New Approaches to Stereocontrolled Glycosylation

A thesis submitted in partial fulfillment of the requirements for the degree of **Doctor of Philosophy** in **Chemistry** at the **University of Canterbury**

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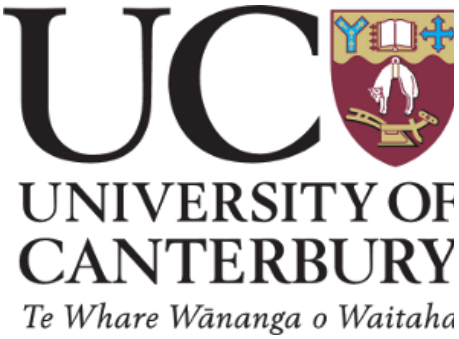

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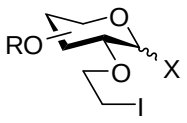
Abstract: New Approaches to Stereocontrolled Glycosylation

Govind Pratap Singh, **University of Canterbury 2015**

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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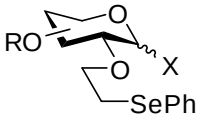

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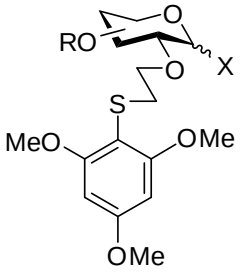

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In particular the use of glucosyl donors **3**, bearing a 2-*O*-(2-(2,4,6- trimethoxyphenyl)thio)ethyl protecting group at the 2-hydroxyl, have shown exceptional *α*-selectivity especially when a completely armed donor was used.

Work within this thesis also describes the use of chiral Brønsted acid catalysts in stereoselective glycosylation reactions. However the yields and stereoselectivity obtained were not very encouraging.

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DECLARATION

I, Govind Pratap Singh, 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 25/06/2015

Dedicated to the
Universal
SELF, guiding me at
every
step of my life

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Thank you.

Abbreviations

The following abbreviations have been used in this thesis:

Å	Angstrom
Ac	Acetyl
All	Allyl
Ar	Aromatic
Aq.	Aqueous
at	Apparent triplet
$BF_3 \cdot OEt_2$	Boron trifluoride diethyl etherate
BINOL	Bi-2-Naphthol
Bn	Benzyl
br.	Broad
Bu	Butyl
Bz	Benzoyl
°C	Degrees Celsius
c	Concentration
Calcd.	Calculated
CAN	Ceric ammonium nitrate
COSY	Correlation spectroscopy
CSA	Camphor sulfonic acid
δ	Chemical shift (ppm)
d	Doublet
DAG	Diacetonegalactose

DBU	1,8-Diazabicyclo[5.4.0]-7-undecene
DCM	Dichloromethane
dd	Doublet of doublets
DMAP	4-(Dimethlyamino)pyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
ES	Electrospray
Et	Ethyl
et al.	*Et alia* (and co-workers)
g	Grams
Gal	Galactose
Gem	Geminal
Glc	Glucose
h	Hour(s)
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation
Hz	Hertz
I	Infrared
J	Coupling constant
L	Litre(s)
lit.	Literature
µ	Micro

m	Multiplet (in NMR)
m	Milli (in units)
m	*Meta*
M+	Molecular mass ion
Man	Mannose
mbar	Millibar
m-CPBA	*Meta*-chloroperbenzoic acid
Me	Methyl
min	Minute(s)
mol	Moles
mmol	Millimoles
m.p.	Melting point
MS	Mass spectrometry
m/z	Mass/charge ratio
ν_{max}	Wavenumber
NBS	*N*-Bromoosuccinimide
NIS	*N*-Iodosuccinimide
NMR	Nuclear magnetic resonance (spectroscopy)
p	*Para*
Ph	Phenyl
PMP	*para*-Methoxyphenyl
Ppm	Parts per million
Pr	Propyl

q	Quartet
R	Generic organic group, unless specified
R_f	Retention factor
rt	Room temperature
s	Singlet
S_N2	Nucleophilic substitution, bimolecular
t	Tertiary
t	Triplet
TBAF	Tetrabutyl ammonium fluoride
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
Tf	Trifluoromethanesulfonyl (triflyl)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
t.l.c.	Thin layer chromatography
TMS	Trimethylsilyl
Triflate	Trifluoromethanesulfonate
TRIP	3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate
TTBP	Tri-*tert*-butylpyrimidine
UV	Ultraviolet
vic	Vicinal

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Chapter 1: Introduction

1.1 Significance of carbohydrates and glycobiology

Amongst the four key classes of biological macromolecules *viz* proteins, DNA, lipids and carbohydrates,[1] carbohydrates show an unrivalled degree of structural diversity.[2] Unlike proteins and DNA, which form linear chains, carbohydrates can form branched polymers and oligomers. The 'Glycocode'[3] – a term used to define the huge structural diversity observed in the carbohydrates, was devised due to the combination of various factors listed below.

(a) Variations in ring size (e.g. furanosyl, pyranosyl);

(b) The inherent difference in the configuration at different chiral centres of monosaccharides (e.g. *gluco, manno, galacto*);

(c) The number of possible sites for a glycosidic linkage to occur, which leads to vast numbers of non-linear structures that polysaccharides and oligosaccharides can adopt.

(d) The anomeric configuration of glycosidic linkages, due to the formation of α- and β-glycosides;

(e) Modification of carbohydrates (e.g. phosphorylation, sulfation, and acetylation).

This structural diversity is responsible for the wide range of functions that carbohydrates play within Nature, and the vital roles they play in various biological events. Carbohydrates are mainly present in the cells in the form of oligosaccharides attached to lipids or proteins (known as glycolipids or glycoproteins, respectively) which are collectively 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). The carbohydrate moieties of these glycoproteins are vital in many biological processes, such as cell growth, cell-cell adhesion and signalling,[4] fertilization,[5] immune defence,[6] neuronal development[7] and

inflammation.[8] Furthermore, protein glycosylation, either as a co- or post-translational modification, may be necessary for correct protein folding, and can also affect the protein's overall stability and conformation,[9] its susceptibility to proteases[10] and its circulatory lifetime.[11]

The importance of carbohydrates in a plethora of biological processes continues to fuel enormous interest in the field of Glycobiology. However the lack of pure and structurally well-defined carbohydrates and glycoconjugates proves to be a major obstacle to further advances in this area.[12] Glycoconjugates are often found in low concentrations and in microheterogeneous forms naturally, making them very difficult to isolate and purify. For example glycoproteins, are commonly found as mixtures in which the same protein structure is attached to a variety of different oligosaccharides, which are termed glycoforms. Frequently these materials differ in biological activity, but their similar structures and physical properties means that isolation of a single protein glycoform is almost impossible.[13]

The total synthesis of oligosaccharides by chemical and/or enzymatic means is therefore of prime importance in Glycobiology. Enzymatic synthesis utilizes glycosyl transferases and glycosidases for the synthesis of oligosaccharides.[14] Though they are efficient catalysts for the synthesis of various oligosaccharides, the availability of enzymes that are capable of performing desired transformations remains a limiting factor in many cases. In terms of stereo- and regiospecificity, enzymes are extremely efficient, and their organization into assembly lines in biological systems allows the production of highly complex carbohydrates. However, their precise selectivity for only a specific acceptor, the high costs of the required donors, and the lack of availability, resulting from limited stability and solubility, are still significant hinderances for the widespread exploitation of glycosyl transferases in synthetic glycochemistry.[15] Therefore

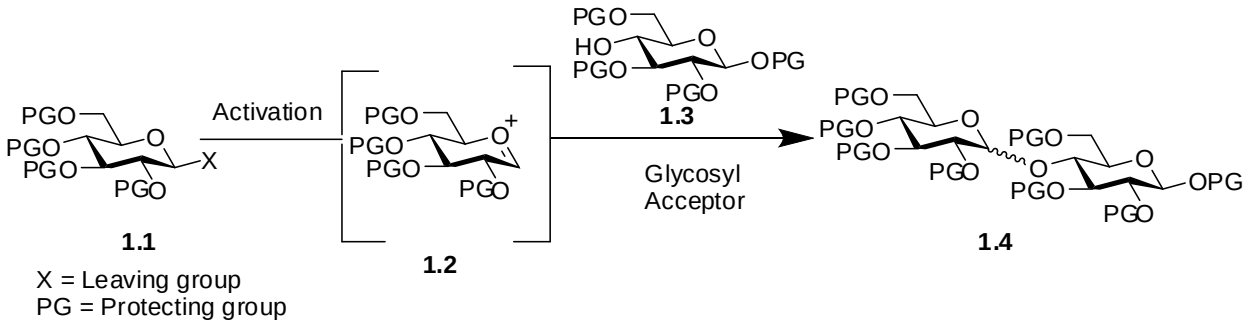
chemical synthesis currently remains the principal synthetic tool available to the scientific community.[16]

1.2 Chemical synthesis of oligosaccharides

In the past, most of the research aimed at improving the efficiency and stereoselectivity of the synthesis of oligosaccharides has focused on the development of new leaving groups, new promoters (activators), and through the optimization of general reaction conditions. However, as these gradual enhancements have not yet been able to completely control the outcome of all glycosylation reactions, studies have additionally been directed towards gaining a better understanding of the mechanisms and energies controlling this fundamental reaction.[17] There are many factors that can have a profound effect on the reactivity of a glycosyl donor and acceptor and influence the selectivity of glycosidic bond formation.

The fundamental reaction performed between two monosaccharide units is the glycosylation reaction. Nature flawlessly and repeatedly executes this reaction to yield complex poly- and oligosaccharides.[18] However, the chemical installation of the glycosidic linkage remains cumbersome, even with the aid of modern technologies. Due to significant research in the field over many years the formation of most glycosidic bonds can be achieved.[17] Unfortunately, it is the inability to effectively predict and control the stereoselectivity of the reaction that has proven to be the synthetic hurdle. Indeed attempted improvement of this reaction has therefore remained an underlying theme throughout the history of carbohydrate chemistry. With recent advances in the rapidly expanding field of Glycobiology,[19] the demand for reliable and stereocontrolled glycosylation methodologies has now increased, thus elevating the priority of the improvement of synthetic capabilities.

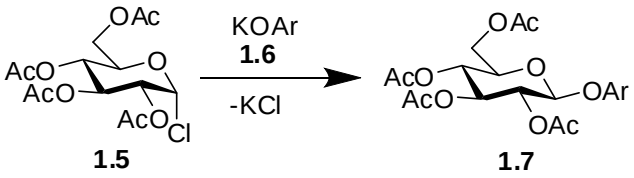
Oligosaccharide assembly hinges upon the linking of pre-formed building blocks by glycosylation. In a typical glycosylation reaction, the coupling of two carbohydrates is achieved by treating a glycosyl donor **1.1**, which bears a suitable anomeric leaving group, with a promoter to generally form an intermediate oxocarbenium 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).[20] A variety of anomeric leaving groups and corresponding activation protocols are available to the synthetic chemist.



Scheme 1.1

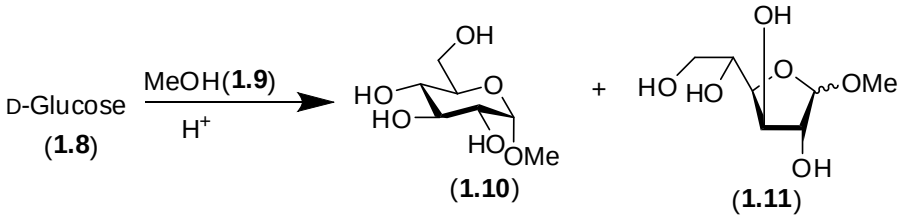
1.3 Historical background and mechanistic insights

The first chemical glycosylation was reported by Arthur Michael some 130 years ago.[21] This reaction proceeded by the nucleophilic displacement of an anomeric leaving group (chloride), from the donor **1.5** using potassium aryloxide **1.6** to get the desired glycoside **1.7** (Scheme 1.2). It is remarkable that even without much structural or other evidence, Michael's vision of how the anomeric substitution would proceed was fundamentally accurate.



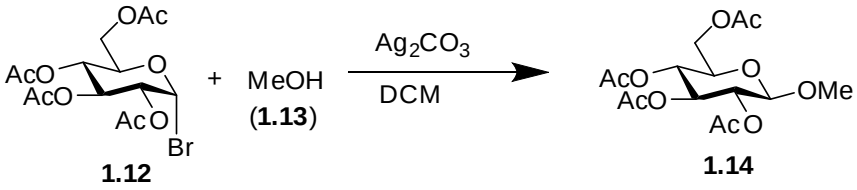
Scheme 1.2

A decade later, Emil Fischer took a different approach to the glycosylation reaction.[22] Fischer perceived the unprotected monosaccharide unit as a hemiacetal, and the reaction was carried out under harsh acidic conditions in an excess of the desired glycosyl acceptor. Although conceptually the simplest way to obtain a glycoside, the Fischer method commonly leads to equilibrium of inter-converting species, all of which are formed in addition to the desired product. For example, D-Glucose **1.8** upon Fischer glycosylation with methanol **1.9** actually results in the formation of α-methyl glucopyranosides (thermodynamically favored) **1.10** and methyl glucofuranosides **1.11** (Scheme 1.3).



Scheme 1.3

In 1901, Koenigs and Knorr[23] (and independently Fischer and Armstrong)[24] took the chemical glycosylation approach a step further by reacting glycosyl halides with alcohol acceptors in the presence of Ag_2CO_3 or Ag_2O. For example, α-glucosyl bromide **1.12** was reacted with methanol **1.13** to give β-methyl glucoside **1.14** in presence of Ag_2CO_3 (Scheme 1.4).



Scheme 1.4

Mechanistic analysis of the glycosylation reaction has led to very interesting insights. In the Koenigs and Knorr glycosylation reaction, the Ag_2CO_3/Ag_2O were used as mild bases with the

primary intention to scavenge the hydrogen halide by-product. It was only much later, that it was realized that the silver salts played an active role by assisting the leaving group departure.[25] Based on the observation that Koenigs-Knorr glycosylation was very selective, leading to complete inversion of the anomeric configuration, it was concluded that the glycosylation reactions were a result of "Walden inversion",[26] otherwise known as concerted nucleophilic substitution.[27]

To provide insight into the glycosylation reaction, the energy required for nucleophilic substitution to occur was calculated for various 1,2-disubstituted cyclohexanes both in the absence or presence of participation. These studies led to the conclusion that the unassisted departure of a leaving group to yield a free ionic species would require much more energy than a concerted nucleophilic displacement that occured *via* intramolecular participation.[28] Consequently, the glycosylation reaction is thought to proceed through a total of four distinct steps:[29]

(a) Formation of the donor–promoter complex **1.16**, which can be reversible or irreversible depending on the system involved;

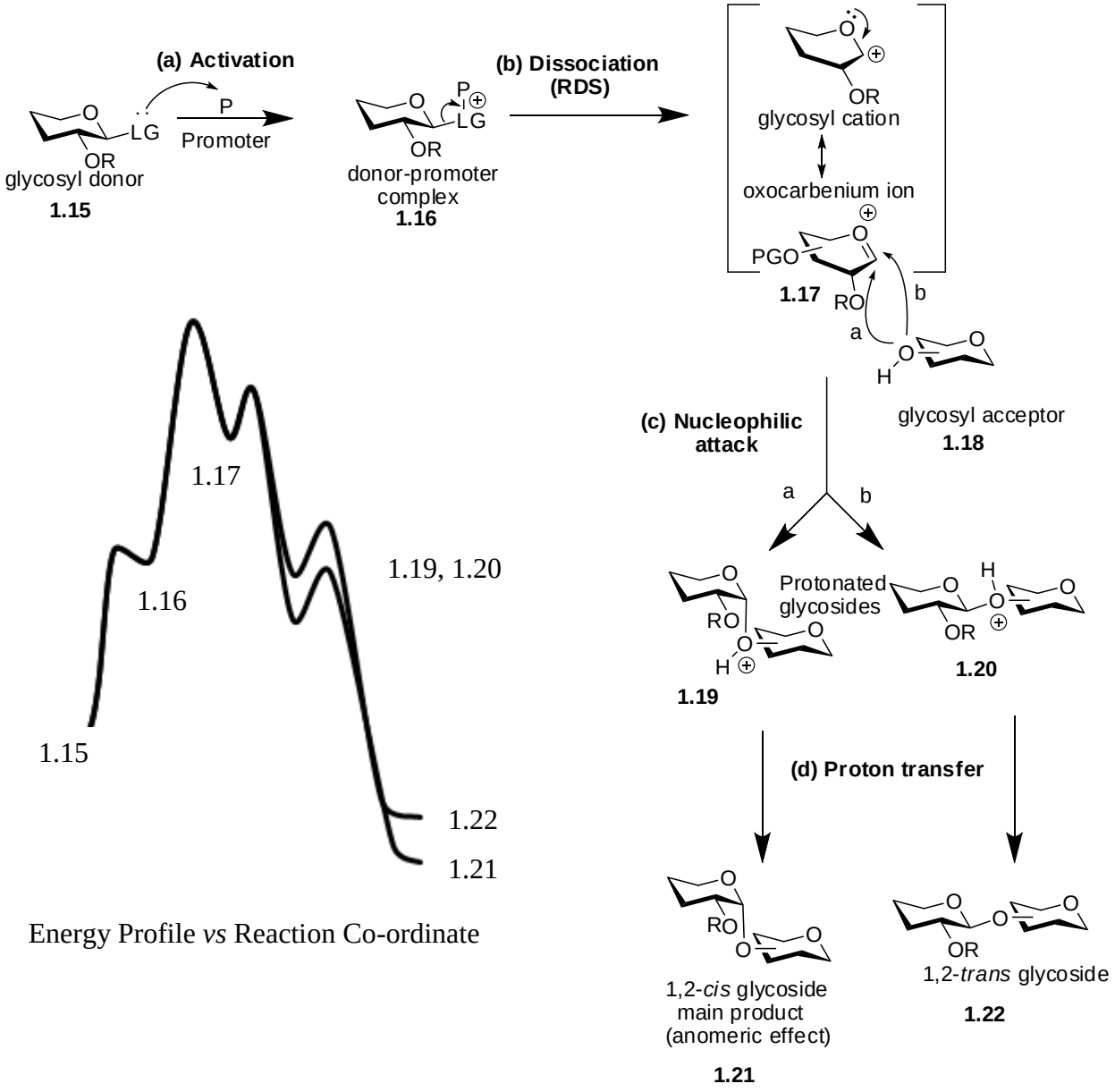
(b) Ionization of the glycosyl donor, a typically irreversible act, and the slowest step (RDS) of the reaction, leading to formation of an oxocarbenium ion **1.17**;

(c) Nucleophilic attack by the glycosyl acceptor, forming protonated glycosides **1.19**, **1.20**;

(d) Proton transfer to give neutral glycoside **1.21**, **1.22**.

Product selectivities can arise from the stabilization provided by the anomeric effect, which is thought to be responsible for product formation under conditions of thermodynamic control. For example, cases have been reported reporting non-kinetically controlled glycosylations, in which

the initially formed β-glycoside is then anomerized into its thermodynamically more stable α-counterpart.[30] A schematic representation of the mechanism is shown in the Scheme 1.5.[17]



Scheme 1.5

1.4 Glycosyl donors

A glycosyl donor is a carbohydrate mono- or oligosaccharide that will react with a suitable glycosyl acceptor to form a new glycosidic bond. By convention, the donor is the member of this pair that contains the resulting anomeric carbon of the new glycosidic bond. The resulting reaction is referred to as a glycosylation, or chemical glycosylation. A leaving group is required at the anomeric position of the glycosyl donor.[31] A selection of some commonly used glycosyl donors is shown below in figure 1.1.

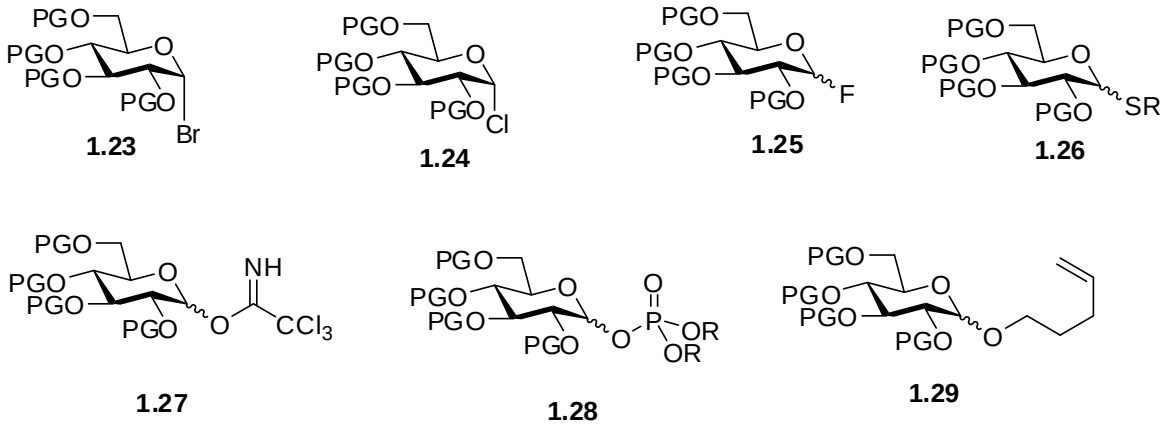


Figure 1.1

Glycosyl bromides **1.23**, 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.[23] 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.[32] Glycosyl chlorides **1.24** can be activated under the same Koenigs-Knorr conditions, however their lower reactivity as compared to glycosyl bromides means that they are rarely used. Glycosyl fluorides **1.25** on the

other hand are very useful glycosyl donors.[33] 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 **1.26**[34] 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 **1.27**, developed by Schmidt as a modification of the original Sinay imidate donor, are very widely used, and are activated by catalytic amounts of hard Lewis acids, including trimethylsilyl triflate (TMSOTf) and $BF_3.OEt_2$.[35] Anomeric phosphate leaving groups **1.28** are less commonly used; these highly reactive donors are generally activated with TMSOTf.[36] Pent-4-enyl glycosides **1.29**,[37] introduced by Fraser-Reid and co-workers, are activated remotely 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 oxocarbenium ion.

1.5 Challenges involved in controlling the regio- and stereoselectivity of glycosylation reactions

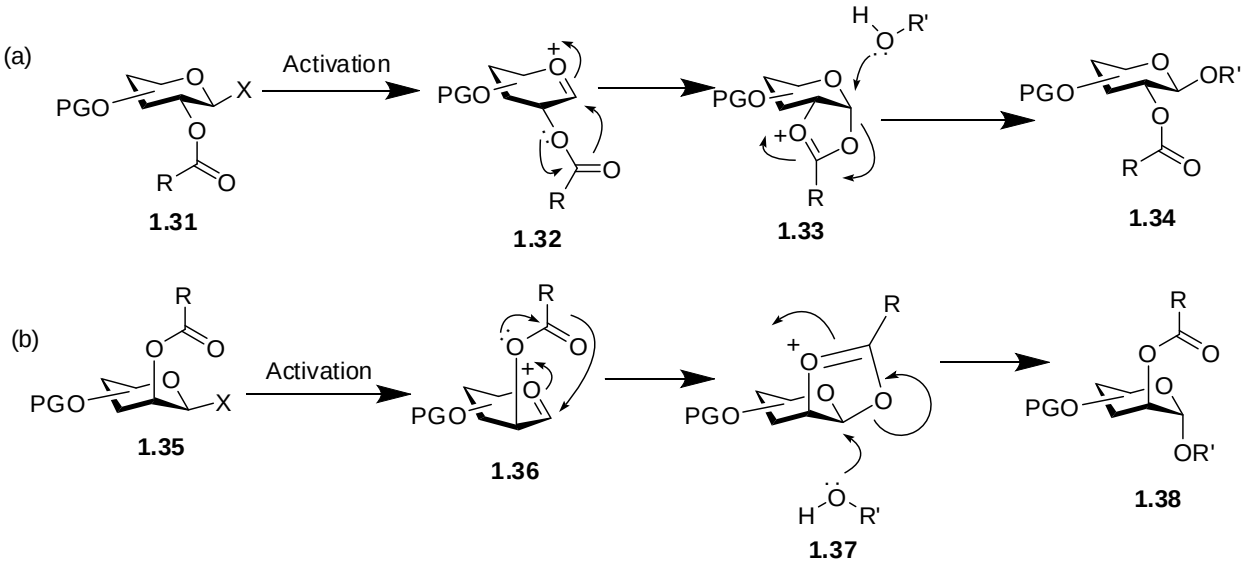
The wide array of orthogonal protecting groups that have been developed allows access to building blocks with a single unprotected hydroxyl group,[38] and so issues of regioselectivity in glycosylation reaction are easily circumvented. There are many complexities to consider when depicting the mechanism of the glycosylation reaction, and often a clear delineation between S_N1 and S_N2 nucleophilic substitution reactions is obscured.[29] Nevertheless, nowadays it is generally presumed that the reaction conditions favor that of a unimolecular S_N1 mechanism, and hence controlling the stereochemistry of the new anomeric linkage requires attention.

The synthesis of complex oligosaccharides by chemical synthesis is generally a very complicated, multi-step process, often culminating in very low yields. Each monosaccharide component of the target oligosaccharide needs a variety of protecting groups, and thus every synthetic route involves multiple strategies to provide orthogonality between the different hydroxyl groups of each sugar unit. Efforts have been made to improve the speed and efficiency of oligosaccharide synthesis by using either one-pot multi-step glycosylation processes,[39] or polymer-supported syntheses,[40] and programmable one-pot strategies.[39a] These approaches are often compromised by the same problem that plagues any glycosylation reaction: the product glycoside is generally formed as an anomeric mixture.[41] Enzyme-based strategies can be important alternatives but, as explained earlier, glycosyl transferase enzymes have a very narrow range of selectivity.[39a] The issue of control of anomeric stereochemistry during glycosylation remains as the principal challenge to be addressed during any 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 problem.[42] Oligosaccharides found on the surface of pathogens and malignant cells frequently possess 1,2-*cis*- linked glycosides as a key structural elements.[43] The possibility of using these structures in carbohydrate-based vaccine candidates has promoted numerous investigations into the construction of these linkages,[44] and although many methods have been developed towards solving this problem, no generally applicable methodology yet exists.

1.6 Stereoselective glycosylation strategies

1.6.1 The synthesis of 1,2-*trans* glycosides by neighboring group participation

In contrast to the difficult 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 classical neighboring group participation (NGP) of 2-*O*-acyl protected glycosyl donors.[45] A schematic representation of the synthesis of a 1,2-*trans* glucoside **1.34** and a 1,2-*trans* mannoside **1.38** are shown below (Scheme 1.5).



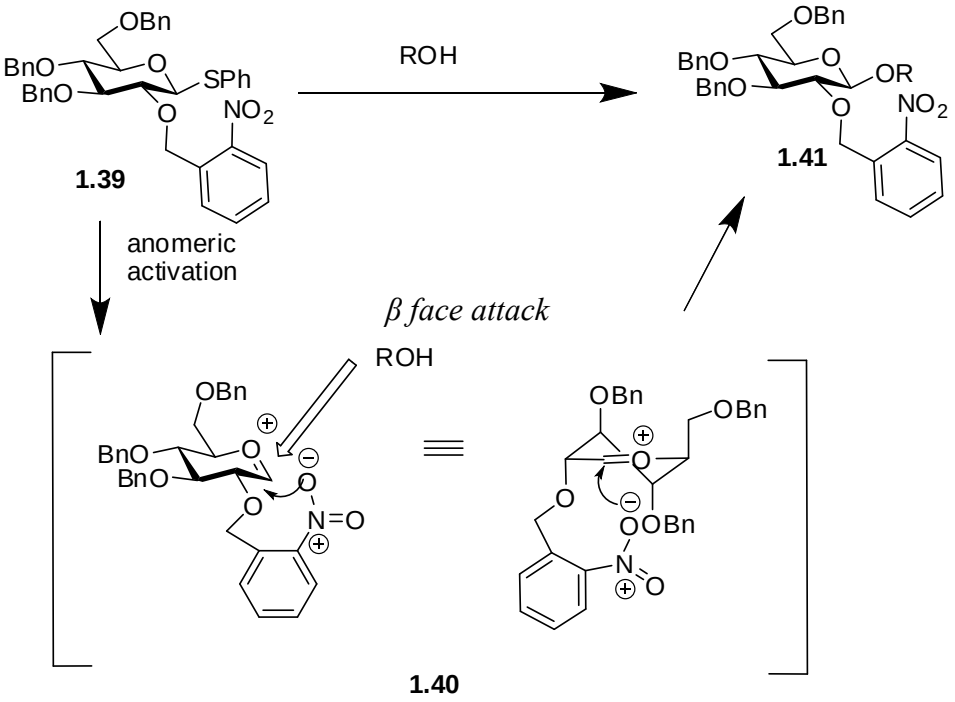
Scheme 1.5

Activation of the glycosyl donor **1.31** results in the formation of an oxocarbenium ion **1.32**. Subsequent neighbouring group participation by the acyl group at the 2-position gives the more stable dioxolenium ion **1.33**. S_N2-like attack by the alcohol of a glycosyl acceptor can now only occur on one face, hence the glycosidic bond formed must be *trans* to the bond at the 2-position, producing the *β*-glycoside **1.34** in the case of glucosides. The same process occurs with the

manno- glycosyl donor **1.35**, though this time, it is the *β*-face of dioxolenium ion **1.37** which is shielded from attack, hence the *α*-glycoside **1.38** 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. However, *N*-acetylglucosamine derivatives often react with low efficiency in glycosylations, as the acetamide can react with both the glycosyl acceptor and the activator.[46] Therefore, an *N*-phthalimido group is often chosen as the protecting group for glucosamine donors. Carbamate protecting groups are also capable of performing neighbouring group participation, and hence *N*-Troc protected glucosamine donors also give 1,2-*trans* glycosides.[47]

More recently, participation of the *o*-nitrobenzyl (oNBn) group was demonstrated, which allowed the stereocontrolled synthesis of glucosides with a 1,2-*trans* linkage.[48] This new ether-type of arming protecting group can broadly extend the concept of the use of participating groups in glycosylation reactions. Easy protection and deprotection of the oNBn group further confirmed its usefulness in synthesis. The proposed mechanism for the stereoselective synthesis of the *β*- glucoside **1.41** from the donor **1.39** containing *o*-nitrobenzyl group at position 2 is shown below (Scheme 1.6).



Scheme 1.6

1.6.2 Stereoselective synthesis of glycosides by manipulating the reaction conditions

1.6.2.1 Temperature

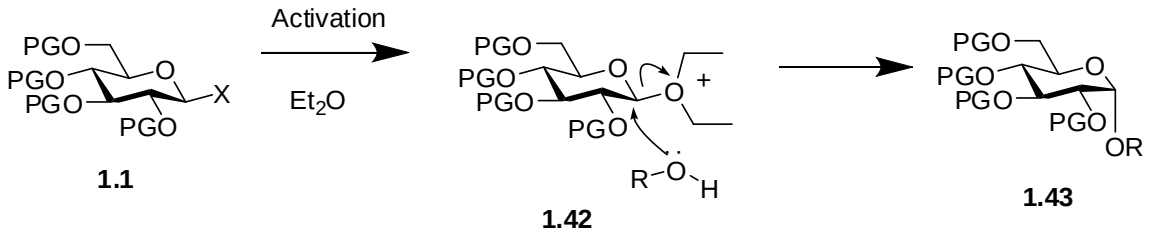
Kinetically controlled glycosylations performed at lower temperatures generally favor *β*-D-glycoside formation,[19],[49] although converse observations have also been reported.[50] Since the *α*-glycoside is thermodynamically favored due to the anomeric effect, it is predominantly formed at high temperatures.

1.6.2.2 Solvent

The simplest method used which favours the synthesis of 1,2-*cis* *α*-glycosides is to employ non-participating protecting groups at the 2-position of the glycosyl donor, such as benzyl ethers, and to tune the reaction conditions towards favoring the desired stereochemical outcome. The most

common way of doing this is to take advantage of the solvent system.[51] As a rule of thumb, ether 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. Diethyl ether selectively coordinates equatorially to the oxocarbenium ion formed upon activation giving the intermediate **1.42**, and hence reaction with a glycosyl acceptor, in an S_N2 fashion, gives the *α*-anomeric product **1.43** (Scheme 1.7).[52]

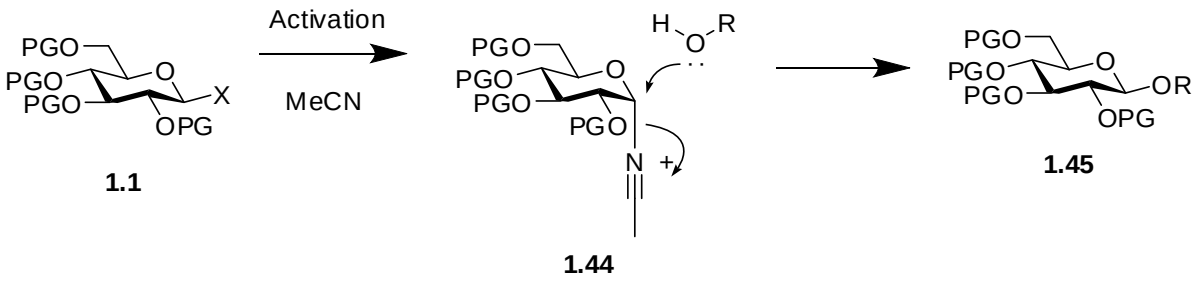


1.1 **1.42** **1.43**

Scheme 1.7

Selectivity is generally observed to increase with a decrease in temperature, and the methodology can be used with a wide range of glycosyl donors[53] and also in solid supported syntheses.[49] Tetrahydrofuran and 1,4-dioxane are other examples of ethereal solvents which can direct *α*-selectivity in glycosylation,[20] whilst the non-ethereal solvent nitromethane also produces *α*-glycosides.[54]

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.[55] In this case, *β*-selectivity is observed due to the stereoselective kinetic formation of a reactive *α*-nitrillium intermediate **1.44**, which undergoes an S_N2 type reaction with the glycosyl acceptor to give the *β*-anomeric product **1.45** (Scheme 1.8).



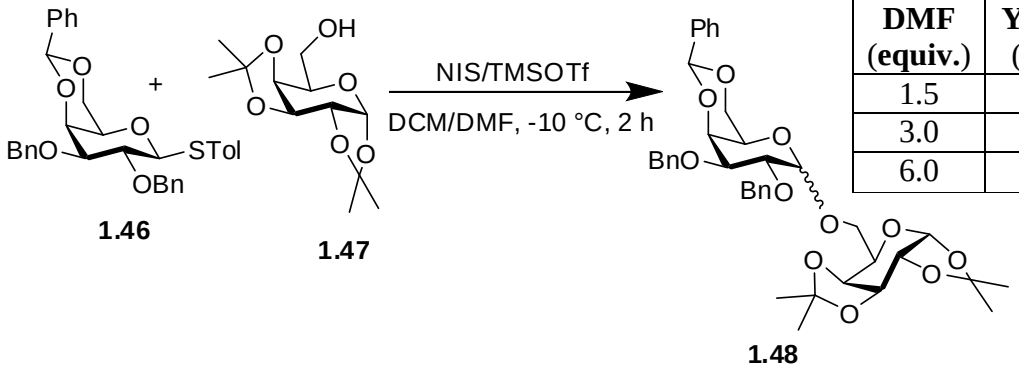
Scheme 1.8

As with the use of diethyl ether as the reaction solvent, selectivity is observed to increase with a decrease in reaction temperature. However, in the case of mannose derived donors, enhanced formation of the β-mannoside is not observed as, in this case, the steric effect of the axially orientated hydroxyl at the 2-position outweighs the directing effect of the acetonitrile.

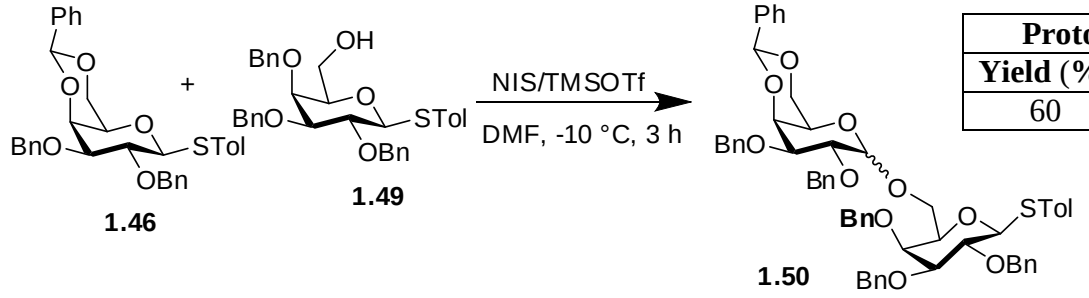
A different direction in studying the reaction solvent effect by using dimethylformamide (DMF) as a co-solvent, was taken by Mong and co-workers.[56] This study employed two conceptually different protocols for glycosylation. First, applying protocol A, a mixture of glycosyl donor, acceptor, and DMF was activated with NIS and TMSOTf. When the concentration of DMF was varied in these reactions, it was found that in the presence of 1.5 equiv. of DMF, moderate stereoselectivity was achieved. However, an increase in the amount of DMF to 3 and 6 equiv. was translated into a significant increase in α-stereoselectivity.

In an alternative protocol (protocol-B), the glycosyl donor was reacted with NIS and TMSOTf in the presence of DMF, followed by the addition of the glycosyl acceptor, and very high α-selectivity was observed.

One specific example of each glycosylation reaction carried out employing protocol A and protocol B, and their outcomes are shown in Scheme 1.9.



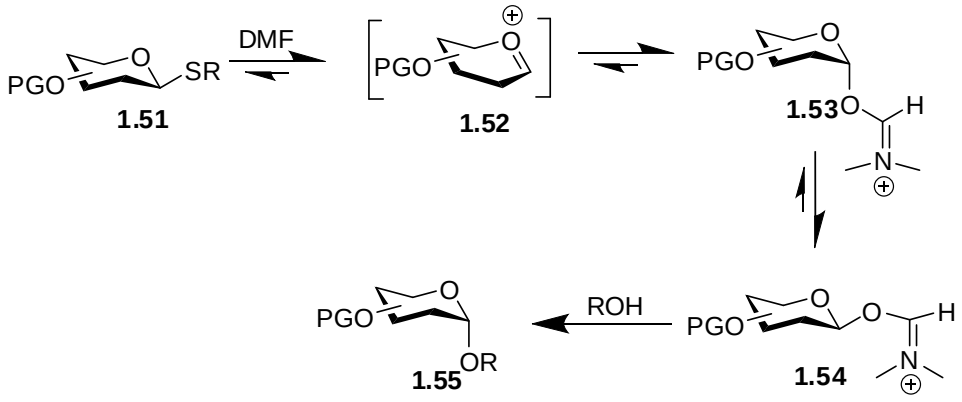
Protocol-A		
DMF (equiv.)	**Yield (%)**	**α:β**
1.5	82	6:1
3.0	87	15:1
6.0	87	19:1



Protocol-B	
Yield (%)	**α:β**
60	36:1

Scheme 1.9

The proposed rationalization behind the observed stereoselectivity is that DMF traps the glycosyl oxocarbenium ion **1.52** resulting in an equilibrating mixture of *α*/*β*-glycosyl *O*-imidates **1.53/1.54** (Scheme 1.10). The more reactive *β*-imidate then reacts faster with the glycosyl acceptor producing the desired *α*-glycoside **1.55** with high selectivity.



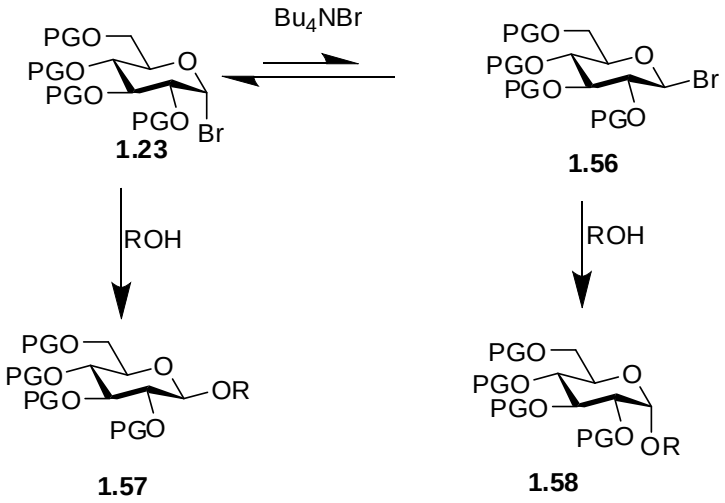
Scheme 1.10

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

1.6.2.3 Promoters, additives, and chelators

Several decades ago, the glycosylation of acceptors of low nucleophilicity was sluggish and inefficient.[23],[25] However with the development of more reactive donors and activation conditions, the efficiency of glycosylation, including the rates of reaction and product yields, has improved tremendously. However, this efficiency has not led to improvements in stereoselectivity; rather it hads been noted that faster reactions often result in decreased stereoselectivity and *vice versa*, thus making it necessary to find a delicate balance between donor reactivity and stereoselectivity.[32] It has become clear over time that milder activating conditions are beneficial for 1,2-*cis* glycosylations.

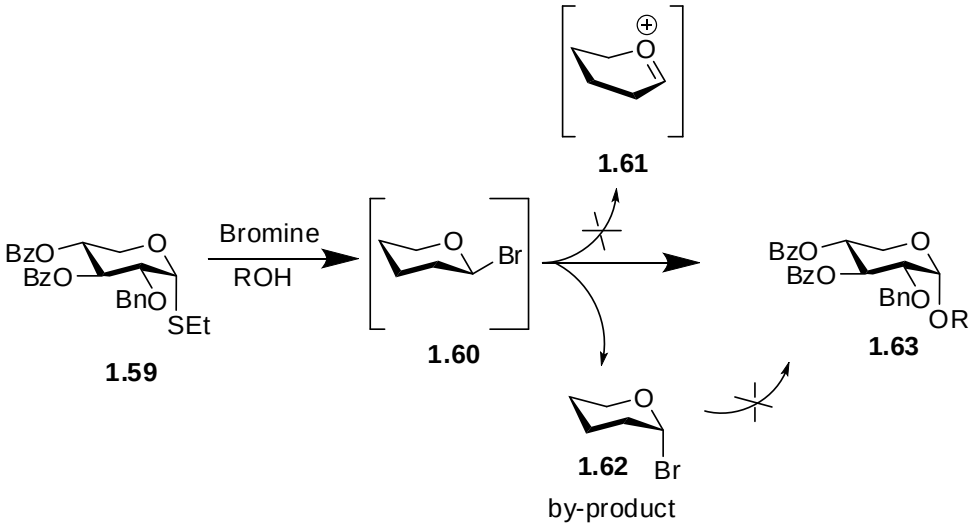
The method of *in situ* anomerization was first reported by Lemieux and co-workers in 1975,[57] and at the time provided a major breakthrough for the synthesis of 1,2-*cis* α-glycosides. It was observed that treatment of a glycosyl halide, commonly a glycosyl bromide, with a catalytic source of the same halide in the presence of a glycosyl acceptor gave predominantly the α-glycoside. This stereochemical outcome was explained using the Curtin-Hammett principle.[58] For example, if the α-bromide **1.23** is treated with a catalytic amount of tetra-*n*-butylammonium bromide (TBAB), equilibrium between the α-bromide **1.23** and the β-bromide **1.56** is established (Scheme 1.11).



Scheme 1.11

Although the equilibrium strongly favors the more stable α-bromide **1.23**, the activation energy for nucleophilic attack by a glycosyl acceptor is much lower for the β-bromide **1.56**. Therefore the1,2-*cis* α-glycoside **1.58** is the major product of the reaction because **1.56** reacts preferentially with the acceptor in an S_N2 type reaction.. If the difference in the energy barriers for the two substitutions is sufficient, then 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 and triflates. It is also vital that a low polarity solvent is used, as in the presence of a polar solvent oxocarbenium ion formation becomes more favorable and so more S_N1-like reactions may occur, reducing anomeric selectivity.

Working on the same principle, Demchenko *et al*. have shown that a bromine-mediated glycosylation of the thioglycoside **1.59** lead exclusively to the *α*- products **1.63** (Scheme 1.12).[59]

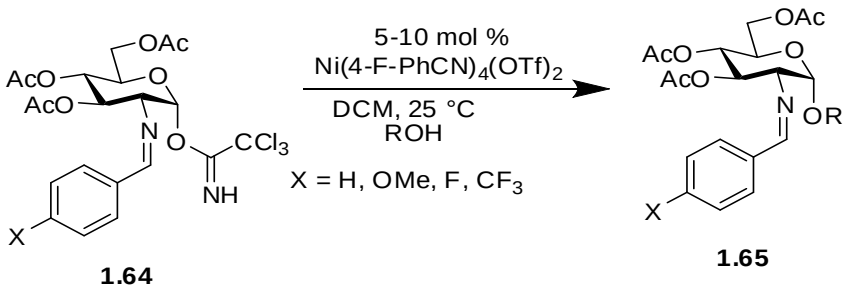


Scheme 1.12

The reason for the α-stereoselectivity lies in the fact that the *β*-bromide **1.60** is the reactive intermediate which in addition withto reaction with the acceptor in an S_N2 fashion to give the α-product, can also undergo rapid anomerization to its *α*-linked counterpart. However, once formed, the *α*-bromide **1.62** is totally unreactive under the reaction conditions, so the yield of glycosylation can be low with secondary alcohols. The *α*-bromide can be reactivated in the presence of a mercury (II) additive. This pathway was found to be very beneficial for the glycosylation of secondary alcohols, but can compromise the *α*-selectivity of glycosylation with primary alcohols.

Whilst many of the current methodologies for glycosylation require the use of stoichiometric amounts of promoters, the use of transition metal catalysts helps achieve greener glycosylation conditions, and offers new opportunities for stereocontrol.[60] Nguyen *et al*. investigated a series

of nickel catalysts as an efficient means for the glycosylation of the *N*-*p*-methoxybenzylidene-protected 2-amino-2-deoxy TCAI donor (**1.64**).[61] The nature of the ligand on nickel was found to be the deciding factor in controlling the stereoselectivity of glycosylation. Thus, it was observed that electron-withdrawing substituents helped decrease the reaction time, which was translated into increased α-selectivity in the product **1.65** (Scheme 1.13).

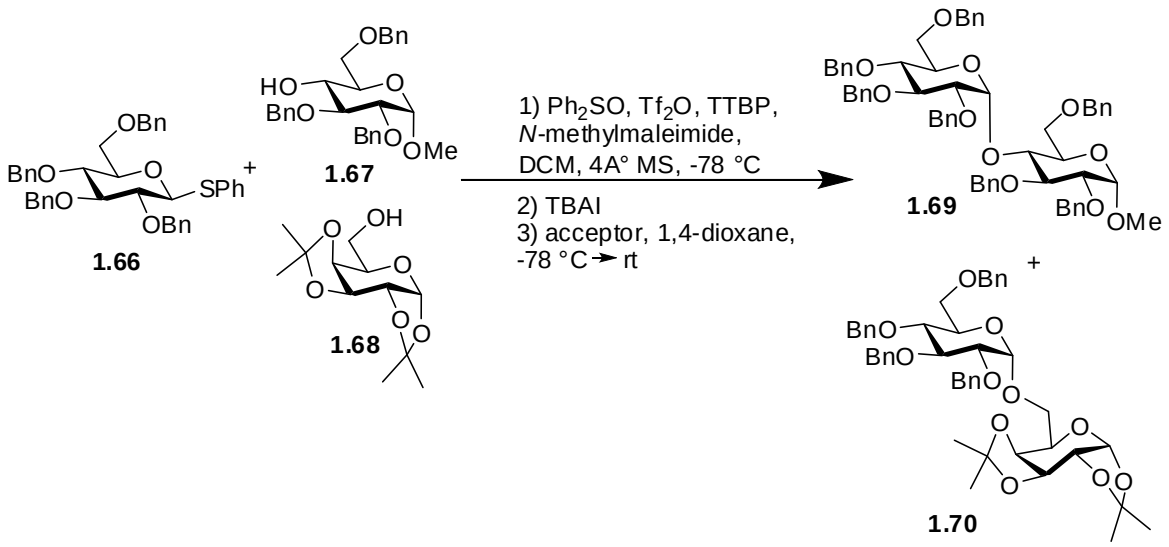


1.64 **1.65**

Scheme 1.13

Another promising new field is the use of chiral thioureas as organocatalysts for glycosylation.[62] As of now, this approach is limited to the synthesis of 2-deoxy α-glycosides[63] and β-selective glycosylation with 2-oxygenated sugars.[64]

Bennett and co-workers recently investigated the activation of thioglycosides with Ph_2SO in the presence of tetrabutylammonium iodide (TBAI). It was observed that this reaction proceeded *via* the intermediacy of a glycosyl iodide.[65] The underpinning idea of using TBAI is that the conversion of α-glycosyl triflates into β-glycosyl iodides would favor the formation of α-glycosides. Thus, when the *S*-phenyl donor **1.66** was preactivated using Ph_2SO/Tf_2O, followed by the addition of TBAI and then the glycosyl acceptors **1.67** or **1.68**, the respective disaccharides **1.69** or **1.70** were obtained with excellent or even complete α-stereoselectivity (Scheme 1.14).

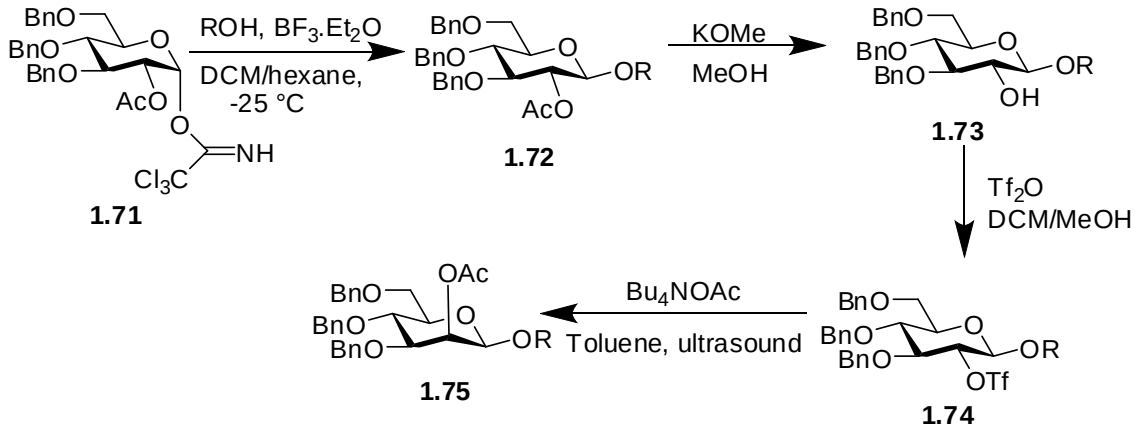


Scheme 1.14

1.6.3 The synthesis of 1,2-*cis* *β*-glycosides by inversion of configuration at position-2

The 1,2-*cis* *β*-mannoside linkage is found in the core pentasaccharide of all *N*-linked glycoproteins,[66] as well as many other biologically relevant oligosaccharides, and therefore the importance of the *β*-mannoside linkage has fuelled great interest in developing methodologies for its synthesis. Whilst solvent effects and *in situ* anomerization 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 of *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 favored. Furthermore the *β*-glycoside is thermodynamically unfavorable due to not only a lack of the anomeric effect but also due to electronic repulsions by the 2-position.[67]

Due to the difficulties in achieving desired 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 discovered by Glisin[68] where direct displacement of the C-2 Sulfonate of gluco and mannopyranosides were done, to form manno and glucopyranosides respectively. The same methodology was employed was employed by Fürstner and co-workers (**Scheme 1.9**).[69]

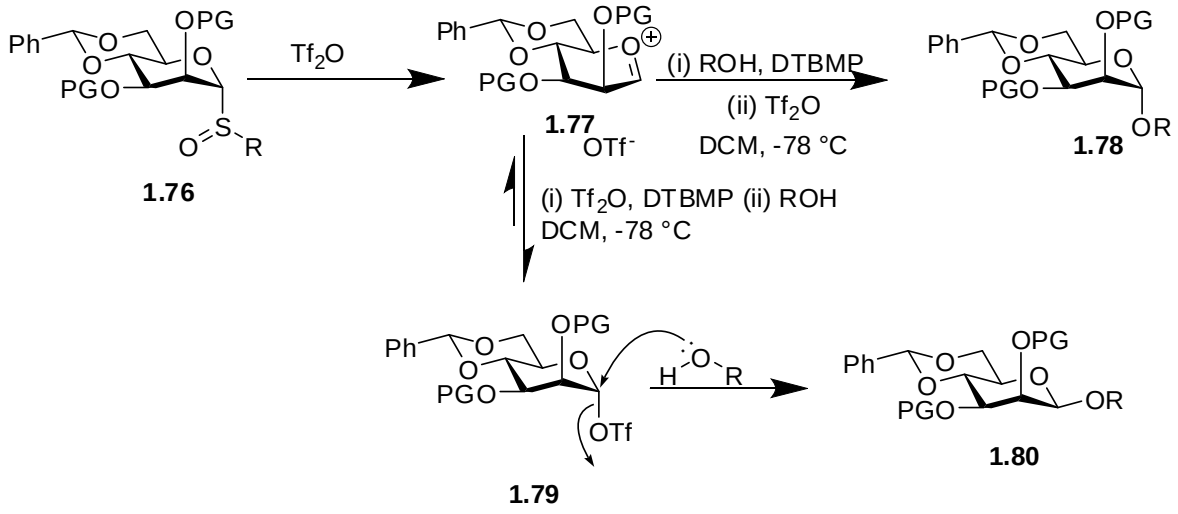


Scheme 1.15

Glycosylation of the trichloroacetimidate donor **1.71** selectively gave the *β*-glucoside **1.72** by neighboring group participation of the acetate group at the 2-position. This was then removed using catalytic methoxide to give the alcohol **1.73** which was then converted to the triflate **1.74** using triflic anhydride. Reaction with tetrabutylammonium acetate under ultrasound gave inversion at the 2-position, and hence the *β*-mannoside product **1.75**. Although the yields of the inversion step were shown to be consistently high (upwards of 80%), clearly the requirement for three additional synthetic steps as compared to a direct glycosylation method is not ideal.

1.6.4 The synthesis of 1,2-*cis* *β*-glycosides by Crich's methodology

An interesting route towards synthesis of *β*-mannosides was pioneered by Crich and co-workers, by applying 'inverse addition methodology'.[70] 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 of the reaction (Scheme 1.10).



Scheme 1.16

If the reaction was carried out under glycosylation conditions (i), where a mixture of glycosyl donor **1.76** and the acceptor were treated with the promoter, then the *α*-mannoside **1.78** was observed to be the major product formed. However, it was discovered that pre-activation of the glycosyl sulfoxide **1.76** 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 **1.80**. It was postulated that this was due to attack of the glycosyl acceptor on the *α*-triflate intermediate **1.79** in an S_N2 manner, which was postulated to be more stable than the glycosyl cation **1.77** and therefore favored at equilibrium. Low temperature NMR

studies subsequently proved that formation of **1.79** did indeed occur under these reactions conditions. In general the *β*-selectivity was shown to be high with primary alcohol acceptors, giving *β*:*α* ratios of greater than 25:1 in some cases. However, when more sterically demanding secondary alcohol acceptors were used the selectivity was observed to diminish. Subsequently, Crich and co-workers developed alternative activation conditions that allowed reaction of thioglycoside donors to give *β*-mannosides *via* the formation of the same *α*-triflate intermediates,[71] and in these cases high *β*-mannoside formation was observed for bulkier acceptors, although the reaction is still not applicable in all situations.

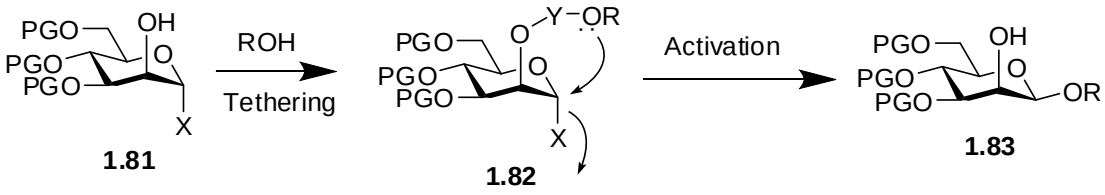
The protecting groups employed on the glycosyl donor were also found to be very important. Clearly it was vital that the protecting group used at the 2-position was non-participating. The presence of a bulky group, for example TBDMS disfavoured S_N2 attack by the acceptor, and thus reduced stereoselectivity. Most important, however, was the presence of the 4,6-*O*-benzylidene acetal in the glycosyl donor. It has been proposed that formation of the oxocarbenium ion is disfavored when this protecting group is used due to the high torsional strain and unfavorable electronic effects inflicted on the intermediate,[72] and hence the presence of a 4,6-*O*-benzylidene greatly favors the formation of the *α*-triflate **1.79**. With more conformationally flexible glycosyl donors increased *β*-mannoside formation was observed.

Although this inverse addition methodology can be employed very successfuly in the synthesis of the challenging *β*-mannoside linkage, there are several drawbacks. The requirement for a 4,6-*O*-benzylidene acetal is very restrictive in terms of protecting group strategies available, 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 as a general solution to the problem of forming *β*-mannosides. Furthermore, it does not work on GlcNAc OH-4 as acceptor.

1.6.5 The synthesis of 1,2-*cis* glycosides by Intramolecular Aglycon Delivery (IAD)

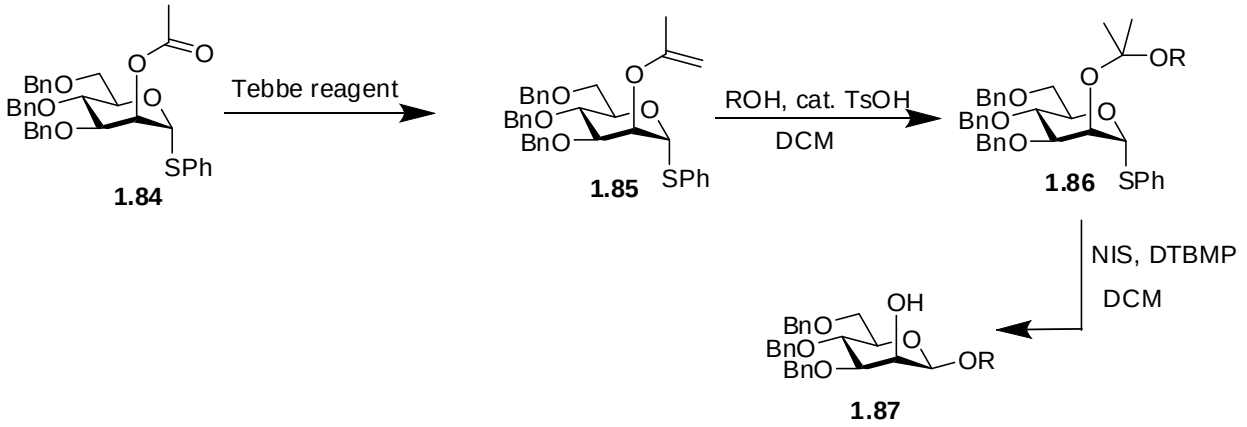
Hindsgaul, in 1991, developed Intramolecular Aglycon Delivery (IAD) as a method for forming *β*-mannosides.[73] The principle behind this technique involves temporarily linking the glycosyl acceptor to the 2-position of a glycosyl donor **1.81** *via* a bridging atom or group (labelled Y), producing a tethered glycoside **1.82** (Scheme 1.17).



Scheme 1.17

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 **1.83**. The group that remains at the 2-position after glycosylation can be cleaved either during or after or the glycosylation reaction to leave the 2-OH position of the product unprotected.

For the synthesis of *β*-mannosides, **1.87**, Hindsgaul and co-workers employed a 2-*O*-methylvinyl ether protected glycosyl donor **1.85**, derived from a Tebbe reaction of the 2-*O*-acetate protected donor **1.84**, to achieve tethering of the glycosyl acceptor as shown below (Scheme 1.18).[74]



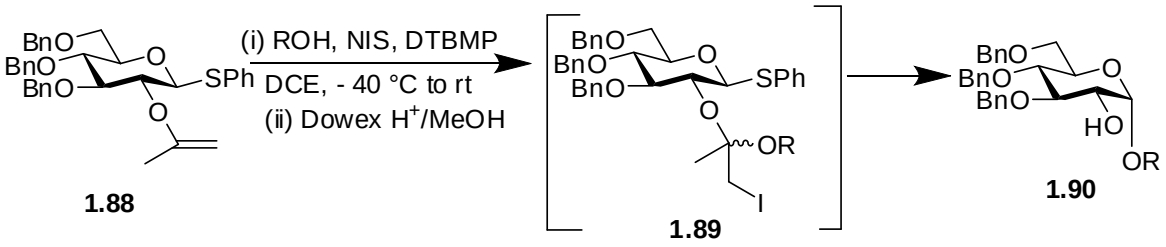
Scheme 1.18

Activation of the anomeric leaving group of the tethered mixed ketal intermediate **1.86** allowed formation of the disaccharide **1.87** with complete stereocontrol for the *β*-anomer. A major drawback encountered in this methodology was that both the tethering and glycosylation steps proceeded in poor yield. It was also observed 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.

The use of a silaketal tethering group for IAD, for the synthesis of *β*-mannosides, was developed by Stork and co-workers.[75] The tethering and glycosylation steps proceeded in higher yield as compared to Hindsgaul's method and complete *β*-selectivity was again observed. However, even this methodology didn't prove to be high yielding and stereoselective for sterically hindered glycosyl acceptors.

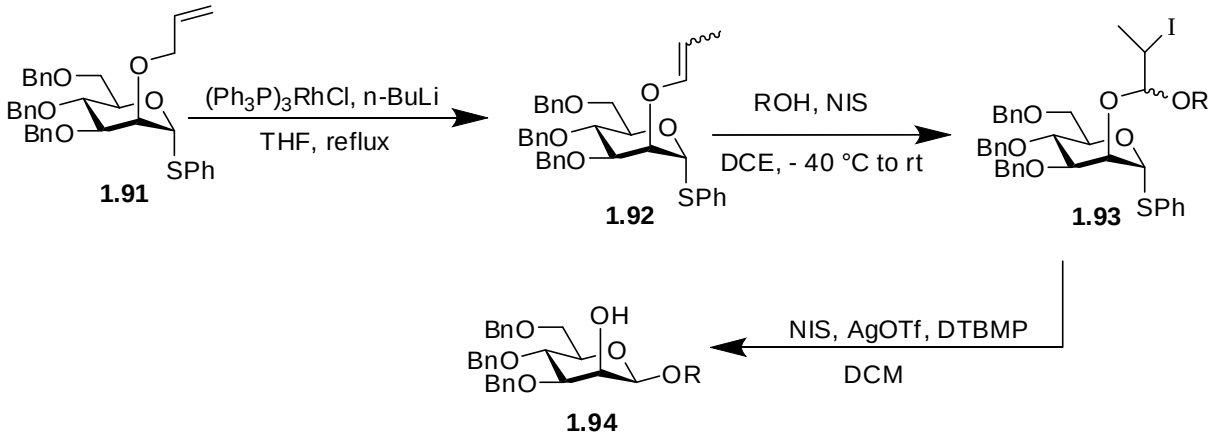
In light of these promising early discoveries, many other investigations into IAD began. It was hoped that this type of methodology could be used as an universal solution for the synthesis of 1,2-*cis* glycosides, regardless of whether they were *gluco* or *manno* in nature. Work by Bols, following the approach of Stork, had already shown that silicon-tethered IAD could be used for the synthesis of *α*-glucosides.[76] Following the work of Hindsgaul, Fairbanks' group discovered

that the tethering step could be improved by the use of NIS as opposed to a catalytic acid, and when used in conjunction with a thioglycoside donor, a one-pot procedure was developed for both *gluco* and *manno* donors. Thus, a method for the synthesis of *cis* α-glucosides was achieved (Scheme 1.19).[77]



Scheme 1.19

Treatment of the donor **1.88** with NIS led to formation of the tethered intermediate **1.89** as the enol ether was 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 of the alcohol at the tertiary centre was perhaps having a limiting effect in the tethering step, and hence an alternative tethering group, an allyl group, was developed and subsequently optimized (Scheme 1.20).[78]



Scheme 1.20

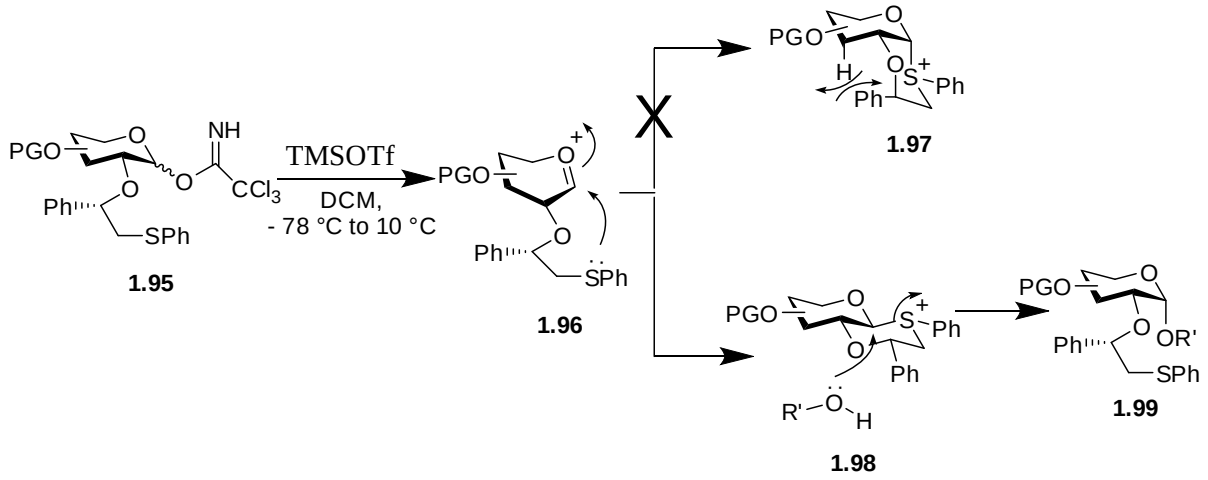
The allyl group of **1.91** was efficiently isomerized by treatment with Wilkinson's catalyst, pre-treated with *n*-butyl lithium, to give the vinyl ether **1.92**.[79] NIS-mediated tethering gave **1.93** which could be glycosylated in the same fashion as before to give the 1,2-*cis* glycoside **1.94**. Although, this procedure gave excellent selectivity and yields for secondary alcohol acceptors with mannose donor systems, it was unfortunate that these results could not be replicated with glucose donor systems, and generally low yields were observed. Despite the somewhat unreliable nature of the allyl IAD methodology for the synthesis of 1,2-*cis* α-glycosides, the methodology was eventually utilized in the synthesis of the Glc_3Man *N*-glycan tetrasaccharide, employing an iterative method and optimized to produce the challenging tetrasaccharide in an efficient and completely stereocontrolled manner.[80]

As well as the development of allyl IAD, the Fairbanks group also extended the idea to the use of a propargyl tethering group.[81] Elsewhere, Ogawa and Ito have extensively exploited the use of a *para*-methoxybenzyl tethering group, and used this methodology to successcompletely synthesize the core *N*-glycan pentasaccharide and even to perform solid supported IAD processes.[82] More recently, the use of naphthyl mediated IAD was also explored.[83]

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 IAD method that can be employed in oligosaccharide synthesis. The major drawbacks in the use of the methodology are the extra tethering step required, and particularly the decrease in efficiency when applied to more extended and hindered donors and acceptors, meaning the technique is still unsuitable for complex oligosaccharide synthesis.

1.6.6 The synthesis of 1,2-*cis* *α*-glycosides *via* *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 acyl 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 neighboring 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 neighboring 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,[84] 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,[85] which gave exclusive 1,2-*cis* *α*-selectivity with a variety of glycosyl acceptors by formation of an intermediate sulfonium ion by neighboring group participation (Scheme 1.21).

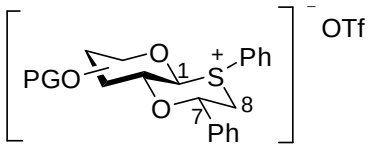


Scheme 1.21

Activation of the trichloroacetimidate donor **1.95** led to the formation of oxocarbenium ion **1.96**. Neighboring group participation from the sulfur then occurred, forming a 6-membered cyclic intermediate. Two intermediates could be formed; a *cis*-decalin type of intermediate **1.97** or a *trans*-decalin type of intermediate **1.98**. However, due to the presence of the chiral auxiliary, the formation of **1.97** is disfavored due to the steric interaction of the phenyl group with the 3-position hydrogen atom. Therefore **1.98** is favored and subsequent S_N2 displacement by the glycosyl acceptor produces the 1,2-*cis* glycoside **1.99**. This elegant methodology has since been applied in the solid-supported synthesis of an α-glucan pentasaccharide.[86] Although the installation of the chiral neighboring group requires a five step manipulation from a commercially available chiral starting material, it was additionally 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 installment of the (1*S*)-phenyl-2-(phenylsulfanyl)ethyl moiety.

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 adopt a β-configuration, probably due to a combination of asteric and stereoelectronic effects. Boons[87] later observed that electron withdrawing substituents on the donor hydroxyls, such as acetates[88] which inductively disarm the ring making the anomeric carbon less reactive, facilitated this neighboring group participation by destabilizing the oxocarbenium ion intermediate **1.96**, and so favoured the equilibrium towards intermediate **1.98**, resulting in better stereoselectivity. Boons confirmed neighboring group participation by the substituent at position 2 by performing two dimensional NMR (HMBC) experiments at – 20 °C which confirmed a 3 bond correlation between H-8 and C-1 in the intermediate **1.98** (Figure 1.2).[85]



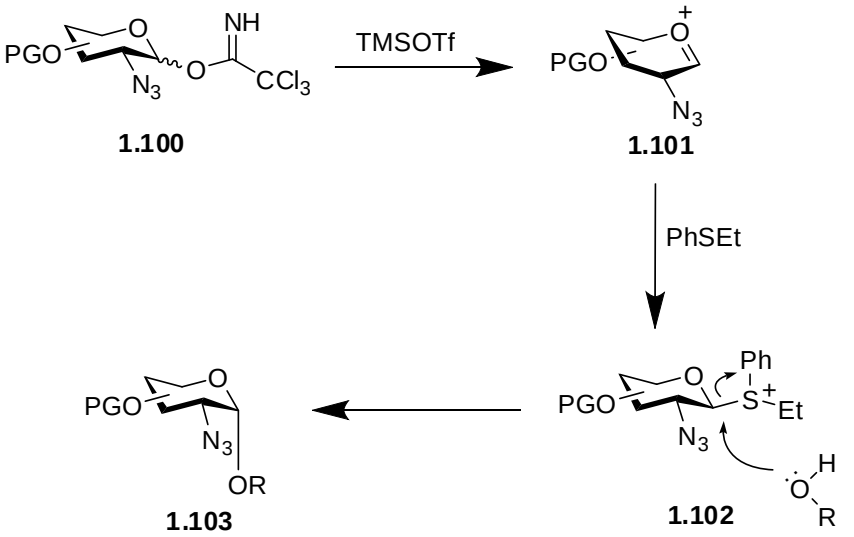
1.98

Figure 1.2

However even if spectroscopic studies showed evidence of neighboring group participation, the reaction could proceed without NGP if a low-energy pathway to the product exists that does not involve NGP. It was suggested by the Woerpel[89] that the diastereoselectivity observed in the Boon's system was not necessarily due to involvement of neighboring group participation, implicating a Curtin-Hammett kinetic scenario: the formation of a low-energy intermediate does not necessitate its involvement in the product-forming pathway. It was generally presumed that the alcohol would directly displace the sulfonium group in an S_N2-like reaction. An alternative explanation would be that the sulfonium ion is a "resting state" for the system, which goes on to react through a higher-energy oxocarbenium ion intermediate giving rise to a Curtin–Hammett

kinetic scenario; in this case the stereoselectivity of the reaction would be dependent on the conformation of the oxocarbenium ion.

Following on from the use of a chiral auxiliary based sulfur neighboring 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 1.22).[90]



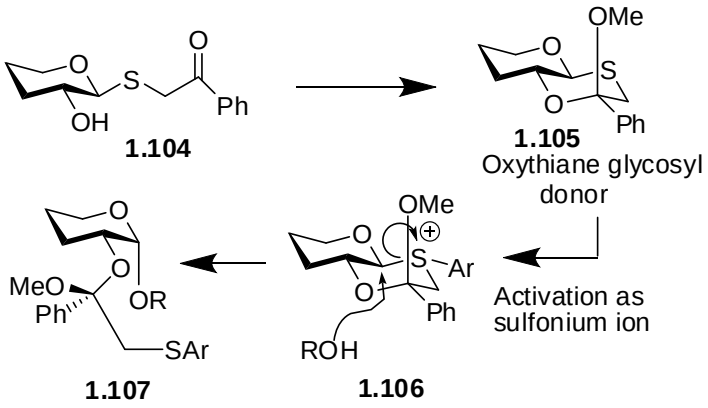
Scheme 1.22

Activation of the 2-azido-2-deoxy glucose donor **1.100** in the presence of a glycosyl acceptor and a large excess (10 equiv.) of either phenyl-thioethyl ether or thiophene was shown to form the α-glycoside **1.103** with high selectivity. Interestingly, the 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 **1.102** was indeed being formed in the reaction, and was exclusively in the β-configuration.

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

Turnbull[91] and co-workers recently designed a new oxathiane donor scaffold where the axial methoxy group was replaced with an *O*-substituent constrained in a bicyclic ring (Scheme 1.23). As in the previous methods, the oxathiane ketal donor was then activated *via S*-arylation. Overall, the novel class of oxathiane glycosyl donors is easily accessible, is highly α-selective for glycosylation, and offers good stability towards common protecting group manipulations.

A novel strategy was employed by Turnbull group[92] to activate the glycosyl donors based on electrophilic aromatic substitution, which exploits the fact that trifloxysulfonium salt is more electrophilic at sulfur than at the anomeric carbon. Sulfoxide donors were activated with triflic anhydride, and allowed to react with trimethoxybenzene to give sulfonium ions. A range of alcohols were glycosylated in good to excellent yields, and with essentially complete α-stereoselectivity.



Scheme 1.23

At the time of designing the oxathiane glycosyl donors, it was assumed that stereoselectivity arises from an S_N2-like displacement of the equatorial sulfonium ion by an acceptor alcohol. However, variation of the oxathiane structure in their later investigations,[93] revealed that some of the sulfonium ions were not completely stereoselective, and probably follow an S_N1-type mechanism. A ketal group on the oxathiane ring significantly reduced the reactivity of the glycosyl donors, to the point at which a methyl glycosyl sulfonium ion (**1.108**) was sufficiently stable to isolate and crystallise from an alcoholic solvent (Figure 1.3).

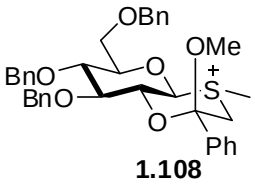
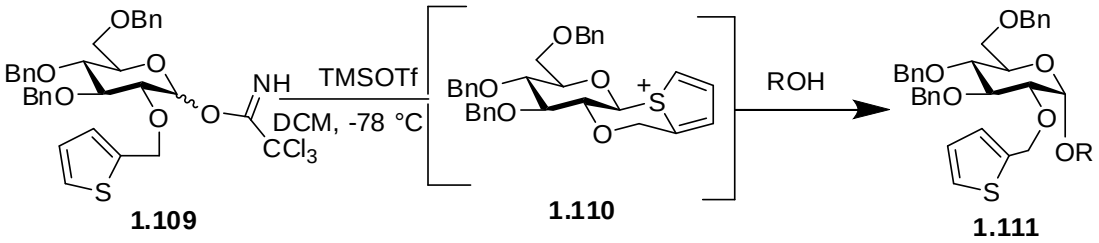


Figure 1.3

In his later studies (explained in details in chapter -2, section 2.6), Turnbull[94] had suggested that that even though NMR studies might show a stable intermediate which should result in a very stereoselective glycosylation reaction, caution should be applied before invoking it as an intermediate on the reaction pathway. NGP seen in intermediate therefore need not directly be reflected in diastereomeric ratio of glycosides formed.

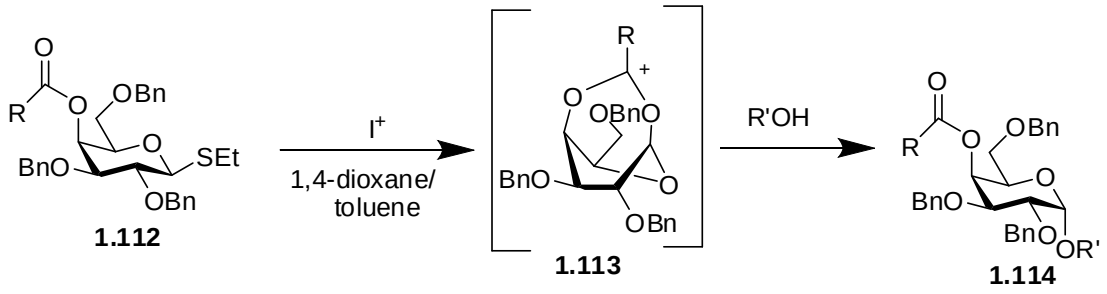
The Boons' method has proven to be a very interesting and effective approach for the formation of *α-cis* glycosides, but it relies on a chiral protecting group and thus is expensive. The Fairbanks group[95] devised a simpler alternative to Boons' methodology, which gives essentially the same stereoselectivity. In this methodology, the use of a 2-*O*-(thiophen-2-yl)methyl protecting group allowed for a highly stereoselective *α*-glucosylation with a trichloroacetimidate donor **1.109**. An increase in stereoselectivity, presumably arising from the intramolecular formation of a transient intermediate thiophenium ion **1.110**, correlated with increased bulk of the glycosyl acceptor (Scheme 1.24).



Scheme 1.24

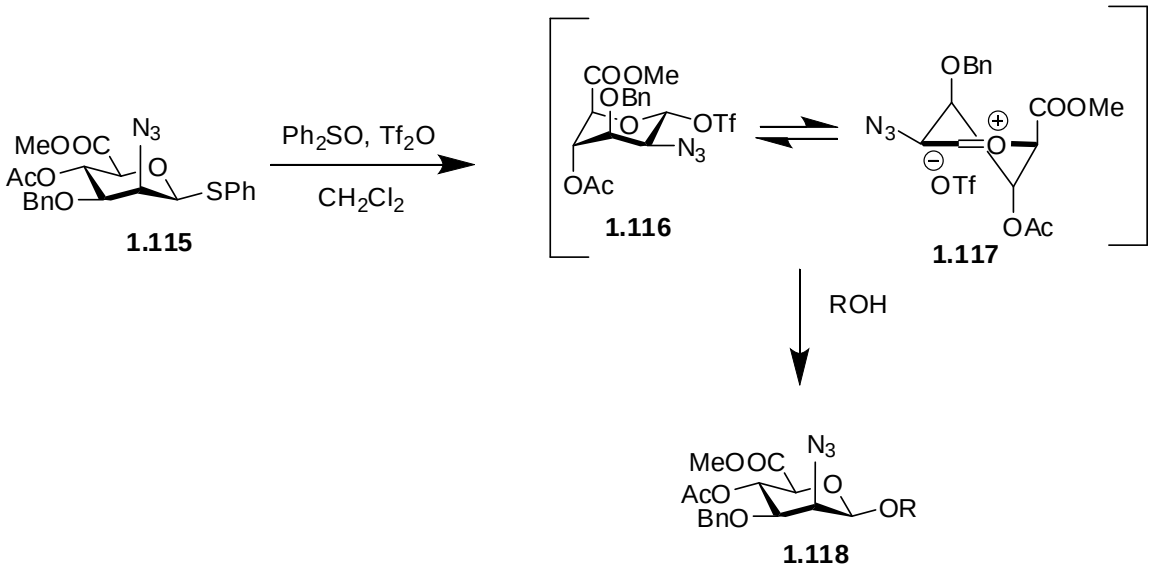
1.6.7 Remote protecting groups

The effects of remote substituents have perhaps been considered of somewhat lesser importance than those of the neighbouring substituent at C-2. However, the idea of participating groups at remote positions has been investigated by several researchers. There have been various reports, ranging from the long-range 6-*O*-acyl or carbonate group assisted synthesis of *α*-glucosides,[96] which both favor or oppose of the idea of remote participation being useful. For glycosyl donors of the D-*galacto* series, a remote effect beneficial for the formation of *α*-galactosides (**1.114**) was noted when a participating moiety was present at C-4 (Scheme 1.25).[97] Similar effects (including C-3 participation) were also reported for donors with L-fuco,[98] L-rhamno,[99] D-manno,[100] and D-gluco[101] stereochemistry.



Scheme 1.25

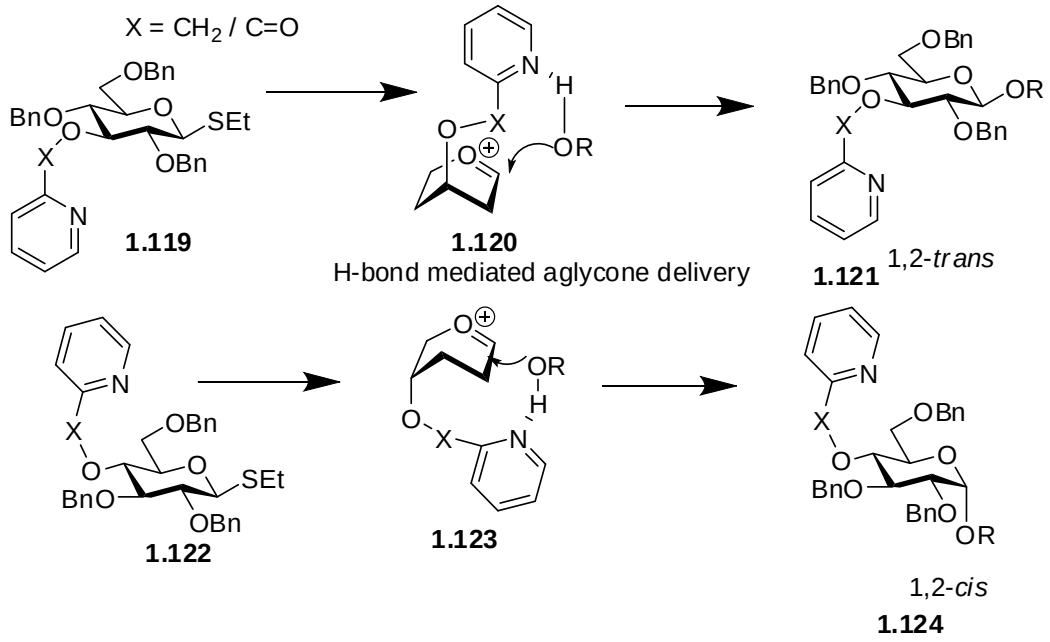
Codée and co-workers investigated the use of a 2-azido-mannouronate ester donor for glycosylation, and observed high 1,2-*cis* selectivity.[102] Investigations concluded that when the thiophenyl donor **1.115** was activated in the presence of diphenyl sulfoxide and triflic anhydride, the anomeric triflate was formed (Scheme 1.26). The latter exists as an interchangeable mixture of conformers with the $^{1}C_{4}$ chair **1.116** as the predominant species. In principle, the triflate can lead to the *β*-linked product *via* an S_N2-like displacement. Alternatively, the reaction can proceed *via* an S_N1-like pathway. In this case, the oxocarbenium ion intermediate will preferentially adopt the $^{3}H_{4}$ half-chair conformation **1.117**, which closely resembles the major $^{1}C_{4}$ conformation of triflate. In this case, the C-5 carboxylate occupies a pseudo-axial position allowing for stabilization of the positive charge. The incoming nucleophile will then attack from the *β*-face to produce the disaccharide with complete 1,2-*cis* selectivity.



Scheme 1.26

A very different stereodirecting effect was reported for remote picolinyl (Pic) and picoloyl (Pico) substituents by Demchenko. Picolinyl protection at C-2 formally participates at the anomeric center and gives 1,2-*trans* glycosides *via* a six-membered ring intermediate.[103] However the action of the remote picolinyl and related picoloyl substituents is totally different. As they are not able to participate at the anomeric center directly, the nitrogen atom of the picolinyl group forms a hydrogen bond with the incoming glycosyl acceptor. As a result, a very high facial selectivity is observed, which is always *syn* with respect to the picolinyl substituent.[104] This rather unexpected involvement of remote picolinyl substituents was termed 'H-bond-mediated aglycone delivery' (HAD). Based on the above hypothesis, it was also shown that under high dilution conditions (5 mM), 4-*O*-picoloyl or picolinyl glucosyl donors gave faster reactions and enhanced selectivity compared to those obtained under standard concentration (50 mM). Thus, glucosyl donors provided high levels of α-selectivity, particularly with *O*-picoloyl protection, whereas a galactosyl donor and a rhamnosyl donor gave high β-selectivity. The synthesis of 1,2-

trans β-glycosides –[o **1.121** and1,2-*cis* α-glycosides **1.124** from 3-*O*-picoloyl/picolinyl **1.119** and 4-*O*-picoloyl/picolinyl glucosyl donor **1.122** respectively are shown below (Scheme 1.27).



Scheme 1.27

1.7 Project objectives

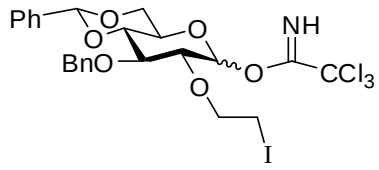
The objective of this project was to develop new methods of stereocontrolled glycosylation. Given the recent advances in neighbouring group participation methods for the synthesis of 1,2-*cis* α-glycosides developed by Boons *et al*., it was postulated that further improvements could be made towards 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[85],[90] suggested that simpler protecting groups could be employed at the 2-position for neighbouring group participation.

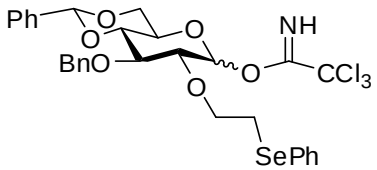
The Fairbanks group has shown similar results by synthesis and utility of a series of 2-*O*-(thiophen-2-yl)-methyl-protected glycosyl donors in a series of stereoselective α-glycosylation reactions.[95] For example an α:β ratio of 8:1 was achieved with diacetone galactose as acceptor at -78 °C, in DCM (Scheme 1.24). It was thought that this selectivity could be improved by the exchange of sulfur for a better nucleophile at position-2. Following these initial studies, the use of softer atoms at the 2-position of an ethyl ether was contemplated in order to increase the propensity for 6-ring NGP, and so increase the levels of α-selectivity- that could be observed.

Following this line of reasoning, Dan Cox, a previous Ph.D. student in the Fairbanks[105] group reported high levels of α-selectivity by use of both iodo- and a selenophenyl groups attached to an ethyl ether at position-2 of a series of completely armed glycosyl donors.[67a] Based on the observation of Boons' that higher stereoselectivity was observed on disarmed donors compared

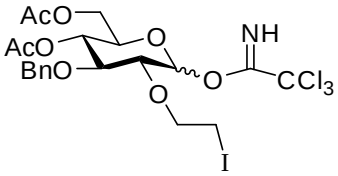
to armed donors,[87] my work focused on the synthesis and investigation of a series of partially disarmed donors with iodo- and a selenophenyl groups attached to an ethyl ether at position-2. The initial targets chosen for investigation are shown below in Figure 1.4.



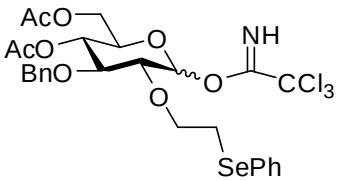
1.125



1.126



1.127



1.128

Figure 1.4

1.8 References

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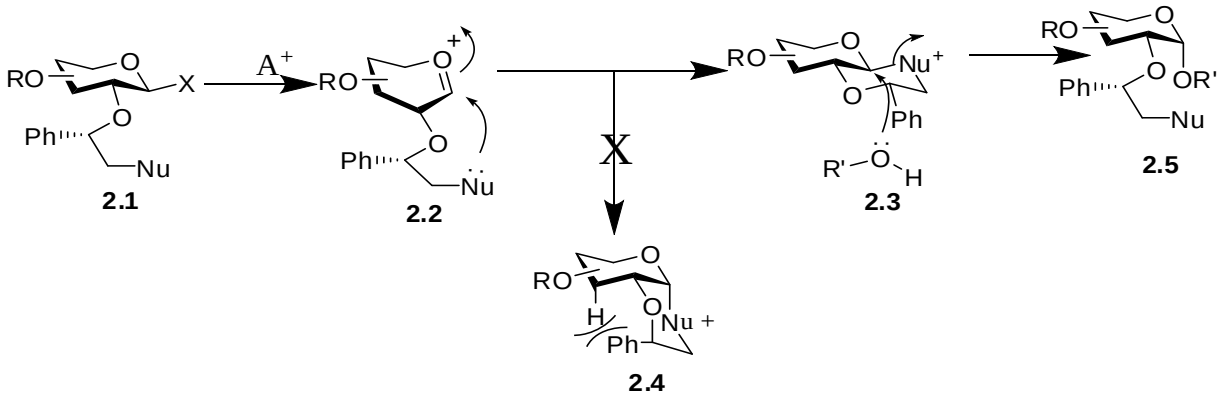
Chapter 2: Synthesis and evaluation of glycosyl donors bearing 2-*O*-(2-(phenylselenyl)ethyl) and 2-*O*-iodoethyl protecting groups

2.1 Introduction

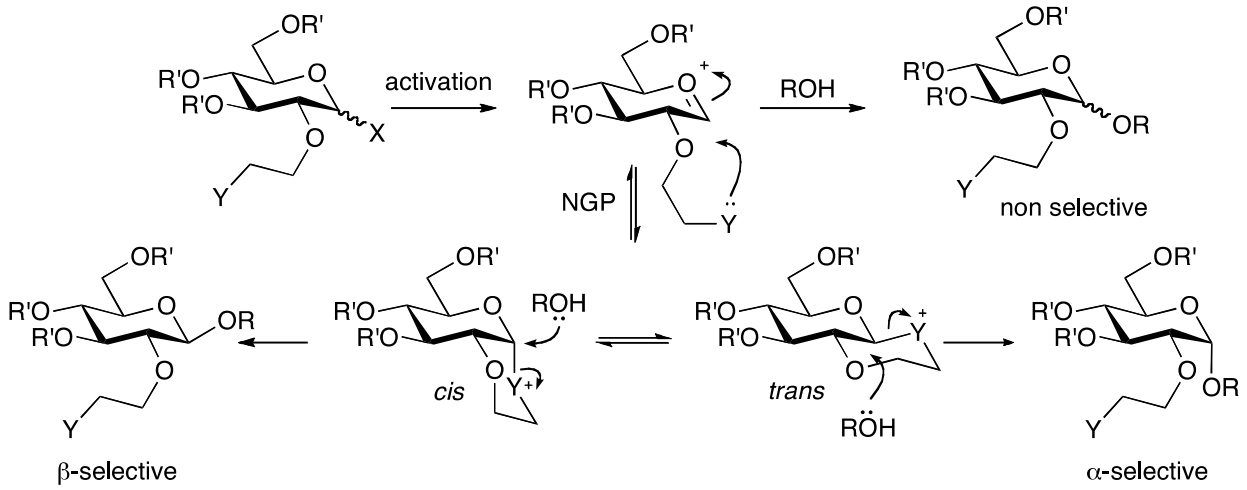
As noted in Chapter 1, this research project was inspired by the works of Boons[1] and relies on neighbouring group participation (NGP) occurring *via* a 6-membered ring forming a *trans* decalin type structure, which the glycosyl acceptor then attacks axially to produce the *α*-glycoside as a major reaction product (Scheme 2.1).



Scheme 2.1

The approach developed by Boons, shown in Scheme 2.1 has proven to be an interesting approach for the formation of *α*-1,2-*cis* glycosides, but it relies on the use of a chiral protecting group and is therefore expensive. So the question arises, if an achiral protecting group is used instead, will it still give *α*-selectivity in the formation of glucosides? Postulated equilibria between glycosyl cation and 6-ring intermediates arising from neighbouring group participation

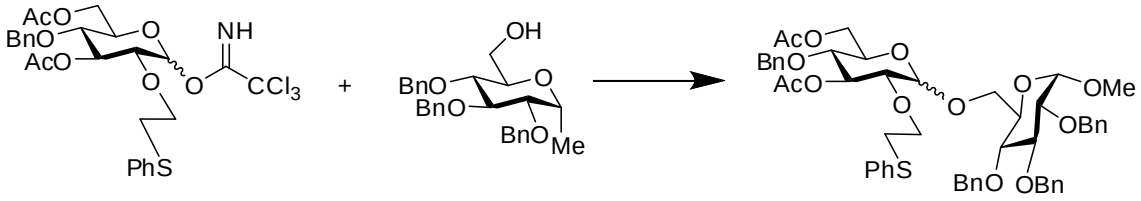
(NGP) of 2-substituted ethyl ethers, and the stereochemical consequences for the outcome of glycosylation is shown in scheme 2.2.



Scheme 2.2

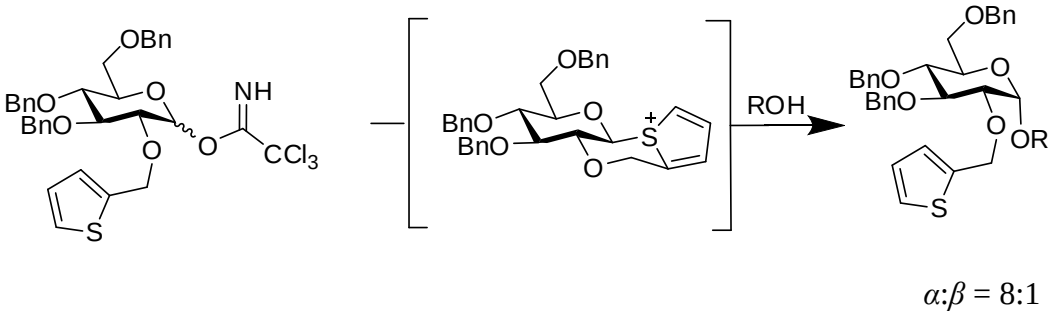
As can been seen in Scheme 2.2, there is possibility of formation of *cis*- and *trans*- decalin 6-membered ring intermediate, *via* NGP. There is also a possibility of equilibria between a glycosyl cation (or other acylic intermediate) and these cyclic species. It may be expected that a glycosyl cation should react with a glycosyl acceptor (ROH) in a predominantly non-selective fashion, whereas a *trans*-decalin cyclic intermediate should react to preferentially produce the α-glycoside product; conversely nucleophilic attack of an acceptor directly on the *cis*-decalin intermediate should lead to the β-glycoside.

Boons,[1a] in his work has shown that even without a chiral auxiliary group at position-2, a stereoselectivity of α:β = 8:1 was achieved by use of an phenylthio ethyl ether protection of the 2-position (Scheme 2.3).



Scheme 2.3

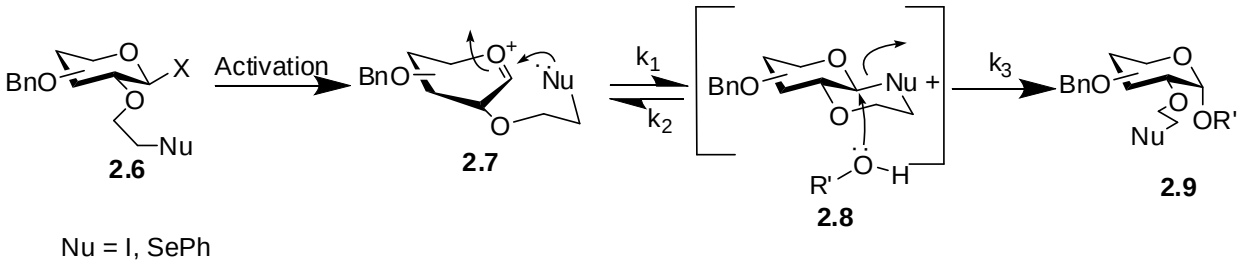
The Fairbanks group has shown similar results by synthesis and utility of a series of 2-*O*-(thiophen-2-yl)-methyl-protected glycosyl donors in a series of stereoselective α-glycosylation reactions.[2] For example an α:β ratio of 8:1 was achieved with diacetone galactose as acceptor at -78 °C, in DCM (Scheme 2.4).



Scheme 2.4

It was thought that this selectivity could be improved by the exchange of sulfur for a better nucleophile at position-2. Following these initial studies, the use of softer atoms at the 2-position of an ethyl ether was contemplated in order to increase the propensity for 6-ring NGP, and so increase the levels of α-selectivity- that could be observed.

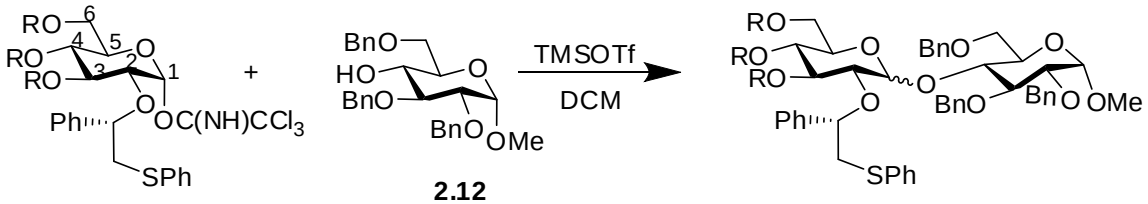
Following this line of reasoning, Dan Cox, a previous Ph.D. student in the Fairbanks[3] group reported high levels of α-selectivity by use of both iodo- and a selenophenyl groups attached to an ethyl ether at position-2 of a series of completely armed glycosyl donors[4] (Scheme 2.5).



Scheme 2.5

Apart from the NGP by the position-2, the question also arises, if the substituents on the ring at other positions affect the outcome in stereoselectivity. The other substituents do affect the intermediates, and probably would affect the stereoselectivity according to Curtin-Hammett principle. The Curtin–Hammett principle states that, for a reaction that has a pair of reactive intermediates or reactants that interconvert rapidly (as is usually the case for conformational isomers), each going irreversibly to a different product, the product ratio will depend both on the difference in energy between the two conformers and the free energy of the transition state going to each product. As a result, the product distribution will not necessarily reflect the equilibrium distribution of the two intermediates. The Curtin–Hammett principle has been invoked to explain selectivity in a variety of stereo- and regioselective reactions.[5]

In subsequent reports, Boons[6] has suggested that there is an equilibrium between intermediate ions of types **(2.2)** and **(2.3)** (Scheme 2.1). If the substituents on the ring stabilize intermediate-**2.3** more effectively, then a higher stereoselectivity is observed. Therefore in Boons' case the completely armed donors (with electron donating groups, such as benzyl groups) at position 3, 4 and 6 showed much lower stereoselectivity than completely disarmed donors (with electron withdrawing groups such as acetyl, benzoyl groups) at position 3, 4 and 6 (Scheme 2.6).



2.10: R = Ac
2.11: R = Bn

2.12

2.13 (R = Ac), α:β = 1:0
2.14 (R = Bn), α:β = 1:1

Scheme 2.6

Based on this report, it was thought important to investigate the electronic effects of the protecting groups at positions 3, 4, and 6, of the donor on the stereochemical outcome of glycosylation.

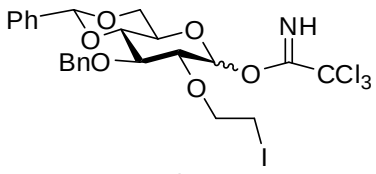
Dan Cox's[3] studies were performed on completely armed glycosyl donors with iodo/selenophenyl ethyl group at position-2, and benzyl groups on positions 3, 4 and 6. It was decided to perform similar studies on a series of partially disarmed donors and completely disarmed donors to get an overall picture of the NGP provided by the iodoethyl and selenophenyl ethyl protecting groups at position 2. The synthesis of a completely disarmed donor, with acetyl group at positions 3, 4 and 6 was undertaken by another researcher.[3] The work reported in this chapter focuses on the synthesis and investigation of a series of partially disarmed donors. Specifically, the donors for investigation contained a benzyl group at position-3, and either a benzylidene acetal or two acetates at position 4 and 6.

The disarming effect of the 4,6-benzylidene acetal group on glycoside reactivity, which is due to a combination of torsional and electronic effects has been well established.[7] The presence of a benzylidene ring should therefore destabilize the oxocarbenium intermediate 2.2, and should promote neighboring group participation by the nucleophilic group attached at the 2 position, favoring the formation of intermediate 2.3. Hence, it was expected that the incorporation of a

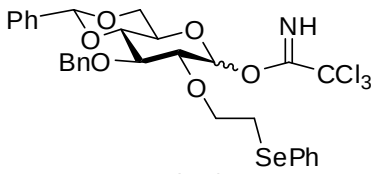
4,6-benzylidene would produce higher levels of α-selectivity. Similarly, incorporation of acetate groups at positions 4 and 6, was expected to produce higher levels of stereoselectivity, due to its –ve inductive effect leading to destabilization of oxocarbenium intermediate, favouring the ring formation.

2.2 General strategy for synthesis of donors

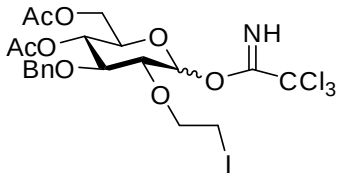
The following set of partially disarmed donors were chosen as synthetic targets (Figure 2.1).



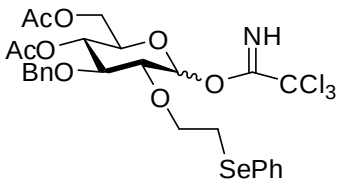
2.15



2.16



2.17



2.18

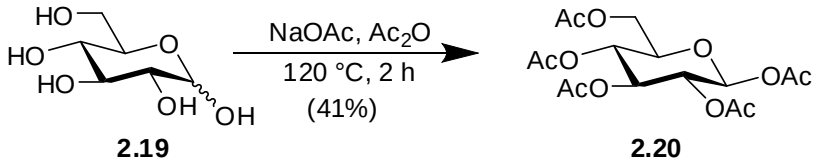
Figure 2.1

The general synthetic strategy envisaged for the synthesis of the donors **2.15** and **2.16** involved selective anomeric protection of D-glucose, followed by 4,6-benzylidene ring formation. Benzylidene ring formation takes place exclusively at hydroxyls 4- and 6-, because this leads to formation of a thermodynamic stable six membered-ring, with the phenyl ring at the acetal centre occupying an equatorial position. Then, it was anticipated that regioselective benzylation at position 3 could be achieved, followed by allylation of position-2. The allyl group could be converted into both to 2-iodoethyl ether and 2-(phenylseleno)ethyl ethers by a short series of

reactions. Finally the anomeric position could be de-protected and converted into a trichloroacetimidate donor as the last step.

2.2.1 Strategy for synthesis of donors 2.15 and 2.16

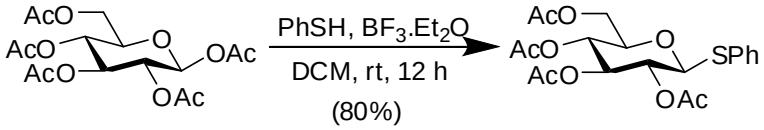
D-Glucose **2.19** was kinetically acetylated on reaction with sodium acetate and acetic anhydride to give glucopentaacetate **2.20** (Scheme 2.7).[8]



2.19 **2.20**

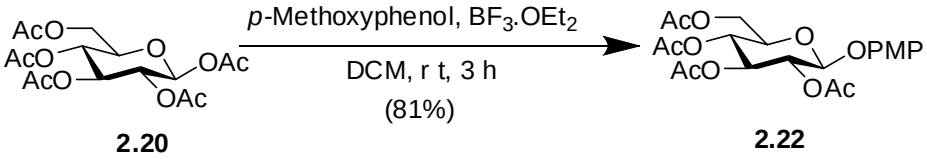
Scheme 2.7

Subsequently two strategies were undertaken to protect the anomeric position. In the first strategy, **2.20** was converted to thiophenyl glycoside by reaction with thiophenol in presence of a Lewis acid, to give the corresponding thioglycoside **2.21** (Scheme 2.8).[9] Similarly **2.20** was converted to the corresponding PMP glycoside **2.22** on reaction with *p*-methoxyphenol in the presence of a Lewis acid (Scheme 2.9).[10] In both the cases, exclusively β glycosides, were formed due to NGP provided by the acetate group at position-2.



