The Stereospecific Formation of 1,2-*cis* Glycosides *via* Allyl-Mediated Intramolecular Aglycon Delivery

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Abstract

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This thesis describes investigations into the possibility and scope of allyl-derived intramolecular aglycon delivery as a tool for the stereospecific formation of 1,2-*cis* glycosides. The three-step procedure involves isomerisation of the 2-*O*-allyl protection of a glycosyl donor, followed by iodonium-mediated tethering to an aglycon alcohol. Activation of the donor induces intramolecular delivery of the aglycon, to afford the 1,2-*cis* glycoside.

The synthesis of ten glycosyl donors, including gluco-, manno- and rhamnopyranosyl and glucofuranosyl donors, as selenoglycosides, thioglycosides and glycosyl fluorides, is described.

Isomerisation was carried out in excellent yield in all cases using a catalyst derived from Wilkinson's catalyst.

The scope of *N*-Iodosuccinimide-mediated tethering is described. Attempted tethering to a selenoglycoside resulted in activation of the donor. Tethering to a thiomethyl glycoside was successful for unhindered alcohols, but sluggish for secondary carbohydrates, and activation of the donor became competitive in these cases. The use of glycosyl fluorides gave good tethering yields for many alcohols, including secondary carbohydrates. For hindered alcohols, tethering of succinimide became competitive, resulting in reduced yields.

Examples of high-yielding tethering reactions using a novel source of iodonium ion are reported. A large excess of aglycon was unnecessary for good yields to be obtained. A 'reverse' tethering approach, whereby a donor with a free 2-hydroxyl is tethered to the isomerised allyl group of an aglycon, was found to be effective using this reagent.

In all cases, activation gave stereospecific glycosylation, furnishing the 1,2-*cis* glycosides. Other glycosylated products still bearing functionality derived from the tether, including mixed acetals and enol ethers, were cleaved by acid treatment, affording further 1,2-*cis* glycoside. Slightly lower glycosylation yields were obtained in the *rhamno* and *glucofurano* systems. Investigations into the glycosylation mechanism were also undertaken.

The stereospecific synthesis of the Glc_3Man *N*-glycan tetrasaccharide *via* an iterative tethering and allyl-mediated intramolecular glycosylation strategy is reported.

Acknowledgements

First and foremost, I would like to thank my supervisor, Antony Fairbanks, for the opportunity to work on this project, and for much helpful advice in the not too distant past.

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My life was made considerably easier by the many co-workers engaged on the IAD concept. For many entertaining and enlightening discussions on this topic, I thank in particular Chris Seward, but also Mahmoud Aloui, Dave Chambers, Seth Ennis, Harry Yeates, Cathie Slinn and Majid Chughtai.

Our collaborators, Mark Wormald and Mukram Mackeen made it all seem a little bit more worthwhile when they found out something interesting using one of the molecules I was able to synthesise. So thanks for that, and for setting the synthetic challenge in the first place.

Everybody else in the Sidgwick lab gets a big acknowledgement too. In addition to those above, especially to Rob, Rich, Mincho, Emma and Yasmin

I'd just like to say hello to the orienteers, who gave me something to do to stop me going completely mad. Although as I write, I have rather lost it. Hello. And a big shout out goes to the tabs. TABS.

Of course, I am grateful to the suppliers of the majority of my funding, the EPSRC, and to Professor Sir Jack E Baldwin for allocating the funds in my favour. In addition, thanks goes to Glaxo for a good price for my soul.

Some aspects of this work have been published in the articles referenced below.

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3. Cumpstey, I.; Fairbanks, A.J; Redgrave, A.J, Stereospecific synthesis of 1,2-*cis* glycosides by allyl mediated intramolecular aglycon delivery.2. The use of glycosyl fluorides, *Org. Lett.* **2001,** *3*, 2371-2374

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Abbreviations

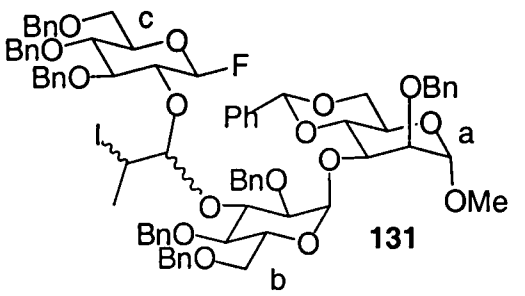
4Å	molecular sieves (4 Ångstrom)
Ac	acetyl
atd	apparent triplet of doublets
AIBN	2,2′-azobis-*iso*-butyronitrile
Ala	alanine
APCI	atmospheric pressure chemical ionisation
APT	attached polarisation transfer
aquint	apparent quintet
Asn	asparagine
at	apparent triplet
BDA	butane diacetal
Bn	benzyl
Bu	butyl
Bz	benzoyl
ca	*circa*
cf	*confer* (compare)
CI	chemical ionisation
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CSA	camphor sulfonic acid
d	doublet
DAG	diacetone galactose
DAST	diethylaminosulfur trifluoride
dat	doublet of apparent triplets
DCE	dichloroethane
DCM	dichloromethane
dd	doublet of doublets
ddat	doublet of doublet of apparent triplets
ddd	doublet of doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarisation transfer
DiBAlH	di-*iso*-butyl aluminium hydride
DMAP	*N*,*N*-dimethylamino-pyridine
DMF	dimethyl formamide
DMTST	dimethyl(thiomethyl) sulfonium triflate
dq	doublet of quartets
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
eg	*exempli gratia* (for example)
ES	electrospray
et al	*et alia* (and co-workers)

Et	ethyl
ether	diethyl ether
FI	field ionisation
g	grams
Glc	glucose
GlcNAc	*N*-acetyl glucosamine
Glu	glutamic acid
h	hours
HMBC	heteronuclear multiple bond correlation (spectroscopy)
HMDS	hexamethyldisilane
HMQC	heteronuclear multiple quantum correlation (spectroscopy)
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation (spectroscopy)
Hz	Hertz
IAD	intramolecular aglycon delivery
IDCP	iodonium di-*sym*-collidine perchlorate
IDCT	iodonium di-*sym*-collidine trifluoromethane-sulfonate
ie	*id est* (that is)
^{i}Pr	*iso*-propyl
IR	infra-red spectroscopy
J	coupling constant
l	litres
M	molecular mass ion
m/z	mass to charge ratio
Man	mannose
Me	methyl
mg	milligrams
MHz	Megahertz
min	minutes
ml	millilitres
mmol	millimoles
MS	mass spectrometry
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance (spectrometry)
NOE	nuclear Overhauser effect
^{n}Pr	*n*-propyl
OST	oligosaccharyl-transferase
p-	*para*-
Ph	phenyl
Phth	phthaloyl
Piv	pivaloyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxylphenyl
q	quartet
R	alkyl
Rha	rhamnose

rhamnose	6-deoxy mannose
RT	room temperature
s	singlet
s	strong
t	triplet
TBAF	tetrabutylammonium fluoride
Tf	triflyl, trifluoromethane-sulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
tlc	thin layer chromatography
TMEDA	tetramethyl ethylene diamine
TMS	trimethylsilyl
Tol	*para*-tolyl
tolyl	*para*-methylphenyl
Tr	trityl, triphenylmethyl
triflate	trifluoromethane-sulfonate
Ts	tosyl, toluenesulfonyl
w	weak

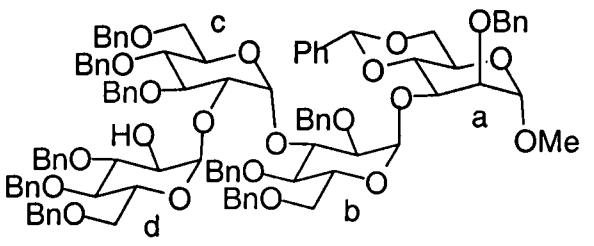
Note Concerning Nomenclature

Carbohydrates and derivatives are numbered according to the carbohydrate convention, and named as given by the IUPAC recommendations of 1996.[1] The two protons on C-6 are labelled H-6 and H-6′. The individual sugar residues in di- tri- and tetrasaccharides are distinguished by the assignment of a lowercase letter, given alphabetically starting from the reducing (or methyl glycosidic) terminus. Tethered materials containing more than one sugar residue are assigned lowercase letters corresponding to the potential glycosylated products. Tethered materials are named based on the glycosyl donor, except where the tethered aglycon is a di- or trisaccharide, in which case the name is based on the aglycon. Examples are given below.



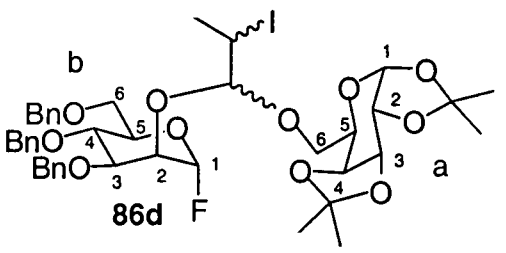
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Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2-iodo-1-(3,4,6-tri-*O*-benzyl-1-deoxy-1-fluoro-β-D-glucopyranos-2-*O*-yl)propyl)-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside

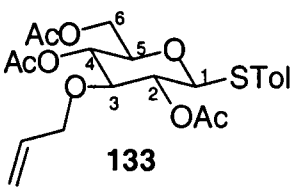


129

Methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside



3,4,6-tri-*O*-benzyl-2-*O*-(1-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-*O*-yl)-2-iodopropyl)-α-D-mannopyranosyl fluoride



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para-tolyl 2,4,6-tri-*O*-acetyl-3-*O*-allyl-1-thio-β-D-glucopyranoside

Chapter 1. General Introduction

1.1 The Importance of Oligosaccharides in Biology

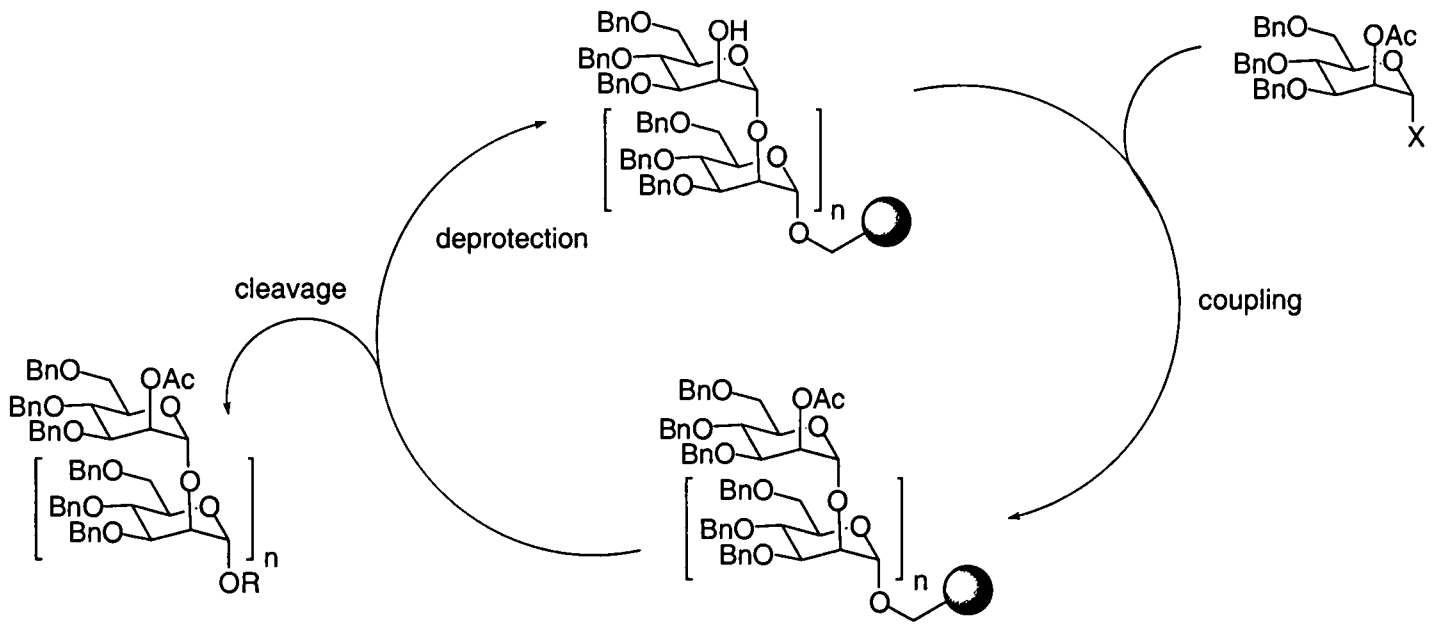
Much work remains to be done in understanding the many and varied roles of carbohydrates in biology. Carbohydrates are a very widespread class of compounds, occurring in nature as mono-[1] poly-[2] and oligosaccharides[3] as well as as glycoconjugates – ie in combination with proteins,[3] lipids[4] or other small molecules.[5] They are well known to have roles as the constituents of cell walls,[6] and as energy sources,[7] but more recently, a host of further biological functions have been elucidated. There is growing interest in the field of glycobiology, which deals with the role of carbohydrates in biological recognition events.[8]

However, the quantities of oligosaccharides isolated from nature are very small, so in order to investigate their interaction with natural receptors, the preparation of oligosaccharides and glycoconjugates must be undertaken.

1.2 The Goal of Oligosaccharide Synthesis

High yielding chemical syntheses of the other two main classes of biooligomers, ie oligonucleotides and oligopeptides (proteins) are well known, and as such are routinely carried out by commercially available robots to form high molecular weight oligomers. For oligosaccharides though, such a general synthetic solution remains elusive.

Recently, Seeberger has reported the chemical synthesis of several oligosaccharides on an automatic solid-phase synthesiser.[9] The process involves a coupling/deprotection sequence with the reducing end of the growing oligosaccharide anchored to the resin (Scheme 1.1). However, good stereoselectivity can only be achieved for the formation of 1,2-*trans* bonds (see Section 1.4.2).



Scheme 1.1: The coupling-deprotection sequence as run in an automated fashion on Seeberger's oligosaccharide synthesiser.

There are many reasons why the oligosaccharide problem remains the last to be solved. Firstly the individual sugar residues in an oligosaccharide are linked *via* acetals. The synthesis of even simple acetals is not a straightforward or high yielding process compared to the synthesis of phosphates (as in oligonucleotides) or amides (as in proteins).

The situation is further compounded by the fact the even when two identical sugar residues are joined to form a disaccharide, many isomers of the product are possible. For a hexopyranose, for example, any of the five hydroxyl groups may be linked to the 1-position of another residue, leading to five

regioisomers. Furthermore, the acetal carbon is a new chiral centre, so two further diastereomeric possibilities exist – with the aglycon axial or equatorial. In addition to the branching and stereoisomerism, the possibility of pyranose and furanose isomers open to carbohydrates, as well as the number of different individual residues in nature, leads to a complexity of structure several orders of magnitude greater than for other biooligomers.[10]

It is the very diversity of possible structures which makes oligosaccharides a useful biological tool in recognition processes,[8] that also leads to a complex synthetic chemical problem. Obviously, these problems of regio- and stereoselectivity must be addressed if a general strategy for oligosaccharide synthesis is to be realised.

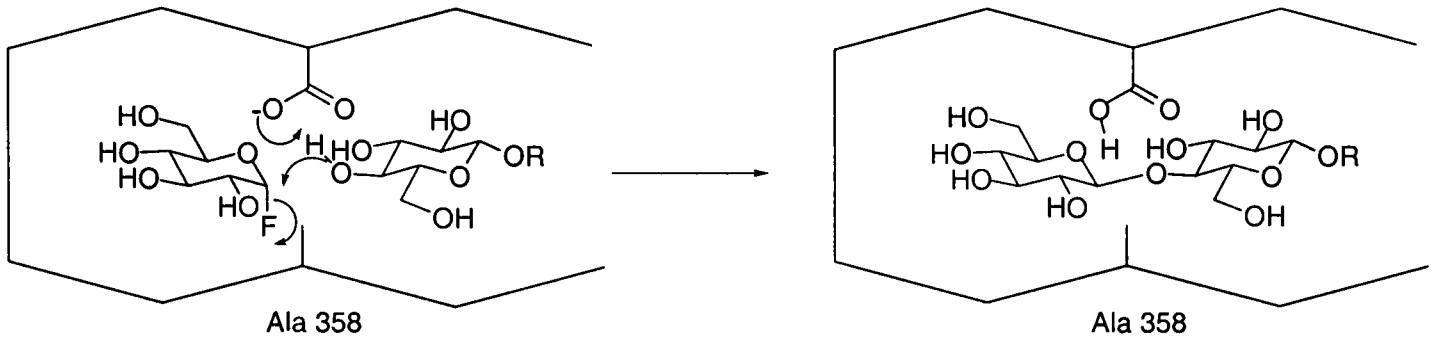
1.3 Enzymatic Synthesis of Glycosidic Bonds

Biosynthesis of oligosaccharides is carried out in a regio- and stereospecific manner by enzymes called glycosyltransferases.[11] Thus the glycosyl donor, a uridine diphosphate glycoside, is bound with the acceptor into the enzyme active site such that in a glycosylation reaction, only a single stereo- and regioisomer is formed, without the need for protecting groups. These enzymes have also been used *in vitro* to good effect in oligosaccharide synthesis.[12] However, the instability of the enzymes, as well as their very low availability from natural sources and the their high cost of their substrates make this approach less attractive.[13a]

In an alternative approach, glycosidases, nature's tools for the cleavage of glycosidic bonds, may be run 'in reverse' using a large excess of the aglycon.

However, the glycosylated product is a substrate for the enzyme, so such reactions may only occur in low yield.[13]

Withers has developed and demonstrated the use of so-called glycosynthases – mutant glycosidases in which the active site has been modified such that hydrolysis may no longer occur, but glycosylation between a glycosyl fluoride donor and an aglycon still goes ahead (Scheme 1.2).[14]

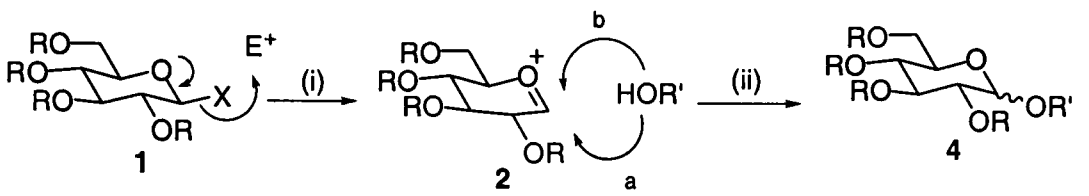


Scheme 1.2: Proposed mechanism of operation of a glycosynthase. The active site of the wild-type glycosidase contains a glutamic acid residue (Glu 358), which, in a key step of the mechanism of hydrolysis or transglycosylation, bonds to the glycosyl donor to give a glycosyl enzyme intermediate. In the case of the glycosynthase mutant, the Glu 358 is replaced by an alanine residue, so the natural hydrolysis pathway cannot operate.

While these are exciting developments, the use of enzymes does not currently offer a general solution to the problem of oligosaccharide synthesis, so the use of classic organic-soluble chemical glycosylations is still the best option for most applications.

1.4 Chemical Synthesis of Glycosidic Bonds

In a typical glycosylation reaction, a glycosyl donor **1** bearing a leaving group at the anomeric position is activated by a suitable electrophile. This results in a glycosyl cation **2**, which is then captured by a glycosyl acceptor **3** to give the glycosylated product **4** (Scheme 1.3).[15]



Scheme 1.3: A general glycosylation reaction. (i) activation of a glycosyl donor **1**; (ii) capture of a glycosyl cation **2** by an acceptor **3** resulting in (a) α or (b) β product **4**

1.4.1 Regioselectivity

In order to avoid any self-condensation reactions, it is usually necessary to have all the hydroxyl groups of the donor protected. Similarly, where the aglycon is another carbohydrate, it is usually necessary to protect all the other hydroxyl groups in order to ensure regioselectivity.

The need for selective access to an individual hydroxyl group of a glycosyl acceptor has led to the development of a wide variety of protecting groups.[16] Consequently, by means of selective protection and/or deprotection, it is generally possible to access any particular hydroxyl group of a given carbohydrate.[17]

1.4.2 Stereoselectivity

Where a glycosyl cation **2** is an intermediate in a glycosylation reaction, the acceptor **3** may attack from either face, and so in most cases, an α/β mixture of products **4** results. It is helpful to consider glycosidic bonds as one of four classes: either 1,2-*cis* or 1,2-*trans*, and with the anomeric substituent either axial or equatorial (Figure 1.1). Various factors influence the propensity of formation of each of these classes in a glycosylation reaction. The 2-substituent effectively hinders access to the *cis* face by the aglycon, thus the formation of 1,2-*cis* glycosides is disfavoured. In addition, an anomeric effect will make the transition states leading to axial anomeric products lower in

energy, so these may predominate. These factors mean that while α-*manno* bonds are generally easy to form, selectivity is difficult for *gluco* bonds, while the selective synthesis of β-mannosides is the most difficult to realise.[18]

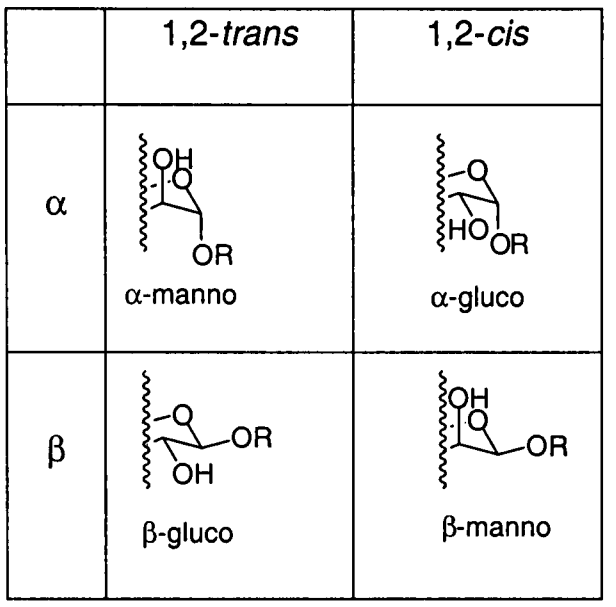


Figure 1.1: the different classes of glycosidic bond

All *N*-linked glycoproteins share a common pentasaccharide core, at the heart of which is a Manβ(1→4)GlcNAc linkage (Figure 1.2).[3] That this most troublesome β-mannosyl linkage – to a very hindered secondary hydroxyl – is present in such a wide range of naturally occurring structures means that interest in this particular problem is very keen.

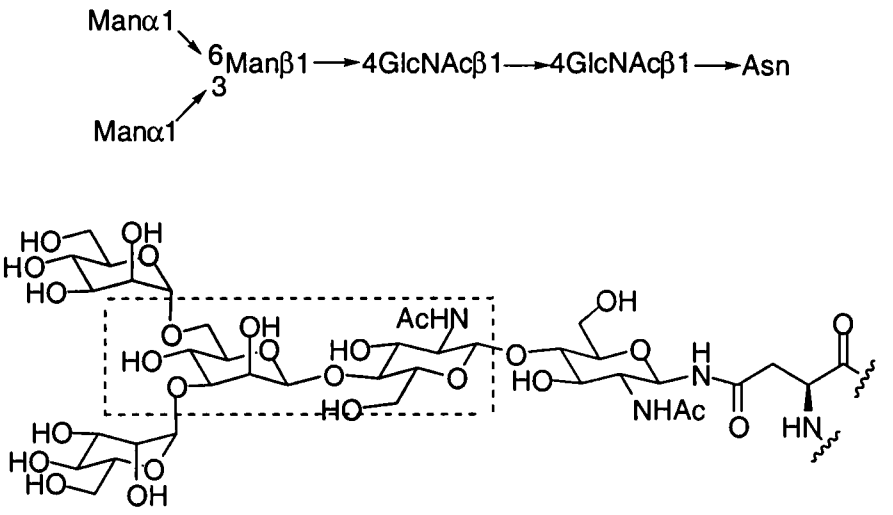
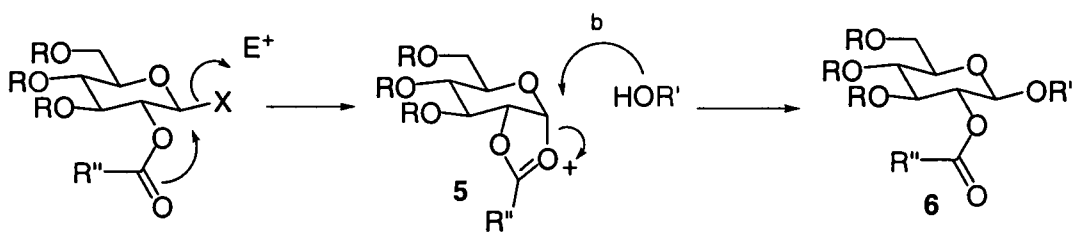


Figure 1.2: the pentasaccharide core of all *N*-linked glycoproteins. The dashed box shows the β-mannosidic linkage.

In organic synthesis, it has been shown that an existing chiral centre in a molecule may be used to good effect to influence the stereochemistry of a new chiral centre formed in a reaction.[19]

This principle of asymmetric induction has also been found to apply to the glycosylation reactions of carbohydrates. It is well known that when glycosylation reactions are carried out with a carbohydrate bearing acyl protection on C-2, that only the 1,2-*trans* products are formed.[18] Participation by the acyl protecting group leads to trapping of the glycosyl cation to form a cyclic oxonium ion **5** which is then opened in an S_N2 manner by the incoming nucleophile to give stereospecifically the 1,2-*trans* glycoside **6** (Scheme 1.4).



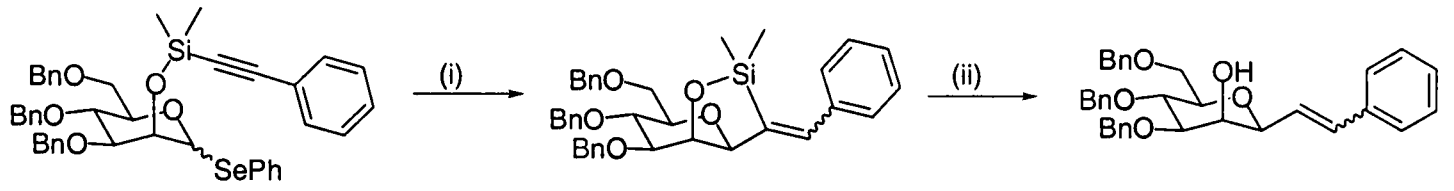
Scheme 1.4: The formation of a 1,2-*trans* bond by use of neighbouring group participation

Thus the stereoselective formation of 1,2-*trans* glycosides is possible by exploiting the stereochemistry at the carbon adjacent to the new chiral centre. The question must then be asked as to whether this same existing stereochemistry could be used in some other way to ensure 1,2-*cis* selectivity.

1.4.3 Intramolecular Aglycon Delivery (IAD)

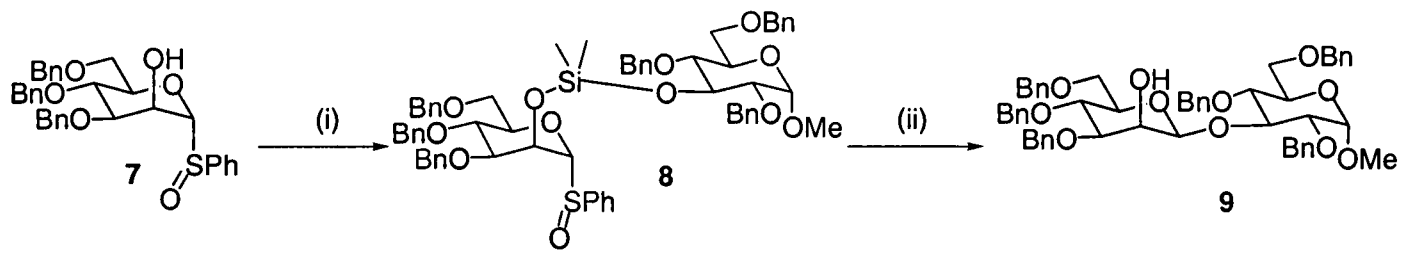
The principle of temporarily tethering a reactive moiety to a stereochemically defined hydroxyl group of a ring system in order to ensure complete stereochemical control of a subsequent reaction had been reported by Stork and co-workers in the context of C-glycoside formation.[20] They had shown

that when a phenylethynyl group was tethered to the hydroxyl group of a carbohydrate *via* silicon, that a radical cyclisation reaction could be induced which, following desilylation, had led to the stereospecific formation of a C-glycosidic bond *cis* to the hydroxyl which had been used to tether the C-aglycon (Scheme 1.5). The 2-, 3- and 6-hydroxyls were all used.



Scheme 1.5: Stork's stereospecific C-glycoside formation using a temporary silicon tether. (i) Bu_3SnH, AIBN, benzene; (ii) TBAF, THF, 69%

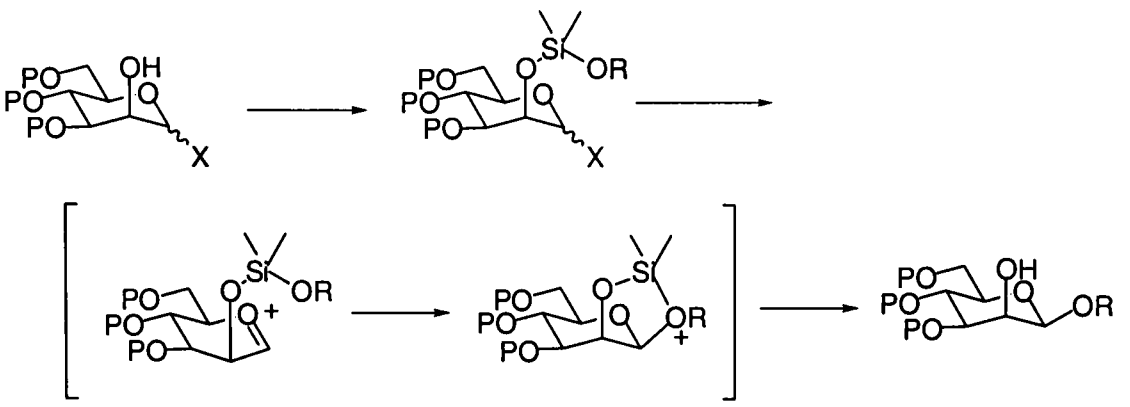
Stork went on to apply the same principle to *O*-glycoside synthesis, in particular to the synthesis of the critical β-mannosidic linkage.[21] An aglycon alcohol 3 was temporarily tethered to the 2-position of a mannosyl donor **7**, *via* a silicon bridge. On activation of the sulfoxide **8**, he found that only the 1,2-*cis* glycosylated product, ie the β-mannoside **9** was formed (Scheme 1.6).



Scheme 1.6: Stork's stereospecific β-mannosylation *via* silicon-tethered IAD. (i) imidazole, DMAP, $(CH_3)_2SiCl_2$, THF, 88%; (ii) Tf_2O, 2,6-di-*tert*-butyl pyridine, DCM, Et_2O, -100°C→RT, 82%

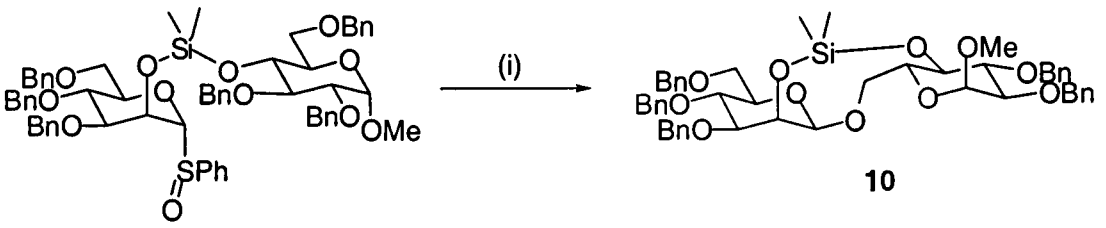
His proposed mechanism involved an intramolecular glycosylation reaction, resulting in the stereospecific delivery of the aglycon to the *cis* face of the

donor, followed by hydrolysis of the silyl tether to give the glycoside with OH-2 free (Scheme 1.7).



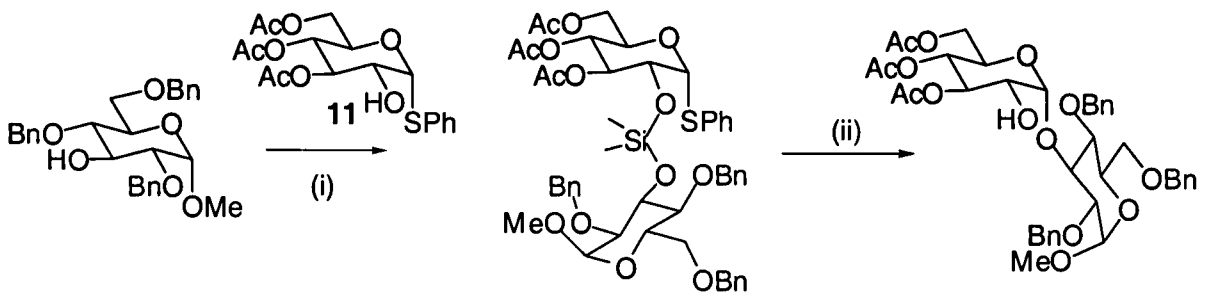
Scheme 1.7: Stork's proposed mechanism for silicon-tethered IAD

This methodology worked well for various primary and secondary carbohydrate alcohols, including the 4-hydroxyl of a protected glucosamine, but interestingly it failed for the hindered 4-hydroxyl of glucose. In this case a (1→6)-linked, 6-debenzylated disaccharide predominated, which was found to derive from the cyclic intermediate **10**. Apparently the silicon-tethered oxygen is not always the most nucleophilic (Scheme 1.8).[21b]



Scheme 1.8: Stork's formation of a silicon-bridged, 6-linked disaccharide.
(i) Tf_2O, 2,6-di-*tert*-butyl pyridine, DCM, Et_2O, -100°C→RT, 82%

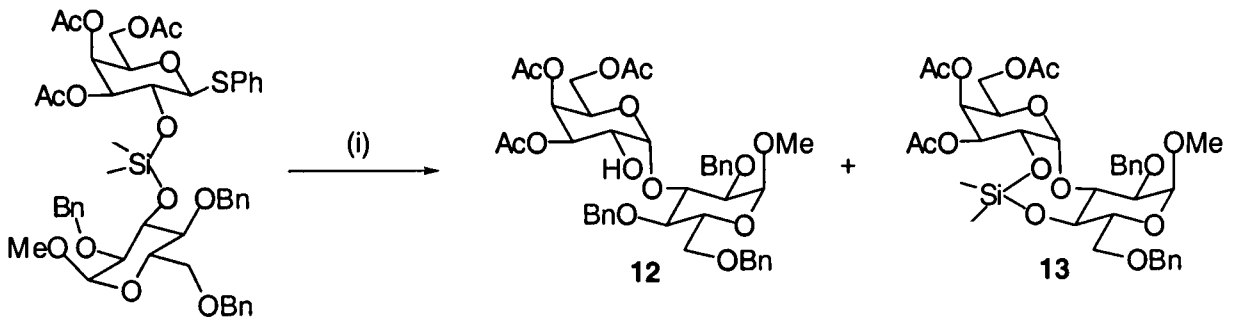
Bols subsequently reported similar results, again using a silaketal as tether, but using *gluco* and *galacto* thioglycoside donors (Scheme 1.9).[22] He found that on activation of the tethered materials, only the 1,2-*cis* isomers were formed in all cases, and proposed a similar mechanism to that of Stork.



Scheme 1.9: Bols' stereospecific formation of α-glucosides *via* silicon-tethered IAD.
(i) Et_3N, $(CH_3)_2SiCl_2$, Et_2O; then **11**, pyridine, 61%; (ii) NIS, $MeNO_2$, DCM, Et_2O, 100°C, 74%

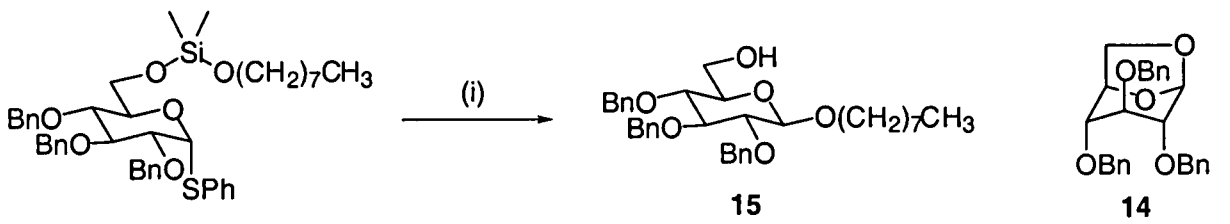
Primary, secondary and tertiary aliphatic alcohols were glycosylated in approximately equal yield, indicating that for the intramolecular reaction the steric bulk of the aglycon was unimportant.[22a] Primary and secondary carbohydrate aglycons were also glycosylated using this methodology, though in rather lower yield. This was explained as a consequence of the reduced nucleophilicity of the aglycon oxygen due to inductive electron withdrawing effects by the other ring oxygens.[22b]

In both *gluco* and *galacto* series, again some anomalous results were obtained, and large silicon-bridged rings were observed. In these cases though (in contrast to that described by Stork above), apparently glycosylation of the silicon-tethered oxygen had occurred as expected, but this had been followed by the formation of a silicon bridge to a neighbouring oxygen with concomitant debenzylation (Scheme 1.10).[23]



Scheme 1.10: Formation of a silicon-bridged disaccharide as reported by Bols.
(i) NIS, $MeNO_2$, 100°C; **12**, 31%; **13**, 46%

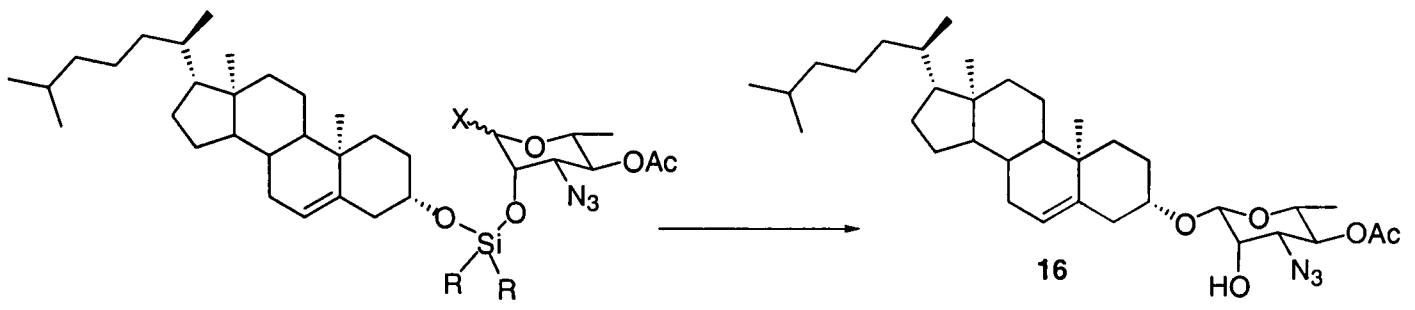
Bols went on to investigate the possibility of long range IAD,[24] analogous to Stork's C-glycoside work. Thus octanol was tethered *via* a silicon bridge to the 3-, 4- and 6-positions of glucopyranose donors, and to the 5-position of a ribofuranose derivative. After activation, the glycosylated products were found to have formed stereospecifically in all cases and in moderate yields, except for the tethering at the 3-position, where a 1:4 α/β mixture was observed, and then in a poor 22% yield. Furthermore in the case of the glucopyranose 6-position, the formation of the 1,6-anhydrosugar **14**, presumably by intramolecular attack of the *other* silaketal oxygen, was found to compete effectively with aglycon delivery (Scheme 1.11).



Scheme 1.11: Long-range IAD as reported by Bols.
(i) NIS, $MeNO_2$, 25°C; **15**, 16%; **14**, 54%

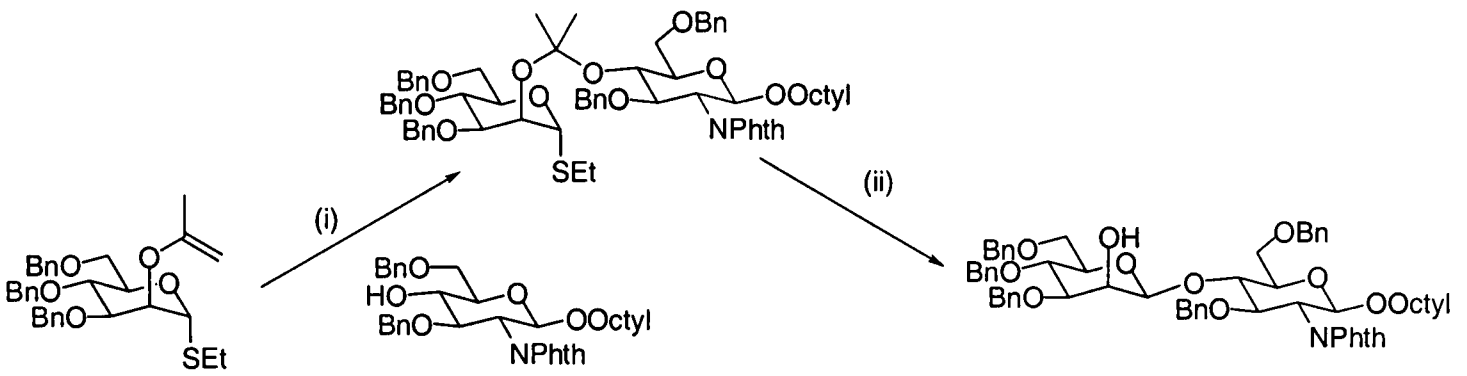
More recently, Packard and Rychnovsky carried out several silicon-based IAD reactions using mycosamine donors with a variety of leaving groups,

namely glycosyl fluorides, thioglycosides, selenoglycosides and glycosyl sulfoxides (Scheme 1.12).[25] Again, in all cases the 1,2-*cis* glycosylated product **16** was formed, but interestingly, a variety of 'trapped' materials were observed, whereby nucleophiles had attached themselves to the silicon resulting in glycosides protected at C-2. Desilylation by treatment with either acid or fluoride was necessary to obtain the β-mycosamine derivatives with OH-2 free.



Scheme 1.12: Packard and Rychnovsky's synthesis of β-mycosamine-steroid conjugates *via* silicon-tethered IAD

Meanwhile, concomitant with Stork's initial *O*-glycoside work, Barresi and Hindsgaul had independently described the concept which they called Intramolecular Aglycon Delivery (IAD), as a tool for the synthesis of β-mannosides.[26] To demonstrate this, they tethered the glycosyl donor and acceptor not by a silicon bridge, but *via* a mixed ketal, derived from the Tebbe methylenation of a 2-*O*-acetate protecting group. Subsequent activation of the thioglycoside donor furnished the β-mannosides for various aglycons, including the 4-position of glucosamine, with no trace of the α-anomers observed (Scheme 1.13).



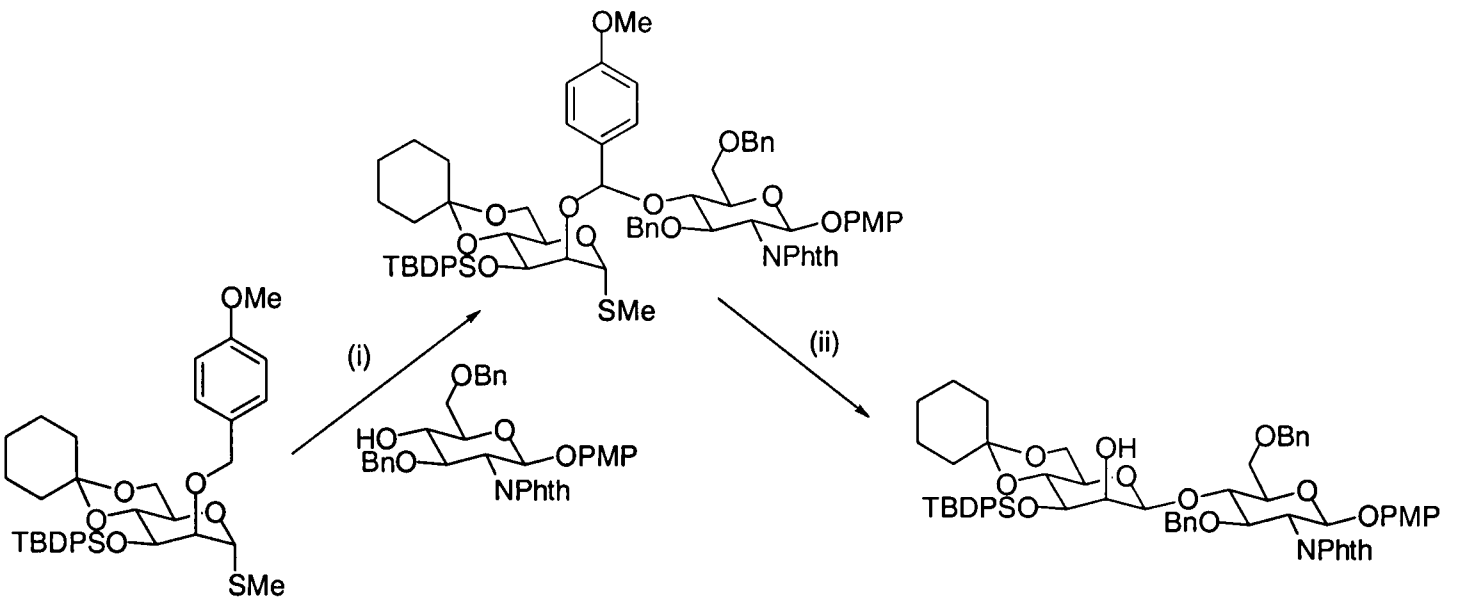
Scheme 1.13: Hindsgaul and Barresi's β-mannosylation *via* intramolecular aglycon delivery (IAD); (i) TsOH (cat), -40°C, DCM, 20 min, 55%; (ii) NIS, DTBMP, -5°C→RT, DCM, 51%

Hindsgaul proposed an S_N2-like mechanism, with aglycon delivery occurring concerted with the departure of the leaving group. Addition of methanol to glycosylation reaction mixtures was found not to compete with the intramolecular glycosylation of a primary carbohydrate aglycon, whereas for a secondary carbohydrate, some of the methyl β-mannoside was observed. This latter observation was explained as being due to trans-acetalation by methanol occurring prior to the more sluggish glycosylation reaction.

Hindsgaul's tethering process used acid catalysis. This was not ideal, as the reaction was extremely water sensitive and was prone to the formation of undesired dimers if the mixture was allowed to equilibrate. Furthermore, the procedure required the handling of the rather unstable mixed ketal intermediates.

Ogawa introduced a modification to the methodology, based on the widely used *para*-methoxybenzyl (PMB) protecting group.[27] In his approach, the 2-*O*-PMB protection of a glycosyl donor (either a glycosyl fluoride or a thioglycoside **17**) was oxidised, and the resulting cation captured by an aglycon alcohol **3** to produce a *para*-methoxybenzylidene acetal **18** as tether.

Subsequent activation of the donor gave rise to an intramolecular glycosylation reaction with the β-mannoside **19** as the sole glycosylated product (Scheme 1.14).



Scheme 1.14: Ogawa's PMB-mediated β-mannosylation *via* IAD
(i) DDQ, 4Å, DCM; (ii) MeOTf, DCE, 4Å, 45°C, 83% over 2 steps

The tethering process was found to be extremely efficient, and no purification of the mixed acetal intermediates was found to be necessary prior to glycosylation. However, the glycosylation reaction was protecting-group dependent. Cyclic 4,6-protection was found to be necessary to avoid low yields.[27b,g] Nevertheless, a number of high yielding oligosaccharide syntheses were then reported (Figure 1.3).[27c]

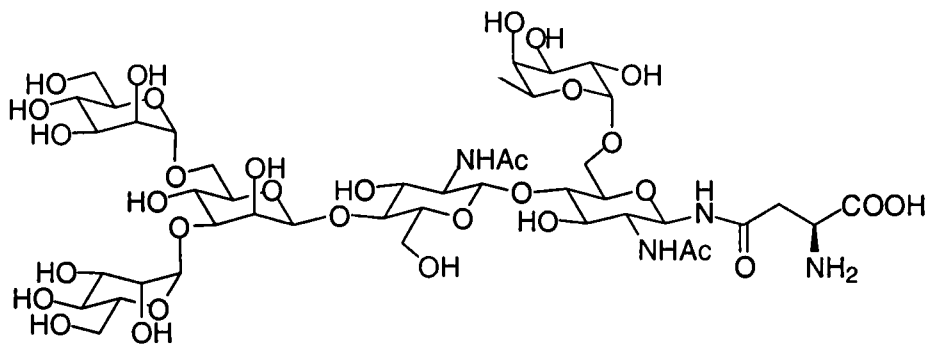
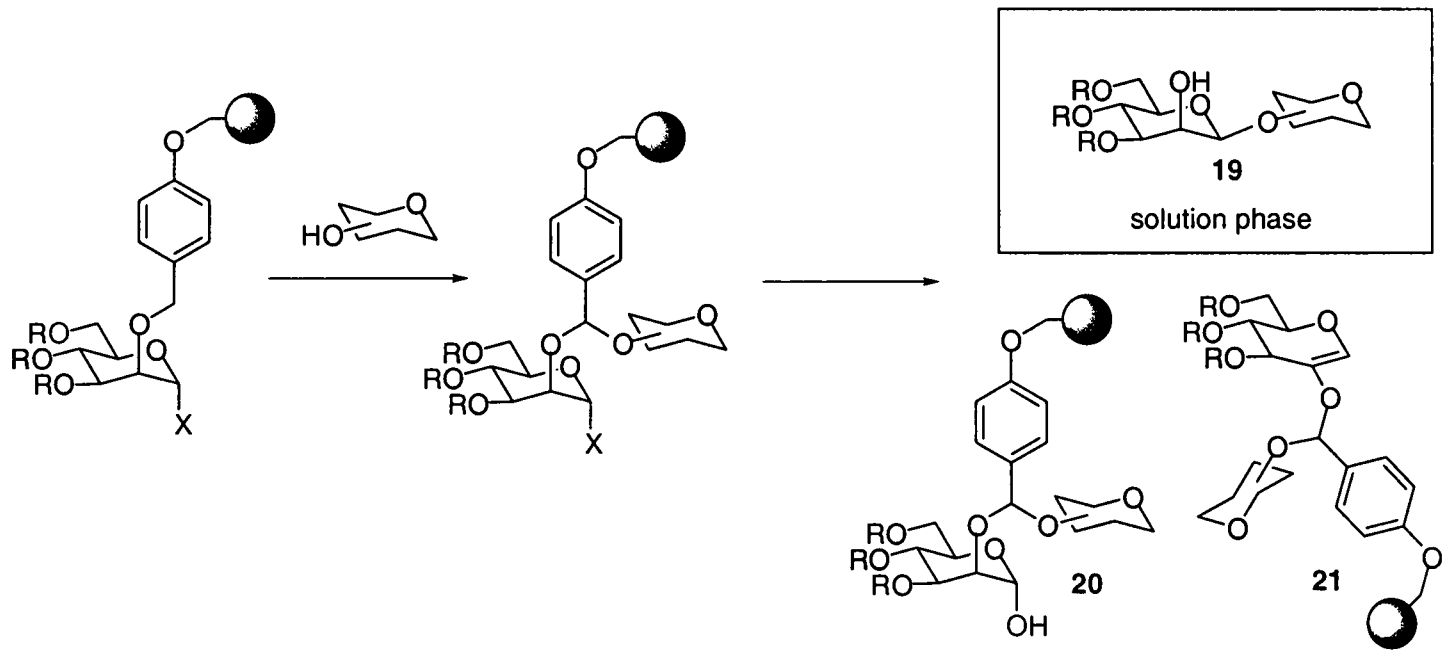


Figure 1.3: Fucose-containing core hexasaccharide as synthesised by Ogawa with PMB-mediated IAD as the key step.

Ogawa went on to investigate the stereochemistry at the acetal centre generated in the tethering reaction.[27d] In the normal 'forward' approach (as in Scheme 1.14), he found that a single (*S*) isomer was formed, but that when a 'reverse' tethering approach was employed, whereby a OH-2 free donor is tethered to a PMB protected aglycon, formation of the (*R*) diastereomer predominated. Apparently the stereoselectivity in the tethering reaction was a kinetic phenomenon. He also noted that both diastereomers reacted at similar rates to give the same β-mannoside in similar yield.

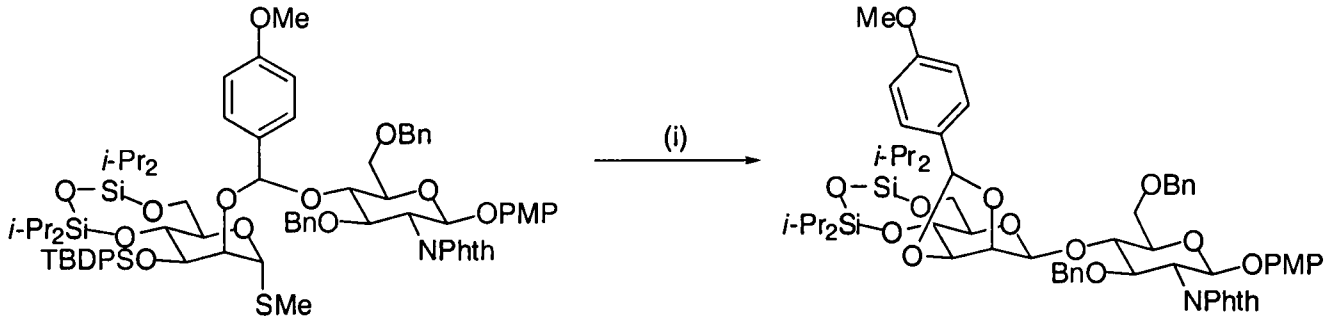
An ingenious twist on the methodology was its application to the solid phase.[27e] It had been found that non-glycosylated by-products from the reaction often retained the PMB group in the molecule, whereas this was lost in the desired glycosylated product. Ogawa realised then, that by linking the donor to a resin *via* a *para*-alkyloxybenzyl group, that tethering and glycosylation could be carried out on the solid phase.



Scheme 1.15: Ogawa's 'gatekeeper-monitored' IAD: a modified PMB group is attached to the solid support, so that following activation of a leaving group X, by-products such as **20** and **21** remain attached to the polymer, whereas the desired IAD product **19** is released into the solution phase, so facilitating purification.

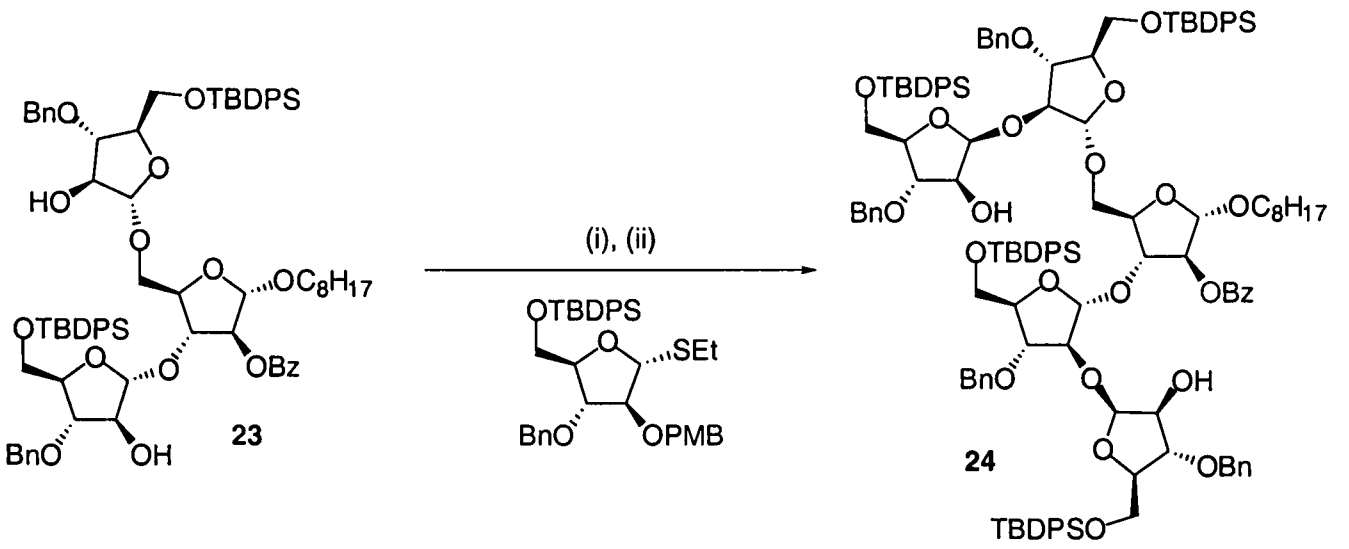
Furthermore, during the glycosylation reaction, the desired glycosylated product would be freed from the solid phase into solution (analogous to loss of the PMB group) whereas many of the undesired by-products would be retained on the resin, thus facilitating purification of the β-mannoside (Scheme 1.15).

No trapping by external nucleophiles of the oxonium ion **22** presumably generated in the IAD reaction has been reported by Ogawa, although intramolecular trapping by O-3 where it is silyl protected has been seen (Scheme 1.16).[27g] The fate of this oxonium species **22** has recently come under scrutiny by Ito.[27f] NMR experiments showed that it was never present in significant amounts in the reaction mixture, but no satisfactory explanation for its hydrolysis to the OH-2 free compound **19** was given.



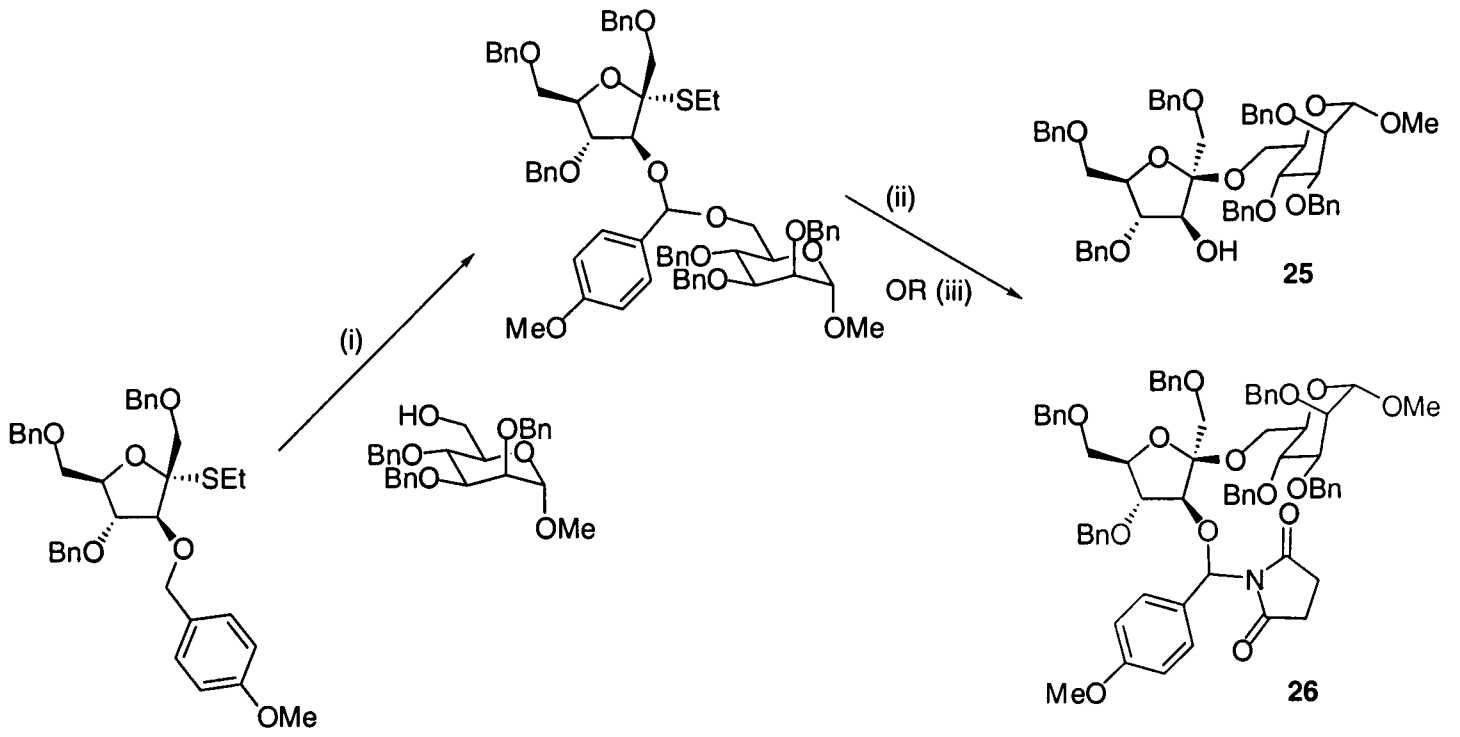
Scheme 1.16: Intramolecular trapping with concomitant desilylation in Ogawa's PMB system. (i) MeOTf, DTBMP, DCE, 4Å, 60°C, 78%

Others have gone on to use the PMB-mediated IAD in a variety of systems. Prandi found PMB-mediated IAD to be effective in the stereospecific synthesis of various β-arabinofuranosides.[28] Particularly impressive was a bis-β-glycosylation of a trisaccharide diol **23** to form a pentasaccharide **24** (Scheme 1.17).[28b]



Scheme 1.17: Prandi's bis-β-arabinosylation using PMB-mediated IAD methodology.
(i) DDQ, DCM, 4Å, 0°C→RT, 75%; (ii) IDCP, DCM, 4Å; then DDQ, CH_3CN, H_2O, 23%

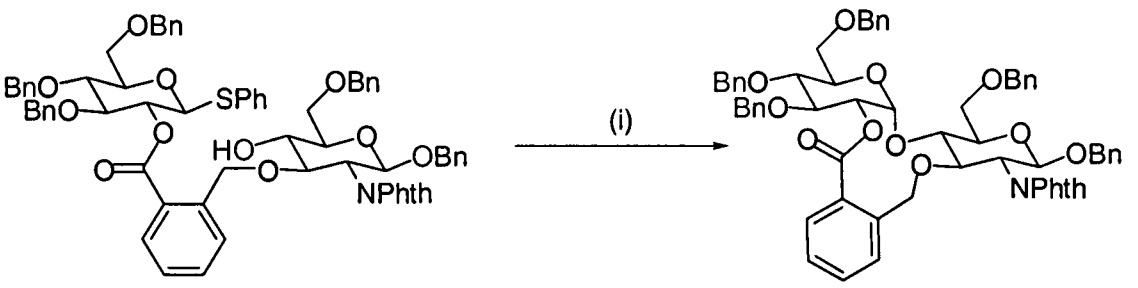
Oscarson has applied the methodology to the synthesis of β-fructofuranosides **25** using thioglyosides as donors.[29] Interestingly, he found that while it proved a useful route when activators with non-nucleophilic counterions (eg DMTST, IDCP) were used, when succinimide was used, the 'succinimide-trapped' material **26** was formed as the sole product. This hemiaminal proved to be more stable to acid hydrolysis than the new-formed β-fructofuranosidic linkage (Scheme 1.18).



Scheme 1.18: Oscarson's synthesis of β-fructofuranosides via IAD.
(i) DDQ, DCM, 4Å; (ii) NIS, DCM, **26** 57%; (iii) DMTST, DCM, **25** 77%

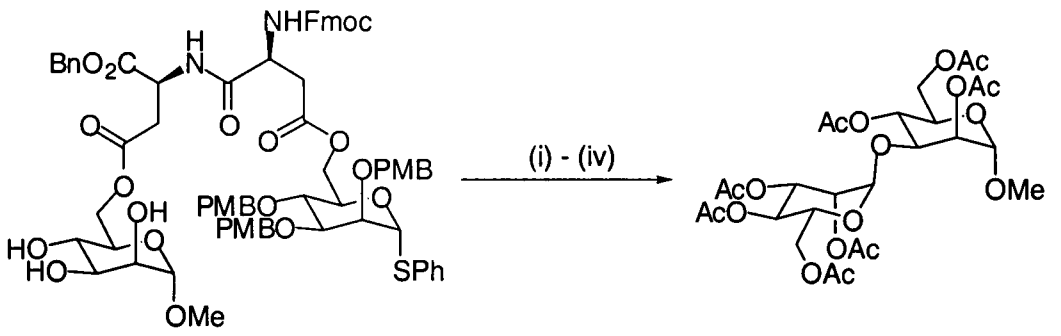
1.4.4 Other Intramolecular Glycosylation Reactions

Other intramolecular glycosylations have been reported, where the glycosyl acceptor is not the tethered oxygen.[30,31] Here stereoselectivity relies on the fact that the tethered material adopts a preferred conformation with the acceptor alcohol closer to either the α- or β-face of the donor (Scheme 1.19).



Scheme 1.19: Ziegler's stereoselective glycosylation using the principle of pre-arranged glycosides. (i) NIS, TMSOTf (cat), DCM, 0°C, 67% (only α)

Various linkers have been used, including an ambitious attempt from within our own group to impart both regio- and stereocontrol by the use of a peptide linker, predisposed towards a conformational preference of its own (Scheme 1.20).[32]



Scheme 1.20: Fairbanks and Tennant-Eyles' peptide templated glycosylation. (i) NIS, AgOTf, DCM; (ii) THF, MeOH, $PrNH_2$; (iii) TFA, DCM; (iv) Ac_2O, pyridine; α(1→3) 25% + two minor products.

1.4.5 Work on IAD Within Our Research Group

As part of our group's ongoing interest in oligosaccharide synthesis, in particular the selective synthesis of 1,2-*cis* bonds, we recently reported an NIS-mediated tethering modification to Hindsgaul's original methodology.[33] Thus a variety of aglycon alcohols were tethered and stereospecifically glycosylated in both *gluco* and *manno* series. In addition, a one-pot procedure whereby tethering and subsequent glycosylation were carried out in a single reaction vessel, without the need for isolation of the intermediate mixed ketals has been reported. A more detailed discussion of this work follows in Section 2.1.

This thesis describes subsequent investigations into this area.

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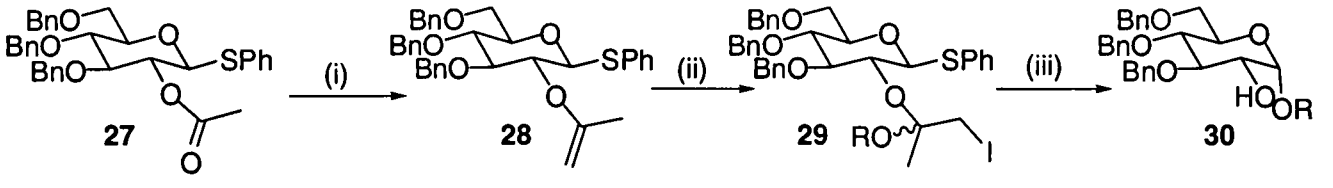
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Chapter 2. The Use of 2-*O*-Allyl Protected Thio- and Selenoglycosides as Donors in the Synthesis of α-Glucosides

2.1 Introduction

Previous work in our group on IAD by Ennis had focussed on adapting Hindsgaul's β-mannoside synthesis to the α-*gluco* system.[1] Hereby Tebbe methylenation of the 2-*O*-acetate protection of a thiophenyl glycoside **27** afforded an enol ether **28** as tether. This approach proved successful when the additional modification of using *N*-Iodosuccinimide (NIS)-mediated tethering (rather than acid catalysis) was employed (Scheme 2.1). Further enhancement of the methodology was the development of a one-pot synthesis, whereby following completion of the tethering process, excess NIS was added to activate the SPh leaving group and allow an intramolecular glycosylation reaction to take place. It is noteworthy that in this procedure, the intramolecular reaction successfully competed with any possible intermolecular glycosylation reaction between the donor **29** and any excess aglycon alcohol present in the reaction mixture.

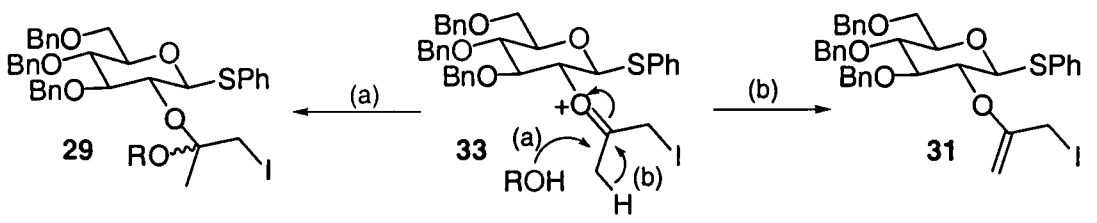


Scheme 2.1: Ennis' modification of the Hindsgaul procedure.
(i) Tebbe reagent; (ii) NIS, ROH, DCE, -40°C→RT; (iii) NIS, DCE, DTBMP, RT

However, the drawback to this methodology was that while a variety of alcohols were tethered and stereospecifically glycosylated, including primary

and secondary aliphatic alcohols and a primary carbohydrate alcohol, tethering of secondary carbohydrate alcohols failed. The only product isolated from such an attempted tethering was the enol ether **31**, presumably arising from loss of a proton from the iodinated species (Scheme 2.2).[2] This failure was a significant one, as in order to be a general oligosaccharide synthesis, the option of linking to the secondary positions on the aglycon sugar is essential. In particular, the tetradecasaccharide precursor to all *N*-linked glycoproteins, $Glc_3Man_9GlcNAc_2$ **32** contains three glucose residues, all of them α-linked to secondary carbohydrate centres.[3]

It was postulated that the increase in steric bulk in moving from primary carbohydrate alcohols, such as diacetone galactose (DAG) **3d**, and the model secondary alcohol cyclohexanol **3c**, to the more hindered secondary carbohydrate alcohols could account for the problem. In a proposed mechanism for the tethering reaction, rapid electrophilic addition of I^+ to the enol ether **28** to give an iodonium ion **33** is followed by rate-determining capture by the aglycon alcohol **3**. The rate of this second step is clearly dependent on the steric bulk of the alcohol. Thus whilst simple, unhindered alcohols were tethered in high yield, for secondary carbohydrates the attack was so slow that the competing reaction pathway, ie loss of a proton leading to the formation of enol ether **31**, came into operation (Scheme 2.2).



Scheme 2.2: (a) Tethering or (b) formation of the enol ether **31**

A potential solution to the problem would be to decrease the steric bulk of the tethering site. Formally we could envisage this occurring by 'moving' the methyl group to form an *n*-prop-1-enyl ether **34** rather than the isopropenyl ether **28** of the Hindsgaul system (Figure 2.1).

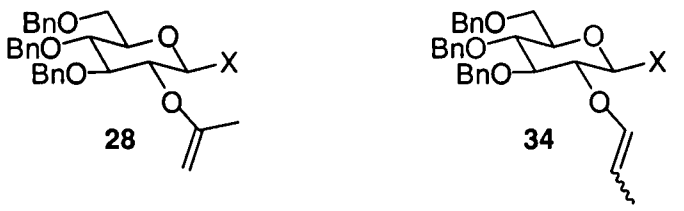
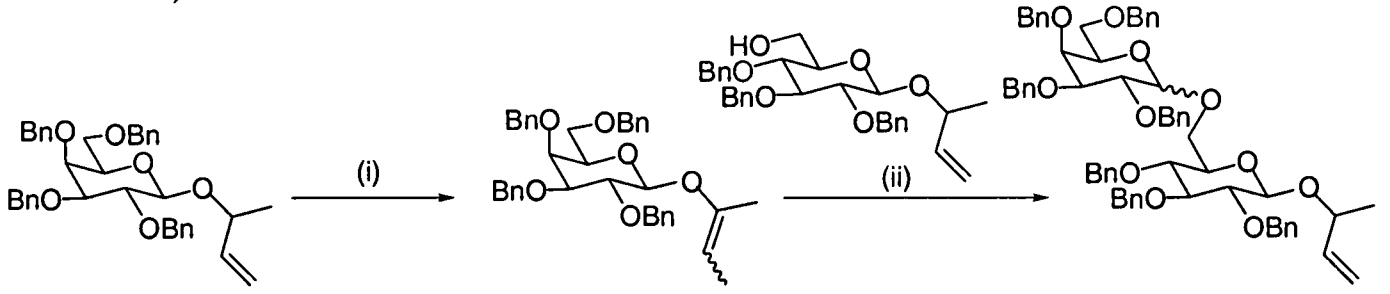


Figure 2.1: 'Moving' the methyl group to form an *n*-prop-1-enyl ether

The *n*-prop-1-enyl ether could be simply derived from the transition metal catalysed isomerisation of an allyl ether. Indeed, Boons and Isles recently reported a highly optimised application of this process to substituted allyl glycosides, where the resulting vinyl glycosides were used as glycosyl donors (Scheme 2.3).[4]



Scheme 2.3: Boons and Isles' isomerisation and glycosylation of substituted allyl glycosides. (i) $(PPh_3)_3RhCl$, BuLi, THF, 70°C, 90%; (ii) TMSOTf, MeCN, 0°C, 75% (4:1 α/β)

It was decided to investigate the use of more reactive leaving groups than the thiophenyl group used in the earlier IAD work by Ennis. Since the identification of thio-[5] and selenoglycosides[6] as glycosyl donors, it has been widely recognised that both classes of compounds are activated by soft electrophiles such as NIS[7], IDCP[8] and MeOTf[9]. In general selenoglycosides are more reactive than thioglycosides, a fact which has been exploited in various

one-pot glycosylation strategies.[10] Furthermore, significant variation in the reactivity of thioglycosides bearing different S-substitution has been observed.[11] It was decided therefore to investigate the use of the more reactive SePh and SMe leaving groups.

Thus the two initial synthetic targets would be the 2-*O*-allyl protected thiomethyl **35** and selenophenyl **36** glucosides, bearing orthogonal protection at the 3-, 4- and 6-positions (Figure 2.2).

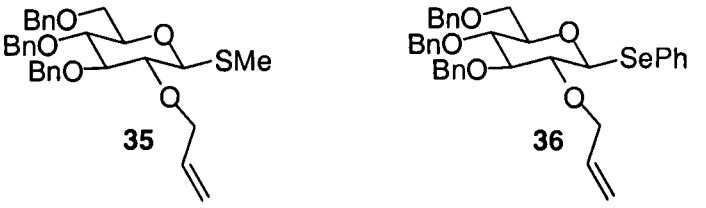
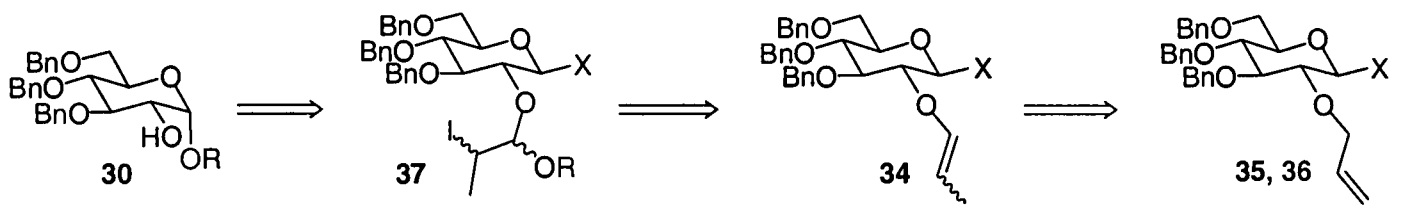


Figure 2.2: The target compounds

Isomerisation under Boons and Isles' conditions would give donors bearing the *n*-prop-1-enyl ether at the 2-position, which could then be used to investigate tethering and IAD on an allyl-derived system (Scheme 2.4).

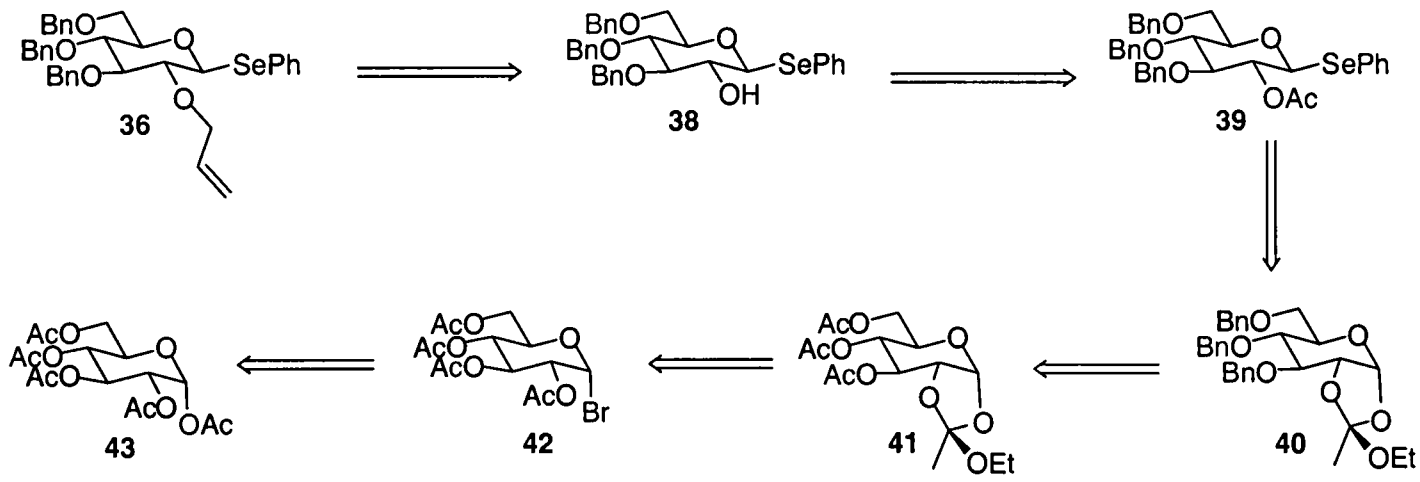


Scheme 2.4: Proposed allyl-mediated tethering and subsequent intramolecular glycosylation, of the mixed acetals **37** resulting in the stereospecific formation of α-glucosides **30**

2.2 Results and Discussion

2.2.1 Synthesis of the 2-*O*-Allyl Protected Selenoglycoside 36

A retrosynthesis of **36** is outlined in scheme 2.5. Introduction of the allyl protection onto the 2-position ought to be a facile two step deprotection/reprotection process from the 2-*O*-acetate **39**. This acetate **39** could be derived from the known orthoester **40** by a Lewis acid catalysed nucleophilic ring opening by selenophenol. Opening of orthoester **40** by selenophenol was not known, but the reaction had been carried out on the *galacto* analogue by Sinaÿ in high yield.[12] Furthermore, Lewis acid catalysed opening of the *gluco* orthoester by other nucleophiles, eg thiophenol, is well known.[2] This made orthoester **40** a particularly attractive intermediate, as it introduced a degree of flexibility into the synthetic scheme. We could envisage using alternative nucleophiles to open the orthoester, leading to different glycosyl donors with which to try the allyl-mediated IAD methodology.

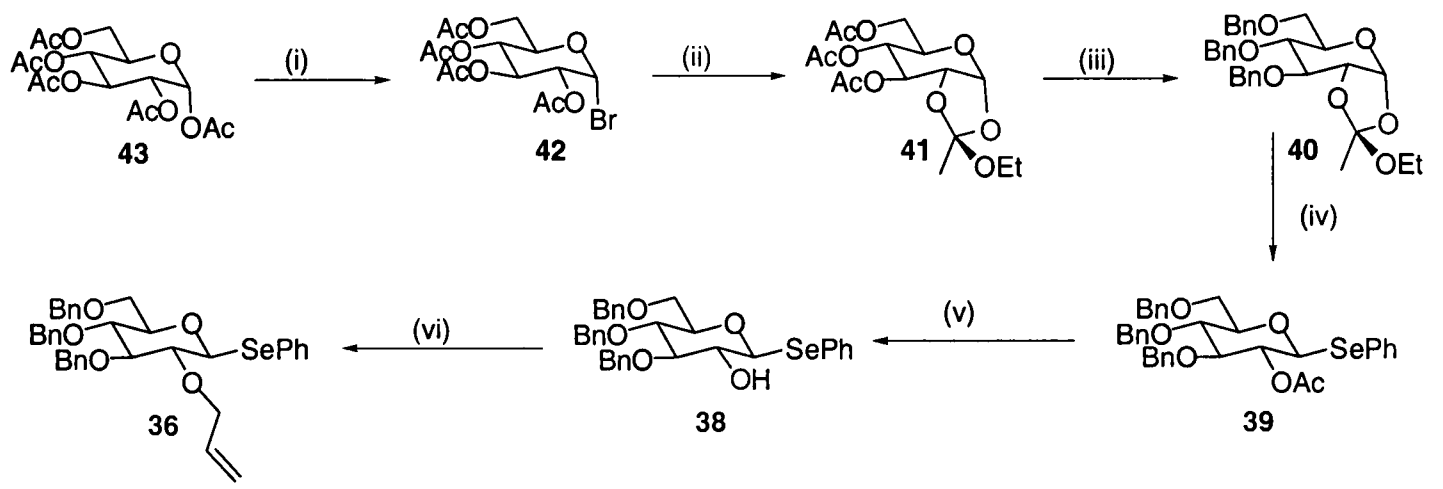


Scheme 2.5: Retrosynthetic analysis for compound **36**

The use of the orthoester intermediate **40** also has the advantage of allowing differentiation of the 2- from the 3-, 4- and 6-positions, so that a protecting

group swap from acetates to the orthogonal benzyl ether protection can take place. The orthoester **40** is made by a literature procedure.[13]

Consequently, commercially available glucose pentaacetate **43** was treated with 33% HBr in acetic acid,[2] to afford the glycosyl bromide **42**. Formation of the ethyl orthoester **41** and subsequent deacetylation and reprotection to form the benzyl ether protected orthoester **40** was carried out under literature conditions,[13] in an overall yield of 57% over 4 steps (Scheme 2.6).

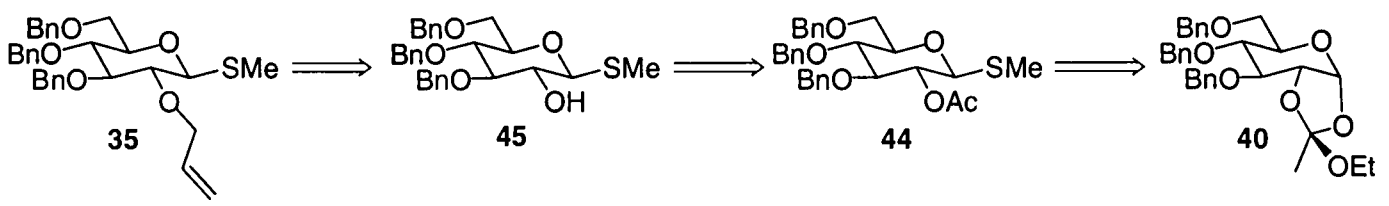


Scheme 2.6: (i) 33% HBr, AcOH 0°C, 89%; (ii) Bu_4NBr, EtOH, CH_2Cl_2, collidine, 40°C, 71%; (iii) Na, MeOH, RT; NaH, BnBr, DMF, 0°C, 90%; (iv) HSePh, MeCN, $HgBr_2$, 50°C, 78%; (v) Na, MeOH, RT, 91%; (vi) allyl bromide, NaH, DMF, 0°C, 92%

Pleasingly, orthoester opening with selenophenol in the presence of a mercury (II) bromide Lewis acid catalyst was found to work well to give the selenoglycoside **39** in a good 78% yield. Deacetylation under Zemplen[14] conditions proceeded smoothly to afford alcohol **38** in 91% yield. This was allylated using sodium hydride and allyl bromide[15] to furnish the desired 2-*O*-allyl protected glucosyl donor **36** in a very satisfactory 92% yield (Scheme 2.6).

2.2.2 Synthesis of the 2-*O*-Allyl Protected Thioglycoside 35

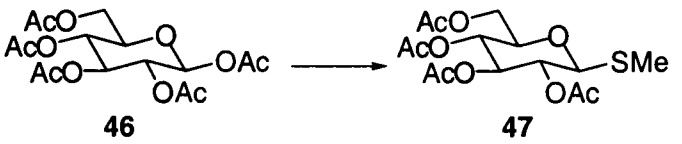
Attention now turned to the synthesis of the thiomethyl compound **35**. It was envisaged that the same benzyl protected orthoester **40** as was used in the selenophenyl case could be used as an intermediate in this synthesis. Opening by a thiomethyl nucleophile could give the acetate protected thioglycoside **44**. Straightforward deacetylation followed by allylation would then furnish the desired 2-*O*-allyl protected species **35** (Scheme 2.7).



Scheme 2.7: Retrosynthesis of compound **35**

Analogous Lewis acid catalysed opening of orthoester **40** with methanethiol was deemed impractical though, as this compound is not only gaseous, but also has an extremely pungent and malodorous stench. An attractive alternative would be the use of an ionic methanethiolate, for example the sodium salt of MeSH, which is a solid, and thus much easier to handle. A reaction of orthoester **40** with this nucleophile in the presence of 15-crown-5 and a Lewis acid, $BF_3.OEt_2$, led to the formation of the desired thioglycoside **44** as a single β anomer, but in a low 14% yield (Table 2.1, entry 1).

Field *et al* developed a methodology for the introduction of thiomethyl groups to the anomeric position of carbohydrates.[16] In this method, hexamethyldisilane, dimethyl disulfide and iodine are mixed together with a peracetylated sugar **46**, and the 1,2-*trans* thioglycoside **47** is formed stereospecifically and in high yield (Scheme 2.8).

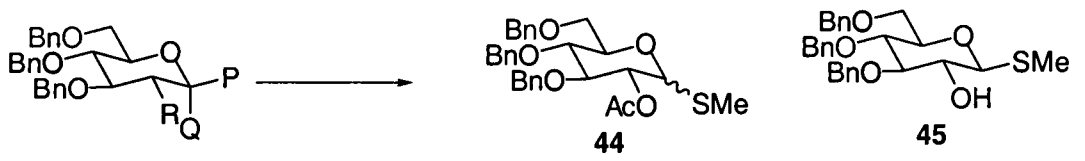


46 47

Scheme 2.8: Field's thioglycoside synthesis.

(i) MeSSMe, HMDS, DCM, I_2, RT, 95%

When orthoester **40** was subjected to these conditions, the desired thioglycoside was formed, but as a 1:1 α/β mixture, and in a disappointing 23% yield (Table 2.1, entry 2). It was decided to try out the Field methodology on the 1,2-di-*O*-acetate protected compound **48**. Diacetate **48** was formed in good yield from hemiacetal **49** by acetylating with acetic anhydride and pyridine. The hemiacetal **49** is readily available in two steps from orthoester **40**.[17] However, subjecting diacetate **48** to Field's conditions gave the thioglycoside in only 41% yield, and as a disappointing 1:1 α/β mixture (Table 2.1, entry 3).



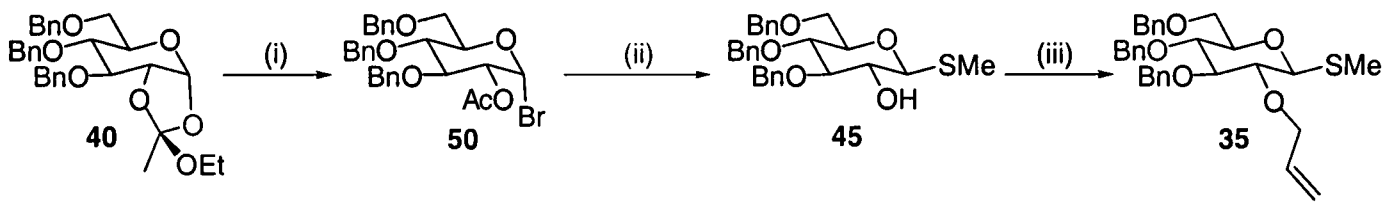
44 45

Entry		P	Q	R	Conditions	Product	α/β ratio	Yield
1	**40**	H	$O_2C(OEt)CH_3$		NaSMe, 15-crown-5, $BF_3.OEt_2$, RT	**44**	β	14%
2	**40**	H	$O_2C(OEt)CH_3$		MeSSMe, $Me_3SiSiMe_3$, I_2, RT	**44**	1:1	23%
3	**48**	OAc, H		OAc	MeSSMe, $Me_3SiSiMe_3$, I_2, RT	**44**	1:1	41%
4	**49**	OH, H		OAc	MeSSMe, Bu_3P, $BF_3.OEt_2$, RT	**44**	1:1	64%
5	**50**	H	Br	OAc	MeSSMe, BuLi, THF, -78°C	**45**	β	68%

Table 2.1: Some attempts to form the thiomethyl glycoside

An alternative approach to thioglycosides, reported by Zhao *et al* employed a Mitsonobu type reaction of a hemiacetal with dimethyl disulfide and triphenyl phosphine in the presence of a Lewis acid catalyst.[18] When hemiacetal **49** was subjected to these conditions, the desired thioglycoside was formed in good yield, but as a disappointing 1:1 α/β mixture (Table 2.1, entry 4).

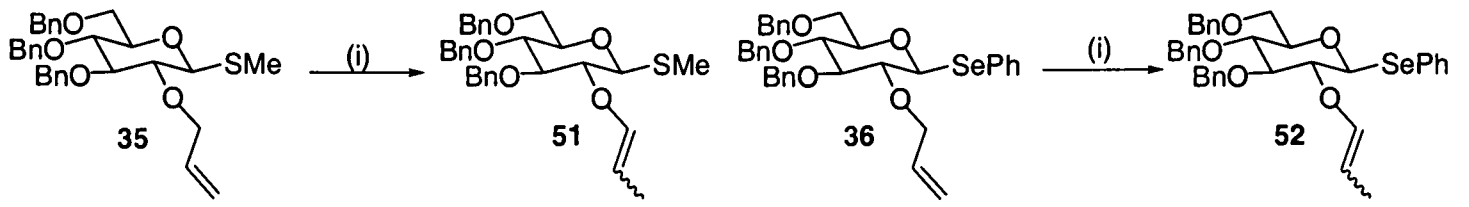
Finally it was found that the bromide **50** could be prepared from the orthoester **40** by treatment with either AcBr or 33% HBr in acetic acid.[13] Treatment of this bromide **50** with LiSMe, prepared *in situ* from BuLi and MeSSMe in THF at -78°C[19] cleanly afforded the deacetylated β-thioglycoside **45** in 68% yield, or 61% overall from the orthoester **40** (Table 2.1, entry 5). Allylation under standard conditions[15] afforded the desired 2-*O*-allyl protected donor **35** in good yield (Scheme 2.9).



Scheme 2.9: (i) AcBr, CH_2Cl_2, 0°C; (ii) MeSSMe, BuLi, THF, -78°C 61% over 2 steps; (iii) allyl bromide, NaH, DMF, RT, 85%

2.2.3 Isomerisation of the 2-*O*-Allyl Protected Donors

We were delighted to find that treatment of the allyl protected donors **35** and **36** with a catalyst prepared from Wilkinson's catalyst and BuLi under Boons and Isles' conditions[4] afforded the enol ethers **51** and **52** in excellent 93% and 94% yields respectively (as diastereomeric mixtures) (Scheme 2.10).



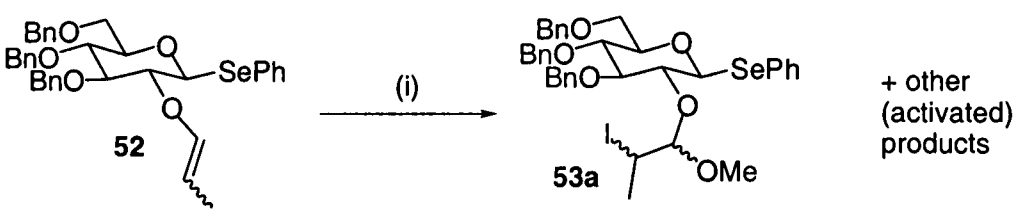
Scheme 2.10: (i) $(Ph_3P)_3RhCl$, BuLi, THF, 70°C; **51**, 93% (E/Z, 27:73); **52**, 94% (E/Z, 31:69)

With the glycosyl donors bearing *n*-prop-1-enyl ethers at the 2-position in hand, attention now turned to attempting the two step tethering and intramolecular glycosylation sequence of reactions.

2.2.4 Tethering and Glycosylation in the Selenophenyl System

Initial investigations into tethering were carried out using the more reactive selenophenyl glycoside **52** and methanol **3a** as a model alcohol. It was decided to initially try out the NIS-mediated tethering conditions used in our group in the modified Hindsgaul isopropenyl system.[1]

Consequently enol ethers **52** and methanol **3a** were treated with NIS in DCM at -50°C and the desired mixed acetals **53a** were isolated in an unsatisfactory 36% yield (Scheme 2.11). However, three other carbohydrate-containing compounds were also isolated from the reaction mixture, all of which had lost the selenophenyl leaving group as shown by mass spectrometry, where the characteristic isotope distribution of selenium was absent, and by ^1H NMR spectroscopy, where a resonance due to SePh was absent at δ_H 7.6.

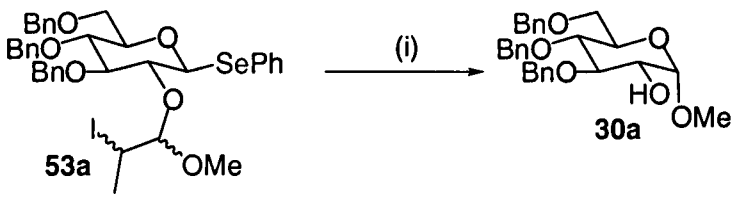


Scheme 2.11: (i) NIS, DCM, 4Å, -50°C, 36%

It appeared that NIS was activating the selenophenyl leaving group under the reaction conditions,[20] showing that the reactivity differential between the enol ether and the SePh group towards NIS was small. It was postulated that by conducting the reaction at lower temperature, greater selectivity for the enol ether could be achieved.

When tethering reactions between enol ethers **52** and methanol or ethanol were carried out in THF at -78°C, only starting materials or intractable mixtures of products were obtained.

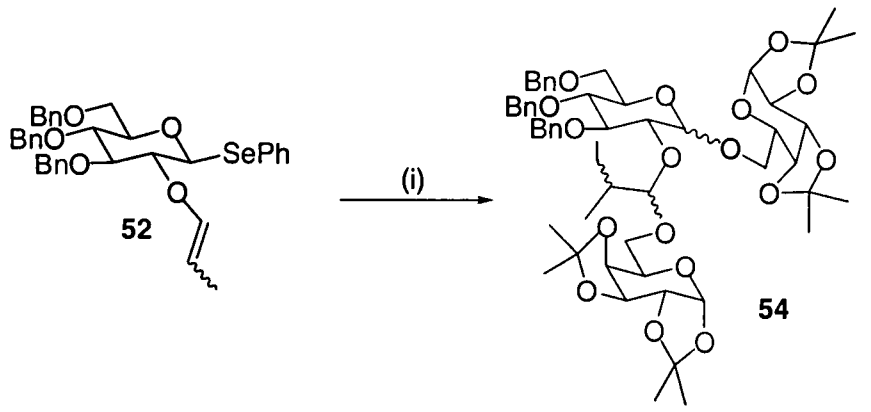
Nevertheless, an intramolecular glycosylation reaction of the isolated tethered materials **53a** was attempted. When the mixed acetals **53a** were treated under suitable activation conditions for SePh[20] (ie NIS, DCE at -40°C in the presence of the hindered base DTBMP), it was pleasing to find that glycosylation occurred in a stereospecific manner to afford the desired α-glucoside **30a** as the sole glycosylated product, in a good 70% yield (Scheme 2.12).



Scheme 2.12: NIS, DCM, DTBMP, -40°C, 70%

It was postulated that if the tethering reaction could be driven to completion by the use of an excess of NIS, then simply allowing the reaction mixture to warm up would activate the SePh group, leading to a one-pot tethering and glycosylation reaction. When such a reaction was attempted, using DAG **3d** as aglycon, the initial tethering reaction did not go to completion (as

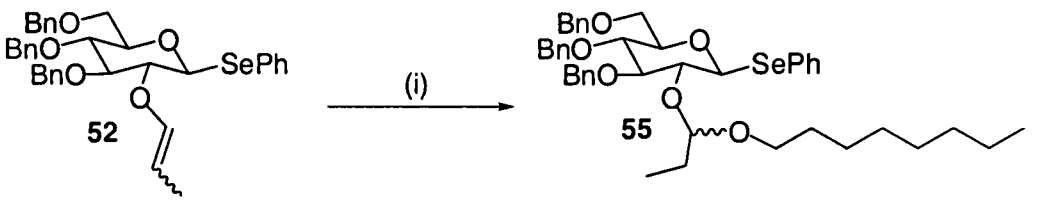
monitored by tlc). The mixture was nevertheless allowed to warm to room temperature, and a mixture of products was formed. MS analysis of the major isolated product **54** indicated a molecular mass of 1118, consistent with the structure shown in scheme 2.13. This structure could arise from either intramolecular glycosylation to form the α-glucoside, followed by trapping of the resulting oxonium ion by excess alcohol in the reaction mixture, or from an intermolecular glycosylation of the tethered material **53a**, in which case an α/β mixture would be expected. However, ^{1}H NMR spectroscopy showed this product **54** to be a mixture of diastereomers, and the anomeric stereochemistry could not be elucidated.



Scheme 2.13: (i) DAG **3d**, NIS, DCM, -78°C→RT

Despite the promising result from the glycosylation reaction, the low reactivity differential between the enol ether and the anomeric leaving group towards I^+ effectively rendered this route impractical for the formation of 1,2-*cis* glycosides. Hindsgaul, in his system, had used acid catalysis to effect the tethering reaction.[21] This seemed an attractive prospect, as the enol ether moiety could be envisaged as being reactive towards H^+, resulting in a tethering reaction, while the selenophenyl group remained inert. Consequently, acid tethering was attempted. When enol ethers **52** and octanol

3m were treated with catalytic etherial HCl, the formation of some tethered product **55** was observed, but the reaction was sluggish, and gave much hydrolysis (Scheme 2.14). Furthermore, investigations in our group by Aloui into the potential of acid tethering to 2-*O*-allyl-derived enol ethers in the *manno* series revealed that pyridinum tosylate produced no reaction whereas tosic acid gave hydrolysis of the tether.[22]



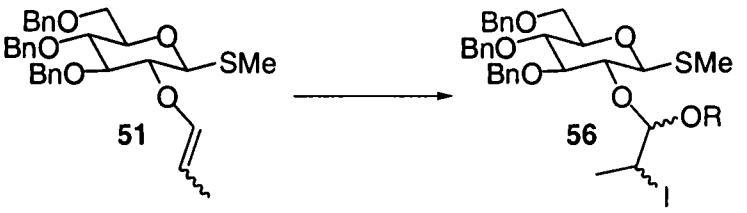
Scheme 2.14: (i) octanol **3m**, HCl (in ether, 0.1 eq), DCE, RT, 4% after 50 min

As this route now seemed fraught with difficulty, it was decided to pursue the thiomethyl glucoside alternative. SMe is a less reactive leaving group than SePh,[23] hence should be less likely to be activated under the tethering conditions.

2.2.5 Tethering in the Thiomethyl System

It was decided to attempt a tethering reaction in the thiomethyl system using NIS-mediated reaction conditions, based on those used in the earlier isopropenyl work from our group[1] and using diacetone galactose **3d** as a model alcohol. Consequently, enol ethers **51** were treated with DAG and NIS in DCM at -40°C in the presence of 4Å sieves. The reaction was allowed to warm to room temperature, and very pleasingly, the desired mixed acetals **56d** were obtained in good yield as a mixture of diastereomers as shown by ^{1}H NMR spectroscopy. A screen of solvents was undertaken. In addition to

DCM, DCE and THF were tried (Table 2.2, entries 5-7). DCE gave the best tethering yield, and so other primary alcohols were also tethered to the enol ethers **51** under these conditions to form the mixed acetals **56** in excellent to good yield (Table 2.2, entries 1,2,8). The model secondary alcohol cyclohexanol **3c** was also tethered in high yield, although it was necessary to use a large excess of the alcohol (Table 2.2, entries 3,4). Even the more bulky secondary carbohydrate alcohols were found to give some of the desired mixed acetal products **56** when subjected to the reaction conditions. This was a significant improvement on earlier results in this area, but nevertheless, the yields were low (Table 2.2, entries 12-15).



