New Approaches to Stereocontrolled Glycosylation

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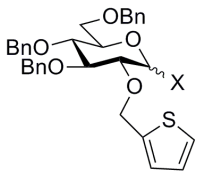
Abstract: New Approaches to Stereocontrolled Glycosylation

Daniel J. Cox, Keble College, D.Phil. Trinity 2011

The conceptually simple process of linking carbohydrate units by glycosylation has proven to be one of the most difficult synthetic processes to control from a stereochemical perspective. In particular it is the stereocontrolled synthesis of 1,2-*cis* glycosyl linkages (e.g. α-glucosides, β-mannosides) which poses the most difficult challenge. The research presented in this thesis describes new ways in which stereocontrol in glycosylation reactions can be achieved.

New methods of neighbouring group participation have been explored, utilising novel protecting groups at the 2-postion of a series of glycosyl donors.



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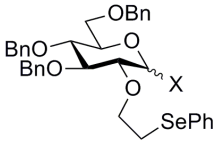

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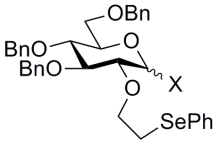

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In particular the use of glycosyl donors **1**, bearing a (thiophen-2-yl)methyl protecting group at the 2-hydroxyl, have shown exceptional α-selectivity especially when used in conjunction with a sterically hindered glycosyl acceptor.

Work within this thesis also describes the first use of chiral Brønsted acid catalysts in the activation of glycosyl donors. It has been clearly demonstrated that not only can such catalysts be used in glycosylation reactions, but also that the chirality of the catalyst can dictate the stereochemical outcome of the reaction. The preliminary studies presented demonstrate that this methodology warrants further investigation.

Declaration

I, Daniel Cox, hereby certify that this thesis has been written by me, that it is a record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

Signature of Candidate

Date 20/09/2011

For Great Grandma

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Dave, Bald Dave, Ruby, Kristina, Emma, James, Alex, Camilo and any others that I may have forgotten! There are plenty of other people in the CRL who have made my time here so enjoyable, and in no particular order I would also like to thank members of the Fleet, Burton, Hamilton and Addlington groups as well as the CRL cricket team for providing so many great memories over these past few years.

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Chapter 1: Introduction

1.1 Significance of Carbohydrates and Glycobiology

The four key classes of biological macromolecules are proteins, DNA, lipids and carbohydrates.[1] Amongst these macromolecules carbohydrates show an unrivalled degree of structural diversity.[2] Whilst proteins and DNA are limited to linear chains, carbohydrates form branched polymers and oligomers. The inherent difference in the configuration of monosaccharides (e.g. *gluco*, *manno*, *galacto*), coupled with variations of ring size (e.g. furanosyl, pyranosyl) and the number of possible sites for a linkage to occur lead to a vast potential in the structures that polysaccharides and oligosaccharides can adopt. Further structural diversity can be found in the anomeric configuration of glycosyl linkages and in modification of the carbohydrates (e.g. phosphorylation, sulfonation, and acetylation). The combination of these features gives rise to huge structural diversity, termed the glycocode.[3,4]

The high structural diversity of carbohydrates is reflected by the wide range of functions they play within nature. It is well established that carbohydrates can play vital roles in various biological events. In a cellular environment the majority of carbohydrates are present in the form of oligosaccharides and are attached to lipids or proteins as glycolipids or glycoproteins respectively; collectively these compounds are known as glycoconjugates. Glycoproteins are of particular interest; up to half of human proteins are *O*- or *N*- glycosylated (through either serine, threonine or asparagine amino acid residues) and the carbohydrate moieties of these glycoproteins are vital in many biological processes, such as cell growth, cell-cell adhesion and signalling,[5,6] fertilisation,[7] immune defence,[8-11] neuronal development[1,12] and inflammation.[13,14] Furthermore protein glycosylation, either as a co- or post-

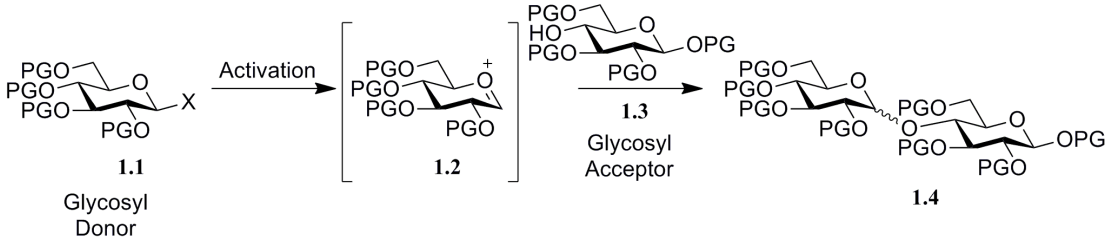
translational modification, can be necessary for correct protein folding[6] and can also affect the protein's stability and conformation,[15] its susceptibility to proteases[16] and its circulatory lifetime.[17]

The importance of carbohydrates in a plethora of biological processes continues to fuel great interest in the field of glycobiology; however a major obstacle to advances in this area is the lack of pure and structurally well-defined carbohydrates and glycoconjugates.[18] These compounds are often found naturally in low concentrations and in microheterogeneous forms, meaning that there is often great difficulty in their isolation and purification. Glycoproteins for example are commonly found as mixtures in which the same protein structures are attached to a variety of different oligosaccharides. These mixtures of glycoproteins are known as glycoforms, and although they may show differing biological activity their similar structures and physical properties mean that isolation of a single glycoform is almost impossible.[19]

Hence studies in glycobiology continue to necessitate the total synthesis of oligosaccharides by chemical and/or enzymatic means. Whilst enzymatic synthesis utilising glycosyl transferases and glycosidases has led to vast improvements in the efficiency of synthetic access to certain oligosaccharides,[20-22] the availability of enzymes that are capable of performing desired transformations remains a limiting factor in many cases. Therefore chemical synthesis currently remains the principal synthetic tool available to the scientific community.

1.2 Chemical Synthesis of Oligosaccharides

Oligosaccharide assembly hinges upon the linking of pre-formed building blocks by glycosylation. In a typical glycosylation reaction, the coupling of two carbohydrates is achieved by treating a glycosyl donor **1.1**, which bears a suitable anomeric leaving group, with a promoter to form an intermediate oxacarbenium ion **1.2**. Glycosyl acceptor **1.3**, strategically protected to have only a single free hydroxyl group, then serves as the nucleophile producing the glycoside product **1.4** (**Scheme 1.1**).[23]



Scheme 1.1. Typical Glycosylation Reaction. X = leaving group, PG = protecting group.

A variety of anomeric leaving groups and corresponding activation protocols are available to the synthetic chemist (**Figure 1.1**). Glycosyl bromides **1.5**, typically formed as the thermodynamically more stable α-anomer, were first used in what became known as the Koenigs-Knorr coupling by activation with silver carbonate.[24] Alternative silver sources, for example silver trifluoromethanesulfonate (AgOTf), can work equally well as promoters, and the efficiency of the procedure can be further improved by using more active catalysts such as mercury or cadmium salts.[25,26] Glycosyl chlorides **1.6** can be activated under the same Koenigs-Knorr conditions, however their lower reactivity compared to glycosyl bromides means that they are rarely used.

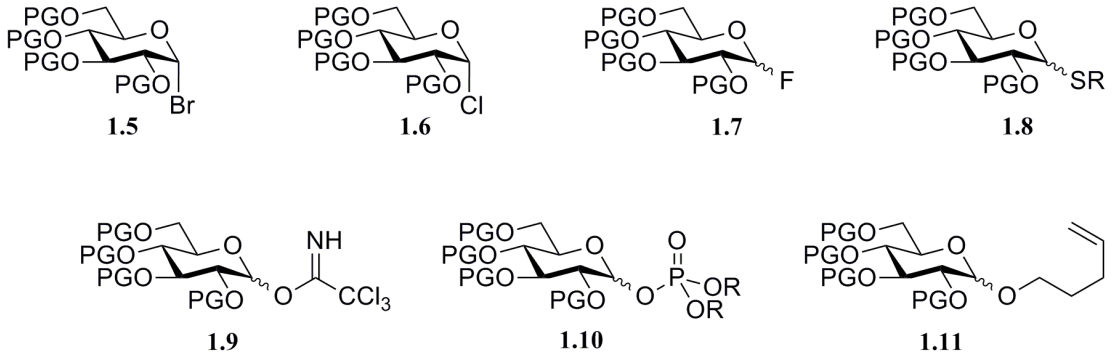


Figure 1.1. Examples of Glycosyl Donors

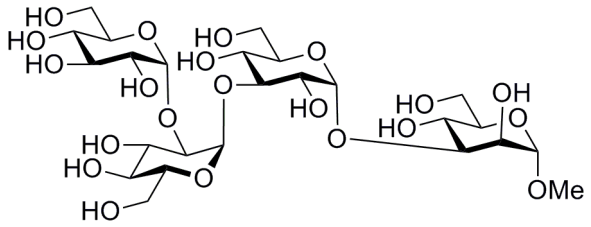
Glycosyl fluorides **1.7** on the other hand are very useful glycosyl donors.[27,28] They can be formed as either the α- or β-anomer, and are completely stable compounds, meaning that they must be activated using strong Lewis acids such as boron trifluoride diethyl etherate ($BF_3.OEt_2$). Thioglycoside donors **1.8**[29-31] are very commonly used and can be activated using soft Lewis acids such as N-iodosuccinimide (NIS) or methylating agents such as MeOTf or dimethyl(methylthio)sulfonium triflate (DMTST). Trichloroacetimidate donors **1.9** developed by Schmidt are increasingly utilised and are activated by catalytic amounts of hard Lewis acids including trimethylsilyl triflate (TMSOTf) and $BF_3.OEt_2$.[32-35] Anomeric phosphate leaving groups **1.10** are less commonly used, and these highly reactive donors and generally activated with TMSOTf.[36,37] Pent-4-enyl glycosides **1.11**[38,39], introduced by Fraser-Reid and co-workers, are activated further away from the anomeric centre by reaction of the alkene with NIS. The iodonium ion formed is subsequently attacked intramolecularly by the anomeric oxygen promoting the formation of an oxacarbenium ion.

The wide array of orthogonal protecting groups that have been developed allows access to building blocks with a single unprotected hydroxyl group,[40] and hence issues of regioselectivity in the glycosylation reaction are easily circumvented. The nature of

the reaction however means that the mechanism usually possesses either partial or complete S_N1 type character, and hence controlling the stereochemistry of the new anomeric linkage requires attention (this will be discussed in due course).

Construction of complex oligosaccharides by chemical synthesis is commonly an arduous and tedious experience; multiple steps are often required for the synthesis of even monosaccharide building blocks, and a variety of different protecting groups are commonly needed when building complex oligosaccharides to provide orthogonality between the different hydroxyl groups of each sugar unit. Although efforts have been made to improve the speed and efficiency of oligosaccharide synthesis by using either one-pot multistep glycosylation processes[41,42] or polymer-supported syntheses,[43-45] these approaches are often compromised by the same problem that plagues any glycosylation reaction: the product glycoside is generally formed as an anomeric mixture.[46,47] The issue of control of anomeric stereochemistry during glycosylation remains the principal challenge to be addressed in oligosaccharide synthesis. In particular it is the stereocontrolled synthesis of 1,2-*cis* glycosyl linkages (e.g. α-glucosides, β-mannosides) which poses the most difficult challenge,[48] and although many methods have been developed towards solving this problem, no generally applicable methodology exists.

The lack of general methodology for the synthesis of 1,2-*cis* glycosides leads to poor efficiency in the chemical synthesis of some oligosaccharides. For example, previously within the group the challenging total synthesis of the Glc_3Man *N*-Glycan tetrasaccharide **1.12** was undertaken (**Figure 1.2**).[49]



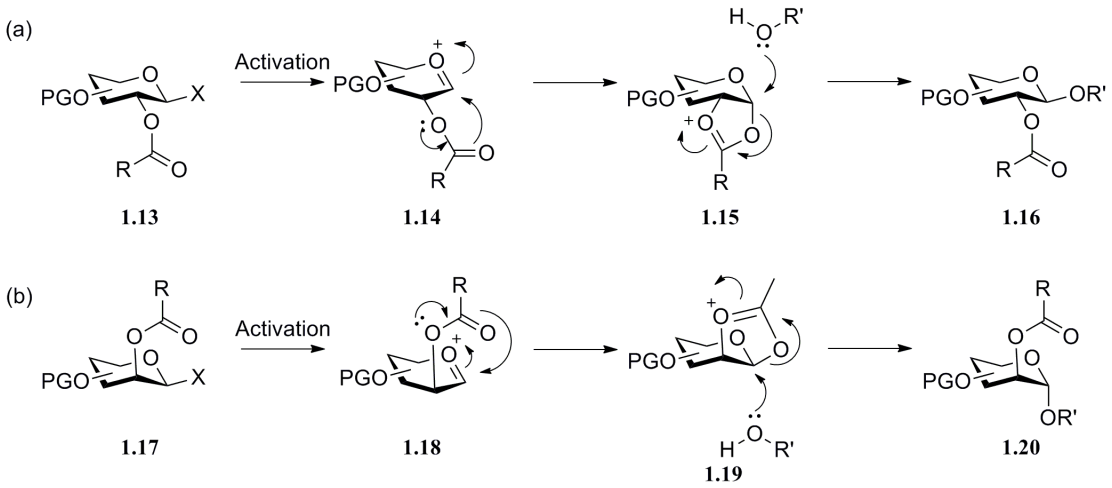
1.12

Figure 1.2. Glc_3Man *N*-Glycan Tetrasaccharide synthesised by Ennis *et al*.[49]

The tetrasaccharide **1.12** contains three 1,2-*cis* glycosidic linkages. Although reaction conditions were tuned to favour formation of the α-linkage, the product of each glycosylation reaction proceeded with at best a 4:1 selectivity in favour of the 1,2-*cis* glycoside. This meant that even in a best case scenario, 20% of the product obtained was undesired. Examples like this show that routine oligosaccharide synthesis will only be possible once robust stereoselective glycosylation procedures become available.[50]

1.3 Synthesis of 1,2-*trans* Glycosides by Neighbouring Group Participation

In contrast to the difficulty in the synthesis of 1,2-*cis* glycosides, the synthesis of 1,2-*trans* glycosides (e.g. β-glucosides, α-mannosides) can usually be achieved with high levels of stereocontrol by taking advantage of the classical neighbouring group participation (NGP) of 2-*O*-acyl protected glycosyl donors (**Scheme 1.2**).[51]



Scheme 1.2. NGP of a 2-*O*-acyl group in (a) Glucose and (b) Mannose.

Activation of the glycosyl donor **1.13** results in the formation of an oxacarbenium ion **1.14**. Subsequent neighbouring group participation by the acyl group at the 2-position gives the more stable dioxolenium ion **1.15**. S_N2 like attack by the alcohol of a glycosyl acceptor can now only occur on one face of the molecule, hence the glycosidic bond formed must be *trans* to the bond at the 2-position, producing the β-glycoside **1.16** in the case of glucosides. The same process occurs with the *manno* glycosyl donor **1.17**, though this time it is the β-face of dioxolenium ion **1.19** which is shielded from attack, hence the α-glycoside **1.20** is formed.

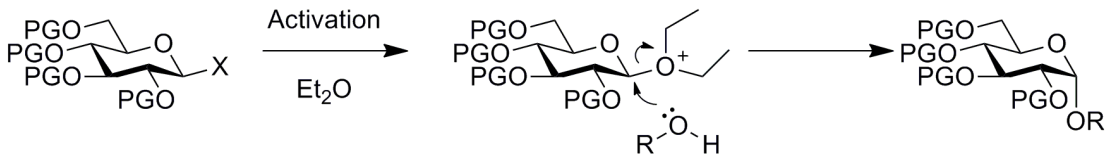
It is also possible to form 1,2-*trans* glycosides from glucosamine donors by employing an amide protecting group at the 2-position. It is known however that *N*-acetyl glucosamine derivatives often react with low efficiency in glycosylations, as

the acetamide can react with both the glycosyl acceptor and the activator.[52-54] Hence an *N*-phthalimido group is often chosen as the protecting group for glucosamine donors. Carbamate protecting groups are also capable of neighbouring group participation, and hence *N*-Troc protected glucosamine donors also give 1,2-*trans* glycosides.[55]

1.4 Synthesis of 1,2-*cis* α-Glycosides using Solvent Effects

The simplest method utilised towards the synthesis of 1,2-*cis* α-glycosides is to employ the use of non-participating protecting groups at the 2-position of the glycosyl donor, such as benzyl ethers, and to tune the reaction conditions towards favouring the desired stereochemical outcome. The most common way of doing this is to take advantage of the solvent system.[56-58] As a rule of thumb, ethereal solvents can be expected to enhance α-selectivity, whilst nitrile solvents enhance β-selectivity.

For example, the synthesis of 1,2-*cis* α-glucosides can be achieved by the use of diethyl ether as the reaction solvent. The diethyl ether selectively coordinates equatorially to the oxacarbenium ion formed upon activation giving the intermediate **1.21**, and hence reaction with the glycosyl acceptor in an S_N2 fashion gives the α-anomeric product **1.22** (**Scheme 1.3**).[51]



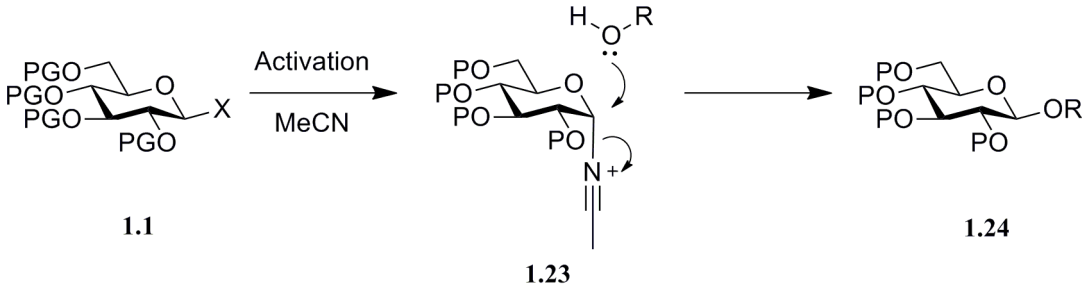
1.1 **1.21** **1.22**

Scheme 1.3. Glycosylation of a Glucose Donor using Et_2O as the solvent.

Selectivity is generally observed to increase with a decrease in temperature, and the methodology can be used with a wide range of glycosyl donors[59-61] and also in solid-

supported syntheses.[62] Tetrahydrofuran and 1,4-dioxane are other examples of ethereal solvents which can direct α-selectivity in glycosylation,[58] whilst the non-ethereal solvent nitroethane also produces α-glycosides.[63] Indeed, it was the use of diethyl ether as part of the solvent mixture that allowed enhanced α-selectivity in the synthesis of Glc_3Man *N*-Glycan tetrasaccharide **1.12** described previously.[49]

Alternatively the formation of β-glucosides can be achieved by using a non-participating group at the 2-position of the glycosyl donor and carrying out the reaction using acetonitrile as the solvent.[64,65] In this case β-selectivity is observed due to the stereoselective kinetic formation of a reactive α-nitrillium intermediate **1.23**, which undergoes an S_N2 type reaction with the glycosyl acceptor to give the β-anomeric product **1.24** (**Scheme 1.4**).



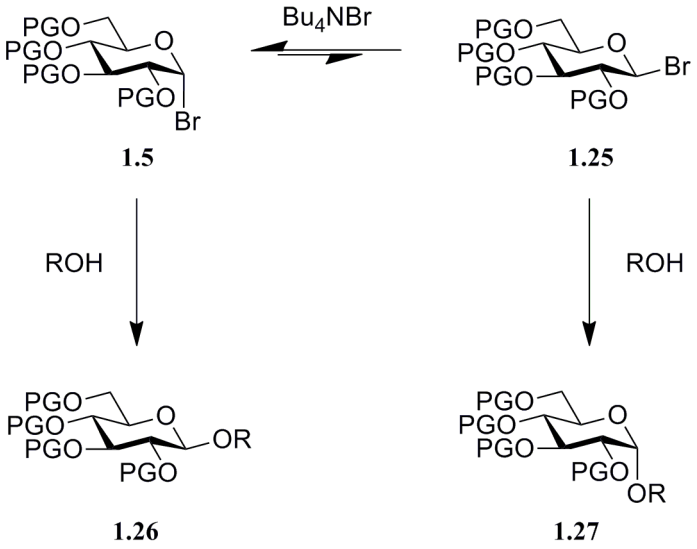
Scheme 1.4. Glycosylation of a Glucose donor using MeCN as the solvent.

As with the use of diethyl ether as the reaction solvent, selectivity is observed to increase with a decrease in reaction temperature. It may be thought that this preference for the formation of an α-nitrillium ion would allow the synthesis of 1,2-*cis* β-mannoside linkages, however in this case the steric effect of the axially orientated hydroxyl at the 2-position outweighs the directing effect of the acetonitrile and therefore enhanced formation of the β-mannoside is not observed.

Whilst the use of solvent effects is a useful tool in stereoselective glycosylation reactions, the results are not always reliable and pure anomeric selectivity is very difficult to achieve. Another problem associated with the approach is that of the solubility of the glycosyl donor and/or acceptor in the chosen solvent. If an additional solvent is required to aid solubility the action of the directing solvent may be diminished, and hence selectivity in the glycosylation reaction may decrease.

1.5 Synthesis of 1,2-cis α-Glycosides by In Situ Anomerisation

The method of in situ anomerisation was first reported by Lemieux and co-workers in 1975,[66] and at the time provided a major breakthrough in the synthesis of α-glycosides. It was observed that treatment of a glycosyl halide, commonly a glycosyl bromide, with a catalytic source of the same halide in the presence of a glycosyl acceptor gave predominantly the α-glycoside. This stereochemical outcome was explained using the Curtin-Hammett principle. For example, if the α-bromide **1.5** is treated with a catalytic amount of tetra-n-butylammonium bromide, an equilibrium between α-bromide **1.5** and β-bromide **1.25** is established (**Scheme 1.5**).



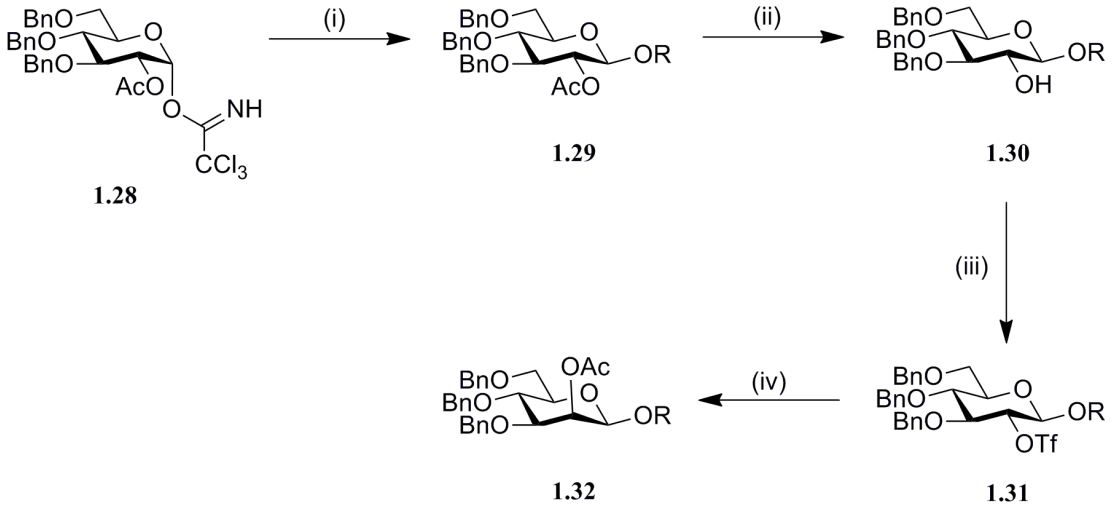
Scheme 1.5. In Situ Anomerisation for a Glycosyl Bromide.

Although the equilibrium strongly favours the more stable α-bromide **1.5**, the activation energy barrier for nucleophilic attack by a glycosyl acceptor is much lower for β-bromide **1.25**. Therefore the 1,2-*cis* α-glycoside **1.27** is the major product of the reaction. If the difference in the energy barriers for the two substitutions is sufficient, pure α-selectivity can be obtained. It is important that the rate of equilibration is much higher than that of the glycosylation reaction, and hence the reaction works best with highly reactive glycosyl donors and poorly reactive glycosyl acceptors. Indeed a highly reactive glycosyl donor is also required for treatment with such mild catalytic activators, and hence the reaction is limited to the use of glycosyl halides. It is also vital that a low polarity solvent is used, as in the presence of a polar solvent oxacarbenium ion formation becomes more favourable and hence a more S_N1 like reaction occurs, reducing anomeric selectivity.

1.6 Synthesis of 1,2-*cis* β-Glycosides by 2-position inversion

Whilst solvent effects and in situ anomerisation protocols are useful tools for the synthesis of 1,2-*cis* α-glycosides, neither method can be used for the preparation of 1,2-*cis* β-glycosides; indeed the formation of β-mannosides presents an even greater challenge than the synthesis α-glucosides. The axially orientated 2-hydroxyl group shields the β-face from attack by the glycosyl acceptor, meaning that even under S_N1 type conditions formation of the α-product is strongly favoured. Furthermore the β-glycoside is thermodynamically unfavourable due to not only a lack of the anomeric effect but also due to electronic repulsions by the 2-position.[67,68] The 1,2-*cis* β-mannoside linkage is found in the core pentasaccharide of all *N*-linked glycoproteins[69] as well as many other biologically relevant oligosaccharides and hence the importance of the β-mannoside linkage has fuelled great interest in developing methodologies for its synthesis.

Due to the difficulties in stereocontrol, an indirect approach to the synthesis of β-mannosides is often employed involving the synthesis of a β-glucoside followed by inversion of stereochemistry at the 2-position. This methodology was employed by Furstner and co-workers (**Scheme 1.6**).[70-72]



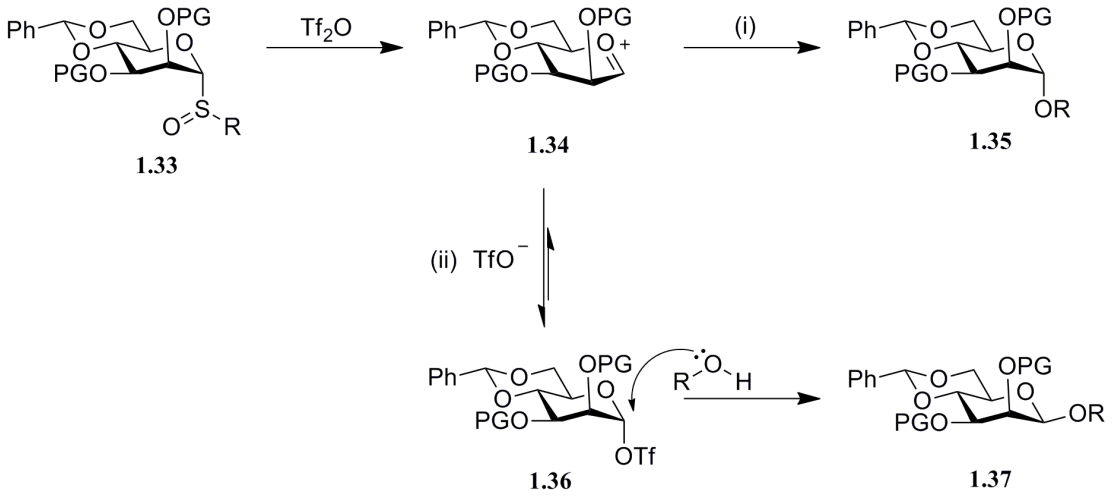
Scheme 1.6. Synthesis of β-mannosides by Furstner and Konetzki.[70]

(i) ROH, cat. $BF_3.OEt_2$, CH_2Cl_2/hexane, -25°C; (ii) KOMe, MeOH; (iii) Tf_2O, CH_2Cl_2/pyridine; (iv) Bu_4NOAc, toluene, ultrasound.

Glycosylation of the trichloroacetimidate donor **1.28** gave the β-glucoside **1.29** by neighbouring group participation of the acetate group at the 2-position. This was then removed using catalytic methoxide to give the alcohol **1.30** which was then converted to the triflate **1.31** using triflic anhydride. Reaction with tetrabutylammonium acetate under ultrasound conditions gave inversion at the 2-position, and hence the β-mannoside product **1.32**. Although yields of the inversion step were shown to be consistently high (upwards of 80%) clearly the requirement for three additional synthetic steps compared to a direct glycosylation method is not ideal.

1.7 Synthesis of 1,2-*cis* β-Glycosides by Crich Methodology

Perhaps the most generally efficient protocol for the synthesis of β-mannosides is the inverse addition methodology pioneered by Crich and co-workers. This approach involves the pre-activation of a glycosyl sulfoxide with triflic anhydride followed by treatment with the glycosyl acceptor. The order of addition of reagents is very important to the stereochemical outcome (**Scheme 1.7**).[73-75]



Scheme 1.7. Synthesis of β-mannosides by Crich *et al*.[74]

(i) ROH, DTBMP, CH_2Cl_2, -78°C then Tf_2O; (ii) Tf_2O, DTBMP, CH_2Cl_2, -78°C then ROH.

If the reaction was carried out under glycosylation conditions (i), where a mixture of the glycosyl donor **1.33** and the acceptor were treated with the promoter, then the α-mannoside **1.35** was observed to be the major product formed. However, it was discovered that pre-activation of the glycosyl sulfoxide **1.33** with triflic anhydride and the hindered base 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) followed by addition of the glycosyl acceptor (conditions (ii)) gave predominantly the β-mannoside **1.37**. It was postulated that this result was due to attack of the glycosyl acceptor in an S_N2 manner with the α-triflate intermediate **1.36**, which was postulated to be more stable than the glycosyl cation **1.34** and therefore favoured at equilibrium. Low temperature

NMR studies subsequently proved that formation of **1.36** did indeed occur under the reactions conditions. In general the β-selectivity was shown to be high with primary alcohol acceptors, giving α:β ratios of greater than 1:25 in some cases. However when more sterically demanding secondary alcohol acceptors were used the selectivity was observed to diminish. Subsequently Crich and co-workers have developed alternative activation conditions that allow reaction of thioglycoside donors to give β-mannosides *via* formation of the same α-triflate intermediates,[76-78] and in these cases high β-mannoside formation can be observed for bulkier acceptors, although it is still not a general observation.

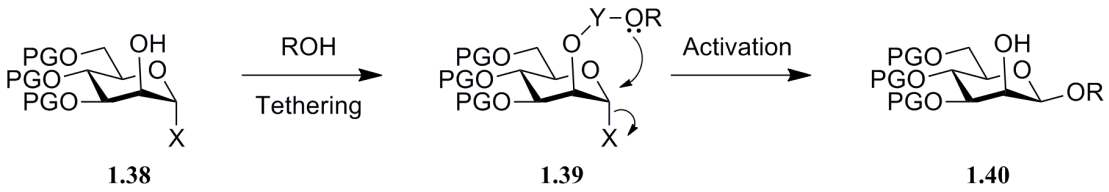
The protecting groups employed on the glycosyl donor were also found to be very important. It was vital that the protecting group used at the 2-position was non-participating; hence benzyl and silyl ethers were favoured. Unsurprisingly S_N2 attack by the acceptor was better suited by the presence of benzyl ethers compared to relatively bulky silyl groups such as TBDMS, and hence greater selectivity was observed with benzyl protection. Presumably smaller silyl groups are unstable to the reaction conditions employed and hence cannot be used. More important, however, was the presence of the 4,6-*O*-benzylidene acetal in the glycosyl donor. It has been proposed that formation of the oxacarbenium ion is disfavoured when this protecting group is used due to the high torsional strain and unfavourable electronic effects inflicted on the intermediate,[79,80] and hence this greatly favours the formation of the α-triflate **1.36**. With more conformationally flexible glycosyl donors increased α-mannoside formation is observed to occur.

Although this inverse addition methodology can be employed very successfully in the synthesis of the challenging β-mannoside linkage, there are obviously several drawbacks. The requirement for a 4,6-*O*-benzylidene acetal is very restrictive in

protecting group strategy and may require the use of undesirable protecting group manipulations and hence additional synthetic steps. The choice of donor is also somewhat limited due to the need for pre-activation and hence the method is not considered a general solution to the problem of forming β-mannosides.

1.8 Synthesis of 1,2-*cis* Glycosides by Intramolecular Aglycon Delivery (IAD)

Intramolecular agylcon delivery (IAD) was first described by Hindsgaul in 1991 as a method of forming β-mannosides.[81] The principle behind this technique involves temporarily linking the glycosyl acceptor to the 2-position of a glycosyl donor **1.38** *via* a bridging atom or group (labelled Y), producing a tethered glycoside **1.39** (**Scheme 1.8**).

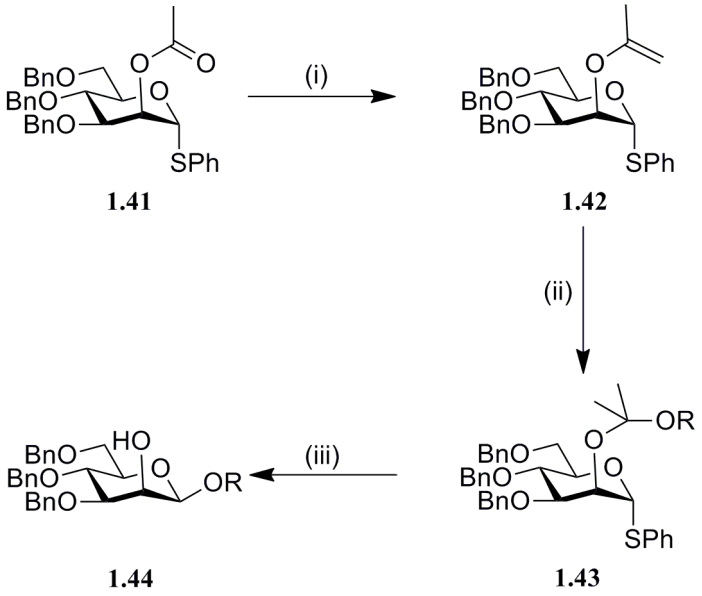


1.38 **1.39** **1.40**

Scheme 1.8. Intramolecular Aglycon Delivery to give β-mannosides.

Activation of the glycosyl donor then results in an intramolecular glycosylation, which as the aglycon is tethered to the cis face of the donor must result in formation of the 1,2-*cis* glycoside **1.40**. The group remaining at the 2-position after glycosylation can be cleaved either after or during the reaction to leave the 2-OH position unprotected. This so-called 'forward' approach is most commonly used; however it is equally possible to use a 'reverse' approach, where the 2-hydroxyl of a glycosyl donor is tethered to a group attached to the glycosyl acceptor at the desired position of glycosylation.

Hindsgaul and co-workers developed this methodology to specifically target the synthesis of β-mannosides,[81-83] such as **1.44**, by employing a 2-*O*-methylvinyl ether protected glycosyl donor **1.42**, derived from a Tebbe reaction of the 2-*O*-acetate protected donor **1.41**, to achieve tethering of the glycosyl acceptor (**Scheme 1.9**).



Scheme 1.9. IAD Synthesis of β-mannosides by Hindsgaul.[81]

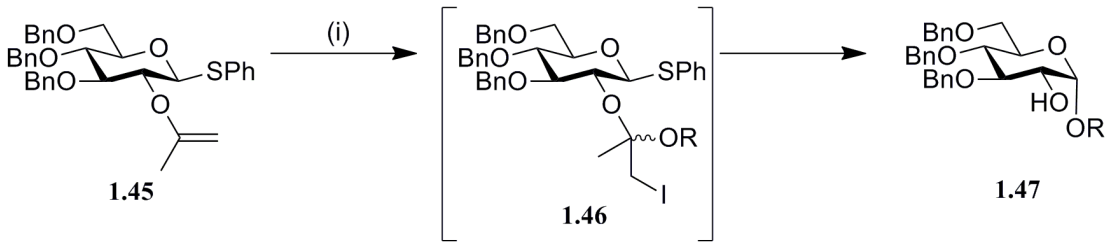
(i) Tebbe reagent; (ii) ROH, cat. TsOH, CH_2Cl_2; (iii) NIS, DTBMP, CH_2Cl_2.

Activation of the anomeric leaving group of the tethered mixed ketal intermediate **1.43** allowed formation of the disaccharide **1.44** with complete stereocontrol for the β-anomer. Unfortunately both the tethering and glycosylation steps were observed to proceed with poor yield, and further limitations were exposed when the synthesis of larger oligosaccharides were attempted. It was generally found that the mixed ketal intermediates were very unstable and showed a propensity for side reactions, leading to the conclusion that IAD via this tethering system was not suited to the synthesis of complex oligosaccharides.

Around the same time Stork and co-workers were also developing an IAD method for the synthesis of β-mannosides using a silaketal tethering group.[84,85] Tethering and

glycosylation steps proceeded in higher yield compared to Hindsgaul's method and complete β-selectivity was again observed, however some limitations were also exposed, especially when more sterically hindered glycosyl acceptors were employed.

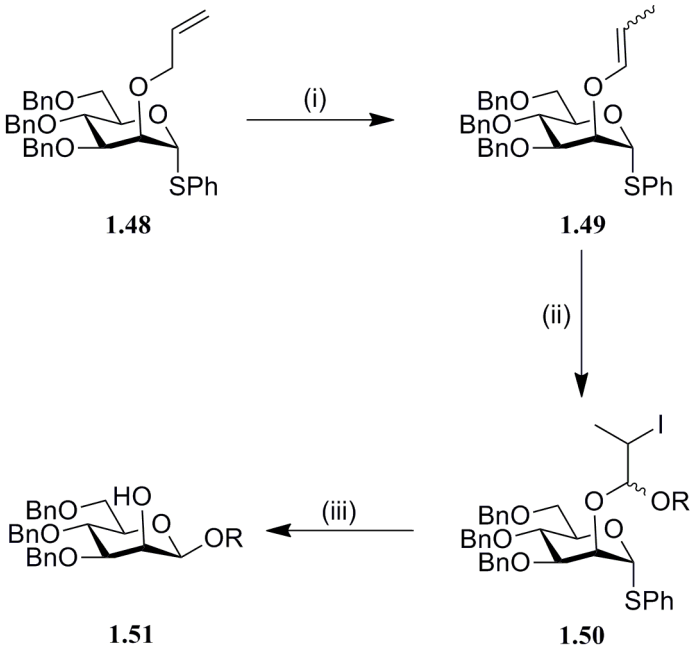
In light of these promising early discoveries however, many investigations into IAD began. In the Fairbanks group, attention turned to the potential use of IAD for the synthesis of 1,2-*cis* α-glycosides; indeed it was thought that IAD had the potential to become a truly general method of forming 1,2-*cis* glycosides, whether they were *gluco* or *manno* in nature. Work by Bols had already shown that silicon-tethered IAD could be used for the synthesis of α-glucosides,[86-88] however initial investigations within the group focused on the use of Hindsgaul's IAD methodology. It was discovered that the tethering step could be improved by the use of NIS as opposed to catalytic acid, and when used in conjunction with a thioglycoside donor a one-pot procedure was developed for both *gluco* and *manno* donors (**Scheme 1.10**).[89]



Scheme 1.10. One-pot IAD strategy: (i) ROH, NIS, DTBMP, DCE, -40°C to rt; then Dowex H^+/MeOH.

Treatment of donor **1.45** with NIS led to formation of the tethered intermediate **1.46** as the enol ether is more reactive than the thioglycoside towards the electrophile. Subsequently the glycosyl donor was activated and the acceptor delivered intramolecularly to give the α-glycoside with complete stereocontrol. Yields were good for primary alcohol acceptors, and the one-pot procedure was actually even

more efficient for mannose donors. Unfortunately, as with Hindsgaul's earlier work, reaction with sterically hindered secondary alcohol carbohydrate acceptors proved problematic. It was thought that attachment at the tertiary centre was perhaps having a limiting effect in the tethering step, and hence an alternative tethering group, an allyl group, was investigated and subsequently optimised within the group (**Scheme 1.11**).[90-94]



Scheme 1.11. Allyl IAD:[90] (i) $(Ph_3P)_3RhCl$, n-BuLi, THF, reflux; (ii) ROH, NIS, DCE, -40°C to rt; (iii) NIS, AgOTf, DTBMP, CH_2Cl_2.

The allyl group of **1.48** was efficiently isomerised by treatment with Wilkinson's catalyst pre-treated with n-butyl lithium to give the vinyl ether **1.49**.[95] NIS mediated tethering gave **1.50** which could be glycosylated in the same fashion as before to give the 1,2-*cis* glycoside **1.51**. Encouragingly this procedure gave excellent selectivity and yields for secondary alcohol acceptors with mannose donor systems, but disappointingly these results could not be replicated with glucose donor systems and generally low yields were observed. Attempts to improve the methodology with the

use of an alternative glycosyl donor, a glycosyl fluoride, failed to substantially increase the yields observed.[91,94] Despite the somewhat unreliable nature of the allyl IAD methodology for the synthesis of 1,2-*cis* α-glycosides, the methodology was eventually utilised in the synthesis of the Glc3Man *N*-glycan tetrasaccharide **1.12**, employed in an iterative fashion and optimised to produce the challenging tetrasaccharide in an efficient and completely stereocontrolled manner.[96]

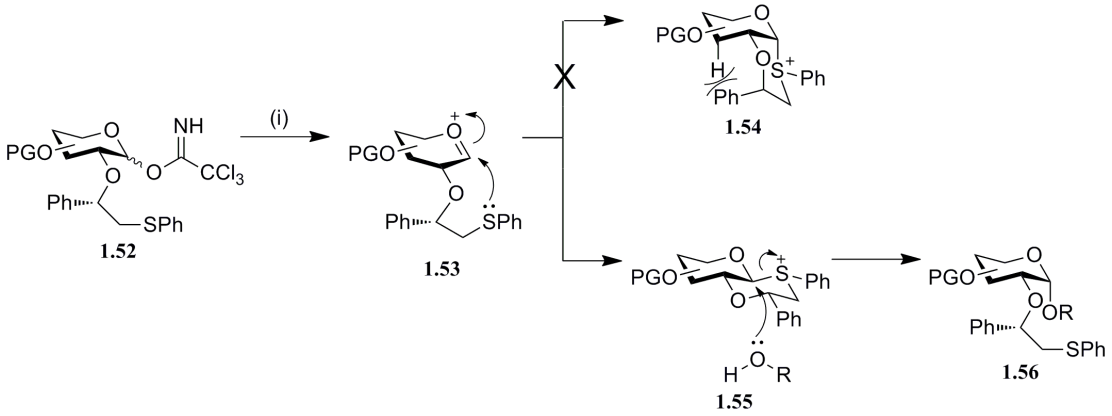
As well as the development of allyl IAD, the Fairbanks group have extended the idea to the use of a propargyl tethering group.[97,98] Elsewhere Ogawa has extensively exploited the use of a *para*-methoxybenzyl tethering group, using the methodology to successfully synthesise the core *N*-glycan pentasaccharide and even to perform solid supported IAD processes.[99-106] More recently the use of naphthyl mediated IAD has also been explored.[107,108]

Intramolecular aglycon delivery is clearly a powerful tool for the synthesis of 1,2-*cis* glycosides, especially β-mannosides. However, the large number of studies in the area is indicative of the fact that there is still no generally applicable method of IAD that can be employed in oligosaccharide synthesis. The major drawback in the use of the methodology is the decrease in efficiency when applied to more extended donors and acceptors, leaving the technique unsuitable for complex oligosaccharide synthesis.

1.9 Synthesis of 1,2-*cis* α-Glycosides by β-Sulfonium Ions

The use of neighbouring group participation for the synthesis of 1,2-*cis* glycosides was up until recently not considered. In the case of a *manno* glycosyl donor participation from the 2-position could only ever give the 1,2-*trans* product as the axially orientated substituent can only interact with the anomeric centre from the β-face. Participation from the 2-position of a *gluco* donor however could be imagined to

give rise to 1,2-*cis* selectivity if the neighbouring group were to coordinate to the anomeric centre in a β-configuration. In 2005 Boons and co-workers reported the use of novel chiral auxiliary based neighbouring groups for the synthesis of both 1,2-*cis* and 1,2-*trans* glycosides. The use of glycosyl donors bearing an (*R*)- or (*S*)-ethoxycarbonylbenzyl moiety was reported,[109,110] with the configuration of the chiral auxiliary influencing whether α- or β-glycosides were formed. Although this method gave rise to very good selectivity, pure anomeric stereocontrol was not achieved. Following on from this research the use of a (1*S*)-phenyl-2-(phenylsulfanyl)ethyl moiety was reported,[50] which gave exclusive 1,2-*cis* α-selectivity with a variety of glycosyl acceptors by formation of a sulfonium ion formed by neighbouring group participation (**Scheme 1.12**).

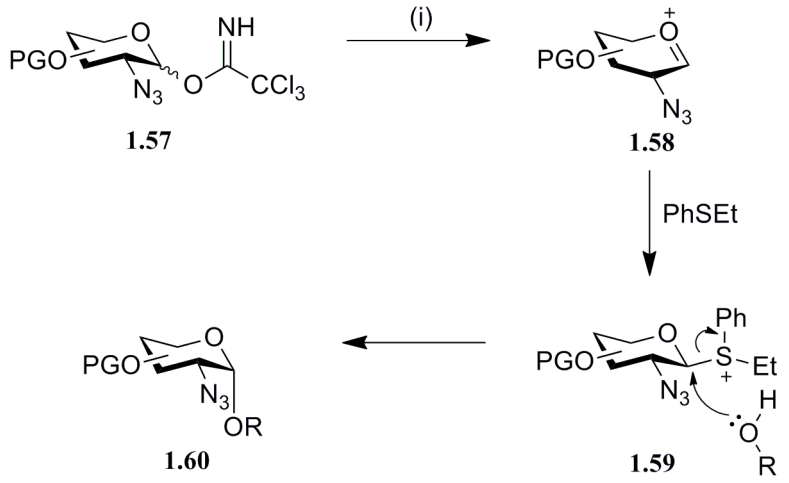


Scheme 1.12. Boons Chiral Auxiliary NGP.[50] (i) TMSOTf, CH_2Cl_2, -78°C to 10°C.

Activation of the trichloroacetimidate donor **1.52** led to formation of the oxacarbenium ion **1.53**. Neighbouring group participation from the sulfur then occurred, forming a 6-membered cyclic intermediate. It could be thought that one of two intermediates could be formed; a *cis*-decalin type intermediate **1.54** or a *trans*-decalin type intermediate **1.55**. However, due to the presence of the chiral auxiliary the formation of **1.54** is disfavoured due to the steric interaction of the phenyl group

with the 3-position hydrogen atom. Hence **1.55** is favoured and subsequent S_N2 displacement with the glycosyl acceptor produces the 1,2-*cis* glycoside **1.56**. This elegant methodology has since been applied in the solid-supported synthesis of an α-glucan pentasaccharide.[111] Although installation of the chiral neighbouring group requires a five step manipulation from a commercially available chiral starting material, it was shown that deprotection of the group led to recovery of the acetic acid (1*S*)-phenyl-2-(phenylsulfanyl)ethyl ester, which could be reused for instalment of the (1*S*)-phenyl-2-(phenylsulfanyl)ethyl moiety. In this deprotection reaction, an acetoxonium ion, generated from a reaction of $BF_3.OEt_2$ with acetic anhydride, reacted with the oxygen of the (1*S*)-phenyl-2-(phenylsulfanyl)ethyl moiety. An intramolecular nucleophilic displacement by sulfur on the resulting intermediate led to the formation of an episulfonium ion and an acetyl ester at the 2-position of the carbohydrate. Nucleophilic attack of acetic acid at the benzylic position of the episulfonium ion subsequently regenerated the acetic acid (1*S*)-phenyl-2-(phenylsulfanyl)ethyl ester with retention of chirality.

Interestingly, as a control reaction, the use a 2-(phenylsulfanyl)ethyl group at the 2-position of the glycosyl donor was investigated. Although the use of this group did not give pure α-selectivity for the glycosylation reaction, the selectivity was still high (α:β ratio, 8:1) despite the absence of any chiral auxiliary. This suggested that there was a general preference for the sulfonium to exist in the β-configuration, most likely due to steric and stereoelectronic effects. Following on from the use of a chiral auxiliary based sulfur neighbouring group, Boons and co-workers reported the use of achiral sulfonium ion intermediates that were formed intermolecularly to produce 1,2-*cis* α-glycosides *via* a β-configured intermediate sulfonium ion (**Scheme 1.13**).[112]



Scheme 1.13. 1,2-*cis* α-Glycosides by Sulfonium Ion Intermediates.[112]

(i) TMSOTf, PhSEt or Thiophene, CH_2Cl_2, -78°C to 0°C.

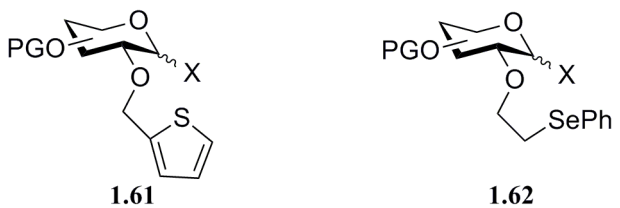
Activation of the 2-azido-2-deoxy glucose donor **1.57** in the presence of glycosyl acceptor and a large excess (10 equivalents) of either phenyl-thioethyl ether or thiophene was shown to form the α-glycoside **1.60** with high selectivity. Interestingly selectivity was observed to increase with an increase in reaction temperature and at 0°C pure α-selectivity was observed in some cases. The reaction was also independent of the protecting group strategy employed, with both electron withdrawing esters and electron donating ethers giving equally high selectivity. NMR studies showed that the sulfonium ion **1.59** was indeed being formed in the reaction, exclusively in the β-configuration.

Although these results were only shown for one glycosyl donor, a 2-azido-2-deoxy glucose derivative, they potentially represent an excellent method of forming 1,2-*cis* α-glycosides if the methodology can be shown to be general for other glycosyl donors. Combined with the results shown for the chiral auxiliary based neighbouring group participation, there is definite evidence that intermediate sulfonium ions are capable of stereocontrol in glycosylation reactions.

1.10 Project Objectives

The objective of this project was to develop new methods of stereocontrolled glycosylation. Given the recent advances in neighbouring group participation methods for the synthesis of 1,2-*cis* α-glycosides developed by Boons *et al*., it was postulated that further improvements could be made towards general methodology for use in oligosaccharide synthesis.

Although the arguments presented for the potentially widespread utility of the chiral auxiliary approach for the control of anomeric stereochemistry were compelling, we reasoned that perhaps chirality was not necessary in the 2-OH protecting group in order to achieve good α-selectivity for the formation of 1,2-*cis* α-glycosides. Indeed it was considered that the inherent preference shown in Boons' research for a sulfonium ion to exist in the β-configuration[50,112] suggested that simpler protecting groups could be employed at the 2-position for neighbouring group participation. We therefore sought to investigate the use of sulfur containing neighbouring groups at the 2-position of a glycosyl donor. By extension it was expected that the formation of selenonium ion intermediates may also show a preference to exist in the β-configuration and hence enhance α-selectivity. We therefore also wished to investigate the effect that selenium based neighbouring groups had on the outcome of glycosylation reactions. The initial targets chosen for investigation are shown below (**Figure 1.3**).



1.61 **1.62**

Figure 1.3. Targets for Investigation

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Chapter 2: Synthesis and Evaluation of Glycosyl donors bearing a 2-O-(thiophen-2-ylmethyl) protecting group

2.1 Introduction

We first sought to investigate how a sulfur containing protecting group at the 2-position of a glycosyl donor could influence the selectivity observed in a glycosylation reaction. Given that research conducted by Boons and co-workers had shown that the addition of thiophene to a glycosylation reaction mixture gave increased α-selectivity in the glycosylation product *via* a β-coordinated sulfonium ion intermediate formed intermolecularly,[1] it was supposed that the same result could be observed intramolecularly. Indeed it was considered that a thiophene appended to the 2-position of the glycosyl donor would give the 1,2-*cis* glycosylation product *via* a β-coordinated *trans*-decalin type thiophenium ion intermediate, which would form preferentially over an α-coordinated *cis*-decalin intermediate. Subsequent S_N2-like substitution by the glycosyl acceptor would give the 1,2-*cis* glycoside (**Figure 2.1**).

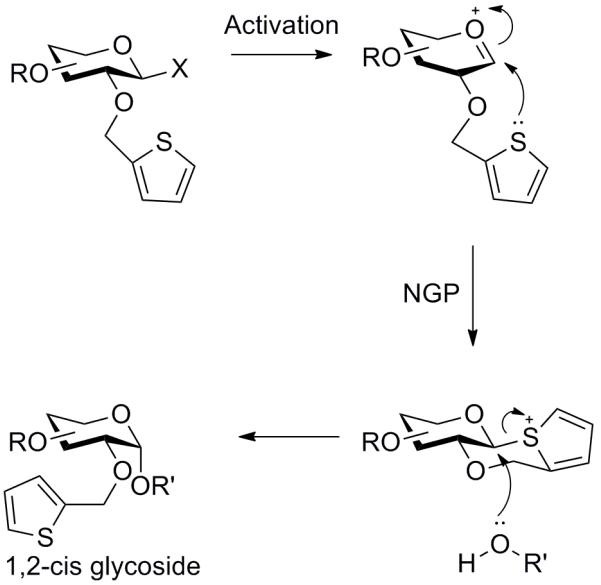


Figure 2.1. Putative α-selective glycosylation process involving neighbouring group participation (NGP) *via* an intermediate β-thiophenium ion.

It is well known that electrophiles generally react with thiophene through carbon and hence it should be noted that participation *via* the 3-position carbon of the thiophene ring could be possible. However, given Boons' findings it was thought that participation by thiophene group would occur *via* sulfur. It was thought that such an approach to the formation of 1,2-*cis* glycosides would be advantageous compared to the work reported by Boons *et al*. where a (1*S*)-phenyl-2-(phenylsulfanyl)ethyl moiety was appended to the 2-position,[2] as this procedure would not require the synthesis of a chiral protecting group but could potentially produce equally good results.