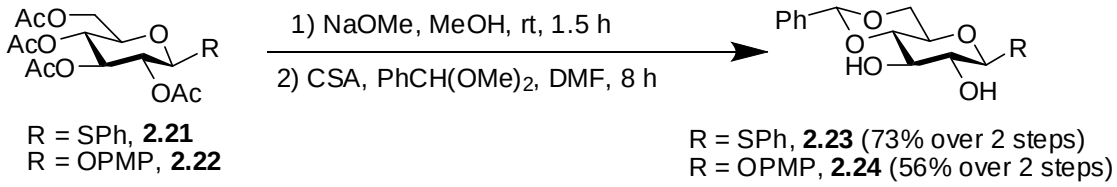
2.20 **2.21**

Scheme 2.8



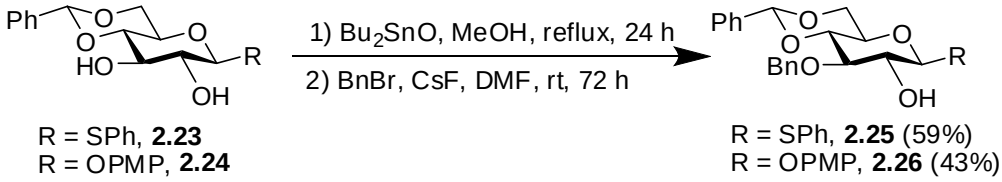
Scheme 2.9

De-acetylation of both **2.21** and **2.22** by the Zemplén method,[11] followed by benzylidene protection of positions 4 and 6, achieved by reaction with benzaldehyde dimethyl acetal in the presence of catalytic acid, yielded diols **2.23** and **2.24**, respectively (Scheme 2.10).[12]



Scheme 2.10

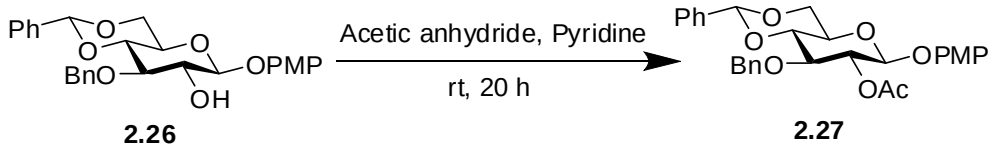
Regioselective benzylation of both **2.23** and **2.24**, on treatment with benzyl bromide after the formation of tin acetals by reaction of the diols with dibutyltin oxide, regioselectively afforded the mono-benzylated products at position 3,[13] **2.25** and **2.26**, respectively (Scheme 2.11).



Scheme 2.11

To confirm that the benzylation had indeed occurred selectively at position-3, **2.26** was acetylated by reaction with acetic anhydride and pyridine to give acetate **2.27**. ^{1}H-NMR clearly

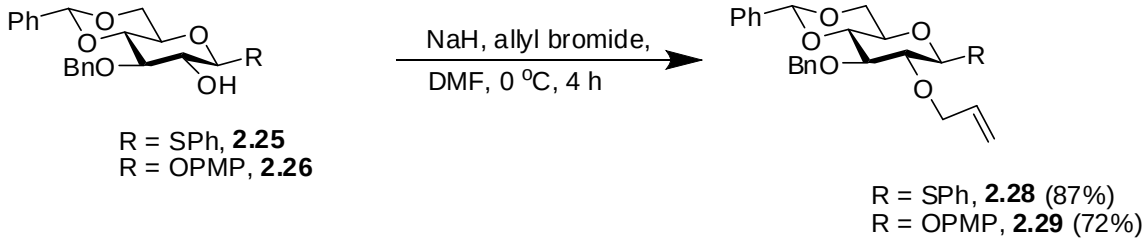
indicated a downfield shift of the H-2 signal, confirming that acetylation had occurred at position-2 (Scheme 2.12).



2.26 **2.27**

Scheme 2.12

Alcohols **2.25** and **2.26** were then allylated at their remaining free hydroxyl groups by reaction with allyl bromide in the presence of sodium hydride, to give allyl ethers **2.28** and **2.29**, respectively (Scheme 2.13).[14]

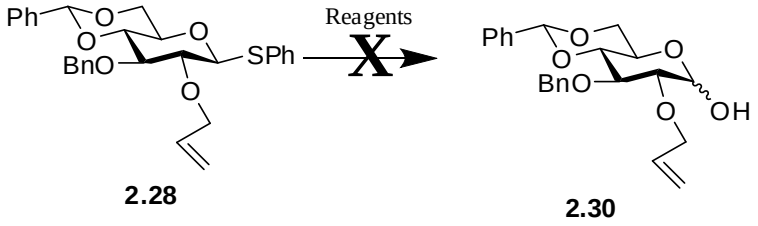


R = SPh, **2.25**
R = OPMP, **2.26**

R = SPh, **2.28** (87%)
R = OPMP, **2.29** (72%)

Scheme 2.13

Following the allylation reaction, various attempts to hydrolyze the SPh group of **2.28** in order to form **2.30** all proved unsuccessful. Generally multiple spots on t.l.c. were seen when reaction was carried on, possibly due to reaction on the double bond of the allyl group. Major product could not be isolated and characterized in any of the conditions (Scheme 2.14).

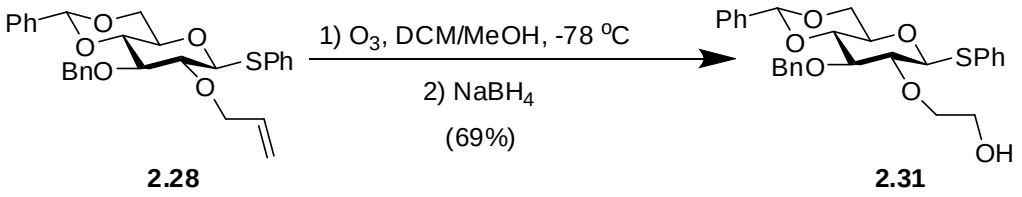


2.28 **2.30**

Sl. No.	Reaction Conditions	Outcome
1.	NBS/H_2O-Acetone, rt	Bromination on allyl group
2.	NIS, TFA/H_2O-DCM, rt	Iodination on ally group
3.	Chloramine-T/H_2O-Acetonitrile, reflux	No Reaction
4.	MeOTf, TTBP/H_2O-Dioxane, reflux	No Reaction
5.	Me_2S_2, Tf_2O/H_2O-DCM, rt	Decomposition
6.	1-Benzenesulfinylpiperidine, Tf_2O/H_2O-DCM, rt	Decomposition

Scheme 2.14

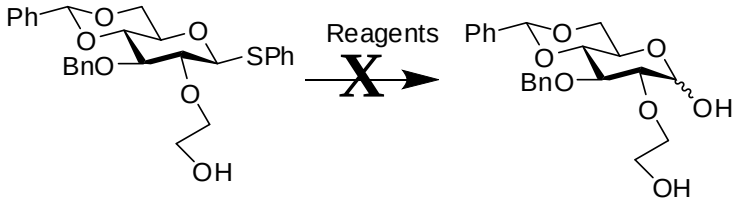
It was thought that perhaps hydrolysis of SPh was difficult due to steric hinderance, so an alternative strategy was attempted in which the allyl group was manipulated before the thioglycoside was attempted. Thus, allylated thiophenyl glycoside **2.28** was subjected to ozonolysis, followed by reduction with $NaBH_4$, which led to the cleavage of double bond, and formation of alcohol **2.31** (Scheme 2.15).[15]



2.28 **2.31**

Scheme 2.15

However **2.31** also proved resistant to hydrolysis, and did not give **2.32**, under either sets of reaction conditions investigated (Scheme 2.16).

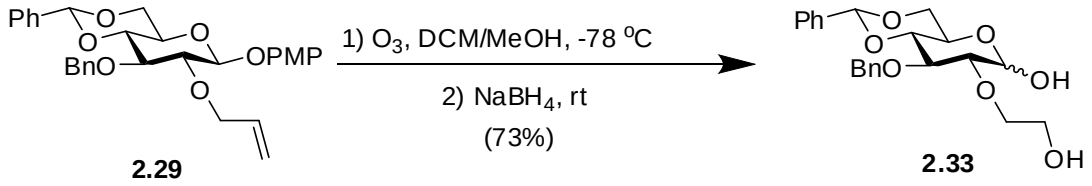


2.31 **2.32**

Sl. No.	Reaction Conditions	Outcome
1.	NBS/H_2O-Acetone, Reflux	Decomposition
2.	NIS, TFA/H_2O-DCM, Reflux	Decomposition

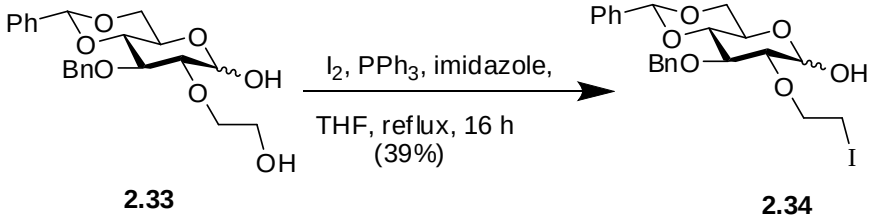
Scheme 2.16

Now the attention shifted back to PMP glycoside. Ozonolysis of PMP glycoside **2.29** not only cleaved the allyl group, but also resulted in cleavage of PMP group at the anomeric position. Thus, the ozonolysis of **2.29**, followed by reduction with sodium borohydride, yielded diol **2.33** (Scheme 2.17).



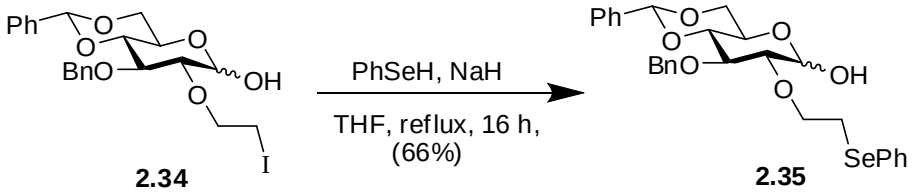
Scheme 2.17

The Appel reaction usually results in the regioselective halogenation of primary hydroxyl groups in the presence of secondary hydroxyl groups.[16] Accordingly reaction of **2.33**, with I_2/PPh_3 in the presence of imidazole, iodide **2.34** albeit in rather low yield (Scheme 2.18).



Scheme 2.18

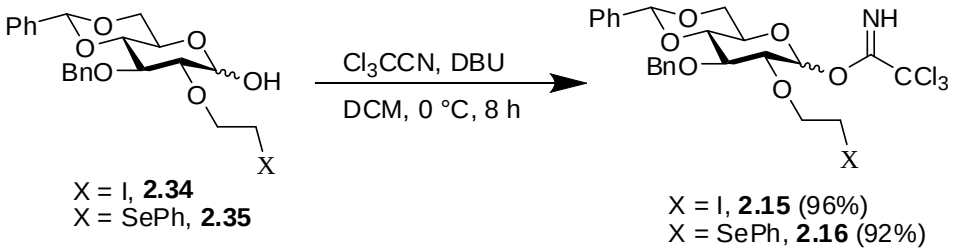
The iodide of **2.34** then converted into phenyl selenyl group by reaction of **2.34** with benzene selenol in the presence of sodium hydride to yield hemiacetal **2.35** (Scheme 2.19).[17]



Scheme 2.19

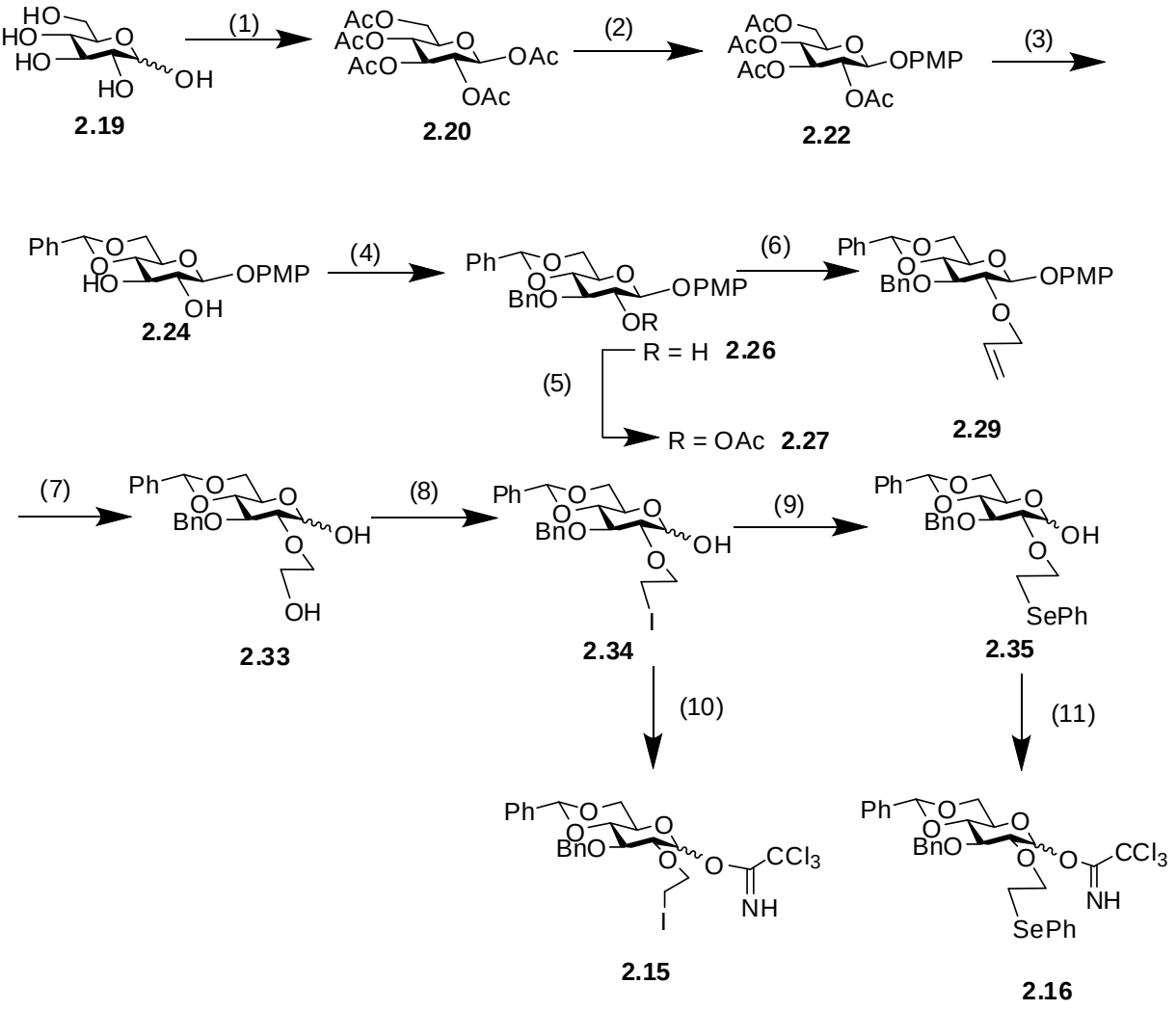
The free hydroxyl group at the anomeric centres of compounds **2.34** and **2.35** was then converted to a trichloroacetimidate by reaction with trichloroacetonitrile in the presence of DBU to yield

donors **2.15** and **2.16** respectively, thus completing the synthesis of first set of donors, required for investigation of the stereochemical outcome of the glycosylation reactions (Scheme 2.20).[18]



Scheme 2.20

The successful route followed for the synthesis of the donors **2.15** (8 steps, overall yield = 1.8%) and **2.16** (9 steps, overall yield = 1.6%) has been summarized in the following scheme (Scheme 2.21).

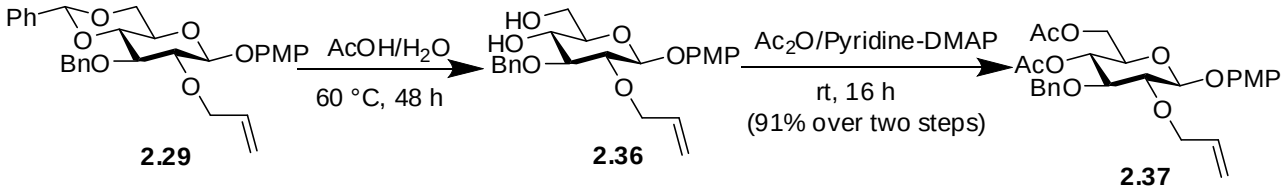


Scheme 2.21: (1) Ac_2O, NaOAc, 120 °C, 2h, 41%; (2) *p*-Methoxyphenol, $BF_3.Et_2O$, DCM, rt, 3 h, 81%; (3) (a) NaOMe, MeOH, 1.5 h; (b) CSA, $PhCH(OMe)_2$, DMF, 8 h, 56% over two steps; (4) (a) Bu_2SnO, MeOH, reflux, 24 h; (b) BnBr, CsF, DMF, 72 h, 43%; (5) Ac_2O, pyridine, rt, 20 h; (6) NaH, allyl bromide, DMF, 0 ^oC, 4 h, 72%; (7) O_3, DCM/MeOH, -78 ^oC then add $NaBH_4$, 73%; (8) I_2, PPh_3, imidazole, THF, reflux, 24 h, 39%; (9) PhSeH, NaH, THF, reflux, 16 h, 66%; (10) Cl_3CCN, DBU, DCM, 0 °C, 8 h, 96%; (11) Cl_3CCN, DBU, DCM, 0 °C, 8 h, 92%.

2.2.2 Strategy for synthesis 2.17 and 2.18

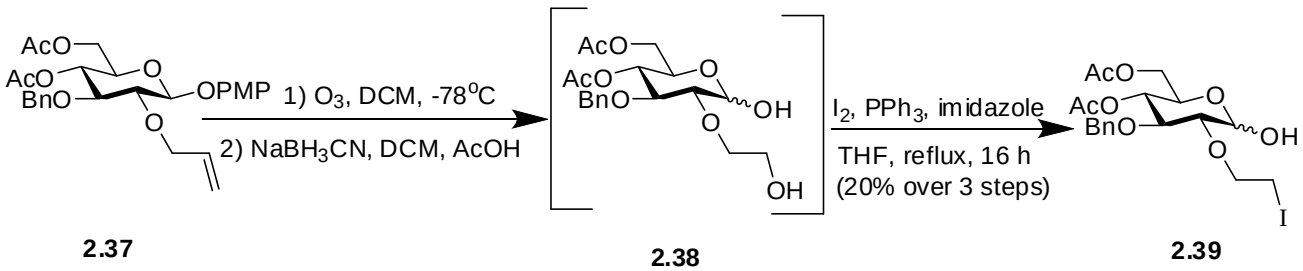
Now the focus shifted to the synthesis of the other two donors, diacetate **2.17**, and **2.18**. The general strategy involved similar steps to those used in the synthesis of **2.15** and **2.16** with the addition of hydrolysis of the benzylidene ring at appropriate step, followed by acetylation in order to introduce acetyl groups at position 4 and 6.

The benzylidene ring of **2.29**, was hydrolyzed by reaction with 80% aq. acetic acid to give diol **2.36**. The free hydroxyl groups at positions 4- and 6- were then acetylated by reaction with acetic anhydride in the presence of pyridine to yield diacetate **2.37** (Scheme 2.22).[19]



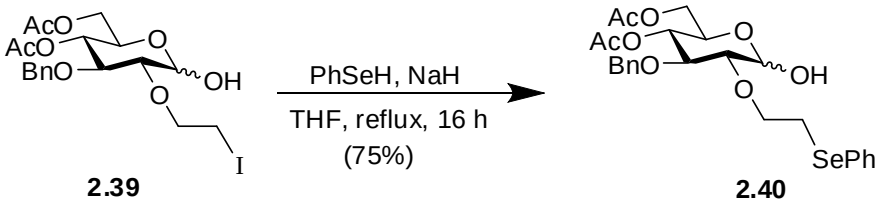
Scheme 2.22

Ozonolysis of **2.37** was followed by reduction with sodium cyanoborohydride to yield diol **2.38**. $NaBH_4$ led to partial reduction of acetate group, therefore a milder reducing agent $NaBH_3CN$ was used. Appel reaction of **2.38** then yielded iodide **2.39** (Scheme 2.23).



Scheme 2.23

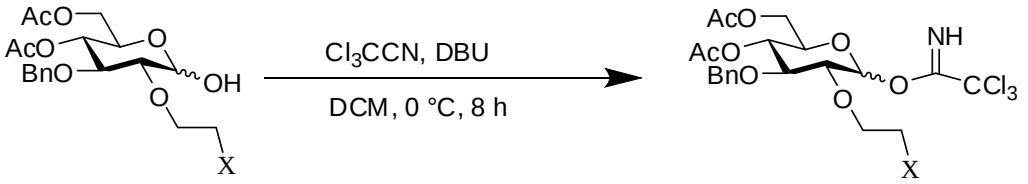
Finally the iodide group was replaced with phenyl-selenyl group by reaction of **2.39** with benzene selenol in the presence of sodium hydride to yield 2-phenylselenoethyl ether **2.40** (Scheme 2.24).



2.39 **2.40**

Scheme 2.24

The free hydroxyl group at the anomeric centres of **2.39** and **2.40** was then converted to a trichloroacetimidate by reaction with trichloroacetonitrile in the presence of DBU to give donors **2.17** and **2.18** respectively, thus completing the synthesis of other two donors required (Scheme 2.25).

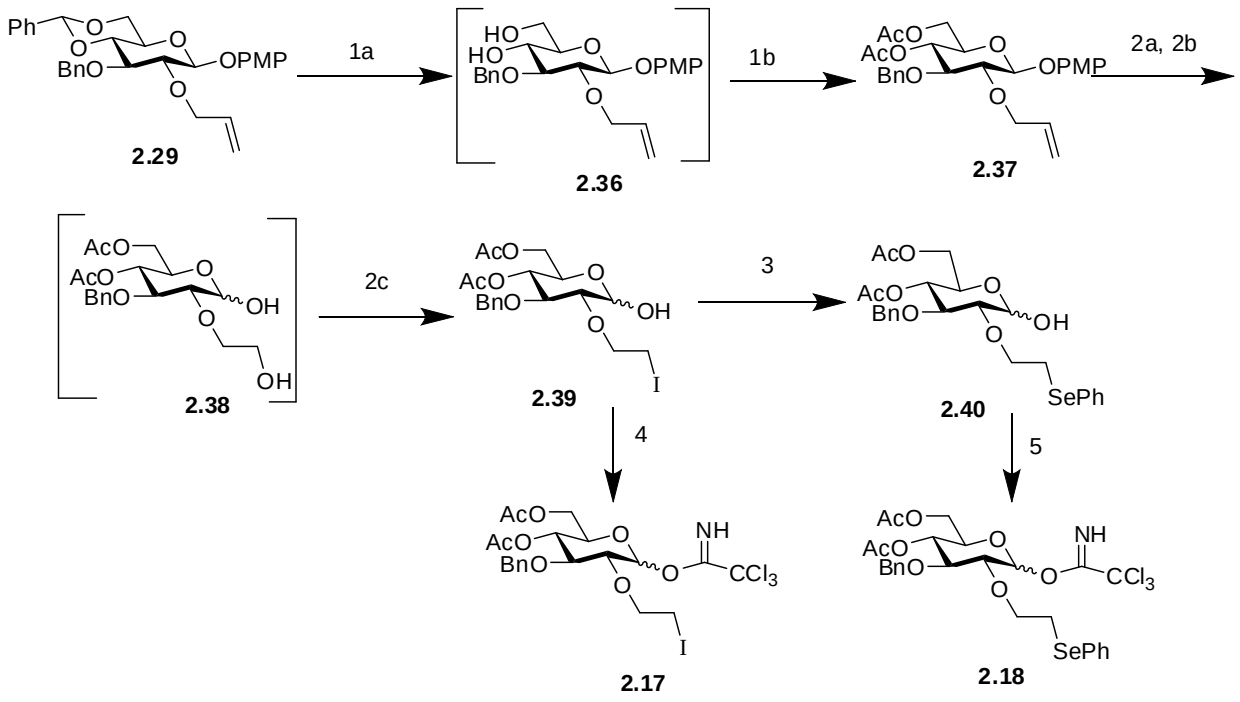


X = I, **2.39**
X = SePh, **2.40**

X = I, **2.17** (89%)
X = SePh, **2.18** (74%)

Scheme 2.25

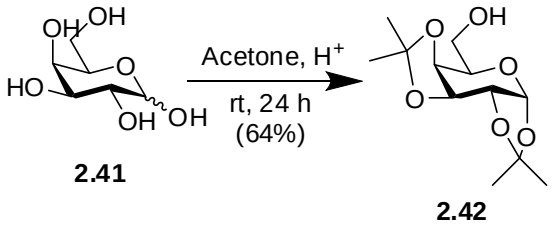
The successful routes followed for the synthesis of the donors **2.17** (10 steps, overall yield = 0.9%) and **2.18** (11 steps, overall yield = 0.8%) is been summarized in the following scheme (Scheme 2.26).



Scheme 2.26: (1) (a) AcOH, H_2O, 60 ^oC; (b) Ac_2O, pyridine, DMAP, 91%; (2) (a) O_3, DCM, -78 ^oC; (b) $NaBH_3CN$, DCM, AcOH; (c) I_2, PPh_3, imidazole, THF, reflux, 16 h, 20% over 3 steps; (3) PhSeH, NaH, THF, reflux, 16 h, 75%; (4) Cl_3CCN, DBU, DCM, 0 °C, 3 h, 89%; (5) Cl_3CCN, DBU, DCM, 0 °C, 3 h, 74%.

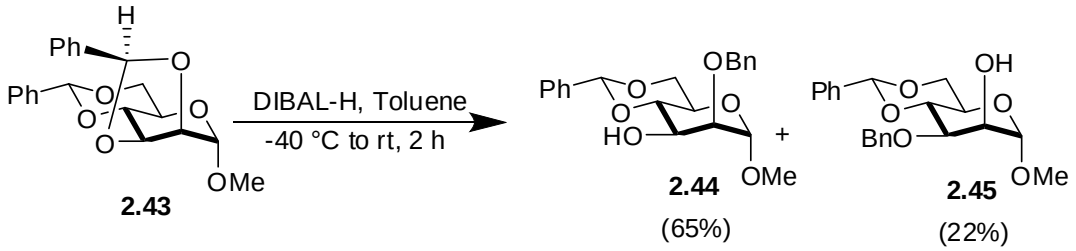
2.3 Synthesis of acceptors and TTBP

Three acceptors were synthesized for use in glycosylation reactions with the donors synthesized above. The first acceptor was diacetone galactose, where all the 2° hydroxyl groups are protected leaving only the 1° hydroxyl group free. D-Galactose **2.41** was reacted with acetone in presence of acid leading to the formation of **2.42** (Scheme 2.27).[20]



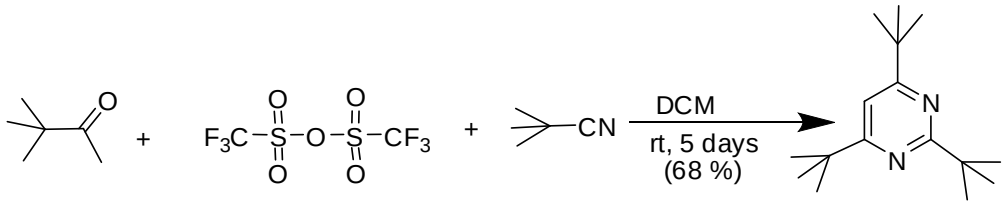
Scheme 2.27

The synthesis of acceptors containing a free 2° OH group was undertaken. *Exo*-dibenzylidene methyl mannopyranoside **2.43** was reduced with DIBAL-H to give a mixture of methyl-2-*O*-benzyl-4,6-di-O-benzylidene-*α*-D-mannopyranoside **2.44** and methyl-3-*O*-benzyl-4,6-di-*O*-benzylidene-*α*-D-mannopyranoside **2.45** which was then separated (Scheme 2.28).[21]



Scheme 2.28

During this study, on several occassions a bulky base was required as a buffer to avoid the reaction mixture from becoming highly acidic. Crich[22] developed a innovative method to synthesize TTBP **2.46**, which acts as a nonnucleophilic base. I synthesized the base following the same methodology (Scheme 2.29).



2.46

Scheme 2.29

2.4 Glycosylation reactions

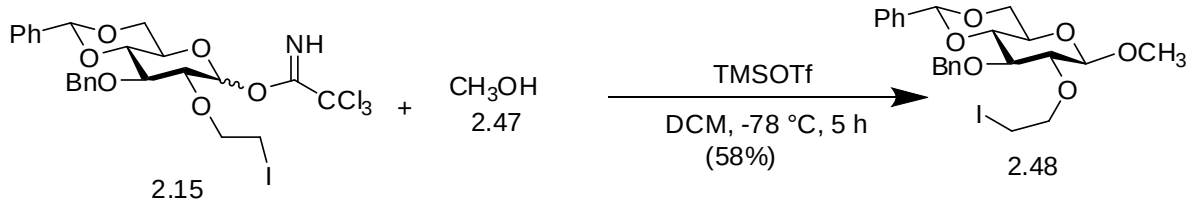
In glycosylation reactions carried out by Dan Cox,[3] the completely armed donors gave optimal stereoselectivity using glycosyl trichloroacetimidates as the donors, and activation with 0.1 eq. TMSOTf at -78 °C. This study sought to improve upon the stereoselectivity reported by him by using the partially disarmed donors with iodoethyl and selenophenyl ethyl groups at position 2 for NGP. Therefore in order to draw a proper comparison this study only investigated glycosylation reactions using glycosyl trichloroacetimidates as donor; additionally all reactions carried out in DCM as solvent, at -78 °C, using 0.1 eq. of TMSOTf as the activator.

To have a proper comparison among the donors, diacetone galactose **2.42** was used as a model acceptor and was glycosylated with all the four donors **2.15**, **2.16**, **2.17** and **2.18**. Additionally the donor **2.15** was used for glycosylation of methanol **2.47** and methyl2-*O*-benzyl-4,6-di-*O*-benzylidene-α-D-mannopyranoside **2.44** as it was the first donor synthesized.

2.4.1 Glycosylation reactions of iodo donors

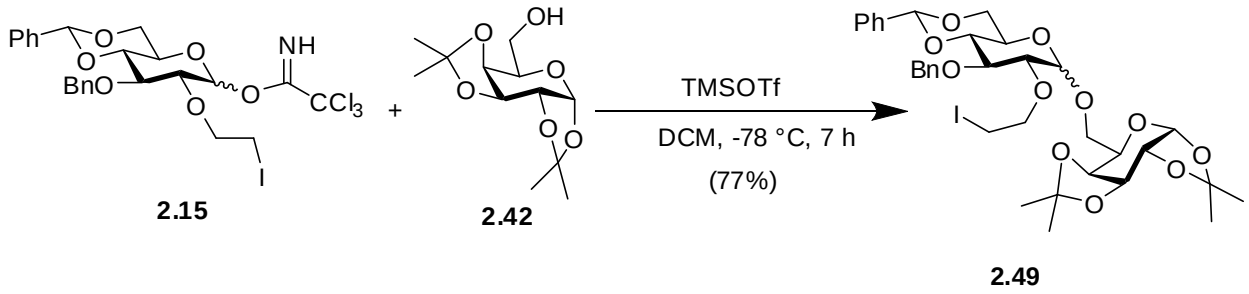
To investigate the effectiveness of iodo group in NGP for stereoselective glycosylation, first glycosylation was undertaken with the trichloroacetamidate donor **2.15**, and MeOH **2.47** (2 eq.)

as the acceptor. Very surprisingly the methyl glycoside **2.48** obtained was almost exclusively as the *β*-anomer (Scheme 2.30).



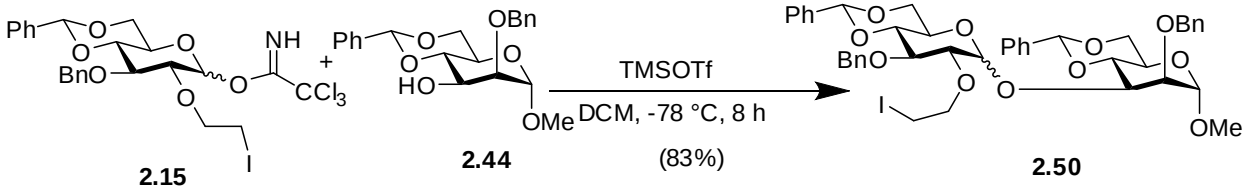
Scheme 2.30

It had been noted that, sterically hindered acceptor results in higher stereoselectivity in similar reactions.[2] The next acceptor chosen for the glycosylation reaction, with the same donor **2.15**, was a sugar with a free 1° hydroxyl group; diacetone galactose **2.42**. The stereoselectivity (*α*:*β* = 1:2) observed was again against our expectations (Scheme 2.31).



Scheme 2.31

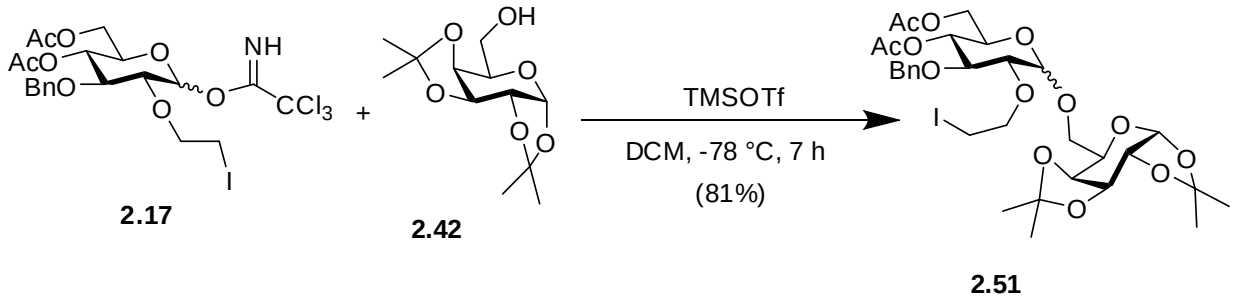
When glycosylation of a sugar with a free 2° hydroxyl **2.44**, was carried out with **2.15**, there was no improvement and no stereoselectivity (*α*:*β* = 1:1) was observed (Scheme 2.32).



2.15 **2.44** **2.50**

Scheme 2.32

When the donor **2.17** took part in glycosylation reaction under the same reaction conditions, disaccharide **2.51** was obtained with stereoselectivity of (α:β = 1:2), raising serious doubt on NGP by the iodo group (Scheme 2.33).

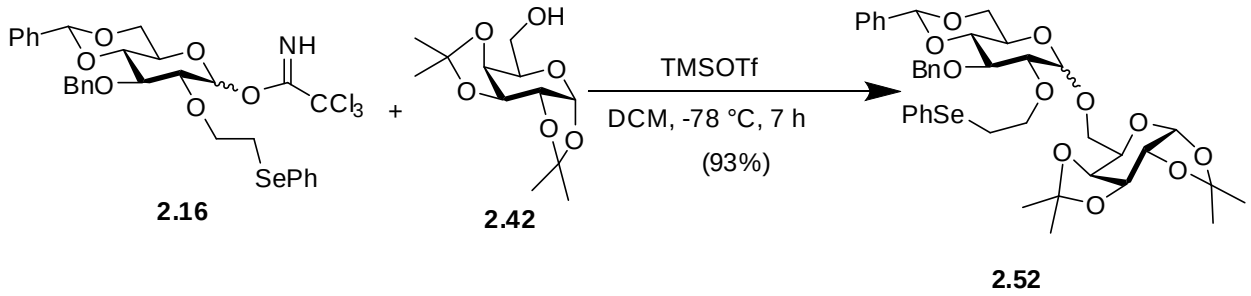


2.17 **2.42** **2.51**

Scheme 2.33

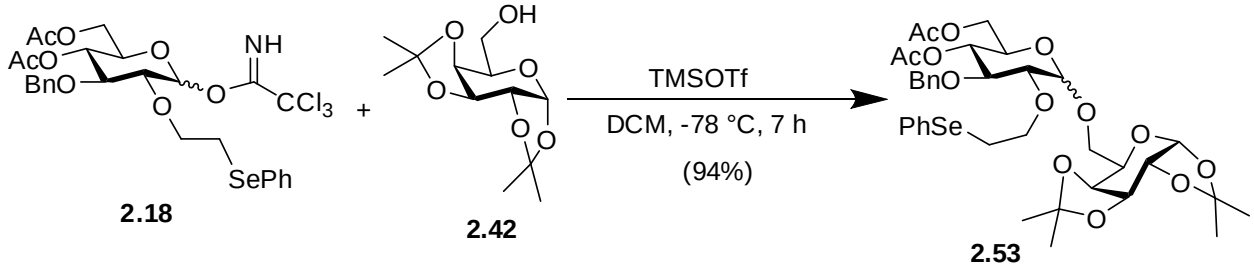
2.4.2 Glycosylation reactions of selenophenyl donors

Continuing with diacetone galactose **2.42** as a model acceptor, it was glycosylated with the donor **2.16** under the same reaction conditions, disaccharide **2.52** was produced, but predominantly as the undesired beta anomer (α:β = 1:3), thus raising serious doubts about the effectiveness of the selenophenyl group in accomplishing 6-ring NGP (Scheme 2.34).



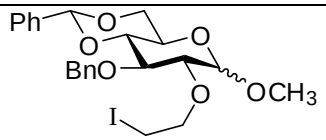
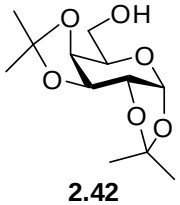
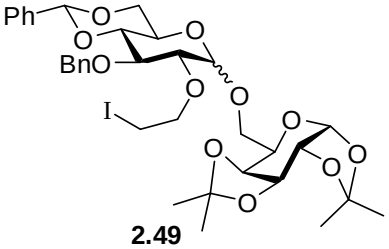
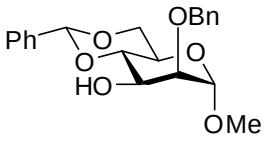
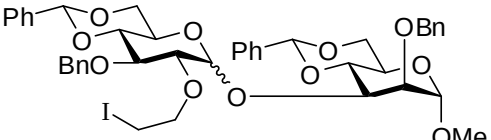
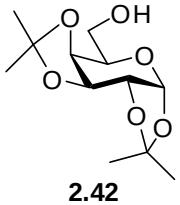
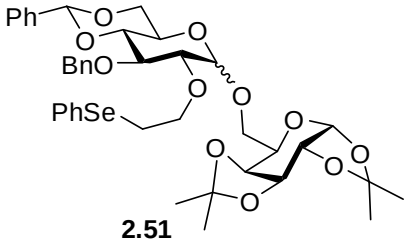
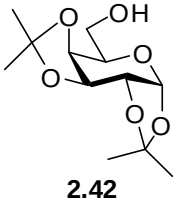
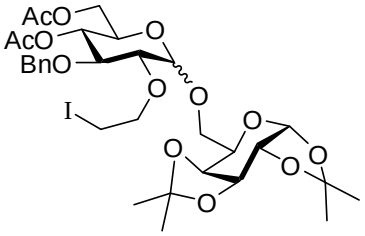
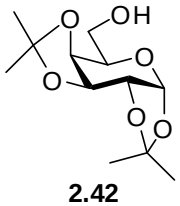
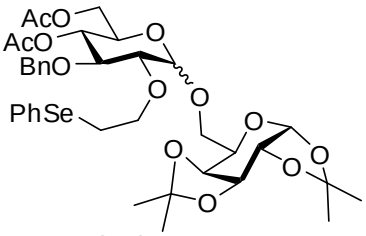
Scheme 2.34

When diacetone galactose **2.42** was glycosylated with donor **2.18**, the product **2.53**, was obtained with stereoselectivity of (α:β = 1:4) (Scheme 2.35).



Scheme 2.35

Glycosylation[a] reactions performed by these donors are summarized below in the table (Table 2.1).

Donors	**Time** (h)	**Acceptors used**	***α*:*β* ratio**[b]	**Yield** (%)	**Product**
2.15	5	CH_3OH **2.47**	1:50	58	 **2.48**
2.15	7	 **2.42**	1:2	77	 **2.49**
2.15	8	 **2.44**	1:1	83	 **2.50**
2.16	7	 **2.42**	1:3	93	 **2.51**
2.17	7	 **2.42**	1:2	81	 **2.52**
2.18	7	 **2.42**	1:4	94	 **2.53**

[a] Reaction conditions: acceptor (2.0 equiv.), TMSOTf (0.1 equiv.), –78 °C, DCM.
[b] Anomeric ratios were determined by integration of appropriate peaks in the ^{1}H NMR spectra.

Table 2.1

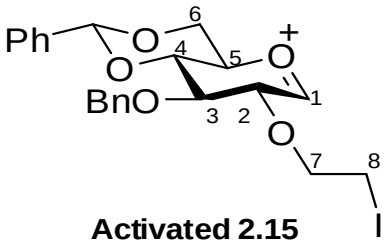
2.5 Low temperature NMR investigations into neighboring group participation of Iodo & SePh Substitutions

The stereoselectivity observed for the glycosylation reactions performed on the four partially disarmed donors investigated contrasted with the results obtained using the completely armed donors reported by Cox.[3] These results raised serious questions as to whether NGP by these two groups was actually occurring. Therefore, based on the studies reported by Boons,[6] we designed a series of experiments to investigate any intermediates produced during the activation of the trichloroacetimidate donors in the presence of a Lewis acid TMSOTf, at -78 °C by recording low temperature NMR spectra.

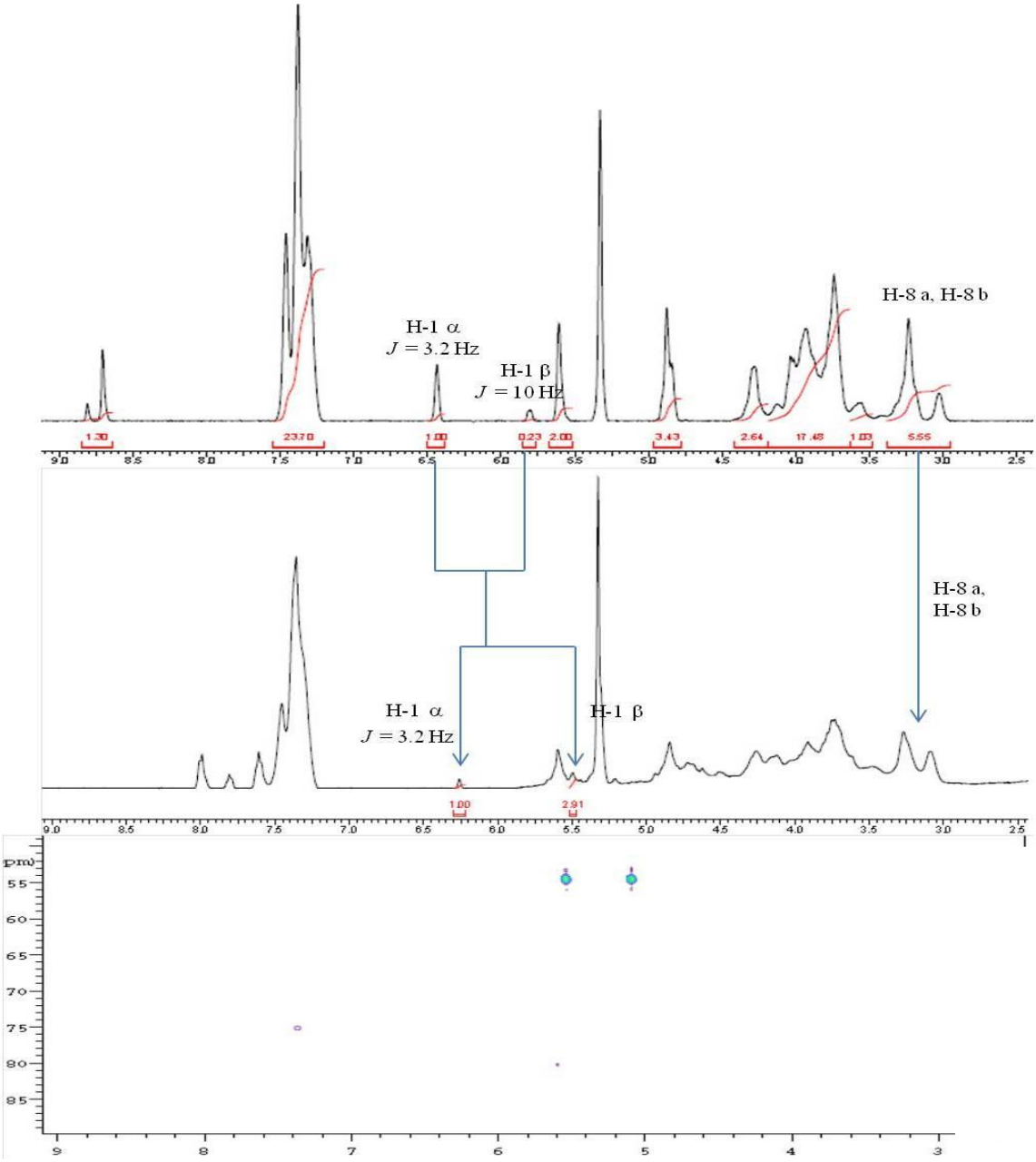
2.5.1 Low temperature NMR investigations into neighboring group participation of iodo substituent

To study the neighboring group participation of the iodo group at position-2 of the donor sugar, trichloroacetimidate **2.15** was activated at low temperature and NMR spectra were recorded at that temperature.

Firstly, ^{1}H NMR spectrum of **2.15** in CD_2Cl_2 was recorded at -78 °C. Subsequently, an equimolar amount of trimethylsilyl trifluoromethanesulfonate was added to the solution at -78 °C. The reaction mixture was kept at -78 °C for 10 min, after which time ^{1}H NMR, followed by HSQC (over 30 min), COSY (over 10 min) and then HMBC (over 40 min) spectra were all recorded at -78 °C. ^{1}H NMR and HMBC spectra are shown below (Figure 2.2).



Activated 2.15

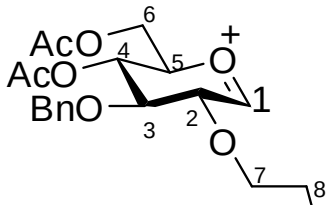


A – ^{1}H-NMR of **2.15** at -78 °C; B - ^{1}H-NMR of activated **2.15** at -78 °C by addition of 1 eq. of TMSOTf; C – HMBC study of activated **2.15** at -78 °C.

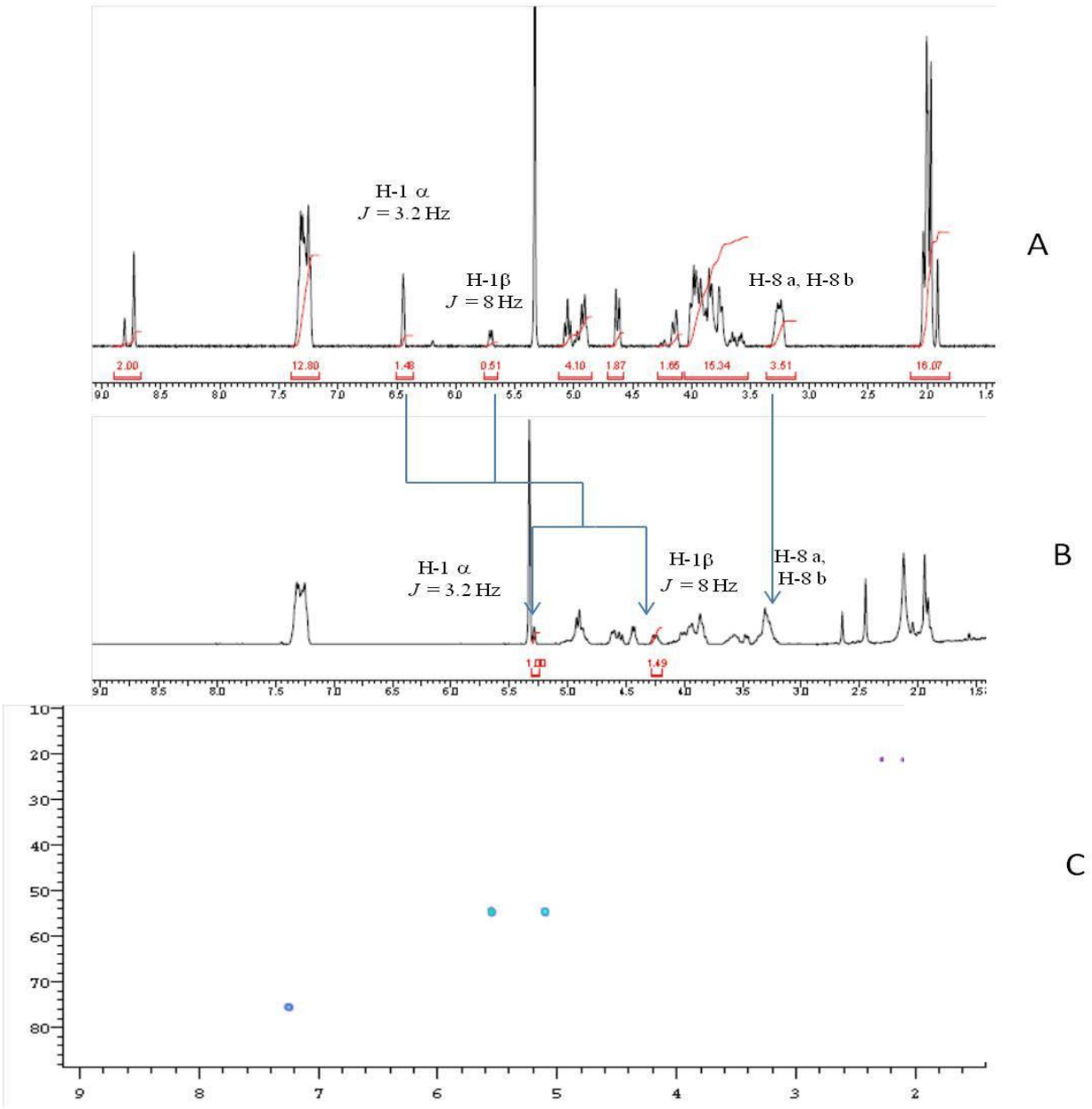
Figure 2.2

To study the neighboring group participation of iodo group at position-2 of the donor sugar, trichloroacetimidate **2.17** was activated at low temperature and NMR spectra ware recorded at that temperature.

Firstly, ^{1}H NMR spectrum of **2.17** CD_2Cl_2 was recorded at -78 °C. Later, an equimolar amount of trimethylsilyl trifluoromethanesulfonate was added to the solution at -78 °C. The reaction mixture was kept at -78 °C for 10 min, after which time ^{1}H NMR, followed by an HSQC (over 30 min), COSY (over 10 min) and then HMBC (over 40 min) spectra were all recorded at -78 °C. ^{1}H NMR and HMBC spectra are shown below (Figure 2.3)



Activated 2.17



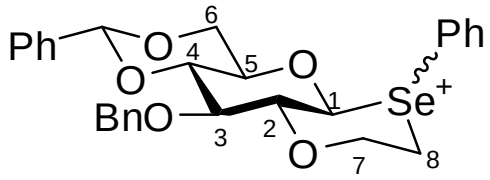
A – ^{1}H-NMR of **2.17** at -78 °C; B - ^{1}H-NMR of activated **2.17** at -78 °C by addition of 1 eq. of TMSOTf; C – HMBC study of activated **2.17** at -78 °C.

Figure 2.3

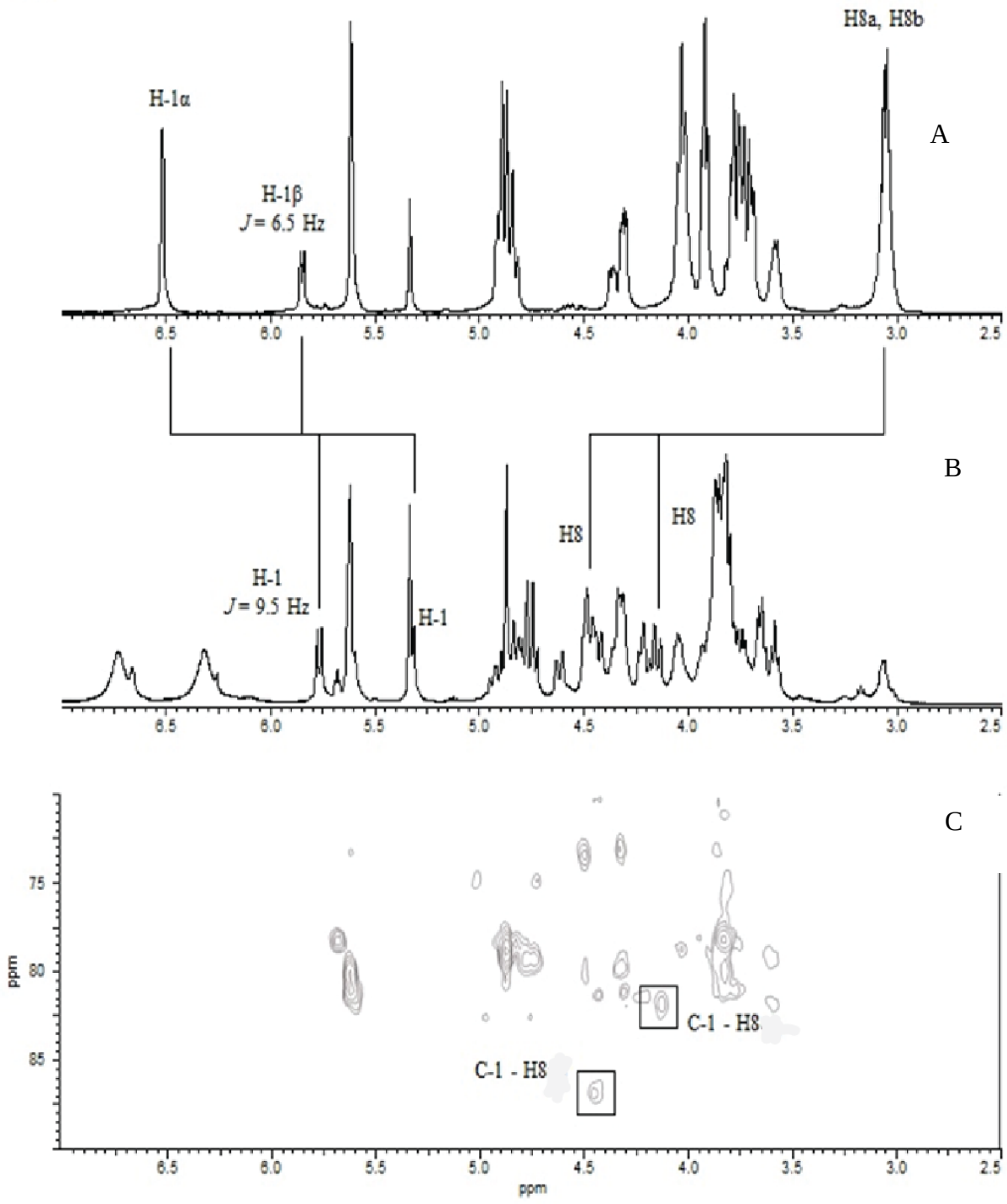
2.5.2 Low temperature NMR investigations into neighboring group participation of selenophenyl substituent

Similarly to study the neighboring group participation of SePh group at position-2 of the donor sugar, trichloroacetimidate **2.16** was activated at low temperature and NMR spectra were recorded at that temperature.

Firstly, ^{1}H NMR spectrum of **2.16** in CD_2Cl_2 was recorded at -78 °C, following which equimolar amount of trimethylsilyl trifluoromethanesulfonate was added to the solution at -78 °C. The reaction mixture was kept at -78 °C for 10 min, after which time ^{1}H NMR, followed by HSQC (over 30 min), COSY (over 10 min) and then HMBC (over 40 min) spectra were all recorded at -78 °C. ^{1}H NMR and HMBC spectra are shown below (Figure 2.4).



Activated 2.16

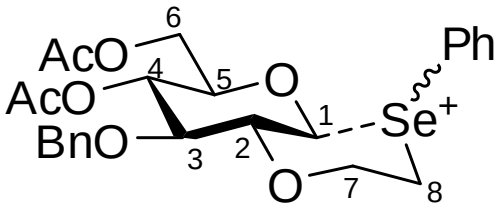


A – ^{1}H-NMR of **2.16** at -78 °C; B - ^{1}H-NMR of activated **2.16** at -78 °C by addition of 1 eq. of TMSOTf; C – HMBC study of activated **2.16** at -78 °C.

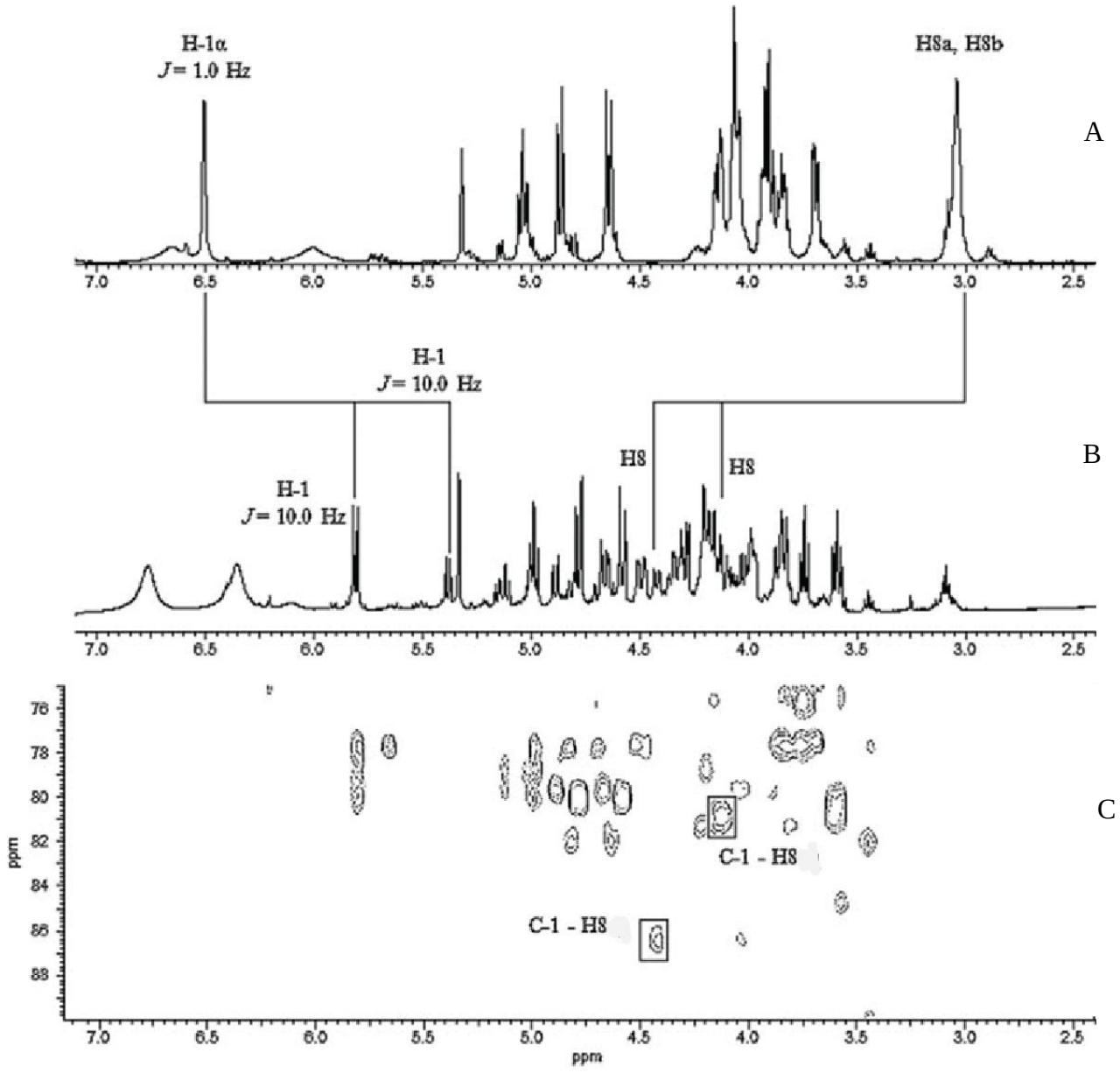
Figure 2.4

Similarly to study the neighboring group participation of SePh group at position-2 of the donor sugar, trichloroacetimidate **2.18** was activated at low temperature and NMR spectra were recorded at that temperature.

Initially, ^{1}H NMR spectrum of **2.18** in CD_2Cl_2 was recorded at -78 °C. An equimolar amount of trimethylsilyl trifluoromethanesulfonate was then added to the solution at -78 °C. The reaction mixture was kept at -78 °C for 10 min, after which time ^{1}H NMR, followed by HSQC (over 30 min), COSY (over 10 min) and then HMBC (over 40 min) spectra were all recorded at -78 °C. ^{1}H NMR and HMBC spectra are shown below (Figure 2.5).



Activated 2.18



A – ^{1}H-NMR of **2.18** at -78 °C; B - ^{1}H-NMR of activated **2.18** at -78 °C by addition of 1 eq. of TMSOTf; C – HMBC study of activated **2.18** at -78 °C.

Figure 2.5

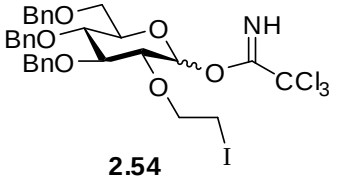
In the partially disarmed systems, for the iodoethyl donors **2.15**, and **2.17** no obvious NMR signal shifts in H-8 or H-1 upon activation were observed, nor were any cross correlations observed between C-1 and H-8a/b in the HMBC spectra, which indicates that NGP did not occur for these disarmed iodo-substituted donors.

However, for the corresponding phenylseleno donors **2.16** and **2.18** evidence of NGP was observed. The activated donors **2.16a** and **2.18a** were *β*-configured, as confirmed by both the $J_{H1,H2}$ (9–10 Hz) and the $J_{H1,C1}$ coupling constants (168 Hz). Both materials showed cross correlation between C-1 and H-8eq in the HMBC spectrum, indicating that NGP occurs. The NMR spectroscopic data suggests that both materials are *β*-configured cyclised intermediates, but differ in that the Ph group attached to Se is either axial or equatorial.[23]

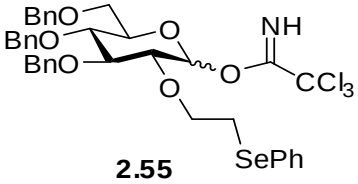
The NMR studies indicated that NGP did indeed occur for all of the disarmed phenylseleno donors, even though these compounds were less *α*-selective than completely armed benzylated donor, which did not undergo NGP according to NMR spectroscopy. Evidence that a cyclic intermediate is formed upon activation of a donor does not necessarily mean that this is the reactive species through which glycosylation occurs. Notably, although all of the cyclic intermediates observed were *β*-configured, as indicated by NMR spectroscopic coupling constants, significant amounts of *β*-glycoside product were formed, indicating that most reaction must take place via intermediates not seen by NMR spectroscopy.

2.6 Discussion

The NMR studies indicated that NGP has indeed occurred for both of the disarmed phenylseleno donors (**2.16** and **2.18**), even though the compounds were less α-selective than their completely armed benzylated counterparts (**2.54**, **2.55**), figure 2.6, which did not undergo NGP according to NMR spectroscopy.[3]



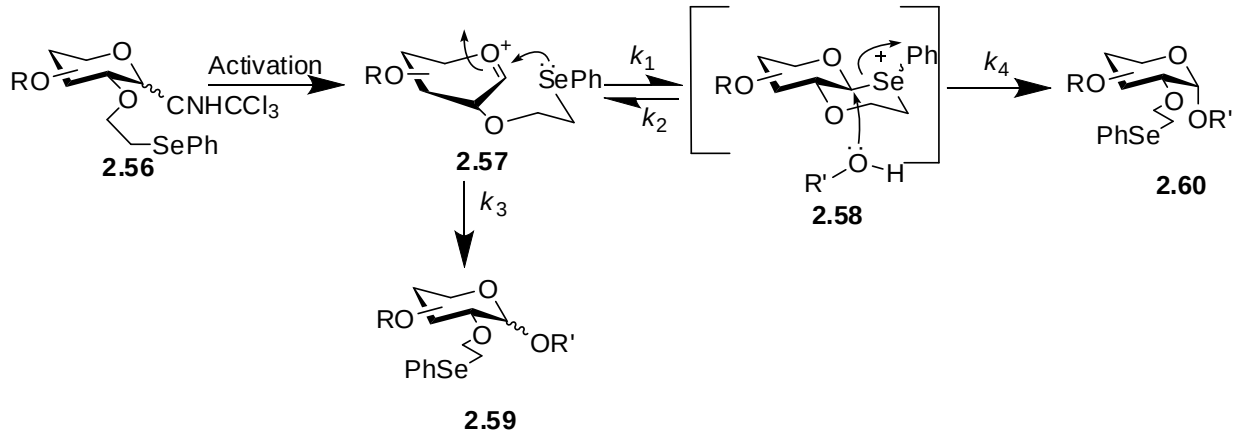
2.54



2.55

Figure 2.6

We further conclude that despite the evidence that a cyclic intermediate is formed upon activation of a donor, this does not necessarily mean that it is the reactive species through which glycosylation occurs. Although all of the cyclic intermediates observed were β-configured, addition of an alcohol resulted, however, in the formation of a mixture of anomers. This unexpected observation can be rationalized by the classical Curtin-Hammett principle which states that an equilibrium exists between the selenonium and oxocarbenium ions (Scheme 2.36). This equilibrium is shifted strongly in the direction of the selenonium ion as shown by the NMR studies. A glycosylation can, however, take place from the much more reactive oxocarbenium ion when the rates of interconversion (k_1 and k_2) are faster than that of glycosylation (k_4).



Scheme 2.36

The question therefore arises as to why the stereoselectivity of the products formed did not match with the configuration of the intermediates observed. A survey of the literature revealed a similar observation in a report by Turnbull.[24]

In this study a bicyclic thioglycoside was activated by methylation to generate a methylsulfonium group that acted both as an anomeric leaving group, and also provided the methylsulfide group in the product (Figure 2.7).

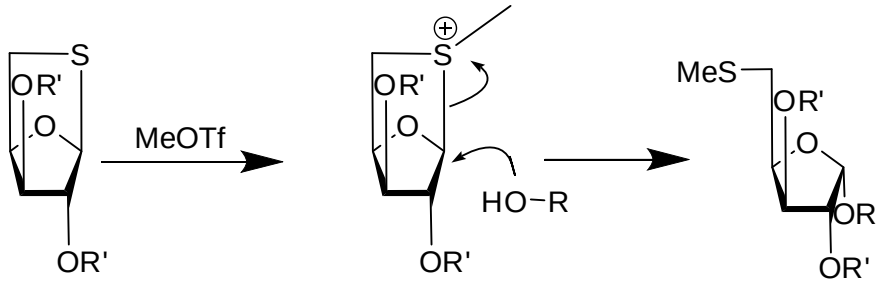


Figure 2.7

The studies done by Boons[6] had shown that activation of a glycosyl donor protected with a 2-*O*-(*S*)-(phenylthiomethyl)benzyl ether chiral auxiliary results in the formation of an anomeric *β*-sulfonium ion, *via* a *trans*-decalin ring, which can be displaced with sugar alcohols to give

corresponding *α*-glycosides. Furthermore, Boons elaborated that formation of *trans*-decalin-like sulfonium ion is favored by the electron withdrawing groups on the donor ring, leading to higher stereoselectivity, by avoiding glycosylation of an oxocarbenium ion intermediate.

Turnbull compared the methylthioxylose sulfonium ion with a *trans*-decalin-like sulfonium ion described by Boons and co-workers to be an *α*-directing participating group by density functional theory calculations, and found it to be more stable. The NMR studies, also detected a very stable key sulfonium intermediate, which should have acted as a participating group to direct the acceptor alcohol to the lower *α* face of the sugar, the glycosylation reaction proceeded with moderate stereoselectivity, apparently *via* an S_N1-type mechanism. The whole study led to the conclusion that even though NMR studies might show a stable intermediate which should result in a very stereoselective glycosylation reaction, caution should be applied before invoking it as an intermediate on the reaction pathway.

In another study, it was suggested by the Woerpel[25] group that Boons' glycosyl sulfonium ion does not necessarily give diastereolectivity due to involvement of neighboring group participation, implicating a Curtin-Hammett kinetic scenario in which the formation of a low-energy intermediate does not necessitate its involvement in the product-forming pathway.

2.7 Conclusions

In an attempt to promote highly stereoselectivity *α*-glycosylation by 6-ring NGP, a selection of glycosyl donors were synthesised that possesed new 2-iodoethyl-ether and 2-(phenylseleno)ethyl-ether protecting groups at the 2-position. Studies done earlier by the Fairbanks group had shown that the "completely-armed" tri-benzylated donors produced *α*-

glucosides as the predominant reaction products.[3] However, low temperature NMR studies did not provide evidence of NGP by the observable formation of cyclised reaction intermediates.

A subsequent investigation with corresponding disarmed glycosyl donors unexpectedly revealed them to be less stereoselective than their completely armed counterparts.

The fact that considerable amounts of *β*-glycoside product were formed from glycosylation of the Se-containing donors indicated that the predominant reaction pathway to product did not occur *via* the observed cyclic species. It can be reasoned from these investigations that selenium is a better participating group than iodine, and is therefore more likely to form the basis of a useful achiral participating neighbouring group designed to promote *α*-glycoside formation. However this work demonstrates that formation of a cyclised intermediate alone is not sufficient to ensure a high level of selectivity during glycosylation. Based on Boons' studies discussed earlier, a completely disarmed donor should have given a higher stereoselectivity compared to the partially disarmed donors mentioned in this study. However, no such results were observed. Likewise, it appears that glycosylation of disarmed donors is not necessarily more stereoselective than that of the corresponding completely armed compounds, even if the latter do show a lower propensity to undergo NGP because of protecting group stabilisation of a glycosyl cation or other acyclic intermediate. An extremely subtle balance exists between alternative reaction pathways during glycosylation. Further, to develop a reliable achiral variant, fine-tuning of protecting group structure is required, that affects high levels of *α*-selectivity through 6-ring NGP.

2.7 References

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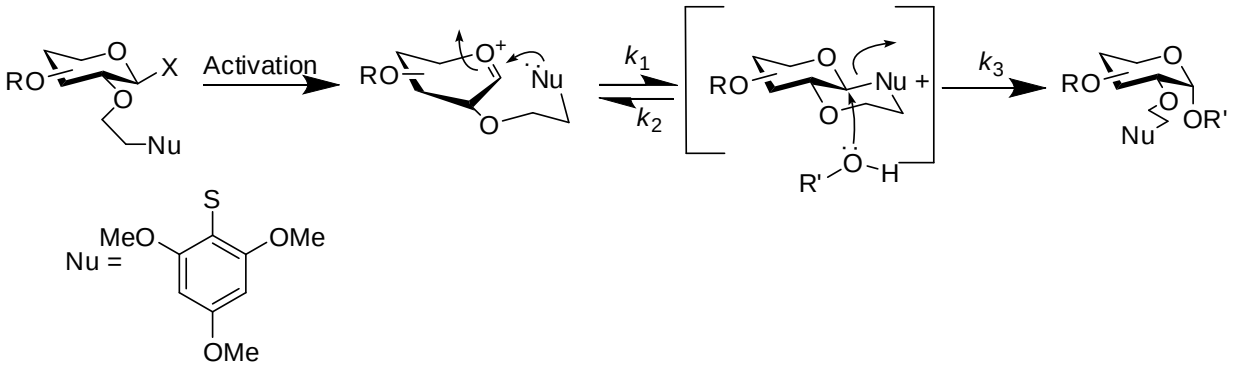
Chapter 3: Development of the 2-*O*-(2-(2,4,6-trimethoxythiophenyl)ethyl) protecting group for stereocontrolled glycosylation

3.1 Introduction

As noted in Chapter 2, this research project was inspired by the works of Boons[1] and relies on neighbouring group participation (NGP) occurring *via* a 6-membered ring an and intermediate a *trans* decalin type structure, which the glycosyl acceptor then attacks axially to produce the α-glycoside as the major reaction product (Scheme 2.1). It was also mentioned that Boons[1a] had shown that even without a chiral auxiliary group at position-2, stereoselectivity of α:β = 8:1 was achieved by use of an ethylthiophenyl group for protection of the 2-position of glycosyl donor (Scheme 2.3). This report led us to investigate the use of more nucleophilic groups, namely iodo- and selenophenyl,at the 2-position of an 2-*O*-ethyl ether in order to increase the propensity for 6-ring NGP, in order to increase the levels of α-selectivity that could be observed. However, as detailed in Chapter 2, the stereoselectivity observed with these novel protecting groups was very disappointing, especially with the disarmed donors (Table 2.1).

Other research in the Fairbanks group investigated the use of a benzeneseleno ethyl ether at the 2-position in a completely disarmed donor.[2] Though low temperature NMR studies had suggested that the selenophenyl ethyl ether did participate in NGP no stereoselectivity was observed. This led us to conclude that cyclic intermediate formed upon activation of the donor, and seen by NMR, was probably not the reactive species through which glycosylation occured.

However, the thiophenyl group reported by Boons,[1a] had undergone both NGP *via* a *trans*-decalin intermediate and gave α-selectivity. We therefore decided to synthesise a donor with a (2,4,6-trimethoxyphenyl)thio ethyl ether at position-2, with the aspiration that we may get effective NGP *via* a β-configured *trans* decalin cyclic intermediate, which was also an intermediate in Turnbull's investigations of successful stereoselective glycosylations,[3] and probably would result in α-stereoselective glycosylation reactions (Scheme 3.1).



Scheme 3.1

3.2 General strategy for the synthesis of donors

The armed **3.1**, partially disarmed **3.2**, and completely disarmed donor **3.3** were chosen as synthetic targets (Figure 3.1).

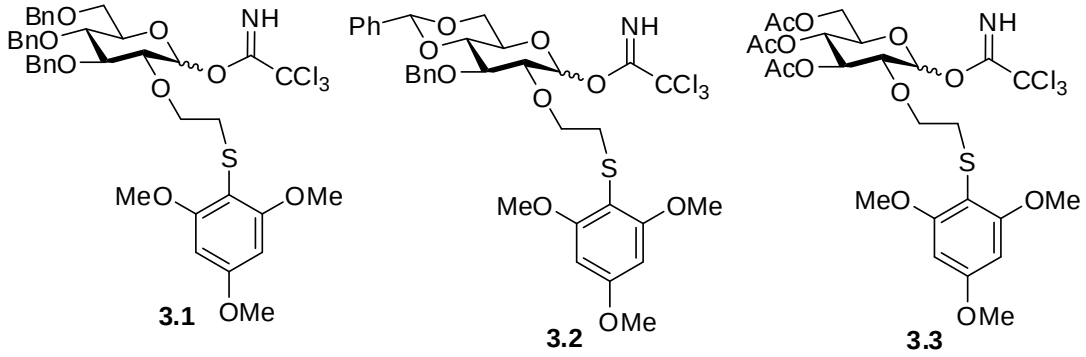


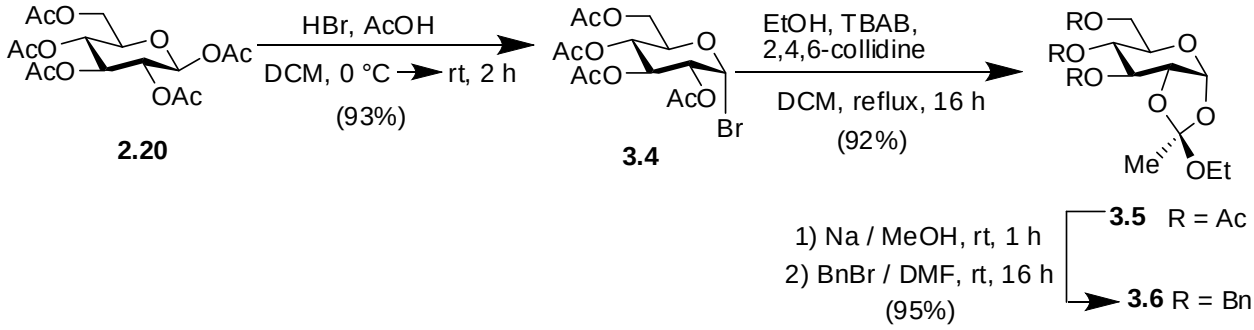
Figure 3.1

The strategy for the synthesis of all the donors involved the synthesis of iodo hemiacetals similar to **2.34** (which was a precursor for synthesis of **3.2**). The iodide was later substituted by the trimethoxythiophenyl group by reaction of with 2,4,6-trimethoxybenzenethiol in the presence of base to yield trimethoxythiophenyl ethyl ether at position-2. The resulting hemiacetals were then converted to the corresponding trichloroacetimidates by reaction with trichloroacetonitrile in presence of DBU**.**

3.2.1 Synthesis of completely armed donor 3.1

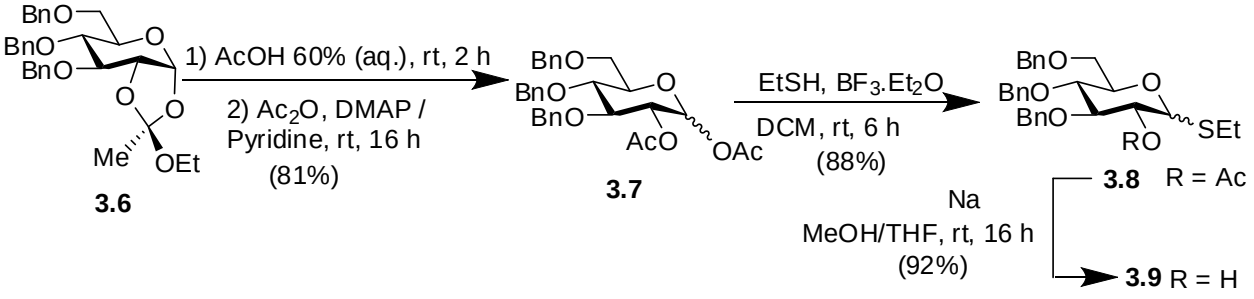
The known orthoester **3.6** was synthesized using standard procedures from *β*-D-glucose pentaacetate **2.20** (Scheme 3.2).[4] Treatment of **2.20** with 33% HBr in glacial acetic acid afforded the *α*-bromide **3.4**[5] in 93% yield. Reaction of **3.4** with ethanol and 2,4,6-collidine in the presence of a catalytic amount of tetrabutylammonium bromide then gave the 3,4,6-*O*-acetyl

protected orthoester **3.5**[4] in 92% yield of. Deprotection of the acetyl groups was carried out under Zemplén conditions,[6] and the resulting product was immediately treated with sodium hydride and benzyl bromide to give orthoester **3.6**[4] in an overall yield of 81% over 3 steps from **2.20**.



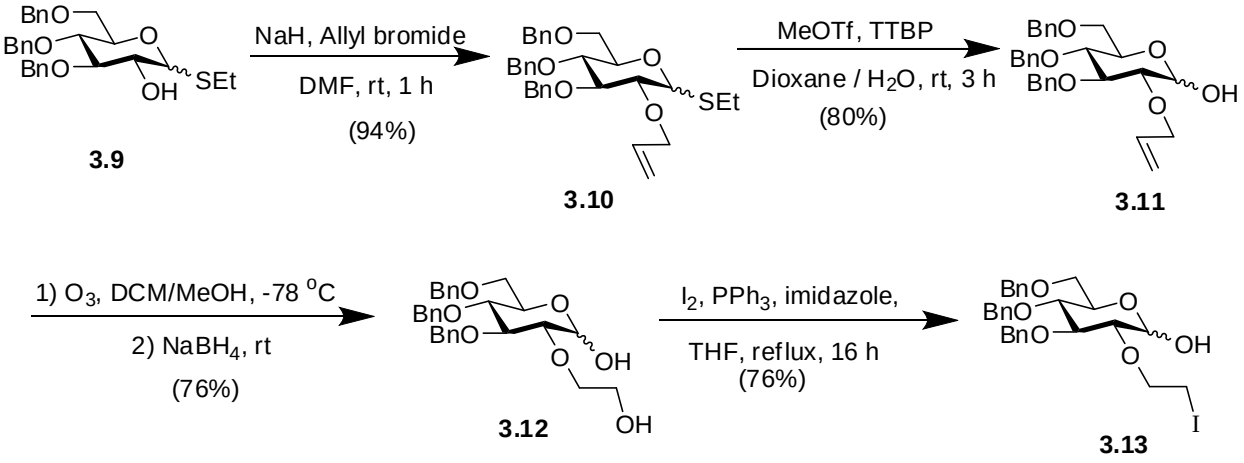
Scheme 3.2

Treatment of orthoester **3.6** with aq. acetic acid produced a mixture of monoacetates, which were immediately converted to an anomeric mixture of diacetates **3.7**[7] (α:β = 13:1) by treatment with acetic anhydride and pyridine. Reaction of **3.7** with ethanethiol and boron trifluoride diethyl etherate then produced the thioethyl glycoside **3.8**[8] (α:β = 1:5) in excellent yield, from which the 2-*O*-acetate was removed by under Zemplén conditions, yielding alcohol **3.9**[9] (Scheme 3.5) with an overall yield of 66% over 3 steps from **3.6** (Scheme 3.3).



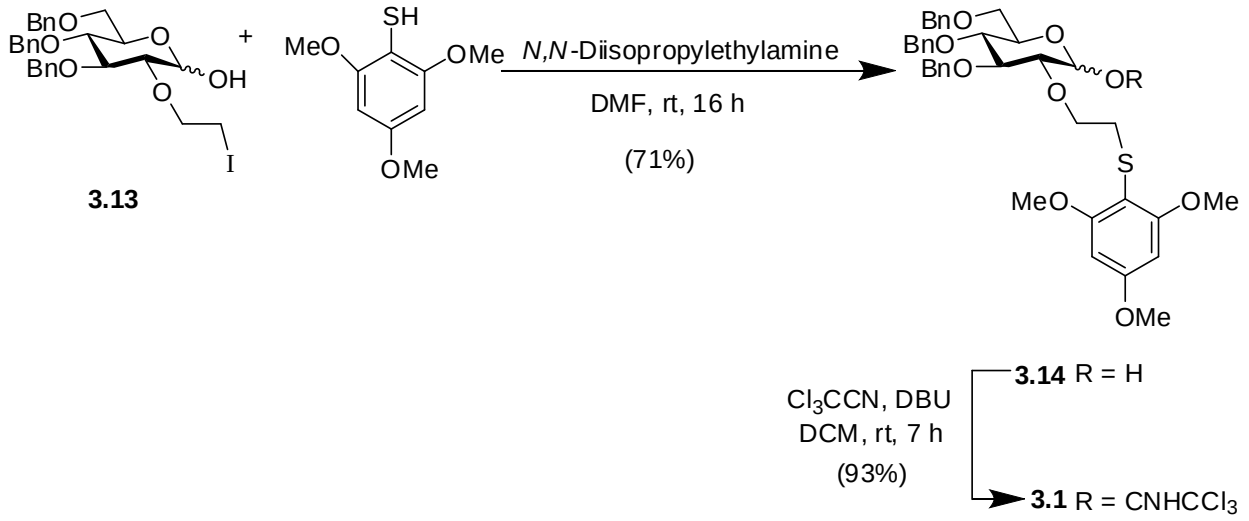
Scheme 3.3

The alcohol **3.9** was then treated with allyl bromide and NaH in DMF, to give the 2-*O*-allyl protected donor **3.10**[10] in 94% yield. Thioglycoside **3.10** was then treated with MeOTf in the presence of TTBP in a mixture of 1,4-dioxane and water to give the hemiacetal **3.11**[2] in a 80% yield. Subsequent ozonolysis proceeded smoothly to give the diol **3.12** (76% yield). The Appel reaction usually results in the regioselective halogenation of primary hydroxyl groups in the presence of secondary hydroxyl groups.[11] Accordingly reaction of **3.12**, with I_2 and PPh_3 in the presence of imidazole gave iodide **3.13** in 76% yield (Scheme 3.4).



Scheme 3.4

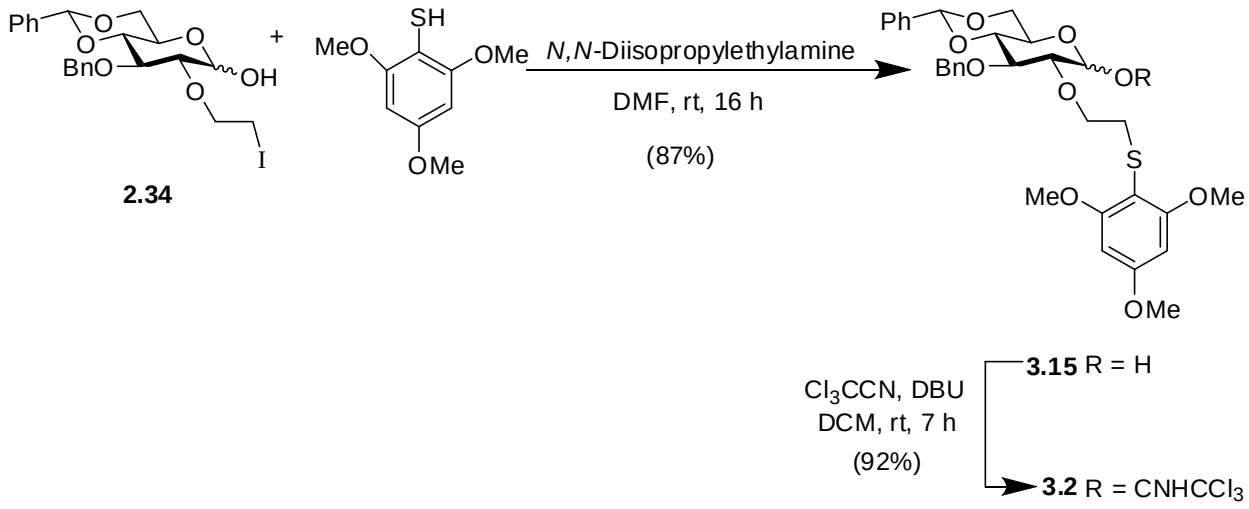
Finally the iodide group was replaced by trimethoxythiophenyl by reaction of **3.13** with trimethoxybenzenethiol in the presence of Hünig's base to yield arylthio ethyl ether **3.14**. Trichloroacetimidate formation was achieved by treatment of **3.14** with trichloroacetonitrile and DBU to afford donor **3.6** in 66% yield over the last two steps (Scheme 3.5).



Scheme 3.5

3.2.2 Synthesis of partially disarmed donor 3.2

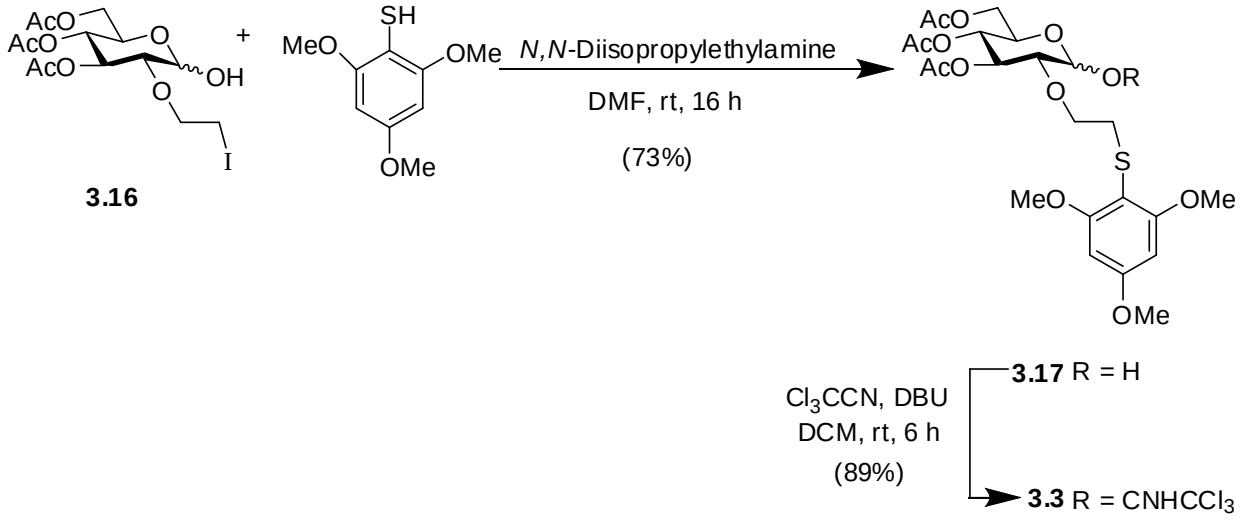
Iodide **2.34** was synthesized as shown in Scheme 2.21 and treated with trimethoxybenzenethiol in the presence of Hünig's base to yield arylthio ethyl ether **3.15**. Treatment with trichloroacetonitrile and DBU to afforded donor **3.2** in 82% yield over two steps (Scheme 3.6).



Scheme 3.6

3.2.3 Synthesis of completely disarmed donor 3.3

Iodide **3.16** was synthesized by another group member as reported in the literature.[2] Reaction of **3.16** with trimethoxybenzenethiol in the presence of Hünig's base gave arylthio ethyl ether **3.17** (73% yield). Treatment with trichloroacetonitrile and DBU then afforded the completely disarmed donor **3.3** in 89% yield (Scheme 3.7).



Scheme 3.7

3.3 Preliminary investigations

Two protocols for glycosylation have been reported by Boons; termed Protocol A and Protocol B.[1b] The glycosylation reactions reported in Chapter 2, all employed 'Protocol A' (Section 2.4), wherein the donor and acceptor were first stirred at -78 °C in DCM, before the addition of a catalytic amount of TMSOTf, and carrying out the glycosylation at -78 °C.

Subsequently the acceptor **2.42** was glycosylated with selenophenyl donor **2.16** using Protocol B. In Protocol B the donor **2.16** was first activated at -78 °C by the addition of 1 eq. of TMSOTf,

then warmed to 0 °C and then cooled down to -78 °C before the acceptor **2.42** and the non nucleophilic base TTBP **2.46** were added. Surprisingly this procedure yielded the disaccharide **2.51** with high α-stereoselectivity (*α*:*β* = 3.5:1), as compared to the stereoselectivity observed employing Protocol A (*α*:*β* = 1:4). However, when the acceptor **2.42** was glycosylated with iodo donor **2.15** using Protocol B, decomposition of the donor occured (Table 3.1).

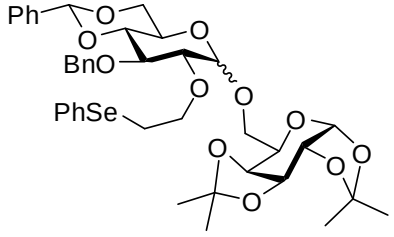
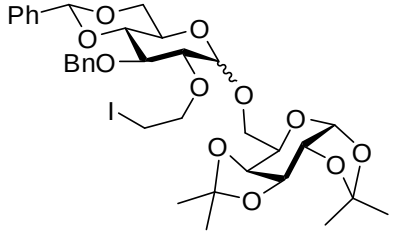
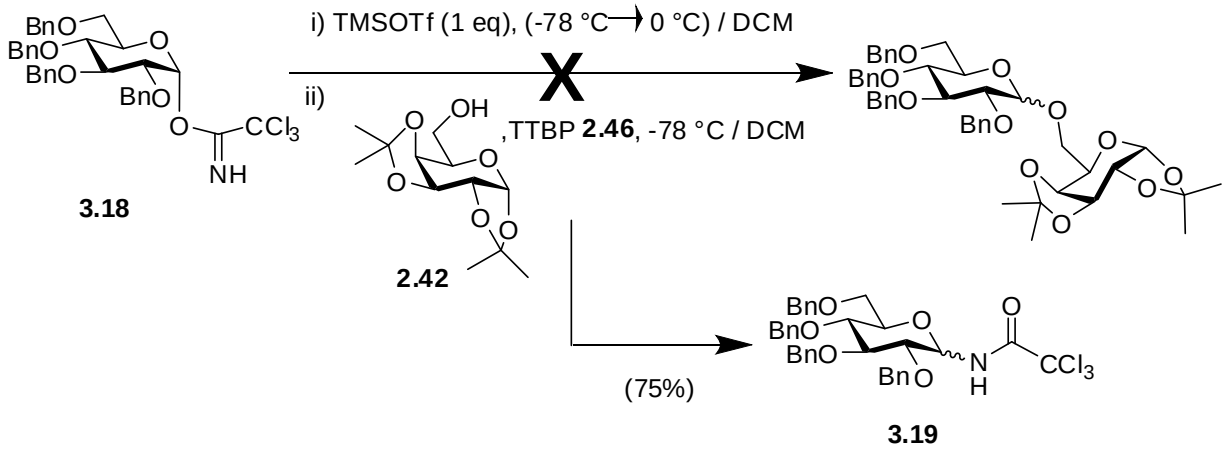
Sl. No.	Donor	Acceptor	Product	Protocol A		Protocol B	
				Yield	*α*:*β*	Yield	*α*:*β*
1.	**2.16**	**2.42**	 **2.51**	93%	1:4	66%	3.5:1
2.	**2.15**	**2.42**	 **2.49**	77%	1:2	Decom-posed	-

Table 3.1

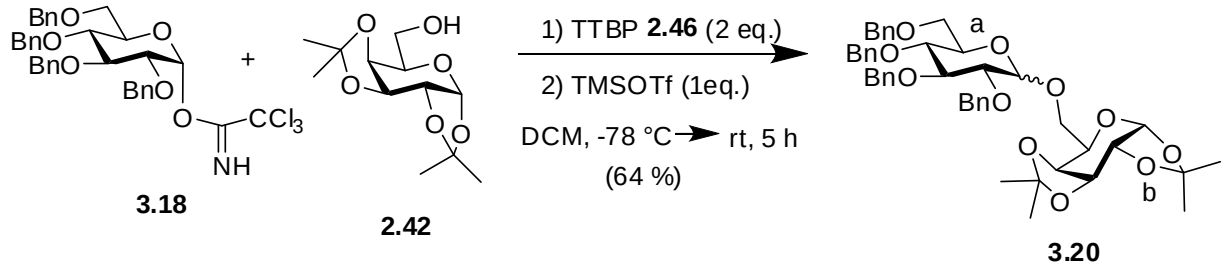
These results implied the that using Protocol B the donor (**2.16**) underwent NGP (Section 2.5.2) i.e. a selenonium ion intermediate was formed; the addition of the acceptor at a much later stage led to attack only on the thermodynamically stable β-configured selenonium ion Thus *α*-selectivity was observed in glycosylation reaction when Protocol B was employed. However as the iodo group did not undergo NGP (Section 2.5.1), the donor (**2.14**) simply decomposed at 0 ^{o}C in presence of 1 eq. of activator TMSOTf.

The next thing that needed to be verified was if the TTBP had any effect on the stereoselectivity of the reaction. The tetrabenzylglucose trichloroacetamidate donor **3.18** was chosen for investigation into the effect of added base. When glycosylation of acceptor **2.42** was carried out with donor **3.18** using Protocol B, only rearrangement of the donor to the amide isomer **3.19** was observed (Scheme 3.8).



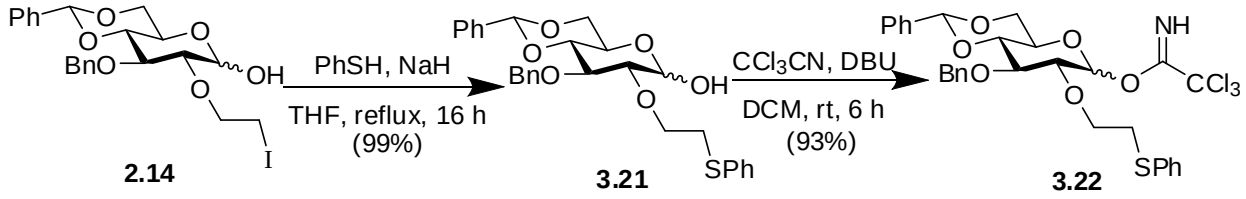
Section 3.8

This unexpected isomerization of the donor, which is a known side reaction of trichloroacetimidates,[12] indicated that in the absence of any NGP, and in absence of acceptor, the rearrangement was facilitated. Therefore a different approach was required to find if TTBP had any effect on the reaction stereoselectivity. The donor **3.18** was stirred with acceptor **2.42** and TTBP **2.46** and then cooled to -78 °C. One equivalent of TMSOTf was then added and solution was allowed to warm to rt. The disaccharide **3.20** was formed with low stereoselectivity (α:β = 1:2.5) (Scheme 3.9), which was very similar to stereoselectivity obtained (α:β = 1:2.25) when protocol A (in absence of TTBP) was employed at same temperature.[13]



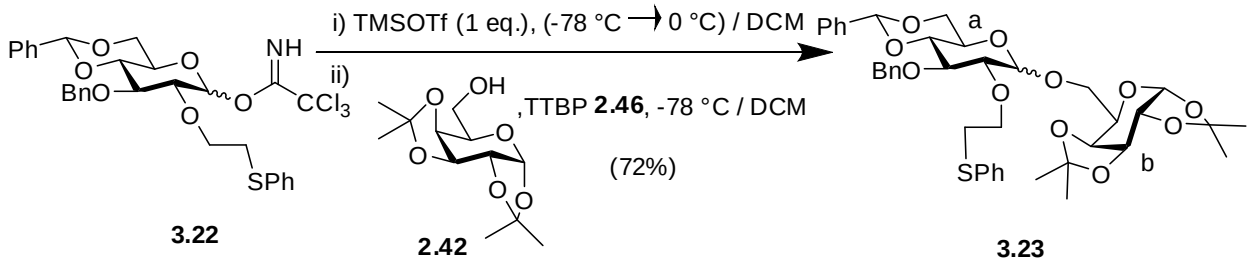
Scheme 3.9

Boons'[1a] use of a thiophenyl group substituted ethyl ether for protection of the 2-position was then investigated for a partially disarmed donor, which was similar to donor **2.16**. Iodide **2.14** was treated with thiophenol in the presence of sodium hydride to yield hemiacetal **3.21**. The free hydroxyl group at the anomeric centre of compound **3.21** was then converted to a trichloroacetimidate by reaction with trichloroacetonitrile in the presence of DBU to yield donor **3.22** (Scheme 3.10).



Scheme 3.10

Glycosylation of the acceptor **2.42** with donor **3.22**, employing Protocol B afforded the disaccharide **3.23** with high stereoselectivity (α:β = 7:2) (Scheme 3.11).However, the stereoselectivity was completely lost when Protocol A (α:β = 1.1:1) was employed using the same donor and acceptor.



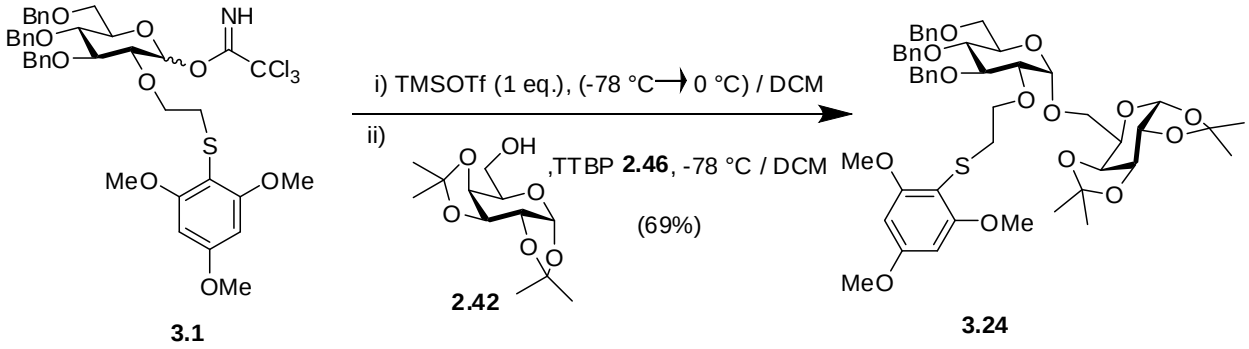
Scheme 3.11

It was therefore concluded that only Protocol B should be employed for all subsequent glycosylation reactions.

3.4 Glycosylation reactions

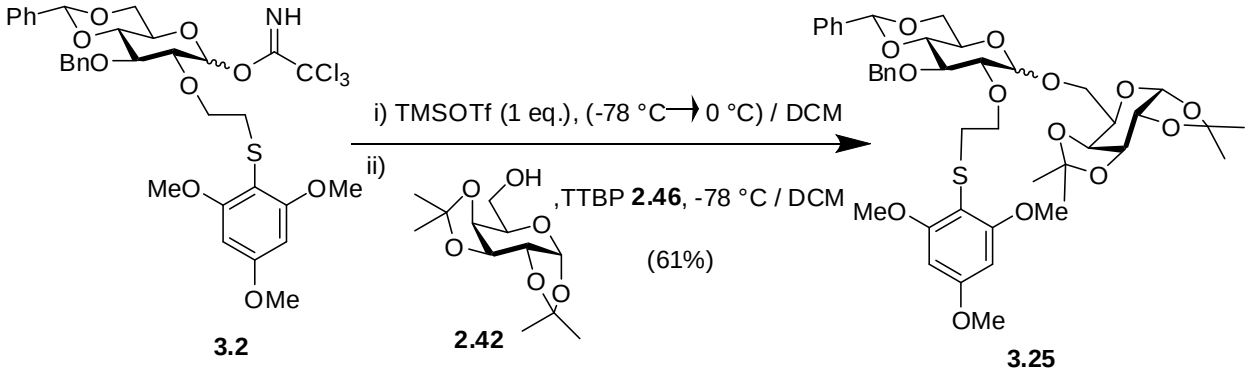
In order to systematically investigate any effect of donor protecting group regime, diacetone galactose **2.42** was glycosylated with all three donors. As explained previously (section **3.3)**, Protocol B was employed for all glycosylation reactions, which involves pre-activation and warming of the glycosyl donor before cooling and addition of the acceptors as described below. A mixture of donor (1 equiv.) and activated molecular sieves (3 Å) in DCM (5 mL) was stirred for 10 min under an atmosphere of nitrogen at rt. The mixture was then cooled to -78 °C, TMSOTf (1 equiv.) was added, and the reaction mixture was allowed to warm to 0 °C over a period of 40 min. The reaction mixture was then re-cooled to -78 °C, and diacetone galactose (1.1 equiv.) and TTBP (2 equiv.) were added. The reaction mixture was allowed to warm slowly to rt and stirred overnight at rt. Following work up, ^{1}H-NMR of the crude product was obtained, and purification of the crude product was further achieved by column chromatography with silica.

Using these conditions the completely armed donor **3.1** yielded exclusively the *α*-disaccharide **3.24** (Scheme 3.12).



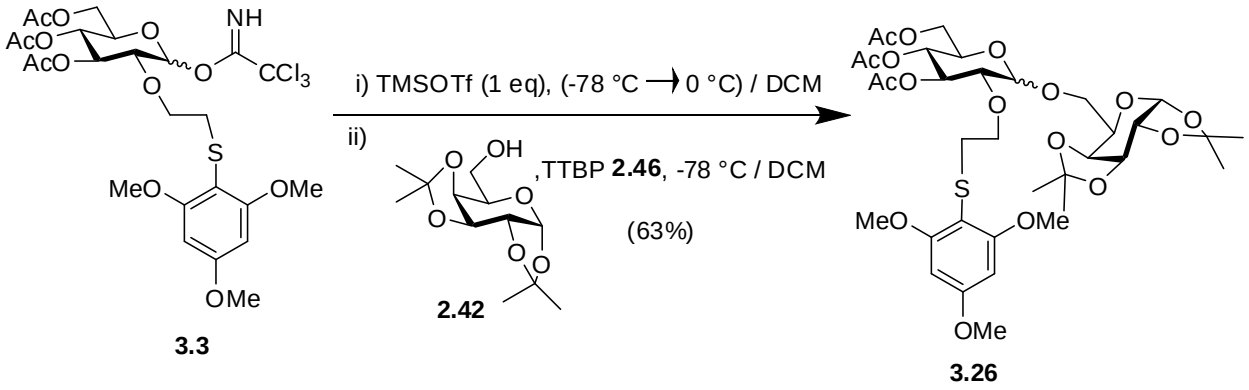
Scheme 3.12

Under identical conditions the partially disarmed donor **3.2** gave disaccharide **3.25** as an anomeric mixture of products, which was in favour of the α-anomer (*α*:*β* = 5:1) (Scheme 3.13).