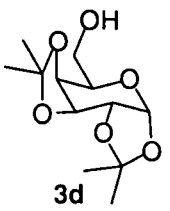
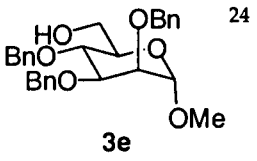
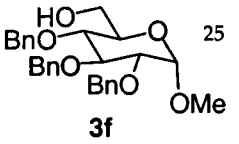
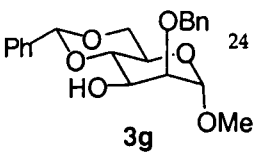
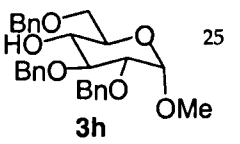
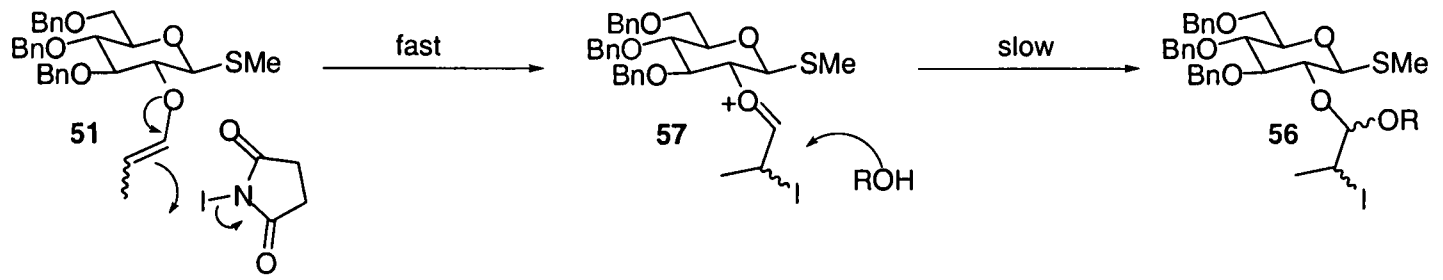
Entry	ROH	eq	eq NIS	solvent	t	T/°C	Product/yield of mixed acetals
1	MeOH **3a**	1.5	3	DCE	1h	-40→-5	**56a** / 98%
2	BnOH **3b**	2	3	DCE	1h	-40→0	**56b** / 95%
3	Cyclohexanol **3c**	1.5	3	DCE	1h	-40→-15	**56c** / 56%
4	Cyclohexanol **3c**	3	3	DCE	1h	-40→	**56c** / 80%
5	 **3d**	1.5	3	DCE	1h	-40→-5	**56d** / 85%
6	**3d**	2	2	DCM	2h	-40→RT	**56d** / 74%
7	**3d**	1.5	3	THF	o/n	-78→RT	**56d** / 59%
8	 **3e**	2	3	DCE	1 h 5 min	-40→5	**56e** / 63%
9	**3e**	1.7	3	MeCN	1 h	-40→0	**56e** / 49%
10	 **3f**	1.5	3	DCE	45 min	-40→	**56f** / 36%
11	**3f**	3	3	DCE	1.5 h	-40→RT	**56f** / 36%
12	 **3g**	3	3	DCE	5 h	-40→-5	**56g** / 22%
13	**3g**	3	3	THF	o/n	-78→RT	**56g** / 16%
14	**3g**	3	3	THF	3.5 h	-78	No rxn
15	 **3h**	3	3	DCE	2h	-40→	**56h** / 5%

Table 2.2: Thiomethyl tethering reactions

It was found that in order to prevent any activation of the thiomethyl leaving group by NIS in the mixture, the tethering reaction times must be limited. In the proposed mechanism, initial rapid addition of I^+ to the enol ethers **51** is followed by a rate determining nucleophilic attack on the iodonium ion by the aglycon alcohol **3**, leading to the desired mixed acetal products **56** (Scheme 2.15). This meant that for some of the more hindered alcohols, the reaction did not have time to go to completion.



Scheme 2.15: mechanism of formation of the mixed acetals **56**

This effectively meant that SMe was still too reactive a leaving group to be useful in the NIS-mediated tethering of secondary carbohydrate alcohols.

2.2.6 Glycosylation in the Thiomethyl System

Having successfully tethered a range of alcohols to the thiomethyl donor, attention turned to the intramolecular glycosylation reaction. A well known set of conditions for the activation of thioglycosides is NIS in conjunction with silver triflate.[26] A glycosylation reaction of the DAG-tethered material **56d** under these conditions was attempted. Duly, a solution of the tethered material **56d** in DCM was treated with NIS and silver triflate in the presence of the hindered base DTBMP. Pleasingly, the sole glycosylated product isolated from the reaction mixture was the desired α-glucoside **30d** (Table 2.3,

entry 1). However, the yield of this reaction was only 25% and there were many other products formed in the reaction, as observed by tlc.

In his previous work on the Hindsgaul-derived system, Ennis had found that following aglycon delivery, the oxonium formed in the glycosylation reaction (*cf* Scheme 2.16) could be trapped out by either excess aglycon alcohol present (in the one pot cases) or by other nucleophiles, such as succinimide, to give mixed ketals,[27] such as **58** and **59** as by-products (Figure 2.4).[1] He had found treatment of these materials with an acidic ion exchange resin to be an effective way of cleaving the tethering ketal whilst leaving the glycosidic linkage intact, thus affording further quantities of the desired 1,2-*cis* glycosides with OH-2 free **30**.

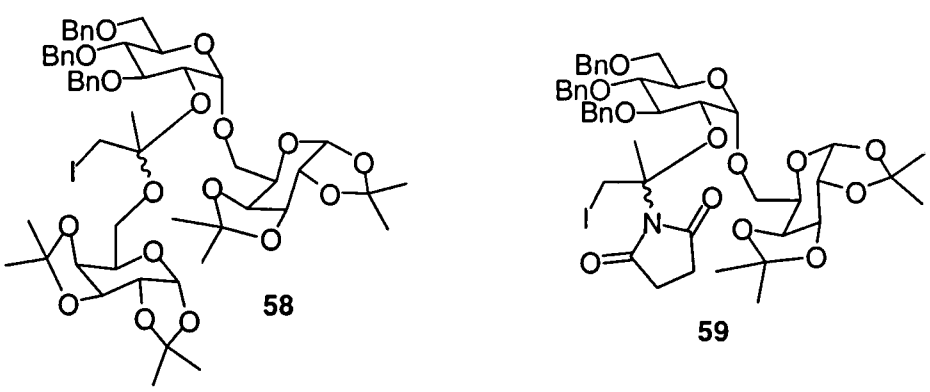
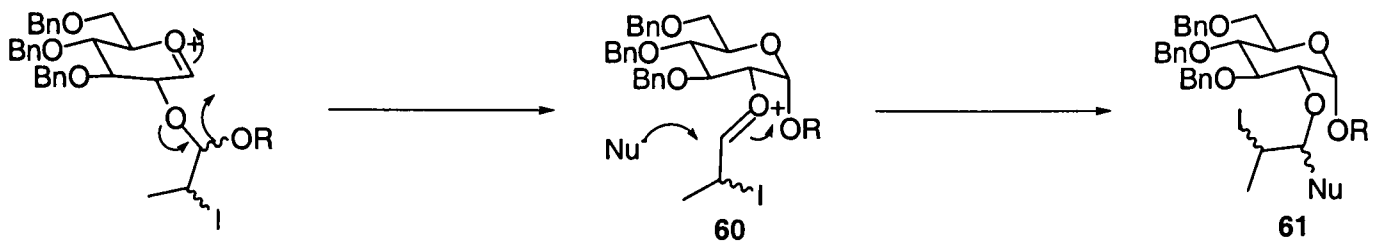


Figure 2.4: alcohol- and succinimide-trapped species

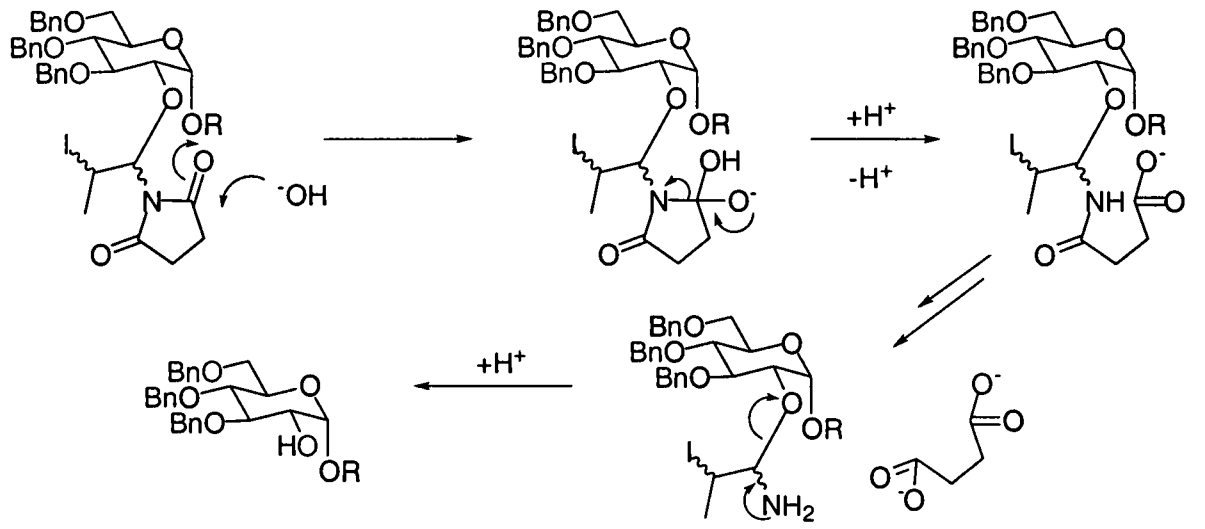
It was postulated that analogous trapped materials were forming in this allyl-derived system. In the proposed mechanism of intramolecular glycosylation, activation of the leaving group followed by aglycon delivery results in the formation of an oxonium ion **60**, which may then hydrolyse to give the desired product. Alternatively, trapping of the oxonium ion **60** by nucleophiles in the reaction mixture results in the formation of trapped materials **61** (Scheme 2.16).



Scheme 2.16: Proposed mechanism for the formation of trapped materials

In the *manno* analogue of this allyl-derived system, Seward demonstrated that compounds corresponding to trapping of an oxonium ion by succinimide, and by the product alcohol, were formed in a glycosylation reaction.[28] That the by-products from the *gluco* glycosylation reaction were degraded (*vide infra*) into further 1,2-*cis* glycosides provides further support for their assignment as the 'trapped' mixed acetals **61**.

Treatment of the combined by-products from the allyl-derived glycosylation reaction with ion exchange resin as before[1] though, was ineffective. Clearly, an acetal is more stable towards acid catalysed hydrolysis than is a ketal, but even the use of a more strongly acidic ion exchange resin produced no change. However, it was found that lithium hydroxide could be used to cleave succinimide-trapped material, presumably *via* hydrolysis of the succinimide ring to give the unstable hemiaminal (Scheme 2.17).

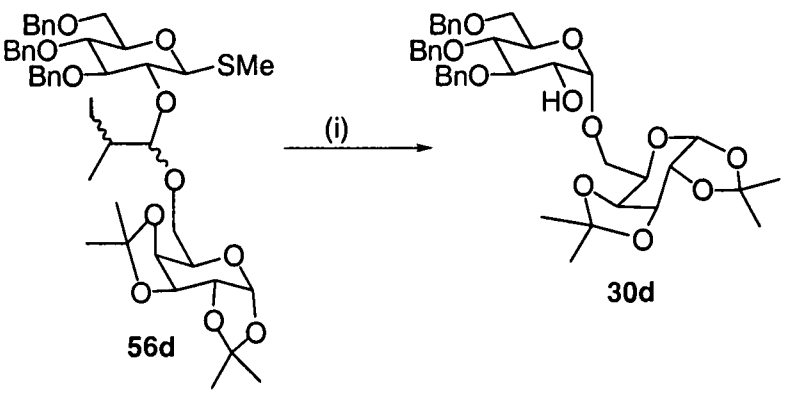


Scheme 2.17: proposed mechanism for the basic hydrolysis of the succinimide-trapped material

Eventually it was discovered that treatment of trapped materials from the allyl-derived IAD reaction with a mixture of trifluoroacetic acid (TFA), methanol, THF and water efficiently cleaved the mixed acetals of the tether, without causing hydrolysis of the anomeric linkage. Alternatively, simple addition of TFA and water directly to the reaction mixture before work-up was found to be effective.

Consequently, when the trapped material from the allyl-derived DAG glycosylation reaction was treated firstly with LiOH and then with TFA, a further 21% of glycosylated product **30d** was obtained. The overall yield was then 46% of the 1,2-*cis* glycoside **30d** (Table 2.3, entry 1). A test reaction where the hindered base was omitted, but under otherwise identical reaction conditions gave a much faster reaction, but with a lower yield of 27% after LiOH treatment (Table 2.3, entry 2).

In order to try to stop the trapping by product alcohol or succinimide, which led to problematic trapped materials, it was decided to try the addition of competitive nucleophiles to the reaction mixture. It was envisaged that such species could trap the oxonium ion **60** formed after IAD, to give more labile products, such as a hemiacetal (from water) or a hemiaminal (from ammonia). Addition of water gave little change, while saturated aqueous ammonia solution prevented any reaction from taking place (Table 2.3, entries 3,4).

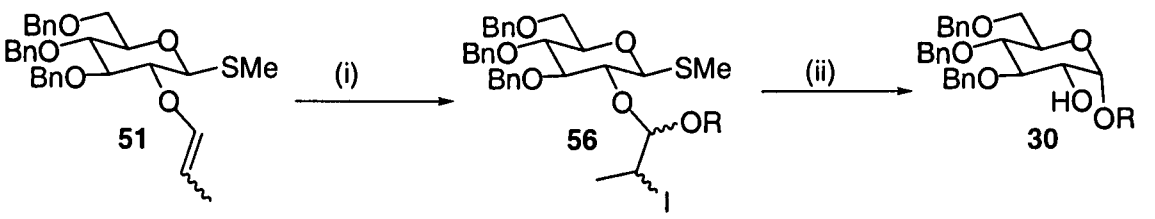


Entry	Conditions	solvent	Yield
1	NIS (3), AgOTf (1), DTBMP (3) 2 days, then LiOH.	DCM	25%
	Trapped material treated with TFA		further 21%
2	NIS (3), AgOTf (1) 15min, then LiOH. Tlc very clean	DCM	27%
3	NIS (3), AgOTf (1), DTBMP (3), H_2O (10), then LiOH, then TFA	DCM	40%
4	NIS (3), AgOTf (1), DTBMP (3), NH_3 (aq) (3 drops).	DCM	No rxn
5	MeOTf (5), DTBMP (3), 2h	DCE	70%

Table 2.3: Glycosylation reactions of DAG tethered material **56d** under various reaction conditions; number of equivalents in parentheses

Lönn demonstrated that methyl triflate was an excellent activator for thioglycosides.[9] He found that S-methylation followed by capture of the developing glycosyl cation by an aglycon resulted in efficient disaccharide formation.

Subjection of DAG-tethered material **56d** to methyl triflate activation, in the presence of the hindered base DTBMP, gave the desired 1,2-*cis* glycoside **30d** in a good 70% yield (Table 2.3, entry 5). Consequently intramolecular glycosylation of the isolated tethered materials **56a-f** was carried out using methyl triflate in the presence of DTBMP in DCE as solvent, followed by acid (TFA) treatment to free the trapped material to give stereospecifically α-glucosides in all cases in good yield (Table 2.4).



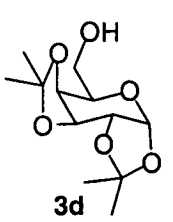
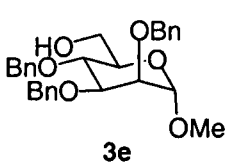
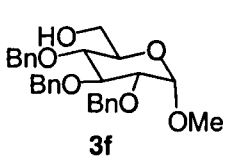
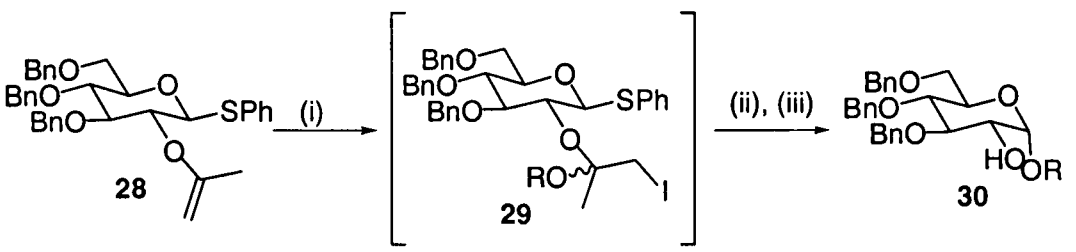
Entry	ROH	Product/ Yield of mixed acetals	Product/ Yield of α-glucoside
1	MeOH **3a**	**56a** / 95%	**30a** / 65%
2	BnOH **3b**	**56b** / 98%	**30b** / 67%
3	Cyclohexanol **3c**	**56c** / 80%	**30c** / 77%
4	 **3d**	**56d** / 85%	**30d** / 70%
5	 **3e**	**56e** / 63%	**30e** / 72%
6	 **3f**	**56f** / 36%	**30f** / 74%

Table 2.4: Tethering and glycosylation yields for the allyl-mediated IAD using a *gluco* thiomethyl donor

2.2.7 Attempted Tethering and Glycosylation Reactions in One Pot

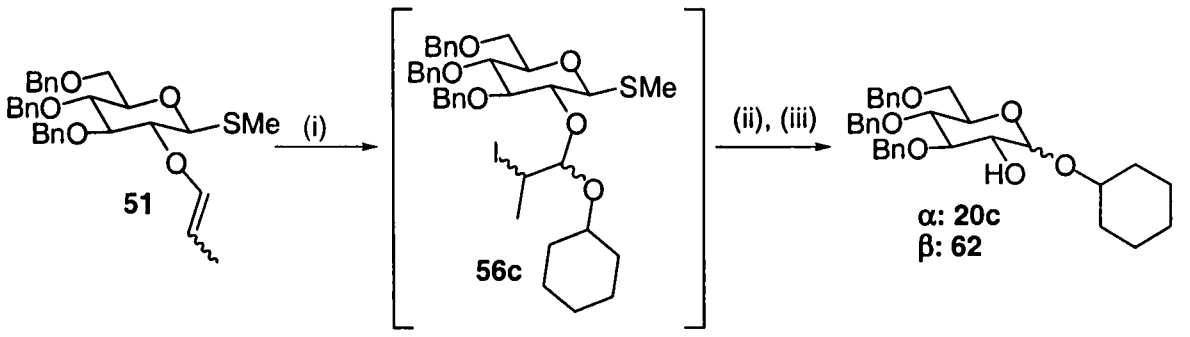
One of the major highlights of our group's early IAD work on the isopropenyl system was the development of a so-called one-pot approach.[1] Hereby a tethering reaction was carried out under standard NIS-mediated conditions (using an excess of the aglycon alcohol **3**), and monitored by tlc. When all the starting enol ether **28** had been seen to be converted to the tethered mixed acetals **29**, further NIS was added in order to activate the anomeric thiophenyl leaving group. An intramolecular glycosylation reaction then took place in the presence of excess aglycon alcohol **3**, leading to the stereospecific

formation of 1,2-*cis* glycosides **30**. This procedure had been effective in both *gluco* and *manno* series (Scheme 2.18).



Scheme 2.18: Ennis' *gluco* one-pot reaction using an isopropenyl tether.
(i) NIS, ROH, DCE, -40°C→RT; (ii) add NIS, DTBMP, RT; then Amberlite (H^+)

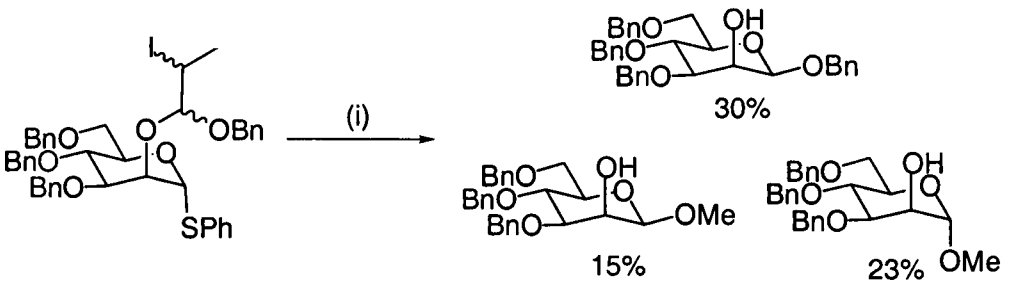
It was decided to try such a one-pot reaction in the allyl-derived system. Consequently, thiomethyl enol ethers **51** and excess cyclohexanol **3c** (3 eq) were treated under standard tethering conditions, but with the addition of the hindered base DTBMP. The reaction was monitored by tlc, and after 20 min was judged to have gone to completion: tlc indicated no remaining enol ether starting materials **51** and the formation of a major non-polar product as observed when mixed acetals **56c** were isolated in earlier tethering reactions. Therefore, the mixture was allowed to warm to room temperature, and methyl triflate was added in order to activate the thiomethyl leaving group and so induce glycosylation. When there were seen to be no further mixed acetals remaining by tlc, the usual TFA work-up was undertaken. The glycosylated product was isolated in an excellent 94% yield, but disappointingly it was found to be a mixture of α **30c** and β **62** anomers (Scheme 2.19).



Scheme 2.19: (i) NIS (3 eq), cyclohexanol (3 eq), DTBMP, DCE, -40°C; (ii) MeOTf, RT; (iii) TFA, H_2O, 94% (α/β, 1.7:1)

Presumably this result arose from an intermolecular glycosylation reaction of the thioglycoside donor **56c** with excess cyclohexanol **3c** present in the reaction mixure acting as a competing pathway over the expected IAD. The lack of stereocontrol in such an intermolecular glycosylation would lead to the observed α/β mixture.

Furthermore, Seward had demonstrated that in the *manno* series, intermolecular glycosylation of an external nucleophile was able to compete with allyl-derived IAD (Scheme 2.20).[28] This suggests that for a stereospecific one-pot reaction to take place, there must be no excess aglycon present. However, as discussed earlier, in order to get the tethering reaction to go to completion, an excess of the aglycon alcohol must be used. These apparent irreconcilable differences meant that no further investigations into an allyl-derived one-pot reaction were carried out.



Scheme 2.20: Seward's competition experiment
(i) MeOH, NIS, AgOTf, DTBMP, 4Å, 50°C; then TFA

2.3 Conclusion

In conclusion, it has been demonstrated that Wilkinson's catalyst-mediated isomerisation of a 2-*O*-allyl protecting group on both selenophenyl **36** and thiomethyl **35** glycosides may be used to good effect as an efficient route to an enol ether. NIS-mediated tethering of aglycon alcohols to the selenophenyl system proved impractical due to competitive activation of the anomeric leaving group. In the thiomethyl case, a variety of alcohols were tethered to form mixed acetal products **56**. Primary and secondary aliphatic alcohols and primary carbohydrate alcohols were tethered in good yields, and secondary carbohydrate alcohols in rather poorer yield, but in all cases yields were better than or comparable to those in the isopropenyl system. Furthermore, upon activation of these systems, the stereospecific formation of α-glucosides *via* allyl-derived IAD has been demonstrated.

Unfortunately, the methodology relies on the rather harsh TFA-mediated hydrolysis of the trapped materials formed in the glycosylation reaction in order for good yields to be obtained.

Furthermore in an attempted one-pot reaction, an α/β mixture of products was obtained, indicating that in this case, unlike the isopropenyl system, an intermolecular glycosylation may successfully compete with the intramolecular reaction.

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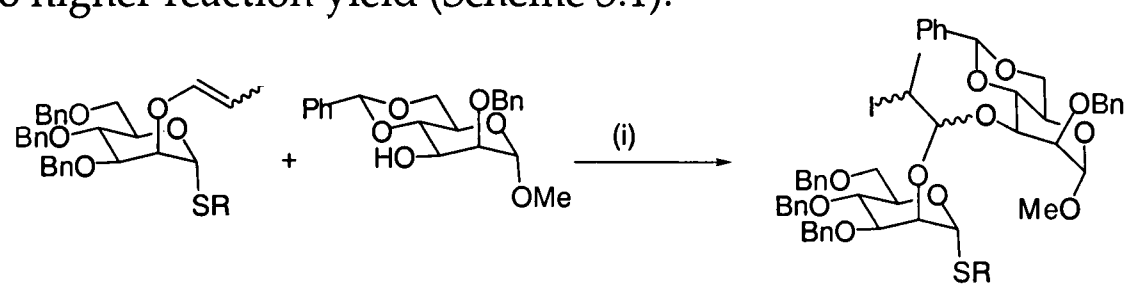
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Chapter 3. The Use of 2-*O*-Allyl Protected Glycosyl Fluorides as Donors in the Synthesis of 1,2-*cis* Glycosides

3.1 Introduction

One of the main problems of the 2-*O*-allyl-mediated IAD as described in Chapter 2 was that during a tethering reaction it was possible that NIS could activate the anomeric leaving group. This phenomenon was very bad in the case of the SePh, where only the extremely nucleophilic methanol was found to tether, and then in low yield. In the SMe system, competitive activation was not a significant drawback for many alcohols, but for those bulky ones which required extended reaction times to allow the reaction to go to completion, activation of SMe by NIS started to become problematic.

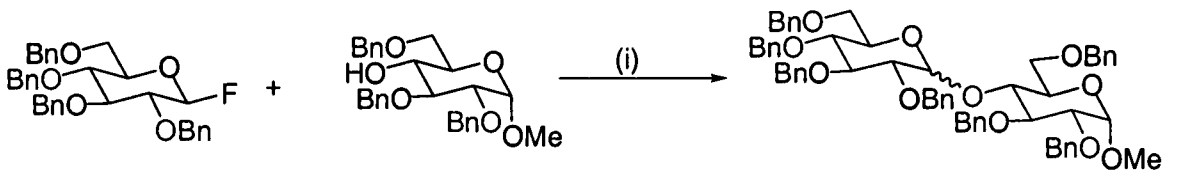
One solution to this would be to use a less reactive thioglycoside as donor. Investigations in our group suggest that thiophenyl glycosides are less reactive than their thiomethyl analogues,[1] and indeed, co-workers investigating similar reactions in the *manno* series found that by using an SPh donor, a tethering reaction could be left on for longer than in the SMe case, leading to higher reaction yield (Scheme 3.1).[2]



Scheme 3.1: Improvement in tethering yield *via* the use of an unreactive thioglycoside
(i) NIS, DCE. 4Å, -40°C→RT; R=Me, 55%; R=Ph, 85%

An alternative idea would be to opt for an orthogonal anomeric leaving group, which could remain intact indefinitely under the tethering reaction conditions. Such a leaving group would be inert to NIS, but when treated with certain activating agents could act as a glycosyl donor, so giving rise to an intramolecular glycosylation reaction.

Glycosyl halides have a long history as donors in glycosylation reactions. The classic glycosylation reaction by Königs and Knorr[3] employed glycosyl bromides, and these compounds, as well as glycosyl chlorides, have been used extensively as donors in conjunction with silver salts as activators.[4] Glycosyl fluorides have also been known for a long while, but they were found to be inert to the activation conditions used for the other glycosyl halides and so could not be used as glycosyl donors. However in 1981, Mukaiyama found that when a glycosyl fluoride was treated with a mixture of the Lewis acid tin (II) chloride and silver perchlorate, it was activated as a donor.[5] He demonstrated this methodology by the synthesis of various glucosides (Scheme 3.2).



Scheme 3.2: Mukaiyama's Lewis acid-mediated activation of glycosyl fluorides
(i) $SnCl_2$, $AgClO_4$, -15°C, ether, 91%, α/β 4:1

Subsequent to this breakthrough, many more Lewis acid based activators were developed, and with the inherent unreactivity of glycosyl fluorides meaning that they were stable to many protecting group manipulations, they became widely used as donors.[6] Owing to their stability towards NIS[7] and

their potential to be activated under orthogonal Lewis acidic conditions, glycosyl fluorides were chosen as a good candidate for a new donor in allyl derived IAD. It was decided to investigate the *manno* series as well as the *gluco* series in this system. Therefore the 2-*O*-allyl protected glucosyl and mannosyl fluorides **63** and **64** were the immediate synthetic targets (Figure 3.1).

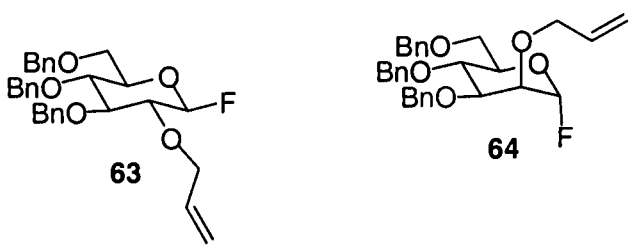
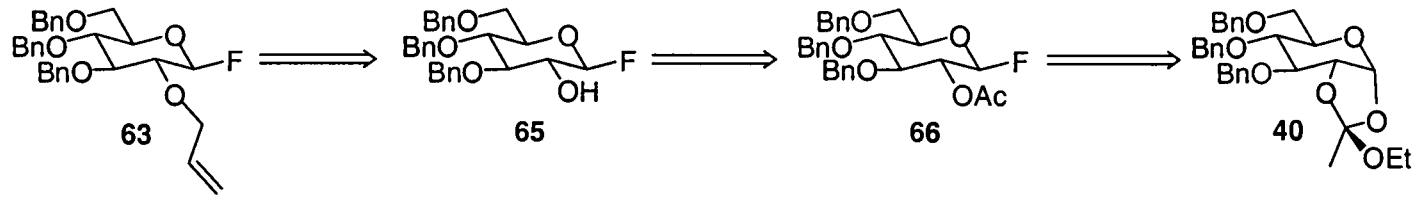


Figure 3.1: The 2-*O*-allyl protected glucosyl and mannosyl fluorides

3.2 Results and Discussion

3.2.1 Synthesis of the 2-*O*-Allyl Protected Glucosyl Fluoride 63

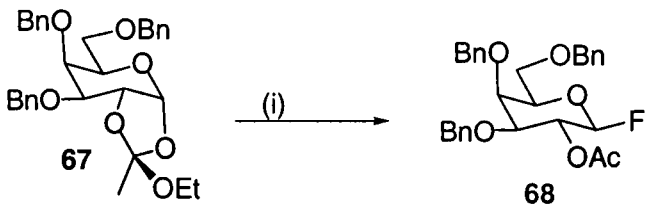
The benzyl protected orthoester **40** whose synthesis is described in Chapter 2 was chosen as starting point for the synthesis of the 2-*O*-allyl protected glucosyl fluoride **63** (Scheme 3.3).



Scheme 3.3: Retrosynthesis of glucosyl fluoride **63**

It was envisaged that a straightforward deacetylation of the 2-*O*-acetyl protected fluoride **66** and allylation of the alcohol **65** so formed would yield the desired 2-*O*-allyl protected glucosyl fluoride **63**. A Lewis acid-mediated ring opening of the orthoester **40** by fluoride could then be a good route to the

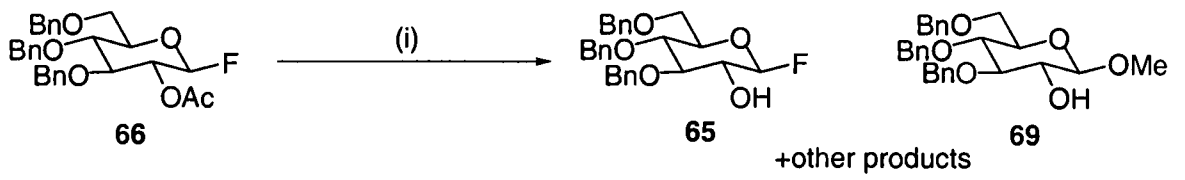
2-*O*-acetyl protected fluoride **66**, bearing differential protection on the 3-, 4- and 6-positions. Diethylamino sulfur trifluoride (DAST) is a versatile reagent developed as a source of fluoride for the direct conversion of hydroxyl functionality to fluoride.[8] DAST has recently been used in our group in a novel direct opening of the *galacto* orthoester **67** to yield the 2-*O*-acetate protected galactosyl fluoride **68** (Scheme 3.4).[9] It was decided to try this methodology on the *gluco* analogue.



Scheme 3.4: DAST-mediated *galacto* orthoester opening.
(i) DAST, DCM, 0°C, 84%

When *gluco* orthoester **40** was treated with DAST in DCM at 0°C, pleasingly, glycosyl fluoride **66** was formed in good yield, exclusively as the β anomer. Interestingly, tlc indicated the initial formation of a more polar species before clean conversion to the final product **66**. No attempt to isolate this initially-formed material was made (Scheme 3.6).

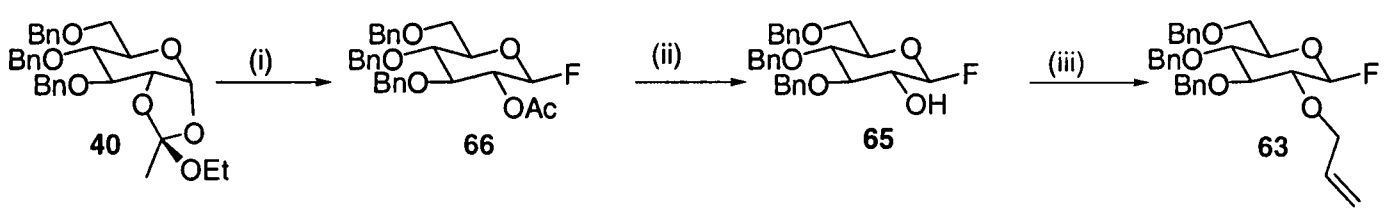
Attempted deacetylation of this fluoride **66** under Zemplen conditions[10] though, gave a complex mixture of products from which two minor components were identified as the desired alcohol **65** and the β-methyl glycoside **69** (Scheme 3.5).



Scheme 3.5: (i) Na, MeOH, RT, **65** 5%; **69** 34%

In his synthesis of the *manno* compound, Ogawa used DiBAlH to deacetylate a glycosyl fluoride,[11] but when applied to this *gluco* system, these conditions also failed, leading to a complex mixture of products.

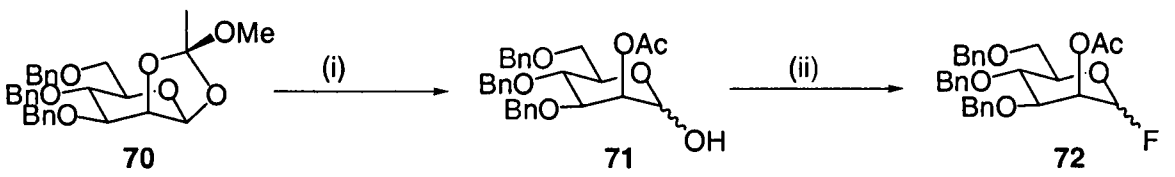
Eventually it was found that an amine-mediated deprotection could be carried out.[12] By heating a solution of the acetate **66** in a mixture of *n*-propylamine, methanol and THF overnight, the desired alcohol **65** was cleanly formed as the sole reaction product, in a good 91% yield over 2 steps. Allylation under standard conditions[13] (allyl bromide, sodium hydride and DMF) proceeded cleanly and in high yield to give the desired 2-*O*-allyl protected glucosyl fluoride **63** (Scheme 3.6).



Scheme 3.6: (i) DAST, DCM, 0˚C; (ii) $^{n}PrNH_2$, MeOH, THF, 45˚C, 91% over 2 steps; (iii) allyl bromide, NaH, DMF, 0˚C, 93%

3.2.2 Synthesis of the 2-*O*-Allyl Protected Mannosyl Fluoride 64

In his investigation into PMB-mediated IAD, Ogawa initially used glycosyl fluorides.[11] His synthetic route involved initial hydrolysis of the orthoester **70** before conversion of the resulting hemiacetal **71** to glycosyl fluorides **72** (as an α/β mixture) by treatment with DAST (Scheme 3.7). Acetate deprotection was achieved with DiBAlH before PMB protection gave the desired β-mannosyl donor **73**.



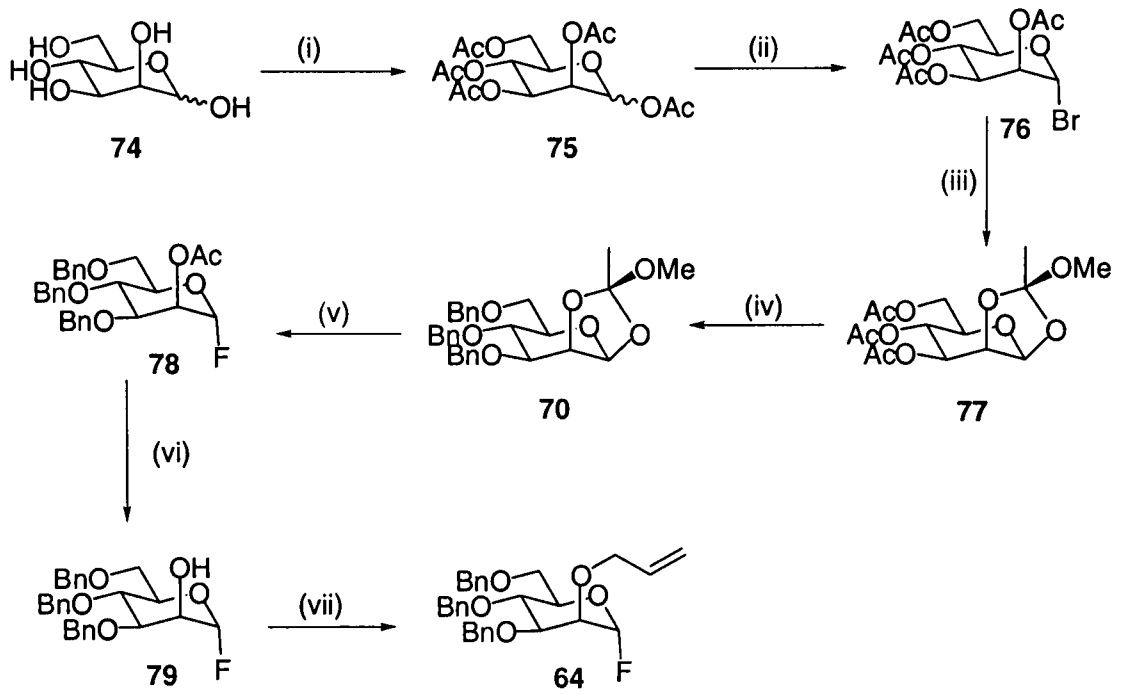
Scheme 3.7: Ogawa's mannosyl fluoride synthesis.
(i) 70% AcOH, RT; (ii) DAST, toluene, 0°C

It was decided to spurn this route due to the inconvenience of working with an α/β mixture, and instead, try to adopt the methods used in the *gluco* system.

Peracetylation of mannose **74** was carried out using Field's iodine-catalysed conditions.[14] Treatment of the pentaacetate **75** with HBr in acetic acid[15] gave the mannosyl bromide **76**, which was converted cleanly to the methyl orthoester **77** under standard conditions[16] in a pleasing 67% yield overall from mannose **74**. Sodium methoxide-mediated deacetylation followed by benzylation[17] gave the desired benzyl protected methyl orthoester **70** in 92% yield (Scheme 3.8).

Pleasingly, direct treatment of orthoester **70** with DAST resulted in the clean formation of the α-fluoride **78** as a single anomer in excellent 98% yield. This compound was deacetylated by treatment with $^{n}PrNH_2$/MeOH/THF as

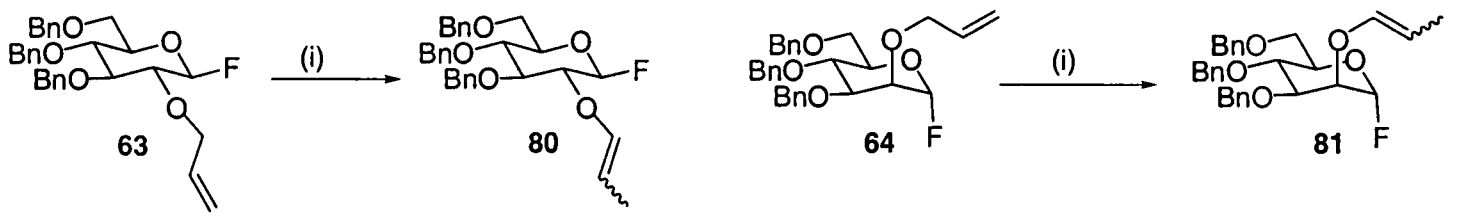
before[12] to give alcohol **79** in 99% yield. Allylation with sodium hydride and allyl bromide[13] gave the desired 2-*O*-allyl protected mannosyl fluoride **64** in a very satisfactory 96% yield (Scheme 3.8).



Scheme 3.8: (i) Ac_2O, I_2; (ii) HBr (33% in AcOH), 0°C; (iii) MeOH, collidine, DCM, 40°C, 67% (over 3 steps); (iv) Na, MeOH; NaH, BnBr, DMF, 0°C, 92%; (v) DAST, DCM, 0°C, 98%; (vi) $^{n}PrNH_2$, MeOH, THF, 99%; (vii) Allyl Bromide, NaH, DMF, 96%

3.2.3 Isomerisation

When the allyl protected donors **63** and **64** were treated with a catalyst prepared from Wilkinson's catalyst and BuLi as earlier,[18] pleasingly the enol ethers **80** and **81** were formed in excellent 94% and 98% yields respectively (as *E*/*Z* mixtures) (Scheme 3.9).



Scheme 3.9: (i) Wilkinson's catalyst, BuLi, THF, 70°C; **80**, 94% (*Z*/*E*, 2.3:1); **81**, 98% (*Z*/*E*, 2.6:1)

With both the glucosyl **80** and mannosyl **81** donors bearing the *n*-prop-1-enyl ethers at the 2-position in hand, attention now turned to attempting the tethering and IAD reactions in the fluoride system.

3.2.4 Tethering

NIS-mediated tethering to the *gluco* enol ethers **80** was carried out under our established reaction conditions.[19] Enol ethers **80** were mixed with a range of alcohols **3a-i** and NIS in DCE at -40°C and allowed to warm to RT. Now with the orthogonal fluoride leaving group, the reactions could be left longer where necessary. Thus the desired mixed acetals **82a-i** were obtained in good to excellent yields for a wide variety of alcohols (Table 3.1). Notable are the cases of the secondary carbohydrate alcohols **3g,h** and the steroid **3i** (Table 3.1, entries 8, 9, 11), whereby longer reaction times were possible, without any activation of the glycosyl fluoride being observed, showing significant improvements over the thiomethyl case.

An interesting side-product isolated from many of the reactions involving the more bulky aglycon alcohols was the 'succinimide-tethered' material **83**, presumably formed by the nucleophilic trapping of the iodonium ion **84** by succinimide formed in the reaction (Figure 3.2). In the proposed mechanism of the tethering reaction, the reaction pathway leading to the desired mixed acetal products **82** is a rate determining nucleophilic attack by the aglycon (*cf* Scheme 2.15). For more bulky alcohols, this nucleophilic attack becomes slower, so in these cases competitive attack by succinimide leads to an increase in the amount of succinimide-tethered product **83** formed.

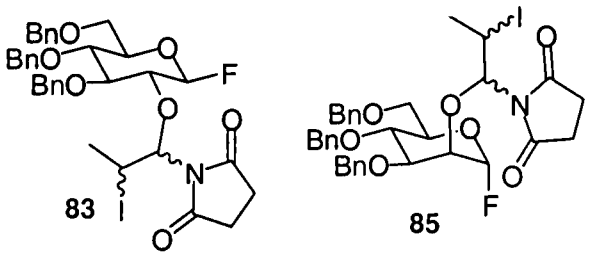
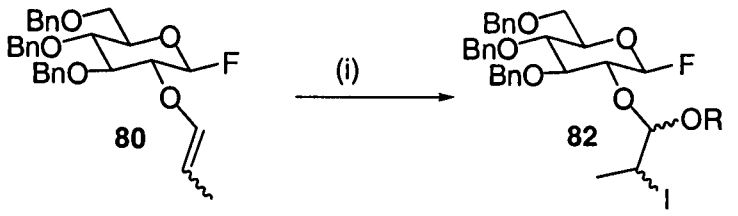


Figure 3.2: Succinimide-tethered materials **83** and **85**.

This side-reaction contrasts well with the case of Ennis' work on the isopropenyl system,[20] where the side-reaction that rose to predominance in the case of more hindered alcohols was the loss of a proton from the initially-formed iodonium ion **33** to form the iodinated enol ether **31** (as described in Chapter 2).

In the case of the steroid **3i** (Table 3.1, entries 11-13), which had low solubility in DCE, a change of solvent to THF was required for tethering in order to avoid low yields.



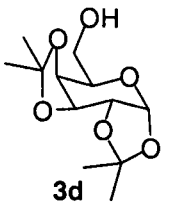
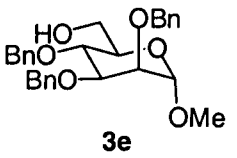
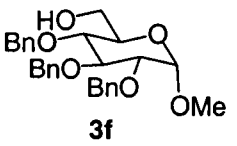
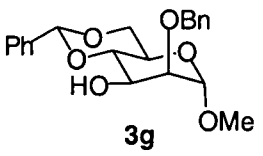
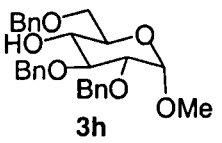
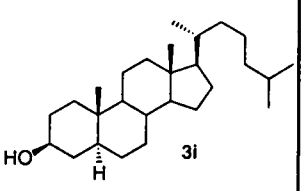
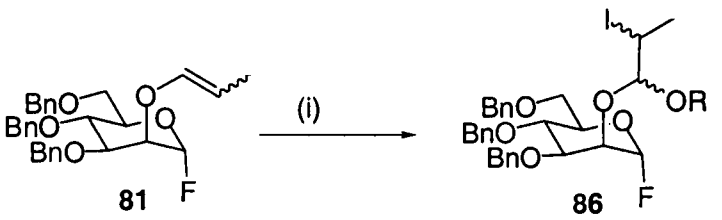
Entry	ROH	eq	eq NIS	solvent	t	T/°C	Product/yield of mixed acetals
1	MeOH **3a**	1.5	3	DCE	1 h 30	-40→	**82a** / >99%
2	BnOH **3b**	1.5	3	DCE	1 h	-40→	**82b** / 98%
3	Cyclohexanol **3c**	2	3	DCE	6 h	-40→	**82c** / 99%
4	 **3d**	2	3	DCE	6 h 15	-40→RT	**82d** / 91%
5	 **3e**	2	3	DCE	16 h	-40→RT	**82e** / 79%
6	 **3f**	1.5	3	DCE	15 h	-40→RT	**82f** / 55%
7	 **3g**	2	3	DCE	18 h 40	-40→RT	**82g** / 52%
8	 **3h**	3	3	DCE	45 h	-40→RT	**82h** / 39%
9	**3h**	3	3	THF	90 h	-40→RT	Very slow
10	 **3i**	2	3	THF	39 h	-40→RT	**82i** / 68%
11	**3i**	2	3	DCM	5 h	-40→RT	**82i** / 27%
12	**3i**	2	3	DCE	19 h	-40→RT	**82i** / 27%

Table 3.1: NIS-mediated *gluco* fluoride tethering reactions

In the *manno* series, tethering to enol ethers **81** proceeded to give the mixed acetals **86** in excellent yield for alcohols **3a,c,d** (Table 3.2, entries 1-3), and in slightly higher yield than the *gluco* equivalents for some of the more bulky carbohydrates **3f,g,j** (Table 3.2, entries 4-6). It is clear that tethering is slightly less efficient for the *gluco* than the *manno* series, possibly due to the more hindered nature of the *gluco* tethering site. Again some succinimide-tethered material **85** was seen in the cases of the more hindered alcohols (Figure 3.2).



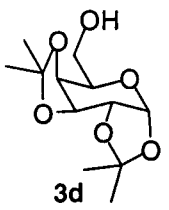
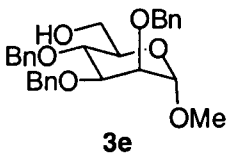
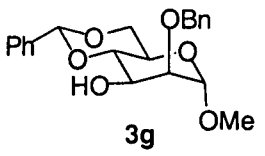
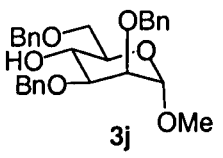
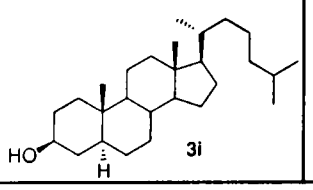
Entry	ROH	eq	eq NIS	solvent	t	T/°C	Product/yield of mixed acetals
1	MeOH **3a**	1.5	3	DCE	1 h 20	-40→	**86a** / 97%
2	Cyclohexanol **3c**	2	3	DCE	15 h	-40→RT	**86c** / 99%
3	 **3d**	2	3	DCE	17 h 30	-40→RT	**86d** / 98%
4	 **3e**	2	3	DCE	15 h	-40→RT	**86e** / 80%
5	 **3g**	2	3	DCE	26 h	-40→RT	**86g** / 83%
6	 **3j**	3	3	DCE	16 h	-40→RT	**86j** / 37%
7	 **3i**	2	3	DCE	18 h	-40→RT	**86i** / 72%

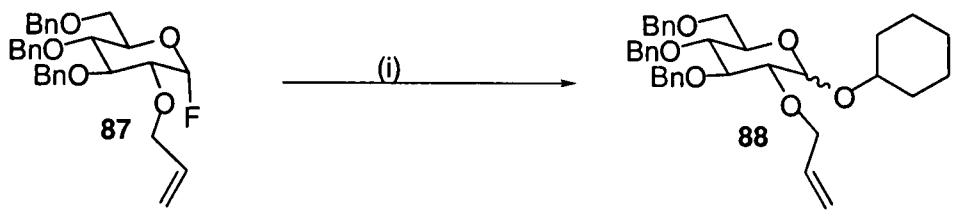
Table 3.2: NIS-mediated *manno* fluoride tethering reactions

3.2.5 Glycosylation

With the tethered materials **82** and **86** in hand, attention turned to the activation of the glycosyl fluorides as donors for an intramolecular glycosylation reaction. Activation of glycosyl fluorides is generally carried out by the use of a Lewis acid.[6] In this case, the mixed acetal tether, which could be susceptible to Lewis acid-catalysed cleavage, must remain intact for IAD to operate and ensure a stereospecific reaction. Therefore differentiation between these two similar reactive centres is required.

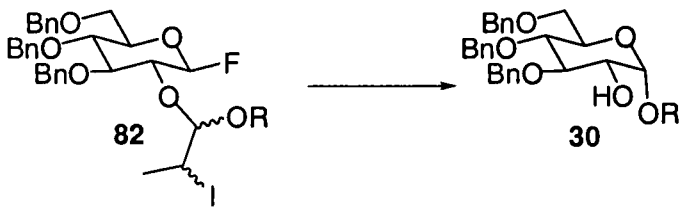
A common set of reaction conditions for the activation of glycosyl fluorides is $BF_3.OEt_2$.[21] It was found that treatment of *gluco* tethered material **82b** under these conditions gave an intractable mixture of products, including none of the desired glycoside **30b** (Table 3.3, entry 2). When the same reaction was carried out in the presence of the hindered base DTBMP, pleasingly some of the 1,2-*cis* glycoside **30b** was formed as the sole glycosylated product, but only in low yield (Table 3.3, entry 1). Furthermore, it was apparent that the other products from these reactions were not 'trapped' materials, ie glycosides bearing mixed acetals at the 2-position as had been formed in the thioglycoside case (see Chapter 2), since they remained unchanged following treatment with TFA.

In a test reaction in an intermolecular system, trimethylsilyl iodide (TMSI), a novel activator, was found to activate glycosyl fluorides, and the 2-*O*-allyl cyclohexyl glycoside **88** was formed in 74% yield (α/β, 10:1) (Scheme 3.10).[22]



Scheme 3.10: (i) cyclohexanol, TMSI, CH_2Cl_2, -78°C, 74% (α/β, 10:1)

Consequently, it was wondered whether TMSI would be an effective activator for glycosyl fluorides in an intramolecular glycosylation reaction. Unfortunately, when the tethered material **82a** was treated with TMSI in DCE at -40°C, the reaction mixture instantly turned brown, and a 2.5:1 α/β mixture of glycosylated products **30a** and **69**, presumably arising from cleavage of the tether and subsequent intermolecular glycosylation, was isolated in 53% yield (Table 3.3, entry 3). When the same reaction was carried out in the presence of the hindered base DTBMP, a complex mixture of products was formed, which included none of the desired glycosylated material (Table 3.3, entry 4).



Entry	Starting material	Conditions	solvent	Product / yield
1	**82b**	$BF_3.OEt_2$, DTBMP then TFA	DCE	**30b** / 19%
2	**82b**	$BF_3.OEt_2$ then TFA	DCE	0
3	**82a**	TMSI, -40°C	DCE	**30a**, **69** / 53% (2.5:1)
4	**82a**	TMSI, DTBMP, -40°C	DCE	0
5	**82f**	Cp_2HfCl_2, $AgClO_4$. led to production of the free aglycon alcohol	DCE	0
6	**82f**	$SnCl_2$, AgOTf, DTBMP, -20→0°C	Et_2O	No reaction
7	**82f**	$SnCl_2$, AgOTf, DTBMP, 50°C	MeCN	**30f** / 45%

Table 3.3: Glycosylation reactions of *gluco* tethered materials **82** under various reaction conditions

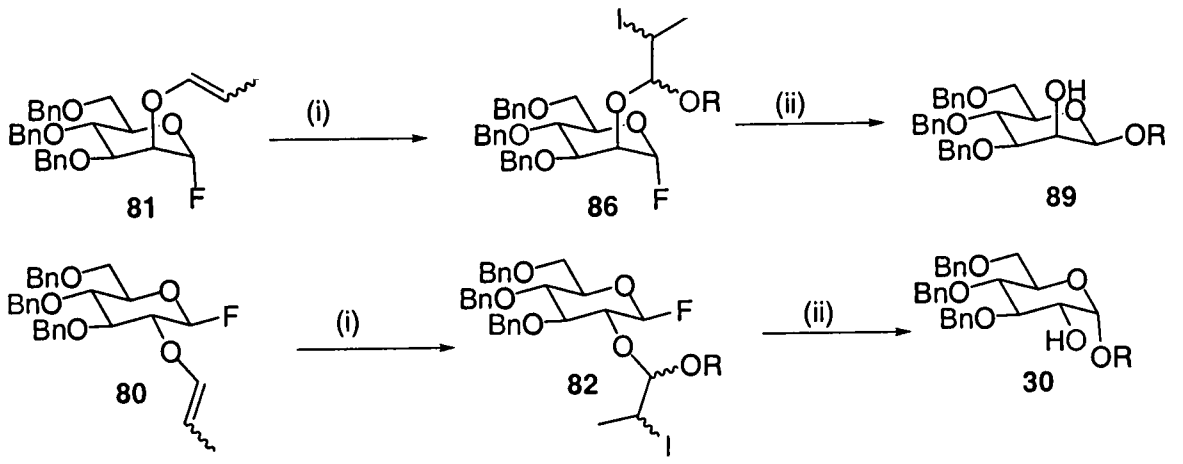
In Ogawa's work on IAD in mannosyl fluorides, two sets of reaction conditions were employed. Firstly, hafnocene dichloride was used in

combination with silver triflate and the hindered base DTBMP.[23] When allyl-derived tethered material **82f** was treated under these reaction conditions, a complex mixture resulted, from which the only identified product was the aglycon alcohol **3f**, formed in 50% yield (Table 3.3, entry 5).

Ogawa's alternative set of conditions, the classic tin (II) chloride, silver triflate with the addition of DTBMP, carried out in ether at -20→0°C[11] gave no reaction when applied to glucose-tethered material **82f** (Table 3.3, entry 6). However, it was found that when a mixture under the same conditions was heated to 50°C with a necessary solvent change to acetonitrile, a glycosylation reaction occurred to give the desired α-glucoside **30f** in a satisfactory 45% yield after TFA treatment (Table 3.3, entry 7).

Tethered materials treated under these conditions furnished the desired α-glucosides **30a-i** and β-mannosides **89a,c,d,f,g,j,i** stereospecifically as the pure 1,2-*cis* anomers in all cases (Table 3.4). The β-*manno* stereochemistry was proved by measuring the $^{1}J_{C1,H1}$ coupling constant, which was between 155 and 161 Hz in all cases.[25]

The efficiency of glycosylation was found to be highly solvent dependent. During the course of this work, it was observed that the glycosylation of the *manno* mixed acetals **86d** in acetonitrile was sluggish, and occurred concomitant with formation of the aglycon alcohol **3d**, presumably resulting from partial hydrolysis of the tether. An otherwise identical reaction in DCE proceeded more quickly and with no hydrolysis. Subsequent reactions were therefore carried out in DCE.



Scheme 3.11: (i) see Tables 3.1 and 3.2; (ii) $SnCl_2$, AgOTf, DTBMP, 4Å, 50°C, see Table 3.4 for yields

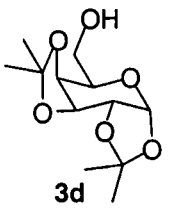
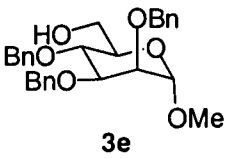
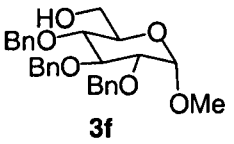
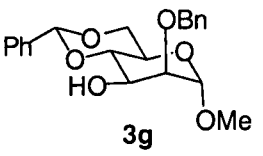
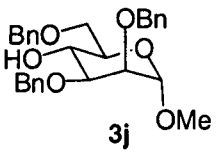
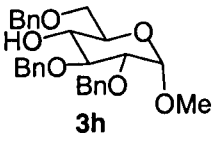
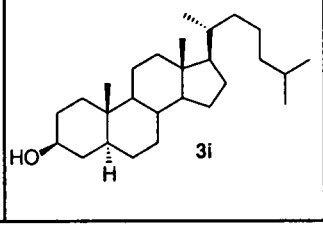
Entry	Alcohol ROH	Product/yield of mixed acetals[a]	Product/yield of glycosylation[c]
1	MeOH **3a**	**82a** / 99% **86a** / 97%	**30a** / 89%[e] **89a** / 76%[e]
2	Cyclohexanol **3c**	**82c** / 99% **86c** / 99%	**30c** / 66%[e] **89c** / 70%[e]
3	 **3d**	**82d** / 91% **86d** / 98%	**30d** / 63%[d] **89d** / 61%[d,f],16%[h]
4	 **3e**	**82e** / 79% **86e** / 80%	**30e** / 44%[e],46%[d] **89e** / 49%[e], 75%[d]
5	 **3f**	**82f** / 55%	**30f** / 45%
6	 **3g**	**82g** / 52% **86g** / 83%	**30g** / 66%[d,g] **89g** / 55%[d,f]
7	 **3j**	**86j** / 37%	**89j** / 50%[d]
8	 **3h**	**82h** / 39%	**30h** / 45%[d]
9	 **3i**	**82i** / 68%[b] **86i** / 72%	**30i** / 87%[d] **89i** / 59%[d]

Table 3.4: Tethering and glycosylation yields

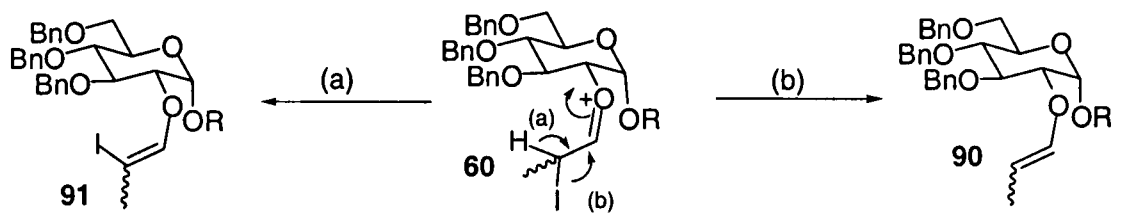
[a] Isolated yields. Reactions carried out in DCE except where otherwise stated. [b] Reaction carried out in THF. [c] Isolated yields. Acid treatment with TFA except where otherwise stated. [d] Reaction carried out in DCE. [e] Reaction carried out in acetonitrile. [f] No acid treatment. [g] Treatment with NIS, H_2O. [h] Reaction carried out in toluene.

Some small quantities of the aglycon alcohols **3** were formed in the glycosylation reactions of some of the more hindered aglycons, in particular **3h** and **3j**, possibly from partial hydrolysis of the tether. In these cases though, as in all the others, the only glycosylated product formed was the 1,2-*cis* glycoside.

In the earlier work on thioglycosides (Chapter 2),[24] tlc monitoring of the glycosylation reaction had indicated the formation of by-products. These were identified as the mixed acetals **61**, probably arising from the trapping out of the oxonium ion **60** produced subsequent to the glycosylation reaction by an external nucleophile. Treatment of these materials with TFA in order to hydrolyse the mixed acetals had increased the yield of the desired 1,2-*cis* glycosides **30**.

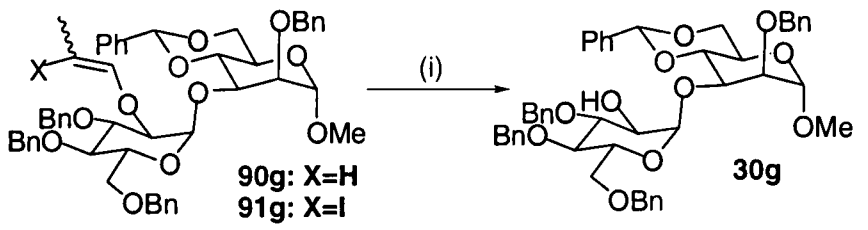
Again, in the course of this work, the reaction tlc indicated the formation of major by-products, which were more prevalent in the *gluco* than the *manno* series. Treatment of these reaction by-products with TFA yielded further 1,2-*cis* glycoside product. However this reaction was much faster than expected for hydrolysis of a mixed acetal, which led us to investigate the identity of the so-called trapped material. Surprisingly the ^{1}H NMR spectrum of the major by-product of the glycosylation of tethered material **82g** was consistent with the enol ethers **90g** as shown by the characteristic methyl double doublets at δ 1.26 and 1.64, and the resonances for the enol ether protons at δ 5.98 and 6.23. This was confirmed by MS analysis, which showed M=844. A minor peak in the mass spectrum was seen for the iodinated enol ethers **91g**, M=970. While the formation of **91g** is easily explained as being due to loss of H^+ from the

oxonium ion **60** produced following intramolecular glycosylation, analogous formation **90g** formally requires loss of I^+ (Scheme 3.12). A possible mechanism could involve nucleophilic attack on iodine by the hindered base DTBMP, which apparently has some affinity for I^+.[26] Alternatively, oxidation of a tin (II) species present in the reaction mixture to tin (IV) could account for this observation. No evidence for the formation of tin (IV) species, though, has been seen.



Scheme 3.12: Proposed mechanism for the formation of enol ethers **90** and **91**

Treatment of these enol ethers **90g** and **91g** with NIS and water resulted in the formation of further desired glycoside **30g**, without any cleavage of the acid-sensitive 4,6-benzylidene protection (Scheme 3.13).



Scheme 3.13: (i) NIS, THF, H_2O

3.3 Conclusion

In summary, it has been demonstrated that glycosyl fluorides can be of use in the 2-*O*-allyl donor IAD approach. The use of fluorides has certain advantages in that tethering efficiency can be increased in the case of bulky secondary carbohydrate alcohols by the use of extended reaction times.

However, competitive nucleophilic trapping by succinimide is a significant limitation to the tethering of more hindered aglycons. In addition, while the glycosylation reactions still occur in a stereospecific manner, the yields are generally slightly lower than for the thioglycoside analogues.

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26. Evidence comes from the fact that a mixture of I_2 and AgOTf alone does not induce electrophilic additon to an enol ether, whereas I_2, AgOTf and DTBMP does. Presumably dissociation of iodine only occurs in the latter case due to the stabilisation afforded the I^+ ion by coordination to the basic nitrogen (See Chapter 4). In addition, such complexes are well characterised for similar pyridine bases such as collidine. For example, see Brayer, G.D.; James, M.N.G. *Acta Crystallogr. Sect. B.,* **1982,** *B38,* 654-657

Chapter 4. Further Studies on Glycosyl Fluorides

4.1 Introduction

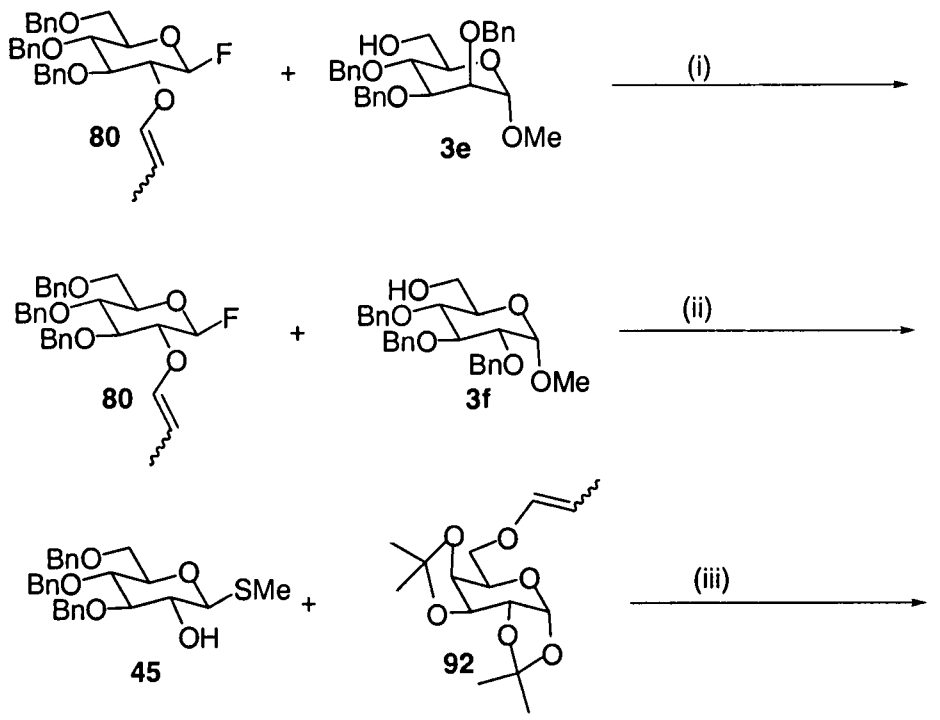
The use of glycosyl fluorides in an allyl-mediated IAD reaction (as described in Chapter 3) led to increased tethering yields for a variety of aglycons compared to the earlier thioglycoside work (as described in Chapter 2). However for some hindered secondary carbohydrates, the yields were still not very good. Furthermore, the glycosylation reaction of fluorides seemed to be less consistent than that of thioglycosides. Thus both the tethering and glycosylation reactions were in need of optimisation. Furthermore, questions as to the mechanism of IAD in this system could be addressed.

4.2 Results and Discussion

4.2.1 Attempts to Optimise the Tethering Reaction

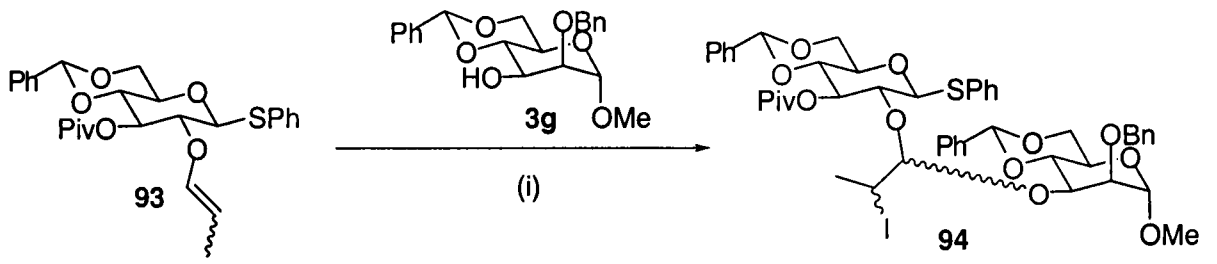
The major by-products in the tethering reactions of the more hindered aglycon alcohols to both *gluco* **80** and *manno* **81** enol ethers were the succinimide-tethered materials **83** and **85**, presumably formed by competitive nucleophilic attack as described in Chapter 3. Thus it was postulated that the use of a source of I^+ with a non-nucleophilic counter-ion would increase the yields of the tethering reactions as the formation of such by-products would be eliminated. Alternatively, if it were possible somehow to increase the nucleophilicity of the aglycon alcohols, then this would also provide a solution.

Typically, an alkoxide is more nucleophilic than its respective alcohol, thus it was proposed that the introduction of base into the tethering reaction would lead to an improvement in efficiency. The use of pyridine as solvent, addition of a diamine base (TMEDA) and pre-treatment of the aglycon alcohol with BuLi were all tried, but in all cases no reaction was seen (Scheme 4.1).



Scheme 4.1: (i) $Me_2N(CH_2)_2NMe_2$, NIS, DCE, -40°C→RT; No reaction after several days; (ii) BuLi, NIS, DCE, -40°C; No reaction after 20 min; (iii) NIS, pyridine, -40°C→RT; No reaction after 1 h 20 [1]

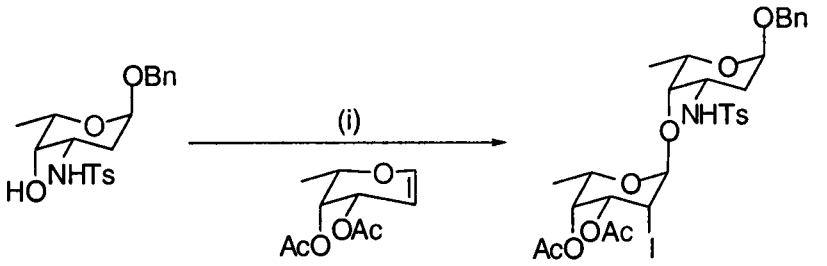
In contrast, addition of the hindered base DTBMP to a tethering reaction had no significant effect on the yield (Scheme 4.2).[2]



Scheme 4.2: (i) NIS, DCM, 4Å, -40°C→RT, 57%; OR NIS, DTBMP, DCM, 4Å, -40°C→RT, 60%

The yellow colour observed on addition of amine bases to the tethering reactions could lead to a possible explanation. The basic nitrogen coordinates to I^+,[3] thus rendering it unavailable for addition to the enol ether. In the case of DTBMP, the nitrogen is so sterically hindered that only a weakly binding complex to the iodine is formed, so addition of I^+ to the enol ether proceeds as usual.

Another classic way to increase the nucleophilicity of a hydroxyl group is through the formation of its tin ether derivative. A particularly encouraging example of this methodology was its use by Thiem in NIS-mediated formation of 2-iodo-2-deoxyglycosides from glycals.[4] In the cases of hindered secondary carbohydrate aglycons, he found that pre-formation of the algycon tin ether gave a significant increase in the yield of a subsequent glycosylation reaction (Scheme 4.3).

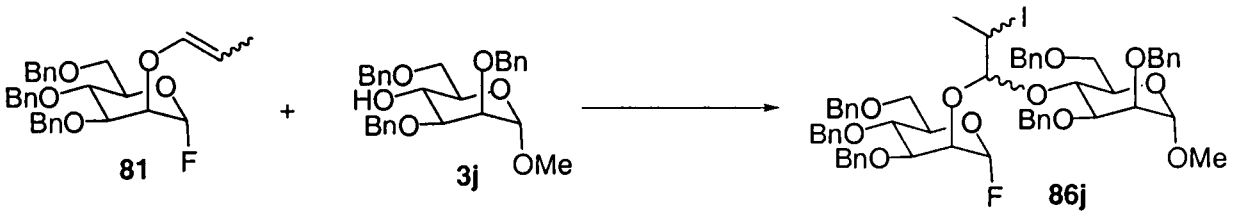


Scheme 4.3: Thiem's use of tin ethers in NIS-mediated glycal glycosylation.
(i) $(Bu_3Sn)_2O$, 4Å, benzene, reflux; (ii) NIS, MeCN, RT, 79%

In an attempt to increase the tethering yield of hindered aglycon **3j**, an analogous reaction was carried out. Thus aglycon **3j** was heated with $(Bu_3Sn)_2O$ and molecular sieves in benzene[4] before treating with the *manno* enol ethers **81** and NIS in the usual way. However, the mixed acetals **86j** were obtained in a slightly worse yield than the use of NIS alone (Table 4.1,

entries 1,2). Attention turned then to the use of possible sources of I^+ with non-nucleophilic counter-ions.

Iodonium di-*sym*-collidine triflate (IDCT) has been reported as just such a source of I^+, with triflate as counter-ion.[5] This compound might be prepared *in situ* from I_2, silver triflate and collidine. It was found that when *manno* enol ethers **81** and aglycon **3j** were added to such a mixture, tethering did take place in a reasonable yield compared to the NIS-mediated reaction (Table 4.1, entry 3). Iodine and a base alone produced no reaction (Table 4.1, entry 4).



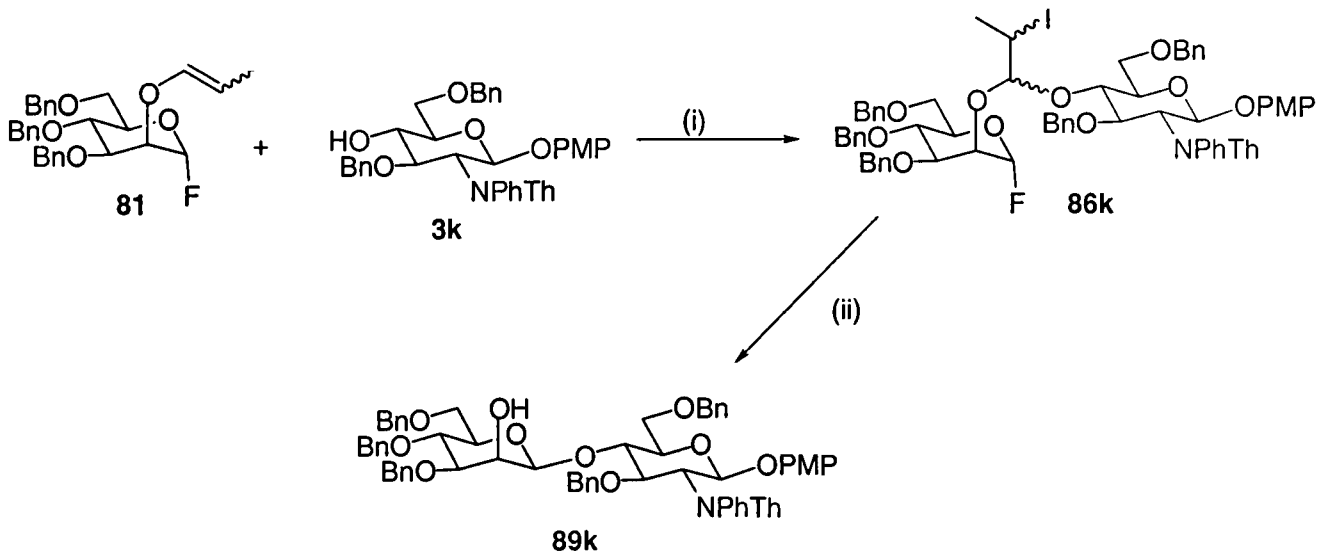
Entry	eq **3j**	Activator	eq	solvent	t	T/°C	yield of mixed acetals
1	3	NIS	3	DCE	16 h	-40→RT	37%
2	3	Pre-form tin ether; then NIS	3	MeCN	4 days	-40→RT	20%
3	3	I_2, collidine, AgOTf	3	DCM	2 h 15	-78→RT	40%
4	3	I_2, collidine	2	DCM	15 h	-78→RT	No reaction
5	1.05	I_2, DTBMP, AgOTf	1.1	DCM	20 h	-78→RT	55%

Table 4.1: tethering reactions

It had been observed that in an attempted tethering reaction using IDCT, after initial rapid formation of tethered material **86j**, the reaction seemed to stop, as monitored by tlc, despite the use of excess reagents; also that NIS-mediated tethering reactions did not work at all in the presence of pyridine and other unhindered amine bases, but proceeded as usual in the presence of the

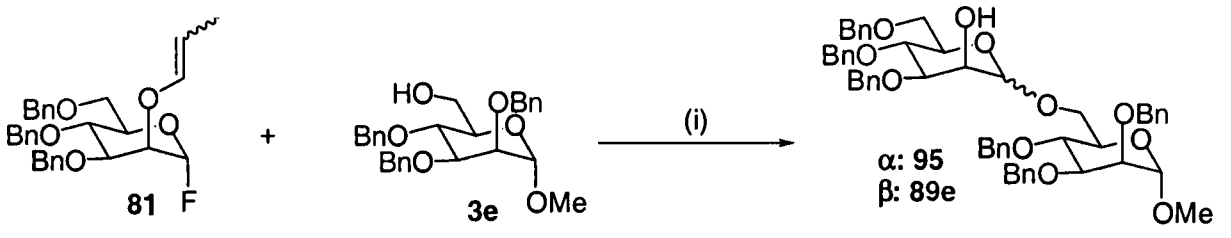
hindered base DTBMP. Consequently it was proposed that a good source of I^+ to be used in a tethering reaction could be generated from I_2, AgOTf and DTBMP. When a tethering reaction was carried out under these conditions, pleasingly the desired mixed acetals **86j** were formed in 55% yield, along with 33% of the enol ethers **81** recovered. No tethering of other nucleophiles was observed (Table 4.1, entry 5).

Having demonstrated a new, high-yielding tethering methodology on a model hindered aglycon **3j**, it was decided to try to apply the allyl-mediated IAD methodology to the synthesis of the crucial Manβ(1→4)GlcNAc linkage found at the heart of the common pentasaccharide core of all *N*-linked glycoproteins.[6] When *manno* enol ethers **81** and partially protected glucosamine derivative **3k**[7] were treated with a mixture of silver triflate, iodine and the hindered base, pleasingly, mixed acetals **86k** were isolated in good 75% yield. These were subjected to the standard glycosylation conditions and the desired β-mannoside **89k** was isolated in good 54% yield as the sole glycosylated product (Scheme 4.4).



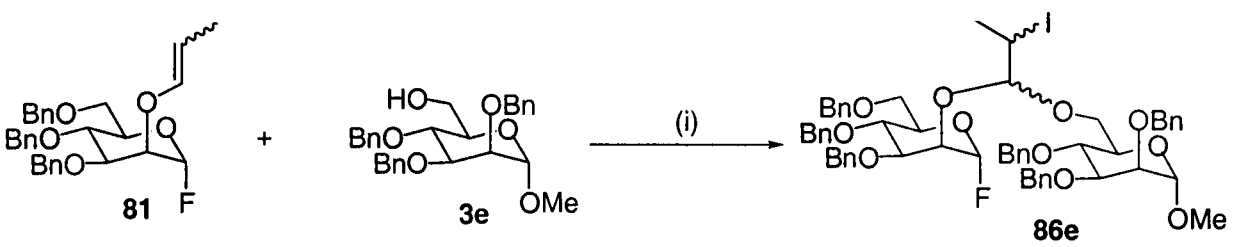
Scheme 4.4: (i) I_2, AgOTf, DTBMP, DCM, 4Å, -78°C→RT, 75%; (ii) $SnCl_2$, AgOTf, DTBMP, DCE, 4Å, 50°C, 54%

ICl could also be seen as a potential source of I^+.[8] However, an initial attempt to tether under analogous conditions to the earlier NIS work resulted in a mixture of α **95** and β **89e** glycosylated products (Scheme 4.5). This could be explained as being the result of intermolecular glycosylation reactions due to activation of the glycosyl fluoride by the HCl formed in the reaction.[9] No mannosyl fluoride components were seen in the product mixture, as shown by the absence of the characteristic double doublet for H-1 at δ *ca* 5.8 ($J_{1,F}$ 50 Hz) in the ^{1}H NMR spectrum.



Scheme 4.5: (i) ICl, MeCN, DCM, 4Å, -50°C→RT; **95** 46%; **89e** 11%

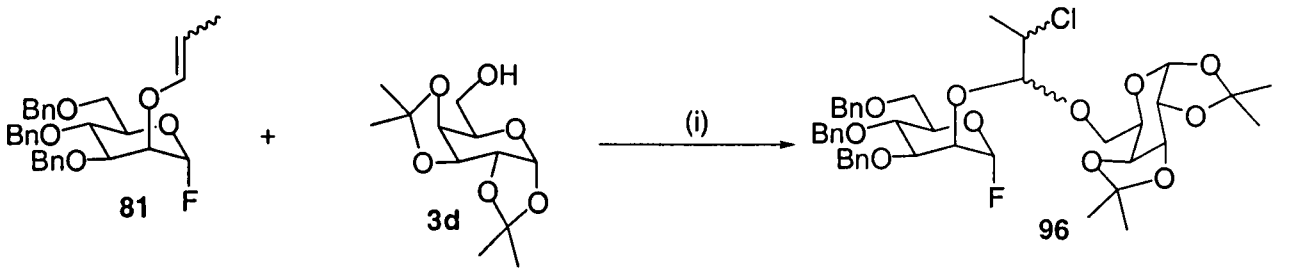
When the reaction was repeated in the presence of the hindered base, the mixed acetals **86e** were isolated in a moderate 37% yield. The only other species isolated from the reaction though, were the starting enol ethers **81** and the donor with OH-2 free **79**, resulting from hydrolysis (Scheme 4.6).



Scheme 4.6: (i) ICl, MeCN, DCM, 4Å, -50°C→RT; **86e** 37%; **81** 21%; **79** 41%

Finally, it was considered that as the iodine atom is large, by using a smaller electrophile for the initial addition to the enol ether, it might be possible to decrease the steric bulk of the tethering site, thus lowering the steric

constraints on the aglycon. Acid tethering, using the very small H^+ as electrophile had been tried and had failed on the allyl system (see Chapter 2). *N*-Chlorosuccinimide (NCS) has been reported as a possible source of Cl^+ in electrophilic addition to enol ethers.[10] Consequently a NCS-mediated tethering reaction between *manno* fluoride enol ethers **81** and DAG **3d** was attempted. The mixed acetal products **96** were obtained, but only in poor yield (Scheme 4.7).

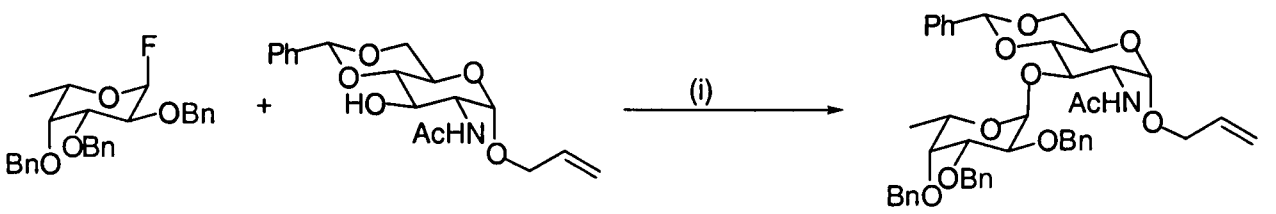


Scheme 4.7: (i) NCS, DCE, 4Å, -40°C→RT, 31%

4.2.2 Attempts to Optimise the Glycosylation Reaction

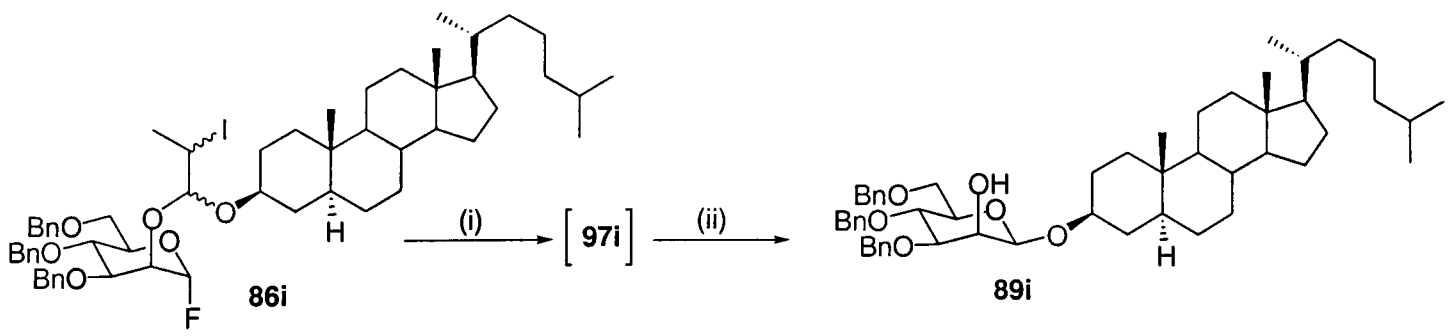
Of the range of glycosylation conditions investigated in Chapter 3, $SnCl_2$/AgOTf/DTBMP was the best activator for glycosyl fluorides in the IAD reaction. Others resulted in hydrolysis of the tether, or the formation of intractable mixtures. However, the intramolecular glycosylation yields do not compare that favourably with those for thioglycosides,[11] so a new activator was sought.

Lithium salts have been reported to activate glycosyl fluorides.[12] In what seems to be an very mild procedure, a mixture of donor and acceptor is treated with a 1M solution of $LiClO_4$ in DCM (Scheme 4.8).



Scheme 4.8: Waldmann's lithium salt-mediated activation of glycosyl fluorides.
(i) $LiClO_4$ (1M in DCM), 4Å, RT, 96%

In order to avoid the use of explosive perchlorate salts, it was decided to try to apply lithium salt-mediated activation of fluorides to the intramolecular system using the more benign lithium iodide. Thus steroid-tethered *manno* fluoride **86i** was treated with an excess (14 eq, equivalent to 0.5 M) of LiI as a suspension in DCM. A reaction occurred resulting in the formation of a single product **97i**, with a different R_f to the desired β-mannoside **89i** as shown by tlc. Interestingly, when the tlc plate was stained with ammonium molybdate, the product initially stained brown, before turning the usual blue colour. While this product survived an aqueous work-up, attempted purification by column chromatography resulted in its entire decomposition, and surprising conversion to the β-mannoside **89i** in 76% yield (Scheme 4.9).

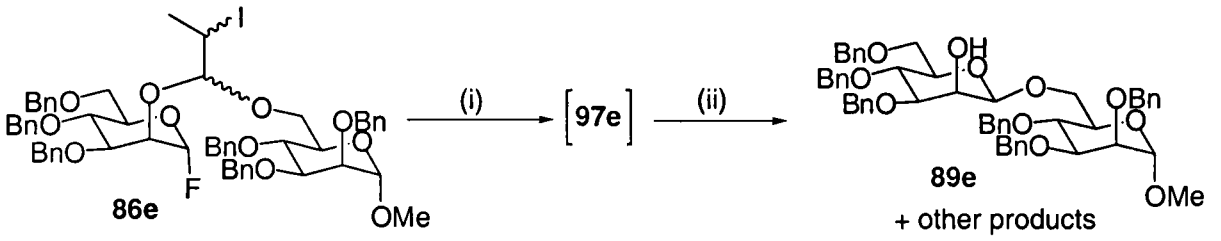


Scheme 4.9: (i) LiI, DCM, RT; (ii) silica column in petrol/EtOAc, 76%

The reaction was repeated in the presence of the hindered base DTBMP, and again tlc indicated complete conversion to a brown-staining product. This

time an attempt at controlled decomposition was made. Thus the reaction was treated with TFA. Again the β-mannoside **89i** was formed, in a slightly lower yield of 67%.

It was decided to apply the conditions to the glycosylation of a carbohydrate aglycon. Thus mannose-tethered acetals **86e** were treated with LiI in DCM. Tlc indicated the quantitative conversion to a brown-staining product. However, during an aqueous work-up this decomposed to give a complex mixture from which the β-mannoside **89e** was isolated in 34% yield (Scheme 4.10). No 1,2-*trans* glycoside was seen. The reaction was repeated and after the clean conversion to a single brown-staining product, as shown by tlc, the mixture was treated with acid. However, this resulted in the formation of an intractable mixture, and none of the β-mannoside **89e**.



Scheme 4.10: (i) LiI, DCM, RT; (ii) aqueous work-up, 34%

It seemed that the brown-staining intermediate **97** could not contain the β-mannosidic linkage, as this is known to be stable to TFA treatment (*cf* Chapter 3). A tentative glycosylated structure with iodide trapped in the tether as shown in Figure 4.1 was therefore ruled out. In fact, it seemed that glycosylation was only taking place during the decomposition of the intermediate **97**.

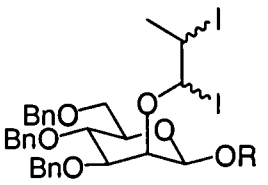


Figure 4.1: Initially-conceived structure for the brown-staining compound **97**

Given the instability of the brown-staining intermediates, and the failure of attempts to isolate them, it was decided to conduct an experiment in deuterated solvent, and to monitor the reaction by ^{1}H NMR spectroscopy. Thus, DAG-tethered mixed acetals **86d** were treated with LiI in $CDCl_3$. Once tlc indicated complete conversion to a brown-staining product, the reaction mixture was filtered and a ^{1}H NMR spectrum was recorded (Figure 4.2b).[13] This showed the presence of two diastereomeric species, as was also the case in the starting material **86d** (Figure 4.2a). The spectrum showed the disappearance of the characteristic double doublet of H-1_b coupling to fluoride ($^1J_{1,F}$ 50 Hz), and the appearance of two singlets at δ_H 7.05 and 7.10, characteristic of glycosyl iodides.[14] In addition, the tether appeared to be intact, as shown by the doublets for $C\underline{H}_3CHI$ at δ_H 1.85 (J 6.8 Hz) and 1.83 (J 6.9 Hz). However, when the sample was removed from the NMR machine, it was immediately apparent that it had decomposed, having changed from a pale yellow to a deep red colour. Re-running the spectrum (Figure 4.2c) showed the complete disappearance of the glycosyl iodide singlets, and of the doublets arising from the tether methyl group. Also noteworthy was the appearance of the characteristic quartet of doublets at δ_H 2.46, indicating the formation of propanal, presumably derived from the tether. That this signal is also visible in Figure 4.2b is probably due to the partial decomposition of the sample during the running of the spectrum. Tlc of this NMR sample showed

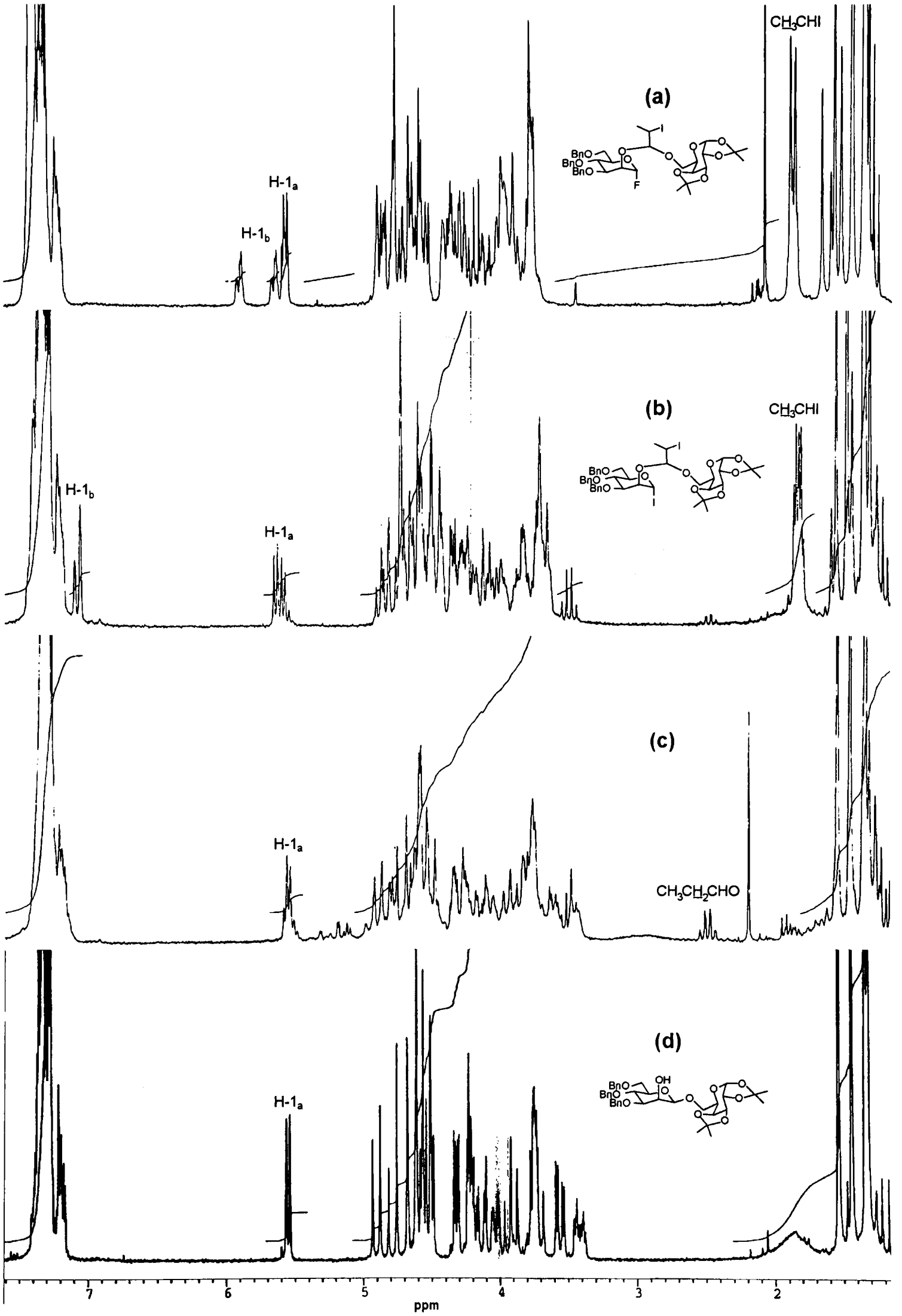
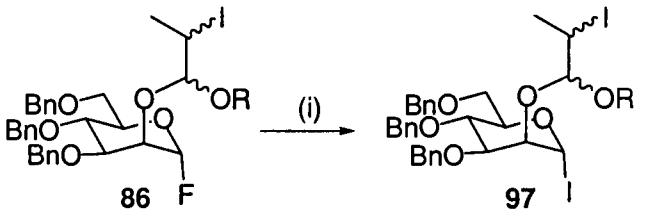


Figure 4.2: 200 MHz ^{1}H NMR spectra of (a) DAG-tethered *manno* fluorides **86d**; (b) the result of treatment with LiI; (c) the same sample as (b) after decomposition; (d) pure β-mannoside **89d**

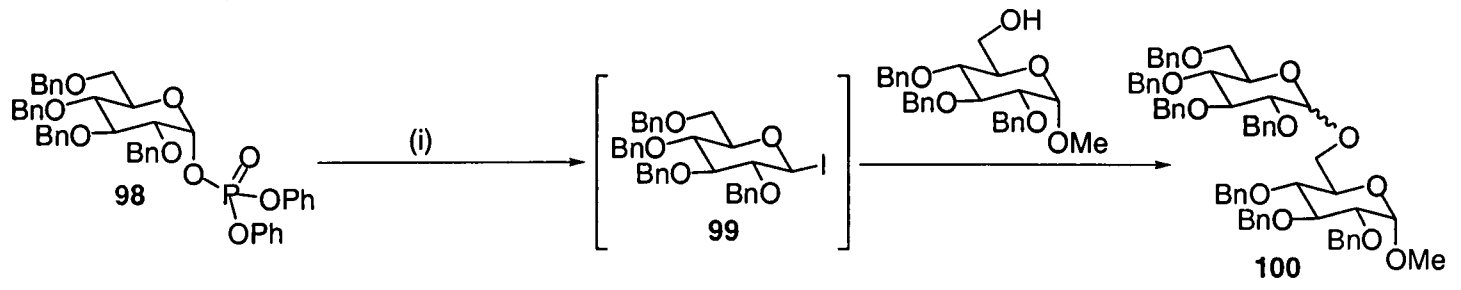
a mixture of products, the major component of which was the β-mannoside **69d** (^{1}H spectrum of pure sample shown in Figure 4.2d).

On the basis of observations thus far, a new structure for the brown-staining intermediate **97** was postulated: the α-mannosyl iodide as shown in Scheme 4.11.



Scheme 4.11: (i) LiI (0.5 M), DCM, 4Å, RT

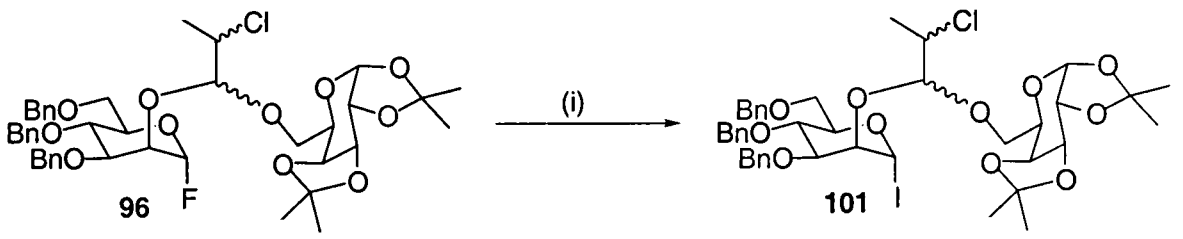
A similar conversion was reported in 1996 by Schmid and Waldmann.[15] They found that treatment of glycosyl phosphates **98** with a combination of lithium iodide and lithium perchlorate led to the formation of a glycosyl iodide **99**. This could then act as a glycosyl donor, without isolation and without the need for addition of an activator, leading to glycosylated products **100** (Scheme 4.12).



Scheme 4.12: Schmid and Waldmann's activation of glycosyl phosphates *via* glycosyl iodides; (i) $LiClO_4$ (1M), LiI (1.5 eq), DCM, 4Å, RT, 63% (α/β, 3:1)

In order to investigate the scope of the reaction, in particular to probe the importance of the iodine in the tether, chloro mixed acetals **96** (prepared by the use of NCS as described earlier) were treated with lithium iodide.

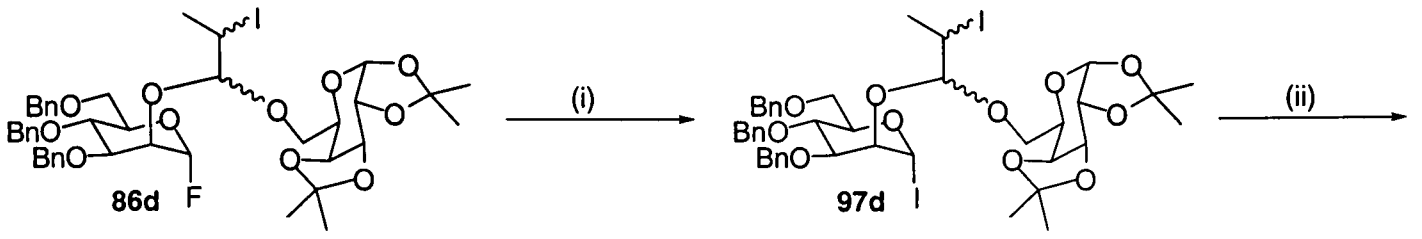
Reaction occurred rapidly to form a single product **101** with similar R_f to the starting material, but which in this case did not stain brown with molybdate. NMR studies of this product again showed two singlets at between δ_H 7.1 and 7.0 in the ^1H spectrum, but in this case, the sample survived long enough to obtain COSY, HMQC and HMBC spectra. All spectra were consistent with the glycosyl iodide **101** structure (Scheme 4.13), and also ruled out the possibility of having iodide trapped in the tether (*cf* Figure 4.1).[16]



Scheme 4.13: (i) LiI, DCM, RT

It seems that treatment of tethered materials **86** with lithium iodide induces an apparently quantitative conversion of fluorides to the glycosyl iodides in all cases. Glycosyl iodides have been known for many years,[17] but have, until relatively recently, been considered much too reactive to be of use in synthesis. Within the last decade though, new routes to their synthesis,[14] as well as their use in glycosylation reactions under very mild conditions have been reported.[18]

In order to try to induce consistent glycosylation in the intramolecular system, it was decided to conduct a number of test reactions. Thus DAG-tethered *manno* fluorides **86d** were treated with LiI in DCM, and after 4 h 30 min, tlc indicated clean conversion to the glycosyl iodide **97d** in all cases. A summary of the different approaches attempted to try to induce glycosylation, and the results, is outlined in Table 4.2.

