

**Developing a Sacrificial Protective
Group to Deliver the 1,2 *cis*
Glycoside**

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A Thesis Submitted in Partial Fulfilment of the
Requirements of the Degree of Doctor of Philosophy
For Nottingham Trent University.

October 2016

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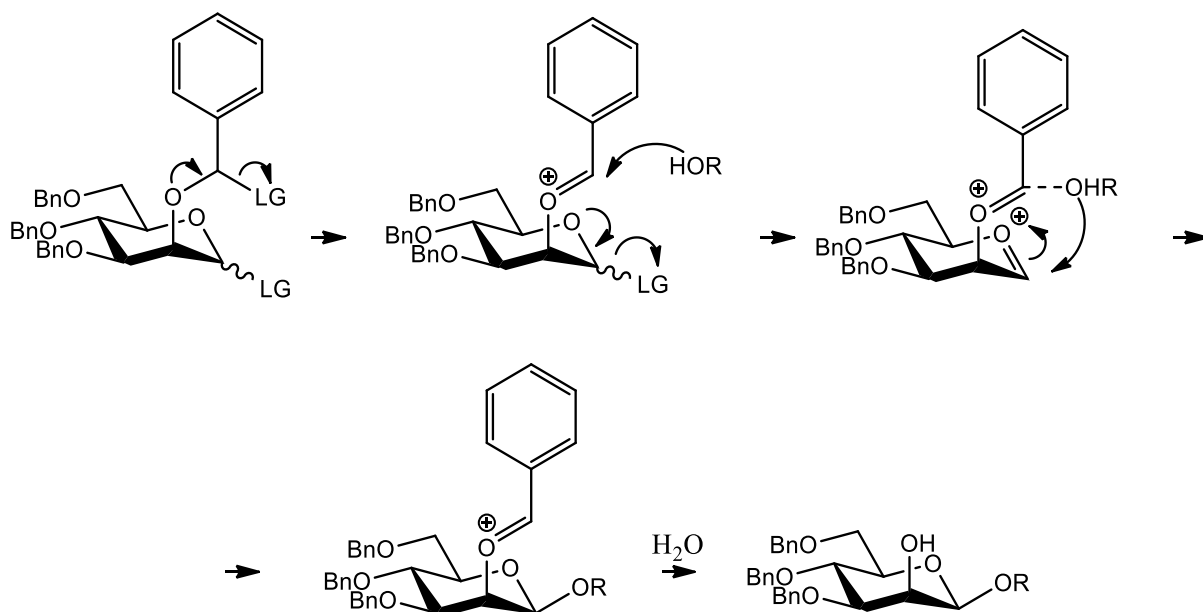
Dedication

Dedication

I would like to dedicate this thesis to grandfather, Cpt. George Douglas Willis. The greatest man I have ever known.

Abstract

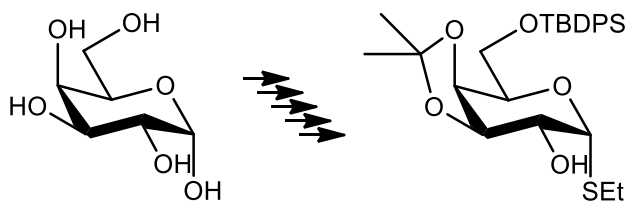
The purpose of this study was to investigate whether the stereochemistry of a newly formed glycoside bond could be controlled through the novel use of an appropriately functionalised sacrificial neighbouring protecting group. This methodology would complement existing chemistries but with the added advantage that it would not require a two-step intramolecular delivery system, but instead involve a single-step synthesis of a *cis* glycoside bond from a neighbouring acetal or ketal group, armed with the same leaving group as the anomeric position.



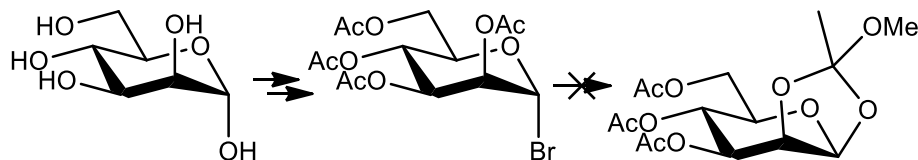
Scheme 1. Proposed approach to a novel neighbouring group direction.

The first goal of the study was the synthesis of a 3,4,6-tri-*O*-protected, 2-*O*-unprotected glycoside donor to which the desired neighbouring group system could be attached. We investigated multiple synthetic routes and approaches to achieve our target donor, which ultimately resulted in an efficient four-step synthesis of ethyl, 3,4,6-tri-*O*-benzyl thioglucopyranoside, and its *n*-pentenyl ether analogue.

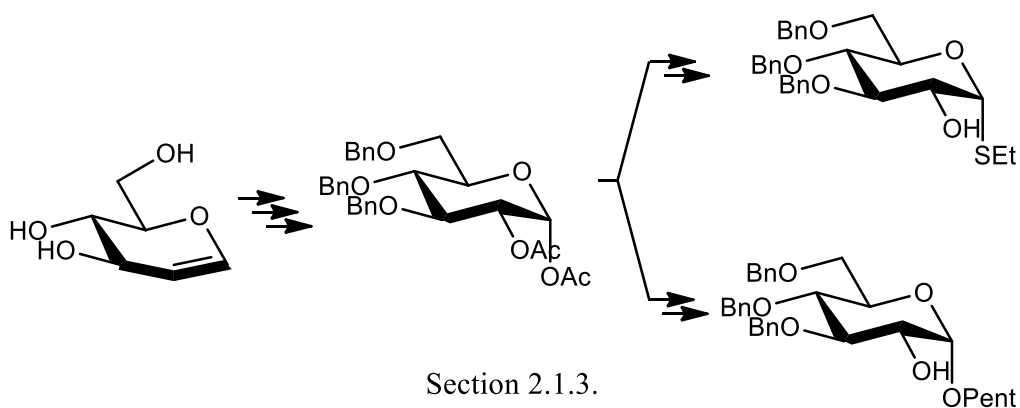
Abstract



Section 2.1.1.



Section 2.1.2.

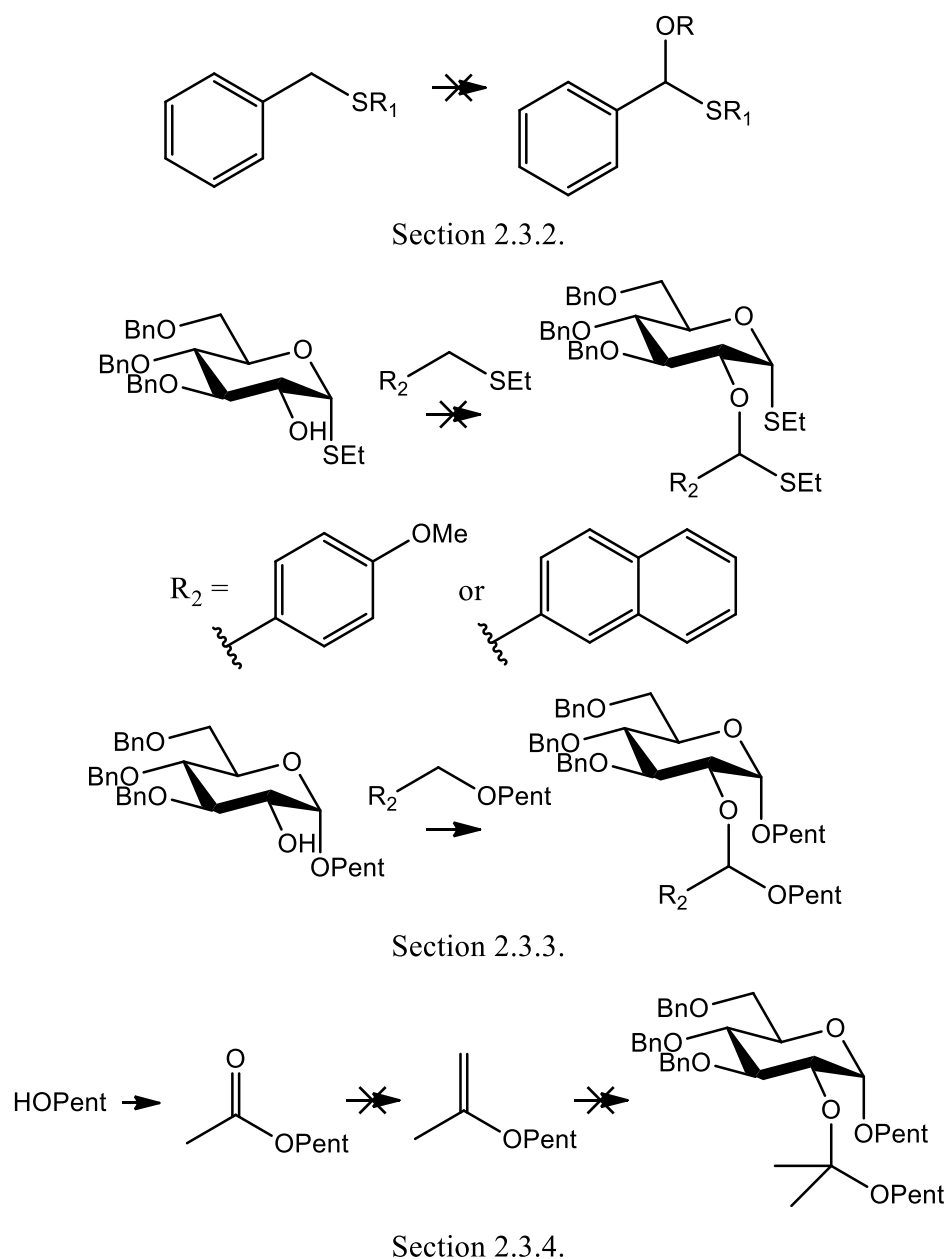


Section 2.1.3.

Scheme 2. Summary of Section 2.1.

We found that attaching a mixed thioacetal, thio ketal acetal, or a ketal to our donor proved to be difficult. Acetals are renowned for their instability, especially glycosidic acetals, and this was confirmed in this study.

Thioacetal derivatives were also explored, but were unfortunately found to be too unstable for further study. We found that *n*-pentenyl ethers were considerably more stable. After multiple attempts, a *para*-methoxy benzyl mixed acetal was found to be very unstable.



Scheme 3. Summary of Section 2.2.

Finally, we identified that an isopropylidene mixed ketal, which is expected to be more stable, would allow us to test our theory. Unfortunately, though, within the time constraints of the project there was not enough time to carry out this final investigation.

Acknowledgements

Firstly, I would like to thank my supervisor Prof. Steve Allin. He put in an incredible amount of effort in helping me get to grips with this thesis, as well as supporting me throughout the ups and downs of the practical work.

Secondly I would like to thank Dr. Ray Leslie, not only was this research done primarily under his area as the carbohydrate chemist but his persistent positive outlook and encouragement kept this project very much alive throughout the 4 years. Also for helping me spice up my writing style to actually be an interesting read.

I would also like to recognise Allied Health for awarding the NTU and Prof. Steve Allin with the funding and stipend that made this research possible. As well as all the facilities at the NTU, EPSRC Swansea Mass Spec. facility and Charnwood Molecular.

My grandad Doug deserves my extra thanks for providing me with much needed financial aid when my stipend ran dry. He, my other grandad Derek, and my parents not only financially supported me, but also picked me up when I was down. My mum deserves a special thanks for helping me through the hell that was re-numbering all the compounds.

I would like to thank my friends and PhD colleagues Tom, Jordan, Zayd, Daniel, Matteo and Karen. Lewis and Robert, for keeping me (somewhat) sane during the practical work of this thesis. And helping me forget that I was doing this PhD during the much needed down time.

To Dr Chris Garner, Prof. John Wallis, Dr Liam Duffy, Mr Mark Sladen, Dr Muriel Funck and Dr Gareth Cave I give my thanks for the much needed technical and academic support.

I have a special thanks to Ellanna, if it wasn't for her incredible love and amazing support, completing this thesis would not have been possible.

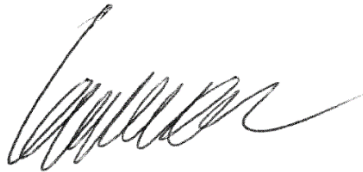
Declaration

Declaration

I certify the work embodied within this thesis is the result of my own research, except where reference has been made to published literature.

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Signed:

A handwritten signature in black ink, appearing to read 'Laurence Grey', written in a cursive style.

Print: Mr Laurence George Grey

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Abbreviations

Abbreviations

Ac	Acetyl
AcOH	Acetic Acid
AcN	Acetonitrile
AgOTf	Silver Triflate
Bn	Benzyl
BSP-Tf ₂ O-TTBP	1-benzenesulfinyl piperidine trifluoromethanesulfonic anhydride 2,4,6- tri-tertbutylpyrimidine
Bz	Benzoyl
¹³ C	Carbon 13
<i>d</i>	Deuterated
d	Doublet
dd	Doublet of doublets
DCM	Dichloromethane
DDQ	2,3-dichloro 4,5-dicyano 1,4-benzoquinone
DMF	Dimethylformamide
DMSO	Dimethylsiloxane
DMAP	Dimethylaminopyridine
dm	Decimetres
equiv.	Equivalences
Et	Ethyl
EtN	Propionitrile
EtOAc	Ethyl Acetate
Gal	Galactoside
GalNAc	<i>N</i> -acetyl-D-galactosamine
Glu	Glucoside
GluNAc	<i>N</i> -acetyl-D-glucosamine
H ¹	Proton
Hex	Hexane
hr.	Hours
iPr	Isopropyl
IR	Infra-red

Abbreviations

j	Joule
kj	Kilojoules
LG	Leaving group
m	Multiplet
<i>m</i>	Meta
<i>m/z</i>	Mass-to-charge ratio
Man	Mannoside
ManNAc	<i>N</i> -acetyl-D-mannosamine
Mol	Mole
Me	Methyl
MeOH	Methanol
Ms	Mass spec.
<i>n</i>	Normal
Naph	Naphthyl
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
<i>o</i>	Ortho
OH	Hydroxyl
OMe	Methoxide
<i>p</i>	Para
Pet-Et	Petroleum Ether
PEG	Poly ethylene glycol
Pent	<i>n</i> -pentenyl, 4-pentenyl
Pr	Propyl
ppm	Parts per million
Ph	Phenyl
Py	Pyridine
<i>q</i>	Quartet
Rf	Retention factor
s	Singlet
t	Triplet
tBu	<i>tert</i> -Butyl
TBDMS	<i>tert</i> -Butyl, dimethyl silyl

Abbreviations

TBDMSCl	<i>tert</i> -Butyl, dimethyl silyl chloride
TBDPSCl	<i>tert</i> -Butyl, diphenyl silyl chloride
TBDPS	<i>tert</i> -Butyl, diphenyl silyl
THF	Tetrahydrofuran
TfO	Trifluoro toluene sulphonate, Triflate
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
TMB	Trimethyl benzyl
TMS	Trimethyl silyl
TMSCl	Trimethyl silyl chloride
Tol	Toluene
Ts	Toluene sulphonate, tosylate
wt.	Weight

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1. Introduction

1. Introduction

1. Introduction

1.1. Glycosides

Carbohydrates play a significant role in biological processes, as well as being one of the most abundant group of biomolecules on the planet. The need for an efficient synthesis of oligosaccharides (Branched or unbranched polysaccharides.) is still on the front of carbohydrate research. Oligosaccharides are found in biology in numerous functions, particularly as protein or lipid bound glycocalyxes protruding out of the membrane of cells. These protruding glycosides function in intercellular interactions, allowing cells to recognise the cell next to it amongst other functions. They are also present on the membranes of bacteria and some viruses for similar functions. These oligosaccharides can be extremely complex in their construct due to the large amount of regio and steric possibilities that the glycosides can assume. They are present on the surface of invading foreign bodies (either bacterial or viral) and can be targeted by the hosts immune system as antigens. Therefore, the glycans presented on the outer surface membrane of the bacterium (or virus) are notable targets for developing vaccines. Some of the carbohydrates are attached to phospholipids, which merge into the ‘fluid mosaic’ of the cells membrane. Figure 1 presents a diagram of the fluid mosaic, outlining the presence of glycopospholipids (1).

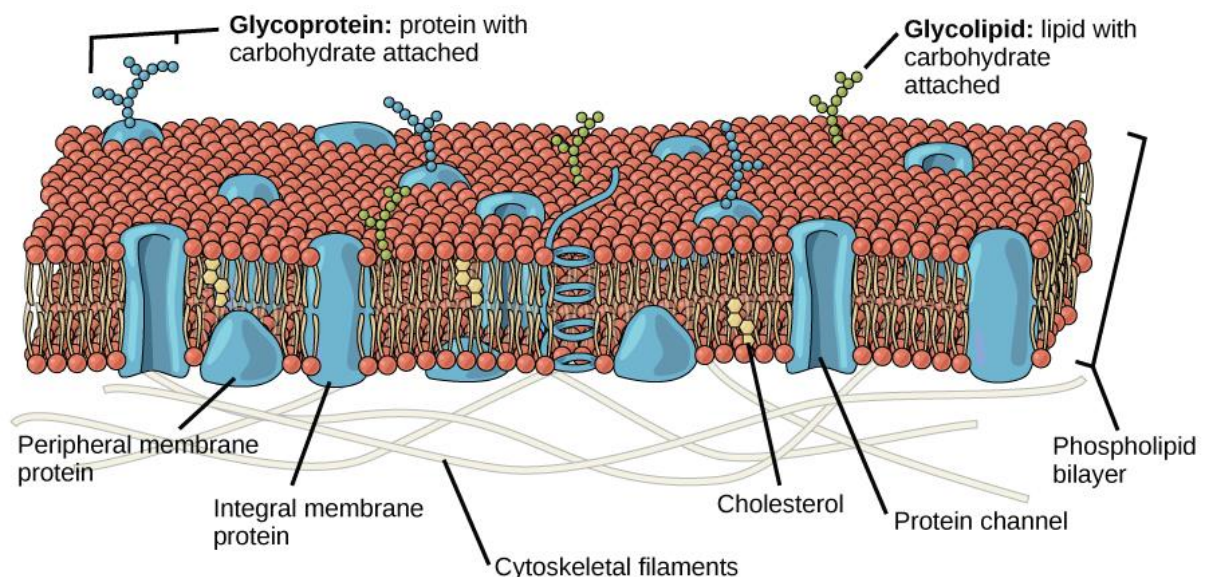


Figure 1. The fluid mosaic model of a cell membrane (1).

An example of an extracellular oligosaccharide is the Forssman antigen, Figure 2, which is a cancer specific antigen that has been used as a vaccine for particular types of

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cancers. The glycocalyx is found on the surface membrane of Forssman positive animal cells. Forssman negative animals, like humans, cannot create the terminal, second, α -N-acetyl-D-galactosamine (α GalNAc), instead only present the single α GalNAc (2). The Forssman antigen is presented on the cell surface as a possible immune response target (3), when a mutation has taken place, for example mutations that some human breast cells undergo in their transformation into cancer cells.

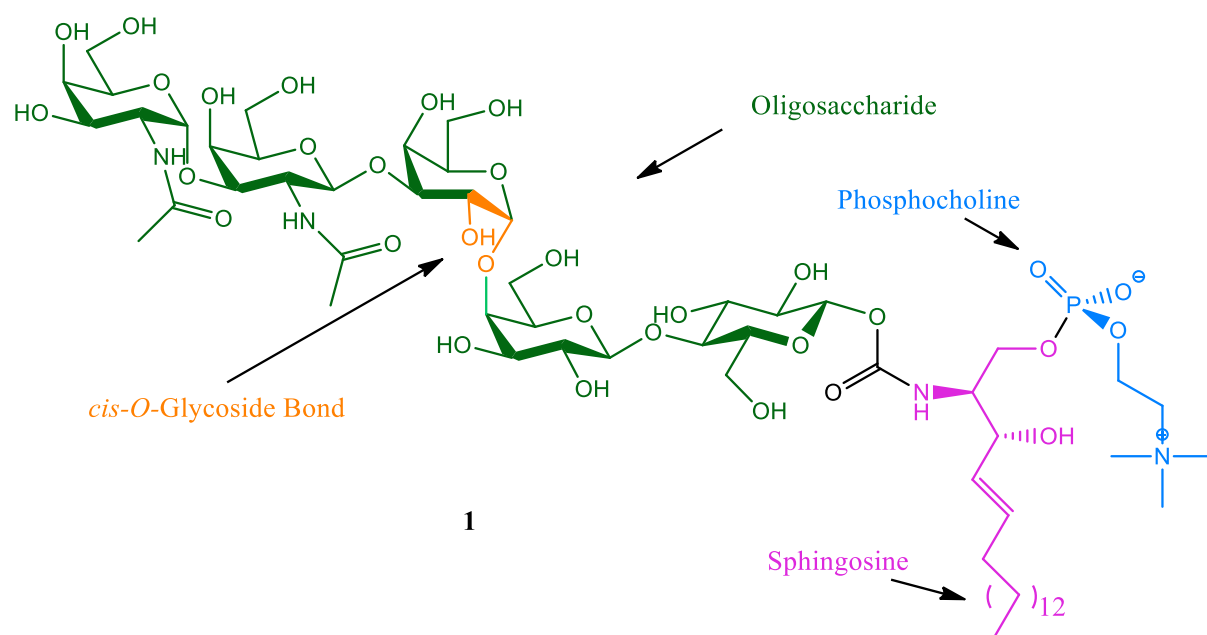


Figure 2. The Forssman Antigen

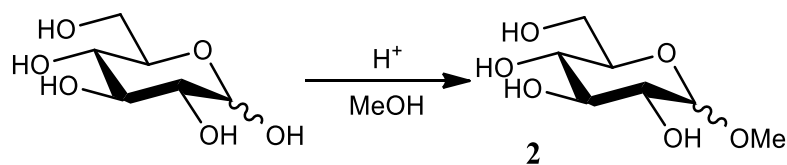
The Forssman antigen, **1**, belongs to a class of glycolipids called sphingoglycolipids. A sphingosine is a 4,5-unsaturated lipid with a functionalised 2-amino-1,3-diol moiety. In this case, the primary alcohol is phosphorylated with a zwitterionic phosphocholine group, allowing it to merge into the lipid bilayer. The glycocalyx is subsequently attached to the secondary amine through a fatty acid residue, thus inducing the protrudance of the Forssman antigen outward from the cell membrane.

Whilst the glycolipid has been named the Forssman antigen due to its presence on Forssman positive animal cells it is not an as antigen. It only becomes an antigen on triggering an immune response to a foreign body. Studies on the Forssman antigens on Forssman positive cells using the antibody have suggested that the function of the Forssman antigen is in intercellular adhesion, but its full function is not yet known (4).

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Unfortunately, all cells have a large amount of different oligosaccharides thus isolating them, in quantities large enough to utilise as vaccines, becomes a complex and high cost task. Hence efficient, controlled oligosaccharide synthesis is a popular challenge to the organic chemist, in particular addressing *cis-O*-glycoside synthesis. This is because the factors which contribute the product of *O*-glycosylation are easily manipulated to the formation of *trans-O*-glycosides, more about this will be covered in the latter part of the section.

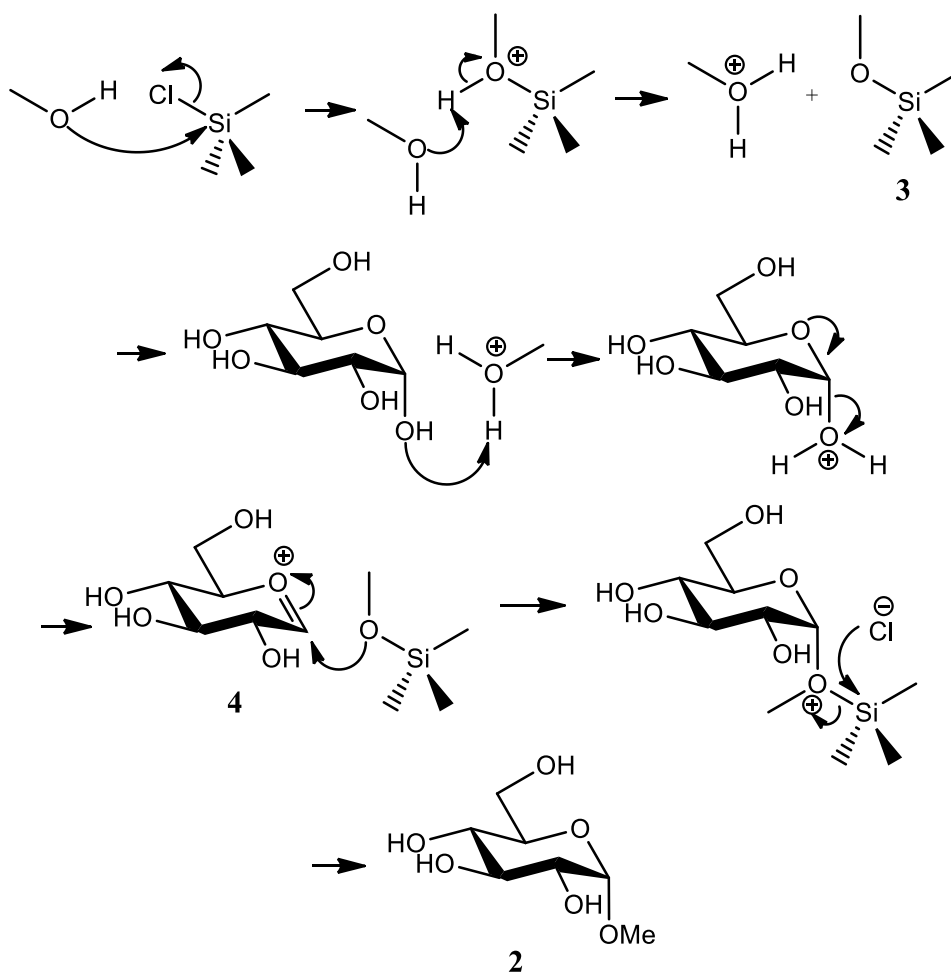
A large amount of work has been done in the field of carbohydrate synthesis. In the 19th century, Emil Fischer pioneered synthetic carbohydrate chemistry by developing the glycosylation of methanol with glucose with an acid catalyst in what became known as the Fischer glycosylation (*Scheme 4*) (5). The glycoside bond is the acetal formed from the 1st position of the carbohydrate ring, also known as the *anomer*.



Scheme 4. Fischer's glycosylation method.

Fischer's reaction was acid catalysed, but over the years since his discovery various acids and Lewis acids were implemented in similar reactions by other researchers. Vincent Ferrières discovered that using different Lewis acids can change the outcome of the reaction regarding the glycosides furano or pyrano forms (6). The Fischer-like reactions are unprotected glycosylation reactions with alcoholic solvents as the acceptor, for coupling two glycosides, the inefficiencies would lie with self-glycosylation products. To overcome this issue, along with the need to use vast excesses of the glycoside acceptor, Koichi Fukase used trimethyl silyl chloride to catalyse the glycosylation (*Scheme 5*) (7).

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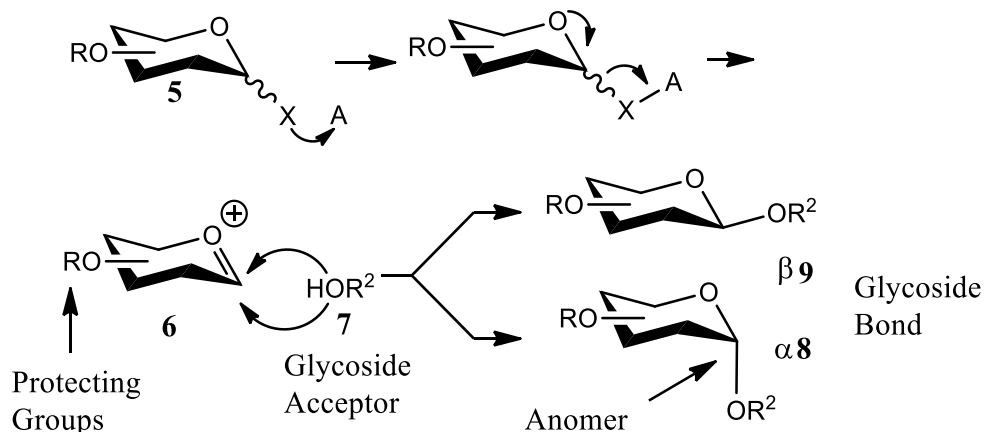


Scheme 5. Mechanism of Fukases modified Fischer glycosylation (7).

The glycosylation of methanol with glucose in *Scheme 5* uses trimethyl silyl chloride, (TMSCl), and water to generate trimethyl methoxy silane, **3**, and MeOH_2^+ . The MeOH_2^+ generates the oxocarbenium ion, **4**, and trimethyl methoxy silane acts as a methoxide ion which attacks the oxocarbenium ion.

Fischer's glycosylation method was the first account of chemical glycosylation and serves as a basis for the majority of glycosylation chemistry that followed. When glycosylating two glycosides to synthesise a disaccharide, the use of protecting groups to prevent self-glycosylation is required and a general overview is shown in *Scheme 6*.

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Scheme 6. General glycosylation reaction.

The reaction involves various parts: a protected glycoside donor **5**, the anomers leaving group **X**, the activating agent **A** and the glycoside acceptor **7**. This reaction is an S_N1 style glycosylation reaction and the rate-determining step of the reaction is the formation of the oxocarbenium ion **6**, on activation of the leaving group. Increasing the nucleophilicity of the leaving group directly increases the rate of glycosylation (8). Conversely, stabilising the oxocarbenium ion **6**, will slow the reaction rate by introducing a more stable intermediate. The acceptor controls the regio selectivity of the glycoside bond formed through protecting groups. The stereochemistry is controlled by numerous factors and is defined as the ratio of **8:9**, or $\alpha:\beta$ (9). Simply alkylating the anomeric hydroxide is not a glycosylation reaction, although the product can be a glycoside.

In Fukases glycosylation of methanol, *Scheme 5*, the glucose is acting as the donor. The anomeric hydroxide acts as the leaving group. The TMSCl in the presence of water and methanol generates the MeOH_2^+ , which activates the anomeric hydroxide and removes it as a cationic MeOH_2^+ . The TMSOMe acts as a glycoside acceptor. Since they were only activating the anomeric hydroxide and reacting the subsequent oxocarbenium ion with a reactive TMSOMe in methanol, there was no need for protecting groups with this method. Self-glycosylation of the glucose would have been a very minor product not only because of the sheer volume of methanol present as it was the solvent, but because the TMSCl works to activate the methanol. The stereochemistry of the anomeric methoxy group is controlled predominantly by the anomeric effect (*Figure 3*)

The anomeric effect occurs when a lone pair on the cyclic oxygen is peri-planar to the

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anomeric anti-bonding orbital of the anomeric C-O bond, and can donate electron density. This effect is strongest when the receiving anomeric carbon's non-cyclic bonding orbital is losing electron density to an electron withdrawing group (10), such as halides, sulphides, oxides. This is why, in methanol, the α anomer is the favoured product of the glycosylation of methanol, and what little of the β anomer is negligible.

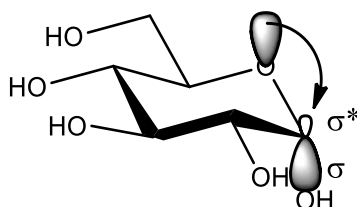


Figure 3. The anomeric effect.

Hexopyranoses and their subsequent pyranosides are most stable in their 4C_1 conformation. C relates to the chair conformer. C_1 relates to the C1 anomer at the lowest position and 4C being the highest cyclic C4 carbon when looking at the chair with the O – C5 and the C2 – C3 bond in the plane. The glycoside bond is written as either α or β , but whether it is *cis* or *trans* is dependent upon the C2 substituent. For example, when the sugar is in its 4C_1 conformation, mannose whose C2 substituent is axial, making its β (equatorial) anomer *cis*. Whereas the C2 substituent of glucoses is equatorial meaning the α anomer is the *cis*.

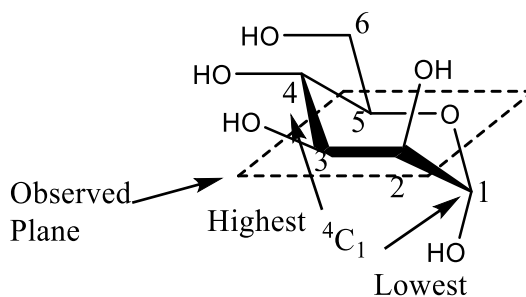


Figure 4. Conformational terms.

When the 2,3,4 and 6-hydroxides are protected, their solubility in water is drastically reduced and thus, less polar, organic solvents are required to dissolve them. The epimerisation of the anomeric centre in water affects the α : β ratio as when solvated, with water, steric influences become a major factor in the anomerisation, increasing the amount of the β product. In polar organic solvents the anomeric effect prevails in determining the α : β ratio at

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equilibrium Figure 5 (11).

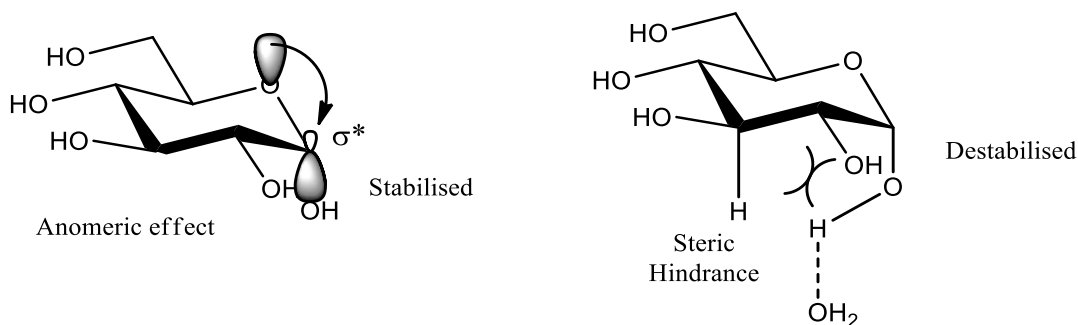
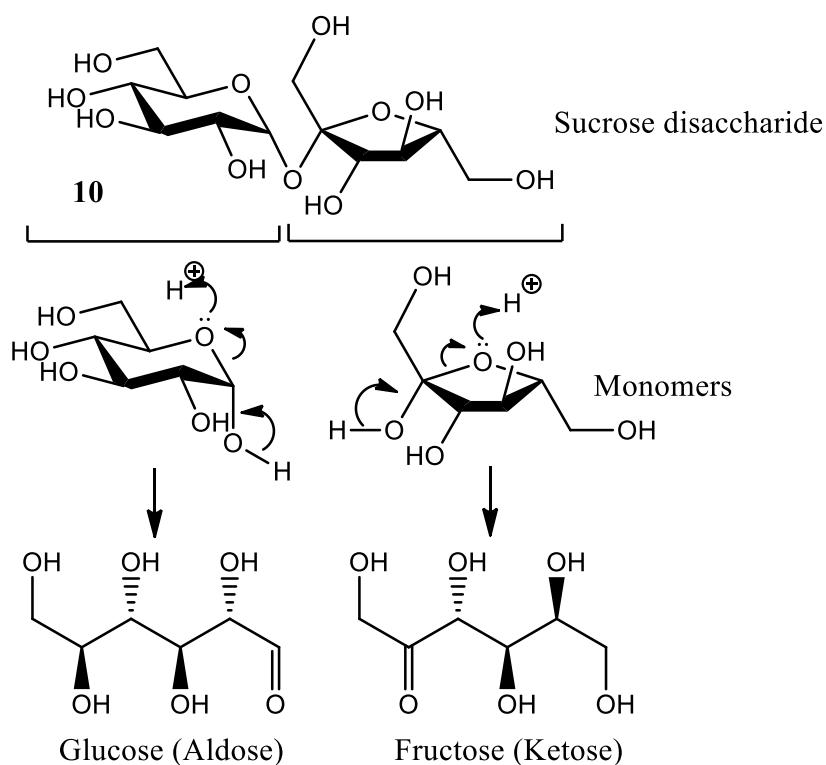


Figure 5. Anomeric v's steric effects.

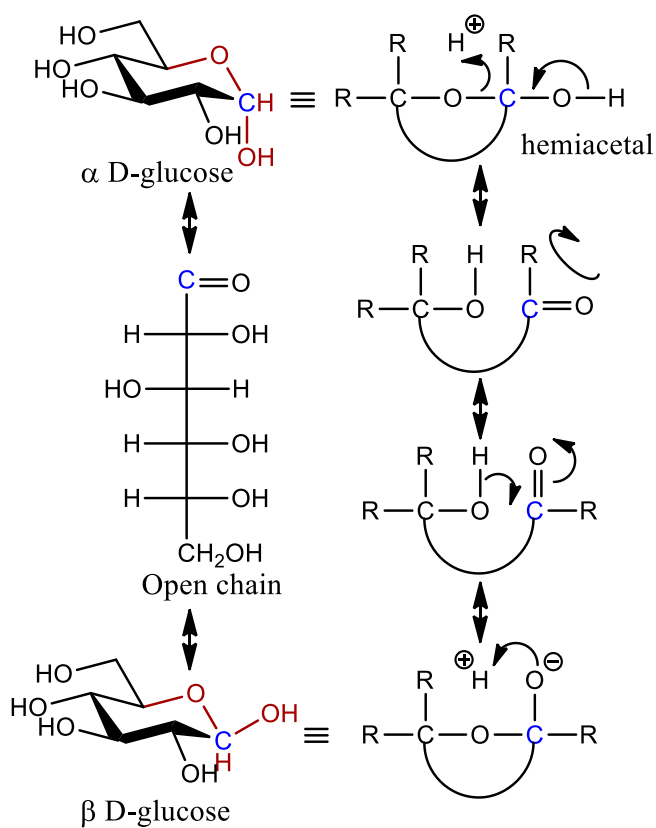
According to the anomeric effect, a sterically less favoured axial α anomer is the most stable configuration in organic solvents. In an aqueous environment the equatorial β anomer becomes more stable as a configuration of D-glucose. This is because the axial components have increased axial – axial and axial – equatorial interactions from becoming solvated. To minimise this, the β anomer becomes the favoured anomer (11).

Anomeric changes can occur through anomerisation. This can be from mutarotation, or from substitution when the leaving group is exchanged either in S_N1 or S_N2 type reactions. The anomeric carbon is the C1-O carbon and can have the functionality of a hemiacetal, an acetal or a carbonyl. Depending on the nature of the anomeric carbon, carbohydrates can be defined as either a ketose or an aldose, of which examples of these can be found in the monosaccharides that make up the disaccharide sucrose, **10**, which are fructose and glucose respectively *Scheme 7*.

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Scheme 7. The components of sucrose.

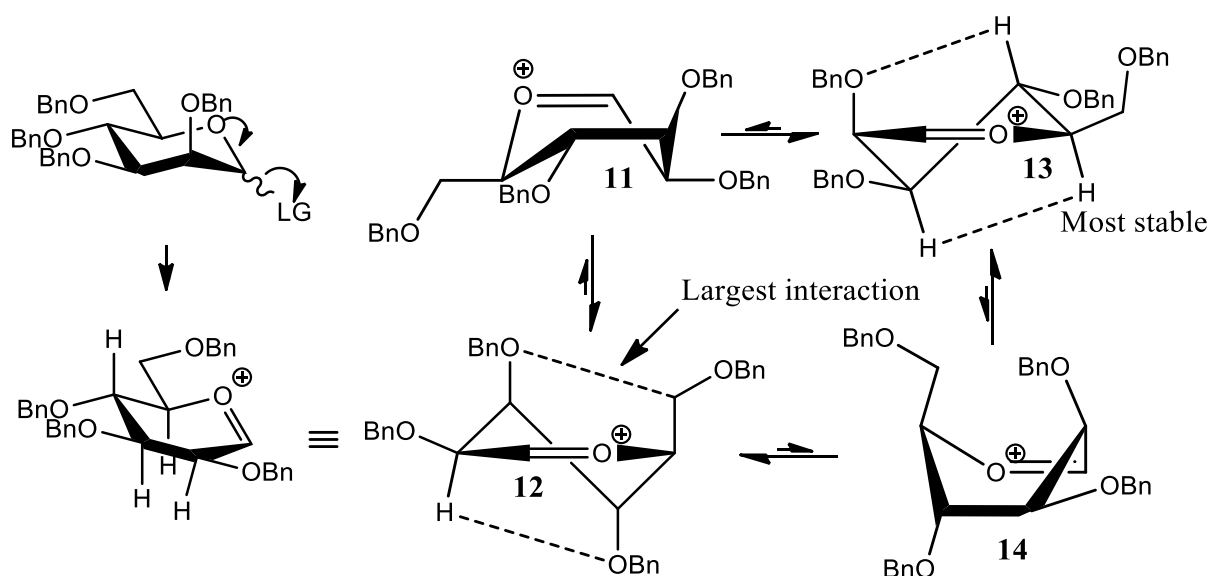


Scheme 8. Mutarotation of a hemiacetal.

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Mutarotation occurs when the anomeric hydroxide and cyclic hemiacetal group exchange a proton via the open chain form of the sugar *Scheme 5*. This does not occur when the anomer is an acetal.

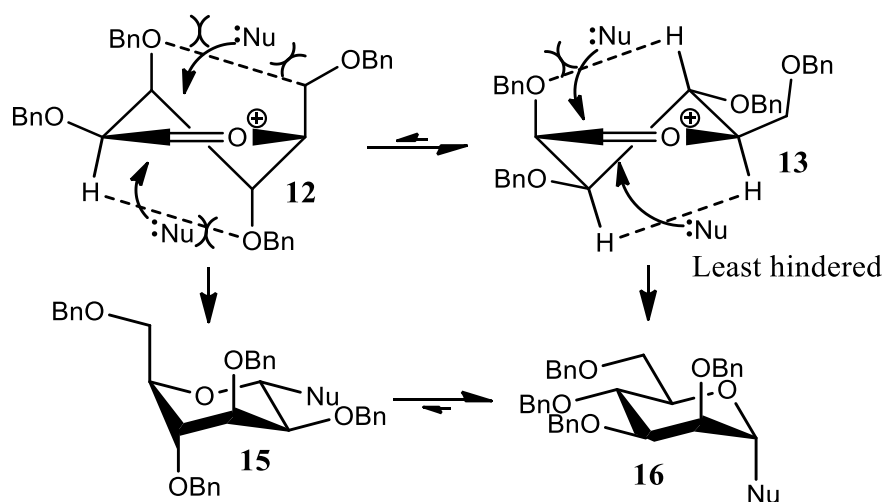
Considering the reactivity of protected glycoside donors in organic solvents, if the anomeric carbon's leaving group is activated then the electron donating ability of the cyclic oxygen will displace the leaving group, creating the reactive oxocarbenium ion, which can exist as 4 conformers (*Scheme 9*) (12) (13).



Scheme 9. Conformational analysis of the oxocarbenium ion.

The example shown in Scheme 9 is that of mannose, whose C2 hydroxide is in an axial position. Once ionised to the oxocarbenium ion, its conformers resemble the conformers of cyclohexene and consist of two unstable boat conformers, **11** and **14**, and two considerably more stable twisted chair conformers. Analysing the pseudo syn-axial interactions, we can calculate that **13** is the more stable of the two. Thus the approach of a nucleophile is most likely to happen from the down position of **13**, resulting in the formation of glycoside **16** as the most favoured product (12) (13).

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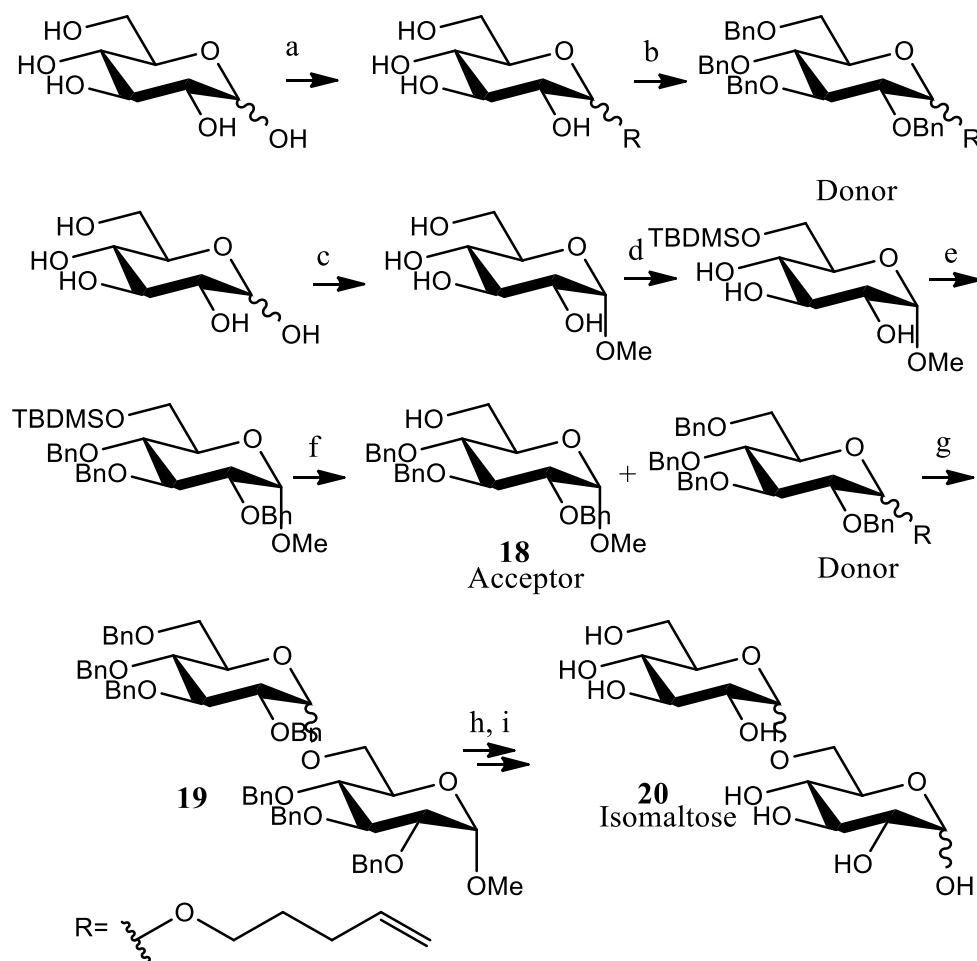


Scheme 10. Favoured approach of the nucleophile to the oxocarbenium ion.

Although the product of the least hindered approach of conformer **12** would result in an equatorial α product, this outcome lacks any anomeric effect and the syn-axial interactions of **15** are considerably larger than any of the corresponding interactions of conformer **16** (*Scheme 10*). The 4C_1 is the most stable conformation.

In oligosaccharide synthesis and complex carbohydrate synthesis, a protecting group strategy needs to be incorporated. The glycoside acceptors and donors need to be protected, not only to prevent self-glycosylation products forming, but to ensure that there is only one regioselected glycoside bond formed, as in the synthesis of isomaltose in *Scheme 11*.

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Scheme 11. Synthesis of isomaltose.

a) 1-penten-4-ol, HCl, overnight, r.t., b) BnBr, NaH, DMF, 8hrs, 0°C, c) MeOH, HCl, overnight, r.t., d) TBDMSO, Et₃N, DMAP, overnight, 36°C, e) BnBr, NaH, DMF, 8hrs, 0°C, f) AcOH, THF, overnight, r.t., g) NIS, DCM, overnight, r.t., h) TfOH, AcOH, overnight, r.t., i) Pd, H₂, Tol, overnight, r.t. (14)

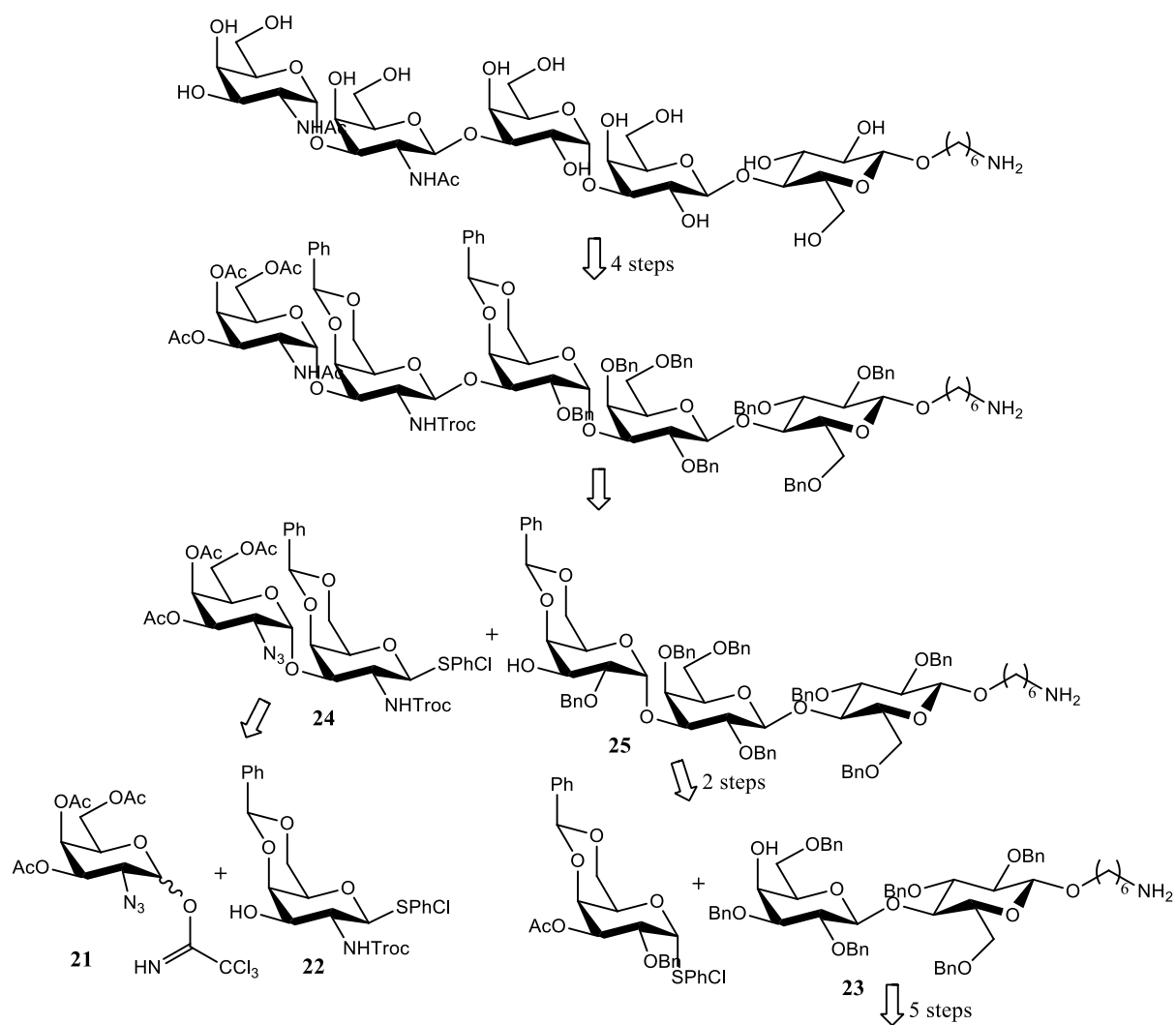
Isomaltose **20** is the disaccharide of two glucose monomers connected by an α 1-6 glycoside bond. Being a disaccharide, it has two anomeric carbons. A hemiacetal which will undergo mutarotation, and an acetal linking the glucosides together (the glycoside bond). In order to create this chemically, treatment of the two glucose monomers separately is required. In nature the glycoside bond is stereoselectively and regioselectively controlled by the enzyme, which acts not only to activate the leaving group and protect the glucosides accordingly, but also direct the approach of the acceptor to the anomer. Natural, or biosynthesised, isomaltose is 100% α (15), whereas the chemical route shown in *scheme 11* generates **20** as approximately 1.6:1 α : β (14).

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In generating the glucoside acceptor, the use of Fischer's glycosylation methodology and protection of the anomeric hydroxide is achieved easily. Taking advantage of the primary (C6) hydroxide also being the target acceptor, the use of steric hindrance to temporarily protect just the primary alcohol with a *tert*-butyl dimethyl silyl (TBDMS) ether allows us to alkylate the C2, 3 and 4 alcohol groups with benzyl ether groups and finally remove the TBDMS, to provide the methyl 2,3,4 tri-*O*-benzyl α -D-glucopyranoside acceptor **18**. More detail into the glycoside donor and leaving group will be covered in the latter part of this introduction.

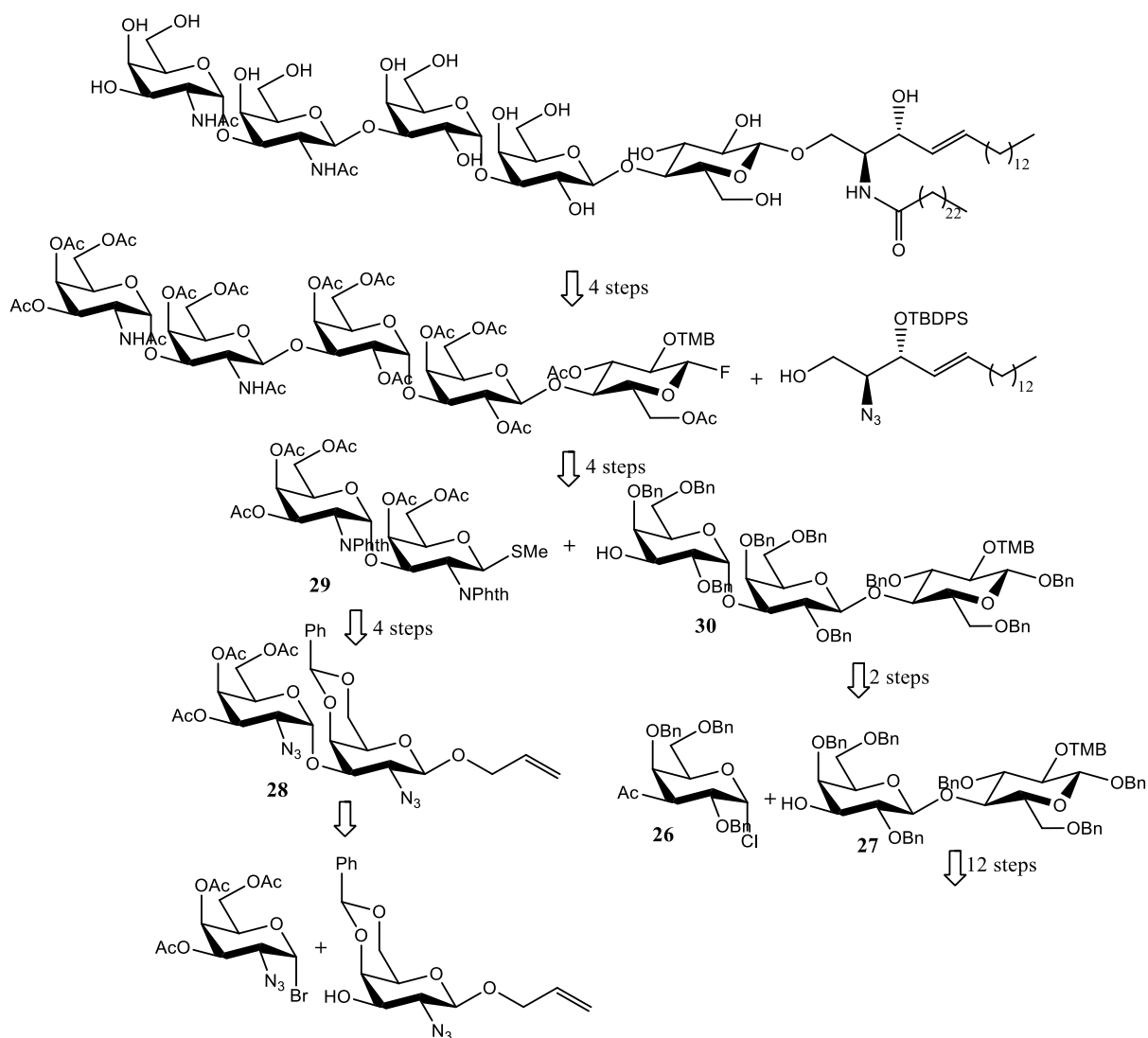
Regarding the Forssman antigen, *Figure 2, 1* and its synthesis. Feng and Ogawa (2011 and 1989, *Scheme 12* and *Scheme 13*) achieved the total synthesis of the Forssman antigen. Both syntheses were convergent 2+3 approaches, although both of their syntheses were successful, there were still issues which could be resolved. Specifically, the stereoselectivity of the glycoside bonds formed and multiple de-protection steps (3) (16).

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Scheme 12. Fengs' retro synthesis of the Forssman antigen (2011).

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Scheme 13. Ogawa's retro synthesis of the Forssman antigen (1989).