Hence the initial target of our investigations was to synthesise a set of glycosyl donors bearing a 2-*O*-(thiophen-2-ylmethyl) protecting group. In order to study the tolerance of the protecting group to a range of glycosylation conditions, three different types of glycosyl donor were chosen for investigation (**Figure 2.2**): glycosyl fluoride **2.1**, which can typically be activated under hard Lewis acidic conditions;[3,4] thioglycoside donor **2.2**, which can generally be activated using soft Lewis acidic conditions;[5,6] and finally trichloroacetimidate donor **2.3**, which can be activated using catalytic amounts of a hard Lewis acid, even at low temperature.[7-10]

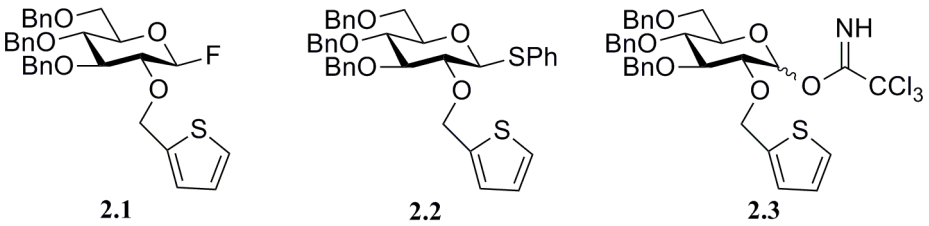


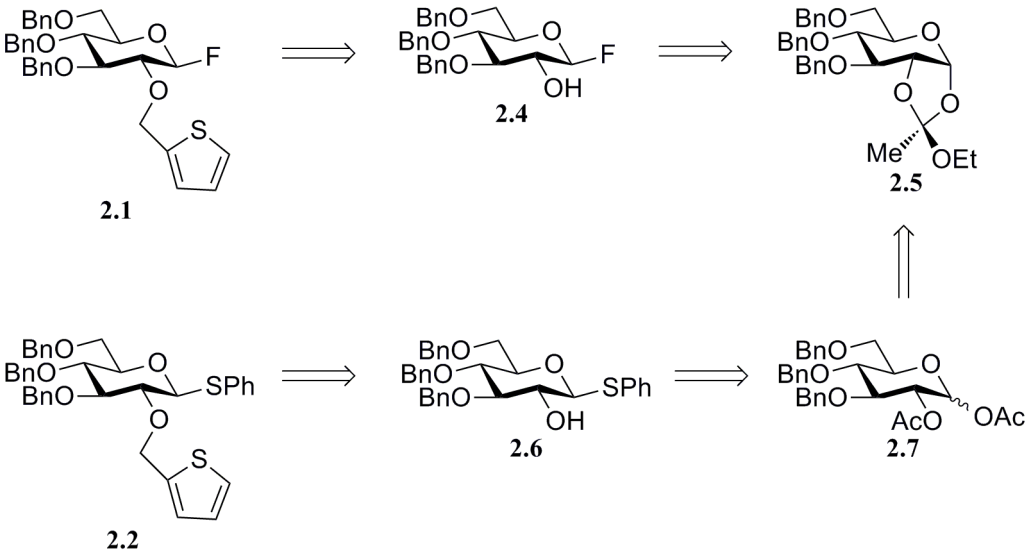
Figure 2.2. Target glycosyl donors.

In the case of the thioglycoside donor **2.2**, the phenyl thioglycoside derivative was chosen over an alkyl derivative as it is less labile and therefore easier to handle. Benzyl protection seemed the logical choice for the hydroxyl groups at the 3, 4 and 6-

positions as they would not only meet the essential requirement of being stable to glycosylation reaction conditions but would also be tolerant to any of the reaction conditions anticipated in the synthesis of the target donors.

2.2 Glycosyl Donor Retrosynthesis

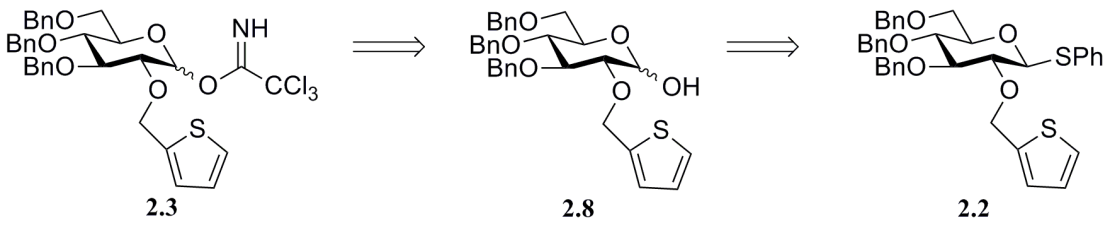
It was envisaged that installation of the thiophen-2-ylmethyl group in our target glycosyl donors would be achieved by taking a glycosyl donor where the 2-position was unprotected and treating it with a 2-halomethyl thiophene. Hence it was imagined that the glycosyl fluoride donor **2.1** could be accessed by alkylation of the glycosyl fluoride **2.4** with the appropriate 2-halomethyl thiophene under basic conditions, in much the same way that a benzyl protecting group is commonly installed on an alcohol using benzyl bromide. The alcohol **2.4** can be obtained in two steps from the orthoester **2.5** using methodology previously described within the group.[11] Reaction of **2.5** with diethylaminosulfur trifluoride (DAST) regioselectively opens the orthoester ring at the anomeric position affording the glycosyl fluoride exclusively in the β-configuration and leaving an acetate group at the 2-position with can be subsequently deprotected to give alcohol **2.4**. Orthoester **2.5** can be accessed in 3 steps from commercially available β-D-glucose pentaacetate using known procedures (**Scheme 2.1**).[12]



Scheme 2.1. Retrosynthetic analysis of glycosyl donors **2.1** and **2.2**.

The thioglycoside **2.2** could likewise by synthesised by alkylation of the corresponding alcohol **2.6**. Alcohol **2.6** was envisaged to be formed from the diacetate **2.7** which in turn could be obtained from **2.5** by acid hydrolysis of the orthoester and subsequent re-acetylation.

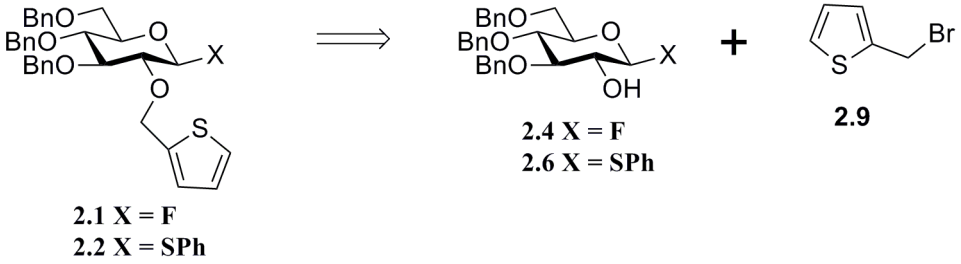
It was decided that formation of the trichloroacetimidate donor would best be left until the final step due to the high reactivity of the group. Hence it was thought that it would be ideal to form the trichloroacetimidate donor **2.3** from the hemiacetal **2.8** by reaction with trichloroacetonitrile and DBU. Hemiacetal **2.8** was envisaged to be formed by hydrolysis of the thioglycoside donor **2.2** using literature conditions (**Scheme 2.2**).[13,14]



Scheme 2.2. Retrosynthetic analysis of glycosyl donor **2.3**.

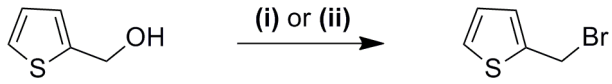
2.3 Synthesis of 2-Bromomethyl Thiophene

The synthesis of our glycosyl donor targets first required the formation of a 2-halomethyl thiophene derivative in order to install the (thiophene-2-yl)methyl protecting group to the 2-position of the glycosyl donors (**Scheme 2.3**).



Scheme 2.3. Retrosynthetic analysis of glycosyl donors **2.1** and **2.2**.

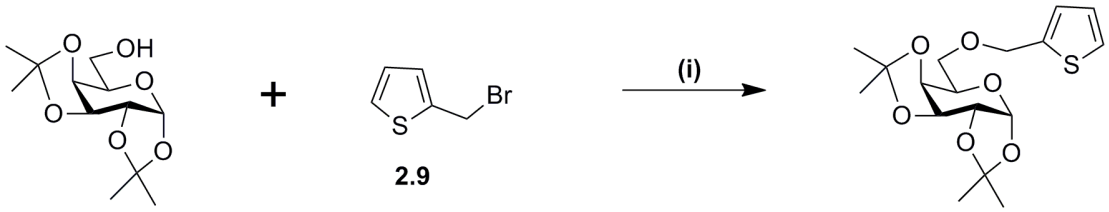
2-Bromomethyl thiophene **2.9** was thought to be a suitable candidate to carry out the alkylation reaction and had previously been synthesised from commercially available 2-thiophenemethanol **2.10**.[15] Whilst Rossi *et al*. had formed the bromide by reaction of the alcohol with phosphorus tribromide, we felt that milder Appel reaction conditions may be more appropriate.[16] Accordingly 2-thiophenemethanol **2.10** was treated with triphenylphosphine and carbon tetrabromide in diethyl ether. Although this method afforded **2.9** in good yield, the triphenylphosphine oxide formed in the reaction proved difficult to remove and column chromatography or distillation was required to purify the product. In order to see if it was possible to avoid this purification an alternative strategy was investigated where 2-thiophenemethanol **2.10** was treated with 33% HBr in glacial acetic acid and the product purified by aqueous work-up. This method afforded 2-bromomethyl thiophene **2.9** in an excellent yield of 85% (**Scheme 2.4**).



2.10 **2.9**

Scheme 2.4. (i) CBr_4, PPh_3, Et_2O, 0^oC to rt, 16 h, 72%; (ii) HBr/AcOH, Et_2O, 0^oC to rt, 16 h, 85%.

At this point a test alkylation was carried out to check that the thiophen-2-ylmethyl could be successfully installed. Diacetone galactose **2.11** was utilized as a model sugar alcohol and was treated with 2-bromomethyl thiophene **2.9** and sodium hydride in *N*,*N*-dimethylformamide (DMF), affording 1:2,3:4-di-*O*-isopropylidene-6-*O*-(thiophen-2-ylmethyl)-D-galactopyranoside **2.12** in an excellent yield of 94% (**Scheme 2.5**).

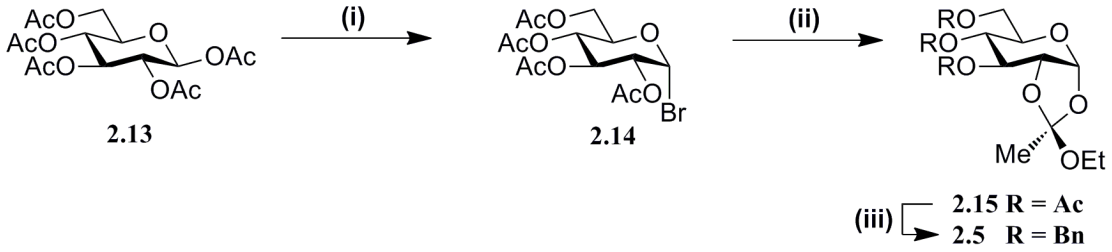


2.11 **2.9** **2.12**

Scheme 2.5. (i) NaH, DMF, 16 h, 94%.

2.4 Synthesis of Glycosyl Donors

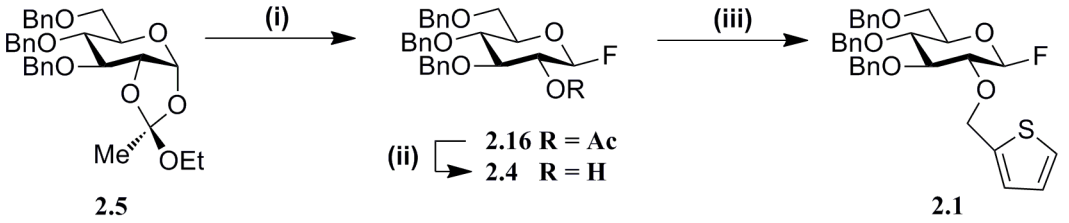
The known orthoester **2.5** was synthesized using standard procedures from commercially available β-D-glucose pentaacetate **2.13** (**Scheme 2.6**).[12] Treatment of **2.13** with 33% HBr in glacial acetic acid afforded the α-bromide **2.14**[17] in an essentially quantitative yield. Reaction of **2.14** with ethanol and the hindered base 2,4,6-collidine in the presence of a catalytic amount of tetrabutylammonium bromide gave the 3,4,6-*O*-acetyl protected orthoester **2.15**[18] in a yield of 92%. Deprotection of the acetyl groups was carried out under Zemplen conditions[19] and the resulting product was immediately treated with sodium hydride and benzyl bromide to give orthoester **2.5**[18] in a total yield of 86% over 3 steps.



Scheme 2.6. (i) HBr/AcOH, CH_2Cl_2, 0°C, 3 h, 99%; (ii) EtOH, 2,4,6-collidine, Bu_4NBr, CH_2Cl_2, 50°C, 16 h, 92%; (iii) NaOMe, MeOH, 1 h; then BnBr, NaH, DMF, 16 h, 95%.

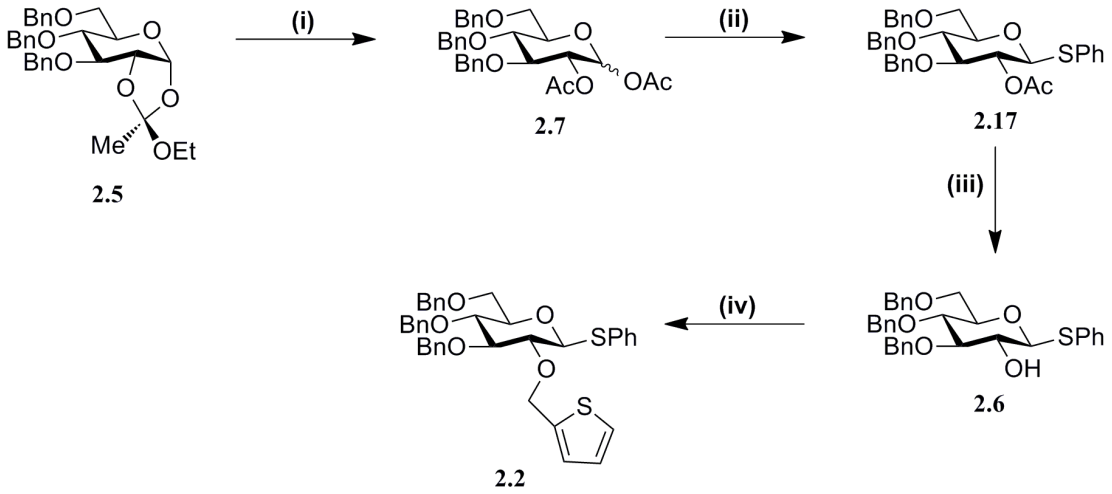
The orthoester **2.5** could now serve as a divergent intermediate for the synthesis of our three target glycosyl donors. First of all the 2-*O*-acetyl glycosyl fluoride **2.16** was accessed by opening of **2.5** with diethylaminosulfur trifluoride (DAST), giving the β-fluoride in high yield. It had previously been discovered within the group that deacetylation of **2.16** under Zemplen conditions resulted in some displacement of the fluoride with methoxide, hence a modified *n*-propylamine mediated deprotection was used to cleanly afford the alcohol **2.4**.[11] Treatment of the alcohol with 2-bromomethyl

thiophene **2.9** and sodium hydride in DMF produced the target glycosyl fluoride **2.1** in an overall yield of 53% in 3 steps from **2.5** (**Scheme 2.7**).



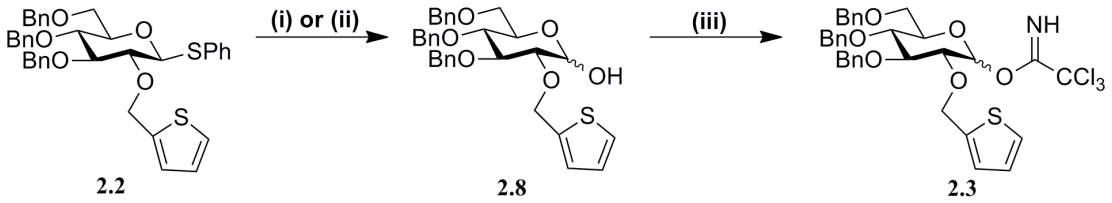
Scheme 2.7. (i) DAST, CH_2Cl_2, 0°C to rt, 4 h, 80%; (ii) THF/MeOH/^{n}PrNH$_2$, 45°C, 16 h, 90%; (iii) **2.9**, NaH, DMF, 16 h, 74%.

Alternatively treatment of orthoester **2.5** with aqueous acetic acid produced a mixture of monoacetates, which were immediately converted to the anomeric mixture of diacetates **2.7**[20] (α:β ratio, 13:1) by treatment with acetic anhydride and pyridine. Reaction of **2.7** with thiophenol and boron trifluoride diethyl etherate produced the β-thiophenyl glycoside **2.17**[21] in excellent yield**,** from which the 2-*O*-acetate was removed by under Zemplen conditions, yielding alcohol **2.6**.[22] Alkylation of **2.6** with **2.9**, again achieved by treatment with sodium hydride in DMF, gave the target thioglycoside donor **2.2** in an overall yield of 48% in 4 steps from **2.5** (**Scheme 2.8**).



Scheme 2.8. (i) $AcOH/H_2O$, 16 h; then Ac_2O, DMAP, pyridine, 16 h, 81%; (ii) PhSH, $BF_3.OEt_2$, CH_2Cl_2, 6 h, 89%; (iii) NaOMe, MeOH/THF, 16h, 85%; (iv) **2.9**, NaH, DMF, 16h, 78%

Finally access to our third target glycosyl donor, trichloroacetimidate **2.3**, was carried out by hydrolysis of thioglycoside **2.2** to give the anomeric mixture of hemiacetals **2.8**. Hydrolysis was mediated by either *N*-iodosuccinimide (NIS) and trifluoroacetic acid (TFA)[13] or by *N*-bromosuccinimide (NBS) in wet acetone,[14] affording the hemiacetals **2.8** in equally good yields and similar anomeric ratios (typically a 2:1 mixture α:β was observed). The mixture of hemiacetals **2.8** was then treated with trichloroacetonitrile and DBU to produce the trichloroacetimidate donor **2.3** as an anomeric mixture (α:β ratio, 15:1) in an overall yield of 67% in 2 steps from **2.2** (**Scheme 2.9**).



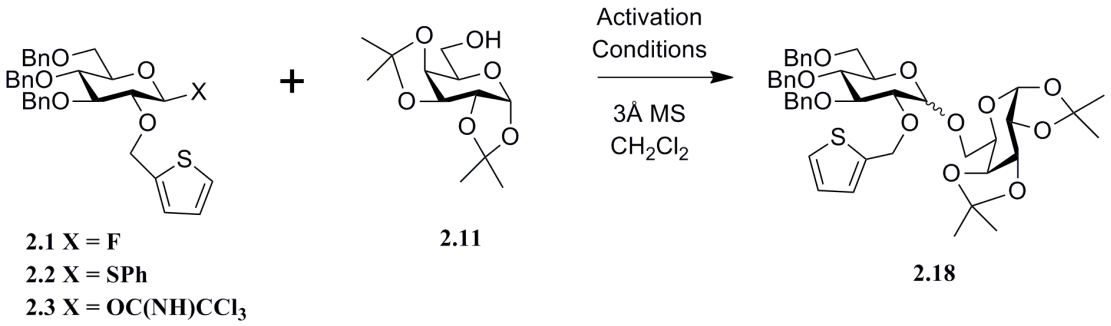
Scheme 2.9. (i) TFA, NIS, CH_2Cl_2/H_2O, 0 °C, 2 h, 84%; (ii) NBS, Acetone/H_2O, 1 h, 82%; (iii) Cl_3CCN, DBU, CH_2Cl_2, 0 °C, 3h, 80%.

2.5 Glycosylation Reactions of donors 2.1, 2.2 and 2.3

With the selection of glycosyl donors **2.1**, **2.2** and **2.3** in hand, attention turned towards preliminary investigations into the neighbouring group participation of the 2-*O*-(thiophen-2-ylmethyl) protecting group and its influence on the stereochemical outcome of a glycosylation reaction.

Diacetone galactose **2.11** was chosen as a model acceptor for our initial glycosylation studies. This acceptor was chosen as it is known that the use of primary sugar alcohols often leads to poor α-selectivity in glycosylation reactions[23] and hence any increase in selectivity due to neighbouring group participation would be obvious. The solvent of choice for our studies was dichloromethane: a non-participating solvent which would not directly influence the stereochemical outcome of the glycosylation. It was decided that the reactions would be studied over a range of temperatures to determine optimum conditions. Boons *et al*. had shown that when using either thiophene or phenyl-thioethyl ether to form an intermediate sulfonium ion intermolecularly that higher temperatures resulted in greater α-selectivity.[1] However, when the same group carried out research on the formation of sulfonium ion intermediates formed intramolecularly very low temperatures were employed at the initiation of reaction to achieve greater selectivity.[2] The initial results of the glycosylation reactions of **2.1**, **2.2** and **2.3** are outlined below (**Table 2.1**).

Table 2.1. Glycosylation of diacetone galactose **2.11** (2 eq.) with donors **2.1**, **2.2** and **2.3**.



2.1 X = F
2.2 X = SPh
2.3 X = $OC(NH)CCl_3$

2.11

2.18

Entry	Glycosyl Donor	Activation Conditions	Time (h)	Temp. (°C)	Yield of **2.18** (%)	α:β ratio[a] (σ)
a	**2.1**	1.5 eq. $BF_3.OEt_2$	0.5	0	45	1:1.25 (0.05)
b	**2.1**	1.5 eq. $BF_3.OEt_2$	1	-40	40	1:1 (0.03)
c	**2.1**	1.5 eq. $BF_3.OEt_2$	1.5	-78	36	2:1 (0.05)
d	**2.2**	1.5 eq. NIS, 0.5 eq. TMSOTf	1	0	36	1.5:1 (0.08)
e	**2.2**	1.5 eq. NIS, 0.5 eq. TMSOTf	2	-40	51	2:1 (0.05)
f	**2.2**	1.5 eq. NIS, 0.5 eq. TMSOTf	3.5	-78	48	6:1 (0.10)
g	**2.3**	0.1 eq. TMSOTf	0.5	0	93	1:1.25 (0.08)
h	**2.3**	0.1 eq. TMSOTf	1	-40	84	9:1 (0.08)
i	**2.3**	0.1 eq. TMSOTf	1.5	-78	71	8:1 (0.03)

[a]Anomeric ratios were determined by integration of appropriate peaks in the ^{1}H nmr spectra. Glycosylation reactions were carried out in triplicate to confirm the reproducibility of results, and α:β ratios are given as a mean average (standard deviation given in brackets).

Glycosyl fluoride **2.1** was activated with supra-stoichiometric quantities boron trifluoride diethyl etherate in the presence of an excess (2 eq.) of diacetone galactose. At all temperatures poor yields of product were observed, with t.l.c. indicating the formation of polar by-products in the reaction. Moreover disaccharide **2.17** was produced as an anomeric mixture of products, and although the α-selectivity increased with decreased reaction temperature, even at -78 ^{o}C only very modest selectivity was observed in favour of the desired α-anomer (α:β ratio, 2:1, **Table 2.1**, entry c).

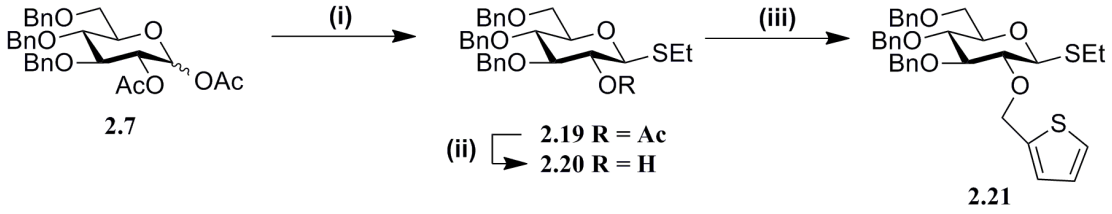
Attention turned to thioglycoside donor **2.2**, which was activated using supra-stoichiometric quantities of NIS with trimethylsilyl trifluoromethanesulfonate (TMSOTf). Again overall yields for glycosylation were poor, and the formation of numerous by-products indicated the non-orthogonal reactivity profile of the thioglycoside and the thiophene moieties. Moreover anomeric selectivity was again modest, though at -78 ^{o}C the desired α-anomer was favoured (α:β ratio, 6:1, **Table 2.1**, entry f).

Finally the use of trichloroacetimidate **2.3** as the donor was investigated. Activation of **2.3** in the presence of **2.11** with a catalytic amount of TMSOTf at 0 ^{o}C produced disaccharide **2.18** in an excellent 93% yield, but with low anomeric selectivity actually slightly in favour of the undesired β-anomer (α:β ratio 1:1.25, **Table 2.1**, entry g). However reducing the reaction temperature to -40 ^{o}C had a marked effect on the stereoselectivity of glycosylation, with **2.18** produced in good yield (84%) and with high stereoselectivity in favour of the desired α-anomer (α:β ratio 9:1, **Table 2.1**, entry h). Lowering the reaction temperature further (entry i) did not improve either the yield or stereoselectivity, so it was concluded that -40 ^{o}C represented the optimum temperature for glycosylation of the trichloroacetimidate donor **2.3**.

The results were very interesting, as although the reactions of the trichloroacetimidate donor **2.3** definitely suggested that a β-coordinated thiophenium ion was being formed and that it was directing the glycosylation to be α-selective, the yields and selectivities obtained when using donors **2.1** and **2.2** were very disappointing and suggested that the activation conditions employed were not orthogonal to the thiophen-2-ylmethyl group. The major difference between the activation conditions of **2.1** and **2.2** compared to **2.3** was that in the former case supra-stoichiometric quantities of Lewis acid were being used, whilst in the latter case catalytic Lewis acid was employed. The

t.l.c analysis of the activation of both glycosyl fluoride **2.1** and thioglycoside **2.2** certainly suggested that degradation of the starting material and/or product was occurring; however none of the by-products observed were able to be isolated cleanly for analysis. Ether protecting groups have been known to be cleaved under Lewis acidic conditions,[24] so it was plausible that in the presence of excess Lewis acid thiophen-2-ylmethyl deprotection was occurring to some extent.

In the case of the thioglycoside **2.2**, although the yields were poor the anomeric selectivity observed at -78 ^{o}C was encouraging (α:β ratio, 6:1, **Table 2.1**, entry f), especially if the reaction was being hindered by the formation of by-products. Hence it was decided that an alternative thioglycoside donor would be investigated. Ethyl thioglycosides can be activated under much milder conditions compared to phenyl thioglycosides and hence thioethyl glycoside donor **2.21** was synthesised for study using the same strategy as employed for the formation of thiophenyl glycoside **2.2** (**Scheme 2.10**).

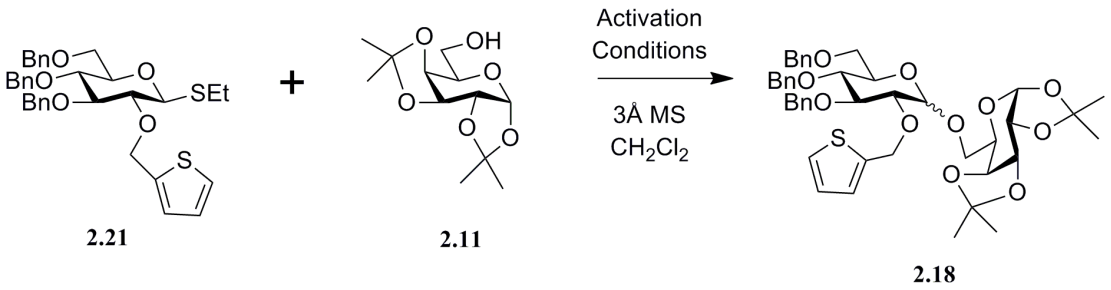


Scheme 2.10. (i) EtSH, $BF_3.OEt_2$, CH_2Cl_2, 6 h, 88%; (ii) NaOMe, MeOH/THF, 16h, 92%; (iii) **2.9**, NaH, DMF, 16h, 81%.

Reaction of the diacetates **2.7** with ethanethiol and boron trifluoride diethyl etherate produced the β-thioethyl glycoside **2.19**[25] which was subsequently deacetylated under Zemplen conditions, yielding alcohol **2.20**.[26] Alkylation of **2.20** with 2-bromomethyl thiophene **2.9** by treatment with sodium hydride in DMF proceeded smoothly to give

the thioglycoside donor **2.21** in an overall yield of 66% in 3 steps from **2.7**. The glycosylation reactions of **2.21** are summarised below (**Table 2.2**).

Table 2.2. Glycosylation of diacetone galactose (2 eq.) with donor **2.21**.



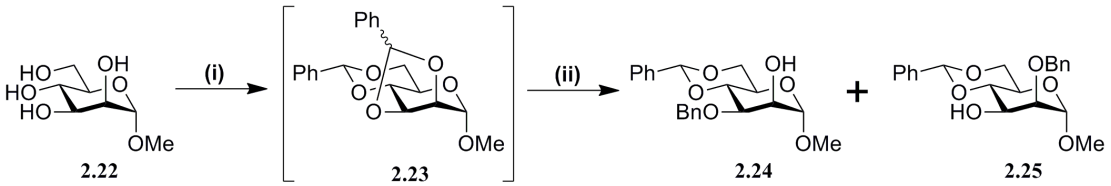
Entry	Glycosyl Donor	Activation Conditions	Time (h)	Temp. (°C)	Yield of **2.18** (%)	α:β ratio[a] (σ)
a	**2.21**	4.5 eq. MeOTf, 4.5 eq TTBP	6	0	55	1.25:1 (0.05)
b	**2.21**	4.5 eq. MeOTf, 4.5 eq TTBP	16	-40	46	1.5:1 (0.08)
c	**2.21**	4.5 eq. MeOTf, 4.5 eq TTBP	16	-78	43	2:1 (0.10)

[a]Anomeric ratios were determined by integration of appropriate peaks in the ^{1}H nmr spectra. Glycosylation reactions were carried out in triplicate to confirm the reproducibility of results, and α:β ratios are given as a mean average (standard deviation given in brackets).

Thioglycoside **2.21** was activated using supra-stoichiometric quantities of methyl trifluoromethanesulfonate (MeOTf) with tri-*tert*-butyl pyrimidine (TTBP) as a hindered base to neutralize the trifluoromethanesulfonic acid produced in the reaction. Disappointingly yields for glycosylation were poor, although the reaction appeared to proceed much more cleanly compared to activation of the thiophenyl glycoside **2.2**. Even more disappointing however was the fact that anomeric selectivity had decreased compared to **2.2**, again suggesting that the action of the neighbouring group was being hindered by the reaction conditions.

2.6 Glycosylation Reactions of 2.3 with a Variety of Acceptors

Having ascertained that trichloroacetimidate donor **2.3** gave good α-selectivity in the glycosylation reaction with diacetone galactose **2.11**, we next set out to investigate glycosylation of **2.3** with a series of different acceptors under the best conditions previously observed. We were particularly interested in the glycosylation of **2.3** with a secondary alcohol acceptor, and hence we began by synthesizing a pair of secondary alcohol acceptors from methyl α-D-mannopyranoside **2.22** using known procedures (**Scheme 2.11**).[27]

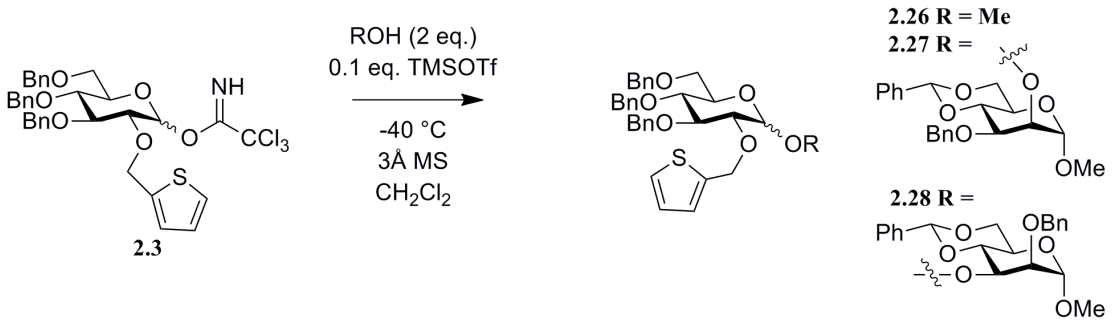


Scheme 2.11. (i) $PhCH(OMe)_2$, CSA (cat.), DMF, 60 °C, 250 mbar, 5 h;
(ii) DIBAL-H, toluene, 0 °C to rt, 2 h, **2.24** 32%, **2.25** 50%.

Treatment of **2.22** with benzaldehyde dimethylacetal and a catalytic amount of camphor sulfonic acid (CSA) gave the mixture of *endo* and *exo* dibenzylidenes **2.23**. The crude mixture **2.23** was then treated with di-*iso*-butyl aluminium hydride (DIBAL-H) to give the mixture of alcohols **2.24** and **2.25**, which were separated by column chromatography, in 32% and 50% yield respectively.

With these acceptors in hand, glycosylation was carried out using donor **2.3** at -40 °C in dichloromethane with a series of alcohol acceptors (**Table 2.3**).

Table 2.3. Glycosylation of **2.3** with a variety of acceptors.

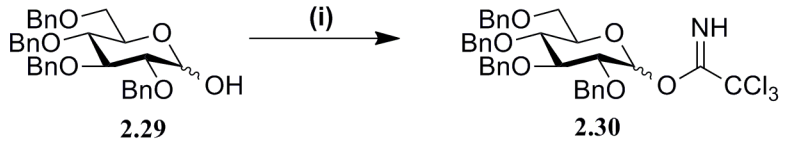


Entry	Acceptor	Product	Time (h)	Temp. (°C)	Yield (%)	α:β ratio[a] (σ)
a	MeOH	**2.26**	0.5	-40	90	1.5:1 (0.03)
b	**2.24**	**2.27**	4.5	-40	55	30:1 (0.57)
c	**2.25**	**2.28**	4.5	-40	54	28:1 (0.70)

[a]Anomeric ratios were determined by integration of appropriate peaks in the ^{1}H nmr spectra. Glycosylation reactions were carried out in triplicate to confirm the reproducibility of results, and α:β ratios are given as a mean average (standard deviation given in brackets).

Glycosylation with methanol as an acceptor produced methyl glycoside **2.26** in a good yield but with low stereoselectivity (α:β ratio 1:1.5, **Table 2.3**, entry a) indicating that the stereoselectivity of glycosylation was dependent on the steric bulk of the glycosyl acceptor. However with the secondary alcohols **2.24** and **2.25** as glycosyl acceptors the α-selectivity observed was considerable; glycosylation of the axial secondary alcohol of **2.24** produced disaccharide **2.27** with very high α-selectivity (α:β ratio 30:1, **Table 2.3**, entry b), whilst reaction of acceptor **2.25** possessing an equatorial secondary alcohol group produced disaccharide **2.28** with equally high selectivity (α:β ratio 28:1, **Table 2.3**, entry c). Although the yields for these reactions were somewhat modest, it is worth noting that these glycosylation reactions were carried out under the optimum conditions observed for glycosylation with diacetone galactose **2.11** and would almost certainly be increased if an optimised procedure was investigated.

At this point a set of control reactions were carried out to confirm that the observed high α-selectivity was due to the presence of the thiophene moiety at the 2-position of the donor. This required the synthesis of a trichloroacetimidate glycosyl donor with a non-participating group at the 2-position. We decided that a benzyl group would be the easiest to employ and hence donor **2.30**[28] was synthesised from commercially available 2,3,4,6-tetra-*O*-benzyl-D-α/β-glucopyranose **2.29** by treatment with trichloroacetonitrile and DBU (**Scheme 2.12**).

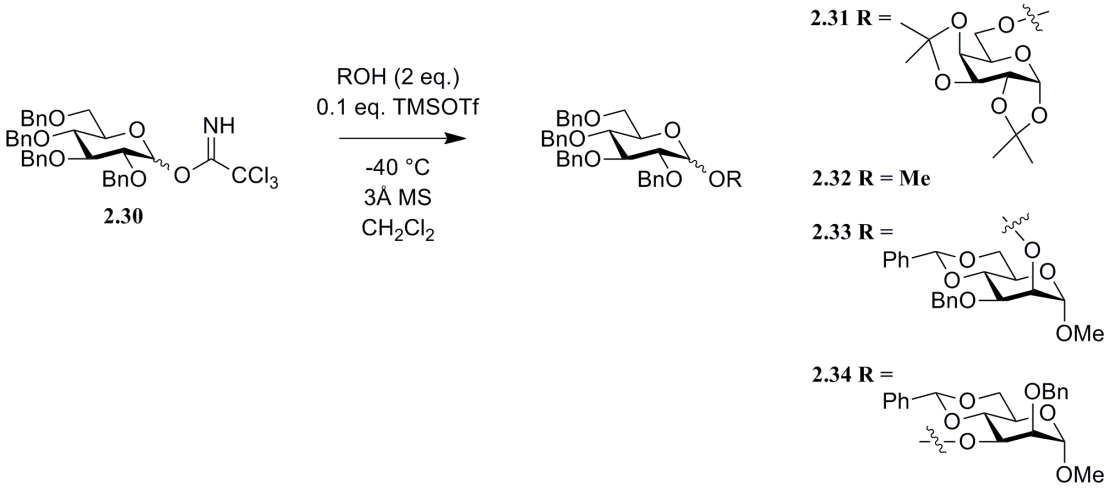


2.29 **2.30**

Scheme 2.12. (i) Cl_3CCN, DBU, CH_2Cl_2, 0 °C, 3h, 91%.

Trichloroacetimidate donor **2.30** was then subjected to glycosylation with the same series of acceptors as previously described under the same reaction conditions (**Table 2.4**).

Table 2.4. Control glycosylation of acceptors with donor **2.30**.



Entry	Acceptor	Product	Time (h)	Temp. (°C)	Yield (%)	α:β ratio[a] (σ)
a	**2.11**	**2.31**	1	-40	80	1:4 (0.05)
b	MeOH	**2.32**	0.5	-40	87	1:8 (0.03)
c	**2.24**	**2.33**	4.5	-40	68	2:1 (0.05)
d	**2.25**	**2.34**	4.5	-40	60	3:1 (0.05)

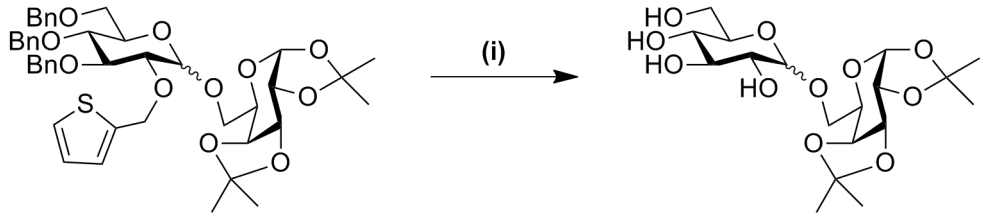
[a]Anomeric ratios were determined by integration of appropriate peaks in the ^{1}H nmr spectra. Glycosylation reactions were carried out in triplicate to confirm the reproducibility of results, and α:β ratios are given as a mean average (standard deviation given in brackets).

Glycosylation of **2.30** with diacetone galactose **2.11** produced disaccharide **2.31**[29] as anomeric mixture in favour of the β-anomer (α:β ratio 1:4, **Table 2.4**, entry a). This inherent preference for β-selectivity for sterically unhindered acceptors was confirmed by glycosylation of **2.30** with methanol, which produced methyl glycosides **2.32**[30] with high β-selectivity (α:β ratio 1:8, **Table 2.4**, entry b). Glycosylation with the more hindered secondary alcohol carbohydrate acceptors **2.24** and **2.25** produced disaccharides **2.33**[29] and **2.34** respectively as mixtures in which the α-anomer was slightly favoured (**Table 2.4**, entries c and d), but in both of these cases the observed stereoselectivity was a factor of 10 lower than that observed for the corresponding 2-

O-(thiophen-2-yl)methyl donor **2.3**, confirming the α-stereo-directing effect of the thiophen-2-ylmethyl group.

2.7 Deprotection of the Thiophen-2-ylmethyl Protecting Group

As an aryl group it was imagined that deprotection of the thiophen-2-ylmethyl protecting group could be achieved in a similar fashion to that of a benzyl group. Benzyl ethers are most commonly removed under hydrogenation conditions using a heterogeneous palladium catalyst.[31,32] In our case, due to the presence of the thiophene group, it was anticipated that any attempt to perform a hydrogenation would result in poisoning of the catalyst. An alternative reductive method of removing benzyl ethers is to perform a Birch reduction with sodium in liquid ammonia.[33,34] To ascertain whether the thiophen-2-ylmethyl protecting group could also be removed under such conditions, disaccharide **2.18** was subjected to Birch reduction conditions (**Scheme 2.13**).

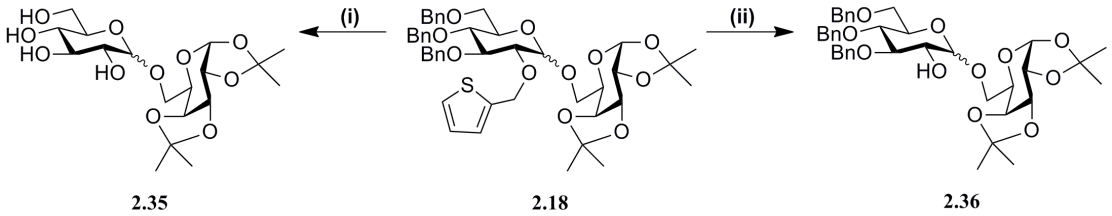


2.18 **2.35**

Scheme 2.13. (i) Na, NH_3(l)/THF, -100 °C, 1 h, 62% .

Pleasingly the reaction cleaved both the benzyl ethers and the thiophen-2-ylmethyl ether to produce known disaccharide **2.35**,[35,36] however in only a moderate yield of 62% yield. Importantly analysis of the NMR spectra showed that the anomeric integrity of the disaccharide had remained unchanged, indicating that the conditions did not cause isomerisation of the glycosidic bond.

Benzyl ethers are also known to be cleaved using Lewis acids such as trimethylsilyl iodide (TMSI).[24] The glycosylation results observed for donors **2.1** and **2.2** (**Table 2.1**), where an excess of Lewis acid was used as an activator, had hinted that deprotection of the thiophen-2-ylmethyl protecting group may have been occurring as a number of polar by-products were observed to form in the reactions. Hence it was decided that a TMSI mediated deprotection of the thiophen-2-ylmethyl group would be investigated. Indeed it was imagined that as thiophene is more electron rich than benzene deprotection may occur more readily for the thiophen-2-ylmethyl group compared with a benzyl group, and hence orthogonal deprotection may be possible (**Scheme 2.14**).



Scheme 2.14. (i) TMSI (4.5 eq.), CH_2Cl_2, 16 h, 85%; (ii) TMSI (1 eq.), CH_2Cl_2, 0 °C, 0.5 h, 78%.

First of all global deprotection was investigated by treating disaccharide **2.18** with an excess (4.5 eq.) of TMSI in anhydrous dichloromethane. Pleasingly deprotection of all the aryl ethers was observed, affording disaccharide **2.35** in a higher yield compared to Birch reduction (**Scheme 2.13**). Secondly selective deprotection of the thiophen-2-ylmethyl group was studied by treating **2.18** with a single equivalent of TMSI. The reaction was initially carried out at room temperature where analysis of the reaction mixture after 30 minutes by mass spectrometry indicated the presence of the selectively cleaved disaccharide **2.36**[37,38] as well as some further debenzylated material. Importantly however no starting material, or product containing the thiophen-2-ylmethyl group, was observed to be present, indicating that the thiophen-

2-yl methyl protecting group was indeed more labile than the benzyl ethers. It was subsequently found that reducing the reaction temperature to 0 °C improved the selectivity for deprotection further and disaccharide **2.36** was obtained in a yield of 78%.

2.8 Conclusions and Future Work

In conclusion, a series of glycosyl donors bearing a 2-*O*-(thiophen-2-ylmethyl) protecting group have been synthesized. Glycosylation with fluoride donor **2.1** and thioglycoside donors **2.2** and **2.21** gave poor yields and low α-selectivity, demonstrating that the activation conditions used were incompatible with the thiophen-2-ylmethyl protecting group. Glycosylation with trichloroacetimidate donor **2.3,** however, proceeded in good to excellent yields with a series of glycosyl acceptors and resulted in highly α-selective glycosylation; higher α-stereoselectivity being observed with more hindered carbohydrate acceptors. Based on comparison with previous work by Boons *et al.*, it is postulated that this high α-selectivity results from the intramolecular formation of an intermediate β-thiophenium ion, which then undergoes S_N2-like substitution by the glycosyl acceptor. Although the stereocontrol during these glycosylation processes is lower than the optimum results reported by Boons using the (S)-(phenylthiomethyl)benzyl moiety at the 2-position,[2] this procedure does not require the synthesis of a chiral acetic acid (1*S*)-phenyl-2-(phenylsulfanyl)ethyl ester, making the use of the thiophen-2-ylmethyl group perhaps more amenable to routine synthetic use.

It has also been shown that the thiophen-2-ylmethyl protecting group can be efficiently and selectively removed in the presence of benzyl ethers, demonstrating

the potential utility of the group as a protecting group in not only carbohydrate chemistry but in any form of organic synthesis.

Recently Boons and co-workers published results indicating that the formation of a β-sulfonium ion intermediate formed intramolecularly on a sugar was dependant on the protecting groups employed.[39] It was observed that electron withdrawing protecting groups such as acetate or benzoate esters, which destabilise the oxacarbenium ion formed upon activation, were critical for formation of a β-sulfonium ion intermediate, and thus α-selectivity, in donors bearing the (1*S*)-phenyl-2-(phenylsulfanyl)ethyl moiety at the 2-position. When benzyl ethers were employed the selectivity was observed to decrease drastically. In light of these findings it suggests that if we were to use electron withdrawing protecting groups at the 3, 4, and/or 6-positions, as opposed to electron donating benzyl groups, we may observe even greater α-selectivity in the glycosylation reactions.

Formation of the β-thiophenium ion may also be aided by increasing the electron density in the thiophene ring. A more electron rich thiophene ring could be imagined to form a more stable thiophenium ion intermediate and consequently increase the α-selectivity observed in the reaction. Hence the introduction of electron donating groups to the ring of the thiophen-2-ylmethyl group would be interesting to investigate. Furthermore substitution on both the ring and at the aryl position of the donor could be imagined to increase the rate at which cyclisation to form the β-thiophenium ion occurs, as this would be expected to limit the number of conformations adopted by the group in accordance with the Thorpe-Ingold (gem-dimethyl) effect.[40] It is obvious that there are many ideas which could improve upon the results already obtained and hence the use of the thiophen-2-ylmethyl group warrants further investigation.

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Chapter 3: Synthesis and Evaluation of Glycosyl donors bearing a 2-*O*-(2-(phenylselenyl)ethyl) protecting group

3.1 Introduction

Given that Boons and co-workers had demonstrated that sulfur containing groups were capable of selectively forming β-thiophenium ions in glycosylation reactions and thus direct α-selectivity in the glycosylation product,[1,2] we felt that investigation into the neighbouring group participation of a selenium containing protecting group was a logical progression. We were immediately drawn to the potential use of the known 2-(phenylselenyl)ethyl protecting group[3,4] as a participating group in glycosylation. It was considered that a 2-(phenylselenyl)ethyl group appended at the 2-postion of a glycosyl donor would give the 1,2-*cis* glycosylation product *via* a β-coordinated *trans*-decalin type selenonium ion intermediate, in much the same way as the thiophen-2-ylmethyl group discussed in chapter 2 (**Figure 3.1**).

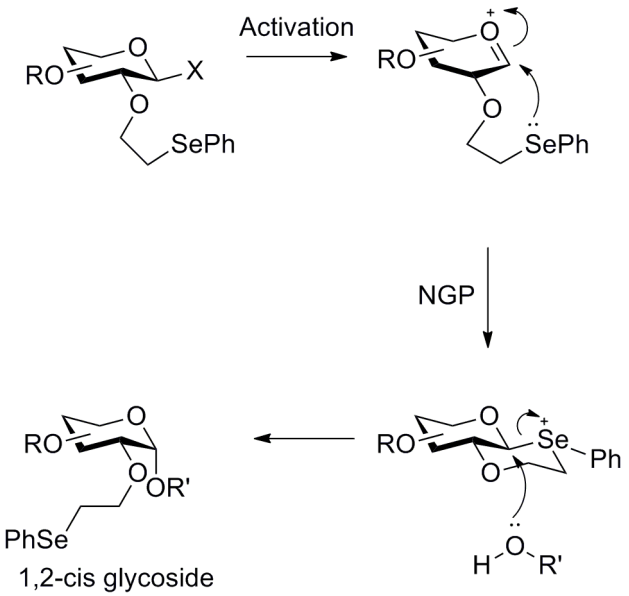
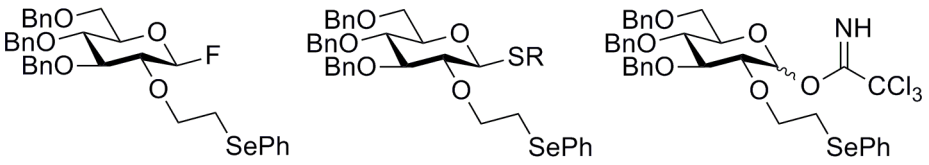


Figure 3.1. Putative α-selective glycosylation process involving neighbouring group participation (NGP) *via* an intermediate β-selenonium ion.

It is reasonable to predict that a selenium derivative will in fact be a better neighbouring group compared to a sulfur derivative due to the expected increase in nucleophilicity. Indeed previous studies support this hypothesis, for example McManus and co-workers have shown that neighbouring group participation of a phenylselenyl group in the solvolysis of 2-(phenylselenyl)ethyl chloride is much faster than the corresponding neighbouring group participation of the thiophenyl group in 2-(phenylthio)ethyl chloride.[5] The important question that needs to be addressed is perhaps not whether neighbouring group participation will occur, but whether the selenonium ion intermediate formed will show the same preference for β-coordination that is observed with sulfonium ions.

We therefore aimed to synthesise a range of glycosyl donors bearing a 2-*O*-(2-(phenylselenyl)ethyl) protecting group in order to investigate their potential for neighbouring group participation in glycosylation reactions. As with our investigations with the thiophen-2-ylmethyl group, we wished to target a range of different glycosyl donors to test the tolerance of the substrate to varying conditions (**Figure 3.2**).



3.1 **3.2 R = Ph** **3.3 R = Et** **3.4**

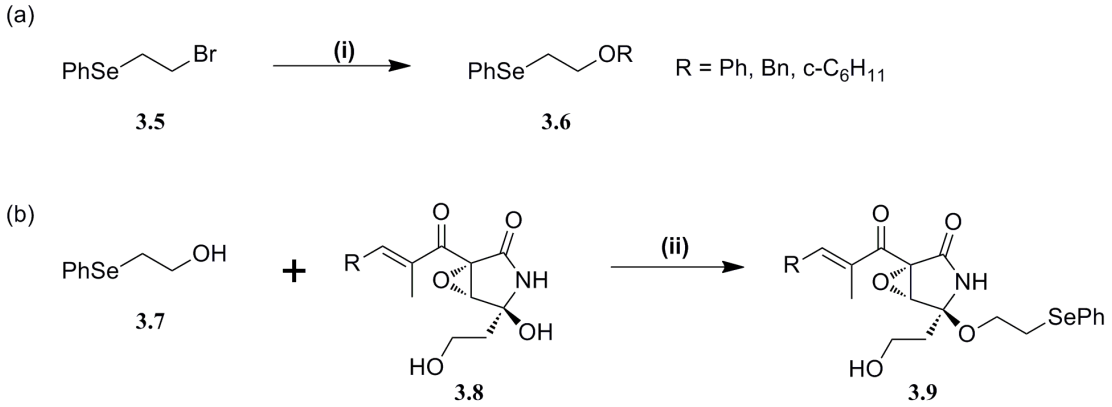
Figure 3.2. Target glycosyl donors.

Our initial targets for synthesis were glycosyl fluoride **3.1**, thioglycoside donors **3.2** and **3.3**, and trichloroacetimidate donor **3.4**. It was anticipated that the phenylselenyl group may not be orthogonal to the activation conditions of the phenyl thioglycoside

3.2, and hence the ethyl thioglycoside **3.3**, which can be activated under milder conditions, would also be synthesised.

3.2 Glycosyl Donor Retrosynthesis

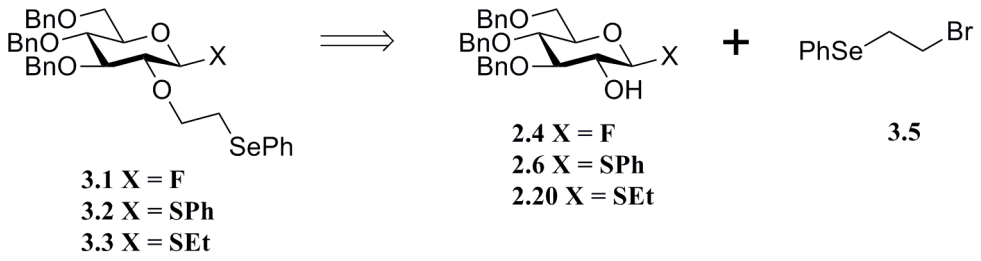
Although examples are limited, the use of the 2-(phenylselenyl)ethyl group as a protecting group for alcohols has been previously reported. In 1975 Ho showed that the group could be installed efficiently on phenol, benzyl alcohol and cyclohexanol and also demonstrated that the moiety was stable to a range of conditions.[3] The group was installed by reaction of the alcohols with 2-(phenylselenyl)ethyl bromide **3.5** and silver nitrate to give the 2-(phenylselenyl)ethyl ethers **3.6** in yields of 80-90%. More recently Yamaguchi *et al*. utilised the group in the total synthesis of lucilactaene,[4] however they installed the group in a different manner using 2-(phenylselenyl)ethanol **3.7** as a nucleophile to attack the carbocation formed when the tertiary alcohol **3.8** was treated with catalytic amounts of *para*-toluenesulfonic acid, producing the protected compound **3.9** in a poor yield of 31% (94% based on recovered starting material) (**Scheme 3.1**).



Scheme 3.1. Examples of 2-(phenylselenyl)ethyl Protected Alcohols.

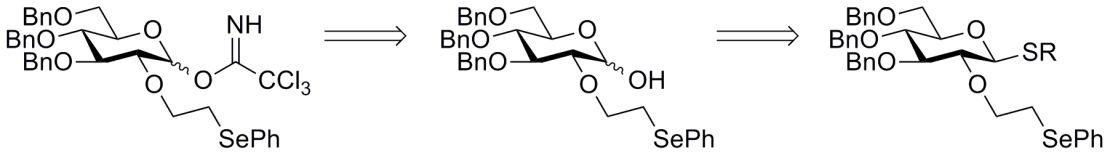
(i) $AgNO_3$, MeCN; (ii) $TsOH.H_2O$, CH_2Cl_2.

To our knowledge these were the only examples of the use of the 2-(phenylselenyl)ethyl ether protecting group in the literature. Given that Yamaguchi's method of installation was not applicable to our targets, we chose to apply Ho's methodology in the formation of our target glycosyl donors. Hence in order to synthesise glycosyl donors **3.1**, **3.2** and **3.3** we planned to treat the corresponding 2-OH glycosyl donors **2.4**, **2.6**, and **2.20**, the synthesis of which was described in chapter 2, with bromide **3.5** under the same conditions described by Ho (**Scheme 3.2**). Bromide **3.5** can be synthesised by reaction of commercially available phenylselenyl bromide (PhSeBr) with ethene.[6]



Scheme 3.2. Retrosynthetic analysis of glycosyl donors **3.1, 3.2** and **3.3**.