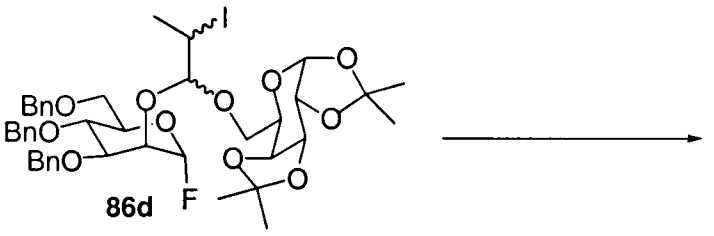


Scheme 4.14: (i) LiI (13 eq), DCM; (ii) see Table

Entry	Conditions	Observation after 3 h
1	Iodine (1 eq)	No β-mannoside **89d** formed; other products formed; intermediate **97d** remaining
2	AgOTf (2.5 eq)	Mostly remaining intermediate **97d**; A little β-mannoside **89d** formed
3	Silica	No β-mannoside **89d** formed; other products formed; no intermediate **97d** remaining
4	40°C	Mostly remaining intermediate **97d**; no β-mannoside **89d** formed
5	Water	β-Mannoside **89d** is major product by tlc; other products formed; no intermediate **97d** remaining

Table 4.2: test reactions of intermediate **97d** under different conditions.

None of the treatments produced the hoped-for clean conversion to the β-mannoside **89d**. Very surprisingly, addition of water showed the most promising result as monitored by tlc (Table 4.2, entry 5). That silver triflate treatment did not lead to rapid and complete consumption of the glycosyl iodide (Table 4.2, entry 2) was particularly surprising until it was realised that the massive excess of LiI (13 eq) used in order to induce reaction had not been compensated for by the use of only 2.5 eq AgOTf. Consequently it was decided to investigate the conditions under which the intermediate **97d** would be formed (Table 4.3).



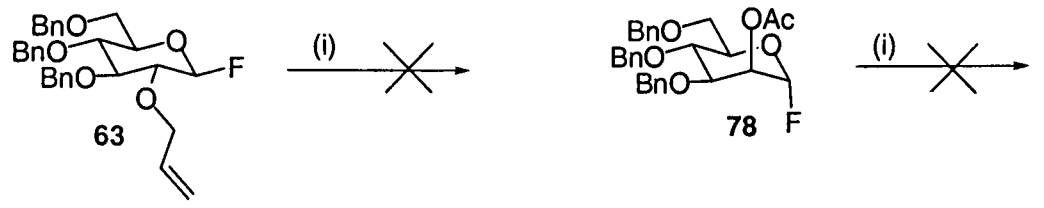
Entry	R	Activator	Solvent / ml	Observation
1	DAG / 0.03 mmol	LiI / 0.04 mmol	DCM	Tlc monitoring showed partial conversion to the brown-staining intermediate. Addition of a further 0.05 mmol then 0.06 mmol LiI saw reaction go to completion.
2	DAG / 0.09 mmol	LiOTf / 1 mmol	DCM / 2 ml	No change by tlc after 5 h. LiI (1.1 eq) added. No change. Recovered 87% starting material **86d**.
3	DAG / 0.03 mmol	LiI.xH_2O / 0.5 mmol	DCM	No reaction
4	DAG / 0.03 mmol	LiI / 0.19 mmol	MeCN / 0.5 ml	No reaction

Table 4.3: attempted formation of glycosyl iodides under different conditions

Thus, treatment of DAG-tethered mixed acetals **86d** in DCM with small increments of LiI led to the complete conversion to the glycosyl iodide **97d** only after the addition of *ca* 5 eq (Table 4.3, entry 1). Subsequent addition of AgOTf (9 eq) to the so-formed glycosyl iodide **97d** resulted in its complete conversion within 5 min to a mixture of products, including the aglycon DAG **3d** and the desired β-mannoside **89d**, as shown by tlc.

Treatment of DAG-tethered *manno* fluoride **86d** with either anhydrous LiI in acetonitrile, or the hydrated salt in DCM, produced no reaction (Table 4.3, entries 3,4). When the fluoride **86d** was treated with lithium triflate, no reaction occurred (Table 4.3, entry 2).

Attempted intermolecular glycosylation reactions under the same conditions in the presence of methanol as an external nucleophile resulted in no reaction, even after prolonged treatment (Scheme 4.15).



Scheme 4.15: (i) LiI, MeOH (1.5 eq), DCM, RT

In summary, a route to tethered mannosyl iodides **97** and **101** by treatment of the respective fluorides **86** and **96** with anhydrous lithium iodide in dichloromethane or chloroform has been demonstrated. The reaction is unusual insofar as while tethered materials **86** and **96** underwent quantitative conversion in a few hours at RT, attempted reactions of fluorides without the tether **63** and **78** failed. This could be due to interference in the reaction by methanol, added as an external nucleophile, or by the requirement of a neighbouring group to participate in the fluoride's departure, a role which the tether acetal could feasibly fulfil. In the case of the 2-*O*-acetyl *manno* derivative **78**, it is possible that the unreactivity is due to its disarmed nature.[19]

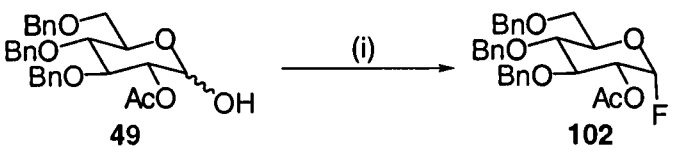
Perhaps surprisingly, a consistent and controlled route to the intramolecular glycosylation of these reputedly very active donors[15] proved elusive. The iodides were stable for many days under the reaction conditions of their formation, however, on handling under standard procedures for work-up (ie filtration of excess solid iodide, aqueous wash or flash column), they decomposed to give mixtures of products in which the β-mannosides **89** were

major components. Also formed in this decomposition/glycosylation reaction were iodine (as judged by the red colour) and propanal (as observed in the ^{1}H NMR spectrum), but the precise mechanism of this reaction is unclear. Attempts to optimise the intramolecular glycosylation of these tethered iodides **97** failed. Consequently this approach was abandoned.

4.2.3 The Use of α-*Gluco* Fluorides

4.2.3.1 Synthesis and Isomerisation of a 2-*O*-Allyl Protected Donor 87

In order to investigate the nature of the mechanism of the glycosylation of glycosyl fluorides, it was decided to try analogous IAD reactions on an α-*gluco* fluoride donor **87**. A large quantity of 2-*O*-acetyl protected α-fluoride **102** was already in hand. This had resulted from the decomposition of the β anomer **66** on allowing to stand on the bench overnight. In order to investigate a superior route to this compound, hemiacetal **49** was treated with DAST.[20] Tlc indicated the formation of a major and a minor product, which appeared by tlc to be the β **66** and α **102** anomers respectively. However, on purification, only the α anomer was isolated, in a poor 18% yield (Scheme 4.16). Apparently the unstable β compound had once again decomposed. No further attempts to optimise a route to α-*gluco* fluorides were made.

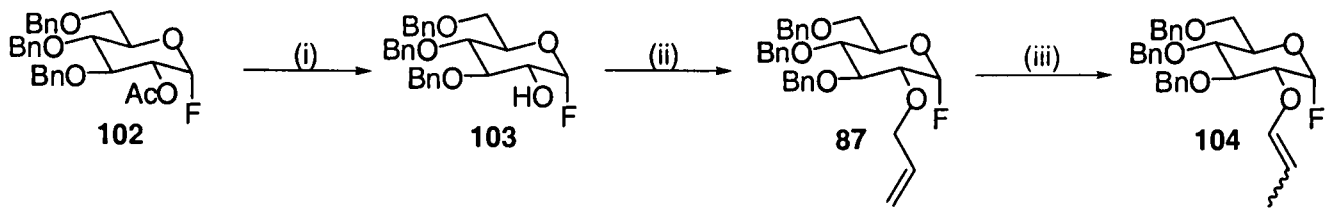


49 **102**

Scheme 4.16: (i) DAST, DCM, 0°C, 18%

In contrast to the β case (see Chapter 3), sodium methoxide-mediated deprotection[21] of acetate **102** proceeded in good yield to give alcohol **103**.

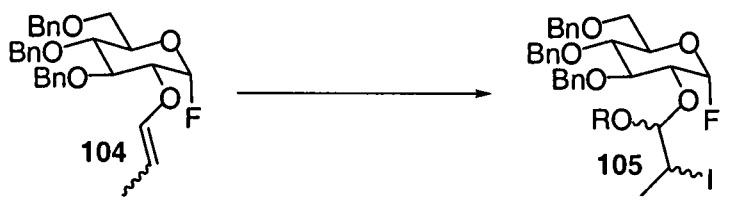
Allylation under standard conditions[22] furnished the desired 2-*O*-allyl protected donor **87** in good 99% yield. Once again isomerisation under Boons and Isles' conditions[23] gave the enol ethers **104** in quantitative yield (Scheme 4.17).



Scheme 4.17: (i) Na, MeOH, quantitative; (ii) allyl bromide, NaH, DMF, 99%; (iii) Wilkinson's catalyst, THF, 70°C, quantitative

4.2.3.2 Tethering and Glycosylation Reactions

Treatment of enol ethers **104** with NIS and aglycon alcohols **3e,g** resulted in the formation of mixed acetals **105e,g** (Table 4.4). The tethering yields were slightly lower than for the β analogues. This can be explained as being due to the increased steric bulk at the tether site by having an axial substituent at the anomeric position.



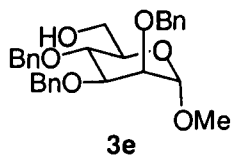
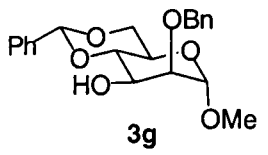
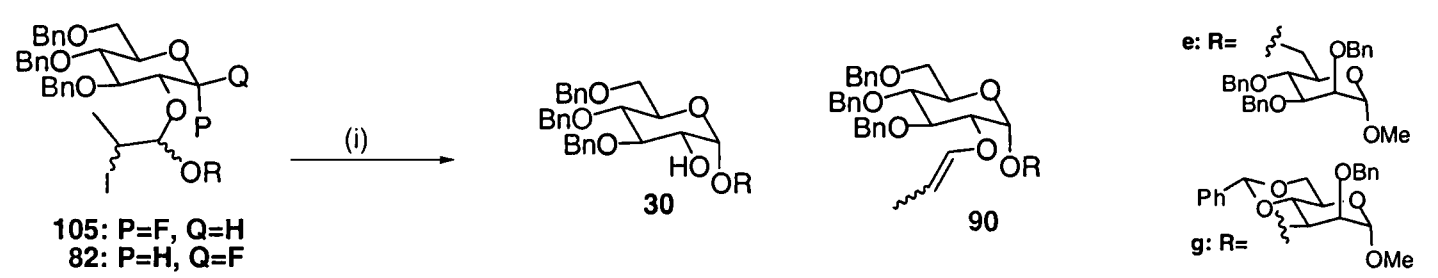
Entry	ROH	eq	eq NIS	solvent	t	T/°C	Product/yield of mixed acetals
1	 **3e**	2	3	DCE	2 h	-40→RT	**105e** / 63%
2	 **3g**	2	3	DCE	16 h 30	-40→RT	**105g** / 30%

Table 4.4: α-*Gluco* fluoride tethering reactions

When mixed acetals **105e,g** were subjected to the same activation conditions as for the analogous β compounds, they were found to be much less reactive. The glycosylation reaction of **105g** was worked up after 45 h, and 81% of starting material was recovered (Table 4.5, entry 5). The glycosylation of the analogous β compound **82g** was complete under the same conditions after just 17 h (Table 4.5, entry 4, from Chapter 3). The glycosylation reaction of **105e** was worked up after 48 h, and 68% of starting material was recovered, along with just 1% of the α-glucoside **30e** (Table 4.5, entry 2). The glycosylation of the β-analogue **82e** was complete under the same conditions after just 19 h in 46% yield (Table 4.5, entry 1, from Chapter 3). However, extended reaction times (for **105e**, Table 4.5, entry 3) or increased



Entry	Starter		T	t	Product, yield		
	α/β				starter	1,2-*cis* glycoside	Enol ethers
1	β	**82e**	50 °C	19 h		**30e** / 46%	
2	α	**105e**	50 °C	48 h	**105e** / 68%	**30e** / 1%	
3	α	**105e**	50 °C	68 h		**30e** / 32%	**90e** / 12%
4	β	**82g**	50 °C	17 h		**30g** / 37%	**90g** / 29%
5	α	**105g**	50 °C	45 h	**105g** / 81%		
6	α	**105g**	60 °C	28 h		**30g** / 68%	

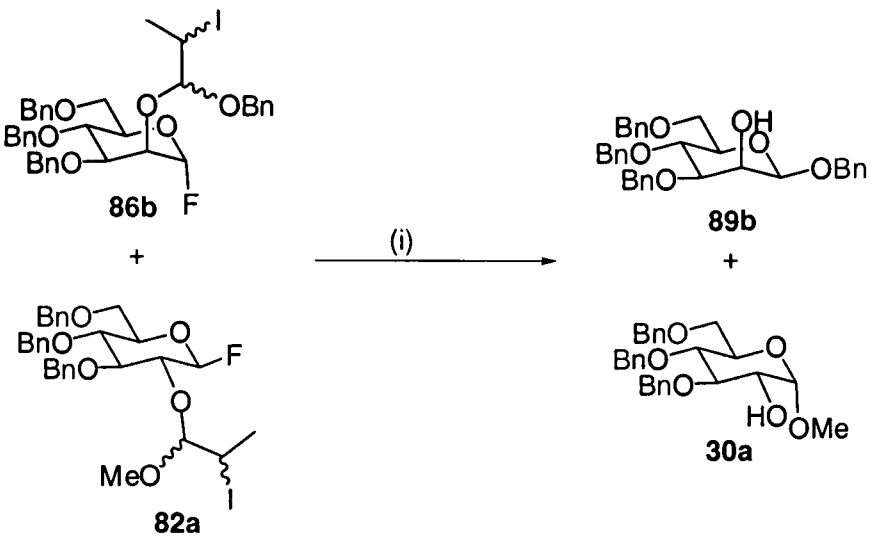
Table 4.5: Comparison of intramolecular glycosylation reactions of α **105** and β **82** *gluco* fluorides; (i) $SnCl_2$, AgOTf, DTBMP, DCE, 4Å

temperatures (for **105g**, Table 4.5, entry 6) did result in the complete consumption of starting materials, and α-glucosides **30e,g** were formed in reasonable yield. No β-glucoside formation was observed.

4.2.4 Competition Experiments

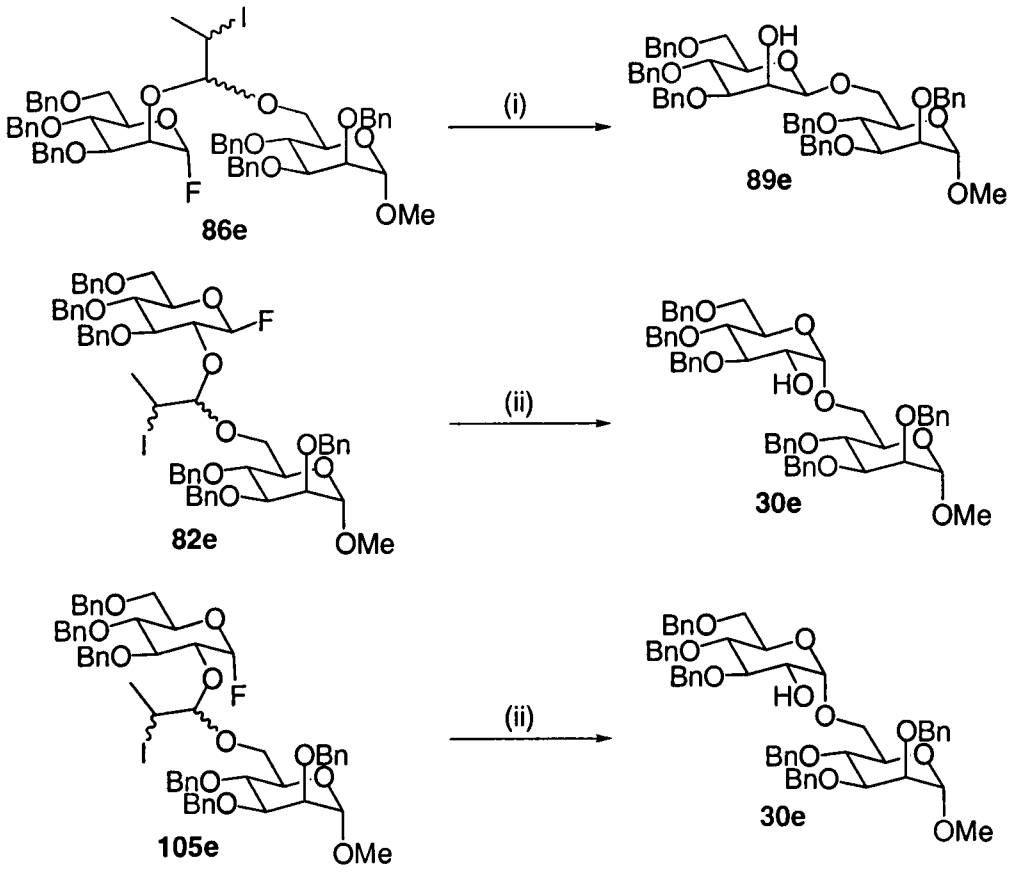
In order to provide further support for an intramolecular mechanism in the glycosylation reaction, it was decided to perform a so-called 'crossover' experiment. Namely, to mix *gluco* mixed acetals tethered to a particular aglycon and *manno* mixed acetals with a different aglycon, and to carry out a subsequent glycosylation reaction in the same vessel. It was expected that if an intramolecular reaction mechanism operated, only the α-glucoside and β-mannoside derived from their respective tethered materials would be formed. Conversely, if some intermolecular mechanism operated, scrambling would occur to give a mixture of all four possible products.

Consequently, *manno* fluoride **86b** bearing tethered benzyl alcohol and *gluco* fluoride **82a** with tethered methanol were mixed and subjected to the standard glycosylation conditions. The two major reaction products were the expected methyl α-glucoside **30a** and benzyl β-mannoside **89b**, formed in 59% and 60% yields respectively (Scheme 4.18). TFA treatment of the by-products afforded further α-glucoside **30a** (9%) and benzyl β-mannoside **89b** (3%). Analysis of the product mixture by tlc and ^{1}H NMR spectroscopy showed that there had been no formation of any of the possible crossover products.



Scheme 4.18: (i) $SnCl_2$, AgOTf, DTBMP, DCE, 50°C; **30a**, 68%; **89b**, 63%

In order to further investigate the reaction mechanism, it was decided to carry out glycosylations in the presence of an external nucleophile. Consequently, α-*gluco* **105e**, β-*gluco* **82e** and α-*manno* **86e** fluorides with tethered mannose acceptor **3e** were treated under the glycosylation reaction conditions in the presence of excess methanol (Scheme 4.19).



Scheme 4.19: (i) $SnCl_2$, AgOTf, DTBMP, MeOH (5 eq), DCE, 50°C; (ii) $SnCl_2$, AgOTf, DTBMP, MeOH (3 eq), DCE, 50°C

In all cases, the respective 1,2-*cis* disaccharides were formed as the major products, but some of the methyl glycosides (α **30a** and β **69** *gluco* and α *manno* **106**) were detected by ^{1}H NMR spectroscopy. These were not separated from the also formed aglycon alcohol **3e**, but were identified by the chemical shifts of the OCH_3 singlets in the ^{1}H NMR spectra. A summary of the products is shown in Table 4.6.

Entry	Donor	t	Yield of			
			Disaccharide	α-Methyl glycoside	β-Methyl glycoside	Aglycon **3e**
1	α-*gluco* **105e**	22 h	**30e** / 58% + **90e** / 31%	**30a** / 2%	**69** / 6%	11%
2	β-*gluco* **82e**	19 h	**30e** / 67%	**30a** / 5%	**69** / 10%	13%
3	α-*manno* **86e**	19 h	**89e** / 50%	**106** / 3%	—	5%

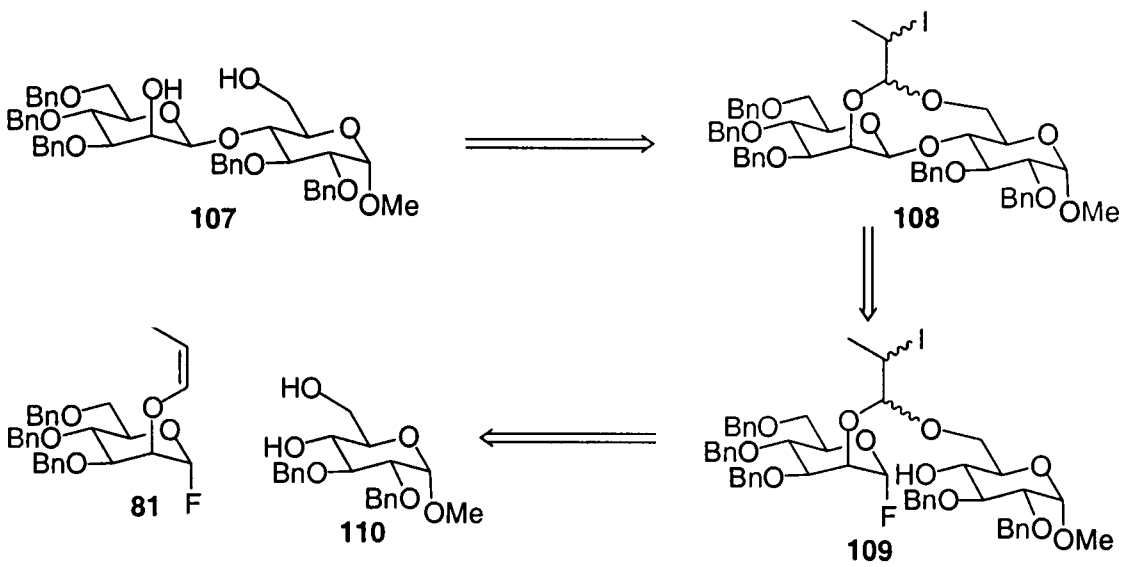
Table 4.6: In the case of the α-*gluco* donor **105e**, 36% of starting material was recovered. For comparison purposes, in this case yields are given over recovered starting material.

4.2.5 An Investigation into Conformation-Controlled Intramolecular Glycosylation Using an Allyl-Derived Tether

Tethering yields for the 4-hydroxyl are low, but β(1→4)-linked mannosides remain an important target, so it was decided to investigate a possible alternative route to these compounds. Intramolecular glycosylation reactions of free hydroxyl groups, where the donor is linked *via* a different hydroxyl group on the acceptor to that which is destined to form the new glycosidic bond, are well known in the literature. In 1986, Shiba used such a reaction in

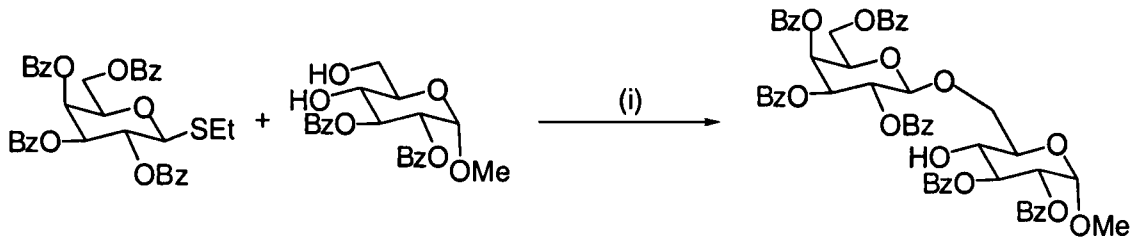
the formation of a *N*-acetylglucosaminyl-β(1→4)-*N*-acetylmuramic acid disaccharide.[24] More recently, Ziegler[25] and Schmidt[26] in particular have demonstrated that such reactions may also show good stereoselectivity as described in Chapter 1.

It was proposed that a (1→4)-linkage (as in **107**) could be derived from the intramolecular glycosylation of a free 4-hydroxyl, when tethering was to a different alcohol in the acceptor molecule, ie OH-6 (Scheme 4.20).



Scheme 4.20: Retrosynthesis of (1→4)-linked disaccharides *via* an intramolecular glycosylation reaction not involving the tethered oxygen

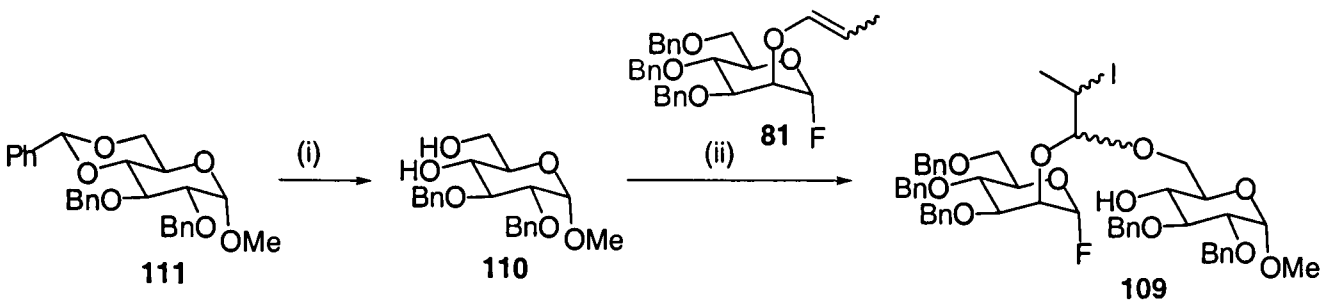
It is well known that the primary OH-6 of glucose is much more reactive than the hindered secondary OH-4. Indeed, the use of a 4,6-diol as glycosyl acceptor, whereby glycosylation occurs solely at the 6-position leaving OH-4 free are widespread in the literature.[27] An example of this as reported by van Boom is shown in Scheme 4.21.



Scheme 4.21: Selective glycosylation of the 6- over the 4-position by van Boom.
(i) NIS, TfOH, DCE, Et_2O, 94%

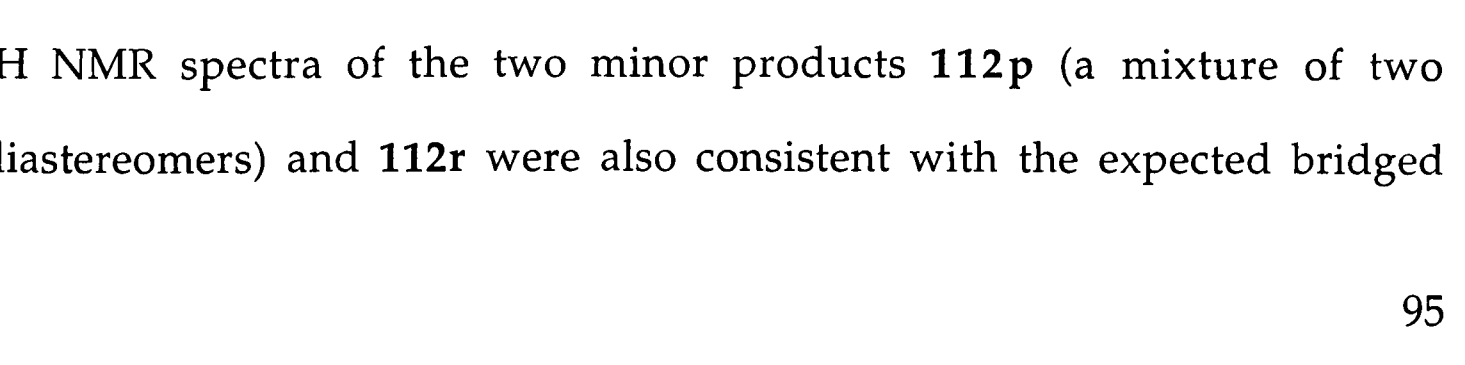
It was postulated therefore that a tethering reaction between *manno* enol ethers **81** and a 4,6-diol **110** would lead exclusively to the acetals tethered through the 6-position **109**. The question then arose as to whether the tethered O-6 or the free OH-4 would be the more nucleophilic oxygen in a subsequent glycosylation; furthermore, if glycosylation did occur through the 4-position, whether any stereoselectivity would be obtained.

Consequently, fully protected glucoside **111** was treated with acid to remove the 4,6-*O*-benzylidene protection, and thus afford diol **110**.[28] Tethering of diol **110** to *manno* fluoride enol ethers **81** under standard NIS-mediated conditions[29] yielded mixed acetals **109** in 73% yield. These were identified as a mixture of three diastereomers (in a 2:1.5:1 ratio) by ^{1}H NMR spectroscopy. The linkage of the tether to O-6 was confirmed by the fact that each of the hydroxyl protons appeared as a doublet in the spectrum, by virtue of coupling only to H-4, rather than a double doublet as would be expected for OH-6. Furthermore, in the HMBC spectrum, the OH protons showed cross-peaks to doublet, but no triplet carbons (Scheme 4.22).[30]



Scheme 4.22: (i) TsOH, MeOH, DCM, 50°C, 76%; (ii) NIS, DCE, 4Å, -40°C→RT, 73%

When mixed acetals **109** were subjected to the standard fluoride glycosylation conditions, two major and three minor products were isolated (Scheme 4.23).



Scheme 4.23: (i) $SnCl_2$, AgOTf, DTBMP, DCE, 4Å, 50°C;

112p, <1%; **112q**, 16%; **112r**, 1%; **112s**, 38%; **112t**, 2%

MS analysis indicated that **112p**, **112q** and **112r** had M=972, corresponding to the expected 9-membered-ring-containing compound **108**. NMR analysis showed the major product **112q** to be a single diastereomer, but the $^3J_{H,H}$ coupling constants around the *manno* ring indicated that this sugar was not in the usual $^4C_1$ conformation – presumably as a result of the extra bridging ring. Following full assignment of the ^1H NMR spectrum using COSY, edited HSQC and HMBC spectra were obtained which showed that the tether was still linking C-2_b and C-6_a and that a (1→4) glycosidic linkage had been formed.

^1H NMR spectra of the two minor products **112p** (a mixture of two diastereomers) and **112r** were also consistent with the expected bridged

(1→4)-glycosylated structure **108**, showing signals for two sugar residues, and characteristic OMe singlets and $C\underline{H}_3CHI$ doublets. These materials were not formed in large enough quantities for further structural elucidation to be possible.

The other two products **112s** and **112t** were shown by MS to have M=846, consistent with loss of iodine. Two representative possible structures, the (1→6)-linked enol ethers **113** and (1→4)-linked bridged acetal **114** are shown in Figure 4.3.

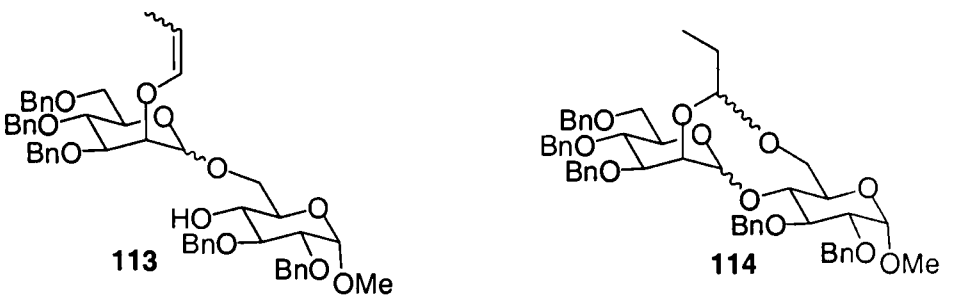
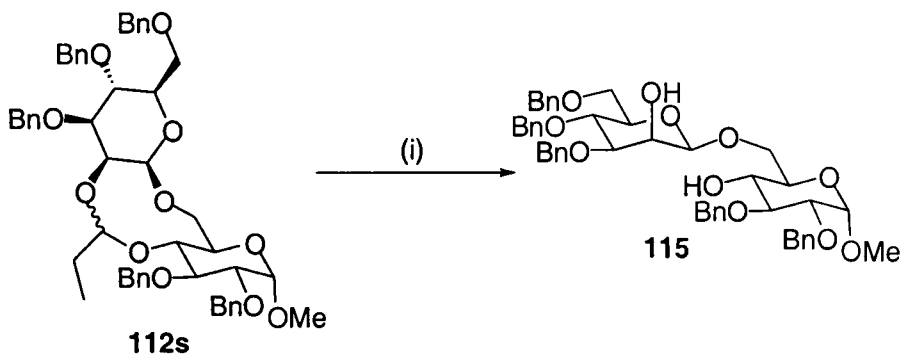


Figure 4.3: two possible structures for **112s** and **112t**

The ^{1}H and ^{13}C NMR spectra of **112s** indicated the presence of a single diastereomer, but contained many broad signals, possibly as a result of two interconverting conformers. Such a phenomenon is surely more likely for a bridged structure as in **114** than of enol ethers **113**. Indeed as just described the bridged compound **112q** showed evidence of an unusual conformation in its NMR spectra. The broad spectra made assignment difficult, but certain insights could be gained. The complex multiplet at δ_H 1.92 could be assigned to one of the diastereotopic protons in the tether, expected to be a ddq. The broad signals at δ_H 1.66 (*ca* 1H) and 0.89 (*ca* 3H) could be assigned to the other CH_2 proton and the tether methyl group respectively. No information about the glycosidic linkage could be obtained from the spectra.

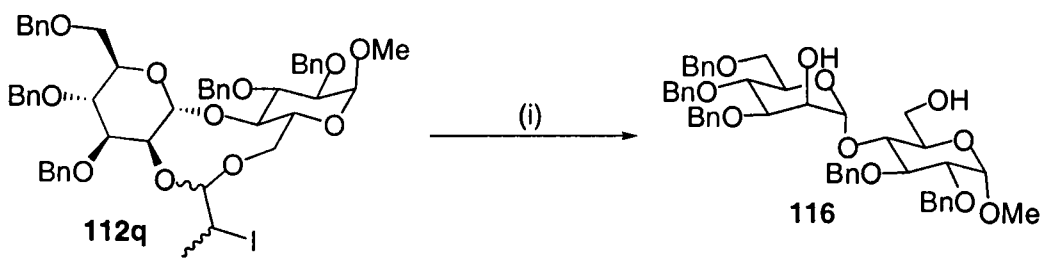
The ^{1}H NMR spectrum of the minor product **112t** was also consistent with a bridged structure, showing a triplet at δ_H 0.69 (J 7.4 Hz) and complex multiplets at δ_H 1.3-1.7, probably arising from the acetal methylene group. **112t** was also a single diastereomer, but again this material was not formed in a large enough quantity for further structural elucidation to be possible.

Treatment of major product **112s** with TFA in order to cleave the tether gave disaccharide **115** in 45 min in 77% yield. The structure of disaccharide **115** was shown to contain the β(1→6) linkage, which gives the probable structure of **112s** as shown in Scheme 4.24.



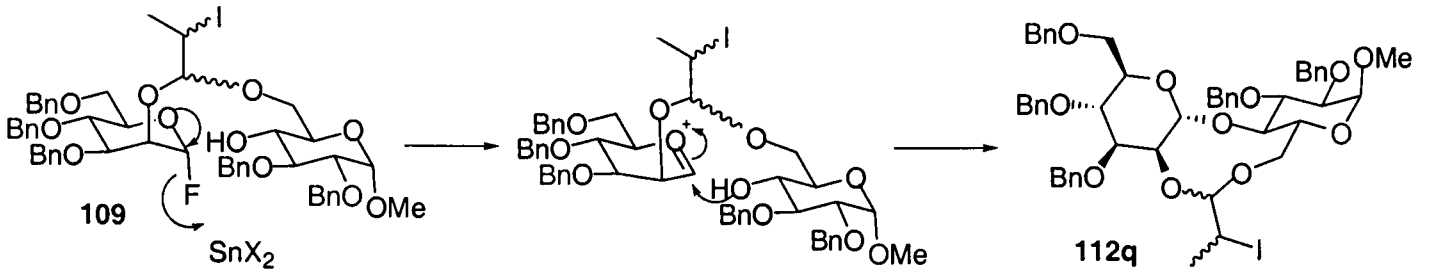
Scheme 4.24: (i) TFA, MeOH, THF, H_2O (5:2:2:1), RT, 77%

Compound **112q** on the other hand required a much longer reaction time for the TFA-mediated cleavage of the tether. After 3 days the reaction was worked up, even though a small amount of starting material remained. The disaccharide product obtained in 75% yield was unambiguously assigned as the α(1→4) linked compound **116**, giving **112q** as shown in Scheme 4.25.



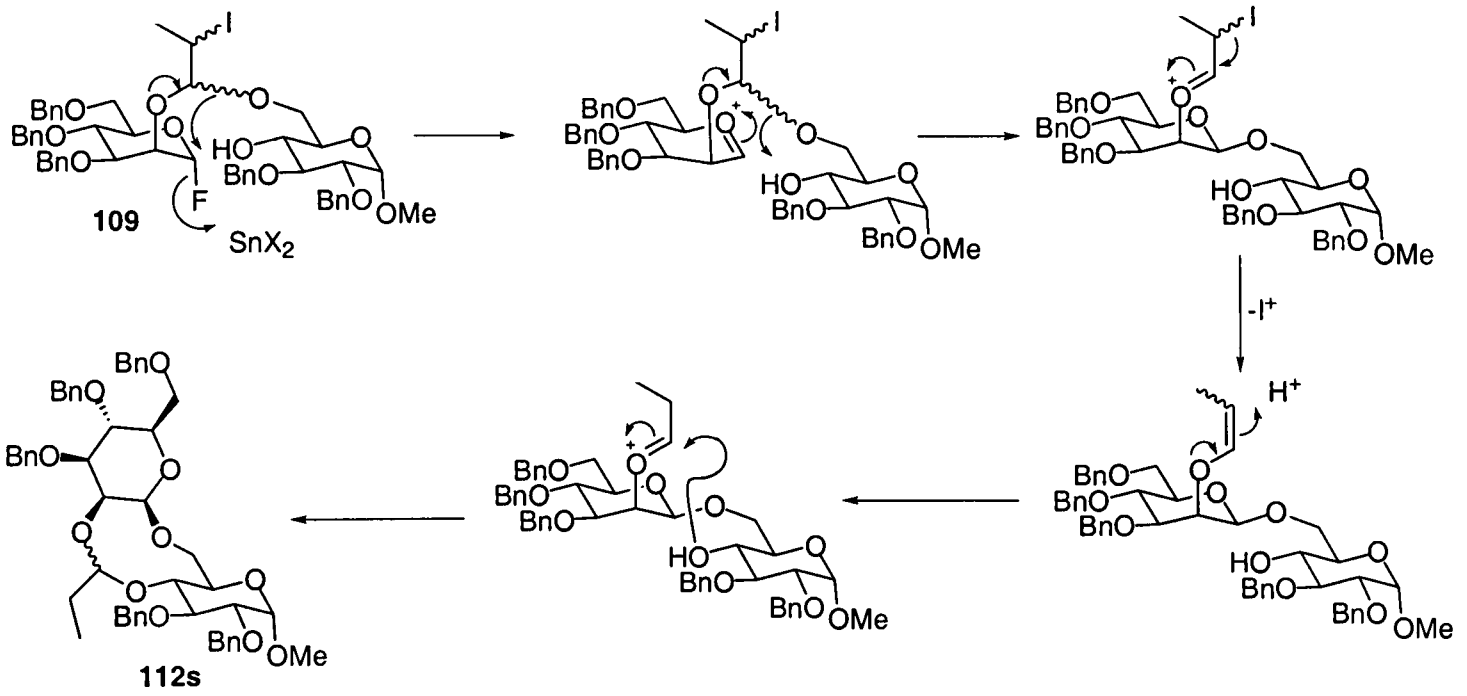
Scheme 4.25: (i) TFA, MeOH, THF, H_2O (5:2:2:1), RT, 75%

That the two major products were formed each as a single diastereomer, from a mixture of three diastereomers as starting material is interesting. In the formation of **112q**, both the existing stereogenic centres in the tether remain intact in the expected mechanism (Scheme 4.26).



Scheme 4.26: proposed mechanism for the formation of **112q**

In a proposed mechanism for the formation of **112s**, glycosylation of the tethered 6-position is followed by formal loss of I^+ from the resulting carbocation (as seen in Chapter 3). This is then followed by intramolecular cyclisation of the free OH-4 onto the enol ether, to give bridged disaccharide **112s**. This mechanism results in the loss of stereochemistry at both centres in the in the tether (Scheme 4.27).



Scheme 4.27: proposed mechanisms for the formation of **112s**

It follows that **112q** must have been formed from a single diastereomer, whereas **112s** could result from any combination of the three. Crucially though, the diastereomers of the starting material react by different mechanisms, resulting in different products.

Unfortunately it appears that the idea of tethering through the 6-hydroxyl and stereoselectively glycosylating through the free OH-4 to give the (1→4)-linked β-mannoside was unsuccessful. Only α(1→4) and β(1→6)-linked products were obtained in this case.

4.2.6 Discussion of the Mechanism of Tin (II) Chloride / Silver Triflate / DTBMP Mediated Glycosylation of Glycosyl Fluorides

That the glycosylation reaction occurs in an intramolecular fashion has been demonstrated, not only by the stereospecific nature of every glycosylation reaction for a wide variety of aglycons and in both the *gluco* and *manno* series, but also by the crossover reaction detailed earlier in this chapter. Inferences can also be made about whether the glycosylation is S_N1 or S_N2-like.

The significantly lower reaction rates of the tethered α-*gluco* fluorides compared to their β analogues could be explained by the operation of a faster, S_N2-like mechanism in the β case. However, this is probably not the correct conclusion to draw. When methanol was added to the glycosylation reaction of α **105e** and β **82e** tethered *gluco* fluorides, the formation of similarly small amounts of methyl glycosides and similar ratios was seen in both cases, apparently irrespective of the anomeric stereochemistry of the starting material. This is suggestive of a common intermediate, and an S_N1-like

mechanism. In this case a better explanation for the difference in reaction rate between the α and β glycosyl fluorides, would be the intrinsic lower reactivity of α anomer arising from its greater stability.[31]

A significantly faster reaction occurred in the α case in the presence of methanol than its absence, suggesting that participation by a nucleophile may assist the departure of the fluoride leaving group, without necessarily resulting in the formation of a glycosidic bond.

Further evidence for an S_N1 pathway comes form the formation of the α-mannoside **116** by a necessarily intramolecular S_N1 reaction where S_N2 would be possible.

4.3 Conclusions

Significant progress towards optimisation of the tethering reaction has been made, with the implementation of a novel source of I^+. In particular, *N*-acetyl glucosamine was tethered and glycosylated by its 4-hydroxyl (the naturally occurring aglycon for β-mannose in the common pentasaccharide core of all *N*-linked glycoproteins) stereospecifically in overall 41% yield.

A route to tethered glycosyl iodides from the tethered fluorides has been described, but unfortunately, no general glycosylation strategy could be found for these species.

Furthermore, various mechanistic investigations were undertaken into the intramolecular glycosylation reaction. In subsequent chapters, attempts to apply the allyl-mediated IAD methodology to the synthesis of biologically interesting compounds are described.

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Chapter 5. The Synthesis of the *N*-Glycan Tetrasaccharide Glc_3Man *via* an Iterative IAD Approach

5.1 Introduction

In the biosynthesis of all *N*-linked glycoproteins, a common precursor, the tetradecasaccharide $Glc_3Man_9GlcNAc_2$ **32** is assembled on dolichol pyrophosphate, and transferred *en bloc* by oligosaccharyl transferase (OST) to the nascent polypeptide chain in the lumen of the endoplasmic reticulum.[1] OST is a complex enzyme made up of various subunits, whose structure and binding properties have not been elucidated.[2]

Shortly after this transfer, the three terminal glucose residues are sequentially trimmed. The terminal α(1→2)-linked residue is cleaved by Glucosidase I, before the remaining two α(1→3)-linked residues are split by another enzyme, Glucosidase II. During these processing stages though, crucial changes to the glycoprotein structure also occur. The monoglucosylated moiety is recognised by molecular chaperones, such as calnexin and calreticulin, and while the oligosaccharide is bound, protein folding occurs.[3] Furthermore, if Glucosidase II cleaves both glucose residues to leave only $Man_9GlcNAc_2$ before protein folding is complete, a quality-control mechanism is found to operate, whereby transfer of a single glucose residue returns the monoglucosylated oligosaccharide moiety. This is then rebound to the chaperone so that folding may continue, and this process is iterated until the glycoprotein has assumed a properly folded state (Figure 5.1).

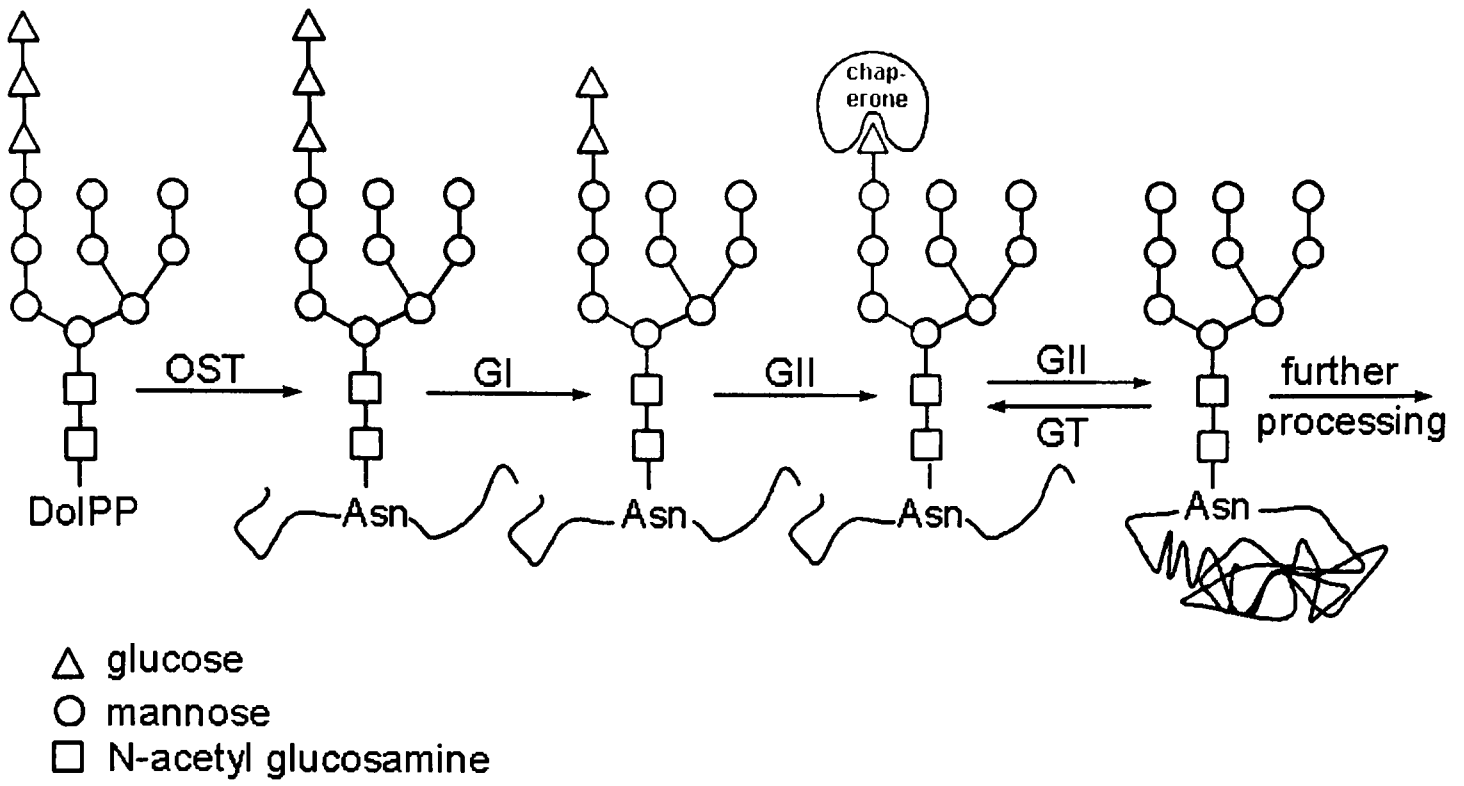


Figure 5.1: Schematic representation of the processing steps of *N*-linked glycoproteins in the endoplasmic reticulum, including: transfer of the oligosaccharide to the peptide chain; trimming by glucosidases I and II (GI and GII); binding to the chaperone resulting in protein folding; reglucosylation of incompletely folded glycoproteins by glucosyl transferase (GT).

It has been proposed that the glucotriose moiety is involved in recognition and binding to OST, possibly inducing a conformational change in the active site.[4] In addition, the tri- di- and monoglucose units in their respective oligosaccharides appear to be important in binding to the active sites of the trimming enzymes (glucosidases I and II) as well as to the chaperones (calnexin and calreticulin).[5] There are two reports in the literature concerning the conformational structure of the glucotriose cap of the tetradecasaccharide **32**.[5,6] Alvarado *et al* studied the NMR conformation of the tetrasaccharide $Glc_3ManOPr$ in D_6-DMSO, and suggested that the glucotriose unit adopts a stable conformation (Figure 5.2).[6]

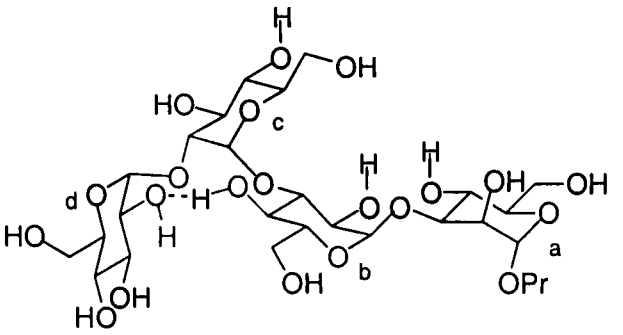


Figure 5.2: Alvarado's proposed conformation of the Glc_3Man tetrasaccharide showing the hydrogen bond between OH-2_d and OH-4_b

In particular, they have suggested the existence of a strong hydrogen bond between OH-2_d and OH-4_b. Such a rigid conformation is consistent with a function as a recognition motif.

A subsequent study by Wormald investigated the conformation in D_2O of the 12-mer $Glc_3Man_7GlcNAc_2$.[5] By measuring NOEs (and their absence) he was able to show that again the glucotriose cap adopts a stable, compact structure, seemingly independent of the mannose residues (Figure 5.3).

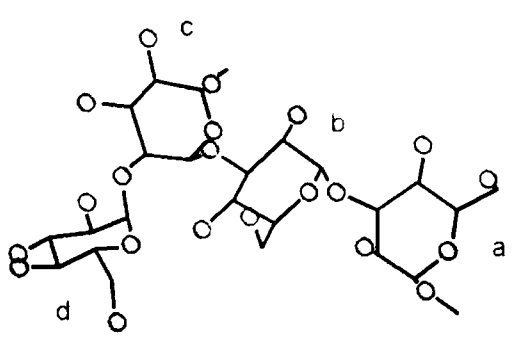
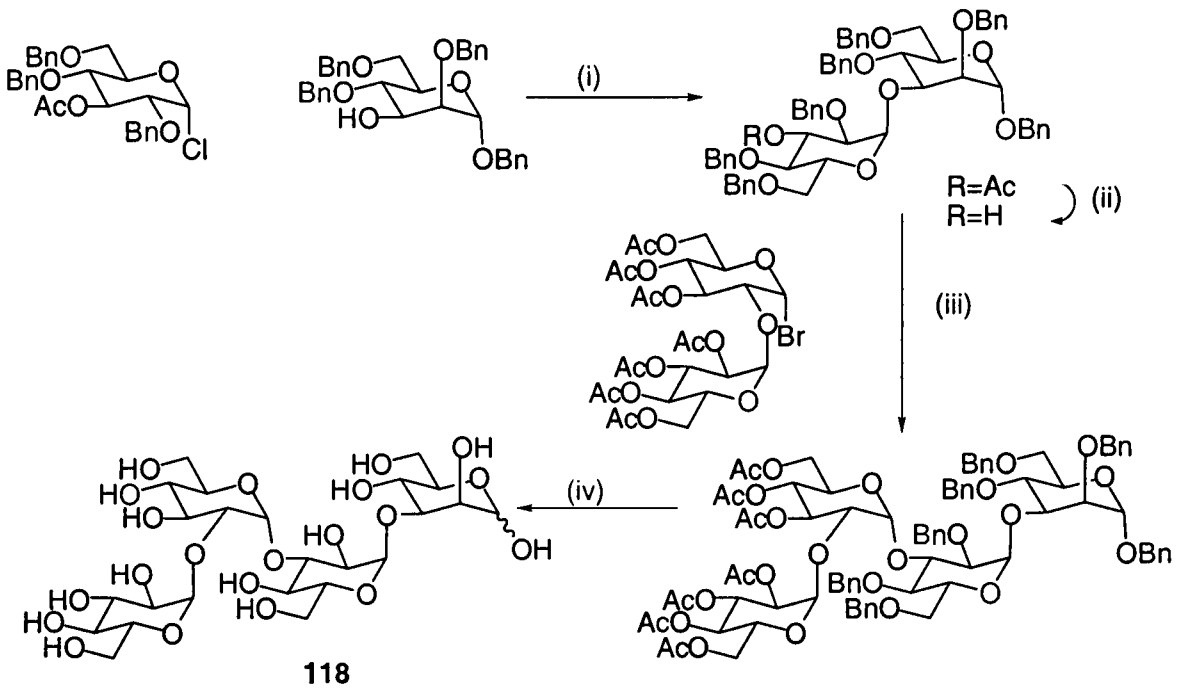


Figure 5.3: Wormald's proposed conformation of the Glc_3Man tetrasaccharide

However, the structure was rather different from that proposed by Alvarado in the DMSO study. In order to investigate whether the differences in the reported conformations of the glucotriose cap were due to a solvent effect, or due to the influence of the rest of the oligosaccharide, Wormald decided to use the NOE method to study the NMR conformation of the tetrasaccharide Glcα(1→2)Glcα(1→3)Glcα(1→3)ManαOMe **117** in different solvents, and to compare the results to the two previously reported conformations. Our group

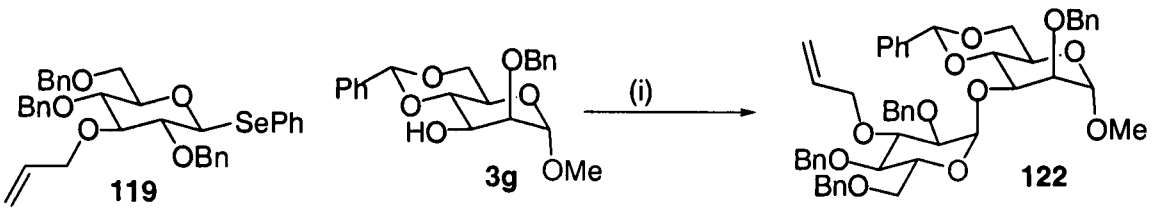
entered into a collaboration to undertake the synthesis of the tetrasaccharide **117**.

In 1983, Ogawa reported a convergent [2+2] synthesis of the reducing tetrasaccharide **118**, using glycosyl halides as donors (Scheme 5.1).[7]



Scheme 5.1: Ogawa's tetrasaccharide synthesis.
(i) $Hg(CN)_2$, $HgBr_2$, DCE, 79%; (iii) AgOTf, 4Å, DCE, 59%; (iv) H_2, Pd/C MeOH then NaOMe, MeOH

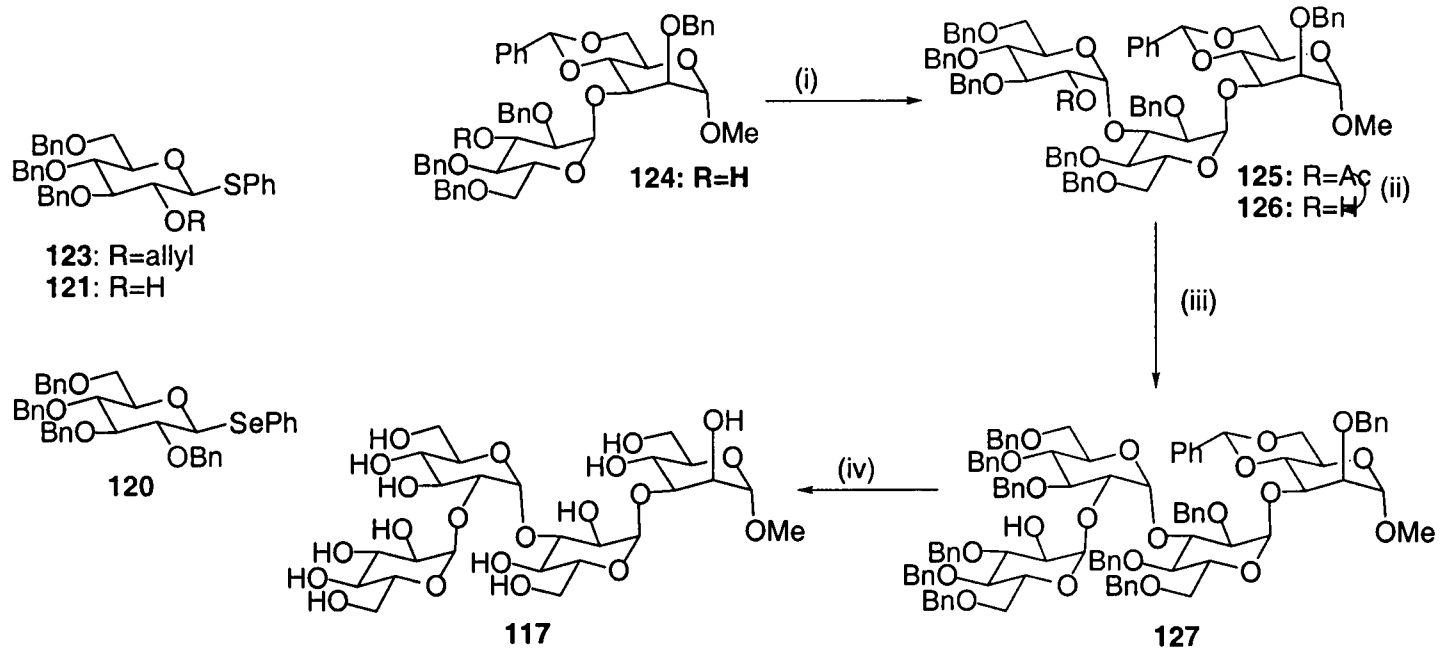
Initial investigations in our own group into the synthesis of the methyl tetrasaccharide **117** involved a similar [2+2] approach.[8] From the four initial building blocks, **119**, **120**, **121** and **3g**, *gluco* donor **119** and *manno* acceptor **3g** were glycosylated to give disaccharide **122** in reasonable yield, and as a separable mixture of anomers (Scheme 5.2). However, the attempted selective activation of selenoglycoside **120** in the presence of thioglycoside acceptor **121** failed to give the desired disaccharide. Instead, only complex mixtures of products were obtained.



Scheme 5.2: Ennis' tetrasaccharide synthesis I

(i) MeOTf, Et_2O, 4Å, RT, 66% (α/β, 5:1)

Instead, a linear [3+1] approach was adopted.[9] Thus glycosylation of thioglycoside **123** with disaccharide acceptor **124** gave trisaccharide **125**. Subsequent deprotection of OH-2_c and glycosylation with selenoglycoside **120** gave the protected tetrasaccharide **127**. Hydrogenation in the presence of palladium (II) acetate removed all the protecting groups to give the desired methyl glycoside **117** (Scheme 5.3).



Scheme 5.3: Ennis and Cumpstey's tetrasaccharide synthesis II

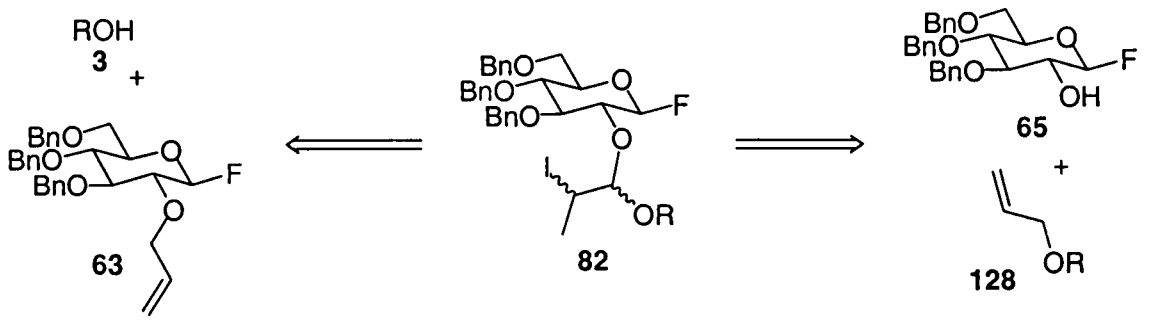
(i) **123**, MeOTf, Et_2O, 4Å, RT, 80% (α/β, 3:1); (ii) $Ti(O^iPr)_4$, $C_6H_{11}MgCl$, THF, RT, 83%; (iii) **120**, NIS, AgOTf, DCE, Et_2O, 4Å, RT, 73% (α/β, 2:1); (iv) H_2, $Pd(OAc)_2$, EtOH, AcOH, RT, 83%;

5.2 Results and Discussion

5.2.1 Retrosynthetic Analysis

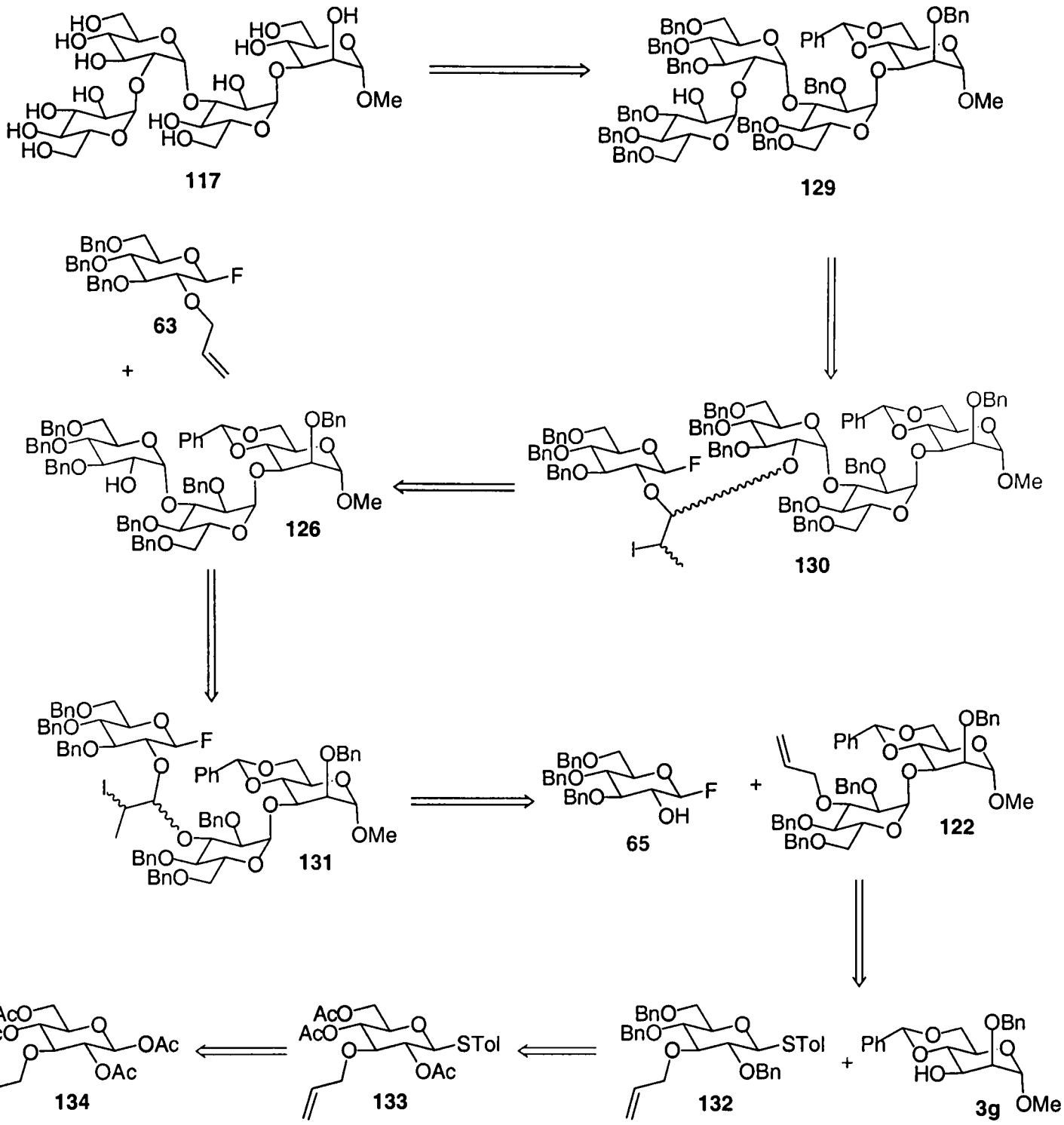
As the tetrasaccharide **117** contains three α-*gluco* bonds, the final two of which could only be obtained as inseparable α/β mixtures in the group's previous linear synthesis, it was proposed that allyl-derived IAD could be applied to this problem, so providing a route to the stereospecific formation of these 1,2-*cis* bonds.

It was noted that in two cases (**122** and **125**) in the previous synthesis, the aglycon was synthesised as its allyl ether derivative, and that a deprotection step was necessary prior to glycosylation. It was postulated that mixed acetals **82** could be derived not only from a 2-*O*-allyl protected donor **63** and an aglycon alcohol **3** in a conventional 'forward' tethering reaction as described thus far, but also from a so-called 'reverse' approach, whereby a donor with OH-2 free **65** is tethered to an allyl-protected aglycon **128** (Scheme 5.4).



Scheme 5.4: 'forward' and 'reverse' approaches to mixed acetals

Such a 'reverse' approach has been found to be effective in other systems.[10] Thus a retrosynthesis based on modification of the group's linear synthesis towards an iterative IAD approach is shown in Scheme 5.5.



Scheme 5.5: Retrosynthesis of tetrasaccharide **117**

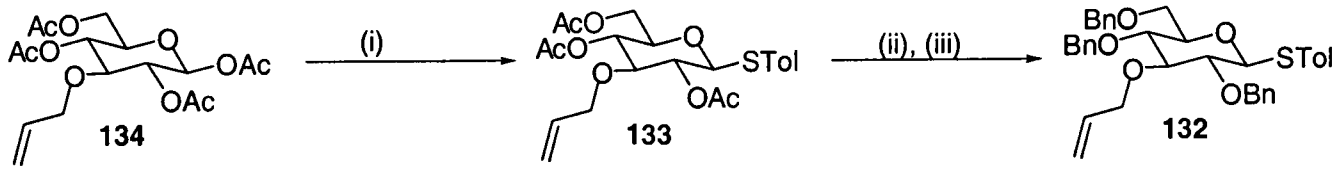
Disconnection of an appropriately protected tetrasaccharide **129** gives trisaccharide alcohol **126** and 2-*O*-allyl protected glucosyl fluoride **63**, the forward reactions being isomerisation, tethering and intramolecular glycosylation. It is clear that the trisaccharide **126** could be the product of an allyl-derived IAD reaction between disaccharide **124** and the same fluoride

63. However, in this case a 'reverse' tethering of donor alcohol **65** to allyl protected aglycon **122** seems to offer a more efficient alternative.

Allyl protected disaccharide **122** could be derived from the intermolecular glycosylation of *manno* acceptor **3g** with allyl protected thioglycoside **132**, in a similar manner to that described earlier. The *gluco* donor **132** could be made by standard transformations from the 3-*O*-allyl protected tetraacetate **134**.

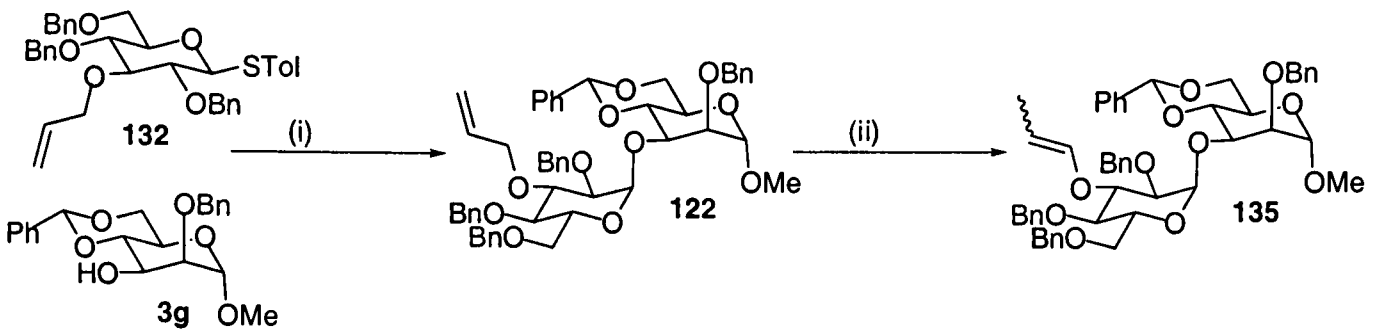
5.22 Synthesis of the Tetrasaccharide

Tetraacetate **134**[11] was treated with thiocresol in the presence of a Lewis acid catalyst to obtain the β-thioglycoside **133** in good yield.[12] Subsequent Zemplen deacetylation[13] and reprotection with benzyl ethers[14] afforded the 3-*O*-allyl donor **132** (Scheme 5.6).



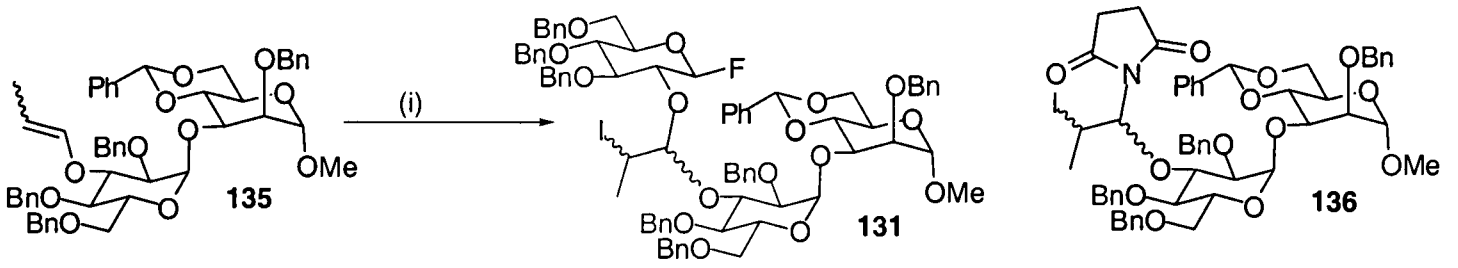
Scheme 5.6: (i) TolSH, $BF_3.OEt_2$, DCM, 0°C, 78%; (ii) Na, MeOH; (iii) NaH, BnBr, DMF, 0°C, 89%

Methyl triflate-mediated intermolecular glycosylation of donor **132** and acceptor **3g** was carried out in ether in order to ensure good α-selectivity,[15] and indeed, disaccharide **122** was obtained as the pure α anomer, albeit in a rather disappointing 50% yield. Allyl isomerisation under the standard conditions[16] cleanly afforded the enol ethers **135** in a good 95% yield (Scheme 5.7).



Scheme 5.7: (i) MeOTf, Et_2O, 50%; (ii) $(Ph_3P)_3RhCl$, BuLi, THF, 70°C, 95%

In an attempted reverse approach tethering reaction, donor alcohol **65** and enol ethers **135** were treated with NIS under standard conditions.[8] While some of the desired mixed acetals **131** were obtained, it was only in a poor 21% yield. Unfortunately, the major product from this reaction was the succinimide-tethered materials **136** (as a mixture of diastereomers, 65%) (Scheme 5.8).

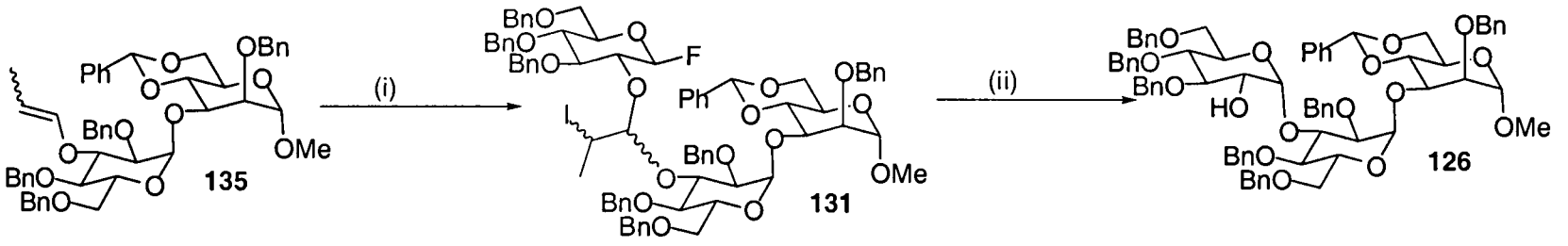


Scheme 5.8: (i) **65**, NIS, DCE, 4Å, -40°C→RT

It was clear that in this case, succinimide could effectively compete with the alcohol in the tethering reaction, so again a source of I^+ with a non-nucleophilic counter-ion was required.

When the alcohol **65** and enol ethers **135** were treated with a mixture of iodine, silver triflate and the hindered base DTBMP in the presence of 4Å molecular sieves, the desired mixed acetals **131** were obtained in a very satisfactory 78% yield.

A glycosylation reaction under standard conditions for glycosyl fluorides (as discussed in Chapter 3) was undertaken. Consequently, mixed acetals **131** were treated with tin (II) chloride, silver triflate and DTBMP in the presence of 4Å sieves, and heated to 50°C. However, even after prolonged treatment (3 days), following work-up it was determined that much starting material remained. Thus, a reaction was carried out under the same conditions, but at the further elevated temperature of 65°C. In this case it was found that the reaction had gone to completion after just 16 h, resulting in the desired α-linked trisaccharide **126** in 37% yield as the sole glycosylated product. However, a large amount (37%) of disaccharide alcohol **124** was also isolated from the reaction, possibly arising from competitive Lewis acid catalysed hydrolysis of the tether (Scheme 5.9).

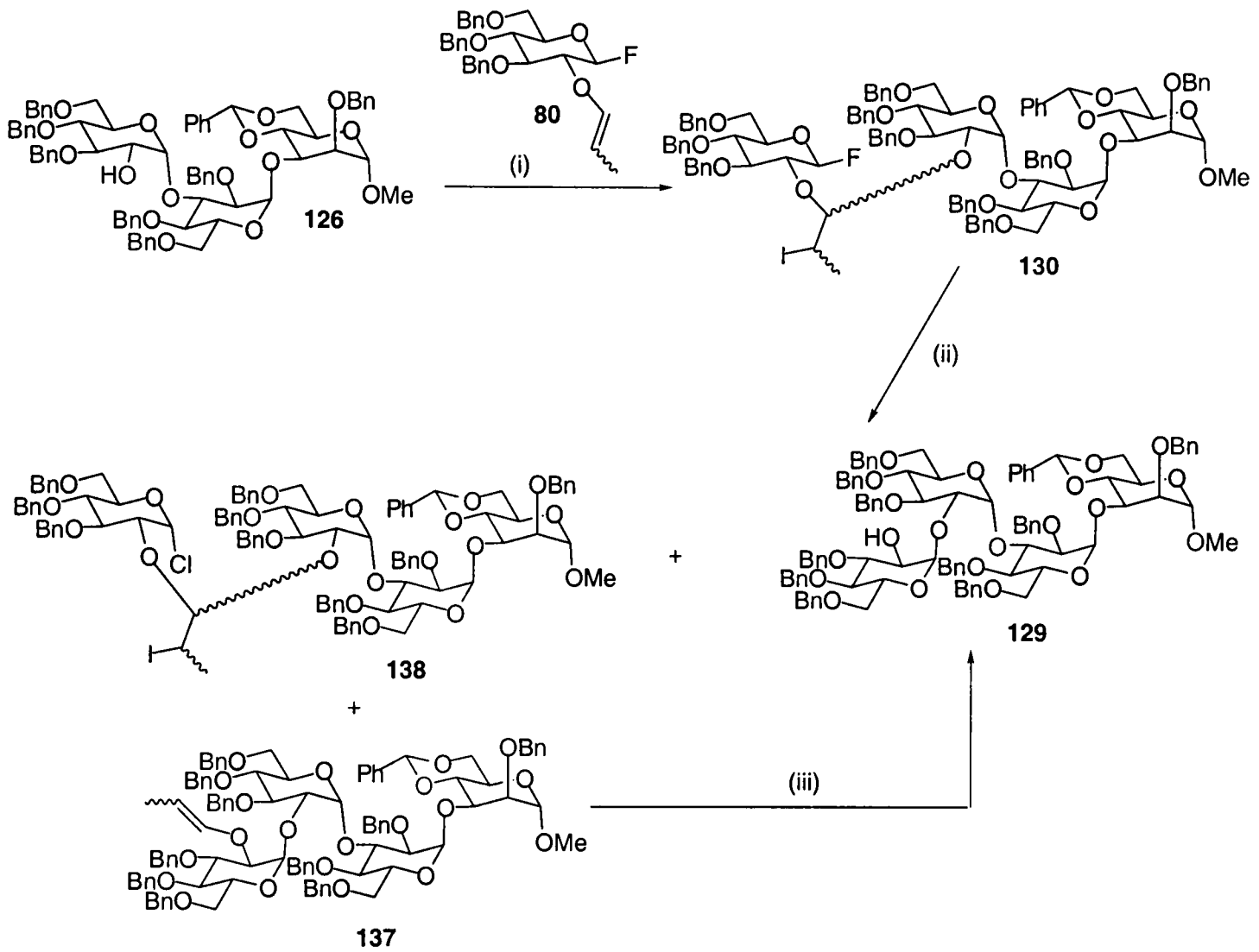


Scheme 5.9: (i) I_2, AgOTf, DTBMP, 4Å, DCM, -78°C→RT, 78%; (ii) $SnCl_2$, AgOTf, DTBMP, 4Å, DCE, 65°C, 37%

Attention now turned to a potential tethering reaction of trisaccharide alcohol **126** to enol ethers **80**. When trisaccharide **126** was treated with the glycosyl fluoride **80** under the new tethering conditions as above, pleasingly the mixed acetals **130** were formed in good 78% yield.

Treatment of mixed acetals **130** under standard fluoride activation conditions at 60°C resulted in the formation of three products: the desired

tetrasaccharide **129** in 10% yield; the enol ethers **137**, which upon treatment with NIS in a THF/water mixture gave further tetrasaccharide **129**, to give an overall yield of 25%; and not previously observed, the tethered glycosyl chlorides **138** as a mixture of two diastereomers in 27% yield (Scheme 5.10).

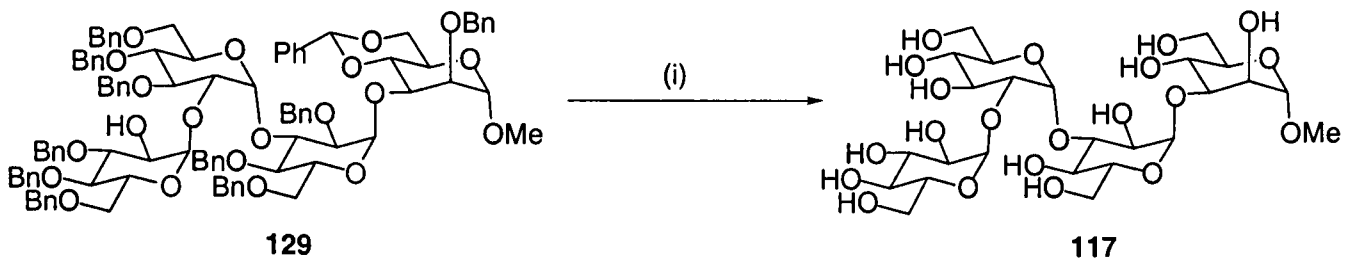


Scheme 5.10: (i) I_2, AgOTf, DTBMP, 4Å, DCM, -78°C→RT, 78%; (ii) $SnCl_2$, AgOTf, DTBMP, 4Å, DCE, 60°C; (iii) NIS, THF, H_2O; **129** 25% overall; **138** 27%

Presumably these chlorides are formed as a result of competitive nucleophilic attack by chloride ion from $SnCl_2$. The sluggish nature of the glycosylation reactions of these larger substrates, as illustrated by the higher temperatures required for them to react, and by the low yields, presumably makes this

attack by chloride more likely. Additionally, a small quantity of trisaccharide **126** was formed in the glycosylation reaction.

Global deprotection of the benzyl ethers and benzylidene acetal was carried out by hydrogenation in the presence of a palladium acetate catalyst,[17] to give the deprotected tetrasaccharide **117** in excellent yield (Scheme 5.11).



129 **117**

Scheme 5.11: (i) H_2, $Pd(OAc)_2$, AcOH, EtOH, 98%

5.3 Results from the NMR Studies[18]

Preliminary studies on the conformation of $Glc_3ManOMe$ **117** in three solvents, water, methanol and DMSO, show that the tetrasaccharide adopts similar multiple conformations in all the solvents. NOE data derived from NMR was used to construct torsion angle maps of the glycosidic linkages. Similar maps of the glycosidic linkages were obtained for all three solvents. This result is different from the two previous conflicting reports of the conformation of the Glc_3Man tetrasaccharide as part of $Glc_3Man_7GlcNAc_2$ in water compared with GlcManOPr in DMSO. In both reports the Glc_3Man conformation was found to be rigid with a different conformation for each oligosaccharide. The present analysis of the tetrasaccharide **117** in DMSO shows that multiple conformations are present, including both of the single conformations previously reported. The current hypothesis is that the

difference in Glc_3Man conformation between $Glc_3Man_7GlcNAc_2$ and $Glc_3ManOPr/Me$ is caused by the larger size of the oligosaccharide and is not due to a solvent effect. The previous observation of a rigid conformation in DMSO is probably due to the limitations of the modelling methods used.

5.4 Conclusion

Allyl-mediated IAD has been shown to be an effective tool for the stereospecific formation of α-*gluco* bonds in the *N*-glycan Glc_3Man tetrasaccharide **117**. The optimised tethering conditions work well on the larger substrates required for this synthesis. Additionally, a 'reverse' approach, whereby an OH-2 free donor is tethered to an allyl-protected acceptor has been described and effectively used in this synthesis.

The glycosylation reactions seem more sluggish than for disaccharide formation though, requiring further elevated temperatures and then only forming the desired glycosides in modest yields.

The NMR studies have given rise to some interesting and unexpected results, which could have far-reaching implications regarding the change in conformational structures of oligosaccharides as their size increases.

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11. I am grateful to my supervisor, Antony Fairbanks, for a supply of tetraacetate **134**

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Chapter 6. The Synthesis of α-Glucofuranosides and β-Rhamnosides *via* Allyl-Mediated IAD

6.1 Introduction

Nature has a very large number of sugar monomers units at its disposal for the construction of poly- and oligosaccharide structures. Some of the most complex carbohydrate structures in nature are the polysaccharides from bacterial capsules and cell walls.[1] It seems to be important in these systems for the bacteria to use unusual structures, which afford them immunological specificity. Often the sugar monomers are derivitised to form, for example, deoxy-, amino- or *O*-methylated analogues.[2] In addition, many of the sugars found therein, for example L-rhamnose, are not found in mammals (Figure 6.1).[3]

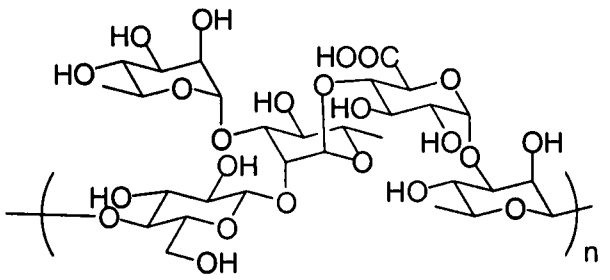
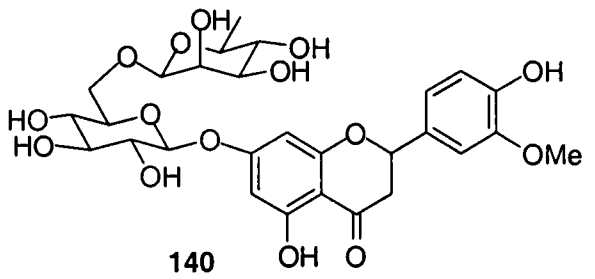


Figure 6.1: The repeating unit of the capsular polysaccharide from Klebsiella K17. Note the α and β-*rhamno* linkages[4]

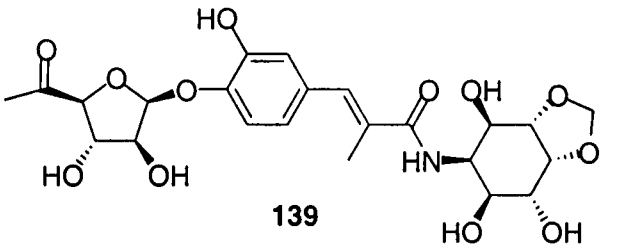
There is an increasing interest in glycobiology in the role and synthesis of furanoside-containing oligosaccharides. In particular, galactofuranosides[5] and arabinofuranosides[1] have been reported as major constituents of

polysaccharides in lower organisms. In contrast, galactose is only known to occur in mammalian systems in its pyranose form.[3]

Such unusual sugars are also common in naturally occurring antibiotics, for example Hygromycin A **139**,[6] which contains a 1,2-*cis*-linked furanoside (Figure 6.2), or as components of many naturally occurring oligosaccharides or glycoconjugates, such as Clematine **140** (Figure 6.2) which was isolated from a traditional Chinese medicine.[7]



140



139

Figure 6.2: Structures of Clematine **140** and Hygromycin A **139**

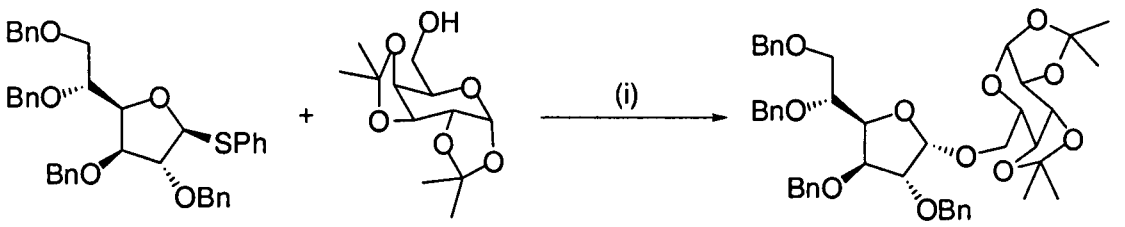
The fact that many of these sugar monomers are non-mammalian lends them a special significance: as these residues are only found in lower organisms, they could be potent antigens, and oligosaccharides containing them may be useful targets in the treatment of fungal or parasitic disease.

6.1.1 Furanoside Synthesis

Synthetic routes towards furanosides have not been investigated as fully as for their pyranose analogues and the stereoselective synthesis of the furanosidic bond is still rather problematic. 1,2-*Trans* bonds may generally still be formed by the use of a participating protecting group at the 2-position,[8] but stereoselective glycosylation in the absence of participating

protection, in particular the formation of 1,2-*cis* bonds, is considerably more difficult.

Recent reports of work to provide a solution to the problem of 1,2-*cis* bond formation in furanose systems include the adaptation of Ogawa's IAD approach to β-fructo- and βarabinofuranoside synthesis (as outlined in Chapter 1).[8,9] Also of interest was the synthesis by Plusquellec of various 1,2-*cis* furanosides from 1,2-*trans* thioglycoside donors, using a weak activator to induce an S_N2-like reaction (Scheme 6.1).[10]



Scheme 6.1: Plusquellec's stereoselective synthesis of 1,2-*cis*-hexofuranosides
(i) NIS, $Sn(OTf)_2$, DCM, 4Å, 0°C, 87% (α/β, 4.6:1)

It was envisaged that allyl-mediated IAD might provide an effective route to 1,2-*cis* glycosides other than the α-gluco- and β-mannopyranosides described thus far. Therefore in order to investigate the wider scope of the methodology, the syntheses of 2-*O*-allyl protected rhamnosyl **141** and glucofuranosyl **142** donors were undertaken (Figure 6.3).

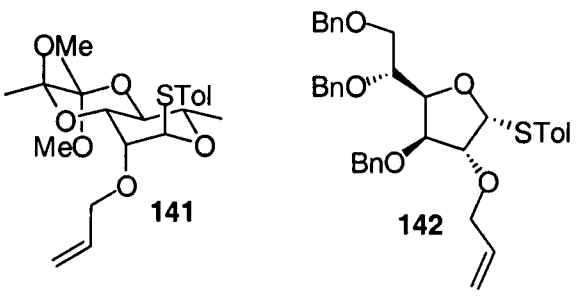


Figure 6.3: 2-*O*-allyl protected rhamnosyl **141** and glucofuranosyl **142** donors

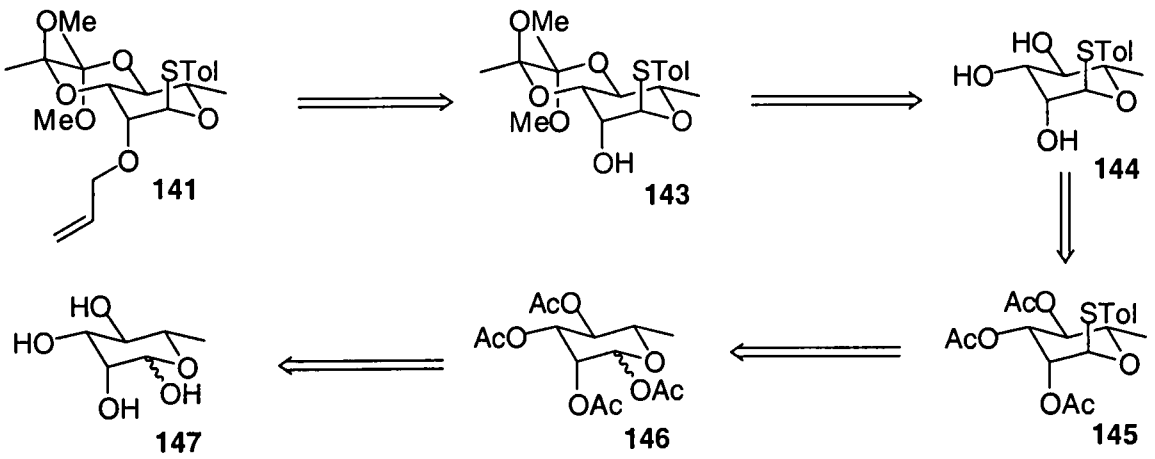
6.2 Results and Discussion

6.2.1 β-Rhamnosides

6.2.1.1 Synthesis of a 2-*O*-Allyl-3,4-BDA protected Rhamnosyl Donor 141

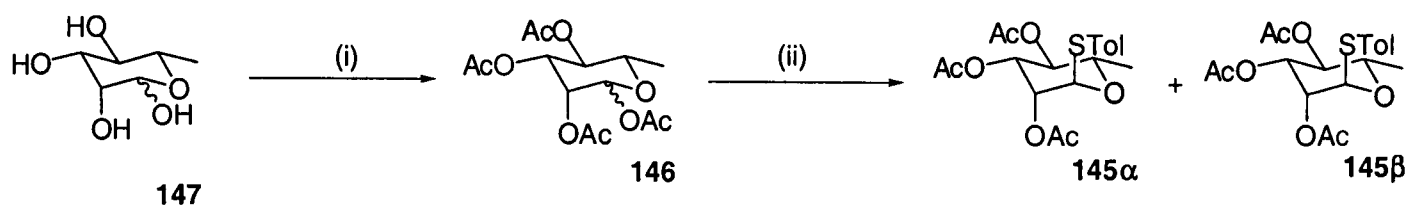
As rhamnose is a 6-deoxy sugar, synthesis of a 2-*O*-allyl protected donor only requires differentiation of the axial OH-2 from the equatorial 3- and 4-hydroxyl groups. This could be achieved by the use of a BDA protecting group.[11]

In addition, this approach has the advantage of providing the opportunity to investigate the potential of IAD using a donor with a different protecting group pattern from the benzyl ethers as used thus far. A thio leaving group may be introduced by a Lewis acid mediated glycosylation of an anomeric acetate **146**. It was decided to use a thiotolyl (*para*-thiocresyl) anomeric leaving group. Thiotolyl glycosides have been reported to be similar in reactivity to thiophenyl glycosides, and have recently received much attention in the literature.[12] An advantage of this leaving group is that the precursor, *para*-thiocresol, is much less smelly than other commonly used thiols such as thiophenol (Scheme 6.2).[13]



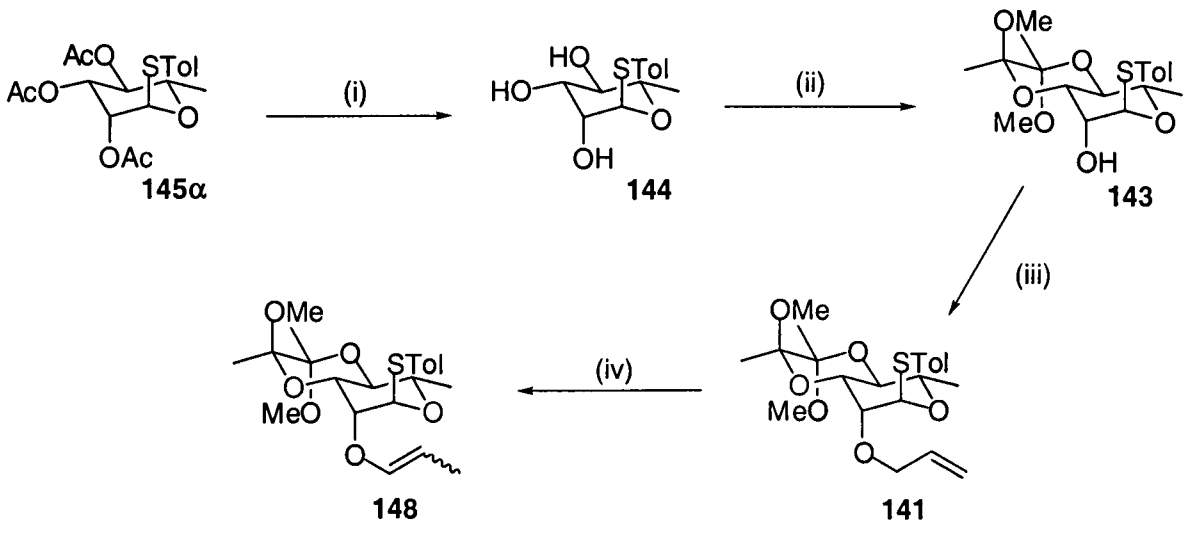
Scheme 6.2: Retrosynthesis of BDA protected *rhamno* donor **141**

Consequently rhamnose **147** was peracetylated using acetic anhydride in combination with iodine.[14] Tetraacetate **146** was treated with *para*-thiocresol and $BF_3.OEt_2$[15] to give thioglycoside **145** as a separable 3.6:1 α/β mixture (Scheme 6.3).



Scheme 6.3: (i) I_2, Ac_2O, RT; (ii) TolSH, $BF_3.OEt_2$, DCM, RT, 76% over 2 steps (α/β, 3.6:1)

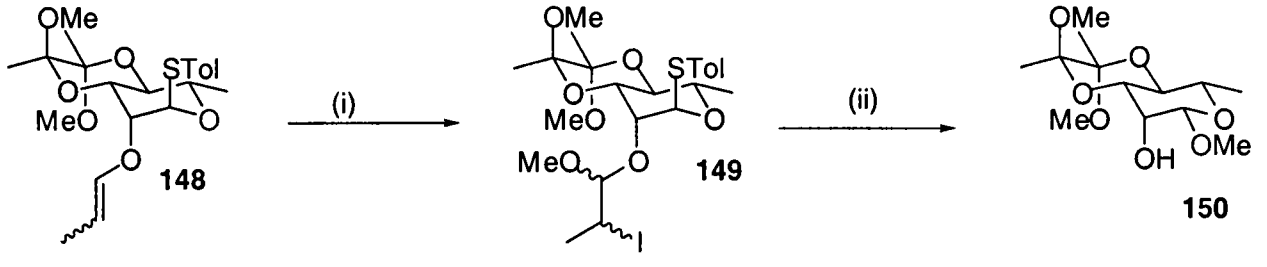
Deacetylation under Zemplen conditions[16] cleanly gave triol **144** in excellent yield. Treatment of triol **144** with butanedione and trimethyl orthoformate in methanol, in the presence of an acid catalyst as described by Ley,[11] afforded the selectively 3,4-protected derivative **143** in 74% yield. Allylation under standard conditions[17] to give fully protected sugar **141** was followed by isomerisation[18] to the enol ethers **148.** In this case the *E* and *Z* isomers were partially separated by column chromatography (Scheme 6.4).



Scheme 6.4: (i) Na, MeOH, RT, 97%; (ii) $CH_3C(O)C(O)CH_3$, $CH(OMe)_3$, CSA, MeOH, 75°C, 74%; (iii) allyl bromide, DMF, NaH, 0°C, 83%; (iv) Wilkinson's catalyst, BuLi, THF, 70°C, 95%

6.2.1.2 Tethering and Glycosylation Reactions Using BDA-protected Rhamnosyl Donor

Enol ethers **148** were treated with NIS and methanol under standard tethering conditions[19] and the desired mixed acetals **149** were obtained in good yield (Scheme 6.5). However, when tethered material **149** was treated under conditions suitable for the activation of thioglycosides,[20] while no other glycosylated products were seen, the desired methyl β-rhamnoside **150** was only obtained in poor yields (Scheme 6.5, Table 6.1).



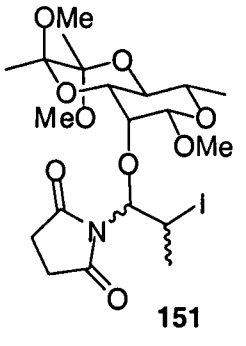
Scheme 6.5: (i) NIS, MeOH, DCE, -40°C→RT, 96%; (ii) see Table 6.1

Entry	Conc. (M)	Conditions	Comments	time	Yield of β-rhamnoside **150**
1	0.04	NIS, DTBMP, AgOTf, DCE, 50°C.	β-rhamnoside **150** isolated	19 h	29%[a]
2	0.11	NIS, DTBMP, AgOTf, DCE, 50°C.	No β-rhamnoside **150** isolated. Succinimide trapped species **151** (2 isomers, 34%) isolated. Treatment with LiOH gave the desired β-rhamnoside **150** (62%).	20 min	21% overall
3		NIS, DTBMP, AgOTf, DCE, RT.	very slow reaction		
4	0.04	I_2, DTBMP, AgOTf, DCE, 50°C.	β-rhamnoside **150** isolated.	2 h	12%

Table 6.1: Glycosylation reactions of methanol tethered species **149**

[a] In this case, a small quantity of succinimide was inseparable from the glycoside.