Both the syntheses are convergent 2+3 routes, because of how they synthesised the 1-3 α -aminogalacto disaccharide, **24** and **29**, (α -GalNac-GalNac) and galacto-lactoside trisaccharide, **25** and **30**, separately, then converged them into the pentasaccharide. Without going into much detail about the syntheses, it's easy to see how one exceeded the other in terms of the overall efficiency of the synthesis. Excluding the initial protection of the α -GalNac-GalNac galactoside monomers but including the synthesis of the protected lactose molecules, **23** and **27**, Ogawa's synthesis involved 27 steps. This is because of the number of protection group manipulations that were required. Not only did this increase the time and cost of the synthesis, but drastically lowered the yield. Whereas Fengs' approach required minimal protecting group manipulations and only involved 13 steps. The other main difference is the anchor that they chose for the glycoside to be attached to, Ogawa linked his to a ceramide

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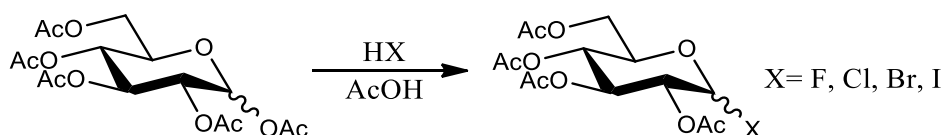
residue, whereas Feng linked his to an aminohexane group. But taking this into account, it only added an extra 3 steps into Ogawa's synthesis. Not only was work put into reducing the number of steps in the synthesis, but also increasing the stereoselectivity of the glycoside bonds formed. For example, Ogawa used more classical anomeric bromide as the leaving group for the synthesis of **28**, which gave an anomeric mixture of 5:1 α : β . Whereas Feng found that using an azide at the C2 position of the galactose and a trichloroacetimidate leaving group he achieved the α -GalNAc-GalNAc as higher ratio, but only took the alpha anomer off the column. (3) (16). Both of these approaches suffered drastically at the lack of stereoselectivity within the glycoside bonds formed. Ogawa and Feng had to separate the anomers of **28** and **24** (respectively) on column chromatography. Not only are the reactions relatively low yielding in the first place, but when they separated the anomers, the single anomer yield was lowered even further. Ogawa and Feng's syntheses of the Forssman antigen are good examples of how far carbohydrate research has come in 22 years.

Therefore, controlling the anomeric stereooutcome of a glycoside bond forming step has become a notable challenge for the carbohydrate chemist. Choosing the correct leaving group for the glycoside donor is an important factor in the challenge, depending on the approach to stereocontrol being utilised. The following sections 1.1.1. – 1.1.4. are on the common leaving groups in glycoside synthesis.

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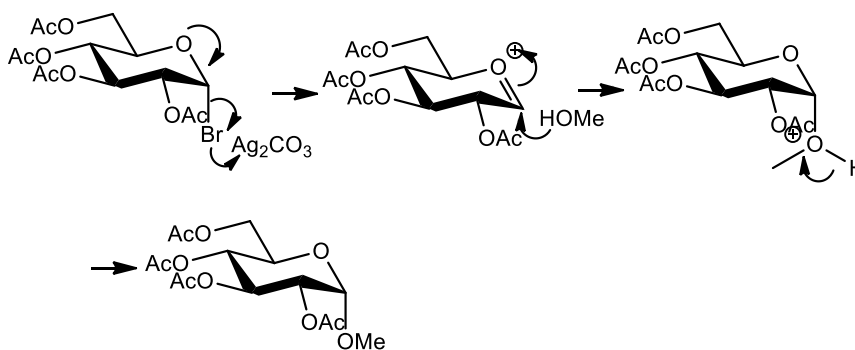
1.1.1. Anomeric Halides

Anomeric halides were amongst the first leaving groups to be implemented in carbohydrate synthesis; due to the electronegativity of an anomeric halide, how good they are as leaving groups and because their synthesis is relatively straightforward. Anomeric halides are typically synthesised from the corresponding glycosyl *O*-acetate and a protic acid (9) (*Scheme 14*).



Scheme 14. Typical glycosyl halide synthesis.

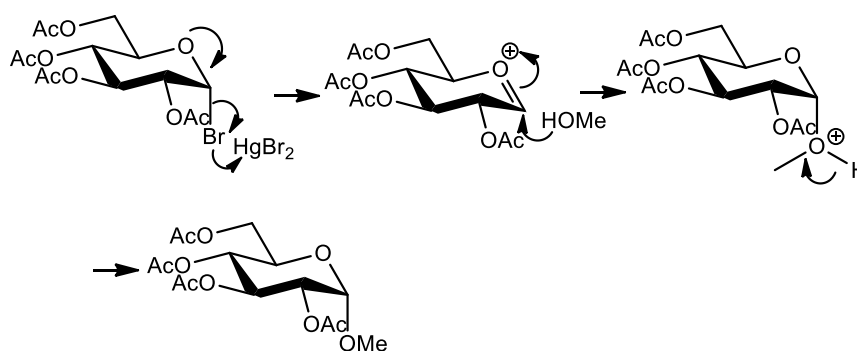
Unfortunately, using a strong acid to synthesise the anomeric halide has limitations regarding the stability and versatility of the other constituents on the carbohydrate. Around the turn of the century, Koenigs-Knorr developed a method as an example of activating the halide leaving group for carbohydrate synthesis (*Scheme 15*).



Scheme 15. The Koenigs-Knorr glycosylation. (17).

Similar to the Fischer glycosylation (*Scheme 4*), the Koenigs-Knorr uses methanol as the acceptor as well as the solvent. The method uses mild activating conditions, and also allows for the use of non-alcoholic solvents. Thus, presenting an acceptor hydroxide that isn't the solvent makes the Koenigs-Knorr method particularly notable. The Koenigs-Knorr method can be modified and performed with mercury(II) bromide as the promoter which is referred to as the Helferich method (*Scheme 16*) (17).

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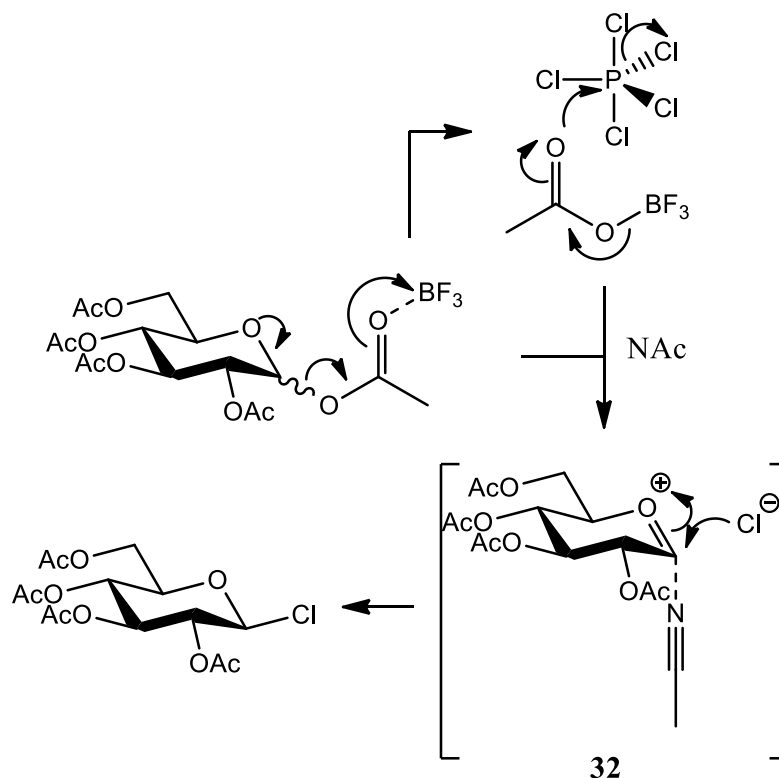
Scheme 16. The Helferich method. (9)

Anomeric chlorides, bromides and iodides were considered to be relatively unstable and too reactive to implement into the glycoside coupling reactions. Rather their uses are primarily found in the preparation of other glycoside donors. An attractive property of anomeric halides is their ability to undergo S_N^2 type reactions, inverting the stereochemistry of the halide, meaning the subsequent donor formed would have the opposite anomeric stereochemistry (9)(p66).

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1.1.1.1. Glycosyl Chlorides

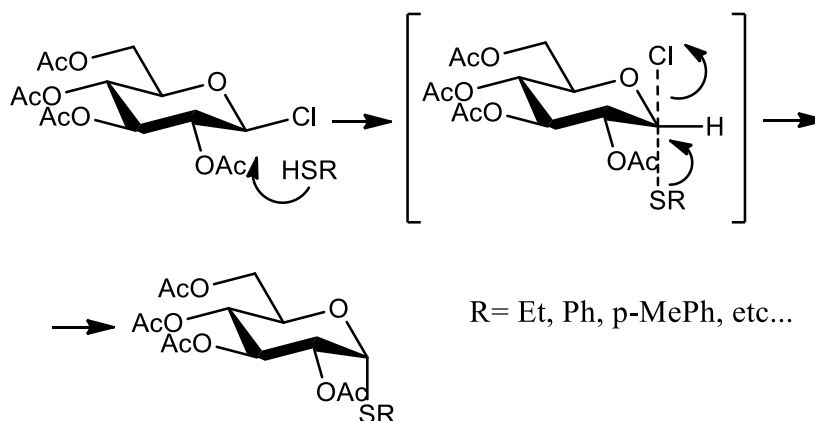
Glycosyl chlorides can be synthesised solely as the β anomer from the corresponding per-*O*-acylated glycoside. The following example of this in *Scheme 17*, takes advantage of an effect known as the nitrile effect with acetonitrile as the solvent, which will be discussed in more detail in Section 1.2.



Scheme 17. Selective synthesis of β -2,3,4,6-tetra acetyl glucopyranosyl chloride. (18)

This method uses the Lewis acid boron trifluoride etherate ($\text{BF}_3 \cdot \text{OEt}_2$) to activate the anomeric acetate and produce the oxocarbenium ion **32**, which the chloride ion subsequently attacks from the β direction to give the β chloride in over 90% yield (18). Once the β glycoside chloride has been obtained, it can be substituted via a S_N^2 style mechanism to afford an anomerically pure α glycoside donor. A good example of this is in the synthesis of α thioglycosides, *Scheme 18*.

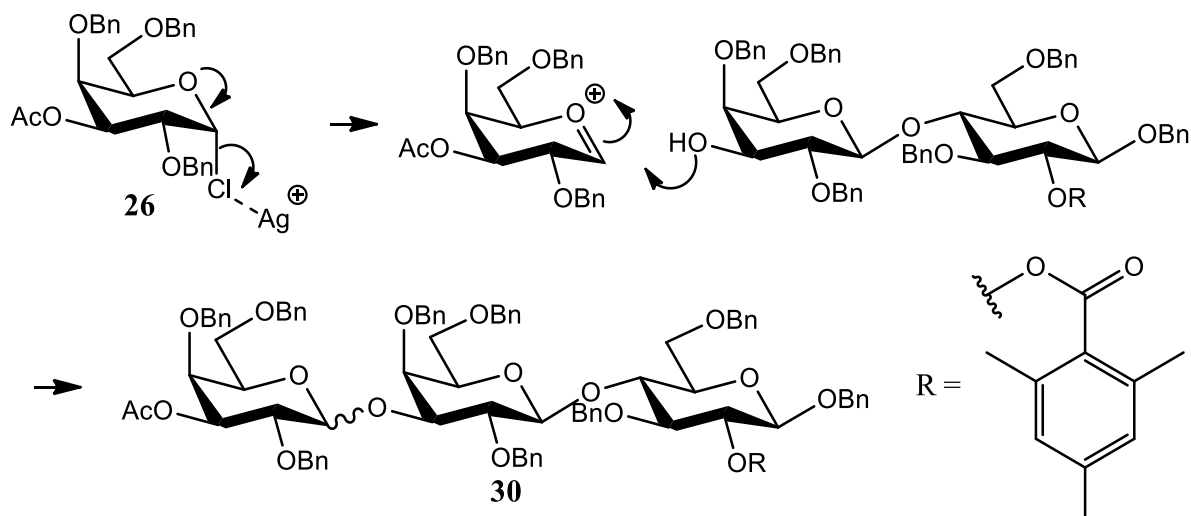
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Scheme 18. Thioglycosides from the corresponding chloride. (19)

Advantage of this was taken by Alexei Demchenko, in his exploration into the super arming of glycoside donors, as anomerically pure α thioglycosides were a requirement for their approach (20).

The glycosyl chloride can be activated in glycosylation reactions, typically with mercury or silver triflates. In Ogawa's synthesis of the Forssmann antigen from section 1.1., in Scheme 13, mentioned earlier, he used a galactosyl chloride, **26**, in the synthesis of the α -galacto-lactoside trisaccharide, **30**. He used silver triflate to activate the chloride then coupled it with the appropriately protected lactoside. He then had to separate the anomers, and manipulate the trisaccharide protecting groups accordingly (*Scheme 19*) (21).

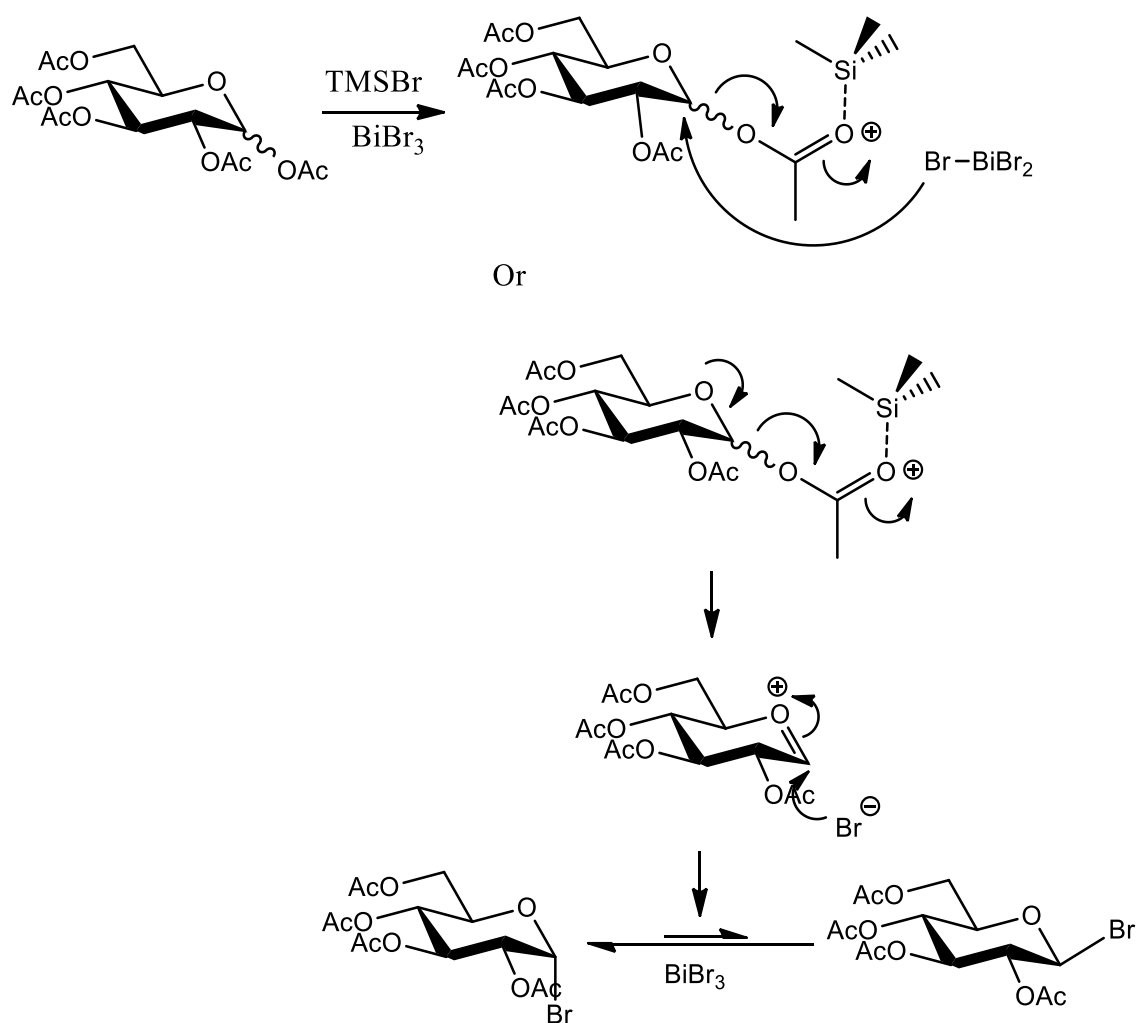


Scheme 19. Ogawa's use of a glycosyl chloride. (21)

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1.1.1.2. Glycosyl Bromides

Glycoside bromides, unlike the chlorides, are easily synthesized as their α anomers as shown with Montero's bismuth - TMSBr bromination of mono, di and trisaccharides from the per-*O*-acetylated pyranose (*Scheme 20*).



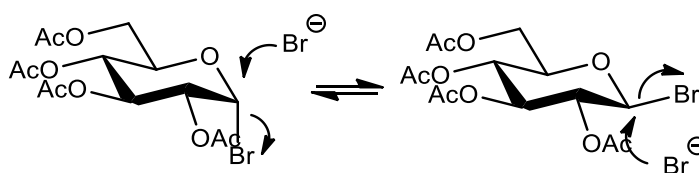
Scheme 20. Montero's bromination. (22)

An attractive feature of Montero's bromination, is that not only that the product formed with α selectivity, but the use of TMSBr with bismuth tribromide as a mild brominating agent. The mild conditions allow the bromination of the terminal anomer of polysaccharides, without effecting the other glycoside bonds, or other substituents on the molecule (22). Montero gives

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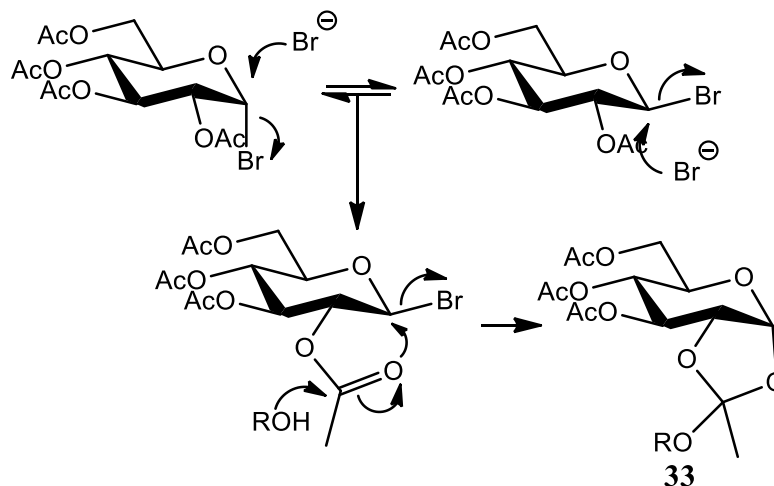
no explanation as to why the product is α selective, but we can stipulate that the bismuth tri Bromide acts to induce in situ anomerisation, and eventually the anomeric effect takes precedence over the steric effects with its neighbouring group participant. The glycosyl bromides can be activated to the corresponding oxocarbenium ion under similar conditions to that of the chloride counterpart, with silver or mercury triflate (23).

A property of the bromide that the corresponding chlorides or fluorides lack is the ability of the bromide to undergo in situ anomerisation with a catalytic amount of tetra-n-butyl ammonium bromide salt (*Scheme 21*).



Scheme 21. Anomerisation of 2,3,4,6-tetra-acetyl glucosyl bromide.

This reaction of acetylated glycosyl bromides with tetra-n-butyl ammonium bromide can be used to synthesise an ortho-ester (*Scheme 22*).



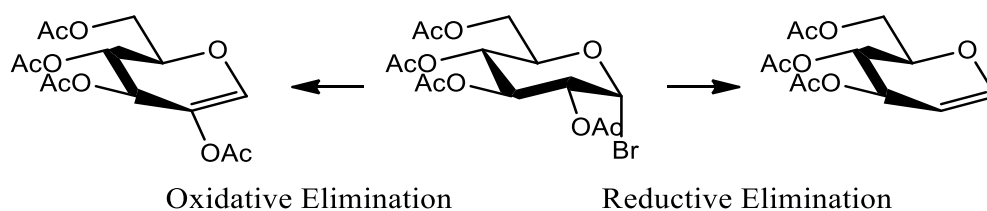
Scheme 22. Synthesis of ortho esters. (9)(p381)

The acetylated glycosyl bromide undergoes anomerisation in dry conditions in the presence of an alcohol and lutidine. The β anomer will be displaced by the neighbouring acetate

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as the carbonyl gets attacked by the alcohol, thus forming the ortho ester. Removing the β anomer from the equilibrium by forming ortho ester **33**, drives the equilibrium to the right, thus pushing the reaction to completion (24).

Acetylated glycosyl bromides can also undergo elimination reactions in the synthesis of glycols. This can either be a reductive or an oxidative elimination reaction, meaning the glycoside can either have the bromide and the neighbouring hydrogen eliminated, or it can have the bromide and the neighbouring oxide moiety eliminated (*Scheme 23*).

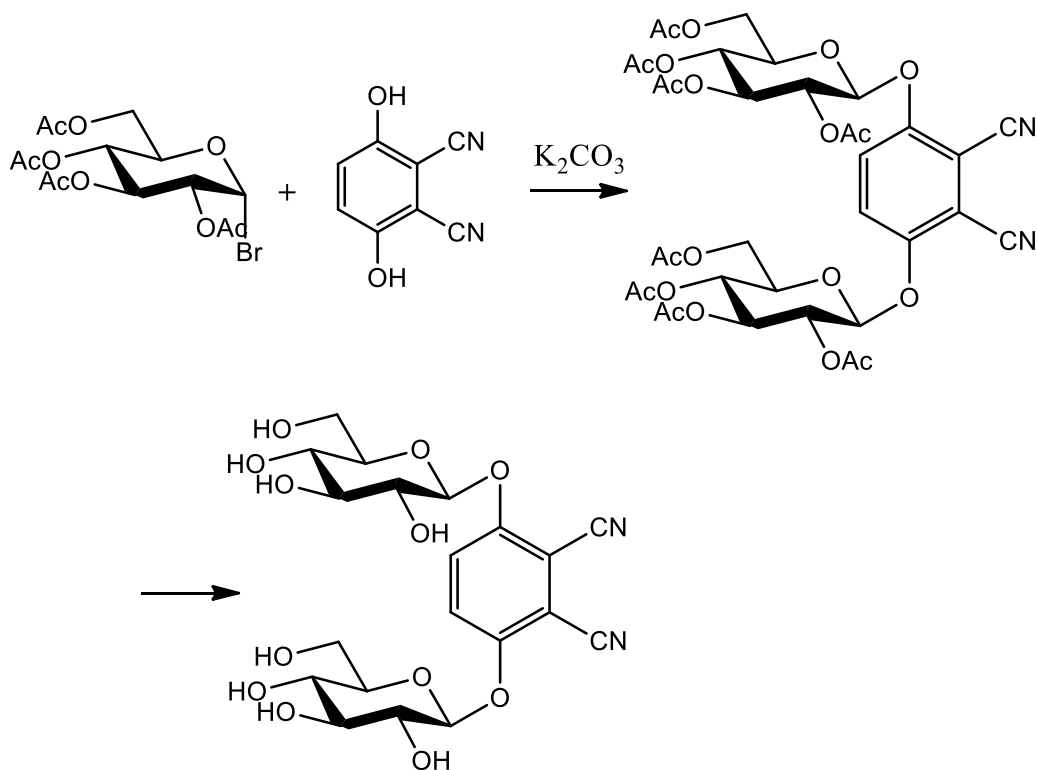


Scheme 23. Reduction of 2,3,4,6-tetra-acetyl bromoglucopyranoside.

Emil Fischer first reduced 2,3,4,6-tetra-acetyl bromoglucopyranoside into its 1-2 unsaturate, and named it a 'glucal'. His reaction was a zinc catalysed reductive elimination of both the bromide and the neighbouring acetate (25).

Anomeric bromides still have a strong presence in oligosaccharide synthesis. In 2015, Thomas Ziegler reported the synthesis of phthalonitriles bridging two β glucoside residues. Their synthesis took advantage of the ability of the α -bromoglucosides to undergo an S_N2 reaction in adding 3,6-dihydroxyphthalonitrile stereoselectively (*Scheme 24*).

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Scheme 24. Thomas Ziegler's 3,6-di-β-D-glucopyranosyl phthalonitrile. (26)

It was decided to use the α bromoglucopyranoside 2,3,4,6-tetra-acetate not only because of the β selective product, but deacylation of the product afforded the bridged glycoside in a high yield with no partial deprotection products being observed (26).

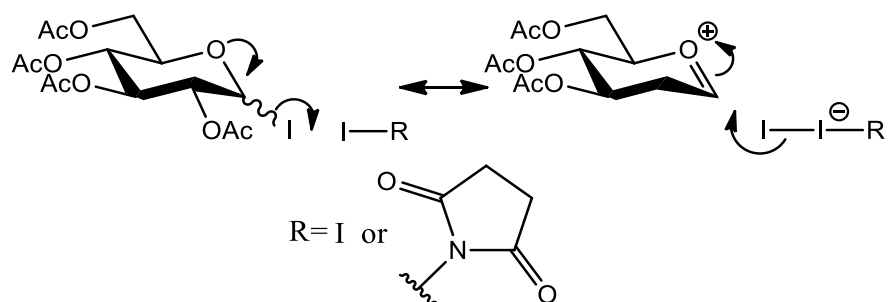
1.1.1.3. Glycosyl Iodides

Glycosyl iodides have been extensively studied over the years since Fischer first prepared tetra-O-acetyl iodo glucosides from the per-O-acetyl glucoside using HI in AcOH in 1910 (27). Since this report Bernd Meyer found that it is possible to synthesis the *per*-O-acetyl iodide from the per-O-acetate using just iodine in trimethylsilyl iodide (TMSI) (28). This is a useful reaction for in situ generation of the iodide for direct use as an intermediate.

Glycosyl iodides share similar properties to their bromide counterpart regarding their ability to undergo S_N2 reactions and anomerisation with the corresponding tetra-*n*-butylammonium halide. Glycosyl bromides can be activated by silver triflate in the S_N1 style glycosylation reaction, whereas glycosyl iodides can be activated with cheaper and milder *n*-

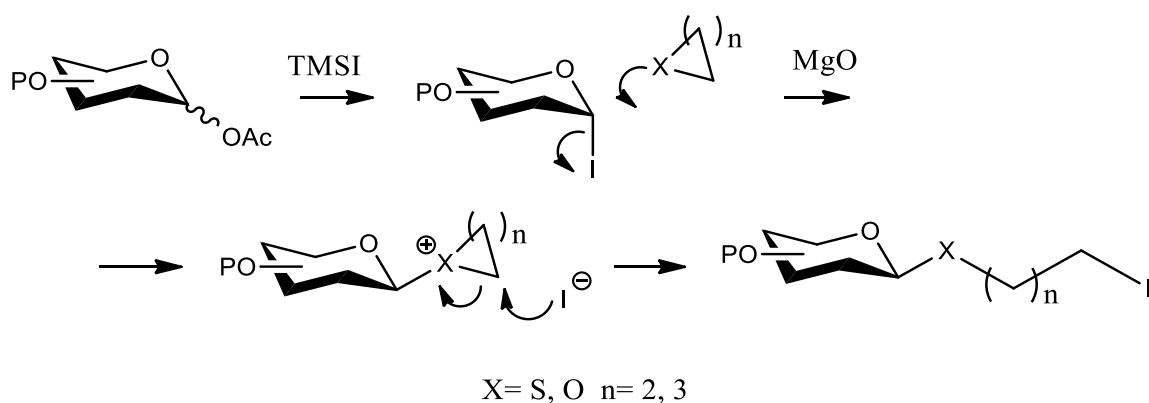
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iodosuccinimide (NIS) or I_2 , Scheme 25, which creates a much cleaner glycosylation reaction possibility (Scheme 25) (9)(p75).



Scheme 25. Activating anomerisation of glycosyliodides (9)(p75).

Iodides differ from the corresponding chloride and bromide in their S_N^2 substitution reaction in how they are able to substitute with weaker nucleophiles, such as strained cyclic ethers and sulphides. The example shown in Scheme 26 is Gervay-Hague's synthesis of functionalised anomeric alkyl chains, and is achieved from in situ formation of the glycosyl iodide with TMS-I from the corresponding glycosyl acetate, and then addition of the cyclic sulphide, or ether, with MgO (The MgO acts to trap the TMS as its acetate preventing interference in the reaction.). The iodide anion then attacks the activated ring to open it forming the corresponding open chain anomeric ether, or sulphide, with a terminal iodide (Scheme 26) (29).

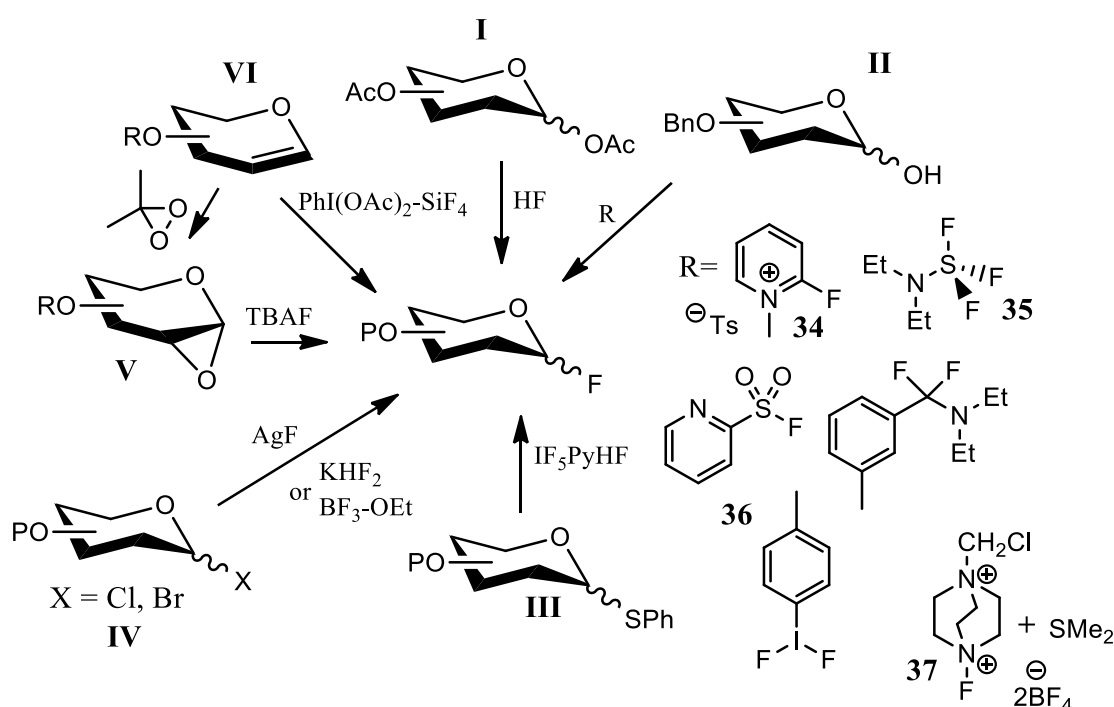


Scheme 26. Anomeric substitution of iodide with a cyclic ether or sulphide (29).

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1.1.1.4. Glycosyl Fluorides

Although anomeric iodides, chlorides and bromides have been extensively used in carbohydrate research, it wasn't until the mid-1980s that the reactions of anomeric fluorides were fully explored, subsequently proving the fluoride to be the most versatile of the anomeric halides. Because of this, anomeric fluorides can be advantageous to an oligosaccharide synthesis and multiple routes to synthesising anomeric fluorides have been developed (*Scheme 27*).

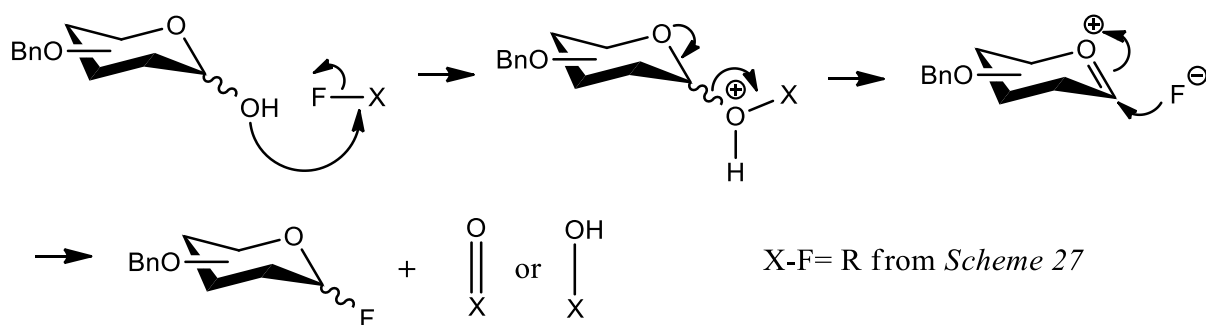


Scheme 27. Synthesis of anomeric fluorides.

I) Is the traditional method from the per-O-acetylated glycosides, similar to Scheme 11 (30).

II) The fluorination of hemiacetals has been extensively studied, in Scheme 27 a select few have been listed. It is assumed that the mechanism proceeds through the oxocarbenium ion as highlighted in *Scheme 28* (9).

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Scheme 28. Fluorination of a hemiacetal.

The fluorinating agent by-product will leave either as the corresponding ketone, or alcohol depending on the fluorinating agent. For example, **36** will leave as the sulphonic acid, whereas selectfluor, **37**, when used with stoichiometric amounts of dimethyl sulphide, generates an in-situ fluorodimethylsulfonium ion which acts to fluorinate the anomer and leave as the corresponding sulphoxide. The counter ion for cationic fluorinating agents is usually tetrafluoroborate or tosylate. Specifically, 2-fluoro-1-methylpyridin-1-ium, **36**, is used as its tosylate, whereas **37** uses two tetrafluoroborate counter ions (31) (32) (33) (34) (35) (36).

III) Glycosyl fluorides can be synthesised from thioglycosides. This is advantageous when fluorinating glycosides with diverse protecting groups, or polysaccharides without fluorinating the other constituents on the carbohydrate. The reagent used is a pyridine-iodinepentafluoride-hydrofluoric salt (IF₅-Py-HF), which is air stable at room temperature without an inert atmosphere. Making this reaction a notable anomeric conversion. IF₅-Py-HF is believed to fluorinate via the S_N1 mechanism, this is because the reaction produces a mixture of anomers from an anomeric pure reactant. It has also been used to fluorinate, non glycosidic, alkyl or aryl sulphides (37) (38).

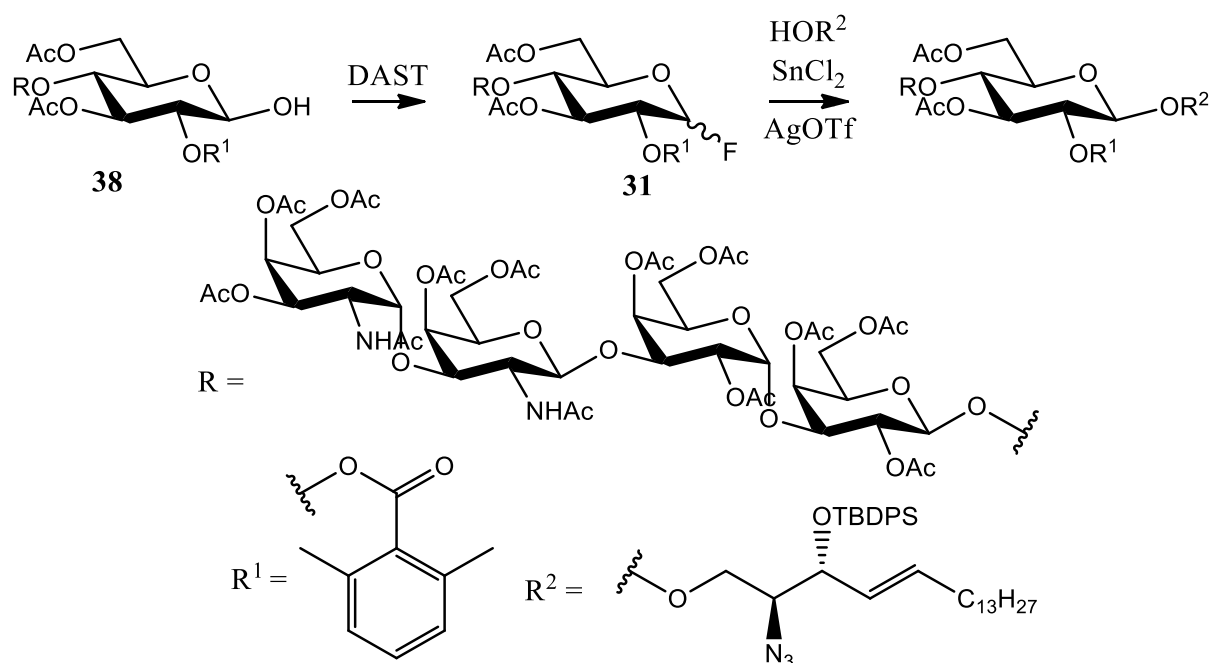
IV) The conversion of other glycosyl halides into the corresponding fluoride, is another method to synthesise glycosyl fluorides. The synthesis can be stereocontrolled depending on the reagent(s) used, the use of silver fluoride in acetonitrile achieves the β anomer, subsequent treatment with boron trifluoride diethyl etherate can generate the α anomer (39).

V and VI) The synthesis of glycosylfluorides from glycals is possible, which also controls the resulting stereochemistry of the C2 hydroxide. Route **e** is the oxidation of the double bond into the epoxide with 3,3-dimethyl-dioxirane, followed by subsequent

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fluorination of the anomer with tetra-*n*-butylammonium fluoride in THF. The resulting glycosyl fluoride is the **glucose** derivative. Route **f** is fluorination, and hydroxylation, of the glycal directly. Shimizu reported that using water and phenyliodanediyl diacetatyl perfluorosilane ($\text{PhI}(\text{OAc})_2\text{-SiF}_4$) will direct the fluoride α to the anomer, whilst hydroxylating the C2 position leads to the trans isomer thus, resulting in the fluoromannoside derivative (40) (41).

The reaction of glycosylfluorides as glycoside donors was recognised when Mukaiyama, Murai and Shoda discovered that activation of the fluoride as a leaving group could be achieved using tin (II) chloride and silver perchlorate. Fluorides can withstand harsher reaction conditions and have a significantly longer shelf life (9) (42). An example of the use of fluorides in carbohydrate synthesis is Ogawa's synthesis of the Forssman antigen (Scheme 13 and Scheme 29). Ogawa synthesised the Forssman antigen as a protected anomeric fluoride, **31**, from the corresponding hemiacetal, **38**, using **DAST** (**35**). He then proceeded to couple the Forssman antigen to the protected ceramide with SnCl_2 and AgOTf in dichloroethane in a 23% yield (16). This route demonstrates a versatile use for anomeric fluorides, not only in the delicate synthesis of the fluoride from a pentasaccharide, but in the glycosylation of the pentasaccharide with a ceramide residue.

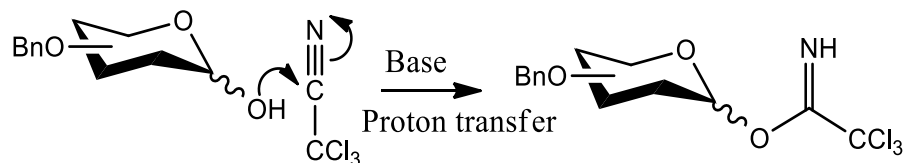


Scheme 29. Ogawa's use of an anomeric fluoride.

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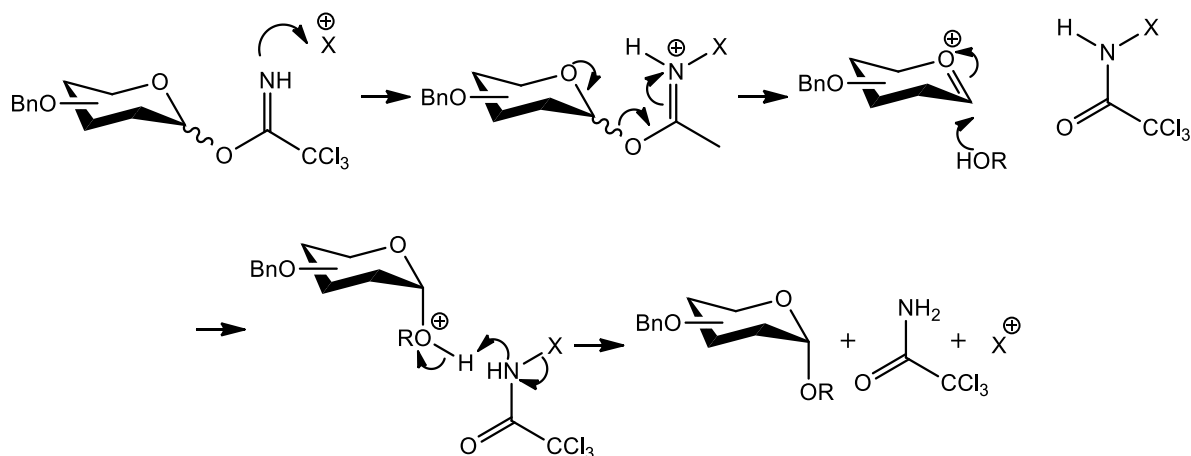
1.1.2. Trichloroacetimidates

Glycosyl-*O*-imidates were introduced by Schmidt in the early 1980's when his research group developed the *O*-trichloroacetimidate as a glycoside donor. The trichloroacetimidate soon became one of the most widely used glycoside donors in carbohydrate synthesis (9).



Scheme 30. Preparation of Schmidt's trichloroacetimidate glycosyl donors. (9)(p144)

One of the attractive features of the trichloroacetimidate donor is its synthesis. Being a base induced reaction means that any constituents on the carbohydrate, such as acetonides or benzylidenes, which are acid labile, will remain untouched. The other attractive feature of the trichloroacetimidate is how it only requires catalytic amounts of the activating agent to achieve full departure of the leaving group. They are typically activated with TMSOTf (43) (*Scheme 31*).

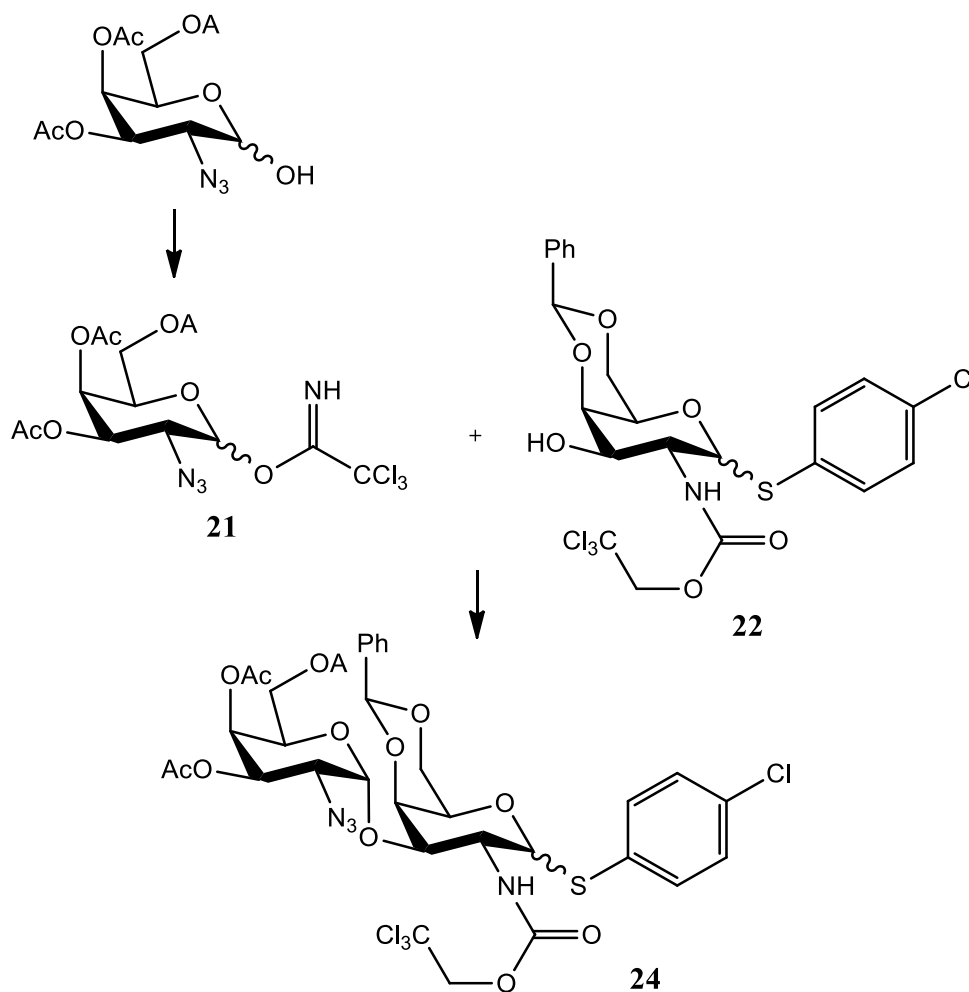


Scheme 31. The regeneration of the activating agent and mechanism of the trichloroacetimidate glycoside donor.

In Fengs' synthesis of the Forssman antigen, from Section 1.1., Scheme 32, the versatility of the trichloroacetimidate was utilised in one of the syntheses of the α -OGalNAc-

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GalNAc terminal disaccharide, **24**. Using the trichloroacetimidate was the most suitable donor in this situation. Synthesising the leaving group with potassium carbonate would not disrupt the acylated constituents on the amino galactoside. Coupling of the amino galactoside (**21**), with the other amino galactoside donor (**22**), already equipped with a thioglycoside leaving group, would proceed with catalytic amounts of the activating agent without activating the thioglycoside. In this way the galacto disaccharide **24** is generated as a protected thioglycoside donor, *Scheme 32* (3).



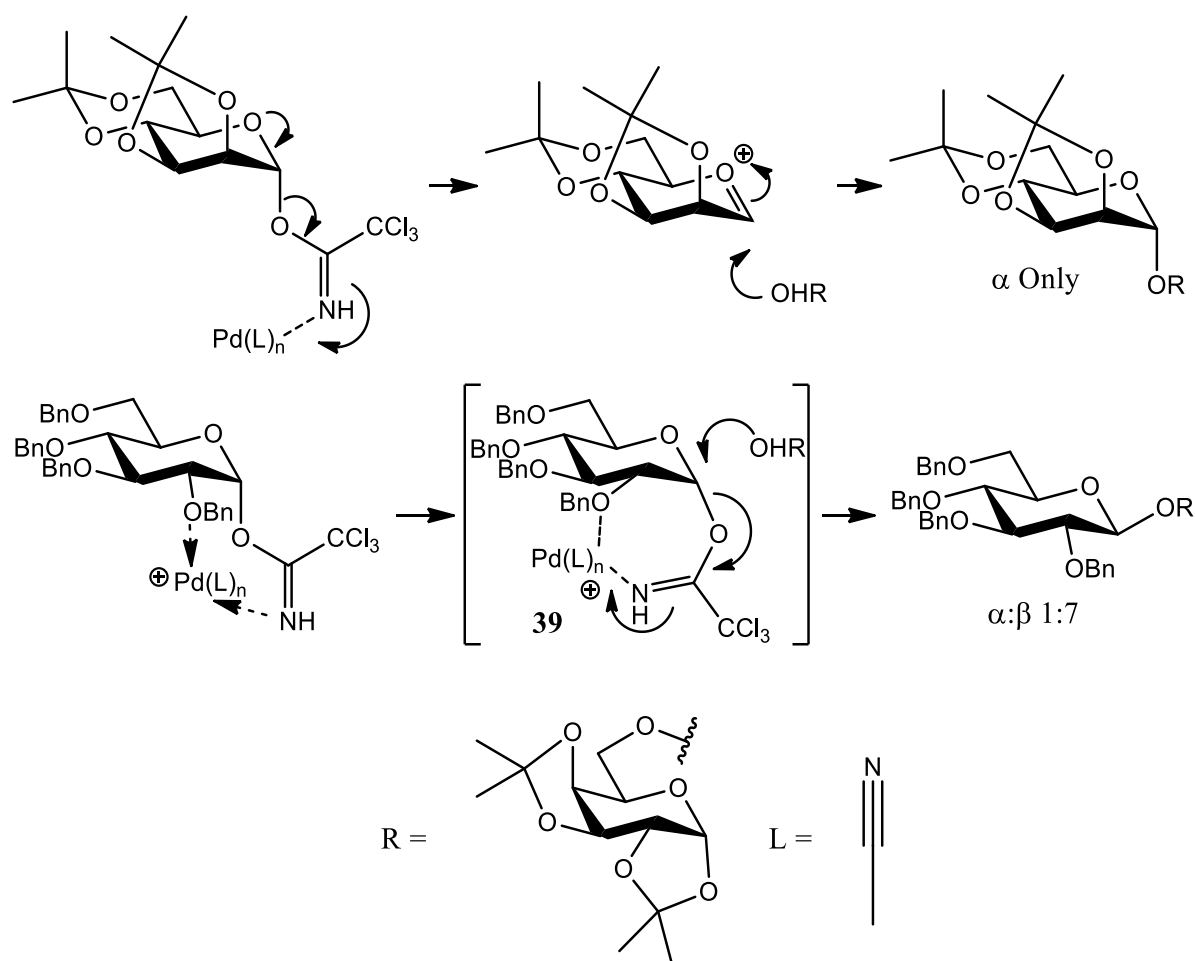
Scheme 32. Fengs' use of the trichloroacetimidate. (3)

Feng claims that the conversion of the amino galactose hemiacetal into **21** was achieved with a yield of 76% using K_2CO_3 (3) (44).

Another feature of trichloroacetimidates that makes them versatile is that they can be activated by a range of compounds. Thus numerous studies have been carried out on the

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anomeric product of glycosylation reactions using various metal complexes. Although the usual activating agent of choice is boron trifluoride diethyl etherate or trimethylsilyl trifluoromethylsulphonate (9), the ability of the nitrogen atom to act as a coordinating ligand means that anomeric imidates are a popular choice as the leaving group for studying the anomeric outcome of glycosylation reactions by varying the catalyst that activates the leaving group. For example, Nguyen reported the activation of trichloroacetimidates using ionic tetrakis(acetonitrile)palladium(II) tetrafluoroborate to promote, a somewhat, stereoselective formation of manno, gluco and rhamno glycoside bonds. (45) They reported high α mannoside selectively, which is to be expected. But their glucoside selectively was almost exclusively β . They speculate that the reaction proceeds through a seven membered intermediate as outlined in *Scheme 33*.



Scheme 33. Nguyen's palladium (II) activated trichloroacetimidate. (45)

The rationale of this approach is that α selectivity of the mannosides arise mainly from

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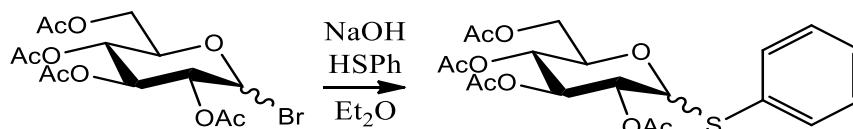
anomeric and steric effects as noted in Scheme 33. The glucosides β selectivity comes from a seven membered intermediate involving the palladium (II), the ether and the imidate **39**. The acceptor can then attack the anomer from the β position. One drawback of the study is that the glycoside bonds formed are 1,2-*trans*, which can also be easily achieved through neighbouring ester group participation (45). The subject of stereocontrolling catalysis and chiral auxiliaries will be covered in more detail in section 1.2.2.2. Chiral Auxiliaries & Asymmetric Catalysis

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1.1.3. Sulphur Based Leaving Groups

1.1.3.1. Thioglycosides

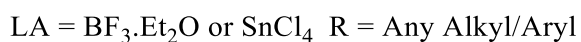
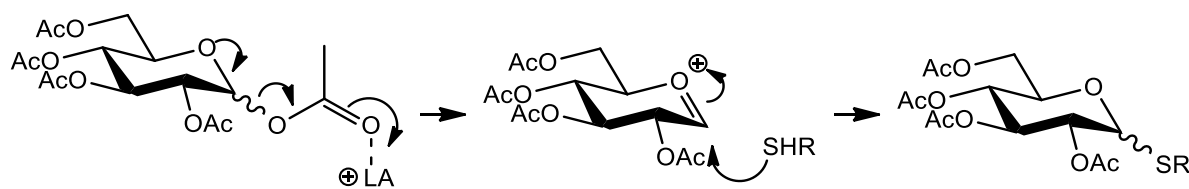
Thioglycosides were first synthesised by Emil Fischer in 1909 as the *S*-phenyl derivative from the tetra-*O*-acetylated bromo glycoside on treatment with sodium hydroxide and thiophenol (46).



Scheme 34. Fischer's thioglycoside. (46)

Although Fischer never described the mechanism, it can be assumed that the reaction proceeds by the S_N2 substitution on the anomeric bromide.

Since Fischer's discovery, there has been extensive research into the reactions of thioglycosides. Boons discovered that upon treatment with iodonium ion, thioglycosides can undergo anomerisation, although unlike the halogens which can anomerise with the corresponding tetra-butyl ammonium salt, the thioglycosides undergo their anomerisation via an intermolecular exchange (47) (9). Up until and Schmidts trichloroacetimidate method, thioglycosides were amongst the most used leaving group in carbohydrate synthesis. The thioglycosides can be activated by a number of different reagents and can be easily synthesised from the corresponding acetate. Thioglycosides can also be synthesised from the acetate via the oxocarbenium ion under Lewis acid conditions, using stannic (IV) chloride, or borontrifluoride etherate, *Scheme 35*.



Scheme 35. Synthesis of thioglycosides using a Lewis acid.

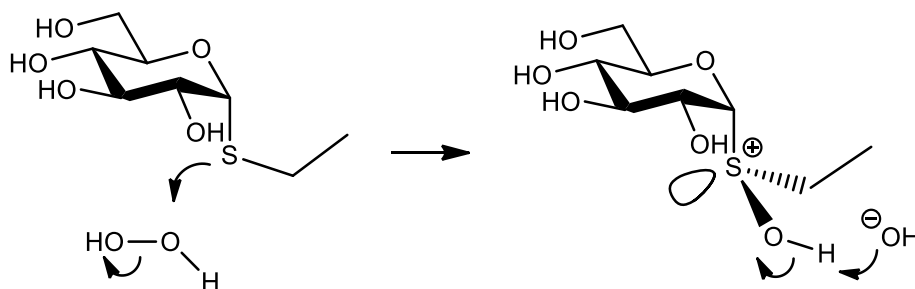
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Obviously a setback of doing it this way is the lack of stereocontrol compared to synthesising them from the substitution of anomerically pure glycosyl bromides. But synthesising them this way does skip the step of brominating the per-*O*-acylated glycoside.

The usual agents for activating the coupling of a thioglycoside is by using *N*-iodosuccinimide and trimethylsilyl trifluoromethanesulfonate/trifluoromethanesulfonic acid in greater than or equal to equimolar amounts. Other Lewis acids or halonium sources can be used to activate them depending on which R group (*Scheme 35*) is used (9). This can be especially useful when chemoselectively synthesising complex oligosaccharides. For example, anomeric 1,1-dicyclohexyl methylene sulphide (IDCP) is resistant through steric hindrance to activation under the same conditions as that of the corresponding anomeric ethyl sulphide (48).

1.1.3.2. Glycosyl Sulphoxides and Sulphones.

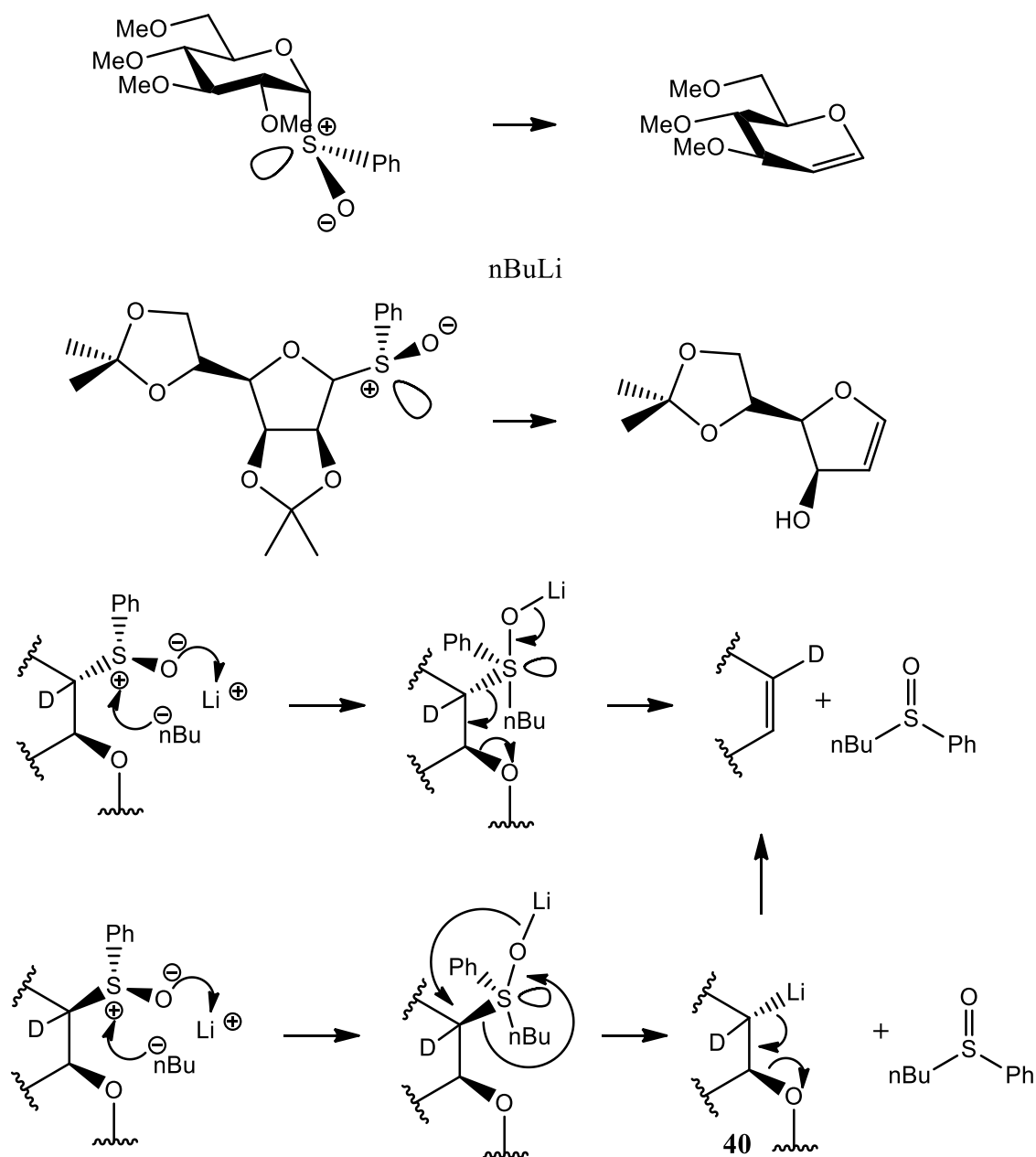
Thioglycosides can be oxidised into the corresponding sulfoxide. This was achieved by a reaction of the thioglycoside with hydrogen peroxide in the late 1930s by Micheel and Schmitz. It can proceed without protecting groups and in wet conditions and yields a single (*S*) sulphonyl stereoisomer (*Scheme 36*) (49).



