cyclohexane/ethyl acetate) after 2 h showed no remaining starting material (R_f 0.68) and formation of a single major product (R_f 0.10). The mixture was concentrated *in vacuo* and the resulting yellow residue purified by flash column chromatography on silica gel (2:1 cyclohexane/ethyl acetate to 9:1 ethyl acetate/methanol) to afford the title compound as a white crystalline solid (11.88 g, 85%); R_f 0.39 (ethyl acetate); $[\alpha]_D^{24} +16.3$ (c 1.39 in MeOH) [lit.²³² $[\alpha]_D^{22} +17.6$ (c 1.25 in MeOH)]; ν_{max} (thin film): 3382 (s, br, OH); m.p. 114-116 °C [lit.²³² m.p. 114-115 °C]; δ_{H} (CD_3OD , 400 MHz): 1.30, 1.49 (6H, 2 x s, $\text{C}(\underline{\text{CH}}_3)_2$), 3.63-3.68 (1H, dd, H5, $J_{5,4}$ 6.8, J_{gem} 11.4), 3.67-3.71 (1H, dd, H5', $J_{5',4}$ 6.5, J_{gem} 11.4), 3.94-3.98 (1H, a-dt, H4, $J_{4,3}$ 2.1, $J_{4,5}/J_{4,5'}$ 6.6), 4.13-4.13 (1H, d, H3, $J_{3,4}$ 2.1), 4.50-4.51 (1H, d, H2, $J_{2,1}$ 3.9), 5.87-5.88 (1H, d, H1, $J_{1,2}$ 3.9); δ_{C} (CD_3OD , 100 MHz): 26.2, 27.2 ($\text{C}(\underline{\text{CH}}_3)_2$), 63.4 (C5), 76.5 (C3), 88.4 (C2), 89.9 (C4), 107.1 (C1), 113.5 ($\underline{\text{C}}(\text{CH}_3)_2$); m/z (ESI+ve): 213 ($[\text{M} + \text{Na}]^+$, 100%); HRMS m/z (ESI+ve): found 213.0736 ($[\text{M} + \text{Na}]^+$); $\text{C}_8\text{H}_{14}\text{NaO}_5$ requires 213.0733.

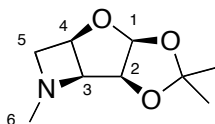
1,2-*O*-Isopropylidene-3,5-di-*O*-trifluoromethanesulfonyl- β -D-arabinofuranose 2.136

Trifluoromethanesulfonic anhydride (2.65 mL, 15.78 mmol) was added to a stirred solution of diol **2.135** (1.00 g, 5.26 mmol) and pyridine (2.55 mL, 31.56 mmol) in dichloromethane (30 mL) at -30 °C under nitrogen atmosphere. TLC analysis (2:1 cyclohexane/ethyl acetate) after 1 h indicated no starting material (R_f 0.05) and formation of a single product (R_f 0.68). The mixture was diluted with dichloromethane (30 mL), washed with 2M hydrochloric acid (3 x 60 mL) and the organic layer dried (MgSO_4) and concentrated *in vacuo* to afford the crude material as a cream solid. Purification *via* flash column chromatography on silica gel (1:1 cyclohexane/ethyl acetate) afforded the title compound as a white crystalline solid (2.26 g, 95%); found: C, 26.54; H, 2.79. $\text{C}_{10}\text{H}_{12}\text{F}_6\text{O}_9\text{S}_2$ requires C, 26.44; H, 2.66; m.p. 67-68 °C (cyclohexane/ethyl acetate); $[\alpha]_D^{25} +7.2$ (c 1.05 in CHCl_3); δ_{H} (C_6D_6 , 400 MHz): 0.83, 1.23 (6H, 2 x s, $\text{C}(\text{CH}_3)_2$), 3.81-3.85 (1H, a-dt, H4, $J_{4,3}$ 2.0, $J_{4,5}/J_{4,5'}$ 6.1), 4.02-4.06 (1H, dd, H5, $J_{5,4}$ 5.9, J_{gem} 10.7), 4.07-4.11 (1H, dd, H5', $J_{5',4}$ 6.3, J_{gem} 10.7), 4.13-4.14 (1H, d, H2, $J_{2,1}$ 3.9), 4.96-4.96 (1H, a-d, H3, $J_{3,4}$ 1.7), 5.26-5.27 (1H, d, H1, $J_{1,2}$ 3.9); δ_{C} (C_6D_6 , 100 MHz): 25.9, 26.6 ($\text{C}(\text{CH}_3)_2$), 72.7 (C5), 81.4 (C4), 84.5 (C2), 87.6 (C3), 106.2 (C1), 114.4 ($\text{C}(\text{CH}_3)_2$), 114.5-124.0 (q, OSO_2CF_3 , $J_{\text{C,F}}$ 320), 114.7-124.2 (q, OSO_2CF_3 , $J_{\text{C,F}}$ 320); m/z (ESI+ve): 477 ($[\text{M} + \text{Na}]^+$, 100%), 931 ($[2\text{M} + \text{Na}]^+$, 49%); HRMS m/z (ESI+ve): found 476.9719 ($[\text{M} + \text{Na}]^+$); $\text{C}_{10}\text{H}_{12}\text{F}_6\text{NaO}_9\text{S}_2$ requires 476.9719.

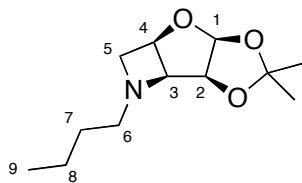
***N*-Benzyl-3,5-dideoxy-3,5-imino-1,2-*O*-isopropylidene- β -D-lyxofuranose 2.137**

Trifluoromethanesulfonic anhydride (1.33 mL, 7.89 mmol) was added to a solution of diol **2.135** (500 mg, 2.63 mmol) and pyridine (1.28 mL, 15.77 mmol) in dichloromethane (20 mL) at -30 °C

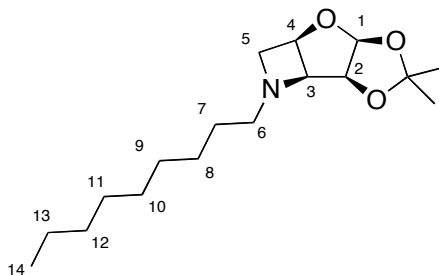
under nitrogen atmosphere, and the mixture stirred and kept between -30 and -25 °C. TLC analysis (2:1 cyclohexane/ethyl acetate) after 1 h indicated no starting material (R_f 0.05) and formation of a single product (R_f 0.69). The mixture was allowed to warm to room temperature, washed with 2M hydrochloric acid (25 mL), the aqueous layer washed with dichloromethane (30 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude ditriflate **2.136** as a cream solid (quant.). This was re-dissolved in dry acetonitrile (20 mL), benzylamine (0.31 mL, 2.89 mmol) and diisopropylethylamine (1.15 mL, 6.58 mmol) added simultaneously and the mixture stirred at room temperature under argon. TLC analysis (2:1 cyclohexane/ethyl acetate) after 12 h showed no starting material and formation of a single product (R_f 0.44). The mixture was concentrated *in vacuo* and the residue purified *via* flash column chromatography on silica gel (2:1 cyclohexane/ethyl acetate) to afford the pure title compound as a cream solid (0.590 g, 86%); $[\alpha]_D^{25}$ -74.6 (c 1.00 in $CHCl_3$); m.p. 60-63 °C; δ_H ($CDCl_3$, 400 MHz): 1.42, 1.79 (6H, 2 x s, $C(\underline{CH}_3)_2$), 3.07-3.11 (1H, dd, H5, $J_{5,4}$ 5.5, J_{gem} 9.0), 3.45-3.48 (1H, ddd, H5', $J_{5',3}$ 0.8, $J_{5',4}$ 1.6, J_{gem} 9.0), 3.65-3.68 (1H, d, H6, J_{gem} 13.1), 3.70-3.73 (1H, a-dt, H3, $J_{3,5'}$ 0.8, $J_{3,2}/J_{3,4}$ 5.8), 3.92-3.96 (1H, d, H6', J_{gem} 13.1), 4.61-4.63 (1H, dd, H2, $J_{2,1}$ 4.5, $J_{2,3}$ 6.0), 4.74-4.77 (1H, dt, H4, $J_{4,5'}$ 1.6, $J_{4,5}/J_{4,3}$ 5.5), 5.95-5.96 (1H, d, H1, $J_{1,2}$ 4.5), 7.21-7.31 (5H, m, 5 x $Ar\underline{H}$); δ_C ($CDCl_3$, 100 MHz): 27.1, 28.1 ($C(\underline{CH}_3)_2$), 58.4 (C5), 61.3 (C6), 68.7 (C3), 77.2 (C4), 82.3 (C2), 110.3 (C1), 114.7 ($C(\underline{CH}_3)_2$), 127.1 ($p\text{-}Ar\underline{CH}$), 128.3, 128.8 (2 x $o\text{-}Ar\underline{CH}$ and 2 x $m\text{-}Ar\underline{CH}$), 138.3 ppm ($ipso\text{-}Ar\underline{C}$); m/z (ESI+ve): 262 ($[M + H]^+$, 100%), 284 ($[M + Na]^+$, 69%); HRMS m/z (ESI+ve): found 262.1438 ($[M + H]^+$); $C_{15}H_{20}NO_3$ requires 262.1438.

3,5-Dideoxy-3,5-imino-1,2-*O*-isopropylidene-*N*-methyl- β -D-lyxofuranose **2.138**

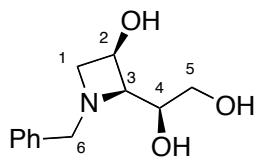
Trifluoromethanesulfonic anhydride (0.53 mL, 3.15 mmol) was added to a stirred solution of diol **2.135** (200 mg, 1.05 mmol) and pyridine (0.51 mL, 6.30 mmol) in dichloromethane (10 mL) at -30 °C under nitrogen atmosphere, and the mixture kept between -30 and -15 °C. TLC analysis (2:1 cyclohexane/ethyl acetate) after 1 h indicated no starting material (R_f 0.05) and formation of a single product (R_f 0.69). The mixture was allowed to warm to rt, washed with 2M hydrochloric acid (10 mL), the aqueous layer washed with dichloromethane (10 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude ditriflate **2.136** as a cream solid (quant.). This material was re-dissolved in acetonitrile (10 mL), cooled to 0 °C, and a solution of diisopropylethylamine (0.46 mL, 2.63 mmol) and methylamine (33% in ethanol, 0.14 mL, 1.16 mmol) in ethanol (1 mL) added dropwise under nitrogen atmosphere and the mixture stirred and slowly allowed to reach rt. TLC analysis (1% triethylamine in ethyl acetate) after 20 h indicated formation of a single product (R_f 0.43). The crude reaction mixture was dry loaded onto silica gel and purified *via* flash column chromatography on silica gel (1% triethylamine in 2:1 cyclohexane/ethyl acetate) to afford the pure title compound as a clear, thin oil (127 mg, 65%); $[\alpha]_D^{25}$ -89.2 (*c* 3.47 in $CHCl_3$); δ_H (CD_3CN , 400 MHz): 1.32, 1.62 (6H, 2 x s, $C(CH_3)_2$), 2.32 (3H, s, H6), 2.98-3.01 (2H, dd, H5, $J_{5,4}$ 5.3, J_{gem} 8.6), 3.31-3.33 (1H, br d, H5', J_{gem} 8.6), 3.44-3.47 (1H, a-t, H3, $J_{3,4}/J_{3,2}$ 5.6), 4.54-4.56 (1H, dd, H2, $J_{2,1}$ 4.6, $J_{2,3}$ 5.8), 4.63-4.66 (1H, a-dt, H4, $J_{4,5'}$ 1.3, $J_{4,5}/J_{4,3}$ 5.3), 5.85-5.86 (1H, d, H1, $J_{1,2}$ 4.6); δ_C (CD_3CN , 100 MHz): 26.9, 28.6 ($C(CH_3)_2$), 44.4 (C6), 60.8 (C5), 71.5 (C3), 78.0 (C4), 83.1 (C2), 110.9 (C1), 114.7 ($C(CH_3)_2$); m/z (ESI+ve): 186 ($[M + H]^+$, 87%), 208 ($[M + Na]^+$, 100%); HRMS m/z (ESI+ve): found 208.0943 ($[M + Na]^+$); $C_9H_{15}NNaO_3$ requires 208.0944.

N*-Butyl-3,5-dideoxy-3,5-imino-1,2-*O*-isopropylidene- β -D-lyxofuranose **2.139*

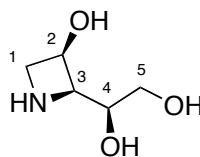
Trifluoromethanesulfonic anhydride (1.33 mL, 7.89 mmol) was added to a solution of diol **2.135** (500 mg, 2.63 mmol) and pyridine (1.28 mL, 15.77 mmol) in dichloromethane (20 mL) at -30 °C under nitrogen atmosphere, and the mixture stirred and kept between -30 and -15 °C. TLC analysis (2:1 cyclohexane/ethyl acetate) after 1 h indicated no starting material (R_f 0.05) and formation of a single product (R_f 0.69). The mixture was allowed to warm to rt, washed with 2M hydrochloric acid (20 mL), the aqueous layer washed with dichloromethane (20 mL) and the combined organic layers dried (MgSO_4) and concentrated *in vacuo* to afford the crude ditriflate **2.136** as a cream solid (quant.). This material was re-dissolved in acetonitrile (20 mL), *n*-butylamine (0.91 mL, 9.21 mmol) added and the mixture stirred under nitrogen at rt. TLC analysis (2:1 cyclohexane/ethyl acetate) after 21 h showed no starting material, and formation of a single product (R_f 0.38). The reaction mixture was directly dry-loaded onto silica gel and purified *via* flash column chromatography on silica gel (5:1 to 2:1 cyclohexane/ethyl acetate) to afford the title compound as a clear, thin oil (323 mg, 54%); $[\alpha]_D^{25}$ -76.5 (c 1.39 in CHCl_3); δ_{H} (CDCl_3 , 400 MHz): 0.86-0.89 (3H, t, H9, $J_{9,8}$ 7.1), 1.24-1.35 (4H, m, H7 and H8), 1.39, 1.72 (6H, 2 x s, $\text{C}(\text{CH}_3)_2$), 2.45-2.58 (2H, m, H6), 2.97-3.01 (1H, dd, H5, $J_{5,4}$ 5.5, J_{gem} 9.1), 3.46-3.51 (2H, m, H3 and H5'), 4.56-4.59 (1H, dd, H2, $J_{2,1}$ 4.6, $J_{2,3}$ 5.9), 4.71-4.74 (1H, dt, H4, $J_{4,3}$ 1.4, $J_{4,5}$ 5.5), 5.91-5.93 (1H, d, H1, $J_{1,2}$ 4.6); δ_{C} (CDCl_3 , 100 MHz): 14.2 (C9), 20.6 (C8), 26.9, 28.3 ($\text{C}(\text{CH}_3)_2$), 30.2 (C7), 57.8 (C6), 58.7 (C5), 69.2 (C3), 77.4 (C4), 82.3 (C2), 110.1 (C1), 114.6 ($\text{C}(\text{CH}_3)_2$); m/z (ESI+ve): 228 ($[\text{M} + \text{H}]^+$, 88%), 250 ($[\text{M} + \text{Na}]^+$, 100%); HRMS m/z (ESI+ve): found 228.1595 ($[\text{M} + \text{H}]^+$); $\text{C}_{12}\text{H}_{22}\text{NO}_3$ requires 228.1594.

3,5-Dideoxy-3,5-imino-1,2-*O*-isopropylidene-*N*-nonyl- β -D-lyxofuranose **2.140**

Trifluoromethanesulfonic anhydride (1.33 mL, 7.89 mmol) was added to a stirred solution of diol **2.135** (500 mg, 2.63 mmol) and pyridine (1.28 mL, 15.77 mmol) in dichloromethane (20 mL) at -30 °C under nitrogen atmosphere, and the mixture kept between -30 and -15 °C. TLC analysis (2:1 cyclohexane/ethyl acetate) after 30 mins indicated no starting material (R_f 0.05) and formation of a single product (R_f 0.69). The mixture was allowed to warm to rt, washed with 2M hydrochloric acid (20 mL), the aqueous layer washed with dichloromethane (20 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude ditriflate **2.136** as a cream solid (quant.). This material was re-dissolved in acetonitrile (20 mL), 1-nonylamine (1.69 mL, 9.21 mmol) added and the mixture stirred at rt under nitrogen atmosphere. TLC analysis (2:1 cyclohexane/ethyl acetate) after 17 h indicated consumption of starting material and formation of a single product (R_f 0.45). The mixture was directly pre-absorbed and purified *via* flash column chromatography on silica gel (5:1 to 2:1 cyclohexane/ethyl acetate) to afford the title compound as a clear thin oil (537 mg, 69%); $[\alpha]_D^{25}$ -59.3 (c 1.02 in $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 0.85-0.89 (3H, t, H14, $J_{14,13}$ 6.7), 1.25-1.34 (14H, m, H7-H13), 1.40, 1.72 (6H, 2 x s, $C(CH_3)_2$), 2.45-2.58 (2H, m, H6), 2.98-3.02 (1H, dd, H5, $J_{5,4}$ 5.6, J_{gem} 8.9), 3.47-3.51 (2H, m, H5' and H3), 4.57-4.60 (1H, dd, H2, $J_{2,1}$ 4.5, $J_{2,3}$ 5.3), 4.71-4.74 (1H, a-dt, H4, $J_{4,5'}$ 1.3, $J_{4,3}/J_{4,5}$ 5.5), 5.92-5.93 (1H, d, H1, $J_{1,2}$ 4.5); δ_C ($CDCl_3$, 100 MHz): 14.3 (C14), 26.9, 28.3 ($C(CH_3)_2$), 22.8, 27.1, 28.1, 29.4, 29.7, 29.7, 32.0 (C7-C13), 58.1 (C6), 58.7 (C5), 69.2 (C3), 77.4 (C4), 82.3 (C2), 110.1 (C1), 114.6 ($C(CH_3)_2$); m/z (ESI+ve): 298 ($[M + H]^+$, 100%), 320 ($[M + Na]^+$, 92%), 617 ($[2M + Na]^+$, 45%); HRMS m/z (ESI+ve): found 298.2375 ($[M + H]^+$); $C_{17}H_{32}NO_3$ requires 298.2377.

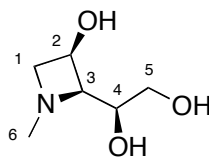
N-Benzyl-1,3-dideoxy-1,3-imino-D-arabinitol 2.142D

The acetonide **2.137** (110 mg, 0.42 mmol) was dissolved in 1:1 water/trifluoroacetic acid (2 mL) and stirred at rt. TLC analysis (9:1 ethyl acetate/methanol) of an aliquot quenched with triethylamine after 24 h showed formation of a single product (R_f 0.49). The mixture was concentrated *in vacuo* and the residue co-evaporated with water (3 x 5 mL) to afford the crude lactol as a clear syrup. This material was re-dissolved in water (3 mL), sodium borohydride (24 mg, 0.63 mmol) added and the mixture stirred at rt. TLC analysis (9:1 ethyl acetate/methanol) after 24 h showed consumption of starting material and formation of a single product (R_f 0.00). The mixture was concentrated *in vacuo* and the residue co-evaporated with methanol (3 x 5 mL). The resulting crude residue was loaded onto a column of Dowex 50WX8 (H^+) ion exchange resin, and the column flushed sequentially with ethanol and water. Subsequent elution with 2M aqueous ammonia afforded the title compound as a clear, colourless syrup which slowly crystallised to a white solid (69 mg, 73%); $[\alpha]_D^{25}$ -66.2 (c 0.39 in H_2O); ν_{max} (thin film): 3381 (s, br, OH); m.p. 96-97 °C; δ_H (D_2O , 500 MHz): 3.12-3.14 (1H, br d, H1, J_{gem} 9.9), 3.39-3.42 (1H, dd, H1', $J_{1',2}$ 6.5, J_{gem} 9.9), 3.42-3.46 (1H, dd, H3, $J_{3,2}$ 6.3, $J_{3,4}$ 9.0), 3.46-3.50 (1H, dd, H5, $J_{5,4}$ 6.2, J_{gem} 12.0), 3.55-3.57 (1H, d, H6, J_{gem} 12.5), 3.63-3.66 (1H, dd, H5', $J_{5',4}$ 2.9, J_{gem} 12.0), 3.80-3.83 (1H, d, H6', J_{gem} 12.5), 4.02-4.05 (1H, ddd, H4, $J_{4,5'}$ 2.9, $J_{4,5}$ 6.2, $J_{4,3}$ 9.0), 4.55-4.58 (1H, a-dt, H2, $J_{2,1}$ 1.8, $J_{2,1'}/J_{2,3}$ 6.4), 7.33-7.43 (5H, m, 5 x ArH); δ_C (D_2O , 125 MHz): 59.3 (C1), 62.1 (C6), 63.0 (C5), 64.0 (C2), 69.3 (C3), 70.0 (C4), 128.5 (p -ArCH), 129.3, 130.2 (2 x o -ArCH and 2 x m -ArCH), 137.2 (*ipso*-ArC); m/z (ESI+ve): 224 ($[M + H]^+$, 63%), 246 ($[M + Na]^+$, 100%), 469 ($[2M + Na]^+$, 77%); HRMS m/z (ESI+ve): found 246.1100 ($[M + Na]^+$); $C_{12}H_{17}NNaO_3$ requires 246.1101.

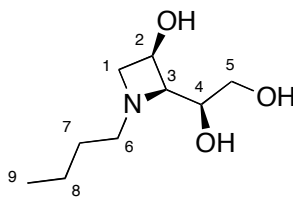
1,3-Dideoxy-1,3-imino-D-arabinitol 2.130D

The D-arabinitol **2.142D** (61.9 mg, 0.227 mmol), ammonium formate (175 mg, 2.77 mmol) and palladium on activated charcoal (10 wt. %, 29.5 mg, 0.023 mmol) were placed in a flame-dried flask with anhydrous methanol (6 mL), and the suspension heated to reflux under argon atmosphere. TLC analysis (14:3:1:1:1 ethanol/pyridine/*n*-butanol/acetic acid/water) after 20 min showed consumption of starting material (R_f 0.73) and formation of a single product (R_f 0.48). The mixture was allowed to cool, filtered through Celite, the pad and flask rinsed with methanol and the combined filtrates concentrated *in vacuo* to afford the crude material as a clear syrup. This material was loaded onto a column of Dowex 50WX8 (H^+) ion exchange resin, the column flushed with water, ethanol, more water and then eluted with 2M aqueous ammonia. The ammoniacal fractions were concentrated *in vacuo* to afford the title compound as a clear, pale yellow syrup (36.5 mg, 99%); [characterised as the HCl salt (a clear syrup)] $[\alpha]_D^{25} -32.4$ (c 0.37 in H_2O); ν_{max} (neat): 3276 (s, br, OH and NH); δ_H (D_2O , 500 MHz): 3.70-3.73 (1H, dd, H5, $J_{5,4}$ 5.0, J_{gem} 12.0), 3.73-3.76 (1H, dd, H5', $J_{5',4}$ 5.4, J_{gem} 12.0), 3.87-3.90 (1H, dd, H1, $J_{1,2}$ 4.4, J_{gem} 11.6), 4.28-4.31 (1H, a-dt, H4, $J_{4,5}/J_{4,5'}$ 5.2, $J_{4,3}$ 7.2), 4.34-4.37 (1H, dd, H1', $J_{1',2}$ 6.8, J_{gem} 11.6), 4.58-4.61 (1H, a-t, H3, $J_{3,4}/J_{3,2}$ 6.9), 4.81-4.85 (1H, m, H2); δ_C (D_2O , 125 MHz): 53.9 (C1), 62.5 (C5), 65.1 (C2), 65.4 (C3), 68.3 (C4); m/z (ESI+ve): 134 ($[M + H]^+$, 100%), 267 ($[2M + H]^+$, 88%); HRMS m/z (ESI+ve): found 156.0631 ($[M + Na]^+$); $C_5H_{11}NNaO_3$ requires 156.0631.

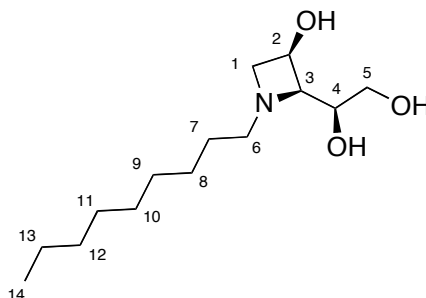
L-Enantiomer 2.130L: Prepared as above from L-arabinitol **2.142L** (120 mg, 0.537 mmol) provided by a co-worker,²⁰⁸ affording the title compound as a clear, pale yellow syrup (69.3 mg, 97%); [characterised as the HCl salt (a clear syrup)] $[\alpha]_D^{25} +31.7$ (c 0.31 in H_2O).

1,3-Dideoxy-1,3-imino-*N*-methyl-D-arabinitol 2.143D

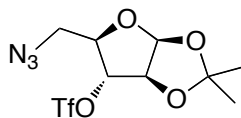
The acetonide **2.138** (106 mg, 0.57 mmol) was dissolved in 1:1 water/trifluoroacetic acid (2 mL) and stirred at rt. TLC analysis (1% triethylamine in ethyl acetate) of an aliquot quenched with triethylamine after 18 h showed no starting material (R_f 0.40) and a single product (R_f 0.10). The mixture was concentrated *in vacuo* and the residue co-evaporated with water (3 x 5 mL) to afford the crude lactol as a clear, straw-coloured syrup. This syrup was re-dissolved in water (3 mL) and sodium borohydride (33 mg, 0.86 mmol) added in small portions to the stirred solution. TLC analysis (1% triethylamine in ethyl acetate) after 22 h showed a single product (R_f 0.00). The mixture was concentrated *in vacuo* and the residue co-evaporated with methanol (3 x 5 mL) to afford the crude as a clear syrup. This material was purified *via* a column of Dowex 50WX8 (H^+) ion exchange resin, and the ammoniacal fraction concentrated *in vacuo* to afford the title compound as a white crystalline solid (77 mg, 92%); found: C, 48.99; H, 8.76; N, 9.42. $C_6H_{13}NO_3$ requires C, 48.97; H, 8.90; N, 9.52; $[\alpha]_D^{25}$ -72.6 (c 0.74 in H_2O); ν_{max} (thin film): 3255, 3425 (s, OH); m.p. 135-136 °C; δ_H (D_2O , 400 MHz): 2.30 (3H, s, H6), 3.22-3.28 (2H, m, H1 and H3), 3.30-3.32 (1H, br d, H1', J_{gem} 9.6), 3.49-3.54 (1H, dd, H5, $J_{5,4}$ 5.8, J_{gem} 12.0), 3.70-3.74 (1H, dd, H5', $J_{5',4}$ 2.7, J_{gem} 12.0), 4.02-4.06 (1H, ddd, H4, $J_{4,5'}$ 2.7, $J_{4,5}$ 5.8, $J_{4,3}$ 8.9), 4.52-4.55 (1H, a-dt, H2, $J_{2,1'}$ 1.7, $J_{2,3}/J_{2,1}$ 6.0); δ_C (D_2O , 100 MHz): 44.3 (C6), 61.4 (C1), 62.8 (C5), 64.0 (C2), 69.8 (C4), 71.1 (C3); m/z (ESI+ve): 148 ($[M + H]^+$, 92%), 170 ($[M + Na]^+$, 100%); HRMS m/z (ESI+ve): found 148.0966 ($[M + H]^+$); $C_6H_{14}NO_3$ requires 148.0968.

N-Butyl-1,3-dideoxy-1,3-imino-D-arabinitol 2.144D

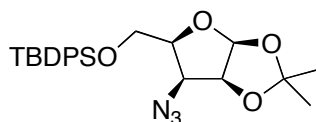
The acetonide **2.139** (319 mg, 1.40 mmol) was dissolved in 1:1 water/trifluoroacetic acid (4 mL) and the mixture stirred at rt. TLC analysis (2:1 cyclohexane/ethyl acetate) of an aliquot quenched with triethylamine after 21 h showed no starting material (R_f 0.38) and formation of a single product (R_f 0.00). The mixture was concentrated *in vacuo* and co-evaporated with water (2 x 3 mL) to afford the crude lactol as a clear syrup. This syrup was re-dissolved in water (4 mL), sodium borohydride (79 mg, 2.10 mmol) added in small portions, and the mixture stirred at rt. TLC analysis (ethyl acetate) after 20 h showed no starting material (R_f 0.38) and formation of a single product (R_f 0.00). The mixture was concentrated *in vacuo* and co-evaporated with methanol (3 x 10 mL) to afford a yellow foam. This crude material was purified *via* a column of Dowex 50WX8 (H^+) ion exchange resin, and the ammoniacal fraction concentrated *in vacuo* to afford the title compound as a tan coloured solid (201 mg, 76%); found: C, 56.98; H, 10.27; N, 7.55. $C_9H_{19}NO_3$ requires C, 57.12; H, 10.12; N, 7.40; $[\alpha]_D^{25}$ -84.5 (c 0.91 in MeOH); ν_{max} (thin film): 3286, 3412 (s, OH); m.p. 112-113 °C; δ_H (D_2O , 400 MHz): 0.85-0.88 (3H, t, H9, $J_{9,8}$ 7.0), 1.22-1.31 (4H, m, H7 and H8), 2.33-2.35 (1H, m, H6), 2.62-2.69 (1H, m, H6'), 3.19-3.29 (3H, m, H1, H1' and H3), 3.48-3.52 (1H, dd, H5, $J_{5,4}$ 6.0, J_{gem} 12.0), 3.70-3.74 (1H, dd, H5', $J_{5',4}$ 2.7, J_{gem} 12.0), 4.04-4.08 (1H, ddd, H4, $J_{4,5'}$ 2.7, $J_{4,5}$ 6.0, $J_{4,3}$ 8.9), 4.52-4.56 (1H, a-dt, H2, $J_{2,1'}$ 1.8, $J_{2,1}/J_{2,3}$ 6.2); δ_C (D_2O , 100 MHz): 13.9 (C9), 20.6 (C8), 29.3 (C7), 58.6 (C6), 59.6 (C1), 63.0 (C5), 64.2 (C2), 69.7 (C3), 69.9 (C4); m/z (ESI+ve): 190 ($[M + H]^+$, 93%), 212 ($[M + Na]^+$, 100%); HRMS m/z (ESI+ve): found 190.1436 ($[M + H]^+$); $C_9H_{20}NO_3$ requires 190.1438.

1,3-Dideoxy-1,3-imino-*N*-nonyl-D-arabinitol 2.145D

The acetone **2.140** (510 mg, 1.71 mmol) was dissolved in 1:1 water/trifluoroacetic acid (5 mL) and stirred at rt. TLC analysis (99:1 ethyl acetate/triethylamine) of an aliquot quenched with triethylamine after 21 h showed a single product (R_f 0.47). The mixture was concentrated *in vacuo* and co-evaporated with water (2 x 3 mL) to afford the crude lactol as a pale brown syrup. This material was re-dissolved in 5:2:1 water/ethanol/1,4-dioxane (8 mL), sodium borohydride (97 mg, 2.57 mmol) added and the mixture stirred at rt. TLC analysis (ethyl acetate) after 19 h showed consumption of starting material (R_f 0.47) and formation of a single product (R_f 0.00). The mixture was concentrated *in vacuo* and the residue co-evaporated with methanol (3 x 10 mL) to afford the crude as an orange/brown syrup. This material was loaded onto a column of Dowex 50WX8 (H^+) ion exchange resin, and the column flushed with water. Subsequent elution with 8:2 ethanol/2M aqueous ammonia afforded the title compound as a brown, waxy solid (373 mg, 84%); $[\alpha]_D^{25}$ -54.7 (c 0.95 in MeOH); ν_{max} (neat): 3311, 3427 (s, OH); m.p. 71-75 °C; δ_H (CD_3OD , 400 MHz): 0.88-0.92 (1H, t, H14, $J_{14,13}$ 6.8), 1.29-1.37 (14H, m, H7-H13), 2.26-2.32 (1H, m, H6), 2.65-2.72 (1H, m, H6'), 3.08-3.12 (1H, dd, H1, $J_{1,2}$ 6.4, J_{gem} 9.2), 3.17-3.21 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 7.0), 3.31-3.34 (1H, m, H1'), 3.51-3.55 (1H, dd, H5, $J_{5,4}$ 5.5, J_{gem} 11.4), 3.66-3.70 (1H, dd, H5', $J_{5',4}$ 3.6, J_{gem} 11.4), 4.00-4.04 (1H, ddd, H4, $J_{4,5'}$ 3.6, $J_{4,5}$ 5.5, $J_{4,3}$ 7.8), 4.46-4.50 (1H, a-dt, H2, $J_{2,1'}$ 1.9, $J_{2,1}/J_{2,3}$ 6.3); δ_C (CH_3OD , 100 MHz): 14.6 (C14), 23.9, 28.6, 28.7, 30.6, 30.8, 30.8, 33.2 (C7-C13), 60.2 (C6), 61.7 (C1), 64.5 (C5), 65.5 (C2), 71.7 (C4), 71.9 (C3); m/z (ESI-ve): 258 ($[M - H]^-$, 94%), 517 ($[2M - H]^-$, 100%); HRMS m/z (ESI+ve): found 260.2220 ($[M + H]^+$); $C_{14}H_{30}NO_3$ requires 260.2220.

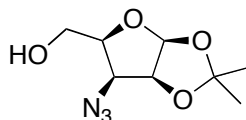
5-Azido-5-deoxy-1,2-O-isopropylidene-3-O-trifluoromethanesulfonyl-β-D-arabinofuranose**2.149**

Sodium azide (148 mg, 2.28 mmol) was added to a stirred solution of ditriflate **2.136** (1.037 g, 2.28 mmol) in acetone (20 mL) at rt. TLC analysis (2:1 cyclohexane/diethyl ether) after 24 h showed no starting material (R_f 0.37) and formation of a single product (R_f 0.46). The mixture was concentrated *in vacuo* and the resulting oily residue partitioned between dichloromethane (30 mL) and 50% brine (30 mL). The aqueous layer was washed with dichloromethane (30 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo* to afford a clear oil. Purification *via* flash column chromatography on silica gel (4:1 cyclohexane/ethyl acetate) afforded the title compound as a clear oil which crystallized to a white solid on standing (763 mg, 96%); found: C, 31.26; H, 3.36; N, 11.96. $C_9H_{12}F_3N_3O_6S$ requires C, 31.13; H, 3.48; N, 12.10; $[\alpha]_D^{25} +26.4$ (c 1.28 in $CHCl_3$); ν_{max} (thin film): 2099 (s, N_3); m.p. 37-38 °C; δ_H ($CDCl_3$, 400 MHz): 1.36, 1.58 (6H, 2 x s, $C(CH_3)_2$), 3.46-3.51 (1H, dd, H5, $J_{5,4}$ 6.5, J_{gem} 12.9), 3.63-3.68 (1H, dd, H5', $J_{5',4}$ 6.6, J_{gem} 12.9), 4.33-4.37 (1H, a-dt, H4, $J_{4,5}/J_{4,5'}$ 6.5, $J_{4,3}$ 2.2), 4.81-4.82 (1H, d, H2, $J_{2,1}$ 3.9), 5.17-5.17 (1H, a-d, H3, $J_{3,4}$ 1.7), 5.99-6.00 (1H, d, H1, $J_{1,2}$ 3.9); δ_C ($CDCl_3$, 100 MHz): 26.2, 26.9 ($C(CH_3)_2$), 51.3 (C5), 83.3 (C4), 84.5 (C2), 88.3 (C3), 105.7 (C1), 114.3 ($C(CH_3)_2$). Could not be identified by mass spectrometry.

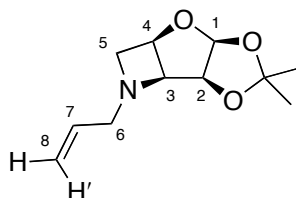
3-Azido-5-O-tert-butylidiphenylsilyl-3-deoxy-1,2-O-isopropylidene-β-D-lyxofuranose 2.150

Trifluoromethanesulfonic anhydride (0.67 mL, 7.92 mmol) was added to a stirred solution of alcohol **2.134** (1.13 g, 2.64 mmol) and pyridine (0.64 mL, 7.92 mmol) in dichloromethane (15 mL)

at -30 °C under nitrogen atmosphere. TLC analysis (2:1 cyclohexane/ethyl acetate) after 30 min indicated consumption of starting material (R_f 0.48) and formation of a single product (R_f 0.77). The mixture was diluted with dichloromethane (50 mL), washed with 2M hydrochloric acid (3 x 60 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude triflate as a straw-coloured syrup (1.45 g). This material was re-dissolved in *N,N*-dimethylformamide (15 mL), sodium azide (0.25 g, 3.85 mmol) added and the mixture heated to 60 °C with stirring. TLC analysis (6:1 cyclohexane/ethyl acetate) after 19 h indicated consumption of starting material (R_f 0.57) and formation of a single major product (R_f 0.38). The mixture was diluted with ethyl acetate (100 mL) and washed with 50% brine (3 x 100 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude as an orange oil (1.15 g). Purification *via* flash column chromatography on silica gel (30:1 to 10:1 cyclohexane/ethyl acetate) afforded the title compound as a clear colourless syrup which crystallised to a white solid on standing (821 mg, 70%); $[\alpha]_D^{25}$ -21.0 (c 0.77 in $CHCl_3$); ν_{max} (neat): 2108 (s, N_3); m.p. 79-80 °C; δ_H ($CDCl_3$, 400 MHz): 1.08 (9H, s, $SiC(CH_3)_3$), 1.32, 1.40 (6H, 2 x s, $C(CH_3)_2$), 3.84-3.88 (1H, dd, H5, $J_{5,4}$ 5.8, J_{gem} 10.6), 4.06-4.10 (1H, dd, H5', $J_{5',4}$ 6.5, J_{gem} 10.6), 4.09-4.12 (1H, m, H3), 4.23-4.28 (1H, a-q, H4, $J_{4,5}/J_{4,5'}/J_{4,3}$ 6.3), 4.74-4.77 (1H, dd, H2, $J_{2,1}$ 4.2, $J_{2,3}$ 5.6), 5.73-5.74 (1H, d, H1, $J_{1,2}$ 4.2), 7.36-7.45 (6H, m, 6 x ArH), 7.68-7.72 (4H, m, 4 x ArH); δ_C ($CDCl_3$, 100 MHz): 19.3 ($SiC(CH_3)_3$), 26.4, 26.6 ($C(CH_3)_2$), 26.9 ($SiC(CH_3)_3$), 61.7 (C3), 63.4 (C5), 80.4 (C2), 81.6 (C4), 105.0 (C1), 114.5 ($C(CH_3)_2$), 127.8 (4 x *o*-ArCH), 129.8 (2 x *p*-ArCH), 133.4, 133.5 (2 x *ipso*-ArC), 135.7, 135.8 (4 x *m*-ArCH); m/z (ESI+ve): 476 ($[M + Na]^+$, 76%), 929 ($[2M + Na]^+$, 100%); HRMS m/z (ESI+ve): found 476.1976 ($[M + Na]^+$); $C_{24}H_{31}N_3NaO_4Si$ requires 476.1976.

3-Azido-3-deoxy-1,2-*O*-isopropylidene- β -D-lyxofuranose 2.151

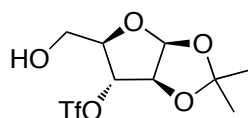
A 1M solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (2.08 mL, 2.08 mmol) was added to a stirred solution of silyl ether **2.150** (791 mg, 1.73 mmol) in tetrahydrofuran (10 mL) at rt. TLC analysis (2:1 cyclohexane/ethyl acetate) after 1 h showed consumption of starting material (R_f 0.63) and formation of a single product (R_f 0.10). The mixture was concentrated *in vacuo* to afford the crude material as a pale yellow syrup. Purification *via* flash column chromatography on silica gel (3:2 cyclohexane/ethyl acetate to ethyl acetate) afforded the title compound as a clear, colourless syrup (336 mg, 90%); $[\alpha]_D^{25}$ -143.9 (c 0.44 in CHCl_3); ν_{max} (neat): 2107 (s, N_3), 3450 (s, OH); δ_{H} (CDCl_3 , 400 MHz): 1.33, 1.59 (6H, 2 x s, $\text{C}(\text{CH}_3)_2$), 2.44-2.48 (1H, dd, OH, $J_{\text{OH},5'}$ 4.5, $J_{\text{OH},5}$ 8.2), 3.75-3.81 (1H, ddd, H5, $J_{5,4}$ 5.3, $J_{5,\text{OH}}$ 8.1, J_{gem} 11.8), 3.86-3.92 (1H, ddd, H5', $J_{5',\text{OH}}$ 3.9, $J_{5',4}$ 7.7, J_{gem} 11.8), 4.14-4.18 (1H, dd, H3, $J_{3,2}$ 5.6, $J_{3,4}$ 7.5), 4.22-4.27 (1H, a-dt, H4, $J_{4,5}$ 5.3, $J_{4,3}/J_{4,5'}$ 7.6), 4.76-4.78 (1H, dd, H2, $J_{2,1}$ 4.0, $J_{2,3}$ 5.6), 5.78-5.79 (1H, d, H1, $J_{1,2}$ 4.0); δ_{C} (CDCl_3 , 100 MHz): 26.2, 26.4 ($\text{C}(\text{CH}_3)_2$), 61.6 (C3), 62.0 (C5), 79.8 (C2), 81.2 (C4), 105.1 (C1), 114.3 ($\text{C}(\text{CH}_3)_2$); m/z (ESI+ve): 238 ($[\text{M} + \text{Na}]^+$, 100%), 453 ($[2\text{M} + \text{Na}]^+$, 56%); HRMS m/z (ESI+ve): found 238.0798 ($[\text{M} + \text{Na}]^+$); $\text{C}_8\text{H}_{13}\text{N}_3\text{NaO}_4$ requires 238.0798.

***N*-Allyl-3,5-dideoxy-3,5-imino-1,2-*O*-isopropylidene- β -D-lyxofuranose 2.153**

Trifluoromethanesulfonic anhydride (0.53 mL, 3.15 mmol) was added to a stirred solution of diol **2.135** (200 mg, 1.05 mmol) and pyridine (0.51 mL, 6.30 mmol) in dichloromethane (5 mL) at -30 °C under nitrogen atmosphere, and the temperature maintained between -30 and -15 °C. TLC

analysis (2:1 cyclohexane/ethyl acetate) after 1 h indicated no starting material (R_f 0.05) and formation of a single product (R_f 0.68). The mixture was allowed to warm to rt, diluted with dichloromethane (10 mL) and washed with 2M hydrochloric acid (20 mL). The aqueous layer was washed with dichloromethane (20 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude ditriflate **2.136** as a cream solid (quant.). This material was re-dissolved in acetonitrile (10 mL), allylamine (0.28 mL, 3.68 mmol) added and the mixture stirred at rt under nitrogen atmosphere. TLC analysis (2:1 cyclohexane/ethyl acetate) after 18 h showed consumption of starting material and formation of a single product (R_f 0.35). The mixture was directly pre-absorbed onto silica gel and purified *via* flash column chromatography on silica gel (5:1 cyclohexane/ethyl acetate) to afford the title compound as a clear, colourless oil (159 mg, 72%); $[\alpha]_D^{25}$ -100.5 (c 0.87 in $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 1.40, 1.73 (6H, 2 x s, $C(CH_3)_2$), 3.04-3.08 (1H, dd, H5, $J_{5,4}$ 5.6, J_{gem} 9.1), 3.15-3.20 (1H, dd, H6, $J_{6,7}$ 6.2, J_{gem} 13.4), 3.22-3.26 (1H, dd, H6', $J_{6,7}$ 6.0, J_{gem} 13.4), 3.48-3.50 (1H, d, H5', J_{gem} 9.1), 3.58-3.61 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 5.8), 4.56-4.59 (1H, dd, H2, $J_{2,1}$ 4.6, $J_{2,3}$ 6.0), 4.74-4.77 (1H, a-dt, H4, $J_{4,5'}$ 1.6, $J_{4,3}/J_{4,5}$ 5.6), 5.06-5.09 (1H, m, H8), 5.13-5.18 (1H, a-dd, H8', J_{gem} 1.5, $J_{8',7}$ 17.2), 5.74-5.84 (1H, a-ddt, H7, $J_{7,6}$ 6.1, $J_{7,8}$ 10.4, $J_{7,8'}$ 17.0), 5.93-5.94 (1H, d, H1, $J_{1,2}$ 4.5); δ_C ($CDCl_3$, 100 MHz): 26.8, 28.2 ($C(CH_3)_2$), 58.5 (C5), 60.2 (C6), 68.3 (C3), 77.5 (C4), 82.0 (C2), 109.9 (C1), 114.5 ($C(CH_3)_2$), 116.9 (C8), 135.2 (C7); m/z (ESI+ve): 212 ($[M + H]^+$, 37%), 234 ($[M + Na]^+$, 100%); HRMS m/z (ESI+ve): found 212.1280 ($[M + H]^+$); $C_{11}H_{18}NO_3$ requires 212.1281.

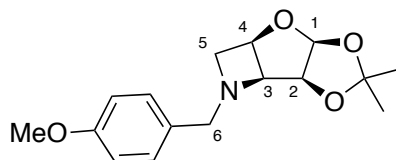
1,2-*O*-Isopropylidene-3-*O*-trifluoromethanesulfonyl- β -D-arabinofuranose **2.158**



Cyanamide (45 mg, 1.06 mmol) was added to a stirred solution of ditriflate **2.136** (241 mg, 0.53 mmol) and diisopropylethylamine (0.23 mL, 1.33 mmol) in anhydrous *N,N*-dimethylformamide (1.2 mL) at 90 °C. TLC analysis (2:1 cyclohexane/ethyl acetate) after 1 h indicated consumption of

starting material (R_f 0.68) and formation of a single major product (R_f 0.39). The mixture was diluted with ethyl acetate (15 mL) and washed with 50% brine (3 x 15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude as an orange oil. Purification *via* flash column chromatography on silica gel (5:1 to 2:1 cyclohexane/ethyl acetate) afforded the title compound as a clear, colourless syrup which slowly crystallised to a white solid (95 mg, 56%); $[\alpha]_D^{25}$ -3.4 (c 0.80 in $CHCl_3$); ν_{max} (thin film): 3477 (s, br, OH); m.p. 34-35 °C; δ_H ($CDCl_3$, 400 MHz): 1.35, 1.55 (6H, 2 x s, $C(CH_3)_2$), 2.16-2.20 (1H, t, 5-OH, $J_{OH,5}$ 6.1), 3.80-3.83 (2H, a-t, H5 and H5', $J_{5,4}/J_{5,OH}$ 5.9, $J_{5',4}/J_{5',OH}$ 5.9), 4.34-4.37 (1H, a-dt, H4, $J_{4,3}$ 2.6, $J_{4,5}/J_{4,5'}$ 5.7), 4.83-4.84 (1H, d, H2, $J_{2,1}$ 4.1), 5.23-5.24 (1H, d, H3, $J_{3,4}$ 2.5), 5.98-5.99 (1H, d, H1, $J_{1,2}$ 4.1); δ_C ($CDCl_3$, 100 MHz): 26.2, 26.8 ($C(CH_3)_2$), 61.5 (C5), 84.9 (C2), 85.3 (C4), 88.5 (C3), 105.5 (C1), 114.1 ($C(CH_3)_2$), 113.8-123.3 (q, SO_2CF_3 , $J_{C,F}$ 319.9); m/z (ESI+ve): 345 ($[M + Na]^+$, 100%), 667 ($[2M + Na]^+$, 97%); HRMS m/z (ESI+ve): found 345.0225 ($[M + Na]^+$); $C_9H_{13}F_3NaO_7S$ requires 345.0226.

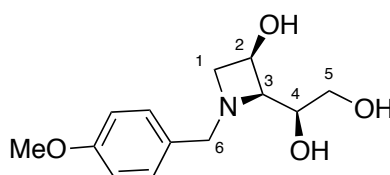
3,5-Dideoxy-3,5-imino-1,2-*O*-isopropylidene-*N*-*para*-methoxybenzyl- β -D-lyxofuranose **2.159**



Diisopropylethylamine (280 μ L, 1.60 mmol) and 4-methoxybenzylamine (92 μ L, 0.70 mmol) were added simultaneously to a stirred solution of ditriflate **2.136** (290 mg, 0.64 mmol) in acetonitrile (4 mL) at rt. TLC analysis (2:1 cyclohexane/ethyl acetate) after 5 h showed no starting material (R_f 0.68) and formation of a single product (R_f 0.29). The mixture was directly pre-absorbed onto silica and purified *via* flash column chromatography on silica gel (1:1 cyclohexane/ethyl acetate to ethyl acetate) to afford the title compound as a white crystalline solid (164 mg, 88%); $[\alpha]_D^{25}$ -73.7 (c 1.00 in $CHCl_3$); m.p. 105-107 °C; δ_H ($CDCl_3$, 400 MHz): 1.42, 1.79 (6H, 2 x s, $C(CH_3)_2$), 3.05-3.09 (1H, dd, H5, $J_{5,4}$ 5.5, J_{gem} 9.1), 3.40-3.43 (1H, ddd, H5', $J_{5',3}$ 0.9, $J_{5',4}$ 1.8, J_{gem} 9.1), 3.58-3.61 (1H, d, H6, J_{gem} 12.8), 3.67-3.70 (1H, a-dt, H3, $J_{3,5'}$ 0.8, $J_{3,2}/J_{3,4}$ 5.8), 3.79 (3H, s, O- CH_3), 3.84-3.88 (1H, d, H6',

J_{gem} 12.8), 4.59-4.62 (1H, dd, H2, $J_{2,1}$ 4.5, $J_{2,3}$ 6.0), 4.72-4.76 (1H, a-dt, H4, $J_{4,5'}$ 1.8, $J_{4,3}/J_{4,5}$ 5.6), 5.94-5.95 (1H, d, H1, $J_{1,2}$ 4.5), 6.82-6.86, 7.20-7.24 (4H, 2 x m, 4 x ArH); δ_{C} (CDCl₃, 100 MHz): 27.2, 28.1 (C(CH₃)₂), 55.4 (OCH₃), 58.1 (C5), 60.7 (C6), 68.5 (C3), 77.1 (C4), 82.3 (C2), 110.2 (C1), 114.7 (C(CH₃)₂), 113.7, 130.0 (2 x *o*-ArCH and 2 x *m*-ArCH), 130.4 (*ipso*-ArC), 158.7 (*p*-ArC); m/z (ESI+ve): 292 ([M + H]⁺, 100%), 314 ([M + Na]⁺, 94%), 605 ([2M + Na]⁺, 84%); HRMS m/z (ESI+ve): found 292.1550 ([M + H]⁺); C₁₆H₂₂NO₄ requires 292.1543.

1,3-Dideoxy-1,3-imino-*N*-para-methoxybenzyl-D-arabinitol 2.160D

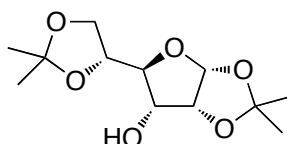


The acetonide **2.159** (219 mg, 0.752 mmol) was dissolved in 1:1 trifluoroacetic acid/water (6 mL) and stirred at rt. TLC (ethyl acetate) of an aliquot quenched with triethylamine after 22 h showed consumption of starting material (R_f 0.75) and formation of a single product (R_f 0.36). The mixture was concentrated *in vacuo* and co-evaporated with water (2 x 20 mL) to afford the crude lactol as a clear yellow syrup. This material was re-dissolved in water (6 mL), sodium borohydride (43 mg, 1.128 mmol) added in small portions and the mixture stirred at rt. Analysis by mass spectrometry after 23 h showed reaction completion. The mixture was quenched with acetic acid and loaded onto a column of Dowex 50WX8 (H⁺) ion exchange resin. The column was flushed with water, ethanol, more water and then eluted with 2M aqueous ammonia. The ammoniacal fractions were concentrated *in vacuo* to afford the title compound as a clear, colourless syrup which slowly crystallised to a pale tan solid (167 mg, 88%); $[\alpha]_D^{25}$ -74.9 (c 0.63 in MeOH); ν_{max} (solid): 3333 (s, OH); m.p. 91-92 °C; δ_{H} (D₂O, 500 MHz): 3.11-3.13 (1H, br d, H1, J_{gem} 10.0), 3.38-3.40 (1H, dd, H1', $J_{1,2}$ 6.5, J_{gem} 10.0), 3.40-3.43 (1H, m, H3), 3.43-3.46 (1H, dd, H5, $J_{5,4}$ 6.3, J_{gem} 12.0), 3.50-3.53 (1H, d, H6, J_{gem} 12.5), 3.60-3.62 (1H, dd, H5', $J_{5',4}$ 2.0, J_{gem} 12.0), 3.74-3.76 (1H, d, H6', J_{gem} 12.5), 3.83 (3H, s, OCH₃), 4.00-4.03 (1H, ddd, H4, $J_{4,5'}$ 2.9, $J_{4,5}$ 6.3, $J_{4,3}$ 9.1), 4.54-4.57 (1H, a-dt,

H₂, $J_{2,1}$ 1.9, $J_{2,1}/J_{2,3}$ 6.3), 6.98-7.01, 7.27-7.30 (4H, 2 x m, 4 x ArH); δ_C (D₂O, 125 MHz): 55.6 (OCH₃), 59.0 (C1), 61.2 (C6), 63.0 (C5), 64.0 (C2), 69.1 (C3), 70.0 (C4), 129.8 (*ipso*-ArC), 114.6, 131.6 (2 x *o*-ArCH and 2 x *m*-ArCH), 159.1 (*p*-ArC); m/z (ESI+ve): 254 ([M + H]⁺, 100%), 276 ([M + Na]⁺, 40%), 529 ([2M + Na]⁺, 44%); HRMS m/z (ESI+ve): found 276.1209 ([M + Na]⁺); C₁₃H₁₉NNaO₄ requires 276.1206.

2.4.2 *Xylo* azetidine triols from ribose

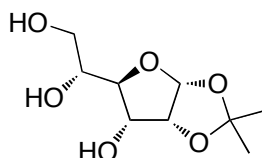
1,2;5,6-Di-*O*-isopropylidene- α -D-allofuranose **2.163**



Dess-Martin periodinane (97.77 g, 230.52 mmol) was added in one portion to a stirred solution of di-acetone-D-glucose **2.161** (40.00 g, 153.68 mmol) in dichloromethane (250 mL) at 0 °C. After 15 min the ice bath was removed, and the solution stirred at rt for 18 h. The mixture was then diluted with dichloromethane (500 mL) and saturated aqueous sodium hydrogen carbonate (1000 mL) containing sodium thiosulfate (0.12 g mL⁻¹), and the mixture stirred vigorously until both phases had cleared. The layers were separated, and the organic layer washed with more of the sodium hydrogen carbonate/sodium thiosulfate solution (250 mL). The aqueous layers were back extracted with ethyl acetate (500 mL), and the combined organic layers dried (MgSO₄) and concentrated *in vacuo* to afford the crude ketone as a white solid (33.32 g). This material was re-dissolved in ethanol (600 mL), cooled to 0 °C and a solution of sodium borohydride (4.88 g, 129.01 mmol) in 1:1 water/ethanol (120 mL) added dropwise with stirring over a period of 40 min. After a further 20 min the ice bath was removed and the solution allowed to warm to rt. TLC analysis (1:1 cyclohexane/ethyl acetate) after a further 1 h showed consumption of starting material (R_f 0.38) and formation of a single product (R_f 0.30). Excess sodium borohydride was quenched with saturated aqueous ammonium chloride, and the mixture diluted with water until the resulting precipitate had

dissolved. The mixture was concentrated to approx. 100 mL *in vacuo*, diluted with ethyl acetate (400 mL) and washed with brine (100 mL). The aqueous layer was extracted with ethyl acetate (200 mL) and the combined organic layers dried (MgSO₄) and concentrated *in vacuo* to afford the title compound as a white solid (32.45 g, 81%); $[\alpha]_D^{25} +38.8$ (*c* 1.03 in CHCl₃) [lit.²³³ $[\alpha]_D^{25} +39.8$ (*c* 0.42 in CHCl₃)]; $\nu_{\max}$ (solid): 3468 (s, OH); m.p. 74-75 °C (toluene) [lit.²³³ m.p. 73 °C]; δ_H (CDCl₃, 400 MHz): 1.36, 1.38, 1.46, 1.57 (12H, 4 x s, 2 x C(CH₃)₂), 2.54-2.56 (1H, d, 3-OH, $J_{OH,3}$ 8.4), 3.79-3.82 (1H, dd, H₄, $J_{4,5}$ 4.7, $J_{4,3}$ 8.5), 3.99-4.03 (1H, dd, H₆, $J_{6,5}$ 6.6, J_{gem} 8.5), 4.02-4.07 (1H, a-dt, H₃, $J_{3,2}$ 5.2, $J_{3,OH}/J_{3,4}$ 8.4), 4.05-4.09 (1H, dd, H_{6'}, $J_{6',5}$ 6.6, J_{gem} 8.5), 4.28-4.32 (1H, dt, H₅, $J_{5,4}$ 4.7, $J_{5,6}/J_{5,6'}$ 6.6), 4.60-4.62 (1H, dd, H₂, $J_{2,1}$ 3.8, $J_{2,3}$ 5.2), 5.80-5.81 (1H, d, H₁, $J_{1,2}$ 3.8); δ_C (CDCl₃, 100 MHz): 25.4, 26.4, 26.6, 26.7 (2 x C(CH₃)₂), 66.0 (C₆), 72.6 (C₃), 75.7 (C₅), 79.1 (C₂), 79.8 (C₄), 104.1 (C₁), 110.0, 113.0 (2 x C(CH₃)₂); *m/z* (ESI-ve): 283 ([M + Na]⁺, 67%), 543 ([2M + Na]⁺, 100%); HRMS *m/z* (ESI+ve): found 283.1156 ([M + Na]⁺); C₁₂H₂₀NaO₆ requires 283.1152.

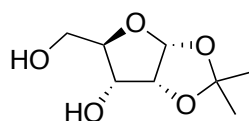
1,2-*O*-Isopropylidene- α -D-allofuranose **2.164**



The di-acetonide **2.163** (1.00 g, 3.84 mmol) was dissolved in 7:3 acetic acid/water (10 mL) and stirred at rt. TLC analysis (ethyl acetate) after 18 h indicated consumption of starting material (R_f 0.64), a minor product (R_f 0.00) and one major product (R_f 0.13). The mixture was concentrated *in vacuo* at 25 °C and the residue repeatedly co-evaporated with water and then toluene to afford a white solid. This crude material was dry loaded from methanolic solution and purified *via* flash column chromatography on silica gel (ethyl acetate to 9:1 ethyl acetate/methanol) to afford the title compound as a white crystalline solid (685 mg, 81%); $[\alpha]_D^{25} +47.0$ (*c* 1.00 in H₂O) [lit.²²⁰ $[\alpha]_D^{20} +46.0$ (*c* 1.00 in H₂O)]; $\nu_{\max}$ (solid): 3181, 3262 (s, br, OH); m.p. 131-133 °C (diethyl ether/methanol) [lit.²³⁴ m.p. 133 °C]; δ_H (D₂O, 400 MHz): 1.39, 1.57 (6H, 2 x s, C(CH₃)₂), 3.62-

3.66 (1H, dd, H6, $J_{6,5}$ 7.2, J_{gem} 11.9), 3.72-3.75 (1H, dd, H6', $J_{6',5}$ 3.6, J_{gem} 11.9), 3.96-4.02 (2H, m, H4, H5), 4.19-4.22 (1H, dd, H3, $J_{3,2}$ 4.7, $J_{3,4}$ 8.8), 4.71-4.73 (1H, a-t, H2, $J_{2,1}/J_{2,3}$ 4.2), 5.86-5.87 (1H, d, H1, $J_{1,2}$ 3.7); δ_{C} (D_2O , 100 MHz): 26.0, 26.2 ($\text{C}(\underline{\text{CH}}_3)_2$), 62.6 (C6), 70.5 (C3), 71.4 (C5), 80.1 (C2), 80.1 (C4), 104.2 (C1), 114.1 ($\underline{\text{C}}(\text{CH}_3)_2$); m/z (ESI+ve): 243 ($[\text{M} + \text{Na}]^+$, 100%), 463 ($[2\text{M} + \text{Na}]^+$, 85%); HRMS m/z (ESI+ve): found 243.0841 ($[\text{M} + \text{Na}]^+$); $\text{C}_9\text{H}_{16}\text{NaO}_6$ requires 243.0839.

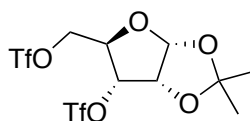
1,2-*O*-Isopropylidene- α -D-ribofuranose **2.165**



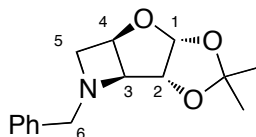
Sodium *meta*-periodate (708 mg, 3.31 mmol) was added to a solution of triol **2.164** (693 mg, 3.15 mmol) in water (7 mL), and the mixture stirred at rt. TLC analysis (9:1 ethyl acetate/methanol) after 1 h showed consumption of starting material (R_f 0.40) and formation of a single product (R_f 0.59). The mixture was diluted with ethanol (14 mL) and stirred for a further 30 mins. The white suspension was filtered through Celite, and the pad washed with ethanol. The combined filtrates were concentrated *in vacuo* to afford a clear, colourless syrup. This material was re-dissolved in 3:1 ethanol/water (20 mL), sodium borohydride (90 mg, 2.38 mmol) added in small portions and the mixture stirred at rt. Analysis by mass spectrometry after 3 h showed reaction completion. The mixture was quenched by drop-wise addition of acetic acid until pH 7, concentrated *in vacuo* and co-evaporated with ethanol to afford the crude material as a clear, colourless gum. This material was pre-absorbed onto silica from methanolic solution and purified *via* flash column chromatography on silica gel (ethyl acetate) to afford the title compound as a white crystalline solid (578 mg, 96%); $[\alpha]_D^{25}$ +49.0 (c 0.94 in CHCl_3) [lit.²³⁵ $[\alpha]_D^{20}$ +45.4 (c 1.6 in CHCl_3)]; ν_{max} (thin film): 3228 (br, OH); m.p. 87-89 °C (cyclohexane/ethyl acetate) [lit.²³⁶ m.p. 85-87 °C]; δ_{H} (CDCl_3 , 400 MHz): 1.37, 1.57 (6H, 2 x s, $\text{C}(\underline{\text{CH}}_3)_2$), 1.92-1.96 (1H, dd, 5-OH, $J_{\text{OH},5'}$ 4.8, $J_{\text{OH},5}$ 8.0), 2.42-2.45 (1H, d, 3-OH, $J_{\text{OH},3}$ 10.7), 3.72-3.78 (1H, ddd, H5, $J_{5,4}$ 3.7, $J_{5,\text{OH}}$ 8.1, J_{gem} 12.2), 3.82-3.86 (1H, ddd,

H4, $J_{4,5'}$ 2.7, $J_{4,5}$ 3.7, $J_{4,3}$ 8.9), 3.93-3.98 (1H, ddd, H5', $J_{5',4}$ 2.7, $J_{5',OH}$ 4.8, J_{gem} 12.2), 3.97-4.03 (1H, ddd, H3, $J_{3,2}$ 5.1, $J_{3,4}$ 8.9, $J_{3,OH}$ 10.7), 4.57-4.60 (1H, dd, H2, $J_{2,1}$ 3.8, $J_{2,3}$ 5.1), 5.81-5.82 (1H, d, H1, $J_{1,2}$ 3.8); δ_C (CDCl₃, 100 MHz): 26.7, 26.7 (C(CH₃)₂), 61.0 (C5), 71.0 (C3), 78.9 (C2), 80.9 (C4), 104.2 (C1), 113.0 (C(CH₃)₂); m/z (ESI-ve): 189 ([M - H]⁻, 100%); HRMS m/z (ESI+ve): found 213.0734 ([M + Na]⁺); C₈H₁₄NaO₅ requires 213.0733.

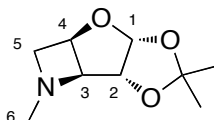
1,2-*O*-Isopropylidene-3,5-di-*O*-trifluoromethanesulfonyl- α -D-ribofuranose **2.166**



Trifluoromethanesulfonic anhydride (1.43 mL, 8.50 mmol) was added drop-wise to a stirred solution of diol **2.165** (538 mg, 2.83 mmol) and pyridine (1.37 mL, 16.94 mmol) in dichloromethane (10 mL) at -30 °C under nitrogen atmosphere. TLC analysis (ethyl acetate) after 1 h showed consumption of starting material (R_f 0.21) and formation of a single product (0.71). The mixture was diluted with dichloromethane (10 mL), washed with 2M hydrochloric acid (3 x 20 mL), dried (MgSO₄) and concentrated *in vacuo* at 25 °C to afford a straw-coloured syrup. Purification *via* flash column chromatography on silica gel (ethyl acetate) afforded the title compound as a clear syrup which crystallised to an off-white solid (1.127 g, 88%); $[\alpha]_D^{25} +75.8$ (c 1.05 in CHCl₃) [lit.²³⁷ $[\alpha]_D^{25} +54$ (c 1.25 in CHCl₃)]; m.p. 50-52 °C; δ_H (C₆D₆, 400 MHz): 0.94, 1.30 (6H, 2 x s, C(CH₃)₂), 3.68-3.72 (1H, dd, H5, $J_{5,4}$ 2.4, J_{gem} 12.0), 3.75-3.78 (1H, a-dt, H4, $J_{4,5}/J_{4,5'}$ 2.3, $J_{4,3}$ 8.8), 3.87-3.89 (1H, m, H2), 4.08-4.12 (1H, dd, H5', $J_{5',4}$ 2.1, J_{gem} 12.0), 4.42-4.46 (1H, dd, H3, $J_{3,2}$ 4.7, $J_{3,4}$ 8.8), 5.12-5.13 (1H, d, H1, $J_{1,2}$ 3.6); δ_C (C₆D₆, 100 MHz): 26.2, 26.4 (C(CH₃)₂), 70.9 (C5), 74.4 (C4), 76.9 (C2), 80.3 (C3), 104.2 (C1), 114.4 (C(CH₃)₂); m/z (ESI+ve): 477 ([M + Na]⁺, 10%), 493 ([M + K]⁺, 100%); HRMS m/z (ESI+ve): found 476.9720 ([M + Na]⁺); C₁₀H₁₂F₆NaO₉S₂ requires 476.9719.

N-Benzyl-3,5-dideoxy-3,5-imino-1,2-O-isopropylidene- α -D-xylofuranose 2.167

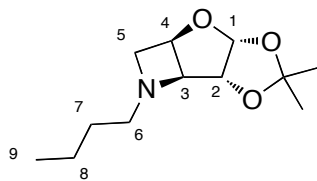
Benzylamine (71 μ L, 0.65 mmol) and diisopropylethylamine (257 μ L, 1.48 mmol) were added simultaneously to a stirred solution of ditriflate **2.166** (268 mg, 0.59 mmol) in acetonitrile (4 mL) at rt. TLC analysis (2:1 Cyclohexane/ethyl acetate) after 22 h showed consumption of starting material (R_f 0.68) and formation of a single product (R_f 0.42). The mixture was concentrated *in vacuo* and the resulting residue purified *via* flash column chromatography on silica gel (5:1 to 3:1 cyclohexane/ethyl acetate) to afford the title compound as a clear, pale yellow syrup (149 mg, 97%); $[\alpha]_D^{25} +47.9$ (c 1.05 in CHCl_3); δ_H (CDCl_3 , 400 MHz): 1.32, 1.42 (6H, 2 x s, $\text{C}(\text{CH}_3)_2$), 3.02-3.05 (1H, dd, H5, $J_{5,4}$ 4.8, J_{gem} 8.9), 3.32-3.35 (1H, d, H5', J_{gem} 8.9), 3.65-3.68 (1H, H6, J_{gem} 12.8), 3.70-3.73 (1H, d, H6', J_{gem} 12.8), 3.82-3.83 (1H, d, H3, $J_{3,4}$ 4.7), 4.35-4.36 (1H, d, H2, $J_{2,1}$ 3.7), 4.88-4.90 (1H, t, H4, $J_{4,5}/J_{4,3}$ 4.7), 6.18-6.18 (1H, d, H1, $J_{1,2}$ 3.7), 7.25-7.35 (5H, m, 5 x ArH); δ_C (CDCl_3 , 100 MHz): 27.4, 27.9 ($\text{C}(\text{CH}_3)_2$), 59.6 (C5), 61.4 (C6), 72.3 (C3), 75.2 (C4), 84.6 (C2), 109.8 (C1), 113.2 ($\text{C}(\text{CH}_3)_2$), 127.5 (*p*-ArCH), 128.5, 128.8 (2 x *o*-ArCH and 2 x *m*-ArCH), 137.9 (*ipso*-ArC); m/z (ESI+ve): 262 ($[\text{M} + \text{H}]^+$, 85%), 284 ($[\text{M} + \text{Na}]^+$, 68%); HRMS m/z (ESI+ve): found 284.1246 ($[\text{M} + \text{Na}]^+$); $\text{C}_{15}\text{H}_{19}\text{NNaO}_3$ requires 284.1257.