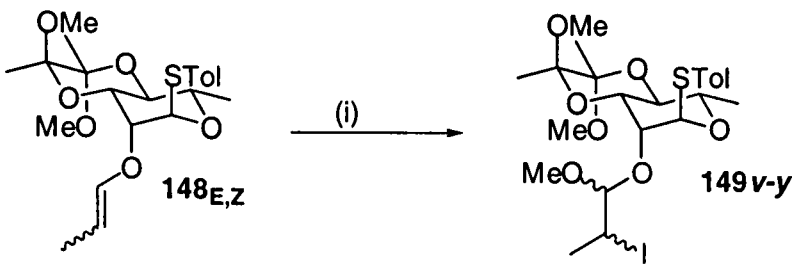
It was found that it was necessary to heat the reaction in order for it to proceed at an appreciable rate (Table 6.1, entries 2, 3). Furthermore, the formation of succinimide-trapped material **151** (Figure 6.4) appears to be concentration dependent (Table 6.1, entries 1, 2). Nevertheless, the low yields are difficult to explain, as no other major products were isolated.



151

Figure 6.4: Succinimide-trapped material **151**

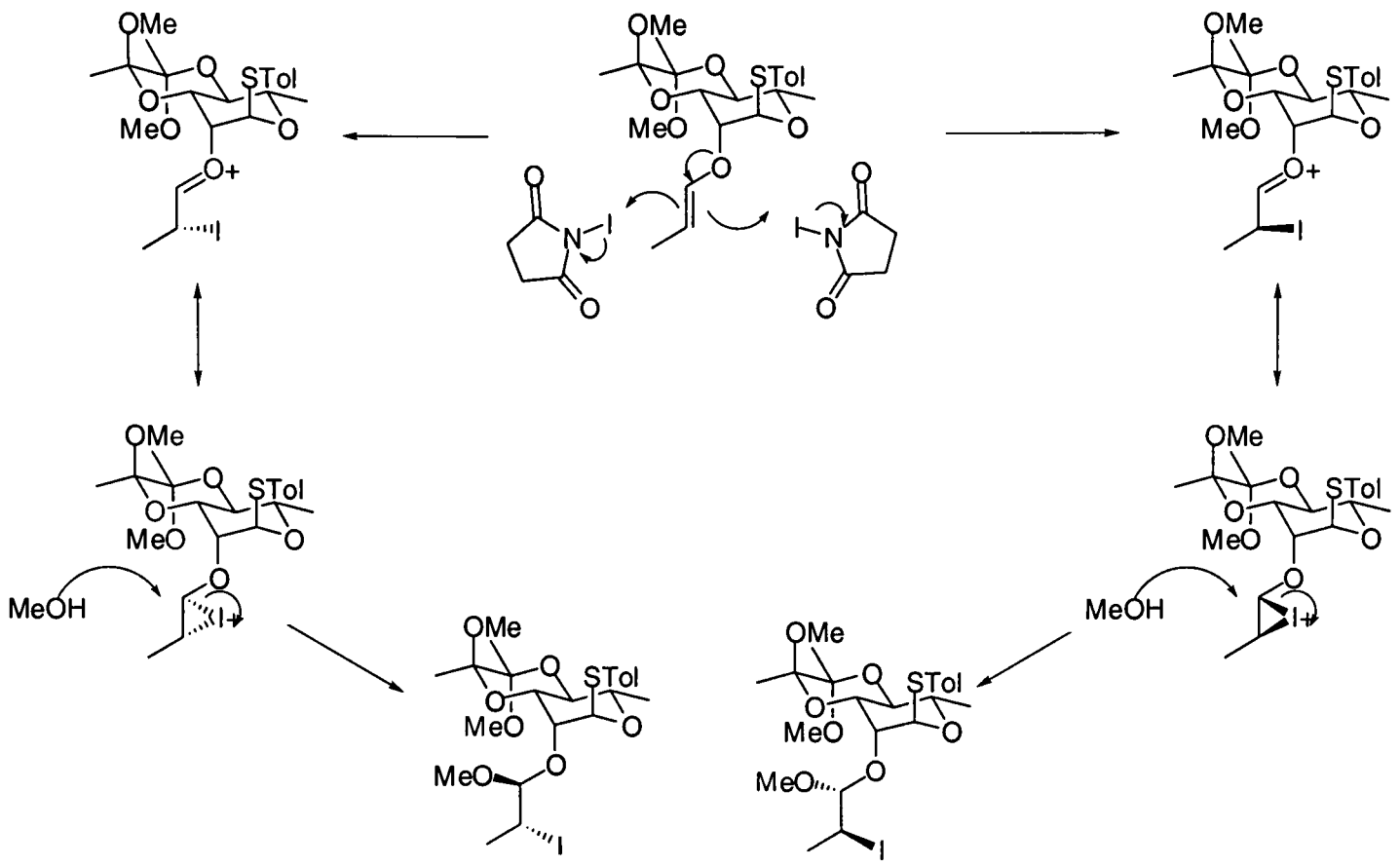
As the *E* and *Z* isomers of the enol ethers **148** were separable by column chromatography, it was decided to treat the pure individual isomers under NIS-mediated tethering conditions in order to further probe the mechanism of the tethering reaction. Consequently, enol ethers $\mathbf{148_E}$ and $\mathbf{148_Z}$ were each treated with NIS in DCE using methanol **3a** as an aglycon alcohol. The results are shown in Table 6.2 (entries 3,4).



entry	E:Z	*v* (5.46)[a]	*w* (5.43)[a]	*x* (5.41)[a]	*y* (5.36)[a]
1	33:67	6	17	60	17
2	68:32	17	8	25	50
3	0:100	3	23	71	3
4	100:0	22	4	4	70

Table 6.2: diastereomeric ratios for mixed acetals **149v-y** from tethering of methanol **3a** to BDA-protected *rhamno* enol ethers **148**. [a] Identified by integration of H-1 signals in the ^{1}H NMR; Assignment (*v*, *w*, *x*, *y*) of each diastereomer is arbitrarily based on the chemical shift of H-1, given in parentheses.

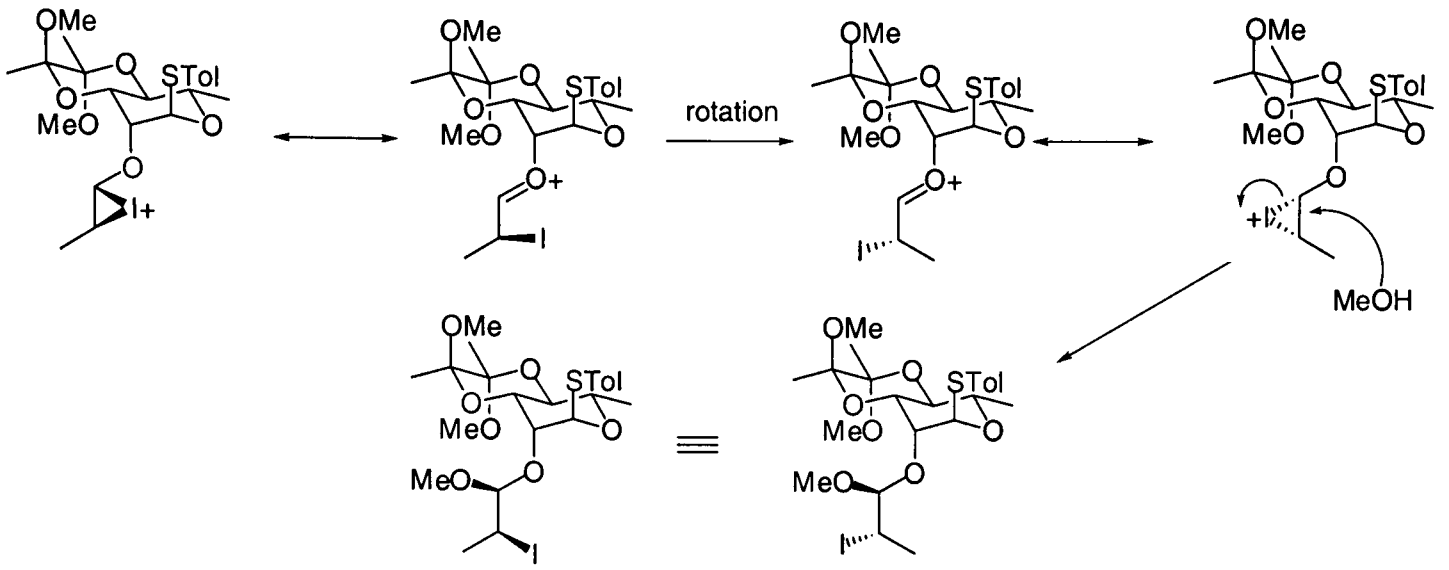
From these results, it is clear that the diastereomeric makeup of the starting enol ethers is key to determining the ratio of mixed acetal products in an NIS-mediated tethering reaction. When the *E* isomer $\mathbf{148_E}$ was used, two of the possible four isomers of mixed acetal **149*v***, **149*y*** predominated (Table 6.2, entry 4), whereas the use of the *Z* isomer $\mathbf{148_Z}$ gave the other two **149*w***, **149*x*** (Table 6.2, entry 3). A possible mechanistic explanation is outlined in Scheme 6.6.



Scheme 6.6: Proposed mechanism for the formation of the *trans* addition products **149*v*** and **149*y*** from the *E* enol ether $\mathbf{148_E}$

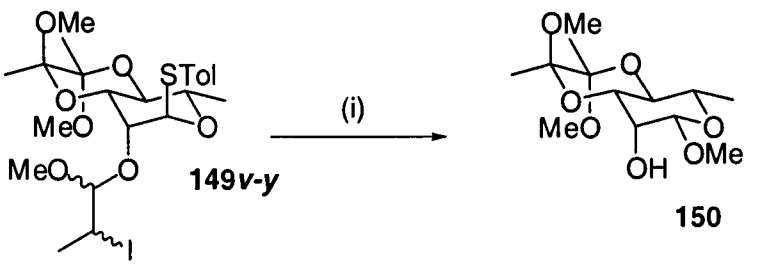
Addition of I^+ to the enol ether **148** results in the cationic species (eg **152**), which has two resonance forms. The bridged iodonium mesomer (eg **152′**) restricts rotation about the OCH–$CHCH_3$ bond. Consequently, nucleophilic attack from the opposite face to the iodine, resulting in an antiperiplanar ring opening of the iodonium ion gives the overall *trans* addition product, with the two isomers resulting from the different orientation of original attack by I^+. It is to be expected that the proximity to the sugar ring will make one face of the enol ether less hindered than the other. Initial electrophilic attack occurs predominantly at the less hindered face, resulting in an unequal distribution of the *trans* addition products. Also though, a small amount of the two minor isomers, which it follows result from overall *cis* addition, is seen in the cases of both *E* and *Z* enol ethers **148**. These probably arise from

some slow rotation about the OCH–$CHCH_3$ bond taking place before addition of the nucleophile (Scheme 6.7).



Scheme 6.7: Proposed mechanism for the formation of a *cis* addition product from the *E* enol ether $\mathbf{148_E}$

By this method of using pure isomers of the enol ethers **148**, it proved possible to isolate samples of mixed acetals **149** with each of the four diastereomers as the major component. It was realised that subjection of these mixed acetals individually to the glycosylation conditions would then show whether the low yields of β-rhamnosides in this case are due to the rather lower propensities of certain isomers to glycosylate than others, or indeed whether every isomer results in the glycoside at all. Consequently mixed acetals **149*v-y*** were treated with NIS, silver triflate and DTBMP and in all cases the β-rhamnoside **150** was isolated in rather low yields (Table 6.3).



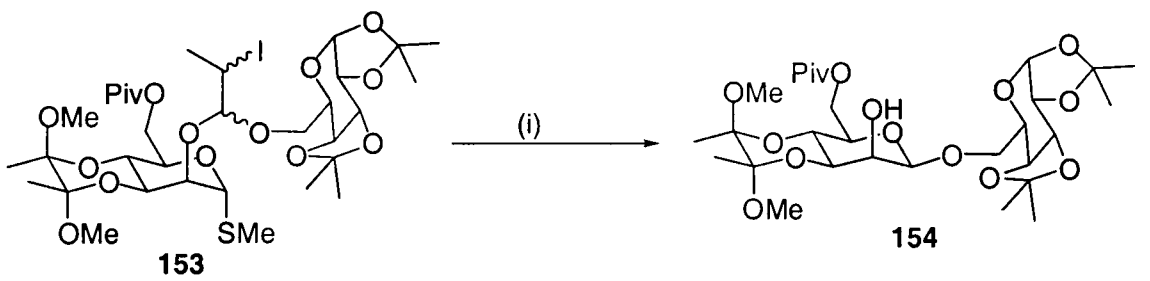
Entry	Starting material **149**	Yield of β-rhamnoside **150**[a]
1	*v*:*w*, 88:12	50%
2	*w*:*v*, 88:12	39%
3	*x*:*y*, 96:4	27%
4	*y*:*x*, 94:6	35%

Table 6.3: yields for the glycosylation of individual mixed acetal diastereomers **149*v-y***

[a] In all cases, small quantities of succinimide were inseparable from the glycoside.

It is clear then that while the yields do vary significantly, each of the diastereomers **149*v-y*** does glycosylate to give the desired 1,2-*cis* glycoside, and the answer to the rather low glycosylation yields in this system has not been found.

Concomitant with this work, a co-worker investigating the potential of allyl-mediated IAD on a BDA-protected *manno* donor **153** also only obtained low yields in a glycosylation reaction (Scheme 6.8).[21]

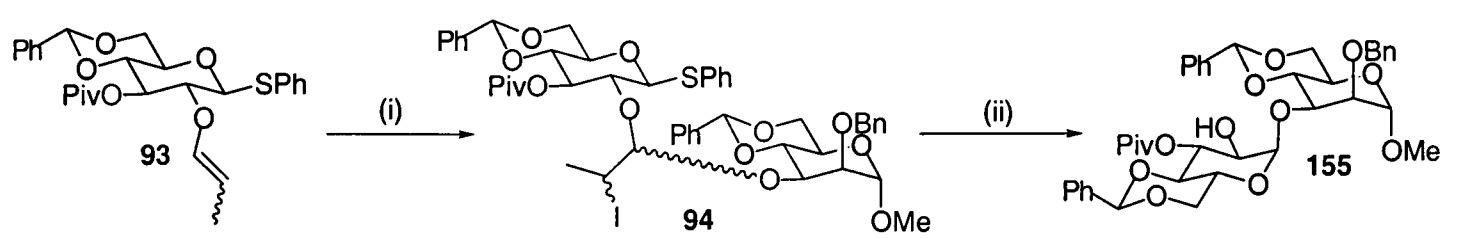


Scheme 6.8: Chambers' BDA-protected β-mannoside synthesis

(i) MeOTf, DTBMP, DCE, RT, 41%

That BDA-protected IAD should be lower-yielding than the benzyl-protected analogue is in stark contrast to Ogawa's work: he found that cyclic 4,6-protection was necessary order to obtain good yields in PMB-derived IAD, and attributed this to the benefits of having a more rigid donor.[22]

4,6-Protection of the *rhamno* system is impossible, but a benzylidene-protected thiophenyl *gluco* donor **93** was synthesised.[23] NIS-mediated tethering of the secondary carbohydrate aglycon **3g** to donor **93** was carried out in DCM in good yield. In this case, when the resulting mixed acetals **94** were treated with NIS and silver triflate in the presence of a hindered base, the α-linked disaccharide **155** was formed in good yield as a single anomer (Scheme 6.9).



Scheme 6.9: (i) NIS, **3g**, DTBMP, CH_2Cl_2, -40°C→RT, 60%; (ii) NIS, DTBMP, AgOTf, DCE, RT, 70%

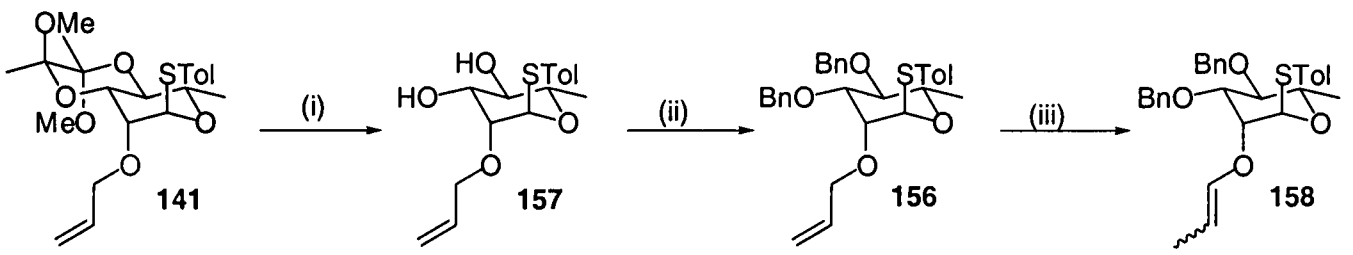
Apparently the 4,6-benzylidene protection is compatible with a high-yielding glycosylation reaction, and this suggests that the low yields from the BDA-protected donor stems from some factor other than ring-rigidity.

It was decided to synthesise a benzyl ether protected rhamnosyl donor.

6.2.1.3 Synthesis of a 2-*O*-Allyl-3,4-di-*O*-Benzyl Protected Rhamnosyl Donor 156

As there was a large quantity of BDA-protected donor **141** in hand, in which the 3- and 4-positions had already been differentiated from the allyl-protected 2-position, it was decided to use this as a starting point.

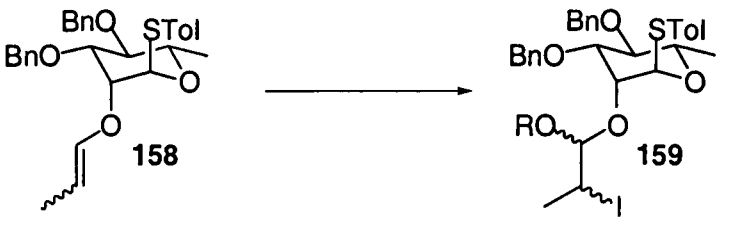
Thus, thioglycoside **141** was treated with TFA to afford diol **157** in 95% yield. Perbenzylation[24] gave the benzyl-protected donor **156**, which was isomerised to the enol ethers **158** under standard conditions[18] (Scheme 6.10).



Scheme 6.10: (i) TFA:H_2O (9:1), 95%; (ii) BnBr, DMF, NaH, 0°C, 88%; (iii) Wilkinson's catalyst, BuLi, THF, 70°C, 80%

6.2.1.4 Tethering and Glycosylation Reactions Using Benzyl-protected Rhamnosyl Donor

NIS-mediated tethering of aglycon alcohols **3a,f,g,i** to *rhamno* enol ethers **158** was undertaken either under standard NIS-mediated conditions[19] (Table 6.4, entries 1, 2) or using iodine, siver triflate and DTBMP (as described in Chapter 4) (Table 6.4, entries 3, 4), and good yields of the mixed acetals **159** were obtained.



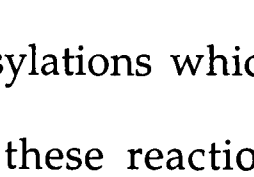
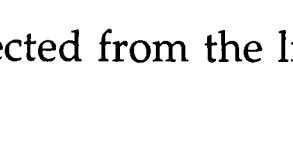
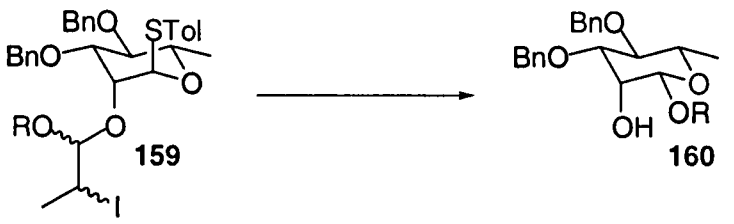
Entry	ROH	eq	Activator / eq	solvent	time	T/°C	Product/yield of mixed acetals
1	MeOH **3a**	1.5	NIS / 3	DCE	1 h	-40→RT	**159a** / 88%
2	 **3f**	2	NIS / 3	DCE	21 h	-40→RT	**159f** / 75%
3	 **3g**	1.05	I_2, AgOTf, DTBMP / 1.3	DCM	6 h 30	-78→RT	**159g** / 82%
4	**3i**	1.05	I_2, AgOTf, DTBMP / 1.3	DCM	6 h 45	-78→RT	**159i** / 69%

Table 6.4: Benzyl-protected rhamnose tethering reactions

Pleasingly, subjection of methanol- **159a** and primary carbohydrate- **159f** tethered materials to thioglycoside activation conditions[20] cleanly furnished the β-rhamnosides **160** in good yield and with no 1,2-*trans* anomers seen (Table 6.5, entries 1, 2). The stereochemistry of the glycosides was assigned by measurement of $^1J_{C\text{-}1,H\text{-}1}$, which was found to be <160 Hz in all cases.[25] Interestingly, NIS/AgOTf seems to be a more efficient activator than MeOTf in this system (Table 6.5, entries 2, 3). In contrast to the BDA-protected glycosylations which required heating in order for efficient reaction to be seen, these reactions were carried out at room temperature. This is as expected from the literature precedent for 'armed' benzylated donors being

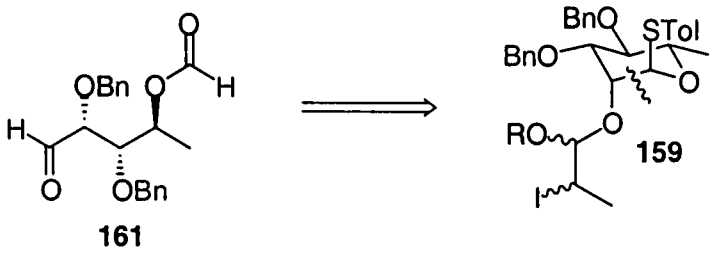
more reactive than their torsionally deactivated BDA-protected counterparts.[26]



Entry	Starting material / R	Conditions	Time	Product/yield of 1,2-*cis* glycoside
1	**159a** / Me	NIS, AgOTf, DTBMP, DCE, 50°C	3 h 30	**160a** / 54%
2	**159f**	NIS, AgOTf, DTBMP, DCE, RT	18 h	**160f** / 62%
3	**159f**	MeOTf, DTBMP, DCE, RT	72 h	Very little reaction
4	**159i**	NIS, AgOTf, DTBMP, DCE, RT	2 h 20	**160i** / 29%

Table 6.5: Benzyl-protected β-rhamnosylation reactions

However, when the steroid-tethered material **159i** was treated under the same conditions, only a relatively poor yield of the β-rhamnoside **160i** was obtained. A quantity of the steroid alcohol **3i** (7%) was isolated from the reaction mixture, along with a rather unusual by-product, which had spectral data consistent with the *arabino* derivative **161**, formed in 7% yield. Such a species would result from the oxidative cleavage of the C-1, C-2 bond, although the precise mechanism for this reaction is not clear (Scheme 6.11).



Scheme 6.11: Formation of a 4-*O*-formyl protected *arabino* derivative from the oxidative cleavage of the *rhamno* C-1, C-2 bond

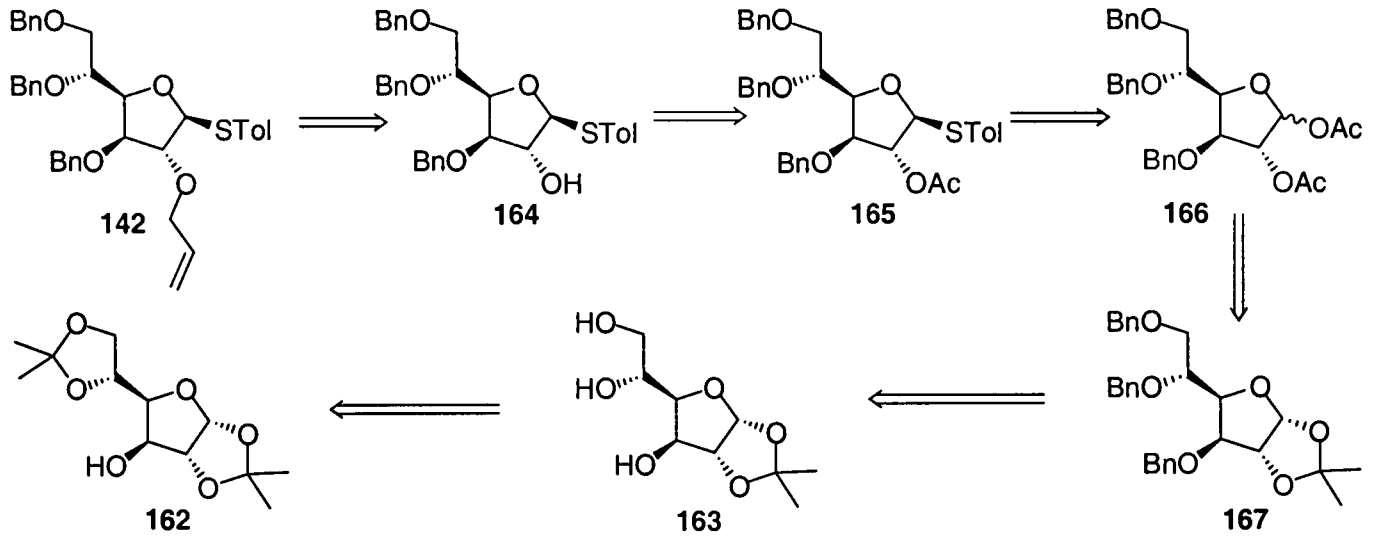
For the case of the tethered material bearing a secondary carbohydrate **159g**, again the aglycon alcohol **3g** and the same by-product **161** were isolated from the glycosylation reaction, but now as major components in the product mixture, being formed in 54% and *ca* 60% yields respectively.[27] In addition, if rhamnoside **160g** was formed at all, it could not be separated by column chromatography from compounds still containing the tether as shown by ^{1}H NMR spectroscopy.

It is not clear why the *rhamno* glycosylation reactions are not as clean as their *gluco*, or particularly *manno* counterparts. The reason could lie with the choice of the thiotolyl leaving group, or the combination of NIS and silver triflate, whose mechanism of action has not been elucidated, as activator. However, the successful results of Seward using the same leaving group and activator in a benzyl-protected *manno* system, although rather limited, do suggest that these are not valid grounds for complaint.[28] Further investigation is needed to find the root of the problem.

6.2.2 α-Glucofuranosides

6.2.2.1 Synthesis of a 2-*O*-Allyl Protected Glucofuranosyl Donor 142

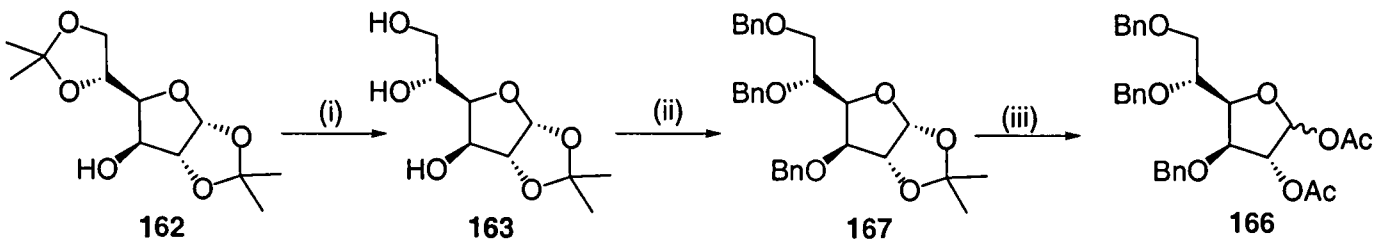
In order to investigate the potential of allyl-mediated IAD as a tool for the synthesis of oligofuranoside systems, it was necessary to synthesise a glycofuranosyl donor bearing 2-*O*-allyl protection and with the remaining hydroxyl groups differentially protected. Again it was decided to use a thiotolyl glycoside as donor. A retrosynthesis of such a glucofuranosyl donor **142** is outlined in Scheme 6.12. Differentiation of the 3-, 5- and 6-positions is obtained by the known selective hydrolysis of the 5,6-acetonide in the presence of the 1,2-ring of diacetone glucose **162** to give triol **163**.[1] Crucially, the potentially problematic formation of the furanose ring is taken care of by the use of diacetone glucose **162** as commercially available starting material.



Scheme 6.12: Retrosynthesis of glucofuranosyl donor **142**

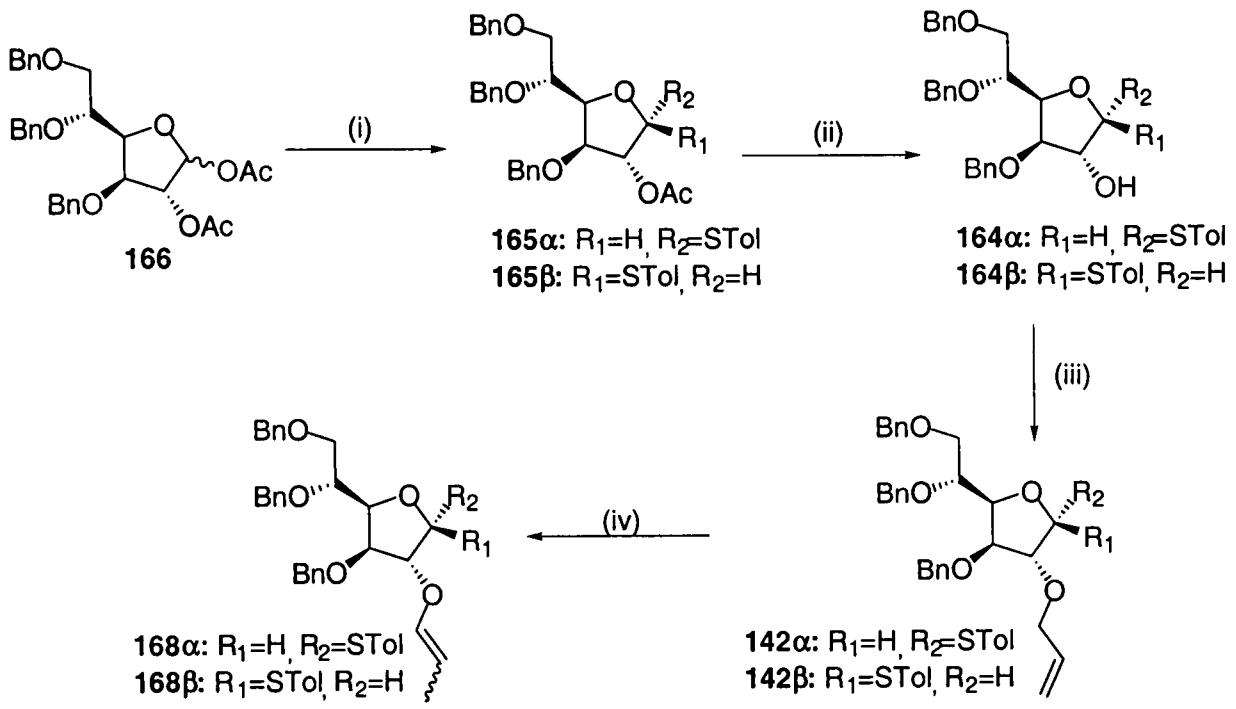
Consequently diacetone glucose **162** was treated with acetic acid to give the selectively deprotected triol **163** in 72% yield.[29] Subsequent perbenzylation[24] of triol **163** gave the fully protected sugar **167.** Acid-mediated deprotection

and acetylation with acetic anhydride and pyridine gave diacetate **166** as a 1:1 α/β mixture (Scheme 6.13).[30]



Scheme 6.13: (i) 75% AcOH, RT, 72%; (ii) BnBr, NaH, DMF, 0°C; (iii) 60% AcOH, 80°C; Ac_2O, pyridine, RT, 69% over 3 steps

Treatment of diacetate **166** with *para*-thiocresol at room temperature in the presence of $BF_3.OEt_2$[15] gave thioglycoside **165** as a disappointing anomeric mixture (1.3:1, β/α)in a poor 31% yield. The anomers were separable by column chromatography. Conducting the reaction at lower temperature gave increased yield and selectivity (58%, 50:1 β/α) (Scheme 6.14). It was decided to investigate the IAD reaction on both α and β donors. Thus amine-mediated deacetylation[31] of **165α** and **165β** gave **164α** and **164β** respectively. Subsequent allylation[17] and isomerisation[18] under standard conditions gave enol ethers **168α** and **168β** in good yields (Scheme 6.14).

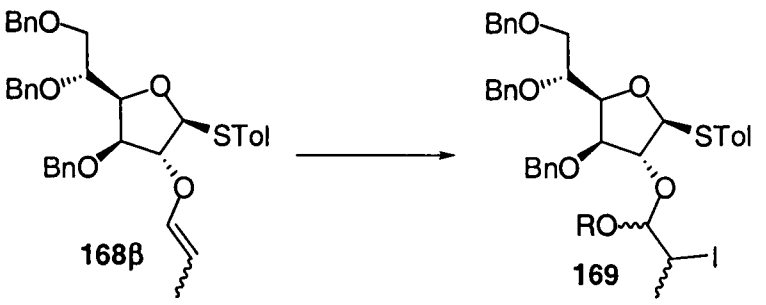


Scheme 6.14: (i) STolH, $BF_3.OEt_2$, -30°C, 58% (β/α, 50:1); (ii) $^nPrNH_2$, MeOH, THF, RT, **164α**, 88%; **164β**, 91%; (vi) allyl bromide, DMF, NaH, 0°C, **142α**, 89%; **142β**, 94%; (vii) Wilkinson's catalyst, BuLi, THF, 70°C, **168α**, 90%, **168β**, 96%

The stereochemistry of **165α**, **165β**, **164α** and **164β** was determined by NOE experiments.[32] In addition $^3J_{1,2}$ for **165α**, **164α**, and **142α** were 4.0-4.6 Hz, whereas for **165β**, **164β**, and **142β** were 1.4-2.4 Hz, thus confirming these assignments.[10, 33]

6.2.2.2 Tethering and Glycosylation Reactions on a Glucofuranose System

Tethering reactions of various aglycon alcohols **3d,e,g** to β-*gluco* enol ethers **168β** were conducted both under NIS-mediated conditions[19] (Table 6.6, entries 1, 2), and by the use of iodine, silver triflate and the hindered base (as described in Chapter 4) (Table 6.6, entries 3, 4), to form mixed acetals **169** in good yield.



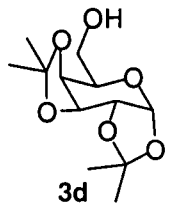
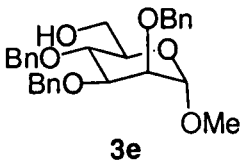
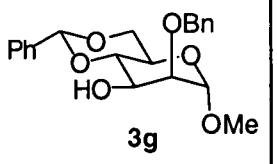
Entry	ROH	eq	Activator / eq	solvent	time	T/°C	Product/yield of mixed acetals
1	 3d	2	NIS / 3	DCE	2 h 30	-40→RT	**169d** / 75%
2	 3e	2	NIS / 3	DCE	4 h	-40→RT	**169e** / 53%
3	**3e**	1.05	I_2, AgOTf, DTBMP / 1.3	DCM	18 h	-78→RT	**169e** / 64%
4	 3g	1.05	I_2, AgOTf, DTBMP / 1.3	DCM	17 h	-78→RT	**169g** / 88%

Table 6.6: glucofuranose tethering reactions

In the cases where NIS was used, unusually, the reaction mixtures turned brown. It was thought that this could have been due to partial activation of the reactive furanosyl donor, although no glycosylated products were isolated. Changing to the alternative source of I^+ gave a rather higher yield (Table 6.6, *cf* entries 2, 3).

Treatment of the DAG-tethered material **169d** under activation conditions for thioglycosides, ie NIS in combination with silver triflate and DTBMP,[20] resulted in the formation of the α-glucofuranoside **170d**, as a single anomer,

in good yield (Table 6.7, entry 1). The anomeric stereochemistry of this and the other α-*glucofurano* disaccharides **170** (*vide infra*) was determined by the $^{3}J_{H1,H2}$ coupling constant, which was between 4.3 and 4.5 Hz in all cases.[10, 33]

When mannose-tethered material **169e** was treated under the same conditions, pleasingly again only a single α anomer of the glycosylated product **170e** was formed, but this time in a rather poor 35% yield (Table 6.7, entry 2). A by-product isolated from this glycosylation reaction had a mass spectrum showing M=1080, consistent with the glycosylated hemiacetal **171** (Figure 6.5). However, on treatment with TFA to hydrolyse the tether, only the aglycon alcohol **3** was isolated. It is possible that the newly-formed glucofuranosidic bond is labile under these acidic conditions. Oscarsson made a similar observation regarding his attempted cleavage of succinimide-trapped materials in his fructofuranoside IAD reactions.[9] Some aglycon alcohol **3e** was also isolated from the glycosylation reaction of **169e**.

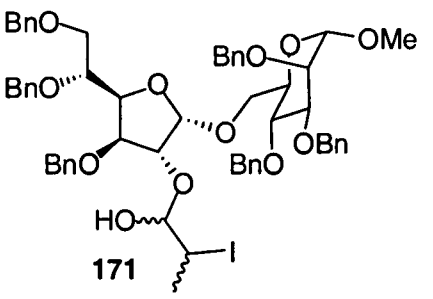
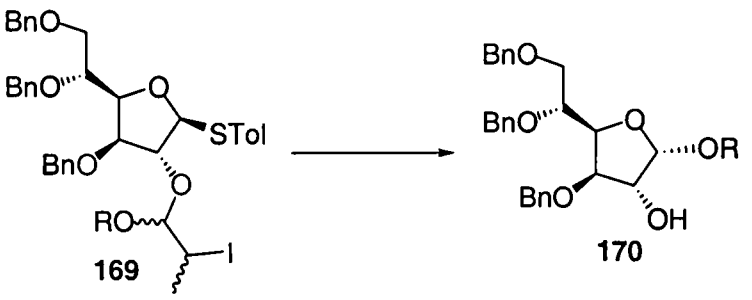


Figure 6.5: glycosylated material with OH trapped in the tether

Treatment of the secondary carbohydrate-tethered material **169g** with NIS, siver triflate and DTBMP resulted in a complex mixture of products. While the 1,2-*cis* glycoside **170g** was formed, as shown by ^{1}H NMR spectroscopy, it could not be separated from the also-formed aglycon alcohol **3g**. The yield was also low (<31%), and many unidentified products were seen (Table 6.7, entry 3).

The use of DMTST as an activator[9] gave a much cleaner glycosylation of **170g**, and the 1,2-*cis* glycoside was isolated without any formation of the aglycon alcohol (Table 6.7, entry 4). However, the yield was still not brilliant, and many unidentified products were seen.



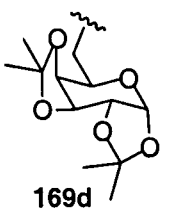
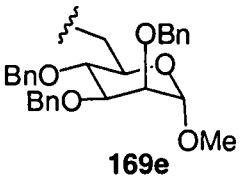
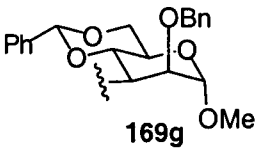
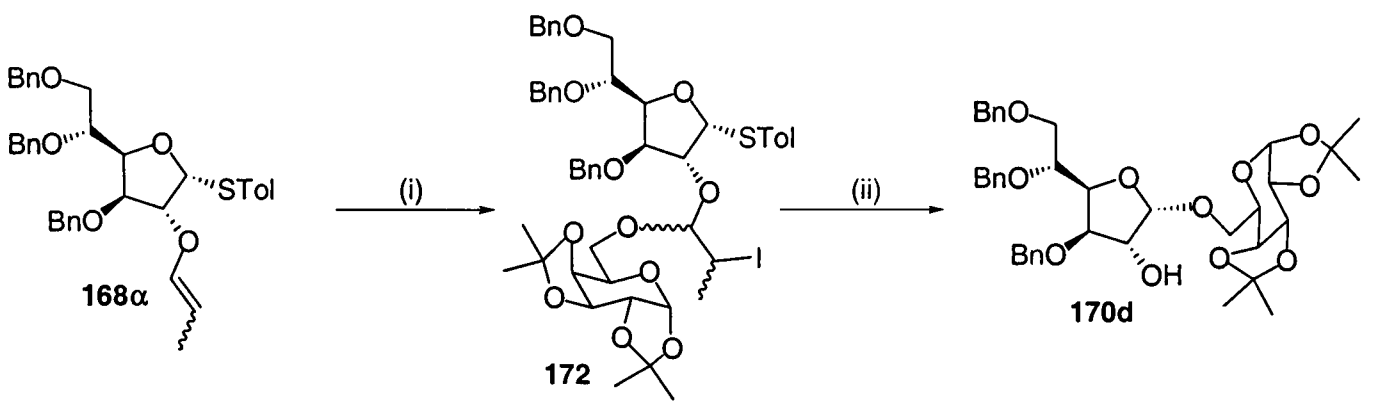
Entry	Starting material / R	Conditions	t	Product/yield of 1,2-*cis* glycoside
1	 **169d**	NIS, AgOTf, DTBMP, DCE, RT	6 h	**170d** / 70%
2	 **169e**	NIS, AgOTf, DTBMP, DCE, RT	5 h	**170e** / 39%
3	**169e**	NIS, AgOTf, DTBMP, DCE, RT		**170g** / <31%[a]
4	 **169g**	MeOTf, Me_2S_2 DTBMP, DCM, RT	5 h	**170g** / 32%

Table 6.7: glucofuranosylation reactions

[a] The disaccharide **170g** could not be separated from the also-formed aglycon **3g**

NIS-mediated tethering of DAG to α-*gluco* enol ethers **168α** gave mixed acetals **172** in a poor 25% yield (Scheme 6.15). This tethering reaction also turned brown, but no trace of glycosylated products could be detected by tlc, and furthermore the donor alcohol **164** was formed in 50% yield, indicating

that hydrolysis of the enol ethers was possibly the most prevalent competing reaction. The tethered material **172** was subjected to the activation conditions, and the α-glucofuranoside **170d** was isolated as the sole glycosylated product, but then only in poor yield. Again, a small quantity of free aglycon **3d** was isolated from the glycosylation reaction.



Scheme 6.15: (i) NIS, DCE, 4Å, -40→RT, 25%; (ii) NIS, AgOTf, DTBMP, DCE, RT, 26%

In summary, glycosylation reactions in the glucofuranose system are still completely stereoselective, in the cases of both 1,2-*cis* and 1,2-*trans* glycosyl donors. However, side-reactions occurring under the glycosylation conditions leading to the decomposition of the tether and release of the aglycon alcohol appear to be prevalent in this system. The difficulties are further compounded by the instability of furanosides to treatment with TFA, so rendering the formation of trapped materials a more significant problem than in pyranoside synthesis. In all, the yields of the 1,2-*cis* glycosides are rather lower than hoped for.

The use of DMTST as an activator appears to show some promise, though, and could be a good starting point for the optimisation of the allyl-derived IAD procedure for the formation of 1,2-*cis* furanosidic bonds.

6.3 Conclusion

The potential of allyl-mediated IAD as a tool for the synthesis of α-glucofuranosyl and β-rhamnosyl bonds has been investigated. The use of iodine, silver triflate and the hindered base DTBMP as a synthetically useful source of I^+ for the tethering reaction has been demonstrated to good effect in both systems. In addition, glycosylation was stereospecific in all cases – only the 1,2-*cis* isomer of glycosylated product was isolated from all glycosylation reactions. The yields were good in certain cases – for benzyl-protected donors with primary aglycons – but for the formation of glycosides with secondary aglycons, the yields were somewhat disappointing. It is to be hoped that future work on these systems using a different leaving group or promoter could provide a solution to the problem of low glycosylation yields.

More generally, future work on the allyl-derived IAD system could include the synthesis of other significant α-glucoside or β-mannoside containing oligosaccharides, such as the complete pentasaccharide core (Figure 1.2). In addition, the use of vinyl glycosides as an even less sterically hindered enol ether (*cf* Figure 2.1) could improve the tethering reaction.

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Chapter 7. Experimental

7.1 General Experimental

Melting points were recorded on a Kofler hot block and are uncorrected. Proton nuclear magnetic resonance spectra were recorded on Bruker DPX 400 or AV 400 (400 MHz), Bruker AMX 500 or DRX 500 (500 MHz) or Bruker DPX 200, AC 200 or Varian Gemini 200 (200 MHz) spectrometers. Spectra were assigned using COSY, edited HSQC, HMQC and/or HMBC experiments. Carbon nuclear magnetic resonance spectra were recorded on Bruker DPX 400 or AV 400 (100.6 MHz), Bruker AMX 500 or DRX 500 (125.7 MHz) or Bruker DPX 200, AC 200 or Varian Gemini 200 (50.3 MHz) spectrometers. Multiplicities were assigned using APT or DEPT sequence. Proton-carbon coupling constants were measured either from proton-coupled carbon spectra (125.7 MHz) or from carbon-coupled HSQC spectra (400 MHz). Fluorine nuclear magnetic resonance spectra were recorded on a Bruker DPX 250 (235 MHz) spectrometer. All chemical shifts are quoted on the δ scale in ppm and coupling constants are quoted once. Residual signals from the solvents were used as an internal reference. Infrared spectra were recorded on a Perkin-Elmer 150 Fourier transform spectrophotometer. Low resolution mass spectra were obtained by atmospheric pressure chemical ionisation (APCI) on a Micromass Platform 1 APCI spectrometer; or by electrospray ionisation (ES) on a Micromass Platform 1 APCI spectrometer, or on a Micromass LCT spectrometer, or on a VG BioQ spectrometer, or by Dave Chambers on a

Micromass ZMD spectrometer, or by the EPSRC Mass Spectrometry Service Centre, Department of Chemistry, University of Wales, Swansea, on a Micromass Quattro II spectrometer; or using chemical ionisation (CI) on a Micromass AutoSpec-oa Tof spectrometer, or by the EPSRC Mass Spectrometry Service Centre on a Micromass Quattro II spectrometer; or using solid probe temperature programmed field ionisation (TOF FI) on a Micromass GCT Tof spectrometer by the Inorganic Chemistry Laboratory. High-resolution mass spectra were performed on a Waters 2790-Micromass LCT electrospray ionisation mass spectrometer, or by the EPSRC Mass Spectrometry Service Centre on a MAT900 XLT electrospray ionisation mass spectrometer, or by the Inorganic Chemistry Laboratory using solid probe temperature programmed field ionisation (TOF FI) on a Micromass GCT Tof spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g/100 ml. Microanalyses were performed by the microanalytical services of Elemental Microanalysis Ltd., Devon. Thin layer chromatography (tlc) was carried out on Merck Kieselgel 0.22-0.25 mm thickness glass-backed sheets pre-coated with $60F_{254}$ silica. Plates were developed using 5% w/v ammonium molybdate in 2M sulfuric acid. Flash column chromatography was carried out using Sorbsil C60 40/60 silica. Solvents and reagents were dried and purified before use according to standard procedures; dichloromethane was distilled from CaH_2 immediately before use; acetonitrile was distilled from CaH_2 and stored over 4Å molecular sieves; methanol was distilled from NaH or anhydrous methanol was purchased from Acros; THF and ether were distilled from solutions of sodium benzophenone ketal immediately before

use; anhydrous DMF and anhydrous dichloroethane were purchased from Aldrich or Acros. Petrol refers to the fraction of light petroleum ether boiling in the range 40-60 °C. Reactions performed under an atmosphere of argon or hydrogen gas were maintained by an inflated balloon.

7.2 Experimental for Chapter 2

2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl bromide 42

1,2,3,4,6-Penta-*O*-acetyl-α-D-glucopyranose **43** (49.5 g, 127 mmol) was added portionwise to a stirred solution of HBr (33% in glacial acetic acid) (87.5 ml) at 0°C. The reaction mixture was allowed to warm to RT. After 45 min, tlc (petrol:ethyl acetate, 1:1) indicated formation of a product (R_f 0.5) and complete consumption of starting material (R_f 0.3). The reaction was quenched with ice water (200 ml) then extracted with CH_2Cl_2 (2 x 200 ml). The organic extracts were washed with $NaHCO_3$ (2 x 200 ml of a saturated aqueous solution), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was recrystallised from ether/petrol to afford 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **42** (46.7 g, 89%) as a white crystalline solid, m.p. 86-88 °C (ether/petrol) [Lit. 88-89 °C][1]; $[\alpha]_D^{22}$ +201 (*c*, 0.5 in $CHCl_3$) [Lit. +194 (*c*, 3.9 in $CHCl_3$)][1]; δ_H (200 MHz, $CDCl_3$) 2.05, 2.08, 2.12, 2.12 (12H, 4 x s, 4 x $COCH_3$), 4.10-4.26 (1H, m, H-6), 4.31-4.38 (2H, m, H-5, H-6'), 4.85 (1H, dd, $J_{1,2}$ 4.0 Hz, $J_{2,3}$ 10.0 Hz, H-2), 5.17 (1H, at, *J* 9.7 Hz, H-4), 5.57 (1H, at, *J* 9.7 Hz, H-3), 6.62 (1H, d, H-1).

3,4,6-Tri-O-acetyl-1,2-O-(exo-ethoxyethylidene)-α-D-glucopyranose 41

2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide **42** (53.0 g, 129 mmol), tetrabutyl ammonium bromide (12.5 g, 38.8 mmol), ethanol (11.8 ml, 206 mmol) and 2,4,6-collidine (20.5 ml, 155 mmol) were dissolved in freshly distilled CH_2Cl_2. The reaction mixture was stirred at 41 °C. After 4h 30 min, tlc

(petrol:ethyl acetate, 1:1) indicated formation of a product (R_f 0.49) and complete consumption of starting material (R_f 0.51). The reaction mixture was allowed to cool then diluted with CH_2Cl_2 (200 ml), washed with $NaHCO_3$ (200 ml of a saturated aqueous solution), water (200 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was recrystallised from ethanol/water to afford 3,4,6-tri-*O*-acetyl-1,2-*O*-(*exo*-ethoxyethylidene)-α-D-glucopyranose **41** (34.6 g, 71%) as a white crystalline solid, m.p. 94-95 °C (ethanol/water) [Lit. 95-96 °C][2]; $[\alpha]_D^{22}$ +31.2 (*c*, 0.5 in $CHCl_3$) [Lit. +34.0 (*c*, 1.0 in $CHCl_3$)][2]; δ_H (200 MHz, $CDCl_3$) 1.17 (3H, t, *J* 7.0 Hz, $OCH_2C\underline{H}_3$), 1.72 (3H, s, $C(O)_3CH_3$), 2.09, 2.10, 2.12 (9H, 3 x s, 3 x $COCH_3$), 3.53 (2H, q, $OC\underline{H}_2CH_3$), 3.84 (1H, dat, $J_{5,6}$ 4.6 Hz, *J* 9.7 Hz, H-5), 4.18-4.20 (2H, m, H-6, H-6′), 4.32 (1H, dd, $J_{1,2}$ 5.2 Hz, $J_{2,3}$ 3.0 Hz, H-2), 4.90 (1H, dd, $J_{3,4}$ 2.3 Hz, $J_{4,5}$ 9.7 Hz, H-4), 5.19 (1H, at, *J* 3.3 Hz, H-3), 5.72 (1H, d, H-1).

***3,4,6-Tri*-O-*benzyl*-1,2-O-(exo-*ethoxyethylidene*)-α-D-*glucopyranose* 40**

3,4,6-Tri-*O*-acetyl-1,2-*O*-(*exo*-ethoxyethylidene)-α-D-glucopyranose **41** (34.0 g, 90.4 mmol) was dissolved in methanol (430 ml) and cooled to 0 °C. Sodium (1.16 g, 50.4 mmol) was dissolved in methanol (70 ml) and added to the sugar solution by cannula under Ar. After 15 min, tlc (ethyl acetate:methanol, 4:1) indicated formation of a product (R_f 0.7) and complete consumption of starting material (R_f 0.9). The reaction mixture was concentrated *in vacuo*.

The residue was dissolved in anhydrous DMF (500 ml) and cooled to 0 °C. Benzyl bromide (48 ml, 410 mmol) was added then sodium hydride (60% in mineral oil) (21.7 g, 542 mmol) was added portionwise. After 15 h 30 min,

tlc (petrol:ethyl acetate, 3:1) indicated formation of a single product (R_f 0.5) and complete consumption of starting material (R_f 0). The reaction was quenched with methanol (150 ml) then concentrated *in vacuo*. The residue was partitioned between ether (200 ml) and water (200 ml). The aqueous layer was extracted with ether (200 ml) and the combined organic extracts washed with water (200 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by dry flash column chromatography (petrol→petrol:ethyl acetate, 1:1) to afford 3,4,6-tri-*O*-benzyl-1,2-*O*-(*exo*-ethoxyethylidene)-α-D-glucopyranose **40** (42.3g, 92%) as a pale yellow oil; $[\alpha]_D^{22}$ +34.9 (*c*, 1.75 in $CHCl_3$) [Lit. +34.8 (*c*, 1.1 in $CHCl_3$)][2]; δ_H (400 MHz, $CDCl_3$) 1.20 (3H, t, *J* 7.1 Hz, $OCH_2C\underline{H}_3$), 1.67 (3H, s, $C\underline{H}_3$), 3.51-3.59 (2H, m, $OC\underline{H}_2CH_3$), 3.65-3.69 (2H, m, H-6, H-6'), 3.71 (1H, dd, $J_{3,4}$ 4.4 Hz, $J_{4,5}$ 9.5 Hz, H-4), 3.78-3.80 (1H, m, H-5), 3.88 (1H, at, *J* 4.0 Hz, H-3), 4.39, 4.60 (2H, ABq, J_{AB} 11.4 Hz, $PhC\underline{H}_2$), 4.42 (1H, dd, $J_{1,2}$ 5.1 Hz, $J_{2,3}$ 3.7 Hz, H-2), 4.50, 4.59 (2H, ABq, J_{AB} 12.2 Hz, $PhC\underline{H}_2$), 4.60, 4.71 (2H, ABq, J_{AB} 11.9 Hz, $PhC\underline{H}_2$), 5.77 (1H, d, H-1), 7.18-7.38 (15H, m, Ar-H).

Phenyl 2-O-acetyl-3,4,6-tri-O-benzyl-1-seleno-β-D-glucopyranoside 39

3,4,6-Tri-*O*-benzyl-1,2-*O*-(*exo*-ethoxyethylidene)-α-D-glucopyranose **40** (8.3 g, 16.0 mmol) was dissolved in distilled acetonitrile (60 ml). Mercuric bromide (57.6 mg, 0.16 mmol) then selenophenol (3.3 ml, 30.0 mmol) were added and the reaction mixture stirred at 50 °C. After 1 h 30 min, tlc (CH_2Cl_2:ether, 30:1) indicated formation of a product (R_f 0.7) and complete consumption of starting material (R_f 0.3). The reaction was quenched with NaOH (200 ml of a 5% aqueous solution) then extracted with CH_2Cl_2 (2 x 200 ml). The combined

organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) and recrystallised from ethanol to afford phenyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-1-seleno-β-D-glucopyranoside **39** (7.85g, 78%) as a white, crystalline solid, m.p. 122-125 °C (ethanol); $[\alpha]_D^{22}$ +2.7 (*c*, 0.33 in $CHCl_3$); ν_{max} 1737 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.01 (3H, s, CH_3), 3.53-3.56 (1H, m, H-5), 3.67-3.72 (2H, m, H-3, H-4), 3.75 (1H, dd, $J_{5,6}$ 4.6 Hz, $J_{6,6'}$ 11.1 Hz, H-6), 3.81 (1H, dd, $J_{5,6'}$ 1.9 Hz, H-6'), 4.55, 4.61 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.60, 4.81 (2H, ABq, J_{AB} 10.8 Hz, PhC$\underline{H}_2$), 4.70, 4.82 (2H, ABq, J_{AB} 11.3 Hz, PhC$\underline{H}_2$), 4.84 (1H, d, $J_{1,2}$ 10.1 Hz, H-1), 5.06-5.11 (1H, m, H-2), 7.22-7.67 (20H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 21.1 (q, CH_3), 68.8, 73.4, 75.1, 75.3 (4 x t, C-6, 3 x Ph$\underline{C}H_2$), 72.6, 77.7, 80.4, 81.7, 84.3 (5 x d, C-1, C-2, C-3, C-4, C-5), 127.6, 127.7, 127.8, 127.9, 128.0, 128.4, 128.5, 128.9, 134.7 (9 x d, Ar-CH), 137.8, 138.0, 138.2 (3 x s, Ar-C), 169.6 (s, C=O); *m/z* (APCI$^+$) 655 (M+Na$^+$, 100%). (Found: C, 66.70; H, 5.47. $C_{35}H_{36}O_6Se$ requires C, 66.56; H, 5.74%).

Phenyl 3,4,6-tri-O-benzyl-1-seleno-β-D-glucopyranoside 38

Phenyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-1-seleno-β-D-glucopyranoside **39** (7.34 g, 11.6 mmol) was suspended in methanol (900 ml). Sodium (870 mg, 37.8 mmol) was dissolved in methanol (100 ml) and added to the sugar solution. After 28 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.45) and complete consumption of starting material (R_f 0.5). 1M HCl was added until pH 7 was reached and the mixture was concentrated to *ca* 150 ml *in vacuo*. The solution was partitioned between ethyl acetate

(400 ml) and water (200 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was recrystallised from ether/petrol to afford phenyl 3,4,6-tri-*O*-benzyl-1-seleno-β-D-glucopyranoside **38** (6.24 g, 91%) as a white, crystalline solid, m.p. 61-63 °C (ether/petrol) [Lit. 60-61 °C (pentane/ether)][3]; $[\alpha]_D^{22}$ –12.2 (*c*, 0.5 in $CHCl_3$) [Lit. -12 (*c*, 0.5 in $CHCl_3$)][3]; δ_H (400 MHz, $CDCl_3$) 3.47-3.54 (2H, m, H-2, H-5), 3.56-3.64 (2H, m, H-3, H-4), 3.76 (1H, dd, $J_{5,6}$ 4.0 Hz, $J_{6,6'}$11.1 Hz, H-6), 3.80 (1H, dd, $J_{5,6'}$ 2.0 Hz, H-6'), 4.55, 4.61 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.57, 4.82 (2H, ABq, J_{AB} 10.8 Hz, PhC$\underline{H}_2$), 4.73 (1H, d, $J_{1,2}$ 9.6 Hz, H-1), 4.84, 4.91 (2H, ABq, J_{AB} 11.2 Hz, PhC$\underline{H}_2$), 7.19-7.68 (20H, m, Ar-H).

Phenyl 2-O-allyl-3,4,6-tri-O-benzyl-1-seleno-β-D-glucopyranoside 36

Phenyl 3,4,6-tri-*O*-benzyl-1-seleno-β-D-glucopyranoside **38** (3.0 g, 5.09 mmol) was dissolved in anhydrous DMF (10 ml) and cooled to 0 °C. Allyl bromide (0.88 ml, 10.18 mmol) was added then sodium hydride (60% in mineral oil) (407 mg, 10.18 mmol) was added portionwise. After 30 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a single product (R_f 0.5) and complete consumption of starting material (R_f 0.3). The reaction was quenched with methanol (5 ml) then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (100 ml) and water (100 ml). The aqueous layer was re-extracted with CH_2Cl_2 (100 ml) and the combined organic extracts washed with brine (30 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was recrystallised from ethanol to afford phenyl 2-*O*-allyl-3,4,6-tri-*O*-benzyl-1-seleno-β-D-glucopyranoside **36** (2.97 g, 92%) as a white, crystalline

solid, m.p. 61-62 °C (ethanol); $[\alpha]_D^{22}$ -7.6 (*c*, 0.5 in $CHCl_3$); ν_{max} 1643 (w, C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.37-3.42 (1H, m, H-2), 3.45-3.49 (1H, m, H-5), 3.62-3.64 (2H, m, H-3, H-4), 3.72 (1H, dd, $J_{5,6}$ 4.3 Hz, $J_{6,6'}$10.9 Hz, H-6), 3.78 (1H, dd, $J_{5,6'}$ 2.0 Hz, H-6'), 4.24 (1H, dd, J_{gem} 11.8 Hz, *J* 6.0 Hz, OC<u>H</u>H'CH=CH_2), 4.34 (1H, dd, *J* 5.6 Hz, OCH<u>H</u>'CH=CH_2), 4.53, 4.59 (2H, ABq, J_{AB} 12.0 Hz, PhC<u>H_2</u>), 4.58, 4.81 (2H, ABq, J_{AB} 10.8 Hz, PhC<u>H_2</u>), 4.80 (1H, d, $J_{1,2}$ 9.8 Hz, H-1), 4.83, 4.89 (2H, ABq, J_{AB} 10.7 Hz, PhC<u>H_2</u>), 5.18 (1H, dd, J_{gem} 1.6 Hz, J_Z 10.4 Hz, CH=CH_E<u>H_Z</u>), 5.28 (1H, dd, J_E 17.2 Hz, CH=C<u>H_E</u>H_Z), 5.97 (1H, ddat, C<u>H</u>=CH_2), 7.17-7.69 (20H, m, Ar-H); δ_C (50.3 MHz, $CDCl_3$) 69.4, 73.9, 74.5, 75.6, 76.3 (5 x t, C-6, 3 x Ph<u>C</u>H_2, O<u>C</u>H_2CH=CH_2), 78.2, 80.6, 81.6, 83.5, 87.2 (5 x d, C-1, C-2, C-3, C-4, C-5), 117.9 (t, CH=<u>C</u>H_2), 128.0, 128.1, 128.2, 128.4, 128.4, 128.8, 128.9, 129.5 (8 x d, Ar-CH), 134.9, 135.1 (2 x d, Ar-CH, <u>C</u>H=CH_2), 138.6, 138.8 (2 x s, Ar-C); *m/z* (APCI$^+$) 653 (M+Na^+, 100%). (Found: C, 68.77; H, 6.09. $C_{36}H_{38}O_5Se$ requires C, 68.67; H, 6.08%).

Methyl 2-O-acetyl-3,4,6-tri-O-benzyl-1-thio-β-D-glucopyranoside 44

3,4,6-Tri-*O*-benzyl-1,2-*O*-(*exo*-ethoxyethylidene)-α-D-glucopyranose **40** (200 mg, 0.39 mmol) was dissolved in freshly distilled CH_2Cl_2 (4 ml) in a flame-dried flask under Ar. Sodium methanethiolate (81 mg, 1.2 mmol) and 15-crown-5 (0.23 ml, 1.2 mmol) were added, and the mixture cooled to 0°C. $BF_3.OEt_2$ (0.073 ml, 0.58 mmol) was added and the reaction mixture was stirred under Ar. After 3 h, tlc (toluene:acetone, 20:1) indicated complete consumption of starting material (R_f 0.3) and formation of minor (R_f 0.4) and major (R_f 0.1) products. The reaction mixture was partitioned between CH_2Cl_2

(30 ml) and $NaHCO_3$ (30 ml of a saturated aqueous solution). The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) to afford methyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **44** (28 mg, 14%) as a colourless oil; $[\alpha]_D^{22}$ +14.7 (*c*, 0.15 in $CHCl_3$); ν_{max} 1746 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.00 (3H, s, $COCH_3$), 2.17 (3H, s, SCH_3), 3.52-3.56 (1H, m, H-5), 3.67-3.78 (4H, m, H-3, H-4, H-6, H-6′), 4.27 (1H, d, $J_{1,2}$ 10.1 Hz, H-1), 4.56, 4.64 (2H, ABq, J_{AB} 12.2 Hz, PhC$\underline{H}_2$), 4.59, 4.80 (2H, ABq, J_{AB} 10.6 Hz, PhC$\underline{H}_2$), 4.70, 4.83 (2H, ABq, J_{AB} 11.3 Hz, PhC$\underline{H}_2$), 5.07 (1H, dd, $J_{2,3}$ 9.1 Hz, H-2), 7.18-7.36 (15H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 11.1 (q, SCH_3), 21.0 (q, $COCH_3$), 68.7, 73.4, 75.2, 75.3 (4 x t, C-6, 3 x Ph$\underline{C}H_2$), 70.9, 77.4, 79.5, 82.6, 84.3 (5 x d, C-1, C-2, C-3, C-4, C-5), 127.6, 127.7, 127.8, 127.9, 128.0, 128.4, 128.4 (7 x d, Ar-CH), 137.8, 138.1, 138.1 (3 x s, Ar-C); *m/z* (APCI$^+$) 545 ($M+Na^+$, 72%). (HRMS Calcd. for $C_{30}H_{38}NO_6S$ (MNH_4^+) 540.2420. Found 540.2421).

Methyl 2-O-acetyl-3,4,6-tri-O-benzyl-1-thio-D-glucopyranoside 44

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-D-glucopyranose **49** (200 mg, 0.41 mmol) and 4Å molecular sieves were added to distilled acetonitrile (2 ml) under Ar. Dimethyl disulfide (0.055 ml, 0.61 mmol), tributylphosphine (0.152 ml, 0.61 mmol) and $BF_3.OEt_2$ (0.26 ml, 2.04 mmol) were added and the reaction mixture was stirred under Ar at RT. After 68 h, tlc (petrol:ethyl acetate, 3:1) indicated the formation of a single product (R_f 0.5) and very little remaining starting material (R_f 0.1). The reaction mixture was partitioned between CH_2Cl_2 (2 x 20 ml) and $NaHCO_3$ (20 ml of a saturated aqueous solution). The

organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) to afford methyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-1-thio-D-glucopyranoside **44**, an inseparable α/β mixture (136 mg, 64%) as a colourless oil; Partial data: δ_H (200 MHz, $CDCl_3$) (α:β ratio 1:1) α isomer 2.04, 2.07 (6H, 2 x s, $COCH_3$, SCH_3), 5.57 (1H, d, $J_{1,2}$ 6.0 Hz, H-1); β isomer 2.00 (3H, s, $COCH_3$), 2.17 (3H, s, SCH_3), 4.27 (1H, d, $J_{1,2}$ 10.1 Hz, H-1).

2-O-Acetyl-3,4,6-tri-O-benzyl-α-D-glucopyranosyl bromide 50

3,4,6-Tri-*O*-benzyl-1,2-*O*-(*exo*-ethoxyethylidene)-α-D-glucopyranose **40** (400 mg, 0.77 mmol) was dissolved in freshly distilled CH_2Cl_2 in a flame-dried flask and cooled to 0 °C under Ar. HBr (33% in acetic acid) (0.7 ml) was added. After 3 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.7) and complete consumption of starting material (R_f 0.6). The reaction was quenched with ice water (30 ml) then extracted with CH_2Cl_2 (30 ml). The organic extracts were washed with $NaHCO_3$ (2 x 20 ml of a saturated aqueous solution), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1 with 1% Et_3N) to afford 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl bromide **50** (312 mg, 73%) as a colourless oil; $[\alpha]_D^{22}$ +149.8 (*c*, 0.45 in $CHCl_3$) [Lit. +139 (*c*, 1 in $CHCl_3$)][2]; δ_H (200 MHz, $CDCl_3$) 2.06 (3H, s, CH_3), 3.69 (1H, dd, $J_{5,6}$ 1.8 Hz, $J_{6,6'}$ 11.1 Hz, H-6), 3.83 (1H, dd, $J_{5,6'}$ 3.2 Hz, H-6′), 3.85-3.90 (1H, m, H-4), 4.07-4.13 (2H, m, H-3, H-5), 4.51, 4.62 (2H, ABq, J_{AB} 12.2 Hz, $PhC\underline{H}_2$), 4.56, 4.83 (2H, ABq, J_{AB} 10.1 Hz, $PhC\underline{H}_2$), 4.78

(1H, dd, $J_{1,2}$ 4.0 Hz, $J_{2,3}$ 9.8 Hz, H-2), 4.80, 4.85 (2H, ABq, J_{AB} 11.3 Hz, PhC$\underline{H}_2$), 6.67 (1H, d, H-1), 7.16-7.38 (15H, m, Ar-H).

Methyl 3,4,6-tri-O-benzyl-1-thio-β-D-glucopyranoside 45

Method 1: from purified bromide **50**

Butyl lithium (1.6 M solution in hexanes) (13.5 ml, 21.6 mmol) and dimethyl disulfide (1.9 ml, 21.6 mmol) were dissolved in freshly distilled THF (3 ml) at -78 °C under Ar and stirred for 15 min. 2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl bromide **50** (4.8 g, 8.6 mmol) was dissolved in freshly distilled THF (3 ml) and added to the reaction mixture by cannula under Ar. The mixture was stirred at at -78 °C. After 16 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.3) and very little remaining starting material (R_f 0.6). Ammonium chloride (30 ml of a saturated aqueous solution) was added. The mixture was diluted with water (200 ml) and extracted with CH_2Cl_2 (2 x 100 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate: 2:1→4:1) to afford methyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **45** (2.83 g, 68%) as a white, crystalline solid, m.p. 76-78 °C (ether/petrol); $[\alpha]_D^{22}$ +4.8 (*c*, 0.25 in $CHCl_3$); ν_{max} 3440 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.20 (3H, s, SCH_3), 3.50-3.53 (1H, m, H-5), 3.55-3.60 (2H, m, H-2, H-3), 3.64 (1H, at, *J* 9.0 Hz, H-4), 3.71 (1H, dd, $J_{5,6}$ 4.3 Hz, $J_{6,6'}$ 11.0 Hz, H-6), 3.75 (1H, dd, $J_{5,6'}$ 2.0 Hz, H-6'), 4.22 (1H, d, $J_{1,2}$ 9.0 Hz, H-1), 4.53, 4.60 (2H, ABq, J_{AB} 12.1 Hz, PhC$\underline{H}_2$), 4.56, 4.83 (2H, ABq, J_{AB} 10.5 Hz, PhC$\underline{H}_2$), 4.86, 4.93 (2H, ABq, J_{AB} 11.3 Hz, PhC$\underline{H}_2$), 7.16-7.39 (15H, m, Ar-H); δ_C

(100.6 MHz, $CDCl_3$) 10.4 (q, SCH_3), 67.7, 72.3, 74.0, 74.1 (4 x t, C-6, 3 x $PhCH_2$), 71.3, 76.2, 78.3, 84.5, 84.8 (5 x d, C-1, C-2, C-3, C-4, C-5), 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 128.4, 128.5 (10 x d, Ar-CH), 136.9, 137.0, 137.4 (3 x s, Ar-C); *m/z* ($APCI^+$) 504 ($M+Na^+$, 100%). (Found: C, 70.00; H, 6.79. $C_{28}H_{32}O_5S$ requires C, 69.97; H, 6.71%);

Also methyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **44** (170 mg, 4%) identical to that previously described.

Method 2: from orthoester **40**

Acetyl bromide (10 ml) was added to 3,4,6-tri-*O*-benzyl-1,2-*O*-(*exo*-ethoxyethylidene)-α-D-glucopyranose **40** (1.0 g, 1.92 mmol) at 0 °C under Ar. After 15 min, tlc (petrol:ethyl acetate, 2:1) indicated formation of a product (R_f 0.5) and complete consumption of starting material (R_f 0.4). Toluene was added and the mixture concentrated *in vacuo* to give crude 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl bromide **50** which was used without purification.

Butyl lithium (1.6 M solution in hexanes) (3.0 ml, 4.81 mmol) and dimethyl disulfide (0.43 ml, 4.81 mmol) were dissolved in freshly distilled THF (5 ml) at -78°C under Ar and stirred for 15 min. The crude residue was dissolved in freshly distilled THF (3 ml) and added to the reaction mixture by cannula under Ar. The mixture was stirred at -78°C. After 1 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.2) and very little remaining starting material (R_f 0.5). Ammonium chloride (30 ml of a saturated aqueous solution) was added and the mixture was partitioned between CH_2Cl_2 (2 x 50 ml) and

water (100 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate: 4:1) to obtain a white solid which was recrystallised from ether/petrol to afford methyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **15** (561 mg, 61%) as a white, crystalline solid, identical to that previously described.

Methyl 2-O-allyl-3,4,6-tri-O-benzyl-1-thio-β-D-glucopyranoside 35

Methyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **45** (2.74 g, 5.71 mmol) was dissolved in anhydrous DMF (10 ml) and cooled to 0 °C. Allyl bromide (1.0 ml, 11.42 mmol) was added then sodium hydride (60% in mineral oil) (457 mg, 11.42 mmol) was added portionwise. After 30 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a single product (R_f 0.8) and complete consumption of starting material (R_f 0.5). The reaction was quenched with methanol (10 ml), brought to pH 7 by addition of 1M HCl and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (3 x 100 ml) and water (200 ml). The combined organic layers were washed with brine (50 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) to afford methyl 2-*O*-allyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **35** (2.52 g, 85%) as a pale yellow oil; $[\alpha]_D^{22}$ –11.1 (*c*, 0.55 in $CHCl_3$); ν_{max} 1647 (w, C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.26 (3H, s, SCH_3), 3.36 (1H, dd, $J_{1,2}$ 9.6 Hz, $J_{2,3}$ 8.6 Hz, H-2) 3.48-3.52 (1H, m, H-5), 3.62 (1H, at, *J* 9.2 Hz, H-4), 3.67 (1H, at, *J* 8.9 Hz, H-3), 3.72 (1H, dd, $J_{5,6}$ 4.4 Hz, $J_{6,6'}$10.9 Hz, H-6), 3.78 (1H, dd, $J_{5,6'}$ 1.9 Hz,

H-6′), 4.30 (1H, ddat, J_{gem} 12.0 Hz, J 1.3 Hz, J 6.0 Hz, OC<u>H</u>H′CH=CH_2), 4.33 (1H, d, H-1), 4.43 (1H, ddat, J 1.3 Hz, J 5.8 Hz, OCH<u>H</u>′CH=CH_2), 4.57, 4.63 (2H, ABq, J_{AB} 12.0 Hz, PhC<u>H</u>$_2$), 4.58, 4.85 (2H, ABq, J_{AB} 10.8 Hz, PhC<u>H</u>$_2$), 4.86, 4.95 (2H, ABq, J_{AB} 10.9 Hz, PhC<u>H</u>$_2$), 5.21 (1H, daq, J_{gem} 1.4 Hz, J_Z 10.4 Hz, CH=CH_E<u>H</u>$_Z$), 5.33 (1H, daq, J_E 17.1 Hz, CH=C<u>H</u>$_E$H$_Z$), 6.01 (1H, ddat, C<u>H</u>=CH_2), 7.15-7.41 (15H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 13.0 (q, SCH_3), 68.9 (t, C-6), 73.4, 75.1, 75.8 (3 x t, 3 x Ph<u>C</u>H$_2$), 74.1 (t, O<u>C</u>H$_2$CH=CH_2), 77.7 (d, C-4), 79.1 (d, C-5), 80.8 (d, C-2), 85.3 (d, C-1), 86.5 (d, C-3), 117.5 (t, CH=<u>C</u>H$_2$), 127.6, 127.7, 127.8, 127.9, 128.0, 128.3, 128.4, 128.4 (8 x d, Ar-CH), 134.6 (d, <u>C</u>H=CH_2), 138.0, 138.2, 138.4 (3 x s, Ar-C); *m/z* (APCI$^+$) 559 (M+K^+, 42), 543 (M+Na^+, 100%). (Found: C, 71.49; H, 6.89. $C_{31}H_{36}O_5S$ requires C, 71.51; H, 6.97%).

Methyl 3,4,6-tri-O-benzyl-2-O-prop-1′-enyl-1-thio-β-D-glucopyranoside 51

Wilkinson's catalyst (448 mg, 0.49 mmol) was dissolved in freshly distilled THF (10 ml) and degassed. Butyl lithium (1.6 M solution in hexanes) (0.45 ml, 0.73 mmol) was added and the mixture stirred for 10 min. Methyl 2-*O*-allyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **35** (2.52 g, 0.485 mmol) was dissolved in freshly distilled THF (10 ml) and heated to 70 °C. The catalyst solution was added by cannula under Ar. After 1 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a single product (R_f 0.55) and complete consumption of starting material (R_f 0.5). The reaction was allowed to cool then diluted with CH_2Cl_2 (20 ml) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1 with 1%

Et_3N) to afford methyl 3,4,6-tri-*O*-benzyl-2-*O*-prop-1′-enyl-1-thio-β-D-glucopyranoside **51** (2.37 g, 94%) as a pale yellow oil; Partial data: δ_H (200 MHz, $CDCl_3$) (*Z*:*E* ratio 2.7:1) *E* isomer 1.57 (3H, dd, *J* 1.5 Hz, *J* 6.9 Hz, OCH=CHC$\underline{H}_3$), 5.05 (1H, dd, J_E 12.2 Hz, OCH=C$\underline{H}$CH$_3$), 6.23 (1H, dd, OC$\underline{H}$=CHCH$_3$); Z isomer 1.64 (3H, dd, *J* 1.6 Hz, *J* 6.9 Hz, OCH=CHC$\underline{H}_3$), 6.16 (1H, dd, J_Z 6.2 Hz, OC$\underline{H}$=CHCH$_3$); *m/z* (APCI$^+$) 543 (M+Na$^+$, 100%). (HRMS Calcd. for $C_{31}H_{40}NO_5S$ (MNH_4^+) 538.2627. Found 538.2627).

Phenyl 3,4,6-tri-O-benzyl-2-O-prop-1′-enyl-1-seleno-β-D-glucopyranoside 52

Wilkinson's catalyst (31 mg, 0.033 mmol) was dissolved in freshly distilled THF (3 ml) and degassed. Butyl lithium (1.2 M solution in hexanes) (0.04 ml, 0.049 mmol) was added and the mixture stirred for 15 min. Phenyl 2-*O*-allyl-3,4,6-tri-*O*-benzyl-1-seleno-β-D-glucopyranoside **36** (205 mg, 0.326 mmol) was dissolved in freshly distilled THF (3 ml) and heated to 70 °C. The catalyst solution was added by cannula under Ar. After 2 h 20 min, the reaction was allowed to cool then diluted with CH_2Cl_2 (20 ml) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) to afford phenyl 3,4,6-tri-*O*-benzyl-2-*O*-prop-1′-enyl-1-seleno-β-D-glucopyranoside **52** (190 mg, 92%) as a pale yellow oil; δ_H (200 MHz, $CDCl_3$) (*Z*:*E* ratio 2.2:1); *m/z* (APCI$^+$) 653 (M+Na$^+$, 45%). (HRMS Calcd. for $C_{36}H_{42}NO_5Se$ (MNH_4^+) 648.2228. Found 648.2234).

NIS-Mediated Tethering in the *Gluco* SePh System

Phenyl 3,4,6-tri-O-benzyl-2-O-(2-iodo-1-methoxypropyl)-1-seleno-β-D-glucopyranoside 53a

N-Iodosuccinimide (58 mg, 0.257 mmol) and 4Å molecular sieves were added to freshly distilled CH_2Cl_2 (1 ml) and cooled to -50 °C under Ar. Methanol **3a** (0.014 ml, 0.34 mmol) was added. Phenyl 2-*O*-prop-1'-enyl-3,4,6-tri-*O*-benzyl-1-seleno-β-D-glucopyranoside **52** (108 mg, 0.172 mmol) was dissolved in freshly distilled CH_2Cl_2 (2 ml) and added to the reaction vessel by cannula under Ar. After 40 min, the reaction mixture was diluted with CH_2Cl_2 (30 ml), washed with sodium thiosulfate (20 ml of a 10% aqueous solution), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 9:1) to afford phenyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-methoxypropyl)-1-seleno-β-D-glucopyranoside **53a** (48 mg, 36%) as a colourless oil; *m/z* ($APCI^+$) 811 ($M+Na^+$, 30), 573 (M-OCH(OMe)CHIMe, 63%).

Glycosylation in the *Gluco* SePh System

Methyl 3,4,6-tri-O-benzyl-α-D-glucopyranoside 30a

Phenyl 3,4,6-tri-*O* -benzyl-2-*O*-(2-iodo-1-methoxypropyl)-1-seleno-β-D-glucopyranoside **53a** (53 mg, 0.067 mmol) was dissolved in freshly distilled CH_2Cl_2 (2 ml) and cooled to -40 °C under Ar. *N*-Iodosuccinimide (22 mg, 0.10 mmol) was added. After 10 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a major product (R_f 0.1) and complete consumption of starting material (R_f 0.6). The reaction mixture was diluted with CH_2Cl_2 (30 ml) and washed with sodium thiosulfate (30 ml of a 10% aqueous solution). The

organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 3:1) to afford methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside **30a** (22 mg, 70%) as a white solid which was recrystallised from ether/petrol, m.p. 78-81 °C (ether/petrol) [Lit. 83-84 °C][4]; $[\alpha]_D^{22}$ +70.8 (*c*, 1.2 in $CHCl_3$) [Lit. +90 (*c*, 1.1 in $CHCl_3$)][4]; δ_H (400 MHz, $CDCl_3$) 2.11 (1H, d, $J_{OH,2}$ 7.4 Hz, OH-2), 3.40 (3H, s, OCH_3), 3.60-3.76 (6H, m, H-2, H-3, H-4, H-5, H-6, H-6'), 4.47, 4.79 (2H, ABq, J_{AB} 10.7 Hz, PhC$\underline{H}_2$), 4.49, 4.62 (2H, ABq, J_{AB} 12.1 Hz, PhC$\underline{H}_2$), 4.78 (1H, d, $J_{1,2}$ 3.2 Hz, H-1), 4.83, 4.88 (2H, ABq, J_{AB} 11.2 Hz, PhC$\underline{H}_2$), 7.11-7.36 (15H, m, Ar-H).

Attempted One-Pot Reaction in the *Gluco* SePh System

3,4,6-Tri-O-benzyl-2-O-(1-(1,2:3,4-di-O-isopropylidene-α-D-galactopyranos-6-O-yl)-2-iodopropyl)-D-glucopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 54

N-Iodosuccinimide (72 mg, 0.32 mmol) and 4Å molecular sieves were added to freshly distilled CH_2Cl_2 (2 ml) and cooled to -78 °C under Ar. 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **3d** (0.41 mg, 0.16 mmol) and phenyl 2-*O*-prop-1'-enyl-3,4,6-tri-*O*-benzyl-1-seleno-β-D-glucopyranoside **52** (100 mg, 0.16 mmol) were dissolved in freshly distilled CH_2Cl_2 (2 ml) and added to the reaction vessel by cannula under Ar. After 40 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a major product (R_f 0.5) and little remaining enol ethers (R_f 0.6) and alcohol (R_f 0.1). The reaction mixture was removed from the cooling bath and allowed to warm to RT. After a further 4 h, tlc

(petrol:ethyl acetate, 3:1) indicated formation of a major product (R_f 0.2). The mixture was diluted with CH_2Cl_2 (30 ml), washed with sodium thiosulfate (30 ml of a 10% aqueous solution), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 3:1) to afford a product tentatively identified as 3,4,6-tri-*O*-benzyl-2-*O*-(1-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-*O*-yl)-2-iodopropyl)-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **54** as a colourless oil; *m/z* (APCI$^+$) 1142 (M+Na$^+$, 100%).

Attempted Acid Tethering

Phenyl 3,4,6-tri-O-benzyl-2-O-(1-octyloxypropyl)-1-seleno-β-D-glucopyranoside 55

Phenyl 3,4,6-tri-*O*-benzyl-2-*O*-prop-1′-enyl-1-seleno-β-D-glucopyranoside **52** (93 mg, 0.15 mmol), octanol (0.05 ml, 0.30 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (2 ml). HCl (1M in ether) (0.015 ml, 0.015 mmol) was added and the reaction mixture stirred at RT under Ar. After 50 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a small amount of a product (R_f 0.55) and remaining enol ethers (R_f 0.5) and alcohol (R_f 0.4). The reaction was quenched with Et_3N (2 ml). The mixture was diluted with CH_2Cl_2 (50 ml), washed with water (50 ml), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 7:1) to afford phenyl 3,4,6-tri-*O*-benzyl-2-*O*-(1-octyloxypropyl)-1-seleno-β-D-glucopyranoside **55** (4 mg, 4%) as a

colourless oil; *m/z* (APCI$^+$) 783 (M+Na$^+$, 5), 573 (M-OCH(OOctyl)CH_2Me, 21%).

NIS-Mediated Tethering in the *Gluco* SMe System

Methyl 3,4,6-tri-O-benzyl-2-O-(2-iodo-1-methoxypropyl)-1-thio-β-D-glucopyranoside 56a

N-Iodosuccinimide (130 mg, 0.577 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (2 ml) and cooled to -40 °C under Ar. Methyl 3,4,6-tri-*O*-benzyl-2-*O*-prop-1′-enyl-1-thio-β-D-glucopyranoside **51** (100 mg, 0.19 mmol) and methanol **3a** (0.012 ml, 0.29 mmol) were dissolved in anhydrous dichloroethane (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to -5 °C over 1 h. After 1 h, the reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1 with 1% Et_3N) to afford methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-methoxypropyl)-1-thio-β-D-glucopyranoside **56a** (128 mg, 98%) as a colourless oil; *m/z* (APCI$^+$) 701 (M+Na$^+$, 100%).

Methyl 3,4,6-tri-O-benzyl-2-O-(1-benzyloxy-2-iodopropyl)-1-thio-β-D-glucopyranoside 56b

N-Iodosuccinimide (103 mg, 0.46 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (1.5 ml) and cooled to -40 °C under Ar. Methyl

3,4,6-tri-*O*-benzyl-2-*O*-prop-1′-enyl-1-thio-β-D-glucopyranoside **51** (80 mg, 0.15 mmol) and benzyl alcohol **3b** (0.03 ml, 0.31 mmol) were dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to 0 °C over 1 h. After 1 h, the reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1 with 1% Et_3N) to afford methyl 3,4,6-tri-*O*-benzyl-2-*O*-(1-benzyloxy-2-iodopropyl)-1-thio-β-D-glucopyranoside **56b** (110 mg, 95%) as a colourless oil; *m/z* (APCI$^+$) 793 (M+K$^+$, 72), 777 (M+Na$^+$, 100), 772 (M+NH_4^+, 35%).

Methyl 3,4,6-tri-O-benzyl-2-O-(1-cyclohexyloxy-2-iodopropyl)-1-thio-β-D-glucopyranoside 56c

N-Iodosuccinimide (130 mg, 0.577 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (2 ml) and cooled to -40 °C under Ar. Methyl 3,4,6-tri-*O*-benzyl-2-*O*-prop-1′-enyl-1-thio-β-D-glucopyranoside **51** (100 mg, 0.19 mmol) and cyclohexanol **3c** (0.061 ml, 0.577 mmol) were dissolved in anhydrous dichloroethane (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to 0 °C over 1 h. After 1 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.6) and complete consumption of starting material (R_f 0.5). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were

dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1 with 1% Et_3N) to afford methyl 3,4,6-tri-*O*-benzyl-2-*O*-(1-cyclohexyloxy-2-iodopropyl)-1-thio-β-D-glucopyranoside **56c** (115 mg, 80%) as a colourless oil; *m/z* ($APCI^+$) 769 ($M+Na^+$, 100%).

Methyl 3,4,6-tri-O-benzyl-2-O-(1-(1,2:3,4-di-O-isopropylidene-α-D-galactopyranos-6-O-yl)-2-iodopropyl)-1-thio-β-D-glucopyranoside 56d

N-Iodosuccinimide (130 mg, 0.577 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (2 ml) and cooled to -40 °C under Ar. 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose **3d** (75 mg, 0.29 mmol) was dissolved in anhydrous dichloroethane (2 ml) and added by cannula under Ar. Methyl 3,4,6-tri-*O*-benzyl-2-*O*-prop-1′-enyl-1-thio-β-D-glucopyranoside **51** (100 mg, 0.19 mmol) was dissolved in anhydrous dichloroethane (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to -5 °C over 1 h. After 1 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.4) and complete consumption of starting material (R_f 0.5). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1 with 1% Et_3N) to afford methyl 3,4,6-tri-*O*-benzyl-2-*O*-(1-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-*O*-yl)-2-iodopropyl)-

1-thio-β-D-glucopyranoside **56d** (147 mg, 84%) as a colourless oil; *m/z* (APCI$^+$) 929 (M+Na$^+$, 100%).

Methyl 3,4,6-tri-O-benzyl-2-O-(2-iodo-1-(methyl 2,3,4-tri-O-benzyl-α-D-mannopyranosid-6-O-yl)propyl)-1-thio-β-D-glucopyranoside 56e

N-Iodosuccinimide (51 mg, 0.23 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (1 ml) and cooled to -40 °C under Ar. Methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **3e** (71 mg, 0.15 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added by cannula under Ar. Methyl 3,4,6-tri-*O*-benzyl-2-*O*-prop-1′-enyl-1-thio-β-D-glucopyranoside **51** (40 mg, 0.077 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and àdded to the reaction vessel by cannula under Ar. The reaction was allowed to warm to 5 °C over 1 h. After 1 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.45) and complete consumption of starting material (R_f 0.5). The reaction was quenched with Et_3N and stirred for 10 min. Sodium thiosulfate (30 ml of a 10% aqueous solution) was added and the mixture extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1 with 1% Et_3N) to afford methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranosid-6-*O*-yl)propyl)-1-thio-β-D-glucopyranoside **56e** (54 mg, 63%) as a colourless oil; *m/z* (APCI$^+$) 1133 (M+Na$^+$, 100%).

Methyl 3,4,6-tri-O-benzyl-2-O-(2-iodo-1-(methyl 2,3,4-tri-O-benzyl-α-D-glucopyranosid-6-O-yl)propyl)-1-thio-β-D-glucopyranoside 56f

N-Iodosuccinimide (130 mg, 0.58 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (2 ml) and cooled to -40 °C under Ar. Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **3f** (134 mg, 0.29 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added by cannula under Ar. Methyl 3,4,6-tri-*O*-benzyl-2-*O*-prop-1′-enyl-1-thio-β-D-glucopyranoside **51** (100 mg, 0.19 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to RT. After 45 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.45) and complete consumption of starting material (R_f 0.5). Sodium thiosulfate (30 ml of a 10% aqueous solution) was added and the mixture extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1 with 1% Et_3N) to afford methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranosid-6-*O*-yl)propyl)-1-thio-β-D-glucopyranoside **56f** (76 mg, 36%) as a colourless oil; *m/z* (APCI$^+$) 1133 (M+Na$^+$, 100%).

Methyl 3,4,6-tri-O-benzyl-2-O-(2-iodo-1-(methyl 2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranosid-3-O-yl)propyl)-1-thio-β-D-glucopyranoside 56g

N-Iodosuccinimide (103 mg, 0.46 mmol), 4Å molecular sieves and methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **3g** (172 mg, 0.46 mmol)

were dissolved in anhydrous dichloroethane (1 ml) and cooled to -40 °C under Ar. Methyl 3,4,6-tri-*O* -benzyl-2-*O*-prop-1'-enyl-1-thio-β-D-glucopyranoside **51** (80 mg, 0.15 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to RT. After 2 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.4) and little remaining starting material (R_f 0.5). Sodium thiosulfate (30 ml of a 10% aqueous solution) was added and the mixture extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosid-3-*O*-yl)propyl)-1-thio-β-D-glucopyranoside **56g** (33 mg, 22%) as a colourless oil; *m/z* ($APCI^+$) 1041 ($M+Na^+$, 100%); ($APCI^-$) 1053 ($M+Cl^-$, 37%).

Methyl 3,4,6-tri-O-benzyl-2-O-(2-iodo-1-(methyl 2,3,6-tri-O-benzyl-α-D-glucopyranosid-4-O-yl)propyl)-1-thio-β-D-glucopyranoside 56h

N-Iodosuccinimide (130 mg, 0.58 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (2 ml) and cooled to -40 °C under Ar. Methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **3h** (268 mg, 0.58 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added by cannula under Ar. Methyl 3,4,6-tri-*O*-benzyl-2-*O*-prop-1'-enyl-1-thio-β-D-glucopyranoside **51** (100 mg, 0.19 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. The reaction was

allowed to warm to RT. After 2 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.5) and little remaining starting material (R_f 0.6). Sodium thiosulfate (30 ml of a 10% aqueous solution) was added and the mixture extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1 with 1% Et_3N) to afford methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranosid-4-*O*-yl)propyl)-1-thio-β-D-glucopyranoside **56h** (11 mg, 5%) as a colourless oil; *m/z* (APCI$^+$) 1149 (M+K$^+$, 72), 1133 (M+Na$^+$, 100), 1128 (M+NH_4^+, 40%).

Glycosylation in the *Gluco* SMe System

Methyl 3,4,6-tri-O-benzyl-α-D-glucopyranoside 30a

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-methoxypropyl)-1-thio-β-D-glucopyranoside **56a** (125 mg, 0.184 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (113 mg, 0.552 mmol) were dissolved in anhydrous dichloroethane (2 ml). Methyl trifluoromethanesulfonate (0.1 ml, 0.922 mmol) was added. After 75 min, tlc (petrol:ethyl acetate, 3:1) indicated the consumption of starting material (R_f 0.6) and the formation of a major (R_f 0.5) and minor (R_f 0.1, 0.4 and 0.6) products. Et_3N (2 ml) was added and the reaction stirred for a further 20 min. The reaction mixture was diluted with CH_2Cl_2 (30 ml) and washed with water (30 ml) and 1M HCl (30 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was stirred in trifluoroacetic acid: THF: water: methanol, 5:2:1:2

(2 ml). After 26 h, tlc (petrol:ethyl acetate, 1:1) indicated the formation of a major product (R_f 0.5). The reaction mixture was diluted with CH_2Cl_2 (30 ml) and washed with $NaHCO_3$ (30 ml of a saturated aqueous solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1→1:1) to afford methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside **30a** (56 mg, 65%) as a white solid identical to that previously described.

Benzyl 3,4,6-tri-O-benzyl-α-D-glucopyranoside 30b

Methyl 3,4,6-tri-*O* -benzyl-2-*O*-(1-benzyloxy-2-iodopropyl)-1-thio-β-D-glucopyranoside **56b** (110 mg, 0.146 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (90 mg, 0.44 mmol) were dissolved in anhydrous dichloroethane (2 ml). Methyl trifluoromethanesulfonate (0.08 ml, 0.73 mmol) was added. After 2 h, water (1 ml) and trifluoroacetic acid (2 ml) were added and the reaction stirred further. After 4 h 20 min, tlc (petrol:ethyl acetate, 2:1) indicated the formation of a major product (R_f 0.5). The reaction mixture was diluted with CH_2Cl_2 (30 ml) and washed with $NaHCO_3$ (30 ml of a saturated aqueous solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (cyclohexane:ethyl acetate, 2:1) to afford benzyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside **30b** (53 mg, 67%) as a colourless oil; $[\alpha]_D^{22}$ +81.6 (*c*, 0.5 in $CHCl_3$) [Lit. +88 (*c*, 0.76 in $CHCl_3$)][4]; δ_H (400 MHz, $CDCl_3$) 3.63 (1H, dd, $J_{5,6}$ 1.9 Hz, $J_{6,6'}$ 10.5 Hz, H-6), 3.64-3.80 (4H, m, H-2, H-3, H-4, H-6′), 3.81-3.85 (1H, m, H-5), 4.50, 4.83 (2H, ABq, J_{AB} 10.6 Hz, PhC$\underline{H}_2$), 4.53, 4.65 (2H,

ABq, J_{AB} 12.1 Hz, PhC$\underline{H}_2$), 4.56, 4.76 (2H, ABq, J_{AB} 11.7 Hz, PhC$\underline{H}_2$), 4.84, 4.95 (2H, ABq, J_{AB} 11.2 Hz, PhC$\underline{H}_2$), 5.04 (1H, d, $J_{1,2}$ 3.4 Hz, H-1), 7.14-7.39 (20H, m, Ar-H).

Cyclohexyl 3,4,6-tri-O-benzyl-α-D-glucopyranoside 30c

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(1-cyclohexyloxy-2-iodopropyl)-1-thio-β-D-glucopyranoside **56c** (80 mg, 0.107 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (66 mg, 0.321 mmol) were dissolved in anhydrous dichloroethane (2 ml). Methyl trifluoromethanesulfonate (0.06 ml, 0.536 mmol) was added. After 2 h 50 min, tlc (petrol:ethyl acetate, 2:1) indicated the consumption of starting material (R_f 0.8) and the formation of a major (R_f 0.5) and minor (R_f 0.7) products. Et_3N (2 ml) was added and the reaction stirred for a further 20 min. The reaction mixture was diluted with CH_2Cl_2 (30 ml) and washed with water (30 ml) and 1M HCl (30 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was stirred in trifluoroacetic acid: THF: water: methanol, 5:2:1:2 (2 ml). After 20 h, tlc (petrol:ethyl acetate, 2:1) indicated the formation of a major product (R_f 0.5). The reaction mixture was diluted with CH_2Cl_2 (30 ml) and washed with $NaHCO_3$ (30 ml of a saturated aqueous solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1→1:1) to afford cyclohexyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside **30c** (44 mg, 77%) as a white solid which recrystallised from ether/petrol, m.p. 92-94 °C (ether/petrol); $[\alpha]_D^{22}$ +90.0 (*c*, 0.3 in $CHCl_3$) [Lit. +60 (*c*, 0.6 in $CHCl_3$)][4];

δ_H (400 MHz, $CDCl_3$) 1.24-1.92 (10H, m, cyclohexyl-H), 2.06 (1H, d, *J* 2.7 Hz, OH-2), 3.61-3.75 (5H, m, H-2, H-3, H-4, H-6, cyclohexyl OCH), 3.77 (1H, dd, $J_{5,6'}$ 3.9 Hz, $J_{6,6'}$10.7 Hz, H-6′), 3.87-3.90 (1H, m, H-5), 4.49, 4.83 (2H, ABq, J_{AB} 10.7 Hz, PhC$\underline{H}_2$), 4.51, 4.65 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.84, 4.99 (2H, ABq, J_{AB} 11.0 Hz, PhC$\underline{H}_2$), 5.03 (1H, d, $J_{1,2}$ 3.5 Hz, H-1), 7.14-7.42 (15H, m, Ar-H).

3,4,6-Tri-O-benzyl-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 30d

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(1-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-*O*-yl)-2-iodopropyl)-1-thio-β-D-glucopyranoside **56d** (64 mg, 0.075 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (46 mg, 0.23 mmol) were dissolved in anhydrous dichloroethane (2 ml). Methyl trifluoromethanesulfonate (0.04 ml, 0.38 mmol) was added. After 2 h, tlc (petrol:ethyl acetate, 3:1) indicated the complete consumption of starting material (R_f 0.5) and the formation of a major (R_f 0.1) and minor (R_f 0.2-0.4) products. Et_3N (2 ml) was added and the reaction mixture stirred for a further 10 min. The mixture was then diluted with CH_2Cl_2 (30 ml) and washed with water (30 ml) and 1M HCl (30 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1) to afford 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **30d** (34 mg, 70%) as a colourless oil; $[\alpha]_D^{22}$ +27.7 (*c*, 0.35 in $CHCl_3$) [Lit. +29 (*c*, 0.9 in $CHCl_3$)][4]; δ_H (400 MHz, $CDCl_3$) 1.34, 1.35, 1.45, 1.54 (12 H, 4 x s, 4 x CH_3), 3.63-3.79 (6H, m, H-2_b, H-3_b, H-4_b, H-6_b, H-$6'_b$, H-6_a), 3.85 (1H, ddd, $J_{4,5}$ 9.9 Hz,

$J_{5,6}$ 2.2 Hz, $J_{5,6'}$3.0 Hz, H-5_b), 3.91 (1H, dd, $J_{5,6'}$ 6.7 Hz, $J_{6,6'}$10.2 Hz, H-$6'_a$), 4.00 (1H, atd, J 6.7 Hz, $J_{4,5}$1.9 Hz, H-5_a), 4.25 (1H, dd, $J_{3,4}$ 7.8 Hz, H-4_a), 4.34 (1H, dd, $J_{1,2}$ 4.9 Hz, $J_{2,3}$ 2.2 Hz, H-2_a), 4.49, 4.83 (2H, ABq, J_{AB} 10.3 Hz, PhC$\underline{H}_2$), 4.50, 4.64 (2H, ABq, J_{AB} 11.7 Hz, PhC$\underline{H}_2$), 4.63 (1H, dd, H-3_a), 4.82, 4.98 (2H, ABq, J_{AB} 10.7 Hz, PhC$\underline{H}_2$), 4.93 (1H, d, $J_{1,2}$ 3.2 Hz, H-1_b), 5.53 (1H, d, H-1_a), 7.12-7.41 (15H, m, Ar-H).