Scheme 36. Micheel and Schmitz sulfoxide. (49)

Glycosyl sulfoxides can also be synthesised from the thioglycoside by oxidation with meta-chloroperoxybenzoic acid (*m*CPBA). They can then be reduced into the corresponding glycol. Gomez describes a method to synthesise both the furanoglucals and pyranoglycals from the sulfoxide by treatment with *n*-butyllithium (*Scheme 37*).

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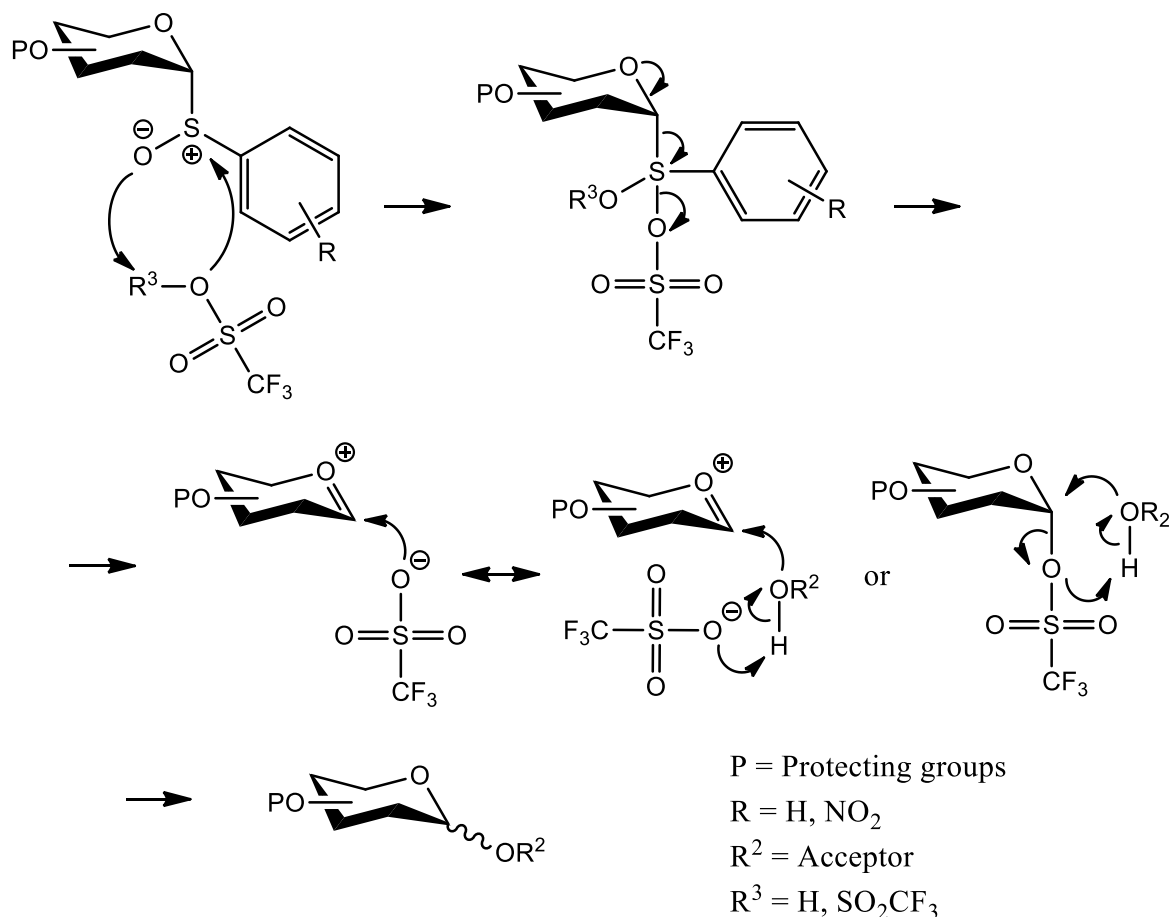
Scheme 37. Reduction of the sulfoxide to the glycal.

Gomez reduced the glycosyl sulfoxide to the glycal with n -butyllithium using a deuterium labelled system to deduce the mechanism. Their experiments resulted in a C1 deuterium present in the glycal product leading them to propose that the C1-C2 trans lithium compound **40** is responsible for the elimination reaction, proceeding regardless of the starting anomer. The C2 methoxide can leave as the lithium salt, whereas the propylidene can leave as acetone and lithium hydroxide (50).

Glycosyl sulfoxides have been used in glycoside bond forming reactions by

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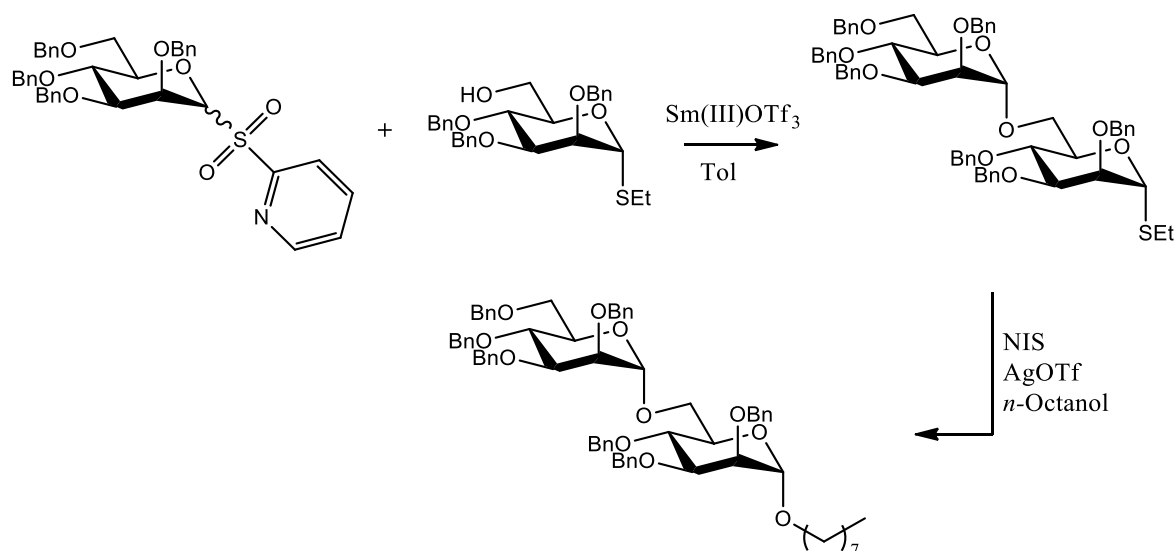
activation with several different compounds, but the most popular is triflic anhydride and a catalytic amount of a hindered base such as 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP). Use of triflic acid as an activator, with catalytic methyl propiolate has also been used to activate glycosyl sulphoxides (*Scheme 38*) (51).



Scheme 38. The glycosylation reaction of glycosyl sulphoxides with triflic acid or the anhydride. (51)

Thioglycosides can be oxidised further into the corresponding sulfones by treatment of the sulphide with potassium permanganate (52). Once oxidised to the sulfones, they can be chemoselectively activated in the presence of a thioglycoside acceptor, to synthesise a disaccharide thioglycoside donor (*Scheme 39*). Lowery displayed that this is possible using samarium (III) triflate to activate a pyridyl sulphone (53).

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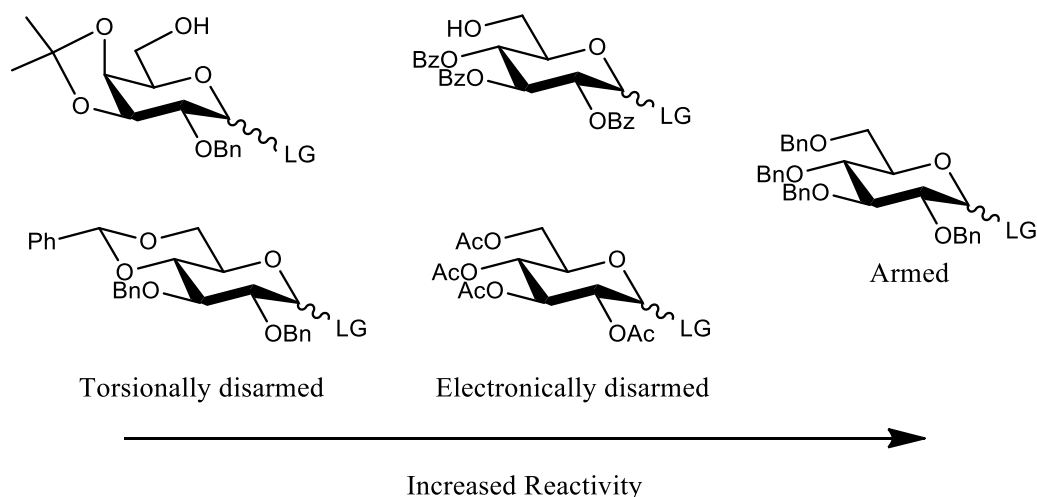


Scheme 39. Synthesis of a disaccharide using chemoselective activation of a sulphone. (53)

Lowery reported $\alpha:\beta$ selectivity of 3:1 from their samarium (III) triflate glycosylation and then 1.4:1 selectivity for the NIS and silver triflate coupling. They rationalise the selective activation of the pyridyl sulphone by its ability to coordinate to the samarium (III) ion through the sulphonyl oxygen and the pyridyl nitrogen. Thus drastically increasing the reactivity of the anomeric sulphone (53).

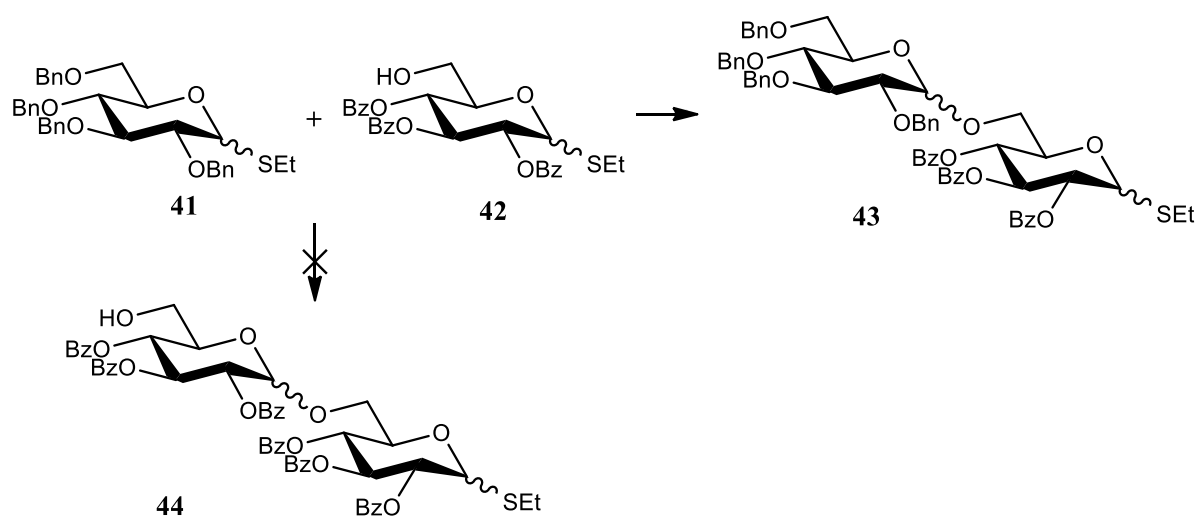
Another attractive property of the thioglycosides is their unique response to the armed-disarmed effect. The armed-disarmed effect, Scheme 40, was initially observed by Fraser-Reid (54), who noticed that the rate of oxocarbenium ion formation is influenced by the nature of the protecting groups on the glycoside donor. Both esters (electron withdrawing) and cyclic acetals (torsionally constraining) slow the rate of oxonium formation which in turn retards the rate of glycosylation. Interestingly the electronic effect is found to be stronger with anomeric sulphides than the corresponding *n*-pentenyl ether (9).

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Scheme 40. The armed disarmed effect.

The rationale of this effect is believed to be as follows; a neighbouring ester group strips electron density from the anomeric leaving group, making the chelation of the leaving group (LG) with its activating agent less likely to occur, thus lowering the rate in which the oxocarbenium ion is formed. Torsional disarming is relatively easier to rationalise in comparison; the oxocarbenium ion and its hexene-like conformers have their energy levels drastically increased due to cyclic protecting groups, thus decreasing the rate in which the oxocarbenium ion is formed. Comparatively torsional disarmed glycosides react slower than electronically disarmed glycosides (54) (55) (56).



Scheme 41. Armed-disarmed effect giving rise to chemoselective glycosylation. (57)

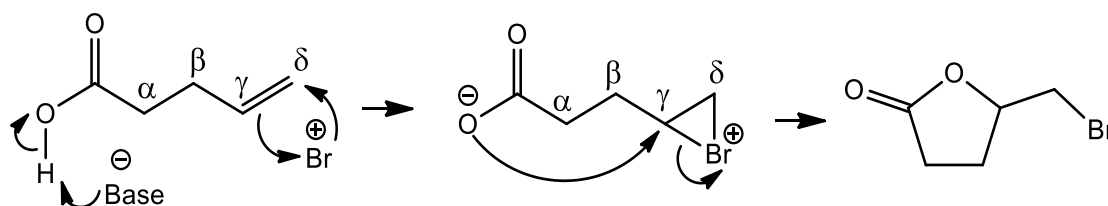
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The best example of how this effect can be exploited synthetically, is the chemoselective activation with stoichiometric amounts of activating agent (*Scheme 41*). For example, the coupling of ethyl thioglucoside donor **41** with the partially protected ethyl thioglucoside donor **42** using equimolar amounts of donor and acceptor proceeds to generate disaccharide **43** exclusively, with no self-condensation product **44** being observed (57).

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1.1.4. N-Pentenyl Glycosides

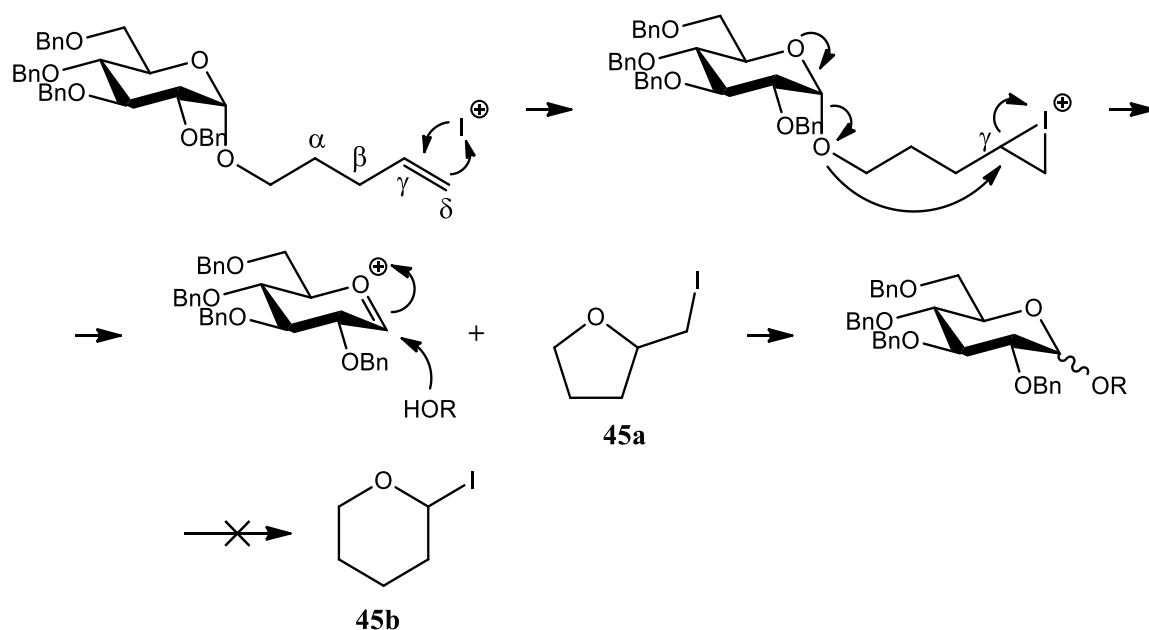
Fraser-Reid initially introduced *n*-pentenyl glycosides in disaccharide synthesis in the late 1980s, although the initial intention of the *n*-pentenyl group was as a protecting group for the anomeric position. Fraser-Reid was quick to realise the potential as a leaving group and utilise the reaction in carbohydrate synthesis (58). They are easily synthesised from the corresponding per-*O*-acylated glycoside, 4-penten-1-ol and a Lewis acid, in a similar fashion to the synthesis of thioglycosides shown in Scheme 35. They can also be synthesised *via* the Fischer glycosylation shown in Scheme 4, using the 4-penten-1-ol instead of methanol (59). Or they can be synthesised from the corresponding halide, similar to reactions discussed in *Scheme 15*, *Scheme 16*, *Scheme 18* and *Scheme 24* (60). Glycosylation using *n*-pentenyl donors is called ‘trans-glycosidation’ in that the donors anomer is in a glycoside bond with *n*-pentenyl ether and the product of the reaction is simply a different glycoside bond (9). The action of *n*-pentenyl ethers is based on a reaction from the turn of the 20th century called iodolactonisation, or halolactonisation (*Scheme 42*).



Scheme 42. Bromolactonisation of 4-penten-1-oic acid.

Bromolactonisation was first recognised in 1902 by Stobbe, its reaction being base induced with analogues of *n*-pentenyl acid. The bromonium ion was formed from *N*-bromo succinimide (NBS) and the base used was sodium carbonate. Once the γ,δ -unsaturated bond forms the bromonium ion, the acid anion would then proceed to attack the γ carbon intramolecularly in the formation of a 5-membered lactone ring. It was found by Fraser-Reid that instead of liberating a proton from the acid, it was possible that the anomeric ether could liberate an oxocarbenium ion once activated in a similar reaction with NIS, but without the need for sodium carbonate (*Scheme 43*). Fraser-Reid's reaction is not iodolactonisation because the product is a tetrahydrofuran, and not a lactone due to the lack of the carbonyl. The typical activating agent for *n*-pentenyl glycosides is NIS and TMSOTf, but they can be activated with just NIS (14).

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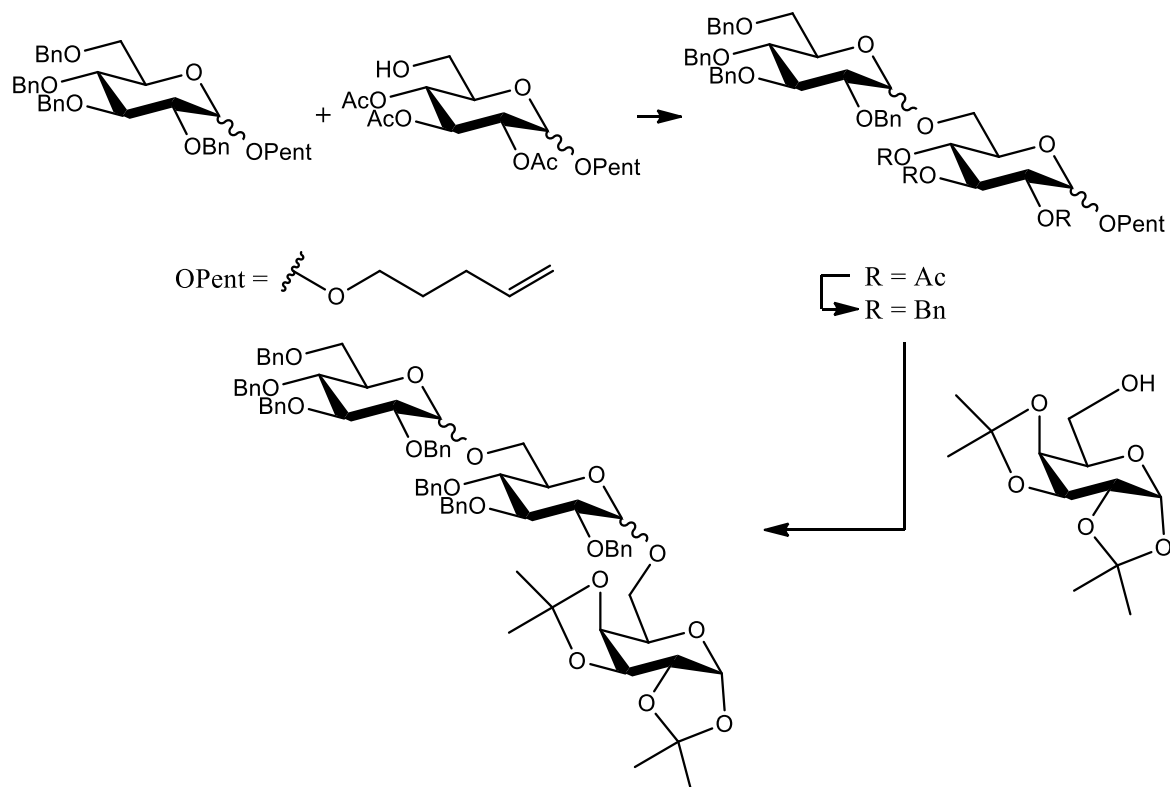


Scheme 43. Fraser-Reid's *n*-pentenyl glycoside.

The intramolecular cyclisation of the *n*-pentenyl ether gives solely the methyl tetrahydro furan product **45a** and not the iodo tetrahydropyran product **45b**. This conforms with Baldwin's rule for favoured and disfavoured products of cyclisation as a favoured 5-*exo*-tet cyclisation. Whereas the 6-*endo*-tet product is disfavoured. These are called 5/6 because of the size of the ring formed, *exo/endo* because of the orientation of the bond broken, where it could be outward of the ring (*exo*) or inward (*endo*). And 'tet' because of the tetrahedral hybridised orbitals of the carbon being attacked (61).

As mentioned earlier, Fraser-Reid used his *n*-pentenyl glycoside in the discovery of the armed – disarmed effect, where he compared the rate of anomeric hydrolysis of alkyl protected *n*-pentenyl glycosides to that of ester protected *n*-pentenyl glycosides. He found that the C2 benzylated *n*-pentenyl glycosides hydrolysed to the corresponding anomeric hydroxyl several orders of magnitudes faster than that of the corresponding ester (54). He proceeded to test his theory in the synthesis of a trisaccharide (Scheme 44).

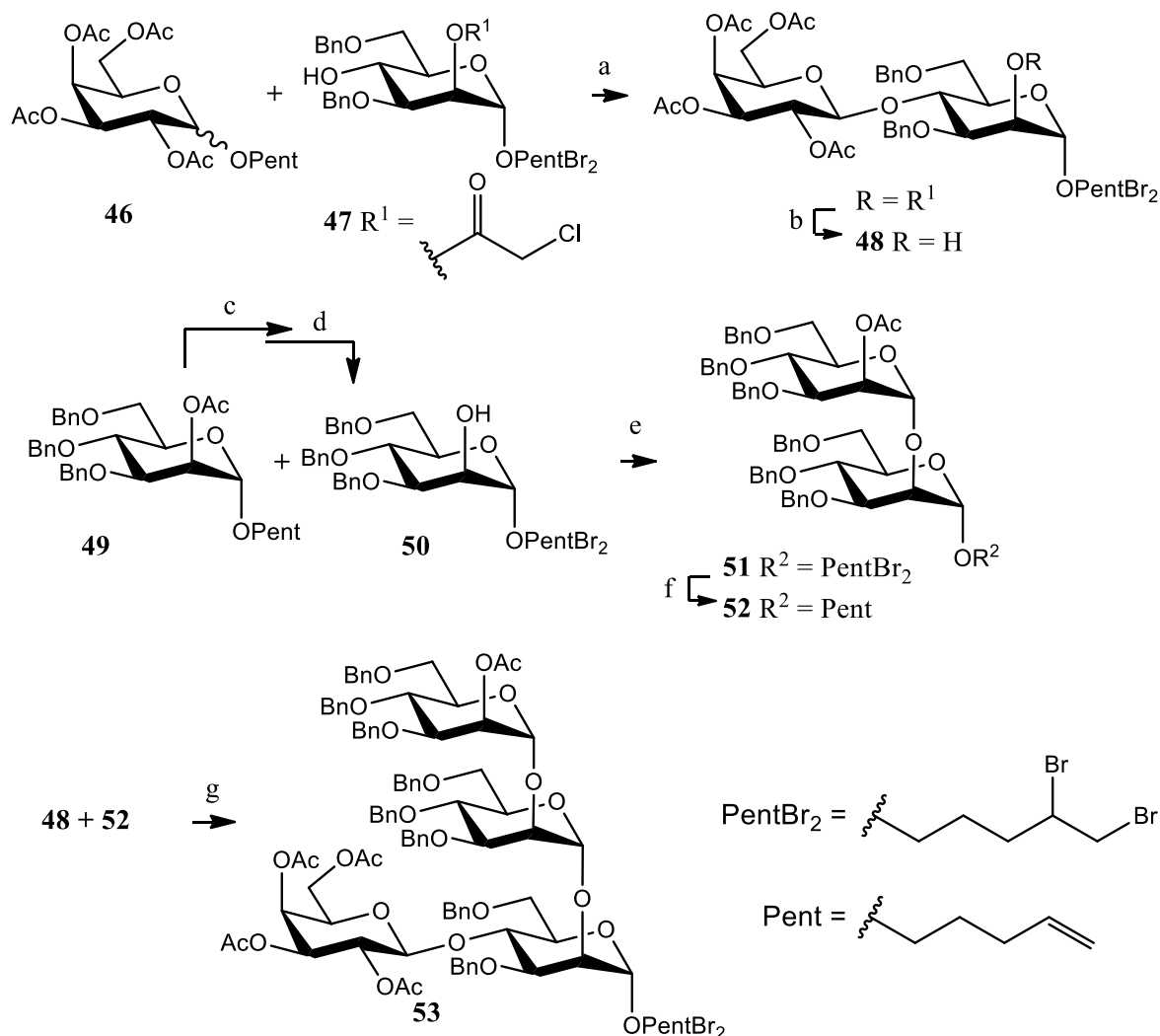
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Scheme 44. First application of the armed-disarmed effect. (54)

An attractive property of *n*-pentenyl glycosides is their ability to have the leaving groups terminal alkene protected as a 4,5-dibromoalkane, which can be easily turned back into the alkene. This allows for a pseudo chemoselective approach to oligosaccharide synthesis. Fraser-Reid used this methodology in the rather elegant, convergent, 2+2 synthesis of a branched tetrasaccharide from the cap of the *Leishmania* lipophosphoglycan (*Scheme 45*) (62).

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Scheme 45. Fraser-Reid's synthesis of the *Leishmania* lipophosphoglycan cap. (62).

a) 46, 47, NIS, DCM b) Thiourea, NaCO₃, EtOAc, c) 49, Br₂, TBAB, DCM, d) NaOMe, MeOH, e) 49, 50, NIS, DCM, f) 51, Zn, TBAI, DCM, g) 48, 52, NIS, DCM.

Fraser-Reid synthesised the β -O-Gal-1-4-Man **48** from the per-*O*-acylated *n*-pentenyl galactoside **46**, and a brominated 2-chloroacetyl-3,6-dibenzyl *n*-pentenyl mannoside **47**. This showed how it is possible to activate the *n*-pentenyl anomer without affecting its corresponding brominated counterpart on **47**, then selectively deacylating the chlorinated acetate with thiourea and sodium hydrogen carbonate in ethylacetate, thus generating a disaccharide acceptor **48**. They then proceeded to synthesise the α -O-Man-1-2-Man disaccharide donor **52** from mannoside donor **49**, which was easily converted into the acceptor **50** by bromination of the *n*-pentenyl leaving group, with TBAB and bromine, and deacylation of the acetate. Coupling **49** with **50** yielded the 4,5-brominated *n*-pentenyl disaccharide **51**.

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Which is then easily de-brominated into the *n*-pentenyl alkene leaving group, with TBAI and zinc dust, thus generating the disaccharide donor **52**. Finally coupling of *n*-pentenyl glycoside **52** with **48**, the brominated acceptor, would furnish the branch tetrasaccharide **53** (62).

In terms of glycoside bond formation, we have only so far discussed activation methods. However, unlike a peptide coupling, there are two possible diastereomeric products (anomers) from a glycosylation reaction. Like all bond forming reactions involving the generation of a new chiral centre there is intense effort focussed around the discovery of a stereocontrolled version of the reaction, and indeed asymmetric glycosylation has seen major efforts over the last twenty years to deliver stereocontrolled glycoside bond formation.

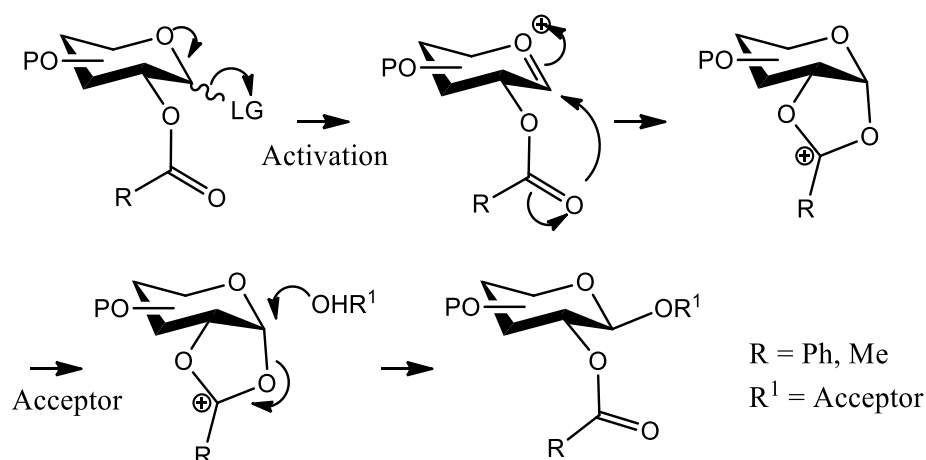
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1.2. Stereocontrol

As mentioned in the previous sections on anomeric leaving groups, the stereochemical outcome of glycoside bond formation is of the utmost importance in oligosaccharide synthesis. Over the years, since glycoside bond forming reactions were first introduced into organic chemistry, there have been numerous investigations into the factors affecting anomeric control. These have included solvent effects, the use of protective groups, temporary tethers, specially designed donors and chiral catalysts to name a few. This section will provide a brief review on some of these attempts to deliver a rational approach asymmetric glycosylation.

1.2.1. Neighbouring Group Participation

The most basic way of controlling the stereochemistry of a glycoside bond is through neighbouring group participation of an ester in the formation of *trans* glycoside bonds (*Scheme 46*). They also happen to be part of the armed-disarmed effect.

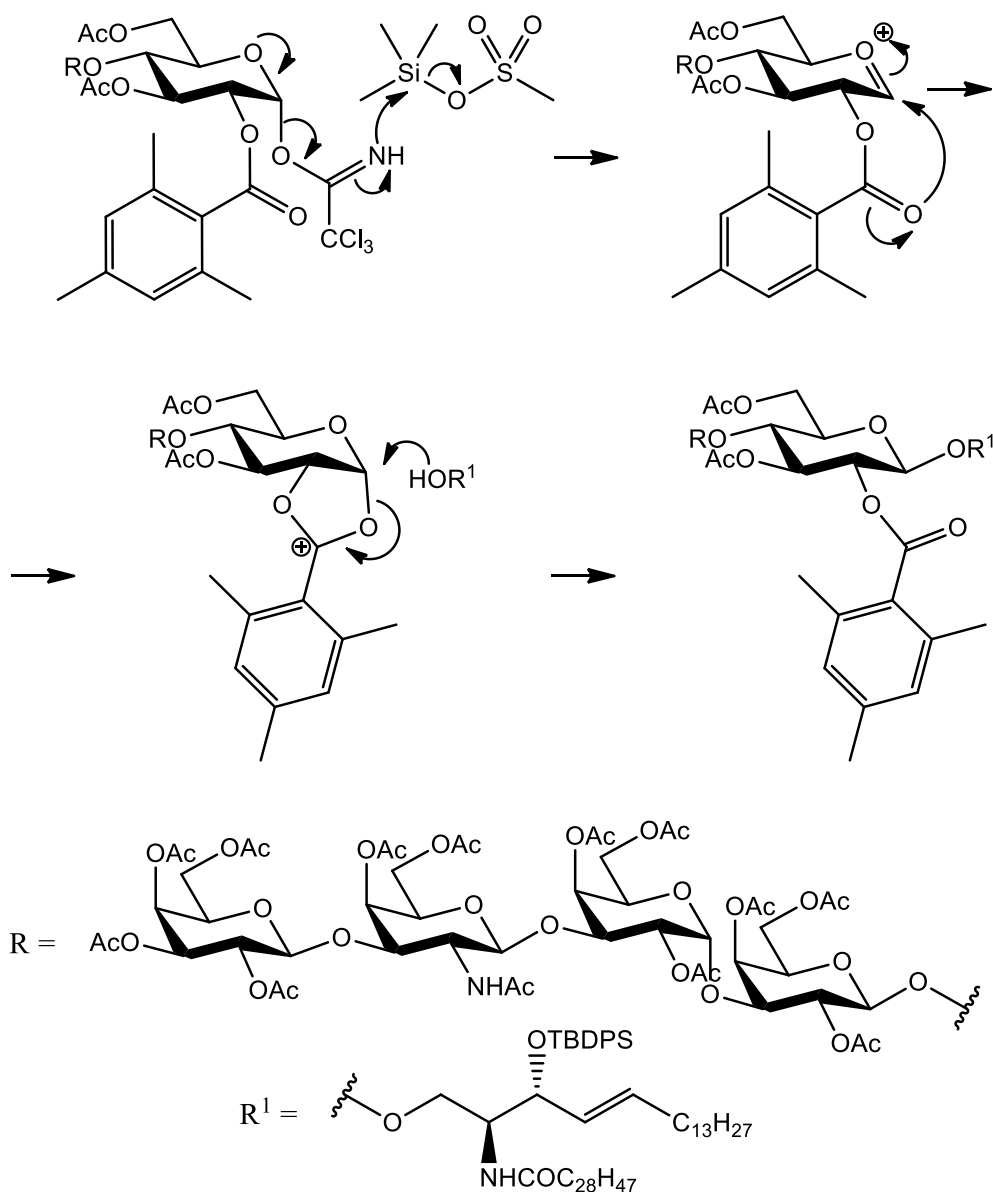


Scheme 46. Neighbouring ester participation in trans glycosylation.

The carbonyl on the C2 ester acts upon the oxocarbenium ion in sharing its charge, whilst simultaneously preventing attack of the acceptor from the *cis* position. Ogawa took advantage of this method in his synthesis of the stage specific embryonic antigen-3 (SSEA-3) (63), globopentaosyl ceramide. A similar pentasaccharide to that of the Forssman antigen from Figure 2, but different in that its terminal galactoside is not an α -2-amino galactoside, but a β -galactoside (*Scheme 47*). Ogawa used the neighbouring ester 2,4,6-trimethylbenzoyl (TMBz)

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because its *trans* selectivity is especially prominent when compared to the other esters available (63).

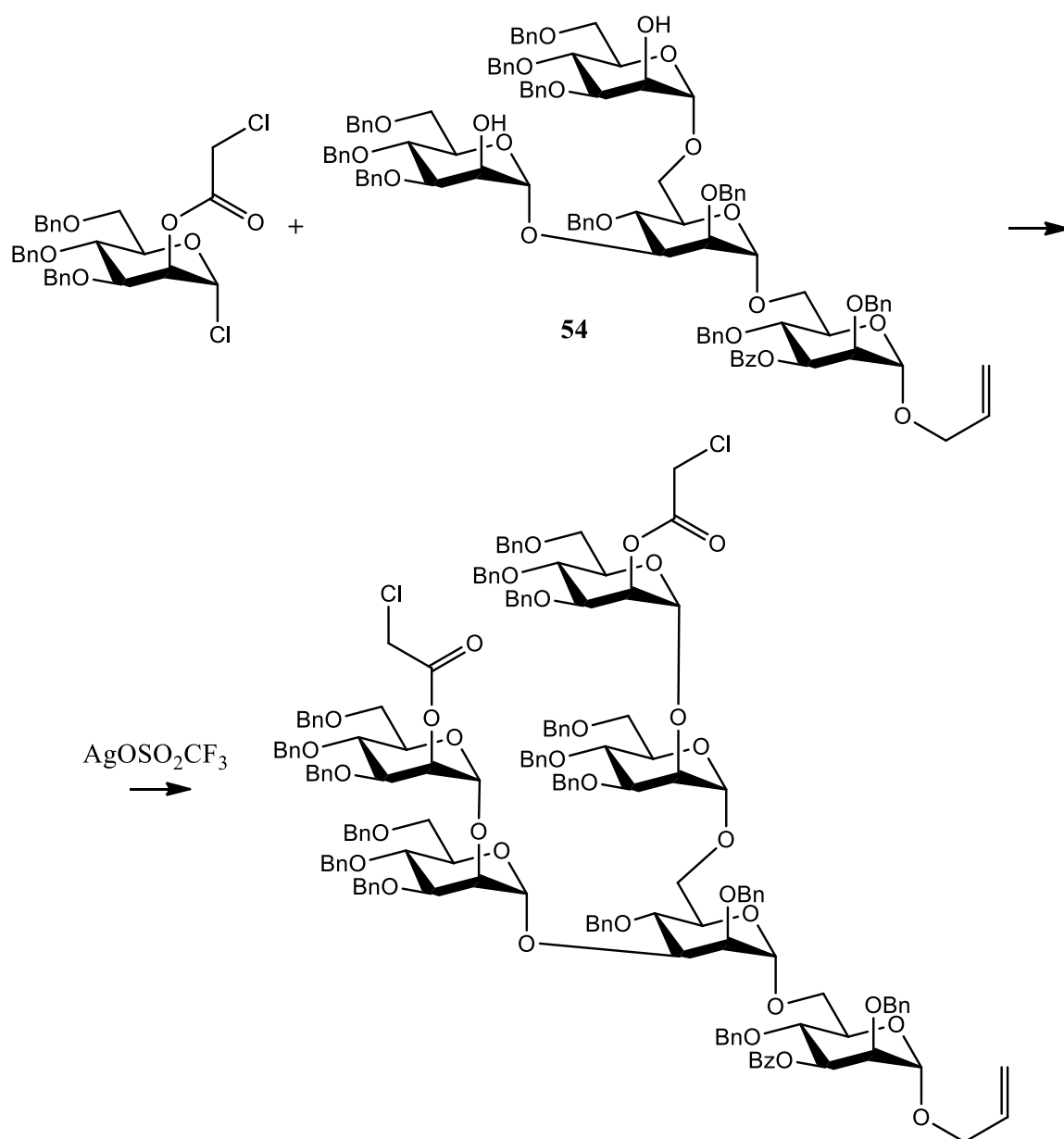


Scheme 47. Ogawa's stereo controlling C2 O-TMBz. (63)

Ogawa found the *trans*, in this case β , selectivity to exceed the selectivity of a neighbouring benzoyl group, which itself shows greater selectivity than the acetate (63). An important factor, besides neighbouring group participation, to take into account when using esters to protect the C2 hydroxyl is whether or not they can be chemoselectively de-protected in the presence of other esters. Fraser-Reid demonstrated the use of a 2-chloroacetate neighbouring ester (*Scheme 45*) which is selectively removed from the disaccharide

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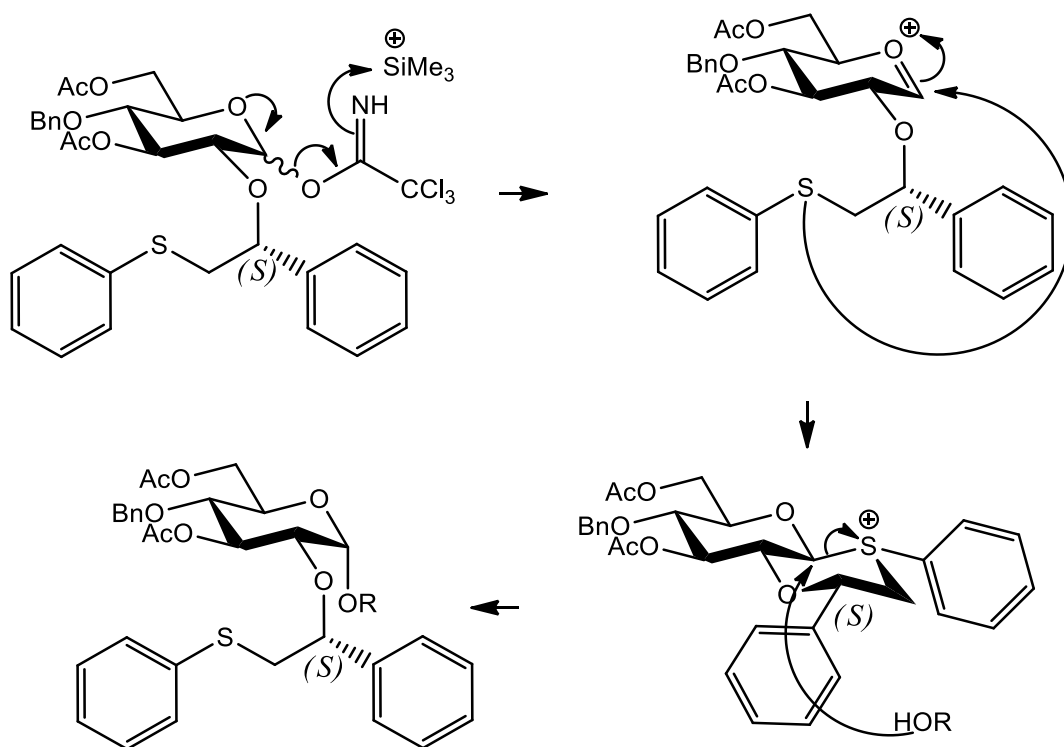
glycosylation product, which contained acetate substituents on the carbohydrate, using thiourea and sodium hydrogen carbonate (63). Ogawa also demonstrated the use of the 2-chloroacetate as a neighbouring group stereocontrolling auxiliary to a chloride donor in the di-mannosylation of a di-hydroxy acceptor (*Scheme 48*). The oligosaccharide synthesised was part of a study in synthesising branched high-mannose type glycopeptides. Ogawa was able to create two glycoside bonds simultaneously onto the same acceptor, **54**, with remarkable *trans* stereoselectivity (64).



Scheme 48. Di-mannosylation using 2-chloroacetate to control the stereochemistry (64).

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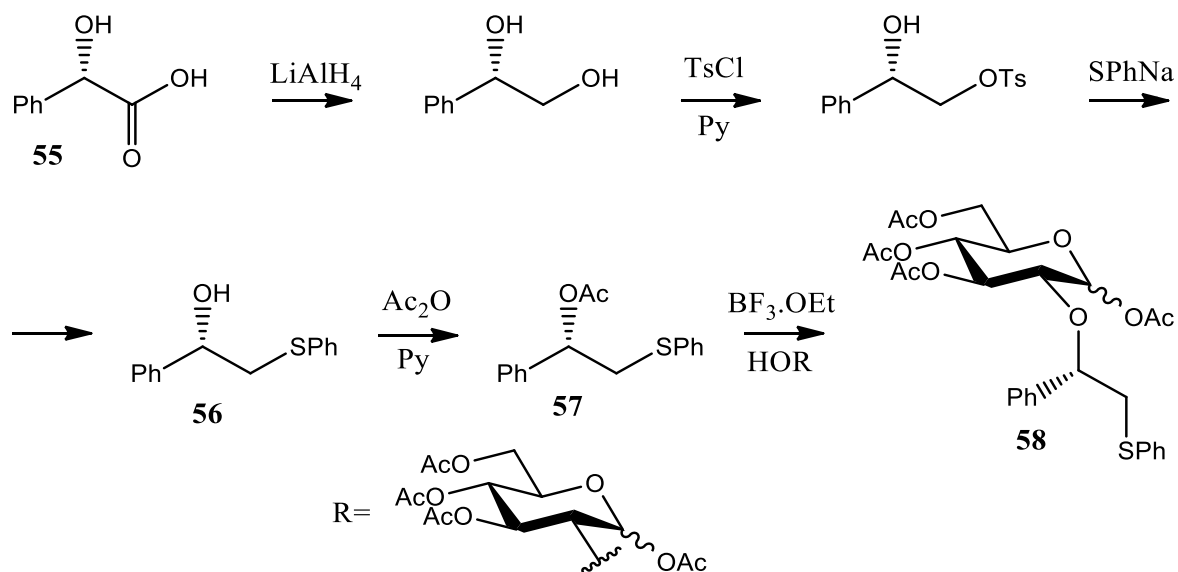
The use of a C-2 ester to deliver what is often referred to as a *trans* 1,2 glycoside is relatively straight forward. However, Boons has recently reported an elegant refinement of neighbouring group participation to synthesise the more difficult to access *cis*-glycoside using the (1*S*)-phenyl-2-(phenylsulfanyl) ethyl protecting group. The method works through a temporary six membered cyclic attack of a phenyl sulfide to the oxocarbenium ion. The (1*S*)-phenyl lies in an equatorial conformation, meaning the oxocarbenium has its β face blocked, thus attack of the acceptor to the oxocarbenium ion has to occur from the α position (*Scheme 49*).



Scheme 49. Boon's neighbouring group participation.

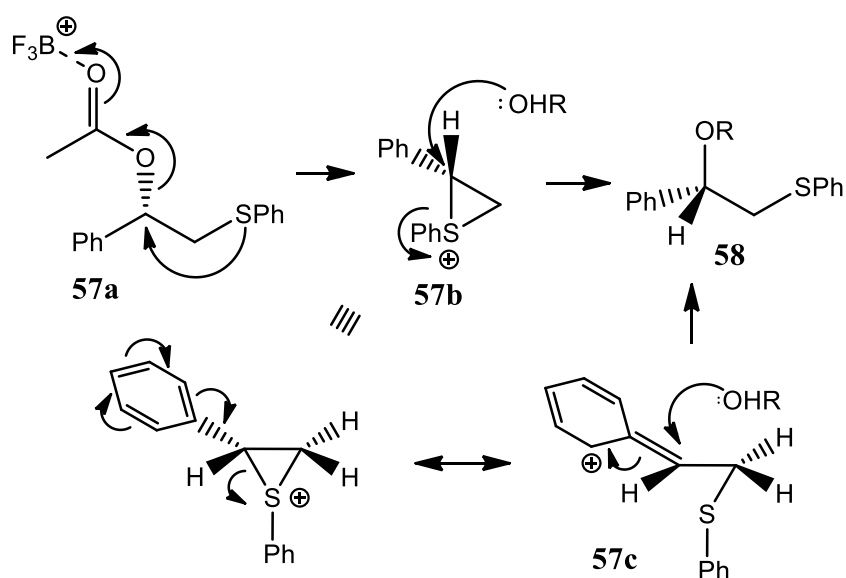
The key problem with this method is that enantiomerically pure reagents can be costly. Luckily for Boons method, the (1*S*)-phenyl-2-(phenylsulfanyl) ethyl group was relatively easily synthesised from readily available (*S*)-mandelic acid (*Scheme 50*). Treatment with LiAlH₄ would afford the diol **55**. Of which the primary alcohol is then selectively tosylated and finally substituted with phenylthiol to generate the sulfide **56**. The secondary alcohol is then acylated with acetic anhydride and pyridine to give ester **57** which is attached to the C-2 hydroxyl using Lewis acid catalysis to give monosaccharide **58**.

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Scheme 50. The synthesis of Boon's (1S)-phenyl-2-(phenylsulfanyl) ethyl neighbouring group (65).

To attach it to the glycoside, the acetate is then activated with $\text{BF}_3 \cdot \text{OEt}_2$ and substituted with the sulphide in the formation of an epi-sulphonium ion, **57b**, which is substituted with the glycosides C2 hydroxide. The subsequent ether formed retains the chirality of the original acetate *Scheme 51* (65).



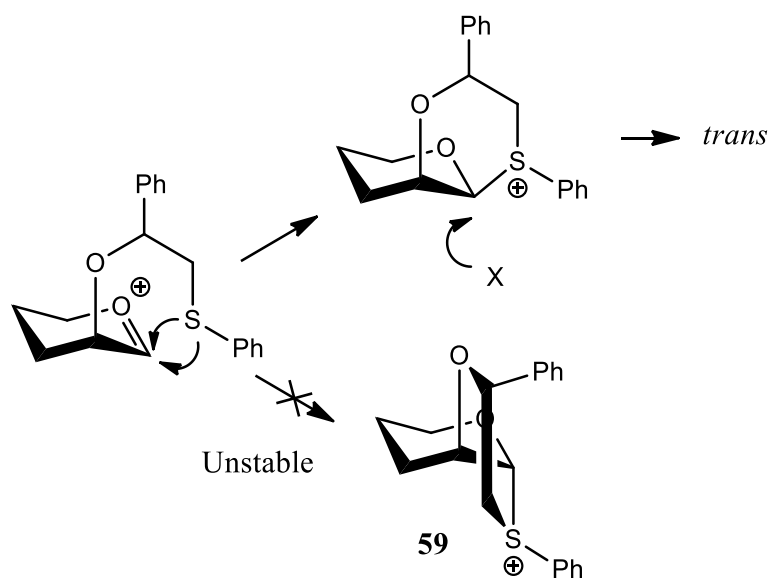
Scheme 51. The mechanism of epi-sulphonium ion formation.

The carbohydrate hydroxyl group attacks the episulphonium ion at the benzylic carbon

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as opposed to the primary carbon because the benzylic carbon will better stabilise the developing positive charge than the primary carbon, thus making it more electrophilic. Not only that, but resonance structures can be drawn due to the nature of the benzylic carbon group stabilisation **57c**, which adds to its ability to stabilise the charge. (66).

Unfortunately, this method has limitation in that it will not work with mannosides or related systems where the C2 substituent is in the axial position. This is because the six-membered intermediate would have to suffer strain in order to form the *trans* decalin intermediate **59** (67), if any of the *cis* decalin forms then the product would be a *trans* mannoside, which is already easily achieved with an ester on the C2 position (*Scheme 52*).

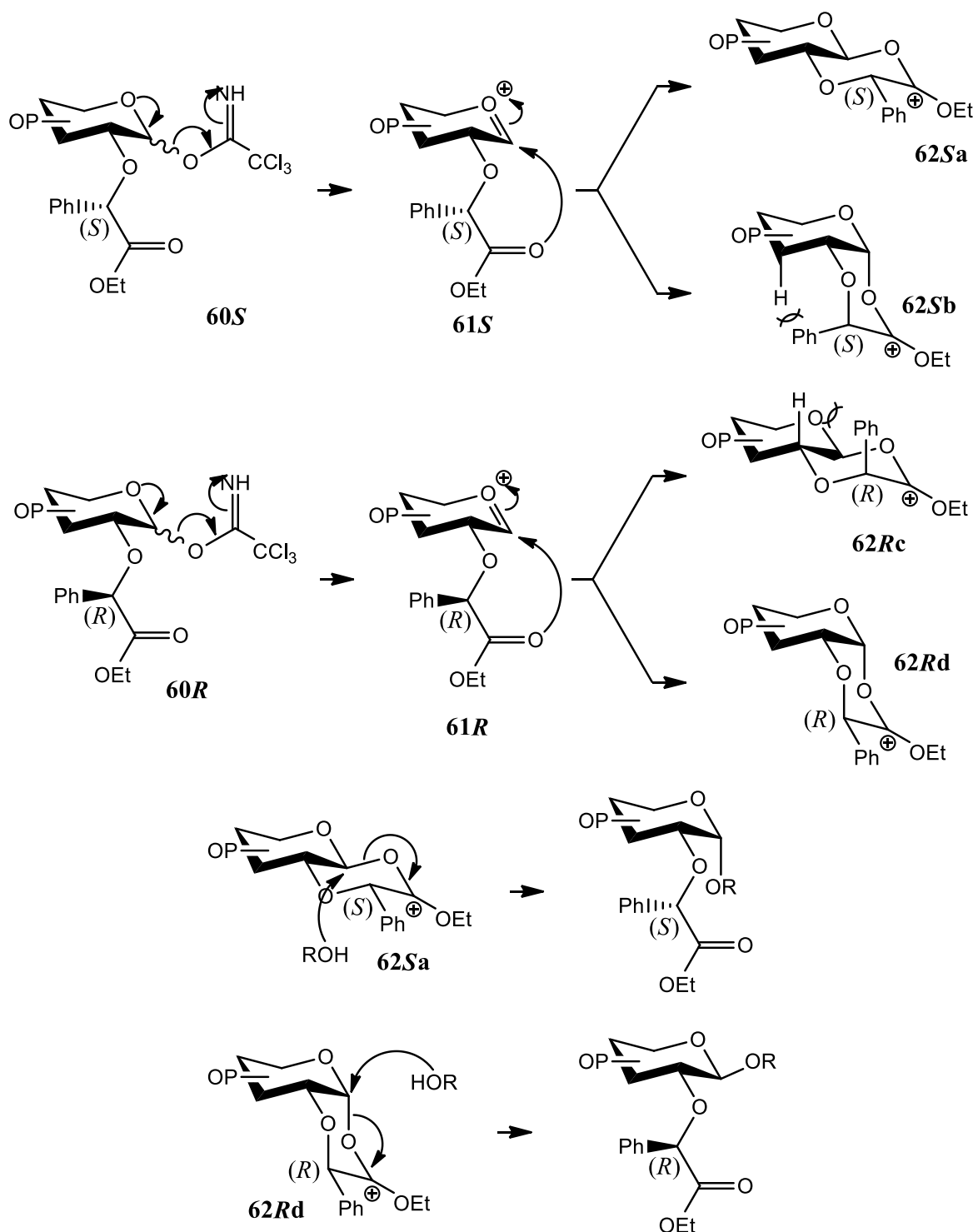


Scheme 52. Boon's neighbouring group direction with mannosides.

A year later Boons followed up with a study of the use of ethyl 2-bromo-2-phenyl acetate as a protective group, with emphasis on the effect of stereochemistry on the outcome of a chimerically assisted glycosylation. As *Scheme 53* outlines the *S* enantiomer is expected to direct the acceptor to give a disaccharide in a *cis* orientation, whereas it would be realistic to assume that the *R* enantiomer would direct the glycosylation into the *trans* orientation. **60S** and **60R** are the *S* and *R* enantiomers at the neighbouring groups phenyl group, respectively. **62** and its variations, are the intermediates that the glycosylation reaction could go through as a result of attack from the neighbouring groups carbonyl (**61**). **62Sb** and **62Rc** are the most hindered cyclic intermediates of the corresponding donor, whereas **62Sa** and **62Rd** are the least hindered

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intermediates, and display stereochemical control of the reaction.

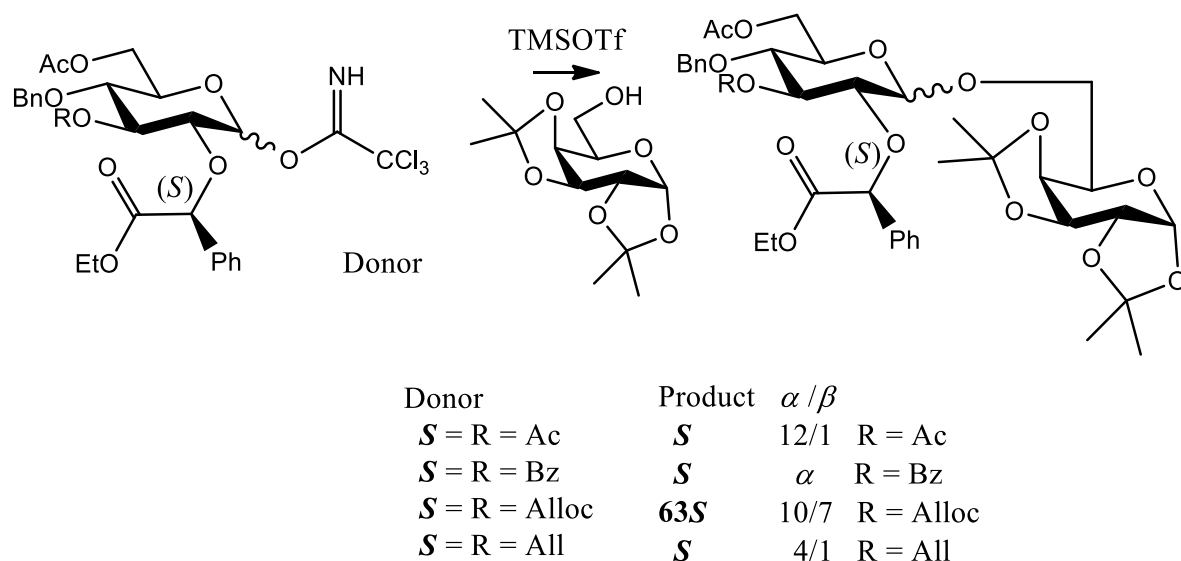


Scheme 53. Boon's neighbouring group participation using both R and S enantiomers (65).

