LEABHARLANN CHOLÁISTE NA TRÍONÓIDE, BAILE ÁTHA CLIATH | TRINITY COLLEGE LIBRARY DUBLIN
Ollscoil Átha Cliath | The University of Dublin

Terms and Conditions of Use of Digitised Theses from Trinity College Library Dublin

Copyright statement

All material supplied by Trinity College Library is protected by copyright (under the Copyright and Related Rights Act, 2000 as amended) and other relevant Intellectual Property Rights. By accessing and using a Digitised Thesis from Trinity College Library you acknowledge that all Intellectual Property Rights in any Works supplied are the sole and exclusive property of the copyright and/or other IPR holder. Specific copyright holders may not be explicitly identified. Use of materials from other sources within a thesis should not be construed as a claim over them.

A non-exclusive, non-transferable licence is hereby granted to those using or reproducing, in whole or in part, the material for valid purposes, providing the copyright owners are acknowledged using the normal conventions. Where specific permission to use material is required, this is identified and such permission must be sought from the copyright holder or agency cited.

Liability statement

By using a Digitised Thesis, I accept that Trinity College Dublin bears no legal responsibility for the accuracy, legality or comprehensiveness of materials contained within the thesis, and that Trinity College Dublin accepts no liability for indirect, consequential, or incidental, damages or losses arising from use of the thesis for whatever reason. Information located in a thesis may be subject to specific use constraints, details of which may not be explicitly described. It is the responsibility of potential and actual users to be aware of such constraints and to abide by them. By making use of material from a digitised thesis, you accept these copyright and disclaimer provisions. Where it is brought to the attention of Trinity College Library that there may be a breach of copyright or other restraint, it is the policy to withdraw or take down access to a thesis while the issue is being resolved.

Access Agreement

By using a Digitised Thesis from Trinity College Library you are bound by the following Terms & Conditions. Please read them carefully.

I have read and I understand the following statement: All material supplied via a Digitised Thesis from Trinity College Library is protected by copyright and other intellectual property rights, and duplication or sale of all or part of any of a thesis is not permitted, except that material may be duplicated by you for your research use or for educational purposes in electronic or print form providing the copyright owners are acknowledged using the normal conventions. You must obtain permission for any other use. Electronic or print copies may not be offered, whether for sale or otherwise to anyone. This copy has been supplied on the understanding that it is copyright material and that no quotation from the thesis may be published without proper acknowledgement.

The Development of Novel Synthetic Methodologies for the Preparation of Glycosidase Inhibitors

16 SEP 2014
ACADEMIC REGISTRY

Declaration

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work. Due acknowledgements and references are given to the work of others. I give permission to the Trinity College Library to lend or copy this thesis upon request.

Aoife Malone

Malone, A.; Scanlan, E. M. *Org. Lett.*, **2013**, *15*, 504.

Malone, A.; Scanlan, E. M. *J. Org. Chem.* **2013**, *78*, 10917.

Declaration

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work. Due acknowledgements and references are given to the work of others.



Aoife Malone

Malone, A.; Scanlan, E. M. *Org. Lett.*, **2013**, *15*, 504.

Malone, A.; Scanlan, E. M. *J. Org. Chem.* **2013**, *78*, 10917.

Table of Contents

TRINITY COLLEGE
5 JAN 2015
LIBRARY DUBLIN

Thesis 10477

Table of Contents		**ii**
Acknowledgements		**vi**
Abstract		**vii**
Abbreviations		**ix**
1.0	**General Introduction**	**1**
1.1	Biological significance of carbohydrates	1
1.1.1	Carbohydrates to glycomimetic drugs	1
1.2	A brief overview	3
1.2.1	Sugars with ring heteroatoms other than oxygen	3
1.2.1.1	Naturally occuring thiosugars	4
1.2.1.2	Naturally occuring azasugars	5
1.2.1.3	Naturally occung glycosylamines and pseudosugars	8
1.3	Therapeutic potential of glycosidase inhibitors	10
1.3.1	Glycosidase inhibitors as anti-diabetic agents	10
1.3.1.1	Digestive glucosidase inhibitors	11
1.3.1.2	Glycogen phosphorylase inhibitors as anti-diabetic agents	13
1.3.2	Glycosidase inhibitors as anti-viral agents	15
1.3.2.1	Glycosidase inhibitors as anti-HIV agents	17
1.3.3	Glycosidase inhibitors as anti-cancer agents	19
1.4	Glycosidase inhibition	20
1.4.1	Mechanism of glycosidase inhibition	20
1.4.1.1	The transition state of glycosidase enzymes	22
1.4.2	What makes a good glycosidase inhibitor?	24
1.4.2.1	Structure function characteristics of glycosidase inhibitors	25
1.4.2.1.1	Sulfur analogs	25
1.4.2.1.2	Nitrogen analogs	26
1.5	Synthetic routes to glycosidase inhibitors	28
1.5.1	Synthetic routes to thiosugar synthesis	28
1.5.2	Synthetic routes to azasugar synthesis	31
1.5.3	Remarks on developed routes to thiosugars and iminosugars	35
1.6	Radicals in synthesis	35
1.6.1	Radical chemistry applied to natural product chemistry	36
1.6.2	Applications of free radicals in carbohydrate chemistry	38
1.6.2.1	Radical chemistry applied to the synthesis of glycosidase inhibitors	41
1.6.3	Thiol-ene click chemistry	43
1.6.3.1	Inter-molecular TEC reactions	44
1.6.3.2	Intra-molecular Thiol-ene click	48
1.6.4	Chemistry of iminyl radicals	50
1.6.4.1	Iminyl radicals in *N*-heterocycle synthesis	51
1.7	Thesis overview	56

20	**Results and discussion**	**58**
21	Intra-molecular thiyl radical cyclisation's for the synthesis of thiosugars	58
22	Proposed catalyst synthesis: Retrosynthetic analysis	59
22.1	Retrosynthetic route B: retention of configuration	61
23	Choice of model system	62
24	Synthesis of singly inverted thiopyranose	62
24.1	Synthesis of a thiol radical precursor	62
24.2	Optimisation of radical thiol-ene cyclisation	65
25	Synthesis of double inverted thiopyranose	68
26	Deprotection of thiosugars 177 and 178	70
27	Application of methodology to a pyranose system	71
27.1	Towards the synthesis of thioseptanoses	71
27.2	Attempt at thioacetate incorporation	74
28	Investigation of 5-exo ring closure reaction	76
28.1	Synthesis of an isopropyl analog	77
28.1.1	Rationalisation of the product distribution and diastereomeric ratio	79
28.2	Synthesis of a phenyl analog	81
28.2.1	Synthesis of phenyl substituted glycosyl alkene	81
28.2.2	Synthesis of thiofuranose derivative from phenyl glycosyl alkene 195	83
28.2.3	Synthesis of a thiofuranose derivative with retained stereochemistry	85
28.3	Extension of substrate scope	87
28.4	Synthesis of a PEGylated fluorophore	91
28.4.1	Rationale for choice of linker and fluorophore	91
28.4.2	Synthesis of Dansyl functionalised thiosugar	92
28.5	Conclusions on 5-exo ring closure	94
29	Thiyl radical cyclisation with in-situ TEMPO trapping	94
29.1	Attempts at TEMPO trapping from radical precursor 197	95
29.2	Future Work	99
31	**Intramolecular iminyl radical cyclisations for the synthesis of iminosugars**	**102**
31.1	Proposed synthetic route	102
32	Photochemical route to iminosugar synthesis	105
32.1	Synthesis of oxime esters as iminyl radical precursors	105
32.2	ESR Spectroscopy of glycosyl oxime esters	109
32.2.1	Photolysis O-Acyl oxime ester 230	110
32.2.2	Photolysis O-Acyl oxime ester 240	111
32.2.3	Photolysis O-Benzoyl oxime ester 242	112
32.3	Initial reactions of oxime esters under photolytic and thermolytic conditions	114

3.3	Thermal route to iminosugar synthesis	116
3.3.1	Synthesis of glycosyl oxime ethers	116
3.3.1.1	Further methods for iminyl radical formation	119
3.3.2	Conclusions on thermolytic cleavage of 248	120
3.4	Synthesis of pyrrolidine oxime ethers	121
3.4.1	Concluding remarks on the attempted synthesis of aldoxime ethers	123
3.5	Synthesis of pyranose and furanose ketoxime ethers and esters for iminyl radical development	124
3.5.1	Synthesis of furanose C-5 oxime esters for ESR evaluation	124
3.5.1.1	EPR data from photolysis of 264	125
3.5.1.2	EPR data from photolysis of 263	127
3.5.2	Synthesis of ketoxime oxime ethers and thermolytic studies	128
3.5.3	Conclusions on synthetic attempts at an intramolecular iminyl radical cyclisation	130
3.6	Glycosyl iminyl radicals in the synthesis of N-linked glycopeptides	131
3.6.1	Concluding remarks on N-linked glycopeptide synthesis	138
4.0	**Synthesis of oxyaminoglycans as potential glycosidase inhibitors**	**141**
4.1	Oxime ligation as a tool for glycoconjugation	141
4.1.1	Proposed synthesis of O/N-O and S/N-O acetals as potential glycosidase inhibitors	142
4.1.2	Stability and anomeric configurations of O/N and S/N acetals	144
4.1.3	Proposed synthetic targets	145
4.2	Preparation of synthetic hydroxylamines	146
4.2.1	Synthesis of 1-oxyaminoglucose	146
4.2.2	Synthesis of oxyamino serine	149
4.2.3	Synthesis of 1,6 oxyamine linked thiosugar disaccharides	150
4.3	Preparation of oximes	152
4.3.1	Synthesis of aglycan derived hydroxylamine glycosides	153
4.3.2	Synthesis of 1,1 oxyamine linked disaccharide	154
4.3.3	Attempted oxime ligation from oxyamine serine x	155
4.3.4	Attempted synthesis of 1,6 oxyamine linked disaccharide	156
4.3.5	Conclusions on oxime conjugation	157
4.4	Synthesis of S/N-O acetals	157
4.4.1	Route A for the preparation of oxyamine linked thiosugars	158
4.4.1.1	Anomerisation of 319	160
4.4.2	Investigation into a compatible protecting group strategy	161
4.4.3	Synthesis of a mixed TBS/acetyl protecting group system	164
4.4.4	Conclusions on synthetic attempts at oxyamine thiosugar synthesis	164
4.5	Protecting group free synthesis of oxyamine linked thiosugars (Route B)	164
4.6	Conclusions	166

5.0 General experimental data 168

5.1 Experimental data for Chapter 2 169

5.2 Experimental data for Chapter 3 222

5.3 Experimental data for Chapter 4 260

6.0 References 287

Acknowledgements

I would like to sincerely thank my supervisor Dr. Eoin Scanlan for his guidance, patience and friendship over the past four years. I couldn't have asked for a better or kinder mentor. Sincere thanks to Dr. John O'Brien for his unwavering enthusiasm and tremendous help with the NMR experiments. To Dr Manuel Rüther for all his help with NMR, IR and the many computer technical problems, to Dr. Martin Feeney and Dr. Gary Hessman for mass spectrometry, and to the Chemistry Department at TCD, thank you for all for your help. I would like to thank Professor John Walton for his help with ESR spectroscopy and Professor Stefan Oscarson for the use of the birch reduction equipment. I would also like to thank Brian Higgins and Jean-Luc Bouissière for all their help, kindness, and insightful discussions. Finally, I would like to thank Science Foundation Ireland for financial assistance.

