Title	Studies in anomerisation of glycosyl thiols and glycosides
Author(s)	Doyle, Lisa M.
Publication Date	2018-06-29
Publisher	NUI Galway
Item record	http://hdl.handle.net/10379/7420

Studies in Anomerisation of Glycosyl Thiols and Glycosides

By

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A Thesis Presented to

The National University of Ireland

For the degree of

Doctor of Philosophy

Based on the research carried out in the

School of Chemistry,

National University of Ireland,

Galway

Under the supervision and direction of

Prof. Paul V. Murphy

National University of Ireland,

Galway

Date: 16th April 2018

Declaration

This thesis has not been submitted before, in whole or in part, to this or any other university for any degree, and is, except where stated otherwise, the original work of the author.

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Lisa Doyle

Acknowledgments

First and foremost, I'd like express my deep gratitude to my supervisor, Prof Paul V. Murphy, for giving me the opportunity to undertake a PhD in his lab. I would like to thank you for all your time, knowledge and guidance throughout my time at NUI Galway. With your direction, I was able to develop as a chemist and do something that I truly enjoyed. I will forever be thankful for that opportunity.

I'd like to express my appreciation to the technical staff in the School of Chemistry at NUI Galway. In particular, I'd like to extend my gratitude to Dr. Roisin McDoohan for support with the NMR, and Marian Vignoles for MS support. I'd like to thank Prof. Pat McArdle for assistance with crystal structure determination. I'd also like to express my appreciation to Science Foundation Ireland for funding during my PhD. None of this work would have been possible without this funding.

I'd like to thank all the Murphy group members, past and present, for your friendship, support and advice. I'd like to thank Dr. Anthony McDonagh, for all your help during the intial period of my PhD. Your enthusiasm for chemistry inspired me to want to do better! Thank you to Karen Fox. You are a genuinely kind person and I feel extremely fortunate to have you as a friend. Thank you to Fiach Meany. You never fail to make me laugh and I will miss our morning coffee runs. Thank you to all the tag rugby team – I don't think I have ever gone out so much in a three month period and I have you to thank for many sore heads. Some of my favourite memories from Galway are from that time. Thank you to the office crew for constantly keeping me in good spirits! Thank you to Claudia Di Salvo, Adele Gabba, Syl Byrne and Dr. Benjamin Chalmers for all your advice and friendship.

Thank you to Shane Hogan – I don't think I could have asked any more from you. You listened to every presentation, read every abstract and were a constant source of support. I would not be where I am today without you and I look forward to our next adventure together

Thank you to my two brothers, Joseph and Matthew, who were always a source of wisdom and support during my PhD. Thank you to Laura Carleton – you have corrected far too many drafts for me and it's a debt I won't be able to repay.

Finally, I'd like to thank my parents, Pauline and Joe. I am your third and final child to obtain a doctoral degree and that serves as a testament to you as parents.

Abstract

The stereoselective generation of 1,2-*cis* linkages continues to be a substantial challenge in carbohydrate chemistry today. Lewis acid-promoted anomerisation of 1,2-*trans* linkages offers a facile method to generate 1,2-*cis* linkages. The primary aim of this thesis was on the development of the anomerisation reaction, focusing on approaches that would improve the rate of reaction and increase selectivity for the desired anomer. The first chapter outlines the importance of carbohydrate chemistry and advances that have been made in anomerisation. The second chapter of this thesis describes the anomerisation of a series of D-xylopyranosides, L-arabinopyranosides and L-fucopyranosides. Elements that led to higher rates of epimerisation were established by a kinetic study using ^{1}H NMR spectroscopy to monitor the anomerisation of the various glycosides under $SnCl_4$-conditions. Crossover experiments were used to confirm that xylopyranosides underwent epimerisation primarily through exocyclic cleavage, as opposed to endocyclic cleavage.

The third and fourth chapters of this thesis detail the stereoselective epimerisation of glycosyl thiols. Glycosyl thiols are widely used in stereoselective synthesis of *S*-glycosides due to their configurational stability. Few methods exist for the stereoselective synthesis of 1,2-*cis* glycosyl thiols. Their epimerization from 1,2-*trans* to 1,2-*cis* thiols was attained using $TiCl_4$, while $SnCl_4$ promoted their axial-to-equatorial epimerization. The formation of a $SnCl_4$-glycosyl thiol complex accounted for the unusual equatorial selectivity obtained. The generation of a 2-phenyl-1,3-oxathiolan-2-ylium cation is thought to somewhat explain the selectivity obtained under $TiCl_4$ conditions.

The final chapter outlines the efforts undertook in developing a synthetic route towards a constrained sialylated galactose compound, which has potential as a hemagglutinin inhibitor for influenza. The outbreak of a lethal strain of influenza remains a continual threat and the development of novel inhibitors is vital, as there is widespread resistance in the influenza virus against neuraminidase and M2 ion channel inhibitors. Research focusing on the development of hemagglutinin binding agents is currently limited. This chapter summarises the development of a synthetic pathway towards a novel hemagglutinin inhibitor based on work carried out previously by the Murphy group.

Symbols and Abbreviations

α	Alpha
β	Beta
δ	Chemical shift in ppm downfield from TMS
°C	Degrees Celsius
$[\alpha]_D$	Specific Rotation
Å	Ångstrom
Ac	Acetate
Ac_2O	Acetic anhydride
AcCl	Acetyl chloride
ACN	Acetonitrile
AcOH	Acetic acid
AgOTf	Silver triflate
AIDS	Acquired immune deficiency syndrome
All	Allyl
Ar	Aromatic
ATR	Attenuated total reflection
BF_3-Et_2O	Boron trifluoride diethyl etherate
Bn	Benzyl
BEt_3	Triethylborane
BH_3	Borane

BH_3-SMe_2	Borane dimethyl sulphide complex
BSP	1-Benzene sulfinyl piperidine
Bu	Butyl
Bz	Benzoyl
BzCl	Benzoyl chloride
c	Concentration
COSY	Correlation Spectroscopy
Calcd	Calculated
CAN	Ceric ammonium nitrate
Cat.	Catalytic
cm^{-1}	Wavenumber (IR units)
CSA	Camphorsulfonic acid
d	Doublet
D_2O	Deuterium oxide
DABCO	1,4-diazabicyclo[2.2.2]octane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	Diisopropylethylamine
DBU	1,8-Diazabicycloundec-7-ene
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
DEPT	Distortionless Enhancement by Polarisation Transfer

DFT	Discrete Fourier transform
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane
DMPU	N,N'-Dimethylpropyleneurea
DMTST	Dimethyl(methylthio)sulfonium trifluoromethanesulfonate
dt	Doublet of triplets
DTT	1,4-Dithiothreitol
EDTA	Ethylenediaminetetraacetic acid
equiv.	Equivalent
ES-HRMS	High-Resolution Mass Spectrometry - Electrospray Ionization
Et	Ethyl
Et_3N	Triethylamine
EtOAc	Ethyl acetate
FT-IR	Fourier Transform Infrared (spectroscopy)
g	Grams
gHMBCAD	Heteronuclear Multiple Bond Correlation
gHSQCAD	Heteronuclear Single Quantum Correlation
GlcNAc	*N*-Acetylglucosamine
h	Hours
HA	Hemagglutinin

HIV	Human immunodeficiency virus
Hz	Hertz
I_2	Iodine
i-Pr	Isopropyl
IDCP	Iodonium dicollidine perchlorate
J	Coupling constant, in Hz
m	Multiplet
M	Molar
M^+	Mass of the molecular ion (mass spectrometry)
mCPBA	meta-Chloroperoxybenzoic acid
MDCK	Madin-Darby Canine Kidney
Me	Methyl
MeOH	Methanol
Me_3P	Trimethylphosphine
MHz	Megahertz
min	Minutes
mL, µL	Milliliter, Microliter
mol, mmol, µmol	Mole, Milimole, Micromole
MSA	Methane sulfonic acid
NA	Neuraminidase
NEP	Nuclear export protein

NIS	*N*-Iodosuccinimide
NMR	Nuclear Magnetic Resonance
OTf	Triflate
Ph	Phenyl
Ph_3P	Triphenylphosphine
ppm	Parts per million
Py	Pyridine
q	Quartet
RNA	Ribonucleic acid
RNP	Ribonucleoprotein
RT	Room temperature
s	Singlet
sat.	Saturated
t	Triplet
TBA	Tetrabutylammonium
TBAF	Tetrabutylammoniumflouride
TBS	*tert*-Butyldimethylsilyl
td	Triplet of doublets
t-Bu	*tert*-Butyl
Tf_2O	Trifluoromethanesulfonic anhydride
TfOH	Triflic acid

THF	Tetrahydrofuran
TLC	Thin Layer Chromotography
TMS	Trimethylsilyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TTBP	2,4,6-Tri-tert-butylpyrimidine

Table of Contents

Declaration i

Acknowledgements ii

Symbols and Abbreviations iii

Table of Contents x

Chapter 1: Carbohydrates and Lewis acid-Catalysed Anomerisation

1.1 Introduction to Carbohydrates 2

1.2 Stereoelectronic Effects 4

1.2 1 The Anomeric Effect 4

1.2 2 Related Stereoelectronic Effects 8

1.3 The Glycosylation Reaction and Stereochemical Control 9

1.3 1 Introduction 9

1.3 2 Mechanistic Pathways 10

1.3 3 Factors that Affect the Stereochemical Outcome 11

1.3 3.1 Protecting Groups 11

1.3 3.2 Glycosyl Donors and Acceptors 15

1.3 3.3 Other Factors 19

1.4 Introduction to Lewis acid-Catalysed Anomerisation 19

1.5 Aim of this Thesis 30

1.6 References 30

Chapter 2: Anomerisation of Pentopyranosides and 6-Deoxyhexopyranosides

2.1 Introduction 39

2.2 Relevant Electronic Effects 41

2.3 Synthesis of *O*- and *S*-glycosides 44

2.4 Anomerisation studies 47

2.4 1 Anomerisation of D-xylose derivatives 48

2.4 2 Anomerisation of L-arabinose derivatives 50

2.4 3 Anomerisation of L-fucose derivatives 53

2.4 4 Summary of results and conclusions 55

2.5 Kinetics 56

2.6 Crossover studies 61

2.7 Conclusions and Future Work 65

2.8 References 66

Chapter 3: Stereoselective Epimerisation of Glycosyl Thiols

3.1 Overview of *S*-glycosides 70

3.2 Glycosyl Thiols and Synthetic Strategies 73

3.3 Synthesis of Glycosyl Thiols 77

3.4 Previous Investigation into Anomerisation towards Axial Glycosyl Thiols 80

3.5 Axial-to-Equatorial Epimerisation in Glycosyl Thiols 86

3.6 Optimisation of Conditions 91

3.6 1 Fucopyranosyl Thiols 91

3.6 2 Arabinopyranosyl Thiols 92

3.6 3 Gulopyranosyl Thiol 94

3.6 4 Galactopyranosyl Thiols 94

3.6 5 Glucopyranosyl Thiols 95

3.6 6 Xylopyranosyl Thiol 97

3.7 Anomerisation in Acetylated Glycosyl Thiols 100

3.8 Conclusions 102

3.9 Bibliography 103

Chapter 4: An NMR Study into Lewis Acid-Promoted Epimerisation

4.1 Introduction 107

4.2 Specificity to Glycosyl Thiols 107

4.3 NMR Study of Glycosyl Thiols with $SnCl_4$ 109

4.3 1 Gulopyranosyl thiol in presence of $SnCl_4$ 110

4.3 2 Rhamnopyranosyl thiols in presence of $SnCl_4$ 112

4.4 NMR Study of Glycosyl Thiols with $TiCl_4$ 118

4.4 1 Gulopyranosyl thiol in presence of $TiCl_4$ 119

4.4 2 Rhamnopyranosyl thiol in presence of $TiCl_4$ 124

4.5 Role of C-2 substituent 129

4.6 Conclusions 132

4.7 Bibliography 133

Chapter 5: Synthesis Towards a Potential Hemagglutinin Inhibitor

5.1 Introduction 137

5.2 Treatments for Influenza 139

5.3 Carbohydrate Conformations, Definitions and Preferences 141

5.4 Retrosynthesis on Inhibitor 144

5.5 Synthesis of Inhibitor to Date 146

5.6 Conclusions and Future Work 151

5.7 Bibliography 152

Chapter 6: Experimental Data

6.1 General Procedure 158

6.2 Chapter 2 Experimental Data 159

6.2 1 Methods for Anomerisation and Kinetic Reactions 159

6.2 2 Experimental Data for *O*- and *S*-Glycosides 159

6.2 3 Experimental Data for Axial Anomers 183

6.3 Chapter 3 Experimental Data 189

6.3 1 Methods for Epimerisation Reactions 189

6.3 2 Experimental Data for Glycosyl Thiols 190

6.4 Chapter 4 Experimental Data 214

6.5 Chapter 5 Experimental Data 223

6.6 Bibliography 234

Chapter 1

Carbohydrates and Lewis acid-Catalysed Anomerisation

1.1 Introduction to Carbohydrates

Carbohydrates are the most abundant biomolecules on earth and are indispensable for all living organisms. Aside from the various roles that carbohydrates have in structural support and metabolism, they play a fundamental part in the way our cells communicate. Complex carbohydrates called glycans coat our cells and form a layer called the glycocalyx. These glycans have enormous importance in various biochemical processes, such as molecular recognition, cell-cell interaction and immunological responses. These processes have implications in cancer growth, inflammation, viral and bacterial infection. This knowledge has intensified interest in glycobiology in order to elucidate these functions and indeed, advances in our understanding has enabled the development of carbohydrate based drugs. These glycomimetics are potential therapeutics as vaccines, anti-metastasis agents and anti-viral therapeutics. Carbohydrates typically exist in nature as complex oligosaccharides or conjugated to biologically relevant compounds such as natural products, proteins, lipids and peptides. The innate complexity of these compounds can make the chemical synthesis of glycomimetics challenging. For instance, synthesising a polysaccharide is a laborious task for several reasons. The monosaccharide building blocks can link in several different ways and can also have multiple linkages. For example, two pyranose molecules can be linked in five different ways via 1-1, 1-2, 1-3, 1-4 and 1-6 linkages. To add to the complexity, the ring size can vary (e.g. furanose, pyranose), the anomeric centre can give rise to α and β-anomers and hydroxyl groups can also be modified (e.g. sulfation, methylation, acetylation). A major challenge in organic chemistry is the construction of glycosidic linkages while controlling the regio- and stereoselectivity.[1]

Carbohydrates are polyhydroxylated hemiacetals that have the general formula $C_n(H_2O)_n$, where n is three or more. The simplest example of a carbohydrate is glyceraldehyde but many contain four carbons (tetroses), five carbons (pentoses) or six carbons (hexoses). They can exist as single sugar units called monosaccharides or condense to form polysaccharides like disaccharides, trisaccharides etc. The most familiar monosaccharide is D-glucose. D-Glucose is one of 16 different stereoisomers, with five of the six hydroxyl groups present being chiral centres. D-Glucose has an enantiomer called L-glucose, where each of the stereocentres possess the opposite configuration. L-glucose does not exist in nature,[2] although there are examples of L-hexoses that occur naturally. There are several different forms that can represent D-glucose which are all identical in terms of absolute configuration. The Fischer projection can suitably

represent the open chain form while the Haworth projection and chair conformation represent the cyclic forms of glucose.

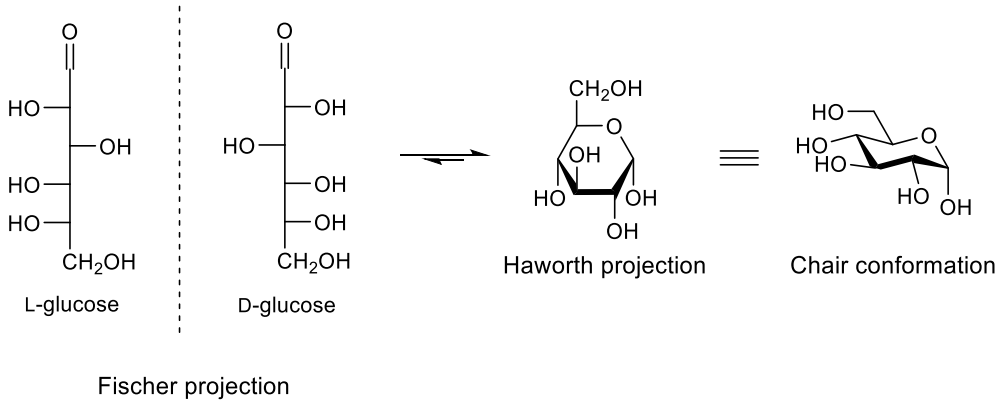


Figure 1.1 Different representations for glucose structures

Monosaccharides generally exist as cyclic hemiacetals, as opposed to their open chain form. These ring systems occur from intramolecular nucleophilic attack of a hydroxyl to the carbonyl of the acyclic system. Five or six membered ring systems can be formed depending on which hydroxyl group reacts with the aldehyde group. A new stereocentre, termed the anomeric centre, is created from the ring closure and the hydroxyl group may be axial or equatorial. These stereoisomers are known as the α- and β-anomer and this assignment is determined by the stereochemical relationship between the anomeric centre and the configuration of the highest stereocentre. If the anomeric hydroxyl group is on the same side as the highest stereocentre then it is the α-anomer. If it is on the opposite side then it is the β-anomer.

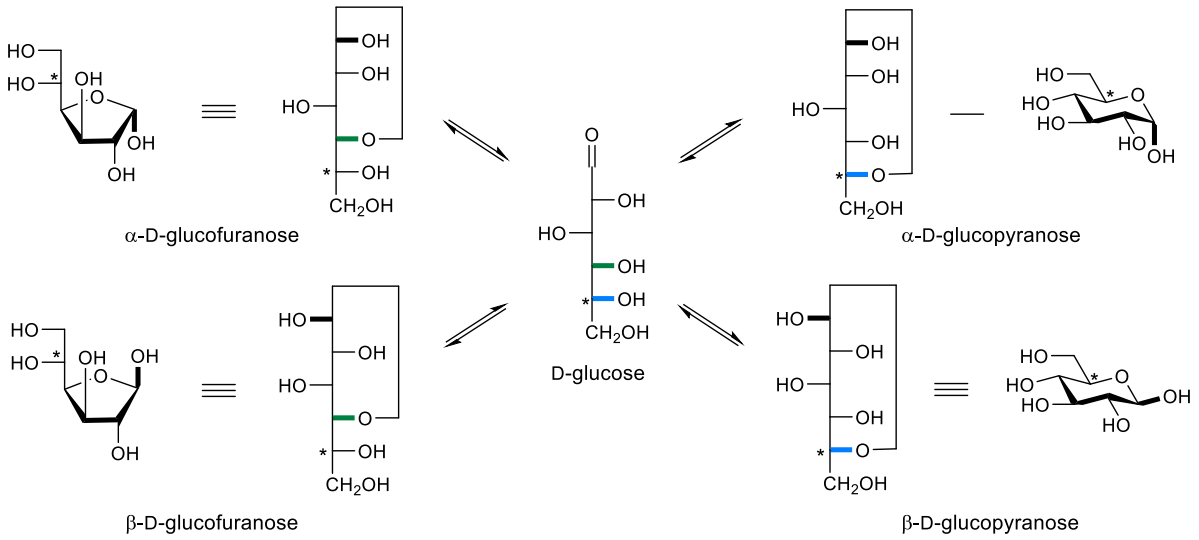


Figure 1.2 Assignment of α- and β-configurations of D-glucopyranose and the furanose. Hydroxyl groups that can form five- and six-membered ring systems highlighted in green and blue. Highest stereocentre marked by asterisk.

1.2 Stereoelectronic effects

1.2 1 The *anomeric effect*

The hemiacetal functionality allows a small amount of the sugar to exist in the open-chain form and this leads to a process known as *mutarotation*, which involves inversion at the anomeric positon (Figure 1.3). In a solution of water, the α-anomer of D-glucose accounts for 36% while the β accounts for 64%, with a trace amount of α/β-D-glucofuranose present (~0.5%). The α-anomer has two 1,3 diaxial interactions between the anomeric hydroxyl group and hydrogens of the C-3 and C-5 so this ratio is initially surprising based on steric considerations alone. For comparison, in monosubsituted cyclohexanes, it is known that the equatorial conformation is favoured, as the axial conformation has unfavourable 1,3-diaxial interactions (Figure 1.4). Understanding the stereoelectronic effects that affect this ratio is a fundamental concept in carbohydrate chemistry. The anomeric effect and other related stereoelectronic effects can help us predict the reactivity of different glycosides, making stereo- and regioselective synthesis of glycomimetics possible.

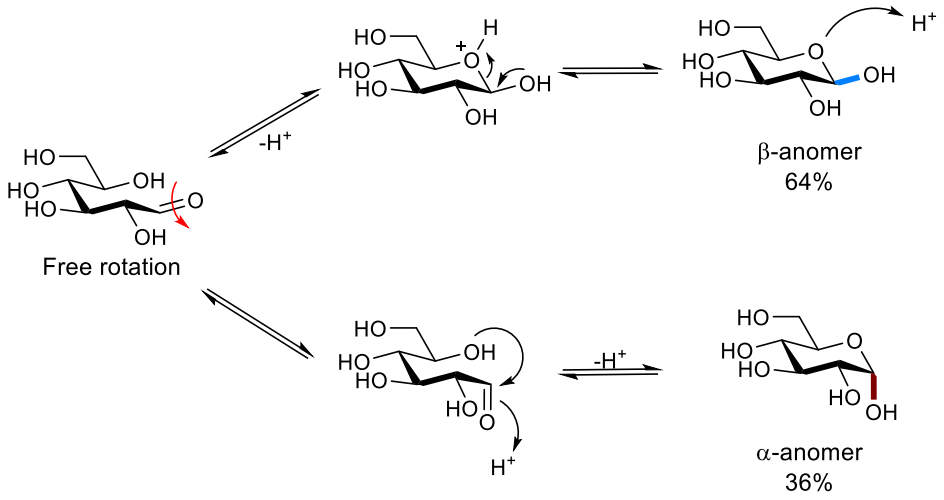


Figure 1.3 *Mutarotation* in D-glucose in solution

The *anomeric effect* refers to the propensity for an electronegative substituent at the C-1 position to assume an axial rather than an equatorial orientation in glycosides in contrast to expectations based on steric considerations alone. The tendency for anomeric alkoxy groups in pyranose rings to occupy an axial orientation was initially observed by J.T. Edward in 1955.[3] In the same year, R.U. Lemieux studied the anomeric equilibrium in fully acetylated aldohexopyranoses and found that the anomeric acetyl groups preferred an axial configuration.[4] Lemieux and Chü[5] later coined the term 'anomeric effect' in 1958 at an American Chemical Society conference and the term is synonymous with the Edward-Lemieux effect.

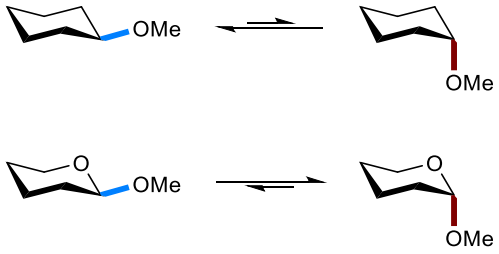


Figure 1.4 Monosubstituted cyclohexanes prefer an equatorial conformation while substituted tetrahydropyrans show an increased preference for the axial conformation

The anomeric effect is a general phenomenom throughout chemistry and can be extended to acyclic molecules. For instance, in a simple hydrocarbon such as butane, the most stable conformation is the antiperiplanar or *anti* conformation as this reduces steric hindrance between the bulky methyl groups. However, in the case of 2-fluoroethanol the synclinical or *gauche* conformation is favoured. The term *gauche* refers to a torsional angle of 60° separating two vicinal groups, in this case the hydroxyl group and fluorine atom. The increased inclination

for the gauche conformation in 2-fluoroethanol can be attributed to the generalized anomeric effect.

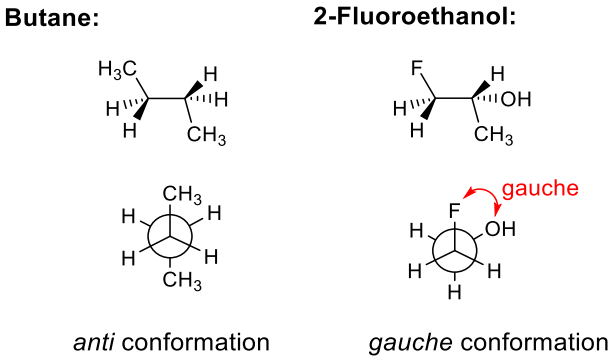


Figure 1.5 Stable conformers in butane and 2-fluoroethanol

There are two widely accepted explanations for the anomeric effect. Edward proposed that there was a destabilising effect due to electrostatic repulsion between an equatorial electronegative group and the dipole of two unshared sp^3 electron pairs on the ring oxygen. This repulsion is alleviated when the electronegative substituent adopts an axial orientation thus somewhat explaining the preference for the axial conformation at the C-1 position.

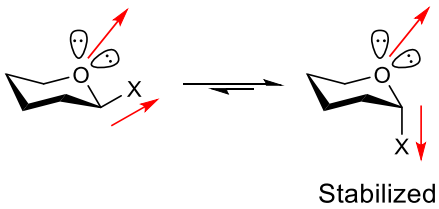


Figure 1.6 The electrostatic model

If the electrostatic model was correct, the preference for the axial anomer should decrease as the polarity of the solvent increases. Polar solvents stabilise the more polar equatorial anomer and the resulting equilibrium should reflect this. Kinzy and Schmidt[6] carried out a study on solvent effects using 2-methoxytetrahydropyrans. Indeed they found that non-polar solvents increased the preference for the axial anomer. For instance, the axial anomer accounted for 83% of the equilibrium mixture in carbon tetrachloride in comparison to 68% in the more polar solvent acetonitrile. However, this theory has been challenged by contradictory experimental results. The Juaristi group investigated the equilibrium ratios of 2-carbomethoxy-1,3-dithiane at lower temperatures using various solvents.[7] They found that the axial anomer was favoured in polar solvents at lower temperatures and the electrostatic model could not solely justify these results. It has also been claimed that the electrostatic model cannot account for variation in

bond distances and angles around the anomeric centre, particularly the shortening of the C-O bond and lengthening of the C-X bond.

The hyperconjugation model was first proposed based on observations in cyclic-halogen ethers.[8] It was found that the C-X bond was significantly longer in the axial anomer in comparison to the equatorial anomer, as well as a shortening in the adjacent C-O bond. These measurements could be explained by the donation of the lone pairs on the ring oxygen into the antibonding (σ*) orbital of the C-X bond. The electrons are more delocalised in the bonds and this is associated with increased stability. This increases the double bond character in the C-O bond and the electron density on the anomeric group. The increase in electron density on the anomeric substituent illustrates why the anomeric effect is stronger with electronegative substituents as they are happy with a partial negative charge. Furthermore, this is only possible when the orbitals are antiperiplanar to each other hence explaining the increased stability of the axial anomer.

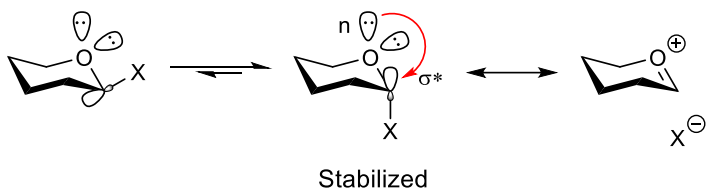


Figure 1.7 The hyperconjugation model

Nonetheless, experimental results have disputed the hyperconjugation model as the main contributor for the anomeric effect. Perrin *et al.*[9] compared the anomeric equilibrium between nitrogen heterocycles and oxygen heterocycles. Nitrogen is less electronegative than oxygen and has weaker electrostatic interactions, but it is a stronger $n \rightarrow \sigma *$ donor. If hyperconjugation was the primary contributor for the anomeric effect, it would be expected that the axial anomer would be dominant in nitrogen heterocycles. However, the opposite results were observed leading to Perrin and co-workers to conclude that $n \rightarrow \sigma *$ interactions could not solely account for the energy difference between the axial and equatorial anomer in non-polar solvents. They also established that the electrostatic model can rationalize geometrical variations, at least in 2-methoxy-1,3-dimethylhexahydropyrimidine. Extensive computational studies[10] also concluded that hyperconjugative interactions could not be responsible for the anomeric effect, but rather electrostatic interactions more suitably explain the anomeric effect.

It is feasible that the origin of the anomeric effect has several contributing elements and both the hyperconjugation and electrostatic model play a role in this general phenomenon.

1.2 2 Related Stereoelectronic Effects

The *reverse anomeric effect* has generated debate among researchers, questioning whether this is a real phenomenon. It describes the tendency of anomeric substituents with a formal positive charge to adopt equatorial rather than axial orientations. The effect, if it exists, may have significance for reactions at the anomeric centre, as many proceed through a partially or fully positively charged aglycon intermediate. It was initially described by Lemeuix and Morgan[11-12] who studied systems containing positively charged nitrogen groups, namely pyridiniums and imidazoles, at the C-1 position. Paulsen *et al.* later examined conformational equilibria in acetylated pentopyranosyl imidazoles and their positively charged counterparts.[13-14] It is generally attributed to increased steric preferences. It may be that favourable dipole interactions are no longer possible which favour the axial anomer.

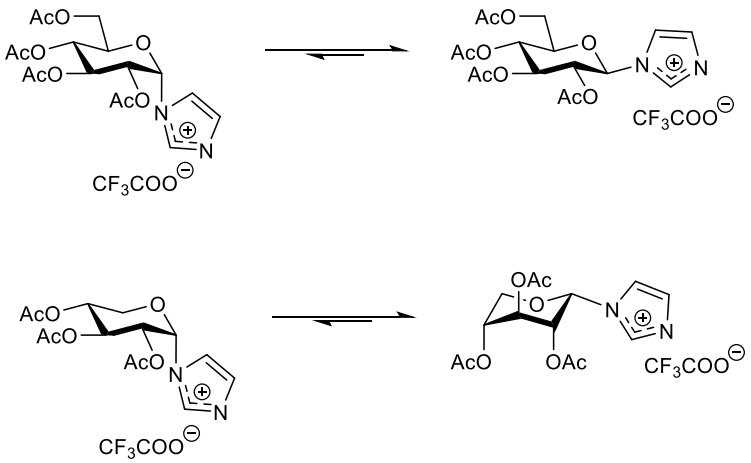


Figure 1.8 Equatorial anomer favoured when the C-1 substituent is positively charged

The anomeric effect can also be referred to as the endo-anomeric effect as a means to differentiate it from the exo-anomeric effect. The *exo-anomeric effect* refers to the tendency of the aglycon to adopt a gauche conformation rather than an antiperiplanar conformation in a glycoside.[15] The exo-anomeric effect is responsible for the conformational preferences around glycosidic bond linkages as well as the helical shape adopted by polysaccharides. The three-dimensional shape of oligosaccharides determines their interaction with receptors and therefore is important for their biological activity. Thus the exo-anomeric effect is important to consider in the synthesis of biologically relevant molecules.[16]

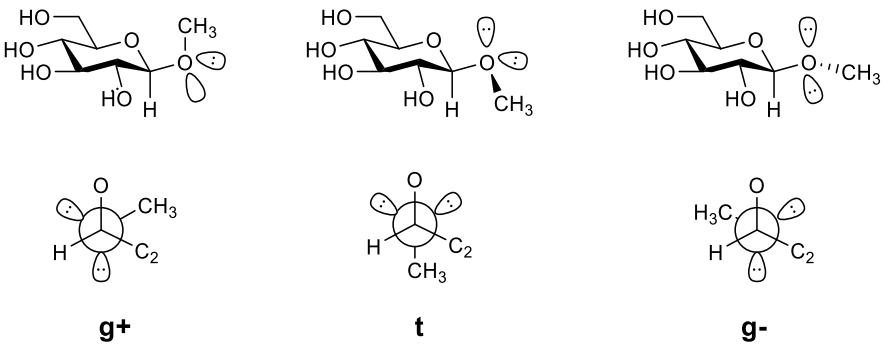
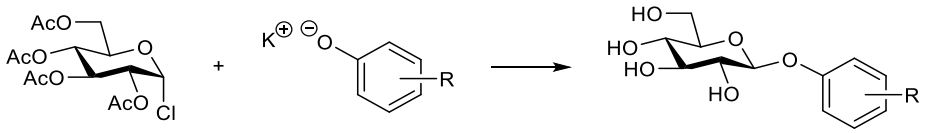


Figure 1.9 Conformations that an aglycon could possibly adopt and Newman projections of each one

1.3 The Glycosylation Reaction and Stereochemical Control

1.3 1 Introduction

The chemical synthesis of complex glycomimetics is a considerable challenge in carbohydrate chemistry and at the core of this complexity lies the construction of glycosidic linkages with the correct stereo- and regioselectivity. In 1879, the American chemist Arthur Michael[17] carried out the first glycosidation reaction when he reacted a glycosyl chloride with potassium salts of various phenols to form the *O*-deacetylated phenyl glycosides. Shortly after, in 1893, Emil Fischer described the glycosylation of simple aliphatic alcohols in the presence of HCl,[18] and this became known as the Fischer glycosylation. Koenigs and Knorr developed a more controlled glycosylation protocol, which utilised a metal salt, silver carbonate, as a promoter and glycosyl halides as acceptors. It enabled more complex aliphatic alcohols to be glycosylated and the Koenigs-Knorr reaction became a mainstay in carbohydrate chemistry. These early glycosylations marked the beginning of a new important discipline of research, with countless adaptations and new synthetic strategies developed.



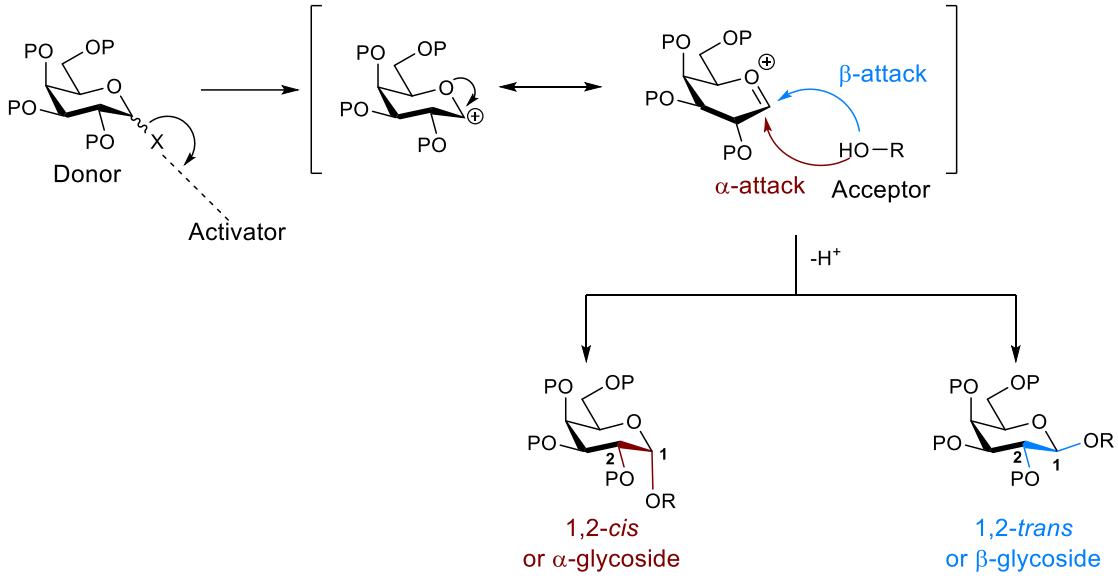
Scheme 1.1 First glycosylation reaction by Arthur Michael

There has been tremendous progress in the development of glycosylation reactions that has enabled the total synthesis of complex glycomimetics. However, accomplishing absolute stereochemical control over the glycosylation reaction has eluded chemists. In 1982, Paulsen wrote that, '*although we have now learned to synthesise oligosaccharides, it should be*

emphasized that each oligosaccharide synthesis remains an independent problem… There are no universal reaction conditions for oligosaccharide synthesis.'[19] This statement remains somewhat true today and thus the optimisation of glycosylation strategies remains an active area of research in carbohydrate chemistry.

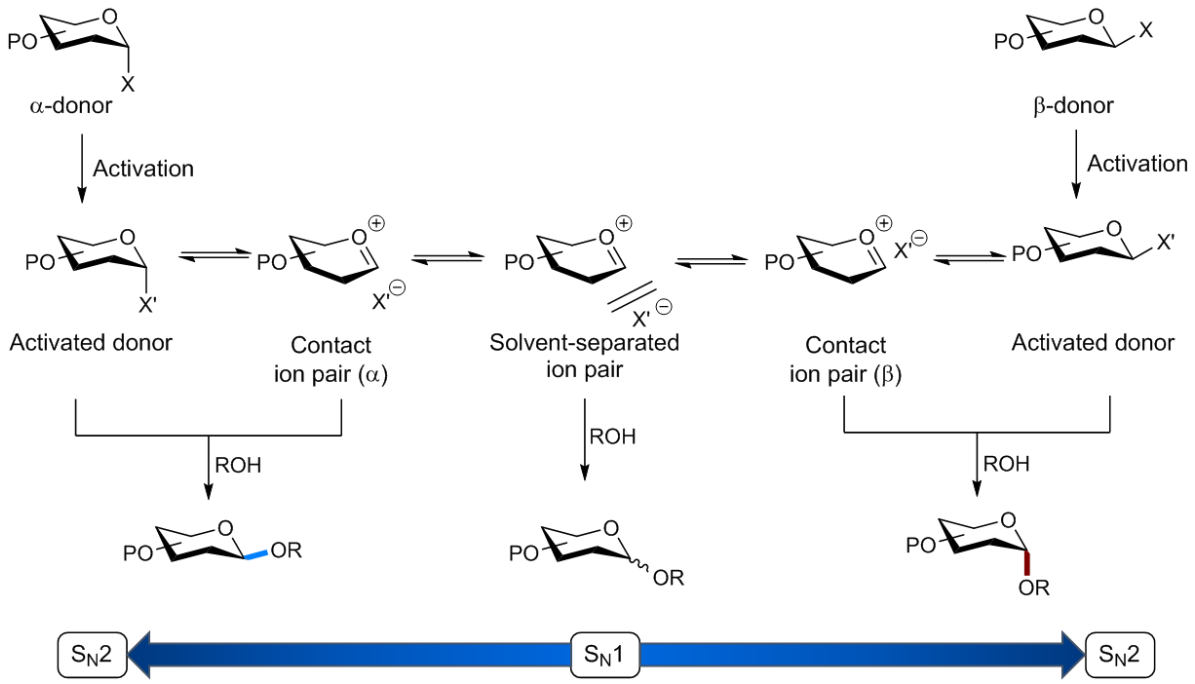
1.3 2 Mechanistic Pathways

The synthesis of a new glycosidic linkages involves the use of a glycosyl donor, a glycosyl acceptor and an activator (Scheme 1.2). The glycosyl donor typically possesses an anomeric leaving group which can be cleaved in the presence of a suitable promotor to form an oxacarbenium intermediate, which is then susceptible to attack from a glycosyl acceptor. If non-participating groups are employed at the C-2 position, then an anomeric mixture is usually obtained as the planar oxacarbenium ion can be attacked from either face. The new *O*-glycosides formed are commonly referred to as α- and β-glycosides or 1,2-*cis* and 1,2-*trans* glycosides, with reference to the orientation of the C-2 substituent. Some other common types of glycosides, such as sialic acid or 2-deoxyglycosides, lack a substituent at the C-2 position and are referred to as α- or β-glycosides.



Scheme 1.2 Glycosylation reactions involve the use of a donor, acceptor and activator

Glycosylation is typically considered to have four steps; activation, dissociation, nucleophilic attack and proton transfer. It is generally considered that most glycosylations will feature both characteristics of S_N1 and S_N2 pathways, frequently with the exact mechanism not immediately apparent. The mechanism can be considered to be somewhere on a continuum between a dissociative S_N1 and associative S_N2 pathway.[20]



Scheme 1.3 General glycosylation mechanistic pathways

There are many elements that can affect the outcome of glycosylation reactions, often in unexpected ways. These factors include the nature of the glycosyl donors and acceptors, the type and orientation of substituents, promoter systems, solvent, temperature and so on. These elements can be manipulated to control the regio- and stereochemistry of the desired product and thus the following section will highlight some of these factors.

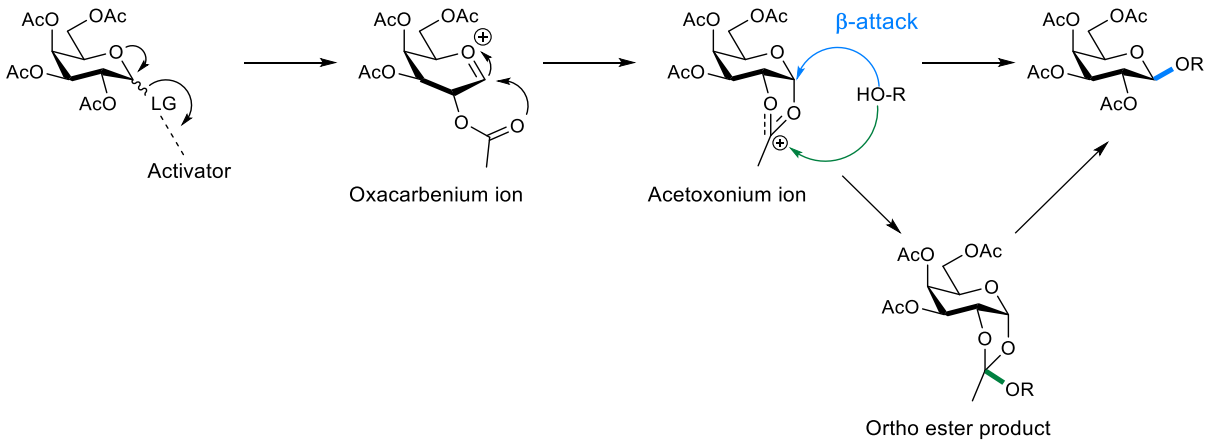
1.3 3 Factors that Affect the Stereochemical Outcome

1.3 3.1 Protecting Groups

It is becoming increasingly apparent that the manner of protecting groups utilized can significantly influence the outcome of a glycosylation reaction. Steric and electronic factors, along with the auxillary group's influence on the conformation of the donor, all need to be considered in glycosylation.

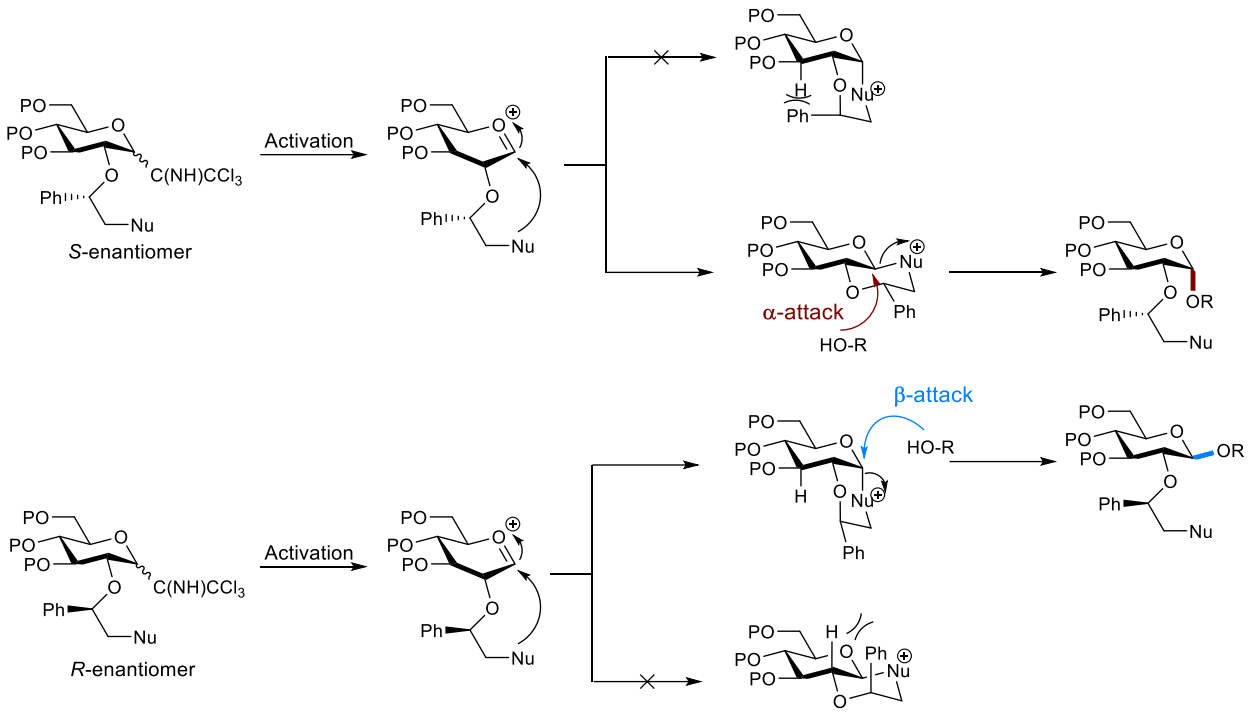
As discussed previously, the use of non-participating groups generally leads to a mixture of products, often with the α-anomer dominant. The stereoselective generation of the 1,2-*trans* anomer has been successfully achieved through the use of protecting groups at the 2-position that contain an acyl group. Through neighbouring group participation, the 1,2-*trans* anomer can be selectively obtained, as shown in Scheme 1.4. The acyl containing group at position-2 can attack the oxacarbenium intermediate and form a cyclic acetoxonium ion. This blocks one side of the face to nucleophilic attack, depending on the orientation of the C-2 group and thus

the nucleophile can only attack from above or below. In the case of gluco- and galactopyranosides, this means the β-anomer is obtained, while in manno- and rhamnopyranosides, the α-anomer is generated selectively. The ortho ester product can be formed, but under Lewis acid-catalysed conditions, it often rearranges to give the *O*-glycoside. It some cases, it appears that this is the primary route in which the desired product is formed.



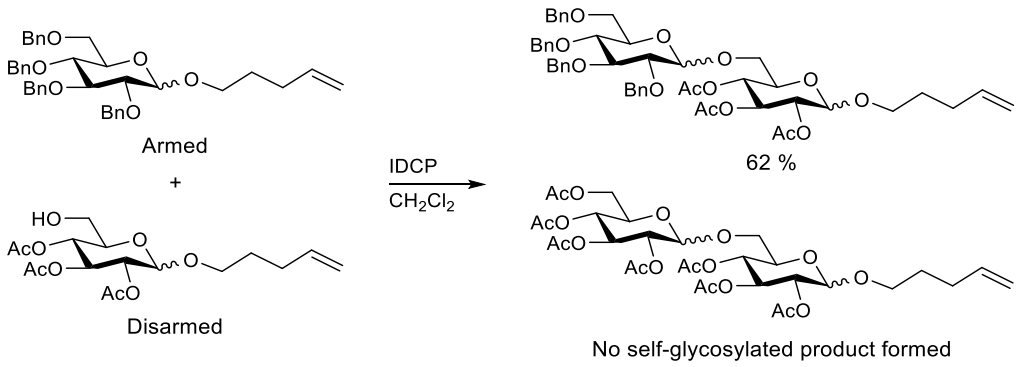
Scheme 1.4 Acyl containing group at position-2 can participate in glycosylation reaction

Over the years, many strategies to selectively generate the 1,2-*trans* and 1,2-*cis* glycosides through the use of auxiliary groups have been developed. For instance, Boons and co-workers[21] developed a chiral neighbouring participarting group at the C-2 position that was selective for the 1,2-*trans* or 1,2-*cis* product, depending on which enantiomer was utilized. Upon formation of the oxacarbenium intermediate, the nucleophilic group at C-2 can participate leading to an intermediate species as either a *trans* or *cis*-decalin system. The use of the *S*-enantiomer led to the generation of primarily the *trans*-decalin, most likely due to unfavourable steric interactions in the *cis*-decalin system between the axial phenyl group and C-3 proton. The *R*-enantiomer generated the *cis*-fused system because of unfavourable interaction in the *trans*-decalin system. Subsequent nucleophilic attack on the *trans*- or *cis*-decalin system gave the 1,2-*cis* and 1,2-*trans* glycosides, respectively. In the same year, Boons *et al.*[22] introduced the auxilary (*S*)-(phenylthiomethyl)benzyl at the C-2 position and illustrated its effectiveness for the generation of 1,2-*cis* disaccharides. These auxiliary groups were used in the solid-supported preparation of a biologically important α-glucan.[23]



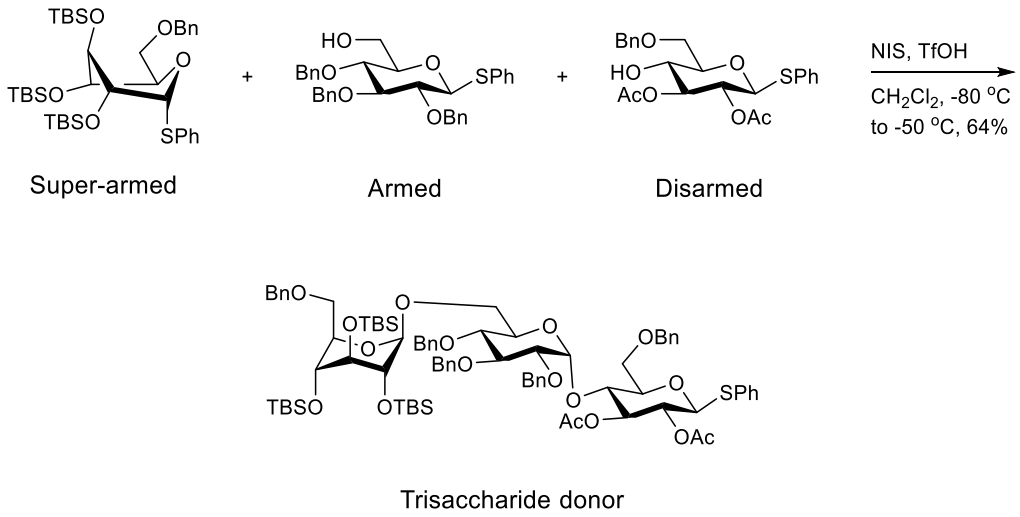
Scheme 1.5 Chiral auxiliary groups used to generate the 1,2-*cis* or 1,2-*trans* anomer

Protecting groups have another important consequence in controlling glycoside reactivity. Fraser-Reid's 'armed-disarmed' effect is a fundamental concept in carbohydrate chemistry. It is an effective way to prevent the self-glycosylation of glycosyl donors when forming disaccharides. According to the armed-disarmed effect, glycosyl donors that are protected with ether groups are armed and can be activated over glycosyl donors with ester protecting groups. This can be explained by the fact that ester protecting groups are more electron withdrawing than ether protecting groups. Thus, acyl containing groups destabilize the electron deficient oxacarbenium intermediate, resulting in a slower reaction pathway. Fraser-Reid and co-workers initially introduced the term 'armed-disarmed' in 1988, when they observed that in a reaction between acetylated and benzylated glycosides, none of the self-glycosylated product was observed.[24]



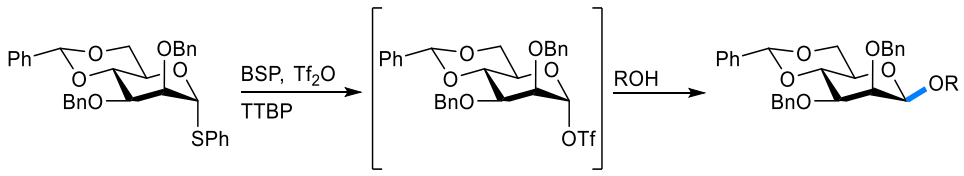
Scheme 1.6 Armed and disarmed donors

The armed-disarmed effect has been revolutionary for oligosaccharide synthesis, particularly in one-pot glycosylation reactions.[25] The armed-disarmed concept has been extended to include 'super-armed' donors.[26] Super armed donors are glycosyl donors that possess bulky silyl groups (*tert*-butyldimethylsilyl, TBS) which cause a change in conformation from $^4C_1$ to a twisted boat conformation. The number of axial groups in the ring is increased and as axial groups are known to be more electron donating than equatorial groups, this increases the reactivity of the donor significantly. 'Super armed' donors are useful for one-pot glycosylations and an example is the synthesis of a trisaccharide donor as shown in Scheme 1.7.[27]



Scheme 1.7 One-pot synthesis using super armed, armed and disarmed glycosyl donors to form a trisaccharide donor

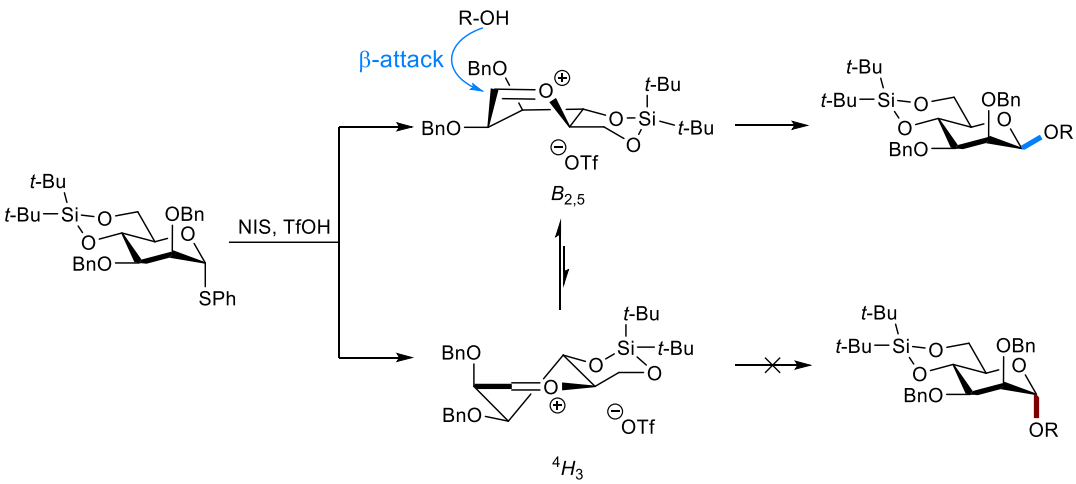
Arm-disarmed effects have also been utilized to solve other synthetic challenges. A well-known example is Crich's β-mannoside synthesis,[28-29] which employs glycosyl donors that have been disarmed, through the introduction of a benzylidene group, which 'locks' the donors into the rigid $^4C_1$ conformation. Activation of these glycosyl donors generates α-mannosyl triflates which then can be substituted in an S_N2 like mechanism to give β-mannosides.



Scheme 1.8 Crich's β-mannosylation

Pederson and Bols *et al.*[30] adapted this reaction with a novel donor mannopyranosyl donor that was constrained with a 4,6-silylene group. They suggested that the conformation of the oxacarbenium intermediate was responsible for the β-selectivity they obtained, rather than an

α-mannosyl triflate. Employing DFT calculations and experimental results, they concluded that a $^4H_3$ conformation was unfavourable in the intermediate cation due to the C-3 and C-4 groups adopting an equatorial orientation and that the oxacarbenium ion would likely adopt a $B_{2,5}$ conformation. The $B_{2,5}$ conformation is susceptible to β-attack, as the nucleophile approaches in a staggered manner.



Scheme 1.9 Possible conformations of intermediate cations suggested by Pederson and Bols

1.3 3.2 Glycosyl Donors and Promoters

The choice of glycosyl donor and promoter should also be examined before embarking on the synthesis of an oligosaccharide. The stability of the donor will affect the formation of the positively charged intermediate and consequently, the mechanistic pathway. Careful planning can allow different glycosyl donors to be used simultaneously, with each only activated in turn by a specific promoter. The next section will examine a few examples of the numerous donor and promoter systems developed.

Glycosyl Halides

In 1901, Koenigs and Knorr[18] and Fischer and Armstrong[31] independently developed a glycosylation protocol, which utilised a metal salt, silver carbonate or silver(I) oxide, as a promoter and glycosyl halides (glycosyl bromides and chlorides) as acceptors. It was initially postulated that the silver salts could scavenge excess HX (X = Cl or Br) in the reaction but it was later found that silver salts could complex with the anomeric halide assisting dissociation and formation of the oxacarbenium intermediate, in an S_N1 type reaction.[32] Zémplén[33] and Helferich[34] later both employed metal(II) salts as promoters in glycosidation reactions with glycosyl halides. Notably, the Helferich method was developed which used mercury (II) cyanide salts as efficient promoters. Today, glycosyl bromides and less frequently, glycosyl

chlorides are still regularly used in glycosylations and the original insoluble promoters have been largely replaced by soluble silver and mercury salts such as AgOTf, Ag_2CO_3, $Hg(CN)_2$ and $HgBr_2$.[19, 35-36]

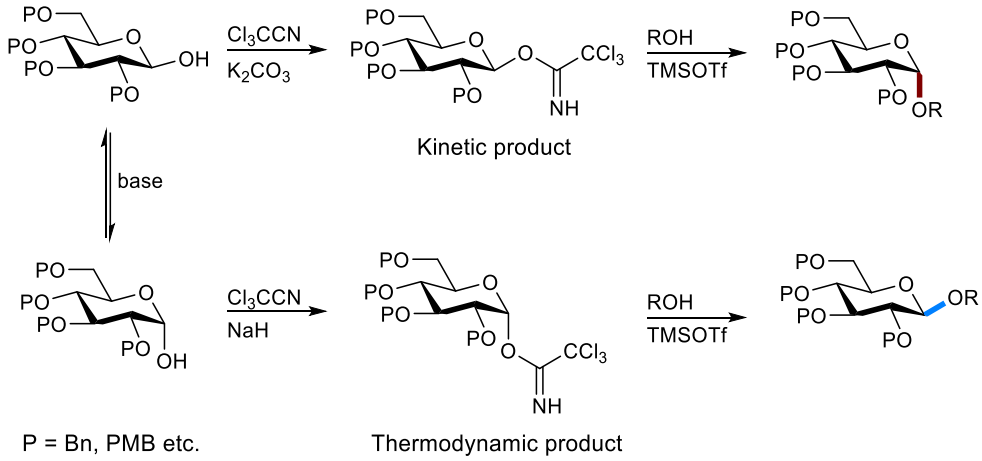
Glycosyl iodides and fluorides have also been used as donors in glycosidation reaction with varying degrees of success. The use of glycosyl iodides was long dismissed due to their instability and short shelf-life. Glycosyl iodides with benzyl ether protecting groups usually require in-situ generation followed by immediate use in glycosylation. However, they have been employed in glycosylation reactions. Gervay-Hague and co-workers[37] showed that various glycosyl iodides could be reacted with oxa- and thio-cycloalkanes to yield *O*-glycosides in high yields, with the β-anomer predominantly generated at lower temperatures. Notably, the glycosyl donor did not require pre-activation prior to the reaction. Mukaiyama[38] and Oscarson[39] also employed glycosyl iodides, generated in-situ, as donor molecules in in the preparation of oligosaccharides, with high α-selectivity obtained.

In 1981, Mukaiyama *et al.*[40] initially employed $SnCl_2$-$AgClO_4$ to activate glycosyl fluorides and demonstrated their effectiveness as donors. Since then, the use of glycosyl fluorides as donors has been much advanced and several different promoter systems have been developed including $Sn(OTf)_2$,[41] TMSOTf,[42] Tf_2O[43] and TfOH.[44] Glycosyl fluorides are more stable than the corresponding bromides and chlorides and thus offer certain advantages. They are valuable donors in the convergent synthesis of various oligosaccharides and glycomimetics. Mukaiyama *et al.* demonstrated that glycosyl fluorides could be selectively activated over thioglycosides by employing protic acids such as TfOH as promoters.[44-45] Nicolau and co-workers have incorporated glycosyl fluorides in the synthesis of a large array of natural products.[46-47]

Glycosyl Imidates

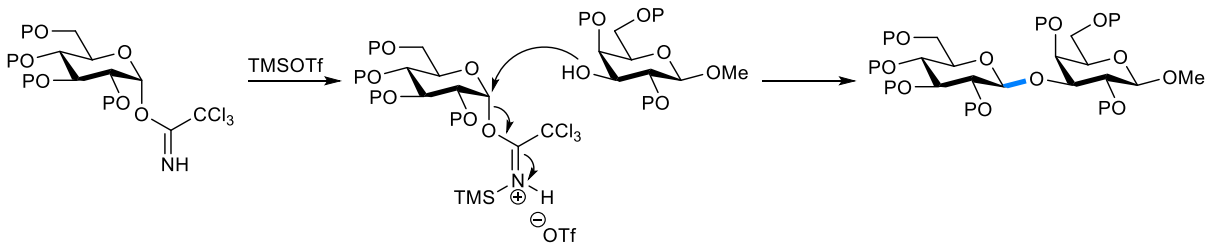
Glycosyl imidates represent an adaptable group of glycosyl donors that have been used extensively in oligosaccharide synthesis. In 1980, Michel and Schmidt[48] introduced the concept of *O*-glycosyl trichloroacetimidates as donors and these proved to be an excellent and versatile glycosyl donor. They are readily prepared by the base-catalysed reaction of a hemiacetal with trichloroacetonitrile. It has been demonstrated that the use of strong bases (DBU, NaH) can selectively generate the thermodynamic axial product while weak bases (K_2CO_3) can generate the equatorial trichloroacetimidate.[6] With a weak base, mutarotation occurs faster than nucleophilic attack on the trichloroacetonitrile molecule. The equatorial C-1 hydroxyl is more nucleophilic than the axial one and consequently the major product is the β-anomer. A strong

base enables complete deprotonation of the anomeric hydroxyl group and alkylation. A strong base also catalyses a slow epimerisation towards the thermodynamic axial product, therefore the α-anomer is formed exclusively.



Scheme 1.10 Base-catalysed formation of trichloroacetimindates and alkylation

Glycosylation reactions with trichloroacetimidates require the use of Lewis acids such as TMSOTf[49] or BF_3-Et_2O.[50] If non-participating protecting groups are used at the C-2 position of the glycosyl donor, the reaction generally proceeds through an S_N2 type reaction, with inversion of stereochemistry at the anomeric centre (Scheme 1.11). If ester protecting groups are employed, the 1,2-*trans* anomer is usually obtained.



Scheme 1.11 Lewis acid-catalysed glycosylation using trichloroacetimidate donor and inversion of stereochemistry

Thioimidates have also been developed as glycosyl donors. Demchenko and co-workers[51] introduced *S*-benzoxazyl (SBox) as a thioimidate donor which proved to be a convenient and flexible donor. Both 1,2-*cis* and 1,2-*trans* glycosidic linkages have been selectively synthesised through the use of *S*Box donors. These donors can be prepared by reacting the potassium salt KSBox with a glycosyl bromide. Various promoters can be utilised including NIS/TfOH, AgOTf, CuOTf and MeOTf.[51] Different generations of thioimidates including *S*-thiazolinyl (STaz)[52] and *S*-glycosyl *O*-methyl phenylcarbamothioates (SNea)[53] have been developed, with

certain advantages over SBox. For instance, STaz is stable towards TfOH-promoted glycosylation and extensive protecting group manipulation.[54]

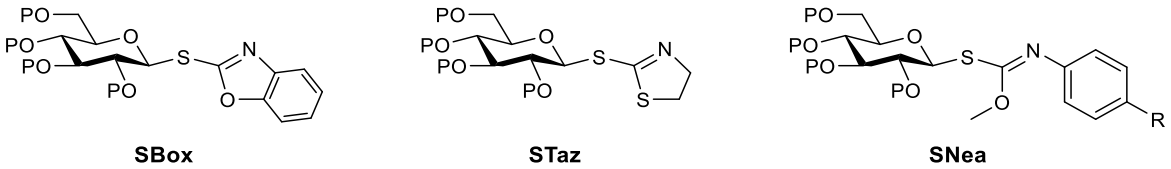
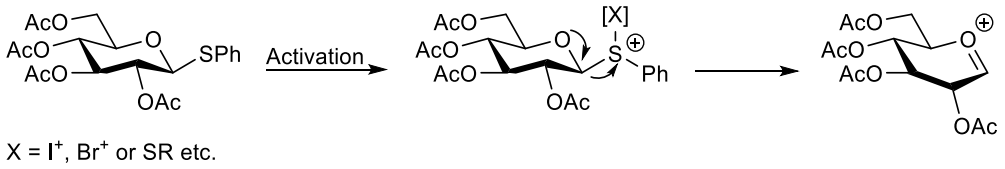


Figure 1.10 Thiomidate donors

Thioglycosides

Thioglycosides are arguably the most valuable glycosyl donors in the preparation of glycosides, as they may activated under conditions that do not affect other glycosyl donors. They are more stable in comparison to other donors such as glycosyl halides or *O*-imidates and can be readily prepared from treatment of glycosyl esters with a thiol and Lewis acid. Often, the soft sulfur atom can be activated by soft electrophilic promoters. Initially, thiophilic salts such as mercury or silver salts were used as promoters. However, employing these salts as promoters often required harsh conditions and led to the generation of side-products. Today, popular activation methods include NIS/TfOH,[55] iodonium dicollidine perchlorate (IDCP)[56] and dimethyl(methylthio)sulfonium triflate (DMTST).[57] When NIS/TfOH is employed, the sulfur atom is activated by addition of I^+ onto the sulfur generating the sulfonium species. Elimination of the sulfonium species generates the cation which is then susceptible to nucleophilic attack. Sulfur containing promoters, like DMTST, are believed to form disulfide bridges which promote the cleavage of the anomeric substituent and glycosylation.



Scheme 1.12 Activation of thioglycosides

Several other types of useful donors have been developed over the years including hemiacetal donors, glycals and glycosyl esters.

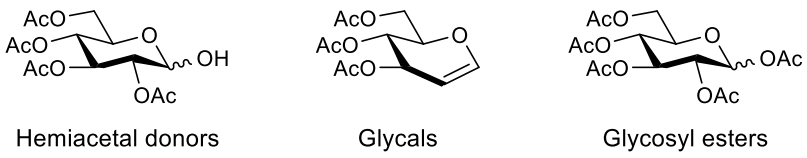


Figure 1.11 Other types of glycosyl donors

1.3 3.3 Other Factors

The nucelophilicity of the glycosyl acceptor can influence the stereochemical outcome of the glycosylation reaction, although this has not been studied as thoroughly as the influence of donor reactivity. Codee *et al.*[58] conducted a study on acceptors with varying degrees of nucleophilicity and concluded that differences in stereoselectivity reflected decreasing nucleophilicity in acceptors, indicating a change in mechanism from an S_N2-like pathway to S_N1.

The choice of solvent in glycosidation can be important in dictating the stereochemistry of the glycosidic linkage, if non-participating groups are present at the C-2 position. Solvents such as diethyl ether, tetrahydrofuran and acetonitrile have been shown to participate in glycosylation.[35, 59] It is postulated that the solvent molecule can attack the oxacarbenium intermediate and block one side to nucleophilic attack, thus generating the opposite anomer in a S_N2 fashion. Diethyl ether and tetrahydrofuran solvent molecules adopt an equatorial orientation, giving rise to axial glycosides while acetonitrile will adopt an axial orientation and give equatorial glycosides.

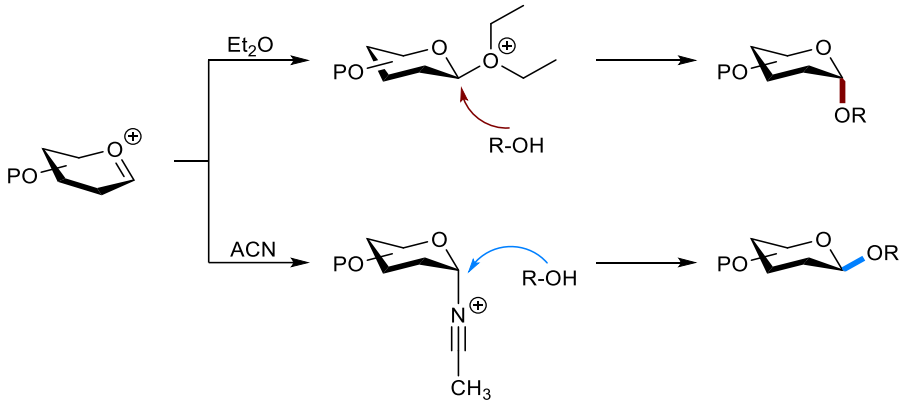


Figure 1.12 Solvent participation leading to α- and β-glycoside

1.4 Introduction to Lewis Acid-Catalysed Anomerisation

Glycosylation that is selective for the 1,2-*cis* glycosidic linkage remains a major synthetic problem and often requires lengthy optimisation of reaction conditions. Glycosides, such as the representative molecules shown in Figure 1.12, are important as potential therapeutics and contain several 1,2-*cis* linkages. Thus, developing practical and versatile methods to synthesise a wide variety of 1,2-*cis* linkages is significant in glycomimetic synthesis.

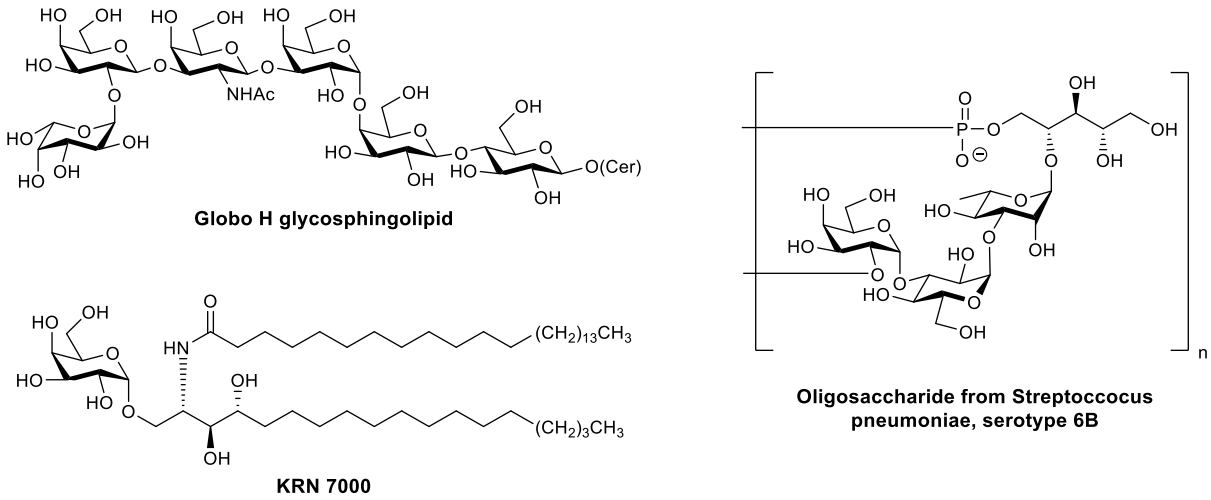
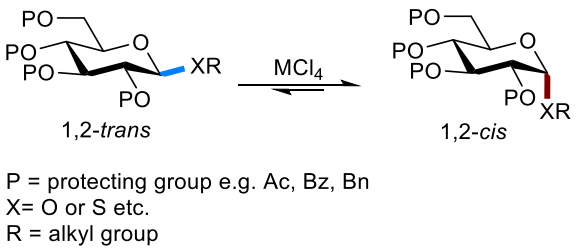


Figure 1.13 1,2-*cis* linkages in important glycosides and glycans

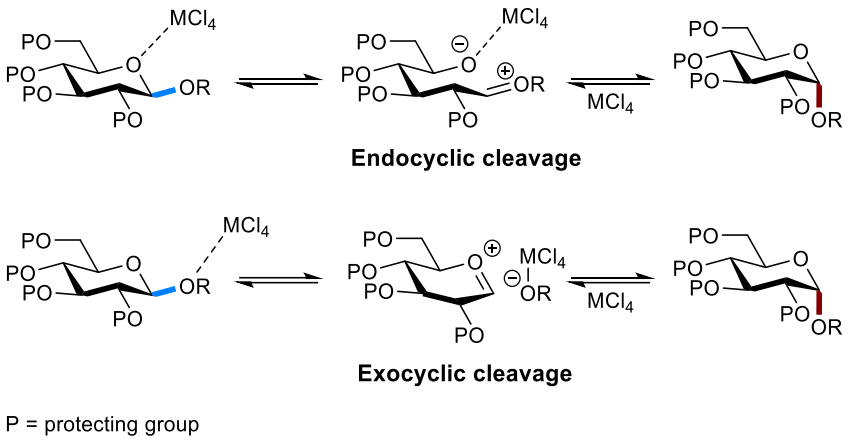
Anomerisation is defined as the epimerisation of anomers and may be promoted through the use of a catalyst, such as a Lewis or Brønsted acid, where the thermodynamically favoured anomer is expected to be predominant in the resulting equilibrium mixture. The anomerisation of equatorially oriented glycosides normally gives rise to the axial anomer and the increased stability of the axial anomer can be attributed to the anomeric effect. In gluco- and galactopyranoses, anomerisation represents a facile way to convert the easily generated 1,2-*trans* anomer into the desired 1,2-*cis* anomer. Recently, heightened interest in anomerisation has focused on approaches that would improve the rate of reaction and increase selectivity for the α-anomer. Through the optimisation of anomerisation strategies, novel expedient paths to less accessible 1,2-*cis* glycosides can be generated.[60]



Scheme 1.13 Anomerisation of 1,2-*trans* glycoside to 1,2-*cis* glycoside.

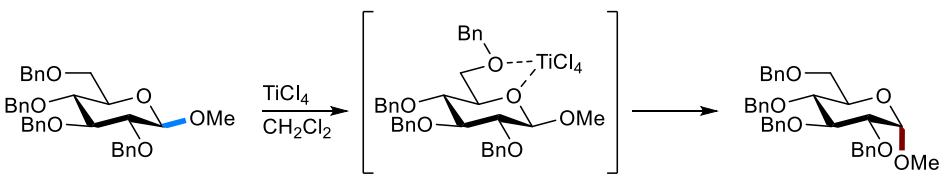
Lewis-acid catalysed anomerisation was first reported in 1928 by Pascu when he discovered that $SnCl_4$ and $TiCl_4$ converted simple alkyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosides to their axial counterparts.[61-62] The reaction was later studied by two well-known carbohydrate chemists, Raymond Lemieux and Bengt Lindberg. They endeavoured to elucidate the mechanism and each proposed two alternate pathways. Lindberg suggested anomerisation could proceed through endocyclic cleavage where the acid could coordinate to the pyranose

oxygen, promoting cleavage of the anomeric carbon to the ring oxygen, resulting in an open chain intermediate.[63] Free rotation and ring closure could then occur. The more stable anomer would be favoured in an equilibrium mixture, due to the anomeric effect, and this results in the α-anomer as the major product.[4] Lemeiux proposed that the acid could coordinate to the aglycon oxygen, promoting the cleavage of the anomeric bond, leading to an intermediate ion pair. This is known as exocyclic cleavage.[64] Lemieux later supported an endocyclic method in a $SnCl_4$-catalysed anomerisation.[65]



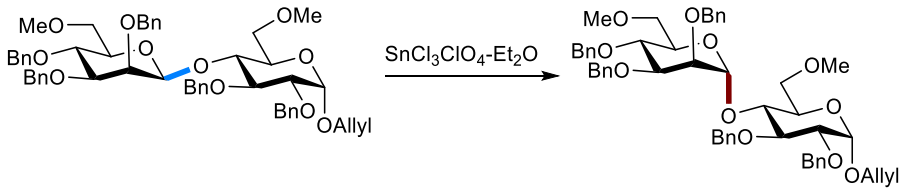
Scheme 1.14 Anomerisation pathways through endocyclic and exocyclic cleavage.

Several advances in anomerisation have been made in recent years and these will be highlighted in this section. Lemieux and Hindsgaul noted in the $SnCl_4$-catalysed anomerisation of isopropyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside that the rate significantly increased in the presence of 1 equivalent of acetic acid.[65] This result was initially surprising as $SnCl_4$ was noted to be a poor catalyst for epimerisation in comparison to $TiCl_4$. They also demonstrated that carboxyl groups could enhance the rate of anomerisation. Koto achieved the anomerisation of methyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside using $TiCl_4$ in CH_2Cl_2, postulating that the rapid anomerisation was due to chelation of $TiCl_4$ to the C-6 oxygen and ring oxygen which promoted endocyclic cleavage.[66] These conditions could be applied to disaccharides to give the axial products in low to moderate yields. Mukaiyama *et al.* adapted this reaction and achieved anomerisation of a disaccharide in a good yield with $TiBr_4$ and $MgBr_2.OEt_2$ in 80% yield.



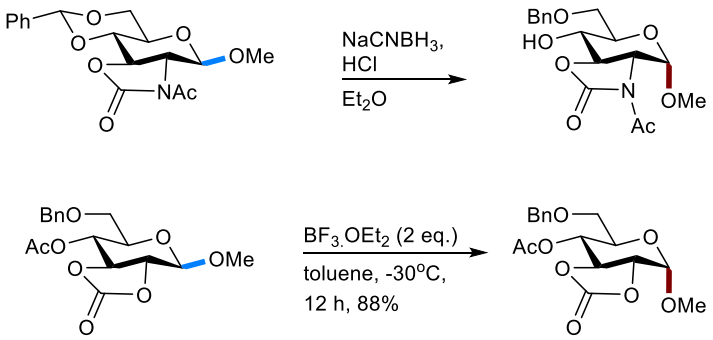
Scheme 1.15 Rapid anomerisation achieved by Koto and postulated chelation to $TiCl_4$.

An example involving the anomerisation of dissacharides was carried out by Kishi and co-workers with the use of a Mukaiyama catalyst ($SnCl_3ClO_4$) and benzylated β-mannopyranoside derivatives.[67] They accounted for the selectivity that could be achieved with mannopyranosides with the Δ2 effect - the unfavourable steric interaction between an equatorial anomeric substituent and the axial C-2 substituent. They concluded that the anomerisation for the disaccharides was principally operating through the endocyclic pathway as only a small amount of the monosaccharides were isolated.



Scheme 1.16 Anomerisation of dissacharide with Mukaiyama reagent ($SnCl_3ClO_4$).

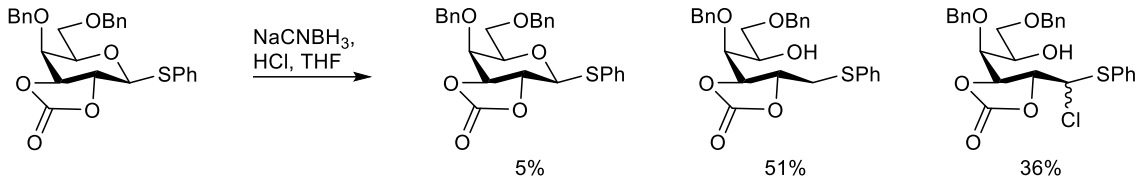
It has been established that the introduction of a 2,3-*trans* carbamate or 2,3-*trans* carbonate group promotes anomerisation in glycosides. This occurrence was initially observed by the Crich and co-workers in the deprotection of a benzylidene group that resulted in anomerisation of a glucoside constrained by 2,3-*trans* carbamate group. They proposed that the 2,3-*trans* carbamate group strained the pyranose ring and this strain facilitated ring opening thus promoting anomerisation via endocyclic cleavage.[68] The Oscarson group reported the anomerisation of a disaccharide carrying a 2,3-*trans*-oxazolidinone with kinetic measurements.[69]



Scheme 1.17 Anomerisation of 2,3-*trans* carbamate derivative by the Crich group and anomerisation of 2,3-*trans* carbonate derivative by Manabe/Ito group.

Manabe and Ito and co-workers incorporated 2,3-*trans* carbamate and 2,3-*trans* carbonate groups into pyranoside and demonstrated these derivatives underwent Lewis-acid catalysed anomerisation easily in comparison to other pyranosides. They presented evidence to support endocyclic cleavage in the case of conformationally restricted pyranosides by inter- and

intramolecular Friedel-Crafts reactions, reduction of the cation to yield the open chain derivative and chloride addition.[70]



Scheme 1.18 Reduction and chlorination of intermediate to yield open-chain products to support endo cleavage.

Satoh and co-workers employed quantum mechanical calculations to show that N-benzyl-2,3-*trans*-carbamate derivatives had lower energy transition states in pathways to *endo*-cleavage than pyranosides without an oxazolidinone group.[71] Satoh and co-workers carried out a further theoretical study to explain the enhanced anomerisation rate of 2,3-*trans* carbonate and 2,3-*trans* carbamate derivatives in comparison to pyranoside derivatives.[72] For this study, different thioglycosides containing 2,3-*trans* cyclic protecting groups were investigated using DFT calculations and experimental values. The transition states calculated for 2,3-*trans* carbamate and 2,3-*trans* carbonate derivatives were found to have the lowest energy barriers and this was in good agreement with experimental values where these derivatives readily formed the α-anomer. In derivatives that did not contain these groups, the energy barrier for endocyclic cleavage was predicted to be higher and in experimental studies, these derivatives did not form the α-anomer. Additionally, in geometry optimised structures of the constrained pyranosides, there is a deformation along the C-2/C-3 bond of ~10° due to the cyclic protecting group. Thus pyranosides containing 2,3-trans carbamate and carbonate groups can be hypothesised to have raised ground state energies, due to inner ring strain, explaining their enhanced rate of anomerisation via endocyclic cleavage.

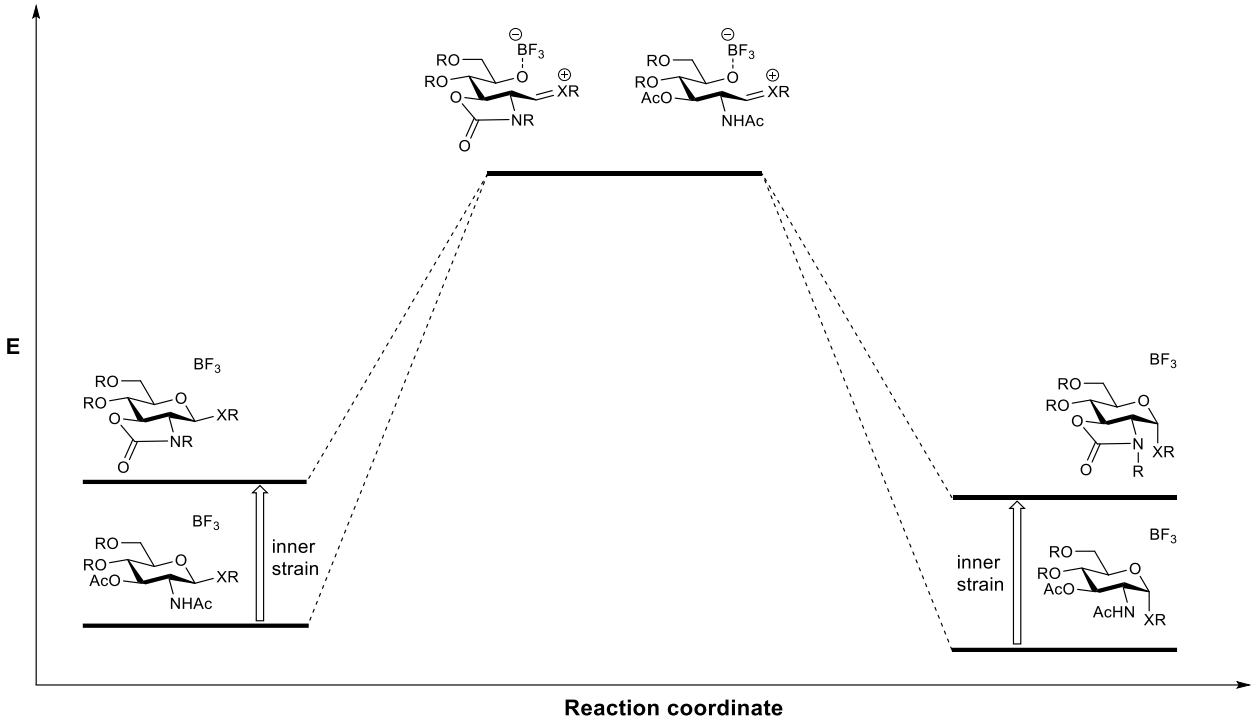


Figure 1.14 Derivatives with 2,3-trans cyclic groups have raised ground state energies and undergo anomerisation at an enhanced rate via endocyclic cleavage.

Manabe, Ito and co-workers investigated substituent effects at the anomeric centre, 2-position and 5-position in 2,3-*trans* carbamate pyranosides in the anomerisation reaction.[73] They found that the *N*-substituent had a substantial effect on the degree of anomerisation achieved. When *N*-benzyl group was replaced by *N*-*o*-nitrobenzyl or *N*-naphthyl group, the yield of α-anomer generated was significantly diminished. They reasoned that an electron donating substituent may increase the lifetime of the acyclic cation created by endocyclic cleavage. They also found that a methyl group at the C-5 position yielded a higher amount of the corresponding α-anomer in comparison to CH_2SPh, CO_2Me or CH_2OAc groups at the C-5 position. They reasoned that the increased steric hindrance at the C-5 position blocked access of the Lewis acid to the ring oxygen, thus inhibiting anomerisation via endocyclic cleavage.