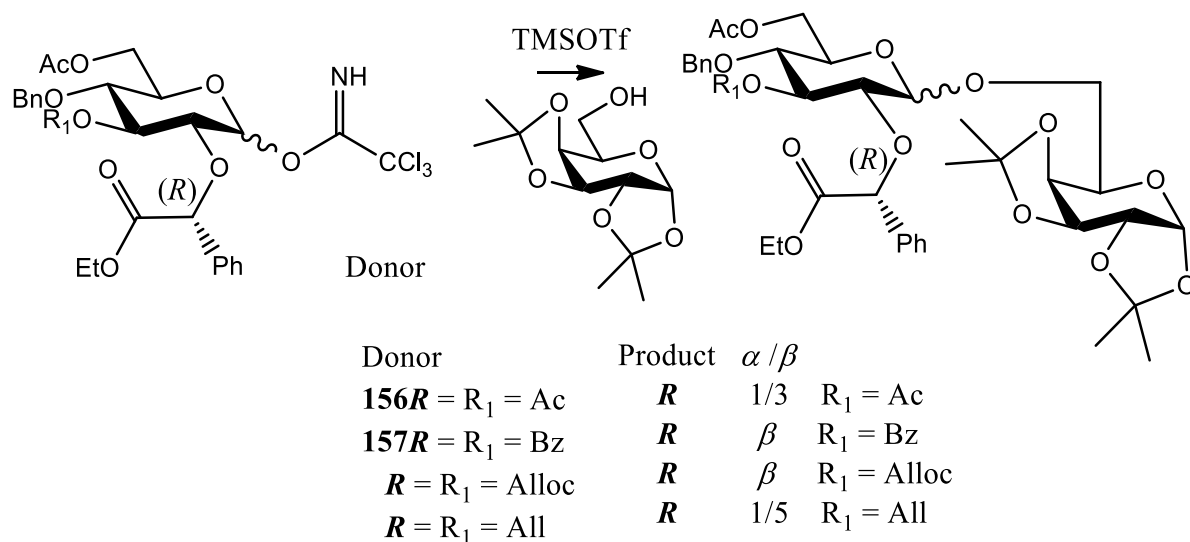
For their study they used an array of variously protected donors. As an example of the

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results, the following reactions were performed using a glucoside trichloroacetimidate as the donor and a diacetone galactose as the acceptor (*Scheme 54* and *Scheme 55*).



Scheme 54. Selectivity observed from the S enantiomer of Boons neighbouring group study.



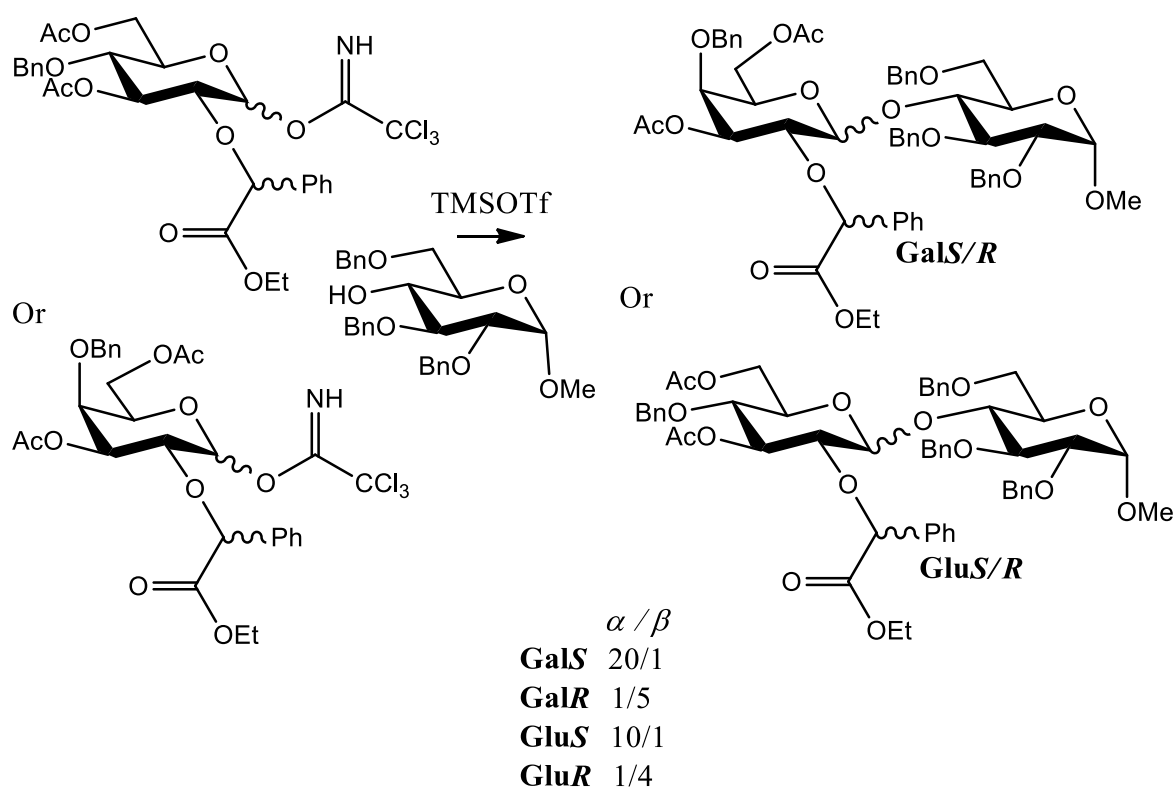
Scheme 55. Selectivity observed from the R enantiomer of Boons neighbouring group study.

Scheme 54 shows the stereoselectivity of the '*S*' donor and *Scheme 55* shows the stereoselectivity of the '*R*' donor. Both schemes also show how changing the C3 protecting group of the donor curiously affected the outcome of the glycosylation considerably. The *S* enantiomers'

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cis selectivity was not as consistent as the *R* enantiomers' *trans* selectivity upon changing the C3 protecting group, **63S** being the notable example. Not only was this an interesting study of the stereocontrolling ability of a chiral C2 group, but also how a substituent on the glycoside donor five bonds away from the anomer can still effect the stereoselectivity of the glycoside bond formed. Within the same study similar findings were observed with a galactoside donor and a C4 glucoside acceptor, as highlighted in

Scheme 56.

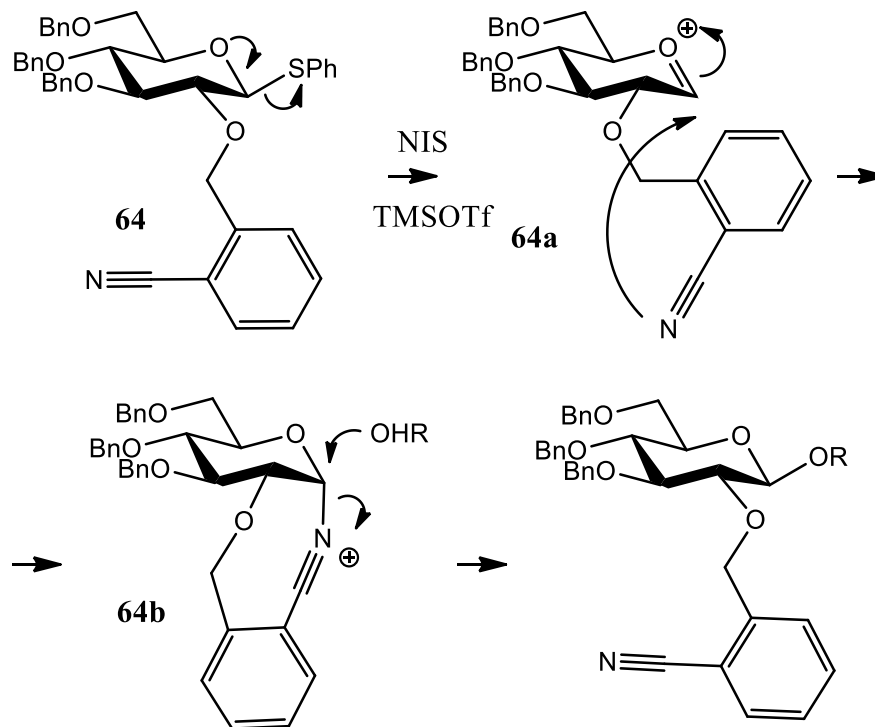


Scheme 56. Boon's neighbouring group participation on galactosides (65).

The neighbouring group participation was nearly as effective on the glucoside as it was on the galactoside. Not only does this research demonstrate an effective measure to nearly complete stereo control, but it also shows evidence for how more distant substituents on the glycoside donor affected the outcome of the glycosylation reaction. Structurally the galactoside donor differs from the glucoside donor by an axial component five bonds away from the anomer.

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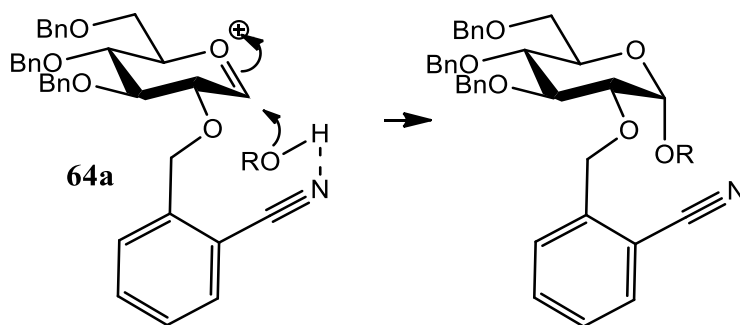
Xue-Wei Liu has also worked on the development of a novel protecting group to control stereochemistry. He reported the use of a C2 ortho cyanobenzyl group to aid in the stereocontrol of glycoside bond formation as outlined in *Scheme 57*.



Scheme 57. Xue-Wei Liu's neighbouring ortho cyanobenzyl group for trans synthesis (68).

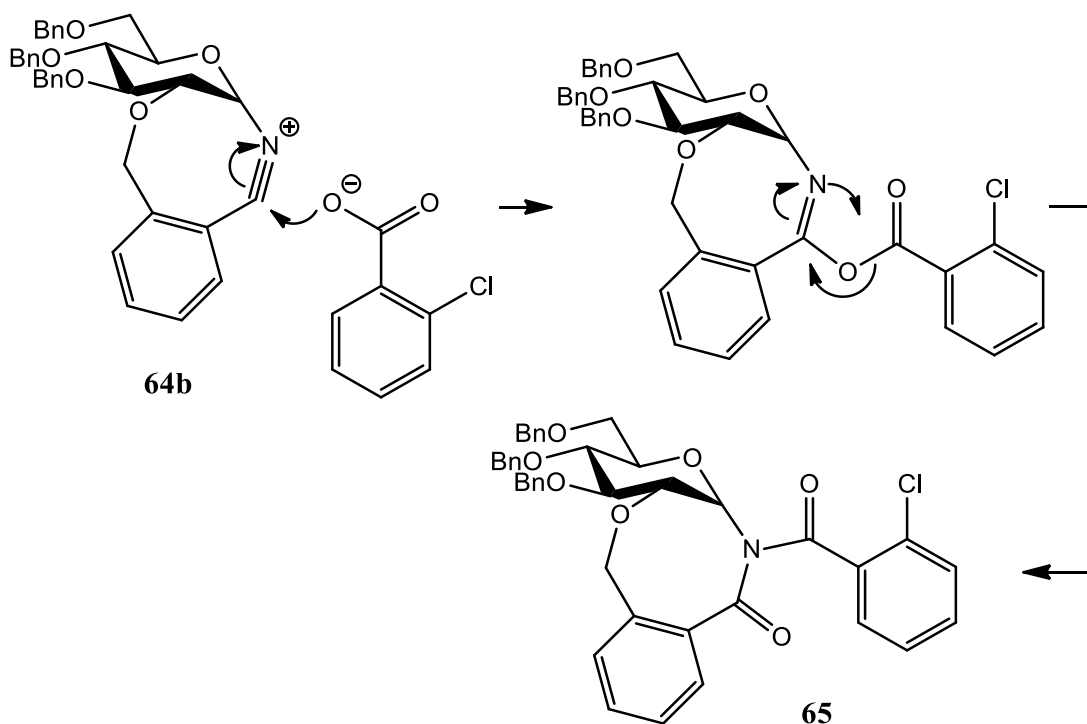
Their proposed mechanism involves an energetically favoured nitrilium ion **64b**, which mimics the nitrile effect in directing the acceptor into the β position (9). The most interesting aspect of their discovery is that the reverse effect is observed when the acceptor's hydroxide is losing electron density, or the nucleophilicity of the oxygen is decreased by a massively electron withdrawing group such as acylated glycosidic acceptors or poly fluorinated alkyl acceptors. Glycosylation of thioglucoside **64** with methyl 2,3,4 tri-*O*-benzyl α -*D*-glucopyranoside acceptor gives only the β (*trans*) anomer, whereas the reaction of **64** with methyl 2,3,4 tri-*O*-acyl α -*D*-glucopyranoside yields only the α (*cis*) anomer. The same anomeric selectivity is observed with the aglycone butanol and 2,2,2,-trifluoroethanol respectively. The β selectivity observed conforms to the mechanism proposed in *Scheme 57*. The α selectivity is considered to be as a result of the nitrile anchoring *via* a hydrogen bond to the acceptors hydroxide group through the hydrogen atom. Which then allows the oxygen to attack the oxocarbenium ion from the α orientation, as outlined in *Scheme 58*.

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Scheme 58. Xue-Wei Liu's neighbouring ortho cyanobenzyl group for cis synthesis (68).

The hypothesis was supported by the observed reaction of the nitrilium ion **64b** with 2-chlorobenzoic acid, trapping the nitrilium ion as its corresponding imideate **65** solely in the α conformer, outlined in *Scheme 59*:



Scheme 59. Xue-Wei Liu's supporting reaction (68).

Computational results suggest that the eight membered nitrilium ring **64b** could be favoured over the direct β glycosylation intermediate by 13.37 kJ mol⁻¹, both of which were found to be more favoured than the free oxocarbenium ion **64a** by 7.37 kJ mol⁻¹ (68).

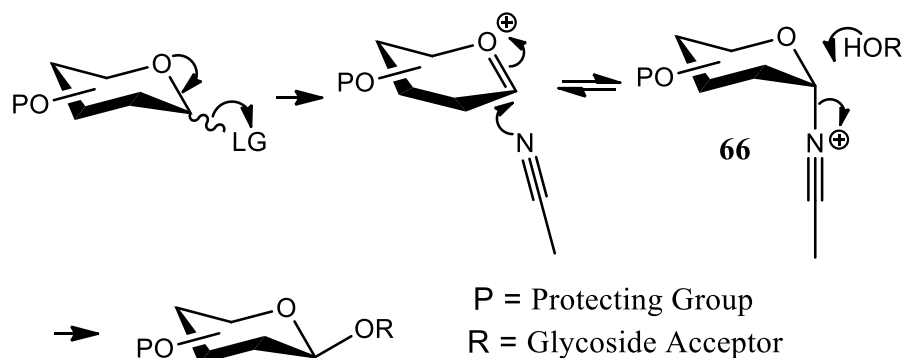
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1.2.2. Environmental effects

It is possible to control the stereochemical outcome of a glycosylation reaction by manipulating the environment in which the reaction is performed. Two examples of this can be by either changing the solvent or adding a chiral auxiliary to the reaction medium. Modifying the catalyst can also effect the stereo outcome of a glycoside bond.

1.2.2.1. Solvent Effects

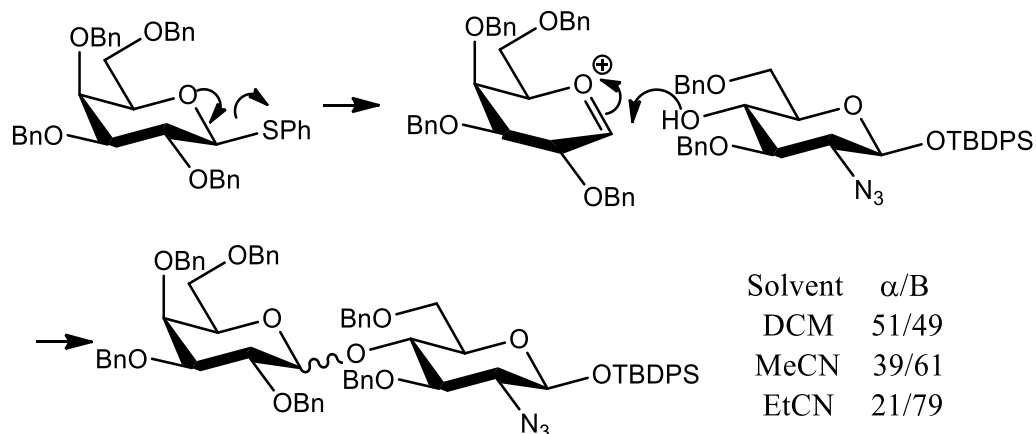
The solvent effect, or sometimes referred to as the nitrile effect, originated from the use of acetonitrile as a solvent for a glycosylation reaction. The acetonitrile acts upon the oxocarbenium ion in the α orientation, **66**, during which, the acceptor can only approach the anomer from the β face. As briefly mentioned in 1.1.1. Anomeric Halides, *Scheme 17*. The nitrile forms a nitrilium ion on reaction with the oxocarbenium species and the resulting intermediate vastly predominates in the α configuration. This means that the acceptor attacks chelated species **66** at the equatorial position to give the β glycoside.



Scheme 60. The nitrile effect (9).

It would therefore be realistic to assume that having more electron donating ability within the solvent molecule could lead to a greater nitrile effect, and more of the final glycoside product would be formed in the β conformation. Nakahara and Hojo published a series of directly comparable reactions in methylene chloride, acetonitrile and propionitrile as solvents, showing a respective increase in β glycosylation (*Scheme 61*) (69) as the electron donating ability of the solvent increased.

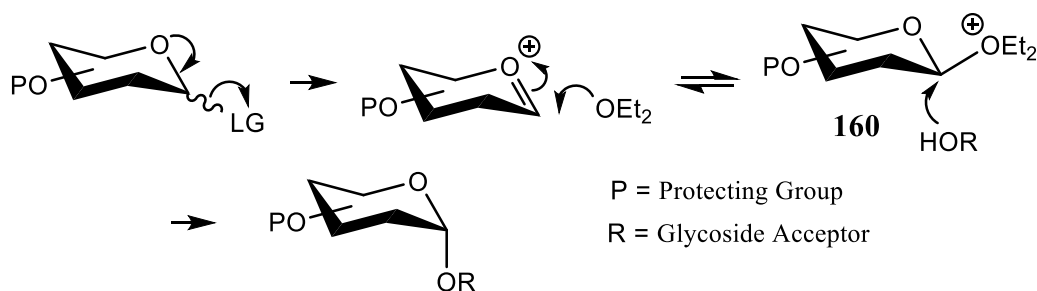
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Scheme 61. A comparison of the solvent effect on glycosylation stereochemistry.

The reaction explored was that of a 1-benzenesulfinyl piperidine trifluoromethanesulfonic anhydride 2,4,6-tri-*tert*butylpyrimidine (BSP-Tf₂O-TTBP) promoted (70) glycosylation of a tetra benzyl phenyl thio galactoside with no participating group at the C2. The results clearly show a direct correlation between increasing the electron donating ability of the solvent and β selectivity.

Hashimoto published a more in-depth table comparing glycosylation reactions performed in acetonitrile or diethyl ether, however this time the solvent interaction of diethyl ether acted upon the oxocarbenium in an opposite manner (71) (*Scheme 62*).

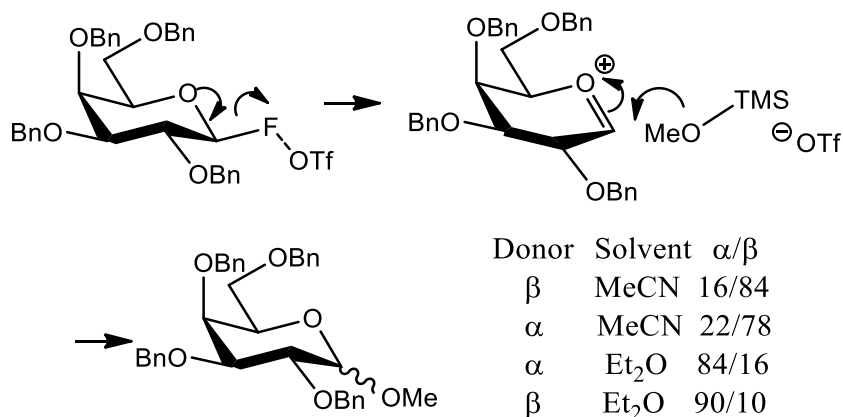


Scheme 62. Solvent effect of diethyl ether.

Their reaction was a modification of the Koenigs–Knorr reaction in which the donor was a 2,3,4,6-tetra-*O*-benzyl glycoside fluoride and trimethyl silyl methoxide as the acceptor, promoted by TMSOTf. They directly compared the same reactions in acetonitrile and diethyl ether. As well as other reactions and coupling reactions. As outlined in *Scheme 63*, α selectivity was observed to be favoured when the glycosylation reaction was performed in diethyl ether

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compared to acetonitrile which favoured the β anomer (71).



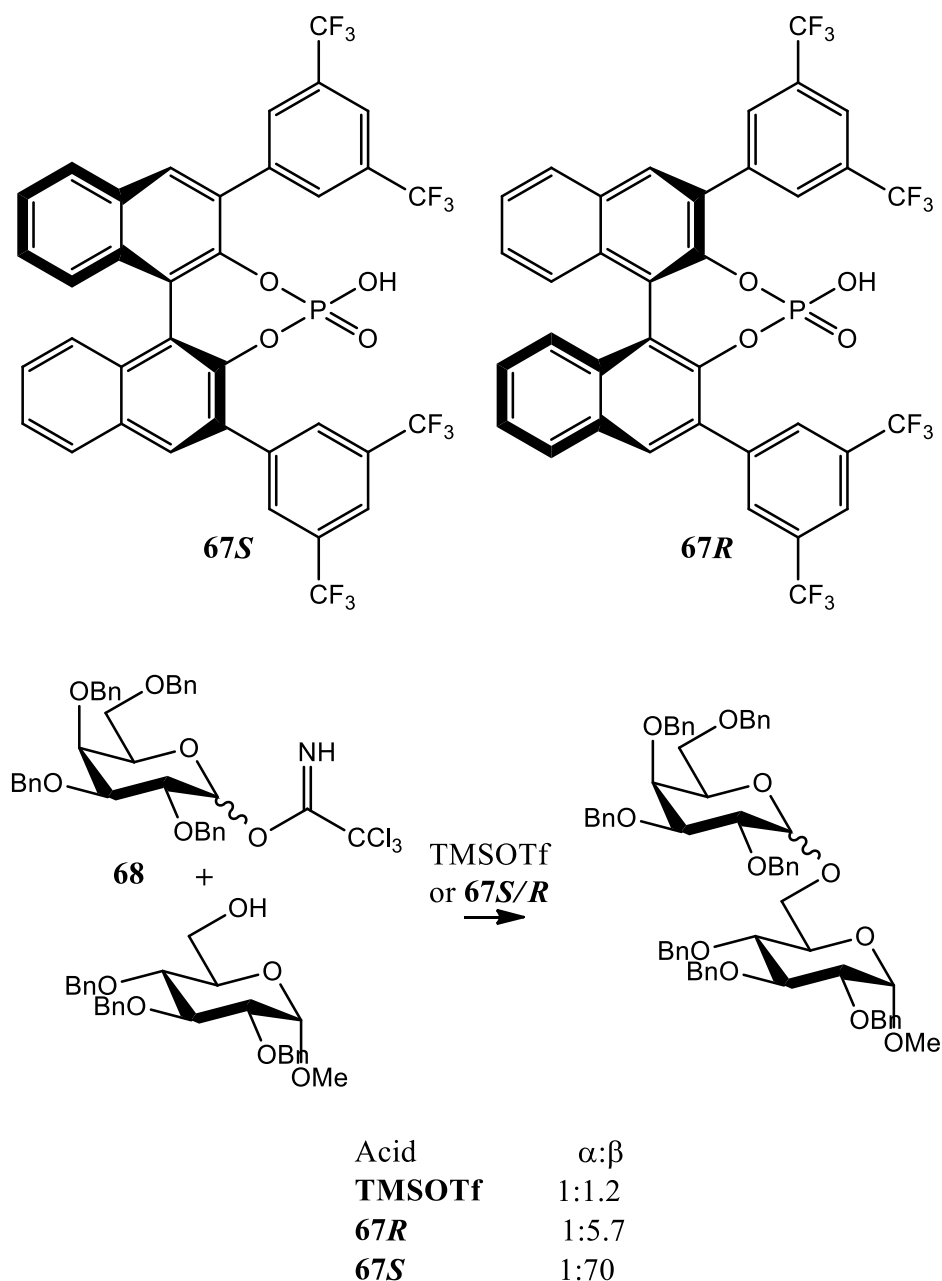
Scheme 63. Nitration vs Ether effect (71).

1.2.2.2. Chiral Auxiliaries & Asymmetric Catalysis

An interesting approach to stereocontrolled glycosylation is the development of a chiral catalyst that is both capable of activating the donor and chelating, and therefore directing the acceptor. Trichloroacetimidate donors are particularly useful for this kind of glycosylation system (see *Scheme 30*) due to the acetamides ability to coordinate through its nitrogen atom (9) (45).

An obvious experiment to test whether stereocontrol of the glycoside bond is possible by manipulation of the activating agent is the use of chiral acids. Fairbanks published a study on the effect of chiral acids as activating agents for trichloroacetimidates. The acid used was (11 β S)-2,6-bis (3,5-bis(trifluoromethyl)phenyl)-4-hydroxydinaphtho [2,1-d:1',2'-f] [1,3,2] dioxaphosphepine 4-oxide as **67S/R** enantiomers. A galactoside trichloroacetimidate donor, **68**, was used with a 6-hydroxyglucosyl acceptor, comparing the standard TMSOTf activation with the **67S/R** enantiomers of the phosphoric acids, as outlined in *Scheme 64*.

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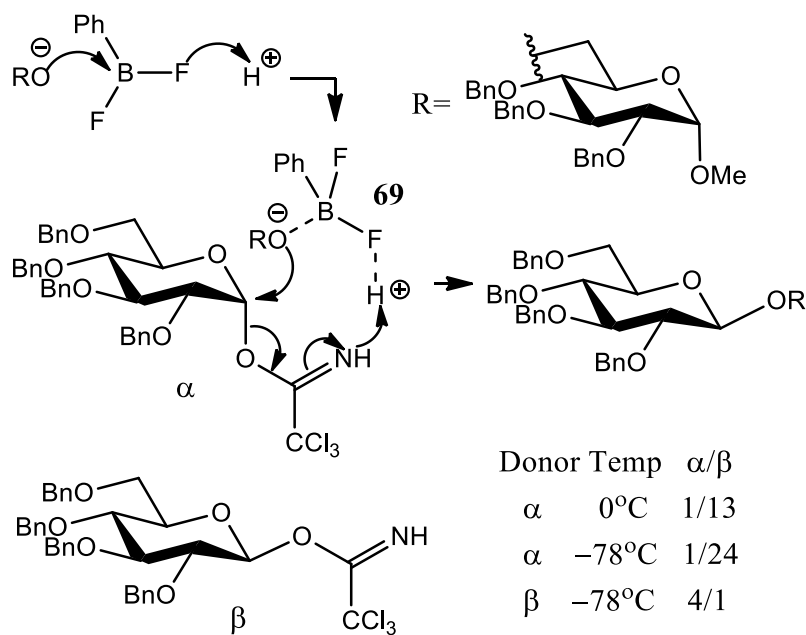
Scheme 64. Fairbanks' chiral phosphoric acid glycosylation (72).

Their findings showed that the two enantiomers did not show opposite anomeric selectivity, rather the *S* enantiomer showed slightly greater selectivity than the *R* enantiomer, with both favouring the formation of the β anomer. Nevertheless, the chirality of the activating agent did affect the anomeric outcome of the glycosylation (72).

A year later Schmidt reported the use of difluoro(phenyl)borane as a promoter for trichloroacetimidates that directed the acceptor into the *trans* position, as outlined in Scheme

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65.



Scheme 65. Schmidt's difluoro(phenyl)borane activator (73).

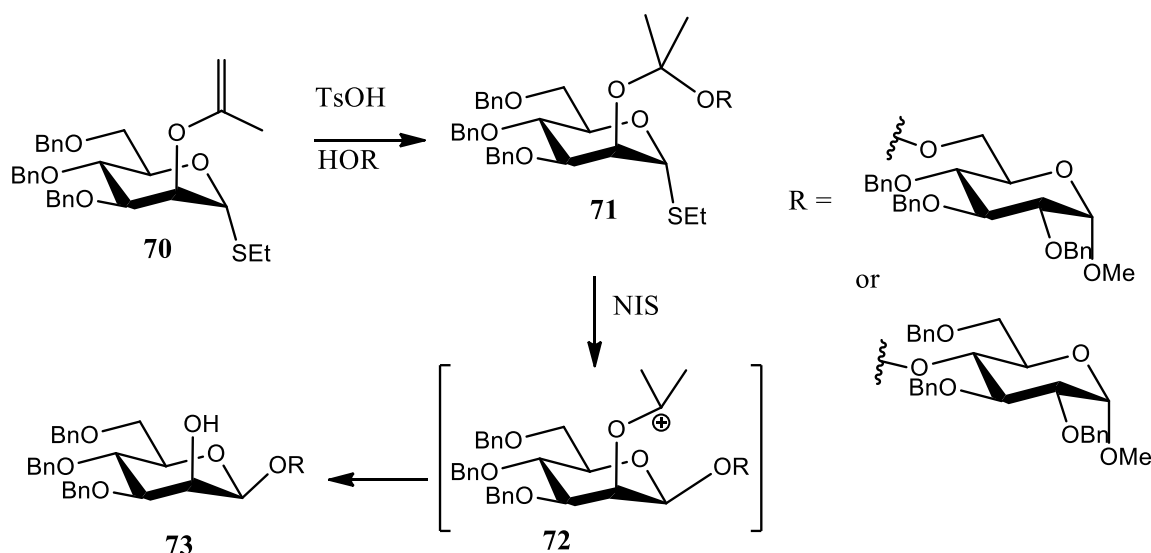
The difluoro(phenyl)borane forms an adduct with the glycoside acceptor, **69**, which then activates the trichloroacetimidate and delivers the glycoside acceptor to the anomer inverting the stereochemistry of the donor in an S_N2 -type reaction. Their results showed significant stereoselectivity when compared with the more traditional methods of activation and the stereoselectivity increased with lower temperatures suggesting that less of the oxocarbenium ion, in the S_N1 type reaction, is formed (73).

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1.2.3. Intramolecular Glycoside Bond Formation

Intramolecular aglycone delivery, is a method of synthesising a glycoside bond by temporary attachment of an acceptor to a donor by means other than a glycoside bond. Migration of the acceptor to the anomeric position then occurs in a controlled manner to effect glycosylation. The method was applied to glycoside synthesis with the belief that using the other substituents to ‘deliver’ the aglycone to the anomer via a cyclic intermediate could control the stereochemistry of the glycoside bond formed.

One of the earliest examples of intramolecular aglycone delivery was developed by Barresi and Hindsgaul in 1994 (74). Their research provided the basis for further investigation into the use of temporary tethers to control stereoselective glycosylation.

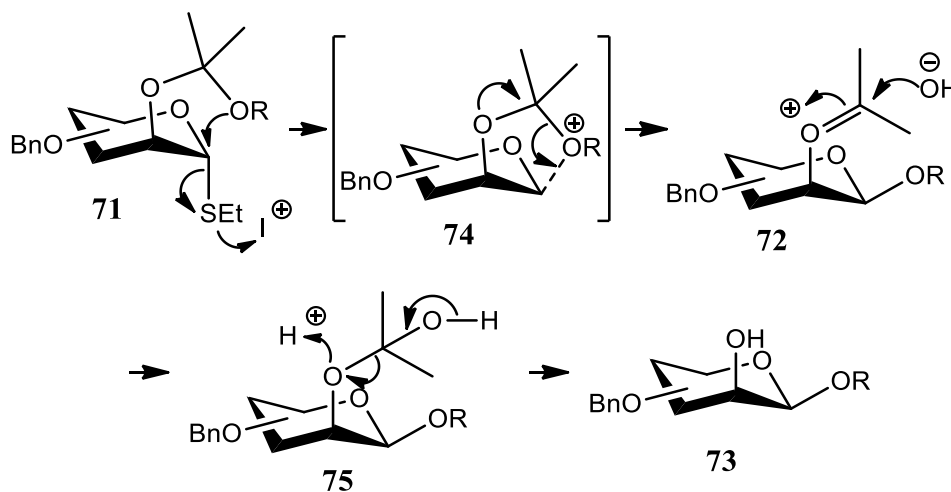


Scheme 66. Hindsgaul's intramolecular aglycone delivery (74).

This method uses a carbon tethering system, which proceeds via toluene sulphonic acid activation of C2 glycosidic isopropylene **70**, outlined in *Scheme 66*, to give the tethered system **71**. NIS promoted glycosylation then proceeded via the proposed intermediate **72** to give, after aqueous workup, disaccharide **73** as the β anomer. Hindsgaul has suggested that the mechanism is a concerted process rather than a stepwise one which involve the classical oxonium ion associated with standard glycosylation chemistry. Thus activation of donor **71** is accompanied by simultaneous migration of the tethered acceptor to produce cyclic intermediate **74** which then collapses to form disaccharide precursor **72**. Finally, hydrolysis of **72** produces

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disaccharide **73** via intermediate **75** (*Scheme 67*).



Scheme 67. Hindsgaul's mechanism of intramolecular aglycone delivery (74).

They reported unoptimised reaction yields of up to 61% with six equivalents of NIS (74). More importantly however they laid out a series of optimisation targets involving study of the tethering system, the donor type and the method of activation, all of which should lead to an important methodological addition to asymmetric glycosylation. This seminal paper initiated a major research effort into intramolecular aglycone delivery, so much so that we can divide the methodology into three main categories based on the type of aglycone delivery system. These are:

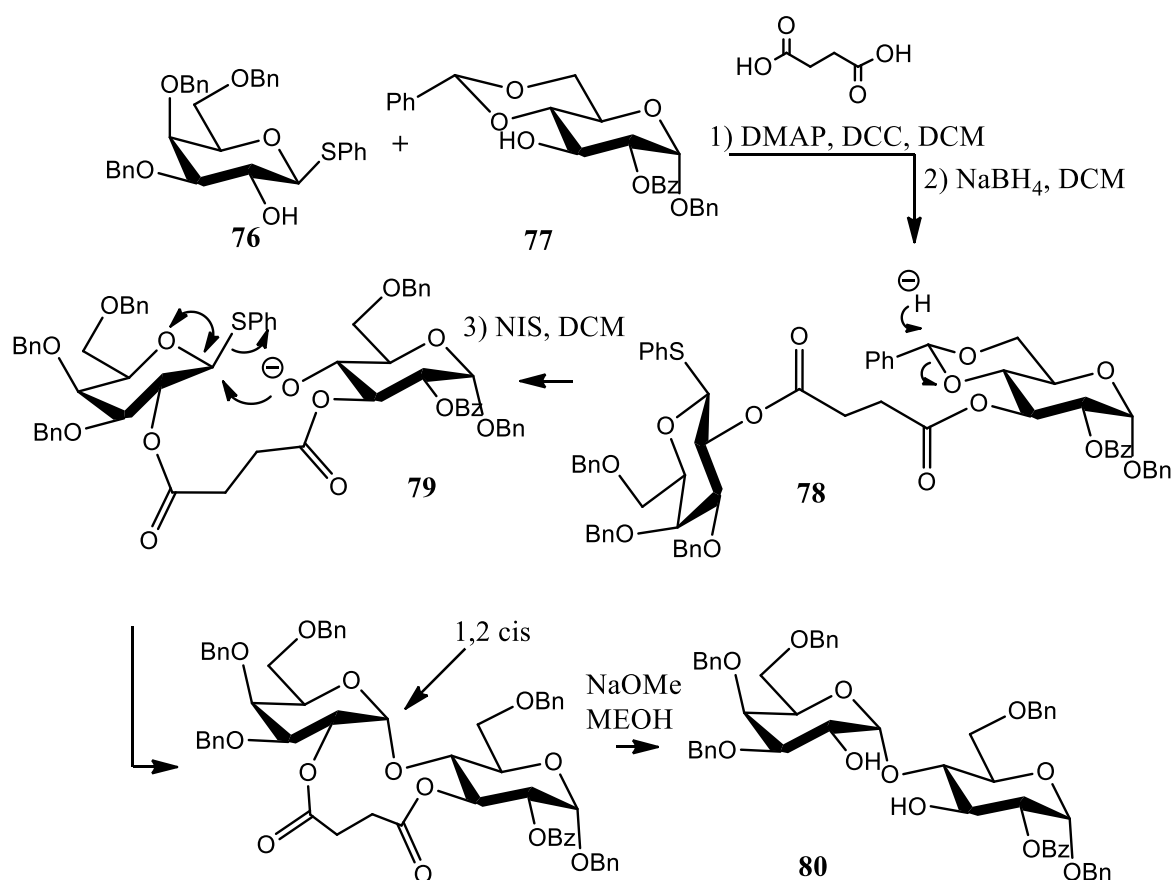
- I.** Neighbouring group participation (as mentioned above and the key part of our study) and intramolecular delivery
- II.** Spacer-mediated
- III.** Leaving group self-displacement.

1.2.3.1. Spacer-mediated

Spacer-mediated glycosylation, outlined in *Scheme 68*, involves the delivery of the acceptor to the anomeric position from a linker that attaches to both the acceptor and donor. The glycoside acceptor can bind onto a spacer moiety already arranged on the glycoside donor,

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then migrate to the anomeric position upon activation, leaving the spacer intact. In other words, the cyclic arrangement of the acceptor and donor is isolable, and not just an intermediate. Ziegler et al describe a way of controlling the stereo selection of a 1,2,-*cis* glycoside bond between a galactoside donor and glucoside acceptor. The glucose acceptor **77** and the galacto donor **76** both react with butan-dioic acid, in the presence of the coupling agent DCC to generate the tethered dimer. The benzylidene is then reduced to a C6 benzyl ether **78**, leaving the C4-hydroxyl free, which attacks the oxocarbenium ion upon activation of the thiol **79**, as outlined in *Scheme 68* (75).



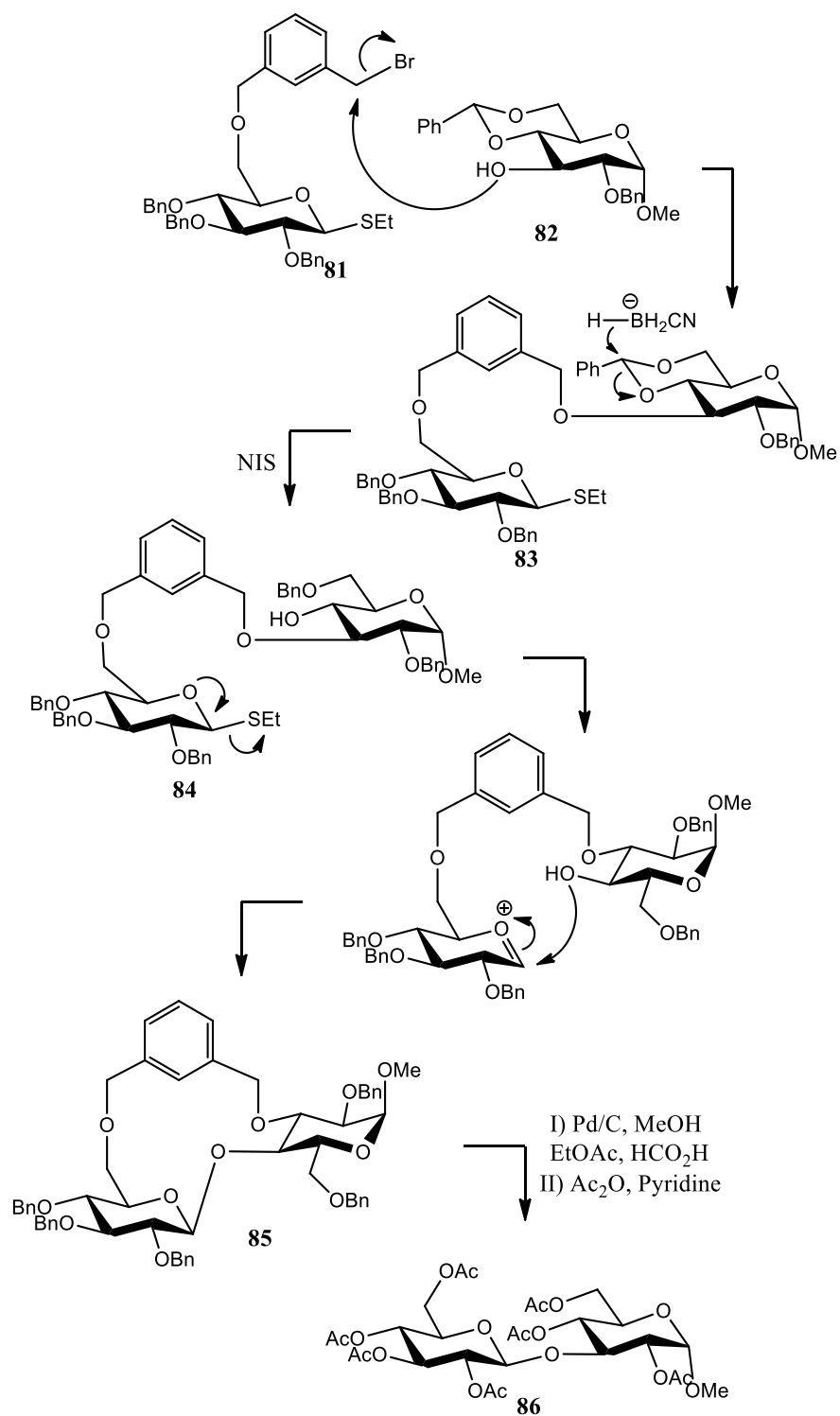
Scheme 68. Ziegler's spacer mediated 1,2-cis glycoside bond formation (75).

An eleven membered glycosidic ring was isolated, which spans the 1,2 positions (in a *cis* configuration) of the donor, and the 3,4 positions of the acceptor. The di-ester spacer can then be hydrolysed, to yield the disaccharide **80** connected only by the resulting glycoside bond. Similar to this spacer mediated intramolecular aglycone delivery, the “rigid spacer glycosylation” was a method proposed by Schmidt in 1998 (76) (*Scheme 69*), whereby the

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spacer is attached to the C6 position of the donor as a meta substituted bromo di-benzyl functionality **81**. As with Ziegler's approach, Schmidt attached the donor through the C3-OH of monosaccharide **82** to give linked system **83**. Reduction of the benzylidene protecting group in **83** gave the linked donor/acceptor pair **84** which, under standard glycosylation conditions produced disaccharide **85** as the β anomer. Finally, hydrogenolysis of all the remaining protecting groups and acylation of the hydroxyls furnished disaccharide **86** (*Scheme 69*).

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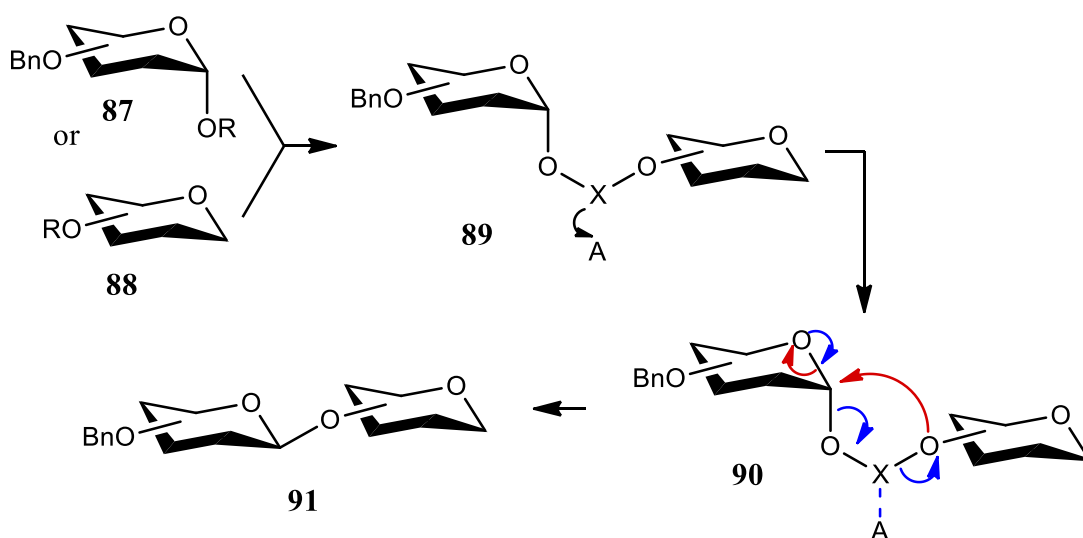


Scheme 69. The rigid spacer glycosylation (76).

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1.2.3.2. 'Self-displacing' glycosylation

A further introduction to the area of intramolecular aglycone delivery was the development of the 'self-displacing' leaving group. In this approach the acceptor is linked to the anomeric hydroxyl group by means of a temporary tether which can then be activated to initiate a glycosylation similar in approach to intramolecular aglycone delivery. The main difference is that the tether is also acting as the leaving group, hence the self-displacement terminology. This method has not shown any level of stereocontrol yet, but it is still relevant as a concept and its further development could lead to the ability to deliver a 1,2-*cis* glycoside synthesis (77).



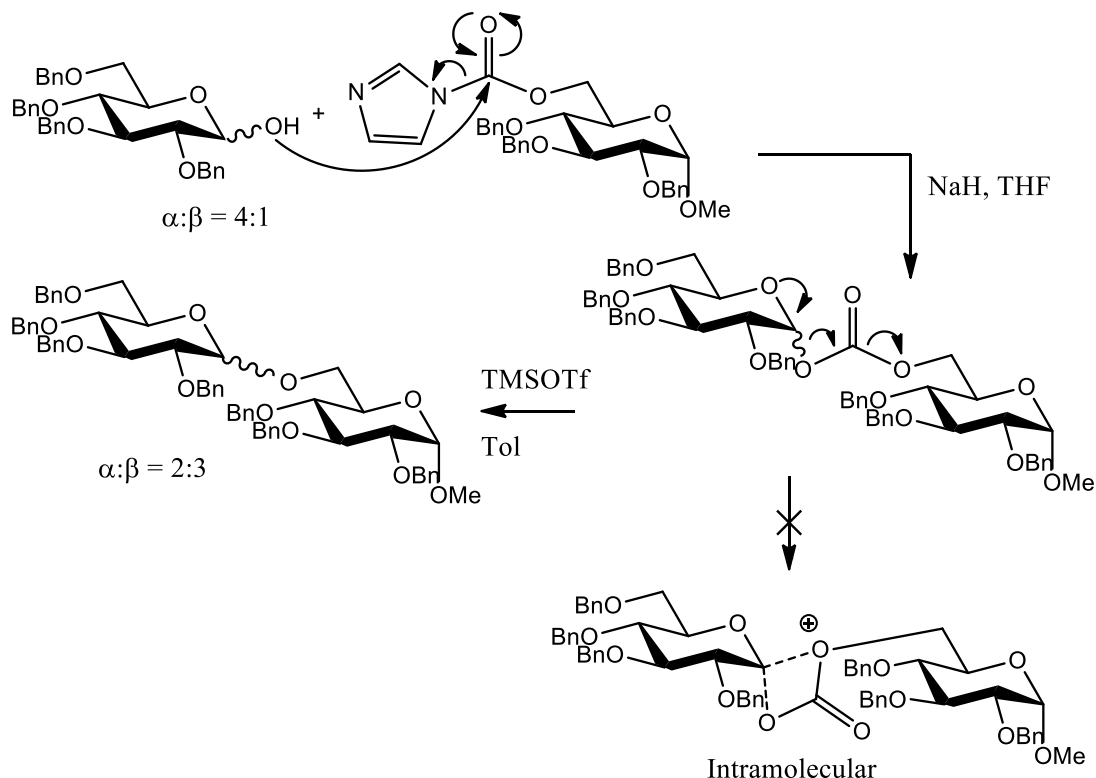
Scheme 70. 'Self-displacing' glycosylation.

Scheme 70 describes the generic approach to leaving group self-displacement glycosylation. In this example the tether is placed at the anomeric position of donor **87**, with the acceptor **88** having a free hydroxyl group, although it should be noted that methodology utilising a 'role reversal' is also possible. A coupling reaction between **87** and **88** produces linked disaccharide **89** which, following activation via intermediate **90**, produces disaccharide **91**. It has been proposed that the mechanism of glycosylation is concerted in nature and therefore, as shown for **90**, the ' α tether' should produce the β disaccharide in a stereocontrolled manner.

The reactions of carbonic tethers, described by Schmidt in 1997 (78), has however

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challenged this theory, Schmidt investigated the reactions of decarboxylative anomeric tether whereby the delivery of the glycoside bond could either proceed intramolecularly, or intermolecularly, from an anomeric carbonic tether, as *Scheme 71* outlines.



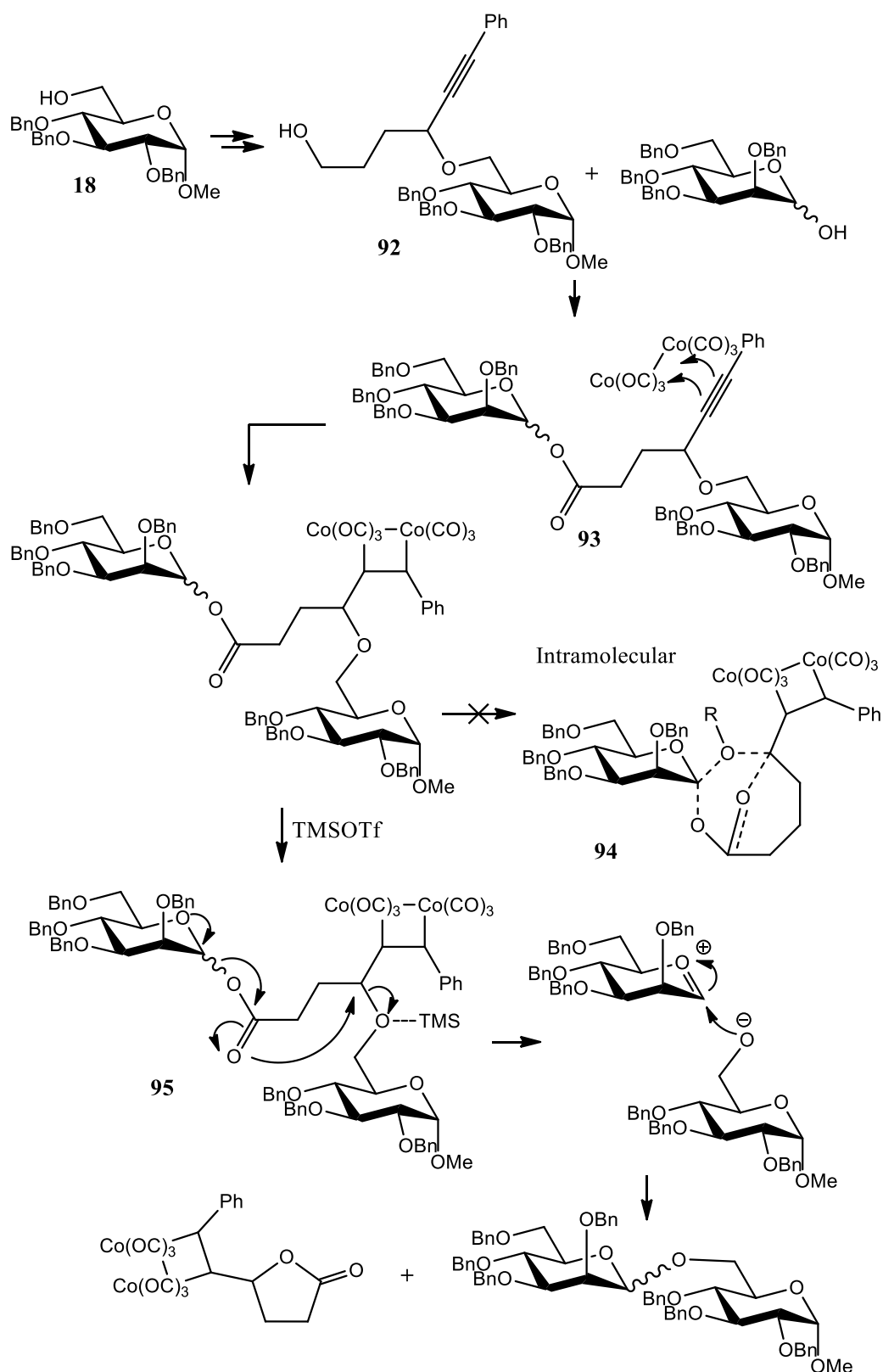
Scheme 71. Schmidt's attempt at a 'self-displacing' glycosylation.

The results of this study were inconclusive, although Schmidt did suggest that glycosylation could be occurring through competing inter and intramolecular pathways and concluded that further research on the reaction could lead to a controlled intramolecular reaction.

Mukai and Hanaokas have also investigated the self-displacement approach based on a cobalt mediated glycosylation as shown in Scheme 72. Their reaction takes advantage of the fact that complexation of dicobalt hexacarbonyl to alkynes produces a species capable of stabilising an adjacent carbocation. Thus acceptor **18** was converted, in a series of steps, into alkynyl glycoside **92** which was subsequently transformed into tethered disaccharide **93**. It was expected that TMS triflate promoted glycosylation should proceed, with concomitant lactonisation, via the bicyclic intermediate **94** to deliver a β mannoside. However, it appears

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that the reaction again proceeds intermolecularly as suggested by structure **95** which simply leads to a classical donor/acceptor pair that couple to produce the disaccharide as a mixture of anomers [76].

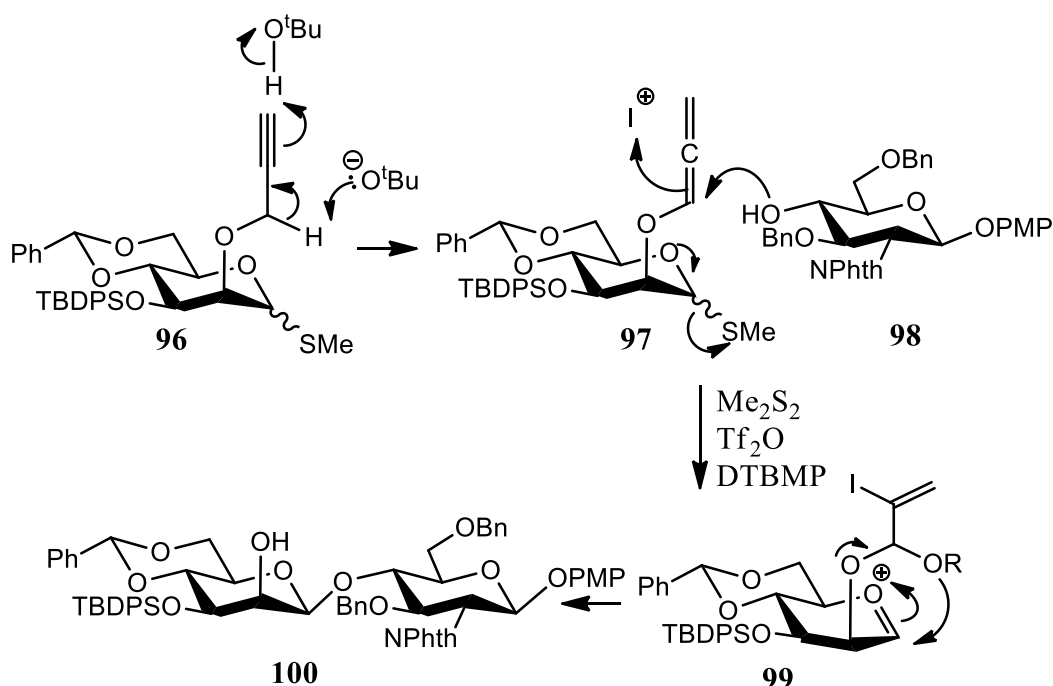


Scheme 72. Mukai and Hanaoka's alkyne – cobalt glycosylation [76].