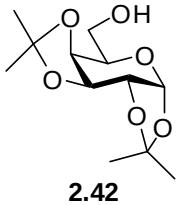
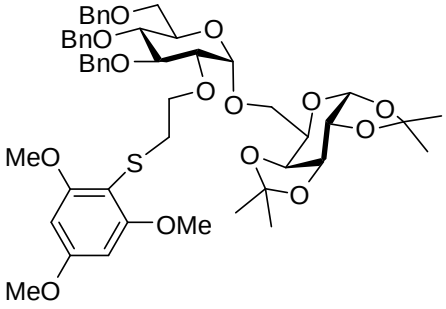
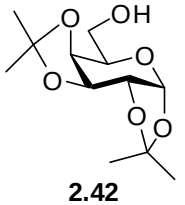
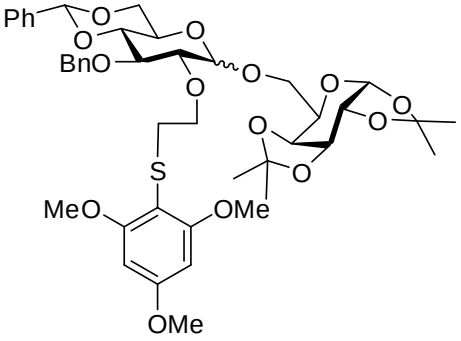
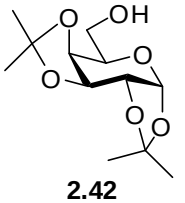
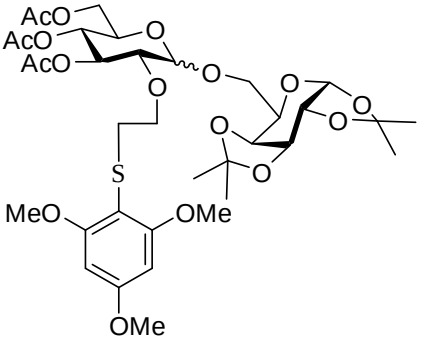
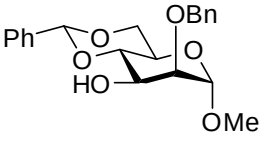
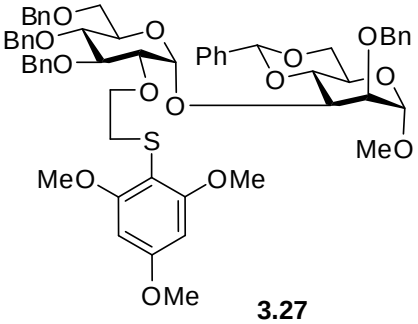
Scheme 3.13

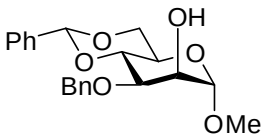
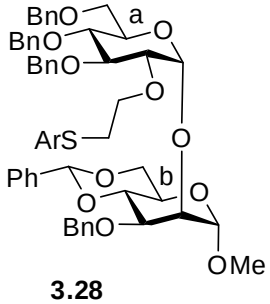
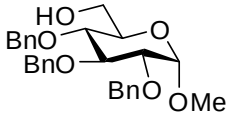
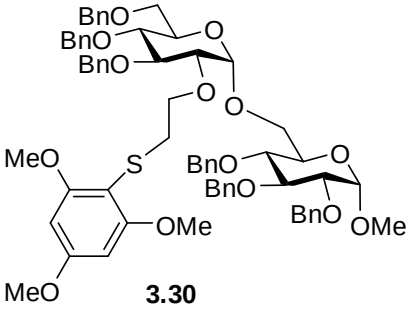
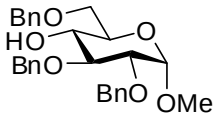
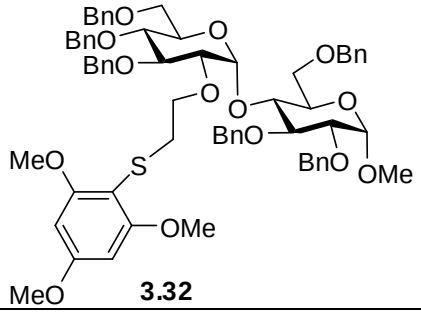
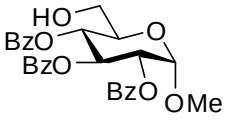
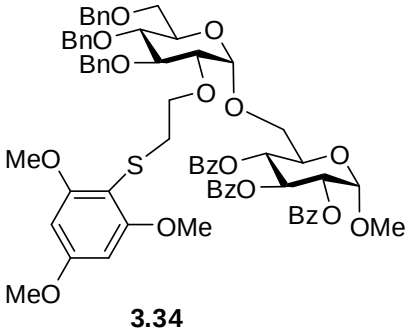
The completely disarmed donor **3.3** yielded disaccharide **3.26** with the stereoselectivity (*α*:*β* = 3.5:1) (Scheme 3.14).



Scheme 3.14

The completely armed donor **3.1** was then used to glycosylate five other acceptors, and pleasingly all the reactions resulted in completely α-selectivity.The glycosylation reactions performed on donors **3.6**, **3.7** and **3.8** are summarized Table 3.2.

Donor	Acceptor	*α*:*β* ratio[a]	Yield (%)	Product
3.1	 **2.42**	1:0	69	 **3.24**
3.2	 **2.42**	5:1	61	 **3.25**
3.3	 **2.42**	3.5:1	63	 **3.26**
3.1	 **2.44**	1:0	63	 **3.27**

3.1	 **2.45**	1:0	65	 **3.28**
3.1	 **3.29**	1:0	68	 **3.30**
3.1	 **3.31**	1:0	61	 **3.32**
3.1	 **3.33**	1:0	76	 **3.34**

[a] Anomeric ratios were determined by integration of appropriate peaks in the ^{1}H NMR spectra of the crude products before column chromatography.

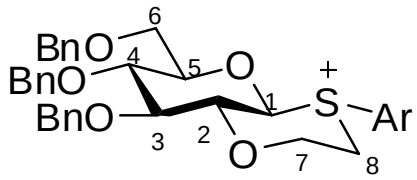
Table 3.2

3.5 Low temperature NMR investigations into neighboring group participation of thioaryl Substituent

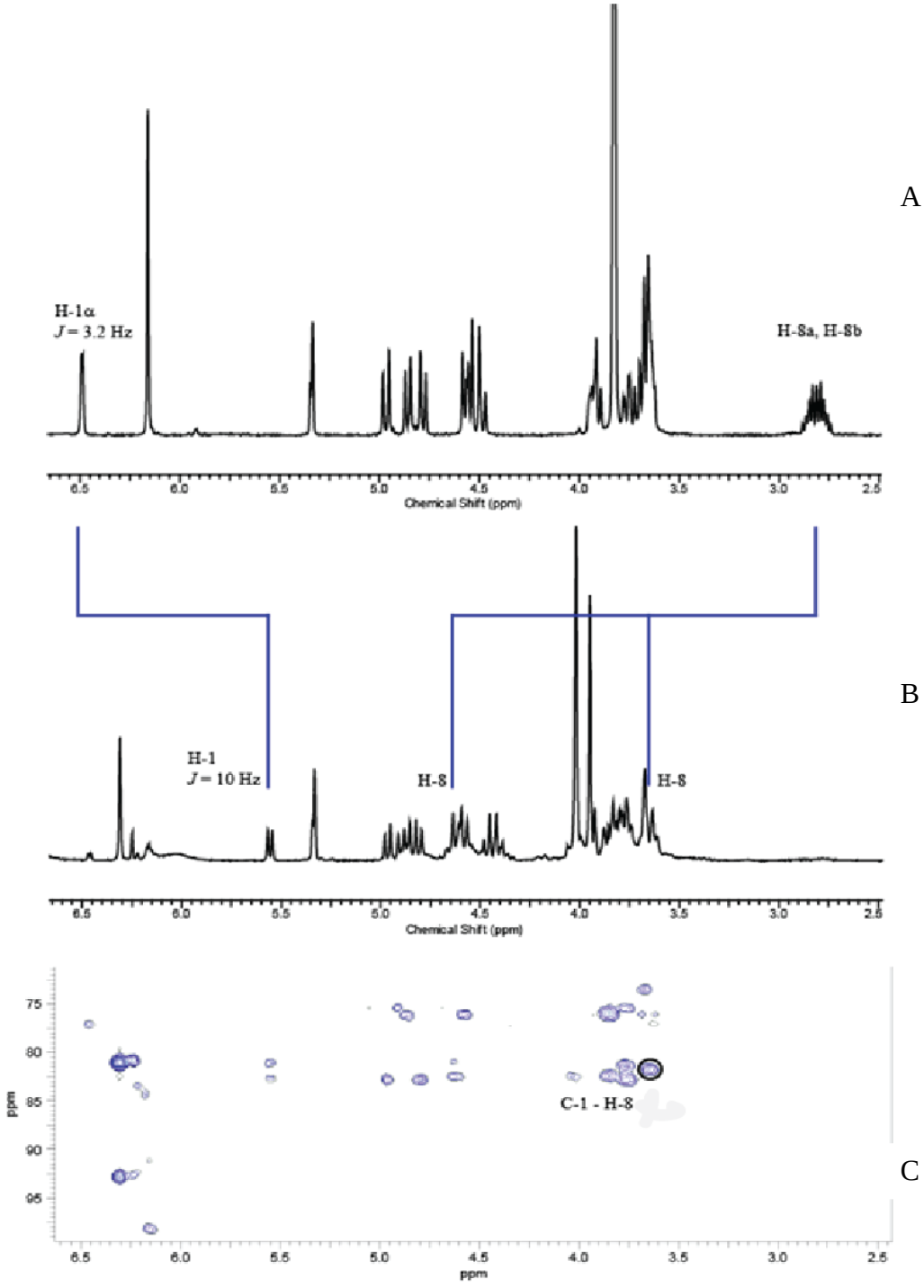
3.5.1 Low temperature NMR investigations into neighbouring group participation during glycosylation of donor 3.1

The complete stereoselectivity shown by donor **3.1** implied that NGP was occurring during the glycosylation reactions. Therefore, based on studies reported by Boons,[14] we undertook a series of experiments to investigate the structure of intermediates produced during activation of **3.1** by TMSOTf, at -78 °C by recording low temperature NMR spectra.

Firstly, the ^{1}H NMR spectrum of **3.1** was recorded in CD_2Cl_2 at -78 °C. Then an equimolar amount of TMSOTf was added to the solution at -78 °C. The mixture was warmed to 0 °C over 40 min and then again cooled to -78 °C, after which time ^{1}H NMR, HSQC, COSY and HMBC (over 40 min) spectra were recorded at -78 °C. The ^{1}H NMR and HMBC spectra are shown in Figure 3.2.



3.1a



A – ^{1}H-NMR of **3.1** at -78 °C; B - ^{1}H-NMR of activated **3.1** at -78 °C by addition of 1 eq. of TMSOTf; C – HMBC study of activated **3.1** at -78 °C.

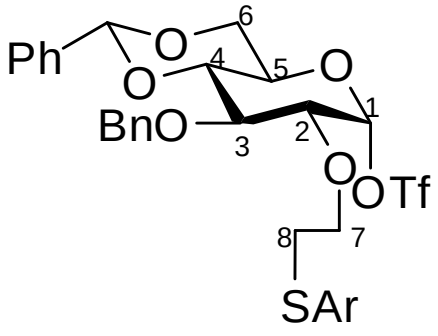
Figure 3.2

Upon activation, the anomeric proton of **3.1** (δ 6.50 ppm, $J_{1,2}$ 3.2 Hz) shifted upfield (δ 5.56, $J_{1,2}$ 10 Hz) and its large vicinal coupling constant implied an equatorial orientation of the anomeric substituent in the intermediate (i.e. that is was β-configured). The H-8 and H-8' protons which had very similar chemical shifts in the spectrum of **3.1** (δ 2.75 ppm, m) were split into two distinct peaks at δ 3.64 and δ 4.69 ppm. The HMBC spectrum, which shows three bond heteronuclear couplings, showed a correlation between C-1 and one of the H8 protons (δ 3.64 ppm), which is marked as a circle on the HMBC spectrum, implying the formation of a cyclic intermediate. However correlation of the other H-8 proton (H-8') with C-1 was not observed. The ^{1}H NMR did provide evidence for the formation of a β-configured *trans*-decalin intermediate. The H-8 and H-8' peaks, which were very similar in the acyclic starting material, would be expected to have different chemical shifts in a cyclic intermediate such as **3.6a**, due to their different environments (axial and equatorial). Therefore the splitting of the single H8/H8' multiplet in the starting materials into two distinct separated peaks for H8 and H8' in the intermediate implies that a cyclic intermediate is formed, and, together with the size of the H-1/H-2 coupling constant ($J_{1,2}$ 10 Hz) provides strong evidence that the cyclic intermediate is a β–configured *trans*-decalin. No oxocarbenium ion, anomeric triflate, or α-sulfonium ion was detected in the NMR spectra.

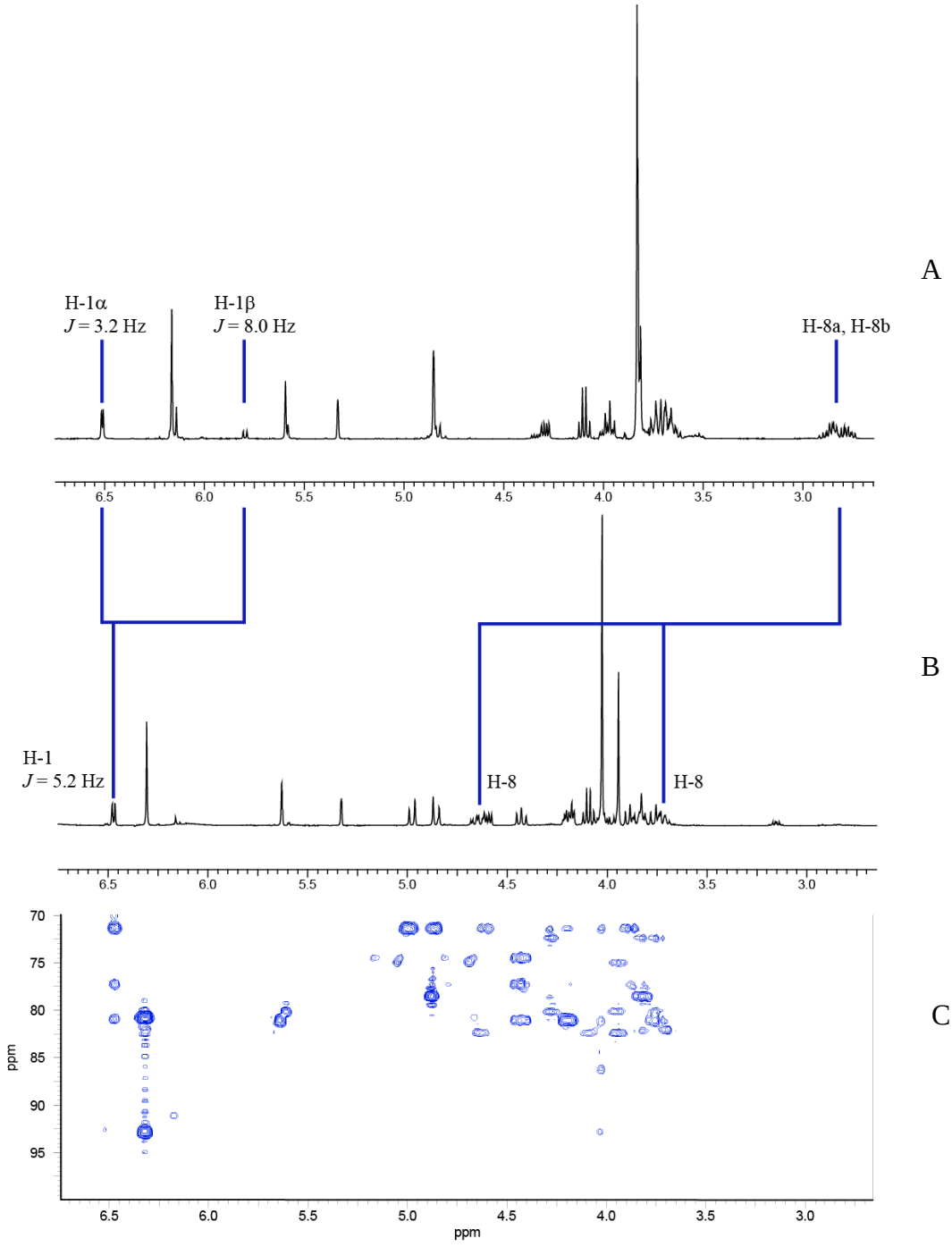
3.5.2 Low temperature NMR investigations into neighbouring group participation during glycosylation of donor 3.2

The high stereoselectivity shown by donor **3.2** and **3.3** indicated role of NGP during the glycosylation reactions. The stereoselectivity observed for the partially disarmed / completely disarmed donors were lower than their armed counterpart, and the observation counteracted with the observations reported in literature.[14] Therefore, based on studies reported by Boons,[14] I undertook a series of experiments to investigate the structure of intermediates produced during activation of **3.2** by TMSOTf, at -78 °C by recording low temperature NMR spectra.

Firstly, the ^{1}H NMR spectrum of **3.2** was recorded in CD_2Cl_2 at -78 °C. Then an equimolar amount TMSOTf was added to the solution at -78 °C. The mixture was then warmed to 0 °C for 40 min and then cooled back to -78 °C, after which time ^{1}H NMR, HSQC, COSY and HMBC (over 40 min) spectra were recorded at -78 °C. The ^{1}H NMR and HMBC spectra are shown in Figure 3.3.



3.2a



A – ^{1}H-NMR of **3.2** at -78 °C; B - ^{1}H-NMR of activated **3.2** at -78 °C by addition of 1 eq. of TMSOTf; C – HMBC study of activated **3.2** at -78 °C.

Figure 3.3

Upon activation, the anomeric proton of **3.2** (δ 6.51 ppm, d, $J_{1,2}$ 3.2 Hz and δ 5.80 ppm, d, $J_{1,2}$ 8.0 Hz: α and β protons respectively) shifted and gave a single peak (δ 6.50, d, $J_{1,2}$ 5.2 Hz, $J_{H1,C1}$ 165.5 Hz). The H-8 and H-8' protons which had very similar chemical shifts in the spectrum of **3.2** (δ 2.85 ppm, m) were split into two distinct peaks at δ 3.73 and δ 4.63 ppm. The HMBC spectrum, which shows three bond heteronuclear couplings, did not show any correlation between C-1 (86.1 ppm) and H8/H8' protons, thus ruling out NGP between SAr and H-1. The HMBC spectrum also did not show any correlation of H-1 with C-7 or with aromatic C of the SAr substituent. Any kind of NGP with either '*O*' at position-2 forming 1,2 epoxide intermediate, or through the aromatic ring at position-2 was ruled out.

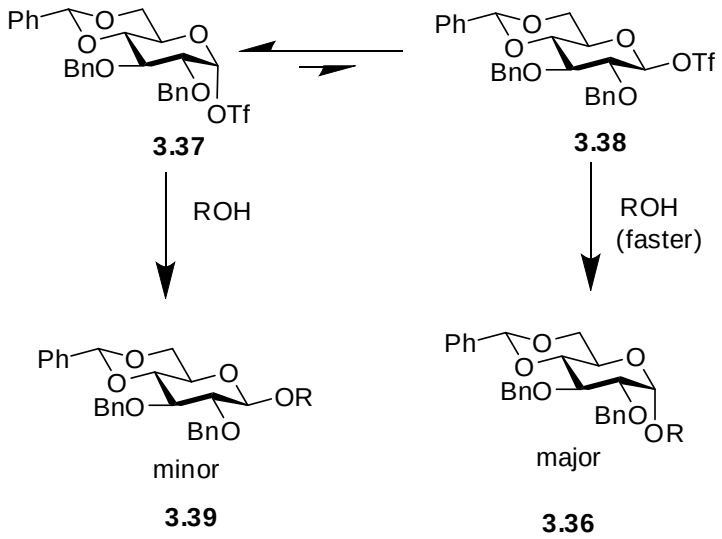
Ruling out all the possible NGPs from position-2, and high δ value of anomeric proton it led us to a conclusion that either α or β triflate is formed as the intermediate. Since the H-1/H-2 coupling constant ($J_{1,2}$ 5.2 Hz) was not conclusive, a closer look to similar triflates reported in literature was needed to reveal the configuration. Crich[15] had characterized tetraacetyl glucosyl-α-triflate and tetraacetyl glucosyl-β-triflate. The α-triflate anomeric proton is seen at δ 6.21 ($J_{H1,C1}$ 184.5 Hz) and β-triflate anomeric proton is seen at δ 5.60. Boons'[1c] reported formation of 2-azidotriacetyldeoxygluco-α-triflate, which showed anomeric peak at (δ 6.50, d, $J_{1,2}$ 3.5 Hz).

Furthermore Crich[16], while investigating the chemistry of 4,6-*O*-benzylidene-D-glycopyranosyl triflates, trapped the intermediate triflate at -78 °C. Activation of either anomer of *S*-phenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-D-glucopyranoside **3.35** with triflic anhydride in dichloromethane at -78 °C in the presence of 2,6-di-*tert*-butyl-4-methylpyridine affords a highly active glycosylating species which, on addition of alcohols, provides α-glucosides **3.36** with high selectivity (Scheme 3.15).

3.35 **3.36**

Scheme 3.15

To probe the nature of the reactive intermediate in the above glucosylation reactions, a CD_2Cl_2 solution of sulfoxide **3.35** and DTBMP was cooled to -78 °C and its ^1H NMR spectrum recorded before addition of cold (-78 °C) Tf_2O. The ^1H NMR spectrum, recorded within minutes of adding the anhydride, showed complete consumption of the sulfoxide and formation of one very major new glucoside. This species was most easily characterized at -78 °C by its very distinct anomeric proton resonance: a doublet at δ 6.3 with $J_{1,2}$ 3.5 Hz, as α-glucosyl triflate **3.37**. It was then established by them that in 4,6 benzylidene-2,3-dibenzylglucosyl triflate, there exist a dynamic system in which the α-triflate **3.37** is in equilibrium with its less stable but more reactive β-anomer **3.38** and that the rate and equilibrium constants are such as to provide preferentially the α-glucoside **3.36** (Scheme 3.16).



Scheme 3.16

Based on these observations it was concluded that intermediate **3.2a** isolated in our studies at -78 °C was *α*-triflate.

3.6 Discussion

In a complete armed donor **3.1**, we concluded that a cyclic intermediate was formed upon activation. The cyclic intermediate observed was *β*-configured, and thus addition of an alcohol resulted in formation of exclusive *α*-glycosides.

Whereas in partially disarmed donor **3.2** and completely disarmed donor **3.3**, NGP does not exist, as observed in the low temperature NMR studies of **3.2**. Based on the mechanism proposed by Crich[16] explained earier in section 3.5, we concluded that the completely disarmed and partially disarmed donors (**3.2** and **3.3**), on activation with TMSOTf, forms triflate at -78 °C. There exists a dynamic equilibrium between a more stable *α*- triflate and more reactive *β*- triflate. The *α*-triflate being stable is trapped in the low temperature NMR experiment and thus shows up in spectra, but the *β*- triflate being more reactive, reacts faster in a S_N2 mechanism leading to high stereoselectivity (*α*:*β* = 5:1) in both cases (Figure 3.4).

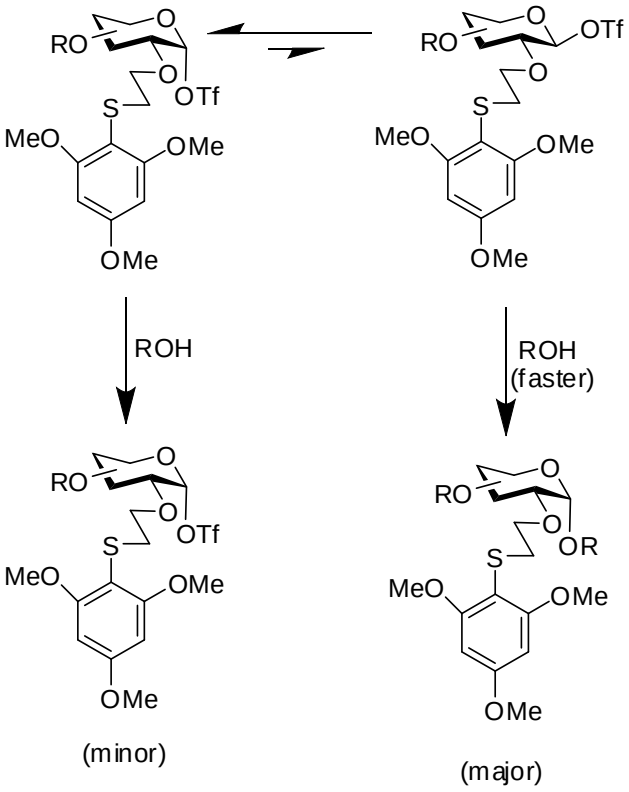
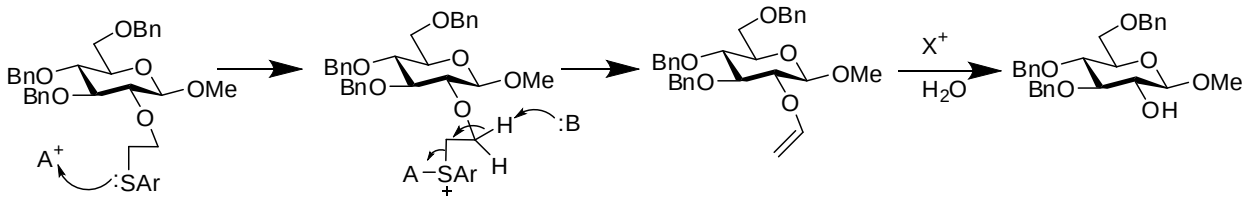


Figure 3.4

3.7 Deprotection Reactions

The utility of a protecting group which controls the stereochemistry of a glycosylation is limited by the ease with which it may be removed at the end of any synthesis. Therefore the deprotection of a model compound, *β*-methyl glucoside **3.40** was investigated under a variety of conditions.

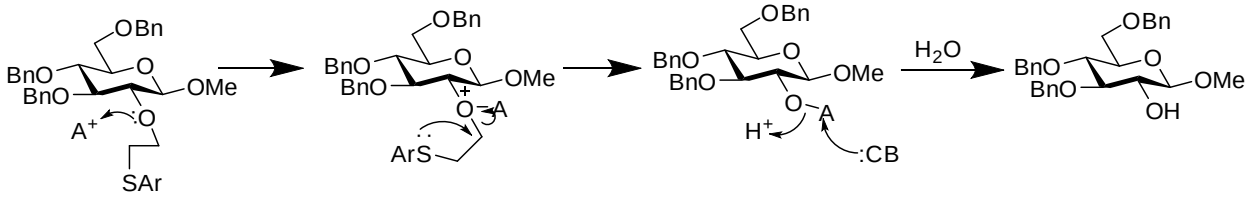
Use of a soft Lewis acid: First a soft Lewis acid was added to the glycoside solution, which was expected to form adduct with sulfur atom. After stirring the solution for different intervals of time, later a powerful non-nucleophilic base was added to facilitate elimination reaction to form a vinyl ether, which can then be removed hydrolytically (Scheme 3.17).



Scheme 3.17

Sl. No.	Reaction Conditions	Outcome
1.	(i) NBS (ii) potassium *tert.* butoxide / DCM, rt→reflux	No Reaction
2.	(i) NIS (ii) potassium *tert.* butoxide, rt→reflux	No Reaction

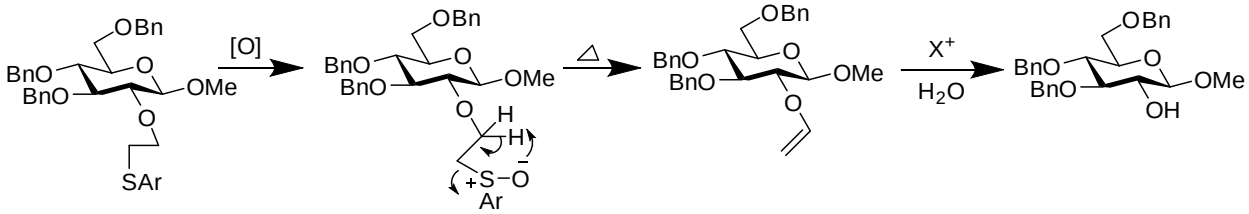
Use of a hard Lewis acid: In the second approach, hard Lewis acid was added to the glycoside solution, which was expected to form an adduct with the oxygen atom. It was expected that 'S' would anchimerically assist elimination of the ethyl ether, to result to direct deprotection of sugar (Scheme 3.18).



Scheme 3.18

Sl. No.	Reaction Conditions	Outcome
1.	TMSI / DCM, rt	Decomposed to yield mixture of products
2.	TMSOTf / DCM, rt→reflux	No Reaction
3.	TFA / DCM, rt	No Reaction
4.	(1) TFA (2) potassium *tert.* butoxide / DCM, rt→reflux	Decomposed to yield mixture of products
5.	BF_3. Et_2O / DCM, rt→reflux	No Reaction

Oxidation to sulfoxide followed by pyrolytic elimination: A third approach that was investigated involved selective oxidation of the sulfur to a sulfoxide, which could be followed by elimination on heating, to give a vinyl ether, which could then be removed hydrolytically (Scheme 3.19).



Scheme 3.19

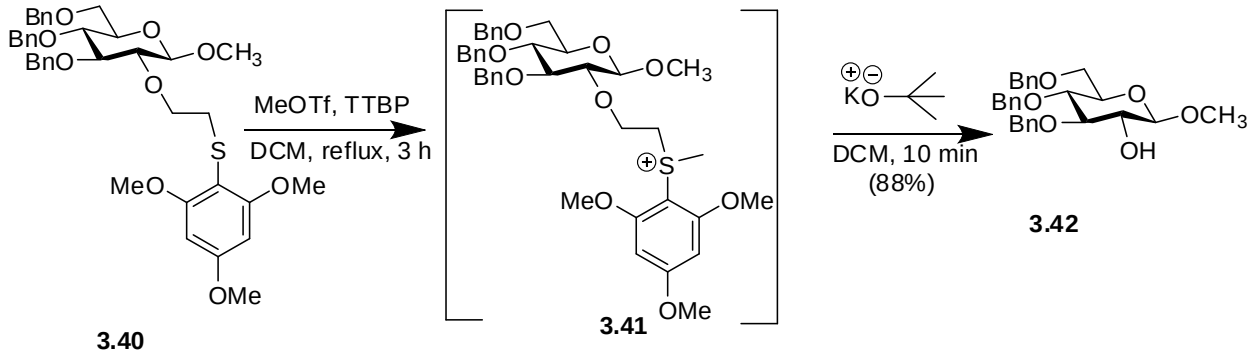
However, reaction of the glycoside **3.40** with 1 eq. of mCPBA, led to formation of mixture of sulfoxide and sulfone. Sulfoxide decomposed when heated to 110 °C in toluene.

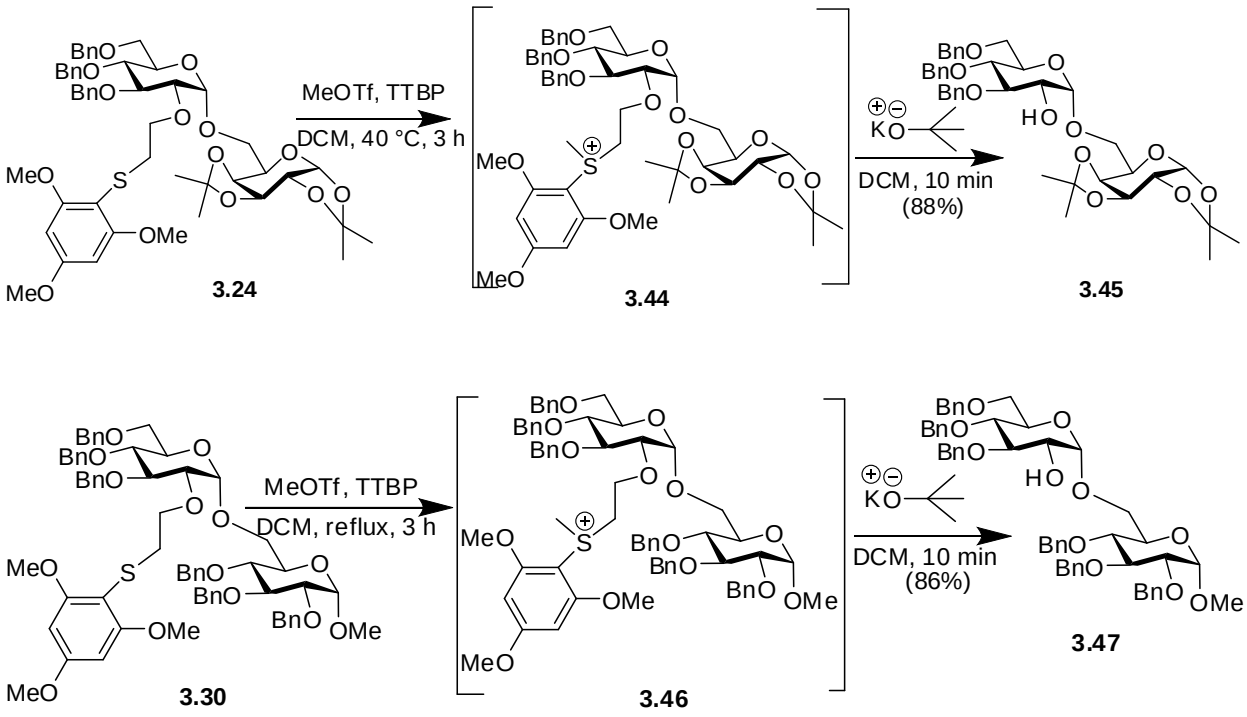
Sulfone can directly be converted to the deprotected sugar, by β elimination on reaction with lithium naphthalenide.[17] But due to unavailability of the chemical in lab, this reaction was not tried out.

Sl. No.	Reaction Conditions	Outcome
1.	mCPBA (1 eq.) / THF, - 78 °C→rt	Sulfoxide + sulfone
2.	(i) 50 % H_2O_2, rt (ii) AcOH / DCM	No Reaction

Since suflides readily undergo methylation, methylation of a 2-(arylthio) ethyl ether can be followed by elimination by use of a non-nucleophilic base to give a vinyl ether, which can then be removed hydrolytically.[18] Sulfide **3.40** was refluxed in DCM, in the presence of MeOTf, to yield a sulfonium ion **3.41**. This sulfonium ion was initially isolated, using column chromatography and was then dissolved in THF, and a non-nucleophilic base potassium *tert*-butoxide was added. Almost instantaneously a new product was observed on t.l.c... On analysis, it was realized that the deprotected sugar **3.42** had formed.

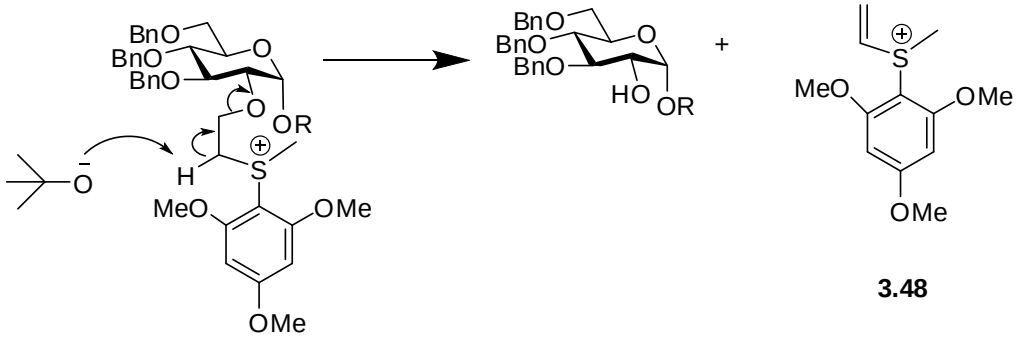
Later the procedure was improved upon, and a one pot reaction was carried in DCM. After the methylation reaction had gone to completion, the reaction mixture was cooled and a non-nucleophilic base potassium *tert*-butoxide was added. Pleasingly this one pot procedure directly yielded the deprotected sugar **3.37**. Two other sugars **3.24** and **3.30** were deprotected in the same manner (Scheme 3.20).





Scheme 3.20

Analysis of the mass spectrum of the reaction mixture indicated that the reaction proceeded *via* a *β*-elimination mechanism following to formation of a sulfur ylid intermediate (Scheme 3.21). A peak corresponding to the elimination product methyl(2,4,6-trimethoxyphenyl)(vinyl)sulfonium **3.48** HRMS (ES^+) calculated for $C_{12}H_{17}O_3S$ (M^+) 241.0898, found 241.0892 was observed (Figure 3.5).[18]



Scheme 3.21

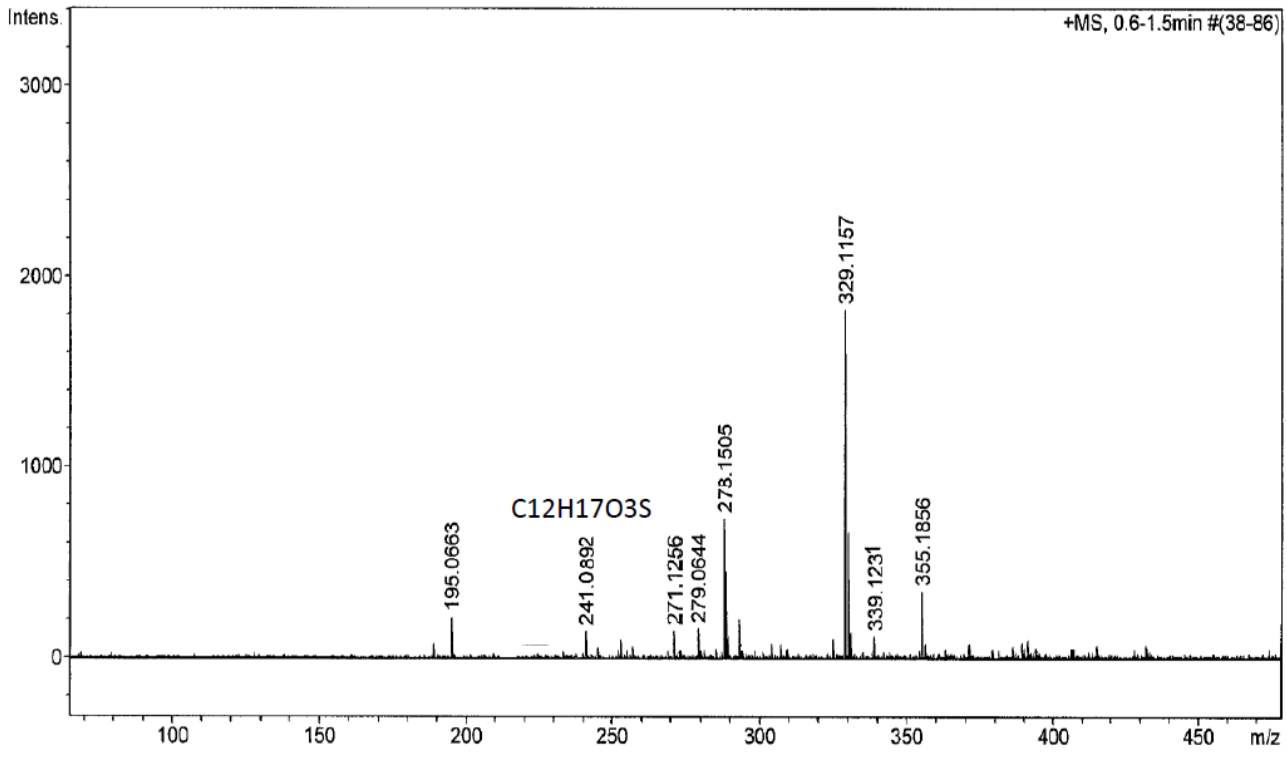
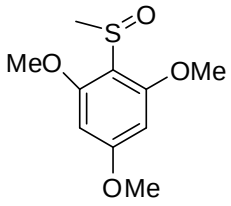


Figure 3.5

However compound **3.48** could not be isolated; work-up actually led to the isolation of sulfoxide **3.43** (Figure 3.6) was purified by column chromatography and was characterized by NMR and mass spectrometry.



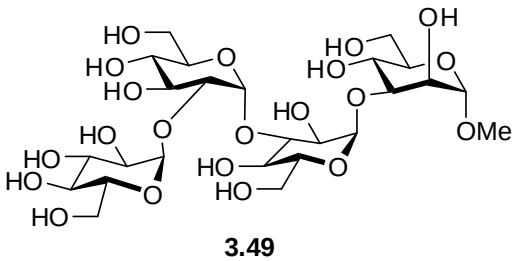
3.43

Figure 3.6

3.8 Attempted synthesis of tetrasaccharide Glc_3Man *N*-glycan tetrasaccharide by NGP

Post-translational modification of proteins by glycosylation[19] is well known to have an important role in protein folding,[20] is able to modulate protein stability and enzymatic activity,[21] and in addition can also affect other important protein properties, such as circulatory lifetime.[22] The most common form of protein glycosylation is *N*-linked glycosylation, in which the oligosaccharides (*N*-glycans) are attached to the side chains of asparagines residues. The interesting and diverse roles played by residues present in the glucose terminated arm have therefore initiated significant interest from the synthetic community.

The tetrasaccharide Glcα(1→2) Glcα(1→3) Glcα(1→3)ManαOMe **3.49** (Figure 3.7) corresponds to the terminal tetrasaccharide portion of the glucose terminated arm of the *N*-glycan tetrasaccharide. Fairbanks' group has reported a completely stereoselective approach to the **3.49** tetrasaccharide in which two of the terminal α-gluco linkages are formed by successive Intramolecular glycosylation reactions using the allyl IAD approach.[23] Synthesis of **3.49** was mulled upon employing novel six membered ring neighbouring group participation in the last two steps.

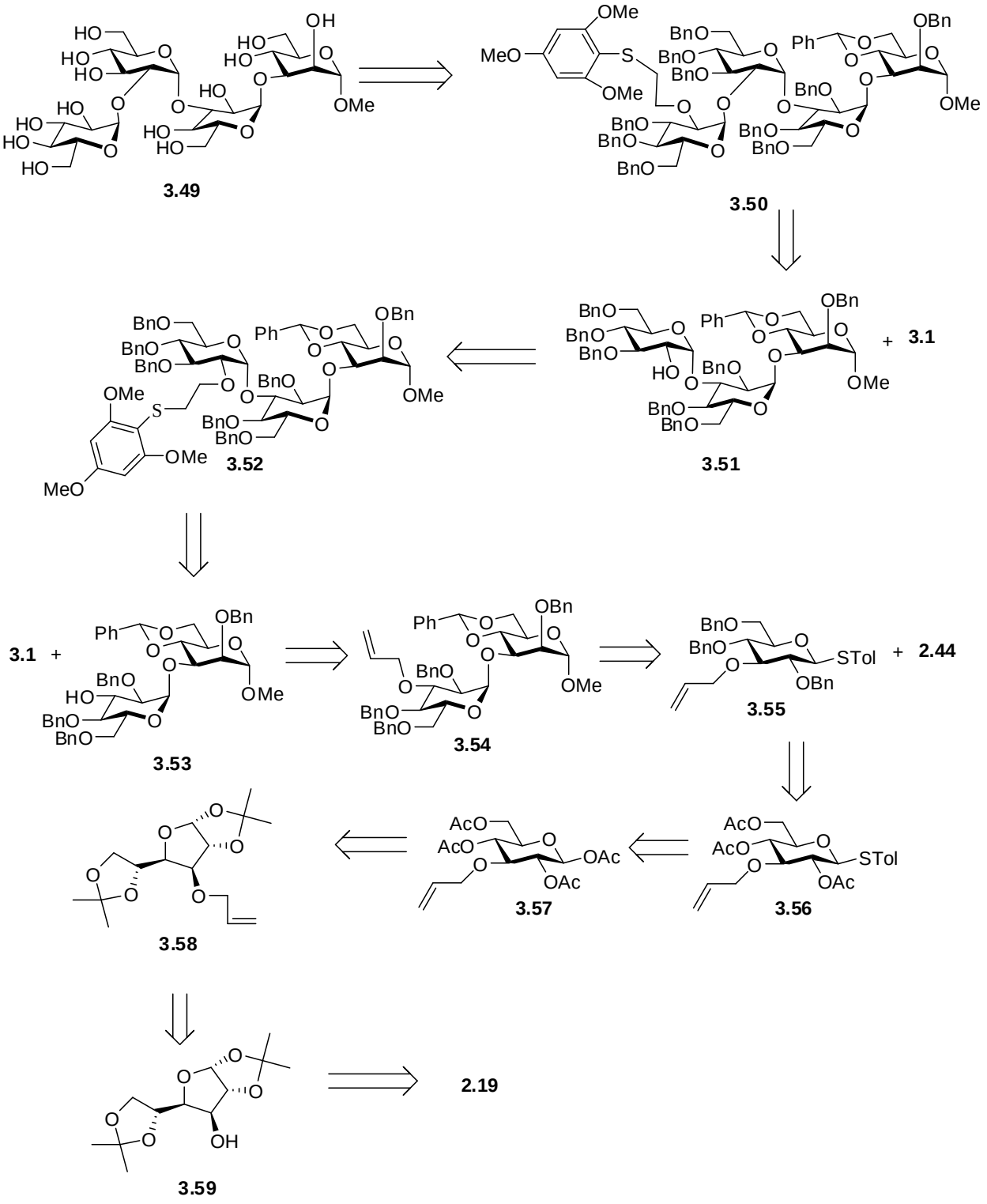


3.49

Figure 3.7

3.8.1 Retrosynthetic Analysis

Thus a retrosynthesis based on modification of the group's linear synthesis towards an iterative NGP approach is shown in Scheme 3.22.



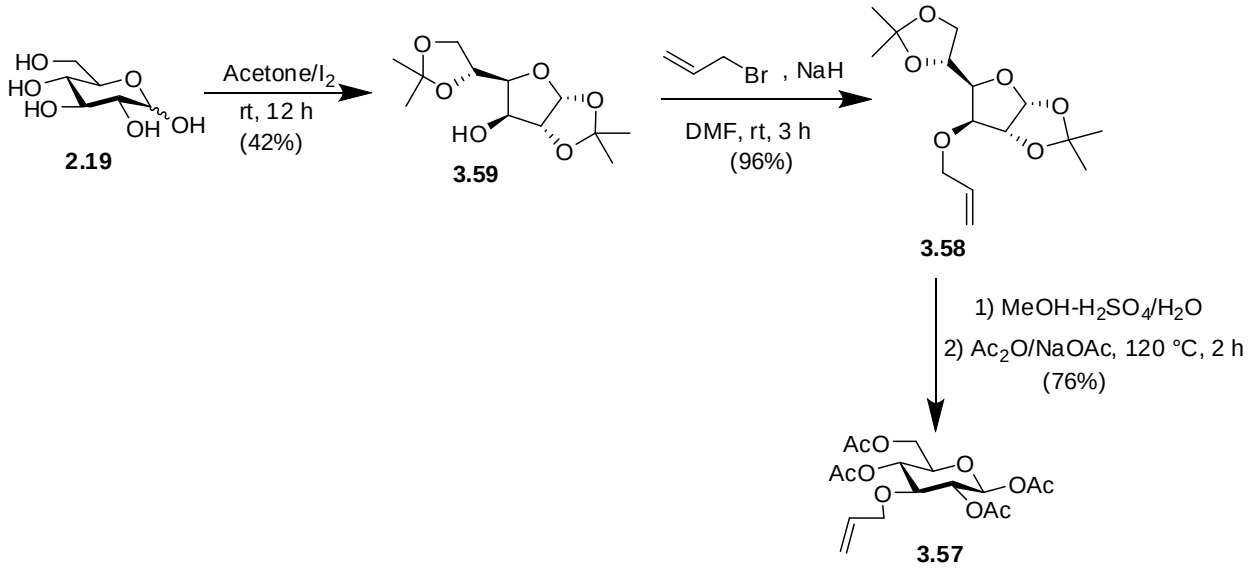
Scheme 3.22

Disconnection of an appropriately protected tetrasaccharide **3.50** gives trisaccharide alcohol **3.51** and 2-*O*-arylthio ethyl ether protected glucosyl trichloroacetamidate **3.1**. It is clear that the trisaccharide **3.52** could be the product of a NGP controlled reaction between disaccharide **3.53** and the same donor **3.1**.

Allyl protected disaccharide **3.54** could be derived from the intermolecular glycosylation of *manno* acceptor **2.44** with allyl protected thioglycoside **3.55**, in diethyl ether to give α product exclusively.[23] The gluco donor **3.55** could be made by standard transformations from the 3-*O*-allyl protected tetraacetate **3.57**.[23] **3.57** can in turn be synthesized from allyl protected glucodiacetonide **3.53**.[24] **3.53** could be synthesized by allylation of glucodiacetonide **3.59**, which in turn could be synthesized by acetonization of D-glucose **2.19**.[25]

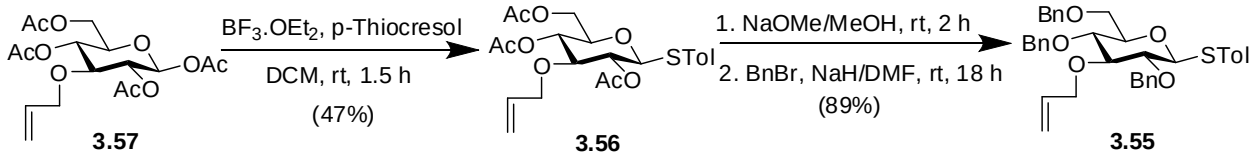
3.8.2 Attempted Synthesis

The known 3-*O*-allyl protected tetraacetate **3.57** was was synthesized using standard procedures from D-glucose pentaacetate **2.20** (Scheme 3.23). Treatment of **2.20** with acetone in the presence of iodine afforded the diacetone glucose **3.59** in 42% yield. The free hydroxyl group at position 3 was allylated on reaction with allyl bromide in the presence of sodium hydride to give **3.58** in 96% yield. Acid hydrolysis followed by acetylation in the presence of sodium acetate and acetic anhydride afforded the 3-*O*-allyl protected tetraacetate **3.57** in 76% yield.



Scheme 3.23

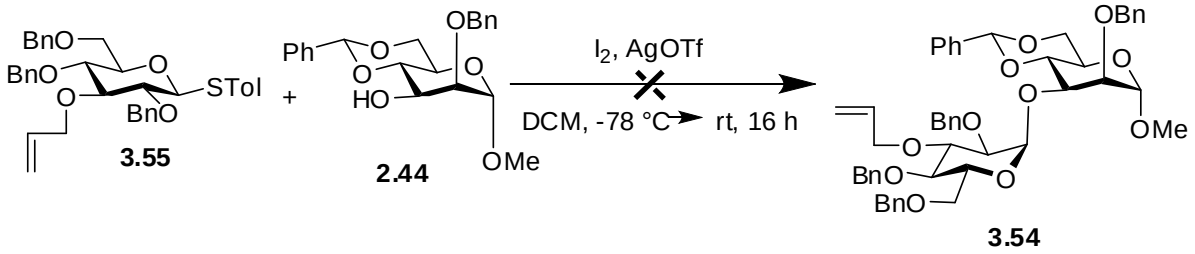
Tetraacetate **3.57** was treated with thiocresol in the presence of a Lewis acid catalyst to obtain the *β*-thioglycoside **3.56** in albeit low yield.[26] Subsequent Zemplén deacetylation[27] and reprotection with benzyl ethers[28] afforded the 3-*O*-allyl donor **3.55** in 89% yield over two steps (Scheme 3.24).



Scheme 3.24

Unfortunately hydrolysis of STol by I_2/AgOTf in presence of base in diethyl ether to yield *α* disaccharide continuously failed on repeated attempts (Scheme 3.25). Though it was a well

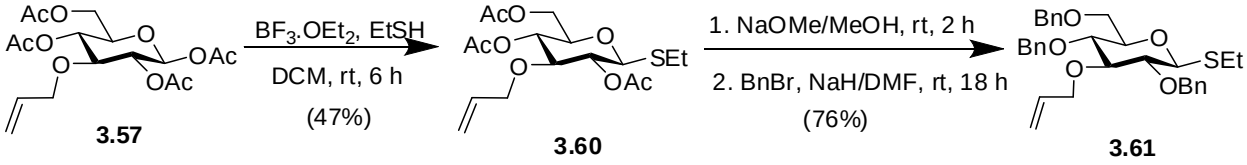
established procedure by Fairbanks' group,[23] this reaction resulted in multiple products, including iodination of allyl group.



Scheme 3.25

It was therefore felt that probably STol was not the best leaving group to be attached on anomeric position, which requires I_2 as activating reagent.

The synthesis route was changed accordingly, to synthesize SEthyl glycoside. Tetraacetate **3.57** was treated with ethanthiol in the presence of a Lewis acid catalyst to obtain the *β*-thioglycoside **3.60** in low yield of 47%.[26] Subsequent Zemplén deacetylation[27] and reprotection with benzyl ethers[28] afforded the 3-*O*-allyl donor **3.61** in a 76% yield over two steps (Scheme 3.26).

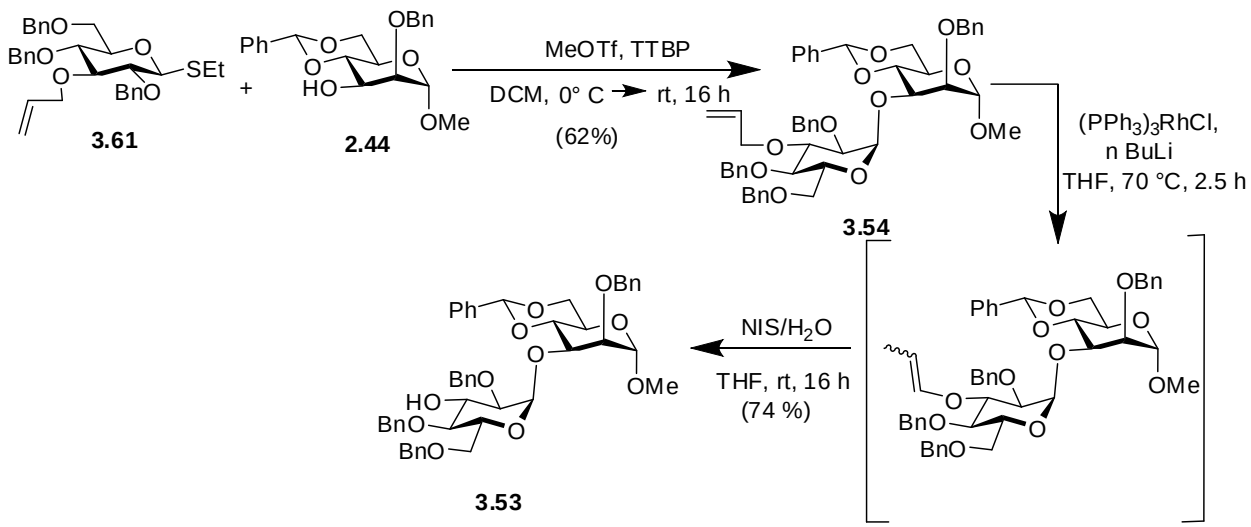


Scheme 3.26

Methyl triflate-mediated intermolecular glycosylation of donor **3.61** and acceptor **2.44** was carried out in ether in order to ensure good *α*-selectivity,[29] and disappointingly again mixture of products were observed. The major product was separated and spectral analysis followed by

HRMS confirmed formation of ethyl glycoside of the donor **3.61**. It was realized later that the anhydrous diethyl ether used in the reaction had very little amount of ethanol as stabilizer. The ethanol competed with the acceptor and led to formation of mixture of products.

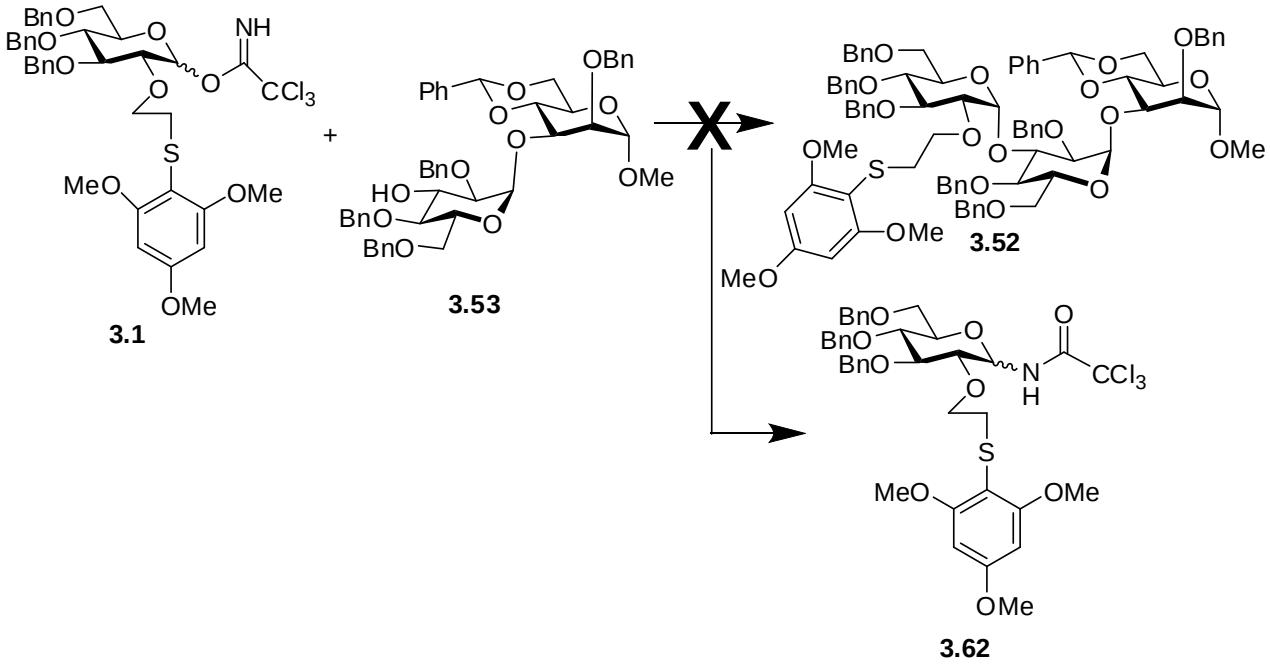
After this a new bottle of anhydrous diethyl ether without stabilizer was used and the methyl triflate-mediated glycosylation reaction indeed afforded the disaccharide **3.54** as the pure α anomer, with a 62% yield. Allyl isomerisation on reaction with Wilkinson's catalyst, followed by the hydrolysis of vinyl ether in presence of NIS/H_2O[30] cleanly afforded the alcohol **3.53** in a 74% yield over two steps (Scheme 3.27).



Scheme 3.27

To afford the trisaccharide in complete α-stereoselectivity, the donor **3.1** was reacted with the disaccharide acceptor **3.53**, using TMSOTf as activator, employing protocol B. However, the glycosylation reaction led to isomerization of trichloroacetamidate donor **3.1** to amide **3.62**. When the reaction was tried out using TMSOTf as activator employing protocol A, again rearrangement of donor was observed. Later a different approach was adopted where in 1 equiv.

of $BF_3.Et_2O$ and 1 equiv. of TMSOTf was added as activator to premixed solution of donor and acceptor at 0 °C and allowed to warm to rt in two different reaction vessels. But in both the cases again rearrangement of the donor was seen. So it was concluded that the donor **3.1** was not a suitable donor for carrying out glycosylation reactions for a sterically hindered secondary glycosyl acceptors. The series of failed glycosylation reactions are tabled down in Scheme 3.28.



Sl. No.	Reaction Conditions	Outcome
1.	1 eq. TMSOTf, -78 °C→rt, Protocol B	Rearrangement of donor to amide
2.	0.1 eq. TMSOTf, -78 °C→rt, Protocol A	Rearrangement of donor to amide
3.	1 eq. TMSOTf, -78 °C→rt, Protocol A	Rearrangement of donor to amide
4.	1 eq. TMSOTf, 0 °C→rt, Protocol A	Rearrangement of donor to amide
5.	1 eq. $BF_3.Et_2O$, 0 °C→rt, Protocol A	Rearrangement of donor to amide

Scheme 3.28

3.9 Conclusions

Significant improvement in stereoselectivity of glycosylation reaction was observed when the achiral ethylthiophenyl ether group at position-2 which was initially used by Boons,[1a] was replaced ethyltrimethoxythiophenyl ether group. It had been suggested that that increasing the stability of sulfonium ion favour an S_N2 mechanism.[31] It was shown by Turnbull[32] that the compound **1.105** (Chapter 1) resuled in complete stereoselectivity, as an axial methoxy group on the oxathiane ring can stabilise a methyl sulfonium ion, when compared to the oxithane ring with absence of methoxy group. Trimethoxy phenyl group, owing to its electron donating methoxy groups thus stabilizes the sulfonium ion which inturn favoured S_N2 attack of acceptor through axial position leading to α- selectivity of the glycosides formed. Boons reported variation of the stereoselectivity of glycosyl donors which undergo 6-ring NGP with the protecting group pattern. In this report[14] he stated that a completely disarmed donor showed highest stereoselectivity, and postulated that the lower stereoselectivity observed during glycosylation with completely armed donors was due to non-selective reaction of the glycosyl cation, which could be accessed according to the Curtin-Hammet principle. However, in the studies reported here it was the completely armed donor that reacted complete α-selectivity, and the completely disarmed donor that showed lower stereoselectivity. In the case of the completely armed donor reported here low temperature NMR studies did strongly indicate the formation of a cyclic β-sulfonium intermediate, thus leading to absolute stereoselectivity. However, in the partially disarmed donor, the low temperature NMR indicated towards absence of NGP. Though the formation of α- triflate intermediate was observed by the low temperature NMR spectra, but the higher stereoselectivity observed in glycosylation was attributed to the fact there existed a

dynamic equilibrium between α- and β- triflate. The α- triflate being stable is trapped in the low temperature NMR stectra, but the β- triflate being more reactive, reacts faster in a S_N2 mechanism leading to high stereoselectivity (α:β = 5:1) in both cases.

In conclusion the trimethoxythiophenylethyl ether is a useful achiral protecting group, that when attached at position 2, which produces α-1,2 *cis* glucosides with complete stereoselectivity when completely armed donors are used. Good α-selectivity is also observed when disarmed donors are used.

The deprotection methodology for the trimethoxythiophenyl ethyl ether proved to be a facile, high yielding one pot reaction which further encourages the use of protecting group at position-2 for effective NGP leading to stereoselective glycosylation.

However, glycosylation reactions carried out with the donor **3.1** resulted in poor yields of the disaccharides, especially with secondary glycosyl acceptors. It suggests that the protecting group at position-2, being a bulky substituent, blocks the anomeric position thus affecting the efficiency of glycosylation. Therefore, when the bulky disaccharide acceptor **3.48** was used for glycosylation, rearrangement of the donor **3.1** was observed, as the acceptor was practically unavailable to the donor.

3.10 References

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Chapter 4: A study into the potential use of organocatalysis for the stereochemical control of glycosylation reactions

4.1 Introduction

Organocatalysis, or the use of small organic molecules to catalyze organic transformations, is a relatively new and popular field within the domain of asymmetric synthesis.[1] Organocatalytic asymmetric assembly reactions are powerful tools that can be used to rapidly construct stereochemically complex molecules from simple precursors.[2] The regioselective and stereoselective synthesis of glycosidic bonds still remains as one of the most challenging areas within organic synthesis. Despite the broad use of organocatalysis within asymmetric synthesis, its application towards oligosaccharide synthesis by diastereoselective glycosylation is still in its infancy.[3] Neighboring-group participation is a powerful method for control of the stereoselectivity of glycosylation reactions. However, this approach generally relies upon multiple protecting-group manipulations in order to synthesize the required oligosaccharides. An in-depth research into the potential applications of organocatalysis for the stereoselective synthesis of glycosides may provide efficient and high yielding synthetic procedures.

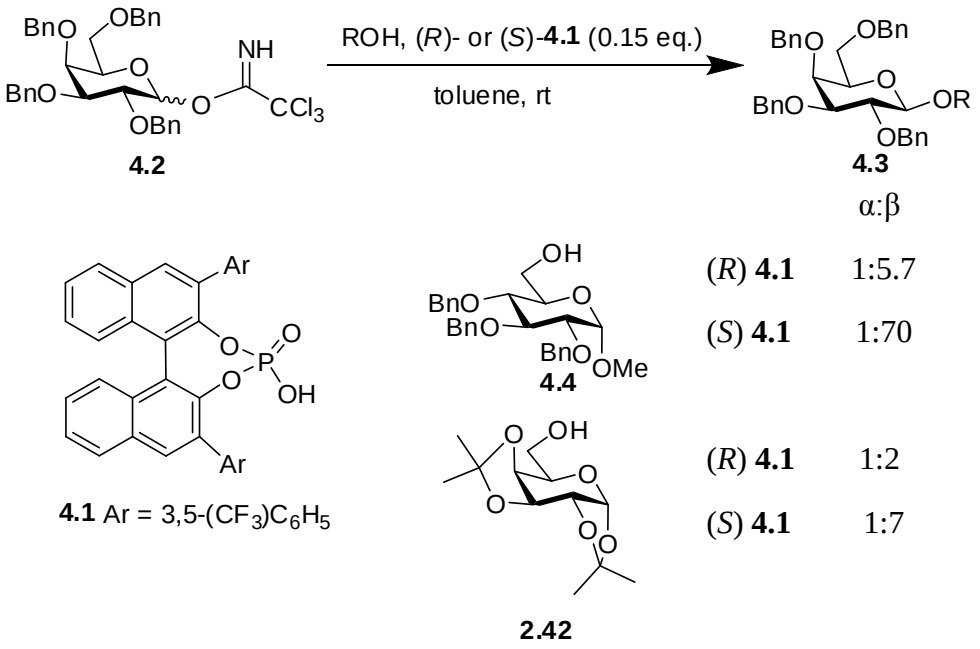
Asymmetric synthesis has frequently been applied to control the diastereoselectivity of a variety of chemical processes.[4] However there are only a very few reports in literature of previous efforts that have been made to control the stereochemical outcome of glycosylation reactions using chiral catalysts. 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,[5] or palladium complexes used in asymmetric

allylic alkylation.[6] It is difficult to see how the use of such transition metal complexes could be applied to glycosylation reactions. However recent developments in the growing field of organocatalysis[1] have provided a section of new asymmetric process that may be more applicable to the control of the diastereoslectivity of glycosyaltion reactions. In particular, the potential use of chiral Brønsted acids for the activation of glycosyl donors represents an attractive prospect for controlling the stereochemistry of the glycosylation product.[7]

4.1.1 Recent developments in the application of organocatalysis to glycosylations

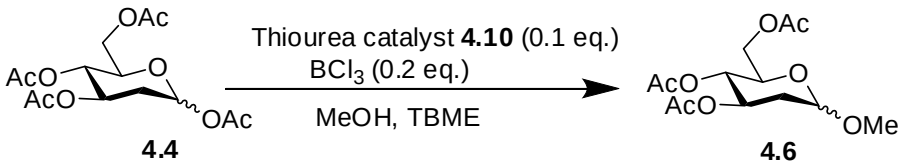
4.1.1.1 Chiral organocatalysts

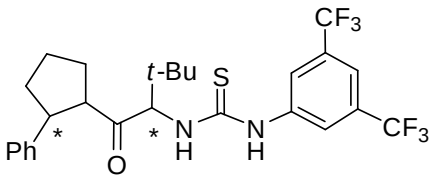
Fairbanks *et al*. reported that *β*-selective glycosylations of glycosyl trichloroacetamidates can be achieved using a chiral BINOL-derived phosphoric acid catalyst **4.1** (Scheme 4.16).[7] It was found that the use of (*R*)-**4.1** generally gave low levels of *β*-selectivity, whereas (*S*)-**4.1** generally afforded the *β*-anomer with high selectivity. The work was the first demonstration that the configuration of a chiral catalyst can have a strong influence on the stereoselectivity of a glycosylation reaction with complex acceptors – an important step towards achieving catalyst control. Further mechanistic investigations are required to understand whether this selectivity arises solely from non-bonded interactions, or whether the catalyst forms covalent bonds with either donor or acceptor (Scheme 4.1).



Scheme 4.1

Chiral thioureas have been employed by Jacobsen *et al*. for the catalytic enantioselective addition of silyl ketene acetals to oxocarbenium ions and preliminary results of the application of this methodology towards glycosylation reactions were also reported (Scheme 4.2).[8] Although the stereoselectivities were low, with methanol as the acceptor it was shown that changing the enantiomer of the thiourea catalyst changed the anomeric selectivity. Interpretation of these results is complicated by the fact that the starting material is a mixture of anomers each of which may react differently. A possible cooperative effect between the boron and the thiourea catalyst **4.5** in this case cannot be ruled out, and therefore the mechanistic basis of these reactions needs further investigation.

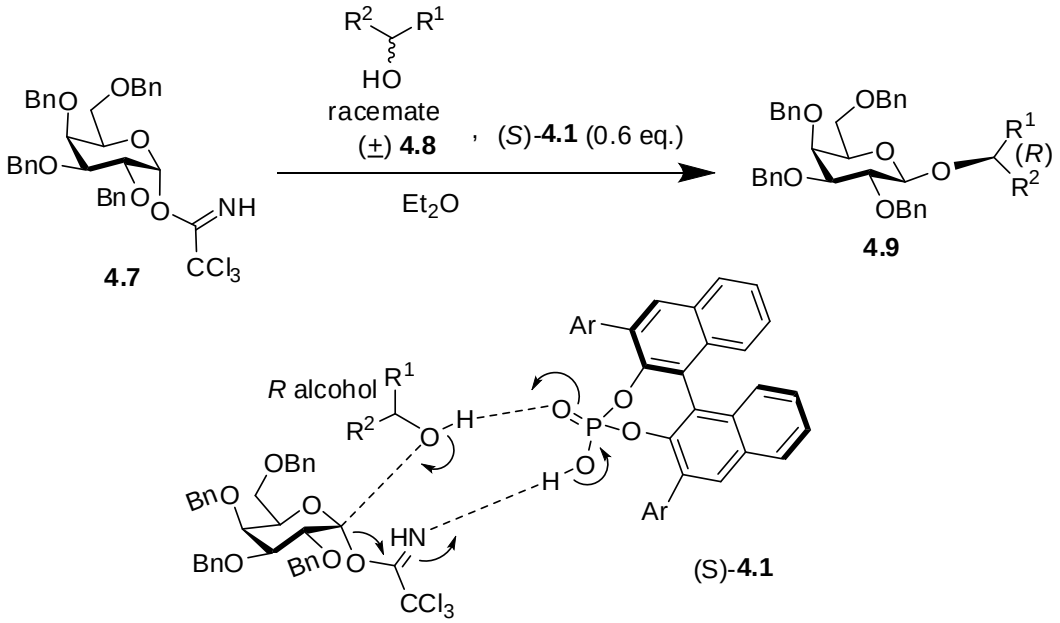




Catalyst	Conv. (%)	α:β
None	19	1:1.1
R/S	94	1:1.7
S/R	56	1.4:1

Scheme 4.2

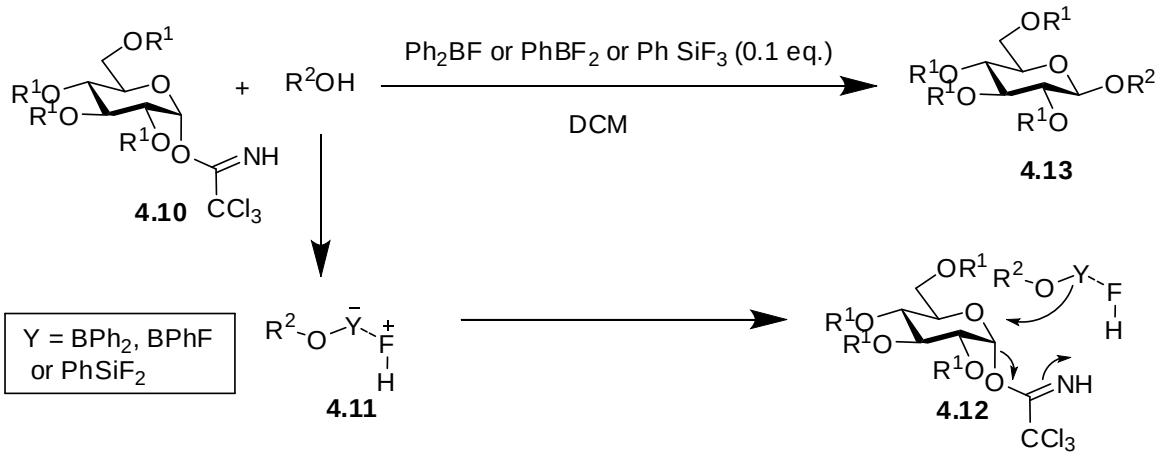
Following on from the work of Fairbanks, the Toshima group[9] used the same chiral phosphoric acid (**4.1**) as an organocatalyst, and demonstrated that glycosylation using a racemic mixture of a chiral alcohol (±) **4.8** as the acceptor was selective for one enantiomer and in addition was *β*-selective. Catalyst (*S*)-**4.1** gave complete diastereoselectivity of *β* glycoside **4.9** exclusively with (*R*) **4.8** alcohol in the presence of a racemic mixture of alcohols (±) **4.8** as the acceptor. A schematic presentation and the mechanism proposed is depicted below in Scheme 4.3.



Scheme 4.3

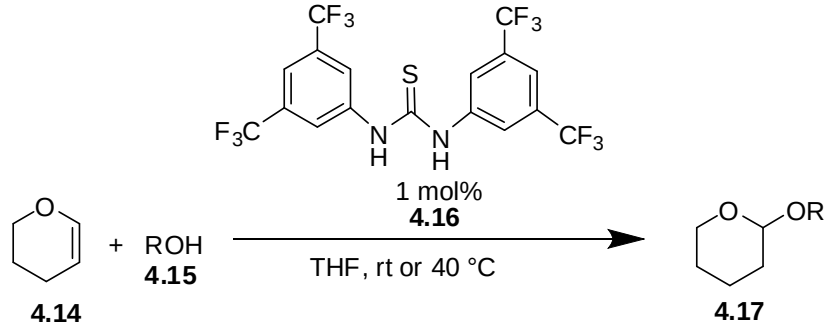
4.1.1.2 Achiral organocatalysts

The catalytic use of phenylboron difluoride, diphenylboron fluoride, and phenylsilyl trifluoride as activators for glycosylation reactions of glycosyl trichloroacetimidates **4.10** was demonstrated by Schmidt *et al*.[10] Good to excellent yields and useful *β*-selectivities were achieved in many of the reported examples (Scheme 4.4). It was proposed that the organoboron or organosilicon catalyst initially activates the acceptor to generate the intermediate (**4.11**); this in turn activates the donor (**4.12**) through hydrogen bonding and then proton transfer. As would be expected from the proposed S_N2-like mechanism, *α*-trichloroacetimidates favor *β*-glycosides **4.13**. However, the reactions do not proceed with complete inversion especially with more hindered alcohols, thus an alternative S_N1 pathway can compete.



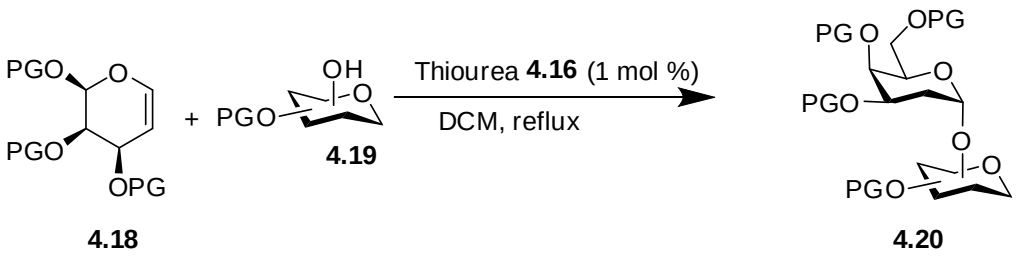
Scheme 4.4

Schreiner *et al*. had reported organocatalytic tetrahydropyranylation of alcohols, using thiourea **4.16** as the organocatalyst leading to formation of **4.17** from **4.14** (Scheme 4.5).[11]



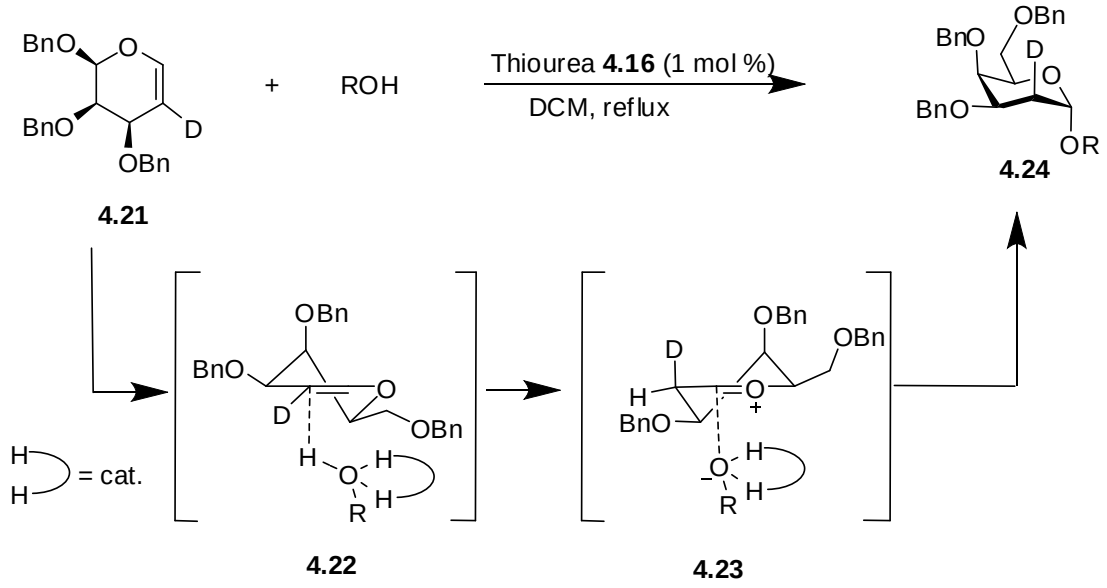
Scheme 4.5

Later McGarrigle *et al*. adopted the same methodology and organocatalyst to develop a glycosylation method.[12] Dihydropyran was replaced with glycols **4.19** to achieve glycosylation reactions affording 2-deoxyglycosides **4.20** (Scheme 4.6). However, by using 1 mol% of thiourea **4.16** in refluxing DCM the desired transformation was achieved with a wide range of galactals **4.18** and acceptors in high yield and exclusively gave the α-anomer. The nature of the acceptor (position/orientation of the free hydroxyl group) did not affect the yield or selectivity for the α-anomer.



Scheme 4.6

When exploring the mechanism of this organocatalyzed reaction, it was shown that anomerization of the *β*-anomer to the more thermodynamically favorable *α*-anomer does not occur under the reaction conditions. When the deuterated galactal **4.21** was used, the newly formed C–O and C–H bonds were found to be *cis* to each other, thus the formation of both bonds is diastereoselective. This led to proposed mechanism (Scheme 4.7) in which the catalyst alcohol complex delivers the proton to the least hindered face of the galactal (**4.22**). The resulting ion-pair intermediate (**4.23**) then rapidly collapses to form the new C–O bond, forming *α* galactoside **4.24**.



Scheme 4.7

In conclusion, over recent years some progress has been made in catalyzing glycosylations with small organic molecules. These readily accessible catalysts provide new opportunities for regio- and stereoselective synthesis of glycosides, especially where it may be possible to develop catalysts capable of overcoming the inherent substrate bias for a given stereochemical outcome in these important reactions. Organocatalysis offers mild reaction conditions, tunable chiral scaffolds, and multiple activation modes, which may lead to general methods for catalyst control of the anomeric configuration of the product formed during glycosylation reactions being developed in the future.

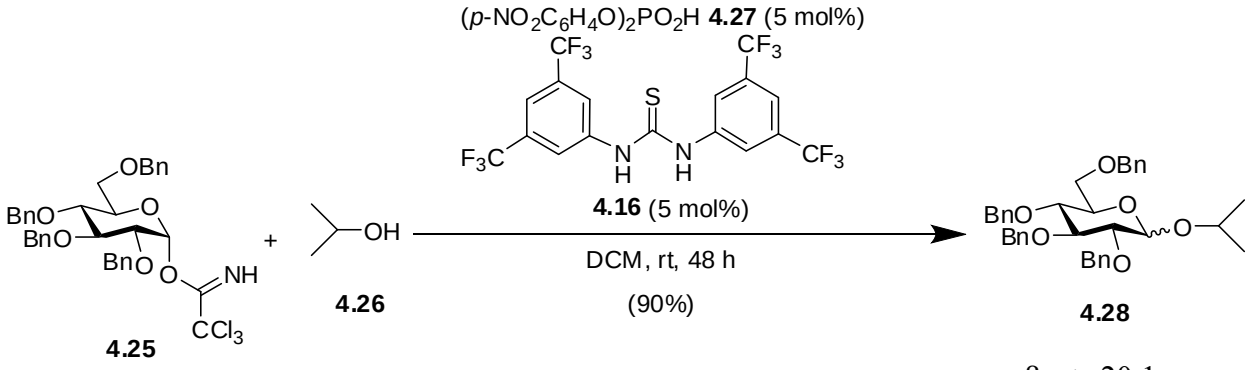
4.2 Cooperative catalysis in glycosylation reactions with *O*-glycosyl trichloroacetimidates as glycosyl donors

4.2.1 Introduction

The use of thioureas for the catalysis of glycosylation reactions using various kinds of donors has been reported by several research groups.[3] As explained in the previous section, Jacobson used a thiourea derivative along with a Lewis acid catalyst to achieve stereoselective glycosylation reactions.[9] Though interesting stereoselectivities were observed in a variety of glycosylation reactions, any co-operative effect of the Lewis acid and the thiourea needs to be investigated further .

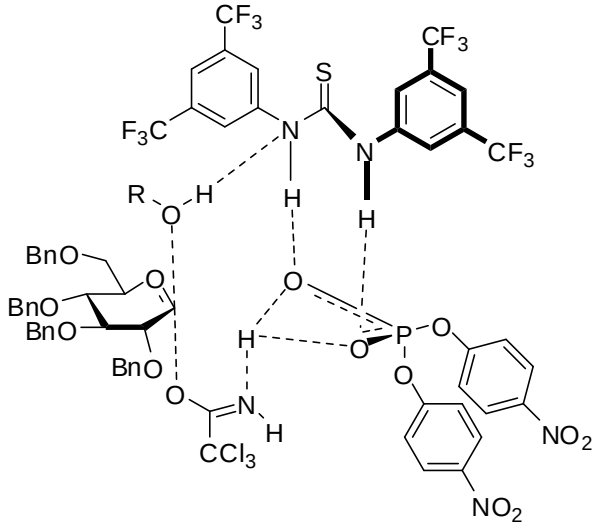
Along similar lines, Schmidt[13] group reported a series of β stereoselective glycosylation reactions by activation of trichloroacetamidate donors with an achiral phosphoric acid and an achiral thiourea as organocatalysts.

One specific example reported by this group is shown in Scheme 4.8. When isopropyl alcohol **4.26** was glycosylated with the donor **4.25**, the resulting glycoside **4.28** was produced with the highest stereoselectivity (β:α > 20:1), when bis(4-nitrophenyl) phosphoric acid **4.27** and 1,3-bis(3,5-bis(trifluoromethyl)phenyl) thiourea **4.16** were used as the catalytic acid and co-catalyst respectively. However, when the reaction was carried out without the co-catalyst **4.16**, the selectivity observed was extremely poor (β:α = 3:2).



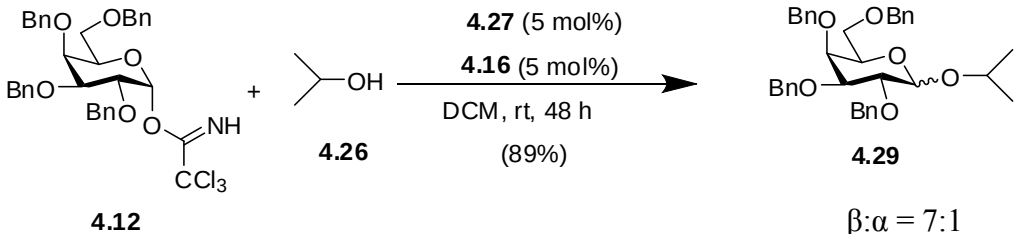
Scheme 4.8

Schmidt proposed that the observed stereoselectivity arose from a co-operative effect between the thiourea and the acid catalyst as shown in Scheme 4.9.



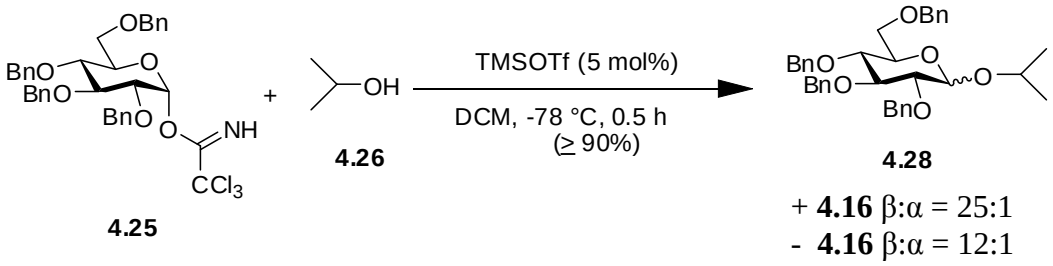
Scheme 4.9

When the reaction was carried out with donor **4.12** under the same reaction conditions, including the co-catalyst **4.16**, the stereoselectivity observed for the resulting glycoside **4.29** was produced with stereoselectivity (β:α = 7:1) (Scheme 4.10).



Scheme 4.10

Interestingly, even when TMSOTf and **4.16** were used as the catalyst and co-catalyst respectively, much higher stereoselectivity (β:α = 25:1) was seen when compared to the reaction that was performed without the co-catalyst (β:α = 12:1) (Scheme 4.11).

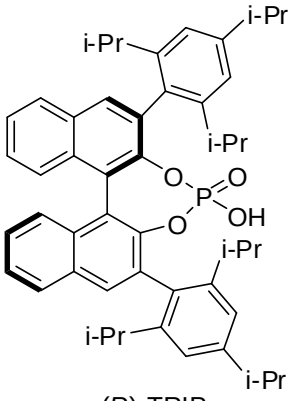


Section 4.11

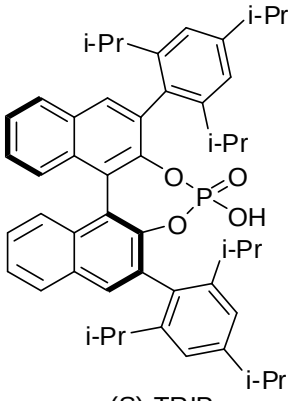
As discussed earlier (Scheme 4.1), the Fairbanks[7] group reported the β-selective glycosylation of **4.12** with diacetone galactose **2.42**, while using the (*S*)-BINOL derived phosphoric acid catalyst (*S*)-**4.1**.

4.2.2 The catalysts and co-catalyst

Glycosylation reactions were carried out with donor **4.12**, acceptor **2.42**, and the BINOL derived phosphoric acid catalyst, "TRIP" (figure 4.1) as the acid catalyst, which is similar in structure to those used previously by the Fairbanks' group,[7] and the co-catalyst **4.16**, used by Schmidt[13]. The choice of TRIP was based on the fact that, it has been used as a powerful Brønsted acid catalyst for asymmetric synthesis.[14] Both (*R*)-TRIP (**4.30**) and (*S*)-TRIP (**4.31**) were used as catalysts to observe any effect of catalyst stereochemistry on the stereoselectivity of glycosylation.



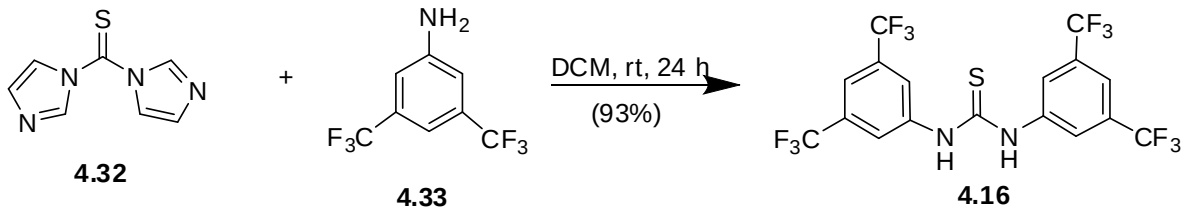
(*R*)-TRIP
4.30



(*S*)-TRIP
4.31

Figure 4.1

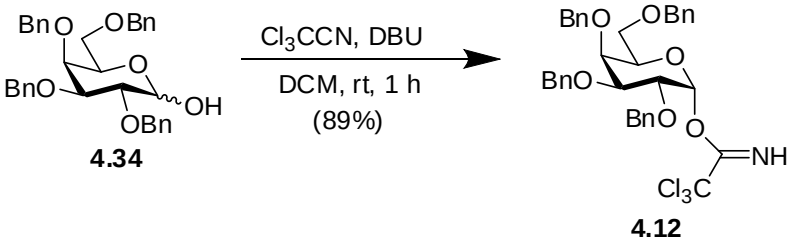
The (*R*) and (*S*) TRIP organocatalysts were purchased and the co-catalyst thiourea derivative (**4.16**) was synthesized starting from thiocarbonyldiimidazole (**4.11**) and *bis*-trifluoromethylaniline (**4.12**) as in Scheme 4.12.[15]



Scheme 4.12

4.2.3 Synthesis of the donor

The trichloroacetimidate donor **4.12**, chosen for direct comparison with Schmidt's[13] and Fairbanks'[7] work, was synthesized by reaction of tetrabenzyl galactopyranose **4.34** with trichloroacetonitrile in presence of catalytic amount of DBU (Scheme 4.11).[16]

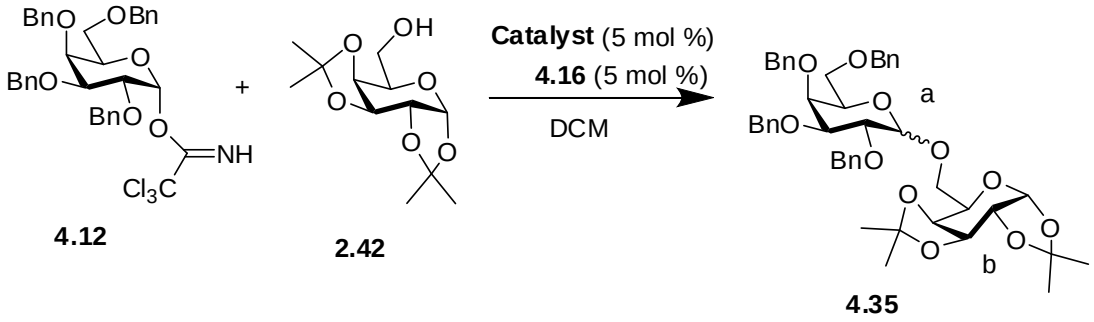


Scheme 4.13

4.2.4 Results and discussions

4.2.4.1 Organocatalytic stereoselective synthesis of DAG glycoside

The glycosylation reaction that was studied is shown in Scheme 4.14.



Scheme 4.14

When diacetone galactose **2.42** was glycosylated with the donor **4.12**, using TMSOTf as the catalyst, in the absence of co-catalyst **4.16**, the disaccharide **4.35** was obtained as a mixture of diastereomers in a ratio of β:α = 3.9:1 (Table 4.1, entry 2). However, in contrast to the report of Schmidt, the addition of co-catalyst **4.16** did *not* lead to any improvement in the stereoselectivity of the reaction (β:α = 3.7:1) (Table 4.1, entry 1). When the asymmetric organocatalysts, (*R*)-TRIP **4.30** and (*S*)-TRIP **4.31** were used along with the co-catalyst **4.16**, both gave very poor stereoselectivity (β:α = 1.5:1) (Table 4.1, entry 3 and 5 respectively). Furthermore in the absence of co-catalyst **4.16**, no stereoselectivity was observed when (*R*)-TRIP **4.30** was used as the catalyst (Table 4.1, entry 4). However, interestingly, when (*S*)-TRIP **4.31** was used as catalyst in absence of the co-catalyst **4.16** an improvement was observed in β stereoselectivity (β:α = 1.5:1) (Table 4.1, entry 5). These results raise serious doubts about any co-operative effect between the catalyst and co-catalyst during the glycosylation reaction. Since only very modest stereoselectivity has been observed further investigations were required.

Interestingly, in terms of product formation it was observed that reactions carried out in the presence of co-catalyst **4.16** proceeded to completion. In the absence of the co-catalyst, reactions did not reach completion even after stirring for 96 h. It was concluded that TRIP alone is not acidic enough to efficiently catalyze the reaction so that it goes to completion as and the co-catalyst certainly improved the catalytic efficiency by some form of synergistic interaction.

In order to investigate the effect of co-catalyst **4.16**, the glycosylation reaction was carried out using only a catalytic amount of **4.16** without using any additional acid catalyst. However **4.16** proved to be a very inefficient catalyst as the maximum yield of disaccharide obtained was only 9% (Table 4.1, entry 7). However, the stereoselectivity of this reaction was found to be the same

(1.5:1, β:α) as when the reactions were carried out using both (*R*)-TRIP **4.30** and (*S*)-TRIP **4.31** together with the co-catalyst **4.16** (Table 4.1, entry 3 and 5 respectively).

Since the stereoselectivity of the glycosylation reactions investigated so far was poor, glycosylations were attempted with the catalyst *bis*(4-nitrophenyl)phosphoric acid **4.27**, which had shown the best results in stereoselectivity in the experiments reported out by the Schmidt group.[13] This acid [pK_a 2.79 (H_2O)] was found to be more effective as the reaction always went to completion either with or without any added co-catalyst. In contrast to the report by Schmidt the stereoselectivity was slightly higher (β:α = 2.3:1) when the reaction was carried out without using the co-catalyst **4.16** (Table 4.1, entry 11), as compared to the reaction performed with the co-catalyst (β:α = 2:1) (Table 4.1, entry 10). Similar observations were made when the reaction was carried out using diphenyl phosphoric acid **4.36** as catalyst. These results directly contradict the report by Schmidt and we can conclude that the transition state suggested by Schmidt it not applicable for reactions with diacetone galactose **2.42** as the acceptor.

The outcomes of glycosylation[a] reactions performed with donor **4.12** and acceptor **2.42** to yield the disaccharide **4.35** are summarized in Table 4.1.

Entry	Catalyst	Co-Catalyst (4.16)	Reaction Status	Time (h)	Temp.	Yield (%)	β:α ratio [b]
1.	TMSOTf	+	Complete	6	-78 °C	74	3.7:1
2.	TMSOTf	-	Complete	6	-78 °C	70	3.9:1
3.	(*R*)-TRIP **4.30**	+	Complete	72	rt	60	1.5:1
4.	(*R*)-TRIP **4.30**	-	Incomplete	96	rt	18	2.5:1
5.	(*S*)-TRIP **4.31**	+	Complete	72	rt	64	1.5:1
6.	(*S*)-TRIP **4.31**	-	Incomplete	96	rt	28	1.1:1
7.	-	+	Incomplete	96	rt	9	1.5:1
8.	Diphenyl phosphoric acid **4.36**	+	Complete	72	rt	65	1.1:1
9.	Diphenyl phosphoric acid **4.36**	-	Incomplete	96	rt	19	1.9:1
10.	*Bis*(4-nitrophenyl) phosphoric acid **4.27**	+	Complete	72	rt	74	2:1
11.	*Bis*(4-nitrophenyl) phosphoric acid **4.27**	-	Complete	72	rt	60	2.3:1
12.	*Bis*(4-nitrophenyl) phosphoric acid **4.27**	+	Complete	3	rt	11	2:1

[a] Reaction conditions: acceptor (1.2 equiv.), Catalyst (0.025 equiv.), Co-Catalyst (0.05 equiv.), DCM.

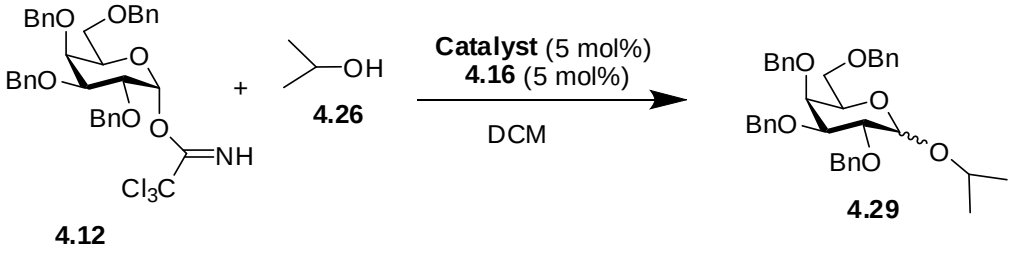
[b] Anomeric ratios were determined by integration of appropriate peaks in the ^{1}H NMR spectra. Glycosylation reactions were carried out in duplicate to confirm the reproducibility of results.

Table 4.1

4.2.4.2 Organocatalytic stereoselective synthesis of isopropyl glycoside

After obtaining unsatisfactory results using diacetone galactose **2.42** as acceptor, the focus was shifted to using isopropyl alcohol **4.26** as the acceptor to determine the stereochemical outcome of these glycosylation reactions. Again the catalysts were varied, in a search for more stereoselective processes catalysts.

The glycosylation reaction is shown below (Scheme 4.15).



Scheme 4.15

The glycosylation reaction shown in Scheme 4.15 using donor **4.12**, isopropyl alcohol **4.26** as acceptor, TMSOTf as the catalyst, and **4.16** as the co-catalyst, yielded the isopropyl galactoside **4.29** in a 25:1 β:α ratio, exactly as reported by the Schmidt group (Table 4.2, entry 1). However when the reaction was carried out without the addition of the co-catalyst, the observed stereoselectivity was (β:α = 23:1), which was significantly higher than that reported by the Schmidt group (12:1) (Table 4.2, entry 2).

When the glycosylation was carried out using *bis*(4-nitrophenyl)phosphoric acid **4.27** as catalyst and co-catalyst **4.16**, the isopropyl galactoside **4.29** was formed in an anomeric ratio that was exactly as reported by Schmidt's group (β:α = 7:1) (Table 4.2, entry 10). When the same reaction was carried out without using the co-catalyst **4.16**, there was a slight reduction in the

stereoselectivity of the reaction (β:α = 5:1) (Table 4.2, entry 11). the use of diphenyl phosphoric acid **4.36** as the catalyst gave very similar results as compared to catalyst **4.27**, *viz* a stereoselectivity of (β:α = 6:1) when the reaction was carried with the co-catalyst **4.16**, and a stereoselectivity of (β:α = 4:1) when reaction was carried on without the co-catalyst **4.16** (Table 4.2, entry 8 and 9 respectively).

To evaluate the efficiency of the asymmetric phosphoric acid catalyst, (*R*)-TRIP **4.30** and (*S*)-TRIP **4.31** were used as catalysts for the glycosylation reaction. Both (*R*)-TRIP **4.30** and (*S*)-TRIP **4.31**, when used with the co-catalyst **4.16**, gave very similar stereoselectivities to those observed by the use of other two organocatalysts *viz* **4.27** and **4.36** (Table 4.2, entry 3 and 5 respectively). However, when (*S*)-TRIP **4.31** was used in absence of co-catalyst **4.16**, an unprecedented improvement in stereoselectivity (β:α = 20:1) was observed, though the yield of the process was poor (25%) (Table 4.2, entry 6). When the reaction was carried out in the presence of only the co-catalyst **4.5**, the lowest stereoselectivity was observed (3.1) (Table 4.2, entry 7).

The glycosylation[c] reactions performed with donor **4.7** and acceptor **4.15** to yield the isopropyl glycoside **4.16** are summarized in Table 4.2.

Entry	Catalyst	Co-Catalyst (4.16)	Reaction Status	Time (h)	Temp.	Yield (%)	β:α ratio [d]
1.	TMSOTf	+	Complete	6	-78 °C	67	25:1
2.	TMSOTf	-	Complete	6	-78 °C	67	23:1
3.	(*R*)-TRIP **4.30**	+	Complete	72	rt	61	6:1
4.	(*R*)-TRIP **4.30**	-	Incomplete	96	rt	28[e]	7:1
5.	(*S*)-TRIP **4.31**	+	Complete	72	rt	64	6:1
6.	(*S*)-TRIP **4.31**	-	Incomplete	96	rt	25[e]	20:1
7.	-	+	Incomplete	96	rt	16[e]	3:1
8.	Diphenyl phosphoric acid **4.36**	+	Complete	72	rt	65	6:1
9.	Diphenyl phosphoric acid **4.36**	-	Incomplete	96	rt	22[e]	4:1
10.	*Bis*(4-nitrophenyl) phosphoric acid **4.27**	+	Complete	72	rt	72	7:1
11.	*Bis*(4-nitrophenyl) phosphoric acid **4.27**	-	Complete	72	rt	71	7:1
12.	*Bis*(4-nitrophenyl) phosphoric acid **4.27**	+	Complete	3	rt	73	5:1

[c] Reaction conditions: acceptor (1.2 equiv.), Catalyst (0.025 equiv.), Co-Catalyst (0.05 equiv.), DCM.

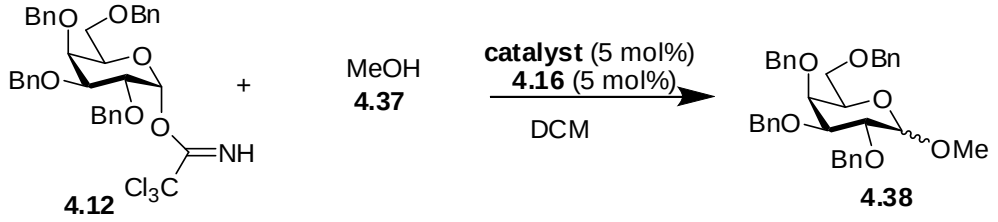
[d] Anomeric ratios were determined by integration of appropriate peaks in the ^{1}H NMR spectra. Glycosylation reactions were carried out in duplicate to confirm the reproducibility of results.

[e] Determined by ^{1}H-NMR

Table 4.2

4.2.4.4 Organocatalytic stereoselective synthesis of methyl glycoside

Finally his organocatalytic glycosylation was carried out using methanol **4.37** as the acceptor and either TMSOTf or *bis*(4-nitrophenyl)phosphoric acid **4.27** as catalysts, both with and without co-catalyst **4.16** as shown in Scheme 4.11.



Scheme 4.16

Strangely, all the reaction conditions investigated led exclusively to the *β*-product. A summary of glycosylation[f] reactions performed with donor **4.12** and methanol **4.37** as acceptor to yield the methyl glycoside **4.38** is shown in Table 4.3.