Further studies were also carried out by Satoh, Manabe, Ito and co-workers into the role of the N-substituent in 2,3-*trans* carbamate derivatives. They found that *N*-substituents that had a carbonyl group present (*e.g.* R= CO_2Me, CO_2Allyl, CO_2Bn, $CO_2CH_2CCl_3$) underwent anomerisation readily and the α-anomer could be isolated in high yields (80-88%). The acetyl group derivative anomerised significantly faster than the other derivatives. Substrates that had an ether group present (*e.g.* R= Bn, PMB) did not undergo anomerisation as easily and a significant amount of β-anomer remained. They concluded that the carbonyl group could be oriented in an anti-conformation and could therefore stabilise the positively charged species

produced by endocyclic cleavage.[74] The one-pot anomerisation of 4 glycosidic linkages in a chitin type tetrasaccharide could be achieved when 2,3-*trans* N-acetyl carbamate groups were incorporated into the tetrasaccharide. This proceeded in the presence of excess $BF_3.OEt_2$ with high selectivity and 83% yield.[74]

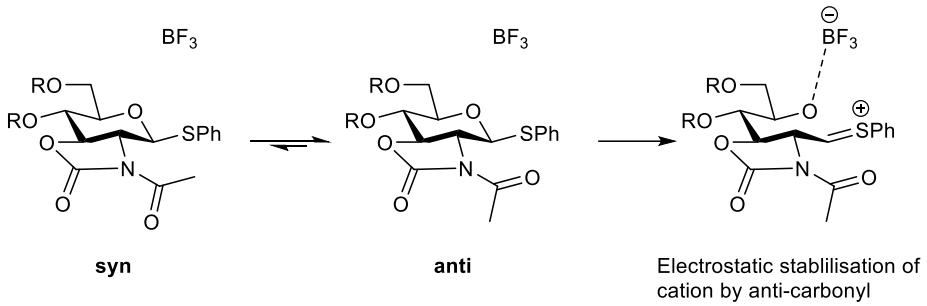
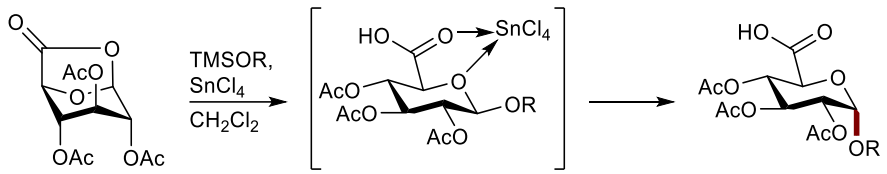


Figure 1.15 Electrostatic stabilisation of positively charged intermediate by anti-carbonyl in *N*-acetyl group.

Ye and co-workers have incorporated 2,3-*trans* carbonate thioglycoside donors in glycosylation reactions and reported that Lewis acids can act as α-directing additives in these reactions.[75] In a glycosylation reaction where the sugar donor is pre-activated and then treated with a nucleophilic acceptor, they obtained a mixture of anomers. They found that addition of $BF_3.OEt_2$ (0.1 or 0.2 equiv.) before isolation of the disaccharide leads to significantly more of the α-product isolated. More recently, Ye and co-workers reported stereo-controlled glycosylation reactions involving *N*-acetyl 2,3-*trans* carbamate thioglycoside donors and phenolic acceptors utilizing a similar methodology as described above. The found that Lewis acid $BF_3.OEt_2$ was α-directing while addition of a base led to the β-product.[76]

The Murphy group first became interested in anomerisation when they investigated the stereoselectivity obtained in an $SnCl_4$-promoted glycosylation. They noted that in a reaction between a lactone donor and a nucleophile, only α-glycosides were obtained, even in the presence of acyl containing groups. It was postulated that the β-glycoside was initially formed and anomerised *in situ* to the corresponding α-anomer.[77-78] Further studies later demonstrated that glucoronides were significantly easier to anomerise in comparison to glucosides. This was reasoned by increased coordination to the Lewis acid by the carbonyl group present at the C-6 position. Murphy and co-workers also studied the glycosylation reaction between a cyclic imidate donor and a phenolic acceptor, finding that the α-glycoside could be obtained in 63% yield, using $SnCl_4$ and TMSOTf.



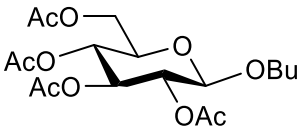
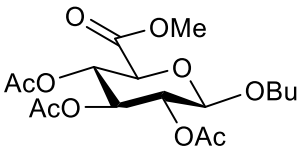
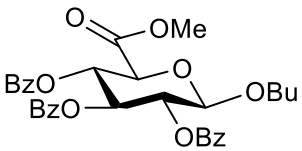
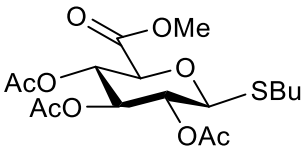
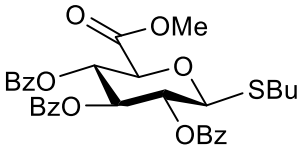
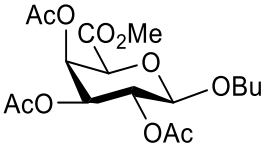
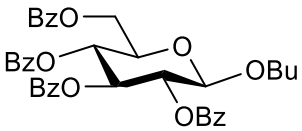
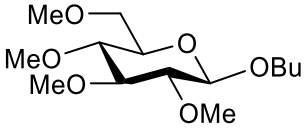
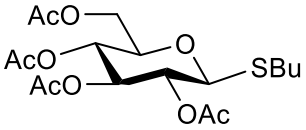
Scheme 1.19 Glycosidation using $SnCl_4$ as promoter gives rise to α-glucouronic acids

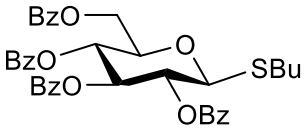
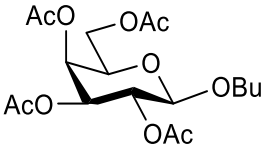
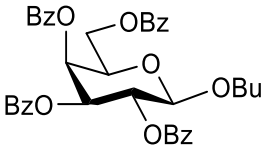
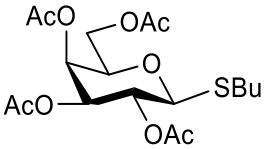
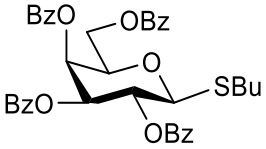
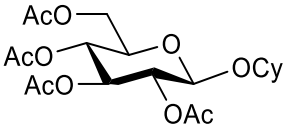
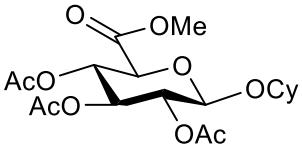
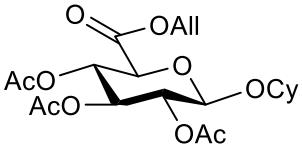
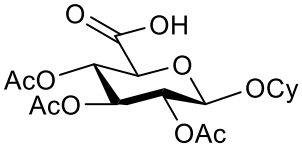
Our group previously quantified electronic and conformational factors that impacted on rates of anomerisation in gluco- and galactopyranoside derivatives, as well as selectivity for the α-anomer.[79] The kinetics of $SnCl_4$-catalyzed anomerisation using 18 different *O*- and *S*-glycosides was established within this study, it was established that the anomerisation of glucouronic acid and galacturonic acid derivatives was considerably faster than their related glucopyranoside and galactopyranoside derivatives. The unprotected acid (entry 18) was found to be ~600 times faster than the corresponding *O*-glycoside (entry 15) and was the fastest derivative to undergo anomerisation of all those investigated. The enhanced rate of anomerisation was concluded to be due to increased coordination of the C-6 carbonyl to the Lewis acid, promoting endocyclic cleavage.

It was found that galactopyranoside derivatives anomerised at a higher rate than their corresponding glucopyranoside derivatives, with the exception of one galactopyranoside derivative (entries 10 and 12). The higher rate obtained for galactopyranoside derivatives is accounted for by the axial C-4 substituent, as axial substituents are known to be less electron-withdrawing than corresponding equatorial substituents, they stabilise the positively charged intermediate. Furthermore, the increased electron density in the galactose ring enhances coordination to the metal centre, increasing the rate of anomerisation.

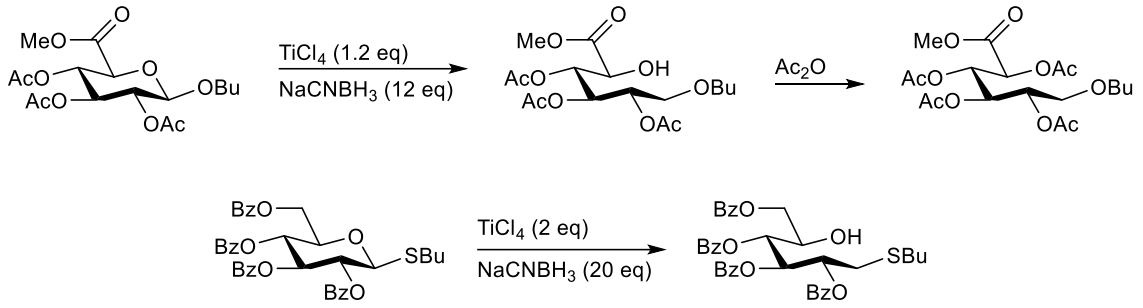
It was also established that *S*-glycosides anomerised at a faster rate than their analogous *O*-glycosides. Sulfur is less electron-withdrawing than oxygen and thus will stabilise an electron deficient intermediate, assuming the predominant pathway is endocyclic. Furthermore, the anomeric equilibrium achieved by the *S*-glycosides is lower in comparison to the *O*-glycosides and this equilibrium is reached faster. Higher rates and α:β ratios were observed for benzoylated *O*- and *S*-glycosides in comparison to their acetylated counterparts. It is feasible that the carbonyl in benzoyl group at the 2-position is more electron rich and could electrostatically stabilise the cation at the anomeric centre.

Table 1.1 Kinetics of $SnCl_4$-catalysed anomerisation of glycosides obtained by Pilgrim and Murphy

Entry	Substrate	$10^6(k_r+k_f)(s^{-1})$	Relative rate	α:β
1		4	1	10:1
2		170	42.5	16:1
3		470	117.5	24:1
4		420	105	4:1
5		920	230	7:1
6		290	72.5	19:1
7		19	4.75	16:1
8		400	100	13:1
9		69	1.725	2:1

10		43	10.75	4:1
11		4.9	1.225	15:1
12		42	10.5	11:1
13		14	3.5	2:1
14		20	5	4:1
15		21	5.25	11.5:1
16		210	52.5	11.5:1
17		1100	275	13:1
18		12000	3000	19:1

Trapping experiments employed by Pilgrim and Murphy indicated that the primary pathway in the epimerisation of *O*- and *S*-glycosides was endocyclic. The open chain form could be trapped by addition of excess sodium cyanoborohydride.



Scheme 1.20 Trapping of open-chain intermediates

Lewis acid-promoted anomerisation has been employed in the synthesis of biologically relevant compounds. The Murphy group employed $TiCl_4$ chelated anomerisation to synthesise analogues of naturally occurring α-*O*-glycolipids from *Sphingomonas* bacteria, with *O*-, *S*- and SO_2-linkages.[80-81] These glycolipid antigens are powerful immunostimulators that can activate Natural Killer T (iNKT) cells**.** A promising example of such a glycolipid is α-galactosylceramide (α-GalCer) which has been shown to potent antitumour agent through stimulation of iNKT cells. Savage and co-workers adapted this methodology in the synthesis of related glycolipids GSL-1B and GSL-1C.[82] Murphy *et al.* investigated the anomerisation of selenium glycosides and applied this reaction to the generation of α-*Se*-GalCer.[83]

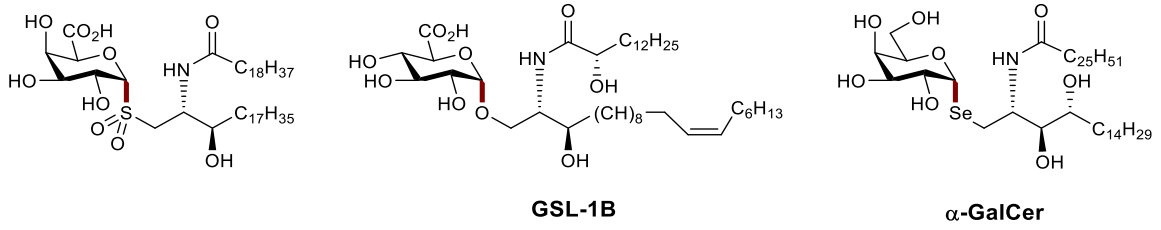
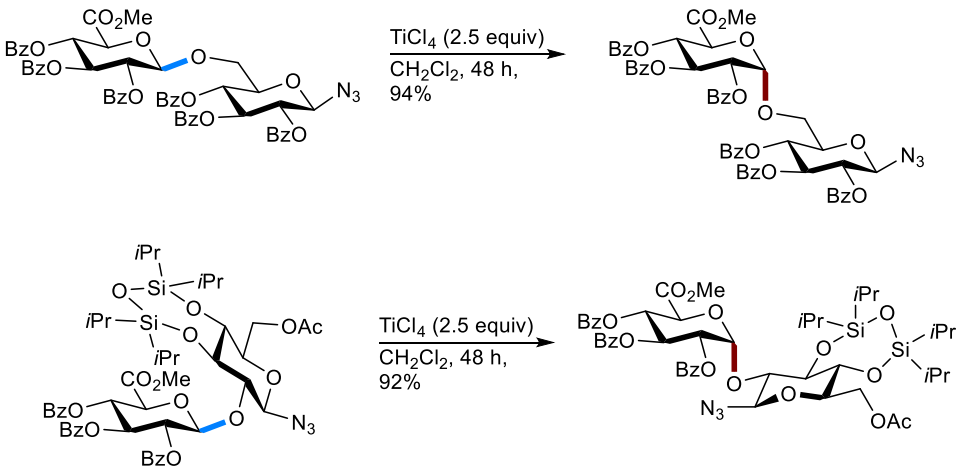


Figure 1.16 Structure of glycolipids prepared by $TiCl_4$-induced anomerisation

Murphy and co-workers investigated the anomerisation of uronic acid derivatives containing an azide at the anomeric position and found that these glycosyl azides underwent anomerisation facilely in the presence of $TiCl_4$. Triazole containing mimetics of Spingomonas bacterial glycolipids were synthesised by McDonagh and Murphy.[84] The regiospecific anomerisation of dissacharides was also achieved by Murphy and co-workers, utilising uronic acid derivatives and $TiCl_4$, with high yields and stereoselectivity.[85]



Scheme 1.21 Regioselective anomerisation of dissacharides

1.5 Aim of this Thesis

The majority of work in the stereoselective generation of 1,2-*cis* linkages via anomerisation has dealt with gluco- and galactopyranosides. The first aim of this thesis was to explore the epimerisation of glycosides such as pentopyranosides and 6-deoxyhexopyranosides. The elements that would lead to higher rates of anomerisation and stereoselectivity in these saccharides could then be established by reaction kinetics. The second part of this thesis will involve the stereoselective epimerisation of glycosyl thiols. Relatively few methods exist to generate the 1,2-*cis* thiol at the anomeric position selectively. The third and fourth chapters will detail efforts to epimerise glycosyl thiols and the surprising selectivity that could obtained through the use of different Lewis acids. The last aim of this thesis was toward the synthesis of a constrained sialylated galactose compound which may act as an inhibitor for the binding of pathogens like influenza.

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Chapter 2

Anomerisation of Pentopyranosides and 6-Deoxyhexopyranosides

2.1 Introduction

There are a relatively small number of different monosaccharides present in mammalian glycans, including glucose, galactose, N-acetylgalactosamine, N-acetylglucosamine, glucuronic acid, mannose, sialic acid, fucose and xylose. In contrast to this, there are more than 340 distinct carbohydrates that are present in bacterial cells and often these are interesting as vaccine candidates as they elicit a strong immune response.[1] Despite the huge diversity in carbohydrates, the majority of anomerisation studies have focused solely on a small number of monosaccharides, largely on derivatives of glucose and galactose. This chapter will detail efforts to explore the anomerisation of different glycosides, namely D-xylopyranosides, L-arabinopyranosides and L-fucopyranosides. The reaction kinetics were established for the various derivatives of these saccharides to investigate how the structure of these saccharides affects the rate of epimerisation.

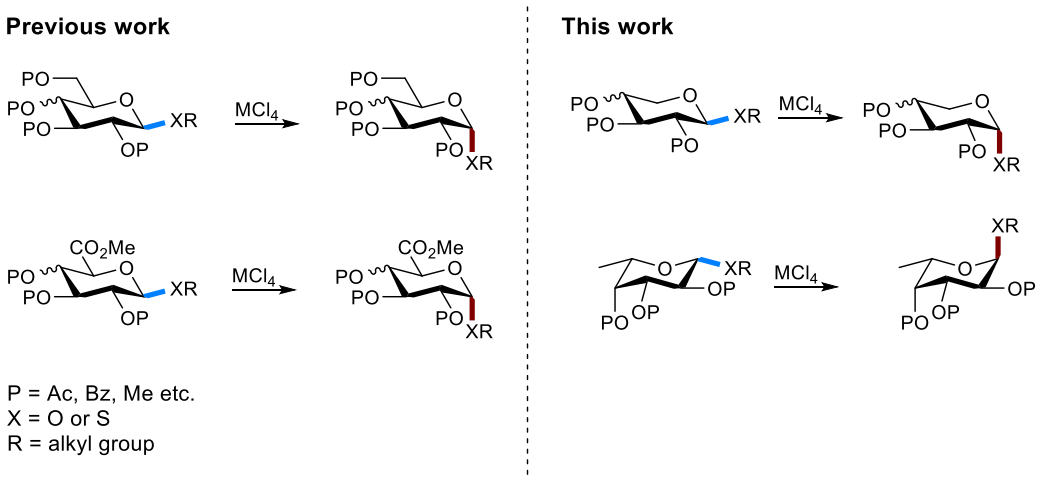


Figure 2.1 This work aimed to explore the anomerisation of xylopyranosides, arabinopyranosides and fucopyranosides

Derivatives (or glycosides) of pentose sugars, including L-arabinose, D-xylose and D-ribose, can exist as pentofuranosides or pentopyranosides, the latter being more common and lacking a CH_2OH group at the C-5 position. L-Fucose and L-rhamnose lack an oxygen functional group at the C-6 position. D-Xylose, L-arabinose and L-fucose are of interest as they are important motifs in natural products and biologically important glycans.[2-4]

D-Xylose and L-fucose are two of the more unusual monosaccharide building blocks that constitute glycans in mammalian cells. D-Xylose is part of proteoglycans, which are proteins that are heavily glycosylated with glycosaminoglycans, and have important roles in cell-cell communication, such as regulating growth factor signalling, inflammation and angiogenesis.[3]

Xylose, as well as fucose, are thought to be involved in signalling events in the Notch receptor, a protein which is involved in cell growth signalling during neurogenesis. D-Xylose is also present in bacterial and plant cells. It is the main building block in xylan, a hemicellulose found in plant cells, thus making it one of the most abundant carbohydrates on earth. D-Xylose can be found in many natural products such as (−)-polycavernoside A[5-6] and clavosides A and B.[7]

Mammalian glycans that contain fucose are involved in various roles in the body including interactions between host cells and microorganisms, blood transfusion reactions, leukocyte adhesion and numerous ontogenic events.[2] A 1,2-*cis* linked fucose residue is present in many important glycans in the body such as blood group antigens A, B and H, Lewis^{b}, Lewis^{y}, sialyl Lewis^{x} and globo-H. Globo-H is a highly antigenic polysaccharide that is overexpressed on cancer cells and currently under development as a carbohydrate based vaccine for metastatic breast cancer.[8]

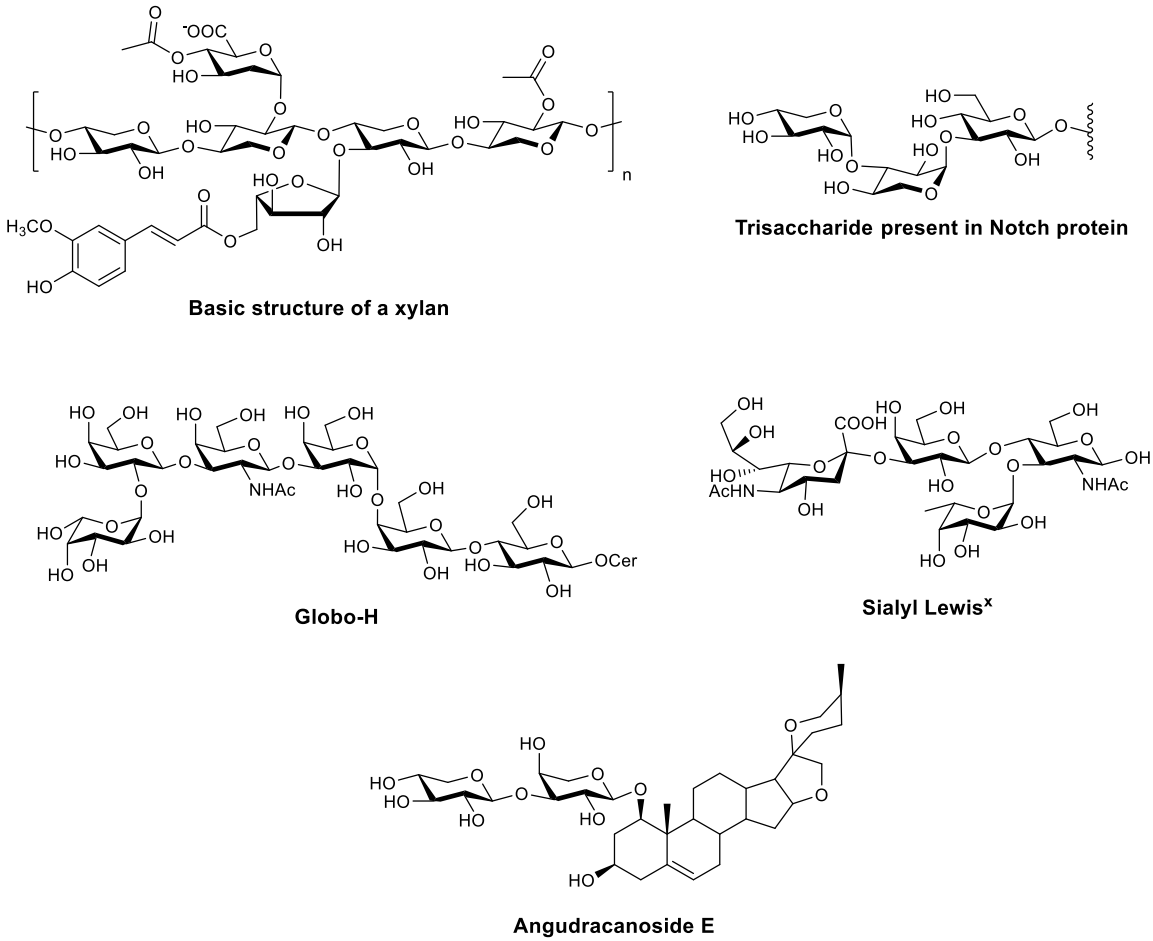


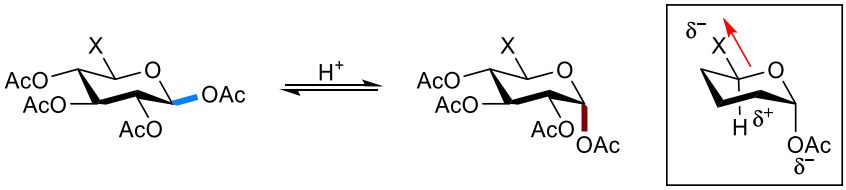
Figure 2.2 Important biological structures that contain xylose, fucose and arabinose residues

L-Arabinose is not found in mammalian cells but is found in plant and bacterial cells. It is a constituent of xylans, a hemicellulose found in plant cells, along with xylose. L-Arabinose is important for the L-arabinose operon, an operon that encodes for enzymes in *Escherichia coli*.[9] L-arabinose can be found in natural products including angudracanoside E,[10] ardisianoside A[11] and saniculasaponin II and III.[12]

2.2 Relevant Electronic Effects

The substitution of any position in the pyranose ring can affect the reactivity and physical properties of the carbohydrate. It was particularly interesting how substitution of the C-5 group would affect the rate of anomerisation in these derivatives. The electronegativity of the C-5 substituent has been found to influence the propensity for the anomeric position to adopt an axial orientation.[13] Lemieux carried out a study varying the equatorial C-5 substituent in acetylated derivatives of glucose and found that increasingly electronegative substituents preferred an axial anomeric configuration. This can be explained by reduced electrostatic repulsion between an axial substituent and an electropositive proton at the C-5 position.

Table 2.1 Effect of electronegative substituents at the C-5

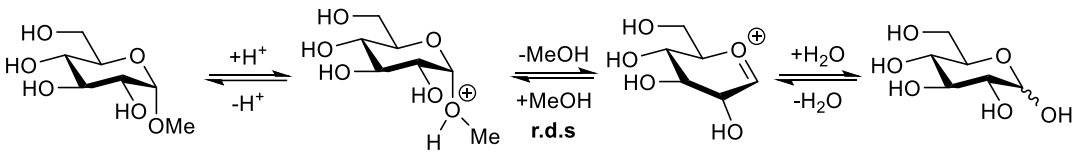


X	Anomeric Effect kcal.mol^{-1}
H	1.3
CH_3	1.31
CH_2I	1.35
CH_2Cl	1.43
CH_2OAc	1.45
CH_2OTs	1.75

Electronic and conformational factors can affect the rate of hydrolysis in glycosidic linkages, glycosylation and anomerisation. These reactions all proceed through a positively charged intermediate and thus understanding the factors that affect hydrolysis and glycosylation aids

interpretation of rate differences in the anomerisation of various glycosides. The next section will focus on factors that affect the rate of hydrolysis.

Glycoside hydrolysis is one of the most studied reactions in carbohydrate chemistry, due to the abundance of glycosidic linkages in nature. Acid-catalysed hydrolysis of a glycosidic linkage is thought to proceed through the fast protonation of the exocyclic oxygen. This is then followed by exocyclic cleavage to give the oxacarbenium intermediate. Water can then attack the cyclic carbocation to give the free sugar as a mixture of anomers. The rate determining step in glycosidic hydrolysis is the formation of the positively charged oxacarbenium intermediate and therefore changes in the glycoside structure that result in the stabilisation of this intermediate will increase the rate of hydrolysis.



Scheme 2.1 Hydrolysis of methyl-α-D-glycopyranoside

Whistler and Rowell[14] demonstrated that if the ring oxygen is replaced by sulfur, there is an increase in the rate of hydrolysis. Sulfur is less basic than oxygen and through the inductive effect, a higher concentration of the protonated aglycon oxygen can exist leading to a higher rate of hydrolysis. Timmel *et al*.[15] found that replacement of the exocyclic oxygen with sulfur led to a decreased rate of hydrolysis. In this case, there will be a lower concentration of the protonated intermediate present, leading to a slower rate of hydrolysis. Studies by Withers and co-workers showed that inductive effects govern the rate of glycosidic hydrolysis. If a hydroxyl group at any position is replaced with fluorine, the reactivity decreases, whereas deoxygenation enhances the rate.[16-17]

It has been observed that the rate of hydrolysis increases with the number of axial hydroxyl groups present in the sugar ring. For instance, the hydrolysis of methyl α-D-galactopyranoside is 5 times faster than hydrolysis of methyl α-D-glucopyranoside.[18] J.T. Edwards initially proposed that the rate increase could be accounted by reduced steric interactions in the transition state caused by 1,3-diaxial interactions between the OH and H in the ground state.[19] Other studies have indicated that electrostatic stabilisation accounts for the increased rate of hydrolysis. Bowen *et al*. employed molecular mechanics calculations to investigate the stability of oxacarbenium ions and concluded that axial OH groups had a stabilizing electrostatic interaction in the transition state despite steric interactions.[20] Miljkovic and his group[21]

addressed the reactivity difference of galactosides and glucosides in acetylosis and reached similar conclusions based on ab initio calculations and experimental evidence.

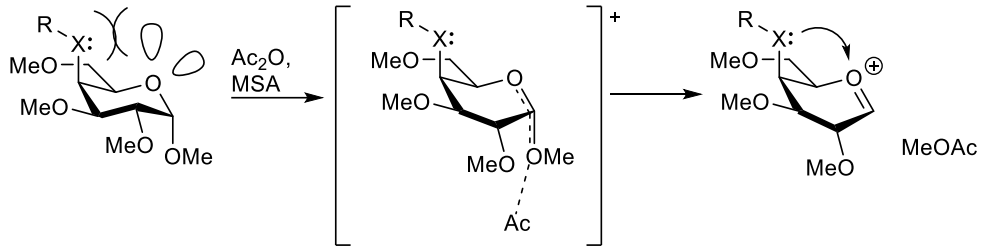


Figure 2.3 Electrostatic stabilization by axial C-4 group

Further evidence came from Bols *et al.*, who found that the base strength of piperidines and pyridazines could be reliably predicted by the stereochemistry of hydroxyl substituents in the 3- and 4-positions in the ring, indicating that axial hydroxyl groups were considerably less electron withdrawing than their equatorial counterparts.[22] The Bols group also synthesised methylated C4 glycoside analogues to demonstrate that electronic effects from the stereochemistry of the hydroxyl groups rather than steric hindrance was the principal reason for rate differences observed in glycosidic hydrolysis.[23] It can be summarised that the rate increase observed in the hydrolysis of galactopyranosides is due to the less electron-withdrawing nature of the axial C4 hydroxyl group which stabilizes a positive charge on the C1 position.

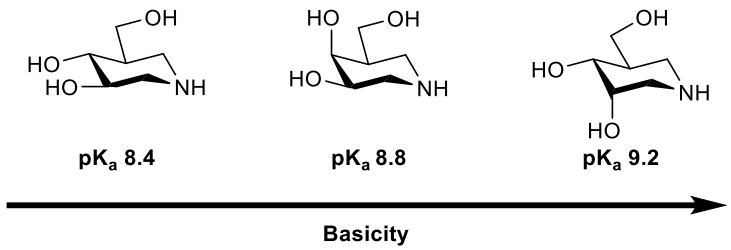


Figure 2.4 The base strength of piperidines increase the number of axial OH groups

A further study was carried out by Bols and co-workers[24] on the hydrolysis of 3,6-anhydroglucosides that locked glucosides in the highly reactive $^{1}C_{4}$ conformations. It was found that methyl 3,6-anhydro-α-D-glucopyranoside, where the number of axial hydroxyl groups was increased, hydrolyzed 446 times faster than the $^{4}C_{1}$ conformer. However, the hydrolysis methyl 3,6-anhydrogalactopyranoside, which has a boat conformation and thus has less axial hydroxyl groups than the corresponding galactoside, had a slower rate of hydrolysis. This indicated that the reactivity of glycosides could be manipulated by changing the conformation of the saccharide.

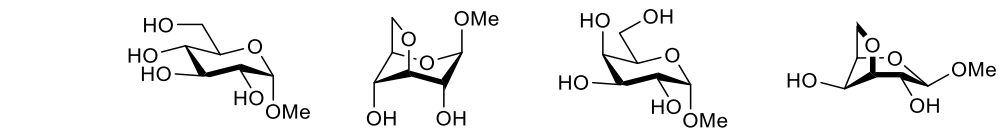


Figure 2.5 Conformational effects on glycoside hydrolysis

2.3 Synthesis of *O*- and *S*-glycoside derivatives

A series of *O*- and *S*-glycosides, including derivatives of D-xylose, L-arabinose and L-fucose, were synthesised to begin the study and subjected to Lewis acid-catalysed conditions. The initial objective of this project was to ascertain whether these simple glycosides could undergo anomerisation. The aim to was then to establish the chemical kinetics of the glycosides under $SnCl_4$-promoted anomerisation and quantify how the electronic properties of each derivatives affected the rate of anomerisation.

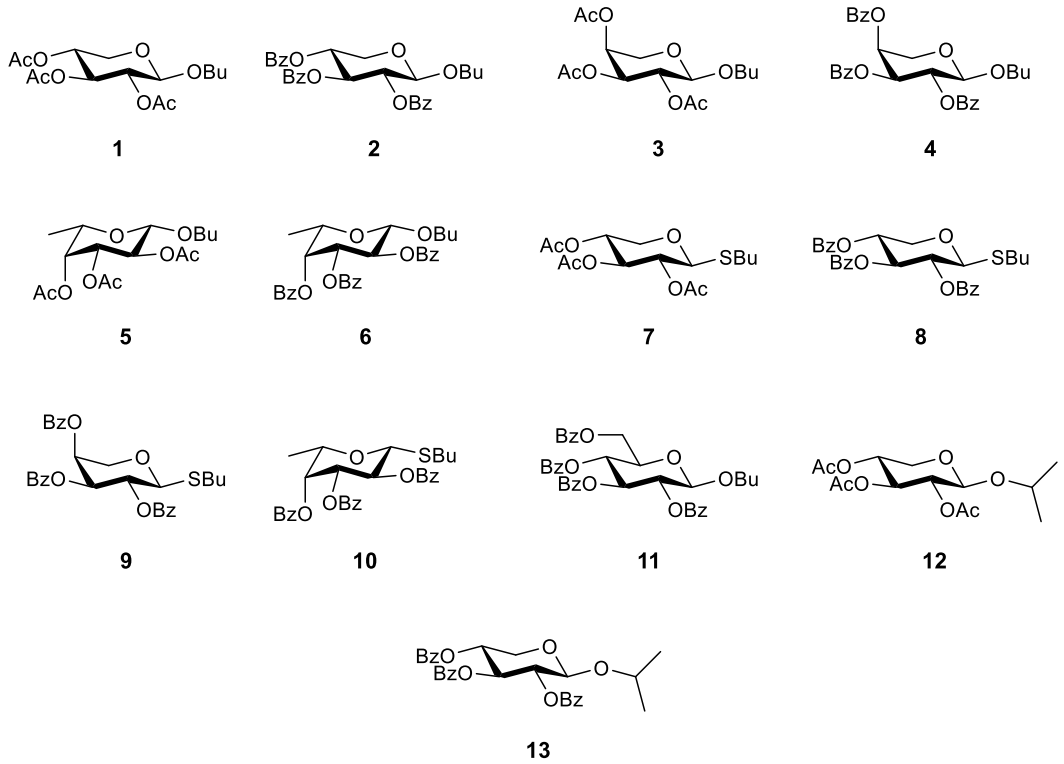
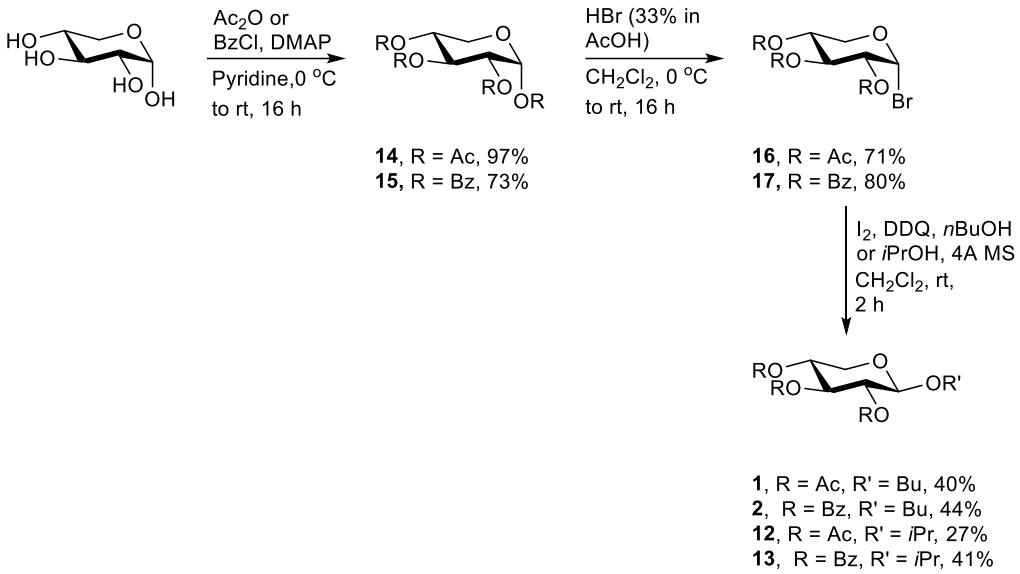


Figure 2.6 *O*- and *S*-glycosides used in kinetic study

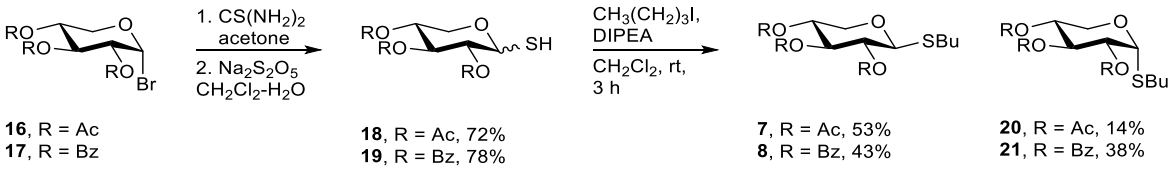
The xylopyranosides **1-2** and **12-13** were synthesised over 3 steps. D-xylose was protected with acetyl or benzoyl groups in high yields (74-97%) and the corresponding bromides were generated, using hydrogen bromide in acetic acid, in good yields (71-80%). The glycosylation was carried out following a procedure developed by the Lemhler group.[25] Isopropanol or n-butanol were utilized as glycosyl acceptors and iodine/DDQ as a

promoter system. DDQ served as an electron transfer molecule for effective activation of the donor sugar in combination with iodine. The yields were low for these reactions (27-44%) but were consistent with values given in the paper. In the glycosylation reaction for **12**, the low yield was attributed to deacetylated product.



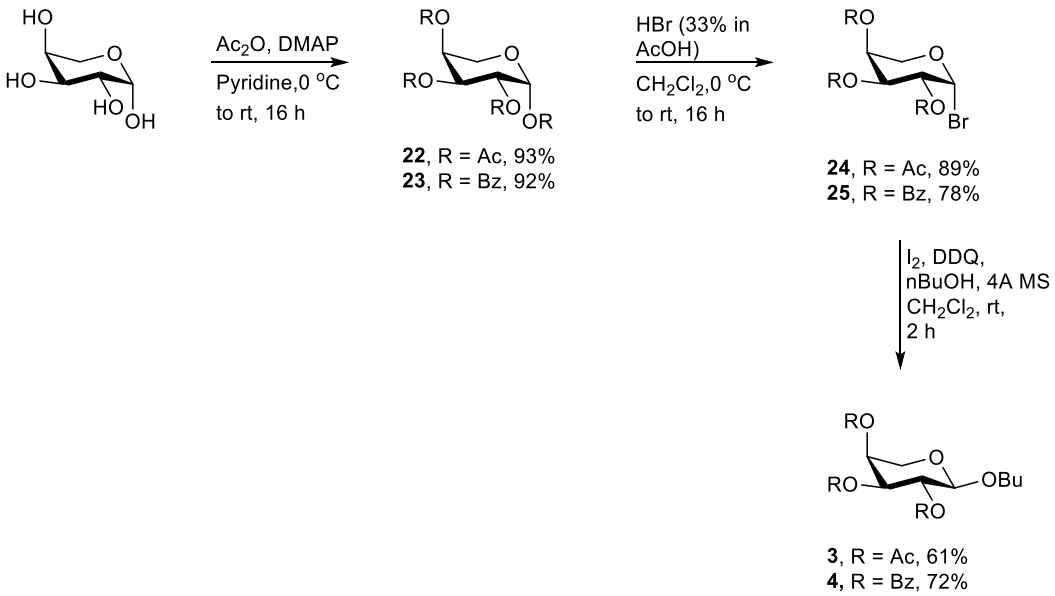
Scheme 2.2 Synthesis of *O*-xylopyranosides

The thio-derivatives of xylose were synthesised starting from the corresponding bromides. The glycosyl thiol was generated using thiourea to form the thiouronium salt and subsequent hydrolysis gave the free thiol, in good yields (72-82%). Thiols **18** and **19** were obtained as a mixture of anomers (α:β =1:2), that proved difficult to separate, and therefore carried on to the next step as a mixture. The thiol was deprotonated using DIPEA to form the thiolate and then underwent nucleophilic addition to iodobutane to form the *S*-butyl derivative, in good yields (67-81%). The two anomers could be separated at this point.

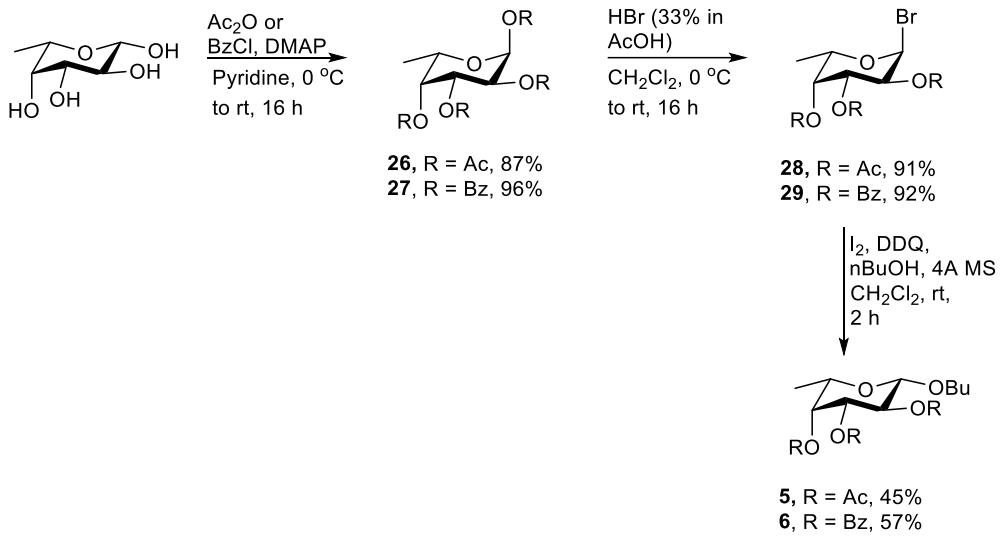


Scheme 2.3 Synthesis of *S*-xylopyranosides

The Lemhler method was carried out for *O*-arabinopyranoside **3** and **4** and *O*-fucopyranosides **5** and **6**. Superior yields were achieved with the arabinopyranoside derivatives in the glycosylation reaction (61-72%), in comparison to that of the xylose compounds, which may be attributed to the more electron donating axial C-4 group.

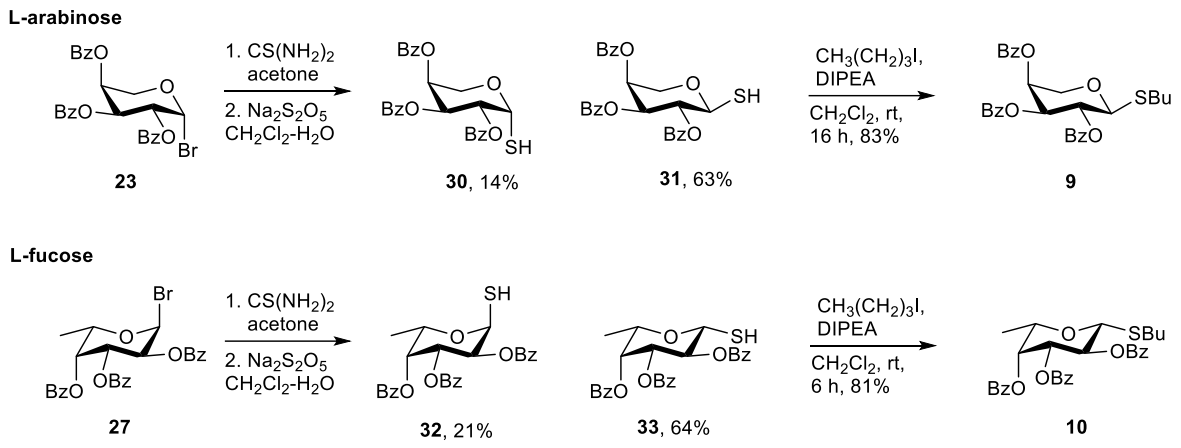


Scheme 2.4 Synthesis of *O*-arabinopyranosides



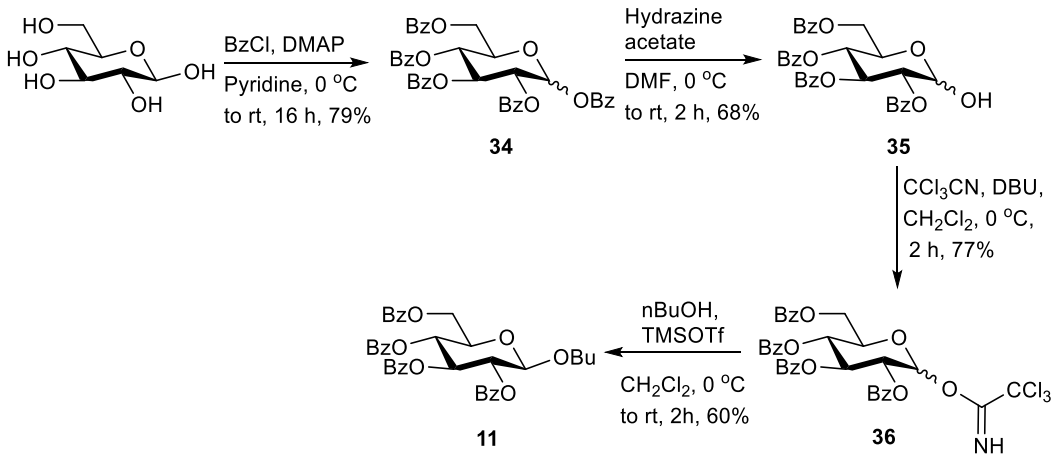
Scheme 2.5 Synthesis of *O*-fucopyranosides

The *S*-butyl derivatives of fucose and arabinose were prepared in the same manner to that of the *S*-butyl derivative of xylose. The thiols were generated from the corresponding bromides in high yields (77-85%) and the anomers were separated by column chromatography, with the equatorial anomer being the major product in each case. The 1,2-*trans* anomer was carried on and reacted with iodobutane to form the desired products, in good yields (81-83%).



Scheme 2.6 Synthesis of *S*-butyl derivatives

As a control compound, **11**, was also synthesised, as the kinetics for this compound had previously been established. Starting from D-glucose, the compound was perbenzoylated in a 70% yield and the corresponding hemiacetal was formed in 68%. Trichloroacetimidate **36** was then generated and used immediately to form *O*-butyl glucose derivative **11**, in a good yield (60%).



Scheme 2.7 Synthesis of *O*-butyl glucose derivative **11**

2.4 Anomerisation studies

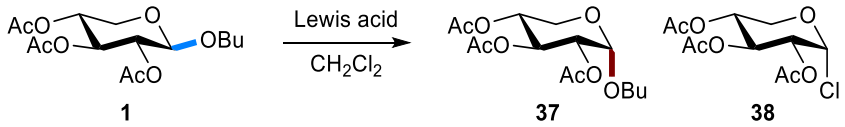
The anomerisation of the various derivatives was initially investigated using Lewis acids $SnCl_4$ and $TiCl_4$, varying the time and temperature to optimise conditions. Each anomerisation was performed on a ~30 mg scale (1 equiv.) in dichloromethane (0.2 M). $TiCl_4$ and $SnCl_4$ (1.0 M in dichloromethane) were used. The substrates were dried for at least ~3 h prior to the reaction. The ratios were determined by ^{1}H NMR spectroscopy after work-up.

A common side-product generated in the epimerisation reactions was the corresponding glycosyl chloride. This was identified by a characteristic H-1 signal that appeared as a doublet shifted downfield between δ 6.0 and δ 6.7 ppm in the ^{1}H NMR spectrum. The chloride was isolated from the reaction mixture or was confirmed by comparison to reported literature.

2.4 1 Anomerisation of D-xylose derivatives

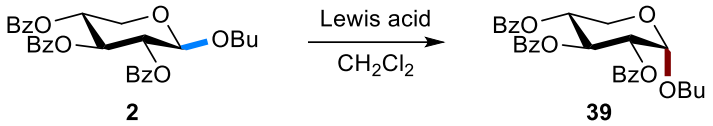
Anomerisation conditions for acetylated xylose derivative **1** are shown Table 2.2. At room temperature, $TiCl_4$ (2.5 eq.) led to the generation of the α-anomer in 51% after 24 hours. However, a significant amount of chloride **38** was also generated. Lowering the temperature to 4 ºC helped to suppress the generation of the chloride side product and 78% of the α-anomer could be generated. Superior ratios were achieved using $SnCl_4$-catalysed conditions and the optimum conditions were at – 30 ºC with 88% of the axial anomer generated (entry 6).

Table 2.2 Anomerisation conditions used for substrate **1** varying Lewis acid, time and temperature.



Entry	Time	Temp.	Lewis acid	Equivalents	%α	%β	%38[26]
1	24 h	rt	$TiCl_4$	2.5	51	35	14
2	24 h	4 °C	$TiCl_4$	2.5	78	22	-
3	24 h	- 30 °C	$TiCl_4$	2.5	70	30	-
4	24 h	rt	$SnCl_4$	2.5	78	17	5
5	24 h	4 °C	$SnCl_4$	2.5	84	15	1
6	24 h	- 30 °C	$SnCl_4$	2.5	88	12	-

Table 2.3 Anomerisation conditions used for substrate **2** varying Lewis acid, time and temperature.



Entry	Time	Temp.	Lewis acid	Equivalents	%α	%β	%40	%41
1	24 h	rt	$TiCl_4$	2.5	-	5	35	60
2	24 h	4 °C	$TiCl_4$	2.5	-	100	-	-
3	24 h	-30 °C	$TiCl_4$	2.5	-	100	-	-
4	2 h	rt	$TiCl_4$	2.5	-	81	-	19
5	24 h	rt	$SnCl_4$	2.5	74	22	-	4
6	24 h	4 °C	$SnCl_4$	2.5	81	17	2	-
7	24 h	-30 °C	$SnCl_4$	2.5	80	20	-	-
8	24 h	rt	$SnCl_4$	5	79	19	5	-

A summary of the anomerisation condition for substrate **2** are shown in Table 2.3. The anomerisation of glycoside **2** was unsuccessful with $TiCl_4$ (2.5 eq.) at room temperature after 24 h, leading to a large percentage of the β-chloride generated, along with the α-chloride.[27] The β-xylopyranosyl chloride **41** underwent a change in conformation to the sterically unfavoured $^1C_4$ conformation due to the strong anomeric effect of the chloride atom.[27] Shortening the reaction time to 2 h did not lead to generation of the α-anomer. Cooling the reaction with $TiCl_4$ to 4 ºC and -30 ºC inhibited the reaction completely and only starting material was recovered. Fortunately, Lewis acid-catalysed anomerisation with $SnCl_4$ proved more effective. The optimum conditions at 4 ºC produced 81% of the α-anomer after 24 h (entry 6).

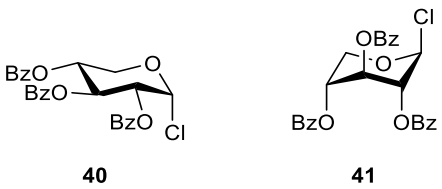
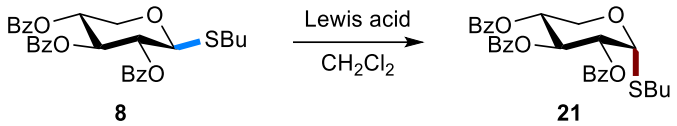


Figure 2.7 Chloride side products generated

Table 2.4 Anomerisation conditions used for derivative **8**



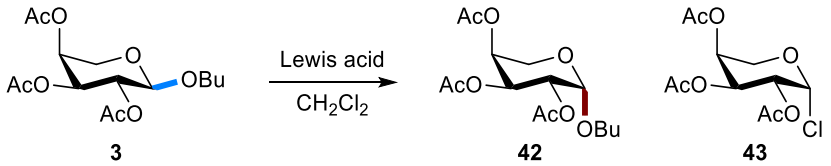
Entry	Time	Temp.	Lewis acid	Equivalents	%α	%β	%40	%41
1	24 h	rt	$TiCl_4$	2.5	11	-	70	19
2	24 h	4 °C	$TiCl_4$	2.5	32	30	-	38
3	24 h	-30 °C	$TiCl_4$	2.5	59	38	-	3
4	24 h	rt	$SnCl_4$	2.5	58	38	4	-
5	24 h	4 °C	$SnCl_4$	2.5	58	39	3	-
6	24 h	-30 °C	$SnCl_4$	2.5	32	67	1	-

Decreased α/β ratios were observed with thioglycoside **8** under Lewis-catalysed conditions, as shown in Table 2.4. Under $TiCl_4$ catalysed conditions at room temperature, 70% of the α-chloride was generated after 24 h. Cooling the reaction led to better results. Lowering the temperature to – 30 ^{o}C suppressed chloride formation and generated 59% of the axial anomer. $SnCl_4$-catalysed anomerisation also yielded desirable results. The optimum results were achieved with $SnCl_4$ (2.5 eq.) at 4 ^{o}C, generating 58% of the α-anomer, after 24 h.

2.4 2 Anomerisation of L-arabinose derivatives

Lewis acids $TiCl_4$ and $SnCl_4$ led to the generation of the axial anomer in substrate **3** with high α/β ratios (Table 2.5). Lowering the temperature of the reaction led to the suppression of the chloride with $TiCl_4$ and optimum conditions were achieved with $TiCl_4$ (2.5 eq.) at 4 ^{o}C after 20 h, generating 86% of the axial anomer. $SnCl_4$ (2.5 eq.) at room temperature also generated 77% of the β-anomer after 20 h.

Table 2.5 Anomerisation conditions used for substrate **3** varying Lewis acid, time and temperature.

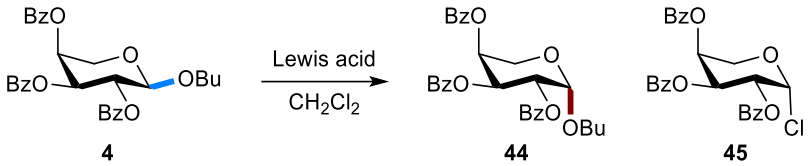


Entry	Time	Temp.	Lewis Acid	Equivalents	%α	%β	%43
1	20 h	rt	$TiCl_4$	2.5	19	71	10
2	20 h	4 °C	$TiCl_4$	2.5	14	86	-
3	20 h	-30 °C	$TiCl_4$	2.5	38	62	-
4	20 h	rt	$SnCl_4$	2.5	17	77	6
5	20 h	4 °C	$SnCl_4$	2.5	20	75	5
6	20 h	-30 °C	$SnCl_4$	2.5	55	41	4

Anomerisation conditions for **4** are shown in Table 2.6. In arabinopyranoside derivative **4**, $TiCl_4$ (2.5 eq.) at room temperature led to the generation of the chloride by product, after 24 h, with no starting material detected. Lowering the reaction temperature to 4 ºC and -30 ºC did lead to anomerisation with $TiCl_4$ but superior results were obtained with $SnCl_4$-induced anomerisation. The axial anomer could be generated up to 77% at room temperature after 24 h with $SnCl_4$ (entry 5).

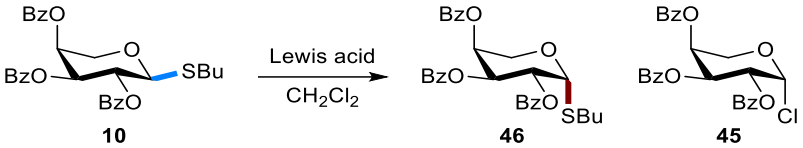
A summary of anomerisation conditions for thioglycoside **10** are shown in Table 2.7. $TiCl_4$ gave the chloride as the major product after 24 h at room temperature (entry 1). Lowering the reaction temperature did not improve the α/β selectivity and led to side product X which could not be isolated through flash chromatography. $SnCl_4$ –catalysed anomerisation gave an improved outcome generating 55% of the axial anomer after 24 h at room temperature. Increasing the equivalents of $SnCl_4$ did not lead to increased α/β selectivity and had a detrimental effect on the reaction.

Table 2.6 Anomerisation conditions used for substrate **4** varying Lewis acid, time and temperature.



Entry	Time	Temp.	Lewis Acid	Equivalents	%α	%β	%45
1	24 h	rt	$TiCl_4$	2.5	-	-	100
2	20 h	4 °C	$TiCl_4$	2.5	30	55	15
3	20 h	-30 °C	$TiCl_4$	2.5	32	68	-
4	2 h	rt	$TiCl_4$	2.5	35	37	28
5	24 h	rt	$SnCl_4$	2.5	16	77	7
6	24 h	4 °C	$SnCl_4$	2.5	19	72	9
7	24 h	-30 °C	$SnCl_4$	2.5	43	56	2

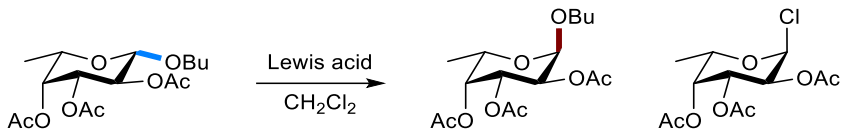
Table 2.7 Anomerisation conditions used for substrate **10** varying Lewis acid, time and temperature.



Entry	Time	Temp.	Lewis Acid	Equivalents	%α	%β	%45	%X
1	24 h	rt	$TiCl_4$	2.5	7	6	87	-
2	24 h	4 °C	$TiCl_4$	2.5	22	14	29	35
3	24 h	-30 °C	$TiCl_4$	2.5	61	30	-	9
4	24 h	rt	$SnCl_4$	2.5	40	56	4	-
5	24 h	4 °C	$SnCl_4$	2.5	45	50	5	-
6	24 h	-30 °C	$SnCl_4$	2.5	74	24	2	-

2.4 3 Anomerisation of L-fucose derivatives

Table 2.8 Anomerisation conditions used for substrate **5** varying Lewis acid, time and temperature.



5 **47** **48**

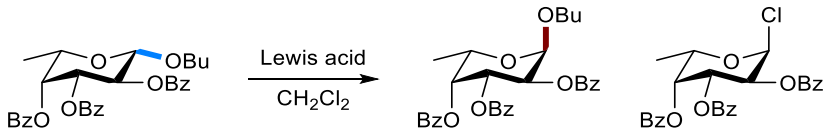
Entry	Time	Temp.	Lewis Acid	Equivalents	%α	%β	%48[28]
1	24 h	rt	$TiCl_4$	2.5	60	16	24
2	24 h	4 °C	$TiCl_4$	2.5	43	50	7
3	24 h	-30 °C	$TiCl_4$	2.5	7	93	-
4	24 h	rt	$SnCl_4$	2.5	77	16	7
5	24 h	4 °C	$SnCl_4$	2.5	48	48	4
6	24 h	-30 °C	$SnCl_4$	2.5	8	89	3

Lewis acid-catalysed anomerisation was possible in substrate **5** with both $TiCl_4$ and $SnCl_4$, as shown in Table 2.8. Lowering the reaction temperature with both Lewis acids led to suppression of epimerisation. At room temperature, 60% of the α-anomer could be formed after 24 h with $TiCl_4$. However, there was also a significant amount of the chloride generated. $SnCl_4$ gave better results with 77% of the axial anomer formed after 24 h at room temperature (entry 4).

Anomerisation results for **6** are summarised in Table 2.9. $TiCl_4$-promoted anomerisation led to the chloride side product as the major product at room temperature (entry 1). However, if the temperature was reduced to – 30 ºC, it was possible to obtain the α-anomer in a 77% yield under $TiCl_4$ conditions (entry 3). $SnCl_4$-chelated anomerisation at room temperature gave 79% of the axial anomer after 24 h (entry 4). Decreasing the reaction temperature inhibited epimerisation and low yields were observed with $SnCl_4$.

The anomerisation of fucopyranosyl derivative **10** proved unsuccessful with $TiCl_4$ (entry 1), as shown in Table 2.10. The chloride side product was the main product at room temperature after 24 h. Lowering the temperature led to the formation of chloride **50** and side product **X**, which could not be isolated by column chromatography. $SnCl_4$ –catalysed conditions were preferable with 51% of the α-anomer generated at room temperature, after 24 h. Decreasing the temperature did not improve yields with $SnCl_4$ –promoted epimerisation.

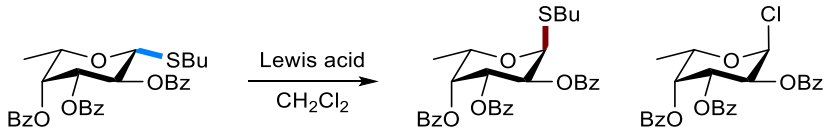
Table 2.9 Anomerisation conditions used for substrate **6** varying Lewis acid, time and temperature.



6 **49** **50**

Entry	Time	Temp.	Lewis Acid	Equivalents	%α	%β	%50	%X
1	24 h	rt	$TiCl_4$	2.5	3	10	87	-
2	24 h	4 °C	$TiCl_4$	2.5	34	8	57	-
3	24 h	-30 °C	$TiCl_4$	2.5	77	13	10	-
4	24 h	rt	$SnCl_4$	2.5	79	17	4	-
5	24 h	4 °C	$SnCl_4$	2.5	28	62	4	6
6	24 h	-30 °C	$SnCl_4$	2.5	4	89	7	-

Table 2.10 Anomerisation conditions used for substrate **10** varying Lewis acid, time and temperature.



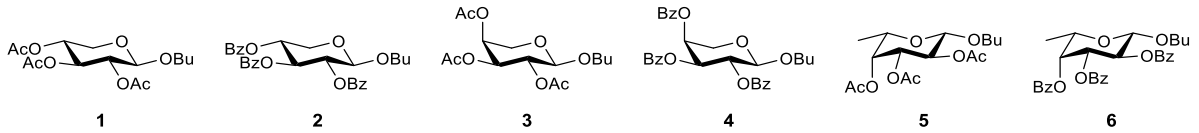
10 **51** **50**

Entry	Time	Temp.	Lewis Acid	Equivalents	%α	%β	%50	%X
1	24 h	rt	$TiCl_4$	2.5	6	6	88	-
2	24 h	4 °C	$TiCl_4$	2.5	7	8	45	40
3	24 h	-30 °C	$TiCl_4$	2.5	7	6	41	46
4	24 h	rt	$SnCl_4$	2.5	51	41	8	--
5	24 h	4 °C	$SnCl_4$	2.5	49	44	7	-
6	24 h	-30 °C	$SnCl_4$	2.5	27	70	3	-

2.4 4 Summary of results

It was established that each glycoside in the initial studies could undergo epimerisation, resulting in an equilibrium mixture that favoured the axial anomer. Under the optimum conditions, the axial anomer accounted for 77-88% of the resulting mixture for *O*-glycosides **1-6**. The thioglycoside derivatives **8-10** had lower α:β ratios in the resulting mixtures (51-59%), which can be explained by the decreased electronegativity of the sulfur atom in comparison to the oxygen atom.

This study indicated that $SnCl_4$ was a superior catalyst to $TiCl_4$ for the majority of glycosides tested. Previous results had indicated that $TiCl_4$ gave improved α/β ratios.[29] However, these results suggest it may dependent on the particular glycoside. $TiCl_4$ is a stronger Lewis acid than $SnCl_4$ and thus may exclusively promote exocyclic cleavage and chloride formation. The reaction temperature also had an impact on the α/β ratios attained. In $SnCl_4$-chelated anomerisation, the preference for the α-anomer increased as the reaction temperature decreased in xylopyranosides **1** and **2**, as shown in Figure 2.8. In arabino- and fucopyranosides **3-6**, the preference decreased at lower temperatures.



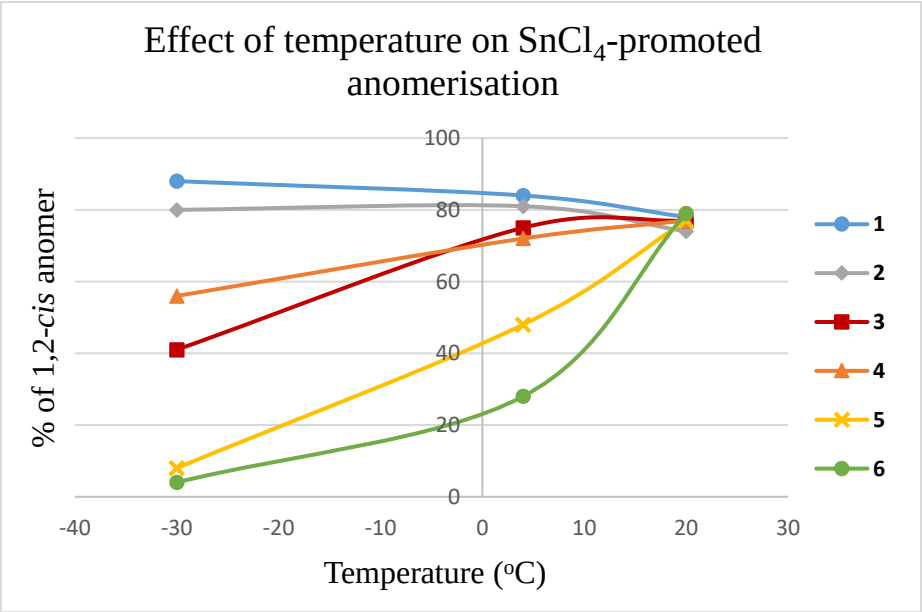


Figure 2.8 Summary of effect of temperature on $SnCl_4$-catalysed epimerisation of *O*-glycosides **1-6**

For $TiCl_4$-promoted anomerisation, the generation of the 1,2-*cis* anomer increased at lower temperatures in xylopyranoside **1**, arabinopyranosides **3-4** and fucopyranoside **6**. The

percentage of the axial anomer decreased as the reaction temperature was lowered in acetylated fucopyranoside **5**. In benzoylated xylopyranoside **2,** the chloride product was exclusively generated.

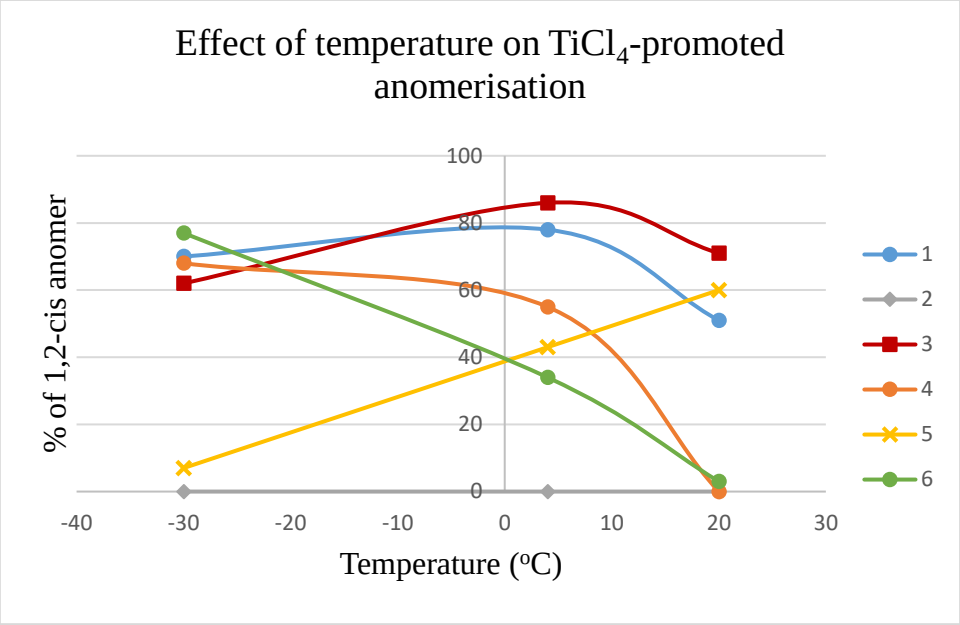


Figure 2.9 Summary of effect of temperature on $TiCl_4$-catalysed epimerisation of *O*-glycosides **1-6**

2.5 Kinetic studies

Reaction kinetics were recorded for *O*- and *S*-glycosides **1-11** by ^{1}H NMR spectroscopy using $SnCl_4$ (0.5 equiv.) as a Lewis acid catalyst in $CDCl_3$ (0.8M) over the course of several days until an equilibrium was attained. The relative integrations of the assignable signals were used to determine the molar concentrations of each anomer present in the reaction over time. An example of a progress curve is shown in Figure 2.10.

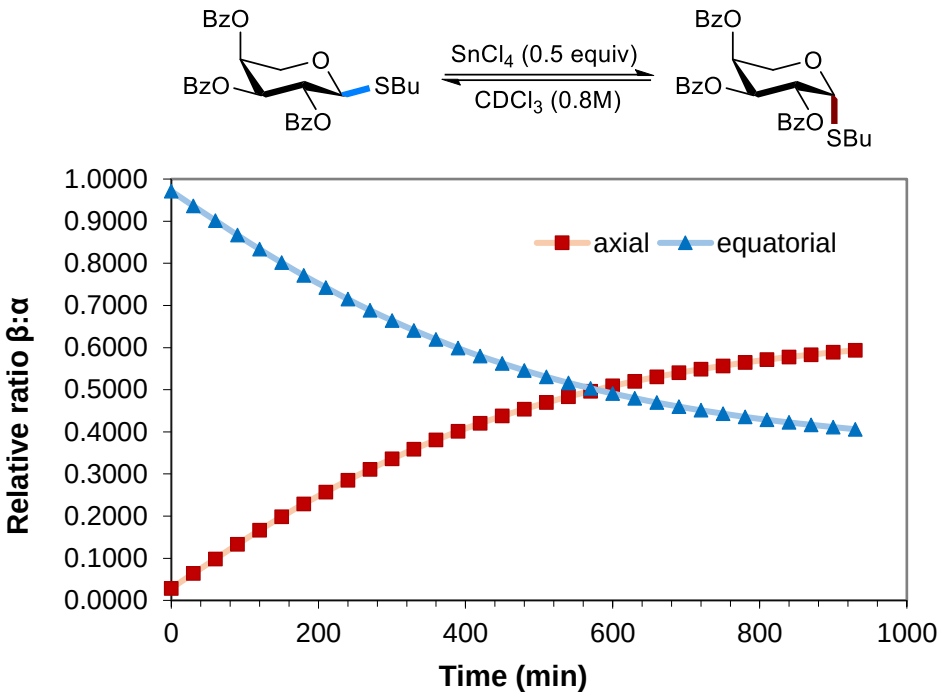


Figure 2.10 Progress curve for $SnCl_4$-catalysed anomerisation of substrate **9** monitored by ^1H NMR spectroscopy.

The data was fitted to the following equation for equilibrium kinetics to ensure that the anomerisation reactions followed first order kinetics.[30] The rate constant was obtained for the combined forward and reverse reaction.

$$ln\left(\frac{[A]_0-[A]_e}{[A]t-[A]_e}\right) = (k_f + k_r)t$$

Equation 1

Where $[A]_0$ is the initial concentration

$[A]_e$ is the equilibrium constant

$[A]_t$ is the concentration at time t

k_f is the rate constant for the forward reaction (equatorial to axial)

k_r is the rate constant for the reverse reaction (axial to equatorial)

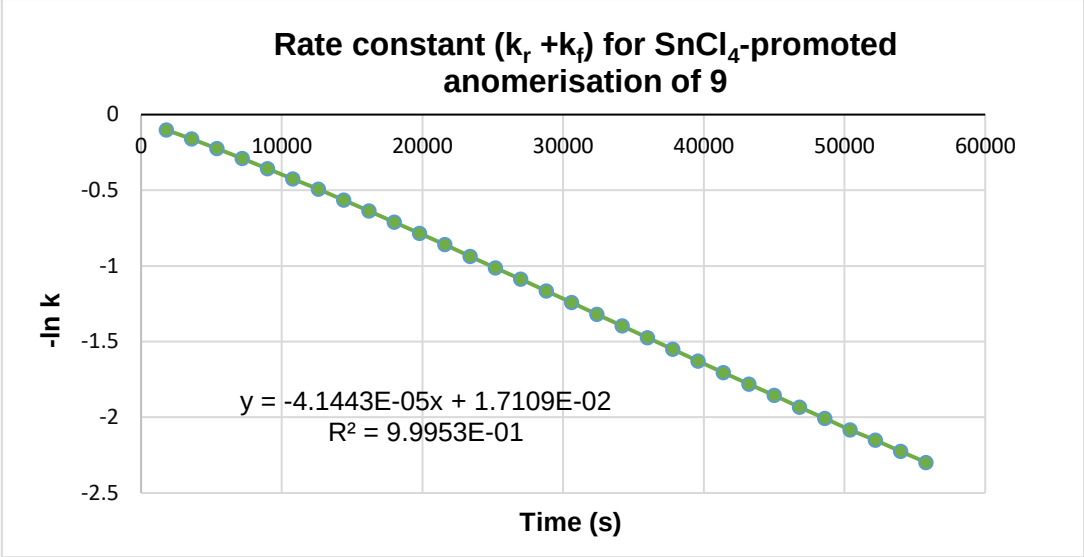
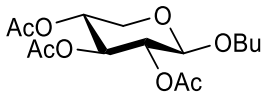
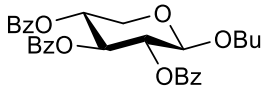
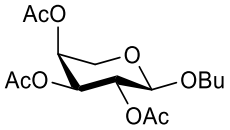
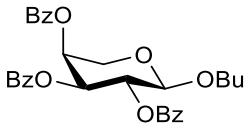
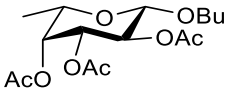
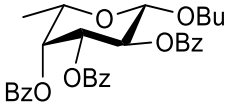
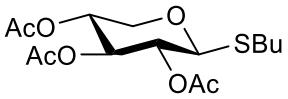
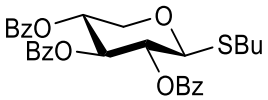
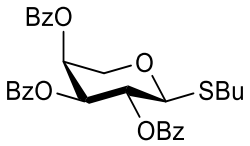
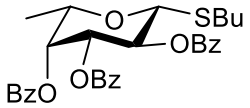
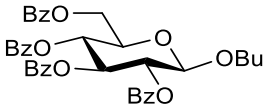


Figure 2.11 Straight line graph obtained for rate of *S*-glycoside **9**

From this equation, a straight line graph could be plotted with the slope (k_r + k_f), with a range of r.m.s values between 0.929 – 0.999. These results are summarised in Table 2.11.

Table 2.11 Summary of chemical kinetics

Entry	Substrate	$10^6(k_f + k_r)(s^{-1})$	Relative rate	axial:equatorial
1	 **1**	17.0	8.9	3.4:1
2	 **2**	23.5	12.4	3.5:1
3	 **3**	3.73	1.96	3.6:1
4	 **4**	11.3	5.9	3.7:1
5	 **5**	1.9	1	4.3:1
6	 **6**	2.8	1.5	5.6:1
7	 **7**	17.3	9.1	1.4:1
8	 **8**	20.4	10.7	1.7:1
9	 **9**	41.4	21.8	2:1

10	 **10**	33.24	17.5	2:1
11	 **11**	14.5	7.6	16:1

In comparison to *O*-glucopyranoside **11**, each glycoside (entries 1-10) reached equilibrium with a considerable percentage of the equatorial anomer remaining. In xylopyranoside **2**, the axial anomer accounted for 78% of the reaction mixture at equilibrium while in glucopyranoside **11**, the axial anomer accounted for 94% of the solution. This reflects the significance of C-5 substituent for the ratio of anomers obtained. Xylopyranoside **2** had a faster rate of epimerisation than glucopyranoside **11** (approximately 1.6 time faster).

It was observed that benzoylated *O*-glycosides underwent anomerisation approximately 1.3 to 3.3 times faster than acetylated counterparts (entries 1-6). Benzoylated thioglycoside **8** was slightly faster than its acetylated counterpart **7** (relative rates 10.5 vs. 9.1). This is consistent with previous results obtained. The C-2 carbonyl is more electron rich in the benzoylated derivatives due to resonance structures and this could have a stabilising interaction with an electron deficient intermediate, thus increasing the population of the cation.

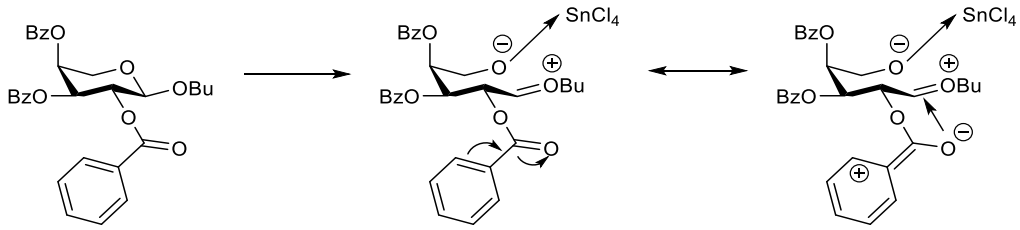


Figure 2.12 Electrostatic stabilisation of endocyclic intermediate by C-2 carbonyl

Xylopyranosides **1** and **2** underwent anomerisation faster than arabinopyranosides **3** and **4**. Benzoylated xylopyranoside **2** underwent anomerisation twice as fast as arabinopyranoside **4** while substrate **1** was five times faster than **3**. These results were initially surprising as previous results had indicated that galactopyranosides with an electron releasing axial group at the C-4 position underwent epimerisation faster than corresponding glucopyranosides. The increased electron density in the ring, due to the axial group, is thought to stabilise an electron deficient intermediate and increase the ability of the glycoside to coordinate to the Lewis acid.

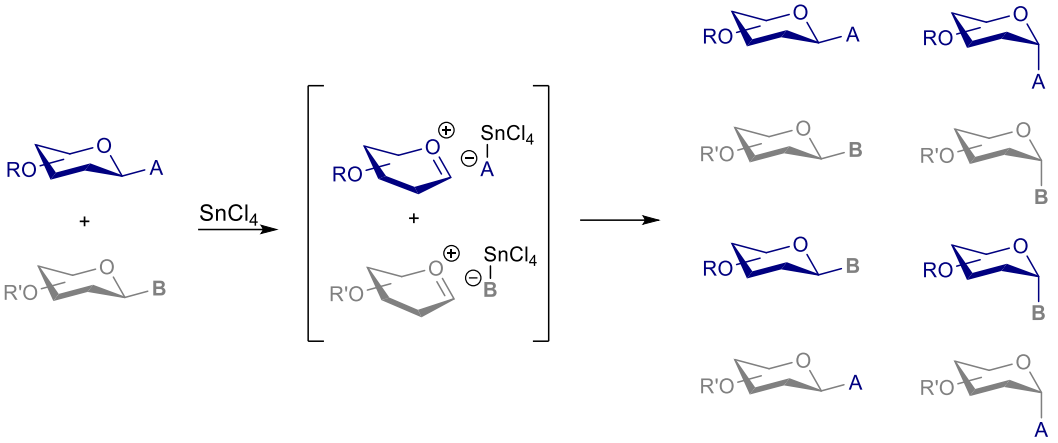
Fucopyranosides **5** and **6** underwent anomerisation extremely slowly, taking 8-9 days to reach equilibrium. The methyl group at the C-5 position in theory should be less electron withdrawing

and stabilise a positively charged intermediate, thus increasing the rate of anomerisation. The reason for the slower rate of epimerisation for the fucopyranosides is not immediately apparent, although electrostatic repulsion between the C-5 proton and anomeric substituent may decrease the preference for the axial anomer.

Arabinose and fucose *S*-glycosides **8** and **9** underwent anomerisation approximately 4 and 12 times faster, respectively, than their corresponding *O*-glycosides (see entries 4 vs 8 and 6 vs 9). This indicated that these glycosides proceeded through endocyclic cleavage in anomerisation, as sulfur is more electron releasing than oxygen. Thus these glycosides should epimerise at a faster rate. The xylose thioglycoside derivative **8** had a slightly slower rate of reaction than its *O*-glycoside counterpart **2** while thioxylopyranoside **7** had approximately the same rate of anomerisation as its oxygen counterpart **1** (see entry 1 vs 7). It was interesting to ascertain whether these findings could indicate that xylopyranosides **1**, **2**, **7** and **8** were undergoing anomerisation predominantly through an exocyclic mechanism. The lack of axial groups in the xylose ring could result in coordination of the Lewis acid to the anomeric substituent, promoting exocyclic cleavage.

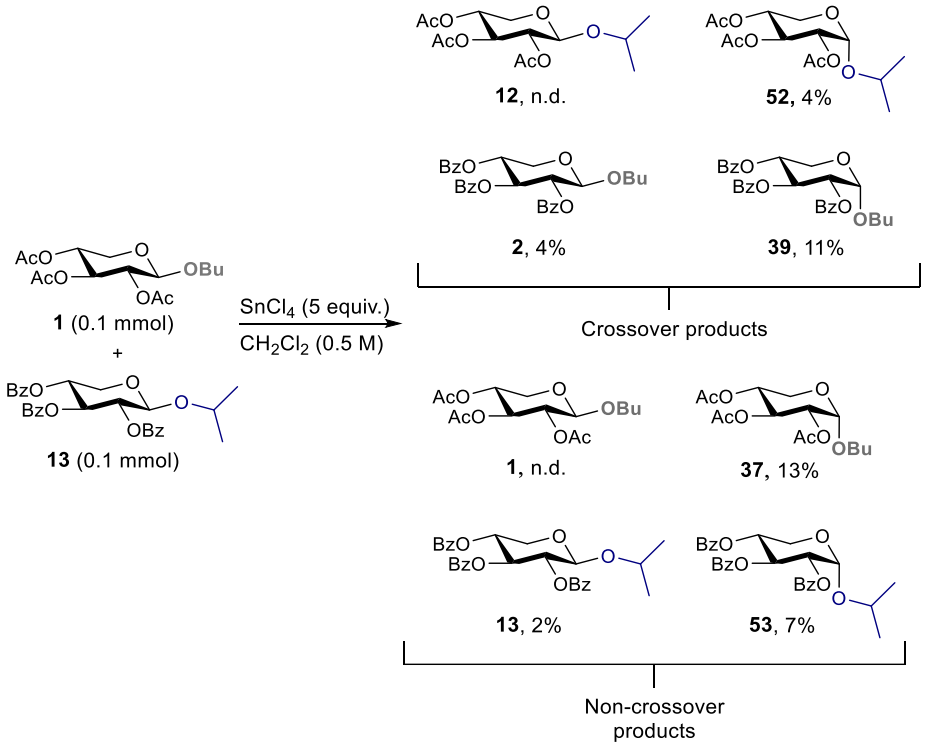
2.6 Crossover studies

A series of crossover experiments were utilized to further examine the mechanism in the glycosides. The design of an appropriate crossover experiment is depicted in Scheme 2.8. Two glycosides (each 0.1 mmol) that had different aglycons were placed in the same reaction vessel and subjected to $SnCl_4$-catalysed conditions. After work-up, the resulting mixture was then purified by column chromatography and the resulting fractions were analysed by ^{1}H NMR spectroscopy and HRMS. If the predominant pathway is exocyclic than crossover of the two reactants is possible when the ion-pair forms and 8 products are possible. The α- and β-anomers of the two starting materials and the α- and β-anomers of the crossover products. The chloride and hemiacetal products are also possible.



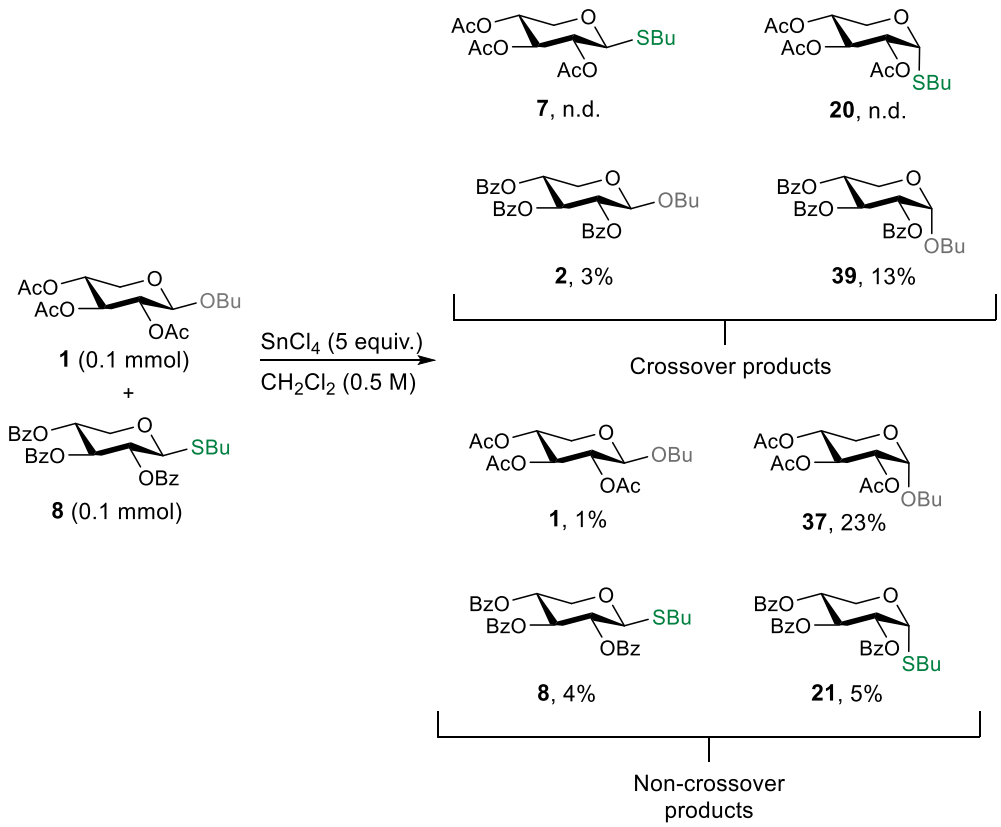
Scheme 2.8 Design of crossover experiment and 8 possible products

To begin the study, the epimerisation of *O*-xylopyranosides **1** and **11** were investigated using the conditions previously described. After purification, the crossover products **39** (11%) and **52** (4%) could be identified by ^{1}H NMR spectroscopy. The equatorial crossover product **2** (4%) was also observed. Non-crossover products **37**, **13** and **53** were also recovered. The benzoylated xylose hemiacetal **54** was also identified by ^{1}H NMR spectroscopy in 8% yield. This supported that hypothesis that *O*-xylopyranosides underwent anomerisation through exocyclic cleavage.