3,5-Dideoxy-3,5-imino-1,2-O-isopropylidene-N-methyl- α -D-xylofuranose 2.168

Diisopropylethylamine (0.27 mL, 1.54 mmol) and a 33 wt% solution of methylamine in ethanol (84 μ L, 0.68 mmol) were added simultaneously to a stirred solution of ditriflate **2.166** (280 mg, 0.62 mmol) in acetonitrile (6 mL) at rt. TLC analysis (2:1 cyclohexane/ethyl acetate) after 18 h showed consumption of starting material (R_f 0.65) and formation of a single product (R_f 0.08). The

mixture was directly dry loaded and purified *via* flash column chromatography on silica gel doped with triethylamine (99:1 ethyl acetate/triethylamine to 94:5:1 ethyl acetate/methanol/triethylamine) to afford the title compound as a clear, pale yellow oil (76 mg, 67%); $[\alpha]_D^{25} +35.5$ (c 0.38 in CHCl_3); δ_{H} (C_6D_6 , 400 MHz): 1.28, 1.44 (6H, 2 x s, $\text{C}(\underline{\text{CH}}_3)_2$), 1.94 (3H, s, H6), 2.36-2.40 (1H, dd, H5, $J_{5,4}$ 4.8, J_{gem} 8.5), 3.16-3.18 (1H, d, H5', J_{gem} 8.5), 3.33-3.35 (1H, d, H3, $J_{3,4}$ 4.6), 4.40-4.41 (1H, d, H2, $J_{2,1}$ 3.6), 4.57-4.60 (1H, a-t, H4, $J_{4,5}/J_{4,3}$ 4.7), 6.26-6.27 (1H, d, H1, $J_{1,2}$ 3.6); δ_{C} (C_6D_6 , 100 MHz): 27.9, 28.5 ($\text{C}(\underline{\text{CH}}_3)_2$), 43.7 (C6), 61.8 (C5), 74.7 (C3), 75.4 (C4), 85.1 (C2), 110.7 (C1), 113.3 ($\text{C}(\underline{\text{CH}}_3)_2$); m/z (ESI+ve): 186 ($[\text{M} + \text{H}]^+$, 15%), 208 ($[\text{M} + \text{Na}]^+$, 28%); HRMS m/z (ESI+ve): found 208.0939 ($[\text{M} + \text{Na}]^+$); $\text{C}_9\text{H}_{15}\text{NNaO}_3$ requires 208.0944.

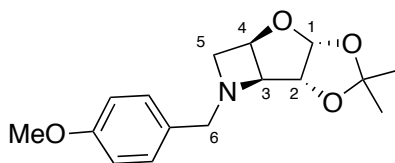
N*-Butyl-3,5-dideoxy-3,5-imino-1,2-*O*-isopropylidene- α -D-xylofuranose **2.169*



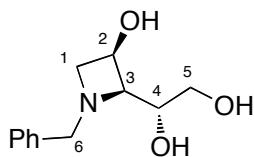
Diisopropylethylamine (0.25 mL, 1.44 mmol) and *n*-butylamine (63 μL , 0.63 mmol) were added simultaneously to a stirred solution of ditriflate **2.166** (262 mg, 0.58 mmol) in acetonitrile (5 mL) at rt. TLC analysis (2:1 cyclohexane/ethyl acetate) after 18 h showed consumption of starting material (R_f 0.65) and formation of a single product (R_f 0.35). The mixture was directly dry loaded and purified *via* flash column chromatography on silica gel (8:1 to 1:1 cyclohexane/ethyl acetate) to afford the title compound as a clear, pale yellow oil (107 mg, 82%); $[\alpha]_D^{25} +29.7$ (c 0.67 in CHCl_3); δ_{H} (C_6D_6 , 400 MHz): 0.79-0.83 (3H, t, H9, $J_{9,8}$ 7.0) 1.11-1.22 (4H, m, H7 and H8), 1.29, 1.46 (6H, 2 x s, $\text{C}(\underline{\text{CH}}_3)_2$), 2.09-2.20 (2H, m, H6), 2.40-2.44 (1H, dd, H5, $J_{5,4}$ 4.9, J_{gem} 8.5), 3.18-3.20 (1H, d, H5', J_{gem} 8.5), 3.42-3.43 (1H, d, H3, $J_{3,4}$ 4.7), 4.46-4.47 (1H, d, H2, $J_{2,1}$ 3.6), 4.63-4.65 (1H, a-t, H4, $J_{4,3}/J_{4,5}$ 4.8), 6.28-6.29 (1H, d, H1, $J_{1,2}$ 3.6); δ_{C} (C_6D_6 , 100 MHz): 14.5 (C9), 21.0, 30.8 (C7 and C8), 27.9, 28.6 ($\text{C}(\underline{\text{CH}}_3)_2$), 57.7 (C6), 60.1 (C5), 73.2 (C3), 75.6 (C4), 85.6 (C2), 110.7 (C1), 113.3

($\text{C}(\text{CH}_3)_2$); m/z (ESI+ve): 228 ($[\text{M} + \text{H}]^+$, 100%), 250 ($[\text{M} + \text{Na}]^+$, 87%); HRMS m/z (ESI+ve): found 228.1586 ($[\text{M} + \text{H}]^+$); $\text{C}_{12}\text{H}_{22}\text{NO}_3$ requires 228.1594.

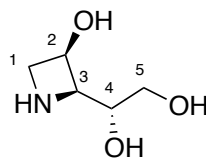
3,5-Dideoxy-3,5-imino-1,2-*O*-isopropylidene-*N*-*para*-methoxybenzyl- α -D-xylofuranose **2.170**



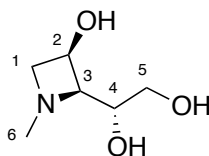
4-Methoxybenzylamine (95 μL , 0.73 mmol) and diisopropylethylamine (0.29 mL, 1.65 mmol) were added simultaneously to a stirred solution of ditriflate **2.166** (300 mg, 0.66 mmol) in acetonitrile (3 mL) at rt. TLC analysis (ethyl acetate) after 18 h showed consumption of starting material (R_f 0.71) and formation of a single major product (R_f 0.51). The mixture was directly pre-loaded onto silica and purified *via* flash column chromatography on silica gel (5:1 to 2:1 cyclohexane/ethyl acetate) to afford the title compound as an off-white crystalline solid (184 mg, 96%); $[\alpha]_D^{25} +53.1$ (c 1.00 in CHCl_3); m.p. 72-73 $^\circ\text{C}$; δ_{H} (CDCl_3 , 400 MHz): 1.30, 1.40 (6H, 2 x s, $\text{C}(\text{CH}_3)_2$), 2.98-3.02 (1H, dd, H5, $J_{5,4}$ 4.8, J_{gem} 9.0), 3.28-3.31 (1H, a-dt, H5', $J_{5',4}/J_{5',3}$ 0.9, J_{gem} 9.0), 3.55-3.58 (1H, d, H6, J_{gem} 12.6), 3.63-3.66 (1H, d, H6', J_{gem} 12.6), 3.78-3.79 (1H, d, H3, $J_{3,4}$ 4.7), 3.80 (3H, s, OCH_3), 4.30-4.31 (1H, d, H2, $J_{2,1}$ 3.7), 4.85-4.87 (1H, a-t, H4, $J_{4,3}/J_{4,5}$ 4.7), 6.15-6.16 (1H, d, H1, $J_{1,2}$ 3.7), 6.83-6.87, 7.18-7.21 (4H, 2 x m, 4 x ArH); δ_{C} (CDCl_3 , 100 MHz): 27.4, 27.9 ($\text{C}(\text{CH}_3)_2$), 55.4 (OCH_3), 59.4 (C5), 60.8 (C6), 72.1 (C3), 75.2 (C4), 84.6 (C2), 109.8 (C1), 113.1 ($\text{C}(\text{CH}_3)_2$), 113.9, 130.0 (2 x *o*-ArCH and 2 x *m*-ArCH), 129.9 (*ipso*-ArC), 159.0 (*p*-ArC); m/z (ESI+ve): 292 ($[\text{M} + \text{H}]^+$, 100%), 314 ($[\text{M} + \text{Na}]^+$, 33%); HRMS m/z (ESI+ve): found 292.1541; $\text{C}_{16}\text{H}_{22}\text{NO}_4$ requires 292.1543.

N-Benzyl-1,3-dideoxy-1,3-imino-L-xylitol 2.171L

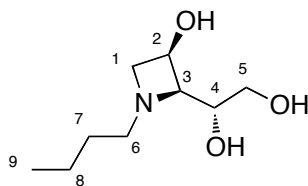
The acetonide **2.167** (149 mg, 0.57 mmol) was dissolved in 1:1 trifluoroacetic acid/water (4 mL) and stirred at rt. TLC (1:1 cyclohexane/ethyl acetate) of an aliquot quenched with triethylamine after 24 h showed consumption of starting material (R_f 0.53) and formation of a single product (R_f 0.12). The mixture was concentrated *in vacuo* and co-evaporated with water (2 x 10 mL) to afford the crude lactol as a clear light brown syrup. This was re-dissolved in water (5 mL), sodium borohydride (43 mg, 1.14 mmol) added and the mixture stirred at rt. TLC analysis (1:1 cyclohexane/ethyl acetate) after 20 h indicated consumption of starting material and formation of a single product (R_f 0.00). The mixture was quenched with acetic acid and loaded onto a column of Dowex 50WX8 (H^+) ion exchange resin. The column was flushed with water, ethanol, more water and then eluted with 2M aqueous ammonia. The ammoniacal fraction was concentrated *in vacuo* to afford the title compound as an off-white crystalline solid (112 mg, 88%); $[\alpha]_D^{25}$ -103.0 (c 0.23 in MeOH); ν_{max} (solid): 3261, 3456 (s, OH); m.p. 179-180 °C (methanol); δ_H (D_2O , 500 MHz): 3.10-3.12 (1H, a-dt, H1, $J_{1,3}/J_{1,2}$ 1.4, J_{gem} 9.8), 3.33-3.36 (1H, dd, H1', $J_{1',2}$ 6.3, J_{gem} 9.8), 3.37-3.40 (1H, ddd, H3, $J_{3,1}$ 0.9, $J_{3,2}$ 6.3, $J_{3,4}$ 9.0), 3.44-3.48 (1H, dd, H5, $J_{5,4}$ 6.6, J_{gem} 11.9), 3.54-3.56 (1H, d, H6, J_{gem} 12.4), 3.59-3.62 (1H, dd, H5', $J_{5',4}$ 3.5, J_{gem} 11.9), 4.02-4.04 (1H, d, H6', J_{gem} 12.4), 4.08-4.12 (1H, ddd, H4, $J_{4,5'}$ 3.5, $J_{4,5}$ 6.6, $J_{4,3}$ 9.1), 4.44-4.47 (1H, a-dt, H2, $J_{2,1}$ 1.8, $J_{2,1'}/J_{2,3}$ 6.3), 7.35-7.43 (5H, m, 5 x ArH); δ_C (D_2O , 125 MHz): 59.2 (C1), 62.7 (C6), 63.4 (C5), 64.5 (C2), 70.5 (C3), 71.9 (C4), 128.3 (p -ArCH), 129.2, 130.2 (2 x o -ArCH and 2 x m -ArCH), 137.5 (*ipso*-ArC); m/z (ESI+ve): 224 ($[M + H]^+$, 100%), 246 ($[M + Na]^+$, 47%); HRMS m/z (ESI+ve): found 224.1279 ($[M + H]^+$); $C_{12}H_{18}NO_3$ requires 224.1281.

1,3-Dideoxy-1,3-imino-L-xylitol 2.101L

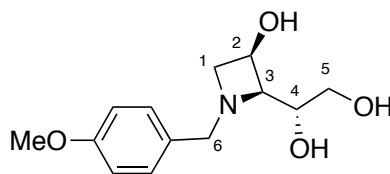
The L-xylitol **2.171L** (40 mg, 0.179 mmol), ammonium formate (113 mg, 1.79 mmol) and palladium on activated charcoal (10 wt. %, 38 mg, 0.036 mmol) were placed in a flame-dried flask with anhydrous methanol (4 mL), and the suspension heated to reflux under argon atmosphere. TLC analysis (14:3:1:1:1 ethanol/pyridine/*n*-butanol/acetic acid/water) after 20 min showed consumption of starting material (R_f 0.82) and formation of a single product (R_f 0.59). The mixture was allowed to cool, filtered through Celite, the pad and flask rinsed with methanol and the combined filtrates concentrated *in vacuo* to give the crude as a clear syrup. The material was loaded onto a column of Dowex 50WX8 (H^+) ion exchange resin, the column flushed with water, ethanol, water and then eluted with 2M aqueous ammonia. The ammoniacal fraction was concentrated *in vacuo* to afford the title compound as a clear, colourless syrup (23.5 mg, 99%); [**characterised as the HCl salt**, a clear colourless syrup] $[\alpha]_D^{25} +3.2$ (c 0.50 in H_2O); ν_{max} (neat): 3313 (s, br, OH and NH); δ_H (D_2O , 400 MHz): 3.58-3.63 (1H, dd, H5, $J_{5,4}$ 5.2, J_{gem} 12.1), 3.70-3.74 (1H, dd, H5', $J_{5',4}$ 3.6, J_{gem} 12.1), 3.91-3.95 (1H, dd, H1, $J_{1,2}$ 4.9, J_{gem} 11.7), 4.29-4.33 (1H, ddd, H4, $J_{4,5'}$ 3.6, $J_{4,5}$ 5.2, $J_{4,3}$ 6.8), 4.34-4.39 (1H, dd, H1', $J_{1',2}$ 7.1, J_{gem} 11.7), 4.58-4.61 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 6.9), 4.79-4.83 (1H, a-dt, H2, $J_{2,1}$ 4.9, $J_{2,3}/J_{2,1'}$ 7.0); δ_C (D_2O , 100 MHz): 54.1 (C1), 63.2 (C5), 64.0 (C2), 67.0, 67.2 (C3 and C4); m/z (ESI+ve): 134 ($[M + H]^+$, 100%), 156 ($[M + Na]^+$, 40%); HRMS m/z (ESI+ve): found 134.0817 ($[M + H]^+$); $C_5H_{12}NO_3$ requires 134.0812.

1,3-Dideoxy-1,3-imino-*N*-methyl-L-xylitol 2.172L

The acetonide **2.168** (122 mg, 0.66 mmol) was dissolved in a 1:1 mixture of water/trifluoroacetic acid (4 mL) and stirred at rt. TLC analysis (ethyl acetate) of an aliquot quenched with triethylamine after 42 h showed consumption of starting material and formation of a single product (R_f 0.05). The mixture was concentrated *in vacuo* and co-evaporated with water (3 x 20 mL) to afford the crude lactol as a light brown syrup. This was re-dissolved in water, and sodium borohydride (50 mg, 1.32 mmol) added in small portions to the stirred solution. Analysis by mass spectrometry after 45 h showed reaction completion. The mixture was directly loaded onto a column of Dowex 50WX8 (H^+) ion exchange resin, and the column flushed with water, ethanol, more water and then eluted with 2M aqueous ammonia. The ammoniacal fraction was concentrated *in vacuo* to afford the title compound as a clear, pale yellow syrup (83 mg, 85%); [characterised as the HCl salt, a clear syrup] $[\alpha]_D^{25}$ -27.7 (c 0.71 in H_2O); $[\alpha]_D^{25}$ -29.8 (c 0.54 in MeOH); ν_{max} (neat): 3265 (s, br, OH); δ_H (D_2O , 500 MHz): 2.97 (3H, s, H6), 3.57-3.61 (1H, dd, H5, $J_{5,4}$ 4.9, J_{gem} 12.2), 3.69-3.72 (1H, dd, H5', $J_{5',4}$ 3.1, J_{gem} 12.3), 4.09-4.12 (1H, dd, H1, $J_{1,2}$ 2.7, J_{gem} 11.8), 4.19-4.23 (1H, dd, H1', $J_{1',2}$ 6.6, J_{gem} 11.8), 4.31-4.34 (1H, m, H4), 4.39-4.42 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 7.3), 4.78-4.81 (1H, m, H2); δ_C (D_2O , 125 MHz): 42.2 (C6), 62.5 (C2), 62.7 (C5), 62.8 (C1), 67.8 (C4), 75.5 (C3); m/z (ESI+ve): 148 ($[M + H]^+$, 100%), 170 ($[M + Na]^+$, 9%); HRMS m/z (ESI+ve): found 148.0968 ($[M + H]^+$); $C_6H_{14}NO_3$ requires 148.0968.

N-Butyl-1,3-dideoxy-1,3-imino-L-xylitol 2.173L

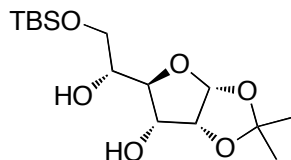
The acetonide **2.169** (107 mg, 0.47 mmol) was dissolved in a 1:1 mixture of trifluoroacetic acid/water (2 mL) and stirred at rt. TLC analysis (1:1 cyclohexane/ethyl acetate) of an aliquot quenched with triethylamine after 20 h showed consumption of starting material (R_f 0.47) and formation of a single product (R_f 0.08). The mixture was concentrated *in vacuo* and co-evaporated with water (2 x 10 mL) to afford a clear, colourless syrup. This was re-dissolved in water (2 mL), sodium borohydride (18 mg, 0.47 mmol) added and the mixture stirred at rt. After 16 h the reaction was judged to be complete by mass spectrometry. The mixture was quenched with saturated aqueous ammonium chloride and loaded onto a column of Dowex 50WX8 (H^+) ion exchange resin. The column was flushed sequentially with water, ethanol, more water, and then eluted with 2M aqueous ammonia. The ammoniacal fraction was concentrated *in vacuo* to afford the title compound as a clear, colourless syrup which slowly crystallised to a white solid (87 mg, 98%); $[\alpha]_D^{25}$ -93.2 (c 0.57 in H_2O); ν_{max} (solid): 3245, 3456 (s, OH); m.p. 72-73 °C; δ_H (D_2O , 400 MHz): 0.85-0.89 (3H, t, H9, $J_{9,8}$ 7.2), 1.23-1.38 (4H, m, H8 and H7), 2.33-2.39 (1H, m, H6), 2.81-2.88 (1H, m, H6'), 3.18-3.22 (1H, ddd, H3, $J_{3,1'}$ 1.1, $J_{3,2}$ 6.1, $J_{3,4}$ 9.2), 3.19-3.23 (1H, dd, H1, $J_{1,2}$ 6.3, J_{gem} 9.9), 3.30-3.33 (1H, ddd, H1', $J_{1',3}$ 1.2, $J_{1',2}$ 1.8, J_{gem} 9.9), 3.44-3.49 (1H, dd, H5, $J_{5,4}$ 6.6, J_{gem} 11.9), 3.61-3.65 (1H, dd, H5', $J_{5',4}$ 3.5, J_{gem} 11.9), 4.04-4.09 (1H, ddd, H4, $J_{4,5'}$ 3.5, $J_{4,5}$ 6.6, $J_{4,3}$ 9.2), 4.43-4.47 (1H, a-dt, H2, $J_{2,1'}$ 1.8, $J_{2,1}/J_{2,3}$ 6.2); δ_C (D_2O , 100 MHz): 13.9 (C9), 20.7, 29.2 (C7 and C8), 59.3 (C6), 59.8 (C1), 63.4 (C5), 64.6 (C2), 71.0 (C3), 71.9 (C4); m/z (ESI+ve): 190 ($[M + H]^+$, 100%), 212 ($[M + Na]^+$, 58%); HRMS m/z (FI+): found 189.1369 ($[M \bullet]$), $C_9H_{19}NO_3 \bullet$ requires 189.1365.

1,3-Dideoxy-1,3-imino-*N*-para-methoxybenzyl-L-xylitol 2.174L

The acetonide **2.170** (184 mg, 0.63 mmol) was dissolved in 1:1 trifluoroacetic acid/water (8 mL) and stirred at rt. TLC analysis (ethyl acetate) of an aliquot quenched with triethylamine after 42 h showed consumption of starting material (R_f 0.58) and formation of a single product (R_f 0.29). The mixture was concentrated *in vacuo* and co-evaporated with water (2 x 20 mL) to afford the crude lactol as a brown oil. This was re-dissolved in water (6 mL), sodium borohydride (48 mg, 1.26 mmol) added and the mixture stirred at rt. Analysis by mass spectrometry after 17 h showed reaction completion. The mixture was quenched with acetic acid, and loaded onto a column of Dowex 50WX8 (H^+) ion exchange resin. The column was flushed with water, ethanol, more water and then eluted with 2M aqueous ammonia. The ammoniacal fractions were concentrated *in vacuo* to afford the title compound as a clear, yellow syrup which slowly crystallised to a pale tan solid (143 mg, 89%); $[\alpha]_D^{25}$ -71.0 (c 0.40 in MeOH); ν_{max} (solid): 3329 (s, br, OH); m.p. 96-98 °C; δ_H (D_2O , 500 MHz): 3.08-3.10 (1H, br d, H1, J_{gem} 9.8), 3.33-3.36 (1H, dd, H1', $J_{1,2}$ 6.3, J_{gem} 9.8), 3.36-3.39 (1H, dd, H3, $J_{3,2}$ 6.4, $J_{3,4}$ 8.9), 3.43-3.47 (1H, dd, H5, $J_{5,4}$ 6.6, J_{gem} 11.9), 3.50-3.52 (1H, d, H6, J_{gem} 12.4), 3.58-3.61 (1H, dd, H5', $J_{5',4}$ 3.6, J_{gem} 11.9), 3.83 (3H, s, OCH_3) 3.95-3.98 (1H, d, H6', J_{gem} 12.4), 4.07-4.11 (1H, ddd, H4, $J_{4,5'}$ 3.6, $J_{4,5}$ 6.6, $J_{4,3}$ 8.9), 4.43-4.46 (1H, a-dt, H2, $J_{2,1}$ 1.5, $J_{2,1'}/J_{2,3}$ 6.3), 6.98-7.00, 7.30-7.32 (4H, 2 x m, 4 x ArH); δ_C (D_2O , 125 MHz): 56.0 (OCH_3), 58.9 (C1), 61.8 (C6), 63.4 (C5), 64.4 (C2), 70.4 (C3), 71.8 (C4), 114.6, 131.6 (2 x *o*-ArCH and 2 x *m*-ArCH), 129.9 (*ipso*-ArC), 159.0 (*p*-ArC); m/z (ESI+ve): 254 ($[M + H]^+$, 100%); HRMS m/z (ESI+ve): found 254.1388 ($[M + H]^+$); $C_{13}H_{20}NO_4$ requires 254.1387.

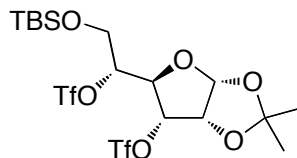
2.4.3 *Ido and gulo* azetidine tetrols from allose and talose

6-*O*-*tert*-Butyldimethylsilyl-1,2-*O*-isopropylidene- α -D-allofuranose **2.181**



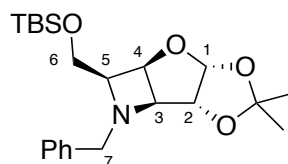
tert-Butyldimethylsilyl chloride (754 mg, 5.00 mmol) was added in one portion to a stirred solution of triol **2.164** (1.000 g, 4.54 mmol) and imidazole (464 mg, 6.81 mmol) in anhydrous *N,N*-dimethylformamide (10 mL) at -20 °C under argon, and the mixture maintained between -20 and -10 °C. TLC analysis (ethyl acetate) after 1.5 h showed consumption of starting material (R_f 0.08) and formation of a single product (R_f 0.70). The mixture was diluted with ethyl acetate (80 mL) and washed with 50% brine (3 x 40 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude material as a clear, colourless syrup. Purification *via* flash column chromatography on silica gel (7:1 to 0:1 cyclohexane/ethyl acetate) afforded the title compound as a white crystalline solid (1.442 g, 94%); $[\alpha]_D^{25} +27.1$ (c 1.00 in $CHCl_3$); ν_{max} (solid): 3466 (s, br, OH); m.p. 84-85 °C; δ_H (CD_3CN , 400 MHz): 0.08 (6H, s, $OSi(CH_3)_2C(CH_3)_3$), 0.90 (9H, s, $OSi(CH_3)_2C(CH_3)_3$), 1.31, 1.49 (6H, 2 x s, $C(CH_3)_2$), 3.00-3.01 (1H, d, 5-OH, $J_{OH,5}$ 4.1), 3.14-3.16 (1H, d, 3-OH, $J_{OH,3}$ 8.0), 3.61-3.66 (1H, m, H6), 3.71-3.77 (2H, m, H6' and H5), 3.78-3.81 (1H, dd, H4, $J_{4,5}$ 3.8, $J_{4,3}$ 8.7), 3.97-4.02 (1H, a-dt, H3, $J_{3,2}$ 4.9, $J_{3,OH}/J_{3,4}$ 8.4), 4.51-4.53 (1H, dd, H2, $J_{2,1}$ 3.7, $J_{2,3}$ 4.9), 5.68-5.69 (1H, d, H1, $J_{1,2}$ 3.7); δ_C (CD_3CN , 100 MHz): -5.1 ($OSi(CH_3)_2C(CH_3)_3$), 19.0 ($OSi(CH_3)_2C(CH_3)_3$), 26.3 ($OSi(CH_3)_2C(CH_3)_3$), 26.9, 27.0 ($C(CH_3)_2$), 65.1 (C6), 72.4 (C3), 72.7 (C5), 80.5, 80.6 (C2 and C4), 105.0 (C1), 113.1 ($C(CH_3)_2$); m/z (ESI+ve): 335 ($[M + H]^+$, 41%), 352 ($[M + NH_4]^+$, 88%), 357 ($[M + Na]^+$, 77%), 691 ($[2M + Na]^+$, 86%), HRMS m/z (ESI+ve): found 357.1690 ($[M + Na]^+$); $C_{15}H_{30}NaO_6Si$ requires 357.1704.

6-*O*-*tert*-Butyldimethylsilyl-1,2-*O*-isopropylidene-3,5-di-*O*-trifluoromethanesulfonyl- α -D-allofuranose **2.182**



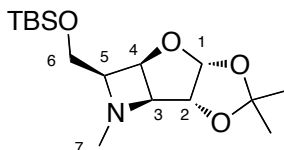
Trifluoromethanesulfonic anhydride (1.51 mL, 8.97 mmol) was added slowly to a stirred solution of diol **2.181** (1.00 g, 2.99 mmol) and pyridine (1.45 mL, 17.94 mmol) in dichloromethane (20 mL) at -30 °C under nitrogen atmosphere, and the temperature maintained below -10 °C. TLC analysis (3:1 cyclohexane/ethyl acetate) after 2 h indicated no starting material (R_f 0.14) and formation of a single product (R_f 0.64). The mixture was diluted with dichloromethane (30 mL), washed with 2M hydrochloric acid (3 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo* at 25 °C to afford the crude material as a yellow syrup. Purification *via* flash column chromatography on silica gel (2:1 cyclohexane/ethyl acetate) afforded the title compound as a clear, colourless syrup (1.76 g, 98%); $[\alpha]_D^{25} +51.3$ (c 1.44 in $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 0.09 (6H, s, $OSi(CH_3)_2C(CH_3)_3$), 0.89 (9H, s, $OSi(CH_3)_2C(CH_3)_3$), 1.39, 1.58 (6H, 2 x s, $C(CH_3)_2$), 3.82-3.87 (1H, dd, H6, $J_{6,5}$ 6.7, J_{gem} 11.0), 3.85-3.90 (1H, dd, H6', $J_{6',5}$ 7.1, J_{gem} 11.0), 4.53-4.55 (1H, dd, H4, $J_{4,5}$ 1.7, $J_{4,3}$ 8.3), 4.79-4.81 (1H, dd, H2, $J_{2,1}$ 3.7, $J_{2,3}$ 4.9), 5.00-5.03 (1H, dd, H3, $J_{3,2}$ 4.9, $J_{3,4}$ 8.3), 5.16-5.19 (1H, a-dt, H5, $J_{5,4}$ 1.7, $J_{5,6}/J_{5,6'}$ 6.9), 5.86-5.87 (1H, d, H1, $J_{1,2}$ 3.7); δ_C ($CDCl_3$, 100 MHz): -5.8, -5.6 ($OSi(CH_3)_2C(CH_3)_3$), 18.3 ($OSi(CH_3)_2C(CH_3)_3$), 25.8 ($OSi(CH_3)_2C(CH_3)_3$), 26.6, 26.9 ($C(CH_3)_2$), 60.3 (C6), 75.8 (C4), 77.4 (C2), 80.3 (C3), 85.0 (C5), 104.0 (C1), 114.9 ($C(CH_3)_2$), 113.7-123.3 and 113.8-123.4 (2 x q, 2 x OSO_2CF_3); m/z (ESI+ve): 616 ($[M + NH_4]^+$, 80%), 621 ($[M + Na]^+$, 100%), 637 ($[M + K]^+$, 55%); HRMS m/z (ESI+ve): found 621.0681 ($[M + Na]^+$); $C_{17}H_{28}F_6NaO_{10}S_2Si$ requires 621.0690.

N*-Benzyl-6-*O*-*tert*-butyldimethylsilyl-3,5-dideoxy-3,5-imino-1,2-*O*-isopropylidene- β -L-idofuranose **2.183*



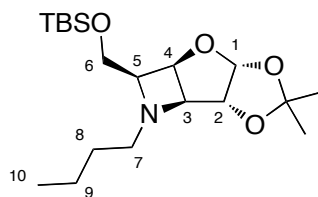
Diisopropylethylamine (275 μ L, 1.578 mmol) and benzylamine (76 μ L, 0.695 mmol) were added simultaneously to a stirred solution of ditriflate **2.182** (378 mg, 0.631 mmol) in acetonitrile (5 mL), and the mixture heated to 50 $^{\circ}$ C. TLC analysis (19:1 toluene/acetone) after 25 h showed consumption of starting material (R_f 0.85) and formation of a single product (R_f 0.71). The mixture was concentrated *in vacuo* to afford an orange residue. Purification *via* flash column chromatography on silica gel (5:1 cyclohexane/ethyl acetate) afforded the title compound as a clear, pale yellow syrup (239 mg, 93%); $[\alpha]_D^{25} +72.7$ (c 0.86 in CHCl_3); δ_{H} (CDCl_3 , 400 MHz): 0.04 (6H, s, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 0.87 (9H, s, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 1.27, 1.39 (6H, 2 x s, $\text{C}(\text{CH}_3)_2$), 3.17-3.21 (1H, a-dt, H5, $J_{5,4}$ 4.8, $J_{5,6}/J_{5,6'}$ 6.3), 3.44-3.48 (1H, dd, H6, $J_{6,5}$ 6.1, J_{gem} 10.5), 3.54-3.57 (1H, d, H7, J_{gem} 12.7), 3.66-3.67 (1H, d, H3, $J_{3,4}$ 4.8), 3.72-3.77 (1H, dd, H6', $J_{6',5}$ 6.5, J_{gem} 10.5), 3.85-3.89 (1H, d, H7', J_{gem} 12.7), 4.14-4.15 (1H, d, H2, $J_{2,1}$ 3.6), 4.86-4.89 (1H, t, H4, $J_{4,5}/J_{4,3}$ 4.8), 6.02-6.03 (1H, d, H1, $J_{1,2}$ 3.6), 7.24-7.34 (5H, m, 5 x ArH); δ_{C} (CDCl_3 , 100 MHz): -5.2, -5.2 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 18.5 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 26.1 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 27.4, 28.0 ($\text{C}(\text{CH}_3)_2$), 60.9 (C7), 62.3 (C6), 68.3 (C5), 69.4 (C3), 75.8 (C4), 84.3 (C2), 110.0 (C1), 113.4 ($\text{C}(\text{CH}_3)_2$), 127.5 (*p*-ArCH), 128.5, 129.3 (2 x *o*-ArCH and 2 x *m*-ArCH), 138.1 (*ipso*-ArC); m/z (ESI+ve): 406 ($[\text{M} + \text{H}]^+$, 93%), 428 ($[\text{M} + \text{Na}]^+$, 91%), 833 ($[\text{2M} + \text{Na}]^+$, 100%); HRMS m/z (ESI+ve): found 428.2215 ($[\text{M} + \text{Na}]^+$); $\text{C}_{22}\text{H}_{35}\text{NNaO}_4\text{Si}$ requires 428.2228.

6-*O*-*tert*-Butyldimethylsilyl-3,5-dideoxy-3,5-imino-1,2-*O*-isopropylidene-*N*-methyl- β -L-idofuranose 2.184

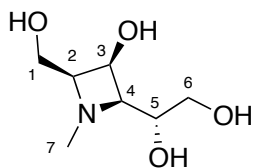


Diisopropylethylamine (131 μ L, 0.75 mmol) and a 33 wt% solution of methylamine in ethanol (41 μ L, 0.33 mmol) were added simultaneously to a stirred solution of ditriflate **2.182** (180 mg, 0.30 mmol) in acetonitrile (4 mL) at 40 $^{\circ}$ C. TLC analysis (3:1 cyclohexane/ethyl acetate) after 15 h showed no starting material (R_f 0.64) and formation of a single major product (R_f 0.42). The mixture was concentrated *in vacuo* to afford a yellow residue, which was purified *via* flash column chromatography on silica gel (5:1 cyclohexane/ethyl acetate) to afford the title compound as a clear, colourless oil (89 mg, 90%); $[\alpha]_D^{25} +47.6$ (c 0.94 in CHCl_3); δ_{H} (CDCl_3 , 400 MHz): 0.05, 0.05 (6H, 2 x s, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 0.87 (9H, s, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 1.34, 1.42 (6H, 2 x s, $\text{C}(\text{CH}_3)_2$), 2.40 (3H, s, H7), 2.93-2.98 (1H, a-dt, H5, $J_{5,4}$ 4.7, $J_{5,6}/J_{5,6'}$ 6.4), 3.50-3.52 (1H, d, H3, $J_{3,4}$ 4.7), 3.52-3.56 (1H, dd, H6, $J_{6,5}$ 6.5, J_{gem} 10.5), 3.73-3.77 (1H, dd, H6', $J_{6',5}$ 6.3, J_{gem} 10.5), 4.52-4.53 (1H, d, H2, $J_{2,1}$ 3.7), 4.87-4.89 (1H, t, H4, $J_{4,3}/J_{4,5}$ 4.7), 6.06-6.07 (1H, d, H1, $J_{1,2}$ 3.7); δ_{C} (CDCl_3 , 100 MHz): -5.2, -5.2 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 18.4 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 26.1 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 27.4, 27.9 ($\text{C}(\text{CH}_3)_2$), 43.3 (C7), 62.2 (C6), 70.3 (C5), 71.4 (C3), 75.9 (C4), 84.0 (C2), 110.1 (C1), 113.5 ($\text{C}(\text{CH}_3)_2$); m/z (ESI+ve): 320 ($[\text{M} + \text{H}]^+$, 91%), 681 ($[2\text{M} + \text{Na}]^+$, 100%); HRMS m/z (ESI+ve): found 352.1904 ($[\text{M} + \text{Na}]^+$); $\text{C}_{16}\text{H}_{31}\text{NNaO}_4\text{Si}$ requires 352.1915.

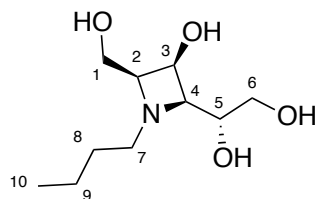
N*-Butyl-6-*O*-*tert*-butyldimethylsilyl-3,5-dideoxy-3,5-imino-1,2-*O*-isopropylidene- β -L-idofuranose **2.185*



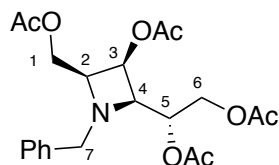
Diisopropylethylamine (131 μ L, 0.75 mmol) and *n*-butylamine (33 μ L, 0.33 mmol) were added simultaneously to a solution of ditriflate **2.182** (180 mg, 0.30 mmol) in acetonitrile (5 mL), and the mixture stirred at 40 $^{\circ}$ C. TLC analysis (3:1 cyclohexane/ethyl acetate) after 16 h indicated consumption of starting material (R_f 0.66) and formation of a single major product (R_f 0.72). The mixture was concentrated *in vacuo* to afford an orange oil, which was purified *via* flash column chromatography on silica gel (8:1 cyclohexane/ethyl acetate) to afford the title compound as a very pale yellow oil (98 mg, 88%); $[\alpha]_D^{25} +67.3$ (c 0.89 in CHCl_3); δ_{H} (CDCl_3 , 400 MHz): 0.04 (6H, s, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 0.87 (9H, s, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 0.87-0.90 (3H, t, H10), 1.25-1.40 (4H, m, H8 and H9), 1.35, 1.43 (6H, 2 x s, $\text{C}(\text{CH}_3)_2$), 2.39-2.45 (1H, dt, H7, $J_{7,8}$ 7.0, J_{gem} 11.6), 2.62-2.66 (1H, dt, H7', $J_{7',8}$ 7.6, J_{gem} 11.6), 2.98-3.02 (1H, m, H5), 3.48-3.52 (1H, dd, H6, $J_{6,5}$ 5.9, J_{gem} 10.5), 3.52-3.53 (1H, d, H3, $J_{3,4}$ 4.4), 3.73-3.77 (1H, dd, H6', $J_{6',5}$ 6.7, J_{gem} 10.5), 4.47-4.48 (1H, d, H2, $J_{2,1}$ 3.6), 4.87-4.90 (1H, a-t, H4, $J_{4,3}/J_{4,5}$ 4.8), 6.05-6.06 (1H, d, H1, $J_{1,2}$ 3.6); δ_{C} (CDCl_3 , 100 MHz): -5.2, -5.2 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 14.1 (C10), 18.5 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 20.6, 30.5 (C8 and C9), 26.1 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 27.4, 28.0 ($\text{C}(\text{CH}_3)_2$), 57.4 (C7), 62.2 (C6), 68.9 (C5), 69.9 (C3), 75.8 (C4), 84.9 (C2), 110.0 (C1), 113.4 ($\text{C}(\text{CH}_3)_2$); m/z (ESI+ve): 372 ($[\text{M} + \text{H}]^+$, 83%); HRMS m/z (ESI+ve): found 372.2556 ($[\text{M} + \text{H}]^+$); $\text{C}_{19}\text{H}_{38}\text{NO}_4\text{Si}$ requires 372.2565.

2,4-Dideoxy-2,4-imino-*N*-methyl-L-iditol 2.187L

The acetone **2.184** (87 mg, 0.264 mmol) was dissolved in 1:1 trifluoroacetic acid/water (4 mL) and stirred at rt. After 72 h the mixture was diluted with water (10 mL) and washed with dichloromethane (3 x 10 mL). The aqueous layer was concentrated *in vacuo* and co-evaporated with water (3 x 20 mL) to afford the crude lactol as a red/brown syrup. This material was re-dissolved in water (3 mL), sodium borohydride (21 mg, 0.535 mmol) added and the mixture stirred at rt. Analysis by mass spectrometry after 18 h showed reaction completion. The mixture was quenched with saturated aqueous ammonium chloride and loaded onto a column of Dowex 50WX8 (H⁺) ion exchange resin. The column was flushed sequentially with water, ethanol and more water, and then eluted with 2M aqueous ammonia. The ammoniacal fraction was concentrated *in vacuo* to afford the title compound as a pale, straw-coloured syrup (22 mg, 47%); $[\alpha]_D^{25} +9.1$ (*c* 0.55 in MeOH); $\nu_{\max}$ (neat): 3297 (s, br, OH); δ_H (D₂O, 400 MHz): 2.48 (3H, s, H7), 3.20-3.24 (1H, dd, H4, $J_{4,3}$ 6.1, $J_{4,5}$ 9.3), 3.33-3.38 (1H, m, H2), 3.46-3.50 (1H, dd, H6, $J_{6,5}$ 6.4, J_{gem} 12.0), 3.62-3.66 (1H, dd, H6', $J_{6',5}$ 3.4, J_{gem} 12.0), 3.67-3.72 (1H, dd, H1, $J_{1,2}$ 5.8, J_{gem} 11.5), 3.84-3.89 (1H, dd, H1', $J_{1',2}$ 7.3, J_{gem} 11.5), 4.00-4.05 (1H, ddd, H5, $J_{5,6'}$ 3.4, $J_{5,6}$ 6.4, $J_{5,4}$ 9.3), 4.53-4.56 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 6.0); δ_C (D₂O, 100 MHz): 44.5 (C7), 59.0 (C1), 63.4 (C6), 65.6 (C3), 70.1 (C2), 70.3 (C4), 71.7 (C5); *m/z* (ESI+ve): 178 ([M + H]⁺, 100%), 200 ([M + Na]⁺, 89%); HRMS *m/z* (ESI+ve): found 200.0894 ([M + Na]⁺); C₇H₁₅NNaO₄ requires 200.0893.

***N*-Butyl-2,4-dideoxy-2,4-imino-L-iditol 2.188L**

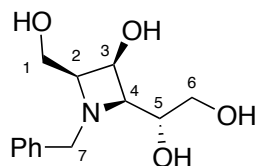
The acetone **2.185** (98 mg, 0.264 mmol) was dissolved in 1:1 trifluoroacetic acid/water (4 mL) and stirred at rt. Analysis by mass spectrometry after 70 h showed reaction completion. The mixture was diluted with water (16 mL) and washed with dichloromethane (4 x 10 mL). The aqueous layer was concentrated *in vacuo* and co-evaporated with water (20 mL) to afford the crude lactol as a pale orange syrup. This was re-dissolved in water (3 mL), sodium borohydride (20 mg, 0.528 mmol) added and the mixture stirred at rt. Analysis by mass spectrometry after 24 h showed reaction completion. The mixture was quenched with saturated aqueous ammonium chloride and loaded onto a column of Dowex 50WX8 (H⁺) ion exchange resin. The column was flushed sequentially with water, ethanol and more water, and then eluted with 2M aqueous ammonia. The ammoniacal fraction was concentrated *in vacuo* to afford the title compound as a clear, pale yellow syrup (51 mg, 88%); $[\alpha]_D^{25}$ -14.6 (*c* 0.48 in MeOH); $\nu_{\max}$ (neat): 3322 (s, br, OH); δ_{H} (CD₃OD, 400 MHz): 0.91-0.93 (3H, t, H₁₀, $J_{10,9}$ 7.3), 1.27-1.38 (2H, m, H₉), 1.40-1.51 (2H, m, H₈), 2.45-2.52 (1H, m, H₇), 2.80-2.87 (1H, m, H_{7'}), 3.16-3.19 (1H, a-t, H₄, $J_{4,5}/J_{4,3}$ 7.1), 3.21-3.26 (1H, m, H₂), 3.46-3.51 (1H, dd, H₆, $J_{6,5}$ 5.8, J_{gem} 11.1), 3.56-3.60 (1H, dd, H_{6'}, $J_{6',5}$ 4.7, J_{gem} 11.1), 3.60-3.63 (1H, dd, H₁, $J_{1,2}$ 4.2, J_{gem} 11.4), 3.88-3.92 (1H, dd, H_{1'}, $J_{1',2}$ 7.3, J_{gem} 11.4), 3.96-4.00 (1H, ddd, H₅, $J_{5,6'}$ 4.7, $J_{5,6}$ 5.8, $J_{5,4}$ 7.6), 4.48-4.51 (1H, a-t, H₃, $J_{3,2}/J_{3,4}$ 6.5); δ_{C} (CD₃OD, 100 MHz): 14.3 (C₁₀), 21.7 (C₉), 31.5 (C₈), 60.3 (C₇), 61.3 (C₁), 64.9 (C₆), 66.0 (C₃), 70.6, 70.7 (C₂ and C₄), 72.1 (C₅); m/z (ESI+ve): 220 ([M + H]⁺, 100%), 242 ([M + Na]⁺, 42%); HRMS m/z (ESI+ve): found 242.1364 ([M + Na]⁺); C₁₀H₂₁NNaO₄ requires 242.1363.

1,3,5,6-tetra-*O*-Acetyl-*N*-benzyl-2,4-dideoxy-2,4-imino-L-iditol 2.189L

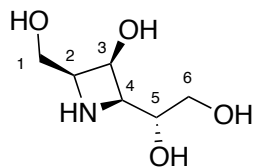
The acetone **2.183** (239 mg, 0.598 mmol) was dissolved in 9:1 trifluoroacetic acid/water (4 mL) and stirred at rt. TLC analysis (3:1 cyclohexane/ethyl acetate) of an aliquot quenched with triethylamine after 3 h indicated consumption of starting material (R_f 0.67) and only baseline material; TLC analysis (ethyl acetate) indicated a single product (R_f 0.24). The mixture was concentrated *in vacuo* and co-evaporated with water (2 x 20 mL) to afford the crude lactol as a clear yellow syrup. This was re-dissolved in water (4 mL), sodium borohydride (45 mg, 1.178 mmol) added and the mixture stirred at rt. TLC analysis (ethyl acetate) after 18 h showed consumption of starting material and formation of a single major product (R_f 0.00). The mixture was quenched with acetic acid and loaded onto a column of Dowex 50WX8 (H^+) ion exchange resin. The column was flushed with water, ethanol, more water and then eluted with 2M aqueous ammonia. The ammoniacal fraction was concentrated *in vacuo* to afford a clear yellow syrup (144 mg). This was re-dissolved in 1:1 pyridine/acetic anhydride (4 mL) and stirred at rt. TLC analysis (2:1 cyclohexane/ethyl acetate) after 23 h showed no starting material (R_f 0.00) and one major product (R_f 0.29). The mixture was concentrated *in vacuo* and co-evaporated with toluene to afford an orange residue. Purification *via* flash column chromatography on silica gel (9:1 to 1:1 cyclohexane/ethyl acetate) afforded the title compound as a clear, colourless syrup (167 mg, 68%); $[\alpha]_D^{25}$ -21.6 (c 0.64 in $CHCl_3$); ν_{max} (thin film): 1743 (s, $OCOCH_3$); δ_H ($CDCl_3$, 500 MHz): 1.87, 1.91, 2.03, 2.14 (12H, 4 x s, 4 x $OCOCH_3$), 3.54-3.58 (1H, m, H2), 3.58-3.61 (1H, dd, H4, $J_{4,3}$ 6.9, $J_{4,5}$ 8.8), 3.62-3.65 (1H, d, H7, J_{gem} 13.6), 3.67-3.70 (1H, dd, H1, $J_{1,2}$ 5.4, J_{gem} 11.4), 3.85-3.88 (1H, d, H7', J_{gem} 13.6), 3.92-3.95 (1H, dd, H6, $J_{6,5}$ 6.2, J_{gem} 12.2), 4.10-4.13 (1H, dd, H1', $J_{1',2}$ 7.4, J_{gem} 11.4), 4.28-4.31 (1H, dd, H6', $J_{6',5}$ 3.0, J_{gem} 12.2), 5.34-5.38 (1H, ddd, H5, $J_{5,6'}$ 3.0, $J_{5,6}$ 6.2, $J_{5,4}$ 8.8), 5.45-5.48 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 6.6), 7.24-7.33 (5H, m, 5 x ArH); δ_C ($CDCl_3$, 125 MHz): 20.8, 20.9,

20.9, 21.0 (4 x OCOCH_3), 61.3 (C7), 62.1 (C1), 63.0 (C6), 63.9 (C4), 64.2 (C2), 65.9 (C3), 71.7 (C5), 127.6 (*p*-ArCH), 128.6, 129.0 (2 x *o*-ArCH and 2 x *m*-ArCH), 137.9 (*ipso*-ArC), 170.4, 170.5, 170.7, 170.7 (4 x OCOCH_3); m/z (ESI+ve): 422 ($[\text{M} + \text{H}]^+$, 38%), 444 ($[\text{M} + \text{Na}]^+$, 100%), 460 ($[\text{M} + \text{K}]^+$, 94%); HRMS m/z (ESI+ve): found 444.1622 ($[\text{M} + \text{Na}]^+$); $\text{C}_{21}\text{H}_{27}\text{NNaO}_8$ requires 444.1629.

***N*-Benzyl-2,4-dideoxy-2,4-imino-L-iditol 2.186L**



Sodium methoxide (4.3 mg, 0.079 mmol) was added to a stirred solution of tetra-acetate **2.189L** (167 mg, 0.396 mmol) in methanol (4 mL) at rt. TLC analysis (2:1 cyclohexane/ethyl acetate) after 21 h showed no starting material (R_f 0.31) and formation of a single product (R_f 0.00). The mixture was loaded onto a column of Dowex 50WX8 (H^+) ion exchange resin, the column flushed with water and then eluted with 2M aqueous ammonia. The ammoniacal fractions were concentrated *in vacuo* to afford the title compound as a clear, colourless syrup (98 mg, 98%); $[\alpha]_D^{25}$ -16.5 (c 0.63 in MeOH); ν_{max} (neat): 3321 (s, br, OH); δ_{H} (CD_3OD , 400 MHz): 3.11-3.14 (1H, dd, H1, $J_{1,2}$ 4.0, J_{gem} 11.1), 3.33-3.37 (2H, m, H2 and H4), 3.44-3.48 (1H, ddd, H6, $J_{6,4}$ 0.8, $J_{6,5}$ 5.8, J_{gem} 11.2), 3.52-3.56 (1H, ddd, H6', $J_{6',4}$ 0.8, $J_{6',5}$ 4.7, J_{gem} 11.2), 3.55-3.59 (1H, ddd, H1', $J_{1',3}$ 0.6, $J_{1',2}$ 7.6, J_{gem} 11.1), 3.60-3.63 (1H, d, H7, J_{gem} 12.5), 4.00-4.05 (1H, m, H5), 4.05-4.08 (1H, d, H7', J_{gem} 12.5), 4.41-4.44 (1H, a-t, H3, $J_{3,4}/J_{3,2}$ 6.4), 7.26-7.39 (5H, m, 5 x ArH); δ_{C} (CD_3OD , 100 MHz): 60.4 (C1), 62.5 (C7), 64.8 (C6), 66.6 (C3), 68.9, 69.5 (C2 and C4), 72.2 (C5), 128.7 (*ipso*-ArC), 129.4, 131.2 (2 x *o*-ArCH and 2 x *m*-ArCH); m/z (ESI+ve): 254 ($[\text{M} + \text{H}]^+$, 100%), 276 ($[\text{M} + \text{Na}]^+$, 97%); HRMS m/z (ESI+ve): found 276.1214 ($[\text{M} + \text{Na}]^+$); $\text{C}_{13}\text{H}_{19}\text{NNaO}_4$ requires 276.1206.

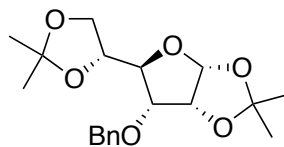
2,4-Dideoxy-2,4-imino-L-itol 2.176L

The L-itol **2.186L** (41 mg, 0.162 mmol), ammonium formate (102 mg, 1.62 mmol) and palladium on activated charcoal (10 wt. %, 34.5 mg, 0.032 mmol) were placed in a flame-dried flask with anhydrous methanol (4 mL), and the suspension heated to reflux under argon atmosphere. TLC analysis (14:3:1:1:1 ethanol/pyridine/*n*-butanol/acetic acid/water) after 30 min showed complete consumption of starting material (R_f 0.71) and formation of a single product (R_f 0.42). The mixture was allowed to cool, filtered through Celite and the pad and flask washed with methanol. The combined filtrates were concentrated *in vacuo* and the resulting clear syrup loaded onto a column of Dowex 50WX8 (H^+) ion exchange resin. The column was flushed with water, ethanol, more water and then eluted with 2M aqueous ammonia. The ammoniacal fraction was concentrated *in vacuo* to afford the title compound as a clear, pale yellow syrup which slowly crystallised to an off-white solid (26.4 mg, quant.); $[\alpha]_D^{25} +17.7$ (c 0.26 in H_2O); ν_{max} (solid): 3264, 3283, 3311, 3492 (s, OH and NH); m.p. 101-102 °C; δ_H (D_2O , 400 MHz): 3.45-3.50 (1H, dd, H6, $J_{6,5}$ 6.3, J_{gem} 11.9), 3.62-3.66 (1H, dd, H6', $J_{6',5}$ 3.5, J_{gem} 11.9), 3.63-3.67 (1H, dd, H1, $J_{1,2}$ 6.3, J_{gem} 11.3), 3.82-3.87 (1H, dd, H1', $J_{1',2}$ 7.0, J_{gem} 11.3), 3.84-3.88 (1H, dd, H4, $J_{4,3}$ 6.3, $J_{4,5}$ 8.6), 3.94-3.99 (1H, ddd, H5, $J_{5,6'}$ 3.5, $J_{5,6}$ 6.3, $J_{5,4}$ 8.7), 3.99-4.04 (1H, a-dt, H2, $J_{2,3}/J_{2,1}$ 6.4, $J_{2,1'}$ 7.0), 4.62-4.65 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 6.4); δ_C (D_2O , 100 MHz): 60.3 (C4), 60.5 (C2), 61.0 (C1), 63.4 (C6), 68.0 (C3), 71.8 (C5); m/z (ESI+ve): 164 ($[M + H]^+$, 65%), 186 ($[M + Na]^+$, 100%); HRMS m/z (ESI+ve): found 186.0734 ($[M + Na]^+$); $C_6H_{13}NNaO_4$ requires 186.0737.

[Data for HCl salt]: $[\alpha]_D^{25} -6.2$ (c 0.50 in MeOH); δ_H (D_2O , 400 MHz): 3.56-3.60 (1H, dd, H6, $J_{6,5}$ 5.2, J_{gem} 12.2), 3.68-3.72 (1H, dd, H6', $J_{6',5}$ 3.5, J_{gem} 12.2), 3.95-4.00 (1H, dd, H1, $J_{1,2}$ 5.3, J_{gem} 12.7), 4.05-4.10 (1H, dd, H1', $J_{1',2}$ 7.2, J_{gem} 12.7), 4.28-4.32 (1H, ddd, H5, $J_{5,6'}$ 3.5, $J_{5,6}$ 5.2, $J_{5,4}$ 8.1),

4.56-4.59 (1H, dd, H4, $J_{4,3}$ 6.7, $J_{4,5}$ 8.1), 4.63-4.67 (1H, m, H2), 4.79-4.82 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 6.5); δ_C (D₂O, 100 MHz): 57.2 (C1), 63.0 (C6), 64.0, 64.0 (C2 and C4), 66.3 (C3), 67.4 (C5).

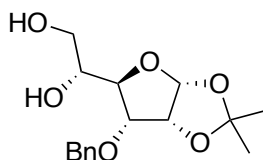
3-*O*-Benzyl-1,2;5,6-di-*O*-isopropylidene- α -D-allofuranose **2.190**



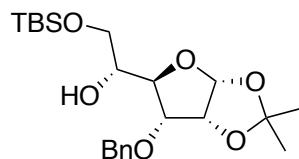
Di-acetone-D-allose **2.163** (1.00 g, 3.84 mmol) and benzyl bromide (1.37 mL, 11.53 mmol) were dissolved in dry *N,N*-dimethylformamide (10 mL) in a flame-dried flask and stirred with freshly-dried powdered 3Å molecular sieves for 20 min under argon. Sodium hydride (60% in mineral oil, 231 mg, 5.76 mmol) was then added in small portions and the mixture stirred at rt. TLC analysis (1:1 cyclohexane/ethyl acetate) after 2 h indicated consumption of starting material (R_f 0.43) and formation of a single major product (R_f 0.63). The mixture was quenched with water, diluted with ethyl acetate (60 mL) and washed with 50% brine (3 x 60 mL). The organic layer was dried (MgSO₄) and concentrated *in vacuo* to afford the crude material as a clear oil. Purification *via* flash column chromatography on silica gel (9:1 to 2:1 cyclohexane/ethyl acetate) afforded the title compound as a white crystalline solid (1.28 g, 95%); $[\alpha]_D^{25} +111.4$ (c 1.00 in CHCl₃) [lit.²³⁸ $[\alpha]_D^{25} +107.0$ (c 1.05 in CHCl₃); m.p. 60-61 °C [lit.²³⁸ m.p. 62-63 °C]; δ_H (CDCl₃, 400 MHz): 1.36, 1.37, 1.39, 1.59 (12H, 4 x s, 2 x C(CH₃)₂), 3.87-3.90 (1H, dd, H3, $J_{3,2}$ 4.5, $J_{3,4}$ 8.7), 3.95-3.98 (1H, dd, H6, $J_{6,5}$ 7.1, J_{gem} 8.2), 3.99-4.03 (1H, dd, H6', $J_{6',5}$ 7.0, J_{gem} 8.2), 4.13-4.16 (1H, dd, H4, $J_{4,5}$ 3.1, $J_{4,3}$ 8.7), 4.35-4.39 (1H, a-dt, H5, $J_{5,4}$ 3.1, $J_{5,6}/J_{5,6'}$ 7.0), 4.57-4.59 (1H, m, H2), 4.58-4.61 (1H, d, CHPh, J_{gem} 11.7), 4.76-4.79 (1H, d, CH'Ph, J_{gem} 11.7), 5.75-5.76 (1H, d, H1, $J_{1,2}$ 3.8), 7.28-7.41 (5H, m, 5 x ArH); δ_C (CDCl₃, 100 MHz): 25.3, 26.3, 26.7, 27.0 (2 x C(CH₃)₂), 65.1 (C6), 72.4 (CH₂Ph), 74.9 (C5), 77.6, 78.0, 78.1 (C2, C3 and C4), 104.0 (C1), 109.8, 113.0 (2 x C(CH₃)₂), 128.2 (*p*-ArCH), 128.4, 128.6 (2 x *o*-ArCH and 2 x *m*-ArCH), 137.6 (*ipso*-ArC); m/z (ESI+ve): 373 ([M + Na]⁺,

100%), 723 ($[2M + Na]^+$, 78%); HRMS m/z (ESI+ve): found 373.1607; $C_{19}H_{26}NaO_6$ requires 373.1622.

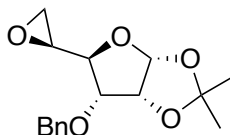
3-*O*-Benzyl-1,2-*O*-isopropylidene- α -D-allofuranose **2.191**



The di-acetonide **2.190** (200 mg, 0.57 mmol) was dissolved in 4:1 acetic acid/water (2 mL) and stirred at rt. TLC analysis (1:1 cyclohexane/ethyl acetate) after 24 h showed consumption of starting material (R_f 0.65) and formation of a single major product (R_f 0.10). The mixture was concentrated *in vacuo* at 30 °C and co-evaporated with water (10 mL) and then toluene (3 x 10 mL) to afford the crude material as a clear, colourless syrup. Purification *via* flash column chromatography on silica gel (1:1 cyclohexane/ethyl acetate to ethyl acetate) afforded the title compound as a clear, colourless syrup (163 mg, 92%); R_f 0.42 (ethyl acetate); $[\alpha]_D^{25} +112.4$ (c 1.39 in $CHCl_3$) [lit.²³⁹ $[\alpha]_D^{28} +108.2$ (c 1.45 in $CHCl_3$)]; ν_{max} (thin film): 3430 (s, br, OH); δ_H ($CDCl_3$, 400 MHz): 1.36, 1.59 (6H, 2 x s, $C(CH_3)_2$), 2.52 (1H, br s, 6-OH), 2.61 (1H, br s, 5-OH), 3.64-3.68 (1H, dd, H6, $J_{6,5}$ 4.6, J_{gem} 12.0), 3.68-3.72 (1H, dd, H6', $J_{6',5}$ 5.6, J_{gem} 12.0), 3.91-3.95 (1H, dd, H3, $J_{3,2}$ 4.4, $J_{3,4}$ 8.9), 3.98-4.02 (1H, m, H5), 4.09-4.12 (1H, dd, H4, $J_{4,5}$ 3.4, $J_{4,3}$ 8.9), 4.54-4.57 (1H, d, $CHPh$, J_{gem} 11.3), 4.60-4.62 (1H, a-t, H2, $J_{2,1}/J_{2,3}$ 4.1), 4.77-4.80 (1H, d, $CH'Ph$, J_{gem} 11.3), 5.76-5.77 (1H, d, H1, $J_{1,2}$ 3.7), 7.30-7.39 (5H, m, 5 x ArH); δ_C ($CDCl_3$, 100 MHz): 26.7, 26.9 ($C(CH_3)_2$), 63.2 (C6), 71.0 (C5), 72.3 (CH_2Ph), 76.9 (C3), 77.4 (C2), 79.2 (C4), 104.3 (C1), 113.4 ($C(CH_3)_2$), 128.5 ($p-ArCH$), 128.4, 128.8 (2 x $o-ArCH$ and 2 x $m-ArCH$), 136.8 ($ipso-ArC$); m/z (ESI+ve): 333 ($[M + Na]^+$, 42%), 349 ($[M + K]^+$, 71%), 643 ($[2M + Na]^+$, 100%); HRMS m/z (ESI+ve): found 333.1304 ($[M + Na]^+$); $C_{16}H_{22}NaO_6$ requires 333.1309.

3-*O*-Benzyl-6-*O*-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene- α -D-allofuranose **2.192**

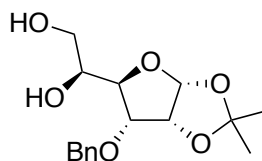
The diol **2.191** (97 mg, 0.31 mmol), 2,6-lutidine (77 μ L, 0.66 mmol) and freshly-dried powdered 3Å molecular sieves were placed in a flame-dried flask with dichloromethane (5 mL), and the resulting suspension stirred under argon at -78 °C for 30 min. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (75 μ L, 0.33 mmol) was then added drop-wise to the stirred solution. TLC analysis (1:1 cyclohexane/ethyl acetate) after 30 min indicated a trace of starting material (R_f 0.08), one major product (R_f 0.67) and a trace second product (R_f 0.87). The mixture was diluted with ethyl acetate (20 mL), washed with 50% brine (2 x 20 mL), dried over magnesium sulfate and concentrated *in vacuo* to afford the crude material as a clear solid. Purification *via* flash column chromatography on silica gel (9:1 to 3:1 cyclohexane/ethyl acetate) afforded the title compound as a white crystalline solid (121 mg, 91%); $[\alpha]_D^{25} +73.0$ (c 0.50 in CHCl_3); ν_{max} (thin film): 3516 (s, s, OH); m.p. 109-110 °C; δ_{H} (CDCl_3 , 400 MHz): 0.06, 0.06 (6H, 2 x s, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 0.89 (9H, s, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 1.35, 1.58 (6H, 2 x s, $\text{C}(\text{CH}_3)_2$), 2.52-2.52 (1H, d, 5-OH, $J_{\text{OH},5}$ 3.2), 3.64-3.68 (1H, dd, H6, $J_{6,5}$ 7.6, J_{gem} 10.4), 3.69-3.72 (1H, dd, H6', $J_{6',5}$ 3.9, J_{gem} 10.4), 3.89-3.93 (1H, m, H5), 3.94-3.97 (1H, dd, H3, $J_{3,2}$ 4.4, $J_{3,4}$ 8.7), 4.04-4.07 (1H, dd, H4, $J_{4,5}$ 4.0, $J_{4,3}$ 8.7), 4.54-4.56 (1H, a-t, H2, $J_{2,1}/J_{2,3}$ 4.1), 4.58-4.61 (1H, d, CHPh , J_{gem} 11.7), 4.75-4.78 (1H, d, $\text{CH}'\text{Ph}$, J_{gem} 11.7), 5.73-5.74 (1H, d, H1, $J_{1,2}$ 3.7), 7.28-7.40 (5H, m, 5 x ArH); δ_{C} (CDCl_3 , 100 MHz): -5.20 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 18.5 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 26.1 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 26.8, 27.0 ($\text{C}(\text{CH}_3)_2$), 64.0 (C6), 72.1, 72.3 (C5 and CH_2Ph), 77.9 (C2 and C3), 78.0 (C4), 104.2 (C1), 113.1 ($\text{C}(\text{CH}_3)_2$), 128.1 ($p\text{-ArCH}$), 128.2, 128.6 (2 x $o\text{-ArCH}$ and 2 x $m\text{-ArCH}$), 137.7 ($ipso\text{-ArC}$); m/z (ESI-ve): 423 ($[\text{M} - \text{H}]^-$, 29%), 459 ($[\text{M} + \text{Cl}]^-$, 100%); HRMS m/z (ESI+ve): found 447.2166 ($[\text{M} + \text{Na}]^+$); $\text{C}_{22}\text{H}_{36}\text{NaO}_6\text{Si}$ requires 447.2173.

5,6-Anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene- β -L-talofuranose **2.198**

Pivaloyl chloride (172 μ L, 1.390 mmol) was added to a stirred solution of diol **2.191** (196 mg, 0.63 mmol), pyridine (154 μ L, 1.90 mmol) and 4-dimethylaminopyridine (12 mg, 0.01 mmol) in dichloromethane (5 mL) at 0 °C under nitrogen atmosphere, and the mixture slowly allowed to reach rt. TLC analysis (ethyl acetate) after 20 h showed consumption of starting material (R_f 0.40) and formation of a single major product (R_f 0.73). The mixture was diluted with ethyl acetate (15 mL), washed with 2M hydrochloric acid (2 x 20 mL), saturated aqueous sodium bicarbonate (20 mL), brine (20 mL), dried over magnesium sulfate and concentrated *in vacuo* to afford the crude 6-*O*-pivolate ester as a clear, colourless syrup. This material was re-dissolved in a solution of triethylamine (0.22 mL, 1.58 mmol) and 4-dimethylaminopyridine (12 mg, 0.01 mmol) in dichloromethane (5 mL), methanesulfonyl chloride (98 μ L, 1.26 mmol) added and the mixture stirred at rt under nitrogen atmosphere. Analysis by mass spectrometry after 18 h showed reaction completion. The mixture was diluted with dichloromethane (15 mL) and poured into saturated aqueous ammonium chloride (20 mL). The layers were separated, the aqueous layer washed with dichloromethane (20 mL) and the combined organic layers washed with brine (10 mL), dried over magnesium sulfate and concentrated *in vacuo* to afford a clear orange oil. Purification *via* flash column chromatography on silica gel (9:1 to 1:1 cyclohexane/ethyl acetate) afforded the mesylate as a clear, colourless syrup (269 mg, 0.57 mmol). This was re-dissolved in methanol (10 mL), potassium carbonate (157 mg, 1.14 mmol) added and the mixture stirred at rt. Analysis by mass spectrometry after 18 h showed reaction completion. The mixture was concentrated to approximately 2 mL at rt, diluted with ethyl acetate (20 mL) and washed with 50% brine (20 mL). The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to afford the crude material as a clear, colourless syrup. Purification *via* flash column chromatography on silica gel (3:1 cyclohexane/ethyl acetate) afforded the title compound as a clear, colourless syrup (128 mg,

69%); $[\alpha]_D^{25} +103.9$ (*c* 0.67 in CHCl_3) [lit.²⁴⁰ $[\alpha]_D^{20} +96.4$ (*c* 0.80 in CHCl_3)]; δ_{H} (CDCl_3 , 400 MHz): 1.35, 1.58 (6H, 2 x s, $\text{C}(\text{CH}_3)_2$), 2.77-2.80 (1H, dd, H6, $J_{6,5}$ 4.3, J_{gem} 5.4), 2.86-2.88 (1H, dd, H6', $J_{6',5}$ 2.7, J_{gem} 5.4), 3.07-3.09 (1H, a-dt, H5, $J_{5,6'}$ 2.7, $J_{5,4}/J_{5,6}$ 4.1), 3.77-3.80 (1H, dd, H3, $J_{3,2}$ 4.2, $J_{3,4}$ 9.0), 4.01-4.05 (1H, dd, H4, $J_{4,5}$ 4.0, $J_{4,3}$ 9.0), 4.55-4.57 (1H, a-t, H2, $J_{2,1}/J_{2,3}$ 3.9), 4.61-4.64 (1H, d, CHPh , J_{gem} 12.0), 4.77-4.80 (1H, d, CH'Ph , J_{gem} 12.0), 5.69-5.70 (1H, d, H1, $J_{1,2}$ 3.6), 7.29-7.40 (5H, m, 5 x ArH); δ_{C} (CDCl_3 , 100 MHz): 26.6, 27.0 ($\text{C}(\text{CH}_3)_2$), 44.4 (C6), 51.2 (C5), 72.6 (CH_2Ph), 77.3, 77.5 (C2 and C4), 79.2 (C3), 104.3 (C1), 113.4 ($\text{C}(\text{CH}_3)_2$), 128.3 (*p*-ArCH), 128.1, 128.7 (2 x *o*-ArCH and 2 x *m*-ArCH), 137.5 (*ipso*-ArC); *m/z* (ESI+ve): 315 ($[\text{M} + \text{Na}]^+$, 100%), 607 ($[\text{2M} + \text{Na}]^+$, 91%); HRMS *m/z* (ESI+ve): found 315.1193 ($[\text{M} + \text{Na}]^+$); $\text{C}_{16}\text{H}_{20}\text{NaO}_5$ requires 315.1203.