To the other members of the fab four, Lyn, Jean and Robin, to Claire, Helen, Moss, Vincent, to the Southern, Connon, Rozas, Colvita and Baker groups thank you for all for the memories, the music, the coffee breaks, the wine day Fridays, the off the wall chats and the friendships, it wouldn't have been the same without you.

I'd like to thank Mum and Dad for their unyielding encouragement, for always having faith in me, and for learning to feign sympathy when columns went wrong. To Orla, James, and Grainne, and to the Mahfoud family thank you for the great support. Lastly, to Omar, thank you, for everything, this wouldn't have been possible without you and I just hope I can be of half of the same help to you!

Abstract

Sugars with heteroatoms other than oxygen in the ring (e.g. iminosugars, thiosugars) are known to exhibit interesting biological activities and possess considerable therapeutic potential. Their biological activity can be principally attributed to their inhibitory effect on glycosyltransferases and glucosidases. Inhibition of these enzymes renders thiosugars and azasugars therapeutically useful against a range of diseases including diabetes, HIV, hepatitis and cancer. The overall aim of this work was the development of novel, efficient and versatile free-radical-based strategies for the syntheses of thio- and azasugars. Free radical chemistry has seldom been employed in carbohydrate chemistry, and a thiyl or iminyl radical cyclisation had previously never been investigated for the preparation of thio- or azasugars.

The use of intramolecular thiyl radical cyclizations for the synthesis of thiosugars has been researched, and a new free-radical-based methodology for the synthesis of biologically important thiosugars has been developed. The methodology is mild and proceeds via either 6-*endo* or 5-*exo* cyclization to furnish the thiosugar ring. This represents the first examples of thiyl radical cyclization being applied to the synthesis of thiosugars. The application of thiyl-radical-mediated 5-*exo*-trig cyclization reactions for the preparation of a series of *C*-linked 4-thiofuranoside sugars has also been investigated. The cyclization reactions were found to proceed in high yield with complete regioselectivity and moderate to excellent diastereoselectivity for a number of benzyl-protected precursors. The diastereoselectivity of the radical cyclization was determined by a number of factors, primarily the stereochemistry at the C-2 position and the nature of the substituents attached to the olefin. The cyclization reactions proceed via transition-state intermediates that favor formation of the 1,2-trans products. For D-sugars, a chairlike transition state is proposed. For L-sugars, both chair- and boatlike transition states could be considered. Inversion of the stereochemistry at C-4 also induced a significant effect on the diastereoselectivity of the radical process. The synthetic route is general for both D- and L-sugars and offers a highly novel and efficient strategy for accessing *C*-linked 4-thiofuranosides. A fluorescently labelled thiosugar was prepared as a putative glycosidase inhibitor.

The syntheses of photochemical and thermally initiated precursors of piperidine based iminyl radicals are described for the synthesis of azasugars. Glycosyl oxime esters as photochemical precursors were prepared with arming and disarming protecting groups and their subsequent iminyl radicals were characterised by ESR spectroscopy. The synthesis of a benzylated glycosyl oxime ether as a thermally initiated precursor of an iminyl radical is presented alongside the various conditions that were attempted to implement an intramolecular cyclisation. Using similar methodology pyrrolidine oxime ethers as thermally initiated precursors of iminyl radicals were synthesised and their thermolytic dissociation investigated. An intramolecular iminyl radical capture of a peptidic alkene was attempted under thermolytic conditions.

The synthesis of a novel *N*-linked thiosugar is presented alongside the preparation of oxyamine linked glycoconjugates.

Abbreviations

4HT	4-hydroxy-TEMPO
ACVA	4,4-Azobis(4-cyanovaleric acid)
AIDS	Acquired Immunodeficiency Syndrome
AMP-DNM	N-[5-(adamantal-1-ylmethoxy)pentyl]-1-deoxynojirimycin
BDE	Bond Dissociation Enthalpies
BER	Borohydride Exchange Resin
BOC	Tert-Butyloxycarbonyl
BVDV	Bovine Viral Diarrhoea Virus
CAN	Ceric Ammonium Nitrate
COSY	Correlation Spectroscopy
DAB	1,4-dideoxy-1,4-imino-D-arabinitol
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
DCN	1,4-dicyanonaphthalene
DEAD	Diethylazodicarboxylate
DENV	Dengue Virus
DIAD	Di-isopropylazodicarboxylate
DICH	Diisopropoxycarbonylhydrazine
DIPEA	*N,N*-Diisopropylethylamine
DMDP	2,5-Dihydrohydroxymethyl-3,4-dihydroxyprrolidine
DMF	Di-methyl formanide
DMJ	Deoxy Mannojirimycin
DNJ	Deoxynojirimycin
DPAP	2,2-dimethoxy-2-phenyl acetophenone
DPP	Dipeptidyl Peptidase
DTBAB	Di-*tert*-butylazodicarboxylate
DTBHN	Di-*tert*-butylhyponitrite
EC_{50}	Effective Concentration
EDA	Ethylenediamine

EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric Excess
emmiPF_6	1-ethyl-2,3-dimethyl-imidazolium hexafluorophosphate
EPR	Electron Paramagnetic Resonance
ER	Endoplasmic Reticulum
ESR	Electron Spin Resonance
G	G-factor
GHz	Giga Hertz
GP	Glycogen Phosphorylase
GPb	Muscle Glycogen Phosphorylase
HAT	Hydrogen Atom Abstraction
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HOBt	Hydroxybenzotriazole
HMPA	Hexamethylphosphoramide
HWE	Horner-Wadsworth-Emmons
K	Kelvin
K_i	Inhibitor Constant
LAB	1,4-dideoxy-1,4-imino-L-arabinitol
μ	Micro
M	Molar
MAP	4-methoxyacetophenone
mCBPA	meta-Chloroperoxybenzoic Acid
MS	Multiple Sclerosis
MW	Mega Watt
NAD^+	Nicotinamide Adenine Dinucleotide
NBS	*N*-bromo-succinamide
NCS	*N*-chloro-succinamide
NIS	*N*-iodo-succinamide
NOE	Nuclear Overhauser Effect
PEG	Polyethylene Glycol
PET	Photoinduced Electron Transfer

PMAP	4-dimethylaminopyridine
PNB	Para-nitro Benzyl
PMB	Para-methoxy Benzyl
Py	Pyridine
RBF	Round Botton Flask
Rf	Retardation Factor
SAR	Structure Activity Relationship
TBS	*Tert*-butyldimethylsilyl
TEC	Thiol-ene Coupling
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
TMS	Trimethylsilyl
TFA	Trifluoroacetic Acid
THF	Tetrahyrdofuran
TOCSY	Total Correlation Spectroscopy
W	Watt
WNV	West Nile Virus

1.0 General Introduction

1.1 Biological significance of carbohydrates

Amino acids and nucleotides have long been recognised for their vital role as information carriers and as building blocks for key biomolecules. Carbohydrates on the other hand, have traditionally been regarded subordinate in terms of biological significance. While their role in the storage and metabolism of energy, and in the structural integrity of cells was well known, they were not considered fundamental information carriers.

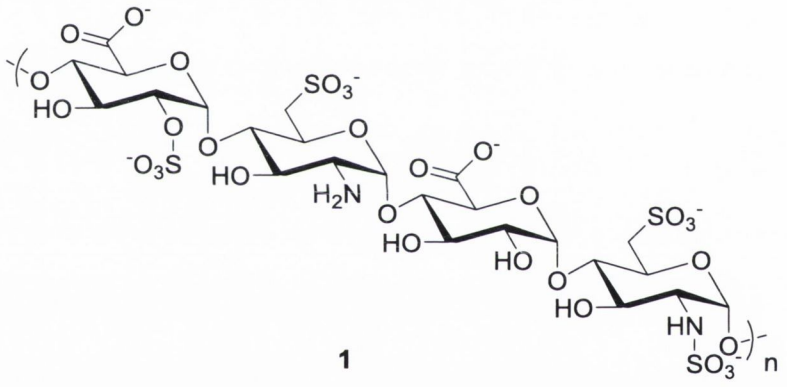
In order to mediate innumerable recognition events, macromolecules require vast diversity in terms of structure and surface topography. In terms of structural diversity, carbohydrates are vastly superior to peptides and nucleotides. The combination of 3 different amino acids can theoretically yield 6 different tripeptides, on the other hand 3 monosaccharide units could hypothetically generate 1056 unique trisaccharides. Their broad diversity originates from their assembly from monoasaccharides which can be linked to each other through the various hydroxyl groups displayed on pyranose or fuanose rings. Each ring can establish several glycosidic linkages, giving rise to branched structures. Further structural variation of carbohydrates can be afforded via acetylation and sulfonation. Recent developments in analytical techniques have allowed for structural and conformational studies of complex carbohydrate analogues and, as such, the extent of structural diversity present in carbohydrates to become more fully recognised. This variable nature renders carbohydrates ideal carriers of biological information, and as fundamental constituents of every cell surface they are involved, almost without exception, whenever specific cell-cell interactions occur.

Oligoscaccharides covalently linked to lipids or proteins (glycoconjugates), have been shown to play a vital role in cell-cell recognition.[1] The information content of glycoconjugates is primarily carried by the carbohydrate portion,[2,3] which also constitutes the largest structural component relative to the attached protein or lipid. Glycoconjugates have been implicated in a vast array of biological processes including fertilisation, hormone activities, tumour cell metastasis and immunological protection.[4] Furthermore carbohydrates function as receptors for viral and bacterial infections.[1,5] During these physiological processes, the dense structural information provided by carbohydrates is

decoded by carbohydrate binding proteins. There exists a need to decipher the structure activity relationship (SAR) between glycans and their protein receptors, therefore international multidisciplinary organisations have been established in Europe,[6] the United States[7] and Japan.[8] Currently over 170 carbohydrate binding proteins have been identified,[7] and these discoveries have led to a resurgence in the field of glycobiology and have led to a continuous supply of carbohydrate related targets for the structure-based design of glycotherapeutics.