Scheme 2.9 Crossover experiment with xylopyranosides **1** and **13**

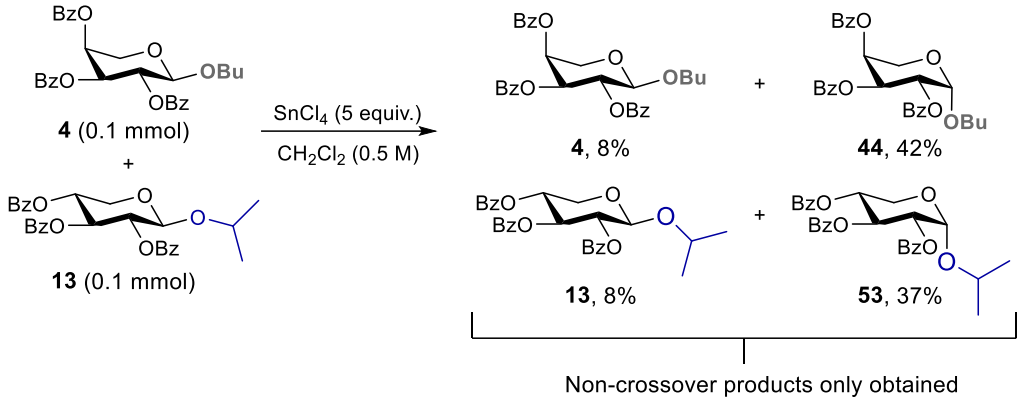
It was then established whether thioxylopyranosides were undergoing anomerisation principally through the exocyclic pathway. *S*-Glycoside **8** and *O*-glycoside **1** were placed under $SnCl_4$ catalysed conditions and the resulting mixture was purified and analysed by ^{1}H NMR spectroscopy. The crossover products **2** (3%) and **39** (13%) were identified. However, none of the acetylated thioxylopyranoside crossover products **7** or **20** were identified from the reaction mixture. There were several side-products, accounting for 6%, that were recovered that were neither the crossover, non-crossover or chloride products. The benzoylated xylose hemiacetal **49** was identified from the reaction mixture in a small amount (1%). It is not apparent why none of the crossover products **7** or **20** were recovered. Non-crossover products **1** (1%), **37** (23%), **8** (4%) and **21** (5%) were also identified. It can be concluded that *S*-xylopyranoside **8** anomerises through the exocyclic pathway to a certain degree, although there may be other side reaction present.



Scheme 2.10 Crossover experiment with *O*-glycoside **1** and *S*-glycoside **8**

To validate the hypothesis that xylopyranosides anomerised primarily through exocyclic cleavage while the other glycosides within the study underwent anomerisation through the endocyclic pathway, arabinopyranoside **4** and fucopyranoside **6** was incorporated into crossover experiments with xylopyranosides. No crossover products were observed in the anomerisation of arabinopyranoside **4** and xylopyranoside **13**. This may be indicate that

arabinopyranoside **4** undergoes Lewis-catalysed anomerisation through the endocyclic pathway. This is supported by evidence from the rates of epimerisation obtained, as for example, a higher rate was obtained for the corresponding thiorabinopyranoside **9.** None of the xylose hemiacetal side-product was recovered in this case.



Scheme 2.11 Crossover experiment with **4** and **13**

It was speculated that the carbonyl in the axial group at the 4-position in arabinose derivatives may coordinate to the $SnCl_4$ centre and promote endocyclic cleavage, as shown in Figure 2.13.

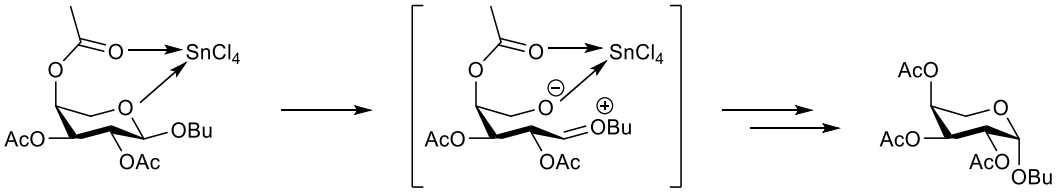
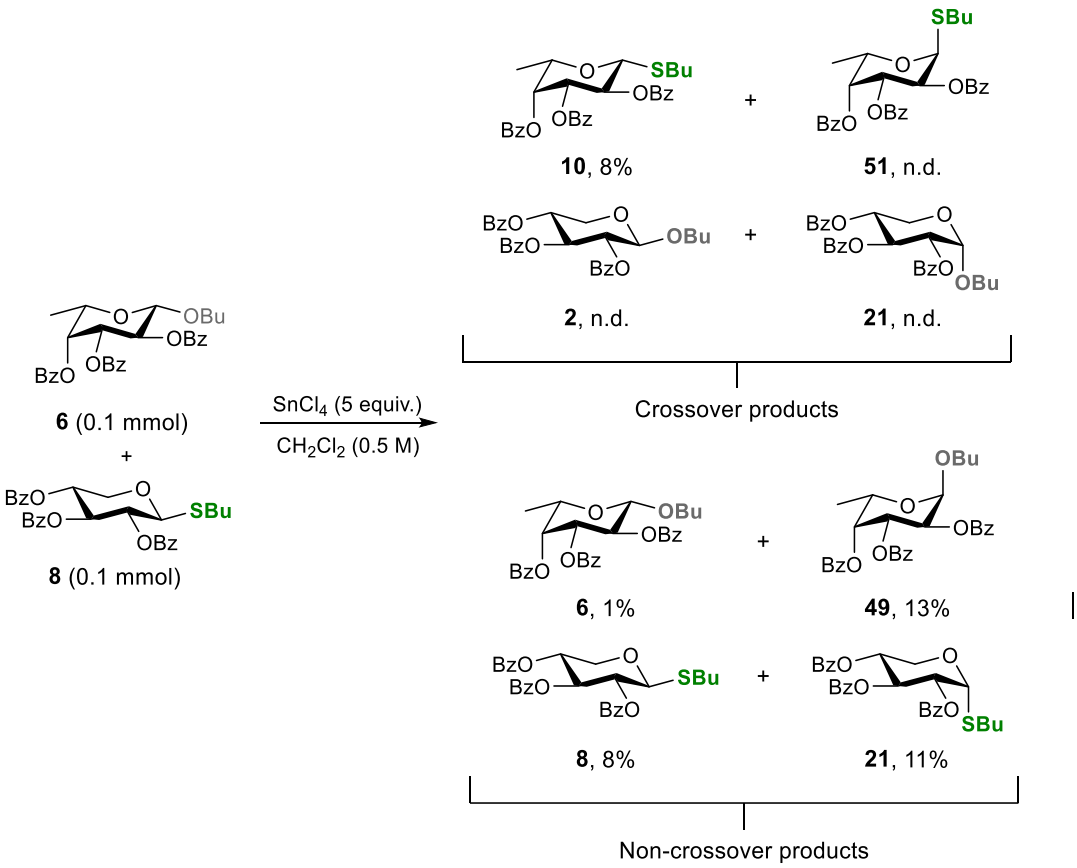


Figure 2.13 Postulated coordination of C-4 group to Lewis acid

A crossover study was carried out using *S*-xylopyranoside **8** and *O*-fucopyranoside **6** using the same conditions as previously shown. Analysis by proton NMR spectroscopy showed the formation of crossover product **10** (8%). The non-crossover products, **6** (1%), **8** (8%), **21** (11%) and **49** (13%) were also identified through NMR spectroscopy, along with unidentified side products which accounted for 7% of the percentage yield. The benzoylated xylose hemiacetal **54** was also identified from the reaction mixture in a 3% yield.



Scheme 2.12 Crossover experiment with *O*-glycoside **6** and *S*-glycoside **8**

The formation of crossover product **10** suggests that fucopyranoside **6** is undergoing anomerisation through exocyclic cleavage. It is feasible that **6** undergoing anomerisation through both endo- and exocyclic cleavage and further study is needed to understand the principal mechanism for the fucopyranosides.

2.7 Conclusions and Future Work

In conclusion, it was established that pentopyranosides and 6-deoxypyranosides can undergo anomerisation to favourably form the axial anomer. For the majority of glycosides within the study, $SnCl_4$ proved to be a superior catalyst compared to $TiCl_4$. The kinetics of 11 different glycosides were established under $SnCl_4$-promoted anomerisation. *O*-xylopyranosides **1** and **2** underwent epimerisation faster than corresponding *O*-arabinopyranosides and *O*-fucopyranosides **3-6**. Crossover experiments established that the xylose derivatives anomerised primarily through the exocyclic pathway. Although, exocyclic cleavage has long been suspected to be a pathway in anomerisation, this is the first time it has shown to be the principal pathway in a glycoside. It was also concluded that anomerisation proceeding through the exocyclic pathway is faster than the endocyclic pathway.

In the future, the anomerisation of more unusual glycosides such as 2-deoxy saccharides could be investigated and this method could to applied to the generation of a biologically relevant compound to demonstrate the effectiveness of this method in the generation of 1,2-*cis* glycosides.

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Chapter 3

Stereoselective Epimerisation of Glycosyl Thiols

3.1 Overview of *S*-glycosides

S-Glycosides can be defined as any glycoside where the anomeric hydroxyl group is replaced with a sulphide (SR) group. In comparison to *O*- and *N*-glycosides, *S*-glycosides rarely occur in nature, although there are a few examples. A major class of natural *S*-glycosides are glucosinolates (GSLs), which constitute a distinct group of plant metabolites that are primarily isolated from an order of flowering plants named *Brassicales*. Structurally they are anions composed of thiohydroximates carrying an *S*-linked β-glucopyranosyl residue and an *O*-linked sulfate residue, and with an amino acid derived, variable side chain. In 2011, an estimated 132 glucosinolates had been isolated from nature in total.[1] Other examples include the clinically useful antibiotic Lincomycin A isolated from *Streptomyces lincolnensis*[2], 1-thio-β-D-glucopyranoside afrostyraxathioside A isolated from the seeds of *Afrostyrax lepidophyllus*[3] and raphanuside, an unusual oxathiane fused *S*-glycoside isolated from *Raphenus savitas*.[4] An example of a natural thiosugar is Salacinol, where the ring oxygen has been replaced by a sulfur atom. Salacinol is a potent α-glucosidase inhibitor isolated from *Salacia reticulate*, a traditional medicine used in the treatment of diabetes.[5]

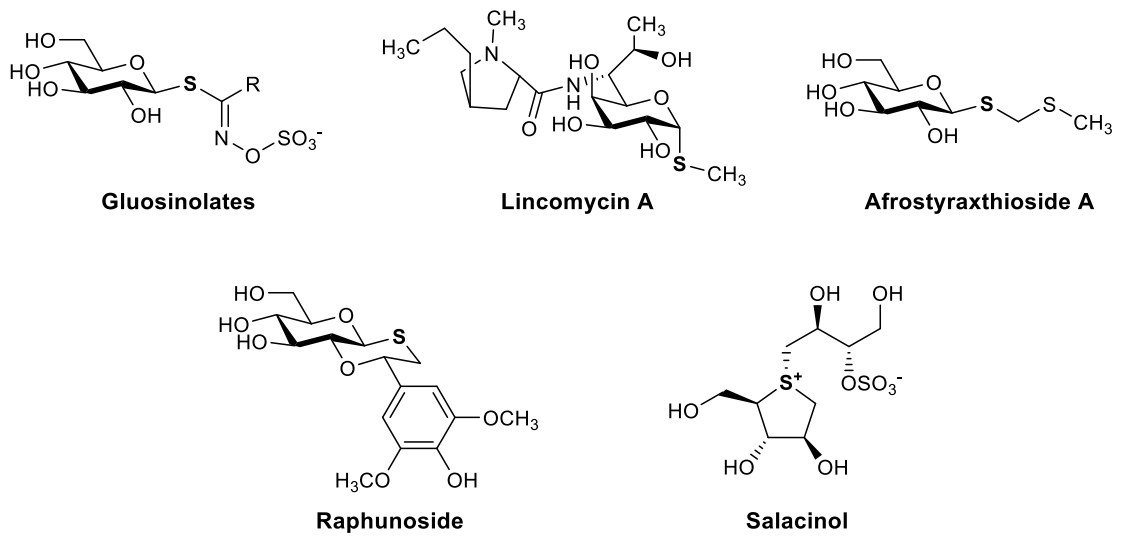
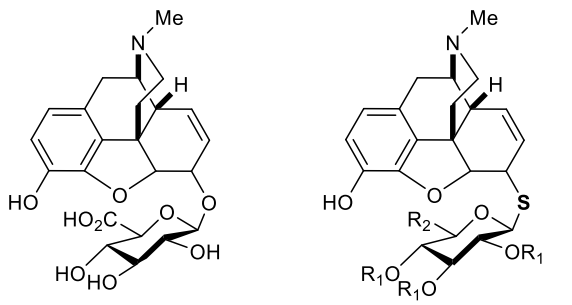


Figure 3.1 Naturally occurring *S*-glycosides and thiosugar

Over the past two decades, there has been intense research in the synthesis of glycomimimetics, where the natural *O* atom in the glycosidic linkage is replaced by and *S*- or *C*-atom. These *S*- or *C*-glycosides are well tolerated by most biologically systems and are less susceptible to acid or enzymatic cleavage.[6] *S*-Glycosides are more flexible about the anomeric linakage in comparison to corresponding *O*-glycosides due to the longer C-S bond and weaker stereoelectronic effects. This can enable thioglycosides to occupy different spaces in binding pockets of target proteins. This has made *S*-glycosides an attractive alternative to natural *O*-

glycosides and several artificial glycolipids, glycopeptides, oligosaccharides[7-10], glycodendrimers[11] and glyconanoparticles[12] containing an *S*-glycosidic linkage have been synthesised.

An early example of the therapeutic potential that thioglycoside analogues may possess was reported by Cashman and co-workers[13] in 2004. They investigated thiosaccharide analogues of morphine- and codeine-6-glucoronide. Morphine-6-glucuronide (M6G) is approximately 100 times more potent than morphine in animals, with significantly reduced respiratory depression, nausea and sedation thus making M6G is an attractive alternative to morphine. However M6G suffers from very low bioavailabiliy due to hydrolysis in the gut, making it unfeasible as a potential therapeutic. Cashman and co-workers prepared several thioglycoside derivatives of M6G and codeine-6-glucuronide (C6G). They found that several derivatives, (i)-(iv), had a higher affinity for μ opioid receptor relative to M6G. The ED_{50} of (i), as shown in Figure 3.2, was comparable to that of morphine in a flick latency test and it could therefore be concluded that thioglycoside derivatives are viable for improving the pharmacological properties of these compounds.



(i) R_1 = Ac, R_2 = CO_2Me
(ii) R_1 = Ac, R_2 = CH_2OAc
(iii) R_1 = H, R_2 = CO_2H
(iv) R_1 = H, R_2 = CH_2OH

Figure 3.2 Thioglycoside analogues of M6G

The Wong group developed a convenient method towards thio-linked glycopeptides and synthesised an *S*-linked analogue of antibiotic tyrocidine A.[14] They demonstrated that the *S*-linked glycopeptide had a better antibiotic profile than tyrocidine A by measuring the biological activity using the minimal inhibitory concentration (MIC) against *B. subtilis* and the minimal hemolytic concentration (MHC) against human erythrocytes to evaluate eukaryotic membrane toxicity.

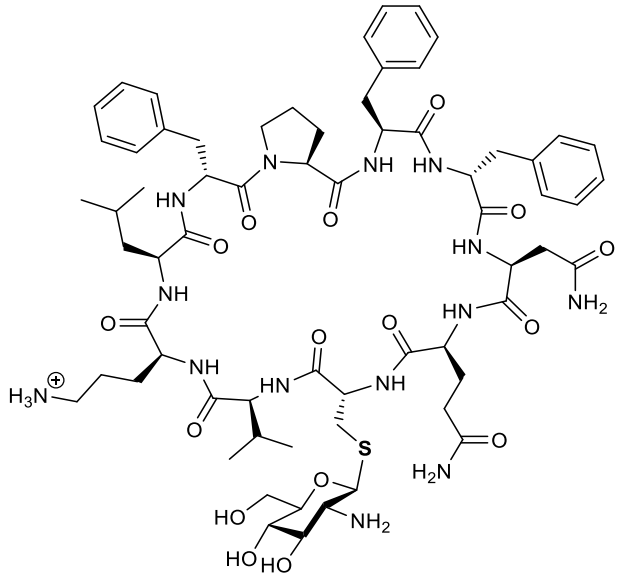


Figure 3.3 Thioanalogue of glycopeptide antibiotic tyrodicine A

The immunostimulatory glycolipid αGalCer (KRN 7000) is potent agonist for murine and human iNKT cells and upon *in-vitro* activation, iNKT cells kill a range of tumour cells. However, stimulation of iNKT cells in clinical trials yielded disappointing results, prompting further investigation into analogues of αGalCer. Zhu, Doherty and co-workers[15] demonstrated that the thioglycoside analogue of potent immunostimulatory glycolipid αGalCer stimulated human iNKT cells in a CD1d-dependent manner and induced similar patterns of cytokine secretion.

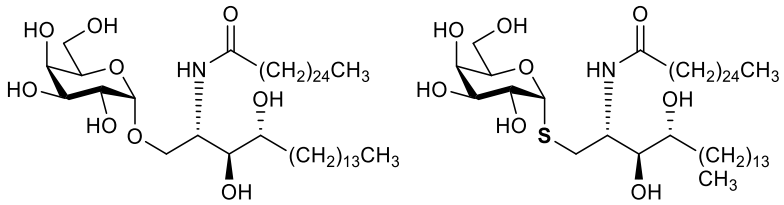


Figure 3.4 αGalCer and corresponding α-*S*-GalCer

Kinne and co-workers[16] demonstrated that simple phenolic thioglycosides were promising therapeutics for treatment of hyperglycaemia in patients with diabetes. Reabsorption of glucose into the kidneys is mediated by sodium-glucose transport proteins SGLT1 and SGLT2 and these thioglycosides could act as selective inhibitors of these proteins.

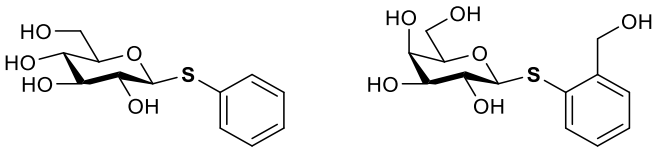


Figure 3.5 Inhibitors of SGLT1 and SGLT2 proteins involved in re-uptake of glucose into kidney

TD139, a thiolinked galectin-3 inhibitor, is a promising new treatment of idiopathic pulmonary fibrosis (IPF), an ultimately fatal, chronic lung disease which is characterised by irreversible deterioration of lung function.[17] TD139 is a highly potent inhibitor of galectin-3, binding at the galactoside binding site and has proven to be well tolerated and effective. Galectin-3 is a protein known to play a central role in fibrosis.

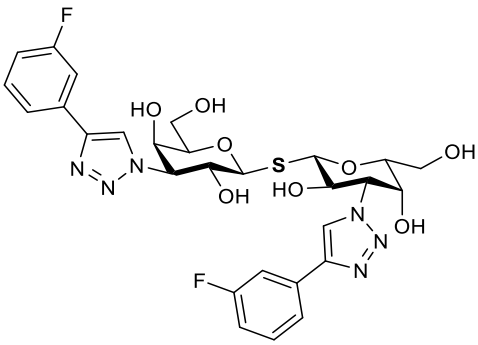


Figure 3.6 TD139

These representative examples illustrate the growing importance of thioglycosides in the development and improvement of novel and current glycomimetics. In addition to their wide application as mimetics of *O*-glycosides, 1-thioglycosides are routinely applied as glycosyl donors in the synthesis of a wide variety of glycosidic linkages. They are arguably the most valuable donor as they can be activated under mild conditions by thiophilic salts that do not affect other glycosyl donors.

3.2 Glycosyl Thiols and Synthetic Strategies

Glycosyl thiols (1-thiosugars) are valuable building blocks in the synthesis of thioglycosides and are frequently used in the synthesis of sulfur containing glycolipids, glycopeptides and oligosaccharides. 1-Thioaldoses have been shown to have a strong pH dependence when undergoing mutarotation.[18] For example, in 1-thio-D-mannopyranoside the anomeric distribution is shifted in favour of the β-anomer at a lower pH, which contrasts normal the anomeric distribution in D-mannopyranose.

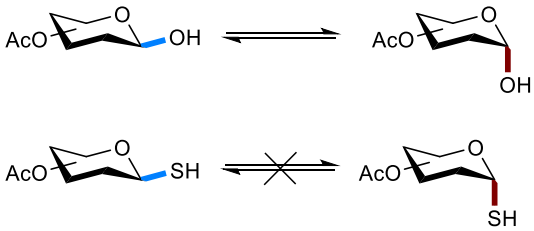
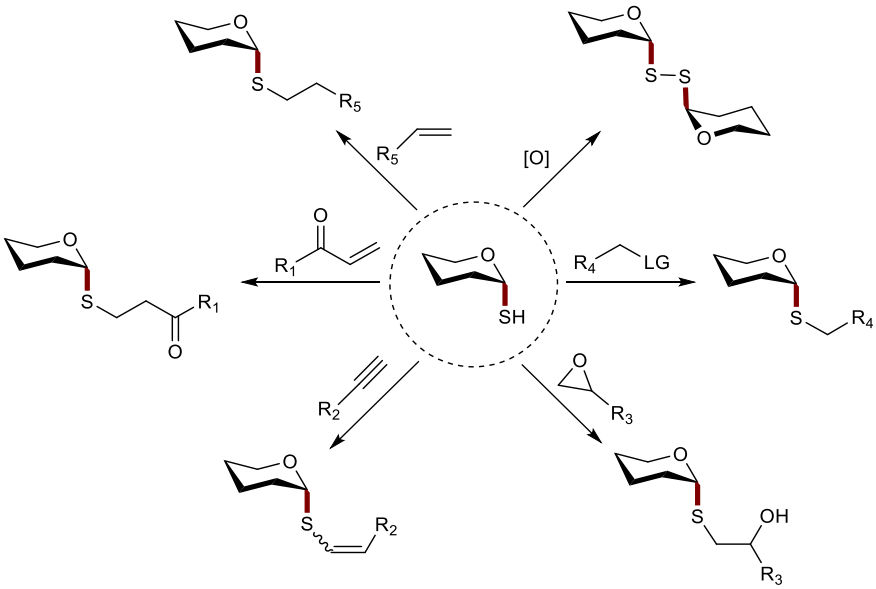


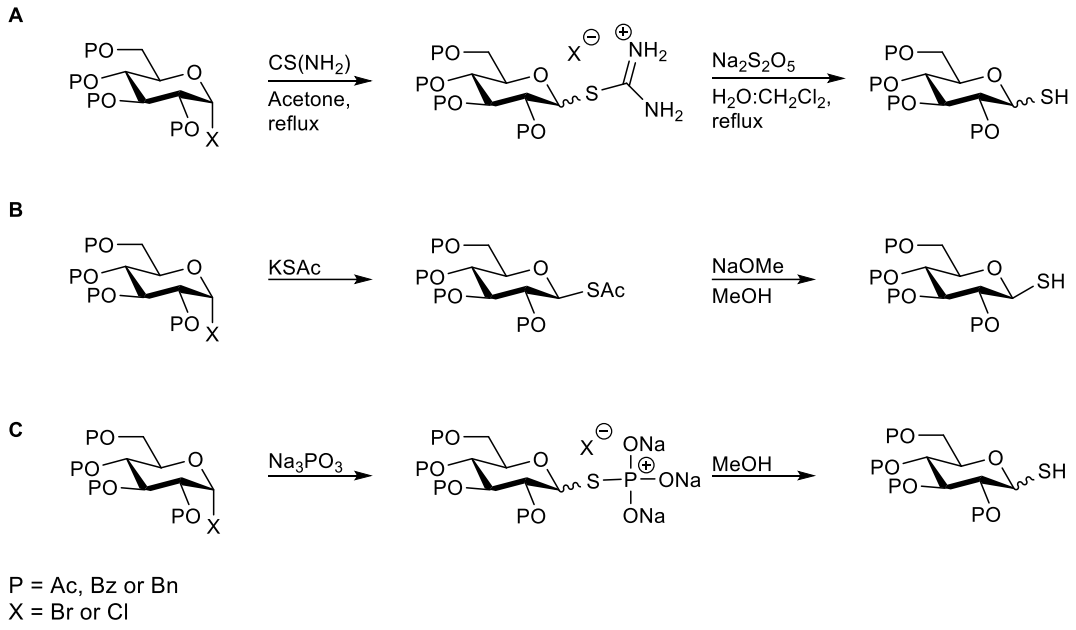
Figure 3.7 Mutarotation occurs readily in glycosyl alcohols but not in glycosyl thiols

However in protected glycosyl thiols, subsequent reactions normally occur faster than mutarotation since sulfur is more nucleophilic than oxygen. Therefore unlike hemiacetals, glycosyl thiols regularly retain their anomeric configuration in subsequent reactions, which makes stereoselective alkylations, conjugate addition, thiol-ene and thiol-yne coupling reactions possible.[19]



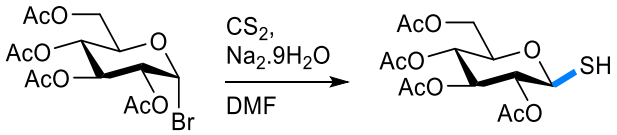
Scheme 3.1 Various reactions that are possible with glycosyl thiols with retention of anomeric stereochemistry

Therefore the stereoselective generation of glycosyl thiols is tremendously useful. There have been several strategies developed for the synthesis of glycosyl thiols. The classical approach involves reacting glycosyl halides with thiourea to form a thiouronium salt, followed by hydrolysis to give the free thiol. This method can give a mixture of anomers where the dominant product is usually dependent on a participating C-2 acyl group (if this group is present). Other methods that employ S_N2 displacement use thioacetates[13] or thiophosphates[20] followed by selective deprotection. DTT mediated selective *S*-deacetylation was developed with high yields and good selectivity.[21] Hydrogen sulfide gas can also be bubbled through glycosyl halides in hydrogen fluoride to obtain a mixture of anomers.[22]



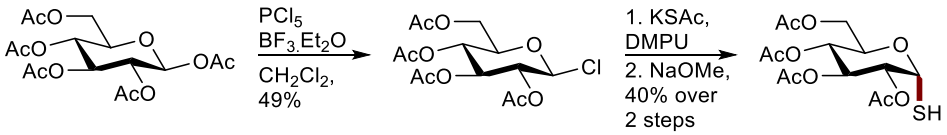
Scheme 3.2 Examples of synthetic strategies for glycosyl thiols that involve S_N2 displacement of a glycosyl halide **A.** Displacement of bromide using thiourea and subsequent hydrolysis to give free thiol. **B.** Thioacetate used as sulfur nucleophile to displace bromide followed by selective deprotection. **C.** Thiophosphate generated followed by hydrolysis to give free thiol

Several methods have been developed for the stereoselective synthesis of either the equatorial or axial anomer. For instance, Misra and co-workers[23] reacted glycosyl bromides with carbon disulfide and sodium sulfide, to selectively obtain the β-anomer.



Scheme 3.3 Generation of β-anomer selectively developed by Misra and co-workers

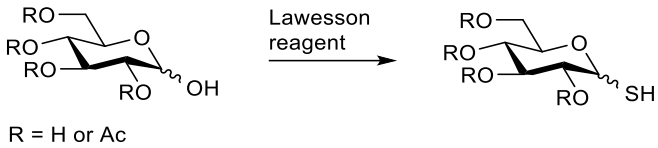
The stereoselective synthesis of the axial glycosyl thiol has proven to be a difficult task. One of the first methods developed involved the use of β-chlorides and subsequent displacement by a nucleophilic sulfur.[24-25]



Scheme 3.4 Use of β-chlorides to selectively prepare α-glycosyl thiols

Davis et al.[26] developed a convenient pathway by reacting glycosyl alcohols with Lawesson's reagent to yield the axial glycosyl thiol. However this reaction proceeds with only moderate

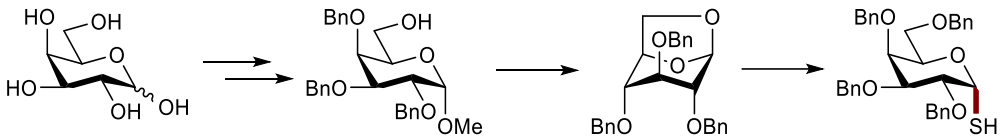
selectivity for the α-glycosyl thiol and thus a reaction that can selectively generate the α-glycosyl thiol is still desirable.



Scheme 3.5 Treatment of unprotected or protected hemacetals with Lawesson reagent to generate glycsoyl thiols.

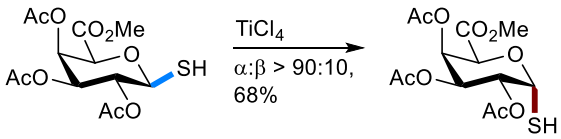
Alternate routes to α-glycosyl thiols often suffer from low yields[27] or are based on a long synthetic route which is disadvantageous for convergent syntheses.[28]

One of the most convenient pathways developed to prepare axially-oriented glycosyl thiols is treatment of 1,2-anhydro sugars[29-30] and 1,6-anhydro sugars or glycosyl trichloroacetimidates[31] with bis-trimethylsilyl sulfide. However, both of these syntheses are limited to the use of non-participating protecting groups and this method cannot be applied to pentopyranoses or 6-deoxyhexopyranoses.



Scheme 3.6 Method developed by Zhu *et al.* to selectively generate α-glycosyl thiols.

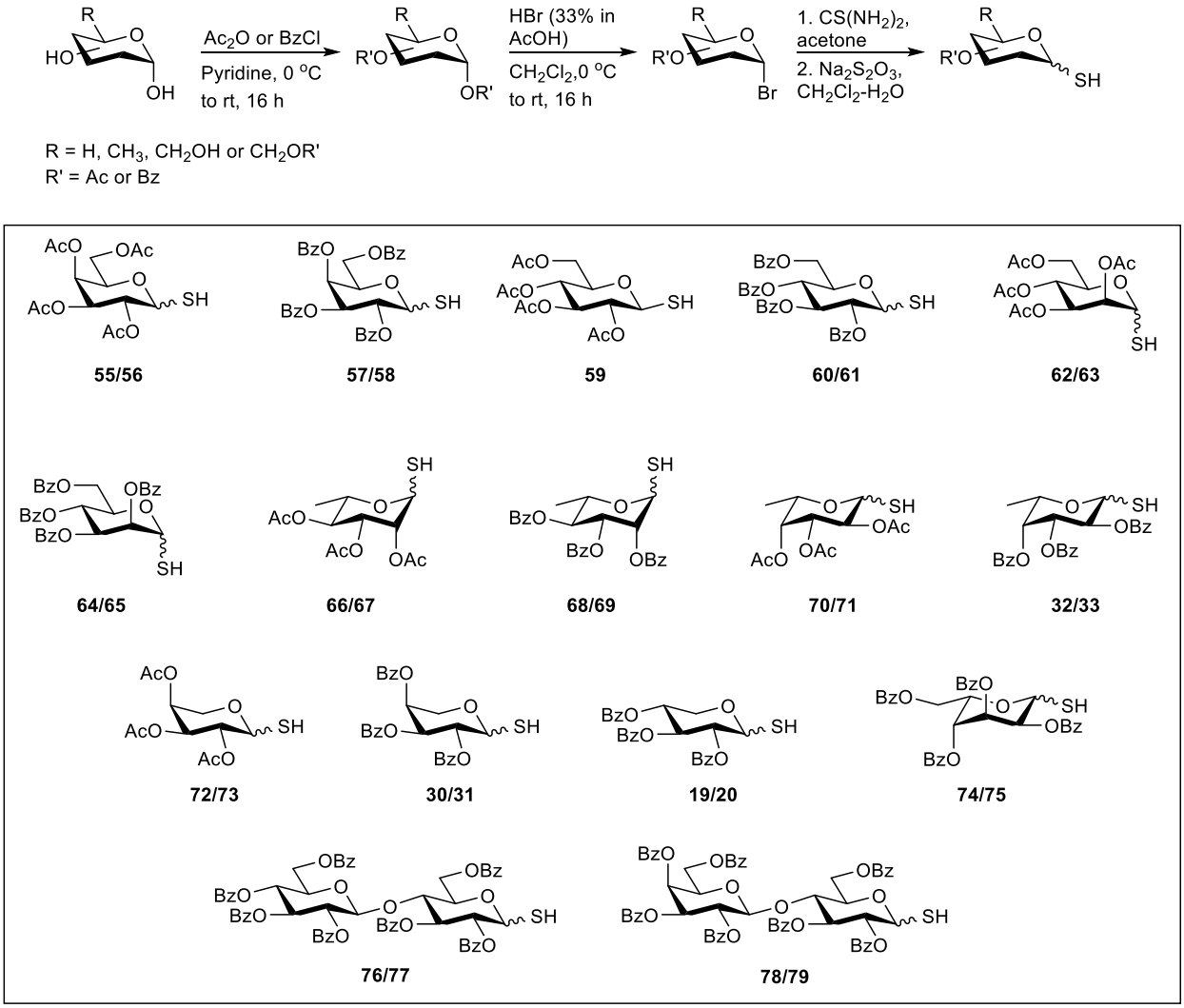
The development of an efficient and expedient route towards α-glycosyl thiols was therefore desirable and our group sought to investigate a means to develop this route. It was theorized that the anomerisation of simple glycosyl thiols could be beneficial in rapidly generating the axial anomer. The anomerisation of a glycosyl thiol had been previously achieved by our group.[9] However, this was for an uronic acid derivative. Further efforts were made by the Murphy group, namely McKinney[32] and O'Sullivan,[33] to investigate the anomerisation of simple glycosyl thiols. Their work will be discussed in further detail in Section 3.4.



Scheme 3.7 Anomerisation of uronic acid derivative achieved by O'Reilly and Murphy

3.3 Synthesis of Glycosyl Thiols

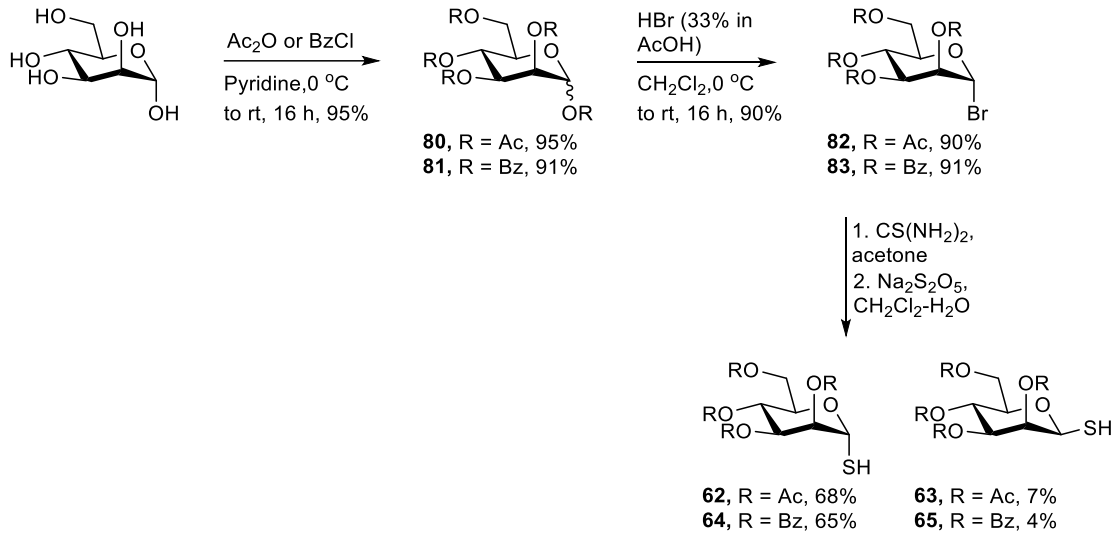
A series of glycosyl thiols were incorporated in this study, as shown in Figure 3.8. A general procedure was used for the preparation of each glycosyl thiol. Acetyl or benzoyl protecting groups were utilized and the corresponding glycosyl bromide was generated using hydrogen bromide in acetic acid. The bromide was then refluxed with thiourea to generate the thiouronium salt. This salt could be hydrolysed in a dichloromethane:water mixture with sodium metabilsulfite to afford the free thiol, generally as an anomeric mixture with the exception of **59**.



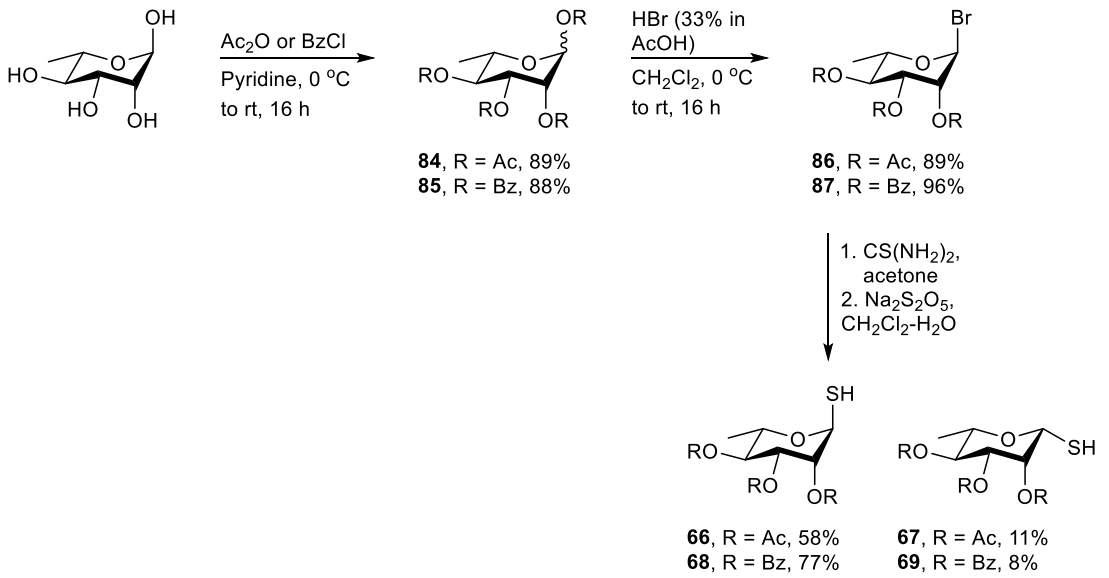
Scheme 3.8 General procedure for synthesis of glycosyl thiols and structures of thiols used in epimerisation study

For L-rhamnose and D-mannose glycosyl thiols, both acetyl and benzoyl protecting groups were used and the fully protected sugar was generated in high yields (88%-95%). The corresponding bromide was then generated in high yields (89%-96%) and subsequently, the thiouronuim salts

were generated. The thiouronium salts were hydrolysed to obtain the free thiol in moderate to high yields (69%-85%). Mixtures of the α/β thiols were obtained, with the major anomer being the α-glycosyl thiol (α:β>5:1).

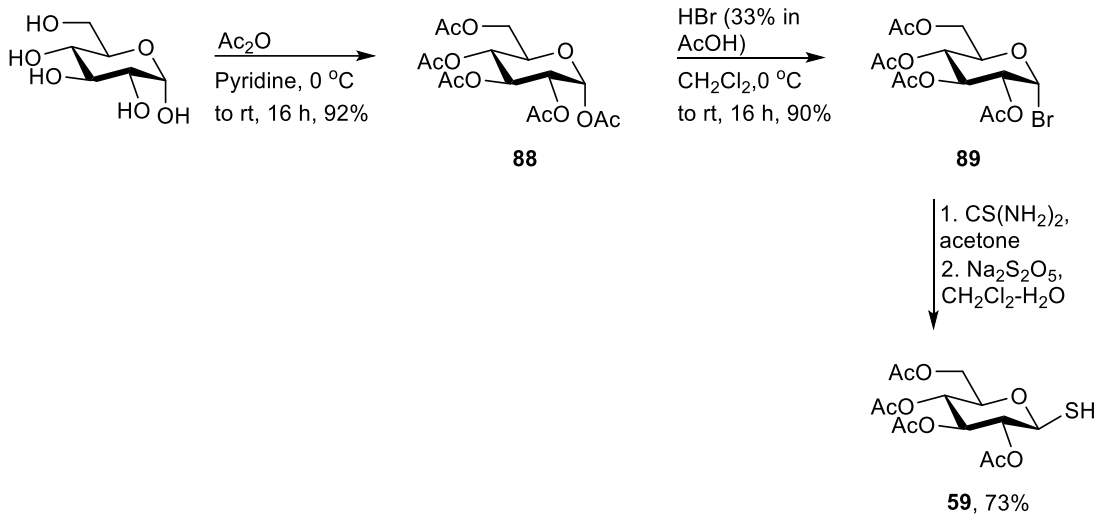


Scheme 3.9 Synthesis of D-mannose thiols.



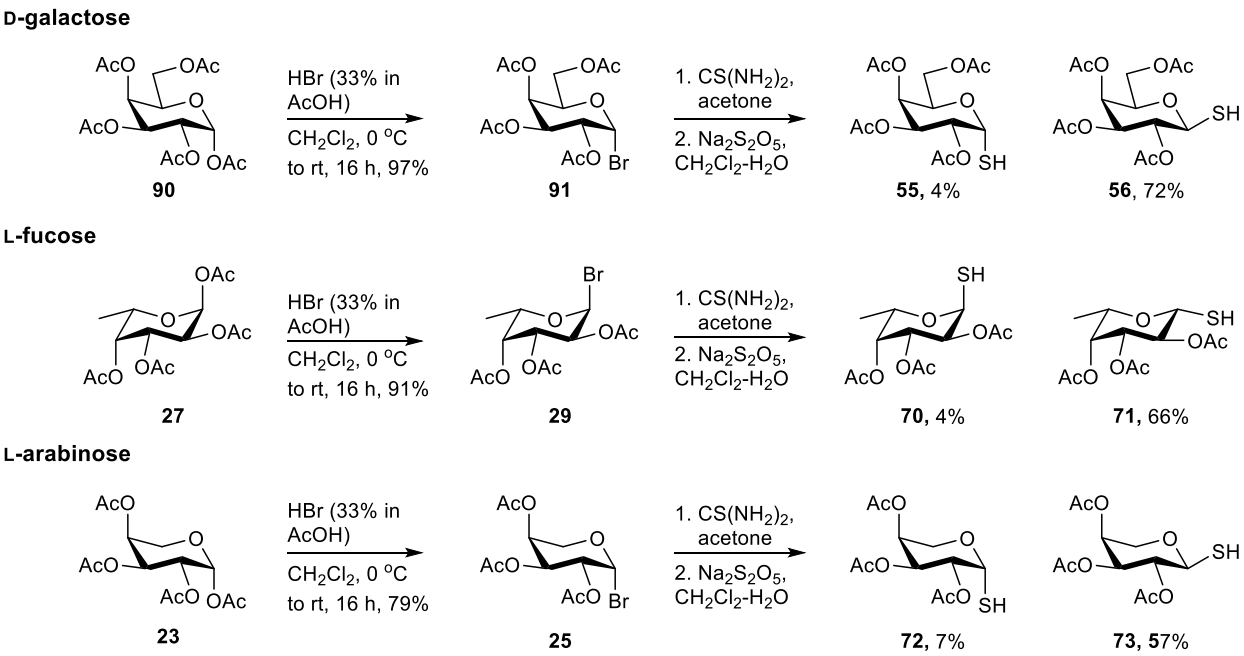
Scheme 3.10 Synthesis of L-rhamnose thiols

Glycosyl thiol **59** was synthesised following the same procedure. The peracetylated glucopyranose was generated in a high yield (92%) before it was reacted with hydrogen bromide to generate the glycosyl bromide (90%). The β-thiol was then selectively generated in a good yield (73%).



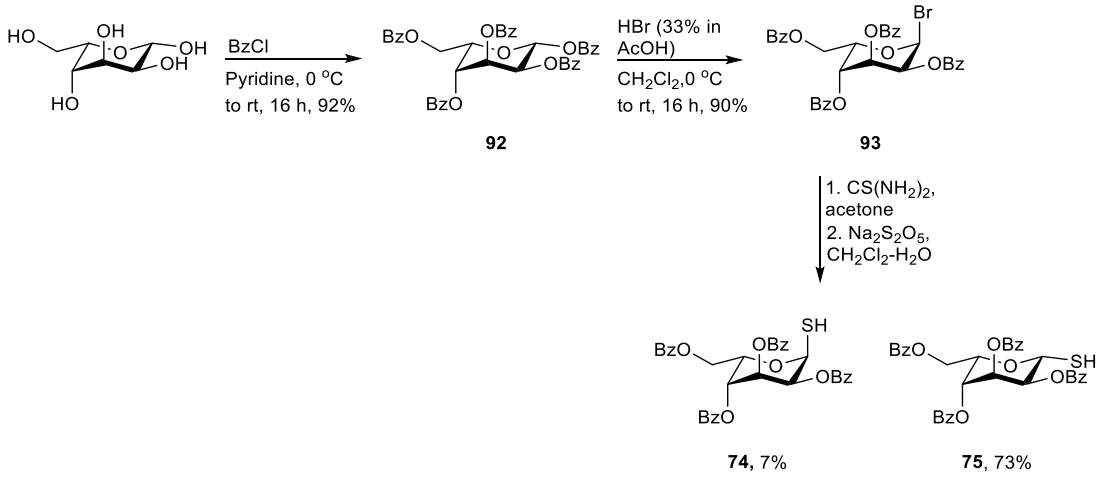
Scheme 3.11 Synthesis of **59**

The synthesis of the benzoylated D-xylose, L-fucose and L-arabinose thiols is shown in Chapter 2. The acetylated glycosyl thiols of galactose, fucose and arabinose were also synthesised as shown in Scheme 3.12. The bromide was generated in high yields (79-92%) and an anomeric mixture of the corresponding glycosyl thiols were then synthesised (64-76%). For these thiols, the equatorial anomer was predominant in the anomeric mixture.



Scheme 3.12 Synthesis of acetylated galactose, fucose and arabinose thiols

Finally, benzoylated gulose thiol **74** and **75** was synthesised using the same general procedure outlined. A mixture of thiols was obtained as the final product with the equatorial anomer dominant (α:β=1:10).



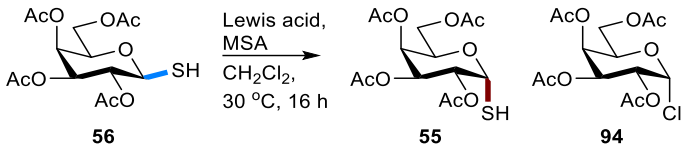
Scheme 3.13 Synthesis of L-gulose thiol **74** and **75**

3.4 Previous Investigation into Anomerisation towards Axial Glycosyl Thiols

It was postulated that the anomerisation of equatorially oriented-glycosyl thiols would be a convenient route towards axially oriented-glycosyl thiols. This would in turn be advantageous for the convergent synthesis of various sulfur-linked glycomimetics. The initial exploration into anomerisation of glycosyl thiols began with Michelle McKinney's MSc. thesis work. McKinney established that methane sulfonic acid (MSA) acted as a promoter in the anomerisation of *O*-glycosides. This was speculated to be due to coordination of the Brønsted acid to the Lewis acid, therefore increasing the Lewis acidity of the Lewis acid. The epimerisation of acetylated and benzoylated-1-thio-galactopyranoses was explored, using Brønsted acids like MSA as co-promoters.[32]

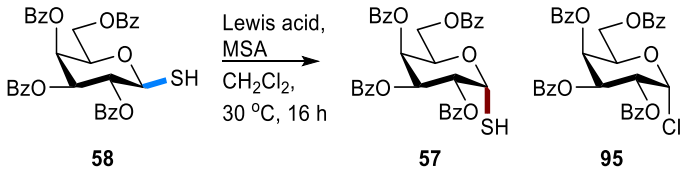
In the epimerisation with **56**, only 30% of the α-anomer could be generated after 16 h using either $TiCl_4$ or $SnCl_4$. MSA, in this case, was not found to have a notable effect on the α:β ratio. The reaction was then explored with the benzoylated galactopyranose **58**.

Table 3.1 Anomerisation of acetylated-1-thio-galactopyranose **56**[32]



Entry	Lewis acid	Equivalents of L.A.	Brønsted acid	%α	%β	%94
1	$SnCl_4$	0.5	-	32	63	5
2	$SnCl_4$	0.5	MSA (0.1 eq.)	30	63	7
3	$SnCl_4$	0.5	MSA (0.3 eq.)	33	56	11
4	$SnCl_4$	0.5	MSA (0.5 eq.)	24	70	6
5	$TiCl_4$	0.5	MSA (0.3 eq.)	8	85	6
6	$TiCl_4$	1	MSA (0.3 eq.)	9	83	8
7	$TiCl_4$	2	MSA (0.3 eq.)	7	83	10
8	$SnCl_4$	1	MSA (0.3 eq.)	25	68	7
9	$SnCl_4$	2	MSA (0.3 eq.)	23	69	8
10	$SnCl_4$	3	MSA (0.3 eq.)	23	65	12

Table 3.2 Anomerisation of benzoylated-1-thio-galactopyranose **58**[32]



Entry	Lewis acid	Equivalents of L.A.	Brønsted acid	%α	%β	%90
1	$SnCl_4$	0.5	-	33	60	6
2	$SnCl_4$	0.5	MSA (0.1 eq.)	33	59	8
3	$SnCl_4$	0.5	MSA (0.3 eq.)	21	66	13
4	$SnCl_4$	0.5	MSA (0.5 eq.)	30	61	9
5	$TiCl_4$	0.5	MSA (0.3 eq.)	45	-	55
6	$TiCl_4$	1	MSA (0.3 eq.)	58	-	42
7	$TiCl_4$	2	MSA (0.3 eq.)	69	-	31
8	$SnCl_4$	1	MSA (0.3 eq.)	24	65	11

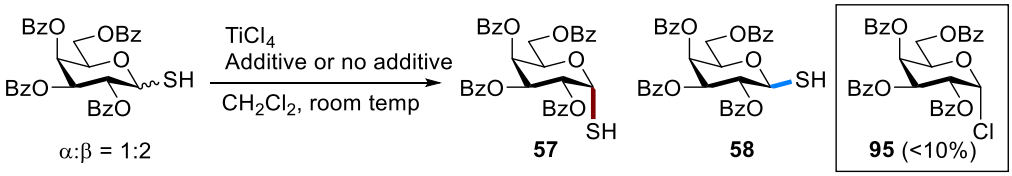
The exploration into anomerisation of benzoylated thiol **58** proved more productive. $SnCl_4$-catalysed anomerisation yielded ~30% of the α-anomer, regardless of MSA being used as a co-promoter. $TiCl_4$ was a more effective catalyst and increasing the equivalents of this Lewis acid to 2 equivalents (entry 7) generated 69% of the α-anomer, with a significant amount of side product generated. These initial results with substrate **58** were promising and warranted further investigation. This work was continued on with the PhD thesis work of Dr. Shane O'Sullivan.[33]

O'Sullivan conducted a wider study in the anomeristion in **58** using $TiCl_4$ alone or in the presence of various co-promoters to increase selectivity for the α-anomer. The α:β ratio was determined by ^{1}H NMR spectroscopic analysis and the percentage of chloride **95** generated in these epimerisation reactions was generally less than 10%. The use of $TiCl_4$ (2.5 equiv) solely resulted in an α:β ratio of 3.7:1 after 17 h (entry 1). Increasing the equivalents of $TiCl_4$ (3 equiv) led to an α:β ratio of 5.3:1 after 17 h and ~9:1 after 72 h (entry 18). The inclusion of additives DABCO, acetonitrile and EDTA led to a decrease in the preference for the axial anomer (entries 13, 15 and 16).[33]

Fortunately, in some experiments that included additives (0.3 equiv, entries 2-12 and 14) with $TiCl_4$ (2.5 equiv), the α:β ratio was found to be greater than the benchmark reaction (3.7:1, entry 1). This was particularly noteworthy for triphenylphosphine, pyridine and triethylamine (entries 9-11), which gave rise to significantly higher α:β ratios (>11:1) than in the absence of the Lewis base. The higher ratio is attributed to a faster rate of reaction in the presence of an additive, which leads to greater advancement towards equilibrium after 16 h.

Reducing the reaction temperature (e.g. 0 ^{o}C) led to lower α:β ratios after 16 h due to a decrease in the reaction rate (data not shown in Table 1). Finally, it was confirmed that pyridine was unable to promote the anomerisation reaction of **58** on its own (entry 19) and use of $TiCl_4$ (3 equiv) and pyridine (0.5 equiv) led to only **57** being detected in the mixture after 16 h (entry 21); this outcome is significantly higher than the corresponding reaction without pyridine (5.3:1, entry 17). Therefore the progress of the reaction was dependent on temperature, concentration of promoter, and Lewis base additive, and could be optimised for formation of **52**.[33]

Table 3.3 $TiCl_4$ promoted anomerisation in absence and presence of additive[33]

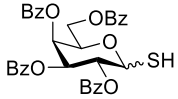
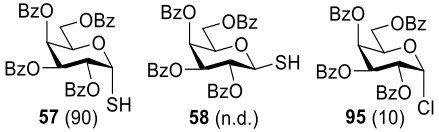
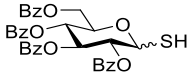
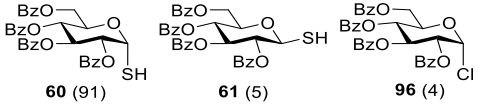
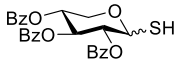
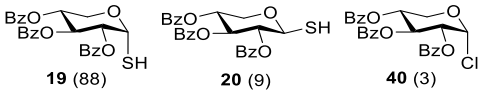
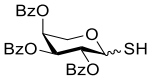
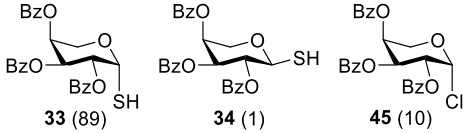
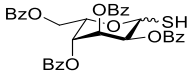
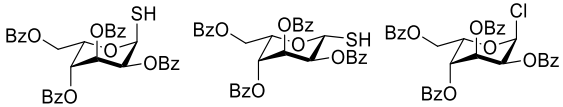
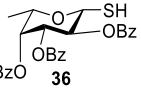
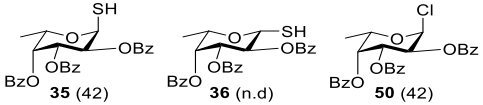
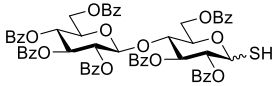
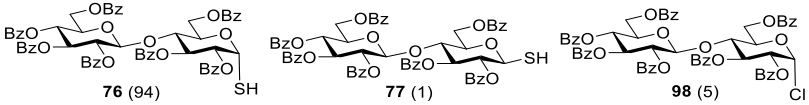
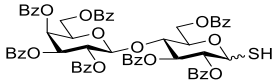
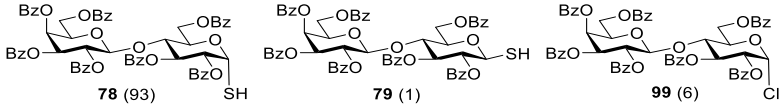


Entry	Additive	Equiv of $TiCl_4$	Equiv of additive	Reaction time (h)	α:β
1	No additive	2.5	-	17	3.7:1
2	Methanesulfonic acid	2.5	0.3	16	5.4:1
3	Sulfamic acid	2.5	0.3	16	4.8:1
4	Sulfuric acid	2.5	0.3	16	7.3:1
5	Sulfuric diamide	2.5	0.3	16	7.6:1
6	Dimethyl sulfone	2.5	0.3	16	5.8:1
7	Methanesulfonamide	2.5	0.3	16	5.8:1
8	Me_3P	2.5	0.3	16	9.6:1
9	Ph_3P	2.5	0.3	16	12.7:1
10	Pyridine	2.5	0.3	16	12.6:1
11	Et_3N	2.5	0.3	16	11.0:1
12	Pyridin-4-amine	2.5	0.3	16	7.5:1
13	DABCO	2.5	0.3	16	2.8:1
14	Dimethylacetamide	2.5	0.3	16	9.8:1
15	Acetonitrile	2.5	0.3	16	1.7:1
16	EDTA	2.5	0.3	16	2.6:1
17	No additive	3.0	-	16	5.3:1
18	No additive	3.0	-	72	8.8:1
19	Pyridine	0	0.5	72	1:2
20	Pyridine	3.0	0.3	72	90:1
21	Pyridine	3.0	0.5	16	α only

Anomerisation of seven other glycosyl thiols **20**, **34**, **36**, **61**, **75**, **77** and **79** were then studied and the results are summarised in Table 3.4. An anomeric mixture of the glycosyl thiols were generally used, with an exception being for L-fucose, where the two thiol anomers were initially separated and **36** was then used in the anomerisation. All reactions were carried out in dichloromethane in the presence of $TiCl_4$ (3 equiv) for 16 h. In the cases of the hexopyranoses **57, 61, 77** and **79** the addition of pyridine led to increased α:β ratios compared to reactions with $TiCl_4$ alone, with the exception of gulose derivative **75**. For the pentopyranose or 6-deoxyhexopyranose derivatives **20, 34** and **36** the use of pyridine either led to no improvement in α:β ratio, or to a reduction in α:β ratio. Nevertheless, high α:β ratios could be achieved for these thiols, in the absence of the Lewis base, with the β-thiol not being detected for the case of the fucose derivatives. The glycosyl chloride was observed to be a by-product in all cases, with the proportion of this product being highest in the case of the 6-deoxyhexopyranoses (fucose).

In each case the axially oriented thiol was isolated and the best yields after chromatography are given in Table 2. In our hands, yield of the thiol products were depleted to levels of <20% by prolonged chromatographic separation on silica gel. It was found to be important to use flash chromatography with a minimum quantity of silica gel and minimise the time the thiols were exposed to silica gel during the chromatographic purification in order to maximise the quantity of thiol isolated. Even minimal contact with silica gel led to some depletion.[33]

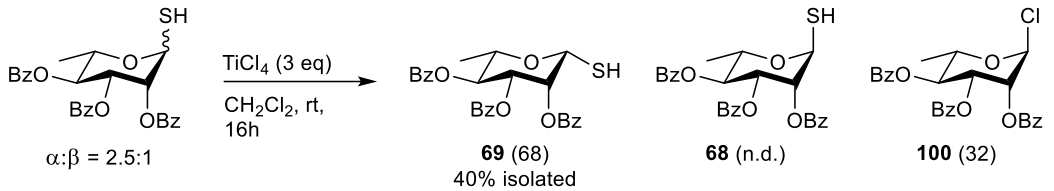
Table 3.4 Anomerisation of glycosyl thiols with $TiCl_4$ in absence or presence of pyridine[33]

Thiol reacting mixture	Reagents and Conditions	Products (relative proportion by NMR spectral analysis)[1]	Yield after work-up	Isolated yield (%) of major anomer[2]
 α:β = 1:2	$TiCl_4$ (3 equiv), pyridine (0.5 equiv), CH_2Cl_2, rt, 16 h	 **57** (90) **58** (n.d.) **95** (10)	93	56 (**58**)
 α:β = 1:4.5	$TiCl_4$ (3 equiv), pyridine (0.5 equiv), CH_2Cl_2, rt, 16 h	 **60** (91) **61** (5) **96** (4)	94	63 (**60**)
 α:β = 1:2	$TiCl_4$ (3 equiv) CH_2Cl_2, room temp, 16 h	 **19** (88) **20** (9) **40** (3)	93	52 (**19**)
 α:β = 2:1	$TiCl_4$ (3 equiv) CH_2Cl_2, rt, 16 h	 **33** (89) **34** (1) **45** (10)	85	48 (**33**)
 α:β = 1:6.3	$TiCl_4$ (3 equiv) CH_2Cl_2, rt, 16 h	 **74** (75) **75** (12) **97** (13)	75	56 (**74**)
 **36**	$TiCl_4$ (3 equiv) CH_2Cl_2, room temp, 16 h	 **35** (42) **36** (n.d) **50** (42)	87[3]	38 (**35**)
 α:β = 1:2	$TiCl_4$ (3 equiv), pyridine (0.5 equiv), CH_2Cl_2, rt, 16 h	 **76** (94) **77** (1) **98** (5)	76	42 (**76**)
 α:β = 1:4	$TiCl_4$ (3 equiv), pyridine (0.5 equiv), CH_2Cl_2, rt, 16 h	 **78** (93) **79** (1) **99** (6)	91	53 (**78**)

[1]n.d. = not detected by ^{1}H-NMR spectroscopy. [2]yield after flash chromatography on a short column of silica gel. [3]an unidentified product was also present (~16%)

3.5 Axial-to-Equatorial Epimerisation in Glycosyl Thiols

Close examination of the reaction reported by O'Sullivan in his PhD thesis indicated that the major product from the anomerisation of a 2.5:1 α:β mixture of 2,3,4-tri-*O*-benzoyl-thio-L-rhamnopyranoside may have been incorrectly assigned to that of the β-anomer. The work reported from this point deals with firstly with the establishment of this product as that of the α-anomer. This led to the original work described in this chapter, which was concerned with axial-to-equatorial epimerisation in acylated 1-thiosugars.



Scheme 3.14 Epimerisation of 2,3,4-tri-*O*-benzoyl-thio-L-rhamnopyranoside with $TiCl_4$

The reaction carried out by O'Sullivan with a 2.5:1 α:β mixture of 2,3,4-tri-*O*-benzoyl-thio-L-rhamnopyranoside with $TiCl_4$, and analysis of the resulting reaction mixture indicated that it contained ~68% of the β-anomer, which was isolated in 40% yield after chromatography. This indicated the reaction was selective for the equatorial anomer. Following this unexpected result, the α-anomer was isolated and investigated under $SnCl_4$-catalysed conditions. The structures of **68** and **69** were supported by NOESY and ^{13}C-NMR and the α-anomer, and thus the β-anomer, was confirmed by X-ray crystal structure determination.

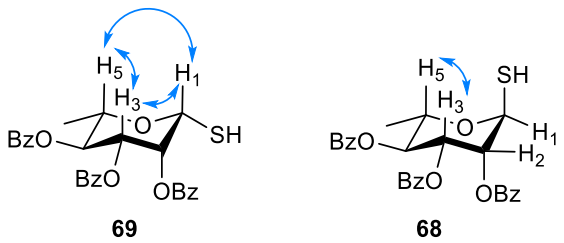


Figure 3.7 NOE correlations observed in **69** and **68.** Correlation between H-1 and H-3/H-5 was not observed in **68**.

Analysis of ^{1}H NMR spectra did not conclusively distinguish between the α- and β-anomer, as the *J*-values for each anomeric proton were similar **68** δ 5.78 (dd, *J* = 7.1, 1.5 Hz) vs. **69** δ 5.12 (dd, *J* = 10.1, 1.3 Hz)). NOESY was employed to observe through space correlations in protons. In the NOESY spectrum of β-anomer **69**, the H-1 proton shows a correlation to the H-3 and H-5 protons, supporting the equatorial configuration. In the NOESY spectrum of α-anomer **68**, a correlation was observed between the H-5 and H-3 proton, but no correlation was observed to

the H-1 proton, indicating that the anomeric proton was equatorial. Analysis of $J_{C1.H1}$ values in coupled ^{13}C NMR spectra further aided assignment of the two anomers. Equatorial arrangement of the proton in the α-anomer typically leads to a higher *J*-value (~170 Hz) while the axial arrangement in the β-anomer has a lower *J*-value (~160 Hz).[34] The $J_{C1.H1}$ value of **68** ($^1J_{C1.H1}$ = 169.6 Hz) and **69** ($^1J_{C1.H1}$ = 151.2 Hz) supported their assignments as the α- and β-anomer, respectively. Finally, an X-ray crystal structure was obtained for **68** confirming that it was the axial anomer.

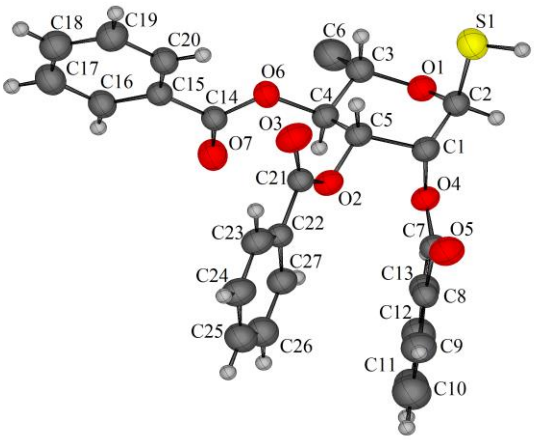
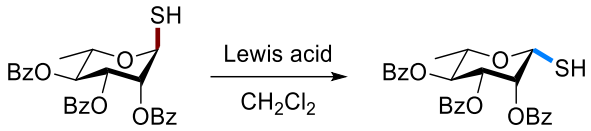


Figure 3.8 Crystal structure of **68**

The anomerisation of **68** was explored with $SnCl_4$, varying the time and temperature, as shown in Table 3.5. $SnCl_4$-promoted anomerisation led to 80% of the β-anomer being generated after 24 h at room temperature, according to ^1H NMR spectroscopic analysis. Lowering the temperature to 4°C curbed the formation of the chloride side product and increased the yield of the equatorial anomer to 82% after 36 h. However, reducing the temperature to -30 °C inhibited the epimerisation. Increasing the equivalents of $SnCl_4$ did not increase the percentage yield of the equatorial anomer (entry 5). Finally, the addition of MSA (0.5 equiv) increased the amount of the β-anomer to 84% after 24 h (entry 7).

Table 3.5 Anomerisation conditions explored with glycosyl thiol **68**

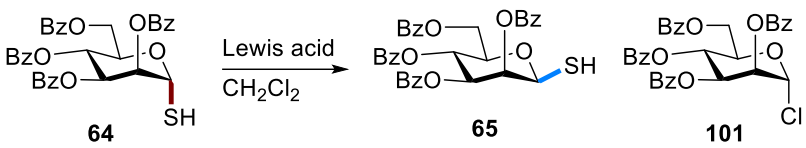


68 **69**

Entry	Time (h)	Temp.	Lewis acid	Equivalents	Additive	%α	%β	%100	Crude % yield
2	24 h	20 ºC	$SnCl_4$	2.5	-	12	80	8	78
3	24 h	4 °C	$SnCl_4$	2.5	-	11	82	7	88
4	24 h	-30 °C	$SnCl_4$	2.5	-	41	51	8	81
5	24 h	4 °C	$SnCl_4$	4	-	10	79	11	87
6	36 h	4 °C	$SnCl_4$	2.5	-	10	82	8	82
7	24 h	4 °C	$SnCl_4$	2.5	MSA (0.5 equiv)	8	84	8	90

Next the epimerisation of mannose thiol **64** was explored (Table 3.6). The $TiCl_4$-promoted epimerisation led to a significant amount of side product formation and the beta thiol only accounted for <20% of the reaction mixture after 20 h. $SnCl_4$-catalysed anomerisation generated 70% of the β-anomer after 20 h at room temperature. Reducing the reaction temperature to 4ºC suppressed side product formation and 76% of the β-anomer was generated after 20 h. Reducing the temperature further to -30 ºC or decreasing the equivalents of the Lewis acid had a negative impact on the selectivity for the β-anomer (entries 4-5).

Table 3.6 Anomerisation conditions explored with mannose thiol **64**



64 **65** **101**

Entry	Time (h)	Temp.	Lewis acid	Equivalents	%α	%β	%101	Crude % yield
1[1]	20	20 ºC	$TiCl_4$	2.5	40	20	40	93
2	20	20 ºC	$SnCl_4$	2.5	30	70	-	97
3	20	4 °C	$SnCl_4$	2.5	24	76	-	94
4	24	-30 °C	$SnCl_4$	2.5	37	63	-	77
5	20	4 °C	$SnCl_4$	1.5	31	69	-	73

[1]Significant amount of side products formed that could not be identified

A series of co-catalysts were explored to improve selectivity the equatorial anomer, as shown in Table 3.7. The additives triphenylphosphine and sulfamic acid did not lead to improved α:β selectivity or a higher rate of reaction (entries 1-2). Fortunately, MSA proved to be an effective co-catalyst and 0.5 equivalents of MSA increased the percentage of β-anomer to 89% after 24 h. Increasing the equivalents of MSA (2 equiv.) enhanced selectivity for the β-anomer and 92% of equatorial anomer was generated after 24 h, according to analysis by ^{1}H NMR spectroscopy. The addition of MSA (1 equiv) without any Lewis acid present confirmed that $SnCl_4$ was also required (entry 5).

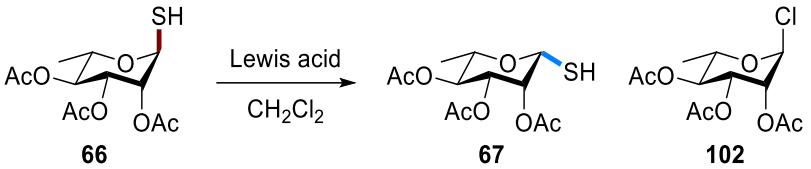
Table 3.7 Additives explored for promotion of anomerisation with glycosyl thiol **64**

Entry	Time (h)	Temp.	Lewis acid	Equivalents	Additive	%α	%β	%101	Crude % yield
1	24	4 °C	$SnCl_4$	2.5	PPh_3 (0.5 equiv)	24	76	-	98
2	24	4 °C	$SnCl_4$	2.5	Sulfamic acid (0.5 equiv)	26	74	-	90
3	24	4 °C	$SnCl_4$	2.5	MSA (0.5 equiv)	11	89	-	97
4	24	4 °C	$SnCl_4$	2.5	MSA (2 equiv)	8	92	-	97
5	24	20 °C	-	-	MSA (1 equiv)	88	12	-	95

$SnCl_4$ promoted epimerisation from acetylated-1-thio-rhamnopyranose **66** and acetylated-1-thio-mannopyranose **62** was then explored. Axial-to-equatorial epimerisation with $SnCl_4$ was achieved with the acetylated derivatives, unlike $TiCl_4$-catalysed equatorial-to-axial anomerisation which required benzoylated glycosyl thiols.

High selectivity was observed for the β-anomer under $SnCl_4$-chelated conditions in rhamnopyranosyl thiol **66** (Table 3.8). The addition of MSA (0.5 equiv.) suppressed the formation of side products and the equatorial anomer was generated in 86% yield (entry 3).

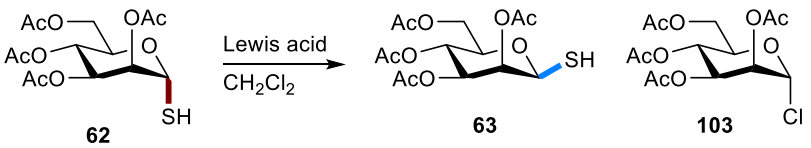
Table 3.8 Epimerisation of acetylated rhamnose thiol **66** with $SnCl_4$



Entry	Time (h)	Temp.	Lewis acid	Equivalents	Additive	%α	%β	%102	Crude % yield
1	24	20 °C	$SnCl_4$	2.5	-	16	80	4	94
2	24	4 °C	$SnCl_4$	2.5	-	12	83	5	87
3	24	4 °C	$SnCl_4$	2.5	MSA (0.5 equiv)	14	86	-	96

Mannopyranosyl thiol **62** was then subjected to $SnCl_4$ conditions, as shown in Table 3.9. It was noted that in the following hour after the addition of $SnCl_4$, a white precipitate formed in the reaction mixture. This amorphous powder was later established to be a complex between the β-glycosyl thiol and $SnCl_4$, which will be discussed in further detail in Chapter 4. The equatorial anomer could be generated in 92% after 24 h with $SnCl_4$ (entry 1). The addition of MSA led to a reduced rate of epimerisation (entry 3), as did decreasing the reaction temperature to 4 °C (entry 2). Care needs to be taken during the work-up of this reaction to maximise the yield. The products are quite water soluble and can be difficult to extract into an organic solvent. The aqueous layer had to be extracted at least twice with ethyl acetate to increasing the amount of material recovered.

Table 3.9 Epimerisation of acetylated mannose thiol **62** with $SnCl_4$



Entry	Time (h)	Temp.	Lewis acid	Equivalents	Additive	%α	%β	%103	Crude % yield
1	24	20 °C	$SnCl_4$	2.5	-	8	92	-	60
2	24	4 °C	$SnCl_4$	2.5	-	10	90	-	58
3	24	4 °C	$SnCl_4$	2.5	MSA (0.5 equiv)	14	86	-	69

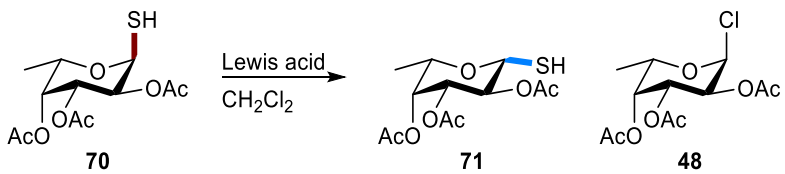
3.6 Optimisation of Conditions

A series of axial glycosyl thiols were then subjected to $SnCl_4$ promoted reactions. The conditions were optimised for each sugar and the isolated yields were obtained for each substrate.

3.6 1 Fucopyranosyl thiols

Axial-to-equatorial anomerisation was explored from **70**, as shown in Table 3.10. It was found that at room temperature, 83% of the β-anomer could be obtained with $SnCl_4$ after 24 h (entry 1). In experiments where the reaction temperature was decreased led to a lower preference for the β-anomer (entries 2-3). The addition of MSA did not improve the α/β ratio (entry 4).

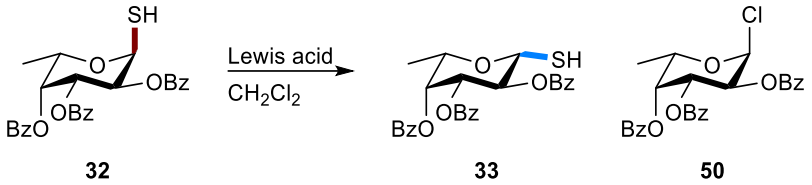
Table 3.10 Epimerisation conditions for fucose derivative **70**



Entry	Time (h)	Temp.	Lewis acid	Equivalents	Additive	%α	%β	%48	Crude % yield
1	24	20 °C	$SnCl_4$	2.5	-	9	83	8	89
2	24	4 °C	$SnCl_4$	2.5	-	16	78	6	92
3	24	-30 °C	$SnCl_4$	2.5	-	63	29	8	95
4	24	4 °C	$SnCl_4$	2.5	MSA (0.5 equiv)	28	70	2	98

The benzoylated-1-thiofucopyranose was also investigated under Lewis acid-catalysed conditions (Table 3.11). The reaction temperature was found to have a substantial effect on the α:β selectivity, as the percentage yield of the equatorial anomer increased as the reaction temperature decreased (entries 1-3). The optimum conditions were found to be -30 °C as 85% of the β-anomer was generated (entry 3). Increasing the equivalents of $SnCl_4$ or the addition of MSA reduced the amount of β-anomer generated (entries 5-6). Under $TiCl_4$-promoted conditions, the α-anomer was the major product with no β-anomer observed by ^{1}H NMR spectroscopy (entry 4).

Table 3.11 Epimerisation conditions for fucopyranosyl thiol **32**



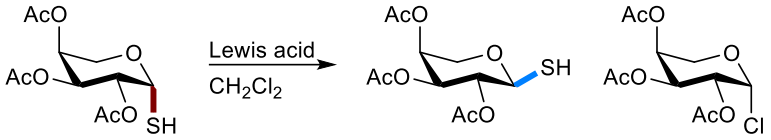
Entry	Time (h)	Temp.	Lewis acid	Equivalents	Additive	%α	%β	%50	Crude % yield
1	24	0 °C	$SnCl_4$	2.5	-	18	73	9	97
2	24	4 °C	$SnCl_4$	2.5	-	12	78	10	82
3	24	-30 °C	$SnCl_4$	2.5	-	12	85	3	88
4	26	20 °C	$TiCl_4$	2.5	-	85	-	15	98
5	24	-30 °C	$SnCl_4$	3	-	59	37	4	98
6	24	4 °C	$SnCl_4$	2.5	MSA (0.5 equiv)	39	61	-	97

3.6 2 Arabinopyranosyl thiols

Anomerisation conditions for **72** are shown in Table 3.12. In the $SnCl_4$-chelated epimerisation of acetylated-1-thioarabinose, the equatorial anomer could be generated in 64% after 24 h at 20 °C (entry 1). Decreasing the reaction temperature led to a diminished preference for the equatorial anomer (entries 2-3) and this was interpreted as the rate of reaction being decreased. The addition of MSA (0.5 equiv) led to poorer α:β ratios at 20 °C and at 4 °C (entries 5-6).

The epimerisation of glycosyl thiol **32** was then explored, summarised in Table 3.13. Under $SnCl_4$ promoted epimerisation, the addition of MSA (0.5 equiv) led to lower α:β ratios at 20 °C and 4 °C after 24 h (entry 1 vs 3 and entry 2 vs 4). The optimum conditions were obtained when the reaction temperature was decreased to -30 °C and the equatorial anomer accounted for 80% of the solution after 24 h (entry 6). However, increasing the reaction time to 48 h led to a diminished preference for the equatorial anomer and lower percentage yield (entry 7).

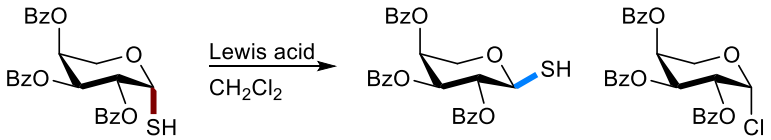
Table 3.12 Epimerisation of arabinopyranosyl thiol **72**



72 **73** **43**

Entry	Time (h)	Temp.	Lewis acid	Equivalents	Additive	%α	%β	%43	Crude % yield
1	24	20 °C	$SnCl_4$	2.5	-	64	46	-	64
2	24	4 °C	$SnCl_4$	2.5	-	58	52	-	68
3	24	-30 °C	$SnCl_4$	2.5	-	21	79	-	66
4	48	-30 °C	$SnCl_4$	2.5	-	32	68	-	62
5	24	20 °C	$SnCl_4$	2.5	MSA (0.5 equiv)	51	49	-	63
6	24	4 °C	$SnCl_4$	2.5	MSA (0.5 equiv)	42	58	-	53

Table 3.13 Epimerisation of arabinopyranosyl thiol **32**



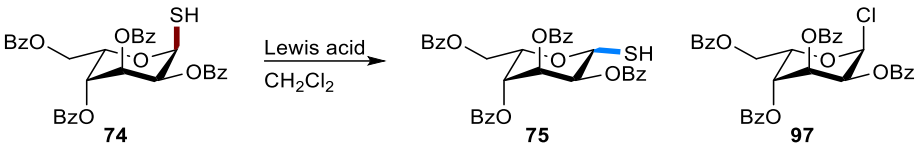
32 **33** **45**

Entry	Time (h)	Temp.	Lewis acid	Equivalents	Additive	%α	%β	%45	Crude % yield
1	24	20 °C	$SnCl_4$	2.5	-	57	38	5	85
2	24	4 °C	$SnCl_4$	2.5	-	60	35	5	88
3	26	20 °C	$SnCl_4$	2.5	MSA (0.5 equiv)	48	38	14	90
4	24	4 °C	$SnCl_4$	2.5	MSA (0.5 equiv)	53	47	-	77
5	24	20 °C	$SnCl_4$	5	-	60	37	3	97
6	24	-30 °C	$SnCl_4$	2.5	-	80	19	1	96
7	48	-30 °C	$SnCl_4$	2.5	-	69	29	2	41

3.6 3 Gulopyranosyl thiol

In the $SnCl_4$-catalysed epimerisation of gulose thiol **74** (Table 3.14)**,** the equatorial anomer was predominant at 20 ºC and 4 ºC after 24 h and the temperature did not have a significant impact on the α:β ratio (entries 1-2). The addition of MSA led to a diminished preference for the β-anomer after 24 h (entry 1 vs entry 3).

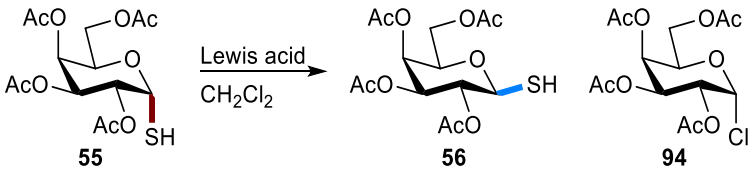
Table 3.14 Axial-to-equatorial anomerisation in **74**



Entry	Time (h)	Temp.	Lewis acid	Equivalents	Additive	%α	%β	%97	Crude % yield
1	24	20 ºC	$SnCl_4$	2.5	-	7	93	-	98
2	24	4 °C	$SnCl_4$	2.5	-	8	92	-	65
3	24	20 ºC	$SnCl_4$	2.5	MSA (0.5 equiv)	13	77	10	97

3.6 4 Galactopyranosyl thiols

Table 3.15 Epimerisation of galactopyranosyl thiol **55**



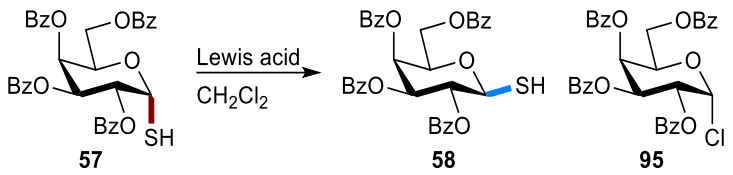
Entry	Time (h)	Temp.	Lewis acid	Equivalents	Additive	%α	%β	%94	Crude % yield
1	24	20 ºC	$SnCl_4$	2.5	-	22	72	6	84
2	24	4 °C	$SnCl_4$	2.5	-	59	41	-	59
3	24	-30 °C	$SnCl_4$	2.5	-	83	17	-	82

Anomerisation conditions for **55** are shown in Table 3.15. The acetylated-1-thiogalactopyranose was found to favour the β-anomer (72%) under $SnCl_4$ conditions at 20 ºC

after 24 h (entry 1). In the other experiments where the reaction temperature was lowered there was a notable decrease in the percentage yield of the β-anomer (entries 2-3).

In substrate **57**, the equatorial anomer accounted for 67% of the reaction mixture under $SnCl_4$-chelated conditions after 24 h at 20 ºC. The use of MSA as an additive led to decreased α:β ratios at 20 ºC and 4 ºC.

Table 3.16 Epimerisation of galactopyranosyl thiol **57**

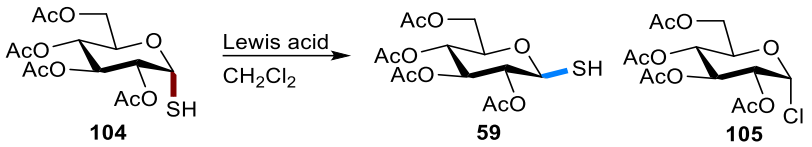


Entry	Time (h)	Temp.	Lewis acid	Equivalents	Additive	%α	%β	%95	% yield
1	24	20 ºC	$SnCl_4$	2.5	-	21	67	12	91
2	24	4 °C	$SnCl_4$	2.5	-	25	66	9	94
3	24	20 ºC	$SnCl_4$	2.5	MSA (0.5 equiv)	33	53	14	91
4	24	4 °C	$SnCl_4$	2.5	MSA (0.5 equiv)	35	61	4	90

3.6 5 Glucopyranosyl thiols

Anomerisation conditions for **104** are shown in Table 3.17. The epimerisation of thiol **104** under $SnCl_4$ conditions led to 75% of the equatorial anomer generated at 20 ºC after 24 h (entry 1). When the reaction temperature was lowered to 4 ºC and -30 ºC, this resulted in decreased epimerisation with a significant amount of the axial anomer remaining (entries 2-3).

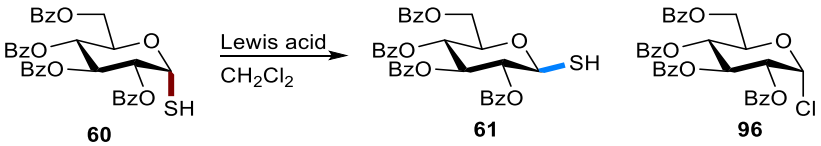
Table 3.17 $SnCl_4$-promoted epimerisation of glucopyranosyl thiol **104**



Entry	Time (h)	Temp.	Lewis acid	Equivalents	Additive	%α	%β	%105	% yield
1	24	20 °C	$SnCl_4$	2.5	-	25	75	-	71
2	24	4 °C	$SnCl_4$	2.5	-	48	52	-	64
3	24	-30 °C	$SnCl_4$	2.5	-	75	25	-	66

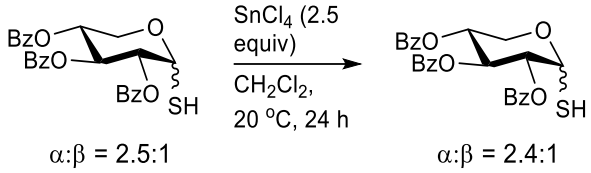
The equatorial anomer was favoured under $SnCl_4$-chelated conditions in glucose thiol **60** at 20 °C and accounted for 62% of the reaction mixture after 24 h (entry 1). The addition of MSA (0.5 equiv) led to a substantial decrease in the percentage yield of the equatorial anomer at 20 °C and 4 °C after 24 h (entries 3-4).