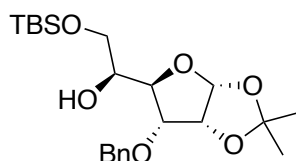
3-*O*-Benzyl-1,2-*O*-isopropylidene- β -L-talofuranose **2.199**



Powdered potassium hydroxide (131 mg, 2.33 mmol) was added to a stirred solution of epoxide **2.198** (68 mg, 0.23 mmol) in 1:1 acetonitrile/water (5 mL), and the mixture heated to 65 °C. TLC analysis (1:1 cyclohexane/ethyl acetate) after 17 h showed consumption of starting material (R_f 0.63) and formation of a single major product (R_f 0.10). The mixture was allowed to cool, diluted with ethyl acetate (20 mL), washed with 50% brine (20 mL), dried over magnesium sulfate and concentrated *in vacuo* to afford a clear, colourless syrup. Purification *via* flash column chromatography on silica gel (1:1 ethyl acetate/cyclohexane to ethyl acetate) afforded the title compound as a clear, colourless syrup (44 mg, 61%); $[\alpha]_D^{25} +42.6$ (*c* 0.23 in CHCl_3); ν_{max} (thin film): 3424 (s, br, OH); δ_{H} (CDCl_3 , 400 MHz): 1.35, 1.58 (6H, 2 x s, $\text{C}(\text{CH}_3)_2$), 2.40 (2H, br s, 5-OH and 6-OH), 3.68-3.79 (3H, m, H5, H6 and H6'), 3.91-3.94 (1H, dd, H3, $J_{3,2}$ 4.3, $J_{3,4}$ 9.0), 4.05-4.08 (1H, dd, H4, $J_{4,5}$ 2.3, $J_{4,3}$ 9.0), 4.55-4.57 (1H, a-t, H2, $J_{2,1}/J_{2,3}$ 4.0), 4.58-4.61 (1H, d, CHPh ,

J_{gem} 11.7), 4.75-4.78 (1H, d, $\text{CH}'\text{Ph}$, J_{gem} 11.7), 5.73-5.74 (1H, d, H1, $J_{1,2}$ 3.6), 7.29-7.40 (5H, m, 5 x ArH); δ_{C} (CDCl_3 , 100 MHz): 26.6, 26.9 ($\text{C}(\text{CH}_3)_2$), 65.1 (C6), 69.8 (C5), 72.5 (CH_2Ph), 77.3 (C2), 77.7 (C3), 80.0 (C4), 104.6 (C1), 113.4 ($\text{C}(\text{CH}_3)_2$), 128.3 ($p\text{-ArCH}$), 128.2, 128.7 (2 x $o\text{-ArCH}$ and 2 x $m\text{-ArCH}$), 137.4 ($ipso\text{-ArC}$); m/z (ESI+ve): 333 ($[\text{M} + \text{Na}]^+$, 29%), 643 ($[2\text{M} + \text{Na}]^+$, 100%); HRMS m/z (ESI+ve): found 333.1303 ($[\text{M} + \text{Na}]^+$); $\text{C}_{16}\text{H}_{22}\text{NaO}_6$ requires 333.1309.

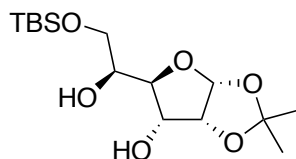
3-*O*-Benzyl-6-*O*-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene- β -L-talofuranose **2.200**



The diol **2.199** (183 mg, 0.590 mmol), 2,6-lutidine (144 μL , 1.239 mmol) and freshly-dried powdered 3Å molecular sieves were placed in a flask with dichloromethane (10 mL), cooled to -78°C and stirred for 30 min. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (142 μL , 0.62 mmol) was then added dropwise to the stirred solution. TLC analysis (1:1 cyclohexane/ethyl acetate) after 1 h indicated a trace of starting material (R_f 0.05), one major product (R_f 0.69) and a trace second product (R_f 0.86). The mixture was diluted with ethyl acetate (30 mL), washed with 50% brine (3 x 40 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude material as a syrup. Purification *via* flash column chromatography on silica gel (5:1 to 3:1 cyclohexane/ethyl acetate) afforded the title compound as a clear, colourless syrup (230 mg, 92%); $[\alpha]_D^{25} +62.8$ (c 0.95 in CHCl_3); ν_{max} (thin film): 3489 (br, OH); δ_{H} (CDCl_3 , 400 MHz): 0.07 (6H, s, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 0.89 (9H, s, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 1.35, 1.58 (6H, 2 x s, $\text{C}(\text{CH}_3)_2$), 2.24-2.25 (1H, d, 5-OH, $J_{\text{OH},5}$ 5.6), 3.63-3.67 (1H, dd, H6, $J_{6,5}$ 5.1, J_{gem} 9.9), 3.69-3.74 (1H, dd, H6', $J_{6',5}$ 7.8, J_{gem} 9.9), 3.76-3.81 (1H, m, H5), 3.96-4.00 (1H, dd, H3, $J_{3,2}$ 4.3, $J_{3,4}$ 9.0), 4.05-4.08 (1H, dd, H4, $J_{4,5}$ 1.7, $J_{4,3}$ 9.0), 4.53-4.55 (1H, a-t, H2, $J_{2,1}/J_{2,3}$ 4.0), 4.60-4.63 (1H, d, CHPh , J_{gem} 11.9), 4.75-4.78 (1H, d, $\text{CH}'\text{Ph}$, J_{gem} 11.9), 5.73-5.74 (1H, d, H1, $J_{1,2}$ 3.7), 7.28-7.40 (5H, m, 5 x ArH); δ_{C} (CDCl_3 , 100 MHz): -5.26 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 18.4 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 26.0 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 26.6,

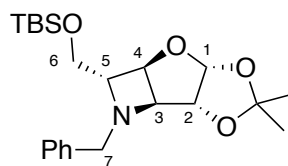
26.9 (C(CH₃)₂), 64.9 (C6), 69.8 (C5), 72.6 (CH₂Ph), 77.5, 77.5, 77.6 (C2, C3 and C4), 104.5 (C1), 113.1 (C(CH₃)₂), 128.1 (*p*-ArCH), 128.2, 128.6 (2 x *o*-ArCH and 2 x *m*-ArCH), 137.8 (*ipso*-ArC); *m/z* (ESI+ve): 447 ([M + Na]⁺, 86%), 871 ([2M + Na]⁺, 100%), 887 ([2M + K]⁺, 73%); HRMS *m/z* (ESI+ve): found 447.2167 ([M + Na]⁺); C₂₂H₃₆NaO₆Si requires 447.2173.

6-*O*-*tert*-Butyldimethylsilyl-1,2-*O*-isopropylidene-β-L-talofuranose **2.201**



The benzyl ether **2.200** (228 mg, 0.537 mmol) and palladium on activated charcoal (10 wt. %, 57 mg, 0.054 mmol) were placed in a flask with 1,4-dioxane (10 mL), the mixture degassed and purged with argon, then degassed and charged with hydrogen and the contents stirred at rt. TLC analysis (1:1 cyclohexane/ethyl acetate) after 21 h showed consumption of starting material (*R_f* 0.69) and formation of a single product (*R_f* 0.26). The mixture was degassed and filtered through Celite, washing the pad and flask with ethyl acetate. The combined filtrates were concentrated *in vacuo* to afford the title compound as a clear, colourless syrup which slowly crystallised to a white solid (180 mg, 100%); $[\alpha]_D^{25} +32.2$ (*c* 0.97 in CHCl₃); *v*_{max} (thin film): 3437 (s, OH); m.p. 70-72 °C; δ_H (CD₃CN, 400 MHz): 0.08 (6H, s, OSi(CH₃)₂C(CH₃)₃), 0.90 (9H, s, OSi(CH₃)₂C(CH₃)₃), 1.31, 1.48 (6H, 2 x s, C(CH₃)₂), 2.77-2.79 (1H, d, 5-OH, *J*_{OH,5} 6.5), 3.03-3.05 (1H, d, 3-OH, *J*_{OH,3} 9.4), 3.57-3.64 (3H, m, H5, H6 and H6'), 3.81-3.83 (1H, dd, H4, *J*_{4,5} 1.8, *J*_{4,3} 9.1), 3.92-3.98 (1H, a-dt, H3, *J*_{3,2} 4.8, *J*_{3,4}/*J*_{3,OH} 9.2), 4.50-4.52 (1H, dd, H2, *J*_{2,1} 3.7, *J*_{2,3} 4.8), 5.69-5.70 (1H, d, H1, *J*_{1,2} 3.7); δ_C (CD₃CN, 100 MHz): -5.2, -5.1 (OSi(CH₃)₂C(CH₃)₃), 18.9 (OSi(CH₃)₂C(CH₃)₃), 26.2 (OSi(CH₃)₂C(CH₃)₃), 26.8, 26.9 (C(CH₃)₂), 65.2 (C6), 70.4 (C5), 71.9 (C3), 79.8 (C4), 80.2 (C2), 105.1 (C1), 113.1 (C(CH₃)₂); *m/z* (ESI+ve): 357 ([M + Na]⁺, 82%), 691 ([2M + Na]⁺, 100%); HRMS *m/z* (ESI+ve): found 357.1707 ([M + Na]⁺); C₁₅H₃₀NaO₆Si requires 357.1704.

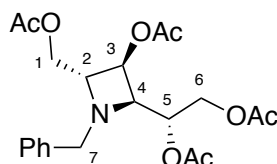
N*-Benzyl-6-*O*-*tert*-butyldimethylsilyl-3,5-dideoxy-3,5-imino-1,2-*O*-isopropylidene- α -D-glucofuranose **2.203*



Trifluoromethanesulfonic anhydride (0.27 mL, 1.605 mmol) was added slowly to a stirred solution of diol **2.201** (179 mg, 0.535 mmol) and pyridine (0.26 mL, 3.210 mmol) in dichloromethane (10 mL) at -30 °C under nitrogen atmosphere, and the resulting mixture maintained between -30 and -20 °C. TLC analysis (1:1 cyclohexane/ethyl acetate) after 1 h showed consumption of starting material (R_f 0.26) and formation of a single product (R_f 0.86). The mixture was diluted with dichloromethane (20 mL), washed with 2M hydrochloric acid (3 x 30 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* at 25 °C to afford the crude ditriflate **2.202** as a clear, yellow syrup. This was re-dissolved in acetonitrile (6 mL), benzylamine (63 μ L, 0.578 mmol) and diisopropylethylamine (233 μ L, 1.338 mmol) added and the mixture stirred at 50 °C. TLC analysis (3:1 cyclohexane/ethyl acetate) after 19 h showed consumption of starting material (R_f 0.64) and formation of a single major product (R_f 0.52). The mixture was allowed to cool and concentrated *in vacuo* to afford the crude material as an orange oil. Purification *via* flash column chromatography on silica gel (95:5 cyclohexane/ethyl acetate) afforded the title compound as a clear, pale yellow oil (140 mg, 65%); $[\alpha]_D^{25} +10.0$ (c 0.71 in CHCl_3); δ_H (CDCl_3 , 400 MHz): 0.07, 0.10 (6H, 2 x s, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 0.94 (9H, s, $\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 1.31, 1.42 (6H, 2 x s, $\text{C}(\text{CH}_3)_2$), 3.39-3.41 (1H, a-t, H5, $J_{5,6}/J_{5,6'}$ 2.8), 3.70-3.73 (1H, dd, H6, $J_{6,5}$ 3.0, J_{gem} 11.4), 3.78-3.81 (1H, dd, H6', $J_{6,5}$ 2.9, J_{gem} 11.4), 3.80-3.84 (1H, d, H7, J_{gem} 13.4), 3.95-3.98 (1H, d, H7', J_{gem} 13.4), 4.07-4.08 (1H, d, H3, $J_{3,4}$ 4.9), 4.27-4.28 (1H, d, H2, $J_{2,1}$ 3.7), 4.80-4.82 (1H, d, H4, $J_{4,3}$ 4.9), 6.13-6.14 (1H, d, H1, $J_{1,2}$ 3.7), 7.21-7.33 (5H, m, 5 x ArH); δ_C (CDCl_3 , 100 MHz): -5.5, -5.4 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 18.2 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 26.0 ($\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$), 27.5, 28.0 ($\text{C}(\text{CH}_3)_2$), 53.8 (C7), 61.7 (C6), 68.5 (C5), 71.3 (C2), 78.4 (C4), 84.0 (C2), 109.6 (C1), 113.0 ($\text{C}(\text{CH}_3)_2$), 127.2 (*p*-ArCH), 128.4, 128.5

(2 x *o*-ArCH and 2 x *m*-ArCH), 139.3 (*ipso*-ArC); *m/z* (ESI+ve): 406 ($[M + H]^+$, 91%), 428 ($[M + Na]^+$, 97%), 833 ($[2M + Na]^+$, 100%); HRMS *m/z* (ESI+ve): found 428.2230 ($[M + Na]^+$); $C_{22}H_{35}NNaO_4Si$ requires 428.2228.

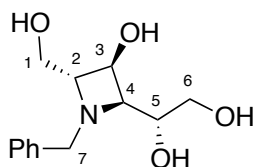
1,3,5,6-tetra-*O*-Acetyl-*N*-benzyl-2,4-dideoxy-2,4-imino-L-gulitol 2.204L



The acetonide **2.203** (138 mg, 0.340 mmol) was dissolved in 9:1 trifluoroacetic acid/water and stirred at rt. TLC analysis (3:1 cyclohexane/ethyl acetate) after 24 h showed consumption of starting material (R_f 0.52) and formation of a single product (R_f 0.00). The mixture was concentrated *in vacuo* and co-evaporated with water (2 x 10 mL) to afford the crude lactol as an orange/brown residue. This was re-dissolved in water (2 mL), sodium borohydride (25.7 mg, 0.680 mmol) added and the mixture stirred at rt. TLC analysis (ethyl acetate) after 66 h showed no starting material (R_f 0.17) and formation of a single product (R_f 0.00). The mixture was quenched with acetic acid and loaded onto a column of Dowex 50WX8 (H^+) ion exchange resin. The column was flushed with water, ethanol, more water and then eluted with 2M aqueous ammonia. The ammoniacal fraction was concentrated *in vacuo* to afford the tetrol (contaminated with trace impurities) as a clear, straw-coloured syrup (82 mg). This material was re-dissolved in 1:1 pyridine/acetic anhydride (4 mL) and stirred at rt. TLC analysis (2:1 cyclohexane/ethyl acetate) after 2.5 h showed consumption of starting material (R_f 0.00) and formation of a single major product (R_f 0.38). The mixture was concentrated *in vacuo* and co-evaporated with toluene to afford an orange residue. Purification *via* flash column chromatography on silica gel (9:1 to 2:1 cyclohexane/ethyl acetate) afforded the title compound as a clear, colourless syrup (91 mg, 67%); $[\alpha]_D^{25}$ -51.4 (c 0.76 in $CHCl_3$); ν_{max} (thin film): 1737 (s, $OCOCH_3$); δ_H ($CDCl_3$, 400 MHz): 1.89, 2.03, 2.04, 2.14 (12H, 4 x s, 4 x $OCOCH_3$), 3.77-3.80 (1H, m, H2), 3.81-3.84 (1H, d, H7, J_{gem} 14.6), 3.91-3.94 (1H, d, H7', J_{gem} 14.6), 3.96-3.99 (1H,

m, H4), 4.00-4.05 (1H, dd, H6, $J_{6,5}$ 6.5, J_{gem} 12.1), 4.14-4.18 (1H, dd, H1, $J_{1,2}$ 4.3, J_{gem} 12.4), 4.22-4.26 (1H, dd, H1', $J_{1',2}$ 3.5, J_{gem} 12.4), 4.27-4.30 (1H, dd, H6', $J_{6',5}$ 3.0, J_{gem} 12.1), 5.16-5.19 (1H, dd, H3, $J_{3,2}$ 3.2, $J_{3,4}$ 7.0), 5.45-5.50 (1H, ddd, H5, $J_{5,6'}$ 3.0, $J_{5,6}$ 6.5, $J_{5,4}$ 8.0), 7.18-7.29 (5H, m, 5 x ArH); δ_{C} (CDCl₃, 100 MHz): 20.8, 21.0, 21.1, 21.1 (4 x OCOCH₃), 54.3 (C7), 62.3 (C1), 63.4 (C6), 64.1 (C4), 65.8 (C2), 68.0 (C3), 71.7 (C5), 127.2 (*p*-ArCH), 127.6, 128.6 (2 x *o*-ArCH and 2 x *m*-ArCH), 139.0 (*ipso*-ArC), 170.3, 170.5, 170.6, 170.7 (4 x OCOCH₃); m/z (ESI+ve): 422 ([M + H]⁺, 40%), 444 ([M + Na]⁺, 100%), 865 ([2M + Na]⁺, 82%); HRMS m/z (ESI+ve): found 444.1630 ([M + Na]⁺); C₂₁H₂₇NNaO₈ requires 444.1629.

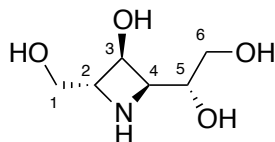
***N*-Benzyl-2,4-dideoxy-2,4-imino-L-gulitol 2.205L**



Sodium methoxide (2.4 mg, 0.044 mmol) was added to a stirred solution of tetra-acetate **2.204L** (91 mg, 0.216 mmol) in methanol (3 mL) at rt. TLC analysis (2:1 cyclohexane/ethyl acetate) after 14 h showed no starting material (R_f 0.38) and formation of a single product (R_f 0.00). The mixture was concentrated *in vacuo* and the resulting residue loaded onto a column of Dowex 50WX8 (H⁺) ion exchange resin, the column flushed with water and then eluted with 2M aqueous ammonia. The ammoniacal fraction was concentrated *in vacuo* to afford the title compound as a clear, colourless syrup (55 mg, 100%); $[\alpha]_D^{25}$ -34.6 (*c* 0.27 in MeOH); ν_{max} (neat): 3312 (br, OH); δ_{H} (CD₃OD, 500 MHz): 3.43-3.46 (1H, dd, H6, $J_{6,5}$ 6.3, J_{gem} 11.1), 3.52-3.59 (4H, m, H6', H1, H1' and H2), 3.70-3.73 (1H, a-t, H4, $J_{4,3}/J_{4,5}$ 6.7), 3.94-3.97 (1H, d, H7, J_{gem} 13.9), 4.07-4.11 (1H, a-dt, H5, $J_{5,6'}$ 4.9, $J_{5,4}/J_{5,6}$ 6.5), 4.16-4.19 (1H, d, H7', J_{gem} 13.9), 4.37-4.39 (1H, dd, H3, $J_{3,2}$ 2.8, $J_{3,4}$ 6.7), 7.20-7.39 (5H, m, 5 x ArH); δ_{C} (CD₃OD, 125 MHz): 56.0 (C7), 61.1 (C1), 65.3 (C6), 67.7 (C3), 69.6 (C4), 72.0 (C5), 72.4 (C2), 128.0 (*p*-ArCH), 129.4, 129.4 (2 x *o*-ArCH and 2 x *m*-ArCH), 140.6 (*ipso*-

ArC); m/z (ESI+ve): 254 ($[M + H]^+$, 100%); HRMS m/z (ESI+ve): found 254.1389 ($[M + H]^+$); $C_{13}H_{20}NO_4$ requires 254.1387.

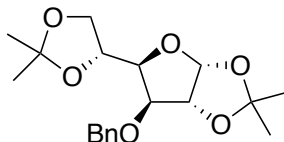
2,4-Dideoxy-2,4-imino-L-gulitol **2.179L**



The L-gulitol **2.205L** (46.5 mg, 0.184 mmol), palladium on activated charcoal (10 wt. %, 31.9 mg, 0.033 mmol) and ammonium formate (104 mg, 1.65 mmol) were suspended in anhydrous methanol (4 mL) under argon, and the mixture heated to reflux. TLC analysis (14:3:1:1:1 ethanol/pyridine/*n*-butanol/acetic acid/water) after 10 min showed consumption of starting material (R_f 0.72) and formation of a single product (R_f 0.56). The mixture was allowed to cool, filtered through Celite and the pad and flask washed with methanol. The combined filtrates were concentrated *in vacuo* to afford the crude material as a clear syrup. This was loaded onto a column of Dowex 50WX8 (H^+) ion exchange resin, the column flushed with water, ethanol, more water and then eluted with 2M aqueous ammonia. The ammoniacal fraction was concentrated *in vacuo* to afford the title compound as a clear, colourless syrup (29.8 mg, 99%) [**characterised as the HCl salt**]; $[\alpha]_D^{25} +6.5$ (c 1.01 in H_2O); ν_{max} (neat): 3303 (br, OH and NH); δ_H (D_2O , 500 MHz): 3.61-3.64 (1H, dd, H6, $J_{6,5}$ 5.3, J_{gem} 12.1), 3.72-3.76 (1H, dd, H6', $J_{6',5}$ 3.7, J_{gem} 12.1), 3.90-3.93 (1H, dd, H1, $J_{1,2}$ 3.9, J_{gem} 13.2), 3.93-3.97 (1H, dd, H1', $J_{1',2}$ 4.9, J_{gem} 13.2), 4.28-4.31 (1H, ddd, H5, $J_{5,6}$ 3.7, $J_{5,6}$ 5.3, $J_{5,4}$ 6.0), 4.42-4.45 (2H, m, H2 and H4), 4.71-4.74 (1H, dd, H3, J 5.9, J 7.6); δ_C (D_2O , 125 MHz): 58.7 (C1), 63.5 (C6), 64.0 (C4), 64.7 (C3), 66.9 (C5), 69.5 (C2); m/z (ESI+ve): 164 ($[M + H]^+$, 100%); HRMS m/z (ESI+ve): found 186.0729 ($[M + Na]^+$); $C_6H_{13}NNaO_4$ requires 186.0737.

2.4.4 *Talo* azetidine tetrol from glucose

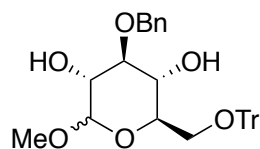
3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose **2.206**



Sodium hydride (60% in mineral oil, 4.61 g, 115.26 mmol) was added in small portions to a stirred solution of di-acetone-D-glucose **2.161** (20.00 g, 76.84 mmol) in anhydrous *N,N*-dimethylformamide (100 mL) at 0 °C under argon atmosphere, and the mixture then stirred at rt for 30 min. The mixture was then cooled to 0 °C, benzyl bromide (15.80 mL, 132.84 mmol) added drop-wise over a period of 10 min, and the resulting contents stirred at rt. TLC analysis (1:1 cyclohexane/ethyl acetate) after 17 h showed no starting material (R_f 0.46) and formation of a single major product (R_f 0.68). Excess sodium hydride was quenched by addition of methanol, the mixture concentrated *in vacuo*, and the resulting slurry diluted with ethyl acetate (150 mL) and washed with 50% brine (3 x 150 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford a clear yellow oil. Purification *via* flash column chromatography on silica gel (98:2 to 67:33 cyclohexane/ethyl acetate) afforded the title compound as a clear, pale yellow oil (25.37 g, 94%); $[\alpha]_D^{25}$ -25.4 (c 0.74 in CHCl_3); δ_{H} (CDCl_3 , 400 MHz): 1.31, 1.38, 1.43, 1.49 (12H, 4 x s, 2 x $\text{C}(\text{CH}_3)_2$), 3.99-4.02 (1H, dd, H6, $J_{6,5}$ 5.8, J_{gem} 8.6), 4.02-4.03 (1H, d, H3, $J_{3,4}$ 3.1), 4.10-4.13 (1H, dd, H6', $J_{6',5}$ 6.2, J_{gem} 8.6), 4.14-4.16 (1H, dd, H4, $J_{4,3}$ 3.1, $J_{4,5}$ 7.8), 4.35-4.40 (1H, a-dt, H5, $J_{5,6}/J_{5,6'}$ 6.0, $J_{5,4}$ 7.8), 4.58-4.59 (1H, d, H2, $J_{2,1}$ 3.7), 4.62-4.65 (1H, d, CHPh , J_{gem} 11.8), 4.67-4.70 (1H, d, $\text{CH}'\text{Ph}$, J_{gem} 11.8), 5.89-5.90 (1H, d, H1, $J_{1,2}$ 3.7), 7.27-7.37 (5H, m, 5 x ArH); δ_{C} (CDCl_3 , 100 MHz): 25.6, 26.4, 26.9, 27.0 (2 x $\text{C}(\text{CH}_3)_2$), 67.6 (C6), 72.5, 72.7 (CH_2Ph and C5), 81.5 (C4), 81.8 (C3), 82.8 (C2), 105.4 (C1), 109.1, 111.9 (2 x $\text{C}(\text{CH}_3)_2$), 128.0 (*p*- ArCH), 127.8, 128.6 (2 x *o*- ArCH and 2 x *m*- ArCH), 137.8 (*ipso*- ArC); m/z (ESI+ve): 373 ($[\text{M} +$

$\text{Na}]^+$, 28%), 389 ($[\text{M} + \text{K}]^+$, 100%); HRMS m/z (ESI+ve): found 373.1617 ($[\text{M} + \text{Na}]^+$); $\text{C}_{19}\text{H}_{26}\text{NaO}_6$ requires 373.1622.

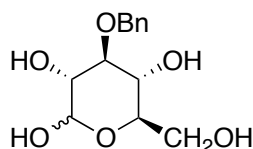
Methyl 3-*O*-benzyl-6-*O*-trityl-D-glucopyranoside **2.208**



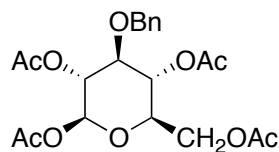
Di-acetonide **2.206** (1.69 g, 4.82 mmol) was dissolved in pre-mixed 95:5 v/v methanol/acetyl chloride (10 mL) and heated to reflux with a drying tube of calcium chloride. After 18 h TLC analysis (1:1 cyclohexane/ethyl acetate) showed consumption of starting material (R_f 0.78) and formation of a single product (R_f 0.05). The mixture was allowed to cool, quenched with solid sodium bicarbonate and filtered through Celite, washing the pad and flask with methanol. The filtrates were concentrated *in vacuo* to afford a pale yellow residue. This material was triturated with ethyl acetate and the resulting insoluble material filtered off. The filtrate was then concentrated *in vacuo* to afford the crude mixture of pyranosides **2.207** (920 mg), which was re-dissolved in anhydrous pyridine (5 mL), trityl chloride (994 mg, 3.56 mmol) added and the mixture stirred at 100 °C under nitrogen. TLC analysis (ethyl acetate) after 4 h showed some remaining starting material (R_f 0.27) and formation of a single product (R_f 0.72). Another portion of trityl chloride (994 mg, 3.56 mmol) was added. TLC analysis after a further 1.5 h showed only a trace of starting material remaining. The mixture was allowed to cool, diluted with ethyl acetate (50 mL), washed with saturated aqueous ammonium chloride (2 x 50 mL), saturated sodium bicarbonate (50 mL) and finally brine (50 mL). The organic layer was dried (MgSO_4) and concentrated *in vacuo* to afford a clear orange syrup. Purification *via* flash column chromatography on silica gel (5:1 to 3:1 cyclohexane/ethyl acetate) afforded the title compound, a white amorphous solid, as a 3.3:1 ratio of α/β anomers (1.168 g, 46%); ν_{max} (solid): 3459 (br, OH); δ_{H} (C_6D_6 , 400 MHz): 1.87-1.89 (1H, d, 2-OH $_{\alpha}$, $J_{\text{OH}_{\alpha},2\alpha}$ 9.4), 2.20-2.23 (3H, m, 4-OH $_{\alpha}$, 2-OH $_{\beta}$, 4-OH $_{\beta}$), 3.07 (3H, s, OCH $_3$ α), 3.32 (3H, s, OCH $_3$ β), 3.32-3.36 (1H, m, H5 $_{\beta}$), 3.35-3.38 (1H, a-t, H3 $_{\beta}$, $J_{3\beta,2\beta}/J_{3\beta,4\beta}$ 8.8), 3.46-3.49 (1H, dd, H6 $_{\beta}$,

$J_{6\beta,5\beta}$ 5.1, J_{gem} 9.9), 3.47-3.51 (1H, dd, $H_{6\alpha}$, $J_{6\alpha,5\alpha}$ 5.6, J_{gem} 9.9), 3.52-3.55 (1H, dd, $H_{6\beta}'$, $J_{6\beta',5}$ 3.1, J_{gem} 9.9), 3.56-3.60 (2H, m, $H_{3\alpha}$, $H_{4\alpha}$), 3.56-3.59 (1H, dd, $H_{6\alpha}'$, $J_{6\alpha',5\alpha}$ 3.0, J_{gem} 9.8), 3.62-3.70 (3H, m, $H_{2\alpha}$, $H_{2\beta}$, $H_{4\beta}$), 3.82-3.86 (1H, ddd, $H_{5\alpha}$, $J_{5\alpha,6\alpha'}$ 3.0, $J_{5\alpha,6\alpha}$ 5.7, $J_{5\alpha,4\alpha}$ 9.5), 4.00-4.01 (1H, d, $H_{1\beta}$, $J_{1\beta,2\beta}$ 7.7), 4.56-4.57 (1H, d, $H_{1\alpha}$, $J_{1\alpha,2\alpha}$ 3.7), 4.68-4.71 (1H, d, $\text{CHPh } \alpha$, J_{gem} 11.7), 4.76-4.79 (1H, d, $\text{CHPh } \beta$, J_{gem} 11.8), 4.95-4.98 (1H, d, $\text{CH'Ph } \alpha$, J_{gem} 11.7), 5.00-5.03 (1H, d, $\text{CH'Ph } \beta$, J_{gem} 11.8), 7.00-7.18, 7.31-7.33, 7.60-7.64 (40H, 3 x m, 20 x $\text{ArH } \beta$ and 20 x $\text{ArH } \alpha$); δ_{C} (C_6D_6 , 100 MHz): 54.8 ($\text{OCH}_3 \alpha$), 56.4 ($\text{OCH}_3 \beta$), 64.3 ($\text{C}_{6\beta}$), 64.4 ($\text{C}_{6\alpha}$), 71.1 ($\text{C}_{5\alpha}$), 71.2 ($\text{C}_{4\beta}$), 71.4 ($\text{C}_{4\alpha}$), 73.4 ($\text{C}_{2\alpha}$), 74.7 ($\text{CH}_2\text{Ph } \beta$), 75.0 ($\text{CH}_2\text{Ph } \alpha$), 75.2, 75.2 ($\text{C}_{2\beta}$ and $\text{C}_{5\beta}$), 83.4 ($\text{C}_{3\alpha}$), 84.3 ($\text{C}_{3\beta}$), 87.2 ($\text{CPh}_3 \beta$), 87.2 ($\text{CPh}_3 \alpha$), 100.0 ($\text{C}_{1\alpha}$), 104.3 ($\text{C}_{1\beta}$), 127.3, 127.8, 128.2, 128.3, 128.4, 128.7, 129.2 (20 x $\text{ArCH } \alpha$ and 20 x $\text{ArCH } \beta$), 139.6, 144.7, 144.7 (4 x *ipso*- $\text{ArC } \alpha$ and 4 x *ipso*- $\text{ArC } \beta$).

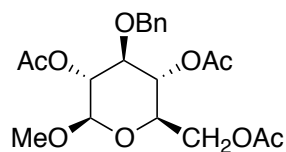
3-*O*-Benzyl-D-glucopyranose 2.211



Di-acetonide **2.206** (9.66 g, 27.57 mmol) was dissolved in 1:1 trifluoroacetic acid/water (40 mL) and stirred at rt. TLC analysis (1:1 ethyl acetate/cyclohexane) after 23 h showed no starting material (R_f 0.68) and formation of one major product (R_f 0.00). The mixture was concentrated *in vacuo* and the resulting clear yellow syrup partitioned between water (60 mL) and 5:1 ethyl acetate/diethyl ether (60 mL), the organic layer extracted with water (60 mL) and the combined clear, colourless aqueous layers concentrated *in vacuo* and the solid mass co-evaporated with toluene to afford a white solid (6.43 g, 86%). Re-crystallisations from ethanol/diethyl ether and ethyl acetate afforded the title compound as a white solid in two crops (combined recovery 4.12 g, 55%); R_f 0.15 (ethyl acetate); equilibrium $[\alpha]_D^{25} +42.9$ (c 0.84 in H_2O) [lit.²⁴¹ equilibrium $[\alpha]_D^{25} +43.2$ (c 0.99 in H_2O)]; m.p. 133-134 °C (ethyl acetate) [lit.²⁴¹ m.p. 134-135 °C (ethanol)].

1,2,4,6-Tetra-*O*-acetyl-3-*O*-benzyl- β -D-glucopyranose 2.212

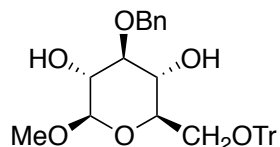
The D-glucopyranose **2.211** (2.33 g, 8.62 mmol) was dissolved in 1:1 acetic anhydride/pyridine (30 mL) and stirred at rt. TLC analysis (1:1 cyclohexane/ethyl acetate) after 14 h showed consumption of starting material (R_f 0.00) and formation of a single product (R_f 0.54). The mixture was concentrated *in vacuo*, co-evaporated with toluene (60 mL) and the resulting white solid redissolved in ethyl acetate (50 mL) and washed successively with 2M hydrochloric acid (2 x 50 mL), saturated aqueous sodium bicarbonate (50 mL) and brine (50 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford a white solid (3.78 g, quant.). Recrystallisation from ethanol afforded the title compound as a white solid (3.22 g, 85%); $[\alpha]_D^{25} +0.1$ (c 0.75 in CHCl_3) [lit.²⁴² $[\alpha]_D^{20} +1.0$ (c 1.04 in CHCl_3)]; ν_{max} (solid): 1741 (s, OCOCH_3); m.p. 100-101 °C (EtOH) [lit.²⁴³ m.p. 95-97 °C (aq. EtOH)]; δ_{H} (CDCl_3 , 400 MHz): 1.97, 1.97, 2.07, 2.10 (12H, 4 x s, 4 x OCOCH_3), 3.70-3.74 (1H, ddd, H5, $J_{5,6}$ 2.3, $J_{5,6'}$ 4.9, $J_{5,4}$ 9.9), 3.72-3.77 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 9.3), 4.06-4.10 (1H, dd, H6, $J_{6,5}$ 2.3, J_{gem} 12.5), 4.20-4.24 (1H, dd, H6', $J_{6',5}$ 4.9, J_{gem} 12.5), 4.61 (2H, a-s, CH_2Ph), 5.13-5.17 (1H, dd, H4, $J_{4,3}$ 9.4, $J_{4,5}$ 9.9), 5.14-5.18 (1H, dd, H2, $J_{2,1}$ 8.2, $J_{2,3}$ 9.4), 5.63-5.65 (1H, d, H1, $J_{1,2}$ 8.2), 7.21-7.35 (5H, m, 5 x ArH); δ_{C} (CDCl_3 , 100 MHz): 20.8, 20.8, 20.9, 21.0 (4 x OCOCH_3), 61.9 (C6), 69.2, 71.6 (C2 and C4), 73.2 (C5), 74.3 (CH_2Ph), 80.1 (C3), 92.1 (C1), 128.1 ($p\text{-ArCH}$), 127.9, 128.6 (2 x $o\text{-ArCH}$ and 2 x $m\text{-ArCH}$), 137.7 ($ipso\text{-ArC}$), 169.2, 169.4, 169.4, 170.8 (4 x OCOCH_3); m/z (ESI+ve): 461 ($[\text{M} + \text{Na}]^+$, 75%), 899 ($[2\text{M} + \text{Na}]^+$, 100%); HRMS m/z (ESI+ve): found 461.1411 ($[\text{M} + \text{Na}]^+$); $\text{C}_{21}\text{H}_{26}\text{NaO}_{10}$ requires 461.1418.

Methyl 2,4,6-tri-*O*-acetyl-3-*O*-benzyl- β -D-glucopyranoside 2.214

A solution of hydrobromic acid in acetic acid (33 wt.%, 1.80 mL, 10.48 mmol) was added dropwise over a period of 20 min to a solution of tetra-acetate **2.212** (1.70 g, 3.88 mmol) in 7:3 acetic acid/dichloromethane (10 mL) at 10 °C, and the resulting mixture stirred at 5 °C. TLC analysis (1:1 cyclohexane/ethyl acetate) after 4 h showed consumption of starting material (R_f 0.58) and formation of a single product (R_f 0.65). The mixture was diluted with dichloromethane (50 mL) and poured into ice water (50 mL). The organic layer was then washed with cold saturated aqueous sodium bicarbonate (2 x 50 mL), water (50 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* at 25 °C to afford the crude bromide **2.213** as a clear syrup (1.78 g). This material was re-dissolved in methanol (25 mL) in a foil-wrapped flask, silver (I) carbonate (1.78 g, 6.46 mmol) added and the mixture stirred at rt in the dark. TLC analysis (1:1 cyclohexane/ethyl acetate) after 17 h showed consumption of starting material (R_f 0.65) and formation of a single major product (R_f 0.47). The mixture was filtered through Celite, the pad and flask washed with methanol, and the combined filtrates concentrated *in vacuo* to afford the crude material as a clear syrup. Purification *via* flash column chromatography on silica gel (6:1 to 4:1 cyclohexane/ethyl acetate) afforded the title compound as a clear, colourless syrup (984 mg, 62%); $[\alpha]_D^{25}$ -28.4 (c 0.76 in CHCl_3) [lit.²⁴⁴ $[\alpha]_D^{25}$ -25.0 (c 1.00 in CHCl_3)]; ν_{max} (thin film): 1744 (s, OCOCH_3); δ_{H} (CDCl_3 , 400 MHz): 1.98, 2.02, 2.09 (9H, 3 x s, 3 x OCOCH_3), 3.49 (3H, s, OCH_3), 3.58-3.63 (1H, ddd, H5, $J_{5,6}$ 2.6, $J_{5,6'}$ 5.0, $J_{5,4}$ 9.9), 3.68-3.72 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 9.3), 4.12-4.15 (1H, dd, H6, $J_{6,5}$ 2.6, J_{gem} 12.2), 4.21-4.25 (1H, dd, H6', $J_{6',5}$ 5.0, J_{gem} 12.2), 4.34-4.36 (1H, d, H1, $J_{1,2}$ 7.9), 4.57-4.60 (1H, d, CHPh , J_{gem} 11.6), 4.60-4.63 (1H, d, CH'Ph , J_{gem} 11.6), 5.03-5.07 (1H, dd, H2, $J_{2,1}$ 7.9, $J_{2,3}$ 9.4), 5.11-5.16 (1H, a-t, H4, $J_{4,3}/J_{4,5}$ 9.6), 7.22-7.35 (5H, m, 5 x ArH); δ_{C} (CDCl_3 , 100 MHz): 20.9, 21.0 (3 x OCOCH_3), 56.9 (OCH_3), 62.4 (C6), 69.8 (C4), 72.2, 72.5 (C2 and C5), 73.9 (CH_2Ph), 80.2

(C3), 101.9 (C1), 128.0 (*p*-ArCH), 127.9, 128.6 (2 x *o*-ArCH and 2 x *m*-ArCH), 137.9 (*ipso*-ArC), 169.4, 169.5, 171.0 (3 x OCOCH₃); *m/z* (ESI+ve): 428 ([M + NH₄]⁺, 92%), 433 ([M + Na]⁺, 100%), 843 ([2M + Na]⁺, 99%); HRMS *m/z* (ESI+ve): found 433.1468 ([M + Na]⁺); C₂₀H₂₆NaO₉ requires 433.1469.

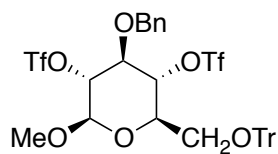
Methyl 3-*O*-benzyl-6-*O*-trityl-β-D-glucopyranoside **2.208β**



Sodium methoxide (13 mg, 0.241 mmol) was added to a stirred solution of tri-acetate **2.214** (970 mg, 2.36 mmol) in methanol (15 mL) at rt. TLC analysis (ethyl acetate) after 18 h showed consumption of starting material (*R_f* 0.81), one major product (*R_f* 0.24) and one minor product (*R_f* 0.40). Mass spectrometry confirmed the presence of mono-acetate(s) species. Another portion of sodium methoxide was added (13 mg, 0.241 mmol) and the mixture heated to 40 °C. TLC analysis after a further 18 h showed reaction completion. The mixture was concentrated *in vacuo* to afford a cloudy paste, which was re-dissolved in dry pyridine (10 mL), 4-dimethylaminopyridine (29 mg, 0.24 mmol) and trityl chloride (987 mg, 3.54 mmol) added and the mixture stirred at rt under nitrogen atmosphere. TLC analysis (ethyl acetate) after 26 h showed some remaining starting material and formation of a single product (*R_f* 0.80). Another portion of trityl chloride (987 mg, 3.54 mmol) was added. TLC analysis after a further 24 h showed complete consumption of starting material. Excess trityl chloride was quenched by addition of methanol and the mixture concentrated *in vacuo*. The resulting residue was diluted with ethyl acetate (100 mL), washed with water (2 x 100 mL) then brine (100 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude material as a clear syrup. Purification *via* flash column chromatography on silica gel (9:1 to 1:1 cyclohexane/ethyl acetate) afforded the title compound as a white solid (1.117 g, 90%); $[\alpha]_D^{25}$ -33.3 (*c* 1.00 in CHCl₃); $\nu_{\max}$ (thin film): 3456 (br, OH); m.p. 176-177 °C (toluene); δ_{H}

(C₆D₆, 500 MHz): 2.11-2.11 (1H, m, 2-OH), 2.12-2.12 (1H, d, 4-OH, $J_{\text{OH},4}$ 2.9), 3.32 (3H, s, OCH₃), 3.32-3.36 (1H, m, H5), 3.35-3.38 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 8.8), 3.47-3.50 (1H, dd, H6, $J_{6,5}$ 5.1, J_{gem} 9.9), 3.53-3.55 (1H, dd, H6', $J_{6',5}$ 3.1, J_{gem} 9.9), 3.62-3.66 (1H, m, H2), 3.65-3.70 (1H, a-dt, H4, $J_{4,\text{OH}}$ 2.8, $J_{4,5}/J_{4,3}$ 9.3), 3.99-4.01 (1H, d, H1, $J_{1,2}$ 7.7), 4.76-4.78 (1H, d, CHPh, J_{gem} 11.8), 5.00-5.03 (1H, d, CH'Ph, J_{gem} 11.8), 7.01-7.18, 7.31-7.33, 7.62-7.64 (20H, 3 x m, 20 x ArH); δ_{C} (C₆D₆, 125 MHz): 56.4 (OCH₃), 64.3 (C6), 71.2 (C4), 74.7 (CH₂Ph), 75.2, 75.2 (C2 and C5), 84.3 (C3), 87.2 (CPh₃), 104.3 (C1), 127.3, 127.8 (4 x *p*-ArCH), 128.2, 128.3, 128.4, 128.6, 129.3 (8 x *o*-ArCH and 8 x *m*-ArCH), 139.6, 144.7 (4 x *ipso*-ArC); m/z (ESI+ve): 243 ([Ph₃C]⁺, 100%), 549 ([M + Na]⁺, 74%); HRMS m/z (ESI+ve): found 549.2253 ([M + Na]⁺); C₃₃H₃₄NaO₆ requires 549.2248.

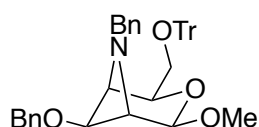
Methyl 3-*O*-benzyl-2,4-di-*O*-trifluoromethanesulfonyl-6-*O*-trityl-β-D-glucopyranoside **2.209β**



Trifluoromethanesulfonic anhydride (0.48 mL, 2.85 mmol) was added slowly to a stirred solution of diol **2.208β** (500 mg, 0.95 mmol) and pyridine (0.46 mL, 5.69 mmol) in dichloromethane (10 mL) at -20 °C under nitrogen atmosphere. Once addition was complete the mixture was allowed to warm to -10 °C and this temperature maintained. TLC analysis (2:1 cyclohexane/ethyl acetate) after 4 h showed consumption of starting material (R_f 0.40) and formation of a single major product (R_f 0.71). The mixture was diluted with dichloromethane (10 mL), washed with 2M hydrochloric acid (3 x 20 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* at 25 °C to afford the crude material as a yellow oil. Purification *via* flash column chromatography on silica gel (8:1 cyclohexane/ethyl acetate) afforded the title compound as an off-white solid foam (680 mg, 90%); $[\alpha]_D^{25}$ -11.6 (*c* 0.85 in CHCl₃); m.p. 46-50 °C; δ_{H} (CDCl₃, 400 MHz): 3.31-3.35 (1H, dd, H6, $J_{6,5}$ 5.5, J_{gem} 10.7), 3.49-3.53 (1H, dd, H6', $J_{6',5}$ 2.3, J_{gem} 10.7), 3.67 (3H, s, OCH₃), 3.70-3.75 (1H, ddd, H5, $J_{5,6'}$ 2.3, $J_{5,6}$ 5.5, $J_{5,4}$ 9.6), 3.91-3.95 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 9.0), 4.55-4.56 (1H, d, H1, $J_{1,2}$ 7.8),

4.76-4.80 (1H, dd, H2, $J_{2,1}$ 7.8, $J_{2,3}$ 9.1), 4.80-4.83 (1H, d, $\underline{\text{CHPh}}$, J_{gem} 9.7), 4.84-4.86 (1H, d, $\underline{\text{CH'Ph}}$, J_{gem} 9.7), 4.97-5.02 (1H, a-t, H4, $J_{4,3}/J_{4,5}$ 9.2), 7.24-7.38, 7.44-7.47 (20H, 2 x m, 20 x $\underline{\text{ArH}}$); δ_{C} (CDCl_3 , 100 MHz): 57.4 ($\underline{\text{OCH}_3}$), 61.8 (C6), 73.2 (C5), 75.9 ($\underline{\text{CH}_2\text{Ph}}$), 79.2 (C3), 80.5 (C4), 84.5 (C2), 87.3 ($\underline{\text{CPh}_3}$), 100.5 (C1), 127.4, 128.0, 128.1, 128.1, 128.3, 128.5, 128.9 (20 x $\underline{\text{ArCH}}$), 135.9, 143.3 (4 x *ipso*- $\underline{\text{ArC}}$); m/z (ESI+ve): 813 ($[\text{M} + \text{Na}]^+$, 100%); HRMS m/z (ESI+ve): found 813.1246 ($[\text{M} + \text{Na}]^+$); $\text{C}_{35}\text{H}_{32}\text{F}_6\text{NaO}_{10}\text{S}_2$ requires 813.1233.

Methyl *N*-benzyl-3-*O*-benzyl-2,4-dideoxy-2,4-imino-6-*O*-trityl- β -D-talopyranoside **2.210**

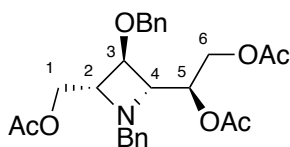


Benzylamine (138 μL , 1.265 mmol) was added to a stirred solution of ditriflate **2.209 β** (200 mg, 0.253 mmol) in acetonitrile (2 mL), and the mixture heated to 70 $^{\circ}\text{C}$. TLC analysis (3:1 cyclohexane/ethyl acetate) after 2 h indicated consumption of starting material (R_f 0.63) and formation of a single product (R_f 0.54). The mixture was allowed to cool and concentrated *in vacuo* to a clear, yellow oil. Purification *via* flash column chromatography on silica gel (98:2 to 90:10 cyclohexane/ethyl acetate) afforded the title compound as a clear, colourless glass (121 mg, 80%); $[\alpha]_D^{25}$ -24.4 (c 0.54 in CHCl_3); m.p. 42-44 $^{\circ}\text{C}$; δ_{H} (C_6D_6 , 500 MHz): 3.28 (3H, s, $\underline{\text{OCH}_3}$), 3.34-3.36 (1H, dd, H2, $J_{2,1}$ 1.2, $J_{2,4}$ 5.3 §), 3.49-3.50 (1H, dd, H4, $J_{4,5}$ 1.2, $J_{4,2}$ 5.3 §), 3.50-3.53 (1H, dd, H6, $J_{6,5}$ 6.5, J_{gem} 9.2), 3.77-3.79 (1H, dd, H6', $J_{6',5}$ 6.7, J_{gem} 9.2), 3.82 (1H, s, H3), 3.98-4.00 (1H, a-dt, H5, $J_{5,4}$ 1.1, $J_{5,6}/J_{5,6'}$ 6.5), 4.25-4.30 (2H, m, $\underline{\text{OCH}_2\text{Ph}}$), 4.29-4.32 (1H, d, $\underline{\text{NCHPh}}$, J_{gem} 14.1), 4.40-4.43 (1H, $\underline{\text{NCH'Ph}}$, J_{gem} 14.1), 4.47-4.47 (1H, d, H1, $J_{1,2}$ 1.2), 7.00-7.56 (25H, 5 x m, 25 x $\underline{\text{ArH}}$); δ_{C} (C_6D_6 , 125 MHz): 55.8 ($\underline{\text{OCH}_3}$), 56.0 ($\underline{\text{NCH}_2\text{Ph}}$), 64.8 (C4), 65.3 (C6), 66.7 (C2), 70.9 ($\underline{\text{OCH}_2\text{Ph}}$), 76.4 (C5), 84.3 (C3), 87.1 ($\underline{\text{OCPh}_3}$), 101.5 (C1), 126.8, 127.2, 128.0, 128.0, 128.1, 128.4, 128.4, 128.7, 128.8, 129.3 (25 x $\underline{\text{ArCH}}$), 138.6, 140.3, 144.8 (5 x *ipso*- $\underline{\text{ArC}}$); m/z (ESI+ve): 598 ($[\text{M} + \text{H}]^+$,

§ Similar long-range couplings have been observed for analogous all-carbon bicyclic systems.²⁴⁵

93%), 620 ($[M + Na]^+$, 86%); HRMS m/z (ESI+ve): found 598.2954 ($[M + H]^+$); $C_{40}H_{40}NO_4$ requires 598.2952.

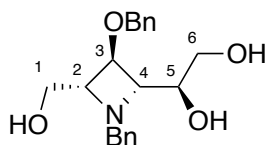
1,5,6-Tri-*O*-acetyl-*N*-Benzyl-3-*O*-benzyl-2,4-dideoxy-2,4-imino-D-talitol **2.215D**



Bicycle **2.210** (96 mg, 0.160 mmol) was dissolved in 1:1 v/v 1,4-dioxane/2M hydrochloric acid (10 mL) and stirred at 50 °C. After 21 h the mixture was allowed to cool, diluted with dichloromethane (50 mL) and washed with saturated aqueous sodium bicarbonate (50 mL). The aqueous layer was extracted with dichloromethane (50 mL) and the combined organic layers washed with brine (50 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude lactol as an off-white solid. This material was re-dissolved in methanol (5 mL), sodium borohydride (8 mg, 0.211 mmol) added and the mixture stirred at rt. TLC analysis (ethyl acetate) after 2 h indicated no starting material (R_f 0.25) and formation of a single product (R_f 0.00). The mixture was quenched with glacial acetic acid and concentrated *in vacuo* to afford the crude triol as a white solid. This was re-dissolved in 1:1 v/v pyridine/acetic anhydride (6 mL) and stirred at rt. TLC analysis (2:1 cyclohexane/ethyl acetate) after 18 h showed consumption of starting material (R_f 0.00) and formation of a single major product (R_f 0.53). The mixture was concentrated *in vacuo* and the residue co-evaporated with toluene (20 mL) to afford a white solid, which was re-dissolved in ethyl acetate (20 mL) and washed sequentially with water (2 x 20 mL), saturated aqueous sodium bicarbonate (20 mL) and brine (20 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude material as a cloudy oil. Purification *via* flash column chromatography on silica gel (95:5 to 80:20 cyclohexane/ethyl acetate) afforded the title compound as a clear, colourless oil (67 mg, 89%); $[\alpha]_D^{25} +28.4$ (c 0.56 in $CHCl_3$); ν_{max} (thin film): 1740 (s, $OCOCH_3$); δ_H ($CDCl_3$, 400 MHz): 1.94, 1.99, 2.00 (9H, 3 x s, 3 x

OCOCH₃), 3.19-3.23 (1H, a-q, H₂, $J_{2,1}/J_{2,1'}/J_{2,3}$ 5.0), 3.33-3.36 (1H, m, H₄), 3.68-3.71 (1H, d, NCHPh, J_{gem} 13.1), 3.69-3.74 (1H, dd, H₁, $J_{1,2}$ 4.8, J_{gem} 11.7), 3.78-3.80 (1H, a-t, H₃, $J_{3,2}/J_{3,4}$ 5.2), 3.78-3.81 (1H, d, NCH'Ph, J_{gem} 13.1), 3.87-3.91 (1H, dd, H_{1'}, $J_{1',2}$ 5.2, J_{gem} 11.7), 4.02-4.07 (1H, dd, H₆, $J_{6,5}$ 6.8, J_{gem} 12.1), 4.31-4.35 (1H, dd, H_{6'}, $J_{6',5}$ 3.0, J_{gem} 12.1), 4.47 (2H, s, OCH₂Ph), 4.93-4.98 (1H, a-dt, H₅, $J_{5,6'}$ 3.0, $J_{5,6}/J_{5,4}$ 6.7), 7.23-7.37 (10H, m, 10 x ArH); δ_{C} (CDCl₃, 100 MHz): 20.9, 21.0 (3 x OCOCH₃), 61.9 (NCH₂Ph), 62.7 (C₆), 64.7 (C₁), 68.8 (C₂), 69.2 (C₄), 71.6 (OCH₂Ph), 72.4 (C₅), 73.0 (C₃), 127.6, 128.2 (2 x *p*-ArCH), 127.8, 128.5, 128.7, 129.1 (4 x *o*-ArCH and 4 x *m*-ArCH), 137.6, 137.9 (2 x *ipso*-ArC); m/z (ESI+ve): 470 ([M + H]⁺, 74%), 492 ([M + Na]⁺, 76%), 961 ([2M + Na]⁺, 100%); HRMS m/z (ESI+ve): found 492.2006 ([M + Na]⁺); C₂₆H₃₁NNaO₇ requires 492.1993.

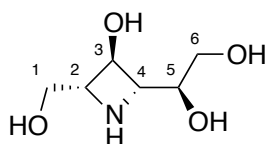
***N*-Benzyl-3-*O*-benzyl-2,4-dideoxy-2,4-imino-D-talitol 2.216D**



Sodium methoxide (2.7 mg, 0.050 mmol) was added to a stirred solution of tri-acetate **2.215D** (67.0 mg, 0.143 mmol) in methanol (4 mL) at rt. TLC analysis (ethyl acetate) after 24 h showed consumption of starting material (R_f 0.90), one major product (R_f 0.11) and one trace product (R_f 0.41). Another portion of sodium methoxide (1.0 mg, 0.019 mmol) was added and the mixture heated to 45 °C. TLC analysis after a further 24 h showed complete disappearance of the R_f 0.41 product. The mixture was concentrated *in vacuo* and the resulting residue purified *via* flash column chromatography on silica gel (9:1 ethyl acetate/methanol) to afford the title compound as a clear, colourless syrup (44.6 mg, 91%); $[\alpha]_D^{25} +17.7$ (*c* 0.35 in MeOH); ν_{max} (thin film): 3388 (s, OH); δ_{H} (CD₃OD, 400 MHz): 3.06-3.17 (3H, m, H₁, H_{1'}, H₂), 3.23-3.26 (1H, dd, H₄, $J_{4,5}$ 4.9, $J_{4,3}$ 5.3), 3.41-3.45 (1H, dd, H₆, $J_{6,5}$ 6.6, J_{gem} 11.0), 3.49-3.53 (1H, dd, H_{6'}, $J_{6',5}$ 5.2, J_{gem} 11.0), 3.55-3.59 (1H, a-dt, H₅, $J_{5,4}/J_{5,6'}$ 5.0, $J_{5,6}$ 6.6), 3.62-3.65 (1H, d, NCHPh, J_{gem} 12.5), 3.90-3.93 (1H, m, H₃),

3.97-4.00 (1H, d, $\text{NCH}'\text{Ph}$, J_{gem} 12.5), 4.47-4.50 (1H, d, OCHPh , J_{gem} 11.7), 4.51-4.54 (1H, d, $\text{OCH}'\text{Ph}$, J_{gem} 11.7), 7.24-7.37 (10H, m, 10 x ArH); δ_{C} (CD_3OD , 100 MHz): 63.3 (C1), 63.5 (NCH_2Ph), 64.7 (C6), 72.3 (C4), 72.3 (OCH_2Ph), 72.5 (C2), 73.7 (C5), 74.1 (C3), 128.5, 128.8 (2 x $p\text{-ArCH}$), 129.0, 129.4, 130.8 (4 x $o\text{-ArCH}$ and 4 x $m\text{-ArCH}$), 139.1, 139.6 (2 x $ipso\text{-ArC}$); m/z (ESI+ve): 344 ($[\text{M} + \text{H}]^+$, 83%), 366 ($[\text{M} + \text{Na}]^+$, 80%), 709 ($[2\text{M} + \text{Na}]^+$, 100%); HRMS m/z (ESI+ve): found 366.1667 ($[\text{M} + \text{Na}]^+$); $\text{C}_{20}\text{H}_{25}\text{NNaO}_4$ requires 366.1676.

2,4-Dideoxy-2,4-imino-D-talitol **2.217D**

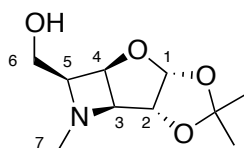


Ammonium formate (60.5 mg, 0.96 mmol) was added to a suspension of D-talitol **2.216D** (32.9 mg, 0.096 mmol) and palladium on activated charcoal (10 wt.%, 20.2 mg, 0.019 mmol) in anhydrous methanol (4 mL), and the resulting mixture stirred at reflux under argon atmosphere. TLC analysis (14:3:1:1:1 ethanol/pyridine/*n*-butanol/acetic acid/water) after 30 min showed consumption of starting material (R_f 0.86) and formation of a single product (R_f 0.63). The mixture was allowed to cool, filtered through Celite and the pad and flask washed with methanol. The combined filtrates were concentrated *in vacuo* to afford the crude material as a cloudy, colourless syrup. This material was loaded onto a column of Dowex 50WX8 (H^+) ion exchange resin, the column flushed with water, 1,4-dioxane, more water and then eluted with 2M aqueous ammonia. The ammoniacal fraction was concentrated *in vacuo* to afford the title compound as a clear, colourless syrup (15.7 mg, 100%) [**characterised as the HCl salt**]; $[\alpha]_D^{25} -13.9$ (c 0.44 in H_2O); v_{max} (neat): 3284 (br, OH and NH); δ_{H} (D_2O , 500 MHz): 3.62-3.65 (1H, dd, H6, $J_{6,5}$ 5.1, J_{gem} 12.1), 3.68-3.71 (1H, dd, H6', $J_{6',5}$ 4.1, J_{gem} 12.1), 3.88-3.92 (1H, dd, H1, $J_{1,2}$ 4.1, J_{gem} 13.3), 3.91-3.95 (1H, dd, H1', $J_{1',2}$ 4.8, J_{gem} 13.3), 4.06-4.09 (1H, a-dt, H5, $J_{5,6'}$ 4.1, $J_{5,6}/J_{5,4}$ 5.3), 4.30-4.32 (1H, dd, H4, $J_{4,5}$ 5.5, $J_{4,3}$ 7.2), 4.33-4.36 (1H, a-dt, H2, $J_{2,1}/J_{2,1'}$ 4.4, $J_{2,3}$ 7.2), 4.57-4.60 (1H, t, H3, $J_{3,4}/J_{3,2}$ 7.2); δ_{C}

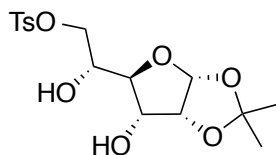
(D₂O, 125 MHz): 58.4 (C1), 62.6 (C6), 64.9 (C3), 67.4, 67.6 (C2 and C4), 68.8 (C5); *m/z* (ESI+ve): 164 ([M + H]⁺, 100%); HRMS *m/z* (ESI+ve): found 164.0913 ([M + H]⁺); C₆H₁₄NO₄ requires 164.0917.

2.4.5 *Ido 1-acetamido azetidine triols from allose*

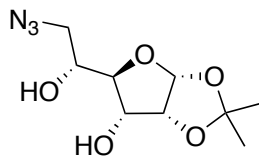
3,5-Dideoxy-3,5-imino-1,2-*O*-isopropylidene-*N*-methyl-β-*L*-idofuranose 2.221



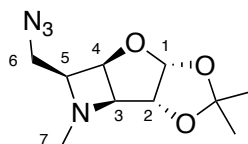
Tetra-*n*-butylammonium fluoride (1M in tetrahydrofuran, 1.35 mL, 1.35 mmol) was added in one portion to a stirred solution of silyl ether **2.184** (371 mg, 1.126 mmol) in tetrahydrofuran (8 mL) at rt. TLC analysis (9:1 ethyl acetate/methanol) after 3.5 h showed a small amount of starting material (*R_f* 0.93) still present, and a single major product (*R_f* 0.46). Another portion of tetra-*n*-butylammonium fluoride (0.90 mL, 0.90 mmol) was added. TLC analysis after a further 3 h showed complete consumption of starting material. The mixture was concentrated *in vacuo* to give the crude material as a yellow syrup. Purification *via* flash column chromatography on silica gel (1:1 cyclohexane/ethyl acetate to ethyl acetate to 95:5 ethyl acetate/methanol) afforded the title compound as a white crystalline solid (221 mg, 91%); $[\alpha]_D^{25} +53.0$ (*c* 0.74 in CHCl₃); *v*_{max} (solid): 3207 (s, br, OH); m.p. 90-93 °C (cyclohexane/ethyl acetate); δ_H (C₆D₆, 400 MHz): 1.28, 1.42 (6H, 2 x s, C(CH₃)₂), 1.99 (3H, s, H7), 2.12 (1H, br s, 6-OH), 2.58-2.62 (1H, m, H5), 3.19-3.21 (1H, d, H3, *J*_{3,4} 4.8), 3.48-3.53 (1H, dd, H6, *J*_{6,5} 5.6, *J*_{gem} 11.2), 3.59-3.63 (1H, dd, H6', *J*_{6',5} 6.5, *J*_{gem} 11.2), 4.33-4.34 (1H, d, H2, *J*_{2,1} 3.6), 4.61-4.63 (1H, t, H4, *J*_{4,3}/*J*_{4,5} 4.8), 6.11-6.12 (1H, d, H1, *J*_{1,2} 3.6); δ_C (C₆D₆, 100 MHz): 27.9, 28.5 (C(CH₃)₂), 42.9 (C7), 61.4 (C6), 70.1 (C5), 71.8 (C3), 76.3 (C4), 84.6 (C2), 110.8 (C1), 113.8 (C(CH₃)₂); *m/z* (ESI+ve): 238 ([M + Na]⁺, 89%), 453 ([2M + Na]⁺, 100%); HRMS *m/z* (ESI+ve): found 238.1047 ([M + Na]⁺); C₁₀H₁₇NNaO₄ requires 238.1050.

1,2-*O*-Isopropylidene-6-*O*-*para*-toluenesulfonyl- α -D-allofuranose 2.222

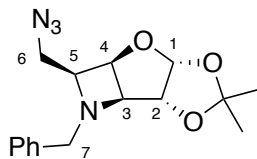
1,2-*O*-Isopropylidene- α -D-allofuranose **2.164** (500 mg, 2.27 mmol) was placed in a flame-dried flask with anhydrous pyridine (10 mL) and stirred under argon with freshly-dried 3 Å powdered molecular sieves for 15 min. The mixture was then cooled to -20 °C, freshly-recrystallised *p*-toluenesulfonyl chloride (519 mg, 2.72 mmol) added in one portion and the mixture allowed to slowly warm to rt. TLC analysis (ethyl acetate) after 18 h showed a small amount of starting material (R_f 0.13), one major product (R_f 0.64), and one minor product (R_f 0.86). The mixture was quenched with methanol and directly dry loaded onto silica. Purification *via* flash column chromatography on silica gel (2:1 to 1:1 to 0:1 cyclohexane/ethyl acetate) afforded recovered starting material (38 mg, 8%), the corresponding di-tosylate (R_f 0.86) as a clear, colourless syrup (312 mg, 26%), and the title compound (R_f 0.64) as a white solid (495 mg, 58%); $[\alpha]_D^{25} +29.7$ (c 0.35 in CHCl_3) [lit.²⁴⁶ $[\alpha]_D^{25} +30.2$ (c 1.00 in CHCl_3)]; ν_{max} (solid): 3391, 3460 (br, OH); m.p. 109.5-110.5 °C (cyclohexane/chloroform) [lit.²⁴⁷ m.p. 117-119 °C]; δ_{H} (CDCl_3 , 400 MHz): 1.35, 1.55 (6H, 2 x s, $\text{C}(\text{CH}_3)_2$), 2.45 (3H, s, $(\text{CH}_3)\text{C}_6\text{H}_4\text{SO}_2$), 2.47-2.50 (1H, d, 3-OH, $J_{\text{OH},3}$ 9.5), 2.53-2.54 (1H, d, 5-OH, $J_{\text{OH},5}$ 3.0), 3.72-3.75 (1H, dd, H4, J 4.5, J 8.6), 4.03-4.14 (3H, m, H3, H5 and H6), 4.21-4.24 (1H, dd, H6', $J_{6',5}$ 2.0, J_{gem} 9.5), 4.56-4.58 (1H, m, H2), 5.76-5.77 (1H, d, H1, $J_{1,2}$ 3.7), 7.34-7.36, 7.79-7.81 (4H, 2 x d, 4 x ArH, J 8.3, J 8.4); δ_{C} (CDCl_3 , 100 MHz): 21.8 ($(\text{CH}_3)\text{C}_6\text{H}_4\text{SO}_2$), 26.6, 26.7 ($\text{C}(\text{CH}_3)_2$), 70.0 (C5), 70.7 (C6), 72.2 (C3), 78.9, 78.9 (C2 and C4), 104.2 (C1), 113.2 ($\text{C}(\text{CH}_3)_2$), 128.2, 130.1 (2 x *o*-ArCH and 2 x *m*-ArCH), 132.7 (*p*-ArC), 145.2 (*ipso*-ArC); m/z (ESI+ve): 397 ($[\text{M} + \text{Na}]^+$, 100%), 413 ($[\text{M} + \text{K}]^+$, 31%), 721 ($[2\text{M} + \text{Na}]^+$, 16%); HRMS m/z (ESI+ve): found 397.0923 ($[\text{M} + \text{Na}]^+$); $\text{C}_{16}\text{H}_{22}\text{NaO}_8\text{S}$ requires 397.0928.

6-Azido-6-deoxy-1,2-O-isopropylidene- α -D-allofuranose 2.223

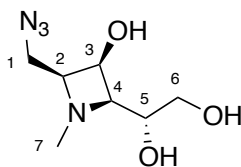
Sodium azide (493 mg, 7.59 mmol) was added to a stirred solution of tosylate **2.222** (568 mg, 1.52 mmol) in *N,N*-dimethylformamide (20 mL) and the mixture heated to 50 °C. The reaction could not be followed reliably by TLC. Analysis by mass spectrometry after 5 days still showed a small amount of starting material. The mixture was heated to 75 °C. Analysis by mass spectrometry after a further 24 h still showed starting material present. The mixture was diluted with ethyl acetate (100 mL) and washed with 80% brine (3 x 50 mL). The aqueous layers were back extracted with ethyl acetate (2 x 80 mL) and the combined organic layers dried (MgSO₄) and concentrated *in vacuo* to afford the crude material as a pale yellow solid (384 mg). This material was found to contain a small amount (~ 2-3 %) of starting material. Purification *via* flash column chromatography on silica gel (1:1 cyclohexane/ethyl acetate to ethyl acetate) afforded the title compound as a white crystalline solid (339 mg, 91%); $[\alpha]_D^{25} +43.1$ (*c* 0.95 in CHCl₃); $\nu_{\max}$ (solid): 2087 (s, N₃), 3435, 3476 (s, OH); m.p. 112-113 °C (cyclohexane/ethyl acetate) [lit.²⁴⁷ m.p. 115-116 °C]; δ_H ((CD₃)₂CO, 500 MHz): 1.30, 1.47 (6H, 2 x s, C(CH₃)₂), 3.29-3.32 (1H, dd, H6, $J_{6,5}$ 3.4, J_{gem} 12.9), 3.42-3.46 (1H, dd, H6', $J_{6',5}$ 8.4, J_{gem} 12.9), 3.81-3.83 (1H, d, 3-OH, $J_{\text{OH},3}$ 9.4), 3.82-3.84 (1H, dd, H4, $J_{4,5}$ 3.7, $J_{4,3}$ 8.8), 4.00-4.04 (1H, a-dq, H5, $J_{5,\text{OH}}/J_{5,6}/J_{5,4}$ 3.9, $J_{5,6'}$ 8.2), 4.08-4.13 (1H, a-dt, H3, $J_{3,2}$ 4.9, $J_{3,\text{OH}}/J_{3,4}$ 9.1), 4.33-4.34 (1H, dd, 5-OH, $J_{\text{OH},6}$ 0.9, $J_{\text{OH},5}$ 4.3), 4.57-4.59 (1H, m, H2), 5.73-5.74 (1H, d, H1, $J_{1,2}$ 3.7); δ_C ((CD₃)₂CO, 125 MHz): 26.9, 27.1 (C(CH₃)₂), 53.8 (C6), 71.6 (C5), 72.4 (C3), 80.6 (C2), 81.2 (C4), 105.1 (C1), 112.9 (C(CH₃)₂); m/z (ESI+ve): 268 ([M + Na]⁺, 100%), 513 ([2M + Na]⁺, 86%); HRMS m/z (ESI+ve): found 268.0899 ([M + Na]⁺); C₉H₁₅N₃NaO₅ requires 268.0904.