1.1.1 Carbohydrates to glycomimetic drugs

Although carbohydrates play a pivotal role in a vast array of biological processes, only a limited number of carbohydrates are clinically approved therapeutics. A prominent exception being low molecular weight heparin **1**, a widely used injectable anticoagulant.



1

Figure 1 Structure of heparin, composed of repeating units (n)

While they function as excellent recognition molecules on the cell surface, many of the intrinsic properties of carbohydrates make them poor choices as small molecule drugs. As a result of their hydrophilic nature and high density of hydroxyl groups they are unable to passively cross through the enterocyte layer in the small intestine, a prerequisite for oral bioavailability. In addition, once in circulation carbohydrates suffer from fast renal excretion.

These problems can be overcome by designing drug compounds of low molecular weight based on the structure of the functional carbohydrate. These so called glycomimetics can

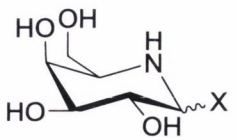
offer superior binding affinities relative to their natural carbohydrate counterparts by optimisation of entropic and enthalpic binding contributions and via pre-organisation of the molecule in the bioactive form (bound conformation). Equally, by reducing their hydrophilicity, oral-bioavailability can be achieved, and by eliminating metabolic 'soft spots', not required for binding affinity, their metabolic stability can be vastly improved.

1.2 A brief overview

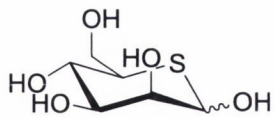
The overall aim of this work is the development of novel synthetic methodologies for the synthesis of potential glycosidase inhibitors. This introductory chapter will outline three different categories of glycosidase inhibitors ; thiosugars (sugar unit with a thiol group in the glycosyl ring in place of oxygen), iminosugars (sugar with an endocyclic nitrogen in place of oxygen), and aminoglycans (sugars with an exocyclic amine group).

1.2.1 Sugars with ring heteroatoms other than oxygen

Displacement of the ring oxygen in a sugar by other heteroatoms such as nitrogen, sulfur or phosphorus leads to significant changes in the physico-chemical properties of the sugar and, consequently, to profound differences in the "information content" of the modified carbohydrate towards biological systems. Such sugars have been isolated in nature, and owing to their altered biological interaction with carbohydrate utilizing or modifying enzymes, have displayed extraordinarily interesting biological activities and tremendous therapeutic potential.



2 : X = OH
3 : X = H



4

Figure 2 Natural sugars with nitrogen and sulfur as the ring heteroatom

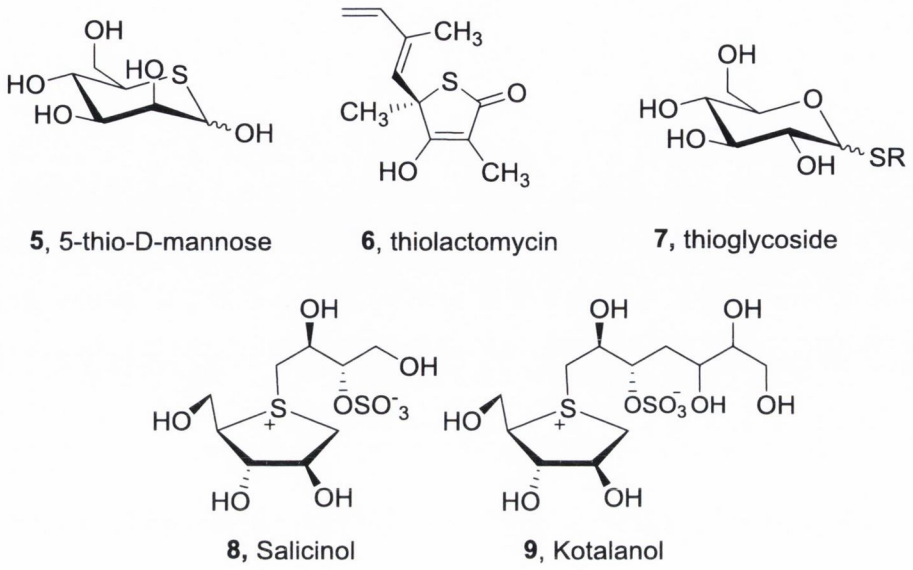
1.2.1.1 Naturally occurring thiosugars

Thiosugars are carbohydrate analogues containing sulfur as the ring heteroatom in place of oxygen. The differences in biological activities between thiosugars and their oxygen counterparts can be explained through differences in geometry, conformation and flexibility. In addition, the sulphide moiety is less electronegative and more polarisable than the ethereal moiety. Many functionalised thiosugars occur naturally and are potential targets for novel carbohydrate based therapeutics.

The first thiosugar isolated form nature, 5-thio-D-mannose **5**, a metabolite of the marine sponge *Clathria pyramide,*[9] is unique as the only known example of a 5-thioaldopyranose from nature. The antibiotic thiolactomycin **6**, a fermentation product from a *Nocordia species*[10] was discovered in 1981. It contains sulfur as a heteroatom and an unsaturated lactone moiety. This compound exhibits increased lipophilicity relative to other thiosugars owing to the unsaturated aliphatic five carbon chain at the *C*-5 position and the lack of multiple ionisable groups. Thiolactomycin was found to be a broad spectrum antibiotic and has been shown to inhibit inducible β-lactamases.[11-13] The most abundant class of naturally occurring thiosugars are the thioglycosides **7**. Although formally defined as thiosugars they contain an oxygen atom as the endocyclic heteroatom and a sulfur atom replacing the glycosidic oxygen atom. This replacement increases the metabolic stability of the glycosidic linkage against enzymatic cleavage. Thioglycoside based antibiotics, such as the lincomycin derviatives are classic examples (Figure 3).

While displaying interesting and versatile therapeutic activities, the principle interest in thiosugars as potential therapeutic agents is derived from their glycosidase inhibition. Glycosidases and glycosyl transferases are enzymes responsible for the hydrolysis and biosynthesis of glycosidic bonds, as such, they play a fundamental role in the control of metabolism of carbohydrates (hydrolysis of polysaccharides) and the metabolism of glycoproteins and glycolipids. Their anomalous functioning is correlated to the development of numerous diseases including cancer,[14,15] diabetes,[16] lysosomal storage disorders[17] and microbial infections.[18] Naturally occurring thiosugars which exhibit activity as glycosidase inhibitors include the 1,4 thioanhydrosugars salicinol[19] **8** and kotalanol[20] **9**, both isolated from the herb *Salacia Reticulate*. Aqueous extracts of the *Salacia* plant have been traditionally used in Indian medicine for the treatment of

diabetes. Ayurvedic medicine advised that a diabetic patient should drink water stored overnight in a mug carved from Kotalahimutu wood.



5, 5-thio-D-mannose **6**, thiolactomycin **7**, thioglycoside

8, Salicinol **9**, Kotalanol

Figure 3 Naturally occurring thiosugars

1.2.1.2 Naturally occurring azasugars

Azasugars or iminosugars, are analogues of simple sugars in which the ring oxygen has been replaced by a nitrogen. Since the discovery of nojirimycin, the first polyhydroxylated piperidine, in 1966, azasugars have emerged as very promising drug candidates for the treatment of a range of diseases.[21] Unlike their thio counterparts, azasugars are abundant in nature. In the past 40 years more than 100 azasugar analogues have been isolated from plants and microorganisms. Due to their vast therapeutic potential much effort has been focused on their synthesis with a large number of polhydroxylated piperidines and pyrrolidines described. Their biological activity can be attributed to their inhibitory effect on glycosyltransferases and glucosidases. Naturally occurring sugar analogues with nitrogen in the ring can be divided into five structural classes

1. Polyhydroxylated piperidines
2. Pyrrolidines
3. Indolizidines
4. Pyrrolizidines
5. Nortropanes

Nojirimycin **10**, the first polyhydroxylated piperidine alkaloid, which mimicks glucose was isolated from *Streptomyces roseochromogens* R-468 and *Streptomyces nojiriensis* SF-426 cultures.[21] It was found to exhibit antibiotic activity by strong glucosidase inhibition.[22-24] Some twenty years later the epimeric mannojorimycin[25] **11** and galactonojirimycin[26] **12** were isolated from a species of *streptomcyes* and were also found to be inhibitors of mannosidases and β-galactosidases respectively. However these compounds were found too unstable as a result of their hemi-aminal structure. The corresponding 1-deoxynojirimycin[23] 1-DNJ **13**, isolated from the roots of the mulberry tree, and 1-deoxy-mannojirimycin[23] 1-DMJ **14**, produced by *Streptomyces lavandulae* SF-425, were both found to be more stable, while maintaining excellent glycosidase inhibition (K_i 0.44 μM and K_i 0.13 μM)

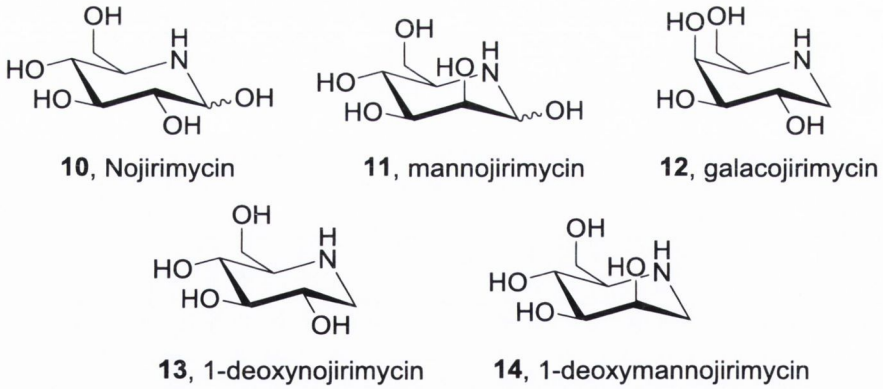


Figure 4 Naturally occurring polyhydroxylated piperidines

2,5-Dihydrohydroxymethyl-3,4-dihydroxyprrolidine **15** (DMDP) was the first pyrrolidine iminosugar isolated.[27] It was extracted from the leaves of *Derris elliptica* in 1976, however its biological activity was not recognised until several years later.[28] **15** inhibits glucosidase I, a glycoprocessing enzyme. It also exhibits moderate antiviral activity and is toxic to insects.[28] In addition **15** can also inhibit multidrug resistant efflux pumps, which

is an attractive target for the treatment of cancer.[29,30] Other notable naturally occurring pyrrolidines include codonospine and radicamines A and B (**17** and **18**), recently isolated from *Lobelia chinesis*.[31] 1,4-dideoxy-1,4-imino-D-arabinitol (DAB) **19** was found to be a potent inhibitor of glycogen phosphorylase and is currently being investigated for the treatment of type II diabetes.[32] Its enantiomer 1,4-dideoxy-1,4-imino-L-arabinitol (LAB) **20** was found to be equally active against a range of glucosidases. In addition LAB was found to be one of the most powerful anti HIV agents amongst 47 screened azasugar derivatives.[33]