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1.2.3.3. Intramolecular Delivery

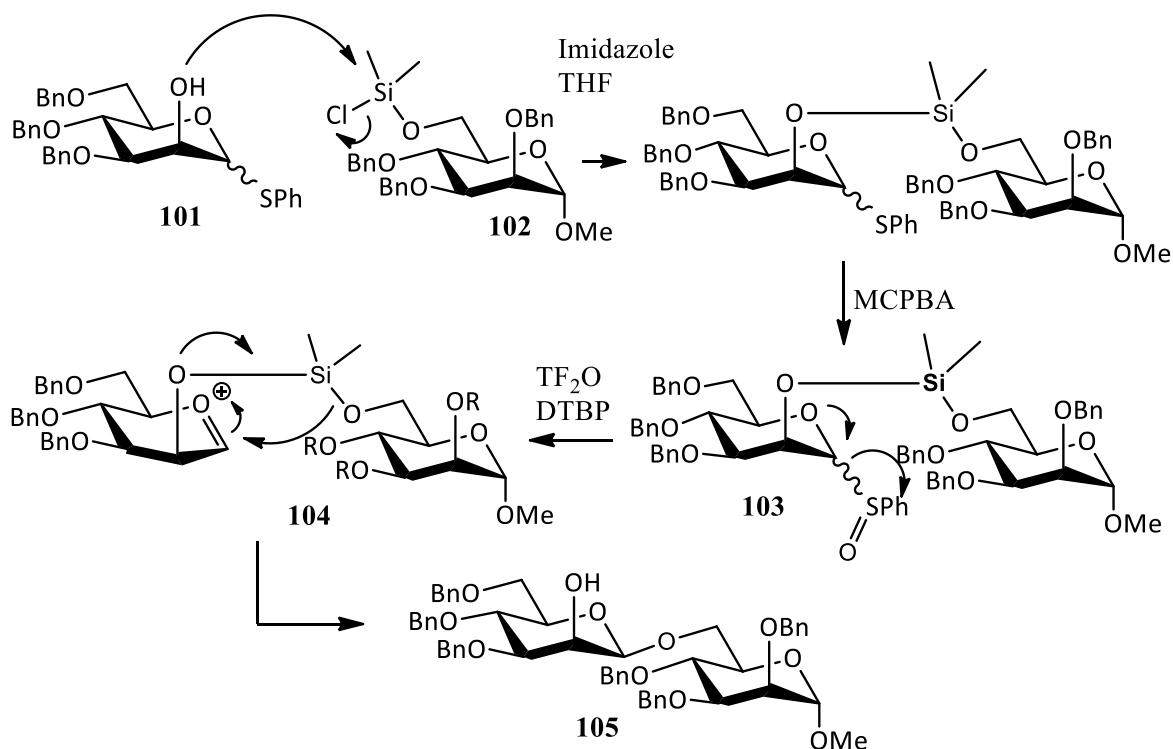
Fairbanks has developed a notable carbon tethering aglycone delivery system, as outlined in *Scheme 73*. Their method, of propargyl mediated intramolecular aglycone delivery [77] proceeds via treatment of the C2 propargyl ether of glycoside **96** with potassium tert butoxide to form the allene **97**. Coupling of **97** with acceptor **98** using an iodonium source gave the tethered dimer **99** which, under standard glycosylation conditions, gave disaccharide **100** exclusively as the β anomer in an excellent yield of 81%.



Scheme 73. Propargyl mediated intramolecular aglycone delivery (79).

Other aglycone delivery systems arise in the literature that do not proceed through the use of a carbon tether. Stork developed an intramolecular delivery system that implemented a silicon tether (80). as outlined in *Scheme 74*. This reaction proceeds *via* a temporary silyl tether that is generated between **101** and **102** to give a tethered dimer. Oxidation with *m*CPBA of the thioether leaving group to yield sulfoxide **103** which was allowed the oxocarbenium ion formation from triflic anhydride and 2,6-di-*tert*-butylpyridine activation of leaving group to give **104**, the temporary silyl tether is then cleaved with an aqueous work up to yield **105**. Glycosylation was achieved with full stereo-selection, in yields of up to 68% (80).

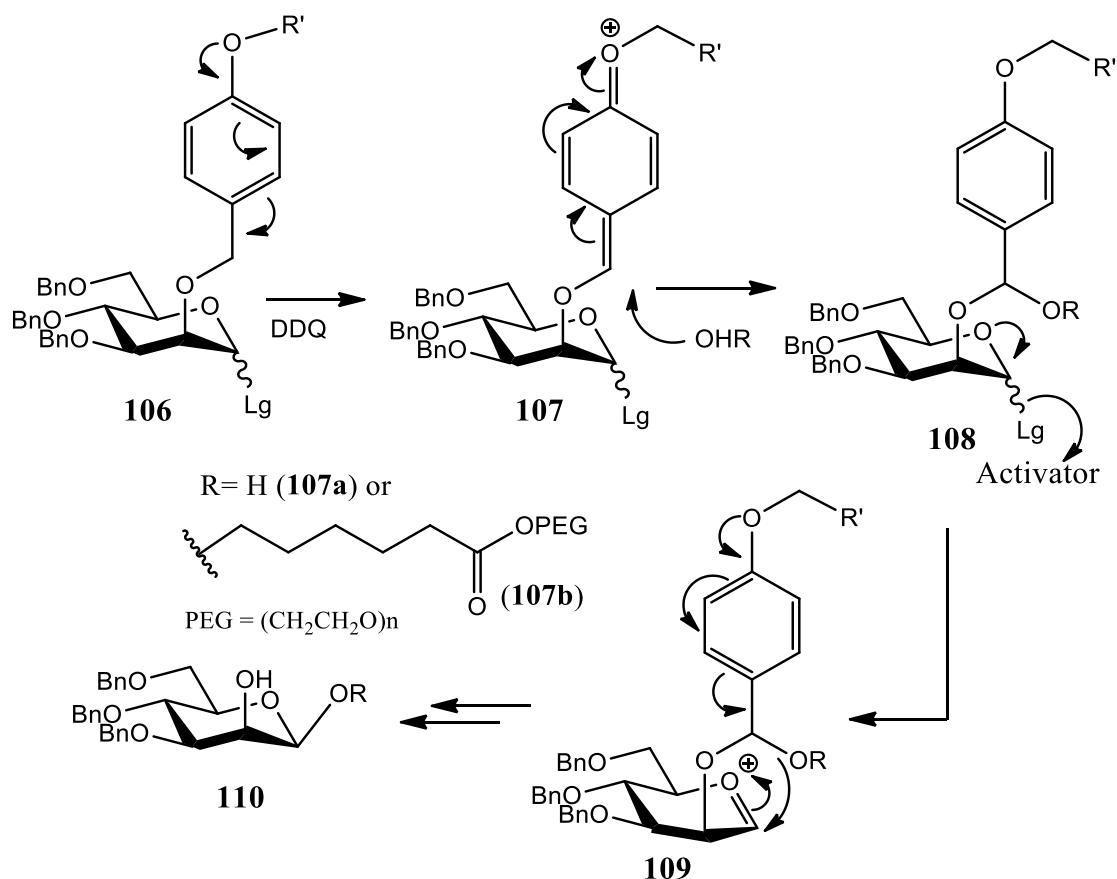
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Scheme 74. Intramolecular aglycone delivery via a temporary dimethyl silyl tether (80).

Ogawa proposed a method of aglycone delivery in the synthesis of β mannosides that utilised the DDQ activation of a donor C2 *para*-methoxy benzyl (PMB) group. It is possible to oxidise the PMB group of donor **106** to the corresponding oxonium ion **107** which is then trapped with an alcohol to give mixed acetal **108**. Upon activation of the leaving group a now familiar intramolecular aglycone delivery occurs to give disaccharide **110** via intermediate **109** (*Scheme 75*) (81) (82).

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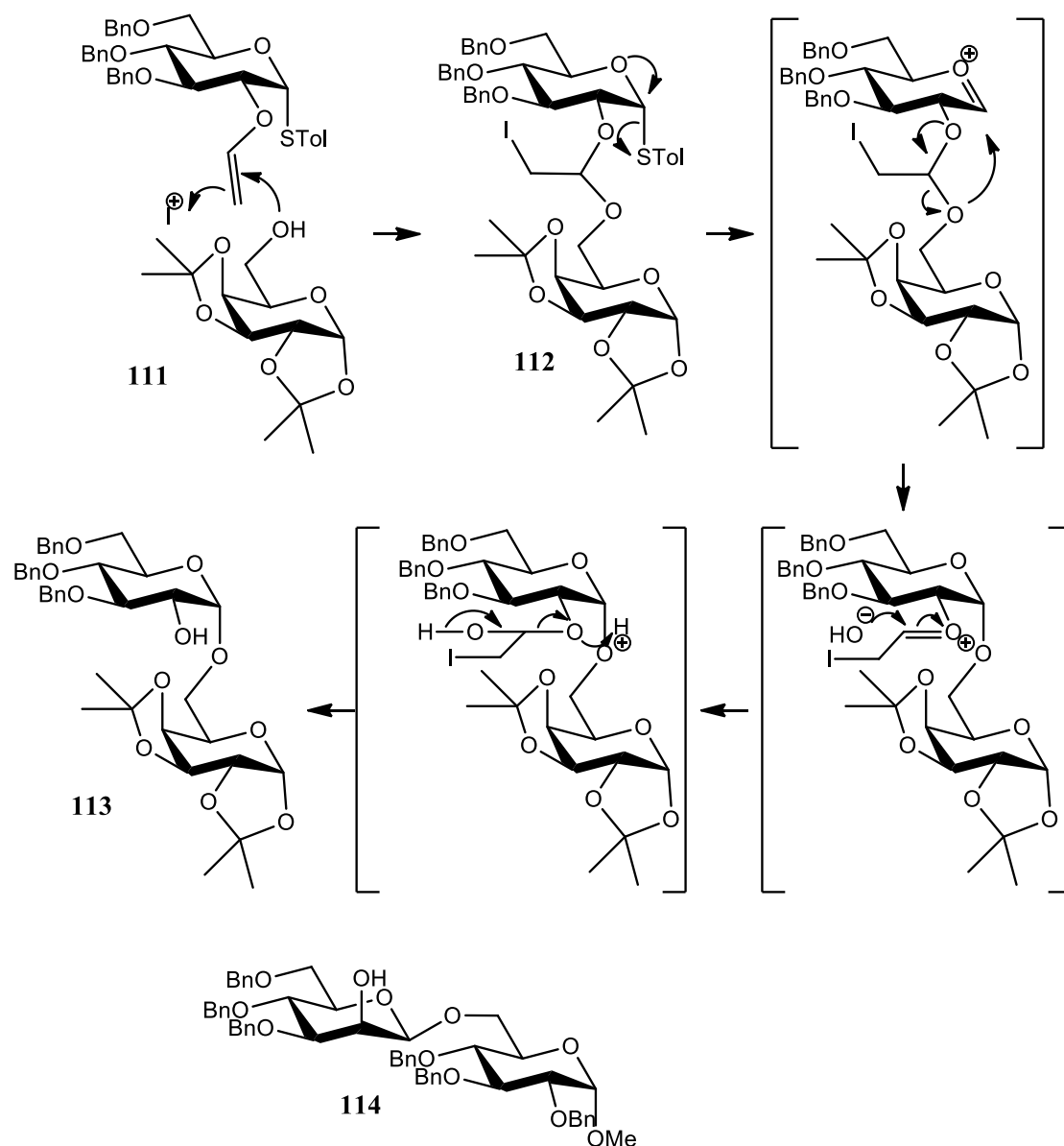


Scheme 75. Ogawa's PMB/para benzyl O-linked polymer aglycone delivery[80].

Problems however have been reported due to the lability of mix acetal **108** which have resulted in excessive hydrolysis. Ogawa has, in part, resolved these issues by utilising a polymer supported system (see **107b**) which simplifies the purification of any acetal intermediates [80].

Fairbanks developed a notable intramolecular aglycone delivery (IAD) system as an advancement of Hindsgaulls IAD (*Scheme 66*). They utilised a neighbouring ethylene group, which was then reacted with NIS and the acceptor **111** to yield the donor – acceptor dimer **112**. Final activation of the donor with AgOTf allowed the acceptor to migrate into the anomer in a stereocontrolled orientation.

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Scheme 76. Fairbanks' ethylene mediated IAD.

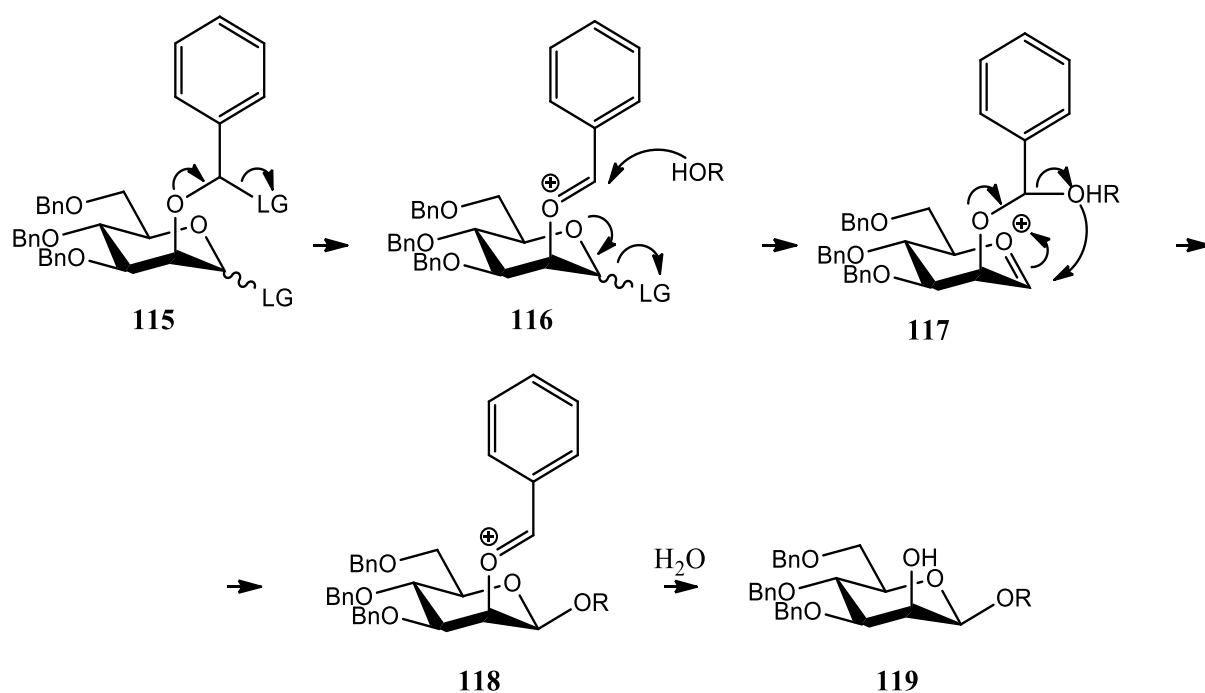
They reported a 52% yield of **113** as the α anomer. Within their study, they surveyed other donor and acceptor systems the best result with a mannose donor, similarly protected and reacting with the glucose acceptor **18** in the synthesis of disaccharide **114** to produce 79% of the β anomer.

2. Results and Discussion

2. Results and Discussion

2.0. Aims

As has been pointed out in the preceding literature review there have been a number of attempts at controlling the stereochemistry of glycosylation and, more specifically, the control of the 1,2 *cis*-glycoside. Unfortunately, most of the examples suffer from drawbacks such as the rather cumbersome three-step tether approach of intramolecular aglycone delivery or have only met success within a limited substrate set. We envisioned the development of a general approach to asymmetric glycosylation through the use of a sacrificial protecting group that is capable of delivering the aglycone in a stereocontrolled manner *via* a mechanism that we are calling neighbouring group direction. As a key feature, asymmetric glycosylation would occur in one step rather than the two step tether and separate glycosylation strategy associated with IAD (*vide supra*).



Scheme 77. Proposed approach to a novel neighbouring group direction.

Scheme 77 outlines our general strategy in which monosaccharide **115** is protected at C-2 with a mixed acetal. The structure of the mixed acetal is notable in that it houses a leaving group (LG) identical to the anomeric donor group that will also be used to effect the glycosylation reaction. The principle behind this strategy then is, like the armed-disarmed effect, simply based on the differing rates of oxonium ion formation. Thus treatment of donor

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115 with two equivalents of activator would initially lead to the formation of the more stable benzylic oxonium species **116** (66) which would then immediately react with the aglycone to form a second mixed acetal **117**. The second equivalent of activator now acts on the anomeric donor to produce cyclic oxocarbenium species **118** which undergoes a familiar aglycone delivery to produce the 1,2 *cis* glycoside **119** in a highly controlled fashion. Thus, approach of the acceptor to the anomer and formation of the glycoside bond will be directed *via* the neighbouring oxocarbenium into a *cis* configuration. This new approach, if successful, would provide a novel approach to controlling the stereoselectivity of a glycoside bond, as a one-pot intramolecular aglycone delivery. At the outset we had assumed that the mixed acetal would act as a protecting group and, after participating in the glycosylation reaction would hydrolyse upon aqueous work-up of the reaction; hence the term ‘sacrificial’ protecting group.

It is possible to expand upon the initial idea, not only by using allylic acetals to provide added stability to the neighbouring oxocarbenium ion, but also alkyl or aryl ketals. Therefore, in addition to structure **115** we also proposed to study the mixed acetals and ketals **120** - **123** as shown in *Figure 6*.

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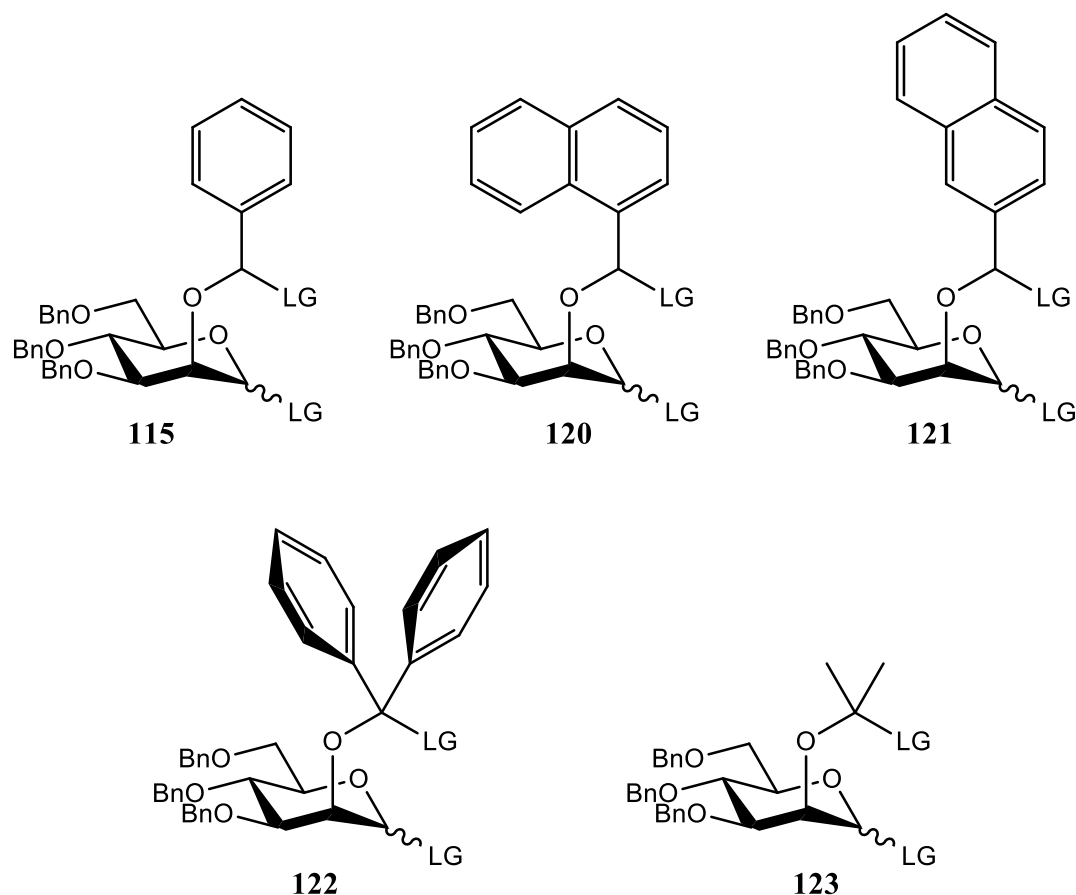


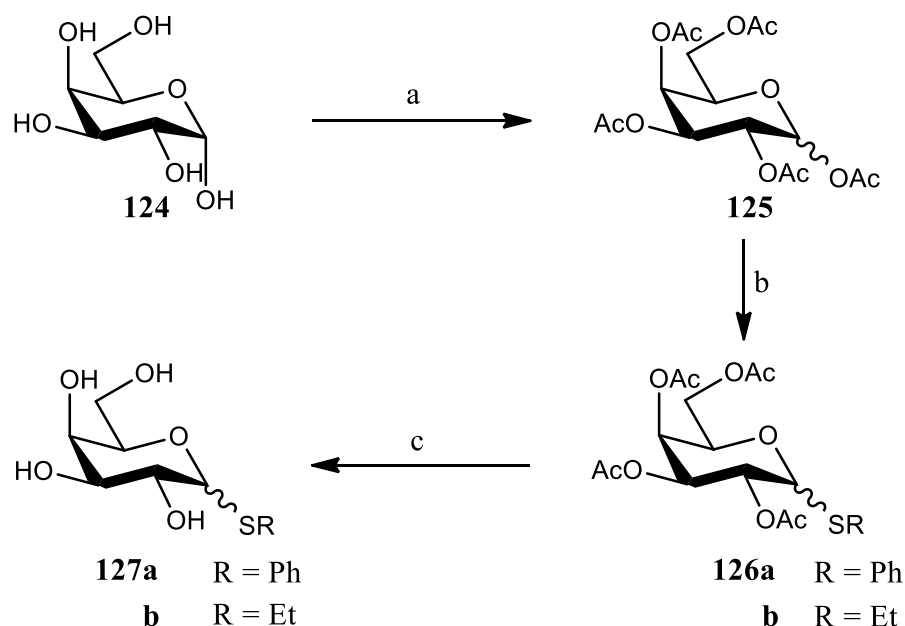
Figure 6. Additional targets for a sacrificial protecting group investigation.

2.1. Synthesis of Donors

2.1.1. Galactoside Donor

Our study required the synthesis of a partially protected glycoside donor, ideally a 3,4,6-tri-*O*-benzyl 2-hydroxy pyranoside, equipped with an anomeric leaving group. We initially decided that the most appropriate leaving group to prove our theory was that of a phenyl thioglycoside, as mentioned in Section 1.1.3 and also that we would target two separate donors based on galactose and mannose respectively. *Scheme 78* outlines our approach to the former of these two targets starting with α -D-galactopyranoside (**124**) which was acylated under standard conditions to give penta-acetate **125**.

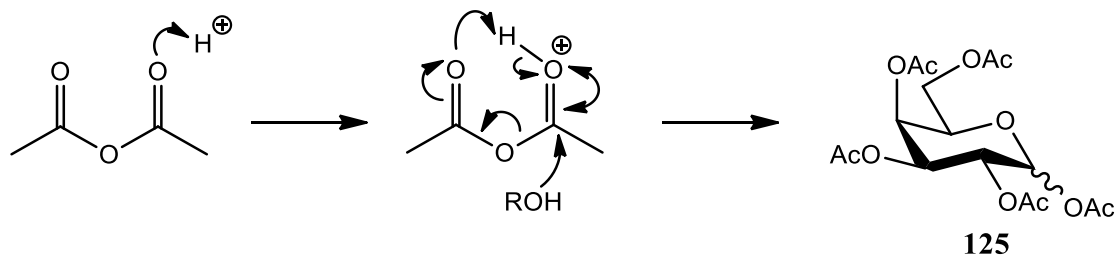
2. Results and Discussion



Scheme 78. Initial stages of galactoside donor synthesis.

a) Ac_2O , H_2SO_4 , r.t., 16 hrs. b) HSR, SnCl_4 , DCM, $0\text{ }^\circ\text{C}$ – r.t., 12 hrs. c) MeOH, NaOMe, $0\text{ }^\circ\text{C}$ – r.t., 36 hrs. (83) (84) (85) (86)

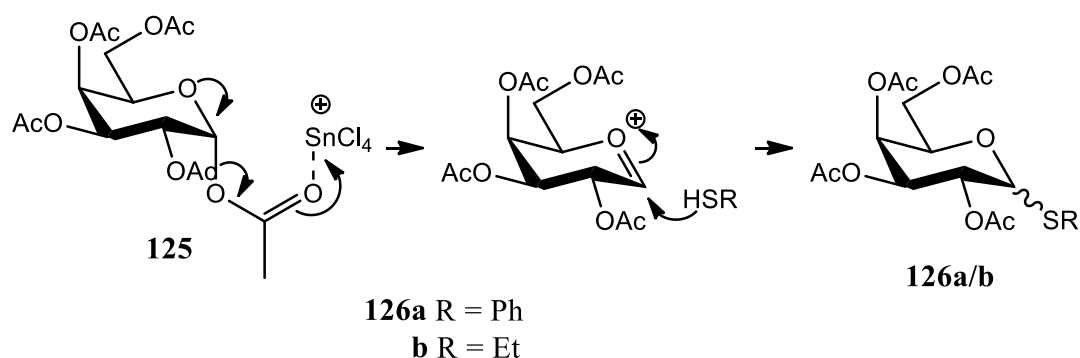
Acylation proved relatively straightforward and follows a nucleophilic acyl substitution mechanism as outlined in *Scheme 79*.



Scheme 79. Acylation of a hydroxide functional group.

The reaction is initiated by protonation of the carbonyl oxygen which renders the carbonyl group more susceptible to nucleophilic attack from the hydroxyl function. Proton transfer and regeneration of the acid catalyst then furnish the acylated product **125** which was purified by recrystallization. With the penta-acetate in hand we turned our attention to preparing the thioacetal which would be our donor in future coupling studies. Reaction of acetate **125** with thiophenol in the presence of tin (IV) chloride gave crude thioglycoside **126a** following the mechanistic pathway outlined in *Scheme 80*.

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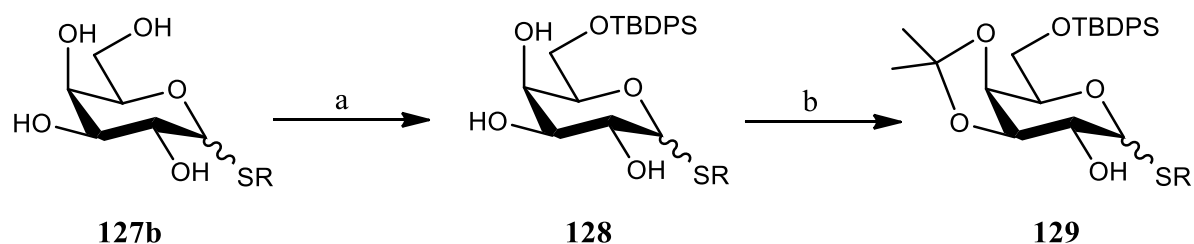


Scheme 80. Thioglycoside synthesis from the anomeric acetate.

Problems arose however when we attempted to purify **126a** since it co-eluted with the starting material when subjected to flash column chromatography. Attempts to solve this problem by utilising different column solvents or fractional recrystallisation proved unsuccessful so we decided to take the crude mixture and subject it to basic hydrolysis to give thioglycoside **127a** along with D-galactose (**124**). Unfortunately, we were still unable to effect purification and so we switched our attention to preparing the ethyl thioglycoside **127b**. Therefore, reaction of acetate **125** with ethanethiol, again using tin (IV) chloride, proceeded smoothly to give, after chromatography, ethyl thioglycoside **126b** in excellent yields. This tetra-acetate was then hydrolysed with a catalytic amount of sodium methoxide in methanol to give tetrol **127b**.

Scheme 81 now outlines the next stage in our synthesis to achieve a glycoside housed with a set of complementary protective groups. We began our synthesis with the chemoselective protection of the primary hydroxyl function using TBDPS chloride to give silyl protected monosaccharide **128** in an acceptable, though disappointing, yield of 62%. We then used the fact that the triol in **128** was arrayed to give both a 1,2 *trans* and a 1,2 *cis* diol embedded in the trihydroxy system which allowed the selective protection of the 3,4 (*cis*) diol as its acetonide to give the alcohol **129**.

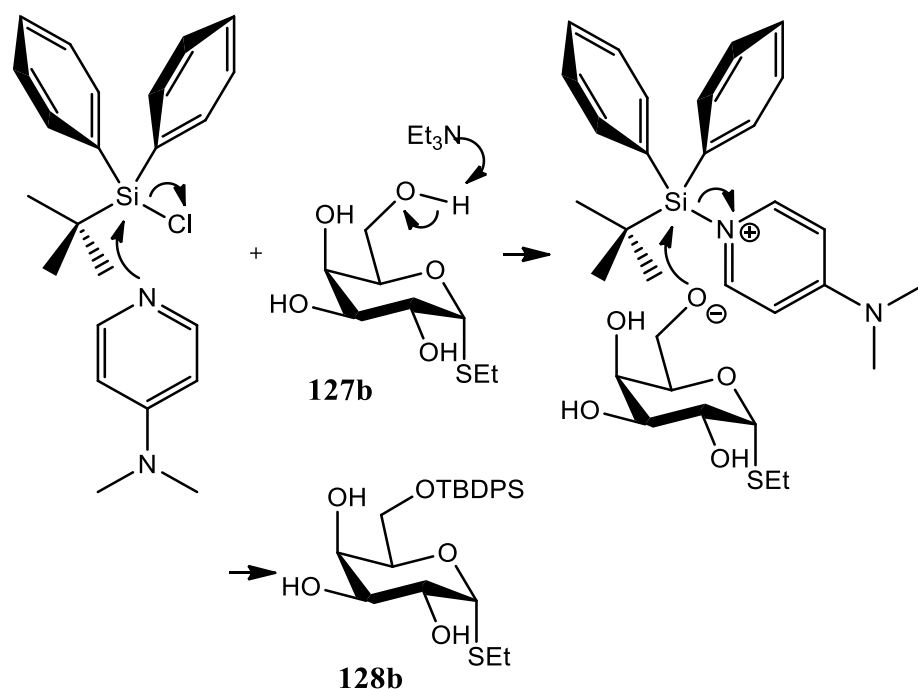
2. Results and Discussion



Scheme 81. Protective group manipulations on ethylthio galactose.

a) TBDPSCl, DMAP, DMF, r.t. – 40 °C, 36 hrs. b) Acetone, 2,2-Dimethoxy Propane, Camphorsulfonic acid, r.t., 2 hrs. (87) (88) (89).

It is interesting to note the relatively poor yield of the silylation of **127b** to produce triol **128** when these reactions usually proceed in high if not quantitative yields. *Scheme 82* below shows the accepted mechanism for silylation of a primary hydroxyl group with TBDPS chloride.

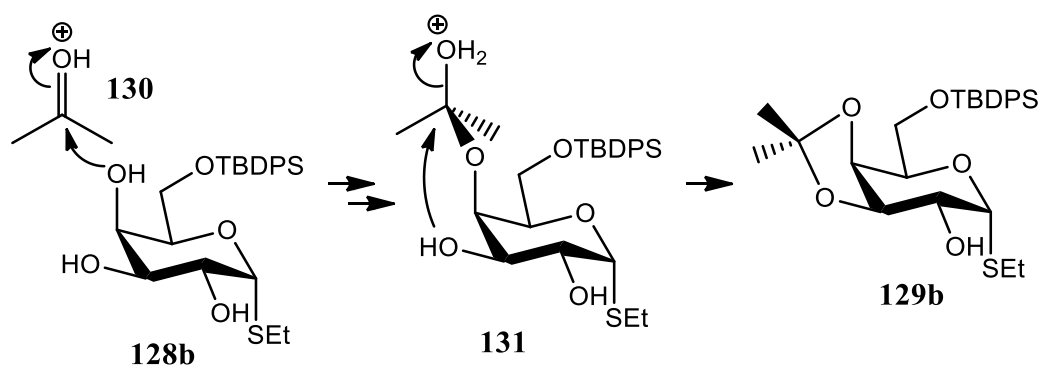


Scheme 82. Mechanism of the silyl ether formation.

Activation of the silyl protective group is achieved with DMAP to produce a salt-like intermediate. This sterically bulky substrate can only be approached by the less hindered primary alcohol of tetrol **127b** which, after deprotonation with triethyl amine gives protected species **128**. Our problems arose due to the insolubility of the starting material in DMF which meant that reaction proceeded at a prohibitively slow rate. On warming the reaction mixture

2. Results and Discussion

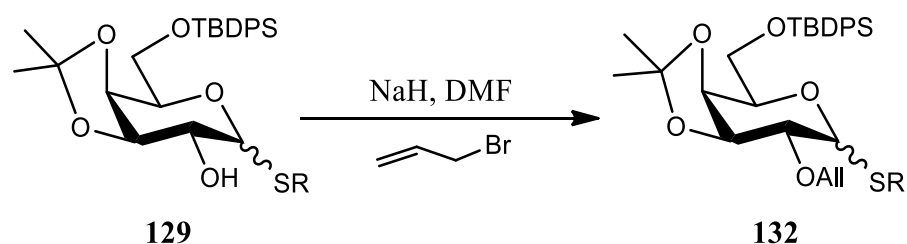
to 40 °C we found that dissolution of the starting material was facilitated and reaction was initiated. However, at these elevated temperatures, we found that protection of the C-4 hydroxyl group was a significant by product and we were therefore forced to monitor the reaction closely by tlc and accept a compromise yield where we quenched the reaction before full consumption of the starting material had occurred. Fortunately acetonide formation proceeded with no such issues to produce alcohol **129** as shown below (*Scheme 83*). In this instance the reaction is under thermodynamic control as opposed to the kinetics of silylation from the previous scheme. *Scheme 83* shows the reaction of triol **128** with oxonium species **130** to give mixed acetal **131**. It should be noted that acetal formation at all three hydroxyl groups is possible but for reasons of simplicity only the reaction at C-3 is shown.



Scheme 83. Formation of the isopropylidene ketal.

Mixed acetal **131** can then cyclise to give both the *trans* and *cis* fused bicyclic systems, however since the *trans* fused acetonide **129** is the more thermodynamically stable, it is the sole product of the reaction. Finally we required to protect the remaining hydroxyl of structure **129**, preferably with a protecting group that would be complementary to both the silyl and ketal protecting groups already in place. Our initial thought was to make the *para*-methoxybenzyl ether which is easily cleaved with DDQ to regenerate the alcohol. However the PMB chloride proved a difficult reagent to purify, and maintain in a pure state, due to its propensity to undergo ‘self-alkylation’. We turned our attention instead to the use of allyl bromide and effected a synthesis of fully protected monosaccharide **132** by treatment of alcohol **129** with sodium hydride and allyl bromide in DMF under standard conditions (*Scheme 84*).

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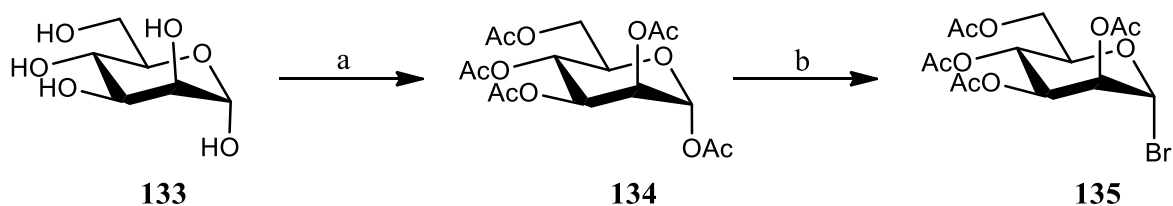
Scheme 84. Allylation of a secondary alcohol.

Although monosaccharide **132** was not our final target in terms of achieving a benzyl protected 2-hydroxyglycosyl donor, the protective group array in place meant that we could access our target easily. We therefore decided to turn our attention to the synthesis of a mannose analogue which would provide us with a second model for our neighbouring group directed glycosylation study.

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2.1.2. Ortho-ester

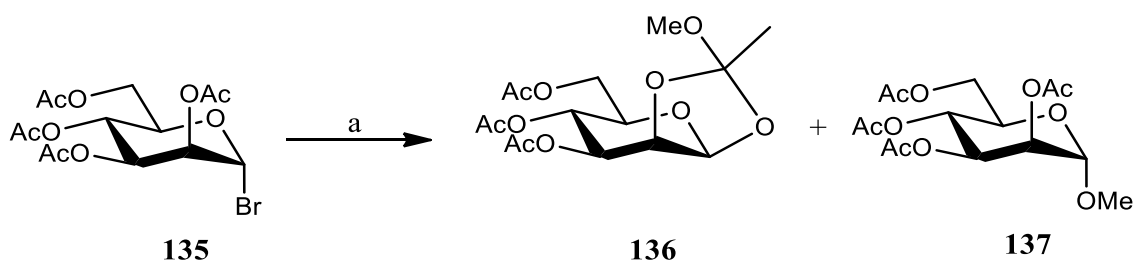
Scheme 85 shows the initial steps in our synthetic approach beginning with α -D-mannopyranoside (**133**) which was acylated under standard conditions to give the penta-acetate **134**. Reaction of the acetate with hydrogen bromide in acetic acid then gave bromo sugar **135** which almost immediately began to cause problems for us.



Scheme 85. Synthesis of acetyl bromo mannoside.

a) Ac_2O , H_2SO_4 , r.t., 24 hrs. b) HBr , AcOH , DCM , r.t., 24 hrs. ¹⁴

The bromosugar proved to be extremely unstable and we therefore used it in the next step of our synthesis without additional purification. Thus crude bromosugar **135** was treated with methanol in the presence of 2,6-lutidine and tetrabutyl ammonium bromide to give *ortho* ester **136** as shown in Scheme 86. (90) (91).



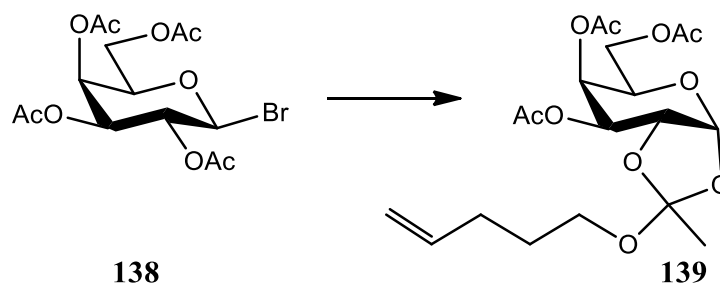
Scheme 86. Synthesis of orthoester.

a) MeOH , 2,6 lutidine, Bu_4NBr , r.t., 36 hrs.

However, all attempts to purify this compound proved futile and the major product from the reaction appeared to be the methyl mannoside **137** produced from migration of the methoxy to the anomeric position. Rather than abandon this approach, we considered that we may be able to use this unexpected rearrangement to our advantage in a shorter synthesis of a 2-hydroxy donor. Using commercially available acetyl bromo galactoside (**138**) as our model

2. Results and Discussion

we treated the bromide with pentenyl alcohol under conditions for ortho ester formation as shown in *Scheme 87*. (90) (91).



Scheme 87. Formation of the n-pentenyl ortho-ester.

a) 4-Penten-1-ol, 2,6-lutidine, Bu₄NBr, r.t., 36 hrs.

Again, however, we encountered problems with isolating and manipulating ortho ester **139** and, despite spectral data indicating we had synthesised the target compound (*Figure 7*), we were forced to abandon this approach to our donor because of the reactions inconsistency. The characteristic signal corresponding to the methyl substituent of the ortho-ester (M01 from *Figure 7*) is observed at around 1.5ppm - the integration is close but not perfect because the NMR shown is of the crude reaction mixture.

2. Results and Discussion

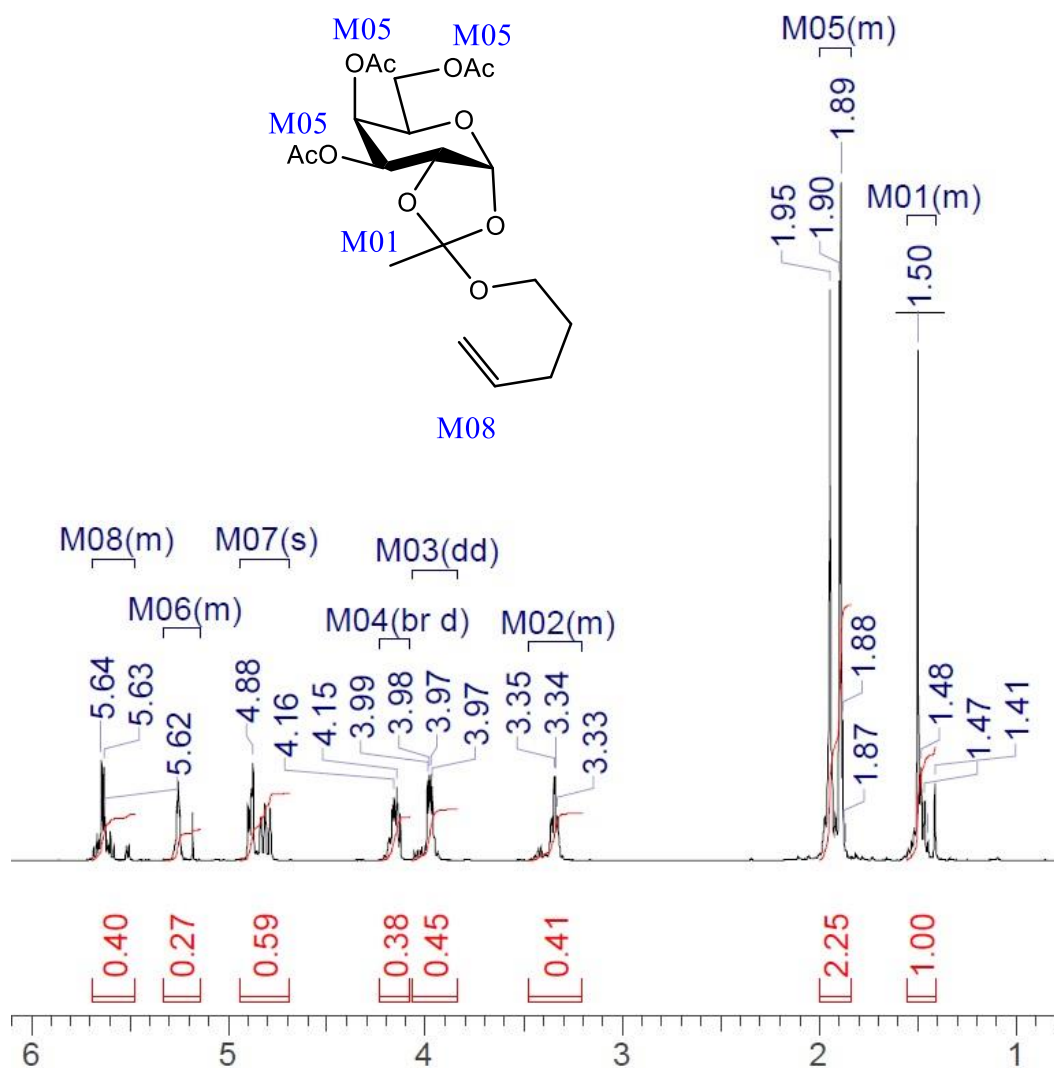
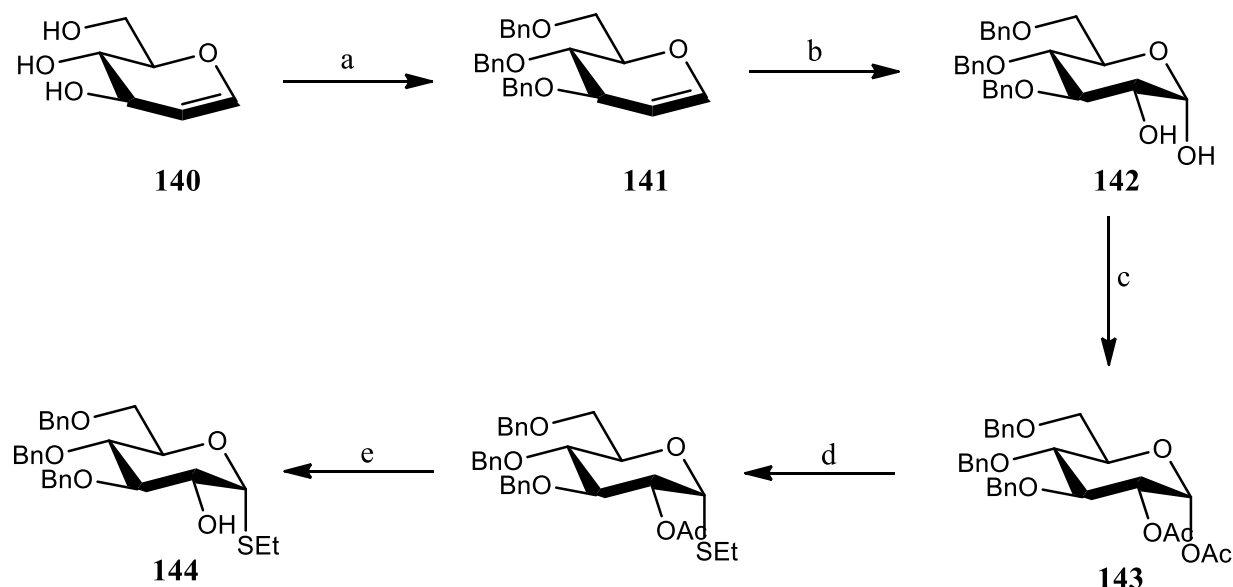


Figure 7. 3,4,6-tri-O-acetyl-1,2-O-(1-methoxyethylidene)- α -D-glucopyranose ^1H NMR.

2. Results and Discussion

2.1.3. Glucal and n-Pentenyl Glycoside

At this stage we decided to re-evaluate our strategy towards our model donor systems. Whilst synthesis of the galactoside donor had been successful it would require a ten step synthetic sequence to gain the monosaccharide with the desired protecting group array which could make multigram production difficult. In addition, our synthesis of a mannoside donor was curtailed as it was plagued by capricious reactions. We therefore looked for a new and more succinct route to a 2-hydroxy donor system and found that Kiessling had recently published a short route from commercially available D-glucal (**140**) as shown below in *Scheme 88* (92).



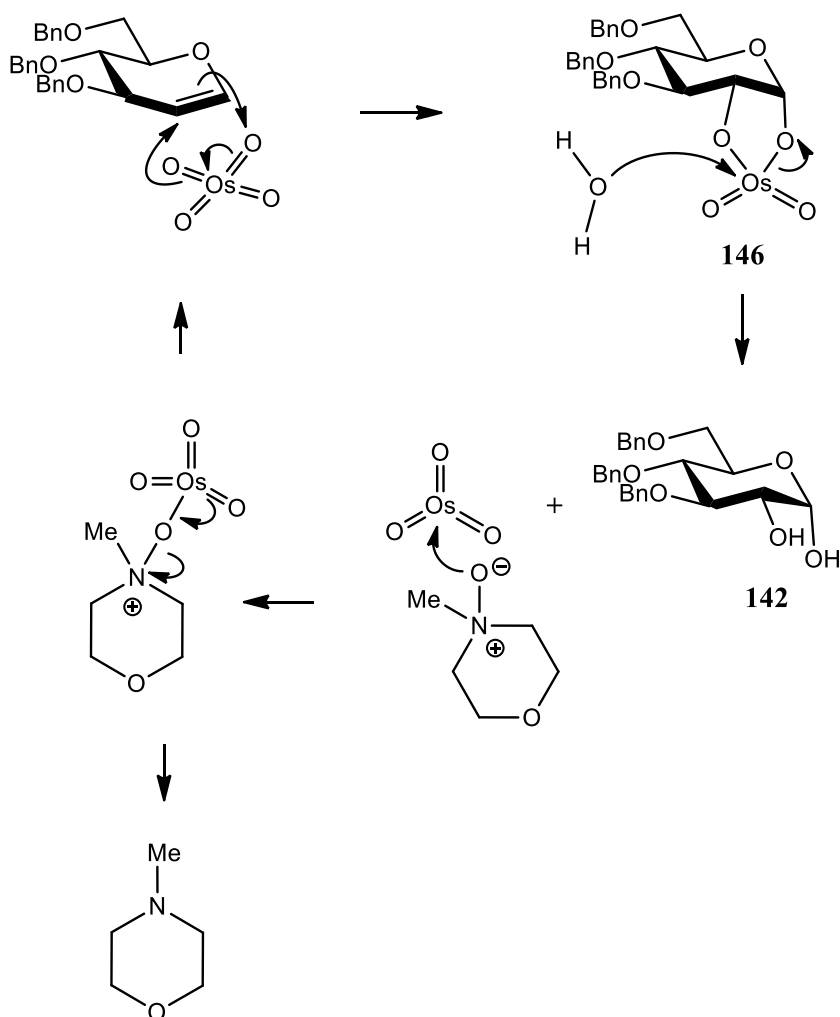
Scheme 88. Synthesis from the corresponding glycal.

a) BnBr, NaH, *n*-Bu₄NI, DMF, 0 °C - r.t., 24 hrs. b) OsO₄, NMO, Acetone, H₂O, r.t., 24 hrs. (92) c) Ac₂O, H₂SO₄, 0 °C - r.t., 24 hrs. d) HSEt, Sn(IV)Cl₄, DCM, 0 °C - r.t. 48 hrs. e) MeOH, MeONa, 0 °C, 5 hrs

Thus we took D-glucal (**140**) and subjected it to standard benzylation conditions to give fully benzylated glucal **141** which was then dihydroxylated using osmium tetroxide and *N*-methyl morpholine-*N*-oxide as co-oxidant to give diol **142** in an excellent yield of 90%. We were delighted to observe that the reaction was almost completely stereoselective, producing the glucose configuration by approach of the osmium tetroxide to the bottom face of the double bond (*Scheme 89*). The mechanism for dihydroxylation is well established and, despite some

2. Results and Discussion

speculation, the key step is accepted as being a (3+2) cycloaddition of the osmium tetroxide to the double bond to give osmate ester **146**. Presumably, in this case, the bottom, convex face of the double bond is far more accessible than the top face and, in addition, the anomeric effect may also contribute to stabilising the transition state (and product) of the reaction which would account for the high selectivity (93) (94) (93).



Scheme 89. Mechanism of osmium tetroxide oxidation with N-methyl morpholine N-oxide.

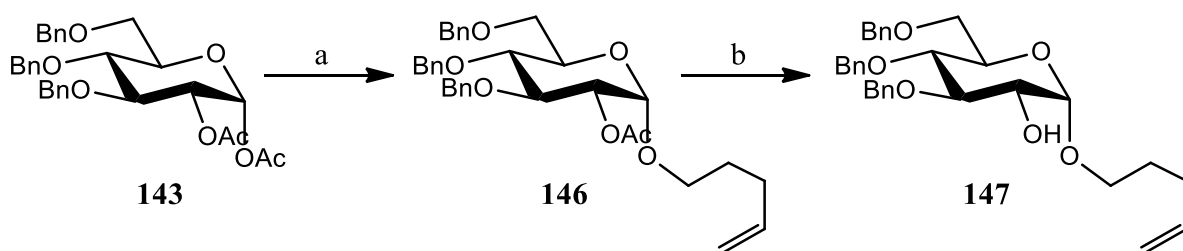
Hydrolysis of the intermediate osmate ester produces the diol as well as osmium trioxide which is reoxidised by NMO back to the tetroxide.

The next step in the synthetic sequence involved acylation of the diol **142** to give the diester **143** which in turn was reacted with ethane thiol in the presence of the Lewis acid tin (IV) chloride to give the thioglycoside. Finally, hydrolysis of the acetate gave 2-hydroxy donor

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144 in only five steps from D-glucal. Not only was this synthesis particularly efficient in comparison to our previous two attempts, but all the reactions proved to be both high yielding and reproducible, making it possible to access multigram quantities of donor for model coupling studies.

Spurred on by the success of our synthesis of the thioglycoside donor we decided to investigate whether this same route could also be used to make an *n*-pentenyl glycoside. This would provide us with two model systems based on significantly different anomeric activators which in turn increased the chances of success in developing our sacrificial protective group methodology. Acetate **143** was therefore reacted with pentenyl alcohol, again in the presence of tin (IV) chloride to give *n*-pentenyl glycoside **146** which was in turn subjected to basic hydrolysis of the remaining ester function to give the analogous 2-hydroxy pentenyl donor **147** (*Scheme 90*).



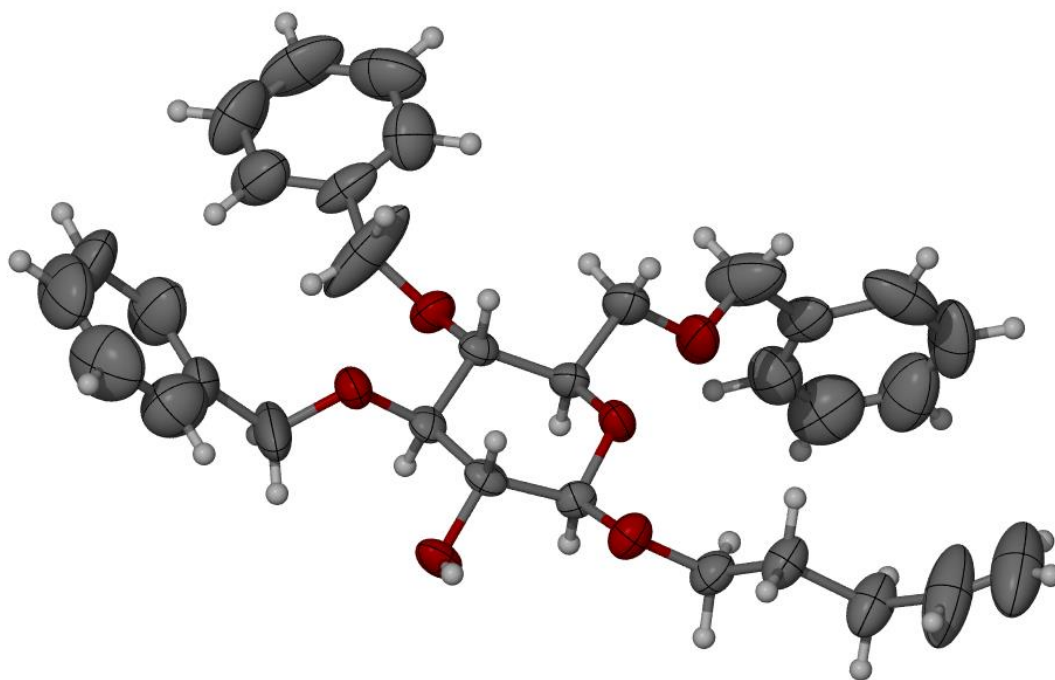
Scheme 90. N-pentenyl glycoside donor

a) 4-penten-1-ol, Sn(IV)Cl₄, DCM, 0 °C - r.t. 48 hrs. e) MeOH, MeONa, 0 °C, 5 hrs.

Interestingly displacement of the anomeric acetate with pentenyl alcohol did not proceed as smoothly as with ethane thiol, presumably due to a competing reaction in which the alcohol reacted with the tin reagent *via* displacement of the chloride. However, we were able to develop conditions based on high dilution, slow addition of the tin reagent and multiple small scale reactions that gave us an acceptable yield for the glycosylation. In addition, the selectivity for the conversion of **143** to **146** favoured formation of the β anomer (*Scheme 90* shows only the α anomer). On deacylation of the ester to yield alcohol **147** we observed that the R_F of the α and β isomers were significantly different, so much so that the anomers were readily separable by column chromatography. In later repetitions of the reactions we found it was also purifiable by recrystallization. The structure of **147** was confirmed by spectroscopic analysis, however the resulting β -anomer was found to be a solid from which we were able to grow crystals of sufficient quality for X-ray crystallography. The resulting X-ray crystal

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structure (*figure 8*) was obtained which confirmed that we had synthesised the glucose donor target **147**.



*Figure 8. X-ray crystal structure of **147**(β).*

2. Results and Discussion

2.2. Synthesis of Acceptors

With the completion of our two donor systems we turned our attention to the synthesis of a series of glycosyl acceptors. *Figure 8* shows our three choices based on testing the complementary nature of the sacrificial protecting group methodology with functionality commonly encountered in complex carbohydrate syntheses. Diacetone galactose (**148**) represents an easily accessible acceptor with a reactive primary hydroxyl group. However, the two acetonide protective groups are acid labile and so we will use this particular acceptor to ensure our methodology is compatible with acid sensitive functionality. Acceptor **18** is also a primary alcohol but the remaining hydroxyl groups are protected as ‘permanent’ benzyl ethers which are commonly used in oligosaccharide synthesis. Finally, monosaccharide **149** also represents a structure with a protective group array featuring only benzyl groups. However, in this case the acceptor is a 4-hydroxy glucopyranoside which represents one of the more difficult glycoside bonds to synthesise in carbohydrate chemistry and will therefore tests the limits of reactivity in our glycosylation methodology. (90) (95) (96).