6-Azido-3,5,6-trideoxy-3,5-imino-1,2-*O*-isopropylidene-*N*-methyl-β-L-idofuranose 2.225

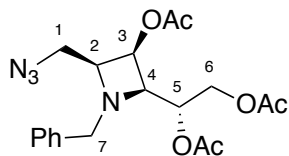
Trifluoromethanesulfonic anhydride (0.21 mL, 1.224 mmol) was added to a stirred solution of diol **2.223** (100 mg, 0.408 mmol) and pyridine (0.20 mL, 2.448 mmol) in dichloromethane (3 mL) at -30 °C under nitrogen atmosphere. TLC analysis (1:1 cyclohexane/ethyl acetate) after 1 h showed consumption of starting material (R_f 0.23) and formation of a single product (R_f 0.80). The mixture was diluted with dichloromethane (7 mL) and washed with 2M hydrochloric acid (3 x 10 mL), dried (MgSO_4) and concentrated *in vacuo* to afford the crude ditriflate **2.224** as a clear yellow syrup (210 mg). This was re-dissolved in acetonitrile (4 mL), diisopropylethylamine (178 μL , 1.020 mmol) and a 33 wt% solution of methylamine in ethanol (56 μL , 0.449 mmol) added simultaneously and the mixture stirred at rt. TLC analysis (1:1 cyclohexane/ethyl acetate) after 21 h showed two trace products (R_f 0.83 and R_f 0.75) and one major product (R_f 0.49). The mixture was directly pre-absorbed onto silica and purified *via* flash column chromatography on silica gel (5:1 to 2:1 cyclohexane/ethyl acetate) to afford the title compound as a clear, colourless oil (67 mg, 68%); $[\alpha]_D^{25} +63.6$ (c 0.94 in CHCl_3); ν_{max} (thin film): 2095 (s, N_3); δ_{H} (CDCl_3 , 500 MHz): 1.35, 1.43 (6H, 2 x s, $\text{C}(\text{CH}_3)_2$), 2.42 (3H, s, H7), 3.00-3.04 (1H, a-dt, H5, $J_{5,4}$ 4.8, $J_{5,6}/J_{5,6'}$ 6.6), 3.22-3.25 (1H, dd, H6, $J_{6,5}$ 6.7, J_{gem} 12.5), 3.43-3.47 (1H, dd, H6', $J_{6',5}$ 6.6, J_{gem} 12.5), 3.58-3.59 (1H, d, H3, $J_{3,4}$ 4.7), 4.53-4.53 (1H, d, H2, $J_{2,1}$ 3.6), 4.89-4.91 (1H, a-t, H4, $J_{4,3}/J_{4,5}$ 4.7), 6.09-6.10 (1H, d, H1, $J_{1,2}$ 3.6); δ_{C} (CDCl_3 , 125 MHz): 27.4, 27.9 ($\text{C}(\text{CH}_3)_2$), 42.8 (C7), 50.5 (C6), 67.5 (C5), 71.3 (C3), 75.6 (C4), 83.9 (C2), 110.2 (C1), 113.8 ($\text{C}(\text{CH}_3)_2$); m/z (ESI+ve): 241 ($[\text{M} + \text{H}]^+$, 100%), 263 ($[\text{M} + \text{Na}]^+$, 60%); HRMS m/z (ESI+ve): found 241.1304 ($[\text{M} + \text{H}]^+$); $\text{C}_{10}\text{H}_{17}\text{N}_4\text{O}_3$ requires 241.1295.

6-Azido-*N*-benzyl-3,5,6-trideoxy-3,5-imino-1,2-*O*-isopropylidene-β-L-idofuranose 2.226

Trifluoromethanesulfonic anhydride (247 μL , 1.467 mmol) was added to a stirred solution of diol **2.223** (120 mg, 0.489 mmol) and pyridine (237 μL , 2.934 mmol) in dichloromethane (4 mL) at -30°C under nitrogen atmosphere, and the temperature maintained between -30 and -20°C . TLC analysis (1:1 cyclohexane/ethyl acetate) after 1 h showed consumption of starting material (R_f 0.23) and formation of a single product (R_f 0.81). The mixture was diluted with dichloromethane (16 mL) and washed with 2M hydrochloric acid (3 x 20 mL), dried (MgSO_4) and concentrated *in vacuo* to afford the crude ditriflate **2.224** as a clear yellow syrup (255 mg). This was re-dissolved in acetonitrile (5 mL), benzylamine (59 μL , 0.538 mmol) and diisopropylethylamine (213 μL , 1.223 mmol) added simultaneously and the mixture stirred at 40°C . TLC analysis (3:1 cyclohexane/ethyl acetate) after 23 h showed consumption of starting material (R_f 0.53) and formation of a single major product (R_f 0.65). The mixture was concentrated *in vacuo* to an orange residue. Purification *via* flash column chromatography on silica gel (9:1 cyclohexane/ethyl acetate) afforded the title compound (contaminated with $\sim 5\%$ of alkene **2.227**) as a clear, straw-coloured oil (116 mg, 75%); ν_{max} (thin film): 2097 (s, N_3); δ_{H} (CDCl_3 , 400 MHz): 1.29, 1.40 (6H, 2 x s, $\text{C}(\text{CH}_3)_2$), 3.02-3.07 (1H, dd, H6, $J_{6,5}$ 6.0, J_{gem} 12.3), 3.21-3.25 (1H, ddd, H5, $J_{5,4}$ 4.8, $J_{5,6}$ 6.0, $J_{5,6'}$ 7.3), 3.38-3.43 (1H, dd, H6', $J_{6',5}$ 7.3, J_{gem} 12.3), 3.60-3.63 (1H, d, H7, J_{gem} 12.5), 3.74-3.76 (1H, d, H3, $J_{3,4}$ 4.8), 3.79-3.82 (1H, d, H7', J_{gem} 12.5), 4.20-4.21 (1H, d, H2, $J_{2,1}$ 3.6), 4.89-4.91 (1H, t, H4, $J_{4,3}/J_{4,5}$ 4.8), 6.07-6.08 (1H, d, H1, $J_{1,2}$ 3.6), 7.26-7.35 (5H, m, 5 x ArH); δ_{C} (CDCl_3 , 100 MHz): 27.4, 28.0 ($\text{C}(\text{CH}_3)_2$), 50.4 (C6), 60.5 (C7), 65.7 (C5), 69.5 (C3), 75.5 (C4), 84.2 (C2), 110.1 (C1), 113.8 ($\text{C}(\text{CH}_3)_2$), 127.8 (*p*-ArCH), 128.6, 129.3 (2 x *o*-ArCH and 2 x *m*-ArCH), 137.4 (*ipso*-ArC); m/z (ESI+ve): 317 ($[\text{M} + \text{H}]^+$, 58%), 339 ($[\text{M} + \text{Na}]^+$, 100%), 655 ($[\text{2M} + \text{Na}]^+$, 80%); HRMS m/z (ESI+ve): found 339.1437 ($[\text{M} + \text{Na}]^+$); $\text{C}_{16}\text{H}_{20}\text{N}_4\text{NaO}_3$ requires 339.1428.

1-Azido-1,2,4-trideoxy-2,4-imino-*N*-methyl-L-iditol 2.228

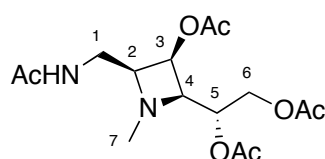
The acetonide **2.225** (61 mg, 0.254 mmol) was dissolved in 1:1 trifluoroacetic acid/water and stirred at rt. TLC analysis (ethyl acetate) of an aliquot quenched with triethylamine after 48 h showed consumption of starting material (R_f 0.71) and formation of a single product (R_f 0.37). The mixture was concentrated *in vacuo* and co-evaporated with water (20 mL) to afford the crude lactol as an orange syrup. This material was re-dissolved in water (4 mL), sodium borohydride (19 mg, 0.508 mmol) added and the mixture stirred at rt. TLC analysis (ethyl acetate) after 16 h showed only baseline material. The mixture was quenched with acetic acid and loaded onto a column of Dowex 50WX8 (H^+) ion exchange resin. The column was flushed with water, ethanol, more water and then eluted with 2M aqueous ammonia. The ammoniacal fraction was concentrated *in vacuo* to afford the title compound as a clear, yellow syrup (41 mg, 80%); $[\alpha]_D^{25} +11.0$ (c 0.50 in H_2O); ν_{max} (neat): 2095 (s, N_3), 3327 (s, br, OH); δ_H (D_2O , 400 MHz): 2.43 (3H, s, H7), 3.09-3.13 (1H, dd, H4, $J_{4,3}$ 6.2, $J_{4,5}$ 9.2), 3.28-3.33 (1H, m, H2), 3.40-3.45 (1H, dd, H1, $J_{1,2}$ 6.5, J_{gem} 12.5), 3.44-3.49 (1H, dd, H6, $J_{6,5}$ 6.5, J_{gem} 11.9), 3.59-3.64 (1H, dd, H1', $J_{1',2}$ 7.9, J_{gem} 12.5), 3.61-3.65 (1H, dd, H6', $J_{6',5}$ 3.4, J_{gem} 11.9), 3.96-4.01 (1H, ddd, H5, $J_{5,6'}$ 3.4, $J_{5,6}$ 6.5, $J_{5,4}$ 9.2), 4.50-4.53 (1H, a-t, H3, $J_{3,4}/J_{3,2}$ 6.0); δ_C (D_2O , 100 MHz): 44.6 (C7), 49.2 (C1), 63.4 (C6), 65.5 (C3), 67.6 (C2), 69.9 (C4), 72.2 (C5); m/z (ESI+ve): 203 ($[M + H]^+$, 41%), 225 ($[M + Na]^+$, 100%); HRMS m/z (ESI+ve): found 225.0962 ($[M + Na]^+$); $C_7H_{14}N_4NaO_3$ requires 225.0958.

1-Azido-3,5,6-tri-*O*-acetyl-2-*N*-benzyl-1,2,4-trideoxy-2,4-imino-L-iditol 2.229

The mixture of acetonide **2.226** and the alkene **2.227** (116 mg, 0.367 mmol) was dissolved in 1:1 v/v trifluoroacetic acid/water (4 mL) and stirred at rt. TLC analysis (3:1 cyclohexane/ethyl acetate) after 27 h showed consumption of starting material (R_f 0.65) and formation of a single major product (R_f 0.09). The mixture was concentrated *in vacuo* and co-evaporated with water (2 x 15 mL) to afford the crude lactol as an orange/brown residue. This was re-dissolved in 1:2 v/v 1,4-dioxane/water, sodium borohydride (27.8 mg, 0.734 mmol) added and the mixture stirred at rt. TLC analysis (3:1 cyclohexane/ethyl acetate) after 20 h showed consumption of starting material and only baseline material. The reaction was quenched by addition of glacial acetic acid, concentrated *in vacuo* and the residue loaded onto a column of Dowex 50WX8 (H^+) ion exchange resin. The column was flushed with water, 1,4-dioxane, more water and then eluted with a 1:1 v/v mixture of 1,4-dioxane/2M aqueous ammonia. The ammoniacal fraction was concentrated *in vacuo* to afford the crude triol. This was re-dissolved in 1:1 v/v pyridine/acetic anhydride (4 mL) and stirred at rt. TLC analysis (1:1 cyclohexane/ethyl acetate) after 20 h showed consumption of starting material (R_f 0.00) and formation of one major product (R_f 0.69). The mixture was concentrated *in vacuo* and co-evaporated with toluene (2 x 10 mL) to afford the crude tri-acetate as a brown residue. Purification *via* flash column chromatography on silica gel (5:1 to 3:1 cyclohexane/ethyl acetate) afforded the title compound as a clear, pale yellow oil (67 mg, 45%); $[\alpha]_D^{25}$ -9.0 (c 0.60 in $CHCl_3$); ν_{max} (thin film): 1741 (s, $OCOCH_3$), 2100 (s, N_3); δ_H ($CDCl_3$, 400 MHz): 1.95, 2.04, 2.18 (9H, 3 x s, 3 x $OCOCH_3$), 2.84-2.89 (1H, dd, H1, $J_{1,2}$ 5.1, J_{gem} 12.6), 3.27-3.32 (1H, dd, H1', $J_{1',2}$ 7.8, J_{gem} 12.6), 3.43-3.48 (1H, m, H2), 3.56-3.60 (1H, dd, H4, $J_{4,3}$ 6.9, $J_{4,5}$ 8.7), 3.60-3.63 (1H, d, $CHPh$, J_{gem} 13.1), 3.87-3.90 (1H, dd, $CH'Ph$, J_{gem} 13.1), 3.90-3.95 (1H, dd, H6, $J_{6,5}$ 6.5, J_{gem} 12.2), 4.29-4.32 (1H, dd, H6', $J_{6',5}$ 2.9, J_{gem} 12.2), 5.34-5.38 (1H, ddd, H5, $J_{5,6'}$ 2.9, $J_{5,6}$ 6.5, $J_{5,4}$ 8.7), 5.49-5.52 (1H,

a-t, H3, $J_{3,2}/J_{3,4}$ 6.7), 7.25-7.35 (5H, m, 5 x ArH); δ_C (CDCl₃, 100 MHz): 20.9, 21.0, 21.0 (3 x OCOCH₃), 50.3 (C1), 61.5 (C7), 63.0 (C6), 63.9 (C4), 64.7 (C2), 66.0 (C3), 71.5 (C5), 127.8 (*p*-ArCH), 128.7, 129.2 (2 x *o*-ArCH and 2 x *m*-ArCH), 137.6 (*ipso*-ArC), 170.3, 170.5, 170.7 (3 x OCOCH₃); m/z (ESI+ve): 405 ([M + H]⁺, 78%), 427 ([M + Na]⁺, 100%), 443 ([M + K]⁺, 19%), 831 ([2M + Na]⁺, 99%); HRMS m/z (ESI+ve): found 427.1582 ([M + Na]⁺); C₁₉H₂₄N₄NaO₆ requires 427.1588.

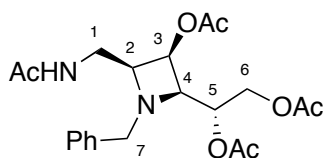
1-Acetamido-3,5,6-tri-*O*-acetyl-1,2,4-trideoxy-2,4-imino-2-*N*-methyl-L-iditol **2.230**



The azido triol **2.228** (35.7 mg, 0.177 mmol) and palladium on activated charcoal (10 wt.%, 18.8 mg, 0.018 mmol) were placed in a flask with water (4 mL), the flask de-gassed and purged with argon, then de-gassed and charged with hydrogen and the contents stirred at rt. TLC analysis (14:3:1:1:1 ethanol/pyridine/*n*-butanol/acetic acid/water) after 2 h indicated consumption of starting material (R_f 0.76) and formation of a single product (R_f 0.28). The mixture was de-gassed and filtered through Celite, washing the pad and flask with methanol. The combined filtrates were concentrated *in vacuo* to afford a pale yellow paste. This was re-dissolved in 1:1 pyridine/acetic anhydride (4 mL) and stirred at rt. TLC analysis (9:1 ethyl acetate/methanol) after 15 h showed consumption of starting material (R_f 0.00) and formation of a single product (R_f 0.26). The mixture was concentrated *in vacuo* and the resulting pale yellow residue purified *via* flash column chromatography on silica gel (95:5 to 90:10 ethyl acetate/methanol) to afford the title compound as a clear, straw-coloured syrup (38.0 mg, 65%); $[\alpha]_D^{25} +25.6$ (c 1.00 in CHCl₃); $\nu_{\max}$ (thin film): 1656 (s, NHCOCH₃), 1738 (s, OCOCH₃); δ_H (CDCl₃, 400 MHz): 1.98, 2.04, 2.09, 2.14 (12H, 4 x s, 4 x RCOCH₃), 2.36 (3H, s, H7), 2.89-2.96 (1H, ddd, H1, $J_{1,NH}$ 3.2, $J_{1,2}$ 7.5, J_{gem} 14.4), 3.20-3.24 (1H, ddd, H2, $J_{2,1'}$ 3.1, $J_{2,3}$ 6.4, $J_{2,1}$ 7.4), 3.26-3.30 (1H, dd, H4, $J_{4,3}$ 6.7, $J_{4,5}$ 9.4), 3.55-3.61 (1H, ddd, H1',

$J_{1',2}$ 3.1, $J_{1',\text{NH}}$ 8.1, J_{gem} 14.4), 3.91-3.96 (1H, dd, H6, $J_{6,5}$ 5.8, J_{gem} 12.2), 4.23-4.27 (1H, dd, H6', $J_{6',5}$ 3.1, J_{gem} 12.2), 5.28-5.31 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 6.5), 5.40-5.44 (1H, ddd, H5, $J_{5,6'}$ 3.1, $J_{5,6}$ 5.8, $J_{5,4}$ 9.4), 6.14-6.15 (1H, a-d, NHAc, $J_{\text{NH},1'}/J_{\text{NH},1''}$ 5.3); δ_{C} (CDCl₃, 100 MHz): 20.8, 20.9, 21.2, 23.3 (4 x RCOCH₃), 37.1 (C1), 43.7 (C7), 62.8 (C6), 65.4 (C4), 67.0 (C2), 67.8 (C3), 71.2 (C5), 170.2, 170.5, 170.7, 171.4 (4 x RCOCH₃); m/z (ESI+ve): 345 ([M + H]⁺, 97%), 367 ([M + Na]⁺, 100%), 711 ([2M + Na]⁺, 99%); HRMS m/z (ESI+ve): found 367.1469 ([M + Na]⁺); C₁₅H₂₄N₂NaO₇ requires 367.1476.

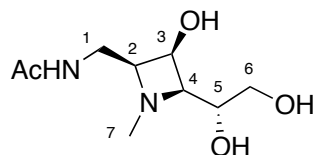
1-Acetamido-3,5,6-tri-*O*-acetyl-2-*N*-benzyl-1,2,4-trideoxy-2,4-imino-L-iditol 2.231



The azido tri-acetate **2.229** (63.6 mg, 0.157 mmol) and palladium on activated charcoal (10 wt. %, 8.3 mg, 0.008 mmol) were placed in a flask with ethanol (4 mL), the contents de-gassed and purged with argon, then de-gassed and charged with hydrogen and the resulting mixture stirred at rt. TLC analysis (1:1 cyclohexane/ethyl acetate) after 2 h showed consumption of starting material (R_f 0.69) and formation of only baseline material. The mixture was filtered through Celite, the pad and flask washed with methanol and the combined filtrates concentrated *in vacuo* to afford the crude amine as a clear syrup. This material was re-dissolved in dichloromethane (4 mL), pyridine (900 μ L, 11.13 mmol) and acetic anhydride (450 μ L, 4.77 mmol) added and the contents stirred at rt. TLC analysis (9:1 ethyl acetate/methanol) after 48 h showed a small amount of starting material (R_f 0.47) and one major product (R_f 0.59). 4-(Dimethylamino)pyridine (20 mg, 0.164 mmol) was then added. TLC analysis after a further 20 h showed reaction completion. The mixture was concentrated *in vacuo* and co-evaporated with toluene (3 x 5 mL) to afford an orange oil. Purification *via* flash column chromatography on silica gel (ethyl acetate to 95:5 ethyl acetate/methanol) afforded the title compound as a clear, very pale yellow syrup (58.7 mg, 89%); $[\alpha]_D^{25} +7.7$ (c 1.25 in CHCl₃); ν_{max}

(thin film): 1657 (s, NHCOCH₃), 1742 (s, OCOCH₃); δ_{H} (CDCl₃, 400 MHz): 1.85, 2.03, 2.06, 2.14 (12H, 4 x s, 4 x RCOCH₃), 2.68-2.74 (1H, ddd, H1, $J_{1,\text{NH}}$ 4.1, $J_{1,2}$ 5.9, J_{gem} 14.4), 3.26-3.32 (1H, ddd, H1', $J_{1',2}$ 3.8, $J_{1',\text{NH}}$ 7.1, J_{gem} 14.4), 3.43-3.45 (1H, a-dt, H2, $J_{2,1'}$ 3.9, $J_{2,1}/J_{2,3}$ 6.4), 3.55-3.59 (1H, dd, H4, $J_{4,3}$ 7.2, $J_{4,5}$ 9.4), 3.56-3.59 (1H, d, H7, J_{gem} 13.2), 3.88-3.91 (1H, d, H7', J_{gem} 13.2), 3.93-3.98 (1H, dd, H6, $J_{6,5}$ 6.3, J_{gem} 12.2), 4.25-4.29 (1H, dd, H6', $J_{6',5}$ 2.9, J_{gem} 12.2), 5.39-5.42 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 7.0), 5.52-5.57 (1H, ddd, H5, $J_{5,6'}$ 2.9, $J_{5,6}$ 6.3, $J_{5,4}$ 9.4), 5.81-5.83 (1H, m, NHAc), 7.24-7.35 (5H, m, 5 x ArH); δ_{C} (CDCl₃, 100 MHz): 20.8, 20.8, 21.1, 23.1 (4 x RCOCH₃), 38.1 (C1), 61.4 (C7), 62.9 (C6), 63.6 (C4), 65.5 (C2), 66.6 (C3), 71.0 (C5), 127.9 (*p*-ArCH), 128.8, 128.9 (2 x *o*-ArCH and 2 x *m*-ArCH), 137.8 (*ipso*-ArC), 170.0, 170.6, 170.8, 171.0 (4 x RCOCH₃); m/z (ESI+ve): 421 ([M + H]⁺, 96%), 443 ([M + Na]⁺, 100%), 863 ([2M + Na]⁺, 98%); HRMS m/z (ESI+ve): found 443.1783 ([M + Na]⁺); C₂₁H₂₈N₂NaO₇ requires 443.1789.

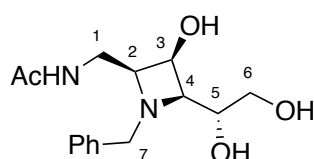
1-Acetamido-1,2,4-trideoxy-2,4-imino-2-*N*-methyl-L-iditol **2.232**



Sodium methoxide (6 mg, 0.011 mmol) was added to a stirred solution of tri-*O*-acetate **2.230** (38 mg, 0.110 mmol) in methanol (2 mL) at rt. TLC analysis (9:1 ethyl acetate/methanol) after 18 h showed consumption of starting material (R_f 0.26) and only baseline material; TLC analysis (14:3:1:1:1 ethanol/pyridine/*n*-butanol/acetic acid/water) showed a single product (R_f 0.61). The mixture was concentrated *in vacuo* and the residue loaded onto a column of Dowex 50WX8 (H⁺) ion exchange resin. The column was flushed with water, ethanol, more water and then eluted with 2M aqueous ammonia. The ammoniacal fraction was concentrated *in vacuo* to afford the title compound as a clear, straw-coloured syrup (22.4 mg, 93%); $[\alpha]_D^{25} +3.8$ (c 0.79 in MeOH); ν_{max} (neat): 1561 (s, NHCOCH₃), 1621 (s, NHCOCH₃), 2462 (br, unknown), 3298 (br, OH); δ_{H} (D₂O, 500 MHz): 1.98 (3H, s, H7), 2.40 (3H, s, NHCOCH₃), 3.05-3.08 (1H, dd, H4, $J_{4,3}$ 6.2, $J_{4,5}$ 8.8),

3.19-3.23 (1H, m, H2), 3.26-3.30 (1H, dd, H1, $J_{1,2}$ 5.4, J_{gem} 13.8), 3.42-3.47 (1H, dd, H1', $J_{1',2}$ 8.5, J_{gem} 13.8), 3.45-3.48 (1H, dd, H6, $J_{6,5}$ 6.5, J_{gem} 11.9), 3.61-3.64 (1H, dd, H6', $J_{6',5}$ 3.3, J_{gem} 11.9), 3.98-4.01 (1H, ddd, H5, $J_{5,6'}$ 3.3, $J_{5,6}$ 6.5, $J_{5,4}$ 9.0), 4.43-4.45 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 5.6); δ_{C} (D₂O, 125 MHz): 22.4 (C7), 37.9 (C1), 44.4 (NHCOCH₃), 63.5 (C6), 65.7 (C3), 67.7 (C2), 69.7 (C4), 72.1 (C5), 175.1 (NHCOCH₃); m/z (ESI+ve): 219 ([M + H]⁺, 72%), 241 ([M + Na]⁺, 100%); HRMS m/z (ESI+ve): found 241.1158 ([M + Na]⁺); C₉H₁₈N₂NaO₄ requires 241.1159.

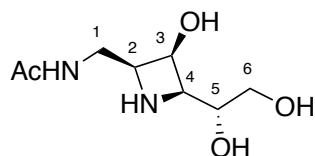
1-Acetamido-2-*N*-benzyl-1,2,4-trideoxy-2,4-imino-L-iditol **2.233**



Sodium methoxide (1.5 mg, 0.028 mmol) was added to a stirred solution of tri-*O*-acetate **2.231** (58.0 mg, 0.138 mmol) in methanol (5 mL) at rt. TLC analysis (9:1 ethyl acetate/methanol) after 18 h showed consumption of starting material (R_f 0.59) and formation of a single product (R_f 0.06); TLC analysis (14:3:1:1:1 ethanol/pyridine/*n*-butanol/acetic acid/water) showed a single product (R_f 0.70). The mixture was concentrated *in vacuo* and the resulting pale yellow syrup loaded onto a column of Dowex 50WX8 (H⁺) ion exchange resin. The column was flushed sequentially with water, methanol, more water and then eluted with 2M aqueous ammonia. The ammoniacal fraction was concentrated *in vacuo* to afford the title compound as a clear, colourless syrup (37.2 mg, 92%); $[\alpha]_D^{25}$ -44.1 (c 1.15 in MeOH); ν_{max} (neat): 1620 (s, NHCOCH₃), 2462 (br, unknown), 3307 (br, OH); δ_{H} (D₂O, 400 MHz): 1.81 (3H, s, NHCOCH₃), 2.61-2.66 (1H, dd, H1, $J_{1,2}$ 4.9, J_{gem} 13.8), 3.18-3.23 (1H, dd, H1', $J_{1',2}$ 8.3, J_{gem} 13.8), 3.30-3.34 (1H, dd, H4, $J_{4,3}$ 6.5, $J_{4,5}$ 8.7), 3.40-3.45 (1H, m, H2), 3.44-3.49 (1H, dd, H6, $J_{6,5}$ 6.5, J_{gem} 11.8), 3.52-3.55 (1H, d, H7, J_{gem} 12.2), 3.61-3.65 (1H, dd, H6', $J_{6',5}$ 3.3, J_{gem} 11.8), 4.05-4.08 (1H, d, H7', J_{gem} 12.2), 4.06-4.11 (1H, ddd, H5, $J_{5,6'}$ 3.4, $J_{5,6}$ 6.6, $J_{5,4}$ 8.7), 4.40-4.43 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 6.0), 7.36-7.46 (5H, m, 5 x ArH); δ_{C} (D₂O, 100 MHz): 22.4 (NHCOCH₃), 38.2 (C1), 62.4 (C7), 63.6 (C6), 65.2 (C3), 65.6 (C2), 68.2 (C4), 71.7 (C5),

128.7 (*p*-ArCH), 129.3, 130.9 (2 x *o*-ArCH and 2 x *m*-ArCH), 137.1 (*ipso*-ArC), 174.7 (NHCOCH₃); *m/z* (ESI+ve): 295 ([M + H]⁺, 100%), 317 ([M + Na]⁺, 97%), 611 ([2M + Na]⁺, 41%); HRMS *m/z* (ESI+ve): found 317.1464 ([M + Na]⁺); C₁₅H₂₂N₂NaO₄ requires 317.1472.

1-Acetamido-1,2,4-trideoxy-2,4-imino-L-iditol 2.219



The L-iditol **2.233** (23.3 mg, 0.079 mmol), palladium on activated charcoal (10 wt. %, 16.7 mg, 0.016 mmol) and ammonium formate (49.7 mg, 0.788 mmol) were placed in a flask with anhydrous methanol (3 mL) and the contents stirred at reflux under argon atmosphere. TLC analysis (14:3:1:1:1 ethanol/pyridine/*n*-butanol/acetic acid/water) after 1.5 h showed consumption of starting material (*R_f* 0.75) and formation of a single product (*R_f* 0.60). The mixture was allowed to cool, filtered through Celite and the pad and flask washed with methanol. The combined filtrates were concentrated *in vacuo* to afford the crude material as a clear syrup, which was loaded onto a column of Dowex 50WX8 (H⁺) ion exchange resin. The column was flushed sequentially with water, ethanol, more water and then eluted with 2M aqueous ammonia. The ammoniacal fraction was concentrated *in vacuo* to afford the title compound as a clear, colourless syrup (16.2 mg, 100%) [characterised as the HCl salt]; $[\alpha]_D^{25}$ -0.3 (*c* 0.66 in MeOH); $\nu_{\max}$ (neat): 1628 (s, NHCOCH₃), 2452 (br, unknown), 3267 (br, OH and NH); δ_H (D₂O, 400 MHz): 2.01 (3H, s, NHCOCH₃), 3.56-3.61 (1H, dd, H₆, *J*_{6,5} 5.0, *J*_{gem} 12.1), 3.59-3.65 (1H, dd, H₁, *J*_{1,2} 6.1, *J*_{gem} 14.8), 3.68-3.72 (1H, dd, H_{6'}, *J*_{6',5} 3.5, *J*_{gem} 12.1), 3.75-3.80 (1H, dd, H_{1'}, *J*_{1',2} 8.0, *J*_{gem} 14.8), 4.26-4.30 (1H, ddd, H₅, *J*_{5,6'} 3.5, *J*_{5,6} 5.0, *J*_{5,4} 7.5), 4.54-4.58 (1H, m, H₄), 4.62-4.68 (1H, a-dt, H₂, *J*_{2,1}/*J*_{2,3} 6.1, *J*_{2,1'} 8.0), 4.74-4.77 (1H, a-t, H₃, *J*_{3,2}/*J*_{3,4} 6.2); δ_C (D₂O, 100 MHz): 22.3 (NHCOCH₃), 36.6 (C₁), 62.4 (C₂), 63.1 (C₆), 64.0 (C₄), 66.4 (C₃), 67.4 (C₅), 175.9 (NHCOCH₃); *m/z* (ESI+ve): 205 ([M + H]⁺, 100%); HRMS *m/z* (ESI+ve): found 227.0999 ([M + Na]⁺); C₈H₁₆N₂NaO₄ requires 227.1002.

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Chapter 3. Homonojirimycin Diastereomers

3.1 Introduction

The 2,6-dideoxy-2,6-imino-D-*glycero*-L-*gulo*-heptitol better known as α -homonojirimycin (α -HNJ, Figure 3.1) is a naturally occurring piperidine iminosugar that was briefly mentioned in Chapter 1. It was originally isolated from *Omphalea diandra* (Euphorbiaceae) in 1988,¹ and can be considered as the α -hydroxymethyl glycoside of the D-*gluco* configured deoxynojirimycin (DNJ). As one would expect from its structure, it was found to exhibit highly potent inhibitory activity against various α -glucosidases. Since its original isolation, α -HNJ and its fifteen stereoisomers (as well as their glycosides) have been isolated from a variety of plant sources,²⁻¹⁰ and/or synthesised by numerous disparate methodologies.^{7,11-27} When compared with their 1-deoxy analogues (e.g. α -HNJ vs DNJ), these compounds are often found to retain similarly potent inhibition of the glycosidases whose natural substrates they directly mimic, but furthermore they commonly exhibit greater enzyme selectivity.^{12,20,21} As such they have collectively been of interest as potential drugs for the treatment of a range of diseases,²⁸ including diabetes, cancer and lysosomal storage disorders.

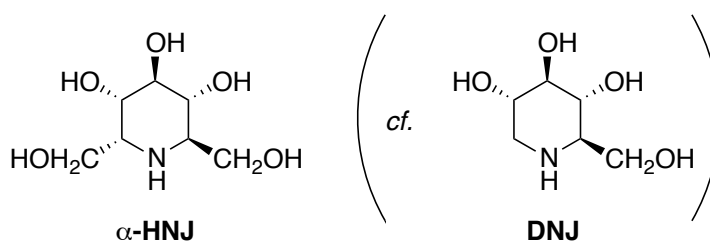


Figure 3.1: Structural comparison of α -HNJ and DNJ

Of those synthetic strategies already reported for the preparation of these compounds, some are quite lengthy or low yielding, or are not readily amenable to the synthesis of all members of the family. Furthermore, two of the stereoisomers have previously only ever been prepared as part of

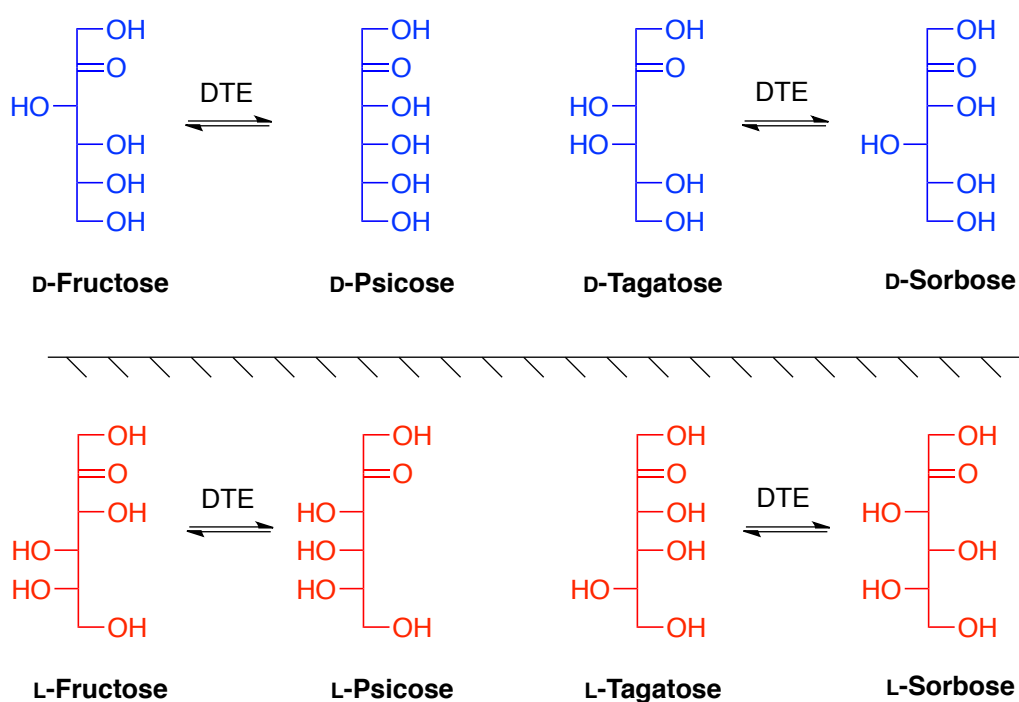
diastereomeric mixtures,²³ and many more have not been fully characterised nor undergone a consistent regime of biological testing. This chapter describes the conception and one half of the execution of a highly concise and divergent strategy for the preparation of all sixteen stereoisomers of α -HNJ, utilising traditional chemical synthesis in tandem with a particular set of “green” biotechnological transformations which enable the interconversion of sugars in water without the need for protecting groups. This latter methodology has hitherto never been adapted for the synthesis of iminosugars, and it is the author’s hope that the results herein will demonstrate the merits of this approach.

3.1.1 Biotechnological transformations of monosaccharides

Of the twenty-four hexoses and twelve pentoses, relatively few are cheaply and readily available from commercial sources: the hexoses D-glucose, -galactose, -fructose, -mannose, -tagatose and L-sorbose; and the pentoses D-arabinose, -ribose, -xylose and L-arabinose. Although some of the remaining rare sugars can be prepared synthetically with relative ease, access to many of them in this manner remains highly impractical in the laboratory, let alone on industrial scale. The increased availability of these rare sugars would provide a boon for industrial use as well as for many avenues of research – not least for groups such as ours which utilise them as chiral-pool starting materials – and as such there is a clear need for the development of robust methods with which to prepare them. Professor Ken Izumori (Rare Sugar Research Center, Kagawa University, Japan) and his group have pioneered a general strategy for the large-scale interconversion of monosaccharides using a combination of enzyme-mediated oxidations, reductions, epimerisations and isomerisations; the collective overall process has been termed “Izumoring” and has been utilised for the production of all tetroses, pentoses and hexoses.²⁹⁻³¹ Each of the key enzymatic transformations involved are outlined below with illustrative examples, and the complete picture for the Izumoring strategy thereby exemplified in the preparation of all thirty-four six-carbon sugars.

3.1.1.1 Epimerisation of ketoses

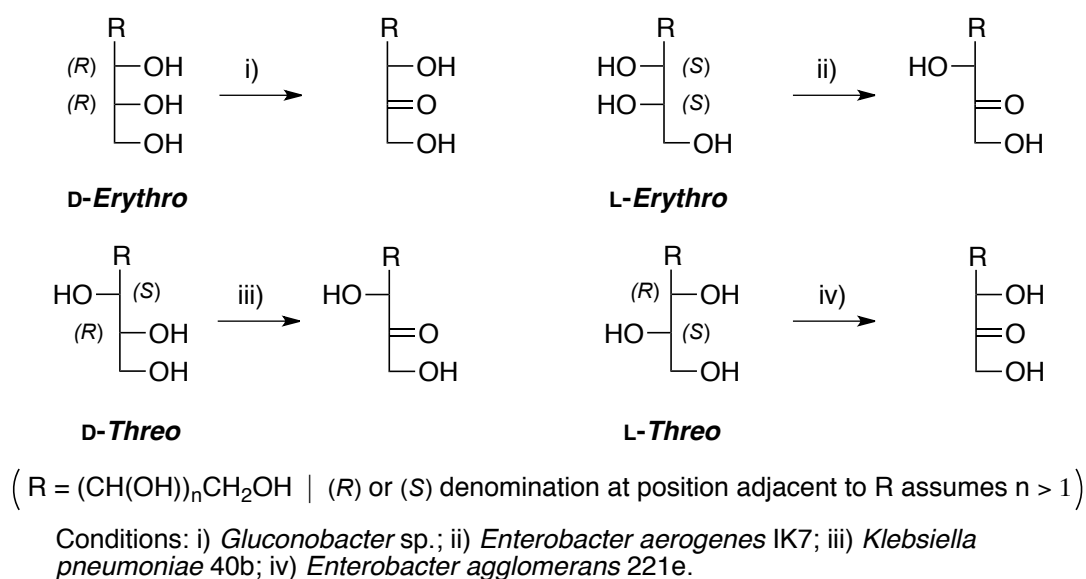
D-Tagatose-3-epimerase (DTE)³²⁻³⁴ is an enzyme that was first isolated by Izumori from *Pseudomonas* sp. ST-24, and can be employed to catalyse the completely regioselective epimerisation of the stereogenic centre alpha to the carbonyl functionality of a ketose, thereby generating an equilibrium mixture of C3-epimers; the enzyme is typically used in an immobilised form on solid support to facilitate its recovery and the isolation of the products. Its sugar-specific name is somewhat misleading however, as the enzyme is in fact highly promiscuous; there is no ketose hitherto reported which cannot be epimerised by DTE. Thus, all the ketohexoses have been interconverted using this methodology (Scheme 3.1): D-psicose from D-fructose,³⁵ D-sorbose from D-tagatose,³⁶ and the corresponding reverse reactions on the enantiomeric pairs.³⁷ Furthermore, the process is clearly amenable to large scale manufacture; approximately 20 kg of D-psicose has been produced from the DTE equilibration of D-fructose in a continuous reactor, with consumption of the equilibrium mass of D-fructose by baker's yeast avoiding the need for product separation.³⁸



Scheme 3.1: The interconversion of ketohexoses *via* epimerisation by DTE

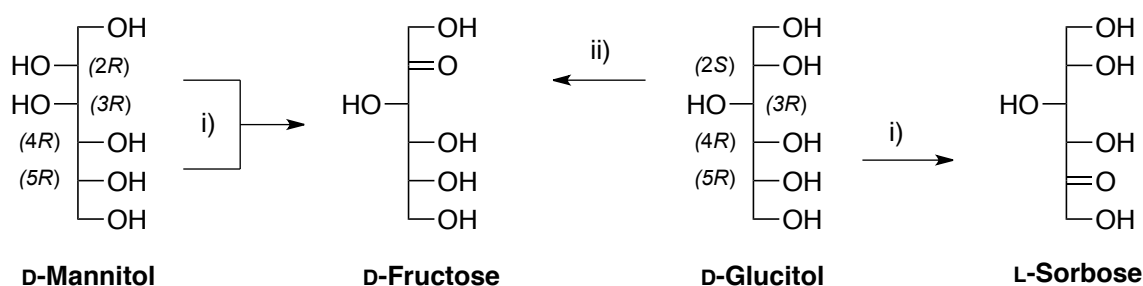
3.1.1.2 The interconversion of polyols and ketoses

In contrast to the DTE reactions which utilise isolated enzyme, the oxidation of carbohydrate polyols to their corresponding ketoses in the Izumoring strategy is carried out with microbial whole cells, and furthermore the reactions go to completion. These microbes contain polyol dehydrogenases (PDHs) which, under aerobic conditions, are able to oxidise the stereogenic centres adjacent to the chain termini of a polyol, e.g. at C2 or C5 of a hexitol. The oxidations, however, are not indiscriminate; PDHs from different microbes are able to recognise the differing absolute configurations of the vicinal diol moieties adjacent to the chain termini (e.g. C2/C3 or C5/C4 of a hexitol) and thus oxidise one or both ends of a polyol with complete stereoselectivity. To achieve full flexibility of substrate differentiation one therefore requires the ability to selectively oxidise any one of the four possible absolute configurations of the diol motif, and indeed this system has been realised *via* the use of four different microbes (Scheme 3.2):³⁹ *Gluconobacter* strains recognise the *R,R* (D-erythro) motif;⁴⁰ *Enterobacter aerogenes* IK7 the *S,S* (L-erythro) motif;⁴¹ *Klebsiella pneumoniae* 40b the *R,S* (D-threo) motif;⁴² and *Enterobacter agglomerans* 221e the *S,R* (L-threo) motif.⁴³ The same microbes catalyse the reverse reactions under oxygen-limited conditions.



Scheme 3.2: The selective oxidation of the four possible diol configurations by microbes

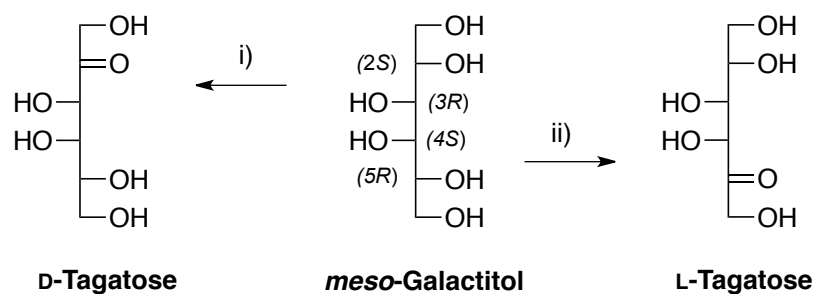
The following examples illustrate some of the myriad possible uses of the different microbes for ketose production. D-Mannitol possesses *R,R* diol motifs at both C2/C3 and C5/C4, and is thus *C*₂ symmetric (Scheme 3.3). *Gluconobacter* sp. can therefore oxidise either C2 or C5, either of which results in the formation of D-fructose.⁴⁰ In contrast, D-glucitol possesses differing diol motifs of *S,R* at C2/C3 and *R,R* at C5/C4; the action of *Gluconobacter* sp. therefore results in the specific oxidation of C5 and the formation of L-sorbose,⁴⁰ whereas the action of *Enterobacter agglomerans* 221e results in the specific oxidation of C2 and the formation of D-fructose.



Conditions: i) *Gluconobacter* sp.; ii) *Enterobacter agglomerans* 221e.

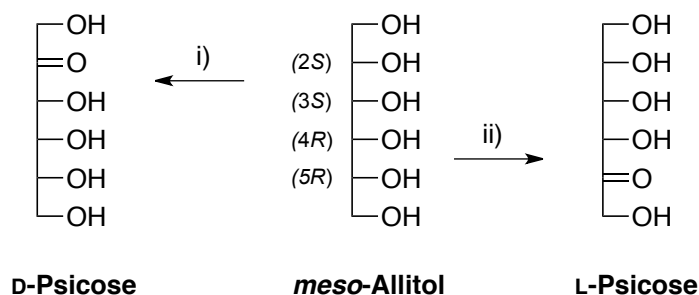
Scheme 3.3: The *R,R* and *S,R* oxidations D-mannitol and D-glucitol

meso-Galactitol possesses an *S,R* diol motif at C2/C3 and an *R,S* motif at C5/C4, and is therefore able to serve as a precursor to both enantiomers of tagatose: the action of *Enterobacter agglomerans* 221e results in the oxidation of C2 and the formation of D-tagatose,⁴³ whereas the action of *Klebsiella pneumoniae* 40b results in the oxidation of C5 and the formation of L-tagatose⁴² (Scheme 3.4). Finally, a similar situation is found with *meso*-allitol, which possesses an *S,S* motif at C2/C3 and an *R,R* motif at C5/C4: the action of *Enterobacter aerogenes* IK7 results in the oxidation of C2 and the formation of D-psicose,⁴⁴ whereas the alternative use of *Gluconobacter* sp. results in the oxidation of C5 and the formation of L-psicose (Scheme 3.5).



Conditions: i) *Enterobacter agglomerans* 221e; ii) *Klebsiella pneumoniae* 40b.

Scheme 3.4: The *S,R* and *R,S* oxidations of *meso*-galactitol



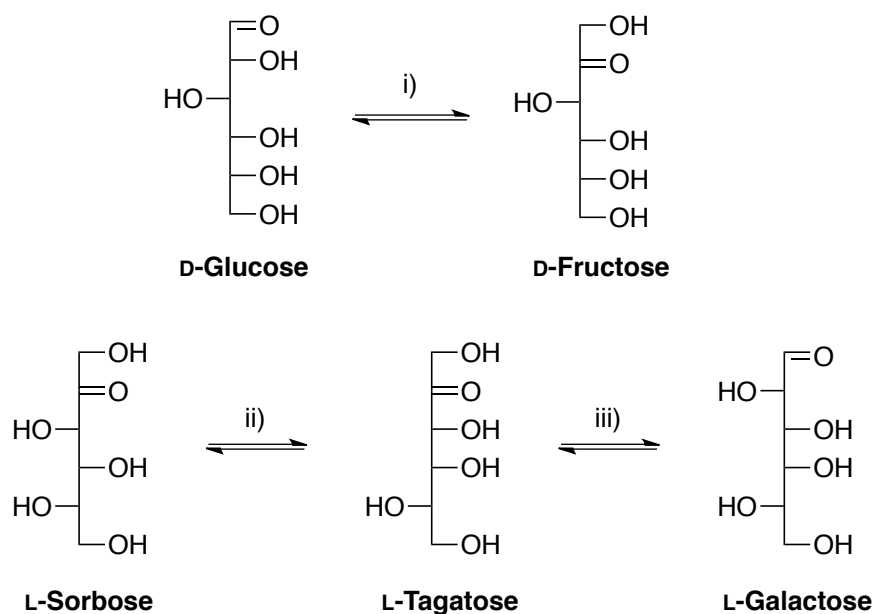
Conditions: i) *Enterobacter aerogenes* IK7; ii) *Gluconobacter* sp.

Scheme 3.5: The *S,S* and *R,R* oxidations of *meso*-allitol

3.1.1.3 Isomerisation of ketoses and aldoses

The final key process involved in the Izumoring strategy is the equilibration of ketose/aldose pairs, as carried out by various aldose isomerases.^{31,45-52} D-Xylose isomerase (EC 5.3.1.5), so-called because it catalyses the isomerisation of D-xylose with D-xylulose, can also catalyse the isomerisation of other ketose/aldose pairs, for example D-glucose with D-fructose (Scheme 3.6). As a result it is one of the most used enzymes industrially,⁴⁸ such as for the mass production of high-fructose corn syrup. Another enzyme which sees prolific use is L-rhamnose isomerase, as it is able to isomerise many ketose/aldose pairs of tetroses, pentoses and hexoses.⁵¹ For example, it can be used for the production of the rare sugar L-galactose from L-tagatose, which in turn is derived from the commonly available L-sorbose *via* DTE epimerisation (Scheme 3.6).⁵⁰ The relevance of aldose

isomerases within the Izumoring framework is therefore that they ultimately provide the only means (other than chemical) of accessing certain aldoses. Furthermore, the aldoses thus obtained can be reduced and the resulting polyols then act as precursors to other sugars *via* further Izumoring manipulations, thereby increasing the number of potential approaches to a particular desired sugar.



Conditions: i) D-xylose isomerase; ii) DTE; iii) L-rhamnose isomerase

Scheme 3.6: Example uses of aldose isomerases

3.1.1.4 The complete Izumoring picture

The collective potential of the biotransformations discussed above is made clearer when one considers the case of an entire family of sugars, as with the illustrated example of the hexoses (Figure 3.2).[†] The ten hexitols, eight ketohexoses and sixteen aldohexoses can thus be arranged in concentric rings (hence “Izumoring”) interlinked by a web of biotransformations mediated by DTE, PDHs (oxidoreductases) and aldose isomerases; additionally, the non-essential reduction of the aldohexoses (white arrows) can be carried out by aldose reductases or alternatively by chemical

[†] Figure from Izumori’s most recent review.³¹ It is reproduced here with the author’s permission.

methods. The hexose family is further subdivided with D-sugars in the blue zone, L-sugars in the pink zone, and the four hexitols possessing either *meso* or dual D- and L-configurations appearing in the yellow zone. Notably, the strategy allows four possible entrances (orange arrows) into the unnatural L-sugars from D-sugars, and any one member of the family can be prepared from any other member in no more than six steps. To illustrate, this allows for the large-scale preparation of L-altrose (a sugar with a current market value of approximately £1000/g) from the abundant D-fructose in only four steps: DTE converts D-fructose to D-psicose; reduction by *Enterobacter aerogenes* IK7 in oxygen-limited conditions furnishes *meso*-allitol; oxidation by *Gluconobacter* sp. then forms L-psicose; and finally reaction with L-rhamnose isomerase yields L-altrose.

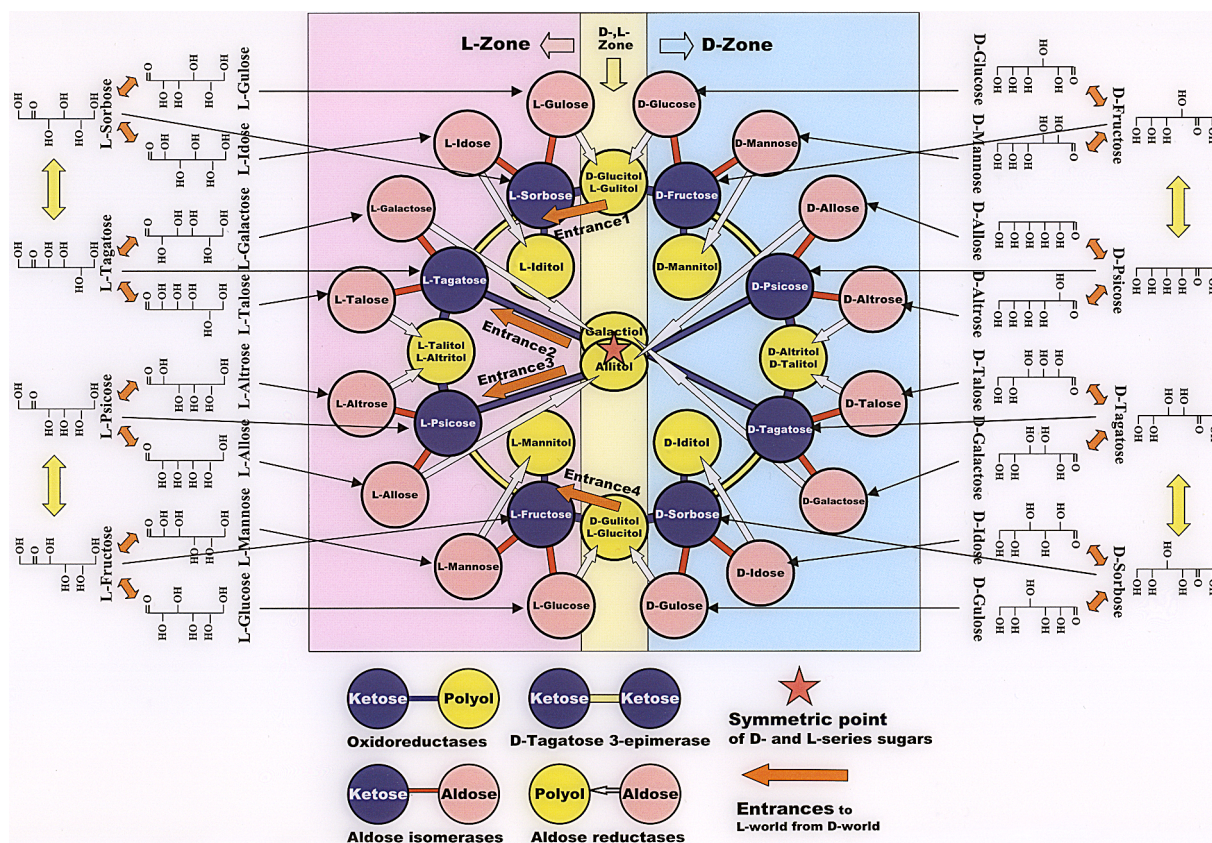


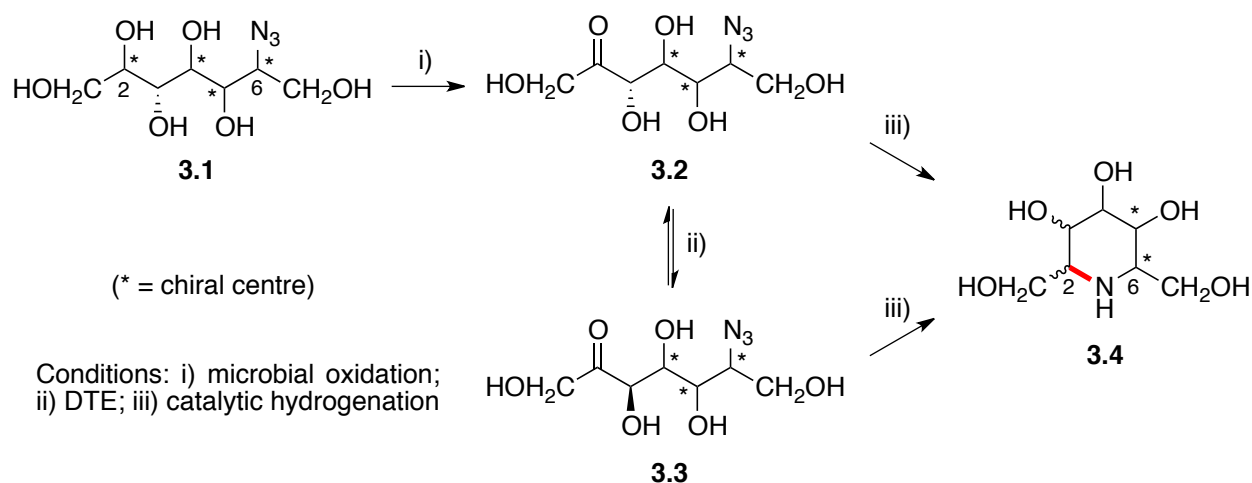
Figure 3.2: The Hexose Izumoring

More recently, these Izumoring principles have also been successfully applied to the interconversions of modified monosaccharides: thus far it has been shown that deoxy sugars can be substrates for DTE,^{39,53} PDHs,^{39,41,53,54} and aldose isomerases;⁵⁵ and methyl-branched sugars are

substrates for both DTE and PDHs.^{56,57} Furthermore, at the onset of this project there was some limited precedent for the interconversion of azido-substituted monosaccharides in a similar fashion, as demonstrated by the PDH oxidation of 1-deoxy-1-azido-D-galactitol, followed by conversion of the resulting azidoketose to 6-deoxy-6-azido-L-galactose by an aldose isomerase.⁵⁸ One of the abiding principle objectives of the Fleet-Izumori collaboration is to probe the boundaries of the Izumoring methodology, in terms of both its substrate tolerance and potential applications. To this end we wished to see if this preliminary success with an azidohexitol could be extended and applied more generally to transformations of other azido-monosaccharide substrates, and if so then investigate the feasibility of using this methodology for the synthesis of all stereoisomers of a particular iminosugar.

3.1.2 Strategy for the preparation of HNJ diastereomers

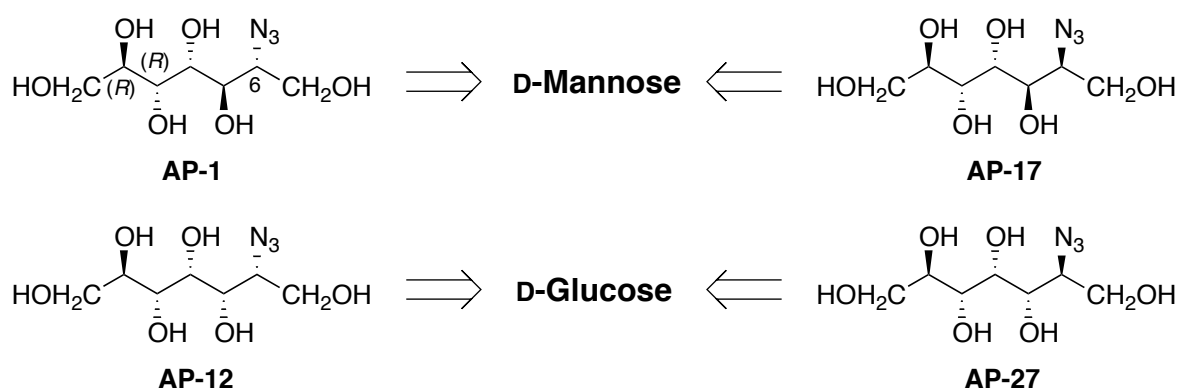
We realised that if the Izumoring transformations could be successfully employed on 6-azidoheptitol substrates, this would potentially allow for the preparation of α -HNJ and its fifteen stereoisomers (2,6-iminoheptitols). The key concepts of the strategy are outlined in Scheme 3.7 (only the relevant stereochemistry is shown for the sake of clarity). Microbial oxidation of a generic



Scheme 3.7: Strategic outline for 2,6-iminoheptitol syntheses

6-azidoheptitol **3.1** would allow access to the generic 6-azidoketoheptose **3.2**. Equilibration of **3.2** by DTE would then allow access to the C3-epimer **3.3**, and catalytic hydrogenation of both **3.2** and **3.3** would effect azide reduction and concomitant intramolecular reductive amination, furnishing four separate 2,6-iminoheptitols **3.4** (newly formed bond shown in red). The appeal of such an approach becomes clear when one considers that it allows for the preparation of all sixteen of the 2,6-iminoheptitols from only four of the possible thirty-two 6-azidoheptitols, as only the configurations at C5 and C6 are critical. The stereocentre at C2 is destroyed during the microbial oxidation, and the configuration at this position in the product is ultimately determined by the diastereoselectivity of the reductive amination. The configuration at C3 will either be conserved from the starting material, or inverted by the action of DTE. Finally, although the stereocentre at C4 of the 6-azidoheptitols cannot be manipulated *via* Izumoring transformations, its configuration is nonetheless unimportant as it becomes a pseudo-asymmetric centre in the products; i.e. either configuration at C4 can furnish all the 2,6-iminoheptitols due to their collective symmetry.

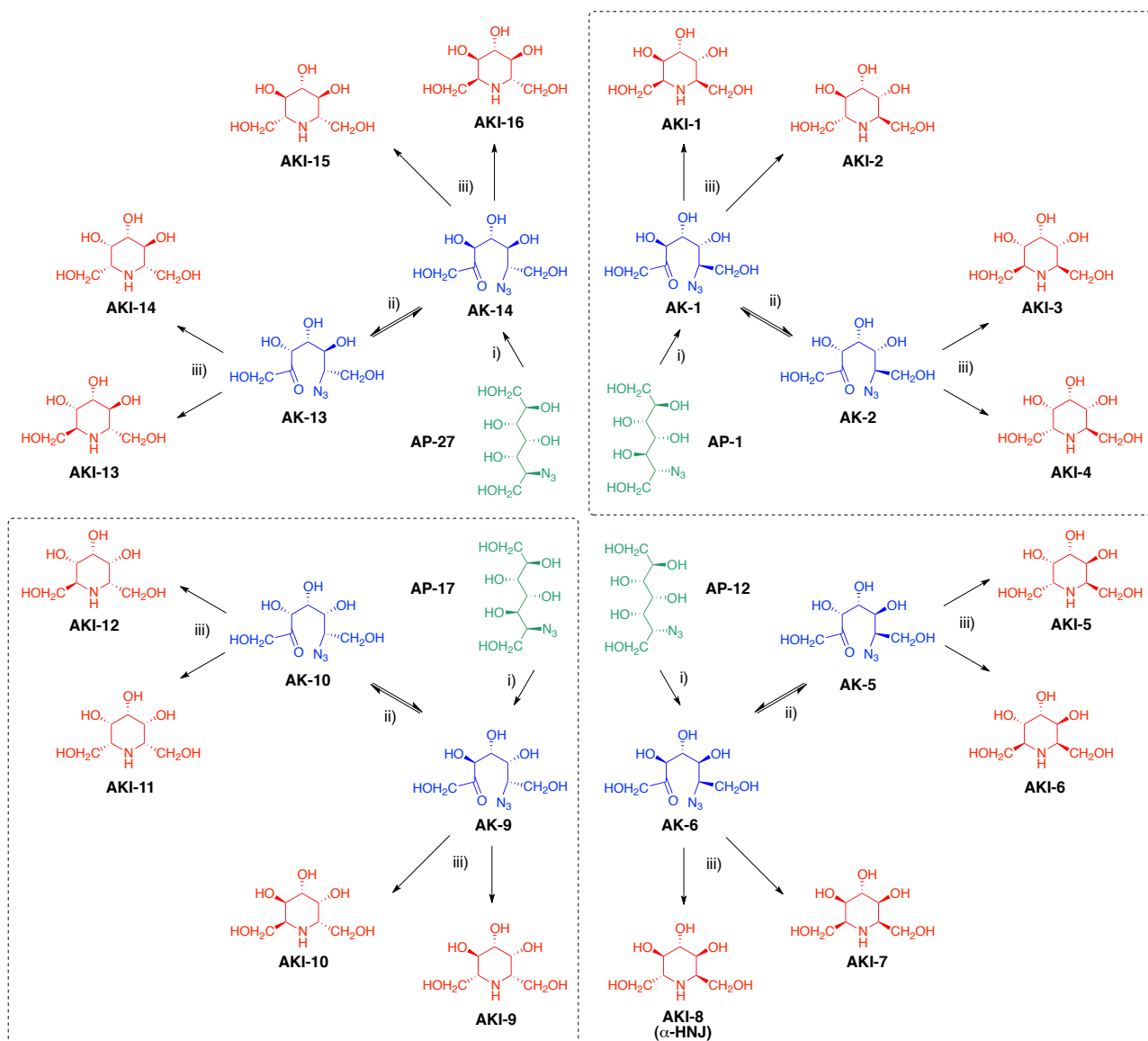
One possible set of 6-azidoheptitols with the four required absolute configurations at C5/C6 can be conceived of as being prepared from the cheap and abundant D-glucose and D-mannose, such that all the stereochemical information of the starting materials is preserved (Scheme 3.8). Thus, the



Scheme 3.8: Access to a set of four suitable 6-azidoheptitols

6-azidoheptitols **AP-1** and **AP-17** could be prepared from D-mannose, and their C5-epimers **AP-12** and **AP-27** respectively could be similarly obtained from D-glucose. Furthermore, all of these 6-

azidoheptitols possess an *R,R* diol moiety at C2/C3, and would thus only require the employment of a single microbe (*Gluconobacter* sp.) for their oxidations. Given these particular 6-azidoheptitol starting materials, the following complete strategy can be constructed (Scheme 3.9). **AP-1**, **AP-12**



Conditions: i) *Gluconobacter* sp.; ii) DTE; iii) catalytic hydrogenation.

Scheme 3.9: 2,6-iminoheptitols from 6-azidoheptitols derived from D-mannose (boxed) and D-glucose

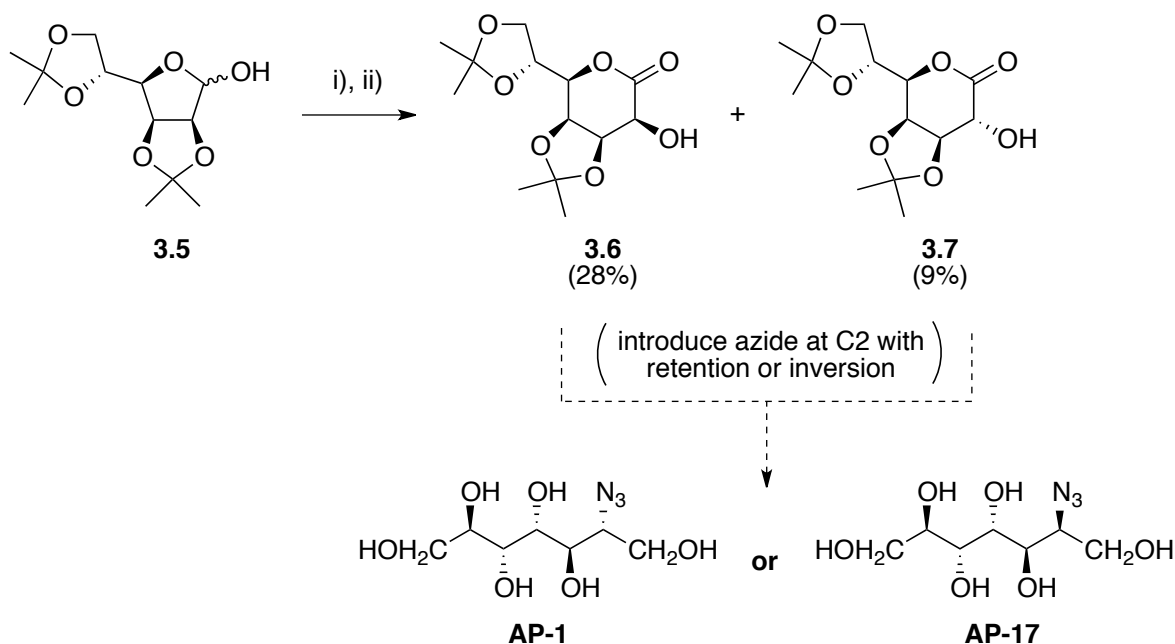
AP-17 and **AP-27** (in green) would provide access to the 6-azidoketoheptoses **AK-1**, **AK-2**, **AK-5**, **AK-6**, **AK-9**, **AK-10**, **AK-13** and **AK-14** (in blue) through a combination of microbial oxidations and DTE epimerisations. Finally, catalytic hydrogenation of these 6-azidoketoheptoses should furnish all sixteen of the 2,6-iminoheptitols, designated as **AKI-1** to **AKI-16** (in red); the ratio of

products thus obtained in each case will be subject to the diastereoselectivity of the reductive aminations.

The work described in this chapter is concerned with the preparation and subsequent manipulation of the 6-azidoheptitols **AP-1** and **AP-17** prepared from D-mannose (boxed quadrants, Scheme 3.9), and the corresponding 2,6-iminoheptitol targets **AKI-1**, **AKI-2**, **AKI-3**, **AKI-4**, **AKI-9**, **AKI-10**, **AKI-11** and **AKI-12**. The analogous syntheses of the 6-azidoheptitols **AP-12** and **AP-27** derived from D-glucose were carried out by a group colleague in parallel to the work herein; those procedures and the efforts from our collaborators towards the remaining 6-azidoketoheptoses and 2,6-iminoheptitols are described in his thesis.⁵⁹

3.2 Syntheses of the 6-azidoheptitols AP-1 and AP-17⁶⁰

The Kiliani ascension of diacetone-D-mannose **3.5** has been previously carried out within the Fleet group on scales of up to 5 kg,⁶¹ and therefore provided ready access to large quantities of the two epimeric D-glycero-D-talo- and D-glycero-D-galacto- heptono-1,5-lactones **3.6** and **3.7** respectively (Scheme 3.10). Either of these lactones represent viable seven-carbon scaffolds with which to prepare both **AP-1** or **AP-17**, as both could potentially result from introduction of an azide group at C2 of **3.6** or **3.7** with either retention or inversion of configuration. The reaction of sodium azide with α -triflates of certain 1,5- and 1,4-lactones of monosaccharides has been shown to proceed with net retention of configuration at C2,^{62,63} favouring the formation of the more stable all



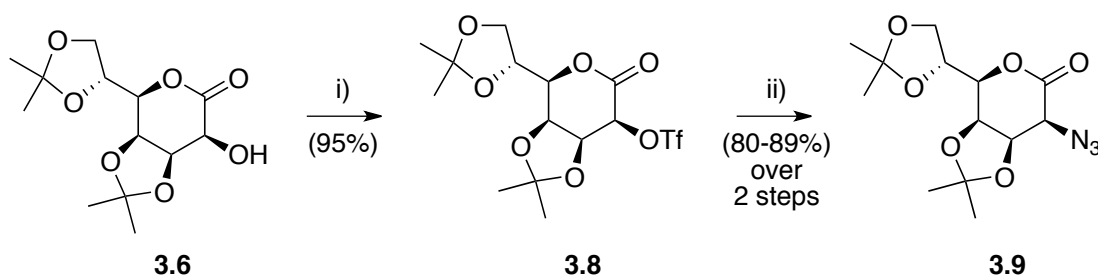
Reagents and conditions: i) NaCN, H₂O, 50 °C, 6 h; ii) H₂SO₄, pH 3

Scheme 3.10: Two possible starting materials for the 6-azidoheptitol syntheses

cis-configured products under thermodynamically-controlled conditions (discussed in more detail below). The reaction of the C2-triflate of **3.6** with sodium azide is amongst those already reported, and has been shown to furnish the corresponding azide with retention of configuration.⁶² This *talo*

azide possesses the correct absolute configuration which corresponds to **AP-1**. Furthermore, the C6-epimer **AP-17** could similarly be prepared *via* introduction of azide with a single inversion of configuration at C2 of **3.6**, whereas its analogous preparation from **3.7** would require two sequential inversions of configuration at C2. The lactone **3.6** was thus chosen as the more appropriate starting material for the project.