Table 3.18 Epimerisation of glucopyranosyl thiol **60**



Entry	Time (h)	Temp.	Lewis acid	Equivalents	Additive	%α	%β	%96	% yield
1	24	20 °C	$SnCl_4$	2.5	-	27	62	11	97
2	24	4 °C	$SnCl_4$	2.5	-	32	60	8	97
3	24	20 °C	$SnCl_4$	2.5	MSA (0.5 equiv)	74	19	7	94
4	26	4 °C	$SnCl_4$	2.5	MSA (0.5 equiv)	54	33	13	91

3.6 6 Xylopyranosyl Thiol

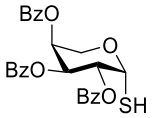
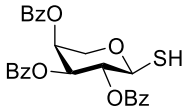
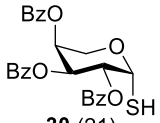
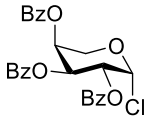
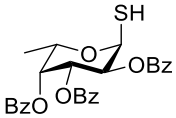
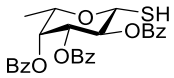
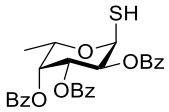
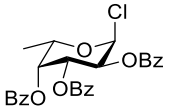
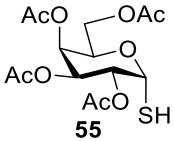
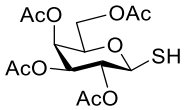
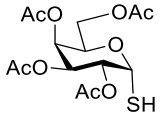
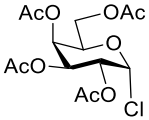
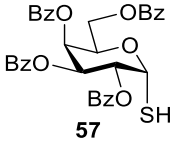
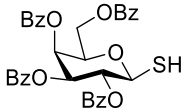
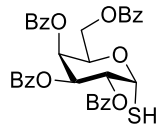
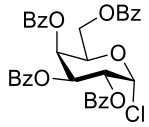
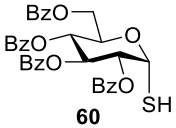
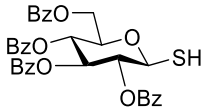
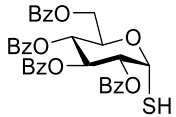
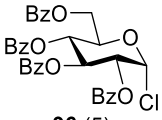
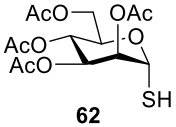
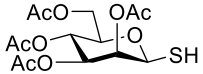
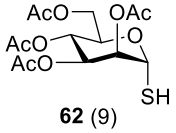
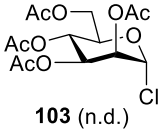


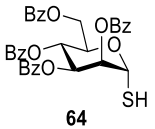
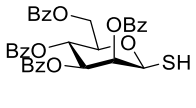
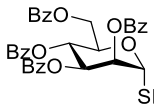
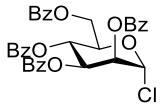
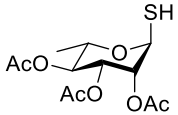
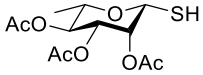
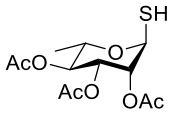
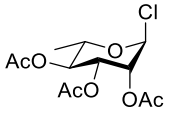
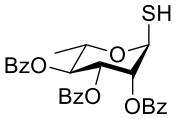
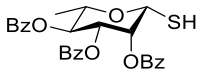
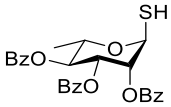
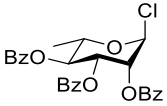
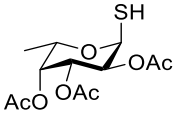
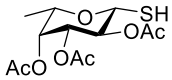
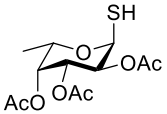
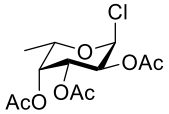
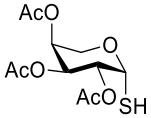
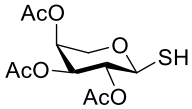
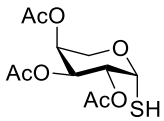
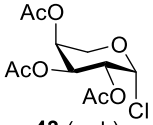
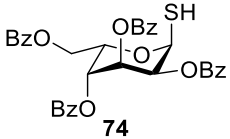
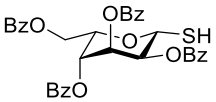
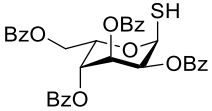
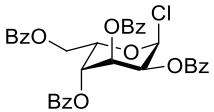
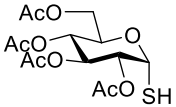
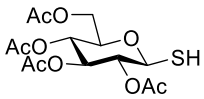
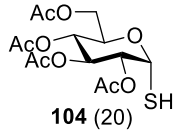
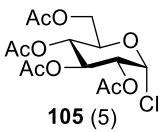
Scheme 3.15 $SnCl_4$-promoted anomerisation of **19/20**

Finally, benzoylated 1-thioxylopyranose was subjected to $SnCl_4$-catalysed conditions. A mixture of anomers (α:β=2.5:1) was treated with $SnCl_4$ and the reaction mixture was analysed by ^{1}H NMR spectroscopy after 24 h. There was no selectivity observed for the equatorial anomer, making it the only glycosyl thiol tested which did not favour an equatorial orientation under $SnCl_4$-chelated conditions.

These initial test experiments indicated that all of the glycosyl thiols favoured an equatorial configuration under $SnCl_4$-promoted epimerisation, with the exception of benzoylated-1-thioxylopyranose. The reactions were scaled up to 100 mg or 200 mg and the isolated yields were obtained under the optimised conditions ascertained for each substrate, as shown in Table 3.19.

Table 3.19 Reverse of anomerisation. Isolated yields for glycosyl thiol derivatives **62**, **64, 66** and **68** on ~200 mg scale and **30, 32, 55, 57, 60, 70, 72, 74** and **104** on ~100 mg scale are given.

Reacting axial thiol	**Reagents and Conditions**	**Products** (relative proportion determined by ^{1}H-NMR spectral analysis)[a]	**Yield after work-up**	**% Isolated yield**[b]
 **30**	$SnCl_4$ (2.5 equiv), CH_2Cl_2, -30 °C, 24h	 **31** (74)  **30** (21)  **45** (5)	97%	54% (**31**)
 **32**	$SnCl_4$ (2.5 equiv), CH_2Cl_2, -30 °C, 24 h	 **32** (82)  **33** (10)  **50** (8)	97%	68% (**32**)
 **55**	$SnCl_4$ (2.5 equiv), CH_2Cl_2, rt, 24 h	 **56** (75)  **55** (19)  **94** (6)	77%	46% (**56**)
 **57**	$SnCl_4$ (2.5 equiv), CH_2Cl_2, rt, 24 h	 **58** (78)  **57** (17)  **95** (5)	97%	59% (**58**)
 **60**	$SnCl_4$ (2.5 equiv), CH_2Cl_2, rt, 24 h	 **61** (71)  **60** (24)  **96** (5)	90%	52% (**61**)
 **62**	$SnCl_4$ (2.5 equiv), CH_2Cl_2, rt, 24 h	 **63** (91)  **62** (9)  **103** (n.d.)	89%	67% (**63**)

 **64**	$SnCl_4$ (2.5 equiv), MSA (2 equiv), CH_2Cl_2, 4 °C, 24h	 **65** (86%)	 **64** (8%)	 **101** (6%)	98%	82% (**65**)
 **66**	$SnCl_4$ (2.5 equiv), MSA (0.5 equiv), CH_2Cl_2, 4 °C, 24 h	 **67** (83)	 **66** (13)	 **102** (4)	96%	78% (**67**)
 **68**	$SnCl_4$ (2.5 equiv), MSA (0.5 equiv), CH_2Cl_2, 4 °C, 24h	 **69** (84%)	 **68** (8%)	 **100** (8%)	90%	78% (**69**)
 **70**	$SnCl_4$ (2.5 equiv), CH_2Cl_2, rt, 24 h	 **71** (81)	 **70** (9)	 **48** (10)	97%	64% (**71**)
 **72**	$SnCl_4$ (2.5 equiv), CH_2Cl_2, rt, 24 h	 **73** (54)	 **72** (46)	 **43** (n.d.)	97%	34% (**73**)
 **74**	$SnCl_4$ (2.5 equiv), CH_2Cl_2, rt, 24 h	 **75** (91%)	 **74** (9%)	 **97** (n.d.)	97%	90% (**75**)
 **104**	$SnCl_4$ (2.5 equiv), CH_2Cl_2, rt, 24 h	 **59** (75)	 **104** (20)	 **105** (5)	74%	51% (**59**)
a: n.d. = not detected by ^{1}H-NMR spectroscopy. b: yield after flash chromatography on a short column of silica gel.						

3.7 Anomerisation in Acetylated Glycosyl Thiols

Equatorial-to-axial anomerisation was also explored in acetylated glycosyl thiols **51** and **54**. It was postulated that coordination between the glycosyl thiol and the Lewis acid would be reduced in an oxygen containing solvent as the solvent molecules could compete to coordinate with the Lewis acid. Carbonyl groups are known to coordinate to Lewis acids such as $SnCl_4$ in both the solid state and in solution, and thus ethyl acetate was used to begin the study. It was speculated that the ethyl acetate would inhibit the formation of a complex between the thiol and $SnCl_4$, that favoured the equatorial anomer, and enable $SnCl_4$ to promote equatorial-to-axial anomerisation.

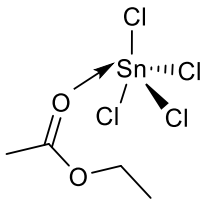
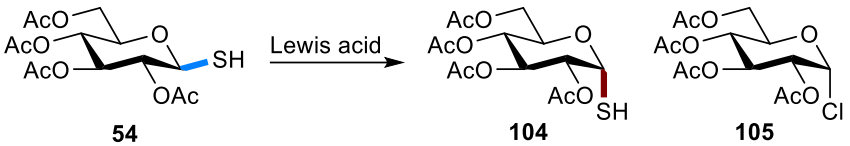


Figure 3.9 Coordination of ethyl acetate to $SnCl_4$

The study began with acetylated glucose thiol **59** and the reaction conditions are summarised in Table 3.20. Little epimerisation took place with $TiCl_4$ at 20 ºC or 4 ºC, using CH_2Cl_2 as a solvent (entries 1-2). If the solvent was changed to a 4:3-EtOAc:CH_2Cl_2 mixture and the concentration of $TiCl_4$ was increased, the axial anomer could be generated in 15% after 48 h (entry 4). $SnCl_4$, in combination with solvent EtOAc, led to an increased rate of epimerisation and increased selectivity for the α-anomer. The axial anomer could be generated in 41% in a 4:3-EtOAc:CH_2Cl_2 mixture at 4 ºC after 24 h (entry 7). Under these conditions, the α-anomer could be isolated in 19%. When the reaction time was increased to 48 h, there was no increase in the percentage of **89** obtained (entry 10). This indicated that the equilibrium was achieved after 24 h. The addition of MSA (0.5 equiv) also did not enhance the selectivity for the α-anomer (entry 9).

Table 3.20 Equatorial-to-axial anomerisation in glucopyranosyl thiol **59**



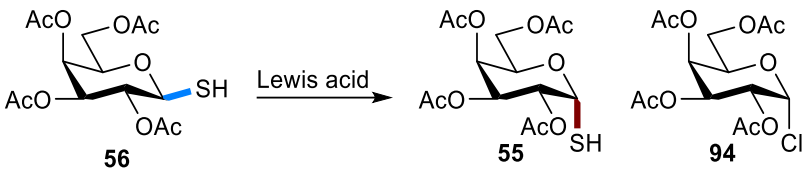
Entry	Time	Temp.	Lewis Acid	Equivalents	Additive	Solvent	%α	%β	%105	Crude % yield
1	24 h	20 °C	$TiCl_4$	2.5	-	CH_2Cl_2	0	100	0	95
2	24 h	4°C	$TiCl_4$	2.5	-	CH_2Cl_2	10	90	0	88
3	24 h	20 °C	$TiCl_4$	2.5	-	EtOAc: CH_2Cl_2 - 4:3	0	100	0	91
4	48 h	20 °C	$TiCl_4$	5	-	EtOAc: CH_2Cl_2 - 4:3	15	85	0	96
5	24 h	20 °C	$TiCl_4$	10	-	EtOAc: CH_2Cl_2 - 4:3	15	85	0	73
6	24 h	20 °C	$SnCl_4$	2.5	-	EtOAc: CH_2Cl_2 - 4:3	35	51	14	80
7[a]	24 h	4°C	$SnCl_4$	2.5	-	EtOAc: CH_2Cl_2 - 4:3	41	59	0	80
8	24 h	-30°C	$SnCl_4$	2.5	-	EtOAc: CH_2Cl_2 - 4:3	12	98	0	87
9	24 h	4°C	$SnCl_4$	2.5	MSA (0.5 equiv)	EtOAc: CH_2Cl_2 - 4:3	40	60	0	78
10	48 h	4°C	$SnCl_4$	2.5	-	EtOAc: CH_2Cl_2 - 4:3	40	60	0	92

a: Under these conditions the axial anomer could be isolated in 19%, after chromatography.

Equatorial-to-axial epimerisation was then explored with acetylated galactose thiol **50**. The axial anomer could be generated in 25% under $SnCl_4$ conditions in a dichloromethane solution at 4 °C (entry 1). If a 3:4 dichloromethane-ethyl acetate solution was employed under the same conditions, then the percentage of the axial anomer increased to 41% (entry 4), which was the best conditions attained. The axial anomer could be isolated from this reaction mixture in a

21% yield. $TiCl_4$-catalysed anomerisation in a 3:4 dichloromethane-ethyl acetate solution led to a small percentage of the axial anomer generated (entry 5).

Table 3.21 Equatorial-to-axial anomerisation in galactopyranosyl thiol **56**



Entry	Time	Temp.	Lewis Acid	Equivalents	Solvent	%α	%β	%94	Crude % yield
1	24 h	4 ºC	$SnCl_4$	2.5	CH_2Cl_2	25	75	n.d.	74
2	24 h	-30 ºC	$SnCl_4$	2.5	CH_2Cl_2	15	85	n.d.	77
3	24 h	20 ºC	$SnCl_4$	2.5	EtOAc: CH_2Cl_2 - 4:3	39	61	n.d.	82
4[a]	24 h	4 ºC	$SnCl_4$	2.5	EtOAc: CH_2Cl_2 - 4:3	41	59	n.d.-	90
5	24 h	20 ºC	$TiCl_4$	2.5	EtOAc: CH_2Cl_2 - 4:3	19	81	n.d.	86

a: Under these conditions, the axial anomer could be isolated in 21%, after chromatography.

3.8 Conclusions

In conclusion, the conditions for equatorial-to-axial anomerisation in benzoylated glycosyl thiols was successfully developed with $TiCl_4$, with moderate to good yields (38-63%). Axial-to-equatorial epimerisation was discovered to possible in glycosyl thiols with $SnCl_4$ and was applied to a wide range of glycosyl thiols, with good yields (34-90%). Ethyl acetate, which can coordinate to Lewis acids such as $SnCl_4$ and $TiCl_4$, was found to somewhat change the selectivity attained in the epimerisation reactions and shift the equilibrium towards the α-anomer. The next chapter will detail the mechanistic study carried out to explain the selectivity obtained in $SnCl_4$ and $TiCl_4$-catalysed anomerisations of glycosyl thiols.

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Chapter 4

An NMR Study into Lewis Acid-Promoted Epimerisation

4.1 Introduction

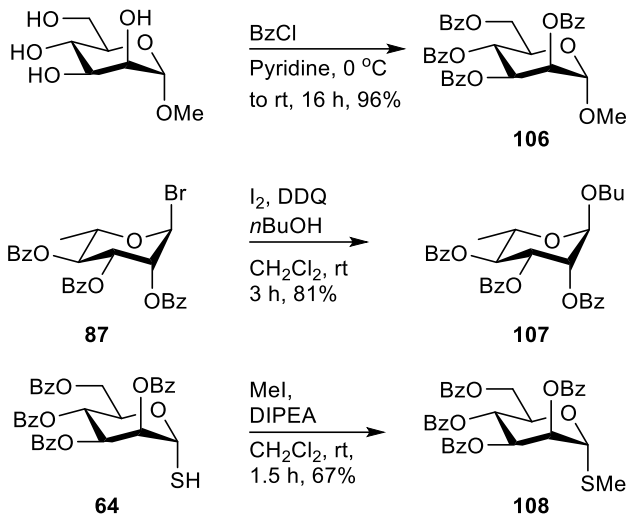
This chapter will detail an NMR study carried out with a view to explaining the stereoselectivity of the Lewis-acid catalysed epimerisation of glycosyl thiols. It was notable that opposing selectivities could be ascertained through the treatment of glycosyl thiols with two different Lewis acids (with the exception of one glycosyl thiol).

An initial objective was to confirm whether the equatorial selectivity achieved with $SnCl_4$ was limited to glycosyl thiols or if there was any axial-to-equatorial epimerisation in *O*- or *S*-glycosides. A second objective was to determine by NMR spectroscopy whether there was a complex forming between the glycosyl thiol and Lewis acid and whether this played a part in influencing the stereoselectivity. Within this study, each glycosyl thiol gave axial selectivity under $TiCl_4$-chelated anomerisation, with the exception of rhamnose thiol **68**, which was selective for the β-anomer. The β-selectivity obtained was unusual and through an NMR study an explanation was sought. Finally, whether the 2-acyl group was required for anomerisation to proceed in glycosyl thiols was investigated.

4.2 Selectivity to Glycosyl Thiols

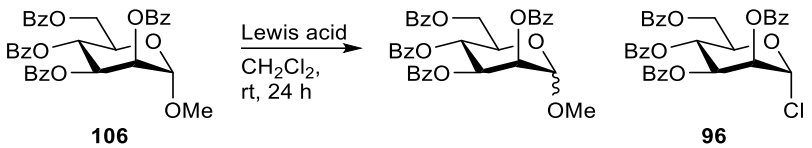
First, it was ascertained whether axial-to-equatorial epimerisation was selective to glycosyl thiols. A number of *O*- and *S*-glycosides were synthesised as outlined in Scheme 4.1. The *O*-mannopyranoside **90** was prepared by benzoylation of methyl α-D-mannopyranoside in a high yield (96%). The rhamnopyranoside **91** was prepared following a procedure developed by the Lemhler group, as outlined in Chapter 2, in a good yield (81%). Finally, thioglycoside **92** was prepared by treating the thiol precursor with DIPEA and methyl iodide to give the desired product.

It was initially suspected that the substituent at the C-2 position may chelate to the Lewis acid and somewhat explain the selectivity obtained in the 1-thiomannopyranoses and 1-thiorhamnospyranoses. Lewis acid conditions were explored with the axial *O*- and *S*-glycosides. In the reaction of *O*-glycosides **106** and **107**, there was no epimerisation observed and the chlorides **96** and **100** were the main side products. In the reaction of **107** under $TiCl_4$ conditions, chloride **100** was the sole product detected after 24 h at 20 ^{o}C (entry 2 in Table 4.2).



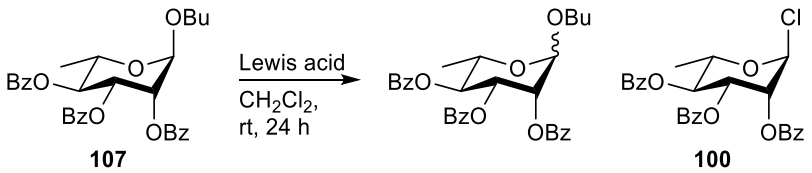
Scheme 4.1 Synthesis of axial *O*- and *S*-glycosides

Table 4.1 Epimerisation of *O*-mannopyranoside **106**



Entry	Time	Temp.	Lewis acid	Equivalents	%α	%β	%96	Crude % yield
1	24 h	20 °C	$TiCl_4$	2.5	83	-	17	88
2	24 h	20 °C	$SnCl_4$	2.5	100	-	n.d.	89

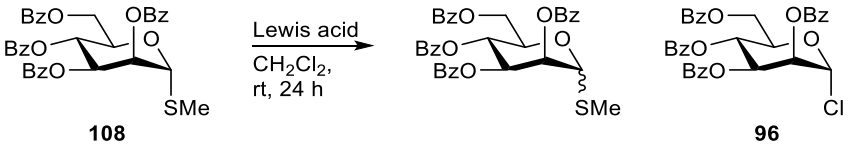
Table 4.2 Epimerisation of *O*-rhamnopyranoside **107**



Entry	Time (h)	Temp.	Lewis acid	Equivalents	%α	%β	%100	Crude % yield
1	24 h	20 °C	$TiCl_4$	2.5	-	-	100	93
2	24 h	20 °C	$SnCl_4$	2.5	98	-	2	98

In the epimerisation of thioglycoside **108**, the β-anomer accounted for 17% of the reaction mixture after 24 h under $SnCl_4$-chelated conditions. The addition of MSA (0.5 equiv) did not increase the selectivity for the equatorial anomer but rather led to the generation of the chloride side product in 20%, after 24 h (entry 2).

Table 4.3 Epimerisation of *S*-mannopyranoside **108**



Entry	Time	Temp.	Lewis acid	Equivalents	Additive	%α	%β	%96	Crude % yield
1	24 h	20 ºC	$SnCl_4$	2.5	-	83	17	n.d.	98
2	24 h	20 ºC	$SnCl_4$	2.5	MSA (0.5 equiv)	66	14	20	95

These experiments confirmed that the thiol group was required for axial-to-equatorial epimerisation under $SnCl_4$ conditions as the selectivity was not observed in the absence of the thiol group.

4.3 NMR Study of Glycosyl Thiols with $SnCl_4$

Various glycosyl thiols were studied in the presence of $SnCl_4$ by NMR spectroscopy to gain evidence for a hypothesis that the thiols coordinate to the Lewis acids and this influences stereoselectivity. It was believed that a complex formed in dichloromethane ultimately contributes to defining the anomeric ratio of the glycosyl thiols generated after work-up in the reactions promoted by $SnCl_4$.

Tin is a group 14 post transition metal and has two common oxidation states; +2, and the slightly more stable +4. $SnCl_4$ is used extensively as a catalyst in many organic transformations such as Friedel-Crafts reactions[1] and numerous others.[2] $SnCl_4$ is known to coordinate with heteroatoms like oxygen, nitrogen and sulfur[3] and several crystal structures have been reported, either as $SnCl_4{\cdot}L$ or $SnCl_4{\cdot}L_2$ complexes.[4-7] Tin(IV) Lewis acids tend to form six-coordinate 1:2 or 1:1 complexes, adopting an octahedral geometry. However five-coordinate structures have also been reported.[8] Examples of structures of $SnCl_4$ complexes, based on X-ray crystal structures determined are shown in Figure 4.1.

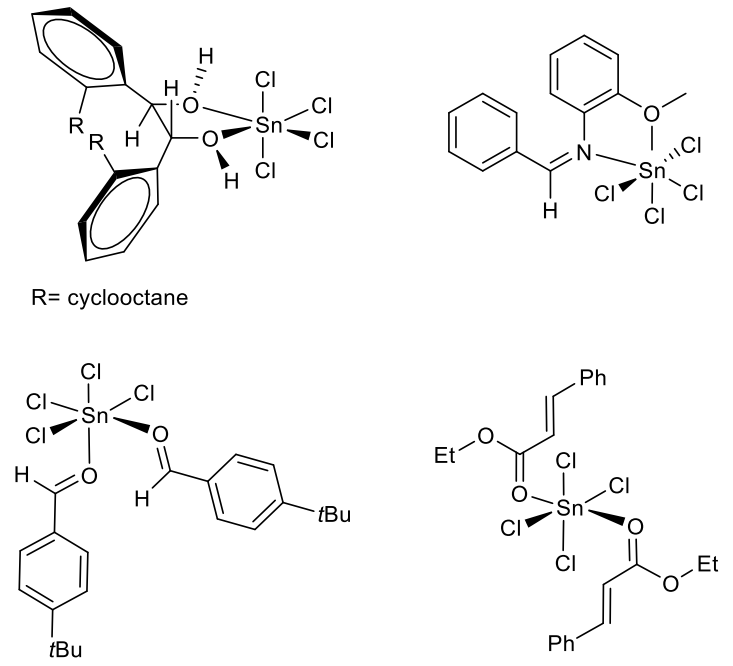


Figure 4.1 Examples of crystal structures of $SnCl_4$-complexes

4.3 1 Gulopyranosyl thiol in presence of $SnCl_4$

To begin the study, NMR analysis of the complex formed between β-gulopyranosyl thiol **75** and $SnCl_4$ (3 equiv) was carried out. The α-gulopyranosyl thiol **74** was dissolved in freshly distilled $CDCl_3$ under an argon atmosphere and $SnCl_4$ (0.34 M in $CDCl_3$) was added in 0.2 mL (1 equiv) additions until 3 equiv had been added.

Herein the complex generated between β-gulopyranosyl thiol **75** and $SnCl_4$ is referred to as **75-$SnCl_4$**. In this species observed in $CDCl_3$ the signal for thiol proton in **75** (δ 2.46 ppm) underwent significant broadening upon the addition of $SnCl_4$. The anomeric proton (δ 5.31 ppm vs δ 5.81 ppm; Δδ = 0.5 ppm) and H-5 proton (δ 4.65 ppm vs δ 4.90 ppm; Δδ = 0.35 ppm) were the most shifted downfield in **75-$SnCl_4$** when compared to **75** (Table 4.4). The other pyranose signals did not change considerably (Δδ < 0.15 ppm). None of the proton signals for the α-thiol **74** under $SnCl_4$ conditions underwent any major shifts (Δδ < 0.04 ppm) and the thiol proton signal at δ 2.26 ppm remained resolved, suggesting it was not coordinating to the Lewis acid.

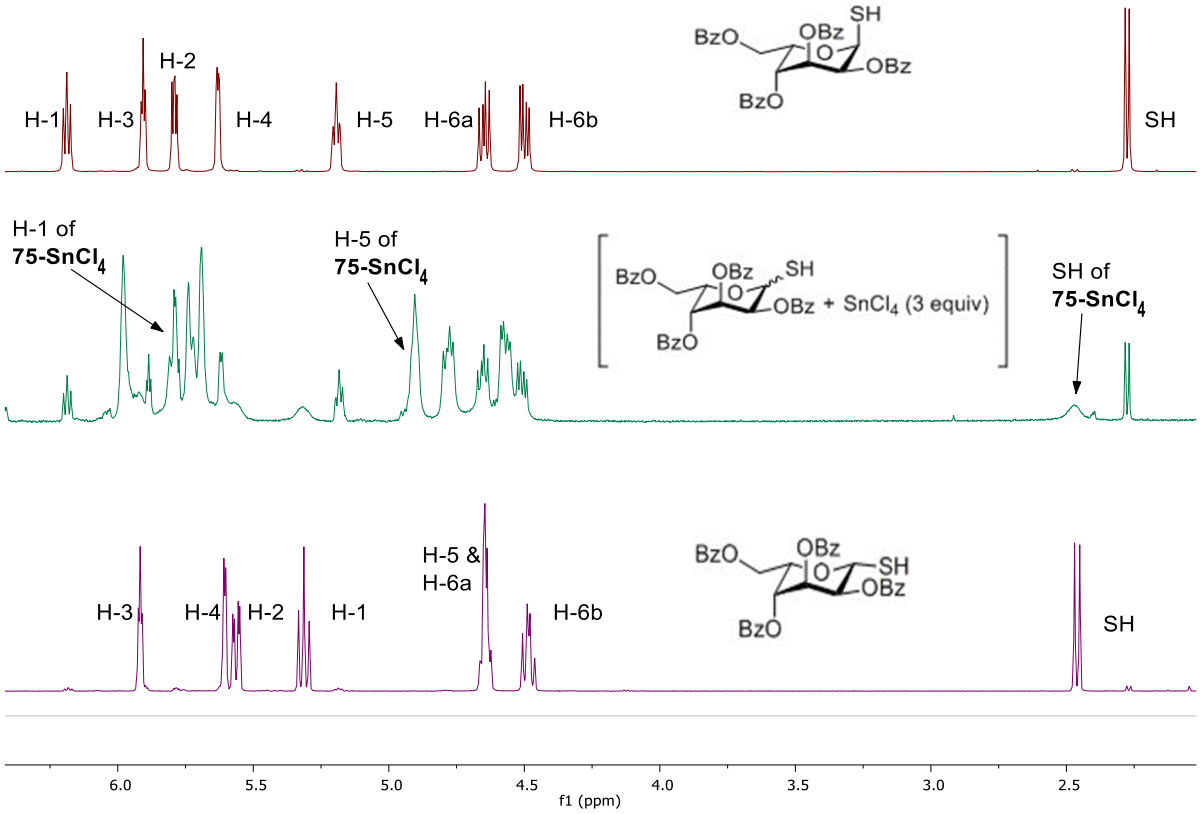


Figure 4.2 ^{1}H NMR spectrum of α-anomer **74** (top spectrum), thiol **74** 4 hours after addition of $SnCl_4$ (3 equiv) (middle spectrum) and β-anomer **75** (bottom spectrum)

Table 4.4 Summary of ^{13}H NMR shifts and *J*-values in **75** and **75-SnCl$_4$**

^{1}H NMR shifts and *J*-values			
Assignment	**75** δ ppm	**75-SnCl$_4$** δ ppm	**Δδ ppm**
H-1	5.31 (t, J = 9.6 Hz)	5.81 (d, *J* = 9.8 Hz)	+ 0.5
H-2	5.56 (dd, *J* = 10.0, 3.2 Hz, 1H)	5.69-5.73 (overlapping signals)	+ 0.15
H-3	5.92 (t, *J* = 3.5 Hz, 1H)	5.97 (br s)	+ 0.05
H-4	5.61 (dd, *J* = 3.8, 1.2 Hz, 1H)	5.69-5.73 (overlapping signals)	+ 0.10
H-5	4.65 (br s) overlaps with H-6a	4.90 (dd, *J* = 6.5, 5.5 Hz)	+ 0.35
H-6a	4.64 (dd) overlaps with H-5	4.79 (dd, J = 12, 6.6 Hz)	+ 0.14
H-6b	4.48 (dd, *J* = 14.0, 8.5 Hz, 1H)	4.58 (dd, *J* = 11.9, 5.4 Hz)?	+ 0.1
SH	2.46 (d, J = 9.6 Hz)	~2.5 (br s)	+ 0.04

In the ^{13}C spectrum of **75-SnCl$_4$**, the most marked shift downfield was for the C-5 carbon (δ 74.14 ppm vs δ 77.83 ppm; Δδ = 3.69 ppm). The C-1 carbon (δ 76.54 ppm vs δ 77.89 ppm; Δδ

= 1.35 ppm) and C-2 carbon (δ 71.33 ppm vs δ 72.24 ppm; Δδ = 0.91 ppm) were also shifted downfield whereas the C-3, C-4 and C-6 signals were all shifted upfield (Δδ < 0.94 ppm). The carbonyl signals in **75-SnCl$_4$** were not discernibly shifted (Δδ < 0.23 ppm). These results suggested that the pyranose oxygen and sulfur atom were involved in chelation to the tin centre. The ^{13}C signals that were apparent for **74** under $SnCl_4$ conditions were not shifted substantially upfield or downfield (Δδ < 0.2 ppm).

Employing ^{119}Sn NMR spectroscopy was useful in determining the nature of the complex of **75-SnCl$_4$**. The ^{119}Sn peak shifted to -153.2 ppm after the addition of $SnCl_4$ (3 equiv) to **74** (after 10 hours), while free $SnCl_4$ appeared at δ -149 ppm. This further supported the hypothesis that a complex was forming between the β-glycosyl thiol and Lewis acid.

Table 4.5 Summary of ^{13}C NMR shifts in **75** and **75-SnCl$_4$**

^{13}C NMR shifts			
Assignment	**75** δ ppm	**75-SnCl$_4$** δ ppm	**Δδ ppm**
C-1	76.54	77.89	+ 1.35
C-2	71.33	72.24	+ 0.91
C-3	68.03	67.09	- 0.94
C-4	68.69	68.55	- 0.14
C-5	74.14	77.83	+ 3.69
C-6	62.49	61.57	- 0.92
C2-C=O	165.18	~165.23	+0.05
C3-C=O	164.5	164.7	+ 0.2
C4-C=O	164.93	164.7	- 0.23
C6-C=O	166.07	166.30	+0.23

4.3 2 Rhamnopyranosyl thiols in presence of SnCl$_4$

Next the rhamnopyranosyl thiol **68** was investigated by NMR spectroscopy in the presence of $SnCl_4$. The thiol **68** (0.068 mmol) was dissolved in $CDCl_3$ (0.75 mL) and 2 equivalents of $SnCl_4$ was added (from a 0.34 M solution in $CDCl_3$). The resulting mixture was analysed by ^{1}H and ^{13}C NMR spectroscopy which provided information on the complex formed between **69** and $SnCl_4$ (**69-SnCl$_4$**).

The doublet (J = 10.0 Hz) at δ 2.61 ppm corresponding to the thiol proton in **69**, was no longer visible as a sharp doublet in the spectrum. The signal for the thiol proton of **69** broadened and

decreased in intensity as $SnCl_4$ was added and a new broad signal appeared downfield between δ 3.20-3.60 ppm for the SH. The integration for this signal, assigned to the SH in **69-SnCl₄**, was equal to integration of other signals assigned to the carbohydrate ring protons for **69-SnCl₄** in the spectrum, with **69-SnCl₄** the most abundant species present. The chloride side product **100** was also present in <30%.

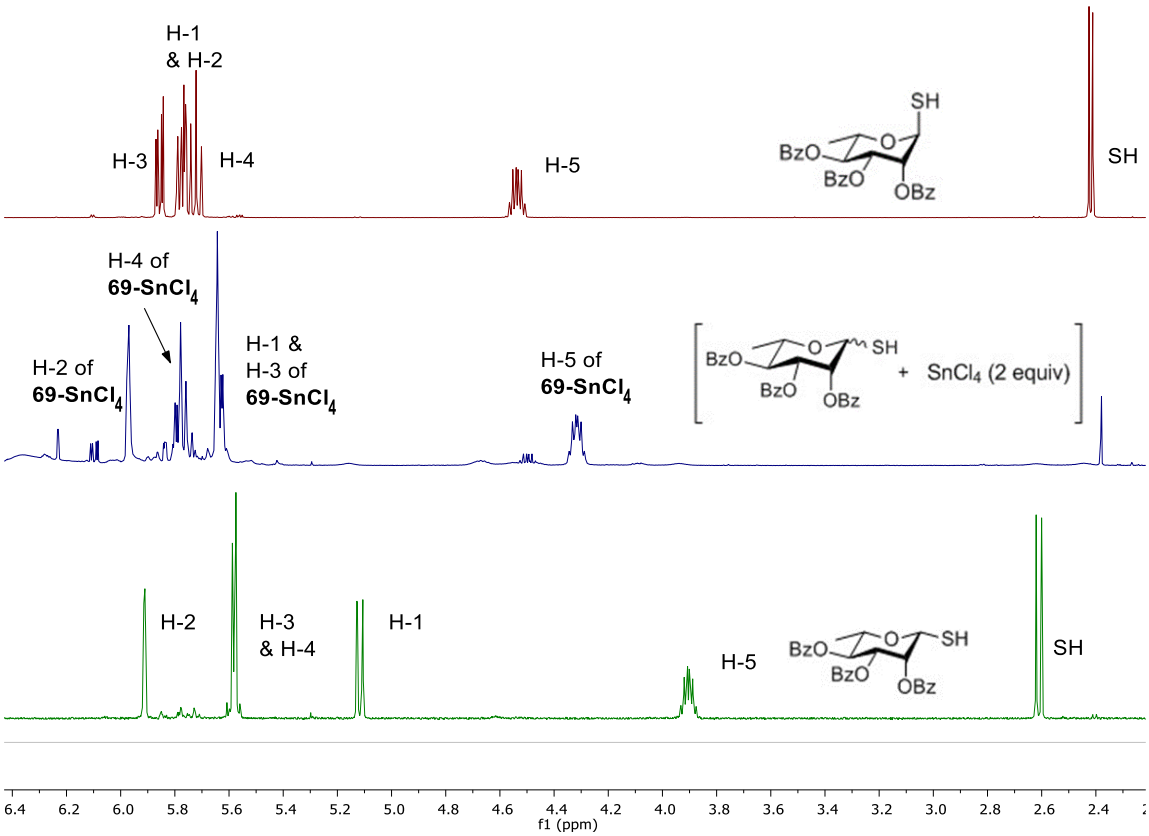


Figure 4.3 ^{1}H NMR spectrum of α-anomer **68** (top spectrum), **69-SnCl₄** complex (middle spectrum) and β-anomer **69** (bottom spectrum)

Table 4.6 Summary of ^{1}H NMR shifts and J-values in **69** and **69-SnCl₄**

^{1}H NMR shifts and *J*-values			
Assignment	**69** δ ppm	**69-SnCl₄** δ ppm	**Δδ ppm**
H-1	5.12 (dd, *J* = 10.1, 1.3 Hz)	5.64 (overlapping peaks)	+ 0.52
H-2	5.91 (q, *J* = 1.2 Hz)	5.97 (d, *J* = 3.4 Hz)	+ 0.06
H-3	5.58 (overlapping signals)	5.64 (overlapping peaks)	+ 0.06
H-4	5.58 (overlapping signals)	5.77 (dd, *J* = 9.3, 2.4 Hz)	+ 0.19
H-5	3.90 (dq, *J* = 9.4, 6.3 Hz)	4.31 dq, *J* = 11.4, 6.0 Hz)	+ 0.41
CH_3	1.44 (d, *J* = 6.3 Hz)	1.59 (d, *J* = 6.3 Hz)	+ 0.18
SH	2.61 (d, *J* = 10.0 Hz)	~3.40 br s	+ 0.79

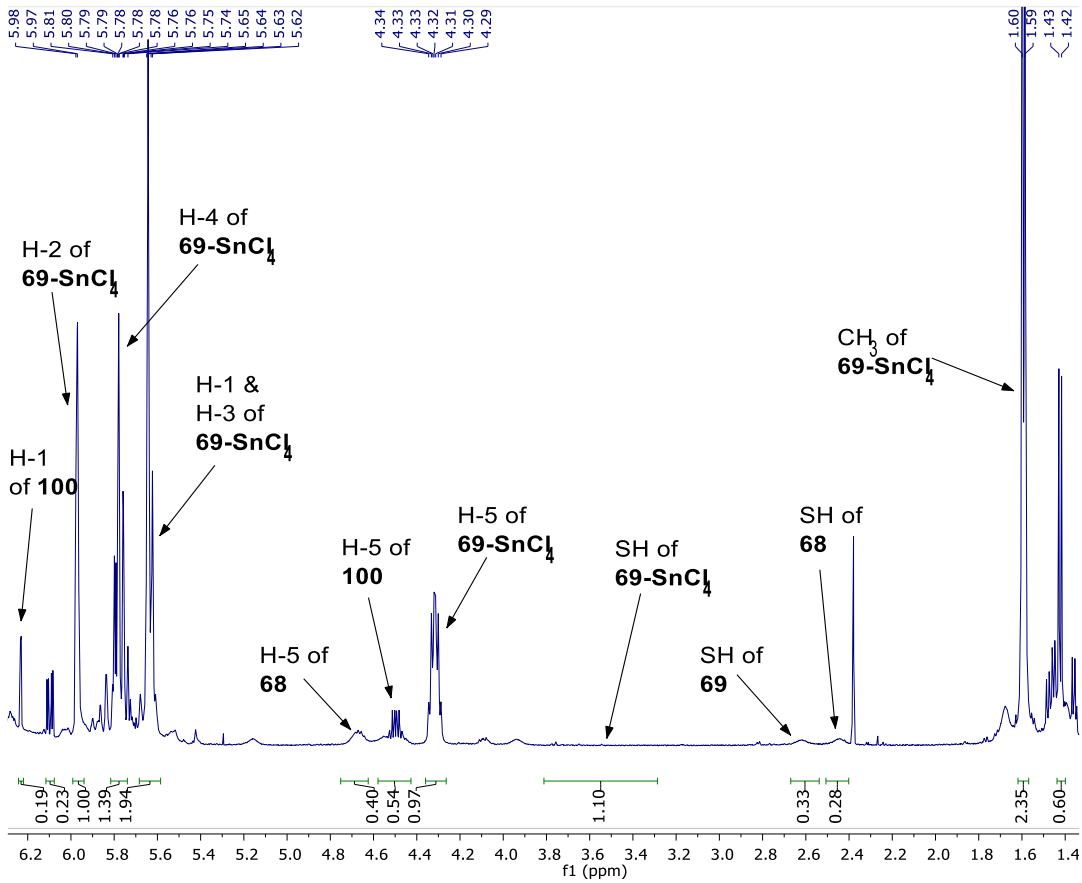


Figure 4.4 ^{1}H-NMR spectrum of the mixture generated after treating **68** with $SnCl_4$ (2 equiv) and left overnight

The anomeric proton (Δδ = 0.42 ppm) and the pyranose H-5 proton (Δδ = 0.41 ppm) in **69-SnCl$_4$** were shifted the furthest downfield, in comparison to **69**. The other signals in the pyranose ring H-2 (Δδ = 0.06 ppm), H-3 (Δδ = 0.06 ppm) and H-4 (Δδ = 0.19 ppm) were shifted to a lesser degree. The methyl group was also shifted slightly downfield (δ 1.44 ppm vs δ 1.59 ppm; Δδ = 0.15 ppm). It was concluded that the pyranose ring maintains its $^{1}C_4$ conformation based upon the coupling constants observed in the ^{1}H-NMR spectrum.

Analysis of the ^{13}C-NMR spectrum of **69-SnCl$_4$** proved valuable in determining the nature of the $SnCl_4$ complex. The greatest shifts downfield in the ^{13}C-NMR spectrum of **69-SnCl$_4$** were for the anomeric carbon (δ 80.3 ppm vs δ 76.8 ppm; Δδ = 3.7 ppm) and for the pyranose C-5 (δ 79.2 ppm vs δ 75.7 ppm; Δδ = 3.5 ppm). In contrast, the signals for the C-2 (δ 72.7 ppm vs δ 69.4 ppm; Δδ = -3.3 ppm) and C-4 (δ 70.8 ppm vs δ 69.6 ppm; Δδ = -3.1 ppm) carbons were shifted upfield. No significant shifts upfield or downfield of more than 0.3 ppm were observed

for the carbonyl peaks. Work-up of this mixture led to hydrolysis of the complex with $SnCl_4$ present and gave a product which contained mostly **69**.

Table 4.7 Summary of ^{13}C NMR shifts in **69** and **69-SnCl4**

^{13}**C NMR shifts**			
Assignment	**69** δ ppm	**69-SnCl4** δ ppm	**Δδ ppm**
C-1	76.7	80.3	+ 3.6
C-2	72.7	69.4	- 3.3
C-3	72.7	72.0	- 0.7
C-4	70.8	69.6	- 1.2
C-5	75.7	79.2	+ 3.5
CH_3	18.0	17.0	- 1.0
C-2-C=O	165.6	165.8	+ 0.2
C-3-C=O	165.6	165.9	+ 0.3
C-4-C=O	165.6	165.3	- 0.2

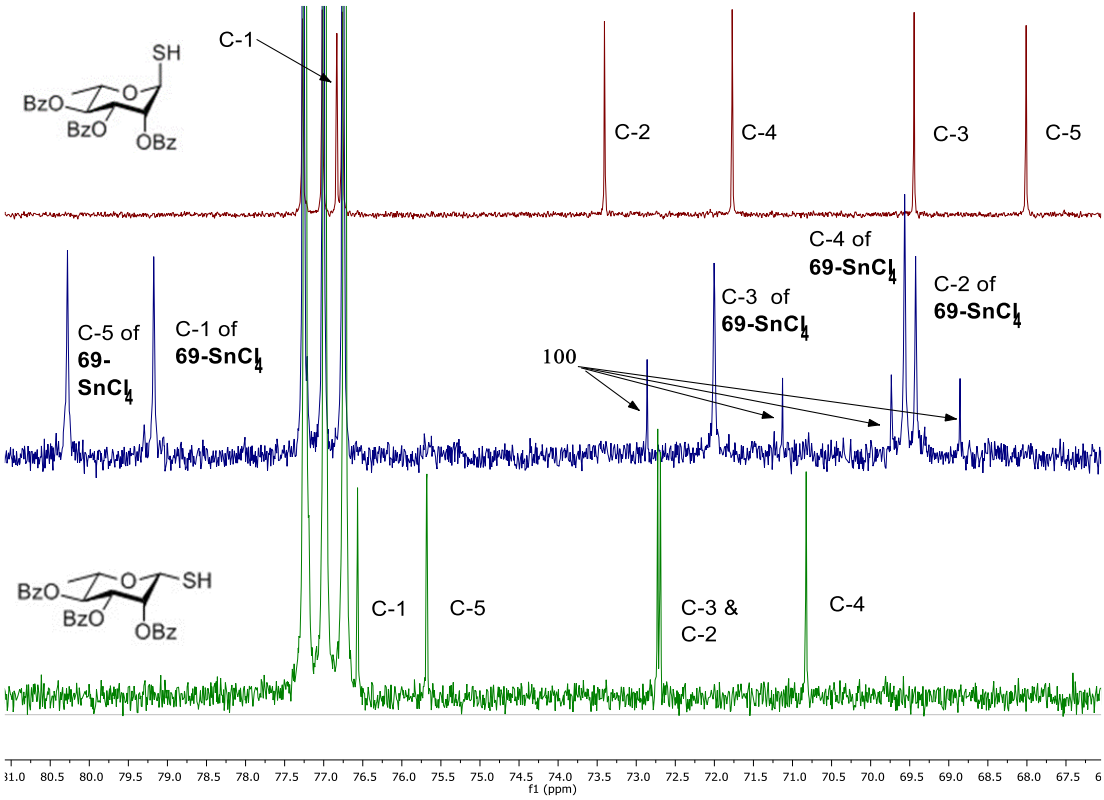


Figure 4.5 ^{13}C NMR spectra of **68** (top spectrum), **69-SnCl4** (middle spectrum) and **69** (bottom spectrum)

The use of ^{119}Sn NMR spectroscopy proved diagnostic for probing the interaction of $SnCl_4$ with **69** in dichloromethane. There was peak at δ -149 ppm in the proton decoupled ^{119}Sn NMR spectrum for free $SnCl_4$ (0.9 M solution in $CDCl_3$) whereas on addition of **68**, with the colourless solution becoming a brick red colour, the ^{119}Sn peak shifted to -188.9 ppm, consistent with formation of a hexavalent tin complex in solution. In a proton coupled ^{119}Sn NMR spectrum, a resolved doublet (*J*= 59.5 Hz) was observed.

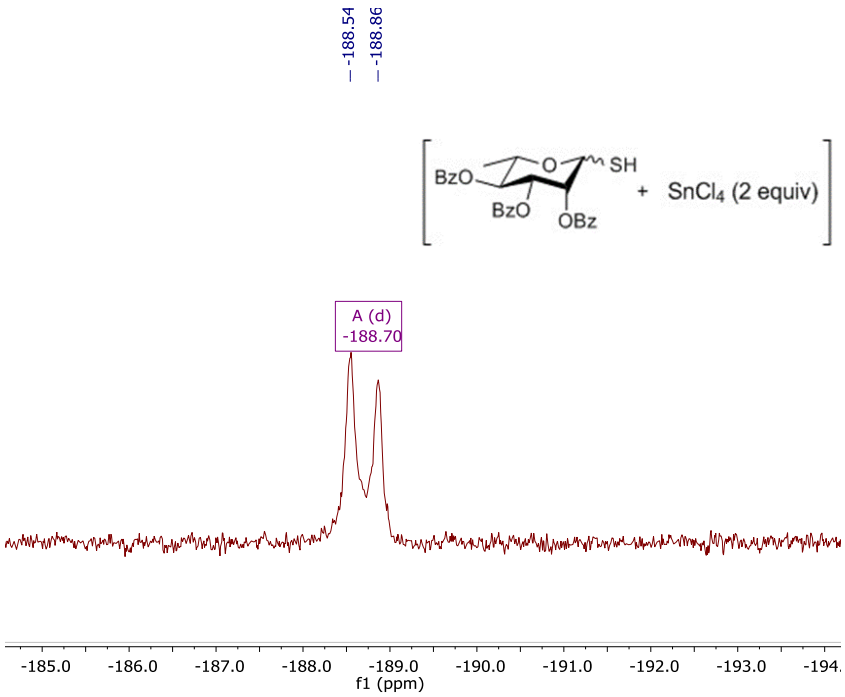


Figure 4.6 Coupled ^{119}Sn spectrum of **69-SnCl$_4$**

Based on the data collated, it was proposed that a complex formed with the pyranose oxygen atom and the thiol group of **69** coordinating to $SnCl_4$ (Figure 4.7). Numerous attempts were made to crystallise this complex with little success. An amorphous powder was repeatedly obtained in crystallisation experiments.

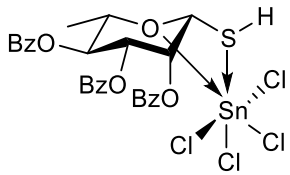


Figure 4.7 Proposed structure of **69-SnCl$_4$**

The acetylated 1-thiorhamnose **66** was then investigated treated with $SnCl_4$ (2 equiv) in $CDCl_3$ (0.75 mL) and the resulting complex (**67-SnCl$_4$**) was analysed by NMR spectroscopy. It was noted in the ^{1}H NMR spectrum for **67-SnCl$_4$**, that the doublet for the thiol proton in **67** (δ 2.49

ppm) was broadened and decreased in intensity. In comparison to the β-thiol **67**, the H-1 proton (δ 4.86 ppm vs δ 5.32 ppm; Δδ = 0.46 ppm) was notably shifted downfield in **67-SnCl$_4$**, as well as the H-5 proton (δ 3.56 ppm vs δ 3.94 ppm; Δδ = 0.38 ppm). The H-4 proton (Δδ = 0.19 ppm) and methyl group (Δδ = 0.14 ppm) was also shifted slightly downfield. The other signals in the pyranose ring remained unaffected (Δδ < 0.02 ppm).

Table 4.8 Summary of ^{1}H shifts and J-values for **67** and **67-SnCl$_4$**

^{1}H NMR shifts and *J*-values			
Assignment	**67** δ ppm	**67-SnCl$_4$** δ ppm	**Δδ ppm**
H-1	4.86 (dd, *J* = 9.7, 1.2 Hz)	5.32 (s)	+ 0.46
H-2	5.43 (q, *J* = 1.7, 1.2)	5.41 (m)	- 0.02
H-3	5.03 (overlapping with H-4)	5.04 (dd, *J* = 10.1, 3.2 Hz)	+ 0.01
H-4	5.03 (overlapping with H-3)	5.22 (t, *J* = 10.0 Hz)	+ 0.19
H-5	3.56 (m)	3.94 (dq, *J* = 9.6)	+ 0.38
CH_3	1.28 (d, *J* = 6.2 Hz)	1.42 (d, *J* = 6.3 Hz)	+ 0.14
SH	2.49 (d, *J* = 9.7 Hz)	[1]	-
[1]Difficult to determine – may be in baseline or overlapping with other peaks further downfield			

Table 4.9 Summary of ^{13}C NMR shifts in **67** and **67-SnCl$_4$**

^{13}C NMR shifts			
Assignment	**67** δ ppm	**67-SnCl$_4$** δ ppm	**Δδ ppm**
C-1	76.0	78.7	+ 2.7
C-2	72.0	69.3	- 2.7
C-3	72.0	72.0	-
C-4	69.9	69.0	- 0.9
C-5	75.3	79.9	+ 4.6
CH_3	17.7	16.7	- 1.0

Analysis of the ^{13}C NMR spectrum revealed a similar trend in the shifts in comparison to **69-SnCl$_4$**. The C-1 (δ 76.0 ppm vs δ 78.7 ppm; Δδ = 2.7 ppm) and C-5 signals (δ 75.3 ppm vs δ 79.9 ppm; Δδ = 4.6 ppm) were most affected in the complex. The C-2 (Δδ = -0.07 ppm), C-4 (Δδ = -0.09 ppm) and CH_3 (Δδ = -1.0 ppm) peaks were shifted upfield while the C-3 signal remained at the same shift. There was no notable shift in any of the carbonyl signals. Decoupled ^{119}Sn NMR spectroscopy revealed a signal at δ –189.8 ppm, indicating the formation of a

hexavalent complex. It was therefore concluded that the nature of the **67-$SnCl_4$** complex was similar to **69-$SnCl_4$**, where the thiol and pyranose oxygen coordinated to the tin centre.

4.4 NMR Study of Glycosyl Thiols with $TiCl_4$

Titanium (IV) chloride ($TiCl_4$) is a powerful Lewis acid and can be used in a variety of different reactions. For example, it is used as catalyst in reactions such as Friedel-Crafts[9] and Ziegler Natta polymerizations.[10] Titanium is a d-metal block element and has 4 valence electrons. Titanium compounds exhibit oxidation states of -1, 0, +2, +3 and +4, with +4 being the most stable compound by far. Coordination numbers for titanium range from 4 to 8, and the most common is 6, preferring a octahedral arrangment.[11] $TiCl_4$ has an oxidation state of +4 and is subsequently diamagnetic, adopting a tetrahedral shape.

Titanium compounds that have states -1, +2 and +3 are paramagnetic and this is important to consider in the NMR analysis of $TiCl_4$ complexes. Paramagnetic compounds are attracted to an external magnetic field and can be characterised by the presence of unpaired electrons. Diamagnetic compounds, on the other hand, have all electrons paired and are repelled by a magnetic field. The presence of unpaired electrons in a paramagnetic compound results in the metal centre having a relatively long relaxation time. This property causes considerable line broadening in the ^{1}H and ^{13}C NMR spectrum of signals for nuclei in close proximity to the metal centre.[12-13] This was helpful in discerning which nuclei may be close to the titanium centre in analysis of glycosyl thiols in the presence of $TiCl_4$.

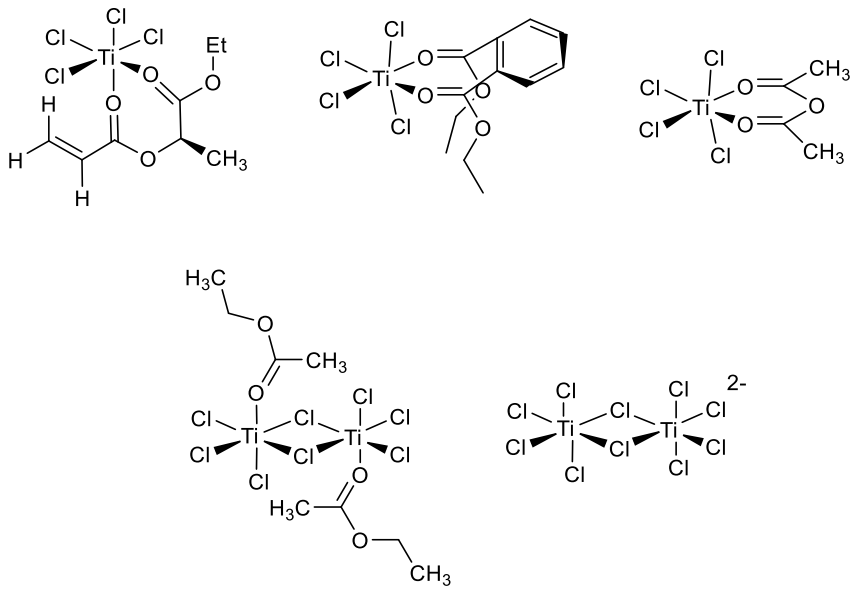


Figure 4.8 $TiCl_4$ complexes based on X-ray crystal structural analysis previously reported

Titanium(IV) Lewis acids typically chelate to Lewis bases, such as oxygen or nitrogen atoms, and show a strong preference for six-coordinate, octahedral configurations.[14-15] Various crystal structures of $TiCl_4$-carbonyl complexes have been reported.[8, 16-19] $TiCl_4$ is known to form binuclear halogen bridges when treated with chloride salts, such as $[Ti_2Cl_9]^-$, $[Ti_2Cl_{10}]^{2-}$ and $[Et_4N]_2[Ti_2Cl_{10}]$.[20]

4.4 1 Gulopyranosyl thiol in presence of $TiCl_4$

Gulopyranosyl thiols **74** and **75** were investigated under $TiCl_4$ conditions using NMR spectroscopy. The β-thiol **75** was dissolved in $CDCl_3$ (0.75 mL) in a flame-dried NMR tube under argon before $TiCl_4$ (0.5 equiv; 0.34 M in $CDCl_3$) was added and the resulting mixture was examined by NMR spectroscopy over time. There were two major species present **74-TiCl₄** and **75-TiCl₄.**

Table 4.10 Summary of ^{1}H shifts and J-values for **74** and **74-TiCl₄**

^{1}H NMR shifts and *J*-values			
Assignment	**74** δ ppm	**74-TiCl₄** δ ppm	**Δδ ppm**
H-1	6.18 (t, J = 6.5 Hz)	6.23 (t, *J* = 6.5 Hz)	+ 0.05
H-2	5.78 (dd, J = 5.8, 3.6)	5.83 (br s)	+ 0.05
H-3	5.89 (t, *J* = 3.8 Hz, 1H)	5.96 (br s)	+ 0.07
H-4	5.62 (d, *J* = 3.9 Hz, 1H)	5.76 (br s)	+ 0.14
H-5	5.18 (t, *J* = 6.4 Hz, 1H)	5.19 (t, *J* = 6.2 Hz)	+ 0.01
H-6a	4.49 (dd, *J* = 11.6, 5.3 Hz, 1H)	4.55 (br s)	+ 0.06
H-6b	4.64 (dd, *J* = 11.6, 7.1 Hz, 1H)	4.80 (br s)	+ 0.16
SH	2.26 (d, J = 7.3 Hz)	2.29 (d, *J* = 7.1 Hz)	+ 0.03

The H-4, H-3 and H-6 protons were all broadened in the ^{1}H NMR spectrum for **74-TiCl₄** in comparison to **74**. This could be an indication that the titanium species was paramagnetic and had oxidation state of +3 or +2, although further study would be needed to confirm this. The signals for protons H-4, H-3 and H-6 are broadened due to their close proximity to the metal centre. The signal for the H-2 proton at δ 5.83 ppm was also slightly broadened while the other signals in the pyranose ring remain resolved and relatively unaffected (Δδ < 0.06 ppm). The shifts for H-4 (Δδ = 0.18) and H-6a (Δδ = 0.16) were shifted the furthest downfield.

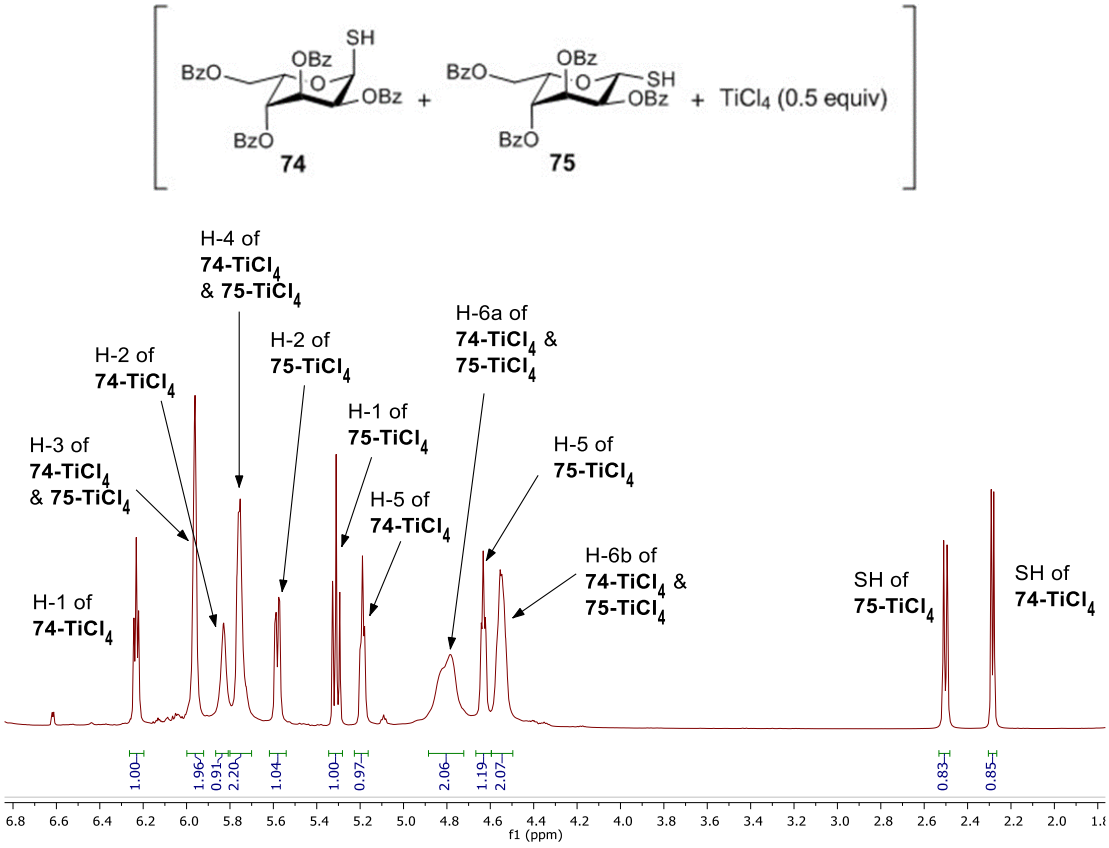


Figure 4.9 ^{1}H NMR spectrum of **74-TiCl4** and **75-TiCl4** after 9 hours

In the ^{13}C NMR spectrum for **74-TiCl4**, the C-3, C-4 and C-6 carbon peaks also were notably broadened. The C-3 (δ 67.62 ppm vs δ 68.97 ppm; Δδ = 0.82 ppm) and C-4 (δ 68.73 ppm vs δ 70.15 ppm; Δδ = 0.84 ppm) signals were shifted downfield. The C-2 and C-5 carbon peak was shifted slight upfield (Δδ = -0.34 ppm; Δδ = -0.15 ppm, respectively), while C-1 and C-6 signals were shifted downfield (Δδ < 0.27 ppm). The signal for C-2 carbonyl peak appeared a sharp singlet at δ 165.15 ppm. The C-3 and C-4 carbonyl signals were difficult to identify due to extreme broadening. Broad signals at δ 166.6 ppm and δ 168.05 ppm were observed and were believed to be carbonyl peaks, but showed no correlation to the H-3 and H-4 protons in the HMBC spectrum. It can be concluded that either the C-3 or C-4 carbonyl coordinates to the titanium centre. The C-6 carbonyl signal was also broadened and shifted downfield (δ ~166.75 ppm vs δ 166.08 ppm; Δδ = ~0.67 ppm).

Table 4.11 Summary of ^{13}C NMR shifts in **74** and **74-TiCl$_4$**

^{13}C NMR shifts			
Assignment	**74** δ ppm	**74-TiCl$_4$** δ ppm	**Δδ ppm**
C-1	76.17	76.08	+ 0.08
C-2	66.68	66.18	- 0.34
C-3	67.62	68.97	+ 0.82
C-4	68.73	70.15	+ 0.84
C-5	65.29	64.72	- 0.15
C-6	62.60	62.76	+ 0.27
C2-C=O	165.20	165.15	+ 0.06
C3-C=O	164.99	166.57, 166.93, 167.71[1]	-
C4-C=O	164.91	166.57, 166.93, 167.71[1]	-
C6-C=O	166.08	~166.75	+ 0.67

[1] broad carbonyl peaks appear at δ 166.57, 166.93 and 167.71 ppm but HMBC shows no correlation to H-3, H-4. Carbonyl signals may belong to **75-TiCl$_4$.**

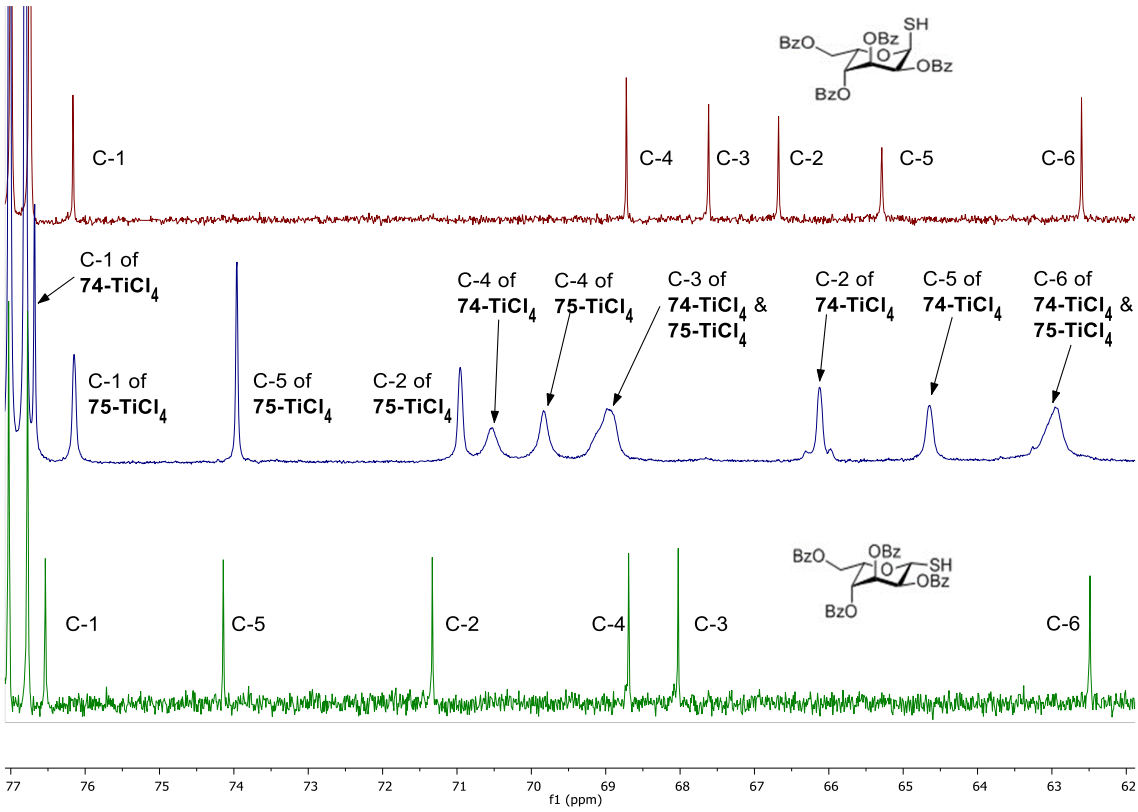


Figure 4.10 ^{13}C (126 MHz) NMR spectra of **74** (top spectrum), **74-TiCl$_4$** and **75-TiCl$_4$** (middle spectrum) and **75** (bottom spectrum)

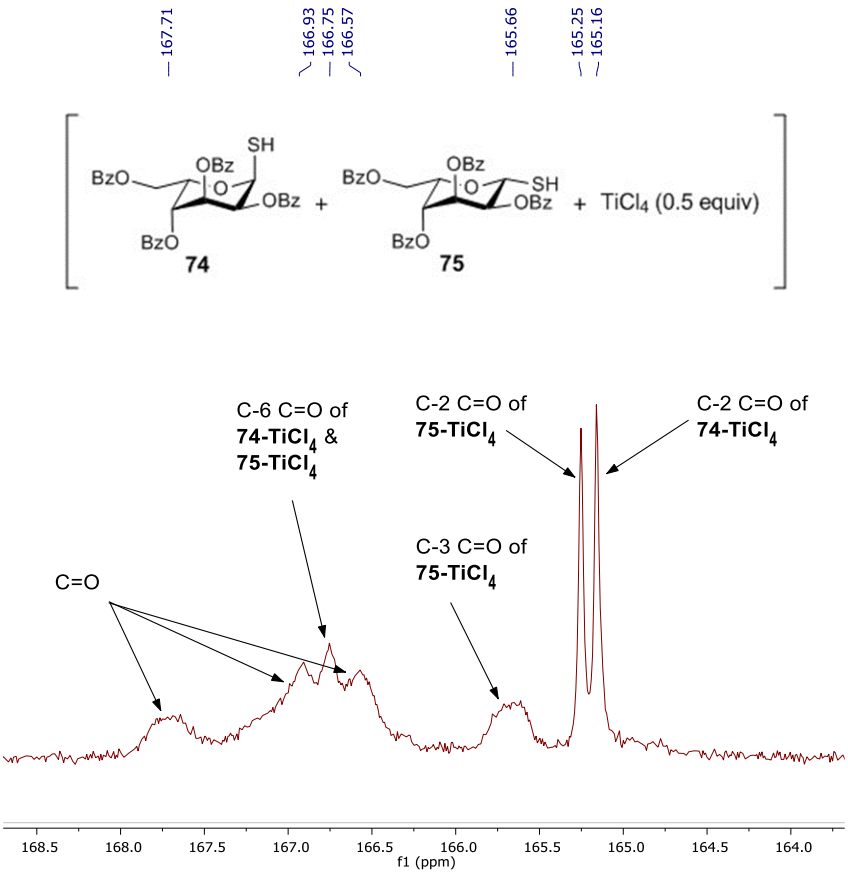


Figure 4.11 Broadening of carbonyl peaks in ^{13}C (126 MHz) spectrum of **74-TiCl$_4$** and **75-TiCl$_4$**

In **75-TiCl$_4$**, broadening was observed in the signals for the H-3, H-4 and H-6 protons in the ^{1}H NMR spectrum. The H-4 (δ 5.61 ppm vs δ 5.76 ppm; Δδ = 0.15 ppm) and H-6a protons (δ 4.64 ppm vs δ 4.80 ppm; Δδ = 0.16 ppm) were the most shifted downfield. The other pyranose protons were all affected by less than Δδ = 0.07 ppm. In the ^{13}C spectrum, the C-3 (Δδ = 0.82 ppm) and C-4 (Δδ = 0.84 ppm) carbon signals were shifted downfield. The C-3, C-4 and C-6 carbons appeared as broad singlets and the other signals in the pyranose ring remained resolved. The peak for the C-3 carbonyl (Δδ = 2.16 ppm) was the most shifted downfield in the spectrum and appeared as a very broad singlet at δ 165.66 ppm. The C-4 carbonyl could not be identified as no correlation to the H-4 proton was observed the gHMBCAD spectrum. The C-2 carbonyl at δ 165.25 ppm was the only carbonyl signal that appeared as a resolved signal, seemingly unaffected in the **75-TiCl$_4$** complex. It can therefore be concluded that the C-3, C-4 or C-6 carbonyl groups may coordinate to $TiCl_4$,

Table 4.12 Summary of ^{1}H shifts and J-values for **75** and **75-TiCl$_4$**

^{1}H NMR shifts and *J*-values			
Assignment	**75** δ ppm	**75-TiCl$_4$** δ ppm	**Δδ ppm**
H-1	5.31 (t, J = 9.6 Hz)	5.31 (t, *J* = 9.8 Hz)	-
H-2	5.56 (dd, *J* = 10.0, 3.2 Hz, 1H)	5.58 (dd, *J* = 10.3, 3.3 Hz)	+ 0.02
H-3	5.92 (t, *J* = 3.5 Hz, 1H)	5.96 (br s)	+ 0.04
H-4	5.61 (dd, *J* = 3.8, 1.2 Hz, 1H)	5.76 (br s)	+ 0.15
H-5	4.65 (overlaps with H-6a)	4.63 (t, *J* = 6.2 Hz)	- 0.02
H-6a	4.64 (dd, overlaps with H-5)	4.80 (br s, overlapping peaks)	+ 0.16
H-6b	4.48 (dd, *J* = 14.0, 8.5 Hz, 1H), looks like q rather than dd	4.55 (br s)	+ 0.07
SH	2.46 (d, J = 9.6 Hz)	2.50 (d, *J* = 9.5 Hz)	+ 0.04

Table 4.13 Summary of ^{13}C NMR shifts in **75** and **75-TiCl$_4$**

^{13}C NMR shifts			
Assignment	**75** δ ppm	**75-TiCl$_4$** δ ppm	**Δδ ppm**
C-1	76.54	76.62	+ 0.08
C-2	71.33	70.99	- 0.34
C-3	68.03	68.85	+ 0.82
C-4	68.69	69.53	+ 0.84
C-5	74.14	73.99	- 0.15
C-6	62.49	62.76	+ 0.27
C2-C=O	165.18	165.25	+ 0.06
C3-C=O	164.5	165.66	+ 2.16
C4-C=O	164.93	166.57, 166.93, 167.71[1]	-
C6-C=O	166.07	~166.75	+ 0.5

[1] broad carbonyl peaks appear at δ 166.57, 166.93 and 167.71 ppm but HMBC shows no correlation to H-3, H-4. Carbonyl signals may belong to **74-TiCl$_4$.**

4.4 2 Rhamnopyranosyl thiol in presence of $TiCl_4$

Reaction of **68** with a 2.5:1 α:β mixture of 2,3,4-tri-*O*-benzoyl-thio-L-rhamnopyranoside with $TiCl_4$, and analysis of the resulting reaction mixture showed that it contained ~68% of the β-anomer. This anomer was subsequently isolated in 40% yield after chromatography. The rhamnopyranosyl thiol **68** was the only thiol within the study to give β-selectivity upon treatment with $TiCl_4$, while the other benzoylated thiols displayed α-selectivity under $TiCl_4$-catalysed conditions and β-selectivity under $SnCl_4$-catalysed conditions. The structures of **68**/**69** in the presence of $TiCl_4$ were investigated using NMR spectroscopy with a view to gaining an explanation for this observation..

The α-thiol **68** was treated with $TiCl_4$ (0.5 equiv) in $CDCl_3$ (0.75 mL) and monitored by NMR spectroscopy over time.. The NMR experiment was also carried out using 2 equivalents of $TiCl_4$ to match conditions used for the preparative method and similar results were obtained. After 10 h, the resulting mixture consisted of three main species - **68-TiCl₄**, **69-TiCl₄** and cation **109**. There was also a small amount of chloride **100** (<8%).

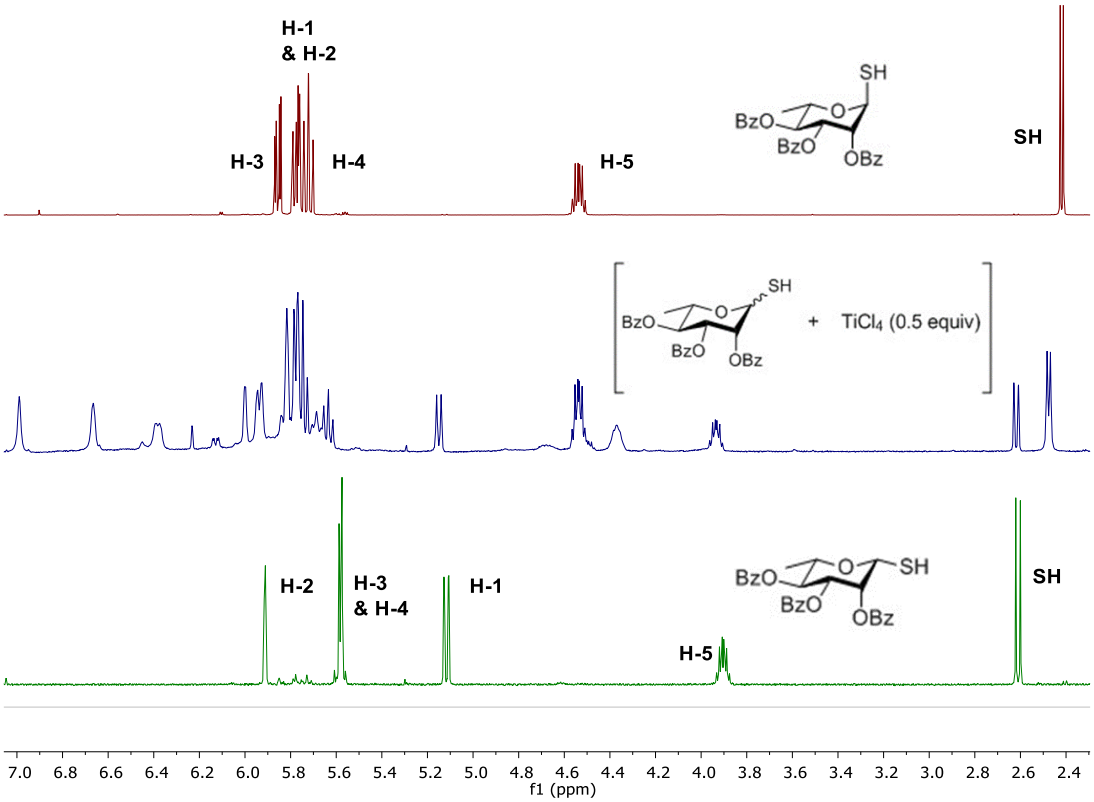


Figure 4.12 ^{1}H NMR spectra of **68** (top spectrum), **68**, 48 hours after addition of $TiCl_4$ (0.5 equiv) (middle spectrum) and **69** (bottom spectrum)

In comparison of **68** to **68-TiCl$_4$**, it was noted that the signal for the SH proton remained unaffected upon the addition of TiCl$_4$, remaining a resolved doublet shifting slightly upfield (δ 2.41 ppm vs δ 2.47 ppm; Δδ = 0.06 ppm). This contrasted the SnCl$_4$-glycosyl thiol complexes where the thiol proton was markedly affected, indicating the sulfur centre did not interact with the titanium centre. Titanium (IV) prefers Lewis bases like oxygen over Lewis bases such as sulfur atoms.[11] The protons in the pyranose ring remained relatively unaffected, with small shifts upfield or downfield (Δδ < 0.09 ppm) . The H-3 proton was shifted the furthest downfield (δ 5.84 ppm vs δ 5.94 ppm; Δδ = 0.09 ppm). In the ^{13}C NMR spectrum, the C-3 (Δδ = 0.68 ppm) and C-4 signals (Δδ = 0.58 ppm) were the most affected.

Table 4.14 Summary of ^{1}H shifts and J-values for **68** and **68-TiCl$_4$**

^{1}H NMR shifts and *J*-values			
Assignment	**68** δ ppm	**68-TiCl$_4$** δ ppm	**Δδ ppm**
H-1	5.78 (dd, *J* = 7.1, 1.5)	5.78 (d, *J* = 7.0 Hz)	-
H-2	5.75 (dd, *J* = 3.3, 1.7)	5.81 (overlapping)	+ 0.06
H-3	5.84 (dd, *J* = 10.1, 3.3)	5.93 (d, *J* = 9.8 Hz)	+ 0.09
H-4	5.71 (t, *J* = 9.9)	5.74 (t, *J* = 9.8 Hz)	+ 0.03
H-5	4.53 (dq, *J* = 9.7, 6.3)	4.54 (dd, *J* = 9.7, 6.1 Hz)	+ 0.01
CH$_3$	1.38 (d, *J* = 6.2)	1.40 (d, *J* = 6.2 Hz)	+ 0.02
SH	2.41 (d, *J* = 6.8)	2.47 (d, *J* = 7.1 Hz)	+0.06

Table 4.15 Summary of ^{13}C NMR shifts in **68** and **68-TiCl$_4$**

^{13}C NMR shifts			
Assignment	**68** δ ppm	**68-TiCl$_4$** δ ppm	**Δδ ppm**
C-1	76.8	77.20	+ 0.4
C-2	73.4	73.57	+ 0.17
C-3	69.4	70.08	+ 0.68
C-4	71.8	72.39	+ 0.59
C-5	68.0	67.95	- 0.05
CH$_3$	17.6	17.54	- 0.06

In the ^{1}H NMR spectrum containing **69-TiCl$_4$**, the most notable shift was for the H-4 signal (δ 5.58 ppm vs δ 5.74 ppm; Δδ = 0.16 ppm). The other signals in the pyranose ring were all

affected by less by Δδ = 0.09 ppm and the signal for the thiol proton remained a resolved doublet at δ 2.62 ppm.

Table 4.16 Summary of ^{1}H shifts and J-values for **69** and **69-TiCl$_4$**

^{1}H NMR shifts and *J*-values			
Assignment	**69** δ ppm	**69-TiCl$_4$** δ ppm	**Δδ ppm**
H-1	5.12 (dd, *J* = 10.1, 1.3 Hz)	5.15 (d, *J* = 9.9 Hz)	+ 0.03
H-2	5.91 (q, *J* = 1.2 Hz)	6.00 (d, *J* = 3.3 Hz)	+ 0.09
H-3	5.58 (overlapping signals)	[1]	-
H-4	5.58 (overlapping signals)	5.74 (t, *J* = 9.8 Hz)	+ 0.16
H-5	3.90 (dq, *J* = 9.4, 6.3 Hz)	3.93 (dt, *J* = 12.2, 6.2 Hz	+ 0.03
CH_3	1.44 (d, *J* = 6.3 Hz)	1.44 (d, *J* = 6.1 Hz)	-
SH	2.61 (d, *J* = 10.0 Hz)	2.62 (d, *J* = 10.0 Hz)	+ 0.01
[1]Difficult to determine shift of H-3 signal due to broadening and overlapping signals			

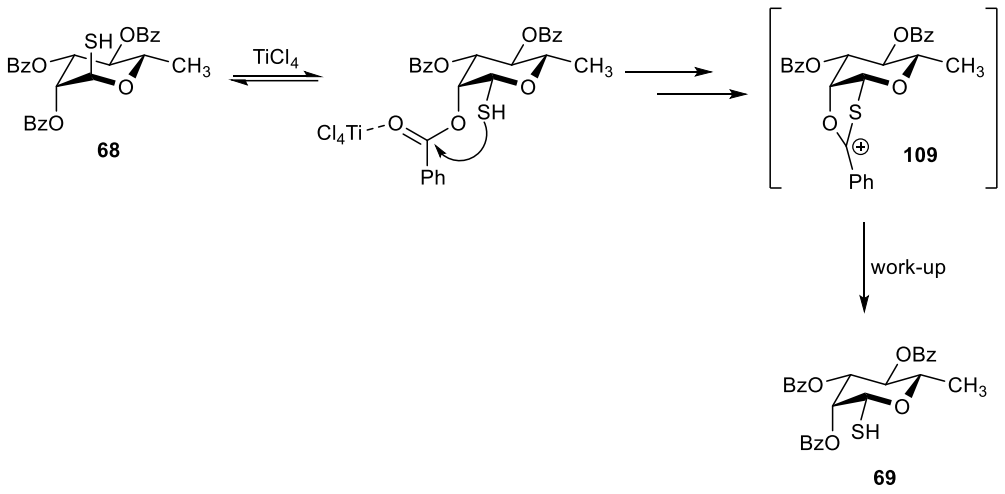
Table 4.17 Selected ^{13}C NMR signals in **69** and **69-TiCl$_4$**

^{13}C NMR shifts			
Assignment	**69** δ ppm	**69-TiCl$_4$** δ ppm	**Δδ ppm**
C-1	76.7	76.52	- 0.18
C-2	72.7	73.01	+ 0.31
C-3	72.7	-	-
C-4	70.8	71.20	+ 0.40
C-5	75.7	75.57	- 0.13
CH_3	18.0	17.97	- 0.03

The appearance of new set of a signals during the NMR experiment, later deduced to be 2-phenyl-1,3-oxathiolan-2-ylium cation **109**, indicated that $TiCl_4$ also induced nucleophilic attack of the thiol at the C-2 carbonyl group, *cis* to the thiol, shifting the equilibrium towards **69** after work-up and thus explaining the β-selectivity obtained. 1,3-Oxathiolium cation and related heterocyclic cations have been reported by various groups in the past.[21-22]

The carbenium carbon atom of **109** was identified by a distinctive signal in the ^{13}C spectrum at δ 214.9 ppm. The signals for C-2 (δ 96.5 ppm; Δδ = +23.8 ppm) and C-1 (δ 86.4 ppm; Δδ = +8.7 ppm) of the cationic species are shifted significantly downfield compared to those of free

69, and support the presence of the nearby positively charged carbon. Work up of this mixture gave a 1:1 mixture of the thiols.



Scheme 4.2 Formation of 2-phenyl-1,3-oxathiolan-2-ylium cation **109**

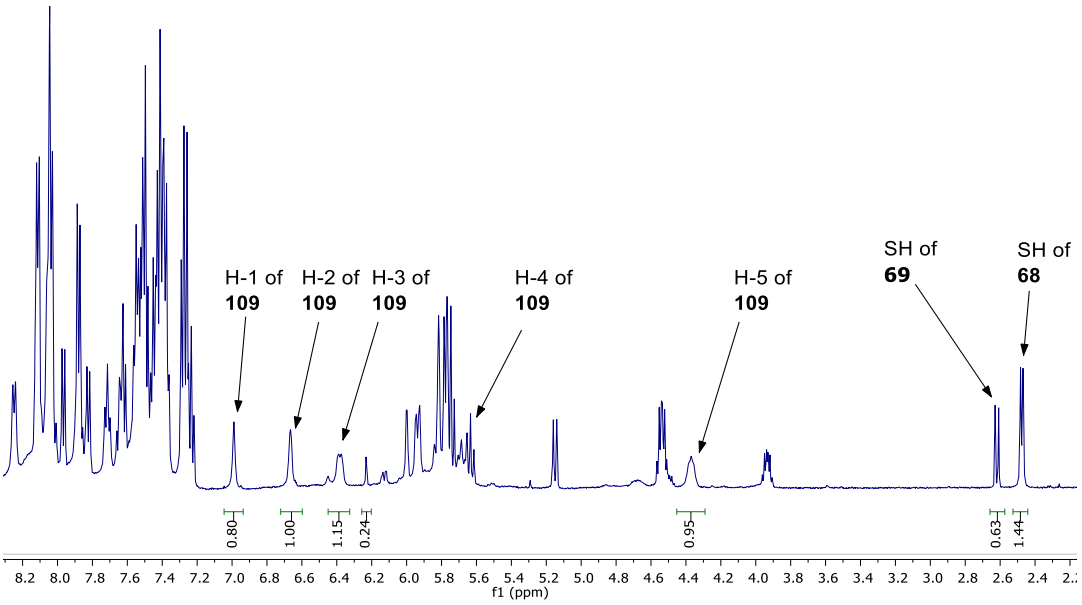


Figure 4.13 ^{1}H NMR (500 MHz) spectrum after treatment of **68** with $TiCl_4$ (0.5 eq) in $CDCl_3$ shows signals for **109**.