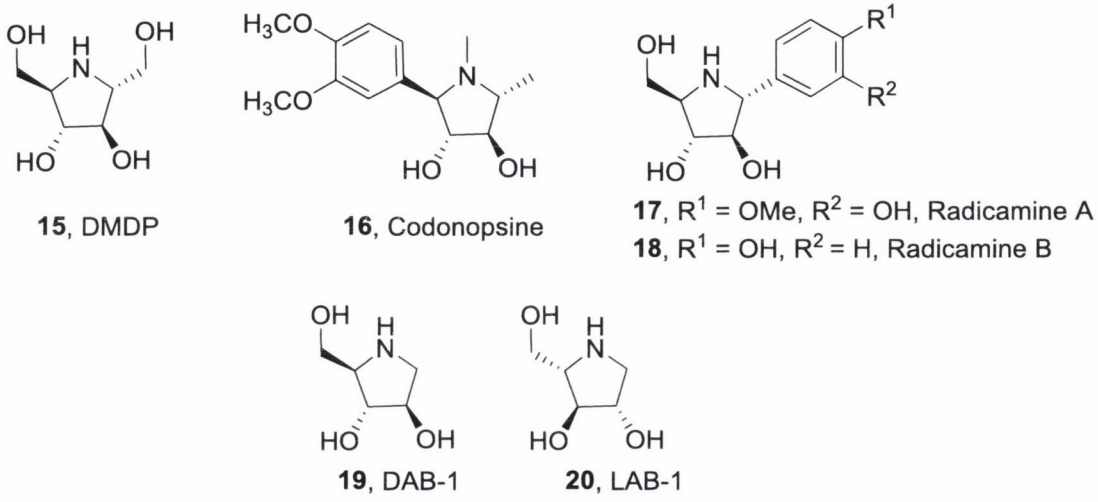
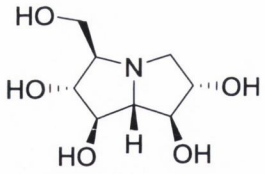
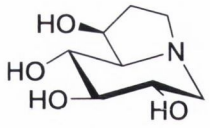


Figure 5 Naturally occurring pyrrolidines

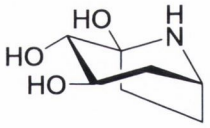
The indolizidines, pyrrolizidines and nortropanes all display bicyclic iminosugar structures (Figure 6). Notable examples of each include the pyrrolizidine causerine[34] **21**, the indolizidine castanospermine[35] **22** and the nortropane calystegine A_3[36] **23**. In particular **22**, isolated from the seeds of *Castanospermum astrale,* displays remarkable biological activity.[35] As a potent inhibitor of α- and β- glycosidases from plant and animal sources, it also inhibits some bacterial α-glucosidases.[37,38] Furthermore, **22** has been proven to prevent clinical signs of experimental autoimmune encephalomyelitis in mice, which could be an attractive strategy for the treatment of human autoimmune diseases such as MS.[37,38] Swainsonine **24**, an indolizidine isolated from *Swainsona canescens*[39] in 1979, has been the subject of intense study owing to its remarkable anti-tumour effect on various types of cancer. This compound will be discussed in a following section.



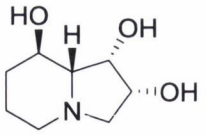
21, Causerine



22, Castanospermine



23, Calystegine A_3

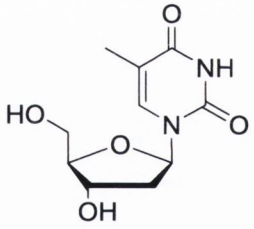


24, Swainsonine

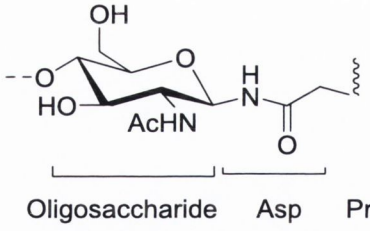
Figure 6 Naturally occurring bicyclic iminosugars

1.2.1.3 Naturally occurring glycosylamines and pseudosugars

Aminosugars, can be defined as carbohydrates in which one (or more) of the hydroxyl groups of the sugar ring has been replaced by an amino group. Replacement of the ring oxygen gives rise to compounds such as nojirimycin, as discussed in the preceding section, however this section is concerned with a class of compounds in which the interglycosidic oxygen has been replaced by an amino group. Nucleosides, wherein a furanose sugar containing a β-glycosidic nitrogen attached to a heterocyclic base such as Thymine, **25**, occur in every living cell as a fundamental component of nucleic acids. *N*-linked glycoproteins, **26**, exist in all eukaryotic organisms and contain oligosaccharides that are β-linked via an amide bond to L-Asparagine in the protein.



25, Thymine



26, *N*-linked glycoprotein

Figure 7 Naturally occurring aminoglycans.

A number of pseudo-oligosaccharides were isolated from various strains of Streptomyces during the 1970s and 1980s, which showed remarkable enzyme inhibitory activity. Included are validomycin A[40] **27**, acrabose[41] **28**, amylastain[41] **29**, adiposin[42] **30** and trestatins[42] **31**. These compounds all contain a similar structural framework, including a

cyclitol bearing substituent that resemble α-D-glucopyranose, and an amine in the interglycosidic linkage. Validomycin A, **27,** is a potent antibiotic, amylostatin XG **29**, exhibits α-glucosidase activity and antimicrobial activity. The most studied of the pseudo-oligosaccharides is **28**.[43] It was discovered by Bayer from a fermentation broth of the *Actynoplanes* strain SE 50 and was found to be a potent α-glucosidase inhibitor, inhibiting α-amylase, glucoamylase and intestinal sucrase.[40,43] **28** is now a licensed therapeutic under the trade name Glucobay® for the treatment of type 2 diabetes.[43]

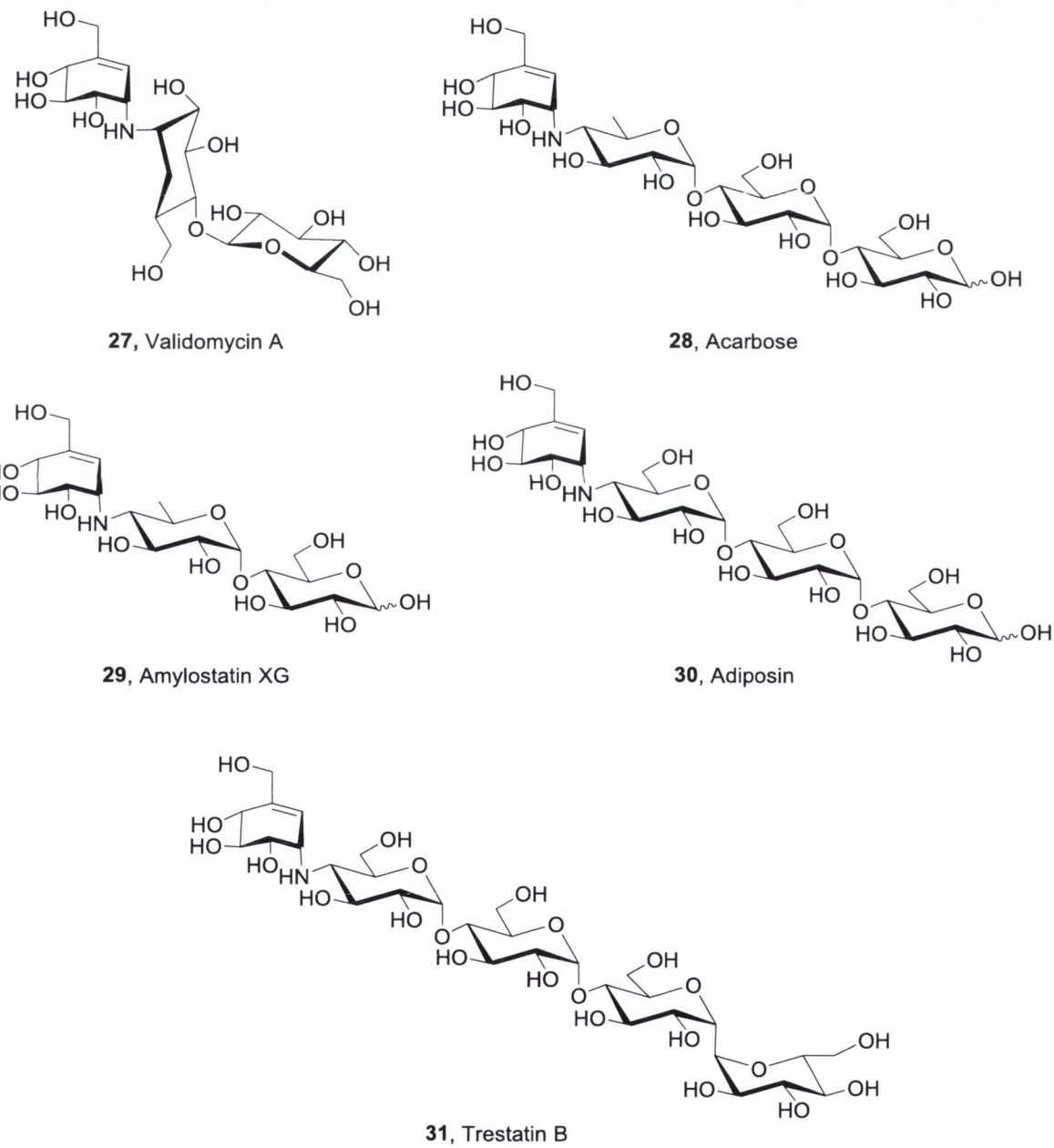


Figure 8 Naturally occurring aminoglycan pseudo oligosaccharides

As for thio- and iminosugars, the efficacy of these compounds as glycosidase inhibitors is thought to be due to their structural resemblance towards the transition state of a sugar ring of the glycosidase enzyme-substrate complex. Enzyme-substrate interactions, particularly those involving glucosidase enzyme-substrate interactions will be discussed in detail later in the chapter.