Treatment of the *D-glycero-D-talo*-heptono-1,5-lactone **3.6** with trifluoromethanesulfonic anhydride and pyridine in dichloromethane at -30 °C effected highly efficient esterification of the C2 hydroxyl, furnishing the crystalline triflate **3.8** in 95% isolated yield after column chromatography (Scheme 3.11). Subsequent stirring of **3.8** with sodium azide in *N,N*-dimethylformamide at room temperature allowed for the efficient installation of azide with retention of configuration at C2, affording the azidolactone **3.9** as the sole product; this two-step procedure was performed several times and successfully scaled up to 45 g of hydroxylactone **3.6**, giving yields of 80-89% over two steps (the procedure had previously only been performed on up to 3 g scale, and in a two-step yield of 76%).⁶²

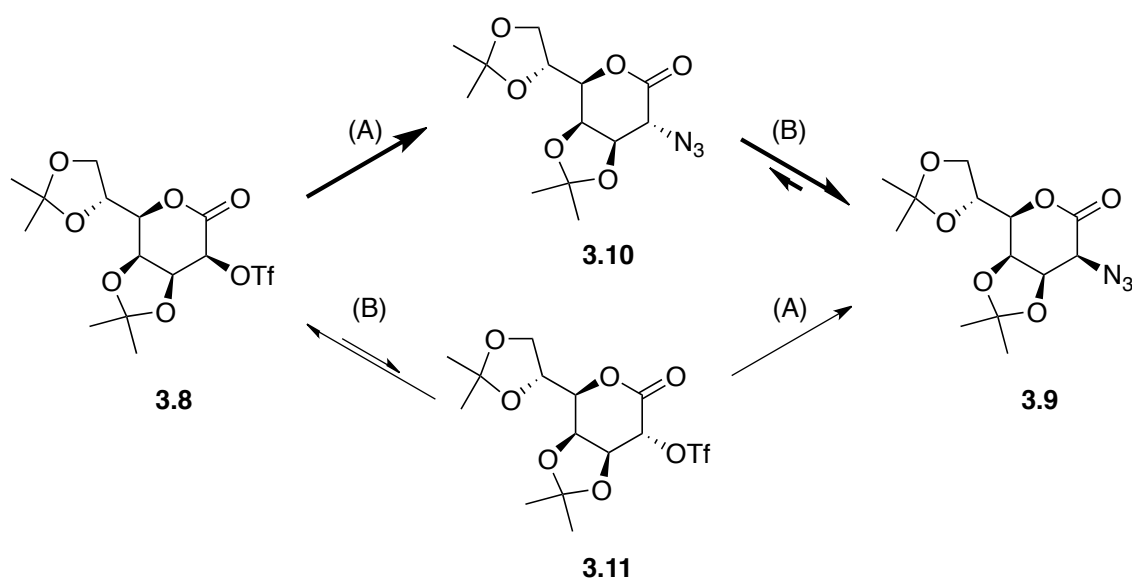


Reagents and conditions: i) $\text{ Tf}_2\text{O}$, pyr., DCM, -30 °C, 2 h; ii) NaN_3 , DMF, rt, 16-20 h.

Scheme 3.11: Introduction of azide with retention of configuration

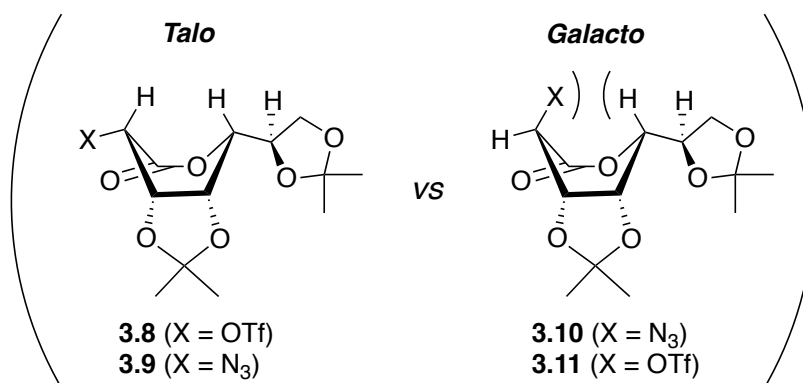
The explanation for this result lies with the appreciable base-sensitivity of the α -protons in such azido- and triflate-functionalised lactones, and their corresponding susceptibility to epimerisation. Thus, under the weakly basic reaction conditions two possible routes to the product *talo*

azidolactone **3.9** are possible (Scheme 3.12): either the initial nucleophilic substitution of the *talo* triflate **3.8** by sodium azide, forming the intermediate *galacto* azidolactone **3.10**, followed by its epimerisation; or the initial epimerisation of the *talo* triflate **3.8**, forming the intermediate *galacto* triflate **3.11** which then undergoes nucleophilic substitution by sodium azide. However, deuterium



(A) = Nucleophilic displacement by azide

(B) = Epimerisation by azide

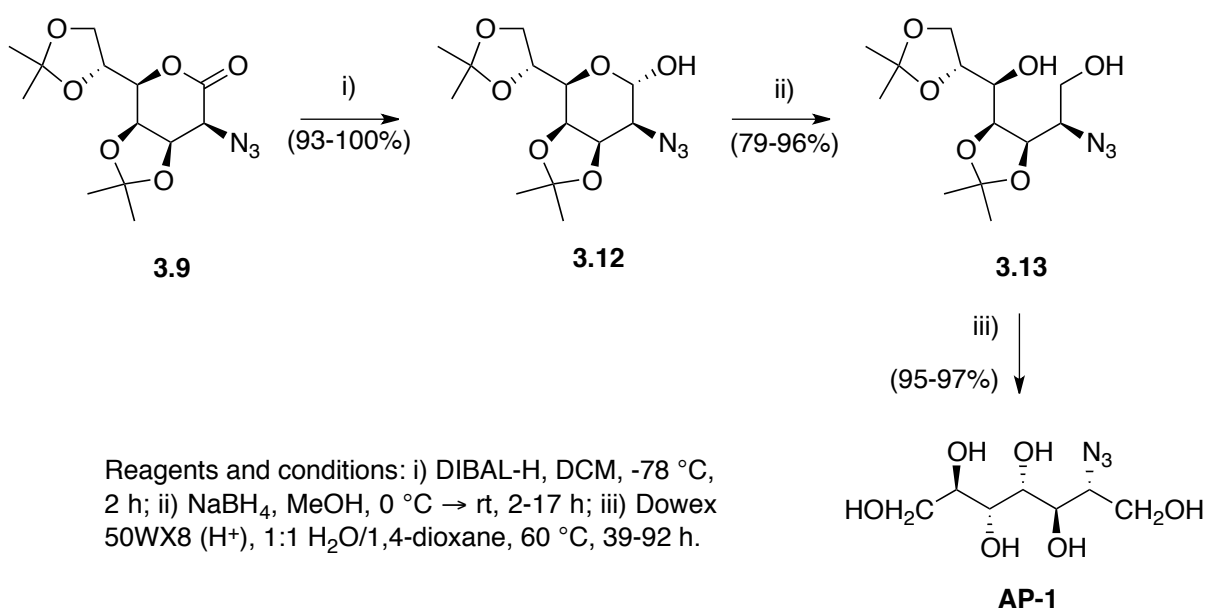


Scheme 3.12: Rationale for the formation of the *talo* azidolactone

labelling experiments⁶² reveal that the predominant course of the reaction is *via* the former route (bold arrows), and this can be rationalised by examination of the participant's boat structures: i.e. the *galacto* configured triflate **3.10** or azidolactone **3.11** are both thermodynamically less stable than their respective *talo* configured counterparts **3.8** and **3.9** as the substituents at C2 occupy the more sterically hindered flagpole position. This therefore manifests in slower nucleophilic

substitution of *galacto* triflate **3.11** by azide in comparison to its equilibration with the *talo* triflate **3.8**, and secondly in the rapid epimerisation of the *galacto* azidolactone **3.10** (once formed) into the *talo* azidolactone **3.9**.

The remaining requirements for the synthesis of **AP-1** were thus the reduction of the lactone functionality in **3.9**, and the hydrolysis of the acetonide groups. In some cases lactones may be readily reduced directly to their corresponding diols using lithium borohydride in etheric solution. However, very brief attempts at reducing **3.9** in this fashion were met with sluggish, incomplete reductions and the formation of unidentified side products, which were assumed to be due to base-induced epimerisation and/or elimination; problems which have been encountered before in similar azidolactone systems.⁶⁴⁻⁶⁶ This approach was therefore rapidly eschewed in favour of a safer, two-stage reduction *via* the corresponding lactol. Thus, in a minor modification to a known procedure,¹³ the azidolactone **3.9** was first reduced in a highly efficient manner with diisobutylaluminium hydride in dichloromethane at -78 °C (Scheme 3.13), affording the lactol **3.12** solely as the α -anomer (as confirmed by X-ray crystallographic analysis, Figure 3.3)⁶⁷ in yields of 93-100% on scales up to 41 g. Subsequent treatment of **3.12** with sodium borohydride in methanolic solution at 0 °C with slow warming to room temperature furnished the diol **3.13** in yields of 79-96% on up to



Scheme 3.13: Completion of the synthesis of the first 6-azidoheptitol

40.9 g scale. Finally, controlled acid hydrolysis of the acetonide functionality in **3.13** was carried out using Dowex 50WX8 (H⁺ form) ion exchange resin in a 1:1 mixture of water and 1,4-dioxane at 60 °C, affording the first 6-azidoheptitol target **AP-1** in excellent yields of 95-97% on scales of up to 32.5 g. This synthetic procedure thus allowed for the relatively concise preparation of over 30 g of **AP-1** (after recrystallisation) in an average yield of 68-69% over five steps from the starting lactone **3.6**.

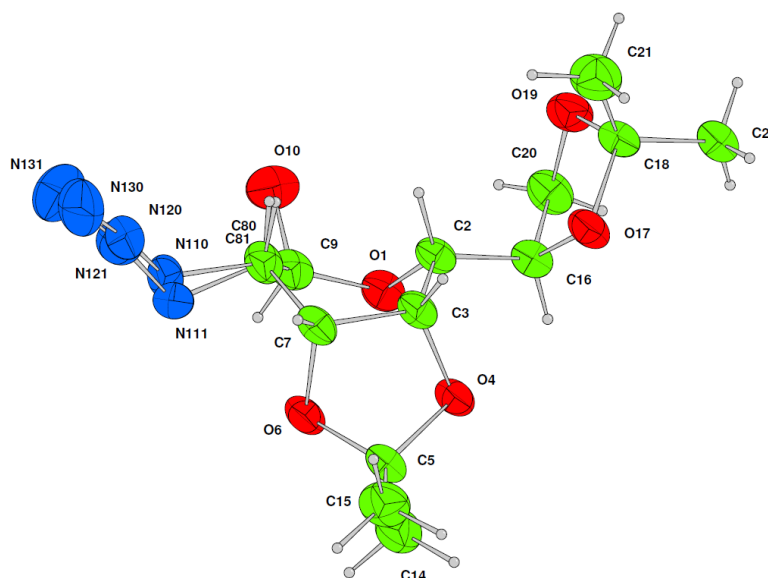
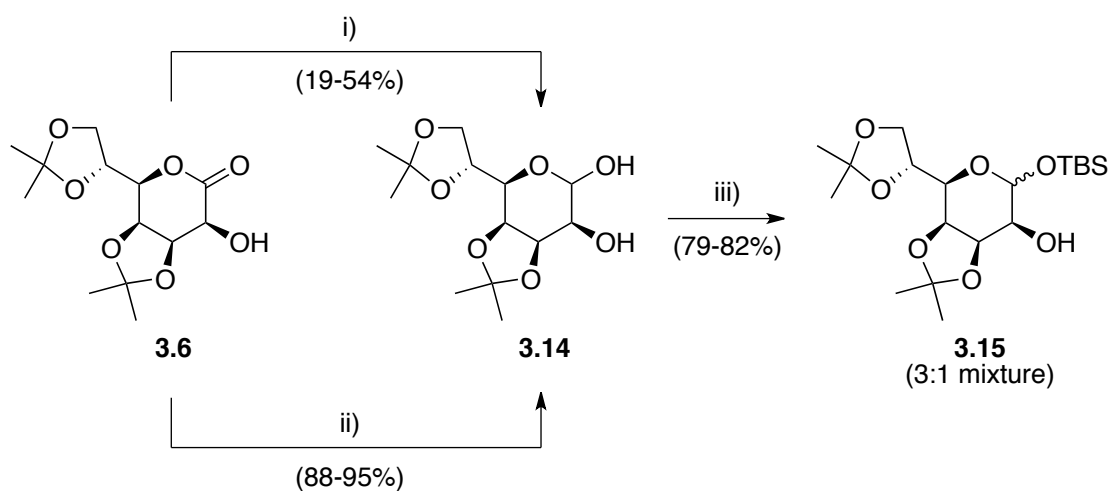


Figure 3.3: Single crystal X-ray structure of azidolactol **3.12**

The preparation of the second target 6-azidoheptitol **AP-17** proved to be more challenging. The isolation of the kinetic *galacto* azidolactone product **3.10** (Scheme 3.12) from the reaction of triflate **3.8** has been reported when using sub-stoichiometric amounts of sodium azide at room temperature in *N,N*-dimethylformamide.⁶² However, it had only been performed on a 200 mg scale and with a poor yield of 40%, and there were therefore doubts about the suitability of this approach towards the larger scale preparations necessary for this project. Indeed, brief attempts at repeating this reaction on similar scale proved unsuccessful, with only very low yields (~10%) of the *galacto* azidolactone **3.10** being obtained due to the equilibration to the more stable *talo* product **3.9** being too rapid under the reaction conditions, even at cryogenic temperatures. Furthermore, even if yields

for this procedure could have been optimised to acceptable levels, there remained serious concerns about whether epimerisation of this highly labile azidolactone could be avoided during the subsequent necessary reductions. In order to circumvent these problems and potential pitfalls, an alternative approach was envisaged involving lactone reduction and protection of the resulting lactol prior to azide introduction.

Early attempts at reducing lactone **3.6** with diisobutylaluminium hydride in dichloromethane at $-78\text{ }^{\circ}\text{C}$ resulted in sluggish reactions and only poor to moderate yields of the desired lactol **3.14** (Scheme 3.14), presumably due to the initial quenching of the reagent by the unprotected hydroxyl, thus forming an aluminium alkoxide intermediate which is deactivated towards reduction. Much more successful results were obtained with the alternative use of borane-tetrahydrofuran complex as the reducing agent;⁶⁸ under these conditions sugar lactones can be fully reduced to their open-chain forms, however with careful reaction monitoring and optimisation of the reagent stoichiometry



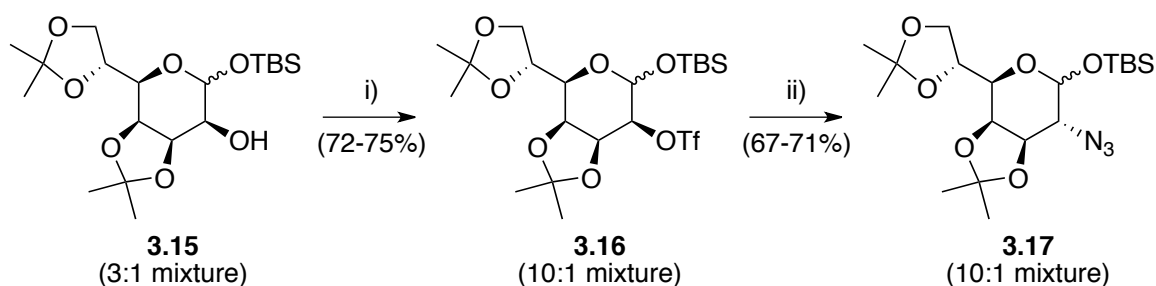
Reagents and conditions: i) DIBAL-H, DCM, $-78\text{ }^{\circ}\text{C}$, 2-21 h; ii) $\text{BH}_3 \cdot \text{THF}$, THF, $0\text{ }^{\circ}\text{C} \rightarrow \text{rt}$, 45-105 min; iii) TBSCl, imid., DMF, rt, $3\text{ \AA}$ molecular sieves, 3-21 h.

Scheme 3.14: Preparation of the protected *talo* lactol intermediate

over-reduction was largely avoided and the lactol **3.14** reliably formed in excellent yields of 88-95% on scales of up to 30 g. The lactol was formed almost exclusively as a single anomer, however the boat structure adopted by these D-*glycero*-D-*talo* systems meant its identity (α or β) could not be

assigned with confidence by NMR analysis as the $J_{1,2}$ values for either would be similar, and attempts at growing a crystal for X-ray analysis were unsuccessful. Nonetheless, one would expect it to be the α -anomer on the grounds of its similarity to the azidolactol **3.12** (Figure 3.3). Finally, selective protection of the anomeric hydroxyl in **3.14** was accomplished by treatment with *tert*-butyldimethylsilyl chloride and imidazole in *N,N*-dimethylformamide, furnishing the anomeric mixture of silyl pyranosides **3.15** in good yields of 79-82% after optimisation.

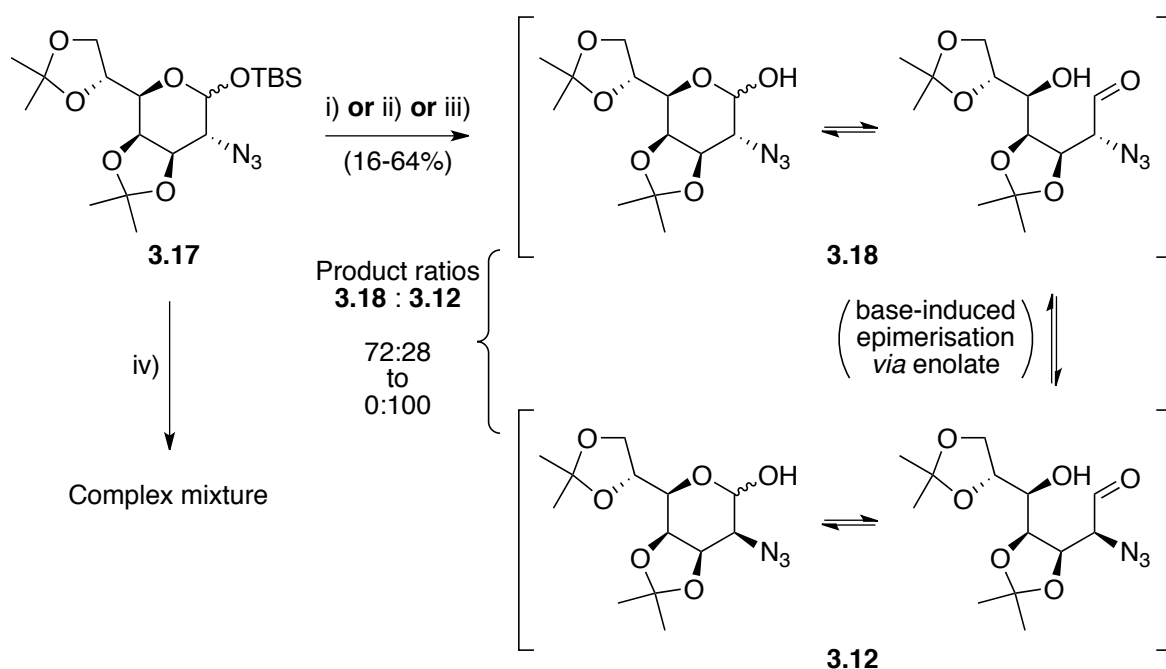
Treatment of the silyl pyranosides **3.15** with trifluoromethanesulfonic anhydride and pyridine in dichloromethane at temperatures between -40 and -30 °C afforded the corresponding mixture of triflates **3.16** which were isolated in good yields of 72-75% after column chromatography (Scheme 3.15); the reaction goes to completion, therefore the different anomeric ratio obtained in the product would appear to indicate that the minor triflate is less stable. Subsequent treatment of **3.16** with sodium azide in *N,N*-dimethylformamide at room temperature resulted in no reaction even after 24 hours, indicating substantial deactivation towards nucleophilic attack (perhaps due to the steric bulk of the TBS group). However, successful displacement was achieved at elevated temperatures, furnishing the desired mixture of *galacto* azides **3.17** in optimised yields of 67-71% when run at 65 °C; reactions run at higher temperatures resulted in reduced yields due to an increased level of decomposition.



Reagents and conditions: i) $\text{ Tf}_2\text{O}$, pyr., DCM, -40 $\leftrightarrow$ -30 °C, 1.5-2.5 h;
 ii) NaN_3 , DMF, 65 °C, 20-64 h

Scheme 3.15: Introduction of azide with inversion of configuration

The synthetic plan at this point had been the selective removal of the silyl group and reduction of the resulting lactol, thereby affording the corresponding di-acetonide-protected azidoheptitol which could be easily purified prior to final acid hydrolysis (in an analogous fashion to the synthesis of **AP-1**). However, despite the absence of a lactone functionality the base-sensitivity of the *galacto* configuration remained problematic, as shown by the desilylation of **3.17** using several well-established fluoride sources⁶⁹ under a variety of conditions (Scheme 3.16). Treatment with the ubiquitous tetra-*n*-butylammonium fluoride in either tetrahydrofuran or dichloromethane, or with ammonium fluoride in refluxing methanol,⁷⁰ led to successful cleavage of the TBS group but



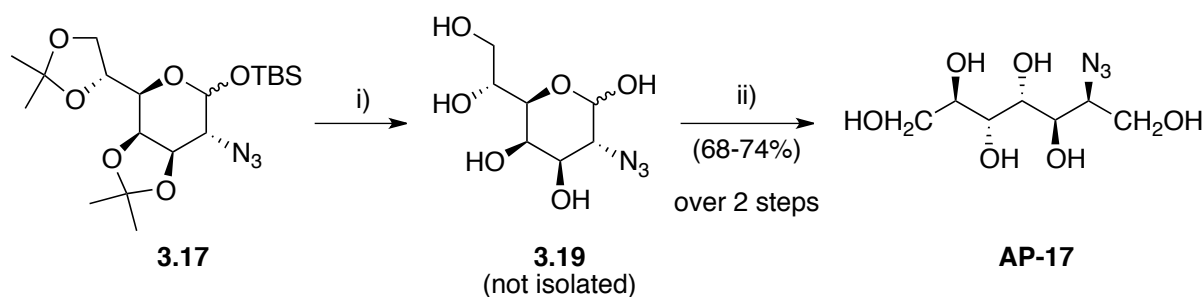
Reagents and conditions: i) TBAF, THF, rt, 18-20 h; ii) TBAF.3H₂O, DCM, rt, 42 h; iii) NH₄F, MeOH, reflux, 3-16 h; iv) pyr.(HF)_x, THF, rt, 22 h.

Scheme 3.16: Epimerisation during fluoride-mediated desilylation

afforded only poor to moderate yields of a mixture of the *galacto* and *talo* azides **3.18** and **3.12** respectively as a result of unavoidable epimerisation due to the basicity of the reagents. Hydrofluoric acid buffered with pyridine in a solution of tetrahydrofuran has been previously employed as a less basic source of fluoride for the removal of silyl groups;⁷¹ however, subjection of

3.17 to these conditions led to a complex, inseparable mixture of products which was not investigated further.

With the use of basic reagents being clearly untenable, attention was then turned to an alternative strategy with which to complete the synthesis; namely that of one-pot acidic hydrolysis of the silyl and acetonide groups, followed by reduction of the resulting unprotected azidolactol. However, although the acetonides in **3.17** were removed easily enough under acidic conditions, the TBS group proved remarkably resistant to hydrolysis: numerous attempts at cleavage with aqueous trifluoroacetic acid at room temperature, *para*-toluenesulfonic acid in aqueous acetone, or Dowex 50WX8 (H⁺ form) resin in aqueous or methanolic mixtures at temperatures up to 90 °C all failed to effect TBS removal. The successful complete deprotection of **3.17** was eventually achieved using the more forceful conditions of 2:1 trifluoroacetic acid/water at 60 °C for almost 2 days, affording the unprotected azidolactol **3.19**, which without isolation was then treated with excess aqueous sodium borohydride to afford the target 6-azidoheptitol **AP-17** in yields of 68-74% over two steps (Scheme 3.17). Notably, no formation of the epimeric **AP-1** was detected during this process, indicating that the *galacto* system is very stable with regard to acid-mediated epimerisation. The completed synthetic protocol thus allowed for the preparation of almost 5 g of pure **AP-17** in total from several batch runs, with an optimised overall yield of 27% over six steps from the starting lactone **3.6**.

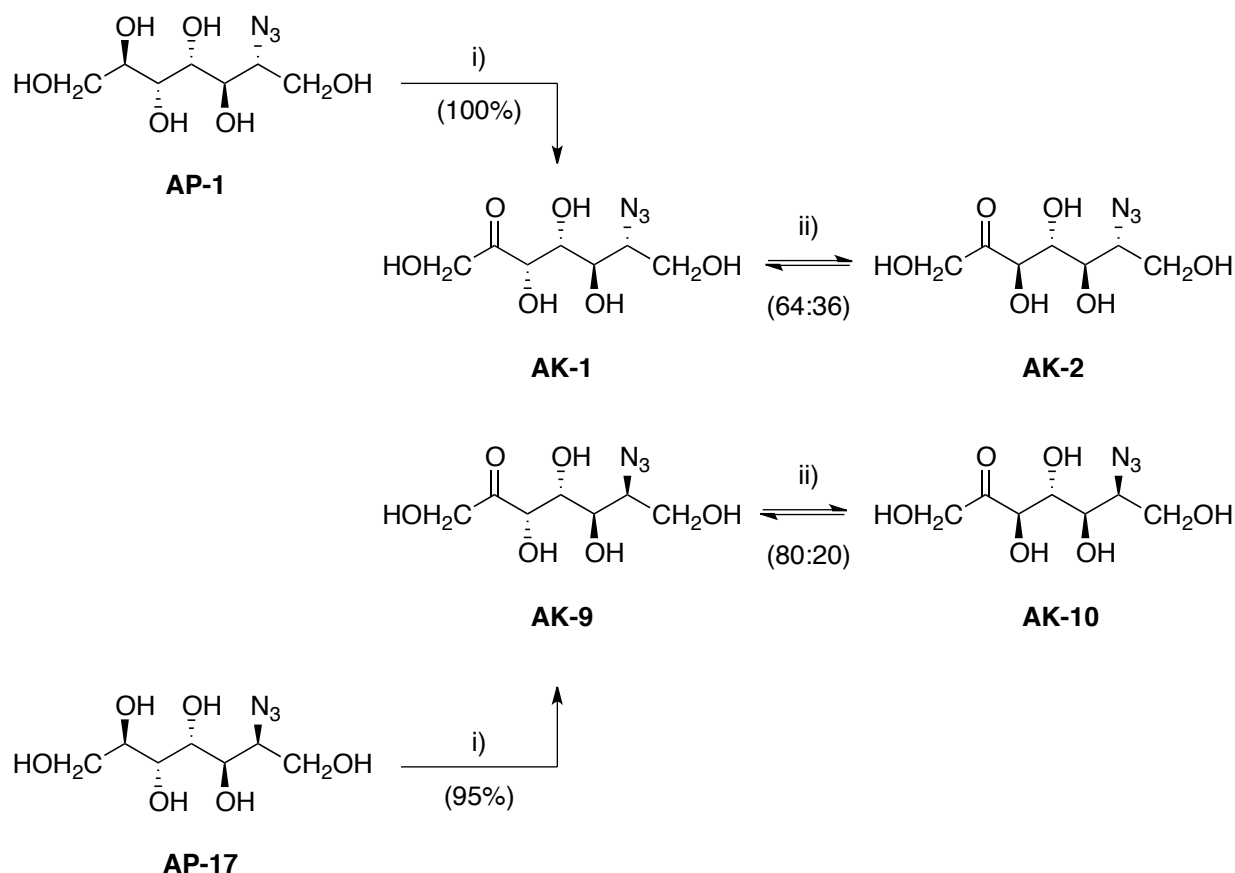


Reagents and conditions: i) 2:1 TFA/H₂O, 60 °C, 39-45 h; ii) NaBH₄, H₂O, rt, 16 h.

Scheme 3.17: Completion of the synthesis of the second 6-azidoheptitol

3.3 Preparation and analysis of the 6-azidoketoheptoses⁶⁰

The 6-azidoheptitols **AP-1** and **AP-17** prepared above were sent to Professor Ken Izumori and his group, who carried out the following biotransformations. As previously discussed in Section 3.1.2, both **AP-1** and **AP-17** possess *R,R* diol motifs at C2/C3 and one would thus expect them to be substrates for *Gluconobacter* sp. In particular, the strain *Gluconobacter thailandicus* NBRC 3254 had been previously employed for the oxidation of unnatural deoxy- and methyl-branched monosaccharide polyols,^{53,56,57} and this augured well for its employment in oxidising the 6-azidoheptitol substrates herein. Much to our satisfaction, this microbe was indeed found to be active on both **AP-1** and **AP-17**, furnishing the 6-azidoketoheptoses **AK-1** and **AK-9** in 100% and 95% yield respectively (Scheme 3.18). Furthermore, D-tagatose-3-epimerase (DTE) was also found to be



Reagents and conditions: i) *Gluconobacter thailandicus* NBRC 3254, H₂O, 30 °C, 20-30 h; ii) DTE, H₂O, 40 °C, 24 h.

Scheme 3.18: Preparation of the four 6-azidoketoheptoses

active on both of these substrates, thereby providing access to their C3 epimers **AK-2** and **AK-10** respectively; the equilibrium ratios thus obtained for the epimeric pairs were 64:36 **AK-1** : **AK-2**, and 80:20 **AK-9** : **AK-10**.

These four 6-azidoketoheptoses were sent to Dr Mark Wormald (Oxford Glycobiology Institute), who carried out their analysis and structural elucidation using a number of NMR experiments (^1H , ^{13}C , COSY, HSQC, HMBC, HSQC-TOCSY and ROESY) in combination with 1D ^1H spectral simulations provided by gNMR (Cherwell Scientific Publishing). Each of the 6-azidoketoheptoses were found to predominantly exist in their furanose forms, with spin systems for open chain or other forms present at less than 2% (Figure 3.4).[‡] The recorded ^1H and ^{13}C data for **AK-1**, **AK-2**, **AK-9** and **AK-10** is shown in Tables 3.1 and 3.2, and their ^1H NMR traces in Figure 3.5.

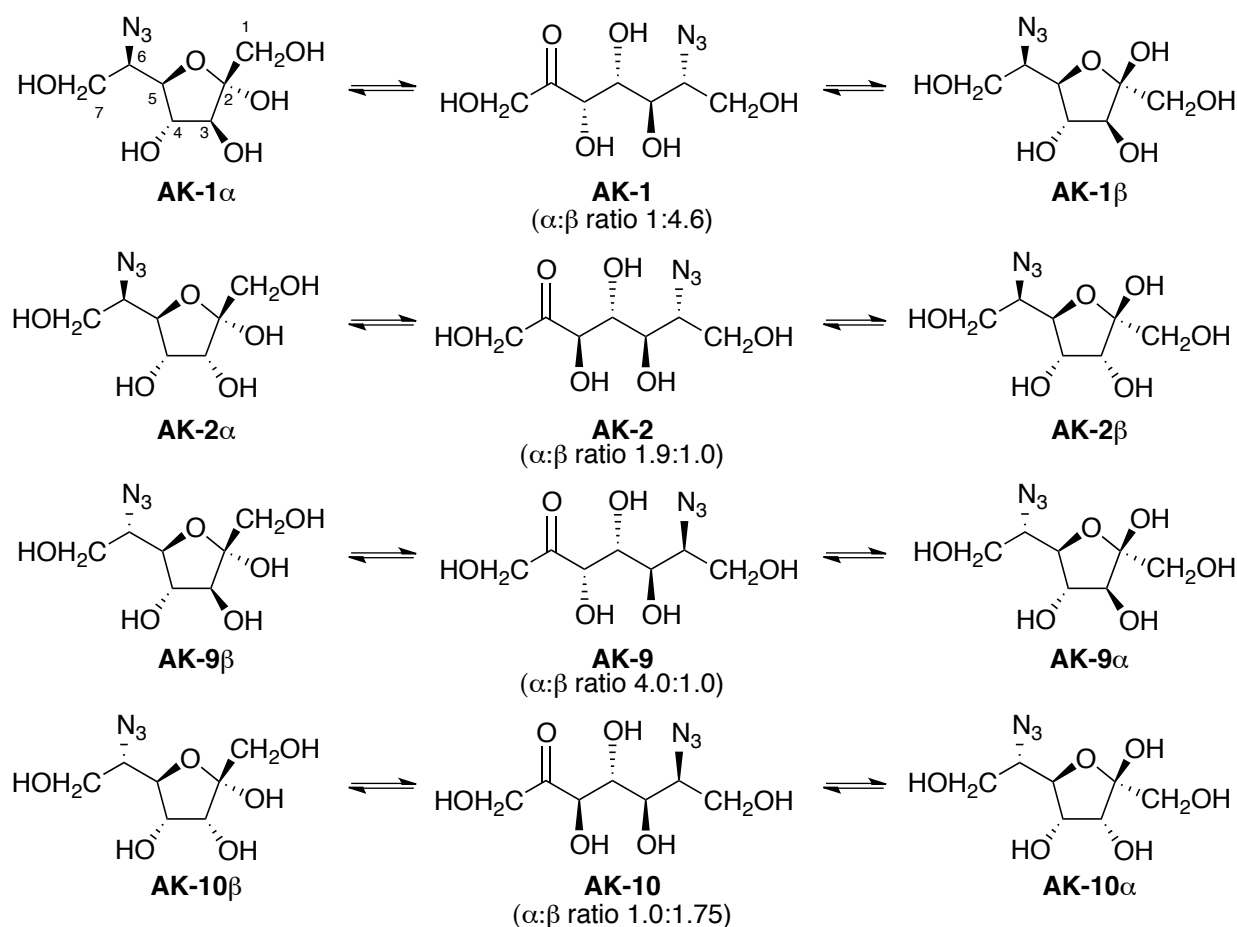


Figure 3.4: Furanose forms of the 6-azidoketoheptoses predominate in aqueous solution

[‡] In accordance with IUPAC guidelines, the description of α or β for the furanose forms of the 6-azidoketoheptoses is determined by the configuration of the azide at C6.

	AK-1				AK-2			
	¹ H			¹³ C	¹ H			¹³ C
	δ (ppm)	mult	³ J _{HH} (Hz)	δ (ppm)	δ (ppm)	mult	³ J _{HH} (Hz)	δ (ppm)
αC1	3.68 ^b	d	~ 12 ^b	63.406	3.609	d	12.2	63.739
	3.66 ^b	d	~ 12 ^b		3.578	d	12.2	
αC2	--	--	--	105.474	--	--	--	103.914
αC3	4.089	d	4.3	82.589	4.101	d	5.9	71.001
αC4	4.144	dd	4.3 / 6.1	77.897	4.208	dd	5.9 / 4.8	71.078
αC5	4.052	dd	6.1 / 5.3	81.307	4.095	dd	4.8 / 5 ^a	82.424
αC6	3.83 ^b	o/l	nd	64.904	3.780 ^a	ddd	5 ^a / 3.4 / 7.6	65.204
αC7	3.84 ^c	o/l	nd	61.582	3.838	dd	11.7 / 3.4	61.644
	3.66 ^c	o/l	nd		3.658	dd	11.7 / 7.6	
βC1	3.582	d	12.1	63.142	3.814 ^b	d	12 ^b	62.933
	3.536	d	12.1		3.601 ^b	d	12 ^b	
βC2	--	--	--	102.522	--	--	--	106.638
βC3	4.086	d	8.0	76.026	4.040	d	4.7	75.414
βC4	4.299	dd	8.0 / 7.0 ^a	76.059	4.536	dd	4.7 / 7.2	72.536
βC5	3.804 ^a	o/l	7.0 ^a / ~6 ^a	79.399	3.963	dd	7.2 / 5.9	81.468
βC6	3.797 ^a	o/l	~6 ^a / 2.7 / 7.1	66.043	3.80 ^b	ddd	5.9 / 3.2 / 8 ^b	66.292
βC7	3.866	dd	12.0 / 2.7	61.250	3.861	dd	12 ^b / 3.2	61.736
	3.664	dd	12.0 / 7.1		3.66 ^c	dd	12 / 8 ^c	

Spectra recorded at 30 °C in D₂O (**AK-1** pH 7.1, **AK-2** pH 7.8) at 500 MHz (¹H) and 125 MHz (¹³C). Chemical shifts referenced to acetone at 2.220 ppm (¹H) and 30.90 ppm (¹³C). o/l = overlapping peaks; nd = not determined; ^a = determined from HSQC spectrum and simulation of the 1D ¹H spectrum; ^b = only determined from HSQC spectrum; ^c = only determined from HMBC spectrum.

Table 3.1: NMR assignment for **AK-1** and **AK-2**

	AK-9				AK-10			
	¹ H		¹³ C		¹ H		¹³ C	
	δ (ppm)	mult	³ J _{HH} (Hz)	δ (ppm)	δ (ppm)	mult	³ J _{HH} (Hz)	δ (ppm)
αC1	3.582	d	12.2	63.16	3.820	d	11.9	62.92
	3.541	d	12.2		3.602	d	11.9	
αC2	--	--	--	102.42	--	--	--	106.68
αC3	4.092	d	8.3	75.69	4.041	d	4.6	75.12
αC4	4.246	dd	8.3 / 7.7	75.96	4.490	dd	4.6 / 7.7	72.69
αC5	3.775	dd	7.7 / 5.8	79.89	3.938	dd	7.7 / 5.7	82.11
αC6	3.657	ddd	5.8 / 4.0 / 8.0	65.43	3.649	ddd	5.7 / 3.6 / 8.1	66.07
αC7	3.860	dd	11.9 / 4.0	61.56	3.877	dd	11.8 / 3.6	61.75
	3.740	dd	11.9 / 8.0		3.726	dd	11.8 / 8.1	
βC1	3.66	s	--	63.48	3.595	d	12.1	64.18
					3.574	d	12.1	
βC2	--	--	--	105.25	--	--	--	104.24
βC3	4.092 ^a	d	5.1	82.55	4.100	d	6.1	70.94
βC4	4.110	dd	5.1 / 6.3	77.92	4.197	dd	6.1 / 5.7	71.85
βC5	4.018	dd	6.3 / 5.2	80.73	4.065	dd	5.7 / 4.5	81.76
βC6	3.70	m	5.2 / 3.8 / 8.0	64.38	3.671	ddd	4.5 / 4.1 / 8.1	64.42
βC7	3.873 ^a	dd	11.9 / 3.8 ^a	61.95	3.873	dd	11.8 / 4.1	62.04
	3.770 ^a	dd	11.9 / 8.0 ^a		3.778	dd	11.8 / 8.1	

Spectra recorded at 30 °C in D₂O (**AK-9** pH 5.4, **AK-10** pH 5.3) at 500 MHz (¹H) and 125 MHz (¹³C). Chemical shifts referenced to acetone at 2.220 ppm (¹H) and 30.90 ppm (¹³C). ^a = determined from HSQC spectrum and simulation of the 1D ¹H spectrum.

Table 3.2: NMR assignment for **AK-9** and **AK-10**

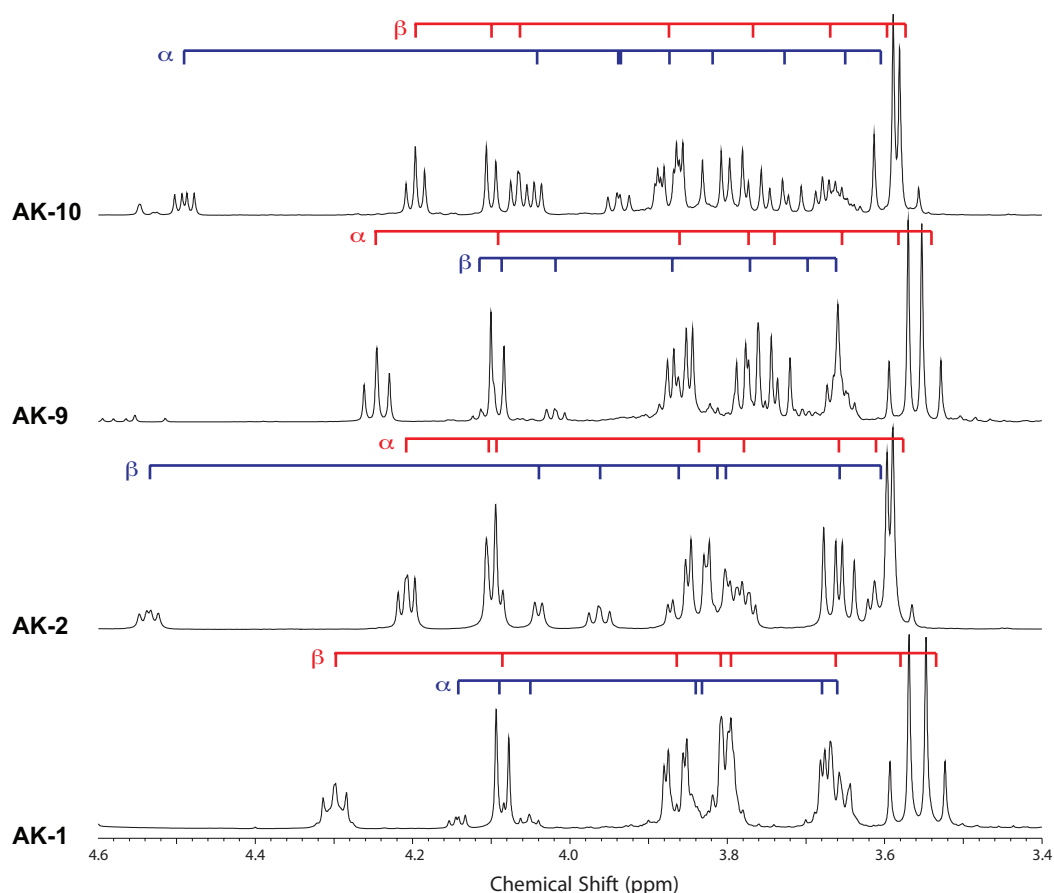
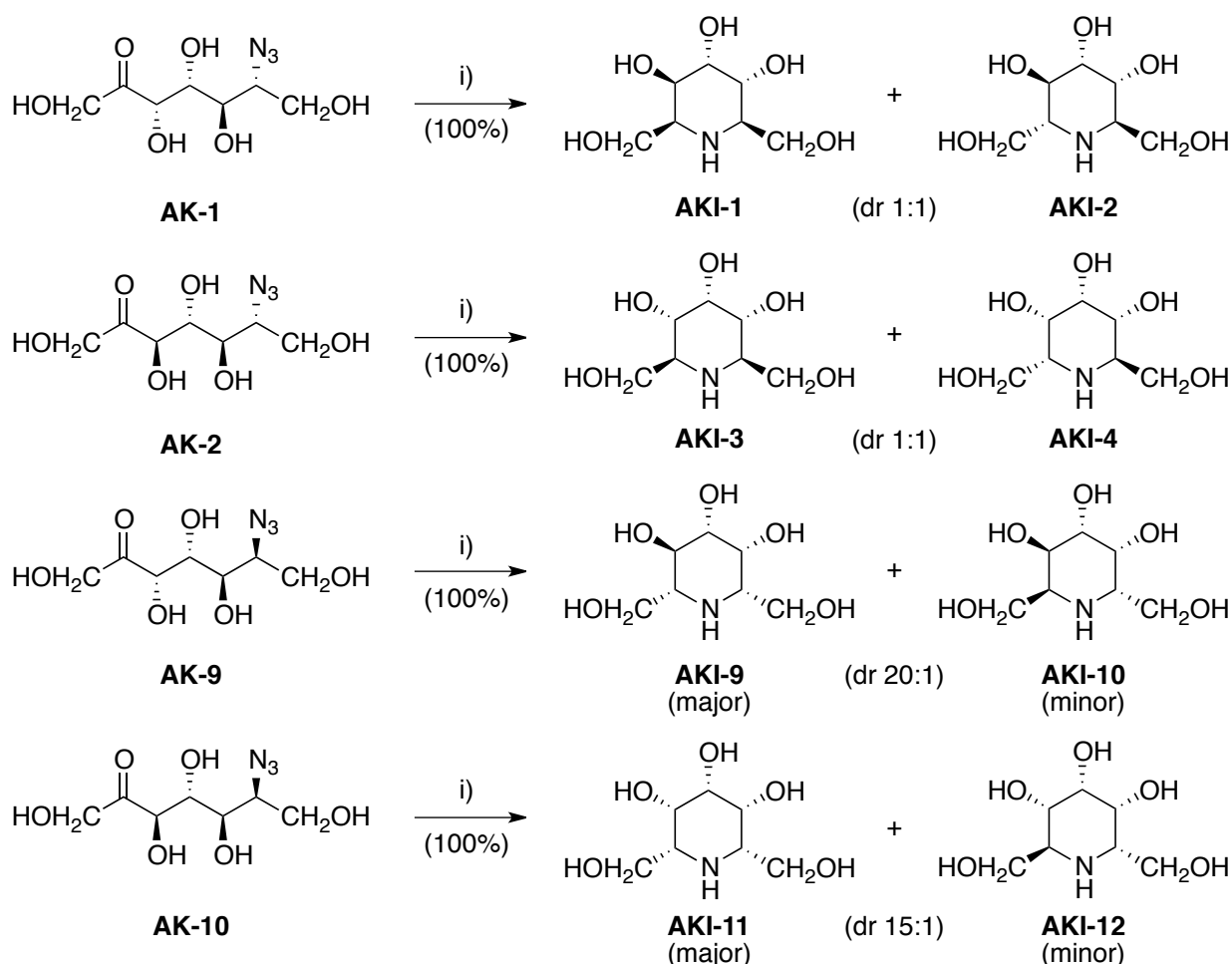


Figure 3.5: Stacked ¹H NMR traces of the 6-azidoketoheptoses, with annotations for the major and minor anomers in each case shown in red and blue respectively

From the data obtained, the α : β ratios of the 6-azidoketoheptofuranoses were found to be: 1:4.6 for **AK-1**; 1.9:1.0 for **AK-2**; 4.0:1.0 for **AK-9**; and 1.0:1.75 for **AK-10** (Figure 3.4). For all of the 6-azidoketoheptoses, assignment of the two predominant spin systems as the furanose forms was based on the chemical shift dispersions of the CH₂ groups, as well as HMBC correlations between C2 and H5. Furthermore, the determinations of each spin system as either the α or β furanose form were based on ROE enhancements (or lack thereof) between H1/H1' and H3: in **AK-1**, for example, one of the spin systems exhibited an ROE enhancement between H1/H1' and H3 and the other did not; the former was therefore identified as the β anomer because in that case H3 and H1/H1' are on the same face of the ring, and the latter identified as the α anomer as in that case they are on opposite faces of the ring.

3.4 Preparation and biological evaluation of the 2,6-iminoheptitols

The final synthetic process of reducing the 6-azidoketoheptoses was also carried out by Professor Ken Izumori and co-workers (Scheme 3.19).⁶⁰ Treatment of **AK-1**, **AK-2**, **AK-9** and **AK-10** with Raney nickel in alkaline aqueous solution at 50 °C under a 1.2 MPa atmosphere of hydrogen effected azide reduction and intramolecular reductive amination of the resulting amine, successfully furnishing four diastereomeric pairs of 2,6-iminoheptitols in quantitative yields; thus **AK-1** gave **AKI-1**/**AKI-2**, **AK-2** gave **AKI-3**/**AKI-4**, **AK-9** gave **AKI-9**/**AKI-10** and **AK-10** gave **AKI-11**/**AKI-12**. The approximate diastereomeric ratios obtained in each case were determined from the ¹H NMR spectra of the product mixtures. No stereoselectivity was observed in the



Reagents and conditions: i) Raney Ni (pH 9.2), H₂ (1.2 MPa), H₂O, 50 °C, 12-24 h.

Scheme 3.19: Preparation of the eight 2,6-iminoheptitols

reduction of either **AK-1** or **AK-2**, whereas similar reductions of **AK-9** and **AK-10** were both highly stereoselective, furnishing product ratios of 20:1 and 15:1 respectively. These observations may be rationalised in terms of the steric hindrance and torsional strain encountered during the reductive aminations; such arguments have been previously presented by Wong for the reduction of similar substrates.⁷²⁻⁷⁴ Specifically, the stereoselectivity of a particular reductive amination appears to be governed by three key factors: the transient cyclic imine favouring adoption of the more stable half-chair conformation in which the number of pseudo-axial substituents, and the severity of their steric interactions, are minimised; the favoured delivery of hydrogen to the ring face presenting the least number of pseudo-axial substituents (and thus the least steric hindrance towards approach); and the favoured reduction of a particular face of the imine to give the incipient product whose formation involves the least torsional strain. The greatest stereoselectivity is thus observed when the latter two factors are synergistic, and the least stereoselectivity when they are antagonistic; however, in the second case the steric hindrance towards hydrogen delivery often proves to be more decisive in the outcome of the reaction.^{73,74}

The transient cyclic imine **3.20** produced during the reduction of **AK-1** could conceivably adopt either the ⁴H₅ or ⁵H₄ conformations without a clear preference, as both possess two pseudo-axial groups in an antiperiplanar arrangement (Figure 3.6). Also, there is no clear discrepancy in the steric hindrance towards hydrogen delivery to either face of either conformer, as in each case it involves interaction with a single pseudo-axial substituent. One could therefore reasonably assume that each conformer exists in more or less equal measure, and that the reaction outcome would be decided by torsional factors. Given this reasoning, the examination of the Newman projections along C2-C3 for the ⁴H₅ and ⁵H₄ conformations of **3.20**, and for the products arising from hydrogen delivery to the *Re* or *Si* faces of the imine in each case, provides an explanation for the equal amounts of **AKI-1** and **AKI-2** formed during the reaction. The case of *Re* addition to the ⁴H₅ conformer of **3.20** is disfavoured, as it involves a build up of torsional strain because the transition state **T.S. 1** must pass through an eclipsed conformation on its way to the product **AKI-1**. In

contrast, *Si* addition to the same conformer is favoured because it proceeds through the transition

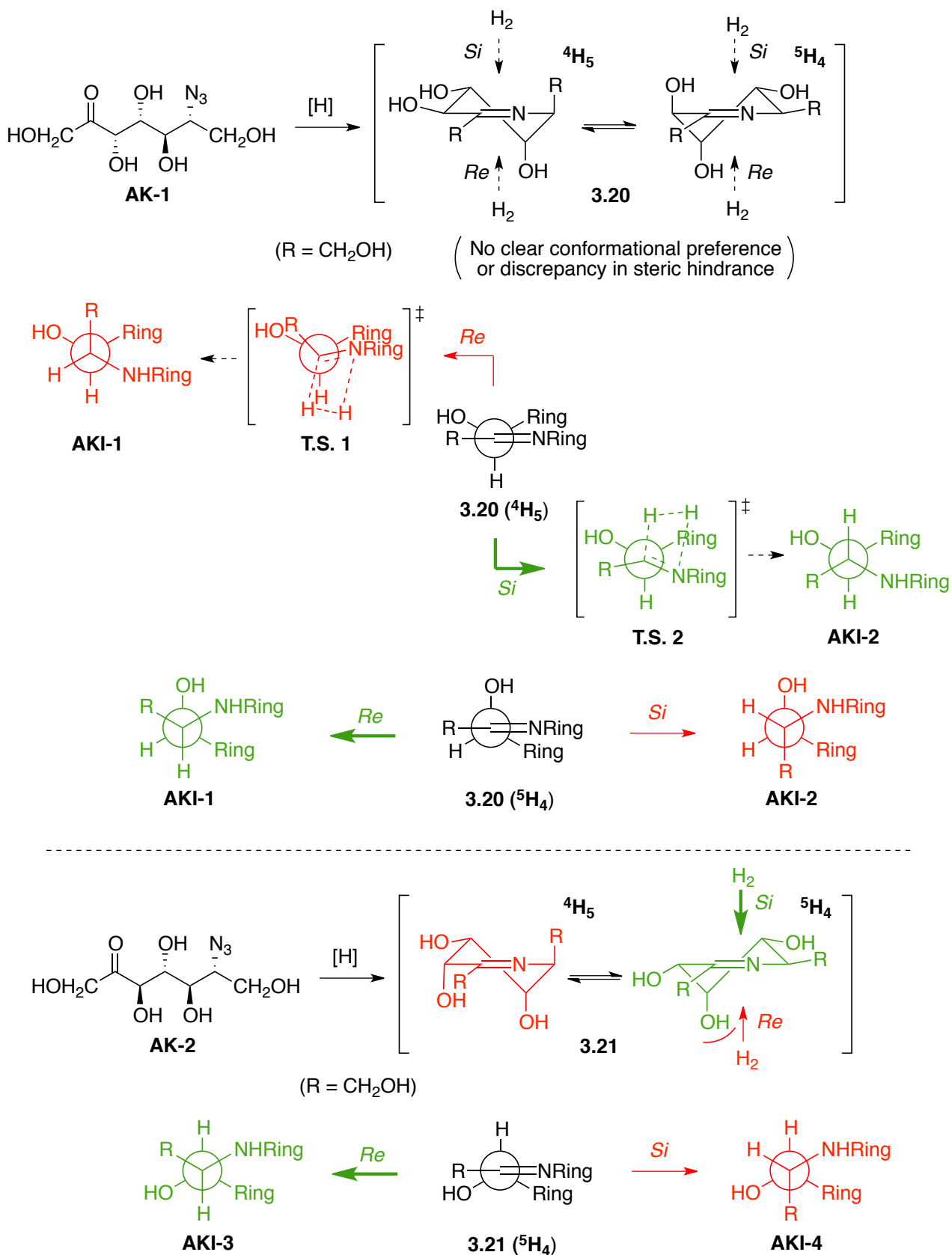


Figure 3.6: Rationale for the lack of stereoselectivity in the reductions of **AK-1** and **AK-2**, with favourable and disfavourable processes shown in green and red respectively

state **T.S. 2** with relief of torsional strain and immediate progression to a staggered conformation in **AKI-2**. The same reasoning dictates that the opposite facial preference holds true for the $^5\text{H}_4$ conformer of **3.20**, thereby favouring formation of **AKI-1** over **AKI-2**. The imine **3.21** produced during the reduction of **AK-2** would clearly be expected to adopt the $^5\text{H}_4$ conformation, as it would then possess only a single pseudo-axial substituent. The lack of stereoselectivity in the reduction of **AK-2** thus appears to be due to competing steric and torsional factors; there is less steric hindrance towards hydrogen delivery to the *Si* face of **3.21**, but such attack must proceed *via* an eclipsed conformation, therefore attack of the *Re* face is favoured in terms of torsional strain. The equal amounts of **AKI-3** and **AKI-4** obtained would indicate that the steric and torsional factors are of equal significance in this case; this may be due to the particularly high torsional strain involved in eclipsing the OH and CH₂OH groups during **AKI-4** formation.

The high degree of stereoselectivity observed in the reductions of **AK-9** and **AK-10**, on the other hand, may both be explained in terms of synergy between steric and torsional factors (Figure 3.7). The imine **3.22** produced during reduction of **AK-9** would clearly favour the $^4\text{H}_5$ conformation, as the alternative $^5\text{H}_4$ conformer not only possesses three pseudo-axial substituents, but would also necessitate a highly disfavoured *syn*-diaxial interaction between an OH and CH₂OH group. Given the predominance of the $^4\text{H}_5$ conformation, the formation of **AKI-9** from *Si* addition of hydrogen would then clearly be favoured, as it involves the least steric hindrance to approach as well as immediate relief of torsional strain. The conformational preference for the imine **3.23** from reduction of **AK-10** is less clear, as both possess two pseudo-axial groups which are involved in a *syn*-diaxial interaction. Nonetheless, the $^5\text{H}_4$ conformation would appear to be the more disfavoured of the two, as the *syn*-diaxial interaction is between an OH and CH₂OH group, as opposed to between two OH groups in $^4\text{H}_5$. Given this conformational preference the formation of **AKI-11** by *Si* addition of hydrogen is clearly favoured, as it would occur with the minimum of steric hindrance and torsional strain.

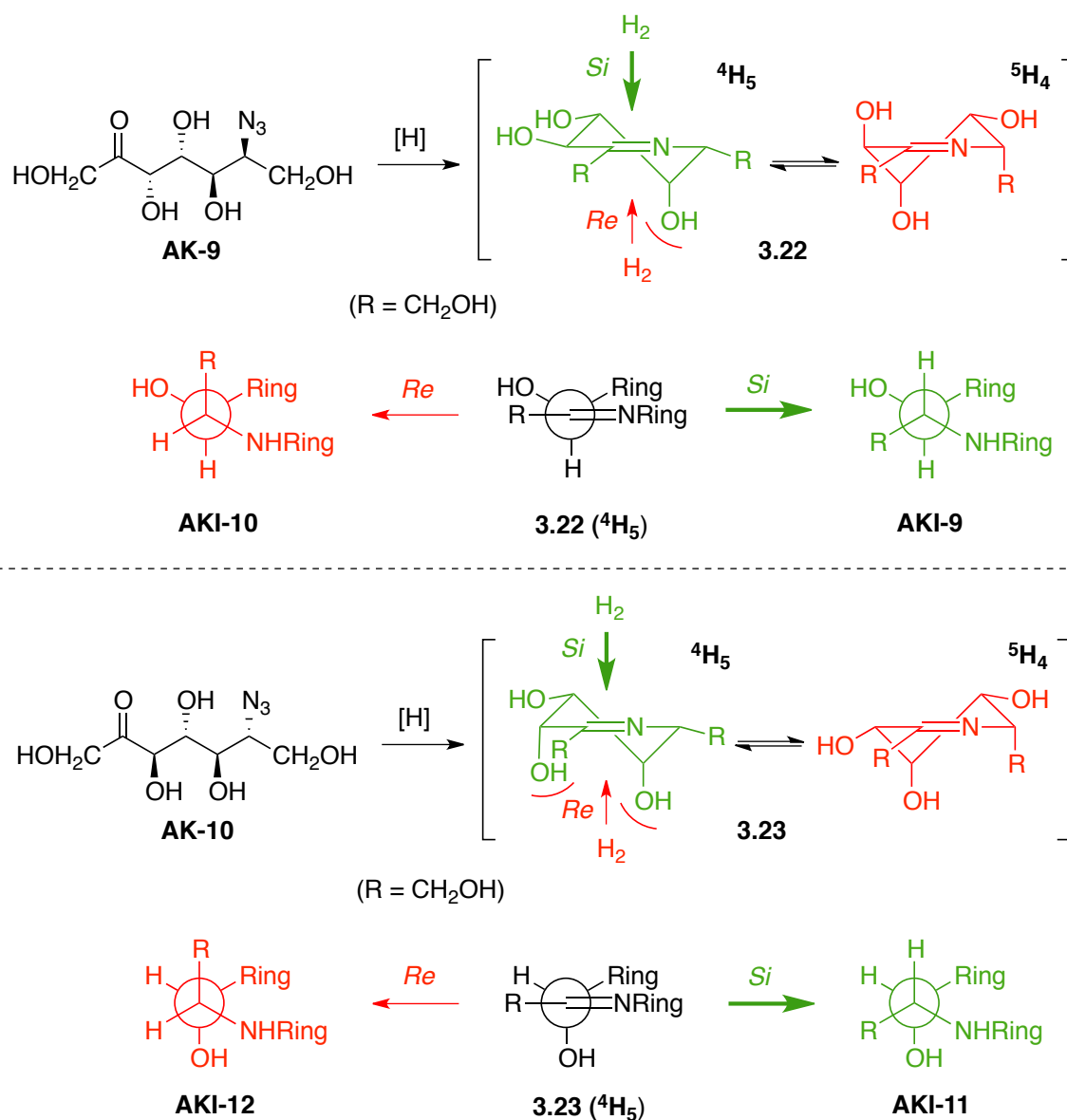


Figure 3.7: Rationale for the highly stereoselective reductions of **AK-9** and **AK-10**, with favourable and disfavourable processes shown in green and red respectively

The four mixtures of 2,6-iminoheptitols were separated, courtesy of Dr Robert Nash (PhytoQuest Limited, Aberystwyth, UK) and Professor Atsushi Kato (University of Toyama, Japan), using ion exchange chromatography with Dowex 1X2 (OH^- form) and Amberlite CG-50 (NH_4^+ form) resins. Their efforts thus allowed the isolation of **AKI-1** (X-ray structure shown in Figure 3.8), **AKI-2**, **AKI-3**, **AKI-4**, **AKI-9** and **AKI-11**. To the best of the author's knowledge this is the first time that **AKI-3** has been isolated, having been prepared previously only as part of a diastereomeric mixture.²³ Unfortunately none of the minor diastereomers **AKI-10** or **AKI-12** could be cleanly

isolated from their mixtures using the above methodology. The separated 2,6-iminoheptitols were assayed against a panel of glycosidases, courtesy of Atsushi Kato (Table 3.3).

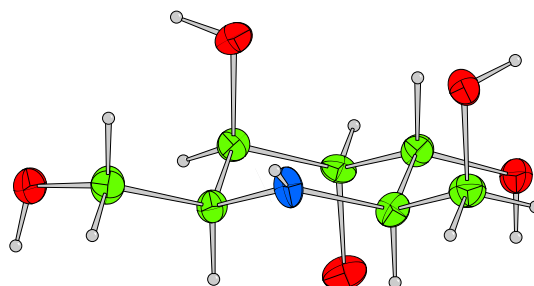


Figure 3.8: Single crystal X-ray structure of **AKI-1**

Concentration of 2,6-iminoheptitols giving 50 % inhibition of various glycosidases

Enzyme	IC ₅₀ (μM)					
	AKI-1	AKI-2	AKI-3	AKI-4	AKI-9	AKI-11
α-Glucosidase						
Yeast	NI ^a (16%) ^b	NI (39%)	NI (4%)	NI (8%)	153	NI (11.4%)
Rice	NI (27%)	161	54	NI (37%)	NI (9.7%)	NI (1.6%)
Rat intestinal maltase	NI (9%)	250	180	NI (34%)	140	NI (34.5%)
β-Glucosidase						
Almond	NI (0%)	NI (0%)	NI (3%)	NI (34%)	NI (2.4%)	NI (11.6%)
<i>A. niger</i>	NI (19%)	NI (15%)	NI (15%)	NI (13%)	NI (10.0%)	NI (15.9%)
Bovine liver	NI (16%)	NI (10%)	NI (20%)	576	NI (9.0%)	NI (4.1%)
α-Galactosidase						
Coffee beans	194	NI (17%)	NI (17%)	93	NI (41.3%)	26
Human lysosome	NI (39%)	424	NI (28%)	5.5	476	8.1
β-Galactosidase						
Bovine liver	NI (19%)	NI (29%)	NI (17%)	271	NI (0%)	NI (1.7%)
Rat intestinal lactase	NI (20%)	NI (2%)	NI (28%)	NI (45%)	NI (16%)	NI (10%)
α-Mannosidase						
Jack beans	NI (4%)	NI (33%)	NI (10%)	NI (36%)	NI (6.7%)	NI (10.3%)
β-Mannosidase						
Snail	NI (8%)	NI (5%)	NI (10%)	NI (4%)	NI (2.8%)	NI (2.5%)
α-L-Fucosidase						
Bovine kidney	126	NI (38%)	NI (16%)	NI (13%)	21	NI (42.0%)
Trehalase						
Porcine kidney	NI (5%)	NI (11%)	NI (13%)	NI (5%)	NI (38.0%)	NI (0%)
α-L-Rhamnosidase						
<i>P. decumbens</i>	NI (23%)	NI (11%)	NI (18%)	NI (25%)	NI (14.5%)	NI (42.9%)

^a NI : No inhibition (less than 50% inhibition at 1000 μM).

^b () : inhibition % at 1000 μM

Table 3.3: Biological assays of the 2,6-iminoheptitols derived from D-mannose

AKI-1 was found to exhibit reasonable inhibition of α -galactosidase (coffee bean, IC_{50} 194 μ M) and good inhibition of α -L-fucosidase (IC_{50} 126 μ M), in contrast with **AKI-2**, which exhibited reasonable inhibition of α -glucosidases (rice and rat intestinal maltase, IC_{50} 161 and 250 μ M respectively), weak inhibition of a different α -galactosidase (human lysosome, IC_{50} 424 μ M) and no inhibition of α -L-fucosidase. These results are in generally good agreement with previous studies.^{3,7,12,13} **AKI-9** showed reasonable inhibition of α -glucosidases (yeast and rat intestinal maltase, IC_{50} 153 and 140 μ M respectively), weak inhibition of α -galactosidase (human lysosome, IC_{50} 476 μ M), but also potent inhibition of α -L-fucosidase (IC_{50} 21 μ M); this significant latter activity is in good agreement with previous results.^{3,19} Comparison of the α -L-fucosidase inhibition of **AKI-1** and **AKI-9** indicates that mimicry of the methyl configuration in α -L-fucose is more important relative to that of the anomeric configuration (Figure 3.9).

AKI-4 displayed weak inhibition of β -glucosidase (bovine liver, IC_{50} 576 μ M), but strong inhibition of α -galactosidases (coffee bean and human lysosome, IC_{50} 93 and 5.5 μ M respectively) and moderate inhibition of β -galactosidase (bovine liver, IC_{50} 271 μ M); results which are in close agreement with previous studies.^{6,7} This potent inhibition of human lysosomal α -galactosidase (α -Gal A) has been rationalised as being due to **AKI-4** deviating from its chair form (which contains

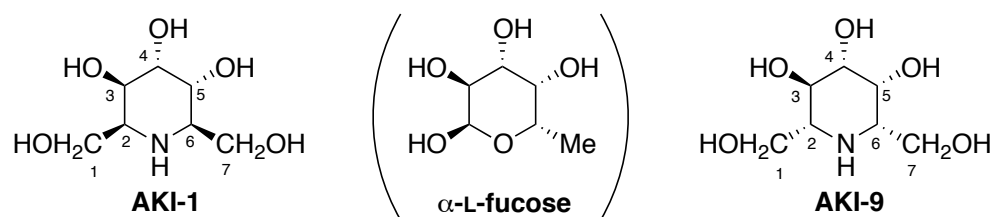


Figure 3.9: Structural basis for α -L-fucosidase inhibition

a *syn*-diaxial interaction between C2-OH and C4-OH), instead adopting an envelope conformation which more closely resembles the galactosyl cation (Figure 3.10).⁷ To the best of the author's knowledge **AKI-3** and **AKI-11** have not previously been subjected to any biological testing.^{23,27} **AKI-3** was found to be a good to moderate, but highly selective, inhibitor of α -glucosidases (rice

and rat intestinal maltase, IC_{50} 54 and 180 μ M respectively). Significantly, **AKI-11** was found to be a highly potent and very selective inhibitor of α -galactosidases (coffee bean and human lysosome, IC_{50} 26 and 8.1 μ M respectively), presumably for similar structural reasons to that of **AKI-4** (Figure 3.10). With such an inhibition profile, **AKI-11** may therefore prove to be of interest in the treatment of Fabry disease (see Chapter 1).