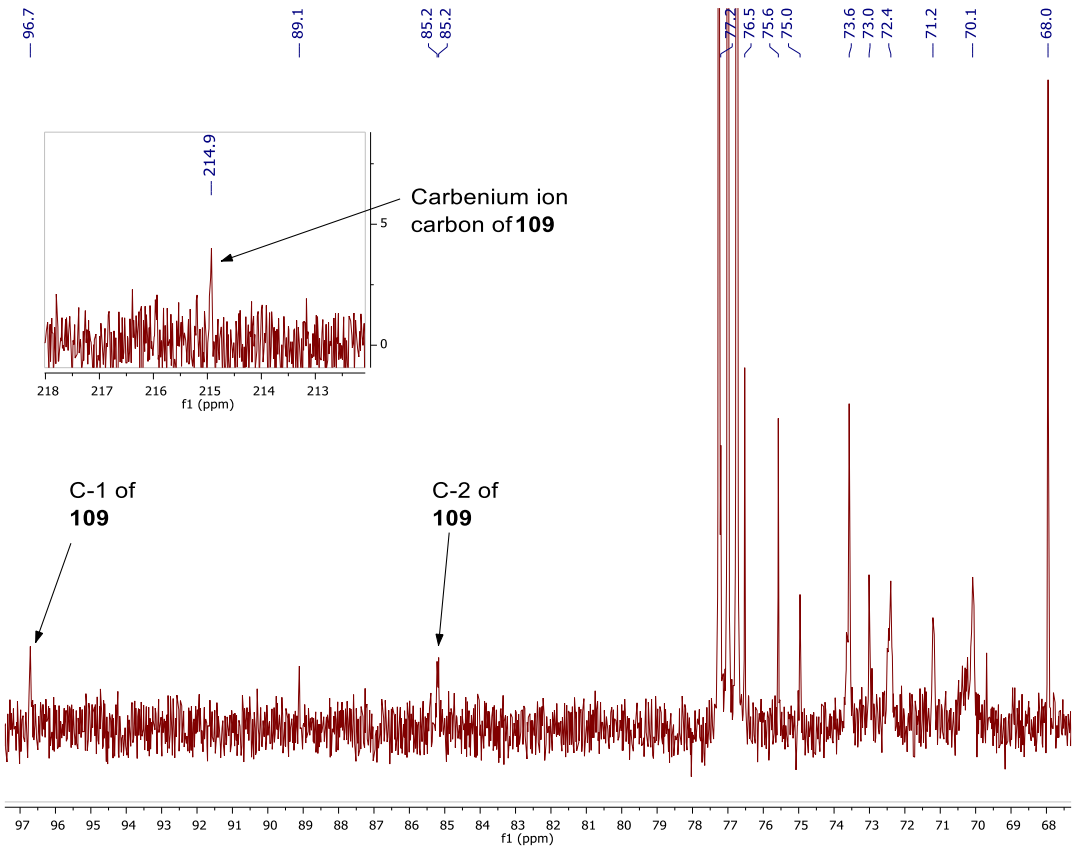
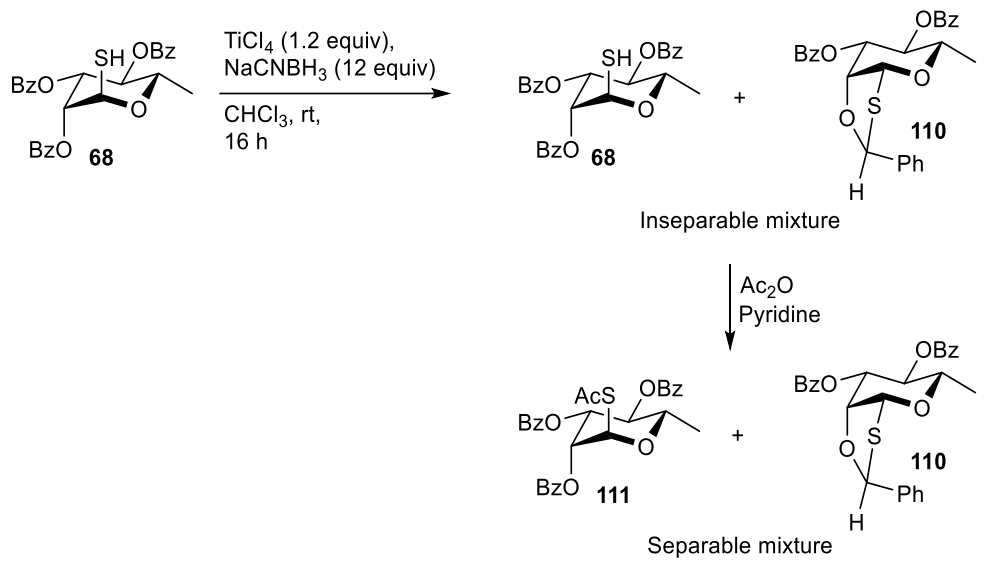


Figure 4.14 ^{13}C NMR (126 MHz) spectrum after treatment of **68** with $TiCl_4$ (0.5 eq) in $CDCl_3$ shows signals for **109**.

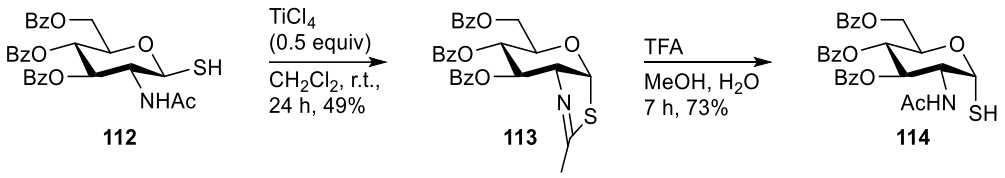
The detection of the cation **109** in the NMR study of rhamnose thiol **68**, encouraged attempts to trap this intermediate *in-situ*, to provide further evidence of its structure. Sodium cyanoborohydride was used as a hydride source with a view to this. The axial rhamnopyranosyl thiol **68** was treated with $TiCl_4$ (1.2 equiv) and sodium cyanoborhydride (12 equiv) in $CHCl_3$ to give **110** and **68** as an inseparable mixture after column chromatography. The mixture was then acetylated to give **110** and acetylated thiol **111** which were separated by chromatography. The formation and isolation of **110** gave further support to the generation of **109**.



Scheme 4.3 Isolation of **110**

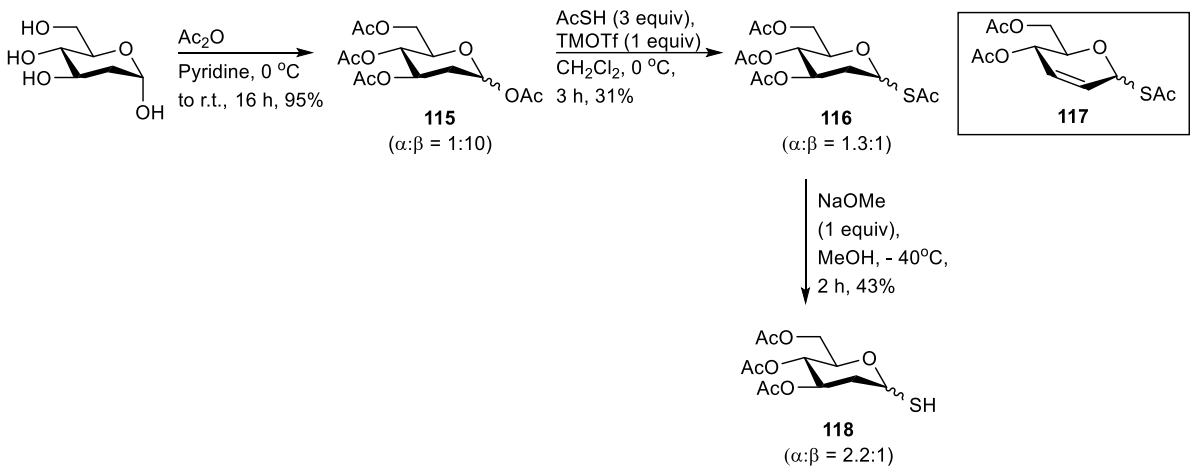
4.5 Role of C-2 substituent

NMR analysis of **68** under $TiCl_4$-conditions revealed the C-2 acyl-containing substituent had a role in influencing the stereochemical outcome of the epimerisation reaction. This indicated that the configuration of the C-2 *O*-acyl group is important in determining the stereochemical outcome of the anomerisation, at least in the $TiCl_4$-promoted anomerisation of **68**. Further evidence came from Claudia Di Salvo,[23] who carried out research into the anomerisation of thiol derivatives of GlcNAc and GalNAc. Di Salvo found that under $TiCl_4$-catalysed conditions with GlcNAc derivative **112**, the stable dihydrothiazole could be formed and isolated. This was subsequently hydrolysed to give the free thiol **114.**



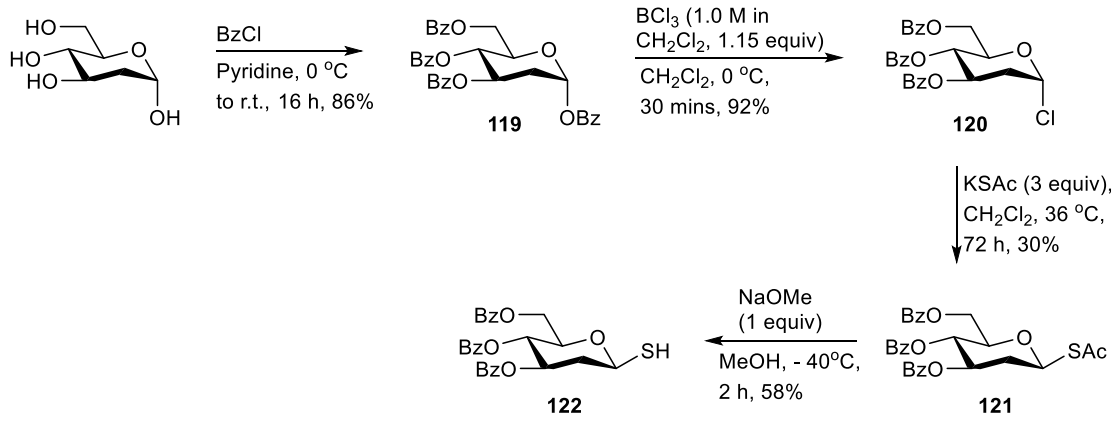
Scheme 4.4 Formation of dihydrothiazole **113** and subsequent hydrolysis to give axial thiol **114**

It was next decided to investigate whether the C-2 substituent is necessary for stereoselective of glycosyl thiols or if the reaction can proceed in a similar manner in the absence of this group. The 2-deoxy derivatives **118** and **122** were synthesised in order to investigate this.



Scheme 4.5 Synthesis of glycosyl thiol **118**

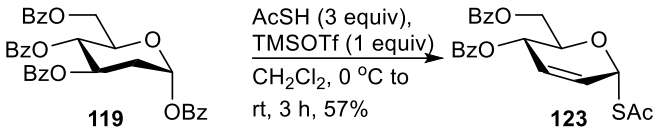
For glycosyl thiol **118**, 2-deoxy-D-glucose was peracetylated (95%) and then treated with thioacetic acid and TMSOTf to generate corresponding thioacetate **116** (31%). This step also resulted in the formation of elimination product **117**[24] (~13%) and contributed to the low yield obtained. The thioacetate group was selectively deprotected with sodium methoxide at – 40 °C to yield the desired product **118** (43%). Similar conditions were employed in an attempt to synthesise glycosyl thiol **122** using TMSOTf and thioacetic acid but resulted in the elimination product **123** only being formed (Scheme 4.7). The reaction was cooled to -40 °C to try and curb the formation of side-product **123**, but led to a complicated mixture of products.



Scheme 4.6 Synthesis of glycosyl thiol **122**

Glycosyl thiol **122** was synthesised beginning with the perbenzoylation of 2-deoxy-D-glucose in a good yield (86%). The chloride **120** was generated in a high yield (92%), by reacting **119** with boron trichloride. Chloride **120** was reacted with potassium thioacetate, heating to 36 °C over 3 days, to obtain thioacetate **121** in a low yield (30%). The free thiol **122** (58%) was then

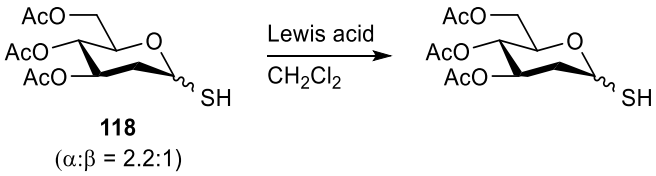
generated through the selective deprotection of the thioacetate position using sodium methoxide at – 40 ºC.



Scheme 4.7 Elimination product formed exclusively

The thiols **118** and **122** were treated with Lewis acids $SnCl_4$ and $TiCl_4$, varying temperature and time. In the epimerisation of **118** under $SnCl_4$ conditions, there was a significant amount of an unidentified side-products formed, which was not the corresponding chloride or elimination product **117** (entries 1-2 in Table 4.18). Under $SnCl_4$-catalysed conditions, there is some indication that axial anomer was disfavoured in **118**, as the percentage yield of the α-anomer was reduced from ~69% to 23% and 32% after 24 h, at room temperature and 4 ºC, respectively. Under $TiCl_4$ conditions, no notable anomerisation occurred and there was a significant number of side products at room temperature after 24 h (entry 3). When the experiment was cooled to 4 ºC with $TiCl_4$ (2.5 equiv), no noticeable epimerisation took place (entry 4). It should be noted that little epimerisation took place with $TiCl_4$ in acetylated glycosyl thiols that had a C-2 group present. Therefore exploration of $TiCl_4$-catalysed anomerisation in benzoylated glycosyl thiol **122** was investigated

Table 4.18 Lewis acid promoted epimerisation of **118**

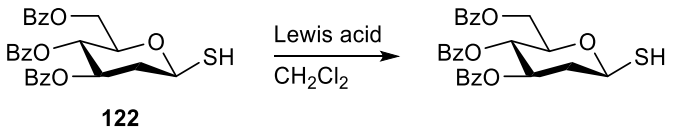


Entry	Time (h)	Temp.	Lewis acid	Equivalents	%α	%β	Crude % yield
1[1]	24 h	20 ºC	$SnCl_4$	2.5	23	77	76
2[1]	24 h	4 °C	$SnCl_4$	2.5	32	68	86
3[1]	24 h	20 ºC	$TiCl_4$	2.5	65	35	73
4	24 h	4 °C	$TiCl_4$	2.5	63	37	78
[1]Significant amount of side products formed that could not be identified							

In the epimerisation of **122,** $TiCl_4$ led to a considerable amount of side product formation and decomposition. There was no discernible proton signals that could be integrated after treatment of **122** with $TiCl_4$ (entries 1-3). Reducing the equivalents of $TiCl_4$ to 1, 0.5 or 0.25 did not lead to epimerisation in **122** (entries 2, 5-6). Reducing the temperature to -30 ºC helped to suppress the formation of side-products but no epimerisation was detectable and ~70% of the starting material accounted for the resulting reaction mixture.

It can be concluded that the C-2 substituent has an important role in $TiCl_4$-catalysed anomerisation of glycosyl thiols as the presence of a C-2 acyl group was necessary to enable epimerisation to occur, particularly for benzoylated glycopyranosyl thiols. The formation of cation **109,** observed in the NMR study of **68** treated with $TiCl_4$, is an important intermediate in the anomerisation of glycosyl thiols and similar cations may influence the equilibrium attained in the various glycosyl thiols within this study.

Table 4.19 Lewis acid promoted epimerisation of **122**



Entry	Time (h)	Temp.	Lewis acid	Equivalents	%α	%β	Crude % yield
1[1]	24 h	20 ºC	$TiCl_4$	3	-	-	63
2[1]	24 h	20 ºC	$TiCl_4$	1	-	-	56
3[1]	24 h	4 °C	$TiCl_4$	1	-	-	90
4	24 h	-30 °C	$TiCl_4$	1	-	~70	92
5[1]	24 h	4 °C	$TiCl_4$	0.5	-	-	92
6[1]	24 h	4 °C	$TiCl_4$	0.25	-	-	91
[1]Significant amount of side products formed with no discernible NMR signals							

4.6 Conclusions and Future Work

In conclusion, the unusual equatorial selectivity observed in $SnCl_4$-promoted anomerisations can be attributed to the formation of a stable complex between $SnCl_4$ and the glycosyl thiol. NMR studies indicate that the pyranose oxygen and sulfur atom are involved with chelating to the metal centre. It may be the case that the equatorial thiol forms a chelate to $SnCl_4$ that is more stable than that of the axial thiol. The $TiCl_4$ may give rise to interaction between the thiol

and its C-2 benzoyl group that influences the equilibrium towards the 1,2-cis glycosyl thiol. This would imply that the anomeric preference is generally not influenced significantly by the anomeric effect but by species generated in the presence of the Lewis acid. NMR studies of glycosyl thiols $TiCl_4$ indicated that the sulfur atom was not involved in the coordination but the carbonyl groups could coordinate to the titanium centre. Coordination of $TiCl_4$ to the C-2 carbonyl group in **69** caused the nucleophilic thiol to attack the C-2 substituent, resulting in the formation of 2-phenyl-1,3-oxathiolan-2-ylium cation **93** and seemingly contributed to the equatorial anomer being predominant in the resulting mixture. The formation of the stable dihydrothiazole **97** from the reaction of GlcNAc derivative **96** with $TiCl_4$ gave further support to this proposal. Finally, studies employing glycosyl thiol derivatives of 2-deoxy-D-glucose supported the theory that C-2 group had a vital role in $TiCl_4$-promoted anomerisation and in dictating the resulting equilibrium.

In the future, further efforts could be made to crystallise $SnCl_4$- and $TiCl_4$-glycosyl thiol complexes to fully determine their structures. IR spectroscopy and variable temperature NMR could also be employed to gain further insight into the nature of the complexes. Computational studies could be utilized to analyse the stability of various possible complexes

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Chapter 5

Synthesis Towards a Potential Hemagglutinin Inhibitor

5.1 Introduction

Influenza, also known as 'the flu', is a respiratory tract infection that is highly contagious and has high mortality. It spreads around the world in an annual outbreak and is estimated to cause 3 to 5 million severe illnesses worldwide, resulting in 250,000 to 500,000 deaths each year.[1] People that are at greater risk from complications or death are usually the old, the young, pregnant women and those who are immunocompromised (such as individuals with chronic medical conditions, HIV/AIDS or undergoing chemotherapy). Seasonal influenza spreads rapidly, particularly in crowded areas such as schools, and is usually transmitted from coughs, sneezes and surfaces contaminated with the virus. Several highly pathogenic strains of the influenza virus have emerged in the last century and resulted in large outbreaks or pandemics that had high morbidity and mortality. These four pandemics (1918, 1957, 1968, 2009) resulted in a huge loss of human life, with the Spanish flu, in 1918, alone resulting in the deaths of around 50 million people.[2] As the influenza virus is highly mutagenic, the appearance of new pathogenic strains remains a continual danger today and thus the development of new therapies is undoubtedly important.

There are three types of the influenza virus, distinguished by segmented negative-sense RNA genomes, which infect people –Type A, Type B and Type C.[3] These virion types are all very similar in structure and are roughly spherical, although they can be filamentous. The influenza virus A can be further characterised by the two surface glycoproteins studded on its viral envelope – hemagglutinin (HA) and neuraminidase (NA), which occur in approximately a 4:1 ratio. There are 16 genetically distinct HA subtypes and 9 NA subtypes known, but only a small number of these are linked to human pandemics – 3 for HA (H1, H2, H3) and 2 for NA (N1 and N2). As the influenza A virion is solely responsible for human pandemics, its structure will now be discussed. It has an envelope, a lipid outer layer that is taken from the host cell, with two large glycoproteins, HA and NA, embedded in the outer layer. These proteins are involved with crucial stages in viral infection and release, thus making them antiviral targets. They are also highly antigenic and important in the body's immune response against influenza. Matrix ion channels, called M2 proteins, traverse the lipid envelope and are pH-gated proton-selective channels that can transport H^+ ions into the viral core.[4]

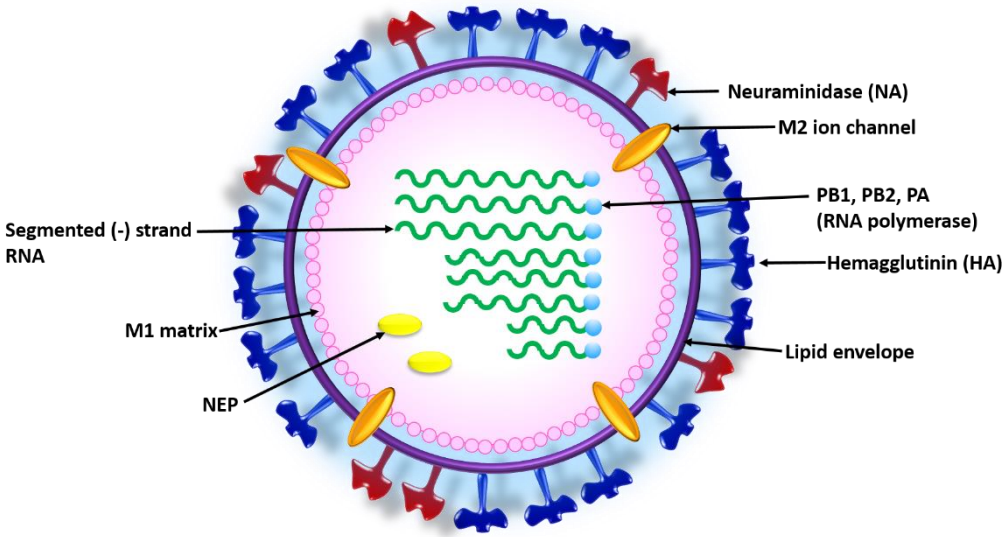


Figure 5.1 Structure of Influenza A virus

Beneath the lipid membrane, embedded with its three integral proteins (HA, NA and M2), is a matrix protein called M1, which encloses a virion core. Within the M1 matrix lies the nuclear export protein (NEP) and the ribonucleoprotein (RNP) complex. The RNP complex consists of 8 negative-sense, single-stranded RNA segments and these are the genetic material of the virus. The viral RNA segments encode for one or two proteins, namely, B1, PB2, PA and NP.[3]

There are two types of mutation that the influenza virus can undergo – *antigenic shift* and *antigenic drift*. The segmented viral RNA genome enables *antigenic shift*, which occurs when two different strains of influenza A infect the same host cell, and the virion particle can acquire a new HA subtype and occasionally a new NA subtype as well. The resulting virus may possess an entirely new antigenic profile which the human population may not have any pre-existing immunity against. Antigenic shift is likely responsible for producing the H1N1 virus that caused the lethal pandemic in 1918. *Antigenic drift* refers to small gene changes that can accumulate to create a new strain of virus particles that can result in the host's immune response becoming ineffective against the microbes.

The HA protein on influenza viruses can recognize terminal sialic acid moieties present on host cell surfaces and bind to these sugars. Sialic acid is often bound to a galactose unit in either an α-2,6- or α-2,3-linkage, resulting in a unique conformation adapted by the sialic acid. In duck epithelial cells, α-2,3-linkages are common, while in human tracheal epithelial cells, α-2,6-linkages are prevalent. However, α-2,3-linkages also occur in human epithelial cells, thus rendering people susceptible to avian influenza viruses.[5-6] After the HA protein binds to the sialic acid, the virion gains access to the cell by receptor mediated endocytosis. The low pH in

the endosome triggers a conformational change in the HA, revealing a fusion peptide that mediates the merging of part of the viral envelope with the endosomal membrane. Hydrogen ions are pumped into the virus matrix through the M2 ion channel, acidifying the virus core and disrupting internal protein-protein interactions, which allow the viral RNAs and other proteins to be released into the host cell. Once released from the virus, RNPs are trafficked to the host cell nucleus where RNA-dependent RNA polymerase begins translating complementary positive sense RNA species. Newly synthesised envelope proteins HA, NA and M2 are trafficked into the Golgi apparatus for modification and subsequently directed to the cell membrane for virion assembly. RNA polymerase and vRNA are assembled into a new virion particle, which is transported to a membrane protrusion, where viral envelope proteins have aggregated. When budding is complete, the NA protein cleaves terminal sialic residues, releasing new viruses from the host cell into the body. The host cell dies after the release of progeny viruses.

5.2 Treatments for Influenza

There are several treatments available for influenza. The first line of defence for prevention and control of influenza infection is often vaccination. Annual vaccinations against influenza is recommended by the WHO for those high at risk. Two vaccines are utilized - trivalent inactivated vaccine (TIV) for those aged 6 months or older, and live attenuated influenza vaccine (LAIV) for healthy individuals aged between 2 and 49 years.[7] Vaccination provides moderate protection against the influenza virus.[8] One study analysed the efficiency of vaccination in over 700,000 elderly people and showed that the risk of hospitalization was reduced by 27% while the risk of death was reduced by 48%.[9] However, influenza viruses constantly mutate due to antigenic drift and antigenic shift, which enable new strains of viruses to evade the adaptive immune responses of humans. It can take 6 months to identify a lethal strain of influenza, develop a vaccine and distribute it. Therefore, the development of a long-lasting vaccine effective against the adaptable virus remains elusive.

The three proteins (HA, NA, and M2) embedded onto the surface of the viral envelope are the primary targets of antiviral drugs. Several neuraminidase inhibitors (NAIs) are currently on the market, including oseltamivir (Tamiflu), zanamivir (Relenza), laninamivir (Inavir) and peramivir, for the treatment of Influenza A and B. They are competitive inhibitors of the NA protein, which is vital for the release of new virions as it cleaves the sialic acid residue on the surface of human cells. Thus NAIs prevent the release of new virion particles and halt the

progression of infection in the body. However, there are variants of influenza that have become resistant to NAIs, particularly oseltamivir.[10] The use of oseltamivir is controversial as it has significant side effects, such as nausea, vomiting and diarrhea, and the benefits in healthy individuals are somewhat limited. In 2013, a systematic review of the value of neuraminidase inhibitors concluded that the combination of misdiagnosis, financial cost, risk of resistance and possible side effects outweighed the small benefits of oseltamivir and zanamivir in the prophylaxis and treatment of healthy individuals.[11] Oseltamivir is only recommended for people who are at high risk of developing complications.

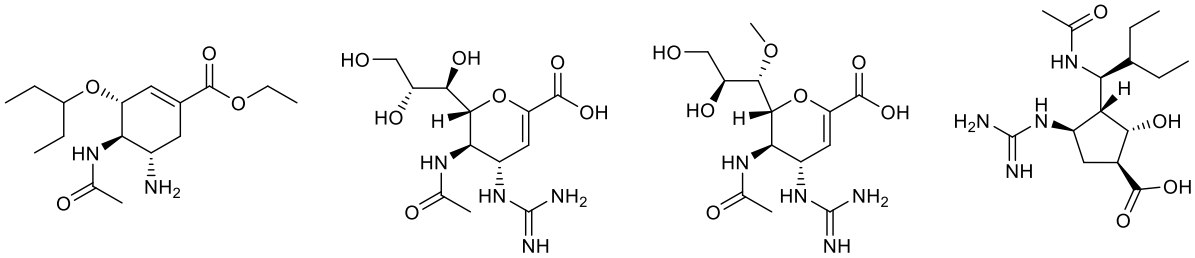


Figure 5.2 Structures of neuraminidase inhibitors

M2 H^+ channel inhibitors, such as adamantane based drugs - amandatine and rimantadine, are also a class of antiviral drugs and the first available treatment of influenza. They act by selectively binding to the M2 proteins, which are responsible for the transportation of protons into the viral core and the subsequent release of the RNP. If these adamantane derivatives are present, the uncoating of the viral core is generally incomplete and the replication of viral RNA is inhibited. However, the M2 gene is highly susceptible to mutations and any change in the five amino acids in the transmembrane results in new strains of influenza that are resistant to current M2 inhibitors. It is now estimated that more than 90% of influenza strains are resistant to the two available drugs.[12-13] It is now recommended by the US Centers for Disease Control and Prevention (CDC) that the use of amandatine and rimantadine should be discontinued, due to widespread viral resistance.

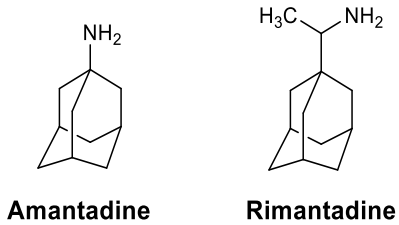
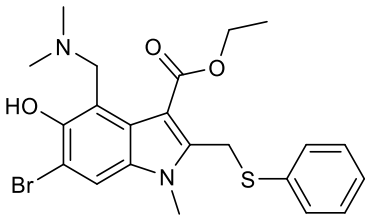


Figure 5.3 Structure of adamatane based therapeutics as selective M2 inhibitors.

HA is a promising antiviral target as it mediates the initial entry of the influenza into the human cell and therefore its inhibition would prevent any infection of the host cell. Several crystal structures of HA have been isolated from influenza viruses and consequently, the structure and purpose of HA is relatively well understood.[14-16] Several types of HA inhibitors are under development, including small molecules, peptides, proteins and antibodies[17] but only one HA inhibitor, arbidol, is currently available on the market. Arbidol is a broad spectrum antiviral drug that was first launched in Moscow in 1993.[18] Currently, it is not approved in Europe or the US and is only available in Russia and China. It is a small molecule containing a highly functionalised indole core. Arbidol is thought to have several functions including inhibition of viral entry and fusion, viral replication and assembly of the viral particles.[19-21] Several studies have demonstrated that arbidol binds to HA and prevents proliferation of the influenza virus.[22-23]



Arbidol

Figure 5.4 Structure of Arbidol

Research concerning the development of anti-influenza therapeutics and novel targets has recently increased, due to the continual threat of seasonal and pandemic influenza, and widespread resistance in influenza strains. In comparison to NA inhibitors, development of HA targeted anti-influenza agents is somewhat limited. It is noteworthy that current small molecule HA inhibitors such as arbidol are not specific to HA but have various functions in vivo. Examining the crystal structures of HA and co-crystal structures of HA and small molecules could facilitate the development of promising HA-specific inhibitors. This could enable target specific driven drug discovery and rational structure modification in promising existing inhibitors.

5.3 Carbohydrate Conformations, Definitions and Preferences

The structure, stereochemistry and conformation a sialic acid residue assumes on the surface of host cells affects the binding strength of HA and this important to consider in the design of a potential inhibitor of HA. Indeed, the 3-dimensional shape of saccharides is important to consider in designing any inhibitor targeted at a carbohydrate-binding protein. Carbohydrate-

protein interactions are generally weak, in the range of mM to μM, and they regularly have multivalent binding sites to increase affinity and selectivity.[24] For the development of therapeutics, this weak interaction must be improved upon (into the range of <100 nm). An explanation for the weak binding is that there is loss in conformational entropy when flexible glycosidic linkages are constrained into a bound state. Therefore, if a potential inhibitor is constrained in an appropriate manner to avoid this entropic penalty, its binding affinity to the target protein can be significantly increased. This is especially relevant in the synthesis of glycomimetics that possess an *S*-glycosidic or *C*-glycosyl linkage as these are more flexible in comparison to *O*-linkages.

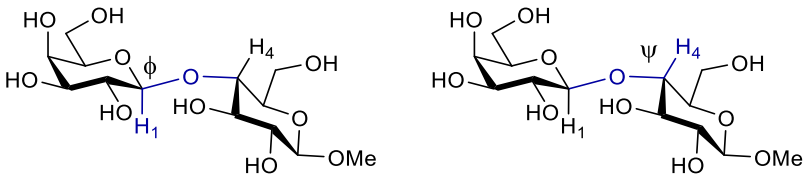


Figure 5.5 Dihedral angles, Φ and Ψ, in lactose

There are two torsional angles to consider in the conformation assumed by disaccharides - Φ and Ψ. Taking lactose for an example, the H1'-C1-O-C4 torsional angle is defined by Φ while the C-1-O-C4-H4 torsional angle is defined by Ψ. It is also important to consider the exo-anomeric effect when considering the 3-dimensional of disaccharides, as this dictates the conformation of the aglycon. The exo-anomeric effect causes the exo conformers to be more stable than the non-exo. The exo-syn Φ conformer is more stable than the exo-anti Φ, due to a lower number of gauche interactions. Using molecular mechanics based modelling, three low energy region were identified in lactose – region I (syn-Φ/syn-Ψ), region II (syn-Φ/anti-Ψ) and region III (anti-Φ/syn-Ψ). NMR studies indicated that the lactose moieties largely populated region I and to a lesser extent region II, with no evidence found for region III. It has also been found that galectins 1, 3, 7, 8 and 9 bind to syn-Φ/syn-Ψ (region I) conformations of lactose.[25] Studies have shown there is increased flexibility in lactose molecules containing an *S*-glycosidic or *C*-glycosyl linkage, leading to smaller barriers between different energy regions, and this is important to consider in the design of potential therapeutics.[26-27] This demonstrates the importance of the 3-D shape has on the binding to carbohydrate proteins.

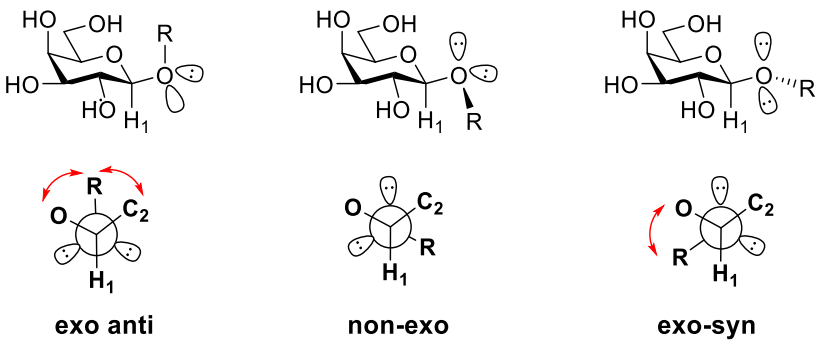


Figure 5.6 Possible conformers of dissacharides – gauche interactions highlighted in red.

In sialic acid-galactose disaccharides, the presence of a quanternary centre reduces the energy difference between the exo-syn and exo-anti, with both conformers being populated. Milton *et al.* carried out a conformational study on isotopically ^{13}C enriched Sia(α2-3)Gal(β1-4)Glc utilizing NMR spectroscopy and molecular modelling.[28] They found three conformational isomers that are populated in Sia(α2-3)Gal(β1-4)Glc - Φ (C1-C2-O2-C3) and Ψ (C2-O2-C3-H3) -70°, +5^0 (exo-syn, syn); -165^0,-20^0 (exo-anti, syn) and -95^0, -45^0. Analysis of crystal structures where sialyl lactose is bound to galectin-1 or galectin-8 demonstrates the exo-syn Φ/syn Ψ conformer is bound and this is also the case for influenza hemmaglutinin. In contrast, the bound conformation for the cholera toxin is the exo-anti Φ/syn Ψ in GM1.[29] This indicates that due to the flexibility in Sia(α2-3)Gal residues, synthesising a constrained mimetic of Sia(α2-3)Gal could lead to increased affinity for the hemagglutinin protein, as long as no steric clashes are introduced between the constrained molecule and the binding site of the protein.

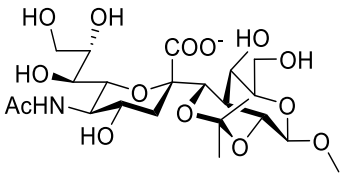


Figure 5.7 Structure of FB127

This led to our group, in collaboration with Prof Robert Woods at the University of Georgia, designing and synthesising a novel constrained Sia(α2-3)Gal compound, FB127, as a potential inhibitor of influenza hemagglutinin.[30] The design of FB127 was developed based on structural information obtained from HA-glycan complexes. FB127 was shown to effectively inhibit HA binding and virus infection in MDCK cells infected with influenza A (in both human H1N1 and avian H5N1 strains). It also displayed resistance to hydrolysis by viral neuraminidase. FB127 has IC_{50} values of ~250 μM. NMR and molecular dynamics show that FB127 is rigid in solution and pre-organized into the conformation for binding unlike native Sia(α2-3)Gal linkages. FB127 thus avoids an entropic pentalty of ~1.5 kcal.mol^{-1} and has an increased

affinity of ~20 fold for HA over the natural disaccharide. A crystal structure of FB127 bound to HA shows that FB127 retains its complementary shape.

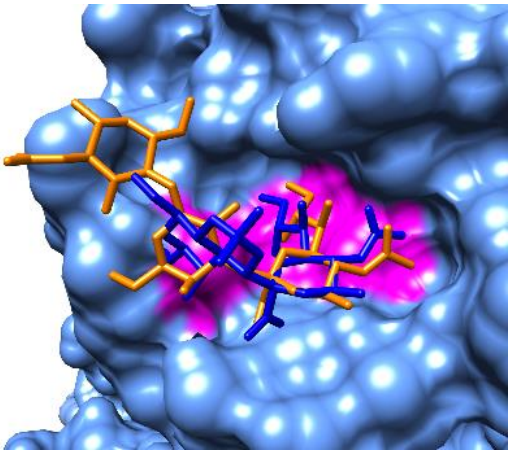


Figure 5.8 FB127 co-crystallised with HA

Now, with evidence in hand that FB127 is an improved inhibitor of HA compared to its non constrained analogue, its structure can provide a basis for the rational modification with a view to generating new structures with improved affinity to HA and improve pharmacokinetic and physiochemical properties. The aim of this project was to synthesise compound **124**, an analogue of FB127 which possesses a *C*-linkage at the 2-position.

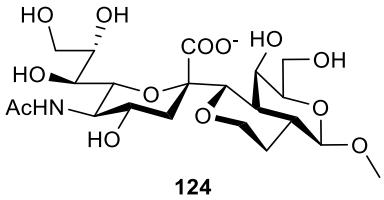
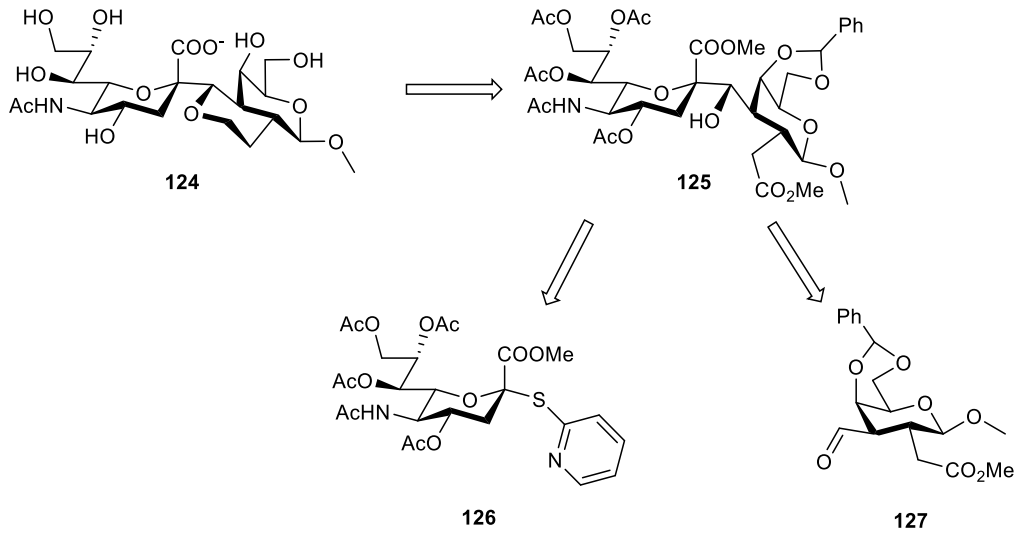


Figure 5.9 Target compound **124**

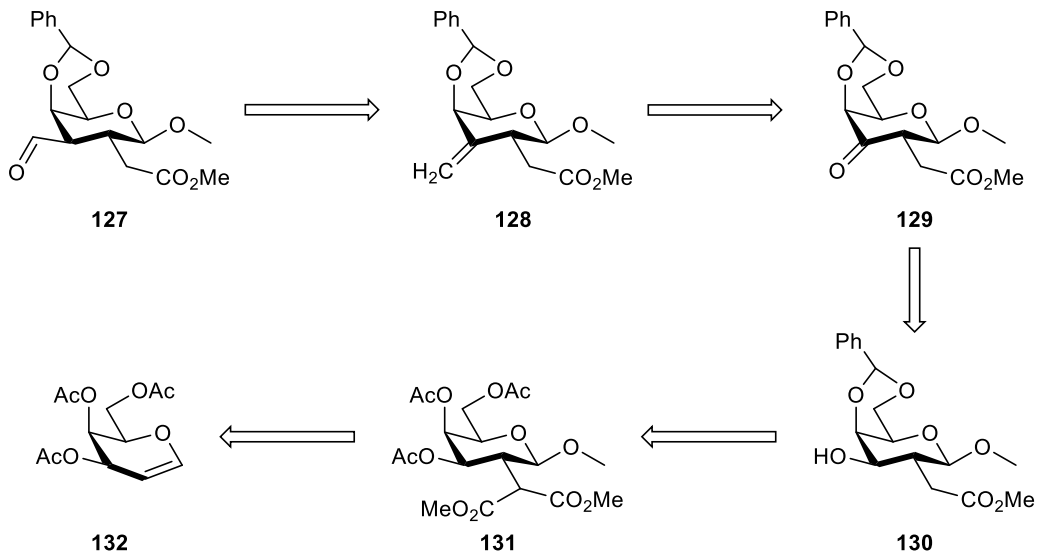
5.4 Retrosynthesis on potential inhibitor

It was envisioned that the target molecule **124** could be constructed through the favourable cyclisation of the secondary alcohol and methyl ester in disaccharide **125**, followed by reduction of the resulting lactone. The construction of precursor **125** was to be realized through the samarium iodide coupling of building blocks **126** and **127**.



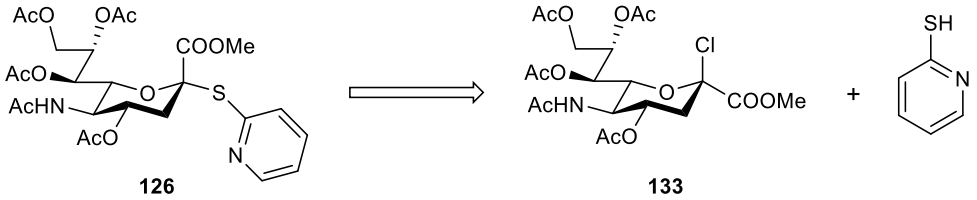
Scheme 5.1 Retrosynthesis of **124**

The retrosynthesis of galactose unit **127** is outlined in Scheme 5.2. It was hoped that aldehyde **127** could be synthesised through the anti-Markovnikov addition to alkene **128** and subsequent oxidation. Alkene **128** was to be constructed via a Wittig reaction with ketone **129**, which could be oxidised from alcohol **130**. In compound **131**, one ester group was to be selectively removed employing a Krapcho decarboxylation. Subsequent deacetylation and protection with a 4,6-*O*-benzylidene acetal group could deliver compound **130**. Finally, the key introduction of the carbon at the C-2 position was envisaged to be achieved through a radical addition of dimethyl malonate to glycal **132**, to obtain glycoside **131**.



Scheme 5.2 Retrosynthesis of galactose unit

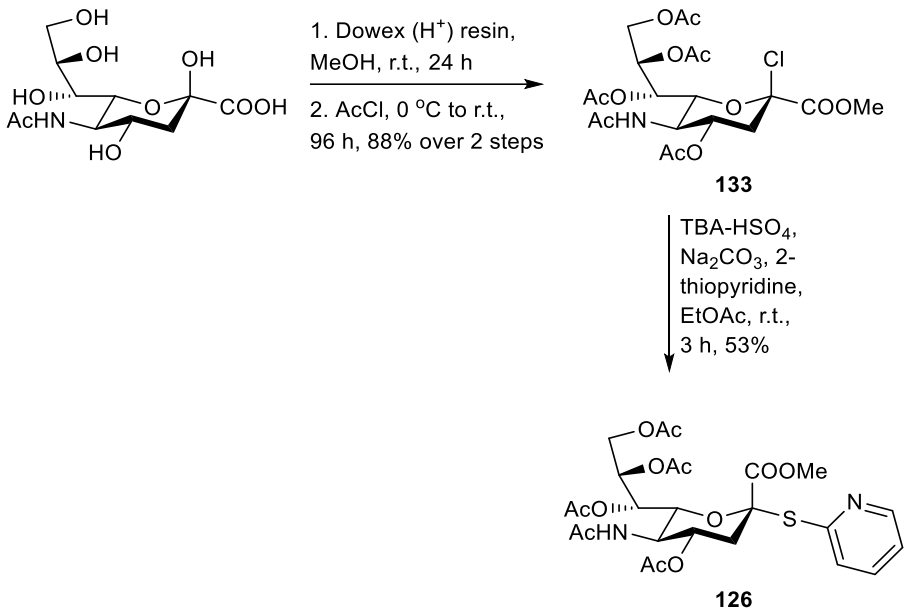
The construction of sialic acid moiety **126** involved a shorter synthetic route. The building block **126** could be synthesised through the coupling of chloride **133** with 2-mercaptopyridine.



Scheme 5.3 Retrosynthesis of sialic acid unit

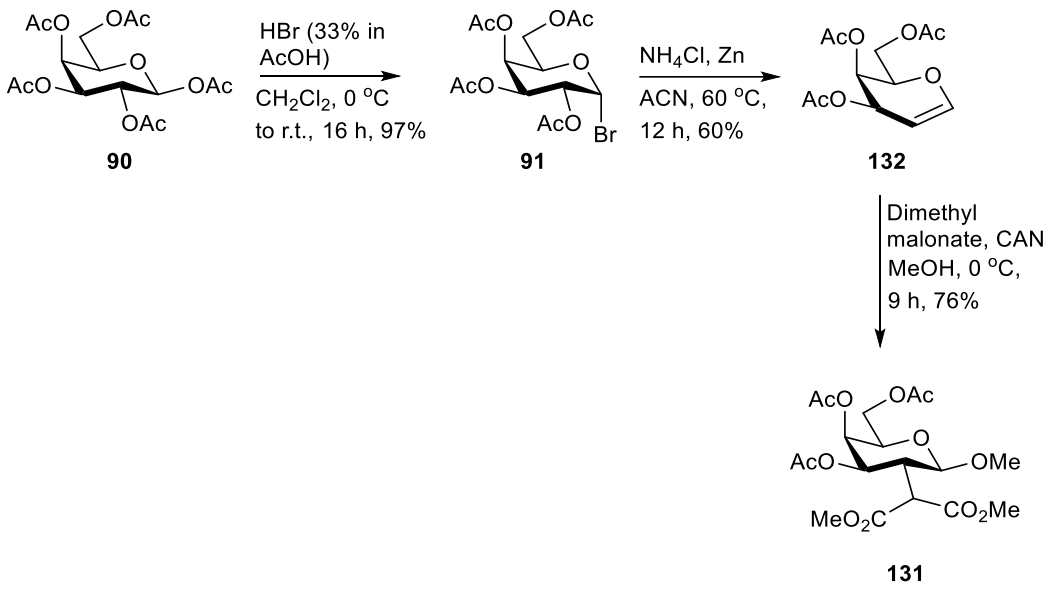
5.5 Synthesis of Inhibitor to Date

N-Acetylneuraminic acid was suspended in anhydrous methanol with Dowex (H^+) resin to protect the carboxylic acid group at the position-2. Upon completion of reaction, the methyl ester was dried under vacuum and suspended in acetyl chloride for 96 h, producing the acetylated glycosyl chloride **133**, in a good yield over 2 steps (88%). The chloride **133** was then immediately reacted with 2-mercaptopyridine to give the desired product **126**, in a moderate yield (53%).



Scheme 5.4 Preparation of building block **126**

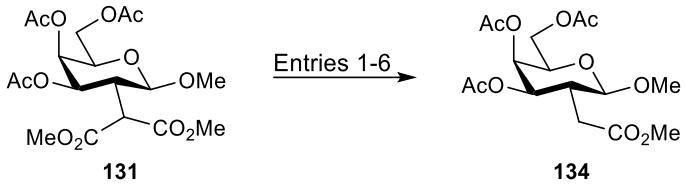
Work then began on the synthesis of the galactose building block. The initial aim was to introduce a new C-C bond at the 2-position. Peracetylated galactose was treated with hydrogen bromide to generate the corresponding bromide **91**, in a high yield (97%). The acetylated galactal **132** was synthesised through treatment of **91** with ammonium chloride and elemental zinc, in a moderate yield (60%). The galactal was then reacted with dimethyl malonoate in a radical reaction, initiated by ceric ammonium nitrate (CAN), in anhydrous methanol. This method was developed by the Linker *et al.*[31] and the product was obtained in a high yield (76%).



Scheme 5.5 Synthesis of **115**

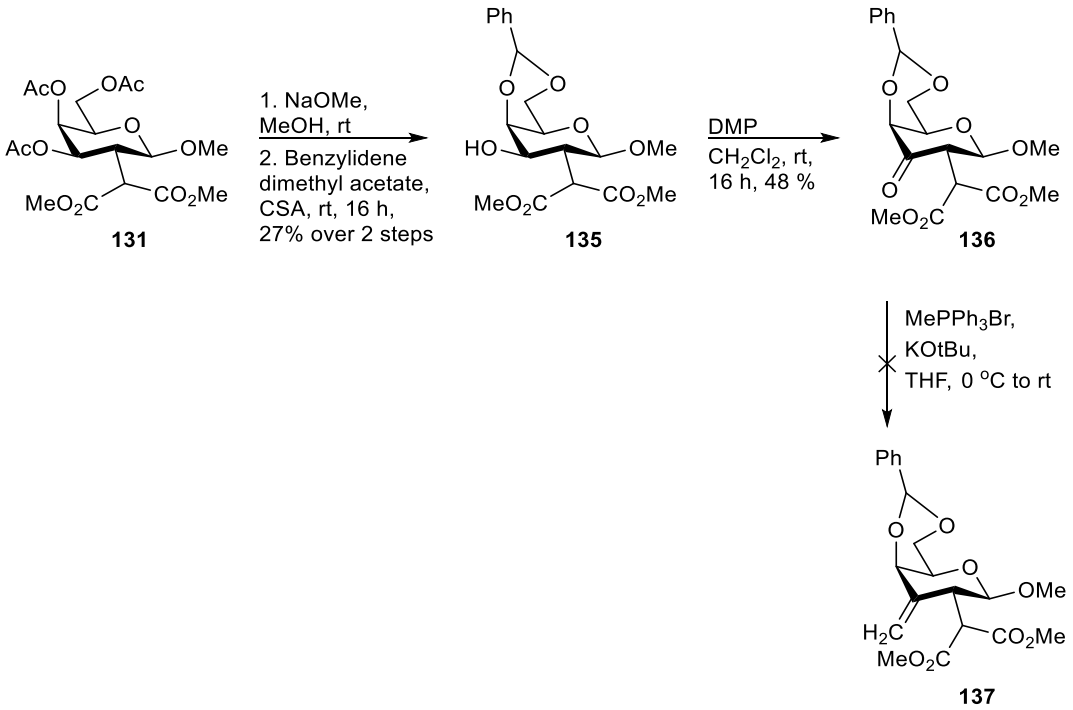
The next step involved the Krapcho decarboxylation to selectively remove one of the methyl ester groups employing a method developed by the Linker group.[32] This is where the first difficulty in the synthetic route was encountered. Glycoside **131** was treated with lithium iodide and heated to 180 °C in DMSO for 4.5 h (entry 1). The yields for this reaction were generally poor and largely varied (0-34%). The scale of the reaction was also found to influence the resulting yield and a larger scale (>1.5 mmol) resulted in decreased yields. It was theorized that heating the reaction mixture to high temperatures led to partial decomposition of DMSO and glycoside **131**, rationalizing the poor yields at 180 °C. Microwave-assisted aqueous decarboxylation was investigated (entry 2) but no product was detected in the resulting mixture.[33] Lowering the temperature to 150 °C led to better results (entry 3). However, in some experiments performed at 150 °C, a significant amount of the starting material remained (~50%). Finally, the best conditions were obtained when the reaction temperature was raised to 160 °C for 4 hours (entry 4). The isolated yield of this reaction varied from 29% to 68%

Table 5.1 Conditions investigated for Krapcho decarboxylation



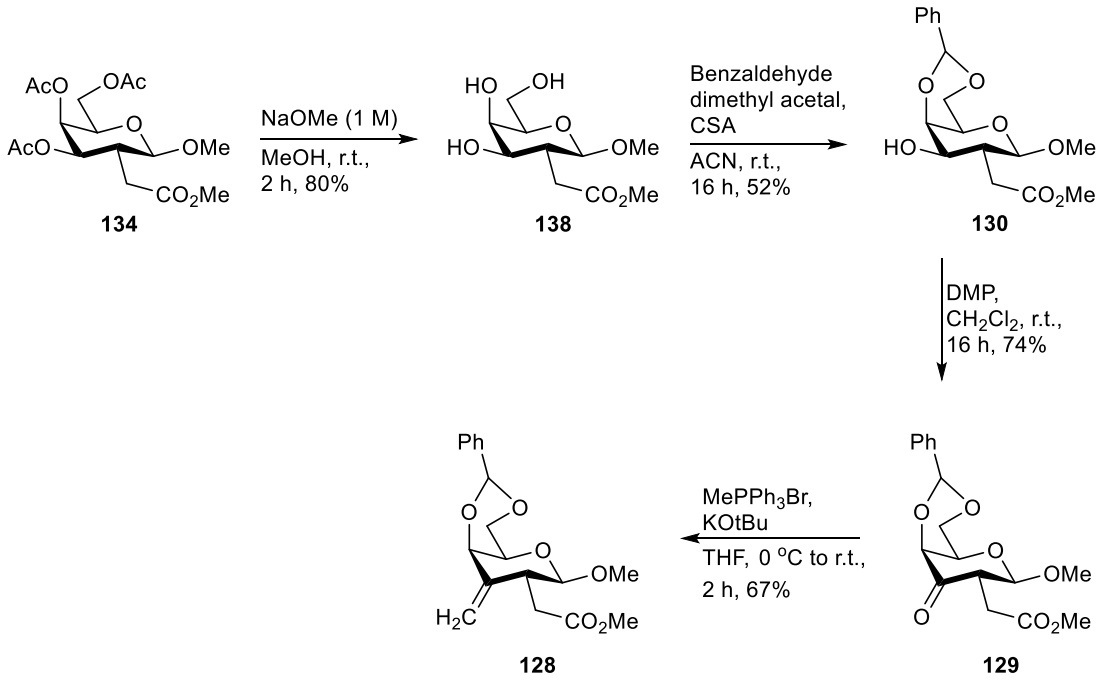
Entry	Conditions	Isolated % yield of product
1	LiI (1.5 equiv), DMSO, 4.5 h, 180 °C	0-34
2	Li_2SO_4, H_2O 210 °C, 30 mins	0
3	LiI (1.5 equiv), DMSO, 4 h, 150 °C	23-62
4	LiI (1.5 equiv), DMSO, 4 h, 160 °C	29-68

Compound **131** was carried forward in the synthesis with a view to performing the decarboxylation at a later stage. A Zemplén deacetylation was carried out on **131** and a 4,6-*O*-benzylidene group was incorporated to generate **135**, in a 27% yield over two steps. The C-3 hydroxyl group was oxidised using Dess Martin periodinane to obtain the desired product in a moderate yield (48%). However, the subsequent Wittig reaction proved unsuccessful with substrate **135** and a complex mixture of products was obtained. This alternative route was considered unattractive as the yield and purity of compounds proved to be quite low.



Scheme 5.6 Attempted synthesis of alkene **137**

The acetate groups were removed from compound **134** sodium methoxide to obtain glycoside **138** in a good yield (80%). Position 4 and 6 were selectively protected under acidic conditions, in a moderate yield (52%). The free hydroxyl group at the C-3 position was then oxidised with Dess Martin Periodinane (DMP) to obtain ketone **129**, in 74% yield. Finally, a Wittig reaction was carried out with ketone **129** and ylide methyltriphenylphosphonium bromide to obtain alkene **128**, in a good yield (67%). X-ray diffraction was obtained of ketone **129** to verify its structure.



Scheme 5.7 Synthesis of alkene **128**

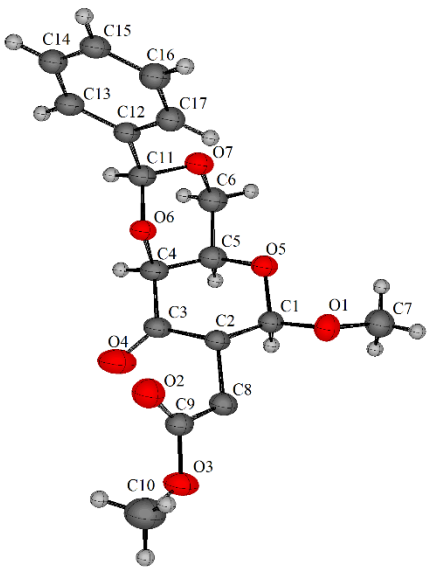
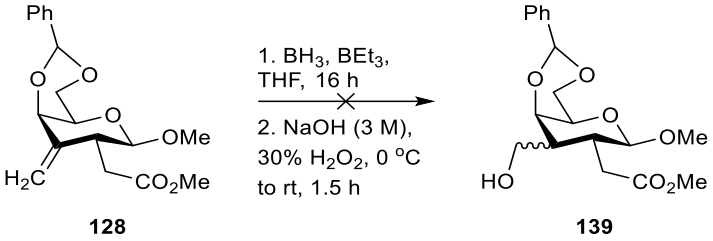


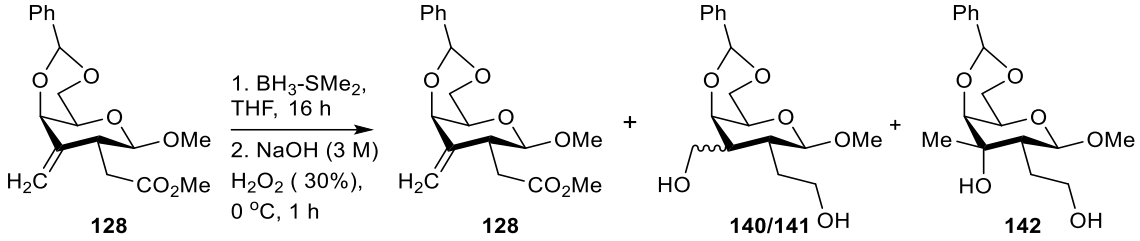
Figure 5.10 Crystal structure of **129**

The hydroboration reaction using conditions developed by Jenifer Hendel at NUI Galway were next investigated. The alkene was treated with borane and triethylborane prior to the addition of sodium hydroxide (3.0 M) and hydrogen peroxide (30%). Unfortunately, starting material **128** was only recovered from this reaction.



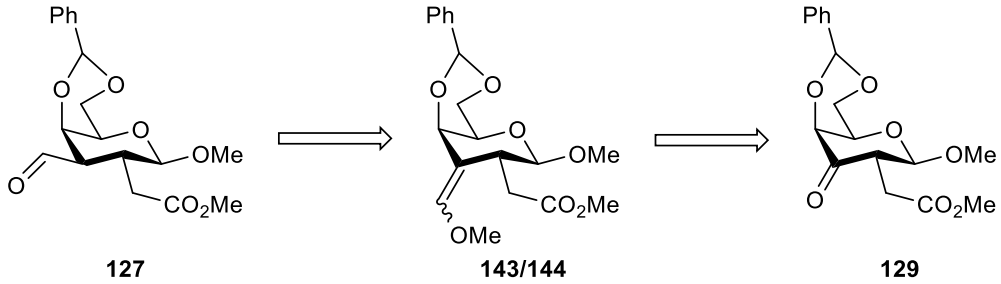
Scheme 5.8 Attempted hydroboration of alkene **139**

Hydroboration conditions developed by the Herdewijn group were adapted.[34] These involved treating **128** with 9-BBN, followed by addition of sodium hydroxide and hydrogen peroxide. This also failed to give alcohol **139** and only starting material was recovered. Finally, treatment of alkene with borane dimethylsulfide, followed by sodium hydroxide and hydrogen peroxide (Scheme 5.9) was investigated. Unfortunately, this reaction also proved unsuccessful and **128** (11%) was recovered unreacted along with alcohols **140, 141** (9%) and **142** (8%) which resulted from reduction of the ester group.



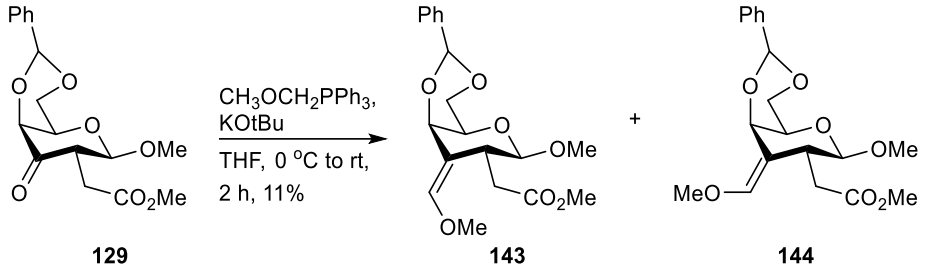
Scheme 5.9 Products obtained after treatment of **128** with BH_3-SMe_2, NaOH and H_2O_2

An alternative route towards aldehyde **127** was considered. Starting from ketone **129**, a Wittig reaction was envisaged to give enols **143** and **144**, which could be subsequently hydrolysed under acidic conditions to give aldehyde **127**.



Scheme 5.10 Revised retrosynthesis for aldehyde **127**

Glycoside **129** was reacted with (methoxymethyl)triphenylphosphonium bromide to obtain the trans and cis isomers **143** and **144**. Unfortunately, the yield for this reaction was reaction very low (11%) and not high enough to be carried forward onto next step. The stability of the benzylidene group under acidic conditions was also a concern, and subsequent hydrolysis with HCl may result also in cleavage of the benzylidene group. Thus the improvement of this synthetic route to give new SiaGal mimetics was left to be revisited and explored in the future.

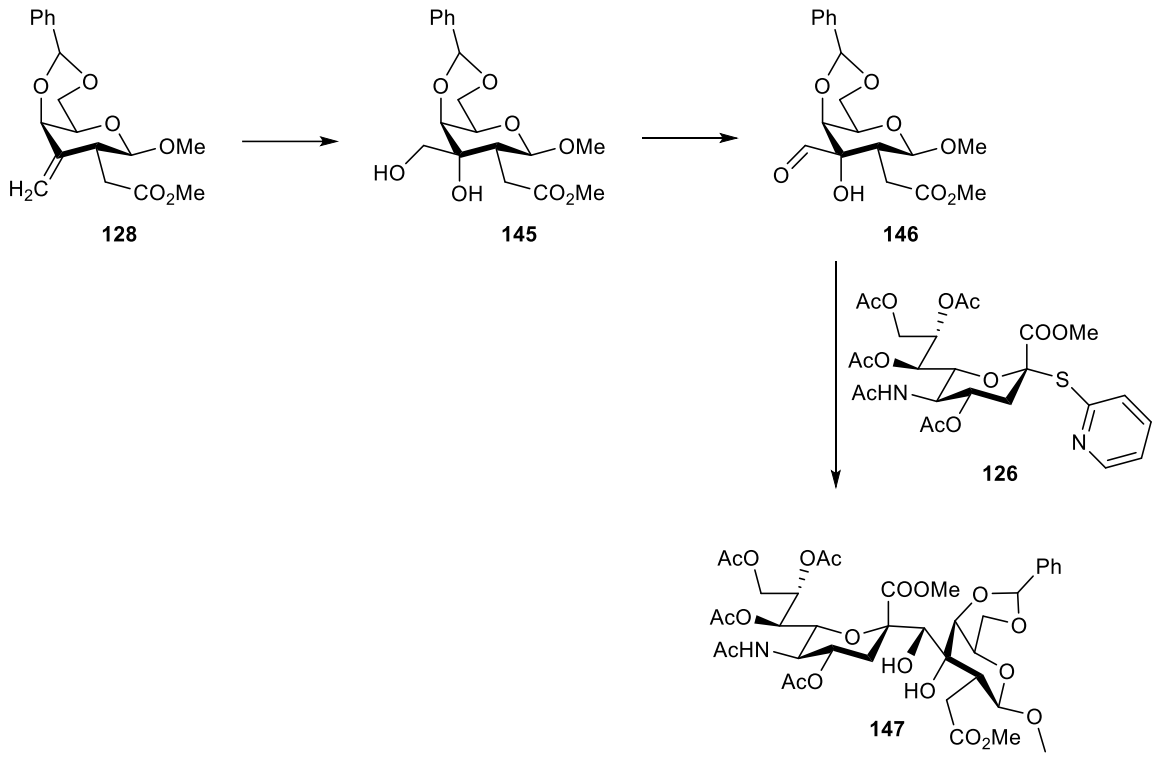


Scheme 5.11 Synthesise of isomers **143** and **144**

5.6 Conclusions and Future Work

This chapter summarises the efforts undertook in developing a synthetic route towards the potential hemagglutinin inhibitor **124**. The sialic acid building block **126** was successfully synthesised over 3 steps in a 47% overall yield. However, the synthesis of galactose unit **127** proved more problematic, with two particularly troublesome steps – the Krapcho decarboxylation and hydroboration. Fortunately, alkene **128** was obtained over 8 steps in an overall yield of 10%. This is a starting place for future endeavours to synthesise the disaccharide **124**.

One alternative route starting from alkene **128**, could involve generation of the corresponding diol. This could be achieved with $KMnO_4$ or OsO_4. The epoxide could also be formed with mCPBA and hydrolysed. Diol **145** could be oxidised to form aldehyde **146.** Aldeyhyde **147** could be coupled with the sialic acid building block to obtain disaccharide **148**. The presence of the additional hydroxyl group at position-3 would affect the conformation adapted by the disaccharide and this may be worthwhile investigating in such glycomimetics.



Scheme 5.12 Alternative Route

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Chapter 6

Experimental Data

6.1 General Procedure

NMR spectra were recorded (25 °C) with a 500 MHz Agilent spectrometer. Data are reported in the following order: chemical shift (δ) in ppm; multiplicities indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); coupling constants (*J*) given in Hertz (Hz). Chemical shifts are reported relative to internal standard Me_4Si in $CDCl_3$ (d 0.0) for ^1H and $CDCl_3$ (d 77.0) for ^{13}C. ^1H NMR spectral signals were assigned with the aid of COSY, ^{13}C NMR spectral signals using DEPT, gHSQCAD and/or gHMBCAD. NMR data for known compounds was in good agreement with previously published data. High resolution mass spectra were measured in positive and/or negative mode as indicated using a Waters LCT Mass Spectrometry instrument. TLC was performed on aluminium sheets precoated with silica gel and spots visualized by UV and charring with H_2SO_4-EtOH (1:20) or cerium molybdate, unless otherwise stated. Chromatography was carried out with silica gel 60 (0.040-0.630 mm) and using a stepwise solvent polarity gradient correlated with TLC mobility, unless otherwise stated. CH_2Cl_2, MeOH, toluene and THF reaction solvents were used as obtained from a Pure Solv™ Solvent Purification System. Optical rotations were determined at the sodium D line at 20°C using a Schmidt and Haensch UniPol L1000. The IR spectra were recorded using thin film with a PerkinElmer Spectrum 100 FT-IR Spectrometer with an ATR attachment. Unless otherwise noted, all commercially available compounds were used as obtained from suppliers without further purification.

6.2 Chapter 2 Experimental Data

6.2 1 Methods for Anomerisation and Kinetic Reactions

Anomerisation Reactions

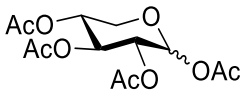
Substrate (~30 mg) was dissolved in anhydrous CH_2Cl_2 (0.2 M) under nitrogen or argon. $SnCl_4$ (1.0 M in CH_2Cl_2) or $TiCl_4$ (1.0 M in CH_2Cl_2) was added at room temperature, and cooled to 4 ^oC or -30 ^oC, if required. The reaction was allowed to react for 24 h before diluting with EtOAc and quenching by addition of 1.0 M $KHSO_4$ (for $SnCl_4$) or 1.0 M NH_4Cl (for $TiCl_4$). The aq. layer was extracted with EtOAc and combined organic layers were washed with satd. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated in vacuo.

Kinetics

The reactant (0.068 mmol) was dried under reduced pressure for at least 24 h prior to the reaction, before dissolving in freshly distilled $CDCl_3$ (0.75 mL) and placed in an NMR tube. $SnCl_4$ (0.1 mL, 0.34 M in $CDCl_3$) was added and the concentration of the anomers was measured by ^1H NMR spectroscopy at 25 ^oC over several days until an equilibrium was attained. The reaction was then diluted with EtOAc, washed with $KHSO_4$, satd. $NaHCO_3$, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting residue was subjected to column chromatography to obtain the axial anomer.

The $CDCl_3$ used in the kinetic experiments was distilled over phosphorus pentoxide and analysed for water content before use. NMR tubes were dried in an oven before use. A fresh solution of $SnCl_4$ was prepared for each sample. The average integration of 2-3 peaks was used to determine the concentration of the α- and β-anomers over time. The rate of reaction was obtained for each reactant at least three times.

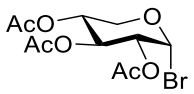
6.2 2 Experimental Data for *O*- and *S*-glycosides



1,2,3,4-Tetra-*O*-acetyl-β-D-xylopyranose (14)[1]

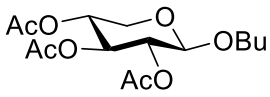
D-xylose (5.0 g, 33.3 mmol), in anhydrous pyridine (42 mL), was cooled to 0 ^oC and acetic anhydride (3.7 mL, 39.6 mmol) was added dropwise to the solution. A catalytic amount of DMAP was added. The solution was allowed to warm to room temperature, stirring for 18 h. The reaction was poured into ice-water and diluted with EtOAc. The layers were separated and

the aq. layer extracted with EtOAc. The combined organic layers were washed with 1.0 M HCl, satd. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Column chromatography (cyclohexane-EtOAc 7:3) gave the title compound as a mixture of anomers (4:1 α:β) as a colourless syrup (10.26 g, 97 %). R_f 0.54 (cyclohexane-EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.26 (d, *J* = 3.5 Hz, 1H. H-1α), 5.72 (d, *J* = 6.9 Hz, 1H, H-1β), 5.47 (t, *J* = 9.8 Hz, 1H, H-3α), 5.21 (t, *J* = 8.3 Hz, 1H, H-3β), 5.06 – 5.00 (overlapping peaks, 2H, H-2α and H-4α), 5.02 – 4.96 (overlapping peaks, 2H, H-2β and H-4β), 4.15 (dd, *J* = 12.1, 4.9 Hz, 1H, H-5aβ), 3.94 (dd, *J* = 11.2, 5.9 Hz, 1H, H-5aα), 3.71 (t, *J* = 11.0 Hz, 1H, H-5bα), 3.53 (dd, *J* = 12.1, 8.4 Hz, 1H, H-5bβ), 2.18 (s, 3H, $C(O)CH_3$), 2.11 (s, 3H, $C(O)CH_3$), 2.06 (s, 3H, $C(O)CH_3$), 2.05 (s, 6H, 2 x $C(O)CH_3$), 2.05 (s, 6H, 2 x $C(O)CH_3$), 2.02 (s, 3H, $C(O)CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 169.8, 169.8, 169.7, 169.3, 169.0, 169.0 (each C=O), 92.0 (C-1β), 89.2 (C-1α), 71.0 (C-3β), 69.5 (C-2β), 69.3 (2s, overlapping peaks, C-2α and C-3α), 68.6 (C-4α), 68.3 (C-4β), 62.8 (C-5β), 60.6 (C-5α), 20.8, 20.8, 20.7, 20.6, 20.6, 20.5 (each $C(O)CH_3$); IR (ATR) cm^{-1}: 1743, 1368, 1207, 1040, 1012; ESI-HRMS calcd for $C_{13}H_{18}O_9Na$ 341.0849, found *m/z* 341.0837 $[M+Na]^+$.



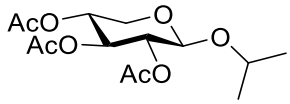
2,3,4-Tri-*O*-acetyl-β-xylopyranosyl bromide (16)[2]

Tetra-O-acetyl-β-D-xylopyranose (9.5 g, 29.9 mmol) was dissolved in anhydrous CH_2Cl_2 (21 mL). HBr (33% in AcOH, 4.9 mL) was added at 0 ºC. The reaction mixture was allowed to warm to room temperature, with stirring, for 3 hours. The reaction mixture was poured into an ice/water mixture and diluted with CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed with cold satd. $NaHCO_3$, H_2O and brine, dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. The residue was recrystallized from diethyl ether:hexanes to give an off white solid (7.2 g, 71%) as the title compound. These steps were performed under light free conditions. R_f 0.59 (cyclohexane-EtOAc 3:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (d, *J* = 4.0 Hz, 1H, H-1), 5.57 (t, *J* = 9.8 Hz, 1H, H-3), 5.04 (ddd, *J* = 11.0, 9.6, 6.0 Hz, 1H, H-4), 4.77 (dd, *J* = 10.0, 3.9 Hz, 1H, H-2), 4.05 (dd, *J* = 11.4, 6.0 Hz, 1H, H-5a), 3.88 (t, *J* = 11.1 Hz, 1H, H-5b), 2.10 (s, 3H, $C(O)CH_3$), 2.06 (s, 3H, $C(O)CH_3$), 2.06 (s, 3H, $C(O)CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8 (2s), 169.7 (each C=O), 87.6 (C-1), 70.9 (C-2), 69.5 (C-3), 68.1 (C-4), 62.5 (C-5), 20.7, 20.7, 20.6 (each $C(O)CH_3$).



Butyl 2,3,4-tri-*O*-acetyl- β-D-xylopyranoside (1)[2]

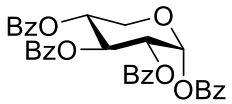
In a flame dried flask with 4Å molecular sieves, I_2 (5.31 g, 20.94 mmol), DDQ (2.37 g, 10.47 mmol) and n-butanol (3.83 mL, 41.87 mmol) in anhydrous CH_2Cl_2 (12 mL) were stirred at room temperature, under nitrogen, for 30 mins. 2,3,4-Tri-*O*-acetyl-β-xylopyranosyl bromide (7.1 g, 20.94 mmol) was added and the reaction mixture was left to stir for 4 h. The reaction mixture was then filtered through a celite bed, washed with $Na_2S_2O_3$ (2% w/v), satd. $NaHCO_3$ and brine. The colourless organic layer was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Column chromatography (4:1 cyclohexane: EtOAc) gave a white solid as the title compound (2.62 g, 38%). R_f 0.32 (cyclohexane-EtOAc 4:1); $[\alpha]_D^{20}$ -56.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.16 (t, *J* = 8.6 Hz, 1H, H-3), 4.98 – 4.89 (overlapping peaks, 2H, H-2 and H-4), 4.46 (d, *J* = 6.8 Hz, 1H, H-1), 4.12 (dd, *J* = 11.8, 5.1 Hz, 1H, H-5a), 3.82 (dt, *J* = 9.6, 6.4 Hz, 1H, OC*H*H), 3.46 (dt, *J* = 9.6, 6.6 Hz, 1H, OCH*H*), 3.36 (dd, *J* = 11.8, 8.8 Hz, 1H, H-5b), 2.05 (s, 3H, C(O)CH_3), 2.05 (s, 3H, C(O)CH_3), 2.04 (s, 3H, C(O)CH_3), 1.59 – 1.51 (overlapping signals, 2H, OCH_2CH_2), 1.40 – 1.30 (overlapping signals, 2H, O(CH_2)CH_2), 0.91 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 169.8, 169.4 (each C=O), 100.7 (C-1), 71.5 (C-3), 70.9 (C-4), 69.4 (C-5), 68.9 (C-2), 62.0 (OCH_2), 31.4 (OCH_2CH_2), 20.8, 20.7, 20.7 (each C(O)CH_3), 19.0 (O(CH_2)CH_2), 13.7 (CH_3); IR (ATR) cm^{-1}: 2937, 1737, 1368, 1222, 1077, 1056; ESI-HRMS calcd for $C_{15}H_{24}O_8Na$ 355.1369, found *m/z* 355.1370 $[M+Na]^+$.



Isopropyl 2,3,4-tri-*O*-acetyl- β-D-xylopyranoside (12)[2]

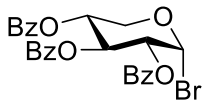
In a flame dried flask with 4Å molecular sieves, I_2 (0.8 g, 3.13 mmol), DDQ (0.36 g, 1.57 mmol) and isopropanol (0.48 mL, 6.26 mmol) in anhydrous CH_2Cl_2 (15.65 mL) were stirred at room temperature, under nitrogen, for 30 mins. 2,3,4-Tri-*O*-acetyl-α-D-xylopyranosyl bromide (0.92 g, 3.12 mmol) was added and the reaction mixture was left to stir for 3 hours. The reaction mixture was then filtered through a celite bed, washed with $Na_2S_2O_3$ (2% w/v), satd. $NaHCO_3$ and brine. The colourless organic layer was dried over Na_2SO_4, concentrated under reduced pressure and subjected to column chromatography (cyclohexane-EtOAc 2:1) to yield the title

compound (0.27 g, 27%) as a white solid. R_f 0.32 (cyclohexane-EtOAc 3:2); $[\alpha]_D^{20}$ -54.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.17 (t, *J* = 8.9 Hz, 1H, H-3), 4.95 (td, *J* = 9.0, 5.3 Hz, 1H, H-4), 4.88 (dd, *J* = 9.0, 7.0 Hz, 1H, H-2), 4.52 (d, *J* = 7.1 Hz, 1H, H-1), 4.11 (dd, *J* = 11.7, 5.3 Hz, 1H, H-5a), 3.90 (hept, *J* = 6.0 Hz, 1H, C*H*$(CH_3)_2$), 3.33 (dd, *J* = 11.7, 9.2 Hz, 1H, H-5b), 2.05 (s, 3H, C(O)CH_3), 2.04 (s, 3H, C(O)CH_3), 2.03 (s, 3H, C(O)CH_3), 1.22 (d, *J* = 6.2 Hz, 3H, CH_3), 1.13 (d, *J* = 6.2 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 169.8, 169.4 (each C=O), 99.5 (C-1), 72.2 (*C*H$(CH_3)_2$), 71.8 (C-3), 71.2 (C-2), 69.0 (C-4), 62.1 (C-5), 23.3, 21.8 (each CH_3), 20.7, 20.7, 20.7 (each C(O)*C*H_3); IR (ATR) cm^{-1}: 2983, 1749, 1366, 1217, 1072, 1060; ESI-HRMS calcd for $C_{14}H_{22}O_8Na$ 341.1212, found *m/z* 341.1212 $[M+Na]^+$.



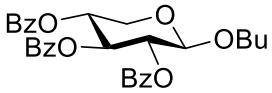
1,2,3,4-Tetra-*O*-benzoyl-α-D-xylopyranose (15)[3]

D-xylose (5.00 g, 33.3 mmol) was dissolved in pyridine (60 mL) and cooled to 0 °C. To this, benzoyl chloride (22 mL, 189 mmol) was added, portion wise, with the reaction being allowed to warm to room temperature overnight, with stirring. The reaction mixture was diluted with CH_2Cl_2 and washed with 1.0 M HCl, water, brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography (petroleum ether-EtOAc 4:1) gave the title compound (17.6 g, 93%) as a white solid. R_f 0.62 (petroleum ether-EtOAc 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17-8.12 (overlapping signals, 2H, Ar-H), 8.02-7.97 (overlapping signals, 2H, Ar-H), 7.97-7.92 (overlapping signals, 2H, Ar-H), 7.92-7.87 (overlapping signals, 2H, Ar-H), 7.69-7.61 (m, 1H, Ar-H), 7.57-7.52 (overlapping signals, 3H, Ar-H), 7.50-7.45 (overlapping signals, 2H, Ar-H), 7.44-7.28 (overlapping signals, 6H, Ar-H), 6.76 (d, *J* = 2.8 Hz, 1H, H-1), 6.27 (t, *J* = 9.8 Hz, 1H, H-3), 5.63 (dd, *J* = 9.9, 2.8 Hz, 1H, H-2), 5.54 (td, *J* = 10.1, 6.1 Hz, 1H, H-4), 4.30 (dd, *J* = 11.3, 5.7 Hz, 1H, H-5a), 4.04 (t, *J* = 11.0 Hz, 1H, H-5b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.84, 165.49, 165.35, 164.58 (each C=O), 133.82, 133.51, 133.44, 133.37, 129.98, 129.96, 129.86, 129.81, 129.73, 129.02, 128.96, 128.84, 128.72, 128.62, 128.46, 128.40 (Ar-C and CH), 90.23 (C-1), 70.27 (C-2), 69.93 (C-3), 69.48 (C-4), 61.21 (C-5); IR (ATR) cm^{-1}: 1730, 1542, 1260, 1108, 1094, 1021, 707; ESI-HRMS calcd for $C_{33}H_{26}O_9Na$ 589.1475, found *m/z* 589.1471 $[M+Na]^+$.



2,3,4-Tri-*O*-benzoyl-α-D-xylopyranosyl bromide (17)[3]

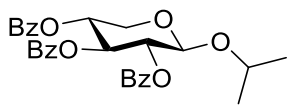
1,2,3,4-Tetra-O-benzoyl-α-D-xylopyranose (17.5 g 30.9 mmol) was dissolved in CH_2Cl_2 (170 mL) and cooled to 0 °C. To this stirring solution was added HBr (33% in AcOH, 53 mL). The reaction was allowed to warm to room temperature overnight with stirring. The reaction mixture was then poured onto ice water, stirred for 15 mins and separated. The aqueous layer was re-extracted with CH_2Cl_2. The combined organic layers were washed with satd. $NaHCO_3$, brine, dried over $MgSO_4$ and the solvent removed under reduced pressure, to give the title compound (15.3 g, 94%) as a white solid. R_f 0.56 (petroleum ether- EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 – 7.96 (overlapping signals, 4H, Ar-H), 7.96 – 7.89 (overlapping signals, 2H, Ar-H), 7.59 – 7.51 (overlapping signals, 2H, Ar-H), 7.50 – 7.44 (m, 1H, Ar-H), 7.44 – 7.38 (overlapping signals, 4H, Ar-H), 7.37 – 7.31 (overlapping signals, 2H, Ar-H), 6.82 (d, *J* = 3.2 Hz, 1H, H-1), 6.23 (t, *J* = 9.8 Hz, 1H, H-3), 5.49 (td, *J* = 10.1, 6.2 Hz, 1H, H-4), 5.28 (dd, *J* = 10.0, 3.4 Hz, 1H, H-2). 4.36 (dd, *J* = 11.4, 5.8 Hz, 1H, H-5a), 4.13 (t, *J* = 11.0 Hz, 1H, H-5b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.52, 165.48, 165.31 (each C=O), 133.74, 133.60, 133.34, 130.04, 129.89, 129.72, 128.53, 128.50, 128.37 (Ar-C and CH), 87.89 (C-1), 71.43 (C-2), 70.01 (C-3), 68.82 (C-4), 62.92 (C-5); IR (ATR) cm^{-1}: 1721, 1601, 1452, 1247, 1091, 1068, 1026, 704; ESI-HRMS calcd for $C_{26}H_{21}O_7$ 445.1287, found *m/z* 445.1284 $[M-Br]^+$.



Butyl 2,3,4-tri-*O*-benzoyl- β-D-xylopyranoside (2)

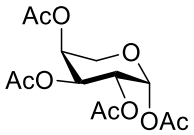
In a flame dried flask with 4Å molecular sieves, I_2 (0.55 g, 2.17 mmol), DDQ (0.25 g, 1.09 mmol) and n-butanol (0.39 mL, 4.34 mmol) in anhydrous CH_2Cl_2 (10.8 mL) were stirred at room temperature, under nitrogen, for 30 mins. 2,3,4-Tri-*O*-benzoyl-α-D-xylopyranosyl bromide (1.14 g, 2.17 mmol) was added and the reaction mixture was left to stir for 3 h. The reaction mixture was filtered through a celite bed, washed with $Na_2S_2O_3$ (2% w/v), satd. $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, the solvent removed under reduced pressure and subjected to column chromatography (cyclohexane-EtOAc 7:1). The resulting residue was recrystallized from ethanol to yield a white powder as the title compound (0.49 g, 44%). R_f 0.32 (cyclohexane-EtOAc 7:1); $[\alpha]_D^{20}$ -29.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500

MHz, $CDCl_3$) δ 8.03 – 7.97 (overlapping signals, 6H, Ar-H), 7.56 – 7.49 (overlapping signals, 3H, Ar-H), 7.41 – 7.33 (overlapping signals, 6H, Ar-H), 5.74 (t, *J* = 7.1 Hz, 1H, H-3), 5.36 (dd, *J* = 7.1, 5.3 Hz, 1H, H-2), 5.29 (td, *J* = 6.9, 4.2 Hz, 1H, H-4), 4.82 (d, *J* = 5.2 Hz, 1H, H-1), 4.43 (dd, *J* = 12.1, 4.2 Hz, 1H, H-5a), 3.88 (dt, *J* = 9.5, 6.3 Hz, 1H, OC*H*H), 3.71 (dd, *J* = 12.2, 6.9 Hz, 1H, H-5b), 3.53 (dt, *J* = 9.5, 6.5 Hz, 1H, OCH*H*), 1.61 – 1.55 (overlapping signals, 2H, OCH_2CH_2), 1.33 (dt, *J* = 14.8, 7.4 Hz, 2H, $O(CH_2)_2CH_2$), 0.83 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.3, 133.3, 133.2 (each C=O), 129.9, 129.8, 128.4, 128.3, 128.3 (Ar-C and CH), 100.0 (C-1), 70.3 (C-2), 70.2 (C-3), 69.2 (C-4), 69.1 (C-5), 61.1 (OCH_2), 31.6 (OCH_2CH_2), 19.1 ($O(CH_2)_2CH_2$), 13.7 (CH_3); IR (ATR) cm^{-1}: 1708, 1604, 1457, 1256, 1072, 1030, 712, 688; ESI-HRMS calcd for $C_{30}H_{30}O_8Na$ 541.1838, found *m/z* 541.1833 $[M+Na]^+$.