Methyl 3,4,6-tri-O-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-O-benzyl-α-D-mannopyranoside 30e

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranosid-6-*O*-yl)propyl)-1-thio-β-D-glucopyranoside **56e** (91 mg, 0.082 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (50 mg, 0.25 mmol) were dissolved in anhydrous dichloroethane (2 ml). Methyl trifluoromethanesulfonate (0.06 ml, 0.41 mmol) was added. After 2 h, tlc (petrol:ethyl acetate, 3:1) indicated the complete consumption of starting material (R_f 0.5) and the formation of a major (R_f 0.1) and minor (R_f 0.2-0.4) products. Water (1 ml) and trifluoroacetic acid (2 ml) were added and the reaction stirred further. After 4 h, the reaction mixture was diluted with CH_2Cl_2 (30 ml) and washed with $NaHCO_3$ (30 ml of a saturated aqueous solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1→1:1) to afford methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **30e** (53 mg, 72%) as a colourless oil; $[\alpha]_D^{22}$ +65.5 (*c*, 1.1 in $CHCl_3$); ν_{max} 3430 (br, OH) cm^{-1};

δ_H (400 MHz, $CDCl_3$) 3.30 (3H, s, OCH_3), 3.59-3.80 (8H, m, H-2_b, H-3_b, H-4_b, H-5_b, H-6_b, H-$6'_b$, H-5_a, H-6_a), 3.79 (1H, dd, $J_{1,2}$ 2.0 Hz, $J_{2,3}$ 3.0 Hz, H-2_a), 3.91 (1H, dd, $J_{3,4}$ 9.4 Hz, H-3_a), 4.04-4.10 (2H, m, H-4_a, H-$6'_a$), 4.47, 4.84 (2H, ABq, J_{AB} 10.8 Hz, PhC$\underline{H}_2$), 4.48, 4.61 (2H, ABq, J_{AB} 12.2 Hz, PhC$\underline{H}_2$), 4.62 (2H, s, PhC$\underline{H}_2$), 4.62, 4.98 (2H, ABq, J_{AB} 11.1 Hz, PhC$\underline{H}_2$), 4.70 (1H, d, H-1_a), 4.71, 4.92 (2H, ABq, J_{AB} 11.1 Hz, PhC$\underline{H}_2$), 4.72 (2H, s, PhC$\underline{H}_2$), 5.00 (1H, d, $J_{1,2}$ 2.9 Hz, H-1_b), 7.14-7.39 (30H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 54.9 (q, CH_3), 67.7, 68.4, 72.0, 72.8, 73.4, 75.0, 75.1, 75.2 (8 x t, 6 x Ph$\underline{C}H_2$, C-6_b, C-6_a), 70.7, 71.3, 73.8, 74.1, 74.2, 77.0, 79.9, 83.3 (8 x d, C-2_b, C-3_b, C-4_b, C-5_b, C-2_a, C-3_a, C-4_a, C-5_a), 98.9, 100.6 (2 x d, C-1_b, C-1_a), 127.4, 127.6, 127.6, 127.7, 127.8, 127.8, 127.9, 127.9, 128.0, 128.1, 128.3, 128.3, 128.4 (13 x d, Ar-CH), 138.0, 138.2, 138.3, 138.4, 138.9 (5 x s, Ar-C); *m/z* (APCI$^+$) 919 (M+Na^+, 55%); (APCI$^-$) 931 (M+Cl^-, 10%). (HRMS Calcd. for $C_{55}H_{61}O_{11}$ (MH^+) 897.4214. Found 897.4229).

Methyl 3,4,6-tri-O-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside 30f

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranosid-6-*O*-yl)propyl)-1-thio-β-D-glucopyranoside **56f** (75 mg, 0.068 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (42 mg, 0.20 mmol) were dissolved in anhydrous dichloroethane (2 ml). Methyl trifluoromethanesulfonate (0.04 ml, 0.34 mmol) was added. After 2 h, tlc (petrol:ethyl acetate, 3:1) indicated the complete consumption of starting material (R_f 0.5) and the formation of a major (R_f 0.1) and minor (R_f 0.3 and 0.5) products. Et_3N (2 ml) was added and the mixture stirred for a further

20 min. After this time, the mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (petrol:ethyl acetate, 3:1→1:1) to afford methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **30f** (30 mg, 50%) as a colourless oil; $[\alpha]_D^{22}$ +82.0 (*c*, 0.85 in $CHCl_3$) [Lit. +74.1 (*c*, 1.0 in $CHCl_3$)][5]; δ_H (400 MHz, $CDCl_3$) 3.36 (3H, s, OCH_3), 3.48 (1H, at, *J* 9.7 Hz, H-4_a), 3.51 (1H, dd, $J_{1,2}$ 3.4 Hz, $J_{2,3}$ 9.7 Hz, H-2_a), 3.54 (1H, dd, $J_{5,6}$ 1.9 Hz, $J_{6,6'}$ 10.8 Hz, H-6_b), 3.61-3.75 (6H, m, H-2_b, H-3_b, H-4_b, H-5_b, H-$6'_b$, H-6_a), 3.76-3.79 (1H, m, H-5_a), 3.93 (1H, dd, $J_{5,6'}$ 4.5 Hz, $J_{6,6'}$ 11.3 Hz, H-$6'_a$), 4.00 (1H, at, *J* 9.3 Hz, H-3_a), 4.44, 4.58 (2H, ABq, J_{AB} 12.3 Hz, PhC$\underline{H}_2$), 4.47, 4.82 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 4.58, 4.92 (2H, ABq, J_{AB} 10.7 Hz, PhC$\underline{H}_2$), 4.60 (1H, d, H-1_a), 4.68, 4.79 (2H, ABq, J_{AB} 12.2 Hz, PhC$\underline{H}_2$), 4.81, 5.00 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 4.82, 4.93 (2H, ABq, J_{AB} 11.1 Hz, PhC$\underline{H}_2$), 4.93 (1H, d, $J_{1,2}$ 3.4 Hz, H-1_b), 7.13-7.39 (30H, m, Ar-H);

The combined minor products were dissolved in trifluoroacetic acid: THF: water: methanol (5:2:1:2, 2 ml) and the mixture stirred for 24 h. After this time, the mixture was diluted with CH_2Cl_2 (30 ml) and washed with $NaHCO_3$ (30 ml of a saturated aqueous solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* and the residue purified by flash column chromatography (petrol:ethyl acetate, 2:1→1:1) to afford further methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **30f** (15 mg, 24%) as a colourless oil identical to that described above.

Attempted one-pot reaction in the *gluco* SMe system

Cyclohexyl 3,4,6-tri-O-benzyl-α-D-glucopyranoside 30c and cyclohexyl 3,4,6-tri-O-benzyl-β-D-glucopyranoside 62

N-Iodosuccinimide (130 mg, 0.577 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (118 mg, 0.577 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (2 ml) and cooled to -40 °C under Ar. Methyl 3,4,6-tri-*O*-benzyl-2-*O*-prop-1′-enyl-1-thio-β-D-glucopyranoside **51** (100 mg, 0.19 mmol) and cyclohexanol **3c** (0.061 ml, 0.577 mmol) were dissolved in anhydrous dichloroethane (4 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm up. After 20 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.6) and complete consumption of starting material (R_f 0.5). Methyl trifluoromethanesulfonate (0.11 ml, 0.96 mmol) was added and the reaction was removed from the cooling bath and allowed to warm to RT. After a further 1 h 35 min, tlc (petrol:ethyl acetate, 3:1) indicated the formation of two major products (R_f 0.3 and R_f 0.35) and various minor, less polar products. Trifluoroacetic acid (4 ml) and water (2 ml) were added and the mixture stirred further. After a further 1 h 30 min, tlc indicated the disappearance of these minor products. The reaction mixture was diluted with ether (30 ml) and washed with $NaHCO_3$ (30 ml of a saturated aqueous solution) and sodium thiosulfate (30 ml of a saturated aqueous solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford cyclohexyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside **62** (36 mg, 35%) as a colourless oil; $[\alpha]_D^{24}$ -4.7 (*c*, 0.9 in $CHCl_3$) [Lit. -4.4 (*c*, 0.25 in $CHCl_3$)][4]; δ_H (200 MHz, $CDCl_3$) 1.23-2.06

(10H, m, cyclohexyl-H), 2.33 (1H, d, $J_{OH,2}$ 1.4 Hz, OH-2), 3.50-3.80 (7H, m, H-2, H-3, H-4, H-5, H-6, H-6′, cyclohexyl OCH), 4.36 (1H, d, $J_{1,2}$ 7.5 Hz, H-1), 4.54, 4.85 (2H, ABq, J_{AB} 11.0 Hz, PhC$\underline{H}_2$), 4.55, 4.63 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.83, 4.96 (2H, ABq, J_{AB} 11.1 Hz, PhC$\underline{H}_2$), 7.16-7.42 (15H, m, Ar-H); *m/z* (APCI$^+$) 555 (M+Na$^+$, 22), 550 (M+NH_4^+, 37%); (APCI$^-$) 1000 (2M+Cl$^-$-OCyclohexyl, 5), 567 (M+Cl$^-$, 55%);

And cyclohexyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside **30c** (60 mg, 59%) as a white solid identical to that previously described.

7.3 Experimental for Chapter 3

2-O-Acetyl-3,4,6-tri-O-benzyl-β-D-glucopyranosyl fluoride 66

3,4,6-Tri-*O*-benzyl-1,2-*O*-(*exo*-ethoxyethylidene)-α-D-glucopyranose **40** (1.0 g, 1.92 mmol) was dissolved in freshly distilled CH_2Cl_2 (8 ml). The mixture was cooled to 0 °C and diethylaminosulfur trifluoride (0.33 ml, 2.50 mmol) was added. The reaction mixture was stirred at 0 °C. After 3h 30 min, tlc (CH_2Cl_2:ether, 14:1) indicated formation of a product (R_f 0.8) and complete consumption of starting material (R_f 0.7). The reaction was quenched with ice water (200 ml) then extracted with ether (2 x 200 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl fluoride **66** (796 mg, 84%) as a colourless oil; $[\alpha]_D^{22}$ +15.3 (*c*, 1.25 in $CHCl_3$); ν_{max} 1750 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.02 (3H, s, C$\underline{H}_3$), 3.67-3.75 (4H, m, H-3, H-5, H-6, H-6′), 3.86 (1H, at, *J* 9.0 Hz, H-4), 4.56, 4.78 (2H, ABq, J_{AB} 11.2 Hz, PhC$\underline{H}_2$), 4.56, 4.63 (2H, ABq, J_{AB} 12.1 Hz, PhC$\underline{H}_2$), 4.71, 4.78 (2H, ABq, J_{AB} 11.6 Hz, PhC$\underline{H}_2$), 5.09-5.15 (1H, m, H-2), 5.27 (1H, dd, $J_{1,2}$ 6.1 Hz, $J_{1,F}$ 52.9 Hz, H-1), 7.16-7.36 (15H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 20.8 (q, $\underline{C}H_3$), 68.4, 73.6, 74.4, 74.9 (4 x t, C-6, 3 x Ph$\underline{C}H_2$), 72.5 (dd, C-2), 75.0, 81.5, 81.6 (3 x d, C-3, C-4, C-5), 106.7 (dd, C-1), 127.7, 127.8, 127.8, 127.9, 128.0, 128.4, 128.4, 128.9 (8 x d, Ar-CH), 137.6, 137.8 (2 x s, Ar-C), 169.4 (s, C=O); δ_F ($CDCl_3$) -136.8 (dd, $J_{1,F}$ 52.9 Hz, $J_{2,F}$ 10.2 Hz); *m/z* (APCI$^+$) 533 (M+K^+, 100), 517 (M+Na^+, 15), 475 (M-F, 5%). (Found: C, 70.49; H, 6.48. $C_{29}H_{31}O_6F$ requires C, 70.43; H, 6.32%).

3,4,6-Tri-O-benzyl-β-D-glucopyranosyl fluoride 65

3,4,6-Tri-*O*-benzyl-1,2-*O*-(*exo*-ethoxyethylidene)-α-D-glucopyranose **40** (5.0 g, 9.6 mmol) was dissolved in freshly distilled CH_2Cl_2 (20 ml) in a flame-dried flask and cooled to 0°C under Ar. Diethylaminosulfur trifluoride (1.65 ml, 12.5 mmol) was added. After 7 h 30 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.45) and complete consumption of starting material (R_f 0.5). The reaction was quenched with water (200 ml) then extracted with ether (2 x 150 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*.

The residue was dissolved in THF (10 ml), methanol (5 ml) and *n*-propylamine (5 ml) and stirred at 45 °C. After 16 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a single product (R_f 0.2). The mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1→4:1) to afford 3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl fluoride **65** (3.94 g, 91%) as a white crystalline solid, m.p. 84 °C (ether/petrol) [Lit 80-82 °C][6]; $[\alpha]_D^{22}$ +31.5 (*c*, 0.55 in $CHCl_3$) [Lit +25.2][6]; δ_H (400 MHz, $CDCl_3$) 3.59-3.80 (6H, m, H-2, H-3, H-4, H-5, H-6, H-6′), 4.54, 4.62 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.57, 4.78 (2H, ABq, J_{AB} 11.1 Hz, PhC$\underline{H}_2$), 4.81, 4.85 (2H, ABq, J_{AB} 11.5 Hz, PhC$\underline{H}_2$), 5.17 (1H, d, $J_{1,2}$ 6.5 Hz, $J_{1,F}$ 53.0 Hz, H-1), 7.17-7.40 (15H, m, Ar-H).

2-O-Allyl-3,4,6-tri-O-benzyl-β-D-glucopyranosyl fluoride 63

3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl fluoride **65** (3.94 g, 8.7 mmol) was dissolved in anhydrous DMF (20 ml) and cooled to 0 °C. Allyl bromide (1.5 ml, 17.4 mmol) was added then sodium hydride (60% in mineral oil) (696 mg, 17.4 mmol) was added portionwise. After 1 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a single product (R_f 0.5) and complete consumption of starting material (R_f 0.2). The reaction was quenched with methanol (6 ml) and the mixture partitioned between CH_2Cl_2 (2 x 100 ml) and water (100 ml). The combined organic layers were washed with brine (50 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) to afford 2-*O*-allyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl fluoride **63** (3.99 g, 93%) as a colourless oil; $[\alpha]_D^{22}$ +9.2 (*c*, 0.5 in $CHCl_3$); ν_{max} 1647 (w, C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.49 (1H, ddd, $J_{1,2}$ 6.9 Hz, $J_{2,3}$ 8.6 Hz, $J_{2,F}$ 12.3 Hz, H-2), 3.59 (1H, ddd, $J_{4,5}$ 9.5 Hz, $J_{5,6}$ 2.6 Hz, $J_{5,6'}$ 3.7 Hz, H-5), 3.64 (1H, at, J 8.7 Hz, H-3), 3.69-3.77 (3H, m, H-4, H-6, H-6′), 4.20 (1H, dd, J_{gem} 12.4 Hz, J 5.8 Hz, OC$\underline{H}$H′CH=CH_2), 4.34 (1H, dd, J 5.7 Hz, OCH$\underline{H}$′CH=CH_2), 4.54, 4.93 (2H, ABq, J_{AB} 10.8 Hz, PhC$\underline{H}_2$), 4.55, 4.64 (2H, ABq, J_{AB} 12.2 Hz, PhC$\underline{H}_2$), 4.80, 4.93 (2H, ABq, J_{AB} 10.8 Hz, PhC$\underline{H}_2$), 5.21 (1H, dd, $J_{1,F}$ 52.8 Hz, H-1), 5.22 (1H, dd, J_{gem} 1.6 Hz, J_Z 10.3 Hz, CH=$CH_E\underline{H}_Z$), 5.32 (1H, dd, J_E 17.3 Hz, CH=C$\underline{H}_E H_Z$), 5.95 (1H, ddt, C$\underline{H}$=CH_2), 7.14-7.38 (15H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 68.3, 73.3, 73.5, 75.0, 75.5 (5 x t, 3 x Ph$\underline{C}H_2$, O$\underline{C}H_2$CH=CH_2, C-6), 74.7, 76.8, 83.4 (3 x d, C-3, C-4, C-5), 81.2 (dd, $^2J_{C\text{-}2,F}$ 21.5 Hz, C-2), 109.7 (dd, $^1J_{C\text{-}1,F}$ 215.5 Hz, C-1), 117.6 (t, CH=$\underline{C}H_2$), 127.7, 127.8, 127.8, 127.9, 127.9, 128.4, 128.4 (7 x d, Ar-CH), 134.3 (d, $\underline{C}$H=CH_2), 137.8, 137.8,

138.2 (3 x s, Ar-C); *m/z* (APCI$^+$) 515 (M+Na$^+$, 10%). (HRMS Calcd. for $C_{30}H_{37}NO_5F$ (MNH_4^+) 510.2656. Found 510.2658).

1,2,3,4,6-Penta-O-acetyl-D-mannopyranose 75

D-Mannose **74** (10 g, 56 mmol) was suspended in acetic anhydride (50 ml) and iodine (2.5 g, 9.8 mmol) was added. Further iodine (100 mg, 0.39 mmol) was dissolved in acetic anhydride (2 ml) and then added to the reaction mixture. After 5 min, tlc (petrol:ethyl acetate, 1:1) indicated formation of a product (R_f 0.4) and complete consumption of starting material (R_f 0). The reaction mixture was partitioned between $Na_2S_2O_3$ (200 ml of a 10% aqueous solution) and CH_2Cl_2 (200 ml). The organic extracts were washed with $NaHCO_3$ (200 ml of a saturated aqueous solution), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 1,2,3,4,6-penta-*O*-acetyl-D-mannopyranose **75** (26.3 g) as a pale yellow oil which was used without further purification.

2,3,4,6-Tetra-O-acetyl-α-D-mannopyranosyl bromide 76

Crude 1,2,3,4,6-penta-*O*-acetyl-D-mannopyranose **75** (26.3 g) was added portionwise to a stirred solution of HBr (33% in acetic acid) (45 ml) at 0°C. The reaction mixture was allowed to warm to RT. After 3 h, tlc (petrol:ethyl acetate, 1:1) indicated formation of a product (R_f 0.5) and complete consumption of starting material (R_f 0.4). The reaction mixture was diluted with CH_2Cl_2 (200 ml) and washed with ice water (2 x 100 ml) then $NaHCO_3$ (2 x 100 ml of a saturated aqueous solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 2,3,4,6-tetra-*O*-acetyl-α-

D-mannopyranosyl bromide **76** (21.7 g) as a pale brown foam which was used without further purification; δ_H (200 MHz, $CDCl_3$) 2.02, 2.08, 2.12, 2.19 (12H, 4 x s, 4 x $COC\underline{H}_3$), 4.14 (1H, dd, $J_{5,6}$ 2.0 Hz, $J_{6,6'}$ 12.0 Hz, H-6), 4.19-4.27 (1H, m, H-5), 4.35 (1H, dd, $J_{5,6'}$ 4.6 Hz, H-6'), 5.37 (1H, at, J 10.0 Hz, H-4), 5.45 (1H, dd, $J_{1,2}$ 1.5 Hz, $J_{2,3}$ 3.7 Hz, H-2), 5.73 (1H, dd, $J_{3,4}$ 10.2 Hz, H-3), 6.30 (1H, d, H-1).

***3,4,6-Tri*-O-*acetyl*-1,2-O-(exo-*methoxyethylidene*)-β-D-*mannopyranose* 77**

Crude 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide **76** (21.7 g), methanol (4.05 ml, 100.1 mmol) and 2,4,6-collidine (8.8 ml, 66.7 mmol) were dissolved in freshly distilled CH_2Cl_2 (200 ml). The reaction mixture was stirred at reflux at 40 °C. After 15 h, tlc (petrol:ethyl acetate, 1:1) indicated formation of a major product (R_f 0.45), a minor product (R_f 0.3) and a small amount of starting material remaining (R_f 0.5). The reaction mixture was allowed to cool then diluted with CH_2Cl_2 (100 ml) and washed with $NaHCO_3$ (150 ml of a saturated aqueous solution) and water (100 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was recrystallised from ether to afford 3,4,6-tri-*O*-acetyl-1,2-*O*-(*exo*-methoxyethylidene)-β-D-mannopyranose **77** (13.6 g, 67% over 3 steps) as a white crystalline solid, m.p. 107-110 °C (ether) [Lit. 112-113 °C][7]; $[\alpha]_D^{25}$ –19.0 (*c*, 0.5 in $CHCl_3$) [Lit. -22.2 (*c*, 2.5 in $CHCl_3$)][7]; δ_H (400 MHz, $CDCl_3$) 1.75 (3H, s, $C(O)_3CH_3$), 2.06, 2.13, 2.19 (9H, 3 x s, 3 x $COCH_3$), 3.49 (3H, s, OCH_3), 3.69 (1H, ddd, $J_{4,5}$ 9.6 Hz, $J_{5,6}$ 2.7 Hz, $J_{5,6'}$ 4.8 Hz, H-5), 4.15 (1H, dd, $J_{6,6'}$ 12.3 Hz, H-6), 4.24 (1H, dd, H-6'), 4.62 (1H, dd, $J_{1,2}$ 2.6 Hz, $J_{2,3}$ 4.0 Hz, H-2), 5.15 (1H, dd, $J_{3,4}$ 9.9 Hz, H-3), 5.31 (1H, at, J 9.7 Hz, H-4), 5.50 (1H, d, H-1).

3,4,6-Tri-O-benzyl-1,2-O-(exo-methoxyethylidene)-β-D-mannopyranose 70

3,4,6-Tri-*O*-acetyl-1,2-*O*-(*exo*-methoxyethylidene)-β-D-mannopyranose **77** (13 g, 35.7 mmol) was dissolved in methanol (200 ml). Sodium (500 mg, 21.0 mmol) was dissolved in methanol (30 ml) and added to the sugar solution by pipette. After 45 min, tlc (ethyl acetate) indicated formation of a product (R_f 0.1) and complete consumption of starting material (R_f 0.8). The reaction mixture was concentrated *in vacuo*.

The residue was dissolved in anhydrous DMF (120 ml) and cooled to 0 °C. Benzyl bromide (19 ml, 161 mmol) was added then sodium hydride (60% in mineral oil) (6.3 g, 161 mmol) was added portionwise. After 15 h 30 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a single product (R_f 0.3) and complete consumption of starting material (R_f 0). The reaction was quenched with methanol (50 ml) and the mixture concentrated *in vacuo*. The residue was partitioned between ether (200 ml) and water (200 ml). The aqueous layer was extracted with ether (100 ml) and the combined organics washed with brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was recrystallised from ethyl acetate/petrol to afford 3,4,6-tri-*O*-benzyl-1,2-*O*-(*exo*-methoxyethylidene)-β-D-mannopyranose **70** (16.7 g, 92%) as a white crystalline solid, m.p. 72-74 °C (ethyl acetate/petrol) [Lit. 71-72 °C][8]; $[\alpha]_D^{25}$ +35.8 (*c*, 0.5 in $CHCl_3$) [Lit. +34 (*c*, 1.35 in $CHCl_3$)][8]; δ_H (400 MHz, $CDCl_3$) 1.80 (3H, s, $C(O)_3CH_3$), 3.34 (3H, s, OCH_3), 3.48 (1H, ddd, $J_{4,5}$ 9.2 Hz, $J_{5,6}$ 2.2 Hz, $J_{5,6'}$ 4.3 Hz, H-5), 3.76 (1H, dd, $J_{6,6'}$ 10.7 Hz, H-6), 3.77-3.80 (1H, m, H-3), 3.81 (1H, dd, H-6′), 3.98 (1H, at, *J* 9.3 Hz, H-4), 4.46 (1H, dd, $J_{1,2}$ 2.3 Hz, $J_{3,4}$ 3.8 Hz, H-2),

4.60, 4.66 (2H, ABq, J_{AB} 12.2 Hz, PhC$\underline{H}_2$), 4.66, 4.95 (2H, ABq, J_{AB} 10.7 Hz, PhC$\underline{H}_2$), 4.82, 4.85 (2H, ABq, J_{AB} 12.4 Hz, PhC$\underline{H}_2$), 5.41 (1H, d, H-1), 7.29-7.46 (15H, m, Ar-H).

2-O-Acetyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl fluoride 78

3,4,6-Tri-*O*-benzyl-1,2-*O*-(*exo*-methoxyethylidene)-β-D-mannopyranose **70** (16.7 g, 32.8 mmol) was dissolved in freshly distilled CH_2Cl_2 (80 ml). The mixture was cooled to 0 °C and diethylaminosulfur trifluoride (5.1 ml, 37.7 mmol) was added. The reaction mixture was stirred at 0 °C. After 7h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.5) and complete consumption of starting material (R_f 0.3). The reaction mixture was diluted with ether (200 ml) then washed with water (2 x 200 ml). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1 with 1% Et_3N) to afford 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl fluoride **78** (15.8 g, 98%) as a pale yellow oil; $[\alpha]_D^{23}$ +13.3 (*c*, 1.0 in $CHCl_3$); ν_{max} 1751 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.17 (3H, s, CH_3), 3.72 (1H, d, $J_{6,6'}$ 10.9 Hz, H-6), 3.82 (1H, dd, $J_{5,6'}$ 2.7 Hz, H-6'), 3.97-3.99 (3H, m, H-3, H-4, H-5), 4.49, 4.87 (2H, ABq, J_{AB} 10.7 Hz, PhC$\underline{H}_2$), 4.52, 4.69 (2H, ABq, J_{AB} 12.1 Hz, PhC$\underline{H}_2$), 4.57, 4.72 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 5.48 (1H, br s, H-2), 5.62 (1H, dd, $J_{1,2}$ 1.9 Hz, $J_{1,F}$ 49.1 Hz, H-1), 7.15-7.38 (15H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 21.0 (q, CH_3), 67.0 (dd, $^2J_{C\text{-}2,F}$ 39.9 Hz, C-2), 68.2 (t, C-6), 72.1, 73.5, 75.3 (3 x t, 3 x Ph$\underline{C}H_2$), 73.3 (d, C-4), 73.8 (dd, $^3J_{C\text{-}5,F}$ 2.0 Hz, C-5), 77.2 (d, C-3), 105.5 (dd, $^1J_{C\text{-}1,H}$ 182.6 Hz, $^1J_{C\text{-}1,F}$ 221.0 Hz, C-1), 127.8, 127.8, 127.9,

128.0, 128.1, 128.4, 128.5 (7 x d, Ar-CH), 137.6, 138.0, 138.1 (3 x s, Ar-C), 170.1 (s, C=O); *m/z* (APCI$^+$) 517 (M+Na$^+$, 18%). (HRMS Calcd. for $C_{29}H_{35}NO_6F$ (MNH_4^+) 512.2448. Found 512.2451). (Found: C, 70.27; H, 6.50. $C_{29}H_{31}O_6F$ requires C, 70.43; H, 6.32%).

3,4,6-Tri-O-benzyl-α-D-mannopyranosyl fluoride 79

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl fluoride **78** (3.0 g, 6.07 mmol) was dissolved in methanol (5 ml), THF (10 ml) and *n*-propylamine (5 ml) and the reaction mixture stirred at 45 °C. After 19 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.2) and complete consumption of starting material (R_f 0.4). The mixture was concentrated *in vacuo* and purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford 3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl fluoride **79** (2.72 g, 99%) as a colourless oil; $[\alpha]_D^{23}$ +34.2 (*c*, 0.5 in $CHCl_3$); ν_{max} 3422 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.70 (1H, dd, $J_{5,6}$ 1.6 Hz, $J_{6,6'}$ 10.8 Hz, H-6), 3.78 (1H, dd, $J_{5,6'}$ 3.5 Hz, H-6′), 3.87-3.90 (1H, m, H-3), 3.94-3.96 (2H, m, H-4, H-5), 4.12-4.13 (1H, m, H-2), 4.54, 4.67 (2H, ABq, J_{AB} 12.2 Hz, PhC$\underline{H}_2$), 4.54, 4.83 (2H, ABq, J_{AB} 10.8 Hz, PhC$\underline{H}_2$), 4.71, 4.74 (2H, ABq, J_{AB} 11.4 Hz, PhC$\underline{H}_2$), 5.68 (1H, dd, $J_{1,2}$ 1.7 Hz, $J_{1,F}$ 49.5 Hz, H-1), 7.17-7.37 (15H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 67.1 (dd, $^2J_{C\text{-}2,F}$ 39.0 Hz, C-2), 68.2 (t, C-6), 72.4, 73.5, 75.2 (3 x t, 3 x Ph$\underline{C}H_2$), 73.2 (d, C-4), 73.4 (dd, $^3J_{C\text{-}5,F}$ 2.7 Hz, C-5), 79.1 (dd, $^3J_{C\text{-}3,F}$ 1.8 Hz, C-3), 107.2 (dd, $^1J_{C\text{-}1,H\text{-}1}$ 181.9 Hz, $^1J_{C\text{-}1,F}$ 217.7 Hz, C-1), 127.7, 127.8, 127.9, 127.9, 128.0, 128.1, 128.4, 128.6 (8 x d, Ar-CH), 137.6, 137.9, 138.0 (3 x s, Ar-C). (Found: C, 71.54; H, 6.50. $C_{27}H_{29}O_5F$ requires C, 71.66; H, 6.46%).

2-O-Allyl-3,4,6-tri-O-benzyl-α-D-mannopyranosyl fluoride 64

3,4,6-Tri-*O*-benzyl-α-D-mannopyranosyl fluoride **79** (960 mg, 2.12 mmol) was dissolved in anhydrous DMF (5 ml) and cooled to 0 °C. Allyl bromide (0.36 ml, 4.24 mmol) was added then sodium hydride (60% in mineral oil) (170 mg, 4.24 mmol) was added portionwise. After 1 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a single product (R_f 0.5) and complete consumption of starting material (R_f 0.2). The reaction mixture was quenched with water (100 ml) and extracted with CH_2Cl_2 (2 x 100 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford 2-*O*-allyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl fluoride **64** (1.01 g, 96%) as a colourless oil; $[\alpha]_D^{27}$ +35.2 (*c*, 1.4 in $CHCl_3$); ν_{max} 1645 (w, C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.71 (1H, dd, $J_{5,6}$ 1.9 Hz, $J_{6,6'}$ 10.9 Hz, H-6), 3.67 (1H, dd, $J_{5,6'}$ 4.5 Hz, H-6′), 3.84-3.85 (1H, m, H-2), 3.86-3.98 (2H, m, H-3, H-5), 4.02 (1H, at, *J* 9.5 Hz, H-4), 4.17 (1H, dd, J_{gem} 13.1 Hz, *J* 6.0 Hz, OC$\underline{H}$H′CH=CH_2), 4.25 (1H, dd, *J* 5.7 Hz, OCH$\underline{H}$′CH=CH_2), 4.51, 4.88 (2H, ABq, J_{AB} 10.8 Hz, PhC$\underline{H}_2$), 4.54, 4.68 (2H, ABq, J_{AB} 12.3 Hz, PhC$\underline{H}_2$), 4.73 (2H, s, PhC$\underline{H}_2$), 5.24 (1H, dd, J_{gem} 1.5 Hz, J_Z 10.3 Hz, CH=$CH_E\underline{H}_Z$), 5.31 (1H, dd, J_E 17.2 Hz, CH=C$\underline{H}_E H_Z$), 5.64 (1H, dd, $J_{1,2}$ 1.8 Hz, $J_{1,F}$ 50.6 Hz, H-1), 5.93 (1H, ddat, C$\underline{H}$=CH_2), 7.16-7.41 (15H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 68.5 (t, C-6), 72.6, 72.6 (2 x t, Ph$\underline{C}H_2$, O$\underline{C}H_2$CH=CH_2), 73.3 (dd, $^2J_{C\text{-}2,F}$ 35.3 Hz, C-2), 73.4, 75.2 (2 x t, 2 x Ph$\underline{C}H_2$), 73.9 (d, C-4), 74.0 (d, C-5), 79.0 (d, C-3), 106.4 (dd, $^1J_{C\text{-}1,H\text{-}1}$ 182.2 Hz, $^1J_{C\text{-}1,F}$ 222.6 Hz, C-1), 118.1 (t, CH=$\underline{C}H_2$), 127.6, 127.7, 127.8, 127.9,

127.9, 128.1, 128.1, 128.3, 128.3, 128.5, 128.7 (11 x d, Ar-CH), 134.5 (d, $\underline{C}H=CH_2$), 138.0, 138.0, 138.1 (3 x s, Ar-C); *m/z* (APCI$^+$) 515 (M+Na$^+$, 100%). (HRMS Calcd. for $C_{30}H_{37}NO_5F$ (MNH_4^+) 510.2656. Found 510.2657). (Found: C, 73.15; H, 6.86. $C_{30}H_{33}O_5F$ requires C, 73.15; H, 6.75%).

3,4,6-Tri-O-benzyl-2-O-prop-1′-enyl-β-D-glucopyranosyl fluoride 80

Wilkinson's catalyst (390 mg, 0.42 mmol) was dissolved in freshly distilled THF (8 ml) and degassed. Butyl lithium (1.6M solution in hexanes) (0.4 ml, 0.63 mmol) was added and the mixture stirred for 1 h. 2-*O*-Allyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl fluoride **63** (2.06 g, 4.19 mmol) was dissolved in freshly distilled THF (8 ml) and heated to 70 °C. The catalyst solution was added by cannula under Ar. After 45 min, the reaction was allowed to cool then diluted with CH_2Cl_2 (20 ml) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1 with 1% Et_3N) to afford 3,4,6-tri-*O* -benzyl-2-*O*-prop-1′-enyl-β-D-glucopyranosyl fluoride **80** (2.02 g, 98%) as a pale yellow oil; Partial data: δ_H (400 MHz, $CDCl_3$) (E:Z, 1:2.3), E isomer 1.58 (3H, dd, *J* 1.6 Hz, *J* 7.0 Hz, OCH=CHC$\underline{H}_3$), 5.08 (1H, dq, J_E 12.2 Hz, OCH=C$\underline{H}$), 5.23 (1H, dd, $J_{1,2}$ 6.3 Hz, $J_{1,F}$ 52.5 Hz, H-1), 6.23 (1H, d, OC$\underline{H}$=CH); Z isomer 1.65 (3H, dd, *J* 1.7 Hz, *J* 6.8 Hz, OCH=CHC$\underline{H}_3$), 4.51 (1H, aquin, *J* 6.6 Hz, OCH=C$\underline{H}$), 5.25 (1H, m, $J_{1,2}$ 6.4 Hz, $J_{1,F}$ 52.7 Hz, H-1), 6.16 (1H, dd, J_Z 6.1 Hz, OC$\underline{H}$=CHCH$_3$); δ_C (100.6 MHz, $CDCl_3$) E isomer 12.2 (q, OCH=CH$\underline{C}H_3$), 102.1 (d, OCH=$\underline{C}$H), 108.4 (dd, $^1J_{C\text{-}1,F}$ 217.0 Hz, C-1), 146.4 (d, O$\underline{C}$H=CH); Z isomer 9.3 (q, OCH=CH$\underline{C}H_3$), 101.5 (d, OCH=$\underline{C}$H), 108.5 (dd, $^1J_{C\text{-}1,F}$ 213.3 Hz, C-1), 145.6 (d, O$\underline{C}$H=CH); *m/z* (ES$^+$) 510

(M+NH_4^+, 100%). (HRMS Calcd. for $C_{30}H_{37}NO_5F$ (MNH_4^+) 510.2656. Found 510.2663).

3,4,6-Tri-O-benzyl-2-O-prop-1′-enyl-α-D-mannopyranosyl fluoride 81

Wilkinson's catalyst (490 mg, 0.53 mmol) was dissolved in freshly distilled THF (6 ml) and degassed. Butyl lithium (1.6M solution in hexanes) (0.50 ml, 0.80 mmol) was added and the mixture stirred for 15 min. 2-*O*-Allyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl fluoride **64** (2.59 g, 5.26 mmol) was dissolved in freshly distilled THF (6 ml) and heated to 70 °C. The catalyst solution was added by cannula under Ar. After 2 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a single product (R_f 0.51) and complete consumption of starting material (R_f 0.49). The reaction was allowed to cool then diluted with CH_2Cl_2 (20 ml) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) to afford 3,4,6-tri-*O*-benzyl-2-*O*-prop-1′-enyl-α-D-mannopyranosyl fluoride **81** (2.53 g, 98%) as a pale yellow oil; Partial data: δ_H (400 MHz, $CDCl_3$) (*Z*:*E*, 2.7:1) E isomer 1.55 (3H, dd, J 1.7 Hz, J 6.8 Hz, OCH=CHC$\underline{H}_3$), 5.02 (1H, dq, J_E 12.4 Hz, OCH=C$\underline{H}$), 5.66 (1H, dd, $J_{1,2}$ 1.9 Hz, $J_{1,F}$ 50.2 Hz, H-1), 6.12 (1H, dq, OC$\underline{H}$=CH); Z isomer 1.63 (3H, dd, *J* 1.6 Hz, *J* 6.9 Hz, OCH=CHC$\underline{H}_3$), 5.62 (1H, dd, $J_{1,2}$ 2.0 Hz, $J_{1,F}$ 50.5 Hz, H-1), 5.97 (1H, dq, J_Z 6.0 Hz, OC$\underline{H}$=CH); δ_C (100.6 MHz, $CDCl_3$) E isomer 12.3 (q, OCH=CH$\underline{C}H_3$), 102.4 (d, OCH=$\underline{C}$H), 105.6 (dd, $^1J_{C\text{-}1,F}$ 221.7 Hz, C-1), 145.5 (d, O$\underline{C}$H=CH); Z isomer 9.4 (q, OCH=CH$\underline{C}H_3$), 104.2 (d, OCH=$\underline{C}$H), 106.1 (dd, $^1J_{C\text{-}1,F}$ 220.7 Hz, C-1), 144.5 (d, O$\underline{C}$H=CH); *m/z* (APCI$^+$) 515 (M+Na^+, 100%). (HRMS Calcd. for $C_{30}H_{37}NO_5F$ (MNH_4^+) 510.2656. Found 510.2663).

3,4,6-Tri-O-benzyl-2-O-(2-iodo-1-methoxypropyl)-β-D-glucopyranosyl fluoride 82a

N-Iodosuccinimide (410 mg, 1.83 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (2 ml) and cooled to -40 °C under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-β-D-glucopyranosyl fluoride **80** (300 mg, 0.61 mmol) and methanol **3a** (0.037 ml, 0.92 mmol) were dissolved in anhydrous dichloroethane (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to RT. After 90 min, the reaction was quenched with sodium thiosulfate (60 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 60 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-methoxypropyl)-β-D-glucopyranosyl fluoride **82a** (399 mg, >99%) as a colourless oil; *m/z* (APCI$^+$) 673 (M+Na$^+$, 15%).

3,4,6-Tri-O-benzyl-2-O-(1-benzyloxy-2-iodopropyl)-β-D-glucopyranosyl fluoride 82b

N-Iodosuccinimide (137 mg, 0.61 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (1.5 ml) and cooled to -40 °C under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-β-D-glucopyranosyl fluoride **80** (100 mg, 0.20 mmol) and benzyl alcohol **3b** (0.031 ml, 0.31 mmol) were dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to 0 °C over 1 h. After

1 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.45) and complete consumption of starting material (R_f 0.5). The reaction was quenched with sodium thiosulfate (20 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(1-benzyloxy-2-iodopropyl)-β-D-glucopyranosyl fluoride **82b** (144 mg, 98%) as a colourless oil; *m/z* (APCI$^+$) 749 (M+Na$^+$, 15%); (APCI$^-$) 761 (M+Cl$^-$, 35%).

3,4,6-Tri-O-benzyl-2-O-(1-cyclohexyloxy-2-iodopropyl)-β-D-glucopyranosyl fluoride 82c

N-Iodosuccinimide (109 mg, 0.49 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (2 ml) and cooled to -40 °C under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-β-D-glucopyranosyl fluoride **80** (80 mg, 0.16 mmol) and cyclohexanol **3c** (0.034 ml, 0.33 mmol) were dissolved in anhydrous dichloroethane (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to RT. After 5 h 45 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.55) and complete consumption of starting material (R_f 0.5). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) to afford 3,4,6-tri-*O*-

benzyl-2-*O*-(1-cyclohexyloxy-2-iodopropyl)-β-D-glucopyranosyl fluoride **82c** (116 mg, 99%) as a colourless oil; *m/z* (APCI$^+$) 741 (M+Na$^+$, 5%).

3,4,6-Tri-O-benzyl-2-O-(1-(1,2:3,4-di-O-isopropylidene-α-D-galactopyranos-6-O-yl)-2-iodopropyl)-β-D-glucopyranosyl fluoride 82d

N-Iodosuccinimide (109 mg, 0.49 mmol), and 4Å molecular sieves were added to anhydrous dichloroethane (1 ml) and cooled to -40 °C under Ar. 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose **3d** (84 mg, 0.82 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-β-D-glucopyranosyl fluoride **80** (80 mg, 0.36 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. The reaction was stirred in the dark and allowed to warm to RT. After 6 h 15 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.5) and complete consumption of starting material (R_f 0.6). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1 with 1% Et_3N) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(1-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-*O*-yl)-2-iodopropyl)-β-D-glucopyranosyl fluoride **82d** (130 mg, 91%) as a colourless oil; *m/z* (APCI$^-$) 913 (M+Cl$^-$, 4%); (APCI$^+$) 901 (M+Na$^+$, 5%).

3,4,6-Tri-O-benzyl-2-O-(2-iodo-1-(methyl 2,3,4-tri-O-benzyl-α-D-mannopyranosid-6-O-yl)propyl)-β-D-glucopyranosyl fluoride 82e

N-Iodosuccinimide (109 mg, 0.49 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (1 ml) and cooled to -40 °C under Ar. Methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **3e** (151 mg, 0.33 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added by cannula under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-β-D-glucopyranosyl fluoride **80** (80 mg, 0.16 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to RT. After 16 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a two products (R_f 0.4 and 0.45) and complete consumption of starting material (R_f 0.5). Sodium thiosulfate (20 ml of a 10% aqueous solution) was added and the mixture extracted with CH_2Cl_2 (2 x 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranosid-6-*O*-yl)propyl)-β-D-glucopyranosyl fluoride **82e** (139 mg, 79%) as a colourless oil; *m/z* (APCI$^-$) 1117 (M+Cl$^-$, 92%).

3,4,6-Tri-O-benzyl-2-O-(2-iodo-1-(methyl 2,3,4-tri-O-benzyl-α-D-glucopyranosid-6-O-yl)propyl)-β-D-glucopyranosyl fluoride 82f

N-Iodosuccinimide (130 mg, 0.58 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (1 ml) and cooled to -40 °C under Ar. Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **3f** (142 mg, 0.31 mmol) was dissolved

in anhydrous dichloroethane (1 ml) and added by cannula under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-β-D-glucopyranosyl fluoride **80** (100 mg, 0.20 mmol) was dissolved in anhydrous dichloroethane (1 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to RT over 15 h. After 15 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a two products (R_f 0.4 and 0.45) and complete consumption of starting material (R_f 0.5). Sodium thiosulfate (20 ml of a 10% aqueous solution) was added and the mixture extracted with CH_2Cl_2 (2 x 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranosid-6-*O*-yl)propyl)-β-D-glucopyranosyl fluoride **82f** (124 mg, 55%) as a colourless oil; *m/z* (APCI$^-$) 1117 (M+Cl$^-$, 100%).

3,4,6-Tri-O-benzyl-2-O-(2-iodo-1-(methyl 2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranosid-3-O-yl)propyl)-β-D-glucopyranosyl fluoride 82g

N-Iodosuccinimide (109 mg, 0.49 mmol), methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **3g** (121 mg, 0.33 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (1 ml) and cooled to -40 °C under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-β-D-glucopyranosyl fluoride **80** (80 mg, 0.16 mmol) was dissolved in anhydrous dichloroethane (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was stirred in the dark and allowed to warm to RT. After 21 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.5) and

complete consumption of starting material (R_f 0.6). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosid-3-*O*-yl)propyl)-β-D-glucopyranosyl fluoride **82g** (83 mg, 52%) as a colourless oil; *m/z* (ES^+) 1029 ($M+K^+$, 74), 1013 ($M+Na^+$, 100), 1008 ($M+NH_4^+$, 15%).

3,4,6-Tri*-O-*benzyl*-2-O-(2-*iodo*-1-(*methyl* 2,3,6-*tri*-O-*benzyl*-α-D-*glucopyranosid*-4-O-*yl*)*propyl*)-β-D-*glucopyranosyl fluoride 82h

N-Iodosuccinimide (109 mg, 0.49 mmol), and 4Å molecular sieves were added to anhydrous dichloroethane (1 ml) and cooled to -40 °C under Ar. Methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **3h** (221 mg, 0.48 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-β-D-glucopyranosyl fluoride **80** (80 mg, 0.16 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. The reaction was stirred in the dark and allowed to warm to RT. After 45 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.7) and complete consumption of starting material (R_f 0.8). Et_3N (1 ml) was added and the mixture was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined

organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1 with 1% Et_3N) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranosid-4-*O*-yl)propyl)-β-D-glucopyranosyl fluoride **82h** (69 mg, 39%) as a colourless oil; *m/z* (ES^+) 1121 ($M+K^+$, 22), 1105 ($M+Na^+$, 100), 1100 ($M+NH_4^+$, 21%).

Further elution yielded recovered methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **3h** (180 mg, 0.39 mmol);

And also 3,4,6-tri-*O* -benzyl-2-*O*-(2-iodo-1-succinimidopropyl)-β-D-glucopyranosyl fluoride **85** (22 mg, 19%) a single isomer, as a colourless oil; $[\alpha]_D^{22}$ -5.2 (*c*, 0.25 in $CHCl_3$); ν_{max} 1713 (s, C=O) cm^{-1}; *m/z* (ES^+) 740 ($M+Na^+$, 67%). (HRMS Calcd. for $C_{34}H_{41}N_2O_7FI$ (MNH_4^+) 735.1943. Found 725.1934).

3,4,6-Tri-O-benzyl-2-O-(1-(cholestan-3-β-yloxy)-2-iodopropyl)-β-D-glucopyranosyl fluoride 82i

N-Iodosuccinimide (89 mg, 0.40 mmol) and 4Å molecular sieves were added to freshly distilled THF (1 ml) and cooled to -40 °C under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-β-D-glucopyranosyl fluoride **80** (71 mg, 0.13 mmol) and cholestan-3β-ol **3i** (103 mg, 0.26 mmol) were dissolved in freshly distilled THF (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was stirred and allowed to warm to RT. After 39 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.8) and complete consumption of starting material (R_f 0.7). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with

CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 10:1→5:1) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(1-(cholestan-3-β-yloxy)-2-iodopropyl)-β-D-glucopyranosyl fluoride **82i** (99 mg, 68%) as a colourless oil; *m/z* (ES^+) 1045 ($M+K^+$, 100), 1029 ($M+Na^+$, 90%);

Further elution yielded recovered cholestan-3β-ol **3i** (60 mg, 0.15 mmol); and 3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl fluoride **65** (15 mg, 23%) as a colourless oil.

3,4,6-Tri-O-benzyl-2-O-(2-iodo-1-methoxypropyl)-α-D-mannopyranosyl fluoride 86a

N-Iodosuccinimide (109 mg, 0.49 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (1.5 ml) and cooled to -40 °C under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-α-D-mannopyranosyl fluoride **81** (80 mg, 0.16 mmol) and methanol **3a** (0.010 ml, 0.24 mmol) were dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to 0 °C over 1 h. After 1 h 20 min, the reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1 with 1% Et_3N) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-methoxypropyl)-α-D-mannopyranosyl fluoride **86a** (102 mg, 97%) as a colourless oil; *m/z*

(APCI$^+$) 673 (M+Na$^+$, 100%).

3,4,6-Tri-O-benzyl-2-O-(1-cyclohexyloxy-2-iodopropyl)-α-D-mannopyranosyl fluoride 86c

N-Iodosuccinimide (109 mg, 0.49 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (2 ml) and cooled to -40 °C under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-α-D-mannopyranosyl fluoride **81** (80 mg, 0.16 mmol) and cyclohexanol **3c** (0.034 ml, 0.33 mmol) were dissolved in anhydrous dichloroethane (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was stirred in the dark and allowed to warm to RT. After 15 h 15 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a single product (R_f 0.6) and complete consumption of starting material (R_f 0.5). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 7:1 with 1% Et_3N) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(1-cyclohexyloxy-2-iodopropyl)-α-D-mannopyranosyl fluoride **86c** (115 mg, 99%) as a colourless oil; *m/z* (APCI$^+$) 757 (M+K$^+$, 12), 741 (M+Na$^+$, 100%).

3,4,6-Tri-O-benzyl-2-O-(1-(1,2:3,4-di-O-isopropylidene-α-D-galactopyranos-6-O-yl)-2-iodopropyl)-α-D-mannopyranosyl fluoride 86d

N-Iodosuccinimide (243 mg, 1.1 mmol), and 4Å molecular sieves were added to anhydrous dichloroethane (1 ml) and cooled to -40 °C under Ar. 1,2:3,4-Di-

O-isopropylidene-α-D-galactopyranose **3d** (212 mg, 0.82 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1'-enyl-α-D-mannopyranosyl fluoride **81** (178 mg, 0.36 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. The reaction was stirred in the dark and allowed to warm to RT. After 17 h 30 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.3) and complete consumption of starting material (R_f 0.5). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1 with 1% Et_3N) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(1-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-*O*-yl)-2-iodopropyl)-α-D-mannopyranosyl fluoride **86d** (311 mg, 98%) as a colourless oil; *m/z* (ES^+) 917 ($M+K^+$, 25%), 901 ($M+Na^+$, 100), 896 ($M+NH_4^+$, 32%).

Further elution yielded recovered 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **3d** (94 mg, 0.36 mmol).

3,4,6-Tri-O-benzyl-2-O-(2-iodo-1-(methyl 2,3,4-tri-O-benzyl-α-D-mannopyranosid-6-O-yl)propyl)-α-D-mannopyranosyl fluoride 86e

N-Iodosuccinimide (109 mg, 0.49 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (1 ml) and cooled to -40 °C under Ar. Methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **3e** (151 mg, 0.33 mmol) was

dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-α-D-mannopyranosyl fluoride **81** (80 mg, 0.16 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. The reaction was stirred in the dark and allowed to warm to RT. After 15 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.4) and complete consumption of starting material (R_f 0.5). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1 with 1% Et_3N) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranosid-6-*O*-yl)propyl)-α-D-mannopyranosyl fluoride **86e** (140 mg, 80%) as a colourless oil; *m/z* (APCI$^+$) 1105 (M+Na$^+$, 5%); (APCI$^-$) 1117 (M+Cl$^-$, 7%).

Further elution yielded recovered methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **3e** (81 mg, 0.17 mmol).

And also 3,4,6-tri-*O* -benzyl-2-*O*-(2-iodo-1-succinimidopropyl)-α-D-mannopyranosyl fluoride **85** (7 mg, 4%) a single isomer, as a colourless oil; $[\alpha]_D^{22}$ +60.0 (*c*, 0.75 in $CHCl_3$); ν_{max} 1709 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.98 (3H, d, *J* 6.8 Hz, CH_3), 2.76 (4H, s, COC$\underline{H}_2$C$\underline{H}_2$CO), 3.66-3.73 (2H, m, H-6, H-6′), 3.90 (3H, br s, H-3, H-4, H-5), 3.99 (1H, br s, H-2), 4.51, 4.62 (2H, ABq, J_{AB} 12.2 Hz, PhC$\underline{H}_2$), 4.51, 4.82 (2H, ABq, J_{AB} 11.0 Hz, PhC$\underline{H}_2$), 4.68, 4.90 (2H, ABq, J_{AB} 11.0 Hz, PhC$\underline{H}_2$), 5.12 (1H, dq, *J* 10.2 Hz, C$\underline{H}$I), 5.39 (1H, dd, $J_{1,2}$

2.0 Hz, $J_{1,F}$ 50.5 Hz, H-1), 5.72 (1H, d, C<u>H</u>N), 7.15-7.47 (15H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 23.2, 25.0 (d, q, <u>C</u>H_3, <u>C</u>HI), 27.9 (t, CO<u>C</u>H_2<u>C</u>H_2CO), 68.4, 73.0, 73.4, 75.1 (4 x t, C-6, 3 x Ph<u>C</u>H_2), 72.7 (dd, $^2J_{C\text{-}2,F}$ 6.6 Hz, C-2), 73.6, 74.2, 78.9 (3 x d, C-3, C-4, C-5), 86.4 (d, <u>C</u>HN), 106.3 (dd, $^1J_{C\text{-}1,F}$ 221.0 Hz, C-1), 127.6, 127.8, 127.8, 128.0, 128.0, 128.3, 128.4, 128.5, 128.6 (9 x d, Ar-CH), 137.5, 137.8, 138.0 (3 x s, Ar-C); *m/z* (ES^+) 735 ($M+NH_4^+$, 100%). (HRMS Calcd. for $C_{34}H_{41}N_2O_7FI$ (MNH_4^+) 735.1943. Found 725.1949).

3,4,6-Tri-O-benzyl-2-O-(2-iodo-1-(methyl 2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranosid-3-O-yl)propyl)-α-D-mannopyranosyl fluoride 86g

N-Iodosuccinimide (109 mg, 0.49 mmol), methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **3g** (121 mg, 0.33 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (1 ml) and cooled to -40 °C under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-α-D-mannopyranosyl fluoride **81** (80 mg, 0.16 mmol) was dissolved in anhydrous dichloroethane (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was stirred in the dark and allowed to warm to RT. After 26 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.4) and complete consumption of starting material (R_f 0.5). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1 with 1% Et_3N) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-

mannopyranosid-3-*O*-yl)propyl)-α-D-mannopyranosyl fluoride **86g** (134 mg, 83%) as a colourless oil; *m/z* (APCI$^-$) 1025 (M+Cl$^-$, 15%);

Further elution yielded recovered methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **3g** (61 mg, 0.16 mmol);

And also 3,4,6-tri-*O* -benzyl-2-*O*-(2-iodo-1-succinimidopropyl)-α-D-mannopyranosyl fluoride **85** (13 mg, 11%) a single isomer, identical to that previously described.

3,4,6-Tri*-O-*benzyl*-2-O-(1-(*cholestan*-3-β-*yloxy*)-2-*iodopropyl*)-α-D-*mannopyranosyl fluoride* 86*i

N-Iodosuccinimide (109 mg, 0.49 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (1 ml) and cooled to -40 °C under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-α-D-mannopyranosyl fluoride **81** (80 mg, 0.16 mmol) and cholestan-3β-ol **3i** (136 mg, 0.33 mmol) were dissolved in anhydrous dichloroethane (3 ml) and added to the reaction vessel by cannula under Ar. The reaction was stirred in the dark and allowed to warm to RT. After 18 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.6) and complete consumption of starting material (R_f 0.5). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 9:1 with 1% Et_3N) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(1-(cholestan-3-β-yloxy)-2-iodopropyl)-α-D-

mannopyranosyl fluoride **86i** (118 mg, 72%) as a colourless oil; *m/z* ($APCI^-$) 1041 ($M+Cl^-$, 18%);

Further elution yielded recovered cholestan-3-β-ol **3i** (78 mg, 0.2 mmol).

3,4,6-Tri-O-benzyl-2-O-(2-iodo-1-(methyl 2,3,6-tri-O-benzyl-α-D-mannopyranosid-4-O-yl)propyl)-α-D-mannopyranosyl fluoride 86j

N-Iodosuccinimide (109 mg, 0.49 mmol), and 4Å molecular sieves were added to anhydrous dichloroethane (1 ml) and cooled to -40 °C under Ar. Methyl 2,3,6-tri-*O*-benzyl-α-D-mannopyranoside **3j** (226 mg, 0.49 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-α-D-mannopyranosyl fluoride **81** (80 mg, 0.16 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. The reaction was stirred in the dark and allowed to warm to RT. After 16 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.5) and complete consumption of starting material (R_f 0.6). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1 with 1% Et_3N) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,6-tri-*O*-benzyl-α-D-mannopyranosid-4-*O*-yl)propyl)-α-D-mannopyranosyl fluoride **86j** (65 mg, 37%) as a colourless oil; *m/z* ($APCI^-$) 1117 ($M+Cl^-$, 8%);

Further elution yielded recovered methyl 2,3,6-tri-*O*-benzyl-α-D-mannopyranoside **3j** (198 mg, 0.42 mmol);

And also 3,4,6-tri-*O* -benzyl-2-*O*-(2-iodo-1-succinimidopropyl)-α-D-mannopyranosyl fluoride **85** (14 mg, 12%) a single isomer, identical to that previously described.

Methyl 3,4,6-tri-O-benzyl-α-D-glucopyranoside 30a

4Å Molecular sieves were suspended in distilled acetonitrile (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (48 mg, 0.236 mmol), silver trifluoromethanesulfonate (61 mg, 0.236 mmol) and anhydrous tin (II) chloride (45 mg, 0.236 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodo-1-methoxypropyl)-β-D-glucopyranosyl fluoride **82a** (77 mg, 0.118 mmol) was dissolved in distilled acetonitrile (2 ml) and added by cannula under Ar and the reaction mixture stirred at 50 °C. After 1 h 50 min, tlc (petrol:ethyl acetate, 3:1) indicated the absence of any starting material. The reaction mixture was concentrated *in vacuo* to ca. 2 ml and trifluoroacetic acid (2 ml) and water (1 ml) were added, and the mixture stirred at RT. After a further 1 h 15 min, tlc (petrol:ethyl acetate, 1:1) indicated the formation of a major product (R_f 0.5). The reaction was quenched with $NaHCO_3$ (30 ml of a saturated aqueous solution) and extracted with ethyl acetate (30 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1→1:1) to afford methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside **30a** (46 mg, 84%) as white crystals identical to those previously described.

Cyclohexyl 3,4,6-tri-O-benzyl-α-D-glucopyranoside 30c

4Å Molecular sieves were suspended in distilled acetonitrile (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (65 mg, 0.318 mmol), silver trifluoromethanesulfonate (82 mg, 0.318 mmol) and anhydrous tin (II) chloride (60 mg, 0.318 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(1-cyclohexyloxy-2-iodopropyl)-β-D-glucopyranosyl fluoride **82c** (77 mg, 0.118 mmol) was dissolved in distilled acetonitrile (4 ml) and added by cannula under Ar and the reaction mixture stirred at 50 °C. After 5 h, tlc (petrol:ethyl acetate, 3:1) indicated the absence of any starting material. The reaction mixture was concentrated *in vacuo* to ca. 2 ml and trifluoroacetic acid (2 ml) and water (1 ml) were added, and the mixture stirred at RT. After a further 45 min, tlc (petrol:ethyl acetate, 3:1) indicated the formation of a major product (R_f 0.3). The reaction was quenched with $NaHCO_3$ (30 ml of a saturated aqueous solution) and extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were washed with brine (20 ml) dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford cyclohexyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside **30c** (56 mg, 66%) as white crystals identical to those previously described.

3,4,6-Tri-O-benzyl-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 30d

4Å Molecular sieves were suspended in anhydrous dichloroethane (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (58 mg, 0.28 mmol), silver trifluoromethanesulfonate (73 mg, 0.28 mmol) and anhydrous tin (II) chloride (54 mg, 0.28 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(1-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-*O*-yl)-2-iodopropyl)-β-D-glucopyranosyl fluoride **82d** (124 mg, 0.14 mmol) was dissolved in anhydrous dichloroethane (2 ml) and added by cannula under Ar and the reaction mixture stirred at 50 °C. After 1 h tlc (petrol:ethyl acetate, 5:1) indicated the absence of any starting material (R_f 0.3) and the formation of a major product (R_f 0.2), while tlc (petrol:ethyl acetate, 3:1) indicated the formation of the major product (R_f 0.6) and the desired glycoside (R_f 0.3). Water (1 ml) was added and the reaction mixture stirred for a further 30 min at RT. Trifluoroacetic acid (1 ml) and EtOAc (5 ml) were added and the reaction stirred for a further 30 min. After this time, the reaction mixture was diluted with EtOAc (30 ml), filtered through celite and washed with $NaHCO_3$ (30 ml of a saturated aqueous solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 1:1) to afford 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **30d** (62 mg, 63%) as a colourless oil, identical to that previously described.

Methyl 3,4,6-tri-O-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-O-benzyl-α-D-mannopyranoside 30e

4Å Molecular sieves were suspended in distilled acetonitrile (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (19 mg, 0.09 mmol), silver trifluoromethanesulfonate (23 mg, 0.09 mmol) and anhydrous tin (II) chloride (17 mg, 0.09 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranosid-6-*O*-yl)propyl)-β-D-glucopyranosyl fluoride **82e** (49 mg, 0.045 mmol) was dissolved in distilled acetonitrile (3 ml) and added by cannula under Ar and the reaction mixture stirred at 50 °C. After 20 h, tlc (petrol:ethyl acetate, 3:1) indicated the absence of any starting material (R_f 0.5) and the formation several products (R_f 0.1-0.5). Trifluoroacetic acid (2 ml) and water (1 ml) were added, and the mixture stirred at RT. After a further 1 h, tlc (petrol:ethyl acetate, 1:1) indicated the formation of a major product (R_f 0.5). The reaction was quenched with $NaHCO_3$ (30 ml of a saturated aqueous solution) and extracted with ethyl acetate (30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1) to afford methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **30e** (18 mg, 44%) as a colourless oil identical to that previously described.

Methyl 3,4,6-tri-O-benzyl-α-D-glucopyranosyl-(1→3)-2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside 30g

4Å Molecular sieves were suspended in anhydrous dichloroethane (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (32 mg, 0.16 mmol), silver trifluoromethanesulfonate (40 mg, 0.16 mmol) and

anhydrous tin (II) chloride (30 mg, 0.16 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosid-3-*O*-yl)propyl)-β-D-glucopyranosyl fluoride **82g** (77 mg, 0.078 mmol) was dissolved in anhydrous dichloroethane (2 ml) and added by cannula under Ar, and the reaction mixture stirred at 50 °C. After 29 h, tlc (petrol:ethyl acetate, 3:1) indicated the formation of a major (R_f 0.3) and minor (R_f 0.6) products. The reaction mixture was diluted with ethyl acetate (50 ml), filtered through celite and washed with $NaHCO_3$ (50 ml of a saturated aqueous solution). The aqueous layer was re-extracted with ethyl acetate (20 ml) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1) to afford methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **30g** (23 mg, 37%) as white crystals, m.p. 145-147 °C (ether/petrol); $[\alpha]_D^{22}$ +42.4 (*c*, 0.25 in $CHCl_3$); ν_{max} 3462 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.65 (1H, d, $J_{OH,2}$ 9.8 Hz, OH-2), 3.34 (3H, s, OCH_3), 3.56 (1H, at, *J* 9.2 Hz, H-4_b), 3.65-3.68 (2H, m, H-6_b, H-$6'_b$), 3.71 (1H, atd, $J_{1,2}$ 3.4 Hz, *J* 9.6 Hz, H-2_b), 3.75 (1H, at, *J* 9.3 Hz, H-3_b), 3.81-3.88 (3H, m, H-2_a, H-5_a, H-6_a), 3.90-3.94 (1H, m, H-5_b), 4.22-4.24 (2H, m, H-4_a, H-$6'_a$), 4.28 (1H, dd, $J_{2,3}$ 3.7 Hz, $J_{3,4}$ 9.2 Hz, H-3_a), 4.47, 4.85 (2H, ABq, J_{AB} 11.0 Hz, PhC$\underline{H}_2$), 4.48, 4.57 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.66, 4.76 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.69, 4.82 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 4.69 (1H, d, $J_{1,2}$ 1.4 Hz, H-1_a), 5.21 (1H, d, H-1_b), 5.63 (1H, s, PhC$\underline{H}$), 7.14-7.49 (25H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 54.9 (q, OCH_3), 63.9, 71.5, 73.8, 76.1, 77.0, 77.6, 78.2, 83.4 (8 x d, C-2_a, C-3_a, C-4_a, C-5_a,

C-2_b, C-3_b, C-4_b, C-5_b), 68.7, 68.8, 73.4, 73.5, 74.8, 75.2 (6 x t, C-6_a, C-6_b, 4 x Ph$\underline{C}H_2$), 100.0, 100.8, 101.8 (3 x d, C-1_a, C-1_b, Ph$\underline{C}$H), 125.6, 127.5, 127.6, 127.6, 127.7, 127.8, 127.8, 127.9, 128.0, 128.2, 128.3, 128.3, 128.3, 128.5, 129.1 (15 x d, Ar-CH), 137.0, 137.8, 137.9, 138.4, 138.7 (5 x s, Ar-C); *m/z* (ES^+) 843 ($M+K^+$, 50), 827 ($M+Na^+$, 100%). (HRMS Calcd. for $C_{48}H_{56}NO_{11}$ (MNH_4^+) 822.3853. Found 822.3842). (Found: C, 71.88; H, 6.58. $C_{48}H_{52}O_{11}$ requires C, 71.62; H, 6.51%).

Also a mixture which according to its ^1H NMR spectrum was mostly enol ethers **90g**, a colourless oil; Partial data: δ_H (400 MHz, $CDCl_3$) (*E*:*Z*, 1:2), *E* isomer 1.26 (3H, dd, *J* 1.4 Hz, *J* 6.8 Hz, OCH=CHC$\underline{H}_3$), 6.23 (1H, d, J_E 12.2 Hz, OC$\underline{H}$=CH); Z isomer 1.64 (3H, dd, *J* 1.7 Hz, *J* 6.7 Hz, OCH=CHC$\underline{H}_3$), 5.98 (1H, dd, J_Z 6.1 Hz, OC$\underline{H}$=CHCH$_3$); δ_C (100.6 MHz, $CDCl_3$) *E* isomer 12.1 (q, OCH=CH$\underline{C}H_3$); Z isomer 9.5 (q, OCH=CH$\underline{C}H_3$), 145.1 (d, O$\underline{C}$H=CH); *m/z* (ES^+) 883 ($M+K^+$, 18), 867 ($M+Na^+$, 100), 862 ($M+NH_4^+$, 12%).

Also visible in the mass spectrum were signals for iodo-enol ethers **91g**; *m/z* (ES^+) 993 ($M+Na^+$, 10), 988 ($M+NH_4^+$, 3%).

This mixture was dissolved in THF (2 ml). Water (0.2 ml) and NIS (9 mg, 0.071 mmol) were added. After 30 min, sodium thiosulfate (30 ml of a 10% aqueous solution) was added and the mixture extracted with CH_2Cl_2 (30 ml). The organic extracts were dried ($MgSO_4$), filtered, Et_3N (3 ml) was added and the mixture concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 3:1) to afford further methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **30g** (18 mg, 29%).

Methyl 3,4,6-tri-O-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-O-benzyl-α-D-glucopyranoside 30h

4Å Molecular sieves were suspended in anhydrous dichloroethane (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (25 mg, 0.12 mmol), silver trifluoromethanesulfonate (31 mg, 0.12 mmol) and anhydrous tin (II) chloride (23 mg, 0.12 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranosid-4-*O*-yl)propyl)-β-D-glucopyranosyl fluoride **82h** (65 mg, 0.06 mmol) was dissolved in anhydrous dichloroethane (2 ml) and added by cannula under Ar and the reaction mixture stirred at 50 °C. After 5 days, tlc (petrol:ethyl acetate, 3:1) indicated the formation of a major product (R_f 0.3) and another minor compound (R_f 0.6). Water (1 ml) and trifluoroacetic acid (2 ml) were added and the reaction stirred further. After 45 min tlc (petrol:ethyl acetate, 3:1) indicated the disappearance of the minor compound (R_f 0.6). The reaction mixture was filtered through celite and partitioned between ethyl acetate (2 x 30 ml) and $NaHCO_3$ (30 ml of a saturated aqueous solution). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2:ether, 30:1) and size exclusion chromatography on Sephadex (CH_2Cl_2;methanol, 1:1) to afford methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside **30h** (24 mg, 45%) as a colourless oil; $[\alpha]_D^{22}$ +35.1 (*c*, 1.1 in $CHCl_3$); ν_{max} 3418 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.38 (3H, s, OCH_3), 3.45 (1H, br d, $J_{OH,2}$ 9.1 Hz, OH-2_b), 3.55 (1H, at, *J* 9.1 Hz, H-3_b), 3.55 (1H, dd, $J_{5,6}$ 1.8 Hz, $J_{6,6'}$ 10.6 Hz, H-6_a), 3.61-3.66 (4H, m, H-2_b, H-2_a, H-3_a, H-$6'_a$),

3.68 (1H, dd, $J_{5,6}$ 1.9 Hz, $J_{6,6'}$ 11.0 Hz, H-6_b), 3.69-3.71 (1H, m, H-5_b), 3.86-3.90 (1H, m, H-5_a), 3.88 (1H, at, *J* 9.5 Hz, H-4_b), 3.93 (1H, dd, $J_{5,6'}$ 3.9 Hz, H-$6'_b$), 3.99 (1H, at, *J* 9.3 Hz, H-4_a), 4.44, 4.57 (2H, ABq, J_{AB} 12.2 Hz, PhC$\underline{H}_2$), 4.49, 4.83 (2H, ABq, J_{AB} 10.6 Hz, PhC$\underline{H}_2$), 4.49, 4.59 (2H, ABq, J_{AB} 11.6 Hz, PhC$\underline{H}_2$), 4.57, 4.69 (2H, ABq, J_{AB} 11.0 Hz, PhC$\underline{H}_2$), 4.59, 4.70 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.61 (1H, d, $J_{1,2}$ 3.6 Hz, H-1_b), 4.79, 5.18 (2H, ABq, J_{AB} 10.6 Hz, PhC$\underline{H}_2$), 5.19 (1H, d, $J_{1,2}$ 3.1 Hz, H-1_a), 7.16-7.36 (30H, m, Ar-H); δ_C (125.7 MHz, $CDCl_3$) 55.2 (q, OCH_3), 68.4 (t, C-6_b), 68.7 (t, C-6_a), 70.0 (d, C-5_b), 71.5 (d, C-5_a), 73.0, 73.2, 73.3, 74.9, 75.1, 75.2 (6 x t, 6 x Ph$\underline{C}H_2$), 74.0, 80.2, 83.6 (3 x d, C-2_b, C-2_a, C-3_a), 76.9 (d, C-3_b), 77.6 (d, C-4_b), 80.5 (d, C-4_a), 97.7 (d, C-1_b), 101.2 (d, C-1_a), 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 127.8, 128.0, 128.1, 128.2, 128.2, 128.3, 128.4 (13 x d, Ar-CH), 137.5, 137.7, 137.7, 137.9, 138.2, 138.7 (6 x s, Ar-C); *m/z* (ES^+) 935 ($M+K^+$, 14), 919 ($M+Na^+$, 100), 916 ($2M+K^++H^+$, 21), 914 ($M+NH_4^+$, 14%). (HRMS Calcd. for $C_{55}H_{64}NO_{11}$ (MNH_4^+) 914.4479. Found 914.4476).

Cholestan-3'-β-yl 3,4,6-tri-O-benzyl-α-D-glucopyranoside 30i

4Å Molecular sieves were suspended in anhydrous dichloroethane (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (16 mg, 0.08 mmol), silver trifluoromethanesulfonate (21 mg, 0.08 mmol) and anhydrous tin (II) chloride (15 mg, 0.08 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(1-(cholestan-3-β-yloxy)-2-iodopropyl)-β-D-glucopyranosyl fluoride **82i** (41 mg, 0.04 mmol) was dissolved in anhydrous dichloroethane (2 ml) and added by cannula under Ar and the reaction mixture stirred at 50 °C. After 4 h, tlc (petrol:ethyl acetate, 7:1) indicated the consumption of

starting material (R_f 0.5) and the formation of a major product (R_f 0.1). Water (1 ml) and trifluoroacetic acid (2 ml) were added and the reaction stirred further. After 30 min tlc (petrol:ethyl acetate, 3:1) indicated the presence of only the major product (R_f 0.6). The reaction mixture was filtered through celite and partitioned between ethyl acetate (2 x 30 ml) and $NaHCO_3$ (30 ml of a saturated aqueous solution). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 7:1) to afford cholestan-3′-β-yl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside **30i** (29 mg, 87%) as white crystals, m.p. 108-109 °C; $[\alpha]_D^{24}$ +98.5 (*c*, 0.20 in $CHCl_3$); ν_{max} 3487 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.59-1.99 (31H, m, steroid CH, CH_2), 0.66, 0.81 (6H, 2 x s, 2 x CH_3), 0.88 (3H, d, *J* 6.5 Hz, CH_3), 0.89 (3H, d, *J* 6.5 Hz, CH_3), 0.91 (3H, d, *J* 6.6 Hz, CH_3), 2.10 (1H, br d, $J_{OH,2}$ 8.0 Hz, OH-2), 3.57-3.79 (4H, m, H-2, H-3, H-4, steroid OCH), 3.68 (1H, dd, $J_{5,6}$ 2.0 Hz, $J_{6,6'}$ 10.5 Hz, H-6), 3.77 (1H, dd, $J_{5,6'}$ 4.0 Hz, H-6′), 3.89-3.92 (1H, m, H-5), 4.49, 4.84 (2H, ABq, J_{AB} 10.7 Hz, PhC$\underline{H}_2$), 4.51, 4.65 (2H, ABq, J_{AB} 11.9 Hz, PhC$\underline{H}_2$), 4.84, 4.99 (2H, ABq, J_{AB} 11.2 Hz, PhC$\underline{H}_2$), 5.04 (1H, d, $J_{1,2}$ 3.6 Hz, H-1), 7.14-7.41 (15H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 12.0, 12.3, 18.6, 22.6, 22.8 (5 x q, 5 x steroid CH_3), 21.2, 23.8, 24.2, 27.8, 28.2, 28.7, 32.0, 36.0, 36.1, 36.8, 39.5, 40.0 (12 x t, 12 x steroid $\underline{C}H_2$), 28.0, 35.5, 35.8, 44.9, 54.2, 56.2, 56.4 (7 x d, 7 x steroid CH), 35.4, 42.6 (2 x s, 2 x steroid C), 68.6, 73.4, 75.0, 75.3 (4 x t, 3 x Ph$\underline{C}H_2$, C-6), 70.4, 73.0, 77.3, 77.3, 83.8 (5 x d, C-2, C-3, C-4, C-5, steroid OCH), 96.9 (d, C-1), 127.6, 127.7, 127.7, 127.9, 127.9, 128.3, 128.3 (7 x d, Ar-CH), 137.9, 138.2, 138.8 (3 x s, Ar-C). (Found: C, 79.25; H, 9.52. $C_{54}H_{76}O_6$ requires C, 78.98; H, 9.33%).

Methyl 3,4,6-tri-O-benzyl-β-D-mannopyranoside 89a

4Å Molecular sieves were suspended in distilled acetonitrile (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (64 mg, 0.314 mmol), silver trifluoromethanesulfonate (81 mg, 0.314 mmol) and anhydrous tin (II) chloride (60 mg, 0.314 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodo-1-methoxypropyl)-α-D-mannopyranosyl fluoride **86a** (102 mg, 0.157 mmol) was dissolved in distilled acetonitrile (2 ml) and added by cannula under Ar and the reaction mixture stirred at 50 °C. After 16 h, tlc (petrol:ethyl acetate, 3:1) indicated the absence of starting material (R_f 0.6). Trifluoroacetic acid (2 ml) and water (1 ml) were added, and the reaction mixture stirred at RT. After 1 h, tlc (petrol:ethyl acetate, 1:1) indicated the formation of a major product (R_f 0.4). The reaction was quenched with $NaHCO_3$ (30 ml of a saturated aqueous solution) and extracted with ethyl acetate (40 ml + 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 1:1) to afford methyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside **8a** (55 mg, 76%) as a colourless oil; $[\alpha]_D^{24}$ -13 (*c*, 0.75 in $CHCl_3$) [Lit. -13 (*c*, 1.0 in $CHCl_3$)][4]; δ_H (500 MHz, $CDCl_3$) 3.47 (1H, ddd, $J_{4,5}$ 9.5 Hz, $J_{5,6}$ 5.0 Hz, $J_{5,6'}$ 1.3 Hz, H-5), 3.57 (3H, s, OCH_3), 3.57-3.60 (1H, m, H-3), 3.74 (1H, dd, $J_{6,6'}$ 10.8 Hz, H-6), 3.80 (1H, dd, H-6'), 3.88 (1H, at, *J* 9.4 Hz, H-4), 4.11 (1H, d, $J_{2,3}$ 3.0 Hz, H-2), 4.35 (1H, s, H-1), 4.55, 4.90 (2H, ABq, J_{AB} 10.8 Hz, PhC$\underline{H}_2$), 4.58, 4.65 (2H, ABq, J_{AB} 12.3 Hz, PhC$\underline{H}_2$), 4.69, 4.78 (2H, ABq, J_{AB}

11.7 Hz, PhC$\underline{H}_2$), 7.22-7.40 (15H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) $^1J_{C\text{-}1,H\text{-}1}$ 156.7 Hz.

Cyclohexyl 3,4,6-tri-O-benzyl-β-D-mannopyranoside 89c

4Å Molecular sieves were suspended in distilled acetonitrile (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (64 mg, 0.312 mmol), silver trifluoromethanesulfonate (80 mg, 0.312 mmol) and anhydrous tin (II) chloride (59 mg, 0.312 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(1-cyclohexyloxy-2-iodopropyl)-α-D-mannopyranosyl fluoride **86c** (112 mg, 0.156 mmol) was dissolved in distilled acetonitrile (2 ml) and added by cannula under Ar and the reaction mixture stirred at 50 °C. After 14 h, tlc (petrol:ethyl acetate, 3:1) indicated the absence of any starting material (R_f 0.6) and the formation of a major (R_f 0.3) and several minor products (R_f 0.5-0.6). The reaction was quenched with $NaHCO_3$ (40 ml of a saturated aqueous solution) and extracted with ethyl acetate (60 ml). The organic layer was washed with water (60 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 3:1) to afford cyclohexyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside **89c** (50 mg, 60%) as a colourless oil; $[\alpha]_D^{24}$ -20 (*c*, 0.4 in $CHCl_3$) [Lit. -19 (*c*, 1.6 in $CHCl_3$)][4]; δ_H (500 MHz, $CDCl_3$) 1.20-2.02 (10H, m, cyclohexyl-H), 2.50 (1H, br s, OH-2), 3.43-3.45 (1H, m, H-5), 3.58 (1H, br d, $J_{3,4}$ 8.6 Hz, H-3), 3.61-3.81 (3H, m, H-6, H-6′, OC$\underline{H}$), 3.86 (1H, at, *J* 9.3 Hz, H-4), 4.08 (1H, br s, H-2), 4.56 (1H, s, H-1), 4.58, 4.63 (2H, ABq, J_{AB} 12.1 Hz, PhC$\underline{H}_2$), 4.58, 4.91 (2H, ABq, J_{AB}

10.7 Hz, PhC$\underline{H}_2$), 4.69, 4.80 (2H, ABq, J_{AB} 11.7 Hz, PhC$\underline{H}_2$), 7.23-7.41 (15H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) $^1J_{C\text{-}1,H\text{-}1}$ 155.3 Hz.

The combined minor products were stirred in trifluoroacetic acid: water: methanol, 2:1:2 (5 ml). After 48 h, tlc (petrol:ethyl acetate, 3:1) indicated the formation of a major product (R_f 0.3). The reaction mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (petrol:ethyl acetate, 3:1) to afford further cyclohexyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside **8c** (8 mg, 10%) identical to that described above.

3,4,6-Tri-O-benzyl-β-D-mannopyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 89d

4Å Molecular sieves were suspended in anhydrous dichloroethane (1 ml) in a flame-dried flask under Ar. 2,6-Di-tert-butyl-4-methylpyridine (57 mg, 0.28 mmol), silver trifluoromethanesulfonate (72 mg, 0.28 mmol) and anhydrous tin (II) chloride (53 mg, 0.28 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(1-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-*O*-yl)-2-iodopropyl)-α-D-mannopyranosyl fluoride **86d** (124 mg, 0.14 mmol) was dissolved in anhydrous dichloroethane (2 ml) and added by cannula under Ar and the reaction mixture stirred at 50 °C. After 2 h 20 min, tlc (petrol:ethyl acetate, 3:1) indicated the absence of starting material (R_f 0.4) and the formation of a major product (R_f 0.1). Water (1 ml) was added and the reaction mixture stirred for a further 1 h 30 min at RT. After this time, the reaction mixture was diluted with CH_2Cl_2 (50 ml), filtered through celite and washed with $NaHCO_3$ (30 ml of a saturated aqueous solution). The organic

layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 1:1) to afford methyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **89d** (60 mg, 61%) as a colourless oil; $[\alpha]_D^{22}$ -50.7 (*c*, 0.55 in $CHCl_3$) [Lit. -53 (*c*, 1.3 in $CHCl_3$)][4]; δ_H (400 MHz, $CDCl_3$) 1.32, 1.34, 1.44, 1.54 (12 H, 4 x s, 4 x CH_3), 3.42 (1H, ddd, $J_{4,5}$ 9.8 Hz, $J_{5,6}$ 2.2 Hz, $J_{5,6'}$ 4.6 Hz, H-5_b), 3.56 (1H, dd, $J_{2,3}$ 3.1 Hz, $J_{3,4}$ 9.2 Hz, H-3_b), 3.70-3.78 (3H, m, H-6_a, H-6_b, H-$6'_b$), 3.92 (1H, at, *J* 9.5 Hz, H-4_b), 4.03 (1H, dat, *J* 2.2 Hz, $J_{5,6}$ 7.8 Hz, H-5_a), 4.13 (1H, dd, $J_{5,6'}$ 2.7 Hz, $J_{6,6'}$11.2 Hz, H-$6'_a$), 4.22 (1H, dd, $J_{3,4}$ 7.9 Hz, $J_{4,5}$ 1.9 Hz, H-4_a), 4.22 (1H, d, H-2_b), 4.32 (1H, dd, $J_{1,2}$ 5.0 Hz, $J_{2,3}$ 2.4 Hz, H-2_a), 4.51 (1H, s, H-1_b), 4.52, 4.90 (2H, ABq, J_{AB} 10.8 Hz, PhC$\underline{H}_2$), 4.54, 4.64 (2H, ABq, J_{AB} 12.1 Hz, PhC$\underline{H}_2$), 4.60 (1H, dd, H-3_a), 4.66, 4.78 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 5.55 (1H, d, H-1_a), 7.18-7.39 (15H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) $^1J_{C\text{-}1b,H\text{-}1b}$ 160.0 Hz.

Methyl 3,4,6-tri-O-benzyl-β-D-mannopyranosyl-(1→6)-2,3,4-tri-O-benzyl-α-D-mannopyranoside 89e

Method 1: Use of acetonitrile as solvent

4Å Molecular sieves were suspended in distilled acetonitrile (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (52 mg, 0.25 mmol), silver trifluoromethanesulfonate (65 mg, 0.312 mmol) and anhydrous tin (II) chloride (48 mg, 0.312 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranosid-6-*O*-yl)propyl)-α-D-mannopyranosyl fluoride **86e** (136 mg, 0.126 mmol) was dissolved in distilled

acetonitrile (2 ml) and added by cannula under Ar and the reaction mixture stirred at 50 °C. After 25 h 30 min, tlc (petrol:ethyl acetate, 3:1) indicated the absence of any starting material (R_f 0.5) and the formation several products (R_f 0.1-0.5). Tlc (petrol:ethyl acetate, 1:1) indicated the formation of the desired product (R_f 0.5). The reaction was quenched with $NaHCO_3$ (4 ml of a saturated aqueous solution) and filtered through celite. The filtrate was concentrated *in vacuo* and the residue stirred in trifluoroacetic acid: water: THF (2:1:2, 5 ml). After 4 h, tlc (petrol:ethyl acetate, 1:1) indicated the formation of a major product (R_f 0.5). The reaction mixture was partitioned between ethyl acetate (60 ml) and $NaHCO_3$ (40 ml of a saturated aqueous solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1→1:1) to afford methyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **89e** (55 mg, 49%) as a colourless oil; $[\alpha]_D^{24}$ +16.0 (*c*, 1.1 in $CHCl_3$) [Lit. +16.5 (*c*, 1.0 in $CHCl_3$)][9]; δ_H (500 MHz, $CDCl_3$) 3.30 (3H, s, CH_3), 3.40 (1H, ddd, $J_{4,5}$ 9.7 Hz, $J_{5,6}$ 4.7 Hz, $J_{5,6'}$ 2.4 Hz, H-5_b), 3.52 (1H, dd, $J_{2,3}$ 3.0 Hz, $J_{3,4}$ 9.2 Hz, H-3_b), 3.70-3.76 (3H, m, H-6_b, H-$6'_b$, H-6_a), 3.78-3.81 (3H, m, H-2_a, H-4_a, H-5_a), 3.90-3.92 (1H, m, H-3_a), 3.92 (1H, at, *J* 9.4 Hz, H-4_b), 4.06 (1H, d, H-2_b), 4.23 (1H, dd, $J_{6,6'}$ 10.0 Hz, H-$6'_a$), 4.37 (1H, s, H-1_b), 4.56, 4.93 (2H, ABq, J_{AB} 11.4 Hz, PhC$\underline{H}_2$), 4.56, 4.63 (2H, ABq, J_{AB} 13.0 Hz, PhC$\underline{H}_2$), 4.57, 4.91 (2H, ABq, J_{AB} 11.0 Hz, PhC$\underline{H}_2$), 4.62 (2H, s, PhC$\underline{H}_2$), 4.69, 4.79 (2H, ABq, J_{AB} 12.3 Hz, PhC$\underline{H}_2$), 4.71, 4.76 (2H, ABq, J_{AB} 12.7 Hz, PhC$\underline{H}_2$), 4.72 (1H, d, $J_{1,2}$ 1.7 Hz, H-1_a), 7.22-7.41 (30H, m, Ar-H); δ_C (125 MHz, $CDCl_3$) $^1J_{C\text{-}1b,H\text{-}1b}$ 157.9 Hz.

And also methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **3e** (19 mg, 6%).

Method 2: Use of dichloroethane as solvent

4Å Molecular sieves were suspended in anhydrous dichloroethane (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (76 mg, 0.37 mmol), silver trifluoromethanesulfonate (95 mg, 0.37 mmol) and anhydrous tin (II) chloride (70 mg, 0.37 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranosid-6-*O*-yl)propyl)-α-D-mannopyranosyl fluoride **86e** (200 mg, 0.185 mmol) was dissolved in anhydrous dichloroethane (3 ml) and added by cannula under Ar and the reaction mixture stirred at 50 °C. After 2 h, tlc (petrol:ethyl acetate, 3:1) indicated the absence of any starting material (R_f 0.7) and the formation two products (R_f 0.1 and 0.5). Water (1 ml) and trifluoroacetic acid (2 ml) were added and the reaction stirred further. After 1 h the reaction mixture was filtered through celite and partitioned between ethyl acetate (50+20 ml) and $NaHCO_3$ (30 ml of a saturated aqueous solution). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1→1:1) to afford methyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **89e** (125 mg, 75%) as a colourless oil, identical to that previously described.

Methyl 3,4,6-tri-O-benzyl-β-D-mannopyranosyl-(1→3)-2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside 89g

4Å Molecular sieves were suspended in anhydrous dichloroethane (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (52 mg, 0.25 mmol), silver trifluoromethanesulfonate (65 mg, 0.25 mmol) and anhydrous tin (II) chloride (48 mg, 0.25 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosid-3-*O*-yl)propyl)-α-D-mannopyranosyl fluoride **86g** (126 mg, 0.127 mmol) was dissolved in anhydrous dichloroethane (2 ml) and added by cannula under Ar and the reaction mixture stirred at 50 °C. After 6 h 30 min, tlc (petrol:ethyl acetate, 5:1) indicated the absence of starting material (R_f 0.5). Tlc (petrol:ethyl acetate, 2:1) indicated the formation of a major product (R_f 0.2). The reaction mixture was diluted with ethyl acetate (50 ml), filtered through celite and washed with $NaHCO_3$ (50 ml of a saturated aqueous solution), water (50 ml), and brine (2 x 20 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1) to afford methyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **89g** (56 mg, 55%) as a colourless oil; $[\alpha]_D^{22}$ +5.1 (*c*, 0.35 in $CHCl_3$); ν_{max} 3479 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.27 (1H, dt, $J_{4,5}$ 9.6 Hz, $J_{5,6}$ 3.5 Hz, H-5_b), 3.32 (3H, s, OCH_3), 3.39 (1H, dd, $J_{2,3}$ 3.1 Hz, $J_{3,4}$ 9.0 Hz, H-3_b), 3.70 (2H, d, H-6_b, H-$6'_b$), 3.79-3.87 (3H, m, H-2_a, H-5_a, H-6_a), 3.89 (1H, at, *J* 9.1 Hz, H-4_b), 3.94 (1H, d, H-2_b), 4.19 (1H, at, *J* 9.7 Hz, H-4_a), 4.26 (1H, s, H-1_b), 4.28 (1H, dd, $J_{5,6}$ 4.2 Hz, $J_{6,6'}$ 9.6 Hz, H-$6'_a$), 4.49, 4.58 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.49 (1H, dd, $J_{2,3}$ 3.3 Hz, $J_{3,4}$ 10.2 Hz, H-3_a), 4.55, 4.87 (2H, ABq, J_{AB} 10.8 Hz, PhC$\underline{H}_2$), 4.62, 4.77 (2H, ABq, J_{AB} 12.2 Hz, PhC$\underline{H}_2$), 4.63, 4.73

(2H, ABq, J_{AB} 12.2 Hz, PhC$\underline{H}_2$), 4.77 (1H, d, $J_{1,2}$ 1.4 Hz, H-1_a), 5.61 (1H, s, PhC$\underline{H}$), 7.21-7.49 (25H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 54.9 (q, OCH_3), 64.0, 68.4, 71.8, 74.0, 75.1, 75.9, 77.2, 80.8 (8 x d, C-2_b, C-3_b, C-4_b, C-5_b, C-2_a, C-3_a, C-4_a, C-5_a), 68.8, 68.9, 71.1, 73.0, 73.5, 75.1 (6 x t, C-6_b, C-6_a, 4 x Ph$\underline{C}H_2$), 96.4 (d, $^1J_{C\text{-}1,H\text{-}1}$ 158.9 Hz, C-1_b), 99.7 (d, $^1J_{C\text{-}1,H\text{-}1}$ 168.6 Hz, C-1_a), 101.8 (d, Ph$\underline{C}$H), 126.0, 127.4, 127.6, 127.7, 127.7, 127.8, 128.0, 128.0, 128.1, 128.2, 128.2, 128.3, 128.4, 128.4, 129.0 (15 x d, Ar-CH), 137.3, 137.6, 138.1, 138.3, 138.5 (5 x s, Ar-C); *m/z* (APCI$^-$) 839 (M+Cl^-, 100%); (ES$^+$) 822 (M+NH_4^+, 100%). (HRMS Calcd. for $C_{48}H_{56}NO_{11}$ (MNH_4^+) 822.3853. Found 822.3864).

Cholestan-3′-β-yl 3,4,6-tri-O-benzyl-β-D-mannopyranoside 89i

4Å Molecular sieves were suspended in anhydrous dichloroethane (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (49 mg, 0.24 mmol), silver trifluoromethanesulfonate (61 mg, 0.24 mmol) and anhydrous tin (II) chloride (46 mg, 0.24 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(1-(cholestan-3-β-yloxy)-2-iodopropyl)-α-D-mannopyranosyl fluoride **86i** (121 mg, 0.12 mmol) was dissolved in anhydrous dichloroethane (2 ml) and added by cannula under Ar and the reaction mixture stirred at 50 °C. After 4 h, tlc (petrol:ethyl acetate, 7:1) indicated the absence of starting material (R_f 0.5) and the formation of a major product (R_f 0.1). Water (1 ml) and trifluoroacetic acid (2 ml) were added and the reaction stirred further. After 30 min the reaction mixture was filtered through celite and partitioned between CH_2Cl_2 (2 x 30 ml) and $NaHCO_3$ (30 ml of a saturated aqueous solution). The combined organic extracts were dried ($MgSO_4$), filtered and

concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford cholestan-3′-β-yl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside **89i** (58 mg, 59%) as colourless crystals, m.p. 100-102 °C (ethanol); $[\alpha]_D^{24}$ -4.9 (*c*, 0.75 in $CHCl_3$); ν_{max} 3435 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.58-2.00 (31H, m, steroid CH, CH_2), 0.66, 0.81 (6H, 2 x s, 2 x CH_3), 0.87 (3H, d, *J* 6.6 Hz, CH_3), 0.88 (3H, d, *J* 6.8 Hz, CH_3), 0.91 (3H, d, *J* 6.5 Hz, CH_3), 2.11 (1H, br s, OH-2), 3.43 (1H, ddd, $J_{4,5}$ 9.7 Hz, $J_{5,6}$ 5.6 Hz, $J_{5,6'}$ 1.9 Hz, H-5), 3.57 (1H, dd, $J_{2,3}$ 3.2 Hz, $J_{3,4}$ 9.1 Hz, H-3), 3.69 (1H, dd, $J_{6,6'}$ 10.7 Hz, H-6), 3.70-3.77 (1H, m, steroid OCH), 3.80 (1H, dd, H-6′), 3.84 (1H, at, *J* 9.3 Hz, H-4), 4.06 (1H, d, H-2), 4.56, 4.91 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 4.57 (1H, s, H-1), 4.58, 4.63 (2H, ABq, J_{AB} 12.1 Hz, PhC$\underline{H}_2$), 4.68, 4.79 (2H, ABq, J_{AB} 11.9 Hz, PhC$\underline{H}_2$), 7.21-7.40 (15H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 12.0, 12.2, 18.7, 22.5, 22.8 (5 x q, 5 x steroid CH_3), 21.2, 23.8, 24.2, 28.2, 28.8, 29.2, 32.1, 34.2, 36.2, 37.0, 39.5, 40.0 (12 x t, 12 x steroid CH_2), 28.0, 35.6, 35.8, 44.6, 54.4, 56.2, 56.5 (7 x d, 7 x steroid CH), 35.4, 42.6 (2 x s, 2 x steroid C), 68.8 (d, C-2), 69.4 (t, C-6), 71.3, 73.4, 75.2 (3 x t, 3 x Ph$\underline{C}H_2$), 74.3 (d, C-4), 75.1 (d, C-5), 77.5 (d, steroid O$\underline{C}$H), 81.7 (d, C-3), 97.2 (d, $^1J_{C\text{-}1,H\text{-}1}$ 155.6 Hz, C-1), 127.5, 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 128.5 (8 x d, Ar-CH), 137.9, 138.2, 138.3 (3 x s, Ar-C). (Found: C, 78.62; H, 9.38. $C_{54}H_{76}O_6$ requires C, 78.98; H, 9.33%).

Methyl 3,4,6-tri-O-benzyl-β-D-mannopyranosyl-(1→4)-2,3,6-tri-O-benzyl-α-D-mannopyranoside 89j

4Å Molecular sieves were suspended in anhydrous dichloroethane (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (25 mg,

0.12 mmol), silver trifluoromethanesulfonate (31 mg, 0.12 mmol) and anhydrous tin (II) chloride (23 mg, 0.12 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,6-tri-*O*-benzyl-α-D-mannopyranosid-4-*O*-yl)propyl)-α-D-mannopyranosyl fluoride **86j** (65 mg, 0.06 mmol) was dissolved in anhydrous dichloroethane (2 ml) and added by cannula under Ar and the reaction mixture stirred at 50 °C. After 6 h 30 min, tlc (petrol:ethyl acetate, 3:1) indicated the absence of starting material (R_f 0.5) and the formation of a major product (R_f 0.1). The reaction mixture was diluted with ether (50 ml), filtered through celite and washed with $NaHCO_3$ (50 ml of a saturated aqueous solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1) to afford methyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-mannopyranoside **89j** (27 mg, 50%) as a colourless oil; $[\alpha]_D^{22}$ +21.4 (*c*, 0.35 in $CHCl_3$); ν_{max} 3416 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.29 (1H, ddd, $J_{4,5}$ 9.7 Hz, $J_{5,6}$ 2.2 Hz, $J_{5,6'}$ 4.5 Hz, H-5_b), 3.34 (3H, s, OCH_3), 3.39 (1H, dd, $J_{2,3}$ 3.3 Hz, $J_{3,4}$ 9.2 Hz, H-3_b), 3.62 (1H, dd, $J_{6,6'}$ 11.2 Hz, H-6_b), 3.65 (1H, dd, H-$6'_b$), 3.75-3.80 (3H, m, H-2_a, H-5_a, H-6_a), 3.86 (1H, at, *J* 9.5 Hz, H-4_b), 3.88 (1H, dd, $J_{5,6'}$ 3.7 Hz, $J_{6,6'}$ 11.0 Hz, H-$6'_a$), 3.97 (1H, dd, $J_{2,3}$ 3.2 Hz, H-3_a), 4.01 (1H, d, H-2_b) 4.32 (1H, at, *J* 9.2 Hz, H-4_a), 4.43, 4.56 (2H, ABq, J_{AB} 12.1 Hz, PhC$\underline{H}_2$), 4.48, 4.54 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.51, 4.86 (2H, ABq, J_{AB} 11.1 Hz, PhC$\underline{H}_2$), 4.57, 4.71 (2H, ABq, J_{AB} 11.7 Hz, PhC$\underline{H}_2$), 4.59, 4.70 (2H, ABq, J_{AB} 11.8 Hz, PhC$\underline{H}_2$), 4.68, 4.72 (2H, ABq, J_{AB} 12.9 Hz, PhC$\underline{H}_2$), 4.69 (1H, s, H-1_b), 4.77 (1H, d, $J_{1,2}$ 1.9 Hz, H-1_a), 7.19-7.36 (30H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 54.7 (q, OCH_3), 67.4 (d, C-2_b), 69.0 (t,

C-6_b), 69.4 (t, C-6_a), 70.9 (d, C-5_a), 70.8, 72.2, 72.5, 73.2, 73.3, 75.0 (6 x t, 6 x Ph$\underline{C}H_2$), 72.9 (d, C-4_a), 73.8 (d, C-4_b), 74.8 (d, C-2_a), 75.5 (d, C-5_b), 79.0 (d, C-3_a), 81.8 (d, C-3_b), 98.9 (d, $^1J_{C\text{-}1,H\text{-}1}$ 172.5 Hz, C-1_a), 100.0 (d, $^1J_{C\text{-}1,H\text{-}1}$ 161.5 Hz, C-1_b), 127.3, 127.4, 127.4, 127.5, 127.5, 127.5, 127.5, 127.6, 127.7, 127.9, 128.0, 128.1, 128.2, 128.2 (14 x d, Ar-CH), 137.9, 138.1, 138.2, 138.2, 138.3, 138.4 (6 x s, Ar-C); *m/z* (APCI$^-$) 931 (M+Cl$^-$, 100%); (ES$^+$) 914 (M+NH_4^+, 100%). (HRMS Calcd. for $C_{55}H_{64}NO_{11}$ (MNH_4^+) 914.4479. Found 914.4473).