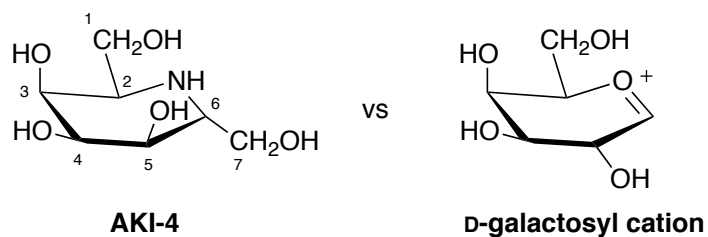
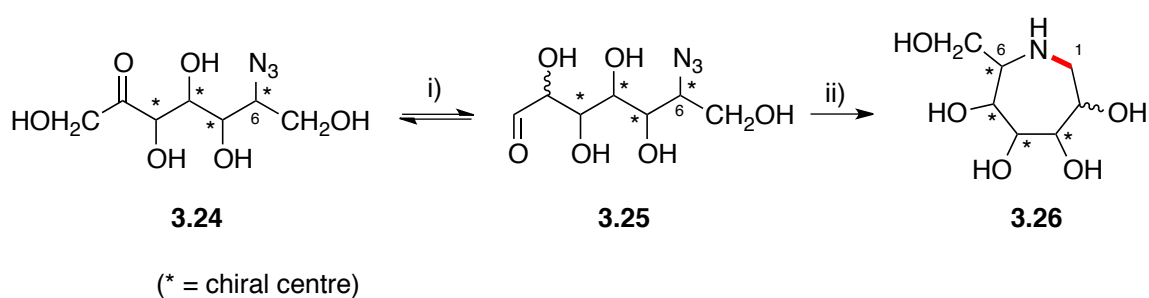


Figure 3.10: Rationale for α -Gal A inhibition

3.5 Conclusions and future work

Two epimeric 6-azidoheptitols have been prepared on multi-gram scales *via* the introduction of azide with inversion or retention of configuration at C2 of a single heptono-1,5-lactone, which is in turn readily available from the Kiliani ascension of D-mannose. The Izumoring biotechnological transformations have been shown to be broadly viable on azido-substituted monosaccharide substrates; thus the prepared 6-azidoheptitols in turn provide access to four separate 6-azidoketoheptoses through a combination of stereoselective oxidation of C2 by *Gluconobacter thailandicus* NBRC 3254, and epimerisation at C3 by D-tagatose-3-epimerase. Subsequent catalytic hydrogenation with Raney nickel furnished four corresponding pairs of 2,6-iminoheptitols with varying levels of diastereoselectivity. Finally, purification of these mixtures by ion exchange chromatography allowed the isolation of six compounds, which were all assayed against a set panel of common glycosidases. The inhibition profiles of two hitherto-untested 2,6-iminoheptitols were thereby determined, and one found to be a highly potent and selective inhibitor of α -galactosidases.

Professor Ken Izumori has very recently discovered an aldose isomerase which is active on 6-azidoketoheptose substrates;⁷⁵ the successful use of this enzyme to augment the processes already described in this thesis could therefore potentially provide access to polyhydroxylated azepanes, which are also of interest as glycosidase inhibitors.²⁸ Thus, each generic 6-azidoketoheptose **3.24** could potentially be isomerised to either of its corresponding aldoses **3.25**, which upon catalytic hydrogenation would furnish two separate 1,6-iminoheptitols **3.26** (Scheme 3.20). These processes are the subject of ongoing investigation within the Fleet and Izumori groups.



Reagents and conditions: i) aldose isomerase; ii) Raney Ni, H₂.

Scheme 3.20: Potential for synthesis of azepane iminosugars

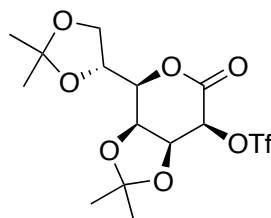
3.6 Experimental

General Experimental

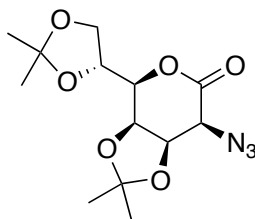
All commercial reagents were used as supplied. THF and DMF were purchased dry from the Aldrich chemical company in sure-seal bottles. Methanol and pyridine were purchased dry from the Fluka chemical company in sure-seal bottles over molecular sieves. All other solvents were used as supplied (Analytical or HPLC grade), without prior purification. Thin layer chromatography (TLC) was performed on aluminium sheets coated with 60 F₂₅₄ silica. Plates were visualised using a spray of 1% w/v potassium permanganate in 1M sodium hydroxide, or a 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate solution in 2M sulfuric acid. Flash column 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. Infrared spectra were recorded on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer using thin films on NaCl plates (thin film) unless otherwise stated. Only the characteristic peaks are quoted. Low resolution mass spectra (*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 NH₃) or atmospheric pressure chemical ionization (APCI). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AMX 500 (¹H: 500 MHz and ¹³C: 125.7 MHz) and Bruker DPX 400 and DQX 400 spectrometers (¹H: 400 MHz and ¹³C: 100.6 MHz) in the deuterated solvent stated. All chemical shifts (δ) 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. Chemical shifts of reference peaks were calibrated according to literature values.⁷⁶

3.6.1 Preparation of the 6-azidoheptitols

3,4:6,7-Di-*O*-isopropylidene-2-*O*-trifluoromethanesulfonyl-D-glycero-D-talo-heptono-1,5-lactone **3.8**



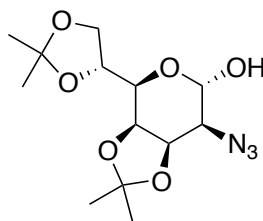
Trifluoromethanesulfonic anhydride (1.63 mL, 9.72 mmol) and pyridine (2.13 mL, 26.37 mmol) were added to a stirred solution of hydroxylactone **3.6** (2.00 g, 6.94 mmol) in dichloromethane (20 mL) at -78 °C under nitrogen atmosphere. TLC analysis (1:1 cyclohexane/ethyl acetate) after 2 h showed complete consumption of starting material (R_f 0.25) and formation of a single product (R_f 0.70). The mixture was quenched with 1M hydrochloric acid (25 mL), the layers separated and the organic layer washed with brine (2 x 25mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford the crude material. Purification *via* flash chromatography on silica gel (2:1 to 1:1 cyclohexane/ethyl acetate) afforded the title compound as a white crystalline solid (2.76 g, 95%); m.p. 119-122 °C (diethyl ether/cyclohexane) [Lit.⁶² m.p. 118-119 °C (diethyl ether/hexane)]; $[\alpha]_D^{25} +44.2$ (c 1.09 in CHCl_3) [Lit.⁶² $[\alpha]_D^{20} +37.0$ (c 1.02 in CHCl_3)]; ν_{max} (thin film): 1781 (s, C=O); δ_{H} (CDCl_3 , 400 MHz): 1.38, 1.41, 1.46, 1.48 (12H, 4 x s, 2 x ($\text{C}(\text{CH}_3)_2$)), 4.06-4.08 (1H, dd, H5, $J_{5,4}$ 1.4, $J_{5,6}$ 8.3), 4.06-4.09 (1H, dd, H7, $J_{7,6}$ 3.6, J_{gem} 9.4), 4.13-4.17 (1H, dd, H7', $J_{7',6}$ 5.9, J_{gem} 9.4), 4.39-4.43 (1H, ddd, H6, $J_{6,7}$ 3.5, $J_{6,7'}$ 5.9, $J_{6,5}$ 8.3), 4.80-4.82 (1H, dd, H4, $J_{4,5}$ 1.4, $J_{4,3}$ 7.8), 4.91-4.94 (1H, dd, H3, $J_{3,2}$ 3.3, $J_{3,4}$ 7.8), 5.24-5.25 (1H, d, H2, $J_{2,3}$ 3.3); δ_{C} (CDCl_3 , 100 MHz): 24.5, 25.0, 25.8, 27.2 (2 x ($\text{C}(\text{CH}_3)_2$)), 66.6 (C7), 72.5 (C6), 72.9 (C4), 73.8 (C3), 76.8 (C5), 78.9 (C2), 110.4, 112.6 (2 x ($\text{C}(\text{CH}_3)_2$)), 162.3 (C1); m/z (ESI+ve): 443 ($[\text{M} + \text{Na}]^+$, 92%), 479 ($[\text{M} + \text{MeCN} + \text{NH}_4]^+$, 71%), 522 (100%), 863 ($[2\text{M} + \text{Na}]^+$, 79%); HRMS m/z (ESI+ve): found 443.0582 ($[\text{M} + \text{Na}]^+$); $\text{C}_{14}\text{H}_{19}\text{F}_3\text{NaO}_9\text{S}$ requires 443.0594.

2-Azido-2-deoxy-3,4:6,7-di-*O*-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone 3.9

Trifluoromethanesulfonic anhydride (12.25 mL, 72.84 mmol) was slowly added to a stirred solution of pyridine (16.00 mL, 197.71 mmol) and hydroxylactone **3.6** (15.00 g, 52.03 mmol) in dichloromethane (200 mL) at -30 °C under nitrogen atmosphere. TLC analysis (1:1 cyclohexane/ethyl acetate) after 40 min showed consumption of starting material (R_f 0.25) and formation of a single product (R_f 0.70). The mixture was poured into 1M aqueous hydrochloric acid (200 mL), the organic layer washed with brine (2 x 200 mL), dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude triflate **3.8** as a yellow syrup. This material was re-dissolved in *N,N*-dimethylformamide (90 mL), sodium azide (4.23 g, 65.04 mmol) added and the mixture stirred at rt. TLC analysis (1:1 cyclohexane/ethyl acetate) after 20 h indicated consumption of starting material and formation of one major product (R_f 0.63). The mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane (200 mL) and 50% brine (200 mL), the organic layer dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude azide as a brown oil. Purification *via* flash chromatography on silica gel (5:1 to 2:1 cyclohexane/ethyl acetate) afforded the title compound as a clear gum (13.05 g, 80%); $[\alpha]_D^{25} +102.3$ (c 1.33 in CHCl_3) [Lit.⁶² $[\alpha]_D^{20} +96.7$ (c 1.13 in CHCl_3)]; ν_{max} (thin film): 1763 (s, C=O), 2119 (s, N_3); δ_{H} (CDCl_3 , 400 MHz): 1.36, 1.38, 1.42, 1.45 (12H, 4 x s, 2 x ($\text{C}(\text{CH}_3)_2$)), 3.86-3.87 (1H, d, H2, $J_{2,3}$ 3.3), 3.97-3.99 (1H, dd, H5, $J_{5,4}$ 1.5, $J_{5,6}$ 8.4), 4.04-4.07 (1H, dd, H7, $J_{7,6}$ 3.7, J_{gem} 9.4), 4.11-4.15 (1H, dd, H7', $J_{7',6}$ 6.0, J_{gem} 9.3), 4.36-4.41 (1H, ddd, H6, $J_{6,7}$ 3.7, $J_{6,7'}$ 6.0, $J_{6,5}$ 8.5), 4.68-4.70 (1H, dd, H4, $J_{4,5}$ 1.6, $J_{4,3}$ 7.8), 4.84-4.87 (1H, dd, H3, $J_{3,2}$ 3.4, $J_{3,4}$ 7.8); δ_{C} (CDCl_3 , 100 MHz): 24.5, 25.0, 25.9, 27.1 (2 x ($\text{C}(\text{CH}_3)_2$)), 59.3 (C2), 66.6 (C7), 72.4 (C6), 72.6 (C4), 75.6 (C3), 76.8 (C5), 110.2, 111.4 (2 x ($\text{C}(\text{CH}_3)_2$)), 166.2 (C1); m/z (ESI+ve): 336 ($[\text{M} + \text{Na}]^+$, 33%),

649 ($[2M + Na]^+$, 100%), 962 ($[3M + Na]^+$, 7%); HRMS m/z (ESI+ve): found 336.1173 ($[M + Na]^+$); $C_{13}H_{19}N_3NaO_6$ requires 336.1166.

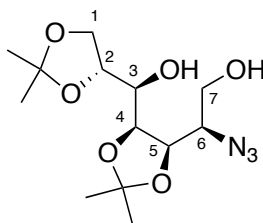
2-Azido-2-deoxy-3,4:6,7-di-*O*-isopropylidene- α -D-glycero-D-talo-heptopyranose **3.12**



Diisobutylaluminium hydride (1.5M in toluene, 33.30 mL, 49.98 mmol) was added under nitrogen atmosphere to a stirred solution of azidolactone **3.9** (13.05 g, 41.65 mmol) in dichloromethane (100 mL) at $-78\text{ }^{\circ}\text{C}$. TLC analysis (1:1 cyclohexane/ethyl acetate) after 2 h showed complete consumption of starting material (R_f 0.62) and formation of a single product (R_f 0.47). The mixture was quenched with saturated aqueous sodium potassium tartrate solution (150 mL) whilst cold, allowed to reach rt, and the emulsion stirred vigorously for 16 h. The layers were separated and the aqueous layer washed with dichloromethane (3 x 150 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the title compound as a white solid (12.25 g, 93%). A small portion was recrystallised from diethyl ether to afford a white crystalline solid; R_f = 0.47 (1:1 cyclohexane/ethyl acetate); m.p. $124\text{--}125\text{ }^{\circ}\text{C}$ (diethyl ether) [Lit.¹³ m.p. $114\text{--}115\text{ }^{\circ}\text{C}$]; $[\alpha]_D^{25} +41.3$ (c 1.00 in CHCl_3) [Lit.¹³ $[\alpha]_D^{20} +41.0$ (c 1.00 in CHCl_3)]; ν_{max} (thin film): 2113 (s, N_3), 3425 (br, s, OH); δ_{H} (CDCl_3 , 400 MHz): 1.37, 1.38, 1.43, 1.48 (12H, 4 x s, 2 x ($\text{C}(\text{CH}_3)_2$)), 3.27–3.27 (1H, d, OH, $J_{\text{OH},1}$ 2.9), 3.51–3.53 (1H, dd, H2, $J_{2,3}$ 2.7, $J_{2,1}$ 6.8), 3.60–3.63 (1H, dd, H5, $J_{5,4}$ 1.7, $J_{5,6}$ 8.0), 3.99–4.02 (1H, dd, H7, $J_{7,6}$ 4.1, J_{gem} 8.8), 4.06–4.10 (1H, dd, H7', $J_{7',6}$ 6.2, J_{gem} 8.8), 4.22–4.27 (1H, ddd, H6, $J_{6,7}$ 4.1, $J_{6,7'}$ 6.2, $J_{6,5}$ 8.0), 4.43–4.45 (1H, dd, H4, $J_{4,5}$ 1.7, $J_{4,3}$ 7.9), 4.58–4.60 (1H, dd, H3, $J_{3,2}$ 2.7, $J_{3,4}$ 7.9), 5.25–5.27 (1H, dd, H1, $J_{1,\text{OH}}$ 2.7, $J_{1,2}$ 6.8); δ_{C} (CDCl_3 , 100 MHz): 25.1, 25.2, 26.0, 27.1 (2 x ($\text{C}(\text{CH}_3)_2$)), 61.1 (C2), 66.9 (C7), 71.1 (C5), 72.9 (C3), 73.5 (C6), 73.7 (C4), 93.0 (C1), 109.7, 110.9 (2 x ($\text{C}(\text{CH}_3)_2$)); m/z (ESI+ve): 333 ($[M + \text{NH}_4]^+$, 89%), 338 ($[M$

+ Na]⁺, 100%); HRMS *m/z* (ESI+ve): found 338.1315 ([M + Na]⁺); C₁₃H₂₁N₃NaO₆ requires 338.1323.

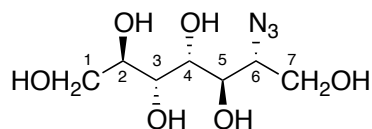
6-Azido-6-deoxy-1,2:4,5-di-*O*-isopropylidene-D-glycero-D-manno-heptitol **3.13**



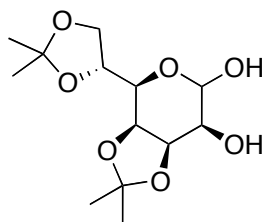
Sodium borohydride (1.47 g, 38.86 mmol) was added in small portions over 10 min to a solution of azidolactol **3.12** (12.25 g, 38.86 mmol) in methanol (80 mL) at 0 °C. Once addition was complete, the mixture was stirred and slowly allowed to reach rt. TLC analysis (1:1 ethyl acetate/cyclohexane) after 17 h showed complete consumption of starting material (*R_f* 0.47) and formation of a single product (*R_f* 0.41). The mixture was quenched by addition of saturated aqueous ammonium chloride (4 mL) and reduced *in vacuo* to afford a white foam. This foam was partitioned between water (150 mL) and ethyl acetate (150 mL), the aqueous layer washed with ethyl acetate (2 x 150 mL) and the combined organic layers dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to afford the crude material as a clear syrup. Purification *via* flash column chromatography on silica gel (4:1 to 2:1 cyclohexane/ethyl acetate) afforded the title compound as a clear syrup which crystallised on standing to give a white solid (11.81 g, 96%); m.p. 68-70 °C [Lit.¹³ m.p. 74-75 °C]; [α]_D²⁵ -46.0 (*c* 0.99 in CHCl₃) [Lit.¹³ [α]_D²⁰ -45.0 (*c* 1.10 in CHCl₃)]; $\nu_{\max}$ (thin film): 2106 (s, N₃), 3463 (br, s, OH); δ_{H} (CD₃CN, 400 MHz): 1.30, 1.36, 1.43 (12H, 3 x s, 2 x C(CH₃)₂), 2.82-2.84 (1H, d, 3-OH, *J*_{OH,3} 9.1), 3.16-3.19 (1H, dd, 7-OH, *J*_{OH,7} 5.2, *J*_{OH,7'} 6.3), 3.61-3.68 (1H, m, H7), 3.71-3.76 (1H, ddd, H3, *J*_{3,4} 0.7, *J*_{3,2} 7.5, *J*_{3,OH} 9.1), 3.90-4.05 (5H, m, H1', H2, H1, H6 and H7'), 4.03-4.07 (1H, dd, H5, *J*_{5,4} 6.8, *J*_{5,6} 9.8), 4.30-4.32 (1H, dd, H4, *J*_{4,3} 0.7, *J*_{4,5} 6.8); δ_{C} (CD₃CN, 100 MHz): 25.1, 25.6, 26.8, 27.2 (2 x C(CH₃)₂), 62.9 (C6), 63.9 (C7), 67.6 (C1), 70.8 (C3), 75.5 (C5), 76.5 (C4), 77.1 (C2), 109.5, 109.8 (2 x C(CH₃)₂); *m/z* (ESI+ve): 340 ([M + Na]⁺,

96%), 657 ($[2M + Na]^+$, 100%); HRMS m/z (ESI+ve): found 340.1476 ($[M + Na]^+$); $C_{13}H_{23}N_3NaO_6$ requires 340.1479.

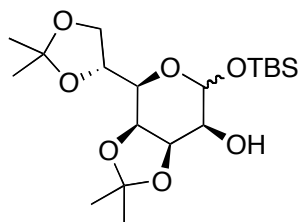
6-Azido-6-deoxy-D-glycero-D-manno-heptitol AP-1



Dowex® 50WX8 H^+ form resin (25.0 g) was placed in a flask containing a solution of di-acetonide **3.13** (11.08 g, 34.92 mmol) in 1:1 v/v water/1,4-dioxane (100 mL) and the mixture stirred at 60 °C. TLC analysis (9:1 ethyl acetate/methanol) after 39 h indicated no remaining starting material (R_f 0.45), and formation of a single product (R_f 0.12). The mixture was filtered and the Dowex® washed with water (3 x 50 mL). The combined filtrates were concentrated *in vacuo* and the residue co-evaporated with methanol (2 x 60 mL) to afford the crude material as a pale cream solid (8.07 g, 96%). Recrystallisation from refluxing isopropyl alcohol (180 mL) followed by washing with cold diethyl ether (30 mL) afforded the pure title compound as a silvery-white crystalline solid (6.99 g, 88%); found: C, 35.53; H, 6.42; N, 17.61. $C_7H_{15}N_3O_6$ requires C, 35.44; H, 6.37; N, 17.71; m.p. 136-138 °C; $[\alpha]_D^{25} +10.9$ (c 1.00 in H_2O); ν_{max} (thin film): 2115 (s, N_3), 3332 (br, s, OH); δ_H (D_2O , 400 MHz): 3.64-3.68 (1H, dd, H1, $J_{1,2}$ 5.8, J_{gem} 11.6), 3.71-3.75 (1H, ddd, H2, $J_{2,1'}$ 2.5, $J_{2,1}$ 5.8, $J_{2,3}$ 8.8), 3.76-3.78 (1H, dd, H3, $J_{3,4}$ 1.0, $J_{3,2}$ 8.8), 3.77-3.82 (1H, dd, H7, $J_{7,6}$ 8.8, J_{gem} 10.9), 3.83-3.86 (1H, dd, H4, $J_{4,3}$ 1.0, $J_{4,5}$ 9.3), 3.83-3.87 (1H, ddd, H6, $J_{6,7'}$ 2.5, $J_{6,5}$ 3.0, $J_{6,7}$ 8.8), 3.84-3.87 (1H, dd, H1', $J_{1',2}$ 2.5, J_{gem} 11.6), 3.92-3.96 (1H, dd, H7', $J_{7',6}$ 2.5, J_{gem} 10.9), 3.94-3.97 (1H, dd, H5, $J_{5,6}$ 3.0, $J_{5,4}$ 9.3); δ_C (D_2O , 100 MHz): 60.8 (C7), 63.8 (C1), 66.4 (C6), 69.5 (C4), 69.8 (C3), 71.2 (C2), 71.2 (C5); m/z (ESI+ve): 260 ($[M + Na]^+$, 100%), 497 ($[2M + Na]^+$, 17%); HRMS m/z (ESI+ve): found 260.0855 ($[M + Na]^+$); $C_7H_{15}N_3NaO_6$ requires 260.0853.

3,4:6,7-Di-*O*-isopropylidene-D-glycero-D-talo-heptopyranose 3.14

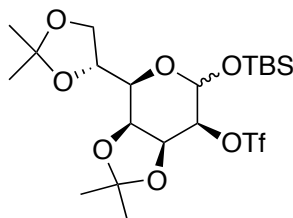
A solution of borane in tetrahydrofuran (1M, 87 mL, 86.73 mmol) was added slowly to a stirred solution of hydroxylactone **3.6** (10.00 g, 34.69 mmol) in anhydrous tetrahydrofuran (15 mL) at 0 °C under nitrogen atmosphere. Once addition was complete the ice bath was removed and the mixture stirred at rt. TLC analysis (ethyl acetate) after 30 min showed a trace of starting material (R_f 0.64) and formation of a single major product (R_f 0.47). The mixture was cooled to 0 °C and quenched with drop-wise addition of methanol until effervescence ceased, then concentrated *in vacuo* and the residue co-evaporated with methanol (2 x 100 mL) to afford the crude as a cream solid. Purification *via* flash column chromatography on silica gel (3:1 cyclohexane/ethyl acetate to neat ethyl acetate) afforded the title compound, a white crystalline solid, as a single anomer (8.91 g, 88%); m.p. 132-134 °C; $\nu_{\max}$ (thin film): 3418 (br, s, OH); $[\alpha]_D^{25} +17.8$ (c 1.02 in CHCl_3); δ_{H} (CD_3CN , 400 MHz): 1.28, 1.30, 1.35, 1.39 (12H, 4 x s, 2 x ($\text{C}(\text{CH}_3)_2$)), 3.31-3.32 (1H, d, 2-OH, $J_{\text{OH},2}$ 6.4), 3.47-3.49 (1H, dd, H5, $J_{5,4}$ 1.2, $J_{5,6}$ 8.0), 3.54-3.58 (1H, a-dt, H2, $J_{2,3}$ 2.8, $J_{2,1}/J_{2,\text{OH}}$ 6.4), 3.86-3.89 (1H, dd, H7, $J_{7,6}$ 4.5, J_{gem} 8.4), 3.98-4.02 (1H, dd, H7', $J_{7',6}$ 6.3, J_{gem} 8.4), 4.06-4.10 (1H, ddd, H6, $J_{6,7}$ 4.6, $J_{6,7'}$ 6.3, $J_{6,5}$ 7.9), 4.27-4.29 (1H, d, 1-OH, $J_{\text{OH},1}$ 5.2), 4.30-4.32 (1H, dd, H4, $J_{4,5}$ 1.4, $J_{4,3}$ 7.9), 4.44-4.47 (1H, dd, H3, $J_{3,2}$ 2.8, $J_{3,4}$ 7.8), 4.82-4.85 (1H, dd, H1, $J_{1,\text{OH}}$ 5.3, $J_{1,2}$ 6.3); δ_{C} (CD_3CN , 100 MHz): 25.5, 25.8, 26.7, 27.5 (2 x ($\text{C}(\text{CH}_3)_2$)), 68.0 (C7), 71.1 (C2), 71.7 (C5), 74.8 (C6), 75.4 (C4), 75.9 (C3), 95.4 (C1), 110.2, 110.7 (2 x ($\text{C}(\text{CH}_3)_2$)); m/z (ESI+ve): 313 ($[\text{M} + \text{Na}]^+$, 75%), 329 ($[\text{M} + \text{K}]^+$, 100%); HRMS m/z (ESI+ve): found 313.1258 ($[\text{M} + \text{Na}]^+$); $\text{C}_{13}\text{H}_{22}\text{NaO}_7$ requires 313.1258.

***tert*-Butyldimethylsilyl 3,4:6,7-di-*O*-isopropylidene-D-glycero-D-talo-heptopyranoside 3.15**

Imidazole (2.96 g, 43.46 mmol) was added to a solution of pyranose **3.14** (8.41 g, 28.97 mmol) in anhydrous *N,N*-dimethylformamide (40 mL), and the mixture stirred with powdered 3 Å molecular sieves at rt for 20 min under nitrogen. *tert*-Butyldimethylsilyl chloride (4.80 g, 31.87 mmol) was then added and the mixture stirred at rt. TLC analysis (3:1 ethyl acetate/cyclohexane) after 3 h indicated a trace of starting material (R_f 0.00), one major product (R_f 0.37) and one minor product (R_f 0.74). The mixture was filtered through Celite, the pad washed with ethyl acetate (200 mL) and the filtrates extracted with 50% brine (3 x 100 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude material as a clear oil. Purification *via* flash column chromatography on silica gel (10:1 cyclohexane/ethyl acetate to ethyl acetate) afforded recovered starting material (0.266 g, 3%), di-silylated material (2.27 g, 15%) and the title compound, a clear oil, as a 3:1 ratio of anomers A:B (9.22 g, 79%); $\nu_{\max}$ (thin film): 3463 (br, s, OH); δ_H (CDCl₃, 400 MHz): 0.12, 0.12 (6H, 2 x s, (CH₃)₂SiC(CH₃)₃ A), 0.12, 0.14 (6H, 2 x s, (CH₃)₂SiC(CH₃)₃ B), 0.90 (9H, s, (CH₃)₂SiC(CH₃)₃ A), 0.92 (9H, s, (CH₃)₂SiC(CH₃)₃ B), 1.36, 1.38, 1.41, 1.51 (12H, 4 x s, 2 x C(CH₃)₂ A), 1.35, 1.36, 1.42, 1.47 (12H, 4 x s, 2 x C(CH₃)₂ B), 2.17-2.18 (1H, d, 2-OH_a, $J_{\text{OHa},2a}$ 6.9), 2.76 (1H, s, 2-OH_b), 3.51-3.53 (1H, dd, H5_b, $J_{5b,4b}$ 1.7, $J_{5b,6b}$ 8.1), 3.59-3.63 (1H, ddd, H2_a, $J_{2a,3a}$ 3.6, $J_{2a,1a}$ 5.2, $J_{2a,\text{OHa}}$ 6.7), 3.67-3.70 (1H, dd, H5_a, $J_{5a,4a}$ 2.0, $J_{5a,6a}$ 8.2), 3.67-3.69 (1H, dd, H2_b, $J_{2b,3b}$ 2.6, $J_{2b,1b}$ 6.1), 3.95-3.98 (1H, dd, H7_a, $J_{7a,6a}$ 4.4, J_{gem} 8.6), 3.95-3.98 (1H, dd, H7_b, $J_{7b,6b}$ 4.4, J_{gem} 8.6), 4.04-4.08 (1H, dd, H7_b', $J_{7b',6b}$ 6.2, J_{gem} 8.7), 4.05-4.08 (1H, dd, H7_a', $J_{7a',6a}$ 6.2, J_{gem} 8.7), 4.19-4.24 (1H, ddd, H6_b, $J_{6b,7b}$ 4.2, $J_{6b,7b'}$ 6.2, $J_{6b,5b}$ 8.1), 4.23-4.28 (1H, ddd, H6_a, $J_{6a,7a}$ 4.6, $J_{6a,7a'}$ 6.1, $J_{6a,5a}$ 8.2), 4.35-4.38 (1H, dd, H4_b, $J_{4b,5b}$ 1.8, $J_{4b,3b}$ 7.7), 4.37-4.40 (1H, dd, H4_a, $J_{4a,5a}$ 2.0, $J_{4a,3a}$ 7.5), 4.41-4.44 (1H, dd, H3_b, $J_{3b,2b}$ 2.5, $J_{3b,4b}$ 7.7), 4.50-4.53 (1H, dd, H3_a, $J_{3a,2a}$ 3.5, $J_{3a,4a}$ 7.4), 5.06-5.07 (1H, d, H1_a, $J_{1a,2a}$ 5.1), 5.06-5.07 (1H, d, H1_b, $J_{1b,2b}$ 6.1); δ_C (CDCl₃,

100 MHz): -5.1, -4.2 ($((\underline{\text{CH}}_3)_2\text{SiC}(\text{CH}_3)_3$ A), -4.7, -4.3 ($((\underline{\text{CH}}_3)_2\text{SiC}(\text{CH}_3)_3$ B), 18.1 ($((\text{CH}_3)_2\text{SiC}(\underline{\text{Me}})_3$ A), 18.4 ($((\text{CH}_3)_2\text{SiC}(\underline{\text{Me}})_3$ B), 25.1, 25.2, 26.2, 27.0 (2 x $\text{C}(\underline{\text{CH}}_3)_2$ B), 25.3, 25.4, 26.0, 27.1 (2 x $\text{C}(\underline{\text{CH}}_3)_2$ A), 25.8 ($((\text{CH}_3)_2\text{SiC}(\underline{\text{CH}}_3)_3$ A), 25.9 ($((\text{CH}_3)_2\text{SiC}(\underline{\text{CH}}_3)_3$ B), 67.0 ($\text{C}_{7\text{b}}$), 67.3 ($\text{C}_{7\text{a}}$), 70.1 ($\text{C}_{5\text{a}}$), 70.5 ($\text{C}_{2\text{a}}$), 70.9 ($\text{C}_{5\text{b}}$), 71.6 ($\text{C}_{2\text{b}}$), 73.1 ($\text{C}_{3\text{a}}$), 73.4 ($\text{C}_{4\text{a}}$), 73.5 ($\text{C}_{6\text{b}}$), 73.9 ($\text{C}_{6\text{a}}$), 74.4 ($\text{C}_{4\text{b}}$), 75.5 ($\text{C}_{3\text{b}}$), 94.8 ($\text{C}_{1\text{b}}$), 94.9 ($\text{C}_{1\text{a}}$), 109.6, 110.2 (2 x $\underline{\text{C}}(\text{CH}_3)_2$ A), 109.5, 110.4 (2 x $\underline{\text{C}}(\text{CH}_3)_2$ B); m/z (ESI+ve): 427 ($[\text{M} + \text{Na}]^+$, 74%), 463 ($[\text{M} + \text{MeCN} + \text{NH}_4]^+$, 100%), 831 ($[2\text{M} + \text{Na}]^+$, 63%); HRMS m/z (ESI+ve): found 427.2123 ($[\text{M} + \text{Na}]^+$); $\text{C}_{19}\text{H}_{36}\text{NaO}_7\text{Si}$ requires 427.2123.

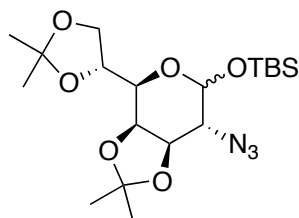
***tert*-Butyldimethylsilyl 3,4:6,7-di-*O*-isopropylidene-2-*O*-trifluoromethanesulfonyl-D-glycero-D-talo-heptopyranoside 3.16**



Trifluoromethanesulfonic anhydride (6.11 mL, 36.3 mmol) was added slowly to a stirred solution of the silyl pyranosides **3.15** (9.79 g, 24.2 mmol) and pyridine (5.87 mL, 72.60 mmol) in dichloromethane (60 mL) at -40 °C under N_2 atmosphere, and the temperature maintained below -15 °C. TLC analysis (3:1 cyclohexane/ethyl acetate) after 2.5 h indicated a small trace of starting material (R_f 0.37) and formation of a single major product (R_f 0.54). The mixture was quenched with water (60 mL), the aqueous layer washed with dichloromethane (60 mL), and the combined organic layers dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude material as a yellow oil. Purification *via* flash column chromatography on silica gel (10:1 to 1:1 cyclohexane/ethyl acetate) afforded the title compound, a clear oil, as a ~ 10:1 mixture of anomers (9.71 g, 75%); [only NMR data for the major anomer quoted] δ_{H} (CDCl_3 , 400 MHz): 0.12, 0.14 (6H, 2 x s, $(\underline{\text{CH}}_3)_2\text{SiC}(\text{CH}_3)_3$), 0.91 (9H, s, $(\text{CH}_3)_2\text{SiC}(\underline{\text{CH}}_3)_3$), 1.36, 1.38, 1.42, 1.51 (12H, 4 x s, 2 x $\text{C}(\underline{\text{CH}}_3)_2$), 3.70-3.72 (1H, dd, H5, $J_{5,4}$ 2.0, $J_{5,6}$ 7.9), 3.94-3.97 (1H, dd, H7, $J_{7,6}$ 4.5, J_{gem} 8.7), 4.05-4.09 (1H, dd, H7', $J_{7',6}$ 6.2, J_{gem} 8.7), 4.23-4.28 (1H, ddd, H6, $J_{6,7}$ 4.6, $J_{6,7'}$ 6.2, $J_{6,5}$ 7.9), 4.44-

4.46 (1H, dd, H4, $J_{4,5}$ 2.0, $J_{4,3}$ 7.3), 4.64-4.66 (1H, dd, H3, $J_{3,2}$ 3.4, $J_{3,4}$ 7.3), 4.71-4.73 (1H, dd, H2, $J_{2,3}$ 3.4, $J_{2,1}$ 5.2), 5.26-5.27 (1H, d, H1, $J_{1,2}$ 5.2); δ_C (CDCl₃, 100 MHz): -5.2, -4.4 ((CH₃)₂SiC(CH₃)₃), 18.0 ((CH₃)₂SiC(CH₃)₃), 25.6 ((CH₃)₂SiC(CH₃)₃), 25.3, 25.6, 25.9, 27.1 (2 x C(CH₃)₂), 67.1 (C7), 70.6 (C5), 71.5 (C3), 73.6 (C6), 73.6 (C4), 84.6 (C2), 91.5 (C1), 109.6, 111.5 (2 x C(CH₃)₂), 112.5-124.9 (q, $J_{C,F}$ 319 Hz, SO₂CF₃); m/z (ESI+ve): 559 ([M + Na]⁺, 77%), 595 ([M + MeCN + NH₄]⁺, 100%); HRMS m/z (ESI+ve): found 559.1625 ([M + Na]⁺); C₂₀H₃₅F₃NaO₉SSi requires 559.1615.

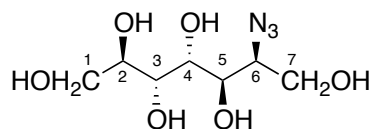
***tert*-Butyldimethylsilyl 2-azido-2-deoxy-3,4:6,7-di-*O*-isopropylidene-D-glycero-D-galactoseptopyranoside 3.17**



Sodium azide (3.53 g, 54.28 mmol) was added to a stirred solution of triflates **3.16** (9.71 g, 18.09 mmol) in *N,N*-dimethylformamide (60 mL) and the mixture heated to 65 °C. After 64 h the mixture was allowed to cool, diluted with ethyl acetate (150 mL) and washed with 50% brine (3 x 100 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford the crude material as an orange oil. Purification *via* flash column chromatography on silica gel (8:1 to 3:1 cyclohexane/ethyl acetate) afforded the title compound, a clear oil, as a ~ 10:1 mixture of anomers (5.52 g, 71%) [only NMR data for the major anomer quoted]; $\nu_{\max}$ (thin film): 2108 (s, N₃); δ_H (C₆D₆, 400 MHz): 0.10, 0.11 (6H, 2 x s, (CH₃)₂SiC(CH₃)₃), 0.95 (9H, s, (CH₃)₂SiC(CH₃)₃), 1.19, 1.30, 1.37, 1.44 (12H, 4 x s, 2 x C(CH₃)₂), 3.28-3.31 (1H, dd, H2, $J_{2,1}$ 2.9, $J_{2,3}$ 8.3), 4.03-4.06 (1H, dd, H7, $J_{7,6}$ 6.5, J_{gem} 8.7), 4.06-4.08 (1H, dd, H4, $J_{4,5}$ 2.6, $J_{4,3}$ 5.3), 4.14-4.16 (2H, m, H5 and H7'), 4.26-4.30 (1H, dd, H3, $J_{3,4}$ 5.4, $J_{3,2}$ 8.3), 4.45-4.50 (1H, m, H6), 4.94-4.95 (1H, d, H1, $J_{1,2}$ 2.9); δ_C (C₆D₆, 100 MHz): -5.3, -4.7 ((CH₃)₂SiC(CH₃)₃), 18.3 ((CH₃)₂SiC(CH₃)₃), 25.8 ((CH₃)₂SiC(CH₃)₃), 25.7, 26.4, 27.1, 28.4 (2 x C(CH₃)₂), 63.1 (C2), 66.9 (C7), 68.6 (C5), 73.1 (C4),

74.0 (C3), 75.0 (C6), 92.3 (C1), 109.3, 109.7 (2 x C(CH₃)₂); *m/z* (ESI+ve): 452 ([M + Na]⁺, 100%); HRMS *m/z* (ESI+ve): found 452.2171 ([M + Na]⁺); C₁₉H₃₅N₃NaO₆Si requires 452.2187.

6-Azido-6-deoxy-L-glycero-D-manno-heptitol AP-17

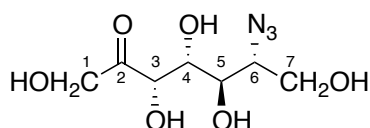


The azides **3.17** (5.51 g, 12.83 mmol) were dissolved in 2:1 trifluoroacetic acid/water (45 mL) and stirred at 60 °C. TLC analysis (9:1 ethyl acetate/methanol) after 39 h indicated consumption of starting material (*R_f* 0.95) and formation of a single major product (*R_f* 0.25). The mixture was allowed to cool, diluted with water (35 mL) and washed with dichloromethane (2 x 60 mL). The aqueous layer was concentrated *in vacuo* and the residue co-evaporated with water (2 x 120 mL) to afford the crude azidoaldose **3.19** as a brown foam. This was re-dissolved in water (50 mL), sodium borohydride (0.73 g, 19.3 mmol) added in small portions and the mixture stirred at rt. TLC analysis (9:1 ethyl acetate/methanol) after 16 h showed consumption of starting material and formation of a single product (*R_f* 0.00). The reaction was quenched by addition of Dowex® 50WX8 H⁺ form resin until pH 1 was obtained, and the resulting mixture stirred for 3 h. The mixture was filtered, the resin washed with water (150 mL) and methanol (100 mL), and the combined filtrates concentrated *in vacuo* to afford a tan solid. Purification *via* flash column chromatography on silica gel (7:2.5:0.5 to 5:4:1 ethyl acetate/isopropyl alcohol/water) afforded the title compound as a pale orange solid (2.25 g, 74%). Recrystallisation from methanol afforded a powdery white solid; $[\alpha]_D^{25}$ -8.5 (*c* 1.00 in H₂O), *v*_{max} (solid): 2090, 2117 (s, N₃), 3238 (s, br, OH); m.p. 159-160 °C (methanol); δ_H (D₂O, 500 MHz): 3.65-3.69 (1H, dd, *J* 5.8, *J* 11.7), 3.74-3.80 (3H, m), 3.84-3.90 (4H, m), 3.90-3.92 (1H, dd, *J* 0.9, *J* 9.6); δ_C (D₂O, 125 MHz): 63.0, 63.9, 64.5, 69.5, 69.5, 69.6, 71.5; *m/z* (ESI+ve): 260 ([M + Na]⁺, 100%), 497 ([2M + Na]⁺, 29%); HRMS *m/z* (ESI+ve): found 260.0850 ([M + Na]⁺); C₇H₁₅N₃NaO₆ requires 260.0853.

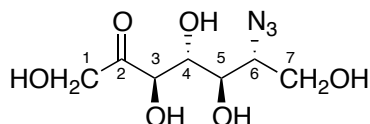
3.6.2 Izumoring procedures and preparation of the 2,6-iminoheptitols

The experimental protocols for the biotechnological transformations and catalytic hydrogenations were provided by Professor Ken Izumori. Separation of the mixtures of 2,6-iminoheptitols was performed by Dr Mark Wormald or Professor Atsushi Kato, using ion exchange chromatography with Dowex 1X2 (OH⁻ form) and Amberlite CG-50 (NH₄⁺ form) resins. Characterisation of the isolated 2,6-iminoheptitols was carried out by the author.

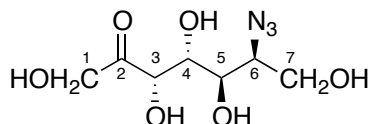
6-Azido-6-deoxy-D-*altro*-hept-2-ulose AK-1



Gluconobacter thailandicus NBRC 3254 was grown aerobically in Erlenmeyer flasks (500 mL) containing medium (0.5 % D-glucose, 0.5 % polypepton, 0.5 % yeast extract and 0.1 % MgSO₄·7H₂O) at 30 °C for 48 h. The collected cells were washed twice with deionised water by centrifugation at 9000 rpm for 10 min. The washed cells were suspended in 50 mM sodium phosphate buffer (pH 7.0) for carrying out the oxidation. The reaction was carried out in a 500 mL Erlenmeyer flask containing 100 mL of an aqueous 5% solution of **AP-1** (5.00 g) at 30 °C, with continuous shaking at 120 rpm with the cells (Cell OD A₆₀₀=30). The formation of product (**AK-1**) was monitored by HPLC; after 20 h the oxidation was quantitative. After this time, the cells were removed by centrifugation at 10,000 rpm for 10 min. The supernatant was decolourised using activated charcoal, which was then removed using centrifugation and filtration. The decolourised supernatant was deionised using ion exchange resin DIAION (SKIB, H⁺) and Amberlite (IRA-411, CO₃²⁻), affording the title compound as a clear, colourless syrup (4.76 g, 96%); $[\alpha]_D^{25} +21.7$ (*c* 0.40 in H₂O).

6-Azido-6-deoxy-D-*allo*-hept-2-ulose AK-2

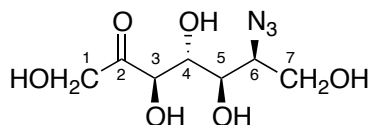
Epimerisation of **AK-1** to **AK-2** was carried out using immobilised D-tagatose-3-epimerase. 200 mL of an aqueous 2% solution of **AK-1** (4.00 g) was shaken at 40 °C in a 500 mL flask containing immobilized enzyme (10.0 g, 2,000 U). The reaction was monitored by HPLC, and was found to have reached its equilibrium after 24 h. At equilibrium the conversion ratio was 64:36 **AKI-1** : **AKI-2**. Immobilised enzyme was removed from the reaction mixture by filtration. The supernatant was deionised using ion exchange resin and concentrated under rotatory evaporation. The products were then separated using Dowex 50W-X2 resin (Ca²⁺), affording the title compound as a clear, colourless syrup (1.10 g, 28%); $[\alpha]_D^{25} +31.0$ (*c* 0.70 in H₂O).

6-Azido-6-deoxy-L-*galacto*-hept-2-ulose AK-9

Gluconobacter thailandicus NBRC 3254 was grown aerobically in Erlenmeyer flasks (500 mL) containing medium (0.5 % D-glucose, 0.5 % polypepton, 0.5 % yeast extract and 0.1 % MgSO₄·7H₂O) at 30 °C for 48 h. The collected cells were washed twice with deionised water by centrifugation at 9000 rpm for 10 min. The washed cells were suspended in 25 mM Tris-HCl buffer (pH 7.0) for carrying out the oxidation. The reaction was carried out in a 500 mL Erlenmeyer flask containing 70 mL of an aqueous 3% solution of **AP-17** (2.10 g) at 30 °C, with continuous shaking at 120 rpm with the cells (Cell OD A600=30). The formation of product (**AK-9**) was monitored by HPLC; after 30 h the oxidation had reached 95%. After this time, the cells were removed by centrifugation at 10,000 rpm for 10 min. The supernatant was decolourised using activated charcoal, which was then removed using centrifugation and filtration. The decolourised supernatant was

deionised using ion exchange resin DIAION (SKIB, H⁺) and Amberlite (IRA-411, CO₃²⁻), affording the title compound as a clear, colourless syrup (1.40 g, 67%); $[\alpha]_D^{25} +25.7$ (*c* 1.00 in H₂O).

6-Azido-6-deoxy-L-*talo*-hept-2-ulose AK-10



Epimerisation of **AK-9** to **AK-10** was carried out using immobilised D-tagatose-3-epimerase. 70 mL of an aqueous 2% solution of **AK-9** (1.40 g) was shaken at 42 °C in a 500 mL flask containing immobilised enzyme (10.0 g, 2,000 U). The reaction was monitored by HPLC, and was found to have reached its equilibrium after 24 h. At equilibrium the conversion ratio was 80:20 **AKI-9** : **AKI-10**. Immobilised enzyme was removed from the reaction mixture by filtration. The supernatant was deionised using ion exchange resin and concentrated under rotary evaporation. The products were then separated using Dowex 50W-X2 resin (Ca²⁺), affording the title compound as a clear, colourless syrup (0.15 g, 11%); $[\alpha]_D^{25} +22.3$ (*c* 1.00 in H₂O).

Preparation of hydrogenation catalyst

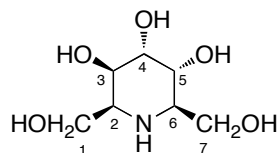
Raney nickel (30.0 g) was dissolved in 20% aqueous sodium hydroxide (300 mL). The catalyst was heated at 80 °C for 6 h and then washed several times with distilled water to obtain pH 9.2. The resultant precipitate was used for hydrogenation of all the 6-azidoketoheptoses.

Hydrogenation of AK-1

The prepared Raney nickel (20.0 g) was added to 200mL of an aqueous 1% solution of **AK-1** (2.00 g), diluted with water (300 mL) and the reactor charged with hydrogen at 1.2 MPa and the contents heated to 50 °C for 12 h. The catalyst was then removed by centrifugation and filtration, and the supernatant fluid concentrated by evaporation under vacuum at 37 °C. The resulting crude

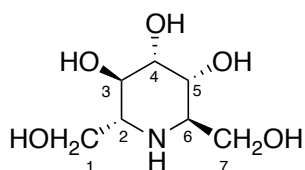
mixture (1.64 g, quant.) consisted of approximately 1:1 **AKI-1** : **AKI-2**. A portion of this mixture (1.10 g) was purified, enabling the isolation of both **AKI-1** and **AKI-2**:

2,6-Dideoxy-2,6-imino-D-glycero-D-gluco-heptitol[§] AKI-1



Received 225 mg of the title compound as a clear syrup which slowly crystallized on standing; m.p. 140-144 °C; $[\alpha]_D^{25} +44.5$ (*c* 0.85 in H₂O) [Lit.³ $[\alpha]_D +41.9$ (*c* 0.43 in H₂O)]; $\nu_{\max}$ (thin film): 3356 (br, s, OH and NH); δ_H (D₂O, 500 MHz): 2.84-2.88 (1H, ddd, H2, $J_{2,1'}$ 3.1, $J_{2,1}$ 5.4, $J_{2,3}$ 10.5), 3.04-3.07 (1H, a-dt, H6, $J_{6,5}$ 1.5, $J_{6,7}/J_{6,7'}$ 6.6), 3.60-3.64 (1H, dd, H7, $J_{7,6}$ 6.7, J_{gem} 11.2), 3.64-3.67 (1H, dd, H7', $J_{7',6}$ 6.5, J_{gem} 11.2), 3.69-3.72 (1H, dd, H1, $J_{1,2}$ 5.5, J_{gem} 11.7), 3.74-3.77 (1H, dd, H3, $J_{3,4}$ 3.2, $J_{3,2}$ 10.6), 3.78-3.81 (1H, dd, H1', $J_{1',2}$ 3.0, J_{gem} 11.6), 3.91-3.92 (1H, dd, H5, $J_{5,6}$ 1.5, $J_{5,4}$ 3.7), 3.98-4.00 (1H, a-t, H4, $J_{4,5}/J_{4,3}$ 3.5); δ_C (D₂O, 125 MHz): 54.4 (C6), 55.9 (C2), 62.1 (C1), 62.1 (C7), 66.7 (C3), 70.0 (C5), 71.6 (C4); *m/z* (ESI+ve): 194 ($[M + H]^+$, 100%); HRMS *m/z* (ESI+ve): found 194.1029 ($[M + H]^+$); C₇H₁₆NO₅ requires 194.1023.

2,6-Dideoxy-2,6-imino-D-glycero-D-manno-heptitol AKI-2



Received 52 mg of the title compound as a clear syrup; $[\alpha]_D^{25} +4.3$ (*c* 0.44 in H₂O) [Lit.³ $[\alpha]_D +4.3$ (*c* 0.62 in H₂O)]; $\nu_{\max}$ (thin film): 3385 (br, s, OH and NH); δ_H (D₂O, 500 MHz): 2.69-2.72 (1H, ddd, H2, $J_{2,1'}$ 3.3, $J_{2,1}$ 5.4, $J_{2,3}$ 8.8), 3.10-3.14 (1H, ddd, H6, $J_{6,5}$ 2.7, $J_{6,7}$ 6.8, $J_{6,7'}$ 7.8), 3.60-3.64 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 9.1), 3.65-3.67 (1H, dd, H4, $J_{4,5}$ 3.0, $J_{4,3}$ 9.1), 3.65-3.69 (1H, dd, H7, $J_{7,6}$ 6.7,

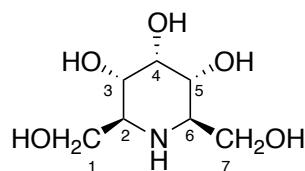
[§] For an explanation of the nomenclature used for the 2,6-iminoheptitols, please see Appendix A.

J_{gem} 11.7), 3.71-3.75 (1H, dd, H7', $J_{7',6}$ 7.9, J_{gem} 11.6), 3.71-3.75 (1H, dd, H1, $J_{1,2}$ 5.6, J_{gem} 11.5), 3.76-3.79 (1H, dd, H1', $J_{1',2}$ 3.2, J_{gem} 11.6), 3.99-4.00 (1H, a-t, H5, $J_{5,6}/J_{5,4}$ 2.8); δ_{C} (D_2O , 125 MHz): 56.3 (C2), 59.2 (C6), 60.0 (C7), 61.7 (C1), 69.2 (C3), 69.8 (C5), 72.4 (C4); m/z (ESI+ve): 194 ($[\text{M} + \text{H}]^+$, 100%); HRMS m/z (ESI+ve): found 194.1029 ($[\text{M} + \text{H}]^+$); $\text{C}_7\text{H}_{16}\text{NO}_5$ requires 194.1023.

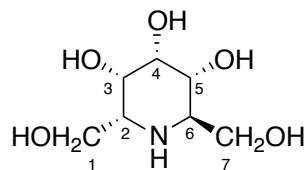
Hydrogenation of AK-2

The prepared Raney nickel (20.0 g) was added to 100mL of an aqueous 1.2% solution of **AK-2** (1.20 g), diluted with water (300 mL) and the reactor charged with hydrogen at 1.2 MPa and the contents heated to 50 °C for 12 h. The catalyst was then removed by centrifugation and filtration, and the supernatant fluid concentrated by evaporation under vacuum at 37 °C. The resulting crude mixture (0.99 g, quant.) consisted of approximately 1:1 **AKI-3** : **AKI-4**. This mixture was purified, enabling the isolation of both **AKI-3** and **AKI-4**:

2,6-Dideoxy-2,6-imino-D-glycero-D-allo-heptitol **AKI-3**



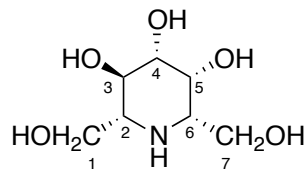
Received 210 mg of the title compound as a white crystalline solid; m.p. 210-212 °C; $[\alpha]_D^{25} +0.13$ (c 0.70 in H_2O); ν_{max} (thin film): 3287 (br, s, OH and NH); δ_{H} (D_2O , 500 MHz): 2.84-2.87 (2H, ddd, H2, H6, $J_{2,1'/6,7'}$ 3.0, $J_{2,1/6,7}$ 6.1, $J_{2,3/6,5}$ 10.3), 3.45-3.48 (2H, dd, H3, H5, $J_{3,4/5,4}$ 2.9, $J_{3,2/5,6}$ 10.4), 3.63-3.66 (2H, dd, H1, H7, $J_{1,2/7,6}$ 6.2, J_{gem} 11.7), 3.82-3.85 (2H, dd, H1', H7', $J_{1',2/7',6}$ 3.0, J_{gem} 11.6), 4.08-4.09 (1H, t, H4, $J_{4,3/4,5}$ 2.9); δ_{C} (D_2O , 125 MHz): 55.3 (C2, C6), 62.1 (C1, C7), 69.4 (C3, C5), 72.5 (C4); m/z (ESI+ve): 194 ($[\text{M} + \text{H}]^+$, 84%), 216 ($[\text{M} + \text{Na}]^+$, 48%), 409 ($[\text{2M} + \text{Na}]^+$, 100%); HRMS m/z (ESI+ve): found 194.1028 ($[\text{M} + \text{H}]^+$); $\text{C}_7\text{H}_{16}\text{NO}_5$ requires 194.1023.

2,6-Dideoxy-2,6-imino-D-glycero-D-altro-heptitol AKI-4

Received 89 mg of the title compound as a clear syrup; $[\alpha]_D^{25} +27.7$ (c 0.75 in H_2O); ν_{max} (thin film): 3356 (br, s, OH and NH); δ_H (D_2O , 500 MHz): 3.02-3.06 (1H, a-dt, H2, $J_{2,1}/J_{2,3}$ 4.3, $J_{2,1'}$ 8.4), 3.08-3.12 (1H, a-dt, H6, $J_{6,7'}$ 5.0, $J_{6,7}/J_{6,5}$ 6.9), 3.61-3.65 (1H, dd, H7, $J_{7,6}$ 7.6, J_{gem} 11.5), 3.66-3.67 (1H, br dd, H5, $J_{5,4}$ 2.6, $J_{5,6}$ 5.9), 3.70-3.73 (1H, dd, H1, $J_{1,2}$ 4.6, J_{gem} 11.5), 3.75-3.78 (1H, dd, H7', $J_{7',6}$ 4.8, J_{gem} 11.5), 3.81-3.85 (1H, dd, H1', $J_{1',2}$ 8.2, J_{gem} 11.5), 3.88-3.89 (1H, a-t, H4, $J_{4,3}/J_{4,5}$ 2.9), 3.89-3.91 (1H, m, H3); δ_C (D_2O , 125 MHz): 54.9 (C6), 55.9 (C2), 60.5 (C1), 61.3 (C7), 69.8 (C5), 69.9 (C4), 70.0 (C3); m/z (ESI+ve): 194 ($[M + H]^+$, 100%), 216 ($[M + Na]^+$, 52%), 409 ($[2M + Na]^+$, 34%); HRMS m/z (ESI+ve): found 216.0840 ($[M + Na]^+$); $C_7H_{15}NNaO_5$ requires 216.0842.

Hydrogenation of AK-9

The prepared Raney nickel (5.00 g) was added to 50 mL of an aqueous 0.6% solution of **AK-9** (0.30 g). The reactor was charged with hydrogen at 1.2 MPa and the contents heated to 50 °C for 24 h. The catalyst was removed by centrifugation and filtration, and the supernatant fluid was concentrated by evaporation under vacuum at 37 °C. The resulting crude mixture (246 mg, quant.) consisted of approximately 20:1 **AKI-9** : **AKI-10**. Purification enabled the isolation of **AKI-9**:

2,6-Dideoxy-2,6-imino-L-glycero-D-manno-heptitol AKI-9

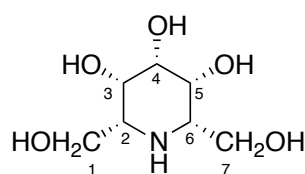
Received 68.3 mg of the title compound as a clear, colourless syrup; $[\alpha]_D^{25} -4.2$ (c 0.27 in MeOH) [lit.¹⁵ $[\alpha]_D^{20} -4.3$ (c 1.30 in MeOH)]; ν_{max} (neat): 3280 (s, br, OH and NH); δ_H (D_2O , 500 MHz):

2.54-2.58 (1H, m, H2), 2.82-2.85 (1H, dt, H6, $J_{6,5}$ 1.4, $J_{6,7}/J_{6,7'}$ 6.7), 3.53-3.55 (1H, m, H4), 3.55-3.58 (1H, t, H3, $J_{3,2}/J_{3,4}$ 9.8), 3.61-3.64 (1H, dd, H7, $J_{7,6}$ 6.7, J_{gem} 11.2), 3.65-3.68 (1H, dd, H7', $J_{7',6}$ 6.7, J_{gem} 11.2), 3.70-3.73 (1H, dd, H1, $J_{1,2}$ 5.5, J_{gem} 11.6), 3.80-3.83 (1H, dd, H1', $J_{1',2}$ 3.0, J_{gem} 11.6), 3.99-4.00 (1H, dd, H5, $J_{5,6}$ 1.4, $J_{5,4}$ 2.7); δ_{C} (D₂O, 125 MHz): 58.5 (C6), 60.7 (C2), 61.7 (C1), 62.0 (C7), 69.2 (C3), 69.6 (C5), 75.7 (C4); m/z (ESI+ve): 194 ([M + H]⁺, 54%), 216 ([M + Na]⁺, 100%); HRMS m/z (ESI+ve): found 216.0842 ([M + Na]⁺); C₇H₁₅NNaO₅ requires 216.0842.

Hydrogenation of AK-10

The prepared Raney nickel (5.00 g) was added to 50 mL of an aqueous 0.26% solution of **AK-10** (0.13 g). The reactor was charged with hydrogen at 1.2 MPa and the contents heated to 50 °C for 24 h. The catalyst was removed by centrifugation and filtration, and the supernatant fluid was concentrated by evaporation under vacuum at 37 °C. The resulting crude mixture (107 mg, quant.) consisted of approximately 15:1 **AKI-11** : **AKI-12**. Purification enabled the isolation of **AKI-11**:

2,6-Dideoxy-2,6-imino-L-glycero-D-altro-heptitol AKI-11



Received 10.2 mg of the title compound as a white crystalline solid; m.p. > 340 °C; $[\alpha]_D^{25}$ -0.09 (*c* 0.44 in H₂O); ν_{max} (solid): 3196, 3259 (s, br, OH and NH); δ_{H} (D₂O, 500 MHz): 2.78-2.81 (2H, a-dt, H2, H6, $J_{2,3}/J_{6,5}$ 1.1, $J_{2,1}/J_{6,7}$ 6.7), 3.64-3.65 (1H, t, H4, $J_{4,3}/J_{4,5}$ 3.1), 3.64-3.68 (2H, dd, H1, H7, $J_{1,2}/J_{7,6}$ 6.9, J_{gem} 11.0), 3.70-3.73 (2H, dd, H1', H7', $J_{1',2}/J_{7',6}$ 6.5, J_{gem} 11.0), 3.94-3.95 (2H, dd, H3, H5, $J_{3,2}/J_{5,6}$ 1.1, $J_{3,4}/J_{5,4}$ 3.1); δ_{C} (D₂O, 125 MHz): 59.5 (C2, C6), 62.2 (C1, C7), 70.3 (C3, C5), 70.6 (C4); m/z (ESI+ve): 194 ([M + H]⁺, 93%), 216 ([M + Na]⁺, 100%); HRMS m/z (ESI+ve): found 216.0839 ([M + Na]⁺); C₇H₁₅NNaO₅ requires 216.0842.

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Appendix A - Deviations from IUPAC nomenclature

IUPAC conventions for the nomenclature of substituted monosaccharide polyols dictate that the name be assigned based on the following criteria (in descending order of priority): the parent sugar whose name comes first in alphabetical order (e.g. allose rather than glucose); the sugar name which includes a D- rather than L- prefix; and the name which gives the lowest possible locant numbering for substituents.

(1) Azetidine iminosugars

Strict adherence to IUPAC guidelines can give differing locant numbering for azetidine iminosugars possessing the same pattern of substitution (Figure A.1). For the sake of consistency and clarity, all the azetidines within this thesis are instead named according to the lowest possible locant numbering (i.e. 1,3- or 2,4- rather than 3,5-).

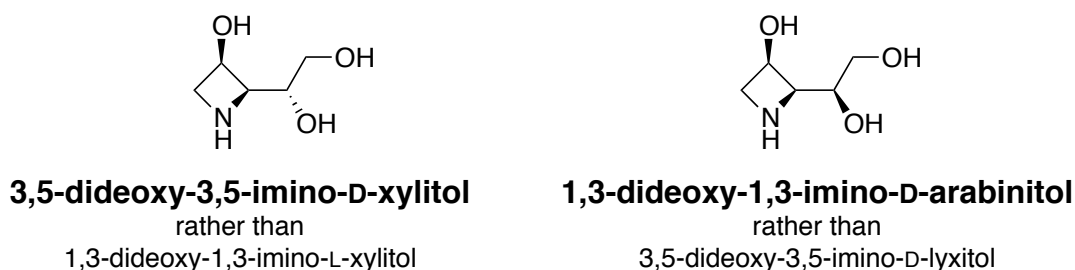


Figure A.1: Comparison of example IUPAC names (bold) with their alternatives

(2) 2,6-Iminoheptitols

The literature contains no consistency with regard to the nomenclature given to the different 2,6-iminoheptitols; instead they are awarded various trivial names derived from structural analogy to different parent sugars (e.g. β -homoa**l**tronojirimycin), or to other 2,6-iminoheptitols (e.g. β -**4,5-di-*epi***-homonojirimycin). There are two possible systematic names for each 2,6-iminoheptitol, depending on which end the carbon backbone is numbered from. For example, **AKI-9** can thus be given L-*glycero*-D-*manno*- or D-*glycero*-D-*galacto*- denominations, of which the latter takes precedence according to IUPAC conventions (Figure A.2). To avoid confusion, however, the systematic names given to all the 2,6-iminoheptitols within this thesis are those which correspond to atom numbering which has been conserved from the 6-azidoketoheptose precursors.

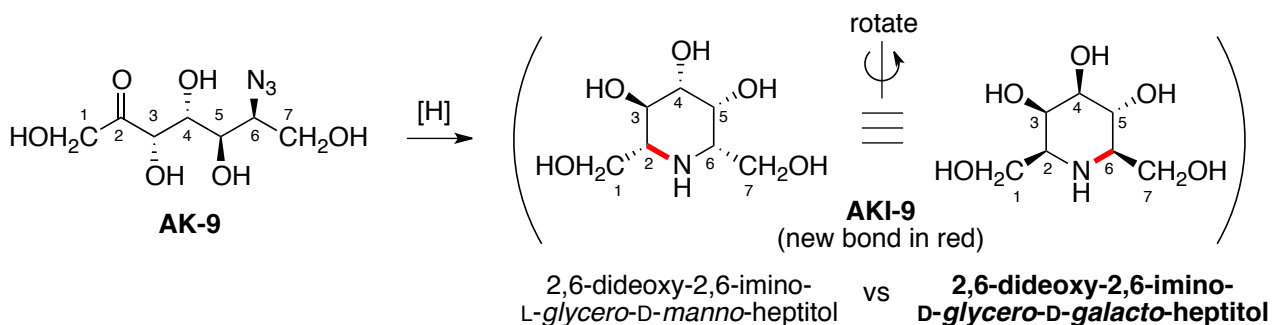


Figure A.2: Example of different systematic names for a single 2,6-iminoheptitol (IUPAC name in bold)

Appendix B – Publications arising from work within this thesis

Related to Chapter 2:

Lenagh-Snow, G. M. J.; Araújo, N.; Jenkinson, S. F.; Rutherford, C.; Nakagawa, S.; Kato, A.; Yu, C.-Y.; Weymouth-Wilson, A. C.; Fleet, G. W. J. **Inhibition of Nonmammalian Glycosidases by Azetidine Iminosugars Derived from Stable 3,5-Di-*O*-triflates of Pentoses** *Org. Lett.* **2011**, *13*, 5834-5837.

Lenagh-Snow, G. M. J.; Araújo, N.; Jenkinson, S. F.; Martínez, R. F.; Shimada, Y.; Yu, C.-Y.; Kato, A.; Fleet, G. W. J. **Azetidine Iminosugars from the Cyclization of 3,5-Di-*O*-triflates of α -Furanosides and of 2,4-Di-*O*-triflates of β -Pyranosides Derived from Glucose** *Org. Lett.* **2012**, *14*, 2142-2145.

Jenkinson, S. F.; Lenagh-Snow, G. M. J.; Fleet, G. W. J.; Thompson, A. L. ***N*-Benzyl-1,3-dideoxy-1,3-imino-L-xylitol** *Acta Cryst.* **2011**, *E67*, o2452.

Edgeley, D. S.; Jenkinson, S. F.; Lenagh-Snow, G. M. J.; Rutherford, C.; Fleet, G. W. J.; Thompson, A. L.; ***N*-Benzyl-3,5-dideoxy-3,5-imino-1,2-*O*-isopropylidene- β -L-lyxofuranose** *Acta Cryst.* **2012**, *E68*, o2410.

Related to Chapter 3:

Lenagh-Snow, G. M. J.; Jenkinson, S. F.; Newberry, S. J.; Kato, A.; Nakagawa, S.; Adachi, I.; Wormald, M. R.; Yoshihara, A.; Morimoto, K.; Akimitsu, K.; Izumori, K.; Fleet, G. W. J. **Eight Stereoisomers of Homonojirimycin from D-Mannose** *Org. Lett.* **2012**, *14*, 2050-2053.

Jenkinson, S. F.; Lenagh-Snow, G. M. J.; Izumori, K.; Fleet, G. W. J.; Watkin, D. J.; Thompson, A. L.; **2-Azido-3,4,6,7-di-*O*-isopropylidene- α -D-glycero-D-talo-heptopyranose** *Acta Cryst.* **2010**, *E66*, o525-o526.

Inhibition of Nonmammalian Glycosidases by Azetidine Iminosugars Derived from Stable 3,5-Di-*O*-triflates of Pentoses

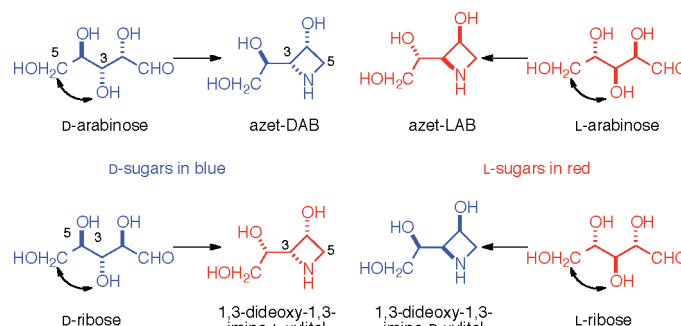
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ABSTRACT



Efficient ring closure of stable crystalline 3,5-di-*O*-triflates of pentofuranosides with amines to form azetidines allowed preliminary evaluation of four-ring iminosugars as glycosidase inhibitors; significant and specific inhibition of nonmammalian α -glucosidases is shown by L-xylo- and L-arabino-iminosugar azetidines.

There are over 200 naturally occurring iminosugars¹ in which the oxygen of the sugar ring is replaced by nitrogen. For example, the pyrrolidine DAB **1D** [Scheme 1] is a 1,4-dideoxy-1,4-imino-pentitol formally derived from a reductive amination from a nitrogen at C4 with the C1 aldehyde

of D-arabinose. DAB **1D**, first isolated from *Angylocaly boutiqueanus* and *Arachnoides standishii*,² has been found in a wide range of plants and is a potent competitive inhibitor of α -D-glucosidases and of glycogen phosphorylase;³ its enantiomer LAB **1L** is a more potent and

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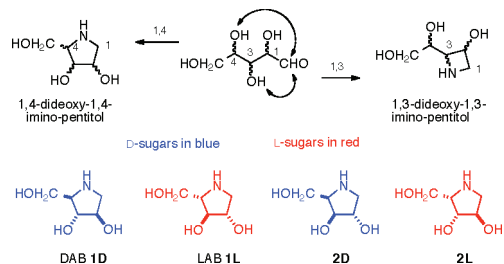
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specific noncompetitive inhibitor of α -D-glucosidases⁴ and an equally potent competitive inhibitor of an α -L-arabinofuranosidase.⁵ The D-iminoxylitol **2D**, isolated from *Angylocalyx pyraertii*, shows no significant glycosidase inhibition;⁶ there are many syntheses of both xylitol enantiomers **2D** and **2L**.⁷ Because of the biological properties of iminosugars and their promise as chemotherapeutic agents,⁸ many pyrrolidine, piperidine, and azepane carbohydrate mimics have been studied. In contrast, there are few examples of carbohydrate azetidines;⁹ there is only one report of any glycosidase inhibition studies on azetidines in which 1,3-dideoxy-1,3-imino-L-xylitol **4L** [Scheme 2] was shown to be a specific inhibitor of amyloglucosidases.¹⁰

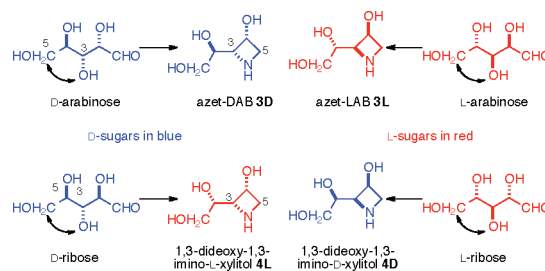
Scheme 1. Azetidine and Pyrrolidine Iminosugars



This paper reports the syntheses of both enantiomers of the azetidine analogues **3** and **4** of the arabinose **1** and xylose **2** pyrrolidines. Formation of the azetidine ring by nucleophilic displacement by nitrogen of triflate leaving groups at C5 and C3 (with inversion) of a protected D-arabinose gave azet-DAB **3D**, whereas a corresponding derivative of L-arabinose gave azet-LAB **3L** [Scheme 2]. A

similar sequence on protected derivatives of D- and L-ribose gave the L-iminoxylitol azetidine **4L** and its enantiomer **4D**, respectively.