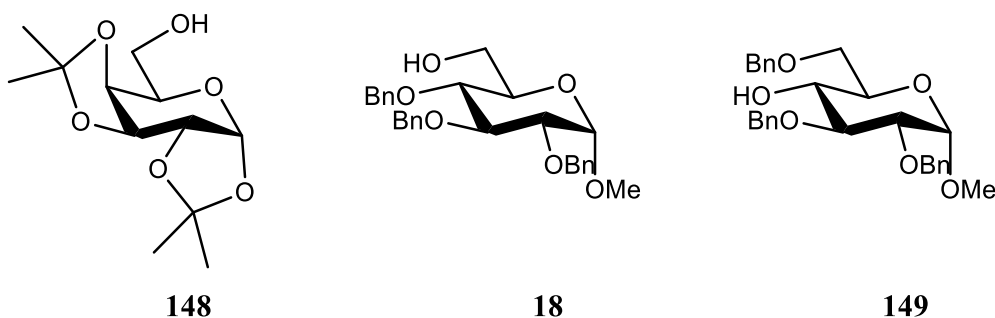
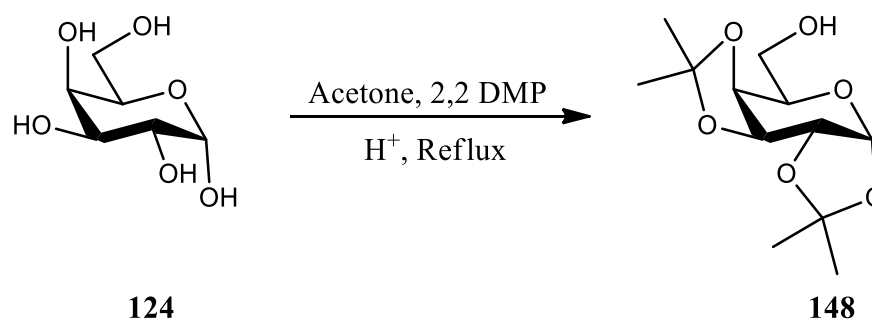


Figure 8. Glycoside acceptors.

We began our study of the glycosyl acceptors with an approach to diacetone galactose (**148**) as shown below in *Scheme 91*. This was essentially a one-step synthesis involving the ketalisation of D-galactose (**124**) with acetone and 2,2-dimethoxypropane under acidic conditions to give the title compound in an excellent yield of 90%.

2. Results and Discussion

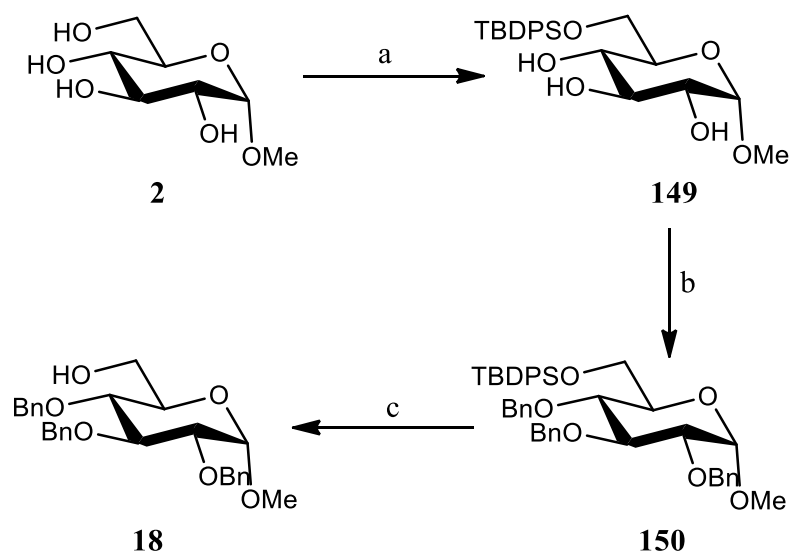


Scheme 91. Synthesis of diacetone galactose.

As with the synthesis of acetonide **129** (*vide supra*) the reaction is performed under thermodynamic control. However, unlike that reaction outlined in *Scheme 83* the reaction shown above has multiple outcomes based on the fact that different diol arrangements could be protected or the monosaccharide could undergo reaction through the furanose form. It is worth noting therefore that only one product was isolated from the reaction mixture in excellent yield and also that purification of the reaction residue could be achieved simply by filtration through a silica plug.

With our first acceptor in hand we turned our attention to the synthesis of the other primary hydroxyl acceptor **18**. *Scheme 92* shows our three stage sequence to the monosaccharide starting from commercially available methyl α -D-glucopyranoside (**2**).

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Scheme 92. Synthesis of 1-O-methyl 2,3,4 tri-O-benzyl glucose acceptor

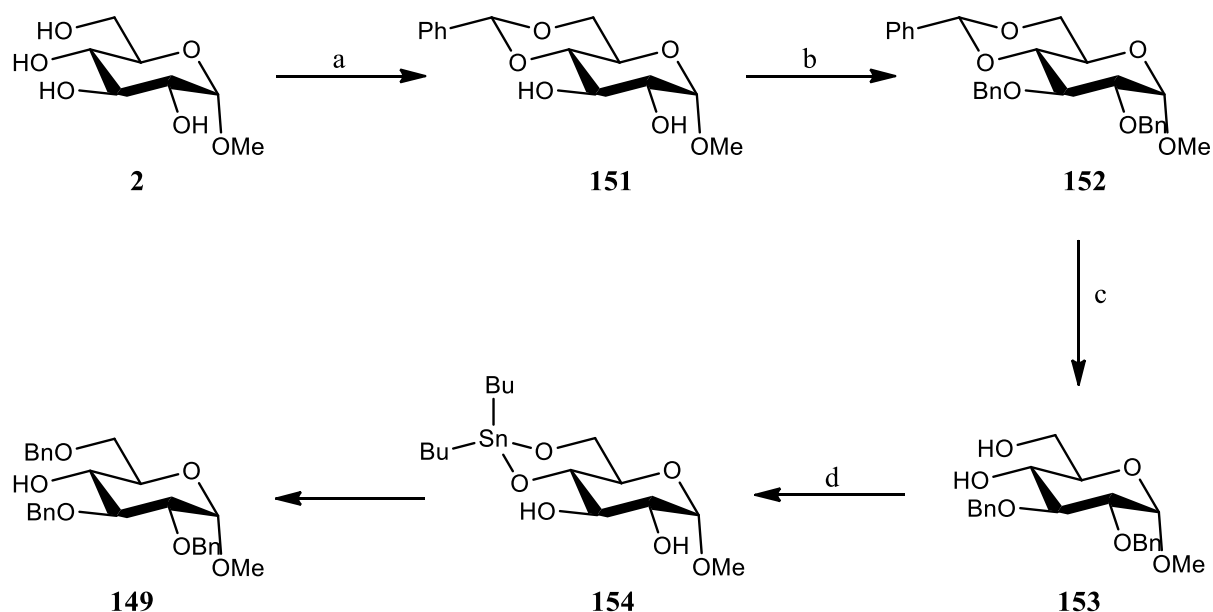
a) TBDPSCl, Et₃N, DMAP, DMF, 40 °C, 48 hrs. b) BnBr, NaH, DMF, 0 °C - r.t., 24 hrs. c) TBAF, THF, r.t., 2 hrs. (85) (86) (95) .

Silylation of the primary hydroxyl group in **2** gave silyl ether **149** using similar reaction conditions to those outlined in *Scheme 81*. Benzylation of the three remaining hydroxyl groups in **149**, again under standard reaction conditions, gave monosaccharide **150** which was treated with tetrabutyl ammonium fluoride to effect selective desilylation and afford acceptor **18** in excellent overall yield. (85) (86) (95) (97).

The synthesis of our final acceptor **149** was slightly more complex, involving a four step strategy and utilising some interesting protecting group methodology. Again our starting material was methyl glucopyranoside (**2**) which was converted to the 4,6 O-benzylidene acetal **151** by reaction with benzaldehyde and its dimethyl acetal under acidic conditions. The reaction is again carried out under thermodynamic control but these conditions favour protection of a 1,3 diol over that of a 1,2 as the monosubstituent can now be placed in the equatorial position to produce, in this case, an almost strain free *trans* decalin system. The remaining two free hydroxyl groups were benzylated under standard conditions to give monosaccharide **152** and the benzylidene was then hydrolysed using aqueous acid to give the 1,3 diol **153**. Finally, we were able to selectively benzylate the primary alcohol in the 1,3 system using tin acetal chemistry by initially reacting the diol with dibutyltin oxide to give the tin acetal intermediate **154** which on reaction with one equivalent of benzyl bromide produced

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the 2,3,6 tribenzyl protected glycoside **149** (Scheme 93).



Scheme 93. Synthesis of 1-O-methyl 2,3,6 tri-O-benzyl glucose acceptor.

a) Benzaldehyde, benzaldehyde dimethyl acetal, TsOH, r.t., 48 hrs, b) BnBr, NaH, DMF, 0 °C - r.t., 24 hrs, c) AcOH, H₂O, 80 °C. d) Bu₂SnO, Tol, (Dean-Stark), then TBAI, BnBr, DMF, r.t., 16 hrs. (98) (96).

Interestingly this final reaction was almost totally chemoselective yielding monosaccharide **149** with only a trace of acceptor **18** being produced as evidenced by tlc analysis of the reaction mixture.

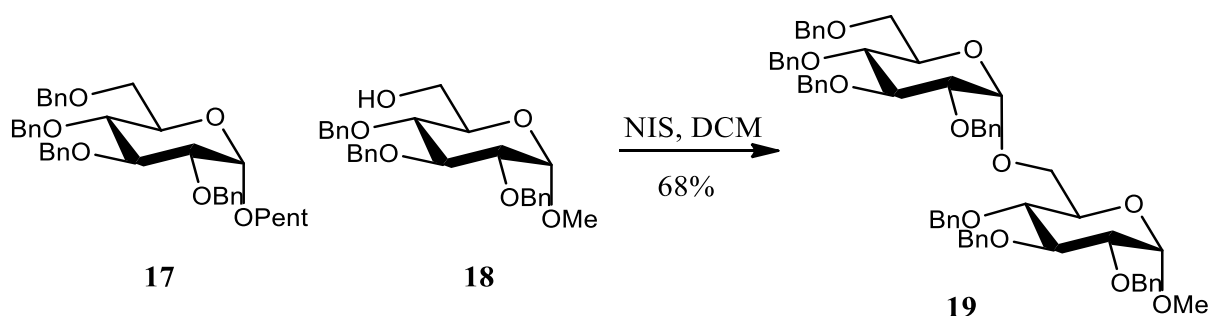
With both our model donor and acceptors now ready we were able to focus on developing our sacrificial protecting group methodology.

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2.3. Sacrificial Protecting Group

2.3.1. Glycosylation Control Reaction

Prior to our investigation into developing a sacrificial protective group we were conscious of the fact that we had not carried out a glycosylation procedure. Although we did not foresee any particular problem with the analysis of such reactions we nevertheless thought it would be advantageous to carry out a test coupling (*Scheme 94*).



Scheme 94. Control reaction.

Thus tetrabenzyl glucoside donor **17** was coupled with acceptor **18** using only NIS in DCM at room temperature overnight. The reaction gave disaccharide **19** in a yield of 68% as a mixture of anomers in a 2:1 ratio by analysing the peaks in the ^1H NMR spectrum observed for the OMe group, as outlined in *Figure 9*.

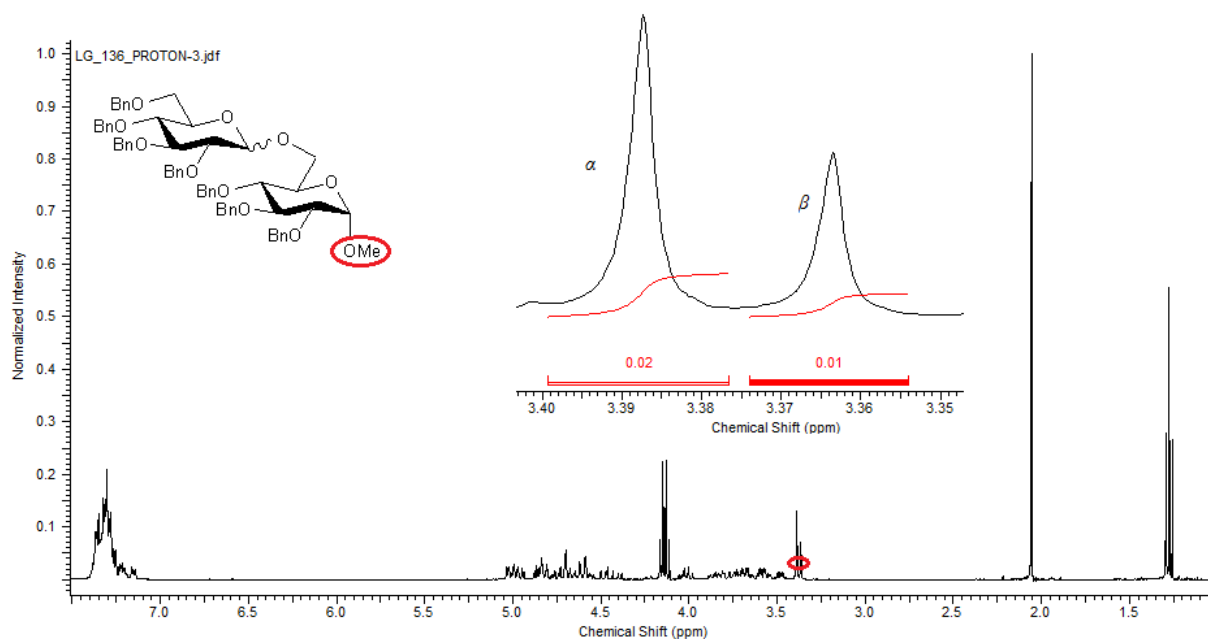
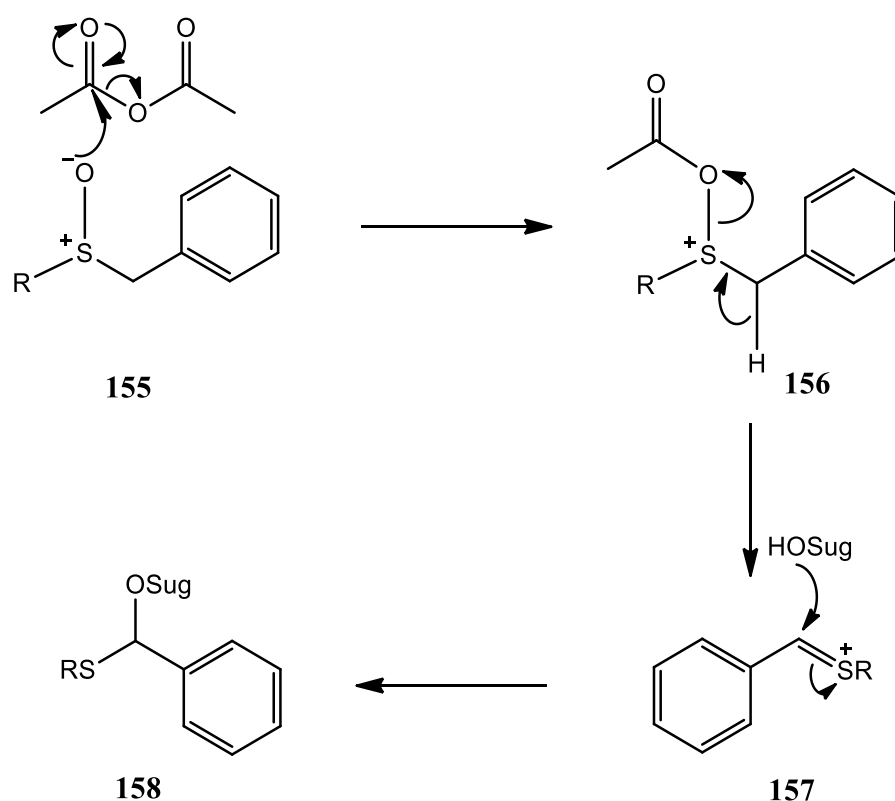


Figure 9. Isomaltose ^1H NMR.

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2.3.2. Pummerer Rearrangement

Our first approach to developing, and introducing, a sacrificial protecting group for the C-2 hydroxy function focussed on the use of the Pummerer rearrangement as outlined in *Scheme 95*. Sulfoxide **155** will react with acetic anhydride to give intermediate **156** which will immediately rearrange to give sulfonium ion **157**. In the absence of water, we would then expect that this sulfonium would react with an alcohol to give mixed thioacetal **158**.

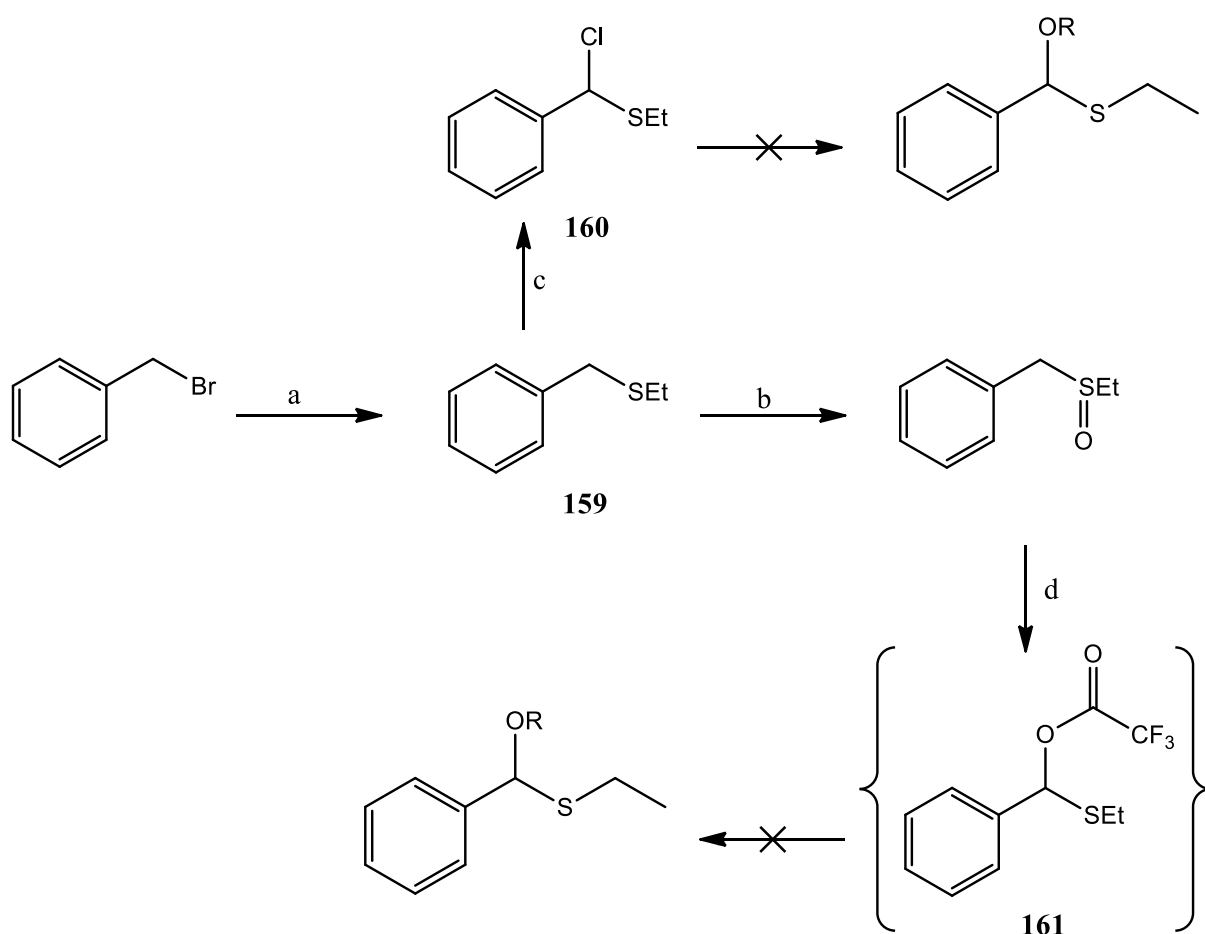


Scheme 95. The Pummerer rearrangement.

As we had generated an ethyl thioglycoside as our donor (see structure **145**) we reasoned we also needed to install a similar thioacetal functionality as our sacrificial protecting group at C-2. Our synthesis therefore began with the reaction of ethane thiol with benzyl bromide under basic conditions to give thioether **159** (*Scheme 96*). Having obtained the thioether in sufficient quantities we had two options for further functionalization. Our first approach was to chlorinate the benzylic position of the thioether to give the chloro thioether **160** according to literature reports. Reaction of the thioether with N-chlorosuccinimide was carried out in carbon tetrachloride in accordance with previously reported conditions and

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appeared to proceed smoothly. The literature stated that reaction was complete when the N-chlorosuccinimide was consumed and was converted to succinimide which floated on the solvent (99) (as opposed to NCS which sank to the bottom of the reaction) which corresponded to our own observations. However, attempts to either isolate the chloro species or trap it *in situ* with a secondary alcohol lead to intractable mixtures and we quickly abandoned this approach. Instead we proceeded with our original intention to introduce the thioketal *via* a classical Pummerer rearrangement.



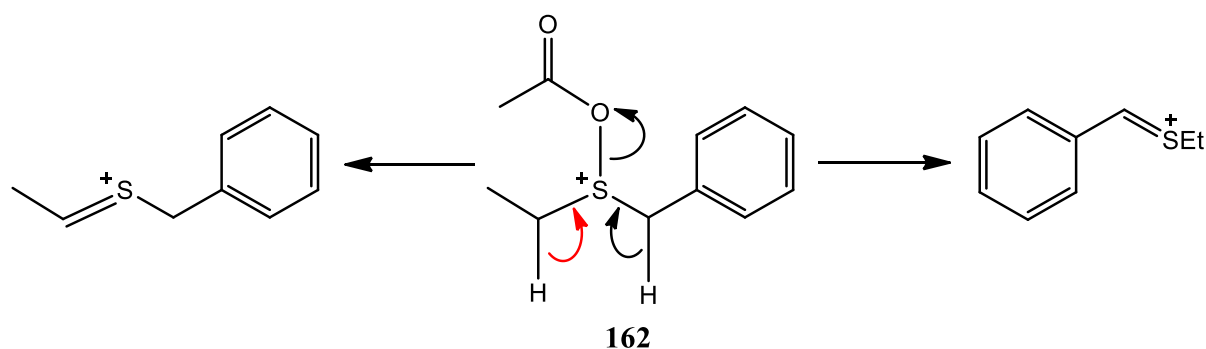
Scheme 96. Studies on the Pummerer reactions.

a) HSEt, DMAP, lutidine 30 min, 0 °C. b) CCl₄, NCS, r.t., 2 hrs. c) KIO₄ (aq), 0 °C, 3 hrs. d) TFAA, DCM, 0 °C, 30 min, then cyclohexanol, 0 °C – r.t., 2 hrs. (100) (101) (102)

Thus oxidation of thioether **159** with aqueous sodium periodate gave the sulfoxide which was treated sequentially with trifluoroacetic anhydride, presumably to give intermediate **161**, and cyclohexanol. Unfortunately, we again could not isolate any thioacetal and despite an intensive investigation, including studying the reaction by NMR, we were unable to

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develop suitable conditions to achieve our goal. It turned out that the Pummerer reaction was not as selective as we had originally hoped for and that rearrangement of an intermediate acylated sulfoxide such as that represented by structure **162** in *Scheme 97* will undergo rearrangement to give both regioisomeric sulfonium ions. Given that both of these sulfonium ions can also produce two stereoisomeric products it is not surprising that we encountered difficulty in executing this reaction.



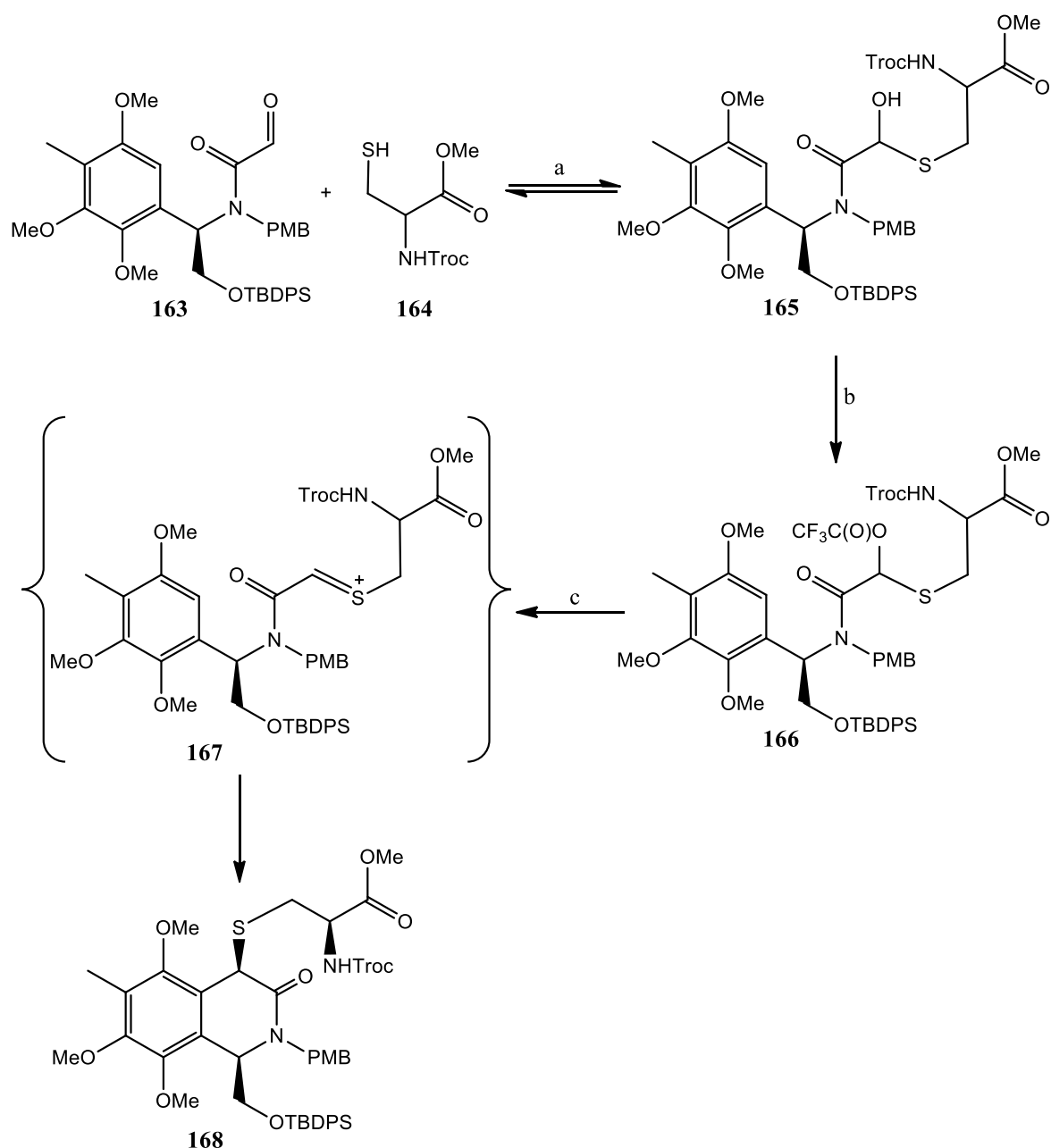
Scheme 97. Regioselectivity in the Pummerer rearrangement.

We were keen therefore not to dismiss the Pummerer reaction as a route to thioacetals and decided to investigate the reaction using the symmetrical dibenzyl sulphide. Unfortunately, similar, complex reaction mixtures were encountered and we decided to reconsider our approach.

Procter has recently introduced a ‘connective Pummerer’ reaction which bypasses the necessity for either sulphide oxidation or rearrangement as outlined in *Scheme 98*. The reaction involves initial nucleophilic addition of a thiol, in this case protected cysteine **163** to a reactive aldehyde **164** to give hemi thioacetal **165**. This thioacetal is then trapped with trifluoroacetic anhydride to give the Pummerer type adduct **166** which on treatment with Lewis acid gives the intermediate sulphonium ion **167** which will immediately cyclise to give the heterocycle **168**.

We were conscious of two factors when attempting to apply this methodology, firstly that Procter had stated that a reactive aldehyde was required in the initial coupling with the thiol and also that all examples of the connective Pummerer to date had involved an intramolecular carbo-cyclisation.

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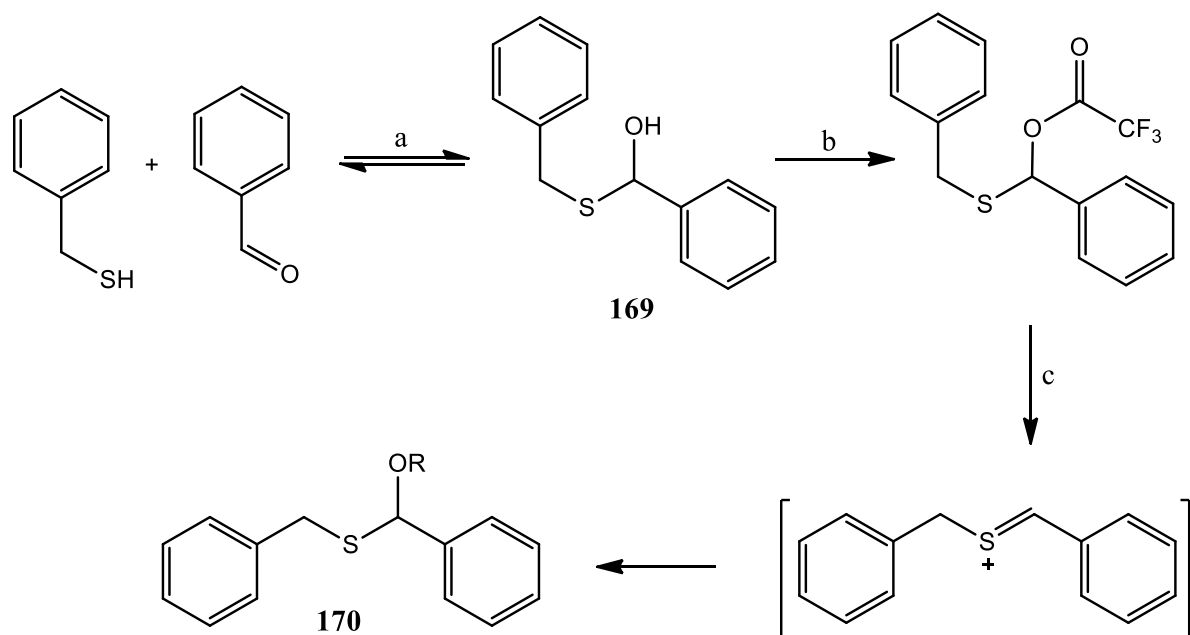
Scheme 98. Procter's connective Pummerer rearrangement (99).

a) DCM, r.t., 24 hrs., b) TFAA, DCM, r.t., 2 hrs., c) $\text{BF}_3 \cdot \text{OEt}$, DCM, r.t., 2 hrs.

Nevertheless, we were keen to try to apply Procter's chemistry to the solution of our own problem associated with the generation of a thioacetal. Thus we mixed benzyl mercaptan with benzaldehyde in dichloromethane and allowed the mixture to equilibrate for 24 hours in an attempt to generate adduct **169**. To this was added trifluoroacetic anhydride and the reaction mixture was stirred for an additional two hours in accordance with literature procedures before finally we added cyclohexanol and a Lewis acid in an attempt to generate thioacetal **170**

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(Scheme 99).



Scheme 99. Application of the Procter protocol to the Pummerer rearrangement.

a) DCM, r.t., 24 hrs., b) TFAA, DCM, r.t., 2 hrs., c) $\text{BF}_3 \cdot \text{OEt}_2$, DCM, ROH, r.t., 2 hrs.

TLC monitoring of the reaction was hopeful as starting material had been consumed, however all attempts at isolating thioacetal **170** proved fruitless. Again we studied the reaction using nmr analysis but we were unable to confirm anything other than trace amounts of our target in the reaction mixture. It may be that the thioacetals we were attempting to prepare were extremely labile, especially under the conditions we were using, and that hydrolysis was a reaction that was competing with our attempts to trap the sulfonium ion with an alcohol. Clearly further investigation of these reactions is needed but unfortunately, with time pressing, we decided to move on in search of a more facile route.

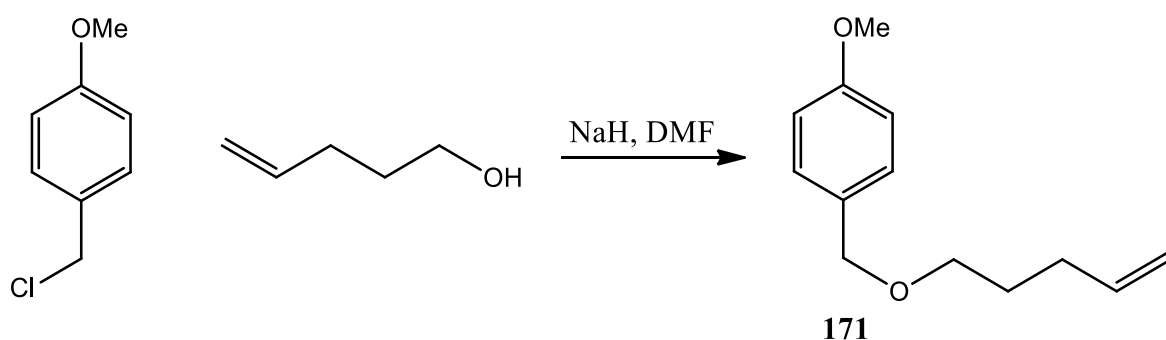
2.3.3. Para Methoxy Benzyl and Methyl Naphthyl

The difficulties we encountered in trying to develop a Pummerer rearrangement in addition to the dearth of literature precedent on the synthesis of acyclic thioacetals lead us to reconsider our approach to a sacrificial protective group.

As outlined in Scheme 75 Ogawa has developed an intramolecular aglycone delivery system based on a *para*-methoxybenzylidene mixed acetal system. We reasoned that this

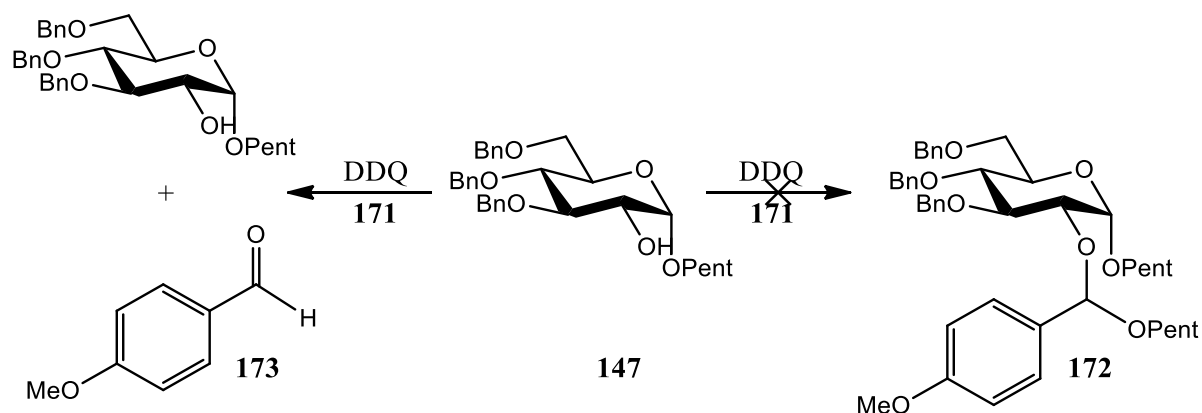
2. Results and Discussion

methodology could be adapted to our neighbouring group direction initially by targeting the synthesis of n-pentenyl-PMB ether (**171**) as shown below in *Scheme 100*.



Scheme 100. Synthesis of PMB-n-pentenyl ether.

Alkylation of n-pentenyl alcohol with PMB chloride under basic conditions thus gave ether **171** in excellent yield. Unfortunately, our attempts to carry out an oxidative coupling of ether **171** with our donor **147** to produce mixed acetal **172** met with failure and we instead isolated the starting monosaccharide along with *para*-methoxybenzaldehyde (**173**) from the reaction mixture (Scheme 101).

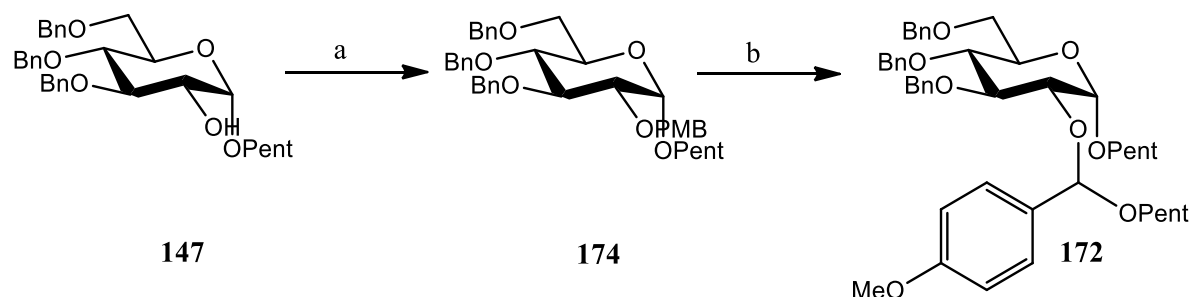


Scheme 101. Attempted synthesis of a mixed acetal

The isolation of *para*-methoxybenzaldehyde was at least a positive outcome from the reaction in that it suggested either that the oxonium ion from **171** had been formed or possibly we had indeed made mixed acetal **172** but it had hydrolysed. This latter result would have been in keeping with Ogawa's own observations that mixed PMB acetals of this type were hydrolytically unstable. We decided therefore to adopt a compromise approach to acetal **172** as shown in *Scheme 102* in which we attempted a two stage synthesis of our donor system. As

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shown below we first reacted monosaccharide **147** with PMB chloride under basic conditions to give the fully protected donor **174**. This precursor was then treated with DDQ and excess pentenyl alcohol in the presence of molecular sieves to try and prevent water entering the reaction mixture and hydrolysing the product *in situ*.



Scheme 102. Alternative synthesis of a mixed acetal.

a) NaH, DMF, PMBCl, r.t. b) DDQ, 4-Penten-1-ol, 4 Å mol sieves, DCM, r.t.

Unfortunately, we were still unable to isolate the mixed acetal **172** with our reaction mixtures essentially consisting of the recovered monosaccharide **147** and *para*-methoxybenzaldehyde. Multiple attempts at optimising the conditions such as basic work-up to avoid any acid contact and purification of the residue on both triethylamine doped silica gel and basic alumina proved fruitless. Our most successful attempt involved the use of the polymer-supported aldehyde scavenger PEG phenylethylenediamine in a bid to remove the *p*-methoxybenzaldehyde impurity. This resulted in the isolation of trace amounts of the target mixed acetal **172** as can be seen in the ^1H NMR spectrum of the reaction in figure 10. Even in this instance hydrolysis was occurring over the time of the ^1H NMR experiment and the ^1H NMR spectrum appears to be a mixture of the desired acetal along with substantial amounts of aldehyde formed *via* hydrolysis.

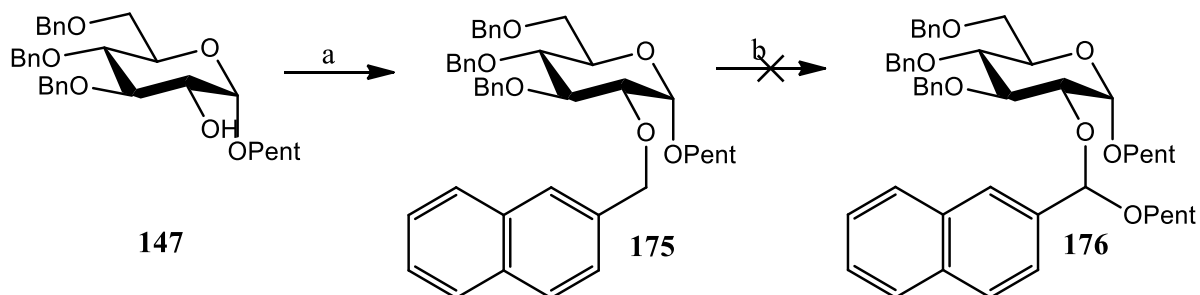
Figure 1 displays the ^1H NMR spectra of compound **1**. The top spectrum shows the ^1H NMR in CDCl_3 , and the bottom spectrum shows the ^1H NMR in $\text{DMSO}-d_6$. Both spectra include chemical shift values (ppm), integration values, and peak assignments (M05(s), M01(m), M03(m), M04(m)). Chemical structures of the compound are shown in the top right corner.

We were now beginning to understand the nature of our target donors and their inherent reactivity and it seemed to us that it wasn't necessarily the chemistry that was causing us the difficulty but rather the lability of our target acyclic acetal (or thioacetal). As mentioned in *Scheme 77* our strategy was based on kinetics, wherein, for a successful glycosylation strategy, we needed to generate the exocyclic oxonium ion before its cyclic counterpart. In designing our sacrificial protective group, we had perhaps chosen a system that was too reactive and therefore also highly acid labile.

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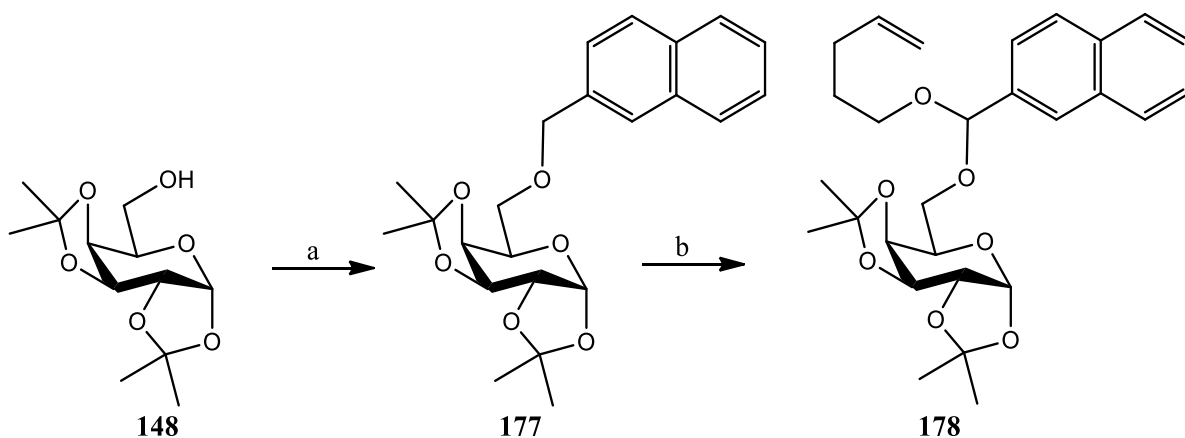
with the use of a polymer supported aldehyde scavenger unfortunately still failed to produce the desired mixed acetal. Repeated attempts to optimise the reaction conditions, as well as studying the reaction by nmr spectroscopy, did indicate that we were able to form the mixed acetal **176** but that it was still an extremely labile functional group and proved impossible for us to isolate.



Scheme 103. Approach to naphthyl-pentenyl mixed acetal.

a) NaH, DMF, 2-naphthyl bromide, r.t. b) DDQ, 4-Penten-1-ol, 4 Å mol sieves, DCM, r.t.

Despite the results from the study of the naphthyl protected sugar, it did appear that the naphthyl based mixed acetal may be slightly more acid stable than its PMB counterpart. Our supply of pentenyl donor **147** was regarded as a precious commodity and we did not want to use too much in a model study of acetal formation. However, we reasoned that the acetal could also be placed on the free hydroxyl of an acceptor where it could still be used as a sacrificial protective group in an asymmetric glycosylation. This convinced us to try a further study using acceptor **148** as the precursor to a mixed acetal as shown below in *Scheme 104*.



Scheme 104. Approach to a mixed acetal for a 'reversed' neighbouring group direction.

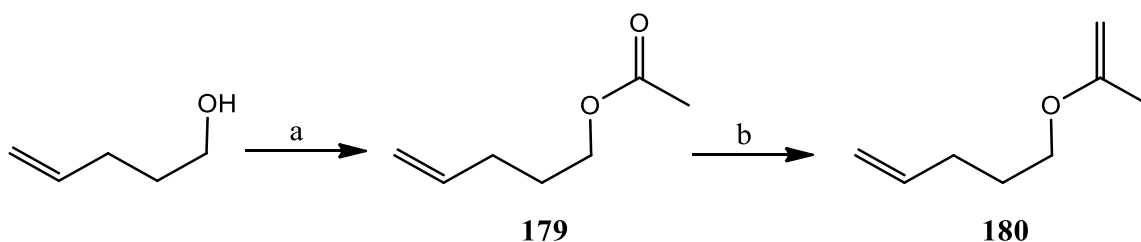
a) NaH, DMF, 2-naphthyl bromide, r.t. b) DDQ, 4-Penten-1-ol, 4 Å mol sieves, DCM, r.t.

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Again, introduction of the naphthyl protecting group was straightforward giving monosaccharide **177** in high yield and multigram quantities. However, once again, after making several attempts to generate mixed acetal **178**, we met the same problem of the aldehyde and alcohols. Deciding we this would be again unsuccessful we were faced with rethinking our approach.

2.3.4. Iso Propylidene

Our attempts at forming both a mixed thioacetal or a mixed acetal had so far been thwarted, which we considered was associated with the lability of the functional group we were targeting. We returned to the literature and to perhaps the earliest example of intramolecular aglycone delivery with Hindsgaul's use of an *iso*-propylidene tether to deliver a stereocontrolled glycosylation. The use of a dimethyl ketal as a sacrificial protective group should certainly cause less problems than the corresponding PMB or naphthyl acetals and so we began a synthesis of a 2-alkoxypropene which would act as a standard hydroxyl protecting group. *Scheme 105* outlines our approach from pentenyl alcohol which was acylated under standard conditions to produce ester **179**.



Scheme 105. Attempted synthesis of 2-Pentenylloxyprene.

a) Ac₂O, Pyridine, r.t. b) Tebbe reagent, THF, Pyridine, -78 °C.

We next attempted to methylenate the carbonyl in ester **179** with Tebbe's reagent according to the literature. Unfortunately, the notoriously difficult Tebbe reaction to generate an enol ether proved our downfall and we were unable, despite repeated attempts, to isolate 2-pentenylloxyprene (**180**). This also proved to be our last attempt at developing a sacrificial protective group as time constraints meant that we had to stop the investigation. (103) (74)

2. Results and Discussion

2.4. Conclusion.

Although our ultimate goal of developing a novel, neighbouring group direction approach to asymmetric glycosylation was, unfortunately, unsuccessful. We did however optimise some efficient syntheses of both donor and acceptor molecules as shown in *Figure 10* below.

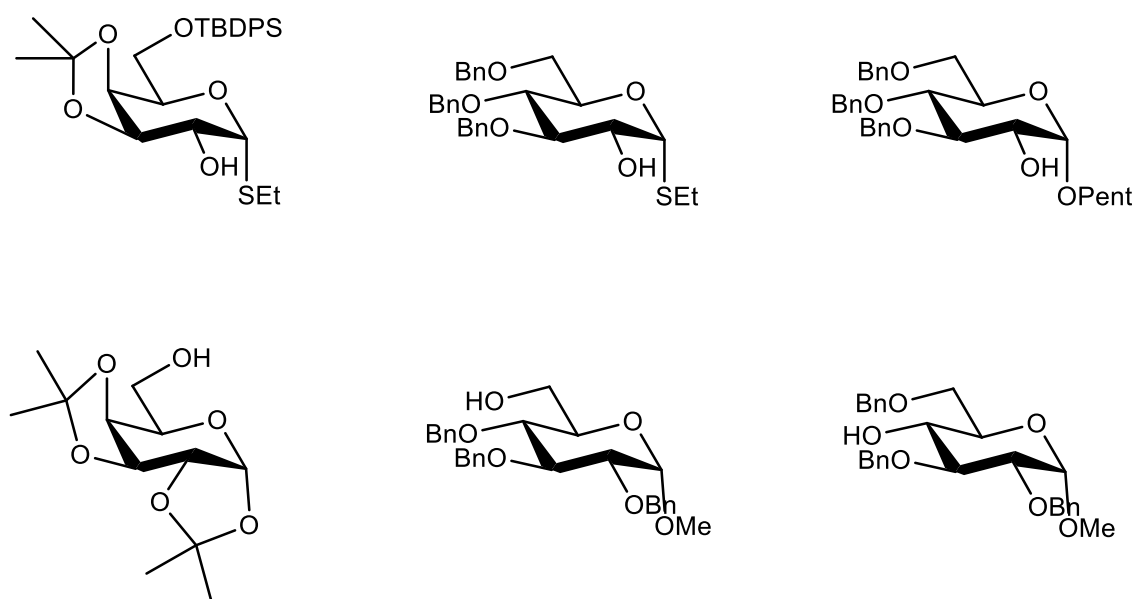


Figure 10. Monosaccharide building blocks.

Perhaps more importantly we gained valuable insight into the nature of mixed, acyclic acetals and thioacetals and their inherent susceptibility to hydrolysis. Our original premise, as laid out in *Scheme 77*, relies on the kinetics of oxonium ion formation and the fact that we should be able to generate oxonium ion **116** faster than the corresponding cyclic species **118**. This should allow us to initiate a reaction cascade that ultimately leads to stereocontrolled glycosylation to deliver a *cis* 1,2 glycoside.

There is a wealth of literature detailing the formation and hydrolysis of cyclic acetals, as well as numerous studies on glycosylation reactions, which gives a keen insight into both their reactivity. Surprisingly however there is relatively limited amount of data concerning acyclic acetals and our major source was that of previous work concerning intramolecular aglycone delivery. We had mistakenly begun the design of our sacrificial protecting group with

2. Results and Discussion

the assumption that a cyclic, secondary oxonium ion of type **118** would show similar stability to an acyclic counterpart. The target for our studies on ‘neighbouring group directed’ glycosylation therefore became monosaccharides with the type of structure represented in **172** as shown in *Figure 11*. Our reasoning here was that we needed to generate a benzylic oxonium ion in order to ensure that the acyclic oxonium was formed before the cyclic form.

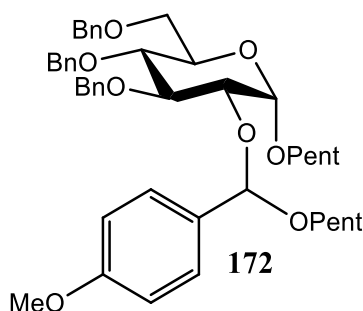
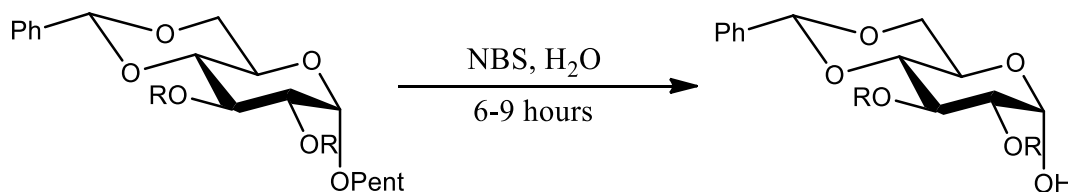


Figure 11. Target donor equipped with sacrificial protecting group.

It now seems obvious that we were overcautious in our approach to developing this piece of methodology and the problems that plagued our attempts to synthesis a mixed acetal were related to its lability. Fraser-Reid’s seminal work on the armed-disarmed effect gives a clear indication of the reactivity of glycosyl donors, indeed a monosaccharide with similar reactivity to one of our own building blocks was the subject of a kinetic study as shown below in *Scheme 106*.



Scheme 106. Hydrolysis of a disarmed donor.

The slow reaction is a consequence of the benzylidene acetal protective group which hinders the donor from adopting a half-chair conformation necessary to accommodate the trigonal planar oxonium ion. It would therefore seem logical to propose a series of protecting groups with the structures outlined below in *Figure 12*. These structures should be much more accessible and would make for a relatively straightforward study, not only asymmetric

2. Results and Discussion

glycosylation but also on oxonium ion stability (104). Unfortunately, (and somewhat annoyingly), as can be seen from the figure, one of the structures corresponds to our final target enol ether **180** which we were in the process of synthesising before we ran out of time.

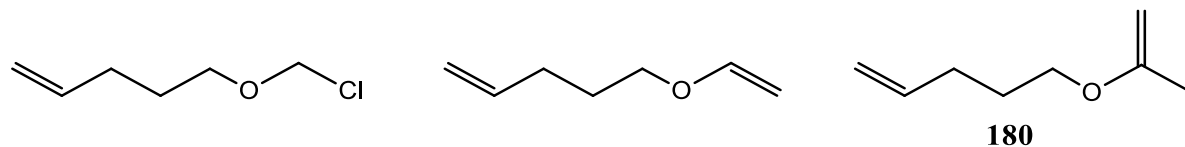
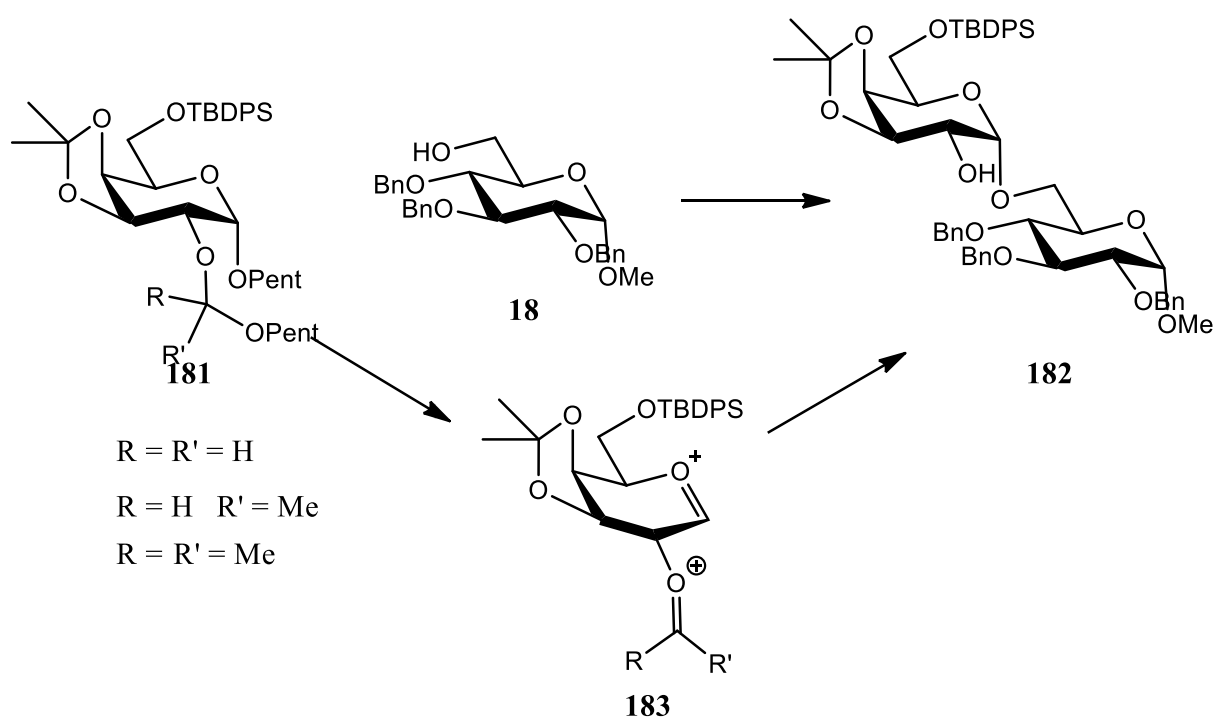


Figure 12. A series of protecting groups for a NGD glycosylation study (104).

Thus as an initial piece of future work we are proposing, as briefly outlined below in *Scheme 107*, a study of the glycosylation of donor **181** with an acceptor such as **18** to give disaccharide **182**. It would also seem logical (especially with the benefit of hindsight) to perform a computational model of the oxonium ions generated in the reaction, represented by intermediate **183**, to calculate the relative energies of the cyclic and acyclic components and therefore aid in the rational design of a sacrificial protective group.



Scheme 107. Future work.

We hope that this work will be carried out in the near future and contribute to the development of a novel methodology for stereocontrolled glycosylation.

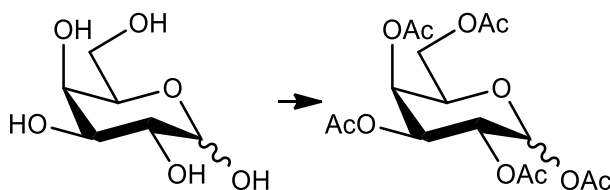
3. Experimental

3. Experimental

General Procedures:

All the reactions were performed from oven dried glassware and metal ware. The solvents were dried from clean activated molecular sieves for 14 – 16 hours before hand. Solvents where necessary, silica and other reagents/reactants were ordered as >98% pure from either Sigma-Aldrich, Fisher Scientific, Alfa Aesar, Acros Organics or TCI Chemicals. Solvent evaporation was performed under Büchi Rotor Vap vacuum stills. Distillation processes were performed under high vacuum through a quick fit – assembled vacuum still from oven dried clean glassware. NMR analysis was obtained from a JEOL Delta2 Nuclear magnetic resonance spectrometer or a Bruker 300 Nuclear magnetic spectrometer. TLC used Fisher scientific brand Silica – glass plates. Flash column chromatography was performed via direct application of the compound, as a concentrated solution onto the column. The solid phase was prepared off column as a silica gel slurry, made with the mobile phase determined from TLC analysis. All reactions that involved heating were warmed under a condenser, and the reactions that involved stirring were stirred at a steady rate with a magnetic stirrer bar. All procedures were carried out under a nitrogen atmosphere where necessary. Procedures that occurred under this project were supervised and cautions of substances hazardous to health (COSHH) were taken with compliance to HR safety regulations.