Cyclohexyl 2-O-allyl-3,4,6-tri-O-benzyl-α-D-glucopyranoside 88α and cyclohexyl 2-O-allyl-3,4,6-tri-O-benzyl-β-D-glucopyranoside 88β

2-*O*-Allyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl fluoride **87** (100 mg, 0.20 mmol) and cyclohexanol **3c** (0.043 ml, 0.41 mmol) were dissolved in freshly distilled CH_2Cl_2 (2 ml) and cooled to -78 °C. Trimethylsilyl iodide (0.032 ml, 0.224 mmol) was added and the mixture stirred under Ar. After 1 h, tlc (petrol:ethyl acetate, 4:1) indicated little change, so the reaction was allowed to warm to -40 °C. After a further 5 h, tlc (petrol:ethyl acetate, 4:1) indicated formation of major (R_f 0.5) and minor (R_f 0.55) products and the complete consumption of starting material (R_f 0.4). The reaction was quenched with Et_3N (2 ml) and the mixture partitioned between CH_2Cl_2 (2 x 20 ml) and water (30 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 7:1) to afford cyclohexyl 2-*O*-allyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside **88β** (8 mg, 7%) as a colourless oil; $[\alpha]_D^{22}$ +14.0 (*c*, 0.1 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.29-2.01 (10H, m, cyclohexyl-H),

3.31 (1H, dd, $J_{1,2}$ 8.0 Hz, $J_{2,3}$ 9.0 Hz, H-2), 3.45 (1H, ddd, $J_{4,5}$ 9.7 Hz, $J_{5,6}$ 5.0 Hz, $J_{5,6'}$ 1.7 Hz, H-5), 3.52 (1H, at, J 9.3 Hz, H-4), 3.60 (1H, at, J 9.1 Hz, H-3), 3.63-3.71 (2H, m, cyclohexyl-OCH, H-6), 3.74 (1H, dd, $J_{6,6'}$ 10.7 Hz, H-6'), 4.21 (1H, dd, J_{gem} 12.2 Hz, J 6.0 Hz, OC$\underline{H}$H'CH=CH_2), 4.42 (1H, d, H-1), 4.43-4.48 (1H, m, OCH$\underline{H}$'CH=CH_2), 4.54, 4.83 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 4.56, 4.61 (2H, ABq, J_{AB} 12.3 Hz, PhC$\underline{H}_2$), 4.79, 4.83 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 5.17 (1H, d, J_Z 10.2 Hz, CH=C$H_E\underline{H}_Z$), 5.29 (1H, d, J_E 17.2 Hz, CH=C$\underline{H}_EH_Z$), 5.96 (1H, ddt, C$\underline{H}$=CH_2), 7.13-7.39 (15H, m, Ar-H); *m/z* (APCI$^+$) 595 (M+Na^+, 20), 590 (M+NH_4^+, 8%). (HRMS Calcd. for $C_{36}H_{48}NO_6$ (MNH_4^+) 590.3482. Found 590.3477);

And cyclohexyl 2-*O*-allyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside **88α** (78 mg, 67%) as a colourless oil; $[\alpha]_D^{22}$ +62.3 (*c*, 0.6 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.17-2.00 (10H, m, cyclohexyl-H), 3.51 (1H, dd, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 9.6 Hz, H-2), 3.57-6.68 (3H, m, cyclohexyl-OCH, H-4, H-6), 3.76 (1H, dd, $J_{5,6'}$ 3.5 Hz, $J_{6,6'}$ 10.5 Hz, H-6'), 3.90 (1H, m, H-5), 3.96 (1H, at, J 9.3 Hz, H-3), 4.16 (1H, ddd, J_{gem} 12.8 Hz, J 6.0 Hz, J 1.3 Hz, OC$\underline{H}$H'CH=CH_2), 4.21 (1H, ddd, J 5.5 Hz, J 1.4 Hz, OCH$\underline{H}$'CH=CH_2), 4.48, 4.84 (2H, ABq, J_{AB} 10.6 Hz, PhC$\underline{H}_2$), 4.49, 4.65 (2H, ABq, J_{AB} 12.1 Hz, PhC$\underline{H}_2$), 4.79, 4.99 (2H, ABq, J_{AB} 10.8 Hz, PhC$\underline{H}_2$), 5.10 (1H, d, H-1), 5.19 (1H, d, J_Z 10.3 Hz, CH=C$H_E\underline{H}_Z$), 5.30 (1H, d, J_E 17.3 Hz, CH=C$\underline{H}_EH_Z$), 5.93 (1H, ddt, C$\underline{H}$=CH_2), 7.14-7.39 (15H, m, Ar-H); *m/z* (APCI$^+$) 595 (M+Na^+, 5%). (HRMS Calcd. for $C_{36}H_{48}NO_6$ (MNH_4^+) 590.3482. Found 590.3470).

7.4 Experimental for Chapter 4

Tethering Using Iodine, Silver Triflate and DTBMP

3,4,6-Tri-O-benzyl-2-O-(2-iodo-1-(methyl 2,3,6-tri-O-benzyl-α-D-mannopyranosid-4-O-yl)propyl)-α-D-mannopyranosyl fluoride 86j

Iodine (46 mg, 0.18 mmol), silver trifluoromethanesulfonate (46 mg, 0.18 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (74 mg, 0.36 mmol) and 4Å molecular sieves were added to freshly distilled CH_2Cl_2 (1 ml) and cooled to -78 °C under Ar. Methyl 2,3,6-tri-*O*-benzyl-α-D-mannopyranoside **3j** (79 mg, 0.17 mmol) was dissolved in freshly distilled CH_2Cl_2 (2 ml) and added by cannula under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-α-D-mannopyranosyl fluoride **81** (80 mg, 0.16 mmol) was dissolved in freshly distilled CH_2Cl_2 (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to RT. After 25 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a major product (R_f 0.5) and little remaining starting materials (R_f 0.6 and 0.2). The reaction was quenched with sodium thiosulfate (40 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,6-tri-*O*-benzyl-α-D-mannopyranosid-4-*O*-yl)propyl)-α-D-mannopyranosyl fluoride **86j** (139 mg, 55%) as a colourless oil as previously described;

Also recovered 3,4,6-tri-*O*-benzyl-2-*O*-prop-1′-enyl-α-D-mannopyranosyl fluoride **81** (26 mg, 33%).

Tethering Using Iodonium Chloride

3,4,6-Tri-O-benzyl-2-O-(2-iodo-1-(methyl 2,3,4-tri-O-benzyl-α-D-mannopyranosid-6-O-yl)propyl)-α-D-mannopyranosyl fluoride 86e

2,6-Di-*tert*-butyl-4-methylpyridine (100 mg, 0.49 mmol) and 4Å molecular sieves were added to freshly distilled CH_2Cl_2 (1 ml) and cooled to -40 °C under Ar. Methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **3e** (151 mg, 0.33 mmol) was dissolved in distilled acetonitrile (1.5 ml) and added to the reaction vessel by cannula under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1'-enyl-α-D-mannopyranosyl fluoride **81** (80 mg, 0.16 mmol) was dissolved in distilled acetonitrile (1.5 ml) and added to the reaction vessel by cannula under Ar. Iodonium chloride (1M solution in CH_2Cl_2) (0.41 ml, 0.41 mmol) was added and the reaction allowed to warm to RT. After 72 h, tlc (petrol:ethyl acetate, 4:1) indicated formation of products (R_f 0.4 and 0.45) and little remaining starting material (R_f 0.5). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1 with 1% Et_3N) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranosid-6-*O*-yl)propyl)-α-D-mannopyranosyl fluoride **86e** (55 mg, 31%) as a colourless oil as previously described;

Also recovered 3,4,6-tri-*O*-benzyl-2-*O*-prop-1′-enyl-α-D-mannopyranosyl fluoride **81** (17 mg, 21%); and 3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl fluoride **79** (30 mg, 41%) as a colourless oil.

Attempted Tethering Using Iodonium Chloride Without Base

Methyl 3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→6)-2,3,4-tri-O-benzyl-α-D-mannopyranoside 95 and methyl 3,4,6-tri-O-benzyl-β-D-mannopyranosyl-(1→6)-2,3,4-tri-O-benzyl-α-D-mannopyranoside 89e

4Å Molecular sieves were added to freshly distilled CH_2Cl_2 (1 ml) and cooled to -40 °C under Ar. Methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **3e** (151 mg, 0.33 mmol) was dissolved in distilled acetonitrile (1.5 ml) and added to the reaction vessel by cannula under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-α-D-mannopyranosyl fluoride **81** (80 mg, 0.16 mmol) was dissolved in distilled acetonitrile (1.5 ml) and added to the reaction vessel by cannula under Ar. Iodonium chloride (1M solution in CH_2Cl_2) (0.49 ml, 0.49 mmol) was added and the reaction allowed to warm to RT. After 16 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of major (R_f 0.1) and minor (R_f 0.15) products and no remaining starting material (R_f 0.6). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1→2:1) to afford methyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-

mannopyranoside **89e** (16 mg, 11%) as a colourless oil identical to that previously described;

Further elution gave methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **95** (67 mg, 46%) as a colourless oil; $[\alpha]_D^{24}$ +50.5 (*c*, 0.65 in $CHCl_3$) [Lit. +60.0 (*c*, 0.24 in $CHCl_3$)][10]; δ_H (400 MHz, $CDCl_3$) 2.38 (1H, d, $J_{OH,2}$ 2.7 Hz, OH-2), 3.28 (3H, s, CH_3), 3.61 (1H, dd, $J_{5,6}$ 2.0 Hz, $J_{6,6'}$ 10.8 Hz, H-6_b), 3.68 (1H, dd, $J_{5,6'}$ 4.2 Hz, H-$6'_b$), 3.67-3.95 (9H, m, H-2_a, H-3_a, H-4_a, H-5_a, H-6_a, H-$6'_a$, H-3_b, H-4_b, H-5_b), 4.12-4.13 (1H, m, H-2_b), 4.47, 4.64 (2H, ABq, J_{AB} 11.9 Hz, PhC$\underline{H}_2$), 4.49, 4.83 (2H, ABq, J_{AB} 11.0 Hz, PhC$\underline{H}_2$), 4.52, 4.92 (2H, ABq, J_{AB} 11.2 Hz, PhC$\underline{H}_2$), 4.57, 4.64 (2H, ABq, J_{AB} 11.6 Hz, PhC$\underline{H}_2$), 4.63 (2H, s, PhC$\underline{H}_2$), 4.70, 4.75 (2H, ABq, J_{AB} 12.4 Hz, PhC$\underline{H}_2$), 4.73 (1H, d, $J_{1,2}$ 1.8 Hz, H-1_a), 5.09 (1H, d, $J_{1,2}$ 1.9 Hz, H-1_b), 7.15-7.40 (30H, m, Ar-H);

Also recovered methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **3e** (93 mg, 0.20 mmol).

Tethering Using *N*-Chlorosuccinimide

***3,4,6-Tri*-O-*benzyl*-2-O-(2-*chloro*-1-(1,2:3,4-*di*-O-*isopropylidene*-α-D-*galactopyranos*-6-O-*yl*)*propyl*)-α-D-*mannopyranosyl fluoride* 96**

N-Chlorosuccinimide (66 mg, 0.49 mmol), and 4Å molecular sieves were added to anhydrous dichloroethane (1 ml) and cooled to -40 °C under Ar. 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose **3d** (85 mg, 0.33 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-α-D-

mannopyranosyl fluoride **81** (80 mg, 0.16 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. The reaction was stirred in the dark and allowed to warm to RT. After 41 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.5) and complete consumption of starting material (R_f 0.6). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(2-chloro-1-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-*O*-yl)propyl)-α-D-mannopyranosyl fluoride 96 (40 mg, 31%) as a colourless oil; *m/z* (APCI$^+$) 804 (M+NH_4^+, 13%).

Synthesis of the Core β-Mannosyl Disaccharide

3,4,6-Tri-O-benzyl-2-O-(2-iodo-1-(para-methoxyphenyl 3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosid-4-O-yl)propyl)-α-D-mannopyranosyl fluoride 86k

Iodine (54 mg, 0.21 mmol), silver trifluoromethanesulfonate (54 mg, 0.21 mmol), 2,6-di-tert-butyl-4-methylpyridine (87 mg, 0.42 mmol) and 4Å molecular sieves were added to freshly distilled CH_2Cl_2 (1 ml) and cooled to -78 °C under Ar. *para*-Methoxyphenyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside **3k** (102 mg, 0.17 mmol) was dissolved in freshly distilled CH_2Cl_2 (2 ml) and added by cannula under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-α-D-mannopyranosyl fluoride **81** (80 mg, 0.16 mmol)

was dissolved in freshly distilled CH_2Cl_2 (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to RT. After 3 h 30 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a major product (R_f 0.2) and little remaining starting materials (R_f 0.6 and 0.1). Sodium thiosulfate (40 ml of a 10% aqueous solution) was added and the mixture extracted with CH_2Cl_2 (2 x 40 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 3:1) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(*para*-methoxyphenyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosid-4-*O*-yl)propyl)-α-D-mannopyranosyl fluoride **86k** (147 mg, 75%) as a colourless oil; *m/z* (ES^+) 1252 ($M+K^+$, 7), 1236 ($M+Na^+$, 100), 1231 ($M+NH_4^+$, 41%);

Also recovered *para*-methoxyphenyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside **3k** (18 mg, 0.03 mmol).

para-*Methoxyphenyl 3,4,6-tri-O-benzyl-β-D-mannopyranosyl-(1→4)-3,6-di-O-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside 89k*

4Å Molecular sieves were suspended in anhydrous dichloroethane (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (50 mg, 0.25 mmol), silver trifluoromethanesulfonate (63 mg, 0.25 mmol) and anhydrous tin (II) chloride (47 mg, 0.25 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodo-1-(*para*-methoxyphenyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosid-4-*O*-yl)propyl)-α-D-mannopyranosyl fluoride **86k** (147 mg, 0.12 mmol) was dissolved in anhydrous dichloroethane

(6 ml) and added by cannula under Ar. The reaction mixture was stirred at 50 °C. After 7 h 30 min, tlc (petrol:ethyl acetate, 3:1) indicated the absence of starting material (R_f 0.5) and the formation of a major (R_f 0.1) and minor (R_f 0.2) products. The reaction was quenched with $NaHCO_3$ (15 ml of a saturated aqueous solution) and the mixture stirred for a further 20 min. The mixture was diluted with ethyl acetate (150 ml), filtered through celite and washed with brine (50 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 3:1→1:1) to afford *para*-methoxyphenyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranosyl-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside **89k** (67 mg, 54%) as a colourless oil; $[\alpha]_D^{25}$ +44.5 (*c*, 1.5 in $CHCl_3$) [Lit. +52 (*c*, 0.59 in $CHCl_3$)][11]; δ_H (400 MHz, $CDCl_3$) 3.35 (1H, ddd, $J_{4,5}$ 9.6 Hz, $J_{5,6}$ 4.5 Hz, $J_{5,6'}$ 1.4 Hz, H-5_b), 3.44 (1H, dd, $J_{2,3}$ 3.3 Hz, $J_{3,4}$ 9.2 Hz, H-3_b), 3.64 (1H, dd, $J_{6,6'}$ 10.7 Hz, H-6_b), 3.72 (3H, s, OCH_3), 3.74-3.77 (2H, m, H-5_a, H-$6'_b$), 3.79 (1H, dd, $J_{5,6}$ 1.9 Hz, $J_{6,6'}$ 11.2 Hz, H-6_a), 3.84 (1H, dd, $J_{5,6'}$ 3.9 Hz, H-$6'_a$), 3.87 (1H, at, *J* 9.2 Hz, H-4_b), 4.05 (1H, d, H-2_b), 4.18 (1H, at, *J* 8.6 Hz, H-3_a), 4.42-4.47 (2H, m, H-2_a, H-4_a), 4.48 (2H, s, PhC$\underline{H}_2$), 4.52, 4.69 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.54, 4.86 (2H, ABq, J_{AB} 10.8 Hz, PhC$\underline{H}_2$), 4.55, 4.94 (2H, ABq, J_{AB} 12.4 Hz, PhC$\underline{H}_2$), 4.56, 4.64 (2H, ABq, J_{AB} 11.8 Hz, PhC$\underline{H}_2$), 4.70 (1H, s, H-1_b), 5.63 (1H, d, $J_{1,2}$ 7.9 Hz, H-1_a), 6.69-6.73 (2H, m, Ar-H), 6.79-6.85 (4H, m, Ar-H), 7.01-7.03 (2H, m, Ar-H), 7.19-7.63 (21H, m, Ar-H), 7.68-7.80 (4H, m, Ar-H); δ_C (125.7 MHz, $CDCl_3$) 55.4, 55.6 (d, q, C-2_a, OCH_3), 67.9 (d, C-2_b), 68.4, 68.8 (2 x t, C-6_a, C-6_b), 71.2, 73.2, 73.4, 74.7, 75.0 (5 x t, 5 x Ph$\underline{C}H_2$), 73.8 (d, C-4_b), 74.6 (d, C-5_a), 75.4 (d, C-5_b), 77.8, 78.0 (2 x d, C-3_a, C-4_a), 81.6 (d,

C-3_b), 97.6 (d, $^1J_{C\text{-}1,H\text{-}1}$ 166.0 Hz, C-1_a), 100.3 (d, $^1J_{C\text{-}1,H\text{-}1}$ 158.1 Hz, C-1_b), 114.2, 118.7, 123.2, 126.9, 127.3, 127.5, 127.6, 127.7, 127.7, 127.7, 127.8, 127.8, 127.9, 128.0, 128.2, 128.2, 128.4, 128.4, 128.4, 133.6 (20 x d, Ar-CH), 137.8, 138.1, 138.2, 138.3, 150.7, 155.3 (6 x s, Ar-C);

Also isolated *para*-methoxyphenyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside **3k** (25 mg, 35%) as a colourless oil.

Typical Procedure for Lithium Iodide-Mediated Formation of Glycosyl Iodides

Enol ethers **23** (0.017 mmol) were dissolved in freshly distilled CH_2Cl_2 (0.5 ml) and lithium iodide (30 mg, 0.22 mmol) was added. The reaction was stirred at RT under Ar. After 4 h 30 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product, which stained brown on tlc when treated with ammonium molybdate stain before reverting to the usual blue colour (R_f 0.6), and complete consumption of starting material (R_f 0.5).

The Use of an α-*Gluco* Fluoride Donor

2-O-Acetyl-3,4,6-tri-O-benzyl-α-D-glucopyranosyl fluoride 102

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl fluoride **66** was allowed to stand on the bench overnight. The resulting brown residue was separated by flash column chromatography (petrol:ethyl acetate, 4:1) to afford 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl fluoride **102** as a colourless oil; $[\alpha]_D^{22}$ +60.5 (*c*, 1.0 in $CHCl_3$); ν_{max} 1747 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.05 (3H, s, C$\underline{H}_3$), 3.70 (1H, dd, $J_{5,6}$ 1.9 Hz, $J_{6,6'}$ 11.0 Hz, H-6), 3.78 (1H, dd, $J_{5,6'}$ 3.4 Hz,

H-6′), 3.83 (1H, at, *J* 9.6 Hz, H-4), 3.97-4.01 (1H, m, H-5), 4.01 (1H, at, *J* 9.6 Hz, H-3), 4.52, 4.64 (2H, ABq, J_{AB} 12.1 Hz, PhC$\underline{H}_2$), 455, 4.83 (2H, ABq, J_{AB} 10.7 Hz, PhC$\underline{H}_2$), 4.76, 4.85 (2H, ABq, J_{AB} 11.4 Hz, PhC$\underline{H}_2$), 4.92 (1H, ddd, $J_{1,2}$ 2.7 Hz, $J_{2,3}$ 10.0 Hz, $J_{2,F}$ 25.0 Hz, H-2), 5.73 (1H, dd, $J_{1,F}$ 53.9 Hz, H-1), 7.16-7.35 (15H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 20.7 (q, $\underline{C}H_3$), 67.7, 73.5, 75.2, 75.5 (4 x t, C-6, 3 x Ph$\underline{C}H_2$), 72.8 (dd, $J_{C\text{-}2,F}$ 20 Hz, C-2), 72.9, 76.7, 79.4 (3 x d, C-3, C-4, C-5), 104.6 (dd, $J_{C\text{-}1,F}$ 221 Hz, C-1), 127.6, 127.8, 127.9, 127.9, 128.4 (5 x d, Ar-CH), 137.7, 137.7, 137.8 (3 x s, Ar-C), 170.2 (s, $\underline{C}$=O); δ_F ($CDCl_3$) -149.3 (dd, $J_{1,F}$ 54.1 Hz, $J_{2,F}$ 23.6 Hz); *m/z* ($APCI^+$) 533 ($M+K^+$, 92), 517 ($M+Na^+$, 25%). (Found: C, 70.63; H, 6.33. $C_{29}H_{31}O_6F$ requires C, 70.43; H, 6.32%).

3,4,6-Tri-O-benzyl-α-D-glucopyranosyl fluoride 103

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl fluoride **102** (1.5 g, 3.0 mmol) was dissolved in methanol (10 ml). Sodium (100 mg, 4.3 mmol) was dissolved in methanol (5 ml) and added to the sugar solution. After 30 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.2) and complete consumption of starting material (R_f 0.5). 1M HCl was added until pH 7 was reached and the mixture was partitioned between CH_2Cl_2 (200 ml) and water (200 ml). The aqueous layer was re-extracted with CH_2Cl_2 (100 ml) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was recrystallised from methanol to afford 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl fluoride **103** (1.38 g, quantitative yield) as a white, crystalline solid, m.p. 108-110 °C (methanol); $[\alpha]_D^{22}$ +79.2 (*c*, 0.5 in $CHCl_3$); ν_{max} 3170 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.14 (1H, d, $J_{OH,2}$ 6.5 Hz,

OH-2), 3.69 (1H, dd, $J_{5,6}$ 2.0 Hz, $J_{6,6'}$ 10.9 Hz, H-6), 3.68-3.89 (4H, m, H-2, H-3, H-4, H-6'), 3.96-3.99 (1H, m, H-5), 4.52, 4.64 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.56, 4.83 (2H, ABq, J_{AB} 10.8 Hz, PhC$\underline{H}_2$), 4.83, 4.93 (2H, ABq, J_{AB} 11.3 Hz, PhC$\underline{H}_2$), 5.67 (1H, dd, $J_{1,2}$ 2.6 Hz, $J_{1,F}$ 53.7 Hz, H-1), 7.17-7.38 (15H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 67.7, 73.5, 75.0, 75.5 (4 x t, C-6, 3 x Ph$\underline{C}H_2$), 72.3 (dd, $J_{C\text{-}2,F}$ 20 Hz, C-2), 73.0, 76.7, 82.0 (3 x d, C-3, C-4, C-5), 107.1 (dd, $J_{C\text{-}2,F}$ 221 Hz, C-1), 127.8, 127.9, 128.0, 128.4, 128.6 (5 x d, Ar-CH), 137.6, 137.8, 138.2 (3 x s, Ar-C); δ_F ($CDCl_3$) -151.2 (dd, $J_{1,F}$ 54.1 Hz, $J_{2,F}$ 23.5 Hz); (Found: C, 71.66; H, 6.47. $C_{29}H_{31}O_6F$ requires C, 71.66; H, 6.46%).

2-O-Allyl-3,4,6-tri-O-benzyl-α-D-glucopyranosyl fluoride 87

3,4,6-Tri-*O*-benzyl-α-D-glucopyranosyl fluoride **103** (1.28 g, 2.82 mmol) was dissolved in anhydrous DMF (15 ml) and cooled to 0 °C. Allyl bromide (0.49 ml, 5.64 mmol) was added then sodium hydride (60% in mineral oil) (225 mg, 5.64 mmol) was added portionwise. After 45 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a single product (R_f 0.6) and complete consumption of starting material (R_f 0.4). The reaction was quenched with methanol (10 ml) then concentrated *in vacuo*. The residue was partitioned between ether (200 ml) and water (200 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was recrystallised from ethanol to afford 2-*O*-allyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl fluoride **87** (1.38 g, 99%) as a white, crystalline solid, m.p. 49-50 °C (ethanol); $[\alpha]_D^{22}$ +27.5 (*c*, 0.38 in $CHCl_3$); ν_{max} 1647 (w, C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.54 (1H, ddd, $J_{1,2}$ 2.6 Hz, $J_{2,3}$ 9.6 Hz, $J_{2,F}$ 25.7 Hz, H-2), 3.70 (1H, dd, $J_{5,6}$ 1.9 Hz,

$J_{6,6'}$10.8 Hz, H-6), 3.75-3.99 (3H, m, H-4, H-5, H-6'), 3.96 (1H, at, *J* 9.3 Hz, H-3), 4.22 (1H, dd, J_{gem} 12.6 Hz, *J* 6.2 Hz, OC<u>H</u>H'CH=CH_2), 4.28 (1H, dd, *J* 5.5 Hz, OCH<u>H</u>'CH=CH_2), 4.51, 4.63 (2H, ABq, J_{AB} 12.1 Hz, PhC<u>H_2</u>), 4.53, 4.86 (2H, ABq, J_{AB} 10.7 Hz, PhC<u>H_2</u>), 4.84, 4.96 (2H, ABq, J_{AB} 10.8 Hz, PhC<u>H_2</u>), 5.24 (1H, dd, J_{gem} 1.1 Hz, J_Z 10.3 Hz, CH=C<u>H_Z</u>H_E), 5.34 (1H, dd, J_{gem} 1.5 Hz, J_E 17.2 Hz, CH=CH_Z<u>H_E</u>), 5.71 (1H, dd, $J_{1,F}$ 53.2 Hz, H-1), 5.96 (1H, ddat, C<u>H</u>=CH_2), 7.16-7.40 (15H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 67.8, 72.7, 73.5, 75.2, 75.8 (5 x t, C-6, 3 x Ph<u>C</u>H_2, O<u>C</u>H_2CH=CH_2), 72.6, 76.5, 81.3 (3 x d, C-3, C-4, C-5), 79.3 (dd, $J_{C\text{-}2,F}$ 20 Hz, C-2), 105.6 (dd, $J_{C\text{-}2,F}$ 221 Hz, C-1), 118.2 (t, CH=<u>C</u>H_2), 127.7, 127.8, 127.9, 127.9, 128.0, 128.4, 128.4 (7 x d, Ar-CH), 134.3 (d, <u>C</u>H=CH_2), 137.7, 138.0, 138.4 (3 x s, Ar-C); δ_F ($CDCl_3$) -149.8; *m/z* (APCI$^+$) 515 (M+Na^+, 100%). (HRMS Calcd. for $C_{30}H_{37}NO_5F$ (MNH_4^+) 510.2656. Found 510.2654).

3,4,6-Tri-O-benzyl-2-O-prop-1'enyl-α-D-glucopyranosyl fluoride 104

Wilkinson's catalyst (38 mg, 0.041 mmol) was dissolved in freshly distilled THF (3 ml) and degassed. Butyl lithium (1.2M solution in hexanes) (0.05 ml, 0.061 mmol) was added and the mixture stirred for 10 min. 2-*O*-Allyl-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl fluoride **97** (200 mg, 0.406 mmol) was dissolved in was dissolved in freshly distilled THF (3 ml) and heated to 65 °C and the catalyst solution was added by cannula under Ar. After 85 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a single product (R_f 0.55) and complete consumption of starting material (R_f 0.5). The reaction was allowed to cool then diluted with CH_2Cl_2 (20 ml) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate,

4:1) to afford 3,4,6-tri-*O*-benzyl-2-*O*-prop-1'enyl-α-D-glucopyranosyl fluoride **104** (200 mg, quantitative yield) as a pale yellow oil; Partial data: δ_H (200 MHz, $CDCl_3$) (*E*:*Z*, 1:2.4) *E* isomer 1.57 (3H, dd, *J* 1.6 Hz, *J* 6.8 Hz, OCH=CHC$\underline{H}_3$), 5.11 (1H, dd, J_E 12.2 Hz, OCH=C$\underline{H}$), 5.71 (1H, dd, $J_{1,F}$ 53.1, $J_{1,2}$ 2.5 Hz, H-1), 6.22 (1H, dd, OC$\underline{H}$=CH); *Z* isomer 1.67 (3H, dd, *J* 1.7 Hz, *J* 6.9 Hz, OCH=CHC$\underline{H}_3$), 5.69 (1H, dd, $J_{1,F}$ 53.3, $J_{1,2}$ 2.6 Hz, H-1), 6.12 (1H, dd, J_Z 6.1 Hz, OC$\underline{H}$=CH); *m/z* (APCI$^+$) 515 (M+Na$^+$, 39%).

3,4,6-Tri-O-benzyl-2-O-(2-iodo-1-(methyl 2,3,4-tri-O-benzyl-α-D-mannopyranosid-6-O-yl)propyl)-α-D-glucopyranosyl fluoride 105e

N-Iodosuccinimide (125 mg, 0.56 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (1 ml) and cooled to -40 °C under Ar. Methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **3e** (172 mg, 0.37 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added by cannula under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1'-enyl-α-D-glucopyranosyl fluoride **104** (91 mg, 0.19 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to RT. After 2 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.5) and complete consumption of starting material (R_f 0.6). Sodium thiosulfate (30 ml of a 10% aqueous solution) was added and the mixture extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-

mannopyranosid-6-*O*-yl)propyl)-α-D-glucopyranosyl fluoride **105e** (126 mg, 63%) as a colourless oil; *m/z* (APCI$^+$) 1110 (M+NH_4^+, 5%).

***3,4,6-Tri*-O-*benzyl*-2-O-(2-*iodo*-1-(*methyl* 2-O-*benzyl*-4,6-O-*benzylidene*-α-*D*-*mannopyranosid*-3-O-*yl*)*propyl*)-α-*D*-*glucopyranosyl fluoride* 105g**

N-Iodosuccinimide (122 mg, 0.54 mmol), methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **3g** (135 mg, 0.36 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (2 ml) and cooled to -40 °C under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-α-D-glucopyranosyl fluoride **104** (89 mg, 0.18 mmol) was dissolved in anhydrous dichloroethane (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was stirred in the dark and allowed to warm to RT. After 17 h, tlc (petrol:ethyl acetate, 4:1) indicated formation of a product (R_f 0.5) and complete consumption of starting material (R_f 0.6). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosid-3-*O*-yl)propyl)-α-D-glucopyranosyl fluoride **105g** (54 mg, 30%) as a colourless oil; *m/z* (APCI$^+$) 1008 (M+NH_4^+, 5%);

Also recovered 3,4,6-tri-*O*-benzyl-2-*O*-prop-1′-enyl-α-D-glucopyranosyl fluoride **104** (12 mg, 13%); and methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **3g** (104 mg, 0.28 mmol).

Methyl 3,4,6-tri-O-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-O-benzyl-α-D-mannopyranoside 30e

4Å Molecular sieves were suspended in anhydrous dichloroethane (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (12 mg, 0.06 mmol), silver trifluoromethanesulfonate (15 mg, 0.06 mmol) and anhydrous tin (II) chloride (11 mg, 0.06 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranosid-6-*O*-yl)propyl)-α-D-glucopyranosyl fluoride **105e** (30 mg, 0.03 mmol) was dissolved in anhydrous dichloroethane (3 ml) and added by cannula under Ar and the reaction mixture stirred at 50 °C. After 68 h, tlc (petrol:ethyl acetate, 3:1) indicated the absence of starting material (R_f 0.5) and the formation of major (R_f 0.1) and minor (R_f 0.4) products. The reaction mixture was diluted with ether (50 ml), filtered through celite and washed with $NaHCO_3$ (50 ml of a saturated aqueous solution). The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1→4:1→0:1) to afford methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **30e** (8 mg, 32%) as a colourless oil identical to that previously described;

Also isolated was methyl 3,4,6-tri-*O*-benzyl-2-*O*-prop-1′-enyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **90e** (4 mg, 12%); *m/z* (ES^+) 995 ($M+NH_4^+$+MeCN, 29), 954 ($M+NH_4^+$, 100%). (HRMS Calcd. for $C_{58}H_{68}NO_{11}$ (MNH_4^+) 954.4792. Found 954.4794).

Methyl 3,4,6-tri-O-benzyl-α-D-glucopyranosyl-(1→3)-2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside 30g

4Å Molecular sieves were suspended in anhydrous dichloroethane (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (21 mg, 0.10 mmol), silver trifluoromethanesulfonate (26 mg, 0.10 mmol) and anhydrous tin (II) chloride (19 mg, 0.10 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosid-3-*O*-yl)propyl)-α-D-glucopyranosyl fluoride **105g** (44 mg, 0.051 mmol) was dissolved in anhydrous dichloroethane (3 ml) and added by cannula under Ar, and the reaction mixture stirred at 60 °C. After 27 h 30 min, tlc (petrol:ethyl acetate, 3:1) indicated the formation of a major product (R_f 0.2) and complete consumption of starting material (R_f 0.5). The reaction mixture was diluted with ethyl acetate (40 ml), filtered through celite and washed with $NaHCO_3$ (50 ml of a saturated aqueous solution). The aqueous layer was re-extracted with ethyl acetate (40 ml) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1) to afford methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **30g** (22 mg, 68%) as white crystals, identical to those previously described.

Competition Experiments – the Use of an External Nucleophile

Methyl 3,4,6-tri-O-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-O-benzyl-α-D-mannopyranoside 30e

Method 1: From the β-*gluco* donor **82e**

4Å Molecular sieves were suspended in anhydrous dichloroethane (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (37 mg, 0.18 mmol), silver trifluoromethanesulfonate (47 mg, 0.18 mmol) and anhydrous tin (II) chloride (34 mg, 0.18 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranosid-6-*O*-yl)propyl)-β-D-glucopyranosyl fluoride **82e** (98 mg, 0.09 mmol) and methanol **3a** (11 μl, 0.27 mmol) were dissolved in anhydrous dichloroethane (3 ml) and added by cannula under Ar and the reaction mixture stirred at 50 °C. After 19 h, tlc (petrol:ethyl acetate, 2:1) indicated the absence of starting material (R_f 0.7) and the formation of major (R_f 0.1) and minor (R_f 0.2) products. The reaction mixture was diluted with ethyl acetate (30 ml), filtered through celite and washed with $NaHCO_3$ (50 ml of a saturated aqueous solution). The aqueous layer was re-extracted with ethyl acetate (30 ml) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1) to afford methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **30e** (54 mg, 67%) as a colourless oil identical to that previously described;

Also isolated was a mixture of methyl glycosides (12 mg) as a colourless oil; ratio (**30a**:**69**:**3e**, 6:11:15) determined by integration of the OCH_3 singlets in the

^{1}H NMR spectrum.[12] δ_H (200 MHz, $CDCl_3$) **3e** 3.32 (3H, s, OCH_3); **30a** 3.42 (3H, s, OCH_3); **69** 3.57 (3H, s, OCH_3).

Method 2: From the α-*gluco* donor **105e**

4Å Molecular sieves were suspended in anhydrous dichloroethane (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (32 mg, 0.16 mmol), silver trifluoromethanesulfonate (40 mg, 0.16 mmol) and anhydrous tin (II) chloride (30 mg, 0.16 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranosid-6-*O*-yl)propyl)-α-D-glucopyranosyl fluoride **105e** (85 mg, 0.079 mmol) and methanol **3a** (10 µl, 0.24 mmol) were dissolved in anhydrous dichloroethane (4 ml) and added by cannula under Ar and the reaction mixture stirred at 50 °C. After 21 h, tlc (petrol:ethyl acetate, 3:1) indicated the absence of any starting material (R_f 0.6) and the formation of major (R_f 0.1) and minor (R_f 0.15) products. The reaction mixture was diluted with ether (30 ml), filtered through celite and washed with $NaHCO_3$ (50 ml of a saturated aqueous solution). The aqueous layer was re-extracted with ether (30 ml) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1→2:1→1:1) to afford methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **30e** (26 mg, 37%) as a colourless oil identical to that previously described;

Also isolated were methyl 3,4,6-tri-*O* -benzyl-2-*O*-prop-1'-enyl-α-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **90e** (15 mg,

20%); and recovered 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-β-D-mannopyranosid-6-*O*-yl)propyl)-α-D-glucopyranosyl fluoride **105e** (31 mg, 36%); and a mixture of methyl glycosides (8 mg) as a colourless oil; ratio (**30a**:**69**:**3e**, 2:6:11) determined by integration of the OCH_3 singlets in the ^1H NMR spectrum.[12] δ_H (200 MHz, $CDCl_3$) **3e** 3.31 (3H, s, OCH_3); **30a** 3.43 (3H, s, OCH_3); **69** 3.57 (3H, s, OCH_3).

Methyl 3,4,6-tri-O-benzyl-β-D-mannopyranosyl-(1→6)-2,3,4-tri-O-benzyl-α-D-mannopyranoside 89e

4Å Molecular sieves were suspended in anhydrous dichloroethane (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (21 mg, 0.10 mmol), silver trifluoromethanesulfonate (27 mg, 0.10 mmol) and anhydrous tin (II) chloride (20 mg, 0.10 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranosid-6-*O*-yl)propyl)-α-D-mannopyranosyl fluoride **86e** (136 mg, 0.13 mmol) an methanol **3a** were dissolved in anhydrous dichloroethane (4 ml) and added by cannula under Ar and the reaction mixture stirred at 50 °C. After 19 h, tlc (petrol:ethyl acetate, 4:1) indicated the absence of any starting material (R_f 0.5) and the formation several products (R_f 0.1-0.5). The reaction was quenched with $NaHCO_3$ (50 ml of a saturated aqueous solution) and extracted with ether (50 + 25 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1→2:1→0:1) to afford methyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-

mannopyranoside **89e** (23 mg, 50%) as a colourless oil, identical to that previously described;

Also isolated was a mixture of methyl glycosides (2 mg) as a colourless oil; ratio (**106**:**3e**, 2:3) determined by integration of the OCH_3 singlets in the ^1H NMR spectrum.[12] δ_H (200 MHz, $CDCl_3$) **3e** 3.31 (3H, s, OCH_3); **106** 3.37 (3H, s, OCH_3).

Competition Experiment – Crossover Reaction

Methyl 3,4,6-tri-O-benzyl-α-D-glucopyranoside 30a and benzyl 3,4,6-tri-O-benzyl-β-D-mannopyranoside 89b

4Å Molecular sieves were suspended in anhydrous dichloroethane (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (55 mg, 0.27 mmol), silver trifluoromethanesulfonate (69 mg, 0.27 mmol) and anhydrous tin (II) chloride (51 mg, 0.27 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodo-1-methoxypropyl)-β-D-glucopyranosyl fluoride **82a** (45 mg, 0.069 mmol) and 3,4,6-tri-*O*-benzyl-2-*O*-(1-benzyloxy-2-iodopropyl)-α-D-mannopyranosyl fluoride **86b** (47 mg, 0.065 mmol) were dissolved in anhydrous dichloroethane (7 ml) and added by cannula under Ar The reaction mixture was stirred at 50 °C. After 5 h, tlc (petrol:ethyl acetate, 2:1) indicated the absence of any starting materials (R_f 0.7 and 0.6) and the formation of two major products (R_f 0.2 and 0.3). The reaction was quenched with $NaHCO_3$ (10 ml of a saturated aqueous solution) and stirred for a further 10 min. The mixture was filtered through celite, diluted with CH_2Cl_2 (100 ml) and washed with brine (50 ml). The organic layer was dried ($MgSO_4$), filtered

and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:2→2:1) to afford benzyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside **89b** (21 mg, 60%) as a colourless oil; $[\alpha]_D^{25}$ -40.7 (*c*, 0.7 in $CHCl_3$) [Lit. -50 (*c*, 1.3 in $CHCl_3$)][B]; δ_H (500 MHz, $CDCl_3$) 2.48 (1H, br s, OH-2), 3.42-3.45 (1H, m, H-5), 3.55 (1H, dd, $J_{2,3}$ 2.9 Hz, $J_{3,4}$ 8.9 Hz, H-3), 3.75 (1H, dd, $J_{5,6}$ 5.3 Hz, $J_{6,6'}$ 10.7 Hz, H-6), 3.80 (1H, at, *J* 10.4 Hz, H-6'), 3.89 (1H, at, *J* 9.3 Hz, H-4), 4.12 (1H, d, H-2), 4.46 (1H, s, H-1), 4.55, 4.90 (2H, ABq, J_{AB} 11.0 Hz, PhC$\underline{H}_2$), 4.59, 4.66 (2H, ABq, J_{AB} 11.9 Hz, PhC$\underline{H}_2$), 4.66, 4.76 (2H, ABq, J_{AB} 11.9 Hz, PhC$\underline{H}_2$), 4.67, 4.96 (2H, ABq, J_{AB} 11.7 Hz, PhC$\underline{H}_2$), 7.20-7.38 (20H, m, Ar-H); HSQC (400 MHz, $CDCl_3$) $^1J_{C\text{-}1,H\text{-}1}$ 157 Hz;

And methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside **30a** (19 mg, 59%) as white crystals identical to those previously described.

No trace of the crossover products were seen by ^{1}H NMR or tlc.

Methyl 2,3-di-O-benzyl-α-D-glucopyranoside 110

Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside **111** (3 g, 6.5 mmol) was dissolved in methanol (75 ml) and CH_2Cl_2 (25 ml). *para*-Toluenesulfonic acid (51 mg, 0.27 mmol) was added and the mixture stirred at 50 °C. After 2 h, tlc (petrol:ethyl acetate, 1:1) indicated formation of a single product (R_f 0.5) and complete consumption of starting material (R_f 0.8). Solid $NaHCO_3$ was added and the mixture was filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1→1:2) to afford methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **110** (1.84 g, 76%) as a colourless oil which recrystallised from ether, m.p. 77-78 °C

(ether) [Lit. 79-80 °C][13]; $[\alpha]_D^{25}$ +15.5 (*c*, 1.0 in $CHCl_3$) [Lit. +17.3 (*c*, 1.2 in $CHCl_3$)][13]; δ_H (400 MHz, $CDCl_3$) 1.92 (1H, dd, *J* 5.7 Hz, *J* 7.0 Hz, OH-6), 2.30 (1H, d, $J_{OH,4}$ 2.6 Hz, OH-4), 3.39 (3H, s, CH_3), 3.49-3.55 (2H, m, H-2, H-4), 3.63 (1H, dat, $J_{5,6}$ 4.1 Hz, *J* 9.7 Hz, H-5), 3.72-3.84 (3H, m, H-3, H-6, H-6′), 4.61 (1H, d, $J_{1,2}$ 3.5 Hz, H-1), 4.67, 4.78 (2H, ABq, J_{AB} 12.1 Hz, PhC$\underline{H}_2$), 4.71, 5.04 (2H, ABq, J_{AB} 11.5 Hz, PhC$\underline{H}_2$), 7.30-7.40 (10H, m, Ar-H).

3,4,6-Tri-O-benzyl-2-O-(2-iodo-1-(methyl 2,3-di-O-benzyl-α-D-glucopyranosid-6-O-yl)propyl)-α-D-mannopyranosyl fluoride 109

N-Iodosuccinimide (206 mg, 0.92 mmol), and 4Å molecular seives were added to anhydrous dichloroethane (2 ml) and cooled to -40 °C under Ar. Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside **110** (228 mg, 0.61 mmol) was dissolved in anhydrous dichloroethane (2 ml) and added to the reaction vessel by cannula under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1′-enyl-α-D-mannopyranosyl fluoride **81** (150 mg, 0.30 mmol) was dissolved in anhydrous dichloroethane (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was stirred in the dark and allowed to warm to RT. After 19 h, tlc (petrol:ethyl acetate, 2:1) indicated formation of a product (R_f 0.5) and complete consumption of enol ether (R_f 0.8). The reaction was quenched with 10% aqueous sodium thiosulfate (30 ml) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 3:1) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3-di-*O*-benzyl-α-D-glucopyranosid-6-*O*-yl)propyl)-α-D-

mannopyranosyl fluoride **109** (220 mg, 73%) as a colourless oil; *m/z* ($APCI^+$) 1048 (M+56, 60), 1010 ($M+NH_4^+$, 22%). (HRMS Calcd. for $C_{51}H_{62}NO_{11}IF$ (MNH_4^+) 1010.3352. Found 1010.3362).

Intramolecular Glycosylation of 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3-di-*O*-benzyl-α-D-glucopyranosid-6-*O*-yl)propyl)-α-D-mannopyranosyl fluoride **109**

4Å Molecular seives were suspended in anhydrous dichloroethane (1 ml) in a flamedried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (67 mg, 0.33 mmol), silver trifluoromethanesulfonate (84 mg, 0.33 mmol) and anhydrous tin (II) chloride (62 mg, 0.33 mmol) were added. 3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3-di-*O*-benzyl-α-D-glucopyranosid-6-*O*-yl)propyl)-α-D-mannopyranosyl fluoride **109** (162 mg, 0.16 mmol) was dissolved in anhydrous dichloroethane (4 ml) and added by cannula under Ar and the reaction mixture stirred at 50 °C. After 22 h, tlc (petrol:ethyl acetate, 3:1) showed the absence of any starting material (R_f 0.2) and the formation of two major products (R_f 0.3 and 0.1). The reaction mixture was diluted with ether (50 ml), filtered through celite and washed with $NaHCO_3$ (30 ml of a saturated aqueous solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 3:1) to afford **112p** (1 mg, <1%) as a colourless oil; Partial data δ_H (200 MHz, $CDCl_3$) 2 isomers, ratio (*x*:*y*, 2:1) isomer *x* 1.84 (3H, d, *J* 6.9 Hz, $C\underline{H}_3CHI$), 3.36 (3H, s, OCH_3); isomer *y* 1.69 (3H,

d, *J* 7.0 Hz, C$\underline{H}_3$CHI), 3.33 (3H, s, OCH_3); *m/z* (ES^+) 1031 ($M+NH_4^+$+MeCN, 100), 990 ($M+NH_4^+$, 62); ($APCI^+$) 1028 (M+56, 7), 995 ($M+Na^+$, 5%);

Also methyl 6,2′-*O*-(2-iodopropylidene)-3′,4′,6′-tri-*O*-benzyl-α-D-mannopyranosyl-(1′→4)-2,3-di-*O*-benzyl-α-D-glucopyranoside **112q** (25 mg, 16%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 1.71 (3H, d, *J* 7.1 Hz, C$\underline{H}_3$CHI), 3.30 (1H, dd, $J_{5,6}$ 4.2 Hz, $J_{6,6'}$ 10.4 Hz, H-6_b), 3.33-3.37 (1H, m, H-$6'_b$), 3.35 (3H, s, OCH_3), 3.54 (1H, dd, $J_{1,2}$ 4.0 Hz, $J_{2,3}$ 8.9 Hz, H-2_a), 3.67 (1H, at, *J* 2.0 Hz, H-3_b), 3.78 (1H, dat, *J* 2.9 Hz, $J_{4,5}$ 9.0 Hz, H-5_a), 3.83 (1H, dd, $J_{3,4}$ 1.6 Hz, $J_{4,5}$ 5.5 Hz, H-4_b), 3.86-4.00 (5H, m, H-3_a, H-4_a, H-6_a, H-5_b, CHI), 4.04 (1H, dd, $J_{5,6'}$ 3.0 Hz, $J_{6,6'}$ 11.5 Hz, H-$6'_a$), 4.08, 4.36 (2H, ABq, J_{AB} 12.1 Hz, PhC$\underline{H}_2$), 4.25, 4.36 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.49-4.54 (3H, m, H-1_a, H-2_b, PhC$\underline{H}$H′), 4.58 (1H, d, *J* 10.7 Hz, PhCH$\underline{H}$′), 4.61, 4.81 (2H, ABq, J_{AB} 11.9 Hz, PhC$\underline{H}_2$), 4.66 (1H, d, *J* 8.7 Hz, CHIC$\underline{H}(O)_2$), 4.81, 5.18 (2H, ABq, J_{AB} 11.7 Hz, PhC$\underline{H}_2$), 5.30 (1H, d, $J_{1,2}$ 7.6 Hz, H-1_b), 7.16-7.45 (25H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 24.2, 24.5 (d, q, $\underline{C}$HI, $\underline{C}H_3$CHI), 55.3 (q, OCH_3), 64.6 (d, C-2_b), 68.5, 68.8 (d, 2 x t, C-5_a, C-6_a, C-6_b), 72.0, 72.9, 73.8, 74.0, 75.0 (4 x Ph$\underline{C}H_2$, C-4_a, C-5_b), 75.5 (d, C-4_b), 77.2 (t, Ph$\underline{C}H_2$), 79.0 (d, C-3_b), 79.9 (d, C-2_a), 80.6 (d, C-3_a), 96.5 (d, C-1_b), 98.6 (d, C-1_a), 105.6 (d, CHI$\underline{C}$H$(O)_2$), 127.0, 127.4, 127.5, 127.6, 127.7, 127.7, 127.8, 127.8, 127.8, 127.9, 128.0, 128.0, 128.0, 128.1, 128.2, 128.2, 128.3, 128.4, 128.5 (19 x d, Ar-CH), 137.7, 137.8, 138.2, 138.4, 139.8 (5 x s, Ar-C); *m/z* (ES^+) 1031 ($M+NH_4^+$+MeCN, 100), 990 ($M+NH_4^+$, 25), 973 ($M+H^+$, 13%); ($APCI^+$) 1028 (M+56, 5%);

Position	δ_H (ppm)	δ_C (ppm)
H-6_a	3.90	105.6 (CHI<u>C</u>H$(O)_2$, ^3J)
H-4_a	3.95	96.5 (C-1_b, ^3J), 80.6 (d, C-3_a, ^2J)
H-$6'_a$	4.04	105.6 (CHI<u>C</u>H$(O)_2$, ^3J)
H-2_b	4.52	105.6 (CHI<u>C</u>H$(O)_2$, ^3J), 96.5 (d, C-1_b, ^2J)
C<u>H</u>$(O)_2$	4.66	64.6 (C-2_b, ^3J), 69 (C-6_a, ^3J), 24 (<u>C</u>H_3<u>C</u>HI, ^2J, ^3J)
H-1_b	5.30	64.6 (C-2_b, ^2J), 73 (C-4_a, ^3J)

Table: Selected HMBC Correlations

Also **112r** (2 mg, 1%) as a colourless oil; Partial data δ_H (200 MHz, $CDCl_3$) 1.64 (3H, d, *J* 7.0 Hz, C<u>H</u>$_3$CHI), 3.35 (3H, s, OCH_3); *m/z* (ES^+) 1031 ($M+NH_4^+$+MeCN, 57), 990 ($M+NH_4^+$, 46%); ($APCI^+$) 1028 (M+56, 7), 995 ($M+Na^+$, 5%);

Also methyl 4,2′-*O*-(propylidene)-3′,4′,6′-tri-*O*-benzyl-β-D-mannopyranosyl-(1′→6)-2,3-di-*O*-benzyl-α-D-glucopyranoside **112s** (53 mg, 38%) as a colourless oil; Partial data δ_H (400 MHz, $CDCl_3$) 0.89 (3H, br s, $CH_2C\underline{H}_3$), 1.67 (1H, br s, $CH_3C\underline{H}H'$), 1.90-1.96 (1H, m, $CH_3CH\underline{H}'$), 3.38 (3H, s, OCH_3), 3.48-3.52 (2H, m), 3.54 (1H, dd, *J* 3.0 Hz, *J* 9.6 Hz), 3.70-3.82 (5H, m) 3.86 (1H, at, *J* 9.7 Hz), 4.20 (1H, br s), 4.50 (1H, d, $J_{1,2}$ 3.6 Hz, H-1_a), 4.57-4.81 (10H, m), 4.83 (1H, d, *J* 10.8 Hz, PhCH<u>H</u>′), 4.95 (1H, d, *J* 10.6 Hz, PhCH<u>H</u>′), 7.20-7.38 (25H, m, Ar-H); δ_C (125.7 MHz, $CDCl_3$) 10.3 (q, <u>C</u>H_3CH_2), 55.1 (q, OCH_3), 69.0 (t, C-6), 72.4, 75.0, 76.4 (3 x d, t), 77.2, 80.0, 80.7, 81.8 (4 x d), 98.0 (d, C-1_a), 106.8 (d, CHI<u>C</u>H$(O)_2$), 127.3, 127.4, 127.6, 127.6, 127.8, 127.8, 127.9, 127.9, 128.0, 128.0,

128.1, 128.1, 128.2, 128.3, 128.3, 128.4 (16 x d, Ar-CH), 138.0, 138.0, 138.0, 138.4, 138.8 (5 x s, Ar-C); *m/z* (ES^+) 905 ($M+NH_4^+$+MeCN, 81), 864 ($M+NH_4^+$, 100%); ($APCI^+$) 902 (M+56, 10), 864 ($M+ NH_4^+$, 5%);

Also **112t** (1 mg, 2%) as a colourless oil; Partial data δ_H (200 MHz, $CDCl_3$) 0.69 (3H, t, *J* 7.4 Hz, $C\underline{H}_3CH_2$), 1.3-1.7 (2H, m, $CH_3C\underline{H}_2$), 3.34 (3H, s, OCH_3); *m/z* (ES^+) 905 ($M+NH_4^+$+MeCN, 100), 864 ($M+NH_4^+$, 64%); ($APCI^+$) 902 (M+56, 5%);

Methyl 3,4,6-tri-O-benzyl-α-D-mannopyranosyl-(1→4)-2,3-di-O-benzyl-α-D-glucopyranoside 116

Methyl 6,2′-*O*-(2-iodopropylidene)-3′,4′,6′-tri-*O*-benzyl-α-D-mannopyranosyl-(1′→4)-2,3-di-*O*-benzyl-α-D-glucopyranoside **112q** (21 mg, 0.021 mmol) was dissolved in THF/TFA/methanol/water (2:5:1:2, 2.5 ml) and stirred at RT. After 72 h, tlc (petrol:ethyl acetate, 1:2) indicated formation of a product (R_f 0.7) and little remaining starting material (R_f 0.8). The reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 1:1) to afford methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→4)-2,3-di-*O*-benzyl-α-D-glucopyranoside **116** (13 mg, 75%) as a colourless oil; $[\alpha]_D^{24}$ +33.1 (*c*, 0.45 in $CHCl_3$); ν_{max} 3451 (br, OH) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.09 (1H, br s, OH-2), 3.37 (1H, br s, OH-6), 3.38 (3H, s, OCH_3), 3.48 (1H, dd, $J_{5,6}$ 8.1 Hz, $J_{6,6'}$ 9.9 Hz, H-6_b), 3.52-3.57 (2H, m, H-2_a, H-5_a), 3.57 (1H, dd, $J_{3,4}$ 8.7 Hz, $J_{4,5}$ 9.5 Hz, H-4_b), 3.65-3.70 (2H, m, H-6_a, H-$6'_b$), 3.75 (1H, dd, $J_{2,3}$ 3.2 Hz, H-3_b), 3.77-3.78 (1H, m, H-2_b), 3.80-3.85 (1H, m, H-5_b), 3.87-3.92 (3H, m, H-3_a, H-4_a, H-$6'_a$), 4.45, 4.78 (2H, ABq, J_{AB} 11.0 Hz,

PhC$\underline{H}_2$), 4.54 (2H, s, PhC$\underline{H}_2$), 4.58 (1H, d, $J_{1,2}$ 3.7 Hz, H-1_a), 4.59, 4.63 (2H, ABq, J_{AB} 11.7 Hz, PhC$\underline{H}_2$), 4.63, 4.75 (2H, ABq, J_{AB} 12.2 Hz, PhC$\underline{H}_2$), 4.63, 5.01 (2H, ABq, J_{AB} 11.0 Hz, PhC$\underline{H}_2$), 5.37 (1H, d, $J_{1,2}$ 1.5 Hz, H-1_b), 7.14-7.38 (25H, m, Ar-H); δ_C (125.7 MHz, $CDCl_3$) 55.1 (q, OCH_3), 60.2 (t, C-6_a), 68.6 (d, C-2_b), 69.1 (t, C-6_b), 70.4 (d, C-5_a), 72.0, 73.2, 73.4, 74.9, 75.5 (5 x t, 5 x Ph$\underline{C}H_2$), 72.2 (d, C-5_b), 74.3 (d, C-4_b), 74.8 (d, C-4_a), 79.8, 79.9 (2 x d, C-2_a, C-3_b), 81.9 (d, C-3_a), 97.9 (d, $^1J_{C\text{-}1,H\text{-}1}$ 166.4 Hz, C-1_a), 101.1 (d, $^1J_{C\text{-}1,H\text{-}1}$ 172.5 Hz, C-1_b), 127.5, 127.7, 127.7, 127.8, 127.9, 128.0, 128.0, 128.1, 128.3, 128.3, 128.4 (11 x d, Ar-CH), 137.2, 137.7, 137.7, 137.8, 138.4 (5 x s, Ar-C); *m/z* (ES^+) 829 ($M+Na^+$, 70), 824 ($M+NH_4^+$, 100%). (HRMS Calcd. for $C_{48}H_{58}NO_{11}$ (MNH_4^+) 824.4010. Found 824.4016).

Methyl 3,4,6-tri-O-benzyl-β-D-mannopyranosyl-(1→6)-2,3-di-O-benzyl-α-D-glucopyranoside 115

Methyl 4,2′-*O*-(propylidene)-3′,4′,6′-tri-*O*-benzyl-β-D-mannopyranosyl-(1′→6)-2,3-di-*O*-benzyl-α-D-glucopyranoside **112s** (49 mg, 0.058 mmol) was dissolved in THF/TFA/methanol/water (2:5:1:2, 2.5 ml) and stirred at RT. After 45 min, tlc (petrol:ethyl acetate, 1:2) indicated formation of a product (R_f 0.7) and little remaining starting material (R_f 0.8). The reaction mixture was quenched with $NaHCO_3$ (30 ml of a saturated aqueous solution) and extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:3) to afford methyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranosyl-(1→6)-2,3-di-*O*-benzyl-α-D-glucopyranoside **115** (36 mg, 75%) as a colourless oil; $[\alpha]_D^{24}$ -3.2 (*c*, 0.25 in $CHCl_3$); δ_H (500 MHz,

$CDCl_3$)[14] 2.43 (2H, br s, 2 x OH), 3.37 (3H, s, OCH_3), 3.41-3.52 (3H, m, H-2_a, H-4_a, H-5_b), 3.54 (1H, dd, $J_{2,3}$ 3.0 Hz, $J_{3,4}$ 8.9 Hz, H-3_b), 3.68-3.77 (4H, m, H-5_a, H-6_a, H-6_b, H-$6'_b$), 3.79 (1H, at, J 9.1 Hz, H-3_a), 3.87 (1H, at, J 9.3 Hz, H-4_b), 4.11 (1H, d, H-2_b), 4.13-4.16 (1H, m, H-$6'_a$), 4.48 (1H, s, H-1_b), 4.53, 4.89 (2H, ABq, J_{AB} 10.8 Hz, PhC$\underline{H}_2$), 4.55, 4.61 (2H, ABq, J_{AB} 12.2 Hz, PhC$\underline{H}_2$), 4.60 (1H, d, $J_{1,2}$ 3.6 Hz, H-1_a), 4.66, 4.77 (2H, ABq, J_{AB} 11.9 Hz, PhC$\underline{H}_2$), 4.67, 4.78 (2H, ABq, J_{AB} 12.2 Hz, PhC$\underline{H}_2$), 4.74, 5.02 (2H, ABq, J_{AB} 11.4 Hz, PhC$\underline{H}_2$), 7.20-7.40 (25H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 55.2 (q, OCH_3), 68.1 (d, C-2_b), 68.7 (t, C-6_a), 69.1 (t, C-6_b), 70.0 (d, C-5_a), 70.6 (d, C-4_a), 71.3, 73.1, 73.4, 75.2, 75.1 (5 x t, 5 x Ph$\underline{C}H_2$), 74.1 (d, C-4_b), 75.1 (d, C-5_b), 79.5 (d, C-2_a), 81.3, 81.3 (2 x d, C-3_a, C-3_b), 98.0 (d, $^1J_{C\text{-}1,H\text{-}1}$ 168.9 Hz, C-1_a), 100.0 (d, $^1J_{C\text{-}1,H\text{-}1}$ 157.5 Hz, C-1_b), 127.5, 127.7, 127.8, 127.8, 127.9, 128.0, 128.0, 128.1, 128.3, 128.3, 128.4, 128.5, 128.6 (13 x d, Ar-CH), 137.8, 137.9, 138.1, 138.7 (4 x s, Ar-C).

7.5 Experimental for Chapter 5

para-*Tolyl* 2,4,6-*tri*-O-*acetyl*-3-O-*allyl*-1-*thio*-β-D-*glucopyranoside* 133β *and* para-*tolyl* 2,4,6-*tri*-O-*acetyl*-3-O-*allyl*-1-*thio*-α-D-*glucopyranoside* 133α

1,2,4,6-Tetra-*O*-acetyl-3-*O*-allyl-β-D-glucopyranoside **134** (2.00 g, 5.15 mmol) was suspended in freshly distilled DCM (10 ml) under Ar in a flame-dried flask. *para*-Thiocresol (766 mg, 6.18 mmol) was added and the mixture cooled to 0°C. $BF_3.OEt_2$ (0.95 ml, 7.73 mmol) was added and the reaction mixture was stirred under Ar. After 30 min, tlc (petrol:ethyl acetate, 3:2) indicated formation of a major product (R_f 0.3) and a minor product (R_f 0.35) and little remaining starting material (R_f 0.2). After a further 50 min, Et_3N (2 ml) was added, and the mixture was diluted with ether (100 ml) and washed with water (100 ml). The aqueous wash was extracted with ether (50 ml) and the combined organic extracts were washed with brine (50 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 3:2) to afford *para*-tolyl 2,4,6-tri-*O*-acetyl-3-*O*-allyl-1-thio-α-D-glucopyranoside **133α** (50 mg, 2%) as a colourless oil; $[\alpha]_D^{21}$ +163.3 (c, 1.75 in $CHCl_3$); ν_{max} 1748 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.03, 2.11, 2.16, 2.32 (12H, 4 x s, 3 x $COCH_3$, $ArCH_3$), 3.80 (1H, at, *J* 9.6 Hz, H-3), 4.04 (1H, dd, $J_{5,6}$ 2.2 Hz, $J_{6,6'}$ 12.3 Hz, H-6), 4.11 (1H, dd, J_{gem} 13.1 Hz, J_{vic} 5.7 Hz, OC<u>H</u>H'CH=CH_2), 4.20-4.26 (2H, m, H-6', OCH<u>H</u>'CH=CH_2), 4.48 (1H, ddd, $J_{4,5}$ 10.1 Hz, $J_{5,6'}$ 5.6 Hz, H-5), 5.02 (1H, dd, $J_{1,2}$ 5.7 Hz, $J_{2,3}$ 10.0 Hz, H-2), 5.04 (1H, at, *J* 9.8 Hz, H-4), 5.17 (1H, d, J_Z 10.4 Hz,

CH=CH$_E$H$_Z$), 5.25 (1H, d, J_E 17.2 Hz, CH=CH$_E$H$_Z$), 5.78-5.88 (1H, m, CH=CH$_2$), 5.82 (1H, d, H-1), 7.11, 7.33 (4H, 2 x d, *J* 8.0 Hz, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 20.7, 20.8, 20.9, 21.0 (4 x q, 3 x COCH$_3$, ArCH$_3$), 62.2, 73.8 (2 x t, C-6, CH$_2$CH=CH$_2$), 68.4, 69.7, 73.1, 77.3 (4 x d, C-2, C-3, C-4, C-5), 85.6 (d, C-1), 116.9 (t, CH=CH$_2$), 129.8, 132.4, 134.3 (3 x d, Ar-CH, CH=CH$_2$), 128.8, 138.0 (2 x s, Ar-C), 169.4, 169.8, 170.7 (3 x s, 3 x C=O); *m/z* (ES+) 475 (M+Na$^+$, 43), 470 (M+NH$_4^+$, 64%). (HRMS Calcd. for $C_{22}H_{32}NO_8S$ (MNH$_4^+$) 470.1849. Found 470.1854);

and also *para*-tolyl 2,4,6-tri-*O*-acetyl-3-*O*-allyl-1-thio-β-D-glucopyranoside **133β** (1.81 g, 78%) as a white solid, m.p. 127-128 °C (ether/petrol); $[\alpha]_D^{21}$ -14.4 (c, 0.9 in $CHCl_3$); ν_{max} 1744 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.08, 2.08, 2.15 (9H, 3 x s, 3 x COCH$_3$), 2.34 (3H, s, ArCH$_3$), 3.57-3.63 (1H, m, H-5), 3.59 (1H, at, *J* 9.2 Hz, H-3), 4.02-4.11 (2H, m, OCH$_2$CH=CH$_2$), 4.13-4.20 (2H, m, H-6, H-6'), 4.56 (1H, d, $J_{1,2}$ 10.1 Hz, H-1), 4.96 (1H, at, *J* 9.5 Hz, H-2), 5.00 (1H, at, *J* 9.8 Hz, H-4), 5.13 (1H, d, J_Z 10.4 Hz, CH=CH$_E$H$_Z$), 5.19 (1H, dd, J_{gem} 1.6 Hz, J_E 17.2 Hz, CH=CH$_E$H$_Z$), 5.75 (1H, ddat, *J* 5.5 Hz, CH=CH$_2$), 7.11, 7.40 (4H, 2 x d, *J* 8.1 Hz, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 21.2, 21.3, 21.5, 21.6 (4 x q, 3 x COCH$_3$, ArCH$_3$), 63.0, 73.5 (2 x t, C-6, CH$_2$CH=CH$_2$), 69.9, 71.7, 76.4, 81.7 (4 x d, C-2, C-3, C-4, C-5), 86.8 (d, C-1), 117.5 (t, CH=CH$_2$), 129.0, 138.8 (2 x s, Ar-C) 130.0, 133.7 (2 x d, Ar-CH), 134.6 (d, CH=CH$_2$), 169.6, 169.7, 171.2 (3 x s, 3 x C=O); *m/z* (ES$^+$) 475 (M+Na$^+$, 100), 470 (M+NH$_4^+$, 77%). (HRMS Calcd. for $C_{22}H_{32}NO_8S$ (MNH$_4^+$) 470.1849. Found 470.1850). (Found: C, 58.50; H, 6.27. $C_{22}H_{28}O_8S$ requires C, 58.39; H, 6.24%).

para-*Tolyl* 3-O-*allyl*-2,4,6-*tri*-O-*benzyl*-1-*thio*-β-D-*glucopyranoside* 132

para-Tolyl 2,4,6-tri-*O*-acetyl-3-*O*-allyl-1-thio-β-D-glucopyranoside **133β** (1.77 g, 3.92 mmol) was suspended in methanol (10 ml). Sodium (5 mg, 0.20 mmol) was dissolved in methanol (5 ml) and added to the sugar solution by pipette. The reaction mixture was stirred under Ar. After 2 h 10 min, tlc (ethyl acetate) indicated formation of a product (R_f 0.6) and complete consumption of starting material (R_f 0.7). The mixture was concentrated *in vacuo*.

The residue was dissolved in DMF (30 ml) and cooled to 0°C. Benzyl bromide (2.09 ml, 17.6 mmol) and sodium hydride (940 mg, 23.5 mmol) were added and the reaction mixture was stirred under Ar. After 1 h 40 min, tlc (petrol:ethyl acetate, 5:1) indicated formation of two products (R_f 0.5 and R_f 0.7) and complete consumption of starting material (R_f 0). Further benzyl bromide (0.35 ml, 2.94 mmol) and sodium hydride (156 mg, 3.91 mmol) were added and the reaction mixture was stirred under Ar. After a further 13 h 30 min, tlc (petrol:ethyl acetate, 5:1) indicated formation of a single product (R_f 0.7). Methanol (8 ml) was added and the mixture was diluted with ether (200 ml) and washed with water (200 ml). The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ether, 4:1) to afford *para*-tolyl 3-*O*-allyl-2,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **132** (2.08 g, 89%) as a white, crystalline solid, m.p. 75 °C (EtOH); $[\alpha]_D^{21}$ –6.5 (*c*, 1.0 in $CHCl_3$); ν_{max} 1646 (w, C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.32 (3H, s, $ArCH_3$), 3.41-3.51 (2H, m, H-2, H-5), 3.53-3.61 (2H, m, H-3, H-4), 3.73 (1H, dd, $J_{5,6}$ 4.8 Hz, $J_{6,6'}$ 10.9 Hz, H-6),

3.79 (1H, dd, $J_{5,6'}$ 2.1 Hz, H-6'), 4.33 (1H, ddat, J_{gem} 12.3 Hz, J_{vic} 5.7 Hz, J 1.4 Hz, OC$\underline{H}$H'CH=CH_2), 4.38 (1H, ddat, J_{vic} 5.7 Hz, J 1.5 Hz, OC$\underline{H}$H'CH=CH_2), 4.55, 4.62 (2H, ABq, J_{AB} 12.1 Hz, PhC$\underline{H}_2$), 4.58 (1H, d, $J_{1,2}$ 9.7 Hz, H-1), 4.59, 4.83 (2H, ABq, J_{AB} 11.1 Hz, PhC$\underline{H}_2$), 4.74, 4.88 (2H, ABq, J_{AB} 10.1 Hz, PhC$\underline{H}_2$), 5.18 (1H, daq, J_Z 10.4 Hz, J 1.4 Hz, CH=$CH_E\underline{H}_Z$), 5.30 (1H, daq, J 1.7 Hz, J_E 17.1 Hz, CH=C$\underline{H}_E H_Z$), 5.98 (1H, ddat, C$\underline{H}$=CH_2), 7.04-7.52 (19H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 21.1 (q, Ar$\underline{C}H_3$), 69.0, 73.4, 74.5, 75.1, 75.5 (5 x t, C-6, $\underline{C}H_2$CH=CH_2, 3 x Ph$\underline{C}H_2$), 77.7, 79.0, 80.7, 86.4, 87.6 (5 x d, C-1, C-2, C-3, C-4, C-5), 116.9 (t, CH=$\underline{C}H_2$), 127.5, 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 129.6, 132.7, 134.9 (11 x d, Ar-CH, $\underline{C}$H=CH_2), 137.7, 138.1, 138.1, 138.4 (4 x s, Ar-C); *m/z* (ES^+) 619 ($M+Na^+$, 32), 614 ($M+NH_4^+$, 100%). (HRMS Calcd. for $C_{37}H_{44}NO_5S$ (MNH_4^+) 614.2940. Found 614.2935). (Found: C, 74.45; H, 6.79. $C_{37}H_{40}O_5S$ requires C, 74.47; H, 6.76%).

Methyl 3-O-allyl-2,4,6-tri-O-benzyl-α-D-glucopyranosyl-(1→3)-2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside 122

Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **3g** (62 mg, 0.168 mmol), *para*-tolyl 3-*O*-allyl-2,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **132** (100 mg, 0.168 mmol) and 4Å molecular sieves were added to freshly distilled ether (2 ml). Methyl trifluoromethanesulfonate (0.095 ml, 0.84 mmol) was added and the mixture stirred at RT under Ar. After 1 h 10 min, tlc (petrol:ethyl acetate, 3:1) indicated the formation of a major product (R_f 0.4) and little remaining starting materials (R_f 0.7 and R_f 0.3). The reaction mixture was partitioned between ether (100 + 50 ml) and

water (100 ml). The organic layer was washed with brine (30 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford methyl 3-*O*-allyl-2,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **122** (76 mg, 50%) as a colourless oil; $[\alpha]_D^{21}$ +93.0 (*c*, 1.0 in $CHCl_3$); ν_{max} 1648 (w, C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.33 (3H, s, OCH_3), 3.46 (1H, dd, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 9.6 Hz, H-2_b), 3.54 (1H, at, *J* 9.4 Hz, H-4_b), 3.64-3.71 (2H, m, H-6_b, H-$6'_b$), 3.78-4.15 (5H, m, H-2_a, H-5_a, H-6_a, H-3_b, H-5_b), 4.18-4.26 (2H, m, H-$6'_a$, OC<u>H</u>H'CH=CH_2), 4.31, 4.54 (2H, ABq, J_{AB} 12.5 Hz, $PhCH_2$), 4.31-4.35 (1H, m, H-4_a), 4.39 (1H, dd, $J_{2,3}$ 2.9 Hz, $J_{3,4}$ 10.0 Hz, H-3_a), 4.42-4.49 (1H, m, OCH<u>H</u>'CH=CH_2), 4.45, 4.58 (2H, ABq, J_{AB} 12.2 Hz, PhC<u>H</u>$_2$), 4.47, 4.88 (2H, ABq, J_{AB} 11.0 Hz, PhC<u>H</u>$_2$), 4.71 (1H, d, $J_{1,2}$ 1.3 Hz, H-1_a), 4.78, 4.93 (2H, ABq, J_{AB} 11.9 Hz, PhC<u>H</u>$_2$), 5.09 (1H, dd, J_Z 10.4 Hz, J_{gem} 1.0 Hz, CH=CH$_E$<u>H</u>$_Z$), 5.22 (1H, dd, J_{gem} 1.6 Hz, J_E 17.2 Hz, CH=C<u>H</u>$_E$H$_Z$), 5.47 (1H, s, PhC<u>H</u>) 5.50 (1H, d, H-1_b), 5.96 (1H, ddat, *J* 5.5 Hz, C<u>H</u>=CH_2), 7.00-7.47 (25H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 54.8 (q, OCH_3), 63.9 (d, C-5_a), 68.6 (t, C-6_b), 68.9 (t, C-6_a), 70.5 (t, Ph<u>C</u>H_2), 70.8 (d, C-5_b), 72.7 (d, C-3_a), 73.4, 73.8, 74.3, 75.0 (4 x t, O<u>C</u>H_2CH=CH_2, 3 x Ph<u>C</u>H_2), 77.2, 77.3 (2 x d, C-2_a, C-4_b), 78.6 (d, C-2_b), 79.6 (d, C-4_a), 81.0 (d, C-3_b), 96.9 (d, C-1_b), 100.6 (d, C-1_a), 102.3 (d, Ph<u>C</u>H), 116.6 (t, CH=<u>C</u>H_2), 126.4, 127.0, 127.1, 127.6, 127.6, 127.8, 127.8, 127.9, 128.1, 128.2, 128.2, 128.3, 128.4, 129.2 (14 x d, Ar-CH), 135.4 (d, <u>C</u>H=CH_2), 137.4, 138.0, 138.0, 138.3, 138.5 (5 x s, Ar-C); *m/z* (ES^+) 867 ($M+Na^+$, 27), 862 ($M+NH_4^+$, 100%). (HRMS Calcd. for $C_{51}H_{60}NO_{11}$ (MNH_4^+) 862.4166. Found 862.4160).

Methyl 2,4,6-tri-O-benzyl-3-O-prop-1′-enyl-α-D-glucopyranosyl-(1→3)-2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside 135

Wilkinson's catalyst (86 mg, 0.093 mmol) was dissolved in distilled THF (4 ml) and degassed. Butyl lithium (1.6 M solution in hexanes) (0.09 ml, 0.14 mmol) was added and the mixture stirred for 10 min under Ar. Methyl 3-*O*-allyl-2,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **122** (786 mg, 0.93 mmol) was dissolved in distilled THF (4 ml) and heated to 70 °C. The catalyst solution was added by cannula under Ar. After 2 h 30 min, tlc (petrol:ethyl acetate, 4:1) indicated the presence of a single compound (R_f 0.3) and starting material (R_f 0.3). The reaction was allowed to cool then diluted with CH_2Cl_2 (20 ml) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford methyl 2,4,6-tri-*O*-benzyl-3-*O*-prop-1′-enyl-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **135** (745 mg, 95%) as a pale yellow oil; Partial data: δ_H (400 MHz, $CDCl_3$) (*E*:*Z*, 1:2.6), *E* isomer 1.51 (3H, dd, *J* 1.6 Hz, *J* 6.8 Hz, OCH=CHC$\underline{H}_3$); *Z* isomer 1.64 (3H, dd, *J* 1.6 Hz, *J* 6.8 Hz, OCH=CHC$\underline{H}_3$); *m/z* (ES^+) 867 ($M+Na^+$, 21), 862 ($M+NH_4^+$, 100%). (HRMS Calcd. for $C_{51}H_{60}NO_{11}$ (MNH_4^+) 862.4166. Found 862.4161).

Methyl 2,4,6-tri-O-benzyl-3-O-(2-iodo-1-(3,4,6-tri-O-benzyl-1-deoxy-1-fluoro-β-D-glucopyranos-2-O-yl)propyl)-α-D-glucopyranosyl-(1→3)-2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside 131

Method 1: *N*-Iodosuccinimide-mediated tethering

N-Iodosuccinimide (184 mg, 0.82 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (1 ml) and cooled to -40 °C under Ar. 3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl fluoride **65** (370 mg, 0.82 mmol) was dissolved in anhydrous dichloroethane (2 ml) and added to the reaction vessel by cannula under Ar. Methyl 2,4,6-tri-*O*-benzyl-3-*O*-prop-1′-enyl-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **135** (230 mg, 0.27 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to RT. After 15 h, tlc (petrol:ethyl acetate, 4:1) indicated the complete consumption of enol ether starting material (R_f 0.3) and the formation of two products (R_f 0.2 and R_f 0.25), plus some remaining starting alcohol **34** (R_f 0.2). The reaction was quenched with Et_3N (1 ml). Sodium thiosulfate (50 ml of a 10% aqueous solution) was added, and the mixture was extracted with CH_2Cl_2 (2 x 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1 and in 50:1→20:1 CH_2Cl_2:ether) to afford methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2-iodo-1-(3,4,6-tri-*O*-benzyl-1-deoxy-1-fluoro-β-D-glucopyranos-2-*O*-yl)propyl)-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **131** (80 mg, 21%) as a colourless oil; *m/z* (ES^+) 1461 ($M+K^+$, 37), 1445 ($M+Na^+$, 100), 1440 ($M+NH_4^+$, 31%). (HRMS Calcd. for $C_{78}H_{88}NO_{16}IF$ (MNH_4^+) 1440.5132. Found 1440.5140).

Also methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2-iodo-1-succinimidopropyl)-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside

136, a mixture of three diastereomers (190 mg, 65%) as a colourless oil; *m/z* (ES^+) 1108 ($M+K^+$, 66), 1092 ($M+Na^+$, 100), 1087 ($M+NH_4^+$, 14%). (HRMS Calcd. for $C_{33}H_{64}N_2O_{13}I$ (MNH_4^+) 1087.3453. Found 1087.3458).

Method 2: Tethering using I_2, AgOTf and DTBMP

Iodine (63 mg, 0.25 mmol), silver trifluoromethanesulfonate (64 mg, 0.25 mmol), 2,6-di-*tert*-butyl-4-methyl pyridine (102 mg, 0.50 mmol) and 4Å molecular sieves were added to freshly distilled CH_2Cl_2 (1 ml) and cooled to -78 °C under Ar. 3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl fluoride **65** (108 mg, 0.24 mmol) was dissolved in freshly distilled CH_2Cl_2 (2 ml) and added to the reaction vessel by cannula under Ar. Methyl 2,4,6-tri-*O*-benzyl-3-*O*-prop-1′-enyl-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **135** (191 mg, 0.23 mmol) was dissolved in freshly distilled CH_2Cl_2 (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to RT. After 14 h, tlc (CH_2Cl_2:ether, 40:1) indicated the presence of three compounds (R_f 0.1, R_f 0.15 and R_f 0.25). Starting materials (R_f 0.1, R_f 0.25). Sodium thiosulfate (50 ml of a 10% aqueous solution) was added then extracted with CH_2Cl_2 (2 x 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Crude ^1H NMR revealed the presence of much enol ether and alcohol starting materials remaining.

Iodine (63 mg, 0.25 mmol), silver trifluoromethanesulfonate (64 mg, 0.25 mmol), 2,6-di-*tert*-butyl-4-methyl pyridine (102 mg, 0.50 mmol) and 4Å molecular sieves were added to freshly distilled CH_2Cl_2 (1 ml) and cooled to -

78 °C under Ar. The crude residue was dissolved in freshly distilled CH_2Cl_2 (3 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to RT. After 16 h 30 min, tlc (CH_2Cl_2:ether, 40:1) indicated the presence of three compounds (R_f 0.1, R_f 0.15 and R_f 0.25). Starting materials (R_f 0.1, R_f 0.25). Sodium thiosulfate (50 ml of a 10% aqueous solution) was added then extracted with CH_2Cl_2 (2 x 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2:ether, 40:1) to afford methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2-iodo-1-(3,4,6-tri-*O*-benzyl-1-deoxy-1-fluoro-β-D-glucopyranos-2-*O*-yl)propyl)-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **131** (250 mg, 78%) as a colourless oil identical to that described above.

Methyl 3,4,6-tri-O-benzyl-α-D-glucopyranosyl-(1→3)-2,4,6-tri-O-benzyl-α-D-glucopyranosyl-(1→3)-2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside 126

4Å Molecular sieves were suspended in anhydrous dichloroethane (5 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (72 mg, 0.35 mmol), silver trifluoromethanesulfonate (90 mg, 0.35 mmol) and anhydrous tin (II) chloride (67 mg, 0.35 mmol) were added. Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(2-iodo-1-(3,4,6-tri-*O*-benzyl-1-deoxy-1-fluoro-β-D-glucopyranos-2-*O*-yl)propyl)-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **131** (250 mg, 0.18 mmol) was dissolved in anhydrous dichloroethane (10 ml) and added by cannula under Ar and the

reaction mixture stirred at 65 °C. After 16 h 20 min, tlc (CH_2Cl_2:ether, 40:1) indicated the absence of any starting material (R_f 0.2) and the formation of a major product (R_f 0.1). The reaction mixture was allowed to cool to RT, then $NaHCO_3$ (10 ml of a saturated aqueous solution) was added and the mixture stirred for a further 10 min. The mixture was diluted with ethyl acetate (150 ml), filtered through Celite and washed with brine (50 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2:ether, 40:1) to afford methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **126** (81 mg, 37%) as a colourless oil; $[\alpha]_D^{22}$ +73.1 (*c*, 1.1 in $CHCl_3$); ν_{max} 3374 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.36 (1H, br s, OH-2_c), 3.19 (2H, br s, H-6, H-6′), 3.36 (3H, s, OCH_3), 3.42 (1H, dd, $J_{1,2}$ 3.7 Hz, $J_{2,3}$ 9.8 Hz, H-2_b), 3.65-3.79 (8H, m), 3.82-3.89 (2H, m), 4.13 (1H, d, *J* 12.3 Hz, PhC<u>H</u>H′), 4.16, 4.47 (2H, ABq, J_{AB} 11.1 Hz, PhC<u>H</u>$_2$), 4.21-4.25 (3H, m, H-3_b, H-5, H-6), 4.34-4.44 (5H, m), 4.48, 4.67 (2H, ABq, J_{AB} 11.8 Hz, PhC<u>H</u>$_2$), 4.72 (1H, d, *J* 11.0 Hz, PhC<u>H</u>H′), 4.75 (1H, br s, H-1_a), 4.82, 4.95 (2H, ABq, J_{AB} 12.0 Hz, PhC<u>H</u>$_2$), 4.83 (2H, s, PhC<u>H</u>$_2$), 4.91 (1H, d, *J* 10.4 Hz, PhC<u>H</u>H′), 5.36 (1H, s, PhC<u>H</u>), 5.51 (1H, d, $J_{1,2}$ 2.9 Hz, H-1_c), 5.62 (1H, d, H-1_b), 7.07-7.44 (40H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 54.8 (q, OCH_3), 63.8, 70.1, 70.5, 72.1, 72.8, 76.1, 76.5, 76.8, 77.4, 78.6, 79.9, 83.3 (12 x d, C-2_a, C-3_a, C-4_a, C-5_a, C-2_b, C-3_b, C-4_b, C-5_b, C-2_c, C-3_c, C-4_c, C-5_c), 67.9, 68.3, 68.9 (3 x t, C-6_a, C-6_b, C-6_c), 70.3, 73.2, 73.6, 74.2, 74.3, 75.2 (6 x t, 7 x Ph<u>C</u>H$_2$), 96.1 (d, C-1_b), 98.6 (d, C-1_c), 100.7 (d, C-1_a), 102.4 (d, Ph<u>C</u>H), 126.3, 127.3, 127.4, 127.4, 127.5, 127.7, 127.7, 127.8, 127.8, 127.8, 128.0, 128.1, 128.1, 128.1, 128.2,

128.3, 128.3, 128.4, 128.5, 129.2 (20 x d, Ar-CH), 137.2, 137.6, 137.8, 137.9, 137.9, 138.0, 138.7, 138.8 (8 x s, Ar-C); *m/z* (ES^+) 1275 ($M+K^+$, 11), 1259 ($M+Na^+$, 100), 1254 ($M+NH_4^+$, 64%). (HRMS Calcd. for $C_{75}H_{84}NO_{16}$ (MNH_4^+) 1254.5790. Found 1254.5782);

And methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **124** (52 mg, 37%) as a colourless oil; $[\alpha]_D^{25}$ +92.4 (*c*, 1.5 in $CHCl_3$); ν_{max} 3385 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.56 (1H, br s, OH-3_b), 3.33-3.36 (1H, m, H-2_b), 3.34 (3H, s, OCH_3), 3.56 (1H, at, *J* 9.4 Hz, H-4_b), 3.67-3.74 (2H, m, H-6_b, H-$6'_b$), 3.79-3.89 (4H, m, H-2_a, H-5_a, H-6_a, H-5_b), 4.14 (1H, at, *J* 9.3 Hz, H-3_b), 4.20, 4.55 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.20-4.24 (1H, m, H-$6'_a$), 4.32 (1H, at, *J* 9.0 Hz, H-4_a), 4.39 (1H, dd, $J_{2,3}$ 2.9 Hz, $J_{3,4}$ 10.1 Hz, H-3_a), 4.47, 4.60 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.51, 4.91 (2H, ABq, J_{AB} 11.3 Hz, PhC$\underline{H}_2$), 4.71 (1H, s, H-1_a), 4.76, 4.93 (2H, ABq, J_{AB} 11.9 Hz, PhC$\underline{H}_2$), 5.42 (1H, s, PhC$\underline{H}$) 5.53 (1H, d, $J_{1,2}$ 3.3 Hz, H-1_b), 6.99-7.44 (25H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 54.8 (q, OCH_3), 63.9 (d, C-5_a), 68.6, 68.9 (2 x t, C-6_a, C-6_b), 70.2, 73.4, 73.7, 74.5 (4 x t, 4 x Ph$\underline{C}H_2$), 70.4 (d, C-5_b), 72.9 (d, C-3_a), 73.3 (d, C-3_b), 77.1, 77.2, 77.8 (3 x d, C-2_a, C-2_b, C-4_b), 79.6 (d, C-4_a), 96.4 (d, C-1_b), 100.6 (d, C-1_a), 102.4 (d, Ph$\underline{C}$H), 126.4, 127.3, 127.5, 127.6, 127.7, 127.9, 128.1, 128.2, 128.3, 128.4, 129.2 (11 x d, Ar-CH), 137.3, 137.8, 137.9, 138.0, 138.6 (5 x s, Ar-C); *m/z* (ES^+) 863 ($M+NH_4^+$+MeCN, 18), 827 ($M+Na^+$, 37), 822 ($M+NH_4^+$, 100%). (HRMS Calcd. for $C_{48}H_{56}NO_{11}$ (MNH_4^+) 822.3853. Found 822.3838).

Methyl 3,4,6-tri-O-benzyl-2-O-(2-iodo-1-(3,4,6-tri-O-benzyl-1-deoxy-1-fluoro-β-D-glucopyranos-2-O-yl)propyl)-α-D-glucopyranosyl-(1→3)-2,4,6-

***tri*-O-*benzyl*-α-*D*-*glucopyranosyl*-(1→3)-2-O-*benzyl*-4,6-O-*benzylidene*-α-*D*-*mannopyranoside* 130**

Iodine (16 mg, 0.061 mmol), silver trifluoromethanesulfonate (16 mg, 0.061 mmol), 2,6-di-*tert*-butyl-4-methyl pyridine (26 mg, 0.13 mmol) and 4Å molecular sieves were added to freshly distilled CH_2Cl_2 (1 ml) and cooled to -78 °C under Ar. 3,4,6-Tri-*O*-benzyl-2-*O*-prop-1'-enyl–β-D-glucopyranosyl fluoride **80** (30 mg, 0.060 mmol) was dissolved in freshly distilled CH_2Cl_2 (1.5 ml) and added to the reaction vessel by cannula under Ar. Methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **126** (71 mg, 0.057 mmol) was dissolved in freshly distilled CH_2Cl_2 (1.5 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to RT. After 15 h, tlc (CH_2Cl_2:ether, 40:1) indicated the formation of two products (R_f 0.3, R_f 0.35) and the complete consumption of starting enol ethers (R_f 0.8). Sodium thiosulfate (50 ml of a 10% aqueous solution) was added then extracted with CH_2Cl_2 (2 x 40 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2:ether, 40:1) to afford methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(3,4,6-tri-*O*-benzyl-1-deoxy-1-fluoro-β-D-glucopyranos-2-*O*-yl)propyl)-α-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **130** (83 mg, 78%) as a colourless oil; *m/z* (ES^+) 1878 ($M+Na^+$, 100%).

Methyl 3,4,6-tri-O-benzyl-α-D-glucopyranosyl-(1→2)-3,4,6-tri-O-benzyl-α-D-glucopyranosyl-(1→3)-2,4,6-tri-O-benzyl-α-D-glucopyranosyl-(1→3)-2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside 129

4Å Molecular sieves were suspended in anhydrous dichloroethane (1 ml) in a flame-dried flask under Ar. 2,6-Di-*tert*-butyl-4-methylpyridine (18 mg, 0.086 mmol), silver trifluoromethanesulfonate (22 mg, 0.086 mmol) and anhydrous tin (II) chloride (16 mg, 0.086 mmol) were added. Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(3,4,6-tri-*O*-benzyl-1-deoxy-1-fluoro-β-D-glucopyranos-2-*O*-yl)propyl)-α-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **130** (80 mg, 0.043 mmol) was dissolved in anhydrous dichloroethane (4 ml) and added by cannula under Ar. The reaction mixture was stirred at 60 °C. After 4 h 15 min, tlc (CH_2Cl_2:ether, 40:1) indicated the absence of any starting material (R_f 0.3, 0.35) and the formation of three products (R_f 0.1, 0.35, 0.4). The reaction mixture was allowed to cool to RT, then $NaHCO_3$ (4 ml of a saturated aqueous solution) was added and the mixture stirred for a further 20 min. The mixture was diluted with ethyl acetate (100 ml), filtered through Celite and washed with brine (50 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue purified by flash column chromatography (CH_2Cl_2:ether, 40:1) to afford methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **129** (7 mg, 10%) as a colourless oil; $[\alpha]_D^{25}$ +94.4 (*c*, 0.25 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 3.15-

3.16 (1H, br m, H-2_d), 3.26 (1H, dd, $J_{5,6}$ 1.6 Hz, $J_{6,6'}$ 11.6 Hz, H-6_d), 3.30 (1H, dd, $J_{5,6}$ 3.1 Hz, H-$6'_d$), 3.34 (3H, s, OCH_3), 3.35 (1H, at, *J* 9.6 Hz, H-3_d), 3.43 (1H, at, *J* 9.5 Hz, H-4_d), 3.48 (1H, dd, $J_{1,2}$ 3.7 Hz, $J_{2,3}$ 9.5 Hz, H-2_x), 3.52 (1H, d, $J_{6,6'}$ 10.0 Hz, H-6_y), 3.65-3.76 (6H, m, H-4_x, H-6_x, H-$6'_x$, H-2_y, H-4_y, H-$6'_y$), 3.82-3.87 (4H, m, H-2_a, H-5_a, H-6_a, H-5_d), 3.91 (1H, dat, *J* 9.9 Hz, H-5_x), 3.96 (1H, at, *J* 9.4 Hz, H-3_y), 4.18-4.24 (4H, m, H-$6'_a$, H-5_y, 2 x PhC<u>H</u>H'), 4.30-4.58 (15H, m, H-3_a, H-4_a, H-3_x, H-1_d, 11 x PhC<u>H</u>H'), 4.68 (1H, d, *J* 11.2 Hz, PhC<u>H</u>H'), 4.70 (1H, d, $J_{1,2}$ 1.3 Hz, H-1_a), 4.70 (1H, d, *J* 10.6 Hz, PhC<u>H</u>H'), 4.73 (1H, d, *J* 11.3 Hz, PhC<u>H</u>H'), 4.82 (1H, d, *J* 10.8 Hz, PhC<u>H</u>H'), 4.85 (1H, d, *J* 10.5 Hz, PhC<u>H</u>H'), 5.02 (1H, d, *J* 11.4 Hz, PhC<u>H</u>H'), 5.07 (1H, d, *J* 11.8 Hz, PhC<u>H</u>H'), 5.38 (1H, s, PhC<u>H</u>), 5.46 (1H, d, $J_{1,2}$ 3.2 Hz, H-1_y), 5.66 (1H, d, H-1_x), 6.99-7.53 (55H, m, Ar-H); δ_C (125.7 MHz, $CDCl_3$) 54.7 (q, OCH_3), 63.6 (d, C-5_a), 68.0, 68.3, 68.5, 68.7 (4 x t, C-6_a, C-6_x, C-6_y, C-6_d), 69.8, 70.0 (2 x d, C-5_x, C-5_d), 71.0, 73.0, 73.4, 73.4, 74.4, 74.6, 74.8, 74.8, 75.8 (9 x t, 9 x Ph<u>C</u>H_2), 71.0 (d, C-5_y), 71.9 (d, C-3_a), 75.5 (d, C-2_y), 76.8 (d, C-4_d), 77.1 (d, C-2_a), 77.7, 78.0, 78.3 (3 x d, C-3_x, C-4_x, C-4_y), 78.7 (d, C-2_x), 80.0 (d, C-4_a), 80.3 (d, C-3_y), 83.8 (d, C-3_d), 95.9 (d, C-1_x, C-1_y, C-1_d), 100.9 (d, C-1_a), 102.0 (d, Ph<u>C</u>H), 126.2, 127.1, 127.1, 127.2, 127.3, 127.5, 127.6, 127.6, 127.7, 127.7, 127.9, 127.9, 127.9, 128.0, 128.1, 128.1, 128.2, 128.2, 128.2, 128.3, 128.3, 128.4, 129.0 (24 x d, Ar-CH), 137.2, 137.6, 137.8, 138.0, 138.1, 138.1, 138.3, 138.3, 138.9, 139.1 (9 x s, Ar-C); *m/z* (ES^+) Isotope Distribution Calcd. for $C_{102}H_{108}O_{21}Na$ (MNa^+) 1694.7 (26), 1693.7 (61), 1692.7 (100), 1691.7 (88%). Found 1694.9 (28), 1693.9 (61), 1692.9 (100), 1691.9 (95%).

In this case, it was not possible to distinguish glucose residues b and c from the NMR data. Consequently, they have been arbitrarily denoted as x and y.

Also a mixture which by ^{1}H NMR spectroscopy contained enol ethers **137**, a colourless oil; Partial data: δ_H (400 MHz, $CDCl_3$) *E* isomer 1.39 (3H, dd, *J* 1.4 Hz, *J* 6.8 Hz, OCH=CHC$\underline{H}_3$), 6.11 (1H, dd obs, OC$\underline{H}$=CH); *Z* isomer 1.64 (3H, dd obs, *J* 1.6 Hz, OCH=CHC$\underline{H}_3$), 5.98 (1H, dd, J_Z 6.5 Hz, OC$\underline{H}$=CH). This mixture was dissolved in THF (4 ml). Water (0.5 ml) and NIS (16 mg, 0.071 mmol) were added. After 30 min, sodium thiosulfate (30 ml of a 10% aqueous solution) was added and the mixture extracted with CH_2Cl_2 (30 ml). The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2:ether, 40:1→20:1) to afford further methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **129** (11 mg, 15%).

And methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(3,4,6-tri-*O*-benzyl-1-chloro-1-deoxy-β-D-glucopyranos-2-*O*-yl)propyl)-α-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **7** as a mixture of two diastereomers (22 mg, 27%); Partial data: δ_H (400 MHz, $CDCl_3$) (*v*:*w*, 4:3), isomer *v* 1.44 (3H, d, *J* 6.9 Hz, CHIC$\underline{H}_3$), 3.33 (3H, s, OCH_3), 6.46 (1H, d, $J_{1,2}$ 3.6 Hz, H-1_d); isomer *w* 1.68 (3H, d, *J* 7.1 Hz, CHIC$\underline{H}_3$), 3.28 (3H, s, OCH_3), 6.01 (1H, d, $J_{1,2}$ 2.8 Hz, H-1_d); *m/z* (ES^+) 1894 ($M+Na^+$, 100%).

Methyl α-D-glucopyranosyl-(1→2)-α-D-glucopyranosyl-(1→3)-α-D-glucopyranosyl-(1→3)-α-D-mannopyranoside 117

Methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **129** (10 mg, 5.9 μmol) was dissolved in ethanol (2.25 ml) and acetic acid (0.25 ml), and palladium (II) acetate (5 mg 0.022 mmol) was added. The mixture was degassed and stirred under H_2. After 22 h, tlc (CMAW) indicated the formation of a single major product (R_f 0.1). The reaction mixture was filtered through Celite and concentrated *in vacuo*. The residue purified by size-exclusion chromatography on Sephadex G-25 (water) to afford methyl α-D-glucopyranosyl-(1→2)-α-D-glucopyranosyl-(1→3)-α-D-glucopyranosyl-(1→3)-α-D-mannopyranoside **117** (4 mg, 98%); $[\alpha]_D^{25}$ +84 (*c*, 0.2 in MeOH); δ_H $(D_2O)^{15}$ 3.41 (3H, s, OCH_3), 3.46 (1H, H-4_d), 3.53 (1H, H-4_c), 3.60 (1H, H-2_d), 3.62 (1H, H-4_b), 3.65 (1H, H-2_b), 3.66 (1H, H-4_a), 3.69 (1H, H-2_c), 3.76 (2H, H-6_b, H-$6'_b$), 3.78 (1H, H-5_a), 3.79 (1H, H-3_d), 3.79 (2H, H-6_c, H-$6'_c$), 3.82 (1H, H-5_b), 3.82 (2H, H-6_d, H-$6'_d$), 3.83 (1H, H-6_a), 3.84 (1H, H-3_c), 3.86 (1H, H-3_a), 3.91 (1H, H-3_b), 3.91 (1H, H-$6'_a$), 3.96 (1H, H-5_d), 4.06 (1H, H-5_c), 4.09 (1H, H-2_a), 4.74 (1H, H-1_a), 5.17 (1H, d, $J_{1,2}$ 3.7 Hz, H-1_d), 5.24 (1H, d, $J_{1,2}$ 4.4 Hz, H-1_b), 5.52 (1H, d, $J_{1,2}$ 3.7 Hz, H-1_c); δ_C $(D_2O)^{15}$ 54.6 (q, OCH_3), 60.0 (t, C-6_c), 60.1 (t, C-6_d), 60.1 (t, C-6_b), 60.7 (t, C-6_a), 65.9 (d, C-3_c), 69.1 (d, C-4_d), 69.1 (d, C-4_c), 69.6 (d, C-2_a), 69.7 (d, C-4_b), 70.1 (d, C-2_b), 71.0 (d, C-5_b), 71.1 (d, C-2_d), 71.3 (d, C-5_c), 71.6 (d, C-5_d), 71.7 (d, C-3_d), 72.4 (d, C-4_a), 72.7 (d, C-5_a), 75.2 (d, C-2_c), 78.4 (d, C-3_a), 79.6 (d, C-3_b), 95.7 (d, C-1_d), 96.4 (d, C-1_c), 100.5 (d, C-1_b), 100.6 (d, C-1_a); *m/z* (ES^+) 703 ($M+Na^+$, 100%). (HRMS Calcd. for $C_{25}H_{48}NO_{21}$ (MNH_4^+) 698.2719. Found 698.2716).