Synthesis of the trichloroacetimidate donor **3.4** was anticipated to be more difficult. Ideally we wished to apply the same synthetic route that was applied in the synthesis of the trichloroacetimidate donor **2.3**, described in chapter 2. This would hence require hydrolysis of either thioglycoside **3.2** or **3.3** to afford the hemiacetal **3.10**, however if we were to apply the same method of hydrolysis described previously[7,8] we would almost certainly observe reaction of either NIS or NBS with the phenylselenyl moiety. However it was thought that hydrolysis of the thioglycoside would still be the most convenient route to the donor **3.4**, and hence we decided that we would attempt to investigate new hydrolysis protocols if the current methodology proved to be unsuccessful (**Scheme 3.3**).

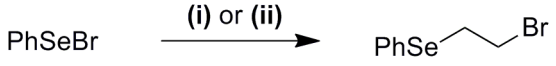


3.4 **3.10** **3.2 R = Ph**
3.3 R = Et

Scheme 3.3. Retrosynthetic analysis of trichloroacetimidate donor **3.4**.

3.3 Synthesis of Glycosyl Donors

Before synthesis of the glycosyl donors could begin, we first needed to synthesise 2-(phenylselenyl)ethyl bromide **3.5**. This was accomplished according to the literature procedure by bubbling ethene gas through a solution of phenylselenyl bromide **3.11** in glacial acetic acid at room temperature (**Scheme 3.4**).[6] The reaction was accompanied by a rapid colour change after only a few minutes which indicated that the reaction was complete. Subsequent aqueous work up afforded the bromide **3.5** in a yield of 81%. It struck us that acetic acid did not seem entirely necessary and hence the reaction was subsequently attempted using dichloromethane as the solvent. Pleasingly the reaction worked equally well with the alternative solvent and in this case simple removal of the dichloromethane *in vacuo* afforded the bromide **3.5** cleanly and in essentially quantitative yield.

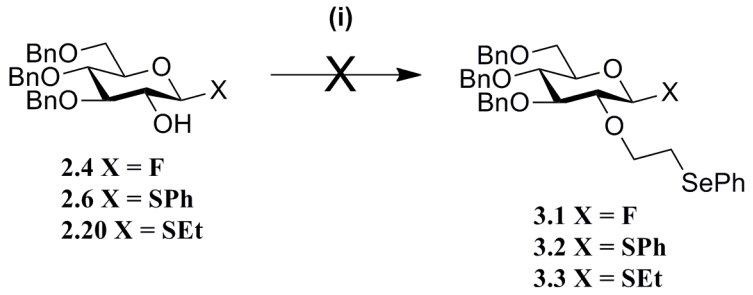


3.11 **3.5**

Scheme 3.4. (i) Ethene, AcOH, 10 min, 81%; (ii) Ethene, CH_2Cl_2, 10 min, 99%.

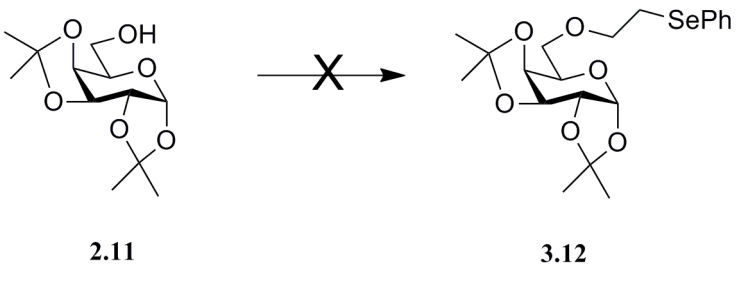
Attention now moved on to alkylation of the bromide with the 2-OH donors **2.4**, **2.6** and **2.20**, the synthesis of which was described in chapter 2. Employing the literature conditions described by Ho,[3] the donors were dissolved in anhydrous acetonitrile and

treated with bromide **3.5** and silver nitrate. Ho reported that the reactions were complete in 10-15 min with the simple alcohols used in the study, however in the case of our glycosyl donors no reaction was observed to occur, even after stirring over long periods of time. Instead a slow degradation of the bromide **3.5** was observed with no formation of the desired 2-*O*-(2-phenylselenyl)ethyl) protected glycosyl donors **3.1**, **3.2** or **3.3** detected (**Scheme 3.5**).



Scheme 3.5. (i) **3.5**, $AgNO_3$, MeCN.

Clearly this result was very disappointing. We felt that it was perhaps the more sterically demanding nature of the secondary alcohol in our donors that was causing the reaction to fail. However, when the reaction was attempted using diacetone galactose **2.11** as a model alcohol acceptor under the same conditions the reaction once again failed (**Scheme 3.6**).



Scheme 3.6. (i) **3.5**, Ag^+, various conditions.

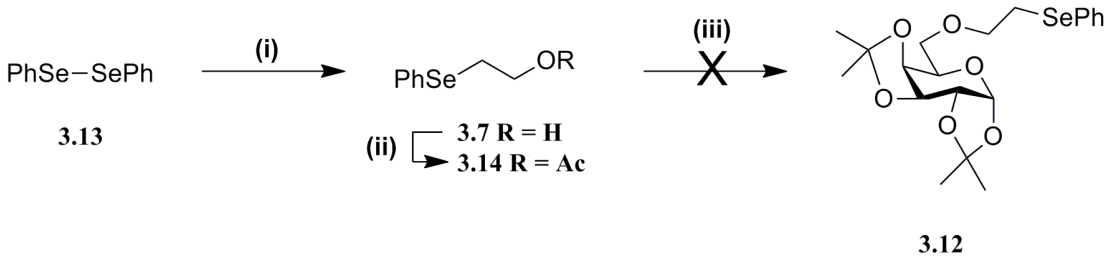
This result led us to investigate a variety of different reaction conditions for the alkylation of **2.11** with the bromide **3.5**, varying the source of silver, the solvent and

the reaction temperature. To summarise however none of the alternative reaction conditions explored yielded formation of the 6-*O*-(2-(phenylselenyl)ethyl) protected diacetone galactose **3.12**. First of all the current reaction conditions ($AgNO_3$/MeCN) were employed with the reaction being heated at reflux, however this simply resulted in quicker degradation of **3.5**. Alternative silver salts were next investigated; unfortunately neither the use of silver triflate or freshly prepared silver oxide improved the reaction. Finally a variation of solvent was carried out; reaction in THF failed to improve the reaction, as did reaction in 1,4-dioxane even though this did allow a higher reflux reaction temperature to be used.

It had become clear that alkylation using the bromide donor **3.5** was not straightforward. As a final attempt to utilise bromide **3.5** an alkylation was attempted under basic conditions. It was felt that forming an alkoxide would significantly increase the nucleophilicity of the alcohol, however it was also expected that bromide **3.5** would be susceptible to elimination under basic conditions. Regardless of these fears the reaction was carried out, treating diacetone galactose **2.11** with NaH in DMF to pre-form the alkoxide followed by addition of bromide **3.5**. Unfortunately no reaction with the sugar was observed to occur. Instead the bromide was observed to be consumed by t.l.c. and a new product formed, which was found to be the corresponding vinyl selenide. In light of these results it was decided that an alternative alkyl donor would be investigated.

3.4 Alternative Alkyl Donors for the Introduction of the 2-(phenylselenyl)ethyl Protecting Group

We first sought to synthesise an alkyl donor bearing a different leaving group that could still be activated with a Lewis acid. We were immediately drawn to the use of an acetate group as the leaving group given that Boons *et al*. had used an acetate based donor in the installation of the (1*S*)-phenyl-2-(phenylsulfanyl)ethyl moiety employed in their chiral neighbouring group participation work.[1] Hence the known (phenylselenyl)ethanol **3.7** was synthesised by treatment of diphenyl diselenide **3.13** with sodium borohydride and 2-chloroethanol.[9] Alcohol **3.7** was then treated with acetic anhydride in pyridine to yield 2-(phenylselenyl)ethyl acetate **3.14** in a 95% yield over two steps (**Scheme 3.7**). Disappointingly when this compound was treated with diacetone galactose **2.11** and $BF_3.OEt_2$ in accordance with the conditions used by Boons, no reaction was observed.

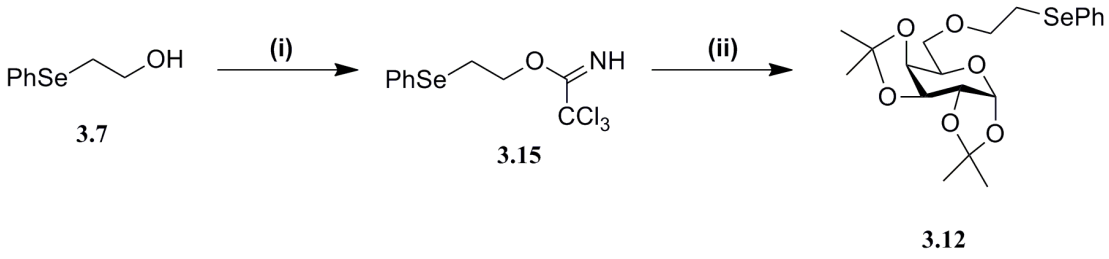


3.12

Scheme 3.7. (i) $NaBH_4$, $ClCH_2CH_2OH$, EtOH, 80^{o}C, 3 h, 96%; (ii) Ac_2O, pyridine, 16 h, 99%; (iii) **2.11**, $BF_3.OEt_2$, CH_2Cl_2.

Again variations to the conditions were applied; heating to reflux in dichloromethane failed to produce **3.12**, whilst switching to alternative solvents; dichloroethane, THF and acetonitrile and subsequently heating to reflux in each also did not change the result of the reaction. As with the attempted reactions using the bromide **3.5**, the donor **3.14** was observed to degrade in all cases as the reaction progressed.

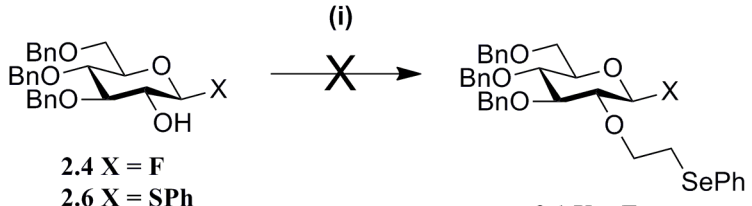
Our attention now turned to the use a trichloroacetimidate alkyl donor. In contrast to the bromide **3.5** and the acetate **3.14**, it was hoped that alkylation using the trichloroacetimidate **3.15** could be achieved using catalytic amounts of Lewis acid activator, which may prove to be more favourable. Trichloroacetimidate **3.15** was efficiently formed by reaction of alcohol **3.7** with trichloroacetonitrile and DBU in a yield of 88%. Pleasingly when diacetone galactose **2.11** was treated with **3.15** and a catalytic amount of TMSOTf, the 6-*O*-2-(phenylselenyl)ethyl protected compound was observed to form, although in a poor yield of only 55% (**Scheme 3.8**).



3.7 **3.15** **3.12**

Scheme 3.8. (i) Cl_3CCN, DBU, CH_2Cl_2, 0 °C, 3 h, 88%; (ii) **2.11**, TMSOTf, CH_2Cl_2, 3 h, 55%.

With a successful alkylation procedure now in hand attention turned back to synthesis of the glycosyl donors. Hence the 2-OH donors **2.4**, **2.6** and **2.20** were each treated with **3.15** and catalytic TMSOTf. Depressingly however, reaction with the more hindered secondary alcohols was not observed (**Scheme 3.9**).



2.4 X = F
2.6 X = SPh
2.20 X = SEt

3.1 X = F
3.2 X = SPh
3.3 X = SEt

Scheme 3.9. (i) **3.15**, TMSOTf, CH_2Cl_2.

In all cases **3.15** was observed to slowly decay. Though it was thought possible that the glycosyl donors themselves could degrade under the reaction conditions due to activation of the anomeric leaving groups, this was not observed and the donors could be recovered cleanly from the reaction mixtures.

Acid promoted alkylation using the alkyl donors **3.5**, **3.14** and **3.15** had all failed, and in all cases consumption of the donor had been observed. This suggested that there was a competing degradation pathway that was occurring faster than alkylation with the alcohol. In the case of donor **3.15**, a combination of a catalytic activation protocol and the use of primary alcohol **2.11** circumvented this problem to some extent, however the low yield of the reaction indicates that degradation was still occurring, and when a secondary alcohol was used degradation once again became faster than alkylation. The mechanism of the reaction is presumed to go *via* an intermediate selenonium ion which forms once the leaving group is activated by the Lewis acid (**Figure 3.3**).

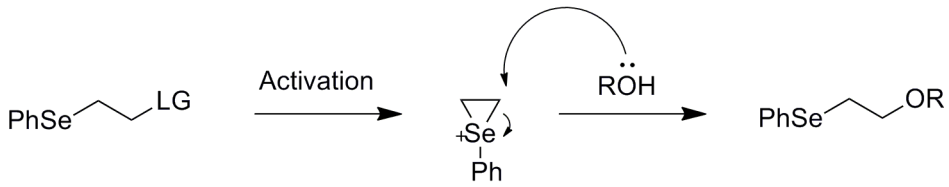
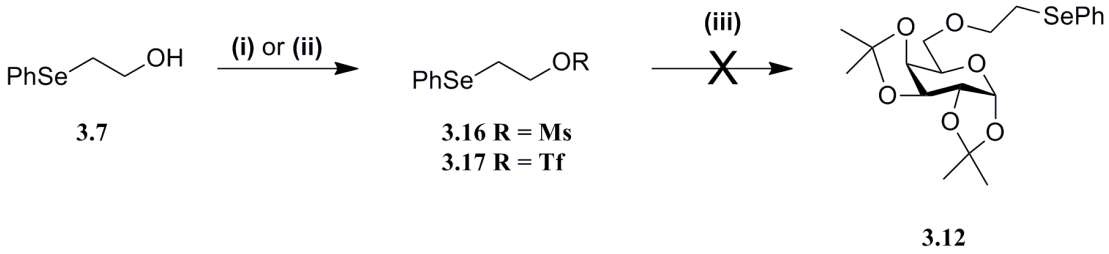


Figure 3.3. Postulated mechanism for the formation of the 2-(phenylselenyl)ethyl protecting group.

It was thought therefore that if formation of this intermediate could be avoided then alkylation may be more successful. We therefore resolved to attempt alkylation under neutral conditions without the presence of a promoter, hoping that S_N2 displacement of the leaving group could be achieved. Given that we were using a poor nucleophile, it was decided that a highly reactive leaving group would be required. Hence the mesylate alkyl donor **3.16** and the triflate alkyl donor **3.17** were both synthesised from

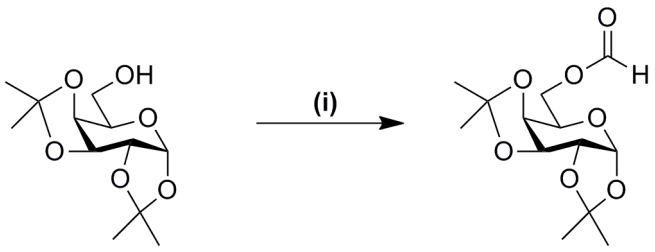
the alcohol **3.7**, by treatment with methylsulfonyl chloride or trifluoromethanesufonic anhydride respectively (**Scheme 3.10**).



3.7 **3.16 R = Ms** **3.17 R = Tf** **3.12**

Scheme 3.10. (i) MsCl, pyridine, 0^{o}C to rt, 2 h, 96%; (ii) Tf_2O, pyridine, CH_2Cl_2, 0^{o}C to rt, 1 h, 90%; (iii) **2.11**, DMF.

Perhaps not unsurprisingly the reactions failed, even when heated at high temperature, indicating that even the primary alcohol sugar was not a good enough nucleophile to give S_N2 displacement of the leaving groups. Interestingly a reaction was observed to occur when the triflate **3.17** was used, however instead of the desired alkylated compound, the formylated galactose **3.18**[10] was formed (**Scheme 3.11**). This indicated that a formylation reaction had taken place, presumably by reaction of DMF with the triflate to form a Vilsmeier-type intermediate.[11]



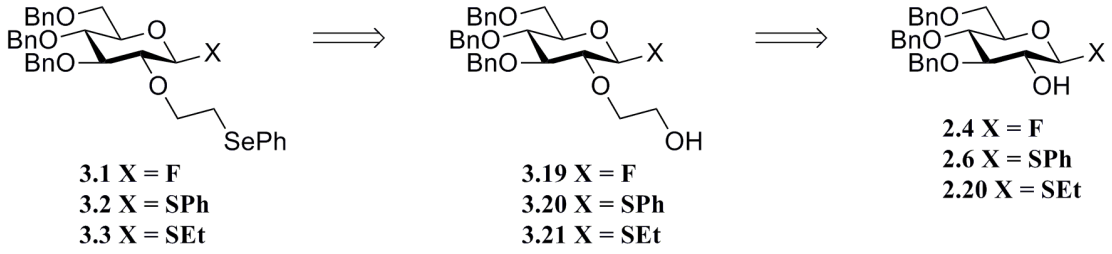
2.11 **3.18**

Scheme 3.11. (i) **3.17**, TTBP, DMF, 0^{o}C to rt, 16 h, 81%.

Given the multitude of failed reactions in the attempt to append the 2-(phenylselenyl)ethyl group to the alcohol *via* an alkylation reaction, it was decided that an alternative route to the compound should be investigated.

3.5 Synthesis of the 2-(phenylselenyl)ethyl Protecting Group *via* an Allyl Group

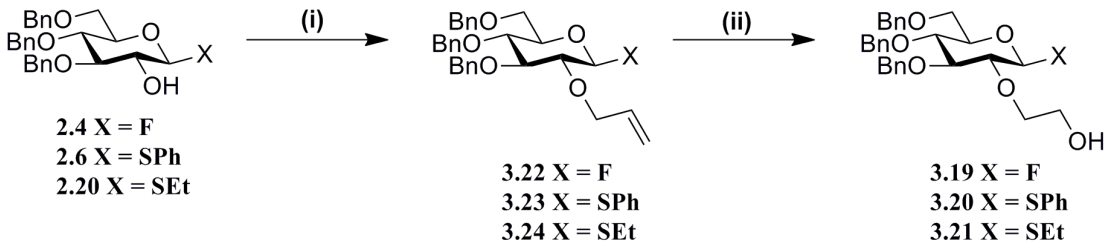
It had become apparent that reaction of a poorly nucleophilic alcohol with an electrophilic system that showed a propensity to degrade under the reactions conditions was not an efficient route to the desired 2-(phenylselenyl)ethyl protected donor systems. Indeed it seemed like an alternative approach where the sugar played the role of electrophile would be a much better technique. It was therefore envisaged that installation of an ethyl moiety bearing a leaving group at the 2-positon of the target glycosyl donors, followed by subsequent displacement of the leaving group using a source of phenyl selenide, would give the 2-*O*-2-(phenylselenyl)ethyl protected target donors (**Scheme 3.12**).



Scheme 3.12. New retrosynthetic analysis of glycosyl donors **3.1, 3.2** and **3.3**.

It was hence envisaged that allyl protection of the alcohols **2.4**, **2.6**, and **2.20**, followed by ozonolysis of the alkene with a reductive work-up would give the 2-*O*-(2-(hydroxyethyl) protected donors **3.19**, **3.20** and **3.21**. Formation of a leaving group and displacement with phenyl selenide would lead to the targets **3.1**, **3.2** and **3.3**. The trichloroacetimidate donor **3.4** could still be synthesised *via* thioglycoside hydrolysis as previously planned.

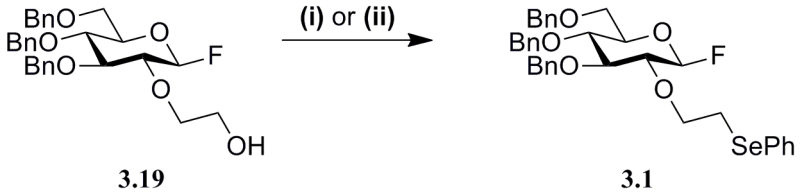
The three alcohols **2.4**, **2.6** and **2.20** were hence treated with allyl bromide and NaH in DMF, forming the 2-*O*-allyl protected donors **3.22**,[12] **3.23**[13] and **3.24**[13] in yields of 84%, 94% and 91% respectively. Ozone is known to be capable of deprotecting benzyl groups,[14] hence the ozonolysis reactions were carried out at -78^{o}C to ensure that no benzyl deprotection occurred. Reaction of the glycosyl fluoride **3.22** proceeded smoothly, and treatment of the crude product with sodium borohydride gave the 2-*O*-(2-hydroxyethyl) protected glycosyl fluoride **3.19** in 81% yield. Ozonolysis of the two thioglycoside compounds required more care. Usually the end point of an ozonolysis reaction is determined by the colour change of the reaction, with a faint blue observed to form when excess ozone is present. With the thioglycosides however, oxidation of the sulfur was possible and hence the end point of the reaction difficult to determine. In the case of thiophenyl glycoside **3.23**, it was found that ozonolysis of the alkene group was fast compared to oxidation of the sulfur, and careful control of the reaction allowed clean production of the desired thioglycoside **3.20** in a 76% yield. Production of ethyl thioglycoside **3.21** proved less straightforward however. In the reaction of **3.24** oxidation of the sulfur atom occurred at a more comparable rate to the ozonolysis of the alkene and hence **3.21** was produced in a relatively poor yield of 59% (**Scheme 3.13**).



Scheme 3.13. (i) Allyl Bromide, NaH, DMF, 2 h, **3.22** 84%, **3.23** 94%, **3.24** 91%;

(ii) O_3, CH_2Cl_2/MeOH, -78^{o}C, 15 min; then $NaBH_4$, -78^{o}C to rt, 1 h, **3.19** 81%, **3.20** 76%, **3.21** 59%.

Attention now turned to the formation of the 2-(phenylselenyl)ethyl group. Although formation of a leaving group and then displacing it with the excellent nucleophile phenyl selenide would be expected to work well, literature methodology does exist for the direct conversion of an alcohol group to a phenylselenyl group in a reaction similar to a Mitsunobu reaction.[15,16] Hence glycosyl fluoride **3.19** was treated with phenyl selenocyanate (PhSeCN) and tributylphosphine as described in the literature (**Scheme 3.14**).



3.19 **3.1**

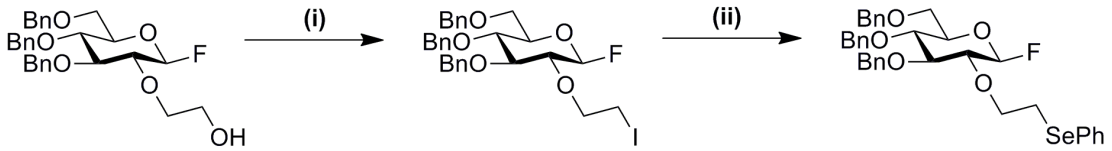
Scheme 3.14. (i) PhSeCN, PBu_3, THF, 4 h, 55%; (ii) *N*-PSP, PBu_3, THF, 4 h, 42%.

Formation of the glycosyl fluoride **3.1** was achieved, however in a poor yield of only 55%. Furthermore when the reaction was repeated, lower yields were observed; this was attributed to the low stability of PhSeCN[17] which resulted in the reagent degrading on the shelf. An alternative source of phenyl selenide, *N*-phenylselenophthalimide (*N*-PSP) was then employed,[17-19] however this gave an even poorer yield than previously observed.

It was hence decided that the original plan of forming a leaving group and displacing it with phenyl selenide would be pursued. At this point it was also considered that it was now possible to introduce other heteroatoms at the end of the ethyl chain which could potentially act as participating groups in glycosylation reactions. It was decided that study of the capacity of iodine to act as a participating group would be interesting; given that iodine is known to be highly nucleophilic and also capable of forming stable iodonium ions, it seemed ideally suited to the task. Indeed there is

literature evidence for iodine stabilising oxacarbenium ions through three-membered rings in the literature.[20] An iodide compound could also serve as a leaving group for the synthesis of the 2-(phenylselenyl)ethyl group, hence its synthesis provided two functions.

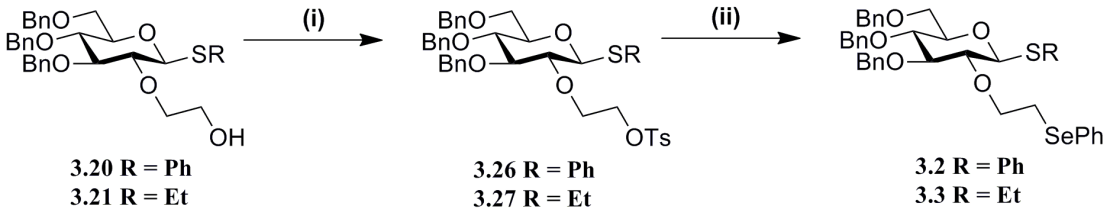
An Appel reaction[21] was carried out on the alcohol **3.19** using I_2, triphenylphosphine and imidazole, producing the iodide **3.25** in a yield of 89%. Subsequent treatment of the iodide **3.25** with sodium phenyl selenide, pre-formed by the reaction of phenyl selenol with NaH, gave the target glycosyl fluoride **3.1** in an excellent yield of 86% (**Scheme 3.15**).



3.19 **3.25** **3.1**

Scheme 3.15. (i) I_2, PPh_3, imidazole, THF, reflux, 16 h, 89%;
(ii) PhSeH, NaH, THF, reflux, 16 h, 86%.

Unfortunately, due to the iodophilic nature of sulfur, the corresponding iodides could not be synthesised from the thioglycoside donors **3.20** and **3.21**. Hence the target 2-(phenylselenyl)ethyl protected donors **3.2** and **3.3** were formed *via* the tosylates **3.26** and **3.27** respectively. Treatment of the alcohol **3.20** with *para*-toluenesulfonyl chloride in pyridine gave the tosylate **3.26** in an 84% yield, whilst treatment of the ethyl thioglycoside **3.21** under the same conditions afforded the tosylate **3.27** in an 85% yield. Treatment of both compounds with sodium phenyl selenide produced the target donors **3.2** and **3.3** in 76% and 75% yields respectively (**Scheme 3.16**).



3.20 R = Ph
3.21 R = Et

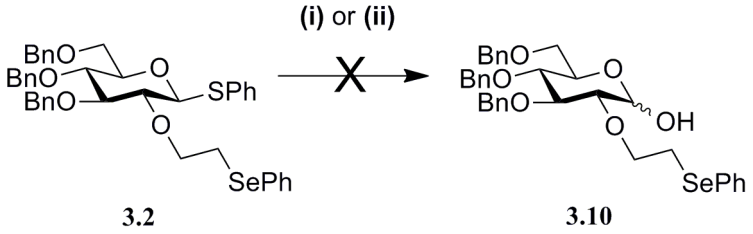
3.26 R = Ph
3.27 R = Et

3.2 R = Ph
3.3 R = Et

Scheme 3.16. (i) TsCl, pyridine, 16 h, **3.26** 84%, **3.27** ;85%;

(ii) PhSeH, NaH, THF, reflux, 16 h, **3.2** 76%, **3.3** 75%.

Attention now turned to the synthesis of the trichloroacetimidate donor **3.4**. The synthesis of this donor hinged upon successful hydrolysis of either of the thioglycosides **3.2** or **3.3** to produce the hemiacetal compound **3.10**. Accordingly, the phenyl thioglycoside **3.2** was submitted to hydrolysis under both the NIS/TFA/CH_2Cl_2/H_2O and the NBS/acetone/H_2O reaction conditions utilised in the hydrolysis of the thioglycoside **2.2** described in chapter 2. As was had feared, use of both of these conditions resulted in the formation of a complex mixture of products, indicating that the phenylselenyl moiety had also reacted with the halonium source (**Scheme 3.17**).

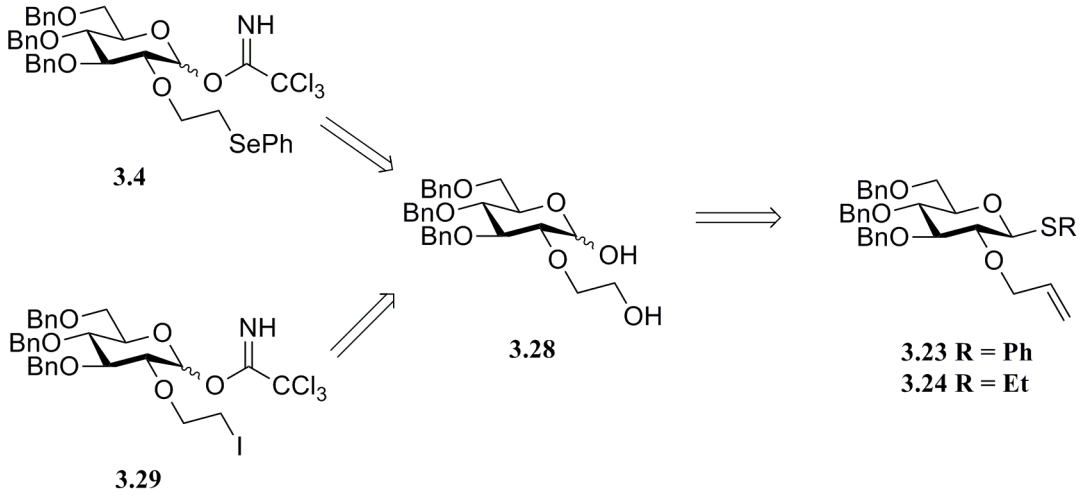


3.2 **3.10**

Scheme 3.17. (i) TFA, NIS, CH_2Cl_2/H_2O, 0 °C; (ii) NBS, Acetone/H_2O.

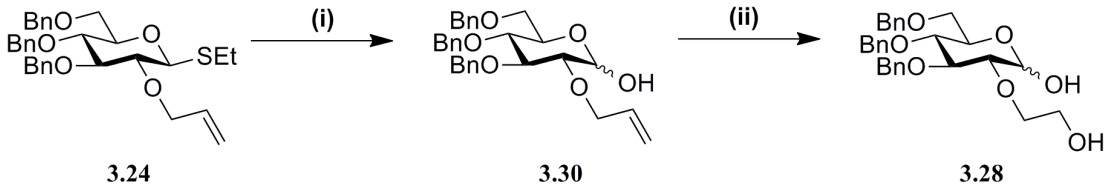
Although we could have turned our attention to the hydrolysis of ethyl thioglycoside **3.3** at this point, we decided that given the already overall poor yield of **3.3** due to the inefficient ozonolysis step this would represent a poor synthetic method of achieving the target donor **3.4**. Additionally synthesis by this method would preclude access to an iodo moiety with a trichloroacetimidate donor. Hence an alternative route was

imagined, where hydrolysis of the thioglycoside would occur before ozonolysis; hydrolysis of either of the allyl protected thioglycosides **3.23** or **3.24**, followed by ozonolysis would give the diol **3.28**. This could then serve as a divergent intermediate towards both the 2-(phenylselenyl)ethyl protected donor **3.4** and the 2-(iodo)ethyl protected donor **3.29**; iodide formation followed by displacement with phenyl selenide and subsequent trichloroacetimidate formation would provide **3.4**, whilst iodination followed by trichloroacetimidate formation would afford **3.29** (**Scheme 3.18**).



Scheme 3.18. New retrosynthetic analysis of glycosyl donors **3.4** and **3.29**.

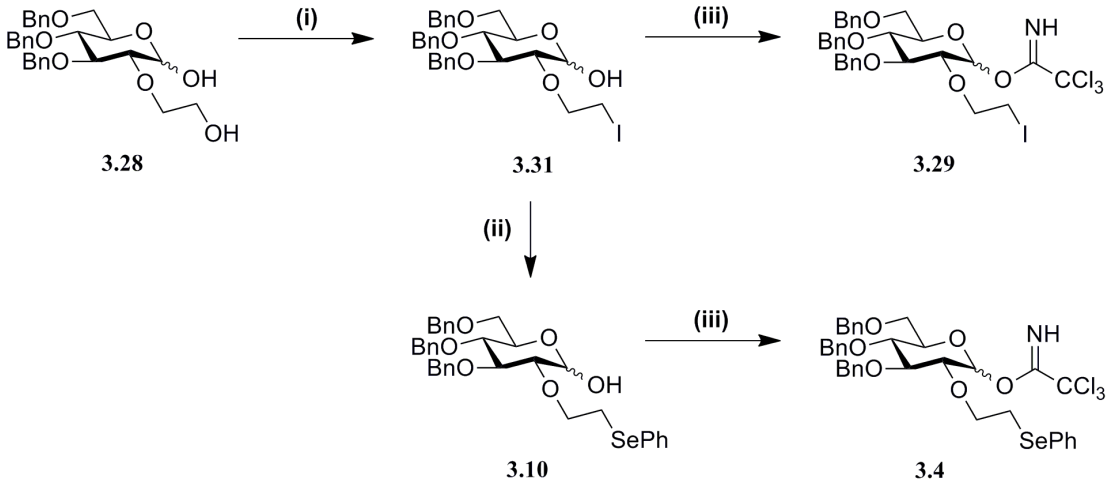
It was anticipated that NIS or NBS mediated hydrolysis of the allyl protected phenyl thioglycoside **3.23** would result in competitive reaction with the alkene. Hence hydrolysis of the ethyl thioglycoside **3.24** was investigated. It was thought that treatment of **3.24** with MeOTf would be selective for the thioglycoside over the alkene, and hence in the presence of water hydrolysis could occur. Pleasingly reaction of **3.24** with MeOTf in the presence of the hindered base TTBP in a mixture of 1,4-dioxane and water produced the hemiacetal **3.30**[22] in a yield of 80%. Subsequent ozonolysis also proceeded smoothly to give the diol **3.28** in 85% yield (**Scheme 3.19**).



Scheme 3.19. (i) MeOTf, TTBP, 1,4-dioxane/H_20, 3 h, 80%;

(ii) O_3, CH_2Cl_2/MeOH, -78^oC, 15 min; then $NaBH_4$, -78^oC to rt, 1 h, 85%.

Appel reaction of **3.28** gave formation of the iodide **3.31** in a 76% yield, leaving the anomeric position untouched. Treatment of **3.31** with trichloroacetonitrile and DBU provided the trichloroacetimidate donor **3.29** in a yield of 84%. Alternatively treatment of **3.31** with sodium phenyl selenide formed the hemiacetal **3.10** in a yield of 81%. Trichloroacetimidate formation was again achieved by treatment with trichloroacetonitrile and DBU to afford donor **3.4** in an 88% yield (**Scheme 3.20**).



Scheme 3.20. (i) I_2, PPh_3, imidazole, THF, reflux, 16 h, 76%;

(ii) PhSeH, NaH, THF, reflux, 16 h, 81%; (iii) Cl_3CCN, DBU, DCM, 0 °C, 3 h, **3.29** 84% **3.4** 88%.

3.6 Glycosylation Reactions of Donors 3.1, 3.2, 3.3 and 3.4

After some arduous synthetic efforts, a selection of glycosyl donors bearing a 2-*O*-(2-(phenylselenyl)ethyl) protecting group were now in hand. Additionally two glycosyl donors, the fluoride **3.25** and the trichloroacetimidate **3.29**, bearing a 2-*0*-(2-iodoethyl) protecting group had also been synthesised (**Figure 3.4**). Attention first however turned to the glycosylation of donors **3.1**, **3.2**, **3.3** and **3.4** to investigate the neighbouring group participation effect of the 2-(phenylselenyl)ethyl group on the stereochemical outcome of glycosylation.

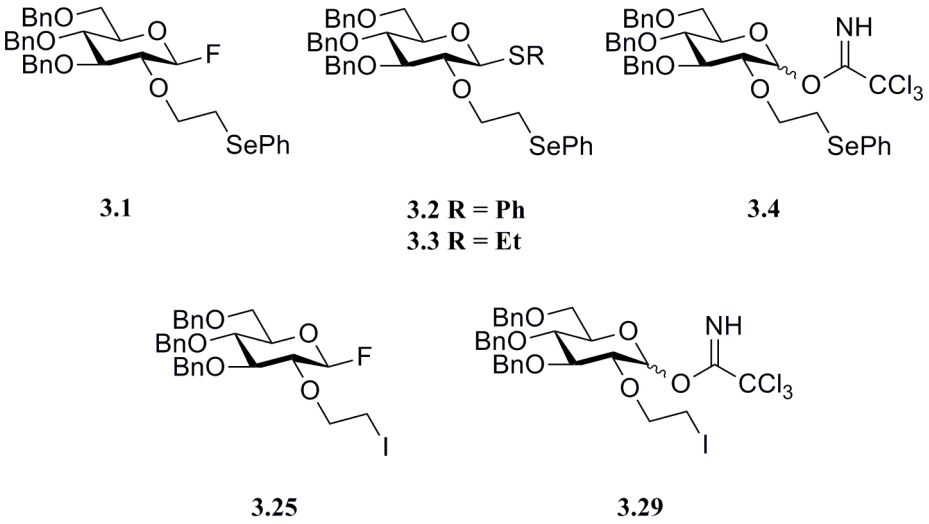
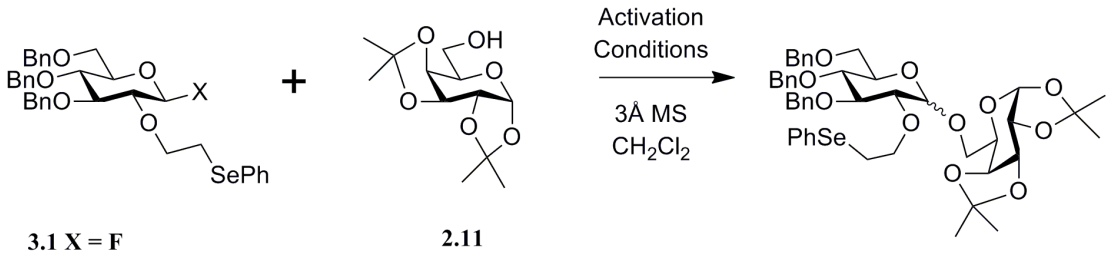


Figure 3.2. Synthesised glycosyl donors.

As with the studies on the 2-*O*-(thiophen-2-ylmethyl) protected glycosyl donors (see chapter 2), initial glycosylations were carried out using diacetone galactose **2.11** (2 eq.) as the glycosyl acceptor. All reactions were carried in dichloromethane over a range of temperatures to determine optimum glycosylation conditions. The results for the glycosylation of donors **3.1**, **3.2**, **3.3** and **3.4** are summarised in **Table 3.1**.

Table 3.1. Glycosylation of diacetone galactose **2.11** (2 eq.) with donors **3.1**, **3.2**, **3.3** and **3.4**.



3.1 X = F
3.2 X = SPh
3.3 X = SEt
3.4 X = $OC(NH)CCl_3$

2.11

3.32

Entry	Glycosyl Donor	Activation Conditions	Time (h)	Temp. (°C)	Yield of **3.32** (%)	α:β ratio[a] (σ)
a	**3.1**	1.5 eq. $BF_3.OEt_2$	1.5	0	74	1:1 (0.08)
b	**3.1**	1.5 eq. $BF_3.OEt_2$	2.5	-40	70	2.25:1 (0.08)
c	**3.1**	1.5 eq. $BF_3.OEt_2$	5	-78	62	4.5:1 (0.05)
d	**3.2**	1.5 eq. NIS, 0.5 eq. TMSOTf	1	0	Reaction Failed	
e	**3.2**	1.5 eq. NIS, 0.5 eq. TMSOTf	2	-40	Reaction Failed	
f	**3.2**	1.5 eq. NIS, 0.5 eq. TMSOTf	3.5	-78	Reaction Failed	
g	**3.3**	4.5 eq. MeOTf, 4.5 eq TTBP	7	0	45	1.25:1 (0.13)
h	**3.3**	4.5 eq. MeOTf, 4.5 eq TTBP	24	-40	38	1.25:1 (0.05)
i	**3.3**	4.5 eq. MeOTf, 4.5 eq TTBP	24	-78	37	1.5:1 (0.05)
j	**3.4**	0.1 eq. TMSOTf	0.5	0	88	1.5:1 (0.05)
k	**3.4**	0.1 eq. TMSOTf	1	-40	83	3:1 (0.05)
l	**3.4**	0.1 eq. TMSOTf	1.5	-78	80	5:1 (0.05)

[a]Anomeric ratios were determined by integration of appropriate peaks in the ^{1}H nmr spectra. Glycosylation reactions were carried out in triplicate to confirm the reproducibility of results, and α:β ratios are given as a mean average (standard deviation given in brackets).

Glycosyl fluoride **3.1** was activated using supra-stoichiometric amounts of $BF_3.OEt_2$. Unlike the case of the equivalent 2-*O*-(thiophen-2-ylmethyl) protected glycosyl donor, good yields of the disaccharide **3.32** were observed and t.l.c. analysis indicated that the reactions progressed relatively cleanly. The preference for α-selectivity was also encouraging; selectivity was observed to increase with a decrease in reaction

temperature with the best results obtained at -78 °C (α:β ratio, 4.5:1, **Table 3.1**, entry c). Although this selectivity was still reasonably modest, it was substantially better than the selectivity observed for the corresponding 2-*O*-(thiophen-2-ylmethyl) protected glycosyl fluoride **2.1** (α:β ratio, 2:1, **Table 2.1**, entry c).

The failed attempted hydrolysis of the thioglycoside donor **3.2** (**Scheme 3.17**) had suggested that activation of the group using the promoter system of NIS/TMSOTf previously employed for the activation of the 2-*O*-(thiophen-2-ylmethyl) protected thiophenyl glycoside **2.2** may prove problematic in the presence of the phenylselenyl moiety. Indeed when glycosylation was attempted under these conditions consumption of the glycosyl donor was observed by t.l.c. analysis and a complex mixture of products was produced. It proved impossible to isolate any of the desired material **3.32** from these reactions. This clearly demonstrated that the use of soft Lewis acid activation conditions were incompatible with the 2-(phenylselenyl)ethyl protecting group.

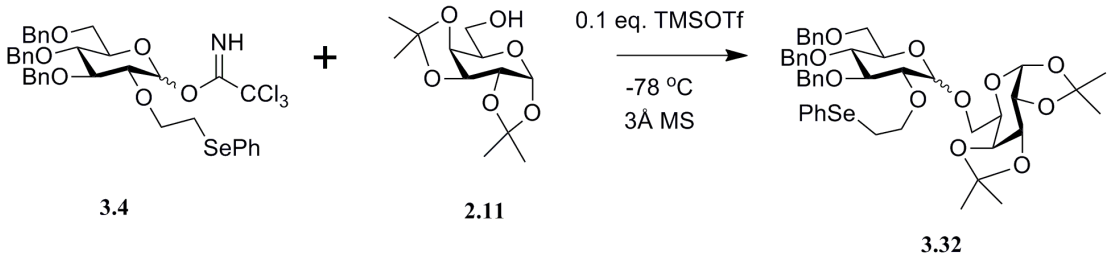
Activation of the ethyl thioglycoside **3.3** was undertaken using supra-stoichiometric quantities of MeOTf in the presence of the hindered base TTBP. The reaction of this thioglycoside proved to be much cleaner than that of **3.2**, indicating greater orthogonality to the phenylselenyl moiety. The formation of polar by-products was still observed however and the yields of disaccharide **3.32** were low in all cases. Furthermore poor selectivity was observed in the glycosylation, with at best only marginal preference for the α-glycoside displayed (α:β ratio, 1.5:1, **Table 3.1**, entry i).

Attention finally turned to the glycosylation of the trichloroacetimidate **3.4**. Activation of **3.4** in the presence of **2.11** with a catalytic amount of TMSOTf at 0 °C produced disaccharide **3.32** in an excellent yield of 88%, but with low anomeric

selectivity (α:β ratio, 1.5:1, **Table 3.1**, entry j). Reduction of the reaction temperature to -78 °C did not significantly alter the yield of disaccharide but did increase the observed selectivity (α:β ratio, 5:1, **Table 3.1**, entry j). However, this selectivity was relatively poor compared to the selectivity observed for the corresponding 2-*O*-(thiophen-2-ylmethyl) protected trichloroacetimidate donor **2.3** (α:β ratio, 9:1, **Table 2.1**, entry h).

Given the relatively poor α-selectivity observed in the glycosylation reactions, it was decided that a solvent variation investigation would be conducted. Altering the polarity of solvent used should impact upon the stabilities of the cationic intermediates formed in the glycosylation reaction and hence alter the anomeric selectivity observed. It was therefore hoped that improved selectivity may be observed by using an alternative solvent. As trichloroacetimidate donor **3.4** had shown the best α-selectivity in the initial investigations it was chosen for the study, with reactions being carried out at a temperature of -78 °C (**Table 3.2**).

Table 3.2. Glycosylation of diacetone galactose **2.11** (2 eq.) with donor **3.4** in a variety of solvents.



3.4 **2.11** **3.32**

Entry	Glycosyl Donor	Solvent	Time (h)	Yield of **3.32** (%)	α:β ratio[a] (σ)
a	**3.4**	DCM	1.5	80	5:1 (0.05)
b	**3.4**	DCE	1.5	78	4.5:1 (0.08)
c	**3.4**	Toluene	1.5	81	4:1 (0.13)
d	**3.4**	MeO^{t}Bu	1.5	75	4:1 (0.05)

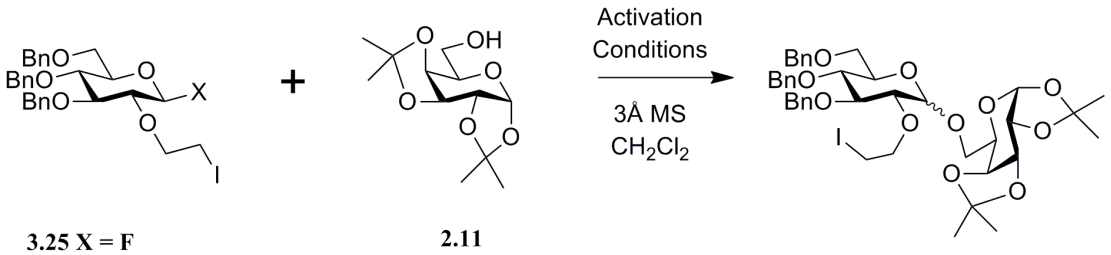
[a]Anomeric ratios were determined by integration of appropriate peaks in the ^{1}H nmr spectra. Glycosylation reactions were carried out in triplicate to confirm the reproducibility of results, and α:β ratios are given as a mean average (standard deviation given in brackets).

Given that we did not wish to use a solvent that could itself direct the selectivity of the glycosylation reaction,[23,24] only a small selection of solvents were available for study. Disappointingly changing the solvent did not effect a large change in the anomeric selectivity, suggesting that an α:β ratio of 5:1 was the best that we could achieve.

3.7 Glycosylation Reactions of Donors 3.25 and 3.29

Attention now turned to the glycosylation of the 2-*O*-(2-iodoethyl) protected glycosyl donors **3.25** and **3.29** and the potential use of an iodine atom as a participating group in glycosylation. The initial results are summarised in **Table 3.3**.

Table 3.1. Glycosylation of diacetone galactose **2.11** (2 eq.) with donors **3.25** and **3.29**.



3.25 X = F
3.29 X = OC(NH)CCl$_3$

2.11

3.33

Entry	Glycosyl Donor	Activation Conditions	Time (h)	Temp. (°C)	Yield of **3.33** (%)	α:β ratio[a] (σ)
a	**3.25**	1.5 eq. BF3.OEt2	0	1.5	74	1:1 (0.08)
b	**3.25**	1.5 eq. BF3.OEt2	-40	2.5	70	2:1 (0.08)
c	**3.25**	1.5 eq. BF3.OEt2	-78	5	62	3:1 (0.05)
d	**3.29**	0.1 eq. TMSOTf	0	1	84	1:1 (0.10)
e	**3.29**	0.1 eq. TMSOTf	-40	2	78	2:1 (0.05)
f	**3.29**	0.1 eq. TMSOTf	-78	4	75	3.5:1 (0.05)

[a]Anomeric ratios were determined by integration of appropriate peaks in the ^{1}H nmr spectra. Glycosylation reactions were carried out in triplicate to confirm the reproducibility of results, and α:β ratios are given as a mean average (standard deviation given in brackets).

The glycosyl fluoride **3.25** was activated with supra-stoichiometric quantities of $BF_3.OEt_2$, producing the disaccharide **3.33** in good to moderate yields. Interestingly the α-selectivity increased with a decrease in temperature, suggesting that the iodine was not only participating in the reaction but also had a preference for formation of the β-coordinated iodonium ion. Compared to the corresponding 2-*O*-(2-

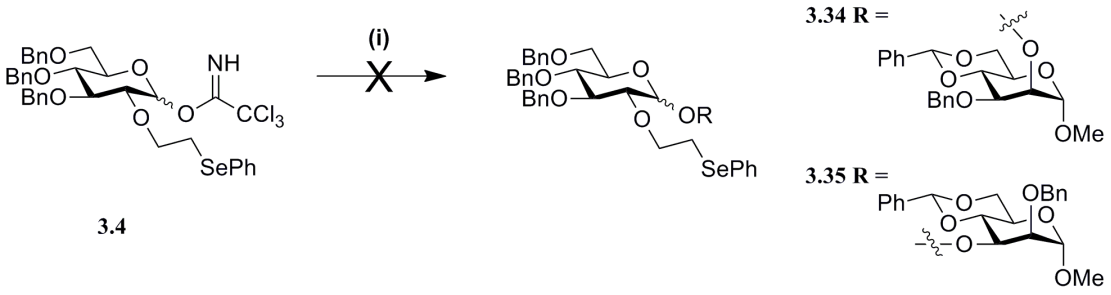
(phenylselenyl)ethyl) protected glycosyl fluoride however the selectivity was not as impressive.

Reaction of the trichloroacetimidate **3.29** with diacetone galactose **2.11** produced higher yields of **3.33** compared to those achieved with donor **3.25.** A preference for α-selectivity was also observed, and the results were marginally better than those observed for **3.25** (α:β ratio, 3.5:1, **Table 3.3**, entry f). However the stereocontrol still fell short of the α-selectivity achieved using the phenylselenyl moiety.

Although the results obtained from the use of these 2-*O*-(2-iodoethyl) protected glycosyl donors were interesting, it was decided that given the lower α-selectivity compared the 2-*O*-(2-phenylselenyl)ethyl) protected donors that further investigations would not be pursued at this time.

3.8 Glycosylation Reactions of 3.4 with a Variety of Acceptors

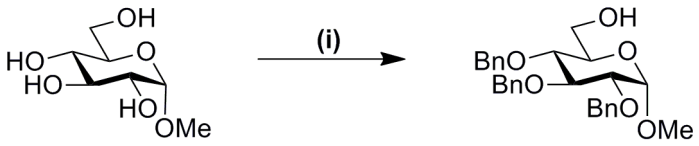
Having ascertained that trichloroacetimidate donor **3.4** gave the best α-selectivity in the glycosylation reaction with diacetone galactose **2.11**, we next set out to investigate glycosylation of this donor with a series of different acceptors under the optimum conditions previously observed. It was decided that for comparative purposes the same selection of acceptors described in chapter 2 would be employed. However, when glycosylation was carried out with the benzylidene protected acceptors **2.24** and **2.25** the desired products **3.34** and **3.35** were not observed to form (**Scheme 3.21**). Analysis of the reaction by t.l.c. indicated that a complex mixture of polar products had formed, whilst analysis of the crude reaction by mass spectrometry suggested that some glycosylation had occurred, however the benzylidene acetals on the donors had also been cleaved at some point in the reaction. Unfortunately however these products could not be isolated from the reaction.



Scheme 3.21. (i) **2.24** or **2.25**, TMSOTf, CH_2Cl_2, 3Å MS, -78 °C, 6 h.

It was clear that this result must have been due to the presence of the phenylselenyl moiety in the molecule: analogous reactions with the thiophene moiety and with per-benzylated donors had not caused such problems. It is known that benzylidene acetals can be cleaved using thiols under acidic conditions,[25] hence a potential explanation for these observations could be that the selenium group is taking part in some kind of acetal cleaving mechanism which occurs either before, after or during glycosylation. It is interesting that no cleavage of the isopropylidene acetals was observed when glycosylation was carried out with diacetone galactose **2.11** however this may be explained by the fact that isopropylidene acetals are generally more stable than benzylidene acetals. Indeed it is possible to cleave benzylidene acetals in the presence of isopropylidenes using thiol/Lewis acid combinations.[26]

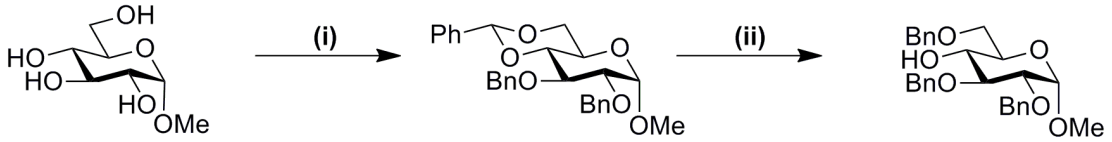
In light of the fact that benzylidene acetal protection was not suitable in the presence of the 2-(phenylselenyl)ethyl protecting group, it was decided that alternative glycosyl acceptors would need to be used. Hence synthesis of the glucose primary alcohol acceptor **3.37**[27] was undertaken in a one-pot procedure from the commercially available methyl glycoside **3.36** as previously described in the literature (**Scheme 3.22**).



3.36 **3.37**

Scheme 3.22. (i) TIPSCl, Imidazole, DMF, 16 h; then BnBr, NaH, DMF, 16 h; then $TBAF{\cdot}H_2O$, THF, 16 h, 93%.

Following this a secondary alcohol glycosyl acceptor **3.39** was synthesised, again starting from the methyl glycoside **3.36**. Treatment of **3.36** with benzaldehyde dimethyl acetal and catalytic camphorsulfonic acid, followed by treatment with benzyl bromide and sodium hydride gave the benzylidene protected glucose derivative **3.38**.[28] Reductive opening of the benzylidene ring with sodium cyanoborohydride subsequently gave selective formation of the 4-OH glycosyl acceptor **3.39**[28] in 67% yield over two steps (**Scheme 3.23**).

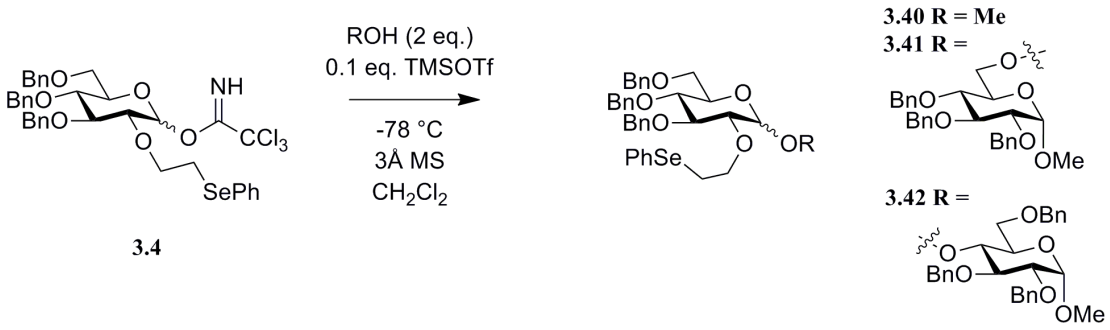


3.36 **3.38** **3.39**

Scheme 3.23. (i) $PhCH(OMe)_2$, CSA (cat.), DMF, 60 °C, 250 mbar, 5 h; then BnBr, NaH, DMF, 16 h 84%; (ii) $NaCNBH_3$, 1M HCl, THF, 0 °C to rt, 16 h, 80%.