Scheme 2. Strategy for the Formation of Azetidines from Protected Pentoses



For the synthesis of azet-DAB **3D**, D-arabinose was converted to the diol **5D**¹¹ in three steps in an overall yield of 33% as previously described [Scheme 3].¹² Esterification of **5D** with triflic anhydride in dichloromethane in the presence of pyridine gave the stable crystalline ditriflate **6D** [mp 67–68 °C; $[\alpha]_D^{25} +7.2$ (*c* 1.1, CHCl₃)] in 95% yield. Reaction of **6D** with benzylamine in acetonitrile in the presence of diisopropylethylamine (DIPEA) afforded the azetidine **7Da** [mp 60–63 °C; $[\alpha]_D^{25} -74.6$ (*c* 1.0, CHCl₃)] in 86% yield. On selective triflation at the primary alcohol, an oxetane cannot be formed as it would be *trans*-fused to the THF ring. Successful cyclizations of ditriflates by double displacements by amines have been reported for the formation of azetidine,¹³ pyrrolidine,¹⁴ and piperidine¹⁵ rings. Removal of the acetonide protecting group in **7Da** with aqueous trifluoroacetic acid gave the lactol which on reduction by sodium borohydride gave the azetidine triol **8Da** [mp 96–97 °C; $[\alpha]_D^{25} -66.2$ (*c* 0.39 in H₂O)]. Hydrogenolysis of the benzyl group in **8Da** with 10% Pd/C and ammonium formate in anhydrous methanol¹⁶ gave the parent azet-DAB **3D**¹⁷ [for the HCl salt $[\alpha]_D^{25} -32.4$ (*c* 0.37 in H₂O)] in 99% yield. A similar sequence of reactions on the enantiomeric diol **5L** derived

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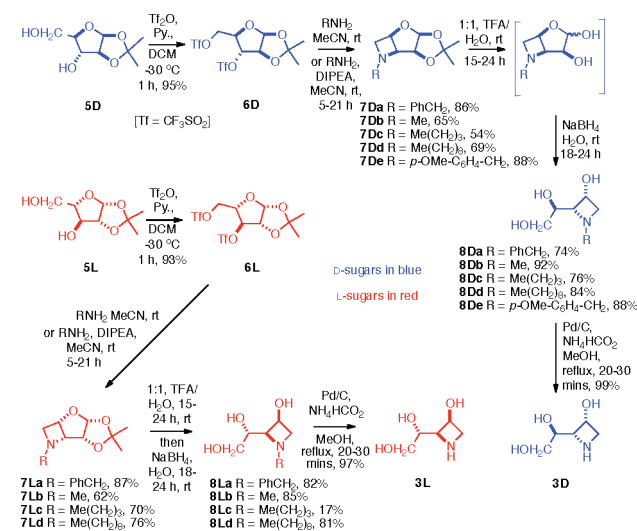
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(17) Selected data for azet-DAB **3D** [as the HCl salt]: δ_H (D₂O, 500 MHz): 3.70–3.73 (1H, dd, H5, $J_{5,4}$ 5.0 Hz, J_{gem} 12.0 Hz), 3.73–3.76 (1H, dd, H5', $J_{5',4}$ 5.4 Hz, J_{gem} 12.0 Hz), 3.87–3.90 (1H, dd, H1, $J_{1,2}$ 4.4 Hz, J_{gem} 11.6 Hz), 4.28–4.31 (1H, a-dt, H4, $J_{4,5}/J_{4,5'}$ 5.2 Hz, $J_{4,3}$ 7.2 Hz), 4.34–4.37 (1H, dd, H1', $J_{1',2}$ 6.8 Hz, J_{gem} 11.6 Hz), 4.58–4.61 (1H, a-t, $J_{3,4}/J_{3,2}$ 6.9 Hz), 4.81–4.85 (1H, m, H2); δ_C (D₂O, 125 MHz): 53.9 (C1), 62.5 (C5), 65.1 (C2), 65.4 (C3), 68.3 (C4).

from L-arabinose gave azet-LAB **3L** [for the hydrochloride salt $[\alpha]_D^{25} +31.7$ (c 0.31 in H_2O)].

Scheme 3. Synthesis of azet-DAB **3D** and azet-LAB **3L**



N-Alkylation of iminosugars significantly modifies the glycosidase inhibition profile of the parent iminosugar,¹⁸ so a series of N-alkyl azetidines was prepared. Reaction of the ditriflate **6D** with methylamine, butylamine, nonylamine, and *p*-methoxybenzylamine gave the corresponding azetidines **7Db** [65%], **7Dc** [54%], **7Dd** [69%], and **7De** [88%] which on subsequent hydrolysis and reduction afforded the *N*-methyl- **8Db** [92%], *N*-butyl- **8Dc** [76%], *N*-nonyl- **8Dd** [84%], and *N*-*p*-methoxybenzyl- **8De** [88%] azetidines, respectively, for biological assays. The corresponding enantiomers were prepared from the L-arabinose ditriflate **6L**.

The protected ribofuranoses **12L** and **12D** were the key intermediates for the respective syntheses of the azetidine xylitols **4D** and **4L** [Scheme 4]. For the synthesis of **4D**, **12L** was prepared from diacetone L-glucose **9L**, readily available from D-glucoheptonolactone.¹⁹ Oxidation of **9L** with Dess-Martin periodinane gave the corresponding ketone which, on reduction with sodium borohydride, formed diacetone L-allose **10L** [91% yield]. Selective hydrolysis of the terminal isopropylidene group with methanol and aqueous sulfuric acid gave the monoacetonide **11L** which

was subjected to oxidation by sodium periodate, followed by borohydride reduction, to afford the 1,2-acetonide **12L** [mp 88–89 °C; $[\alpha]_D^{25} -60.2$ (c 0.5, MeOH), 82% over three steps; 75% from **9L**]. The protected enantiomer **12D** was prepared by a similar sequence of reactions from diacetone glucose **9D**.²⁰ Reaction of benzylamine in the presence of DIPEA with the stable crystalline ditriflate **13L** [mp 41–42 °C; $[\alpha]_D^{25} -93.2$ (c 0.55, $CHCl_3$)], from esterification of the diol **12L** by triflic anhydride in 93% yield, afforded the protected azetidine **14La** [oil, $[\alpha]_D^{25} -52.7$ (c 0.51, $CHCl_3$), 95%]. Hydrolysis of the isopropylidene protecting group with aqueous trifluoroacetic acid, followed by reduction of the resulting lactol with sodium borohydride in water, produced the *N*-benzyl-azetidine **15Da** [mp 182–183 °C; $[\alpha]_D^{25} +106.8$ (c 0.23, MeOH)] in 87% yield. The structure of the enantiomeric L-iminoxylitol **15La** [mp 179–180 °C; $[\alpha]_D^{25} -103.0$ (c 0.23, MeOH)] was firmly established by X-ray crystallographic analysis.²¹ Removal of the benzyl group in **15Da** by transfer hydrogenation with ammonium formate and 10% Pd/C in methanol gave the D-iminolyxitol **4D**²² [for the hydrochloride salt $[\alpha]_D^{25} -6.9$ (c 0.29, H_2O)] in 82% yield; the overall yield of **4D** from the L-ribose diol **12L** was 63%. The enantiomeric D-iminolyxitol **4D** [for the hydrochloride salt $[\alpha]_D^{25} +3.2$ (c 0.50, H_2O)] was similarly prepared from **12D**.

Both enantiomers of the *N*-methyl- **14b**, *N*-butyl- **14c**, and *N*-*p*-methoxybenzyl- **14d** azetidines were prepared by efficient cyclizations of the ditriflates **13** with methylamine, butylamine, and *p*-methoxybenzylamine (**14Lb** 78%, **14Db** 67%, **14Lc** 91%, **14Dc** 82%, **14Ld** 86%, **14Dd** 96%). Acid hydrolysis and subsequent borohydride reduction gave the corresponding unprotected iminopentitols **15b**, **15c**, and **15d** (**15Db** 79%, **15Lb** 85%, **15Dc** 65%, **15Lc** 98%, **15Dd** 80%, **15Ld** 89%) allowing preliminary biological evaluation.

The inhibition profiles of the parent iminopentitols **3** and **4** against a range of glycosidases were investigated [Table 1]; the effect of *N*-alkylation is shown in the tables in the Supporting Information. The specific inhibition reported by Jager¹⁰ by L-iminoxylitol azetidine **4L** was confirmed, showing good inhibition against *Rhizopus sp.* and *A. niger* amyloglucosidase [IC₅₀ 25 and 414 μM, respectively]; **4L**, which also inhibited bacterial (*A. niger*) α-glucosidase, did not inhibit mammalian or plant glycosidases and thus was highly specific for bacterial enzymes. The D-xylo-azetidine enantiomer **4D** did not inhibit any glycosidases. azet-LAB **3L** was a good inhibitor of *A. niger* α-glucosidase, rat intestinal lactase, and *Rhizopus sp.*

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(22) Selected data for iminolyxitol **4D** [as the HCl salt]: δ_H (D_2O , 500 MHz): 3.59–3.62 (1H, dd, H5, $J_{5,4}$ 5.2 Hz, J_{gem} 12.1 Hz), 3.40–3.74 (1H, m, H5'), 3.92–3.95 (1H, dd, H1, $J_{1,2}$ 4.5 Hz, J_{gem} 11.6 Hz), 4.30–4.31 (1H, m, H4), 4.34–4.38 (1H, dd, H1', $J_{1',2}$ 7.3 Hz, J_{gem} 11.3 Hz), 4.58–4.61 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 6.7 Hz), 4.75 (H2, under HDO peak); δ_C (D_2O , 125 MHz): 54.1 (C1), 63.2 (C5), 64.0 (C2), 67.0 (C3), 67.2 (C4).

Scheme 4. Synthesis of Azetidine-xylitols **4D** and **4L**

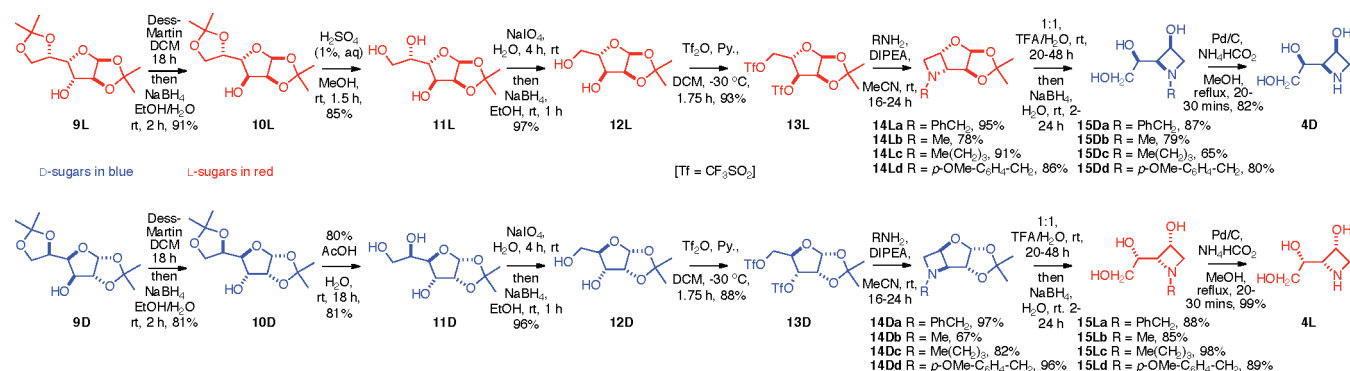


Table 1. Concentration of Iminosugars Giving 50% Inhibition of Various Glycosidases

enzyme	IC ₅₀ (μM)			
α-Glucosidase				
Rice	NI ^a (0%) ^b	NI (4.8%)	NI (12.1%)	NI (11.9%)
Yeast	NI (6.7%)	NI (6.0%)	NI (16.0%)	NI (0%)
Rat intestinal maltase	NI (21.7%)	NI (17.8%)	607	NI (20.9%)
<i>A. niger</i>	175	NI (6.3%)	39	NI (6.4%)
β-Glucosidase				
Almond	NI (9.3%)	NI (9.6%)	347	755
Bovine liver	NI (20.5%)	NI (4.7%)	997	NI (40.7%)
α-Galactosidase				
Coffee beans	NI (14.1%)	NI (0.2%)	NI (7.6%)	NI (37.0%)
Human lysosome	NI (0%)	NI (0%)	NI (2.5%)	NI (0.6%)
β-Galactosidase				
Bovine liver	NI (0%)	NI (2.1%)	NI (25.2%)	NI (27.5%)
Rat intestinal lactase	NI (0%)	NI (0%)	70	241
α-Mannosidase				
Jack beans	NI (1.7%)	NI (0.6%)	NI (2.4%)	713
β-Mannosidase				
Snail	NI (4.9%)	NI (0%)	NI (0%)	NI (0%)
α-L-Rhamnosidase				
<i>P. decumbens</i>	NI (2.3%)	NI (5.7%)	634	NI (3.8%)
α-L-Fucosidase				
Bovine epididymis	NI (4.6%)	NI (0%)	NI (4.6%)	NI (8.5%)
Trehalase				
Rat intestinal trehalase	NI (0%)	NI (6.4%)	NI (11.7%)	NI (17.3%)
Amyloglucosidase				
<i>A. niger</i>	414	NI (5.7%)	105	NI (8.4%)
<i>Rhizopus</i> sp	25	NI (1.2%)	19	NI (0%)

^a NI : No inhibition (less than 50% inhibition at 1000 μM); ^b () : Inhibition % at 1000 mM.

amyloglucosidase, with IC₅₀ values of 39, 70, and 19 μM, respectively. The inhibition profile of **3L** was not as specific as that of **4L**. azet-DAB **3D** also showed broad, but

weaker, inhibition of a number of enzymes. In particular, **3D** was a weak inhibitor of α-D-mannosidase in contrast to the weak inhibition of α-L-rhamnosidase by the enantiomer **3L**; enantiomers of inhibitors of α-D-mannosidase are usually equally potent inhibitors of α-L-rhamnosidase.²³ *N*-Alkylation of **3D** preserved the inhibition of α-D-mannosidase but significantly increased the specificity.

In summary, the reaction of amines with stable ditri-flates allowed the efficient formation of 1,3-iminopentitols; the scope and limitation of the formation of iminosugar azetidines by this method has yet to be determined. While other biological properties are under investigation, it is clear that azetidine iminosugars may be easily accessible and are worthy of further investigation.

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Supporting Information Available. Experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Azetidine Iminosugars from the Cyclization of 3,5-Di-*O*-triflates of α -Furanosides and of 2,4-Di-*O*-triflates of β -Pyranosides Derived from Glucose

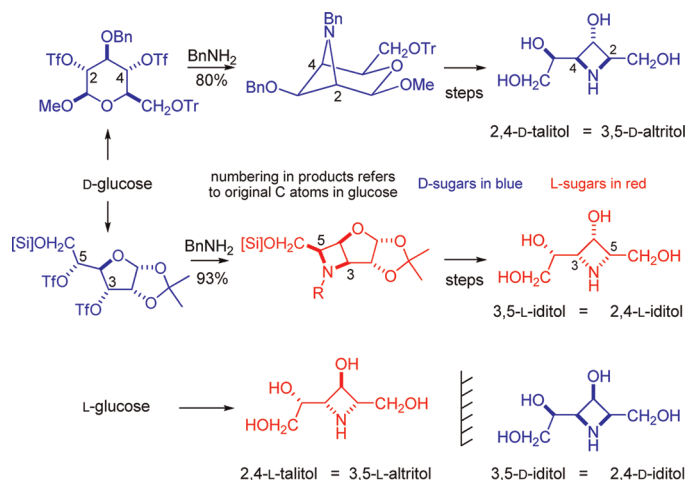
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ABSTRACT



Primary amines with either 3,5-di-*O*-ditriflates of α -furanosides or 2,4-di-*O*-triflates of β -pyranosides form bicyclic azetidines in high yield.

Applications of azetidines¹ include use in polymeric materials² and in a wide range of bioactive compounds.³ Natural and synthetic azetidine carboxylic acids⁴ are common proline substitutes and components of

nonproteinogenic amino acids and are being studied as a new class of foldamers.⁵ Accordingly there is much current

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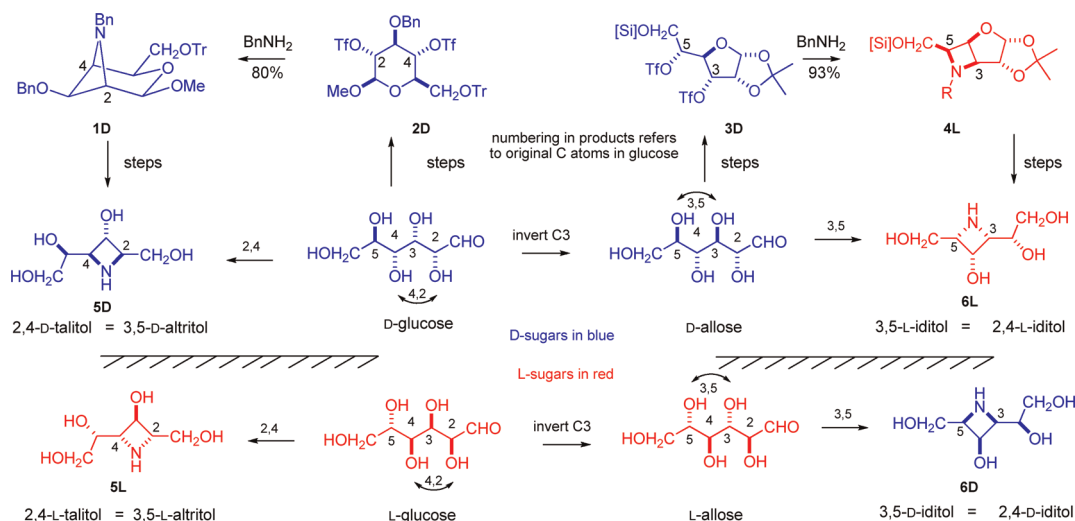
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Scheme 1. Strategy for the Synthesis of Azetidine 2,4-Dideoxy-2,4-iminohexitols from Glucose



interest in the different strategies for the synthesis of azetidines.⁶

Five, six, and seven ring iminosugars⁷ as mimics of monosaccharides are the most general class of inhibitors of glycosidases and interact with many other enzymes and receptors concerned with carbohydrate processing. In contrast there are very few examples of azetidine imino sugars;⁸ *N*-alkyl hydroxyazetidines have been designed as potent transition state analogue inhibitors of purine nucleoside phosphorylase with subnanomolar K_i .⁹ Azetidine iminosugar analogues of pentoses have been found to be specific inhibitors of nonmammalian glycosidases.^{10,11} DMDP, the most common natural iminosugar, is a 2,5-dideoxy-2,5-iminoheptitol and is a bioactive mimic of fructose and glucose.¹² Reported examples of corresponding azetidine analogues, 2,4-dideoxy-2,4-iminoheptitols, are rare.¹³

This paper reports the syntheses of analogues in which the azetidine ring was formed in excellent yield by amine

double displacements of ditriflates at C2 and C4, or at C3 and C5, of protected hexoses [Scheme 1]. The *cis*-2,4-di-*O*-triflate pyranoside **2D** derived from D-glucose with benzylamine gave the bicyclic azetidine **1D** in 80% yield as a key intermediate in the synthesis of 3,5-dideoxy-3,5-imino-D-altritol **5D**.¹⁴ Inversion of configuration at C3 of D-glucose to D-allose allowed the formation of a ditriflate **3D** in which the C3 OH group is *trans* to the carbon side chain; reaction of **3D** with benzylamine afforded the *cis*-fused azetidine **4L** in 93% yield, as a precursor to 2,4-dideoxy-2,4-imino-L-iditol **6L**. The L-enantiomers of many iminosugars have significant bioactivities compared to the corresponding D-natural products.¹⁵ Accordingly, the enantiomers **5L** and **6D** were prepared by identical sequences from L-glucose, readily available from D-glucoheptonolactone.¹⁶ The amine cyclization of such sugar-derived ditriflates is likely to provide an efficient general access to highly functionalized homochiral azetidines. Preliminary studies on the inhibition of glycosidases by **5** and **6** are described.

The β -pyranoside **12L**, with only the C2 and C4 hydroxyl groups unprotected, was the key intermediate in the synthesis of 2,4-dideoxy-2,4-imino-L-talitol **5L** from diacetone-L-glucose **7L** [Scheme 2]. Reaction of **7L** with benzyl bromide and sodium hydride in DMF gave the benzyl ether **8L** (88%). Hydrolysis with aqueous trifluoroacetic acid afforded the pyranose **9L** (81%). Acetylation with acetic anhydride in pyridine formed the tetraacetate **10L β** (75%) with a small amount of the α -anomer **10L α** . **10L** with hydrogen bromide in acetic acid, followed by treatment of the resulting crude bromide with methanol in the presence of silver carbonate, afforded the fully

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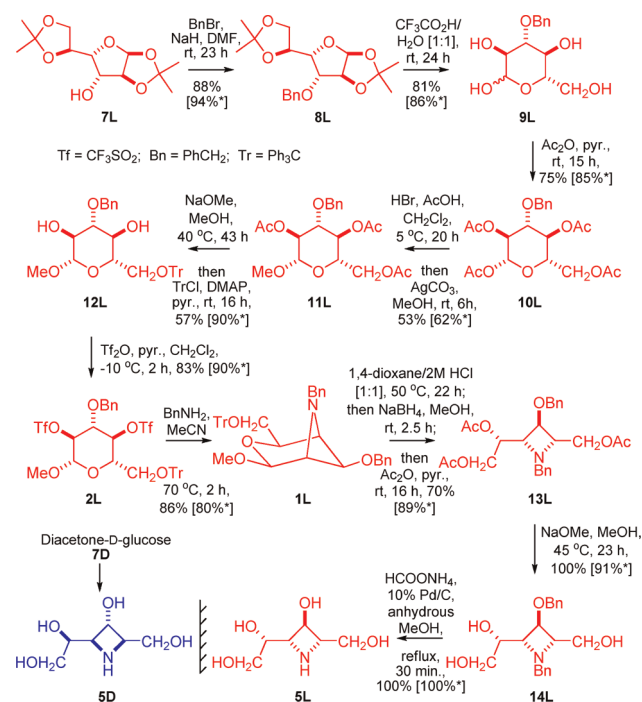
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(14) The equivalence of 2,4-dideoxy-2,4-imino- and of 3,5-dideoxy-3,5-imino-hexitols is shown in Scheme 1. IUPAC carbohydrate nomenclature names **5** as 3,5-dideoxy-3,5-imino-altritol and **6** as 2,4-dideoxy-2,4-imino-iditol.

protected β -glucoside **11L** (53%). Sodium methoxide in methanol removed the acetate protecting groups in **11L** to allow subsequent protection of the primary alcohol by treatment with trityl chloride in pyridine in the presence of DMAP to afford the diol **12L** (57%). Esterification of the free hydroxyl groups in **12L** with triflic anhydride in dichloromethane in the presence of pyridine afforded the ditriflate **2L** (83%) which with benzylamine in acetonitrile underwent a highly efficient cyclization to produce the bicyclic azetidine **1L** in 86% yield. All attempts to get the α -anomer of **2L** to undergo a similar cyclization in a significant yield were unsuccessful; further studies are in progress to determine the propensity of similar anomeric pyranose ditriflates to form azetidines. Hydrolysis of **1L** with aqueous hydrochloric acid in dioxane removed both the trityl and anomeric protecting groups; reduction of the crude lactol with sodium borohydride in methanol and subsequent acetylation of the resulting triol with acetic anhydride in pyridine afforded the triacetate **13L** (70%), allowing easy purification. Removal of the acetates from **13L** by sodium methoxide in methanol gave **14L** (100%); subsequent transfer hydrogenation with ammonium formate in anhydrous methanol in the presence of 10% palladium on charcoal removed both benzyl groups from **14L** to form the target azetidine **5L**¹⁷ {100%, [α]_D²⁵ +15.5 (*c* 0.49, H₂O) for the hydrochloride salt} in an overall yield of 8% from **7L**. The enantiomer **5D** {[α]_D²⁵ –13.9 (*c* 0.44, H₂O) for the hydrochloride salt} was prepared by a similar procedure in 22% overall yield from diacetone-D-glucose **7D**.

The synthesis of 2,4-dideoxy-2,4-imino-L-iditol **6L**, an epimer of **5L**, via azetidine ring formation between C3 and C5 [Scheme 3], required initial epimerization of C3 in diacetone glucose **7D** to the allose **15D**.¹⁸ Selective removal of the exocyclic acetone in **15D** by hydrolysis with aqueous acetic acid afforded the triol **16D** (81%). Reaction

Scheme 2. Synthesis of Azetidines **5L** and **5D**^a



^a * = yield for enantiomers prepared from **7D**.

of **16D** with *tert*-butyldimethylsilyl chloride in DMF gave the silyl ether **17D** (94%), which on esterification of the free hydroxyl groups at C3 and C5 formed the ditriflate **3D** (98%). Reaction of the ditriflate **3D** with benzylamine in the presence of diisopropylethylamine (DIPEA) gave the fused azetidine **4L** (93%). Treatment of **4L** with aqueous trifluoroacetic acid removed both the silyl and isopropylidene protecting groups; reduction of the resulting lactol with sodium borohydride in water afforded a triol **19L**, which was isolated as the nonpolar triacetate **18L** [68% overall yield from **4L**]. Removal of the esters from **18L** with sodium methoxide in methanol gave **19L** (98%), which on hydrogenolysis of the *N*-benzyl group by transfer hydrogenation formed the iminoiditol **6L**¹⁹ {[α]_D²⁵ –6.2 (*c* 0.5, MeOH) for the hydrochloride salt} (100%). The overall yield of **6L** from **15D** was 46%. The enantiomer **6D** {[α]_D²⁵

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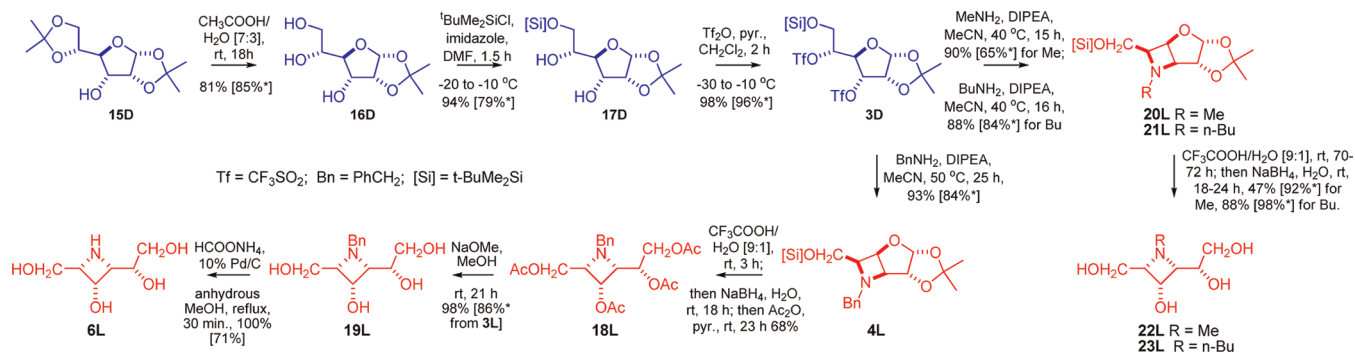
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(17) Selected data for a HCl salt of 3,5-dideoxy-3,5-imino-D-altritol **5D**: δ_{H} (D₂O, 500 MHz): 3.62–3.65 (1H, dd, H6, *J*_{6,5} 5.1 Hz, *J*_{gem} 12.1 Hz), 3.68–3.71 (1H, dd, H6', *J*_{6',5} 4.1 Hz, *J*_{gem} 12.1 Hz), 3.88–3.92 (1H, dd, H1, *J*_{1,2} 4.1 Hz, *J*_{gem} 13.3 Hz), 3.91–3.95 (1H, dd, H1', *J*_{1',2} 4.8 Hz, *J*_{gem} 13.3 Hz), 4.06–4.09 (1H, a-dt, H5, *J*_{5,6'} 4.1 Hz, *J*_{5,6}/*J*_{5,4} 5.3 Hz), 4.30–4.32 (1H, dd, H4, *J*_{4,5} 5.5 Hz, *J*_{4,3} 7.2 Hz), 4.33–4.36 (1H, a-dt, H2, *J*_{2,1}/*J*_{2,1'} 4.4 Hz, *J*_{2,3} 7.2 Hz), 4.57–4.60 (1H, t, H3, *J*_{3,4}/*J*_{3,2} 7.2 Hz); δ_{C} (D₂O, 125 MHz): 58.4 (C1), 62.6 (C6), 64.9 (C3), 67.4, 67.6 (C2 and C4), 68.8 (C5).

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(19) Selected data for 3,5-dideoxy-3,5-imino-D-altritol **6L**: mp 101–102 °C; δ_{H} (D₂O, 400 MHz): 3.45–3.50 (1H, dd, H6, *J*_{6,5} 6.3 Hz, *J*_{gem} 11.9 Hz), 3.62–3.66 (1H, dd, H6', *J*_{6',5} 3.5 Hz, *J*_{gem} 11.9 Hz), 3.63–3.67 (1H, dd, H1, *J*_{1,2} 6.3 Hz, *J*_{gem} 11.3 Hz), 3.82–3.87 (1H, dd, H1', *J*_{1',2} 7.0 Hz, *J*_{gem} 11.3 Hz), 3.84–3.88 (1H, dd, H4, *J*_{4,3} 6.3 Hz, *J*_{4,5} 8.6 Hz), 3.94–3.99 (1H, ddd, H5, *J*_{5,6'} 3.5 Hz, *J*_{5,6} 6.3 Hz, *J*_{5,4} 8.7 Hz), 3.99–4.04 (1H, a-dt, H2, *J*_{2,3}/*J*_{2,1} 6.4 Hz, *J*_{2,1'} 7.0 Hz), 4.62–4.65 (1H, a-t, H3, *J*_{3,2}/*J*_{3,4} 6.4 Hz); δ_{C} (D₂O, 100 MHz): 60.3 (C4), 60.5 (C2), 61.0 (C1), 63.4 (C6), 68.0 (C3), 71.8 (C5). Selected data for HCl salt of 3,5-dideoxy-3,5-imino-D-altritol **6L**: δ_{H} (D₂O, 400 MHz): 3.56–3.60 (1H, dd, H6, *J*_{6,5} 5.2 Hz, *J*_{gem} 12.2 Hz), 3.68–3.72 (1H, dd, H6', *J*_{6',5} 3.5 Hz, *J*_{gem} 12.2 Hz), 3.95–4.00 (1H, dd, H1, *J*_{1,2} 5.3 Hz, *J*_{gem} 12.7 Hz), 4.05–4.10 (1H, dd, H1', *J*_{1',2} 7.2 Hz, *J*_{gem} 12.7 Hz), 4.28–4.32 (1H, ddd, H5, *J*_{5,6'} 3.5 Hz, *J*_{5,6} 5.2 Hz, *J*_{5,4} 8.1 Hz), 4.56–4.59 (1H, dd, H4, *J*_{4,3} 6.7 Hz, *J*_{4,5} 8.1 Hz), 4.63–4.67 (1H, m, H2), 4.79–4.82 (1H, a-t, H3, *J*_{3,2}/*J*_{3,4} 6.5 Hz); δ_{C} (D₂O, 100 MHz): 57.2 (C1), 63.0 (C6), 64.0, 64.0 (C2 and C4), 66.3 (C3), 67.4 (C5).

Scheme 3. Synthesis of Azetidines **6L and **6D**^a**



^a * = yield for enantiomers prepared from **15L**.

+12.1 (*c* 0.5, MeOH) for the hydrochloride salt} was also prepared from diacetone-L-allose **15L** by a similar route in an overall yield of 33%.

N-Alkylation of imino sugar mimics can affect their biological properties significantly;²⁰ the ring closure of the ditriflate **3D** proceeded in good yield with a number of amines, allowing access to *N*-alkyl azetidines. Reaction of the ditriflate **3D** with methylamine in acetonitrile in the presence of DIPEA formed the protected azetidine **20L** (90%); with butylamine under the same conditions **21L** was obtained (88%), illustrating the general efficiency of the ring closure. Hydrolysis of **20L** with aqueous trifluoroacetic acid followed by reduction with sodium borohydride gave the *N*-methyl azetidine **22L** (47%); similar treatment of **20L** afforded the *N*-butyl analogue **23L** (88%).

Inhibition by the azetidine iminosugars of the activity of the following glycosidases was studied:²¹ α -glucosidases (rice, yeast, rat intestinal maltase, *A. niger*), β -glucosidases (almond, bovine liver), α -galactosidase (coffee beans), β -galactosidase (bovine liver), α -mannosidase (Jack bean),

β -mannosidase (snail), α -L-rhamnosidase (*P. decumbens*), α -L-fucosidase (bovine kidney), trehalase (porcine kidney), and amyloglucosidases (*A. niger*, *Rhizopus sp.*). The *N*-benzyl-D-iditol **19D** showed potent and specific inhibition of rice and rat intestinal maltase [IC₅₀ 27 and 71 μ M, respectively] whereas the parent D-iditol **6D** showed no inhibition. The imino-L-talitol **5L** was a moderate inhibitor of rice and rat intestinal maltase [IC₅₀ 481 and 176 μ M, respectively]. The imino-L-iditol **6L** showed weak but selective α -galactosidase inhibition [IC₅₀ 416 μ M].

In summary, bicyclic azetidines may be formed by high yielding cyclizations of ditriflates of both pyranosides and furanosides. While this paper has illustrated the value of this strategy in the synthesis of iminosugar azetidines, this strategy may provide a general approach to the synthesis of enantiomerically pure highly functionalized azetidines and, in particular, allow easy access to a new range of azetidine carboxylic acids.

Acknowledgment. This work was supported by EPSRC (G.L.S.), Junta de Extremadura (N.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).

Supporting Information Available. Experimental procedures and full spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.

(20) (a) Axamawaty, M. T. H.; Fleet, G. W. J.; Hannah, K. A.; Namgoong, S. K.; Sinnott, M. L. *Biochem. J.* **1990**, *266*, 245–249. (b) Rawlings, A. J.; Lomas, H.; Pilling, A. W.; Lee, M. J.-R.; Alonzi, D. S.; Rountree, J. S. S.; Jenkinson, S. F.; Fleet, G. W. J.; Dwek, R. A.; Jones, J. H.; Butters, T. D. *ChemBioChem* **2009**, *10*, 1101–1105.

(21) For details of assays, see: (a) Mercer, T. B.; Jenkinson, S. F.; Nash, R. J.; Miyauchi, S.; Kato, A.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2009**, *20*, 2368–2373. (b) 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. Tables of the glycosidase inhibition by the azetidines are shown in the Supporting Information.

N-Benzyl-1,3-dideoxy-1,3-imino-L-xylitol

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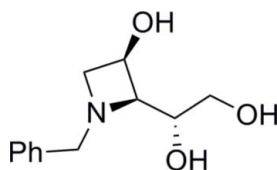
Received 16 August 2011; accepted 19 August 2011

Key indicators: single-crystal X-ray study; $T = 150$ K; mean $\sigma(\text{C}—\text{C}) = 0.004$ Å; R factor = 0.045; wR factor = 0.102; data-to-parameter ratio = 10.6.

The structure determination confirms the stereochemistry of the title compound, $\text{C}_{12}\text{H}_{17}\text{NO}_3$, which contains a four-membered azetidine ring system. The absolute configuration was determined by the use of D-glucose as the starting material. In the crystal, $\text{O}—\text{H} \cdots \text{O}$ and $\text{O}—\text{H} \cdots \text{N}$ hydrogen bonds link the molecules into layers in the ab plane.

Related literature

For related literature on azetidines, see: Krämer *et al.* (1997); Michaud *et al.* (1997a,b); Dekaris & Reissig (2010); Soengas *et al.* (2011). For related literature on iminosugars, see: Asano *et al.* (2000); Watson *et al.* (2001). For details of the cryostat, see: Cosier & Glazer (1986).



Experimental

Crystal data

$\text{C}_{12}\text{H}_{17}\text{NO}_3$
 $M_r = 223.27$
Orthorhombic, $P2_12_12_1$
 $a = 6.2309$ (2) Å
 $b = 9.3918$ (4) Å
 $c = 19.9175$ (9) Å
 $V = 1165.56$ (8) Å³
 $Z = 4$
Mo $K\alpha$ radiation
 $\mu = 0.09$ mm⁻¹
 $T = 150$ K
 $0.20 \times 0.10 \times 0.07$ mm

Data collection

Nonius KappaCCD diffractometer
Absorption correction: multi-scan
(*DENZO/SCALEPACK*;
Otwinowski & Minor, 1997)
 $T_{\min} = 0.97$, $T_{\max} = 0.99$
6149 measured reflections
1541 independent reflections
1098 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.065$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.045$
 $wR(F^2) = 0.102$
 $S = 0.95$
1541 reflections
146 parameters
H-atom parameters constrained
 $\Delta\rho_{\max} = 0.49$ e Å⁻³
 $\Delta\rho_{\min} = -0.49$ e Å⁻³

Table 1

Hydrogen-bond geometry (Å, °).

$D—H \cdots A$	$D—H$	$H \cdots A$	$D \cdots A$	$D—H \cdots A$
$\text{O4}—\text{H41} \cdots \text{O16}^{\text{i}}$	0.84	2.18	2.825 (4)	134
$\text{O16}—\text{H161} \cdots \text{O1}^{\text{ii}}$	0.84	1.90	2.735 (4)	171
$\text{O1}—\text{H11} \cdots \text{N6}^{\text{i}}$	0.86	1.86	2.719 (4)	171

Symmetry codes: (i) $-x + 2, y + \frac{1}{2}, -z + \frac{3}{2}$; (ii) $-x + 1, y - \frac{1}{2}, -z + \frac{3}{2}$.

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: LH5318).

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supplementary materials

Acta Cryst. (2011). E67, o2452 [doi:10.1107/S160053681103399X]

***N*-Benzyl-1,3-dideoxy-1,3-imino-L-xylitol**

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Comment

Azetidines (Michaud *et al.*, 1997*a,b*; Dekaris & Reissig, 2010; Soengas *et al.*, 2011) are a relatively unstudied class of iminosugars (Asano *et al.*, 2000; Watson *et al.*, 2001) but initial results (Krämer *et al.*, 1997) have shown that they can exhibit interesting biological activity. The title compound was formed from a protected ribofuranose derived from *D*-glucose (Fig. 1).

The molecular structure of the title compound is shown in Fig. 2. The four-membered ring system adopts a puckered conformation. The structure consists of hydrogen bonded layers of molecules in the *ab* plane (Fig. 3, Fig. 4). Each molecule is a hydrogen-bond donor and acceptor for three hydrogen bonds. Only classical hydrogen bonding was considered.

Experimental

The title compound was recrystallized from methanol: $[\alpha]_D^{25} -103.0$ (*c* 0.23 in MeOH); m.p. 452–453 K.

Refinement

In the absence of significant anomalous scattering, Friedel pairs were merged and the absolute configuration was assigned by the use of *D*-glucose as the starting material.

The H atoms were all located in a difference map, but those attached to C 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 $U_{\text{iso}}(\text{H})$ (in the range 1.2–1.5 times U_{eq} of the parent atom), after which the positions were refined with riding constraints.

Figures



Fig. 1. Synthetic Scheme.

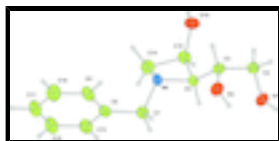


Fig. 2. The title compound with displacement ellipsoids drawn at the 50% probability level. H atoms are shown as spheres of arbitrary radius.

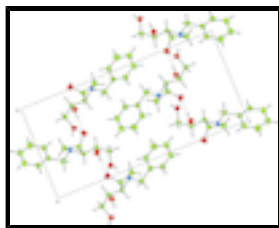


Fig. 3. Packing diagram of the compound projected along the *a* axis. Hydrogen bonding is denoted by dotted lines.

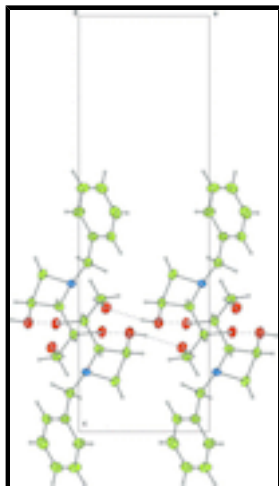


Fig. 4. Packing diagram of the compound projected along the *b* axis. Hydrogen bonding is denoted by dotted lines.

***N*-Benzyl-1,3-dideoxy-1,3-imino-*L*-xylitol**

Crystal data

$C_{12}H_{17}NO_3$

$M_r = 223.27$

Orthorhombic, $P2_12_12_1$

Hall symbol: P 2ac 2ab

$a = 6.2309 (2) \text{ \AA}$

$b = 9.3918 (4) \text{ \AA}$

$c = 19.9175 (9) \text{ \AA}$

$V = 1165.56 (8) \text{ \AA}^3$

$Z = 4$

$F(000) = 480$

$D_x = 1.272 \text{ Mg m}^{-3}$

Mo $K\alpha$ radiation, $\lambda = 0.71073 \text{ \AA}$

Cell parameters from 1467 reflections

$\theta = 5\text{--}27^\circ$

$\mu = 0.09 \text{ mm}^{-1}$

$T = 150 \text{ K}$

Prism, colourless

$0.20 \times 0.10 \times 0.07 \text{ mm}$

Data collection

Nonius KappaCCD
diffractometer

graphite

ω scans

Absorption correction: multi-scan
(*DENZO/SCALEPACK*; Otwinowski & Minor, 1997)

$T_{\min} = 0.97$, $T_{\max} = 0.99$

6149 measured reflections

1541 independent reflections

1098 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.065$

$\theta_{\max} = 27.5^\circ$, $\theta_{\min} = 5.2^\circ$

$h = -8 \rightarrow 8$

$k = -12 \rightarrow 12$

$l = -25 \rightarrow 25$

Refinement

Refinement on F^2	Hydrogen site location: inferred from neighbouring sites
Least-squares matrix: full	H-atom parameters constrained
$R[F^2 > 2\sigma(F^2)] = 0.045$	Method = modified Sheldrick, $w = 1/[\sigma^2(F^2) + (0.05P)^2 + 0.13P]$, where $P = [\max(F_o^2, 0) + 2F_c^2]/3$
$wR(F^2) = 0.102$	$(\Delta/\sigma)_{\max} = 0.0002627$
$S = 0.95$	$\Delta\rho_{\max} = 0.49 \text{ e } \text{\AA}^{-3}$
1541 reflections	$\Delta\rho_{\min} = -0.49 \text{ e } \text{\AA}^{-3}$
146 parameters	Extinction correction: Larson (1970), Equation 22
0 restraints	Extinction coefficient: 400 (70)
Primary atom site location: structure-invariant direct methods	

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 ($\text{\AA}^2$)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
O1	0.7910 (3)	0.89266 (18)	0.79718 (9)	0.0257
C2	0.8327 (4)	0.7498 (3)	0.81847 (12)	0.0246
C3	0.9587 (4)	0.6675 (3)	0.76640 (12)	0.0212
O4	1.1771 (3)	0.71531 (19)	0.75988 (9)	0.0261
C5	0.8472 (4)	0.6736 (3)	0.69895 (12)	0.0206
N6	0.9436 (3)	0.5853 (2)	0.64366 (9)	0.0198
C7	1.0678 (4)	0.6647 (3)	0.59325 (12)	0.0248
C8	1.1061 (4)	0.5768 (3)	0.53082 (12)	0.0252
C9	1.2467 (4)	0.4615 (3)	0.53077 (13)	0.0286
C10	1.2791 (5)	0.3829 (3)	0.47302 (15)	0.0384
C11	1.1727 (5)	0.4177 (3)	0.41474 (14)	0.0366
C12	1.0312 (5)	0.5309 (3)	0.41392 (14)	0.0373
C13	0.9984 (5)	0.6088 (3)	0.47187 (13)	0.0313
C14	0.7214 (4)	0.5438 (3)	0.62186 (13)	0.0277
C15	0.6349 (4)	0.5921 (3)	0.69017 (12)	0.0245
O16	0.6117 (3)	0.48138 (19)	0.73784 (9)	0.0277
H22	0.9101	0.7535	0.8624	0.0291*
H21	0.6964	0.7000	0.8265	0.0280*
H31	0.9716	0.5645	0.7806	0.0250*
H51	0.8349	0.7719	0.6843	0.0251*
H72	1.2057	0.6871	0.6139	0.0252*
H71	0.9916	0.7537	0.5814	0.0268*
H91	1.3207	0.4363	0.5701	0.0319*

supplementary materials

H101	1.3719	0.3075	0.4739	0.0480*
H111	1.1995	0.3646	0.3761	0.0436*
H121	0.9557	0.5547	0.3747	0.0440*
H131	0.9009	0.6860	0.4710	0.0365*
H141	0.7104	0.4397	0.6145	0.0348*
H142	0.6670	0.5939	0.5830	0.0324*
H151	0.5114	0.6524	0.6881	0.0289*
H41	1.1628	0.8040	0.7623	0.0399*
H161	0.4864	0.4499	0.7314	0.0409*
H11	0.8789	0.9468	0.8187	0.0398*

Atomic displacement parameters ($\text{\AA}^2$)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0245 (9)	0.0213 (9)	0.0312 (9)	0.0011 (8)	−0.0042 (8)	−0.0039 (9)
C2	0.0288 (15)	0.0219 (14)	0.0231 (13)	−0.0006 (12)	−0.0021 (11)	0.0021 (11)
C3	0.0174 (12)	0.0210 (13)	0.0251 (13)	−0.0022 (11)	−0.0003 (11)	0.0004 (12)
O4	0.0193 (9)	0.0254 (10)	0.0336 (10)	0.0013 (8)	−0.0012 (8)	−0.0025 (9)
C5	0.0242 (13)	0.0189 (12)	0.0187 (11)	−0.0011 (11)	0.0015 (11)	−0.0004 (11)
N6	0.0205 (10)	0.0233 (11)	0.0157 (10)	−0.0008 (10)	−0.0005 (9)	−0.0030 (10)
C7	0.0226 (13)	0.0283 (15)	0.0236 (13)	−0.0042 (13)	0.0003 (12)	−0.0009 (12)
C8	0.0246 (14)	0.0304 (15)	0.0206 (12)	−0.0055 (13)	0.0004 (11)	0.0012 (12)
C9	0.0224 (13)	0.0402 (17)	0.0232 (13)	0.0039 (13)	0.0016 (12)	0.0029 (13)
C10	0.0325 (16)	0.0423 (18)	0.0404 (16)	0.0075 (15)	0.0068 (15)	−0.0048 (16)
C11	0.0372 (16)	0.0458 (19)	0.0267 (14)	0.0000 (16)	0.0051 (14)	−0.0056 (15)
C12	0.0399 (17)	0.0489 (19)	0.0232 (14)	−0.0010 (17)	−0.0029 (14)	−0.0025 (14)
C13	0.0350 (16)	0.0333 (16)	0.0256 (13)	0.0041 (14)	−0.0033 (12)	0.0017 (14)
C14	0.0212 (13)	0.0347 (16)	0.0273 (14)	−0.0005 (13)	−0.0055 (12)	−0.0009 (13)
C15	0.0174 (12)	0.0286 (15)	0.0275 (12)	0.0059 (12)	−0.0002 (11)	0.0017 (13)
O16	0.0215 (9)	0.0282 (10)	0.0335 (10)	−0.0042 (8)	−0.0010 (9)	0.0070 (9)

Geometric parameters ($\text{\AA}$, $^\circ$)

O1—C2	1.431 (3)	C8—C9	1.393 (4)
O1—H11	0.862	C8—C13	1.385 (4)
C2—C3	1.513 (3)	C9—C10	1.382 (4)
C2—H22	1.000	C9—H91	0.939
C2—H21	0.982	C10—C11	1.376 (4)
C3—O4	1.439 (3)	C10—H101	0.914
C3—C5	1.514 (3)	C11—C12	1.381 (4)
C3—H31	1.011	C11—H111	0.932
O4—H41	0.839	C12—C13	1.382 (4)
C5—N6	1.504 (3)	C12—H121	0.939
C5—C15	1.538 (3)	C13—H131	0.945
C5—H51	0.971	C14—C15	1.532 (3)
N6—C7	1.471 (3)	C14—H141	0.991
N6—C14	1.503 (3)	C14—H142	0.967
C7—C8	1.512 (3)	C15—O16	1.416 (3)
C7—H72	0.976	C15—H151	0.956

C7—H71	0.990	O16—H161	0.844
C2—O1—H11	106.9	C7—C8—C13	120.2 (2)
O1—C2—C3	111.7 (2)	C9—C8—C13	118.2 (2)
O1—C2—H22	108.3	C8—C9—C10	120.5 (3)
C3—C2—H22	111.6	C8—C9—H91	120.3
O1—C2—H21	109.7	C10—C9—H91	119.2
C3—C2—H21	108.5	C9—C10—C11	120.3 (3)
H22—C2—H21	106.9	C9—C10—H101	119.4
C2—C3—O4	113.2 (2)	C11—C10—H101	120.3
C2—C3—C5	110.5 (2)	C10—C11—C12	120.0 (3)
O4—C3—C5	110.0 (2)	C10—C11—H111	118.9
C2—C3—H31	109.8	C12—C11—H111	121.1
O4—C3—H31	104.4	C11—C12—C13	119.5 (3)
C5—C3—H31	108.7	C11—C12—H121	120.9
C3—O4—H41	101.8	C13—C12—H121	119.6
C3—C5—N6	116.5 (2)	C8—C13—C12	121.4 (3)
C3—C5—C15	118.5 (2)	C8—C13—H131	119.5
N6—C5—C15	89.19 (17)	C12—C13—H131	119.1
C3—C5—H51	109.8	N6—C14—C15	89.48 (18)
N6—C5—H51	109.6	N6—C14—H141	111.2
C15—C5—H51	111.8	C15—C14—H141	113.5
C5—N6—C7	115.48 (19)	N6—C14—H142	115.3
C5—N6—C14	89.22 (17)	C15—C14—H142	116.3
C7—N6—C14	114.8 (2)	H141—C14—H142	109.7
N6—C7—C8	111.6 (2)	C5—C15—C14	86.89 (19)
N6—C7—H72	106.5	C5—C15—O16	112.1 (2)
C8—C7—H72	109.0	C14—C15—O16	114.5 (2)
N6—C7—H71	109.8	C5—C15—H151	113.7
C8—C7—H71	109.9	C14—C15—H151	114.9
H72—C7—H71	109.9	O16—C15—H151	112.5
C7—C8—C9	121.6 (2)	C15—O16—H161	104.4

Hydrogen-bond geometry (Å, °)

<i>D</i> —H $\cdots$ <i>A</i>	<i>D</i> —H	H $\cdots$ <i>A</i>	<i>D</i> $\cdots$ <i>A</i>	<i>D</i> —H $\cdots$ <i>A</i>
C11—H111 $\cdots$ O4 ⁱ	0.93	2.55	3.457 (4)	164
C15—H151 $\cdots$ O4 ⁱⁱ	0.96	2.59	3.377 (4)	139
O4—H41 $\cdots$ O16 ⁱⁱⁱ	0.84	2.18	2.825 (4)	134
O16—H161 $\cdots$ O1 ^{iv}	0.84	1.90	2.735 (4)	171
O1—H11 $\cdots$ N6 ⁱⁱⁱ	0.86	1.86	2.719 (4)	171

Symmetry codes: (i) $-x+5/2, -y+1, z-1/2$; (ii) $x-1, y, z$; (iii) $-x+2, y+1/2, -z+3/2$; (iv) $-x+1, y-1/2, -z+3/2$.

Fig. 1

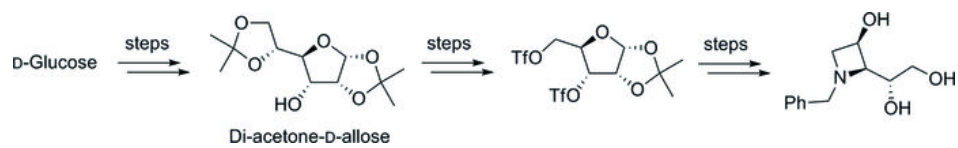


Fig. 2

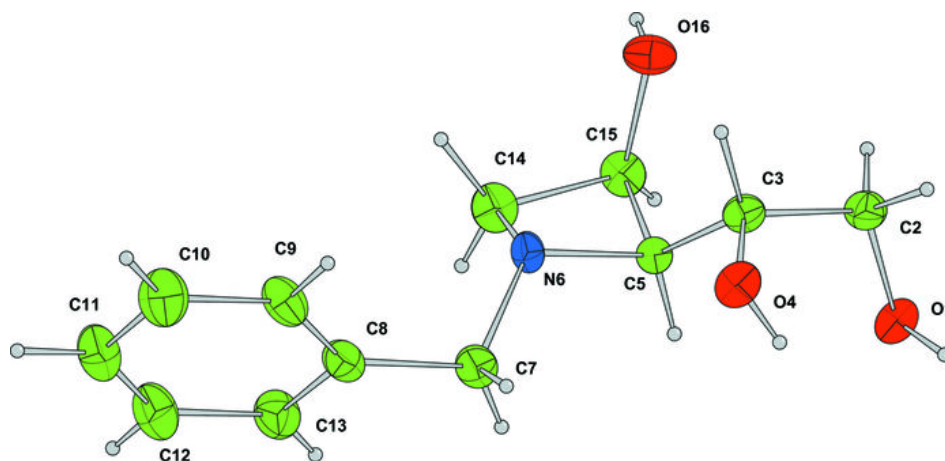


Fig. 3

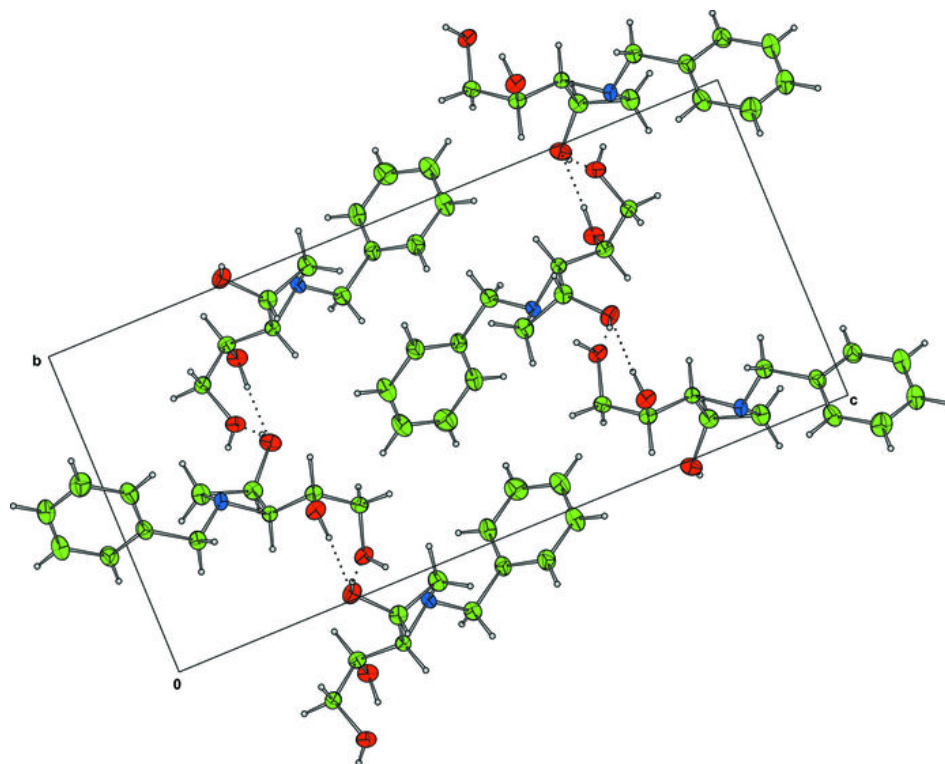
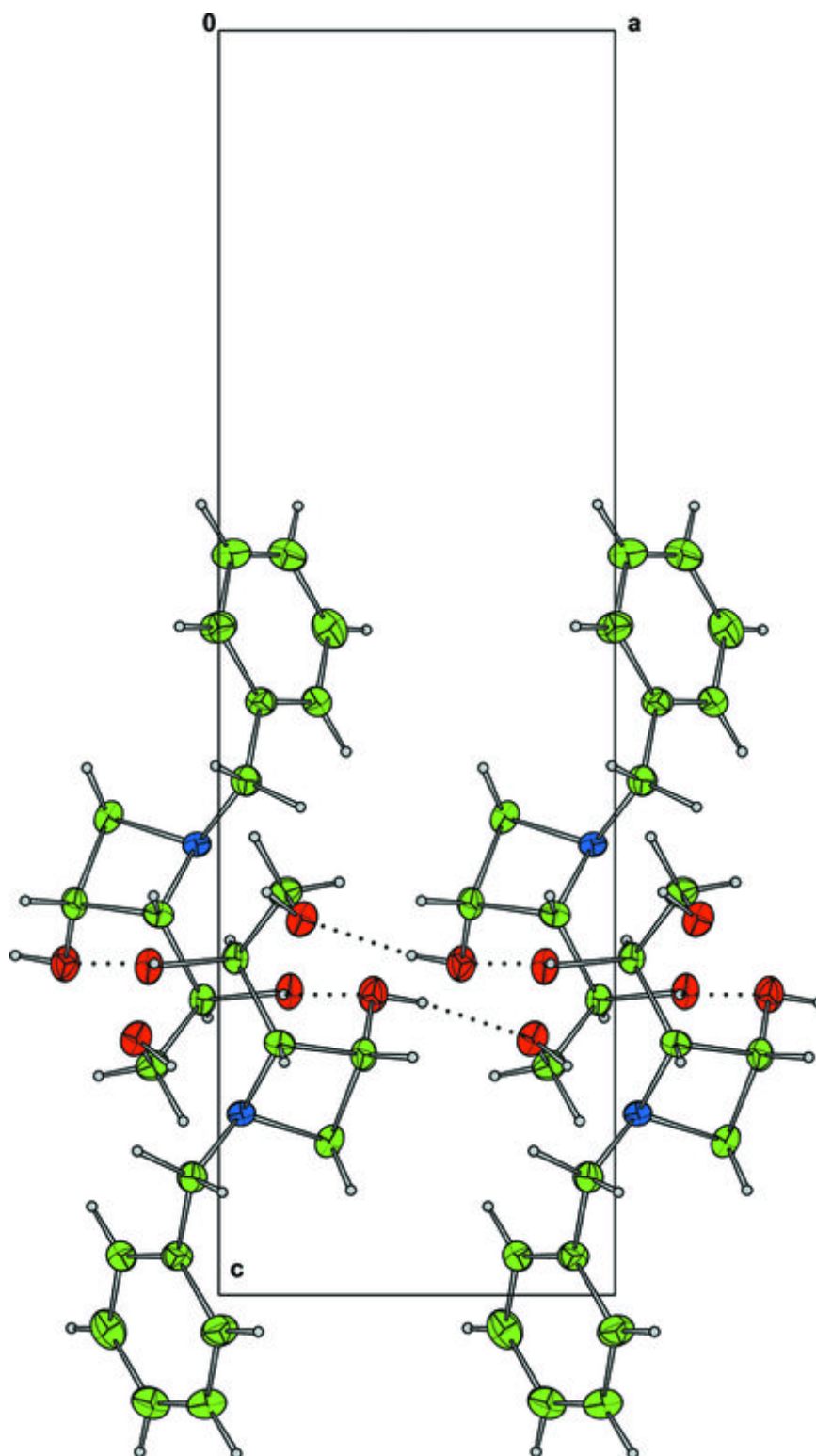


Fig. 4



Acta Crystallographica Section E

Structure Reports

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N-Benzyl-3,5-dideoxy-3,5-imino-1,2-O-isopropylidene- β -L-lyxofuranoseDavid S. Edgeley,^a Sarah F. Jenkinson,^{b*} Gabriel Lenagh-Snow,^b Catherine Rutherford,^b George W. J. Fleet^b and Amber L. Thompson^a^aDepartment of Chemical Crystallography, Chemistry Research Laboratory, University of Oxford, Oxford OX1 3TA, England, and ^bDepartment of Organic Chemistry, Chemistry Research Laboratory, University of Oxford, Oxford OX1 3TA, England
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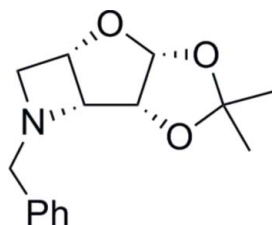
Received 30 June 2012; accepted 4 July 2012

Key indicators: single-crystal X-ray study; $T = 150$ K; mean $\sigma(\text{C}-\text{C}) = 0.003$ Å; R factor = 0.033; wR factor = 0.087; data-to-parameter ratio = 9.5.

X-ray crystallography confirmed the formation, structure and relative stereochemistry of the title compound, $\text{C}_{15}\text{H}_{19}\text{NO}_3$, which contains a sterically congested four-membered azetidine ring system. The absolute configuration was determined by the use of L-arabinose as the starting material.

Related literature

For related literature on azetidines, see: Krämer *et al.* (1997); Michaud *et al.* (1997a,b); Dekaris & Reissig (2010); Soengas *et al.* (2011); Jenkinson *et al.* (2011); Lenagh-Snow *et al.* (2011, 2012); Lee *et al.* (2012). For related literature on iminosugars, see: Asano *et al.* (2000); Watson *et al.* (2001). For details of the cryostat, see: Cosier & Glazer (1986). For details of hydrogen refinement, see: Cooper *et al.* (2010). For references to the Chebychev polynomial, see: Prince (1982); Watkin (1994).

**Experimental***Crystal data* $\text{C}_{15}\text{H}_{19}\text{NO}_3$
 $M_r = 261.32$
Monoclinic, $P2_1$
 $a = 9.1674$ (2) Å
 $b = 5.7551$ (1) Å
 $c = 13.1112$ (3) Å
 $\beta = 106.9544$ (8)° $V = 661.67$ (2) Å³
 $Z = 2$
Mo $K\alpha$ radiation
 $\mu = 0.09$ mm⁻¹
 $T = 150$ K
 $0.24 \times 0.23 \times 0.07$ mm*Data collection*Nonius KappaCCD diffractometer
Absorption correction: multi-scan
(*DENZO* and *SCALEPACK*;
Otwinowski & Minor, 1997)
 $T_{\min} = 0.94$, $T_{\max} = 0.99$ 13110 measured reflections
1638 independent reflections
1544 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.014$ *Refinement* $R[F^2 > 2\sigma(F^2)] = 0.033$
 $wR(F^2) = 0.087$
 $S = 0.94$
1638 reflections
172 parameters1 restraint
H-atom parameters constrained
 $\Delta\rho_{\max} = 0.17$ e Å⁻³
 $\Delta\rho_{\min} = -0.18$ e Å⁻³

Data collection: *COLLECT* (Nonius, 2001); cell refinement: *DENZO* and *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* and *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: LH5500).

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supplementary materials

Acta Cryst. (2012). E68, o2410 [doi:10.1107/S1600536812030656]

N-Benzyl-3,5-dideoxy-3,5-imino-1,2-O-isopropylidene- β -L-lyxofuranose

David S. Edgeley, Sarah F. Jenkinson, Gabriel Lenagh-Snow, Catherine Rutherford, George W. J. Fleet and Amber L. Thompson

Comment

Azetidines (Michaud *et al.*, 1997*a*; Michaud *et al.*, 1997*b*; Dekaris & Reissig, 2010; Soengas *et al.*, 2011) are a relatively unstudied class of iminosugars (Asano *et al.*, 2000; Watson *et al.*, 2001, Michaud *et al.*, 1997*a*; Michaud *et al.*, 1997*b*; Dekaris & Reissig, 2010; Soengas *et al.*, 2011) but initial results (Krämer *et al.*, 1997; Lee *et al.*, 2012) have shown some interesting biological activity.

Azetidine formation can be achieved by the double displacement of ditriflates with amines (Jenkinson *et al.*, 2011; Lenagh-Snow *et al.*, 2011; Lenagh-Snow *et al.*, 2012). X-Ray crystallography confirmed the structure and relative stereochemistry of the formation of the title compound **3** (Fig. 1) from the displacement of a 3,5-*O*-ditriflate **2** with benzylamine. The absolute stereochemistry was determined by the use of L-arabinose as the starting material.

The five membered rings adopt envelope conformations with O7 and C10 out of the plane, and the azetidine ring adopts a puckered conformation (Fig. 2, Fig. 3).

Experimental

The title compound was recrystallized from cyclohexane/pentane. $[\alpha]_D^{25} +76.0$ (*c* 0.50 in CHCl₃); m.p. 337–339 K.

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 Å) and $U_{\text{iso}}(\text{H})$ (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* and *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* and *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).

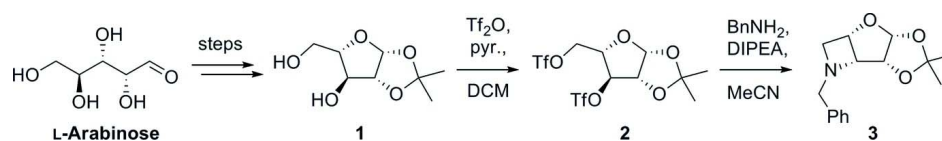


Figure 1

Synthetic Scheme.

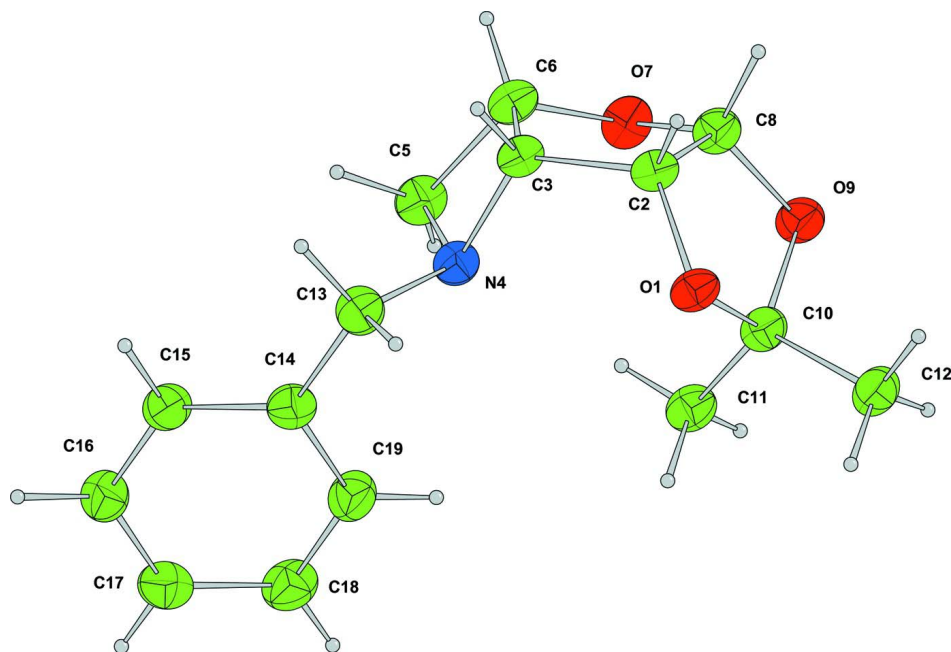
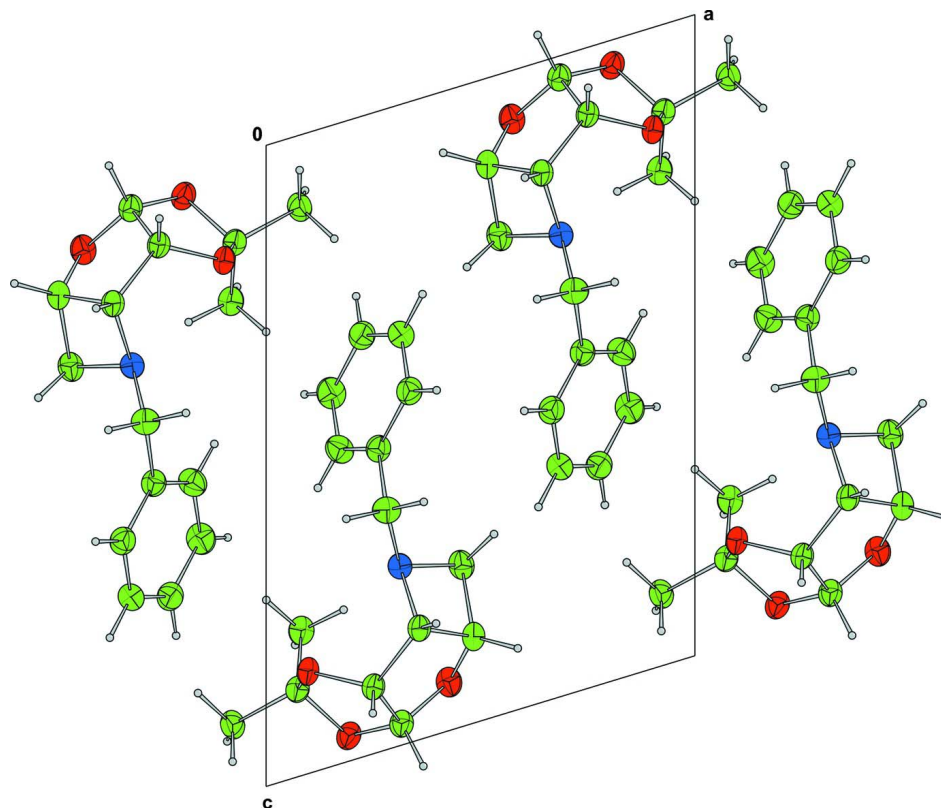


Figure 2

The title compound with displacement ellipsoids drawn at the 50% probability level. H atoms are shown as spheres of arbitrary radius.