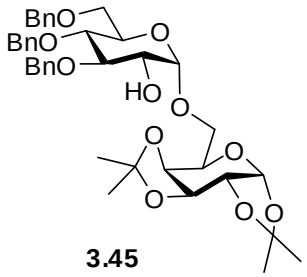
Entry	Catalyst	Co-Catalyst 4.16	Reaction Status	Time (h)	Temp.	Yield (%)	*β*:*α*[g]
1.	TMSOTf	+	Complete	0.5	-78 °C	71	1:0
2.	TMSOTf	-	Complete	0.5	-78 °C	71	1:0
3.	*Bis*(4-nitrophenyl) phosphoric acid **4.27**	+	Complete	4	rt	65	1:0
4.	*Bis*(4-nitrophenyl) phosphoric acid **4.27**	+	Complete	72	rt	64	1:0
5.	*Bis*(4-nitrophenyl) phosphoric acid **4.27**	-	Complete	48 h	rt	60	1:0

[f] Reaction conditions: acceptor (1.2 equiv.), Catalyst (0.025 equiv.), Co-Catalyst **4.16** (0.05 equiv.), DCM.
[g] Anomeric ratios were determined by integration of appropriate peaks in the ^{1}H NMR spectra. Glycosylation reactions were carried out in duplicate to confirm the reproducibility of results.

Table 4.3

4.2.4.5 Verification of anomerization under reaction conditions

Since the reaction times for most of the glycosylation reactions were very long (up to 72 h), there was also a need to verify whether any anomerization of the product occurred in the acidic conditions provided by the catalyst. Therefore a pure α disaccharide **3.45** (Figure 4.2) (20 mg) was stirred in DCM along with (i) catalysts (5 mol %) **4.27**, **4.36**, **4.30** and **4.31** along with co-catalyst (5 mol %) **4.16** in different reaction vessels, (ii) with co-catalyst **4.16** (5 mol %) alone. ^{1}H-NMRs of the aliquots of all the reaction vessels were recorded at intervals of 1 h, 3 h, 6 h, 24 h, 48 h and 72 h, however there was no isomerization of the α diastereomer to β diastereomer seen at any time, it was concluded that the observed anomeric stereochemistry is not a result of product equilibration.



3.45

Figure 4.2

4.2.5 Conclusions

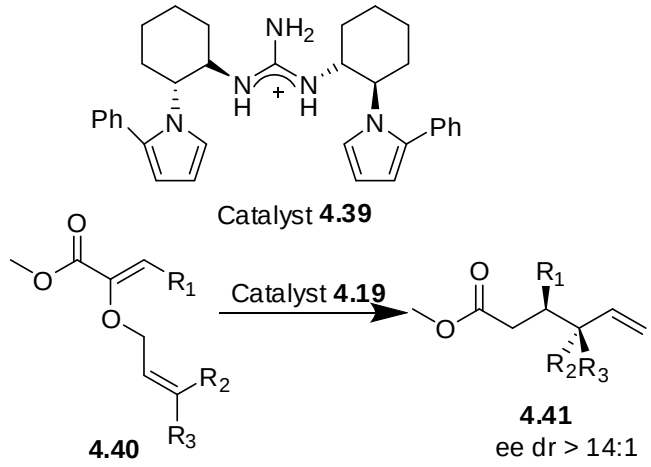
It is well-established that the stereochemical outcome of glycosylation reactions can be highly dependent on the acceptor used in glycosylation step. In particular, a match or mis-match of donor and acceptor may occur.[17] In these studies, it was found that the smaller the acceptor that was used, the higher the β-stereoselectivity that was obtained. Undoubtedly, the thiourea derivative co-catalyst **4.16** assisted the catalyst in making the reaction faster, especially in the

cases where the catalyst was itself not a strong enough acidic, and thus reactions performed in the its presence was not effective in improving the stereochemical outcome of the reaction, and in many cases the reaction gave better selectivity when the co-catalyst was not used. The β-stereoselectivity observed when using TMSOTf, either with or without the co-catalyst **4.16**, was always higher than when the organocatalysts were used, either with or without the co-catalyst. So, the existence and role of the transition state suggested by Schmidt's group in their explanation of the high stereoselectivity they observed appears to be highly dubious. Indeed their stereoselectivtites were highly acceptor specific, casting significant doubt on the utility of their work. The co-operative effect between the catalyst and co-catalyst needs to be investigated further.

4.3 Hydrogen-bond donor and Brønsted acid organocatalysis

A guanidinium salt was selected as a potential catalyst for glycosylation reactions of trichloroacetimidate donors by a catalytic Brønsted acid activation mechanism. Glycosylation reactions of trichloroacetimidates are generally catalysed using Lewis acids as opposed to Brønsted acids, and examples of catalytic Brønsted acid activated glycosylation protocols are limited.[18] However as mentioned above the Fairbanks group have previously reported that *β*-selective glycosylations of glycosyl trichloroacetamidates can be achieved with a chiral BINOL-derived phosphoric acid catalyst **4.1** (Scheme 4.1).

Guanidinium salts have been used as organocatalysts for a variety of purposes including diastereo- and enantioselective Claisen rearrangement.[19] One example is shown in Scheme 4.17.



Scheme 4.17

Detailed theoretical investigations of this reaction revealed that catalyst **4.19** works by stabilizing the transition state with multiple non-covalent interactions like hydrogen bonding and electrostatic interactions, as shown below (Figure 4.3).

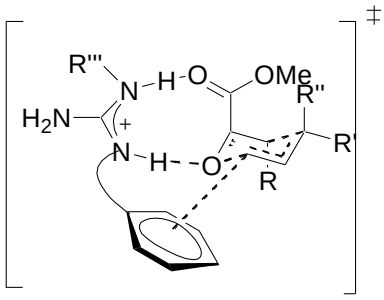
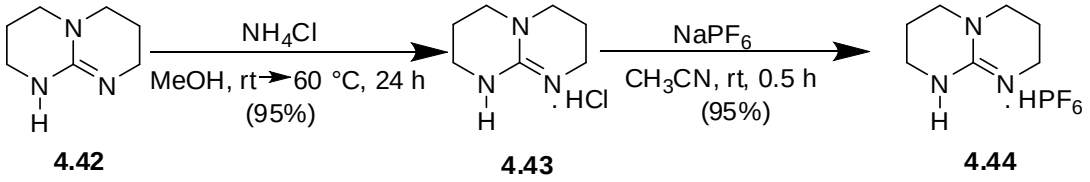


Figure 4.3

As the transition state involved the guanidiniun salt acting as both a H-bond donor and acceptor in co-operative acid-base catalysis the possible application of such catalysts for the cooperative glycosylation of alcohols using trichlroacetmidate donors was investigated.

4.3.1 Synthesis of the organocatalyst

The guanidinium organocatalyst 1,5,7-triazabicyclo[4.4.0]dec-5-enium hexafluorophosphate **4.44**, was prepared in two steps starting from a guanidine derivative **4.42** (Scheme 4.18). 1,5,7-Triazabicyclo[4.4.0]dec-5-ene TBD **4.42** was first treated with ammonium chloride to give TBD.HCl **4.43**.[20] This salt was then treated with $NaPF_6$ to give the desired organocatalyst TBD.HPF_6 **4.44**.[21] We decided to investigate the potential application of **4.44** instead of the chloride **4.43** as we required a non-nucleophilic counter ion which would not compete during the glycosylation reaction.

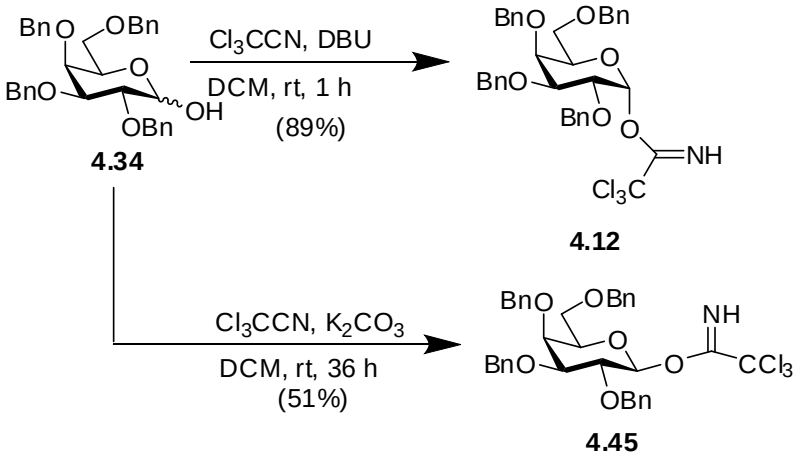


4.42 **4.43** **4.44**

Scheme 4.18

4.3.2 Synthesis of the donors

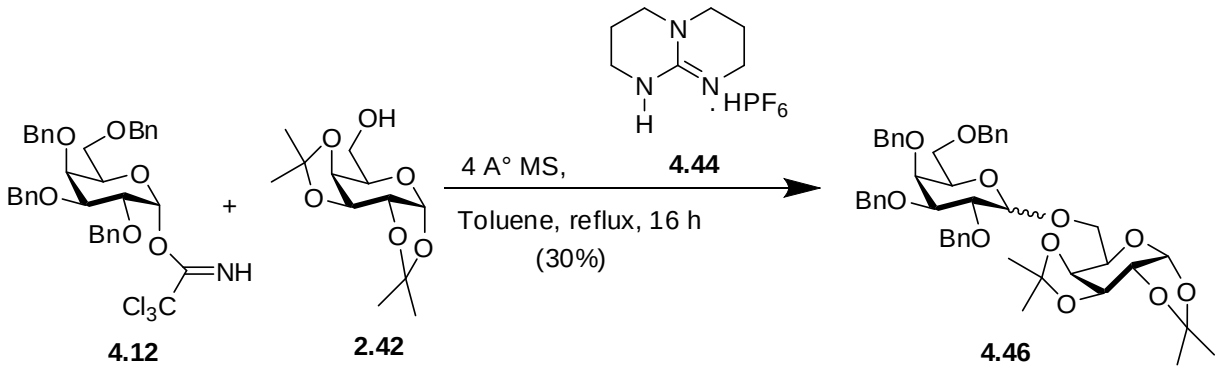
Tetrabenzyl-α-D-galactopyranosyl trichloroacetimidate **4.12** and tetrabenzyl-β-D-galactopyranosyl trichloroacetimidate **4.45** were prepared as donors from tetrabenzylgalactopyranose **4.34** by treatment with trichloroacetonitrile and either DBU and K_2CO_3 as bases respectively (Scheme 4.19).



Scheme 4.19

4.3.3 Results and discussions

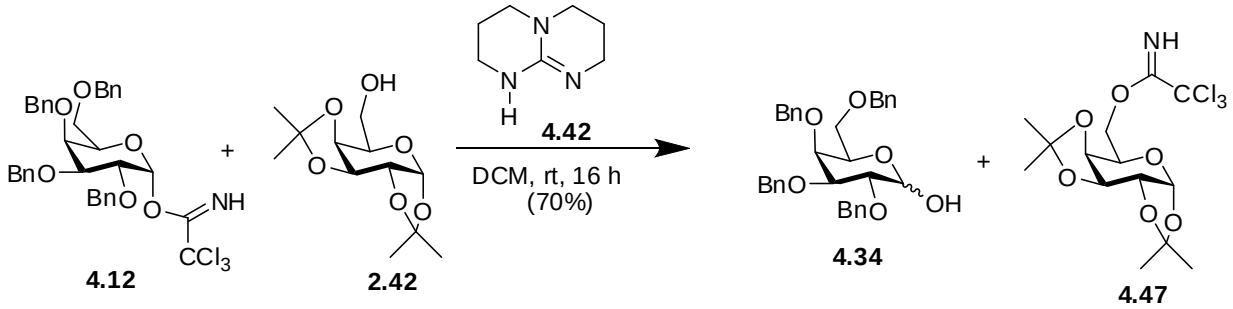
Glycosylation of both **4.12** and **4.45** was attempted using **4.44** as an organocatalytic activator. Initially, the glycosylations were attempted in DCM as the solvent and using diacetone galactose **2.42** as the acceptor. At rt no glycosylation was seen. So, the reaction was repeated by refluxing the mixture in DCM overnight. Under these conditions disaccharide **4.46** was obtained but in a very poor yield of 20%. The reaction was then repeated by refluxing the reaction mixture in toluene for 16 h. Glycosylation was more effective under these conditions and disaccharide **4.46** (α:β = 1:1) was prodcuced in yields of 30% and 40% of from **4.12** and **4.45** respectively (Scheme 4.20).



Scheme 4.20

A control glycosylation reaction was also carried out without using the organocatalyst, and **4.12** as donor. Formation of the disaccharide **4.46**, with stereoselectivity (α:β = 5:1), and same yield of 30%, was observed. It was concluded that the glycosylation observed in those harsh conditions had occurred due to the thermal energy provided, unaided from organocatalyst.

Finally, the Guanidine TBD **4.42** was itself used as possible organocatalyst. Very surprisingly, this led to the transfer of the trichloroacetimidate group from the donor to the acceptor molecule resulting in the formation of diacetone galactose-6-trichloroacetimidate **4.47** (Scheme 4.21).



Scheme 4.21

Due to lack of any observable organocatalytic effect resulting from the addition of either guanidine **4.42** or guanidiunium salt **4.44** to these glycosylation reactions this avenue of investigation was abandoned.

4.3.4 Conclusion

The guanidine salt chosen for organocatalysis was not acidic enough [pK_a ≈ 13 (H_2O)],[22] to activate the trichloroacetamidate donor. Organic acids with lower pKa needs to be investigated to utlize them as effective organocatalytic acid in glycosylation reactions.

4.4 References

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Chapter 5: Experimental

5.1 General chemical procedures

Unless otherwise stated, reagents were obtained from commercial sources and used as received. HPLC–grade solvents were used for reactions and in case of moisture–sensitive reactions; solvents were dried by literature procedures and freshly distilled as required. Melting points were recorded on an Electrothermal melting point apparatus. Thin Layer Chromatography (t.l.c.) was carried out on Merck Kieselgel $60F_{254}$ pre-coated glass-backed plates. Visualisation of the plates was achieved using a UV lamp (λ_{max} = 254 or 365 nm), and/or ammonium molybdate (5% in 2 M sulfuric acid). Flash column chromatography was carried out using Sorbsil C60 40/60 silica.

Nuclear Magnetic Resonance

^{1}H and ^{13}C NMR spectra were recorded on Agilent 400–MR and Varian 500 INOVA instruments operating for ^{1}H NMR at 400 and 500 MHz, respectively and at 100 and 125 MHz, respectively, for ^{13}C NMR. All the ^{1}H NMR spectra recorded in deutrated solvents were referenced to the solvent peak and/or TMS: $CDCl_3$, 7.26 ppm; CD_3CN, 2.0 ppm; CD_3OD, 3.3 ppm; DMSO, 2.6 ppm. ^{13}C NMR were all referenced to their solvent peaks: chloroform, 77.0 ppm; acetonitrile, 36.8 ppm; methanol, 49.3 ppm; DMSO, 39.6 ppm. When required, gCOSY, 1–D TOCSY, HSQC, HSQC “non-decoupled”and HMBC experiments were performed using standard pulse sequences.

Mass Spectrometry

Mass spectra were recorded by Dr. Marie Squire and Dr. Alexander on either a DIONEX Ultimate 3000 or Bruker MaXis 4G spectrometer, operated in high resolution positive ion

electrospray mode. Samples were prepared by dissolving in an appropriate solvent at the required concentration.

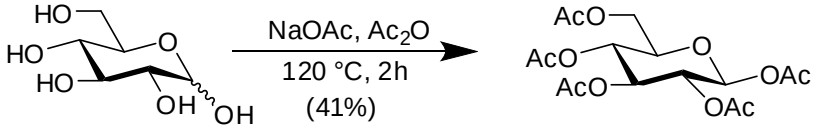
Infrared Spectroscopy

Infrared spectra were recorded on a Perkin–Elmer Spectrum One FTIR instrument operating in diffuse reflectance mode with samples prepared as KBr pellets (KBr) or on a Bruker FTIR spectrometer with Alpha's Platinum ATR single reflection diamond where the neat samples were recorded.

Carbohydrates and derivatives have been named in accordance with IUPAC recommendations and numbered according to the carbohydrate convention. The two protons on C-6 are labelled H-6 and H-6′.

5.2 Experimental for chapter 2

Penta-*O*-acetyl-*β*-D-glucopyranose[1] **2.20**

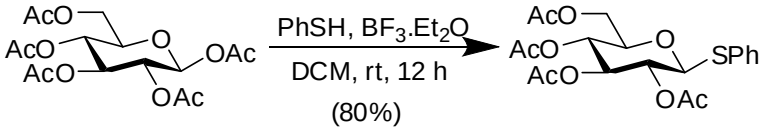


2.19 **2.20**

Sodium acetate (55.0 g, 676 mmol) was added to acetic anhydride (400 mL) and the mixture was heated to 120 °C for 30 min. Glucose (**2.19**) (60.0 g, 333 mmol) was then added slowly over 30 min. After 90 min t.l.c. (petrol:ethyl acetate, 1:1) showed complete consumption of starting material (R_f 0) and the formation of single product (R_f 0.7). The mixture was then cooled to rt and of water and ice (400 mL) was added. The ensuing precipitate was filtered, and was then recrystallized (ethanol) to give penta-*O*-acetyl-*β*-D-glucopyranose **2.20** (66.0 g, 51%) as white crystalline solid; m. p. 130 - 132 °C (ethanol) (lit.[1] 131 - 132 °C); $[\alpha]_D^{20}$ + 4.2 (*c*, 1.0 in $CHCl_3$)

(lit.[1] $[\alpha]_D^{25}$ +5 (*c*, 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$)[1]: 2.01, 2.03, 2.03, 2.09, 2.12 (15H, 5 x s, 5 x CH_3CO_2), 3.84 (1H, ddd, $J_{4,5}$ 9.9 Hz, $J_{5,6}$ 2.2 Hz, $J_{5,6'}$ 4.4 Hz, H-5), 4.11 (1H, dd, $J_{6,6'}$ 12.5 Hz, H-6), 4.29 (1H, dd, H-6'), 5.11-5.16 (2H, m, H-2, H-4), 5.25 (1H, at, *J* 9 Hz, H-3), 5.71 (1H, d, $J_{1,2}$ 8.3 Hz, H-1).

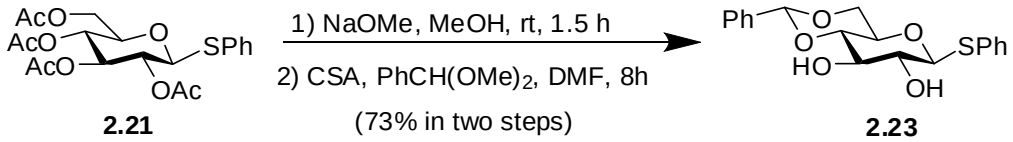
Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-*β*-D-glucopyranoside[2] **2.21**



2.20 **2.21**

2.20 (20.0 g, 46.2 mmol) was dissolved in DCM (40 mL) under a nitrogen atmosphere. Thiophenol (7.40 mL, 71.8 mmol) was added and the solution was cooled to 0 °C. $BF_3.Et_2O$ (18.4 mL, 148 mmol) was added and the mixture was left to stir at rt for 12 h, after which t.l.c. (petrol:ethyl acetate, 2:1) showed complete consumption of starting material (R_f 0.2), and formation of a major product (R_f 0.3). The mixture was diluted with DCM (200 mL), washed with saturated aq. sodium bicarbonate solution (3 x 150 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was recrystallized (petrol/ethyl acetate) to afford phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-*β*-D-glucopyranose **2.21** (18.0 g, 80%) as white crystalline solid; m. p. 112 - 115 °C (petrol/ethyl acetate) (lit.[2] 118 - 120 °C); $[\alpha]_D^{20}$ – 15.3 (*c*, 1.0 in $CHCl_3$) (lit.[2] $[\alpha]_D^{23}$ - 22.7 (*c*, 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$):[2] 1.99, 2.02, 2.08, 2.09 (12H, 4 x s, 4 x CH_3CO_2), 3.71-3.75 (1H, ddd, $J_{4,5}$ 10.2 Hz, $J_{5,6}$ 2.2 Hz, $J_{5,6'}$ 4.4 Hz, H-5), 4.16-4.25 (2H, m, H-6, H-6'), 4.71 (1H, d, $J_{1,2}$ 10.1 Hz, H-1), 4.99 (1H, at, *J* 9.4 Hz, H-2), 5.04 (1H, at, *J* 9.4 Hz, H-4), 5.22 (1H, at, *J* 9.7 Hz, H-3), 7.30–7.34 (3H, m, Ar-CH), 7.48–7.51 (2H, m, Ar-CH).

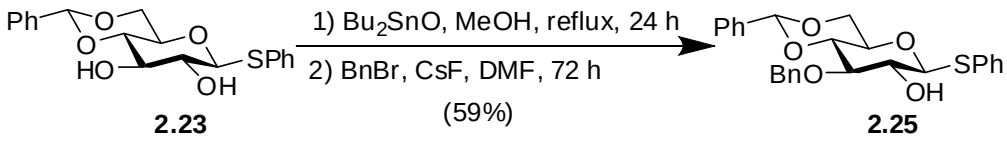
Phenyl 4,6-*O*-benzylidene-1-thio-*β*-D-glucopyranoside[3] **2.23**



2.21 **2.23**

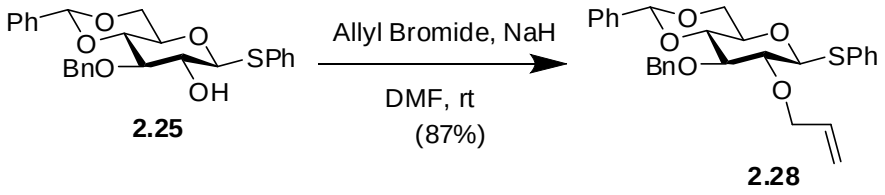
Sodium methoxide (0.220 g, 4.00 mmol) was dissolved in anhydrous Methanol (150 mL) and the solution was cooled to rt. **2.21** (15.7 g, 40.0 mmol) was added portion wise and the mixture was stirred at rt under a nitrogen atmosphere. After 90 min, t.l.c. (petrol:ethyl acetate, 1:1) indicated the formation of a single product (R_f 0) and the complete consumption of starting material (R_f 0.45). The mixture was then concentrated *in vacuo*. DMF (100 mL), benzaldehyde dimethylacetal (7.20 mL, 48.0 mmol) and camphor sulfonic acid (1.86 g, 8.00 mmol) were added, and the mixture was rotated in a round bottom flask on a rotator evaporator at 60 °C, under a pressure of 240 mbar. After 4 h, t.l.c. (petrol:ethyl acetate, 1:1) showed the formation of a major product (R_f 0.3). The reaction was quenched by the addition of triethylamine (0.840 mL, 6.00 mmol) and concentrated *in vacuo*. The residue was dissolved in ethyl acetate (150 mL), then washed with water (2 x 100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was recrystallized (Petrol/Ethyl acetate) to afford phenyl 4,6-*O*-benzylidene-1-thio-*β*-D-glucopyranoside **2.23** (9.00 g, 73%) as white crystalline solid; m. p. 178 - 180 °C (petrol/ethyl acetate) (lit.[3] 172 – 174 °C); $[\alpha]_D^{20}$ + 32.4 (*c*, 1.0 in $CHCl_3$) (lit.[3] $[\alpha]_D^{20}$ + 27.8 (*c*, 1.07 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$)[3]: 2.82, 3.07 (2 x 1H, 2 x bs, 2 x OH), 3.46–3.55 (3H, m, H-2, H-3, H-4), 3.77-3.86 (2H, m, H-5, H-6), 4.38-4.40 (1H, m, H-6'), 4.63-4.65 (1H, d, $J_{1,2}$ 9 Hz, H-1), 5.54 (1H, s, CHPh), 7.25-7.55 (10H, m, Ar-CH).

Phenyl-3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-*β*-D-glucopyranoside[4] **2.25**



2.23 (1.07 g, 2.98 mmol) was dissolved in methanol (25 mL). Dibutyl tin oxide (0.900 g, 3.57 mmol) was added and the reaction was refluxed at 65 °C for 24 h. After cooling to rt the solvent was removed to yield a yellow oil. The residue was dissolved in DMF (25 mL) and the mixture was stirred at rt. Benzyl bromide (0.425 mL, 3.57 mmol) and cesium (I) fluoride (0.600 g, 3.87 mmol) were added and the solution was stirred for 48 h. At this point t.l.c. (petrol:ethyl acetate, 3:1) indicated complete consumption of starting material (R_f 0.1), and the formation of a major product (R_f 0.3). The mixture was then concentrated *in vacuo* and the residue extracted with DCM (50 mL). The organic layer was washed with potassium fluoride (50 mL of 1M), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by flash chromatography (petrol:ethyl acetate, 3:1) yielded phenyl-3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-*β*-D-glucopyranoside **2.25** (0.790 g, 59%) as white crystalline solid; m. p. 131 - 134 °C (petrol/ethyl acetate) (lit.[5] 132 - 134 °C); $[\alpha]_D^{20}$ - 44.3 (*c*, 1.0 in $CHCl_3$) (lit.[6] $[\alpha]_D^{20}$ - 41 (*c*, 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$)[5]: 2.56 (1H, s, OH), 3.50 – 3.54 (2H, m, H-2 and H-5), 3.68 (2H, m, H-3 and H-4), 3.85 (1H, at, *J* 10.27 Hz, H-6), 4.39 (1H, dd, $J_{6',6}$ 10.45 Hz, $J_{6',5}$ 5.0 Hz, H-6'), 4.63 (1H, d, $J_{1,2}$ 9.7 Hz, H-1), 4.79, 4.95 (2H, ABq, J_{AB} 11.6 Hz, CH_2Ph), 5.57 (1-H, s, CH-Ph), 7.55–7.25 (15-H, m, Ar-CH).

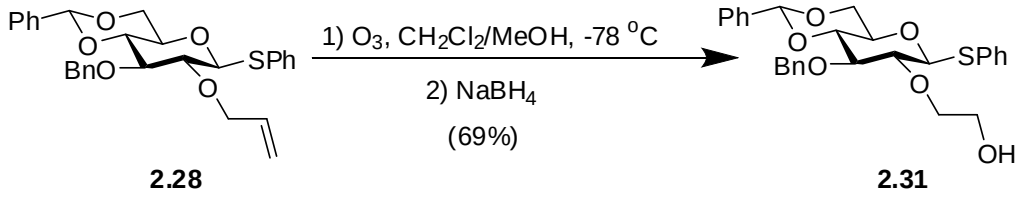
Phenyl-2-*O*-allyl-3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-*β*-D-glucopyranoside[7] **2.28**



2.25 (0.500 g, 1.10 mmol) was dissolved in anhydrous DMF (2 mL). To it was added a suspension of sodium hydride (0.104 g, 2.20 mmol) in anhydrous DMF (2 mL) at 0 °C slowly under a nitrogen atmosphere. Allyl bromide (0.200 mL, 2.40 mmol) was then added slowly in the mixture. The reaction was then allowed to warm till rt and was then stirred for 1h, at this time t.l.c. (petrol:ethyl acetate, 4:1) showed complete absence of starting material (R_f 0.3) and formation of a major product (R_f 0.5). The reaction was quenched by the addition of methanol (5 mL) and concentrated *in vacuo*. The residue was dissolved in diethyl ether (50 mL) and washed with water (100 mL) and aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petrol:ethyl acetate, 8:1) yielded phenyl-2-*O*-allyl-3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-*β*-D-glucopyranoside **2.28** (0.472 g, 87%) as white crystalline solid, m. p. 117 – 119 °C (petrol/ethyl acetate); $[\alpha]_D^{20}$ (*c*, 1.0 in $CHCl_3$); ν_{max} (KBr) 1700 (s, C=C) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 3.35-3.45 (2H, m, H-2, H-5), 3.65 (1H, at, *J* 9.5 Hz, H-6), 3.75 (2H, m, H-3, H-4), 4.33 (3H, m, H-6', $OC\underline{H}_2CH=CH_2$), 4.68 (1H, d, $J_{1,2}$ 9.7 Hz, H-1), 4.78, 4.90 (2H, ABq, J_{AB} 12 Hz, $-OCH_2Ph$), 5.18 (1H, d, J_z 10.2 Hz, *J* 1.5 Hz, $CH=CH_E\underline{H}_z$), 5.28 (1H, m, J_E 16 Hz, J_{gem} 1.5 Hz $CH=C\underline{H}_EH_z$), 5.55 (s, 1H, CH-Ph), 5.98 (1H, m, $C\underline{H}=CH_2$), 7.52-7.24 (15H, m, Ar-CH). δ_C (126 MHz, $CDCl_3$): 69.0 (t, C-6), 70.5 (d, C-5), 75.0 (d, C-2), 75.6 (t, CH_2Ph), 80.5 (d, C-4), 81.6 (d, C-3), 88.5 (t, $\underline{C}H_2CH=CH_2$), 101.4 (d, CHPh), 117.6 (t, $CH_2CH=\underline{C}H_2$), 126.3, 128.0, 128.1, 128.4, 128.5, 128.7, 129.3, 132.6, 133.5,

135.0, 137.6, 138.6 (12 types of aromatic-C, $CH_2\underline{C}H=CH_2$); HRMS (ES^+) calculated for $C_{19}H_{31}O_5S$ (MH^+) 491.1886, found 491.1885.

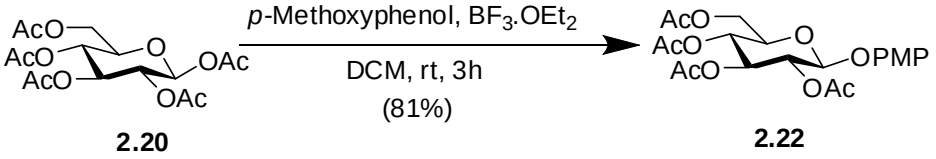
Phenyl-2-*O*-(2-hydroxyethyl)-3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-*β*-D-glucopyranoside[8]
2.31



2.28 **2.31**

A solution of **2.23** (0.100 g, 0.21 mmol) in DCM: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 $NaBH_4$ (0.036 g, 0.93 mmol) in small portions after which t.l.c. (petrol:ethyl acetate, 4:1) showed complete consumption of starting material (R_f 0.7) and formation of a major product (R_f 0.1). The mixture was then allowed to warm to rt and concentrated *in vacuo*. Purification by flash chromatography (petrol:ethyl acetate, 3:1) yielded phenyl-2-*O*-(2-hydroxyethyl)-3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-*β*-D-glucopyranoside **2.25** (0.07 g, 69%) as white crystalline solid; δ_H (500 MHz, $CDCl_3$): 2.95 (1H, bs, OH), 3.40 (1H, at, H-2), 3.45 (1H, m, H-5), 3.5 (3H, m, H-6, -$OC\underline{H}_2CH_2OH$, 3.63–3.82 (2H, m, -$OCH_2C\underline{H}_2OH$), 3.90 (2H, m, H-3, H-4), 4.39 (1H, m, H-6'), 4.65 (1H, d, $J_{1,2}$ 10.0 Hz, H-1), 4.78, 4.96 (2H, ABq, J_{AB} 12 Hz, -OCH_2Ph), 5.58 (s, 1H, -CHPh), 7.26-7.52 (m, 15-H, Ar-CH); HRMS (ES^+) calculated for $C_{18}H_{31}O_6S$ (MH^+) 495.1836, found 491.1842.

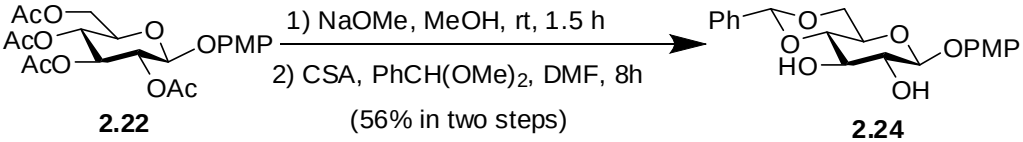
(*p*-Methoxyphenyl) 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranoside[9] 2.22



2.20 **2.22**

To a stirred solution of **2.20** (25.0 g, 64.1 mmol) in DCM (150 mL), *p*-methoxyphenol (12.0 g, 124 mmol) was added and was stirred at rt for 5 min under a nitrogen atmosphere. $BF_3.Et_2O$ (11.6 mL, 124 mmol) was added to the mixture and was stirred at rt for 3 h. The mixture was poured onto saturated aq. sodium bicarbonate solution (200 mL), extracted with DCM (3 x 50 mL), washed with saturated aq. sodium bicarbonate solution (2 x 75 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol:ethyl acetate, 4:1, R_f 0.3) to afford (*p*-methoxyphenyl) 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranoside **2.22** as white crystalline solid (23.5 g, 81%); m. p. 101 – 103 °C (petrol/ethyl acetate) (lit.[9] 102 – 104 °C); $[\alpha]_D^{20}$ – 10.5 *(c,* 1.0 in $CHCl_3$), lit.[9] $[\alpha]_D^{20}$ - 16 *(c,* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$)[9]: 2.02-2.08 (12H, m, $-OCOCH_3$), 3.76 (3H, s, $-OCH_3$), 3.77 (1H, m, H-5), 4.10-4.28 (2H, m, H-6, H-6'), 4.95 (1H, d, $J_{1,2}$ 7.1 Hz, H-1), 5.10-5.30 (3H, m, H-2, H-3, H-4), 6.79-6.95 (4H, m, Aromatic – H); HRMS (ES^+) calculated for $C_{21}H_{26}O_{11}Na$ (MNa^+) 477.1367, found 477.1376.

(*p*-Methoxyphenyl) 3-*O*-benzyl-4,6-*O*-benzylidene-*β*-D-glucopyranoside[3] 2.24

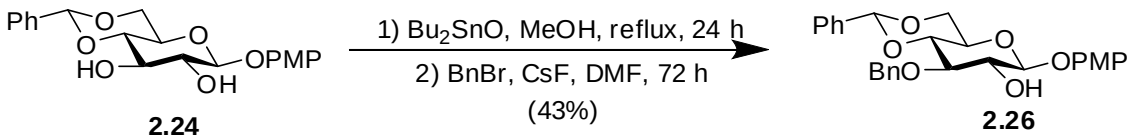


2.22 **2.24**

Sodium methoxide (0.250 g, 4.63 mmol) was dissolved in anhydrous methanol (150 mL) and the solution was stirred at rt. **2.22** (21.0 g, 46.3 mmol) was added portionwise and the mixture was

stirred at rt under a nitrogen atmosphere. After 90 min, t.l.c. (petrol:ethyl acetate, 1:1), indicated the formation of a single product (R_f 0) and the complete consumption of starting material (R_f 0.5). The mixture was then concentrated *in vacuo*. DMF (75 mL), benzaldehydedimethylacetal (8.30 mL, 55.0 mmol) and camphorsulfonic acid (2.20 g, 9.30 mmol) were added and the mixture was rotated on a round bottomed flask on a rotator evaporator at 60 °C under pressure of 240 mbar for 8 h. After this time t.l.c. (petrol:ethyl acetate, 3:2) showed formation of a major product (R_f 0.1) and the complete consumption of starting material (R_f 0.5). The reaction was quenched by the addition of triethylamine (0.97 mL, 6.94 mmol) and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate (1 L), then washed with water (2 x 300 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Recrystallization (propanol/methanol) yielded (*p*-methoxyphenyl) 3-*O*-benzyl-4,6-*O*-benzylidene-*β*-D-glucopyranoside **2.24** (10.0 g, 56%); m. p. 192 – 195 °C (propanol/methanol); $[\alpha]_D^{20}$ – 51.3 (*c*, 1.0 in MeOH); ν_{max} (KBr) 3560 (br, OH) cm^{-1}; δ_H (400 MHz, CD_3OD): 3.52-3.56 (3H, m, H-2, H-3 and H-4), 3.72-3.84 (5H, m, H-5, H-6, -OCH_3), 4.28-4.32 (dd, $J_{6,6'}$ 10.4 Hz, $J_{6'5}$ 5.0 Hz 1H, H-6'), 5.60 (1H, s, -CHPh), 4.91 (d, 1H, $J_{1,2}$ 8Hz, H-1), 6.83-7.04 (9H, m, Aromatic – H); δ_C (100 MHz, CD_3OD): 155.8-114.7 (8 C, Ar-C), 102.2 (d, C-1), 101.8 (d, CHPh), 80.2 (d, C-4), 74.2 (d, C-3), 72.5 (d, C-2), 68.0 (d, C-5), 66.0 (t, C-6), 54.2 (q, -OMe); HRMS (ES^+) calculated for $C_{20}H_{22}O_7Na$ (MNa^+) 397.1257, found 397.1263.

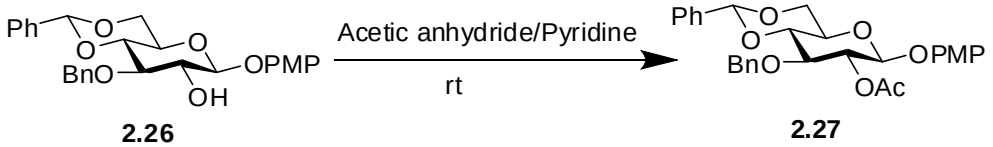
(*p*-Methoxyphenyl) 3-*O*-benzyl-4,6-*O*-benzylidene-*β*-D-glucopyranoside[4] **2.26**



2.24 **2.26**

2.24 (6.50 g, 17.4 mmol) was dissolved in methanol (200 mL). Dibutyltin oxide (5.20 g, 20.8 mmol) was added and the reaction was stirred under reflux for 24 h. The solvent was removed and the residue was dissolved in DMF (200 mL) and the mixture was stirred at rt. Then benzyl bromide (2.47 mL, 20.8 mmol) and cesium fluoride (3.42g, 34.7 mmol), were added and the solution was stirred for 72 h at which t.l.c. (petrol:ethyl acetate, 2:1) showed formation of a major product (R_f 0.5), but t.l.c. (DCM:diethyl ether, 19:1) showed a major spot at R_f 0.8 and minor spots at R_f 0.9. The mixture was then concentrated *in vacuo*, and the residue extracted with DCM (400 mL), and the organic layer was with KF solution (400 mL, 1M conc.), dried ($MgSO_4$), filtered and concentrated in *in vacuo*. Recrystallization (methanol) yielded (*p*-methoxyphenyl) 3-*O*-benzyl-4,6-*O*-benzylidene-*β*-D-glucopyranoside **2.26** (3.50 g, 43%) as white crystalline solid; m. p. 198 – 201 °C (methanol); $[\alpha]_D^{20}$ - 22.1 (*c*, 1.0 in $CHCl_3$); ν_{max} (KBr) 3560 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 2.53 (1H, bs, OH), 3.50-3.59 (1H, m, H-5), 3.71-3.86 (7H, m, H-2, H-3, H-4, H-6, -OCH_3), 4.37 (1H, m, H-6'), 4.90 (1H, d, $J_{1,2}$ 8Hz, H-1), 4.83, 5.00 (2H, ABq, J_{AB} 12 Hz, -OCH_2Ph), 5.60 (1H, s, CHPh), 6.82-7.51 (14H, 14H, Aromatic – H); δ_C (100 MHz, CD_3OD): 55.6 (q, -OMe), 66.6 (t, C-6), 68.7 (d, C-5), 74.1 (d, C-2), 74.7 (t, CH_2Ph), 80.2 (d, C-4), 81.2 (d, C-3), 101.3 (d, CHPh), 102.5 (d, C-1), 159.2-114.6 (14 C, Ar-C); HRMS (ES^+) calculated for $C_{27}H_{28}O_7Na$ (MNa^+) 487.1727, found 487.1732.

(*p*-Methoxyphenyl) 2-*O*-acetyl-3-*O*-benzyl-4,6-*O*-benzylidene-*β*-D-glucopyranoside[10] **2.27**

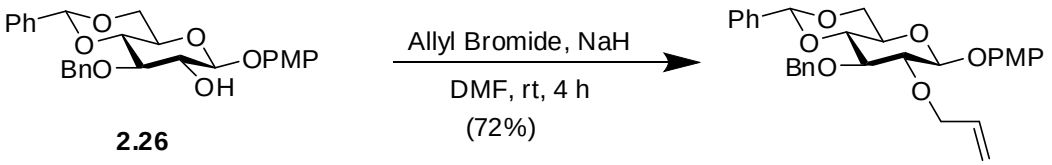


2.26 **2.27**

It was cross verified that **2.26** was indeed 3- benzyl product and not the 2- benzyl by acetylating it (stirring in Ac_2O/Pyridine 1:1 for 20 h) to give (*p*-methoxyphenyl) 2-*O*-acetyl-3-*O*-benzyl-4,6-

O-benzylidene-*β*-D-glucopyranoside **2.27**, m. p. 122 – 126 °C (petrol/ethyl acetate), $[\alpha]_D^{20}$ + 1.6 (*c*, 0.125 in $CHCl_3$); ν_{max} (KBr) 1747 (s, C=O) cm^{-1}; The free hydroxyl group at position 2 gets acetylated and H-2 shows bathochromic shift (3.57 to 5.27). δ_H (400 MHz, $CDCl_3$): 2.03 (3H, s, -$COCH_3$), 3.58 (1H, m, H-5), 3.76-3.86 (6H, m, H-3, H-4, H-6, -OCH_3), 4.41 (1H, m, H-6'), 4.72 (1H, d, J_{gem} 12Hz, -OCH<u>H</u>'Ph), 4.94 (2H, m, -OC<u>H</u>H'Ph, H-1), 5.27 (1H, at, *J* 8 Hz, H-2), 5.601 (1H, s, CHPh), 6.80-7.58 (14H, m, Aromatic – H); δ_C (100 MHz, $CDCl_3$): 55.6 (q, OCH_3), 66.4 (d, C-5), 68.6 (t, C-6), 72.8 (d, C-2), 74.2 (t, OCH_2Ph), 78.4 (d, C-4), 81.3 (d, C-4), 101.1 (d, CHPh), 101.3 (d, C-1), 155.7-114.6 (12 C, Ar-C), 169.3 (s, -OO<u>C</u>CH_3); HRMS (ES^+) calculated for $C_{29}H_{30}O_8Na$ (MNa^+) 529.1832, found 529.1834.

(*p*-Methoxyphenyl)-2-*O*-allyl-3-*O*-benzyl-4,6-*O*-benzylidene-*β*-D-glucopyranoside[7] **2.29**

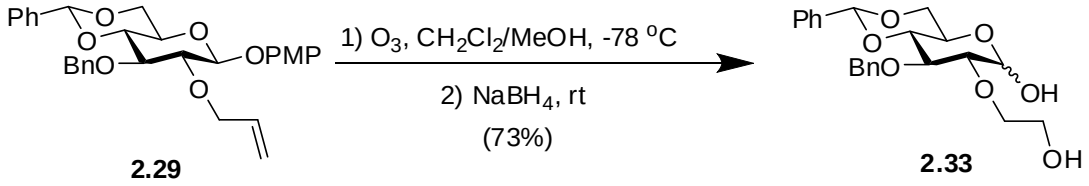


2.26 **2.29**

2.26 (3.00 g, 6.40 mmol) was dissolved in anhydrous DMF (20 mL) and to it was added a suspension of sodium hydride (0.330 g, 13.7 mmol), anhydrous DMF (20 mL) at 0 °C under a nitrogen atmosphere. Allyl bromide (1.17 mL, 13.7 mmol) was then added slowly to the mixture. Once the addition was complete the reaction was then allowed to warm to rt and stirred. After 4 h t.l.c. (petrol:ethyl acetate, 4:1) showed complete consumption of starting material (R_f 0.1) and formation of a single product (R_f 0.3). The reaction was then quenched by the addition of methanol (20 mL) and then concentrated *in vacuo*. The residue was dissolved in DCM (30 mL), washed with water (2 x 15 mL), brine (15 mL) and dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petrol:ethyl acetate, 6:1) yielded (*p*-

methoxyphenyl)-2-*O*-allyl-3-*O*-benzyl-4,6-*O*-benzylidene-*β*-D-glucopyranoside **2.29** (2.33 g, 72%) as white crystalline solid; m. p. 177 – 180 °C (petrol/ethyl acetate); $[\alpha]_D^{20}$ – 34.6 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 3.56 (m, 1H, H-5), 3.62 (1H, m, H-2), 3.71-3.86 (6H, m, H-3, H-4, H-6, -OCH_3), 4.49 (2H, m, -$OC\underline{H}_2CH=CH_2$), 4.37 (1H, m, H-6'), 4.85 (1H, d, J_{gem} 11.2 Hz, -$OCH\underline{H}'_2Ph$), 4.98 (2H, m, -$OC\underline{H}H'Ph$, H-1), 5.21 (1H, d, J_Z 10 Hz, -$OCH_2CH=C\underline{H}zH_E$), 5.35 (1H, d, J_E 16 Hz, -$OCH_2CH=CHz\underline{H}_E$), 5.59 (1H, s, CHPh), 6.00 (1H, m, -$OCH_2C\underline{H}=CH_2$), 6.84-7.52 (14H, m, Aromatic – H); δ_C (100 MHz, $CDCl_3$): 55.6 (q, -OMe), 68.7 (d, C-5), 66.2 (t, C-6), 74.282 (d, C-2), 75.1 (t, CH_2Ph), 80.8 (d, C-4), 81.1 (d, C-3), 81.6 (t, -$O\underline{C}H_2CH=CH_2$), 101.2 (d, CHPh), 103.3 (d, C-1), 114.6-155.6 (14C, Ar-C, -$OCH_2\underline{C}H=CH_2$, -$OCH_2CH=\underline{C}H_2$); HRMS (ES^+) calculated for $C_{30}H_{32}O_7Na$ (MNa^+) 527.2040, found 527.2051.

3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2-hydroxyethyl)-*α*/*β*-D-glucopyranose 2.33

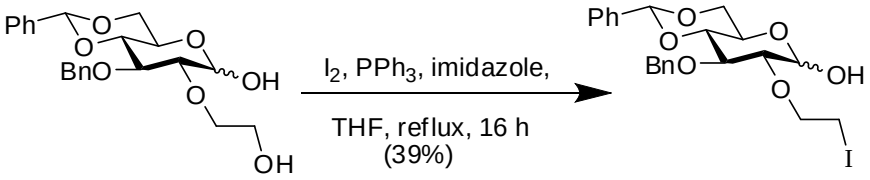


2.29 **2.33**

A solution of **2.29** (0.200 g, 0.400 mmol) in DCM:MeOH (9 mL, 2:1) was treated with ozone at – 78 °C until the solution turned blue. The reaction was quenched by the addition of $NaBH_4$ (0.027 g, 0.720 mmol) in small portions over 90 min. On completion of the addition of $NaBH_4$, t.l.c. (DCM:MeOH, 195:5) showed formation of a major product (R_f 0.4) and complete disappearance of starting material (R_f 0.95). The mixture was then allowed to warm to rt and then concentrated *in vacuo.* The residue was dissolved in ethyl acetate (20 mL), then washed with saturated aq. sodium bicarbonate solution (2 x 5 mL), brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (DCM:MeOH, 97:3) followed by recrystallization yielded 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-hydroxyethyl)-*α*/*β*-

D-glucopyranose **2.33** (0.117 g, 73%) as white crystalline solid; m. p. 148 – 151 °C (petrol/ethyl acetate); ν_{max} (KBr) 3,400 (br, O-H) cm^{-1}; δ_H (400 MHz, $CDCl_3$) [1:1.4 mixture of *α*:*β* anomers observed]: 3.34 (1H, at, *J* 8 Hz, H-2 *β*), 4.46 (1H, m, -OC<u>H</u>H'CH_2OH *α*), 3.58 (1H, dd, $J_{2,3}$ 12 Hz, $J_{1,2}$ 3.6 Hz, H-2 *α*), 3.78-3.83 (10H, m, -$OCH_2C\underline{H}_2$OH *α*, -$OCH_2C\underline{H}_2$OH *β*, -OC<u>H</u>H'CH_2OH *β*, H-3 *α*, H-3 *β*, H-5 *α*, H-6 *α*, H-6 *β*), 3.84-3.93 (2H, m, -OCH<u>H</u>'CH_2OH *α*, -OCH<u>H</u>'CH_2OH *β*), 4.00 (1H, at, *J* 8 Hz, H-4 *α*), 4.09 (1H, m, H-5 *β*), 4.29-4.36 (2H, m, H-6' *α*, H-6' *β*), 4.73 (1H, d, $J_{1,2}$ 8 Hz, H-1 *β*), 4.77, 4.97 (4H, ABq, J_{AB} 12 Hz, CH_2Ph *α*, CH_2Ph *β*), 5.34 (1H, d, $J_{1,2}$ 3.6 Hz, H-1 *α*), 5.57 (1H, s, CHPh *β*), 5.58 (1H, s, CHPh *α*), 7.26-7.48 (20 H, m, 10 x Ar-CH *α*, 10 x Ar-CH *β*); δ_C (100 MHz, $CDCl_3$): 62.2 (d, C-5 *β*), 62.3, 62.5 (2 x t, -$OCH_2\underline{C}H_2$OH *α*, -$OCH_2\underline{C}H_2$OH *β*), 66.2 (t, -O<u>C</u>H_2CH_2OH *α*), 68.7 (d, C-6 *β*), 69.0 (d, C-6 *α*), 73.0 (d, C-5 *α*), 74.5 (d, -O<u>C</u>H_2CH_2OH *β*), 75.0, 75.2 (2 x t, -CH_2Ph *α*, -CH_2Ph *β*), 77.8 (d, C-4 *α*), 80.5, 80.8 (2 x d, C-3 *α*, C-3 *β*), 81.8 (d, C-4 *β*), 82.2, 83.4 (2 x d, C-2 *α*, C-2 *β*), 91.7 (d, C-1 *β*), 97.4 (d, C-1 *α*), 101.2, 101.3 (2 x d, -CHPh *α*, -CHPh *β*), 126.0 – 134.5 (16 C, 8 x Ar-CH *α*, 8 x Ar-CH *β*); HRMS (ES^+) calculated for $C_{22}H_{26}O_7Na$ (MNa^+) 425.1570, found 425.1575.

3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2-iodoethyl)-*α*/*β*-D-glucopyranose[11] **2.34**

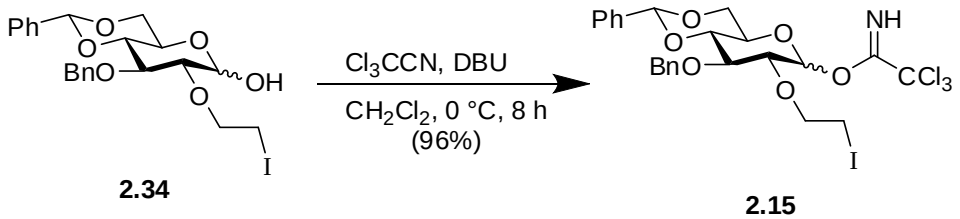


2.33 **2.34**

2.33 (0.214 g, 0.500 mmol) was dissolved in THF (10 mL) under a nitrogen atmosphere. Then I_2 (0.191 g, 0.760 mmol), imidazole (0.051 g, 0.760 mmol) and PPh_3 (0.200 g, 0.760 mmol) were added to the solution. The mixture was then heated to reflux. After 16 h, t.l.c. (petrol:ethyl acetate, 2:1) indicated the formation of a major product (R_f 0.3) and the complete consumption

of starting material (R_f 0.1). The reaction was cooled to rt and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol:ethyl acetate, 5:1) to afford 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-iodoethyl)ether-*α*/*β*-D-glucopyranose **2.34** (0.112 g, 39%) as white crystalline solid; m. p. 179 – 182 °C (petrol/ethyl acetate); δ_H (400 MHz, $CDCl_3$) [1:1.6 mixture of *α*:*β* anomers observed]: 3.08 (1H, bs, -OH *α*), 3.27 (7H, m, -OH *β*, H-2 *α*, H-2 *β*, H-3 *α*, H-3 *β*, H-4 *α*, H-4 *β*), 3.50 (1H, m, H-5 *α*), 3.69 (6H, m, H-5 *β*, -$OCH_2C\underline{H}_2I$ *α*, -$OCH_2C\underline{H}_2I$ *β*, -$OCH\underline{H}'CH_2I$ *α*), 3.82-4.17 (5H, m, -$OCH\underline{H}'CH_2I$ *β*, -$OC\underline{H}H'CH_2I$ *α*, -$OC\underline{H}H'CH_2I$ *β*, H-6' *α*, H-6' *β*), 3.35 (2H, m, -$OCH\underline{H}'CH_2I$ *α*, -$OCH\underline{H}'CH_2I$ *β*), 4.48 (1H, d, $J_{1,2}$ 8Hz, H-1 *β*), 4.81, 4.96 (4H, ABq, J_{AB} 12 Hz, CH_2Ph *α*, CH_2Ph *β*), 5.36 (1H, d, $J_{1,2}$ 3.6 Hz, H-1 *α*), 5.58 (2H, s, CHPh *α*, CHPh *β*), 7.27-7.50 (20 H, m, 10 x Ar-CH *α*, 10 x Ar-CH *β*); δ_C (100 MHz, $CDCl_3$): 3.2, 3.6 (2 x t, -$OCH_2\underline{C}H_2I$ *α*, -$OCH_2\underline{C}H_2I$ *β*), 62.5, 66.3 (2 x t, C-6 *α*, C-6 *β*), 68.6, 69.0 (2 x t, -$O\underline{C}H_2CH_2I$ *α*, -$O\underline{C}H_2CH_2I$ *β*), 72.5, 73.5 (2 x d, C-5 *α*, C-5 *β*), 75.1, 75.2 (2 x t, -CH_2Ph *α*, -CH_2Ph *β*), 78.1 (d, C-4 *α*), 80.5, 80.6 (2 x d, C-3 *α*, C-3 *β*), 81.6 (d, C-4 *β*), 82.0, 83.6 (2 x d, C-2 *α*, C-2 *β*), 92.1 (d, C-1 *β*), 97.4 (d, C-1 *α*), 101.2, 101.3 (2 x d, -CHPh *α*, -CHPh *β*), 126.0-138.5 (16 C, 8 x Ar-CH *α*, 8 x Ar-CH *β*); HRMS (ES^+) calculated for $C_{22}H_{25}O_6NaI$ (MNa^+) 535.0584, found 535.0594.

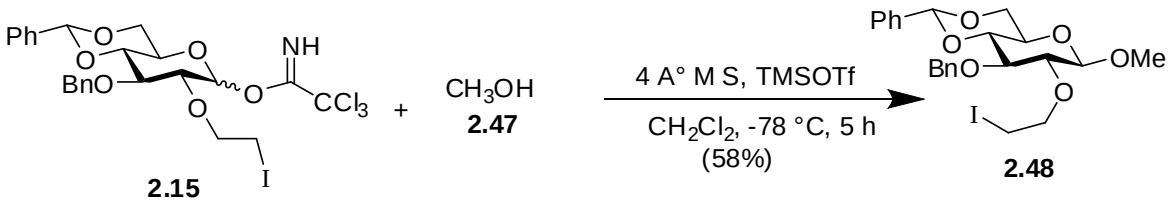
3-(*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2-iodoethyl) -*α*/*β*-D-glucopyranosyl) trichloroacetimidate[12] **2.15**



2.34 **2.15**

2.28 (0.091 g, 0.178 mmol) was dissolved in distilled DCM (3 mL) under a nitrogen atmosphere. DBU (0.011 mL, 0.071 mmol), followed by trichloroacetonitrile (0.182 mL, 1.78 mmol), were added to the solution at 0° C. After 8 h, t.l.c. (petrol:ethyl acetate, 3:1, with 1% TEA) indicated the formation of a major product (R_f 0.4) and the complete consumption of starting material (R_f 0.2). The reaction was cooled to rt and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol:ethyl acetate, 7:1, with 1% TEA) to afford 3-(*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-iodoethyl)ether-*α*/*β*-D-glucopyranosyl) trichloroacetimidate **2.10** (0.112 g, 96%) as colorless oil; ν_{max} (KBr) 3451 (w, N-H), 1674 (s, C=N) cm^{-1}; δ_H (400 MHz, $CDCl_3$) [3.5:1 mixture of *α*:*β* anomers observed]: 3.15 (4H, m, -$OCH_2C\underline{H}_2I$ *α*, -$OCH_2C\underline{H}_2I$ *β*), 3.56 -3.87 (6H, m, H-3 *α*, H-3 *β*, -$OC\underline{H}_2CH_2I$ *α*, - $OC\underline{H}_2CH_2I$ *β*), 3.89 -4.09 (8H, m, H-2 *α*, H-2 *β*, H-4 *α*, H-4 *β*, H-5 *α*, H-5 *β*, H-6' *α*, H-6' *β*), 4.32 – 4.36 (1H, dd, $J_{6,6'}$ 10.4 Hz, $J_{6,5}$ 4.8 Hz, H-6 *α*), 4.38-4.42 (1H, dd, $J_{6,6'}$ 10.4 Hz, $J_{6,5}$ 4.8 Hz, H-6 *β*), 4.85, 4.93 (4H, ABq, J_{AB} 12 Hz, CH_2Ph *α*, CH_2Ph *β*), 5.57 (1H, s, CHPh *β*), 5.59 (1H, s, CHPh *α*), 5.84 (1H, d, $J_{1,2}$ 7.8 Hz, H-1 *β*), 6.51 (1H, d, $J_{1,2}$ 3.6 Hz, H-1 *α*), 7.26-7.51 (20 H, m, 10 x Ar-CH *α*, 10 x Ar-CH *β*), 8.62 (1H, s, NH *α*), 8.73 (1H, s, NH *β*); ^{13}C (100 MHz, $CDCl_3$): 2.3, 2.4 (2 x t, -$OCH_2\underline{C}H_2I$ *α*, -$OCH_2\underline{C}H_2I$ *β*), 65.1, 66.6 (2 x t, C-6 *α*, C-6 *β*), 68.5, 68.7 (2 x t, -$O\underline{C}H_2CH_2I$ *α*, -$O\underline{C}H_2CH_2I$ *β*), 72.4, 74.0 (2 x d, C-5 *α*, C-5 *β*), 75.1, 75.2 (2 x t, -CH_2Ph *α*, -CH_2Ph *β*), 77.3, 77.7, 79.6, 80.5, 81.1 (6 x d, C-2 *α*, C-2 *β*, C-3 *α*, C-3 *β*, C-4 *α*, C-4 *β*), 81.2, 81.4 (2 x s, $\underline{C}Cl_3$ *α*, $\underline{C}Cl_3$ *β*), 94.6 (d, C-1 *β*), 97.9 (d, C-1 *α*), 101.3, 101.3 (2 x d, -CHPh *α*, -CHPh *β*), 125.9–138.4 (16 C, 8 x Ar-CH *α*, 8 x Ar-CH *β*), 161.3 (s, $\underline{C}$=NH); HRMS (ES^+) calculated for $C_{24}H_{25}NO_6Cl_3INa$ (MNa^+) 677.9678, found 677.9694.

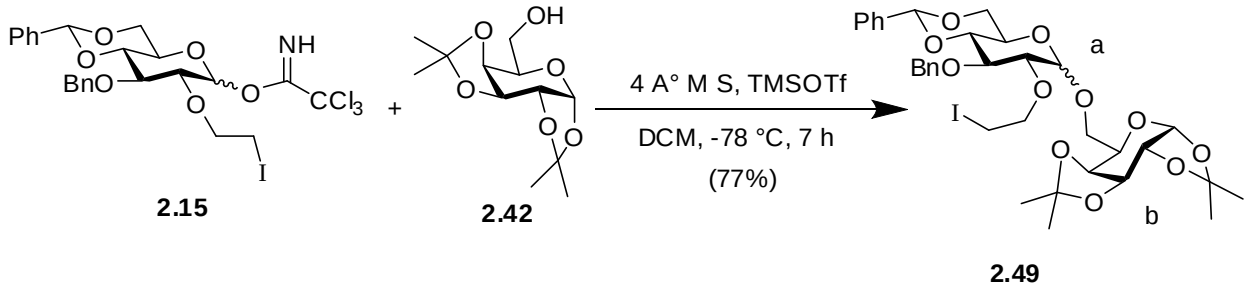
Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-iodoethyl)-*α*-D-glucopyranoside[13]



A solution of 3-(*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-iodoethyl)ether-*α*/*β*-D-glucopyranosyl) trichloroacetimidate **2.15** (0.100 g, 0.153 mmol) and methanol **2.47** (5.20 μL, 0.306 mmol) in freshly distilled DCM (2 mL) was added to a flame-dried round-bottom flask containing activated 4 Å molecular sieves (0.100 g). The mixture was cooled to -78 °C under a nitrogen atmosphere, then TMSOTf (3.00 μL, 0.015 mmol) was added. After 5 h, t.l.c. (petrol:ethyl acetate, 3:1) showed formation of a major product (R_f 0.7) and the complete consumption of the trichloroacetimidate starting material (R_f 0.8) was observed. The reaction was quenched with saturated aq. sodium bicarconate solution (2 mL) and filtered through Celite®. The mixture was diluted with DCM (20 mL), washed with saturated aq. sodium bicarbonate solution (2 x 10 mL), and the aqueous layer extracted with DCM (2 x 20 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) to afford methyl 2-*O*-(2-iodoethyl)-3-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-glucopyranoside **2.48** (0.048 g, 58%) as a white crystalline solid; m. p. 125 – 128 °C (petrol/ethyl acetate); [δ_H (400 MHz, $CDCl_3$) [1:50 mixture of *α*:*β* anomers observed, major *β* anomer quoted]: 3.21-3.29 (3H, m, -$CH_2C\underline{H_2}I$, H-3), 3.42-3.47 (1H, m, H-5), 3.58 (1H, bs, -OCH_3), 3.61-3.74 (2H, m, H-2, H-4), 3.76-3.81 (1H, at, *J* 10Hz, H-6), 3.92-4.09 (2H, m, -$CH_2C\underline{H_2}I$), 4.34-4.41 (2H, m, H-1, H-6'), 4.83, 4.92 (4H, ABq, J_{AB} 11.2 Hz, CH_2Ph), 5.57 (1H, s, CHPh), 7.27-7.50 (10H, m, Ar-CH); δ_H (400 MHz, DMSO-D_6) [1:50

mixture of *α*:*β* anomers observed, major *β* anomer quoted]: 3.17-3.29 (2H, m, -$CH_2C\underline{H}_2I$), 3.42-3.48 (5H, m, H-3, H-5, -OCH_3), 3.64-3.66 (2H, m, H-2, H-4), 3.70-3.75 (1H, at, *J* 10Hz, H-6), 3.81-3.98 (2H, m, -$CH_2C\underline{H}_2I$), 4.21-4.25 (1H, m, H-6'), 4.44 (1H, d, $J_{1,2}$ 8 Hz, H-1), 4.78 (2H, s, CH_2Ph), 5.66 (1H, s, CHPh), 7.25-7.43 (10H, m, Ar-CH); δ_C (100 MHz, $CDCl_3$): [major *β* anomer quoted] 3.3 ($OCH_2\underline{C}H_2I$), 65.9 (d, C-5), 68.7 (t, C-6), 73.5 (t, $O\underline{C}H_2CH_2I$), 75.1 (t, $Ar\underline{C}H_2$), 80.5, 81.4, 82.4 (3 x d, C-2, C-3, C-4), 101.2 (d, CHPh), 104.5 (d, $\underline{C}$HPh), 126.0, 127.7, 127.9, 128.2, 128.7, 129.0 (6 x d, Ar-CH), 137.3, 138.4 (2 x s, Ar-C); HRMS (ES^+) calculated for $C_{23}H_{27}O_6INa$ (MNa^+) 549.0746, found 549.0747.

3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2-iodoethyl)-*α*/*β*-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranose[14] **2.49**

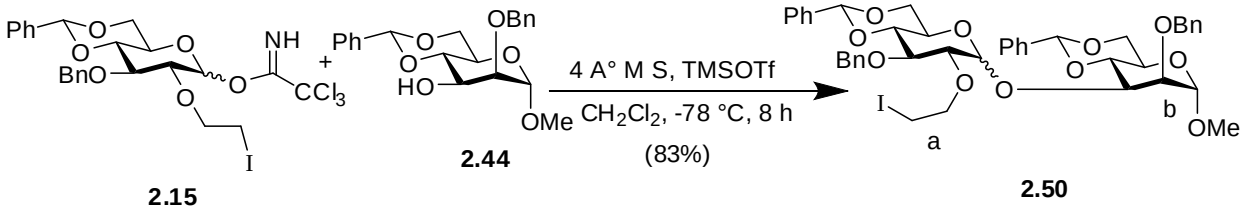


A solution of 3-(*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-iodoethyl)-*α*/*β*-D-glucopyranosyl) trichloroacetimidate **2.15** (0.100 g, 0.153 mmol) and 1,2:3,4–di–*O*–isopropylidene–*α*–D–galactopyranose **2.42** (0.080 g, 0.306 mmol) in freshly distilled DCM (2 mL) was added to a flame-dried round-bottom flask containing activated 4 Å molecular sieves (0.100 g). The mixture was cooled to -78 °C under a nitrogen atmosphere, then TMSOTf (3μL, 0.015 mmol) was added. After 7 h, t.l.c. (toluene:ethyl acetate, 4:1) showed formation of a major product (R_f 0.7) and the complete consumption of the trichloroacetimidate starting material (R_f 0.8). The reaction was quenched with saturated aq. sodium bicarbonate solution (2 mL) and filtered through Celite®.

The mixture was diluted with DCM (20 mL), washed with saturated aq. sodium bicarbonate solution (2 x 10 mL), and the aqueous layer extracted with DCM (20 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) to afford 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-iodoethyl)-*α*/*β*-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside **2.49** (0.176 g, 77%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) [1:2 mixture of *α*:*β* anomers observed]: 1.35, 1.37, 1.47, 1.56, 1.58, 1.61, 1.63 (24H, 8 x s, 4 x CH_3*α*, 4 x CH_3*β*), 3.27-3.34 (5H, m, $OCH_2C\underline{H}_2I$ *α*, $OCH_2C\underline{H}_2I$ *β*, H-5b *α*), 3.40 (1H, m, H-5_b*β*), 3.53 (1H, m, H-5_a *α*), 3.60-3.87 (9H, m, H-2_a *α*, H-2_a *β*, H-5_a *β*, H-2_b *α*, H-4_b *α*, H-4_b *β*, H-5_b *α*, H-5_b *β*, H-6'$_a$ *α*/*β*), 3.93-4.09 (9H, m, H-2_a *α*, H-2_a *β*, H-3_a *α*, H-3_a *β*, H-4_a *α*, H-4_b *β*, H-6_b *α*, H-6_b *β*, H-6'$_a$ *α*/*β*), 4.16-4.24 (2H, m, $OC\underline{H}_2CH_2I$ *α*/*β*,), 4.33-4.47 (4H, m, $OC\underline{H}_2CH_2I$ *α*/*β*, H-6_a *α*, H-6_a *β*), 4.50 (1H, d, $J_{1,2}$ 8 Hz, H-1_a *β*), 4.61 (2H, m, H-6'$_b$ *α*, H-6'$_b$ *β*), 4.82-4.93 (4H, m, $C\underline{H}_2$Ph *α*, $C\underline{H}_2$Ph *β*), 5.05 (1H, d, $J_{1,2}$ 3.5 Hz, H-1_a *α*), 5.56 (4H, s, CHPh *α*, CHPh *β*, H-1_b *α*, H-1_b *β*), 7.27-7.50 (20H, m, 10 x Ar-CH*α*, 10 x Ar-CH*β*); δ_C (100 MHz, $CDCl_3$): 3.8, 3.9 (2 x t, $OCH_2\underline{C}H_2I$ *α*, $OCH_2\underline{C}H_2I$ *β*), 24.5, 24.8, 24.9, 25.0, 25.9, 26.0, 26.1, 26.2 (4 x q, CH_3 *α*, 4 x q, CH_3 *β*), 62.5, 65.7 (2 x t, C-6_a *α*, C-6_a *β*), 66.0, 66.8 (2 x t, C-6_b *α*, C-6_b *β*), 67.4, 68.7 (2 x t, $O\underline{C}H_2CH_2I$ *α*, $O\underline{C}H_2CH_2I$ *β*), 69.0, 70.4 (2 x t, $Ar\underline{C}H_2$ *α*, $Ar\underline{C}H_2$ *β*), 70.6, 70.7, 70.8, 70.9, 71.4, 72.0, 73.6, 75.2, 76.7, 77.3, 78.2, 80.4, 80.6, 81.4, 82.1, 82.5 (16 x d, C-2_a *α*, C-3_a *α*, C-4_a *α*, C-5_a *α*, C-2_a *β*, C-3_a *β*, C-4_a *β*, C-5_a *β*, C-2_b *α*, C-3_b *α*, C-4_b *α*, C-5_b *α*, C-2_b *β*, C-3_b *β*, C-4_b *β*, C-5_b *β*), 96.4 (d, C-1_a *β*), 98.0 (d, C-1_a *α*), 101.1 (d, C-1_b *β*), 101.3 (d, C-1_b *α*), 104.5, 104.5 (d, $\underline{C}$HPh *α*, $\underline{C}$HPh *β*), 108.7, 108.7, 109.4, 109.5 (4 x s, $\underline{C}(CH_3)_2$ x 2 *α*, $\underline{C}(CH_3)_2$ x 2 *β*), 126.0, 126.5, 126.6, 127.2, 127.6, 127.7, 127.9, 128.1, 128.2, 128.3, 128.4, 129.0 (12 x d, Ar-CH), 137.3, 137.4,

138.3, 138.6 (4 x s, Ar-C); HRMS (ES+) Calculated for $C_{34}H_{43}O_{11}INa$ (MNa+) 777.1742, found 777.1752).

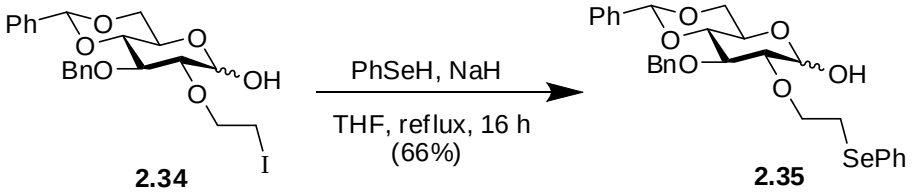
Methyl 3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2-iodoethyl) -*α*/*β*-D-glucopyranosyl-(1→3)-2-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-mannopyranoside[15] **2.50**



A solution of 3-(*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-iodoethyl)ether-*α*/*β*-D-glucopyranosyl) trichloroacetimidate **2.15** (0.100 g, 0.153) and methyl-2-O-benzyl-4,6-di-O-benzylidene-*α*-D-mannopyranoside **2.44** (0.114, 0.306 mmol) in freshly distilled DCM (2 mL) was added to a flame-dried round-bottom flask containing activated 4 Å molecular sieves (0.100 g). The mixture was cooled to -78 °C under a nitrogen atmosphere, then TMSOTf (3 μL, 0.015 mmol) was added. After 8 h, t.l.c. (toluene:ethyl acetate, 4:1) showed formation of a major product (R_f 0.6) and the complete consumption of trichloroacetimidate starting material (R_f 0.8). The reaction was quenched with saturated aq. sodium bicarbonate solution (2 mL) and filtered through Celite®. The mixture was diluted with DCM (20 mL), washed with saturated aq. sodium carbonate solution (2 x 10 mL), and the aqueous layer extracted with DCM (20 mL). The combined organic extracts were washed with brine (25 mL), dried (MgSO4), filtered and concentrated *in vacuo*. The residue was purified by The residue was purified by flash column chromatography (petrol:ethyl acetate, 7:1) to afford 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-iodoethyl)ether-*α*/*β*-D-glucopyranosyl-(1→3)-methyl-2-O-benzyl-4,6-di-O-benzylidene-*α*-D-mannopyranoside **2.50** (0.110, 83%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) [1:1 mixture of *α*:*β* anomers observed]: 2.86-3.09 (4H, m, -$OCH_2C\underline{H}_2I$ *α*, -$OCH_2C\underline{H}_2I$ *β*) 3.35, 3.37 (6H, 2 x s, -

OMe *α*, -OMe *β*), 3.42-3.99 (20H, m, H-2_a *α*, H-2_a *α*, H-2_a *β*, H-3_a *α*, H-3_a *β*, H-4_a *α*, H-4_a *β*, H-6_a *α*, H-6_a *β*, H-2_b *α*, H-2_b *β*, H-3_b *α*, H-3_b *β*, H-4_b *α*, H-4_b *β*, H-5_b *α*, H-5_b *β*), 4.09-4.39 (8H, m, -OC$\underline{H}_2$CH_2I *α*, OC$\underline{H}_2$CH_2I *β*, H-6_b *α*, H-6_b *β*, H-6'$_b$ *α*, H-6'$_b$ *β*), 4.59 (1H, d, $J_{1,2}$ 8 Hz, H-1_a *β*), 4.71-4.93 (10H, m, H-1_b *α*, H-1_b *β*, PhC$\underline{H}_{2a}$ *α*, PhC$\underline{H}_{2a}$ *β*, PhC$\underline{H}_{2b}$ *α*, PhC$\underline{H}_{2b}$ *β*), 5.38 (1H, d, $J_{1,2}$ 3.5 Hz, H-1_a *α*), 5.43, 5.47 (2H, 2 x s, CHPh$_b$ *α*, CHPh$_b$ *β*), 5.61, 5.63 (2H, 2 x s, CHPh$_a$ *α*, CHPh$_a$ *β*) 7.18-7.47 (40H, m, 20 x Ar-CH *α*, 20 x Ar-CH *β*); δ_C (100 MHz, $CDCl_3$): 2.8, 3.1 (OC$H_2\underline{C}H_2$I *α*, OC$H_2\underline{C}H_2$I *β*), 54.8, 54.9 (2 x q, -OCH_3 *α*, -OCH_3 *β*), 68.7, 68.8, 68.9, 69.0 (4 x t, C-6_a *α*, C-6_a *β*, C-6_b *α*, C-6_b *β*), 70.8, 70.8 (2 x t, -O$\underline{C}H_2CH_2$I *α*, -OCH_2CH_2I *β*), 73.2, 73.3, 74.8, 75.0 (4 x t, CH_2Ph$_a$ *α*, CH_2Ph$_a$ *β*, CH_2Ph$_b$ *α*, CH_2Ph$_b$ *β*), 63.1, 63.9, 64.2, 66.1, 73.9, 76.6, 77.7, 77.8, 79.4, 80.3, 80.8, 81.4, 81.7, 81.7, 82.4, 82.4 (16 x d, C-2_a *α*, C-3_a *α*, C-4_a *α*, C-5_a *α*, C-2_a *β*, C-3_a *β*, C-4_a *β*, C-5_a *β*, C-2_b *α*, C-3_b *α*, C-4_b *α*, C-5_b *α*, C-2_b *β*, C-3_b *β*, C-4_b *β*, C-5_b *β*), 98.3 (d, C-1_a *α*), 102.3 (d, C-1_b *β*), 99.8, 100.4, 101.0, 101.3, 101.7, 102.6 (6 x d, C-1_b *α*, C-1_b *β*, CHPh$_a$ *α*, CHPh$_a$ *β*, CHPh$_b$ *α*, CHPh$_b$ *β*), 126.0–129.3 (24 x d, Ar-CH *α*, Ar-CH *β*), 137.4–138.6 (8 x s, Ar-C); HRMS (ES^+) Calculated for $C_{34}H_{43}O_{11}INa$ (MNa^+) 777.1742, found 777.1752.

3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2-(phenylselenyl)ethyl)-*α*/*β*-D-glucopyranose[16] **2.35**

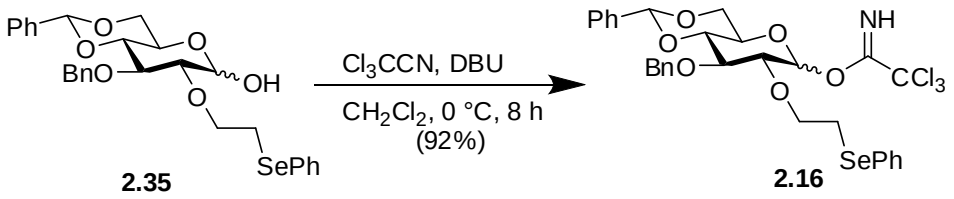


2.34 **2.35**

Selenophenol (0.120 mL, 1.15 mmol) was added to a stirred suspension of sodium hydride (0.018 g, 0.750 mmol) in THF (5 mL). After 30 min, 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-iodoethyl)-*α*/*β*-D-glucopyranose **2.34** (0.300 g, 0.590 mmol) was added as a solution in THF (5 ml) and the reaction was then heated to reflux. After 16 h, t.l.c (toluene:ethyl acetate, 2:1)

indicated the formation of a single major product (R_f 0.65) and the complete consumption of starting material (R_f 0.60). The reaction was diluted with DCM (20 mL) and washed with water (20 mL). The aqueous layer was then extracted with DCM (2 x 20 mL) and the combined organic extracts were washed with saturated aq. sodium bicarbonate solution (20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-(phenylselenyl)ethyl)-*α*/*β*-D-glucopyranose **2.35** (0.210 g, 66%) as a white crystalline solid; m. p. 128 – 130 °C (petrol/ethyl acetate); δ_H (400 MHz, $CDCl_3$) [1.4:1 mixture of *α*:*β* anomers observed]: 3.05-3.08 (4H, m, OCH_2CH_2SePh *α*, $OCH_2C\underline{H}_2SePh$ *β*), 3.22 (1H, at, *J* 5.0 Hz, H-2 *β*), 3.39-3.44 (3H, m, H-2 *α*, H-3 *α*, H-3 *β*), 3.49-3.97 (8H, m, H-4 *α*, H-4 *β*, H-5 *α*, H-5 *β*, H-6' *α*, H-6' *β*), 4.02-4.20 (4H, m, $OC\underline{H}_2CH_2SePh$ *α*, $OC\underline{H}_2CH_2SePh$ *β*), 4.29-4.36 (2H, m, H-6 *α*, H-6 *β*), 4.74-4.92 (5H, m, $PhCH_2$ *α*, $PhCH_2$ *β*, H-1 *β*), 4.26 (1H, d, $J_{1,2}$ 3.3 Hz, H-1 *α*), 7.26-7.49 (30H, m, 15 x Ar-CH *α*, 15 x Ar-CH *β*); δ_C (100 MHz, $CDCl_3$): 27.4, 27.9 (2 x t, $OCH_2\underline{C}H_2SePh$ *α*, $OCH_2\underline{C}H_2SePh$ *β*), 62.5, 66.4 (2 x d, C-5 *α*, C-5 *β*), 68.7, 69.0 (2 x t, C-6 *α*, C-6 *β*), 71.2, 72.4 (2 x t, $O\underline{C}H_2CH_2SePh$ *α*, $O\underline{C}H_2CH_2SePh$ *β*), 75.0, 75.1 (2 x t, CH_2Ph *α*, CH_2Ph *β*), 78.1, 80.5, 80.7, 81.5, 81.8, 83.8 (6 x d, C-2 *α*, C-2 *β*, C-3 *α*, C-3 *β*, C-4 *α*, C-4 *β*), 91.9 (d, C-1 *β*), 97.5 (d, C-1 *α*), 101.2, 101.3 (2 x d, CHPh *α*, CHPh *β*), 126.0–132.8 (24 x Ar-C); HRMS (ES^+) Calculated for $C_{28}H_{30}O_6SeNa$ (MNa^+) 565.1099, found 565.1105.

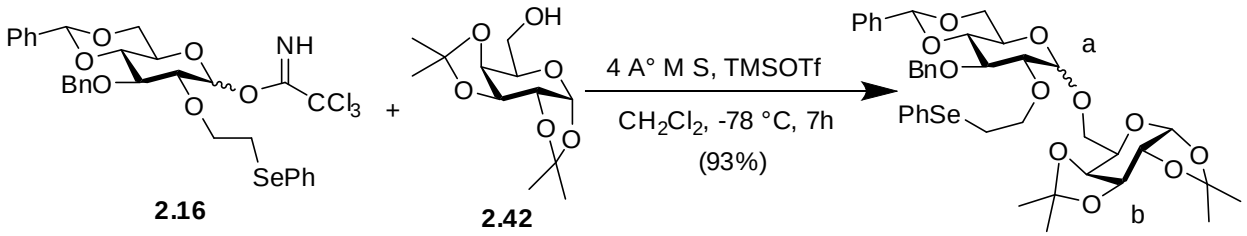
3-(*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2-(phenylselenyl)ethyl)-*α*/*β*-D-glucopyranosyl) trichloroacetimidate[17] 2.16



3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-(phenylselenyl)ethyl)-*α*/*β*-D-glucopyranose **2.35** (0.060 g, 0.111 mmol) was dissolved in distilled DCM (2.5 mL) under a nitrogen atmosphere. The solution was cooled to 0 °C, and to it were added DBU (0.005 mL, 0.044 mmol) followed by trichloroacetonitrile (0.143 mL, 1.11 mmol). After 8 h, t.l.c. (petrol:ethyl acetate, 3:1, with 1% TEA) indicated the formation of a major product (R_f 0.5) and the complete consumption of starting material (R_f 0.2). The reaction was warmed to rt and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol:ethyl acetate, 8:1, with 1% TEA) to afford 3-(*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-(phenylselenyl)ethyl)-*α*/*β*-D-glucopyranosyl) trichloroacetimidate **2.16** (0.072 g, 92%) as colorless oil; ν_{max} (KBr) 3350 (w, N-H), 1673 (s, C=N) cm^{-1}; δ_H (400 MHz, $CDCl_3$) [1.6:1 mixture of *α*:*β* anomers observed]: 2.99-3.04 (5H, m, -$OCH_2C\underline{H}_2SePh$ *α*, $OCH_2C\underline{H}_2SePh$ *β*, H-5 *α*/*β*), 3.49-3.79 (7H, m, H-2 *α*, H-2 *β*, H-3 *α*, H-3 *β*, H-4 *α*, H-4 *β*, H-5 *α*/*β*), 3.84–3.92 (2H, m, $OC\underline{H}_2CH_2SePh$ *α*/*β*), 3.94–4.08 (4H, m, $OC\underline{H}_2CH_2SePh$ *α*/*β*, H6’ *α*, H-6’ *β*), 4.33 (1H, dd, $J_{6,6'}$ 10.4 Hz, $J_{6,5}$ 5.4 Hz, H-6 *α*), 4.38 (1H, dd, $J_{6,6'}$ 10.4 Hz, $J_{6,5}$ 5.4 Hz, H-6 *β*), 4.79-4.93 (4H, m, CH_2Ph *α*, CH_2Ph *β*), 5.56 (1H, s, CHPh *β*), 5.58 (1H, s, CHPh *α*), 5.80 (1H, d, $J_{1,2}$ 7.8 Hz, H-1 *β*), 6.48 (1H, d, $J_{1,2}$ 4.0 Hz, H-1 *α*), 7.26–7.51 (30 H, m, 15 x Ar-CH *α*, 15 x Ar-CH *β*), 8.57 (1H, s, NH *α*), 8.69 (1H, s, NH *β*); δ_C (100 MHz, $CDCl_3$): 26.7, 26.9 (2 x t, -$OCH_2\underline{C}H_2SePh$ *α*, -$OCH_2\underline{C}H_2SePh$ *β*), 65.1, 66.6 (2 x d, C-6 *α*, C-6 *β*), 68.6, 68.7 (2 x t, -$O\underline{C}H_2CH_2SePh$ *α*, -$O\underline{C}H_2CH_2SePh$ *β*), 71.2, 72.8 (2 x d, C-5 *α*, C-5 *β*), 75.0, 75.2 (2

x t, -CH_2Ph *α*, -CH_2Ph *β*), 77.3, 77.7, 79.7, 80.6, 80.8, 81.0 (6 x d, C-2 *α*, C-2 *β*, C-3 *α*, C-3 *β*, C-4 *α*, C-4 *β*), 81.1, 81.3 (2 x s, $\underline{C}Cl_3$ *α*, $\underline{C}Cl_3$ *β*), 94.5 (d, C-1 *β*), 98.0 (d, C-1 *α*), 101.3, 101.3 (2 x d, -$\underline{C}$HPh *α*, -$\underline{C}$HPh *β*), 125.9–138.4 (24 C, 12 x Ar-CH *α*, 12 x Ar-CH *β*), 161.0, 161.2 (2 x s, $\underline{C}$=NH *α*, $\underline{C}$=NH *β*); HRMS (ES^+) calculated for $C_{30}H_{30}O_6NCl_3SeNa$ (MNa^+) 708.0186, found 708.0198.

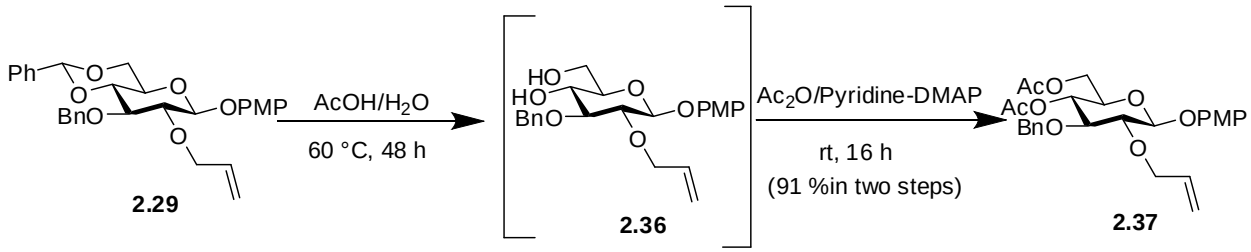
3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2-(phenylselenyl)ethyl)-*α*/*β*-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranose[18] **2.52**



A solution of 3-(*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-(phenylselenyl)ethyl)-*α*/*β*-D-glucopyranosyl) trichloroacetimidate **2.16** (0.060 g, 0.086 mmol) and 1,2:3,4–di–*O*–isopropylidene–*α*–D–galactopyranose **2.42** (0.045, 0.172) in freshly distilled DCM (1 mL) was added to a flame-dried round-bottom flask containing activated 4 Å molecular sieves (0.100 g). The mixture was cooled to -78 °C under a nitrogen atmosphere, then TMSOTf (1.5 μL, 0.008 mmol) was added. After 7 h, t.l.c. (petrol:ethyl acetate, 3:1) showed formation of a major product (R_f 0.45) and the complete consumption of trichloroacetimidate starting material (R_f 0.50). The reaction was quenched with saturated aq. sodium bicarbonate solution (2 mL) and filtered through Celite®. The mixture was diluted with DCM (20 mL), washed with saturated aq. sodium bicarbonate solution (2 x 10 mL), and the aqueous layer extracted with DCM (20 mL). The

combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-(phenylselenyl)ethyl)-*α*/*β*-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside **2.52** (0.065 g, 93%) as a colorless oil; δ_H (400 MHz, $CDCl_3$) [1:3 mixture of *α*:*β* anomers observed]: 1.34 (12H, m, 2 x CH_3 *α*, 2 x CH_3 *β*), 1.46, 1.47, 1.53, 1.55 (12H, 4 x s, 2 x CH_3 *α*, 2 x CH_3 *β*), 3.06-3.18 (5H, m, $OCH_2C\underline{H}_2SePh$ *α*, $OCH_2C\underline{H}_2SePh$ *β*, H-5_b *α*), 3.40 (1H, m, H-5_b *β*), 3.53 (1H, m, H-5_a *α*), 3.49 (1H, dd, $J_{6,6'}$ 8.2 Hz, $J_{5,6}$ 3.2 Hz H-6_b *α*), 3.58-3.82 (8H, m, H-2_a *α*, H-2_a *β*, H-5_a *β*, H-2_b *α*, H-4_b *α*, H-4_b *β*, H-5_b *α*, H-5_b *β*), 3.84-4.13 (7H, m, H-2_a *α*, H-2_a *β*, H-3_a *α*, H-3_a *β*, H-4_a *α*, H-4_b *β*, H-6_b *β*), 4.16-4.24 (4H, m, $OC\underline{H}_2CH_2SePh$ *α*/*β*, H-6_a *α*/*β* H-6'$_a$ *α*, H-6'$_a$ *β*), 4.33-4.47 (3H, m, $OC\underline{H}_2CH_2SePh$ *α*/*β*, H-6_a *α*/*β*), 4.48 (1H, d, $J_{1,2}$ 8 Hz, H-1_a *β*), 4.61 (2H, m, H-6'$_b$ *α*, H-6'$_b$), 4.80-4.88 (4H, m, $C\underline{H}_2Ph$ *α*, $C\underline{H}_2Ph$ *β*), 5.02 (1H, d, $J_{1,2}$ 3.5 Hz, H-1_a *α*), 5.53 (4H, s, CHPh *α*, CHPh *β*, H-1_b *α*, H-1_b *β*), 7.27-7.50 (30H, m, 15 x Ar-CH *α*, 15 x Ar-CH *β*); δ_C (100 MHz, $CDCl_3$): 24.4, 24.6 ($OCH_2\underline{C}H_2SePh$ *α*, $OCH_2\underline{C}H_2SePh$ *β*), 24.9, 25.0, 25.9, 26.0, 26.1, 26.2, 27.0, 27.1 (4 x q, CH_3 *α*, 4 x q, CH_3 *β*), 62.5, 62.5 (2 x t, C-6_a *α*, C-6_a *β*), 65.8, 66.0 (2 x t, C-6_b *α*, C-6_b *β*), 66.9, 67.3 (2 x t, $O\underline{C}H_2CH_2SePh$ *α*, $O\underline{C}H_2CH_2SePh$ *β*), 68.9, 69.0 (2 x t, $Ar\underline{C}H_2$ *α*, $Ar\underline{C}H_2$ *β*), 70.2, 70.4, 70.6, 70.7, 70.8, 70.9, 71.3, 72.4, 75.0, 75.1, 78.2, 80.5, 80.6, 81.3, 82.0, 82.4 (16 x d, C-2_a *α*, C-3_a *α*, C-4_a *α*, C-5_a *α*, C-2_a *β*, C-3_a *β*, C-4_a *β*, C-5_a *β*, C-2_b *α*, C-3_b *α*, C-4_b *α*, C-5_b *α*, C-2_b *β*, C-3_b *β*, C-4_b *β*, C-5_b *β*), 96.3 (d, C-1_a *β*), 98.0 (d, C-1_a *α*), 101.1 (d, C-1_b *α*), 101.2 (d, C-1_b *β*), 104.6, 104.6 (d, $\underline{C}$HPh *α*, $\underline{C}$HPh *β*), 108.6, 108.6, 109.2, 109.4 (4 x s, $\underline{C}(CH_3)_2$ x 2 *α*, $\underline{C}(CH_3)_2$ x 2 *β*), 126.0, 126.5, 126.6,126.9, 127.2, 127.3 127.6, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 129.0, 129.1, 129.2, 130.4 (18 x d, Ar-CH), 132.2, 132.6, 137.3, 137.4, 138.3, 138.6 (6 x s, Ar-C); HRMS (ES^+) Calculated for $C_{40}H_{48}O_{11}SeNa$ (MNa^+) 807.2254, found 807.2258).

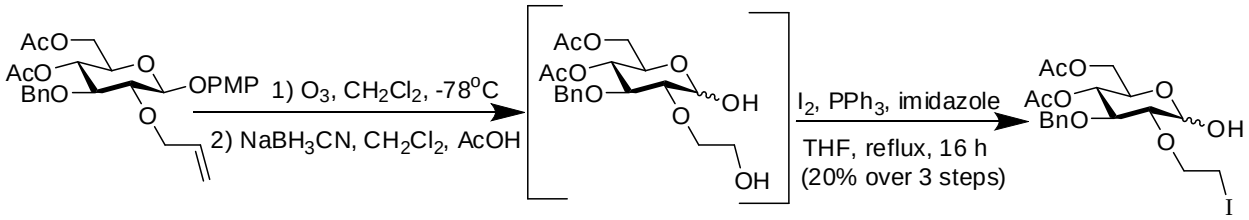
(*p*-Methoxyphenyl)-2-*O*-allyl-3-*O*-benzyl-4,6-diacetyl-*β*-D-glucopyranoside[19] **2.37**



Acetic acid (aq. 80%, 6 mL) was added to a solution of **2.29** (100 mg, 0.200 mmol) in DCM (1 mL). The mixture was then stirred at 60 °C. After 48 h, t.l.c. (petrol:ethyl acetate, 3:1) indicated the formation of a major product (R_f 0.1) and the complete consumption of starting material (R_f 0.8). The mixture was diluted with DCM (10 mL) and carecompletely washed with saturated aq. $NaHCO_3$ (2 x 15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue (**2.36**) was dissolved in the mixture of Ac_2O:pyridine (1:1, 5 mL) and DMAP (0.005 g, 0.040 mmol) was added. The mixture was then stirred at rt. After 16 h, t.l.c. (petrol:ethyl acetate, 3:1) indicated the formation of a major product (R_f 0.3) and the complete consumption of starting material (R_f 0.1). The mixture was then repeatedly co-evaporated with toluene (4 x 25 mL). The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford (*p*-methoxyphenyl)-2-*O*-allyl-3-*O*-benzyl-4,6-diacetyl-*β*-D-glucopyranoside **2.37** (0.091 g, 91%) as a white crystalline solid; m. p. 63 – 65 °C (petrol/ethyl acetate); $[\alpha]_D^{20}$ - 62.8 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.93, 2.06 (2 x s, 6H, 2 x $COC\underline{H}_3$) 3.82 (m, 3H, H-2, H-4, H-5), 3.78 (3H, s, -OCH_3), 4.07-4.11 (1H, dd, $J_{6,6'}$ 9.2 Hz, $J_{6,5}$ 3.8 Hz, H-6), 4.21-4.25 (1H, dd, $J_{6',6}$ 9.2 Hz, $J_{6',5}$ 3.8 Hz, H-6'), 4.29-4.33 (1H, dd, J_{gem} 9.2 Hz, J_{vic} 3.8 Hz, -OC$\underline{H}$H'CH=CH_2), 4.47 – 4.51 (1H, dd, J_{gem} 9.2 Hz, J_{vic} 3.8 Hz, -OCH$\underline{H}$'CH=CH_2), 4.67, 4.87 (2H, ABq, J_{AB} 11.2 Hz, CH_2Ph), 4.81 (1H, d, $J_{1,2}$ 11.2 Hz, H-1), 5.05 (1H, at, *J* 8 Hz, H-3), 5.19 (1H, d, J_z 10 Hz, -$OCH_2CH=H_E\underline{H}_Z$),

5.86 (1H, d, J_E 16 Hz, -$OCH_2CH=\underline{H}_EH_Z$) 6.01 (1H, m, -$OCH_2C\underline{H}=CH_2$), 6.79-7.52 (9H, m, Aromatic – H); δ_C (100 MHz, $CDCl_3$): 20.7, 20.7 (2 x q, 2 x $CO\underline{C}H_3$) 55.6 (q, -OMe), 62.5 (t, C-6), 69.6 (d, C-3), 73.8 (t, -$O\underline{C}H_2CH=CH_2$) 75.2 (t, CH_2Ph) 72.0, 81.3, 81.4 (3 x d, C-2, C-4, C-5), 102.8 (d, H-1), 114.5 (t, -$OCH_2CH=\underline{C}H_2$), 117.3-128.4 (5 x d, ArC-H), 134.7 (-$OCH_2\underline{C}H=CH_2$), 138.2, 151.3, 155.5 (3 x s, Ar-C), 169.5, 170.7 (2 x s, 2 x $\underline{C}OCH_3$); HRMS (ES^+) calculated for $C_{27}H_{32}O_9Na$ (MNa^+) 523.1938, found 523.1945.

3-*O*-Benzyl-4,6-diacetyl-2-*O*-(2-iodoethyl)-*α*/*β*-D-glucopyranose[11] **2.39**



2.37 **2.38** **2.39**

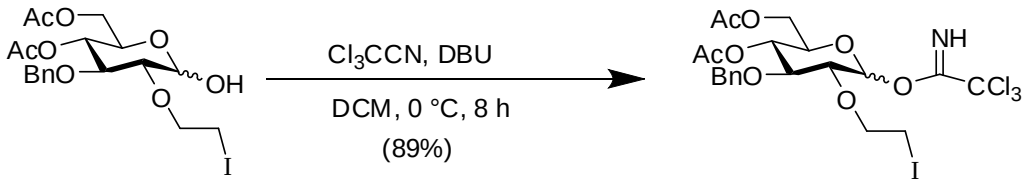
2.37 (5.00 g, 10.00 mmol) was dissolved in DCM (150 mL) under N_2 and cooled to -78 °C. Ozone was then bubbled through the solution until it turned a deep blue. The excess ozone was then removed by bubbling N_2 through the solution until the colour had dissipated. Dimethyl sulfide (3.7 mL, 50 mmol) was then added, and the solution was then allowed to warm to room temperature over an hour. The reaction was then concentrated under vacuum to remove the excess dimethyl sulfide before re-dissolving in DCM (150 mL) and acetic acid (4.0 mL, 66.0 mmol). The solution was then cooled to 0 °C and sodium cyanoborohydride (1.51 g, 24 mmol) was added portionwise before the reaction was left to stir. After 16h, t.l.c. (petrol:ethyl acetate, 1:4) showed formation of a major product (R_f 0.2), complete disappearance of starting material (R_f 0.95). The reaction was then quenched by the addition of H_2O (25 mL). Brine (100 mL) was then added and the organic layer separated before the aqueous layer was extracted with DCM (2

x 100 mL). The combined organic layers were then dried ($MgSO_4$), filtered and concentrated *in vacuo* and purified by flash column chromatography (petrol:ethyl acetate, 1:4) to afford 3-*O*-benzyl-4,6-diacetyl-2-*O*-(2-hydroxyethyl)-*α*/*β*-D-glucopyranose **2.38** (2.00 g) as a colorless oil.

The residue (**2.38**) was dissolved in THF (100 mL) under a nitrogen atmosphere. I_2 (1.92 g, 7.55 mmol), imidazole (0.514 g, 7.55 mmol) and PPh_3 (1.98 g, 7.55 mmol) were added and the mixture was heated to reflux. After 16 h, t.l.c. (petrol:ethyl acetate, 2:1) indicated the formation of a major product (R_f 0.3) and the complete consumption of starting material (R_f 0.0). The reaction was cooled to rt and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol:ethyl acetate, 5:2) to afford 3-*O*-benzyl-4,6-diacetyl-2-*O*-(2-iodoethyl)ether-*α*/*β*-D-glucopyranose **2.39** (1.00 g, 20%) as colorless oil; ν_{max} (KBr) 1744 (s, C=O); δ_H (400 MHz, $CDCl_3$) [1:1 mixture of *α*:*β* anomers observed]: 1.92, 1.93, 2.06, 2.07 (12 H, 4 x s, 2 x COC$\underline{H}_3$ *α*, 2 x COC$\underline{H}_3$ *β*), 3.03 (2H, bs, -OH *α*, -OH *β*), 3.22–3.30 (6H, m, -OH *β*, -OCH$_2$C$\underline{H}_2$I *α*, OCH$_2$C$\underline{H}_2$I *β*, H-2 *α*/*β*), 3.52-3.62 (3H, m, H-2 *α*/*β*, H-3 *α*, H-3 *β*), 3.87-4.22 (10H, m, H-6 *α*, H-6 *β*, H-6' *α*, H-6' *β*, -OC$\underline{H}_2$CH$_2$I *α*, -OC$\underline{H}_2$CH$_2$I *β*, H-4 *α*, H-4 *β*), 3.82-4.17 (5H, m, -OCH$\underline{H}$'CH$_2$I *β*, -OC$\underline{H}$H'CH$_2$I *α*, -OC$\underline{H}$H'CH$_2$I *β*, H-6' *α*, H-6' *β*), 4.63-4.88 (5H, m, C$\underline{H}_2$Ph *α*, C$\underline{H}_2$Ph *β*, H-1 *β*), 4.98-5.03 (2H, m, H-5 *α*, H-5 *β*), 5.37 (1H, d, $J_{1,2}$ 2.8 Hz, H-1 *α*), 7.25-7.35 (10 H, m, 5 x Ar-CH *α*, 5 x Ar-CH *β*); δ_C (100 MHz, $CDCl_3$): 2.9, 3.3 (2 x t, -OCH$_2$C$\underline{H}_2$I *α*, -OCH$_2$C$\underline{H}_2$I *β*), 20.7, 20.7, 20.7, 20.7 (4 x q, 2 x CO$\underline{C}$H$_3$ *α*, 2 x CO$\underline{C}$H$_3$ *β*), 62.2, 62.4 (2 x t, C-6 *α*, C-6 *β*), 68.0, 68.0 (2 x d, C-2 *α*, C-2 *β*), 69.5, 69.6 (2 x t, -O$\underline{C}$H$_2$CH$_2$I *α*, -O$\underline{C}$H$_2$CH$_2$I *β*), 75.4, 75.7 (2 x t, -$\underline{C}$H$_2$Ph *α*, -$\underline{C}$H$_2$Ph *β*), 72.1, 73.1, 78.6, 80.7, 81.3, 83.4 (6 x d, C-3 *α*, C-3 *β*, C-4 *α*, C-4 *β*, C-5 *α*, C-5 *β*), 91.2 (d, C-1 *β*), 97.4 (d, C-1 *α*), 127.7-128.4 (6 x d, 3 x Ar-CH *α*, 3 x Ar-CH *β*), 138.1, 138.1 (Ar-C *α*, Ar-C *β*), 169.6-171.4 (4C, 2 x CH$_3$$\underline{C}$O *α*, 2 x CH$_3$$\underline{C}$O *β*); HRMS ($ES^+$) calculated for $C_{19}H_{25}O_8NaI$ (MNa^+) 531.0486, found 531.0494.

3-(*O*-Benzyl-4,6-acetyl-2-*O*-(2-iodoethyl) -*α*/*β*-D-glucopyranosyl) trichloroacetimidate[12]

2.17

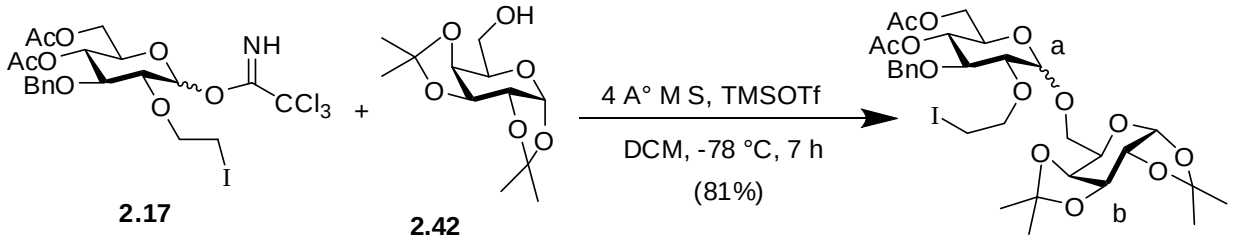


2.39 **2.17**

2.39 (0.144 g, 0.283 mmol) was dissolved in distilled DCM (3 mL) under a nitrogen atmosphere and cooled to 0 °C. DBU (0.017 mL, 0.112 mmol), and trichloroacetonitrile (0.284 mL, 2.83 mmol), were added, and the mixture was then allowed to stir. After 8 h, t.l.c. (petrol:ethyl acetate, 2:1, with 1% TEA) indicated the formation of a major product (R_f 0.5), and the complete consumption of starting material (R_f 0.1). The reaction was cooled to rt and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol:ethyl acetate, 3:1, with 1% TEA) to afford 3-(*O*-benzyl-4,6-acetyl-2-*O*-(2-iodoethyl)ether-*α*/*β*-D-glucopyranosyl) trichloroacetimidate **2.17** (0.164 g, 89%) as colorless oil; ν_{max} (KBr) 1740 (s, C=O), 1672 (s, C=N) cm^{-1}; δ_H (400 MHz, $CDCl_3$) [2:1 mixture of *α*:*β* anomers observed]: 1.93, 1.95, 2.05 (12 H, 2 x s, 2 x COC<u>H</u>$_3$ *α*, 2 x COC<u>H</u>$_3$ *β*), 3.18 (4H, m, -OCH$_2$C<u>H</u>$_2$I *α*, OCH$_2$C<u>H</u>$_2$I *β*), 3.62–4.25 (14H, m, -OC<u>H</u>$_2$CH$_2$I *α*, OC<u>H</u>$_2$CH$_2$I *β*, H-5 *α*, H-5 *β*, H-3 *α*, H-3 *β*, H-6 *α*, H-6 *β*, H-6' *α*, H-6' *β*, H-4 *α*, H-4 *β*) 4.67, 4.90 (4H, ABq, J_{AB} 11.6 Hz, C<u>H</u>$_2$Ph *α*, C<u>H</u>$_2$Ph *β*), 5.08 (2H, m, H-2 *α*, H-2 *β*), 5.73 (1H, d, $J_{1,2}$ 8 Hz, H-1 *β*), 6.53 (1H, d, $J_{1,2}$ 3.2 Hz, H-1 *α*), 7.25-7.35 (10 H, m, 5 x Ar-CH *α*, 5 x Ar-CH *β*), 8.62, 8.71 (N-H *α*, N-H *β*); δ_C (100 MHz, $CDCl_3$): 2.1, 2.2 (2 x t, -OCH$_2$<u>C</u>H$_2$I *α*, -OCH$_2$<u>C</u>H$_2$I *β*), 20.6, 20.6, 20.7, 20.7 (4 x q, 2 x CO<u>C</u>H$_3$ *α*, 2 x CO<u>C</u>H$_3$ *β*), 61.8, 61.9 (2 x t, C-6 *α*, C-6 *β*), 68.8, 69.3 (2 x d, C-2 *α*, C-2 *β*), 70.5, 71.8 (2 x t, -CH$_2$Ph *α*, -CH$_2$Ph *β*), 72.8, 73.3 (2

x t, -O<u>C</u>H$_2$CH$_2$I *α*, -O<u>C</u>H$_2$CH$_2$I *β*), 70.5, 71.8, 75.3, 77.3, 77.9, 79.9 (6 x d, C-3 *α*, C-3 *β*, C-4 *α*, C-4 *β*, C-5 *α*, C-5 *β*), 81.0, 81.3 (2 x s, <u>C</u>Cl$_3$ *α*, <u>C</u>Cl$_3$ *β*) 93.7 (d, C-1 *β*), 97.6 (d, C-1 *α*), 127.7, 127.8, 127.9, 128.0, 128.3, 128.4 (6 C, 3 x Ar-CH *α*, 3 x Ar-CH *β*), 138.1, 138.1 (Ar-C *α*, Ar-C *β*), 160.8, 160.9 (2 x s, <u>C</u>=NH *α*, <u>C</u>=NH *β*), 169.5, 169.5, 170.6, 170.6 (4 x s, 4C, 2 x CH$_3$<u>C</u>O *α*, 2 x CH$_3$<u>C</u>O *β*); HRMS (ES$^+$) calculated for $C_{21}H_{25}NO_8Cl_3INa$ (MNa^+) 673.9582, found 673.9589.