Attention now returned to the glycosylation of donor **3.4** with a variety of glycosyl acceptors. Reactions were carried out at -78 °C as this had been the optimum temperature observed for the reactions. The results are summarised below (**Table 3.4)**.

Table 3.4. Glycosylation of **3.4** with a variety of acceptors.



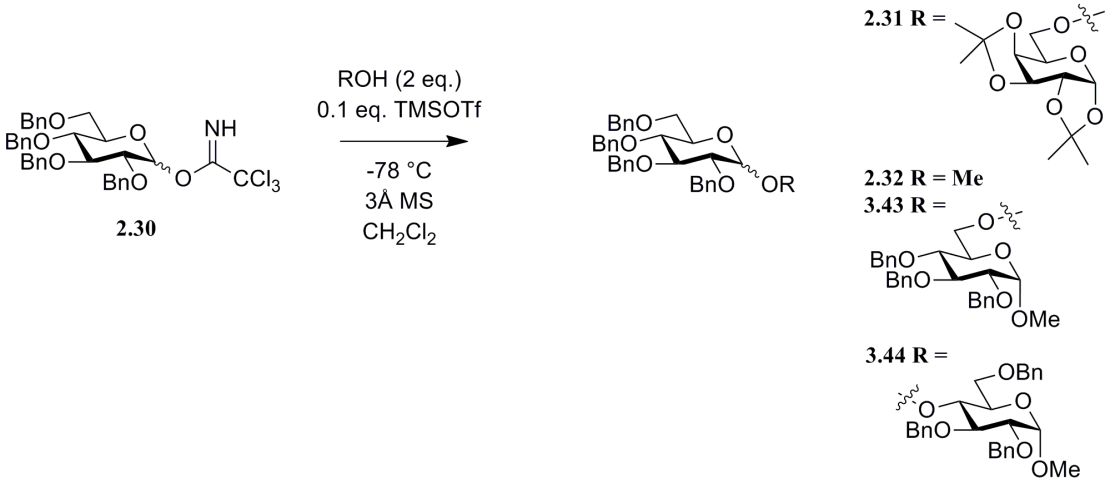
Entry	Acceptor	Product	Time (h)	Temp. (°C)	Yield (%)	α:β ratio[a] (σ)
a	MeOH	**3.40**	1	-78	88	1:1 (0.05)
b	**3.37**	**3.41**	1.5	-78	83	2:1 (0.10)
c	**3.39**	**3.42**	3.5	-78	61	2:1 (0.10)

[a]Anomeric ratios were determined by integration of appropriate peaks in the ^{1}H nmr spectra. Glycosylation reactions were carried out in triplicate to confirm the reproducibility of results, and α:β ratios are given as a mean average (standard deviation given in brackets).

Glycosylation with methanol as an acceptor produced methyl glycoside **3.40** in a good yield but without stereocontrol (α:β ratio 1:1, **Table 3.4**, entry a). This was to be expected as the glycosylation reactions with the corresponding 2-*O*-(thiophen-2-ylmethyl) protected trichloroacetimidate donor **2.3** had shown that the stereoselectivity of the reaction was dependent upon the steric bulk of the glycosyl acceptor. Reaction with the glucose primary alcohol acceptor **3.37** gave a very disappointing result. Whilst reaction with the diacetone galactose primary alcohol **2.11** gave an α:β ratio of 5:1, switching to a glucose based primary alcohol resulted in a diminished selectivity (α:β ratio 2:1, **Table 3.4**, entry b). Furthermore when the secondary alcohol acceptor **3.39**, which was expected to give higher selectivity due to the increased steric bulk, was employed poor selectivity was again observed (α:β ratio 2:1, **Table 3.4**, entry c). These results were somewhat puzzling and suggested that neighbouring group participation may not be occurring, or if it was it was sensitive to

the configuration of the glycosyl acceptor being used. At this point a set of control reactions with the per-benzylated trichloroacetimidate donor **2.30** were carried out for comparison.

Table 2.4. Control glycosylation of acceptors with donor **2.30**.



Entry	Acceptor	Product	Time (h)	Temp. (°C)	Yield (%)	α:β ratio[a] (σ)
a	**2.11**	**2.31**	1.5	-78	85	1:2.25 (0.05)
b	MeOH	**2.32**	1	-78	88	1:7 (0.03)
c	**3.37**	**3.43**	1.5	-78	83	1:1 (0.10)
d	**3.39**	**3.44**	4.5	-78	61	1.5:1 (0.08)

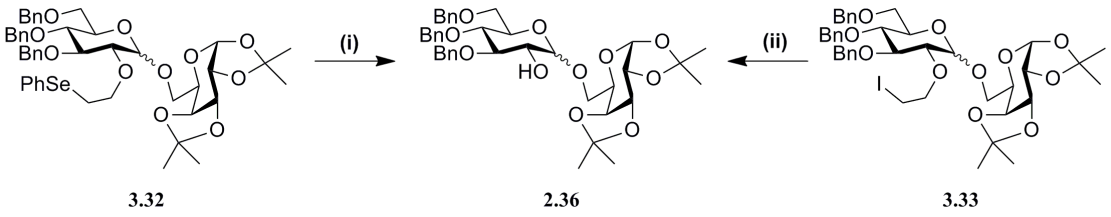
[a]Anomeric ratios were determined by integration of appropriate peaks in the ^{1}H nmr spectra. Glycosylation reactions were carried out in triplicate to confirm the reproducibility of results, and α:β ratios are given as a mean average (standard deviation given in brackets).

Glycosylation of **2.30** with diacetone galactose **2.11** produced disaccharide **2.31**[29] in favour of the β-anomer (α:β ratio 1:2.25, **Table 3.5**, entry a). Given that under the same conditions with donor **3.4** the observed α:β ratio was 5:1, this supported the fact that neighbouring group participation of the 2-*O*-(2-(phenylselenyl)ethyl) group was enhancing α-selectivity in the reaction. Likewise the high β-selectivity observed for formation of the methyl glycosides **2.32**[30] (α:β ratio 1:7, **Table 3.5**, entry b) compared with reaction of MeOH with **3.4** (α:β ratio 1:1, **Table 3.4**, entry a) again suggested

that neighbouring group participation was taking place. Reaction of donor **2.30** with primary alcohol acceptor **3.37** produced disaccharide **3.43**[31]; greater α-selectivity (α:β ratio 1:1, **Table 3.5**, entry c) was observed compared to the primary alcohol acceptor **2.11** (α:β ratio 1:2.25, **Table 3.5**, entry a), suggesting that acceptor **3.37** does show a greater preference for forming the α-anomer, which may explain the lower selectivity observed when **3.37** was reacted with **3.4**. Finally reaction of the bulkier secondary alcohol acceptor **3.39** with donor **2.30** produced disaccharide **3.44**[32] (α:β ratio 1.5:1, **Table 3.5**, entry d); the observed selectivity was very similar to that of the reaction of **3.4** with **3.39** (α:β ratio 2:1, **Table 3.4**, entry c). This suggested that the glycosylation was not proceeding through a selenonium ion intermediate in this case, implying that the selenonium ion intermediate perhaps blocked attack at the anomeric centre due to its own sterics.

3.9 Deprotection of the 2-(phenylselenyl)ethyl and 2-iodoethyl Protecting Groups

Deprotection of the 2-(phenylselenyl)ethyl protecting group is known in the literature.[3] It is well established that selenoxides can undergo *syn* elimination;[33] hence oxidation of the 2-(phenylselenyl)ethyl group followed by subsequent elimination gives a vinyl ether, which can be removed under acidic conditions. Accordingly, a sample of disaccharide **3.32** was treated with hydrogen peroxide in THF. Warming the reaction to reflux affected the elimination step, and subsequent treatment of the vinyl ether with NIS in THF/H_2O afforded the deprotected disaccharide **2.36**[34,35] in a yield of 76% (**Scheme 3.24**).



3.32 **2.36** **3.33**

Scheme 3.24. (i) H_2O_2, THF, 1 h; then reflux 1 h; then NIS, H_2O/THF, 16 h, 76%; (ii) KO^{t}Bu, THF, reflux, 3h; then NIS/H_2O/THF, 16 h, 73%.

The 2-iodoethyl protecting group was removed in a similar manner. Treatment with potassium *tert*-butoxide in THF at reflux affected elimination to give the vinyl ether, which was again treated with NIS in THF/H_2O to afford **2.36** in 73% yield.

3.10 Conclusions and Future Work

In conclusion a series of glycosyl donors have been synthesized bearing a 2-(phenylselenyl)ethyl protecting group at the 2-postion. Glycosylation of the thioglycoside donors **3.2** and **3.3** showed a lack of orthogonality to the presence of the phenylselenyl moiety, and hence gave poor yields of product and low α-selectivity. Reaction of the glycosyl fluoride **3.1** and the trichloroacetimidate donor **3.4** proceeded in better yield and showed preference towards α-selectivity. Further investigations however revealed that increases in α-selectivity were not generally observed and the choice of glycosyl acceptor influenced how selective the reaction was. Furthermore the phenylselenyl moiety was shown to be non-orthogonal to benzylidene protection in the glycosyl acceptor.

In addition two novel glycosyl donors **3.25** and **3.29** bearing a 2-*O*-(2-iodoethyl) protecting group were synthesized. Interestingly the iodine appeared to have a participating effect, enhancing selectivity for the α-glycoside to increasing extent as the reaction temperature was decreased. However, the α-selectivity produced by these

glycosyl donors was not as high as the selectivity produced by the 2-*O*-(2-(phenylselenyl)ethyl) protected glycosyl donors.

Given that the α-selectivity observed for the donors discussed in this chapter are poor compared to the α-selectivity produced by the 2-*O*-(thiophen-2-ylmethyl) protected donors discussed in chapter 2, there is little enthusiasm given towards further investigation of the use of these donors. Whilst the recently published work by Boons *et al*. would suggest that the use of electron withdrawing ester protecting groups in the sugar would improve selectivity,[36] this research is clearly inferior to the work discussed in chapter 2. The comparatively poor selectivity, coupled with orthogonality issues and the lack of selectivity observed when using secondary alcohol donors means that the use of the 2-(phenylselenyl)ethyl group is never likely to be applicable to complex oligosaccharide synthesis.

Perhaps the most useful aspect to come out of this research is the development of methodology allowing functionalization onto an ethyl moiety appended at the 2-postion. The efficient synthesis of the 2-hydroxyethyl protected glycosyl donors from allyl protected precursors can potentially be used as a gateway to a large number of functionalities capable of participating in a glycosylation reaction. Hence this methodology could be applied in the continuing search for a general method of stereocontrolled glycosylation.

3.11 References

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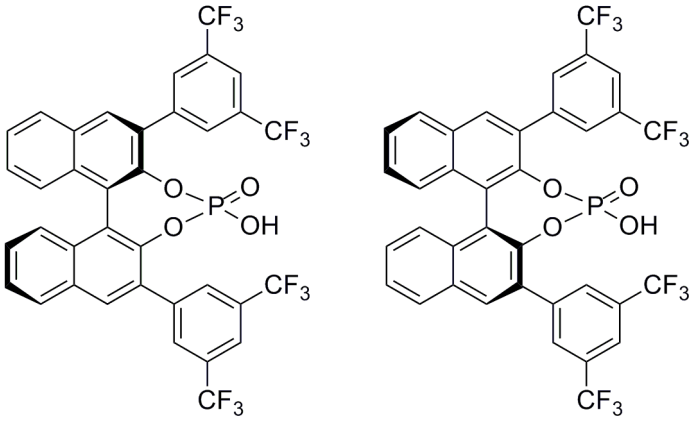
Chapter 4: Glycosylation Catalysed by a Chiral Brønsted Acid

4.1 Introduction

Asymmetric synthesis has frequently been applied to control the diastereoselectivity of a variety of processes; however there are very few reports in the literature of previous efforts that have been made to control the stereochemical outcome of glycosylation reactions using chiral catalysts. This is perhaps not surprising, as much of the work in the field of asymmetric catalysis has focused on the use of transition metal complexes, for example titanium complexes used in the Sharpless epoxidation,[1] or palladium complexes used in asymmetric allylic alkylation.[2] It is difficult to see how the use of transition metal complexes could be applied to glycosylation reactions, however recent developments in the growing field of organocatalysis[3] may represent a more applicable approach. In particular the potential use of chiral Brønsted acids in the activation of glycosylation reactions represents an attractive prospect for controlling the stereochemistry of the glycosylation product.

The first example of chiral Brønsted acid catalysis was only reported relatively recently by Jacobsen and co-workers in 1998.[4] Since this ground-breaking report enantioselective catalysis by chiral Brønsted acids has become of great interest.[5,6] In particular the levels of stereochemical control obtained using BINOL-derived phosphoric acid catalysts[7] has been impressive. BINOL-derived phosphoric acids, such as (*R*)- and (*S*)-**4.1** (**Figure 1**) have been shown to provide excellent levels of enantioselectivity in the catalysis of a number of different reactions, such as Mannich[8] and Mannich-type reactions,[9] Strecker reactions,[10] transfer hydrogenations[11,12] and aldehyde activations.[13]



(*R*)-**4.1** (*S*)-**4.1**

Figure 4.1. Examples of BINOL-derived Phosphoric Acids

It was therefore decided that it would interesting to investigate the use of BINOL-derived phosphoric acids such as **4.1** in the catalytic activation of glycosylation reactions. Glycosylation reactions are generally activated using Lewis acids as opposed to Brønsted acids, and examples of catalytic Brønsted acid activated glycosylation protocols are limited.[14] However, considering the wide variety of glycosyl donors that are available to the synthetic chemist it seemed that Brønsted acid catalysed procedures should be achievable. Indeed, Jacobsen and co-workers recently reported the use of enantioselective thiourea-catalysed additions to oxacarbenium ions,[15] where tentative investigations were made into the organocatalytic activation of 2-deoxy glycosyl acetates.

In our mind, the most suitable glycosyl donor for a catalytic activation protocol would be a trichloroacetimidate donor.[16,17] Trichloroacetimidate donors are generally activated using catalytic quantities of Lewis acids such as BF_3OEt_2 and TMSOTf, however there seems no reason why they cannot also be activated using Brønsted acids. A literature search on the activation of trichloroacetimidates with Brønsted acids revealed that Toste had actually reported the activation of a trichloroacetimidate

leaving group in a non-carbohydrate context using catalytic amounts of a BINOL-derived phosphoric acid.[18] We therefore reasoned that activation of a trichloroacetimidate glycosyl donor using a BINOL-derived phosphoric acid would indeed be possible.

It is often the case when using BINOL-derived phosphoric acids that protonation occurs followed by the formation of a tight ion pair between the protonated species and the conjugate base *via* a hydrogen bonding interaction.[7] However Toste observed that upon activation of the trichloroacetimidate a tight ion pair was formed between the conjugate base and an episulfonium ion formed intramolecularly. Based on the findings of Toste, it was imagined that activation of a trichloroacetimidate glycosyl donor would result in the formation of a tight ion pair between the conjugate base and the oxacarbenium ion. Due to the chiral nature of the conjugate base, it was hoped that there would be a preference for coordination to one face of the oxacarbenium ion over the other, and hence subsequent attack by the glycosyl acceptor would have to occur onto the opposite face, resulting in high stereocontrol in the glycosylation (**Figure 4.2**).

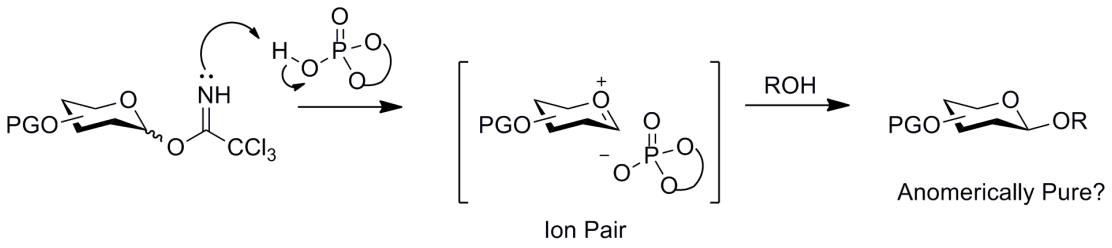


Figure 4.2. Postulated glycosylation process for activation of a trichloroacetimidate donor with a BINOL-derived phosphoric acid.

4.2 Synthesis of Trichloroacetimidate Glycosyl Donors

We initiated our investigation by considering the effect that different monosaccharides would have on the stereochemical outcome of the glycosylation reaction. We postulated that the conjugate base would coordinate to the oxacarbenium on either the α- or β-face, and this facial selectivity would be strongly influenced by the orientation of the hydroxyl groups on the sugar ring. Hence we decided to synthesise a range of trichloroacetimidate donors; specifically a *gluco*, *manno* and *galacto* trichloroacetimidate. In order to investigate the dependence of the stereochemical outcome of glycosylation upon the stereochemistry of the phosphoric acid, protection of the hydroxyl groups of the glycosyl donors with non-participating protecting groups was required. Hence the tetra-benzyl protected *gluco*, *manno* and *galacto* trichloroacetimidate donors **2.30**, **4.2** and **4.3** were chosen for study (**Figure 4.3**).

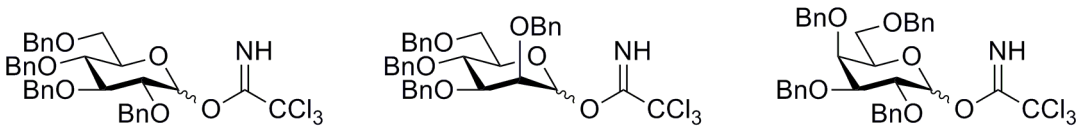
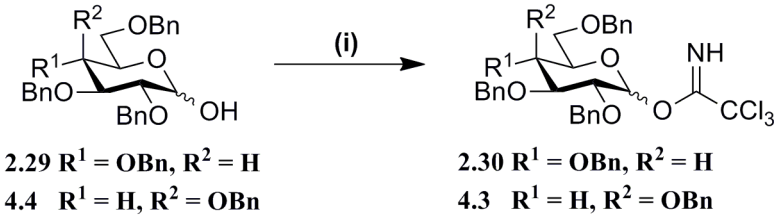


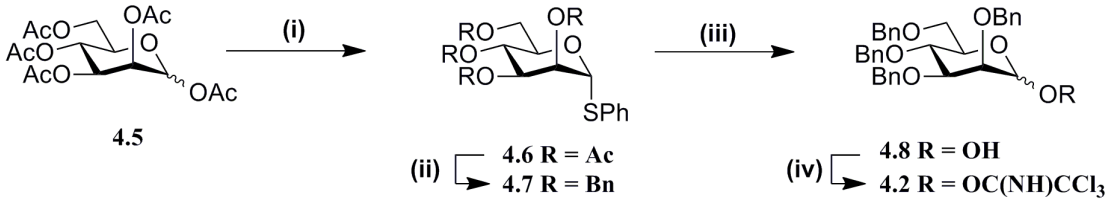
Figure 4.1. Trichloroacetimidate target donors.

The synthesis of trichloroacetimidate donor **2.30**[19] was previously described in chapter 2; commercially available 2,3,4,6-tetra-*O*-benzyl-D-α/β-glucopyranose **2.29** was treated with trichloroacetonitrile and DBU to afford the donor **2.30** in a yield of 91%. The *galacto* trichloroacetimidate **4.3** could likewise be synthesised by treatment of 2,3,4,6-tetra-*O*-benzyl-D-α/β-galactopyranose **4.4** with trichloroacetonitrile and DBU, affording **4.3**[20,21] in a yield of 88% (**Scheme 4.1**).



Scheme 4.1. (i) Cl_3CCN, DBU, CH_2Cl_2, 0 °C, 3 h, **2.30** 91%, **4.3** 88%.

Synthesis of the mannose donor **4.2** required a slightly longer synthesis. Treatment of the per-acetylated mannose **4.5** with thiophenol and $BF_3.OEt_2$ gave the thioglycoside **4.6**.[22] Deacetylation of **4.6** was achieved by treatment under Zemplen conditions[23] and the crude material was immediately benzyl protected by treatment with benzyl bromide and sodium hydride in DMF, producing the tetra-*O*-benzyl protected mannose **4.7**.[22] Hydrolysis of the thioglycoside was achieved by treatment with NBS in a mixture of acetone and water to give the hemiacetals **4.8**[24], which were then reacted with trichloroacetonitrile and DBU to afford donor **4.2**[24] in an overall yield of 71% over 4 steps (**Scheme 4.2**).



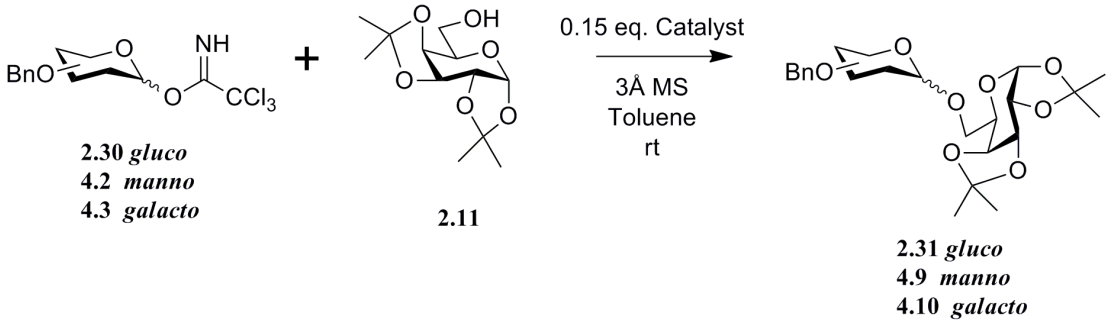
Scheme 4.2. (i) PhSH, $BF_3.OEt_2$, CH_2Cl_2, 6 h, 87% (ii) NaOMe, MeOH, 1 h; then BnBr, NaH, DMF, 16 h, 93%; (iii) NBS, acetone/H_2O, 1 h, 97%; (iv) Cl_3CCN, DBU, CH_2Cl_2, 0 °C, 3 h, 90%.

4.3 Glycosylation Reactions Catalysed by a Chiral Brønsted Acid

With the three donors now in hand, attention turned to carrying out glycosylation reactions using both enantiomers of the BINOL-derived phosphoric acid **4.1** as the catalytic activator.

Glycosylation reactions were carried out using diacetone galactose **2.11** as the glycosyl acceptor, and all reactions were carried out in toluene with 3Å molecular sieves. Toluene is commonly the solvent of choice for enantioselective reactions utilising BINOL-derived phosphoric acids as the non-polar solvent aids the formation of a tight ion pair in the reaction. More polar solvents will solvate the ions better and as a result diminish the selectivity of the reaction. In addition to the phosphoric acid **4.1**, TMSOTf was utilised as an achiral activator for the trichloroacetimidates so comparison of the stereochemical outcomes could be made. In each case it was decided that 0.15 eq. of the catalysts would be used. The results for the glycosylation reactions of donors **2.30**, **4.2** and **4.3** are summarised in **Table 4.1**.

Table 4.1. Glycosylation of diacetone galactose **2.11** (2 eq.) with donors **2.30**, **4.2** and **4.3** catalysed by chiral phosphoric acid **4.1**.



2.30 ***gluco***
4.2 ***manno***
4.3 ***galacto***

2.11

2.31 ***gluco***
4.9 ***manno***
4.10 ***galacto***

Entry	Glycosyl Donor	Catalyst	Time (h)	Product	Yield (%)	α:β ratio[a] (σ)
a	**2.30**	TMSOTf	0.25	**2.31**	97	1:1.3 (0.05)
b	**2.30**	(*R*)-**4.1**	48	**2.31**	66	1:2 (0.08)
c	**2.30**	(*S*)-**4.1**	48	**2.31**	75	1:2 (0.08)
d	**4.2**	TMSOTf	0.25	**4.9**	85	7:1 (0.03)
e	**4.2**	(*R*)-**4.1**	48	**4.9**	67	5.2:1 (0.05)
f	**4.2**	(*S*)-**4.1**	48	**4.9**	66	5.6:1 (0.05)
g	**4.3**	TMSOTf	0.25	**4.10**	98	1.2:1 (0.10)
h	**4.3**	(*R*)-**4.1**	48	**4.10**	77	1:2 (0.10)
i	**4.3**	(*S*)-**4.1**	48	**4.10**	80	1:7 (0.05)

[a]Anomeric ratios were determined by integration of appropriate peaks in the ^{1}H nmr spectra. Glycosylation reactions were carried out in triplicate to confirm the reproducibility of results, and α:β ratios are given as a mean average (standard deviation given in brackets).

Reaction of the glucose trichloroacetimidate **2.30** with diacetone galactose **2.11** with TMSOTf as the catalyst gave disaccharide **2.31**[25] in an excellent yield of 97%. The reaction was complete in a matter of minutes at room temperature and formed an anomeric mixture slightly favouring the β-anomer (α:β ratio, 1:1.2, **Table 4.1**, entry a),. Use of both (*R*)-**4.1** and (*S*)-**4.1** pleasingly gave efficient glycosylation in modest to good yields, however the reaction with the chiral phosphoric acids was observed to be much slower than with TMSOTf, requiring 48 h to reach completion; this was fully expected as literature examples showed that reactions using BINOL-derived phosphoric acids could often take a long time to reach completion. Both enantiomers

of **4.1** were observed to produce the same selectivity (α:β ratio, 1:2, **Table 4.1**, entries a and b); although this was a slight increase in β-selectivity compared to activation with the achiral catalyst, the difference was not significant enough to conclude that the chiral catalyst had affected the stereochemical outcome.

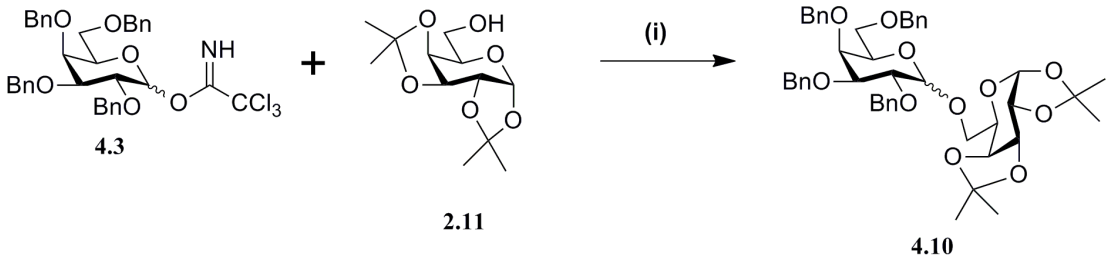
Reaction of the mannose trichloroacetimidate **4.2** with **2.11** catalysed by TMSOTf gave the disaccharide **4.9**[26] as predominantly the α-anomer (α:β ratio, 7:1, **Table 4.1**, entry d). Catalysis with phosphoric acids **4.1** produced **4.9** in modest yields and similar selectivity; both enantiomers produced slightly more β-anomer in the product compared to TMSOTf.

Finally the galactose trichloroacetimidate **4.3** was reacted with **2.11**. Reaction catalysed by TMSOTf produced the disaccharide **4.10**[27] in excellent yield as an almost equimolar anomeric mixture of compounds in which the α-anomer predominated slightly (α:β ratio, 1.2:1, **Table 4.1**, entry g). Interestingly when glycosylation was undertaken using (*R*)-**4.1** the anomeric ratio of the products was altered and the β-anomer now predominated (α:β ratio, 1:2, **Table 4.1**, entry h). When the glycosylation was catalysed using (*S*)-**4.1** the disaccharide product **4.10** was isolated in similar yield to when (*R*)-**1** had been used, but significantly, the anomeric ratio of product was altered considerably – the β-anomer was now markedly favoured over the α-anomer (α:β ratio, 1:7, **Table 4.1**, entry i).

It was intriguing that in the case of the *gluco* and *manno* donors **2.30** and **4.2** no significant increase in anomeric selectivity was observed when using the chiral acid catalysts, however with the *galacto* donor **4.3** the anomeric selectivity was first switched when (*R*)-**4.1** was used and then significantly increased when (*S*)-**4.1** was used. It was proposed that for the glucose donor **2.30**, as all the substituents on the

carbohydrate ring are in the equatorial position, that upon formation of the oxacarbenium ion the conjugate base could coordinate to either face of the sugar and hence no significant selectivity was observed. With mannose donor **4.2** it was quite likely that the sterically hindering axial 2-postion substituent was blocking the β-face of the oxacarbenium ion, greatly favouring the formation of the α-anomeric product and far outweighing any effect that the chiral acid could have. With galactose donor **4.3** however, the presence of the axial 4-position substituent clearly resulted in the chiral catalysts favouring coordination to the α-face of the oxacarbenium ion, hence producing β-selectivity in the reaction product.

At this point a second control reaction was undertaken. In order to confirm that an intermediate glycosyl phosphate was not being formed in the reaction, activation of the galactose trichloroacetimidate donor **4.3** was investigated using an achiral phosphoric acid catalyst. Accordingly donor **4.3** was reacted with diacetone galactose **2.11** with diphenyl phosphoric acid as the catalyst (**Scheme 4.3**).



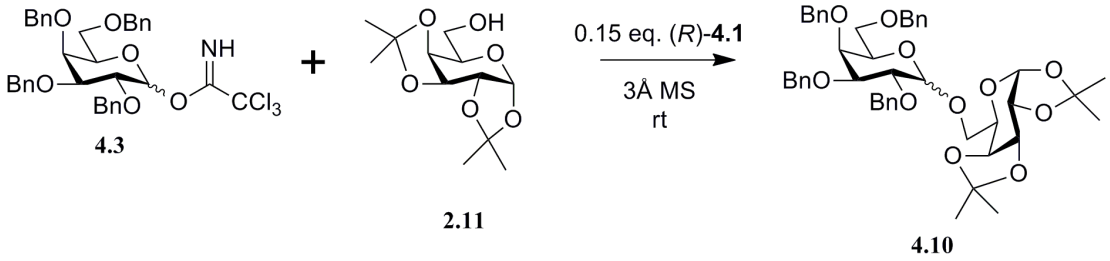
Scheme 4.3. (i) $(PhO)_2PO_2H$, toluene, 3Å MS, 48 h 19%, 168 h 57%, α:β ratio 1:1.9.

Reaction of **4.3** and **2.11** using diphenyl phosphoric acid as the catalyst proceeded even slower than with the chiral catalysts **4.1**. After 48 h the reaction was quenched and the product **4.10** isolated in a 19% yield. The observed α:β ratio for the product **4.10** was 1:1.9; similar to the result observed when (*R*)-**4.1** was used as the catalyst (α:β ratio, 1:2, **Table 4.1**, entry h) but significantly lower than the selectivity obtained

when (*S*)-**4.1** was used (α:β ratio, 1:7, **Table 4.1**, entry i). When the reaction was allowed to stir for 7 days complete consumption of the starting material was observed and **4.10** was isolated in a 57% yield with the same α:β ratio.

In light of these results we were confident that we had demonstrated that the stereochemical outcome of the glycosylation reaction was dependent on the chirality of the acid catalyst used. To further confirm that the selectivity was a result of ion pair formation between the oxacarbenium ion and the conjugate base of the acid, a solvent study was performed using (*R*)-**4.1** as the catalyst (**Table 4.2**).

Table 4.2. Glycosylation of diacetone galactose **2.11** (2 eq.) with donor **4.3** catalysed by (*R*)-**4.1** in a range of solvents.



Entry	Solvent/ Concentration	Catalyst	Product	Yield (%)	α:β ratio[a] (σ)
a	DCM/73mM	(*R*)-**4.1**	**4.10**	67	1:1.1 (0.05)
b	DCE/73mM	(*R*)-**4.1**	**4.10**	63	1:1 (0.05)
c	Toluene/73mM	(*R*)-**4.1**	**4.10**	88	1:2 (0.10)
d	Toluene/24mM	(*R*)-**4.1**	**4.10**	80	1:1.7 (0.15)
e	Toluene/12mM	(*R*)-**4.1**	**4.10**	77	1:1.8 (0.10)

[a]Anomeric ratios were determined by integration of appropriate peaks in the ^{1}H nmr spectra. Glycosylation reactions were carried out in triplicate to confirm the reproducibility of results, and α:β ratios are given as a mean average (standard deviation given in brackets).

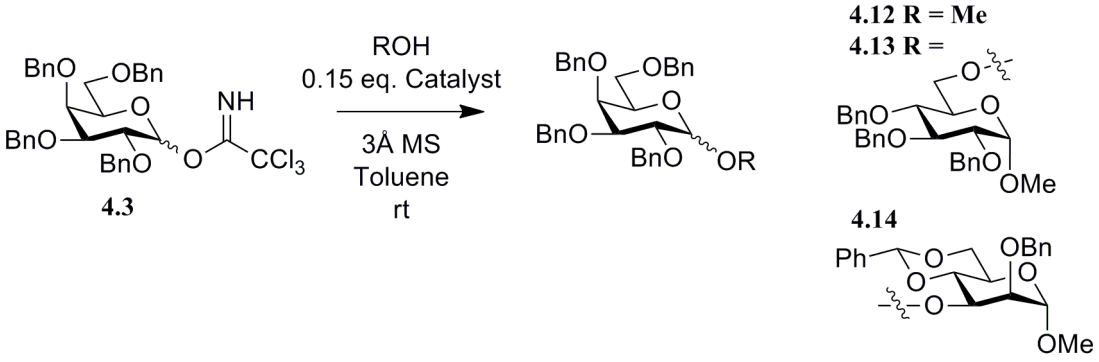
Glycosylation of donor **4.3** with diacetone galactose **2.11** in dichloromethane gave a poor yield of **4.10** compared to the analogous reaction in toluene. Furthermore the selectivity was observed to drop (α:β ratio, 1:1.1, **Table 4.2**, entry a) and he same was

observed in dichloroethane. This result was expected, as the more polar solvents would more efficiently solvate the ions, resulting in greater ion pair separation and hence poor selectivity. Following on from a report on the observation of interesting concentration effects on the stereochemical outcome of glycosylation processes,[28] glycosylation of **4.3** catalysed by (*R*)-**4.1** was undertaken at three different substrate concentrations in toluene. No effective changes were seen in the stereochemical outcome of these reactions, indicating no participation of the solvent in the glycosylation process.

4.4 Glycosylation Reactions of 4.3 with a Variety of Acceptors

Attention now turned to variation of the glycosyl acceptor. The glycosylation results for the reaction of **4.3** with a range of acceptors are outlined below (**Table 4.3**).

Table 4.3. Glycosylation of donor **4.3** with a variety of acceptors.



Entry	Acceptor	Catalyst	Time (h)	Product	Yield (%)	α:β ratio[a] (σ)
a	MeOH	TMSOTf	0.25	**4.12**	97	1:10 (0.08)
b	MeOH	(*R*)-**4.1**	16	**4.12**	87	1:47 (2.07)
c	MeOH	(*S*)-**4.1**	16	**4.12**	88	β only
d	**3.37**	TMSOTf	0.25	**4.13**	99	1:1.2 (0.08)
e	**3.37**	(*R*)-**4.1**	48	**4.13**	84	1:5.7 (0.13)
f	**3.37**	(*S*)-**4.1**	48	**4.13**	88	β only
g	**2.25**	TMSOTf	0.25	**4.14**	97	1:3.9 (0.08)
h	**2.25**	(*R*)-**4.1**	72	**4.14**	71	1:6 (0.10)
i	**2.25**	(*S*)-**4.1**	72	**4.14**	73	1:4.9 (0.10)

[a]Anomeric ratios were determined by integration of appropriate peaks in the ^{1}H nmr spectra. Glycosylation reactions were carried out in triplicate to confirm the reproducibility of results, and α:β ratios are given as a mean average (standard deviation given in brackets).

Perhaps surprisingly the most stereoselective reactions were obtained using MeOH as the acceptor (**Table 4.3**, entries a-c). With TMSOTf activation these reactions were complete within 15 minutes, and the methyl glycosides **4.12**[29] were isolated in 97% yield as an anomeric mixture in which the β-anomer predominated (α:β ratio, 1:10, **Table 4.3**, entry a). Use of the chiral acid **4.1** as catalytic activator again led to a slower glycosylation reaction, though notably this reaction was complete in 16 hours,

and was hence considerably faster than when diacetone galactose **2.11** had been used as the acceptor. Use of (*R*)-**4.1** led to the isolation of glycoside **4.12** in an 87% yield as almost entirely the β-anomer (α:β ratio, 1:47, **Table 4.3**, entry b). Subsequently the use of (*S*)-**4.1** as the activator led to the formation of **4.12** in 88% yield as the pure β-anomer. The variation in stereochemical outcome of these reactions, although the β-anomer predominated in each case, does again indicate an influence of the chirality of the catalyst on the stereoselectivity of the glycosylation process.

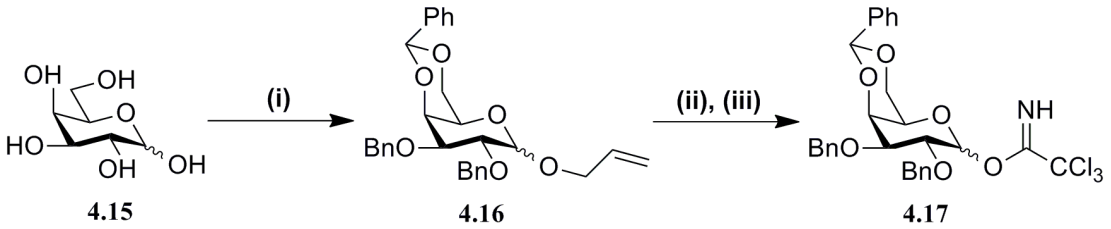
Attention then moved to other carbohydrate acceptors, which themselves may have more of an inherent stereochemical preference (i.e. match/mis-match with the donor). The use of the *gluco* configured primary alcohol acceptor **3.37** with TMOSTf as the activator led to the formation of disaccharide **4.13**[30] in excellent yield as an almost equimolar anomeric mixture (α:β ratio, 1:1.2, **Table 4.3**, entry d). Glycosylation catalysed by (*R*)-**4.1**, though slower (48 h to reach completion), produced disaccharide **4.13** in good yield and with significantly increased β-stereoselectivity (α:β ratio, 1:5.7, **Table 4.3**, entry e). The trend was continued when (*S*)-**4.1** was used as the catalytic activator, and disaccharide **4.13** was produced as exclusively the β-anomer (**Table 4.3**, entry f).

However when the *manno* secondary alcohol acceptor **2.25** was used two things became apparent. Firstly the glycosylation catalysed by TMSOTf was itself β-selective (α:β ratio, 1:3.9, **Table 4.3**, entry g). Secondly glycosylation catalysed by the chiral acids **4.1** was both considerably slower, and, in this instance, no significant difference between the stereochemical outcomes of the two reactions was observed. In this one instance the (*R*)-enantiomer was the slightly more β-selective of the two (α:β ratio, 1:6, **Table 4.3**, entry h).

These results indicated that the selectivity of the reaction was not only dependent upon the stereochemistry of the glycosyl donor, but also of the acceptor.

4.5 Influence of the Glycosyl Donor Protecting Group Pattern

To conclude our initial studies into the use of chiral Brønsted acid catalysed glycosylations, we wished to investigate the effect the protecting group strategy had on the stereochemical outcome of the reaction. Specifically we wished to investigate how the presence of a 4,6-*O*-benzylidene protecting group on the glycosyl donor would affect the outcome of the reaction. It was imagined that by introducing an acetal at the 4,6-*O*-position the conformational flexibility of the molecule would be greatly reduced, which could have a significant effect on interactions between the oxacarbenium ion and the conjugate bases. Hence the 4,6-*O*-benzylidene protected glycosyl trichloroacetimidate **4.17** was synthesised from D-galactose **4.15** (**Scheme 4.4**).



4.15 **4.16** **4.17**

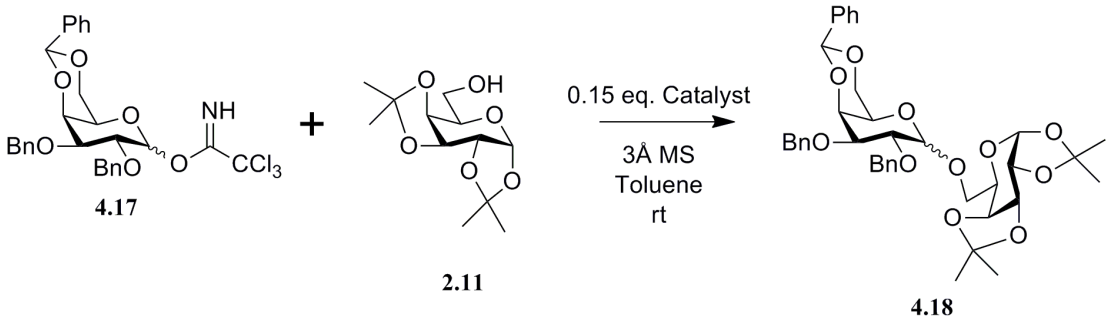
Scheme 4.4. (i) $PhCH(OMe)_2$, CSA, DMF, 60 °C, 250 mbar, 1.5 h; then AllBr, NaH, DMF, 0.5 h; then BnBr, NaH, DMF, 3.5 h, 60%; (ii) $[Ir(coa)(PPh_2Me)_2]PF_6$, H_2, THF, 16h; then NIS, H_2O, 16 h; (iii) Cl_3CCN, DBU, CH_2Cl_2, 0 °C, 2 h, 57%.

Allyl 2,3-di-O-benzyl-4,6-O-benzylidene-α/β-D-galactopyranoside **4.16** was synthesized in one-pot procedure.[31] Treatment of D-galactose **4.15** with benzylidene dimethyl acetal and catalytic CSA gave 4,6-*O*-benzylidene protection. The crude reaction mixture was then treated with allyl bromide and sodium hydride for 0.5 h

before the reaction was diluted with benzyl bromide and further sodium hydride was added. Column chromatography afforded **4.16** in a 60% yield. Isomerisation of the allyl group with (1,5-cyclooctadiene)bis(methyl-diphenylphosphine)iridium(I) hexafluorophosphate gave the vinyl ether which was immediately cleaved with NIS/H_2O. The crude mixture was then reacted with trichloroacetonitrile and DBU to afford the trichloroacetimidate **4.17** in a 57% yield over two steps.

With donor **4.17** in hand, glycosylation was carried out with diacetone galactose **2.11**. The results are summarized below (**Table 4.4**).

Table 4.4. Glycosylation of diacetone galactose **2.11** (2 eq.) with donors **4.18** catalysed by chiral phosphoric acid **4.1**.



Entry	Glycosyl Donor	Catalyst	Product	Yield (%)	α:β ratio[a]
a	**4.17**	TMSOTf	**4.18**	94	1:1.1
b	**4.17**	(*R*)-**4.1**	**4.18**	76	1:1.2
c	**4.17**	(*S*)-**4.1**	**4.18**	92	1:3.4

[a]Anomeric ratios were determined by integration of appropriate peaks in the 1H nmr spectra. Glycosylation reactions were carried out in triplicate to confirm the reproducibility of results.

In this instance the use of TMSOTf as activator produced disaccharide **4.18** as an almost equimolar mixture (α:β ratio, 1:1.1, **Table 4.4**, entry a). This ratio remained essentially unchanged when the (*R*)-enantiomer of **4.1** was used as the catalyst (α:β ratio, 1:1.2, **Table 4.4**, entry b). However when (*S*)-**4.1** was used the reaction was

again found to favour formation of the β-anomer (α:β ratio, 1:3.4, **Table 4.4**, entry c). These results showed that introduction of the conformationally rigid protecting group had decreased the β-selectivity previously observed with donor **4.3**. Although the decrease in selectivity was not large, these results suggested that the oxacarbenium ion was previously adopting a favourable conformation for interaction with the chiral conjugate base which it could no longer form.

4.6 Conclusions and Future Work

In conclusion, it has been demonstrated for the first time that trichloroacetimidate glycosyl donors can be activated using a chiral Brønsted acid. Furthermore our results have shown that the stereochemical outcome of a glycosylation reaction can be affected by the chirality of a catalytic acid that is used as an activator. Compared to activation with an achiral Lewis acid (TMSOTf) our reactions have shown that the chiral acid **4.1** generally increases β-selectivity in the glycosylation product. Whilst the (*R*)-enantiomer of **4.1** induced quite low levels of β-selectivity, the use of the (*S*)-enantiomer of **4.1** generally caused highly selective β-glycosylation, and in certain cases the β-product was formed exclusively; although these observations did indicate that β-selectivity is to some extent still dependent on the identity of the glycosyl acceptor employed.

The ultimate objective of a research program such as this would be to develop a chiral catalytic activating system that was β-selective for one enantiomer of the catalyst, and α-selective for the other, independently of the identities of glycosyl donor and acceptor. These initial results show that such a 'Holy-Grail' of glycosylation chemistry is very distant target, however they do serve as an introduction to the notion that chiral catalysts can be used in glycosylation chemistry. Indeed these results have

proven that that the stereochemical outcome of glycosylation is dependent on the chirality of the activating catalyst, and hence this exciting new method of stereocontrolled glycosylation certainly warrants further investigation.

An obvious starting point for future investigations would be a thorough study of differently substituted BINOL-derived phosphoric acids; indeed our own results suggested that chiral acid **4.1** had a 'good fit' for galactose donors, and hence a detailed study of the BINOL-derived phosphoric acids available may uncover more favourable catalyst/sugar matches. Recent developments have also led to the discovery of more active BINOL-based catalysts such as chiral *N*-triflyl thiophosphoramides,[32] which can potentially allow faster reactions and greater efficiency. Research has also been carried out using the silver salts of chiral phosphoric acids.[33] It can be imagined that such compounds may have an application in glycosylation chemistry. Whilst Koenigs-Knorr type activation of glycosyl halides using such compounds may not be appropriate given the need for stoichiometric amounts of silver, silver salts of chiral acids could still be potentially useful additives in glycosylation protocols and their use could extend to the activation of a wide range or glycosyl donors.

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Chapter 5: Experimental

5.1 General Experimental

All reactions involving moisture sensitive reagents were performed under an atmosphere of argon or nitrogen *via* standard vacuum Schlenk line techniques. All glassware for such reactions was flame-dried and cooled under an atmosphere of argon. Reactions conducted at -78°C were cooled by means of an acetone/dry ice bath; those conducted at -40°C by were cooled means of an acetonitrile/dry ice bath; those conducted at 0°C were cooled by means of an ice bath. Solvent was removed under reduced pressure using a Buchi^{TM} rotary evaporator.

Solvents and reagents

Diethyl ether, toluene, dichloromethane and acetonitrile were dried by passing them through a column of activated basic alumina. Tetrahydrofuran was distilled from sodium/benzophenone under argon atmosphere prior to use. *N*,*N*-Dimethylformamide, pyridine and methanol were purchased from Aldrich in sure/seal^{TM} bottles. All other solvents were used as supplied (analytical or HPLC grade) without purification. Petroleum ether (Petrol) refers to the fraction of light petroleum ether boiling in the range 40-60°C. Reagents were used as supplied without further purification unless otherwise stated.

Chromatography

Thin Layer Chromatography (t.l.c.) was carried out on Merck Silica Gel $60F_{254}$ aluminium-backed plates. Visualisation of the plates was achieved using a UV lamp (λ_{max} = 254 or 365 nm), and/or ammonium molybdate (5% in 2M H_2SO_4), and/or sulphuric acid (5% in EtOH) and/or iodine and/or vanillin and/or potassium

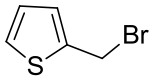
permanganate. Flash column chromatography was carried out using Sorbsil C60 40/60 silica.

Characterising data

Melting points were recorded on a Kofler hot block and are uncorrected. Proton and carbon nuclear magnetic resonance (δ_H, δ_C) spectra were recorded on Bruker DPX200 (200MHz), Bruker DPX250 (250MHz), Bruker DPX 400 (400 MHz), Bruker AV400 (400MHz), and Bruker AV500 (500MHz) spectrometers. All chemical shifts are quoted on the δ-scale in ppm using residual solvent as an internal standard. ^{1}H and ^{13}C spectra were assigned using COSY, DEPT, HSQC, HMBC, TOCSY and DPFGSE-TOCSY. Low resolution mass spectra were recorded on a Micromass Platform 1 spectrometer or a Micromass LCT Premier spectrometer using atmospheric pressure electrospray ionisation in either positive or negative polarity (ES^+ and/or ES^-). High resolution mass spectra were recorded by Mr. Robin Procter, Dr Lingzhi Gong or Mr Colin Sparrow on ether a Walters 2790-Micromass LCT electrospray ionisation or a Bruker FT-ICR mass spectrometer using electrospray ionisation (ESI) pr chemical ionisation (CI) techniques as stated. *M/z* values are reported in Daltons and are followed by their percentage abundance in parentheses. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a water-jacketed 1 cm^3 cell with a path length of 1 dm, and are quoted in units of $°.cm^2.g^{-1}$. Concentrations (*c*) are given in g / 100 cm^3, solvent and temperature are recorded. Microanalyses were performed by the Inorganic Chemistry Laboratory Elemental Analysis service and obtained on an Elementar vario EL instrument.

5.2 Chapter 2

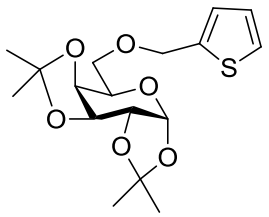
2-Bromomethyl thiophene 2.9[1]



2.9

2-Thiophenemethanol **2.10** (1.66ml, 17.5 mmol) was dissolved in anhydrous ether (50 ml) under an argon atmosphere. The mixture was cooled to 0°C and HBr (33% in glacial acetic acid, 4 ml) was added. The reaction was allowed to warm to room temperature. After 16 h, t.l.c. (petrol:ethyl acetate, 1:1) indicated the formation of a single product (R_f 0.9) and complete consumption of starting material (R_f 0.7). The reaction was diluted with ice and water (50 ml) and the aqueous layer extracted with ether (2 × 25 ml). The combined organic extracts were washed with cold saturated sodium bicarbonate solution until neutral pH and then washed with brine (50 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 2-bromomethyl-thiophene **2.9** (2.64 g, 85%) as a pale yellow liquid. These data are in agreement with those reported in the literature; δ_H (400 MHz, $CDCl_3$) 4.77 (2H, br s, $ArCH_2Br$), 6.96 (1H, dd, *J* 5.31 Hz, *J* 3.54 Hz, Ar-H), 7.13 (1H, d, *J* 3.54 Hz, Ar-H), 7.34 (1H, d, *J* 5.31 Hz, Ar-H); δ_C ($CDCl_3$) 26.8 (t, $ArCH_2Br$), 127.1, 127.2, 128.1 (3 × d, 3 × Ar-CH), 140.4 (s, Ar-C)

1,2:3,4-di-*O*-isopropylidene-6-*O*-(thiophen-2-yl)methyl-α-D-galactopyranoside 2.12

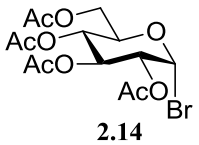


2.12

1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside **2.11** (1.00 g, 3.85 mmol) was dissolved in anhydrous DMF (10 ml) and then slowly added to a suspension of sodium hydride (0.138 g, 5.77 mmol) in anhydrous DMF (10 mL) at 0 °C under an argon atmosphere. 2-bromomethyl-thiophene **2.9** (1.021 g, 5.77 mmol) was then added slowly as a solution in anhydrous DMF (5 ml). Once the addition of the 2-bromomethyl thiophene solution was complete, the reaction was allowed to warm to room temperature. After 16 h, t.l.c (petrol:ethyl acetate, 4:1) indicated the formation of a single product (R_f 0.7) and complete consumption of starting material (R_f 0.4). The reaction was quenched with methanol (20 ml) and concentrated *in vacuo*. The resulting residue was dissolved in ether (50 ml), washed with water (50 ml), and the aqueous layer extracted with ether (2 × 25 ml). 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, 15:1) to afford 1,2:3,4-di-*O*-isopropylidene-6-*O*-(thiophen-2-yl)methyl-α-D-galactopyranoside **2.12** (1.28 g, 94%) as a pale yellow oil; $[\alpha]_D^{25}$ + 17.0 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.34, 1.34, 1.45, 1.54 (12H, 4 x s, 4 x CH_3), 3.62-3.72 (2H, m, H-6,H-6'), 3.96-4.00 (1H, m, H-5), 4.27 (1H, dd, $J_{3,4}$ 7.8 Hz, $J_{4,5}$ 1.8 Hz, H-4), 4.32 (1H, dd, $J_{1,2}$ 5.1 Hz, $J_{2,3}$ 2.3 Hz, H-2), 4.60 (1H, dd, $J_{3,4}$ 7.9 Hz, $J_{2,3}$ 2.4 Hz, H-3), 4.70-4.81 (2H,

m, $ArCH_2$), 5.55 (1H, d, $J_{1,2}$ 4.8 Hz, H-1), 6.96-7.03 (4H, m, 4 x ArH); δ_C (100 MHz, $CDCl_3$) 24.4, 24.9, 26.0, 26.1 (q, 4 x CH_3), 66.9 (d, C-5), 67.8 (t, C-6), 68.4 ($Ar\underline{C}H_2$), 70.5, 70.6, 71.1 (3 x d, C-2, C-3, C-4), 96.3 (d, C-1), 108.5, 109.2 (2 x s, $\underline{C}(CH_3)_2$), 125.8, 126.5, 126.6, (3 x d, 3 x $Ar\underline{C}H$), 141.0 (s, $Ar\underline{C}$) ; *m/z* 374 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{17}H_{24}O_6SNa$ (MNa^+) 379.1186. Found 379.1182). (Found: C, 57.34; H, 6.78. $C_{17}H_{24}O_6S$ requires C, 57.28; H, 6.79%).