1.3 Therapeutic potential of glycosidase inhibitors

As glucosidases play an important role in control of cell surface carbohydrate structure and function, moieties that are known to be implicated in the immune response, inhibition of the glucosidase enzymes has been shown to be therapeutically useful against a range of diseases including diabetes,[16] HIV,[44] hepatitis[45] and cancer.[14,15]

1.3.1 Glucosidase inhibitors as anti-diabetic agents

Diabetes mellitus is a hormonal deficiency disease characterised by chronic elevated blood glucose levels. There are two different manifestations of diabetes: Type 1 being characterised by the autoimmune mediated destruction of pancreatic β-cells resulting in total insulin deficiency.[46-48] Type 2 diabetes is characterised by insulin resistance and/or abnormal insulin secretion. Today, the worldwide prevalence of diabetes has reached pandemic proportions, as changing lifestyles leads to reduced physical activity and increased levels of obesity, factors which are linked to the development of type II diabetes. In 2010, 285 million people were reported to be suffering from diabetes, a number which is estimated to almost double by 2030.[49] In recent years it has also been proposed that elevated blood glucose levels can induce vascular damage and cause myocardial infarctions, coronary heart disease and cerebral apoplexy.[50] Therefore, careful control of blood glucose levels can also delay or protect at risk patients from developing heart diseases.[51-54]

At present, alongside diet and exercise, hypoglycemic drugs are used in the treatment of type 2 diabetes. Antidiabetic drugs can be classified into five different classes:

1. Insulin secretogogues such as the sulfonylureases.
2. Insulin sensitizers such as biguanides and thiazolidinediones.
3. Insulin mimics e.g glucagan like peptide analogues and agonists.
4. DPP IV inhibitors.
5. α-glucosidase inhibitors

Some of the aforementioned drugs have unacceptable side effects or lose effectiveness over time, therefore the search for a new antidiabetic drug continues to be of considerable interest. Glucosidase inhibitors are one of the principle classes of oral antidiabetic agents.[55] They exert their therapeutic action by regulating the absorption of dietary carbohydrates or *via* inhibition of glycogen phosphorylase, an enzyme which mediates glucose biosynthesis in the liver.

1.3.1.1 Digestive glucosidase inhibitors

Digestive α-glucosidases, located in the small intestine are enzymes which hydrolyse dietary carbohydrates to monosaccharides, which are subsequently absorbed through the intestinal wall. In the 1970s it was proven that inhibition of these enzymes regulated the absorption of dietary carbohydrates and that these inhibitors could be therapeutically useful for the treatment of type 2 diabetes. Acarbose **28**, the first generation α-glucosidase inhibitor was superseded by a second generation α-glucosidase inhibitor featuring an iminosugar structure. DNJ, a naturally occurring α-glucosidase inhibitor isolated from the leaves of the mulberry tree has been traditionally used in Chinese medicine for the treatment of diabetes. However while DNJs *in vitro* profile was excellent[56] its' *in vivo* profile was only moderate when tested.[57] As a result a large series of DNJ derivatives were developed and analysed for optimised *in vivo* activity.[58-60] An *N*-alkylated azasugar, Miglitol **32**, showed potent inhibition of glycogenolysis of glycogen in studies with hepatocytes and it is now a commercially available treatment, introduced on the market in 1999 under the trade name Diastabol® to treat type 2 diabetes.[61, 62.]

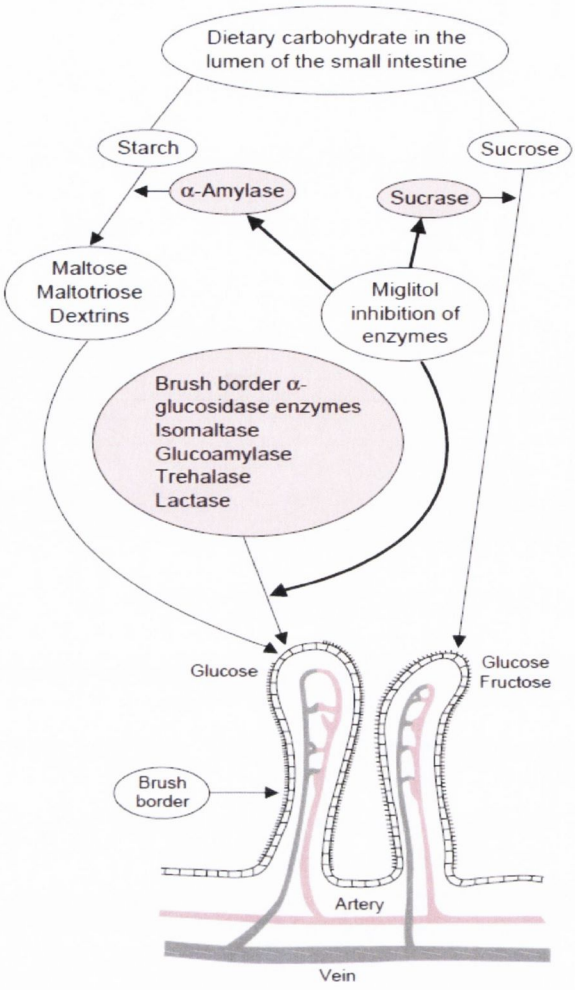
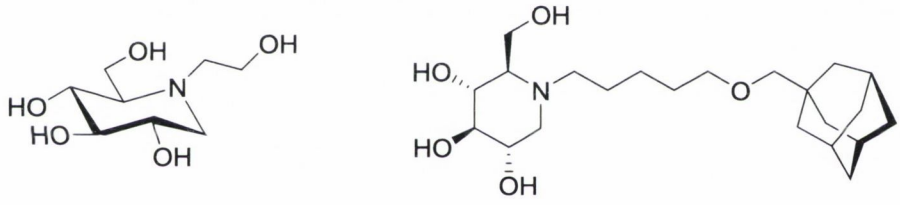


Figure 9[66] Inhibitory action of Miglitol **32**

The mechanism of action against intestinal α-glucosidases differs between the carbasugar **28,** and the iminosugar, Miglitol **32**. **28** has poor absorption from the gastrointestinal tract with the mean systemic bioavailability ranging between 0.5 % and 1.6 %.[63] Poor absorption results in a longer retention time of the drug in the intestine and colon thus resulting in gastrointestinal side effects. In contrast **32** was designed to be almost completely absorbed from the intestinal tract thus leading to lessened gastrointestinal discomfort.[64, 65] Notably, comparative studies have shown that **32** had similar efficacy to **28** but at lower therapeutic doses.[66] **32** is also capable of hydrolysing both 1,6 and 1,4 glycosidic linkages while **28** hydrolysis solely 1,4 linkages.[67] It has been suggested that the former's broader specificity is a result of its closer structural similarity to glucose unlike the pseudopolysaccharide **28**.[67] In addition, in combination with other oral antidiabetic agents or insulin, **32** improved glycaemia control in patients for whom metabolic control was suboptimal despite dietary and pharmacological intervention.[66]

As previously mentioned, both naturally occurring 1,4 thioanhydrosugars salicinol, **8**, and kotalanol, **9**, are potent inhibitors of intestinal α-glucosidases, with IC_{50} values of 1.1 nM and 0.38 μM respectively.[19,20] Both compounds share a common zwitterioic sulfonium-sulfate structure and a polyhydroxylated side.

Attention has recently focused on the lipophilic *N*-[5-(adamantal-1-ylmethoxy)pentyl]-1-deoxynojirimycin (AMP-DNM), **33**, a glucosidase inhibitor capable of inhibiting the synthesis of glycosylceramide and carbohydrate assimilation, thus enhancing insulin sensitivity.[68,69] It has also been suggested as a good candidate for improving glucose homeostasis and hepatic steatosis, symptoms of the first stage of non-alcoholic liver disease.[70] Furthermore, **33** was found to protect mice against atherosclerosis development, via stimulation of reverse cholesterol transportation, thus significantly decreasing the amount of lipids present in plasma.[71]



32, Miglitol **33**, AMP-DNM

Figure 10 Stuctures of iminosugars Miglitol**, 32,** and AMP-DNM**, 33.**

1.3.1.2 Glycogen phosphorylase inhibitors as anti-diabetic agents

Glycogen phosphorylase (GP) is the principle regulatory enzyme of the liver, being responsible for the control of blood glucose levels. While not a glycosidase itself, it is of fundamental pharmacological importance. As type 2 diabetes exhibits an increase in hepatic glucose production, targeting of GP could provide a novel potential treatment.[72] A viable approach to modulate the activity of GP would be through the use of glucose derivatives as inhibitors.[73] Iminosugars, isofagomine, **34**, (IC_{50} = 0.7 μM), azofagomine, **35**, (IC_{50} = 0.7 μM) and noeuromycin, **36**, (IC_{50} = 4 μM) show excellent inhibition of GP. Bois *et al.*[74] showed that *N*-substitution of **34** retained micromolar activity while experiments with fagomine **37** or DNJ, **13**, resulted in considerable loss in activity thus

illustrating significant specificity within azasugars. Pentose iminosugar DAB, **19**, shows strong inhibition of GP with K_i values in the nanomolar range.[75]

Organic synthesis, protein crystallography and biological assays led to the discovery of gluporanosylidene-spiro-hydantoin, **38**, (K_i = 3.4 μM) as an extremely potent GP inhibitor,[76] however access to this compound is limited due to the long synthetic pathway. Crystallographic investigations of GP inhibitor complexes have recently been carried out in order to ascertain mechanistic aspects of inhibition.[77] It was found that glycopyranosylidene-spiro-oxathiolates, bearing aromatic residues, exhibit excellent inhibition of muscle glycogen phosphorylase (GPb).[78]

To date the most potent inhibitors of muscle GPb are 2-napthyl oxathiazol, **39**, and 2 napthyl isoxazoline, **40**, with inhibition constants in the low nanomolar range. X ray crystallography has demonstrated that the 2-napthyl moiety is capable of interaction with multiple amino acid residues in the enzymes active site's less active T-state configuration.[79]

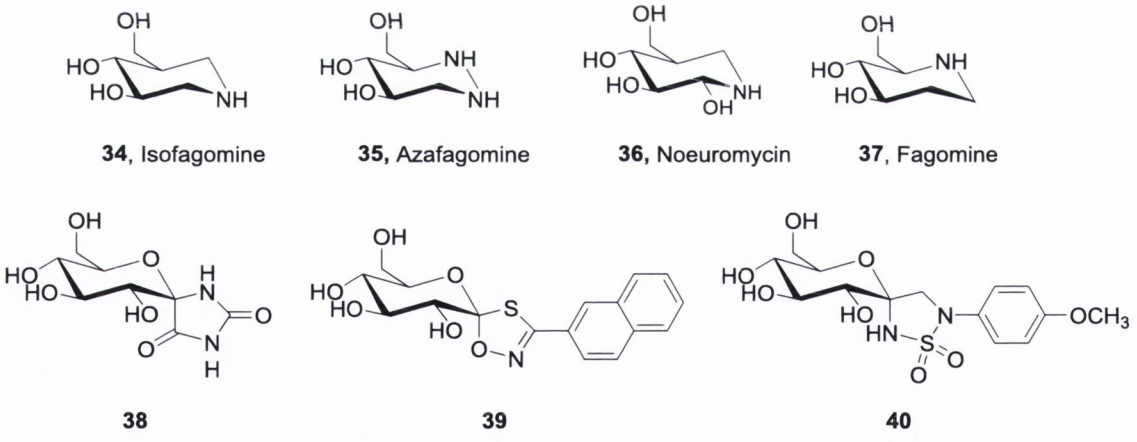


Figure 11 Inhibitors active against digestive glucosidases

1.3.2 Glucosidase inhibitors as anti-viral agents

Asparagine-linked (*N*-linked) oligosaccharides are present in many secretory and membrane proteins. More than 30 enzymes, located in the cytosol, endoplasmic reticulum (ER) and the golgi apparatus are required in order to generate, attach and process the oligosaccharides. The attachment and processing of sugar units is not random but controlled with exquisite precision both by the cell and the three dimensional structure of the protein itself. Correct protein glycosylation is imperative for promoting protein folding in the ER, stabilising cell surface glycoproteins and providing recognition epitopes that activate the innate immune system.[80]