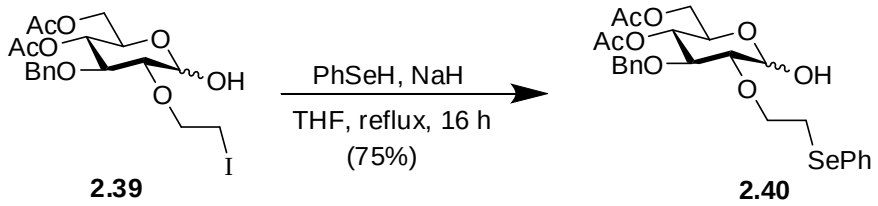
3-*O*-benzyl-4,6-diacetyl-2-*O*-(2-iodoethyl)-*α*/*β*-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside[14] **2.51**



A solution of 3-(*O*-benzyl-4,6-diacetyl-2-*O*-(2-iodoethyl)-*α*/*β*-D-glucopyranosyl) trichloroacetimidate **2.17** (0.140 g, 0.215 mmol) and 1,2:3,4–di–*O*–isopropylidene–*α*–D–galactopyranose **2.42** (0.112 g, 0.430 mmol) in freshly distilled DCM (2 mL) was added to a flame-dried round-bottom flask containing activated 4Å molecular sieves (0.100 g). The mixture was cooled to -78 °C under a nitrogen atmosphere, then TMSOTf (4.5 μL, 0.022 mmol) was added. After 7 h, t.l.c. (toluene:ethyl acetate, 3:1) showed formation of a major product (R_f 0.6) and the complete consumption of the trichloroacetimidate starting material (R_f 0.7). The reaction was quenched with saturated aq. sodium bicarbonate solution (2 mL) and filtered through Celite®. The mixture was diluted with DCM (20 mL), washed with saturated aq. sodium bicarbonate solution (2 x 10 mL), and the aqueous layer extracted with DCM (20 mL). The

combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (toluene:ethyl acetate, 6:1) to afford 3-*O*-benzyl-4,6-diacetyl-2-*O*-(2-iodoethyl)-*α*/*β*-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside **2.51** (0.130 g, 81%) as a colourless oil; δ_H (400 MHz, DMSO-D_6) [1:2 mixture of *α*:*β* anomers observed]: 1.25-1.44 (24H, m, 4 x CH_3*α*, 4 x CH_3*β*), 1.91-1.96 (12H, m, 2 x COC$\underline{H}_3$ *α*, 2 x COC$\underline{H}_3$ *β*), 3.20-3.29 (5H, m, $OCH_2C\underline{H}_2I$ *α*, $OCH_2C\underline{H}_2I$ *β*, H-5_b *α*/*β*), 3.49-3.94 (14H, m, H-2_a *α*, H-2_a *β*, H-3_a *α*, H-3_a *β*, H-4_a *α*, H-4_a *β*, H-3_b *α*, H-3_b *β*, H-5_b *α*/*β*, H-6_b *α*, H-6_b *β*, H-$6'_b$ *α*, H-$6'_b$ *β*, -OC$\underline{H}$'CH_2I *α*/*β*), 4.03-4.09 (3H, m, -OC$\underline{H}$H'CH_2I *α*, -OC$\underline{H}$H'CH_2I *β*, -OCH$\underline{H}$'CH_2I *α*/*β*), 4.20-4.33 (4H, m, H-5_a *α*, H-5_a *β*, H-4_b *α*, H-4_b *β*), 4.33-4.47 (4H, m, H-6_a *α*, H-6_a *β*, H-$6'_a$ *α*, H-$6'_a$ *β*), 4.51 (1H, d, $J_{1,2}$ 8 Hz, H-1_a *β*), 4.55-4.82 (6H, m, C$\underline{H}_2$Ph *α*, C$\underline{H}_2$Ph *β*, H-2_b *α*, H-2_b *β*), 5.01 (1H, d, $J_{1,2}$ 3.5 Hz, H-1_a *α*), 5.43 (2H, d, $J_{1,2}$ 4.8 Hz, H-1_b *α*, H-1_b *β*), 7.25-7.33 (10H, m, 5 x Ar-CH *α*, 5 x Ar-CH *β*); δ_C (100 MHz, DMSO-D_6): 5.7, 5.8 (2 x t, $OCH_2\underline{C}H_2I$ *α*, $OCH_2\underline{C}H_2I$ *β*), 20.9, 20.9, 21.0, 21.0 (4 x q, 2 x CO$\underline{C}H_3$ *α*, 2 x CO$\underline{C}H_3$ *β*), 24.6, 24.7, 24.8, 25.1, 25.2, 25.3, 26.3, 26.4 (4 x q, CH_3 *α*, 4 x q, CH_3 *β*), 62.4, 62.5 (2 x t, C-6_b *α*, C-6_b *β*), 66.2, 66.5 (2 x t, C-6_a *α*, C-6_a *β*), 67.3, 67.4 (2 x t, $O\underline{C}H_2CH_2I$ *α*, $O\underline{C}H_2CH_2I$ *β*), 69.7, 69.8 (2 x t, Ar$\underline{C}H_2$ *α*, Ar$\underline{C}H_2$ *β*), 70.1, 70.2, 70.3, 70.4, 70.5, 70.6, 70.8, 70.9, 71.0, 72.8, 74.6, 74.8, 78.5, 79.8, 80.9, 82.1 (16 x d, C-2_a *α*, C-3_a *α*, C-4_a *α*, C-5_a *α*, C-2_a *β*, C-3_a *β*, C-4_a *β*, C-5_a *β*, C-2_b *α*, C-3_b *α*, C-4_b *α*, C-5_b *α*, C-2_b *β*, C-3_b *β*, C-4_b *β*, C-5_b *β*), 96.1, 96.1 (2 X d, C-1_b *α*, C-1_b*β*) 96.6 (d, C-1_a *β*), 98.0 (d, C-1_a *α*), 108.2, 108.3, 108.7, 108.8 (4 x s, $\underline{C}(CH_3)_2$ x 2 *α*, $\underline{C}(CH_3)_2$ x 2 *β*), 127.8, 127.9, 128.1, 128.2, 128.5, 128.6 (6 x d, Ar-CH), 138.9, 139.0 (2 x s, Ar-C), 169.8, 169.8, 170.5, 170.5 (4 x s, 4C, 2 x $CH_3\underline{C}O$ *α*, 2 x $CH_3\underline{C}O$ *β*); HRMS (ES+) Calculated for $C_{34}H_{43}O_{11}INa$ (MNa+) 777.1742, found 777.1752).

3-*O*-Benzyl-4,6-diacetyl-2-*O*-(2-(phenylselenyl)ethyl)-*α*/*β*-D-glucopyranose[16] **2.40**

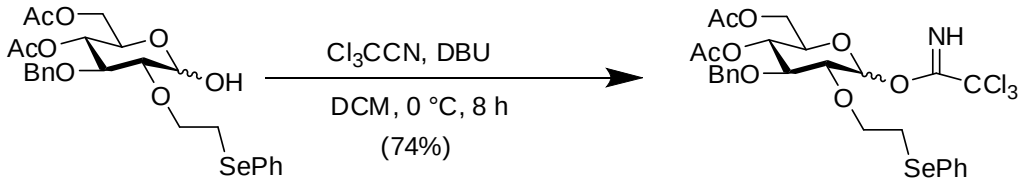


2.39 **2.40**

Selenophenol (0.140 mL, 1.30 mmol) was added to a stirred suspension of sodium hydride (0.016 g, 0.650 mmol) in THF (5 mL). After 30 min, 3-*O*-benzyl-4,6-diacetyl-2-*O*-(2-iodoethyl)-*α*/*β*-D-glucopyranose **2.39** (0.240 g, 0.470 mmol) was added as a solution in THF (5 ml) and the reaction was then heated to reflux. After 16 h, t.l.c (toluene:ethyl acetate, 2:1) indicated the formation of a single major product (R_f 0.55) and the complete consumption of starting material (R_f 0.50). The reaction was cooled and diluted with DCM (20 mL) and washed with water (20 mL). The aqueous layer was then extracted with DCM (2 x 20 mL) and the combined organic extracts were washed with saturated aq. sodium bicarbonate solution (20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford 3-*O*-benzyl-4,6-diacetyl-2-*O*-(2-(phenylselenyl)ethyl)-*α*/*β*-D-glucopyranose **2.40** (0.190 g, 75%) as colorless oil; (KBr) 1740 (s, C=O), 1672 (s, C=N) cm^{-1}; δ_H (400 MHz, $CDCl_3$) [1:1 mixture of *α*:*β* anomers observed]: 1.90-2.09 (12 H, m, 2 x COC$\underline{H}_3$ *α*, 2 x COC$\underline{H}_3$ *β*), 3.03-3.08 (4H, m, OCH_2CH_2SePh *α*, $OCH_2C\underline{H}_2SePh$ *β*), 3.14 (1H, bs, -OH *α*/-OH *β*) 3.26 (1H, at, *J* 5.0 Hz, H-2 *β*), 3.46-3.58 (3H, m, H-2 *α*, H-3 *α*, H-3 *β*), 3.48-3.58 (4H, m, H-4 *α*, H-4 *β*, H-5 *α*, H-5 *β*), 3.80-4.23 (12H, m, $OC\underline{H}_2CH_2SePh$ *α*, $OC\underline{H}_2CH_2SePh$ *β*, , H-6' *α*, H-6' *β*, H-6 *α*, H-6 *β*), 4.60-4.85 (4H, m, $PhCH_2$ *α*, $PhCH_2$ *β*), 4.97 (1H, at, *J* 9.2 Hz, H-1 *β*), 5.29 (1H, d, $J_{1,2}$ 3.3 Hz, H-1 *α*), 7.26-7.49 (20H, m, 10 x Ar-CH *α*, 10 x Ar-CH *β*); δ_C (100 MHz, $CDCl_3$): 20.7, 20.7, 20.7, 20.7 (4 x q, 2 x CO$\underline{C}H_3$ *α*, 2

x CO<u>C</u>H$_3$ *β*), 27.3, 27.6 (2 x t, OCH$_2$<u>C</u>H$_2$SePh *α*, OCH$_2$<u>C</u>H$_2$SePh *β*), 62.2, 62.4 (2 x t, C-6 *α*, C-6 *β*), 68.0, 69.4 (2 x t, C-5 *α*, C-5 *β*), 69.6, 70.7 (2 x t, O<u>C</u>H$_2$CH$_2$SePh *α*, O<u>C</u>H$_2$CH$_2$SePh *β*), 72.0, 72.1 (2 x t, CH$_2$Ph *α*, CH$_2$Ph *β*), 75.2, 75.3, 78.6, 80.7, 81.4, 83.5 (6 x d, C-2 *α*, C-2 *β*, C-3 *α*, C-3 *β*, C-4 *α*, C-4 *β*), 91.1 (d, C-1 *β*), 97.2 (d, C-1 *α*), 127.1, 127.2, 127.3, 127.5, 127.6, 127.7, 127.8, 127.9, 128.4, 129.1, 129.2, 129.3, 132.6, 132.8, 138.2, 138.3 (16 x Ar-C), 169.5, 169.6, 170.8, 170.8 (4C, 2 x CH$_3$<u>C</u>O *α*, 2 x CH$_3$<u>C</u>O *β*); HRMS (ES$^+$) calculated for $C_{25}H_{30}O_8NaSe$ (MNa$^+$) 561.0994, found 561.0998.

3-(*O*-Benzyl-4,6-diacetyl-2-*O*-(2-(phenylselenyl)ethyl)-*α*/*β*-D-glucopyranosyl) trichloroacetimidate[17] **2.18**

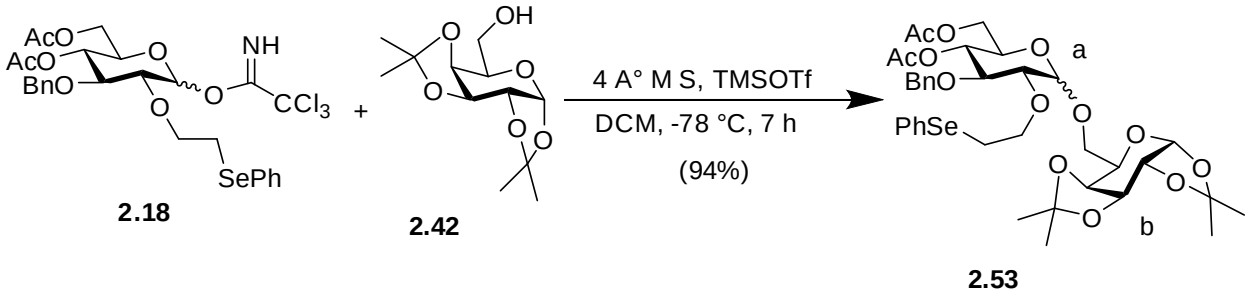


2.40 **2.18**

3-*O*-Benzyl-4,6-diacetyl-2-*O*-(2-(phenylselenyl)ethyl)-*α*/*β*-D-glucopyranose **2.40** (0.190 g, 0.353 mmol) was dissolved in distilled DCM (10 mL) under a nitrogen astmosphere. The solution was cooled to 0 °C, and DBU (0.018 mL, 0.118 mmol) and trichloroacetonitrile (0.354 mL, 3.53 mmol) were added, and the kept for stirring. After 8 h, t.l.c. (petrol:ethyl acetate, 2:1, with 1% TEA) indicated the formation of a major product (R_f 0.7) and the complete consumption of starting material (R_f 0.2). The reaction was warmed to rt and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol:ethyl acetate, 4:1, with 1% TEA) to afford 3-(*O*-benzyl-4,6-diacetyl-2-*O*-(2-(phenylselenyl)ethyl)-*α*/*β*-D-glucopyranosyl) trichloroacetimidate **2.18** (0.177 g, 74%) as colorless oil; ν_{max} (KBr) 3319 (w, N-H), 1745 (s, C=O), 1673 (s, C=N) cm^{-1}; δ_H (400 MHz, $CDCl_3$) [50:1 mixture of *α*:*β* anomers observed, major *α* anomer quoted]:

1.95, 2.04 (6H, 2 x s, 2 x COC<u>H</u>$_3$) 3.01 (2H, m, -OCH$_2$C<u>H</u>$_2$SePh), 3.67 (1H, dd, $J_{2,3}$ 9.6 Hz, $J_{1,2}$ 3.2 Hz, H-2), 3.79-3.97 (3H, m, OC<u>H</u>$_2$CH$_2$SePh, H-3), 4.04–4.21 (3H, m, H-6, H-6', H-4), 4.64, 4.87 (2H, ABq, J_{AB} 11.2 Hz, -OCH$_2$Ph), 5.09 (1H, at, *J* 10 Hz, H-5), 6.51 (1H, d, $J_{1,2}$ 3.6 Hz, H-1), 7.23–7.48 (10 H, m, Ar-CH), 8.60 (1H, s, NH); δ_C (100 MHz, $CDCl_3$): 20.6, 20.7 (2 x q, 2 x CO<u>C</u>H$_3$), 26.9 (t, -OCH$_2$<u>C</u>H$_2$SePh), 61.8 (t, C-6), 68.7 (d, C-5), 70.4, 70.6 (2 x t, <u>C</u>H$_2$Ph, -O<u>C</u>H$_2$CH$_2$SePh), 75.2 (d, C-3), 77.9 (d, C-4), 93.07 (d, C-1), 127.1, 127.7, 127.9, 128.3, 129.1, 129.7, 132.7, 138.2 (8 C, 12 x Ar-C), 161.0 (s, <u>C</u>=NH), 169.5, 170.6 (2 x s, 2 x <u>C</u>OCH$_3$); HRMS (ES^+) calculated for $C_{27}H_{30}O_8NCl_3SeNa$ (MNa^+) 704.0094, found 704.0098.

3-*O*-Benzyl-4,6-diacetyl-2-*O*-(2-(phenylselenyl)ethyl)-*α*/*β*-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside[18] **2.53**

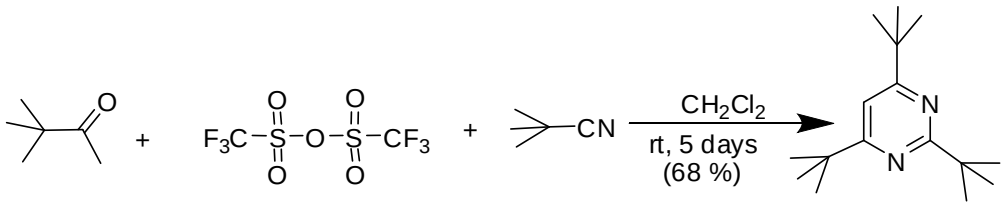


A solution of 3-(*O*-benzyl-4,6-diacetyl-2-*O*-(2-(phenylselenyl)ethyl)-*α*/*β*-D-glucopyranosyl) trichloroacetimidate **2.18** (0.130 g, 0.191 mmol) and 1,2:3,4–di–*O*–isopropylidene–*α*–D–galactopyranose **2.42** (0.100, 0.380) in freshly distilled DCM (1 mL) was added to a flame-dried round-bottom flask containing activated 4 Å molecular sieves (0.100 g). The mixture was cooled to -78 °C under a nitrogen atmosphere, then TMSOTf (1.5 μL, 0.008 mmol) was added. After 7 h, t.l.c. (toluene:ethyl acetate, 6:1) showed formation of a major product (R_f 0.5) and the

complete consumption of trichloroacetimidate starting material (R_f 0.7). The reaction was quenched with saturated aq. sodium bicarbonate solution (2 mL) and filtered through celite®. The mixture was diluted with DCM (20 mL), washed with saturated aq. sodium bicarbonate solution (2 x 10 mL), and the aqueous layer extracted with DCM (20 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 5:1) to afford 3-*O*-benzyl-4,6-diacetyl-2-*O*-(2-(phenylselenyl)ethyl)-*α*/*β*-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside **2.53** (0.140 g, 94%) as a colorless oil; δ_H (400 MHz, CD_3CN) [1:4 mixture of *α*:*β* anomers observed]: 1.32-1.53 (24H, m, 4 x CH_3 *α*, 4 x CH_3 *β*), 1.96-2.03 (12H, m, 2 x $COCH_3$ *α*, 2 x $COCH_3$ *β*), 3.10-3.14 (4H, m, OCH_2CH_2SePh *α*, OCH_2CH_2SePh *β*), 3.24 (2H, at, *J* 6.8 Hz, H-2_a *α*, H-2_a *β*), 3.93 (10H, m, H-5_b *α*, H-5_b *β*, H-6_a *α*, H-6_a *β*, H-$6'_a$ *α*, H-$6'_a$ *β*, H-6_b *α*, H-6_b *β*, H-$6'_b$ *α*, H-$6'_b$ *β*), 3.91-4.02 (7H, m, -OCH_2CH_2SePh *α*/*β*, H-3_a *α*, H-3_a *β*, H-4_a *α*, H-4_a *β*), 4.21-4.40 (5H, m, -OCH_2CH_2SePh *α*/*β*, H-5_a *β*, H-5_a *β*), 4.41-4.62 (2H, m, H-2_b *α*, H-2_b *β*), 4.71-4.78 (2H, m, H-3_b *α*, H-3_b *β*), 4.45 (1H, d, $J_{1,2}$ 8 Hz, H-1_a *β*), 4.58-4.89 (8H, m, CH_2Ph *α*, CH_2Ph *β*, H-4_b *α*, H-4_b *β*, H-5_b *α*, H-5_b *β*), 5.03 (1H, d, $J_{1,2}$ 3.5 Hz, H-1_a *α*), 5.49 (2H, d, $J_{1,2}$ 4 Hz, H-1_b *α*, H-1_b *β*), 7.27-7.53 (20H, m, 10 x Ar-CH *α*, 10 x Ar-CH *β*); δ_C (100 MHz, CD_3CN): 19.9, 19.9, 20.1, 21.1 (4 x q, 2 x $COCH_3$ *α*, 2 x $COCH_3$ *β*), 23.7, 23.8 (2 x t, OCH_2CH_2SePh *α*, OCH_2CH_2SePh *β*), 24.2, 24.3, 24.4, 25.3, 25.3, 25.4, 25.4, 26.7 (8 x q, 4 x CH_3 *α*, 4 x CH_3 *β*), 62.2, 62.2 (2 x t, OCH_2CH_2SePh *α*, OCH_2CH_2SePh *β*), 66.3, 66.8, 67.3, 67.5 (4 x t, C-6_a *α*, C-6_a *β*, C-6_b *α*, C-6_b *β*), 69.4, 69.7 (2 x d, C-2_b *α*, C-2_b *β*), 70.3, 70.4, 70.5, 70.6, 70.7, 70.9, 71.0, 71.3, 71.4, 71.8 (8 x d, C-3_a *α*, C-4_a *α*, C-5_a *α*, C-3_a *β*, C-4_a *β*, C-5_a *β*, C-3_b *α*, C-4_b *α*, C-3_b *β*, C-4_b *β*), 74.7, 74.9 (2 x t, $ArCH_2$ *α*, $ArCH_2$ *β*), 80.3, 81.2 (2 x d, C-2_a *α*, C-2_a *β*), 78.4, 82.2 (2 x d, C-5_b *α*, C-5_b *β*), 96.2 (d, C-1_a *β*), 96.5 (d, C-1_a *α*), 103.7, 103.7 (2 x d,

C-1_b *α*, C-1_b *β*), 108.4, 108.4, 108.9, 108.9 (4 x s, 2 x $\underline{C}(CH_3)_2$ *α*, 2 x $\underline{C}(CH_3)_2$ *β*), 126.6-131.7 (12 x d, Ar-CH), 131.8, 131.9, 138.7, 138.9 (4 x s, Ar-C), 169.6, 169.6, 170.3, 170.3 (4C, 2 x $CH_3\underline{C}O$ *α*, 2 x $CH_3\underline{C}O$ *β*); HRMS (ES^+) Calculated for $C_{37}H_{48}O_{13}SeNa$ (MNa^+) 803.2150, found 803.2168).

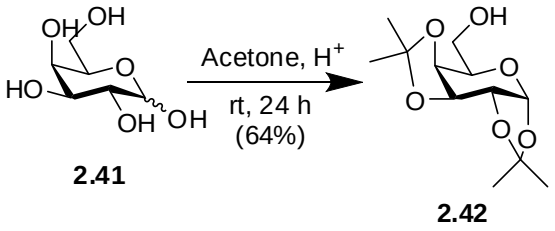
2,4,6-Tri-*tert*-butylpyrimidine[20] **2.46**



2.46

A solution of picoline (6.57 mL, 52 mmol) in DCM (10 mL) was slowly added to a solution containing Tf_2O (10.1 mL, 60 mmol) and trimethylacetonitrile (12.5 mL, 110 mol) in DCM (35 mL) at 20 °C under a nitrogen atmosphere. After stirring for 5 days, additional trimethylacetonitrile (2 mL, 18 mmol) was added. The mixture was stirred for a further 24 h, then quenched by the addition of saturated aq. sodium bicarbonate solution (10 mL), washed with brine (1 x 10 mL), dried ($MgSO_4$) and concentrated in vacuum. The residue was recrystallized (MeOH) to give 2,4,6-tri-*tert*-butylpyrimidine **2.46** (9 g, 68%) as white solid; m. p. 77 - 78 °C (MeOH) (lit. 77 - 78 °C);[20] δ_H (400 MHz, $CDCl_3$): δ_H (400 MHz, $CDCl_3$): 1.31, 1.37 (27H, 2 x s, 9 x CH_3), 7.00 (1H, s, Ar-CH).

1,2:3,4–di–*O*–isopropylidene–*α*–D–galactopyranose[21] **2.42**



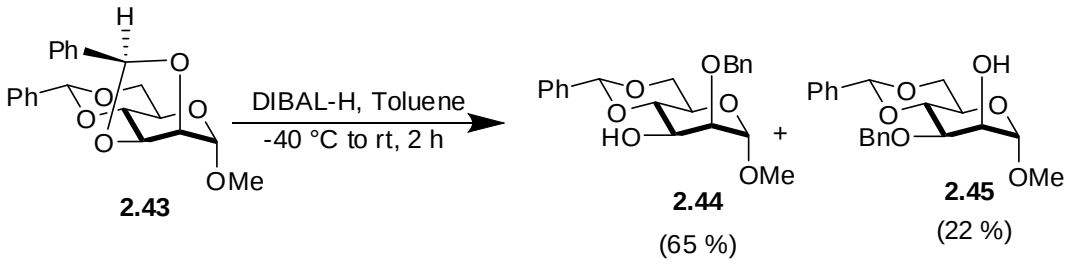
2.41 **2.42**

2.41 (20.0 g, 112 mmol) was dissolved in acetone (500 mL), in a flame dried flask containing 4 Å molecular sieves (c.a. 20g). Sulfuric acid (5.00 mL, 94 mmol) was added to the mixture and was stirred in under a nitrogen atmosphere. After 24 h, t.l.c. (petrol:ethyl acetate, 1:1) indicated the formation of a major product (R_f 0.4) and the complete consumption of starting material (R_f 0). The mixture was quenched by the addition of triethylamine (10 mL) and filtered through Celite®. Mixture was diluted with ethyl acetate (5 L) and washed with saturated aq. sodium bicarbonate solution (5 L), followed by brine solution (5 L). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography yielded 1,2:3,4–di–*O*–isopropylidene–*α*–D–galactopyranose **2.42** (18.3 g, 64%) as colourless oil; $[\alpha]_D^{20}$ -60.1 (*c*, 1.0 in $CHCl_3$), (lit.[22] $[\alpha]_D^{20}$ – 57.5 (*c*, 3.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$):[22] 1.32 (6H, s, 2 x CH_3), 1.46 (3H, s, CH_3), 1.53 (3H, s, CH_3), 3.75 (1H, t, *J* 7.5 Hz, H-4), 3.84–3.88 (2H, m, H-2, H-5), 4.27 (1H, d, *J 7.7* Hz, H-3), 4.33 (1H, dd, $J_{6,6'}$ 4.9 Hz, $J_{6,5}$ 2.3 Hz, H-6), 4.61 (1H, dd, $J_{6',5}$ 7.9 Hz, $J_{6',5}$ 2.3 Hz, H-6'), 5.57 (1H, d, $J_{1,2}$ 5.1 Hz, H-1); HRMS (ES^+) calculated for $C_{12}H_{20}O_6Na$ (MNa^+) 261.1325, found 261.1338.

Methyl-2-*O*-benzyl-4,6-di-*O*-benzylidene-*α*-D-mannopyranoside[23] **2.44**

and

Methyl-3-*O*-benzyl-4,6-di-*O*-benzylidene-*α*-D-mannopyranoside[23] **2.45**

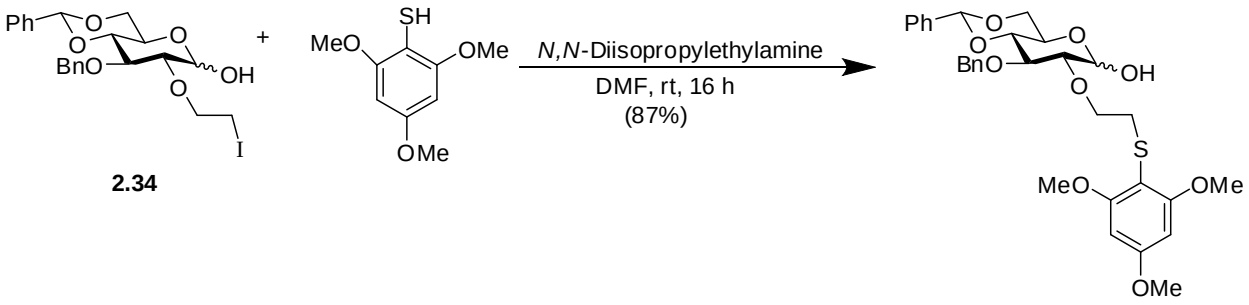


Exo-dibenzylidene methylmannopyranoside **2.43** (14.8 g, 40.0 mmol) was dissolved in freshly distilled toluene (200 mL), and cooled at – 40 °C under a nitrogen atmosphere. Di-isobutylaluminium hydride (100 mL, 100 mmoL of 1 M solution in toluene) was slowly added to the mixture and then the mixture was slowly allowed to warm to rt. After 2 h, t.l.c. (petrol:ethyl acetate, 3:1) indicated complete consumption of starting material (R_f 0.8) and formation of two products (R_f 0.4 and 0.3). Methanol was added drop wise to quench the reaction and then the reaction was diluted with DCM (350 mL). The organic layer was washed with Rochelle's salt (300 mL of 10% solution), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification with flash chromatography (petrol:ethyl acetate, 4:1) yielded methyl-2-*O*-benzyl-4,6-di-O-benzylidene-*α*-D-mannopyranoside **2.44** (9.73 g 65%), first as white crystalline solid; m. p. 44 – 46 °C (petrol/ethyl acetate) (lit.[23] 43 – 45 °C); $[\alpha]_D^{20}$ + 3.4 (*c*, 1.0 in $CHCl_3$) (lit.[23] $[\alpha]_D^{25}$ + 2.8 (*c*, 0.5 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) [23]: 3.31 (3H, s, OMe), 3.69 – 3.80 (3H, m, H-2, H-3, H-5), 3.86 (at, 1H, J 9.4 Hz, H-4), 4.05 (1H, dd, *J* 9.9 Hz, *J* 3.5 Hz, H-6), 4.23 (1H, dd, 1H, *J* 9.4 Hz, *J* 4.0 Hz, H-6'), 4.60-4.75 (3H, m, H-1, CH_2Ph), 5.57 (1H, s, CHPh), 7.26-7.50 (10H, m, Ar – H); HRMS (ES^+) calculated for $C_{21}H_{25}O_6$ (MH^+) 373.1646, found 373.1654;

followed by methyl-3-*O*-benzyl-4,6-di-*O*-benzylidene-*α*-D-mannopyranoside **2.45** (3.25 g, 22%) as colorless oil; $[\alpha]_D^{20}$ + 57.7 (*c*, 1.0 in $CHCl_3$) (lit.[23] $[\alpha]_D^{25}$ + 54.0 (*c*, 0.5 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$):[23] 2.67 (1H, bs, OH), 3.39 (3H, s, OMe), 3.79–3.93 (3H, m, H-3, H-5, H-6), 4.06 (d, 1H, *J* 3 Hz, H-2), 4.10 (1H, at, *J* 9.2 Hz, H-4), 4.29 (dd, 1H, $J_{6/6'}$ 9.5 Hz, $J_{6'/5}$ 4.1 Hz, H6'), 4.78 (1H, s, H-1), 4.72, 4.86 (2H, ABq, J_{AB} 11.6 Hz, -OCH_2Ph), 5.62 (s, 1H, PhCH), 7.27–7.53 (m, 10H, Ar – H); HRMS (ES^+) calculated for $C_{21}H_{25}O_6$ (MH^+) 373.1646, found 373.1652.

5.3 Experimental for chapter 3

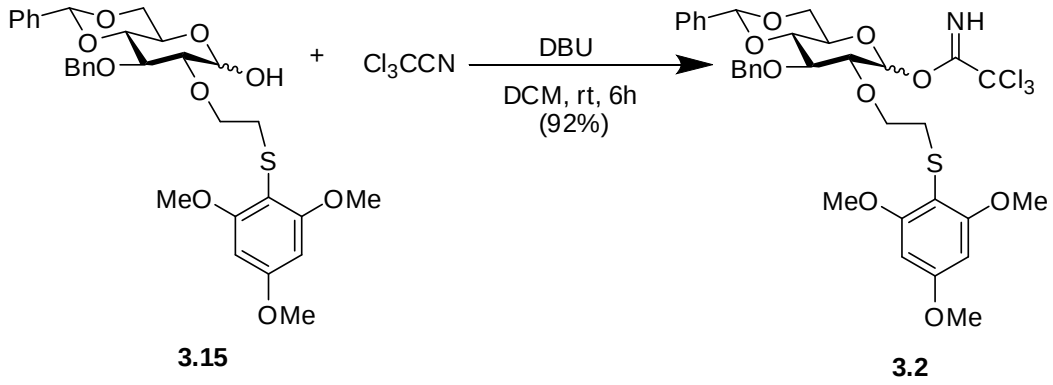
3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*/*β*-D-glucopyranose[24] **3.15**



3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2-iodoethyl)-*α*/*β*-D-glucopyranose **2.34** (300 mg, 0.59 mmol) was dissolved in DMF (10 mL) under a nitrogen atmosphere. Hünig's base (0.12 mL, 0.70 mmol) and 2,4,6-trimethoxybenzenethiol (140 mg, 0.70 mmol) were added, and the mixture was stirred at rt. After 16 h, t.l.c. (petrol:ethyl acetate, 1:1) indicated the complete consumption of starting material (R_f 0.6) and the formation of product (R_f 0.4). The solution was then concentrated *in vacuo* and the residue was purified by flash chromatography (petrol:ethyl acetate, 3:2) to afford 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-(2,4,6-

trimethoxybenzenethio)ethyl)-*α*/*β*-D-glucopyranose **3.15** (300 mg, 87%) as white amorphous solid; ν_{max} (KBr) 3408 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) [1:1 mixture of *α*:*β* anomers observed]: 2.80-3.03 (4H, m, $CH_2C\underline{H}_2SAr$ *α*, $CH_2C\underline{H}_2SAr$ *β*), 3.25 (1H, at, *J* 7.90 Hz, H-5 *α*/*β*), 3.40-3.51 (2H, m, H-2 *α*, H-2 *β*), 3.58-3.73 (9H, m, H-5 *α*/*β*, $C\underline{H}_2CH_2SAr$ *α*, $C\underline{H}_2CH_2SAr$ *β*, H-6 *α*, H-6 *β*, H-6' *α*, H-6' *β*), 3.76-3.87 (18H, m, 3 x OCH_3 *α*, 3 x OCH_3 *β*), 3.98-4.11 (2H, m, H-4 *α*, H-4 *β*), 4.30-4.41 (2H, m, H-3 *α*, H-3 *β*) 4.66-4.83 (4H, $C\underline{H}_2Ph$ *α*, $C\underline{H}_2Ph$ *β*), 4.89 (1H, d, $J_{1,2}$ 11.3 Hz, H-1 *β*), 5.32 (1H, d, $J_{1,2}$ 3.5 Hz, H-1 *α*), 5.55 (2H, s, CHPh *α*, CHPh *β*), 6.15 (4H, s, 2 x SAr-CH *α*, 2 x SAr-CH) 7.24-7.54 (20H, m, 10 x Ar-CH *α*, 10 x Ar-CH *β*); δ_C (100 MHz, $CDCl_3$): 34.6, 35.4 (2 x t, $CH_2\underline{C}H_2SAr$ *α*, $CH_2\underline{C}H_2SAr$ *β*) 55.4, 55.9, 56.1, 56.2 (4 x q, 2 x OMe *α*, 2 x OMe *β*), 62.4, 62.6 (2 x d, $\underline{C}HPh$ *α*, $\underline{C}HPh$ *β*), 69.0, 69.1 (2 x d, C-2 *α*, C-2 *β*), 69.8, 70.0 (2 x t, C-6 *α*, C-6 *β*) 70.6, 71.2 (2 x t, $\underline{C}H_2CH_2SAr$ *α*, $\underline{C}H_2CH_2SAr$ *β*), 75.0, 75.1 (2 x d, C-4 *α*, C-4 *β*), 76.7, 78.10 (2 x d, C-5 *α*, C-5 *β*), 80.8, 80.9 (2 x t, CH_2Ph, *α*, CH_2Ph *β*), 81.1, 81.6 (2 x d, $SAr\underline{C}$-H *α*, SArC-H *β*), 81.9, 90.6 (2 x d, C-3 *α*, C-3 *β*), 91.1 (d, C-1 *α*), 91.8 (d, C-1 *β*), 101.1, 101.2 (2 x d, $\underline{C}HPh$ *α*, $\underline{C}HPh$ *β*), 125.0, 126.0, 127.5, 127.6, 127.8, 127.8, 127.9, 128.1, 128.2, 128.3, 128.5, 128.6 (12 x d, 6 x $Ar\underline{C}$-H *α*, 6 x $Ar\underline{C}$-H *β*), 134.4, 135.6, 136.3, 138.7 (4 x s, 2 x $Ar\underline{C}$ *α*, 2 x $Ar\underline{C}$ *β*), 161.9 (s, $SAr\underline{C}$-OMe), 162.3 (s, $SAr\underline{C}$-OMe); HRMS (ES^+) calculated for $C_{48}H_{52}O_{11}Na$ (MNa^+) 607.1972, found 607.1972.

3-(*O*-Benzyl4,6-*O*-benzylidene-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*/*β*-D-glucopyranosyl) trichloroacetimidate[12] **3.2**

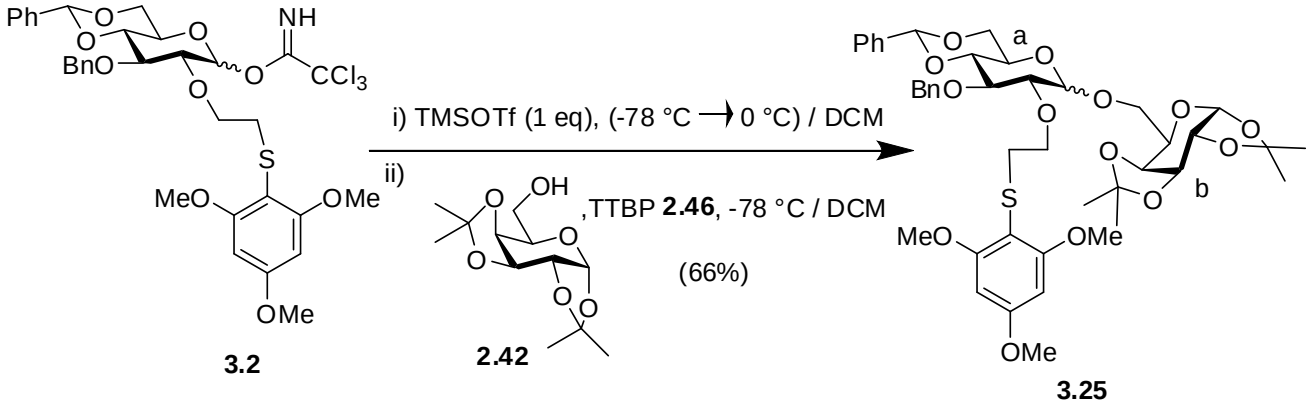


3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*/*β*-D-glucopyranose **3.15** (0.15 g, 0.26 mmol) was dissolved in distilled DCM (2.5 mL) under a nitrogen atmosphere. The solution was cooled to 0 °C, DBU (0.012 mL, 0.104 mmol) and trichloroacetonitrile (0.34 mL, 2.60 mmol) were added sequentially. After 6 h, t.l.c. (petrol:ethyl acetate, 1:1, with 1% TEA) indicated the formation of a major product (R_f 0.6) and the complete consumption of starting material (R_f 0.5). The reaction was warmed to rt and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol:ethyl acetate, 3:1, with 1% TEA) to afford 3-(*O*-benzyl4,6-*O*-benzylidene-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*/*β*-D-glucopyranosyl) trichloroacetimidate **3.2** (0.20 g, 92%) as a white amorphous solid; ν_{max} (KBr) 3350 (w, N-H), 1679 (s, C=N) cm^{-1}; δ_H (400 MHz, $CDCl_3$) [4:1 mixture of *α*:*β* anomers observed]: 2.76-2.96 (10H, m, $OCH_2C\underline{H}_2SAr$ *α*, $OCH_2C\underline{H}_2SAr$ *β*), 3.60-3.79 (20H, m, $OC\underline{H}_2CH_2SAr$ *α*, $OC\underline{H}_2CH_2SAr$ *β*, H-2 *α*, H-2 *β*, H-3 *α*, H-3 *β*, H-5 *α*, H-5 *β*, H-6 *α*, H-6 *β*), 3.79-3.92 (45H, m, 3 x OMe *α*, 3 x OMe *β*), 3.94-4.02 (5H, H-4 *α*, H-4 *β*), 4.28-4.40 (5H, m, H-6' *α*, H-6' *β*), 4.76-4.91 (10H, m, CH_2Ph *α*, CH_2Ph *β*), 5.53-5.59 (5H, m, CHPh *α*, CHPh *β*), 5.75

(1H, d, $J_{1,2}$ 7.6 Hz, H-1 *β*), 6.09-6.16 (10H, m, SArC-H *α*, SArC-H *β*), 6.47 (1H, d, $J_{1,2}$ 3.8 Hz, H-1 *α*), 7.22-7.54 (50H, m, ArC-H *α*, ArC-H *β*), 8.53-8.63 (5H, m, N-H *α*, N-H *β*); δ_C (100 MHz, $CDCl_3$): 33.6, 34.0 (2 x t, $OCH_2\underline{C}H_2SAr$ *α*, $OCH_2\underline{C}H_2SAr$ *β*), 55.3, 55.3, 56.1, 56.1 (4 x q, *o*-OMe *α*, *o*-OMe *β*, *p*-OMe *α*, *p*-OMe *β*), 65.0, 66.6 (2 x d, C-2 *α*, C-2 *β*), 68.6, 68.7 (2 x t, C-6 *α*, C-6 *β*), 71.1, 72.0 (2 x t, CH_2Ph *α*, CH_2Ph *β*), 74.8, 75.1 (2 x t, $O\underline{C}H_2CH_2SAr$ *α*, $O\underline{C}H_2CH_2SAr$ *β*), 77.7, 79.8 (2 x d, C-4 *α*, C-4 *β*) 80.4, 80.8 (2 x d, C-5 *α*, C-5 *β*), 80.9, 81.0 (2 x s, CCl_3 *α*, CCl_3 *β*), 81.2, 81.3 (2 x d, C-3 *α*, C-3 *β*), 91.0, 91.2 (2 x d, SAr$\underline{C}$-H *α*, SAr$\underline{C}$-H *β*), 94.7 (d, C-1 *α*), 98.0 (s, C-1 *β*), 101.0, 101.0 (2 x s, S$\underline{C}$Ar *α*, S$\underline{C}$Ar *β*), 101.2, 101.2 (2 x d, -CHPh *α*, -CHPh *β*), 126.0, 126.0, 127.5, 127.6, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 129.0 (12 x d, 6 x ArC-H *α*, 6 x ArC-H *β*), 137.1, 138.3, 138.6 (4 x s, 2 x ArC *α*, 2 x ArC *β*), 161.0, 161.3, 161.8, 161.9, 162.0, 162.0 (6 x s, C=NH *α*, C=NH *β*, S-ArC-OMe *o α*, S-ArC-OMe *o β*, S-ArC-OMe *p α*, S-ArC-OMe *p β*); HRMS (ES^+) calculated for $C_{33}H_{36}O_9NCl_3SNa$ (MNa^+) 750.1068, found 750.1086.

3-*O*-Benzyl4,6-*O*-benzylidene-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*/*β*-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside (Protocol B)[25]

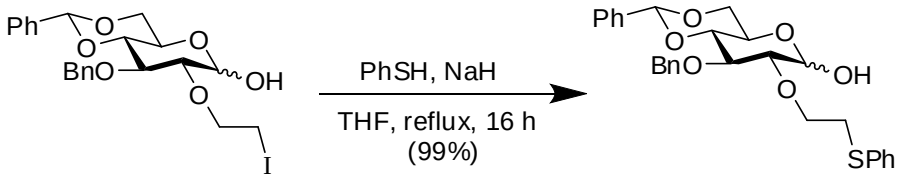
3.25



A mixture of donor 3-*O*-benzyl4,6-*O*-benzylidene-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*/*β*-D-glucopyranosyl trichloroacetimidate **3.2** (150 mg, 0.20 mmol) and activated molecular sieves (3 Å) (100 mg) was stirred in DCM (5 mL) for 10 min under a nitrogen atmosphere at rt. The mixture was then cooled to -78 °C, and TMSOTf (37 µL, 0.20 mmol) was added. The mixture was then allowed to warm to 0 °C over a period of 40 min. The mixture was again cooled to -78 °C, diacetone-D-galactose **2.42** (73 mg, 0.24 mmol) and TTBP **2.46** (100 mg, 0.40 mmol) were added. The mixture was stirred and allowed to warm slowly to rt. After 16 h, t.l.c. (petrol:ethyl acetate, 3:2) indicated the formation of a major product (R_f 0.6) and the complete consumption of donor (R_f 0.8). The reaction was quenched by the addition of saturated aq. $NaHCO_3$ (5 mL), the organic phase was separated, dried ($MgSO_4$), filtered, and was then concentrated *in vacuo*. The residue was purified by flash chromatography (petrol:ethyl acetate, 11:4) to afford 3-*O*-benzyl4,6-*O*-benzylidene-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*/*β*-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside **3.25** (0.110 g, 66%) as colorless oil; δ_H (400 MHz, $CDCl_3$) [5:1 mixture of *α*:*β* anomers observed]: 1.33-1.60 (72H, m, 4 x CH_3 *α*, 4 x CH_3 *β*), 2.80-3.02 (12 H, m, $CH_2C\underline{H}_2SAr$ *α*, $CH_2C\underline{H}_2SAr$ *β*), 3.43 (5H, dd, $J_{4,5}$ 9.2 Hz, $J_{5,6}$ 3.6 Hz, H-5_a *α*), 3.50-3.63 (8H, m, H-5_a *β*, H-4_a *α*, H-4_a *β*, H-4_b *β*), 3.63-3.86 (87H, m, 3 x OMe *α*, 3 x OMe *β*, H-4_b *α*, H-5_b *α*, H-5_b *β*, $OC\underline{H}_2CH_2SAr$ *α*, $OC\underline{H}_2CH_2SAr$ *β*, H-6_a *α*, H-6_b *α*) 3.86-4.08 (22H, m, H-2_a *α*, H-2_a *β*, H-3_a *α*, H-3_a *β*, H-3_b *α*, H-3_b *β*, H-6_a *β*, H-6_b *β*) 4.20 - 4.37 (12H, H-$6'_a$ *α*, H-$6'_a$ *β*, H-$6'_b$ *α*, H-$6'_b$), 4.47 (1H, $J_{1,2}$ 9.20 Hz, H-1_a *β*), 4.61 (6H, m, H-2_b *α*, H-2_b *β*), 4.73 - 4.85 (12H, m, CH_2Ph *α*, CH_2Ph *β*) 5.04 (5H, d, $J_{1,2}$ 3.57 Hz, H-1_a *α*), 5.46-5.58 (12H, m, CHPh *α*, CHPh *β*, H-1_b *α*, H-1_b *β*) 6.13 (12H, SArC-H *α*, SArC-H *β*), 7.19-7.52 (60H, m, ArC-H *α*, ArC-H *β*); δ_C (100 MHz, $CDCl_3$): 22.7, 24.3, 24.4, 24.5, 24.9, 25.0, 25.9, 26.0 (8 x q, 4 x CH_3 *α*, 4 x CH_3 *β*), 31.9, 34.2 (2 x t, $CH_2\underline{C}H_2SAr$ *α*, $CH_2\underline{C}H_2SAr$ *β*), 55.3, 55.3, 56.1, 56.1

(4 x q, *o*-OMe *α*, *o*-OMe *β*, *p*-OMe *α*, *p*-OMe *β*), 62.4, 62.5 (2 x t, C-6_a *α*, C-6_a *β*) 66.0, 66.2 (2 x t, C-6_b *α*, C-6_b *β*), 67.2, 67.3, 68.1, 68.8, 69.1, 69.7, 70.5, 70.6, 70.7, 70.8, 78.3, 80.5 (12 x d, C-2_a *α*, C-2_a *β*, C-3_a *α*, C-3_a *β*, 2_b *α*, C-2_b *β*, C-3_b *α*, C-3_b *β* C-4_b *α*, C-4_b *β*, C-5_b *α*, C-5_b *β*), 71.2, 71.6 (2 x t, O<u>C</u>H_2CH_2SAr *α*, O<u>C</u>H_2CH_2SAr *β*), 74.9, 75.0 (2 x t, CH_2Ph *α*, CH_2Ph *β*), 80.9, 81.1, 82.0, 82.6 (4 x d, C-4_a *α*, C-4_a *β*, C-5_a *α*, C-5_a *β*), 91.0, 91.0 (2 x d, SAr<u>C</u>-H *α*, SAr<u>C</u>-H *β*), 96.3, 96.3 (2 x d, CHPh *α*, CHPh *β*), 98.6, 98.6 (2 x d, C-1_a *α*, C-1_a *β*), 101.1, 101.2 (2 x d, C-1_b *α*, C-1_b *β*), 104.6, 104.6 (2 x s, S<u>C</u>Ar *α*, S<u>C</u>Ar *β*), 108.6, 109.2, 109.3, 109.5 (4 x s, 2 x <u>C</u>$(CH_3)_2$ *α*, 2 x <u>C</u>$(CH_3)_2$ *β*), 126.0, 126.1, 127.4, 127.5, 127.8, 128.0, 128.1, 128.1, 128.2, 128.3, 128.8, 129.0 (12 x d, 5 x ArC-H *α*, 5 x ArC-H *β*), 137.5, 138.6, 138.8, 138.9 (4 x s, 2 x ArC *α*, 2 x ArC *β*),s 161.6, 161.8, 162.0, 163.5 (4 x s, S-ArC-OMe *o α*, S-ArC-OMe *o β*, S-ArC-OMe *p α*, S-ArC-OMe *p β*); HRMS (ES^+) calculated for $C_{43}H_{54}O_{14}SNa$ (MNa^+) 849.3137, found 849.3132.

3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2-(phenylthionyl)ethyl)-*α*/*β*-D-glucopyranose[16] **3.21**

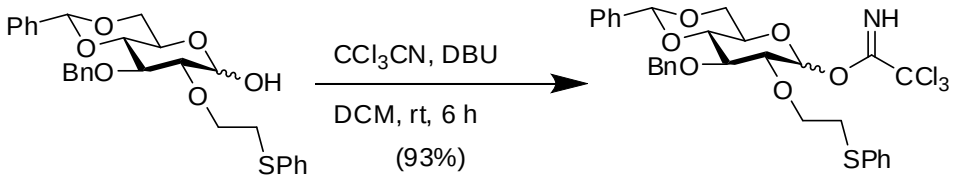


2.14 **3.21**

Thiophenol (0.117 mL, 1.15 mmol) was added to a stirred suspension of sodium hydride (0.018 g, 0.750 mmol) in THF (5 mL). After 30 min, 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-iodoethyl)-*α*/*β*-D-glucopyranose **2.14** (0.300 g, 0.590 mmol) was added as a solution in THF (5 ml) and the reaction was then heated to reflux. After 16 h, t.l.c (toluene:ethyl acetate, 2:1) indicated the formation of a single major product (R_f 0.75) and the complete consumption of starting material (R_f 0.70). The reaction was diluted with DCM (20 mL) and washed with water (20 mL). The aqueous layer was further extracted with DCM (2 x 20 mL) and the combined organic extracts

were then washed with saturated aq. sodium bicarbonate solution (20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 2:1) to afford 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-(phenylthionyl)ethyl)-*α*/*β*-D-glucopyranose **3.21** (0.290 g, 99%) as a white amorphous solid; ν_{max} (KBr) 3400 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) [1:1 mixture of *α*:*β* anomers observed]: 3.02-3.18 (4H, m, $OCH_2C\underline{H}_2SPh$ *α*, $OCH_2C\underline{H}_2SPh$ *β*), 3.21 (1H, m, H-2 *α*/*β*), 3.34-3.53 (2H, m, H-5 *α*, H-5 *β*), 3.61 (1H, m, H-2 *α*/*β*), 3.63-3.86 (6H, m, H-2 *α*, H-2 *β*, H-3 *α*, H-3 *β*, H-6 *α*, H-6 *β*), 3.86-4.08 (4H, m, $OC\underline{H}_2CH_2SPh$ *α*, $OC\underline{H}_2CH_2SPh$ *β*), 4.12 (2H, m, H-4 *α*, H-4 *β*), 4.19-4.42 (2H, m, H-6' *α*, H-6' *β*), 4.65-5.00 (5H, m, CH_2Ph *α*, CH_2Ph *β*, H-1 *β*), 5.26 (1H, d, $J_{1,2}$ 3.72 Hz, H-1 *α*), 5.54-5.62 (2H, m, CHPh *α*, CHPh *β*), 7.13-7.69 (30H, m, ArC-H); δ_C (100 MHz, $CDCl_3$): 33.9, 34.1 (2 x t, $OCH_2\underline{C}H_2SPh$ *α*, $OCH_2\underline{C}H_2SPh$ *β*), 62.5, 66.3, 68.7, 69.0 (4 x d, C-4 *α*, C-4 *β*, C-5 *α*, C-5 *β*), 70.6, 71.6 (2 x t, C-6 *α*, C-6 *β*), 80.6, 80.7 (2 x t, $O\underline{C}H_2CH_2SPh$ *α*, $O\underline{C}H_2CH_2SPh$ *β*), 81.5, 81.8 (2 x t, CH_2Ph *α*, CH_2Ph *β*), 75.0, 75.1, 78.0, 83.9 (4 x d, C-2 *α*, C-2 *β*, C-3 *α*, C-3 *β*), 91.9 (d, C-1 *β*), 97.5 (d, C-1 *α*), 101.2, 101.3 (2 x d, CHPh *α*, CHPh *β*), 126.0, 126.1, 126.4, 126.5, 127.6, 127.7, 127.9, 127.9, 128.0, 128.2, 128.3, 128.4, 128.9, 128.9, 129.0, 129.5, 129.6 (18 x d, 9 x ArC-H *α*, 9 x ArC-H *β*), 135.6, 135.7, 137.2, 137.3, 138.3, 138.5 (6 x s, 3 x Ar-C *α*, 3 x Ar-C *β*); HRMS (ES^+) Calculated for $C_{28}H_{30}O_6SNa$ (MNa^+) 517.1655, found 517.1665.

3-(*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2-(phenylthionyl)ethyl)-*α*/*β*-D-glucopyranosyl) trichloroacetimidate[17] **3.22**

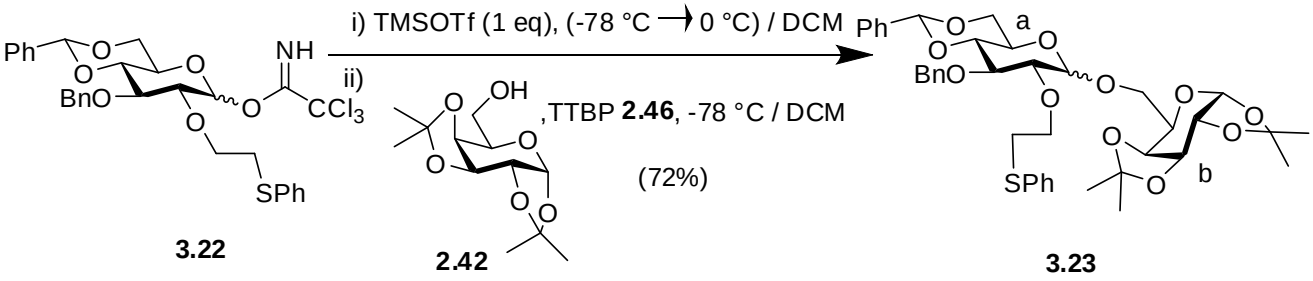


3.21 **3.22**

3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2-(phenylthionyl)ethyl)-*α*/*β*-D-glucopyranose **3.21** (0.26 g, 0.53 mmol) was dissolved in distilled DCM (2.5 mL) under a nitrogen atmosphere. The solution was cooled to 0 °C, DBU (0.025 mL, 0.220 mmol), and trichloroacetonitrile (0.36 mL, 5.30 mmol) were added sequentially. After 6 h, t.l.c. (petrol:ethyl acetate, 4:1, with 1% TEA) indicated the formation of a major product (R_f 0.5) and the complete consumption of starting material (R_f 0.2). The reaction was warmed to rt and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol:ethyl acetate, 6:1, with 1% TEA) to afford 3-(*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-(phenylthionyl)ethyl)-*α*/*β*-D-glucopyranosyl) trichloroacetimidate **3.22** (0.27 g, 93%) as colorless oil; ν_{max} (KBr) 3350 (w, N-H), 1673 (s, C=N) cm^{-1}; δ_H (400 MHz, $CDCl_3$) [3:1 mixture of *α*:*β* anomers observed]: 3.05-3.11 (8H, m, -$OCH_2C\underline{H}_2SPh$ *α*, $OCH_2C\underline{H}_2SPh$ *β*), 3.55-4.15 (28H, m, H-2 *α*, H-2 *β*, H-3 *α*, H-3 *β*, H-4 *α*, H-4 *β*, H-5 *α*, H-5 *β*, H-6 *α*, H-6 *β*, $OC\underline{H}_2CH_2SPh$ *α*, $OC\underline{H}_2CH_2SPh$ *β*), 4.32-4.36 (3H, dd, $J_{6,6'}$ 10 Hz, $J_{5,6'}$ 5.6 Hz, H-6' *α*), 4.37-4.43 (1H, dd, $J_{6,6'}$ 10 Hz, $J_{5,6'}$ 5.6 Hz, H-6' *β*), 4.81-4.96 (8H, m, CH_2Ph *α*, CH_2Ph *β*), 5.57, 5.59 (4H, 2 x s, CHPh *α*, CHPh *β*), 5.82 (1H, d, $J_{1,2}$ 8.0 Hz, H-1 *β*), 6.49 (3H, d, $J_{1,2}$ 4.0 Hz, H-1 *α*), 7.26–7.51 (60 H, m, 15 x Ar-CH *α*, 15 x Ar-CH *β*), 8.60, 8.71 (4H, 2 x s, NH *α*, NH *β*); δ_C (100 MHz, $CDCl_3$): 33.3, 33.5 (2 x t, -$OCH_2\underline{C}H_2SPh$ *α*, -$OCH_2\underline{C}H_2SPh$ *β*), 65.1, 66.6 (2 x d, C-6 *α*, C-6 *β*), 68.6, 68.7 (2 x t, -$O\underline{C}H_2CH_2SPh$ *α*, -$O\underline{C}H_2CH_2SPh$ *β*), 75.0, 75.2 (2 x t, -CH_2Ph *α*, -CH_2Ph *β*), 70.3, 72.0, 71.2, 72.8, 76.7, 77.7, 79.9, 81.3 (8 x d, C-2 *α*, C-2 *β*, C-3 *α*, C-3 *β*, C-4 *α*, C-4 *β*, C-5 *α*, C-5 *β*), 80.6, 81.0 (2 x s, $\underline{C}Cl_3$ *α*, $\underline{C}Cl_3$ *β*), 94.5 (d, C-1 *β*), 98.0 (d, C-1 *α*), 101.3, 101.3 (2 x d, -$\underline{C}HPh$ *α*, -$\underline{C}HPh$ *β*), 126.0, 126.1, 126.4, 126.5, 127.6, 127.7, 127.9, 127.9, 128.0,

128.2, 128.3, 128.4, 128.9, 128.9, 129.0, 129.5, 129.6 (18 x d, 9 x ArC-H *α*, 9 x ArC-H *β*), 135.6, 135.7, 137.2, 137.3, 138.3, 138.5 (6 x s, 3 x Ar-C *α*, 3 x Ar-C *β*), 161.2, 161.3 (2 x s, C=NH *α*, C=NH *β*); HRMS (ES^+) calculated for $C_{30}H_{30}O_6NCl_3SNa$ (MNa^+) 660.0751, found 660.0769.

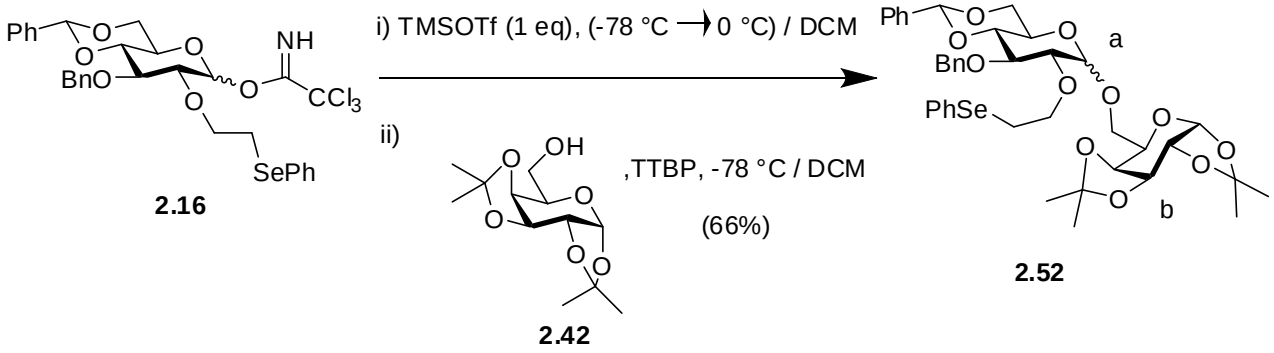
3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2-(phenylselenyl)ethyl)-*α*/*β*-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside (Protocol B)[25] 3.23



A mixture of donor 3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2-(thiophenyl)ethyl)-*α*/*β*-D-glucopyranosyl trichloroacetimidate **3.22** (100 mg, 0.17 mmol) and activated molecular sieves (4 Å) (100 mg) was stirred in DCM (5 mL) for 10 min under a nitrogen atmosphere at rt. The reaction was cooled to -78 °C, TMSOTf (32 µL, 0.17 mmol) was added, and the mixture was then allowed to warm to 0 °C over a period of 40 min. The mixture was then cooled to -78 °C, and glycosyl acceptor 1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside **2.42** (49 mg, 0.19 mmol) and TTBP (85 mg, 0.34 mmol) were added. The mixture was then allowed to warm slowly to rt. After 16 h, t.l.c. (petrol:ethyl acetate, 4:1) indicated the formation of a major product (R_f 0.3) and the complete consumption of donor (R_f 0.4). The reaction was quenched by the addition of saturated aq. $NaHCO_3$ (5 mL) and the organic phase was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol:ethyl acetate, 11:4) to afford 3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2-(thiophenyl)ethyl)-

α/*β*-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside **3.23** (0.090 g, 72%) as colorless oil; δ_H (400 MHz, CD_3CN) [3.5:1 mixture of *α*:*β* anomers observed]: 1.30-1.52 (54H, m, 4 x CH_3 *α*, 4 x CH_3 *β*), 3.12-3.18 (9H, m, $OCH_2C\underline{H}_2SPh$ *α*, $OCH_2C\underline{H}_2SPh$ *β*), 3.50 (3.5H, dd, $J_{6,6'}$ 8.2 Hz, $J_{5,6}$ 3.2 Hz H-6_b *α*), 3.59-4.08 (41.5H, m, H-2_b *α*, H-2_b *β*, H-3_b *α*, H-3_b *β*, H-4_b *α*, H-4_b *β*, H-5_b *α*, H-5_b *β*, H-6_b *β*, H-3_a *α*, H-3_a *β*, H-4_a *α*, H-4_a *β*, H-5_a *α*, H-5_a *β*, H-6_b *β*, H-6'$_b$ *α*, H-6'$_b$ *β*, H-6_a *α*), 4.21-4.38 (14.5H, m, $OC\underline{H}_2CH_2SPh$ *α*, $OC\underline{H}_2CH_2SPh$ *β*, H-6_a *β*, H-6'$_a$ *α*, H-6'$_a$ *β*), 4.50 (1H, d, $J_{1,2}$ 8.0 Hz, H-1_a *β*), 4.65 (4.5H, m, H-2_a *α*, H-2_a *β*), 4.77-4.83 (9H, m, $C\underline{H}_2Ph$ *α*, $C\underline{H}_2Ph$ *β*), 5.03 (3.5H, d, $J_{1,2}$ 3.5 Hz, H-1_a *α*), 5.49 (4.5H, m, H-1_b *α*, H-1_b *β*), 5.61 (4.5H, s, CHPh *α*, CHPh *β*), 7.18-7.56 (67.5H, m, 15 x Ar-CH *α*, 15 x Ar-CH *β*); δ_C (100 MHz, CD_3CN): 23.7, 23.8, 23.9, 24.2, 24.3, 25.4, 25.5, 25.6 (8 x q, 4 x CH_3 *α*, 4 x CH_3 *β*), 32.8, 33.0 (2 x t, $OCH_2\underline{C}H_2SPh$ *α*, $OCH_2\underline{C}H_2SPh$ *β*), 62.5, 62.5 (2 x t, C-6_a *α*, C-6_a *β*), 65.8, 66.2 (2 x t, C-6_b *α*, C-6_b *β*), 66.8, 67.2 (2 x t, $O\underline{C}H_2CH_2SPh$ *α*, $O\underline{C}H_2CH_2SPh$ *β*), 68.3, 68.6 (2 x t, $Ar\underline{C}H_2$ *α*, $Ar\underline{C}H_2$ *β*), 69.3, 69.5, 70.4, 70.5, 70.6, 70.9, 71.0, 71.3, 74.2, 74.3, 77.7, 80.4, 80.5, 80.7, 80.9, 81.5 (16 x d, C-2_a *α*, C-3_a *α*, C-4_a *α*, C-5_a *α*, C-2_a *β*, C-3_a *β*, C-4_a *β*, C-5_a *β*, C-2_b *α*, C-3_b *α*, C-4_b *α*, C-5_b *α*, C-2_b *β*, C-3_b *β*, C-4_b *β*, C-5_b *β*), , 82.6, 82.6 (2 x s, S$\underline{C}$Ar *α*, S$\underline{C}$Ar *β*), 96.3 (d, C-1_a *α*), 97.8 (d, C-1_a *β*), 100.8 (d, C-1_b *β*), 101.0 (d, C-1_b *α*), 104.4, 104.4 (d, $\underline{C}$HPh *α*, $\underline{C}$HPh *β*), 108.4, 108.4, 108.9, 108.9 (4 x s, 2 x $\underline{C}(CH_3)_2$ *α*, 2 x $\underline{C}(CH_3)_2$ *β*), 126.0, 126.5, 126.6,126.9, 127.2, 127.3 127.6, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 129.0, 129.1, 129.2, 130.4 (18 x d, Ar-CH), 132.2, 132.6, 137.3, 137.4, 138.3, 138.6 (6 x s, Ar-C); HRMS (ES^+) Calculated for $C_{40}H_{48}O_{11}SNa$ (MNa^+) 759.2809, found 759.2804.

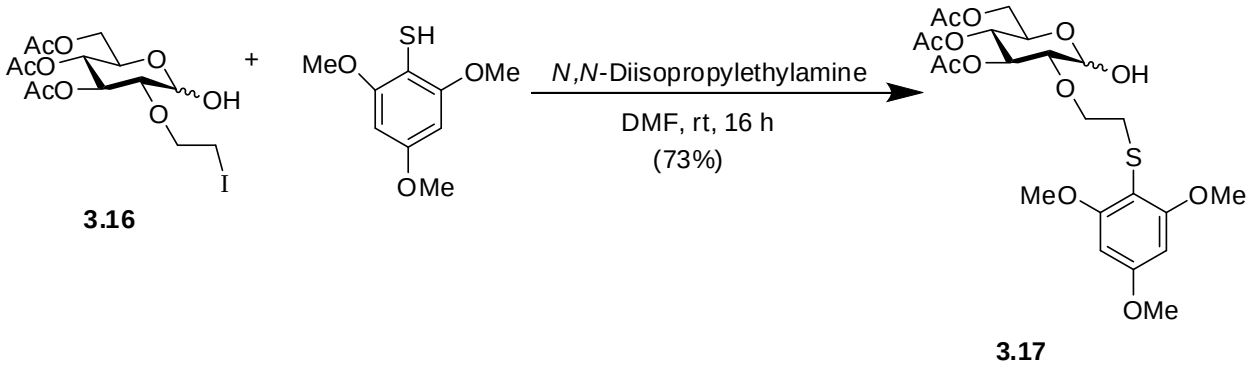
3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2-(phenylselenyl)ethyl)-*α*/*β*-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside (Protocol B):[25] **2.52**



A mixture of donor 3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2-(phenylselenyl)ethyl)-*α*/*β*-D-glucopyranosyl trichloroacetimidate **3.22** (100 mg, 0.17 mmol) and activated molecular sieves (4 Å) (100 mg) was stirred in DCM (5 mL) for 10 min under a nitrogen atmosphere at rt. The reaction was cooled to -78 °C, TMSOTf (32 µL, 0.17 mmol) was added, and the mixture was then allowed to warm to 0 °C over a period of 40 min. The mixture was then cooled to -78 °C, and glycosyl acceptor 1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside **2.42** (49 mg, 0.19 mmol) and TTBP (85 mg, 0.34 mmol) were added. The mixture was then allowed to warm slowly to rt. After 16 h, t.l.c. (petrol:ethyl acetate, 4:1) indicated the formation of a major product (R_f 0.3) and the complete consumption of donor (R_f 0.4). The reaction was quenched by the addition of saturated aq. $NaHCO_3$ (5 mL) and the organic phase was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol:ethyl acetate, 11:4) to afford 3-*O*-Benzyl-4,6-*O*-benzylidene-2-*O*-(2-(phenylselenyl)ethyl)-*α*/*β*-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside **2.52** (0.088 g, 66%) as colorless oil; δ_H (400 MHz, $CDCl_3$) [3.5:1 mixture of *α*:*β* anomers observed]: 1.34 (12H, m, 2 x CH_3 *α*, 2 x CH_3 *β*), 1.46, 1.47, 1.53, 1.55 (12H, 4 x s, 2 x CH_3 *α*, 2 x CH_3 *β*), 3.06-3.18 (5H, m, $OCH_2C\underline{H}_2$SePh *α*, $OCH_2C\underline{H}_2$SePh *β*, H-5_b *α*), 3.40 (1H, m, H-5_b *β*), 3.53 (1H, m, H-5_a *α*), 3.49 (1H, dd, $J_{6,6'}$ 8.2 Hz, $J_{5,6}$ 3.2 Hz H-6_b *α*), 3.58-3.82 (8H, m, H-2_a *α*, H-2_a *β*, H-5_a *β*, H-2_b *α*, H-4_b *α*, H-4_b *β*, H-5_b *α*, H-5_b *β*), 3.84-4.13 (7H, m, H-2_a *α*, H-

2_a *β*, H-3_a *α*, H-3_a *β*, H-4_a *α*, H-4_b *β*, H-6_b *β*), 4.16-4.24 (4H, m, OC<u>H</u>$_2$CH$_2$SePh *α*/*β*, H-6_a *α*/*β* H-6'$_a$ *α*, H-6'$_a$ *β*), 4.33-4.47 (3H, m, OC<u>H</u>$_2$CH$_2$SePh *α*/*β*, H-6_a *α*/*β*), 4.48 (1H, d, $J_{1,2}$ 8 Hz, H-1_a *β*), 4.61 (2H, m, H-6'$_b$ *α*, H-6'$_b$), 4.80-4.88 (4H, m, C<u>H</u>$_2$Ph *α*, C<u>H</u>$_2$Ph *β*), 5.02 (1H, d, $J_{1,2}$ 3.5 Hz, H-1_a *α*), 5.53 (4H, s, CHPh *α*, CHPh *β*, H-1_b *α*, H-1_b *β*), 7.27-7.50 (30H, m, 15 x Ar-CH *α*, 15 x Ar-CH *β*).

3,4,6-Triacetyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*/*β*-D-glucopyranose[24] **3.17**

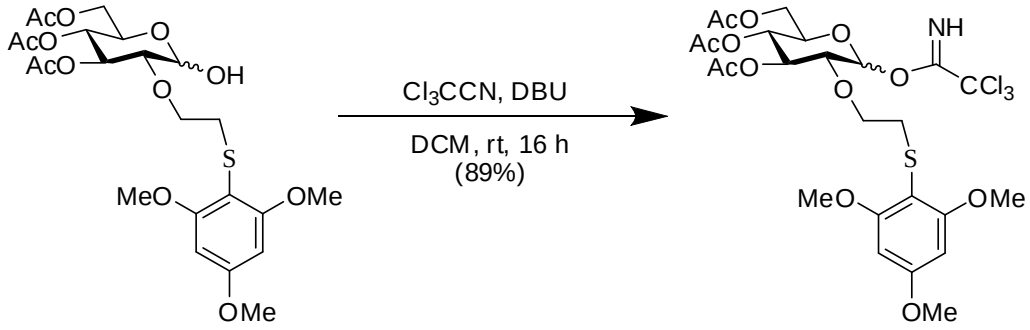


3.16 **3.17**

3,4,6-Tri-*O*-acetyl-2-*O*-(2-iodoethyl)-*α*/*β*-D-glucopyranose **3.16** (345 mg, 0.75 mmol) was dissolved in DMF (10 mL)) under a nitrogen atmosphere. Hünig's base (0.16 mL, 0.90 mmol) and 2,4,6-trimethoxybenzenethiol (180 mg, 0.90 mmol) were added, and the mixture was stirred at rt. After 16 h, t.l.c. (toluene:ethyl acetate, 1:1) indicated the complete consumption of starting material (R_f 0.6) and the formation of a major product (R_f 0.4). The solution was then concentrated *in vacuo* and the residue obtained was purified by flash chromatography (petrol:ethyl acetate, 3:2) to afford 3,4,6-triacetyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*/*β*-D-glucopyranose **3.17** (290 mg, 73.0%) as white amorphous solid; ν_{max} (KBr) 1740 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) [2:1 mixture of *α*:*β* anomers observed]: 2.00, 2.07 (27H, 2 x s, 3 x $COCH_3$ *α*, 3 x $COCH_3$ *β*), 2.73-3.00 (6H, m, $CH_2C\underline{H}_2SAr$ *α*, $CH_2C\underline{H}_2SAr$ *β*), 3.33 (1H, at, *J* 7.90

Hz, H-2 *β*), 3.43 - 3.52 (2H, m, H-2 *α*), 3.52 - 3.59 (3H, H-5 *α*, H-5 *β*), 3.64-3.93 (32H, m, C$\underline{H}_2$CH$_2$SAr *α*, C$\underline{H}_2$CH$_2$SAr *β*, 3 x OCH$_3$ *α*, 3 x OCH$_3$ *β*), 4.02-4.18 (3H, m, H-6 *α*, H-6 *β*), 4.19-4.35 (3H, H-6' *α*, H-6' *β*), 4.73 (1H, d, $J_{1,2}$ 7.63 Hz, H-1 *β*), 4.88 - 5.02 (3H, m, H-4 *α*, H-4 *β*), 5.05 - 5.16 (1H, H-3 *β*), 5.25 - 5.42 (4H, m, H-1 *α*, H-3 *α*), 6.07 - 6.21 (6H, m, ArC-H *α*, ArC-H *β*); δ_C (100 MHz, $CDCl_3$): 20.6, 20.6, 20.7, 20.7, 20.8, 20.8 (6 x q, 3 x CO$\underline{C}$H$_3$ *α*, 3 x CO$\underline{C}$H$_3$ *β*), 34.4, 35.3 (2 x t, OCH$_2\underline{C}$H$_2$SAr *α*, OCH$_2\underline{C}$H$_2$SAr *β*), 55.4, 55.4, 56.1, 56.1 (4 x q, 2 x OMe *α*, 2 x OMe *β*), 62.0, 62.2 (2 x t, C-6), 67.6 (d, C-5 *α*), 68.3, 68.3 (d, C-4 *α*, C-4 *β*), 68.7 (t, O$\underline{C}$H$_2$CH$_2$SAr *α*/*β*), 70.3 (d, C-3 *α*), 71.8 (d, C-5 *β*), 71.9 (t, O$\underline{C}$H$_2$CH$_2$SAr *α*/*β*), 74.8 (d, C-3 *β*), 78.4 (d, C-2 *α*), 81.8 (d, C-2 *β*), 90.9 (d, C-1 *α*), 91.1, 91.2 (2 x d, SAr$\underline{C}$-H *α*, SArC-H *β*), 96.9 (d, C-1 *β*), 161.9, 161.9, 162.0, 162.0 (4 x s, S-ArC-OMe *o α*, S-ArC-OMe *o β*, S-ArC-OMe *p α*, S-ArC-OMe *p β*), 169.8, 169.9, 170.0, 170.3, 170.3, 170.9, 170.9 (6 x s, 3 x C=O *α*, 3 x C=O *β*); HRMS (ES$^+$) calculated for $C_{23}H_{32}O_{12}SNa$ (MNa^+) 555.1506, found 555.1517.

3,4,6-Triacetyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*/*β*-D-glucopyranosyl) trichloroacetimidate[12] **3.3**

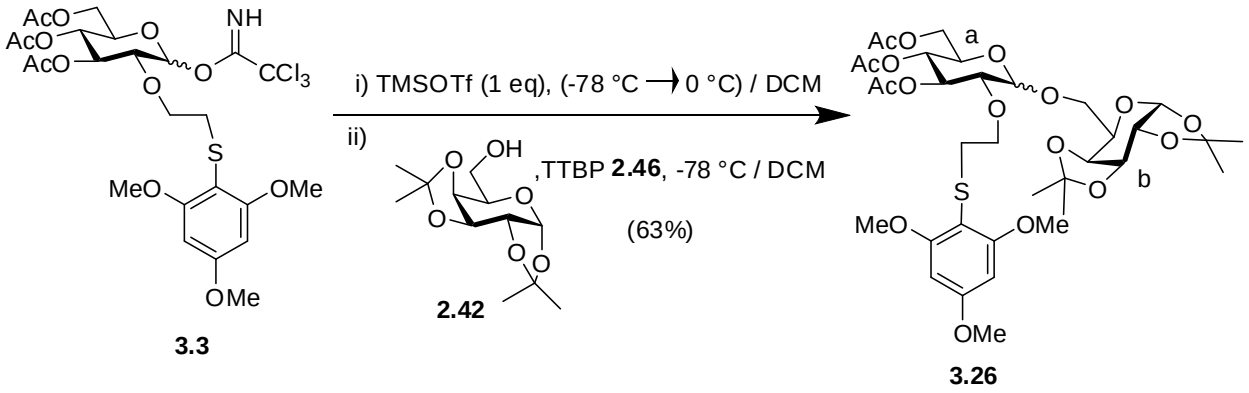


3.17 **3.3**

3,4,6-Triacetyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*/*β*-D-glucopyranose **3.17** (125 mg, 0.235 mmol) was dissolved in DCM (10 mL) under a nitrogen atmosphere. Trichloroacetonitrile (0.16 mL, 2.35 mmol) and DBU (0.011 mL, 0.094 mmol) were added, and the reaction was

stirred at 0 °C. After 6 h, t.l.c. (petrol:ethyl acetate, 4:1, with 1% TEA) indicated the formation of a major product (R_f 0.5) and the complete consumption of starting material (R_f 0.2). The reaction was warmed to rt and concentrated *in vacuo* and the residue was purified by flash chromatography (petrol:ethyl acetate, 6:1, with 1% TEA) to afford 3,4,6-triacetyl-2-*O*-(2-(phenylthionyl)ethyl)-*α*/*β*-D-glucopyranosyl) trichloroacetimidate **3.3** (127 g, 89%) as colorless oil; ν_{max} (KBr) 1748 (s, C=O), 1674 (s, C=NH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) [mixture of *α*:*β* anomers observed, major *α* anomer quoted] 2.00-2.07 (9H, m, 3 x C(O)C$\underline{H}_3$), 2.72-2.82 (2H, m, $OCH_2C\underline{H}_2SAr$), 3.56-3.61 (2H, m, $OC\underline{H}_2CH_2SAr$), 3.73 (1H, dd, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 10.0 Hz, H-2), 3.83, 3.86 (9H, 2 x s, 3 x OCH_3), 4.06-4.19 (2H, m, H-5, H-6), 4.25 (1H, dd, $J_{6,6'}$ 12.4, $J_{5,6'}$ 4.4 Hz, H-6'), 5.09 (1H, m, H-4), 5.38 (1H, at, *J* 10.0 Hz, H-3), 6.14 (2H, d, SArC-H), 6.52 (1H, d, $J_{1,2}$ 3.2 Hz, H-1), 8.58 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 20.5, 20.6, 20.7 (3 x q, 3 x C(O)$\underline{C}H_3$), 33.8 (t, $OCH_2\underline{C}H_2SAr$), 55.4, 56.1 (2 x q, 2 x OMe), 61.6 (t, C-6), 67.9 (d, C-4), 69.9 (d, C-5), 70.8 (t, $O\underline{C}H_2CH_2SAr$), 71.6 (d, C-3), 75.2 (s, OC(NH)$\underline{C}Cl_3$), 76.6 (d, C-2), 91.0 (d, SAr$\underline{C}$-H), 93.6 (d, C-1), 161.0 (s, C=NH), 161.9, 162.0 (2 x s, S-ArC-OMe *o*, S-ArC-OMe *p*), 162.0 (s, SArC-OMe), 170.0, 170.1, 170.5 (3 x s, 3 x C=O); HRMS (ES^+) calculated for $C_{25}H_{32}Cl_3NO_{12}SNa$ (MNa^+) 698.0602, found 698.0619.

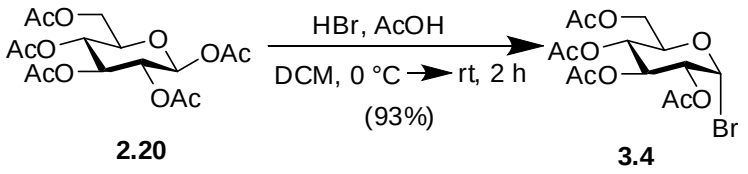
3,4,6-Triacetyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*/*β*-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside (Protocol B)[25] 3.26



A mixture of donor afford 3,4,6-triacetyl-2-*O*-(2-(phenylthionyl)ethyl)-*α*/*β*-D-glucopyranosyl) trichloroacetimidate **3.3** (80 mg, 0.12 mmol) and activated molecular sieves (3 Å) (100 mg) was stirred in DCM (5 mL) for 10 min under a nitrogen atmosphere at rt. The reaction was then cooled to -78 °C, TMSOTf (22 µL, 0.12 mmol) was added, and the mixture was then allowed to warm to 0 °C over a period of 40 min. The mixture was then cooled to -78 °C, and glycosyl acceptor 1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside **2.42** (44 mg, 0.14 mmol) and TTBP **2.46** (60 mg, 0.24 mmol) were added. The mixture was then allowed to warm slowly to rt. After 16 h, t.l.c. (petrol:diethyl ether, 1:2) indicated the formation of a major product (R_f 0.4) and the complete consumption of donor (R_f 0.8). The reaction was quenched by addition of saturated aq. $NaHCO_3$ (5 mL), and the organic phase was separated, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol:diethyl ether, 2:3) to afford 3,4,6-triacetyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*/*β*-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside **3.26** (0.058 g, 63%) as colorless oil; δ_H (400 MHz, $CDCl_3$) [3.5:1 mixture of *α*:*β* anomers observed]: 1.29, 1.30, 1.32, 1.33, 1.42, 1.44, 1.48, 1.54 (60H, 8 x s, 4 x CH_3 *α*, 4 x CH_3 *β*), 1.98, 1.99, 2.00, 2.01, 2.06, 2.07 (54H, 6 x s, 3 x C(O)C$\underline{H}_3$ *α*, 3 x C(O)C$\underline{H}_3$ *β*), 2.72-2.84 (9H, m, $OCH_2C\underline{H}_2SAr$ *α*, $OCH_2C\underline{H}_2SAr$ *β*), 3.28 (1H, at, *J* 8.0 Hz, H-

$2_a\,\beta$), 3.49 (3.5H, dd, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 10.0 Hz, H-$2_a\,\alpha$), 3.52-3.80 (14.5H, m, H-$4_b\,\alpha$, H-$4_b\,\beta$, H-5_b α, H-$5_b\,\beta$, H-$5_a\,\beta$, H-$6_b\,\alpha$, H-$6_b\,\beta$), 3.81-3.85 (40.5H, m, 3 x OMe α, 3 x OMe β), 3.98-4.12 (17H, m, H-$5_b\,\alpha$, H-$5_b\,\beta$, H-$5_a\,\alpha$, H-$6'_b\,\alpha$, H-$6'_b\,\beta$, H-$6_a\,\alpha$, H-$6_a\,\beta$), 4.18-4.32 (18H, m, O$\underline{C}$H$_2$CH$_2$SAr α, O$\underline{C}$H$_2$CH$_2$SAr β, H-$2_b\,\alpha$, H-$2_b\,\beta$, H-$6'_a\,\alpha$, H-$6'_a\,\beta$), 4.45 (1H, d, $J_{1,2}$ 8.0 Hz, H-$1_a\,\beta$), 4.57-4.61 (4.5H, m, H-$3_b\,\alpha$, H-$3_b\,\beta$), 4.96-5.01 (4.5H, m, H-$4_a\,\alpha$, H-$4_a\,\beta$), 5.05 (1H, d, $J_{1,2}$ 3.6 Hz, H-$1_a\,\alpha$), 5.10 (1H, m, H-$3_a\,\beta$), 5.36 (3.5H, at, J 9.6 Hz, H-$3_a\,\alpha$), 5.49-5.51 (4.5H, m, H-$1_b\,\alpha$, H-$1_b\,\beta$), 6.18 (9H, m, 2 x SArCH α, 2 x SArC-H β); δ_C (100 MHz, $CDCl_3$) 20.6, 20.7, 20.7, 20.8, 20.8, 20.9 (6 x q, 3 x C(O)$\underline{C}$H$_3$ α, 3 x C(O)$\underline{C}$H$_3$ β), 24.3, 24.4, 24.5, 24.5, 25.0, 25.9, 26.0, 26.1 (8 x q, 4 x (C)$\underline{C}$H$_3$ α, 4 x (C)$\underline{C}$H$_3$ β), 33.9 (t, OCH$_2\underline{C}$H$_2$SAr α), 34.0 (t, OCH$_2\underline{C}$H$_2$SAr β), 55.3, 55.4, 56.0, 56.1 (4 x q, 2 x OMe α, 2 x OMe β), 62.1 (t, C-$6_a\,\alpha$), 62.2 (t, C-$6_a\,\beta$), 66.5 (d, C-$5_a\,\alpha$), 67.2 (d, C-$5_b\,\alpha$), 67.4 (d, C-$5_b\,\beta$), 67.8 (t, O$\underline{C}$H$_2$CH$_2$SAr), 68.6 (d, C-$4_a\,\alpha$), 68.6 (d, C-$4_a\,\beta$), 69.6 (t, C-$6_b\,\alpha$), 70.4 (t, C-$6_b\,\beta$), 70.5 (d, C-$2_b\,\alpha$), 70.6 (d, C-$2_b\,\beta$), 70.7 (d, C-$3_b\,\beta$), 70.8 (d, C-$3_b\,\alpha$), 71.2, 71.2 (2 x d, C-$4_b\,\alpha$, C-$4_b\,\beta$), 71.5 (d, C-$5_a\,\beta$), 72.0 (d, C-$3_a\,\alpha$), 73.9 (t, O$\underline{C}$H$_2$CH$_2$SAr), 76.7 (d, C-$3_a\,\beta$), 78.2 (d, C-$2_a\,\alpha$), 79.5 (d, C-$2_a\,\beta$), 91.0, 91.1 (2 x d, SAr$\underline{C}$-H α, SArC-H β), 96.2 (d, C-$1_b\,\alpha$), 96.4 (d, C-$1_b\,\beta$), 97.6 (d, C-$1_a\,\alpha$), 100.8, 100.8 (2 x s, S$\underline{C}$Ar α, S$\underline{C}$Ar β), 104.0 (d, C-$1_a\,\beta$), 108.8, 108.9, 109.4, 109.6 (4 x s, 2 x ($\underline{C}$)CH$_3$ α, 2 x ($\underline{C}$)CH$_3$ β), 126.9, 127.3, 129.2, 129.3, 129.7, 130.4, 132.5, 132.9 (8 x ArC), 161.6, 161.8, 161.9, 162.0 (4 x s, S-ArC-OMe *o* α, S-ArC-OMe *o* β, S-ArC-OMe *p* α, S-ArC-OMe *p* β), 169.9 (s, C=O), 170.0 (s, C=O), 170.3 (s, C=O), 170.3 (s, C=O), 170.8 (s, C=O), 170.9 (s, C=O); HRMS (ES^+) calculated for $C_{35}H_{50}O_{17}SNa$ (MNa^+) 797.2660, found 797.2669.

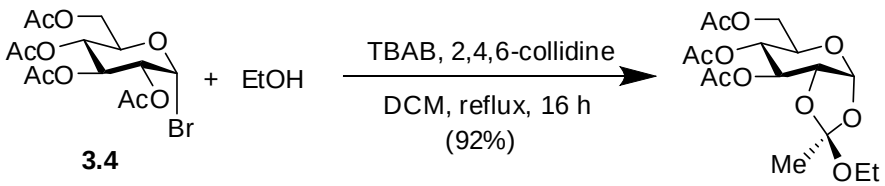
2,3,4,6-Tetra-*O*-acetyl-1-α-D-glucopyranosyl bromide[26] **3.4**



2.20 **3.4**

2.20 (10.0 g, 25.6 mmol) was dissolved in DCM (20 mL) and cooled to 0 °C under a nitrogen atmosphere. HBr (33% in AcOH, 20 mL) was added dropwise and the reaction was then allowed to warm to rt and then stirred for 2 h, after which t.l.c. (petrol:ethyl acetate, 2:1) showed complete consumption of starting material (R_f 0.2), and formation of a major product (R_f 0.3). The mixture was poured into ice-water (50 mL) and the flask was washed with DCM (200 mL). The organic layer was separated and washed with saturated aq. sodium bicarbonate solution (6 x 50 mL) until no effervescence occurs. The organic layer was washed with water, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was recrystallized (petrol/diethyl ther) to give 2,3,4,6-tetra-*O*-acetyl-1-*α*-D-glucopyranosyl bromide **3.4** (9.75 g, 93%) as white crystalline solid; m. p. 85 - 86 °C (petrol/diethyl ether) (lit.[26] 88 – 89 °C); δ_H (400 MHz, $CDCl_3$):[3] 2.01-2.09 (12H, m, 4 x CH_3CO_2), 4.11 (1H, m, H-6), 4.27-4.235 (2H, m, H-4, H-6'), 4.81-4.85 (1H, m, H-5), 5.18 (1H, m, H-2), 5.55 (1H, at, *J* 10.0 Hz, H-3), 5.20 (1H, d, $J_{1,2}$ 3.6 Hz, H-1).

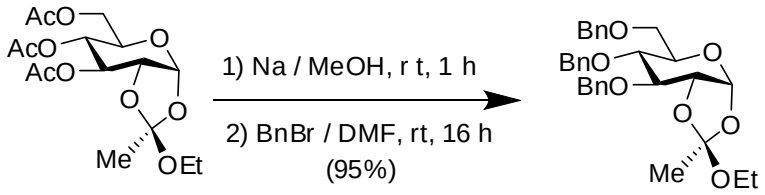
3,4,6-Tri-*O*-acetyl-1,2-*O*-(exo-ethoxyethylidine)-*α*-D-glucopyranoside[27] **3.5**



3.4 **3.5**

2,3,4,6-Tetra-*O*-acetyl-*α*-D-glucopyranosyl bromide **3.4** (52.5 g, 127.7 mmol) and tetra-*N*-butylammonium bromide (4.1 g, 12.8 mmol) were dissolved in freshly distilled DCM (300 ml). Ethanol (14.9 ml, 166.0 mmol) and 2,4,6-collidine (21.9 ml, 255 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 DCM (2 x 150 ml). The combined organic extracts were washed with saturated aq. sodium bicarbonate solution (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 **3.5** (44.1 g, 92%) as a white crystalline solid; m. p. 95 – 96 °C (petrol/ethyl acetate) (lit.[27] 95 – 96 °C); $[\alpha]_D^{20}$ + 38.4 (*c*, 1.0 in $CHCl_3$), lit.[27] $[\alpha]_D^{20}$ + 34.0 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$):[27] 1.18 (3H, t, *J* 7.1 Hz, CH_3CH_2) 1.72 (3H, s, CH_3), 2.09, 2.10, 2.11 (9H, 3 x s, 3 x $COCH_3$), 3.54 (2H, q, *J* 7.1 Hz, CH_3CH_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).

3,4,6-Tri-*O*-benzyl-1,2-*O*-(exo-ethoxyethylidine)-*α*-D-glucopyranoside[28] **3.6**

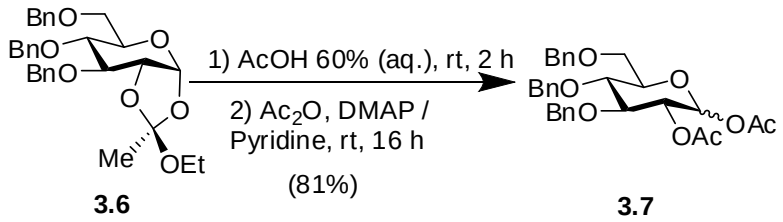


3.5 **3.6**

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 **3.5** (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 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 a nitrogen atmosphere. Benzyl bromide (14.9 ml, 125.0 mmol) was then added slowly and the reaction mixture was then allowed to warm to rt. 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 and the reaction mixture was then concentrated *in vacuo*. The residue was dissolved in ether (200 ml), washed with water (500 ml), and the aqueous layer was re-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 (petrol:ethyl acetate, 5:1) to afford 3,4,6-tri-*O*-benzyl-1,2-*O*-(exo-ethoxyethylidine)-*α*-D-glucopyranoside **3.6** (13.9 g, 95%) as a pale yellow oil; $[\alpha]_D^{20}$ + 34.8 (*c*, 1.0 in $CHCl_3$), lit.[28] $[\alpha]_D^{20}$ + 35.8 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$):[28] 1.26 (3H, t, *J* 7.1 Hz, CH_3CH_2) 1.73 (3H, s, CH_3), 3.57-3.64 (2H, m, CH_3CH_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, PhCHH'), 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, PhCHH'), 4.62-4.68 (3H, m, 3 x PhCHH'), 4.77 (1H, d, *J* 11.9, PhCHH'), 5.84 (1H, d, *J*1,2 5.3 Hz, H-1), 7.21-7.48 (15H, m, 15 x ArC-H).

1,2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-*α*,*β*-D-glucopyranoside[29] **3.7**

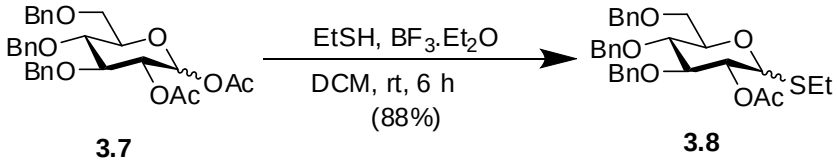


3.6 **3.7**

3,4,6-Tri-*O*-benzyl-1,2-*O*-(exo-ethoxyethylidine)-*α*-D-glucopyranoside **3.6** (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 750 mL toluene and left under high vacuum for 2 h. The residue and DMAP (0.34 g, 2.79 mmol) were dissolved in anhydrous pyridine (100 ml) and the mixture was then cooled to 0 °C under a nitrogen atmosphere. Acetic anhydride (5.27 ml, 55.8 mmol) was then added slowly and the reaction was then 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 mixture was cooled to 0 °C, quenched by the addition of ethanol (75 ml) and concentrated *in vacuo*. The residue was dissolved in ether (100 ml) and washed with 1M HCl (100 ml), saturated aq. sodium bicarbonate (100 ml), brine (100 ml). The organic extracts were 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 **3.7** (12.0 g, 81%) as a pale yellow oil; δ_H (400 MHz, $CDCl_3$)[29] [13:1 mixture of *α*:*β* anomers observed, major *α* anomer quoted] 2.00, 2.14 (6H, 2 x s, 2 x 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, PhCHH'), 4.52-4.67 (3H, m, 1 x PhCHH', 2 x PhCHH'), 4.79, 4.88 (2H, ABq, J_{AB} 11.4,

$PhCH_2$), 4.85 (1H, d, *J* 10.6, PhCHH'), 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 x ArC-H).

Ethyl 2-*O*-acetyl-3-4-6-tri-*O*-benzyl-1-thio-*α*/*β*-D-glucopyranoside[30] **3.8**

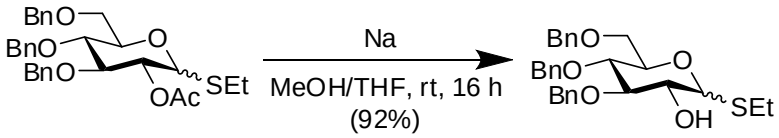


3.7 **3.8**

1,2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-*α*,*β*-D-glucopyranoside **3.7** (4.00 g, 7.50 mmol) was dissolved in freshly distilled DCM (80 ml) under a nitrogen atmosphere. Ethanethiol (0.810 ml, 11.2 mmol) was added and the mixture then cooled to 0 °C. $BF_3.Et_2O$ (1.30 ml, 9.75 mmol) was added dropwise and the mixture was then 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). 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 DCM (250 ml) and washed with saturated aq. sodium bicarbonate (100 ml), water (100 ml), and brine (100 ml). The organic phase extracts were 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-*α*/*β*-D-glucopyranoside **3.8** (3.54 g, 88%) as pale yellow oil. δ_H (400 MHz, $CDCl_3$)[30] [1:5 mixture of *α*:*β* anomers observed, major *β* anomer quoted] 1.33 (3H, t, *J* 7.4 Hz, SCH_2CH_3), 2.05 (3H, s, CH_3), 2.78 (2H, m, SCH_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

ArCHH'), 4.76 (1H, d, *J* 11.4 Hz, ArCHH'), 4.86 (1H, d, *J* 10.6 Hz, ArCHH'), 4.88 (1H, d, *J* 11.3 Hz, ArCHH'), 5.10 (1H, at, *J* 9.2 Hz, H-2), 7.26–7.41(15H, m, ArH).

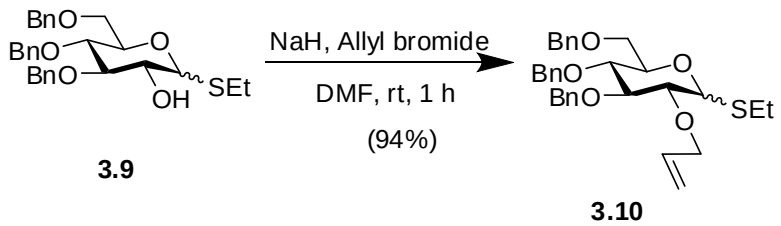
Ethyl 3-4-6-tri-*O*-benzyl-1-thio-*β*-D-glucopyranoside[31] **3.9**



3.8 **3.9**

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-*α*/*β*-D-glucopyranoside **3.8** (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 (3 g) was added and the mixture stirred for 15 min until pH 7. 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- *α*/*β*-D-glucopyranoside **3.9** (1.17 g, 92%) as a pale yellow oil. δ_H (400 MHz, $CDCl_3$) [1:5 mixture of *α*:*β* anomers observed, major *β* anomer quoted] 1.26 (3H, t, *J* 7.4 Hz, SCH_2CH_3), 2.45 (1H, d, $J_{OH,2}$ 2.0 Hz, OH), 2.78 (2H, m, SCH_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 PhCHH'), 4.84-4.95 (3H, m, 3 x PhCHH'), 7.21-7.39 (15H, m, 15 x Ar-H).

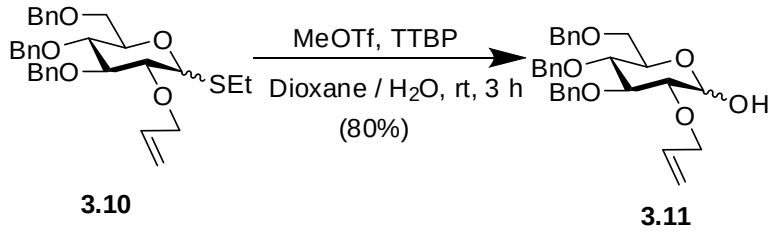
Ethyl 2-*O*-allyl-3-4-6-tri-*O*-benzyl-1-thio-*β*-D-glucopyranoside[32] **3.10**



3.9 **3.10**

Ethyl 3-4-6-tri-*O*-benzyl-1-thio-*β*-D-glucopyranoside **3.9** (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 and the reaction was then allowed to warm to rt. 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 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 **3.10** (1.11 g, 94%) as pale yellow oil. δ_H (400 MHz, $CDCl_3$) [1:5 mixture of *α*:*β* anomers observed, major *β* anomer quoted] 1.30 (3H, t, *J* 7.2 Hz, SCH_2CH_3), 2.75 (2H, m, SCH_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, dd_{at}, J_{gem} 11.3 Hz, J_{vic} 6.0 Hz, *J* 1.4 Hz, OCHH'CH=CH2), 4.39 (1H, dd_{at}, J_{gem} 11.2 Hz, J_{vic} 5.5 Hz, *J* 1.8 Hz, OCHH'CH=CH2), 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, $CH=CH_EH_Z$), 5.30 (1H, daq, J_E 17.0 Hz, *J* 1.8 Hz, $CH=CH_EH_Z$), 5.99 (1H, ddat, J_E 17.0 Hz, J_Z 10.4 Hz, *J* 5.9 Hz, $CH=CH_2$), 7.19-7.33 (15H, m, 15 x Ar-H).

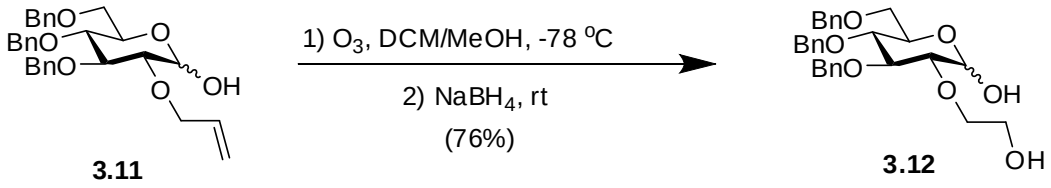
2-*O*-Allyl-3,4,6-tri-*O*-benzyl-*α*/*β*-D-glucopyranose[33] **3.11**



3.10 **3.11**

Ethyl 2-*O*-allyl-3-4-6-tri-*O*-benzyl-1-thio-*β*-D-glucopyranoside **3.10** (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 DCM (20 ml) and washed with water (20 ml). The aqueous layer was then extracted with DCM (2 x 20 ml), and the combined organic extracts were washed with saturated aq. sodium bicarbonate (20 ml) and brine (20 ml). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford 2-*O*-allyl-3,4,6-tri-*O*-benzyl-*α*/*β*-D-glucopyranose **3.11** (0.196 g, 80%) as white crystalline solid. 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, OCHH'CH=CH2), 4.39 (1H, dd_{at}, J_{gem} 11.7 Hz, J_{vic} 5.7 Hz, *J* 1.4 Hz, OCHH'CH=CH2) 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, $CH=CH_EH_Z$), 5.27 (1H, daq, J_E 17.2 Hz, *J* 1.6 Hz, $CH=CH_EH_Z$), , 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, $CH=CH_2$), 7.14-7.35 (15H, m, 15 x Ar-H).