2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide 2.14[2]

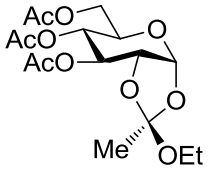


2.14

1,2,3,4,6-penta-*O*-acetyl-D-glucopyranoside **2.13** (50.0 g, 128.2 mmol) was dissolved in freshly distilled CH_2Cl_2 (200 ml) under an argon atmosphere. The mixture was cooled to 0°C and HBr (33% in glacial acetic acid, 50 ml) was added. The reaction was allowed to warm to room temperature. After 3 h, t.l.c. (petrol:ethyl acetate, 3:1) indicated the formation of a single product (R_f 0.6) and complete consumption of starting material (R_f 0.3). The reaction was diluted with ice and water (500 ml) and the aqueous layer extracted with CH_2Cl_2 (2 x 100 ml). The combined organic extracts were washed with cold saturated sodium bicarbonate solution until neutral pH (3 x 100 ml) then brine (150 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **4** (52.6 g, 99%) as a white crystalline solid. These data are in agreement with those reported in the literature; m.p 87-88°C (petrol/ethyl acetate); $[\alpha]_D^{23}$ + 190.2 (*c*, 1.0 in $CHCl_3$) [Lit. m.p 88-89°C; $[\alpha]_D^{20}$ + 194.0 (*c*, 3.9 in $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 2.03, 2.04, 2.09, 2.10 (12H, 4 x s, 4 x CH_3), 4.12 (1H, d, $J_{6,6'}$ 10.9 Hz, H-6), 4.26-4.34 (2H, m, H-5, H-6'), 4.83 (1H, dd, $J_{1,2}$ 4.0 Hz, $J_{2,3}$ 9.9 Hz, H-

2), 5.15 (1H, at, *J* 9.7 Hz, H-4), 5.55 (1H, at, *J* 9.7 Hz, H-3), 6.60 (1H, d, $J_{1,2}$ 4.0 Hz, H-1); *m/z* (ES^+) 430 ($M+NH_4^+$, 97) 428 ($M + NH_4^+$, 100%)

3,4,6-Tri-*O*-acetyl-1,2-*O*-(exo-ethoxyethylidine)-α-D-glucopyranoside 2.15[3]

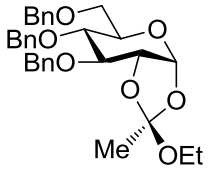


2.15

2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide **2.14** (52.5 g, 127.7 mmol) and tetra-butylammonium bromide (4.1 g, 12.8 mmol) were dissolved in freshly distilled CH_2Cl_2 (300 ml). Ethanol (14.9 ml, 166.0 mmol) and 2,4,6-collidine (21.9 ml, 255.4 mmol) were added and the reaction mixture refluxed at 50°C. After 16 h t.l.c. (petrol:ethyl acetate, 3:1) indicated the formation of a single product (R_f 0.4) and complete consumption of starting material (R_f 0.6). The reaction was diluted with water (125 ml) and the aqueous layer extracted with CH_2Cl_2 (2 x 150 ml). The combined organic extracts were washed with saturated sodium bicarbonate (2 x 100 ml) then brine (100 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by recrystallisation (ethanol) to afford 3,4,6-tri-*O*-acetyl-1,2-*O*-(exo-ethoxyethylidine)-α-D-glucopyranoside **2.15** (44.1 g, 92%) as a white crystalline solid. These data are in agreement with those reported in the literature; m.p 95-96°C; $[\alpha]_D^{23}$ + 37.5 (*c*, 1.0 in $CHCl_3$) [Lit. m.p 95-96°C; $[\alpha]_D^{20}$ + 34 (*c*, 1.0 in $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 1.18 (3H, t, *J* 7.1 Hz, $C\underline{H}_3CH_2$) 1.72 (3H, s, CH_3), 2.09, 2.10, 2.11 (9H, 3 x s, 3 x $COC\underline{H}_3$), 3.54 (2H, q, *J* 7.1 Hz, $CH_3C\underline{H}_2$), 3.92-3.97 (1H, m, H-5), 4.19-4.20 (2H, m, H-6, H-6'), 4.32 (1H, dd, $J_{1,2}$ 5.0 Hz, $J_{2,3}$ 2.8 Hz, H-2), 4.90 (1H, dd, $J_{3,4}$ 3.0 Hz, $J_{4,5}$ 9.4 Hz, H-4), 5.19 (1H,

at, *J* 2.9 Hz, H-3), 5.71 (1H, d, $J_{1,2}$ 5.0 Hz, H-1); *m/z* (ES^+) 399 ($M+Na^+$, 85) 394 ($M+NH_4^+$, 100%).

3,4,6-Tri-*O*-benzyl-1,2-*O*-(exo-ethoxyethylidine)-α-D-glucopyranoside 2.5[4]

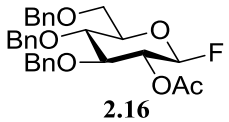


2.5

A solution of sodium (0.32 g) in methanol (20 ml) was added to a stirred solution of 3,4,6-tri-*O*-acetyl-1,2-*O*-(exo-ethoxyethylidine)-α-D-glucopyranoside **2.15** (10.5 g, 27.9 mmol) in methanol (80 ml). After 1 h, t.l.c (petrol:ethyl acetate, 1:1) indicated the formation of a single product (R_f 0) and complete consumption of starting material (R_f 0.7). The reaction mixture was concentrated *in vacuo* and subsequently left under high vacuum for 2 h. The residue was then dissolved in anhydrous DMF (100 ml) and slowly added to a suspension of sodium hydride (6.66 g, 166.6 mmol) in anhydrous DMF (100 ml) at 0 °C under an argon atmosphere. Benzyl bromide (14.9 ml, 125.0 mmol) was then added slowly to the reaction mixture. Once the addition of benzyl bromide was complete, the reaction mixture was allowed to warm to room temperature. After 16 h, t.l.c (petrol:ethyl acetate, 1:1) indicated the formation of a single product (R_f 0.9) and complete consumption of starting material (R_f 0). Methanol (50 ml) was added portion-wise in order to quench the reaction. The reaction was then concentrated *in vacuo*. The resulting residue was dissolved in ether (200 ml), washed with water (500 ml), and the aqueous layer extracted with ether (2 x 200 ml). The combined organic extracts were washed with brine (200 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (toluene:ethyl acetate, 9:1) to afford 3,4,6-tri-*O*-benzyl-1,2-

O-(exo-ethoxyethylidine)-α-D-glucopyranoside **2.5** (13.9 g, 95%) as a pale yellow oil. These data are in agreement with those reported in the literature; $[\alpha]_D^{23}$ + 35.8 (*c*, 1.0 in $CHCl_3$) [Lit. $[\alpha]_D^{20}$ + 34.8 (*c*, 1.1 in $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.1 Hz, $C\underline{H}_3CH_2$) 1.73 (3H, s, CH_3), 3.57-3.64 (2H, m, $CH_3C\underline{H}_2$), 3.69-3.76 (2H, m, H-6, H-6'), 3.79 (1H, dd, $J_{3,4}$ 4.55 Hz, $J_{4,5}$ 9.6 Hz, H-4), 3.85-3.89 (1H, m, H-5), 3.94 (1H, dd, $J_{2,3}$ 3.5 Hz, $J_{3,4}$ 4.3 Hz, H-3), 4.45 (1H, d, *J* 11.4, PhC$\underline{H}$H'), 4.49 (1H, dd, $J_{1,2}$ 5.3 Hz, $J_{2,3}$ 3.5 Hz, H-2), 4.56 (1H, d, *J* 12.1, PhC$\underline{H}$H'), 4.62-4.68 (3H, m, 3 x PhCH$\underline{H}$'), 4.77 (1H, d, *J* 11.9, PhC$\underline{H}$H'), 5.84 (1H, d, $J_{1,2}$ 5.3 Hz, H-1), 7.21-7.48 (15H, m, 15 x Ar-H); *m/z* (ES^+) 543 ($M+Na^+$, 70) 538 ($M+NH_4^+$, 100%).

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl fluoride 2.16[5]

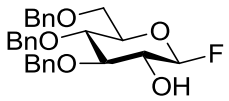


2.16

3,4,6-Tri-*O*-benzyl-1,2-*O*-(exo-ethoxyethylidine)-α-D-glucopyranoside **2.5** (2.10 g, 4.04 mmol) was dissolved in freshly distilled CH_2Cl_2 (15 ml) under an argon atmosphere. The mixture was cooled to 0°C and diethylaminosulfur trifluoride (0.69 ml, 5.25 mmol) was added. The reaction was allowed to warm to room temperature. After 4 h, t.l.c. (toluene:ethyl acetate, 9:1) indicated the formation of a single product (R_f 0.5) and complete consumption of starting material (R_f 0.4). The reaction was diluted with CH_2Cl_2 (70 ml) and then quenched with water (100 ml). The aqueous layer was extracted with dichloromethane (3 x 100 ml) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 12:1) to afford 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl fluoride **2.16** (1.86 g, 93%) as a colourless oil. These data are in agreement with those reported in the literature; $[\alpha]_D^{25}$

+ 16.5 (*c*, 1.0 in $CHCl_3$) [Lit. $[\alpha]_D^{20}$ + 15.5 (*c*, 2.19 in $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 2.03 (3H, s, CH_3), 3.68-3.79 (4H, m, H-3, H-5, H-6, H-6'), 3.87 (1H, at, *J* 9.1 Hz, H-4), 4.57, 4.79 (2H, ABq, J_{AB} 11.6 Hz, $PhCH_2$), 4.57, 4.65 (2H, ABq, J_{AB} 12.1 Hz, $PhCH_2$), 4.72, 4.79 (2H, ABq, J_{AB} 11.6 Hz, $PhCH_2$), 5.14 (1H, ddd, $J_{1,2}$ 6.3 Hz, $J_{2,3}$ 7.8 Hz, $J_{2,F}$ 10.3 Hz, H-2), 5.28 (1H, dd, $J_{1,2}$ 6.3 Hz, $J_{1,F}$ 53.1 Hz, H-1), 7.17-7.31 (15H, m, 15 x Ar-H); *m/z* (ES^+) 517 ($M+Na^+$, 85) 512 ($M+NH_4^+$, 100%).

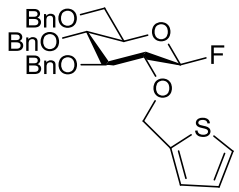
3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl fluoride 2.4[6]



2.4

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl fluoride **2.16** (1.82 g, 3.68 mmol) was dissolved in a mixture of THF (10 mL), Methanol (5 mL) and n-propylamine (5 mL) under an argon atmosphere. The reaction was heated to 45 °C. After 16 h, t.l.c. (petrol:ethyl acetate, 4:1) indicated the formation of a single product (R_f 0.3) and complete consumption of starting material (R_f 0.5). The reaction mixture was concentrated *in vacuo* and the residue purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford 3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl fluoride **2.4** (1.50 g, 90%) as a white crystalline solid. These data are in agreement with those reported in the literature; m.p 81-82 °C (petrol/ethyl acetate); $[\alpha]_D^{25}$ +24.5 (*c*, 1.0 in $CHCl_3$) [Lit. m.p 80-82 °C; $[\alpha]_D^{25}$ + 25.2 (*c*, 1.5 in $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 3.61 (1H, at, *J* 8.2 Hz, H-4), 3.67-3.81 (5H, m, H-2, H-3, H-5, H-6, H-6'), 4.55, 4.63 (2H, ABq, J_{AB} 12.1 Hz, $PhCH_2$), 4.58, 4.78 (2H, ABq, J_{AB} 10.8 Hz, $PhCH_2$), 4.82, 4.86 (2H, ABq, J_{AB} 11.6 Hz, $PhCH_2$), 5.26 (1H, dd, $J_{1,2}$ 6.3 Hz, $J_{1,F}$ 53.1 Hz, H-1), 7.18-7.37 (15H, m, 15 x Ar-H); *m/z* (ES^+) 475 ($M+Na^+$, 90) 470 ($M+NH_4^+$, 100%).

3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-ylmethyl)-β-D-glucopyranosyl fluoride 2.1

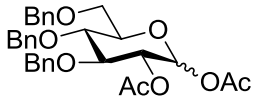


2.1

3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl fluoride **2.4** (0.273 g, 0.603 mmol) was dissolved in anhydrous DMF (2.5 ml) and then slowly added to a suspension of sodium hydride (0.600 g, 0.90 mmol) in anhydrous DMF (2.5 mL) at 0 °C under an argon atmosphere. 2-bromomethyl-thiophene **2.9** (0.214 g, 1.206 mmol) was then added slowly as a solution in anhydrous DMF (2.5 ml). Once the addition of the 2-bromomethyl thiophene solution was complete, the reaction was allowed to warm to room temperature. After 16 h, t.l.c (petrol:ethyl acetate, 4:1) indicated the formation of a single product (R_f 0.6) and complete consumption of starting material (R_f 0.3). The reaction was quenched with methanol (5 ml) and concentrated *in vacuo*. The resulting residue was dissolved in ether (25 ml), washed with water (50 ml), and the aqueous layer extracted with ether (2 × 25 ml). 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, 15:1) to afford fluoride **2.1** (0.244 g, 74%) as a pale yellow oil. These data are in agreement with those reported in the literature; $[\alpha]_D^{25}$ + 9.7 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.50-3.75 (6H, m, H-2, H-3, H-4, H-5, H-6, H-6'), 4.52, 4.80 (2H, ABq, J_{AB} 10.9 Hz, $ArCH_2$), 4.54, 4.62 (2H, ABq, J_{AB} 12.1 Hz, $ArCH_2$), 4.76, 4.95 (2H, ABq, J_{AB} 11.1 Hz, $ArCH_2$), 4.86, 5.03 (2H, ABq, J_{AB} 11.9 Hz, $ArCH_2$), 5.24 (1H, dd, $J_{1,2}$ 6.6 Hz, $J_{1,F}$ 52.6 Hz, H-1), 6.98 (1H, dd, *J* 5.1 Hz, *J* 3.3 Hz, Ar-H), 7.03 (1H, d, *J* 3.3 Hz, Ar-H), 7.12-7.14 (2H, m, 2 × Ar-H), 7.25-7.35 (14H, m, 14 × Ar-H); δ_C (100

MHz, $CDCl_3$) 68.3 (t, C-6), 68.5, 73.6, 75.1, 75.6 (4 × t, 4 × Ar<u>C</u>H_2), 74.8 (dd, $J_{5,F}$ 4.8 Hz, C-5), 76.8 (d, C-4), 81.1 (dd, $J_{2,F}$ 20.8 Hz, C-2), 83.3 (dd, $J_{3,F}$ 11.2 Hz, C-3), 109.8 (dd, $J_{1,F}$ 215.7 Hz, C-1), 126.3, 126.7, 127.1, 127.8, 127.9, 127.9, 128.0, 128.0, 128.4 (9 × d, 9 × Ar-CH), 137.8, 137.8, 138.2, 140.0 (4 × s, 4 × Ar-C); *m/z* (ES^+) 571 ($M+Na^+$, 80) 566 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{32}H_{33}FO_5SNa$ (MNa^+) 571.6546. Found 571.6544). (Found: C, 70.08; H, 6.06. $C_{32}H_{33}FO_5S$ requires C, 70.05; H, 6.06%)

1,2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α,β-D-glucopyranoside 2.7[7]

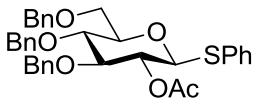


2.7

3,4,6-Tri-*O*-benzyl-1,2-*O*-(exo-ethoxyethylidine)-α-D-glucopyranoside **2.5** (14.5 g, 27.8 mmol) was dissolved in glacial acetic acid (60% in water, 250 ml) and stirred at room temperature. After 16 h, t.l.c (petrol:ethyl acetate, 1:1) indicated the formation of a single product (R_f 0.6) and complete consumption of starting material (R_f 0.9). The reaction mixture was co-evaporated with toluene and subsequently left under high vacuum for 2 h. The crude residue and DMAP (0.34 g, 2.79 mmol) were dissolved in anhydrous pyridine (100 ml) and the mixture cooled to 0°C under a nitrogen atmosphere. Acetic anhydride (5.27 ml, 55.8 mmol) was then slowly added. Once addition of acetic anhydride was complete, the reaction was allowed to warm to room temperature. After 16 h, t.l.c (petrol:ethyl acetate, 1:1) indicated the formation of a single product (R_f 0.9) and complete consumption of starting material (R_f 0.6). The reaction was cooled to 0°C and quenched with ethanol (75 ml). The reaction mixture was concentrated *in vacuo*. The residue was dissolved in ether (100 ml) and washed with 1M HCl (100 ml), then saturated sodium bicarbonate (100 ml), then brine (100

ml). The organic phase was then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (toluene:ethyl acetate, 8:1) to afford 1,2-O-Acetyl-3,4,6-tri-O-benzyl-α,β-D-glucopyranoside **2.7** (12.0 g, 81%) as a pale yellow oil. These data are in agreement with those reported in the literature; δ_H (400 MHz, $CDCl_3$) [13:1 mixture of α:β anomers observed, major α anomer quoted] 2.00, 2.14 (6H, 2 × s, 2 × CH_3), 3.70 (1H, dd, $J_{5,6}$ 1.8 Hz, $J_{6,6'}$ 10.9 Hz, H-6), 3.77-3.87 (2H, m, H-4, H-6'), 3.94 (1H, ddd, $J_{4,5}$ 10.1 Hz, $J_{5,6}$ 1.8 Hz, $J_{5,6'}$ 3.3 Hz, H-5), 4.03 (1H, at, *J* 9.5 Hz, H-3), 4.45 (1H, d, *J* 11.37, PhC<u>H</u>H'), 4.52-4.67 (3H, m, 1 × PhC<u>H</u>H', 2 × PhCH<u>H</u>'), 4.79, 4.88 (2H, ABq, J_{AB} 11.4, $PhCH_2$), 4.85 (1H, d, *J* 10.6, PhC<u>H</u>H'), 5.09 (1H, dd, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 10.0 Hz, H-2), 6.34 (1H, d, $J_{1,2}$ 3.6 Hz, H-1), 7.17-7.39 (15H, m, 15 × Ar-H); *m/z* (ES^+) 552 ($M+NH_4^+$, 100%).

Phenyl 2-*O*-acetyl-3-4-6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside 2.17[8]

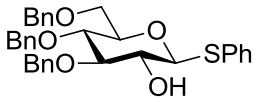


2.17

1,2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α,β-D-glucopyranoside **2.7** (4.06 g, 7.59 mmol) was dissolved in freshly distilled CH_2Cl_2 (80 ml) under a nitrogen atmosphere. Thiophenol (1.16 ml, 11.4 mmol) was added and the mixture then cooled to 0°C. Boron trifluoride diethyl etherate (1.40 ml, 9.90 mmol) was added dropwise to the mixture. Once addition of the boron trifluoride diethyl etherate was complete, the mixture was allowed to warm to room temperature. After 6 h, t.l.c (petrol:ethyl acetate, 7:3) indicated the formation of a single product (R_f 0.8) and complete consumption of starting material (R_f 0.7). The reaction was diluted with CH_2Cl_2 (250 ml) and washed with saturated sodium bicarbonate (100 ml), then water (100 ml), and then brine (100 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The

residue was purified by flash column chromatography (petrol:ethyl acetate, 9:1) to afford Phenyl 2-*O*-acetyl-3-4-6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **2.17** (3.97 g, 89%) as a white crystalline solid. These data are in agreement with those reported in the literature; m.p 112-113°C (methanol); $[\alpha]_D^{23}$ + 9.4 (*c*, 1.1 in $CHCl_3$) [Lit. m.p 113°C; $[\alpha]_D^{20}$ + 10 (*c*, 1.0 in $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 2.01 (3H, s, CH_3), 3.54-3.58 (1H, m, H-5), 3.71-3.73 (2H, m, H-3, H-4), 3.77 (1H, dd, $J_{5,6}$ 4.9 Hz, $J_{6,6'}$ 11.0 Hz, H-6), 3.84 (1H, dd, $J_{5,6'}$ 1.8 Hz, $J_{6,6'}$ 11.0 Hz, H-6'), 4.59 (1H, d, *J* 10.1 Hz, PhC<u>H</u>H'), 4.63 (1H, d, $J_{1,2}$ 9.5 Hz, H-1), 4.64-4.72 (3H, m, 3 × PhCH<u>H</u>'), 4.81-4.84 (2H, m, 2 × PhC<u>H</u>H'), 5.03 (1H, at, *J* 9.5 Hz, H-2), 7.18-7.35 (18H, m, 18 × Ar-H), 7.45-7.53 (2H, m, 2 × Ar-H); *m/z* (ES^+) 607 ($M+Na^+$, 60) 602 ($M+NH_4^+$, 100%).

Phenyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside 2.6[9]

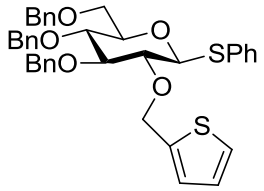


2.6

A solution of sodium (0.23 g) in methanol (10 ml) was added to a stirred solution of Phenyl 2-*O*-acetyl-3-4-6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **2.7** (1.50 g, 2.57 mmol) in Methanol-THF (20 ml, 1:1). After 16 h, t.l.c (petrol:ethyl acetate, 7:3) indicated the formation of a single product (R_f 0.7) and complete consumption of starting material (R_f 0.8). Amberlite 120 (H^+) resin was added and the mixture stirred for 15 min until pH neutral. The reaction was filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford phenyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **2.6** (1.18 g, 85%) as a white crystalline solid. These data are in agreement with those reported in the literature; m.p 72-73°C (ethanol); $[\alpha]_D^{23}$ -9.7 (*c*, 1.0 in $CHCl_3$) [Lit. m.p 71-73°C; $[\alpha]_D^{20}$ - 11.5 (*c*, 1.4 in $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 2.45 (1H, d, $J_{OH,2}$ 2.0 Hz, OH),

3.49-3.58 (2H, m, H-2, H-5), 3.60-3.66 (2H, m, H-3, H-4), 3.76 (1H, dd, $J_{5,6}$ 4.4 Hz, $J_{6,6'}$ 11.0 Hz, H-6), 3.82 (1H, dd, $J_{5,6'}$ 1.8 Hz, $J_{6,6'}$ 11.0 Hz, H-6'), 4.53 (1H, d, $J_{1,2}$ 9.6 Hz, H-1), 4.56-4.66 (3H, m, 3 x PhCHH'), 4.84-4.95 (3H, m, 3 x PhCHH'), 7.21-7.39 (18H, m, 18 x Ar-H), 7.58-7.61 (2H, m, 2 x Ar-H); *m/z* (ES^+) 565 ($M+Na^+$, 90) 560 ($M+NH_4^+$, 100%).

Phenyl 3,4,6-tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-1-thio-β-D-glucopyranoside 2.2

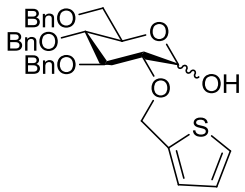


2.2

Phenyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **2.6** (0.244 g, 0.45 mmol) was dissolved in anhydrous DMF (5 ml) and then slowly added to a suspension of sodium hydride (0.600 g, 0.90 mmol) in anhydrous DMF (5 mL) at 0 °C under an argon atmosphere. 2-bromomethyl-thiophene **2.9** (0.119 g, 0.67 mmol) was then added slowly as a solution in anhydrous DMF (5 ml). Once the addition of the 2-bromomethyl-thiophene solution was complete, the reaction was allowed to warm to room temperature. After 16 h, t.l.c (toluene:ethyl acetate, 9:1) indicated the formation of a single product (R_f 0.8) and complete consumption of starting material (R_f 0.6). The reaction was quenched with methanol (5 ml) and concentrated *in vacuo*. The resulting residue was dissolved in ether (100 ml), washed with water (100 ml), and the aqueous layer extracted with ether (2 x 100 ml). The combined organic extracts were washed with brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (toluene:ethyl acetate, 12:1) to afford phenyl 3,4,6-tri-*O*-benzyl-2-*O*-(thiophen-2-yl)methyl-1-thio-β-D-glucopyranoside **2.2** (0.223 g, 78%) as a white crystalline solid; m.p 84-85°C

(petrol/ethyl acetate); $[\alpha]_D^{25}$ – 2.0 (*c*, 1.05 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.49-3.54 (2H, m, H-2, H-5), 3.66 (1H, at, *J* 9.35, H-4), 3.70-3.75 (2H, m, H-3, H-6), 3.80 (1H, dd, $J_{5,6'}$ 10.7 Hz, $J_{6,6'}$ 1.9 Hz, H-6'), 4.56, 4.63 (2H, ABq, J_{AB} 11.9 Hz, $ArCH_2$), 4.60, 4.84 (2H, ABq, J_{AB} 11.3 Hz, $ArCH_2$), 4.65 (1H, d, $J_{1,2}$ 9.6 Hz, H-1) 4.87, 4.97 (2H, ABq, J_{AB} 10.7 Hz, $ArCH_2$), 4.93, 5.03 (2H, ABq, J_{AB} 11.0 Hz, $ArCH_2$), 6.98 (1H, dd, *J* 5.05 Hz, *J* 3.28 Hz, Ar-H), 7.02 (1H, m, Ar-H), 7.19-7.36 (21H, m, 21 x Ar-H); δ_C (100 MHz, $CDCl_3$) 69.0 (t, C-6), 69.5, 73.4, 75.1, 76.0 (4 x t, 4 x Ar<u>C</u>H_2), 77.7 (d, C-4), 79.1 (d, C-2), 80.5 (d, C-5), 86.6 (d, C-3), 87.5 (d, C-1), 126.2, 126.7, 126.9, 127.5, 127.6, 127.7, 127.8, 127.8, 127.9, 127.9, 128.4, 128.4, 128.5, 128.9, 132.0 (15 x d, 15 x Ar-CH), 133.7, 138.0, 138.2, 138.4, 140.3 (5 x s, 5 x Ar-C); *m/z* (ES^+) 656 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{38}H_{38}O_5S_2Na$ (MNa^+) 661.2053. Found 661.2049). (Found: C, 71.46; H, 6.05. $C_{38}H_{38}O_5S_2$ requires C, 71.44; H, 6.00%)

3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-α/β-D-glucopyranose 2.8



2.8

Method 1

3,4,6-tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-1-thio-β-D-glucopyranoside **2.2** (1.00 g, 1.57 mmol) was dissolved in CH_2Cl_2-H_2O (16.5 mL, 10:1) and the mixture cooled to 0°C. N-iodosuccinimide (0.352 g, 1.57 mmol) and TFA (0.12 ml, 1.57 mmol) were added and the mixture stirred vigorously. After 2 h, t.l.c (toluene:ethyl acetate, 9:1) indicated the formation of a single major product (R_f 0.1) and complete consumption of starting material (R_f 0.8). The reaction was quenched with triethylamine (0.5 mL), then

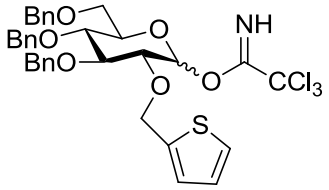
sodium thiosulfate (5 ml of a 10% solution). The reaction mixture was diluted with CH_2Cl_2 (15 ml), washed with saturated sodium bicarbonate (30 ml), and the aqueous layer extracted with CH_2Cl_2 (2 x 15 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 1:1) to afford 3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-α/β-D-glucopyranose **2.8** (0.724 g, 84%) as a clear oil: υ_{max} (KBr) 3510 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) [2:1 mixture of α:β anomers observed] 3.43 (0.5H, at, *J* 8.47, H-2β), 3.53-3.72 (7H, m, H-2α, H-3α, H-4α, H-6α, H-6'α, H-3β, H-4β, H-6β, H-6'β), 4.98-4.09 (1.5H, m, H-5α, H-5β), 4.48-4.62 (4.5H, m, 3 x ArC<u>H</u>H'α, 3 x ArC<u>H</u>H'β), 4.70 (0.5H, d, $J_{1,2}$ 7.83, H-1β), 4.78-5.02 (7H, m, 5 x ArC<u>H</u>H'α, 4 x ArC<u>H</u>H'β), 5.13-5.16 (0.5H, m, ArC<u>H</u>H'β), 5.19 (1H, br s, H-1α), 6.95-7.04 (2H, m, 3 x Ar-H), 7.13-7.19 (3H, m, 3 x Ar-H), 7.25-7.39 (22H, m, 21 x Ar-H), δ_C (100 MHz, $CDCl_3$) 67.7, 68.7 (2 x t, C-6α, C-6β), 68.8, 73.5, 75.1, 75.8 (4 x t, 4 x Ar<u>C</u>H_2), 70.2 (d, C-5α/β), 74.6, 77.8, 77.8, 79.5 (4 x d, C-3α, C-3β, C-4α, C-4β), 81.8, (d, C-5α/β), 82.7 (d, C-2α), 84.4 (d, C-2β), 91.4 (d, C-1α), 97.4 (d, C-1 β), 126.0, 126.4, 126.7, 126.8, 126.8, 127.1, 127.7, 127.7, 127.8, 127.8, 127.9, 128.0, 128.0, 128.1, 128.4, 128.4 (16 x d, 16 x Ar-CH), 137.7, 137.8, 138.2, 138.7, 140.6 (5 x s, 5 x Ar-C); *m/z* (ES^+) 564 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{32}H_{34}O_6SNa$ (MNa^+) 569.1968. Found 569.1964). (Found: C, 70.50; H, 6.25. $C_{32}H_{34}O_6S$ requires C, 70.31; H, 6.27%).

Method 2

3,4,6-tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-1-thio-β-D-glucopyranoside **2.2** (1.00 g, 1.57 mmol) was dissolved in acetone-H_2O (16.5 mL, 10:1) and the mixture cooled to 0°C. N-bromosuccinimide (0.838 g, 4.71 mmol) was added and the mixture stirred vigorously. After 1 h, t.l.c (toluene:ethyl acetate, 9:1) indicated the formation of a

single major product (R_f 0.1) and complete consumption of starting material (R_f 0.8). The reaction mixture was diluted with CH_2Cl_2 (30 ml), washed with saturated sodium bicarbonate (30 ml), and the aqueous layer extracted with CH_2Cl_2 (2 x 15 ml). The organic phase 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-2-*O*-(thiophen-2-yl)-α/β-D-glucopyranose **2.8** (0.711 g, 82%) as a clear oil.

_O_-(3,4,6-Tri-_O_-benzyl-2-_O_-(thiophen-2-yl)-α/β-D-glucopyranosyl) trichloroacetimidate 2.3

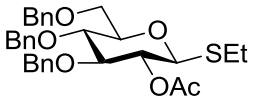


2.3

3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-α/β-D-glucopyranose **2.8** (0.700 g, 1.28 mmol) was dissolved in freshly distilled CH_2Cl_2 (8 ml) at 0 °C under an argon atmosphere. DBU (0.078 ml, 0.51 mmol) was added followed by trichloroacetonitrile (1.31 ml, 12.8 mmol). After 5 h, t.l.c (petrol:ethyl acetate, 4:1, with 1% added triethylamine) indicated the formation of a single product (R_f 0.4) and complete consumption of starting material (R_f 0.1). The reaction was concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 7:1, with 1% added triethylamine) to afford. *O*-(3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-α/β-D-glucopyranosyl) trichloroacetimidate **2.3** (0.710 g, 80%) as a pale yellow oil; υ_{max} (KBr) 3345 (w, NH), 1659 (s, C=N) cm^{-1}; δ_H (400 MHz, $CDCl_3$) [15:1 mixture of α:β anomers observed, major α anomer quoted] 3.67-3.70 (1H, m, H-5), 3.76-3.83 (3H, m, H-2, H-6, H-6'), 3.98-4.07 (2H, m, H-3, H-4), 4.49, 4.63 (2H,

ABq, J_{AB} 12.0 Hz, $ArCH_2$), 4.54, 4.87 (2H, ABq, J_{AB} 10.6 Hz, $ArCH_2$), 4.83, 5.00 (2H, ABq, J_{AB} 10.8 Hz, $ArCH_2$), 4.85, 4.93 (2H, ABq, J_{AB} 12.1 Hz, $ArCH_2$), 6.52 (1H, d, $J_{1,2}$ 3.4 Hz, H-1), 6.97 (1H, dd, *J* 5.1, *J* 3.4 Ar-H), 7.00 (1H, m, Ar-H), 7.15-7.17 (2H, m, 2 x Ar-H), 7.27-7.38 (14H, m, 14 x Ar-H), 8.61 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 68.0 (t, C-6), 73.1 (d, C-4), 73.5, 73.6, 75.0, 75.4 (4 x t, 4 x Ar<u>C</u>H_2), 78.8 (d, C-2), 81.3 (d, C-5), 84.4 (d, C-3), 94.4 (s, OC(NH)<u>C</u>Cl_3), 97.6 (d, C-1), 126.2, 126.6, 126.9, 127.7, 127.8, 127.9, 128.0, 128.1, 128.1, 128.4, 128.4, 128.6 (12 x d, 12 x Ar-CH), 137.8, 138.0, 138.6, 140.5, (4 x s, 4 x Ar-C), 163.6 (s, C=NH); *m/z* (ES^+) 709 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{34}H_{34}{}^{35}Cl_3NO_6SNa$ (MNa^+) 714.0501. Found 714.0504).

Ethyl 2-*O*-acetyl-3-4-6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside 2.19[10]

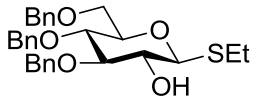


2.19

1,2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-α,β-D-glucopyranoside **2.7** (4.00 g, 7.50 mmol) was dissolved in freshly distilled CH_2Cl_2 (80 ml) under a nitrogen atmosphere. Ethanethiol (0.810 ml, 11.2 mmol) was added and the mixture then cooled to 0°C. Boron trifluoride diethyl etherate (1.30 ml, 9.75 mmol) was added dropwise to the mixture. Once addition of the boron trifluoride diethyl etherate was complete, the mixture was allowed to warm to room temperature. After 6 h, t.l.c (petrol:ethyl acetate, 2:1) indicated the formation of a single product (R_f 0.8) and complete consumption of starting material (R_f 0.7). The reaction was diluted with CH_2Cl_2 (250 ml) and washed with saturated sodium bicarbonate (100 ml), then water (100 ml), and then brine (100 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 9:1) to

afford Ethyl 2-*O*-acetyl-3-4-6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **2.19** (3.54 g, 88%) as pale yellow oil. These data are in agreement with those reported in the literature; $[\alpha]_D^{25}$ + 10.2 (*c*, 1.0 in $CHCl_3$) [Lit. $[\alpha]_D^{25}$ + 8.6 (*c*, 1.0 in $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.4 Hz, $SCH_2C\underline{H}_3$), 2.05 (3H, s, CH_3), 2.78 (2H, m, $SC\underline{H}_2CH_3$), 3.57 (1H, m, H-5), 3.74 (1H, at, *J* 9.0 Hz, H-3), 3.77 (1H, at, *J* 8.8 Hz, H-4), 3.78 (1H, dd, $J_{5,6}$ 4.5 Hz, $J_{6,6'}$ 11.3 Hz, H-6), 3.83 (1H, dd, $J_{6,6'}$ 11.1 Hz, $J_{5,6'}$ 1.9 Hz, H-6'), 4.43 (1H, d, $J_{1,2}$ 10.0 Hz, H-1), 4.62-4.68 (3H, m, 3 x ArC<u>H</u>H'), 4.76 (1H, d, *J* 11.4 Hz, ArC<u>H</u>H'), 4.86 (1H, d, *J* 10.6 Hz, ArC<u>H</u>H'), 4.88 (1H, d, *J* 11.3 Hz, ArC<u>H</u>H'), 5.10 (1H, at, *J* 9.2 Hz, H-2), 7.26–7.41(15H, m, ArH); *m/z* (ES^+) 554 ($M+NH_4^+$, 100%).

Ethyl 3-4-6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside 2.20[11]

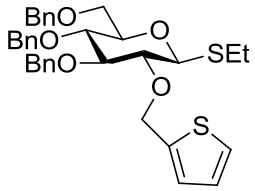


2.20

A solution of sodium (0.23 g) in methanol (10 ml) was added to a stirred solution of Ethyl 2-*O*-acetyl-3-4-6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **2.19** (1.38 g, 2.57 mmol) in Methanol-THF (20 ml, 1:1). After 16 h, t.l.c (petrol:ethyl acetate, 2:1) indicated the formation of a single product (R_f 0.6) and complete consumption of starting material (R_f 0.8). Amberlite 120 (H^+) resin was added and the mixture stirred for 15 min until pH neutral. The reaction was filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford ethyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **2.20** (1.17 g, 92%) as a pale yellow oil. These data are in agreement with those reported in the literature; $[\alpha]_D^{23}$ -13.0 (*c*, 1.0 in $CHCl_3$) [Lit. $[\alpha]_D^{20}$ - 12.8 (*c*, 2.o in $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, *J* 7.4 Hz, $SCH_2C\underline{H}_3$), 2.45 (1H, d, $J_{OH,2}$ 2.0 Hz, OH), 2.78 (2H,

m, $SC\underline{H}_2CH_3$), 3.49-3.58 (2H, m, H-2, H-5), 3.60-3.66 (2H, m, H-3, H-4), 3.76 (1H, dd, $J_{5,6}$ 4.4 Hz, $J_{6,6'}$ 11.0 Hz, H-6), 3.82 (1H, dd, $J_{5,6'}$ 1.8 Hz, $J_{6,6'}$ 11.0 Hz, H-6'), 4.53 (1H, d, $J_{1,2}$ 9.6 Hz, H-1), 4.56-4.66 (3H, m, 3 x PhC<u>H</u>H'), 4.84-4.95 (3H, m, 3 x PhCH<u>H</u>'), 7.21-7.39 (15H, m, 15 x Ar-H); *m/z* (ES^+) 517 ($M+Na^+$, 90) 512 ($M+NH_4^+$, 100%).

Ethyl 3,4,6-tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-1-thio-β-D-glucopyranoside 2.21

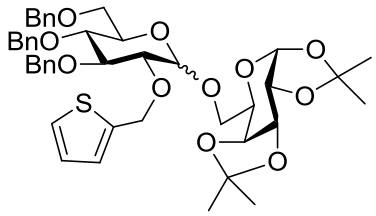


2.21

Ethyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **2.20** (0.222 g, 0.45 mmol) was dissolved in anhydrous DMF (5 ml) and then slowly added to a suspension of sodium hydride (0.600 g, 0.90 mmol) in anhydrous DMF (5 mL) at 0 °C under an argon atmosphere. 2-bromomethyl-thiophene **2.9** (0.119 g, 0.67 mmol) was then added slowly as a solution in anhydrous DMF (5 ml). Once the addition of the 2-bromomethyl-thiophene solution was complete, the reaction was allowed to warm to room temperature. After 16 h, t.l.c (toluene:ethyl acetate, 9:1) indicated the formation of a single product (R_f 0.8) and complete consumption of starting material (R_f 0.6). The reaction was quenched with methanol (5 ml) and concentrated *in vacuo*. The resulting residue was dissolved in ether (100 ml), washed with water (100 ml), and the aqueous layer extracted with ether (2 x 100 ml). The combined organic extracts were washed with brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (toluene:ethyl acetate, 12:1) to afford ethyl 3,4,6-tri-*O*-benzyl-2-*O*-(thiophen-2-yl)methyl-1-thio-β-D-glucopyranoside **2.21** (0.215 g, 81%) as a pale yellow oil; $[\alpha]_D^{25}$ – 4.1 (*c*, 1.00 in

$CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.3 Hz, $SCH_2C\underline{H}_3$), 2.77 (2H, m, $SC\underline{H}_2CH_3$), 3.40-3.50 (2H, m, H-2, H-5), 3.60-3.78 (4H, m, H-3, H-4, H-6, H-6'), 4.56, 4.63 (2H, ABq, J_{AB} 11.9 Hz, $ArCH_2$), 4.60, 4.84 (2H, ABq, J_{AB} 11.3 Hz, $ArCH_2$), 4.65 (1H, d, $J_{1,2}$ 9.6 Hz, H-1) 4.87, 4.97 (2H, ABq, J_{AB} 10.7 Hz, $ArCH_2$), 4.93, 5.03 (2H, ABq, J_{AB} 11.0 Hz, $ArCH_2$), 6.98 (1H, dd, *J* 5.05 Hz, *J* 3.28 Hz, Ar-H), 7.02 (1H, m, Ar-H), 7.19-7.36 (16H, m, 21 x Ar-H); δ_C (100 MHz, $CDCl_3$) 69.0 (t, C-6), 69.5, 73.4, 75.1, 76.0 (4 x t, 4 x $Ar\underline{C}H_2$), 77.7 (d, C-4), 79.1 (d, C-2), 80.5 (d, C-5), 86.6 (d, C-3), 87.5 (d, C-1), 126.2, 126.7, 127.5, 127.7, 127.8, 127.9, 128.4, 128.4, 128.5, 128.9, 132.0 (11 x d, 11 x Ar-CH), 133.7, 138.2, 138.4, 140.3 (4 x s, 4 x Ar-C); *m/z* (ES^+) 608 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{34}H_{38}O_5S_2Na$ (MNa^+) 613.2053. Found 613.2057). (Found: C, 71.46; H, 6.05. $C_{38}H_{38}O_5S_2$ requires C, 69.12; H, 6.48%)

3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside 2.18



2.18

Method 1

To a flame-dried round-bottom flask containing activated 3Å molecular sieves (0.100 g) was added a solution of 3,4,6-tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-β-D-glucopyranosyl fluoride **2.1** (125 mM) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside **2.11** (2 eq.) in freshly distilled CH_2Cl_2. The reaction mixture was cooled to the designated temperature under an argon atmosphere, then $BF_3.OEt_2$ (1.5

eq.) was added. The reaction was monitored by t.l.c. (toluene:ethyl acetate, 9:1) until the formation of a major product (R_f 0.4) and complete consumption of starting material (R_f 0.6) was observed. The reaction was quenched with saturated sodium bicarbonate solution and filtered through Celite®. The mixture was diluted with CH_2Cl_2, washed with saturated sodium bicarbonate solution (ml), and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 15:1) to afford 3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside **2.18** as a colourless oil; δ_H (400 MHz, $CDCl_3$) [1:1 mixture of α:β anomers observed] 1.34 (12H, br s, 2 × $CH_3\alpha$, 2 × $CH_3\beta$), 1.46, 1.47, 1.53, 1.55 (12H, 4 × s, 2 × $CH_3\alpha$, 2 × $CH_3\beta$), 3.44 (1H, m, H-$5_b\beta$), 3.50 (1H, at, *J* 8.4 Hz, H-$2_b\beta$), 3.59-3.86 (10H, m, H-$2_a\alpha$, H-$5_a\alpha$, H-$2_a\beta$, H-$5_a\beta$, H-$2_b\alpha$, H-$5_b\alpha$, H-$6_b\alpha$, H-$6'_b\alpha$, H-$6_b\beta$, H-$6'_b\beta$), 3.99 (1H, at, *J* 9.4 Hz, H-$4_b\beta$), 4.04-4.65 (12H, m, H-$3_a\alpha$, H-$4_a\alpha$, H-$6_a\alpha$, H-$6'_a\alpha$, H-$3_a\beta$, H-$4_a\beta$, H-$6_a\beta$, H-$6'_a\beta$, H-$3_b\alpha$, H-$4_b\alpha$, H-$1_a\beta$, H-$3_a\beta$), 4.74-5.31 (16H, m, 8 × $PhCH_2\alpha$, 8 × $PhCH_2\beta$), 5.00 (1H, d, $J_{1,2}$ 4.3 Hz, H-$1_b\alpha$), 5.54 (1H, d, $J_{1,2}$ 5.1 Hz, H-$1_a\beta$), 5.60 (1H, d, $J_{1,2}$ 5.1 Hz, H-$1_a\alpha$) 6.95-7.38 (36H, m, 36 × Ar-CH); δ_C (100 MHz, $CDCl_3$) 66.3, 66.9 (2 × t, C-$6_a\alpha$, C-$6_a\beta$), 68.3, 68.7, (2 × t, C-$6_b\alpha$, C-$6_b\beta$), 70.0, 73.5, 75.1, 75.8 (4 × t, 4 × Ar$\underline{C}H_2$), 65.7, 67.4, 70.2, 70.5, 70.7, 70.9, 71.5, 74.7, 77.5, 79.3, 81.2, 81.9, 84.3 (13 × d, C-2_a-C-$5_a\alpha/\beta$, C-2_b-C-$5_b\alpha/\beta$), 95.4 (d, C-$1_a\beta$), 96.3 (d, C-$1_a\alpha$), 97.0 (d, C-$1_b\alpha$), 104.4 (d, C-$1_b\beta$), 125.9, 126.0, 126.5, 126.6, 127.2, 127.6, 127.6, 127.7, 127.7, 127.9, 127.9, 128.1, 128.2, 128.4 (14 × d, 14 × Ar-CH), 137.9, 138.1, 138.3, 138.7, 138.9, 140.9, 141.2 (7 × s, 7 × Ar-C); *m/z* (ES^+) 806 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{44}H_{52}O_{11}S_1Na$ (MNa^+) 811.3123. Found 811.3118).

Method 2

To a flame-dried round-bottom flask containing activated 3Å molecular sieves (0.100g) was added a solution of 3,4,6-tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-1-thio-β-D-glucopyranoside **2.2** (125 mM), 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside **2.11** (2 eq.), and N-iodosuccinimide (1.5eq) in freshly distilled CH_2Cl_2. The reaction mixture was cooled to the designated temperature under an argon atmosphere, then TMSOTf (0.5 eq.) was added. The reaction was monitored by t.l.c. (toluene:ethyl acetate, 9:1) until the formation of a major product (R_f 0.4) and complete consumption of starting material (R_f 0.6) was observed. The reaction was quenched with sodium thiosulfate (10% solution) and filtered through Celite®. The mixture was diluted with CH_2Cl_2, washed with sodium thiosulfate (10% solution), and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 15:1) to afford 3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside **2.18** as a colourless oil.

Method 3

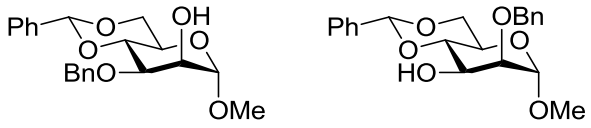
To a flame-dried round-bottom flask containing activated 3Å molecular sieves (0.100 g) was added a solution of *O*-(3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-α/β-D-glucopyranosyl) trichloroacetimidate **2.3** (125 mM) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside **2.11** (2 eq.) in freshly distilled CH_2Cl_2. The reaction mixture was cooled to the designated temperature under an argon atmosphere, then TMSOTf (0.1 eq.) was added. The reaction was monitored by t.l.c. (toluene:ethyl acetate, 9:1) until the formation of a major product (R_f 0.4) and complete consumption of starting

material (R_f 0.6) was observed. The reaction was quenched with saturated sodium bicarbonate solution and filtered through Celite®. The mixture was diluted with CH_2Cl_2, washed with saturated sodium bicarbonate solution, and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 15:1) to afford 3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside **2.18** as a colourless oil.

Method 4

To a flame-dried round-bottom flask containing activated 3Å molecular sieves (0.100g) was added a solution of Ethyl 3,4,6-tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-1-thio-β-D-glucopyranoside **2.21** (125 mM), 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside **2.11** (2 eq.), and TTBP (4.5eq) in freshly distilled CH_2Cl_2. The reaction mixture was cooled to the designated temperature under an argon atmosphere, then MeOTf (4.5 eq.) was added. The reaction was monitored by t.l.c. (toluene:ethyl acetate, 9:1) until the formation of a major product (R_f 0.4) and complete consumption of starting material (R_f 0.6) was observed. The reaction was diluted with CH_2Cl_2 and washed with saturated sodium bicarbonate, then water, and then brine. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 15:1) to afford 3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside **2.18** as a colourless oil.

Methyl-3-*O*-benzyl-4,6-di-*O*-benzylidene-α-D-mannopyranoside 2.24[12] **and Methyl-2-*O*-benzyl-4,6-di-*O*-benzylidene-α-D-mannopyranoside 2.25**[12]



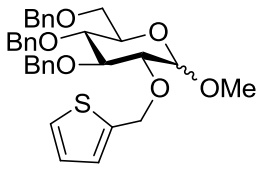
2.24 **2.25**

Benzaldehyde dimethylacetal (9.74 ml, 64.89 mmol) was added to a solution of methyl α-D-mannopyranoside **2.22** (5.04 g, 25.96 mmol) and camphor sulfonic acid (0.060 g, 0.260 mmol) in DMF (75 ml). The resulting solution was heated to 60 °C on a rotary evaporator under a pressure of 250 mbar. After 3 h, TLC (petrol/ethyl acetate, 3:1) indicated complete conversion of starting material (Rf 0.0) to two products (Rf 0.50 and 0.80). Further benzaldehyde dimethyl acetal (4.87 ml, 32.45 mmol) and camphor sulfonic acid (0.030 g, 0.130 mmol) was added to the reaction mixture. After 2 h, TLC (petrol/ethyl acetate, 3:1) indicated the formation of a single product (Rf 0.80). The solvent was removed *in vacuo*, the residue coevaporated with toluene (50 ml), then dissolved in DCM (100 ml), and washed with saturated sodium bicarbonate solution (50 ml) and brine (50 ml). The organic phase was then dried (MgSO4), filtered and concentrated *in vacuo*. The resulting crude mixture of *endo* and *exo*-dibenzylidene derivatives **2.23** was dissolved in freshly distilled toluene (150 ml) and cooled to -40 °C under an atmosphere of argon. Di-*iso*-butyl aluminium hydride (64.89 ml, 64.89 mmol of a 1 M solution in toluene) was slowly added to the reaction mixture and then the mixture was allowed to slowly warm to RT. After 2h, t.l.c (petrol:ethyl acetate, 3:1) indicated complete consumption of starting material (R_f 0.80) and formation of two products (R_f 0.40 and R_f 0.30). MeOH was added dropwise to quench the reaction and then the reaction was diluted with CH_2Cl_2 (250 ml). The organic layer was washed with Rochelle's Salt (10% solution, 200 ml), then

brine (200 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 3:1) to afford Methyl-3-*O*-benzyl-4,6-di-*O*-benzylidene-α-D-mannopyranoside **2.24** (3.05 g, 32%) as a colourless oil . These data are in agreement with those reported in the literature; (R_f 0.30); $[\alpha]_D^{18}$ + 26.1 (*c*, 0.6 in EtOH) [Lit. $[\alpha]_D^{20}$ + 30 (*c*, 0.4 in EtOH]; δ_H (400 MHz, $CDCl_3$) 2.67 (1H, s, OH), 3.39 (3H, s, OMe), 3.79–3.93 (3H, m, H-3, H-5, H-6), 4.06 (1H, d, *J* 3.0 Hz, H-2), 4.10 (1H, at, *J* 9.2 Hz, H-4), 4.29 (1H, dd, *J* 4.1 Hz, *J* 9.5 Hz, H-6'), 4.72 (1H, d, *J* 11.6 Hz, OCH2Ph), 4.78 (1H, s, H-1), 4.86 (1H, d, J 11.6 Hz, OCH2Ph), 5.62 (1H, s, O2CHPh), 7.27–7.53 (10H, m, Ar-H); *m/z* (ES^+) 395 ($M+Na^+$, 100%).

and methyl-2-*O*-benzyl-4,6-di-*O*-benzylidene-α-D-mannopyranoside **2.25** (4.76 g, 50%) as a white crystalline solid. These data are in agreement with those reported in the literature; (R_f 0.40); m.p 43-45°C; $[\alpha]_D^{18}$ + 1.4 (*c*, 1.0 in $CHCl_3$) [Lit. m.p 44-46°C; $[\alpha]_D^{20}$ + 1.10 (*c*, 1.0 in $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 2.38 (1H, br s, OH), 3.31 (3H, s, OMe), 3.69-3.80 (3H, m), 3.86 (1H, at, *J* 9.4 Hz), 4.03 (1H, dd, *J* 9.9 Hz, *J* 3.5 Hz), 4.21 (1H, dd, *J* 9.4 Hz, *J* 4.0 Hz), 4.60-4.71 (3H, m), 5.52 (1H, s, PhC<u>H</u>), 7.20-7.50 (10H, m, 10 x Ar-H); δ_C (100 MHz, $CDCl_3$) 55.0, 63.3, 68.7, 68.8, 73.7, 78.5, 79.5, 99.4, 102.1, 126.3, 127.0, 127.8, 128.0, 128.1, 128.3, 128.6, 129.0, 129.1, 129.8, 134.5, 137.4, 137.6; *m/z* (ES^+) 395 ($M+Na^+$, 100%).

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(thiophen-2-ylmethyl)-α/β-D-glucopyranoside 2.26

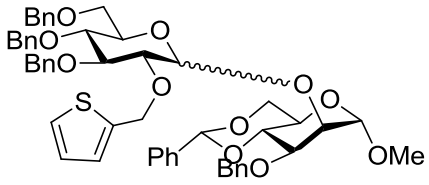


2.26

To a flame-dried round-bottom flask containing activated 3Å molecular sieves (0.100 g) was added a solution of *O*-(3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-α/β-D-glucopyranosyl) trichloroacetimidate **2.3** (125 mM) and MeOH (2 eq.) in freshly distilled CH_2Cl_2. The reaction mixture was cooled to -40 °C under an argon atmosphere, then TMSOTf (0.1 eq.) was added. The reaction was monitored by t.l.c. (toluene:ethyl acetate, 9:1) until the formation of a major product (R_f 0.5) and complete consumption of starting material (R_f 0.6) was observed. The reaction was quenched with saturated sodium bicarbonate solution and filtered through Celite®. The mixture was diluted with CH_2Cl_2, washed with saturated sodium bicarbonate solution, and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 15:1) to afford Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(thiophen-2-ylmethyl)-α/β-D-glucopyranoside **2.26** as a colourless oil. δ_H (400 MHz, $CDCl_3$) [1.5:1 mixture of α:β anomers observed] 3.38-3.50 (3.33H, m, H-2α, H-2β, H-5α, H-5β), 3.60 (5H, br s, OCH_3), 3.61-3.65 (3.33H, m, H-3α, H-3β, H-4α, H-4β), 3.68-3.78 (3.33H, m, H-6α, H-6β, H-6'α, H-6'β), 4.29 (0.66H, d, $J_{1,2}$ 7.8 Hz, H-1β), 4.31 (1H, d, $J_{1,2}$ 3.0 Hz, H-1α), 4.51-4.98 (13.33H, m, 8 × Ar-CHα, 8 × Ar-CHβ), 6.75 (1.66H, m, Ar-CHα, Ar-CHβ), 6.91 (1.66H, m, Ar-CHα, Ar-CHβ), 7.15-7.17 (3.33H, m, 2 × Ar-CHα, 2 × Ar-CHβ), 7.28-7.37 (23.33H, m, 14 × Ar-CHα, 14 × Ar-CHβ); δ_C (100 MHz, $CDCl_3$)

57.1 (q, O<u>C</u>H$_3$), 68.8 (t, C-6), 73.5, 75.1, 75.3, 75.8 (4 × t, 4 × Ar<u>C</u>H$_2$), 74.9 (d, C-5), 77.8 (d, C-3), 81.9 (d, C-2), 84.4 (d, C-4), 104.5 (d, C-1), 126.8, 127.6, 127.6, 127.7, 127.8, 127.9, 128.0, 128.4, 128.4, 129.3 (10 × d, 10 × Ar-CH), 138.0, 138.1, 138.5, 142.9 (4 × s, 4 × Ar-C); *m/z* (ES$^+$) 578 (M+NH$_4^+$, 100%). (HRMS (ES$^+$) Calcd. for $C_{33}H_{36}O_6S_1Na$ (MNa$^+$) 583.2125. Found 583.2119).