Penta-*O*-Acyl D-Galactopyranoside **125**

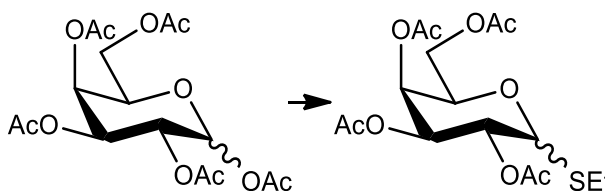


D-galactose (20.58 g, 0.114 mol) was mixed with acetic anhydride (125 mL, 1.13 mol, 9.9 eqv.) at rt. H₂SO₄ (3 drops, <0.1 mmol) was added, and the reaction was stirred for 16 h. The reaction was then diluted with EtOAc (200 mL) and quenched with saturated NaHCO₃ (200 mL) and extracted twice with EtOAc (2 × 200 mL). The combine organic phases were washed twice with water (2 x 200 mL) and once with brine (200 mL). The organic phase was dried with MgSO₄ and concentrated to afford a crude yellow oil. The residue was purified via silica gel chromatography using a 10% – 100% EtOAc in hexanes gradient to afford *pentaacetate* **125** as white crystals (42.6 g, 96%, α:β ~6:1). ¹H NMR (CDCl₃, 400 MHz) δ 6.14 (d 0.86H, C1H (α)), 5.69 (d, 0.14H, *J* = 8 Hz, C1H (β)), 5.41 (d, 1H, *J* = 4 Hz, C3H), 5.32 (dt, 1H, *J* =

3. Experimental

4, 8 Hz, C4H), 4.18-4.02 (m, 3H, C5,6,4H), 3.89 (dd, 1H, $J = 4, 4$, C6H), 2.16 (s, 3H, Ac), 2.11 (s, 3H, Ac), 2.04 (s, 6H, 2Ac), 1.98 (s, 3H, Ac). Literature ^1H NMR (CDCl_3 , 400 MHz) δ 5.69 (d, 1H, $J = 8.3$ Hz), 5.42 (d, 1H, $J = 3.0$ Hz), 5.33 (dd, 1H, $J = 10.4, 8.3$ Hz), 5.07 (dd, 1H, $J = 10.4, 3.4$ Hz), 4.14 (m, 2H), 4.05 (t, 1H, $J = 6.6$ Hz), 2.16 (s, 3H), 2.12 (s, 3H), 2.04 (s, 6H), 1.99 (s, 3H) (105). ^{13}C NMR (CDCl_3 , 100 MHz) δ 169.8, 169.7, 169.6, 169.3, 168.1, 89, 68.2, 66.9, 66.8, 65.9, 60.7, 20. M.p. 141 – 142 °C. Specific Rotation $[\alpha]_{\text{D}}^{20} +0.41$ (1.8 mg/mL in EtOH). ν_{max} : 2990, 2917, 2162, 2030, 1746, 1737, 1373, 1211, 1041, 958, 901 cm^{-1} .

Ethane 2,3,4,6 tetra-*O*-acetyl D-thiogalactopyranoside **126b**

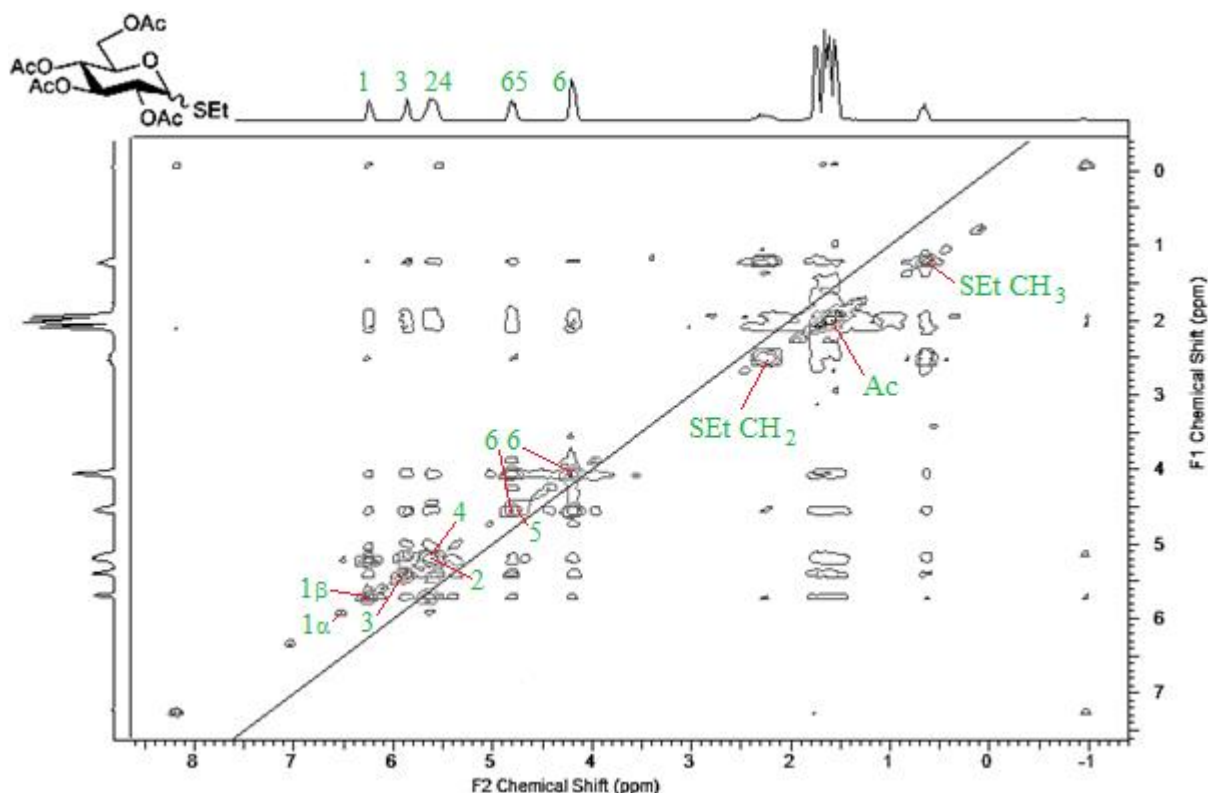


Pentaacetate 125 (12.31 g, 0.032 mol) was dissolved in 100 mL of DCM at 0 °C. HSEt (1.85, 0.035 mol, 1.1 eqv.) and SnCl_4 (2 mL, 0.001 mol as a 2 N solution in DCM) were added, the reaction was stirred and allowed to warm to r.t. The reaction was stirred for 4 days, and further SnCl_4 (6 mL, 0.012 mol as a 2 N solution in DCM) was added every 24 h. The reaction was quenched with 1mol HCL (200 mL), and extracted with DCM (3×150 mL). The combined organic phases were then washed with water (2×150 mL) and brine (150 mL). It was then dried over MgSO_4 and concentrated. The resulting yellow oil was purified via silica gel chromatography using a 10–100% EtOAc in hexanes gradient to afford **thioglycoside 126b** as a colourless oil, which later crystallised and formed a white solid (6.57g 62.6%, $\alpha:\beta = 1:6.3$). ^1H NMR (CDCl_3 , 400 MHz) δ 6.33 (d, 0.19H, $J = 8$ Hz, C1H (α)), 5.71 (d, 0.81H, $J = 4$ Hz, C1H (β)), 5.42-5.3 (m 1H, C3H), 4.61-4.56 (m, 2H, $J = 4$ Hz, C2,4H), 4.16-4.04 (m, 3H, C5,6H), 2.61-2.45 (m, 2H, SEt CH_2), 2.11 (s, 3H, Ac), 2.04 (s, 3H, Ac), 2.01 (s, 3H, Ac), 1.96 (s, 3H, Ac), 1.28-1.19 (m, 3H, SEt CH_3), Literature ^1H NMR (CDCl_3 , 250 MHz): δ 5.36 (dd, 1H, $J = 3.3, 1.0$ Hz), 5.17 (dd, 1H, $J = 9.9, 9.8$ Hz), 4.98 (dd, 1 H, $J = 10.0, 3.3$ Hz), 4.43 (d, 1H, $J = 9.8$ Hz), 4.14-4.00 (m, 2H), 3.90-3.84 (m, 1H), 2.74-2.56 (m, 2H), 2.09 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H), 1.92 (s, 3H), 1.28-1.19 (m, 3H, $J = 7.4$ Hz) (106). ^{13}C NMR (CDCl_3 , 100 MHz) δ 171.8, 170.7, 170.1, 76.8, 76.3, 75.6, 74.4, 72.7, 68.1, 62.8, 24.1, 21.1, 20.7, 18.4. M.p. 104 – 105°C. Specific Rotation $[\alpha]_{\text{D}}^{20} +0.28$ (1.4 mg/mL in EtOH). ν_{max} : 2972, 2871, 1750, 1741,

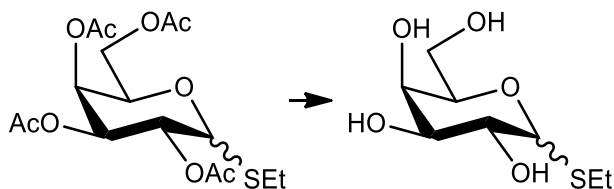
3. Experimental

1446, 1368, 1225, 1211, 1117, 1079, 1049, 945, 912 cm^{-1} .

Peak assignment by ^1H (COSY) NMR:



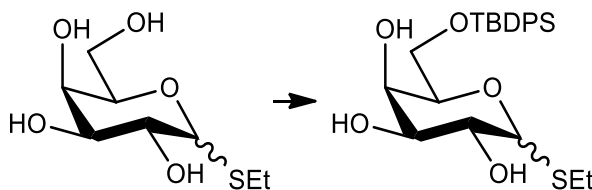
Ethane D-thiogalactopyranoside **127b**



Thioglycoside 126b (6.45 g, 0.02 mol) was dissolved in 100 mL of Methanol at 0 °C. NaOMe (6.5 mL, 25% wt. solution in Methanol) was added and the reaction was stirred and allowed to warm to r.t. The reaction was stirred for 24 h. The reaction was quenched with ion exchange resin amberlite ir-120(H). The organic phase was then concentrated and dried under high vacuum. The resulting brown solid **tetrol 127b** which was taken onto the next stage without purification (5.26 g 117%).

3. Experimental

Ethane 6-*O*-tert-butyldiphenylsilyl D-thiogalactopyranoside **128**

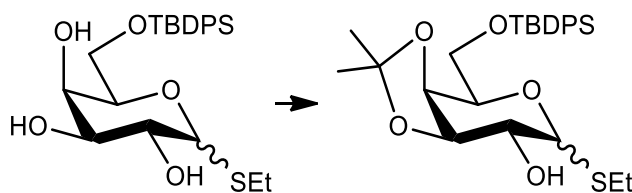


Tetrol 127b (5.7 g, 0.026 mol) was dissolved in 100 mL of DMF at r.t. Triethylamine (10 mL), dimethyl amino pyridine (6.5 g) and tert-butyl diphenyl silyl chloride (7.86 g, 0.0286 mol, 1.1 eqv.) were added, the reaction was stirred for 24 h at room temperature. 3.5 g of TBDPSCl (approx. 0.5 eqv.) was added and it was heated to 40 °C and stirred for a further 4 days. Finally, it was heated to 77 °C and stirred for a final 6 hours before the reaction was cooled and quenched with water (100 mL), and extracted with Et₂O (3 × 100 mL). The combined organic phases were then washed with water (2 x 150 mL) and brine (100 mL). It was then dried over MgSO₄ and concentrated. The resulting yellow oil was purified via silica gel chromatography using a 50–100% EtOAc in hexanes gradient to afford **silane 128** as a colourless oil (7.53 g 62%).

¹H NMR (CDCl₃, 400 MHz) δ 7.72–7.66 (m 4H Ar), 7.45–7.35 (m 6H Ar), 5.42 (d, 1H, J = 5.6 Hz, C1H), 4.24 (dd, 1H, J = 6.4, 6.4 Hz, C3H), 4.19 (dd, 1H, J = 8, 5.2 Hz, C2H), 4.11 (d, 1H J = 5.28 Hz, C4H), 3.89–3.8 (m, 2H, C5,6H), 3.55 (dd, 1H J = 9.64, 4 Hz, C6H), 2.56 (dq, 2H J = 8 Hz SEt CH₂), 1.26 (t, 3H J = 7.64 Hz SEt CH₃), 1.04 (s, 9H, *t*-Bu). Literature ¹H NMR (CDCl₃, 360 MHz) δ 7.65 (m, 4H), 7.40 (m, 6H), 5.42 (d, 1H, J = 5.5 H), 4.17 (dd, 1H, J = 5.5, 5.5 Hz), 4.12 (dd, 1H, J = 9.9, 5.5 Hz), 4.11 (d, 1H, J = 3.3 Hz), 3.91 (dd, 1H, J = 10.7, 5.5 Hz), 3.70 (dd, 1H, J = 10.7, 5.2 Hz), 3.54 (dd, 1H, J = 9.9, 3.3 Hz), 2.62 (dq, 1H, J = 7.4 Hz), 2.55 (dq, 1H, J = 7.4 Hz), 1.26 (t, 3H, J = 7.4 Hz), 1.05 (s, 9H) (107). ¹³C NMR (CDCl₃, 100 MHz) δ 132.8, 129.2, 127.2, 85.2, 84.7, 71, 63, 36, 31, 23.7, 23.3, 18.6. Specific Rotation [α]_D²⁰ +0.98 (3 mg/mL in EtOH). ν_{max} : 3372 (Broad), 2929, 2957, 2347, 2125, 2081, 1750, 1660, 1428, 1387, 1256, 1140, 1094, 1059, 824 cm⁻¹

3. Experimental

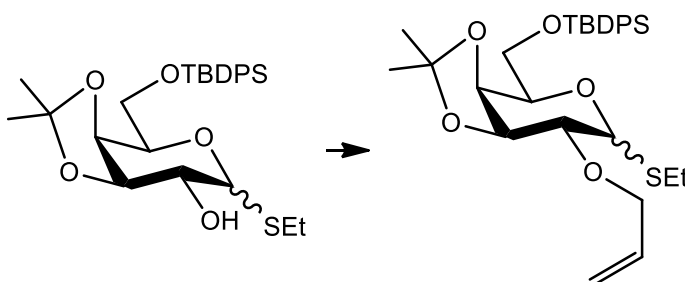
Ethane 3,4 O-(1-methylethylidene) 6-O-tert-butyldiphenylsilyl D-thiogalactopyranoside **129**



Silane 128 (7.45g, 0.026 mol) was dissolved in 100 mL of acetone at r.t. Dimethoxy propane (10 mL) and camphorsulfonic acid (1 g approx.) were added, the reaction was stirred for 16 h at room temperature. The reaction was quenched with saturated NaHCO₃ (100 mL), and extracted with Et₂O (3 × 100 mL). The combined organic phases were then washed with water (2 × 100 mL) and brine (100 mL). It was then dried over MgSO₄ and concentrated. The resulting yellow oil was purified via silica gel chromatography using a 50% EtOAc in hexanes to afford **acetoneide 129** as a colourless oil (6.16 g 76.7%). ¹H NMR (CDCl₃, 400 MHz) δ 7.74–7.68 (m, 4H Ar), 7.45–7.36 (m, 6H, Ar), 5.24 (d 1H, J = 5.12 Hz C1H), 4.38 (t 1H, J = 5.2 Hz, C3H), 4.19 (d 1H, J = 5.28 Hz C2H), 3.99 (d 1H, J = 2.16 Hz, C4H), 3.86 (d 1H, J = 2.64 Hz), 3.85 (dd 2H, J = 8, 1.24 Hz), 3.8 (t 1H, J = 6.64 Hz), 2.59 (q 2H, J = 6.4 Hz S-Et CH₂), 1.88 (s 6H) 1.23 (t 3H J = 9.4 S-Et CH₃), 1.17 (s 6H, *i*-Pr 2Me) 1.07 (s 9H, *t*-Bu). Literature ¹H NMR: δ 7.72–7.38 (m, 10H, aromatic protons), 5.09 (t, 1H, J = 9.6 Hz, H-2), 4.35 (d, 1H, J $\frac{1}{4}$ 9.9 Hz, H-1), 4.16 (d, 1H, J = 3.0 Hz, H-4), 3.95–3.91 (m, 2H, H-6), 3.62 (dd, 1H, $J_{2,3}$ = 9.3 Hz, $J_{3,4}$ = 3.2 Hz, H-3), 3.51 (t, 1H, J = 5.0 Hz, H-5), 2.68 (m, 2H, SCH₂CH₃), 2.15 (s, 3H, OCOCH₃), 1.24 (t, 3H, J = 7.5 Hz, SCH₂CH₃), 1.06 (s, 9H, Ph₂SiC(CH₃)₃) (108). ¹³C NMR (CDCl₃, 100 MHz) δ 135.7, 133.3, 129.8, 127.78, 109.5, 84.1, 79.4, 77.7, 76.7, 73.7, 63, 28.4, 26.9, 15. Specific Rotation [α]_D²⁰ +0.30 (4.9 mg/mL in EtOH). ν_{max} : 3411 (Broad), 3071, 3060, 2981, 2931, 2857, 2130, 2017, 1739, 1589, 1473, 1428, 1374, 1242, 1217, 1112, 1105, 1083, 1046, 1008, 875 cm⁻¹

3. Experimental

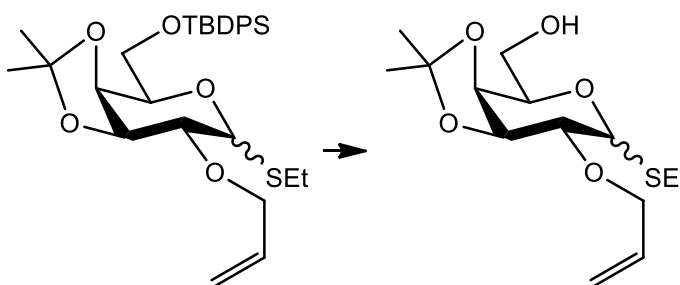
Ethane 2-O-allyl 3,4 O-(1-methylethylidene) 6-O-tert-butyldiphenylsilyl D-thiogalactopyranoside **132**



Acetanide 129 (2.18 g, 0.00435 mol) was dissolved in 25 mL of DMF at r.t. Allyl bromide (0.44 mL 0.0052 mol, 1.2 eqv.) and tetra-n-butyl ammonium iodide (1 eqv. approx.) were added and dissolved. This was cannulated onto NaH (0.24 g, 0.0061 mol, 1.4 eqv. 60% dispersal in mineral oil.) mixed with 5 mL of DMF at 0 °C. The reaction was stirred for 4 h and allowed to warm to room temperature. The reaction was quenched with water (50 mL), and extracted with Et₂O (3 × 50 mL). The combined organic phases were then washed with water (2 x 50 mL) and brine (50 mL). It was then dried over MgSO₄ and concentrated. The resulting yellow oil was purified via silica gel chromatography using a 20% EtOAc in hexanes to afford **allyl ether 132** as a colourless oil (1.91 g 81.2%). ¹H NMR (CDCl₃, 400 MHz) δ 7.73-7.66 (m 4H, Ar), 7.45-7.36 (m, 6H, Ar), 5.99-5.89 (m, 1H, Vinyl CH₁), 5.58 (d, 1H, J = 8 Hz, C1H), 5.33-5.23 (m, 2H, Allyl CH₂), 4.46 (dd, 1H J = 8, 4.28 Hz, C3H), 4.29-4.11 (m 4H, C2,4H, C2-CH₂), 3.97-3.77 (m 3H, C5,6H), 2.61-2.52 (m 2H, SEt CH₂), 1.25 (t 3H J = 9.2 Hz, SEt CH₃), 1.15 (s 6H, *i*-Pr 2Me) 0.97 (s 9H, *t*-Bu). ¹³C NMR (CDCl₃, 100 MHz) δ 135.8, 134.7, 130, 129.9, 129.6, 127.8, 117.9, 109.3, 84.9, 83.6, 78.2, 76.2, 73.4, 68.9, 63.1, 28.1, 26.9, 23.7, 14.7. Specific Rotation $[\alpha]_D^{20}$ +0.15 (0.5 mg/mL in EtOH). ν_{max} : 3457 (Broad), 3071 2956, 2930, 2857, 2212, 1749, 1589, 1472, 1425, 1380, 1243, 1218, 1106, 1047, 998, 923, 875 cm⁻¹

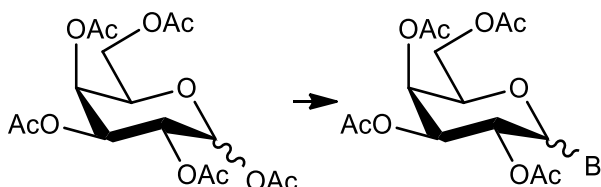
3. Experimental

Ethane 2-*O*-allyl 3,4-*O*-(1-methylethylidene) D-thiogalactopyranoside 132b



Allyl ether 132 (0.42 g, 0.775 mmol, 1 eqv.) was dissolved in 15 mL THF at r.t. tetra-*n*-butyl ammonium fluoride (0.85 mmol, 1.1 eqv., 1 mol solution in THF) was added. The reaction was stirred for 4.5 h. The reaction was then concentrated under reduced pressure and diluted with 20 mL of EtOAc. The reaction was washed with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with water (2 × 20 mL) and brine (20 mL). It was then dried over MgSO₄ and concentrated. The resulting off white oil was purified via silica gel chromatography using a 15% EtOAc in hexanes to afford **Ethane 2-*O*-allyl 3,4-*O*-(1-methylethylidene) D-thiogalactopyranoside 132b** as a colourless oil (0.22 g, 70.4%). ¹H NMR (CDCl₃, 400 MHz) δ 5.96-5.86 (m 1H), 5.38 (d 1H, *J* = 5.28 Hz), 5.25 (q 2H, *J* = 9.72 Hz), 4.31 (dd 1H, *J* = 7, 3.44 Hz), 4.29-4.12 (d 4H), 3.96-3.91 (m 1H), 3.81-3.74 (m 2H), 2.6-2.54 (m, 2H), (t 3H *J* = 3 Hz).

2,3,4,6 tetraacetyl D-bromo galactopyranoside 138

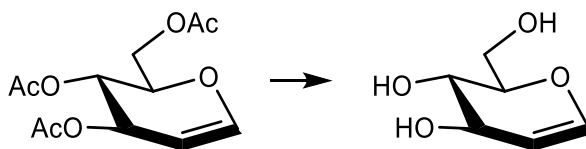


Acetate 125 (6.4 g, 0.016 mol) was dissolved in DCM (60 mL) in dry conditions, in a round bottomed flask equipped with a dropping funnel, and cooled to 0 °C. HBr in acetic acid solution (60 mL, 33% solution) was added into the dropping funnel, and proceeded to be added dropwise into the reaction medium over a period of 3 hours. The reaction was then allowed to warm to room temperature and left to stir for a further 16 hours. The reaction was then cautiously quenched with saturated sodium carbonate (100 mL) solution and transferred to a separating funnel. The aqueous phase was then extracted with DCM (3x50 mL). The combined organic phases were then washed with water (2x50 mL) and brine (50 mL), dried over magnesium sulphate and concentrated under vacuum. The residue was then purified by column chromatography to yield **bromide 138** as an off white solid (3.7 g, 54.83%). ¹H NMR

3. Experimental

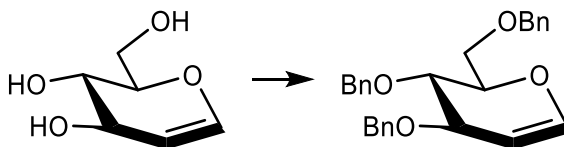
(CDCl₃, 400 MHz) δ 6.62 (d 1H, J = 4 Hz, C1H), 5.43 (m, 1H, C3H), 5.3 (dd 1H, J = 10.7, 3.4 Hz, C2H), 4.95 (dd 1H, J = 10.7, 4 Hz, C4H), 4.4 (t 1H, J = 6.4 Hz, C6H), 4.06 (m, 2H, C5,6H), 2.06 (s, 3H, Ac), 2.02 (s, 3H, Ac), 1.97 (s, 3H, Ac), 1.92 (s, 3H, Ac), Literature ¹H NMR (CDCl₃, 400 MHz) δ 6.69 (d 1H, J = 3.9 Hz), 5.51 (m, 1H), 5.39 (dd 1H, J = 10.6, 3.3 Hz), 5.04 (dd, 1H, J = 10.6, 3.9 Hz), 4.48 (t 1H, J = 6.5 Hz), 4.18 (dd, 1H, J = 11.4, 6.4 Hz), 4.09 (dd 1H, J = 11.4, 6.7 Hz), 2.14 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H) (105). ¹³C NMR (CDCl₃, 100 MHz) δ 170.3, 170, 169.9, 169.8, 88.2, 71.1, 68, 67.8, 67, 60.9, 20.7, 20.6, 20.6, 20.6. Specific Rotation $[\alpha]_D^{20}$ +1.03 (0.8 mg/mL in EtOH,). ν_{\max} : 3448, 3428, 2978, 2916, 2850, 2037, 1986, 1744, 1430, 1370, 1325, 1214, 1129, 1096, 1046, 1033, 846 cm⁻¹.

D-Glucal 140



3,4,6-tri-O-acetyl glucal (2.24 g, 0.00823 mol) was dissolved in 25 mL of Methanol at 0 °C. NaOMe (2.5 mL, 25% wt. solution in Methanol) was added and the reaction was stirred and allowed to warm to r.t. The reaction was stirred for 16 h. The reaction was quenched with ion exchange resin amberlite ir-120(h). The organic phase was then concentrated and dried under high vacuum. The resulting brown solid **glucal 140** was taken onto the next stage without purification (1.46 g, 122%).

Tri-O-benzyl D-glucal 141

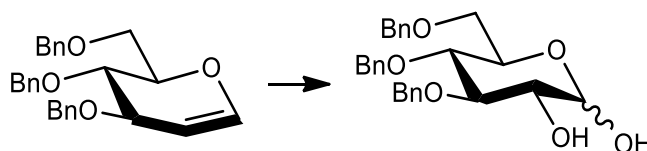


Triol 140 (7.55 g, 0.0517 mol) was dissolved in 50 mL of DMF at 0 °C. Benzyl bromide (30 mL 0.17 mol, 3.3 eqv.) and tetra-n-Butyl Ammonium Iodide (9.4 g) were added and dissolved. This was cannulated onto NaH (10.3g, 0.186mol, 3.6eqv. 60% dispersal in mineral oil.) mixed with 50ml of DMF at 0 °C. The reaction was stirred for 16 h and allowed to warm to room temperature. The reaction was quenched with water (150 mL), and extracted with Et₂O (3 × 200 mL). The combined organic phases were then washed with water (2 x 200 mL) and brine (200 mL). It was then dried over MgSO₄ and concentrated. The resulting yellow oil was purified

3. Experimental

via basic (5% triethylamine treated) silica gel chromatography using a 12% EtOAc in hexanes to afford **benzyl ether 141** as a white crystal (11.62 g, 54%). M.p. 54-56 °C. ^1H NMR (CDCl_3 , 400 MHz) δ 7.39-7.25 (m 15H, Ar), 6.44 (dd 1H, J = 4.92, 1.28 Hz, C1H), 4.9-4.85 (m 1H, C3H), 4.69-4.57 (m 6H, Bn), 4.25-4.23 (m 1H, C4H), 4.12-4.08 (m 1H, C2H), 3.92-3.77 (m 3H, C6,5H), Literature ^1H NMR (CDCl_3 , 400 MHz) δ 7.25–7.16 (m, 15H), 6.35 (dd 1H, J = 6.1, 1.1 Hz), 4.80 (dd, J = 6.2, 2.7 Hz, 1H), 4.76 (d, J = 11.3 Hz, 1H), 4.56 (d 1H, J = 11.3 Hz), 4.55 (d 1H, J = 11.8 Hz), 4.54 – 4.45 (m, 3H), 4.16 – 4.12 (m, 1H), 3.99 (ddd 1H, J = 8.2, 5.0, 2.9 Hz), 3.79 (dd 1H, J = 8.7, 6.2 Hz), 3.74 (dd 1H, J = 10.7, 5.0 Hz), 3.69 (dd 1H, J = 10.7, 2.9 Hz) (109). ^{13}C NMR (CDCl_3 , 100 MHz) δ 144.9, 138.4, 138.3, 138.1, 127.9, 127.9, 127.8, 100.1, 76.9, 75.8, 74.9, 73.6, 70.7, 68.6. ν_{max} : 3400, 3087, 3064, 3028, 2896, 2859, 1968, 1722, 1650, 1600, 1586, 1495, 1452, 1366, 1245, 1120, 1098, 1043, 1006, 970 cm^{-1} .

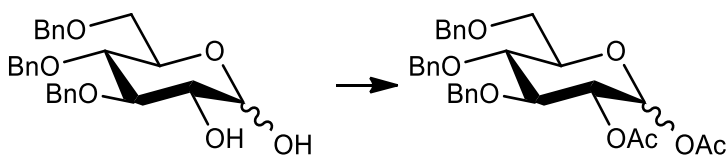
3,4,6-tri-*O*-benzyl D-glucopyranose 142



Benzyl ether 141 (11.62 g 0.0279 mol) was dissolved in 100 mL of acetone at r.t. NMO (3.68 g, 0.0314 mol, 1.126 eqv.), water (50 mL) and OsO_4 (1.56 mL, 10 mg/100 mL *t*-butyl alcohol) were added and the reaction was stirred for 16 h at room temperature. The reaction was washed with water (100 mL), and extracted with EtOAc (3×100 mL). The combined organic phases were then washed with water (2 x 100 mL) and brine (100 mL). The Aqueous phase was disposed of as heavy metal waste. The organic phase was then dried over MgSO_4 and concentrated. The resulting off white oil was purified via silica gel chromatography using a 20–100% EtOAc in hexanes gradient to afford **diol 142** as a colourless glass (9.15 g 72.88%). ^1H NMR (CDCl_3 , 400 MHz) δ 7.43-7.16 (m 15H, Ar), 5.26 (d 1H, J = 6.96 Hz, C1H), 5.00-4.94 (m 1H, C3H), 4.90-4.55 (m 6H, Bn), 4.09 (dt 1H J = 12.4, 4 Hz, C2H), 3.87 (dd 1H J = 12.32, 3.2 Hz, C4H), 3.73-3.53 (m 3H, C5,6H), 2.94 (br s 1H, OH) 2.25 (br s 1H, OH), Literature ^1H NMR (CDCl_3 , 200 MHz) δ 7.39-7.16 (m, 15 H), 5.27 (t, J = 3.4 Hz), 4.85 (m), 4.55-4.47 (m), 4.06 (dt, J = 3.4, 9.7 Hz), 3.81 (t, J = 9.0 Hz), 3.35 (d, J = 3.2 Hz), 2.43 (br s), 2.22 (d, J = 3.4 Hz), 1.61 (br s) (110). ^{13}C NMR (CDCl_3 , 100 MHz) δ 138, 128.7, 128, 101.8, 75.3, 74.1, 73.5, 72.2, 71.2, 69.2, 68.5, 67.7. ν_{max} : 3458 (Broad), 2927, 2869, 1765, 1496, 1453, 1366, 1234, 1044, 1027, 910 cm^{-1} . m/z Theoretical 468.2381 ($[\text{M}+\text{NH}_4]^+$), observed 468.2371 ($[\text{M}+\text{NH}_4]^+$). Specific Rotation $[\alpha]_{\text{D}}^{20}$ -0.18 (0.6 mg/mL in EtOH).

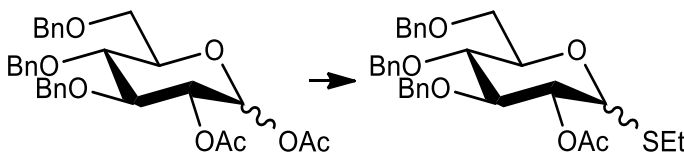
3. Experimental

1,2-di-*O*-acetyl 3,4,6-tri-*O*-benzyl D-glucopyranoside **143**



Diol 142 (10.38 g, 0.023 mmol) was mixed with acetic anhydride (100 mL) at r.t. H_2SO_4 (1 drop, <0.1 mmol) was added, and the reaction was stirred for 16 h. The reaction was then diluted with EtOAc (200 mL) and quenched with saturated NaHCO_3 (200 mL) and extracted twice with EtOAc (2×200 mL). The combine organic phases were washed twice with water (2×200 mL) and once with brine (200 mL). The organic phase was dried with MgSO_4 and concentrated to afford a crude yellow oil. The residue was purified via silica gel chromatography using a 10% – 100% EtOAc in hexanes gradient to afford **acetate 143** as a colourless glass (9.4 g 80.1%). ^1H NMR (CDCl_3 , 400 MHz) δ ppm 7.38–7.19 (m 15H, Ar), 6.24 (d 0.55H, $J = 3.54$ Hz, C1H (α)), 5.61 (d 0.45H, $J = 8.23$ Hz, C1H (β)), 5.06–5.01 (m 1H, C3H), 4.87–4.74 (m 6H, Bn), 4.64–4.45 (m 2H, C2,4H), 3.98–3.62 (m 3H, C5,6H), 2.12 (s 1.65H, Ac(α)), 2.04 (s 1.35H, Ac (β)) 1.97 (s 3H, Ac), Literature ^1H NMR (CDCl_3 , 100 MHz): δ 7.28–7.07 (m, 15H), 6.28 (d, 1H, $J = 10$ Hz), 5.13 (dd, 1H, $J = 9.2$ Hz, 9.6 Hz), 4.89–4.63 (m, 5H), 4.50 (m, 2H), 3.75 (m, 4H), 3.57 (m, 1H), 1.99 (s, 3H), 1.97 (s, 3H) (111). ^{13}C NMR (CDCl_3 , 100 MHz) δ 170, 169.6, 169.3, 138.1, 137.9, 137.8, 128.6, 128.6, 128.5, 128.1, 128, 128, 92.3, 90, 82.8, 80, 77.4, 75.5, 75.5, 75.3, 75.2, 68.1, 21.9, 20.9, 20.8. ν_{max} : 3063, 3032, 2872, 1748, 1497, 1454, 1360, 1234, 1213, 1129, 1078, 1053, 1027, 911 cm^{-1} . Specific Rotation $[\alpha]_{\text{D}}^{20}$ -0.10 (2.8 mg/mL in EtOH).

Ethane 2-*O*-acetyl 3,4,6-tri-*O*-benzyl D-thioglucopyranoside **143b**

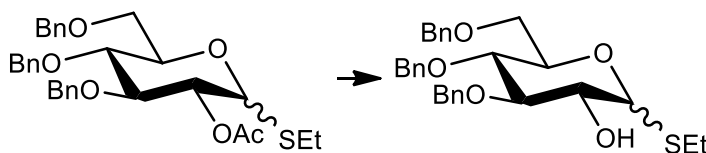


Acetate 143 (2.04 g, 0.04 mol) was dissolved in 25 mL of DCM at 0°C . HSEt (0.35 mL, 4.8 mmol, 1.2 eqv.) and SnCl_4 (2 mL, 0.001 mol as a 2 molar solution in DCM) were added, the reaction was stirred and allowed to warm to r.t. The reaction was stirred for two days, and further SnCl_4 (2 mL 0.001 mol as a 2molar solution in DCM) was added every 24 h. The reaction was quenched with 1mol HCL (25 mL), and extracted with DCM (3×25 mL). The combined organic phases were then washed with water (2×25 mL) and brine (25 mL). It was then dried over MgSO_4 and concentrated. The resulting yellow oil was purified via silica gel chromatography using a 20–100% EtOAc in hexanes gradient to afford **Ethane 2-*O*-acetyl**

3. Experimental

3,4,6-tri-*O*-benzyl *D*-thioglucopyranoside 143b as a colourless clear glass (1.47 g, 68.4%, $\alpha:\beta$ 2:3). ^1H NMR (CDCl_3 , 400 MHz) δ 7.35-7.24 (m 15H, Ar), 5.58 (d 1H J = 5.52 Hz, C1H), 5.04-4.97 (m, 1H, C3H), 4.85-4.69 (m 3H, Bn), 4.56 (dd, 1H, J = 11, 4 Hz, C2H), 4.38-4.09 (m 4H, Bn), 4.26 (dt, 1H J = 8.4, 2.8 Hz, C4H), 3.72-3.54 (m 3H, C5,6H), 2.74-2.60 (m 0.8H (α), SEt CH_2), 2.60-2.45 (m 1.2H (β), SEt CH_2), 2.01 (s 3H, Ac), 1.23 (t 3H, J = 15.12 Hz, SEt CH_3). Literature ^1H NMR (CDCl_3): δ 7.26–7.41 (m, 15H, Ar-H) 5.10 (t, 1H, J = 9.2 Hz, H-2), 4.88 (d, 1H, J = 11.3 Hz, CH_2Ph), 4.86 (d, 1H, J = 10.6 Hz, CH_2Ph), 4.76 (d, 1H, J = 11.4 Hz, CH_2Ph), 4.68 (d, 1H, J = 12.1 Hz, CH_2Ph), 4.64 (d, 1H, J = 11.0 Hz, CH_2Ph), 4.62 (d, 1H, J = 12.2 Hz, CH_2Ph), 4.43 (d, 1H, J = 10.0 Hz, H-1), 3.83 (dd, 1H, J = 11.1, 1.9 Hz, H-6b), 3.78 (dd, 1H, J = 11.3, 4.5 Hz, H-6a), 3.77 (t, 1H, J = 8.8 Hz, H-4), 3.74 (t, 1H, J = 9.0 Hz, H-3), 3.57 (m, 1H, H-5), 2.78 (m, 2H, SCH_2CH_3), 2.05 (s, 3H, CH_3CO), 1.33 (t, 3H, J = 7.4 Hz, SCH_2CH_3), (112). ^{13}C NMR (CDCl_3 , 100 MHz) δ ppm 170.8, 137.7, 14.9, 128.6, 127.9, 127.7, 84.6, 82, 80.9, 75.6, 75.2, 73.5, 69.1, 63, 24.3, 21. ν_{max} : 2964, 2346, 2021, 1743, 1364, 1228, 1099, 1037 cm^{-1} . Specific Rotation $[\alpha]_{\text{D}}^{20}$ -0.10 (5.6 mg/mL in EtOH).

Ethane 3,4,6-tri-*O*-benzyl *D*-thioglucopyranoside 144

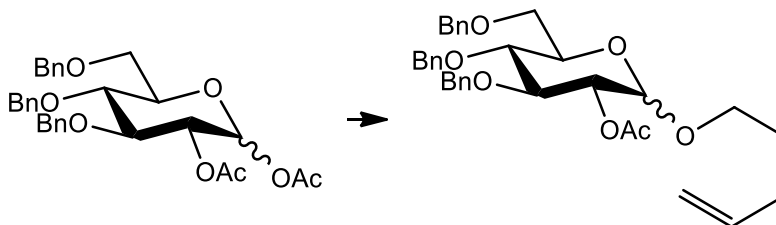


Ethane 2-*O*-acetyl 3,4,6-tri-*O*-benzyl thioglucoside (3.3 g, 0.00615 mol) was dissolved in 300 mL of Methanol at 0 °C. NaOMe (3 mL, 25% w.t. solution in Methanol) was added and the reaction was stirred and allowed to warm to r.t. The reaction was stirred for 16 h. The reaction was quenched with ion exchange resin amberlite ir-120(h). The organic phase was then concentrated and dried under high vacuum. The resulting off white solid **alcohol 144** was recrystallized to a white powder from Hexane (3 g, 98.4%, $\alpha:\beta$ 2:3). M.p. 88 – 89 °C. ^1H NMR (400 MHz, $\text{CHLOROFORM-}d$) δ ppm 7.40-7.22 (m, 15H, Ar), 5.35 (d, J = 5.49 Hz, 1H, C1H), 4.97-4.58 (m, 6H, Bn), 4.35 (d 1H, J = 9.61 Hz, C3H), 4.34-4.31 (m, 1H, C2H), 4.21-4.09 (m 1H, C4H) 3.72-3.47 (m, 3H, C5,6H), 2.71-2.67 (m 0.8H, (α)SEt CH_2), 2.68-2.57 (m, 1.2H, (β)SEt CH_2), 1.38-1.23 (m, 3H, SEt CH_3), Literature ^1H NMR (CDCl_3): δ 7.1-7.4 (m, 15H, Ar's), 4.8-5.0 (m, 3H. Bn's), 4.5-4.6 (m, 3H, Bn's), 4.3 (d, 1H. J = 9 Hz, H-1), 3.4-3.8 (m. 6H, H-2-H-6b). 2.70 (2 dq, 2H. CH_2S). 1.30 (t. 3H. J = 7.0 Hz, Me) (113). ^{13}C NMR (100 MHz, $\text{CHLOROFORM-}d$) δ ppm 138.5, 138.1, 128.6, 128.1, 128, 86.5, 84.5, 79.7, 77.7, 74.8, 73.5,

3. Experimental

72.1, 61.8, 24.7, 15.3. ν_{max} : 3273, 2921, 2883, 1454, 1971, 1354, 1151, 1072, 1057, 1015, 960 cm^{-1} . Specific Rotation $[\alpha]_{\text{D}}^{20} +1.29$ (3.6 mg/mL in EtOH).

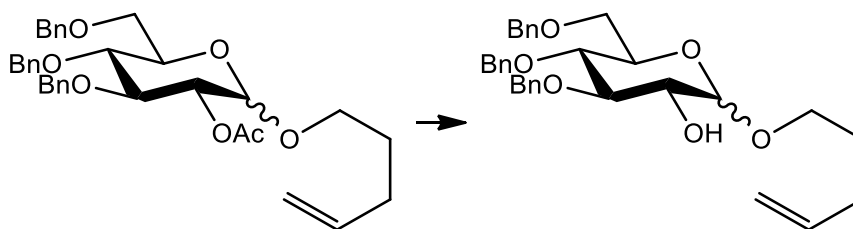
4-penten-1-yl (2-*O*-acetyl) (3,4,6-tri-*O*-benzyl) D-glucopyranoside **97**



Acetate 143 (1.67 g, 0.00312 mol) was dissolved in 25 mL of DCM at 0 °C. 4-penten-1-ol (0.32 mL, 1.2 eqv.) and SnCl_4 (2 mL, 0.001 mol as a 2m solution in DCM) were added, the reaction was stirred and allowed to warm to r.t. The reaction was stirred for 3 days, and SnCl_4 (2 mL 0.001 mol as a 2 N solution in DCM) was added every 24 h. The reaction was quenched with 1mol HCL (25 mL), and extracted with DCM (3 \times 25 mL). The combined organic phases were then washed with water (2 x 25 mL) and brine (25 mL). It was then dried over MgSO_4 and concentrated. The resulting yellow oil was purified via silica gel chromatography using a 20–100% EtOAc in hexanes gradient to afford ***n*-pentenyl glycoside 146** as a colourless clear glass (1.3 g, 74.3%). ^1H NMR (CDCl_3 , 400 MHz) δ ppm 7.39-7.15 (m, 15H, Ar), 5.86-5.75 (m, 1H, Vinyl CH), 5.08-4.94 (m, 3H, C1H, Vinyl CH_2), 4.84-4.50 (m, 6H, Bn), 4.36 (d 1H, $J = 7.89$ Hz, C3H), 3.93-3.85 (m, 1H, C2H), 3.80-3.64 (m, 4H C4,5,6H), 3.54-3.39 (m, 2H, Pent CH_2), 2.17-2.06 (m, 2H, Pent CH_2), 1.98 (s, 3H, Ac), 1.68 (dd 2H, $J = 13.40, 6.62$ Hz Pent CH_2). ^{13}C NMR (CDCl_3 , 100 MHz) δ 172.9, 137, 131.87, 131.8, 131.3, 119, 104.5, 86.1, 80.7, 79.1, 78.8, 78.5, 78.3, 77, 71.4, 71.1, 33.1, 32.1, 24.2. ν_{max} : 3490, 3030, 2924, 1749, 1729, 1497, 1453, 1366, 1315, 1215, 1051, 1027, 911 cm^{-1} . Specific Rotation $[\alpha]_{\text{D}}^{20} +0.34$ (1.5 mg/mL in EtOH).

3. Experimental

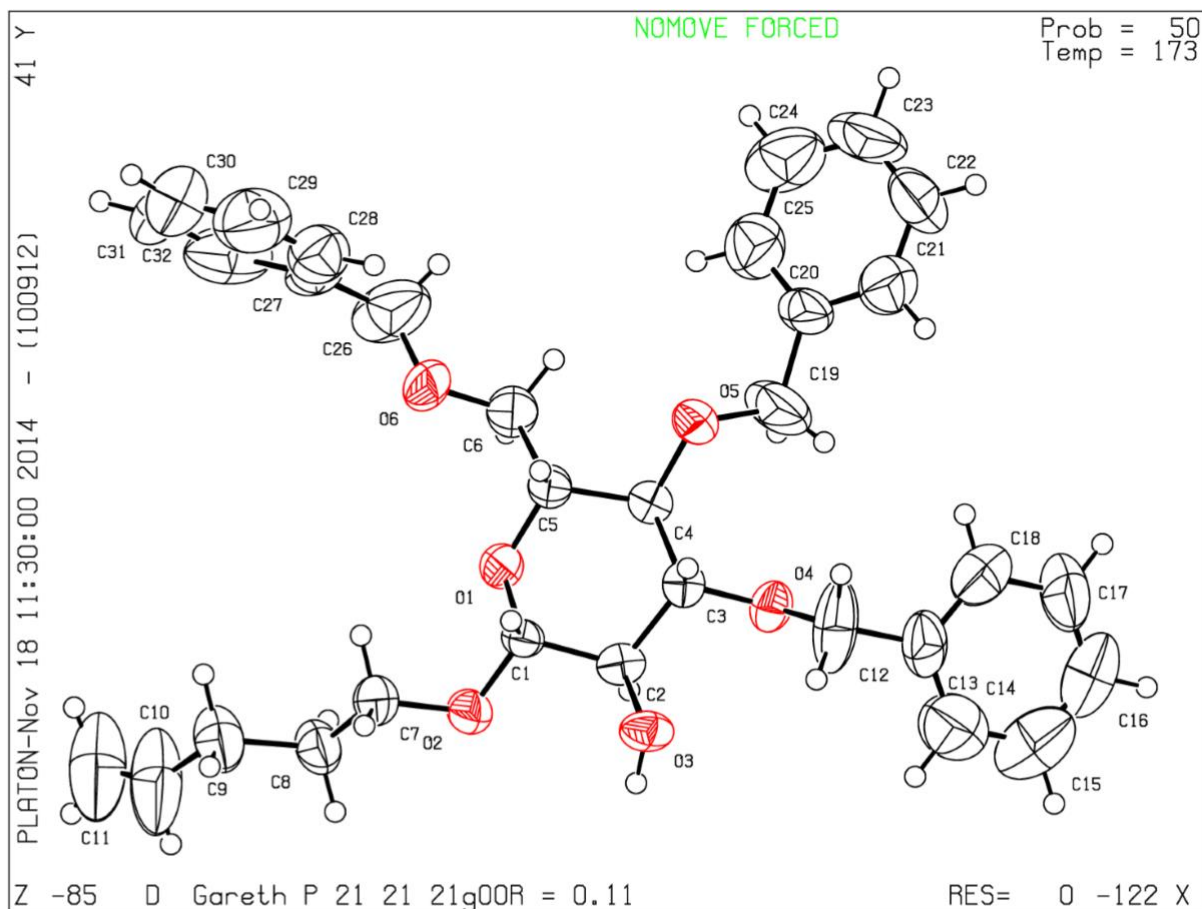
4-penten-1-yl 3,4,6-tri-*O*-benzyl-D-glucopyranoside **147**



n-pentenyl glycoside **146** ($1.3, 2.318 \times 10^{-3}$ mol) was dissolved in 300 mL of Methanol at 0 °C. NaOMe (3 mL, 25% w.t. solution in Methanol) was added and the reaction was stirred and allowed to warm to r.t. The reaction was stirred for 16 h. The reaction mixture was concentrated under vacuo. The off-white syrup was diluted with ethyl acetate and transferred into a separating funnel where it was washed with water. The aqueous phase was extracted with 2x100 mL of ethyl acetate. The Combined organic phase was washed with 2x100 mL of water and 100 mL of brine, it was then dried over magnesium sulphate and concentrated under high vacuum. The resulting off white solid, **alcohol 147**, was recrystallized to a white crystalline solid from 20% dichloromethane in Hexane (1.168 g, 97.2%). ^1H NMR (CDCl_3 , 400 MHz) δ ppm 7.41-7.25 (m, 15H, Ar), 5.84 (ddt 1H, $J = 17.02, 10.28, 6.65, 6.65$ Hz, Vinyl CH), 5.09-4.94 (m, 3 H, C1H, Vinyl CH_2), 4.88-4.82 (m 1H, C3H), 4.69-4.53 (m, 6H, Bn), 4.26 (d 1H, $J=7.32$ Hz, C2H), 3.96 (dt 1H, $J = 9.58, 6.53$ Hz, C4H), 3.81-3.67 (m, 3H, C6H, Pent CH_2), 3.65-3.48 (m, 2H, C5,6H), 2.45 (br s, 1H, OH), 2.20-2.13 (m, 2H, Pent CH_2), 1.84-1.69 (m, 2H, Pent CH_2). M.p. 61-62°C, m/z Theoretical 517.259 (M-H), observed 517.2594 (M-H), Theoretical 536.2992 ($[\text{M}+\text{NH}_4]^+$), observed 536.3007 ($[\text{M}+\text{NH}_4]^+$). Specific rotation $[\alpha]_{\text{D}}^{20} +0.15$ (1.7 mg/mL in EtOH). ν_{max} : 3088, 3062, 3029, 2905, 2867, 1497, 1453, 1358, 1207, 1130, 1064, 1026, 1000, 912 cm^{-1} .

3. Experimental

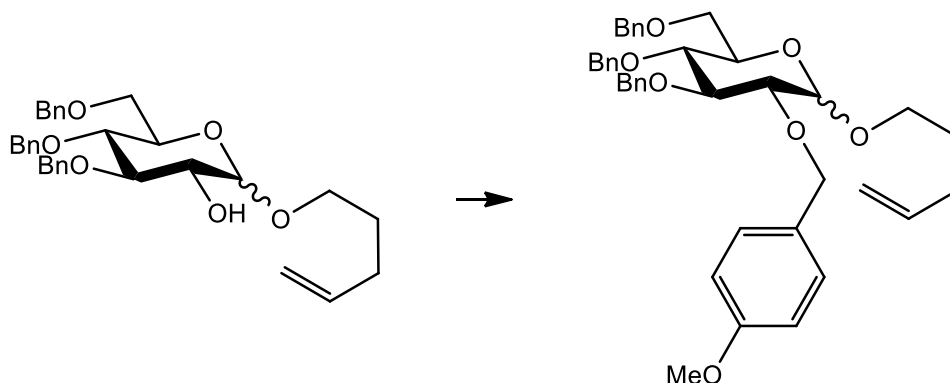
Crystal cell (single anomer purified from column chromatography): $a = 5.2868(2)$, $b = 18.3054(5)$, $c = 29.7257(8)$, $\alpha = 90$, $\beta = 90$, $\gamma = 90$, Space group P 21 21 21,



3. Experimental

4-penten-1-yl 2-O-p-methoxybenzyl-3,4,6-tri-O-benzyl-D-glucopyranoside

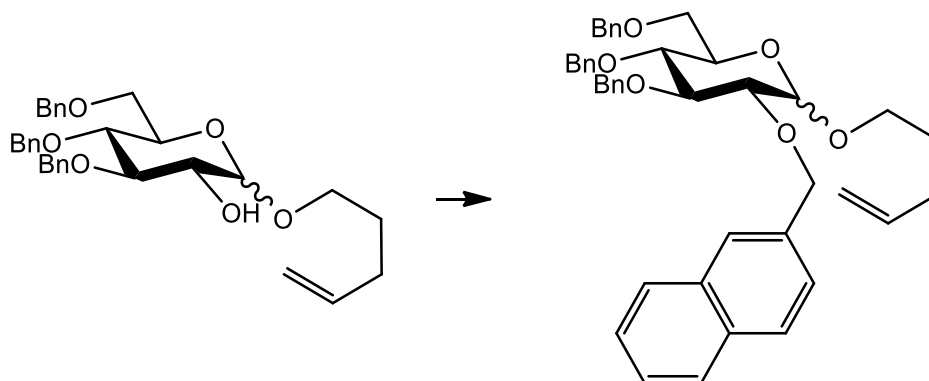
174



n-pentenyl glycoside **147** (0.94 g, 0.00181 mol) was dissolved in 5 mL of DMF at 0 °C. *p*-Methoxy benzylchloride (0.35 mL, 1.2 eqv.) and tetra-*n*-Butyl Ammonium Iodide (0.1 g) were added and dissolved. Neat NaH (0.05 g 1.2 eqv) was added. The reaction was stirred for 16 h at 0 °C and allowed to warm to room temperature. The reaction was quenched with water (15 mL), and extracted with Et₂O (3 × 20 mL). The combined organic phases were then washed with water (2 x 20 mL) and brine (20 mL). It was then dried over MgSO₄ and concentrated. The resulting yellow oil was purified with silica gel chromatography using a 12% EtOAc in hexanes to afford *p*-methoxy benzyl ether **174** as a white solid (0.996 g, 86.2%). ¹H NMR (CDCl₃, 400 MHz) δ ppm 7.41-7.25 (m 15H, Bn), 7.22-7.15 (m 2H, *p*-Bn), 6.94-6.85 (m 2H, *p*-Bn), 5.88 (ddt 1H, *J* = 17.02, 10.31, 6.63, 6.63 Hz, Vinyl CH), 5.11-4.90 (m 4H, C1,3H, Vinyl CH₂), 4.90-4.49 (m 8H, Bn CH₂), 4.42 (dd 1H, *J* = 7.78 Hz, C2H), 4.05-3.98 (m 1H, C4H), 3.83-3.80 (m 3H, OMe), 3.80-3.71 (m 2 H, C5,6H), 3.71-3.42 (m 3H, C6H, Pent CH₂), 2.27-2.13 (m 2H, Pent CH₂), 1.87-1.74 (m 2H, Pent CH₂). M.p. 67 – 68. Specific rotation [α]_D²⁰ +0.03 (1.1 mg/mL in EtOH). ν_{max} : 3062, 2933, 2861, 1586, 1514, 1451, 1367, 1302, 1251, 1172, 1117, 1059, 1036, 949 cm⁻¹.

3. Experimental

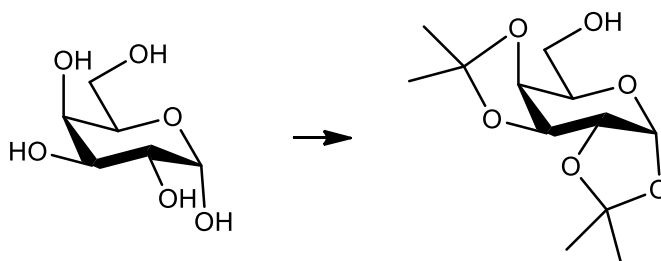
4-penten-1-yl 2-*O*-(2-methyl) naphthyl-3,4,6-tri-*O*-benzyl-D-glucopyranoside **175**



n-pentenyl glycoside **147** (1.03 g, 0.00199 mol) was dissolved in 5 mL of DMF at 0 °C. 2-(bromomethyl) naphthalene (0.52g, 1.2 eqv.) and tetra-*n*-Butyl Ammonium Iodide (0.1g) were added and dissolved. Neat NaH (0.06g, 1.2 eqv) was added. The reaction was stirred for 16h at 0°C and allowed to warm to room temperature. The reaction was quenched with water (15 mL), and extracted with Et₂O (3 × 20 mL). The combined organic phases were then washed with water (2 x 20 mL) and brine (20 mL). It was then dried over MgSO₄ and concentrated. The resulting yellow oil was purified with silica gel chromatography using a 12% EtOAc in hexanes to afford (2-*methyl*) naphthyl ether **175** as an off white solid (0.84 g, 64.2%). ¹H NMR (CDCl₃, 400 MHz) δ 7.87-7.73 (m, 5H). 7.51-7.41 (m 4H), 7.37-7.23 (m 13H), 5.83 (ddt 1H, J=17.05, 10.26, 6.56, 6.56 Hz, CH Vinyl), 5.11-4.74 (m 7H, C1,3,2H and Bn(4Hs)) 4.62-4.49 (m 3H, C4H Vinyl CH₂), 4.45-4.4 (m 1H, C6H), 4.04-3.95 (m 1H, C5H), 3.79-3.42 (m 7H, C6H, Bn(4Hs), Pent CH₂), 2.23-2.14 (m 2H, Pent CH₂), 1.83-1.72 (m 2H, Pent CH₂), m/z Theoretical 658.3295 (M), observed 658.3287 (M), Theoretical 676.3633 ([M+NH₄]⁺), observed 676.3621 ([M+NH₄]⁺). ν_{max}: 3057, 2927, 2871, 2176, 2022, 1719, 1451, 1369, 1354, 1275, 1118, 1058, 1037, 1028, 964 cm⁻¹. Specific rotation [α]_D²⁰ +0.14 (0.7 mg/mL in EtOH).