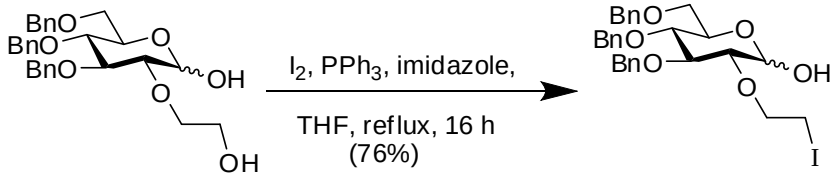
3,4,6-Tri-*O*-benzyl-2-*O*-(2-hydroxyethyl)ether-*α*/*β*-D-glucopyranose[34] **3.12**



3.11 **3.12**

A solution of 2-*O*-allyl-3,4,6-tri-*O*-benzyl-*α*/*β*-D-glucopyranose **3.11** (121 mg, 0.246 mmol) in DCM-Methanol (3 mL, 1:1) was treated with ozone at -78 °C until the solution turned blue. The reaction was then quenched by the addition of $NaBH_4$ (19 mg, 0.492 mmol) in small portions over 50 min. The reaction mixture was allowed to warm to rt 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 **3.12** (101 mg, 76%) as a colourless oil; 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', OCH_2CH_2OH, OCH_2CH_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, PhCH2), 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).

3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodoethyl)-*α*/*β*-D-glucopyranose[11] **3.13**

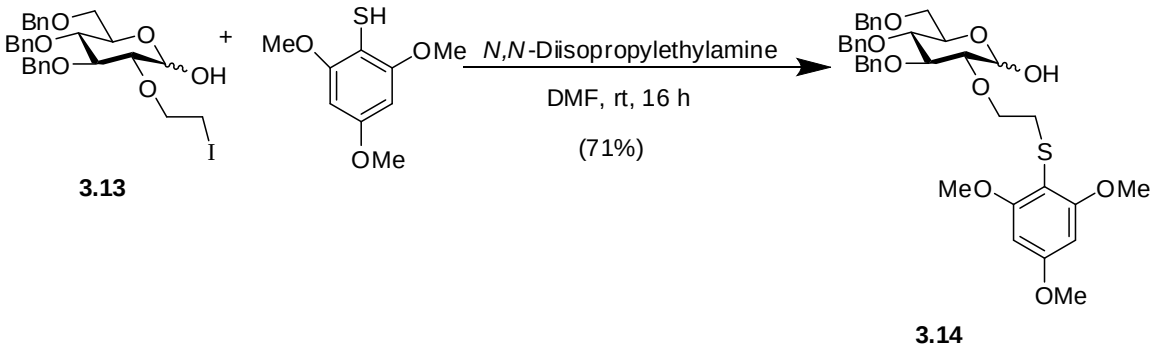


3.12 **3.13**

3,4,6-Tri-*O*-benzyl-2-*O*-(2-hydroxyethyl)ether-*α*/*β*-D-glucopyranose **3.12** (0.249 g, 0.504 mmol) was dissolved in freshly distilled THF (5 ml) under an atmosphere of argon. 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 was then 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 acetate, 6:1) to afford 3,4,6-tri-*O*-benzyl-2-*O*-(2-iodoethyl)-*α*/*β*-D-glucopyranose **3.13** (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_2CH_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, $OCHH'CH_2I$), 3.93-3.99 (1H, m, $OCHH'CH_2I$), 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).

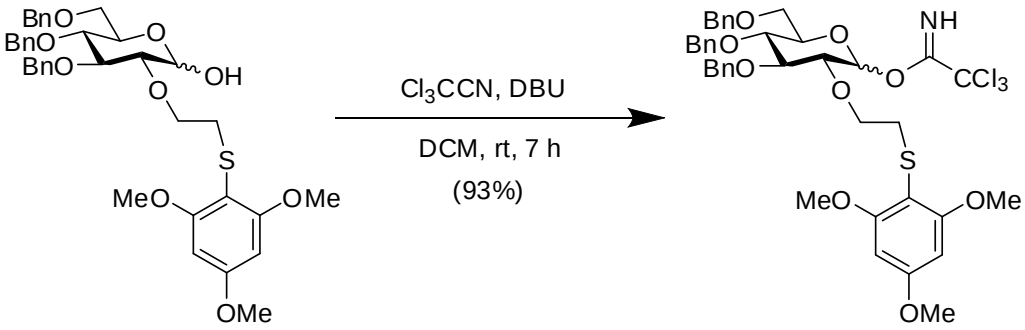
3,4,6-Tribenzyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*/*β*-D-glucopyranose[24] **3.14**



3,4,6-Tri-*O*-benzyl-2-*O*-(2-iodoethyl)-*α*/*β*-D-glucopyranose **3.13** (140 mg, 0.28 mmol) was dissolved in DMF (10 mL) under a atmosphere of nitrogen. Hünig's base (0.06 mL, 0.34 mmol) and 2,4,6-trimethoxybenzenethiol (68 mg, 0.34 mmol) were added, and the mixture was stirred at rt. After 16 h, t.l.c. (petrol:ethyl acetate, 3:2) indicated the complete consumption of starting material (R_f 0.7) and the formation of a major product (R_f 0.4). The solution was then concentrated *in vacuo*, and the residue was purified by flash chromatography (petrol:ethyl acetate, 3:1) to afford 3,4,6-triacetyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*/*β*-D-glucopyranose

3.14 (135 mg, 71%) as white amorphous solid; δ_H (400 MHz, $CDCl_3$) [2:1 mixture of *α*:*β* anomers observed]: 3.02-3.07 (6H, m, $OCH_2C\underline{H}_2SAr$ *α*, $OCH_2C\underline{H}_2SAr$ *β*), 3.20 (1H, at *J* 10.0 Hz, H-2 *β*), 3.40 (2H, dd, $J_{1,2}$ 3.3 Hz, $J_{2,3}$ 8.2 Hz, H-2 *α*), 3.56-3.94 (46H, m, 3 x OCH_3 *α*, 3 x OCH_3 *β*, H-3 *α*, H-3 *β*, H-4 *α*, H-4 *β*, H-5 *α*, H-5 *β*, H-6 *α*, H-6 *β*, H-6' *α*, H-6' *β*, $OC\underline{H}H'CH_2SAr$ *α*, $OC\underline{H}H'CH_2SAr$ *β*, $OCH\underline{H}'CH_2SAr$ *β*), 4.02-4.09 (2H, m, $OCH\underline{H}'CH_2SAr$ *α*), 4.48-4.91 (19H, m, H-1 *β*, 3 x $PhCH_2$ *α*, 3 x $PhCH_2$ *β*), 5.34 (2H, d, $J_{1,2}$ 3.3 Hz, H-1 *α*), 6.14 (6H, s, 2 x SArCH *α*, 2 x SArCH *β*), 7.09-7.32 (45H, m, 15 x Ar-CH *α*, 15 x Ar-CH *β*); δC (100 MHz, $CDCl_3$): 34.5 (t, $OCH_2\underline{C}H_2SAr$ *α*), 35.1 (t, $OCH_2\underline{C}H_2SAr$ *β*), 55.3, 55.4, 56.1, 56.2 (4 x q, 2 x OMe *α*, 2 x OMe *β*), 68.6 (t, C-6_a *α*), 62.2 (t, C-6_a *β*), 70.2 (t, $O\underline{C}H_2CH_2SAr$ *β*), 70.5 (t, $O\underline{C}H_2CH_2SAr$ *α*), 73.5, 73.8, 74.9, 75.0, 75.5, 76.7 (6 x t, 3 x $PhCH_2$ *α*, 3 x $PhCH_2$ *β*), 72.0, 76.9, 77.8, 77.9, 81.4, 81.6, 84.2, 85.0 (8 x d, C-2 *α*, C-2 *β*, C-3 *α*, C-3 *β*, C-4 *α*, C-4 *β*, C-5 *α*, C-5 *β*), 91.0, 91.1, 91.2 (3 x d, SAr$\underline{C}$-H *α*, SArC-H *β*, C-1 *β*), 91.5 (d, C-1 *α*), 127.0, 127.2, 127.3, 127.4, 127.5, 127.6, 127.7,127.7, 127.8, 127.9, 127.9, 128.0, 128.1, 128.2, 128.3, 128.3, 128.4, 128.4 (18 x d, 9 x ArCH *α*, 9 x ArCH *β*), 137.8, 137.9, 138.2, 138.3, 138.8, 138.9 (6 x s, 3 x ArC *α*, 3 x ArC *β*), 161.6, 161.8, 161.9, 162.0 (4 x s, S-ArC-OMe *o α*, S-ArC-OMe *o β*, S-ArC-OMe *p α*, S-ArC-OMe *p β*); HRMS (ES^+) calculated for $C_{35}H_{50}O_{17}SNa$ (MNa^+) 797.2660, found 797.2669.

3,4,6-Tribenzyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*-D-glucopyranosyl) trichloroacetimidate[12] **3.1**

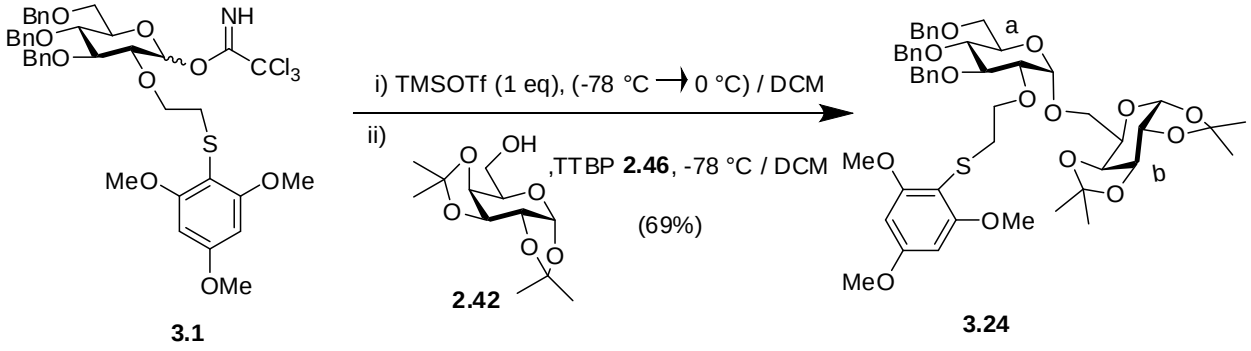


3.14 **3.1**

3,4,6-triacetyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*/*β*-D-glucopyranose **3.14** (160 mg, 0.235 mmol) was dissolved in DCM (10 mL) under a nitrogen atmosphere. Trichloroacetonitrile (0.16 mL, 2.35 mmol) and DBU (0.011 mL, 0.094 mmol) were added, and the reaction was stirred at 0 °C. After 7 h, t.l.c. (petrol:ethyl acetate, 3:2, with 1% TEA) indicated the formation of a major product (R_f 0.8) and the complete consumption of starting material (R_f 0.2). The reaction was warmed to rt and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol:ethyl acetate, 4:1, with 1% TEA) to afford 3,4,6-tribenzyl-2-*O*-(2-(phenylthionyl)ethyl)-*α*-D-glucopyranosyl) trichloroacetimidate **3.1** (190 mg, 93%) as colorless oil; ν_{max} (KBr) 3345(w, NH), 1664 (s, C=NH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.76-2.90 (2H, m, $OCH_2C\underline{H}_2SAr$), 3.58-3.78 (6H, m, $OC\underline{H}_2CH_2SAr$, H-2, H-3, H-6, H-6'), 3.83 (9H, s, 3 x OCH_3), 3.89-3.95 (2H, m, H-4, H5), 4.45, 4.58 (2H, ABq, J_{AB} 11.9 Hz, $PhCH_2$), 4.50, 4.83 (2H, ABq, J_{AB} 10.8 Hz, $PhCH_2$), 4.77, 4.94 (2H, ABq, J_{AB} 10.9 Hz, $PhCH_2$), 6.13 (2H, s, 2 x SArCH), 6.49 (1H, d, $J_{1,2}$ 3.4 Hz, H-1), 7.10-7.34 (15H, m, Ar-H), 8.46 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 33.9 (t, $OCH_2\underline{C}H_2SAr$), 55.4 (t, C-6), 56.0, 56.1 (2 x q, 2 x OMe), 68.1 (t, $O\underline{C}H_2CH_2SAr$), 73.0, 73.4, 75.3 (3 x t, 3 x $Ar\underline{C}H_2$), 70.4, 75.5, 80.3, 81.1 (4 x d, C-2, C-3, C-4, C-5), 90.9 (d, $SAr\underline{C}$-H), 91.3

(s, <u>C</u>Cl$_3$), 94.0 (d, C-1), 100.9 (s, S<u>C</u>Ar), 127.5, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5 (9 x d, Ar-CH), 137.8, 138.2, 138.8, (3 x s, 3 x ArC), 161.6, 161.9, 162.2 (3 x s, S-ArC-OMe *o*, S-ArC-OMe *p*, C=NH); HRMS (ES$^+$) calculated for $C_{40}H_{44}O_9Cl_3SNa$ (MNa^+) 842.1694, found 842.1711.

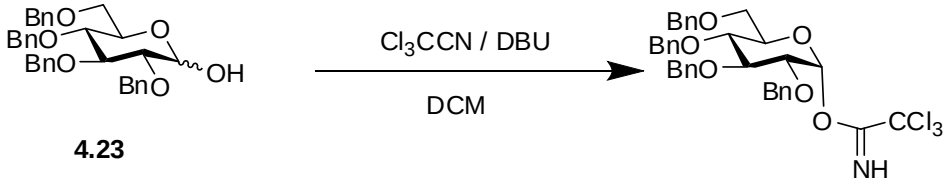
3,4,6-Tribenzyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside (Protocol B)[25] **3.24**



A mixture of donor 3,4,6-tribenzyl-2-*O*-(2-(phenylthionyl)ethyl)-*α*-D-glucopyranosyl) trichloroacetimidate **3.1** (120 mg, 0.15 mmol) and activated molecular sieves (3 Å) (100 mg) in DCM (5 mL) was stirred for 10 min under a nitrogen atmosphere at rt. The mixture was cooled to -78 °C, TMSOTf (26 µL, 0.15 mmol) was added, and the mixture was then allowed to warm to 0 °C over a period of 40 min. After cooling of the mixture to -78 °C, glycosyl acceptor 1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside **2.42** (48 mg, 0.18 mmol) and TTBP **2.46** (80 mg, 0.30 mmol) were added. The mixture was then allowed to warm slowly to rt. After 16 h, t.l.c. (toluene:ethyl acetate, 4:1) indicated the formation of a major product (R_f 0.4) and the complete consumption of donor (R_f 0.7). The reaction was quenched by the addition of saturated aq. sodium bicarbonate solution (5 mL), the organic phase was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (toluene:ethyl

acetate, 8:1) to afford 3,4,6-tribenzyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside **3.24** (0.095 g, 69%) as colorless oil; $[\alpha]_D^{20}$ - 0.5 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 1.32-1.54 (12H, m, 4 x CH_3), 2.85-2.98 (2H, m, $OCH_2C\underline{H}_2SAr$), 3.41 (1H, dd, $J_{2,3}$ 9.24, $J_{1,2}$ 3.37 Hz, H-2_a), 3.59-3.69 (4H, m, H-6_a, H-$6'_a$, H-6_b, H-$6'_b$), 3.72-3.91 (14H, m, 3 x OCH_3, $OC\underline{H}_2CH_2SAr$, H-4_a, H-4_b, H-5_b), 4.01 (1H, at, *J* 9.4 Hz, H-3_a), 4.31 (2H, m, H-2_b, H-3_b), 4.44-4.91 (7H, m, 3 x $PhCH_2$, H-5_a), 5.03 (1H, d, $J_{1,2}$ 4.1 Hz, H-1_a), 5.49 (1H, d, $J_{1,2}$ 5.1 Hz, H-1_b), 6.12 (2H, s, 2 x SArC-H), 7.12-7.32 (15H, m, Ar-CH); δ_C (100 MHz, $CDCl_3$) 24.5, 24.9, 26.0, 26.1 (4 x q, 4 x CH_3), 34.0 ($OCH_2\underline{C}H_2SAr$), 55.3, 56.0 (2 x q, 2 x OCH_3), 65.8, 66.5 (2 x t, C-6_a, C-6_b), 68.4 ($O\underline{C}H_2CH_2SAr$), 70.2, 70.5, 70.6, 70.7, 70.8, 77.5 (6 x d, C-4_a, C-5_a, C-2_b, C-3_b, C-4_b, C-5_b), 73.4, 74.9, 75.5 (3 x t, 3 x CH_2Ph), 81.2 (d, C-2_a), 81.7 (d, C-3_a) 91.0 (d, SArC-H), 96.2 (d, C-1_b), 97.3 (d, C-1_a), 108.5 (s, $\underline{C}(CH_3)_2$), 109.1 (s, $\underline{C}(CH_3)_2$), 127.4, 127.5, 127.6, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4 (9 x d, 9 x Ar-CH), 138.0, 138.4, 139.0 (3 x Ar-C), 161.8, 162.0 (2 x s, S-ArC-OMe *o*, S-ArC-OMe *p*); HRMS (ES^+) calculated for $C_{50}H_{62}O_{14}SNa$ (MNa^+) 941.3752, found 941.3769.

_O_-(2,3,4,6-tetra-_O_-benzyl)-_α_-D-glucopyranosyl trichloroacetimidate[35] **4.24**

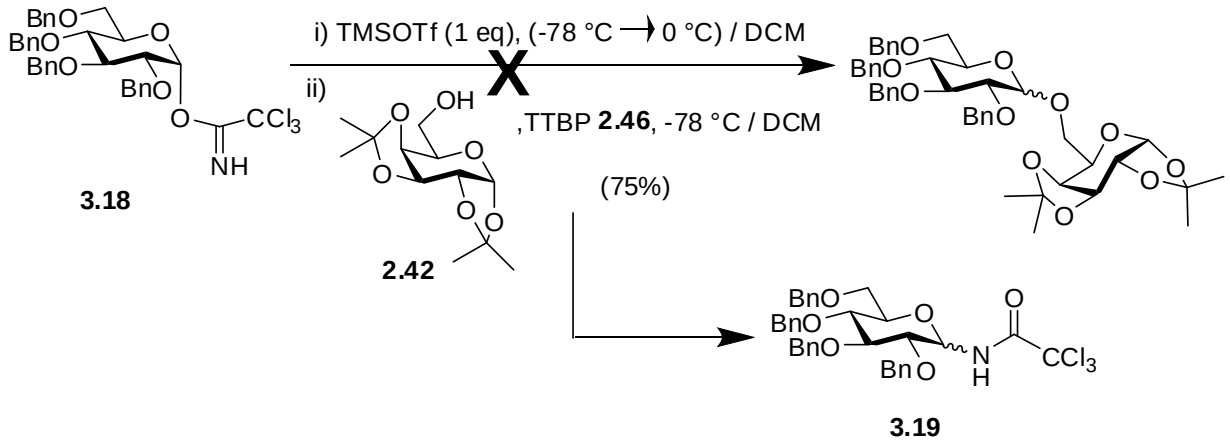


4.23 **4.24**

2,3,4,6-Tetra-*O*-benzyl-D-*α*/*β*-glucopyranose **4.23** (165 mg, 0.305 mmol) was dissolved in DCM (5 mL) under N_2. Trichloroacetonitrile (0.21 mL, 3.05 mmol) and DBU (0.014 mL, 0.122 mmol) were added, and the reaction was stirred at 0 °C. After 5 h, t.l.c. (petrol:ethyl acetate, 3:1, with 1% TEA) indicated the formation of a major product (R_f 0.5) and the complete consumption of

starting material (R_f 0.1). The reaction was warmed to rt and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (petrol:ethyl acetate, 5:1, with 1% TEA) to afford *O*-(2,3,4,6-tetra-*O*-benzyl)-*α*-D-glucopyranosyl trichloroacetimidate **4.24** (205 mg, 100%) as colorless oil; δ_H (400 MHz, $CDCl_3$):[36] 3.63-3.83 (4H, m, H-2, H-5, H-6, H-6'), 3.96-4.10 (2H, m, H-3, H-4), 4.45-4.91 (8H, m, 4 x CH_2Ph), 6.53 (1H, d, $J_{1,2}$ 3.4 Hz, H-1), 7.10-7.34 (20H, m, Ar-H), 8.58 (1H, br s, NH).

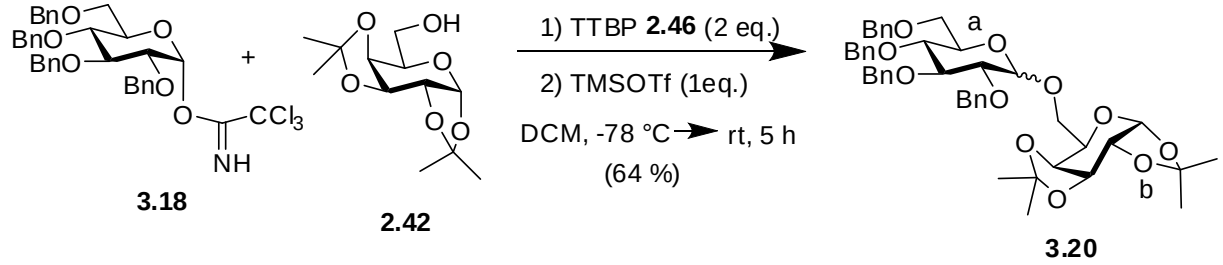
***N*-Trichloroacetyl-2,3,4,6-tetra-*O*-benzyl-*α*/*β*-D-glucopyranosylamine 3.19**



A mixture of donor *O*-(2,3,4,6-tetra-*O*-benzyl)-*α*-D-glucopyranosyl trichloroacetimidate **3.18** (200 mg, 0.29 mmol) and activated molecular sieves (3 Å) (100 mg) was stirred in DCM (5 mL) for 10 min under a nitrogen atmosphere at rt. The mixture was cooled to -78 °C, TMSOTf (53 µL, 0.29 mmol) was added, and the reaction mixture was allowed to warm to 0 °C over a period of 40 min. The mixture was then cooled to -78 °C, glycosyl acceptor 1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside **2.42** (103 mg, 0.37 mmol) and TTBP **2.46** (147 mg, 0.59 mmol) were added. The reaction mixture was allowed to warm slowly to rt. After 16 h, t.l.c. (petrol:ethyl acetate, 3:2) indicated the formation of a major product (R_f 0.7) and the complete consumption of the donor (R_f 0.8). The reaction was quenched by the addition of saturated aq.

sodium bicarbonate solution (5 mL), the organic phase was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol:ethyl acetate, 9:1) to afford *N*-trichloroacetyl-2,3,4,6-tetra-*O*-benzyl-*α*/*β*-D-glucopyranosylamine **3.19** (0.150 g, 75%) as colorless oil; δ_H (400 MHz, $CDCl_3$) [6:1 mixture of *α*:*β* anomers observed, major *α* anomer quoted]:[37] 3.63-3.70 (3H, m, H-2, H-4, H-5), 3.73-3.81 (2H, m, H-2, H-6), 3.88 (1H, dd, $J_{6,6'}$ 9.0 Hz, $J_{5,6'}$ 5.2 Hz H-6'), 3.47-3.92 (8H, m, 4 x CH_2Ph), 5.60 (1H, at, *J* 8.0 Hz, H-1), 7.12-7.37 (21H, m, 20 x Ar-CH, NH); δ_C (100 MHz, $CDCl_3$):[9] 68.0 (t, C-6), 71.8 (d, C-4), 72.9, 73.6, 75.1, 75.5 (4 x t, 4 x CH_2Ph), 76.5 (d, C-5), 76.9 (d, C-1), 77.2 (d, C-2), 81.6 (d, C-3), 92.3 (s, CCl_3), 127.2-138.1 (12 x d, 12 x ArC-H), 136.9, 137.8, 138.2, 138.2 (4 x s, 4 x ArC), 162.1 (s, C=O).

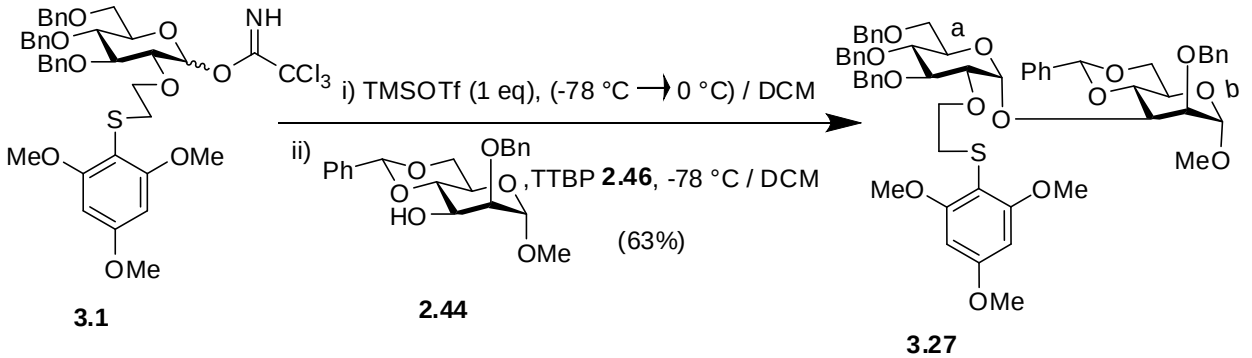
2,3,4,6-Tribenzyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*/*β*-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside (Protocol B-modified) 3.20



A mixture of donor *O*-(2,3,4,6-tetra-*O*-benzyl)-*α*-D-glucopyranosyl trichloroacetimidate **3.18** (200 mg, 0.29 mmol), acceptor 1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside **2.42** (103 mg, 0.37 mmol), TTBP **2.46** (147 mg, 0.59 mmol) and activated molecular sieves (3 Å) (100 mg) in DCM (5 mL) was stirred for 10 min under a nitrogen atmosphere at rt. After the mixture was cooled to -78 °C, TMSOTf (53 µL, 0.29 mmol) was added, and the reaction mixture was stirred for 5 h -78 °C. The reaction mixture was then allowed to warm slowly to rt. After a further 16 h,

t.l.c. (petrol:ethyl acetate, 3:2) indicated the formation of a major product (R_f 0.6) and the complete consumption of the donor (R_f 0.8). The reaction was quenched by the addition of saturated aq. sodium bicarbonate solution (5 mL), the organic phase was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (petrol:diethyl ether, 7:1) to afford 2,3,4,6-Tribenzyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*/*β*-D-glucopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside **3.20** (0.145 g, 64%) as colorless oil; δ_H (400 MHz, $CDCl_3$) [1:2.5 mixture of *α*:*β* anomers observed]:[38] 1.32, 1.46, 1.51, 1.54 (42H, 4 x br s, 4 x CH_3 *α*, 4 x CH_3 *β*), 3.42-3.49 (7H, m, H-2a *α*, H-5a *α*, H-2a *β*, H-5a *β*), 3.57-3.85 (21H, m, H-2b *α*, H-4b *α*, H-5b *α*, H-4a *α*, H-6a *α*, H-6'a *α*, H-2b *β*, H-4b *β*, H-5b *β*, H-4a *β*, H-6a *β*, H-6'a *β*), 3.99 (1H, at, J 9.2 Hz, H-3a *α*), 4.02-4.11 (4.5H, m, H-3a *β*, H-6b *α*, H-6'b *α*), 4.17 (2.5H, dd, $J_{5,6}$ 3.5 Hz, $J_{6,6'}$ 10.8 Hz, H-6b *β*), 4.25 (2.5H, m, H-6'b *β*), 4.31-4.37 (3.5H, m, H-3b *α*, H-3b *β*), 4.46 (2.5H, d, $J_{1,2}$ 7.9 Hz, H-1a *β*), 4.49-5.07 (28H, 4 x $PhCH_2$ *α*, 4 x $PhCH_2$ *β*), 4.58 (1H, d, $J_{1,2}$ 2.4 Hz, H-1a *α*), 5.53 (1H, d, $J_{1,2}$ 5.1 Hz, H-1b *α*), 5.57 (2.5H, d, $J_{1,2}$ 5.1 Hz, H-1b *β*), 7.12-7.45 (70H, m, 20 x Ar-CH *α*, 20 x Ar-CH *β*).

3,4,6-Tribenzyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*-D-glucopyranosyl-(1→3)-methyl-2-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-mannopyranoside (Protocol B)[25] 3.27

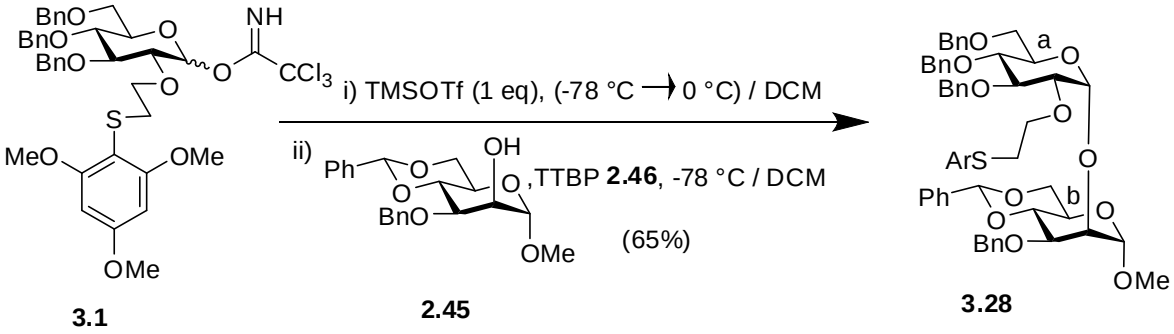


3.1 **2.44** **3.27**

A mixture of 3,4,6-tribenzyl-2-*O*-(2-(phenylthionyl)ethyl)-*α*-D-glucopyranosyl) trichloroacetimidate **3.1** (120 mg, 0.15 mmol) and activated molecular sieves (3 Å, 100 mg) in DCM (5 mL) was stirred for 10 min under a nitrogen atmosphere at rt. The mixture was cooled to -78 °C, TMSOTf (26 µL, 0.15 mmol) was added, and the mixture was then allowed to warm to 0 °C over a period of 40 min. After re-cooling of the mixture to -78 °C, methyl-2-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-mannopyranoside **2.44** (76 mg, 0.18 mmol) and TTBP **2.46** (80 mg, 0.30 mmol) were added. The mixture was then allowed to warm slowly to rt. After 16 h, t.l.c. (toluene:ethyl acetate, 4:1) indicated the formation of a major product (R_f 0.3) and the complete consumption of **3.1** (R_f 0.7). The reaction was quenched by the addition of saturated aq. sodium bicarbonate (5 mL), the organic phase was separated, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (toluene:ethyl acetate, 10:1) to afford 3,4,6-tribenzyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*-D-glucopyranosyl-(1→3)-methyl-2-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-mannopyranoside **3.27** (0.092 g, 63%) as colorless oil; $[\alpha]_D^{20}$ + 10.3 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, CD_3CN): 2.81-2.90 (2H, m, $OCH_2C\underline{H}_2SAr$), 3.25 (3H, s, OCH_{3b}), 3.35-3.57 (3H, m, H-2_a, H-6_a, H-$6'_a$), 3.65-3.93 (17H, m, 3 x OCH_3, $OC\underline{H}_2CH_2SAr$, H-4_a, H-3_a, H-3_b, H-4_b, H-5_b, H-6_b), 4.08 (1H, m, H-2_b), 4.19-4.29 (2H, m, H-$6'_b$, H-5_a), 4.48-5.07, 4.69 (9H, m, 4 x $PhCH_2$, H-1_b), 5.36 (1H, d, $J_{1,2}$ 3.2 Hz, H-1_a), 5.70 (1H, s, PhCH), 6.21 (2H, s, 2 x SArC-H), 7.12-7.32 (25H, m, Ar-CH); δ_C (100 MHz, CD_3CN): 34.3 ($OCH_2\underline{C}H_2SAr$), 54.3 (q, OCH_{3b}), 55.1, 55.7 (2 x q, 2 x OCH_{3a}), 64.0, 69.4 (2 x t, C-6_a, C-6_b), 70.6 ($O\underline{C}H_2CH_2SAr$), 71.9, 72.8, 74.6, 74.7, 74.8 (5 x d, C-4_a, C-5_a, C-3_b, C-4_b, C-5_b), 75.6, 75.7, 77.8, 77.9 (4 x t, 3 x CH_2Ph), 78.6 (d, C-2_b), 80.9, 81.1 (2 x d, C-2_a, C-3_a) 91.2 (d, SArC-H), 98.0 (d, C-1_a), 100.7 (d, C-1_b), 101.3 (CHPh), 101.4 (s, S$\underline{C}$Ar), 127.3, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.8 (15 x d, 15 x Ar-CH), 138.1, 138.6,

138.7, 138.8, 139.4 (4 x Ar-C), 161.8, 161.9 (2 x s, S-ArC-OMe *o*, S-ArC-OMe *p*); HRMS (ES^+) calculated for $C_{59}H_{66}O_{14}SNa$ (MNa^+) 1053.4065, found 1053.4079.

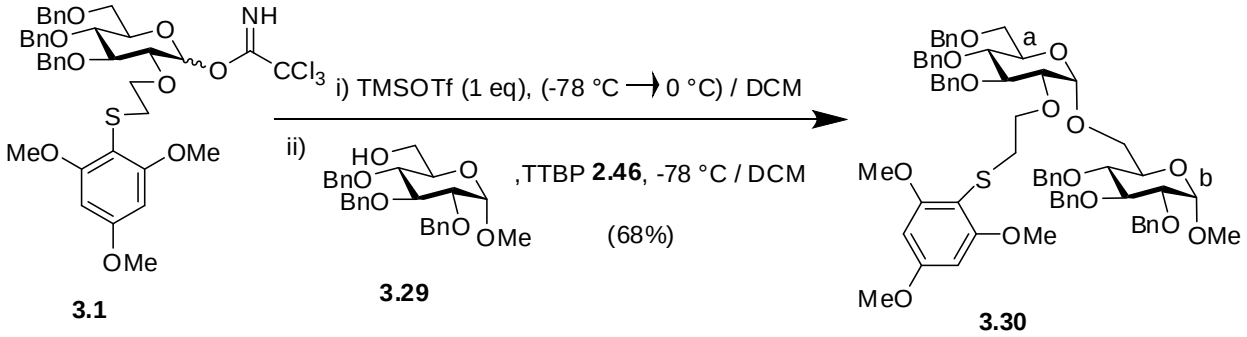
3,4,6-Tribenzyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*-D-glucopyranosyl-(1→2)-methyl-3-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-mannopyranoside (Protocol B)[25] 3.28



A mixture of 3,4,6-tribenzyl-2-*O*-(2-(phenylthionyl)ethyl)-*α*-D-glucopyranosyl) trichloroacetimidate **3.1** (120 mg, 0.15 mmol) and activated molecular sieves (3 Å, 100 mg) in DCM (5 mL) was stirred for 10 min under a nitrogen atmosphere at rt. The mixture was cooled to -78 °C, TMSOTf (26 µL, 0.15 mmol) was added, and the mixture was then allowed to warm to 0 °C over a period of 40 min. After re-cooling of the mixture to -78 °C, methyl-3-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-mannopyranoside **2.45** (76 mg, 0.18 mmol) and TTBP **2.46** (80 mg, 0.30 mmol) were added. The mixture was then allowed to warm slowly to rt. After 16 h, t.l.c. (toluene:ethyl acetate, 4:1) indicated the formation of a major product (R_f 0.3) and the complete consumption of **3.1** (R_f 0.7). The reaction was quenched by the addition of saturated aq. sodium bicarbonate (5 mL), the organic phase was separated, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (toluene:ethyl acetate, 10:1) to afford 3,4,6-tribenzyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*-D-glucopyranosyl-(1→2)-methyl-3-*O*-benzyl-4,6-*O*-benzylidene-*α*-D-mannopyranoside **3.28** (0.095 g, 65%) as colorless

oil; $[\alpha]_D^{20}$ + 25.1 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 2.77-2.94 (2H, m, $OCH_2C\underline{H}_2SAr$), 3.26 (3H, s, OCH_{3b}), 3.42 (1H, dd, $J_{2,3}$ 9.24, $J_{1,2}$ 3.37 Hz, H-2_a), 3.52-3.61 (2H, m, H-6_a, H-$6'_a$), 3.62-3.95 (12H, m, 3 x OCH_3, $OC\underline{H}_2CH_2SAr$, H-4_a), 3.87-3.97 (5H, m, H-3_a, H-3_b, H-4_b, H-5_b, H-6_b), 4.06 (1H, m, H-2_b), 4.24 (1H, dd, $J_{5,6}$ 3.2 Hz, $J_{6,6'}$ 12.2Hz, H-$6'_b$), 4.30 (1H, m, H-5_a), 4.43-5.05, 4.71 (9H, m, 4 x $PhCH_2$, H-1_b), 5.37 (1H, d, $J_{1,2}$ 3.2 Hz, H-1_a), 5.68 (1H, s, PhCH), 6.06 (2H, s, 2 x SArC-H), 7.12-7.32 (25H, m, Ar-CH); δ_C (100 MHz, $CDCl_3$): 34.5 ($OCH_2\underline{C}H_2SAr$), 54.7 (q, OCH_{3b}), 55.3, 56.0 (2 x q, 2 x OCH_{3a}), 64.1, 68.7 (2 x t, C-6_a, C-6_b), 68.8 ($O\underline{C}H_2CH_2SAr$), 69.9, 70.6, 72.6, 73.4, 75.2 (5 x d, C-4_a, C-5_a, C-3_b, C-4_b, C-5_b), 75.4, 75.5, 75.9, 77.5 (4 x t, 3 x CH_2Ph), 79.0 (d, C-2_b), 81.1, 81.2 (2 x d, C-2_a, C-3_a) 91.0 (d, SArC-H), 98.3 (d, C-1_a), 100.9 (d, C-1_b), 101.3 (CHPh), 101.7 (s, S$\underline{C}$Ar), 126.1, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.7 (15 x d, 15 x Ar-CH), 137.8, 138.0, 138.2, 138.6, 139.1 (4 x Ar-C), 161.6, 162.0 (2 x s, S-ArC-OMe *o*, S-ArC-OMe *p*); HRMS (ES^+) calculated for $C_{59}H_{66}O_{14}SNa$ (MNa^+) 1053.4065, found 1053.4056.

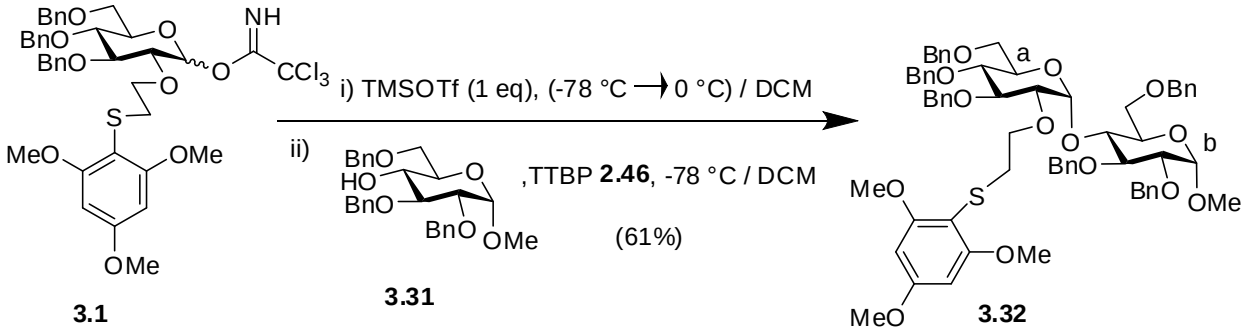
3,4,6-Tribenzyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*-D-glucopyranosyl-(1→6)-methyl-2,3,4-*O*-tribenzyl-*α*-D-glucopyranoside (Protocol B)[25] 3.30



A mixture of 3,4,6-tribenzyl-2-*O*-(2-(phenylthionyl)ethyl)-*α*-D-glucopyranosyl) trichloroacetimidate **3.1** (120 mg, 0.15 mmol) and activated molecular sieves (3 Å, 100 mg) in

DCM (5 mL) was stirred for 10 min under a nitrogen atmosphere at rt. The mixture was cooled to -78 °C, TMSOTf (26 µL, 0.15 mmol) was added, and the mixture was then allowed to warm to 0 °C over a period of 40 min. After re-cooling of the mixture to -78 °C, methyl-2,3,4-*O*-tribenzyl-*α*-D-glucopyranoside **3.29** (84 mg, 0.18 mmol) and TTBP **2.46** (80 mg, 0.30 mmol) were added. The mixture was then allowed to warm slowly to rt. After 16 h, t.l.c. (toluene:ethyl acetate, 4:1) indicated the formation of a major product (R_f 0.3) and the complete consumption of **3.1** (R_f 0.7). The reaction was quenched by the addition of saturated aq. sodium bicarbonate (5 mL), the organic phase was separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (toluene:ethyl acetate, 10:1) to afford 3,4,6-tribenzyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*-D-glucopyranosyl-(1→6)-methyl-2,3,4-*O*-tribenzyl-*α*-D-glucopyranoside **3.30** (0.114 g, 68%) as white amorphous solid; $[\alpha]_D^{20}$ + 48.2 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 2.82-3.02 (2H, m, $OCH_2C\underline{H}_2SAr$), 3.26 (4H, m, OCH_{3b}, H-2_a), 3.51-3.66 (5H, m, H-3_a, H-2_b, H-5_b, H-6_a, H-$6'_a$), 3.71-3.92 (16H, m, $OC\underline{H}_2CH_2SAr$, 3 x OCH_{3a}, H-4_b, H-6_b, H-$6'_b$, H-4_a, H-5_a), 3.99 (1H, at, *J* 8.8 Hz, H-3_b), 4.67 (1H, d, $J_{1,2}$ 3.2 Hz, H-1_b), 4.51-5.04, (12H, m, 6 x $PhCH_2$), 5.04 (1H, d, $J_{1,2}$ 3.2 Hz, H-1_a), 6.13 (2H, s, 2 x SArC-H), 7.12-7.43 (30H, m, Ar-CH); δ_C (100 MHz, $CDCl_3$): 34.2 (t, $OCH_2\underline{C}H_2SAr$), 55.0 (q, OCH_{3b}), 55.3, 56.0 (2 x q, OCH_{3a}), 66.4 (d, C-6_b), 68.9 (d, C-6_a), 70.2 (t, $O\underline{C}H_2CH_2SAr$), 70.3, 70.4 (2 x d, C-5_a, C-4_b), 73.2, 73.4, 74.7, 74.8, 75.6, 76.6 (6 x t, 6 x CH_2Ph), 75.2 (d, C-5_b), 78.1, 81.2, 81.4 (4 x d, C-2_a, C-3_a, C-4_a), 80.6 (d, C-3_b), 82.1 (d, C-2_b), 91.4 (d, SArC-H), 97.4 (d, C-1_b), 97.9 (d, C-1_a), 101.9 (s, S$\underline{C}$Ar), 127.2, 127.3, 127.3, 127.4, 127.4, 127.5, 127.6, 127.7, 127.7, 127.8, 127.9, 127.9, 128.1, 128.1, 128.2, 128.2, 128.3, 128.3 (18 x d, 18 x Ar-CH), 138.2, 138.4, 138.6, 138.7, 139.0, 139.1 (6 x Ar-C), 161.8, 162.1 (2 x s, S-ArC-OMe *o*, S-ArC-OMe *p*); HRMS (ES^+) calculated for $C_{66}H_{74}O_{14}SNa$ (MNa^+) 1145.4691, found 1145.4713.

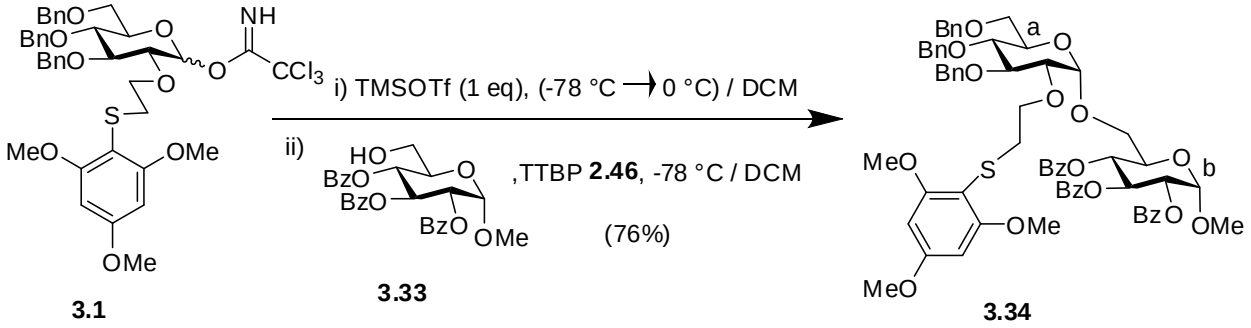
3,4,6-Tribenzyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*-D-glucopyranosyl-(1→4)-methyl-2,3,6-*O*-tribenzyl-*α*-D-glucopyranoside (Protocol B)[25] 3.32



A mixture of 3,4,6-tribenzyl-2-*O*-(2-(phenylthionyl)ethyl)-*α*-D-glucopyranosyl) trichloroacetimidate **3.1** (120 mg, 0.15 mmol) and activated molecular sieves (3 Å,100 mg) in DCM (5 mL) was stirred for 10 min under a nitrogen atmosphere at rt. The mixture was cooled to -78 °C, TMSOTf (26 µL, 0.15 mmol) was added, and the mixture was then allowed to warm to 0 °C over a period of 40 min. After re-cooling of the mixture to -78 °C, methyl-2,3,6-*O*-tribenzyl-*α*-D-glucopyranoside **3.31** (84 mg, 0.18 mmol) and TTBP (80 mg, 0.30 mmol) were added. The mixture was then allowed to warm slowly to rt. After 16 h, t.l.c. (toluene:ethyl acetate, 4:1) indicated the formation of a major product (R_f 0.3) and the complete consumption of **3.1** (R_f 0.7). The reaction was quenched by the addition of saturated aq. sodium bicarbonate (5 mL), the organic phase was separated, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (toluene:ethyl acetate, 10:1) to afford 3,4,6-tribenzyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*-D-glucopyranosyl-(1→4)-methyl-2,3,6-*O*-tribenzyl-*α*-D-glucopyranoside **3.32** (0.102 g, 61%) as colorless oil; $[\alpha]_D^{20}$ + 30.6 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, CD_3CN): 2.76-2.93 (2H, m, $OCH_2C\underline{H_2}SAr$), 3.36 (3H, s, OCH_{3b}), 2.80

(1H, m, H-2_a), 3.43-3.61 (6H, m, OC<u>H</u>$_2$CH_2SAr, H-2_b, H-5_b, H-6_a, H-6'$_a$), 3.67-3.88 (17H, m, 3 x OCH_{3a}, H-3_a, H-2_a, H-4_b, H-6_b, H-6'$_b$, H-4_a, H-5_a, H-3_b), 4.78 (1H, d, $J_{1,2}$ 3.2 Hz, H-1_b), 4.41-4.94, (12H, m, 6 x $PhCH_2$), 5.04 (1H, d, $J_{1,2}$ 3.2 Hz, H-1_a), 6.22 (2H, s, 2 x SArC-H), 7.20-7.36 (30H, m, Ar-CH); δ_C (100 MHz, CD_3CN): 34.3 (t, OCH_2<u>C</u>H_2SAr), 54.5 (q, OCH_{3b}), 55.2, 55.8 (2 x q, OCH_{3a}), 66.1 (d, C-6_b), 69.3 (d, C-6_a), 69.9 (t, O<u>C</u>H_2CH_2SAr), 70.3, 70.5 (2 x d, C-5_a, C-4_b), 72.3, 72.8, 74.3, 74.5, 74.8, 77.9 (6 x t, 6 x CH_2Ph), 78.0, 80.5, 81.0, 81.1 (4 x d, C-2_a, C-3_a, C-4_a, C-5_b), 81.2, 81.6 (2 x d, C-3_b, C-2_b), 91.6 (d, SArC-H), 97.0 (d, C-1_b), 97.7 (d, C-1_a), 101.7 (s, S<u>C</u>Ar), 127.2, 127.3, 127.3, 127.4, 127.4, 127.5, 127.6, 127.7, 127.7, 127.8, 127.9, 127.9, 128.1, 128.1, 128.2, 128.2, 128.3, 128.3 (18 x d, 18 x Ar-CH), 138.7, 138.8, 138.9, 138.9, 139.0, 139.3 (6 x Ar-C), 162.0, 162.1 (2 x s, S-ArC-OMe *o*, S-ArC-OMe *p*); HRMS (ES^+) calculated for $C_{66}H_{74}O_{14}SNa$ (MNa^+) 1145.4691, found 1145.4707.

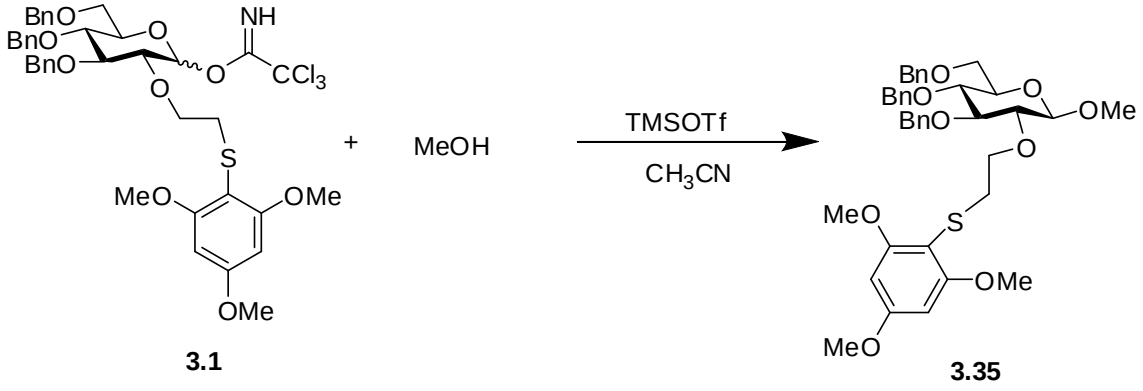
3,4,6-Tribenzyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*-D-glucopyranosyl-(1→6)-methyl-2,3,4-*O*-tribenzyl-*α*-D-glucopyranoside (Protocol B)[25] **3.34**



A mixture of 3,4,6-tribenzyl-2-*O*-(2-(phenylthionyl)ethyl)-*α*-D-glucopyranosyl) trichloroacetimidate **3.1** (120 mg, 0.15 mmol) and activated molecular sieves (3 Å, 100 mg) in DCM (5 mL) was stirred for 10 min under a nitrogen atmosphere at rt. The mixture was cooled to -78 °C, TMSOTf (26 µL, 0.15 mmol) was added, and the mixture was then allowed to warm to 0 °C over a period of 40 min. After re-cooling of the mixture to -78 °C, methyl-2,3,4-*O*-

tribenzoyl-*α*-D-glucopyranoside **3.33** (91 mg, 0.18 mmol) and TTBP **2.46** (80 mg, 0.30 mmol) were added. The mixture was then allowed to warm slowly to rt. After 16 h, t.l.c. (toluene:ethyl acetate, 4:1) indicated the formation of a major product (R_f 0.5) and the complete consumption of **3.1** (R_f 0.7). The reaction was quenched by the addition of saturated aq. sodium bicarbonate (5 mL), the organic phase was separated, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (toluene:ethyl acetate, 10:1) to afford 3,4,6-tribenzyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*-D-glucopyranosyl-(1→6)-methyl-2,3,4-*O*-tribenzoyl-*α*-D-glucopyranoside **3.34** (0.132 g, 76%) as colorless oil; $[\alpha]_D^{20}$ + 102.3 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 2.79-2.98 (2H, m, $OCH_2C\underline{H}_2SAr$), 3.26 (4H, m, OCH_{3b}, H-2_a), 3.50-3.72 (8H, m, $OC\underline{H}_2CH_2SAr$, H-3_a, H-4_a, H-5_a, H-6_a, H-$6'_a$, H-6_b), 3.79-3.85 (9H, 2 x s, 3 x OCH_{3a}), 3.85-3.91(2H, m, H-4_b, H-$6'_b$), 4.32-4.88 (6H, m, 3 x $PhCH_2$), 4.95 (1H, d, $J_{1,2}$ 3.2 Hz, H-1_a), 5.18 (1H, d, $J_{1,2}$ 3.2 Hz, H-1_b), 5.25 (1H, dd, $J_{4,5}$ 9.6Hz, $J_{5,6}$ 3.6 Hz, H-5_b), 6.04-6.16 (3H, m, 2 x SArC-H, H-2_b), 7.12-8.00 (30H, m, Ar-CH); δ_C (100 MHz, $CDCl_3$): 33.9 (t, $OCH_2\underline{C}H_2SAr$), 55.3 (d, C-5_a), 55.6 (q, OCH_{3b}), 55.9, 56.0 (2 x q, OCH_{3a}), 66.8 (d, C-6_b), 68.3 (d, C-4_a), 68.4 (d, C-6_a), 69.7 (t, $O\underline{C}H_2CH_2SAr$), 70.3, 70.6 (2 x d, C-2_a, C-3_a), 72.2 (d, C-5_b), 73.4, 74.7, 75.4 (3 x t, 3 x $\underline{C}H_2Ph$), 76.7 (d, C-3_b), 81.1 ,81.5 (2 x d, C-2_b, C-4_b), 91.0 (d, SArC-H), 96.7 (d, C-1_b), 97.1 (d, C-1_a), 100.9 (s, S$\underline{C}$Ar), 127.4, 127.5, 127.6, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.3, 128.3, 128.4, 128.4, 128.9, 129.0, 129.1, 129.3, 129.6 (18 x d, 18 x Ar-CH), 129.9, 133.0, 133.3, 138.0, 138.7, 138.9 (6 x s, 6 x Ar-C), 161.8, 162.1 (2 x s, S-ArC-OMe *o*, S-ArC-OMe *p*), 165.3, 165.7, 165.8 (3 x s, 3 x O$\underline{C}$OArC); HRMS (ES^+) calculated for $C_{66}H_{68}O_{17}SNa$ (MNa^+) 1187.4069, found 1187.4066.

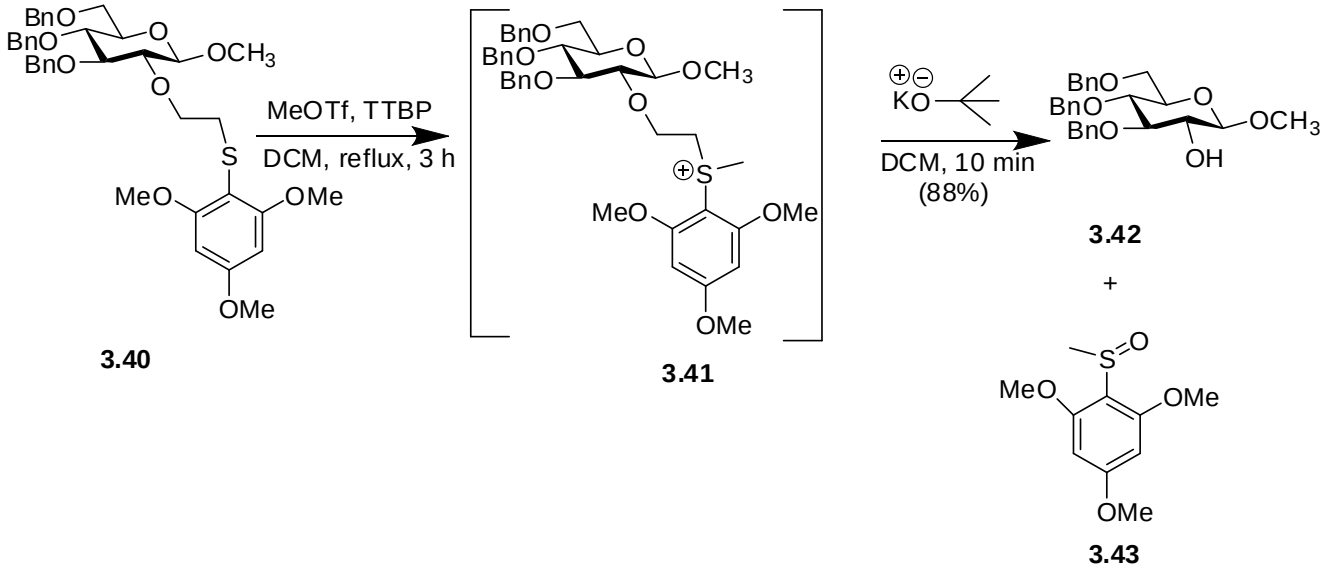
Methyl 2-*O*-(2-(phenylthionyl)ethyl)-3,4,6- benzyl-*β*-D-glucopyranoside 3.35



A solution of 3,4,6-tribenzyl-2-*O*-(2-(phenylthionyl)ethyl)-*α*-D-glucopyranosyl) trichloroacetimidate **3.1** (200 mg, 0.25 mmol) and methanol (7.0 μL, 0.50 mmol) in freshly distilled CH_3CN (2 mL) was added to a flame-dried round-bottom flask containing activated 4 Å molecular sieves (0.100 g). The mixture was cooled to 0 °C under a nitrogen atmosphere, then TMSOTf (5.00 μL, 0.025 mmol) was added. After 5 h, t.l.c. (petrol:ethyl acetate, 3:2) showed formation of a major product (R_f 0.6) and the complete consumption of the trichloroacetimidate starting material (R_f 0.7) was observed. The reaction was quenched with saturated aq. sodium bicarconate solution (2 mL) and filtered through Celite®. The mixture was diluted with DCM (20 mL), washed with saturated aq. sodium bicarbonate solution (2 x 10 mL), and the aqueous layer extracted with DCM (2 x 20 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford methyl 2-*O*-(2-(phenylthionyl)ethyl)-3,4,6- benzyl-*β*-D-glucopyranoside **3.35** (0.135 g, 78%) as a white

crystalline solid; m. p. 75 – 77 °C (petrol/ethyl acetate); [δ_H (400 MHz, $CDCl_3$): 2.88-2.92 (2H, m, $OCH_2C\underline{H}_2SAr$), 3.19 (1H, at, *J* 6.6 Hz, H-2), 3.42 (1H, m, H-4), 3.49-3.53 (5H, m, $OC\underline{H}_3$, H-3, H-5), 3.62-3.76 (3H, m, H-6, $OC\underline{H}_2CH_2SAr$), 3.82 (9H, s, 3 x OCH_3), 3.89-3.97 (1H, m, H-6'), 4.16 (1H, d, $J_{1,2}$ 7.6 Hz, H-1), 4.72-4.91 (6H, m, 3 x CH_2Ph), 6.13 (2H, s, 2 x SArC-H), 7.11-7.32 (15H, m, Ar-CH); δ_C (100 MHz, $CDCl_3$): 34.1 (t, $OCH_2\underline{C}H_2SAr$), 55.3, 56.1, 57.0 (3 x q, 3 x OCH_3), 69.0 (t, $O\underline{C}H_2CH_2SAr$), 72.2 (t, C-6), 73.5, 74.8, 75.0 (3 x t, 3 x $\underline{C}H_2Ph$), 75.6 (d, C-4), 77.7 (d, C-5), 82.9 (d, C-2), 84.5 (d, C-3), 91.0 (d, SArC-H), 101.3 (s, $S\underline{C}Ar$), 104.4 (d, C-1), 127.5, 127.6, 127.7, 127.7, 127.9, 128.0, 128.1, 128.3, 128.3) (9 x d, 9 x Ar-CH), 138.1, 138.2, 138.6 (3 x s, 3 x Ar-C), 161.7, 162.0 (2 x s, S-ArC-OMe *o* *α*, S-ArC-OMe *p*); HRMS (ES^+) calculated for $C_{39}H_{46}O_9SNa$ (MNa^+) 713.2754, found 713.2762.

Methyl 3,4,6-tri-*O*-benzyl-*β*-D-glucopyranoside 3.42

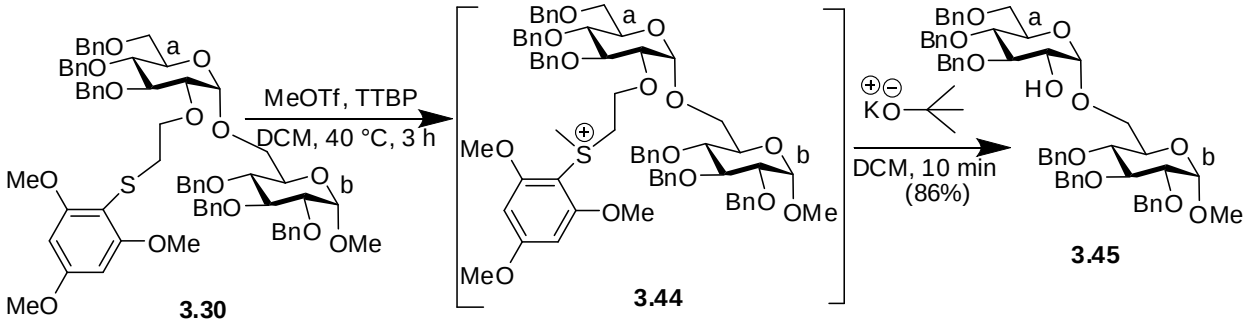


MeOTf (51 µL, 0.45 mmol), and TTBP **2.46** (144 mg, 0.58 mmol) were added to the solution of methyl 2-*O*-(2-(phenylthionyl)ethyl)-3,4,6- benzyl-*β*-D-glucopyranoside **3.40** (200 mg, 0.29

mmol) in DCM (10 mL), and refluxed at 40 °C under a nitrogen atmosphere. After 3 h, t.l.c (petrol:ethyl acetate, 2:1) indicated the formation of a single product (R_f 0) and complete consumption of starting material (R_f 0.5). The solution was cooled to rt over 1 h, after which potassium *tert*-butoxide (67 mg, 0.58 mmol) was added portion wise. After 10 min, t.l.c. (petrol:ethyl acetate, 2:1) indicated fornation of a mojor product (R_f 0.3), apart from a minor spot (R_f 0.6) **3.43**, and complete consumption of starting material (R_f 0). The reaction mixture was diluted with DCM (50 mL), and the mixture was washed with water (20 mL), saturated aq. sodium bicarbonate (20 ml) and brine (20 ml). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) to afford methyl 3,4,6-tri-O-benzyl-*β*-D-glucopyranoside **3.42** (0.118 g, 88%) as white crystalline solid. m. p. 71 - 72 °C (petrol/ethyl acetate) (lit.[39] 71 - 72 °C); $[\alpha]_D^{20}$ -4.2 (*c*, 1.0 in $CHCl_3$) (lit.[39] $[\alpha]_D^{25}$ -4.7 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$)[39]: 3.53 (1H, ddd, $J_{4,5}$ 9.9 Hz, H-5), 3.61 (3H, s, CH_3O), 3.57–3.70 (3H, m, H-2, H-3, H-4), 3.75 (1H, dd, $J_{5,6'}$ 4.3 Hz, H-6), 3.81 (1H, dd $J_{5,6'}$ 2.1, $J_{6,6'}$ 10.8 Hz, H-6'), 4.23 (1H, d, $J_{1,2}$ 7.3 Hz, H-1), 4.60, 4.68 (2H, ABq, *J* 12.2 Hz, CH_2Ph), 4.59, 4.88 (2H, ABq, *J* 10.8 Hz, CH_2Ph), 4.90, 4.97 (2H, ABq, *J* 11.3 Hz, CH_2Ph), 7.20–7.44 (15H, m, ArC-H).

3.43: δ_H (400 MHz, $CDCl_3$): 2.28 (3H, s, $SOCH_3$), 3.82, 3.88 (9H, 2 x s, 3 x OCH_3), 6.15 (2H, s, ArC-H); δ_C (100 MHz, $CDCl_3$): 18.3 (q, $SOCH_3$), 55.4, 56.2 (2 x q, *o* OCH_3, *p* OCH_3), 91.0 (d, Ar C-H), 103.6 (s, Ar-CSO), 161.5, 161.6 (2 x s, *o*, *p* Ar-$COCH_3$); HRMS (ES^+) calculated for $C_{10}H_{14}O_4SNa$ (MNa^+) 253.0504, found 253.0511.

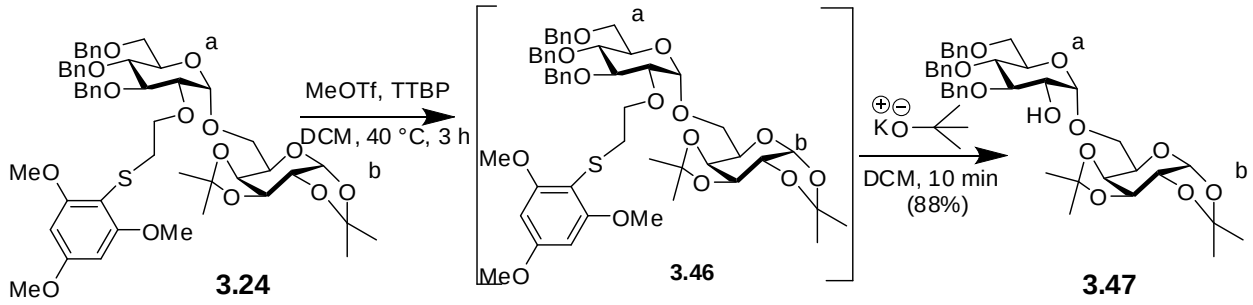
Methyl 3,4,6-tri-*O*-benzyl-*α*-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-*α*-D-glucopyranoside 3.45



MeOTf (26 µL, 0.22 mmol), and TTBP (72 mg, 0.30 mmol) were added to the solution of 3,4,6-tribenzyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*-D-glucopyranosyl-(1→6)-methyl-2,3,4-*O*-tribenzyl-*α*-D-glucopyranoside **3.30** (165 mg, 0.15 mmol) in DCM (10 mL), and refluxed at 40 °C under a nitrogen atmosphere. After 3 h, t.l.c (petrol:ethyl acetate, 2:1) indicated the formation of a single product (R_f 0) and complete consumption of starting material (R_f 0.3). The solution was cooled to rt over 1 h, after which potassium *tert*-butoxide (33 mg, 0.29 mmol) was added portion wise. After 10 min, t.l.c. (petrol:ethyl acetate, 2:1) indicated fornation of a mojor product (R_f 0.2), and complete consumption of starting material (R_f 0). The reaction mixture was diluted with DCM (50 mL), and the mixture was washed with water (20 mL), saturated aq. sodium bicarbonate (20 ml) and brine (20 ml). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford methyl 3,4,6-tri-*O*-benzyl-*α*-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-*α*-D-glucopyranoside **3.45** (0.116 g, 86%) as colorless oil; $[\alpha]_D^{20}$ + 81.2 (*c*, 1.0 in $CHCl_3$) (lit.[40] $[\alpha]_D^{22}$ + 73.6 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$): [40] 3.28 (3H, s, OCH_3), 3.38-3.46 (3H, m, H-2_b, 4_b, 4_a), 3.54-3.72 (7H, m, H-5_b, 6_b, 2_a, 3_a, 5_a, 6_a, $6'_a$), 3.85 (1H, dd, $J_{5,6}$ 4.3, 9.7 Hz, H-

6_b), 3.92 (1H, at, $J_{2,3}$ 9 Hz, H-3_b), 4.36, 4.39 (2H, ABq, *J* 12Hz, CH_2Ph), 4.49 (2H, d, *J* 11.9 Hz, CH_2Ph), 4.53 (1H, d, $J_{1,2}$ 3.6 Hz, H-1_b), 4.59 (1H, d, *J* 12 Hz, CHH'Ph), 4.69-4.76 (4H, m, 2 x CH_2Ph), 4.83-4.86 (3H, m, H-1_a, CH_2Ph), 4.92 (1H, d, *J* 11 Hz, CHH'Ph), 7.05-7.31 (30H, m, ArC-H).

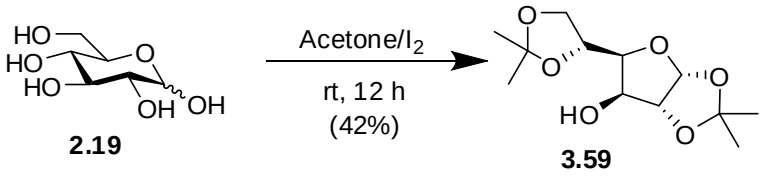
3,4,6-tri-O-benzyl-*α*-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-*α*-D-galactopyranose 3.47



MeOTf (28 µL, 0.24 mmol), and TTBP (76 mg, 0.32 mmol) were added to the solution of 3,4,6-tribenzyl-2-*O*-(2-(2,4,6-trimethoxybenzenethio)ethyl)-*α*-D-glucopyranosyl-(1→6)- 1,2:3,4-di-*O*-isopropylidene-*α*-D-galactopyranose **3.24** (150 mg, 0.16 mmol) in DCM (10 mL), and refluxed at 40 °C under a nitrogen atmosphere. After 3 h, t.l.c. (petrol:ethyl acetate, 2:1) indicated the formation of a single product (R_f 0) and complete consumption of starting material (R_f 0.4). The solution was cooled to rt over 1 h, after which potassium *tert*-butoxide (35 mg, 0.32 mmol) was added portion wise. After 10 min, t.l.c. (petrol:ethyl acetate, 2:1) indicated fornation of a mojor product (R_f 0.3), and complete consumption of starting material (R_f 0). The reaction mixture was diluted with DCM (50 mL), and the mixture was washed with water (20 mL), saturated aq. sodium bicarbonate (20 ml) and brine (20 ml). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 4:1) to afford 3,4,6-tri-O-benzyl-*α*-D-glucopyranosyl-(1→6)-1,2:3,4-di-*O*-

isopropylidene-*α*-D-galactopyranose **3.47** (97 mg, 88%) as colourless oil, $[\alpha]_D^{22}$ + 28.6 (*c*, 0.3 in $CHCl_3$) [lit.[40] $[\alpha]_D^{22}$ + 27 (*c*, 0.3 in $CHCl_3$), [δ_H (400 MHz, $CDCl_3$):[40] 1.34, 1.36, 1.46, 1.54 (12H, s, 3 x CH_3), 3.64-3.79 (7H, m, H-2_a, 3_a, 4_a, 5_a, 6_a, 6'$_a$, 6_b), 3.92 (1H, m, H-6'$_b$), 4.00 (1H, at, *J* 4 Hz, H-5_b), 4.27-4.34 (2H, m, H-2_b, H-4_b), 4.47, 4.44 (2H, ABq, *J* 7 Hz, CH_2Ph), 4.59-4.63 (2H, m, H-3_b, CHH'Ph), 4.79, 4.81 (2H, ABq, *J* 7 Hz, CH_2Ph), 4.90 (1H, d, $J_{1,2}$ 3.3 Hz, H-1_a), 4.95 (1H, d, *J*=11 Hz, CHH'Ph), 5.50 (1H, d, $J_{1,2}$ 5 Hz, H-1_b), 7.13-7.41 (15H, m, ArC-H).

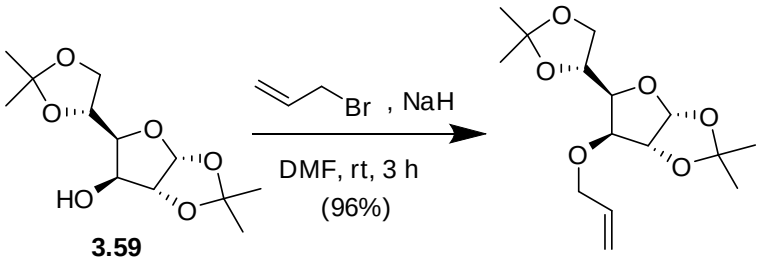
1,2:5,6-Di-*O*-isopropylidene-*α*-D-glucofuranose[41] **3.59**



2.19 **3.59**

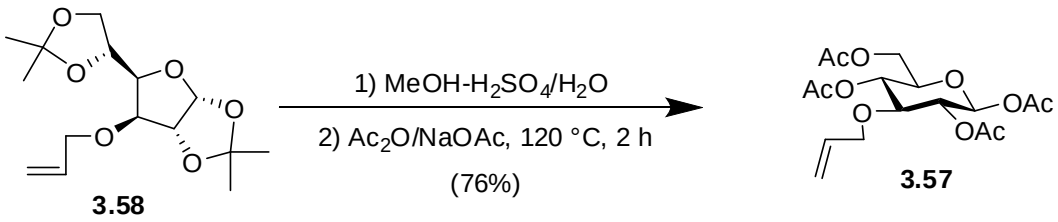
Iodine (7.50 g, 39.4 mmol) was dissolved in acetone (1.5 L) and D–Glucose **2.19** (25.0 g, 139 mmol) was added and stirred at rt. After 12 h, t.l.c. ($CHCl_3$:MeOH, 9:1) showed formation major spot (R_f 0.75) with respect to the starting material (R_f 0.05). Iodine was consumed by adding dilute sodiumthiosulfate to make solution colorless. After that it was extracted thrice with DCM (2 L), which was washed with water (2 x 500 mL), brine (500 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (petrol:ethyl acetate, 4:1) yielded 1,2:5,6-di-*O*-isopropylidene-*α*-D-glucofuranose **3.59** (15.0 g, 42%) as white crystalline solid; m. p. 106 – 108 °C (petrol/ethyl acetate) (lit.[42] 105 – 107 °C); $[\alpha]_D^{20}$ - 11.0 (*c*, 1.0 in $CHCl_3$), lit.[42] $[\alpha]_D^{20}$ – 13.5 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$):[42] 1.32 (3H, s, -CH_3), 1.36 (s, 3H, -CH_3), 1.44 (s, 3H, -CH_3), 1.49 (s, 3H, -CH_3), 2.21 (bs, OH), 3.97 – 3.99 (m, 1H, H-4), 4.04 – 4.08 (dd, $J_{6,6'}$ 8.0 Hz, $J_{6,5}$ 2.3 Hz 1H, H-6), 4.14–4.18 (1H, at, *J* 8.8 Hz H-6'), 4.33 (m, 2H, H-3, H-5), 4.52–4.53 (1H, d, *J* 4.5, H-2), 5.94–5.95 (d, 1H, H-1).

3-Allyl-1,2:5,6-diacetonegluco-D-furanose[7] **3.58**



3.59 (13.0 g, 50.0 mmol) was dissolved in anhydrous DMF (100 mL) and then to it was added suspension of sodium hydride (3.10 g, 107 mmol) in DMF (100 mL) at 0 °C under a nitrogen atmosphere. Allyl Bromide (11.2 mL, 124 mmol) was tfhen added slowly to the mixture. After 3 h, t.l.c. (petrol:ethyl acetate, 2:1) showed complete disappearance of starting material (R_f 0.1) and formation of a major product (R_f 0.7). The reaction was quenched by the addition of methanol and concentrated *in vacuo*. The residue was dissolved in diethyl ether (1 L), washed with water (2 x 100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (petrol:ethyl acetate, 7:1) yielded 3-allyl-1,2:5,6-diacetonegluco-D-furanose **3.58** (14.5 g, 96%) as colorless oil; $[\alpha]_D^{20}$ - 37.5 (*c*, 1.0 in $CHCl_3$), (lit.[43] $[\alpha]_D^{20}$ - 23.5 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$):[44] 1.29 (3H, s, -CH_3), 1.32 (3H, s, -CH_3), 1.40 (3H, s, -CH_3), 1.47 (3H, s, -CH_3), 3.86–4.12 (6H, m, -OC$\underline{H_2}$CH=CH_2, H-3, H-5, H-6, H-6'), 4.29 (dd, 1H, $J_{4,3}$ 7.5 Hz, $J_{4,5}$ 6.0 Hz, H-4), 4.52 (d, 1H, *J* 3.7 Hz, H-2), 5.18 (dd, 1H, J_z 10.8 Hz, J_{gem} 1.5 Hz, -$OCH_2CH=CH_E\underline{H_z}$), 5.30 (dd, 1H, J_E 15.8 Hz, J_{gem} 1.5 Hz, -$OCH_2CH=C\underline{H_E}H_z$), 5.82 – 5.94 (2H, m, H-1, -$OCH_2C\underline{H}=CH_2$).

3-allyl-1,2,4,6-tetraacetyl-*β*-gluco-D-pyranose[7] **3.57**

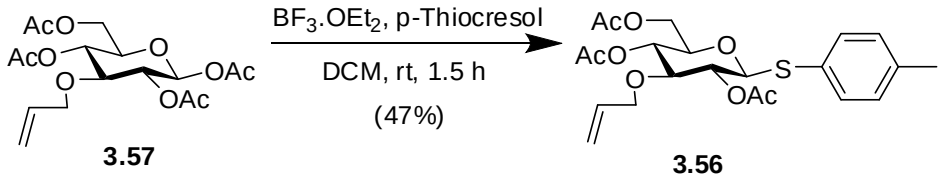


3.58 **3.57**

A mixture of **3.58** (0.900 g, 3.00 mmol) and 4% aq. H_2SO_4 (20 mL) was stirred at rt for 18 h. The resulting solution was then stirred with $CaCO_3$ (2 g) for 2h. The mixture was filtered and the residue was repeatedly washed with methanol. The combined filtrate and the washings were evaporated under reduced pressure. The residual syrupy material was treated with minimal volume of water and filtered to remove some insoluble material. The residual was then concentrated *in vacuo* to give a syrup. This syrup was added slowly (over 15 minutes) to pre heated (heated over half an hour) solution of sodium acetate (0.656 g, 8.00 mmol) at 120 °C in 10 mL of acetic ahydride. After 2 h, t.l.c. (petrol:ethyl acetate, 3:1) showed complete absence of starting material (R_f 0) and formation of a major product (R_f 0.3). The reaction was cooled to rt and then 10 mL of water and ice was added. The precipitate was filtered out. Purification by flash chromatography (petrol:ethyl acetate, 4:1) yielded 3-allyl-1,2,4,6-tetraacetyl-*β*-gluco-D-pyranose **3.57** (0.850 g, 76%) as white crystalline solid; m. p. 89 – 91 °C (petrol/ethyl acetate), $[\alpha]_D^{20}$ + 0.3 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 2.05–2.08 (12H, 4 x s, 4 x CH_3COO), 3.62 (1H, ddd, $J_{4,5}$ 9.5 Hz, $J_{5,6}$ 3.1 Hz, $J_{5,6'}$ 2.4 Hz, 1H, H-5), 3.71 (2H, m, H-3), 4.07 (3H, m, H-6', $OC\underline{H}_2CH=CH_2$), 4.19 (1H, m, H-6), 5.15 (4H, m, H-2, H-4, $CH=CH_E\underline{H}_Z$, $CH=C\underline{H}_EH_Z$), 5.62 (1H, d, $J_{1,2}$ 8.4Hz, H-1), 5.78 (1H, m, $C\underline{H}=CH_2$); δ_C (100 MHz, $CDCl_3$): 20.7, 20.7, 20.8, 20.8 (4 x q, 4 x $CO\underline{C}H_3$), 61.8, 73.1 (2 x t, C-6, $\underline{C}H_2CH=CH_2$), 69.0, 71.5, 73.0, 79.6 (4 x d, C-2, C-3, C-4,

C-5), 92.0 (d, C-1), 117.2 (t, CH=$\underline{C}H_2$), 134.0 (d, $\underline{C}$H=CH2), 169.0, 169.2, 170.7 (3 x s, 3 x C=O); HRMS (ES^+) calculated for $C_{17}H_{24}O_{10}Na$ (MNa^+) 411.1267, found 411.1272.

***p*-Tolyl 2,4,6-tri-*O*-acetyl-3-*O*-allyl-1-thio-*β*-D-glucopyranoside**[45] **3.56**

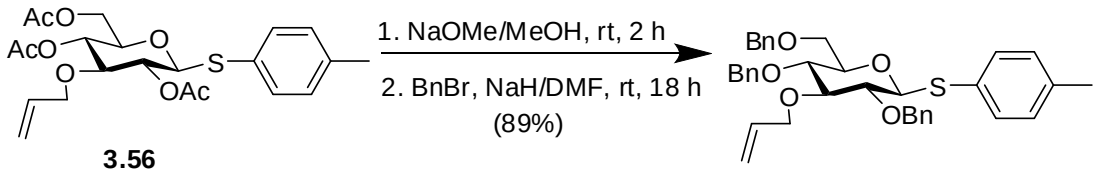


3.57 **3.56**

Tetraacetate **3.57** (2.00 g, 5.15 mmol) was suspended in freshly distilled DCM (10 mL). *p*-Thiocresol (766 mg, 6.18 mmol) was added and the mixture cooled to 0° C. $BF_3.OEt_2$ (0.95 mL, 0.73 mmol) was added and the mixture was stirred under a nitrogen atmosphere. After 1.5 h, t.l.c. (petrol:ethyl acetate, 3:2) indicated the formation of a major product (R_f 0.3) and the complete consumption of starting material (R_f 0.25). Triethylamine (2 mL) was then added, and the mixture was then diluted with ether (100 mL) and washed with water (100 mL). The aqueous layer was re-extracted with ether (50 mL), and the combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (3:2, petrol:ethyl acetate) to afford the desired *β* thioglycoside **3.56** (1.10 g, 47%) as a white solid; m. p. 118-120 °C (petrol/ethyl acetate), lit. [45] 127–128 °C; $[\alpha]_D^{20}$ – 16.2 (*c*, 1.0 in $CHCl_3$), (lit.[45] $[\alpha]_D^{20}$ - 14.4 (*c*, 0.9 in $CHCl_3$); ν_{max} (KBr) 1740 (s, C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$):[45] 2.08, 2.08, 2.15 (9H, 3 x s, 3 x $COCH_3$), 2.34 (3H, s, $ArCH_3$), 3.57–3.63 (1H, m, H-5), 3.59 (1H, at, *J* 9.2 Hz, H-3), 4.02–4.11 (2H, m, $OC\underline{H}_2CH=CH_2$), 4.13–4.20 (2H, m, H-6, H-6'), 4.56 (1H, d, $J_{1,2}$ 10.1 Hz, H-1), 4.96 (1H, at, *J* 9.5 Hz, H-2), 5.00 (1H, at, *J* 9.8 Hz, H-4), 5.13 (1H, d, J_Z 10.4 Hz, $CH=CH_E\underline{H}_Z$), 5.19 (1H, dd, *J*gem 1.6 Hz, J_E 17.2 Hz, $CH=C\underline{H}_EH_Z$), 5.75 (1H, m, $C\underline{H}=CH_2$), 7.11, 7.40 (4H, 2 x d, *J* 8.1 Hz, Ar–H); δ_C (100 MHz, $CDCl_3$):[45] 21.2, 21.3, 21.5, 21.6 (4 x q, 3 x $CO\underline{C}H_3$, $Ar\underline{C}H_3$), 63.0, 73.5 (2 x t, C-6,

$\underline{C}H_2CH=CH_2$), 69.9, 71.7, 76.4, 81.7 (4 x d, C-2, C-3, C-4, C-5), 86.8 (d, C-1), 117.5 (t, $CH=\underline{C}H_2$), 129.0, 138.8 (2 x s, Ar–C) 130.0, 133.7 (2 x d, Ar–CH), 134.6 (d, $\underline{C}H=CH2$), 169.6, 169.7, 171.2 (3 x s, 3 x C=O); HRMS (ES^+) calculated for $C_{22}H_{28}O_8SNa$ (MNa^+) 475.1403, found 475.1401.

***p*-Tolyl 3-*O*-allyl-2,4,6-tri-*O*-benzyl-1-thio-*β*-D-glucopyranoside**[45] **3.55**

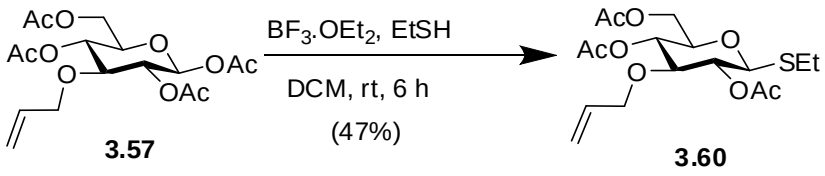


3.56 **3.55**

Acetylated thioglycoside **3.56** (1.77 g, 3.92 mmol) was suspended in methanol (10 mL). Sodium (5.00 mg, 0.200 mmol) was dissolved in methanol (5 mL), and the solution then added to the mixture, which was then stirred under a nitrogen atmosphere. After 2 h, t.l.c. (ethyl acetate) indicated the formation of a single product (R_f 0.6) and the complete consumption of the starting material (R_f 0.7). The mixture was then concentrated *in vacuo*, and The residue was then dissolved in DMF (30 mL) and the solution cooled to 0 °C. Benzyl bromide (2.44 mL, 20.6 mmol) and sodium hydride (1.10 g, 27.5 mmol) were added and the mixture was stirred under N_2. After 18 h, t.l.c. (petrol:ethyl acetate, 5:1) indicated the formation of a major product (R_f 0.7) and the complete consumption of starting material (R_f 0.0). Methanol (10 mL) was added slowly, and the mixture was then diluted with ether (200 mL), and washed with water (200 mL). The organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and the residue was purified by flash column chromatography (petrol:ethyl acetate, 8:1) to afford benzylated thioglycoside **3.55** (2.08 g, 89%) as a white, crystalline solid, m. p. 71 - 73 °C (EtOH), (lit.[45] 75 °C (EtOH)); $[\alpha]_D^{20}$ – 6.3 (*c*, 1.0 in $CHCl_3$), (lit.[45] $[\alpha]_D^{20}$ - 6.5 (*c*, 1.0 in $CHCl_3$); ν_{max} (KBr) 3025 (s, Ar-C-H)

cm^{-1}; δ_H (400 MHz, $CDCl_3$):[45] 2.32 (3H, s, $ArCH_3$), 3.41–3.51 (2H, m, H-2, H-5), 3.53–3.61 (2H, m, H-3, H-4), 3.73 (1H, dd, $J_{5,6}$ 4.8 Hz, $J_{6,6'}$ 10.9 Hz, H-6), 3.79 (1H, dd, $J_{5,6'}$ 2.1 Hz, H-60), 4.27–4.40 (2H, m, -OC$\underline{H}_2$CH=CH_2), 4.55, 4.62 (2H, ABq, J_{AB} 12.1 Hz, $PhCH_2$), 4.58 (1H, d, $J_{1,2}$ 9.7 Hz, H-1), 4.59, 4.83 (2H, ABq, J_{AB} 11.1 Hz, $PhCH_2$), 4.74, 4.88 (2H, ABq, J_{AB} 10.1 Hz, $PhCH_2$), 5.18 (1H, daq, J_Z 10.4 Hz, J 1.4 Hz, CH=C$H_E\underline{H}_Z$), 5.30 (1H, daq, J 1.7 Hz, J_E 17.1 Hz, CH=C$\underline{H}_E H_Z$), 5.98 (1H, ddat, C$\underline{H}$=CH_2), 7.04–7.52 (19H, m, Ar–H); δ_C (100 MHz, $CDCl_3$):[45] 21.1 (q, $ArCH_3$), 69.0, 73.4, 74.5, 75.1, 75.5 (5 x t, C-6, $\underline{C}H_2$CH=CH_2, 3 x $PhCH_2$), 77.7, 79.0, 80.7, 86.4, 87.6 (5 x d, C-1, C-2, C-3, C-4, C-5), 116.9 (t, CH=$\underline{C}H_2$), 127.5, 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 129.6, 132.7, 134.9 (11 x d, Ar–CH, $\underline{C}$H=CH_2), 137.7, 138.1, 138.1, 138.4 (4 x s, Ar–C); HRMS (ES^+) calculated for $C_{37}H_{40}O_5SNa$ (MNa^+) 619.2494, found 619.2499.

Ethyl 2,4,6-tri-*O*-acetyl-3-*O*-allyl-1-thio-*β*-D-glucopyranoside[45] **3.60**

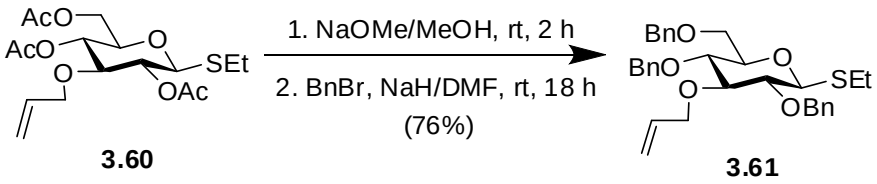


3.57 **3.60**

Tetraacetate **3.57** (5.00 g, 13.00 mmol) was suspended in freshly distilled DCM (50 mL). Ethanethiol (1.5 mL, 20.00 mmol) was added and the mixture cooled to 0° C. $BF_3.OEt_2$ (2.50 mL, 18.00 mmol) was added and the mixture was stirred under a nitrogen atmosphere. After 6 h, t.l.c. (petrol:ethyl acetate, 3:2) indicated the formation of a major product (R_f 0.3) and the complete consumption of starting material (R_f 0.2). Triethylamine (2 mL) was then added, and the mixture was then diluted with ether (500 mL) and washed with water (200 mL). The aqueous layer was re-extracted with ether (100 mL), and 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, 2:1) to afford the desired *β* thioglycoside

3.60 (2.30 g, 47%) as a white solid; m. p. 118-120 °C (petrol/ethyl acetate), $[\alpha]_D^{20}$ – 28.3 (*c*, 1.0 in $CHCl_3$), ν_{max} (KBr) 1745 (s, C=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.25 (3H, t, J_{vic} 7.5 Hz, $SCH_2C\underline{H}_3$), 2.07, 2.08, 2.09 (9H, 3 x s, 3 x $COCH_3$), 2.70 (2H, m, $SC\underline{H}_2CH_3$), 3.57–3.61 (2H, m, H-2, H-4), 4.02–4.13 (3H, m, H-6, $OC\underline{H}_2CH=CH_2$), 4.19 (1H, dd, $J_{6,6'}$ 12.5 Hz, $J_{6',5}$ 5.5 Hz H-6'), 4.38 (1H, d, $J_{1,2}$ 10.0 Hz, H-1), 5.00–5.04 (2H, m, H-3, H-5), 5.13 (1H, d, J_Z 10.0 Hz, $CH=CH_E\underline{H}_Z$), 5.19 (1H, d, J_E 17.0 Hz, $CH=C\underline{H}_EH_Z$), 5.77 (1H, m, $C\underline{H}=CH_2$); δ_C (125 MHz, $CDCl_3$): 14.8 (q, $SCH_2\underline{C}H_3$) 20.8, 20.9, 21.0 (3 x q, 3 x $CO\underline{C}H_3$), 23.9 (t, $S\underline{C}H_2CH_3$) 62.5 (t, C-6), 69.5 (t, $\underline{C}H_2CH=CH_2$), 71.2 (d, C-5), 73.1, 76.2 (2 x d, C-3, C-4), 81.2 (d, C-2), 83.6 (d, C-1), 117.0 (t, $CH=\underline{C}H_2$), 134.6 (d, $\underline{C}H=CH2$), 169.2, 169.3, 171.2 (3 x s, 3 x C=O); HRMS (ES^+) calculated for $C_{17}H_{26}O_8SNa$ (MNa^+) 413.1246, found 413.1243.

Ethyl 3-*O*-allyl-2,4,6-tri-*O*-benzyl-1-thio-*β*-D-glucopyranoside[45] **3.61**

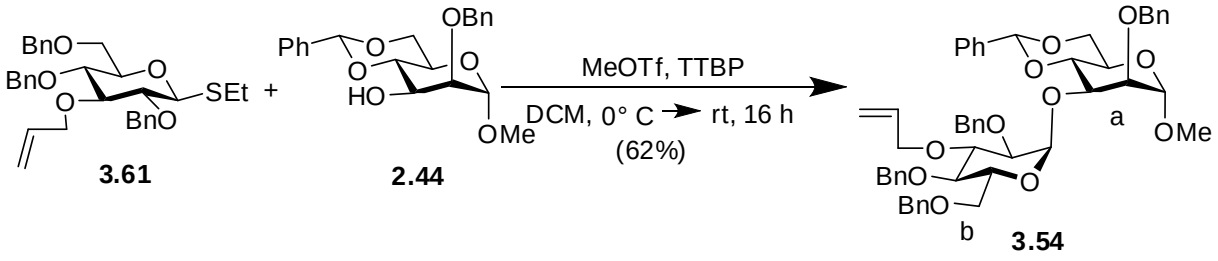


3.60 **3.61**

Acetylated thioglycoside **3.60** (2.30 g, 3.92 mmol) was suspended in methanol (20 mL). Sodium (14.0 mg, 0.60 mmol) was dissolved in methanol (5 mL), and this solution was then added to the mixture, which was then stirred under a nitrogen atmosphere. After 2 h, t.l.c. (petrol:ethyl acetate, 3:2) indicated the formation of a single product (R_f 0.0) and the complete consumption of the starting material (R_f 0.5). The mixture was then concentrated *in vacuo*, and The residue was then dissolved in DMF (50 mL) and the solution cooled to 0 °C. Benzyl bromide (6.00 mL, 50.0 mmol) and sodium hydride (0.87 g, 36.0 mmol) were added, and the mixture was stirred under N_2. After 18 h, t.l.c. (petrol:ethyl acetate, 2:1) indicated the formation of a major product (R_f 0.7) and the complete consumption of starting material (R_f 0.0). Methanol (50 mL) was

added slowly, and the mixture was then diluted with ether (200 mL), and washed with water (200 mL). The organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and the residue was purified by flash column chromatography (petrol:ethyl acetate, 10:1) to afford benzylated thioglycoside **3.61** (2.10 g, 76%) as a white, crystalline solid, m. p. 32 - 34 °C (petrol/ethyl acetate); $[\alpha]_D^{20}$ + 3.4 (*c*, 1.0 in $CHCl_3$); ν_{max} (KBr) 1647 (w, C=C) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 1.32 (3H, t, J_{vic} 7.5 Hz, $SCH_2C\underline{H}_3$), 2.79 (2H, m, $SC\underline{H}_2CH_3$), 3.38 (1H, at, *J* 8.5 Hz H-2), 3.42 (1H, m, H-5), 3.51–3.57 (2H, m, H-3, H-4), 3.65–3.75 (2H, m, H-6, H-6'), 4.33–4.39 (2H, m, -$OC\underline{H}_2CH=CH_2$), 4.42 (1H, d, $J_{1,2}$ 10.0 Hz, H-1), 4.54, 4.62 (2H, ABq, J_{AB} 12.1 Hz, $PhCH_2$), 4.59, 4.83 (2H, ABq, J_{AB} 11.1 Hz, $PhCH_2$), 4.74, 4.88 (2H, ABq, J_{AB} 10.1 Hz, $PhCH_2$), 5.17 (1H, d, J_Z 10.5 Hz, $CH=CH_E\underline{H}_Z$), 5.30 (1H, d, J_E 17.5 Hz, $CH=C\underline{H}_EH_Z$), 5.98 (1H, m, $C\underline{H}=CH_2$), 7.04-7.52 (15H, m, Ar-CH); δ_C (125 MHz, $CDCl_3$): 15.1 (q, $SCH_2\underline{C}H_3$), 25.0 (t, $S\underline{C}H_2CH_3$) 69.2 (t, C-6), 74.5 (t, $\underline{C}H_2CH=CH_2$) 73.4, 75.1, 75.6 (3 x t, 3 x $Ph\underline{C}H_2$), 77.9 (d, C-3/C-4), 79.1 (d, C-5), 81.7 (d, C-2), 85.0 (d, C-3/C-4), 86.4 (d, C-1), 116.8 (t, $CH=\underline{C}H_2$), 127.6, 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 128.5, 128.6 (9 x d, Ar–CH), 135.0 (d, $\underline{C}H=CH_2$), 138.0, 138.1, 138.2 (3 x s, Ar–C); HRMS (ES^+) calculated for $C_{32}H_{38}O_5SNa$ (MNa^+) 557.2241, found 557.2336.

Methyl 3-*O*-allyl-2,4,6-tri-*O*-benzyl-*α*-D-glucopyranosyl-(1→3)-2-*O*-benzyl-(R)-4,6-*O*-benzylidene-*α*-D-mannopyranoside[4] **3.54**

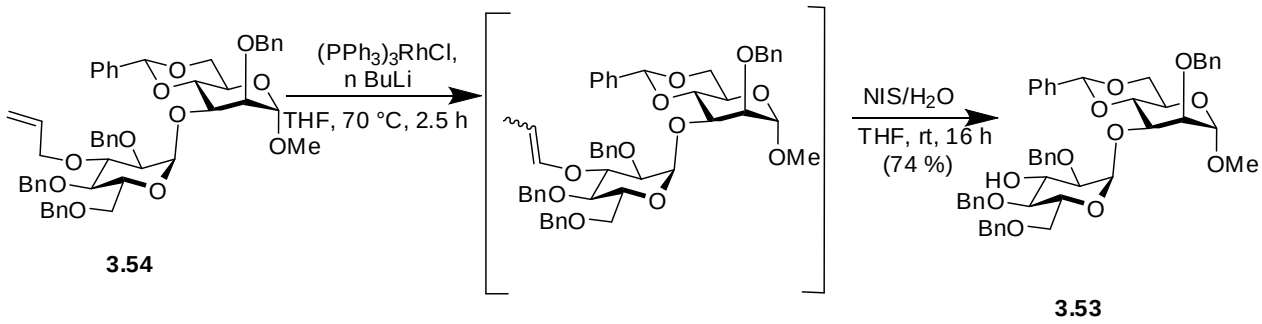


Alcohol **2.44** (1.00 g, 2.68 mmol), benzylated thioglycosyde **3.61** (1.30 g, 2.43 mmol), and TTBP **2.46** (2.00 g, 12.15 mmol) were dissolved in dry diethyl ether (10 mL) in a flame dried flask containing 4 Å molecular sieves (c.a. 500 mg). The mixture was cooled to 0° C, MeOTf (0.82 mL, 7.30 mmol) was added and the solution stirred. After 16 h, t.l.c. (petrol:ethyl acetate, 3:1) indicated the formation of a single product (R_f 0.7) and the complete consumption of the thioglycoside (R_f 0.9). TEA (1 mL) was added, the solution was stirred for 10 min, and then filtered through Celite®. The filtrate was then concentrated *in vacuo*, and the residue

purified by flash column chromatography (petrol:ethyl acetate, 7:1) to afford the disaccharide **3.54** (1.35 g, 62%) as colorless oil; $[\alpha]_D^{20}$ + 93.6 (*c*, 1.0 in $CHCl_3$), (lit.[45] $[\alpha]_D^{20}$ + 93.0 (*c*, 1.0 in $CHCl_3$); ν_{max} (KBr) 3025 (s, Ar-C-H) cm^{-1}; δ_H (400 MHz, $CDCl_3$):[45]3.33 (3H, s, OCH_3), 3.46 (1H, dd, $J_{1,2}$ 3.6 Hz, $J_{2,3}$ 9.6 Hz, H-2_b), 3.54 (1H, at, *J* 9.4 Hz, H-4_b), 3.64–3.71 (2H, m, H-6_b, H-$6'_b$), 3.78–4.15 (5H, m, H-2_a, H-5_a, H-6_a, H-3_b, H-5_b), 4.18–4.26 (2H, m, H-$6'_a$, OC<u>H</u>H'CH=CH_2), 4.31, 4.54 (2H, ABq, J_{AB} 12.5 Hz, $PhCH_2$), 4.31–4.35 (1H, m, H-4a), 4.39 (1H, dd, $J_{2,3}$ 2.9 Hz, $J_{3,4}$ 10.0 Hz, H-3_a), 4.42–4.49 (1H, m, OCH<u>H</u>'CH=CH_2), 4.45, 4.58 (2H, ABq, J_{AB} 12.2 Hz, $PhCH_2$), 4.47, 4.88 (2H, ABq, J_{AB} 1.0 Hz, $PhCH_2$), 4.71 (1H, d, $J_{1,2}$ 1.3 Hz, H-1_a), 4.78, 4.93 (2H, ABq, J_{AB} 11.9 Hz, $PhCH_2$), 5.09 (1H, dd, J_Z 10.4 Hz, J*gem* 1.0 Hz, CH=CH_E<u>H</u>$_Z$), 5.22 (1H, dd, *Jgem* 1.6 Hz, J_E 17.2 Hz, CH=C<u>H</u>$_E$$H_Z$), 5.47 (1H, s, PhCH), 5.50 (1H, d, H-1b), 5.96 (1H, m, C<u>H</u>=CH_2), 7.00–7.47 (25H, m, Ar–CH); δ_C (100 MHz, $CDCl_3$):[45] 54.8 (q, OCH_3), 63.9 (d, C-5_a), 68.6 (t, C-6_b), 68.9 (t, C-6_a), 70.5 (t, $PhCH_2$), 70.8 (d, C-5_b), 72.7 (d, C-3_a), 73.4, 73.8, 74.3, 75.0 (4 x t, O<u>C</u>H_2CH=CH_2, 3 x $PhCH_2$), 77.2, 77.3 (2 x d, C-2_a, C-4_b), 78.6 (d, C-2_b), 79.6 (d, C-4_a), 81.0 (d, C-3_b), 96.9 (d, C-1_b), 100.6 (d, C-1_a), 102.3 (d, PhCH), 116.6 (t, CH=<u>C</u>H_2), 126.4, 127.0, 127.1, 127.6, 127.6, 127.8, 127.8, 127.9, 128.1, 128.2, 128.2,

128.3, 128.4, 129.2 (14 x d, Ar–CH), 135.4 (d, $\underline{C}H=CH_2$), 137.4, 138.0, 138.0, 138.3, 138.5 (5 x s, Ar–C); HRMS (ES^+) calculated for $C_{55}H_{58}O_{11}Na$ (MNa^+) 917.3871, found 917.3879.