3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-ylmethyl)-α/β-D-glucopyranosyl-(1→2)-methyl-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside 2.27

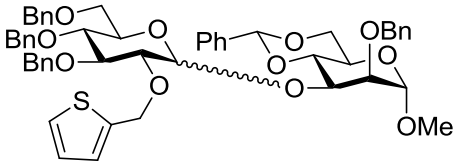


2.27

To a flame-dried round-bottom flask containing activated 3Å molecular sieves (0.100 g) was added a solution of *O*-(3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-α/β-D-glucopyranosyl) trichloroacetimidate **2.3** (125 mM) and methyl-3-*O*-benzyl-4,6-di-*O*-benzylidene-α-D-mannopyranoside **2.24** (2 eq.) in freshly distilled CH_2Cl_2. The reaction mixture was cooled to -40 °C under an argon atmosphere, then TMSOTf (0.1 eq.) was added. The reaction was monitored by t.l.c. (toluene:ethyl acetate, 9:1) until the formation of a major product (R_f 0.5) and complete consumption of starting material (R_f 0.6) was observed. The reaction was quenched with saturated sodium bicarbonate solution and filtered through Celite®. The mixture was diluted with CH_2Cl_2, washed with saturated sodium bicarbonate solution, and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 15:1) to afford 3,4,6-Tri-*O*-

benzyl-2-*O*-(thiophen-2-ylmethyl)-α/β-D-glucopyranosyl-(1→2)-methyl-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **2.27** as a colourless oil; δ_H (400 MHz, $CDCl_3$) [30:1 mixture of α:β anomers observed, major α anomer quoted] 3.38 (3H, br s, OCH_3), 3.50 (1H, m, H-5_b), 3.54-3.63 (3H, m, H-2_b, H-3_b, H-4_b), 3.68-3.71 (2H, m, H-6_b, H-$6'_b$), 3.80-3.83 (2H, m, H-5_a, H-6_a), 3.96 (1H, dd, $J_{2,3}$ 3.5 Hz, $J_{3,4}$ 9.9 Hz, H-3_a), 4.15 (1H, m, H-4_a), 4.24 (1H, m, H-2_a), 4.33 (1H, m, H-$6'_a$), 4.45, 4.51 (2H, ABq, J_{AB} 12.1 Hz, $PhCH_2$), 4.47, 4.75 (2H, ABq, J_{AB} 11.1 Hz, $PhCH_2$), 4.48 (1H, d, $J_{1,2}$ 4.0 Hz, H-1_b), 4.67, 4.85 (2H, ABq, J_{AB} 12.6 Hz, $PhCH_2$), 4.80, 4.97 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 4.82, 5.19 (2H, ABq, J_{AB} 11.4 Hz, $PhCH_2$), 4.84 (1H, s, H-1_a), 5.63 (1H, s, PhCH), 6.83 (1H, d, *J* 3.8 Hz, Ar-CH), 6.93 (1H, d, *J* 3.5 Hz, Ar-CH), 7.13-7.15 (2H, m, 2 × Ar-CH), 7.24-7.53 (24H, m, 24 × Ar-CH); δ_H (400 MHz, $CDCl_3$) [selected β anomer information] 5.60 (0.03H, s, PhCH); δ_C (100 MHz, $CDCl_3$) 55.0 (q, O<u>C</u>H_3), 63.9 (d, C-5_a), 68.6, 69.1, 69.1, 71.0, 73.4, 75.2, 75.9 (7 × t, C-6_a, C-6_b, 5 × Ar<u>C</u>H_2), 73.7, 74.9, 75.7, 77.4, 78.3, 81.2, 84.4 (7 × d, C-2_a, C-3_a, C-4_a, C-2_b, C-3_b, C-4_b, C-5_b), 99.8 (d, C-1_b), 101.6 (d, Ph<u>C</u>H), 102.8 (d, C-1_a), 126.1, 127.4, 127.7, 127.7, 127.9, 127.9, 128.0, 128.1, 128.2, 128.4, 128.4, 128.5, 128.9, 129.6 (14 × d, 14 × Ar-CH), 137.6, 137.8, 137.9, 138.4, 142.3 (5 × s, 5 × Ar-C); *m/z* (ES^+) 918 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{53}H_{56}O_{11}S_1Na$ (MNa^+) 923.3436. Found 923.3434).

3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-ylmethyl)-α/β-D-glucopyranosyl-(1→3)-methyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside 2.28

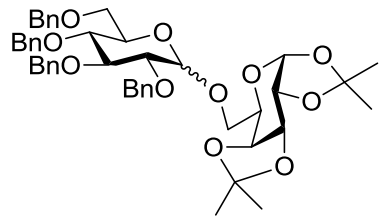


2.28

To a flame-dried round-bottom flask containing activated 3Å molecular sieves (0.100 g) was added a solution of *O*-(3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-α/β-D-glucopyranosyl) trichloroacetimidate **2.3** (125 mM) and methyl-2-*O*-benzyl-4,6-di-*O*-benzylidene-α-D-mannopyranoside **2.25** (2 eq.) in freshly distilled CH_2Cl_2. The reaction mixture was cooled to -40 °C under an argon atmosphere, then TMSOTf (0.1 eq.) was added. The reaction was monitored by t.l.c. (toluene:ethyl acetate, 9:1) until the formation of a major product (R_f 0.5) and complete consumption of starting material (R_f 0.6) was observed. The reaction was quenched with saturated sodium bicarbonate solution and filtered through Celite®. The mixture was diluted with CH_2Cl_2, washed with saturated sodium bicarbonate solution, and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 15:1) to afford 3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-ylmethyl)-α/β-D-glucopyranosyl-(1→2)-methyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **2.27** as a colourless oil; δ_H (400 MHz, $CDCl_3$) [28:1 mixture of α:β anomers observed, major α anomer quoted] 3.36 (3H, s, OCH_3), 3.47 (1H, m, H-2_b), 3.52-3.69 (4H, m, H-3_b, H-4_b, H-5_b, H-6_b), 3.79-3.99 (4H, m, H-3_a, H-5_a, H-6_a, H-$6'_b$), 4.26 (1H, m, H-$6'_a$), 4.39 (2H, m, H-2_a, H-4_a), 4.47, 4.61 (2H, ABq, J_{AB} 11.9 Hz, $PhCH_2$), 4.52, 4.59 (2H, ABq, J_{AB} 11.6 Hz, $PhCH_2$), 4.57 (1H, d, $J_{1,2}$ 1.3 Hz, H-1_b), 4.58, 4.78 (2H, ABq, J_{AB} 10.6 Hz, $PhCH_2$), 4.72, 4.95 (2H,

ABq, J_{AB} 11.1 Hz, $PhCH_2$), 4.74 (1H, br s, H-1_a), 4.75, 4.90 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 5.58 (1H, s, PhCH), 6.76 (1H, d, *J* 3.8 Hz, Ar-CH), 6.79 (1H, d, *J* 3.5 Hz, Ar-CH), 7.15-7.48 (26H, m, 26 × Ar-CH); δ_H (400 MHz, $CDCl_3$) [selected β anomer information] 3.37 (0.04H, s, OCH_3), 5.61 (0.04H, s, PhCH); δ_C (100 MHz, $CDCl_3$) 54.9 (q, O<u>C</u>H_3), 64.0 (d, C-5_a), 65.6, 68.6, 68.9, 73.5, 73.8, 75.0, 75.6 (7 × t, C-6_a, C-6_b, 5 × Ar<u>C</u>H_2), 70.9, 73.0, 75.2, 77.3, 78.8, 81.2, 84.8 (7 × d, C-2_a, C-3_a, C-4_a, C-2_b, C-3_b, C-4_b, C-5_b), 99.8 (d, C-1_b), 101.3 (d, C-1_a), 102.5 (d, Ph<u>C</u>H), 126.0, 126.3, 126.4, 126.4, 127.5, 127.6, 127.7, 127.7, 127.8, 127.9, 127.9, 128.0, 128.2, 128.2, 128.3, 128.3, 128.3, 128.4, 128.4, 128.5, 129.0, 129.2, 129.3, 129.4 (24 × d, 24 × Ar-CH), 137.4, 138.0, 138.5, 138.6, 142.7 (5 × s, 5 × Ar-C); *m/z* (ES^+) 918 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{53}H_{56}O_{11}S_1Na$ (MNa^+) 923.3436. Found 923.3431).

2,3,4,6-Tetra-*O*-benzyl-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside 2.31[13]

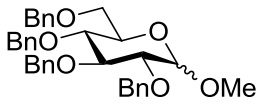


2.31

To a flame-dried round-bottom flask containing activated 3Å molecular sieves (0.100 g) was added a solution of *O*-(2,3,4,6-tetra-*O*-benzyl)-α/β-D-glucopyranosyl trichloroacetimidate **2.30** (125 mM) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside **2.11** (2 eq.) in freshly distilled CH_2Cl_2. The reaction mixture was cooled to the designated temperature under an argon atmosphere, then TMSOTf (0.1 eq.) was added. The reaction was monitored by t.l.c. (toluene:ethyl acetate, 9:1) until the formation of a major product (R_f 0.3) and complete consumption of starting

material (R_f 0.6) was observed. The reaction was quenched with saturated sodium bicarbonate solution and filtered through Celite®. The mixture was diluted with CH_2Cl_2, washed with saturated sodium bicarbonate solution, and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 15:1) to afford 2,3,4,6-Tetra-*O*-benzyl-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside **2.31** as a colourless oil. These data are in agreement with those reported in the literature; δ_H (400 MHz, $CDCl_3$) [1:4 mixture of α:β anomers observed] 1.32, 1.46, 1.51, 1.54 (15H, 4 × br s, 4 × CH_3α, 4 × CH_3β), 3.42-3.49 (2.5H, m, H-2_bα, H-5_bα, H-2_bβ, H-5_bβ), 3.57-3.85 (7.5H, m, H-2_aα, H-4_aα, H-5_aα, H-4_bα, H-6_bα, H-6'$_b$α, H-2_aβ, H-4_aβ, H-5_aβ, H-4_bβ, H-6_bβ, H-6'$_b$β), 3.99 (0.25H, at, *J* 9.2 Hz, H-3_bα), 4.02-4.11 (1.5H, m, H-3_bβ, H-6_aα, H-6'$_a$α), 4.17 (1H, dd, $J_{5,6}$ 3.5 Hz, $J_{6,6'}$ 10.8 Hz, H-6_aβ), 4.25 (1H, m, H-6'$_a$β), 4.31-4.37 (1.25H, m, H-3_aα, H-3_aβ), 4.46 (1H, d, $J_{1,2}$ 7.9 Hz, H-1_bβ), 4.49-5.07 (10H, 4 × $PhCH_2$α, 4 × $PhCH_2$β), 4.58 (0.25H, d, $J_{1,2}$ 2.4 Hz, H-1_bα), 5.53 (1H, d, $J_{1,2}$ 5.1 Hz, H-1_aα), 5.57 (1H, d, $J_{1,2}$ 5.1 Hz, H-1_aβ), 7.12-7.15 (2.5H, m, 2 × Ar-CHα, 2 × Ar-CHβ), 7.24-7.39 (20H, m, 16 × Ar-CHα, 16 × Ar-CHβ), 7.41-7.44 (2.5H, m, 2 × Ar-CHα, 2 × Ar-CHβ); *m/z* (ES^+) 800 ($M+NH_4^+$, 100%).

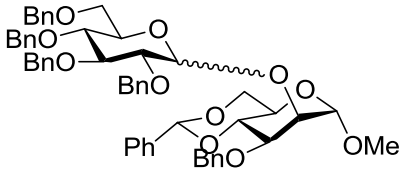
Methyl 2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranoside 2.32[14]



2.32

To a flame-dried round-bottom flask containing activated 3Å molecular sieves (0.100 g) was added a solution of *O*-(2,3,4,6-tetra-*O*-benzyl)-α/β-D-glucopyranosyl trichloroacetimidate **2.30** (125 mM) and MeOH (2 eq.) in freshly distilled CH_2Cl_2. The reaction mixture was cooled to the designated temperature under an argon atmosphere, then TMSOTf (0.1 eq.) was added. The reaction was monitored by t.l.c. (toluene:ethyl acetate, 9:1) until the formation of a major product (R_f 0.4) and complete consumption of starting material (R_f 0.6) was observed. The reaction was quenched with saturated sodium bicarbonate solution and filtered through Celite®. The mixture was diluted with CH_2Cl_2, washed with saturated sodium bicarbonate solution, and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 15:1) to afford methyl 2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranoside **2.32** as a colourless oil. These data are in agreement with those reported in the literature; δ_H (400 MHz, $CDCl_3$) [1:8 mixture of α:β anomers observed, major β anomer quoted] 3.42-3.48 (2H, m, H-2, H-5), 3.55 (3H, s, OCH_3), 3.60-3.71 (3H, m, H-3, H-4, H-6), 3.76 (1H, dd, $J_{5,6}$ 2.1 Hz, $J_{6,6'}$ 10.9 Hz, H-6'), 4.32 (1H, d, $J_{1,2}$ 7.5 Hz, H-1), 4.53, 4.80 (2H, ABq, J_{AB} 11.3 Hz, $PhCH_2$), 4.56, 4.63 (2H, ABq, J_{AB} 12.3 Hz, $PhCH_2$), 4.72, 4.82 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 4.92, 4.93 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 7.14-7.17 (2H, m, 2 × PhCH), 7.24-7.36 (18H, m, 18 × PhCH); *m/z* (ES^+) 554 ($M+NH_4^+$, 100%).

2,3,4,6-Tetra-*O*-benzyl-α/β-D-glucopyranosyl-(1→2)-methyl-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside 2.33

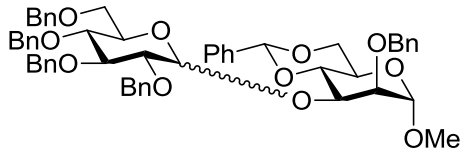


2.33

To a flame-dried round-bottom flask containing activated 3Å molecular sieves (0.100 g) was added a solution of *O*-(2,3,4,6-tetra-*O*-benzyl)-α/β-D-glucopyranosyl trichloroacetimidate **2.30** (125 mM) and methyl-3-*O*-benzyl-4,6-di-*O*-benzylidene-α-D-mannopyranoside **2.24** (2 eq.) in freshly distilled CH_2Cl_2. The reaction mixture was cooled to the designated temperature under an argon atmosphere, then TMSOTf (0.1 eq.) was added. The reaction was monitored by t.l.c. (toluene:ethyl acetate, 9:1) until the formation of a major product (R_f 0.5) and complete consumption of starting material (R_f 0.6) was observed. The reaction was quenched with saturated sodium bicarbonate solution and filtered through Celite®. The mixture was diluted with CH_2Cl_2, washed with saturated sodium bicarbonate solution, and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 15:1) to afford 2,3,4,6-Tetra-*O*-benzyl-α/β-D-glucopyranosyl-(1→2)-methyl-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **2.33** as a colourless oil; δ_H (400 MHz, $CDCl_3$) [2:1 mixture of α:β anomers observed] 3.29 (4.5H, br s, $OCH_3\alpha$, $OCH_3\beta$), 3.57 (1H, dd, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 9.6 Hz, H-$2_b\alpha$), 3.60-3.70 (2H, m, H-$5_b\alpha$, H-$2_b\beta$, H-$5_b\beta$), 3.72-3.80 (4H, m, H-$4_b\alpha$, H-$6_b\alpha$, H-$6'_b\alpha$, H-$6_b\beta$, H-$6'_b\beta$), 3.83-3.88 (3.5H, m, H-$3_a\alpha$, H-$5_a\alpha$, H-$3_b\beta$, H-$4_b\beta$, H-$5_a\beta$), 4.00-4.04 (3H, m, H-$2_a\alpha$, H-$6_a\alpha$, H-$2_a\beta$, H-$6_a\beta$), 4.20-4.23 (3H, m, H-$4_a\alpha$, H-$6'_a\alpha$, H-

$4_a\beta$, H-$6'_a\beta$), 4.27-4.31 (1.5H, m, H-$3_a\alpha$, H-$3_a\beta$), 4.37-5.04 (15.5H, H-$1_a\alpha$, 10 × $PhCH_2\alpha$, 10 × $PhCH_2\beta$), 4.52 (0.5H, s, H-$1_a\beta$), 4.72 (1H, d, $J_{1,2}$ 1.8 Hz, H-$1_a\alpha$), 5.50 (1H, s, PhCHα), 5.58 (1H, d, $J_{1,2}$ 3.8 Hz, H-$1_b\alpha$), 5.65 (0.5H, s, PhCHβ), 7.13-7.19 (6H, m, 4 × Ar-CHα, 4 × Ar-CHβ), 7.24-7.51 (39H, m, 26 × Ar-CHα, 26 × Ar-CHβ); δ_C (100 MHz, $CDCl_3$) [major α anomer quoted] 54.8 (q, O<u>C</u>H_3), 64.3 (d, C-5_a), 68.7, 68.8 (2 × t, C-6_a, C-6_b), 71.4, 73.5, 73.9, 75.2, 75.6 (5 × t, 5 × Ar<u>C</u>H_2), 70.7, 74.6, 76.7, 77.5, 79.2, 81.4 (6 × d, C-2_a, C-3_a, C-4_a, C-3_b, C-4_b, C-5_b), 79.8 (d, C-2_b), 97.4 (d, C-1_b), 101.1 (d, C-1_a), 101.3 (d, Ph<u>C</u>H), 126.0, 127.4, 127.5, 127.6, 127.7, 127.9, 127.9, 128.0, 128.0, 128.2, 128.2, 128.3, 128.3, 128.4, 128.8 (15 × d, 15 × Ar-CH), 137.8, 138.9, 138.2, 138.4, 139.0 (5 × s, 5 × Ar-C); *m/z* (ES^+) 912 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{48}H_{51}O_{11}Na$ (MNa^+) 836.3329. Found 836.3319).

2,3,4,6-Tetra-*O*-benzyl-α/β-D-glucopyranosyl-(1→3)-methyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside 2.34

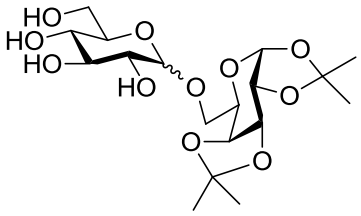


2.34

To a flame-dried round-bottom flask containing activated 3Å molecular sieves (0.100 g) was added a solution of *O*-(2,3,4,6-tetra-*O*-benzyl)-α/β-D-glucopyranosyl trichloroacetimidate **2.30** (125 mM) and methyl-2-*O*-benzyl-4,6-di-*O*-benzylidene-α-D-mannopyranoside **2.25** (2 eq.) in freshly distilled CH_2Cl_2. The reaction mixture was cooled to the designated temperature under an argon atmosphere, then TMSOTf (0.1 eq.) was added. The reaction was monitored by t.l.c. (toluene:ethyl acetate, 9:1) until the formation of a major product (R_f 0.5) and complete consumption of starting material (R_f 0.6) was observed. The reaction was quenched with saturated sodium

bicarbonate solution and filtered through Celite®. The mixture was diluted with CH_2Cl_2, washed with saturated sodium bicarbonate solution, and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 15:1) to afford 2,3,4,6-Tetra-*O*-benzyl-α/β-D-glucopyranosyl-(1→3)-methyl-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **2.34** as a colourless oil; δ_H (400 MHz, $CDCl_3$) [3:1 mixture of α:β anomers observed] 3.33 (1H, s, $OCH_3\beta$), 3.34 (3H, s, $OCH_3\alpha$), 3.52 (1.33H, m, H-$2_b\alpha$, H-$2_b\beta$), 3.56-3.71 (4.33H, m, H-$5_b\alpha$, H-$6_b\alpha$, H-$6'_b\alpha$, H-$4_b\beta$, H-$5_b\beta$, H-$6_b\beta$, H-$6'_b\beta$), 3.80-3.90 (5.33H, m, H-$4_b\alpha$, H-$2_a\alpha$, H-$5_a\alpha$, H-$6_a\alpha$, H-$3_b\beta$, H-$2_a\beta$, H-$5_a\beta$, H-$6_a\beta$), 4.00 (1H, at, *J* 9.2 Hz, H-$3_b\alpha$), 4.23-4.39 (4H, m, H-$3_a\alpha$, H-$4_a\alpha$, H-$6'_a\beta$, H-$3_a\beta$, H-$4_a\alpha$, H-$6'_a\beta$), 4.43-4.99 (13.33H, 10 × $PhCH_2\alpha$, 10 × $PhCH_2\beta$), 4.59 (0.33H, d, $J_{1,2}$ 7.8 Hz, H-$1_b\beta$), 4.70 (0.33H, d, $J_{1,2}$ 1.8 Hz, H-$1_a\beta$), 4.72 (1H, d, $J_{1,2}$ 1.8 Hz, H-$1_a\alpha$), 5.47 (1H, s, PhCHα), 5.54 (1H, d, $J_{1,2}$ 3.8 Hz, H-$1_b\alpha$), 5.56 (0.33H, s, PhCHβ), 6.98-7.01 (1.33H, m, Ar-CHα, Ar-CHβ), 7.13-7.48 (38.66H, m, 29 × Ar-CHα, 29 × Ar-CHβ); δ_C (100 MHz, $CDCl_3$) [major α anomer quoted] 54.9 (q, O<u>C</u>H_3), 63.9 (d, C-5_a), 68.7, 69.0 (2 × t, C-6_a, C-6_b), 73.4, 73.5, 73.9, 75.0, 75.5 (5 × t, 5 × Ar<u>C</u>H_2), 70.9, 72.8, 77.3, 77.4, 78.9 (5 × d, C-2_a, C-3_a, C-4_a, C-4_b, C-5_b), 79.7 (d, C-2_b), 81.4 (d, C-3_b), 96.9 (d, C-1_b), 100.0 (d, C-1_a), 102.4 (d, Ph<u>C</u>H), 126.3, 126.4, 127.2, 127.5, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.3, 128.3, 128.5, 129.3 (17 × d, 17 × Ar-CH), 137.4, 138.0, 138.3, 138.5, 138.7 (5 × s, 5 × Ar-C); *m/z* (ES^+) 912 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{48}H_{51}O_{11}Na$ (MNa^+) 836.3329. Found 836.3336).

α/β-D-glucopyranosyl--(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose 2.35[15,16]



2.35

Method 1

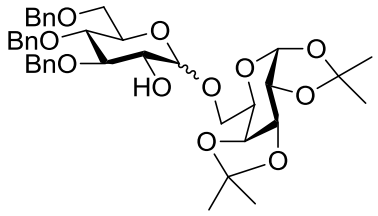
NH_3(l) was condensed into a round bottom flask containing a stirrer bar at - 100 °C. A sample of 3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside **2.18** (α:β ratio 9:1) (0.200 g, 0.254 mmol) was added to the reaction as a solution in THF (10 ml). Small pieces of sodium were then added over the period of 1 h until the blue colour of the solution persisted. The reaction was quenched by addition of ammonium chloride and then allowed to warm to temperature. The reaction was then diluted with EtOAc (20 ml) washed with water (20 ml) and the aqueous layer extracted with EtOAc (2 x 20 ml). The combined organic layers were washed with brine (20 ml), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 1:2) to afford α/β-D-glucopyranosyl--(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose 2.35 (0.070 g, 62%) as a colourless oil. These data are in agreement with those reported in the literature; δ_H (400 MHz, $CDCl_3$) [9:1 mixture of α:β anomers observed, major α-anomer quoted] 1.30, 1.32, 1.41, 1.52 (12H, 4 x s, 4 x CH_3), 3.53-3.76 (5H, m, H-2_b, H-3_b, H-4_b, H-5_a, H-6_a), 3.69 (1H, dd, $J_{6,6'}$ 10.8 Hz, $J_{5,6}$ 5.2 Hz, H-6_b), 3.80 (1H, m, H-$6'_b$), 3.84–3.86 (1H, m, H-6_a'), 3.96 (1H, m, H-5_b), 4.25 (1H, dd, $J_{4,5}$ 1.5 Hz, $J_{3,4}$ 8.0 Hz, H-4_a), 4.29 (1H, dd, $J_{2,3}$

2.4 Hz, $J_{1,2}$ 4.9 Hz, H-2_a), 4.59 (1H, m, H-3_a), 4.86 (1H, d, $J_{1,2}$ 3.5 Hz, H-1_b), 5.51 (1H, d, $J_{1,2}$ 4.9 Hz, H-1_a); *m/z* (ES^+) 445 ($M+Na^+$, 100%).

Method 2

A sample of 3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside **2.18** (α:β ratio 9:1) (0.200 g, 0.254 mmol) was dissolved in freshly distilled CH_2Cl_2 (10 ml) under an atmosphere of argon. The reaction was cooled to 0 °C and TMSI (0.163 ml, 1.14 mmol) was added. The reaction was allowed to warm to room temperature. After 16 h t.l.c. (petrol:ethyl acetate, 1:2) indicated the formation of a major product (R_f 0.3) and complete consumption of starting material (R_f 0.9). The reaction was diluted with CH_2Cl_2 (20 ml) and washed with water (20 ml). The aqueous layer was then extracted with CH_2Cl_2 (2 x 20 ml) and the combined organic extracts were washed with saturated sodium bicarbonate (20 ml) then brine (20 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 1:2) to afford α/β-D-glucopyranosyl--(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **2.35** (0.096 g, 85%) as a colourless oil. These data are in agreement with those reported in the literature.

3,4,6-Tri-*O*-benzyl-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside 2.36[17,18]



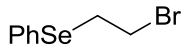
2.36

A sample of 3,4,6-Tri-*O*-benzyl-2-*O*-(thiophen-2-yl)-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside **2.18** (α:β ratio 9:1) (0.200 g, 0.254 mmol) was dissolved in freshly distilled CH_2Cl_2 (10 ml) under an atmosphere of argon. The reaction was cooled to 0 °C and TMSI (0.036 ml, 0.254 mmol) was added. The reaction was stirred at 0 °C for 30 min, after which time t.l.c. (toluene:ethyl acetate, 9:1) indicated the formation of a major product (R_f 0.2) and complete consumption of starting material (R_f 0.4). The reaction was diluted with CH_2Cl_2 (20 ml) and washed with water (20 ml). The aqueous layer was then extracted with CH_2Cl_2 (2 x 20 ml) and the combined organic extracts were washed with saturated sodium bicarbonate (20 ml) then brine (20 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 6:1) to afford α/β-D-glucopyranosyl--(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **2.36** (0.137 g, 78%) as a colourless oil. These data are in agreement with those reported in the literature; δ_H (400 MHz, $CDCl_3$) [9:1 mixture of α:β anomers observed, major α-anomer quoted] 1.34, 1.35, 1.45, 1.54 (12H, 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* 9.9 Hz, *J* 3.0 Hz, *J* 2.2 Hz, H-5_b), 3.91 (1H, m, H-$6'_a$), 3.99-4.01 (1H, m, H-5_a), 4.25 (1H, dd, *J* 7.9 Hz, *J* 1.9 Hz H-4_a), 4.34

(1H, dd, $J_{1,2}$ 4.9 Hz, $J_{2,3}$ 2.2 Hz, H-2_a), 4.63 (1H, dd, $J_{2,3}$ 2.2 Hz, $J_{3,4}$ 7.8 Hz, H-3_a), 4.49, 4.83 (2H, ABq, *J* 10.3 Hz, $PhCH_2$), 4.50, 4.64 (2H, ABq, *J* 11.7 Hz, $PhCH_2$), 4.93 (1H, d, $J_{1,2}$ 3.2 Hz, H-1_b), 4.82, 4.98 (2H, ABq, *J* 10.7 Hz, $PhCH_2$), 5.53 (1H, d, $J_{1,2}$ 4.9 Hz, H-1_a), 7.12-7.41 (15H, m 15 x Ar-H); *m/z* (ES^+) 715 ($M+Na^+$, 100%).

5.3 Chapter 3

2-Bromoethyl phenyl selenide 3.5[19]



3.5

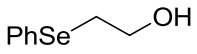
Method 1

Phenyl selenyl bromide **3.11** (2.18 g, 9.2 mmol) was dissolved in glacial acetic acid (65 ml). Ethene gas was bubbled through the reaction mixture until a colour change from dark brown to pale orange was observed. The reaction was concentrated *in vacuo* (co-evaporating with water, then toluene). The residue was dissolved in ether (50 ml) and washed with cold saturated sodium bicarbonate until pH neutral. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*, to afford 2-bromoethyl phenyl selenide **3.5** (1.974 g, 81%) as an orange liquid. These data are in agreement with those reported in the literature; δ_H (400 MHz, $CDCl_3$) 3.25-3.30 (2H, m, PhSeC$\underline{H}_2$CH_2Br), 3.55-3.60 (2H, m, PhSeCH_2C$\underline{H}_2$Br), 7.30-7.33 (3H, m, Ar-H), 7.54-7.56 (2H, m, Ar-H).

Method 2

Phenyl selenyl bromide **3.11** (2.18 g, 9.2 mmol) was dissolved in dichloromethane (50 ml). Ethene gas was bubbled through the reaction mixture until a colour change from dark brown to pale orange was observed. The reaction was concentrated *in vacuo* to afford 2-bromoethyl phenyl selenide **3.5** (2.404 g, 99%) as an orange liquid. These data are in agreement with those reported in the literature.

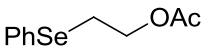
2-Phenylselenoethanol 3.7[20]



3.7

Sodium borohydride (1.88 g, 49.8 mmol) was added in portions to a stirred solution of diphenyl diselenide **3.13** (5.20 g, 16.6 mmol) in ethanol at 0 °C. Once addition of the sodium borohydride was complete, 2-chloroethanol (2.23 ml, 33.2 mmol) was added and the reaction stirred at reflux. After 3 h, t.l.c (petrol:ethyl acetate, 2:1) indicated the formation of a single product (R_f 0.4) and complete consumption of 2-chloroethanol (R_f 0.5). The reaction was filtered through Celite® and the solvent removed *in vacuo*. The resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1) to afford 2-phenylselenoethanol **21** (6.39 g, 96%) as a pale yellow oil. These data are in agreement with those reported in the literature; δ_H (400 MHz, DMSO-d_6) 3.02 (2H, at, *J* 7.1 Hz, PhSeC$\underline{H}_2$CH$_2$OH), 3.63 (2H, m, PhSeCH$_2$C$\underline{H}_2$OH), 4.99 (1H, t, *J* 5.6 Hz, PhSeCH$_2$CH$_2$O$\underline{H}$), 7.20-7.29 (3H, m, Ar-H), 7.46-7.48 (2H, m, Ar-H).

2-(Phenylselenyl)ethyl acetate 3.14

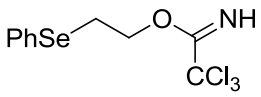


3.14

2-Phenylselenoethanol **3.7** (0.173 g 0.86 mmol) was dissolved in anhydrous pyridine (2 ml) and the mixture cooled to 0°C under a nitrogen atmosphere. Acetic anhydride (0.16 ml, 1.72 mmol) was then slowly added. Once addition of acetic anhydride was complete, the reaction was allowed to warm to room temperature. After 16 h, t.l.c (petrol:ethyl acetate, 2:1) indicated the formation of a single product (R_f 0.9) and complete consumption of starting material (R_f 0.6). The reaction was cooled to 0°C

and quenched with ethanol (0.5 ml) and then concentrated *in vacuo*. The resulting residue was passed through a silica plug (petrol:ethyl acetate, 4:1) to afford 2-(phenylselenyl)ethyl acetate **2.14** (0.209 mg, 100%) as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) 2.01 (3H, s, CH_3), 3.08 (2H, at, *J* 7.2 Hz, PhSeC$\underline{H}_2$CH$_2$OAc), 4.29 (2H, at, *J* 7.3 Hz, PhSeCH$_2$C$\underline{H}_2$OAc), 7.26-7.31 (3H, m, Ar-H), 7.53-7.56 (2H, m, Ar-H); δ_C (100 MHz, $CDCl_3$) 20.9 (q, CH_3), 25.4 (t, PhSe$\underline{C}$H$_2$CH$_2$OAc), 63.8 (t, PhSeCH$_2\underline{C}$H$_2$OAc), 127.3, 129.2, 133.0 (3 x d, 3 x Ar-CH), 170.8 (s, C=O).

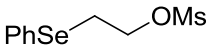
2-(Phenylselenyl)ethyl trichloroacetimidate 3.15



3.15

2-Phenylselenoethanol **3.7** (0.200 g, 0.99 mmol) was dissolved in freshly distilled CH_2Cl_2 (5 ml) at 0 °C under an argon atmosphere. DBU (0.059 ml, 0.40 mmol) was added followed by trichloroacetonitrile (1.00 ml, 9.94 mmol). After 1.5 h, t.l.c (petrol:ethyl acetate, 4:1, with 1% added triethylamine) indicated the formation of a single product (R_f 0.7) and complete consumption of starting material (R_f 0.2). The reaction was concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 7:1, with 1% added triethylamine) to afford 2-(phenylselenyl)ethyl-*O*-trichloroacetimidate **3.15** (0.336 g, 98%) as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) 3.24 (2H, at, *J* 7.5 Hz, PhSeC$\underline{H}_2$CH$_2$OC(NH)CCl$_3$), 4.52 (2H, at, *J* 7.5 Hz, PhSeCH$_2$C$\underline{H}_2$OC(NH)CCl$_3$), 7.27-7.32 (3H, m, Ar-H), 7.57-7.60 (2H, m, Ar-H) 8.34 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 24.6 (t, PhSe$\underline{C}$H$_2$CH$_2$OC(NH)CCl$_3$), 68.4 (t, PhSeCH$_2\underline{C}$H$_2$OC(NH)CCl$_3$), 91.3 (s, CCl_3), 127.4, 129.2, 133.0 (3 x d, 3 x Ar-CH), 129.0 (s, Ar-C), 162.4 (s, C=NH).

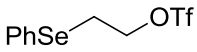
2-(Phenylselenyl)ethyl methanesulfonate 3.16



3.16

2-Phenylselenoethanol **3.7** (0.185 g 0.92 mmol) was dissolved in anhydrous pyridine (4 ml) and the mixture cooled to 0°C under a nitrogen atmosphere. Methane sulfonyl chloride (0.08 ml, 1.01 mmol) was then slowly added. After 2 h, t.l.c (petrol:ethyl acetate, 4:1) indicated the formation of a single product (R_f 0.8) and complete consumption of starting material (R_f 0.2). The reaction was diluted with CH_2Cl_2 (10 ml), washed with saturated ammonium chlrodie solution (10ml), and the aqueous layer extracted with CH_2Cl_2 (2 x 5 ml). The combined organic extracts were washed with brine (10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 2-(Phenylselenyl)ethyl-*O*-methanesulfonate **3.16** (0.257 g, 100%) as a pale yellow oil. 2-(Phenylselenyl)ethyl-*O*-methanesulfonate **3.16** was used immediately without characterisation.

2-(Phenylselenyl)ethyl trifluoromethanesulfonate 3.17

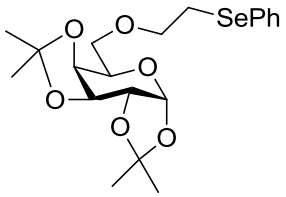


3.17

2-Phenylselenoethanol **3.7** (0.186 g 0.92 mmol) and anhydrous pyridine (0.25 ml) were dissolved in freshly distilled CH_2Cl_2 (4 ml) and the mixture cooled to 0°C under a nitrogen atmosphere. Trifluoromethane sulfonic anhydride (0.18 ml, 1.01 mmol) was then slowly added. After 0.5 h, t.l.c (petrol:ethyl acetate, 4:1) indicated the formation of a single product (R_f 0.8) and complete consumption of starting material (R_f 0.2). The reaction was diluted with CH_2Cl_2 (10 ml), washed with saturated ammonium chlrodie solution (10ml), and the aqueous layer extracted with CH_2Cl_2 (2

x 5 ml). The combined organic extracts were washed with brine (10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford 2-(Phenylselenyl)ethyl-*O*-trifluoromethanesulfonate **3.17** (0.290 g, 95%) as a pale yellow oil. 2-(Phenylselenyl)ethyl-*O*-trifluoromethanesulfonate **3.17** was used immediately without characterisation.

1,2:3,4-di-*O*-isopropylidene-6-*O*-(2-(phenylselenyl)ethyl)-α-D-galactopyranoside 3.12

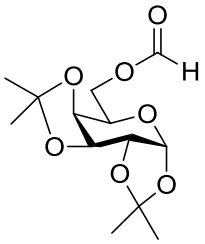


3.12

1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside **2.11** (0.100 g, 0.385 mmol) was dissolved in anhydrous CH_2Cl_2 (2 ml). 2-(phenylselenyl)ethyl-*O*-trichloroacetimidate **3.15** (0.156 g 0.462 mmol) was and then slowly added as a solution in CH_2Cl_2 (2 ml) at 0 °C under an argon atmosphere. TMSOTf (7 µl, 0.038 mmol) was then added and the reaction allowed to warm to room temperature. After 3 h, t.l.c (petrol:ethyl acetate, 4:1) indicated the formation of a major product (R_f 0.7) and complete consumption of starting material (R_f 0.4). The reaction was quenched with methanol (4 ml) and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 15:1) to afford 1,2:3,4-di-*O*-isopropylidene-6-*O*-(2-(phenylselenyl)ethyl)-α-D-galactopyranoside **3.12** (0.094 g, 55%) as a pale yellow oil; $[\alpha]_D^{25}$ + 3.2 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.31, 1.31, 1.41, 1.49 (12H, 4 x s, 4 x CH_3), 3.04-3.07 (2H, m, $OCH_2C\underline{H}_2SePh$), 3.60-3.68 (3H, m, H-6, $OC\underline{H}_2CH_2SePh$), 3.73-3.77 (1H, m, H-5), 3.96 (1H, dd, $J_{6,6'}$ 10.1 Hz, $J_{5,6}$ 2.2 Hz, H-

6'), 4.22 (1H, dd, $J_{3,4}$ 3.7 Hz, $J_{4,5}$ 2.4 Hz, H-4), 4.30(1H, dd, $J_{1,2}$ 5.1 Hz, $J_{2,3}$ 7.9 Hz, H-2), (1H, dd, $J_{3,4}$ 3.7 Hz, $J_{2,3}$ 7.9 Hz, H-3), 5.53 (1H, d, $J_{1,2}$ 4.9 Hz, H-1), 7.20-7.28 (2H, m, 2 x ArH), 7.51-7.56 (2H, m, 2 x ArH); δ_C (100 MHz, $CDCl_3$) 24.4, 24.9, 26.0, 26.1 (q, 4 x CH_3), 26.7 (t, $OCH_2\underline{C}H_2SePh$), 66.8 (d, C-5), 69.5 (t, C-6), 70.5, 70.6, 71.1 (3 x d, C-2, C-3, C-4), 70.9 (t, $O\underline{C}H_2CH_2SePh$), 96.3 (d, C-1), 108.6, 109.2 (2 x s, $\underline{C}(CH_3)_2$), 126.9, 129.0, 132.7, 133.3 (4 x ArC); *m/z* 462 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{20}H_{28}O_6SeNa$ (MNa^+) 467.0949. Found 467.0955). (Found: C, 54.14; H, 6.38. $C_{17}H_{24}O_6S$ requires C, 54.18; H, 6.37%).

6-*O*-Formyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside 3.18[21]

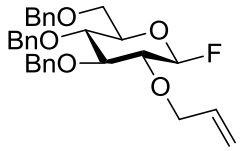


3.18

1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside **2.11** (0.199 g, 0.765 mmol) was dissolved in anhydrous DMF (5 ml) and cooled to 0 °C under an atmosphere of argon. 2-(Phenylselenyl)ethyl trifluoromethanesulfonate **3.17** (0.383 g, 1.15 mmol) was added as a solution in anhydrous DMF (2 ml) and the reaction mixture was allowed to warm to room temperature. After 16 h, t.l.c (petrol:ethyl acetate, 4:1) indicated the formation of a single product (R_f 0.4) and complete consumption of starting material (R_f 0.1). The reaction was concentrated *in vacuo*, and the resulting residue was dissolved in ether (20 ml), washed with water (20 ml), and the aqueous layer extracted with ether (2 x 10 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 (toluene:ethyl acetate, 4:1) to afford 6-*O*-Formyl-

1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside **28** (0.179 g, 81%) as a clear oil. These data are in agreement with those reported in the literature; δ_H (400 MHz, $CDCl_3$) 1.34, 1.35, 1.46, 1.53 (12H, 4 x s, 4 x CH_3), 4.02-4.09 (1H, m, H-5), 4.23-4.37 (4H, m, H-2, H-4, H-6, H-6'), 4.64 (1H, dd, $J_{2,3}$ 7.9 Hz, $J_{3,4}$ 2.4 Hz, H-3), 5.56 (1H, d, $J_{1,2}$ 5.1 Hz, H-1), 8.10 (1H, s, CHO); *m/z* (ES^+) 306 ($M+NH_4^+$, 100%).

2-*O*-Allyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl fluoride 3.22[22]

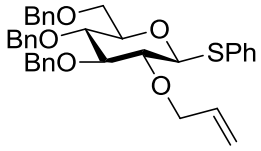


3.22

3,4,6-Tri-*O*-benzyl-β-D-glucopyranosyl fluoride **2.4** (1.35 g, 2.98 mmol) was dissolved in anhydrous DMF (5 ml) and then slowly added to a suspension of sodium hydride (0.239 g, 5.97 mmol) in anhydrous DMF (5 mL) at 0 °C under an argon atmosphere. Allyl bromide (0.52 mL, 5.97 mmol) was then added slowly to the reaction mixture. Once the addition of allyl bromide was complete, the reaction was allowed to warm to room temperature. After 1 h, t.l.c (petrol:ethyl acetate, 4:1) indicated the formation of a single product (R_f 0.6) and complete consumption of starting material (R_f 0.25). The reaction was quenched with methanol (5 ml) and concentrated *in vacuo*. The resulting residue was dissolved in ether (50 ml), washed with water (100 ml), and the aqueous layer extracted with ether (2 x 50 ml). The combined organic extracts were washed with brine (100 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 **3.22** (1.24 g, 84%) as a colourless oil. These data are in agreement with those reported in the literature; $[\alpha]_D^{25}$ +11.3 (*c*, 1.05 in $CHCl_3$) [Lit. $[\alpha]_D^{22}$ + 9.2 (*c*, 0.5 in

$CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 3.47 (1H, ddd, $J_{1,2}$ 6.8 Hz, $J_{2,3}$ 8.6 Hz, $J_{2,F}$ 15.4 Hz, H-2), 3.56 (1H, ddd, $J_{4,5}$ 9.5 Hz, $J_{5,6}$ 3.8 Hz, $J_{5,6'}$ 2.7 Hz, H-5), 3.66 (1H, at, *J* 8.7 Hz, H-3), 3.67-3.75 (3H, m, H-4, H-6, H-6'), 4.18 (1H, ddat, J_{gem} 12.4 Hz, J_{vic} 5.8 Hz, *J* 1.3 Hz, OC<u>H</u>H'CH=CH_2), 4.33 (1H, ddad, J_{gem} 12.4 Hz, J_{vic} 5.8 Hz, *J* 1.3 Hz, OCH<u>H</u>'CH=CH_2), 4.52, 4.81 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 4.53, 4.62 (2H, ABq, J_{AB} 12.3 Hz, $PhCH_2$), 4.78, 4.91 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 5.18 (1H, dd, $J_{1,2}$ 6.8 Hz, $J_{1,F}$ 52.8 Hz, H-1), 5.20 (1H, daq, J_Z 10.4 Hz, *J* 1.3 Hz, CH=CH_E<u>H</u>$_Z$), 5.31 (1H, daq, J_E 17.2 Hz, *J* 1.5 Hz, CH=C<u>H</u>$_E$H$_Z$), 5.93 (1H, ddat, J_E 17.2 Hz, J_Z 10.4 Hz, *J* 5.8 Hz, C<u>H</u>=CH_2), 7.12-7.17 (2H, m, 2 x Ar-H), 7.25-7.36 (13H, m, 13 x Ar-H); *m/z* (ES^+) 510 ($M+NH_4+$, 100%).

Phenyl 2-*O*-allyl-3-4-6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside 3.23[12]

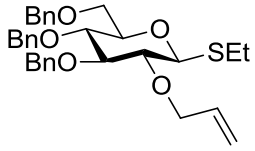


3.23

Phenyl 3-4-6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **2.6** (1.20 g, 2.21 mmol) was dissolved in anhydrous DMF (4 ml) and then slowly added to a suspension of sodium hydride (0.177 g, 4.42 mmol) in anhydrous DMF (4 mL) at 0 °C under an argon atmosphere. Allyl bromide (0.38 mL, 4.42 mmol) was then added slowly to the reaction mixture. Once the addition of allyl bromide was complete, the reaction was allowed to warm to room temperature. After 1 h, t.l.c (petrol:ethyl acetate, 4:1) indicated the 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 (5 ml) and concentrated *in vacuo*. The resulting residue was dissolved in ether (50 ml), washed with water (100 ml), and the aqueous layer extracted with ether (2 x 50 ml). The

combined organic extracts were washed with brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) to afford Phenyl 2-*O*-allyl-3-4-6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **3.23** (1.21 g, 94%) as a white crystalline solid. These data are in agreement with those reported in the literature; m.p 51-52 °C; $[\alpha]_D^{25}$ – 14.4 (*c*, 1.05 in $CHCl_3$) [Lit. m.p 51-52 °C; $[\alpha]_D^{25}$ – 17.3 (*c*, 1.0 in $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 3.39 (1H, dd, $J_{1,2}$ 9.9 Hz, $J_{2,3}$ 8.6 Hz, H-2), 3.51 (1H, m, H-5), 3.62 (1H, at, *J* 9.2 Hz, H-4), 3.67 (1H, at, *J* 9.2 Hz, H-3), 3.72 (1H, dd, $J_{6,6'}$ 10.9 Hz, $J_{5,6}$ 4.8 Hz, H-6), 3.79 (1H, dd, $J_{6,6'}$ 10.9 Hz, $J_{5,6'}$ 2.0 Hz, H-6'), 4.26 (1H, ddat, J_{gem} 11.9 Hz, J_{vic} 6.1 Hz, *J* 1.3 Hz, OC<u>H</u>H'CH=CH_2), 4.39 (1H, ddat, J_{gem} 11.9 Hz, J_{vic} 5.6 Hz, *J* 1.5 Hz, OCH<u>H</u>'CH=CH_2), 4.55, 4.61 (2H, ABq, J_{AB} 12.0 Hz, $PhCH_2$), 4.59, 4.84 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 4.62 (1H, d, $J_{1,2}$ 9.9 Hz, H-1), 4.85, 4.92 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 5.20 (1H, daq, J_Z 10.4 Hz, *J* 1.5 Hz, CH=CH_E<u>H</u>$_Z$), 5.30 (1H, daq, J_E 17.2 Hz, *J* 1.6 Hz, CH=C<u>H</u>$_E$H$_Z$), 5.99 (1H, ddat, J_E 17.2 Hz, J_Z 10.4 Hz, *J* 5.9 Hz, C<u>H</u>=CH_2), 7.20-7.36 (18H, m, 18 x Ar-H), 7.57-7.60 (2H, m, 2 x Ar-H); *m/z* (ES^+) 601 ($M+NH_4^+$, 100%).

Ethyl 2-*O*-allyl-3-4-6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside 3.24[12]

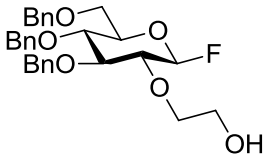


3.24

Ethyl 3-4-6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **2.20** (1.09 g, 2.21 mmol) was dissolved in anhydrous DMF (4 ml) and then slowly added to a suspension of sodium hydride (0.177 g, 4.42 mmol) in anhydrous DMF (4 mL) at 0 °C under an argon atmosphere. Allyl bromide (0.38 mL, 4.42 mmol) was then added slowly to the

reaction mixture. Once the addition of allyl bromide was complete, the reaction was allowed to warm to room temperature. After 1 h, t.l.c (petrol:ethyl acetate, 4:1) indicated the 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 (5 ml) and concentrated *in vacuo*. The resulting residue was dissolved in ether (50 ml), washed with water (100 ml), and the aqueous layer extracted with ether (2 x 50 ml). The combined organic extracts were washed with brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) to afford Ethyl 2-*O*-allyl-3-4-6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **3.24** (1.11 g, 94%) as pale yellow oil. These data are in agreement with those reported in the literature; $[\alpha]_D^{25}$ – 10.2 (*c*, 1.00 in $CHCl_3$) [Lit. $[\alpha]_D^{25}$ – 14.3 (*c*, 1.0 in $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.2 Hz, $SCH_2C\underline{H}_3$), 2.75 (2H, m, $SC\underline{H}_2CH_3$), 3.13 (1H, dd, $J_{1,2}$ 9.8 Hz, $J_{2,3}$ 8.5 Hz, H-2), 3.41 (1H, at, *J* 9.0 Hz, H-4), 3.48-3.51 (1H, m, H-5), 3.64 (1H, at, *J* 9.0 Hz, H-3), 3.72 (1H, dd, $J_{6,6'}$ 10.3 Hz, $J_{5,6}$ 3.9 Hz, H-6), 3.73 (1H, dd, $J_{6,6'}$ 10.3 Hz, $J_{5,6'}$ 2.0 Hz, H-6'), 4.22 (1H, ddat, J_{gem} 11.3 Hz, J_{vic} 6.0 Hz, *J* 1.4 Hz, $OC\underline{H}H'CH=CH_2$), 4.39 (1H, ddat, J_{gem} 11.2 Hz, J_{vic} 5.5 Hz, *J* 1.8 Hz, $OCH\underline{H}'CH=CH_2$), 4.54, 4.63 (2H, ABq, J_{AB} 12.0 Hz, $PhCH_2$), 4.59, 4.84 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 4.61 (1H, d, $J_{1,2}$ 9.8 Hz, H-1), 4.85, 4.92 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 5.20 (1H, daq, J_Z 10.4 Hz, *J* 1.8 Hz, $CH=CH_E\underline{H}_Z$), 5.30 (1H, daq, J_E 17.0 Hz, *J* 1.8 Hz, $CH=C\underline{H}_EH_Z$), 5.99 (1H, ddat, J_E 17.0 Hz, J_Z 10.4 Hz, *J* 5.9 Hz, $C\underline{H}=CH_2$), 7.19-7.33 (15H, m, 15 x Ar-H), *m/z* (ES^+) 552 ($M+NH_4^+$, 100%).

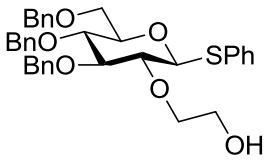
3,4,6-Tri-*O*-benzyl-2-O-(2-hydroxyethyl)ether-β-D-glucopyranosyl fluoride 3.19



3.19

A solution of 2-*O*-Allyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl fluoride **3.22** (121 mg, 0.246 mmol) in CH_2Cl_2-methanol (3 mL, 1:1) was treated with ozone at -78 °C until the solution turned blue. The reaction was quenched by the addition of $NaBH_4$ (42 mg, 1.105 mmol) in small portions over 10 min. The reaction mixture was allowed to warm to room temperature and then 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-(2-hydroxyethyl)ether-β-D-glucopyranosyl fluoride **3.19** (101 mg, 81%) as a colourless oil; $[\alpha]_D^{25}$ + 30.0 (*c*, 1.0 in $CHCl_3$); υ_{max} (KBr) 3480 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.40 (1H, br s, -$CH_2CH_2O\underline{H}$), 3.51 (1H, m, H-2), 3.60 (1H, a dt, *J* 9.6 Hz, *J* 3.0 Hz, C$\underline{H}$H'CH_2OH), 3.63-3.84 (7H, m, H-3, H-4, H-6, H-6', CH$\underline{H}$'$_2CH_2OH$, $CH_2C\underline{H}_2OH$), 3.91 (1H, ddd, $J_{4,5}$ 10.9, $J_{5,6}$ 5.1, $J_{5,6'}$ 3.0, H-5) 4.57, 4.66 (2H, ABq, J_{AB} 12.1 Hz, $PhCH_2$), 4.59, 4.84 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 4.91 (2H, br s, $PhCH_2$), 5.19 (1H, dd, $J_{1,2}$ 7.1 Hz, $J_{1,F}$ 52.8 Hz, H-1), 7.17-7.42 (15H, m, 15 x Ar-H), δ_C (100 MHz, $CDCl_3$) 62.3 ($CH_2\underline{C}H_2OH$), 68.2 (t, C-6), 73.7, 73.9, 75.0 (3 x t, 3 x $PhCH_2$), 74.8 (d, C-5), 75.8 (t, $\underline{C}H_2CH_2OH$), 77.2 (d, C-4), 81.9 (dd, $J_{2,F}$ 22.4 Hz, C-2), 83.2 (d, C-3), 109.7 (dd, $J_{1,F}$ 215.7 Hz, C-1), 127.8, 128.0, 128.0, 128.0, 128.5, 128.5, 128.6, 128.6 (8 x d, 8 x Ar-CH), 137.7, 137.8, 137.8 (3 x s, 3 x Ar-C); *m/z* (ES^+) 519 ($M+Na^+$, 90) 514 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{29}H_{33}FO_6Na$ (MNa^+) 519.2153. Found 519.2148). (Found: C, 70.38; H, 6.87. $C_{29}H_{33}FO_6$ requires C, 70.14; H, 6.70%).

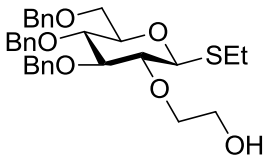
Phenyl 3-4-6-tri-O-benzyl-2-O-(2-hydroxyethyl)ether-1-thio-β-D-glucopyranoside 3.20



3.20

A solution of phenyl 2-*O*-allyl-3-4-6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **3.23** (141 mg, 0.242 mmol) in CH_2Cl_2-methanol (3 mL, 1:1) was treated with ozone at -78 °C until the solution turned blue. The reaction was quenched by the addition of $NaBH_4$ (42 mg, 1.089 mmol) in small portions over 10 min. The reaction mixture was allowed to warm to room temperature and then concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford Phenyl 3-4-6-tri-O-benzyl-2-O-(2-hydroxyethyl)ether-1-thio-β-D-glucopyranoside **3.20** (104 mg, 76%) as a white crystalline solid; m.p 57-59 °C (petrol/ethyl acetate); $[\alpha]_D^{25}$ - 2.6 (*c*, 0.5 in $CHCl_3$); υ_{max} (KBr) 3495 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.80 (1H, br s, -$CH_2CH_2O\underline{H}$), 3.41 (1H, m, H-2), 3.53 (1H, ddd, $J_{4,5}$ 9.6 Hz, $J_{5,6}$ 4.3 Hz, $J_{5,6'}$ 2.0 Hz, H-5), 3.64-3.96 (8H, m, H-3, H-4, H-6, H-6', $C\underline{H}_2CH_2OH$, $CH_2C\underline{H}_2OH$), 4.57, 4.63 (2H, ABq, J_{AB} 11.9 Hz, $PhCH_2$), 4.61 (1H, d, $J_{1,2}$ 9.9 Hz, H-1), 4.62, 4.84 (2H, ABq, J_{AB} 10.8 Hz, $PhCH_2$), 4.88, 4.94 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 7.21-7.37 (18H, m, 18 x Ar-H), 7.59-7.63 (2H, m, 2 x Ar-H); δ_C (100 MHz, $CDCl_3$) 62.4 ($CH_2\underline{C}H_2OH$), 68.9 (t, C-6), 73.5, 74.8, 75.1, 75.9 (4 x t, 3 x $PhCH_2$, $\underline{C}H_2CH_2OH$), 78.0 (d, C-4), 79.2 (d, C-5), 80.7 (d, C-2), 86.7 (d, C-3), 87.6 (d, C-1), 127.6, 127.7, 127.8, 127.9, 128.4, 128.5, 128.5, 128.6, 129.0, 132.0 (10 x d, 10 x Ar-CH), 133.3, 137.9, 137.9, 138.2 (4 x s, 4 x Ar-C); *m/z* (ES^+) 609 ($M+Na^+$, 95) 604 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{35}H_{38}O_6SNa$ (MNa^+) 609.2281. Found 609.2280). (Found: C, 71.46; H, 6.51. $C_{35}H_{38}O_6S$ requires C, 71.65; H, 6.53%).