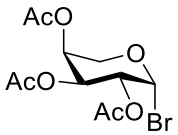
Isopropyl 2,3,4-tri-*O*-benzoyl- β-D-xylopyranoside (13)

In a flame dried flask with 4Å molecular sieves, I_2 (0.58 g, 2.26 mmol), DDQ (0.26 g, 1.13 mmol) and isopropanol (0.35 mL, 4.53 mmol) in anhydrous CH_2Cl_2 (10.8mL) were stirred at room temperature, under nitrogen, for 30 mins. 1,2,3,4-Tetra-*O*-benzoyl-α-D-xylopyranosyl bromide (1.19 g, 2.26 mmol) was added and the reaction mixture was left to stir for 3 hours. The reaction mixture was then filtered through a celite bed, washed with $Na_2S_2O_3$ (2% w/v), satd. $NaHCO_3$ and brine. The colourless organic layer was dried over Na_2SO_4, concentrated under reduced pressure and subjected to column chromatography (cyclohexane-EtOAc 6:1) to yield the title compound (0.47 g, 41%) as a white solid. R_f 0.28 (cyclohexane-EtOAc 6:1); $[\alpha]_D^{20}$ -32.6 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.96 (overlapping signals, 6H, Ar-H), 7.56 – 7.47 (overlapping signals, 3H, Ar-H), 7.39 – 7.33 (overlapping signals, 6H, Ar-H), 5.76 (t, *J* = 7.3 Hz, 1H, H-3), 5.35 – 5.26 (overlapping signals, 2H, H-2 and H-4), 4.90 (d, *J* = 5.5 Hz, 1H, H-1), 4.44 (dd, *J* = 12.1, 4.3 Hz, 1H, H-5a), 4.00 (hept, *J* = 6.2 Hz, 1H, $CH(CH_3)_2$), 3.69 (dd, *J* = 12.1, 7.2 Hz, 1H, H-5b), 1.27 (d, *J* = 6.2 Hz, 3H, CH_3), 1.12 (d, *J* = 6.1 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.5, 165.4, 165.1 (each C=O), 133.3, 133.2, 133.1, 129.9, 129.8, 129.8, 129.5, 129.3, 129.2, 128.4, 128.3 (Ar-C and CH), 98.6 (C-1), 71.7 ($CH(CH_3)_2$), 70.7 (C-2), 70.75 (C-3), 69.3 (C-4), 61.3 (C-5), 23.3 (CH_3), 21.7 (CH_3); IR (ATR) cm^{-1}: 2975, 1720, 1602, 1452, 1249, 1089, 1068, 1026, 705, 686; ESI-HRMS calcd for $C_{29}H_{28}O_8Na$ 527.1682, found *m/z* 527.1685 $[M+Na]^+$.



1,2,3,4-Tetra-*O*-acetyl-β-L-arabinopyranose (22)[4]

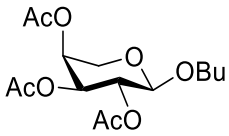
L-(-)-arabinose (3.0 g, 19.98 mmol) was dissolved in dry pyridine (50 mL) and cooled to 0 ºC. Acetic anhydride (15.1 mL, 159.9 mmol) was added portion wise. The solution was stirred at 0 ºC for 30 mins, before allowing the reaction mixture to warm to room temperature stirring overnight. Reaction mixture was poured onto an ice-water mixture and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with 1.0 M HCl (x 2), water, satd. $NaHCO_3$ and water. The organic layer was dried over Na_2SO_4, filtered, concentrated in vacuo and purified through column chromatography (cyclohexane-EtOAc 7:3) to yield a colourless residue as the title compound (5.92 g, 93%). R_f 0.26 (cyclohexane-EtOAc 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (d, *J* = 3.1 Hz, 1H, H-1), 5.40 – 5.38 (m, 1H, H-4), 5.38 – 5.35 (overlapping signals, 2H, H-2 and H-3), 4.08 – 4.05 (m, 1H, H-5a), 3.83 (dd, *J* = 13.3, 2.0 Hz, 1H, H-5b), 2.16 (s, 3H, C(O)CH_3), 2.16 (s, 3H, C(O)CH_3), 2.03 (2s, 6H, 2 x C(O)CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 170.1, 169.8, 169.1 (each C=O), 90.2 (C-1), 68.4 (C-2), 67.0 (C-4), 66.7 (C-3), 62.8 (C-5), 20.9, 20.9, 20.7, 20.6 (each C(O)*C*H_3); IR (ATR) cm^{-1}: 1741, 1370, 1209, 1044, 1008; ES-HRMS calcd for $C_{13}H_{18}O_9Na$ 341.0849, found m/z 341.0847 $[M+Na]^+$.



2,3,4-Tri-*O*-acetyl-β-L-arabinopyranosyl bromide (24)[5]

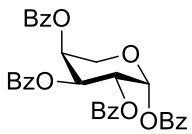
1,2,3,4-Tetra-O-acetyl-β-L-arabinopyranose (5.91 g, 18.58 mmol) was dissolved in dry CH_2Cl_2 (36 mL) and cooled to 0 ºC. HBr (33% in AcOH, 9.2 mL) was added at 0 ºC. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. The reaction mixture was then poured into an ice/water mixture and diluted with CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed with satd. $NaHCO_3$ (x2) and water, dried over Na_2SO_4, filtered and concentrated in vacuo to yield the title compound (4.97 g, 79%) as a white solid. R_f 0.5 (cyclohexane-EtOAc 3:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (d, *J* = 3.7 Hz, 1H, H-1), 5.43 – 5.38 (overlapping signals, 2H, H-3 and H-4), 5.09 (ddd, *J* = 11.8, 3.9, 1.6 Hz, 1H, H-2), 4.21 (dt, *J* = 14.0, 1.0 Hz, 1H, H-5a), 3.94 (dd, *J* = 13.3, 1.8

Hz, 1H, H-5b), 2.16 (s, 3H, C(O)CH_3), 2.12 (s, 3H, C(O)CH_3), 2.03 (s, 3H, C(O)CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 170.0, 169.8 (each C=O), 89.6 (C-1), 67.9 (C-2), 67.8 (C-4), 67.6 (C-3), 64.7 (C-5), 20.8, 20.7, 20.6 (each C(O)*C*H_3); IR (ATR) cm^{-1}: 1733, 1369, 1208, 1067, 1042.



Butyl 2,3,4-tri-*O*-acetyl-α-L-arabinopyranoside (3)

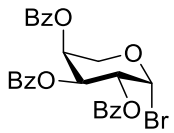
In a flame dried flask with 4Å molecular sieves, I_2 (0.90 g, 3.35 mmol), DDQ (0.40 g, 1.8 mmol) and n-butanol (0.65 mL, 7.08 mmol) in dry CH_2Cl_2 (11.0 mL) were stirred at room temperature, under nitrogen, for 30 mins. 2,3,4-Tri-O-acetyl-β-L-arabinopyranosyl bromide (1.2 g, 3.5 mmol) was added and the reaction mixture was left to stir for 4 hours. The reaction mixture was then filtered through a celite bed, washed with $Na_2S_2O_3$ (2% w/v), satd. $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 , concentrated under reduced pressure and purified through column chromatography (cyclohexane-EtOAc 3:2) to yield a yellow oil (0.45 g, 61%) as the title compound. R_f 0.29 (cyclohexane-EtOAc 3:2); $[\alpha]_D^{20}$ +4.93 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.26 (td, J = 3.4, 1.8 Hz, 1H, H-4), 5.18 (dd, J = 9.4, 6.9 Hz, 1H, H-2), 5.04 (dd, J = 9.4, 3.5 Hz, 1H, H-3), 4.40 (d, J = 6.8 Hz, 1H, H-1), 4.03 (dd, J = 13.0, 3.4 Hz, 1H, H-5a), 3.86 (dt, J = 9.6, 6.3 Hz, 1H, OC*H*H), 3.62 (dd, J = 13.0, 1.8 Hz, 1H, H-5b), 3.46 (dt, J = 9.6, 6.7 Hz, 1H. OCH*H*), 2.13 (s, 3H, C(O)CH_3), 2.06 (s, 3H, C(O)CH_3), 2.03 (s, 3H, C(O)CH_3), 1.58 – 1.52 (overlapping signals, 2H, OCH_2CH_2), 1.41 – 1.33 (overlapping signals, 2H, $O(CH_2)CH_2$), 0.91 (t, J = 7.4 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 170.2, 169.4 (C=O), 101.0 (C-1), 70.2 (C-3), 69.5 (C-2), 69.3 (C-5), 67.7 (C-4), 63.1 (OCH_2), 31.5 (OCH_2CH_2), 21.0, 20.8, 20.7 (each C(O)*C*H_3), 19.1 ($O(CH_2)CH_2$), 13.8 (CH_3); IR cm^{-1}: 2960, 1741, 1369, 1222, 1048, 1020; ES-HRMS calcd for $C_{15}H_{24}O_8Na$ 355.1369, found m/z 355.1368 $[M+Na]^+$.



1,2,3,4-Tetra-*O*-benzoyl-α-L-arabinopyranose (23)[6]

L-(-)-arabinose (5.0 g, 33.3 mmol) was dissolved in anhydrous pyridine (30 mL) and cooled to 0 °C. Benzoyl chloride (22 mL, 189.8 mmol) was added dropwise to the solution over 10

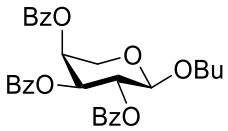
minutes. A catalytic amount of DMAP was added. The solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with EtOAc (100 mL), washed with 1.0 M HCl, water and brine. The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure and subjected to column chromatography (EtOAc-cyclohexane 1:8) to yield the title compound (17.34 g, 92%) as a white solid. R_f 0.24 (cyclohexane-EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 – 8.09 (overlapping signals, 4H, Ar-H), 7.90 – 7.86 (overlapping signals, 4H, Ar-H), 7.68 – 7.59 (overlapping signals, 2H, Ar-H), 7.55 – 7.44 (overlapping signals, 6H, Ar-H), 7.33 – 7.28 (overlapping signals, 4H, Ar-H), 6.86 (d, *J* = 1.6 Hz, 1H, H-1), 6.09 – 6.04 (overlapping signals, 2H, H-2 and H-3), 5.93 – 5.83 (m, 1H, H-4), 4.45 – 4.35 (m, 1H, H-5a), 4.18 (dd, *J* = 13.4, 2.0 Hz, 1H, H-5b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.74, 165.72, 165.56, 164.67 (each C=O), 133.82, 133.56, 133.43, 133.39, 129.90, 129.74, 129.34, 129.12, 128.92, 128.78, 128.73, 128.61, 128.40, 128.38 (Ar-C and CH), 91.08 (C-1), 69.48 (C-4), 68.18 (C-3), 67.76 (C-2), 63.01 (C-5); IR cm^{-1}: 1717, 1601, 1453, 1245, 1096, 1051, 706, 685; ES-HRMS calcd for $C_{33}H_{26}O_9Na$ 589.1475, found *m/z* 589.1471 $[M+Na]^+$.



2,3,4-Tri-*O*-benzoyl-β-L-arabinopyranosyl bromide (25)[7]

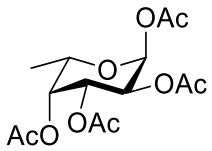
1,2,3,4-Tetra-O-benzoyl-β-L-arabinopyranose (15.4 g, 27.2 mmol) was dissolved in CH_2Cl_2 (120 mL) and the mixture cooled to 0 °C. To this stirring solution was added HBr (33% in AcOH, 47 mL). The reaction was allowed warm to room temperature overnight with stirring. The reaction mixture was then poured onto ice water, stirred for 15 mins and separated. The aqueous layer was re-extracted with CH_2Cl_2. The combined organic layers were washed with satd. $NaHCO_3$, brine, dried over $MgSO_4$. The solvent was removed under reduced pressure, to give the title compound (13.9 g, 97%) as a white solid. R_f 0.34 (cyclohexane-EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 – 8.07 (overlapping signals, 2H, Ar-H), 8.03 – 8.00 (overlapping signals, 2H, Ar-H), 7.87 – 7.83 (overlapping signals, 2H, Ar-H), 7.65 – 7.60 (m, 1H, Ar-H), 7.57 – 7.53 (overlapping signals, 1H, Ar-H), 7.52 – 7.44 (overlapping signals, 3H, Ar-H), 7.43 – 7.38 (overlapping signals, 2H, Ar-H), 7.32 – 7.27 (overlapping signals, 2H, Ar-H), 6.92 (d, *J* = 3.9 Hz, 1H, H-1), 5.99 (dd, *J* = 10.5, 3.4 Hz, 1H, H-3), 5.82 (dt, *J* = 3.3, 1.6 Hz, 1H, H-4), 5.70 (dd, *J* = 10.5, 3.9 Hz, 1H, H-2), 4.48 (d, *J* = 12.9 Hz, 1H, H-5a), 4.23 (dd, *J* = 13.5, 1.9 Hz, 1H, H-5b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 165.5, 165.4 (each C=O),

133.8, 133.6, 133.4, 130.0, 129.9, 129.7, 129.2, 129.2, 128.9, 128.6, 128.6, 128.4 (Ar-C and CH), 89.8 (C-1), 68.9 (C-4), 68.7 (C-2), 68.5 (C-3), 65.0 (C-5); IR (ATR) cm^{-1}: 1721, 1601, 1452, 1247, 1091, 1068, 1026, 704; ESI-HRMS calcd for $C_{26}H_{21}O_7$ 445.1287, found m/z 445.1284 $[M-Br]^+$.



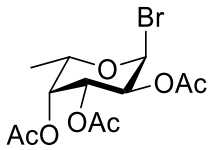
Butyl 2,3,4-tri-*O*-benzoyl-α-L-arabinopyranoside (4)

In a flame dried flask with 4Å molecular sieves, I_2 (0.06 g, 0.25 mmol), DDQ (0.025g, 0.125 mmol) and n-butanol (0.045 mL, 0.125 mmol) in dry CH_2Cl_2 (0.5 mL) were stirred at room temperature, under nitrogen, for 30 mins. The bromide (0.13 g, 0.03 mmol) was added and the reaction mixture was left to stir for 3 h. The reaction mixture was then filtered through a celite bed, washed with $Na_2S_2O_3$ (2% w/v), satd. $NaHCO_3$ (x3) and brine (x2). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure and purified through column chromatography cyclohexane-EtOAc 4:1) to yield a white powder (0.09 g, 72%) as the title compound. R_f 0.26 (cyclohexane-EtOAc 4:1); $[\alpha]_D^{20}$ +155.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 – 8.00 (overlapping signals, 4H, Ar-H), 7.96 – 7.93 (overlapping signals, 2H, Ar-H), 7.59 – 7.52 (overlapping signals, 2H, Ar-H), 7.51 – 7.47 (m, 1H, Ar-H), 7.46 – 7.40 (overlapping signals, 4H, Ar-H), 7.36 – 7.31 (overlapping signals, 3H, Ar-H), 5.72 – 5.67 (overlapping signals, 2H, H-2 and H-4), 5.61 (dd, *J* = 8.4, 3.4 Hz, 1H, H-3), 4.74 (d, *J* = 5.9 Hz, 1H, H-1), 4.32 (dd, *J* = 12.7, 4.5 Hz, 1H, H-5a), 3.96 – 3.87 (overlapping signals, 2H, H-5b and OC*H*H), 3.54 (dt, *J* = 9.6, 6.6 Hz, 1H, OCH*H*), 1.64 – 1.55 (overlapping signals, 2H, OCH_2CH_2), 1.35 – 1.27 (overlapping signals, 2H, $O(CH_2)_2CH_2$), 0.80 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 165.6, 165.2 (each C=O), 133.3, 133.3, 133.2, 129.9, 129.8, 129.8, 129.4, 129.2, 128.4, 128.4, 128.3, 110.0 (each Ar-C and CH), 77.2 (C-1), 70.4 (C-3), 70.0 (C-2), 69.5 (OCH_2), 68.3 (C-4), 62.2 (C-5), 31.5 (OCH_2CH_2), 19.1 ($O(CH_2)_2CH_2$), 13.7 (CH_3); IR (ATR) cm^{-1}: 1719, 1604, 1457, 1256, 1071, 1030, 712, 688; ES-HRMS calcd for $C_{30}H_{30}O_8Na$ 541.1838, found *m/z* 541.1849 $[M+Na]^+$.



1,2,3,4-Tetra-*O*-acetyl-α-L-fucopyranose (26)[8]

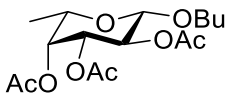
L-Fucose (1.0 g, 6.1 mmol) was dissolved in dry pyridine (17 mL) and cooled to 0ºC. Acetic anhydride (3.45 mL, 36.5 mmol) was added portion wise, before allowing the reaction mixture to warm to room temperature stirring overnight. The reaction mixture was poured onto an ice-water mixture and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with 1.0 M HCl (x2), satd. $NaHCO_3$, water, dried over Na_2SO_4 and concentrated in vacuo. Chromatography (cyclohexane-EtOAc 3:1) gave the title compound as a colourless viscous oil (1.76 g, 87%). R_f 0.44 (cyclohexane-EtOAc 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (d, J = 2.6 Hz, 1H, H-1), 5.36 – 5.29 (overlapping signals, 3H, H-2, H-3 & H-4), 4.26 (q, J = 6.4 Hz, 1H, H-5), 2.17 (s, 3H, C(O)*C*H$_3$), 2.14 (s, 3H, C(O)CH$_3$), 2.00 (s, 3H, C(O)CH$_3$), 1.99 (s, 3H, C(O)CH$_3$), 1.15 (d, J = 6.7 Hz, 3H, CH$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 170.1, 169.9, 169.1 (each C=O), 89.9 (C-1), 70.6 (C-4), 67.8 (C-3), 67.2 (C-5), 66.4 (C-2), 20.9, 20.6, 20.6, 20.5 (each C(O)*C*H$_3$), 15.9 (CH$_3$); IR cm^{-1}: 2990, 1739, 1369, 1209, 1068, 1010; ES-HRMS calcd for $C_{14}H_{20}O_9Na$ 355.1005, found *m/z* 355.1006 $[M+Na]^+$.



2,3,4-Tri-*O*-acetyl-α-L-fucopyranosyl bromide (28)[9]

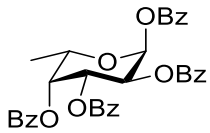
1,2,3,4-Tetra-*O*-acetyl-α-L-fucopyranose (3.4 g, 10.23 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and cooled to 0ºC. HBr (33% in AcOH, 5 mL) was added and the reaction mixture was allowed to warm to room temperature, stirring for 3 hours. The reaction mixture was then poured into an ice/water mixture and separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed with satd. $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated in vacuo to yield the title compound (3.25 g, 91%) as a yellow oil. R_f 0.42 (cyclohexane-EtOAc 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.69 (d, *J* = 3.9 Hz, 1H, H-1), 5.41 (dd, *J* = 10.6, 3.3 Hz, 1H, H-2), 5.36 (dd, *J* = 3.4, 1.2 Hz, 1H, H-4), 5.03 (dd, *J* = 10.6, 3.9 Hz, 1H, H-3), 4.41 (q, *J* = 6.6 Hz, 1H, H-5), 2.17 (s, 3H, C(O)CH$_3$), 2.11 (s, 3H, C(O)CH$_3$), 2.01

(s, 3H, C(O)CH_3), 1.22 (d, *J* = 6.5 Hz, 3H, CH_3);^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 170.1, 169.8 (each C=O), 89.3 (C-1), 70.0 (C-4), 69.8 (C-5), 68.4 (C-2), 67.9 (C-3), 20.8, 20.6, 20.6 (each C(O)*C*H_3), 15.6 (CH_3); IR (ATR) cm^{-1}: 2989, 1742, 1369, 1210, 1073, 1018.



Butyl 2,3,4-tri-*O*-acetyl-β-L-fucopyranoside (5)

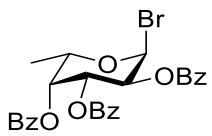
In a flame dried flask with 4Å molecular sieves, I_2 (1.0 g, 4.08 mmol), DDQ (0.46 g, 2.04 mmol) and n-butanol (0.75 mL, 8.15 mmol) in dry CH_2Cl_2 (13 mL) were stirred at room temperature, under nitrogen, for 30 mins. 2,3,4-Tri-*O*-acetyl-α-L-fucopyranosyl bromide (1.44 g, 4.08 mmol) was added and the reaction mixture was left to stir for 3 h. The reaction mixture was then filtered through a celite bed, washed with $Na_2S_2O_3$ (2% w/v), satd. $NaHCO_3$ and brine. The colourless organic layer was dried over Na_2SO_4 , concentrated under reduced pressure and subjected to column chromatography (cylcohexane-EtOAc 2:1) to yield the title compound as a colourless oil (0.63 g; 45 %). R_f 0.17 (cylcohexane-EtOAc 3:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.23 (dd, J = 3.5, 1.1 Hz, 1H, H-4), 5.18 (dd, J = 10.5, 7.9 Hz, 1H. H-2), 5.02 (dd, J = 10.5, 3.5 Hz, 1H, H-3), 4.42 (d, J = 7.9 Hz, 1H, H-1), 3.91 (dt, J = 9.6, 6.2 Hz, 1H, OC*H*H), 3.79 (qd, J = 6.4, 1.1 Hz, 1H, H-5), 3.46 (dt, J = 6.9, 4.1, 2.7 Hz, 1H, OCH*H*), 2.17 (s, 3H, CO)*C*H_3), 2.04 (s, 3H, C(O)*C*H_3), 1.98 (s, 3H, C(O)*C*H_3), 1.64 – 1.48 (overlapping signals, 2H, OCH_2CH_2), 1.40 – 1.30 (overlapping signals, 2H, $O(CH_2)_2CH_2$), 1.23 (d, J = 6.4 Hz, 3H, CH_3), 0.90 (t, J = 7.4 Hz, 3H, CH_2CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 170.3, 169.5 (each C=O), 101.2 (C-1), 71.4 (C-3), 70.4 (C-4), 69.8 (OCH_2), 69.1 (C-2), 69.1 (C-5), 31.4 (OCH_2CH_2), 20.8, 20.7, 20.7 (each C(O)*C*H_3), 19.0 ($O(CH_2)_2CH_2$), 16.1 (CH_3), 13.8 (CH_2CH_3); IR cm^{-1}: 3707, 2966, 1744, 1367, 1215, 1174, 1033, 1017; ES-HRMS calcd for $C_{16}H_{26}O_8Na$ 369.1525, found *m/z* 369.1522 $[M+Na]^+$.



1,2,3,4-Tetra-*O*-benzoyl-α-L-fucopyranoside (27)[10]

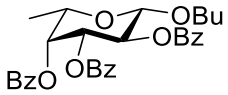
L-Fucose (1.0 g, 6.1 mmol) was dissolved in pyridine (17 mL) and cooled to 0 ºC. Benzoyl chloride (3.60 mL, 31.0 mmol) was added to this slowly, portion wise, before the reaction mixture was allowed to warm to room temperature overnight with stirring. MeOH (15 mL) was

then added and stirred for 15 mins to decompose the excess benzoyl chloride. The mixture was diluted with CH_2Cl_2 and washed with 1.0 M HCl (x2), water, brine and dried over Na_2SO_4 and the solvent removed under reduced pressure. Chromatography (cylcohexane-EtOAc 4:1) gave the title compound (3.4 g, 96 %), as a white solid. R_f 0.21 (cylcohexane-EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 – 8.11 (overlapping signals, 4H, Ar-H), 7.84 (overlapping signals, 4H, Ar-H), 7.69 – 7.60 (overlapping signals, 2H, Ar-H), 7.52 (overlapping signals, 4H, Ar-H), 7.45 (overlapping signals, 2H, Ar-H), 7.31 – 7.26 (overlapping signals, 4H, Ar-H), 6.87 (d, J = 3.7 Hz, 1H, H-1), 6.08 (dd, J = 10.8, 3.3 Hz, 1H, H-3), 5.99 (dd, J = 10.8, 3.7 Hz, 1H, H-2), 5.90 (dd, J = 3.3, 1.2 Hz, 1H, H-4), 4.63 (dt, J = 7.4, 6.1 Hz, 1H, H-5), 1.32 (d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 165.8, 165.6, 164.7 (each C=O), 133.8, 133.6, 133.4, 133.3, 130.0, 129.9, 129.7, 129.3, 129.2, 129.0, 128.9, 128.7, 128.7, 128.4, 128.3 (each Ar-C), 90.9 (C-1), 71.4 (C-4), 69.0 (C-3), 68.0 (C-5), 67.7 (C-2), 16.2 (CH_3); IR (ATR) cm^{-1}: 1721, 1602, 1452, 1247, 1092, 705, 685; ES-HRMS calcd for $C_{34}H_{28}O_9Na$ 603.1631, found *m/z* 603.1627 $[M+Na]^+$.



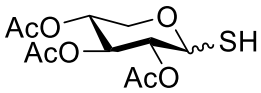
2,3,4-Tri-*O*-benzoyl-α-L-fucopyranosyl bromide (29)[10]

1,2,3,4-Tetra-*O*-benzoyl-α-L-fucopyranoside (2.20 g, 3.77 mmol) was dissolved in anhydrous CH_2Cl_2 (22 mL) and cooled to 0ºC. HBr (33% in AcOH, 6.2 mL) was added to the reaction mixture and it was allowed to warm to room temperature over 90 mins. The reaction mixture was then poured onto an ice-water mixture, stirred for 15 minutes and separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with satd. $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated under reduced pressure to yield a white solid (1.86 g, 92%). R_f 0.4 (cylcohexane-EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 – 8.07 (overlapping signals, 2H, Ar-H), 8.02 – 7.98 (overlapping signals, 2H. Ar-H), 7.81 – 7.78 (overlapping signals, 2H, Ar-H), 7.65 – 7.61 (m, 1H, Ar-H), 7.57 – 7.49 (overlapping signals, 3H, Ar-H), 7.47 – 7.43 (m, 1H, Ar-H), 7.40 (t, *J* = 7.8 Hz, 2H, Ar-H), 7.29 – 7.25 (overlapping signals, 2H, Ar-H), 6.94 (d, *J* = 3.9 Hz, 1H, H-1), 6.01 (dd, *J* = 10.5, 3.4 Hz, 1H, H-3), 5.84 (dd, *J* = 3.4, 1.4 Hz, 1H, H-4), 5.61 (dd, *J* = 10.5, 3.9 Hz, 1H, H-2), 4.69 (q, *J* = 6.5 Hz, 1H, H-5), 1.36 (d, *J* = 6.5 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 165.6, 165.4 (each C=O), 133.7, 133.6, 133.3, 130.0, 129.9, 129.7, 129.0, 128.9, 128.7, 128.3 (each Ar-C and CH), 89.4 (C-1), 70.8 (C-4), 70.4 (C-5), 69.3 (C-3), 68.6 (C-2), 15.8 (CH_3).



Butyl 2,3,4-tri-*O*-benzoyl-β-L-fucopyranoside (6)

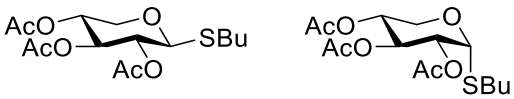
In a flame dried flask with 4Å molecular sieves, I_2 (0.71 g, 2.79 mmol), DDQ (0.32g, 1.39mmol) and n-butanol (0.51 mL, 5.57 mmol) in dry CH_2Cl_2 (14 mL) were stirred at room temperature, under nitrogen, for 30 mins. The bromide (1.10 g, 2.04 mmol) was added and the reaction mixture was left to stir for 2.5 hours. The reaction mixture was then filtered through a celite bed, washed with $Na_2S_2O_3$ (2% w/v), satd. $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure and purified through column chromatography (cylcohexane-EtOAc 3:2) to yield the title compound (0.57 g, 57%) as a white solid. R_f 0.29 (2:3 EtOAc-cyclohexane); $[\alpha]_D^{20}$ -179.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 – 8.08 (overlapping signals, 2H, Ar-H), 7.98 – 7.94 (overlapping signals, 2H, Ar-H), 7.82 – 7.77 (overlapping signals, 2H, Ar-H), 7.63 – 7.58 (m, 1H, Ar-H), 7.53 – 7.45 (overlapping signals, 3H, Ar-H), 7.44 – 7.40 (m, 1H, Ar-H), 7.38 (t, *J* = 7.7 Hz, 2H, Ar-H), 7.25-7.21 (overlapping signals, 2H, Ar-H), 5.74 (dd, *J* = 10.5, 8.0 Hz, 1H, H-4), 5.71 (d, *J* = 3.6 Hz, 1H, H-2), 5.55 (dd, *J* = 10.4, 3.5 Hz, 1H, H-3), 4.74 (d, *J* = 8.0 Hz, 1H, H-1), 4.07 (q, *J* = 6.4 Hz, 1H, H-5), 3.97 (dt, *J* = 9.8, 6.3 Hz, 1H, OC*H*H), 3.55 (dt, *J* = 9.8, 6.8 Hz, 1H, OCH*H*), 1.60 – 1.47 (overlapping signals, 2H, OCH_2CH_2), 1.36 (d, *J* = 6.4 Hz, 3H, CH_3), 1.30 – 1.18 (overlapping signals, 2H, $O(CH_2)_2CH_2$), 0.75 (t, *J* = 7.4 Hz, 3H, $O(CH_2)_3CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 165.7, 165.3 (each C=O), 133.4, 133.2, 133.0, 130.0, 129.8, 129.7, 129.3, 129.0, 128.5, 128.3, 128.2 (Ar-C and CH), 101.5 (C-1), 72.2 (C-3), 71.2 (C-2), 70.0 (OCH_2), 69.9 (C-4), 69.7 (C-5), 31.4 (OCH_2CH_2), 18.9 ($O(CH_2)_2CH_2$), 16.4 (CH_3), 13.6 (CH_2CH_3); IR (ATR) cm^{-1}: 1722, 1602, 1452, 1259, 1066, 1026, 705; ES-HRMS calcd for $C_{31}H_{32}O_8Na$ 555.1995, found *m/z* 555.1996 $[M+Na]^+$.



2,3,4-Tri-*O*-acetyl-1-thio-D-xylopyranose (18)[11]

1,2,3,4-Tetra-O-acetyl-α-D-xylopyranosyl bromide (0.91 g, 3.1 mmol) was dissolved in acetone (23.5 mL) and to this solution was added thiourea (0.41 g, 5.27 mmol). The reaction was heated to reflux (60 °C) and stirred overnight. The reaction mixture was cooled to room temperature before it was concentrated in vacuo. The salt was used without any purification. It was suspended in a 3:2 CH_2Cl_2-H_2O mixture (25 mL) to which sodium metabisulfite (0.77

g, 4.0 mmol) was added. The reaction mixture was heated to reflux (71 °C) and stirred for 30 mins. The solution was allowed to cool to room temperature, the layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, dried over Na_2SO_4, concentrated under reduced pressure and subjected to column chromatography (petroleum ether-EtOAc 2:1) to give the title compound (0.65 g, 72%) as a white solid, as a mixture of anomers (α:β 1:2). R_f 0.28 & 0.26 (cyclohecane-EtOAc 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (t, *J* = 5.9 Hz, 1H, H-1α), 5.34 (t, *J* = 8.8 Hz, 1H, H-3α), 5.17 (t, *J* = 8.7 Hz, 1H, H-3β), 5.02 – 4.88 (overlapping peaks, 4H, H-2α, H-2β, H-4α and H-4β), 4.57 (t, *J* = 9.3 Hz, 1H, H-1β), 4.21 (dd, *J* = 11.7, 5.4 Hz, 1H, H-5aβ), 4.04 (dd, *J* = 11.7, 9.3 Hz, 1H, H-5aα), 3.88 (dd, *J* = 11.8, 5.3 Hz, 1H, H-5bα), 3.38 (dd, *J* = 11.6, 9.6 Hz, 1H, H-5bβ), 2.28 (d, *J* = 9.8 Hz, 1H, SHβ), 2.10 (s, 3H, C(O)CH_3), 2.09 (s, 3H, C(O)CH_3), 2.06 (s, 3H, C(O)CH_3), 2.06 (s, 3H, C(O)CH_3), 2.05 (s, 3H, C(O)CH_3), 2.04 (s, 3H, C(O)CH_3), 1.95 (d, *J* = 6.4 Hz, 1H, SHα); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 169.8, 169.7, 169.7, 169.6 (each C=O), 78.9 (C-1β), 77.0 (C-1α), 73.3 (C-2β), 72.4 (C-3β), 70.4 (C-2α), 68.8 (C-3α), 68.6, 68.6 (overlapping peaks, C-4α and C-4β), 66.2 (C-5β), 60.4 (C-5α), 20.7, 20.7, 20.7 (overlapping peaks, each C(O)CH_3); IR (ATR) cm^{-1}: 1735, 1365, 1211, 1067, 1035; ESI-HRMS calcd for $C_{11}H_{20}O_7NS$ 310.0960, found *m/z* 310.0956 $[M+NH_4]^+$.



7 **20**

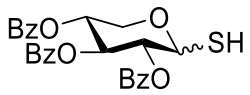
Butyl 2,3,4-tri-*O*-acetyl-1-α/β-D-thioxylopyranoside (7 and 20)[12]

2,3,4-Tri-*O*-acetyl-1-thio-D-xylopyranose (0.3 g, 1.0 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL), to which DIPEA (0.38 mL, 2.16 mmol) and iodobutane (0.53 mL, 4.62 mmol) was added at room temperature. The mixture was allowed to stir for 3 h until TLC indicated the reaction was complete and was then was concentrated under reduced pressure. The resulting residue was subjected to column chromatography (4:1 cyclohexane-EtOAc) to give a separable pair of anomers (α-anomer: 0.05 g, 14%; β-anomer: 0.19 g, 53%) as pale yellow solids.

Analytical data for 20 R_f 0.3 (cyclohexane-EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53 (d, *J* = 5.4 Hz, 1H, H-1), 5.34 (t, *J* = 9.4 Hz, 1H, H-3), 4.98 – 4.87 (overlapping peaks, 2H, H-2 and H-4), 4.03 (t, *J* = 10.8 Hz, 1H, H-5a), 3.79 (dd, *J* = 11.3, 5.7 Hz, 1H, H-5b), 2.59 – 2.47 (overlapping signals, 2H, SCH_2), 2.07 (s, 3H, C(O)CH_3), 2.04 (s, 6H, 2 x C(O)CH_3), 1.62 – 1.52 (overlapping signals, 2H, SCH_2CH_2), 1.45 – 1.34 (overlapping signals, 2H,

S(CH_2)$_2$C*H*$_2$), 0.91 (t, *J* = 7.3 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0 (2s), 169.7 (each C=O), 82.2 (C-1), 70.8 (C-2), 69.6 (C-3), 69.2 (C-4), 59.2 (C-5), 31.5 (SCH$_2$*C*H$_2$), 30.0 (SCH$_2$), 21.9 (S(CH$_2$)$_2$*C*H$_2$), 20.8, 20.7 (overlapping peaks, each C(O)CH$_3$), 13.6 (CH$_3$); IR (ATR) cm^{-1}: 2931, 1747, 1367, 1211, 1068, 1038; ESI-HRMS calcd for $C_{15}H_{28}O_7NS$ 366.1586, found *m/z* 366.1587 [M+NH$_4$]$^+$.

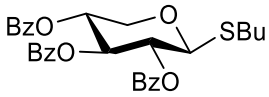
Analytical data for 7 R_f 0.24 (cyclohexane-EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.18 (t, *J* = 8.5 Hz, 1H, H-3), 4.99 – 4.93 (overlapping peaks, 2H, H-2 and H-4), 4.51 (d, *J* = 8.7 Hz, 1H, H-1), 4.22 (dd, *J* = 11.6, 5.1 Hz, 1H, H-5a), 3.38 (dd, *J* = 11.6, 9.1 Hz, 1H, H-5b), 2.73 – 2.60 (overlapping signals, 2H, SCH$_2$), 2.07 (s, 3H, C(O)CH$_3$), 2.05 (s, 6H, 2 x C(O)CH$_3$), 1.61 – 1.53 (overlapping signals, 2H, SCH$_2$C*H*$_2$), 1.44 – 1.36 (overlapping signals, 2H, S(CH$_2$)$_2$*C*H$_2$), 0.91 (t, *J* = 7.3 Hz, 3H, CH$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 169.8, 169.4 (each C=O), 83.8 (C-1), 72.3 (C-3), 69.8 (C-2), 68.7 (C-4), 65.6 (C-5), 31.6 (SCH$_2$*C*H$_2$), 29.7 (SCH$_2$), 21.9 (S(CH$_2$)$_2$*C*H$_2$), 20.7, 20.7, 20.7 (each C(O)CH$_3$), 13.6 (CH$_3$); IR (ATR) cm^{-1}: 2957, 1748, 1366, 1207, 1063, 1051; ESI-HRMS calcd for $C_{15}H_{28}O_7NS$ 366.1586, found *m/z* 366.1582 [M+NH$_4$]$^+$.



2,3,4-Tri-*O*-benzoyl-1-thio-D-xylopyranose (19)[3]

1,2,3,4-Tetra-O-benzoyl-α-D-xylopyranosyl bromide (11.6 g, 22.1 mmol) was dissolved in acetone (170 mL) and to this solution was added thiourea (2.86 g, 37.6 mmol). The reaction was heated to reflux (60 °C) and stirred overnight. The clear solution was cooled to room temperature and concentrated under reduced pressure. The salt was used without any purification. It was suspended in a 3:2 CH_2Cl_2-H_2O mixture (200 mL) to which sodium metabisulfite (5.46 g, 28.7 mmol) was added. The reaction mixture was heated to reflux (42 °C) and stirred for 4 h. The solution was cooled to room temp and separated. The aqueous layer was re-extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, dried over $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography (petroleum ether-EtOAc 3:1) gave the title compound (8.28 g, 78%) as a white solid, as a mixture of anomers (α:β 1:2). R_f 0.34 & 0.45 (petroleum ether-EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 – 8.02 (overlapping signals, 2H, Ar-H), 8.00 – 7.92 (overlapping signals, 10H, Ar-H), 7.59 – 7.46 (overlapping signals, 16H, Ar-H), 7.44 – 7.30 (overlapping signals, 12H, Ar-H), 5.97 (t, *J* = 8.3 Hz, 1H, H-3α), 5.94 (dd, *J* = 7.1, 5.1 Hz, 1H, H-1α), 5.80 (t, *J* = 8.0 Hz, 1H, H-

3β), 5.44 – 5.40 (overlapping signals, 2H, H-2α and H-2β), 5.39 – 5.31 (overlapping signa;s, 2H, H-4α and H-4β), 5.01 (dd, *J* = 9.4, 7.7 Hz, 1H, H-1β), 4.56 (dd, *J* = 11.9, 4.8 Hz, 1H, H-5aβ), 4.30 (dd, *J* = 11.9, 8.5 Hz, 1H, H-5aα), 4.18 (dd, *J* = 11.9, 5.0 Hz, 1H, H-5bα), 3.70 (dd, *J* = 11.9, 8.4 Hz, 1H, H-5bβ), 2.46 (d, *J* = 9.4 Hz, 1H, SHβ), 2.14 (d, *J* = 6.7 Hz, 1H, SHα); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.50, 165.44, 165.39, 165.37, 165.29, 165.27 (each C=O), 133.60, 133.44, 133.41, 130.00, 129.89, 129.85, 129.82, 129.75, 129.00, 128.96, 128.85, 128.75, 128.52, 128.43, 128.41, 128.38 (Ar-C and CH), 78.84 (C-1β), 77.41 (C-1α), 73.19 (C-2β), 71.79 (C-3β), 71.03 (C-2α), 69.19 (C-4β), 69.15 (C-3α), 69.05 (C-4α), 65.42 (C-5β), 61.44 (C-5α); IR (ATR) cm^{-1}:1720, 1601, 1451, 1246, 1090, 1068, 706; ESI-HRMS calcd for $C_{26}H_{22}O_7SNa$ 501.0984, found m/z 501.0986 [M+ Na]$^+$.



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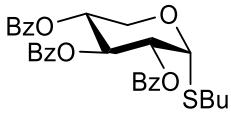


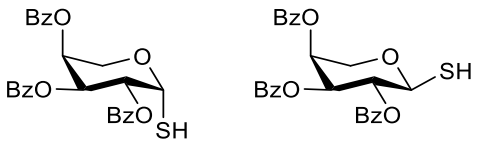
21

Butyl 2,3,4-tri-*O*-benzoyl-1-α/β-D-thioxylopyranoside (8 and 21)

2,3,4-Tri-*O*-benzoyl-1-thio-D-xylopyranose (0.5 g, 1.05 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL), to which DIPEA (0.36 mL, 2.09 mmol) and iodobutane (0.53 mL, 4.75 mmol) was added at rt. The mixture was allowed to stir for 3 h until TLC indicated the reaction was complete and was then was concentrated under reduced pressure. The resulting residue was subjected to column chromatography (13:1 cyclohexane-EtOAc) to give a separable pair of anomers (α-anomer: 0.21 g, 38%; β-anomer: 0.24 g, 43%) as white solids.

Analytical data for 21 R_f 0.3 (cyclohexane -EtOAc 12:1); $[\alpha]_D^{20}$ +73 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 – 7.90 (overlapping signals, 6H, Ar-H), 7.54 – 7.49 (overlapping signals, 2H, Ar-H), 7.49 – 7.44 (m, 1H, Ar-H), 7.43 – 7.29 (overlapping signals, 6H, Ar-H), 5.99 (t, *J* = 9.2 Hz, 1H, H-3), 5.77 (d, *J* = 5.3 Hz, 1H, H-1), 5.43 (dd, *J* = 9.6, 5.3 Hz, 1H, H-2), 5.37 (td, *J* = 9.4, 5.5 Hz, 1H, H-4), 4.28 (t, *J* = 10.7 Hz, 1H, H-5a), 4.10 (dd, *J* = 11.3, 5.4 Hz, 1H, H-5b), 2.65 – 2.53 (overlapping signals, 2H, SCH_2), 1.63 – 1.53 (overlapping signals, 2H, SCH_2CH_2), 1.42 – 1.31 (overlapping signals, 2H, $S(CH_2)_2CH_2$), 0.87 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 165.5, 165.5 (each C=O), 133.4, 133.4, 133.2, 130.0, 129.8, 129.7, 129.2, 129.1, 129.0, 128.4, 128.4, 128.3 (Ar-C and CH), 82.8 (C-1), 71.5 (C-2), 70.1 (C-3), 69.9 (C-4), 59.7 (C-5), 31.6 (SCH_2CH_2), 30.2 (SCH_2), 21.9 ($S(CH_2)_2CH_2$), 13.6 (CH_3); IR (ATR) cm^{-1}: 2958, 1720, 1452, 1251, 1093, 1068, 704, 687; ESI-HRMS calcd for $C_{30}H_{34}O_7SN$ 552.2056, found *m/z* 552.2047 [M+NH_4]$^+$.

Analytical data for 8 R_f 0.21 (cyclohexane -EtOAc 12:1); $[\alpha]_D^{20}$ +35.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 – 7.95 (overlapping signals, 6H, Ar-H), 7.56 – 7.47 (overlapping signals, 3H, Ar-H), 7.41 – 7.31 (overlapping signals, 6H, Ar-H), 5.77 (t, *J* = 7.2 Hz, 1H, H-3), 5.44 (t, *J* = 7.0 Hz, 1H, H-2), 5.31 (td, *J* = 7.3, 4.3 Hz, 1H, H-4), 4.96 (d, *J* = 7.1 Hz, 1H, H-1), 4.60 (dd, *J* = 11.9, 4.4 Hz, 1H, H-5a), 3.72 (dd, *J* = 12.0, 7.4 Hz, 1H, H-5b), 2.81 – 2.67 (overlapping signals, 2H, SC*H*$_2$), 1.67 – 1.56 (overlapping signals, 2H, SCH$_2$C*H*$_2$), 1.46 – 1.35 (overlapping signals, 2H, , S(CH$_2$)$_2$C*H*$_2$), 0.90 (t, *J* = 7.4 Hz, 3H, CH$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.5, 165.3, 165.2 (each C=O), 133.4, 133.3, 129.9, 129.9, 129.0, 128.4, 128.4, 128.3 (Ar-C and CH), 83.7 (C-1), 71.1 (C-3), 70.2 (C-2), 69.1 (C-4), 64.1 (C-5), 31.7 (SCH$_2$*C*H$_2$), 30.4 (S*C*H$_2$), 21.9 (S(CH$_2$)$_2$*C*H$_2$), 13.6 (CH$_3$); IR (ATR) cm^{-1}: 1717, 1453, 1246, 1094, 1067, 1028, 704; ESI-HRMS calcd for $C_{30}H_{30}O_7SNa$ 557.1610, found *m/z* 557.1611 $[M+Na]^+$.



30 **31**

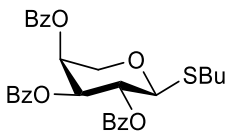
2,3,4-Tri-*O*-benzoyl-1-thio-α/β-L-arabinopyranose (30 and 31)[13]

2,3,4-Tri-*O*-benzoyl-β-L-arabinopyranosyl bromide (2.38 g, 4.53 mmol) was dissolved in acetone (23 mL) and to this solution, thiourea (0.59 g, 7.70 mmol) was added. The reaction was heated to reflux (70 ^{o} C) and stirred overnight. The salt precipitated out overnight and was dried under reduced pressure. The salt was used without any further purification and was suspended in a 3:2 CH_2Cl_2-H_2O mixture (35 mL) to which sodium metabisulfite (1.12 g, 5.89 mmol) was added. The reaction mixture was heated to reflux (80 ^{o} C) and left to stir for 2 hours. The solution was allowed to cool to room temperature and separated. The aqueous layer was re-extracted with CH_2Cl_2 and the combined organic layer were washed with water, dried over Na_2SO_4, with the solvent then being removed under reduced pressure. Chromatography (cyclohexane-EtOAc 5:1) gave the title compounds as a seperable pair of anomers (α-anomer: 1.38g, 63%; β-anomer: 0.31 g, 14%,) as a white solid and colourless viscous oil, respectively.

Analytical data for 31 R_f 0.29 (cyclohexane-EtOAc 5:1); $[\alpha]_D^{20}$ 184.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 – 8.05 (overlapping signals, 2H, Ar-H), 8.03 – 7.99 (overlapping signals, 2H, Ar-H), 7.94 – 7.88 (overlapping signals, 2H, Ar-H), 7.62 – 7.57 (m, 1H, Ar-H), 7.57 – 7.52 (m, 1H, Ar-H), 7.50 – 7.44 (overlapping signals, 3H, Ar-H), 7.44 – 7.38 (overlapping signals, 2H, Ar-H), 7.37 – 7.29 (overlapping signals, 2H, Ar-H), 5.74

(overlapping signals, 2H, H-2 and H-4), 5.62 (dd, *J* = 8.9, 3.5 Hz, 1H, H-3), 4.96 (t, *J* = 8.8 Hz, 1H, H-1), 4.41 (dd, *J* = 13.0, 3.6 Hz, 1H, H-5a), 3.96 (dd, *J* = 13.1, 1.9 Hz, 1H, H-5b), 2.52 (d, *J* = 9.5 Hz, 1H, SH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 165.5, 165.4 (each C=O), 133.5, 133.4, 133.4, 129.9, 129.8, 129.8, 129.3, 129.0, 128.8, 128.5, 128.5, 128.4 (Ar-C and CH), 79.0 (C-1), 72.2 (C-2), 71.3 (C-3), 68.8 (C-4), 66.6 (C-5); $^{1}J_{C1.H1}$ = 157.7 Hz; IR cm^{-1}: 2573, 1714, 1601, 1450, 1260, 1247, 1083, 1067, 707, 685. ES-HRMS calcd for $C_{26}H_{22}O_7SNa$ 501.0984, found *m/z* 501.0971 [M+Na]$^+$.

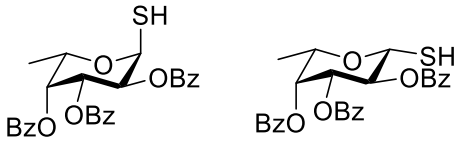
Analytical data for 30 R_f 0.41 (cyclohexane-EtOAc 5:1);); $[\alpha]_D^{20}$ +252.5 (*c* 0.57, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 – 8.05 (overlapping signals, 2H, Ar-H), 8.04 – 8.00 (overlapping signals, 2H, Ar-H), 7.89 (overlapping signals, 2H, Ar-H), 7.57 (overlapping signals, 2H, Ar-H), 7.53 – 7.39 (overlapping signals, 5H, Ar-H), 7.32 (overlapping signals, 2H, Ar-H), 6.10 (t, *J* = 4.8 Hz, 1H, H-1), 5.90 – 5.80 (overlapping signals, 2H, H-2 and H-3), 5.73 (q, *J* = 2.5 Hz, 1H, H-4), 4.57 (dd, *J* = 13.2, 1.9 Hz, 1H, H-5a), 4.06 (dd, *J* = 13.1, 3.3 Hz, 1H, H-5b), 2.00 (d, *J* = 5.9 Hz, 1H, SH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 165.4, 165.4 (each C=O), 133.6, 133.4, 133.4, 129.9, 129.8, 129.7, 129.4, 129.0, 128.8, 128.5, 128.4 (each Ar-C and CH), 78.1 (C-1), 69.1 (overlapping signals, C-3 and C-4), 67.9 (C-2), 61.9 (C-5); IR (ATR) cm^{-1}: 2572, 1721, 1601, 1452, 1243, 1083, 1024, 705, 685; ES-HRMS calcd for $C_{26}H_{22}O_7SNa$ 501.0984, found *m/z* 501.0978 [M+Na]$^+$.



Butyl 2,3,4-tri-*O*-benzoyl-1-thio-α-L-arabinopyranoside (9)[14]

2,3,4-Tri-*O*-benzoyl-1-thio-α-L-arabinopyranose (0.50 g, 1.05 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL), to which DIPEA (0.36 mL, 2.09 mmol) and iodobutane (0.53 mL, 4.75 mmol) was added at room temperature. The mixture was allowed to stir overnight and when TLC indicated the reaction was complete, the reaction was concentrated under reduced pressure. The resulting residue was subjected to column chromatography (12:1 cyclohexane-EtOAc) to give the title compound (0.47 g, 83%), as a white solid. R_f 0.43 (cyclohexane – EtOAc 5:1); $[\alpha]_D^{20}$ +132.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 – 7.99 (overlapping signals, 4H, Ar-H), 8.00 – 7.92 (overlapping signals, 2H, Ar-H), 7.60 – 7.52 (overlapping signals, 2H, Ar-H), 7.52 – 7.47 (m, 1H, Ar-H), 7.47 – 7.38 (overlapping signals, 4H, Ar-H), 7.39 – 7.31 (overlapping signals, 2H, Ar-H), 5.79 (t, *J* = 7.9 Hz, 1H, H-2), 5.72 (q,

J = 3.4 Hz, 1H, H-4), 5.64 (dd, *J* = 8.2, 3.4 Hz, 1H, H-3), 4.88 (d, *J* = 7.7 Hz, 1H, H-1), 4.43 (dd, *J* = 12.7, 4.3 Hz, 1H, H-5a), 3.93 (dd, *J* = 12.8, 2.2 Hz, 1H, H-5b), 2.81 (ddd, *J* = 12.8, 8.3, 6.3 Hz, 1H, SC*H*H), 2.74 (dt, *J* = 12.6, 7.5 Hz, 1H, SCH*H*), 1.69 – 1.57 (overlapping signals, *J* = 6.7 Hz, 2H, SCH_2CH_2), 1.41 (h, *J* = 7.3 Hz, 2H, $S(CH_2)_2CH_2$), 0.90 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 165.5, 165.3 (each C=O), 133.4, 133.4, 133.3, 129.9, 129.9, 129.8, 129.4, 129.0, 128.5, 128.4, 128.4 (Ar-C and CH), 83.92 (C-1), 71.2 (C-3), 69.3 (C-2), 68.7 (C-4), 31.9 (SCH_2), 30.3 (SCH_2CH_2), 22.0 ($S(CH_2)_2CH_2$), 13.6 (CH_3); IR (ATR) cm^{-1}: 2960, 1727, 1451, 1251, 1082, 1067, 1026, 704; ES-HRMS calcd for $C_{26}H_{22}O_7SNa$ 557.1610, found *m/z* 557.1605 $[M+Na]^+$.



32 **33**

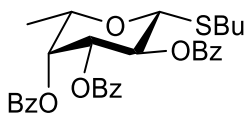
2,3,4-Tri-*O*-benzoyl-1-thio-α/β-L-fucopyranose (32 and 33)[3]

2,3,4-Tri-*O*-benzoyl-α-L-fucopyranosyl bromide **27** (2.52 g, 4.68 mmol) was dissolved in acetone (45 mL) and to this solution, thiourea (0.61 g, 7.96 mmol) was added. The reaction was heated to reflux (70 ^{o} C) and stirred overnight. The solution was allowed to cool to room temperature and concentrated in vacuo. The salt was used without any further purification. It was suspended in a 3:2 CH_2Cl_2-H_2O mixture (45 mL) to which sodium metabisulfite (1.16 g, 6.08 mmol) was added. The reaction mixture was heated to reflux (42 ^{o}C) and left to stir for 5 h. The solution was allowed to cool to room temperature and separated. The aqueous layer was re-extracted with CH_2Cl_2 and the combined organic layer were washed with water, dried over Na_2SO_4, with the solvent then being removed under reduced pressure. Chromatography (cyclohexane-EtOAc 4:1) gave the title compounds (α-anomer: 0.57 g, 25 %; β-anomer: 1.40 g, 61 %) as white solids.

Analytical data for 32 R_f 0.35 (cyclohexane-EtOAc 4:1); $[\alpha]_D^{20}$ -265.1 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.12 – 8.09 (overlapping signals, 2H, Ar-H), 7.99 – 7.96 (overlapping signals, 2H, Ar-H), 7.81 – 7.77 (overlapping signals, 2H, Ar-H), 7.65 – 7.59 (m, 1H, Ar-H), 7.55 – 7.48 (overlapping signals, 3H, Ar-H), 7.46 – 7.41 (m, 1H, Ar-H), 7.41 – 7.36 (overlapping signals, 2H, Ar-H), 7.28 – 7.22 (overlapping signals, 3H, Ar-H), 6.23 (t, *J* = 5.1 Hz, 1H, H-1), 5.86 (dd, *J* = 10.7, 3.2 Hz, 1H, H-3), 5.81 (dd, *J* = 10.7, 5.1 Hz, 1H, H-2), 5.78 (dd, *J* = 3.3, 1.2 Hz, 1H, H-4), 4.80 (q, *J* = 6.4 Hz, 1H, H-5), 1.95 (d, *J* = 5.1 Hz, 1H, S*H*), 1.30

(d, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 165.6, 165.5 (each C=O), 133.5, 133.5, 133.2, 129.9, 129.9, 129.7, 129.3, 129.1, 128.9, 128.6, 128.5, 128.3 (each Ar-C and CH), 78.1 (C-1), 71.6 (C-5), 68.7 (C-3), 68.5 (C-2), 66.2 (C-4), 16.1 (CH_3); $^1J_{C1.H1}$ = 170.3 Hz; IR (ATR) cm^{-1}: 2578, 1719, 1602, 1451, 1255, 1094, 1068, 705, 685; ES-HRMS calcd for $C_{27}H_{24}O_9S_1Na_1$ 515.1140, found *m/z* 589.1029 [M+Na]$^+$.

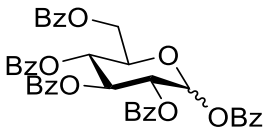
Analytical data for 33 R_f 0.21 (cyclohexane-EtOAc 4:1); $[\alpha]_D^{20}$ +197.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, J = 8.0, 1.4 Hz, 2H, Ar-H), 7.96 (overlapping signals, 2H, Ar-H), 7.77 (overlapping signals, 2H, Ar-H), 7.65 – 7.60 (m, 1H, Ar-H), 7.51 (overlapping signals, 3H, Ar-H), 7.40 (overlapping signals, 3H, Ar-H), 7.26 – 7.21 (overlapping signals, 2H, Ar-H), 5.76 (d, J = 3.4 Hz, 1H, H-4), 5.72 (t, J = 9.8 Hz, 1H, H-2), 5.57 (dd, J = 10.0, 3.4 Hz, 1H, H-3), 4.85 (t, J = 9.7 Hz, 1H, H-1), 4.13 (q, J = 6.5, 6.1 Hz, 1H, H-5), 2.51 (d, J = 9.7 Hz, 1H, SH), 1.36 (d, J = 6.4 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 165.6, 165.5 (each C=O), 133.5, 133.4, 133.2, 129.9, 129.8, 129.7, 129.2, 129.2, 128.8, 128.6, 128.4, 128.3 (Ar-C and CH), 79.0 (C-1), 74.4 (C-5), 72.8 (C-3), 72.0 (C-2), 71.2 (C-4), 16.7 (CH_3); $^1J_{C1.H1}$ = 154.0 Hz; IR (ATR) cm^{-1}: 2565, 1718, 1601, 1451, 1255, 1092, 1067, 703, 685; ES-HRMS calcd for $C_{27}H_{24}O_9S_1Na_1$ 515.1140, found *m/z* 589.1049 [M+Na]$^+$.



Butyl 2,3,4-Tri-*O*-benzoyl-1-thio-β-L-fucopyranoside (10)

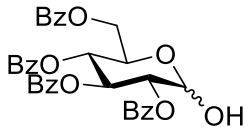
2,3,4-Tri-*O*-benzoyl-1-thio-β-L-fucopyranoside (0.5 g, 1.02 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL), to which DIPEA (0.36 mL, 2.09 mmol) and iodobutane (0.53 mL, 4.75 mmol) were added. The mixture was stirred for 6 h at room temperature until TLC indicated the reaction was complete. The reaction was concentrated under reduced pressure and the resulting residue was subjected to column chromatography (cyclohexane-EtOAc 10:1) to give the title compound (0.452 g, 81%), as a white solid. R_f 0.34 (cyclohexane -EtOAc 10:1); $[\alpha]_D^{20}$ -191.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 – 8.07 (overlapping signals, 2H, Ar-H), 8.00 – 7.93 (overlapping signals, 2H, Ar-H), 7.80 – 7.76 (overlapping signals, 2H, Ar-H), 7.64 – 7.57 (m, 1H, Ar-H), 7.52 – 7.46 (overlapping signals, 3H, Ar-H), 7.44 – 7.34 (overlapping signals, 3H, Ar-H), 7.26 – 7.20 (overlapping signals, 2H, Ar-H), 5.82 (t, J = 9.9 Hz, 1H, H-2), 5.76 (d, J = 3.5 Hz, 1H, H-4), 5.59 (dd, J = 9.9, 3.4 Hz, 1H, H-3), 4.77 (d, J = 9.8 Hz, 1H, H-1), 4.11 (q, J = 6.4 Hz, 1H, H-5), 2.87 (ddd, J = 12.3, 8.7, 6.2 Hz, 1H, SC*H*H), 2.78 (ddd, J = 12.3, 8.7, 6.8 Hz, 1H, SCH*H*), 1.71 – 1.58 (overlapping signals, 2H, SCH_2CH_2), 1.49 – 1.37

(overlapping signals, 2H, $S(CH_2)_2CH_2$), 1.35 (d, J = 6.4 Hz, 3H, CH_3), 0.91 (t, J = 7.3 Hz, 3H, $S(CH_2)_3CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 165.6, 165.4 (each C=O), 133.4, 133.2, 133.2, 129.9, 129.7, 129.7, 129.4, 129.3, 128.5, 128.3, 128.2 (Ar-C and CH), 83.7 (C-1), 73.8 (C-5), 73.2 (C-3), 71.3 (C-4), 68.1 (C-2), 31.8 (SCH_2CH_2), 29.5 (SCH_2), 22.0 ($S(CH_2)_2CH_2$), 16.7 (CH_3), 13.6 ($S(CH_2)_3CH_3$); IR (ATR) cm^{-1}: 2960, 1721, 1451,1256, 1094, 1067, 1026, 703; ES-HRMS calcd for $C_{31}H_{32}O_7SNa$ 571.1766, found *m/z* 571.1744 $[M+Na]^+$.



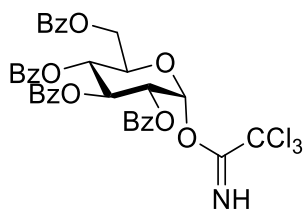
α/β-D-Glucopyranose pentabenzoate (34)[15]

Benzoyl chloride (48.0 mL, 34.4 mmol) was added dropwise to a solution of D-glucose (10.0 g, 55.5 mmol) in pyridine (120 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirring overnight, before it was diluted with EtOAc (300 mL), and washed with 1.0 M HCl, water and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Recrystallisation from acetone:water gave the title compound (30.68 g, 43.78 mmol, 79%) as a mixture of anomers (α:β = 1.6:1). R_f 0.44 (cyclohexane-EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 – 8.15 (overlapping signals, 2H, Ar-H), 8.14 – 8.10 (m, 1H, Ar-H), 8.06 – 8.01 (overlapping signals, 5H, Ar-H), 7.97 – 7.84 (overlapping signals, 12H, Ar-H), 7.68 (d, J = 1.5 Hz, 1H, Ar-H), 7.64 – 7.58 (m, 1H, Ar-H), 7.59 – 7.28 (overlapping signals, 28H, Ar-H), 6.86 (d, J = 3.7 Hz, 1H, H-1α), 6.32 (t, J = 10.3 Hz, 1H, H-3α), 6.30 (d, J = 5.4 Hz, 1H, H-1β), 6.04 (t, J = 9.5 Hz, 1H, H-3β), 5.89 – 5.81 (overlapping signals, 3H, H-2β, H-4β and H-4α), 5.69 (dd, J = 10.3, 3.7 Hz, 1H, H-2α), 4.69 – 4.60 (overlapping signals, 3H, H-5α, H-6aα and H-6aβ), 4.54 – 4.47 (overlapping signals, 2H, H-6bα and H-6bβ), 4.41 (ddd, J = 9.8, 4.8, 3.0 Hz, 1H, H-5β); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 166.1, 165.9, 165.7, 165.3, 165.1, 165.1, 164.6, 164.4 (each C=O), 133.9, 133.8, 133.6, 133.5, 133.5, 133.4, 133.3, 133.1, 133.1, 130.2, 130.2, 130.0, 129.9, 129.8, 129.8, 129.8, 129.8, 129.7, 129.5, 129.0, 128.8, 128.8, 128.7, 128.7, 128.5, 128.5, 128.5, 128.4, 128.4, 128.4, 128.3 (Ar-C and CH), 92.7 (C-1β), 90.0 (C-1α), 73.2 (C-5β), 72.8 (C-3β), 70.8 (C-2β), 70.5, 70.5, 70.4 (C-2α, C-3α and C-5α), 69.1 (C-5β), 68.8 (C-4α), 62.4 (C-6β); IR (ATR) cm^{-1}: 3065, 1728, 1451, 1262, 1092, 1068, 1020, 707; ESI-HRMS calcd for $C_{41}H_{36}NO_{11}$ 718.2288, found *m/z* 718.2253 $[M+NH_4]^+$.



2,3,4,6-Tetra-*O*-benzoyl-α/β-D-glucopyranose (35)[15]

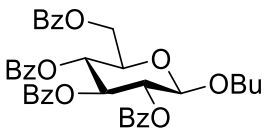
D-Glucopyranose pentabenzoate (3.0 g, 4.3 mmol) and hydrazine acetate (0.79 g, 8.56 mmol) were dissolved in anhydrous DMF (100 mL) and heated to 40 ºC before allowing to cool to room temperature, over 4 h. The reaction mixture was diluted with EtOAc and washed with water (x3) and brine, dried over Na_2SO_4 and concentrated in vacuo. Chromatography (cylcohexane-EtOAc 3:1) gave the title compound (1.7 g, 2.9 mmol, 68%) as a white solid, as a mixture of anomers (α:β- 3.2:1). R_f 0.27 (cylcohexane-EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 – 8.02 (overlapping signals, 4H, Ar-H), 8.00 – 7.96 (overlapping signals, 4H, Ar-H), 7.96 – 7.92 (overlapping signals, 2H, Ar-H), 7.92 – 7.84 (overlapping signals, 4H, Ar-H), 7.59 – 7.46 (overlapping signals, 4H, Ar-H), 7.45 – 7.33 (overlapping signals, 10H, Ar-H), 7.32 – 7.26 (overlapping signals, 2H, Ar-H), 6.25 (t, *J* = 10.0 Hz, 1H, H-3α), 5.97 (t, *J* = 9.7 Hz, 1H, H-3β), 5.77 (d, *J* = 3.6 Hz, 1H, H-1α), 5.73 (t, *J* = 9.8 Hz, 2H, H-4α), 5.37 – 5.34 (m, 1H, H-2β), 5.32 (dd, *J* = 10.2, 3.6 Hz, 1H, H-2α), 5.07 (d, *J* = 8.0 Hz, 1H, H-1β), 4.72 – 4.62 (overlapping peaks, 3H, H-5α, H-6aα and H-6aβ), 4.51 (dd, *J* = 12.2, 5.1 Hz, 1H, H-6bβ), 4.46 (dd, *J* = 12.0, 4.3 Hz, 1H, H-6bα), 4.20 (ddd, *J* = 10.1, 5.1, 3.0 Hz, 1H, H-5β), 3.14 (br s, 1H, OH), 1.57 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.8, 166.4, 166.3, 165. 9, 165.9, 165.8, 165.3, 165.2 (each C=O), 133.6, 133.5, 133.4, 133.4, 133.3, 133.2, 133.1, 130.0, 129.9, 129.9, 129.8, 129.8, 129.7, 129.7, 129.60, 129.1, 128.9, 128.9, 128.7, 128.7, 128.4, 128.4, 128.4, 128.3, 128.3 (each Ar-C and CH), 96.1 (C-1β), 90.5 (C-1α), 74.3 (C-2β), 72.5 (C-5β), 72.3 (C-3β), 72.3 (C-2α), 70.2 (C-3α), 69.5 (C-4)α, 67.8 (C-5α), 62.9 (C-6α).



2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate (36)[15]

Hemiacetal (1.73 g, 2.89 mmol) was dissolved in anhydrous CH_2Cl_2 (28 mL) and cooled to 0 ºC. Trichloroacetonitrile (2.9 mL, 28.9 mmol) and DBU (0.13 mL, 0.87 mmol) were added to the reaction mixture dropwise and stirred at 0 ºC for 2.5 h. The solvent was partially removed under reduced pressure and immediately subjected to column chromatography (cylcohexane-EtOAc 4:1) to give the title compound as a white solid (1.65 g, 2.23 mmol, 77%). R_f 0.40 (cylcohexane-EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H, NH), 8.06 – 8.01

(overlapping signals, 2H, Ar-H), 7.98 – 7.91 (overlapping signals, 4H, Ar-H), 7.89 – 7.85 (overlapping signals, 2H, Ar-H), 7.58 – 7.53 (m, 1H, Ar-H), 7.52 – 7.48 (overlapping signals, 2H, Ar-H), 7.45 – 7.40 (overlapping signals, 3H, Ar-H), 7.38 – 7.33 (overlapping signals, 4H, Ar-H), 7.32 – 7.27 (overlapping signals, 2H, Ar-H), 6.84 (d, *J* = 3.6 Hz, 1H, H-1), 6.28 (t, *J* = 10.0 Hz, 1H, H-3), 5.82 (t, *J* = 10.0 Hz, 1H, H-4), 5.63 (dd, *J* = 10.2, 3.7 Hz, 1H, H-2), 4.70 – 4.61 (overlapping signals, 2H, H-5 and H-6a), 4.49 (dd, *J* = 12.4, 5.0 Hz, 1H, H-6b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 165.6, 165.4, 165.2 (each C=O), 160.5 (C=NH), 133.5, 133.3, 133.1, 129.9, 129.7, 129.7, 129.5, 128.8, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3 (Ar-C and CH), 93.1 (C-1), 90.7 (CCl_3), 70.7 (2s, C-2 and C-5), 70.2 (C-3), 68.6 (C-4), 62.5 (C-6).

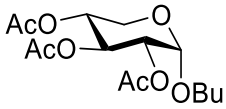


Butyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (11)[15]

A mixture of trichloroacetimidate (1.6 g, 2.15 mmol) and 4 Å molecular sieves was placed under reduced pressure for 2.5 h. Anhydrous CH_2Cl_2 (24 mL) and dry nBuOH (0.30 mL, 3.24 mmol) were added and the reaction mixture was stirred under N_2 for 40 mins. The reaction mixture was cooled to 0 ^{o} C and a solution of TMSOTf (40 µL, 0.22 mmol) in dry CH_2Cl_2 (1.2 mL) was added dropwise. After stirring for 2 h at 0 ^{o} C the reaction was quenched by the addition of solid $NaHCO_3$ (200 mg), the reaction was stirred for a further 20 mins before filtering through celite. The solvent was removed under reduced pressure and immediately purified through column chromatography (cyclohexane-EtOAc 4:1) to yield the glycoside as a white solid (800 mg, 1.28 mmol, 59%). R_f 0.21 (cylcohexane-EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, J = 7.1, 0.9 Hz, 2H, Ar-H), 7.96 (dd, J = 7.1, 0.7 Hz, 2H, Ar-H), 7.90 (dd, J = 8.2, 1.3 Hz, 2H, Ar-H), 7.83 (dd, J = 7.1, 0.7 Hz, 2H, Ar-H), 7.56 – 7.47 (overlapping signals, 3H, Ar-H), 7.45 – 7.36 (overlapping signals, 5H, Ar-H), 7.34 (t, J = 7.8 Hz, 2H, Ar-H), 7.28 (t, J = 7.8 Hz, 2H, Ar-H), 5.90 (t, J = 9.7 Hz, 1H, H-3), 5.67 (t, J = 9.7 Hz, 1H, H-4), 5.52 (dd, J = 9.8, 7.8 Hz, 1H, H-2), 4.83 (d, J = 7.8 Hz, 1H, H-1), 4.64 (dd, J = 12.1, 3.3 Hz, 1H, H6a), 4.51 (dd, J = 12.1, 5.3 Hz, 1H, H-6b), 4.15 (ddd, J = 9.2, 5.2, 3.3 Hz, 1H, H-5), 3.91 (dt, J = 9.7, 6.4 Hz, 1H, OC*H*H), 3.55 (dt, J = 9.7, 6.7 Hz, 1H, OCH*H*), 1.53 – 1.44 (overlapping signals, 2H, OCH_2CH_2), 1.29 – 1.19 (overlapping signals, 2H, $O(CH_2)_2CH_2$), 0.74 (d, J = 7.4 Hz, 2H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.2, 165.8, 165.2, 165.1 (each C=O), 133.4, 133.2, 133.1, 133.1, 129.8, 129.8, 129.7, 129.6, 129.4, 128.9, 128.8, 128.4, 128.3, 128.3, 128.3 (Ar-C and CH), 101.3 (C-1), 73.0 (C-3), 72.2 (C-5), 72.0 (C-2), 70.0 (OCH_2), 69.9 (C-4), 63.3

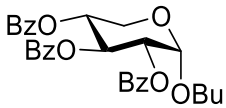
(C-6), 31.4 (OCH_2CH_2), 18.9 ($O(CH_2)_2CH_2$), 13.6 (CH_3); IR (ATR) cm^{-1}: 2959, 1720, 1451, 1250, 1090, 1067, 1026, 705, 685; ESI-HRMS calcd for $C_{38}H_{36}O_{10}Na$ 675.2206, found *m/z* 675.2206 $[M+Na]^+$

6.2 3 Analytical Data for Axial Anomers



Butyl 2,3,4-tri-*O*-acetyl-α-D-xylopyranoside (37)

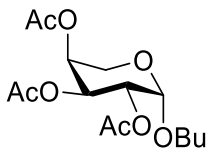
R_f 0.38 (cyclohexane- EtOAc 4:1); $[\alpha]_D^{20}$ -51.6 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.48 (t, *J* = 9.8 Hz, 1H, H-3), 4.99 (d, *J* = 3.7 Hz, 1H, H-1), 4.99 – 4.91 (m, 1H, H-4), 4.79 (dd, *J* = 10.2, 3.6 Hz, 1H, H-2), 3.77 (dd, *J* = 10.9, 5.9 Hz, 1H, H-5a), 3.69 (dt, *J* = 9.8, 6.5 Hz, 1H, OC*H*H), 3.62 (t, *J* = 10.8 Hz, 1H, H-5b), 3.39 (dt, *J* = 9.8, 6.5 Hz, 1H, OCH*H*), 2.17 (s, 3H, C(O)*C*H_3), 2.06 (s, 3H, C(O)*C*H_3), 2.03 (s, 3H, C(O)*C*H_3), 1.62 – 1.54 (overlapping signals, 2H, OCH_2CH_2), 1.44 – 1.34 (overlapping signals, 2H, $O(CH_2)CH_2$), 0.93 (t, *J* = 7.4 Hz, 3H, CH_3);^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 170.1, 170.0 (each C=O), 95.6 (C-1), 71.2(C-2), 69.7 (C-3), 69.5 (C-4), 68.2 (C-5), 58.2 (OCH_2), 30.9 (OCH_2CH_2), 20.8, 20.7, 20.7 (each C(O)*C*H_3), 19.2 ($O(CH_2)_2CH_2$), 13.8 (CH_3); IR (ATR) cm^{-1}: 2922, 1741, 1369, 1223, 1078, 1058. 1030; ESI-HRMS calcd for $C_{15}H_{24}O_8Na$ 355.1369, found *m/z* 355.1368 $[M+Na]^+$.



Butyl 2,3,4-tri-*O*-benzoyl- β-D-xylopyranoside (39)

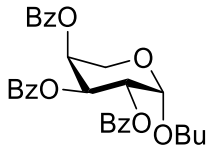
R_f 0.27 (cyclohexane-EtOAc 7:1); $[\alpha]_D^{20}$ +71.13 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.95 (overlapping signals, 4H, Ar-H), 7.95 – 7.89 (overlapping signals, 2H, Ar-H), 7.55 – 7.49 (overlapping signals, 2H, Ar-H), 7.47 – 7.42 (m, 1H, Ar-H), 7.42 – 7.35 (overlapping signals, 4H, Ar-H), 7.34 – 7.28 (overlapping signals, 2H, Ar-H), 6.16 (t, *J* = 9.8 Hz, 1H, H-3), 5.39 (td, *J* = 10.1, 5.8 Hz, 1H, H-4), 5.28 – 5.23 (overlapping peaks, 2H, H-1 and H-2), 4.07 (dd, *J* = 10.8, 5.9 Hz, 1H, H-5a), 3.87 (t, *J* = 10.8 Hz, 1H, H-5b), 3.78 (dt, *J* = 9.9, 6.4 Hz, 1H, OC*H*H), 3.45 (dt, *J* = 9.8, 6.5 Hz, 1H, OCH*H*), 1.65 – 1.51 (overlapping signals, 2H, OCH_2CH_2), 1.41 – 1.30 (overlapping signals, 2H, $O(CH_2)_2CH_2$), 0.84 (t, *J* = 7.3 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.85, 165.80, 165.63 (each C=O), 133.33, 133.28, 133.09, 129.85, 129.82, 129.68, 129.39, 129.16, 129.13, 128.41, 128.29, 128.28 (Ar-C and CH), 96.07 (C-1), 71.98 (C-2), 70.34 (C-4), 70.07 (C-3), 68.46 (OCH_2), 58.59 (C-5), 31.38 (OCH_2CH_2),

19.19 ($O(CH_2)_2CH_2$), 13.68 (CH_3); IR (ATR) cm^{-1}: 2951, 1719, 1252, 1094, 1043, 705, 687; ESI-HRMS calcd for $C_{30}H_{30}O_8Na$ 548.1838, found *m/z* 548.1833 $[M+Na]^+$.



Butyl 2,3,4-tri-*O*-acetyl-β-L-arabinopyranoside (42)

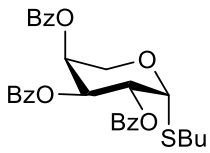
R_f 0.48 (2:3 EtOAc-cyclohexane); $[\alpha]_D^{20}$ +150.3 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.37 – 5.33 (overlapping signals, 2H, H-3 and H-4), 5.15 (dd, *J* = 9.9, 3.5 Hz, 1H, H-2), 5.07 (d, *J* = 3.6 Hz, 1H, H-1), 3.96 (dd, *J* = 13.2, 1.2 Hz, 1H, H5a), 3.72 – 3.64 (overlapping signals, 2H, H-5b and OC*H*H), 3.40 (dt, *J* = 9.7, 6.5 Hz, 1H, OCH*H*), 2.14 (s, 3H, $C(O)CH_3$), 2.07 (s, 3H, $C(O)CH_3$), 2.01 (s, 3H, $C(O)CH_3$), 1.61 – 1.53 (overlapping signals, 2H, OCH_2CH_2), 1.44 – 1.34 (overlapping signals, 2H, $O(CH_2)CH_2$), 0.93 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 170.4, 170.1 (each C=O), 96.3 (C-1), 69.2 (C-3), 68.5 (C-5), 68.2 (C-2), 67.3 (C-4), 60.3 (OCH_2), 31.4 (OCH_2CH_2), 20.9, 20.8, 20.7 (each $C(O)CH_3$), 19.2 ($O(CH_2)CH_2$), 13.7 (CH_3); IR (ATR) cm^{-1}: 2961, 1740, 1371, 1217, 1062; ESI-HRMS calcd for $C_{15}H_{28}O_8N$ 350.1815, found *m/z* 350.1820 $[M+NH_4]^+$.



Butyl 2,3,4-tri-*O*-benzoyl-β-L-arabinopyranoside (44)

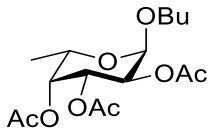
R_f 0.31 (cyclohexane-EtOAc 6:1); ^1H NMR (500 MHz, $CDCl_3$) δ 8.12 – 8.08 (overlapping signals, 2H, Ar-H), 8.00 – 7.97 (m, 1H, Ar-H), 7.89 – 7.82 (overlapping signals, 2H, Ar-H), 7.62 – 7.57 (m, 1H, Ar-H), 7.54 – 7.42 (overlapping signals, 4H, Ar-H), 7.41 – 7.36 (overlapping signals, 2H, Ar-H), 7.29 – 7.25 (overlapping signals, 3H, Ar-H), 5.94 (dd, *J* = 10.7, 3.6 Hz, 1H, H-3), 5.75 (dt, *J* = 3.5, 1.6 Hz, 1H, H-4), 5.71 (dd, *J* = 10.7, 3.6 Hz, 1H, H-2), 5.32 (d, *J* = 3.5 Hz, 1H, H-1), 4.21 (dd, *J* = 13.2, 1.4 Hz, 1H, H-5a), 3.95 (dd, *J* = 13.1, 2.0 Hz, 1H, H-5b), 3.79 (dt, *J* = 9.8, 6.4 Hz, 1H, OC*H*H), 3.47 (dt, *J* = 9.8, 6.5 Hz, 1H, OCH*H*), 1.63 – 1.56 (overlapping signals, 2H, OCH_2CH_2), 1.44 – 1.34 (overlapping signals, 2H, $O(CH_2)_2CH_2$), 0.86 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 165.8, 165.6 (each C=O), 133.3, 133.3, 133.1, 129.8, 129.8, 129.7, 129.3, 129.3, 128.5, 128.5, 128.4, 128.3, 128.3 (Ar-C and CH), 96.8 (C-1), 70.3 (C-4), 69.5 (C-2), 68.4 (OCH_2), 68.1 (C-3), 60.5

(C-5), 31.4 (OCH_2CH_2), 19.2 ($O(CH_2)_2CH_2$), 13.7 (CH_3); IR (ATR) cm^{-1}: 2959, 1719, 1451, 1248, 1092, 1068, 1026, 705, 686; ESI-HRMS calcd for $C_{30}H_{34}O_8N$ 536.2284, found *m/z* 536.2285 $[M+NH_4]^+$.



Butyl 2,3,4-tri-*O*-benzoyl-1-thio-β-L-arabinopyranoside (46)

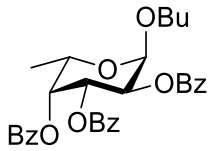
R_f 0.23 (cylcohexane-EtOAc 12:1); $[\alpha]_D^{20}$ +239.7 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.12 – 8.06 (overlapping signals, 2H, Ar-H), 7.64 – 7.57 (m, 1H, Ar-H), 7.56 – 7.43 (overlapping signals, 4H, Ar-H), 7.43 – 7.36 (overlapping signals, 2H, Ar-H), 7.32 – 7.23 (overlapping signals, 2H, Ar-H), 5.90 – 5.85 (overlapping peaks, 2H, H-1 and H-2), 5.80 (dd, *J* = 10.1, 3.1 Hz, 1H, H-3), 5.74 (dt, *J* = 3.5, 1.9 Hz, 1H, H-4), 4.57 (dd, *J* = 13.2, 1.5 Hz, 1H, H-5a), 3.98 (dd, *J* = 13.2, 2.5 Hz, 1H, H-5b), 2.66 – 2.54 (overlapping signals, 2H, SCH_2), 1.65 – 1.52 (overlapping signals, 2H, SCH_2CH_2), 1.45 – 1.32 (overlapping signals, 2H, $S(CH_2)_2CH_2$), 0.88 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 165.7, 165.4 (each C=O), 133.4, 133.4, 133.2, 129.9, 129.9, 129.7, 129.6, 129.2, 129.1, 128.5, 128.5, 128.3 (each C=O), 83.2 (C-1), 69.8 (C-4), 69.3 (C-2), 68.5 (C-3), 60.9 (C-5), 31.6 (SCH_2CH_2), 30.0 (SCH_2), 21.9 ($S(CH_2)_2CH_2$), 13.6 (CH_3); IR (ATR) cm^{-1}: 2958, 1720, 1451, 1249, 1068, 1025, 703, 686; ESI-HRMS calcd for $C_{30}H_{34}O_7SN$ 552.2056, found *m/z* 552.2057 $[M+NH_4]^+$.



Butyl 2,3,4-tri-*O*-acetyl-α-L-fucopyranoside (47)

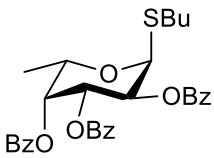
Rf 0.41 (cylcohexane-EtOAc 2:1); $[\alpha]_D^{20}$ -134.3 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.36 (dd, *J* = 10.7, 3.4 Hz, 1H, H-3), 5.30 (d, *J* = 3.3 Hz, 1H, H-4), 5.10 (dd, *J* = 10.8, 3.8 Hz, 1H, H-2), 5.05 (d, *J* = 3.6 Hz, 1H, H-1), 4.16 (q, *J* = 6.5 Hz, 1H, H-5), 3.68 (dt, *J* = 9.8, 6.5 Hz, 1H, OC*H*H), 3.41 (dt, *J* = 9.8, 6.5 Hz, 1H, OCH*H*), 2.16 (s, 3H, $C(O)CH_3$), 2.07 (s, 3H, $C(O)CH_3$), 1.99 (s, 3H, $C(O)CH_3$), 1.61 – 1.52 (overlapping signals, 2H, OCH_2CH_2), 1.43 – 1.33 (overlapping signals, 2H, $O(CH_2)_2CH_2$), 1.14 (d, *J* = 6.6 Hz, 3H, CH_3), 0.93 (t, *J* = 7.4 Hz, 3H, CH_2CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 170.5, 170.1 (each C=O), 96.0 (C-1), 71.2 (C-4), 68.4 (C-2), 68.2, 68.1 (overlapping peaks, C-3 and OCH_2), 64.2 (C-5), 31.4

(OCH_2CH_2), 20.8, 20.7, 20.7 (each C(O)CH_3), 19.2 ($O(CH_2)_2CH_2$), 15.9 (CH_3), 13.7 (CH_2CH_3); IR (ATR) cm^{-1}: 2917, 1743, 1371, 1220, 1048; ESI-HRMS calcd for $C_{16}H_{26}O_8Na$ 369.1525, found *m/z* 369.1522 $[M+Na]^+$.



Butyl 2,3,4-tri-*O*-benzoyl-α-L-fucopyranoside (49)

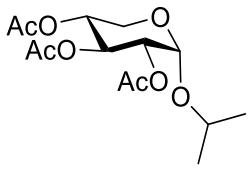
R_f 0.41 (cylcohexane-EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 – 8.08 (overlapping signals, 2H, Ar-H), 8.01 – 7.96 (overlapping signals, 2H, Ar-H), 7.82 – 7.77 (overlapping signals, 2H, Ar-H), 7.65 – 7.59 (m, 1H, Ar-H), 7.50 (overlapping signals, 3H, Ar-H), 7.45 – 7.40 (m, 1H, Ar-H), 7.40 – 7.35 (overlapping signals, 2H, Ar-H), 7.26 – 7.21 (overlapping signals, 2H, Ar-H), 5.96 (dd, J = 10.7, 3.5 Hz, 1H, H-3), 5.76 (dd, J = 3.5, 1.3 Hz, 1H, H-4), 5.64 (dd, J = 10.7, 3.7 Hz, 1H, H-2), 5.32 (d, J = 3.7 Hz, 1H, H-1), 4.43 (qd, J = 6.5, 1.2 Hz, 1H, H-5), 3.78 (dt, J = 9.8, 6.4 Hz, 1H, OC*H*H), 3.48 (dt, J = 9.9, 6.5 Hz, 1H, OCH*H*), 1.62 – 1.56 (overlapping signals, 2H, OCH_2CH_2), 1.44 – 1.33 (overlapping signals, 2H, $O(CH_2)_2CH_2$), 1.28 (d, J = 6.6 Hz, 3H, CH_3), 0.86 (t, J = 7.4 Hz, 3H, CH_2CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 166.0, 165.7 (each C=O), 133.3, 133.2, 133.0, 129.9, 129.8, 129.6, 129.6, 129.5, 129.4, 129.4, 128.5, 128.5, 128.3, 128.2 (each Ar-C and CH), 96.5 (C-1), 72.1 (C-4), 69.4 (C-2), 68.9 (C-3), 68.4 (OCH_2), 64.8 (C-5), 31.5 (OCH_2CH_2), 19.2 ($O(CH_2)_2CH_2$), 16.1 (CH_3), 13.7 (CH_2CH_3); IR (ATR) cm^{-1}: 2959, 1721, 1452, 1261, 1095, 1026, 706, 686; ESI-HRMS calcd for $C_{31}H_{36}O_8N$ 550.2441, found *m/z* 550.2443 $[M+NH_4]^+$.