Methyl -2,4,6-tri-*O*-benzyl-*α*-D-glucopyranosyl-(1→3)-2-*O*-benzyl-(R)-4,6-*O*-benzylidene-*α*-D-mannopyranoside[46] **3.53**

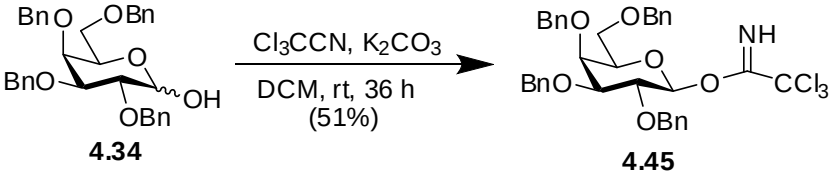


Wilkinson's catalyst (86 mg, 0.093 mmol) was dissolved in distilled THF (4 mL) and degassed. n-Butyl lithium (0.09 mL, 0.14 mmol, 1.6 M solution in hexanes) was added and the mixture stirred for 10 min under a nitrogen atmosphere. Allyl protected disaccharide **3.54** (786 mg, 0.93 mmol) was dissolved in distilled THF (4 mL) and the mixture heated to 70 °C. The catalyst solution prepared above was then added *via* cannula under a nitrogen atmosphere. After 2 h, 30 min, t.l.c. (petrol:ethyl acetate, 4:1) indicated the presence of a single compound, the vinyl ether (R_f 0.3). The mixture was then allowed to cool to rt, and to the mixture was added H_2O (5 mL), and NIS (1.05 g, 4.65 mmol). The mixture was stirred for 16 h at rt, after which t.l.c. (petrol:ethyl acetate, 2:1) indicated the formation of a single product (R_f 0.7), and the complete consumption of starting material (R_f 0.6). The solution was then concentrated *in vacuo* and the residue obtained was purified by flash chromatography (petrol:ethyl acetate, 7:2) to afford methyl -2,4,6-tri-*O*-benzyl-*α*-D-glucopyranosyl-(1→3)-2-*O*-benzyl-(R)-4,6-*O*-benzylidene-*α*-D-mannopyranoside **3.53** (0.55 g, 74.0%) as white solid; m. p. 43 – 45 °C (petrol/ethyl acetate); $[\alpha]_D^{20}$ + 104 (*c*, 1.0 in $CHCl_3$); ν_{max} (KBr) 3758 (br, OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 3.30–3.34

(4H, m, OCH_3, H-2_b), 3.53 (1H, at, *J* 9.4 Hz, H-4_b), 3.64–3.71 (2H, m, H-6_b, H-$6'_b$), 3.78–3.84 (4H, m, H-2_a, H-5_a, H-3_b, H-5_b), 4.11 (1H, at, *J* 8.8 Hz, H-6_a), 4.31, 4.54 (2H, ABq, J_{AB} 12.5 Hz, $PhCH_2$), 4.31–4.35 (1H, m, H-4_a), 4.23 (1H, m, H-$6'_a$), 4.36 (1H, dd, $J_{2,3}$ 2.9 Hz, $J_{3,4}$ 10.0 Hz, H-3_a), 4.45, 4.58 (2H, ABq, J_{AB} 12.2 Hz, $PhCH_2$), 4.47, 4.88 (2H, ABq, J_{AB} 1.0 Hz, $PhCH_2$), 4.68 (1H, d, $J_{1,2}$ 1.3 Hz, H-1_a), 4.78, 4.90 (2H, ABq, J_{AB} 11.9 Hz, $PhCH_2$), 5.40 (1H, s, PhCH), 5.50 (1H, d, H-1b), 7.00–7.47 (25H, m, Ar–H); δ_C (100 MHz, $CDCl_3$): 54.8 (q, OCH_3), 63.9 (d, C-5_a), 68.7 (t, C-6_b), 68.9 (t, C-6_a), 70.3 (t, $PhCH_2$), 70.4 (d, C-5_b), 72.9 (d, C-3_a), 73.4, 73.5, 73.8 (3 x t, 3 x $PhCH_2$), 74.5, 77.2 (2 x d, C-2_a, C-4_b), 77.3 (d, C-2_b), 77.9 (d, C-4_a), 79.6 (d, C-3_b), 96.4 (d, C-1_b), 100.6 (d, C-1_a), 102.4 (d, PhCH), 126.4, 127.0, 127.1, 127.6, 127.6, 127.8, 127.8, 127.9, 128.1, 128.2, 128.2, 128.3, 128.4, 129.2 (14 x d, Ar–CH), 137.4, 138.0, 138.0, 138.3, 138.5 (5 x s, Ar–C); HRMS (ES^+) calculated for $C_{48}H_{52}O_{11}Na$ (MNa^+) 827.3401, found 827.3411.

5.4 Experimental for chapter 4

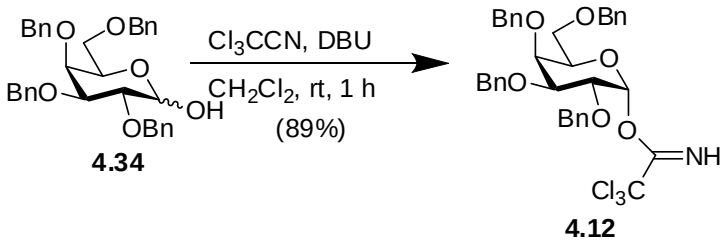
2,3,4,6-Tetrabenzyl-*β*-D-glucopyranosyl trichloroacetimidate[49] 4.45



Trichloroacetonitrile (1.8 mL, 13.0 mmol) and K_2CO_3 (flame dried) (5.80 g, 40.0 mmol) were added to a solution of **4.34** (500 mg, 0.93 mmol) in anhydrous DCM (50 mL) and the mixture was stirred at rt. After 36 h, t.l.c. (petrol:ethyl acetate, 4:1, with 1% TEA) indicated the formation of a major product (R_f 0.4) and a minor product (R_f 0.6), and complete disappearance of starting material (R_f 0.1). The mixture was then concentrated *in vacuo* and the residue was purified by flash column chromatography (petrol:ethyl acetate, 8:1, with 1% TEA) and the

major product was isolated to afford 2,3,4,5-terabenzyl-*β*-D-glucopyranosyl trichloroacetimidate **4.45** as a white crystalline solid (300 mg, 51%); m. p. 90 – 92 °C (petrol/ethyl acetate); ν_{max} (KBr) 3336 (w, N-H), 1673 (s, C=N) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 3.39-3.49 (2H, m, H-6, H-6'), 3.50-3.60 (1H, m, H-3), 3.99 (1H, m, H-2), 4.06-4.18 (2H, m, H-4, H-5), 4.44-4.97 (8H, m, 4 x $OC\underline{H}_2Ph$), 5.75 (1H, d, $J_{1,2}$ 7.6 Hz, H-1), 7.26-7.33 (20H, m, Ar-CH), 8.51 (1H, s, N-H); δ_C (100 MHz, $CDCl_3$): 68.1 (t, C-6), 73.1, 73.4, 73.5, 74.4 (4 x t, 4 x $O\underline{C}H_2Ph$), 74.8, 75.2, 78.1 (3 x d, C-2, C-4, C-5), 82.2 (d, C-3), 98.7 (d, C-1), 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4 (9 x d, ArCH), 138.3, 138.3, 138.5, 138.5 (4 x s, 4 x ArC), 161.5 (s, C=NH).

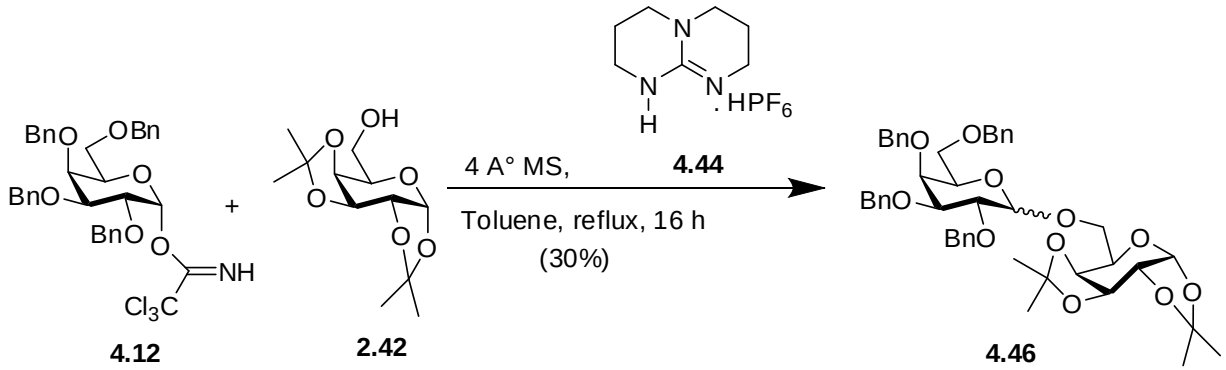
2,3,4,6-Tetrabenzyl-*α*-D-glucopyranosyl trichloroacetimidate[50] **4.12**



To a solution of **4.34** (800 mg, 1.48 mmol) in anhydrous DCM (10 mL) were added trichloroacetonitrile (1.7 mL, 12.3 mmol) and DBU (0.090 mL, 0.59 mmol) and the mixture was stirred at rt. After 1 h, t.l.c. (petrol:ethyl acetalte, 4:1, with 1% TEA) indicated the formation of a major product (R_f 0.6) and a minor product (R_f 0.4), and complete disappearance of starting material (R_f 0.1). The solvent was then concentrated *in vacuo* and the residue was purified by flash column chromatography (petrol:ethyl acetate, 10:1, with 1% TEA) and the major product was isolated to afford 2,3,4,5-terabenzyl-*α*-D-glucopyranosyl trichloroacetimidate **4.12** as a colorless oil (900 mg, 89%); ν_{max} (KBr) 3336 (w, N-H), 1673 (s, C=N) cm^{-1}; δ_H (400 MHz, $CDCl_3$):[50] 3.48-3.63 (2H, m, H-6, H-6'), 3.96-4.08 (2H, m, H-3, H-2), 4.10-4.19 (1H, m, H-5), 4.19-4.24 (1H, m, H-4), 4.38-4.50 (8H, m, 4 x $OC\underline{H}_2Ph$), 6.53 (1H, d, $J_{1,2}$ 3.2 Hz, H-1), 7.24-7.34 (20H, m, Ar-CH), 8.51 (1H, s, N-H); δ_C (100 MHz, $CDCl_3$): 68.3 (t, C-6), 72.2, 72.9, 72.9,

73.4 (4 x t, 4 x O<u>C</u>H$_2$Ph), 74.6, 74.9, 75.9 (3 x d, C-2, C-4, C-5), 78.0 (d, C-3), 95.2 (d, C-1), 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3 (9 x d, ArCH), 137.8, 138.4, 138.5, 138.6 (4 x s, 4 x ArC), 161.2 (s, C=NH).

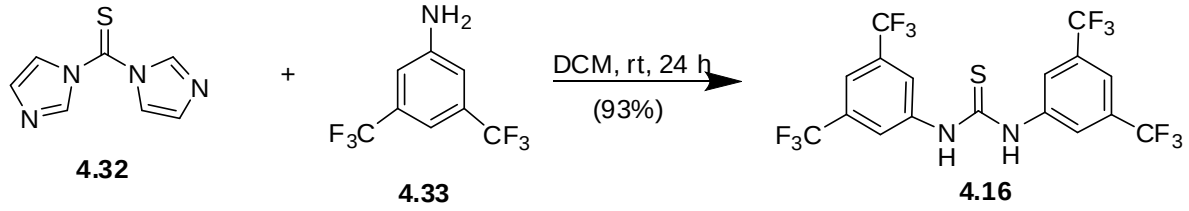
2,3,4,6-tetraacetyl-*α*/*β*-D-galactopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside 4.46



A solution of 2,3,4,6-tetracetyl-*α*-D-galactopyranosyl trichloroacetimidate **4.12** (0.050 g, 0.073 mmol), 1,2:3,4–di–*O*–isopropylidene–*α*–D–galactopyranose **2.42** (0.021, 0.079) and 1,5,7-triazabicyclo[4.4.0]dec-5-enium hexafluorophosphate **4.44** (3.8 mg, 0.015 mmol) in freshly distilled toluene (5 mL) was added to a flame-dried round-bottom flask containing activated 4 Å molecular sieves (0.100 g). The mixture was refluxed under a nitrogen atmosphere. After 16 h, t.l.c. (petrol:ethyl acetate, 2:1) showed formation of a minor product **4.46** (R_f 0.7) together with some starting material **4.12** (R_f 0.9) and **2.42** (R_f 0.3). The reaction was quenched with saturated aq. sodium bicarbonate solution (5 mL) and filtered through Celite®. The mixture was diluted with DCM (20 mL), washed with saturated aq. sodium bicarbonate solution (2 x 10 mL), and the aqueous layer was extracted with DCM (20 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) to afford 2,3,4,6-tetraacetyl-*α*/*β*-D-galactopyranosyl-(1→6)-1:2,3:4-di-*O*-isopropylidene-D-galactopyranoside **4.46** (0.020 g, 30%)

as a colorless oil; δ_H (400 MHz, $CDCl_3$) [1:1 mixture of *α*:*β* anomers observed]: 1.32-1.53 (24H, m, 4 x CH_3 *α*, 4 x CH_3 *β*), 1.96-2.03 (12H, m, 2 x $COCH_3$ *α*, 2 x $COCH_3$ *β*), 3.44-3.82 (12H, m, H-6_a *α*, H-6'$_a$ *α*, H-6_a *β*, H-6'$_a$ *β*, H-6_b *α*, H-6'$_b$ *α*, H-6_b *β*, H-6'$_b$ *β*, H-5_a *α*, H-5_a *β*, H-4_b *α*, H-4_b *β*), 3.90-4.36 (12H, m, H-2_a *α*, H-2_a *β*, H-2_b *α*, H-2_b *β*, H-3_a *α*, H-3_a *β*, H-3_b *α*, H-3_b *β*, H-4_a *α*, H-4_a *β*, H-5_b *α*, H-5_b *β*), 4.39-5.07 (8H, m, 4 x CH_2Ph *α*, 4 x CH_2Ph *β*), 4.41 (1H, m, H-1_a *β*), 5.00 (1H, d, $J_{1,2}$ 3.2 Hz, H-1_a *α*), 5.10 (1H, d, $J_{1,2}$ 3.5 Hz, H-1_b *β*), 5.18 (1H, d, $J_{1,2}$ 3.5 Hz, H-1_b *α*), 7.25-7.43 (40H, m, 20 x Ar-CH *α*, 20 x Ar-CH *β*); δ_C (100 MHz, $CDCl_3$): 24.4, 24.6, 24.9, 25.0, 25.3, 25.9, 26.0, 26.1 (8 x q, 4 x CH_3 *α*, 4 x CH_3 *β*), 65.8, 66.3, 67.4, 68.6 (4 x t, C-6_a *α*, C-6_a *β*, C-6_b *α*, C-6_b *β*), 68.7, 69.2 (2 x d, C-2_b *α*, C-2_b *β*), 69.6, 70.5, 70.6, 70.7, 70.8, 70.9, 71.4, 72.7, 73.0, 73.1 (8 x d, C-3_a *α*, C-4_a *α*, C-5_a *α*, C-3_a *β*, C-4_a *β*, C-5_a *β*, C-3_b *α*, C-4_b *α*, C-3_b *β*, C-4_b *β*), 73.3, 73.4, 73.5, 73.6, 74.5, 74.8, 75.0, 76.4 (8 x t, 4 x $\underline{C}H_2Ph$ *α*, 4 x $\underline{C}H_2Ph$ *β*), 77.3, 78.9 (2 x d, C-2_a *α*, C-2_a *β*), 79.1, 81.9 (2 x d, C-5_b *α*, C-5_b *β*), 96.3 (d, C-1_a *α*), 96.4, 97.5 (C-1_b *α*, C-1_b *β*), 104.6 (d, C-1_a *β*), 108.5, 108.6, 109.2, 109.3 (4 x s, $\underline{C}(CH_3)_2$ x 2 *α*, $\underline{C}(CH_3)_2$ x 2 *β*), 127.4-128.76 (24 x d, 12 x Ar-CH *α*, 12 x Ar-CH *β*), 137.9, 138.0, 138.5, 138.6, 138.7, 138.8, 138.9, 140.0 (8 x s, 4 x Ar-C *α*, 4 x Ar-C *β*); HRMS (ES^+) Calculated for $C_{46}H_{54}O_{11}Na$ (MNa^+) 801.4068, found 801.4072.

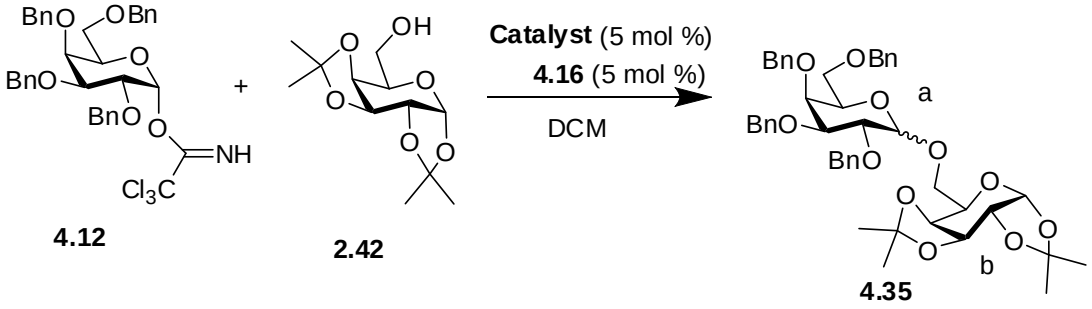
***N*,*N*'-bis[3,5-bis(trifluoromethyl)phenyl]thiourea**[51] **4.16**



To a mixture of 1,1' – thiocarbonyldiimidazole **4.32** (500 mg, 2.81 mmol) in DCM (3 mL) was added 3,5 – bis(trifluoromethyl)aniline **4.33** (0.91 mL, 5.90 mmol) under a nitrogen atmosphere. The resulting solution was stirred for 24 h at rt. The solvent was evaporated and diethyl ether (25

mL) was then added. The organic phase was washed with aq. HCl (1 M, 3 x 10 mL), saturated aq. sodium bicarbonate solution (3 x 10 mL), and brine (3 x 10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was recrystallized ($CHCl_3$) to afford *N*,*N*'-bis[3,5-bis(trifluoromethyl)phenyl]thiourea **4.16** as white crystalline solid (1.13 g, 93%); m. p. 167 – 168 °C ($CHCl_3$) (lit.[51] 172 – 173 °C); δ_H (400 MHz, $CDCl_3$): [51] 1.55 (2H, s, 2 x N-H), 7.78 (2H, s, C-H_{para}), 7.87 (4H, s, C-H_{ortho}); δ_C (100 MHz, [d_4] methanol): 120.47 (d, CH), 123.17 (s, C_q), 125.87 (d, CH), 132.67 (s, C_q), 142.51 (s, C_q), 182.20 (s, C=S); δ_F (380 MHz, $CDCl_3$): -63.06; HRMS (ES^+) calculated for $C_{17}H_9F_{12}N_2S$ (MH^+) 501.0297, found 501.0300.

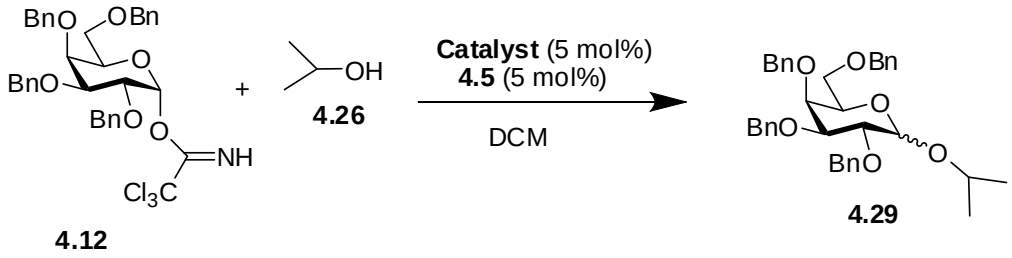
2,3,4,6-Tetra-*O*-benzyl-*α*/*β*-D-glucopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-glucopyranoside[52] **4.35**



O-(2,3,4,6-Tetra-*O*-benzyl-*α*-D-galactopyranosyl) trichloroacetimidate **4.12** (100 mg, 0.14 mmol), 1,2:3,4-di-*O*-isopropylidene-*α*-D-galactopyranoside **2.42** (50 mg, 0.18 mmol) and the cocatalyst **4.16** (3.5 mg, 0.007 mmol) were dissolved in freshly distilled DCM (2 mL) and stirred at rt for 5 min under a nitrogen atmosphere. The phosphoric acid derived catalyst (0.0035 mmol) was then added. aftert.l.c. (petrol:ethyl acetate, 5:1) indicated the complete consumption of the trichloroacetimidate starting material (R_f 0.7) and the formation of 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 residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) to afford 2,3,4,6-tetra-*O*-benzyl-*α*/*β*-D-galactopyranosyl-(1→6)-1:2,3:4-Di-*O*-isopropylidene-D-galactopyranoside **4.35** as a pale yellow oil; δ_H (400 MHz, $CDCl_3$)[53] [Data provided for 1:1 mixture of *α*:*β* anomers] 1.26, 1.30, 1.32, 1.40, 1.43, 1.49, 1.51, 1.63 (24H, 8 x s, 4 x CH_3 *α*, 4 x CH_3 *β*), 3.50-3.59 (6H, m, H-6_a *α*, H-6_a *β*, H-$6'_a$ *α*, H-$6'_a$ *β*, H-3_b *α*, H-3_b *β*), 3.68-3.84 (4H, m, H-4_b *α*, H-4_b *β*, H-5_b *α*, H-5_b *β*), 3.88 (1H, br d, *J* 2.7 Hz, H-2_a *α*), 3.98-4.16 (7H, m, H-4_a *α*, H-4_a *β*, H-5_a *α*, H-5_a *β*, H-2_a *β*, H-3_a *α*, H-2_b *α*/*β*), 4.22 (1H, dd, *J* 7.9 Hz, *J* 2.1 Hz, H-3_a *β*), 4.30-4.34 (3H, m, H-6_b *α*, H-6_b *β*, H-2_b *α*/*β*), 4.39-4.52 (5H, m, H-1_a *β*, CH_2Ph *α*, CH_2Ph *β*), 4.60 (2H, m, H-$6'_b$ *α*, H-$6'_b$ *β*), 4.59-5.06 (12H, m, 3 x CH_2Ph *α*, 3 x CH_2Ph *β*), 5.01 (1H, d, $J_{1,2}$ 3.4 Hz, H-1_a*α*), 5.50 (1H, d, $J_{1,2}$ 5.1 Hz, H-1_a*α*), 5.55 (1H, d, $J_{1,2}$ 4.8 Hz, H-1a*β*), 7.23-7.45 (40H, m, 20 x ArC-H *α*, 20 x ArC-H *β*); δ_C (100 MHz, $CDCl_3$) 24.4, 24.5, 24.9, 25.0, 25.1, 25.9, 26.0, 26.1 (8 x q, 4 x CH_3 *α*, 4 x CH_3 *β*), 65.8 (d, C-5_b *α*/*β*), 66.3 (t, C-6_a *α*), 67.4 (t, C-6_a *β*), 68.6 (d, C-5_b *α*/*β*), 68.7, 69.1 (2 x d, C-2_a *α*, C-2_a *β*), 69.6, 70.5 (C-2_b *α*, C-2_b *β*), 70.6, 70.7, 70.8, 70.9 (4 x d, C-3_b *α*, C-3_b *β*, C-4_b *α*, C-4_b *β*), 71.4, 72.7, 72.8, 73.0, 73.1, 73.2, 73.3, 73.4, 73.5, 73.6 (10 x t, C-6_b *α*, C-6_b *β*, 4 x CH_2Ph *α*, 4 x CH_2Ph *β*), 74.5, 74.8 (2 x d, C-4_b *α*, C-4_b *β*), 74.9 (d, C-3_a *α*/*β*), 78.9, 79.1 (2 x d, C-5_a *α*, C-5_a *β*), 81.9 (d, C-3_a *α*/*β*), 96.3, 96.4 (2 x d, C-1_b *α*, C-1_b *β*), 97.5 (d, C-1_a *α*), 104.6 (d, C-1_a *β*), 108.5, 108.6, 109.2, 109.3 (4 x s, 2 x $\underline{C}(CH_3)_2$ *α*, 2 x $\underline{C}(CH_3)_2$ *β*), 127.3, 127.4, 127.4, 127.5, 127.6, 127.6, 127.7, 127.8, 127.8, 127.9, 127.9, 128.0, 128.0, 128.1, 128.1, 128.2, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5, 128.6, 128.7 (24 x d, 12 x Ar$\underline{C}$-H *α*, 12 x Ar$\underline{C}$-H *β*) 137.9, 138.0, 138.5, 138.6, 138.8, 138.9, 139.0, 139.1 (8 x s, 4 x Ar-C *α*, 4 x Ar-C *β*); HRMS (ES^+) calculated for $C_{46}H_{54}O_{11}Na$ (MNa^+) 805.3558, found 805.3568.

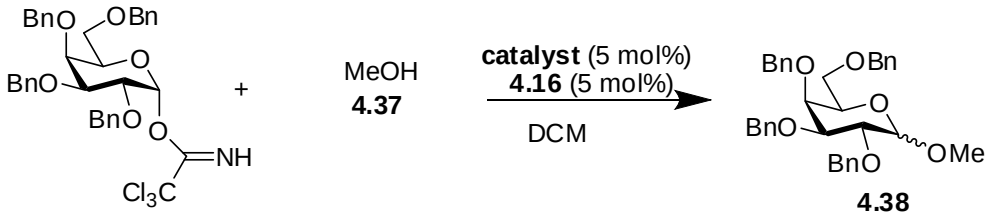
Isopropyl 2,3,4,6-Tetra-*O*-benzyl-*α*/*β*-D-galactopyranoside[52] **4.29**



O-(2,3,4,6-Tetra-*O*-benzyl-*α*-D-galactopyranosyl) trichloroacetimidate **4.12** (100 mg, 0.14 mmol), propan-2-ol **4.26** (14 μL, 0.18 mmol) and the cocatalyst **4.16** (3.5 mg, 0.007 mmol) were dissolved in freshly distilled DCM (2 mL) and stirred at rt for 5 min in a nitrogen atmosphere. The phosphoric acid catalyst (0.0035 mmol) was then added. Aftert.l.c. (toluene:ethyl acetate, 9:1) indicated the complete consumption of starting material (R_f 0.7) and the formation of product (R_f 0.68) the reaction was quenched by the addition of triethylamine and filtered through Celite®. Then the reaction was then allowed to run for 72 h. The mixture was then concentrated *in vacuo* and The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) to afford isopropyl 2,3,4,6-tetra-*O*-benzyl-*α*/*β*-D-galactopyranoside **4.29** as a pale yellow oil; δ_H (400 MHz, CD_3CN) [Data provided for 1:3 mixture of *α*:*β* anomers] 1.15-1.23 (24H, m, CH($\underline{CH_3}$)$_2$ *α*, 3 x CH($\underline{CH_3}$)$_2$ *β*), 3.49-3.64 (16H, m, H-2 *α*, 3 x H-2 *β*, H-5 *α*, 3 x H-5 *β*, H-6 *α*, 3 x H-6 *β*, H-6' *α*, 3 x H-6 *β*), 3.88-4.04 (12H, m, H-3 *α*, 3 x H-3 *β*, H-4 *α*, 3 x H-4 *β*, $\underline{CH}(CH_3)_2$ *α*, 3 x $\underline{CH}(CH_3)_2$ *β*), 4.45 (3H, d, $J_{1,2}$ 8.0 Hz, 3 x H-1 *β*), 4.48-4.89 (32H, m, 4 x CH_2Ph *α*, 12 x CH_2Ph *β*), 5.07 (1H, d, $J_{1,2}$ 3.2 Hz, H-1 *α*), 7.26-7.50 (80H, m, 20 x ArC-H *α*, 60 x ArC-H *β*); δ_C (100 MHz, CD_3CN) 20.8, 21.4, 22.8, 23.0 (4 x q, CH($\underline{C}H_3$)$_2$ *α*, CH($\underline{C}H_3$)$_2$ *β*), 68.9 (t, C-6 *β*), 69.1 (t, C-6 *α*), 69.3 (d, C-3 *α*), 71.4 (d, C-3 *β*), 72.0, 72.2 (2 x d, C-4 *α*, C-4 *β*), 72.3, 72.8, 72.9, 74.3, 74.4, 74.5, 74.6, 75.6 (8 x t, 4 x $\underline{C}H_2$Ph *α*, 4 x $\underline{C}H_2$Ph *β*), 74.3,74.3 (2 x d, $\underline{C}H(CH_3)_2$ *α*, $\underline{C}H(CH_3)_2$ *β*), 76.1 (d, C-5 *α*), 78.5 (d, C-2 *α*), 79.3 (d, C-5 *β*), 79.3 (d, C-2 *β*), 95.3 (d, C-1 *α*),

101.9 (d, C-1 *β*), 127.3, 127.3, 127.4, 127.4, 127.5, 127.5, 127.6, 127.6, 127.7, 127.7, 127.8, 127.8, 127.9, 127.9, 128.0, 128.0, 128.1, 128.1, 128.2, 128.2, 128.2, 128.3, 128.3, 128.4 (24 x d, 12 x Ar<u>C</u>-H *α*, 12 x Ar<u>C</u>-H *β*) 138.6, 138.8, 138.9, 139.0, 139.1, 139.1, 139.2, 139.3 (8 x s, 4 x Ar-C *α*, 4 x Ar-C *β*); HRMS (ES^+) calculated for $C_{37}H_{42}O_6Na$ (MNa^+) 605.2861, found 605.2867.

Methyl 2,3,4,6-Tetra-*O*-benzyl-*α*/*β*-D-galactopyranoside[52] **4.38**

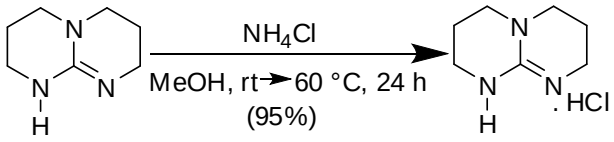


4.12 **4.38**

O-(2,3,4,6-Tetra-*O*-benzyl-*α*-D-galactopyranosyl) trichloroacetimidate **4.12** (100 mg, 0.14 mmol), methanol **4.37** (6 μL, 0.18 mmol) and the cocatalyst **4.16** (3.5 mg, 0.007 mmol) were dissolved in freshly distilled DCM (2 mL) and stirred at rt for 5 min in a nitrogen atmosphere. The phosphoric acid derived catalyst (0.0035 mmol) was then added. When t.l.c. (petrol:ethyl acetate, 5:2) indicated the complete consumption of starting material (R_f 0.7) and the formation of product (R_f 0.65) the reaction was quenched by the addition of triethylamine and filtered through Celite®. The mixture was then concentrated *in vacuo* and The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) to afford methyl 2,3,4,6-tetra-*O*-benzyl-*β*-D-galactopyranoside **4.38** as a pale yellow oil, $[\alpha]_D^{20}$ – 1.4 (*c*, 1.0 in $CHCl_3$), lit.[54] $[\alpha]_D^{20}$ – 0.9 (*c*, 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$): 3.52-3.63 (5H, m, CH_3, H-3, H-5), 3.82 (1H, at, *J* 8.4 Hz, H-2), 3.91 (1H, m, H-4), 4.29 (1H, d, $J_{1,2}$ 7.2 Hz), 4.41-4.46 (2H, m, H-6, H-6'), 4.61-4.97 (8H, m, 4 x CH_2Ph), 7.25-7.39 (20H, m, ArC-H); δ_C (100 MHz, $CDCl_3$) 57.0 (q, OCH_3), 68.9 (d, C-3), 73.2 (d, C-4), 73.4 (t, C-6), 73.5, 73.6, 74.5, 75.1 (4 x t, 4 x <u>C</u>H_2Ph), 79.6 (d, C-2), 82.1 (d,

C-5), 105.0 (d, C-1), 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.3, 128.4, 128.5 (12 x d, 12 x ArC-H) 137.9, 138.5, 138.6, 138.8 (4 x s, 4 x Ar-C); HRMS (ES^+) calculated for $C_{35}H_{38}O_6Na$ (MNa^+) 577.2560, found 577.2569.

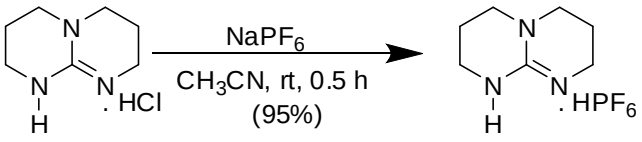
1,5,7-Triazabicyclo[4.4.0]dec-5-enium chloride[47] **4.20**



4.19 **4.20**

Ammonium chloride (0.1605 g, 3.00 mmol) was suspended in methanol (2 mL) and stirred under a nitrogen atmosphere at rt. 1,5,7-triazabicyclo[4.4.0]dec-5-ene **4.19** (417 mg, 3.00 mmol) was added to the solution over a period of 30 min. The mixture was stirred for a further 3 h and the solvent was then evaporated. The residue was heated at 60 °C under vacuum for 24 h to afford 1,5,7-triazabicyclo[4.4.0]dec-5-enium chloride **4.20** (500 mg, 95%), as a white solid; δ_H (400 MHz, $CDCl_3$): [47] 1.79 (1H, bs, N-H), 1.97-2.03 (4H, m, H-2, H-2', H-5, H-5'), 3.27-3.35 (8H, m, H-1, H-1', H-3, H-3', H-4, H-4', H-6, H-6'), 8.70 (1H, bs, $N\text{-}H^{(+)}$); δ_C (100 MHz, $CDCl_3$): 20.6 (t, C-2, C-5), 37.9 (C-3, C-4), 46.84 (t, C-1, C-6), 151.8 (s, C-7); HRMS (ES^+) calculated for $C_7H_{14}N_3$ (M^+ - Cl) 140.1182, found 140.1188.

1,5,7-Triazabicyclo[4.4.0]dec-5-enium hexafluorophosphate[48] **4.21**

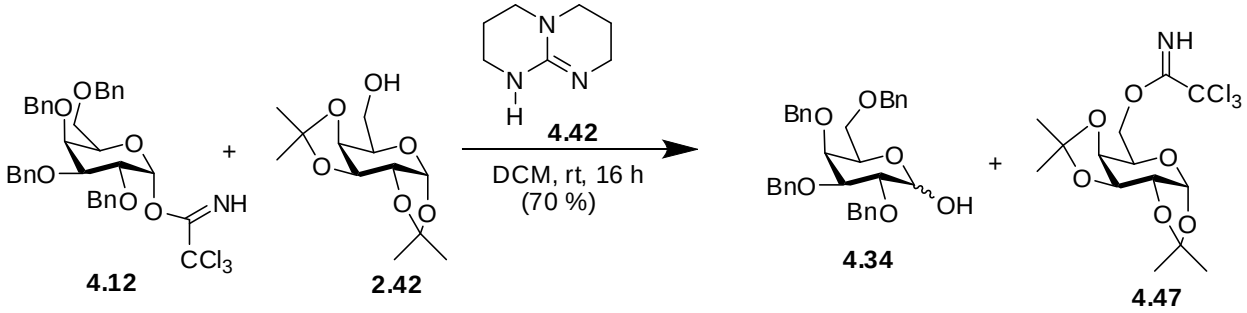


4.20 **4.21**

$NaPF_6$ (0.447 g, 2.66 mmol) was added to a stirred solution of 1,5,7-triazabicylo[4.4.0]dec-5-enium chloride **4.20** (0.465g, 2.66 mmol) in anhydrous acetonitrile (5 mL), and was stirred at rt

for 30 min under a nitrogen atmosphere. The mixture was then filtered through Celite® which was washed with acetonitrile (5 mL). The filtrate was then concentrated *in vacuo* to afford 1,5,7-triazabicylo[4.4.0]dec-5-enium hexafluorophosphate **4.21** (0.720 g, 95%) as a white crystalline solid; ν_{max} (KBr) 1637 (s, C=N), 3260 (s, sharp, N-H) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 2.02-2.08 (4H, m, H-2, H-2', H-5, H-5'), 3.34-3.37 (8H, m, H-1, H-1', H-3, H-3', H-4, H-4', H-6, H-6'), 8.70 (1H, bs, N-$H^{(+)}$); δ_C (100 MHz, $CDCl_3$): 20.6 (t, C-2, C-5), 37.9 (t, C-3, C-4), 46.9 (t, C-1, C-6); δ_F (380 MHz, $CDCl_3$): -73.15, -71.25; δ_P (162 MHz, $CDCl_3$): -157.4, -153.0, -148.6, -144.2, -135.4, -131.0; HRMS (ES^+) calculated for $C_7H_{14}N_3$ (M^+ - PF_6) 140.1182, found 140.1183.

1,2:3,4–di–*O*–isopropylidene-6-trichloroacetimidate–*α*–D–galactopyranose 4.47



A solution of 2,3,4,6-tetracetyl-*α*-D-galactopyranosyl trichloroacetimidate **4.12** (0.100 g, 0.146 mmol), 1,2:3,4–di–*O*–isopropylidene–*α*–D–galactopyranose **2.42** (0.078, 0.300) and 1,5,7-triazabicyclo[4.4.0]dec-5-enium **4.42** (3.2 mg, 0.030 mmol) in freshly distilled DCM (5 mL) was added to a flame-dried round-bottom flask containing activated 4 Å molecular sieves (0.100 g). The mixture was refluxed under a nitrogen atmosphere. After 16 h, t.l.c. (petrol:ethyl acetate, 2:1) showed formation of two products **4.34** (R_f 0.2), **4.47** (R_f 0.7), and complete disappearance of starting material **4.12** (R_f 0.3). The reaction was quenched with saturated aq. sodium bicarbonate solution (5 mL) and filtered through Celite®. The mixture was diluted with DCM (20

mL), washed with saturated aq. sodium bicarbonate solution (2 x 10 mL), and the aqueous layer was extracted with DCM (20 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (petrol:ethyl acetate, 6:1) to afford 1,2:3,4–di–*O*–isopropylidene-6-trichloroacetimidate–*α*–D–galactopyranose **4.47** (0.045 g, 70%) as a white solid; m.p. 63-65 °C; $[\alpha]_D^{20}$ - 35.0 (*c*, 1.0 in $CHCl_3$); ν_{max} (KBr) 1,667 (s, C=NH) cm^{-1}; δ_H (400 MHz, $CDCl_3$): 1.31, 1.32, 1.45, 1.48 (12H, 4 x s, 4 x CH_3), 4.20 (1H, t, *J* 7.5 Hz, H-4), 4.28–4.32 (2H, m, H-2, H-5), 4.39 (1H, d, *J 7.7* Hz, H-3), 4.54 (1H, dd, $J_{6,6'}$ 4.9 Hz, $J_{6,5}$ 2.3 Hz, H-6), 4.61 (1H, dd, $J_{6',5}$ 7.9 Hz, $J_{6',5}$ 2.3 Hz, H-6'), 5.53 (1H, d, $J_{1,2}$ 5.1 Hz, H-1), 8.31 (1H, s, NH); δ_C (100 MHz, $CDCl_3$): 24.4, 24.9, 25.9, 26.0 (4 x q, 4 x CH_3), 65.4 (t, C-6), 67.8, 70.5, 70.6, 71.0 (4 x d, C-2, C-3, C-4, C-5), 96.3 (d, C-1), 108.8, 109.6 (2 x s, $\underline{C}(CH_3)_2$), 162.6 (s, $\underline{C}$=NH); HRMS (ES^+) Calculated for $C_{13}H_{17}O_6NCl_3$ (MH^+) 404.0429, found 412.0438.

6.5 References

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[28]. "New approach to Stereocontrolled Glycosylation" D.Phil. thesis by D. Co*x*, Supervisor – Prof. A. J. Fairbanks, University of Oxford, **2011**, Chapter – 5, Page – 111.

[29]. "New approach to Stereocontrolled Glycosylation" D.Phil. thesis by D. Co*x*, Supervisor – Prof. A. J. Fairbanks, University of Oxford, **2011**, Chapter – 5, Page – 112.

[30]. "New approach to Stereocontrolled Glycosylation" D.Phil. thesis by D. Co*x*, Supervisor – Prof. A. J. Fairbanks, University of Oxford, **2011**, Chapter – 5, Page – 122.

[31]. "New approach to Stereocontrolled Glycosylation" D.Phil. thesis by D. Co*x*, Supervisor – Prof. A. J. Fairbanks, University of Oxford, **2011**, Chapter – 5, Page – 123.

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[33]. "New approach to Stereocontrolled Glycosylation" D.Phil. thesis by D. Co*x*, Supervisor – Prof. A. J. Fairbanks, University of Oxford, **2011**, Chapter – 5, Page – 165.

[34]. "New approach to Stereocontrolled Glycosylation" D.Phil. thesis by D. Co*x*, Supervisor – Prof. A. J. Fairbanks, University of Oxford, **2011**, Chapter – 5, Page – 166.

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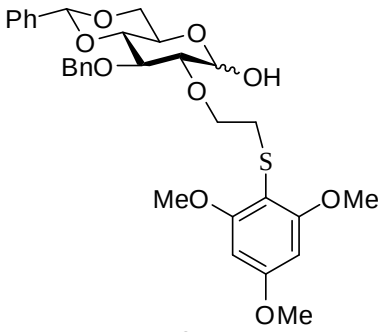
Appendix



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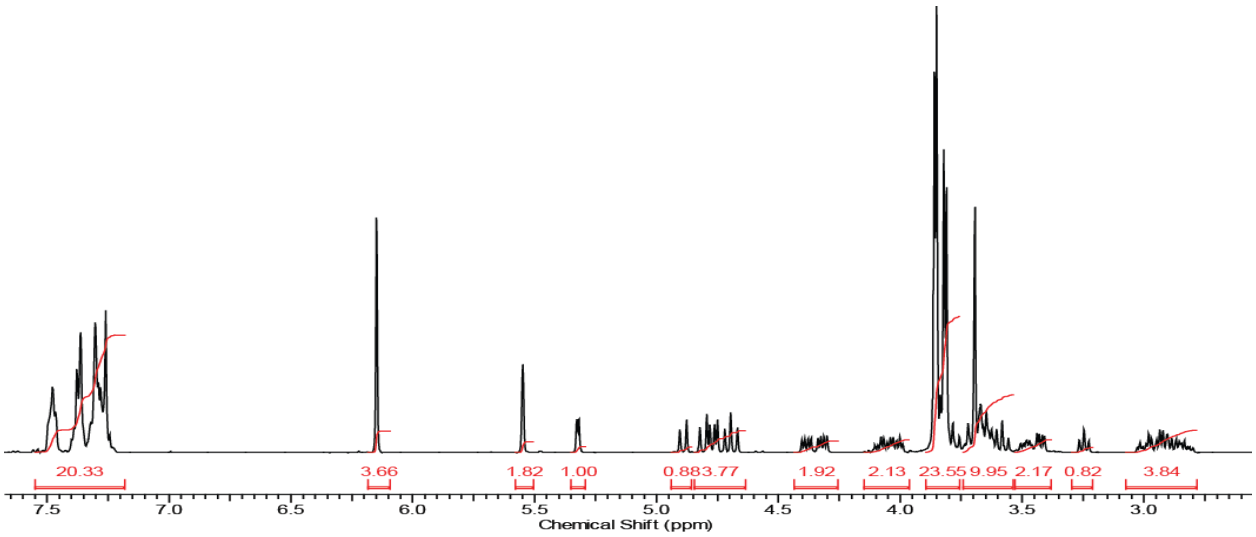

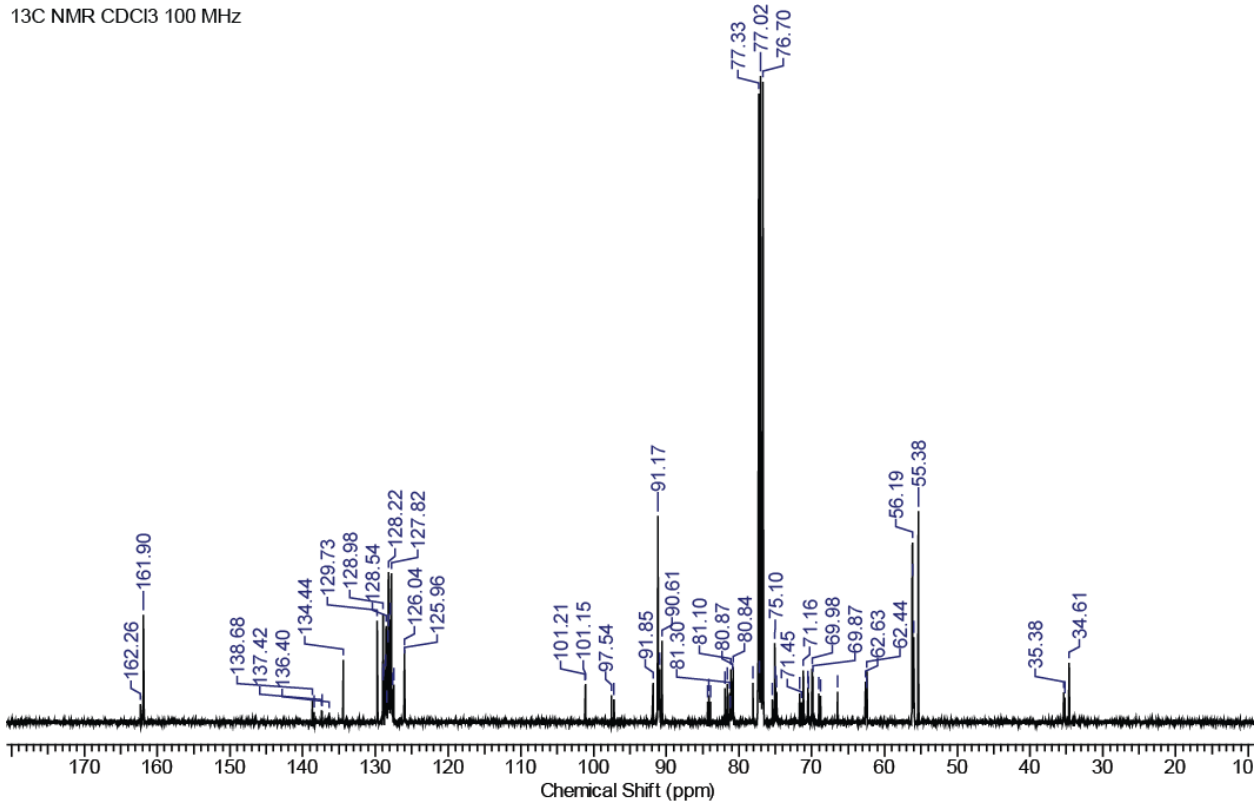
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138.68
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134.44
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128.98
128.54
128.22
127.82
126.04
125.96
101.21
101.15
97.54
91.85
91.17
90.61
81.30
81.10
80.87
80.84
75.10
71.45
71.16
69.98
69.87
62.63
62.44
56.19
55.38
35.38
34.61
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140
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120
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100
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60
50
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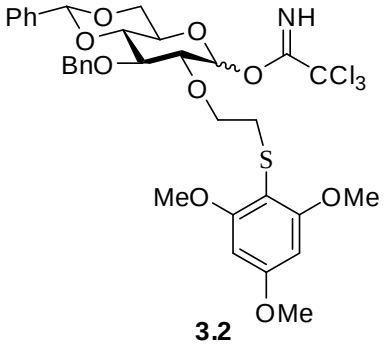
10
Chemical Shift (ppm)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S
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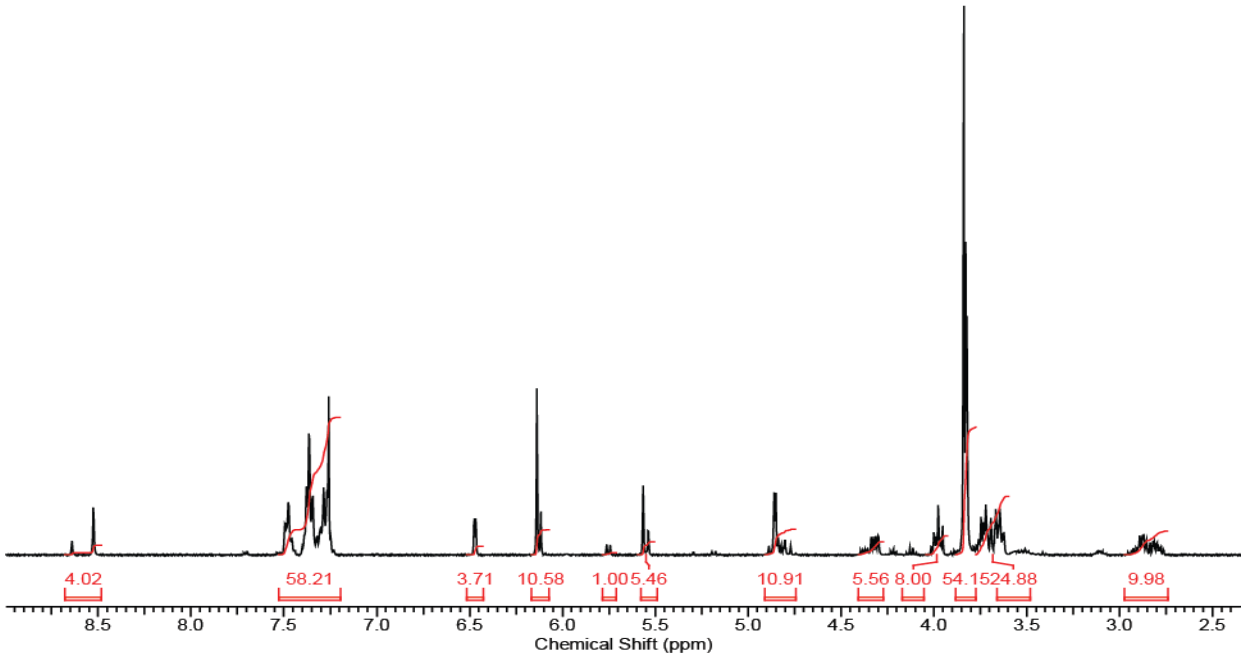
OMe
OMe

3.2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9.98
8.5
8.0
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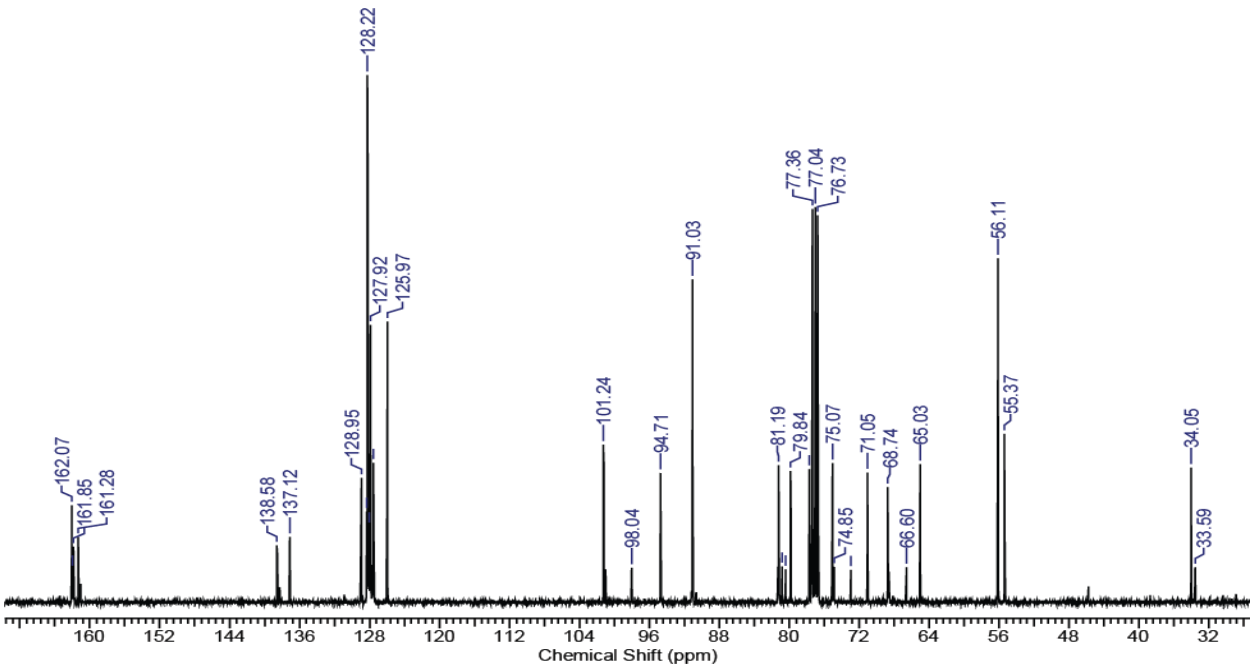
Chemical Shift (ppm)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137.12
128.95
128.22
127.92
125.97
101.24
98.04
94.71
91.03
81.19
79.84
77.36
77.04
76.73
75.07
74.85
71.05
68.74
66.60
65.03
56.11
55.37
34.05
33.59
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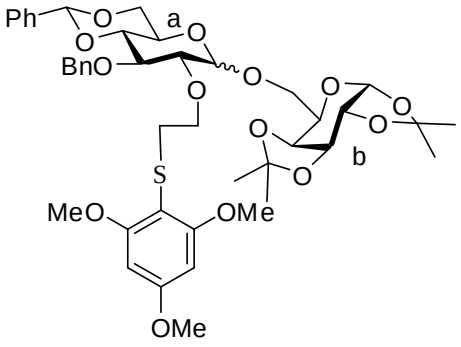
136
128
120
112
104
96
88
80
72
64
56
48
40
32
Chemical Shift (ppm)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O
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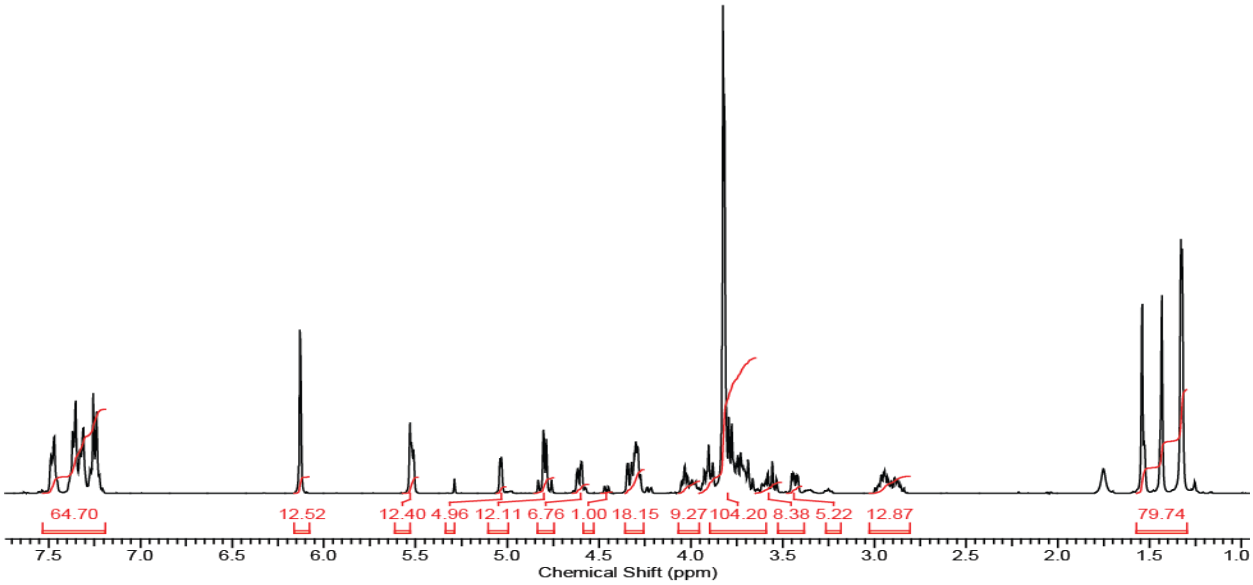
O
O
O
O
b
S
MeO
OMe
OMe

3.25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5.22
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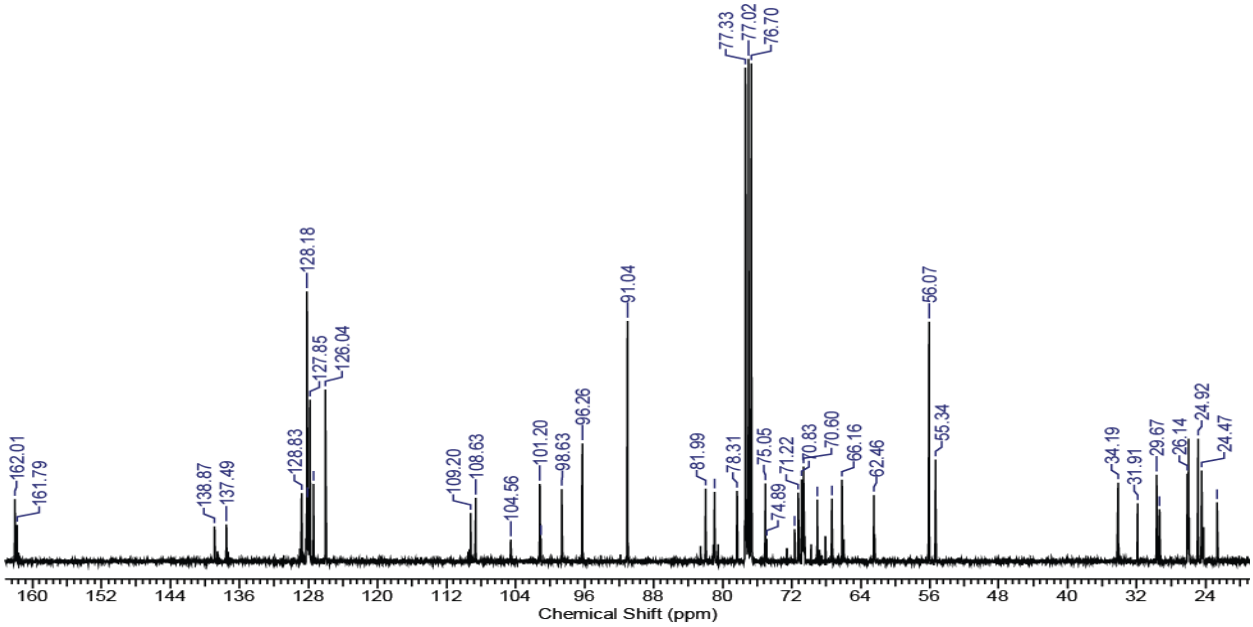
79.74
Chemical Shift (ppm)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128.83
109.20
108.63
104.56
101.20
98.63
96.26
81.99
78.31
75.05
74.89
71.22
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62.46
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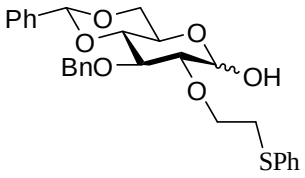
26.14
24.92
24.47
Chemical Shift (ppm)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BnO
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O
SPh

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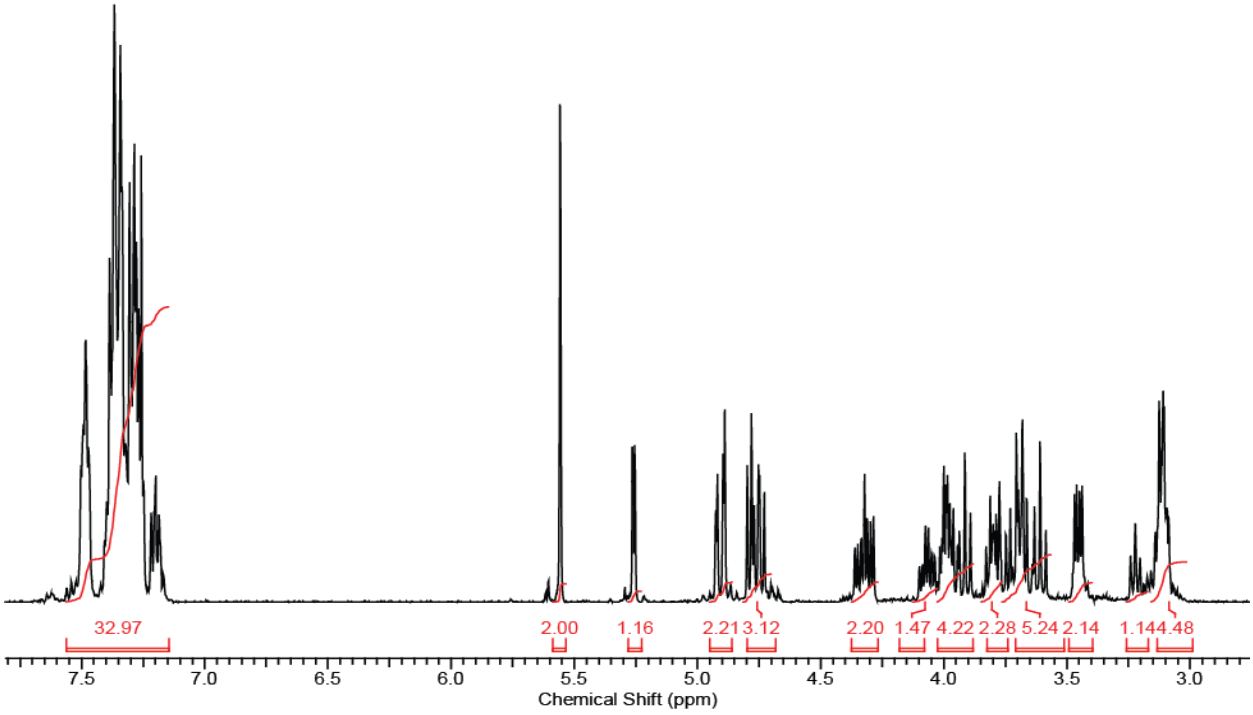
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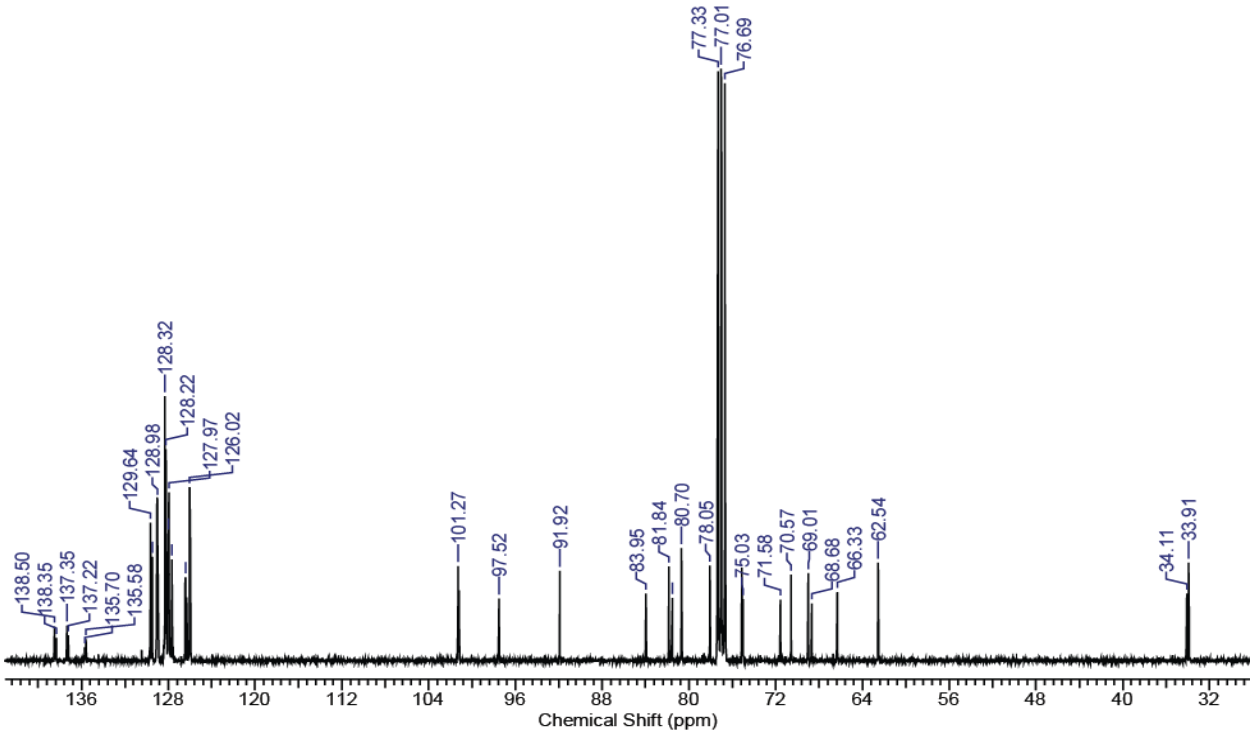
Chemical Shift (ppm)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66.33
62.54
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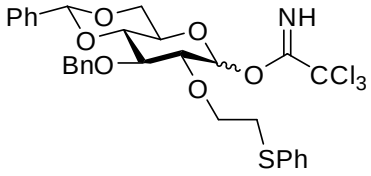
88
80
72
64
56
48
40
32
Chemical Shift (ppm)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O
CCl3
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SPh

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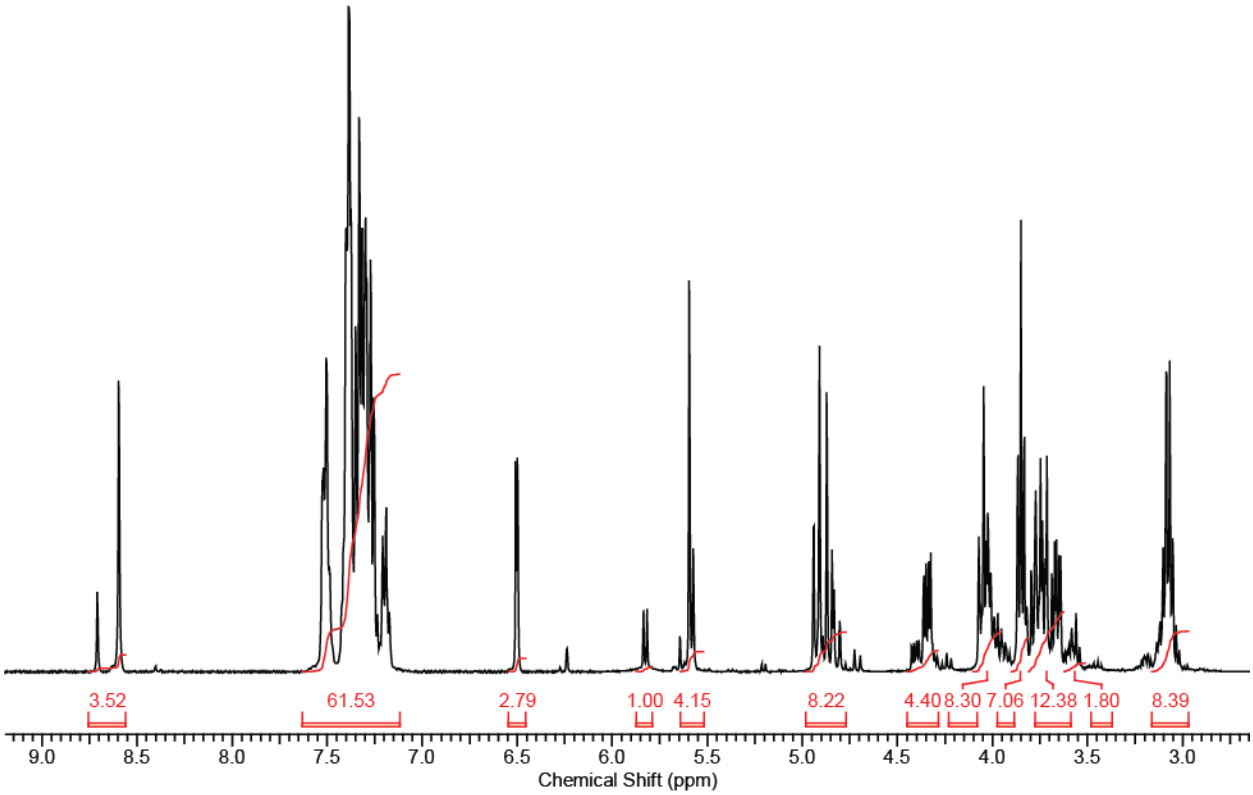
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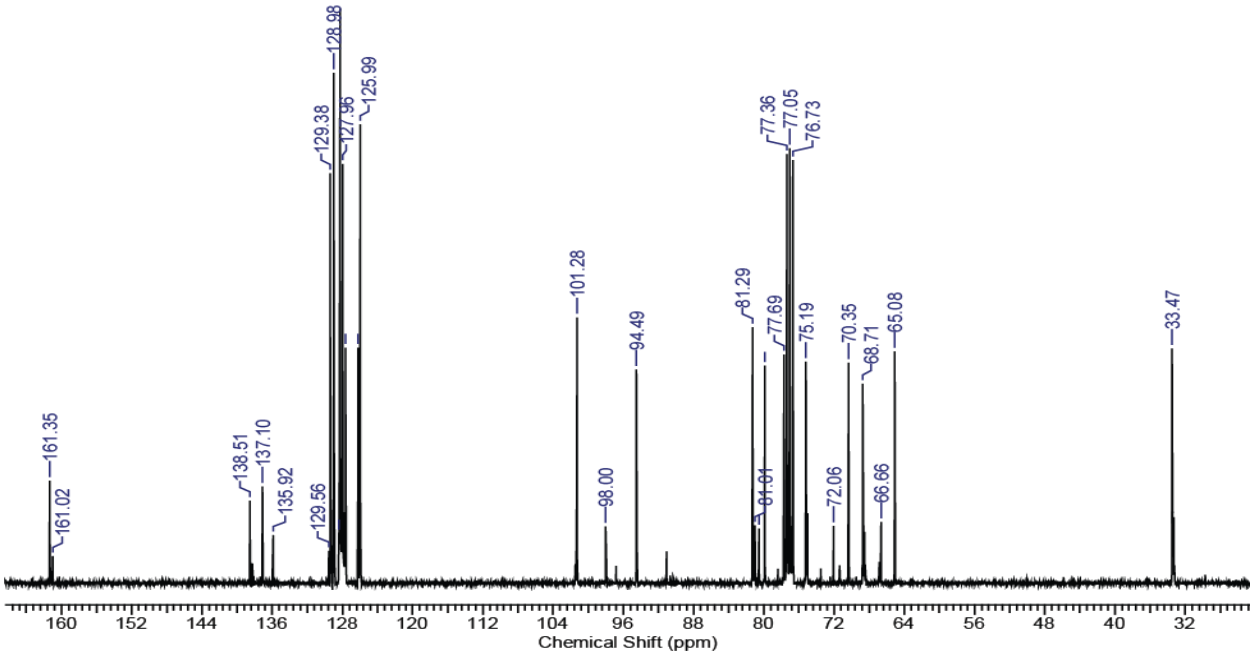
Chemical Shift (ppm)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72
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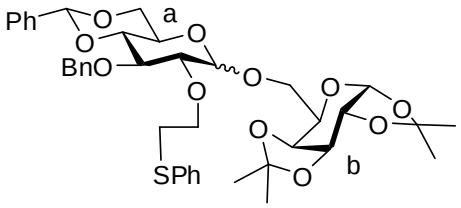
32
Chemical Shift (ppm)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O
b
SPh

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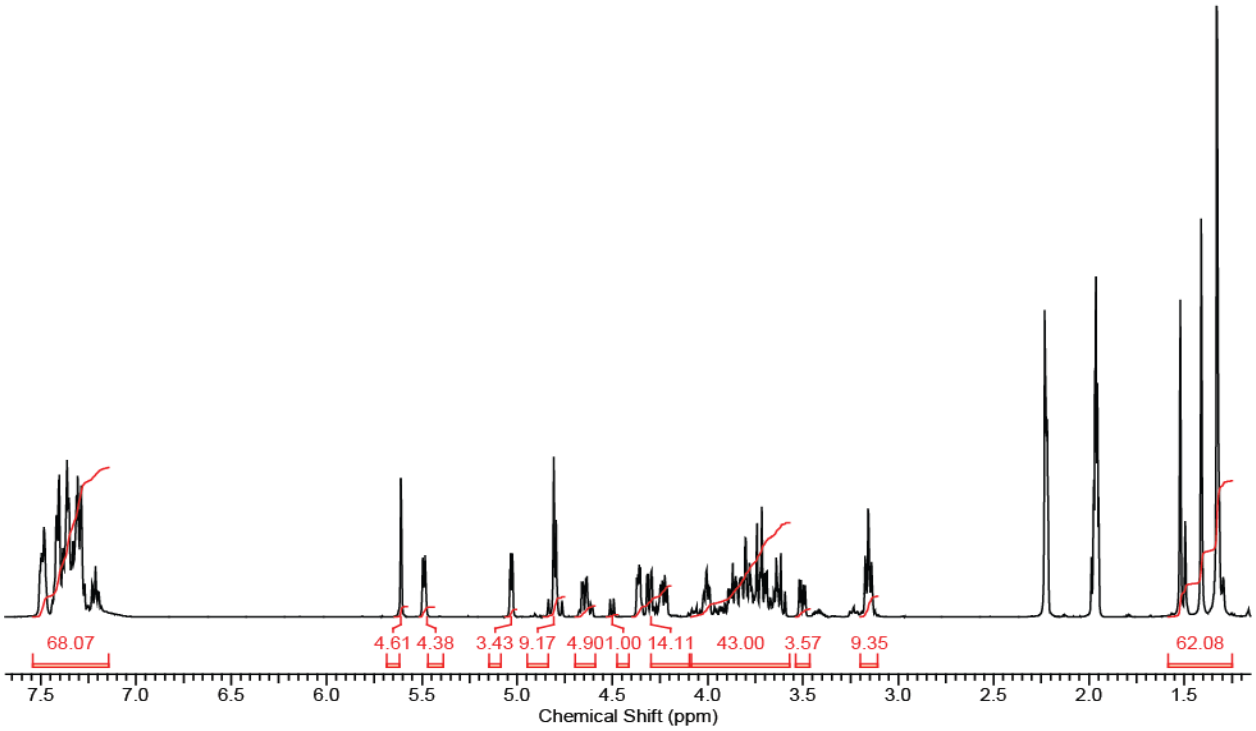
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9.35
62.08
7.5
7.0
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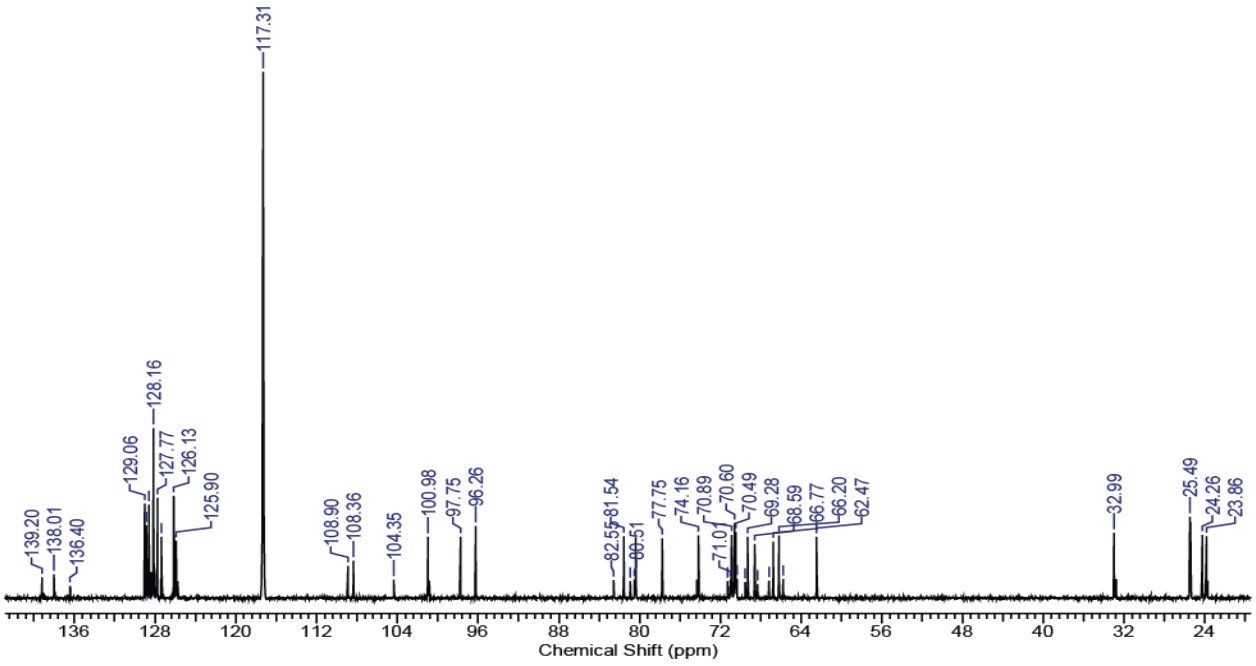
1.5
Chemical Shift (ppm)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81.54
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70.49
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68.59
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66.20
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32.99
25.49
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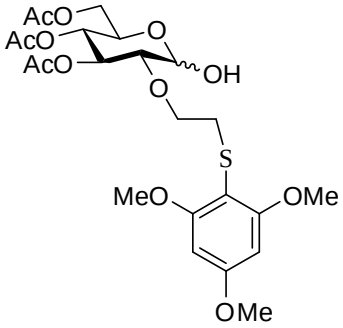
72
64
56
48
40
32
24
Chemical Shift (ppm)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AcO
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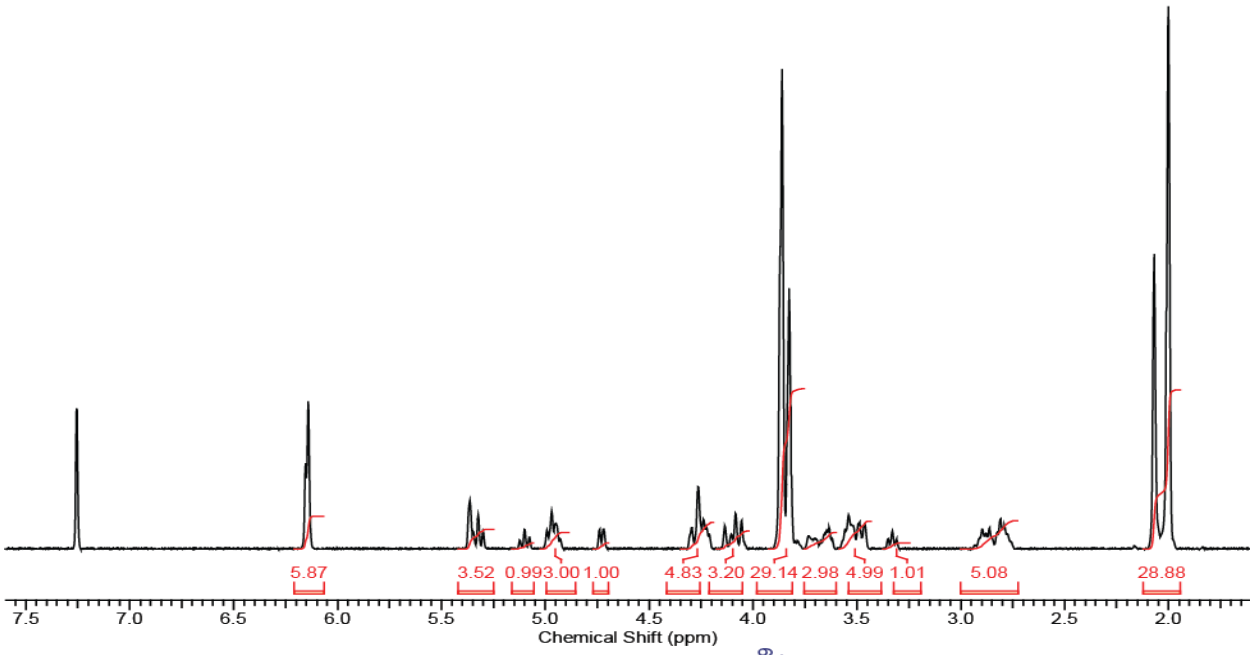
OH
O
S
MeO
OMe
OMe

3.17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4.99
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5.08
28.88
7.5
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3.0
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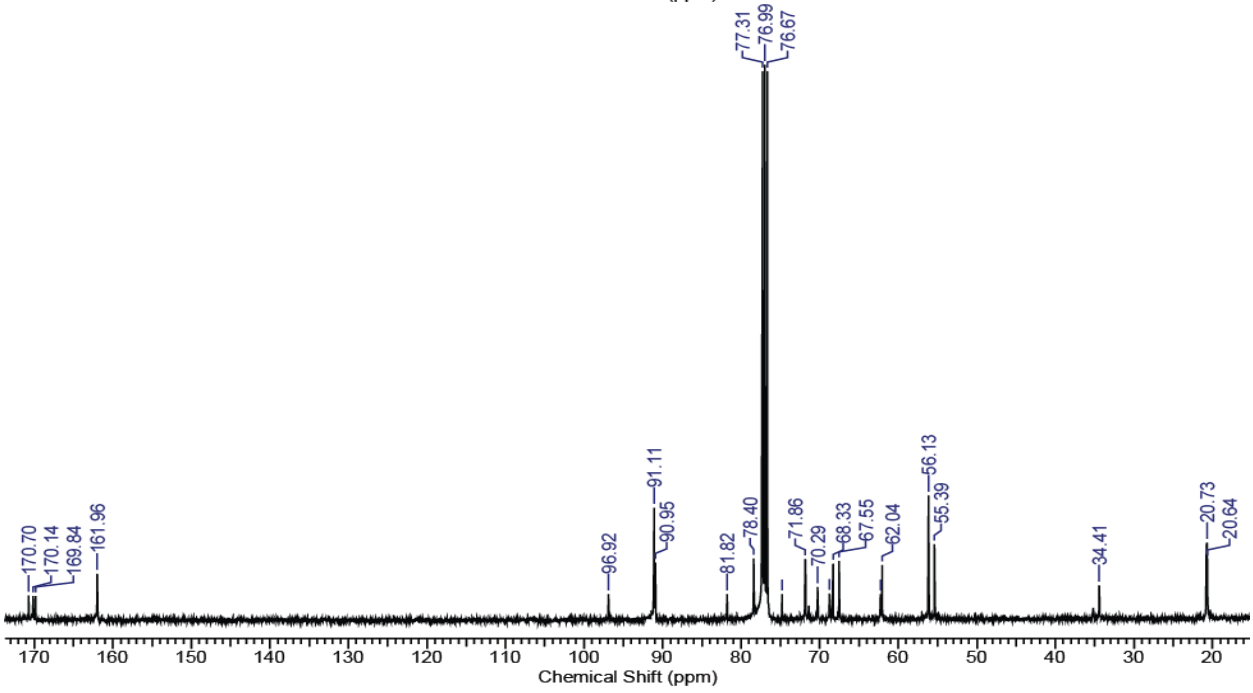
2.0
Chemical Shift (ppm)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68.33
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56.13
55.39
34.41
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70
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50
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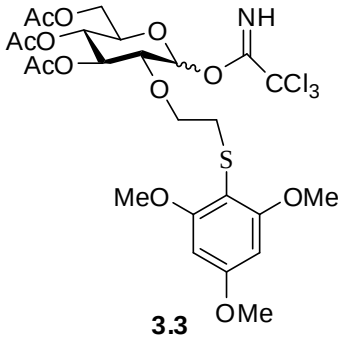
30
20
Chemical Shift (ppm)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CCl3
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S
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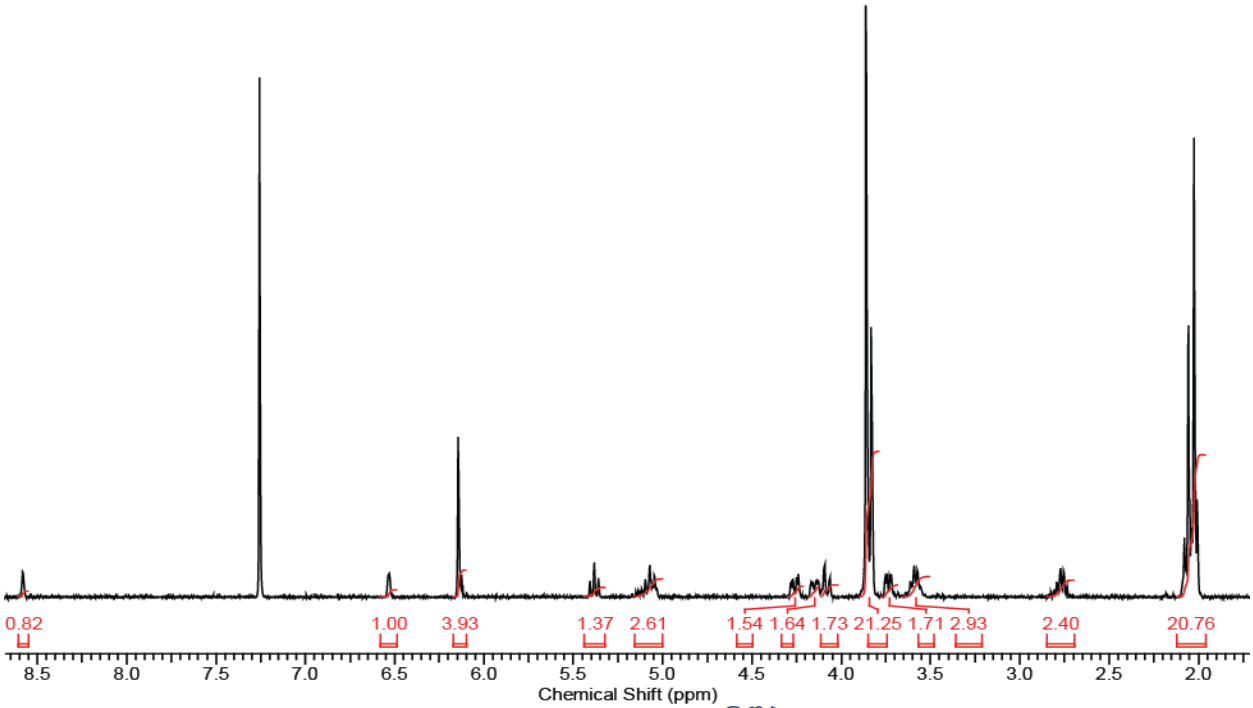
OMe
OMe

3.3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8.0
7.5
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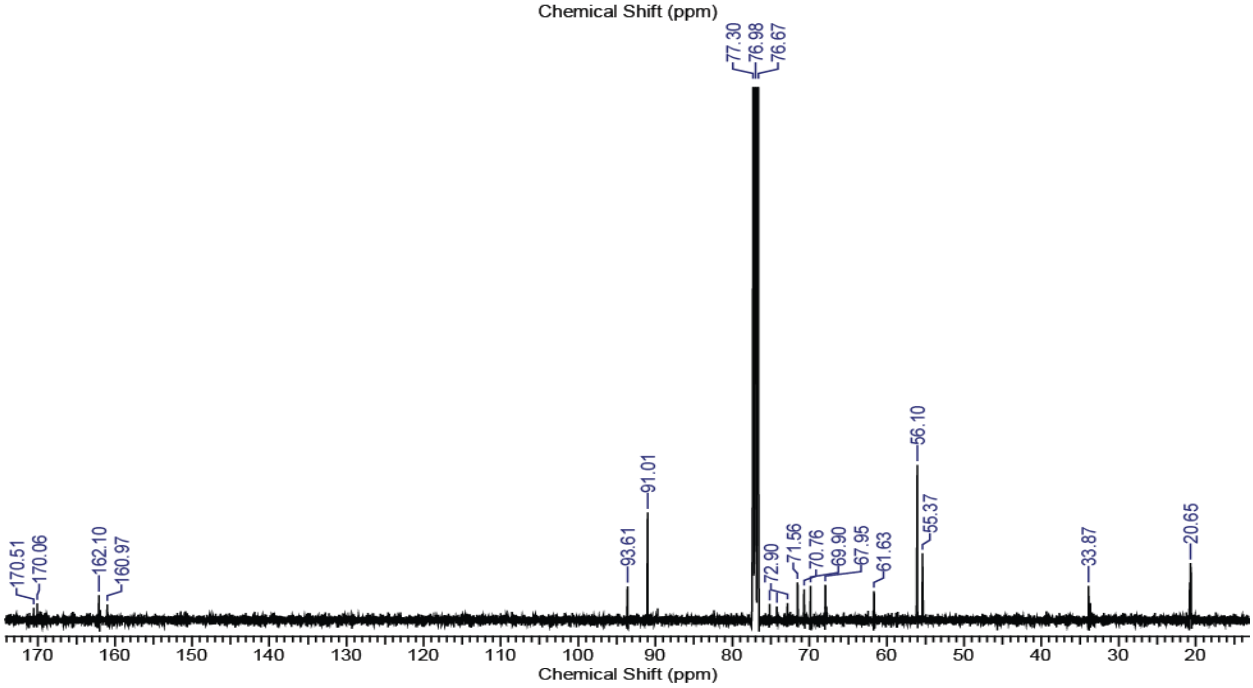
Chemical Shift (ppm)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150
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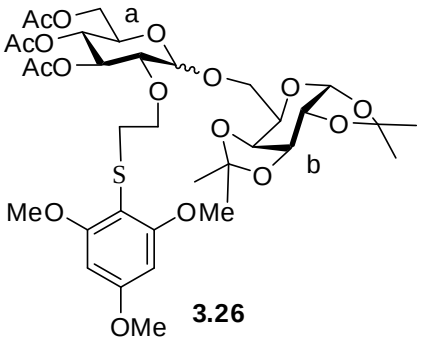
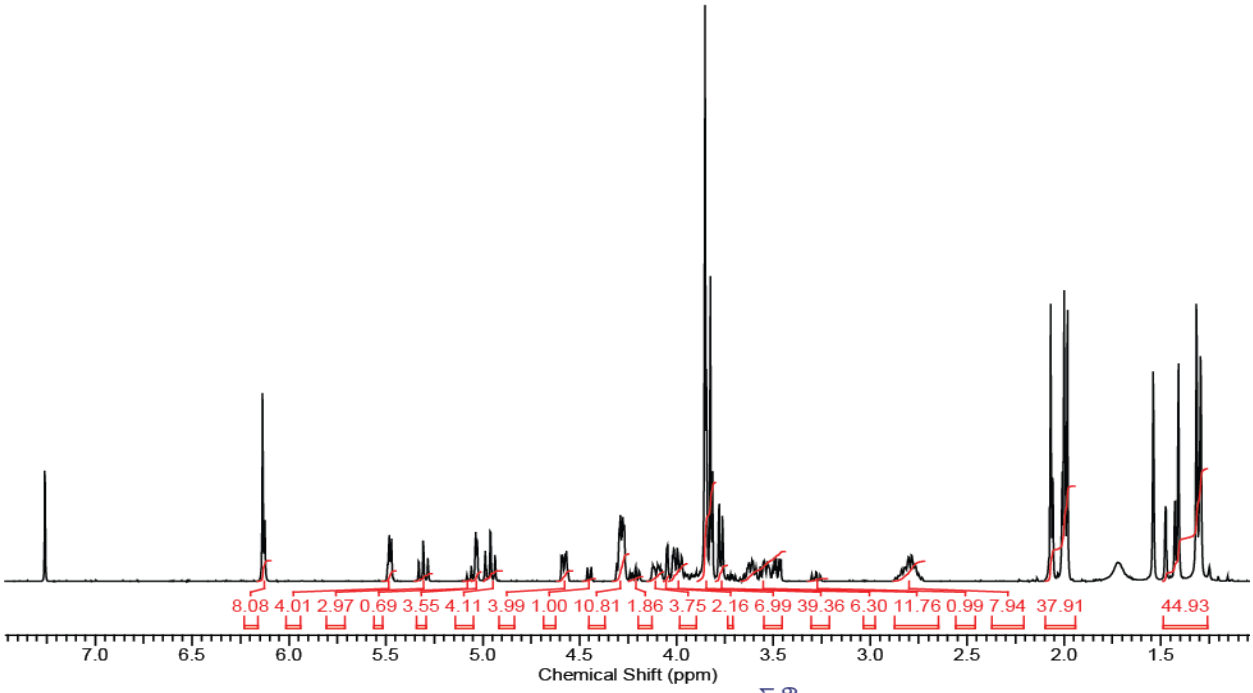
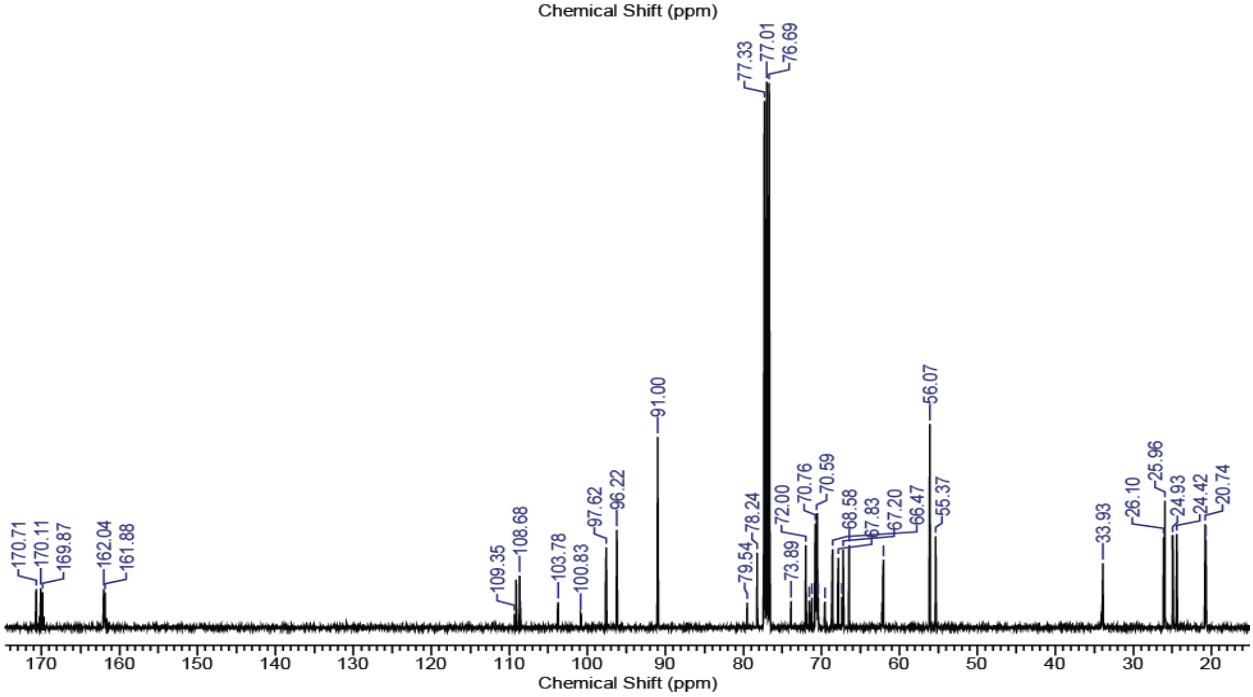
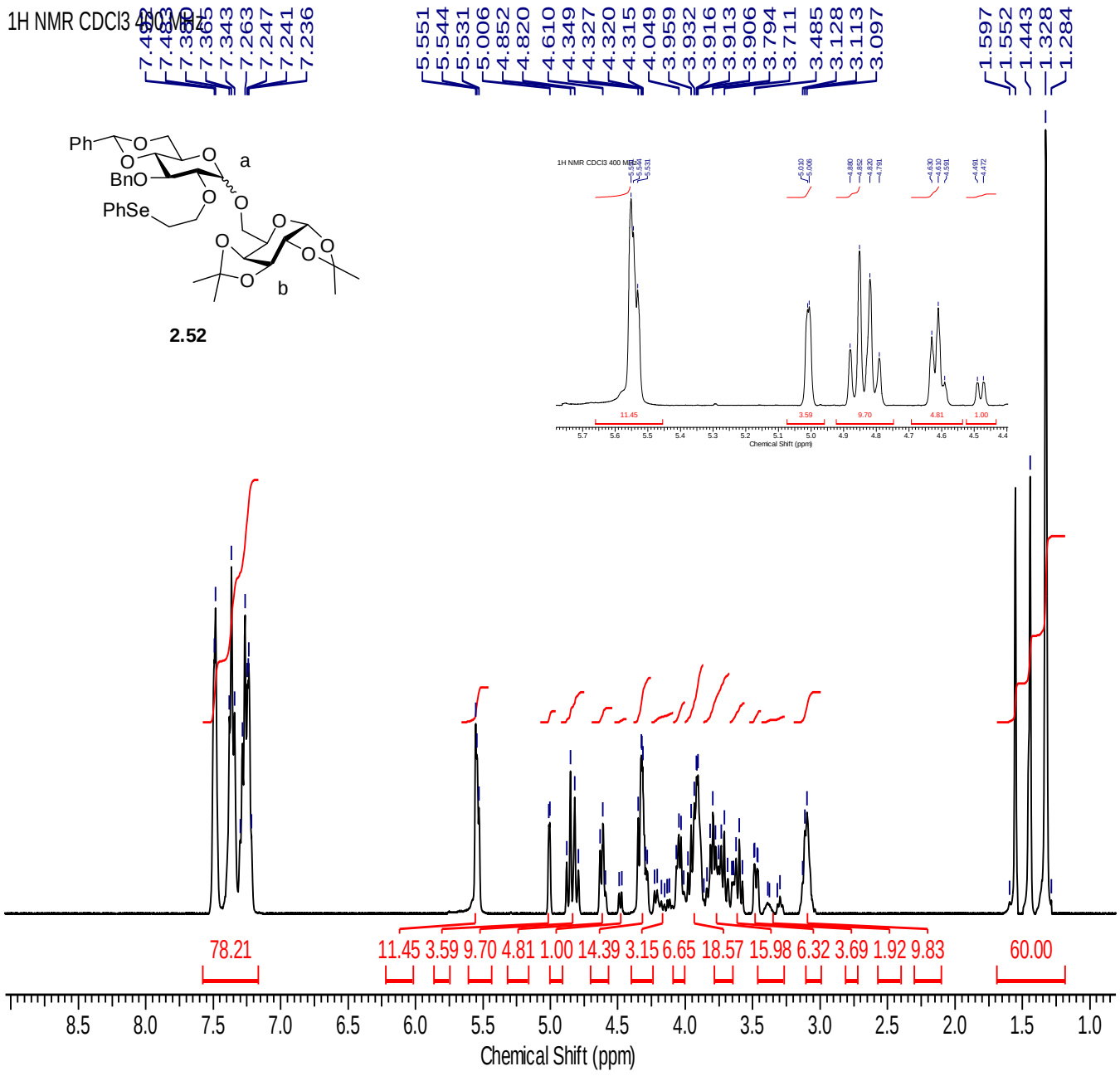
110
100
90
80
70
60
50
40
30
20
Chemical Shift (ppm)

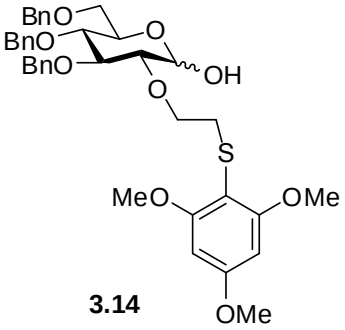

AcO
AcO
AcO
a
O
O
O
O
O
O
O
O
b
S
MeO
OMe
OMe

3.26

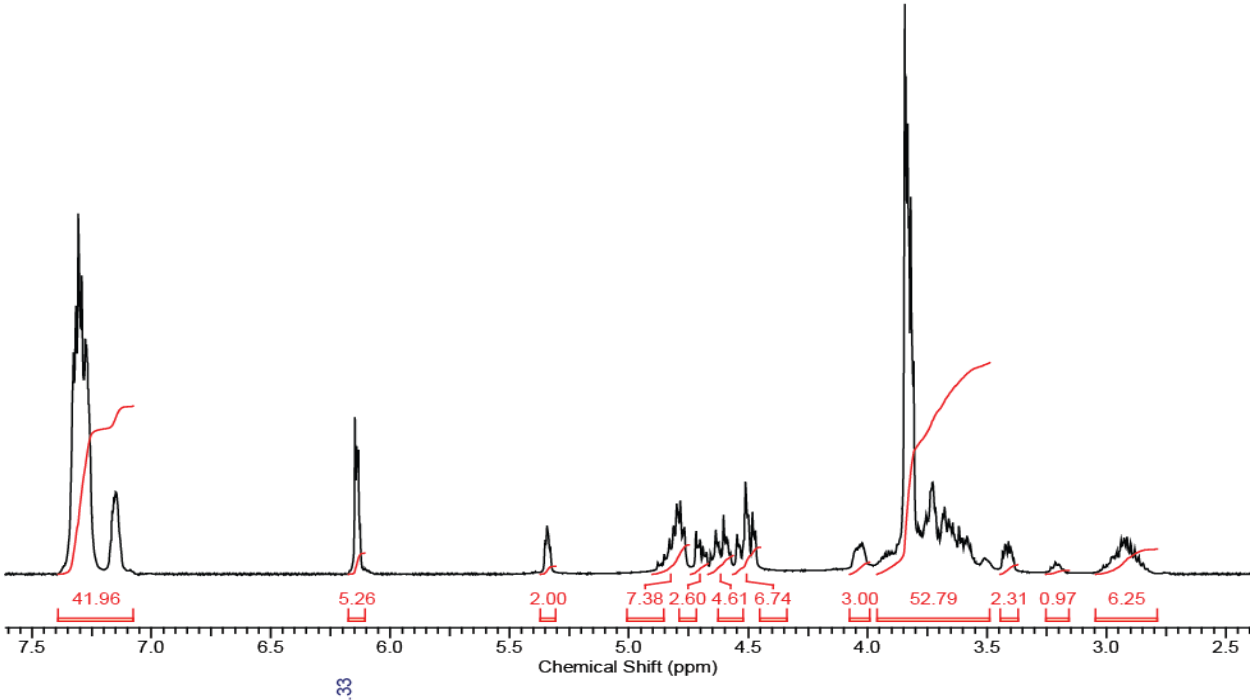

8.08 4.01 2.97 0.69 3.55 4.11 3.99 1.00 10.81 1.86 3.75 2.16 6.99 39.36 6.30 11.76 0.99 7.94 37.91 44.93
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
Chemical Shift (ppm)

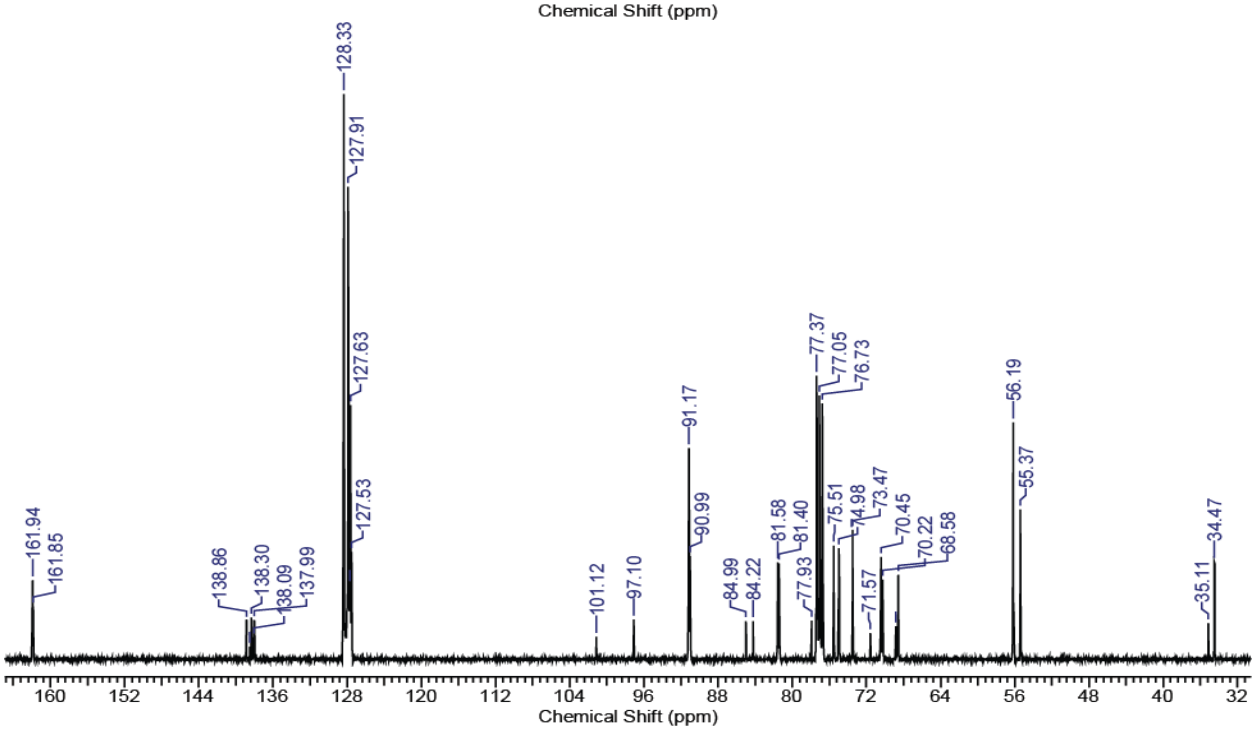

77.33
77.01
76.69
91.00
56.07
170.71
170.11
169.87
162.04
161.88
109.35
108.68
103.78
100.83
97.62
96.22
79.54
78.24
73.89
72.00
70.76
70.59
68.58
67.83
67.20
66.47
55.37
33.93
26.10
25.96
24.93
24.42
20.74
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
Chemical Shift (ppm)