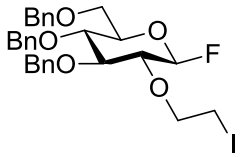
Ethyl 3-4-6-tri-O-benzyl-2-O-(2-hydroxyethyl)ether-1-thio-β-D-glucopyranoside 3.21



3.21

A solution of ethyl 2-*O*-allyl-3-4-6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **3.24** (129 mg, 0.242 mmol) in CH_2Cl_2-Methanol (3 mL, 1:1) was treated with ozone at -78 °C until the solution turned blue. The reaction was quenched by the addition of $NaBH_4$ (42 mg, 1.089 mmol) in small portions over 10 min. The reaction mixture was allowed to warm to room temperature and then concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford Ethyl 3-4-6-tri-O-benzyl-2-O-(2-hydroxyethyl)ether-1-thio-β-D-glucopyranoside **3.21** (77 mg, 59%) as a pale yellow oil; $[\alpha]_D^{25}$ - 4.6 (*c*, 1.00 in $CHCl_3$); υ_{max} (KBr) 3477 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.24 (3H, t, *J* 7.4 Hz, $SCH_2C\underline{H}_3$), 2.63-2.76 (3H, m, $-CH_2CH_2O\underline{H}$, $SC\underline{H}_2CH_3$), 3.24 (1H, m, H-2), 3.39 (1H, m, H-5), 3.52-3.85 (8H, m, H-3, H-4, H-6, H-6', $C\underline{H}_2CH_2OH$, $CH_2C\underline{H}_2OH$), 4.30 (1H, d, $J_{1,2}$ 9.9 Hz, H-1), 4.47, 4.53 (2H, ABq, J_{AB} 12.1 Hz, $PhCH_2$), 4.50, 4.72 (2H, ABq, J_{AB} 10.7 Hz, $PhCH_2$), 4.79, 4.84 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 7.08-7.11 (2H, m 2 x Ar-H), 7.17-7.27 (13H, m, 13 x Ar-H), δ_C (100 MHz, $CDCl_3$) 15.1 ($SCH_2\underline{C}H_3$), 24.9 ($S\underline{C}H_2CH_3$), 62.1 ($CH_2\underline{C}H_2OH$), 68.9 (t, C-6), 73.5, 74.8, 75.0, 75.8 (4 x t, 3 x $PhCH_2$, $\underline{C}H_2CH_2OH$), 78.1 (d, C-4), 79.2 (d, C-5), 81.4 (d, C-2), 85.1 (d, C-3), 86.7 (d, C-1), 127.6, 127.8, 127.9, 127.9, 128.4, 128.5, 128.5, (7 x d, 7 x Ar-CH), 137.9, 138.0, 138.1 (3 x s, 3 x Ar-C); *m/z* (ES^+) 561 ($M+Na^+$, 95) 556 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{31}H_{38}O_6SNa$ (MNa^+) 561.2287. Found 561.2281). (Found: C, 69.14; H, 7.11. $C_{31}H_{38}O_6S$ requires C, 69.12; H, 7.11%).

3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodoethyl)-β-D-glucopyranosyl fluoride 3.25

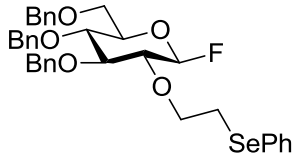


3.25

3,4,6-Tri-*O*-benzyl-2-O-(2-hydroxyethyl)ether-β-D-glucopyranosyl fluoride **3.19** (0.250 g, 0.504 mmol) was dissolved in freshly distilled THF (5 ml) under an atmosphere of argon. A mixture iodine (0.191 g, 0.756 mmol), imidazole (0.051 g, 0.756 mmol) and PPh_3 (0.147 g, 0.756 mmol) were added as a solution in THF (5 ml) and the reaction heated to reflux. After 16 h, t.l.c (petrol:ethyl acetate, 4:1) indicated formation of a single major product (R_f 0.6) and complete consumption of starting material (R_f 0.2). The reaction was cooled to rt and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (petrol:ethyl aceatate, 10:1) to afford 3,4,6-Tri-*O*-benzyl-2-O-(2-iodoethyl)-β-D-glucopyranosyl fluoride **3.25** (0.272 g, 89%) as a white crystalline solid; m.p 61-63 °C (petrol/ethyl acetate); $[\alpha]_D^{25}$ – 4.7 (*c*, 1.0 in $CHCl_3$); υ_{max} (KBr) 3850 (br, C-I) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.12-3.16 (2H, m, $OCH_2C\underline{H}_2I$), 3.35 (1H, ddd, $J_{1,2}$ 6.9 Hz, $J_{2,3}$ 8.7 Hz, $J_{2,F}$ 12.4 Hz, H-2), 3.46-3.50 (1H, m, H-5), 3.54 (1H, at, *J* 8.7 Hz, H-3), 3.59-3.65 (3H, m, H-4, H-6, H-6'), 3.79-3.85 (1H, m, $OC\underline{H}H'CH_2I$), 3.93-3.99 (1H, m, $OCH\underline{H}'CH_2I$), 4.46, 4.54 (2H, ABq, J_{AB} 11.8 Hz, $PhCH_2$), 4.46, 4.72 (2H, ABq, J_{AB} 11.2 Hz, $PhCH_2$), 4.74, 4.88 (2H, ABq, J_{AB} 11.1 Hz, $PhCH_2$), 5.09 (1H, dd, $J_{1,2}$ 6.9 Hz, $J_{1,F}$ 52.6 Hz, H-1), 7.06-7.29 (15H, m, 15 x Ar-H), δ_C (100 MHz, $CDCl_3$) 2.5 ($OCH_2\underline{C}H_2I$), 68.2 (C-6), 72.9 ($O\underline{C}H_2CH_2I$), 73.6, 74.8, 75.0 (3 x $PhCH_2$), 74.8 (C-5), 76.9 (C-4), 82.2 (C-2, $J_{2,F}$ 22.4 Hz), 83.3 (C-3), 109.5 (C-1, $J_{1,F}$ 215.70), 127.8, 127.8, 127.9, 127.9 (4 x ArCH), 128.4, 128.5 (2 x ArC); *m/z* (ES^+) 629 ($M+Na^+$, 95) 624 ($M+NH_4^+$, 100%). (HRMS

(ES^+) Calcd. for $C_{29}H_{32}O_5FINa$ (MNa^+) 629.1176. Found 629.1180). (Found: C, 57.46; H, 5.34. $C_{29}H_{32}O_5FI$ requires C, 57.43; H, 5.32%).

3,4,6-Tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-β-D-glucopyranosyl fluoride 3.1

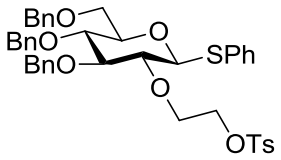


3.1

PhSeH (0.079 ml, 0.500 mmol) was added to a stirred suspension of NaH (0.012 g, 0.500 mmol) in THF (5 ml). After 30 min, 3,4,6-Tri-*O*-benzyl-2-O-(2-iodoethyl)-β-D-glucopyranosyl fluoride **3.25** (0.242 g, 0.400 mmol) was added as a solution in THF (5 ml) and the reaction heated to reflux. After 16 h, t.l.c (petrol:ethylacetate, 4:1) indicated formation of a single major product (R_f 0.5) and complete consumption of starting material (R_f 0.6). The reaction was diluted with CH_2Cl_2 (20 ml) and washed with water (20 ml). The aqueous layer was then extracted with CH_2Cl_2 (2 x 20 ml) and the combined organic extracts were washed with saturated sodium bicarbonate (20 ml) then brine (20 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 10:1) to afford 3,4,6-Tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-β-D-glucopyranosyl fluoride **3.1** (0.218 g, 86%) as a pale yellow oil; $[\alpha]_D^{25}$ + 2.5 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.08 (2H, m, $OCH_2C\underline{H}_2SePh$), 3.39-3.46 (1H, m, H-2), 3.56-3.63 (2H, m, H-3, H-5), 3.68-3.74 (3H, m, H-4, H-6, H-6'), 3.88-3.94 (1H, m, $OC\underline{H}H'CH_2SePh$), 4.03-4.09 (1H, m, $OCH\underline{H}'CH_2SePh$), 4.55, 4.64 (2H, ABq, J_{AB} 12.3 Hz, $PhCH_2$), 4.55, 4.82 (2H, ABq, J_{AB} 10.6 Hz, $PhCH_2$), 4.79, 4.94 (2H, ABq, J_{AB} 11.0 Hz, $PhCH_2$), 5.09 (1H, dd, $J_{1,2}$ 6.6 Hz, $J_{1,F}$ 52.8 Hz, H-1), 7.16-7.36 (20H, m, 20 x Ar-H), δ_C (100 MHz, $CDCl_3$) 27.0

($OCH_2\underline{C}H_2SePh$), 68.3 (C-6), 71.9 ($O\underline{C}H_2CH_2SePh$), 73.6, 74.8, 75.0 (3 x $PhCH_2$), 75.0 (C-5), 75.5 (C-4), 82.2 (C-2, $J_{2,F}$ 22.1 Hz), 83.3 (C-3), 109.5 (C-1, $J_{1,F}$ 214.7 Hz), 127.0, 127.8, 127.8, 127.9, 127.9, 128.4, 128.5, 129.1, 129.7 (9 x ArCH), 137.8, 137.9, 138.3 (3 x ArC); *m/z* (ES^+) 659 ($M+Na^+$, 100%). (HRMS (ES^+) Calcd. for $C_{35}H_{37}O_5F^{79}SeNa$ (MNa^+) 659.1685. Found 659.1698). (Found: C, 66.40; H, 6.45. $C_{35}H_{37}O_5FSe$ requires C, 66.35; H, 6.34%).

Phenyl 3-4-6-tri-O-benzyl-2-O-(2-ethyl *p*-toluenesulfonate)-1-thio-β-D-glucopyranoside 3.26

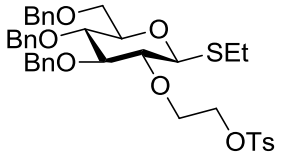


3.26

Phenyl 3-4-6-tri-O-benzyl-2-O-(2-hydroxyethyl)ether-1-thio-β-D-glucopyranoside **3.20** (0.098 g, 0.167 mmol) was dissolved in anhydrous pyridine (1 ml) and the mixture cooled to 0°C under a nitrogen atmosphere. *p*-Toluenesulfonyl chloride (0.096 g, 0.501 mmol) was added and the reaction allowed to warm to room temperature. After 16 h, t.l.c (petrol:ethyl acetate, 2:1) indicated the formation of a single product (R_f 0.7) and complete consumption of starting material (R_f 0.5). The reaction mixture was concentrated *in vacuo* and the resulting residue purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford phenyl 3-4-6-tri-O-benzyl-2-O-(2-ethyl *p*-toluenesulfonate)-1-thio-β-D-glucopyranoside **3.26** (0.112 g, 90%) as a colourless oil; $[\alpha]_D^{25}$ – 4.0 (*c*, 0.65 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.40 (3H, s,CH_3), 3.24 (1H, dd, $J_{1,2}$ 9.9 Hz, $J_{2,3}$ 8.6 Hz, H-2), 3.45 (1H, ddd, $J_{4,5}$ 9.1 Hz, $J_{5,6}$ 4.6 Hz, $J_{5,6'}$ 1.8 Hz, H-5), 3.52-3.61 (2H, m, H-3, H-4), 3.70 (1H, dd, $J_{5,6}$ 4.6 Hz, $J_{6,6'}$ 10.9 Hz, H-6), 3.77 (1H, dd, $J_{5,6'}$ 1.8 Hz, $J_{6,6'}$ 10.9 Hz, H-6') 3.88, 3.99, 4.14, 4.23

(4H, 4 x m, CH_2CH_2OTs), 4.44 (1H, d, $J_{1,2}$ 9.9 Hz, H-1), 4.54, 4.60 (2H, ABq, J_{AB} 11.9 Hz, $PhCH_2$), 4.57 (1H, d, *J* 11.9 Hz, PhCHH'), 4.79-4.82 (3H, m, $PhCH_2$, PhCHH'), 7.18-7.36 (20H, m, 20 x Ar-H), 7.51-7.53 (2H, m, 2 x Ar-H), 7.73-7.76 (2H, m, 2 x Ar-H); δ_C (100 MHz, $CDCl_3$) 21.6 (q, CH_3), 68.9 (t, C-6), 69.2, 70.3 (CH_2CH_2OTs), 73.4, 75.0, 75.8, (3 x t, 3 x $PhCH_2$), 77.6 (d, C-4), 79.0 (d, C-5), 81.4 (d, C-2), 86.3 (d, C-3), 87.2 (d, C-1), 127.6, 127.7, 127.9, 127.9, 128.0, 128.4, 128.5, 129.0, 129.8, 131.9 (10 x d, 10 x Ar-CH), 138.0, 138.2 (2 x s, 2 x Ar-C); *m/z* (ES^+) 763 ($M+Na^+$, 60) 758 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{42}H_{44}O_8S_2Na$ (MNa^+) 763.2370. Found 763.2372).

Ethyl 3-4-6-tri-O-benzyl-2-O-(2-ethyl *p*-toluenesulfonate)-1-thio-β-D-glucopyranoside 3.27

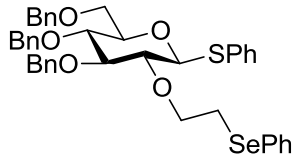


3.27

Ethyl 3-4-6-tri-*O*-benzyl-2-*O*-(2-hydroxyethyl)ether-1-thio-β-D-glucopyranoside **3.21** (0.090 g, 0.167 mmol) was dissolved in anhydrous pyridine (1 ml) and the mixture cooled to 0°C under a nitrogen atmosphere. *p*-Toluenesulfonyl chloride (0.096 g, 0.501 mmol) was added and the reaction allowed to warm to room temperature. After 16 h, t.l.c (petrol:ethyl acetate, 2:1) indicated the formation of a single product (R_f 0.6) and complete consumption of starting material (R_f 0.4). The reaction mixture was concentrated *in vacuo* and the resulting residue purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford ethyl 3-4-6-tri-O-benzyl-2-O-(2-ethyl *p*-toluenesulfonate)-1-thio-β-D-glucopyranoside **3.27** (0.098 g, 85%) as a colourless oil; $[\alpha]_D^{25}$ – 4.8 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.21 (3H, t, *J* 7.4

Hz, $SCH_2C\underline{H}_3$), 2.34 (3H, s, CH_3), 2.58-2.68 (2H, m, $SC\underline{H}_2CH_3$), 3.09 (1H, m, H-2), 3.34 (1H, m, H-5), 3.45-3.47 (2H, m, H-3, H-4), 3.57 (1H, dd, $J_{5,6}$ 4.8 Hz, $J_{6,6'}$ 10.9 Hz, H-6), 3.64 (1H, dd, $J_{5,6'}$ 1.8 Hz, $J_{6,6'}$ 10.9 Hz, H-6'), 3.80, 3.94, 4.08, 4.12 (4H, 4 x m, CH_2CH_2OTs), 4.20 (1H, d, $J_{1,2}$ 9.9 Hz, H-1), 4.47, 4.53 (2H, ABq, J_{AB} 12.1 Hz, $PhCH_2$), 4.50, 4.72 (2H, ABq, J_{AB} 10.7 Hz, $PhCH_2$), 4.79, 4.84 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 7.07-7.09 (2H, m, 2 x Ar-H), 7.19-7.25 (17H, m, 17 x Ar-H), δ_C (100 MHz, $CDCl_3$) 15.1 ($SCH_2\underline{C}H_3$), 21.6 (CH_3), 25.0 ($S\underline{C}H_2CH_3$), 69.0 (C-6), 69.1, 70.3 (CH_2CH_2OTs), 73.4, 75.0, 75.7, (3 x t, 3 x $PhCH_2$), 77.8 (C-4), 79.0 (C-5), 82.5 (C-2), 84.7 (C-3), 86.2 (C-1), 127.6, 127.7, 127.7, 127.8, 128.0, 128.4, 128.5, 129.0, 129.8, 131.9 (10 x Ar-CH), 138.0, 138.1, 138.4 (3 x Ar-C); *m/z* (ES^+) 715 ($M+Na^+$, 100%). (HRMS (ES^+) Calcd. for $C_{38}H_{44}O_8S_2Na$ (MNa^+) 715.2375. Found 715.2380). (Found: C, 65.80; H, 6.45. $C_{38}H_{44}O_8S_2$ requires C, 65.87; H, 6.40%).

Phenyl 3-4-6-tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-1-thio-β-D-glucopyranoside 3.2

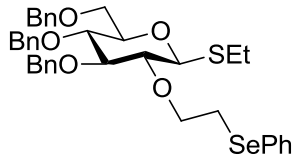


3.2

PhSeH (0.079 ml, 0.500 mmol) was added to a stirred suspension of NaH (0.012 g, 0.500 mmol) in THF (5 ml). After 30 min, phenyl 3-4-6-tri-O-benzyl-2-O-(2-ethyl *p*-toluenesulfonate)-1-thio-β-D-glucopyranoside **3.26** (0.296 g, 0.400 mmol) was added as a solution in THF (5 ml) and the reaction heated to reflux. After 16 h, t.l.c (petrol:ethylacetate, 4:1) indicated formation of a single major product (R_f 0.5) and complete consumption of starting material (R_f 0.6). The reaction was diluted with CH_2Cl_2 (20 ml) and washed with water (20 ml). The aqueous layer was then extracted

with CH_2Cl_2 (2 x 20 ml) and the combined organic extracts were washed with saturated sodium bicarbonate (20 ml) then brine (20 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 10:1) to afford phenyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-1-thio-β-D-glucopyranoside **3.2** (0.220 g, 76%) as a pale yellow oil; $[\alpha]_D^{25}$ + 1.4 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.08 (2H, m, $OCH_2C\underline{H}_2SePh$), 3.27 (1H, dd, $J_{1,2}$ 9.8 Hz, $J_{2,3}$ 6.5 Hz, H-2), 3.45 (1H, m, H-5), 3.52-3.78 (4H, m, H-3, H-4, H-6, H-6'), 3.96-4.08 (2H, m, $OC\underline{H}_2CH_2SePh$), 4.51 (1H, d, $J_{1,2}$ 9.8 Hz, H-1), 4.50, 4.58 (2H, ABq, J_{AB} 12.1 Hz, $PhCH_2$), 4.54, 4.72 (2H, ABq, J_{AB} 11.2 Hz, $PhCH_2$), 4.78, 4.88 (2H, ABq, J_{AB} 10.7 Hz, $PhCH_2$), 7.18-7.50 (25H, m, 25 x Ar-H), δ_C (100 MHz, $CDCl_3$) 26.5 ($OCH_2\underline{C}H_2SePh$), 69.1 (C-6), 72.6, 73.6, 75.0, 75.8 (3 x $PhCH_2$, $O\underline{C}H_2CH_2SePh$), 76.9 (C-4), 78.1 (C-5), 81.3 (C-2), 84.8 (C-3), 86.5 (C-1), 126.9, 127.6, 127.7, 127.7, 127.8, 127.8, 128.3, 128.4, 128.4, 129.0, 129.3 (11 x Ar-CH), 132.4, 133.1, 133.2 (3 x Ar-C); *m/z* (ES^+) 748 ($M+Na^+$, 100%). (HRMS (ES^+) Calcd. for $C_{41}H_{42}O_5S^{79}SeNa$ (MNa^+) 749.1814. Found 749.1801). (Found: C, 67.64; H, 5.89. $C_{41}H_{42}O_5SSe$ requires C, 67.85; H, 5.83%).

Ethyl 3-4-6-tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-1-thio-β-D-glucopyranoside 3.3

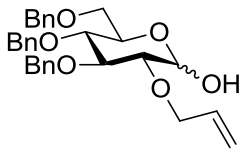


3.3

PhSeH (0.079 ml, 0.500 mmol) was added to a stirred suspension of NaH (0.012 g, 0.500 mmol) in THF (5 ml). After 30 min, ethyl 3-4-6-tri-O-benzyl-2-O-(2-ethyl *p*-toluenesulfonate)-1-thio-β-D-glucopyranoside **3.27** (0.252 g, 0.400 mmol) was added

as a solution in THF (5 ml) and the reaction heated to reflux. After 16 h, t.l.c (petrol:ethylacetate, 4:1) indicated formation of a single major product (R_f 0.5) and complete consumption of starting material (R_f 0.6). The reaction was diluted with CH_2Cl_2 (20 ml) and washed with water (20 ml). The aqueous layer was then extracted with CH_2Cl_2 (2 x 20 ml) and the combined organic extracts were washed with saturated sodium bicarbonate (20 ml) then brine (20 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 10:1) to afford phenyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-1-thio-β-D-glucopyranoside **3.3** (0.206 g, 75%) as a pale yellow oil; $[\alpha]_D^{25}$ + 2.0 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.4 Hz, $SCH_2C\underline{H}_3$), 2.68-2.75 (2H, m, $SC\underline{H}_2CH_3$), 3.10 (2H, m, $OCH_2C\underline{H}_2SePh$), 3.24 (1H, m, H-2), 3.37 (1H, m, H-5), 3.52-3.75 (4H, m, H-3, H-4, H-6, H-6'), 3.95-4.02 (2H, m, $OC\underline{H}_2CH_2SePh$), 4.38 (1H, d, $J_{1,2}$ 9.9 Hz, H-1), 4.46, 4.54 (2H, ABq, J_{AB} 12.0 Hz, $PhCH_2$), 4.51, 4.72 (2H, ABq, J_{AB} 10.6 Hz, $PhCH_2$), 4.78, 4.88 (2H, ABq, J_{AB} 11.3 Hz, $PhCH_2$), 7.11-7.37 (20H, m, 20 x Ar-H), δ_C (100 MHz, $CDCl_3$) 15.1 ($SCH_2\underline{C}H_3$), 25.0 ($S\underline{C}H_2CH_3$), 26.9 ($OCH_2\underline{C}H_2SePh$), 69.0 (C-6), 72.6, 73.4, 75.0, 75.8 (3 x $PhCH_2$, $O\underline{C}H_2CH_2SePh$), 77.9 (C-4), 79.1 (C-5), 82.0 (C-2), 84.9 (C-3), 86.4 (C-1), 126.9, 127.6, 127.7, 127.7, 127.8, 128.3, 128.4, 128.4, 129.0 (9 x Ar-CH), 132.4 (Ar-C); *m/z* (ES^+) 701 ($M+Na^+$, 100%). (HRMS (ES^+) Calcd. for $C_{37}H_{42}O_5S^{79}SeNa$ (MNa^+) 701.1816. Found 701.1807). (Found: C, 65.34; H, 6.43. $C_{37}H_{42}O_5SSe$ requires C, 65.57; H, 6.25%).

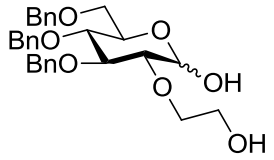
2-*O*-Allyl-3,4,6-tri-*O*-benzyl-α/β-D-glucopyranose 3.30[23]



3.30

Ethyl 2-*O*-allyl-3-4-6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside **3.24** (0.267 g, 0.500 mmol) and TTBP (0.372 g, 1.50 mmol) were dissolved in a mixture of 1,4-dioxane and water (10.5 ml, 20:1). MeOTf (1.50 mmol) was added and reaction stirred at rt. After 3 h, t.l.c (petrol:ethyl acetate, 4:1) indicated the formation of a single product (R_f 0.3) and complete consumption of starting material (R_f 0.6). The reaction was diluted with CH_2Cl_2 (20 ml) and washed with water (20 ml). The aqueous layer was then extracted with CH_2Cl_2 (2 x 20 ml) and the combined organic extracts were washed with saturated sodium bicarbonate (20 ml) then brine (20 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford 2-*O*-allyl-3,4,6-tri-*O*-benzyl-α/β-D-glucopyranose **3.30** (0.196 g 80%) as white crystalline solid. These data are in agreement with those reported in the literature; m.p 134-136°C [Lit. m.p 134-136°C]; δ_H (400 MHz, $CDCl_3$) [5:1 mixture of α:β anomers observed, major α anomer quoted] 3.34 (1H, m, H-2), 3.52-3.64 (4H, m, H-3, H-4, H-6, H-6'), 3.90 (1H, m, H-5), 4.26 (1H, ddat, J_{gem} 11.7 Hz, J_{vic} 6.1 Hz, J 1.4 Hz, OC<u>H</u>H'CH=CH_2), 4.39 (1H, ddat, J_{gem} 11.7 Hz, J_{vic} 5.7 Hz, J 1.4 Hz, OCH<u>H</u>'CH=CH_2) 4.53, 4.63 (2H, ABq, J_{AB} 12.1 Hz, $PhCH_2$), 4.56, 4.82 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 4.85 (2H, br s, $PhCH_2$), 5.15 (1H, daq, J_Z 10.4 Hz, J 1.5 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), , 5.35 (1H, dd, $J_{1,2}$ 3.3 Hz, H-1), 5.96 (1H, ddat, J_E 17.2 Hz, J_Z 10.4 Hz, J 5.9 Hz, C<u>H</u>=CH_2), 7.14-7.35 (15H, m, 15 x Ar-H); *m/z* (ES^+) 513 ($M+Na^+$, 100%).

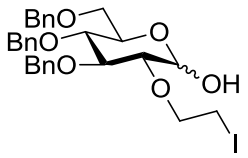
3,4,6-Tri-*O*-benzyl-2-*O*-(2-hydroxyethyl)ether-α/β-D-glucopyranose 3.28



3.28

A solution of 2-*O*-allyl-3,4,6-tri-*O*-benzyl-α/β-D-glucopyranose **3.30** (121 mg, 0.246 mmol) in CH_2Cl_2-Methanol (3 mL, 1:1) was treated with ozone at -78 °C until the solution turned blue. The reaction was quenched by the addition of $NaBH_4$ (42 mg, 1.105 mmol) in small portions over 10 min. The reaction mixture was allowed to warm to room temperature and then 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*-(2-hydroxyethyl)ether-α/β-D-glucopyranose **3.28** (101 mg, 76%) as a colourless oil; υ_{max} (KBr) 3470 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) [5:1 mixture of α:β anomers observed, major α anomer quoted] 3.31 (1H, m, H-2), 3.50-3.75 (8H, m, H-3, H-4, H-6, H-6', $OC\underline{H}_2CH_2OH$, $OCH_2C\underline{H}_2OH$), 3.90 (1H, m, H-5) 4.57, 4.66 (2H, ABq, J_{AB} 12.1 Hz, $PhCH_2$), 4.59, 4.84 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 4.91 (2H, br s, $PhCH_2$), 5.38 (1H, dd, $J_{1,2}$ 3.3 Hz, H-1), 7.14-7.35 (15H, m, 15 x Ar-H), δ_C (100 MHz, $CDCl_3$) 62.2 ($OCH_2\underline{C}H_2OH$), 68.7 (C-6), 70.3 (C-5), 72.6, 73.5, 74.2 (3 x $PhCH_2$), 75.8 ($O\underline{C}H_2CH_2OH$), 78.0, 80.9, 81.6 (C-2, C-3, C-4), 90.9 (C-1), 127.8, 127.9, 127.9, 128.0, 128.4, 128.4, 128.5, 128.5 (8 x Ar-CH), 137.7, 137.8, 137.8 (3 x Ar-C); *m/z* (ES^+) 517 ($M+Na^+$, 100%). (HRMS (ES^+) Calcd. for $C_{29}H_{34}O_7Na$ (MNa^+) 517.2202. Found 517.2210). (Found: C, 70.55; H, 6.99. $C_{29}H_{34}O_7$ requires C, 70.43; H, 6.93%).

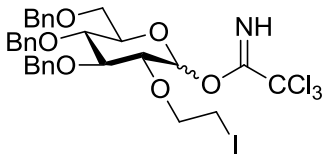
3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodoethyl)-α/β-D-glucopyranose 3.31



3.31

3,4,6-Tri-*O*-benzyl-2-*O*-(2-hydroxyethyl)ether-α/β-D-glucopyranose **3.28** (0.249 g, 0.504 mmol) was dissolved in freshly distilled THF (5 ml) under an atmosphere of argon. A mixture iodine (0.191 g, 0.756 mmol), imidazole (0.051 g, 0.756 mmol) and PPh_3 (0.147 g, 0.756 mmol) were added as a solution in THF (5 ml) and the reaction heated to reflux. After 16 h, t.l.c (petrol:ethyl acetate, 4:1) indicated formation of a single major product (R_f 0.4) and complete consumption of starting material (R_f 0.1). The reaction was cooled to rt and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (petrol:ethyl aceatate, 6:1) to afford 3,4,6-3,4,6-tri-*O*-benzyl-2-*O*-(2-iodoethyl)-α/β-D-glucopyranose **3.31** (0.231 g, 76%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) [5:1 mixture of α:β anomers observed, major α anomer quoted] 3.12-3.16 (2H, m, $OCH_2C\underline{H}_2I$), 3.35 (1H, dd, $J_{1,2}$ 3.3 Hz, $J_{2,3}$ 8.2 Hz, H-2), 3.46-3.55 (2H, m, H-4, H-5), 3.59-3.65 (3H, m, H-4, H-6, H-6'), 3.79-3.85 (1H, m, $OC\underline{H}H'CH_2I$), 3.93-3.99 (1H, m, $OCH\underline{H}'CH_2I$), 4.46, 4.54 (2H, ABq, J_{AB} 11.8 Hz, $PhCH_2$), 4.46, 4.72 (2H, ABq, J_{AB} 11.2 Hz, $PhCH_2$), 4.74, 4.88 (2H, ABq, J_{AB} 11.1 Hz, $PhCH_2$), 5.35 (1H, d, $J_{1,2}$ 3.3 Hz, H-1), 7.06-7.29 (15H, m, 15 x Ar-H), δ_C (100 MHz, $CDCl_3$) 3.0 ($OCH_2\underline{C}H_2I$), 68.5 (C-6), 70.5 ($O\underline{C}H_2CH_2I$), 72.0, 73.5, 75.0 (3 x $PhCH_2$), 74.8 (C-5), 76.9 (C-4), 82.2 (C-2), 83.3 (C-3), 91.5 (C-1,), 127.8, 127.8, 127.9, 127.9 (4 x ArCH), 128.4, 128.5 (2 x ArC); *m/z* (ES^+) 627 ($M+Na^+$, 95) 622 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{29}H_{33}O_6INa$ (MNa^+) 627.1220. Found 627.1210). (Found: C, 57.51; H, 5.58. $C_{29}H_{33}O_6I$ requires C, 57.62; H, 5.50%).

_O_-(3,4,6-Tri-_O_-benzyl-2-_O_-(2-iodoethyl)-α/β-D-glucopyranosyl) trichloroacetimidate 3.29

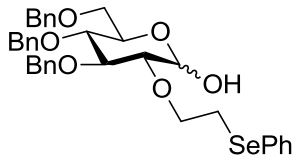


3.29

3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodoethyl)-α/β-D-glucopyranose **3.31** (0.773 g, 1.28 mmol) was dissolved in freshly distilled CH_2Cl_2 (8 ml) at 0 °C under an argon atmosphere. DBU (0.078 ml, 0.51 mmol) was added followed by trichloroacetonitrile (1.31 ml, 12.8 mmol). After 5 h, t.l.c (petrol:ethyl acetate, 4:1, with 1% added triethylamine) indicated the formation of a single product (R_f 0.6) and complete consumption of starting material (R_f 0.4). The reaction was concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 7:1, with 1% added triethylamine) to afford *O*-(3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodoethyl)-α/β-D-glucopyranosyl) trichloroacetimidate **3.29** (0.835 g, 84%) as a colourless oil; υ_{max} (KBr) 3345 (w, NH), 1659 (s, C=N) cm^{-1}; δ_H (400 MHz, $CDCl_3$) [15:1 mixture of α:β anomers observed, major α anomer quoted] 3.14-3.17 (2H, m, $OCH_2C\underline{H}_2I$), 3.60-4.04 (8H, m, H-2, H-3, H-4, H-5, H-6, H-6', $OC\underline{H}_2CH_2I$), 4.49, 4.63 (2H, ABq, J_{AB} 12.0 Hz, $PhCH_2$), 4.54, 4.87 (2H, ABq, J_{AB} 10.6 Hz, $PhCH_2$), 4.83, 5.00 (2H, ABq, J_{AB} 10.8 Hz, $PhCH_2$), 6.67 (1H, d, $J_{1,2}$ 3.4 Hz, H-1), 7.11-7.29 (15H, m, 15 x Ar-H), 8.61 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 3.0 ($OCH_2\underline{C}H_2I$), 68.0 (C-6), 70.5 ($O\underline{C}H_2CH_2I$), 73.5, 73.6, 75.0, 75.4 (3 x $Ar\underline{C}H_2$), 73.5, 78.8, 81.2, 84.4 (C-2, C-3, C-4, C-5), 94.4 ($OC(NH)\underline{C}Cl_3$), 97.6 (C-1), 126.2, 126.6, 126.9, 127.7, 127.8, 127.9, 128.1, 128.4, (8 x Ar-CH), 137.8, 138.0, 138.6 (3 x Ar-C), 163.8 (s, C=NH); *m/z* (ES^+) 765 ($M+NH_4^+$,

100%). (HRMS (ES^+) Calcd. for $C_{31}H_{33}{}^{35}Cl_3NO_6INa$ (MNa^+) 770.0316. Found 770.0319).

3,4,6-Tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-α/β-D-glucopyranose 3.10

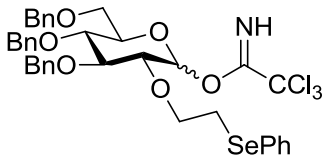


3.10

PhSeH (0.079 ml, 0.500 mmol) was added to a stirred suspension of NaH (0.012 g, 0.500 mmol) in THF (5 ml). After 30 min, 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodoethyl)-α/β-D-glucopyranose **3.31** (0.242 g, 0.400 mmol) was added as a solution in THF (5 ml) and the reaction heated to reflux. After 16 h, t.l.c (petrol:ethylacetate, 4:1) indicated formation of a single major product (R_f 0.3) and complete consumption of starting material (R_f 0.4). The reaction was diluted with CH_2Cl_2 (20 ml) and washed with water (20 ml). The aqueous layer was then extracted with CH_2Cl_2 (2 x 20 ml) and the combined organic extracts were washed with saturated sodium bicarbonate (20 ml) then brine (20 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 10:1) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-α/β-D-glucopyranose **3.10** (0.205 g, 81%) as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) [5:1 mixture of α:β anomers observed, major α anomer quoted] 3.02-3.07 (2H, m, $OCH_2C\underline{H}_2SePh$), 3.35 (1H, dd, $J_{1,2}$ 3.3 Hz, $J_{2,3}$ 8.2 Hz, H-2), 3.41-3.55 (2H, m, H-4, H-5), 3.59-3.65 (3H, m, H-4, H-6, H-6'), 3.79-3.85 (1H, m, $OC\underline{H}H'CH_2SePh$), 3.93-3.99 (1H, m, $OCH\underline{H}'CH_2SePh$), 4.45, 4.53 (2H, ABq, J_{AB} 11.8 Hz, $PhCH_2$), 4.46, 4.72 (2H, ABq, J_{AB} 11.2 Hz, $PhCH_2$), 4.70, 4.83 (2H, ABq, J_{AB} 11.1 Hz, $PhCH_2$), 5.25 (1H, d, $J_{1,2}$ 3.3 Hz, H-1), 7.06-7.37 (20H, m, 20 x Ar-H), δ_C (100 MHz, $CDCl_3$)

26.9 ($OCH_2\underline{C}H_2SePh$), 68.9 (C-6), 70.3 ($O\underline{C}H_2CH_2SePh$), 72.0, 73.5, 75.0 (3 x $PhCH_2$), 74.8, 76.9, 82.2, 83.3 (C-2, C-3, C-4, C-5), 91.5 (C-1,), 127.0, 127.2, 127.6, 127.7,127.7, 127.9, 127.9, 128.0, 128.3, 128.4 (10 x ArCH), 131.5, 132.6, 132.8, 133.3 (4 x ArC); *m/z* (ES^+) 657 ($M+Na^+$, 95) 652 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{35}H_{38}O_6{}^{79}SeNa$ (MNa^+) 657.1731. Found 657.1719). (Found: C, 66.51; H, 6.23. $C_{35}H_{38}O_6Se$ requires C, 66.34; H, 6.04%).

_O_-(3,4,6-Tri-_O_-benzyl-2-_O_-(2-(phenylselenyl)ethyl)-α/β-D-glucopyranosyl) trichloroacetimidate 3.4

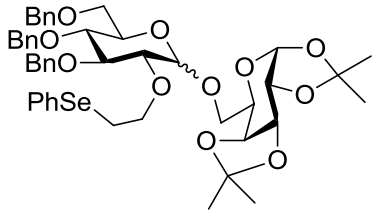


3.4

3,4,6-Tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-α/β-D-glucopyranose **3.10** (0.812 g, 1.28 mmol) was dissolved in freshly distilled CH_2Cl_2 (8 ml) at 0 °C under an argon atmosphere. DBU (0.078 ml, 0.51 mmol) was added followed by trichloroacetonitrile (1.31 ml, 12.8 mmol). After 5 h, t.l.c (petrol:ethyl acetate, 4:1, with 1% added triethylamine) indicated the formation of a single product (R_f 0.6) and complete consumption of starting material (R_f 0.4). The reaction was concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 7:1, with 1% added triethylamine) to afford *O*-(3,4,6-Tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-α/β-D-glucopyranosyl) trichloroacetimidate **3.4** (0.901 g, 88%) as a colourless oil; υ_{max} (KBr) 3345 (w, NH), 1662 (s, C=N) cm^{-1}; δ_H (400 MHz, $CDCl_3$) [15:1 mixture of α:β anomers observed, major α anomer quoted] 3.02-3.09 (2H, m, $OCH_2C\underline{H_2}SePh$), 3.60-4.04 (8H, m, H-2, H-3, H-4, H-5, H-6, H-6', $OC\underline{H_2}CH_2SePh$), 4.48, 4.63 (2H, ABq, J_{AB} 11.3 Hz, $PhCH_2$), 4.52, 4.84 (2H, ABq,

J_{AB} 10.6 Hz, $PhCH_2$), 4.83, 5.00 (2H, ABq, J_{AB} 12.0 Hz, $PhCH_2$), 6.69 (1H, d, $J_{1,2}$ 3.4 Hz, H-1), 7.10-7.34 (20H, m, 29 x Ar-H), 8.54 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 26.9 ($OCH_2\underline{C}H_2SePh$), 68.3 (C-6), 70.3 ($O\underline{C}H_2CH_2SePh$), 73.5, 73.7, 75.1 (3 x $Ar\underline{C}H_2$), 73.1, 78.5, 81.0, 84.4 (C-2, C-3, C-4, C-5), 94.0 ($OC(NH)\underline{C}Cl_3$), 97.5 (C-1), 126.2, 126.6, 127.0, 127.1, 127.3, 127.7, 127.7, 127.9, 128.1, 128.4, (10 x Ar-CH), 137.8, 138.0, 138.6, 138.8 (4 x Ar-C), 164.0 (s, C=NH); *m/z* (ES^+) 795 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{37}H_{38}{}^{35}Cl_3NO_6{}^{79}SeNa$ (MNa^+) 800.0828. Found 800.0821).

3,4,6-Tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside 3.32



3.32

Method 1

To a flame-dried round-bottom flask containing activated 3Å molecular sieves (0.100 g) was added a solution of 3,4,6-tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-β-D-glucopyranosyl fluoride **3.1** (125 mM) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside **2.11** (2 eq.) in freshly distilled CH_2Cl_2. The reaction mixture was cooled to the designated temperature under an argon atmosphere, then $BF_3.OEt_2$ (1.5 eq.) was added. The reaction was monitored by t.l.c. (toluene:ethyl acetate, 9:1) until the formation of a major product (R_f 0.4) and complete consumption of starting material (R_f 0.6) was observed. The reaction was quenched with saturated sodium bicarbonate solution and filtered through Celite®. The mixture was diluted with

CH_2Cl_2, washed with saturated sodium bicarbonate solution (ml), and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 15:1) to afford 3,4,6-Tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside **3.32** as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) [1:1 mixture of α:β anomers observed] 1.34 (12H, br s, 2 × CH_3α, 2 × CH_3β), 1.46, 1.47, 1.53, 1.55 (12H, 4 × s, 2 × CH_3α, 2 × CH_3β), 3.10-3.14 (4H, m, $OCH_2C\underline{H}_2$SePhα/β), 3.44 (1H, m, H-5_bβ), 3.50 (1H, at, *J* 8.4 Hz, H-2_bβ), 3.54-3.86 (10H, m, H-2_aα, H-5_aα, H-2_aβ, H-5_aβ, H-2_bα, H-5_bα, H-6_bα, H-6'$_b$α, H-6_bβ, H-6'$_b$β), 3.99 (1H, at, *J* 9.4 Hz, H-4_bβ), 4.04-4.65 (20H, m, H-3_aα, H-4_aα, H-6_aα, H-6'$_a$α, H-3_aβ, H-4_aβ, H-6_aβ, H-6'$_a$β, H-3_bα, H-4_bα, H-1_aβ, H-3_aβ, O$\underline{C}H_2CH_2$SePhα/β), 4.74-5.31 (12H, m, 6 × $PhCH_2$α, 6 × $PhCH_2$β), 4.98 (1H, d, $J_{1,2}$ 4.1 Hz, H-1_bα), 5.52 (1H, d, $J_{1,2}$ 5.1 Hz, H-1_aβ), 5.57 (1H, d, $J_{1,2}$ 5.1 Hz, H-1_aα), 7.08-7.38 (40H, m, 20 × Ar-CHα, 20 × Ar-CHβ); δ_C (100 MHz, $CDCl_3$) 26.8, 26.9 ($OCH_2\underline{C}H_2$SePhα/β), 66.3, 66.9 (C-6_aα, C-6_aβ), 68.3, 68.7, (C-6_bα, C-6_bβ), 70.5, 70.6 (O$\underline{C}H_2CH_2$SePhα/β), 73.5, 75.1, 75.8 (3 × Ar$\underline{C}H_2$), 70.7, 70.9, 71.2, 71.5, 74.7, 77.6, 79.5, 81.1, 81.6, 84.3 (C-2_a-C-5_aα/β, C-2_b-C-5_bα/β), 95.4 (d, C-1_aβ), 96.2 (d, C-1_aα), 97.1 (d, C-1_bα), 104.4 (d, C-1_bβ), 126.0, 126.5, 126.6, 127.2, 127.6, 127.7, 127.9, 128.1, 128.2, 128.4 (10 × Ar-CH), 137.9, 138.1, 138.3, 138.7, 140.9, 141.2 (6 x Ar-C); *m/z* (ES^+) 899 ($M+Na^+$, 100%). (HRMS (ES^+) Calcd. for $C_{47}H_{56}O_{11}{}^{79}SeNa$ (MNa^+) 899.2886. Found 899.2880). (Found: C, 64.23; H, 6.58. $C_{47}H_{56}O_{11}Se$ requires C, 64.45; H, 6.44%).

Method 2

To a flame-dried round-bottom flask containing activated 3Å molecular sieves (0.100g) was added a solution of ethyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-

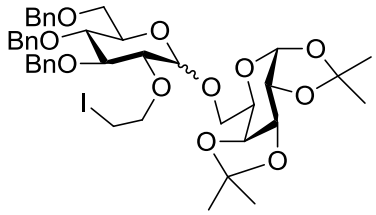
(phenylselenyl)ethyl)-1-thio-β-D-glucopyranoside **3.3** (125 mM), 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside **2.11** (2 eq.), and TTBP (4.5eq) in freshly distilled CH_2Cl_2. The reaction mixture was cooled to the designated temperature under an argon atmosphere, then MeOTf (4.5 eq.) was added. The reaction was monitored by t.l.c. (toluene:ethyl acetate, 9:1) until the formation of a major product (R_f 0.4) and complete consumption of starting material (R_f 0.6) was observed. The reaction was diluted with CH_2Cl_2 and washed with saturated sodium bicarbonate, then water, and then brine. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 15:1) to afford 3,4,6-Tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside **3.32** as a colourless oil.

Method 3

To a flame-dried round-bottom flask containing activated 3Å molecular sieves (0.100 g) was added a solution of *O*-(3,4,6-Tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-α/β-D-glucopyranosyl) trichloroacetimidate **3.4** (125 mM) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside **2.11** (2 eq.) in freshly distilled CH_2Cl_2. The reaction mixture was cooled to the designated temperature under an argon atmosphere, then TMSOTf (0.1 eq.) was added. The reaction was monitored by t.l.c. (toluene:ethyl acetate, 9:1) until the formation of a major product (R_f 0.4) and complete consumption of starting material (R_f 0.6) was observed. The reaction was quenched with saturated sodium bicarbonate solution and filtered through Celite®. The mixture was diluted with CH_2Cl_2, washed with saturated sodium bicarbonate solution, and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by

flash column chromatography (toluene:ethyl acetate, 15:1) to afford 3,4,6-Tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside **3.31** as a colourless oil.

3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodoethyl)-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside 3.33



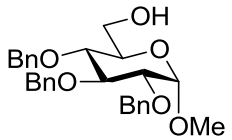
3.33

Method 1

To a flame-dried round-bottom flask containing activated 3Å molecular sieves (0.100 g) was added a solution of 3,4,6-tri-*O*-benzyl-2-*O*-(2iodoethyl)-β-D-glucopyranosyl fluoride **3.25** (125 mM) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside **2.11** (2 eq.) in freshly distilled CH_2Cl_2. The reaction mixture was cooled to the designated temperature under an argon atmosphere, then $BF_3.OEt_2$ (1.5 eq.) was added. The reaction was monitored by t.l.c. (toluene:ethyl acetate, 9:1) until the formation of a major product (R_f 0.4) and complete consumption of starting material (R_f 0.7) was observed. The reaction was quenched with saturated sodium bicarbonate solution and filtered through Celite®. The mixture was diluted with CH_2Cl_2, washed with saturated sodium bicarbonate solution (ml), and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 15:1) to afford 3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodoethyl)-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-

galactopyranoside **3.33** as a colourless oil; δ_H (400 MHz, $CDCl_3$) [1:1 mixture of α:β anomers observed] 1.34 (12H, br s, 2 × CH_3α, 2 × CH_3β), 1.46, 1.47, 1.53, 1.55 (12H, 4 × s, 2 × CH_3α, 2 × CH_3β), 3.12-3.16 (4H, m, $OCH_2C\underline{H}_2$Iα/β), 3.40 (1H, m, H-5_bβ), 3.46 (1H, at, *J* 8.0 Hz, H-2_bβ), 3.50-3.79 (10H, m, H-2_aα, H-5_aα, H-2_aβ, H-5_aβ, H-2_bα, H-5_bα, H-6_bα, H-6'$_b$α, H-6_bβ, H-6'$_b$β), 3.97-4.63 (20H, m, H-3_aα, H-4_aα, H-6_aα, H-6'$_a$α, H-3_aβ, H-4_aβ, H-4_bβ, H-6_aβ, H-6'$_a$β, H-3_bα, H-4_bα, H-1_aβ, H-3_aβ, $O\underline{C}H_2CH_2$Iα/β), 4.71-5.25 (12H, m, 6 × $PhCH_2$α, 6 × $PhCH_2$β), 4.95 (1H, d, $J_{1,2}$ 4.1 Hz, H-1_bα), 5.55 (1H, d, $J_{1,2}$ 5.0 Hz, H-1_aβ), 5.60 (1H, d, $J_{1,2}$ 5.0 Hz, H-1_aα), 7.07-7.29 (30H, m, 15 × Ar-CHα, 15 × Ar-CHβ); δ_C (100 MHz, $CDCl_3$) 4.6, 4.7 ($OCH_2\underline{C}H_2$Iα/β), 66.3, 66.4 (C-6_aα, C-6_aβ), 68.2, 68.7, (C-6_bα, C-6_bβ), 70.1, 70.3 ($O\underline{C}H_2CH_2$Iα/β), 73.2, 75.4, 75.3 (3 × Ar$\underline{C}H_2$), 70.6, 70.9, 71.4, 71.5, 74.7, 77.6, 79.5, 81.0, 81.2, 84.3 (C-2_a-C-5_aα/β, C-2_b-C-5_bα/β), 94.9 (d, C-1_aβ), 96.0 (d, C-1_aα), 97.0 (d, C-1_bα), 103.4 (d, C-1_bβ), 126.0, 126.5, 126.6, 127.2, 127.6, 127.7, 127.9, 128.1, 128.2, 128.4 (10 × Ar-CH), 137.9, 138.1, 138.3, 138.7, 140.9, 141.2 (6 x Ar-C); *m/z* (ES^+) 869 ($M+Na^+$, 100%). (HRMS (ES^+) Calcd. for $C_{41}H_{51}O_{11}INa$ (MNa^+) 869.2374. Found 869.2381). (Found: C, 58.25; H, 6.13. $C_{41}H_{51}O_{11}I$ requires C, 58.16; H, 6.07%).

Methyl-2,3,4-O-benzyl-α-D-glucopyranose 3.37[24]



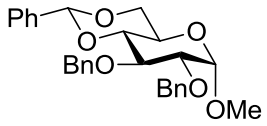
3.37

Methyl α-D-glucopyranoside (5.00 g, 25.75 mmol) and imidazole (5.26 g, 77.25 mmol) were dissolved in anhydrous DMF (40 ml) and the reaction mixture cooled to 0 °C. TIPSCl (6.06 ml, 28.33 mmol) was slowly added and then the reaction mixture

was allowed to warm to RT. After 16 h the reaction mixture was concentrated *in vacuo* and the resulting residue dissolved in CH_2Cl_2 (100 ml). The organic layer was washed with H_2O (100 ml) and the aqueous layer extracted with CH_2Cl_2 (2 x 100 ml). The combined organic layers were washed with brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was dried under high vacuum for 2 h and then dissolved in anhydrous DMF (150 ml). The reaction mixture was cooled to 0 °C and NaH (60% in mineral oil, 5.15 g, 128.79 mmol) was added. The mixture was allowed to warm to RT, then BnBr (15.63 ml, 128.79 mmol) was slowly added. After 16 h the reaction was quenched with MeOH and concentrated *in vacuo*. The resulting residue was dissolved in Et_2O (200 ml) and washed with H_2O (200 ml). The aqueous layer was extracted with Et_2O (2 x 100 ml) and the combined organic layers washed with brine (200 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was combined with TBAF·H_2O (13.47 g, 51.50 mmol) and dissolved in THF (50 ml). After 16 h, t.l.c (petrol:ethyl acetate, 1:1) indicated the formation of a single major product (R_f 0.45). The reaction was diluted with H_2O (50 ml) and the aqueous layer extracted with CH_2Cl_2 (4 x 50 ml). The combined organic layers were washed with brine (100 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 1:1) to afford methyl-2,3,4-*O*-benzyl-α-D-glucopyranose **5b** (11.12 g, 93%) as a white crystalline solid. These data are in agreement with those reported in the literature; $[\alpha]_D^{18}$ + 26.2 (*c*, 1.0 in $CHCl_3$) [Lit. $[\alpha]_D^{21}$ + 27.5 (*c*, 1.0 in $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 1.65 (1H, s, OH), 3.33 (3H, s, OMe), 3.45-3.52 (2H, m), 3.60-3.73 (2H, m), 3.73 (1H, dd, *J* 11.6 Hz, *J* 2.0 Hz), 3.98 (1H, at, *J* 9.4 Hz), 4.54 (1H, d, $J_{1,2}$ 3.3 Hz, H-1), 4.60-4.65 (2H, m), 4.76-4.87 (3H, m), 4.97 (1H, d, *J* 10.9 Hz), 7.22-7.34 (15H, m, 15 x Ar-H); δ_C (100 MHz, $CDCl_3$) 55.2, 61.9, 70.7, 73.4,

75.0, 75.8, 80.0, 82.0, 98.2 (C-1), 127.6, 127.9, 128.0, 128.1, 128.1, 128.4, 128.5, 138.1, 138.1, 138.7; *m/z* (ES^+) 487 ($M+Na^+$, 100%).

Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside[25]

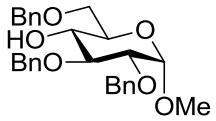


3.38

Benzaldehyde dimethylacetal (9.74 ml, 64.89 mmol) was added to a solution of methyl α-D-glucopyranoside **3.36** (5.04 g, 25.96 mmol) and camphor sulfonic acid (0.060 g, 0.260 mmol) in DMF (75 ml). The resulting solution was heated to 60 °C on a rotary evaporator under a pressure of 250 mbar. After 5 h, t.l.c (petrol/ethyl acetate, 3:1) indicated complete conversion of starting material (Rf 0.0) to a single product (Rf 0.30). The reaction mixture was cooled to 0 °C and NaH (60% in mineral oil, 5.15 g, 128.79 mmol) was added. The mixture was allowed to warm to RT, then BnBr (15.63 ml, 128.79 mmol) was slowly added. After 16 h, t.l.c (petrol/ethyl acetate, 3:1) indicated the formation of a single product (R_f 0.7). the reaction was quenched with MeOH and concentrated *in vacuo*. The resulting residue was dissolved in Et_2O (200 ml) and washed with H_2O (200 ml). The aqueous layer was extracted with Et_2O (2 x 100 ml) and the combined organic layers washed with brine (200 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) to afford Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside **3.37** (7.74 g, 84%) as a colourless gum. These data are in agreement with those reported in the literature; $[\alpha]_D^{18}$ + 21.2 (*c*, 1.0 in $CHCl_3$) [Lit. $[\alpha]_D^{21}$ + 21.9 (*c*, 1.0 in $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 3.37 (3H, s, CH_3), 3.46-3.64 (2H, m), 3.99 (1H, at, *J* 9.1 Hz), 4.23 (1H, dd, *J* 9.3 Hz, *J* 3.8 Hz), 4.53 (1H, d, *J*

3.3 Hz, H-1), 4.65, 4.77 (2H, ABq, *J* 12.1 Hz, $PhCH_2$), 4.76, 4.86 (2H, ABq, *J* 11.5 Hz, $PhCH_2$), 5.49 (1H, s, PhCH), 7.23-7.44 (15H, m, 15 x ArCH); *m/z* (ES^+) 378 ($M+Na^+$, 100%).