Butyl 2,3,4-Tri-*O*-benzoyl-1-thio-α-L-fucopyranoside (51)

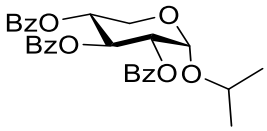
R_f 0.28 (cylcohexane-EtOAc 10:1); $[\alpha]_D^{20}$ -212.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 – 8.08 (overlapping signals, 2H, Ar-H), 8.02 – 7.94 (overlapping signals, 2H, Ar-H), 7.84 – 7.75 (overlapping signals, 2H, Ar-H), 7.63 – 7.59 (m, 1H, Ar-H), 7.54 – 7.46 (overlapping signals, 3H, Ar-H), 7.45 – 7.34 (overlapping signals, 3H, Ar-H), 7.26 – 7.21 (overlapping signals, 2H, Ar-H), 5.93 (d, *J* = 3.9 Hz, 1H, H-1), 5.85 – 5.78 (overlapping signals, 2H, H-2 and H-3), 5.78 – 5.71 (m, 1H, H-4), 4.77 (q, *J* = 6.4 Hz, 1H, H-5), 2.68 – 2.59 (m, 1H,

SC*H*H), 2.56 (dt, *J* = 12.9, 7.4 Hz, 1H, SCH*H*), 1.68 – 1.56 (overlapping signals, 2H, SCH_2CH_2), 1.42 – 1.34 (overlapping signals, 2H, $S(CH_2)CH_2$), 1.30 (d, *J* = 6.6 Hz, 3H, CH_3), 0.88 (t, *J* = 7.4 Hz, 3H, $S(CH_2)_3CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 165.8, 165.5 (each C=O), 133.4, 133.3, 133.1, 129.9, 129.7, 129.4, 129.2, 129.2, 128.6, 128.4, 128.2 (Ar-C and CH), 82.9 (C-1), 71.8 (C-4), 69.4, 69.0 (C-2 and C-3), 65.3 (C-5), 31.7 (SCH_2CH_2), 30.1 (SCH_2), 21.9 ($S(CH_2)_2CH_2$), 16.1 (CH_3), 13.6 $S(CH_2)_3CH_3$); IR (ATR) cm^{-1}: 2957, 1721, 1451, 1257, 1095, 1068, 1026, 704, 686; ESI-HRMS calcd for $C_{31}H_{32}O_7SNa$ 571.1766, found *m/z* 571.1767 $[M+Na]^+$.



Isopropyl 2,3,4-tri-*O*-acetyl-α-D-xylopyranoside (52)

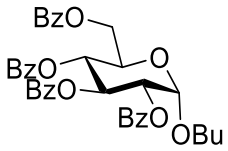
R_f 0.46 (cyclohexane-EtOAc 2:1); $[\alpha]_D^{20}$ +132.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.48 (t, *J* = 9.8 Hz, 1H, H-3), 5.11 (d, *J* = 3.6 Hz, 1H, H-1), 4.95 (td, *J* = 10.0, 6.1 Hz, 1H, H-4), 4.74 (dd, *J* = 10.2, 3.7 Hz, 1H, H-2), 3.84 (hept, *J* = 6.3 Hz, 1H, $CH(CH_3)_2$), 3.78 – 3.67 (overlapping signals, 2H, H-5a and H-5b), 2.06 (s, 3H, $C(O)CH_3$), 2.03 (s, 6H, 2 x $C(O)CH_3$), 1.24 (d, *J* = 6.3 Hz, 3H, CH_3), 1.11 (d, *J* = 6.3 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 170.1, 170.0 (each C=O), 93.9 (C-1), 71.2 (C-2), 70.7 ($CH(CH_3)_2$), 69.7, 69.6 (C-3 and C-4), 58.2 (C-5), 23.1, 21.4 (each CH_3), 20.8, 20.7, 20.7 (each $C(O)CH_3$); IR (ATR) cm^{-1}: 2976, 1743, 1367, 1214, 1038; ESI-HRMS calcd for $C_{14}H_{26}O_8N$ 336.1658, found *m/z* 336.1660 $[M+NH_4]^+$.



Isopropyl 2,3,4-tri-*O*-benzoyl- α-D-xylopyranoside (53)

R_f 0.35 (cyclohexane-EtOAc 6:1); $[\alpha]_D^{20}$ +77.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 – 7.96 (overlapping signals, 4H, Ar-H), 7.95 – 7.92 (overlapping signals, 2H, Ar-H), 7.54 – 7.49 (overlapping signals, 2H, Ar-H), 7.47 – 7.43 (m, 1H, Ar-H), 7.41 – 7.36 (overlapping signals, 4H, Ar-H), 7.34 – 7.30 (overlapping signals, 2H, At-H), 6.15 (t, *J* = 9.9 Hz, 1H, H-3), 5.39 (dd, *J* = 10.2, 6.0 Hz, 1H, H-4), 5.37 (d, *J* = 3.8 Hz, 1H, H-1), 5.21 (dd, *J* = 10.1, 3.8 Hz, 1H, H-2), 4.06 (dd, *J* = 10.8, 5.9 Hz, 1H, H-5a), 3.98 – 3.87 (overlapping signals, 2H, H-5a

and C*H*(CH_3)$_2$), 1.28 (d, *J* = 6.2 Hz, 3H, CH_3), 1.07 (d, *J* = 6.1 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 165.8, 165.7 (each C=O), 133.3, 133.3, 133.1, 129.8, 129.8, 129.7, 129.4, 129.2, 129.2, 128.4, 128.4, 128.3 (Ar-C and CH), 94.6 (C-1), 72.0 (C-2), 71.4 (*C*H(CH_3)$_2$), 70.4 (C-4), 70.1 (C-3), 58.7 (C-5), 23.3, 21.7 (each CH_3); IR (ATR) cm^{-1}: 2980, 1719, 1602, 1454, 1275, 1253, 1096, 1038, 705, 688; ESI-HRMS calcd for $C_{29}H_{32}O_8N$ 522.2128, found *m/z* 522.2128 [M+NH_4]$^+$.



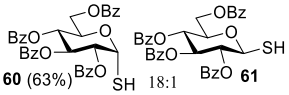
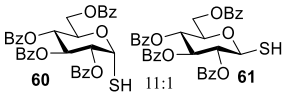
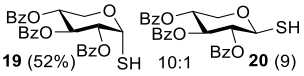
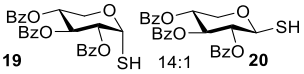
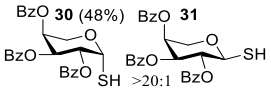
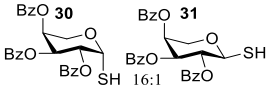
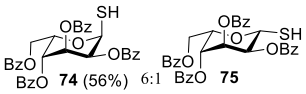
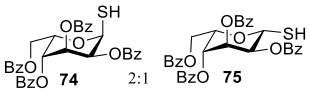
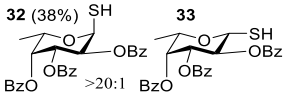
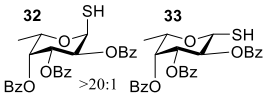
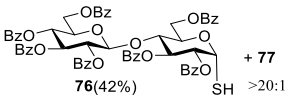
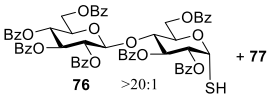
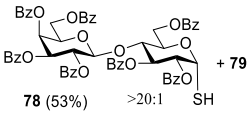
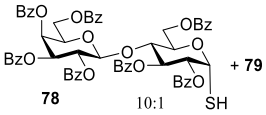
Butyl 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranoside (145)[15]

R_f 0.33 (cylcohexane-EtOAc 5:1);^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.99 (d, *J* = 7.7 Hz, 2H, Ar-H), 7.95 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.87 (d, *J* = 7.7 Hz, 2H, Ar-H), 7.52 (dt, *J* = 21.5, 7.4 Hz, 3H, Ar-H), 7.45 – 7.33 (overlapping signals, 7H, Ar-H), 7.29 (t, *J* = 7.7 Hz, 2H, Ar-H), 6.20 (t, *J* = 9.8 Hz, 1H, H-3), 5.67 (t, *J* = 9.8 Hz, 1H, H-4), 5.34 (d, *J* = 3.8 Hz, 1H, H-1), 5.30 (dd, *J* = 10.1, 3.7 Hz, 1H, H-2), 4.64 – 4.58 (m, 1H, H-6a), 4.52 – 4.43 (overlapping signals, 2H, H-6b and H-5), 3.80 (dt, *J* = 10.0, 6.5 Hz, 1H, OC*H*H), 3.50 (dt, *J* = 9.9, 6.6 Hz, 1H, OCH*H*), 1.65 – 1.54 (overlapping signals, 2H, OCH_2CH_2), 1.35 (h, *J* = 7.4 Hz, 2H, O(CH_2)$_2$C*H*$_2$), 0.83 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.2, 165.8, 165.8, 165.3 (each C=O), 133.4, 133.3, 133.1, 129.9, 129.7, 129.7, 129.1, 128.9, 128.4, 128.4, 128.2 (Ar-H), 96.0 (C-1), 72.0 (C-2), 70.6 (C-3), 69.6 (C-4), 68.7 (O*C*H$_2$), 67.7 (C-5), 63.1 (C-6), 31.3 (OCH_2CH_2), 19.2 (O(CH_2)$_2$*C*H$_2$), 13.7 (CH_3); IR (ATR) cm^{-1}: 2957, 1716, 1451, 1266, 1094, 1067, 1026, 706, 686; ESI-HRMS calcd for $C_{38}H_{36}O_{10}Na$ 675.2206, found *m/z* 675.2207 [M+NH_4]$^+$.

6.3 Chapter 3 Experimental Data

6.3 1 Methods for Epimerisation Reactions

Table 6.1 More details on use of pyridine[16]

Reactant	Additive	Products, ratio (isolated yield of major anomer)
60, **61** (2:9)	pyridine (0.5 equiv)	
60, **61** (2:9)	-[a]	
19, **20** (1:2)	-	
19, **20** (1:2)	pyridine [b] (0.5 equiv)	
31, **30** (2:1)	-	
31, **30** (2:1)	pyridine (0.5 equiv)[c]	
74, **75** (1:6)	-	
74, **75** (1:6)	pyridine (0.5 equiv)[d]	
33		
33	pyridine (0.5 equiv)[e]	
76, **77** (1:2)	pyridine (0.5 equiv)	
76, **77** (1:2)	-[f]	
78, **79** (1:4)	pyridine (0.5 equiv)	
78, **79** (1:4)	-[g]	

Footnotes to Table 6.1

[a]The stereoselectivity was reduced in absence of pyridine. An isolated yield was not obtained for **60** from this reaction.

[b]The amount of glycosyl chloride was present in the final reaction mixture (before chromatography) to ~13%, compared with 6% in the reaction without pyridine, even though the stereoselectivity was higher. An isolated yield was not obtained for **19** from this reaction.

[c] The stereoselectivity was lower than in absence of pyridine. An isolated yield was not obtained for **30** from this reaction

[d] The stereoselectivity was lower than in the absence of pyridine. An isolated yield was not obtained for **74** in this reaction.

[e] There was little difference observed in the stereoselectivity in the presence of pyridine. An isolated yield was not obtained for **33** from this reaction

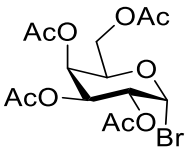
[f] There was little difference in selectivity in the presence of pyridine. An isolated yield was not obtained for this reaction.

[g] The stereoselectivity was lower in absence of pyridine. An isolated yield was not obtained from this reaction.

Method A (Epimerisation with $TiCl_4$) The thiol (1.0 equiv) was dissolved in CH_2Cl_2 (0.1 M) under nitrogen or argon. For some thiols pyridine (1.0 M in CH_2Cl_2, 0.5 equiv) was then added (see Table 6.1). A 1.0 M solution of $TiCl_4$ in anhydrous CH_2Cl_2 (3 equiv) was then added and the mixture was stirred at room temp for 16 h. The deep coloured solution lightened in appearance during the course of the reaction. The mixture was then diluted with CH_2Cl_2 and washed with satd aq NH_4Cl. The organic and aq layers were separated, and the aq layer extracted with further CH_2Cl_2. The organic extracts were combined and washed with satd aq $NaHCO_3$, brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. Chromatography of the residue gave the isolated products.

Method B (Epimerisations with $SnCl_4$) The axial thiol (100 mg or 200 mg) was dried under reduced pressure for at least 3 h prior to reaction in a flame dried flask. The thiol was then dissolved in anhydrous CH_2Cl_2 (1 mL or 2 mL) under nitrogen or argon and $SnCl_4$ (1.0 M in CH_2Cl_2, 2.5 eq) was added slowly. For **64**, **66** and **68**, MSA (1.0 M in CH_2Cl_2, 0.5 or 2 equiv) was added. The reaction was stirred at room temp for 24 h, or at 4 ^oC or -30 ^oC, as required. The reaction was diluted with EtOAc and quenched by addition of 1.0 M $KHSO_4$. The aq layer was extracted with EtOAc and the combined organic portion was washed with satd aq NaHCO3 and brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure.

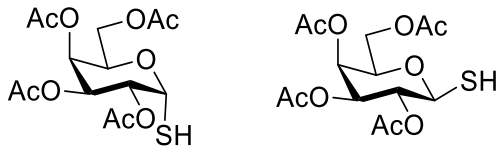
6.3 2 Experimental Data for Glycosyl Thiols



2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (91)[17]

Peracetylated galactose (10 g, 25.62 mmol) was dissolved in anhydrous CH_2Cl_2 (50 mL) and cooled to 0 ^oC. HBr (33% in AcOH, 12.65 mL) was added and the reaction mixture was allowed to stir overnight, warming to room temperature. The reaction was poured onto an ice-water mixture and stirred for 15 mins. The mixture was diluted with CH_2Cl_2 and separated. The organic layer was washed with satd. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give a viscous oil as the title compound (10.25 g, 97 %). R_f 0.46 (cyclohexane-EtOAc 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (d, *J* = 3.9 Hz, 1H, H-1), 5.52 (dd, *J* = 3.3, 1.3 Hz, 1H, H-4), 5.41 (dd, *J* = 10.6, 3.3 Hz, 1H, H-3), 5.05 (dd, *J* = 10.6, 4.0 Hz, 1H, H-2), 4.49 (dd, *J* = 7.3, 6.0 Hz, 1H, H-5), 4.19 (dd, *J* = 11.4, 6.4 Hz, 1H, H-6a), 4.11 (dd,

J = 11.4, 6.7 Hz, 1H, H-6b), 2.15 (s, 3H, C(O)CH_3), 2.12 (s, 3H, C(O)CH_3), 2.06 (s, 3H, C(O)CH_3), 2.01 (s, 3H, C(O)CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.3, 170.1, 169.9, 169.7 (each C=O), 88.1 (C-1), 71.1 (C-5), 68.0 (C-3), 67.8 (C-2), 67.0 (C-4), 60.8 (C-6), 20.7, 20.6, 20.6, 20.6 (each C(O)*C*H_3); IR (ATR) cm^{-1}: 1742, 1369, 1207, 1075.



2,3,4,6-Tetra-*O*-acetyl-1-thio-D-galactopyranose (55 and 56)[18]

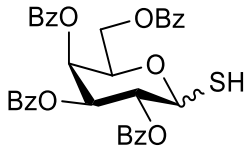
2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (4.0 g, 9.73 mmol) was dissolved in acetone (48 mL) and to this solution, thiourea (1.26 g, 16.54 mmol) was added. The reaction was heated to reflux (70 °C) and stirred overnight. The solution was allowed to cool to room temperature and concentrated in vacuo. The salt was used without any further purification. The salt (4.74 g, 9.73 mmol) was suspended in a 3:2 CH_2Cl_2-H_2O mixture (80 mL) to which sodium metabisulfite (2.40 g, 12.65 mmol) was added. The reaction mixture was heated to reflux (64 °C) and left to stir for 2.5 h. The solution was allowed to cool to room temperature and separated. The aqueous layer was re-extracted with CH_2Cl_2 and the combined organic layer were washed with water, dried over Na_2SO_4, with the solvent then being removed under reduced pressure. Chromatography (cyclohexane-EtOAc 2:1 → 3:2) gave the title compounds (α-anomer: 0.125 g, 4%; β-anomer: 2.562 g, 72%), as a viscous oil and white solid, respectively.

The equatorial thiol **56** (1.0 g) was dissolved in EtOAc (10 mL) under nitrogen or argon. $SnCl_4$ (1.0 M in CH_2Cl_2, 2.5 eq.) was added and the mixture was stirred at room temperature for 24 h. The reaction was diluted with EtOAc and quenched by addition of 1.0 M $KHSO_4$. The aq. layer was extracted with EtOAc and combined organic layers were washed with satd. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated in vacuo and column chromatography (cyclohexane-EtOAc 2:1→3:2) gave **55** (210 mg, 21%). Reaction of **55** (100 mg, 0.27 mmol) by Method B gave **56** (46.0 mg, 46%).

Analytical data for 55 R_f 0.25 (cyclohexane-EtOAc 3:2); $[\alpha]_D^{20}$ +172.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (t, *J* = 5.1 Hz, 1H, H-1), 5.47 (dd, *J* = 3.1, 1.3 Hz, 1H, H-4), 5.28 (dd, *J* = 10.9, 5.1 Hz, 1H, H-2), 5.24 (dd, *J* = 10.8, 3.1 Hz, 1H, H-3), 4.62 (t, *J* = 6.5 Hz, 1H, H-5), 4.14 (dd, *J* = 11.3, 6.5 Hz, 1H, H-6a), 4.07 (dd, *J* = 11.3, 6.6 Hz, 1H, H-6b), 2.15 (s, 3H, C(O)CH_3), 2.09 (s, 3H, C(O)CH_3), 2.06 (s, 3H, C(O)CH_3), 2.01 (s, 3H, C(O)CH_3), 1.83

(d, J = 5.1 Hz, 1H, SH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 170.1, 169.9, 169.9 (each C=O), 77.7, 67.7, 67.5, 67.4, 67.1, 61.4, 20.7, 20.7, 20.6, 20.6 (each C(O)CH_3); IR (ATR) cm^{-1}: 2951, 1725, 1369, 1242, 1087, 1067; ES-HRMS calcd for $C_{14}H_{20}O_9SNa$ 387.0726, found m/z 387.0722 $[M+Na]^+$.

Analytical data for 56 R_f 0.21 (cyclohexane-EtOAc 3:2); $[\alpha]_D^{20}$ +35.9 (c 1.0, $CHCl_3$), [Lit. $[\alpha]_D^{19}$ +32.0 (c 3.5, $CHCl_3$)][18]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (dd, J = 3.5, 1.2 Hz, 1H, H-4), 5.18 (t, J = 9.9 Hz, 1H. H-2), 5.02 (dd, J = 10.1, 3.4 Hz, 1H, H-3), 4.53 (t, J = 9.8 Hz, 1H, H-1), 4.13 (dd, J = 6.6, 1.1 Hz, 2H, H-6a and H-6b), 3.94 (td, J = 6.6, 1.2 Hz, 1H, H-5), 2.37 (d, J = 9.9 Hz, 1H, SH), 2.17 (s, 3H, C(O)CH_3), 2.09 (s, 3H, C(O)CH_3), 2.05 (s, 3H, C(O)CH_3), 1.99 (s, 3H, C(O)CH_3);^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 170.1, 170.0, 169.8 (each C=O), 79.2 (C-1), 75.0 (C-5), 71.6 (C-3), 70.8 (C-2), 67.2 (C-4), 61.5 (C-6), 20.8, 20.7, 20.7, 20.5 (each C(O)CH_3); $^1J_{C1.H1}$ = 155.3 Hz; IR (ATR) cm^{-1}: 2546, 1740, 1370, 1212, 1083, 1043; ES-HRMS calcd for $C_{14}H_{20}O_9SNa$ 387.0726, found m/z 387.0729 $[M+Na]^+$.



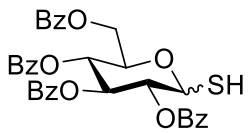
2,3,4,6-Tetra-*O*-benzoyl-1-thio-α/β-D-galactopyranose (57 and 58)[15]

The reaction of a mixture of anomers **57** and **58** (1.0 g, 1.6 mmol), according to Method A, gave **57** as a white solid (560 mg, 56 %) after flash chromatography using a short column of silica gel (petroleum ether-CH_2Cl_2-Et_2O 14:10:1 or cyclohexane-EtOAc 7:3 as eluant). Reaction of **57** (100 mg, 0.16 mmol) according to Method B and column chromatography (cyclohexane-EtOAc 6:1→5:1) gave **58** (59 mg, 59%).

Analytical data for 57 $[\alpha]_D^{20}$ +158.3 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 – 8.06 (overlapping signals, 2H, Ar-H), 8.05 – 8.01 (overlapping signals, 2H, Ar-H), 8.00 – 7.96 (overlapping signals, 2H, Ar-H), 7.82 – 7.77 (overlapping signals, 2H, Ar-H), 7.65 – 7.61 (m, 1H, Ar-H), 7.59 – 7.37 (overlapping signals, 9H, Ar-H), 7.29 – 7.22 (overlapping signals, 2H, Ar-H), 6.32 (t, J = 5.1 Hz, 1H, H-1), 6.06 (dd, J = 3.3, 1.3 Hz, 1H, H-4), 5.94 – 5.82 (overlapping signals, 2H, H-2 and H-3), 5.05 (t, J = 6.4 Hz, 1H, H-5), 4.61 (dd, J = 11.4, 6.7 Hz, 1H, H-6a), 4.42 (dd, J = 11.4, 6.2 Hz, 1H, H-6b), 1.99 (d, J = 5.1 Hz, 1H, SH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 165.5, 165.4, 165.4 (each C=O), 133.6, 133.3, 133.2, 129.9, 129.9, 129.8, 129.7, 129.4, 129.0, 128.9, 128.8, 128.6, 128.5, 128.4, 128.3 (each Ar-C and CH), 78.2

(C-1), 68.8 (C-4), 68.5 (C-3), 68.3 (C-2), 67.9 (C-5), 62.2 (C-6); $^{1}J_{C1.H1}$ = 172.4 Hz; IR cm^{-1}: 1717, 1604, 1453, 1249, 1093, 1068, 1026, 704, 684; ES-HRMS calcd for $C_{34}H_{32}O_9SN$ 630.1798, found m/z 630.1794 $[M+NH_4]^+$.

Analytical data for 58 R_f 0.15 (cyclohexane-EtOAc 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 – 8.06 (overlapping signals, 2H, Ar-H), 8.04 – 7.98 (overlapping signals, 2H, Ar-H), 7.99 – 7.94 (overlapping signals, 2H, Ar-H), 7.80 – 7.73 (overlapping signals, 2H, Ar-H), 7.65 – 7.59 (m, 1H, Ar-H), 7.57 – 7.47 (overlapping signals, 4H, Ar-H), 7.45 – 7.35 (overlapping signals, 5H, Ar-H), 7.27 – 7.20 (overlapping signals, 2H, Ar-H), 6.05 (d, *J* = 3.4 Hz, 1H, H-4), 5.77 (t, *J* = 9.8 Hz, 1H, H-2), 5.64 (dd, *J* = 10.1, 3.4 Hz, 1H, H-3), 4.93 (t, *J* = 9.6 Hz, 1H, H-1), 4.66 (dd, *J* = 10.8, 5.9 Hz, 1H, H-6a), 4.45 – 4.35 (overlapping signals, 2H. H-5 and H-6b), 2.58 (d, *J* = 9.5 Hz, 1H, SH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 165.4, 165.4 (each C=O), 133.6, 133.4, 133.3, 133.3, 129.9, 129.8, 129.7, 129.3, 129.0, 128.6, 128.6, 128.4, 128.4, 128.2 (Ar-C and CH), 79.4 (C-1), 75.5 (C-5), 72.3 (C-3), 71.9 (C-2), 68.3 (C-4), 62.1 (C-6); $J_{C1.H1}$ = 155.2 Hz.



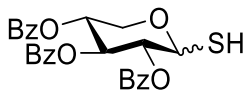
2,3,4,6-Tetra-*O*-benzoyl-1-thio-D-glucopyranose (60 and 61)[19]

The reaction of a mixture of anomers **60** and **61** (1.00 g, 1.63 mmol), according to Method A, gave **60** (629 mg, 63 %) as a white solid after flash chromotography (cyclohexane-EtOAc 7:3). Reaction of **60** (100 mg, 0.16 mmol) according to Method B and column chromatography (cyclohexane-EtOAc 5:1) gave **61** (52 mg, 52%).

Analytical data for 60 *Rf* 0.53 (3:7 EtOAc-petroleum ether); $[\alpha]_D^{20}$ +102.0 (*c* 0.79, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 – 8.04 (overlapping signals, 2H, Ar-H), 8.01 – 7.97 (overlapping signals, 2H, Ar-H), 7.96 – 7.92 (overlapping signals, 2H, Ar-H), 7.89 – 7.86 (overlapping signals, 2H, Ar-H), 7.59 – 7.48 (overlapping signals, 3H, Ar-H), 7.47 – 7.34 (overlapping signals, 7H, Ar-H), 7.34 – 7.28 (overlapping signals, 2H, Ar-H), 6.20 (t, *J* = 5.7 Hz, 1H, H-1), 6.08 (t, *J* = 9.9 Hz, 1H, H-3), 5.72 (t, *J* = 9.9 Hz, 1H, H-4), 5.50 (dd, *J* = 10.2, 5.6 Hz, 1H, H-2), 4.86 (ddd, *J* = 10.1, 4.6, 2.6 Hz, 1H, H-5), 4.64 (dd, *J* = 12.4, 2.8 Hz, 1H, H-6a), 4.49 (dd, *J* = 12.4, 4.6 Hz, 1H, H-6b), 2.08 (d, *J* = 5.7 Hz, 1H, SH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 165.7, 165.2, 165.2 (each C=O), 133.6, 133.5, 133.3, 133.1, 130.0, 129.9, 129.8, 129.7, 129.6, 128.9, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3 (each Ar-C), 77.6 (C-1),

71.2 (C-2), 70.3 (C-3), 69.2 (C-4), 68.9 (C-5), 62.6 (C-6); IR (ATR) cm^{-1}: 1721, 1602, 1452, 1260, 1090, 1069, 1027, 707; ESI-HRMS calcd for $C_{34}H_{28}O_9SNa$ 635.1352, found m/z 635.1349 $[M+Na]^+$.

Analytical data for 61 R_f 0.29 (cyclohexane-EtOAc 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 – 8.02 (overlapping signals, 2H, Ar-H), 7.98 – 7.95 (overlapping signals, 2H, Ar-H), 7.91 – 7.87 (overlapping signals, 2H, Ar-H), 7.83 – 7.78 (overlapping signals, 2H, Ar-H), 7.57 – 7.47 (overlapping signals, 3H, Ar-H), 7.44 – 7.37 (overlapping signals, 5H, Ar-H), 7.36 – 7.32 (overlapping signals, 2H, Ar-H), 7.29 – 7.26 (overlapping signals, 2H, Ar-H), 5.89 (t, *J* = 9.6 Hz, 1H, H-3), 5.72 (t, *J* = 9.8 Hz, 1H, H-4), 5.51 (t, *J* = 9.6 Hz, 1H, H-2), 4.90 (t, *J* = 9.7 Hz, 1H, H-1), 4.63 (dd, *J* = 12.3, 3.0 Hz, 1H, H-6a), 4.49 (dd, *J* = 12.3, 5.0 Hz, 1H, H-6b), 4.18 (ddd, *J* = 10.0, 5.0, 3.0 Hz, 1H, H-5), 2.48 (d, *J* = 9.8 Hz, 1H, SH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 165.7, 165.4, 165.1 (each C=O), 133.5, 133.3, 133.1, 129.9, 129.8, 129.8, 129.7, 129.5, 128.9, 128.7, 128.4, 128.4, 128.3, 128.3 (Ar-C and CH), 79.2 (C-1), 76.7 (C-5), 74.2 (C-2), 73.8 (C-3), 69.4 (C-4), 63.1 (C-6).



2,3,4-Tri-*O*-benzoyl-1-thio-D-xylopyranose (19 and 20)

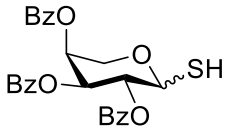
1,2,3,4-Tetra-O-benzoyl-α-D-xylopyranosyl bromide (11.6 g, 22.1 mmol) was dissolved in acetone (170 mL) and to this solution was added thiourea (2.86 g, 37.6 mmol). The reaction was heated to reflux (60 °C) and stirred overnight. The clear solution was cooled to room temp and concentrated under reduced pressure. The salt was used without any purification. It was suspended in a 3:2 CH_2Cl_2-H_2O mixture (200 mL) to which sodium metabisulfite (5.46 g, 28.7 mmol) was added. The reaction mixture was heated to reflux (42 °C) and stirred for 4 h. The solution was cooled to room temp and separated. The aqueous layer was re-extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, dried over $MgSO_4$ and the solvent removed under reduced pressure. Chromatography (petroleum ether-EtOAc 3:1) gave the title compound (8.28 g, 78%) as a white solid, as a mixture of anomers (α:β 1:2).

The reaction of a mixture of anomers **4** (500 mg, 1.04 mmol), according to Method A, gave **4α** as a white solid (260 mg, 52 %) after flash chromatography (cyclohexane-EtOAc 4:1).

Selected analytical data for 20 ^{1}H NMR (500 MHz, $CDCl_3$): 5.80 (t, *J* = 8.0 Hz, 1H, H-3β), 4.56 (dd, *J* = 11.9, 4.8 Hz, 1H, H-5β), 3.70 (dd, *J* = 11.9, 8.4 Hz, 1H, H-5β), 2.46 (d, *J* =

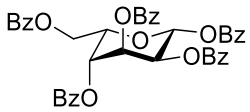
9.4 Hz, 1H, SHβ); ^{13}C NMR (126 MHz, $CDCl_3$) δ 78.84 (C-1β), 73.19 (C-2β), 71.79 (C-3β), 69.19 (C-4β), 65.42 (C-5β) ESI-HRMS calcd for $C_{26}H_{22}O_7SNa$ 501.0984, found m/z 501.0986 $[M+ Na]^+$.

Analytical data for 19 R_f 0.61 (3:7 EtOAc-petroleum ether); $[\alpha]_D^{20}$ +45.6 (*c* 0.92, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 – 8.00 (overlapping signals, 2H, Ar-H), 7.98 – 7.94 (overlapping signals, 4H, Ar-H), 7.60 – 7.48 (overlapping signals, 3H, Ar-H), 7.43 – 7.32 (overlapping signals, 6H, Ar-H), 5.97 (t, *J* = 8.4 Hz, 1H, H-3), 5.94 (dd, *J* = 6.8, 4.9 Hz, 1H, H-1), 5.41 (dd, *J* = 8.5, 4.7 Hz, 1H, H-2), 5.34 (td, *J* = 8.3, 4.9 Hz, 1H, H-4), 4.30 (dd, *J* = 11.9, 8.5 Hz, 1H, H-5a), 4.18 (dd, *J* = 11.9, 5.0 Hz, 1H, H-5b), 2.14 (d, *J* = 6.7 Hz, 1H, SH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.50, 165.30, 165.27 (each C=O), 133.60, 133.42, 133.41, 130.00, 129.85, 129.75, 128.99, 128.96, 128.75, 128.52, 128.43, 128.41, 128.39 (each Ar-C), 77.41 (C-1), 71.03 (C-2), 69.15 (C-3), 69.05 (C-4), 61.44 (C-5); IR (ATR) cm^{-1}: 1722, 1602, 1452, 1315, 1259, 1094, 1094, 1070, 707; ESI-HRMS calcd for $C_{28}H_{25}O_7SNaN$ 542.1249, found m/z 542.1230 $[M+ACN+Na]^+$.



2,3,4-Tri-*O*-benzoyl-1-thio-L-arabinopyranose (30 and 31)[20]

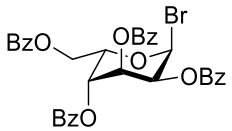
The reaction of the mixture of anomers **30** and **31** (1.00 g, 2.09 mmol), according to Method A, gave 854 mg of residue after work-up. A portion of this residue (100 mg) was subjected to chromatography and gave **30** as a white solid (56 mg, 48 %) after chromatography (cyclohexane-EtOAc 4:1). Reaction of **31** (100 mg, 0.21 mmol) according to Method B, cooling to -30 ºC for 24 h, and chromatography (cyclohexane-EtOAc 5:1) gave **5α** (50.3 mg, 50%). Analytical data shown in Chapter 2 Experimental.



β-L-Gulopyranose pentabenzoate (92)

L-Gulose (0.8 g, 4.44 mmol) was dissolved in pyridine (12 mL) and cooled to 0 ºC. Benzoyl chloride (3.20 mL, 27.53 mmol) was added to this slowly, portion wise, before the reaction mixture was allowed to warm to room temperature overnight with stirring. The reaction was

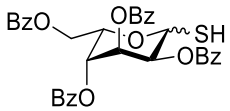
poured onto an ice-water mixture. The mixture was diluted with ethyl acetate and the layers were separated. The organic layer was washed with 1.0 M HCl, satd. $NaHCO_3$, water, brine and dried over Na_2SO_4 and the solvent removed under reduced pressure. Chromatography (cyclohexane-EtOAc 5:1) gave the title compound (2.97 g, 95%), as a white solid. R_f 0.17 (cyclohexane-EtOAc 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 – 8.16 (overlapping signals, 2H, Ar-H), 8.12 – 8.06 (overlapping signals, 4H, Ar-H), 8.00 – 7.98 (overlapping signals, 2H, Ar-H), 7.84 – 7.82 (overlapping signals, 2H, Ar-H), 7.64 (overlapping signals, 2H, Ar-H), 7.58 – 7.36 (overlapping signals, 11H, Ar-H), 7.29 (t, *J* = 7.8 Hz, 2H, Ar-H), 6.65 (d, *J* = 8.2 Hz, 1H, H-1), 6.08 (pseudo t, *J* = 3.8 Hz, 1H, H-3), 5.87 (dd, *J* = 8.2, 3.4 Hz, 1H, H-2), 5.68 (dd, *J* = 4.3, 1.8 Hz, 1H, H-4), 4.89 (td, *J* = 7.4, 1.9 Hz, 1H, H-5), 4.65 (dd, *J* = 11.6, 7.0 Hz, 1H, H-6a), 4.54 (dd, *J* = 11.6, 6.0 Hz, 1H, h-6b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 165.1, 165.0, 164.8, 164.7 (each C=O), 133.8, 133.8, 133.8, 133.4, 133.2, 130.2, 130.1, 129.9, 129.8, 129.7, 129.4, 128.9, 128.8, 128.7, 128.7, 128.6, 128.5, 128.4, 128.3 (Ar-C and CH), 91.2 (C-1), 72.2 (C-5), 68.5 (C-3), 68.4 (C-4), 68.2 (C-2), 62.3 (C-6); IR (ATR) cm^{-1}: 1721, 1602, 1451, 1064, 703, 685; ES-HRMS calcd for $C_{41}H_{32}O_{11}Na$ 723.1842, found m/z 723.1840 $[M+Na]^+$.



2,3,4,6-Tetra-*O*-benzoyl-α-L-gulopyranosyl bromide (93)

Perbenzoylated gulose (2.96 g, 4.22 mmol) was dissolved in anhydrous CH_2Cl_2 (22 mL) and cooled to 0ºC. HBr (33% in AcOH, 7.3 mL) was added to the reaction mixture and it was allowed to warm to room temperature, stirring overnight. The reaction mixture was then poured onto an ice-water mixture and stirred for 15 mins. The layers were separated and washed with satd. $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated under reduced pressure to yield a white foam (2.17 g, 78%) as the title compound. R_f 0.46 (cyclohexane-EtOAc 6:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 – 8.27 (overlapping signals, 2H, Ar-H), 8.15 – 8.11 (overlapping signals, 2H, Ar-H), 8.04 – 7.99 (overlapping signals, 2H, Ar-H), 7.95 – 7.90 (overlapping signals, 2H, Ar-H), 7.67 – 7.61 (overlapping signals, 2H, Ar-H), 7.58 – 7.46 (overlapping signals, 6H, Ar-H), 7.43 – 7.39 (overlapping signals, 2H, Ar-H), 7.37 – 7.33 (overlapping signals, 2H, Ar-H), 6.91 (d, *J* = 4.5 Hz, 1H, H-1), 5.92 (t, *J* = 3.9 Hz, 1H, H-3), 5.65 (overlapping signals, 2H, H-2 and H-4), 5.07 (t, *J* = 6.3 Hz, 1H, H-5), 4.63 (dd, *J* = 11.8, 7.3 Hz, 1H, H-6a), 4.52 (dd, *J* = 11.8, 5.1 Hz, 1H, H-6b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 165.0, 165.0, 164.8 (each C=O), 134.0, 133.7, 133.7, 133.2, 130.5, 130.1, 130.1, 130.0, 129.8,

129.8, 129.4, 128.9, 128.7, 128.7, 128.6, 128.5, 128.5, 128.5, 128.5, 128.4 (Ar-C and CH), 84.5 (C-1), 68.3 (C-5), 68.3 (C-2), 66.3 (C-3), 66.0 (C-4), 62.2 (C-6); IR (ATR) cm^{-1}: 1721, 1601, 1451, 1243, 1065, 703, 685; ES-HRMS calcd for $C_{34}H_{27}O_9BrNa$ 682.0736, found m/z 682.0736 $[M+Na]^+$.



2,3,4,6-Tetra-*O*-benzoyl-1-thio-L-gulopyranose (74 and 75)

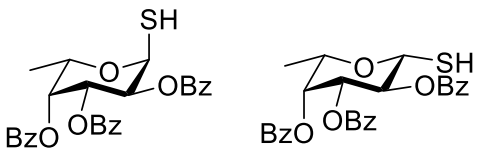
2,3,4,6-Tetra-*O*-benzoyl-α-L-gulopyranosyl bromide (2.17 g, 3.29 mmol) was dissolved in acetone (19 mL) and to this solution, thiourea (0.43 g, 5.59 mmol) was added. The reaction was heated to reflux (70 º C) and stirred overnight. The solution was allowed to cool to room temperature and concentrated in vacuo. The salt was used without any further purification. The salt (2.42 g, 3.29 mmol) was suspended in a 3:2 CH_2Cl_2-H_2O mixture (35 mL) to which sodium metabisulfite (0.81 g, 4.28 mmol) was added. The reaction mixture was heated to reflux and left to stir for 5 h. The solution was allowed to cool to room temperature and separated. The aqueous layer was re-extracted with CH_2Cl_2 and the combined organic layer were washed with water, dried over Na_2SO_4, with the solvent then being removed under reduced pressure. Chromatography (cyclohexane-EtOAc 7:1) gave the title compound (1.80 g, 89%) as a mixture of anomers (α:β 1:6), as a white solid. Chromatography (cyclohexane-EtOAc 7:1) of a mixture gave samples of the two anomers for analytical purposes.

The reaction of a mixture of anomers **74** and **75** (500 mg, 0.82 mmol), according to Method A, gave **74** (281 mg, 56%) as a white solid after purification by flash chromotography (cyclohexane-EtOAc 7:1). Reaction of **74** (100 mg, 0.16 mmol) according to Method B and column chromatography (cyclohexane-EtOAc 7:1) gave **75** (90 mg, 90%).

Analytical data for 74 R_f 0.32 (cyclohexane-EtOAc 7:1); $[\alpha]_D^{20}$ -60.9 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 7.7 Hz, 2H), 8.13 (d, *J* = 7.7 Hz, 2H), 8.02 (d, *J* = 7.7 Hz, 2H), 7.93 (d, *J* = 7.8 Hz, 2H), 7.68 – 7.58 (overlapping signals, 2H, Ar-H), 7.58 – 7.45 (overlapping signals, 6H, Ar-H), 7.39 (overlapping signals, 4H, Ar-H), 6.18 (t, *J* = 6.5 Hz, 1H, H-1), 5.89 (t, *J* = 3.8 Hz, 1H, H-3), 5.78 (dd, *J* = 5.9, 3.6 Hz, 1H, H-2), 5.62 (d, *J* = 4.0 Hz, 1H, H-4), 5.18 (t, *J* = 6.4 Hz, 1H, H-5), 4.64 (dd, *J* = 11.6, 7.1 Hz, 1H, H-6a), 4.49 (dd, *J* = 11.6, 5.2 Hz, 1H, H-6b), 2.27 (d, *J* = 7.3 Hz, 1H, S*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 165.2, 165.0, 164.9 (each C=O), 133.8, 133.7, 133.5, 133.2, 130.3, 130.0, 129.9, 129.7, 129.5, 128.9, 128.9, 128.7, 128.6, 128.5, 128.4 (Ar-H and CH), 76.2 (C-1), 68.7 (C-4), 67.6 (C-3), 66.7 (C-

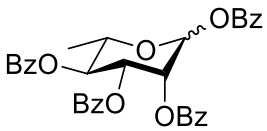
2), 65.3 (C-5), 62.6 (C-6); $^{1}J_{C1.H1}$ = 169.4 Hz; IR (ATR) cm^{-1}: 1718, 1602, 1451, 1245, 1090, 1066, 703, 685; ES-HRMS calcd for $C_{34}H_{32}O_9N_1S_1$ 630.1798, found m/z 630.1796 $[M+NH_4]^+$.

Analytical data for 75 R_f 0.27 (cyclohexane-EtOAc 7:1); $[\alpha]_D^{20}$ -8.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 – 8.13 (overlapping signals, 2H, Ar-H), 8.09 – 8.05 (overlapping signals, 2H, Ar-H), 8.04 – 8.00 (m, 1H, Ar-H), 7.89 – 7.85 (overlapping signals, 2H, Ar-H), 7.68 – 7.62 (overlapping signals, 2H, Ar-H), 7.57 – 7.48 (overlapping signals, 6H, Ar-H), 7.42 (overlapping signals, 2H, Ar-H), 7.33 (overlapping signals, 2H, Ar-H), 5.91 (t, *J* = 3.4 Hz, 1H, H-3), 5.60 (d, *J* = 3.5 Hz, 1H, H-4), 5.56 (dd, *J* = 10.0, 3.1 Hz, 1H, H-2), 5.31 (t, *J* = 9.8 Hz, 1H, H-1), 4.67 – 4.61 (overlapping signals, 2H, H-5 and H-6a), 4.51 – 4.45 (m, 1H, H-6b), 2.45 (d, *J* = 9.5 Hz, 1H, SH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 165.2, 164.9, 164.5 (each C=O), 133.9, 133.8, 133.4, 133.2, 130.1, 129.9, 129.8, 129.5, 129.1, 129.0, 128.7, 128.7, 128.4, 128.4 (each Ar-C and CH), 76.5 (C-1), 74.1 (C-5), 71.3 (C-2), 68.7 (C-4), 68.0 (C-3), 62.5 (C-6); IR (ATR) cm^{-1}: 1719, 1602, 1451, 1244, 1090, 703, 685; ES-HRMS calcd for $C_{34}H_{32}O_9SNa$ 635.1352, found m/z 635.1357 $[M+Na]^+$.



2,3,4-Tri-*O*-benzoyl-1-thio-α/β-L-fucopyranose (32 and 33)

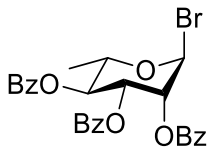
The reaction of **33** (500 mg, 1.02 mmol), according to Method A, gave 437 mg of residue after work-up. A portion of this residue (80 mg) was subjected to chromatography and gave **32** as a white solid (34 mg, 38 %) after chromatography (cyclohexane-EtOAc 7:3). Reaction of **32** (100 mg, 0.16 mmol) according to Method B, cooling to -30 ºC, and column chromatography (cyclohexane-EtOAc 4:1) gave **33** (68 mg, 68%). Analytical data shown in Chapter 2 Experimental.



1,2,3,4-Tetra-*O*-benzoyl-α/β-L-rhamnopyranose (85)[21]

L-Rhamnose monohydrate (2.5 g, 15.2 mmol) was dissolved in pyridine (32 mL) and cooled to 0 ºC. Benzoyl chloride (11.7 mL, 100.5 mmol) was added to this slowly, portion wise, before the reaction mixture was allowed to warm to room temperature overnight with stirring. MeOH

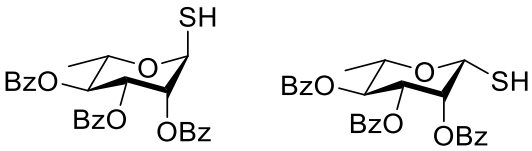
(30 mL) was then added and stirred for 15 mins to decompose the excess benzoyl chloride. The mixture was diluted with CH_2Cl_2 and washed with 1.0 M HCl (x2), water, brine and dried over Na_2SO_4 and the solvent removed under reduced pressure. Chromatography (cyclohexane-EtOAc 4:1) gave the title compound (7.84 g, 89%), as a mixture of anomers (2:1 α:β), as a white solid. R_f 0.31 (cyclohexane-EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 – 8.15 (overlapping signals, 4H, Ar-H), 8.15 – 8.09 (overlapping signals, 4H, Ar-H), 8.02 – 7.92 (overlapping signals, 4H, Ar-H), 7.89 – 7.80 (overlapping signals, 4H, Ar-H), 7.71 – 7.61 (overlapping signals, 4H, Ar-H), 7.59 – 7.48 (overlapping signals, 8H, Ar-H), 7.47 – 7.32 (overlapping signals, 6H, Ar-H), 7.30 – 7.25 (overlapping signals, 5H, Ar-H), 6.55 (d, *J* = 1.9 Hz, 1H, H-1α), 6.35 (d, *J* = 1.2 Hz, 1H, H-1β), 6.07 (dd, *J* = 1.3 Hz, 1H, H-2β), 5.99 (dd, *J* = 10.2, 3.5 Hz, 1H, H-3α), 5.86 (dd, *J* = 3.5, 2.0 Hz, 1H, H-2α), 5.80 (t, *J* = 10.0 Hz, 1H, H-4α), 5.74 – 5.71 (overlapping signals, 2H, H-3β and H-4β), 4.35 (dq, *J* = 9.8, 6.2 Hz, 1H, H-5α), 4.09 (dq, *J* = 8.4, 6.1 Hz, 1H, H-5β), 1.48 (d, *J* = 6.2 Hz, 3H, CH_3β), 1.40 (d, *J* = 6.2 Hz, 3H, CH_3α); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 165.7, 165.7, 165.6, 165.3, 164.2, 164.0 (each C=O), 133.9, 133.7, 133.7, 133.5, 133.5, 133.4, 133.3, 130.2, 130.1, 130.0, 130.0, 129.8, 129.8, 129.7, 129.4, 129.1, 129.1, 129.1, 128.9, 128.8, 128.7, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3 (Ar-C and CH), 91.4 (C-1α), 91.2 (C-1β), 71.8 (C-5β), 71.4 (C-3β/C-4β), 71.2 (C-3β/C-4β), 71.2 (C-4α), 69.9 (C-3α), 69.8 (C-2α), 69.6 (C-2β), 69.4 (C-5α), 17.7 (2s, C-6α and C-6β); IR (ATR) cm^{-1}: 1720, 1601, 1451, 1254, 1066, 1022, 704, 684; ES-HRMS calcd for $C_{34}H_{28}O_9Na$ 603.1631, found *m/z* 603.1611 $[M+Na]^+$.



2,3,4-Tri-*O*-benzoyl-α-rhamnopyranosyl bromide (87)[22]

1,2,3,4-Tetra-O-benzoyl-α/β-L-rhamnopyranose (7.7 g, 13.3 mmol) was dissolved in anhydrous CH_2Cl_2 (70 mL) and cooled to 0°C. HBr (33% in AcOH, 23 mL) was added to the reaction mixture and it was allowed to warm to room temperature, stirring overnight. The reaction mixture was then poured onto an ice-water mixture, stirred for 15 minutes and separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with satd. $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated under reduced pressure to yield a white solid (6.34g, 89%) as the title compound. R_f 0.37 (cyclohexane-EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 – 8.06 (overlapping signals, 2H, Ar-H), 8.03 – 7.97

(overlapping signals, 2H, Ar-H), 7.86 – 7.80 (overlapping signals, 2H, Ar-H), 7.66 – 7.58 (m, 1H, Ar-H), 7.58 – 7.47 (overlapping signals, 3H, Ar-H, Ar-H), 7.46 – 7.37 (overlapping signals, 3H, Ar-H), 7.30 – 7.23 (overlapping signals, 2H, Ar-H), 6.55 (d, *J* = 1.5 Hz, 1H, H-1), 6.20 (dd, *J* = 10.3, 3.4 Hz, 1H, H-3), 5.87 (dd, *J* = 3.4, 1.6 Hz, 1H, H-2), 5.77 (t, *J* = 10.1 Hz, 1H, H-4), 4.43 (dq, *J* = 9.8, 6.2 Hz, 1H, H-5), 1.43 (d, *J* = 6.2 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 165.3, 165.2 (each C=O), 133.8, 133.8, 133.6, 133.3, 130.2, 130.0, 129.8, 129.7, 128.9, 128.9, 128.9, 128.7, 128.5, 128.5, 128.3 (Ar-C and CH), 83.9 (C-1), 73.4 (C-2), 71.5 (C-5), 71.0 (C-4), 68.9 (C-3), 17.2 (*C*H_3).



2,3,4-Tri-*O*-benzoyl-1-thio-α/β-L-rhamnopyranose (68 and 69)

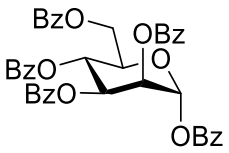
2,3,4-Tri-O-benzoyl-α-rhamnopyranosyl bromide (1.6 g, 2.79 mmol) was dissolved in acetone (23 mL) and to this solution, thiourea (0.36 g, 4.74 mmol) was added. The reaction was heated to reflux (70 º C) and stirred overnight. The solution was allowed to cool to room temperature and concentrated in vacuo. The salt was used without any further purification. It was suspended in a 3:2 CH_2Cl_2-H_2O mixture (50 mL) to which sodium metabisulfite (0.69 g, 3.62 mmol) was added. The reaction mixture was heated to reflux (45 º C) and left to stir for 4 h. The solution was allowed to cool to room temperature and separated. The aqueous layer was re-extracted with CH_2Cl_2 and the combined organic layer were washed with water, dried over Na_2SO_4, with the solvent then being removed under reduced pressure. Chromatography (cyclohexane-EtOAc 3:1) gave the title compounds (α-anomer: 1.06 g, 77%; β-anomer: 0.11 g, 8%).

Reaction of **68** (211 mg, 0.43 mmol) according to Method B, cooling to 4 ºC and addition of MSA (1.0 M in CH_2Cl_2, 0.5 eq), and column chromatography (cyclohexane-EtOAc 5:1) gave **69** (164.0 mg, 78%).

Analytical data for 68 R_f 0.42 (cyclohexane-EtOAc 3:1); $[\alpha]_D^{20}$ +139.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 – 8.07 (overlapping signals, 2H, Ar-H), 8.02 – 7.97 (overlapping signals, 2H, Ar-H), 7.86 – 7.80 (overlapping signals, 2H, Ar-H), 7.64 – 7.59 (m, 1H, Ar-H), 7.56 – 7.47 (overlapping signals, 3H, Ar-H), 7.46 – 7.38 (overlapping signals, 3H, Ar-H), 7.29 – 7.23 (overlapping signals, 2H, Ar-H), 5.84 (dd, *J* = 10.1, 3.3 Hz, 1H, H-3), 5.78 (dd, *J* = 6.8, 1.7 Hz, 1H, H-1), 5.75 (dd, *J* = 3.3, 1.7 Hz, 1H, H-2), 5.71 (t, *J* = 9.9 Hz, 1H, H-

4), 4.53 (dq, *J* = 9.7, 6.2 Hz, 1H, H-5), 2.41 (d, *J* = 6.9 Hz, 1H, SH), 1.38 (d, *J* = 6.2 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 165.5, 165.5 (each C=O), 133.6, 133.4, 133.2, 129.9, 129.8, 129.8, 129.7, 129.3, 129.2, 128.9, 128.6, 128.5, 128.3 (Ar-C and CH), 76.8 (C-1), 73.4 (C-2), 71.8 (C-4), 69.4 (C-3), 68.0 (C-5), 17.6 (CH_3); $^1J_{C1.H1}$ = 169.6 Hz; IR (ATR) cm^{-1}: 2584, 1714, 1601, 1453, 1252, 1090, 1068, 714, 686. ES-HRMS calcd for $C_{27}H_{24}O_7SNa$ 515.1140, found m/z 515.1131 [M+Na]$^+$.

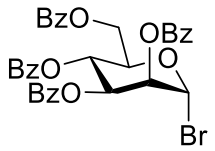
Analytical data for 69 R_f 0.36 (cyclohexane-EtOAc 3:1); $[\alpha]_D^{20}$ +157.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 – 8.09 (overlapping signals, 2H, Ar-H), 7.94 – 7.91 (overlapping signals, 2H, Ar-H), 7.78 – 7.75 (overlapping signals, 2H, Ar-H), 7.66 – 7.62 (m, 1H, Ar-H), 7.53 – 7.48 (overlapping signals, 3H, Ar-H), 7.43 (m, 1H, Ar-H), 7.40 – 7.35 (overlapping signals, 2H, Ar-H), 7.26 – 7.22 (overlapping signals, 2H, Ar-H), 5.92 – 5.90 (m, 1H, H-2), 5.59 – 5.56 (overlapping signals, 2H, H-3 and H-4), 5.12 (dd, J = 10.1, 1.3 Hz, 1H, H-1), 3.90 (dq, J = 6.2, 3.3 Hz, 1H, H-5), 2.61 (d, J = 10.0 Hz, 1H, SH), 1.44 (d, J = 6.3 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 165.6, 165.5 (each C=O), 133.6, 133.4, 133.2, 130.0, 129.7, 129.7, 129.1, 129.0, 128.9, 128.6, 128.4, 128.2 (Ar-C and CH), 76.6 (C-1), 75.7 (C-5), 72.7 (C-2), 72.7 (C-3), 70.8 (C-4), 18.0 (CH_3); $^1J_{C1.H1}$ = 151.2 Hz; IR (ATR) cm^{-1}: 2564, 1718, 1601, 1451, 1252, 1092, 1067, 703, 685; ES-HRMS calcd for $C_{27}H_{24}O_7SNa$ 515.1140, found m/z 515.1134 [M+Na]$^+$.



α-D-Mannopyranose pentabenzoate (81)[23]

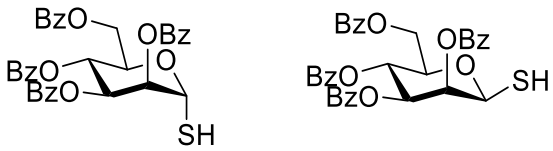
D-Mannose (1.0 g, 5.55 mmol) was dissolved in pyridine (15 mL) and cooled to 0 ºC. Benzoyl chloride (4.50 mL, 38.85 mmol) was added to the reaction mixture portion-wise, before it was allowed to warm to room temperature overnight with stirring. The reaction mixture was poured onto an ice-water mixture and stirred for 15 mins. It was then washed with 1 M HCl (x3), satd. $NaHCO_3$, water and dried over Na_2SO_4. The solvent was removed under reduced pressure and recrystallization from MeOH:acetone gave the title compound (3.57 g, 91%). R_f 0.28 (cyclohexane-EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 – 8.16 (overlapping signals, 2H, Ar-H), 8.12 – 8.05 (overlapping signals, 4H, Ar-H), 7.98 – 7.93 (overlapping signals, 2H, Ar-H), 7.88 – 7.83 (overlapping signals, 2H, Ar-H), 7.72 – 7.66 (m, 1H, Ar-H), 7.65 – 7.61 (m, 1H, Ar-H), 7.60 – 7.49 (overlapping signals, 4H, Ar-H), 7.48 – 7.35 (overlapping signals, 7H,

Ar-H), 7.31 – 7.27 (overlapping signals, 2H, Ar-H), 6.63 (d, *J* = 1.9 Hz, 1H, H-1), 6.28 (t, *J* = 10.2 Hz, 1H, H-4), 6.07 (dd, *J* = 10.3, 3.3 Hz, 1H, H-3), 5.91 (dd, *J* = 3.3, 2.1 Hz, 1H, H-2), 4.70 (dd, *J* = 12.3, 2.6 Hz, 1H, H-6a), 4.57 (dt, *J* = 10.1, 3.2 Hz, 1H, H-5), 4.50 (dd, *J* = 12.3, 3.7 Hz, 1H, H-6b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.0, 165.7, 165.3, 165.1, 163.8 (each C=O), 134.5, 134.1, 133.6, 133.5, 133.4, 133.0, 130.6, 130.1, 129.9, 129.8, 129.8, 129.8, 129.0, 128.9, 128.8, 128.8, 128.7, 128.7, 128.5, 128.4, 128.4 (Ar-C and CH), 91.4 (C-1), 71.2 (C-5), 70.0 (C-3), 69.4 (C-2), 66.2 (C-4), 62.3 (C-6); IR (ATR) cm^{-1}: 1723, 1601, 1451, 1256, 1090, 703, 685; ES-HRMS calcd for $C_{41}H_{32}O_{11}K$ 739.1582, found m/z 739.1582 $[M+K]^+$.



2,3,4,6-Tetra-*O*-benzoyl-α-mannopyranosyl bromide (83)[23]

α-D-Mannopyranose pentabenzoate (3.57 g, 22.83 mmol) was dissolved in anhydrous CH_2Cl_2 (27 mL) and cooled to 0°C. HBr (33% in AcOH, 8.4 mL) was added to the reaction mixture and it was allowed to warm to room temperature, stirring overnight. The reaction mixture was then poured onto an ice-water mixture and stirred for 15 mins. It was diluted with CH_2Cl_2, then separated and washed with satd. $NaHCO_3$, brine, dried over Na_2SO_4 and the solvent was removed to yield the title compound as a colourless viscous oil (3.06 g, 91%). R_f 0.41 (cyclohexane-EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 – 8.08 (overlapping signals, 2H, Ar-H), 8.05 – 8.01 (overlapping signals, 2H, Ar-H), 8.00 – 7.95 (overlapping signals, 2H, Ar-H), 7.86 – 7.82 (overlapping signals, 2H, Ar-H), 7.62 – 7.57 (overlapping signals, 2H, Ar-H), 7.55 – 7.50 (m, 1H, Ar-H), 7.47 – 7.34 (overlapping signals, 7H, Ar-H), 7.30 – 7.26 (overlapping signals, 2H, Ar-H), 6.59 (d, *J* = 1.6 Hz, 1H, H-1), 6.29 (dd, *J* = 10.2, 3.1 Hz, 1H, H-3), 6.24 (t, *J* = 10.0 Hz, 1H, H-4), 5.91 (dd, *J* = 3.1, 1.7 Hz, 1H, H-2), 4.74 (dd, *J* = 12.5, 2.5 Hz, 1H, H-6a), 4.66 (dt, *J* = 9.7, 3.1 Hz, 1H, H-5), 4.51 (dd, *J* = 12.5, 3.8 Hz, 1H, H-6b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 165.3, 165.3, 165.0 (each C=O), 133.7, 133.6, 133.4, 133.2, 129.9, 129.9, 129.8, 129.7, 129.6, 128.8, 128.7, 128.7, 128.6, 128.5, 128.5, 128.4 (Ar-C and CH), 83.3 (C-1), 73.1 (C-5), 72.9 (C-2), 69.1 (C-3), 65.9 (C-4), 61.7 (C-6); IR (ATR) cm^{-1}: 1721, 1602, 1451, 1247, 1088, 703, 685.



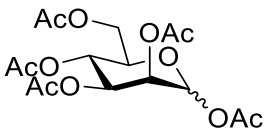
2,3,4,6-Tetra-*O*-benzoyl-1-thio-α/β-D-mannopyranose (64 and 65)[24]

2,3,4,6-Tetra-*O*-benzoyl-α-mannopyranosyl bromide (3.06 g, 4.64 mmol) was dissolved in acetone (45 mL) and thiourea (0.60 g, 7.88 mmol) was added. The reaction was heated to reflux (70 ºC) and stirred overnight. The solution was allowed to cool to room temperature and concentrated in vacuo. The thiouronium salt was used without any further purification. The salt (3.41 g, 4.64 mmol) was suspended in a 3:2 CH_2Cl_2-H_2O mixture (55 mL) to which sodium metabisulfite (1.15 g, 6.04 mmol) was added. The reaction mixture was heated to reflux (50 ºC) and left to stir for 2 h. The solution was allowed to cool to room temperature and separated. The aqueous layer was re-extracted with CH_2Cl_2 and the combined organic layer were washed with water, dried over Na_2SO_4, with the solvent then being removed under reduced pressure. Chromatography (petroleum ether-EtOAc 7:3) gave the title compounds as a separable pair of anomers (α-anomer: 2.67 g, 65%; β-anomer: 0.17 g, 4%) as white solids.

Reaction of **64** (202 mg, 0.33 mmol) according to method B, cooling to 4 ºC and addition of MSA (1.0 M in CH_2Cl_2, 2 eq.), and column chromatography (cyclohexane-EtOAc 4:1) gave **65** (165.6 mg, 82%).

Analytical data for 64 R_f 0.24 (cyclohexane-EtOAc 3:1); $[\alpha]_D^{20}$ -105.2 (*c* 1.0, $CHCl_3$) [Lit. $[\alpha]_D^{20}$ –30.5 (c=1.0, $CHCl_3$)][24]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 – 8.07 (overlapping signals, 2H, Ar-H), 8.05 – 7.99 (overlapping signals, 2H, Ar-H), 7.99 – 7.94 (overlapping signals, 2H, Ar-H), 7.88 – 7.81 (overlapping signals, 2H, Ar-H), 7.61 – 7.55 (overlapping signals, 2H, Ar-H), 7.54 – 7.50 (m, 1H, Ar-H), 7.46 – 7.35 (overlapping signals, 7H, Ar-H), 7.31 – 7.25 (overlapping signals, 2H, Ar-H), 6.18 (t, J = 10.1 Hz, 1H, H-4), 5.90 (dd, J = 10.1, 3.2 Hz, 1H, H-3), 5.86 (dd, J = 6.7, 1.6 Hz, 1H, H-1), 5.80 (dd, J = 3.2, 1.7 Hz, 1H, H-2), 4.80 (dt, J = 10.1, 3.3 Hz, 1H, H-5), 4.73 (dd, J = 12.3, 2.6 Hz, 1H, H-6a), 4.49 (dd, J = 12.3, 3.9 Hz, 1H, H-6b), 2.45 (d, J = 6.7 Hz, 1H, SH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 165.5, 165.3, 165.2 (each C=O), 133.5, 133.5, 133.3, 133.1, 129.8, 129.8, 129.8, 129.7, 129.1, 128.8, 128.8, 128.6, 128.5, 128.4, 128.3 (Ar-C and CH), 77.1 (C-1), 72.8 (C-2), 69.9 (C-5), 69.6 (C-3), 66.7 (C-4), 62.5 (C-6); $^1J_{C1.H1}$ = 170.4 Hz; IR (ATR) cm^{-1}: 1715, 1602, 1452, 1241, 1088, 703; ES-HRMS calcd for $C_{34}H_{28}O_9SNa$ 635.1352, found m/z 635.1362 $[M+Na]^+$.

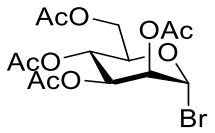
Analytical data for 65 R_f 0.16 (cyclohexane-EtOAc 3:1); $[\alpha]_D^{20}$ -36.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 – 8.08 (overlapping signals, 4H, Ar-H), 7.93 – 7.89 (overlapping signals, 2H, Ar-H), 7.82 – 7.78 (overlapping signals, 2H, Ar-H), 7.66 – 7.63 (m, 1H, Ar-H), 7.62 – 7.57 (m, 1H, Ar-H), 7.52 – 7.48 (m, 1H, Ar-H), 7.48 – 7.42 (overlapping signals, 5H, Ar-H), 7.38 – 7.32 (overlapping signals, 2H, Ar-H), 7.28 – 7.24 (overlapping signals, 2H, Ar-H), 6.03 (t, *J* = 10.0 Hz, 1H, H-4), 5.96 (dd, *J* = 3.3, 1.2 Hz, 1H, H-2), 5.66 (dd, *J* = 10.1, 3.3 Hz, 1H, H-3), 5.20 (dd, *J* = 10.0, 1.2 Hz, 1H, H-1), 4.73 (dd, *J* = 12.2, 2.7 Hz, 1H, H-6a), 4.51 (dd, *J* = 12.2, 4.5 Hz, 1H, H-6b), 4.20 (ddd, *J* = 10.0, 4.5, 2.7 Hz, 1H, H-5), 2.65 (d, *J* = 10.0 Hz, 1H, SH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.11, 165.59, 165.31, 165.25 (each C=O), 133.65, 133.49, 133.29, 133.09, 130.00, 129.80, 129.79, 129.77, 129.75, 128.93, 128.79, 128.73, 128.69, 128.43, 128.42, 128.29 (Ar-C and CH), 77.00 (C-5, overlapping with $CDCl_3$), 76.91 (C-1), 72.96 (C-3), 72.52 (C-2), 66.13 (C-4), 63.04 (C-6); $^1J_{C1.H1}$ = 148.0 Hz; IR (ATR) cm^{-1}: 2161, 1716, 1604, 1452, 1248, 1067, 1025, 703, 684; ES-HRMS calcd for $C_{34}H_{28}O_9SNa$ 635.1352, found m/z 635.1354 $[M+Na]^+$.



D-Mannopyranose pentaacetate (80)[25]

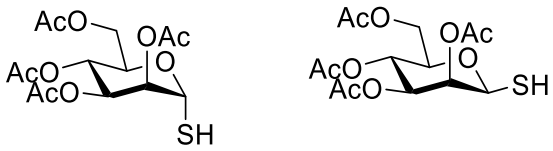
D-Mannose (2.0 g, 11.1 mmol) was dissolved in pyridine (30 mL) and cooled to 0 ºC. Acetic anhydride (7.3 mL, 77.7 mmol) was added to the reaction mixture portion-wise, before it was allowed to warm to room temperature overnight with stirring. The reaction mixture was poured onto an ice-water mixture and stirred for 15 mins. It was then washed with 1 M HCl (x3), satd. $NaHCO_3$, water and dried over Na_2SO_4. The solvent was removed under reduced pressure and purified through column chromatography (1:2 cylohexane-EtOAc) to give the title compound (4.09 g, 95%), as mixture of anomers (7:1 α:β), as a viscous colourless oil. R_f 0.23 (cyclohexane-EtOAc 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.09 (d, *J* = 1.9 Hz, 1H, H-1α), 5.86 (d, *J* = 1.2 Hz, 1H, H-1β), 5.49 (d, *J* = 3.3 Hz, 1H, H-2β), 5.38 – 5.34 (overlapping signals, 2H, H-3α and H-4α), 5.32 – 5.29 (m, 1H, H-4β), 5.27 (d, *J* = 2.2 Hz, 1H, H-2α), 5.14 (dd, *J* = 10.0, 3.3 Hz, 1H, H-4β), 4.32 (d, *J* = 5.4 Hz, 1H, H-6aβ), 4.29 (dd, *J* = 12.4, 4.9 Hz, 1H, H-6aα), 4.16 (d, *J* = 2.3 Hz, 1H, H-6bβ), 4.11 (dd, *J* = 12.4, 2.4 Hz, 1H, H-6bα), 4.07 – 4.03 (m, 1H, H-5α), 3.81 (ddd, *J* = 9.9, 5.5, 2.3 Hz, 1H, H-5β), 2.22 (s, 3H, O(CO)CH_3), 2.18 (s, 6H, 2 x O(CO)CH_3), 2.17 (s, 3H, O(CO)CH_3), 2.11 (s, 3H, O(CO)CH_3), 2.10 (s, 3H, O(CO)CH_3), 2.06 (s, 6H, 2 x O(CO)CH_3), 2.01 (s, 6H, 2 x O(CO)CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6,

170.2, 169.9, 169.7, 169.7, 169.5, 169.5, 168.3, 168.0 (each C=O), 90.6 (C-1α), 90.4 (C-1β), 73.3 (C-5β), 70.6 (C-3β), 70.6 (C-5α), 68.7 (C-3α), 68.3 (C-2α), 68.2 (C-2β), 65.5 (C-4α), 65.4 (C-4β), 62.1 (C-6α), 62.0 (C-6β), 20.8, 20.7, 20.7, 20.7, 20.7, 20.6, 20.6, 20.5 (each O(CO)*C*H_3); IR (film) cm^{-1}: 2981, 1722, 1369, 1244, 1081, 1066; ES-HRMS calcd for $C_{16}H_{22}O_{11}Na$ 413.1060, found m/z 413.1063 $[M+Na]^+$.



2,3,4,6-Tetra-*O*-acetyl-α-mannopyranosyl bromide (81)[26]

D-Mannopyranose pentaacetate (4.04 g, 10.35 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL) and cooled to 0°C. HBr (33% in AcOH, 20 mL) was added to the reaction mixture and it was allowed to warm to room temperature, stirring overnight. The reaction mixture was then poured onto an ice-water mixture and stirred for 15 mins. It was diluted with CH_2Cl_2, then separated and washed with satd. $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated under reduced pressure to yield a colourless viscous oil (3.83 g, 90%) as the title compound. R_f 0.56 (cyclohexane-EtOAc 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (d, *J* = 1.6 Hz, 1H, H-1), 5.72 (dd, *J* = 10.2, 3.4 Hz, 1H, H-3), 5.45 (dd, *J* = 3.5, 1.6 Hz, 1H, H-2), 5.37 (t, *J* = 10.2 Hz, 1H, H-4), 4.33 (dd, *J* = 12.5, 5.0 Hz, 1H, H-6a), 4.23 (ddd, *J* = 10.3, 5.0, 2.1 Hz, 1H, H-5), 4.14 (dd, *J* = 12.6, 2.2 Hz, 1H, H-6b), 2.18 (s, 3H, O(CO)CH_3), 2.11 (s, 3H, O(CO)CH_3), 2.08 (s, 3H, O(CO)CH_3), 2.01 (s, 3H, O(CO)CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 169.6, 169.5 (each C=O), 83.0 (C-1), 72.8 (C-5), 72.1 (C-2), 67.9 (C-3), 65.3 (C-4), 61.4 (C-6), 20.7, 20.7, 20.6, 20.6 (each O(CO)*C*H_3); IR (ATR) cm^{-1}: 1721, 1256, 1081, 1066, 1024.



2,3,4,6-Tetra-*O*-acetyl-1-thio-α/β-D-mannopyranose (62 and 63)[27]

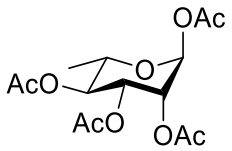
Freshly prepared bromide (3.82 g, 9.29 mmol) was dissolved in acetone (48 mL) and thiourea (1.2 g, 15.8 mmol) was added. The reaction was heated to reflux (70 °C) and stirred overnight. The solution was allowed to cool to room temperature and concentrated in vacuo. The thiouronium salt was used without any further purification. The salt (4.5 g, 9.29 mmol) was suspended in a 3:2 CH_2Cl_2-H_2O mixture (75 mL) to which sodium metabisulfite (2.3 g, 12.08

mmol) was added. The reaction mixture was heated to reflux (70 ºC) and left to stir for 2 h. The solution was allowed to cool to room temperature and separated. The aqueous layer was re-extracted with CH_2Cl_2 and the combined organic layer were washed with water, dried over Na_2SO_4, with the solvent then being removed under reduced pressure. Chromatography (cyclohexane-EtOAc 3:2→1:1) gave the title compounds as a pair of anomers (α-anomer: 2.27 g, 68%; β-anomer: 0.23 g, 7%) as a viscous light yellow oil and a white solid.

Reaction of **62** (200 mg, 0.55 mmol) according to Method B and column chromatography (cyclohexane-EtOAc 5:1) gave **63** (133.6 mg, 66.8%).

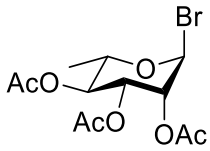
Analytical data for 62 R_f 0.42 (cyclohexane-EtOAc 1:1); $[\alpha]_D^{20}$ +71.3 (*c* 1.0, $CHCl_3$) [Lit. $[\alpha]_D^{20}$ +78.6 (*c* 0.77, $CHCl_3$)][27]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57 (d, *J* = 6.8 Hz, 1H, H-1), 5.37 – 5.29 (overlapping signals, 3H, H-2, H-3 and H-4), 4.37 (ddd, *J* = 7.8, 5.1, 2.2 Hz, 1H, H-5), 4.31 (dd, *J* = 12.3, 5.1 Hz, 1H, H-6a), 4.13 (dd, *J* = 12.3, 2.3 Hz, 1H, H-6b), 2.28 (d, *J* = 6.9 Hz, 1H, SH), 2.17 (s, 3H, O(CO)CH_3), 2.11 (s, 3H, O(CO)CH_3), 2.06 (s, 3H, O(CO)CH_3), 2.01 (s, 3H, O(CO)CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 169.9, 169.8, 169.6 (each C=O), 76.9 (C-1), 71.8 (C-2), 69.6 (C-5), 68.5 (C-3), 66.1 (C-4), 62.1 (C-6), 20.9, 20.7, 20.7, 20.6 (each O(CO)*C*H_3); $^1J_{C1.H1}$ = 170.0 Hz; IR (film) cm^{-1}: 2570, 1737, 1368, 1209, 1048; ES-HRMS calcd for $C_{14}H_{20}O_9SNa$ 387.0726, found m/z 387.0720 $[M+Na]^+$.

Analytical data for 63 R_f 0.25 (cyclohexane-EtOAc 1:1); $[\alpha]_D^{20}$ -17.8 (*c* 1.0, $CHCl_3$) [Lit. $[\alpha]_D^{19}$ -29.7 (*c* 0.78, $CHCl_3$)][27]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (dd, *J* = 3.3, 1.4 Hz, 1H, H-2), 5.23 (t, *J* = 10.0 Hz, 1H, H-4), 5.08 (dd, *J* = 10.1, 3.4 Hz, 1H, H-3), 4.89 (dd, *J* = 9.8, 1.3 Hz, 1H, H-1), 4.25 (dd, *J* = 12.4, 5.7 Hz, 1H, H-6a), 4.13 (dd, *J* = 12.5, 2.3 Hz, 1H, H-6b), 3.71 (ddd, *J* = 9.8, 5.7, 2.3 Hz, 1H, H-5), 2.54 (d, *J* = 9.7 Hz, 1H, SH), 2.24 (s, 3H), 2.10 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 170.1, 170.0, 169.5 (each C=O), 76.9 (C-5), 76.3 (C-1), 72.0 (C-3), 71.6 (C-2), 65.2 (C-4), 62.6 (C-6), 20.8, 20.6, 20.6, 20.5 (each O(CO)*C*H_3); $^1J_{C1.H1}$ = 152.1; Hz; IR (film) cm^{-1}: 2560, 1740, 1366, 1210, 1067, 1044; ES-HRMS calcd for $C_{14}H_{20}O_9SNa$ 387.0726, found m/z 387.0730 $[M+Na]^+$.



1,2,3,4-Tetra-O-acetyl-α-L-rhamnopyranose (84)[28]

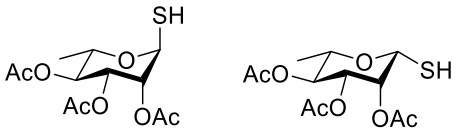
L-Rhamnose monohydrate (2.50 g, 15.23 mmol) was dissolved in pyridine (42 mL) and cooled to 0 °C. Acetic anhydride (8.62 mL, 91.4 mmol) was added to this slowly, portion wise, before the reaction mixture was allowed to warm to room temperature overnight with stirring. The reaction mixture was poured onto an ice-water mixture and stirred for 15 mins. It was then washed with 1 M HCl (x3), satd. $NaHCO_3$, water and dried over Na_2SO_4. The solvent was removed under reduced pressure and co-evaporated with toluene. The title compound was taken without further purification (4.39 g, 88%) as a light yellow viscous oil. R_f 0.42 (cyclohexane-EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (d, *J* = 1.9 Hz, 1H, H-1), 5.31 (dd, *J* = 10.1, 3.6 Hz, 1H, H-3), 5.25 (dd, *J* = 3.5, 2.0 Hz, 1H, H-2), 5.12 (t, *J* = 10.0 Hz, 1H, H-4), 3.94 (dtd, *J* = 9.8, 6.5, 5.9 Hz, 1H, H-5), 2.17 (s, 3H, C(O)C*H*$_3$), 2.16 (s, 3H, C(O)C*H*$_3$), 2.06 (s, 3H, C(O)C*H*$_3$), 2.01 (s, 3H, C(O)C*H*$_3$), 1.24 (d, *J* = 6.2 Hz, 3H, C*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 169.8, 169.8, 168.3 (each C=O), 90.6 (C-1), 70.5 (C-4), 68.7 (C-3), 68.7 (C-5), 68.6 (C-2), 20.9, 20.8, 20.7, 20.7 (each C(O)*C*H$_3$), 17.4 (CH_3); IR (ATR) cm^{-1}: 1743, 1368, 1209, 1044, 1024; ES-HRMS calcd for $C_{16}H_{23}O_9NNa$ 396.1271, found m/z 396.1267 $[M+CH_3CN+Na]^+$.



2,3,4-Tri-*O*-acetyl-α-rhamnopyranosyl bromide (86)[29]

1,2,3,4-Tetra-O-acetyl-α-L-rhamnopyranose (4.3 g, 12.9 mmol) was dissolved in anhydrous CH_2Cl_2 (24 mL) and cooled to 0°C. HBr (33% in AcOH, 6.4 mL) was added to the reaction mixture and it was allowed to warm to room temperature, stirring for 3 h. The reaction mixture was then poured onto an ice-water mixture, separated and washed with satd. $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated under reduced pressure to yield a colourless viscous oil (4.36 g, 96%) as the title compound. R_f 0.37 (cyclohexane-EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (dd, *J* = 1.7, 0.7 Hz, 1H, H-1), 5.68 (dd, *J* = 10.2, 3.4 Hz, 1H, H-3), 5.45 (dd, *J* = 3.4, 1.6 Hz, 1H, H-2), 5.16 (t, *J* = 10.1 Hz, 1H, H-4), 4.12 (dqd, *J* = 9.9, 6.2, 0.8 Hz, 1H, H-

5), 2.17 (s, 3H, O(CO)C*H*$_3$), 2.09 (s, 3H, O(CO)C*H*$_3$), 2.01 (s, 3H, O(CO)C*H*$_3$), 1.29 (d, *J* = 6.3 Hz, 3H, C*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 169.7, 169.6 (each *C*=O), 83.7 (C-1), 72.5 (C-2), 71.1 (C-5), 70.3 (C-4), 67.9 (C-3), 20.8, 20.8, 20.6 (each O(CO)*C*H$_3$), 17.0 (CH$_3$).



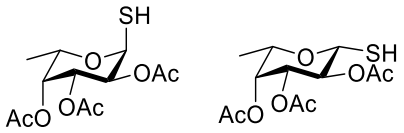
2,3,4-Tri-*O*-acetyl-1-thio-α/β-L-rhamnopyranose (66 and 67)[30]

2,3,4-Tri-*O*-acetyl-α-rhamnopyranosyl bromide (2.2 g, 6.2 mmol) was dissolved in acetone (33 mL) and to this solution, thiourea (0.8 g, 10.6 mmol) was added. The reaction was heated to reflux (70 ^{o} C) and stirred overnight. The solution was allowed to cool to room temperature and concentrated in vacuo. The salt was used without any further purification. The salt (1.70 g, 3.96 mmol) was suspended in a 3:2 CH_2Cl_2-H_2O mixture (40 mL) to which sodium metabisulfite (0.98 g, 5.15mmol) was added. The reaction mixture was heated to reflux (85 ^{o}C) and left to stir for 15 mins. The solution was allowed to cool to room temperature and separated. The aqueous layer was re-extracted with CH_2Cl_2 and the combined organic layer were washed with water, dried over Na_2SO_4, with the solvent then being removed under reduced pressure. Chromatography (cyclohexane-EtOAc 4:1→3:2) gave the title compounds as a separable pair of anomers (α-anomer: 0.67 g, 55%; β-anomer: 0.17 g, 14%) as a white solid and viscous oil.

Reaction of **62** (201 mg, 0.66 mmol) according to Method B, cooling to 4 ^{o}C and addition of MSA (1.0 M in CH_2Cl_2, 0.5 eq.), and column chromatography (cyclohexane-EtOAc 3:1) gave **63** (158 mg, 78%).

Analytical data for 66 R_f 0.4 (cyclohexane-EtOAc 3:2); $[\alpha]_D^{20}$ -97.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.48 (dd, *J* = 7.0, 1.3 Hz, 1H, H-1), 5.34 – 5.29 (overlapping signals, 2H, H-2 & H-3), 5.10 (dd, *J* = 10.5, 8.6 Hz, 1H, H-4), 4.21 (dq, *J* = 10.0, 6.2 Hz, 1H, H-5), 2.24 (d, *J* = 6.9 Hz, 1H, SH), 2.16 (d, *J* = 1.3 Hz, 3H, O(CO)C*H*$_3$), 2.07 (d, *J* = 1.1 Hz, 3H, O(CO)C*H*$_3$), 2.00 (d, *J* = 1.3 Hz, 3H, O(CO)C*H*$_3$), 1.24 (d, *J* = 6.2 Hz, 3H, C*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.97, 169.91, 169.87 (each *C*=O), 76.69 (C-1), 72.33 (C-2), 71.05 (C-4), 68.49 (C-3), 67.64 (C-3), 20.89, 20.77, 20.63 (each O(CO)*C*H$_3$), 17.28 (*C*H$_3$); $^1J_{C1.H1}$ = 169.2; Hz; IR (ATR) cm^{-1}: 2556, 1732, 1601, 1372, 1203, 1066, 1047; ES-HRMS calcd for $C_{12}H_{18}O_7SNa$ 329.0671, found *m/z* 329.0660 $[M+Na]^+$.

Analytical data for 67 R_f 0.25 (cyclohexane-EtOAc 3:2); $[\alpha]_D^{20}$ +21.4 (*c* 0.62, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (q, *J* = 1.7, 1.2, 1.2 Hz, 1H, H-2), 5.07 – 5.01 (overlapping signals, 2H, H-3 and H-4), 4.86 (dd, *J* = 9.8, 1.2 Hz, 1H, H-1), 3.61 – 3.54 (m, 1H, H-5), 2.49 (d, *J* = 9.7 Hz, 1H, SH), 2.23 (s, 3H, C(O)CH_3), 2.05 (s, 3H, C(O)CH_3), 1.98 (s, 3H, C(O)CH_3), 1.28 (d, *J* = 6.2 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 170.1, 169.8 (each C=O), 76.0 (C-1), 75.3 (C-5), 72.0 (C-2), 71.9 (C-3), 69.9 (C-4), 20.8, 20.6, 20.6 (each C(O)*C*H_3), 17.7 (CH_3); $^1J_{C1.H1}$ = 151.5 Hz; IR (ATR) cm^{-1}: 1741, 1371, 1249, 1212, 1049; ES-HRMS calcd for $C_{11}H_{17}O_7S$ 305.0695, found *m/z* 305.0694 $[M-H^+]^-$.



2,3,4-Tri-*O*-acetyl-1-thio-L-fucopyranose (70 and 71)[31-32]

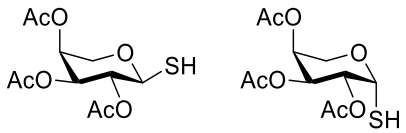
2,3,4-Tri-*O*-acetyl-α-L-fucopyranosyl bromide (3.20 g, 9.06 mmol) was dissolved in acetone (46 mL) and to this solution, thiourea (1.17 g, 15.40 mmol) was added. The reaction was heated to reflux (70 ^{o} C) and stirred overnight. The solution was allowed to cool to room temperature and concentrated in vacuo. The salt was used without any further purification. The salt (3.89 g, 9.06 mmol) was suspended in a 3:2 CH_2Cl_2-H_2O mixture (75 mL) to which sodium metabisulfite (2.24 g, 11.78 mmol) was added. The reaction mixture was heated to reflux (85 ^{o}C) and left to stir for 45 mins. The solution was allowed to cool to room temperature and separated. The aqueous layer was re-extracted with CH_2Cl_2 and the combined organic layer were washed with water, dried over Na_2SO_4, with the solvent then being removed under reduced pressure. Chromatography (cyclohexane-EtOAc 2:1) gave the title compounds, as a separable pair of anomers (α-anomer: 0.11 g, 4%; β-anomer: 1.84 g, 66%), as a white solid and colourless oil, respectively.