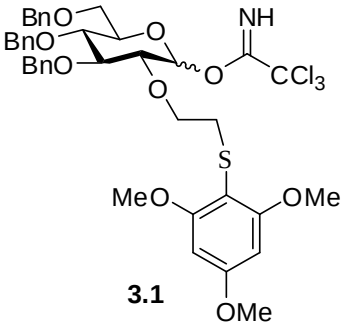

1H NMR CDCl3 400MHz
7.463
7.440
7.365
7.343
7.263
7.247
7.241
7.236
5.551
5.544
5.531
5.006
4.852
4.820
4.610
4.349
4.327
4.320
4.315
4.049
3.959
3.932
3.916
3.913
3.906
3.794
3.711
3.485
3.128
3.113
3.097
1.597
1.552
1.443
1.328
1.284
Ph
BnO
PhSe
a
b
2.52
78.21
11.45 3.59 9.70 4.81 1.00 14.39 3.15 6.65 18.57 15.98 6.32 3.69 1.92 9.83
60.00
Chemical Shift (ppm)


BnO
BnO
BnO
O
OH
O
S
MeO
OMe
OMe

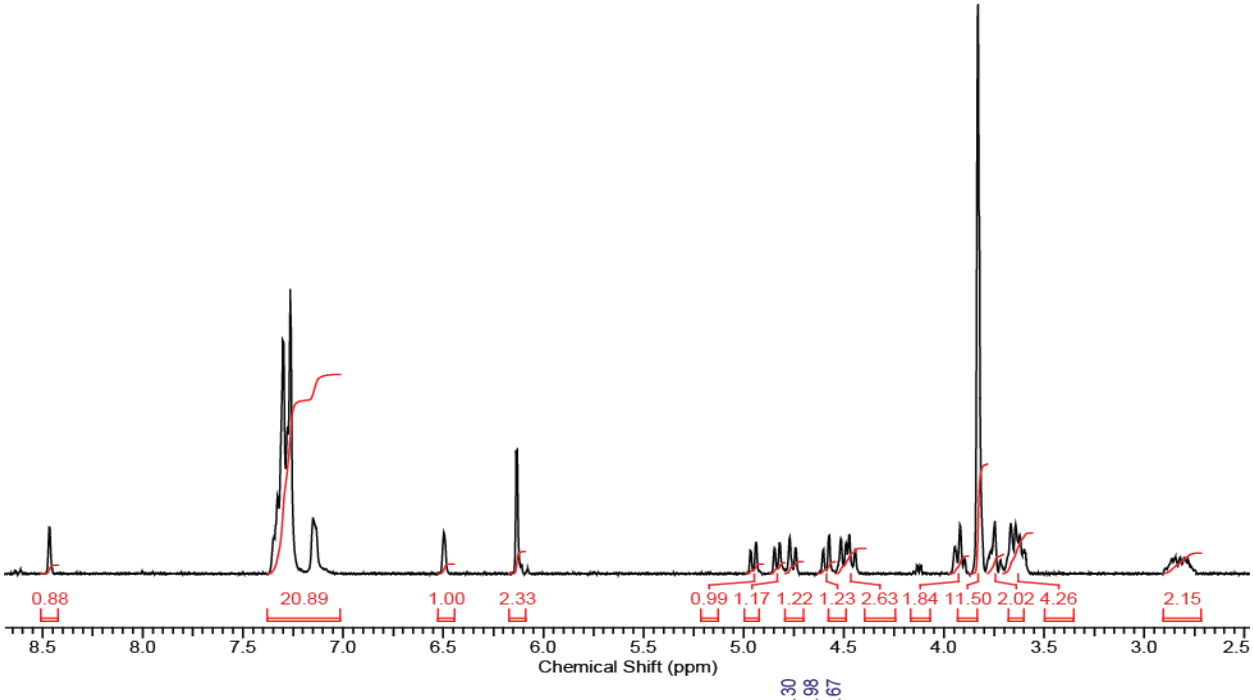
3.14

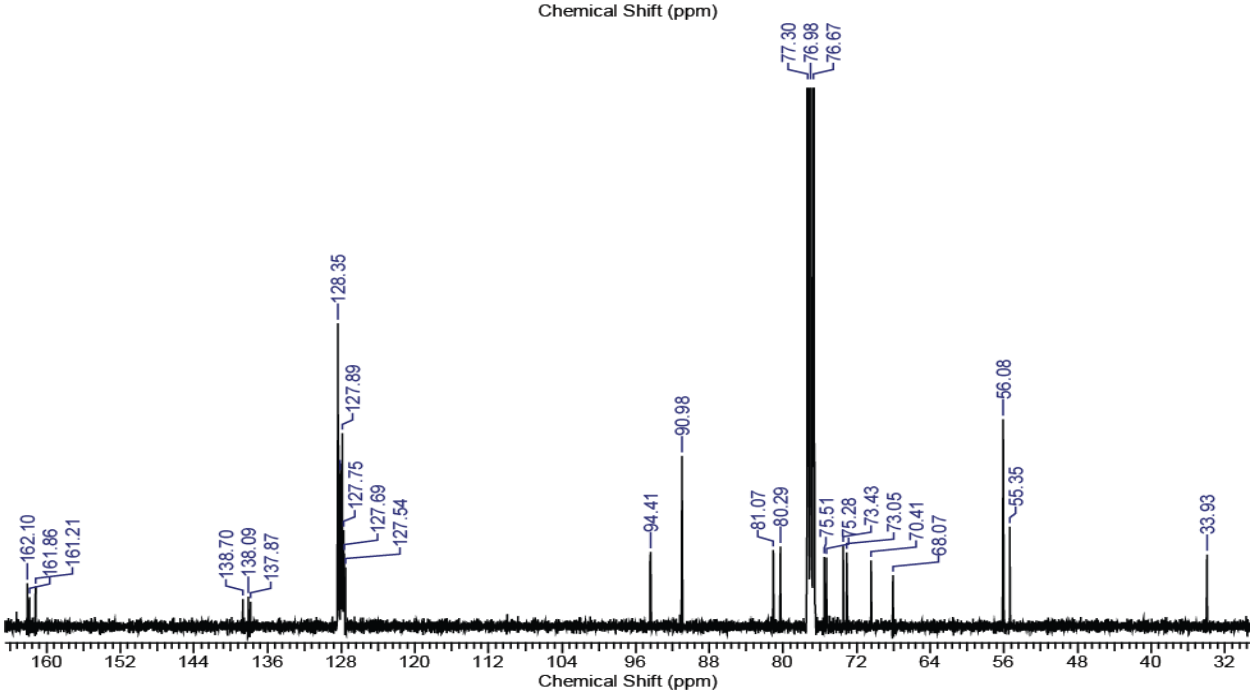

41.96
5.26
2.00
7.38
2.60
4.61
6.74
3.00
52.79
2.31
0.97
6.25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
Chemical Shift (ppm)

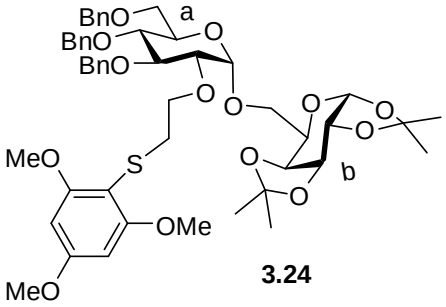

128.33
127.91
127.63
127.53
161.94
161.85
138.86
138.30
138.09
137.99
101.12
97.10
91.17
90.99
84.99
84.22
81.58
81.40
77.93
77.37
77.05
76.73
75.51
74.98
73.47
71.57
70.45
70.22
68.58
56.19
55.37
35.11
34.47
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
Chemical Shift (ppm)


BnO
BnO
BnO
O
NH
O
CCl3
O
S
MeO
OMe
OMe

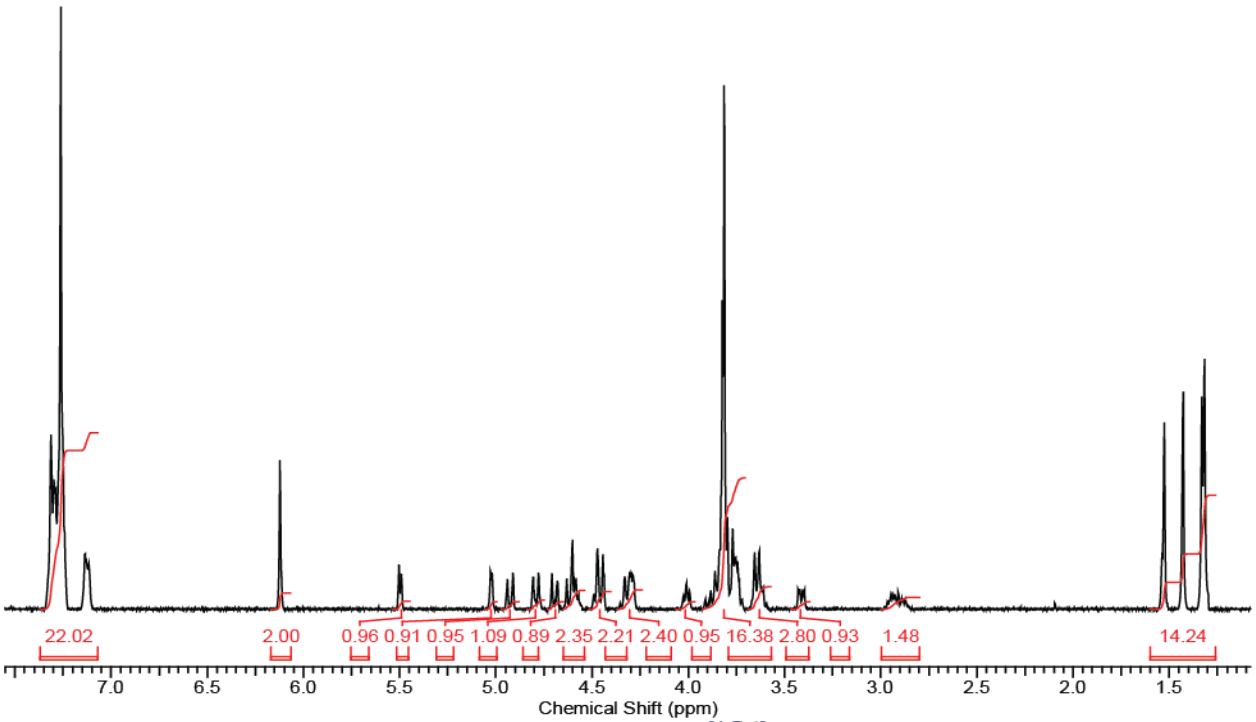
3.1

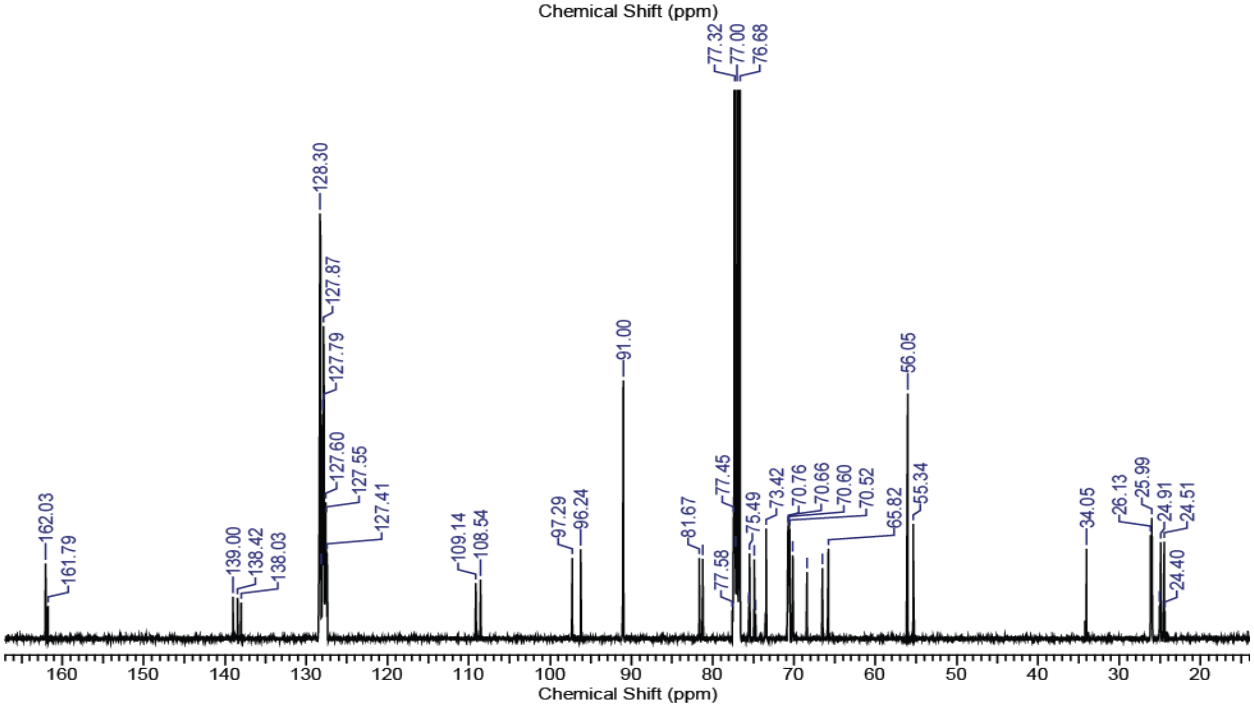

0.88
20.89
1.00
2.33
0.99
1.17
1.22
1.23
2.63
1.84
11.50
2.02
4.26
2.15
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
Chemical Shift (ppm)

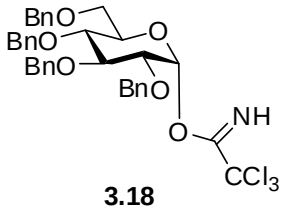

77.30
76.98
76.67
128.35
127.89
127.75
127.69
127.54
162.10
161.86
161.21
138.70
138.09
137.87
94.41
90.98
81.07
80.29
75.51
75.28
73.43
73.05
70.41
68.07
56.08
55.35
33.93
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
Chemical Shift (ppm)


BnO
BnO
BnO
a
O
O
O
O
O
O
O
O
O
b
MeO
S
OMe
MeO

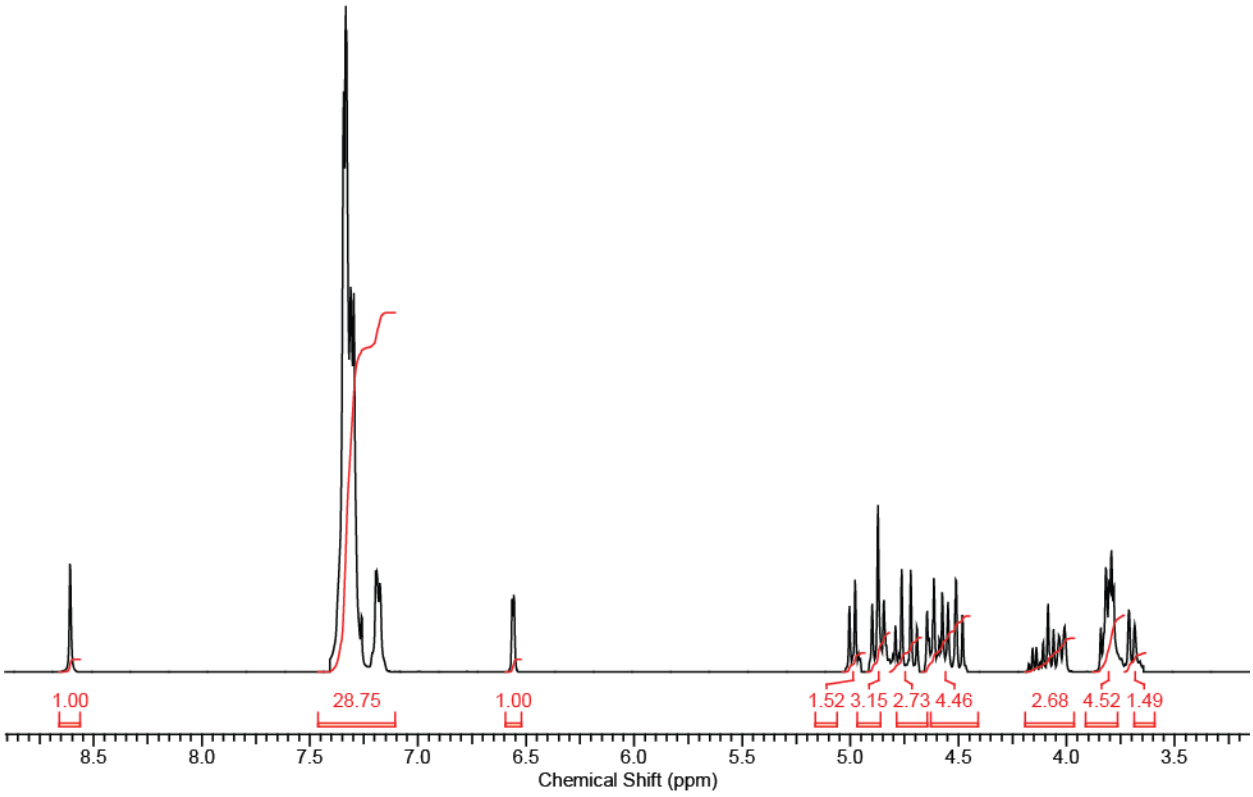
3.24

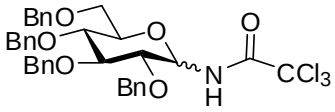

22.02
2.00
0.96 0.91 0.95 1.09 0.89 2.35 2.21 2.40 0.95 16.38 2.80 0.93
1.48
14.24
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)


77.32
77.00
76.68
128.30
127.87
127.79
127.60
127.55
127.41
91.00
56.05
162.03
161.79
139.00
138.42
138.03
109.14
108.54
97.29
96.24
81.67
77.45
77.58
75.49
73.42
70.76
70.66
70.60
70.52
65.82
55.34
34.05
26.13
25.99
24.91
24.51
24.40
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
Chemical Shift (ppm)

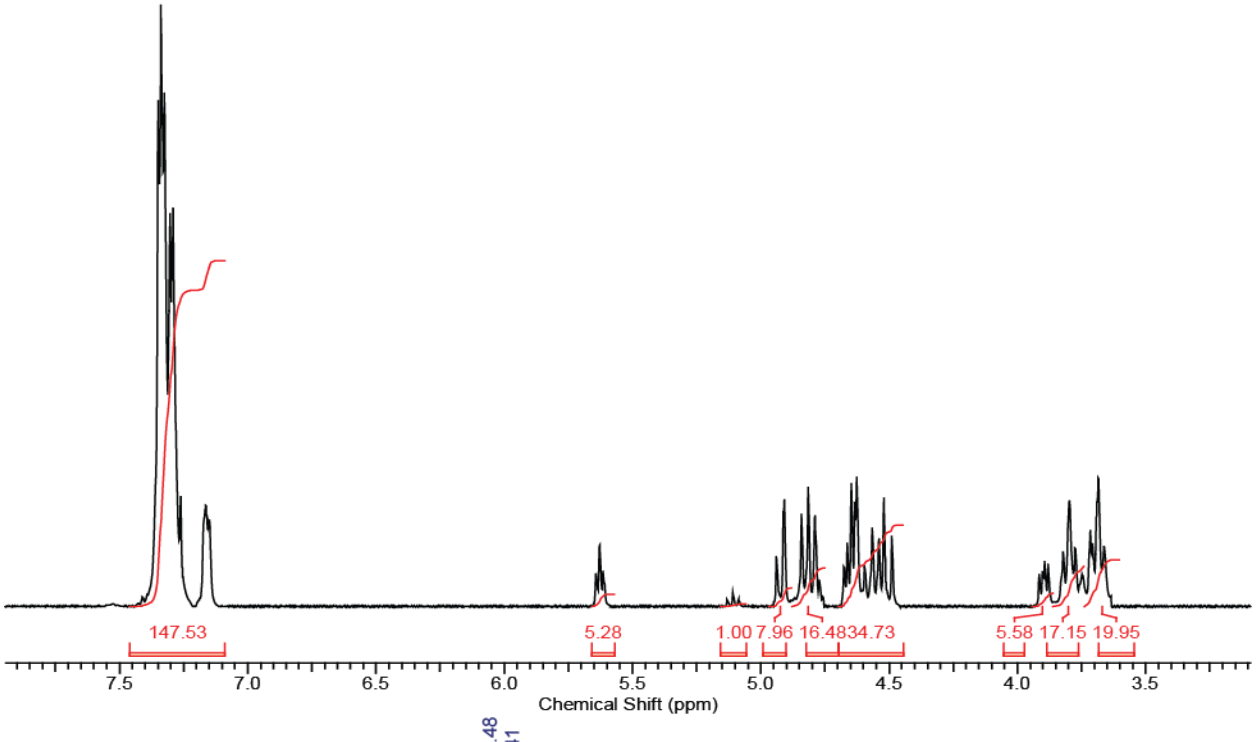

BnO
BnO
BnO
BnO
O
O
NH
CCl3

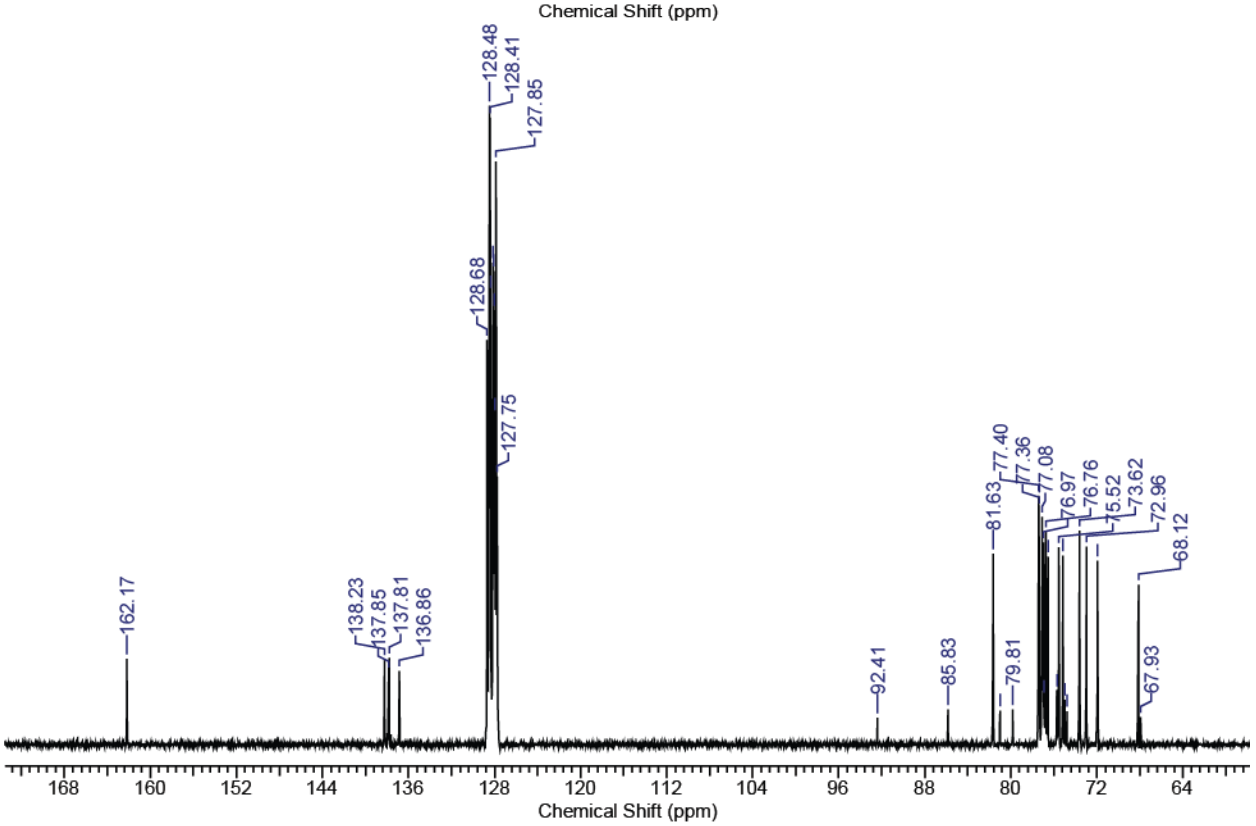
3.18

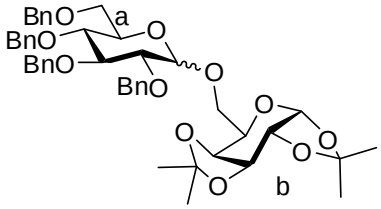

1.00
28.75
1.00
1.52
3.15
2.73
4.46
2.68
4.52
1.49
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
Chemical Shift (ppm)


BnO
BnO
BnO
BnO
O
N
H
O
CCl3

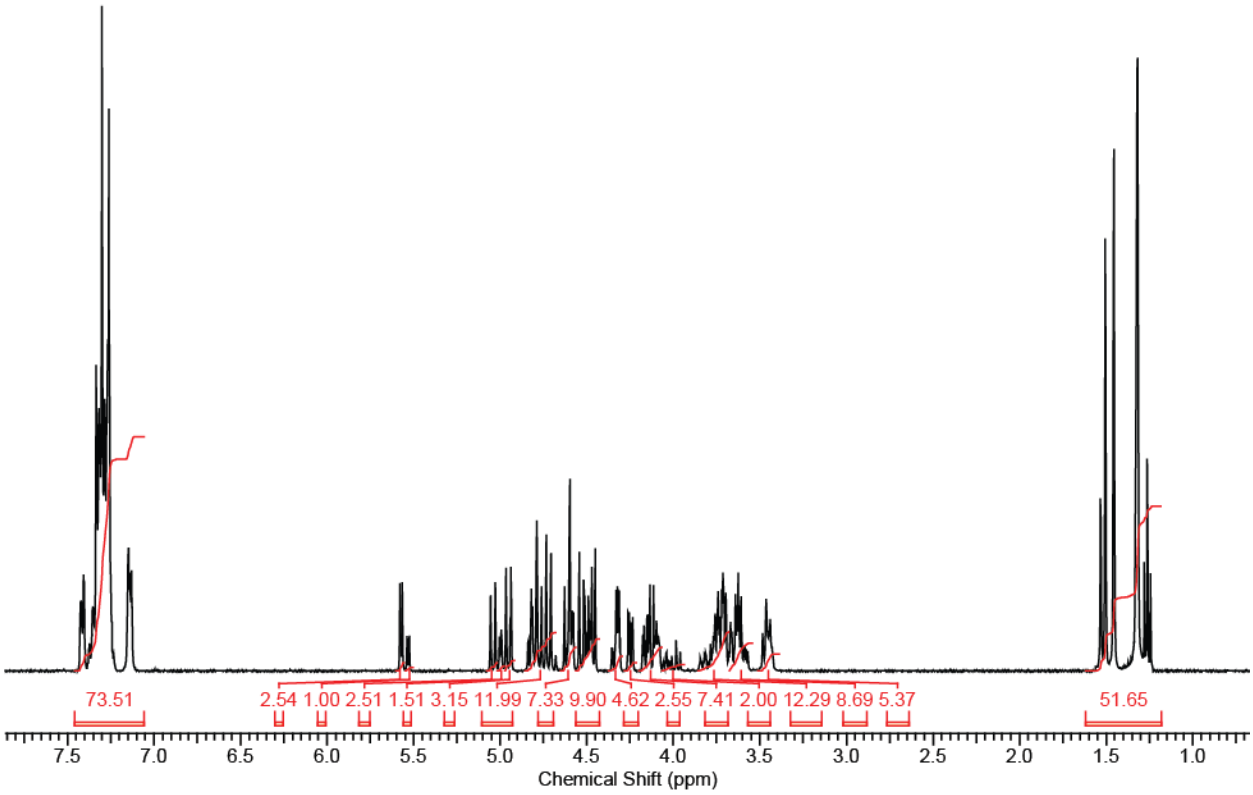
3.19

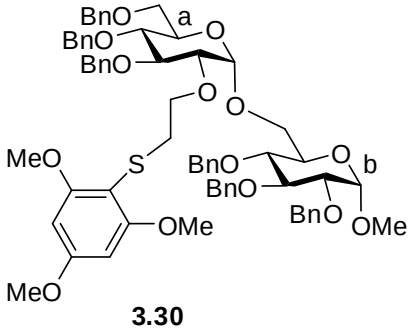

147.53
5.28
1.00
7.96
16.48
34.73
5.58
17.15
19.95
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
Chemical Shift (ppm)


162.17
138.23
137.85
137.81
136.86
128.68
128.48
128.41
127.85
127.75
92.41
85.83
81.63
79.81
77.40
77.36
77.08
76.97
76.76
75.52
73.62
72.96
68.12
67.93
168
160
152
144
136
128
120
112
104
96
88
80
72
64
Chemical Shift (ppm)

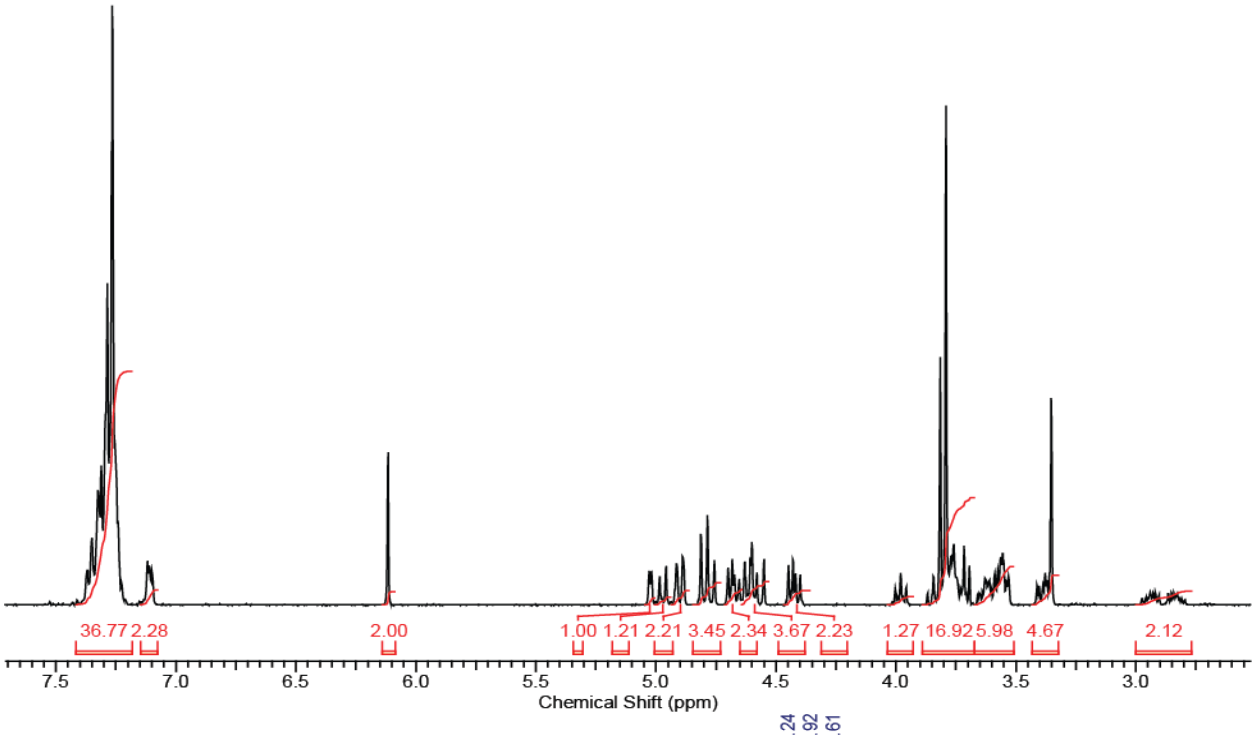

BnO
a
BnO
BnO
O
BnO
O
O
O
O
O
b

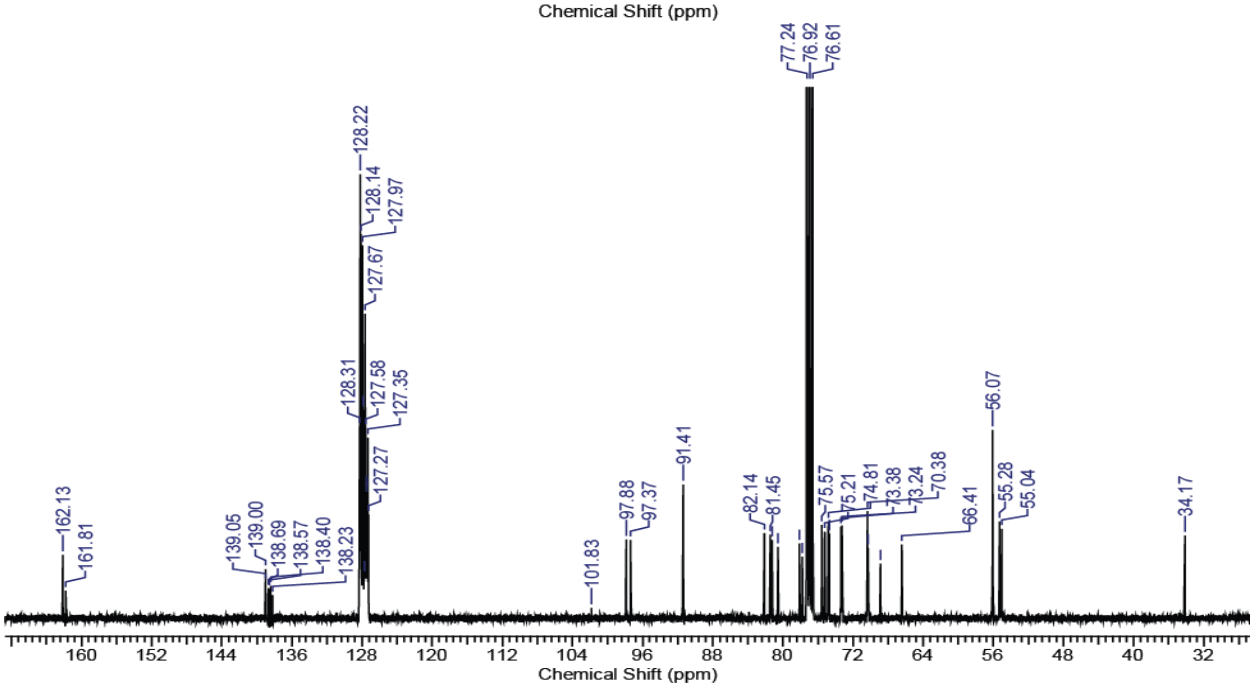
3.20

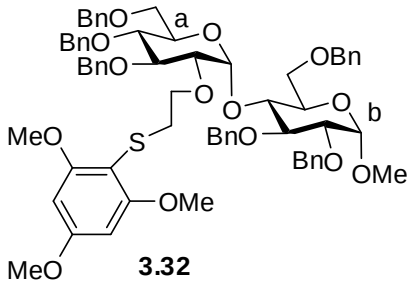

73.51
2.54 1.00 2.51 1.51 3.15 11.99 7.33 9.90 4.62 2.55 7.41 2.00 12.29 8.69 5.37
51.65
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
Chemical Shift (ppm)


BnO
a
BnO
BnO
O
O
O
MeO
S
BnO
O
b
BnO
BnO
OMe
MeO

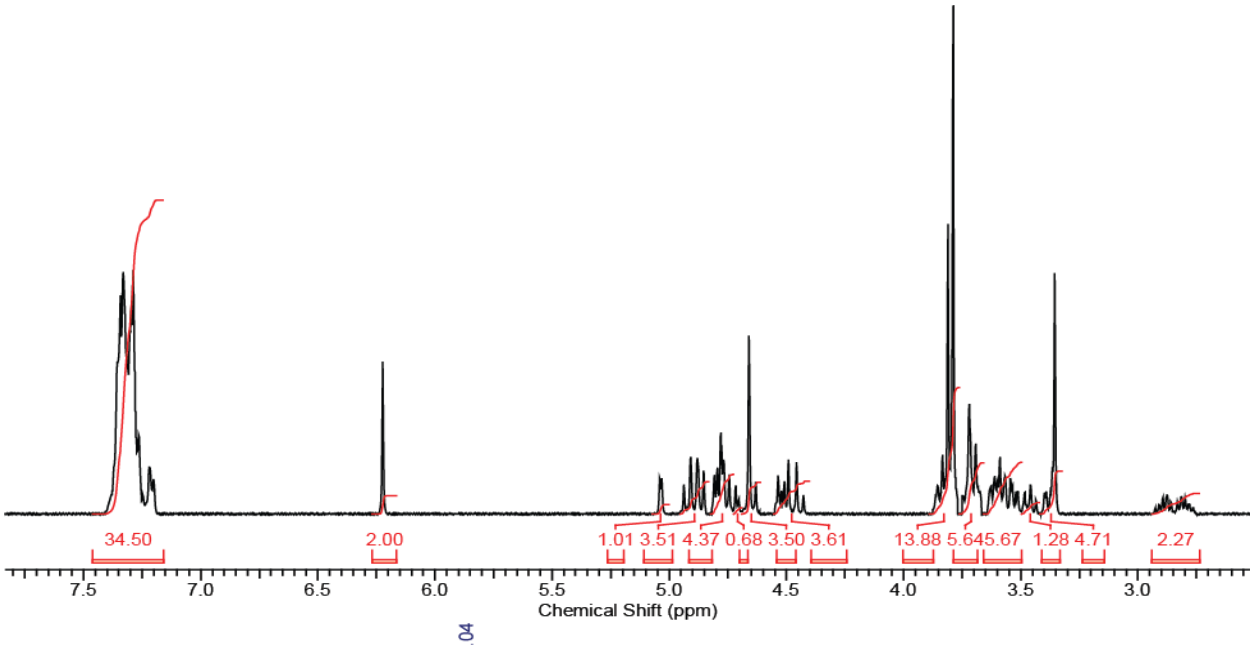
3.30

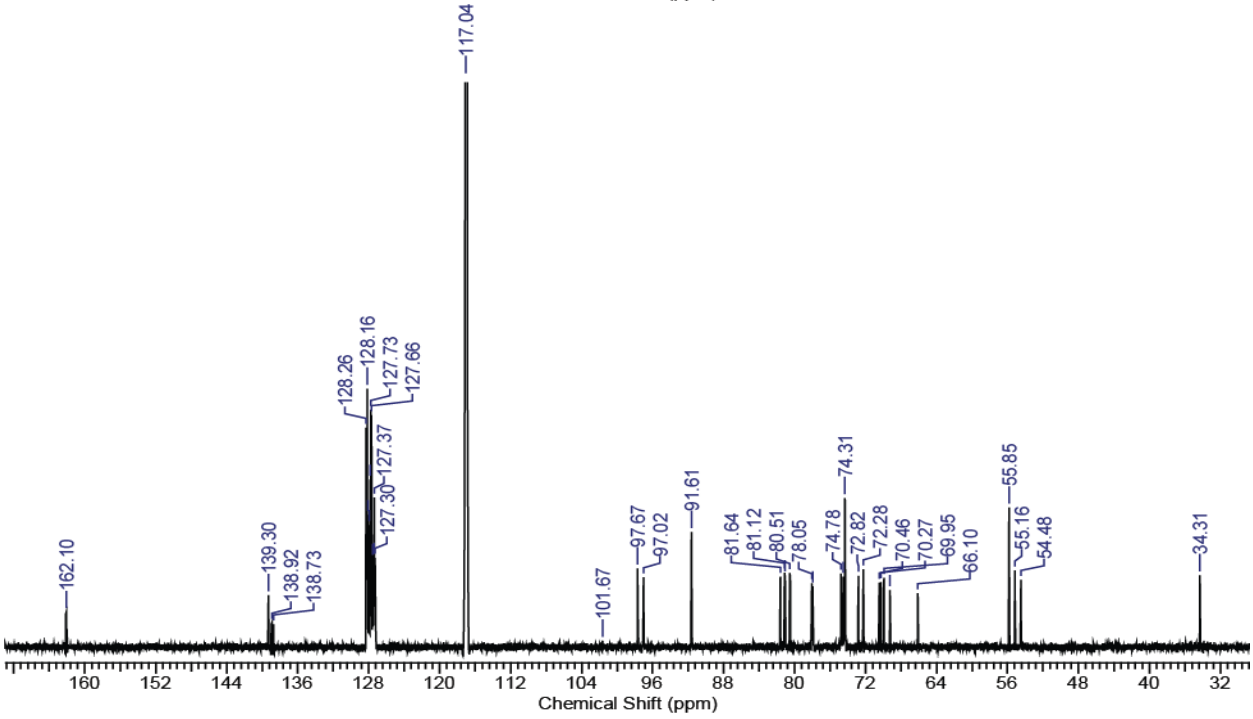

36.77 2.28
2.00
1.00 1.21 2.21 3.45 2.34 3.67 2.23
1.27 16.92 5.98 4.67
2.12
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
Chemical Shift (ppm)

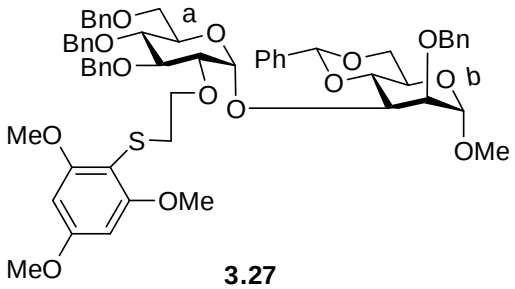

77.24
76.92
76.61
128.22
128.14
127.97
127.67
128.31
127.58
127.35
127.27
162.13
161.81
139.05
139.00
138.69
138.57
138.40
138.23
101.83
97.88
97.37
91.41
82.14
81.45
75.57
75.21
74.81
73.38
73.24
70.38
66.41
56.07
55.28
55.04
34.17
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
Chemical Shift (ppm)


BnO
a
O
BnO
BnO
OBn
O
O
O
b
MeO
S
BnO
BnO
OMe
OMe
MeO

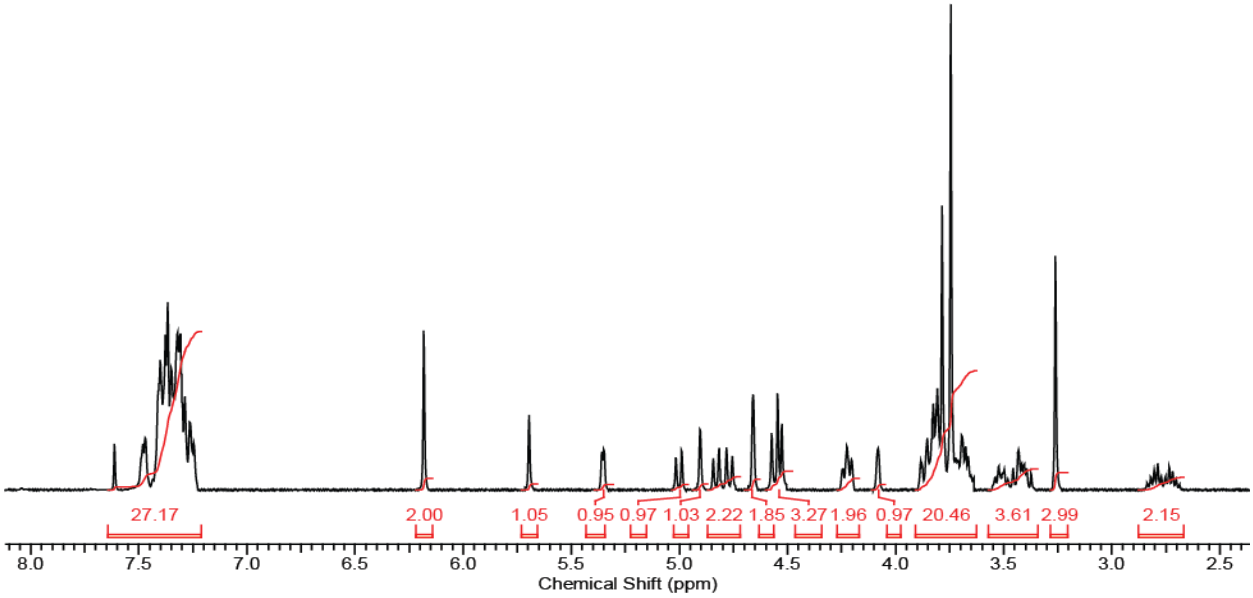
3.32

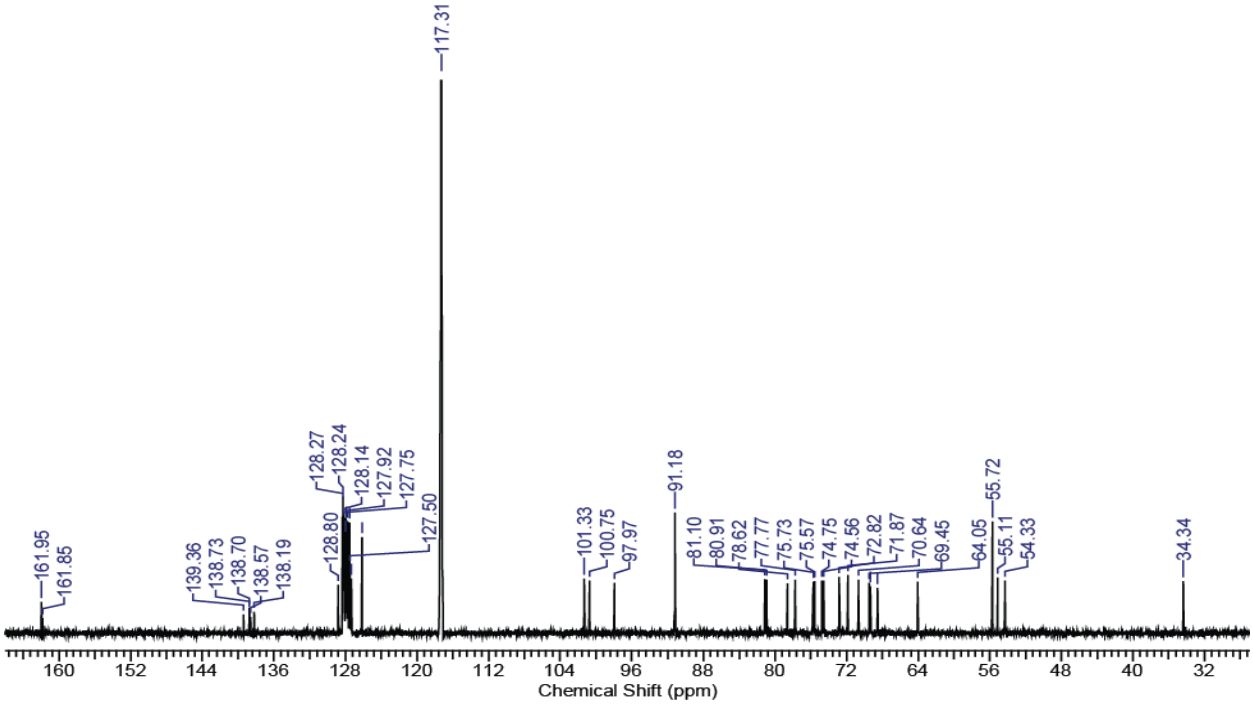

34.50
2.00
1.01
3.51
4.37
0.68
3.50
3.61
13.88
5.64
5.67
1.28
4.71
2.27
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
Chemical Shift (ppm)

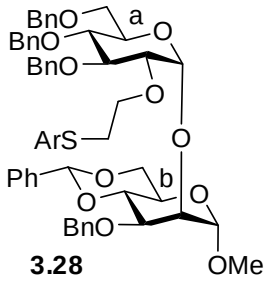

162.10
139.30
138.92
138.73
128.26
128.16
127.73
127.66
127.37
127.30
117.04
101.67
97.67
97.02
91.61
81.64
81.12
80.51
78.05
74.78
74.31
72.82
72.28
70.46
70.27
69.95
66.10
55.85
55.16
54.48
34.31
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
Chemical Shift (ppm)


BnO
BnO
BnO
a
O
O
O
Ph
O
O
OBn
O
b
OMe
MeO
S
OMe
MeO

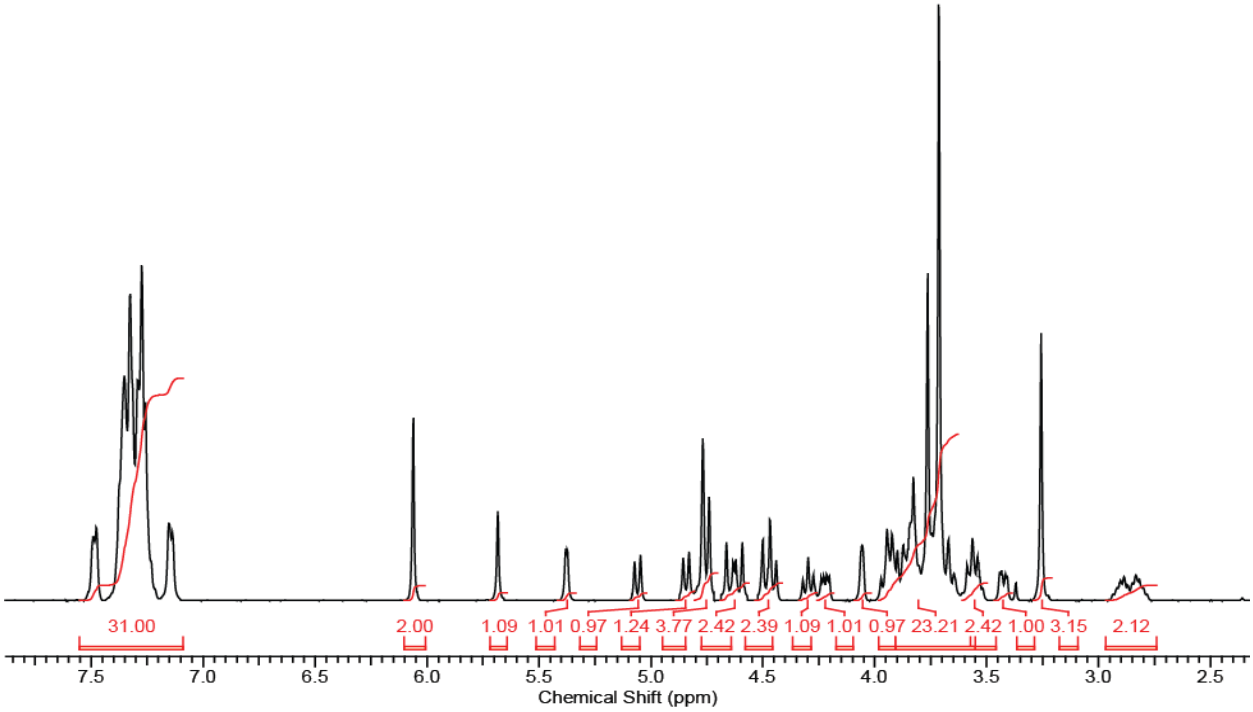
3.27

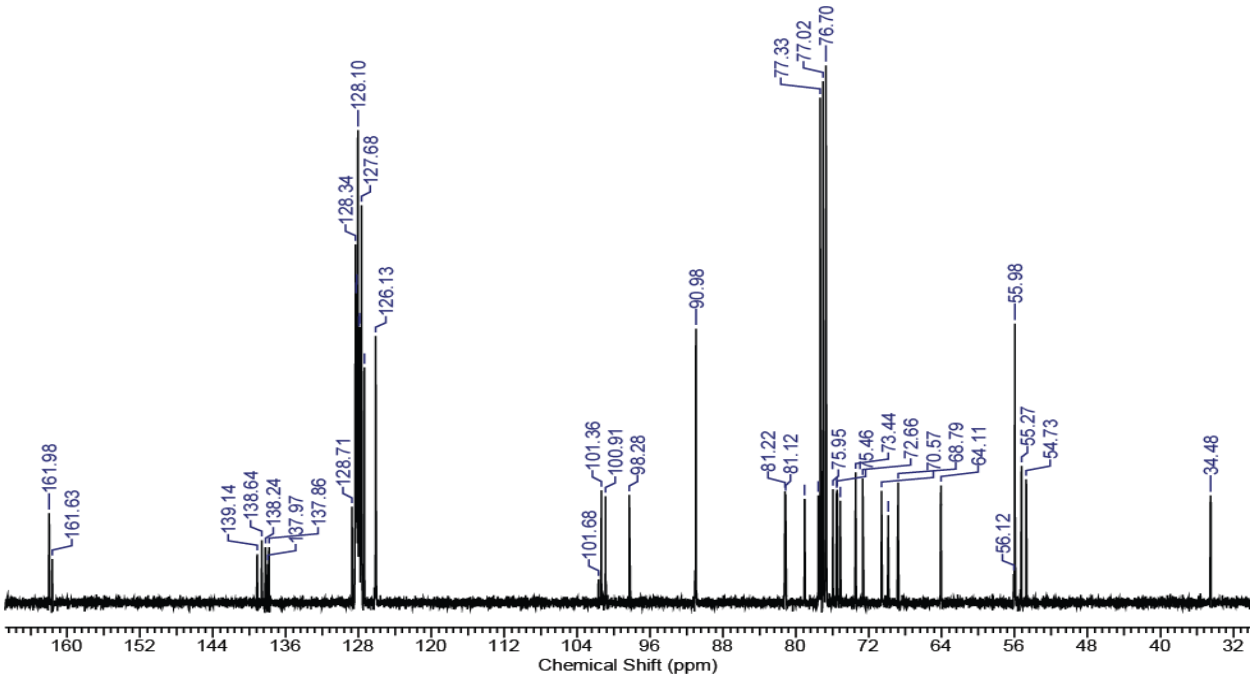

27.17
2.00
1.05
0.95
0.97
1.03
2.22
1.85
3.27
1.96
0.97
20.46
3.61
2.99
2.15
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
Chemical Shift (ppm)

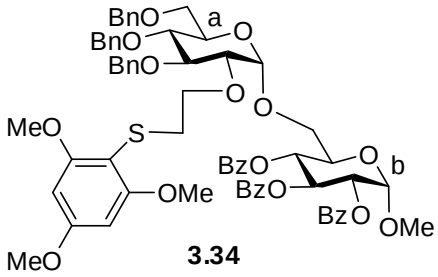

117.31
161.95
161.85
139.36
138.73
138.70
138.57
138.19
128.80
128.27
128.24
128.14
127.92
127.75
127.50
101.33
100.75
97.97
91.18
81.10
80.91
78.62
77.77
75.73
75.57
74.75
74.56
72.82
71.87
70.64
69.45
64.05
55.72
55.11
54.33
34.34
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
Chemical Shift (ppm)


BnO
BnO
BnO
a
O
O
ArS
O
Ph
O
O
b
O
BnO
OMe

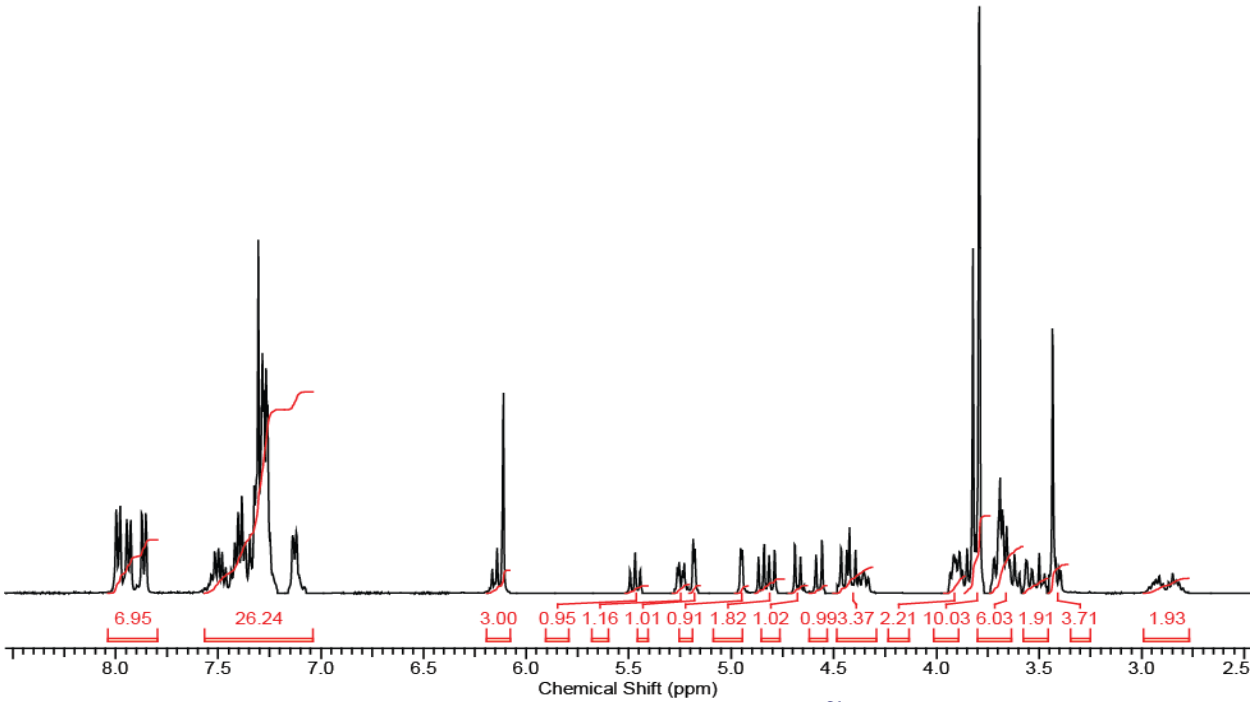
3.28

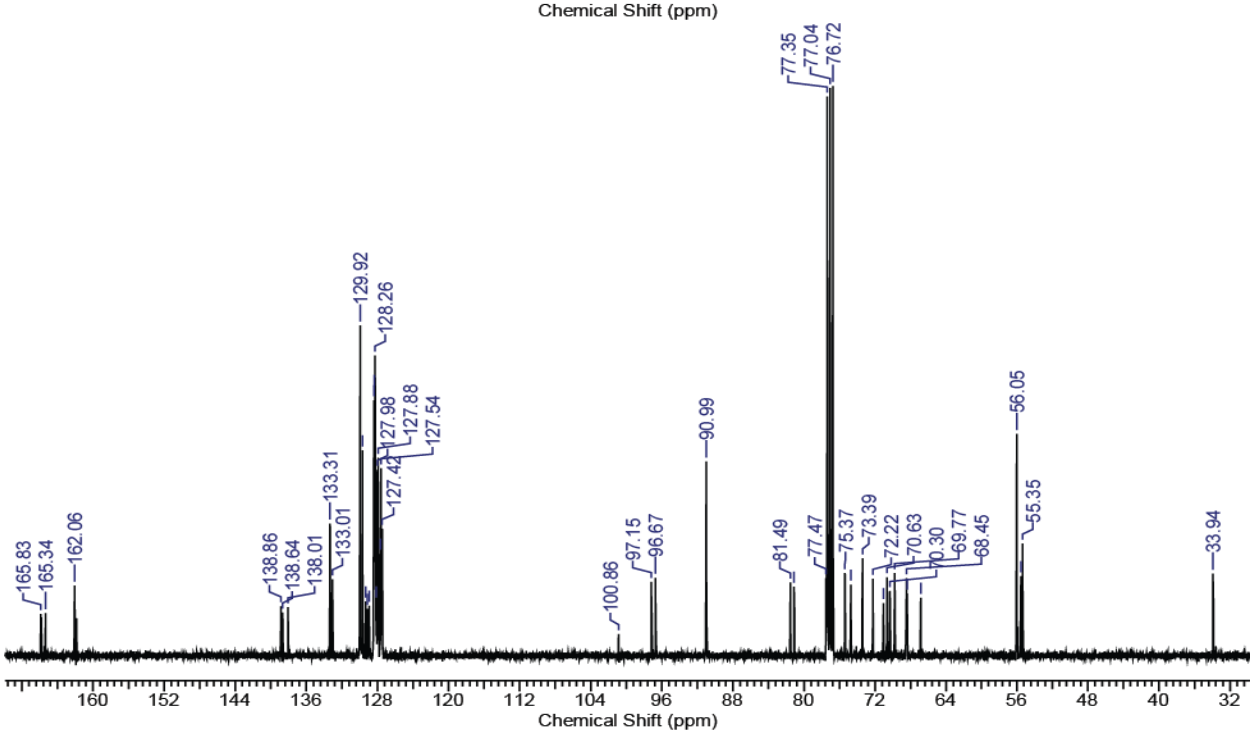

31.00
2.00
1.09
1.01
0.97
1.24
3.77
2.42
2.39
1.09
1.01
0.97
23.21
2.42
1.00
3.15
2.12
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
Chemical Shift (ppm)

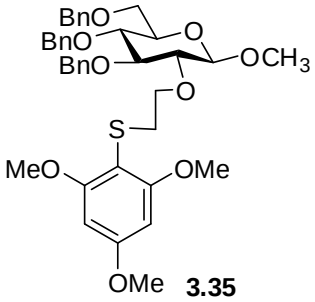

161.98
161.63
139.14
138.64
138.24
137.97
137.86
128.71
128.34
128.10
127.68
126.13
101.68
101.36
100.91
98.28
90.98
81.22
81.12
77.33
77.02
76.70
75.95
75.46
73.44
72.66
70.57
68.79
64.11
56.12
55.98
55.27
54.73
34.48
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
Chemical Shift (ppm)


BnO
a
BnO
BnO
O
O
O
MeO
S
BzO
O
b
BzO
OMe
BzO
OMe
MeO

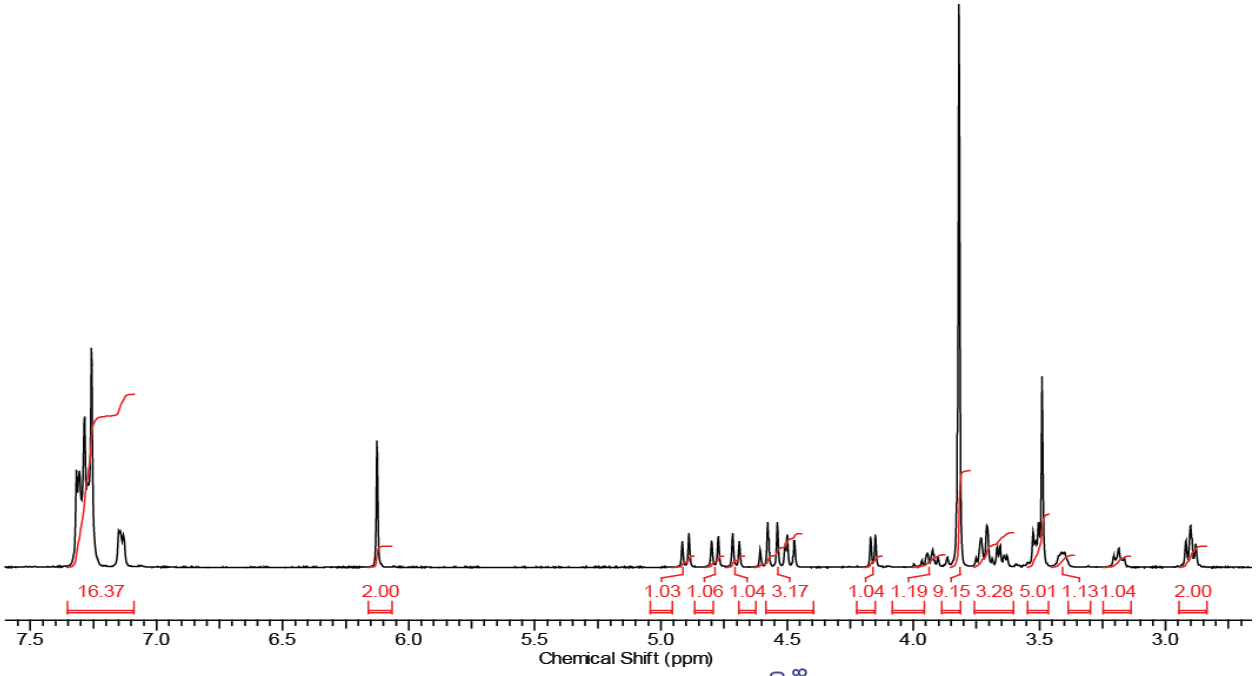
3.34

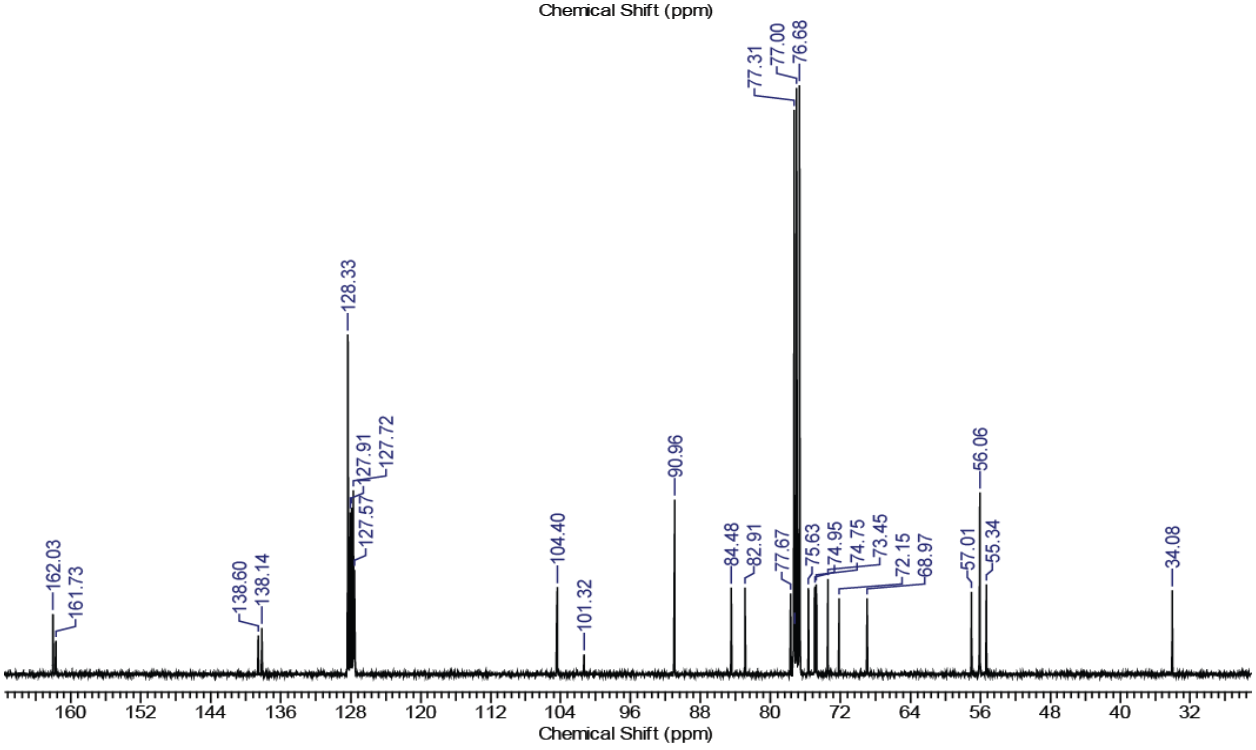

6.95
26.24
3.00
0.95
1.16
1.01
0.91
1.82
1.02
0.99
3.37
2.21
10.03
6.03
1.91
3.71
1.93
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
Chemical Shift (ppm)

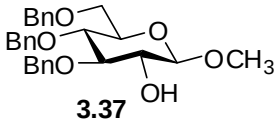

77.35
77.04
76.72
129.92
128.26
127.98
127.88
127.54
127.42
133.31
133.01
90.99
56.05
55.35
165.83
165.34
162.06
138.86
138.64
138.01
100.86
97.15
96.67
81.49
77.47
75.37
73.39
72.22
70.63
70.30
69.77
68.45
33.94
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
Chemical Shift (ppm)


BnO
BnO
BnO
O
OCH3
O
S
MeO
OMe
OMe

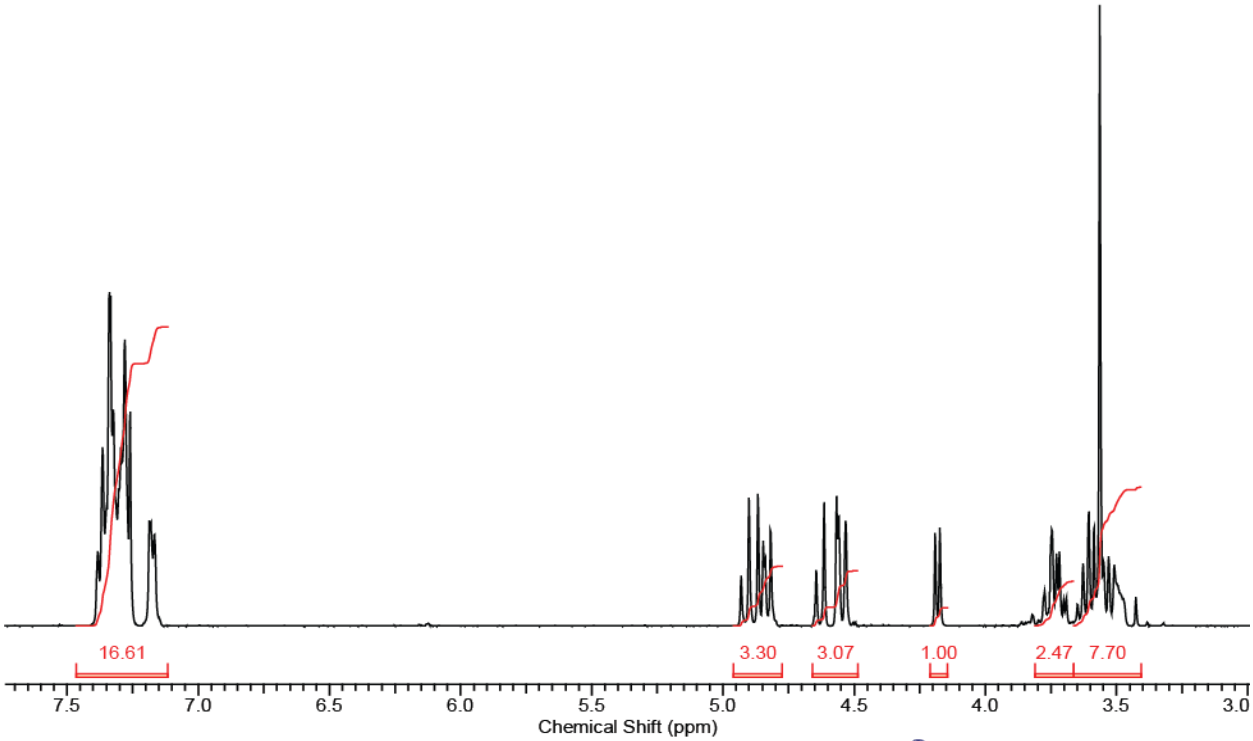
3.35

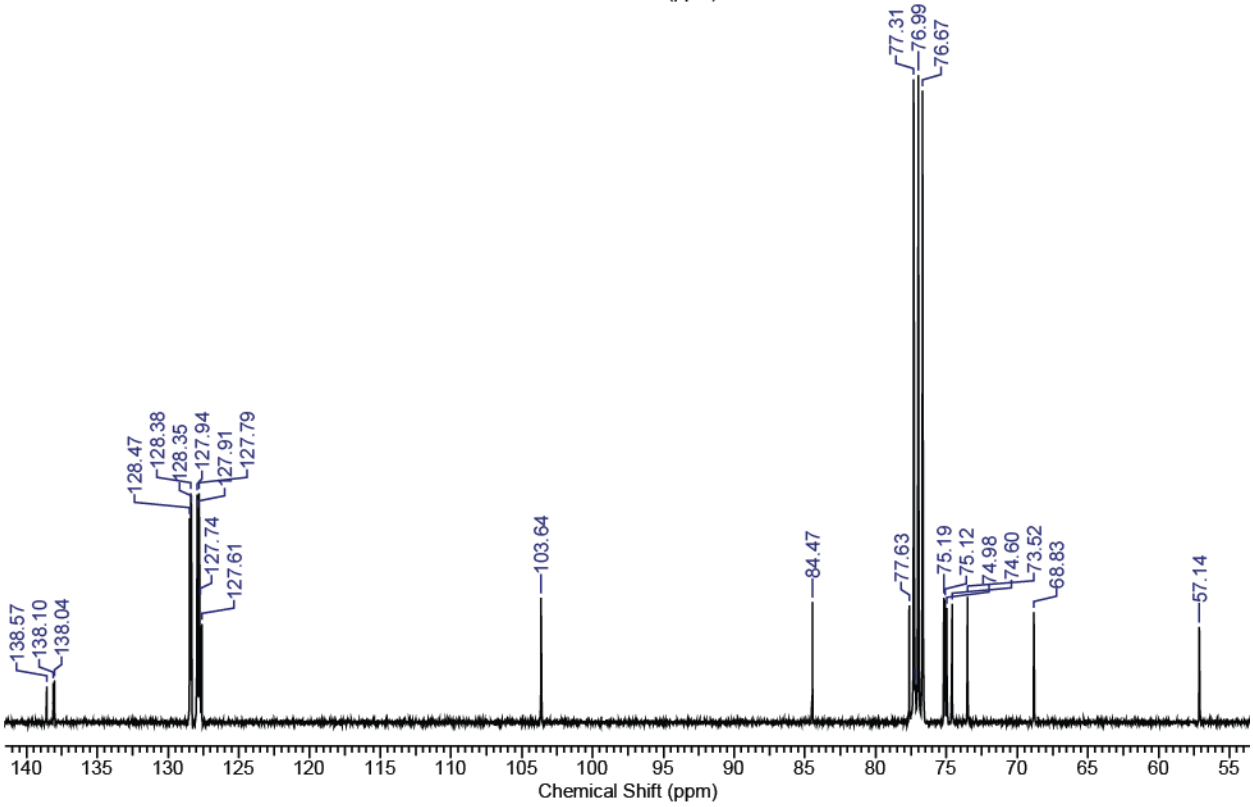

16.37
2.00
1.03 1.06 1.04 3.17
1.04 1.19 9.15 3.28 5.01 1.13 1.04
2.00
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0
Chemical Shift (ppm)

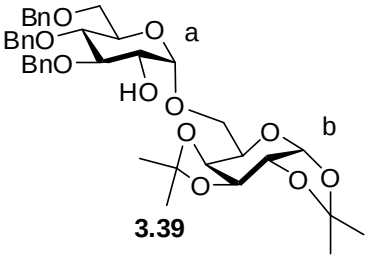

162.03
161.73
138.60
138.14
128.33
127.91
127.72
127.57
104.40
101.32
90.96
84.48
82.91
77.67
77.31
77.00
76.68
75.63
74.95
74.75
73.45
72.15
68.97
57.01
56.06
55.34
34.08
160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32
Chemical Shift (ppm)


BnO
BnO
BnO
O
OCH3
OH

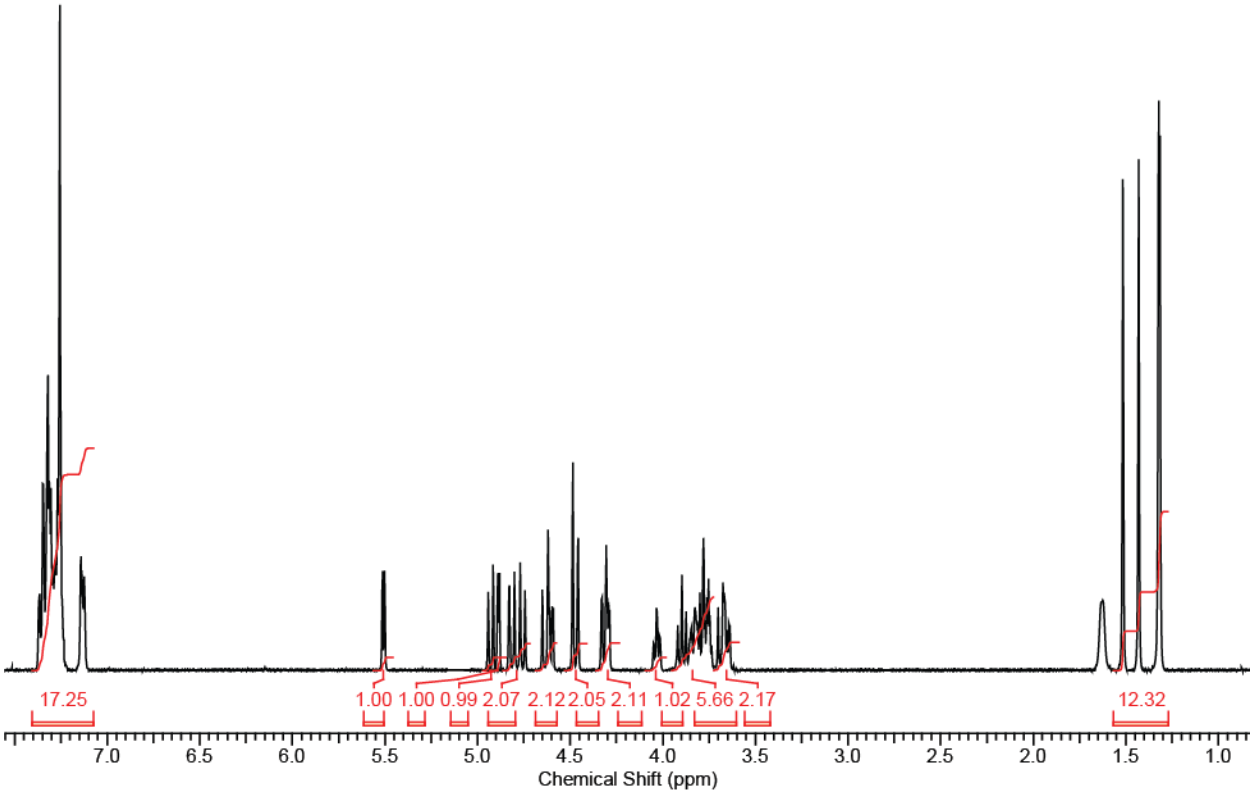
3.37

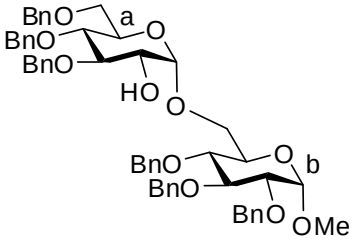

16.61
3.30
3.07
1.00
2.47
7.70
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
Chemical Shift (ppm)


77.31
76.99
76.67
128.47
128.38
128.35
127.94
127.91
127.79
127.74
127.61
138.57
138.10
138.04
103.64
84.47
77.63
75.19
75.12
74.98
74.60
73.52
68.83
57.14
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
Chemical Shift (ppm)

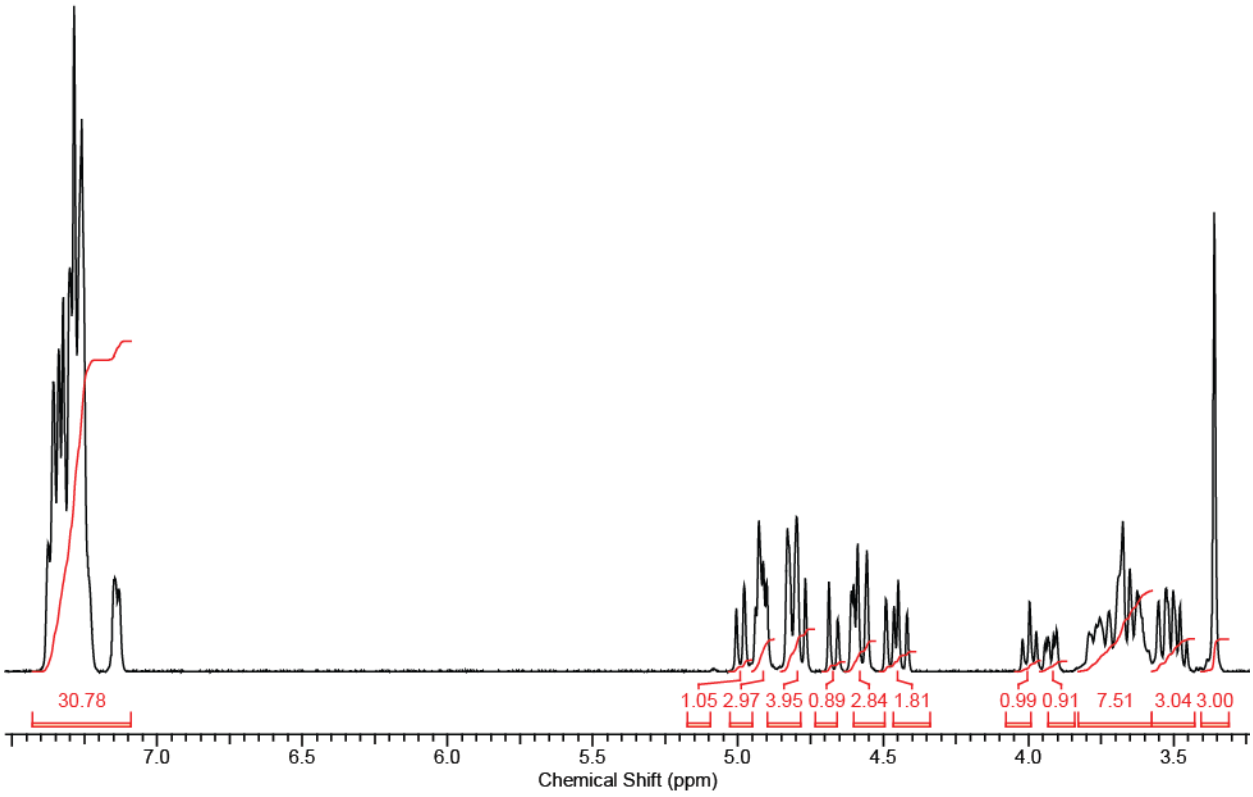

BnO
BnO
BnO
O
a
HO
O
O
O
b
O
O
O
O

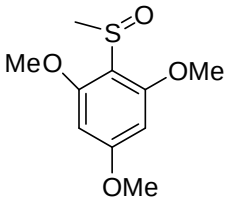
3.39


17.25
1.00 1.00 0.99 2.07 2.12 2.05 2.11 1.02 5.66 2.17
12.32
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)

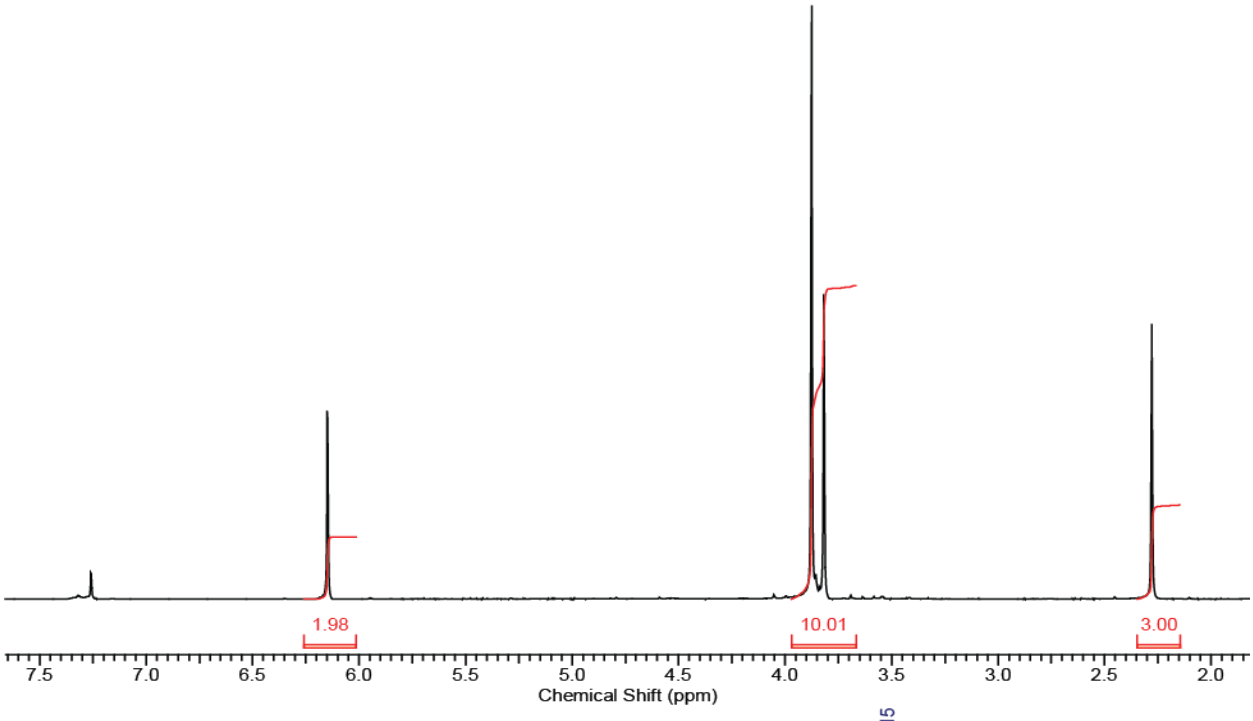

BnO
a
O
BnO
BnO
HO
O
BnO
O
b
BnO
BnO
OMe

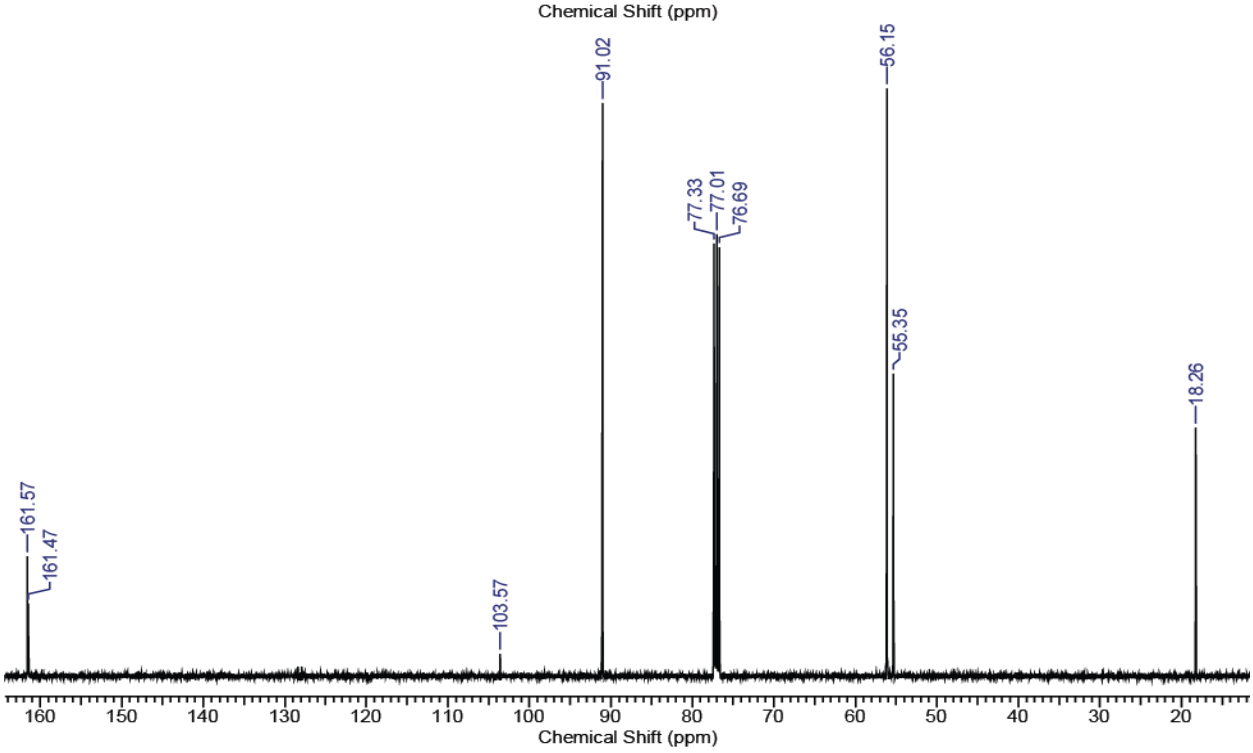
3.41

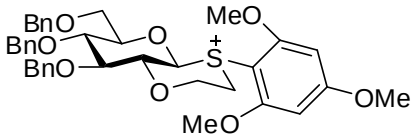

30.78
1.05 2.97 3.95 0.89 2.84 1.81
0.99 0.91 7.51 3.04 3.00
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
Chemical Shift (ppm)


S
O
MeO
OMe
OMe

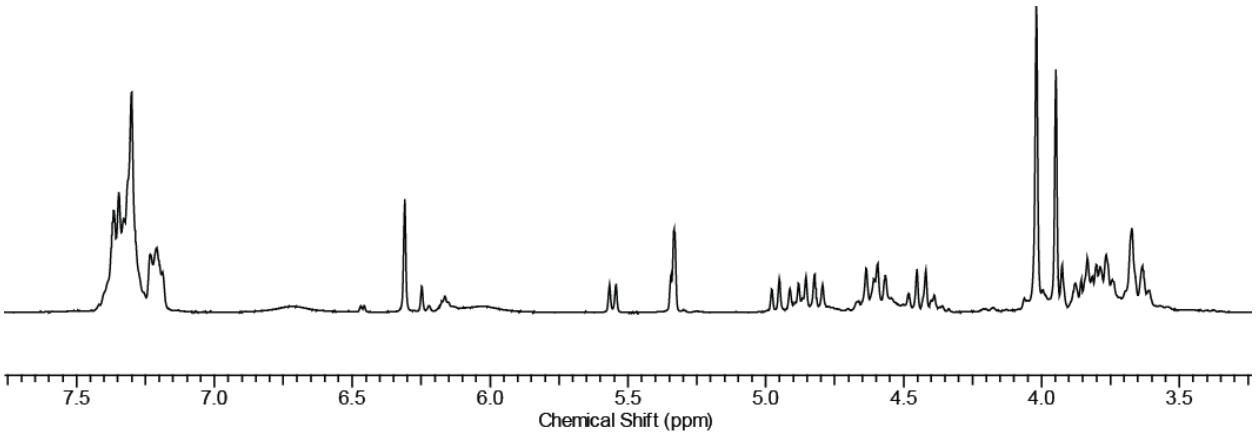
3.40


1.98
10.01
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
Chemical Shift (ppm)

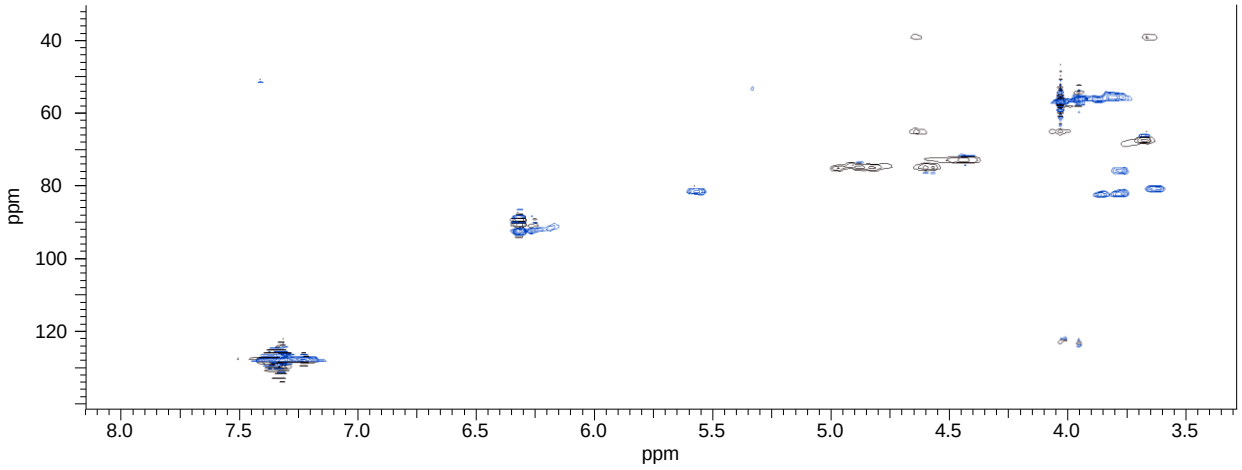

161.57
161.47
103.57
91.02
77.33
77.01
76.69
56.15
55.35
18.26
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
Chemical Shift (ppm)



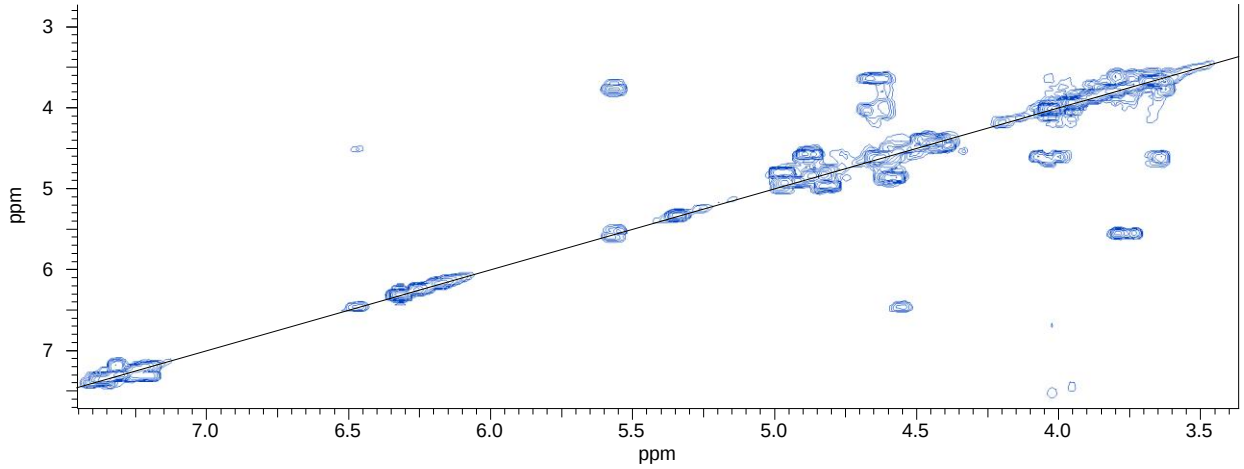
3.1a



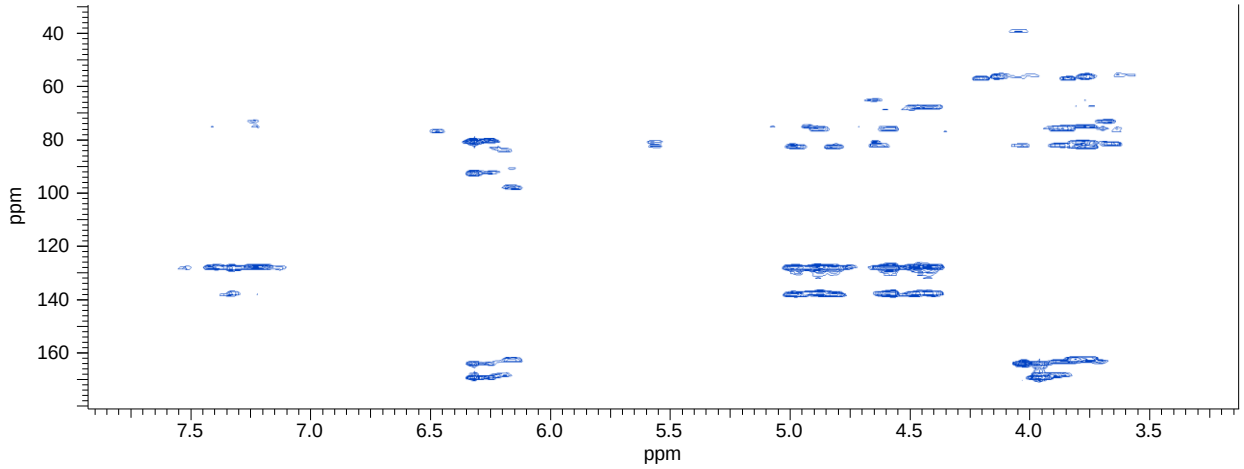
^{1}H NMR for Low Temperature NMR Study of Compound 3.1



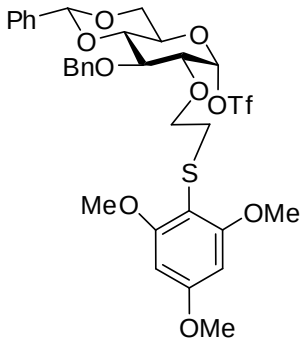
HSQC for Low Temperature NMR Study of Compound 3.1



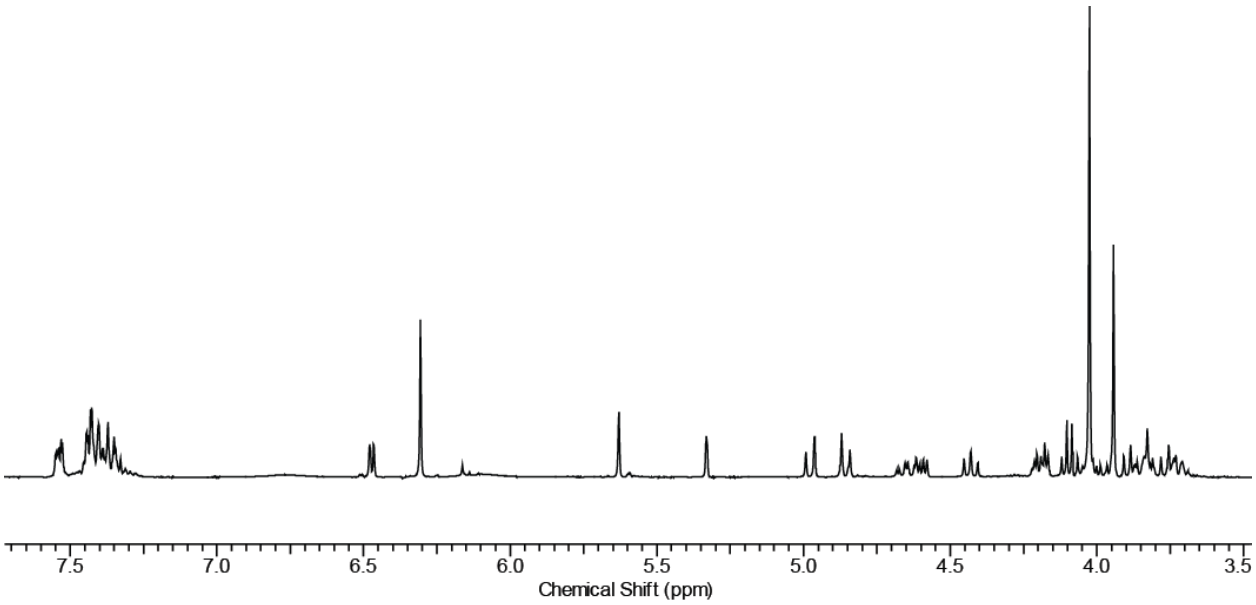
COSY for Low Temperature NMR Study of Compound 3.1



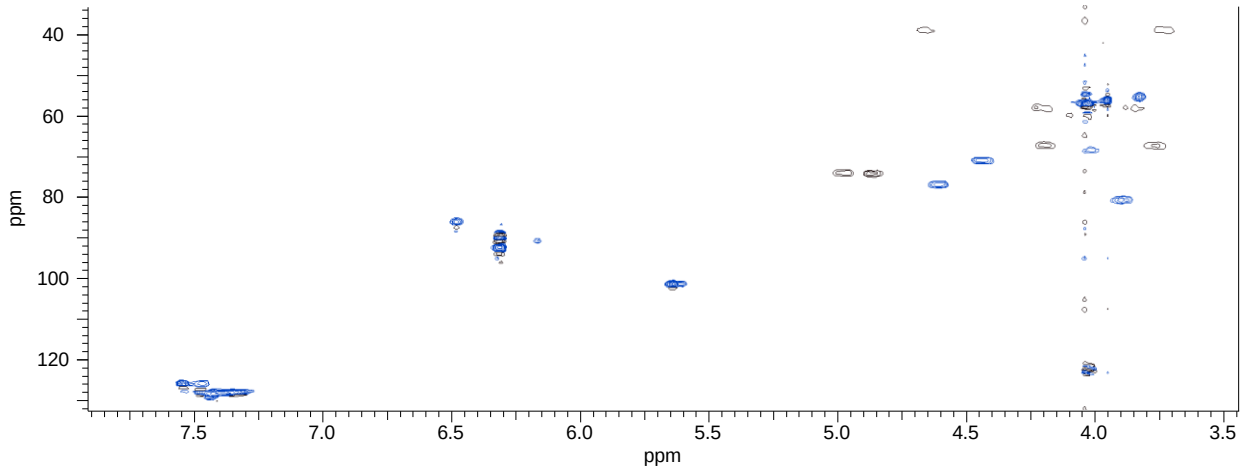
HMBC for Low Temperature NMR Study of Compound 3.1



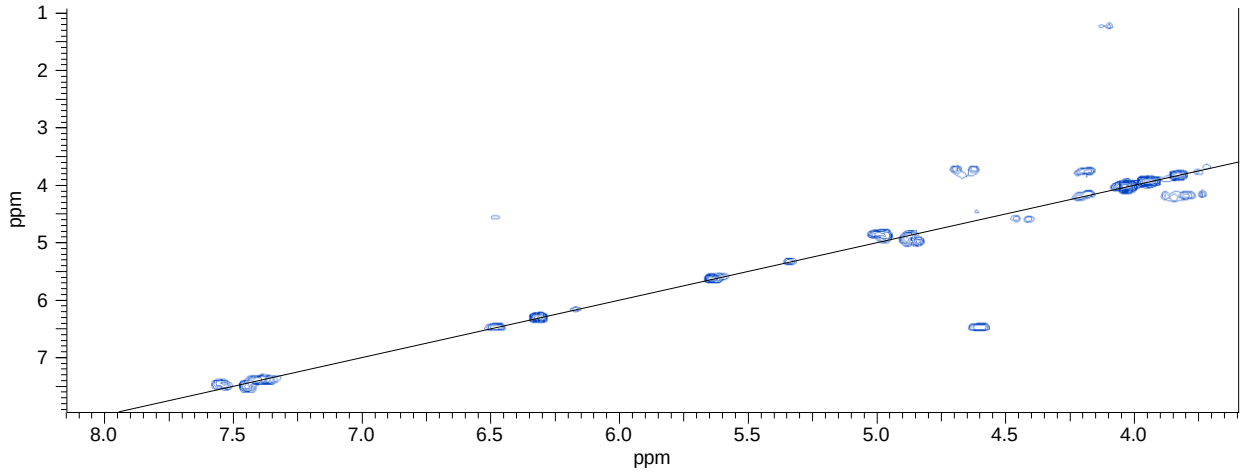
3.2a



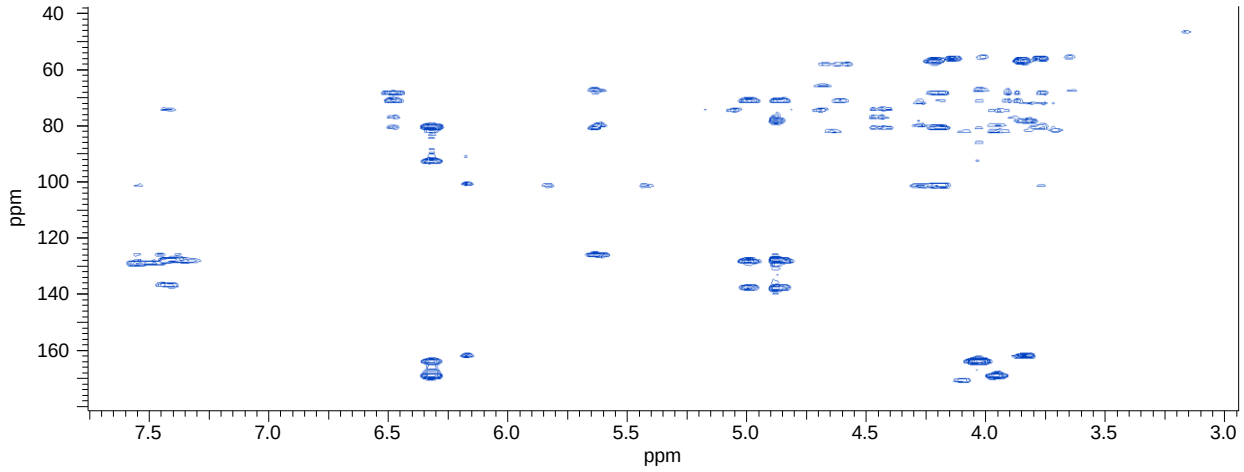
^{1}H NMR for Low Temperature NMR Study of Compound 3.2



HSQC for Low Temperature NMR Study of Compound 3.2



COSY for Low Temperature NMR Study of Compound 3.2



HMBC for Low Temperature NMR Study of Compound 3.2