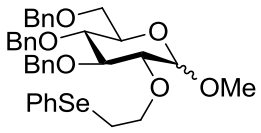
Methyl-2,3,4-*O*-benzyl-α-D-glucopyranose 3.39[26]



3.39

Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside **3.37** (3.35 g, 10.00 mmol) was dissolved in THF (50 ml). The reaction was cooled to 0 C and then $NaCNBH_3$ (15.00 mmol) and 1M HCl in dioxane (15 ml) were added. The mixture was allowed to warm to rt and stirred overnight. T.l.c (petrol/ethyl acetate, 3:1) indicated formation of a single product (R_f 0.4) and complete consumption of starting material (R_f 0.7). The reaction diluted with CH_2Cl_2 (100 ml) and washed with water (100 ml). The aqueous layer was then extracted with CH_2Cl_2 (2 x 100 ml) and the combined organic extracts were washed with saturated sodium bicarbonate (100 ml) then brine (100 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 10:1) to afford Methyl-2,3,4-*O*-benzyl-α-D-glucopyranose **3.39** (2.69 g, 80%) as a colourless gum. These data are in agreement with those reported in the literature; $[\alpha]_D^{18}$ + 25.2 (*c*, 1.0 in $CHCl_3$) [Lit. $[\alpha]_D^{21}$ + 26.2 (*c*, 1.0 in $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 3.40 (3H, s, CH_3), 3.54 (1H, dd, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 10.3 Hz), 3.58-3.75 (4H, m, H-4, H-5, H-6, H-6'), 3.88 (1H, at, *J* 10.3 Hz, H-3), 4.51-5.07 (7H, m, 3 x $PhCH_2$, H-1), 7.28-7.40 (15H, m, 15 x ArCH); *m/z* (ES^+) 380 ($M+Na^+$, 100%).

Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-α/β-D-glucopyranoside 3.40

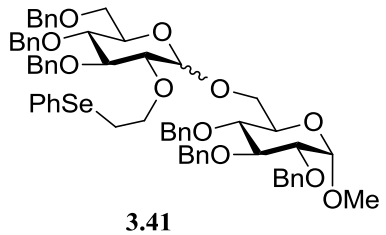


3.40

To a flame-dried round-bottom flask containing activated 3Å molecular sieves (0.100 g) was added a solution of *O*-(3,4,6-Tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-α/β-D-glucopyranosyl) trichloroacetimidate **3.4** (125 mM) and MeOH (2 eq.) in freshly distilled CH_2Cl_2. The reaction mixture was cooled to -40 °C under an argon atmosphere, then TMSOTf (0.1 eq.) was added. The reaction was monitored by t.l.c. (toluene:ethyl acetate, 9:1) until the formation of a major product (R_f 0.5) and complete consumption of starting material (R_f 0.6) was observed. The reaction was quenched with saturated sodium bicarbonate solution and filtered through Celite®. The mixture was diluted with CH_2Cl_2, washed with saturated sodium bicarbonate solution, and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 15:1) to afford Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-α/β-D-glucopyranoside **3.40** as a colourless oil. δ_H (400 MHz, $CDCl_3$) [1:1 mixture of α:β anomers observed] 3.10-3.14 (4H, m, $OCH_2C\underline{H}_2SePh\alpha/\beta$), 3.38-3.50 (4H, m, H-2α, H-2β, H-5α, H-5β), 3.60 (2H, br s, $CH_3\alpha/\beta$), 3.61-3.65 (4H, m, H-3α, H-3β, H-4α, H-4β), 3.68-3.78 (4H, m, H-6α, H-6β, H-6'α, H-6'β), 4.02-4.05 (4H, m, $O\underline{C}H_2CH_2SePh\alpha/\beta$), 4.29 (1H, d, $J_{1,2}$ 7.8 Hz, H-1β), 4.31 (1H, d, $J_{1,2}$ 3.0 Hz, H-1α), 4.51-4.98 (12H, m, 3 × Ar-CHα, 3 × Ar-CHβ), 7.15-7.43 (40H, m, 20 × Ar-CHα, 20 × Ar-CHβ); δ_C (100 MHz, $CDCl_3$) 26.8, 26.9 ($OCH_2\underline{C}H_2SePh\alpha/\beta$), 57.1 ($\underline{C}H_3$), 68.8 (C-

6), 70.5 (O<u>C</u>$H_2$$CH_2$SePhα/β), 75.1, 75.3, 75.8 (3 × Ar<u>C</u>H_2), 74.9 (C-5), 77.8 (C-3), 81.9 (d, C-2), 84.4 (d, C-4), 104.5 (d, C-1), 126.8, 127.6, 127.6, 127.7, 127.8, 127.9, 128.0, 128.4, 128.4, 129.3 (10 × d, 10 × Ar-CH), 138.0, 138.1, 138.5, 142.9 (4 × s, 4 × Ar-C); *m/z* (ES^+) 666 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{36}H_{40}O_6{}^{79}SeNa$ (MNa^+) 671.1888. Found 671.1880). (Found: C, 66.70; H, 6.28. $C_{36}H_{40}O_6Se$ requires C, 66.76; H, 6.23%).

3,4,6-Tri-O-benzyl-2-O-(2-(phenylselenyl)ethyl)-α/β-D-galactopyranosyl-(1→6)-methyl-2,3,4-tri-O-benzyl-α-D-glucopyranoside 3.41

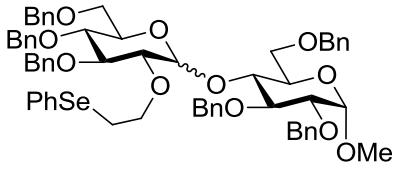


3.41

To a flame-dried round-bottom flask containing activated 3Å molecular sieves (0.100 g) was added a solution of *O*-(3,4,6-Tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-α/β-D-glucopyranosyl) trichloroacetimidate **3.4** (125 mM) and Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside **3.37** (2 eq.) in freshly distilled CH_2Cl_2. The reaction mixture was cooled to -40 °C under an argon atmosphere, then TMSOTf (0.1 eq.) was added. The reaction was monitored by t.l.c. (toluene:ethyl acetate, 9:1) until the formation of a major product (R_f 0.5) and complete consumption of starting material (R_f 0.6) was observed. The reaction was quenched with saturated sodium bicarbonate solution and filtered through Celite®. The mixture was diluted with CH_2Cl_2, washed with saturated sodium bicarbonate solution, and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by

flash column chromatography (toluene:ethyl acetate, 15:1) to afford Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-α/β-D-glucopyranoside **3.40** as a colourless oil. δ_H (400 MHz, $CDCl_3$) [2:1 mixture of α:β anomers observed] 3.08-3.12 (6H, m, $OCH_2C\underline{H}_2SePh\alpha/\beta$), 3.14 (6H, s, OMeα), 3.16 (3H, s, OMeβ), 3.39 (1H, dd, $J_{2,3}$ 9.7 Hz, $J_{3,4}$ 2.9 Hz, H-$3_b\beta$), 3.43 (1H, m, H-$3_a\beta$), 3.50 (2H, dd, $J_{1,2}$ 3.4 Hz, $J_{2,3}$ 9.6 Hz, H-$2_a\alpha$), 3.61-3.66 (2H, m, H-$2_a\beta$, H-$6_b\beta$), 3.73-3.87 (10H, m, H-$6_a\alpha$, H-$6_b\alpha$, H-$6'_b\alpha$, H-$4_a\beta$, H-$4_b\beta$, H-$6_a\beta$, H-$6'_b\beta$), 3.88-3.94 (4H, m, H-$4_a\alpha$, H-$5_a\alpha$), 3.96-4.08 (8H, m, H-$4_b\alpha$, H-$6'_a\alpha$, H-$5_a\beta$, $OC\underline{H}_2CH_2SePh\alpha/\beta$), 4.11 (2H, dd, $J_{2,3}$ 10.2 Hz, $J_{3,4}$ 2.7 Hz, H-$3_b\alpha$), 4.16 (1H, dd, $J_{1,2}$ 7.5 Hz, $J_{2,3}$ 9.7 Hz, H-$2_b\beta$), 4.21-4.32 (10H, m, H-$2_b\alpha$, H-$3_a\alpha$, H-$5_b\alpha$, $PhC\underline{H}_2\alpha$, H-$5_b\beta$, $PhC\underline{H}_2\beta$), 4.34-4.38 (3H, m, $PhC\underline{H}_2\alpha$, H-$6'_a\beta$), 4.44 (2H, d, $J_{1,2}$ 7.5 Hz, H-$1_b\beta$), 4.46-5.13 (28H, m, H-$1_a\alpha$, 8 x $PhC\underline{H}H'\alpha$, H-$1_a\beta$, 10 x $PhC\underline{H}H'\beta$), 5.29 (2H, d, $J_{1,2}$ 3.4 Hz, H-$1_b\alpha$), 7.04-7.45 (105H, m, 35 x Ar-Hα, 35 x Ar-Hβ); δ_C (100 MHz, C_6D_6) 54.9, 55.0, 68.7, 69.0, 70.0, 70.7, 71.3, 72.7, 72.8, 73.0, 73.5, 73.7, 74.7, 74.8, 75.1, 75.2, 75.3, 75.5, 76.2, 78.3, 78.6, 78.6, 79.9, 81.1, 81.2, 82.3, 82.4, 82.7, 98.2, 98.4, 104.6, 127.4, 127.6, 127.7, 127.8, 128.0, 128.1, 128.2, 128.2, 128.4, 128.5, 128.5, 128.6, 128.6, 138.7, 139.2, 139.2, 139.5, 139.7, 139.8; *m/z* (ES^+) 1103 ($M+Na^+$, 100%). (HRMS (ES^+) Calcd. for $C_{63}H_{68}O_{11}{}^{79}SeNa$ (MNa^+) 1103.3825. Found 1103.3830). (Found: C, 70.12; H, 6.39. $C_{63}H_{68}O_{11}Se$ requires C, 70.05; H, 6.35%).

3,4,6-Tri-O-benzyl-2-O-(2-(phenylselenyl)ethyl)-α/β-D-galactopyranosyl-(1→4)-methyl-2,3,6-tri-O-benzyl-α-D-glucopyranoside 3.42

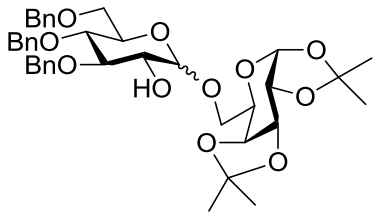


3.42

To a flame-dried round-bottom flask containing activated 3Å molecular sieves (0.100 g) was added a solution of *O*-(3,4,6-Tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-α/β-D-glucopyranosyl) trichloroacetimidate **3.4** (125 mM) and Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside **3.37** (2 eq.) in freshly distilled CH_2Cl_2. The reaction mixture was cooled to -40 °C under an argon atmosphere, then TMSOTf (0.1 eq.) was added. The reaction was monitored by t.l.c. (toluene:ethyl acetate, 9:1) until the formation of a major product (R_f 0.5) and complete consumption of starting material (R_f 0.6) was observed. The reaction was quenched with saturated sodium bicarbonate solution and filtered through Celite®. The mixture was diluted with CH_2Cl_2, washed with saturated sodium bicarbonate solution, and the aqueous layer extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 15:1) to afford Methyl 3,4,6-tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-α/β-D-glucopyranoside **3.42** as a colourless oil. δ_H (400 MHz, $CDCl_3$) [2:1 mixture of α:β anomers observed] 3.09-3.13 (6H, m, $OCH_2C\underline{H}_2SePh\alpha/\beta$), 3.16 (6H, s, OMeα), 3.18 (3H, s, OMeβ), 3.39 (1H, dd, $J_{2,3}$ 9.5 Hz, $J_{3,4}$ 2.2 Hz, H-$3_b\beta$), 3.43-3.47 (2H, m, H-$3_a\beta$, H-$2_a\alpha$), 3.61-3.66 (2H, m, H-$2_a\beta$, H-$6_b\beta$), 3.70-3.84 (10H, m, H-$6_a\alpha$, H-$6_b\alpha$, H-$6'_b\alpha$, H-$4_a\beta$, H-$4_b\beta$, H-$6_a\beta$, H-$6'_b\beta$), 3.88-3.94 (4H, m, H-$4_a\alpha$, H-$5_a\alpha$), 3.93-4.05 (8H, m, H-$4_b\alpha$, H-$6'_a\alpha$, H-$5_a\beta$,

OC<u>H</u>$_2$CH$_2$SePhα/β), 4.09 (2H, dd, $J_{2,3}$ 10.0 Hz, $J_{3,4}$ 3.0 Hz, H-3$_b$α), 4.16 (1H, dd, $J_{1,2}$ 7.1 Hz, $J_{2,3}$ 9.7 Hz, H-2$_b$β), 4.21-4.32 (10H, m, H-2$_b$α, H-3$_a$α, H-5$_b$α, PhC<u>H</u>$_2$α, H-5$_b$β, PhC<u>H</u>$_2$β), 4.34-4.38 (3H, m, PhC<u>H</u>$_2$α, H-6'$_a$β), 4.47 (2H, d, $J_{1,2}$ 7.1 Hz, H-1$_b$β), 4.53-5.10 (28H, m, H-1$_a$α, 8 x PhC<u>H</u>H'α, H-1$_a$β, 10 x PhC<u>H</u>H'β), 5.25 (2H, d, $J_{1,2}$ 3.4 Hz, H-1$_b$α), 7.08-7.44 (105H, m, 35 x Ar-Hα, 35 x Ar-Hβ); δ_C (100 MHz, C_6D_6) 54.8, 55.2, 68.6, 69.2, 70.1, 70.4, 71.6, 72.6, 72.9, 73.0, 73.5, 73.6, 74.7, 74.8, 75.1, 75.2, 75.4, 75.5, 76.0, 78.0, 78.6, 78.7, 79.4, 80.9, 81.1, 82.3, 82.5, 82.7, 98.2, 98.7, 104.5, 127.1, 127.6, 127.7, 127.8, 128.0, 128.1, 128.2, 128.3, 128.3, 128.4, 128.5, 128.6, 128.8, 138.7, 139.0, 139.1, 139.3, 139.3, 139.4; *m/z* (ES^+) 1103 ($M+Na^+$, 100%). (HRMS (ES^+) Calcd. for $C_{63}H_{68}O_{11}{}^{79}SeNa$ (MNa^+) 1103.3825. Found 1103.3830). (Found: C, 70.12; H, 6.39. $C_{63}H_{68}O_{11}Se$ requires C, 70.05; H, 6.35%).

3,4,6-Tri-*O*-benzyl-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside 2.36[17,18]



2.36

Method 1

3,4,6-Tri-*O*-benzyl-2-*O*-(2-(phenylselenyl)ethyl)-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside **3.32** (α:β ratio 5:1) (0.223 g, 0.254 mmol) was dissolved in freshly distilled THF (10 ml) under an atmosphere of argon. The reaction was cooled to 0 °C and H_2O_2 (1 ml, 30% solution in THF) was added. The reaction was warmed to rt and for 1 h, after which time t.l.c. (toluene:ethyl acetate, 9:1) indicated the formation of a major product (R_f 0.5) and complete

consumption of starting material (R_f 0.4). NIS (0.381 mmol) and water (1 ml) were added and the reaction stirred for 16 h, after which t.l.c indicated the formation of a single product (R_f 0.2) The reaction was diluted with CH_2Cl_2 (20 ml) and washed with water (20 ml). The aqueous layer was then extracted with CH_2Cl_2 (2 x 20 ml) and the combined organic extracts were washed with saturated sodium bicarbonate (20 ml) then brine (20 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 6:1) to afford α/β-D-glucopyranosyl--(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **2.36** (0.137 g, 76%) as a colourless oil. These data are in agreement with those reported in the literature; δ_H (400 MHz, $CDCl_3$) [5:1 mixture of α:β anomers observed, major α-anomer quoted] 1.34, 1.35, 1.45, 1.54 (12H, 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* 9.9 Hz, *J* 3.0 Hz, *J* 2.2 Hz, H-5_b), 3.91 (1H, m, H-$6'_a$), 3.99-4.01 (1H, m, H-5_a), 4.25 (1H, dd, *J* 7.9 Hz, *J* 1.9 Hz H-4_a), 4.34 (1H, dd, $J_{1,2}$ 4.9 Hz, $J_{2,3}$ 2.2 Hz, H-2_a), 4.63 (1H, dd, $J_{2,3}$ 2.2 Hz, $J_{3,4}$ 7.8 Hz, H-3_a), 4.49, 4.83 (2H, ABq, *J* 10.3 Hz, $PhCH_2$), 4.50, 4.64 (2H, ABq, *J* 11.7 Hz, $PhCH_2$), 4.93 (1H, d, $J_{1,2}$ 3.2 Hz, H-1_b), 4.82, 4.98 (2H, ABq, *J* 10.7 Hz, $PhCH_2$), 5.53 (1H, d, $J_{1,2}$ 4.9 Hz, H-1_a), 7.12-7.41 (15H, m 15 x Ar-H); *m/z* (ES^+) 715 ($M+Na^+$, 100%).

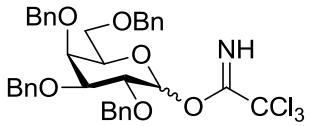
Method 2

3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodoethyl)-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside **3.33** (α:β ratio 3.5:1) (0.215 g, 0.254 mmol) was dissolved in freshly distilled THF (10 ml) under an atmosphere of argon. The reaction was cooled to 0 °C and H_2O_2 (1 ml, 30% solution in THF) was added. The reaction was warmed to rt and for 1 h, after which time t.l.c. (toluene:ethyl acetate, 9:1)

indicated the formation of a major product (R_f 0.5) and complete consumption of starting material (R_f 0.4). NIS (0.381 mmol) and water (1 ml) were added and the reaction stirred for 16 h, after which t.l.c indicated the formation of a single product (R_f 0.2) The reaction was diluted with CH_2Cl_2 (20 ml) and washed with water (20 ml). The aqueous layer was then extracted with CH_2Cl_2 (2 x 20 ml) and the combined organic extracts were washed with saturated sodium bicarbonate (20 ml) then brine (20 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 6:1) to afford α/β-D-glucopyranosyl--(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **2.36** (0.128 g, 73%) as a colourless oil. These data are in agreement with those reported in the literature.

5.4 Chapter 4

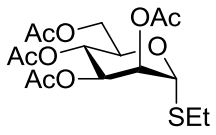
O-(2,3,4,6-Tetra-O-benzyl-α/β-D-galactopyranosyl) trichloroacetimidate 4.3[27,28]



4.3

2,3,4,6-Tetra-*O*-benzyl-α/β-D-galactopyranose (1.00 g, 1.850 mmol) was dissolved in freshly distilled CH_2Cl_2 (20 ml) and cooled to 0 °C under an argon atmosphere. DBU (0.114 ml, 0.740 mmol) was added followed by trichloroacetonitrile (0.946 ml, 9.248 mmol). After 2 h, t.l.c (petrol:ethyl acetate, 3:1, with 1% added triethylamine) indicated the formation of two products (R_f 0.58 and R_f 0.39) and complete consumption of starting material (R_f 0.16). The reaction was concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1, with 1% added triethylamine) to afford *O*-(2,3,4,6-Tetra-*O*-benzyl-α/β-D-galactopyranosyl) trichloroacetimidate **2** (1.10 g, 87%) as a pale yellow oil. These data are in agreement with those reported in the literature; (400 MHz, $CDCl_3$) [7.9:1 mixture of α:β anomers observed] 3.49-3.71 (18.8H, m), 3.77 (1H, at, *J* 6.6 Hz), 3.99-4.21 (25.7H, m), 4.27 (7.9H, dd, *J* 10.0 Hz, *J* 3.4 Hz), 4.39-4.50 (17.8H, m), 4.74-5.01 (43.5H, m), 5.78 (1H, d, $J_{1,2}$ 8.1 Hz, H-1β), 6.55 (1H, d, $J_{1,2}$ 3.5 Hz, H-1α), 7.25-7.38 (178H, m), 8.54 (7.9H, br s, NHβ), 8.65 (1H, br s, NHα); δ_C (100 MHz, $CDCl_3$) 60.4, 68.3, 72.2, 72.9, 73.0, 73.5, 74.4, 74.6, 74.8, 75.0, 75.3, 75.9, 77.9, 78.1, 82.2, 91.5, 95.2, 98.7, 127.5, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.2, 128.3, 128.3, 128.4, 128.5, 137.8, 138.3, 138.4, 138.5, 138.5, 161.3; *m/z* (ES^+) 604 ($M+Na^+$, 100%).

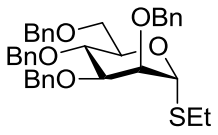
Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside 4.6[29]



4.6

D-mannose pentaacetate (11.1 g, 28.4 mmol) and ethanethiol (6.32 mL, 85.3 mmol) were dissolved in anhydrous CH_2Cl_2 (200 mL). Boron trifluoride diethyl etherate (10.8 mL, 85.3 mmol) was added and the mixture stirred at rt under an atmosphere of argon. After 16 h t.l.c. (petrol:ethyl acetate 2:1) indicated formation of a major product (R_f 0.35) and consumption of starting material (R_f 0.25). The reaction mixture was quenched by addition of sodium hydrogen carbonate (200 mL of a saturated solution), stirred for a further 2 h, separated and the organic layer dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate 2:1) to afford ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside **4.6** (5.86 g, 53%) as a white crystalline solid. These data are in agreement with those reported in the literature; m.p. 104-105°C [lit. 107-108°C]; $[\alpha]_D^{20}$ + 115 (*c*, 1.2 in $CHCl_3$) [Lit. $[\alpha]_D^{20}$ + 104 (*c*, 0.88 in $CHCl_3$)]; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, *J* 7.4 Hz, $SCH_2C\underline{H}_3$), 1.99, 2.05, 2.10, 2.17 (12H, 4 x s, 4 x CH_3), 2.57-2.72 (2H, m, $SC\underline{H}_2CH_3$), 4.10 (1H, dd, $J_{5,6}$ 2.2 Hz, $J_{6,6'}$ 12.2.Hz, H-6), 4.32 (1H, dd, $J_{5,6'}$ 5.3 Hz, H-6'), 4.40 (1H, ddd, $J_{4,5}$ 9.2 Hz, H-5), 5.25-5.35 (4H, m, H-1, H-2, H-3, H-4).

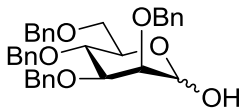
Ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-mannopyranoside 4.7[29]



4.7

A solution of sodium (0.32 g) in methanol (20 ml) was added to a stirred solution of ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside **4.6** (5.00 g, 12.69 mmol) in methanol (80 ml). After 1 h, t.l.c (petrol:ethyl acetate, 1:1) indicated the formation of a single product (R_f 0) and complete consumption of starting material (R_f 0.7). The reaction mixture was concentrated *in vacuo* and subsequently left under high vacuum for 2 h. The residue was then dissolved in anhydrous DMF (100 ml) and slowly added to a suspension of sodium hydride (6.66 g, 166.6 mmol) in anhydrous DMF (100 ml) at 0 °C under an argon atmosphere. Benzyl bromide (14.9 ml, 125.0 mmol) was then added slowly to the reaction mixture. Once the addition of benzyl bromide was complete, the reaction mixture was allowed to warm to room temperature. After 16 h, t.l.c (petrol:ethyl acetate, 1:1) indicated the formation of a single product (R_f 0.9) and complete consumption of starting material (R_f 0). Methanol (50 ml) was added portion-wise in order to quench the reaction. The reaction was then concentrated *in vacuo*. The resulting residue was dissolved in ether (200 ml), washed with water (500 ml), and the aqueous layer extracted with ether (2 x 200 ml). The combined organic extracts were washed with brine (200 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford Ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-mannopyranoside **4.7** (Crude 6.89 g, 93%). The crude material was carried forward to the next reaction unpurified.

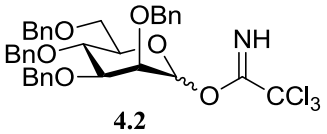
2,3,4,6-Tetra-*O*-benzyl-α/β-D-mannopyranose 4.8[30]



4.8

Ethyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-mannopyranoside **4.7** (1.080 g, 1.85 mmol) was dissolved in acetone-H_2O (16.5 mL, 10:1) and the mixture cooled to 0°C. N-bromosuccinimide (0.838 g, 4.71 mmol) was added and the mixture stirred vigorously. After 1 h, t.l.c (toluene:ethyl acetate, 9:1) indicated the formation of a single major product (R_f 0.1) and complete consumption of starting material (R_f 0.8). The reaction mixture was diluted with CH_2Cl_2 (30 ml), washed with saturated sodium bicarbonate (30 ml), and the aqueous layer extracted with CH_2Cl_2 (2 x 15 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 1:1) to afford 2,3,4,6-Tetra-*O*-benzyl-α/β-D-mannopyranose **4.8** (0.970 g, 97%) as a clear oil. These data are in agreement with those reported in the literature; δ_H (400 MHz, $CDCl_3$) [9:1 mixture of α:β anomers observed, major α-anomer quoted] 3.66-3.90 (5H, m, H-2, H-3, H-5, H-6, H-6'), 4.09 (1H, at, *J* 9.7 Hz, H-4), 4.40-4.93 (8H, m, 4 x $PhCH_2$), 5.22 (1H, d, $J_{1,2}$ 1.5 Hz, H-1), 7.02-7.43 (20H, m, 20 x ArCH); *m/z* (ES^+) 563 ($M+Na^+$, 100%).

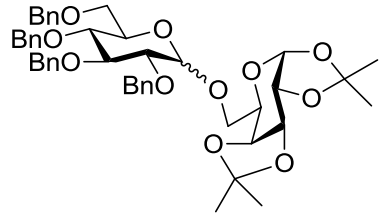
O-(2,3,4,6-Tetra-O-benzyl-α/β-D-mannopyranosyl) trichloroacetimidate 4.2



4.2

2,3,4,6-Tetra-*O*-benzyl-α/β-D-mannopyranose **4.8** (1.00 g, 1.850 mmol) was dissolved in freshly distilled CH_2Cl_2 (20 ml) and cooled to 0 °C under an argon atmosphere. DBU (0.114 ml, 0.740 mmol) was added followed by trichloroacetonitrile (0.946 ml, 9.248 mmol). After 2 h, t.l.c (petrol:ethyl acetate, 3:1, with 1% added triethylamine) indicated the formation of two products (R_f 0.58 and R_f 0.39) and complete consumption of starting material (R_f 0.16). The reaction was concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1, with 1% added triethylamine) to afford *O*-(2,3,4,6-Tetra-*O*-benzyl-α/β-D-mannopyranosyl) trichloroacetimidate **4.2** (1.17 g, 90%) as a pale yellow oil; (400 MHz, $CDCl_3$) [15:1 mixture of α:β anomers observed, major α-anomer quoted] 3.69-4.12 (5H, m, H-2, H-3, H-5, H-6, H-6'), 4.18 (1H, at, *J* 9.3 Hz, H-4), 4.49-4.94 (8H, m, 4 x $PhCH_2$), 6.39 (1H, d, $J_{1,2}$ 1.6 Hz, H-1), 7.14-7.48 (20H, m, 20 x ArCH), 8.54 (1H, s, NH); *m/z* (ES^+) 604 ($M+Na^+$, 100%).

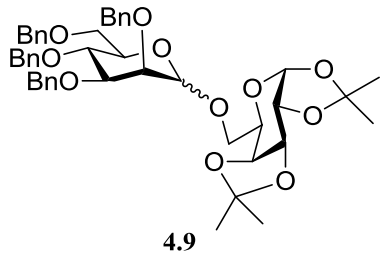
2,3,4,6-Tetra-*O*-benzyl-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-glucopyranoside 2.31[13]



2.31

A solution of *O*-(2,3,4,6-Tetra-*O*-benzyl-α/β-D-glucoopyranosyl) trichloroacetimidate **2.30** (50 mg, 0.073 mmol) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside **2.11** (38 mg, 0.146 mmol) in freshly distilled toluene (1 mL) were added to a flame-dried round-bottomed flask containing activated 3 Å molecular sieves (100 mg) under argon. The reaction mixture was stirred for 10 min, before the reaction was activated by addition of either TMSOTf (2μl, 0.011 mmol) or (*R*)/(*S*)-**1** (8.5 mg, 0.011 mmol). When t.l.c (petrol:ethyl acetate, 4:1) indicated the complete consumption of starting material (R_f 0.4) and the formation of product (R_f 0.2) the reaction was quenched by the addition of triethylamine and filtered through Celite®. The mixture was then concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 3:1) to afford. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 15:1) to afford 2,3,4,6-Tetra-*O*-benzyl-α/β-D-glucopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside **2.31** as a colourless oil; data as previously described.

2,3,4,6-Tetra-*O*-benzyl-α/β-D-mannopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-glucopyranoside 4.9[31]

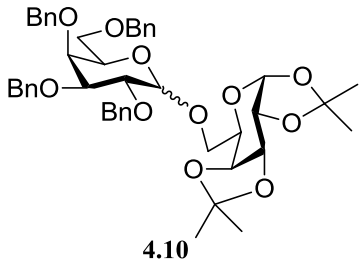


4.9

A solution of *O*-(2,3,4,6-Tetra-*O*-benzyl-α/β-D-mannopyranosyl) trichloroacetimidate **4.2** (50 mg, 0.073 mmol) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside **2.11** (38 mg, 0.146 mmol) in freshly distilled toluene (1 mL) were added to a flame-dried round-bottomed flask containing activated 3 Å molecular sieves (100 mg) under argon. The reaction mixture was stirred for 10 min, before the reaction was activated by addition of either TMSOTf (2μl, 0.011 mmol) or (*R*)/(*S*)-**1** (8.5 mg, 0.011 mmol). When t.l.c (petrol:ethyl acetate, 4:1) indicated the complete consumption of starting material (R_f 0.4) and the formation of product (R_f 0.2) the reaction was quenched by the addition of triethylamine and filtered through Celite®. The mixture was then concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 3:1) to afford. The resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 15:1) to afford 2,3,4,6-Tetra-*O*-benzyl-α/β-D-gmannopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside **4.9** as a colourless oil. These data are in agreement with those reported in the literature; δ_H (400 MHz, $CDCl_3$) [7:1 mixture of α:β anomers observed, major α anomer quoted] 1.32 (6H, s, 2 x CH_3), 1.43 (3H, s, CH_3), 1.50 (3H, s, CH_3), 3.66–3.80 (4H, m), 3.81–3.86 (2H, m), 3.89 (1H, br s), 3.92–4.06 (3H, m), 4.14 (1H, dd, *J* 7.9, *J* 1.3 Hz), 4.29 (1H, dd, *J* 5.3, *J* 2.6 Hz), 4.48-4.85

(8H, m, 4 x $PhCH_2$), 5.02 (1H, d, $J_{1,2}$ 1.3 Hz, H-1_a), 5.51 (1H, d, $J_{1,2}$ 5.3 Hz), 7.13–7.40 (20H, m, 20 x ArCH); *m/z* (ES^+) 800 ($M+NH_4^+$, 100%).

2,3,4,6-Tetra-*O*-benzyl-α/β-D-galactopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside 4.10

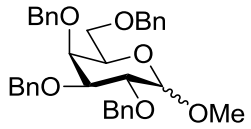


4.10

A solution of *O*-(2,3,4,6-Tetra-*O*-benzyl-α/β-D-galactopyranosyl) trichloroacetimidate **4.3** (50 mg, 0.073 mmol) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside **2.11** (38 mg, 0.146 mmol) in freshly distilled toluene (1 mL) were added to a flame-dried round-bottomed flask containing activated 3 Å molecular sieves (100 mg) under argon. The reaction mixture was stirred for 10 min, before the reaction was activated by addition of either TMSOTf (2µl, 0.011 mmol) or (*R*)/(*S*)-**1** (8.5 mg, 0.011 mmol). When t.l.c (petrol:ethyl acetate, 4:1) indicated the complete consumption of starting material (R_f 0.4) and the formation of product (R_f 0.2) the reaction was quenched by the addition of triethylamine and filtered through Celite®. The mixture was then concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 3:1) to afford 2,3,4,6-Tetra-*O*-benzyl-α/β-D-galactopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside **4.10** as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) [Data provided for 1:7 mixture of α:β anomers] 1.32 (48H, s), 1.45 (24H, s), 1.50 (24H, s), 3.50-3.59 (28H, m), 3.70 (7H, dd, *J* 10.7 Hz, *J* 7.5 Hz), 3.74-3.79 (2H, m), 3.84 (7H, dd, *J* 9.9 Hz, *J* 7.9 Hz), 3.90 (7H, br d, *J* 2.7 Hz), 3.95-3.98 (1H, m), 4.01-4.10 (13H, m), 4.14

(7H, dd, *J* 10.7 Hz, *J* 3.4 Hz), 4.23 (7H, dd, *J* 7.9 Hz, *J* 2.1 Hz), 4.30-4.34 (9H, m), 4.39-4.52 (24H, m), 4.59-4.63 (16H, m), 4.71-4.86 (24H, m), 4.93-4.96 (8H, m), 5.03 (1H, d, $J_{1,2}$ 3.4 Hz, H-$1_b\alpha$), 5.07 (7H, d, *J* 10.9 Hz), 5.52 (1H, d, $J_{1,2}$ 5.1 Hz, H-$1_a\alpha$), 5.58 (7H, d, $J_{1,2}$ 4.8 Hz, H-$1_a\beta$), 7.23-7.41 (146H, m), 7.45-7.48 (14H, m); δ_C (100 MHz, $CDCl_3$) 24.4, 25.1, 26.0, 26.0, 67.4, 68.6, 69.6, 70.5, 70.7, 71.5, 73.1, 73.3, 73.5, 74.5, 74.7, 79.1, 81.9, 96.4, 104.7, 108.6, 109.3, 127.3, 127.5, 127.5, 127.8, 127.9, 128.1, 128.3, 128.4, 128.4, 128.6, 137.9, 138.6, 139.0; *m/z* (ES^+) 800 ($M+NH_4^+$, 100%).

Methyl 2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranoside 4.12[32]

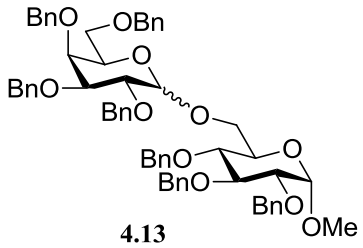


4.12

A solution of *O*-(2,3,4,6-Tetra-*O*-benzyl-α/β-D-galactopyranosyl) trichloroacetimidate **4.3** (50 mg, 0.073 mmol) in freshly distilled toluene (1 mL) was added to a flame-dried round-bottomed flask containing activated 3 Å molecular sieves (100 mg) under argon. Anhydrous MeOH (6 μl, 0.146 mmol) was added and the reaction mixture was stirred for 10 min, before the reaction was activated by addition of either TMSOTf (2μl, 0.011 mmol) or (*R*)-**1** (8.5 mg, 0.011 mmol). When t.l.c (petrol:ethyl acetate, 4:1) indicated the complete consumption of starting material (R_f 0.4) and the formation of a single product (R_f 0.3) the reaction was quenched by the addition of triethylamine and filtered through Celite®. The mixture was then concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford methyl 2,3,4,6-tetra-*O*-benzyl-α/β-D-galactopyranoside **4.12** as a pale yellow oil. These data are in agreement with

those reported in the literature; δ_H (400 MHz, $CDCl_3$) [Data provided for 1:10 mixture of α:β anomers] 3.39 (3H, s, OCH_3α), 3.51-3.55 (20H, m, H-3β, H-5β), 3.56 (30H, s, OCH_3β), 3.57-3.63 (22H, m, H-6α, H-6α', H-6β, H-6'β), 3.82 (10H, dd, $J_{1,2}$ 7.5 Hz, $J_{2,3}$ 9.7 Hz, H-2β), 3.91 (10H, br d, *J* 2.4 Hz, H-4β), 3.93-3.99 (3H, m, H-3α, H-4α, H-5α), 4.03-4.07 (1H, m, H-2α), 4.29 (10H, d, $J_{1,2}$ 7.5 Hz, H-1β), 4.39-4.51 (22H, m, 2 x PhC<u>H</u>H'α, 2 x PhC<u>H</u>H'β), 4.58 (1H, d, *J* 11.6 Hz, PhC<u>H</u>H'α), 4.64 (10H, d, *J* 11.6 Hz, PhC<u>H</u>H'β), 4.69-4.78 (33H, m, H-1α, 2 x PhC<u>H</u>H'α, 3 x PhC<u>H</u>H'β), 4.84-4.88 (2H, m, 2 x PhC<u>H</u>H'α), 4.92 (10H, d, *J* 10.9 Hz, PhC<u>H</u>H'β), 4.94-4.97 (11H, m, PhC<u>H</u>H'α, PhC<u>H</u>H'β), 7.25-7.40 (220H, m, 20 x Ar-Hα, 20 x Ar-Hβ); δ_C (100 MHz, $CDCl_3$) 57.0, 68.9, 73.0, 73.4, 73.4, 73.6, 74.5, 75.1, 79.6, 82.1, 105.0, 127.5, 127.5, 127.8, 127.9, 128.1, 128.1, 128.3, 128.4, 128.4, 137.9, 138.5, 138.6, 138.8; *m/z* (ES^+) 572 ($M+NH_4^+$, 100%).

2,3,4,6-Tetra-*O*-benzyl-α/β-D-galactopyranosyl-(1→6)-methyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 4.13[33]

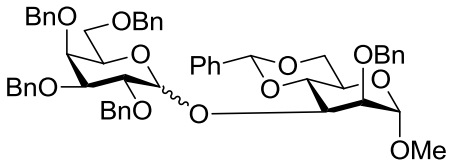


4.13

A solution of *O*-(2,3,4,6-Tetra-*O*-benzyl-α/β-D-galactopyranosyl) trichloroacetimidate **4.3** (50 mg, 0.073 mmol) and methyl-2,3,4-*O*-benzyl-α-D-glucopyranose **3.37** (68 mg, 0.146 mmol) in freshly distilled toluene (1 mL) were added to a flame-dried round-bottomed flask containing activated 3 Å molecular sieves (100 mg) under argon. The reaction mixture was stirred for 10 min, before the reaction was activated by addition of either TMSOTf (2μl, 0.011 mmol) or (*R*)-**1** (8.5

mg, 0.011 mmol). When t.l.c (petrol:ethyl acetate, 4:1) indicated the complete consumption of starting material (R_f 0.4) and the formation of product (R_f 0.3) the reaction was quenched by the addition of triethylamine and filtered through Celite®. The mixture was then concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford 2,3,4,6-Tetra-*O*-benzyl-α/β-D-galactopyranosyl-(1→6)-methyl-2,3,4-tri-*O*-benzyl- α-D-glucopyranoside **4.13** as a pale yellow oil. These data are in agreement with those reported in the literature; δ_H (400 MHz, C_6D_6) [Data provided for 1:1.2 mixture of α:β anomers] 3.12 (3H, s, OMeα), 3.14 (3.6H, s, OMeβ), 3.39 (1.2H, dd, $J_{2,3}$ 9.7 Hz, $J_{3,4}$ 2.9 Hz, H-3_bβ), 3.43 (1.2H, m, H-3_aβ), 3.50 (1H, dd, $J_{1,2}$ 3.4 Hz, $J_{2,3}$ 9.6 Hz, H-2_aα), 3.61-3.66 (2.4H, m, H-2_aβ, H-6_bβ), 3.73-3.87 (7.8H, m, H-6_aα, H-6_bα, H-6'$_b$α, H-4_aβ, H-4_bβ, H-6_aβ, H-6'$_b$β), 3.88-3.94 (2H, m, H-4_aα, H-5_aα), 3.96-4.08 (3.2H, m, H-4_bα, H-6'$_a$α, H-5_aβ), 4.11 (1H, dd, $J_{2,3}$ 10.2 Hz, $J_{3,4}$ 2.7 Hz, H-3_bα), 4.16 (1.2H, dd, $J_{1,2}$ 7.5 Hz, $J_{2,3}$ 9.7 Hz, H-2_bβ), 4.21-4.32 (8.6H, m, H-2_bα, H-3_aα, H-5_bα, PhC$\underline{H}_2$α, H-5_bβ, PhC$\underline{H}_2$β), 4.34-4.38 (3.2H, m, PhC$\underline{H}_2$α, H-6'$_a$β), 4.44 (1.2H, d, $J_{1,2}$ 7.5 Hz, H-1_bβ), 4.46-5.13 (26.6H, m, H-1_aα, 10 x PhC$\underline{H}$H'α, H-1_aβ, 12 x PhC$\underline{H}$H'β), 5.29 (1H, d, $J_{1,2}$ 3.4 Hz, H-1_bα), 7.04-7.20 (47.4H, m, 21 x Ar-Hα, 22 x Ar-Hβ), 7.24-7.45 (29.6H, m, 14 x Ar-Hα, 13 x Ar-Hβ); δ_C (100 MHz, C_6D_6) 54.9, 55.0, 68.7, 69.0, 70.0, 70.7, 71.3, 72.7, 72.8, 73.0, 73.5, 73.7, 74.7, 74.8, 75.1, 75.2, 75.3, 75.5, 76.2, 78.3, 78.6, 78.6, 79.9, 81.1, 81.2, 82.3, 82.4, 82.7, 98.2, 98.4, 104.6, 127.4, 127.6, 127.7, 127.8, 128.0, 128.1, 128.2, 128.2, 128.4, 128.5, 128.5, 128.6, 128.6, 138.7, 139.2, 139.2, 139.5, 139.7, 139.8; *m/z* (ES^+) 1004 ($M+NH_4^+$, 100%).

2,3,4,6-Tetra-*O*-benzyl-α/β-D-glucopyranosyl-(1→2)-methyl-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside 4.14

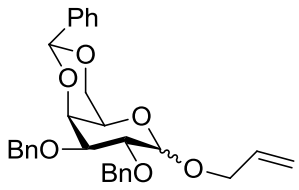


4.14

A solution of *O*-(2,3,4,6-Tetra-*O*-benzyl-α/β-D-galactopyranosyl) trichloroacetimidate **4.3** (50 mg, 0.073 mmol) and methyl-2-*O*-benzyl-4,6-di-*O*-benzylidene-α-D-mannopyranoside **2.25** (54 mg, 0.146 mmol) in freshly distilled toluene (1 mL) were added to a flame-dried round-bottomed flask containing activated 3 Å molecular sieves (100 mg) under argon. The reaction mixture was stirred for 10 min, before the reaction was activated by addition of either TMSOTf (2μl, 0.011 mmol) or (*R*)/(*S*)-**1** (8.5 mg, 0.011 mmol). When t.l.c (toluene:ethyl acetate, 4:1) indicated the complete consumption of starting material (R_f 0.7) and the formation of a single major product (R_f 0.5) the reaction was quenched by the addition of triethylamine and filtered through Celite®. The mixture was then concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (toluene:ethyl acetate, 12:1) to afford 2,3,4,6-Tetra-*O*-benzyl-α/β-D-glucopyranosyl-(1→2)-methyl-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **4.14** as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) [Data provided for 1:6 mixture of α:β anomers] 3.31 (18H, s, $OCH_3\beta$), 3.32 (3H, s, $OCH_3\alpha$), 3.38 (6H, dd, *J* 8.6 Hz, *J* 5.1 Hz), 3.42-3.49 (8H, m), 3.52 (6H, dd, *J* 9.6 Hz, *J* 2.8 Hz), 3.55-3.59 (1H, m), 3.69 (6H, at, *J* 8.3 Hz), 3.73-3.90 (29H, m), 3.95 (6H, br d, *J* 2.5 Hz), 4.00 (1H, dd, *J* 10.0 Hz, *J* 3.7 Hz), 4.22-4.38 (32H, m), 4.51 (1H, d, *J* 12.1 Hz, PhC<u>H</u>H'α), 4.56 (6H, d, $J_{1,2}$ 7.8 Hz, H-$1_b\beta$), 4.59-4.87 (59H, m), 4.95 (6H, d, *J* 11.6 Hz, PhC<u>H</u>H'β), 5.44 (1H, s, PhC<u>H</u>α),

5.54 (1H, d, $J_{1,2}$ 3.8 Hz, H-$1_b\alpha$), 5.61 (6H, s, PhC<u>H</u>β), 7.15-7.39 (196H, m), 7.49-7.51 (14H, m); δ_C (100 MHz, $CDCl_3$) [major β anomer quoted] 54.8 (O<u>C</u>H_3), 64.2, 68.2, 68.8, 72.4, 73.2, 73.5, 74.5, 74.9, 76.7, 78.2, 79.6, 82.8, 100.3 (C-1_a), 101.4 (Ph<u>C</u>H), 103.6 (C-1_b), 125.3, 126.2, 126.3, 127.2, 127.2, 127.3, 127.5, 127.5, 127.8, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.7, 129.0 (17 x Ar<u>C</u>H), 137.8, 137.9, 139.0 (3 x Ar<u>C</u>); *m/z* (ES^+) 917 ($M+Na^+$, 100%). (HRMS (ES^+) Calcd. for $C_{55}H_{58}O_{11}Na$ (MNa^+) 917.3877. Found 917.3872).

Allyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α/β-D-galactopyranoside 4.16[34]

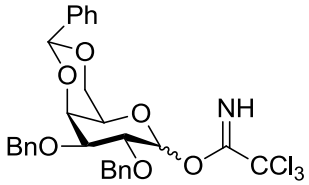


4.16

Benzaldehyde dimethyl acetal (3.19 ml, 21.25 mmol) was added to a solution of D-Galactose **4.15** (3.19 g, 17.71 mmol) and camphor sulfonic acid (0.041 g, 0.177 mmol) in DMF (50 ml). The resulting solution was heated to 60 °C on a rotary evaporator under a pressure of 250 mbar. After 1.5h, t.l.c (ethyl acetate) indicated the formation of a single product (R_f 0.30) and complete consumption starting material (R_f 0). The crude reaction mixture was diluted with DMF (50 ml) and allyl bromide (2.30 ml, 26.57 mmol). The mixture was cooled to 0 °C and NaH (60% in mineral oil, 0.850 g, 21.25 mmol) was added. After addition was complete, the reaction mixture was stirred for 0.5 h at RT and then diluted with benzyl bromide (8.43 ml, 70.84 mmol). The reaction was again cooled to 0 °C and further NaH (60% in mineral oil, 2.125 g, 53.13 mmol) added. After 3.5 h at RT, t.l.c (petrol:ethyl acetate, 3:1) indicated the formation of two major products (R_f 0.33 and R_f 0.26). Methanol (25 ml)

was added portion-wise in order to quench the reaction. The reaction was then concentrated *in vacuo*. The resulting residue was dissolved in ether (100 ml), washed with water (200 ml), and the aqueous layer extracted with ether (2 x 100 ml). The combined organic extracts were washed with brine (200 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 3:1) to afford Allyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α/β-D-galactopyranoside **4.16** (5.2 g, 60%) as a white solid . These data are in agreement with those reported in the literature; δ_H (400 MHz, $CDCl_3$) [4:1 mixture of α:β anomers observed] 3.33 (4H, m), 3.39 (1H, m), 3.45-3.54 (2H, m), 3.57 (4H, dd, *J* 9.6 Hz, *J* 3.8 Hz), 3.70-3.85 (3H, m), 3.90 (4H, dd, *J* 9.6 Hz, *J* 7.9 Hz), 3.94-3.96 (1H, m), 4.00-4.19 (13H, m), 4.22-4.53 (11H, m), 4.63-4.82 (15H, m), 4.88-5.04 (4H, m), 5.15-5.23 (5H, m), 5.29-5.39 (5H, m), 5.50-5.58 (5H, m), 5.91-6.03 (5H, m), 7.21-7.60 (75H, m); δ_C (100 MHz, $CDCl_3$) [major α anomer quoted] 66.4, 69.2, 70.2, 72.1, 74.0, 75.3, 78.5, 79.2, 101.3, 102.7, 117.2, 126.5, 127.5, 127.7, 127.8, 127.9, 128.1, 128.1, 128.3, 128.3, 128.9, 134.3, 135.3, 137.8, 138.5, 138.9; *m/z* (ES^+) 485 ($M+Na^+$, 100%).

_O_-(2,3-di-_O_-benzyl-4,6-_O_-benzylidene-α-D-galactopyranosyl) trichloroacetimidate 4.17



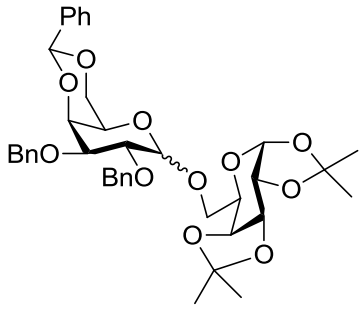
4.17

(1,5-Cyclooctadiene)bis(methyl-diphenylphosphine)iridium(I) hexafluorophosphate (0.073 g, 0.086 mmol) was dissolved in freshly distilled THF (10 ml). The reaction

mixture was placed under a hydrogen atmosphere, resulting in a colour change from red to colourless. Allyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α/β-D-galactopyranoside **4.16** (0.843 g, 1.725 mmol) was then added as a solution in freshly distilled THF (10 ml). After 16h, N-Iodosuccinimide (2.04 g, 8.625 mmol) was added followed by H_2O (5 ml). After 16 h, t.l.c (petrol:ethyl acetate, 1:1) indicated the formation of a single major product (R_f 0.2) and complete consumption of starting material (R_f 0.5). The reaction was diluted with CH_2Cl_2 (40 ml) and the organic layer washed with sodium thiosulfate (10% solution, 40 ml). The aqueous layer was extracted with CH_2Cl_2 (2 x 20 ml). The combined organic layers were washed with saturated sodium bicarbonate solution (40 ml), then brine (40 ml), dried ($MgSO_4$), filtered concentrated *in vacuo*. The residue was dried under high vacuum for 2 h, and then the crude mixture of 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α/β-D-galactopyranoses was dissolved in freshly distilled CH_2Cl_2 (20 ml) and cooled to 0 °C under an argon atmosphere. DBU (0.107 ml, 0.690 mmol) was added followed by trichloroacetonitrile (0.882 ml, 8.625 mmol). After 2 h, t.l.c (petrol:ethyl acetate, 4:1, with 1% added triethylamine) indicated the formation of a single major product (R_f 0.3) and complete consumption of starting material (R_f 0.05). The reaction was concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1, with 1% added triethylamine) to afford *O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranosyl) trichloroacetimidate **4.17** (0.590 g, 57%, 2 steps) as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) [10:1 mixture of α:β anomers observed] 3.67-3.70 (1H, m), 3.84 (10H, br s), 3.96-4.14 (23H, m), 4.23-4.31 (32H, m), 4.64-4.94 (44H, m), 5.50 (1H, s, PhCHα), 5.52 (10H, s, PhCHβ), 6.23 (1H, d, $J_{1,2}$ 3.8 Hz, H-1β), 6.65 (10H, d, $J_{1,2}$ 3.4 Hz, H-1α), 7.26-7.43 (143H, m) 7.50-7.55 (22H, m), 8.27 (1H, br s, NHβ), 8.57 (1H, br s, NHα); δ_C (100 MHz, $CDCl_3$) 65.2, 69.0, 72.3, 73.1, 74.5, 74.6, 75.1,

95.5, 101.1, 126.3, 127.4, 127.5, 127.7, 128.1, 128.2, 128.3, 128.3, 129.1, 137.6, 138.2, 138.3, 161.0. 163.6; *m/z* (ES^+) 508 ($M+Na^+$, 100%). (HRMS (ES^+) Calcd. for $C_{55}H_{58}O_{11}Na$ (MNa^+) 508.0383. Found 508.0375).

2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α/β-D-galactopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside 4.18



4.18

A solution of *O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranosyl) trichloroacetimidate **4.17** (43 mg, 0.073 mmol) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside **2.11** (38 mg, 0.146 mmol) in freshly distilled toluene (1 mL) were added to a flame-dried round-bottomed flask containing activated 3 Å molecular sieves (100 mg) under argon. The reaction mixture was stirred for 10 min, before the reaction was activated by addition of either TMSOTf (2μl, 0.011 mmol) or (*R*)/(*S*)-**1** (8.5 mg, 0.011 mmol). When t.l.c (petrol:ethyl acetate, 4:1) indicated the complete consumption of starting material (R_f 0.4) and the formation of a single major product (R_f 0.3) the reaction was quenched by the addition of triethylamine and filtered through Celite®. The mixture was then concentrated *in vacuo* and the resulting residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-α/β-D-galactopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside **4.18** as a pale yellow oil; δ_H (400 MHz, $CDCl_3$) [Data provided for 1:3.4 mixture of α:β anomers] 1.33 (26.4H, s), 1.46

(13.2H, s), 1.51 (13.2H, s), 3.03 (3.4H, br s), 3.57 (3.4H, dd, *J* 9.5 Hz, *J* 3.7 Hz), 3.73 (3.4H, dd, *J* 10.6 Hz, *J* 7.3 Hz), 3.77-3.79 (3.4H, m), 3.87 (3.4H, dd, *J* 9.5 Hz, *J* 7.8 Hz), 3.99-4.05 (5.4H, m), 4.07 (1H, d, *J* 3.5 Hz), 4.09-4.13 (6.4H, m), 4.17-4.34 (18.6H, m), 4.45 (3.4H, d, $J_{1,2}$ 7.8 Hz, H-$1_b\beta$), 4.57-4.61 (4.4H, m), 4.71-4.85 (15.2H, m), 5.08 (4.4H, m), 5.49-5.52 (5.4H, m, H-$1_a\alpha$, PhC<u>H</u>α, PhC<u>H</u>β), 5.59 (3.4H, d, $J_{1,2}$ 5.1 Hz, H-$1_a\beta$), 7.25-7.42 (48.4H, m), 7.47-7.57 (17.6H, m); δ_C (100 MHz, $CDCl_3$) 24.4, 25.0, 26.0, 26.1 (4 x <u>C</u>H_3), 66.4, 67.3, 69.2, 69.6, 70.5, 70.8, 72.1, 74.2, 75.0, 75.5, 78.2, 78.8, 96.4 (C-$1_a\beta$), 101.2 (C-$1_b\alpha$), 104.3, 104.4 (Ph<u>C</u>Hα/β), 108.6 (C-$1_a\alpha$), 109.3 (C-$1_b\beta$), 126.4, 126.5, 127.4, 127.6, 127.8, 128.1, 128.1, 128.3, 128.3, 128.5, 128.9, 129.0 (12 x Ar<u>C</u>H), 137.8, 138.5, 139.0 (3 x Ar<u>C</u>); *m/z* (ES^+) 708 ($M+NH_4^+$, 100%). (HRMS (ES^+) Calcd. for $C_{39}H_{46}O_{11}Na$ (MNa^+) 713.2932. Found 713.2925).

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