Glycosidase inhibitors such as iminosugars have been identified as submicromolar range inhibitors of many hydrolytic enzymes, including ER α-glucosidases I and II, which are involved in processing glycoproteins.[81,82] The correct folding and assembly of many nascent glycoproteins is dependent on interactions with chaperones proteins such as calnexin, in the ER. Stepwise removal by ER α-glucosidases of terminal glucose residues from *N*-glycan chains attached to nascent glycoproteins enables the glycoproteins to interact with the chaperones calnexin and calreticulin, which bind solely to monoglucosylated glycoproteins (Figure 12).[83,84] Interaction with calnexin is crucial for the correct folding of some, but not all, glycoproteins, viral glycoproteins that depend on this interaction can thus be specifically targeted by inhibitors of ER α-glucosidases.[18]

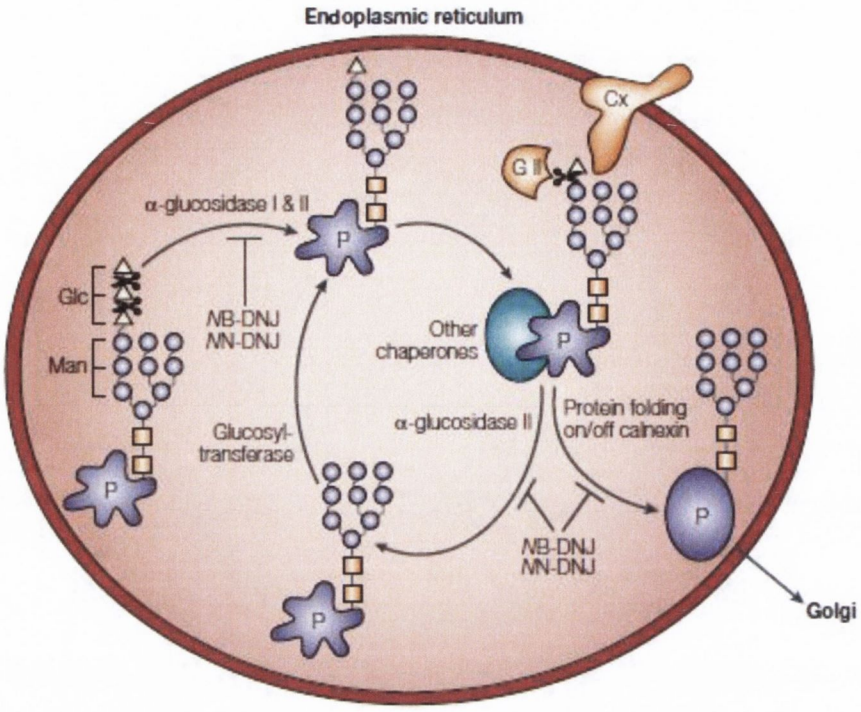


Figure 12[80] Inhibitory action of glycosidase inhibitors within the ER

Mammalian viruses do not encode their own carbohydrate-modifying enzymes, instead they use the host-cell glycosylation machinery to create their envelope glycoproteins. As with some cellular host proteins, the folding of certain viral glycoproteins has been shown to be calnexin-dependent.[85,86] Therefore, targeting the ER α-glucosidases at a low level could disrupt the folding of these proteins, and potentially be therapeutically useful in the treatment of viral infections, without affecting host-cell viability. The use of glucosidase inhibitors as anti-viral agents is currently being investigated as a potential treatment of a wide array of infections involving viruses with glycosylated envelopes. Examples include HIV, herpes simplex virus type 1, influenza viruses, parainfluenza virus, and measles virus, as well as several members of the *Flaviviridae* family, such as bovine viral diarrhoea virus (BVDV), dengue virus (DENV), West Nile virus (WNV), Japanese encephalitis virus, and hepatitis C virus (HCV).[80]

1.3.2.1 Glycosidase inhibitors as anti-HIV agents

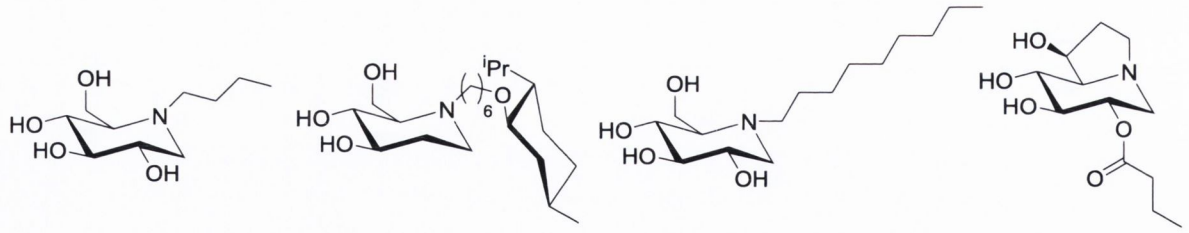
The HIV virus, the causative agent of AIDS, is known to cause a deterioration of the immune system which is characterised by increased susceptibility of the host to opportunist infections. The membranous envelope of the HIV virus which originates from host cells contains glycoproteins gp120 and gp41. Gp41 spans the envelope and is bound non-covalently to gp120 which projects from the viral surface. Entry of the virus into a host cell is mediated by the binding of viral glycoprotein gp120 to the host receptor protein $CD4^+$ and a chemokine co-receptor (CCR5 or CXCR4). Receptor binding results in conformational changes in gp120 which expose gp41. The hydrophobic terminus of gp41 embeds itself in the host cell membrane, pulling the virus and host cell together so that membrane fusion and viral entry can occur. With 30 potential *N*-glycan sites between them, gp41 and gp120 are among the most heavily *N*-glycosylated viral proteins known. They carry a mixture of oligomannose and complex glycans. Treatment of HIV-1 with iminosugar *N*-butyldeoxynojirimycin (NB-DNJ), **41**, an ER α-glucosidase inhibitor, suppresses viral infectivity and prevents syncytium formation *in vitro*.[18,87] Following treatment with **41** binding of progeny virions to CD4 occurs, however the conformational shift of gp120 that results in exposure of gp41 does not occur, and the process of viral fusion is therefore prevented. **41** was evaluated in Phase II clinical trials as an anti-HIV agent, but it was not possible to achieve sufficiently high serum concentrations of the drug[88,89] and no major impact was observed on viraemia.[89] However, importantly it was noted that **41** was well tolerated, with the main side effect being gastrointestinal distress due to intestinal disaccharidase inhibition.[89]

1.3.2.2 Clinical testing of the antiviral activity of iminosugars

While exhibiting great potential, the development of imino sugars as broad-spectrum antiviral agents has been limited by their relatively low efficacy and unfavourable toxicity profiles. Imino sugars **13** and ***41*** have 50% effective concentration (EC_{50}) values at the millimolar level. However when **41** was evaluated in Phase II clinical trials as an anti-HIV agent it was found that therapeutic concentrations were difficult to achieve *in vivo* thus, their antiviral utility is limited.[88,89] Deoxynojirimcyin derivatives with longer alkylated side chains on the nitrogen atom, such as *N*-nonyl-DNJ (NNDNJ), **43**, have

dramatically improved antiviral efficacies, with EC_{50} values in the low micromolar range.[90] However, such modification also increased the cytotoxicity of the imino sugar. In this context Chang *et al.*[90] have investigated the therapeutic profile of *N*-alkylated deoxynojirimycins against BVDV and DENV viruses. They found that an oxygenated alkyl side chain bearing a terminal ring, alkyl or aromatic, was critical for maintaining strong antiviral activity coupled with low cytotoxicity. Notably they found **42** capable of inhibiting in vitro DENV infection with 90% effective concentration at submicromolar concentrations.[90] Castanosperimine **22** and 6-*O*-butanoyl-Castonspermine (Celgosivir), **44**, have been found to inhibit HIV replication and HIV mediated syncytium *in vitro*.[91,92] The Catanospermine prodrug, **44**, developed by MIGENIX Inc. reached phase II clinical trials for the treatment of chronic hepatitis C. However the trials were abandoned in late 2007 as it was proven inefficient as a monotherapy, however **44** showed a synergistic effect with the current standard.[93] **44** has now re-entered a new clinical trial in combination with PEGylated IFNalpha2b and ribarvirin for the treatment of chronic HCV.[94] **44** has also proven active against all four serotypes of the dengue virus and pre-clinical testing has shown very promising results.[94]

While work is still ongoing in the development of an anti-viral glycosidase inhibitor, an important long-term and attractive advantage of this approach is that, as the enzymes are host-cell and not virus-encoded, emergence of drug-resistant viruses are less likely to occur.



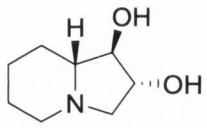
41, DB-DNJ **42** **43**, N-nonyl-DNJ **44**, Celgosivir

Figure 13 Glycosidase inhibitors exhibiting antiviral activity

1.3.3 Glycosidase inhibitors as anti-cancer agents

Changes in protein glycosylation are early indicators of cellular changes in many diseases, notably cancer[95] and rheumatoid arthritis,[96] providing useful diagnostic markers and insights into disease progression and pathogenesis. The use of glycosidase inhibitors to prevent catabolic glucosidase is currently being considered as a potential therapeutic strategy against cancer.[97] The most recognised iminosugars exhibiting antitumoural activity are **22** and swainisome **24**. **24** is an inhibitor of mannosidase II and has shown a potent anticancer effect on various types of cancer, but can also stimulate the immune system and prevent the toxicity on hematopoietic system from chemotherapy. **24** was included in phase I clinical trials for treating advanced tumours and showed considerable improvement in some patients with advanced malignancies.[98] No activity was noted however in phase II trials for renal carcinoma[99] and despite the promising results obtained in some clinical tests, the trials were ended due to hepatoxicity associated with swainisome. In addition to inhibiting α-mannosidase II, the title compound also inhibited lysosomal α-mannosidase with a similar K_i value. The lack of selectivity led to an accumulation of oligomannose in tissues and body fluids, and thus induced a phenocopy of human mannosidases, resulting in the development of a lysosomal storage disorder.[100] Therefore a search for new glycosidase inhibitor with better pharmacological profiles is warranted in the search for new antitumor agents.