7.6 Experimental for Chapter 6

1,2,3,4-Tetra-O-acetyl-L-rhamnopyranose 146

L-Rhamnose **147** (10.0 g, 61 mmol) was suspended in acetic anhydride (40 ml). Iodine (250 mg, 0.98 mmol) was dissolved in acetic anhydride (10 ml). The mixture was warmed until an exothermic reaction was initiated, then added to the sugar suspension. The reaction mixture was kept cool in a water bath. After 10 min, tlc (petrol:ethyl acetate, 1:1) indicated formation of major (R_f 0.5) and minor (R_f 0.45) products and the absence of starting material (R_f 0). The reaction was diluted with CH_2Cl_2 (200 ml), washed with $Na_2S_2O_3$ (200 ml of a 10% aqueous solution) and $NaHCO_3$ (200 ml of a saturated aqueous solution), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 1,2,3,4-tetra-*O*-acetyl-L-rhamnopyranose **146** (20.1 g, 99%) as a pale yellow oil which was used without further purification. (α/β ratio 1.6:1 by ^1H NMR).

para-*Tolyl 2,3,4-tri-O-acetyl-1-thio-α-L-rhamnopyranoside 145α and* para-*Tolyl 2,3,4-tri-O-acetyl-1-thio-β-L-rhamnopyranoside 145β*

Crude 1,2,3,4-tetra-*O*-acetyl-L-rhamnopyranose **146** (18.7 g, 56 mmol) and *para*-thiocresol (10.7 g, 86.2 mmol) were dissolved in CH_2Cl_2 (50 ml). $BF_3.OEt_2$ (9.1 ml, 74.7 mmol) was added and the reaction mixture stirred at RT under Ar. After 3 h, tlc (petrol:ethyl acetate, 3:2) indicated formation of two products (R_f 0.5 and 0.45) complete consumption of starting materials (R_f 0.35 and 0.3). The reaction mixture was diluted with CH_2Cl_2 (300 ml) and washed with $NaHCO_3$ (300 ml of a saturated aqueous solution), dried ($MgSO_4$),

filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1) and recrystallised from ether/petrol to afford *para*-tolyl 2,3,4-tri-*O*-acetyl-1-thio-L-rhamnopyranoside **145** (α/β ratio 3.6:1 determined by ^{1}H NMR spectroscopy) (17.0 g, 76%);

Separation of the anomers by flash column chromatography gave *para*-tolyl 2,3,4-tri-*O*-acetyl-1-thio-α-L-rhamnopyranoside **145α** as white crystals, m.p. 112-114 °C (ether/petrol); $[\alpha]_D^{25}$ -87.2 (*c*, 3.4 in $CHCl_3$); ν_{max} 1749 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, $J_{5,6}$ 6.1 Hz, CH_3-6), 2.00, 2.07, 2.13 (9H, 3 x s, 3 x $COCH_3$), 2.32 (3H, s, $ArCH_3$), 4.36 (1H, dq, $J_{4,5}$ 9.7 Hz, H-5), 5.13 (1H, at, *J* 10.0 Hz, H-4), 5.28 (1H, dd, $J_{2,3}$ 3.5 Hz, $J_{3,4}$ 10.1 Hz, H-3), 5.32 (1H, d, $J_{1,2}$ 1.3 Hz, H-1), 5.48 (1H, dd, H-2), 7.11, 7.35 (4H, 2 x d, *J* 8.1 Hz, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 17.3 (q, C-6), 20.6, 20.8, 20.9, 21.1 (4 x q, $ArCH_3$, 3 x $CO\underline{C}H_3$), 67.6, 69.3, 71.1, 71.2 (4 x d, C-2, C-3, C-4, C-5), 86.0 (d, $^1J_{C\text{-}1,H\text{-}1}$ 168.2 Hz, C-1), 129.3, 138.2 (2 x s, Ar-C), 129.9, 132.4 (2 x d, Ar-CH), 169.9, 170.0, 170.0 (3 x s, 3 x C=O); *m/z* (CI^+) 414 ($M+NH_4^+$, 76), 273 (M-STol, 100%). (HRMS Calcd. for $C_{19}H_{28}NO_7S$ (MNH_4^+) 414.1586. Found 414.1581). (Found: C, 57.49; H, 6.27. $C_{19}H_{24}O_7S$ requires C, 57.56; H, 6.10%);

And *para*-tolyl 2,3,4-tri-*O*-acetyl-1-thio-β-L-rhamnopyranoside **145β** as white crystals, m.p. 103-107 °C (ether/petrol); $[\alpha]_D^{25}$ +23.5 (*c*, 1.5 in $CHCl_3$); ν_{max} 1749 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, $J_{5,6}$ 6.1 Hz, CH_3-6), 1.98, 2.04, 2.21 (9H, 3 x s, 3 x $COCH_3$), 2.34 (3H, s, $ArCH_3$), 3.52 (1H, dq, $J_{4,5}$ 9.6 Hz, H-5), 4.83 (1H, d, $J_{1,2}$ 1.2 Hz, H-1), 4.99 (1H, dd, $J_{2,3}$ 3.5 Hz, $J_{3,4}$ 10.1 Hz, H-3), 5.11 (1H, at, *J* 9.8 Hz, H-4), 5.64 (1H, dd, H-2), 7.13, 7.40 (4H, 2 x d, *J* 8.0 Hz, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 17.7 (q, C-6), 20.6, 20.6, 20.7, 21.1 (4 x q, $ArCH_3$, 3 x

$COCH_3$), 70.2, 70.9, 71.8, 74.9 (4 x d, C-2, C-3, C-4, C-5), 85.7 (d, $^1J_{C\text{-}1,H\text{-}1}$ 153.4 Hz, C-1), 129.4, 138.4 (2 x s, Ar-C), 129.9, 132.7 (2 x d, Ar-CH) 169.8, 170.2, 170.3 (3 x s, 3 x C=O); *m/z* (CI^+) 414 ($M+NH_4^+$, 100), 273 (M-STol, 96%). (HRMS Calcd. for $C_{19}H_{28}NO_7S$ (MNH_4^+) 414.1586. Found 414.1586). (Found: C, 57.65; H, 6.30. $C_{19}H_{24}O_7S$ requires C, 57.56; H, 6.10%).

para-*Tolyl 1-thio-α-L-rhamnopyranoside 144*

para-Tolyl 2,3,4-tri-*O*-acetyl-1-thio-α-L-rhamnopyranoside **145α** (9.4 g 23.7 mmol) was suspended in methanol (70 ml). Sodium (60 mg, 2.6 mmol) was dissolved in methanol (10 ml) and then added to the sugar solution. The reaction mixture was stirred at RT. After 1 h 40 min, tlc (petrol:ethyl acetate, 1:1) indicated formation of a major product (R_f 0.1) and no remaining starting material (R_f 0.7). The reaction mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (ethyl acetate:methanol, 9:1) to afford *para*-tolyl 1-thio-α-L-rhamnopyranoside **144** (6.23 g, 97%) as a white solid which recrystallised from ether to give white crystals, m.p. 95-96 °C (ether); $[\alpha]_D^{25}$ -207 (*c*, 0.25 in $CHCl_3$); ν_{max} 3342 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, $J_{5,6}$ 6.2 Hz, CH_3-6), 2.34 (3H, s, $ArCH_3$), 3.57 (1H, at, *J* 9.4 Hz, H-4), 3.81 (1H, dd, $J_{2,3}$ 2.9 Hz, $J_{3,4}$ 9.3 Hz, H-3), 4.12-4.19 (1H, m, H-5), 4.22 (1H, d, H-2), 5.41 (1H, s, H-1), 7.04, 7.30 (4H, 2 x d, *J* 8.0 Hz, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 17.5 (q, C-6), 21.0 (q, $ArCH_3$), 69.3, 72.1, 72.5, 73.2 (4 x d, C-2, C-3, C-4, C-5), 88.2 (d, C-1), 129.8, 131.9 (2 x d, Ar-CH), 130.1, 137.4 (2 x s, Ar-C); *m/z* (CI^+) 288 ($M+NH_4^+$, 42), 271 ($M+H^+$, 4%). (HRMS Calcd. for $C_{13}H_{22}NO_4S$ (MNH_4^+) 288.1270. Found 288.1269). (Found: C, 57.61; H, 6.71.

$C_{13}H_{18}O_4S$ requires C, 57.76; H, 6.71%).

(2'S, 3'S) para-Tolyl 3,4-O-(2',3'-dimethoxybutan-2',3'-diyl)-1-thio-α-L-rhamnopyranoside 143

para-Tolyl 1-thio-α-L-rhamnopyranoside **144** (145 mg 0.54 mmol) was suspended in anhydrous methanol (5 ml). 2,3-Butanedione (0.15 ml, 1.72 mmol), trimethyl orthoformate (0.50 ml, 4.62 mmol) and camphorsulfonic acid (15 mg, 0.064 mmol) were added and the reaction mixture stirred under Ar at 75 °C. After 16 h, tlc (petrol:ethyl acetate, 1:1) indicated formation of a major product (R_f 0.6) and no remaining starting material (R_f 0.1). Triethylamine (4 ml) was added and the mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 3:1) to afford (2'S, 3'S) *para*-tolyl 3,4-*O*-(2',3'-dimethoxybutan-2',3'-diyl)-1-thio-α-L-rhamnopyranoside **143** (153 mg, 74%) as a colourless oil; $[\alpha]_D^{25}$ -262 (*c*, 1.0 in $CHCl_3$); ν_{max} 3410 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, $J_{5,6}$ 6.5 Hz, CH_3-6), 1.32, 1.34 (6H, 2 x s, 2 x $C(O)_2CH_3$), 2.33 (3H, s, $ArCH_3$), 2.69 (1H, d, $J_{OH,2}$ 1.8 Hz, OH-2), 3.25, 3.31 (6H, 2 x s, 2 x OCH_3), 3.78 (1H, at, *J* 9.7 Hz, H-4), 3.99 (1H, dd, $J_{2,3}$ 3.1 Hz, $J_{3,4}$ 10.0 Hz, H-3), 4.18 (1H, br s, H-2), 4.26-4.30 (1H, m, H-5), 5.43 (1H, s, H-1), 7.11, 7.35 (4H, 2 x d, *J* 8.0 Hz, Ar-H); δ_C (125.7 MHz, $CDCl_3$) 16.3, 17.5, 17.7 (3 x q, 2 x $C(O)_2\underline{C}H_3$, C-6), 21.0 (q, $ArCH_3$), 47.6, 48.0 (2 x q, 2 x OCH_3), 67.5, 68.5, 68.6, 71.2 (4 x d, C-2, C-3, C-4, C-5), 88.0 (d, C-1), 99.7, 100.1 (2 x s, 2 x $\underline{C}(O)_2CH_3$), 129.7, 131.9 132.0 (3 x d, Ar-CH), 130.2, 137.5 (2 x s, Ar-C); *m/z* (ES^+) 786 ($2M+NH_4^+$, 5), 402 ($M+NH_4^+$, 41), 353 (M-OMe, 100%). (HRMS

Calcd. for $C_{19}H_{32}NO_6S$ (MNH_4^+) 402.1950. Found 402.1949).

(2'S, 3'S) para-Tolyl 2-O-allyl-3,4-O-(2',3'-dimethoxybutan-2',3'-diyl)-1-thio-α-L-rhamnopyranoside 141

(2'S, 3'S) *para*-Tolyl 3,4-*O*-(2',3'-dimethoxybutan-2',3'-diyl)-1-thio-α-L-rhamnopyranoside **143** (118 mg 0.31 mmol) was dissolved in anhydrous DMF (2 ml) and cooled to 0 °C. Allyl bromide (0.053 ml, 0.62 mmol) then sodium hydride (60% in mineral oil) (25 mg, 0.62 mmol) were added. After 2 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a single product (R_f 0.6) and almost complete consumption of starting material (R_f 0.3). The reaction was quenched with water (50 ml) and extracted with ether (50 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 8:1) to afford (2'S, 3'S) *para*-tolyl 2-*O*-allyl-3,4-*O*-(2',3'-dimethoxybutan-2',3'-diyl)-1-thio-α-L-rhamnopyranoside **141** (108 mg, 83%) as a colourless oil; $[\alpha]_D^{25}$ -289 (*c*, 0.25 in $CHCl_3$); ν_{max} 1653 (w, C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, $J_{5,6}$ 6.3 Hz, CH_3-6), 1.32, 1.33 (6H, 2 x s, 2 x $C(O)_2CH_3$), 2.33 (3H, s, $ArCH_3$), 3.26, 3.31 (6H, 2 x s, 2 x OCH_3), 3.81 (1H, at, *J* 9.9 Hz, H-4), 3.89 (1H, dd, $J_{1,2}$ 1.3 Hz, $J_{2,3}$ 3.0 Hz, H-2), 3.97 (1H, dd, $J_{3,4}$ 10.2 Hz, H-3), 4.16 (1H, ddat, J_{gem} 13.5 Hz, *J* 5.8 Hz, *J* 1.4 Hz, $OC\underline{H}H'CH=CH_2$), 4.20-4.29 (2H, m, H-5, $OCH\underline{H}'CH=CH_2$), 5.16 (1H, dd, J_{gem} 1.7 Hz, J_Z 10.4 Hz, $CH=CH_E\underline{H_Z}$), 5.29 (1H, daq, *J* 1.7 Hz, J_E 17.3 Hz, $CH=C\underline{H_E}H_Z$), 5.42 (1H, d, H-1), 5.92 (1H, ddat, $C\underline{H}=CH_2$), 7.11, 7.34 (4H, 2 x d, *J* 8.1 Hz, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 16.6, 17.7, 17.8 (3 x q, 2 x $C(O)_2\underline{C}H_3$, C-6), 21.1 (q, $ArCH_3$), 47.6, 47.9 (2 x q, 2 x OCH_3), 67.9, 68.9, 68.9,

77.5 (4 x d, C-2, C-3, C-4, C-5), 71.7 (t, O$\underline{C}H_2CH=CH_2$), 87.2 (d, C-1), 99.5, 99.8 (2 x s, 2 x $\underline{C}(O)_2CH_3$), 117.1 (t, CH=$\underline{C}H_2$), 129.7, 131.7 (2 x d, Ar-CH), 131.0, 135.0 (2 x s, Ar-C) 137.4 (d, $\underline{C}H=CH_2$); *m/z* (ES^+) 483 ($M+NH_4^+$+MeCN, 15), 442 ($M+NH_4^+$, 40), 425 ($M+H^+$, 100), 393 (M-OMe, 81%). (HRMS Calcd. for $C_{22}H_{36}NO_6S$ (MNH_4^+) 442.2263. Found 442.2265).

***(2'S, 3'S)* para-*Tolyl* 3,4- O-*(2',3'-dimethoxybutan-2',3'-diyl)*-2-O-*prop-1''-enyl-1-thio-α-L-rhamnopyranoside* 148**

Wilkinson's catalyst (471 mg, 0.51 mmol) was dissolved in freshly distilled THF (6 ml) and degassed. Butyl lithium (1.6M solution in hexanes) (0.48 ml, 0.76 mmol) was added and the mixture stirred for 10 min. (2'S, 3'S) *para*-Tolyl 2-*O*-allyl-3,4-*O*-(2',3'-dimethoxybutan-2',3'-diyl)-1-thio-α-L-rhamnopyranoside **141** (2.16 g, 5.09 mmol) was dissolved in freshly distilled THF (6 ml) and heated to 70 °C. The catalyst solution was added by cannula under Ar. After 30 min, tlc (petrol:ether, 8:1) indicated formation of two products (R_f 0.2 and R_f 0.25) and complete consumption of starting material (R_f 0.1). The reaction was allowed to cool then diluted with CH_2Cl_2 (20 ml) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ether, 8:1) to afford (2'S, 3'S) *para*-tolyl 3,4-*O*-(2',3'-dimethoxybutan-2',3'-diyl)-2-*O*-prop-1''-enyl-1-thio-α-L-rhamnopyranoside **148** (2.04 g, 95%) as a colourless oil. (*Z*:*E*, 1.8:1). Isomers were separated by flash column chromatography (petrol:ether, 8:1). *E* isomer, a colourless oil; $[\alpha]_D^{25}$ -254 (*c*, 0.5 in $CHCl_3$); ν_{max} 1673 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, $J_{5,6}$ 6.3 Hz, CH_3-6), 1.32, 1.35 (6H, 2 x s, 2 x $C(O)_2CH_3$), 1.52 (3H, dd, *J*

1.5 Hz, *J* 6.8 Hz, OCH=CHC<u>H</u>$_3$), 2.34 (3H, s, ArCH$_3$), 3.27, 3.31 (6H, 2 x s, 2 x OCH$_3$), 3.80 (1H, at, *J* 9.9 Hz, H-4), 4.03 (1H, dd, $J_{2,3}$ 3.1 Hz, $J_{3,4}$ 10.1 Hz, H-3), 4.18 (1H, d, H-2), 4.25 (1H, dq, $J_{4,5}$ 9.6 Hz, H-5), 4.88 (1H, dq, J_E 12.7 Hz, OCH=C<u>H</u>), 5.49 (1H, s, H-1), 6.14 (1H, dd, OC<u>H</u>=CH), 7.12, 7.36 (4H, 2 x d, *J* 8.1 Hz, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 12.4 (q, CH=CH<u>C</u>H$_3$), 16.6, 17.7, 17.8 (3 x q, 2 x C(O)$_2$<u>C</u>H$_3$, C-6), 21.0 (q, ArCH$_3$), 47.6, 47.9 (2 x q, 2 x OCH$_3$), 67.7, 67.8, 68.8, 77.6 (4 x d, C-2, C-3, C-4, C-5), 85.6 (d, C-1), 99.6, 100.2 (2 x s, 2 x <u>C</u>(O)$_2$CH$_3$), 102.5 (d, OCH=<u>C</u>H), 129.8, 131.9 (2 x d, Ar-CH), 130.6, 137.6 (2 x s, Ar-C) 144.7 (d, O<u>C</u>H=CH);

Z isomer, a colourless oil; $[\alpha]_D^{25}$ -366 (*c*, 1.0 in $CHCl_3$); ν_{max} 1668 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, d, $J_{5,6}$ 6.1 Hz, CH$_3$-6), 1.32, 1.34 (6H, 2 x s, 2 x C(O)$_2$CH$_3$), 1.61 (3H, dd, *J* 1.7 Hz, *J* 6.7 Hz, OCH=CHC<u>H</u>$_3$), 2.33 (3H, s, ArCH$_3$), 3.27, 3.32 (6H, 2 x s, 2 x OCH$_3$), 3.86 (1H, at, *J* 9.9 Hz, H-4), 4.03 (1H, dd, $J_{2,3}$ 3.1 Hz, $J_{3,4}$ 10.1 Hz, H-3), 4.08 (1H, d, H-2), 4.26 (1H, dq, $J_{4,5}$ 9.6 Hz, H-5), 4.58 (1H, aquint, *J* 6.7 Hz, OCH=C<u>H</u>), 5.38 (1H, s, H-1), 5.96 (1H, dd, J_Z 6.0 Hz, OC<u>H</u>=CH), 7.12, 7.35 (4H, 2 x d, *J* 8.1 Hz, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 9.5 (q, CH=CH<u>C</u>H$_3$), 16.7, 17.7, 17.8 (3 x q, 2 x C(O)$_2$<u>C</u>H$_3$, C-6), 21.1 (q, ArCH$_3$), 47.6, 48.0 (2 x q, 2 x OCH$_3$), 67.9, 68.1, 68.9, 79.5 (4 x d, C-2, C-3, C-4, C-5), 86.8 (d, C-1), 99.6, 100.0 (2 x s, 2 x <u>C</u>(O)$_2$CH$_3$), 105.6 (d, OCH=<u>C</u>H), 129.8, 132.1 (2 x d, Ar-CH), 130.5, 137.7 (2 x s, Ar-C) 143.8 (d, O<u>C</u>H=CH);

For the *E*/*Z* mixture; *m/z* (ES$^+$) 483 (M+NH$_4^+$+MeCN, 27), 442 (M+NH$_4^+$, 29), 425 (M+H$^+$, 64), 393 (M-OMe, 100%). (HRMS Calcd. for $C_{22}H_{36}NO_6S$ (MNH$_4^+$) 442.2263. Found 442.2261).

(2′S, 3′S) **para-*Tolyl* 3,4- O-(2′,3′-*dimethoxybutan*-2′,3′-*diyl*)-2-O-(2-*iodo*-1-*methoxypropyl*)-1-*thio*-α-L-*rhamnopyranoside* 149**

N-Iodosuccinimide (239 mg, 1.1 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (2 ml) and cooled to -40 °C under Ar. (2′S, 3′S) *para*-tolyl 3,4-*O*-(2′,3′-dimethoxybutan-2′,3′-diyl)-2-*O*-prop-1′′-enyl-1-thio-α-L-rhamnopyranoside **149** (150 mg, 0.35 mmol) and methanol **3a** (0.022 ml, 0.53 mmol) were dissolved in anhydrous dichloroethane (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to 0 °C over 55 min. After this time, the reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ether, 8:1) to afford (2′S, 3′S) *para*-tolyl 3,4-*O*-(2′,3′-dimethoxybutan-2′,3′-diyl)-2-*O*-(2-iodo-1-methoxypropyl)-1-thio-α-L-rhamnopyranoside **149** (197 mg, 96%) as a colourless oil. *m/z* (ES^+) 641 ($M+NH_4^+$+MeCN, 12), 600 ($M+NH_4^+$, 3), 583 ($M+H^+$, 3%). (HRMS Calcd. for $C_{23}H_{39}NO_7SI$ (MNH_4^+) 600.1492. Found 600.1496).

Data for individual isomers:

isomer *v* δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, $J_{5,6}$ 6.0 Hz, CH_3-6), 1.31, 1.34 (6H, 2 x s, 2 x $C(O)_2CH_3$), 1.87 (3H, d, *J* 6.9 Hz, $CHIC\underline{H}_3$), 2.33 (3H, s, $ArCH_3$), 3.24, 3.32, 3.37 (9H, 3 x s, 3 x OCH_3), 3.74 (1H, at, *J* 10.0 Hz, H-4), 3.99 (1H, dd, $J_{2,3}$ 2.5 Hz, $J_{3,4}$ 10.3 Hz, H-3), 4.07 (1H, dd, $J_{1,2}$ 1.4 Hz, H-2), 4.24 (1H, dq, $J_{4,5}$ 9.6 Hz, H-5), 4.65 (1H, d, *J* 2.6 Hz, $(O)_2C\underline{H}CHI$), 4.67 (1H, dq, $C\underline{H}I$), 5.46 (1H, d, H-1),

7.11-7.13, (2H, m, Ar-H), 7.34-7.36 (2H, m, Ar-H);

isomer *w* δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, $J_{5,6}$ 6.2 Hz, CH_3-6), 1.29, 1.31 (6H, 2 x s, 2 x $C(O)_2CH_3$), 1.92 (3H, d, *J* 6.8 Hz, CHIC$\underline{H}_3$), 2.33 (3H, s, $ArCH_3$), 3.27, 3.31, 3.33 (9H, 3 x s, 3 x OCH_3), 3.79 (1H, at, *J* 10.0 Hz, H-4), 3.98 (1H, dd, $J_{2,3}$ 2.6 Hz, $J_{3,4}$ 10.4 Hz, H-3), 4.17 (1H, dd, $J_{1,2}$ 1.3 Hz, H-2), 4.24 (1H, dq, $J_{4,5}$ 9.7 Hz, H-5), 4.42 (1H, d, *J* 5.7 Hz, $(O)_2C\underline{H}CHI$), 4.51 (1H, dq, C$\underline{H}$I), 5.44 (1H, d, H-1), 7.11-7.13, (2H, m, Ar-H), 7.34-7.36 (2H, m, Ar-H);

isomer *x* δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, $J_{5,6}$ 6.2 Hz, CH_3-6), 1.28, 1.30 (6H, 2 x s, 2 x $C(O)_2CH_3$), 1.88 (3H, d, *J* 7.2 Hz, CHIC$\underline{H}_3$), 2.34 (3H, s, $ArCH_3$), 3.23, 3.31, 3.50 (9H, 3 x s, 3 x OCH_3), 3.82 (1H, at, *J* 9.9 Hz, H-4), 3.98 (1H, dd, $J_{2,3}$ 3.0 Hz, $J_{3,4}$ 10.3 Hz, H-3), 4.18 (1H, dd, $J_{1,2}$ 1.2 Hz, H-2), 4.20 (1H, dq, *J* 5.8 Hz, C$\underline{H}$I), 4.25 (1H, dq, $J_{4,5}$ 9.7 Hz, H-5), 4.31 (1H, d, $(O)_2C\underline{H}CHI$), 5.41 (1H, s, H-1), 7.11-7.14, (2H, m, Ar-H), 7.34-7.37 (2H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 16.5, 17.6, 17.8 (3 x q, 2 x $C(O)_2\underline{C}H_3$, C-6), 21.1 (q, $ArCH_3$), 23.0 (q, CHI$\underline{C}H_3$), 27.1 (q, $\underline{C}HICH_3$), 47.6, 47.9 (2 x q, 2 x OCH_3), 54.8 (q, OCH_3), 68.0, 68.4, 68.7, (3 x d, C-3, C-4, C-5), 74.4 (d, C-2), 88.0 (d, C-1), 99.6, 99.9 (2 x s, 2 x $\underline{C}(O)_2CH_3$), 105.1 (d, $(O)_2\underline{C}HCHI$), 129.9, 132.3 (2 x d, Ar-CH), 130.5, 137.8 (2 x s, Ar-C);

isomer *y* δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, $J_{5,6}$ 6.0 Hz, CH_3-6), 1.29, 1.31 (6H, 2 x s, 2 x $C(O)_2CH_3$), 1.81 (3H, d, *J* 6.8 Hz, CHIC$\underline{H}_3$), 2.34 (3H, s, $ArCH_3$), 3.24, 3.32, 3.55 (9H, 3 x s, 3 x OCH_3), 3.85 (1H, at, *J* 9.5 Hz, H-4), 3.98-4.02 (2H, m, H-2, H-3), 4.06 (1H, dq, *J* 4.0 Hz, C$\underline{H}$I), 4.24 (1H, dq, $J_{4,5}$ 9.7 Hz, H-5), 4.78 (1H, d, $(O)_2C\underline{H}CHI$), 5.36 (1H, s, H-1), 7.12-7.14, (2H, m, Ar-H), 7.34-7.36 (2H, m, Ar-H).

(2'S, 3'S) Methyl 3,4-O -(2',3'-dimethoxybutan-2',3'-diyl)-β-L-rhamnopyranoside 150

(2'S, 3'S) *para*-Tolyl 3,4-*O*-(2',3'-dimethoxybutan-2',3'-diyl)-2-*O*-(2-iodo-1-methoxypropyl)-1-thio-α-L-rhamnopyranoside **149** was dissolved in anhydrous dichloroethane (3 ml). 2,6-Di-*tert*-butyl-4-methylpyridine (138 mg, 0.67 mmol), *N*-iodosuccinimide (227 mg, 1.0 mmol) and silver trifluoromethanesulfonate (87 mg, 0.34 mmol) were added. The reaction mixture was stirred at 50 °C under Ar. After 20 min, tlc (petrol:ethyl acetate, 6:1) indicated the absence of starting material (R_f 0.6). Tlc (petrol:ethyl acetate, 1:1) indicated formation of two major products (R_f 0.15 and R_f 0.25). The reaction mixture was partitioned between CH_2Cl_2 (60 ml) and $Na_2S_2O_3$ (50 ml of a 10% aqueous solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 1:1) to afford (2'S, 3'S) methyl 3,4-*O*-(2',3'-dimethoxybutan-2',3'-diyl)-2-*O*-(2-iodo-1-succinimidopropyl)-β-L-rhamnopyranoside **151*v*** (52 mg, 28%), a single isomer as a colourless oil; ν_{max} 1713 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.26, 1.27 (6H, 2 x s, 2 x $C(O)_2CH_3$), 1.27 (3H, d, $J_{5,6}$ 6.1 Hz, CH_3-6), 2.14 (3H, d, *J* 6.9 Hz, CHIC$\underline{H}_3$), 2.55-2.77 (4H, m, C$\underline{H}_2$C$\underline{H}_2$), 3.18, 3.26 (6H, 2 x s, 2 x OCH_3), 3.34 (1H, dq, $J_{4,5}$ 9.2 Hz, H-5), 3.39 (3H, s, OCH_3-1), 3.57 (1H, dd, $J_{2,3}$ 2.8 Hz, $J_{3,4}$ 10.4 Hz, H-3), 3.67 (1H, at, *J* 9.9 Hz, H-4), 3.77 (1H, dd, $J_{1,2}$ 0.9 Hz, H-2), 4.21 (1H, d, H-1), 5.29 (1H, dq, *J* 10.2 Hz, CHI), 5.42 (1H, d, CHN); δ_C (100.6 MHz, $CDCl_3$) 16.3, 17.5, 17.7 (3 x q, 2 x $C(O)_2\underline{C}H_3$, C-6), 24.4 (d, CHI), 25.4 (q, CHI$\underline{C}H_3$), 27.9, 27.9 (2 x t, $\underline{C}H_2\underline{C}H_2$), 47.5, 48.1 (2 x q, 2 x OCH_3), 56.9 (q, OCH_3-1), 68.0, 70.1, 70.9, 77.4 (4 x d, C-2,

C-3, C-4, C-5), 88.1 (d, CHN), 99.6, 99.8 (2 x s, 2 x $\underline{C}(O)_2CH_3$), 100.7 (d, C-1), 175.9, 177.8 (2 x s, 2 x C=$\underline{O}$); *m/z* (APCI$^+$) 580 (M+Na$^+$, 10), 575 (M+NH_4^+, 10), 526 (M-OMe, 90%). (HRMS Calcd. for $C_{20}H_{36}N_2O_9I$ (MNH_4^+) 575.1466. Found 575.1470);

And (2′S, 3′S) methyl 3,4-*O*-(2′,3′-dimethoxybutan-2′,3′-diyl)-2-*O*-(2-iodo-1-succinimidopropyl)-β-L-rhamnopyranoside **151*w*** (12 mg 7%), another single isomer as a colourless oil; δ_H (400 MHz, $CDCl_3$) 1.26, 1.36 (6H, 2 x s, 2 x $C(O)_2CH_3$), 1.31 (3H, d, $J_{5,6}$ 6.1 Hz, CH_3-6), 1.75 (3H, d, *J* 7.1 Hz, CHIC$\underline{H}_3$), 2.66 (4H, br s, C$\underline{H}_2$C$\underline{H}_2$), 3.19, 3.26 (6H, 2 x s, 2 x OCH_3), 3.36 (1H, dq, $J_{4,5}$ 9.7 Hz, H-5), 3.40 (3H, s, OCH_3-1), 3.60 (1H, dd, $J_{2,3}$ 2.7 Hz, $J_{3,4}$ 10.4 Hz, H-3), 3.70 (1H, dd, $J_{1,2}$ 0.9 Hz, H-2), 3.84 (1H, at, *J* 9.9 Hz, H-4), 4.23 (1H, d, H-1), 5.03 (1H, dq, *J* 9.7 Hz, CHI), 5.47 (1H, d, CHN); δ_C (100.6 MHz, $CDCl_3$) 16.4, 17.8, 18.0 (3 x q, 2 x $C(O)_2\underline{C}H_3$, C-6), 19.4 (d, CHI), 24.3 (q, CHI$\underline{C}H_3$), 28.0 (t, $\underline{C}H_2\underline{C}H_2$), 47.2, 48.0 (2 x q, 2 x OCH_3), 56.7 (q, OCH_3-1), 68.1, 70.3, 71.2, 76.3 (4 x d, C-2, C-3, C-4, C-5), 87.8 (d, CHN), 99.5, 100.1 (2 x s, 2 x $\underline{C}(O)_2CH_3$), 100.8 (d, C-1); *m/z* (APCI$^+$) 575 (M+NH_4^+, 7), 526 (M-OMe, 25%). (HRMS Calcd. for $C_{20}H_{36}N_2O_9I$ (MNH_4^+) 575.1466. Found 575.1471).

(2′S, 3′S) Methyl 3,4-*O*-(2′,3′-dimethoxybutan-2′,3′-diyl)-2-*O*-(2-iodo-1-succinimidopropyl)-β-L-rhamnopyranoside **151*v*** (52 mg) and **151*w*** (12 mg) were separately dissolved in methanol (2 ml) and treated with LiOH (25 mg and 5 mg respectively). In both cases, tlc (petrol:ethyl acetate, 1:1) indicated formation of a single product (R_f 0.2) and disappearance of starting material (R_f 0.25 and R_f 0.15 respectively). The reaction mixtures were combined and concentrated *in vacuo*. The residue was purified by flash column

chromatography (petrol:ethyl acetate, 1:2) to afford (2′S, 3′S) methyl 3,4-*O*-(2′,3′-dimethoxybutan-2′,3′-diyl)-β-L-rhamnopyranoside **150** (21 mg, 21% overall) as a colourless oil; $[\alpha]_D^{25}$ -122.7 (*c*, 1.0 in $CHCl_3$); ν_{max} 3472 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.30, 1.35 (6H, 2 x s, 2 x $C(O)_2CH_3$), 1.33 (3H, d, $J_{5,6}$ 6.1 Hz, CH_3-6), 2.46 (1H, br s, OH-2), 3.25, 3.27 (6H, 2 x s, 2 x OCH_3), 3.46 (1H, dq, $J_{4,5}$ 9.3 Hz, H-5), 3.55 (3H, s, OCH_3-1), 3.66 (1H, dd, $J_{2,3}$ 3.0 Hz, $J_{3,4}$ 10.1 Hz, H-3), 4.01 (1H, br s, H-2), 3.75 (1H, at, *J* 9.6 Hz, H-4), 4.41 (1H, d, $J_{1,2}$ 0.8 Hz, H-1); δ_C (125.7 MHz, $CDCl_3$) 16.4, 17.5, 17.7 (3 x q, 2 x $C(O)_2\underline{C}H_3$, C-6), 47.5, 47.9 (2 x q, 2 x OCH_3), 56.8 (q, OCH_3-1), 67.8, 69.4, 70.0, 70.4 (4 x d, C-2, C-3, C-4, C-5), 99.6, 100.1 (2 x s, 2 x $\underline{C}(O)_2CH_3$), 100.8 (d, $^1J_{C\text{-}1,H\text{-}1}$ 156.6 Hz, C-1); *m/z* (ES^+) 315 ($M+Na^+$, 14), 310 ($M+NH_4^+$, 62), 261 (M-OMe, 100%). (HRMS Calcd. for $C_{313}H_{28}NO_7$ (MNH_4^+) 310.1866. Found 310.1867).

Phenyl 4,6-O-benzylidene-2-O-(2-iodo-1-(methyl 2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranosid-3-O-yl)propyl)-3-O-pivaloyl-1-thio-β-D-glucopyranoside 94

N-Iodosuccinimide (163 mg, 0.23 mmol), 2,6-di-*tert*-butyl-4-methyl pyridine (99 mg, 0.48 mmol), methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **3g** (90 mg, 0.282 mmol) and 4Å molecular sieves were added to anhydrous dichloromethane (2 ml) and cooled to -40 °C under Ar. Phenyl 4,6-*O*-benzylidene-3-*O*-pivaloyl-2-*O*-prop-1′-enyl-1-thio-β-D-glucopyranoside **93** (234 mg, 0.484 mmol) was dissolved in anhydrous dichloromethane (2 ml) and added to the reaction vessel by cannula under N_2. The reaction was allowed to warm to RT. After 16 h, tlc (cyclohexane:ethyl

acetate, 4:1) indicated the complete consumption of starting material (R_f 0.7). After a further 24 h, the solvent had all evaporated off. Tlc (cyclohexane:ethyl acetate, 4:1) indicated the formation of two major products (R_f 0.45 and 0.5), plus some remaining starting alcohol(R_f 0.4). The reaction was quenched with Et_3N (2 ml) and stirred for 5 min. Sodium thiosulfate (50 ml of a 10% aqueous solution) was added and the mixture extracted with CH_2Cl_2 (2 x 50 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (cyclohexane:ethyl acetate, 6:1) to afford phenyl 4,6-*O*-benzylidene-2-*O*-(2-iodo-1-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosid-3-*O*-yl)propyl)-3-*O*-pivaloyl-1-thio-β-D-glucopyranoside **94.** (142 mg, 60%) as a white foam. *m/z* (ES^+) 1000 ($M+NH_4^+$, 53%).

Methyl 4,6-O-benzylidene-3-O-pivaloyl-α-D-glucopyranosyl-(1→3)-2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside 155

Phenyl 4,6-*O* -benzylidene-2-*O*-(2-iodo-1-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosid-3-*O*-yl)propyl)-3-*O*-pivaloyl-1-thio-β-D-glucopyranoside **94** (133 mg, 0.136 mmol) was dissolved in anhydrous dichloroethane (4 ml). 2,6-Di-*tert*-butyl-4-methylpyridine (56 mg, 0.272 mmol), silver trifluoromethanesulfonate (35 mg, 0.136 mmol) and *N*-iodosuccinimide (92 mg, 0.409 mmol) were added. After 14 h 30 min, tlc (petrol:ethyl acetate, 4:1) indicated the formation of a major product (R_f 0.3) and the absence of starting material (R_f 0.4). The reaction mixture was partitioned between CH_2Cl_2 (2 x 50 ml) and $Na_2S_2O_3$ (50 ml of a 10% aqueous

solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 3:1) to afford methyl 4,6-*O*-benzylidene-3-*O*-pivaloyl-α-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **155** (67 mg, 70%) as a colourless oil; $[\alpha]_D^{22}$ +40.6 (*c*, 0.65 in $CHCl_3$); ν_{max} 1736 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.23 (9H, s, $C(CH_3)_3$), 2.56 (1H, d, $J_{OH,2}$ 11.5 Hz, OH-2_b), 3.37 (3H, s, OCH_3), 3.59 (1H, at, *J* 9.6 Hz, H-4_b), 3.67 (1H, ddd, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 9.7 Hz, H-2_b), 3.72 (1H, at, *J* 10.3 Hz, H-6_b), 3.79-3.90 (3H, m, H-2_a, H-5_a, H-5_b), 3.89 (1H, at, *J* 10.3 Hz, H-6_a), 4.20-4.26 (3H, m, H-3_a, H-4_a, H-$6'_b$), 4.28 (1H, dd, $J_{5,6'}$ 4.5 Hz, $J_{6,6'}$ 9.9 Hz, H-$6'_a$), 4.74 (1H, d, $J_{1,2}$ 1.4 Hz, H-1_a), 4.77 (2H, s, PhC$\underline{H}_2$), 5.28 (1H, d, H-1_b), 5.42 (1H, at, *J* 9.7 Hz, H-3_b), 5.50, 5.62 (2H, 2 x s, 2 x PhC$\underline{H}$), 7.27-7.48 (15H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 27.6 (q, $C(\underline{C}H_3)_3$), 37.8 (s, $\underline{C}(CH_3)_3$), 55.4 (q, OCH_3), 63.9, 64.3, 72.1, 72.2, 75.7, 77.8, 78.9, 79.3 (8 x d, C-2_a, C-3_a, C-4_a, C-5_a, C-2_b, C-3_b, C-4_b, C-5_b), 69.1, 69.3, (2 x t, C-6_a, C-6_b), 73.9 (t, Ph$\underline{C}H_2$), 100.1, 101.2, 101.5, 101.9 (4 x d, C-1_a, C-1_b, 2 x Ph$\underline{C}$H), 126.4, 126.7, 127.9, 128.4, 128.5, 128.7, 129.1, 129.3, 129.5 (9 x d, Ar-CH), 136.4 (s, Ar-C), 176.9 (s, C=O); *m/z* (ES^+) 729 ($M+Na^+$, 30), 724 ($M+NH_4^+$, 100%). (HRMS Calcd. for $C_{39}H_{50}NO_{12}$ (MNH_4^+) 724.3333. Found 724.3331).

para-*Tolyl* 2-O-*allyl*-1-*thio*-α-L-*rhamnopyranoside* 157

(2'S, 3'S) *para*-Tolyl 2-*O*-allyl-3,4-*O*-(2',3'-dimethoxybutan-2',3'-diyl)-1-thio-α-L-rhamnopyranoside **141** (159 mg 0.38 mmol) was dissolved in trifluoroacetic acid (1.8 ml) and water (0.2 ml) and stirred at RT. After 10 min, tlc

(petrol:ethyl acetate, 3:1) indicated formation of a single product (R_f 0.2) and disappearance of starting material (R_f 0.7). The reaction mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (petrol:ethyl acetate, 5:2→1:1) to afford *para*-tolyl 2-*O*-allyl-1-thio-α-L-rhamnopyranoside **157** (110 mg, 95%) as a colourless oil; $[\alpha]_D^{25}$ -289 (*c*, 0.25 in $CHCl_3$); ν_{max} 3392 (br, OH), 1646 (w, C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, $J_{5,6}$ 6.2 Hz, CH_3-6), 2.34 (3H, s, $ArCH_3$), 2.70 (2H, br s, OH), 3.50 (1H, at, *J* 9.5 Hz, H-4), 3.77 (1H, dd, $J_{2,3}$ 3.7 Hz, $J_{3,4}$ 9.5 Hz, H-3), 3.92 (1H, dd, $J_{1,2}$ 1.2 Hz, H-2), 4.00 (1H, ddat, J_{gem} 12.6 Hz, *J* 6.2 Hz, *J* 1.2 Hz, OC<u>H</u>H'CH=CH_2), 4.12 (1H, dq, $J_{4,5}$ 9.4 Hz, H-5), 4.19 (1H, ddat, *J* 5.5 Hz, *J* 1.4 Hz, OCH<u>H</u>'CH=CH_2), 5.21 (1H, dd, J_{gem} 1.4 Hz, J_Z 10.3 Hz, CH=CH_E<u>H_Z</u>), 5.29 (1H, daq, *J* 1.5 Hz, J_E 17.3 Hz, CH=C<u>H_E</u>H_Z), 5.50 (1H, d, H-1), 5.90 (1H, ddat, C<u>H</u>=CH_2), 7.13, 7.36 (4H, 2 x d, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 17.4 (q, C-6), 21.1 (q, $ArCH_3$), 68.9, 71.9, 74.2, 79.2 (4 x d, C-2, C-3, C-4, C-5), 71.3 (t, $OCH_2CH=CH_2$), 85.1 (d, C-1), 118.3 (t, CH=<u>C</u>H_2), 129.8, 132.0, 133.8 (3 x d, Ar-CH, <u>C</u>H=CH_2), 130.4, 137.7 (2 x s, Ar-C); *m/z* (TOF FI^+) 310 (M^+, 100%). (HRMS Calcd. for $C_{16}H_{22}O_4S$ (M^+) 310.1239. Found 310.1237).

para-*Tolyl 2-O-allyl-3,4-di-O-benzyl-1-thio-α-L-rhamnopyranoside 156*

para-Tolyl 2-*O*-allyl-1-thio-α-L-rhamnopyranoside **157** (500 mg 1.61 mmol) was dissolved in anhydrous DMF (15 ml) and cooled to 0 °C. Benzyl bromide (0.57 ml, 4.84 mmol) then sodium hydride (60% in mineral oil) (258 mg, 6.44 mmol) were added. After 14 h 30 min, tlc (petrol:ethyl acetate, 4:1) indicated formation of a single product (R_f 0.6) and complete consumption of

starting material (R_f 0.1). The reaction mixture was quenched with methanol (4 ml) and partitioned between ether (100 ml) and water (100 ml). The aqueous layer was re-extracted with ether (50 ml) and the combined organic extracts were washed with brine (50 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ether, 8:1) to afford *para*-tolyl 2-*O*-allyl-3,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside **156** (693 mg, 88%) as a colourless oil; $[\alpha]_D^{25}$ -120.7 (*c*, 0.75 in $CHCl_3$); ν_{max} 1648 (w, C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, $J_{5,6}$ 6.3 Hz, CH_3-6), 2.34 (3H, s, $ArCH_3$), 3.63 (1H, at, *J* 9.4 Hz, H-4), 3.85 (1H, dd, $J_{2,3}$ 3.2 Hz, $J_{3,4}$ 9.3 Hz, H-3), 3.95 (1H, dd, $J_{1,2}$ 1.6 Hz, H-2), 4.09-4.20 (3H, m, $OC\underline{H}_2CH=CH_2$, H-5), 4.65, 4.97 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 4.73 (2H, s, $PhCH_2$), 5.20 (1H, dd, J_{gem} 1.6 Hz, J_Z 10.2 Hz, $CH=CH_E\underline{H}_Z$), 5.28 (1H, daq, *J* 1.5 Hz, J_E 17.2 Hz, $CH=C\underline{H}_EH_Z$), 5.43 (1H, d, H-1), 5.92 (1H, ddat, $C\underline{H}=CH_2$), 7.11-7.42 (14H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 17.8 (q, C-6), 21.1 (q, $ArCH_3$), 69.1, 76.4, 77.2, 79.8 (4 x d, C-2, C-3, C-4, C-5), 71.5, 72.2, 75.5 (3 x t, $O\underline{C}H_2CH=CH_2$, 2 x $PhCH_2$), 86.1 (d, C-1), 118.0 (t, $CH=\underline{C}H_2$), 127.6, 127.7, 127.9, 128.0, 128.3, 128.4, 129.8, 131.8, 134.7 (9 x d, Ar-CH, $\underline{C}H=CH_2$), 130.9, 137.4, 138.1, 138.5 (4 x s, Ar-C); *m/z* ($APCI^+$) 546 (M+56, 100), 508 ($M+NH_4^+$, 5), 491 ($M+H^+$, 10%); (CI^+) 508 ($M+NH_4^+$, 100%). (HRMS Calcd. for $C_{30}H_{38}NO_4S$ (MNH_4^+) 508.2522. Found 508.2524). (Found: C, 73.60; H, 7.12. $C_{30}H_{34}O_4S$ requires C, 73.44; H, 6.98%).

para-*Tolyl 3,4-di-O-benzyl-2-O-prop-1'-enyl-1-thio-α-L-rhamnopyranoside 158*

Wilkinson's catalyst (120 mg, 0.13 mmol) was dissolved in freshly distilled THF (3 ml) and degassed. Butyl lithium solution in hexanes (0.12 ml, 0.20 mmol) was added and the mixture stirred for 10 min. *para*-Tolyl 2-*O*-allyl-3,4-di-*O*-benzyl-1-thio-α-L-rhamnopyranoside **156** (640 mg, 1.31 mmol) was dissolved in freshly distilled THF (3 ml) and heated to 75 °C. The catalyst solution was added by cannula under Ar. After 1 h 30 min, tlc (petrol:ether, 4:1) indicated formation of two products (R_f 0.5 and R_f 0.55) and complete consumption of starting material (R_f 0.45). The reaction was allowed to cool then diluted with CH_2Cl_2 (4 ml) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ether, 8:1) to afford *para*-tolyl 3,4-di-*O*-benzyl-2-*O*-prop-1'-enyl-1-thio-α-L-rhamnopyranoside **158** (513 mg, 80%) as a colourless oil; ν_{max} 1671 (C=C) cm^{-1}; Partial data: δ_H (400 MHz, $CDCl_3$) (*E*:*Z*, 1.4:1), *E* isomer 1.35 (3H, d, $J_{5,6}$ 6.1 Hz, CH_3-6), 1.54 (3H, dd, *J* 1.6 Hz, *J* 6.9 Hz, OCH=CHC$\underline{H}_3$), 3.63 (1H, at, *J* 9.3 Hz, H-4), 4.92 (1H, dq, J_E 12.5 Hz, OCH=C$\underline{H}$CH$_3$), 5.45 (1H, d, $J_{1,5}$ 1.5 Hz, H-1), 6.09 (1H, dq, OC$\underline{H}$=CHCH$_3$); *Z* isomer 1.36 (3H, d, $J_{5,6}$ 6.2 Hz, CH_3-6), 1.65 (3H, dd, *J* 1.5 Hz, *J* 6.7 Hz, OCH=CHC$\underline{H}_3$), 3.67 (1H, at, *J* 9.3 Hz, H-4), 4.10 (1H, dd, $J_{1,2}$ 1.8 Hz, $J_{2,3}$ 2.8 Hz, H-2), 4.58 (1H, aquin, *J* 6.6 Hz, OCH=C$\underline{H}$CH$_3$), 5.37 (1H, d, H-1), 5.91 (1H, dq, J_Z 6.1 Hz, OC$\underline{H}$=CHCH$_3$); δ_C (100.6 MHz, $CDCl_3$) *E* isomer 12.4 (q, OCH=CH$\underline{C}$H$_3$), 17.8 (q, C-6), 21.1 (q, ArCH_3), 72.2, 75.5 (2 x t, 2 x PhCH_2), 85.4 (d, C-1), 102.4 (d, OCH=$\underline{C}$HCH$_3$), 144.0 (d, O$\underline{C}$H=CHCH$_3$); Z isomer 9.5 (q, OCH=CH$\underline{C}$H$_3$), 17.9 (q, C-6), 21.1 (q, ArCH_3), 72.2, 75.5 (2 x t, 2 x PhCH_2), 86.3 (d, C-1), 104.8 (d, OCH=$\underline{C}$HCH$_3$), 144.9 (d, O$\underline{C}$H=CHCH$_3$); *m/z* (APCI$^+$) 546 (M+56, 100), 491 (M+H$^+$, 11%); (CI$^+$) 508 (M+NH_4^+, 100), 491 (M+H$^+$, 17%).

(HRMS Calcd. for $C_{30}H_{38}NO_4S$ (MNH_4^+) 508.2522. Found 508.2526). (Found: C, 73.56; H, 7.11. $C_{30}H_{34}O_4S$ requires C, 73.44; H, 6.98%).

para-*Tolyl* 3,4-*di*-O-*benzyl*-2-O-(2-*iodo*-1-*methoxypropyl*)-1-*thio*-α-L-*rhamnopyranoside* 159a

N-Iodosuccinimide (138 mg, 0.61 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (2 ml) and cooled to -40 °C under Ar. *para*-Tolyl 3,4-di-*O*-benzyl-2-*O*-prop-1'-enyl-1-thio-α-L-rhamnopyranoside **158** (100 mg, 0.20 mmol) and methanol **3a** (0.013 ml, 0.30 mmol) were dissolved in anhydrous dichloroethane (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to RT over 1 h. After this time, the reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ether, 8:1) to afford *para*-tolyl 3,4-di-*O*-benzyl-2-*O*-(2-iodo-1-methoxypropyl)-1-thio-α-L-rhamnopyranoside **159a** (117 mg, 88%) as a colourless oil; *m/z* (APCI$^+$) 704 (M+56, 100), 666 ($M+NH_4^+$, 10%); (ES$^+$) 671 ($M+Na^+$, 100%). (HRMS Calcd. for $C_{31}H_{41}NO_5SI$ (MNH_4^+) 666.1750. Found 666.1760).

para-*Tolyl* 3,4-*di*-O-*benzyl*-2-O-(2-*iodo*-1-(*methyl* 2,3,4-*tri*-O-*benzyl*-α-D-*glucopyranosid*-6-O-*yl*)*propyl*)-1-*thio*-α-L-*rhamnopyranoside* 159f

N-Iodosuccinimide (138 mg, 0.61 mmol) and 4Å molecular sieves were added to anhydrous dichloroethane (2 ml) and cooled to -40 °C under Ar. Methyl

2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **3f** (189 mg, 0.41 mmol) was dissolved in anhydrous dichloroethane (2 ml) and added to the reaction vessel by cannula under Ar. *para*-Tolyl 3,4-di-*O*-benzyl-2-*O*-prop-1'-enyl-1-thio-α-L-rhamnopyranoside **158** (99 mg, 0.20 mmol) was dissolved in anhydrous dichloroethane (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to RT. After 21 h, tlc (petrol:ether, 4:1) indicated complete consumption of the enol ether (R_f 0.5). Tlc (petrol:ethyl acetate, 3:1) indicated formation of a major (R_f 0.7) and two minor (R_f 0.6 and 0.4) products and remaining aglycon (R_f 0.3). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ether, 3:1) to afford *para*-tolyl 3,4-di-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranosid-6-*O*-yl)propyl)-1-thio-α-L-rhamnopyranoside **159f** (164 mg, 75%) as a colourless oil; *m/z* ($APCI^+$) 1136 (M+56, 20%); (ES^+) 1139 ($M+NH_4^+$+MeCN, 11), 1098 ($M+NH_4^+$, 14%); (HRMS Calcd. for $C_{58}H_{69}NO_{10}SI$ (MNH_4^+) 1098.3687. Found 1098.3678).

Also *para*-tolyl 3,4-di-*O*-benzyl-2-*O*-(2-iodo-1-succinimidopropyl)-1-thio-α-L-rhamnopyranoside **173*v*** (18 mg, 12%), a single isomer as a colourless oil; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, $J_{5,6}$ 6.1 Hz, CH_3-6), 2.00 (3H, d, *J* 7.0 Hz, CHIC$\underline{H}_3$), 2.35 (3H, s, $ArCH_3$), 2.56 (4H, br s, CH_2CH_2), 3.53 (1H, at, *J* 9.4 Hz, H-4), 3.93 (1H, dd, $J_{2,3}$ 2.9 Hz, $J_{3,4}$ 9.3 Hz, H-3), 4.01 (1H, dq, $J_{4,5}$ 9.4 Hz, H-5), 4.06 (1H, at, *J* 2.3 Hz, H-2), 4.65, 4.91 (2H, ABq, J_{AB} 11.0 Hz, PhC$\underline{H}_2$), 4.70, 4.87 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 5.08 (1H, d, $J_{1,2}$ 1.6 Hz, H-1), 5.09 (1H, dq, *J*

10.2 Hz, CHI), 5.58 (1H, d, CHN), 7.12-7.49 (14H, m, Ar-H); *m/z* (ES^+) 774 ($M+MeCN+NH_4^+$, 9), 733 ($M+NH_4^+$, 13%);

Also *para*-tolyl 3,4-di-*O*-benzyl-2-*O*-(2-iodo-1-succinimidopropyl)-1-thio-α-L-rhamnopyranoside **173*w*** (4 mg, 3%), a single isomer as a colourless oil; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, $J_{5,6}$ 6.1 Hz, CH_3-6), 1.71 (3H, d, *J* 7.0 Hz, CHIC$\underline{H}_3$), 2.34 (3H, s, $ArCH_3$), 2.57 (4H, s, CH_2CH_2), 3.81 (1H, at, *J* 9.2 Hz, H-4), 3.94 (1H, dd, $J_{2,3}$ 2.5 Hz, $J_{3,4}$ 9.0 Hz, H-3), 4.02 (1H, dq, $J_{4,5}$ 9.3 Hz, H-5), 4.12 (1H, br s, H-2), 4.64, 4.97 (2H, ABq, PhC$\underline{H}_2$), 4.66, 4.93 (2H, ABq, PhC$\underline{H}_2$), 4.86 (1H, dq, *J* 9.6 Hz, CHI), 5.23 (1H, d, $J_{1,2}$ 2.1 Hz, H-1), 5.61 (1H, d, CHN), 7.11-7.53 (14H, m, Ar-H); *m/z* (ES^+) 774 ($M+MeCN+NH_4^+$, 37), 733 ($M+NH_4^+$, 41%);

And recovered methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **3f** (121 mg, 0.261 mmol).

para*-Tolyl 3,4-di-O-benzyl-2-O-(2-iodo-1-(methyl 2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranosid-3-O-yl)propyl)-1-thio-α-L-rhamnopyranoside 159*g

Iodine (61 mg, 0.24 mmol), silver trifluoromethanesulfonate (61 mg, 0.24 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (100 mg, 0.48 mmol), methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **3g** (72 mg, 0.19 mmol) and 4Å molecular sieves were added to freshly distilled CH_2Cl_2 (2 ml) and cooled to -78 °C under Ar. *para*-Tolyl 3,4-di-*O*-benzyl-2-*O*-prop-1′-enyl-1-thio-α-L-rhamnopyranoside **158** (90 mg, 0.18 mmol) was dissolved in freshly distilled CH_2Cl_2 (3 ml) and added to the reaction vessel by cannula under Ar.

The reaction was allowed to warm to RT. After 6 h 30 min, tlc (petrol:ethyl acetate, 4:1) indicated complete consumption of starting material (R_f 0.8) and formation of a major product (R_f 0.7). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ether, 3:1) to afford *para*-tolyl 3,4-di-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosid-3-*O*-yl)propyl)-1-thio-α-L-rhamnopyranoside **159g** (148 mg, 82%) as a white foam; *m/z* (ES^+) 1027 ($M+K^+$, 62), 1011 ($M+Na^+$, 100), 1006 ($M+NH_4^+$, 65%).

para-*Tolyl 3,4-di-*O-*benzyl-2-*O-*(*1-(cholestan-3-β-yloxy)-2-iodopropyl)-1-thio-α-L-rhamnopyranoside 159i*

Iodine (57 mg, 0.22 mmol), silver trifluoromethanesulfonate (57 mg, 0.22 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (91 mg, 0.44 mmol), cholestan-3-β-ol **3i** (70 mg, 0.18 mmol) and 4Å molecular sieves were added to freshly distilled CH_2Cl_2 (1 ml) and cooled to -78 °C under Ar. *para*-Tolyl 3,4-di-*O*-benzyl-2-*O*-prop-1'-enyl-1-thio-α-L-rhamnopyranoside **158** (90 mg, 0.18 mmol) was dissolved in freshly distilled CH_2Cl_2 (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to RT. After 6 h 45 min, tlc (petrol:ethyl acetate, 4:1) indicated complete consumption of starting material (R_f 0.8) and formation of a major product (R_f 0.9). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined

organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ether, 11:1) to afford *para*-tolyl 3,4-di-*O*-benzyl-2-*O*-(1-(cholestan-3-β-yloxy)-2-iodopropyl)-1-thio-α-L-rhamnopyranoside **159i** (118 mg, 69%) as a white foam; *m/z* (ES^+) 1027 ($M+Na^+$, 22%).

Methyl 3,4-di-O-benzyl-β-L-rhamnopyranoside 160a

para-Tolyl 3,4-di-*O*-benzyl-2-*O*-(2-iodo-1-methoxypropyl)-1-thio-α-L-rhamnopyranoside **159a** (114 mg, 0.18 mmol) was dissolved in anhydrous dichloroethane (3 ml). 2,6-Di-*tert*-butyl-4-methylpyridine (73 mg, 0.35 mmol), *N*-iodosuccinimide (119 mg, 0.53 mmol) and silver trifluoromethanesulfonate (46 mg, 0.18 mmol) were added. The reaction mixture was stirred at RT for 30 min under Ar, then heated to 50 °C. After 3 h, tlc (petrol:ether, 4:1) indicated the absence of starting material (R_f 0.5). Tlc (petrol:ethyl acetate, 3:1) indicated formation of several products(R_f 0.55, 0.5 and 0.1). The reaction mixture was allowed to cool and then trifluoroacetic acid (2 ml) and water (1 ml) were added, and the mixture stirred further. After a further 2 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a major product (R_f 0.1). The reaction mixture was partitioned between $NaHCO_3$ (30 ml of a saturated aqueous solution) and CH_2Cl_2 (2 x 30 ml). The combined organic extracts were washed with sodium thiosulfate (30 ml of a 10% aqueous solution) dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1) to afford methyl 3,4-di-*O*-benzyl-β-L-rhamnopyranoside **160a** (34 mg, 54%) as a colourless oil; ν_{max} 3480 (br,

OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, $J_{5,6}$ 6.2 Hz, CH_3-6), 2.39 (1H, br s, OH-2), 3.33 (1H, dq, $J_{4,5}$ 9.2 Hz, H-5), 3.51-3.60 (2H, m, H-3, H-4), 3.55 (3H, s, OCH_3), 4.11 (1H, br s, H-2), 4.31 (1H, d, $J_{1,2}$ 1.0 Hz, H-1), 4.66, 4.95 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 4.69, 4.78 (2H, ABq, J_{AB} 12.2 Hz, PhC$\underline{H}_2$), 7.28-7.41 (10H, m, Ar-H); δ_C (125.7 MHz, $CDCl_3$) 17.7 (q, C-6), 56.7 (q, OCH_3), 68.2, 71.3, 79.6, 81.3 (4 x d, C-2, C-3, C-4, C-5), 71.3, 75.3 (2 x t, $PhCH_2$), 100.5 (d, $^1J_{C\text{-}1,H\text{-}1}$ 156.0 Hz, C-1), 127.6, 127.7, 127.8, 128.0, 128.3, 128.4 (6 x d, Ar-CH), 137.7, 138.2 (2 x s, Ar-C); *m/z* (ES^+) 739 ($2M+Na^+$, 7), 734 ($2M+NH_4^+$, 11), 417 ($M+MeCN+NH_4^+$, 46), 381 ($M+Na^+$, 15), 376 ($M+NH_4^+$, 100%). (HRMS Calcd. for $C_{21}H_{30}NO_5$ (MNH_4^+) 376.2124. Found 376.2124).

Methyl 3,4-di-O-benzyl-β-L-rhamnopyranosyl-(1→6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside 160f

para-Tolyl 3,4-di-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranosid-6-*O*-yl)propyl)-1-thio-α-L-rhamnopyranoside **159f** (70 mg, 0.065 mmol) was dissolved in anhydrous dichloroethane (3 ml). 2,6-Di-*tert*-butyl-4-methylpyridine (27 mg, 0.13 mmol), *N*-iodosuccinimide (44 mg, 0.20 mmol) and silver trifluoromethanesulfonate (17 mg, 0.065 mmol) were added and the mixture stirred under Ar at RT. After 17 h 30 min, tlc (petrol:ethyl acetate, 3:1) indicated the complete consumption of starting material (R_f 0.6) and the formation of a major product (R_f 0.1). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) and extracted with CH_2Cl_2 (2 x 30 ml). The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column

chromatography (petrol:ethyl acetate, 3:1→1:1) to afford methyl 3,4-di-*O*-benzyl-β-L-rhamnopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **160f** (32 mg, 62%); $[\alpha]_D^{24}$ +32.2 (*c*, 1.4 in $CHCl_3$); ν_{max} 3452 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, $J_{5,6}$ 6.4 Hz CH_3-6_b), 2.26 (1H, br s, OH-2_b), 3.32 (1H, dq, $J_{4,5}$ 8.7 Hz, H-5_b), 3.37 (3H, s, OCH_3), 3.49-3.56 (3H, m, H-2_a, H-3_b, H-4_b), 3.64 (1H, at, *J* 9.5 Hz, H-4_a), 3.71-3.76 (2H, m, H-5_a, H-6_a), 4.00 (1H, at, *J* 9.3 Hz, H-3_a), 4.14 (1H, br d, *J* 1.9 Hz, H-2_b), 4.23 (1H, dd, $J_{5,6'}$ 3.6 Hz, $J_{6,6'}$ 11.5 Hz, H-$6'_a$), 4.44 (1H, s, H-1_b), 4.61 (1H, d, $J_{1,2}$ 3.5 Hz, H-1_a), 4.64, 4.96 (2H, ABq, J_{AB} 10.8 Hz, PhC$\underline{H}_2$), 4.66, 4.82 (2H, ABq, J_{AB} 12.5 Hz, PhC$\underline{H}_2$), 4.69, 4.77 (2H, ABq, J_{AB} 11.5 Hz, PhC$\underline{H}_2$), 4.76, 4.87 (2H, ABq, J_{AB} 10.3 Hz, PhC$\underline{H}_2$), 4.87, 5.00 (2H, ABq, J_{AB} 10.7 Hz, PhC$\underline{H}_2$), 7.27-7.40 (25H, m, Ar-H); δ_C (125.7 MHz, $CDCl_3$) 17.8 (q, C-6_b), 55.1 (q, OCH_3), 66.9, 71.0, 73.3, 75.0, 75.4, 75.6 (6 x t, 5 x Ph$\underline{C}H_2$, C-6_a), 68.2, 69.7, 71.4, 77.2, 79.5, 79.6, 81.0, 81.9 (8 x d, C-2_a, C-3_a, C-4_a, C-5_a, C-2_b, C-3_b, C-4_b, C-5_b), 98.1 (d, $^1J_{C\text{-}1,H\text{-}1}$ 167.9 Hz, C-1_a), 99.3 (d, $^1J_{C\text{-}1,H\text{-}1}$ 157.1 Hz, C-1_b), 127.5, 127.6, 127.7, 127.8, 127.8, 127.9, 127.9, 128.0, 128.1, 128.2, 128.3, 128.3, 128.3 (13 x d, Ar-CH), 137.7, 138.0, 138.2, 138.3, 138.7 (5 x s, Ar-C); *m/z* (APCI$^+$) 846 (M+56, 12), 808 (M+NH_4^+, 7%); (APCI$^-$) 825 (M+Cl^-, 32), 699 (M-Bn, 95%). (HRMS Calcd. for $C_{48}H_{58}NO_{10}$ (MNH_4^+) 808.4061. Found 808.4069).

Cholestan-3'-β-yl 3,4-di-O-benzyl-β-L-rhamnopyranoside 160i

para-Tolyl 3,4-di-*O*-benzyl-2-*O*-(1-(cholestan-3-β-yloxy)-2-iodopropyl)-1-thio-α-L-rhamnopyranoside **159i** (102 mg, 0.10 mmol) was dissolved in anhydrous dichloroethane (9 ml). 2,6-Di-*tert*-butyl-4-methylpyridine (42 mg, 0.20 mmol),

N-iodosuccinimide (69 mg, 0.31 mmol) and silver trifluoromethanesulfonate (26 mg, 0.10 mmol) were added and the mixture stirred under Ar at RT. After 2 h 20 min, tlc (petrol:ethyl acetate, 3:1) indicated the absence of starting material (R_f 0.9) and the formation of a various products (R_f 0.5-0.9). The reaction mixture was partitioned between CH_2Cl_2 (2 x 40 ml) and sodium thiosulfate (40 ml of a saturated aqueous solution). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford cholestan-3′-β-yl 3,4-di-*O*-benzyl-β-L-rhamnopyranoside **160i** (21 mg, 29%) as a colourless oil; $[\alpha]_D^{24}$ +25.4 (*c*, 0.8 in $CHCl_3$); ν_{max} 3469 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.65, 0.80 (6H, 2 x s, 2 x steroid CH_3), 0.86 (3H, d, *J* 6.3 Hz, steroid CH_3), 0.90 (3H, d, *J* 6.9 Hz, steroid CH_3), 0.90 (3H, d, *J* 6.4 Hz, steroid CH_3), 0.93-1.99 (31H, m, steroid CH, CH_2), 1.34 (3H, d, $J_{5,6}$ 6.2 Hz, CH_3-6), 2.44 (1H, br s, OH-2), 3.30 (1H, dq, $J_{4,5}$ 8.8 Hz, H-5), 3.51-3.57 (2H, m, H-3, H-4), 3.63-3.69 (1H, m, steroid OCH), 4.05 (1H, br s, H-2), 4.52 (1H, s, H-1), 4.65, 4.95 (2H, ABq, J_{AB} 10.9 Hz, PhC$\underline{H}_2$), 4.68, 4.78 (2H, ABq, J_{AB} 11.9 Hz, PhC$\underline{H}_2$), 7.27-7.40 (15H, m, Ar-H); δ_C (125.7 MHz, $CDCl_3$) 12.0, 12.3, 18.6, 22.5, 22.8 (5 x q, 5 x steroid CH_3), 17.9 (q, C-6), 21.2, 23.8, 24.2, 27.7, 28.2, 28.7, 32.1, 35.8, 36.1, 36.8, 39.5, 40.0 (12 x t, 12 x steroid CH_2), 28.0, 35.5, 35.8, 44.9, 54.4, 56.3, 56.5 (7 x d, 7 x steroid CH), 35.6, 42.6 (2 x s, 2 x steroid C), 69.0, 71.3, 77.7, 79.6, 81.5 (5 x d, C-2, C-3, C-4, C-5, steroid O$\underline{C}$H), 71.2, 75.5 (2 x t, 2 x Ph$\underline{C}H_2$), 97.2 (d, $^1J_{C\text{-}1,H\text{-}1}$ 158.3 Hz, C-1), 127.7, 127.8, 127.9, 128.1, 128.4, 128.4 (6 x d, Ar-CH), 137.9, 138.6 (2 x s, Ar-C); *m/z* (ES^+) 737 ($M+Na^+$, 24), 732 ($M+NH_4^+$, 100%). (HRMS Calcd. for $C_{47}H_{74}NO_5$ (MNH_4^+) 732.5567. Found 732.5563);

And 2,3-di-*O*-benzyl-5-deoxy-4-*O*-formyl-L-arabinose **161** (2 mg, 6%) as a colourless oil; $[\alpha]_D^{24}$ +13.7 (*c*, 0.3 in $CHCl_3$); ν_{max} 1724 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, $J_{4,5}$ 6.2 Hz, CH_3-5), 3.90 (1H, dd, $J_{2,3}$ 3.7 Hz, $J_{3,4}$ 5.2 Hz, H-3), 3.93 (1H, dd, $J_{1,2}$ 1.4 Hz, H-2), 4.55, 4.63 (2H, ABq, J_{AB} 11.3 Hz, PhC$\underline{H}_2$-3), 4.56, 4.76 (2H, ABq, J_{AB} 11.9 Hz, PhC$\underline{H}_2$-2), 5.24 (1H, dq, H-4), 7.27-7.35 (10H, m, Ar-H), 7.88 (1H, s, $\underline{H}$C(O)O), 9.73 (1H, d, H-1); δ_C (125.7 MHz, $CDCl_3$) 16.1 (q, C-5), 69.8 (d, C-4) 80.1 (d, C-3), 82.6 (d, C-2), 73.4, 74.2 (2 x t, 2 x Ph$\underline{C}H_2$), 128.0, 128.1, 128.3, 128.4, 128.4, 128.5 (6 x d, Ar-CH), 136.4, 136.9 (2 x s, Ar-C) 159.8 (d, H$\underline{C}$(O)O), 202.9 (d, C-1); *m/z* (ES^+) 397 ($M+Na^+$+MeOH, 100), 392 ($M+NH_4^+$+MeOH, 13%). (HRMS Calcd. for $C_{21}H_{30}NO_6$ (MNH_4^++MeOH) 392.2073. Found 392.2079);

And cholestan-3-β-ol **3i** (3 mg, 7%) as a white solid.

Glucofuranose Experimental

1,2-O-Isopropylidene-α-D-glucofuranose 163

1,2:5,6-Di-*O*-*iso*propylidene-α-D-glucofuranose **162** (15.0 g, 58 mmol) was dissolved in acetic acid (150 ml) and water (50 ml) and stirred at RT. After 14 h, tlc (ethyl acetate) indicated formation of a product (R_f 0.2) and complete consumption of starting material (R_f 0.6). The reaction mixture was concentrated *in vacuo* and recrystallised from methanol/ether to afford 1,2-*O*-*iso*propylidene-α-D-glucofuranose **163** (9.1 g, 72%) as white crystals, m.p. 159 °C (ether/methanol) [Lit. 158-159 °C][16]; $[\alpha]_D^{25}$ -17.6 (*c*, 1.0 in H_2O) [Lit. -11.4 (*c*, 2.79 in H_2O)][16]; δ_H (400 MHz, D_2O) 1.28, 1.44 (6H, 2 x s, 2 x C$\underline{H}_3$), 3.56 (1H, dd, $J_{5,6}$ 6.0 Hz, $J_{6,6'}$ 12.2 Hz, H-6), 3.72 (1H, dd, $J_{5,6'}$ 2.7 Hz, H-6′), 3.84 (1H, ddd, $J_{4,5}$

8.8 Hz, H-5), 4.01 (1H, dd, $J_{3,4}$ 2.6 Hz, H-4), 4.24 (1H, d, H-3), 4.62 (1H, d, $J_{1,2}$ 3.6 Hz, H-2), 5.94 (1H, d, H-1).

3,5,6-Tri-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose 167

1,2-*O*-*Iso*propylidene-α-D-glucofuranose **163** (9.1 g, 41 mmol) was dissolved in anhydrous DMF (300 ml). Benzyl bromide (22 ml, 186 mmol) was added and the mixture cooled to 0°C. Sodium hydride (60% in mineral oil) (9.9 g, 248 mmol) was added portionwise and the reaction mixture was stirred under Ar. After 16 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a product (R_f 0.6) and complete consumption of starting material (R_f 0.1). The reaction was quenched with methanol (90 ml) then concentrated to *ca* half its volume *in vacuo*. The mixture was diluted with CH_2Cl_2 (200 ml) and washed with water (2 x 100 ml) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 3,5,6-tri-*O*-benzyl-1,2-*O*-*iso*propylidene-α-D-glucofuranose **167** as a pale brown oil which was used without purification.

1,2-Di-O-acetyl-3,5,6-tri-O-benzyl-D-glucofuranose 166

Crude 3,5,6-tri-*O*-benzyl-1,2-*O*-*iso*propylidene-α-D-glucofuranose **167** was dissolved in acetic acid (100 ml) and water (60 ml) and stirred at 80 °C. After 4 h, tlc indicated no reaction, and 1M HCl (20 ml) was added. After a further 7 h, tlc (petrol:ethyl acetate, 2:1) indicated formation of a major product (R_f 0.1) and no remaining starting material (R_f 0.8). The reaction mixture was concentrated *in vacuo* and co-evaporated with toluene.

The residue was dissolved in acetic anhydride (30 ml) and pyridine (30 ml) and stirred at RT. After 15 h, tlc (petrol:ethyl acetate, 2:1) indicated formation of a major product (R_f 0.4) and little remaining starting material (R_f 0.1). The reaction mixture was diluted with ether (200 ml), washed with $NaHCO_3$ (250 ml of a saturated aqueous solution), 1M HCl (200 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by dry flash column chromatography (petrol:ethyl acetate, 1:0→2:1) to afford 1,2-di-*O*-acetyl-3,5,6-tri-*O*-benzyl-D-glucofuranose **167** (15.3 g, 69% over 3 steps) as a pale yellow oil.[17] Partial data: δ_H (200 MHz, $CDCl_3$) (α:β, 1.5:1), α anomer 5.32 (1H, dd, $J_{1,2}$ 4.4 Hz, $J_{2,3}$ 2.1 Hz, H-2), 6.38 (1H, d, H-1); β anomer 5.25 (1H, s, H-2), 6.13 (1H, s, H-1).[18]

para-*Tolyl* 2-O-*acetyl-3,5,6-tri*-O-*benzyl-1-thio*-α-D-*glucofuranoside* 165α *and* para-*Tolyl* 2-O-*acetyl-3,5,6-tri*-O-*benzyl-1-thio*-β-D-*glucofuranoside* 165β

Method 1: Reaction carried out at 0 °C

1,2-Di-*O*-acetyl-3,5,6-tri-*O*-benzyl-D-glucofuranose **166** (1.0 g, 1.87 mmol) and *para*-thiocresol (348 mg, 2.81 mmol) were dissolved in freshly distilled CH_2Cl_2 (5 ml) and cooled to 0 °C. $BF_3.OEt_2$ (0.3 ml, 2.43 mmol) was added and the mixture stirred under Ar. After 45 min, tlc (petrol:ethyl acetate, 2:1) indicated complete consumption of starting material (R_f 0.5) and formation of two major products (R_f 0.6 and 0.65). After a further 2 h, the reaction mixture was partitioned between CH_2Cl_2 (2 x 100 ml) and $NaHCO_3$ (100 ml of a saturated aqueous solution). The combined organic extracts were dried ($MgSO_4$),

filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford *para*-tolyl 2-*O*-acetyl-3,5,6-tri-*O*-benzyl-1-thio-α-D-glucofuranoside **165α** (154 mg, 13%) as a colourless oil; $[\alpha]_D^{24}$ +60.5 (*c*, 1.0 in $CHCl_3$); ν_{max} 1749 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.16 (3H, s, $COC\underline{H}_3$), 2.34 (3H, s, $ArCH_3$), 3.71 (1H, dd, $J_{5,6}$ 5.5 Hz, $J_{6,6'}$ 10.6 Hz, H-6), 3.91 (1H, dd, $J_{5,6'}$ 1.8 Hz, H-6'), 4.06 (1H, ddd, $J_{4,5}$ 9.3 Hz, H-5), 4.15 (1H, dd, $J_{2,3}$ 0.6 Hz, $J_{3,4}$ 3.4 Hz, H-3), 4.42 (1H, dd, H-4), 4.49, 4.80 (2H, ABq, J_{AB} 11.2 Hz, $PhC\underline{H}_2$), 4.56, 4.76 (2H, ABq, J_{AB} 11.6 Hz, $PhC\underline{H}_2$), 4.62 (2H, s, $PhC\underline{H}_2$), 5.54 (1H, dd, $J_{1,2}$ 4.6 Hz, H-2), 5.72 (1H, d, H-1), 7.09-7.40 (19H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 20.7, 21.1 (2 x q, $ArCH_3$, $CO\underline{C}H_3$), 71.0, 72.0, 72.7, 73.4 (4 x t, 3 x $Ph\underline{C}H_2$, C-6), 75.5, 77.2, 78.8, 81.5 (4 x d, C-2, C-3, C-4, C-5), 89.6 (d, C-1), 127.4, 127.5, 127.6, 127.7, 127.7, 127.7, 127.8, 128.3, 128.3, 128.4, 129.7, 131.9 (12 x d, Ar-CH), 131.1, 137.3, 137.4, 138.4, 138.6 (5 x s, Ar-C), 169.8 (s, $\underline{C}$=O); *m/z* (ES^+) 657 ($M+NH_4^+$+MeCN, 34), 621 ($M+Na^+$, 21), 616 ($M+NH_4^+$, 100), 599 ($M+H^+$, 3%). (HRMS Calcd. for $C_{36}H_{42}NO_6S$ (MNH_4^+) 616.2733. Found 616.2727);

And *para*-tolyl 2-*O*-acetyl-3,5,6-tri-*O*-benzyl-1-thio-β-D-glucofuranoside **165β** (213 mg, 18%) as a colourless oil; $[\alpha]_D^{24}$ -88.9 (*c*, 1.0 in $CHCl_3$); ν_{max} 1748 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.09 (3H, s, $COC\underline{H}_3$), 2.33 (3H, s, $ArCH_3$), 3.73 (1H, dd, $J_{5,6}$ 4.8 Hz, $J_{6,6'}$ 10.7 Hz, H-6), 3.90 (1H, dd, $J_{5,6'}$ 1.9 Hz, H-6'), 4.11 (1H, d, $J_{3,4}$ 3.8 Hz, H-3), 4.18 (1H, ddd, $J_{4,5}$ 9.3 Hz, H-5), 4.30 (1H, dd, H-4), 4.44, 4.71 (2H, ABq, J_{AB} 11.1 Hz, $PhC\underline{H}_2$), 4.53, 4.85 (2H, ABq, J_{AB} 11.5 Hz, $PhC\underline{H}_2$), 4.61, 4.65 (2H, ABq, J_{AB} 12.4 Hz, $PhC\underline{H}_2$), 5.34 (1H, d, $J_{1,2}$ 1.4 Hz, H-1), 5.44 (1H, d, H-2), 7.09-7.42 (19H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 20.9, 21.1 (2 x q, $ArCH_3$,

$COCH_3$), 70.1, 71.8, 72.5, 73.7 (4 x t, 3 x Ph$\underline{C}H_2$, C-6), 75.8, 80.2, 80.7, 81.2 (4 x d, C-2, C-3, C-4, C-5), 91.0 (d, C-1), 127.4, 127.5, 127.6, 127.7, 127.8, 128.2, 128.3, 128.3, 129.6, 129.7, 131.9 (11 x d, Ar-CH), 131.5, 137.4, 137.5, 138.5, 138.6 (5 x s, Ar-C), 169.8 (s, C=O); *m/z* (ES^+) 657 ($M+NH_4^+$+MeCN, 33), 616 ($M+NH_4^+$, 60%). (HRMS Calcd. for $C_{36}H_{42}NO_6S$ (MNH_4^+) 616.2733. Found 616.2732).
And further α/β mixture (223 mg, 19%) as a colourless oil.

Method 2: Reaction carried out at -30 °C

1,2-Di-*O*-acetyl-3,5,6-tri-*O*-benzyl-D-glucofuranose **166** (2.99 g, 5.61 mmol) and *para*-thiocresol (836 mg, 6.74 mmol) were dissolved in freshly distilled CH_2Cl_2 (15 ml) in a flame-dried flask and cooled to -30 °C under Ar. $BF_3.OEt_2$ (1.04 ml, 8.42 mmol) was added and the mixture stirred under Ar. After 40 min, the mixture had warmed to -20 °C. At this time, tlc (petrol:ethyl acetate, 2:1) indicated little remaining starting material (R_f 0.5) and formation of a major product (R_f 0.6). The reaction was quenched with Et_3N (2 ml), and the mixture partitioned between CH_2Cl_2 (120 + 60 ml) and water (100 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford *para*-tolyl 2-*O*-acetyl-3,5,6-tri-*O*-benzyl-1-thio-α-D-glucofuranoside **165α** (37 mg, 1%) as a colourless oil identical to that previously described;
And *para*-tolyl 2-*O*-acetyl-3,5,6-tri-*O*-benzyl-1-thio-β-D-glucofuranoside **165β** (1.93 g, 58%) as a colourless oil identical to that previously described;

para-*Tolyl 3,5,6-tri*-O-*benzyl-1-thio-α-D-glucofuranoside 164α*

para-Tolyl 2-*O*-acetyl-3,5,6-tri-*O*-benzyl-1-thio-α-D-glucofuranoside **165α** (135 mg, 0.23 mmol) was dissolved in methanol (1 ml), THF (2 ml) and *n*-propylamine (1 ml) and stirred at RT. After 21 h, tlc (petrol:ethyl acetate, 4:1) indicated complete consumption of starting material (R_f 0.7) and formation of a major product (R_f 0.4). The reaction mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford *para*-tolyl 3,5,6-tri-*O*-benzyl-1-thio-α-D-glucofuranoside **164α** (110 mg, 88%) as white crystals, m.p. 108-109 °C (ether/petrol); $[\alpha]_D^{25}$ +57.3 (*c*, 1.0 in $CHCl_3$); ν_{max} 3406 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.35 (3H, s, $ArCH_3$), 2.66 (1H, d, $J_{OH,2}$ 3.5 Hz, OH-2), 3.74 (1H, dd, $J_{5,6}$ 6.0 Hz, $J_{6,6'}$ 10.7 Hz, H-6), 3.94 (1H, dd, $J_{5,6'}$ 2.1 Hz, H-6'), 4.07 (1H, ddd, $J_{4,5}$ 9.1 Hz, H-5), 4.16 (1H, dd, $J_{2,3}$ 0.9 Hz, $J_{3,4}$ 3.4 Hz, H-3), 4.40 (1H, br s, H-2), 4.46 (1H, dd, H-4), 4.52, 4.60 (2H, ABq, J_{AB} 11.6 Hz, $PhC\underline{H}_2$), 4.54, 4.85 (2H, ABq, J_{AB} 11.5 Hz, $PhC\underline{H}_2$), 4.62 (2H, s, $PhC\underline{H}_2$), 5.61 (1H, d, $J_{1,2}$ 4.0 Hz, H-1), 7.11-7.42 (19H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 21.1 (q, $ArCH_3$), 71.4 (t, C-6), 72.2, 72.6, 73.4 (3 x t, 3 x $Ph\underline{C}H_2$), 75.7, 75.8 (2 x d, C-2, C-5), 79.3 (d, C-4), 83.4 (d, C-3), 92.8 (d, C-1), 127.4, 127.4, 127.5, 127.6, 127.8, 128.2, 128.3, 128.4, 129.8, 132.2 (10 x d, Ar-CH), 130.0, 137.6, 137.7, 138.5, 138.8 (5 x s, Ar-C); *m/z* (ES^+) 615 ($M+NH_4^+$+MeCN, 15), 574 ($M+NH_4^+$, 32), 557 ($M+H^+$, 11%). (HRMS Calcd. for $C_{34}H_{40}NO_5S$ (MNH_4^+) 574.2627. Found 574.2623). (Found: C, 73.16; H, 6.54. $C_{34}H_{36}O_5S$ requires C, 73.35; H, 6.52%).

para-*Tolyl 3,5,6-tri*-O-*benzyl-1-thio-β-D-glucofuranoside 164β*

para-Tolyl 2-*O*-acetyl-3,5,6-tri-*O*-benzyl-1-thio-β-D-glucofuranoside **165β** (195 mg, 0.33 mmol) was dissolved in methanol (5 ml), THF (10 ml) and *n*-propylamine (5 ml) and stirred at RT. After 14 h, tlc (petrol:ethyl acetate, 2:1) indicated complete consumption of starting material (R_f 0.7) and formation of a major product (R_f 0.6). The reaction mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (petrol:ethyl acetate, 4:1→3:1) to afford *para*-tolyl 3,5,6-tri-*O*-benzyl-1-thio-β-D-glucofuranoside **164β** (2.10 g, 91%) as a colourless oil; $[\alpha]_D^{25}$ -132.2 (*c*, 1.25 in $CHCl_3$); ν_{max} 3406 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.34 (3H, s, $ArCH_3$), 2.40 (1H, d, $J_{OH,2}$ 3.8 Hz, OH-2), 3.75 (1H, dd, $J_{5,6}$ 5.2 Hz, $J_{6,6'}$ 10.7 Hz, H-6), 3.91 (1H, dd, $J_{5,6'}$ 2.0 Hz, H-6'), 4.04 (1H, dd, $J_{2,3}$ 1.2 Hz, $J_{3,4}$ 4.3 Hz, H-3), 4.17 (1H, ddd, $J_{4,5}$ 9.0 Hz, H-5), 4.37 (1H, br s, H-2), 4.39 (1H, dd, H-4), 4.46, 4.62 (2H, ABq, J_{AB} 11.6 Hz, $PhC\underline{H}_2$), 4.50, 4.76 (2H, ABq, J_{AB} 11.2 Hz, $PhC\underline{H}_2$), 4.61 (2H, s, $PhC\underline{H}_2$), 5.19 (1H, d, $J_{1,2}$ 2.4 Hz, H-1), 7.09-7.40 (19H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 21.1 (q, $ArCH_3$), 70.6 (t, C-6), 72.0, 72.6, 73.4 (3 x t, 3 x $PhCH_2$), 76.3 (d, C-5), 79.5 (d, C-2), 80.7 (d, C-4), 83.2 (d, C-3), 93.2 (d, C-1), 127.4, 127.6, 127.7, 128.2, 128.3, 128.4, 129.7, 131.4 (8 x d, Ar-CH), 131.8, 137.1, 137.7, 138.5, 138.7 (5 x s, Ar-C); *m/z* (ES^+) 615 ($M+NH_4^+$+MeCN, 8), 574 ($M+NH_4^+$, 18), 557 ($M+H^+$, 6%). (HRMS Calcd. for $C_{34}H_{40}NO_5S$ (MNH_4^+) 574.2627. Found 574.2627).

para-*Tolyl* 2-O-*allyl*-3,5,6-*tri*-O-*benzyl*-1-*thio*-α-D-*glucofuranoside* 142α

para-Tolyl 3,5,6-tri-*O*-benzyl-1-thio-α-D-glucofuranoside **164α** (80 mg, 0.14 mmol) was dissolved in anhydrous DMF (2 ml) and cooled to 0 °C. Allyl bromide (25 μl, 0.29 mmol) was added then sodium hydride (60% in mineral

oil) (12 mg, 0.29 mmol) was added. After 30 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a single product (R_f 0.7) and little remaining starting material (R_f 0.6). After a further 30 min, the reaction mixture was partitioned between ether (50 ml) and ammonium chloride (30 ml of a saturated aqueous solution). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 8:1) to afford *para*-tolyl 2-*O*-allyl-3,5,6-tri-*O*-benzyl-1-thio-α-D-glucofuranoside **142α** (76 mg, 89%) as a colourless oil; $[\alpha]_D^{23}$ +76.3 (*c*, 1.2 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.34 (3H, s, $ArCH_3$), 3.72 (1H, dd, $J_{5,6}$ 6.0 Hz, $J_{6,6'}$ 10.6 Hz, H-6), 3.93 (1H, dd, $J_{5,6'}$ 2.1 Hz, H-6′), 4.04-4.09 (3H, m, H-5, $OC\underline{H}_2CH=CH_2$), 4.11-4.15 (2H, m, H-2, H-3), 4.45 (1H, dd, $J_{3,4}$ 3.6 Hz, $J_{4,5}$ 8.9 Hz, H-4), 4.55, 4.87 (2H, ABq, J_{AB} 11.7 Hz, $PhC\underline{H}_2$), 4.57, 4.60 (4H, 2 x s, 2 x $PhC\underline{H}_2$), 5.23 (1H, dq, J_Z 10.4 Hz, J 1.4 Hz, $CH=CH_E\underline{H}_Z$), 5.34 (1H, dq, J_E 17.2 Hz, J 1.6 Hz, $CH=C\underline{H}_EH_Z$), 5.69 (1H, d, $J_{1,2}$ 4.6 Hz, H-1), 5.92 (1H, ddt, J 5.6 Hz, $C\underline{H}=CH_2$), 7.08-7.42 (19H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 21.1 (q, $ArCH_3$), 71.6, 72.0, 72.2, 72.6, 73.4 (5 x t, C-6, 3 x $Ph\underline{C}H_2$, $O\underline{C}H_2CH=CH_2$), 75.9, 78.7, 81.6, 83.2 (4 x d, C-2, C-3, C-4, C-5), 90.9 (d, C-1), 117.8 (t, $CH=\underline{C}H_2$), 127.4, 127.4, 127.6, 127.6, 127.7, 127.9, 128.3, 128.3, 128.4, 129.5, 131.5, 134.0 (12 x d, Ar-CH, $\underline{C}H=CH_2$), 132.2, 136.7, 137.7, 138.5, 138.9 (5 x s, Ar-C); *m/z* (ES^+) 619 ($M+Na^+$, 28), 614 ($M+NH_4^+$, 100), 597 ($M+H^+$, 5%). (HRMS Calcd. for $C_{37}H_{44}NO_5S$ (MNH_4^+) 614.2940. Found 614.2946).

para-*Tolyl* 2-O-*allyl*-3,5,6-*tri*-O-*benzyl*-1-*thio*-β-D-*glucofuranoside* 142β

para-Tolyl 3,5,6-tri-*O*-benzyl-1-thio-β-D-glucofuranoside **164β** (2.1 g, 3.78 mmol) was dissolved in anhydrous DMF (10 ml) and cooled to 0 °C. Allyl bromide (0.65 ml, 7.55 mmol) then sodium hydride (60% in mineral oil) (300 mg, 7.55 mmol) were added. After 1 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a single product (R_f 0.5) and little remaining starting material (R_f 0.2). The reaction mixture was partitioned between ether (100 + 50 ml) and water (100 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ether, 4:1) to afford *para*-tolyl 2-*O*-allyl-3,5,6-tri-*O*-benzyl-1-thio-β-D-glucofuranoside **142β** (2.12 g, 94%) as a colourless oil; $[\alpha]_D^{23}$ -99.9 (*c*, 2.0 in $CHCl_3$); ν_{max} 1646 (w, C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.34 (3H, s, $ArCH_3$), 3.74 (1H, dd, $J_{5,6}$ 5.3 Hz, $J_{6,6'}$ 10.7 Hz, H-6), 3.93 (1H, dd, $J_{5,6'}$ 2.0 Hz, H-6′), 3.97-4.00 (2H, m, $OC\underline{H}H'CH=CH_2$), 4.10-4.12 (2H, m, H-2, H-3), 4.20 (1H, ddd, $J_{4,5}$ 9.1 Hz, H-5), 4.31 (1H, dd, $J_{3,4}$ 3.8 Hz, H-4), 4.52, 4.62 (2H, ABq, J_{AB} 11.6 Hz, $PhC\underline{H}_2$), 4.52, 4.80 (2H, ABq, J_{AB} 11.6 Hz, $PhC\underline{H}_2$), 4.62 (2H, s, $PhC\underline{H}_2$), 5.20 (1H, dq, J_Z 10.4 Hz, J 1.5 Hz, $CH=CH_E\underline{H}_Z$), 5.26 (1H, dq, J_E 17.3 Hz, J 1.7 Hz, $CH=C\underline{H}_EH_Z$), 5.30 (1H, d, $J_{1,2}$ 1.7 Hz, H-1), 5.84 (1H, ddt, J 5.5 Hz, $C\underline{H}=CH_2$), 7.09-7.42 (19H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 21.1 (q, $ArCH_3$), 70.6, 70.8, 72.0, 72.5, 73.4 (5 x t, C-6, 3 x $Ph\underline{C}H_2$, $O\underline{C}H_2CH=CH_2$), 76.2, 81.2, 81.3, 86.3 (4 x d, C-2, C-3, C-4, C-5), 91.0 (d, C-1), 117.6 (t, $CH=\underline{C}H_2$), 127.4, 127.4, 127.6, 127.6, 127.7, 127.8, 128.2, 128.3, 128.4, 129.6, 131.4, 133.9 (12 x d, Ar-CH, $\underline{C}H=CH_2$), 131.9, 137.0, 137.7, 138.6, 138.9 (5 x s, Ar-C); *m/z* (ES^+) 619 ($M+Na^+$, 33), 614 ($M+NH_4^+$, 100), 597 ($M+H^+$, 7%). (HRMS Calcd. for $C_{37}H_{44}NO_5S$ (MNH_4^+) 614.2940. Found 614.2938).

para-*Tolyl* 3,5,6-*tri*-O-*benzyl*-2-O-*prop*-1'-*enyl*-1-*thio*-α-D-*glucofuranoside* *168α*

Wilkinson's catalyst (20 mg, 0.022 mmol) was dissolved in anhydrous THF (1 ml) and degassed. Butyl lithium (1.6M solution in hexanes) (20 µl, 0.032 mmol) was added and the mixture stirred for 10 min. *para*-Tolyl 2-*O*-allyl-3,5,6-tri-*O*-benzyl-1-thio-α-D-glucofuranoside **142α** (69 mg, 0.12 mmol) was dissolved in anhydrous THF (2 ml) and heated to 70 °C. The catalyst solution was added by cannula under Ar. After 1 h 30 min, tlc (petrol:ether, 4:1) indicated formation of a single product (R_f 0.5) and complete consumption of starting material (R_f 0.4). The reaction was allowed to cool then diluted with CH_2Cl_2 (*ca* 5 ml) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 8:1) to afford *para*-tolyl 3,5,6-tri-*O*-benzyl-2-*O*-prop-1'-enyl-1-thio-α-D-glucofuranoside **168α** (62 mg, 90%) as a colourless oil; Partial data: δ_H (400 MHz, $CDCl_3$) (*E*:Z, 1:2.2), *E* isomer 1.53 (3H, dd, *J* 1.7 Hz, *J* 6.8 Hz, OCH=CHC$\underline{H}_3$), 2.33 (3H, s, ArCH_3), 5.67 (1H, d, $J_{1,2}$ 4.3 Hz, H-1), 6.00 (1H, daq, J_E 12.4 Hz, *J* 1.4 Hz, OC$\underline{H}$=CH); *Z* isomer 1.62 (3H, dd, *J* 1.8 Hz, *J* 6.8 Hz, OCH=CHC$\underline{H}_3$), 2.33 (3H, s, ArCH_3), 5.68 (1H, d, $J_{1,2}$ 4.2 Hz, H-1), 5.86 (1H, daq, J_Z 6.0 Hz, *J* 1.7 Hz, OC$\underline{H}$=CH); δ_C (50.3 MHz, $CDCl_3$) *E* isomer 12.4 (q, OCH=CH$\underline{C}H_3$), 21.1 (q, ArCH_3), 90.2 (d, C-1), 102.6 (d, OCH=$\underline{C}$H); *Z* isomer 9.5 (q, OCH=CH$\underline{C}H_3$), 21.1 (q, ArCH_3), 90.6 (d, C-1), 104.0 (d, OCH=$\underline{C}$H), 143.8 (d, O$\underline{C}$H=CH); *m/z* (ES^+) 619 ($M+Na^+$, 87%); ($APCI^+$) 652 (M+56, 7), 614 ($M+NH_4^+$, 3), 597 ($M+H^+$, 3%). (HRMS Calcd. for $C_{37}H_{44}NO_5S$ (MNH_4^+) 614.2940. Found 614.2935).

para-*Tolyl* 3,5,6-*tri*-O-*benzyl*-2-O-*prop*-1′-*enyl*-1-*thio*-β-D-*glucofuranoside* *168β*

Wilkinson's catalyst (320 mg, 0.35 mmol) was dissolved in anhydrous THF (6 ml) and degassed. Butyl lithium (1.6M solution in hexanes) (0.32 ml, 0.52 mmol) was added and the mixture stirred for 10 min. *para*-Tolyl 2-*O*-allyl-3,5,6-tri-*O*-benzyl-1-thio-β-D-glucofuranoside **142β** (2.07 g, 3.47 mmol) was dissolved in anhydrous THF (6 ml) and heated to 70 °C. The catalyst solution was added by cannula under Ar. After 2 h, tlc (CH_2Cl_2:petrol, 4:1) indicated formation of a two products (R_f 0.45 and 0.5) and complete consumption of starting material (R_f 0.4). The reaction was allowed to cool then diluted with CH_2Cl_2 (*ca* 5 ml) and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 8:1) to afford *para*-tolyl 3,5,6-tri-*O*-benzyl-2-*O*-prop-1′-enyl-1-thio-β-D-glucofuranoside **168β** (1.99 g, 96%) as a colourless oil. Partial data: δ_H (400 MHz, $CDCl_3$) (*E*:*Z*, 1:1.7), *E* isomer 1.50 (3H, dd, *J* 1.5 Hz, *J* 6.7 Hz, OCH=CHC$\underline{H}_3$), 2.33 (3H, s, ArCH_3), 4.83 (1H, dq, J_E 12.5 Hz, OCH=C$\underline{H}$), 5.31 (1H, d, $J_{1,2}$ 1.2 Hz, H-1), 5.97 (1H, daq, *J* 1.5 Hz, O$\underline{C}$H=CH); *Z* isomer 1.53 (3H, dd, *J* 1.9 Hz, *J* 6.7 Hz, OCH=CHC$\underline{H}_3$), 2.33 (3H, s, ArCH_3), 5.30 (1H, d, $J_{1,2}$ 1.8 Hz, H-1), 5.84 (1H, daq, J_Z 6.2 Hz, *J* 1.7 Hz, O$\underline{C}$H=CH); δ_C (100.6 MHz, $CDCl_3$) *E* isomer 12.4 (q, OCH=CH$\underline{C}H_3$), 21.1 (q, ArCH_3), 90.8 (d, C-1), 102.6 (d, OCH=$\underline{C}$H), 143.8 (d, O$\underline{C}$H=CH); *Z* isomer 9.3 (q, OCH=CH$\underline{C}H_3$), 21.1 (q, ArCH_3), 91.1 (d, C-1), 104.4 (d, OCH=$\underline{C}$H), 142.9 (d, O$\underline{C}$H=CH); *m/z* (ES^+) 619 ($M+Na^+$, 100), 614

(M+NH_4^+, 67), 597 (M+H^+, 23%). (HRMS Calcd. for $C_{37}H_{41}O_5S$ (MH^+) 597.2675. Found 597.2674).

para-*Tolyl* 3,5,6-*tri*-O-*benzyl*-2-O-(1-(1,2:3,4-*di*-O-*isopropylidene*-α-D-*galactopyranos*-6-O-*yl*)-2-*iodopropyl*)-1-*thio*-β-D-*glucofuranoside* 169d

N-Iodosuccinimide (68 mg, 0.30 mmol), and 4Å molecular sieves were added to anhydrous dichloroethane (1 ml) and cooled to -40 °C under Ar. 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose **3d** (52 mg, 0.20 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. *para*-Tolyl 3,5,6-tri-*O*-benzyl-2-*O*-prop-1′-enyl-1-thio-β-D-glucofuranoside **168β** (60 mg, 0.1 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. The reaction was stirred and allowed to warm to RT. After 1 h 35 min, tlc (petrol:ethyl acetate, 6:1) indicated formation of a major product (R_f 0.2), and complete consumption of starting material (R_f 0.5). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1 with 1% Et_3N) to afford *para*-tolyl 3,5,6-tri-*O*-benzyl-2-*O*-(1-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-*O*-yl)-2-iodopropyl)-1-thio-β-D-glucofuranoside **169d** (107 mg, 75%) as a colourless oil. *m/z* (ES^+) 1005 (M+Na^+, 41), 1000 (M+NH_4^+, 5), 877 (M-STol+NH_4^+, 25%). (HRMS Calcd. for $C_{49}H_{63}NO_{11}SI$ (MNH_4^+) 1000.3167. Found 1000.3170).

para-*Tolyl* 3,5,6-*tri*-O-*benzyl*-2-O-(2-*iodo*-1-(*methyl* 2,3,4-*tri*-O-*benzyl*-α-D-*mannopyranosid*-6-O-*yl*)*propyl*)-1-*thio*-β-D-*glucofuranoside* 169e

Method 1: *N*-Iodosuccinimide-mediated tethering

N-Iodosuccinimide (113 mg, 0.50 mmol), and 4Å molecular sieves were added to anhydrous dichloroethane (1 ml) and cooled to -40 °C under Ar. Methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **3e** (156 mg, 0.34 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. *para*-Tolyl 3,5,6-tri-*O*-benzyl-2-*O*-prop-1'-enyl-1-thio-β-D-glucofuranoside **168β** (100 mg, 0.17 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. The reaction was stirred and allowed to warm to RT. After 9 h, tlc (petrol:ethyl acetate, 6:1) indicated formation of a single major product (R_f 0.7), and complete consumption of starting material (R_f 0.8). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 40 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 7:1) to afford *para*-tolyl 3,5,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranosid-6-*O*-yl)propyl)-1-thio-β-D-glucofuranoside **169e** (106 mg, 53%) as a colourless oil; *m/z* (ES^+) 1245 ($M+NH_4^+$+MeCN, 55), 1209 ($M+Na^+$, 100), 1204 ($M+NH_4^+$, 92%).