Reaction of **70** (100 mg, 0.33 mmol) according to Method B and chromatography (cyclohexane-EtOAc 3:1) gave **71** (64 mg, 64%).

Analytical data for 70 R_f 0.37 (cyclohexane-EtOAc 2:1); $[\alpha]_D^{20}$ -108.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97 (t, *J* = 4.6 Hz, 1H, H-1), 5.31 (dd, *J* = 2.5, 1.3 Hz, 1H, H-4), 5.30 – 5.21 (overlapping peaks, 2H, H-2 and H-3), 4.52 (q, *J* = 6.5 Hz, 1H, H-5), 2.17 (s, 3H, O(CO)CH_3), 2.09 (s, 3H, O(CO)CH_3), 2.00 (s, 3H, O(CO)CH_3), 1.80 (d, *J* = 5.1 Hz, 1H, SH), 1.16 (d, *J* = 6.5 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 170.0, 169.9 (each C=O), 77.7 (C-1), 70.8 (C-4), 68.0 (C-3), 67.5 (C-2), 65.4 (C-5), 20.8, 20.6, 20.6 (each

O(CO)*C*H_3) , 15.9 (CH_3); $^1J_{C1.H1}$ = 168.8 Hz; IR (ATR) cm^{-1}: 1741, 1369, 1257, 1059, 1016; ES-HRMS calcd for $C_{14}H_{21}NO_7SNa$ 370.0936, found *m/z* 370.0923 $[M+Na+NH_4]^+$.

Analytical data for 71 R_f 0.24 (cyclohexane-EtOAc 2:1); $[\alpha]_D^{20}$ -26.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.28 (dd, *J* = 3.4, 1.2 Hz, 1H, H-4), 5.16 (t, *J* = 9.9 Hz, 1H, H-2), 5.02 (dd, *J* = 10.1, 3.4 Hz, 1H, H-3), 4.50 (t, *J* = 9.8 Hz, 1H, H-1), 3.84 (qd, *J* = 6.4, 1.2 Hz, 1H, H-5), 2.33 (d, *J* = 10.0 Hz, 1H, SH), 2.19 (s, 3H, O(CO)CH_3), 2.09 (s, 3H, O(CO)CH_3), 1.99 (s, 3H, O(CO)CH_3), 1.23 (d, *J* = 6.4 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 170.0, 169.9 (each C=O), 78.8 (C-1), 73.8 (C-5), 72.0 (C-3), 71.0 (C-2), 70.3 (C-4), 20.8, 20.7, 20.6 (each O(CO)*C*H_3), 16.4 (CH_3); IR (film) cm^{-1}: 2590, 1727, 1370, 1248, 1212, 1051; ES-HRMS calcd for $C_{14}H_{21}NO_7SNa$ 370.0936, found *m/z* 370.0933 $[M+Na+NH_4]^+$.



2,3,4-Tri-*O*-acetyl-1-thio-L-arabinopyranose (72 and 73)[33]

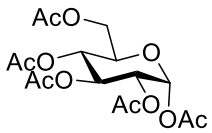
2,3,4-Tri-*O*-acetyl-β-L-arabinopyranosyl bromide (4.97 g, 14.66 mmol) was dissolved in acetone (73 mL) and to this solution, thiourea (1.9 g, 25.0 mmol) was added. The reaction was heated to reflux (70 ° C) and stirred overnight. The reaction mixture was concentrated in vacuo to yield a yellow foam. The salt was used without any further purification and was suspended in a 3:2 CH_2Cl_2-H_2O mixture (120 mL) to which sodium metabisulfite (3.6 g, 19.1 mmol) was added. The reaction mixture was heated to reflux (80 ° C) and left to stir for 15 mins. The solution was allowed to cool to room temperature and separated. The aqueous layer was re-extracted with CH_2Cl_2 and the combined organic layer were washed with water, dried over Na_2SO_4, with the solvent then being removed under reduced pressure. Chromatography (cyclohexane-EtOAc 8:2 → 7:3) gave the title compounds as a seperable pair of anomers (α-anomer: 2.45 g, 57%; β-anomer: 0.29 g, 7%) as a white solid and colourless viscous oil, respectively.

Reaction of **72** (100 mg, 0.34 mmol) according to Method B and column chromatography (cyclohexane-EtOAc 7:3) gave **73** (34 mg, 34%).

Analytical data for 73 R_f 0.19 (cyclohexane-EtOAc 7:3); $[\alpha]_D^{20}$ +57.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz,$CDCl_3$) δ 5.31 (dd, *J* = 3.9, 2.1 Hz, 1H, H-4), 5.19 (t, *J* = 8.9 Hz, 1H, H-2), 5.05 (dd, *J* = 9.2, 3.5 Hz, 1H, H-3), 4.56 (t, *J* = 9.2 Hz, 1H, H-1), 4.09 (dd, *J* = 13.1, 3.1 Hz,

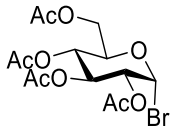
1H, H-5a), 3.69 (dd, *J* = 13.1, 1.7 Hz, 1H, H-5b), 2.37 (d, *J* = 9.7 Hz, 1H, SH), 2.15 (s, 3H, C(O)CH_3), 2.10 (s, 3H, C(O)CH_3), 2.04 (s, 3H, C(O)CH_3);^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 169.9, 169.8 (C=O), 79.1 (C-1), 71.3 (C-2), 70.8 (C-3), 67.9 (C-4), 67.1 (C-5), 20.9, 20.8, 20.6 (each C(O)*C*H_3); $^1J_{C1.H1}$ = 151.6 Hz; IR (ATR) cm^{-1}: 2971, 1721, 1368, 1244, 1067, 1025; ES-HRMS calcd for $C_{14}H_{25}O_8S$ 353.1270, found *m/z* 353.1268 $[M+H+C_3H_8O]^+$.

Analytical data for 72 R_f 0.24 (cyclohexane-EtOAc 7:3); $[\alpha]_D^{20}$ +221.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (d, *J* = 5.6 Hz, 1H, H-1), 5.31 (m, 1H, H-4), 5.28 – 5.24 (overlapping signals, 2H, H-2 and H-3), 4.30 (dd, *J* = 13.0, 2.0 Hz, 1H, H-5a), 3.76 (dd, *J* = 13.0, 3.5 Hz, 1H, H-5b), 2.13 (s, 3H, C(O)CH_3), 2.11 (s, 3H, C(O)CH_3), 2.05 (s, 3H, C(O)CH_3), 1.85 (d, *J* = 5.8 Hz, 1H, SH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 169.8, 169.7 (each C=O), 77.6 (C-1), 68.3 (C-2), 68.0 (C-4), 67.0 (C-3), 61.6 (C-5), 20.9, 20.7, 20.7 (each C(O)*C*H_3); $^1J_{C1.H1}$ = 167.7 Hz; IR (ATR) cm^{-1}: 2545, 1741, 1370, 1211, 1083, 1061; ES-HRMS calcd for $C_{11}H_{16}O_7SNa$ 315.0514, found *m/z* 353.0518 $[M+Na]^+$.



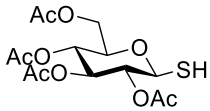
α-D-Glucopyranose pentaacetate (88)[34]

D-glucose (2.5 g, 13.88 mmol) was dissolved in anhydrous pyridine (30 mL) and cooled to 0 °C. Acetic anhydride (9.2 mL, 97.14 mmol) was added slowly, portionwise, and the reaction mixture was left to stir overnight warming to room temperature. The reaction was then poured onto an ice-water mixture and stirred for 15 mins. EtOAc was added to the mixture and the layers were separated. The organic layer was washed with 1.0 M HCl (x3), satd $NaHCO_3$ and water, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a white solid as the title compound (5.33 g, 98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (d, *J* = 3.7 Hz, 1H, H-1), 5.47 (t, *J* = 9.9 Hz, 1H, H-3), 5.14 (t, *J* = 9.9 Hz, 1H, H-4), 5.10 (dd, *J* = 10.3, 3.7 Hz, 1H, H-2), 4.27 (dd, *J* = 12.7, 4.2 Hz, 1H, H-6a), 4.15 – 4.07 (m, 2H, H-5 and H-6b), 2.18 (s, 3H, C(O)CH_3), 2.10 (s, 3H, C(O)CH_3), 2.04 (s, 3H, C(O)CH_3), 2.03 (s, 3H, C(O)CH_3), 2.02 (s, 3H, C(O)CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 170.2, 169.6, 169.3, 168.7 (each C=O), 89.0 (C-1), 69.8 (2s, C-3 and C-5), 69.2 (C-2), 67.9 (C-4), 61.4 (C-6), 20.8, 20.7, 20.6, 20.5, 20.4 (each C(O)*C*H_3); IR (ATR) cm^{-1}: 1736, 1367, 1214, 1069, 1030; ES-HRMS calcd for $C_{16}H_{22}O_{11}Na$ 413.1060, found *m/z* 413.1057 $[M+Na]^+$.



2,3,4,6-Tetra-*O*-acetyl-α-glucopyranosyl bromide (89)[35]

Peracetylated glucose (3.6 g, 9.22 mmol) was dissolved in anhydrous CH_2Cl_2 (18 mL) and cooled to 0 ºC. HBr (33% in AcOH, 4.5 mL) was added and the reaction mixture was allowed to stir overnight, warming to rt. The reaction was poured onto an ice-water mixture and stirred for 15 mins. The mixture was diluted with CH_2Cl_2 and separated. The organic layer was washed with satd. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give a white solid as the title compound (4.97 g, 90%). R_f 0.6 (cyclohexane-EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (d, *J* = 4.0 Hz, 1H, H-1), 5.56 (t, *J* = 9.7 Hz, 1H, H-3), 5.16 (t, *J* = 9.7 Hz, 1H, H-4), 4.84 (dd, *J* = 10.0, 4.1 Hz, 1H, H-2), 4.36 – 4.28 (overlapping signals, 2H, H-5 and H-6a), 4.16 – 4.11 (m, 1H, H-6b), 2.10 (s, 3H, C(O)CH_3), 2.10 (s, 3H, C(O)CH_3), 2.06 (s, 3H, C(O)CH_3), 2.04 (s, 3H, C(O)CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 169.8, 169.7, 169.4 (each C=O), 86.5 (C-1), 72.1 (C-5), 70.6 (C-2), 70.1 (C-3), 67.1 (C-4), 60.9 (C-6), 20.6, 20.6, 20.6, 20.5 (each C(O)*C*H_3).

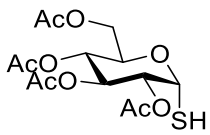


2,3,4,6-Tetra-*O*-acetyl-1-thio-β-D-glucopyranose (59)[35]

2,3,4,6-Tetra-*O*-acetyl-α-glucopyranosyl bromide (3.60 g, 8.75 mmol) was dissolved in acetone (43 mL) and to this solution, thiourea (1.13 g, 14.88 mmol) was added. The reaction was heated to reflux (70 ºC) and stirred overnight. A white precipitate formed. The solution was allowed to cool to room temperature and concentrated in vacuo. The salt was used without any further purification. The salt (4.27 g, 8.75 mmol) was suspended in a 3:2 CH_2Cl_2-H_2O mixture (70 mL) to which sodium metabisulfite (1.16 g, 11.38 mmol) was added. The reaction mixture was heated to reflux (62 ºC) and left to stir for 2.5 h. The solution was allowed to cool to room temperature and separated. The aqueous layer was re-extracted with CH_2Cl_2 and the combined organic layer were washed with water, dried over Na_2SO_4, with the solvent then being removed under reduced pressure. Chromatography (cyclohexane-EtOAc 3:2) gave the title compound (2.33 g, 73%) as a white solid.

Reaction of **104** (100 mg, 0.27 mmol) according to Method B and column chromatography (chloroform-EtOAc 12:1) gave **59** (50.8 mg, 51%).

R_f 0.24 (cyclohexane-EtOAc 3:2); $[\alpha]_D^{20}$ +14.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (t, *J* = 9.4 Hz, 1H, H-3), 5.11 (t, *J* = 9.7 Hz, 1H, H-4), 4.98 (t, *J* = 9.5 Hz, 1H, H-2), 4.55 (t, *J* = 9.6 Hz, 1H, H-1), 4.25 (dd, *J* = 12.5, 4.8 Hz, 1H, H-6a), 4.13 (dd, *J* = 12.5, 2.2 Hz, 1H, H-6b), 3.73 (ddd, *J* = 10.0, 4.8, 2.2 Hz, 1H, H-5), 2.31 (d, *J* = 9.6 Hz, 1H, SH), 2.10 (s, 3H, $C(O)CH_3$), 2.08 (s, 3H, $C(O)CH_3$), 2.03 (s, 3H, $C(O)CH_3$), 2.01 (s, 3H, $C(O)CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 170.1, 169.6, 169.3 (each C=O), 78.7 (C-1), 76.3 (C-5), 73.5 (2s, overlapping signals, C-3 and C-2), 68.1 (C-4), 62.0 (C-6), 20.7, 20.7, 20.6, 20.5 (each $C(O)CH_3$); $^1J_{C1.H1}$ = 155.3 Hz; IR (film) cm^{-1}: 2950, 2583, 1732, 1365, 1237, 1215, 1027; ES-HRMS calcd for $C_{14}H_{20}O_9SNa$ 387.0726, found *m/z* 387.0708 $[M+Na]^+$.

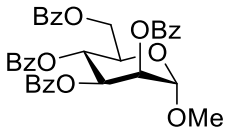


2,3,4,6-Tetra-*O*-acetyl-1-thio-α-D-glucopyranose (104)[36]

The equatorial thiol **59** (1.0 g) was dissolved in EtOAc (10 mL) under nitrogen or argon. $SnCl_4$ (1.0 M in CH_2Cl_2, 2.5 eq.) was added and the mixture was stirred at room temperature for 24 h. The reaction was diluted with EtOAc and quenched by addition of 1.0 M $KHSO_4$. The aq. layer was extracted with EtOAc and combined organic layers were washed with satd. $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated in vacuo and column chromatography (chloroform-EtOAc 12:1) gave **104** (191 mg, 19%) which was used for the axial to equatorial anomerisation experiments.

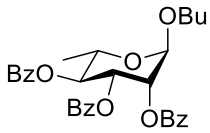
R_f 0.29 (chloroform-EtOAc 12:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (t, *J* = 5.2 Hz, 1H, H-1), 5.38 (t, *J* = 9.8 Hz, 1H, H-3), 5.09 – 5.00 (overlapping signals, 2H, H-4 and H-2), 4.44 (ddd, *J* = 10.3, 4.4, 2.3 Hz, 1H, H-5), 4.29 (dd, *J* = 12.5, 4.3 Hz, 1H, H-6a), 4.11 (dd, *J* = 12.5, 2.2 Hz, 1H, H-6b), 2.10 (s, 3H, $C(O)CH_3$), 2.08 (s, 3H, $C(O)CH_3$), 2.04 (s, 3H, $C(O)CH_3$), 2.03 (s, 3H, $C(O)CH_3$), 1.92 (d, J = 4.5 Hz, 1H, SH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 170.0, 169.7, 169.5 (each C=O), 77.1 (C-1), 70.3 (C-2), 69.9 (C-3), 68.3 (2s, overlapping signals, C-4 and C-5), 61.7 (C-6), 20.7, 20.7, 20.7, 20.6 (each $C(O)CH_3$); $^1J_{C1.H1}$= 171.7 Hz; IR (film) cm^{-1}: 2951, 2564, 1737, 1362, 1222, 1035; ES-HRMS calcd for $C_{14}H_{20}O_9SNa$ 387.0726, found *m/z* 387.0725 $[M+Na]^+$.

6.4 Chapter 4 Experimental Data



Methyl 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranoside (106)[23]

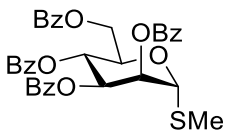
Methyl α-D-mannopyranoside (1.0 g, 5.2 mmol) was dissolved in anhydrous pyridine (12 mL) and cooled to 0 °C. Benzoyl chloride (3.6 mL, 30.9 mmol) was added slowly and the reaction mixture was allowed to warm to room temperature, with stirring, overnight. MeOH (12 mL) was added to decompose excess benzoyl chloride and stirred for 15 mins. The mixture was washed with 1.0 M HCl, water and brine and then dried over Na_2SO_4. The solvent was removed under reduced pressure and column chromatography (cyclohexane-EtOAc 4:1) gave the title compound (3.0 g, 96%). R_f 0.28 (cyclohexane-EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 – 8.09 (overlapping signals, 2H, Ar-H), 8.07 – 8.04 (overlapping signals, 2H, Ar-H), 7.97 – 7.93 (overlapping signals, 2H, Ar-H), 7.85 – 7.82 (overlapping signals, 2H, Ar-H), 7.61 – 7.54 (overlapping signals, 2H, Ar-H), 7.53 – 7.47 (m, 1H, Ar-H), 7.45 – 7.33 (overlapping signals, 7H, Ar-H), 7.28 – 7.25 (overlapping signals, 2H, Ar-H), 6.11 (t, *J* = 10.1 Hz, 1H, H-4), 5.92 (dd, *J* = 10.1, 3.3 Hz, 1H, H-3), 5.70 (dd, *J* = 3.4, 1.8 Hz, 1H. H-2), 5.01 (d, *J* = 1.8 Hz, 1H, H-1), 4.71 (dd, *J* = 12.1, 2.6 Hz, 1H, H-6a), 4.50 (dd, *J* = 12.1, 4.5 Hz, 1H, H-6b), 4.42 (ddd, *J* = 10.1, 4.5, 2.6 Hz, 1H, H-5), 3.55 (s, 3H, OCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.2, 165.4, 165.4 (2s) (each C=O), 133.4, 133.4, 133.1, 133.0, 129.9, 129.8, 129.8, 129.7, 129.7, 129.3, 129.1, 129.0, 128.6, 128.4, 128.3 (Ar C and CH), 98.7 (C-1), 70.4 (C-2), 70.0 (C-3), 68.7 (C-5), 66.9 (C-4), 62.9 (C-6), 55.6 (OCH_3); IR (film) cm^{-1}: 1721, 1601, 1451, 1314, 1254, 1094, 1065, 705, 685; ESI-HRMS calcd for $C_{35}H_{30}O_{10}Na$ 633.1737, found m/z 633.1732 [M+ Na]$^+$.



Butyl 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranoside (107)

In a flame dried flask containing 4Å molecular sieves, I_2 (1.41 g, 5.57 mmol), DDQ (0.63 g, 2.79 mmol) and *n*-butanol (1.02 mL, 11.14 mmol) in dry CH_2Cl_2 (27 mL) were stirred at room temperature, under nitrogen, for 30 mins. 2,3,4-Tri-*O*-benzoyl-α-rhamnopyranosyl bromide **87**[22] (3 g, 5.57 mmol) was added and the reaction mixture was left to stir for 2 hours. The reaction mixture was then filtered through celite, washed with $Na_2S_2O_3$ (2% w/v), satd.

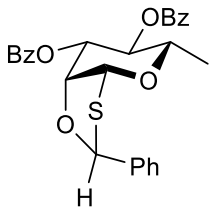
$NaHCO_3$ (x 2) and brine. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Column chromatography (cylcohexane-EtOAc 7:1) gave the title compound (2.43 g, 81%) as a light yellow solid. R_f 0.45 (cyclohexane-EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 – 8.09 (overlapping signals, 2H, Ar-H), 8.00 – 7.95 (overlapping signals, 2H, Ar-H), 7.85 – 7.80 (overlapping signals, 2H, Ar-H), 7.63 – 7.57 (m, 1H, Ar-H), 7.53 – 7.46 (overlapping signals, 3H, Ar-H), 7.43 – 7.35 (overlapping signals, 3H, Ar-H), 7.28 – 7.22 (overlapping signals, 2H, Ar-H), 5.85 (dd, *J* = 10.2, 3.5 Hz, 1H, H-3), 5.71 – 5.64 (overlapping signals, 2H, H-2 and H-4), 5.00 (d, *J* = 1.7 Hz, 1H, H-1), 4.20 (dq, *J* = 9.8, 6.3 Hz, 1H, H-5), 3.80 (dt, *J* = 9.6, 6.6 Hz, 1H, OC*H*H), 3.55 (dt, *J* = 9.6, 6.5 Hz, 1H, OCH*H*), 1.72 – 1.62 (overlapping signals, 2H, OCH_2CH_2), 1.53 – 1.43 (overlapping signals, 2H, $O(CH_2)_2CH_2$), 1.37 (d, *J* = 6.3 Hz, 3H, CH_3), 0.99 (t, *J* = 7.4 Hz, 3H, CH_2CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8, 165.6, 165.5 (each C=O), 133.4, 133.3, 133.0, 129.9, 129.7, 129.7, 129.5, 129.4, 129.3, 128.6, 128.4, 128.2 (Ar-C and CH), 97.5 (C-1), 72.0 (C-4), 71.1 (C-2), 70.1 (C-3), 68.2 (OCH_2), 66.6 (C-5), 31.5 (OCH_2CH_2), 19.4 ($O(CH_2)_2CH_2$), 17.7 (CH_3), 13.9 (CH_2CH_3); IR (ATR) cm^{-1}: 1724, 1602, 1451, 1315, 1260, 1094, 1067, 706, 686; ESI-HRMS calcd for $C_{31}H_{32}O_8Na_1$ 555.1995, found m/z 555.1989 $[M+ Na]^+$.



Methyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-α-D-mannopyranoside (108)[37]

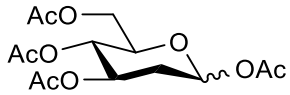
2,3,4,6-Tetra-*O*-benzoyl-thio-α-D-mannopyranose **64**[24] (0.2 g, 0.33 mmol) was dissolved in anhydrous CH_2Cl_2 and DIPEA (0.12 mL, 1.47 mmol) followed by methyl iodide (0.09 mL, 0.69 mmol) were added slowly at room temperature. After 1.5 hours, the solvent was removed under reduced pressure and the residue was purified by column chromatography (cyclohexane-EtOAc 6:1) to yield the title compound as a white solid (0.137 g, 0.22 mmol, 67%). R_f 0.34 (cyclohexane-EtOAc 6:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 – 8.06 (overlapping signals, 4H, Ar-H), 8.00 – 7.95 (overlapping signals, 2H, Ar-H), 7.87 – 7.83 (overlapping signals, 2H, Ar-H), 7.64 – 7.56 (overlapping signals, 2H, Ar-H), 7.55 – 7.50 (m, 1H, Ar-H), 7.48 – 7.36 (overlapping signals, 7H, Ar-H), 7.32 – 7.25 (overlapping signals, 2H, Ar-H), 6.16 (t, *J* = 10.0 Hz, 1H, H-4), 5.87 (dd, *J* = 9.9, 3.3 Hz, 1H, H-3), 5.84 (dd, *J* = 3.3, 1.5 Hz, 1H, H-2), 5.48 (d, *J* = 1.5 Hz, 1H, H-1), 4.82 (ddd, *J* = 10.1, 4.6, 2.6 Hz, 1H, H-5), 4.71 (dd, *J* = 12.2, 2.6 Hz, 1H, H-6a), 4.56 (dd, *J* = 12.2, 4.6 Hz, 1H, H-6b), 2.27 (s, 3H, S-C*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 165.4, 165.4, 165.3 (each C=O), 133.5, 133.5, 133.2, 133.1, 129.8, 129.8, 129.7, 129.7,

129.3, 128.9, 128.9, 128.6, 128.5, 128.4, 128.3 (Ar-C and CH), 83.7 (C-1), 71.8 (C-2), 70.5 (C-3), 69.2 (C-5), 67.1 (C-4), 62.9 (C-6), 13.9 (S-CH_3); IR cm^{-1}: 1720, 1602, 1451, 1314, 1251, 1090, 1067, 704, 685; ESI-HRMS calcd for $C_{35}H_{30}O_9SNa$ 649.1508, found m/z 649.1509 $[M+Na]^+$.



(3a*R*,5*S*,6*S*,7*R*,7a*R*)-6-(benzoyloxy)-5-methyl-2-phenyltetrahydro-2*H*,3a*H*-[1,3]oxathiolo [4,5-*b*]pyran-7-yl benzoate (110)

A mixture of 2,3,4-tri-*O*-benzoyl-1-thio-α-L-rhamnopyranose (0.30 g, 0.61 mmol) and sodium cyanborohydride (0.46 g, 7.3 mmol) were dried under vacuum for 3 h prior to reaction. To this mixture was added $CHCl_3$ (3 mL) followed by $TiCl_4$ (0.34 M in $CHCl_3$, 0.73 mmol), and the reaction was left to stir overnight, at room temperature. The mixture was quenched by addition of satd $NaHCO_3$ and solid $NaHCO_3$ (50 mg). The mixture stirred for 15 minutes and then diluted with EtOAc. The aq. layer was extracted with EtOAc and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to column chromatography (cyclohexane-EtOAc 7:1) to give a mixture of the α-anomer and the title intermediate as an inseparable mixture (43 mg; 1:1). The mixture was then dissolved in pyridine (1 mL) and acetic anhydride (0.5 mL) was added at room temperature. TLC analysis indicated reaction was complete after 1 h and the mixture was concentrated under reduced pressure. Column chromatography (cyclohexane-EtOAc 10:1) of the residue gave the title compound (8.8 mg; 3%). R_f 0.29 (cyclohexane-EtOAc 9:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 – 7.90 (overlapping signals, 4H, Ar-H), 7.60 – 7.55 (overlapping signals, 2H, Ar-H), 7.53 – 7.45 (overlapping signals, 2H, Ar-H), 7.43 – 7.31 (overlapping signals, 7H, Ar-H), 6.11 (s, 1H, H'), 5.73 (t, *J* = 9.9 Hz, 1H, H-4), 5.60 (dd, *J* = 10.2, 3.9 Hz, 1H, H-3), 5.49 (s, 1H, H-1), 4.63 (d, *J* = 3.7 Hz, 1H, H-2), 3.91 (dq, *J* = 12.0, 6.0 Hz, 1H, H-5), 1.40 (d, *J* = 6.3 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 165.6 (each C=O), 138.7, 133.3, 133.3, 130.0, 129.7, 129.3, 129.1, 128.5, 128.4, 128.3, 127.5 (each Ar-C and CH), 87.1 (O*C*HPhS), 84.9 (C-1), 84.2 (C-2), 74.6 (C-5), 72.4 (C-3), 71.0 (C-4), 18.0 (CH_3); IR (ATR) cm^{-1}: 2983, 1721, 1602, 1452, 1273, 1091, 1064, 707; ES-HRMS calcd for $C_{27}H_{28}O_6SN$ 494.1637, found *m/z* 494.1631 $[M+NH_4]^+$.



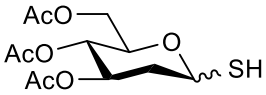
1,3,4,6-Tetra-O-acetyl-2-deoxy-D-arabino-hexopyranose (115)[38]

2-Deoxy-D-arabino-hexopyranose (2-deoxy-D-glucose) (1 g, 6.1 mmol) was suspended in anhydrous pyridine (16.9 mL) and cooled to 0 °C. Acetic anhydride (3.5 mL, 36.6 mmol) was added slowly at 0 °C and the reaction mixture was allowed to warm to room temperature, stirring overnight. The reaction mixture was then diluted with EtOAc and washed with 1.0 M HCl, satd. $NaHCO_3$ and water. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to yield the title compound (1.9 g, 95 %) a viscous colourless oil, as a pair of anomers (α:β = 1:10). β-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (dd, *J* = 9.9, 2.3 Hz, 1H, H-1), 5.11 – 4.99 (overlapping peaks, 2H, H-3 and H-4), 4.32 (dd, *J* = 12.3, 4.9 Hz, 1H, H-6a), 4.09 (dd, *J* = 12.3, 2.3 Hz, 1H, H-6b), 3.75 (ddd, *J* = 9.2, 4.8, 2.2 Hz, 1H, H-5), 2.35 (ddd, *J* = 12.6, 4.9, 2.3 Hz, 1H, H-2a), 2.12 (s, 3H, O(CO)CH_3), 2.09 (s, 3H, O(CO)CH_3), 2.05 (s, 3H, O(CO)CH_3), 2.04 (s, 3H, O(CO)CH_3), 1.87 (q, *J* = 11.0 Hz, 1H, H-2b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 170.1, 169.7, 168.8 (each C=O), 91.1 (C-1), 72.9 (C-5), 70.1 (C-3), 68.3 (C-4), 62.0 (C-6), 34.7 (C-2), 20.9, 20.8, 20.8, 20.7 (each O(CO)*C*H_3) IR (ATR) cm^{-1}: 2962, 1733, 1367, 1212, 1032; ESI-HRMS calcd for $C_{14}H_{20}O_9Na$ 355.1005, found *m/z* 355.1002 $[M+Na]^+$.

3,4,6-Tri-O-acetyl-2-deoxy-1-*S*-acetyl-1-thio-D-arabinohexopyranose (116)[11]

1,3,4,6-Tetra-O-acetyl-2-deoxy-D-arabino-hexopyranose (1.5 g, 4.5 mmol) was co-evaporated with toluene before drying under vacuum for 12 h prior to reaction. The peracetylated sugar was dissolved in anhydrous CH_2Cl_2 (45 mL) before cooling to 0 °C. Thioacetic acid (0.97 mL, 13.5 mmol) and TMSOTf (0.8 mL, 4.5 mmol) were added dropwise at 0 °C. The reaction was left to stir at 0 °C for 3 h before it was poured onto satd. $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, concentrated in vacuo and subjected to column chromatography (cyclohexane-EtOAc 2:1) to isolate the title product as a viscous colourless oil (0.48 g, 31%), as a mixture of anomers (α:β = 1.3:1). R_f 0.28 (cyclohexane-EtOAc 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.11 (t, *J* = 3.6 Hz, 1H, H-1α), 5.31 (dd, *J* = 12.4, 2.1 Hz, 1H, H-1β), 5.12 – 4.95 (overlapping peaks, 4H, H-3α,

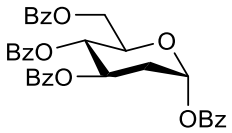
H-3β, H-4α and H-4β), 4.32 (dd, *J* = 12.4, 4.4 Hz, 1H, H-6aα), 4.30 – 4.26 (m, 1H H-6aβ), 4.07 (dd, *J* = 12.8, 2.1 Hz, 1H, H-6bβ), 4.02 (dd, *J* = 12.4, 2.3 Hz, 1H, H-6bα), 3.94 (dt, *J* = 9.5, 3.0 Hz, 1H, H-5α), 3.76 (ddd, *J* = 9.5, 4.5, 2.0 Hz, 1H, H-5β), 2.40 (overlapping peaks, 4H, H-2aβ and S(CO)CH_3), 2.37 (s, 3H, S(CO)CH_3), 2.31 – 2.26 (overlapping peaks, 2H, H-2aα and H-2bα), 2.07 (s, 6H, 2 x O(CO)CH_3), 2.04 (s, 6H, 2 x O(CO)CH_3), 2.03 (s, 6H, 2 x O(CO)CH_3), 2.00 – 1.90 (m, 1H, H-2bβ); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.3, 192.2 (S(*C*=O)CH_3), 170.7, 170.7, 170.1, 170.1, 169.7, 169.7 (each C=O), 78.6 (C-1α), 76.7 (C-1β), 76.5 (C-5β), 71.8 (C-5α), 71.7 (C-3β), 69.8 (C-3α), 68.8 (C-4α), 68.3 (C-4β), 62.2, 62.0 (overlapping signals, C-6α and C-6β), 35.8, 35.6 (overlapping signals, C-2α and C-2β, 31.3, 30.6 (each S(CO)*C*H_3), 20.9, 20.9, 20.8, 20.7, 20.7, 20.7 (each O(CO)*C*H_3); IR (ATR) cm^{-1}: 2917, 1739, 1705, 1366, 1217, 1049; ESI-HRMS calcd for $C_{14}H_{20}O_8SNa$ 371.0777, found *m/z* 371.0778 $[M+Na]^+$.



3,4,6-Tri-O-acetyl-2-deoxy-1-thio-D-arabino-hexopyranose (118)[39]

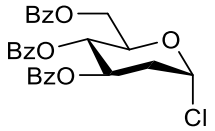
Thioacetate **116** (0.17 g, 0.48 mmol) was dried under reduced pressure for 2 h before it was dissolved in anhydrous MeOH (9.6 mL). The reaction mixture was cooled to -40 ºC and freshly prepared sodium methoxide solution (1.0 M, 0.48 mmol) was added to the reaction mixture. The reaction mixture was left to stir for 1 h at -40 ºC, until T.L.C. indicated consumption of **116**. NH_4Cl (0.02 g) was added to the reaction mixture at -40 ºC and left to stir for 5 mins. The reaction was then warmed to room temperature and, upon dissolution of salts, was concentrated under reduced pressure. The crude residue was suspended between CH_2Cl_2 and H_2O, separated and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated and purified through chromatography (cyclohexane-EtOAc 3:2) to yield the title compound (64 mg, 43%) as a colourless solid, as a mixture of anomers (α:β = 2.2:1). R_f 0.52 (cyclohexane-EtOAc 3:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (t, *J* = 5.7 Hz, 1H, H-1α), 5.28 (ddd, *J* = 11.7, 9.3, 5.1 Hz, 1H, H-3α), 5.04 – 4.96 (overlapping peaks, 3H, H-4α, H-3β and H-4β), 4.74 (ddd, *J* = 11.2, 8.6, 2.0 Hz, 1H, H-1β), 4.42 (ddd, *J* = 9.8, 4.5, 2.2 Hz, 1H, H-5α), 4.33 (dd, *J* = 12.4, 4.5 Hz, 1H, H-6aα), 4.25 (dd, *J* = 12.3, 4.9 Hz, 1H, H-6aβ), 4.14 – 4.04 (overlapping peaks, 2H, H-6bα and H-6bβ), 3.65 (ddt, *J* = 7.1, 4.9, 2.3 Hz, 1H, H-5β), 2.56 – 2.51 (m, 1H, H-2aβ), 2.48 (d, *J* = 8.6 Hz, 1H, SHβ), 2.30 (dd, *J* = 13.5, 5.1 Hz, 1H, H-2aα), 2.23 – 2.14 (overlapping peaks, 2H, SHα and H-2bβ), 2.09 (s, 6H, 2 x C(O)CH_3), 2.06 (s, 3H, C(O)CH_3), 2.04 (s, 3H, C(O)CH_3), 2.03 (s, 3H, C(O)CH_3), 2.03 (s, 3H, C(O)CH_3), 1.91

– 1.81 (m, 1H, H-2bβ); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 170.8, 170.7, 170.2, 170.1, 169.8 (each C=O), 76.3 (C-5β), 75.3 (C-1α), 74.8 (C-1β), 71.5, 69.3, 68.8, 68.8, 68.5, 62.5 (C-6β), 62.1 (C-6α), 40.4 (C-2β), 36.5 (C-2α), 20.9, 20.9, 20.8, 20.7, 20.7, 20.7 (each $C(O)CH_3$); IR (ATR) cm^{-1}: 2955, 2572, 1736, 1366, 1216, 1047; ESI-HRMS calcd for $C_{12}H_{17}O_7S$ 305.0695, found *m/z* 305.0695 $[M-H]^-$.



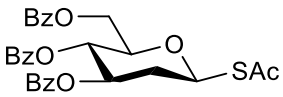
1,3,4,6-Tetra-O-benzoyl-2-deoxy-α-D-arabino-hexopyranose (119)[7]

2-Deoxy-D-glucose (1.0 g, 6.1 mmol) was suspended in anhydrous pyridine (16.9 mL) and cooled to 0 ºC. Benzoyl chloride (4.67 mL, 40.2 mmol) was added slowly at 0 ºC and the reaction mixture was allowed to warm to room temperature, stirring overnight. The reaction mixture was then diluted with EtOAc and washed with 1.0 M HCl, satd. $NaHCO_3$ and water. The organic layer was dried over Na_2SO_4, filtered, concentrated in vacuo and subjected to column chromatography (cyclohexane-EtOAc 5:1) to yield the title compound (3.0 g, 86%) a white solid. R_f 0.38 (cyclohexane-EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 – 8.05 (overlapping signals, 2H, Ar-H), 8.05 – 8.00 (overlapping signals, 2H, Ar-H), 8.00 – 7.93 (overlapping signals, 4H, Ar-H), 7.63 – 7.56 (m, 1H, Ar-H), 7.55 – 7.48 (overlapping signals, 3H, Ar-H), 7.47 – 7.32 (overlapping signals, 8H, Ar-H), 6.30 (dd, *J* = 9.2, 2.4 Hz, 1H, H-1), 5.70 (t, *J* = 9.2 Hz, 1H, H-4), 5.56 (td, *J* = 10.1, 5.1 Hz, 1H, H-3), 4.66 (dd, *J* = 12.0, 3.1 Hz, 1H, H-6a), 4.52 (dd, *J* = 12.2, 5.1 Hz, 1H, H-6b), 4.26 (ddd, *J* = 8.8, 4.9, 3.1 Hz, 1H, H-5), 2.78 (ddd, *J* = 12.7, 5.3, 2.4 Hz, 1H, H-2a), 2.28 (dt, *J* = 12.5, 9.9 Hz, 1H, H-2b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 165.7, 165.4, 164.4 (each C=O), 133.7, 133.6, 133.4, 133.3, 133.0, 130.0, 129.8, 129.8, 129.7, 129.2, 129.0, 128.5, 128.4, 128.4, 128.3 (Ar-C and CH), 91.7 (C-1), 73.0 (C-5), 70.9 (C-3), 69.2 (C-4), 63.2 (C-6), 34.8 (C-2); $^1J_{C1.H1}$= 166.2 Hz; IR (ATR) cm^{-1}: 1723, 1601, 1452, 1314, 1252, 1094, 1068, 706, 685; ESI-HRMS calcd for $C_{34}H_{28}O_9Na$ 603.1631, found *m/z* 603.1633 $[M+Na]^+$.



3,4,6-Tri-*O*-benzoyl-2-deoxy-D-glucopyranosyl chloride (120)[40]

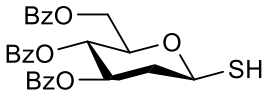
1,3,4,6-Tetra-*O*-benzoyl-2-deoxy-D-glucopyranose (1.0 g, 1.7 mmol) was dissolved in anhydrous CH_2Cl_2 (9 mL) before cooling to 0 °C. Boron trichloride (1.0 M in CH_2Cl_2, 2 mL) was added and the reaction was stirred at 0 °C for 30 mins. The reaction was then diluted with CH_2Cl_2 and rapidly washed with ice-cold satd. $NaHCO_3$, dried over Na_2SO_4 and concentrated under reduced pressure to yield a white powder as the title compound (0.78 g, 92%). R_f 0.5 (cyclohexane-EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 – 8.01 (overlapping signals, 2H, Ar-H), 8.01 – 7.96 (overlapping signals, 2H, Ar-H), 7.96 – 7.89 (overlapping signals, 2H, Ar-H), 7.58 – 7.48 (overlapping signals, 3H, Ar-H), 7.45 – 7.41 (overlapping signals, 2H, Ar-H), 7.41 – 7.33 (overlapping signals, 4H, Ar-H), 6.35 (d, *J* = 3.8 Hz, 1H, H-1), 5.89 (td, *J* = 10.5, 5.0 Hz, 1H, H-3), 5.69 (t, *J* = 9.9 Hz, 1H, H-4), 4.70 – 4.61 (overlapping peaks, 2H, H-5 and H-6a), 4.48 (dd, *J* = 12.3, 4.5 Hz, 1H, H-6b), 2.83 (dd, *J* = 13.5, 5.1 Hz, 1H, H-2a), 2.39 (ddd, *J* = 13.6, 11.2, 3.9 Hz, 1H, H-2b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 165.6, 165.4 (each C=O), 133.5, 133.3, 133.1, 130.2, 129.8, 129.8, 129.7, 129.6, 128.5, 128.5, 128.4, 128.4 (Ar-C and CH), 90.4 (C-1), 71.3 (C-5), 69.1 (2s, C-3 and C-4), 62.4 (C-6), 39.2 (C-2); IR (ATR) cm^{-1}: 1712, 1602, 1451, 1275, 1244, 1097, 1069, 705, 685.



3,4,6-Tri-*O*-benzoyl-2-deoxy-1-*S*-acetyl-1-thio-β-D-arabino-hexopyranose (121)

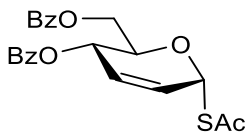
3,4,6-Tri-*O*-benzoyl-2-deoxy-D-glucopyranosyl chloride (0.75 g, 1.52 mmol) and potassium thioacetate (0.52 g, 4.55 mmol) were dried under vacuum for 3 h before dissolving in anhydrous CH_2Cl_2 (8.9 mL). The reaction mixture was then heated to 36 °C and left to stir for 72 h, until TLC indicated consumption of **120**. The reaction was then diluted with $CHCl_3$, washed with brine and satd. $NaHCO_3$, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography (cylcohexane-EtOAc 4:1) and the title compound was isolated as off-white solid (0.238 g, 29%) R_f 0.38 (cyclohexane-EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 – 8.00 (overlapping signals, 2H, Ar-H), 7.96 – 7.90 (overlapping signals, 4H, Ar-H), 7.61 – 7.43 (overlapping signals, 3H, Ar-H), 7.46 – 7.31 (overlapping signals, 6H, Ar-H), 5.60 (t, *J* = 9.7 Hz, 1H, H-4), 5.52 (dd, *J* = 12.3, 2.2 Hz, 1H,

H-1), 5.47 (ddd, *J* = 11.1, 9.4, 5.2 Hz, 1H, H-3), 4.56 (dd, *J* = 12.3, 2.7 Hz, 1H, H-6a), 4.43 (dd, *J* = 12.3, 5.0 Hz, 1H, H-6b), 4.17 (ddd, *J* = 9.9, 5.0, 2.7 Hz, 1H, H-5), 2.66 (ddd, *J* = 12.6, 5.2, 2.2 Hz, 1H, H-2a), 2.38 (s, 3H, S(CO)CH_3), 2.17 (q, *J* = 12.3 Hz, 1H, H-2b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.2 (S(*C*=O)CH_3), 166.2, 165.8, 165.4 (each C=O), 133.4, 133.3, 133.0, 129.8, 129.7, 129.7, 129.2, 129.0, 128.4, 128.3 (each Ar-C and CH), 76.9 (C-1), 76.7 (C-5), 72.6 (C-3), 69.3 (C-4), 63.4 (C-5), 35.9 (C-2), 30.7 S(CO)*C*H_3); IR (ATR) cm^{-1}: 1715, 1602, 1451, 1315, 1255, 1095, 1066, 705, 686; ESI-HRMS calcd for $C_{29}H_{30}O_8SN$ 552.1692, found *m/z* 552.1694 $[M+NH_4]^+$.



3,4,6-Tri-*O*-benzoyl-2-deoxy-1-thio-β-D-arabino-hexopyranose (122)[41]

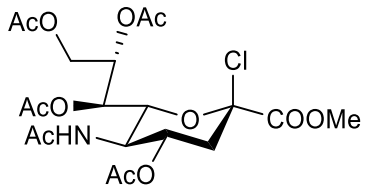
Thioacetate **105** (0.24g, 0.45 mmol) was dried under reduced pressure for 2 h before it was dissolved in a 4:5 MeOH-CH_2Cl_2 solution (9 mL). The reaction mixture was cooled to -40 ºC and freshly prepared sodium methoxide solution (1.0 M, 0.45 mmol) was added to the reaction mixture. The reaction mixture was left to stir for 2 h at - 40 ºC, until T.L.C. indicated consumption of **121**. NH_4Cl (0.02 g) was added to the reaction mixture at -40 ºC and left to stir for 5 mins. The reaction was then warmed to room temperature and, upon dissolution of salts, was concentrated under reduced pressure. The residue was suspended between CH_2Cl_2 and H_2O, separated and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, the solvent removed under reduced pressure and column chromatography (cyclohexane-EtOAc 3:1) gave the title compound (0.139 g, 58%) as a white powder. R_f 0.33 (cyclohexane-EtOAc 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 – 8.00 (overlapping signals, 2H, Ar-H), 7.96 – 7.90 (overlapping signals, 4H, Ar-H), 7.56 – 7.45 (overlapping signals, 3H, Ar-H), 7.44 – 7.30 (overlapping signals, 6H, Ar-H), 5.58 (t, *J* = 9.7 Hz, 1H, H-4), 5.39 (ddd, *J* = 11.2, 9.4, 5.1 Hz, 1H, H-3), 4.94 (ddd, *J* = 10.9, 8.4, 2.0 Hz, 1H, H-1), 4.59 (dd, *J* = 12.2, 2.9 Hz, 1H, H-6a), 4.46 (dd, *J* = 12.2, 5.3 Hz, 1H, H-6b), 4.04 (ddd, *J* = 9.8, 5.3, 2.9 Hz, 1H, H-5), 2.82 (ddd, *J* = 13.0, 5.2, 2.0 Hz, 1H, H-2a), 2.54 (d, *J* = 8.4 Hz, 1H, SH), 2.06 (q, *J* = 11.5 Hz, 1H, H-2b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.2, 165.8, 165.4 (each C=O), 133.4, 133.3, 133.0, 129.8, 129.7, 129.7, 129.7, 129.2, 129.0, 128.4, 128.3 (Ar-C and CH), 76.5 (C-5), 75.0 (C-1), 72.4 (C-3), 69.5 (C-4), 63.6 (C-6), 40.7 (C-2); IR (ATR) cm^{-1}: 1718, 1602, 1451, 1267, 1094, 1067, 706, 686; ESI-HRMS calcd for $C_{27}H_{24}O_7SNa$ 515.1140, found *m/z* 515.1151 $[M+Na]^+$.



1-*S*-acetyl-4,6-di-*O*-benzoyl-2,3-dideoxy-1-thio-α-D-*erytho*-hex-2-enopyranose (123)

1,3,4,6-Tetra-*O*-benzoyl-2-deoxy-α-D-arabino-hexopyranose (0.50 g, 0.86 mmol) was co-evaporated with toluene before drying under vacuum for 12 h prior to reaction. The peracetylated sugar was dissolved in anhydrous CH_2Cl_2 (8.6 mL) before cooling to 0 ^oC. Thioacetic acid (0.18 mL, 2.58 mmol) and TMSOTf (0.16 mL, 0.86 mmol) were added dropwise at 0 ^oC. The reaction was left to stir at 0 ^oC for 3 h before it was poured onto satd. $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, concentrated in vacuo and subjected to column chromatography (cyclohexane-EtOAc 2:1) to isolate the title product as a viscous colourless oil (0.48 g, 57%), as the title compound. R_f 0.39 (cyclohexane-EtOAc 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 – 7.95 (overlapping signals, 4H, Ar-H), 7.61 – 7.49 (overlapping signals, 2H, Ar-H), 7.46 – 7.34 (overlapping signals, 4H, Ar-H), 6.34 (q, *J* = 2.2 Hz, 1H, H-3), 6.03 (d, *J* = 10.1 Hz, 1H, H-1), 5.98 (dt, *J* = 10.1, 2.4 Hz, 1H, H-2), 5.74 (dd, *J* = 9.3, 2.1 Hz, 1H, H-4), 4.58 (dd, *J* = 12.0, 3.1 Hz, 1H, H-6a), 4.45 (dd, *J* = 12.0, 5.9 Hz, 1H, H-6b), 4.26 (ddd, *J* = 9.2, 5.8, 3.1 Hz, 1H, H-5), 2.34 (s, 3H, $S(CO)CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.3 ($S(C{=}O)CH_3$), 166.2, 165.7 (each C=O), 133.5, 133.0, 129.8, 129.7, 128.5, 128.5, 128.3 (Ar-C and CH), 128.2, 128.1 (overlapping peaks, C-1 and C-2), 78.3 (C-3), 70.1 (C-5), 65.8 (C-4), 63.6 (C-6), 30.9 ($S(CO)CH_3$); ESI-HRMS calcd for $C_{22}H_{24}OSN$ 430.1324, found *m/z* 430.1316 $[M+Na]^+$.

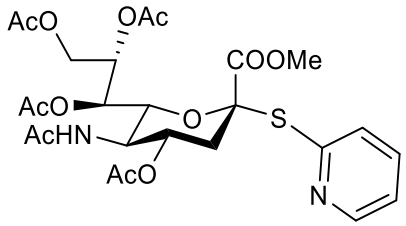
6.5 Chapter 5 Experimental Data



Methyl 5-acetamido-4,7,8,9-tetra-OAc-2-chloro-3,5- dideoxy-β-D-glycero-D-galacto-2-nonulopyranosylonate (133)[42]

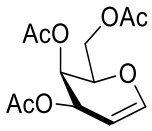
N-Acetylneuraminic acid (1.00 g, 3.24 mmol) and ion exchange resin (Dowex, W50X8, H+, 1.00 g) were dissolved in anhydrous methanol (32 mL) and the mixture was stirred for 24 h at room temperature. When TLC indicated the reaction was complete, the reaction was concentrated under reduced pressure to yield the product (0.92 g, 88%) as a white solid. R_f 0.66 (EtOAc-AcOH-H_2O 4:1:1). The methyl ester was carried on without any further purification.

Neu5NAc methyl ester (0.92 g, 2.84 mmol) was dissolved in acetyl chloride (60 mL) at 0 ºC. The reaction mixture was stirred at room temperature in a closed reaction vessel for 96 h. Removal of the solvents and coevaporation with toluene delivered the product in a quantitative yield (1.45 g, 100%) as a colourless solid. R_f 0.46 (100% EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.67 – 5.59 (m, 1H, NH), 5.48 (dd, *J* = 6.9, 2.4 Hz, 1H, H-7), 5.41 (td, *J* = 10.8, 4.8 Hz, 1H, H-4), 5.18 (td, *J* = 6.4, 2.6 Hz, 1H, H-8), 4.44 (dd, *J* = 12.5, 2.7 Hz, 1H, H-9a), 4.37 (dd, *J* = 10.9, 2.4 Hz, 1H, H-6), 4.22 (q, *J* = 10.4 Hz, 1H, H-5), 4.07 (dd, *J* = 12.6, 5.9 Hz, 1H, H-9b), 3.88 (s, 3H, CO_2CH_3), 2.79 (dd, *J* = 13.8, 4.9 Hz, 1H, H-3a), 2.28 (dd, *J* = 13.9, 11.2 Hz, 1H, H-3b), 2.13 (s, 3H, O(CO)CH_3), 2.09 (s, 3H, O(CO)CH_3), 2.06 (s, 3H, O(CO)CH_3), 2.06 (s, 3H, O(CO)CH_3), 1.91 (s, 3H, NH(CO)CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.0, 170.6, 170.4, 170.0, 169.7, 165.6 (each C=O), 96.6 (C-2), 73.9 (C-6), 69.9 (C-8), 68.7 (C-4), 66.9 (C-7), 62.0 (C-9), 53.8 (CO_2CH_3), 48.7 (C-5), 40.6 (C-3), 23.1 (NH(CO)*C*H_3), 20.9, 20.8, 20.7, 20.7 (each O(CO)*C*H_3).



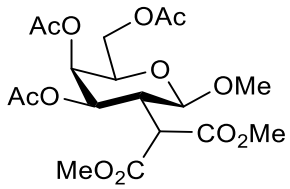
Thiophenyl(methyl-5-acetamido-4,7,8,9-tetra-OAc-3,5-dideoxy-α-D-glycero-D-galacto-2-nonulopyranosylate) (126)[42]

Methyl 5-acetamido-4,7,8,9-tetra-OAc-2-chloro-3,5-dideoxy-β-D-glycero-D-galacto-2-nonulopyranosylonate (1.45 g, 2.84 mmol) and tributylammonium hydrogen sulfate (1.00 g, 2.99 mmol) were dissolved in EtOAc (17.2 mL) and sodium carbonate solution (17.23 mL, 1.0 M) was added to the reaction mixture. Thiopyridine (1.61 g, 14.5 mmol) was then added and the reaction mixture was stirred for 3 h at room temperature. The mixture was diluted with EtOAc and washed with brine, water, dried over Na_2SO_4 and concentrated in vacuo. The crude residue was subjected to column chromatography (diethyl ether). A second column chromatographic separation was performed (cyclohexane-EtOAc 8:1 → EtOAc → EtOAc:MeOH 95:5) and delivered the product (0.877 g, 53%) as a white solid. R_f 0.26 (cyclohexane-EtOAc 8:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, *J* = 4.8 Hz, 1H, Ar-H), 7.68 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.57 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.20 (t, *J* = 6.8, 5.4 Hz, 1H, Ar-H), 5.32 (d, *J* = 8.0 Hz, 1H, H-7), 5.24 (tt, *J* = 6.6, 3.0 Hz, 1H, H-8), 5.18 (d, *J* = 9.9 Hz, 1H, NH), 4.91 (td, *J* = 11.0, 4.5 Hz, 1H, H-4), 4.29 (dd, *J* = 12.6, 2.6 Hz, 1H, H-9a), 4.15 – 4.08 (overlapping signals, 2H, H-6 and H-9b), 4.05 (t, *J* = 10.4 Hz, 1H, H-5), 3.68 (s, 3H, CO_2CH_3), 2.88 (dd, *J* = 12.9, 4.6 Hz, 1H, H-3a), 2.20 (t, *J* = 12.4 Hz, 1H, H-3b), 2.13 (s, 3H, $O(CO)CH_3$), 2.07 (s, 3H, $O(CO)CH_3$), 2.04 (s, 3H, $O(CO)CH_3$), 2.03 (s, 3H, $O(CO)CH_3$), 1.88 (s, 3H, $NH(CO)CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 170.6, 170.1, 170.0, 169.9, 168.2 (each C=O), 153.0 (Ar-C), 149.8, 137.3, 129.2, 122.8 (Ar-CH), 86.2 (C-2), 74.6 (C-6), 69.3 (2s, overlapping signals, C-4 and C-8), 67.4 (C-7), 61.9 (C-9), 53.0 ($CO_2\mathit{C}H_3$), 49.4 (C-5), 38.4 (C-3), 23.2 ($NH(CO)\mathit{C}H_3$), 21.0, 20.8, 20.8, 20.8 (each $O(CO)\mathit{C}H_3$); IR (ATR) cm^{-1}: 3047, 1731, 1654, 1370, 1218, 1036, 774, 732; ES-HRMS calcd for $C_{25}H_{33}O_{12}N_2S$ 585.1754 found *m/z* 585.1755 $[M+H]^+$.



3,4,6-Tri-*O*-acetyl-D-galactal (132)[43]

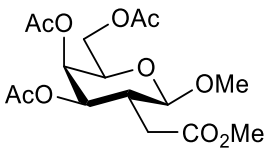
2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (10.42 g, 25.35 mmol) was dried for 3 h under reduced pressure before dissolving in anhydrous acetonitrile (101 mL), under nitrogen. Zinc dust (12.43 g, 190.13 mmol) and NH_4Cl (10.17 g, 190.13 mmol) were added and the reaction was heated to 60ºC, with stirring, for 12 h, until TLC indicated reaction was complete. The reaction mixture was filtered through celite, concentrated and purified through column chromatography (cyclohexane-EtOAc 3:1) to give the title compound as a colourless oil (4.16 g, 60%). R_f 0.45 (cyclohexane-EtOAc 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.47 (dd, *J* = 6.4, 1.7 Hz, 1H, H-1), 5.56 (p, *J* = 2.1 Hz, 1H, H-3), 5.44 (dd, *J* = 4.1, 2.2 Hz, 1H, H-4), 4.77 – 4.70 (m, 1H, H-2), 4.33 (t, *J* = 6.5 Hz, 1H, H-5), 4.28 (dd, *J* = 11.5, 7.3 Hz, 1H, H-6a), 4.22 (dd, *J* = 11.4, 5.2 Hz, 1H, H-6b), 2.13 (s, 3H, $C(O)CH_3$), 2.09 (s, 3H, $C(O)CH_3$), 2.03 (s, 3H, $C(O)CH_3$); ^{13}C NMR (126 MHz, CDCl3) δ 170.5, 170.2, 170.1 (each C=O), 145.4 (C-1), 98.8 (C-2), 72.8 (C-5), 63.9 (C-3), 63.7 (C-4), 61.9 (C-6), 20.8, 20.7, 20.6 (each $C(O)CH_3$); IR (ATR) cm^{-1}: 2964, 1738, 1651, 1370, 1212, 1031; ES-HRMS calcd for $C_{12}H_{16}O_7Na$ 295.0794 found *m/z* 295.0792 $[M+Na]^+$.



Methyl-3,4,6-tri-O-acetyl-2-deoxy-2-C-[(bis(methoxycarbonyl))-methyl]-β-D-galactopyranoside(131)[44]

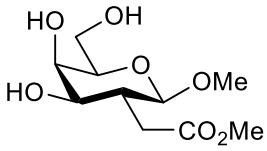
A solution of glycal (6.79 g, 24.94 mmol) and malonate (28.55 mL, 249.4 mmol) in anhydrous MeOH (50 mL) was cooled to 0 ºC under an argon atmosphere. At 0 ºC, a solution of CAN (41.0 g, 74.8 mmol) in MeOH (50 mL) was added dropwise, over a period of 8 h until TLC showed consumption of **132**. After stirring for an additional 30 mins at 0 ºC, ice-cold sodium thiosulfate was added and the mixture extracted with CH_2Cl_2 (x4), dried over Na_2SO_4, concentrated under reduced pressure and purified through column chromatography (cyclohexane-EtOAc 3:2) to yield the title compound as a viscous colourless oil (8.2 g, 76%). R_f 0.32 (cyclohexane-EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.31 (d, *J* = 3.2 Hz, 1H, H-

4), 5.15 (dd, *J* = 12.1, 3.2 Hz, 1H, H-3), 4.88 (d, *J* = 8.8 Hz, 1H, H-1), 4.19 (dd, *J* = 11.2, 6.6 Hz, 1H, H-6a), 4.13 (dd, *J* = 11.1, 7.0 Hz, 1H, H-6b), 3.89 (t, *J* = 6.8 Hz, 1H, H-5), 3.74 (s, 3H, CO_2CH_3), 3.73 (s, 3H, CO_2CH_3), 3.68 (d, *J* = 3.6 Hz, 1H, C*H*$(CO_2CH_3)_2$), 3.49 (s, 3H, OCH_3), 2.82 (ddd, *J* = 12.3, 8.7, 3.7 Hz, 1H, H-2), 2.14 (s, 3H, $C(O)CH_3$), 2.04 (s, 3H, $C(O)CH_3$), 1.98 (s, 3H, $C(O)CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 170.3, 169.7, 168.7, 168.4 (each C=O), 101.9 (C-1), 70.5 (C-5), 69.6 (C-3), 66.0 (C-4), 61.5 (C-6), 57.5 (OCH_3), 52.5, 52.4 (each CO_2*C*H_3), 47.6 (*C*H$(CO_2CH_3)_2$), 41.9 (C-2), 20.7, 20.7, 20.5 (each C(O)*C*H_3); IR (ATR) cm^{-1}: 2957, 1736, 1370, 1217, 1035; ES-HRMS calcd for $C_{18}H_{25}O_{12}$ 433.1346 found *m/z* 433.1342 $[M-H]^-$.



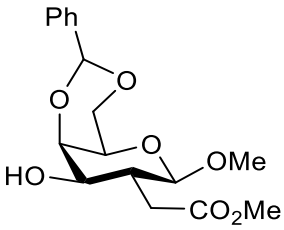
Methyl-3,4,6-tri-O-acetyl-2-deoxy-2-(2-methoxyl-2-oxoxethyl)-β-D-galactopyranoside (134)[45]

A solution of methyl-3,4,6-tri-O-acetyl-2-deoxy-2-C-[(bis(methoxycarbonyl))-methyl]-β-D-galactopyranoside (1.29 g, 2.97 mmol) and lithium iodide (0.6 g, 4.45 mmol) was dissolved in DMSO (35 mL) and placed on the kugelrohr for 4 h at 160 °C. The reaction was then allowed to cool before the kugelrohr was placed under vacuum and heated to 110 °C to remove DMSO. The product was adsorbed onto silica gel and subjected to flash chromatography (cyclohexane-EtOAc 1:1) to yield the title compound as a pale yellow oil (0.762 g, 68%). R_f 0.44 (cyclohexane-EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.29 (d, J = 3.4 Hz, 1H, H-4), 4.92 (dd, J = 11.6, 3.1 Hz, 1H, H-3), 4.40 (d, J = 8.3 Hz, 1H, H-1), 4.19 (dd, J = 11.2, 6.5 Hz, 1H, H-6a), 4.13 (dd, J = 11.6, 6.9 Hz, 1H, H-6b), 3.87 (t, J = 6.6 Hz, 1H, H-5), 3.67 (s, 3H, CO_2CH_3), 3.52 (s, 3H, OCH_3), 2.52 – 2.43 (overlapping signals, 2H, H-2 and C*H*HCO_2CH_3), 2.42 – 2.34 (m, 1H, CH*H*CO_2CH_3), 2.13 (s, 3H, $C(O)CH_3$), 2.05 (s, 3H, $C(O)CH_3$), 1.99 (s, 3H, $C(O)CH_3$); ^{13}C NMR (126 MHz, CDCl3) δ 171.9, 170.4, 170.3, 170.1 (each C=O), 103.6 (C-1), 71.3 (C-3), 70.6 (C-5), 65.8 (C-4), 61.6 (C-6), 57.2 (OCH_3), 51.6 (CO_2*C*H_3), 38.6 (C-2), 31.4 (*C*$H_2CO_2CH_3$), 20.7, 20.7, 20.5 (each C(O)*C*H_3); ES-HRMS calcd for $C_{16}H_{24}O_{10}Na$ 399.1267 found *m/z* 399.1264 $[M+Na]^+$.



Methyl 2-deoxy-2-(2-methoxy-2-oxoethyl)-β-D-galactopyranoside (138)

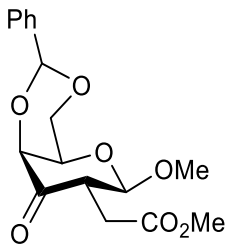
A freshly prepared solution of sodium methoxide (1.0 M, 10.36 mmol) was added to a solution of **134** (0.76 g, 2.01 mmol) in MeOH (8.6 mL). The reaction was stirred at room temperature until TLC indicated the reaction was complete after 3 h. Dowex H^+ resin was added to the reaction mixture and stirred for 15 mins. The reaction mixture was filtered, concentrated under vacou to yield the title compound as a white crystalline solid (0.416 g, 80%). R_f 0.17 (dichloromethane-MeOH 8:1); ^{1}H NMR (500 MHz, CD_3OD) δ 4.19 (d, *J* = 8.6 Hz, 1H, H-1), 3.79 – 3.70 (overlapping peaks, 3H, H-4, H-6a and H-6b), 3.64 (s, 3H, CO_2CH_3), 3.48 – 3.40 (overlapping peaks, 5H, H-3, H-5 and OCH_3), 2.60 (dd, *J* = 15.1, 4.7 Hz, 1H, C*H*HCO_2CH_3), 2.34 (dd, *J* = 15.1, 7.4 Hz, 1H, CH*H*CO_2CH_3), 2.27 – 2.16 (m, 1H, H-2); ^{13}C NMR (126 MHz, CD_3OD) δ 174.0 (C=O), 104.5 (C-1), 75.3 (C-5), 71.8 (C-3), 67.8 (C-4), 61.3 (C-6), 55.8 (OCH_3), 50.6 (CO_2CH_3), 40.9 (C-2), 31.9 (*C*$H_2CO_2CH_3$); IR (ATR) cm^{-1}: 3466, 2958, 1717, 1375, 1239, 1041, 1014; ES-HRMS calcd for $C_{10}H_{18}O_7Na$ 273.0950 found *m/z* 273.0950 $[M+Na]^+$.



Methyl 4,6-O-benzylidene-2-deoxy-(2-methoxy-2-oxoethyl)-β-D-galactopyranoside (130)

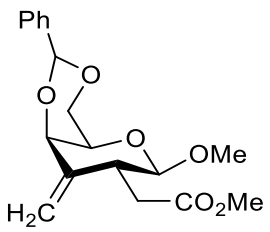
Glycoside **138** (0.322 g, 1.29 mmol) and camphor sulfonic acid (0.005 g, 0.006 mmol) were dissolved in anhydrous acetonitrile (9.2 mL) and to this, benzaldehyde dimethyl acetal (0.4 mL, 2.58 mmol) was added. The reaction mixture was left to stir for 16 h at room temperature, before DIPEA (0.5 mL) was added and left to stir for a further hour. The solvent was removed under reduced pressure and flash chromatography (cylcohexane-EtOAc 1:1) gave the title compound as a white solid (0.228 g, 52%). R_f 0.19 (cylcohexane-EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.50 (overlapping signals, 2H, Ar-H), 7.40 – 7.34 (overlapping signals, 3H, Ar-H), 5.58 (s, 1H, C*H*Ph), 4.35 (d, *J* = 12.8 Hz, 1H, H-6a), 4.29 (d, *J* = 8.7 Hz, 1H, H-1), 4.13 – 4.05 (overlapping signals, 2H, H-4 and H-6b), 3.72 – 3.64 (overlapping signals, 4H, H-

3 and CO_2CH_3), 3.50 (s, 3H, OCH_3), 3.44 (s, 1H, H-5), 2.62 (dd, *J* = 15.8, 5.6 Hz, 1H, C*H*HCO_2CH_3), 2.54 (dd, *J* = 15.9, 5.8 Hz, 1H, CH*H*CO_2CH_3), 2.41 – 2.32 (m, 1H, H-2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3 (C=O), 137.6, 129.2, 128.2, 126.5 (Ar-C and CH), 103.6 (C-1), 101.3 (*C*HPh), 74.3 (C-4), 71.4 (C-3), 69.5 (C-6), 66.6 (C-5), 56.9 (OCH_3), 51.6 (CO_2*C*H_3), 41.5 (C-2), 31.6 (*C*$H_2CO_2CH_3$); IR (ATR) cm^{-1}: 3403, 2873, 1737, 1375, 1239, 1047, 1014, 732, 695; ES-HRMS calcd for $C_{17}H_{22}O_7Na$ 361.1263 found *m/z* 361.1261 [M+Na]$^+$.



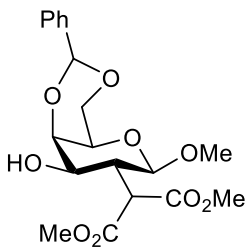
Methyl 4,6-O-benzylidene-2-deoxy-2-(2-methoxy-2-oxoethyl)-β-D-xylo-hexopyranosid-3-ulose (129)

To a solution of Dess-Martin Periodinae (0.81 g, 1.9 mmol) in CH_2Cl_2 (9.5 mL), was added sugar (0.215 g, 0.634 mmol) in CH_2Cl_2 (5.3 mL). Reaction mixture was stirred at room temperature for 16 h before pouring into beaker containing satd. $NaHCO_3$ and $Na_2S_2O_3$ satd (1:1, 12 mL). After 30 mins of stirring, the layers were separated and the aq. layer was extracted with CH_2Cl_2. The organic layers, were combined, concentrated in vacuo and subjected to column chromatography (cyclohexane-EtOAc 3:2) to give the title compound (0.157 g, 74 %) as a white powder. R_f 0.27 (cylcohexane-EtOAc 3:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.49 (overlapping signals, 2H, Ar-H), 7.39 – 7.33 (overlapping signals, 3H, Ar-H), 5.62 (s, 1H, C*H*Ph), 4.60 (d, *J* = 8.8 Hz, 1H, H-1), 4.48 (dd, *J* = 12.7, 1.5 Hz, 1H, H-6a), 4.30 (d, *J* = 1.4 Hz, 1H, H-4), 4.19 (dd, *J* = 12.7, 1.9 Hz, 1H, H-6b), 3.68 (s, 3H, CO_2CH_3), 3.61 – 3.51 (m, 4H, overlapping peaks, OCH_3 and H-5), 3.41 (dt, *J* = 8.8, 5.4 Hz, 1H, H-2), 2.71 (dd, *J* = 17.1, 5.8 Hz, 1H, C*H*HCO_2CH_3), 2.65 (dd, *J* = 17.1, 4.9 Hz, 1H, CH*H*CO_2CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.8 (C-3: C=O), 172.1 (C=O), 137.1, 129.2, 128.2, 126.3 (each Ar-C and CH), 103.9 (C-1), 100.9 (*C*HPh), 78.9 (C-4), 68.8 (C-6), 66.1 (C-5), 57.1 (OCH_3), 51.8 (CO_2*C*H_3), 50.5 (C-2), 28.4 (*C*$H_2CO_2CH_3$); IR (ATR) cm^{-1}: 2945, 1745, 1732, 1227, 1069, 982, 772, 702; ES-HRMS calcd for $C_{17}H_{20}O_7Na$ 359.1107 found *m/z* 359.1110 [M+Na]$^+$.



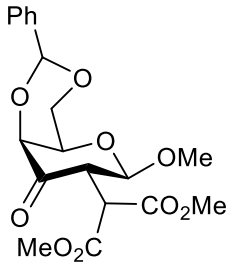
Methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-(2-methoxy-2-oxoethyl)-3-methylidene-β-D-xylo-hexopyranose (128)

Methyl triphenylphosphonium bromide (0.25 g, 0.699 mmol) was dried under vacuum prior to dissolving in anhydrous THF (1.7 mL) and cooling to 0 ºC. Potassium *tert*-butoxide (0.65 mL, 1.0 M in THF) was added to the reaction mixture and stirred for 15 mins at 0 ºC. Glycoside **X** (0.157 g, 0.466 mmol) in anhydrous THF (1.7 mL) was added to the reaction mixture at 0 ºC and the mixture was allowed to warm to room temperature, stirring for 2 hours. Acetone (4 mL) was added to quench the reaction, when TLC indicated the reaction was complete, and the reaction mixture was filtered through a celite bed. The mixture was concentrated in vacuo and subjected to column chromatography (cyclohexane-EtOAc 2:1) to isolated the title compound as a white solid (0.1045 g, 67%). R_f 0.33 (cyclohexane-EtOAc 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.48 (overlapping signals, 2H, Ar-H), 7.38 – 7.30 (overlapping signals, 3H, Ar-H), 5.60 (s, 1H, C*H*Ph), 5.26 (d, *J* = 1.9 Hz, 1H, C=C*H*H), 4.97 (d, *J* = 2.0 Hz, 1H, C=CH*H*), 4.35 (dd, *J* = 12.7, 1.5 Hz, 1H, H-6a), 4.31 (d, *J* = 1.4 Hz, 1H, H-4), 4.22 (d, *J* = 8.8 Hz, 1H, H-1), 4.13 (dd, *J* = 12.2, 1.9 Hz, 1H, H-6b), 3.67 (s, 3H, CO_2CH_3), 3.51 (s, 3H, OCH_3), 3.42 (d, *J* = 1.7 Hz, 1H, H-5), 3.18 (dtt, *J* = 8.6, 6.4, 2.0 Hz, 1H, H-2), 2.59 (d, *J* = 1.8 Hz, 1H, C*H*HCO_2CH_3), 2.58 (d, *J* = 1.8 Hz, 1H, CH*H*CO_2CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6 (C=O), 143.8 (*C*=CH_2), 137.9, 129.0, 128.1, 126.5 (Ar-C and CH), 113.9 (C=*C*H_2), 105.4 (C-1), 101.1 (*C*HPh), 78.4 (C-4), 69.5 (C-6), 69.0 (C-5), 56.7 (OCH_3), 51.6 (CO_2*C*H_3), 40.6 (C-2), 32.0 (*C*$H_2CO_2CH_3$); ES-HRMS calcd for $C_{18}H_{22}O_6Na$ 357.1314 found *m/z* 357.1314 $[M+Na]^+$.



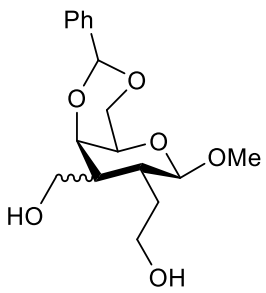
Methyl 4,6-O-benzylidene-2-deoxy-2-(1,3-dimethoxy-1,3-dioxopropan-2-yl)-β-D-galactopyranoside (135)

A freshly prepared solution of sodium methoxide (1.0 M, 10.36 mmol) was added to a solution of **131** (0.5 g, 1.15 mmol) in MeOH (5 mL). The reaction was stirred at room temperature until TLC indicated the reaction was complete after 12 h. Dowex H^+ resin was added to the reaction mixture and stirred for 15 mins. The reaction mixture was filtered, concentrated under vacou to yield the title compound as a white crystalline solid (0.322 g, 90%). R_f 0.18 (100% EtOAc). The glycoside was used without any further purification. The deprotected glycoside (0.322 g, 1.04 mmol) and camphor sulfonic acid (~0.001 g, 0.005 mmol) were dissolved in anhydrous acetonitrile (7.7 mL) and to this, benzaldehyde dimethyl acetal (0.31 mL, 2.09 mmol) was added. The reaction mixture was left to stir for 16 h at room temperature, before DIPEA (0.12 mL) was added and left to stir for a further hour. The reaction mixture was concentrated under reduced pressure and flash chromatography (cylcohexane-EtOAc 3:2 → 1:1) gave the title compound as a white solid (0.124 g, 30%). R_f 0.10 (cyclohexane-EtOAc 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.49 (overlapping signals, 2H, Ar-H), 7.41 – 7.34 (overlapping signals, 3H, Ar-H), 5.59 (s, 1H, C*H*Ph), 4.73 (d, *J* = 8.8 Hz, 1H, H-1), 4.35 (dd, *J* = 12.4, 1.5 Hz, 1H, H-6a), 4.13 – 4.06 (overlapping signals, 2H, H-4 and H-6b), 3.95 – 3.91 (overlapping signals, 2H, H-3 and C*H*$(CO_2CH_3)_2$), 3.75 (s, 3H, CO_2CH_3), 3.73 (s, 3H, CO_2CH_3), 3.47 (overlapping signals, 4H, H-5 and OCH_3), 2.70 (ddd, *J* = 12.4, 8.9, 4.0 Hz, 1H, H-2), 2.47 (d, *J* = 11.3 Hz, 1H, OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7, 169.5 (each C=O), 129.2, 128.2, 126.5 (Ar-C and CH), 102.1 (C-1), 101.4 (*C*H$(CO_2CH_3)_2$), 74.4 (C-4), 69.4, 69.4 (overlapping peaks, C-3 and C-6), 66.6 (C-5), 57.3 (OCH_3), 52.4 (2s, each CO_2*C*H_3), 48.3 (*C*H$(CO_2CH_3)_2$), 45.1 (C-2); ES-HRMS calcd for $C_{19}H_{24}O_9Na$ 419.1318 found *m/z* 419.1314 $[M+Na]^+$.



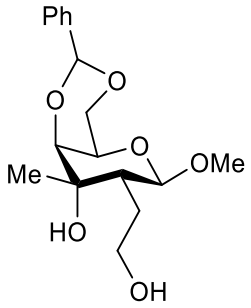
Methyl 2-deoxy-2-(1,3-dimethoxy-1,3-dioxopropan-2-yl)-4-6-*O*-ethylidene-β-D-xylo-hexopyranosid-3-ulose (136)

To a solution of Dess-Martin Periodinae (0.37 g, 0.87 mmol) in CH_2Cl_2 (4 mL), was added **135** (0.115 g, 0.29 mmol) in CH_2Cl_2 (2.4 mL). Reaction mixture was stirred at room temperature for 16 h before pouring into beaker containing satd. $NaHCO_3$ and $Na_2S_2O_3$ satd (1:1 solution, 10 mL). After 30 mins of stirring, the layers were separated and the aq. layer was extracted with CH_2Cl_2. The organic layers, were combined, concentrated in vacuo and purified through flash chromatography (cyclohexane-EtOAc 2:1) to give the title compound as a white powder (0.054 g, 48 %). R_f 0.14 (cyclohexane-EtOAc 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.48 (overlapping signals, 2H, Ar-H), 7.41 – 7.31 (overlapping signals, 3H, Ar-H), 5.62 (s, 1H, C*H*Ph), 5.00 (d, *J* = 8.4 Hz, 1H, H-1), 4.48 (d, *J* = 12.4 Hz, 1H, H-6a), 4.30 (s, 1H, H-4), 4.18 (dd, *J* = 12.5, 1.9 Hz, 1H, H-6b), 3.92 (d, *J* = 5.0 Hz, 1H, C*H*(CO_2CH_3)$_2$), 3.76 (s, 3H, CO_2CH_3), 3.73 (s, 3H, CO_2CH_3), 3.68 (dd, *J* = 8.5, 5.0 Hz, 1H, H-2), 3.62 (s, 1H, H-5), 3.51 (s, 3H, OCH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.5 (C-3 C=O), 168.7 (2s, each C=O), 137.0, 129.3, 128.2, 126.3 (Ar-C and CH), 102.9 (C-1), 100.9 (*C*HPh), 78.6 (C-4), 68.7 (C-6), 65.8 (C-5), 57.5 (OCH_3), 53.9 (C-2), 52.6 (2s, each CO_2CH_3), 47.6 (*C*H(CO_2CH_3)$_2$); ES-HRMS calcd for $C_{19}H_{22}O_9Na$ 417.1162 found *m/z* 417.1162 $[M+Na]^+$.



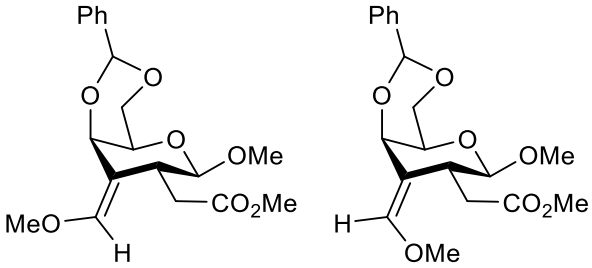
Methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-(2-hydroxyethyl)-3-(hydroxymethyl)-β-D-galactopyranoside (140) & methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-(2-hydroxyethyl)-3-(hydroxymethyl)-β-D-gulopyranoside (141)

Alkene **128** (0.05 g, 0.15 mmol) was dissolved in anhydrous THF (1.3 mL) and to this was added, BH_3-SMe_2 (2.0 M in THF, 0.1 mL). The reaction mixture was left to stir overnight before cooling to 0 ^oC. NaOH (3.0 M, 0.1 mL) and H_2O_2 (30%, 0.1 mL) was added at 0 ^oC and left to stir for 1 h. Diethyl ether was added, the layers separated and the aqueous layer was extracted 3 times with diethyl ether. The combined layers were dried over Na_2SO_4, filtered, dried in vacuo and the resulting residue was subjected to column chromatography (cyclohexane-EtOAc 3:2 → EtOAc → EtOAc-MeOH 9:1) to yield a mixture of the primary alcohols (4 mg, 9%). R_f 0.10 (cyclohexane-EtOAc 3:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.51 (overlapping signals, 2H, Ar-H), 7.51 – 7.45 (overlapping signals, 2H, Ar-H), 7.39 – 7.31 (overlapping signals, 6H, Ar-H), 5.59 (overlapping signals, 2H, 140-C*H*Ph and 141-C*H*Ph), 4.42 (d, *J* = 9.1 Hz, 1H, H-1), 4.35 – 4.30 (overlapping signals, 2H, 140-H-6a and 141-H-6a), 4.25 (d, *J* = 8.6 Hz, 1H, H-1), 4.14 – 4.06 (overlapping signals, 4H, 140-H-5, 141-H5, 140-H-6a and 141-H-6b), 3.94 – 3.88 (overlapping signals, 4H, 2 x C*H*H, 2 x CH_2CH*H*), 3.79 – 3.69 (overlapping signals, 5H, 2 x CH*H*, 2 x CH_2CH*H* and H-4), 3.56 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 3.44 (s, 1H, H-4), 2.74 (s, 1H, OH), 2.57 (s, 1H. OH), 2.44 (s, 1H, OH), 2.32 – 2.19 (signals, 2H, H-2 and H-3), 2.18 – 2.08 (m, 1H, H-2), 1.81 – 1.67 (m, 3H), 1.66 – 1.60 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.1, 137.6 (Ar-C), 129.2, 129.0, 128.3, 128.2, 126.4, 126.2 (Ar-CH), 106.5 (C-1), 103.1 (C-1), 101.4 (*C*HPh), 101.2 (*C*HPh), 75.9 (C-5), 73.8 (C-5), 69.9 (C-6), 69.8 (C-6), 68.7 (C-4), 66.7 (C-4), 62.2, 62.2, 62.1, 59.5 (each *C*H_2OH), 56.6 (OCH_3), 56.3 (OCH_3), 45.3 (C-3), 44.5 (C-3), 36.7 (C-2), 34.5 (C-2), 31.1 (*C*$H_2$$CH_2$OH), 30.9 (*C*$H_2$$CH_2$OH); ES-HRMS calcd for $C_{17}H_{28}O_6N$ 342.1917 found *m/z* 342.1911 $[M+NH_4]^+$.



Methyl 4,6-*O*-benzylidene-2-deoxy-2-(2-hydroxyethyl)-3-*C*-methyl-β-D-gulopyranoside (142)

Alkene **128** (0.05 g, 0.15 mmol) was dissolved in anhydrous THF (1.3 mL) and to this was added, BH_3-SMe_2 (2.0 M in THF, 0.1 mL). The reaction mixture was left to stir overnight before cooling to 0 ^oC. NaOH (3.0 M, 0.1 mL) and H_2O_2 (30%, 0.1 mL) was added at 0 ^oC and left to stir for 1 h. Diethyl ether was added, the layers separated and the aqueous layer was extracted 3 times with diethyl ether. The combined layers were dried over Na_2SO_4, filtered, dried in vacuo and the resulting residue was subjected to column chromatography (cyclohexane-EtOAc 3:2 → EtOAc → EtOAc-MeOH 9:1) to yield the title compound (4 mg, 8%). R_f 0.15 (cyclohexane-EtOAc 3:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.45 (overlapping signals, 2H, Ar-H), 7.38 – 7.30 (overlapping signals, 3H, Ar-H), 5.56 (s, 1H, C*H*Ph), 4.65 (d, *J* = 8.9 Hz, 1H, H-1), 4.35 (d, *J* = 12.4 Hz, 1H, H-6a), 4.07 (dd, *J* = 12.5, 1.8 Hz, 1H, H-6b), 3.87 (s, 1H, H-4), 3.79 (dt, *J* = 9.6, 4.5 Hz, 1H, CH_2C*H*HOH), 3.68 (td, *J* = 10.5, 3.3 Hz, 1H, CH_2CH*H*OH), 3.56 – 3.47 (overlapping signals, 4H, H-5 and OCH_3), 2.06 – 1.89 (overlappings signals, 2H, H-2 and C*H*HCH_2OH), 1.80 – 1.68 (m, 1H, CH*H*CH_2OH), 1.59 (s, 1H, OH), 1.35 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2 (Ar-C), 128.7, 128.0, 126.2 (Ar-CH), 102.1 (C-1), 100.8 (*C*HPh), 79.2 (C-5), 72.6 (C-3), 70.0 (C-6), 65.4 (C-4), 60.7 (CH_2*C*H_2OH), 56.6 (OCH_3), 43.0 (C-2), 26.8 (*C*$H_2$$CH_2$OH), 24.8 ($CH_3$); ES-HRMS calcd for $C_{17}H_{23}O_6$ 323.1495 found *m/z* 323.1497 $[M-H]^-$.



Methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-(methoxymethylidene)-2-(2-methoxy-2-oxoethyl)-β-D-xylo-hexopyranoside (143 and 144)

(Methoxymethyl)triphenylphosphonium chloride (0.076 g, 0.22 mmol) was dried for 1 h prior to dissolving in anhydrous THF (0.35 mL). Potassium *tert*-butoxide was added to the solution at 0 ^{o}C and stirred for 15 mins at 0 ^{o}C. Methyl 4,6-O-benzylidene-2-deoxy-2-(2-methoxy-2-oxoethyl)-β-D-xylo-hexopyranosid-3-ulose (0.05g, 0.15 mmol) was dissolved in THF (0.55 mL) and added to the reaction mixture at 0 ^{o}C, before stirring for 2 h allowing the reaction mixture to warm to room temperature.The reaction was then quenched with acetone (2 mL), filtered through a celite bed and concentrated under reduced pressure. The resulting residue was subjected to column chromatography (cyclohexane-EtOAc 2:1) to yield the resulting isomers as a white powder (6 mg, 11%). R_f 0.32 (cyclohexane-EtOAc 2:1); NMR data for major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.49 (overlapping signals, 2H, Ar-H), 7.40 – 7.29 (overlapping signals, 3H, Ar-H), 6.21 (d, J = 1.9 Hz, 1H, C=C*H*(OCH_3)), 5.55 (s, 1H, C*H*Ph), 4.54 (d, J = 8.4 Hz, 1H, H-1), 4.33 (d, J = 12.4 Hz, 1H, H-6a), 4.09 (dd, J = 12.4, 2.0 Hz, 1H, H-6b), 4.01 (s, 1H, H-4), 3.65 (s, 3H, CO_2CH_3), 3.57 – 3.45 (overlapping signals, 6H, C=CH(OC*H*$_3$) and OCH_3), 3.47 (s, 1H, H-5), 3.03 – 2.96 (m, 1H, H-2), 2.89 – 2.77 (overlapping signals, 2H, C*H*$_2$$CO_2CH_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2 (C=O), 148.2 (C=*C*H(OCH_3)), 138.1 (Ar-C), 128.9, 128.1, 126.5 (Ar-CH), 111.2 (C-3), 104.2 (C-1), 101.1 (CHPh), 76.0 (C-4), 69.8 (C-6), 69.6 (C-5), 60.0 (C=CH(O*C*H_3)), 56.5 (O*C*H_3), 51.2 (CO_2*C*H_3), 37.8 (C-2), 32.3 (*C*$H_2$$CO_2CH_3$); ES-HRMS calcd for $C_{19}H_{24}O_7Na$ 387.1420 found *m/z* 387.1436 $[M+Na]^+$.

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