In this context Xiao's group have reported[101] the use of a microtiterplate based method applied to live cells in order to screen for antitumoural activity using a library of iminosugar derivatives. Macci and co-workers[102] have focused attention on Lentiginosine, a potent amyglucosidase inhibitor. They found that lentiginosine's unnatural enantiomer D-lentiginosine, **45,** induced caspase-dependent apoptosis on tumour cells at low concentrations, in contrast to the natural enantionmer. Promising anti-cancer activity has also been noted in pyrrolidine and piperidine based iminosugar motifs.[103,104] 1-DNJ, **13**, was found to inhibit the metastasis of B16F10 melanoma cells, studies on its antimetastatic mechanism suggested that this compound could be a good candidate as an adjuvant of other antimetastatic agents such as cisplatin.[104]



45, D-lentiginosine

Figure 14 Structure of bicyclic iminosugar D-lentiginosine **45**

1.4 Glycosidase Inhibition

Glycosidases, as previously mentioned, are enzymes responsible for the breakdown of di-oligo- and polysacharrides. These enzymes are involved in many pivotal anabolic and catabolic processes ranging from glycosylation of proteins in the golgi apparatus to plant cell-wall biosynthesis, and from digestion of dietary carbohydrates to defence mechanisms against microbial infection. The extreme stability of the glycosidic bond and the catalytic rates achieved by glycosidases imply that they are among the most proficient of all enzymes.[105]

Glycosidases act by catalysing the exocyclic C-O bond hydrolysis. Given their multiple roles *in vivo* inhibition of these enzymes in a number of different processes, glycosidase inhibitors can be of therapeutic interest for a wide range of diseases including diabetes,[16] HIV,[44] and cancer[14,15] as previously mentioned. A vast number of glycosidase inhibitors have been prepared or isolated from nature. Studying these inhibitors may not only lead to therapeutic agents, but also to a deeper understanding of the structure-function relationships of enzyme specificity. Armed with an understanding of these relationships it is envisaged that improved glycosidase inhibitors may be synthesised thus leading to improved drug therapy.

1.4.1 Mechanism of glycosidase inhibition

Glycosidase hydrolysis proceeds via two different mechanisms, resulting in net retention or inversion of anomeric configuration. The pioneering work of Koshland[106] in 1953 in which he postulated the mechanisms for glycosidase hydrolysis is still widely accepted. In the classical mechanism glycosidases contain two carboxylate containing amino acid residues which are responsible for hydrolysis of the glycosidic bond. Retention of

configuration proceeds via a double displacement strategy consisting of two inverting steps. In this mechanism, one carboxylate residue protonates the exocyclic oxygen transforming the aglycon into a good leaving group, thus permitting formation of the oxocarbenium transition state. This oxocarbenium then reacts with the second carboxylate, giving an intermediate ester which is displaced by the nucleophilic attack of a water molecule to afford the reduced sugar with overall retention of configuration.[107,108] Inversion of stereochemistry proceeds in a single step. One of the catalytic residues acts as an acid while the other behaves as a base. Protonation of the exocyclic oxygen by the acidic carboxyl residue and the departure of the aglycan leaving group is accompanied by the concomitant nucleophilic attack by a water molecule that has been deprotonated by the basic carboxylate residue.[107,108]

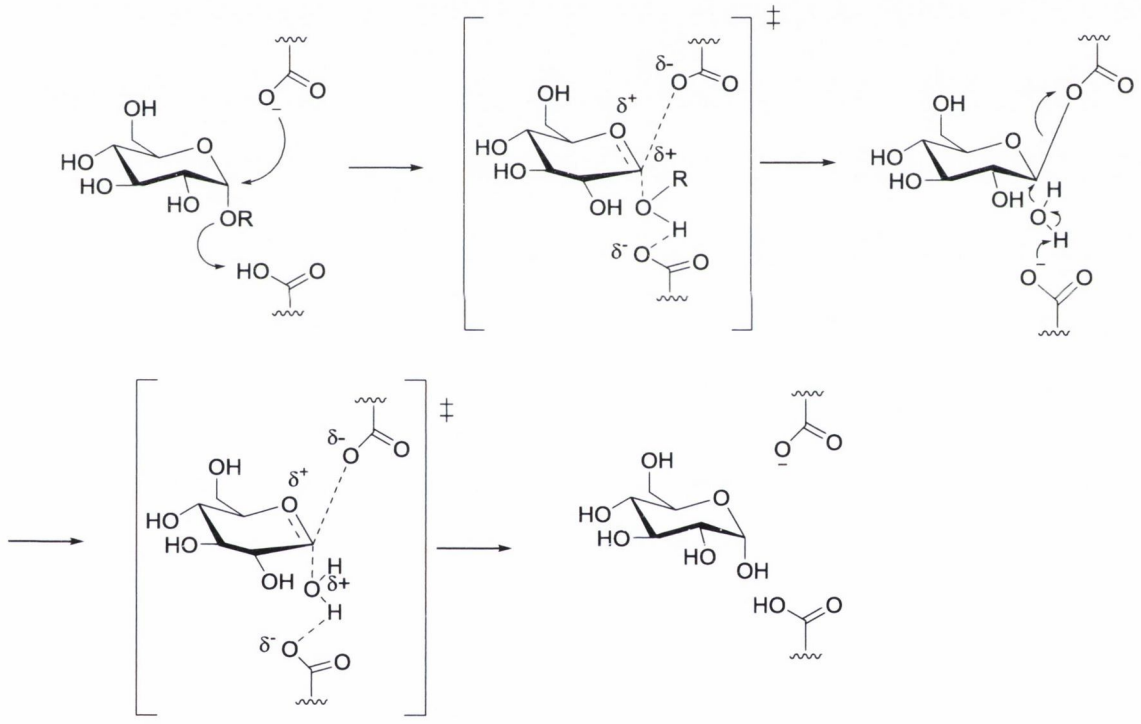


Figure 15 Proposed Mechanism for glycosidase hydrolysis with retention of configuration

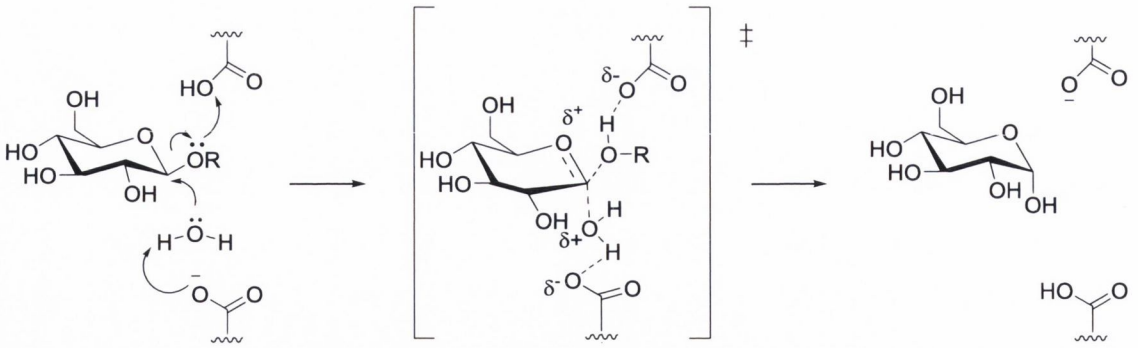


Figure 16 Proposed mechanism for glycosidase hydrolysis with inversion of configuration

Alternative mechanisms have been suggested for substrates containing *N*-acetylhexosamine moieties. It has been postulated that hydrolysis of these glycans proceeds via a substrate assisted mechanism.[109,110] Additional glycosidases rely on NAD^+ as a cofactor and proceed via a ketone intermediate. Recently it has been suggested that certain *endo*-mannosides may undergo their own substrate assisted mechanism via an epoxide intermediate.[111]

There are currently 130 families of glycosidases classified by sequence similarity.[112] These families are divided into those that are retaining glycosidases and those that are inverting glycosidases. One known exception however is the GH97 family which contains members that are capable of hydrolysing glycosidic linkages via either mechanism. GH97 enzymes have an unusual Ca^{2+} ion dependence; this may provide an environment with the requisite malleability to accommodate both mechanisms.[113-115]

1.4.1.1 The transition state of glycosidase enzymes

In both the inverting and retaining hydrolysis mechanisms the transition states formed share the following characteristics;

(i) A trigonal anomeric centre.

(ii) Half-chair or boat conformation

(iii) Significant positive charge

The short lived transition state of glycosidases possesses substantial oxocarbenium character. It consists of partially formed or broken bonds between the attacking

nucleophile (carboxylate group/deprotonated water molecule) and the exocyclic oxygen of the leaving group (or the attacking water molecule in the deglycosylation step of the retaining mechanism). As such, the anomeric carbon changes to sp^2 hybridisation predominantly along the bond between the anomeric carbon and endocyclic oxygen.[107] This is a result of donation of the lone pair of electrons in O-5 into the O-5-C-1 bond. This double bond character imposed on the pyranose ring imparts a conformational distortion from a ground state chair conformation to planarity of C-5, O-5, C-1 and C-2 in order to allow orbital overlap of the lone pair and scissile bond. The molecule therefore takes on a more energetically unfavourable half-chair or boat conformation (Figure 17).[107,116] Also present is a considerable build-up of positive charge, delocalised along the bond bridging the anomeric carbon and endocyclic oxygen.