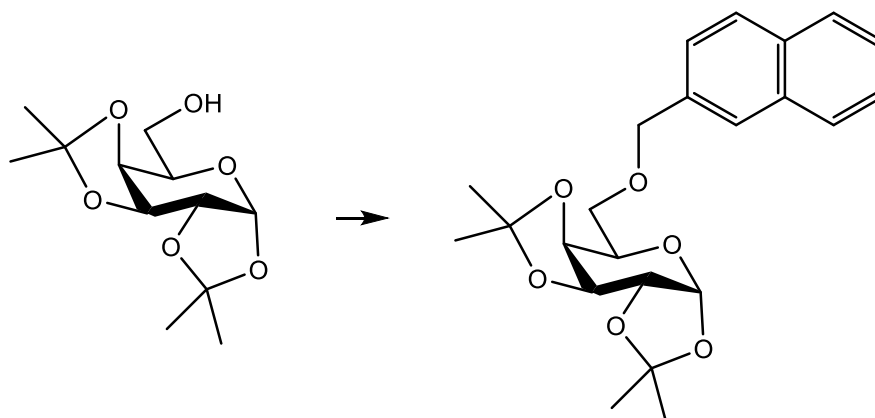
3. Experimental

1,2:3,4-Di-O-isopropylidene- α -D-galactopyranose **148**



Galactose (10 g) was stirred in acetone (100 mL) with a catalytic amount of camphorsulphonic acid. 2,2-dimethoxypropane (2.1 eqv.) was added into the mixture gradually over a minute. The mixture was then brought to reflux, and stirred until dissolution occurred. Once dissolution had occurred the reaction was then allowed to cool to room temperature. The solution was then concentrated under vacuo and the crude syrup was dissolved in 100 mL ethyl acetate. The was then transferred to a separating funnel where it was washed with 100 mL of water. The aqueous phase was then extracted with a further 2x100 mL of ethyl acetate. The combined organic phases where washed with a further 2x100 mL of water and 100 mL of brine. The ethyl acetate was then dried over magnesium sulphate and concentrated to an off-white syrup. The crude syrup was then purified with flash column chromatography (20% EtOAc – Hexane to neat EtOAc) to yield **148** as a pure colourless oil. Specific rotation $[\alpha]_D^{20}$ -0.84 (3.3 mg/mL in EtOH). ν_{\max} : 3411 (broad), 2986, 2938, 2894, 2034, 1653, 1520, 1381, 1210, 1166, 1096, 1067, 1000, 918, 899 cm^{-1} .

1,2:3,4-Di-O-isopropylidene-6-(2-methyl) naphthyl- α -D-galactopyranose **177**

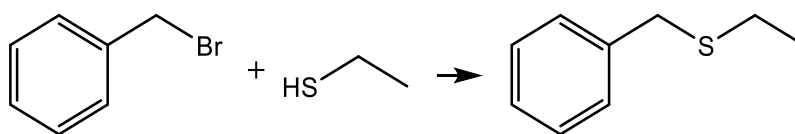


Alcohol 148 (3.145 g, 0.012 mol) was dissolved in 50ml of DMF at 0 °C. 2-(bromomethyl) naphthalene (2.67 g 0.012 mol) and tetra-n-Butyl Ammonium Iodide (1 g) were added and dissolved. NaH (0.5 g as a 60% dispersion in mineral oil) was added. The reaction was stirred

3. Experimental

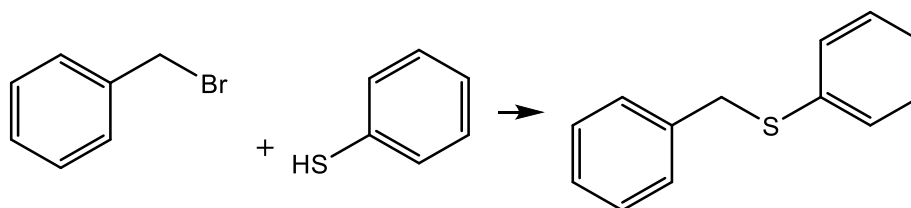
for 16h at 0°C and allowed to warm to room temperature. The reaction was quenched with water (150 mL), and extracted with Et₂O (3 × 200 mL). The combined organic phases were then washed with water (2 × 200 mL) and brine (200 mL). It was then dried over MgSO₄ and concentrated. The resulting yellow oil was purified via basic (5% triethylamine treated) silica gel chromatography using a 12% EtOAc in hexanes to afford **(2-methyl) naphthyl ether 177** as a colourless oil (11.62g, 54%). ¹H NMR (CDCl₃, 400 MHz) δ 7.85-7.77 (m 4H), 7.52-7.42 (m 3H), 5.56 (d 1H, *J* = 5.03 Hz, C1H), 4.83-4.68 (m 2H, CH₂ Naph), 4.60 (dd 1H, *J* = 7.95, 2.34 Hz, C3H), 4.34-4.26 (m 2H, C24H), 4.06-4.00 (m 1H, C6H), 3.77-3.65 (m 2H, C5,6H), 1.56-1.51 (m 3H), 1.45-1.42 (m 3H), 1.33 (s 6H). Literature (114). *v*_{max}: 3237, 2985, 2936, 2907, 2176, 2035, 2020, 1978, 1509, 1380, 1278, 1253, 1210, 1168, 1101, 1068, 1002, 890 cm⁻¹. Specific rotation [*α*]_D²⁰ -0.48 (1.4 mg/mL in EtOH).

Benzyl Ethyl Sulphide 159



Ethane thiol (7 mL) was dissolved in 25 mL of DMF at r.t. with benzyl bromide (7 mL) and dissolved. To the solution 7 mL of lutidine was added dropwise at 0 °C. A small amount of TBAI was added and the reaction was stirred for 4 h and allowed to warm to room temperature. And then overnight. The reaction was quenched with water (50 mL), and extracted with Et₂O (3 × 50 mL). The combined organic phases were then washed with water (2 × 50 mL) and brine (50 mL). It was then dried over MgSO₄ and concentrated to afford **sulphide 159** as a colourless liquid (5.35g, 86%). ¹H NMR (CDCl₃, 400 MHz) δ 7.31-7.22 (m 5H), 3.73 (s 2H), 2.44 (q 2H, *J* = 7.38, 11.04), 1.242 (t, *J* = 7.41, 3H), ¹³C NMR (CDCl₃, 400 MHz) δ 138.5, 128.9, 128.8, 128.4, 126.8, 35.5, 25.2, 14.3. *m/z* Theoretical 151.0582 (M-H), observed 151.0585 (M-H).

Benzyl Phenyl Sulphide 159b

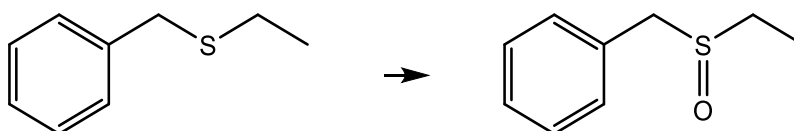


Phenylthiol (0.67g, 0.0061mol) was dissolved in 25 mL of DMF at r.t. with benzyl bromide

3. Experimental

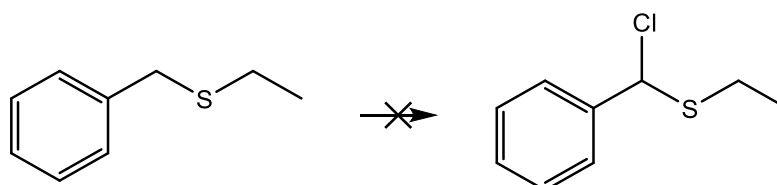
(1.25 g 0.00732 mol, 1.2 eqv.) and dissolved. The solution was cannulated onto NaH (0.24 g, 0.0061 mol 60% dispersal in mineral oil.) mixed with 5 ml of DMF at 0 °C. The reaction was stirred for 4 h and allowed to warm to room temperature. The reaction was quenched with water (50 mL), and extracted with Et₂O (3 × 50 mL). The combined organic phases were then washed with water (2 x 50 mL) and brine (50 mL). It was then dried over MgSO₄ and concentrated to afford **benzyl phenyl sulphide 159b** as a colourless liquid (1.12 g, 91.7%). ¹H NMR (CDCl₃, 400 MHz) δ 7.30-7.19 (m 10H), 4.15 (s 2H),

Benzyl Ethyl Sulphoxide 159c



EtSBn 159 (4.96 g) was dissolved in Methanol (50 mL) stirred and cooled to 0 °C. An aqueous solution of KIO₄ (7.5 g in 50 mL) was added dropwise from a dropping funnel over an hour and the reaction was allowed to warm to room temperature. The reaction was stirred for a further 24 h. The solution was then concentrated, diluted with water (10 mL) and transferred to a separating funnel, the aqueous phase was extracted with chloroform (3x50 mL). The combined organic phases were washed with water (2x50 mL) and brine (50 mL) and dried over magnesium sulphate. The solution was then concentrated under vacuum to yield the **sulphide 159c** as an off white solid. ¹H NMR (CDCl₃, 400 MHz) δ 7.2 – 7.3 (m, 5H), 3.88 (q, J₁= 10.59, J₂= 12.9, 2H), 2.44 – 2.60 (m, 2 H), 1.24 (t, J= 7.5, 3H). *m/z* Theoretical 169.0682 (M+H), observed 169.0678 (M+H). Specific rotation [α]_D²⁰ -0.05 (1.7 mg/mL in EtOH).

1-Chloro 1-Phenyl Methyl Ethyl sulphide 159d

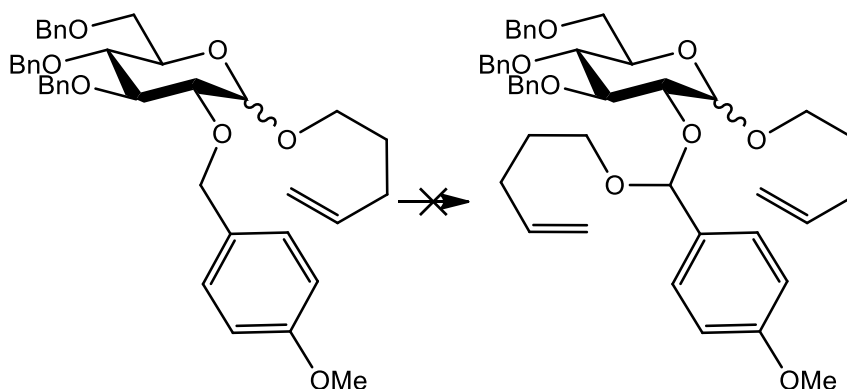


Benzyl Ethyl Sulphide 159 (0.5 mL) was dissolved in CCl₄ (10 mL) under an inert N₂ atmosphere from a N₂ balloon, and septum, and stirred at room temperature. NCS (0.44 g) was added. Once the NCS had dissolved the solution was left to stir for 16 hours. The reaction was

3. Experimental

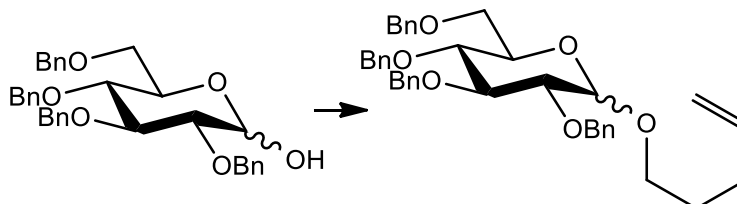
then quenched with aqueous sodium thiosulphate (10% solution) and transferred to a separating funnel. Where it was separated and the aqueous phase extracted into DCM (3x10 mL). The combined organic phases were then washed with water (2x10) and brine (10 mL) before being dried over magnesium sulphate and concentrated under vacuum to yield an odorous of-white liquid. H^1 NMR analysis showed mainly starting material.

4-penten-1-yl 2-O-*p*-methoxybenzyl-(O-*n*-penten-1-yl)-3,4,6-tri-O-benzyl-D-glucopyranoside **172**



p-methoxy benzyl ether **174** (51 mg, 0.08 mmol) was dissolved in DCM (10 mL) with 4Å-molecular sieves and under an inert, dry, N_2 atmosphere from a schlenk line, and stirred at room temperature. N-Penten-1-ol (7 mg) was injected, and the solution was cooled to 0 °C. DDQ (230 mg) was added and the solution was left to stir for 8 hours. The reaction was then quenched with aqueous sodium hydrogen carbonate (20 ml, 20% solution) and transferred to a separating funnel. The DCM was separated and the aqueous phase extracted into DCM (1x10 mL). The combined organic phases were then dried over magnesium sulphate and concentrated under vacuum to yield an odorous of-white liquid. The residue was then purified by basic aluminium column chromatography with DCM – Hexane (25%). H^1 NMR analysis showed some of the mixed acetal **172**, but mainly alcohol **147** and *p*-methoxy benzaldehyde.

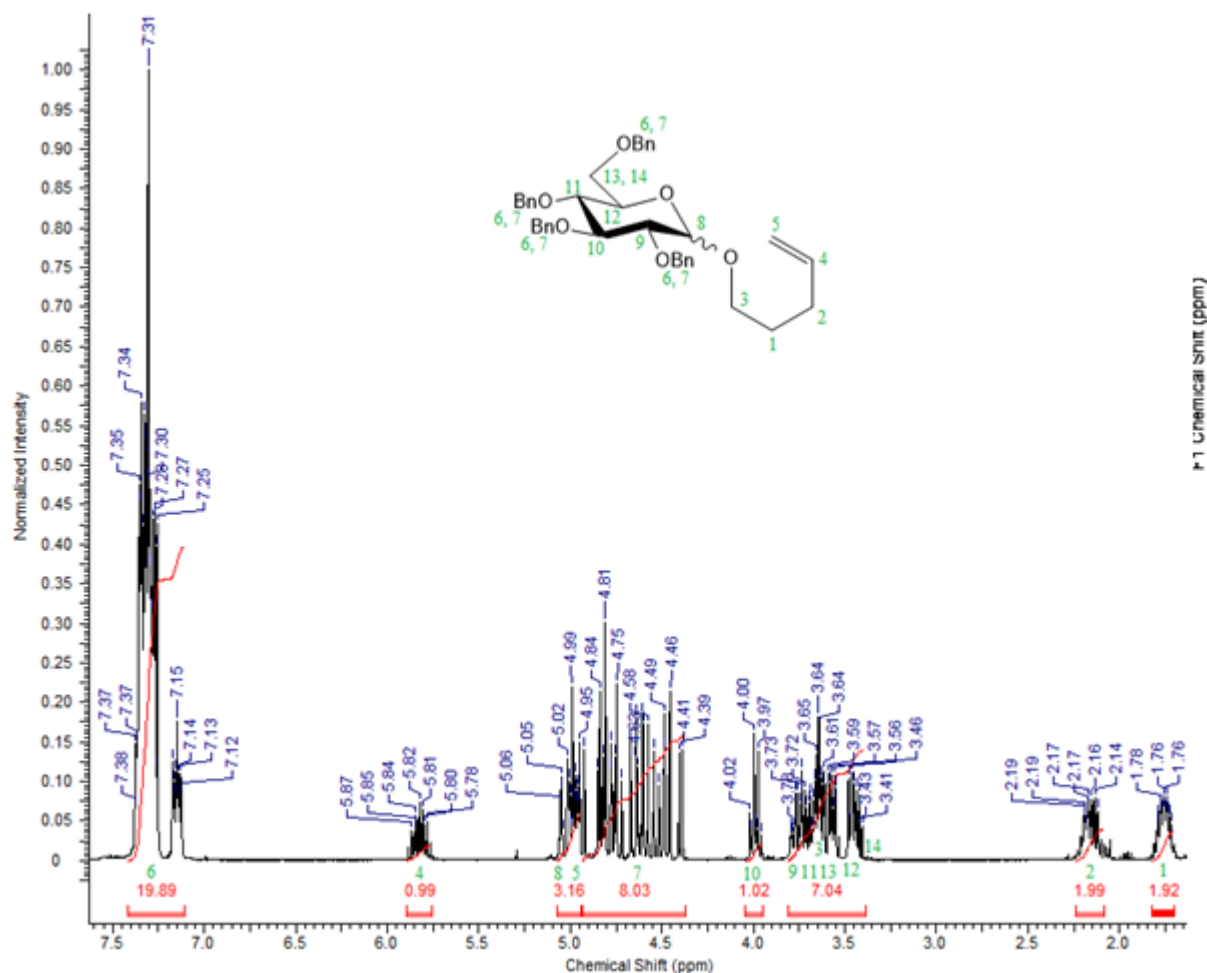
4-penten-1-yl 2,3,4,6-tetra-O-benzyl-D-glucopyranoside **17**



2,3,4,6-tetra-O-benzyl glucopyranoside (1.01 g, 0.00187mol) was dissolved in 25 mL of DMF at r.t. with 5-bromopent-1-ene (0.33 mL 0.0028mol, 1.5eqv.) and dissolved and cooled to -84 °C. The solution was cannulated onto NaH (0.0822 g, 0.002 mol, 1.1 eqv. 60% dispersal in

3. Experimental

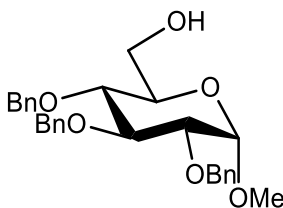
mineral oil.) mixed with 5ml of DMF also cooled to -84 °C. The reaction was stirred for 16 h and allowed to warm to room temperature. The reaction was quenched with water (50 mL), and extracted with Et₂O (3 × 50 mL). The combined organic phases were then washed with water (2 x 50 mL) and brine (50 mL). It was then dried over MgSO₄, concentrated and purified under flash column chromatography (Hexanes:EtOAc 4:1) afford **glycoside 17** as a colourless oil (0.863g, 75.8%). ¹H NMR (CDCl₃, 400 MHz):



Literature ¹H NMR (500 MHz, CDCl₃) mixture of anomers ($\alpha/\beta = 1.2:1$) δ 7.40-7.21 (m, 22H), 7.15 (ddd 3H, $J = 11.3, 7.3, 2.0$ Hz), 5.81 (ddd 1H, $J = 17.0, 10.3, 8.3$ Hz), 5.03 (dd 1H, $J = 3.6, 1.8$ Hz), 5.02-4.89 (m, 4H), 4.85-4.69 (m, 5H), 4.67-4.50 (m, 3H), 4.47 (dd 1H, $J = 11.4, 3.4$ Hz), 4.38 (d 1H, $J = 7.7$ Hz), 4.03-3.91 (m, 2H), 3.81-3.69 (m, 2H), 3.69-3.59 (m, 4H), 3.58-3.50 (m, 2H), 3.48-3.39 (m, 2H), 2.22-2.07 (m, 3H), 1.81-1.69 (m, 3H) (115). ν_{max} : 3063, 3031, 2916, 2875, 2865, 1964, 1640, 1496, 1471, 1451, 1403, 1369, 1356, 1316, 1278, 1199, 1118, 1058, 1039, 998, 949, 913 cm⁻¹. Specific rotation $[\alpha]_{\text{D}}^{20}$ -0.03 (0.6 mg/mL in EtOH).

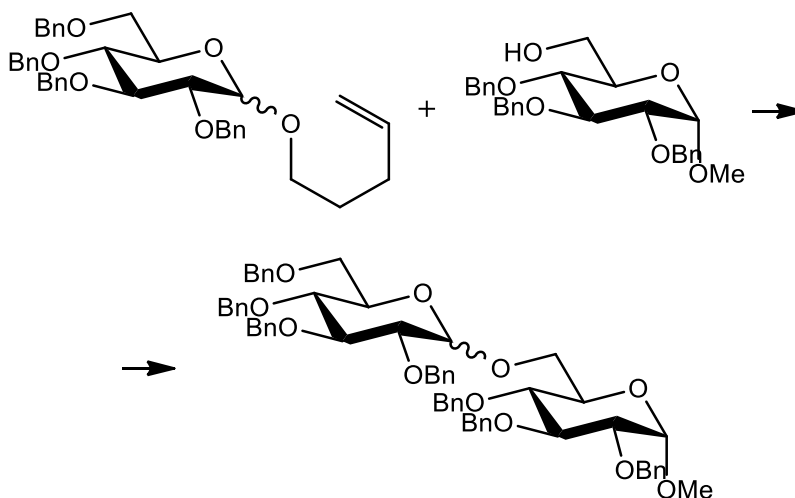
3. Experimental

α -Methyl 2,3,4-tri-*O*-benzyl-D-glucopyranoside 18



^1H NMR (CDCl_3 , 400 MHz) δ 7.56-7.48 (m, 3H, Ar), 7.44-7.30 (m, 12H, Ar), 5.61-5.55 (m, 1H, C1H), 4.98-4.83 (m, 3H, Bn), 4.77-4.58 (m, 3H, Bn), 4.33-4.24 (m, 1H, C5H), 4.13-4.03 (m, 1H, C2H), 3.91-3.81 (m, 1H, C3H), 3.78-3.69 (m, 1H, C4H), 3.67-3.55 (m, 2H, C6H₂), 3.41 (s, 3H), Literature ^1H NMR (400 MHz, CDCl_3): δ 7.34-7.29 (m, 15H, Ar-H), 5.00-4.62 (m, 6H, $\text{PhCH}_2\text{O}-$), 4.56 (d 1H, $J = 3.5\text{Hz}$, 1-H), 4.02-3.48 (m, 7H), 3.36 (s 3H, OCH_3) (116). ν_{max} : 3482, 3032, 2699, 2948, 2928, 2902, 2871, 1727, 1497, 1452, 1361, 1347, 1208, 1187, 1160, 1141, 1085, 1068, 1056, 1026, 1017, 993, 970, 912 cm^{-1} , Specific rotation $[\alpha]_{\text{D}}^{20}$ -0.30 (3.7 mg/mL in EtOH).

Methyl *O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl) -(1 \rightarrow 6)-2,3,4-tri-*O*-benzyl- α -D-glucopyranoside 19



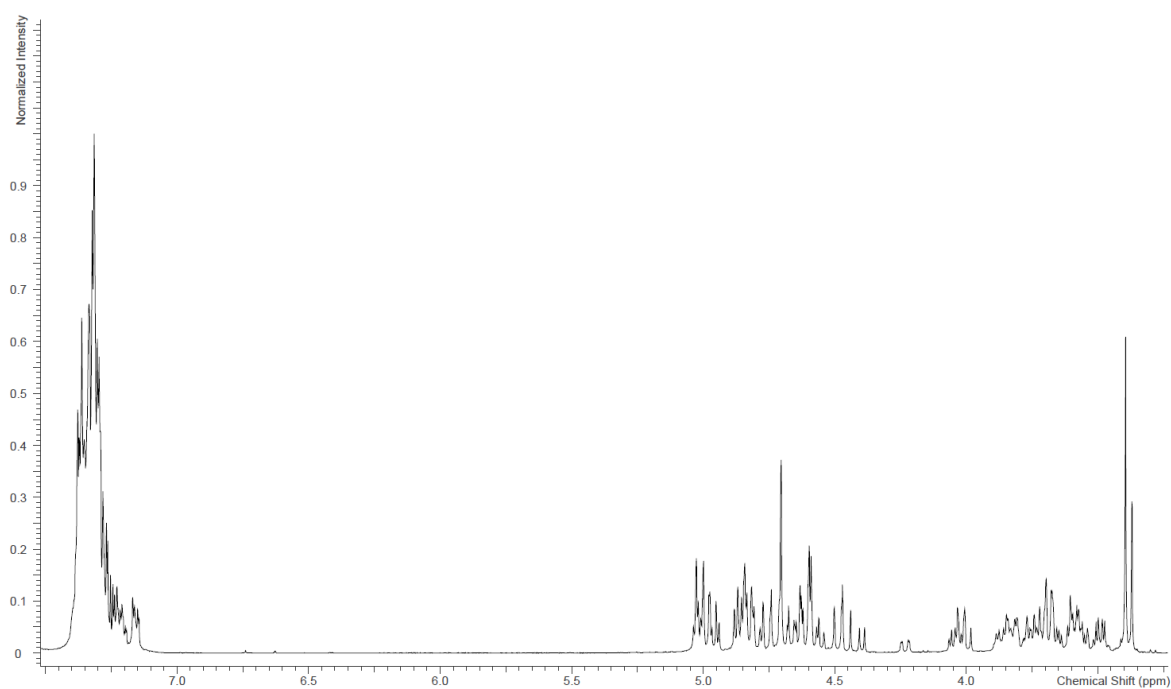
Glucoside 17 (0.449 g, 0.000738mol) and **glucoside 18** (0.312g, 0.00067mol) were mixed together with a stirrer bar and activated 4Å molecular sieves (1g) under high vacuum for an hour. The mixture was then flushed with nitrogen and to which was added stock dry DCM (5 mL). The mixture was cooled to 0°C and NIS (0.332g, 0.00147mol) was added. The reaction was stirred at 0 °C until the reaction mixture had turned pink-purple. It was then allowed to warm to r.t. and stirred for a further 16 h. The reaction was then quenched with aqueous sodium thiosulphate (10% solution) and transferred to a separating funnel. Where it was separated and the aqueous phase extracted into DCM (3x10 mL). The combined organic

3. Experimental

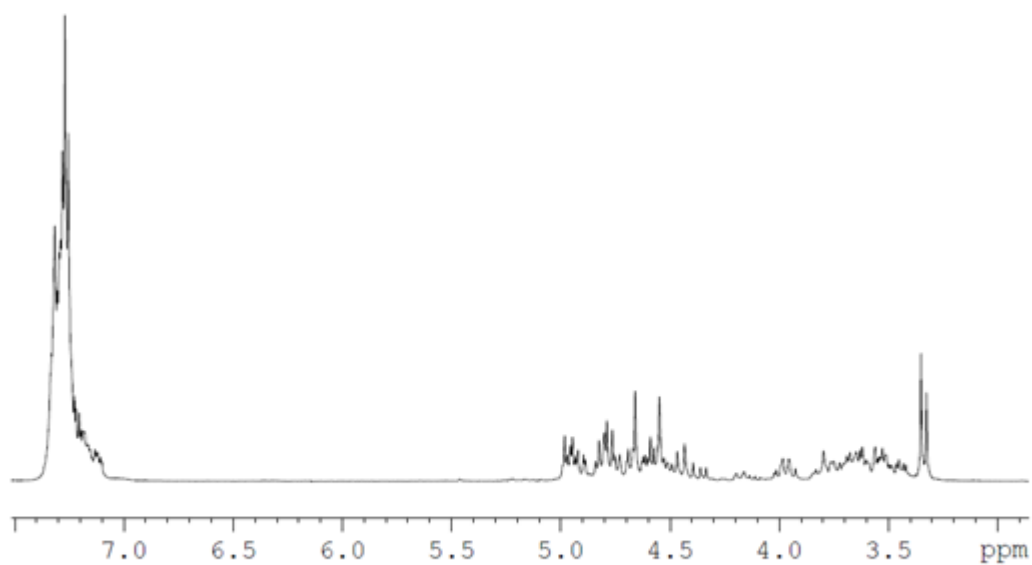
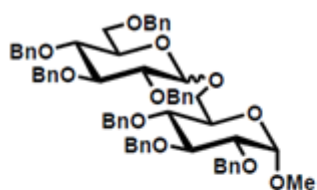
phases were then washed with water (2x10 mL) and brine (10 mL) before being dried over magnesium sulphate and concentrated under vacuum to yield the crude colourless oil, which was purified under flash column chromatography (EtOAc – hexanes 10%) to yield the **disaccharide 19**, as a mixture of anomers, as a colourless oil (0.450g, 68%) (α : β 2:1 by ^1H NMR). ^{13}C NMR (CDCl_3 , 100 MHz) δ 135.8, 125.3, 125, 124.6, 94.9, 94.2, 77.1, 77.1, 74, 73.7, 72.7, 71.9, 70.4, 67.3, 67.2, 65.5, 65.4, 52.1. ν_{max} : 3108, 3088, 3063, 3029, 2905, 2862, 1497, 1453, 1358, 1207, 1186, 1160, 1131, 1099, 1064, 1026, 1001, 912, 732, 694 cm^{-1} . Specific rotation $[\alpha]_{\text{D}}^{20}$ -0.08 (1.5 mg/mL in EtOH).

3. Experimental

Our ^1H NMR:



Literature ^1H NMR (14):



4. References

4. References

- (1) OpenStax College, Biology.
<http://cnx.org/contents/s8Hh0oOc@9.10:EygPBN19@9/Eukaryotic-Cells2013>, Accessed Feb 29, 2016.
- (2) Hakomori, S.-I.; Wang, S.-M.; Young Jr, W. W.; "Isoantigenic expression of Forssman glycolipid in human gastric and colonic mucosa: Its possible identity with "A-like antigen" in human cancer.", *Proc. Natl. Acad. Sci. U.S.A.*, 1977, 74, 3023–3027.
- (3) Feng, J.; Hevey, R.; Ling, C.-C.; "Synthesis of a Forssman antigen derivative for use in a conjugate vaccine.", *Carbohydr. Res.*, 2011, 346, 2650–2662.
- (4) Goldenberg, A. 2006. Generative medicine. GNU Free Documentation,
http://www.generativemedicine.org/wiki/wiki.pl/Forssman_antigen, Accessed Feb 17, 2016.
- (5) Fischer, E.; "Ueber die Glucoside der Alkohole." *Ber. Dtsch. Chem. Ges.*, 1893, 26, 2400–2412.
- (6) Ferrières, V.; Bertho, J.-N.; Plusquellec, D.; "A new synthesis of O-glycosides from totally O-unprotected glycosyl donors." *Tetrahedron Lett*, 1995, 36, 2749-27523.
- (7) Izumi, M.; Fukase K.; Kusumoto, S.; "TMSCl as a Mild and Effective Source of Acidic Catalysis in Fischer Glycosidation and Use of Propargyl Glycoside for Anomeric Protection." *Biosci. Biotechnol. Biochem.*, 2002, 66, 211–214.
- (8) Clayen, J.; Greeves N.; Warren, S.; *Organic Chemistry.*, Oxford University Press Inc: New York, 2012.
- (9) Demchenko, A. V.; *Handbook of Chemical Glycosylation.*, Wiley-VCH: Heidelberg, 2008
- (10) IUPAC Gold Book. International Union of Pure and Applied Chemistry,
<http://goldbook.iupac.org/A00372.html>, Accessed Mar 2, 2016.
- (11) Davis, B. G.; Fairbanks, A. J., *Carbohydrate Chemistry Oxford Chemistry Primers.* Oxford University Press: New York, 2002.
- (12) Lepage, M. L.; Bodlenner, A.; Compain, P.; "Stereoselective Synthesis of α -Glycosyl Azides by TMSOTf-Mediated Ring Opening of 1,6-Anhydro Sugars.", *Eur. J. Org. Chem.*, 2013, 10, 1963–1972.
- (13) Sinnott, M. L.; "Catalytic Mechanisms of Enzymic Glycosyl Transfer." *Chem. Rev.*, 1990, 90, 1171-1202.
- (14) Kaeothip, S.; Pornsuriyasak, P.; Demchenko, A. V.; "Silver(I) tetrafluoroborate as a potent promoter for chemical glycosylation." *Tetrahedron Lett.*, 2008, 49, 1542–1545.
- (15) Lai, H.-Y. L.; Axerlrod, B.; "The specificity of the synthetic reaction of two yeast α -

4. References

glucosidases.” *Biochim. Biophys. Acta.*, 1975, 391, 121–128.

(16) Nunomura, S.; Mori, M.; Ito, Y.; Ogawa, T.; “A total synthesis of Forssman glycolipid, globopentaosyl ceramide.” *Tetrahedron Lett.*, 1989, 30, 6713–6716.

(17) Burckhardt, H.; Ernst, S.-H.; “Eine neue Methode zur Synthese von Glykosiden der Phenole.” *Ber. Dtsch. Chem. Ges.*, 1933, 66, 378–383.

(18) Selivanov, S. I.; Ibatullina, F. M.; “Reaction of 1,2-trans-glycosyl acetates with phosphorus pentachloride: new efficient approach to 1,2-trans-glycosyl chlorides.” *Tetrahedron Lett.*, 2002, 52, 9577–9580.

(19) UC Davis Chemwiki. The University of California,
http://chemwiki.ucdavis.edu/Core/Organic_Chemistry/UMM_chemwiki_project/Alkyl_Halides/Substitution_reactions_of_alkyl_halides%3A_two_mechanisms, Accessed Jun 17, 2016.

(20) Heuckendorff, M.; Premathilake, H. D.; Pornsuriyasak, P.; Madsen, A. Ø.; Pedersen, C. M.; Bols, M.; and Demchenko, A. V.; “Superarming of Glycosyl Donors by Combined Neighboring and Conformational Effects.” *Org. Lett.*, 2013, 15, 4904–4907.

(21) Ogawa, T.; Nunomura, S.; “A total synthesis of a stage specific embryonic antigen-3 (SSEA-3), globopentaosyl ceramide, IV3GalGb4Cer. Use of 2,4,6-trimethylbenzoyl group as a stereocontrolling auxiliary.” *Tetrahedron Lett.*, 1988, 29, 5681–5684.

(22) Montero, J.-L.; Winum, J.-Y.; Leydet, A.; Kamal, M.; Pavia, A. A.; Roque, J.-P.; “A convenient synthesis of peracetylated glycosyl halides using bismuth(III) halides as catalysts.”, *Carbohydr. Res.*, 1997, 297, 175–180.

(23) Mitchell, S. A.; Pratt, M. R.; Hruby V. J.; Polt, R.; “Solid-Phase Synthesis of O-Linked Glycopeptide Analogues of Enkephalin.”, *J. Org. Chem.*, 2001, 66, 2327–2342.

(24) Talley, E. A.; Reynolds, D. D.; Evan, W. L.; “Synthesis of certain disaccharide acetates in the mannose series.” *J. Am. Chem. Soc.*, 1943, 65, 575–582.

(25) Fischer, E.; Zsch, K.; Sitzber. kgl. preuss. Akad Wiss., 1913, 16, 311–314

(26) Crucius, G.; Hanack, M.; Ziegler, T.; “Synthesis of Glycoconjugated Phthalonitriles for New Phthalocyanine-Based Photosensitizers.” *J. Carb. Chem.*, 2015, 34, 263–302.

(27) Fischer, E.; Fischer, H.; “Über einige Derivate des Milchzuckers und der Maltose und über zwei neue Glucoside.” *Ber. Dtsch. Chem. Ges.*, 1910, 43, 2521–2536.

(28) Thiem, J.; Meyer, B.; “Synthesen mit Iod- und Bromtrimethylsilan in der Saccharidchemie.” *Ber. Dtsch. Chem. Ges.*, 1980, 113, 3075–3085.

(29) E.-Badry, M. H.; G.-Hague, J.; “Thermal effect in b-selective glycosylation reactions using glycosyl iodides.” *Tetrahedron Lett.* 2005, 46, 6727–6728.

4. References

- (30) Wolfrom, M. L.; *Advances in Carbohydrate Chemistry*, Vol 13, Academic press: London, 1961.
- (31) Mukaiyama, T.; Hashimoto, Y.; Shoda, S.-I.; "Stereoselective Synthesis of 1,2-cis-Glycofuranosides." *Chem. Lett.*, 1983, 12, 935-938.
- (32) Rosenbrook Jr., W.; Riley, D.A.; Lartey, P.A.; "A new method for the synthesis of glycosyl fluorides." *Tetrahedron Lett.* 1985, 26, 3-4.
- (33) Nielsen, M. K.; Ugaz, C. R.; Li, W.; Doyle, A. G.; "PyFluor: A Low-Cost, Stable, and Selective Deoxyfluorination." *J. Am. Chem. Soc.* 2015, 137, 9571-9574.
- (34) Kobayashi, S.; Yoneda, A.; Fukuhara, T.; Hara, S.; "Deoxyfluorination of alcohols using N,N-diethyl- α,α -difluoro-(m-methylbenzyl)amine." *Tetrahedron* 2004, 60, 6923-6930.
- (35) Caddick, S.; Gazzard, L.; Motherwell, W. B.; Wilkinson, J. A.; "Preparation of 1-fluoroglycosides from 1-arylthio and 1-arylselenoglycosides using 4-methyl(difluoroiodo)benzene." *Tetrahedron*, 1996, 52, 149-156.
- (36) Burkart, M. D.; Zhang Z.; Hung S.-C.; Wong, C.-H.; "A New Method for the Synthesis of Fluoro-Carbohydrates and Glycosides Using Selectfluor." *J. Am. Chem. Soc.*, 1997, 119, 11743-11746.
- (37) Hara, S.; Kunigami, M.; "Synthesis of glycosyl fluorides from (phenylthio)glycosides using IF₅-pyridine-HF." *Carbohydr. Res.*, 2015, 417, 78-80.
- (38) Hara, S.; Monoi, M.; Umemura, R.; Fuse, C.; "IF₅-pyridine-HF: air- and moisture-stable fluorination reagent." *Tetrahedron*, 2012, 68, 10145-10150.
- (39) Fritz, M.; Klemer, A.; "Glycosyl Fluorides and Azides." In *Advances in Carbohydrate Chemistry*, Elsevier Inc.: Amsterdam 1962
- (40) Danishefsky, S. J.; Gordon, D. M.; "Displacement reactions of a 1,2-anhydro- α -D-hexopyranose: Installation of useful functionality at the anomeric carbon." *Carbohydr. Res.*, 1990, 206, 361-366.
- (41) Shimizu, M.; Nakahara, Y.; Yoshioka, H.; "Stereocontrolled halofluorination of glycals with silicon tetrafluoride, leading to a facile synthesis of glycosyl fluorides." *J. Fluorine Chem.*, 1999, 97, 57-60.
- (42) Mukaiyama, T.; Murai, Y.; Shoda, S.-I.; "An Efficient Method for Glucosylation of Hydroxy Compounds Using Glucopyranosyl Fluoride." *Chem. Lett.*, 1981, 10, 431-432.
- (43) Michel, J.; Schmidt, R. R.; "Facile Synthesis of α - and β -O-Glycosyl Imidates; Preparation of Glycosides and Disaccharides." *Angew. Chem. Int. Ed.*, 1980, 19, 731-732.
- (44) Koeller, K. M.; Smith, M. E. B.; Wong, C.-H.; "Chemoenzymatic Synthesis of PSGL-1

4. References

Glycopeptides:.” *Bioorg. Med. Chem.* 2000, 8, 1017-1025.

(45) Yang, J.; C.-Vanosdell, C.; Mensah, E. A.; Nguyen, H. M.; “Cationic Palladium(II)-Catalyzed Stereoselective Glycosylation with Glycosyl Trichloroacetimidates.” *J. Org. Chem.*, 2008, 73, 794–800.

(46) Delbrück, K.; Fischer, E.; “Über Thiophenol-glucoside.” *Ber. Dtsch. Chem. Ges.*, 1909, 42, 1476-1482.

(47) Boons, G.-J.; Stauch, T.; “Stereoselectivity in glycosidic bond formation: Studies on the Anomerisation of Thioglycosides.” *Synth. Lett.*, 1996, 9, 906-908.

(48) Boons, G.-J.; Geurtsen, R.; Holmes, D.; “Chemoselective glycosylations (part 1): Differences in size of anomeric leaving groups can be exploited in chemoselective glycosylations.” *Tetrahedron Lett.*, 1995, 36, 6325-6328.

(49) Schmitz, H.; Fritz, M.; “Das Verhalten von Sulfoxyden gegenüber Sulfit.” *Ber. Dtsch. Chem. Ges.* 1939, 72, 992–994.

(50) Gómez, A. M.; Casillas, M.; Barrio, A.; Gawel, A.; López, J. C.; “Synthesis of Pyranoid and Furanoid Glycals from Glycosyl Sulfoxides by Treatment with Organolithium Reagents.” *Eur. J. Org. Chem.* 2008, 23, 3933–3942.

(51) Balcerzak, A. K.; Ferreira, S. S.; Trant, J. F.; Ben, R. N.; “Structurally diverse disaccharide analogs of antifreeze glycoproteins and their ability to inhibit ice recrystallization.” *Bioorg. Med. Chem. Lett.*, 2012, 22, 1719–1721.

(52) Drisko, R. W.; Bonner, W. A.; “Oxidations of Certain Polyacetyl- β -D-thioglycosides to the Corresponding Sulfones.” *J. Am. Chem. Soc.*, 1948, 70, 2435–2438.

(53) Lowary, T. L.; Chang, G. X.; “A Glycosylation Protocol Based on Activation of Glycosyl 2-Pyridyl Sulfones with Samarium Triflate.” *Org. Lett.* 2000, 2, 1505-1508.

(54) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Reid, B.; “Armed and disarmed n-pentenyl glycosides in saccharide couplings leading to oligosaccharides.” *J. Am. Chem. Soc.*, 1988, 110, 5583–5584.

(55) Reid, B.; Wu, Z.; Andrews, C. W.; Skowronski, E.; Bowen, J. P.; “Torsional effects in glycoside reactivity: saccharide couplings mediated by acetal protecting groups.” *J. Am. Chem. Soc.*, 1991, 113, 1434–1435.

(56) Reid, B.; López, J. C. *Reactivity Tuning in Oligosaccharide Assembly*, Springer Science & Business Media: Berlin, 2011.

(57) Veeneman, G. H.; Leettwen, S. H.; Boom, J. H.; “Iodonium Ion Promoted Reactions at the Anomeric Centre II. An Efficient Thioglycoside Mediated Approach Toward the

4. References

- Formation of 1,2 trans Linked Glycosides and Glycosidic Esters.” *Tetrahedron Lett.* 1990, 31, 1331-1334.
- (58) Osborn, H.; 2003. *Carbohydrates*. Cambridge, Massachusetts: Academic Press.
- (59) Konradsson, P.; Roberts, C.; Reid, B.; “Conditions for modified Fischer glycosidations with n-pentenol and other alcohols.” *Recl. Trav. Chim. Pays-Bas*, 1991, 110, 23-24.
- (60) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Reid, B.; “Armed and disarmed n-pentenyl glycosides in saccharide couplings leading to oligosaccharides.” *J. Am. Chem. Soc.*, 1988, 110, 5583–5584.
- (61) Baldwin, J. E. “Rules for ring closure.” *Journal of the Chemical Society, Chem. Commun.*, 1976, 18, 734-736.
- (62) Reid, B.; Arasappan, A.; “n-Pentenyl Glycoside Methodology in the Stereoselective Construction of the Tetrasaccharyl Cap Portion of Leishmania Lipophosphoglycan.” *J. Org. Chem.*, 1996, 61, 2401-2406.
- (63) Ogawa, T.; Nunomura, S.; “A total synthesis of a stage specific embryonic antigen-3 (SSEA-3), globopentaosyl ceramide, IV3GalGb4Cer. Use of 2,4,6-trimethylbenzoyl group as a stereocontrolling auxiliary.” *Tetrahedron Lett.*, 1988, 29, 5681–5684.
- (64) Clayen, J.; Nukada, T.; Ogawa, T.; “Synthesis of a branched mannohexaoside, a part structure of a high-mannose-type glycan of a glycoprotein.” *Carbohydr. Res.*, 1985, 136, 135–152.
- (65) Kim, J.-H.; Yang, H.; Park, J.; Boons, G.-J.; “A General Strategy for Stereoselective Glycosylations.” *J. Am. Chem. Soc.*, 2005, 127, 12090-12097.
- (66) Clayden, J. *Organic Chemistry*, 2nd Ed., Oxford University Press: New York, 2012.
- (67) Master Organic Chemistry. *MasterOrganicChemistry.com*, <http://www.masterorganicchemistry.com/2014/08/05/fused-rings/>, Accessed 0Sep 2, 2016
- (68) Liu, X.-W.; Hoang, K. L. M.; “The intriguing dual-directing effect of 2-cyanobenzyl ether for a highly stereospecific glycosylation reaction.” *Nat. Commun.* 2014, 5.
- (69) Ueki, A.; Hirota, M.; Kobayashi, Y.; Komatsu, K.; Takano, Y.; Iwaoka, M.; Nakahara, Y.; Hojo, H.; Nakahara, Y.; 2008. “Stereoselective synthesis of benzyl-protected β -galactosides by propionitrile-mediated glycosylation.” *Tetrahedron*, 2014, 64, 2611–2618.
- (70) Crich, D.; Smith, M.; “1-Benzenesulfinyl Piperidine/Trifluoromethanesulfonic Anhydride: A Potent Combination of Shelf-Stable Reagents for the Low-Temperature Conversion of Thioglycosides to Glycosyl Triflates and for the Formation of Diverse Glycosidic Linkages.” *J. Am. Chem. Soc.*, 2001, 123, 9015-9020.

4. References

- (71) Hashimoto, S.; Hayashi, M.; Noyori, R.; "Glycosylation using Glucopyranosyl Fluorides and Silicon-Based Catalysts. Solvent Dependency of the Stereoselection." *Tetrahedron Lett.*, 1984, 25, 1379-1382.
- (72) Cox, D. J.; Smith, M. D.; Fairbanks, A. J.; "Glycosylation Catalysed by a Chiral Brønsted Acid." *Org. Lett.*, 2010, 12, 1452-1455.
- (73) Kumar, A.; Kumar, V.; Dere, R. T.; Schmidt, R. R.; "Glycoside Bond Formation via Acid - Base Catalysis." *Org. Lett.*, 2011, 13, 3612-3615.
- (74) Hindsgaul, O.; Barresi, F.; "The synthesis of β -mannopyranosides by intramolecular aglycon delivery: scope and limitations of the existing methodology." *Can. J. Chem.*, 1994, 72, 1447-1465.
- (75) Hürttlen, J.; Ziegler, T.; Ritter, A. "Intramolecular glycosylation of prearranged glycosides part 5. α -(1 \rightarrow 4)-Selective glucosylation of glucosides and glucosamines." *Tetrahedron Lett.*, 1997, 38, 3715-3718.
- (76) Schmidt, R. R.; Huchel, U.; "Intramolecular glycoside bond formation — A rigid spacer concept for the diastereoselective linkage between glycosyl donor and acceptor." *Tetrahedron Lett.*, 1998, 39, 7693-7694.
- (77) Jung, K.-H.; Müller, M.; Schmidt, R. R.; "Intramolecular O-Glycoside Bond Formation." *Chem. Rev.*, 2000, 100, 4423–4442.
- (78) Schmidt, R. R.; Scheffler, G.; "Decarboxylative Glycosylation Reaction Intra- Versus Intermolecular Reaction Course." *Tetrahedron Lett.*, 1997, 38, 2943-2946.
- (79) Attolino, E.; Rising, T. W. D. F.; Heidecke, C. D.; Fairbanks, A. J.; "Propargyl mediated intramolecular aglycon delivery (IAD): applications to the synthesis of core N-glycan oligosaccharides." *Tetrahedron: Asymmetry*, 2007, 18, 1721-1734.
- (80) Stork, G.; Kim, G.; "Stereocontrolled synthesis of disaccharides via the temporary silicon connection." *J. Am. Chem. Soc.*, 1992, 114, 1087-1088.
- (81) Ogawa, T.; Ito, Y.; "A Novel Approach to the Stereoselective Synthesis of β -Mannosides." *Angew. Chem. Int. Ed.*, 1994, 33, 1765-1767.
- (82) Ogawa, T.; Yukishige, I.; "Intramolecular Aglycon Delivery on Polymer Support: Gatekeeper Monitored Glycosylation." *J. Am. Chem. Soc.*, 1997, 119, 5562-5566.
- (83) Maier, M. A.; Yannopoulos, C. G.; Maier, M. A.; Yannopoulos, C. G.; Mohamed, N.; Roland, A.; Fritz, H.; Mohan, V.; Just, G.; Manoharan, M.; "Synthesis of Antisense Oligonucleotides Conjugated to a Multivalent." *Bioconjugate Chem.*, 2003, 14, 18-29.
- (84) Blom, P.; Ruttens, B.; Hoof, S. V.; Hubrecht I.; Eycken, J. V.; "A Convergent Ring-

4. References

Closing Metathesis Approach to Carbohydrate-Based Macrolides with Potential Antibiotic Activity.” *J. Org. Chem.*, 2003, 72, 5514-5522.

(85) Roy, N.; Mukherjee, A.; Das S.; Mukherjee, I.; “Synthesis of a Blocked Tetrasaccharide Related to the Repeating Unit of the Antigen from *Shigella dysenteriae* Type 9 in the Form of Its Methyl (R)-Pyruvate Ester and 2-(Trimethylsilyl)Ethyl Glycoside.” *J. Carb. Chem.*, 2003, 22, 521–535.

(86) Santos, M.; Pérez, S.; “An efficient approach to partially O-methylated α -D-mannopyranosides using bis-tert-butyldiphenylsilyl ethers as intermediates.” *Tetrahedron*, 1996, 52, 10785-10798.

(87) Lowary, T. L.; Eichler, E.; Bundle, D. R.; “Oligosaccharide recognition by antibodies: Synthesis and evaluation of talose oligosaccharide analogues.” *Can. J. Chem.*, 2002, 80, 1112-1130.

(88) Abbas, S. A.; Piskorz, C. F.; Matta, K. L.; “Synthesis of 2-acetamido-2-deoxy-4-O-(2-O-methyl- β -D-galactopyranosyl)-d-glucopyranose (N-acetyl-2'-O-methyl lactosamine).” *Carbohydr. Res.*, 1987, 167, 131-141

(89) Chem-Station Int. Ed. Chem-Station. <http://www.chem-station.com/en/reactions-2/2014/03/p-methoxybenzyl-pmb-protective-group.html>, Accessed Dec 8, 2014.

(90) Pearson, T. D. Z.; “Routes to Stereocontrolled Aglycone Delivery using Neighbouring Group Direction.”, MChem Thesis, Nottingham Trent University, 2013

(91) Chappell, R.; MChem Thesis, Nottingham Trent University, 2013.

(92) Sanders W. J.; Kiessling, L. L.; “Stereoselective, Lewis Acid-Catalyzed Glycosylation of Alcohols by Glucose 1,2-Cyclic Sulfites.” *Tetrahedron Lett.*, 1994, 35, 7335–7338.

(93) Burckhardt, H.; *Advances in Carbohydrate Chemistry*, Vol. 7, Academic Press: New York, 1952.

(94) Chemtube3d. University of Liverpool. http://www.chemtube3d.com/ethene_oso4.html. Accessed Sep 8, 2016.

(95) Grey, L.; “New Approaches to Glycoside Bond Formation”, BSc. Dissertation, Nottingham Trent University, 2012.

(96) Stevenson, S.; MRes Thesis, Nottingham Trent University, 2014.

(97) Ibbotson, L.; “Development of New Strategies for Glycosidic Bond Formation”, MRes Thesis, Nottingham Trent University, 2014.

(98) David, S.; Thieffry A.; Veyrières, A.; “A Mild Procedure for the Regiospecific Benzylation and Allylation of Polyhydroxy-compounds via their Stannylenes Derivatives in

4. References

Non-polar Solvents.” J. Chem. Soc. Perkin Transactions 1981, 1, 1796-1801.

(99) Smith, L. H. S.; Coote, S. C.; Sneddon, H. F.; Procter, D. J.; “Beyond the Pummerer Reaction: Recent Developments in Thionium Ion Chemistry.” *Angew. Chem. Int. Ed.*, 2010, 49, 5832–5844.

(100) Chemgaroo Chemgapedia. Wiley Information Services GmbH.

http://www.chemgapedia.de/vsengine/vlu/vsc/en/ch/2/vlu/oxidation_reduktion/sulf_oxi.vlu.html, Accessed Jun 11, 2013.

(101) Matsugi, M.; Shibata, N.; Kita, Y.; “Asymmetric Pummerer Rearrangement and Related Reactions.” *Adv. Sulf. Chem.*, 2000, 215-248.

(102) Chemgaroo Chemgapedia. Wiley Information Services GmbH.

[http://www.chemgapedia.de/vsengine/vlu/vsc/en/ch/2/vlu/oxidation_reduktion/sulf_oxi.vlu/P](http://www.chemgapedia.de/vsengine/vlu/vsc/en/ch/2/vlu/oxidation_reduktion/sulf_oxi.vlu/Page/vsc/en/ch/2/oc/reaktionen/formale_systematik/oxidation_reduktion/oxidation/addition_sauerstoff/oxidation_sulfid_sulfoxid_sulfon/durchfuehrung.vscml.html)
[age/vsc/en/ch/2/oc/reaktionen/formale_systematik/oxidation_reduktion/oxidation/addition_sauerstoff/oxidation_sulfid_sulfoxid_sulfon/durchfuehrung.vscml.html](http://www.chemgapedia.de/vsengine/vlu/vsc/en/ch/2/vlu/oxidation_reduktion/sulf_oxi.vlu/P), Accessed Aug 14, 2016.

(103) Corey, E. J.; Li, J. J.; *Named Reactions for Homologation*, Part 1., John Wiley Hoboken & Sons: New Jersey, 2009

(104) Reid, B.; Tatsuta, K.; Thiem, J.; *Glycoscience: Chemistry and Chemical Biology I – III.*, Springer Science + Business Media: Berlin, 2012

(105) Menye, J.-R.; Nie, X.; Wang, G.; “Synthesis of octahydropyrano[3,2-b]pyrrole-2-carboxylic acid derivatives from d-mannose.” *Carbohydr. Res.*, 2008, 343, 1743–1753.

(106) Vic, G.; Hastings, J. J.; Howarth, O. W.; Crout, D. H. G.; “Chemoenzymatic synthesis of ethyl 1-thio-(β -D-galactopyranosyl)-O- β -D-glycopyranosyl disaccharides using the β -galactosidase from *Bacillus circulans*.” *Tetrahedron: Asymmetry*, 1996, 7, 709-720.

(107) Bundle, D. R.; Alibés, R.; “Synthesis of Tethered Trisaccharides To Probe Inter-Saccharide Flexibility in Carbohydrate–Protein Interactions.” *J. Org. Chem.*, 1998, 63, 6288–6301.

(108) Roy, S.; Sarkar, S. K.; Roy, N.; “Synthesis of a Tetrasaccharide Related to the Repeating Unit of the Antigen from *Shigella dysenteriae* Type 9 in the Form of Its 2-(Trimethylsilyl)ethyl Glycoside.” *Synth. Commun.*, 2004, 34, 1125-1139.

(109) Wang, B.; Xiong, D.-C.; and Ye, X.-S.; “Direct C–H Trifluoromethylation of Glycals by Photoredox Catalysis.” *Org. Lett.* 2015, 17, 5698-5701.

(110) Carpintero, M.; Nieto, I.; Mayoralas, A.; “Stereospecific Synthesis of α - and β -C-Glycosides from Glycosyl Sulfoxides: Scope and Limitations.” *J. Org. Chem.*, 2001, 66,

4. References

1768-1774.

(111) Nokwequa, M. G.; Nkambulea, C. M.; and Gammon, D. W.; "Armed–disarmed effect on the stability of cysteine thioglucosides." *Carbohydr. Res.*, 2012, 359, 18-23.

(112) Plé, K.; Chwalek, M.; Nazabadioko, L.; "Synthesis of l-arabinopyranose containing hederagenin saponins." *Tetrahedron*, 2005, 61, 4347-4362.

(113) Bols, M.; "Efficient stereocontrolled glycosidation of secondary sugar hydroxyls by silicon tethered intramolecular glycosidation." *Tetrahedron*, 1993, 49, 10049-10060.

(114) Liao, W.; Locke, R. D.; Matta, K. L.; "Selectin ligands: 2,3,4-tri-O-acetyl-6-O-(2-naphthyl)methyl (NAP) α -D-galactopyranosyl imidate as a novel glycosyl donor for the efficient total synthesis of branched mucin core 2-structure containing the NeuAc α 2,3(SO₃Na-6)Gal β 1,3GalNAc α sequence." *Chem. Commun.*, 2000, 5, 369-370.

(115) Palanivel, A.; Chennaiah, A.; Dubbu, S.; Mallick, A.; Vanka, Y. D.; "AuCl₃-AgOTf promoted O-glycosylation using anomeric sulfoxides as glycosyl donors at room temperature." *Carbohydr. Res.*, 2017, 437, 43-49.

(116) Qiana, P.; Yaoa, W.; Huanga, L.; Menga, X.; Li, Z.; "A mild and efficient method for the selective cleavage of primary p-methoxybenzyl protecting group of saccharides by CO₂(CO)₈–Me₂PhSiH–CO system." *Tetrahedron Lett.*, 2015, 37, 5238-5241.

(117) Mukai, C.; Itoh, T.; Hanaoka, M.; "New glycosylation reaction based on alkyne-Co₂(CO)₆ complex." *Tetrahedron Lett.*, 1997, 38, 4595–4598.

(118) VanRheenen, V.; Kelly, R. C.; Cha, D. Y.; "An improved catalytic OsO₄ oxidation of olefins to cis-1,2-glycols using tertiary amine oxides as the oxidant." *Tetrahedron Lett.*, 1976, 17, 1973-1976.

(119) Lin, Y. H.; Ghosh, B.; Mong, K.-K. T.; "In situ formation of β -glycosyl imidinium triflate from participating thioglycosyl donors: elaboration to disarmed–armed iterative glycosylation." *Chem. Commun.*, 2012, 48, 10910-10912.

(120) Pérez S.; and Santos, M.; "An efficient approach to partially O-methylated α -D-mannopyranosides using bis-tert-butyldiphenylsilyl ethers as intermediates." *Tetrahedron* 1996, 52, 10785-10798.

(121) Roy N.; Roy, S.; "Synthesis of a Blocked Tetrasaccharide Related to the Repeating Unit of the Antigen from *Shigella dysenteriae* Type 9 in the Form of Its Methyl (R)-Pyruvate Ester and 2-(Trimethylsilyl)Ethyl Glycoside." *J. Carb. Chem.*, 2003, 22, 521-535.