Method 2: Tethering using I_2, AgOTf and DTBMP

Iodine (55 mg, 0.22 mmol), silver trifluoromethanesulfonate (56 mg, 0.22 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (116 mg, 0.57 mmol) and 4Å molecular sieves were added to freshly distilled CH_2Cl_2 (1 ml) and cooled to -78 °C under Ar. Methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **3e** (82 mg, 0.18 mmol) was dissolved in freshly distilled CH_2Cl_2 (2 ml) and added by cannula under Ar. *para*-Tolyl 3,5,6-tri-*O*-benzyl-2-*O*-prop-1'-enyl-1-thio-β-D-glucofuranoside **168β** (100 mg, 0.17 mmol) was dissolved in freshly distilled CH_2Cl_2 (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to RT. After 18 h, tlc (petrol:ethyl acetate, 6:1) indicated formation of a single major product (R_f 0.7), and little remaining starting material (R_f 0.8). The reaction was quenched with sodium thiosulfate (40 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 40 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 7:1) to afford *para*-tolyl 3,5,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranosid-6-*O*-yl)propyl)-1-thio-β-D-glucofuranoside **169e** (128 mg, 64%) as a colourless oil as previously described;

Also recovered *para*-tolyl 3,5,6-tri-*O*-benzyl-2-*O*-prop-1'-enyl-1-thio-β-D-glucofuranoside **168β** (20 mg, 20%).

***para*-Tolyl 3,5,6-tri-O-benzyl-2-O-(2-iodo-1-(methyl 2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranosid-3-O-yl)propyl)-1-thio-β-D-glucofuranoside 169g**

Iodine (55 mg, 0.22 mmol), silver trifluoromethanesulfonate (56 mg, 0.22 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (116 mg, 0.57 mmol) and 4Å molecular sieves were added to freshly distilled CH_2Cl_2 (1 ml) and cooled to -78 °C under Ar. Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **3g** (65 mg, 0.18 mmol) was dissolved in freshly distilled CH_2Cl_2 (2 ml) and added by cannula under Ar. *para*-Tolyl 3,5,6-tri-*O*-benzyl-2-*O*-prop-1′-enyl-1-thio-β-D-glucofuranoside **168β** (100 mg, 0.17 mmol) was dissolved in freshly distilled CH_2Cl_2 (2 ml) and added to the reaction vessel by cannula under Ar. The reaction was allowed to warm to RT. After 17 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a two major products (R_f 0.55 and 0.5), and little remaining starting material (R_f 0.6). The reaction was quenched with sodium thiosulfate (40 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 40 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 7:1→3:1) to afford *para*-tolyl 3,5,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosid-3-*O*-yl)propyl)-1-thio-β-D-glucofuranoside **169g** (161 mg, 88%) as a colourless oil; *m/z* (ES^+) 1153 ($M+NH_4^+$+MeCN, 22), 1117 ($M+Na^+$, 58%);

Also recovered *para*-tolyl 3,5,6-tri-*O*-benzyl-2-*O*-prop-1′-enyl-1-thio-β-D-glucofuranoside **168β** (9 mg, 9%).

para-*Tolyl* *3,5,6-tri*-O-*benzyl*-2-O-(*1*-(*1,2:3,4-di*-O-*isopropylidene*-α-*D*-*galactopyranos*-6-O-*yl*)-*2-iodopropyl*)-*1-thio*-α-*D*-*glucofuranoside* 172

N-Iodosuccinimide (68 mg, 0.30 mmol), and 4Å molecular sieves were added to anhydrous dichloroethane (1 ml) and cooled to -40 °C under Ar. 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose **3d** (52 mg, 0.20 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. *para*-Tolyl 3,5,6-tri-*O*-benzyl-2-*O*-prop-1'-enyl-1-thio-α-D-glucofuranoside **168α** (60 mg, 0.1 mmol) was dissolved in anhydrous dichloroethane (1.5 ml) and added to the reaction vessel by cannula under Ar. The reaction was stirred and allowed to warm to RT. After 1 h 35 min, tlc (petrol:ethyl acetate, 6:1) indicated formation of two products (R_f 0.2 and 0.1), and complete consumption of starting material (R_f 0.5). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) then extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1 with 1% Et_3N) to afford *para*-tolyl 3,5,6-tri-*O*-benzyl-2-*O*-(1-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-*O*-yl)-2-iodopropyl)-1-thio-α-D-glucofuranoside **172** (25 mg, 22%) as a colourless oil. *m/z* (APCI$^+$) 1038 (M+56, 15), 1000 (M+NH_4^+, 27%). (HRMS Calcd. for $C_{49}H_{63}NO_{11}SI$ (MNH_4^+) 1000.3167. Found 1000.3168);

Also isolated *para*-tolyl 3,5,6-tri-*O*-benzyl-1-thio-α-D-glucofuranoside **164α** (30 mg, 54%); and recovered *para*-tolyl 3,5,6-tri-*O*-benzyl-2-*O*-prop-1'-enyl-1-thio-α-D-glucofuranoside **168α** (3 mg, 5%); and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **3d** (43 mg, 0.17 mmol).

3,5,6-Tri-O-benzyl-α-D-glucofuranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 170d

Method 1: From the 1,2-*trans* thioglycoside starting material **169d**

para-Tolyl 3,5,6-tri-*O*-benzyl-2-*O*-(1-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-*O*-yl)-2-iodopropyl)-1-thio-β-D-glucofuranoside **169d** (85 mg, 0.087 mmol) was dissolved in anhydrous dichloroethane (7 ml). 2,6-Di-*tert*-butyl-4-methylpyridine (35 mg, 0.17 mmol), *N*-iodosuccinimide (59 mg, 0.26 mmol) and silver trifluoromethanesulfonate (22 mg, 0.087 mmol) were added and the mixture stirred under Ar at RT. After 6 h, tlc (petrol:ethyl acetate, 3:1) indicated the complete consumption of starting material (R_f 0.6) and the formation of a major product (R_f 0.3). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) and extracted with CH_2Cl_2 (2 x 30 ml). The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1) to afford 3,5,6-tri-*O*-benzyl-α-D-glucofuranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **170d** (44 mg, 75%) as a colourless oil; $[\alpha]_D^{22}$ -18.2 (*c*, 0.55 in $CHCl_3$); ν_{max} 3467 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.33, 1.34, 1.46, 1.53 (12H, 4 x s, 4 x CH_3), 3.68 (1H, dd, $J_{5,6}$ 6.1 Hz, $J_{6,6'}$ 10.5 Hz, H-6_b), 3.79 (1H, dd, $J_{5,6}$ 7.9 Hz, $J_{6,6'}$ 10.0 Hz, H-6_a), 3.86-3.90 (2H, m, H-$6'_a$, H-$6'_b$), 4.03 (1H, ddd, $J_{4,5}$ 8.4 Hz, $J_{5,6'}$2.0 Hz, H-5_b), 4.06-4.11 (2H, m, H-5_a, H-3_b), 4.27-4.29 (2H, m, H-4_a, H-2_b), 4.33 (1H, dd, $J_{1,2}$ 5.1 Hz, $J_{2,3}$ 2.3 Hz, H-2_a), 4.37 (1H, dd, $J_{3,4}$ 4.3 Hz,, H-4_b), 4.52, 4.70 (2H, ABq, J_{AB} 11.8 Hz, PhC$\underline{H}_2$), 4.54, 4.80 (2H, ABq, J_{AB} 11.6 Hz, PhC$\underline{H}_2$), 4.58 (2H, s, PhC$\underline{H}_2$), 4.58-4.61 (1H, m, H-3_a), 5.21 (1H, d, $J_{1,2}$ 4.4 Hz, H-1_b), 5.52 (1H, d,

H-1_a), 7.16-7.37 (15H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 24.4, 24.9, 25.9, 26.1 (4 x q, 4 x CH_3), 65.5 (d, C-5_a), 67.1 (t, C-6_a), 70.5, 70.5, 70.8, 75.5 (4 x d, C-2_a, C-3_a, C-4_a, C-2_b), 71.3, 71.7, 72.6, 73.3 (4 x t, 3 x Ph$\underline{C}H_2$, C-6_b), 76.0 (d, C-5_b), 78.2 (d, C-4_b), 83.7 (d, C-3_b), 96.3 (d, C-1_a), 102.4 (d, C-1_b), 108.9, 109.3 (2 x s, 2 x $\underline{C}(CH_3)_2$), 127.3, 127.4, 127.4, 127.5, 127.5, 127.6, 128.2, 128.3, 128.3 (9 x d, Ar-CH), 137.9, 138.6, 138.9 (3 x s, Ar-C); *m/z* (ES^+) 751 ($M+NH_4^+$+MeCN, 22%), 715 ($M+Na^+$, 26), 710 ($M+NH_4^+$, 100%). (HRMS Calcd. for $C_{39}H_{52}NO_{11}$ (MNH_4^+) 710.3540. Found 710.3541).

Method 2: From the 1,2-*cis* thioglycoside starting material **172**

para-Tolyl 3,5,6-tri-*O*-benzyl-2-*O*-(1-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-*O*-yl)-2-iodopropyl)-1-thio-α-D-glucofuranoside **172** (22 mg, 0.022 mmol) was dissolved in anhydrous dichloroethane (2 ml). 2,6-Di-*tert*-butyl-4-methylpyridine (9 mg, 0.044 mmol), *N*-iodosuccinimide (15 mg, 0.067 mmol) and silver trifluoromethanesulfonate (6 mg, 0.022 mmol) were added and the mixture stirred under Ar at RT. After 5 h, tlc (petrol:ethyl acetate, 3:1) indicated the complete consumption of starting material (R_f 0.6) and the formation of a major product (R_f 0.3). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) and extracted with CH_2Cl_2 (2 x 30 ml). The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 3:1→2:1) to afford 3,5,6-tri-*O*-benzyl-α-D-glucofuranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **170d** (4 mg, 26%) as a colourless oil identical to that previously described;

Methyl 3,5,6-tri-O-benzyl-α-D-glucofuranosyl-(1→6)-2,3,4-tri-O-benzyl-α-D-mannopyranoside 170e

para-Tolyl 3,5,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranosid-6-*O*-yl)propyl)-1-thio-β-D-glucofuranoside **169e** (103 mg, 0.087 mmol) was dissolved in anhydrous dichloroethane (7 ml). 2,6-Di-*tert*-butyl-4-methylpyridine (35 mg, 0.17 mmol), *N*-iodosuccinimide (59 mg, 0.26 mmol) and silver trifluoromethanesulfonate (22 mg, 0.087 mmol) were added and the mixture stirred under Ar at RT. After 5 h, tlc (petrol:ethyl acetate, 3:1) indicated the complete consumption of starting material (R_f 0.7) and the formation of a major product (R_f 0.3). The reaction was quenched with sodium thiosulfate (30 ml of a 10% aqueous solution) and extracted with CH_2Cl_2 (2 x 30 ml). The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1) to afford methyl 3,5,6-tri-*O*-benzyl-α-D-glucofuranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **170e** (30 mg, 39%) as a colourless oil; $[\alpha]_D^{22}$ +35.6 (*c*, 0.5 in $CHCl_3$); ν_{max} 3383 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.31 (3H, s, OCH_3), 3.63 (1H, dd, $J_{5,6}$ 6.7 Hz, $J_{6,6'}$ 10.5 Hz, H-6_b), 3.68-3.71 (1H, m, H-5_a), 3.79-3.82 (2H, m, H-2_a, H-6_a), 3.84 (1H, dd, $J_{5,6'}$ 1.9 Hz, H-$6'_b$), 3.89 (1H, dd, $J_{2,3}$ 2.9 Hz, $J_{3,4}$ 9.6 Hz, H-3_a), 4.01-4.07 (2H, m, H-4_a, H-5_b), 4.09 (1H, dd, $J_{2,3}$ 2.0 Hz, $J_{3,4}$ 4.4 Hz, H-3_b), 4.18 (1H, dd, $J_{5,6'}$ 3.6 Hz, $J_{6,6'}$ 11.3 Hz, H-$6'_a$), 4.25 (1H, dd, $J_{1,2}$ 4.3 Hz, H-2_b), 4.34 (1H, dd, $J_{4,5}$ 8.0 Hz, H-4_b), 4.46 (2H, s, PhC$\underline{H}_2$), 4.49, 4.67 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.55, 4.81 (2H, ABq, J_{AB} 11.6 Hz, PhC$\underline{H}_2$), 4.63 (2H, s, PhC$\underline{H}_2$), 4.67, 4.93 (2H,

ABq, J_{AB} 10.8 Hz, PhC$\underline{H}_2$), 4.69, 4.77 (2H, ABq, J_{AB} 12.2 Hz, PhC$\underline{H}_2$), 4.70 (1H, s, H-1_a), 5.28 (1H, d, H-1_b), 7.23-7.38 (30H, m, Ar-H); δ_C (100.6 MHz, $CDCl_3$) 54.8 (q, OCH_3), 67.6 (t, C-6_a), 71.3 (d, C-5_a), 71.7, 72.1, 72.1, 72.7, 72.8, 73.2, 75.1 (7 x t, 6 x Ph$\underline{C}H_2$, C-6_b), 74.4, 74.5 (2 x d, C-2_a, C-4_a), 75.6 (d, C-2_b), 76.3 (d, C-5_b), 78.4 (d, C-4_b), 79.9 (d, C-3_a), 83.7 (d, C-3_b), 99.0 (d, C-1_a), 102.6 (d, C-1_b), 127.2, 127.3, 127.4, 127.5, 127.5, 127.5, 127.6, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.3 (14 x d, Ar-CH), 138.0, 138.1, 138.4, 138.4, 138.6, 139.0 (6 x s, Ar-C); *m/z* (ES^+) 919 ($M+Na^+$, 54), 914 ($M+NH_4^+$, 100%). (HRMS Calcd. for $C_{55}H_{64}NO_{11}$ (MNH_4^+) 914.4479. Found 914.4467).

Methyl 3,5,6-tri-O-benzyl-α-D-glucofuranosyl-(1→3)-2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside 170g

Dimethyl disulfide (24 µl, 0.26 mmol) and methyl trifluoromethanesulfonate (30 µl, 0.26 mmol) were dissolved in freshly distilled CH_2Cl_2 (1 ml) and stirred under Ar at RT. After 5 min, 2,6-di-*tert*-butyl-4-methylpyridine (68 mg, 0.33 mmol) was added and the mixture cooled to 0 °C. *para*-Tolyl 3,5,6-tri-*O*-benzyl-2-*O*-(2-iodo-1-(methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranosid-3-*O*-yl)propyl)-1-thio-β-D-glucofuranoside **169g** (72 mg, 0.066 mmol) was dissolved in freshly distilled CH_2Cl_2 (2 ml) and added by cannula under Ar. After 5 h, tlc (petrol:ethyl acetate, 3:1) indicated very little remaining starting material (R_f 0.6) and the formation of major (R_f 0.4) and minor (R_f 0.4-0.5) products. The reaction was quenched with Et_3N and the mixture partitioned between ether (40 ml) and brine (40 ml). The aqueous layer was re-extracted with ether (20 ml) and the combined organic extracts

dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 7:2) to afford methyl 3,5,6-tri-*O*-benzyl-α-D-glucofuranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **170g** (17 mg, 32%) as a colourless oil; $[\alpha]_D^{22}$ +12.8 (*c*, 0.5 in $CHCl_3$); ν_{max} 3498 (br, OH) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.37 (3H, s, OCH_3), 3.67 (1H, dd, $J_{5,6}$ 5.7 Hz, $J_{6,6'}$ 10.8 Hz, H-6_b), 3.78-3.89 (4H, m, H-2_a, H-5_a, H-6_a, H-$6'_b$), 4.00 (1H, ddd, $J_{4,5}$ 8.0 Hz, $J_{5,6'}$ 2.1 Hz, H-5_b), 4.04 (1H, dd, $J_{2,3}$ 2.3 Hz, $J_{3,4}$ 4.5 Hz, H-3_b), 4.14 (1H, at, *J* 9.5 Hz, H-4_a), 4.23-4.28 (3H, m, H-3_a, H-$6'_a$, H-2_b), 4.35 (1H, dd, H-4_b), 4.48, 4.67 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.52, 4.75 (2H, ABq, J_{AB} 11.6 Hz, PhC$\underline{H}_2$), 4.52, 4.56 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.59, 4.67 (2H, ABq, J_{AB} 12.0 Hz, PhC$\underline{H}_2$), 4.67 (1H, d, $J_{1,2}$ 1.3 Hz, H-1_a), 5.28 (1H, d, $J_{1,2}$ 4.5 Hz, H-1_b), 5.59 (1H, s, PhC$\underline{H}$), 7.23-7.47 (25H, m, Ar-H); δ_C (125.7 MHz, $CDCl_3$) 54.8 (q, OCH_3), 63.8 (d, C-5_a), 68.7 (t, C-6_a), 70.7 (t, C-6_b), 71.4, 72.3, 73.2, 73.8 (4 x t, 4 x Ph$\underline{C}H_2$), 75.2 (d, C-3_a), 75.9, 76.0 (2 x d, C-2_b, C-5_b), 78.0, (d, C-2_a, C-4_a, C-4_b), 83.4 (d, C-3_b), 100.2 (d, C-1_a), 101.5 (d, Ph$\underline{C}$H), 102.8 (d, C-1_b), 125.9, 127.2, 127.3, 127.3, 127.4, 127.5, 127.7, 128.1, 128.1, 128.2, 128.3, 128.9 (12 x d, Ar-CH), 137.2, 137.7, 137.9, 138.5, 138.8 (5 x s, Ar-C); *m/z* (ES^+) 827 ($M+Na^+$, 46), 822 ($M+NH_4^+$, 100%). (HRMS Calcd. for $C_{48}H_{56}NO_{11}$ (MNH_4^+) 822.3853. Found 822.2863).

Appendix 1. Diastereomeric Distributions of Mixed Acetals

Table A1.1: diastereomeric ratios for mixed acetals **56** from *gluco* SMe enol ethers **51** (Z/E, 71:29)

entry	ROH	*v*	*w*	*x*	*y*
1	**3a**	49	40	11	
2	**3b**	54	37	9	
3	**3c**	60	6	34	
4	**3d**	17	71	12	
5	**3e**	55	36	9	
6	**3f**	48	38	14	
7	**3g**	71	29		

All reactions were carried out with NIS in DCE;

Assignment (*v*, *w*, *x*, *y*) of each diastereomer is entirely arbitrary.

Table A1.2: Comparison of diastereomeric distribution of mixed acetals **56** from forward and reverse tethering reactions on *gluco* SMe donor

entry			*E:Z*	*v*	*w*	*x*	*y*
1	**3d**	Forward		17	71	12	
2		Reverse	33:67	8	10	38	44
3	**3f**	Forward		48	38	14	
4		Reverse	40:60	3		28	69

All reactions were carried out with NIS in DCE;

Assignment (*v*, *w*, *x*, *y*) of each diastereomer is entirely arbitrary, but for each aglycon is the same in the forward as in the reverse tethering approach.

Table A1.3: diastereomeric ratios for mixed acetals **86** from *manno* fluoride enol ethers **81** (Z/E, 72:28)

Entry	ROH	*v*	*w*	*x*	*y*
1 [c]	**3a**	47	35	18	
2 [c]	**3a**	47	35	18	
3 [d]	**3b**	39	28	19	14
4 [d]	**3c**	65	35		
5 [d]	**3d**	68	32		
6 [c]	**3e**	68	32		
7 [c, d, e]	**3g**	64	19	17	
8 [d]	**3i**	66	34		
9 [a,e]	**3j**	76	24		
10 [d]	**3j**	58	21	21	
11 [b]	**3j**	100			
12 [b, d, e]	**3k**	78	11	11	

All reactions carried out with NIS in DCE unless otherwise stated; [a] Carried out using I_2, AgOTf, collidine, DCM; [b] Carried out using I_2, AgOTf, DTBMP, DCM;
Identified by integration of signals in the ^{1}H NMR; [c] OCH_3; [d] H-1 (mannose); [e] $CHIC\underline{H}_3$;
Assignment (*v*, *w*, *x*, *y*) of each diastereomer is entirely arbitrary. Where the same compound is listed more than once, this diastereomeric assignment is the same in all cases.

Table A1.4: diastereomeric ratios for mixed acetal producs **82** of tethering reactions to *gluco* β-fluoride enol ethers **80** (Z/E, 70:30)

entry	ROH	*v*	*w*	*x*	*y*
1 [c, e]	**3a**	57	17	17	9
2 [e]	**3b**	48	27	14	11
3 [e]	**3d**	69 (2 isomers)		31 (2 isomers)	
4 [e]	**3e**	62	38		
5 [e]	**3e**	70	30		
6 [e]	**3e**	67	33		
7 [e]	**3g**	57	43		
8 [c]	**3h**	65	35		

All reactions carried out with NIS in DCE unless otherwise stated; [a] Carried out using I_2, AgOTf, collidine, DCM; [b] Carried out using I_2, AgOTf, DTBMP, DCM;
Identified by integration of signals in the ^1H NMR; [c] OCH_3; [d] H-1 (mannose); [e] $CHIC\underline{H}_3$;
Assignment (*v*, *w*, *x*, *y*) of each diastereomer is entirely arbitrary. Where the same compound is listed more than once, this diastereomeric assignment is the same in all cases.

Table A1.5: diastereomeric ratios for mixed acetal products**105** of tethering reactions to *gluco* α-fluoride enol ethers **104** (Z/E, 71:29)

entry	ROH	*v*	*w*	*x*	*y*
1	**3a**	44	28	17	14
3	**3e**	42	42	16	
2	**3g**	38	38	24	

All reactions carried out with NIS in DCE unless otherwise stated; [a] Carried out using I_2, AgOTf, collidine, DCM; [b] Carried out using I_2, AgOTf, DTBMP, DCM;
Identified by integration of signals in the ^{1}H NMR; [c] OCH_3; [d] H-1 (mannose); [e] $CHIC\underline{H}_3$;
Assignment (*v*, *w*, *x*, *y*) of each diastereomer is entirely arbitrary.

Table A1.6: diastereomeric ratios for mixed acetal products **149*v-y*** of tethering reactions of methanol **3a** to BDA-protected *rhamno* enol ethers **148**

entry	E:Z	*v* (5.46)	*w* (5.43)	*x* (5.41)	*y* (5.36)
1	33:67	6	17	60	17
2	68:32	17	8	25	50
3	0:100	3	23	71	3
4	100:0	22	4	4	70

All reactions carried out with NIS in DCE; Identified by integration of H-1 signals in the ^{1}H NMR;
Assignment (*v*, *w*, *x*, *y*) of each diastereomer is arbitrarily based on the chemical shift of H-1, given in parentheses.

Table A1.8: diastereomeric ratios for the mixed acetal products **159** of tethering reactions to benzyl-protected *rhamno* enol ethers **158** (*Z*/*E*, 42:58)

entry	ROH	*v*	*w*	*x*	*y*
1[c]	**3a**	33	27	25	15
2[c,e]	**3f**	45	24	24	6
3[b,e]	**3g**	64	19	17	

All reactions carried out with NIS in DCE unless otherwise stated; [b] Carried out using I_2, AgOTf, DTBMP, DCM;

Identified by integration of signals in the ^{1}H NMR; [c] OCH_3; [e] $CHIC\underline{H}_3$;

Assignment (*v*, *w*, *x*, *y*) of each diastereomer is entirely arbitrary.

Table A1.9: diastereomeric ratios for the mixed acetal products **169**, **172** of tethering reactions to benzyl-protected *glucofurano* enol ethers **168** (*Z*/*E*, 42:58)

entry	Donor	ROH	E/Z	*v*	*w*	*x*	*y*
1[e]	**168**β	**3d**	44:56	40	30	15	15
2	**168**β	**3e**	30:70	63	27	10	
3[b, c]	**168**β	**3e**	30:70	63	29	8	
4[b, e]	**168**β	**3g**	30:70	50	41	9	
5[d]	**168**α	**3d**	32:68	46	33	21	

All reactions carried out with NIS in DCE unless otherwise stated; [b] Carried out using I_2, AgOTf, DTBMP, DCM;

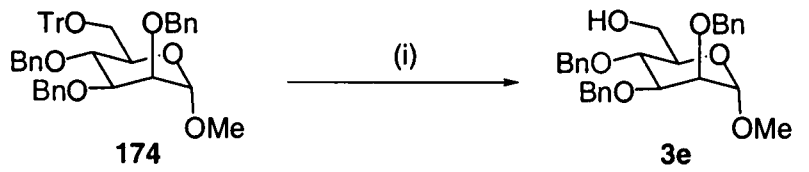
Identified by integration of signals in the ^{1}H NMR; [c] OCH_3; [d] H-1; [e] $CHIC\underline{H}_3$;

Assignment (*v*, *w*, *x*, *y*) of each diastereomer is entirely arbitrary. Where the same compound is listed more than once, this diastereomeric assignment is the same in all cases.

Appendix 2. Synthesis of Aglycon Alcohols 3e and 3g

A2.1 Synthesis of Mannose Aglycon With OH-6 Free 3e

The 6-hydroxyl of mannose was accessed *via* a selectively tritylated compound **174**.[1] Thus the fully protected sugar **174** was heated in ethanol and acetic acid[2] to hydrolyse the trityl group, giving the tribenzyl derivative **3e** in 81% yield (Scheme A2.1).

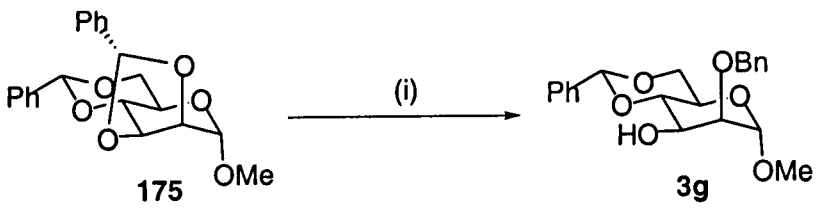


174 **3e**

Scheme A2.1: (i) EtOH, AcOH, H_2O, 80°C, 81%

A2.2 Synthesis of Mannose Aglycon With OH-3 Free 3g

The 3-hydroxyl of mannose was accessed *via* a reductive ring-opening of the *endo*-dibenzylidene **175** according to a modification of Liptak's original procedure[3]. Thus dibenzylidene **175**[4] was treated with DiBAlH in toluene at -40 °C, and good selectivity for reductive ring-opening of the 2,3- over the 4,6-benzylidene was seen. Moreover, this reduction occurred in a further selective fashion, such that the desired 2-*O*-benzyl derivative **3g** was formed as the major product in 87% yield. None of the undesired 3-*O*-benzyl isomer **176** was isolated (Scheme A2.2).



175 **3g**

Scheme A2.2: (i) $(^{i}Bu)_2AlH$, PhMe, -40 °C, 87%

A2.3 Experimental

Methyl 2,3,4-tri-O-benzyl-α-D-mannopyranoside 3e

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-trityl-α-D-mannopyranoside **174** (2.05 g, 2.91 mmol) was dissolved in ethanol (40 ml) and acetic acid (50% in water) (40 ml) and stirred at 80 °C. After 5 h, tlc (petrol:ethyl acetate, 3:1) indicated formation of a single product (R_f 0.2) and no remaining starting material (R_f 0.7). The reaction mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (petrol:ethyl acetate 4:1→1:1) to afford methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **3e** (1.09 g, 81%) as a colourless oil; $[\alpha]_D^{24}$ +33.0 (*c*, 1.0 in $CHCl_3$) [Lit. +29 (*c*, 0.2 in $CHCl_3$)];[5] δ_H (400 MHz, $CDCl_3$) 3.31 (3H, s, OCH_3), 3.63 (1H, ddd, $J_{4,5}$ 9.2 Hz, $J_{5,6}$ 4.5 Hz, $J_{5,6'}$ 3.0 Hz, H-5), 3.76-3.81 (2H, m, H-2, H-6) 3.85 (1H, dd, $J_{6,6'}$ 11.5 Hz, H-6'), 3.90 (1H, dd, $J_{2,3}$ 2.9 Hz, $J_{3,4}$ 9.5 Hz, H-3), 3.98 (1H, at, J 9.5 Hz, H-4), 4.65 (2H, s, $PhCH_2$), 4.66, 4.95 (2H, ABq, J_{AB} 11.4 Hz, $PhCH_2$), 4.70, 4.80 (2H, ABq, J_{AB} 12.4 Hz, $PhCH_2$), 4.71 (1H, d, $J_{1,2}$ 1.7 Hz, H-1), 7.27-7.39 (10H, m, Ar-H).

Methyl 2-O-benzyl-4,6-O-benzylidene-α-D-mannopyranoside 3g

Endo methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside **175** (4.06 g, 10.9 mmol) was dissolved in toluene (50 ml) and cooled to -40 °C. Di-*iso*-butyl aluminium hydride (1.5M solution in toluene) (8.0 ml, 12.1 mmol) was added and the reaction mixture stirred under Ar. After 20 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a single product (R_f 0.6) and remaining starting material (R_f 0.8). Further di-*iso*-butyl aluminium hydride (1.5M

solution in toluene) (8.0 ml, 12.1 mmol) was added and the reaction mixture stirred under Ar. After a further 20 min, tlc (petrol:ethyl acetate, 3:1) indicated formation of a single product (R_f 0.6) and very little remaining starting material (R_f 0.8). The reaction was quenched by the dropwise addition of methanol (10 ml). The mixture was diluted with CH_2Cl_2 (450 ml) and washed with H_2O (200 ml). Brine (200 ml) and ethyl acetate (250 ml) were added in order to facilitate the separation. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate 3:1) and recrystallised from ethanol to afford methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **3g** (3.57 g, 87%) as white crystals, m.p. 84-85 °C (ether/petrol) [lit 85-87 °C (ether/petrol)];[6] $[\alpha]_D^{26}$ +0.8 (*c*, 1.0 in $CHCl_3$) [Lit. +3 (*c*, 1.0 in $CHCl_3$)];[6] δ_H (200 MHz, $CDCl_3$) 2.36 (1H, d, $J_{OH,3}$ 8.0 Hz, OH-3), 3.37 (3H, s, OCH_3), 3.41-3.96 (4H, m, H-2, H-4, H-5, H-6) 4.09 (1H, ddd, $J_{2,3}$ 3.7 Hz, $J_{3,4}$ 9.3 Hz, H-3), 4.27 (1H, dd, $J_{5,6'}$ 3.7 Hz, $J_{6,6'}$ 9.1 Hz, H-6'), 4.69, 4.77 (2H, ABq, J_{AB} 11.8 Hz, $PhCH_2$), 4.76 (1H, d, $J_{1,2}$ 1.6 Hz, H-1), 5.59 (1H, s, PhCH), 7.27-7.53 (10H, m, Ar-H).

References for Appendix 2

1. I am grateful to Richard Tennant-Eyles for a supply of this compound.

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6. Bernlind, C.; Oscarson, S.; Widmalm, G. *Carbohydr.Res.*, **1994**, *263*; 173-180

Appendix 3. NMR Spectra for Glycosyl Iodide 101

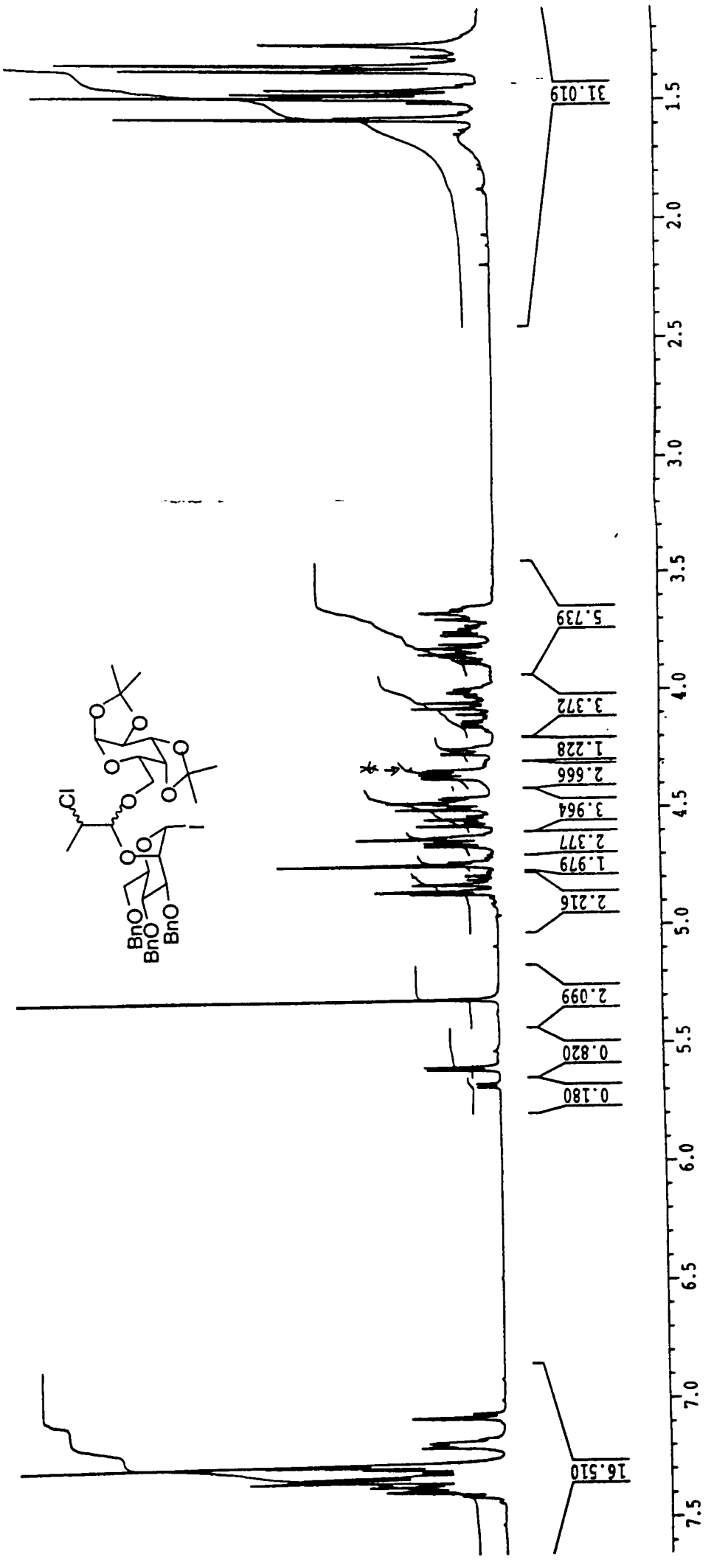


Figure A3.1: 400 MHz ^{1}H spectrum of iodide **101**

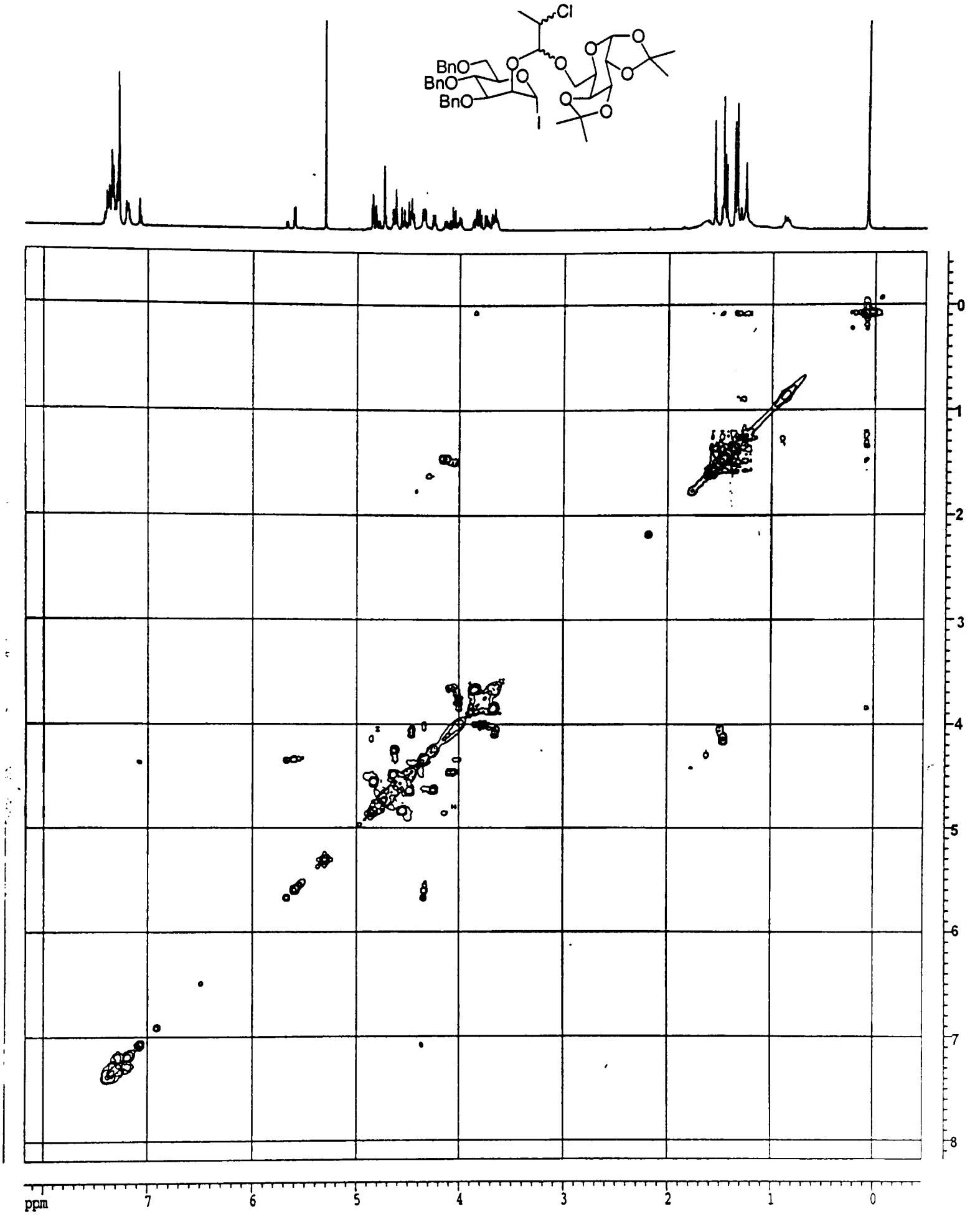


Figure A3.2: 400 MHz COSY spectrum of iodide **101**

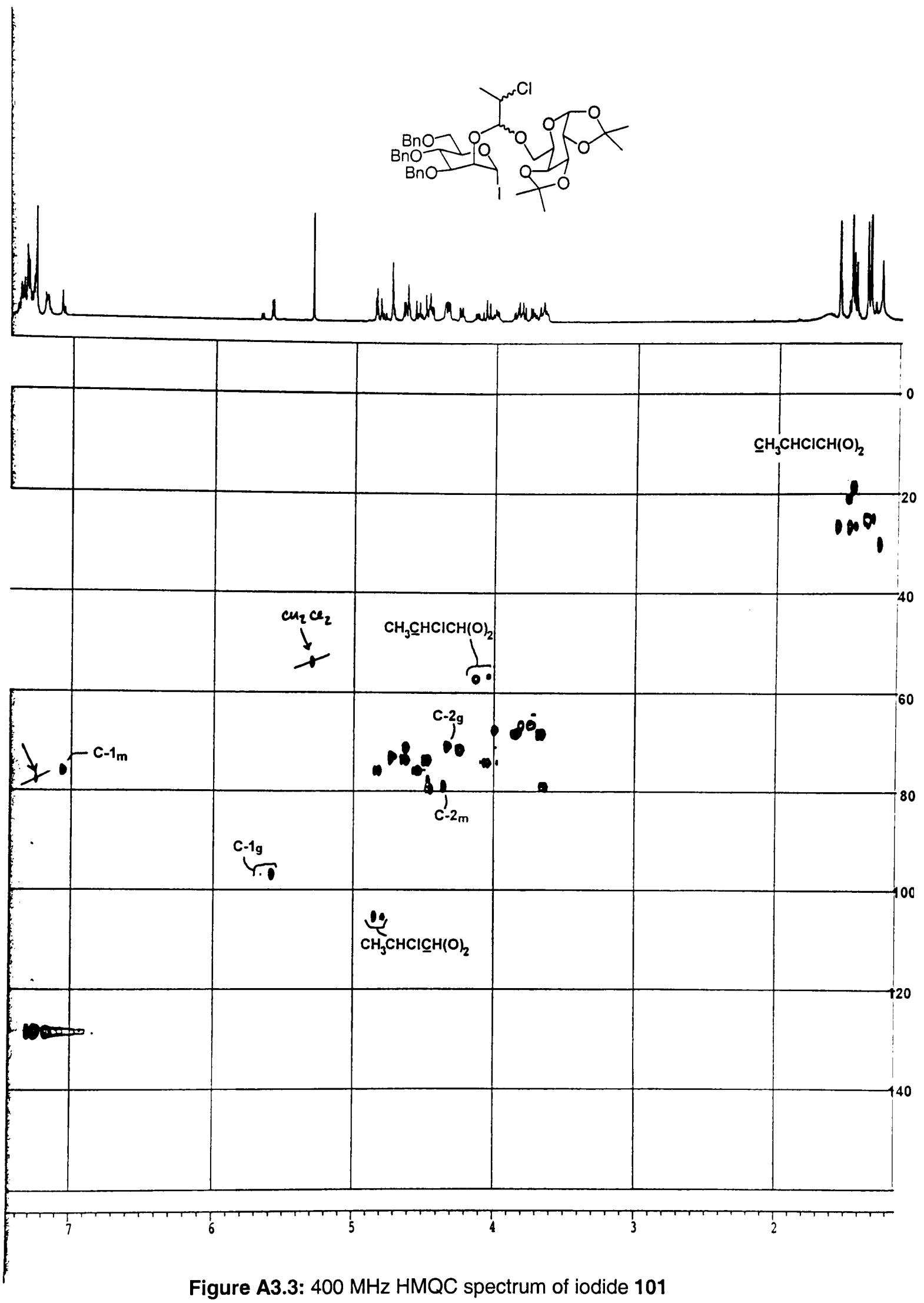


Figure A3.3: 400 MHz HMQC spectrum of iodide **101**

Appendix 4. NMR Spectra for Tethered Material 109

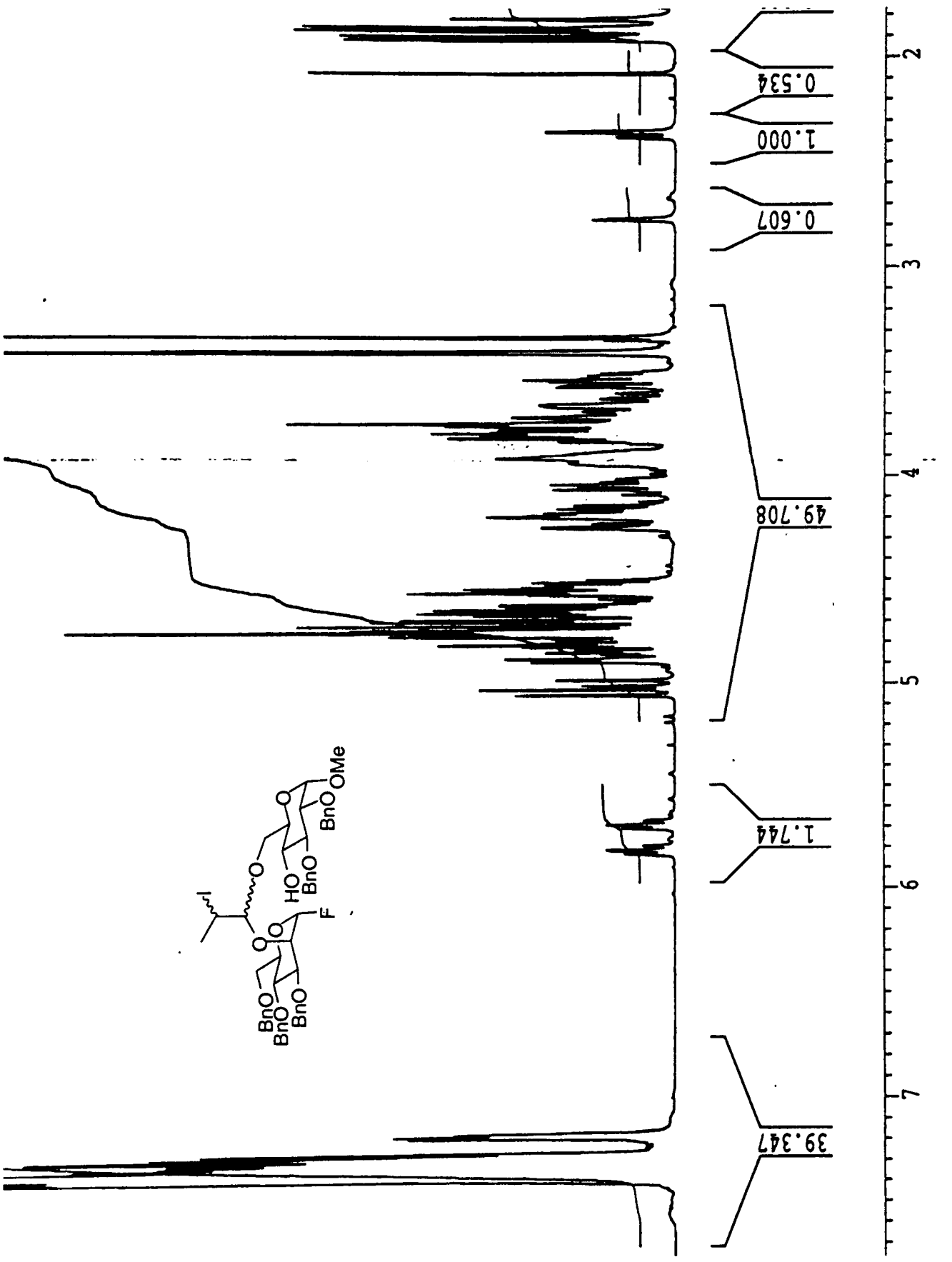


Figure A4.1: 400 MHz ^{1}H spectrum of tethered material **109**

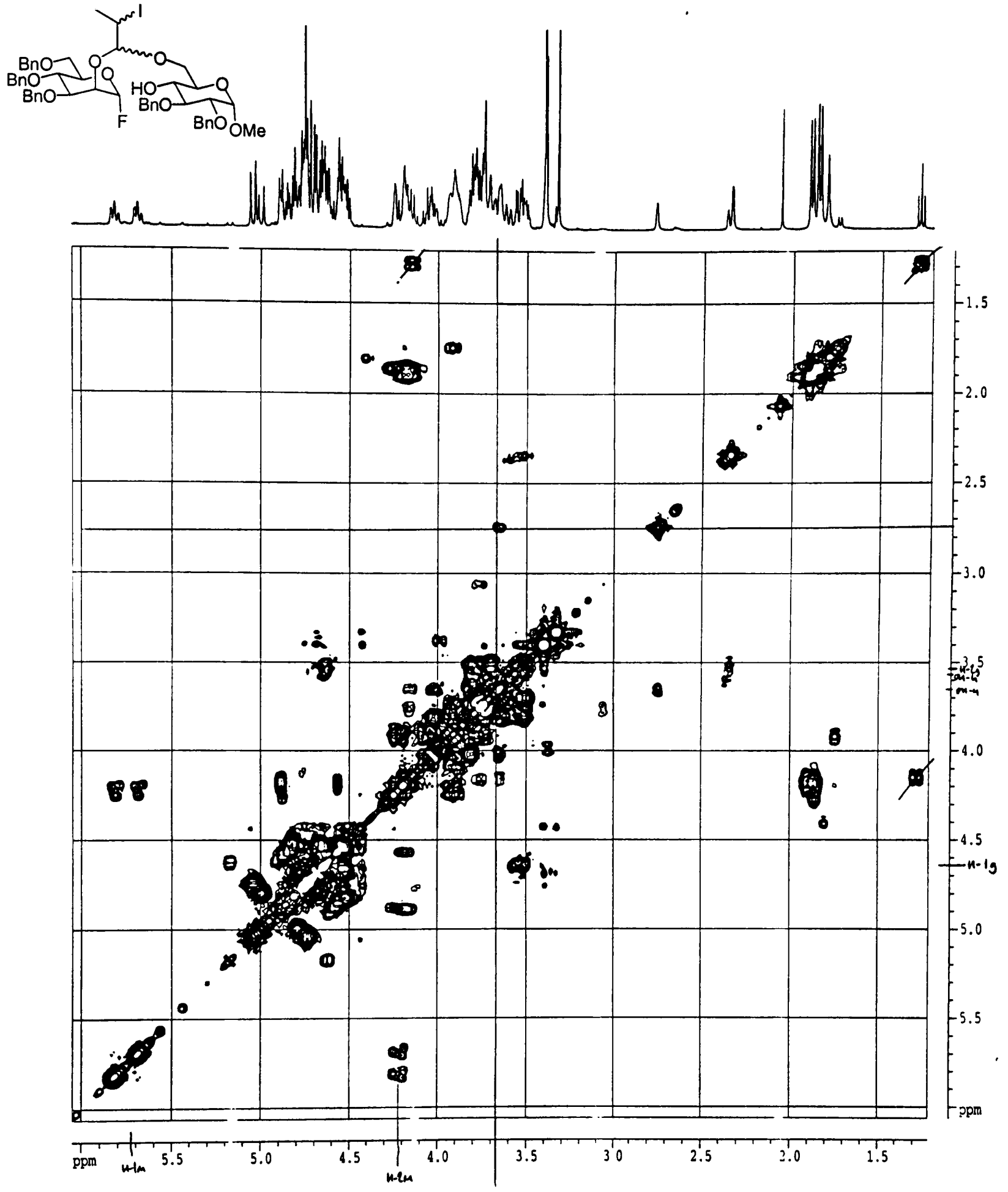


Figure A4.2: 400 MHz COSY spectrum of tethered material **109**

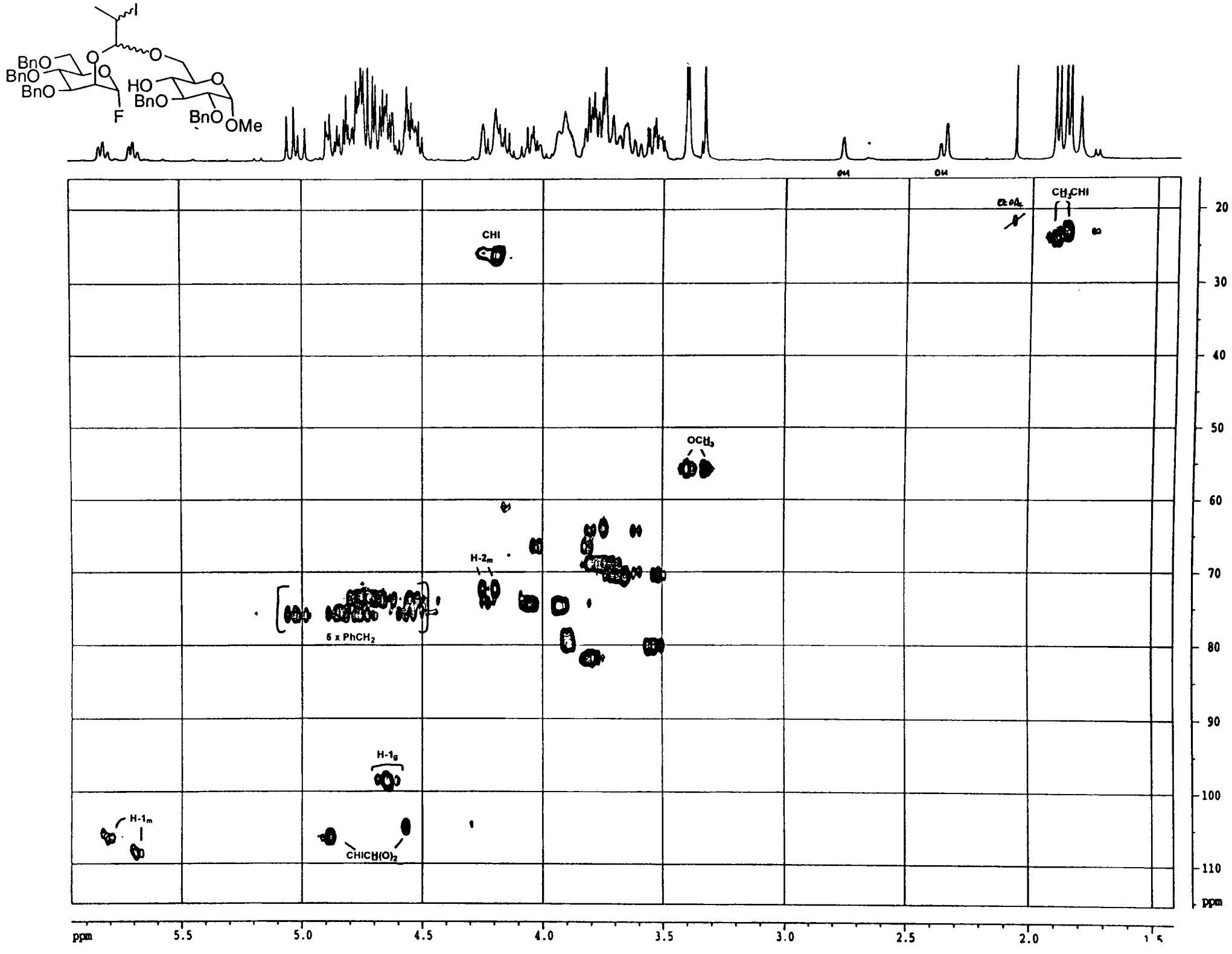


Figure A4.3: 400 MHz edited HSQC spectrum of tethered material **109**

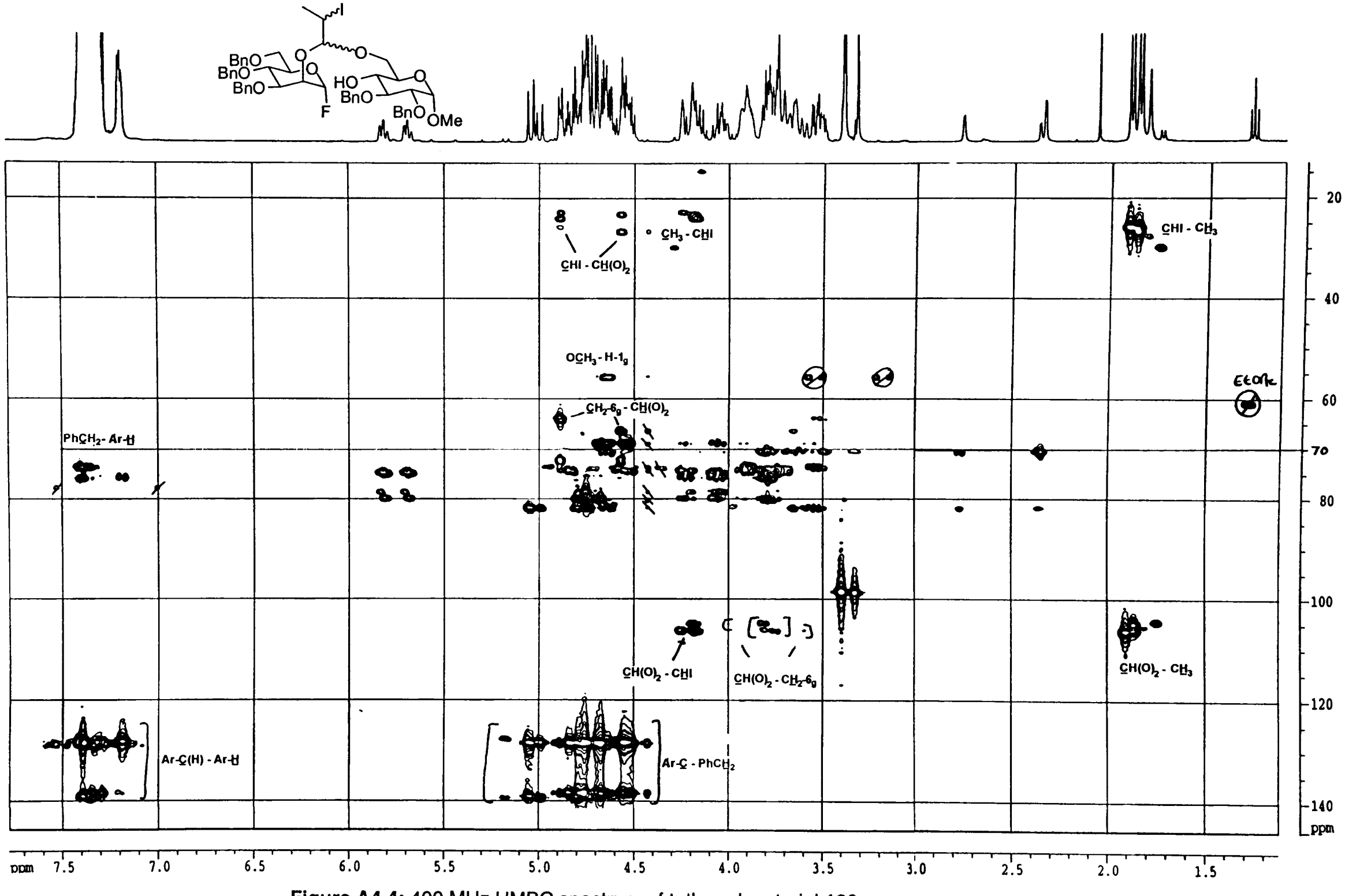


Figure A4.4: 400 MHz HMBC spectrum of tethered material **109**

Appendix 5. NMR Spectrum for Deprotected Tetrasaccharide 117 [1]

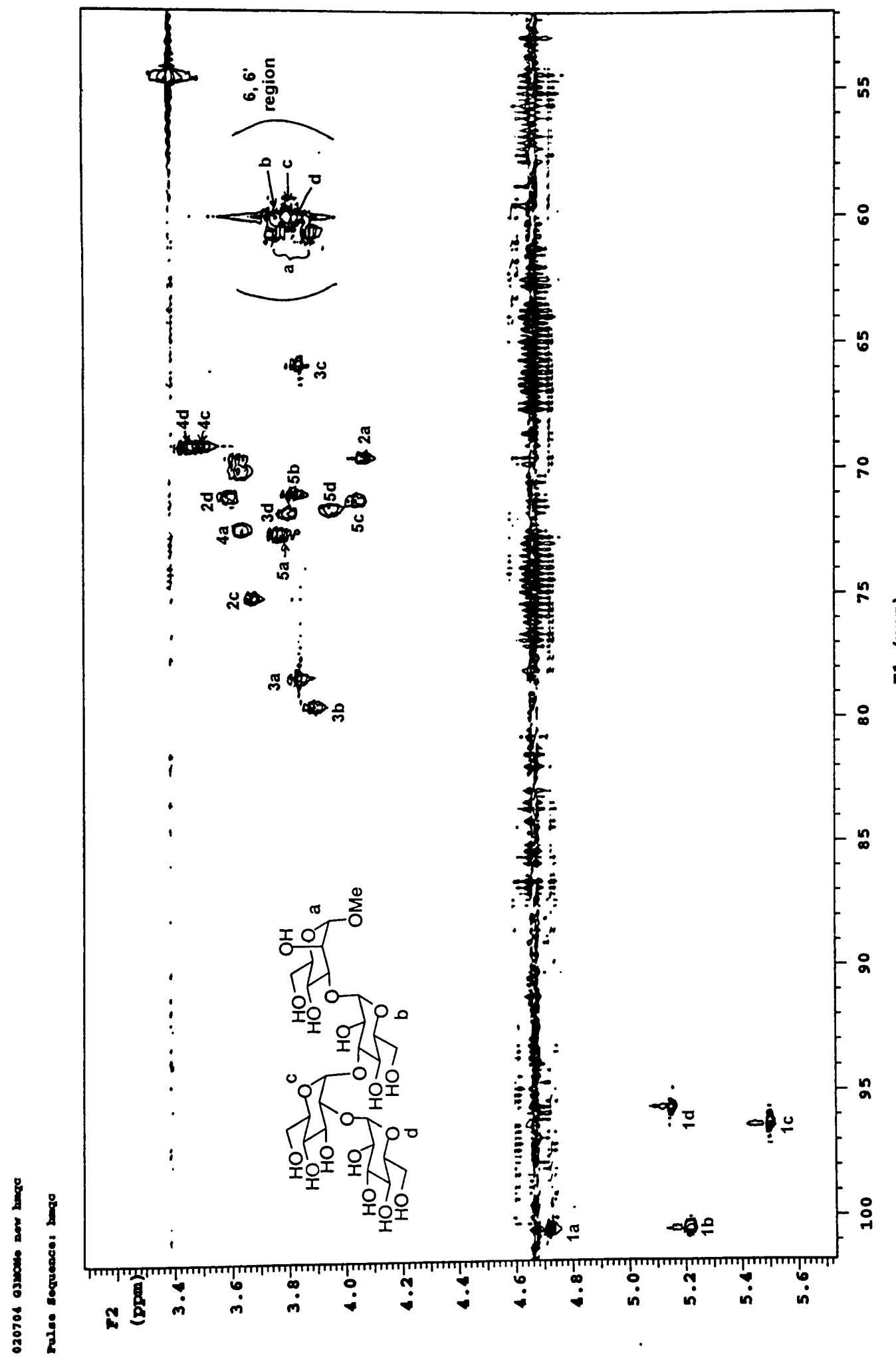
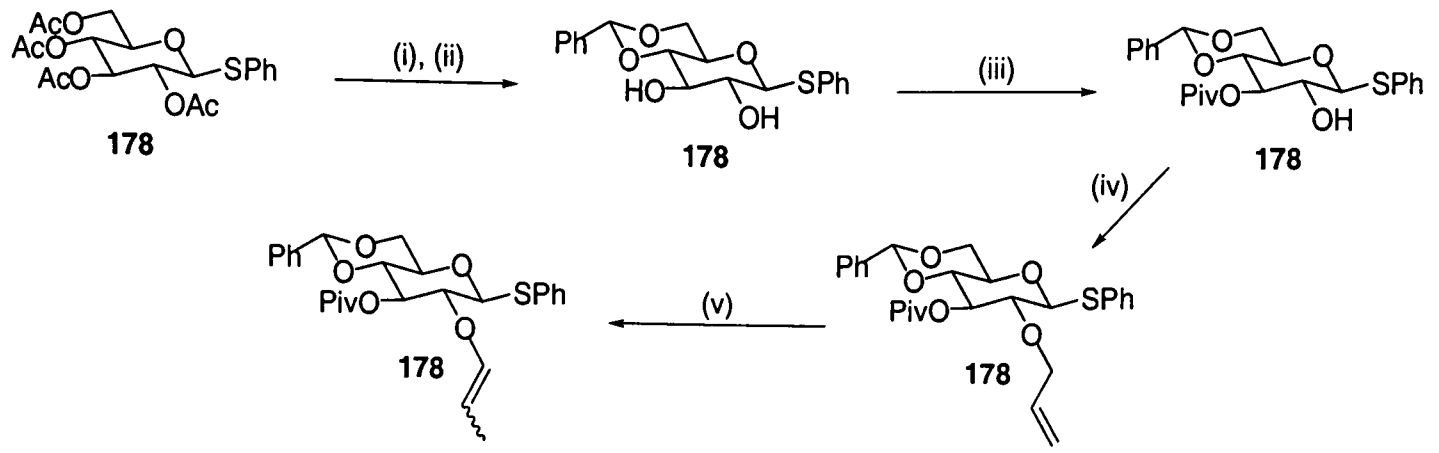


Figure A5.1: HMQC spectrum of deprotected tetrasaccharide **117**

[1] Spectrum acquired and assigned by Mukram Mackeen

Appendix 6. Synthesis of a 4,6-Benzylidene-Protected Donor for Allyl-Mediated IAD

The 4,6-protection was introduced by Liptak's method.[1] Thus, thioglycoside **177** was deacetylated with sodium methoxide,[2] and the residue treated with benzylidene dimethylacetal under reduced pressure in the presence of an acid catalyst. The monobenzylidene derivative **178** was isolated in good yield. Regioselective pivaloylation was carried out with pivaloyl chloride in pyridine to give the 3-*O*-pivaloyl compound **179** in good yield,[3] along with a small quantity of the fully protected sugar **180**. Allylation of alcohol **179** using sodium hydride and allyl bromide[4] was carried out in good yield to give the 2-*O*-allyl-protected donor **181**. Care was needed though, to ensure that the pivaloyl ester was not hydrolysed under the basic reaction conditions. It was necessary to carry out the reaction under strictly anhydrous conditions, and once finished, to quench with saturated ammonium chloride solution, thus rapidly neutralising the mixture. Allyl isomerisation was carried out under Boons and Isles' conditions[5] to give the enol ethers **93** in excellent yield (Scheme A6).



Scheme A6: (i) Na, MeOH, RT; (ii) $PhCH(OMe)_2$, DMF, CSA, 60°C, 260-280 mbar, 89%; (iii) PivCl, pyridine, 0°C, 60%; (iv) allyl bromide, NaH, DMF, 0°C, 70%; (v) Wilkinson's Catalyst, BuLi, THF, 70°C, 92%;

Experimental

Phenyl 4,6-O-benzylidene-1-thio-β-D-glucopyranoside 178

Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose **177** (5.00 g, 10.96 mmol) was suspended in methanol (50 ml). Sodium (185 mg, 8.04 mmol) was dissolved in methanol (20 ml) and added to the sugar solution by pipette. The reaction mixture was stirred under Ar. After 25 min, tlc (ethyl acetate:methanol, 4:1) indicated formation of a product (R_f 0.7) and complete consumption of starting material (R_f 0.9). 1M HCl was added until pH 7 was reached, then the mixture was concentrated *in vacuo*.

The crude residue was suspended in anhydrous DMF (15 ml). Benzaldehyde dimethyl acetal (3.3 ml, 21.9 mmol) and camphorsulfonic acid (254 mg, 1.1 mmol) were added. The reaction mixture was stirred on a rotary evaporator at 60 °C, 260-280 mbar. After 1 h, tlc (ethyl acetate) indicated formation of a product (R_f 0.7) and complete consumption of starting material (R_f 0). Triethylamine (6 ml) was added, and the mixture was diluted with

CH_2Cl_2 (200 ml) and washed with water (150 + 100 ml). The combined aqueous washes were then re-extracted with CH_2Cl_2 (80 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by recrystallisation to afford phenyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside **178** (3.68 g, 89%) as a white, crystalline solid, m.p. 180-181 °C (ethyl acetate/petrol) [Lit. 188 °C][6]; $[\alpha]_D^{23}$ -47.5 (*c*, 1.0 in $CHCl_3$) [Lit. -56 (*c*, 0.2 in $CHCl_3$)][6]; δ_H (400 MHz, $CDCl_3$) 2.74 (1H, br s, OH-2), 2.89 (1H, br s, OH-3), 3.48 (1H, at, *J* 9.2 Hz, H-2), 3.49-3.56 (2H, m, H-4, H-5), 3.79 (1H, at, *J* 10.0 Hz, H-6), 3.86 (1H, at, *J* 8.8 Hz, H-3), 4.39 (1H, dd, $J_{5,6'}$ 4.3 Hz, $J_{6,6'}$ 10.5 Hz, H-6'), 4.65 (1H, d, $J_{1,2}$ 9.2 Hz, H-1), 5.54 (1H, s, PhC<u>H</u>), 7.34-7.57 (10H, m, Ar-H).

Phenyl 4,6-O-benzylidene-3-O-pivaloyl-1-thio-β-D-glucopyranoside 179

Phenyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside **178** (700 mg, 1.86 mmol) was dissolved in pyridine (4 ml) and cooled to -20°C. Pivaloyl chloride (0.46 ml, 3.72 mmol) was added and the reaction mixture was stirred under Ar. After 4 h, tlc (ethyl acetate:petrol, 1:3) indicated formation of a product (R_f 0.5) and complete consumption of starting material (R_f 0.1). The mixture was diluted with EtOAc (100 ml) and washed with 1M HCl (100 ml), sodium bicarbonate (100 ml of a saturated aqueous solution), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2:diethyl ether, 30:1) to afford phenyl 4,6-*O*-benzylidene-3-*O*-pivaloyl-1-thio-β-D-glucopyranoside **179** (512 mg, 60%) as a white, crystalline solid, m.p. 134-135 °C (methanol) [Lit. 131-132 °C][3]; $[\alpha]_D^{22}$

-78.7 (*c*, 1.0 in $CHCl_3$) [Lit. -71.2 (*c*, 0.68 in $CHCl_3$)][3]; δ_H (400 MHz, $CDCl_3$) 1.23 (9H, s, $C(CH_3)_3$), 2.89 (1H, d, $J_{OH,2}$ 3.2 Hz, OH-2), 3.55-3.60 (2H, m, H-2, H-5), 3.67 (1H, at, *J* 9.5 Hz, H-4), 3.80 (1H, at, *J* 10.2 Hz, H-6), 4.41 (1H, dd, $J_{5,6'}$ 4.8 Hz, $J_{6,6'}$ 10.5 Hz, H-6'), 4.72 (1H, d, $J_{1,2}$ 9.8 Hz, H-1), 5.19 (1H, at, *J* 9.2 Hz, H-3), 5.53 (1H, s, PhC<u>H</u>), 7.33-7.57 (10H, m, Ar-H).

also recrystallisation from diethyl ether/petrol of mixed fractions gave further phenyl 4,6-*O*-benzylidene-3-*O*-pivaloyl-1-thio-β-D-glucopyranoside **179** (84 mg, 10%) identical to that described above.

Also phenyl 4,6-*O*-benzylidene-2,3-di-*O*-pivaloyl-1-thio-β-D-glucopyranoside **180** (110 mg, 11%) as white crystals m.p. 149 °C; $[\alpha]_D^{26}$ -56.1 (*c*, 1.0 in $CHCl_3$); ν_{max} 1742 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.17, 1.24 (18H, 2 x s, 2 x $C(CH_3)_3$), 3.59 (1H, atd, *J* 9.7 Hz, $J_{5,6'}$ 5.0 Hz, H-5) 3.72 (1H, at, *J* 9.7 Hz, H-4), 3.82 (1H, at, *J* 10.2 Hz, H-6), 4.41 (1H, dd, $J_{6,6'}$10.7 Hz, H-6'), 4.83 (1H, d, $J_{1,2'}$ 10.3 Hz, H-1), 5.09 (1H, dd, $J_{2,3}$ 10.1 Hz, H-2), 5.40 (1H, at, *J* 9.5 Hz, H-3), 5.53 (1H, s, PhC<u>H</u>), 7.34-7.50 (10H, m, Ar-H); δ_C ($CDCl_3$) 27.0, 27.1 (2 x q, 2 x $C(\underline{C}H_3)_3$), 38.7, 38.7 (2 x s, 2 x $\underline{C}(CH_3)_3$), 68.4 (t, C-6), 69.7, 70.6, 72.2, 78.4 (4 x d, C-2, C-3, C-4, C-5), 87.2 (d, C-1), 101.0 (d, Ph<u>C</u>H), 125.8, 128.2, 128.3, 128.9, 129.0, 132.7 (6 x d, Ar-CH), 132.2, 136.8 (2 x s, Ar-C), 176.5, 177.1 (2 x s, 2 x C=O); *m/z* (ES^+) 1079 ($2M+Na^+$, 15), 567 ($M+K^+$, 29), 551 ($M+Na^+$, 100), 546 ($M+NH_4^+$, 21%). (HRMS Calcd. for $C_{29}H_{40}NO_7S$ (MNH_4^+) 546.2525. Found 546.2529). (Found: C, 65.55; H, 7.00. $C_{29}H_{36}O_7S$ requires C, 65.89; H, 6.86%).

Phenyl 2-O-allyl-4,6-O-benzylidene-3-O-pivaloyl-1-thio-β-D-glucopyranoside 181

Phenyl 4,6-*O*-benzylidene-3-*O*-pivaloyl-1-thio-β-D-glucopyranoside **179** (1.75 g, 3.94 mmol) was dissolved in anhydrous DMF (15 ml) and cooled to 0 °C. Allyl bromide (0.68 ml, 7.88 mmol) was added then sodium hydride (60% in mineral oil) (236 mg, 5.91 mmol) was added portionwise, and the reaction mixture stirred under N_2. After 25 min, tlc (ethyl acetate:petrol, 1:3) indicated formation of a single product (R_f 0.8) and very little remaining starting material (R_f 0.7). The reaction mixture was diluted with diethyl ether (200 ml) and washed with NH_4Cl (200 ml of a saturated aqueous solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by biotage (CH_2Cl_2:cyclohexane, 3:1→CH_2Cl_2) and recrystallised from ethanol to afford phenyl 2-*O*-allyl-4,6-*O*-benzylidene-3-*O*-pivaloyl-1-thio-β-D-glucopyranoside **181** (1.34 g, 70%) as white crystals, m.p. 133-135 °C; $[\alpha]_D^{22}$ –51.2 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$)) 1.23 (9H, s, $C(CH_3)_3$), 3.47 (1H, at, *J* 9.3 Hz, H-2) -3.54 (1H, atd, *J* 9.6 Hz, $J_{5,6'}$ 4.9 Hz, H-5), 3.62 (1H, at, *J* 9.4 Hz, H-4), 3.78 (1H, at, *J* 10.0 Hz, H-6), 4.12 (1H, ddat, J_{gem} 12.2 Hz, *J* 1.4 Hz, *J* 5.6 Hz, OC<u>H</u>H'CH=CH_2), 4.39 (1H, dd, $J_{6,6'}$ 10.3 Hz, H-6'), 4.37-4.41 (1H, m, OCH<u>H</u>'CH=CH_2), 4.80 (1H, d, $J_{1,2}$ 9.6 Hz, H-1), 5.17 (1H, dd, J_{gem} 1.4 Hz, J_Z 10.4 Hz, CH=CH_E<u>H_Z</u>), 5.27 (1H, daq, J_E 17.2 Hz, *J* 1.6 Hz, CH=C<u>H_E</u>H_Z), 5.37 (1H, at, *J* 9.2 Hz, H-3), 5.50 (1H, s, PhCH), 5.89 (1H, ddat, C<u>H</u>=CH_2), 7.30-7.56 (10H, m, Ar-H); δ_C ($CDCl_3$) 27.1 (q, C(<u>C</u>H_3)$_3$), 38.8 (s, <u>C</u>$(CH_3)_3$), 68.6, 74.0 (2 x t, C-6, O<u>C</u>H_2CH=CH_2), 70.2, 74.2, 78.8, 79.0 (4 x d, C-2, C-3, C-4, C-5), 88.4 (d, C-1), 101.0 (d, Ph<u>C</u>H), 117.2 (t, CH=<u>C</u>H_2), 125.8, 127.9, 128.1, 128.8, 129.0, 132.1 (6 x d, Ar-CH), 133.1, 136.9 (2 x s, Ar-C) 134.1 (d, <u>C</u>H=CH_2), 177.0 (s, C=O); *m/z* (ES^+) 991 ($2M+Na^+$, 10), 523 ($M+K^+$, 28), 507

(M+Na^+, 100%). (HRMS Calcd. for $C_{27}H_{36}NO_6S$ (MNH_4^+) 502.2263. Found 502.2248). (Found: C, 66.92; H, 6.70. $C_{27}H_{32}O_6S$ requires C, 66.92; H, 6.66%).

Phenyl 4,6-O-benzylidene-3-O-pivaloyl-2-O-prop-1'-enyl-1-thio-β-D-glucopyranoside 182

Wilkinson's catalyst (259 mg, 0.28 mmol) was dissolved in anhydrous THF (4 ml) and degassed. Butyl lithium (1.6 M solution in hexanes) (0.26 ml, 0.41 mmol) was added and the mixture stirred for 30 min. Phenyl 2-*O*-allyl-4,6-*O*-benzylidene-3-*O*-pivaloyl-1-thio-β-D-glucopyranoside **181** (1.34 g, 2.77 mmol) was dissolved in anhydrous THF (4 ml) and heated to 70 °C. The catalyst solution was added by cannular under N_2. After 2 h, tlc (diethyl ether:cyclohexane, 1:6) indicated formation of a two products (R_f 0.25 and R_f 0.3) and complete consumption of starting material (R_f 0.2). The reaction was allowed to cool then diluted with CH_2Cl_2 (20 ml) and concentrated *in vacuo*. The residue was purified by biotage (petrol:ethyl acetate, 6:1) to afford phenyl 4,6-*O*-benzylidene-3-*O*-pivaloyl-2-*O*-prop-1'-enyl-1-thio-β-D-glucopyranoside **93** (1.23 g, 92%) as a white solid. Partial data: δ_H (400 MHz, $CDCl_3$) (*E*:*Z* ratio 3:1) *E* isomer 1.50 (3H, dd, *J* 1.7 Hz, *J* 6.9 Hz, OCH=CHC$\underline{H}_3$), 4.77 (1H, d, $J_{1,2}$ 9.5 Hz, H-1), 4.97 (1H, dq, J_E 12.1 Hz, OCH=C$\underline{H}$), 5.37 (1H, at, *J* 9.2 Hz, H-3), 5.98 (1H, dd, OC$\underline{H}$=CH); *Z* isomer 1.17 (9H, s, $C(CH_3)_3$),1.56 (3H, dd, *J* 1.6 Hz, *J* 6.9 Hz, OCH=CHC$\underline{H}_3$), 3.52-3.62 (3H, m, H-2, H-4, H-5), 3.75-3.80 (1H, m, H-6), 4.36-4.73 (2H, m, H-6', OCH=C$\underline{H}$), 4.81 (1H, d, $J_{1,2}$ 9.8 Hz, H-1), 5.42 (1H, at, *J* 9.2 Hz, H-3), 5.49 (1H, s, PhC$\underline{H}$), 5.90 (1H, dd, J_Z 6.1 Hz, OC$\underline{H}$=CH); δ_C *E* isomer 12.1 (q, OCH=CH$\underline{C}H_3$), 27.0 (q, $C(\underline{C}H_3)_3$), 68.5 (t, C-6), 87.1 (d, C-1),

101.0 (d, Ph<u>C</u>H), 102.1 (d, OCH=<u>C</u>H), 146.5 (d, O<u>C</u>H=CH); Z isomer 9.3 (q, OCH=CH<u>C</u>H_3), 27.0 (q, C(<u>C</u>H_3)$_3$), 68.5 (t, C-6), 70.4, 73.5, 78.5, 80.5 (4 x d, C-2, C-3, C-4, C-5), 87.1 (d, C-1), 101.0 (d, Ph<u>C</u>H), 101.8 (d, OCH=<u>C</u>H), 125.8, 128.1, 128.9, 133.1 (4 x d, Ar-CH), 132.0, 136.8 (2 x s, Ar-C), 145.8 (d, O<u>C</u>H=CH), 176.9 (s, C=O); *m/z* (thermospray$^+$) 502 (M+NH_4^+, 100%).

References for Appendix 6

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Appendix 7. NOE Spectra for Glucofuranosyl Derivatives

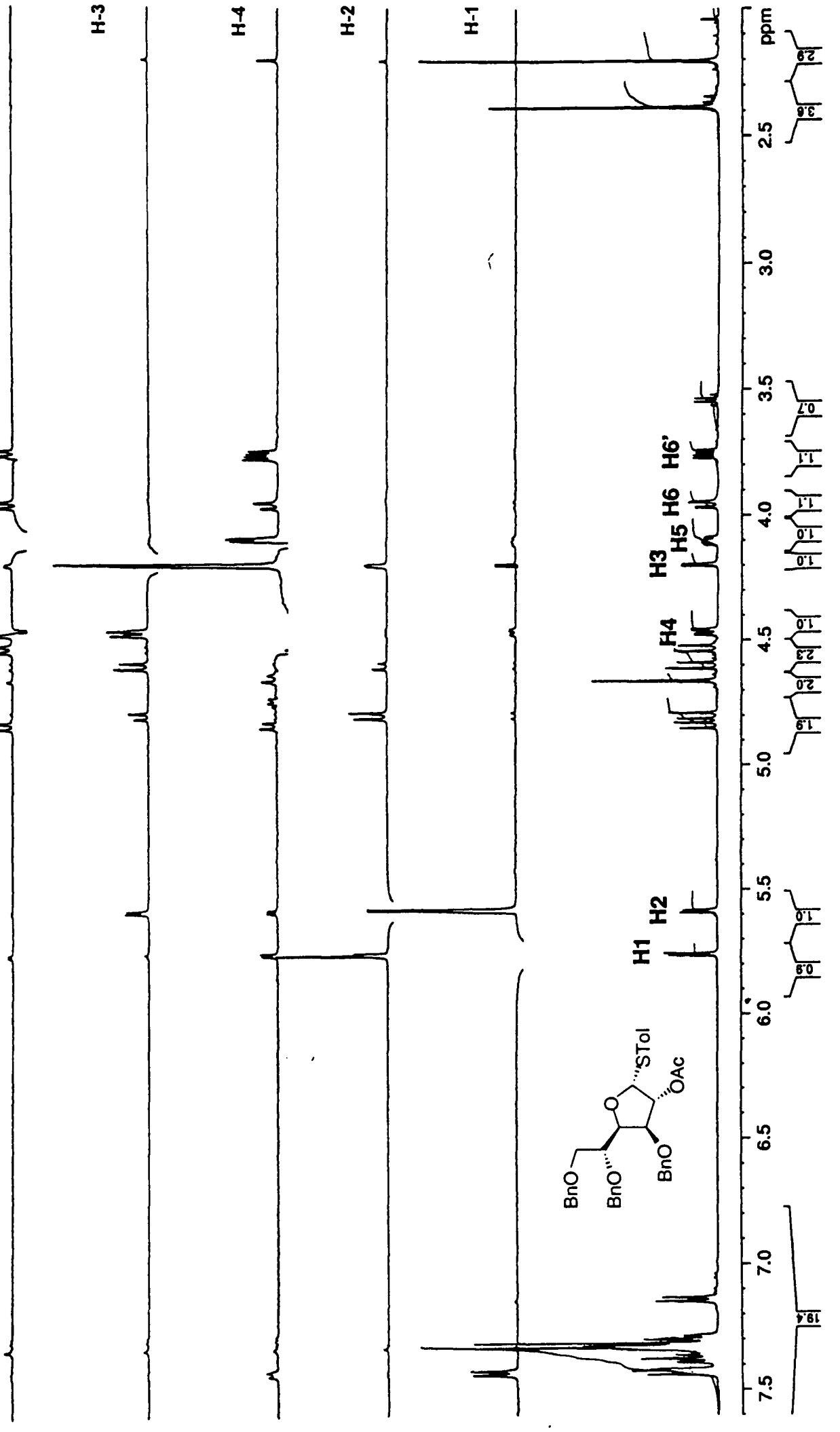


Figure A7.1: 500 MHz GOESY spectra of α acetate **165α** with irradiation of H-1, H-2, H-3, H-4 and H-5

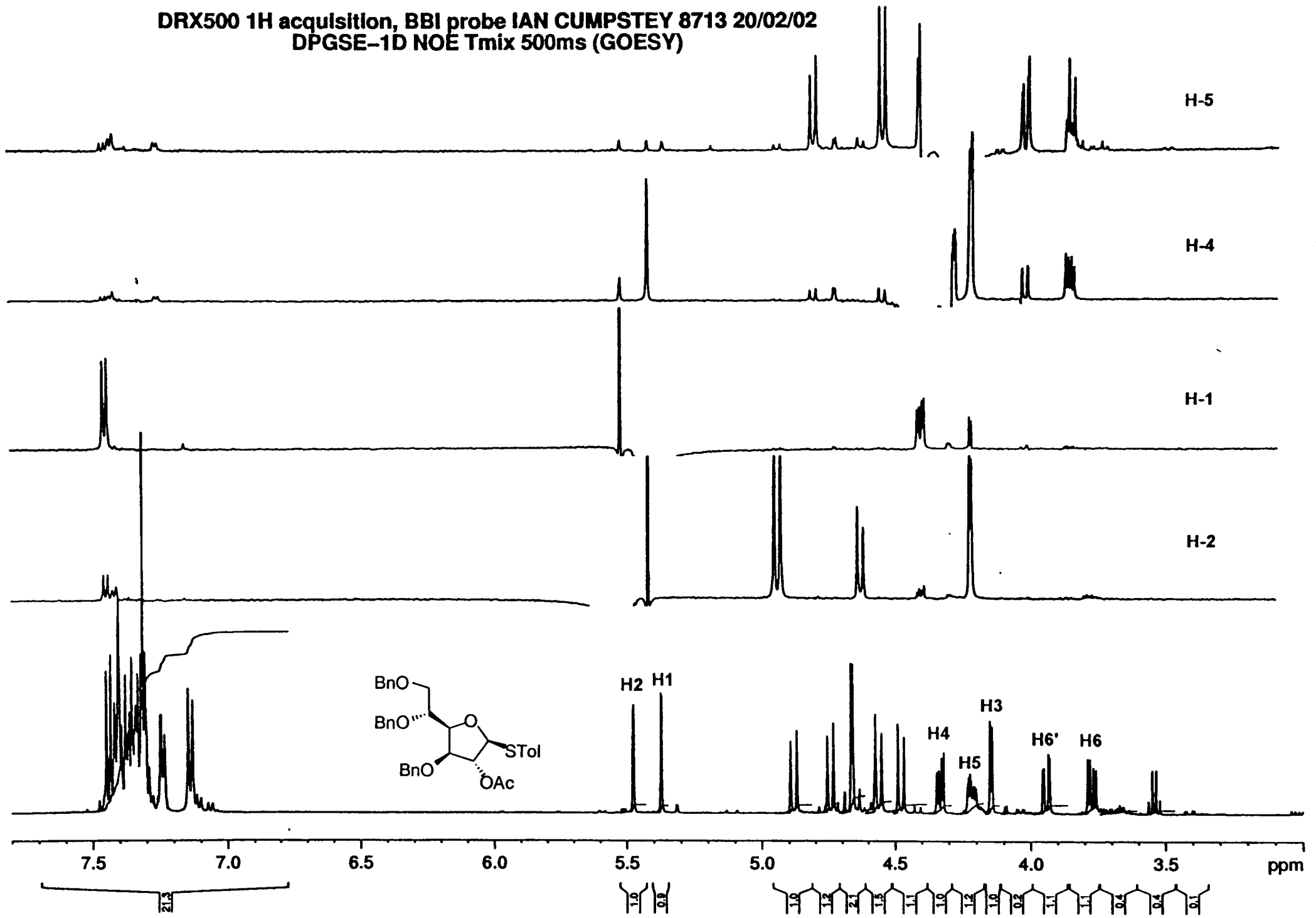


Figure A7.2: 500 MHz GOESY spectra of acetate **165β** with irradiation of H-1, H-2, H-4 and H-5

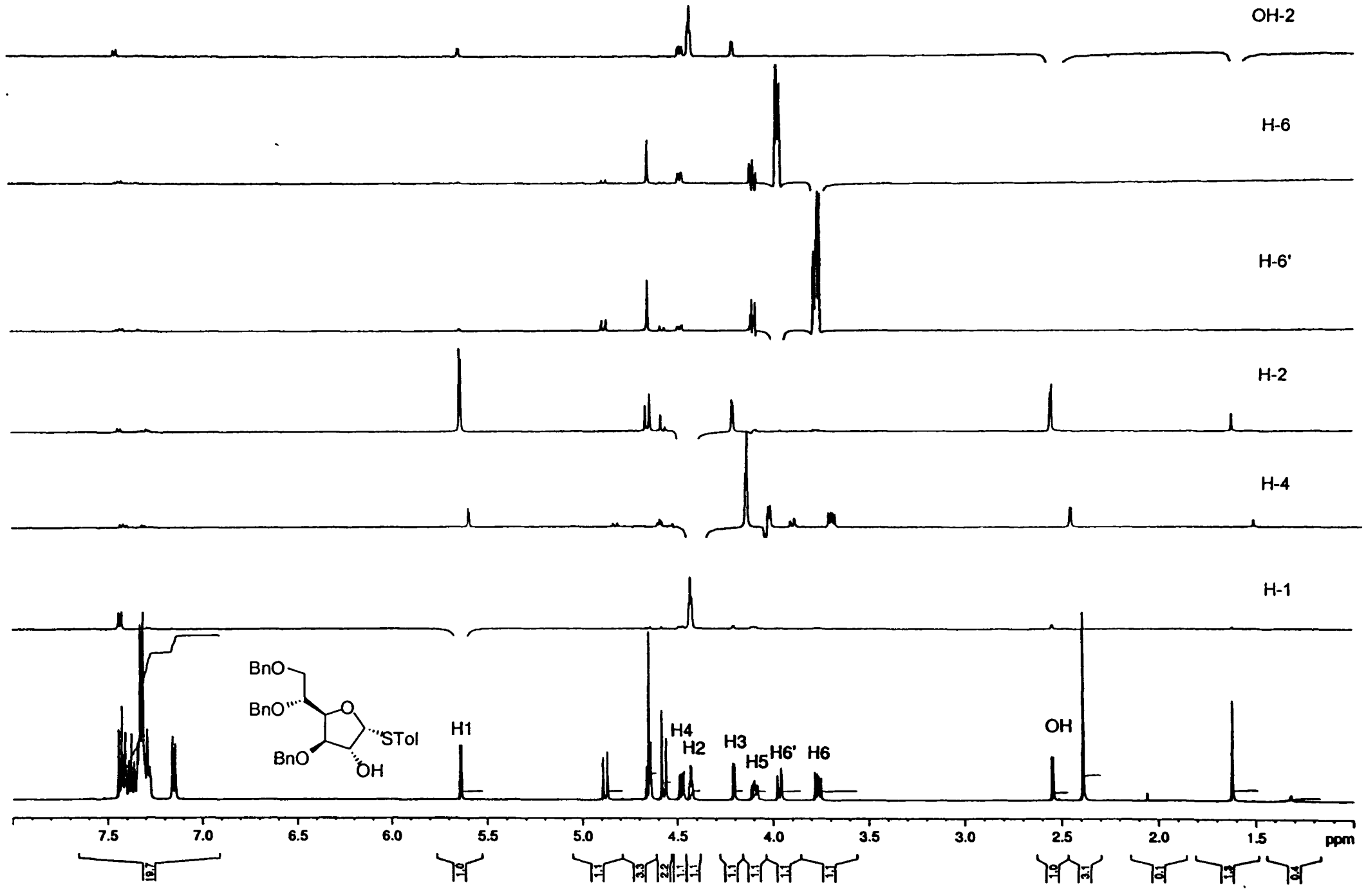


Figure A7.3: 500 MHz GOESY spectra of alcohol **164α** with irradiation of H-1, H-2, OH-2, H-6 and H-6'

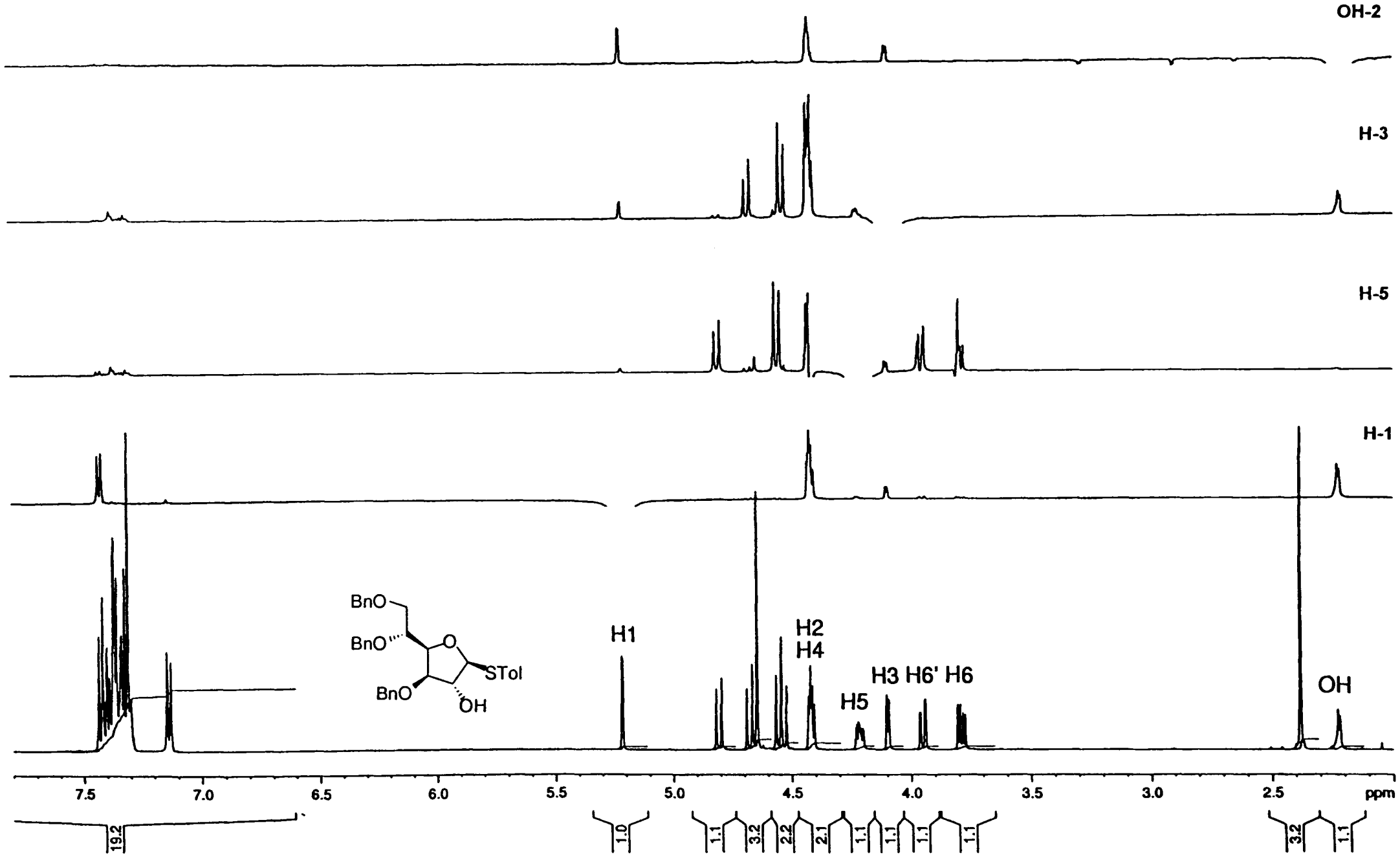
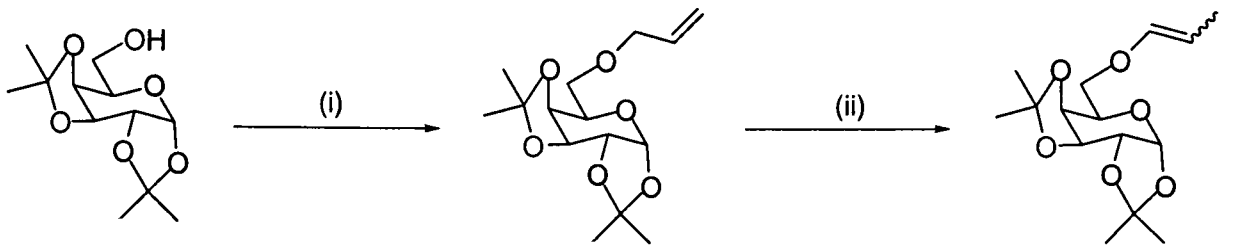


Figure A7.4: 500 MHz GOESY spectra of alcohol **164β** with irradiation of H-1, OH-2, H-3 and H-5

Appendix 8. Synthesis of Prop-1-enyl Protected Aglycon 92

In order to investigate the possibility of a 'reverse approach' tethering (see Chapter 5), diacetone galactose **3d** was allylated[1] and the double bond isomerised[2] under standard conditions to give aglycon enol ethers **92** (Scheme A8).



Scheme A8: (i) allyl bromide, NaH, DMF, 0°C, 90%; (ii) Wilkinson's catalyst, BuLi, THF, 70°C, 76%

6-O-Allyl-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose 182

1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose **3d** (500 mg, 1.92 mmol) was dissolved in anhydrous DMF (5 ml) and cooled to 0 °C. Allyl bromide (0.33 ml, 3.85 mmol) and then sodium hydride (60% in mineral oil) (154 mg, 3.85 mmol) were added. After 30 min, tlc (ethyl acetate:petrol, 1:3) indicated formation of a single product (R_f 0.5) and complete consumption of starting material (R_f 0.1). The reaction was quenched with methanol (4 ml) and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (2 x 50 ml) and water (100 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford 6-*O*-allyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **182** (519 mg, 90%) as a colourless oil; $[\alpha]_D^{22}$ –83.6 (*c*, 0.55 in $CHCl_3$) [Lit $[\alpha]_{576}$ +72 (*c*, 1.0 in $CHCl_3$)][3]; δ_H (400 MHz,

$CDCl_3$) 1.34, 1.35, 1.46, 1.55 (12H, 4 x s, 4 x Me), 3.59 (1H, dd, $J_{5,6}$ 6.7 Hz, $J_{6,6'}$ 10.1 Hz, H-6), 3.67 (1H, dd, $J_{5,6'}$ 5.8 Hz H-6'), 3.97-4.00 (1H, m, H-5), 4.02 (1H, ddat, J 1.4 Hz, J_{gem} 13.0 Hz, J 5.8 Hz, $OC\underline{H}H'CH{=}CH_2$), 4.08 (1H, ddat, J 1.3 Hz, J 5.7 Hz, $OCH\underline{H}'CH{=}CH_2$), 4.27 (1H, dd, $J_{3,4}$ 8.0 Hz, $J_{4,5}$ 1.9 Hz, H-4), 4.32 (1H, dd, $J_{1,2}$ 5.0 Hz, $J_{2,3}$ 2.4 Hz, H-2), 4.60 (1H, dd, H-3), 5.18 (1H, ddaq, J 1.3 Hz, J_Z 10.4 Hz, $OCH_2CH{=}CH_E\underline{H}_Z$), 5.29 (1H, ddaq, J 1.6 Hz, J_E 17.3 Hz, $OCH_2CH{=}C\underline{H}_EH_Z$), 5.55 (1H, d, H-1), 5.93 (1H, ddat, $OCH_2C\underline{H}{=}CH_2$).

1,2:3,4-di-O-isopropylidene-6-O-prop-1'-enyl-α-D-galactopyranose 92

Wilkinson's catalyst (154 mg, 0.17 mmol) was dissolved in freshly distilled THF (3 ml) and degassed. Butyl lithium (1.5M solution in hexanes) (0.4 ml, 0.26 mmol) was added and the mixture stirred for 10 min. 6-*O*-Allyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **182** (498 mg, 1.66 mmol) was dissolved in freshly distilled THF (3 ml) and heated to 70 °C. The catalyst solution was added by cannula under Ar. After 30 min, the reaction was allowed to cool then diluted with CH_2Cl_2 and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1 with 1% Et_3N) to afford 1,2:3,4-di-*O*-isopropylidene-6-*O*-prop-1'-enyl-α-D-galactopyranose **92** (380 mg, 76%) as a colourless oil. Partial data: δ_H (200 MHz, $CDCl_3$) *E* isomer 4.81 (1H, dq, J_E 12.6 Hz, J 6.6 Hz, $OCH{=}C\underline{H}$), 5.54 (1H, d, $J_{1,2}$ 4.9 Hz, H-1), 6.25 (1H, dd, J 1.5 Hz, $OC\underline{H}{=}CH$); *Z* isomer 4.43 (1H, aquint, J 6.7 Hz, $OCH{=}C\underline{H}$), 5.54 (1H, d, $J_{1,2}$ 4.9 Hz, H-1), 5.98 (1H, dd, J 1.7 Hz J_Z 6.2 Hz, $OC\underline{H}{=}CH$); *m/z* (APCI$^+$) 301 ($M+H^+$, 15%); (HRMS Calcd. for $C_{15}H_{24}O_6$ (MH^+) 301.1651. Found 301.1650).

References for Appendix 8

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