**Figure 3**

Packing diagram of the title compound projected along the *b*-axis.

***N*-Benzyl-3,5-dideoxy-3,5-imino-1,2-*O*-isopropylidene- β -L-lyxofuranose**

Crystal data

$C_{15}H_{19}NO_3$

$M_r = 261.32$

Monoclinic, $P2_1$

Hall symbol: $P\ 2_1yb$

$a = 9.1674\ (2)\ \text{\AA}$

$b = 5.7551\ (1)\ \text{\AA}$

$c = 13.1112\ (3)\ \text{\AA}$

$\beta = 106.9544\ (8)^\circ$

$V = 661.67\ (2)\ \text{\AA}^3$

$Z = 2$

$F(000) = 280$

$D_x = 1.312\ \text{Mg m}^{-3}$

Mo $K\alpha$ radiation, $\lambda = 0.71073\ \text{\AA}$

Cell parameters from 1627 reflections

$\theta = 5\text{--}27^\circ$

$\mu = 0.09\ \text{mm}^{-1}$

$T = 150\ \text{K}$

Plate, colourless

$0.24 \times 0.23 \times 0.07\ \text{mm}$

Data collection

Nonius KappaCCD

diffractometer

Graphite monochromator

ω scans

Absorption correction: multi-scan

(*DENZO* and *SCALEPACK*; Otwinowski & Minor, 1997)

$T_{\min} = 0.94$, $T_{\max} = 0.99$

13110 measured reflections

1638 independent reflections

1544 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.014$

$\theta_{\max} = 27.4^\circ$, $\theta_{\min} = 5.4^\circ$

$h = -11 \rightarrow 11$

$k = -7 \rightarrow 6$

$l = -16 \rightarrow 16$

Refinement

Refinement on F^2

Least-squares matrix: full

 $R[F^2 > 2\sigma(F^2)] = 0.033$
 $wR(F^2) = 0.087$
 $S = 0.94$

1638 reflections

172 parameters

1 restraint

Primary atom site location: structure-invariant
direct methods

Hydrogen site location: difference Fourier map

H-atom parameters constrained

Method, part 1, Chebychev polynomial,

(Watkin, 1994, Prince, 1982) [weight] =

 $1.0/[A_0*T_0(x) + A_1*T_1(x) \cdots + A_{n-1}*T_{n-1}(x)]$

where A_i are the Chebychev coefficients listed

below and $x = F/F_{\max}$ Method = Robust

Weighting (Prince, 1982) $W = [\text{weight}]^*$
 $[1-(\Delta F/6*\sigma F)^2]^2$ A_i are: 22.1 34.0 17.6

5.07

 $(\Delta/\sigma)_{\max} = 0.0003$
 $\Delta\rho_{\max} = 0.17 \text{ e } \text{\AA}^{-3}$
 $\Delta\rho_{\min} = -0.18 \text{ e } \text{\AA}^{-3}$

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 ($\text{\AA}^2$)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
O1	0.09793 (13)	0.5625 (2)	0.84062 (10)	0.0269
C2	0.25050 (17)	0.6293 (3)	0.89568 (13)	0.0260
C3	0.35745 (18)	0.6618 (3)	0.82587 (13)	0.0262
N4	0.31206 (15)	0.5481 (3)	0.72006 (11)	0.0264
C5	0.45568 (19)	0.4116 (4)	0.74729 (15)	0.0318
C6	0.48402 (19)	0.4783 (3)	0.86494 (14)	0.0292
O7	0.42651 (14)	0.3113 (3)	0.92411 (10)	0.0319
C8	0.31601 (19)	0.4200 (3)	0.96665 (14)	0.0284
O9	0.19278 (13)	0.2728 (3)	0.96037 (10)	0.0313
C10	0.07349 (18)	0.3246 (3)	0.86343 (14)	0.0274
C11	0.0820 (2)	0.1650 (3)	0.77364 (14)	0.0306
C12	−0.07829 (19)	0.3058 (4)	0.88768 (15)	0.0333
C13	0.2813 (2)	0.6967 (3)	0.62624 (14)	0.0309
C14	0.2617 (2)	0.5526 (4)	0.52659 (14)	0.0288
C15	0.3343 (2)	0.6152 (4)	0.45124 (14)	0.0320
C16	0.3150 (2)	0.4828 (4)	0.35950 (14)	0.0353
C17	0.2236 (2)	0.2866 (4)	0.34202 (15)	0.0346
C18	0.1518 (2)	0.2208 (4)	0.41731 (16)	0.0379
C19	0.1714 (2)	0.3523 (4)	0.50899 (15)	0.0343
H21	0.2489	0.7722	0.9365	0.0300*
H31	0.3962	0.8232	0.8266	0.0305*
H51	0.4416	0.2480	0.7305	0.0388*
H52	0.5313	0.4779	0.7148	0.0374*
H61	0.5871	0.5325	0.9042	0.0348*
H81	0.3666	0.4639	1.0430	0.0337*
H112	0.0678	0.0054	0.7931	0.0457*
H113	0.0002	0.2059	0.7092	0.0453*
H111	0.1807	0.1782	0.7612	0.0454*
H121	−0.0909	0.1489	0.9112	0.0506*
H123	−0.1589	0.3444	0.8220	0.0494*

H122	−0.0782	0.4156	0.9454	0.0507*
H132	0.1871	0.7872	0.6208	0.0373*
H131	0.3679	0.8067	0.6310	0.0372*
H151	0.3977	0.7507	0.4630	0.0386*
H161	0.3646	0.5290	0.3064	0.0422*
H171	0.2100	0.2000	0.2782	0.0423*
H181	0.0896	0.0854	0.4067	0.0458*
H191	0.1208	0.3077	0.5589	0.0420*

Atomic displacement parameters ($\text{\AA}^2$)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0214 (5)	0.0238 (6)	0.0331 (6)	0.0007 (5)	0.0041 (4)	0.0028 (5)
C2	0.0234 (7)	0.0239 (8)	0.0291 (7)	−0.0006 (6)	0.0051 (6)	−0.0014 (7)
C3	0.0234 (7)	0.0242 (8)	0.0299 (7)	−0.0018 (6)	0.0063 (6)	−0.0014 (6)
N4	0.0255 (6)	0.0246 (7)	0.0293 (7)	−0.0002 (6)	0.0081 (5)	−0.0014 (6)
C5	0.0287 (8)	0.0290 (9)	0.0385 (9)	0.0023 (7)	0.0108 (7)	−0.0040 (8)
C6	0.0225 (7)	0.0289 (9)	0.0349 (8)	−0.0002 (7)	0.0063 (6)	−0.0003 (7)
O7	0.0293 (6)	0.0270 (6)	0.0393 (6)	0.0054 (5)	0.0100 (5)	0.0060 (6)
C8	0.0251 (7)	0.0274 (9)	0.0313 (8)	0.0014 (7)	0.0058 (6)	0.0036 (7)
O9	0.0264 (6)	0.0333 (7)	0.0311 (6)	−0.0017 (5)	0.0034 (5)	0.0078 (5)
C10	0.0248 (7)	0.0257 (8)	0.0299 (8)	−0.0007 (7)	0.0054 (6)	0.0049 (7)
C11	0.0291 (8)	0.0254 (8)	0.0361 (8)	−0.0019 (7)	0.0077 (7)	0.0013 (7)
C12	0.0264 (7)	0.0366 (10)	0.0376 (8)	−0.0030 (8)	0.0105 (6)	0.0037 (8)
C13	0.0365 (8)	0.0249 (8)	0.0318 (8)	−0.0035 (8)	0.0106 (7)	−0.0007 (7)
C14	0.0268 (7)	0.0279 (9)	0.0307 (8)	0.0010 (7)	0.0066 (6)	−0.0015 (7)
C15	0.0289 (8)	0.0330 (10)	0.0326 (8)	−0.0028 (8)	0.0069 (6)	0.0022 (7)
C16	0.0307 (8)	0.0430 (12)	0.0337 (9)	0.0009 (8)	0.0116 (7)	0.0003 (8)
C17	0.0306 (8)	0.0374 (10)	0.0342 (8)	0.0042 (8)	0.0070 (7)	−0.0071 (8)
C18	0.0374 (9)	0.0322 (10)	0.0447 (10)	−0.0062 (8)	0.0129 (8)	−0.0080 (9)
C19	0.0357 (9)	0.0317 (10)	0.0379 (9)	−0.0066 (8)	0.0147 (7)	−0.0034 (8)

Geometric parameters ($\text{\AA}$, $^\circ$)

O1—C2	1.4271 (19)	C11—H112	0.972
O1—C10	1.433 (2)	C11—H113	0.981
C2—C3	1.535 (2)	C11—H111	0.967
C2—C8	1.534 (2)	C12—H121	0.972
C2—H21	0.984	C12—H123	0.983
C3—N4	1.480 (2)	C12—H122	0.985
C3—C6	1.542 (2)	C13—C14	1.513 (2)
C3—H31	0.994	C13—H132	0.993
N4—C5	1.484 (2)	C13—H131	1.003
N4—C13	1.457 (2)	C14—C15	1.390 (2)
C5—C6	1.536 (2)	C14—C19	1.399 (3)
C5—H51	0.967	C15—C16	1.391 (3)
C5—H52	0.990	C15—H151	0.957
C6—O7	1.429 (2)	C16—C17	1.385 (3)
C6—H61	0.986	C16—H161	0.974
O7—C8	1.435 (2)	C17—C18	1.389 (3)

C8—O9	1.395 (2)	C17—H171	0.950
C8—H81	1.005	C18—C19	1.387 (3)
O9—C10	1.4456 (19)	C18—H181	0.952
C10—C11	1.513 (3)	C19—H191	0.941
C10—C12	1.519 (2)		
C2—O1—C10	109.99 (13)	O9—C10—C12	107.79 (14)
O1—C2—C3	115.67 (13)	O1—C10—C12	108.68 (15)
O1—C2—C8	104.34 (14)	C11—C10—C12	112.21 (15)
C3—C2—C8	104.59 (14)	C10—C11—H112	109.1
O1—C2—H21	109.4	C10—C11—H113	108.9
C3—C2—H21	109.7	H112—C11—H113	109.0
C8—C2—H21	113.1	C10—C11—H111	110.3
C2—C3—N4	116.83 (13)	H112—C11—H111	108.8
C2—C3—C6	105.56 (14)	H113—C11—H111	110.7
N4—C3—C6	89.27 (13)	C10—C12—H121	109.5
C2—C3—H31	113.4	C10—C12—H123	107.6
N4—C3—H31	115.1	H121—C12—H123	111.0
C6—C3—H31	113.9	C10—C12—H122	108.6
C3—N4—C5	91.22 (12)	H121—C12—H122	109.0
C3—N4—C13	117.65 (15)	H123—C12—H122	111.1
C5—N4—C13	116.97 (14)	N4—C13—C14	110.62 (16)
N4—C5—C6	89.30 (13)	N4—C13—H132	108.6
N4—C5—H51	114.2	C14—C13—H132	110.1
C6—C5—H51	116.3	N4—C13—H131	111.3
N4—C5—H52	112.1	C14—C13—H131	107.0
C6—C5—H52	113.7	H132—C13—H131	109.2
H51—C5—H52	109.9	C13—C14—C15	120.71 (17)
C3—C6—C5	86.95 (13)	C13—C14—C19	120.65 (16)
C3—C6—O7	106.25 (13)	C15—C14—C19	118.64 (17)
C5—C6—O7	113.33 (15)	C14—C15—C16	120.39 (18)
C3—C6—H61	118.1	C14—C15—H151	119.4
C5—C6—H61	117.3	C16—C15—H151	120.3
O7—C6—H61	112.3	C15—C16—C17	120.55 (17)
C6—O7—C8	109.39 (14)	C15—C16—H161	120.0
C2—C8—O7	107.62 (14)	C17—C16—H161	119.4
C2—C8—O9	105.91 (13)	C16—C17—C18	119.59 (18)
O7—C8—O9	111.33 (16)	C16—C17—H171	119.4
C2—C8—H81	113.1	C18—C17—H171	121.0
O7—C8—H81	108.9	C17—C18—C19	119.92 (19)
O9—C8—H81	110.0	C17—C18—H181	120.5
C8—O9—C10	108.58 (13)	C19—C18—H181	119.6
O9—C10—O1	104.85 (14)	C14—C19—C18	120.89 (17)
O9—C10—C11	111.18 (15)	C14—C19—H191	119.8
O1—C10—C11	111.77 (14)	C18—C19—H191	119.3

Hydrogen-bond geometry (Å, °)

<i>D</i> —H $\cdots$ <i>A</i>	<i>D</i> —H	H $\cdots$ <i>A</i>	<i>D</i> $\cdots$ <i>A</i>	<i>D</i> —H $\cdots$ <i>A</i>
C11—H111 $\cdots$ N4	0.97	2.58	3.266 (3)	128

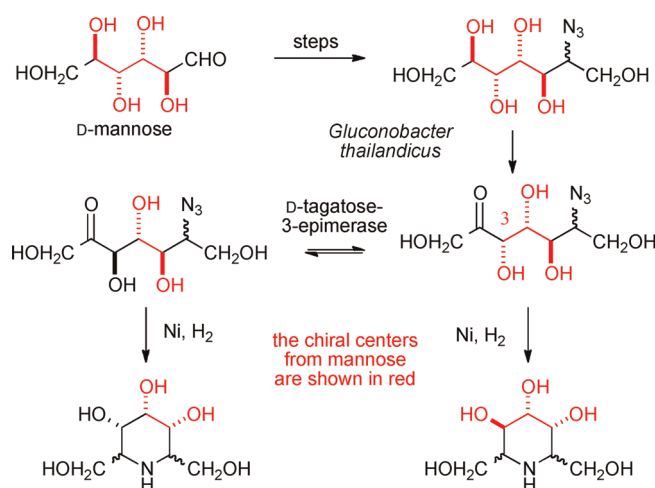
Eight Stereoisomers of Homonojirimycin
from D-MannoseGabriel M. J. Lenagh-Snow,[†] Sarah F. Jenkinson,^{†,‡} Scott J. Newberry,[†] Atsushi Kato,[§]
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ABSTRACT



Although there are 32 6-azidoheptitols, there are only 16 homonojirimycin (HNJ) stereoisomers. Two epimeric azidoalditols derived from D-mannose allow the synthesis in water of eight stereoisomers of HNJ.

Homonojirimycin (HNJ) **1** is a seven carbon imino-sugar¹ which was made² before it was recognized as a

natural product from *Omphalea diandra* (Euphorbiaceae).³ Many of the stereoisomers of HNJ, as well as corresponding glycosides, have subsequently been isolated from a wide range of plants⁴ and synthesized by many different routes.⁵

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This paper describes the synthesis of eight (**2**–**9**) of the 15 diastereomers of HNJ from D-mannose by a divergent biotechnological strategy in water that depends on the isomerization of monosaccharides by the techniques of Izumoring [Scheme 1].⁶

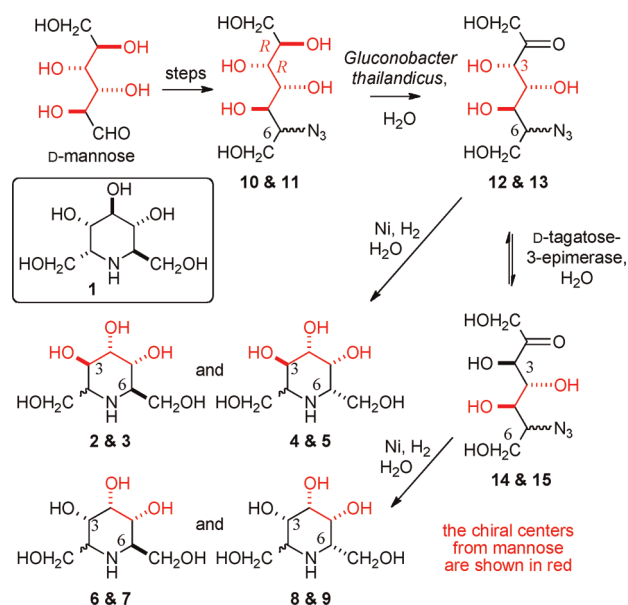
Chain extension and functional group manipulation allowed the conversion of D-mannose to the two epimeric 6-azido-heptitols **10**/**11** in which all the chiral centers are preserved. *Gluconobacter thailandicus* specifically recognizes a terminal diol stereochemical motif with an *R,R* configuration adjacent to the terminal carbon and thus allowed the oxidation of **10**/**11** to the azidoketoses **12**/**13**. D-Tagatose-3-epimerase (DTE) is a promiscuous enzyme that epimerizes C3 of a ketose; there is no ketose so far reported that is not a substrate for DTE. DTE equilibrated

the azidoketoses **12**/**13** with their C3 epimers **14**/**15**. Hydrogenation of each of the four azidoketoses by Raney nickel resulted in reduction of the azide to the corresponding amine which underwent intramolecular reductive amination to give two epimeric HNJ's.

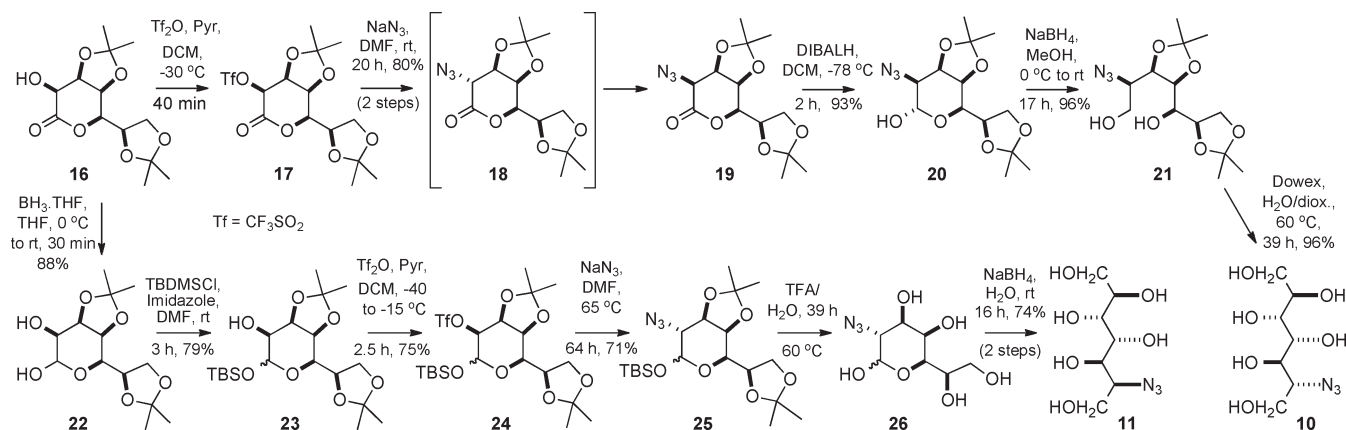
The seven carbon lactone diacetone **16**, which may be prepared on a scale up to 10 kg by a Kiliani reaction on diacetone mannose,⁷ is a key intermediate for the synthesis of the epimeric 6-azido-heptitols **10**/**11** [Scheme 2]. Esterification of the free alcohol in **16** with triflic anhydride afforded the crystalline triflate **17**; reaction of **17** with sodium azide in DMF resulted in nucleophilic substitution with retention to give **19** in an overall yield of 80% for the two steps.⁸ The all *cis*-azide **19** is more stable than the epimeric azidolactone **18**;⁹ it was not possible to readily isolate **18** from reaction of **17** with sodium azide. Reduction of the base-sensitive azidolactone **19** with DIBALH in dichloromethane gave the lactol **20**¹⁰ [93% yield] which on further reduction with sodium borohydride in methanol afforded the protected diol **21** [96% yield]. Removal of the acetonides in **21** by acid hydrolysis with Dowex in water gave the azidoheptitol **10** [mp 136–138 °C, $[\alpha]_D^{25} +10.9$ (*c* 1.0, H₂O)] in an overall yield of 69% from **16**. For the epimer **11**, the lactone **16** was reduced by THF/borane to give the lactol **22** [88% yield] in which the anomeric hydroxyl group was protected as the corresponding TBDMS ether **23** [79%]. Esterification of the hydroxyl group at C2 of **23** with triflic anhydride gave the triflate **24** [75%] which, with sodium azide in DMF, resulted in nucleophilic substitution with inversion to give **25** [71%]. Removal of the silyl ether and diacetone groups in **25** by aqueous trifluoroacetic acid gave the unprotected lactols **26**; reduction of **26** with sodium borohydride in water gave the azidoheptitol **11** [mp 159–160 °C, $[\alpha]_D^{25} -8.5$ (*c* 1.0, H₂O)] in an overall yield of 27% from **16**.

Oxidation of the (*R,R*) stereochemical motif adjacent to the terminal carbon in the epimeric azidoheptitols **10** and **11** by *Gluconobacter thailandicus* gave complete conversion to the azidoketoses **12** [$[\alpha]_D^{25} +21.7$ (*c* 0.4, H₂O)] and **13** [$[\alpha]_D^{25} +25.7$ (*c* 1.0, H₂O)] respectively [Scheme 3].

Scheme 1. Summary of Synthesis of HNJ Stereoisomers



Scheme 2. Synthesis of Azidoheptitols



Scheme 3. Biotechnological Synthesis of HNJ Stereoisomers

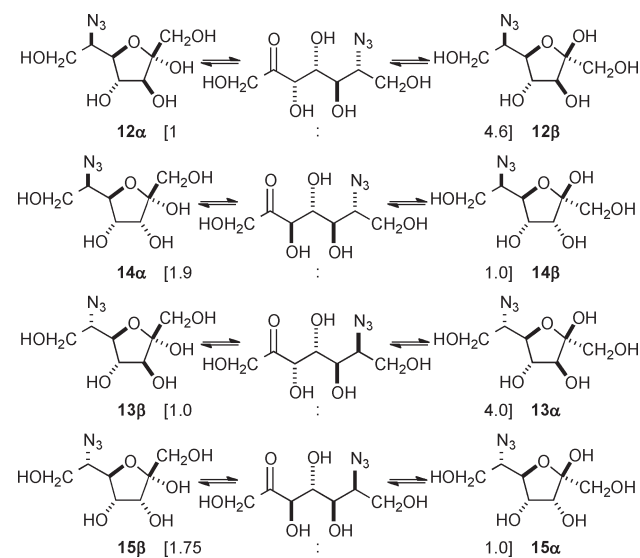
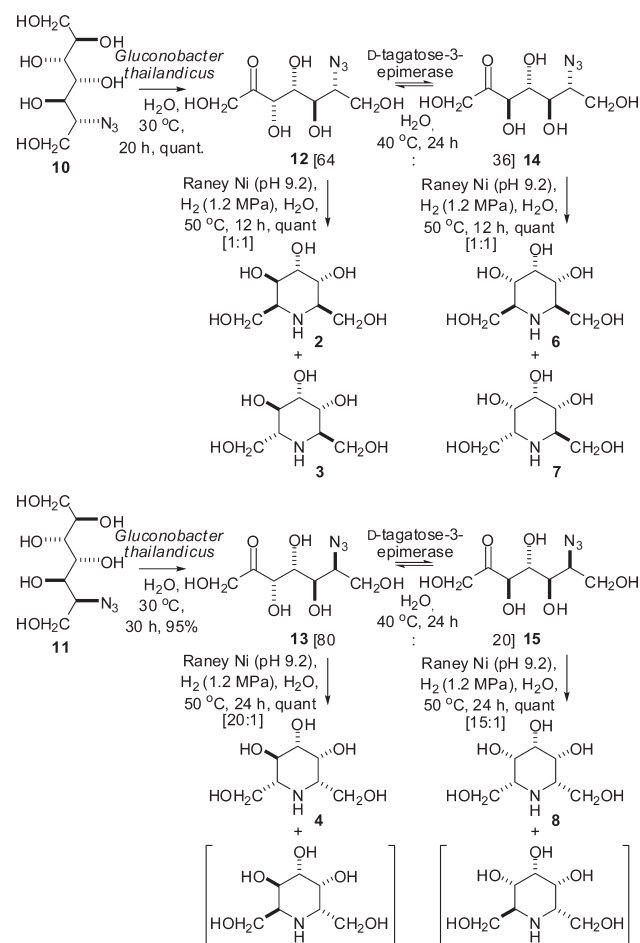


Figure 1. Ratio of anomers of azidoketoses.

Reaction of DTE with **12** caused equilibration with the C3 epimer **14** $\{[\alpha]_D^{25} +31.0$ (c 0.7, H_2O) $\}$ in a ratio of 64:36. Similarly DTE caused equilibration of **13** with **15** $\{[\alpha]_D^{25} +22.3$ (c 1.0, H_2O) $\}$.

Each of the azidoketoses is predominantly an equilibrium mixture of the α and β furanose anomers,¹¹ with very minor amounts (<2%) of other forms [Figure 1]. As shown in Figure 2, **12** exists in an α : β ratio of 1.0:4.6, **14**

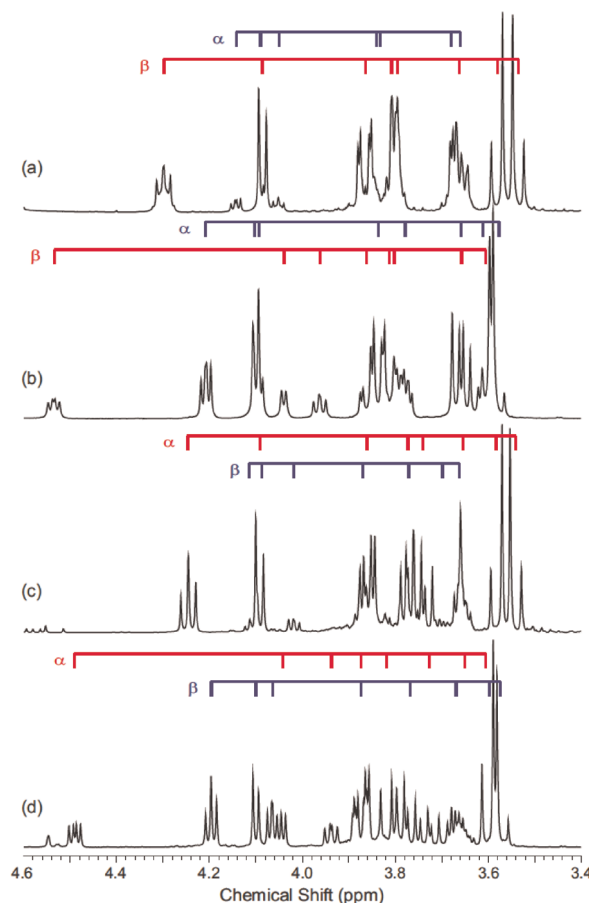
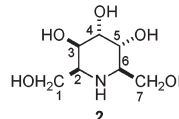
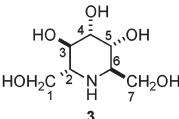
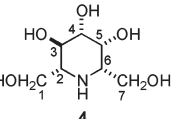
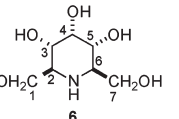
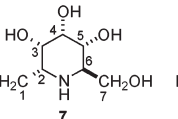
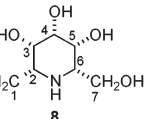


Figure 2. ¹H NMR spectra of azidoketoses (500 MHz) in D₂O: (a) **12**, (b) **14**, (c) **13**, (d) **15**. Full NMR analysis is reported in Supporting Information.

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Table 1. Properties of HNJ Diastereomers^a

compound							
$[\alpha]_D^{25}$	+44.5 (c 0.85, H ₂ O) [Lit. ^{5a} +41.9 (c 0.43, H ₂ O)]	+4.3 (c 0.44, H ₂ O) [Lit. ^{5a} +4.3 (c 0.62, H ₂ O)]	-4.2 (c 0.27, MeOH) [Lit. ^{5c} -4.3 (c 1.3, MeOH)]	+0.1 (c 0.70, H ₂ O)	+27.7 (c 0.75, H ₂ O)	-0.1 (c 0.44, H ₂ O)	
m.p.	140–144 °C	syrup	syrup	210–212 °C	syrup	>340 °C	
δ_C (D ₂ O, 125 MHz)	C1	61.7	61.7	62.1	60.5	62.2	
	C2	55.9	56.3	60.7	55.3	59.5	
	C3	66.7	69.2	69.2	69.4	70.3	
	C4	71.6	72.4	75.7	72.5	70.6	
	C5	70.0	69.8	69.6	69.4	70.3	
	C6	54.4	59.2	58.5	55.3	59.5	
	C7	62.1	60.0	62.0	62.1	62.2	
δ_H (D ₂ O, 500 MHz)	H1	3.71 (dd, <i>J</i> 5.5, 11.7)	3.73 (dd, <i>J</i> 5.6, 11.5)	3.72 (dd, <i>J</i> 5.5, 11.6)	3.65 (dd, <i>J</i> 6.2, 11.7)	3.72 (dd, <i>J</i> 4.6, 11.5)	3.67 (dd, <i>J</i> 6.9, 11.0)
	H1'	3.80 (dd, <i>J</i> 3.0, 11.6)	3.78 (dd, <i>J</i> 3.2, 11.6)	3.82 (dd, <i>J</i> 3.0, 11.6)	3.84 (dd, <i>J</i> 3.0, 11.6)	3.83 (dd, <i>J</i> 8.2, 11.5)	3.72 (dd, <i>J</i> 6.5, 11.0)
	H2	2.86 (ddd, <i>J</i> 3.1, 5.4, 10.5)	2.71 (ddd, <i>J</i> 3.3, 5.4, 8.8)	2.54–2.58 (m)	2.86 (ddd, <i>J</i> 3.0, 6.1, 10.3)	3.04 (a-dt, <i>J</i> 4.3, 8.4)	2.80 (a-dt, <i>J</i> 1.1, 6.7)
	H3	3.76 (dd, <i>J</i> 3.2, 10.6)	3.62 (a-t, <i>J</i> 9.1)	3.57 (a-t, <i>J</i> 9.8)	3.47 (dd, <i>J</i> 2.9, 10.4)	3.89–3.91 (m)	3.95 (dd, <i>J</i> 1.1, 3.1)
	H4	3.99 (a-t, <i>J</i> 3.5)	3.66 (dd, <i>J</i> 3.0, 9.1)	3.53–3.55 (m)	4.09 (t, <i>J</i> 2.9)	3.89 (t, <i>J</i> 2.9)	3.65 (t, <i>J</i> 3.1)
	H5	3.92 (dd, <i>J</i> 1.5, 3.7)	4.00 (a-t, <i>J</i> 2.8)	4.00 (dd, <i>J</i> 1.4, 2.7)	3.47 (dd, <i>J</i> 2.9, 10.4)	3.67 (dd, <i>J</i> 2.6, 5.9)	3.95 (dd, <i>J</i> 1.1, 3.1)
	H6	3.06 (a-dt, <i>J</i> 1.5, 6.6)	3.12 (ddd, <i>J</i> 2.7, 6.8, 7.8)	2.84 (dt, <i>J</i> 1.4, 6.7)	2.86 (ddd, <i>J</i> 3.0, 6.1, 10.3)	3.10 (a-dt, <i>J</i> 5.0, 6.9)	2.80 (a-dt, <i>J</i> 1.1, 6.7)
	H7	3.62 (dd, <i>J</i> 6.7, 11.2)	3.67 (dd, <i>J</i> 6.7, 11.7)	3.63 (dd, <i>J</i> 6.7, 11.2)	3.65 (dd, <i>J</i> 6.2, 11.7)	3.63 (dd, <i>J</i> 7.6, 11.5)	3.67 (dd, <i>J</i> 6.9, 11.0)
H7'	3.66 (dd, <i>J</i> 6.5, 11.2)	3.73 (dd, <i>J</i> 7.9, 11.6)	3.67 (dd, <i>J</i> 6.7, 11.2)	3.84 (dd, <i>J</i> 3.0, 11.6)	3.77 (dd, <i>J</i> 4.8, 11.5)	3.72 (dd, <i>J</i> 6.5, 11.0)	

^a a-t = apparent triplet; a-dt = apparent double triplet.

in an α:β ratio of 1.9:1.0, **13** in an α:β ratio of 4.0:1.0, and **15** in an α:β ratio of 1.0:1.75.

Hydrogenation of the azidoketoses in the presence of Raney nickel in each case caused reduction of the azide to the corresponding amine, followed by intramolecular amination to give iminoheptitols; examination of the crude product from the reduction showed the clean formation of two iminosugars. The reduction of azidoketoses **12** [to **2** and **3**] and **14** [to **6** and **7**] showed no stereoselectivity in the reduction of the intermediate imine. In contrast, hydrogenation of **13** gave **4** together with **5** in a 20:1 ratio. A similar highly stereoselective reduction of **15** gave **8** and **9** in a ratio of 15:1.

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(11) The description of α and β for the furanose forms of the azidoketoses is determined by the configuration of C6 bearing the azido group consistent with IUPAC nomenclature.

The stereoselectivity in the cyclic reductive aminations may be rationalized by the arguments of Wong;¹² greater selectivity was found with synergy in steric hindrance and torsional strain, with the least selectivity where these effects were opposed. The crude reaction mixtures were separated by ion exchange chromatography by a combination of Dowex 1 × 2 (OH[−] form) and Amberlite CG-50(NH₄⁺ form) to afford six iminoheptitols for which the properties are reported in Table 1. It was not possible to obtain pure samples of iminoheptitols **5** and **9** formed as the minor products from the hydrogenation of **13** and **15**, respectively; further investigations for the separation of the iminoheptitols is in progress.

In summary, biotechnological syntheses of eight stereoisomers of HNJ from D-mannose are described; a similar sequence from D-glucose, which should provide the other eight stereoisomers, is under investigation.

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Supporting Information Available. Experimental procedures and full spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.

2-Azido-3,4;6,7-di-*O*-isopropylidene- α -D-glycero-D-talo-heptopyranose

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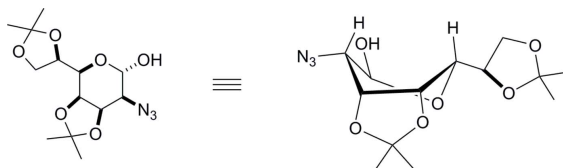
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Key indicators: single-crystal X-ray study; $T = 150$ K; mean $\sigma(\text{C}-\text{C}) = 0.003$ Å; disorder in main residue; R factor = 0.027; wR factor = 0.070; data-to-parameter ratio = 8.3.

In the title compound, $\text{C}_{13}\text{H}_{21}\text{N}_3\text{O}_6$, the six-membered ring adopts a twist-boat conformation with the azide group in the bowsprit position. The azide group is disordered over two sets of sites in a 0.642 (10):0.358 (10) ratio. The crystal structure consists of $\text{O}-\text{H}\cdots\text{O}$ hydrogen-bonded trimer units. The absolute configuration was determined from the use of D-mannose as the starting material.

Related literature

For Izumoring techniques, see: Izumori (2002, 2006); Yoshihara *et al.* (2008); Gullapalli *et al.* (2010); Rao *et al.* (2008, 2009); Jones *et al.* (2008); Jenkinson *et al.* (2009). For the synthesis of homonojirimycins, see: Compain *et al.* (2009); Asano (2009); Watson *et al.* (2001) and for their isolation, see: Ikeda *et al.* (2000); Asano *et al.* (1998); Kite *et al.* (1988). For the synthesis of the azidoheptitol, see: Beacham *et al.* (1991); Bruce *et al.* (1990); Myerscough *et al.* (1992). For the weighting scheme, see: Prince (1982); Watkin (1994).



Experimental

Crystal data

$\text{C}_{13}\text{H}_{21}\text{N}_3\text{O}_6$
 $M_r = 315.33$
 Trigonal, $R3$

$a = 16.8793$ (2) Å
 $c = 15.1043$ (3) Å
 $V = 3726.83$ (10) Å³

$Z = 9$
 Mo $K\alpha$ radiation
 $\mu = 0.10$ mm⁻¹

$T = 150$ K
 $0.70 \times 0.50 \times 0.30$ mm

Data collection

Nonius KappaCCD diffractometer
 Absorption correction: multi-scan
 (DENZO/SCALEPACK;
 Otwinowski & Minor, 1997)
 $T_{\min} = 0.63$, $T_{\max} = 0.97$

23870 measured reflections
 1889 independent reflections
 1770 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.034$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.027$
 $wR(F^2) = 0.070$
 $S = 0.87$
 1889 reflections
 227 parameters

43 restraints
 H-atom parameters constrained
 $\Delta\rho_{\max} = 0.16$ e Å⁻³
 $\Delta\rho_{\min} = -0.16$ e Å⁻³

Table 1

Hydrogen-bond geometry (Å, °).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$\text{O10}-\text{H101}\cdots\text{O6}^i$	0.84	1.93	2.761 (3)	171

Symmetry code: (i) $-x + y + 1, -x + 1, z$.

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: LH2989).

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supplementary materials

Acta Cryst. (2010). E66, o525-o526 [doi:10.1107/S1600536810003995]

2-Azido-3,4,6,7-di-*O*-isopropylidene- α -D-glycero-D-talo-heptopyranose

S. F. Jenkinson, G. M. J. Lenagh-Snow, K. Izumori, G. W. J. Fleet, D. J. Watkin and A. L. Thompson

Comment

The enzymatic interconversion of monosaccharides has been developed by Izumori (2002, 2006) and has been seen to be generally applicable for the 1-deoxy ketohexoses (Yoshihara *et al.*, 2008, Gullapalli *et al.*, 2010; Rao *et al.*, 2009) and branched sugars (Rao *et al.*, 2008; Jones *et al.*, 2008). The methodology has also been applied to azido heptitols (Jenkinson *et al.*, 2009) and thus to the synthesis of 2,6-dideoxy-2,6-iminoheptitols (homonojirimycins), seven carbon imino sugars (Compain *et al.*, 2009; Asano *et al.*, 2009; Watson *et al.*, 2001) which are a family of glycosidase inhibitors. A number of homonojirimycins have been isolated as natural products from medicinal plants (Ikeda *et al.*, 2000; Asano *et al.*, 1998; Kite *et al.*, 1988).

A Kiliani cyanide reaction on diacetone mannose gave the lactone diacetone **1** (Beacham *et al.*, 1991; Myerscough *et al.*, 1992). Esterification of **1** (Fig. 1) with triflic anhydride in pyridine followed by reaction with sodium azide in DMF gave the azide **2** with retention of configuration at C2; the stereochemistry of **2** was established by X-ray crystallographic analysis (Bruce *et al.*, 1990). Reduction of the lactone **2** afforded the lactol **3**, a key intermediate for the synthesis of four of the possible sixteen iminoheptitols **4** by Izumoring techniques. The reported crystal structure of **3** determines the configuration of both the azide at C2 and the anomeric position.

The X-ray structure shows that the six-membered ring in the title compound adopts a twist boat conformation with the azide in the bowsprit position and the anomeric alcohol group in the less hindered α -position (Fig. 2). There is significant disorder in the structure with the azide occupying two possible sites. The compound exists as repeating hydrogen bonded trimer units (Fig.3, Fig. 4, Fig. 5). The absolute configuration was determined from the use of D-mannose as the starting material. Only classical hydrogen bonding was considered.

Experimental

The title compound was recrystallised from diethyl ether: m.p. 397-398 K; $[\alpha]_D^{25} +41.3$ (c, 1.0 in CHCl₃) {Lit. (Myerscough *et al.*, 1992) m.p. 387-388 K; $[\alpha]_D^{20} +41.0$ (c, 1.0 in CHCl₃)}.

Refinement

In the absence of significant anomalous scattering, Friedel pairs were merged and the absolute configuration was assigned from the starting material D-mannose. Changes in illuminated volume were kept to a minimum, and were taken into account (Görlitz, 1999) by the multi-scan inter-frame scaling (DENZO/SCALEPACK, Otwinowski & Minor, 1997).

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.

Figures

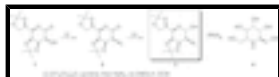


Fig. 1. Synthetic Scheme

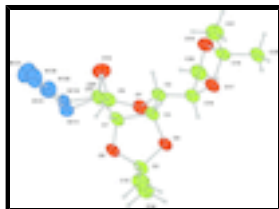


Fig. 2. The title compound with displacement ellipsoids drawn at the 50% probability level. H atoms are shown as spheres of arbitrary radius.

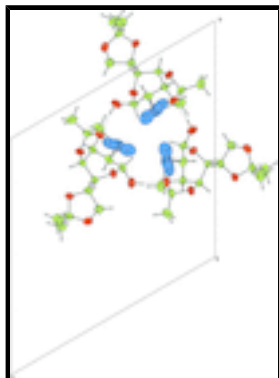


Fig. 3. Hydrogen bonded trimer unit. Hydrogen bonds are shown as dotted lines.

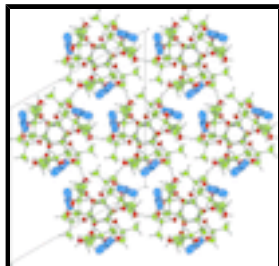


Fig. 4. Packing diagram for the title compound projected along the *c*-axis. Hydrogen bonds are shown by dotted lines.

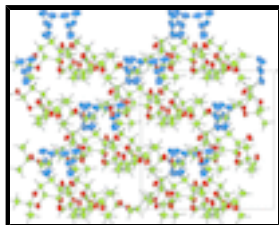


Fig. 5. Packing diagram for the title compound projected along the *b*-axis. Hydrogen bonds are shown by dotted lines.

2-Azido-3,4;6,7-di-*O*-isopropylidene- α -D-glycero- D-*talo*-heptopyranose

Crystal data

$C_{13}H_{21}N_3O_6$

$M_r = 315.33$

Trigonal, $R\bar{3}$

Hall symbol: $R\bar{3}$

$a = 16.8793(2) \text{ \AA}$

$c = 15.1043(3) \text{ \AA}$

$D_x = 1.264 \text{ Mg m}^{-3}$

Mo $K\alpha$ radiation, $\lambda = 0.71073 \text{ \AA}$

Cell parameters from 1885 reflections

$\theta = 5\text{--}28^\circ$

$\mu = 0.10 \text{ mm}^{-1}$

$T = 150 \text{ K}$

$$V = 3726.83 (10) \text{ \AA}^3$$

$$Z = 9$$

$$F(000) = 1512$$

Plate, colourless

$$0.70 \times 0.50 \times 0.30 \text{ mm}$$

Data collection

Nonius KappaCCD
diffractometer

graphite

 ω scans

Absorption correction: multi-scan
(DENZO/SCALEPACK; Otwinowski & Minor,
1997)

$$T_{\min} = 0.63, T_{\max} = 0.97$$

23870 measured reflections

1889 independent reflections

1770 reflections with $I > 2\sigma(I)$

$$R_{\text{int}} = 0.034$$

$$\theta_{\max} = 27.5^\circ, \theta_{\min} = 5.2^\circ$$

$$h = -21 \rightarrow 21$$

$$k = -21 \rightarrow 21$$

$$l = -19 \rightarrow 19$$

Refinement

Refinement on F^2

Least-squares matrix: full

$$R[F^2 > 2\sigma(F^2)] = 0.027$$

$$wR(F^2) = 0.070$$

$$S = 0.87$$

1889 reflections

227 parameters

43 restraints

Primary atom site location: structure-invariant direct
methods

Hydrogen site location: inferred from neighbouring
sites

H-atom parameters constrained

Method, part 1, Chebychev polynomial, (Watkin,
1994, Prince, 1982) [weight] = $1.0/[A_0 \cdot T_0(x) +$
 $A_1 \cdot T_1(x) \cdots + A_{n-1} \cdot T_{n-1}(x)]$

where A_i are the Chebychev coefficients listed be-
low and $x = F/F_{\max}$ Method = Robust Weighting
(Prince, 1982) $W = [\text{weight}] \cdot [1 - (\Delta F / 6 \cdot \sigma(\Delta F))^2]^2$ A_i are: 35.7 56.9 32.2 12.2 2.39

$$(\Delta/\sigma)_{\max} = 0.0004$$

$$\Delta\rho_{\max} = 0.16 \text{ e \AA}^{-3}$$

$$\Delta\rho_{\min} = -0.16 \text{ e \AA}^{-3}$$

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($\text{\AA}^2$)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$	Occ. (<1)
O1	0.73085 (8)	0.56052 (8)	0.60278 (11)	0.0388	
C2	0.71163 (11)	0.63258 (11)	0.58727 (14)	0.0334	
C3	0.60997 (11)	0.59051 (10)	0.56713 (13)	0.0348	
O4	0.55748 (8)	0.55027 (8)	0.64559 (12)	0.0420	
C5	0.49780 (12)	0.45418 (11)	0.63308 (14)	0.0398	
O6	0.53523 (9)	0.43128 (8)	0.55852 (11)	0.0414	
C7	0.57940 (12)	0.51014 (10)	0.50233 (14)	0.0370	
C9	0.72913 (13)	0.51340 (12)	0.52439 (14)	0.0407	
O10	0.81499 (10)	0.55590 (10)	0.48357 (13)	0.0511	
C14	0.50399 (17)	0.40362 (15)	0.71240 (16)	0.0540	

supplementary materials

C15	0.40195 (14)	0.43489 (16)	0.61352 (17)	0.0544	
C16	0.74277 (12)	0.69311 (12)	0.66864 (14)	0.0376	
O17	0.72041 (8)	0.76403 (8)	0.65905 (12)	0.0420	
C18	0.80336 (12)	0.84914 (11)	0.63848 (14)	0.0408	
O19	0.87138 (8)	0.82461 (9)	0.62410 (12)	0.0457	
C20	0.84636 (13)	0.74546 (14)	0.67731 (16)	0.0468	
C21	0.79042 (17)	0.88864 (16)	0.55377 (18)	0.0588	
C22	0.82716 (16)	0.91340 (13)	0.71627 (16)	0.0519	
H21	0.7470	0.6687	0.5353	0.0391*	
H31	0.5978	0.6378	0.5436	0.0413*	
H71	0.5361	0.5093	0.4580	0.0446*	
H91	0.7123	0.4508	0.5415	0.0490*	
H141	0.4682	0.3379	0.7027	0.0810*	
H142	0.4804	0.4199	0.7637	0.0803*	
H143	0.5683	0.4214	0.7219	0.0805*	
H152	0.3632	0.3698	0.6047	0.0812*	
H153	0.3773	0.4541	0.6630	0.0797*	
H151	0.4011	0.4664	0.5607	0.0801*	
H161	0.7134	0.6569	0.7208	0.0440*	
H201	0.8648	0.7629	0.7392	0.0552*	
H202	0.8739	0.7101	0.6556	0.0567*	
H212	0.8455	0.9466	0.5425	0.0887*	
H213	0.7396	0.9001	0.5601	0.0886*	
H211	0.7793	0.8473	0.5054	0.0875*	
H222	0.8852	0.9682	0.7049	0.0781*	
H223	0.8309	0.8835	0.7700	0.0772*	
H221	0.7802	0.9302	0.7229	0.0777*	
H101	0.8447	0.5336	0.5065	0.0762*	
C80	0.66053 (13)	0.51225 (11)	0.45706 (13)	0.0399	0.642 (10)
N110	0.6365 (5)	0.4337 (5)	0.3965 (5)	0.0459	0.642 (10)
N120	0.6176 (3)	0.4422 (3)	0.3203 (3)	0.0485	0.642 (10)
N130	0.5963 (4)	0.4412 (3)	0.2497 (2)	0.0824	0.642 (10)
C81	0.66053 (13)	0.51225 (11)	0.45706 (13)	0.0399	0.358 (10)
N111	0.6151 (11)	0.4225 (12)	0.4122 (11)	0.0617	0.358 (10)
N121	0.6429 (6)	0.4295 (6)	0.3378 (7)	0.0510	0.358 (10)
N131	0.6661 (7)	0.4252 (6)	0.2652 (4)	0.0936	0.358 (10)
H801	0.6910	0.5680	0.4222	0.0469*	0.642 (10)
H811	0.6898	0.5645	0.4171	0.0473*	0.358 (10)

Atomic displacement parameters ($\text{\AA}^2$)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0408 (6)	0.0341 (6)	0.0477 (7)	0.0235 (5)	−0.0023 (5)	0.0055 (5)
C2	0.0319 (7)	0.0255 (7)	0.0436 (8)	0.0150 (6)	−0.0009 (6)	0.0042 (6)
C3	0.0331 (8)	0.0254 (7)	0.0461 (9)	0.0149 (6)	−0.0014 (6)	0.0017 (6)
O4	0.0358 (6)	0.0264 (6)	0.0545 (7)	0.0084 (5)	0.0071 (5)	−0.0027 (5)
C5	0.0368 (8)	0.0246 (7)	0.0493 (9)	0.0088 (6)	−0.0017 (7)	−0.0007 (6)
O6	0.0444 (7)	0.0234 (5)	0.0493 (7)	0.0117 (5)	−0.0005 (5)	0.0004 (5)

C7	0.0401 (8)	0.0251 (7)	0.0449 (9)	0.0156 (6)	−0.0042 (7)	0.0014 (6)
C9	0.0454 (9)	0.0324 (8)	0.0518 (10)	0.0251 (7)	0.0036 (8)	0.0077 (7)
O10	0.0522 (8)	0.0543 (8)	0.0632 (8)	0.0390 (7)	0.0123 (7)	0.0181 (7)
C14	0.0670 (13)	0.0407 (10)	0.0523 (12)	0.0254 (10)	−0.0002 (10)	0.0048 (8)
C15	0.0359 (9)	0.0534 (12)	0.0609 (13)	0.0125 (9)	−0.0035 (9)	−0.0009 (9)
C16	0.0341 (8)	0.0311 (7)	0.0438 (9)	0.0133 (7)	−0.0011 (6)	0.0024 (6)
O17	0.0318 (6)	0.0271 (5)	0.0606 (8)	0.0100 (5)	0.0033 (5)	−0.0025 (5)
C18	0.0361 (8)	0.0287 (8)	0.0475 (9)	0.0086 (7)	0.0026 (7)	0.0017 (7)
O19	0.0317 (6)	0.0391 (7)	0.0562 (8)	0.0100 (5)	0.0028 (5)	0.0012 (6)
C20	0.0368 (9)	0.0405 (9)	0.0573 (11)	0.0150 (8)	−0.0072 (8)	−0.0021 (8)
C21	0.0641 (13)	0.0517 (12)	0.0538 (11)	0.0239 (11)	−0.0022 (10)	0.0072 (9)
C22	0.0556 (12)	0.0312 (9)	0.0533 (11)	0.0099 (8)	0.0038 (9)	−0.0034 (8)
C80	0.0489 (10)	0.0299 (8)	0.0448 (9)	0.0226 (7)	−0.0012 (7)	−0.0005 (6)
N110	0.064 (4)	0.033 (3)	0.043 (3)	0.026 (3)	0.004 (3)	−0.0027 (19)
N120	0.049 (2)	0.0377 (17)	0.049 (2)	0.0148 (14)	0.0016 (15)	−0.0079 (14)
N130	0.104 (4)	0.063 (2)	0.052 (2)	0.021 (2)	−0.0091 (19)	−0.0184 (15)
C81	0.0489 (10)	0.0299 (8)	0.0448 (9)	0.0226 (7)	−0.0012 (7)	−0.0005 (6)
N111	0.072 (7)	0.034 (4)	0.060 (6)	0.013 (4)	0.032 (4)	0.001 (3)
N121	0.053 (4)	0.045 (3)	0.052 (4)	0.022 (3)	0.000 (3)	0.002 (3)
N131	0.112 (7)	0.094 (6)	0.050 (4)	0.033 (5)	0.009 (4)	−0.010 (3)

Geometric parameters (Å, °)

O1—C2	1.4261 (18)	C15—H152	0.966
O1—C9	1.419 (2)	C15—H153	0.985
C2—C3	1.524 (2)	C15—H151	0.963
C2—C16	1.515 (2)	C16—O17	1.431 (2)
C2—H21	0.991	C16—C20	1.520 (2)
C3—O4	1.431 (2)	C16—H161	0.968
C3—C7	1.538 (2)	O17—C18	1.452 (2)
C3—H31	0.986	C18—O19	1.419 (2)
O4—C5	1.4309 (19)	C18—C21	1.508 (3)
C5—O6	1.436 (2)	C18—C22	1.511 (3)
C5—C14	1.505 (3)	O19—C20	1.430 (2)
C5—C15	1.511 (3)	C20—H201	0.983
O6—C7	1.434 (2)	C20—H202	0.978
C7—H71	0.986	C21—H212	0.971
C7—C80	1.515 (3)	C21—H213	0.974
C7—H71	0.986	C21—H211	0.962
C7—C81	1.515 (3)	C22—H222	0.969
C9—O10	1.398 (2)	C22—H223	0.974
C9—H91	0.982	C22—H221	0.971
C9—C80	1.534 (3)	C80—N110	1.491 (8)
C9—O10	1.398 (2)	C80—H801	0.971
C9—H91	0.982	N110—N120	1.221 (8)
C9—C81	1.534 (3)	N120—N130	1.123 (6)
O10—H101	0.838	C81—N111	1.477 (19)
C14—H141	0.974	C81—H811	0.975
C14—H142	0.971	N111—N121	1.201 (16)

supplementary materials

C14—H143	0.982	N121—N131	1.179 (13)
C2—O1—C9	113.04 (12)	C5—C15—H153	111.3
O1—C2—C3	108.58 (13)	H152—C15—H153	108.8
O1—C2—C16	106.97 (13)	C5—C15—H151	110.7
C3—C2—C16	113.98 (14)	H152—C15—H151	108.9
O1—C2—H21	109.4	H153—C15—H151	108.8
C3—C2—H21	108.7	C2—C16—O17	109.54 (13)
C16—C2—H21	109.2	C2—C16—C20	111.86 (16)
C2—C3—O4	109.97 (14)	O17—C16—C20	103.32 (14)
C2—C3—C7	109.94 (14)	C2—C16—H161	109.8
O4—C3—C7	104.67 (12)	O17—C16—H161	110.2
C2—C3—H31	109.7	C20—C16—H161	111.9
O4—C3—H31	110.6	C16—O17—C18	108.78 (13)
C7—C3—H31	111.8	O17—C18—O19	105.35 (14)
C3—O4—C5	110.27 (13)	O17—C18—C21	109.73 (16)
O4—C5—O6	104.70 (14)	O19—C18—C21	108.44 (17)
O4—C5—C14	109.19 (15)	O17—C18—C22	108.82 (15)
O6—C5—C14	107.89 (15)	O19—C18—C22	111.41 (16)
O4—C5—C15	109.94 (15)	C21—C18—C22	112.81 (17)
O6—C5—C15	110.88 (16)	C18—O19—C20	106.42 (14)
C14—C5—C15	113.82 (17)	C16—C20—O19	102.19 (15)
C5—O6—C7	107.99 (12)	C16—C20—H201	110.8
C3—C7—O6	103.40 (13)	O19—C20—H201	110.7
C3—C7—H71	111.3	C16—C20—H202	112.1
O6—C7—H71	110.5	O19—C20—H202	111.9
C3—C7—C80	111.47 (14)	H201—C20—H202	109.0
O6—C7—C80	109.47 (13)	C18—C21—H212	108.5
H71—C7—C80	110.5	C18—C21—H213	109.9
C3—C7—O6	103.40 (13)	H212—C21—H213	108.2
C3—C7—H71	111.3	C18—C21—H211	110.0
O6—C7—H71	110.5	H212—C21—H211	109.8
C3—C7—C81	111.47 (14)	H213—C21—H211	110.3
O6—C7—C81	109.47 (13)	C18—C22—H222	109.1
H71—C7—C81	110.5	C18—C22—H223	109.8
O1—C9—O10	110.79 (15)	H222—C22—H223	110.3
O1—C9—H91	107.3	C18—C22—H221	109.1
O10—C9—H91	109.7	H222—C22—H221	108.8
O1—C9—C80	111.36 (13)	H223—C22—H221	109.8
O10—C9—C80	107.23 (15)	C9—C80—C7	111.64 (15)
H91—C9—C80	110.5	C9—C80—N110	106.6 (3)
O1—C9—O10	110.79 (15)	C7—C80—N110	114.6 (3)
O1—C9—H91	107.3	C9—C80—H801	108.4
O10—C9—H91	109.7	C7—C80—H801	107.6
O1—C9—C81	111.36 (13)	N110—C80—H801	107.8
O10—C9—C81	107.23 (15)	C80—N110—N120	116.4 (6)
H91—C9—C81	110.5	N110—N120—N130	173.3 (6)
C9—O10—H101	106.7	C9—C81—C7	111.64 (15)
C5—C14—H141	110.3	C9—C81—N111	108.6 (8)
C5—C14—H142	108.7	C7—C81—N111	100.5 (5)

H141—C14—H142	109.5	C9—C81—H811	111.2
C5—C14—H143	108.9	C7—C81—H811	110.2
H141—C14—H143	109.4	N111—C81—H811	114.3
H142—C14—H143	110.1	C81—N111—N121	110.6 (11)
C5—C15—H152	108.4	N111—N121—N131	172.0 (13)

Hydrogen-bond geometry (Å, °)

<i>D</i> —H $\cdots$ <i>A</i>	<i>D</i> —H	H $\cdots$ <i>A</i>	<i>D</i> $\cdots$ <i>A</i>	<i>D</i> —H $\cdots$ <i>A</i>
C15—H153 $\cdots$ O10 ⁱ	0.99	2.51	3.361 (3)	145
O10—H101 $\cdots$ O6 ⁱⁱ	0.84	1.93	2.761 (3)	171
C80—H801 $\cdots$ O4 ⁱⁱⁱ	0.97	2.36	3.296 (3)	161
C81—H801 $\cdots$ O4 ⁱⁱⁱ	0.97	2.36	3.296 (3)	161
C80—H811 $\cdots$ O4 ⁱⁱⁱ	0.97	2.34	3.296 (3)	166
C81—H811 $\cdots$ O4 ⁱⁱⁱ	0.97	2.34	3.296 (3)	166

Symmetry codes: (i) $-x+y+2/3, -x+4/3, z+1/3$; (ii) $-x+y+1, -x+1, z$; (iii) $-y+4/3, x-y+2/3, z-1/3$.

Fig. 1

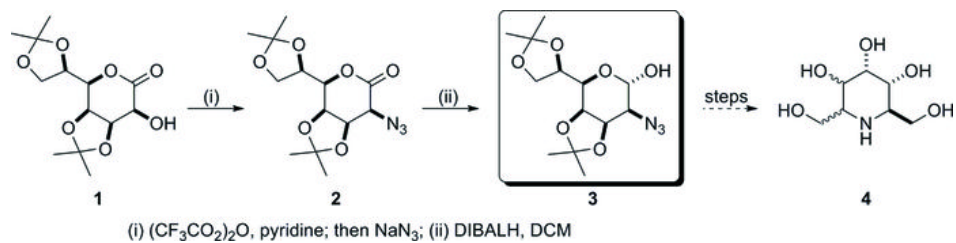


Fig. 2

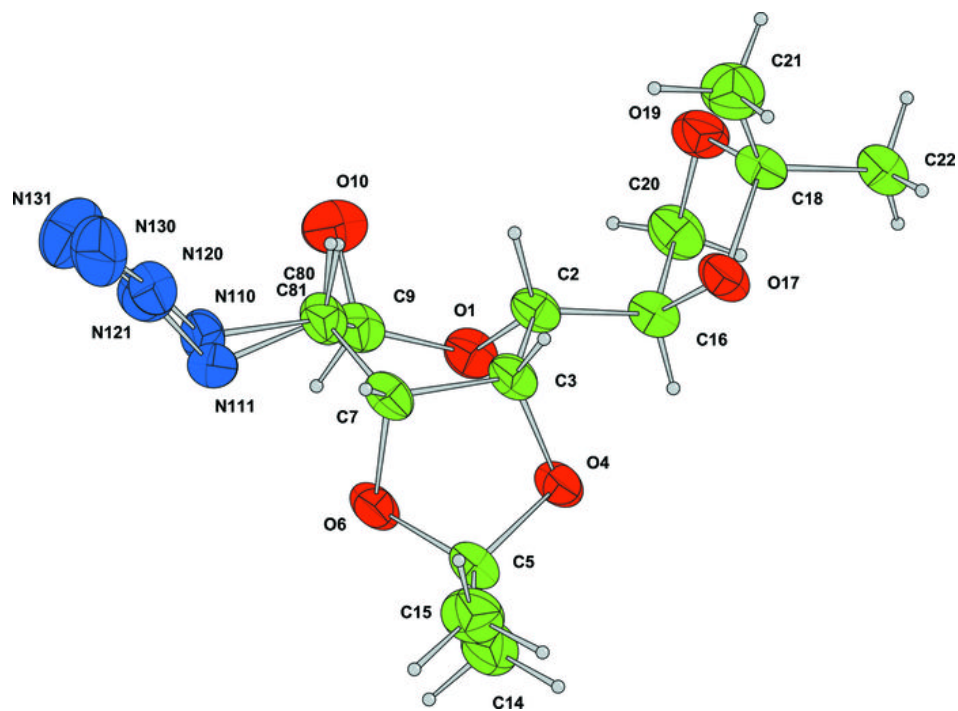


Fig. 3

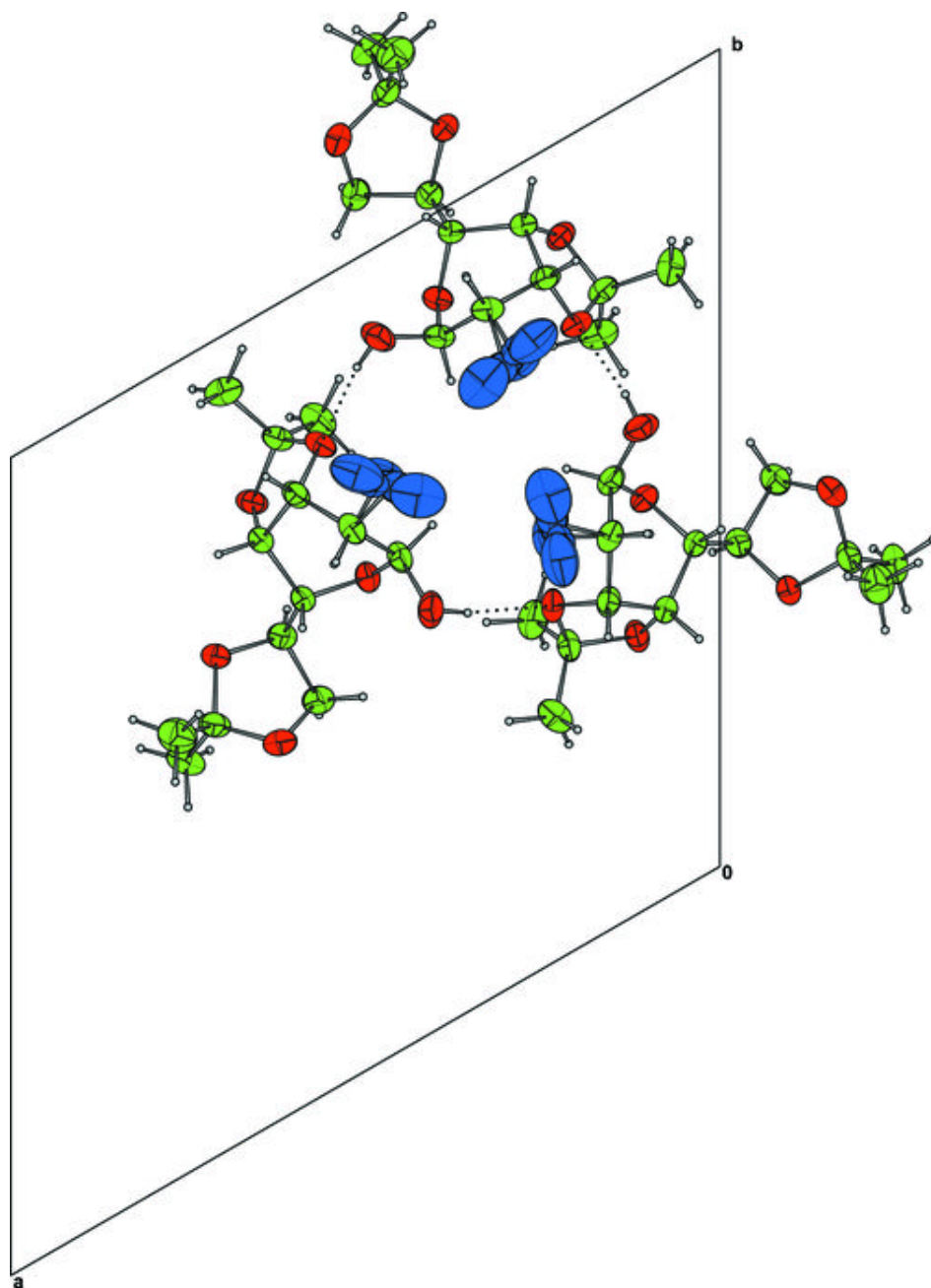


Fig. 4

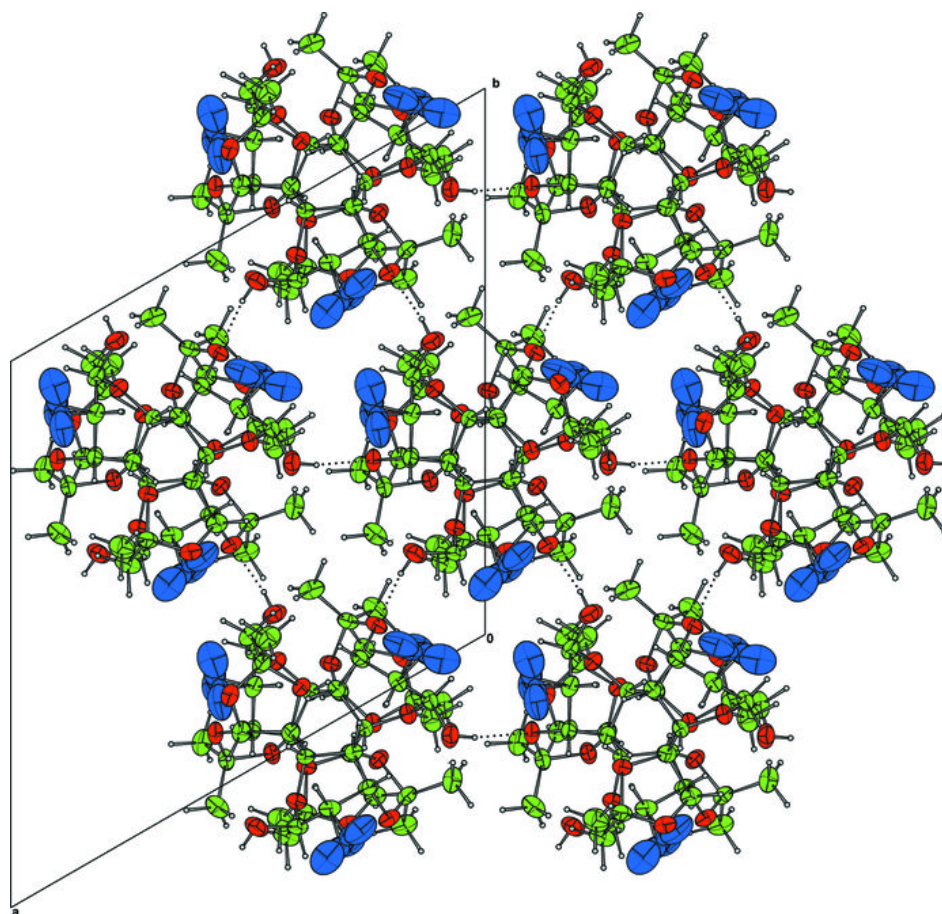


Fig. 5