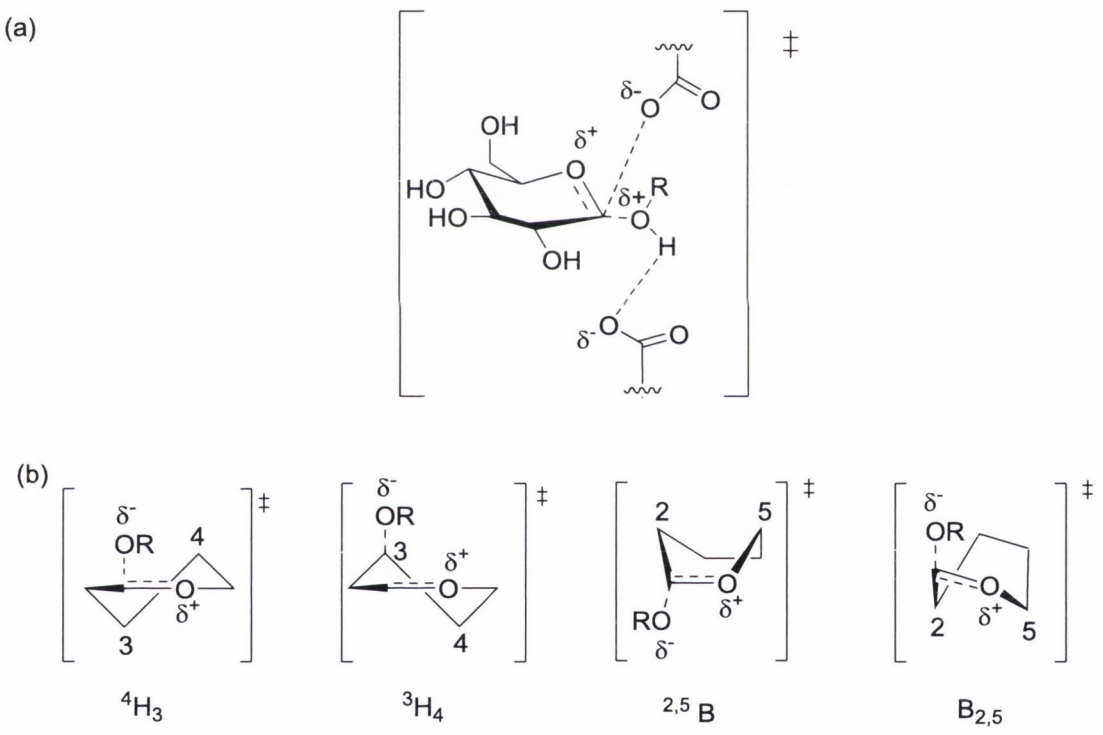


Figure 17

(a) The transition state of inverting glycosidase hydrolysis

(b) Possible conformations of the oxocarbenium transition state in glycosidase-mediated hydrolysis

Contrary to the general assumption that all substrates of glycosidases adopt a half chair conformation in the transition state, recent crystallographic studies have shown this

hypothesis is not correct for all cases. For example while α-sialidases appear to hydrolyse substrates in a half chair conformation the 11 xylanases are believed to necessitate a $^{2,5}B$ transition state conformation in the substrate.[117] This, and other examples, illustrate the continued need for further mechanistic and structural studies on glycosidases in the persuit of efficient glycosidase inhibitor design.

1.4.2 What makes a good glycosidase inhibitor?

In the 1940s it was proposed by Pauling that enzyme inhibitors capable of mimicking the transition state structure provide potent enzyme inhibition as the transition state is the point of greatest stabilisation by the enzyme.[118] Correspondingly, much effort has been focused on the preparation of transition state analogues. The design of such analogues generally involves the incorporation of one or more of the features of the transition state such as charge and/or geometry.

At physiological pH the ring nitrogen of azasugars becomes protonated and the structure thus resembles the transition state of glucosidases by virtue of the positive charge.[119] Thiosugars on the other hand are referred to as substrate inhibitors owing to the inability of the ring sulfur to become protonated.[120] This results in thiosugars commonly being less potent than azasugars but also less toxic. However, excellent inhibitions have been noted for some thiosugars.[121-125] The preparation of sulfonium salts which contain a permanent positive charge on the endocyclic thiol moiety has been the subject of recent research.[126-130] Imino- and thiosugar compounds are typically found in the relaxed chair conformation in solution however distortion may occur upon enzyme binding.[107,116] A further approach to achieve transition state mimics is to distort the conformation of the ring in order to mimic the geometry of the transition state. Compounds that possess flattened pyranose rings have been shown to inhibit glycosidases, **28**, which exhibits a cyclitol ring is a classic example.[14]

1.4.2.1 Structure function characteristics of glycosidase inhibitors

(i) Sulfur analogues

Salicinol **8**, and kotalanol **9**, as previously mentioned, are naturally occurring glycosidase inhibitors. Both include a trivalent, positively charged sulfur atom in place of the endocyclic oxygen, thereby mimicking the positive charge associated with the transition state oxocarbenium ion of glycosidases.[127,131,132] Higher analogues of salicinol have been synthesised by the group of Mario Pinto,[126,127,131,132] among others,[131] who have ascertained that the sulphate group at C-3 is imperative for good enzymatic affinity, as analogues with the sulphate group absent or present on another position exhibited higher K_i values against human maltase glycoamylase.[133] Change in the configuration of the heteroatom was found to decrease the potency,[134] of the corresponding inhibitor alongside increasing the ring size of the sulphonium salt to a six membered system.[135] The length of the polyhydroxylated chain was also modified and tested for inhibitory activity, in addition to introducing selenium as an endocyclic heteroatom.[130] This has led to the preparation of the most powerful zwitterionic glucosidase inhibitors to date **46** and **47** both with K_i values of 0.1μ M.[130] It must be appreciated that the strucutures of **8** and **9** were elucidated recently in 1996 and 1998 respectively, 30 years after the discovery of nojirimycins as a glycosidase inhibitor. Therefore the preparation of salicinol analogues and the study of their structure activity relationships is still ongoing.

Prior to the discovery of **8** and **9** rationally designed sulfonium ion glycosidase inhibitors have been synthesised. Siriwardena *et al.*[136] have described the preparation of a sulfonium salt mimic of swainsonine **48**. It's inhibition of α-mannosidases was slightly lower than that of swainsonine but comparable to inhibition by **13**.[136] As previously eluded to, thiosugars lacking a trivalent positive charge on the ring heteroatom have been classified as substrate inhibitors rather than transition state analogues.[120] These analogues, therefore often exhibit less potent biological activity than the corresponding azasugar analogues. Distortion of the ring conformation, in order to mimic the geometry of the transition state, was a rational approach to inhibitor design pursued by Vasella and co-workers.[120] However the thiolactone oxime **49**, prepared was found to be 1000 times less potent against β-glucosidase than the corresponding aza analogues, thus highlighting the fundamental importance of the presence of a positively charged heteroatom. Nevertheless

aminoglycans such as **28** display some of the highest reported glycosidase inhibition constants.[14] Thus, in this context, Andrews *et al.*[137] have synthesised novel heteroanalogues of methyl maltoside **50**, containing sulfur as the heteroatom in the ring of the non-reducing sugar and nitrogen in the interglycosidic linkage. The compound was found to be an inhibitor of maltose binding by glucoamylase G2 with a K_i value of 4+/-0.3 μM, making this compound a stronger inhibitor of glucoamylase than 1-DNJ (96 μM).[137]

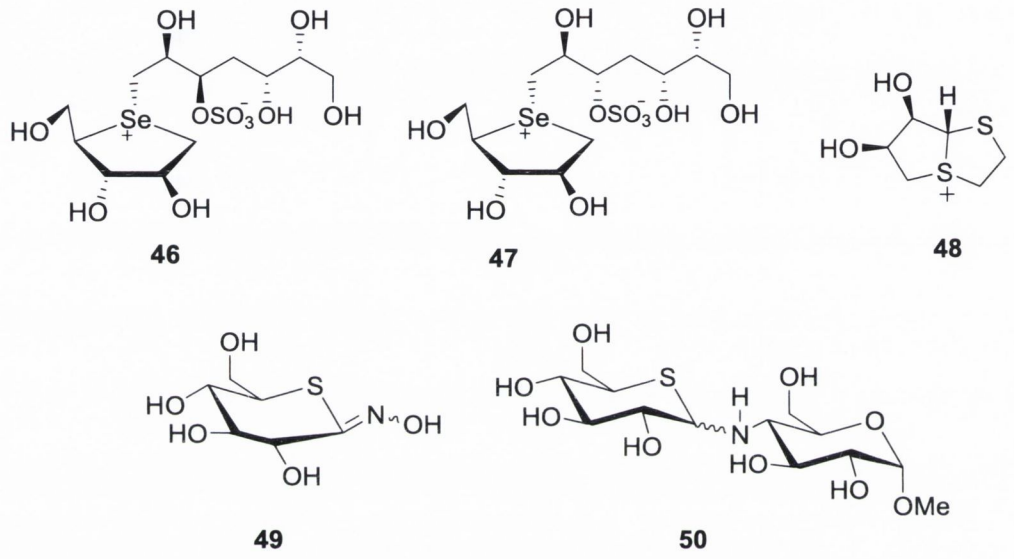
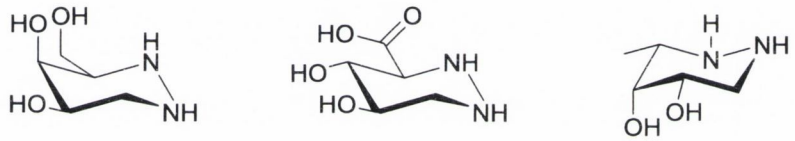


Figure 18 Rationally designed thiosugar analogues

(ii) Nitrogen analogues

Since the discovery of nojirimycin as a potent inhibitor of various glycosidases, many structural analogues have been synthesised with the aim of improving the inhibitory activity of naturally occurring glycosidase inhibitors. The work of the Bols group in the 1990s[138-140] and the Ichikawa group[141-143] led to the synthesis of isofagomine **34**, a synthetic iminosugar with a nitrogen in place of the anomeric carbon. The therapeutic activity of isofagomine and related analogues as active inhibitors of glycogen phosphorylase was alluded to in Section 1.3.2. The nitrogen can accept a positive charge at physiological pH and thus mimic the transition state of glycosidases. This family of iminosugar compounds tends to inhibit β-glycosidases more potently than α-glycosidases, this is presumed to be due to the accumulation of charge at different positions in the

transition state for the different enzymes. Modifications of **34** ensued to include a hydroxyl group at C2 and the resultant hemiaminal, noeuromycin **36**, was found to strongly inhibit both α- and β-glucosidases.[144] Mutarotation at C-2 allows the compound to bind proteins in both the *manno* and *gluco* forms however similarily to nojirimycin, decomposition occurs at neutral pH. Azofagomine **35**, an iminosugar incorporating two amino groups was next considered as a potentially superior transition state inhibitor.[145-147] Either nitrogen may become protonated, and as such this molecule was expected to better reflect the charge distribution in the transition state oxocarbenium ion. A wide range of stereoisomeric isofagomines have been prepared mimicking D-galacotose **51**, D-glucoronic acid **52,** and D-fucose **53**, among others. All of which are extremely potent inhibitors of both α- and β- glycosidases with K_i values in the low micromolar or nanomolar range.[147,148]



51 **52** **53**

Figure 19 Rationally designed iminosugar analogues

Further work on the rational design of transition state inhibitors has focused on designing inhibitors that incorporate the positive charge and flattened chair conformation of the transition state, therefore more closely replicating the desired structure. Amidine inhibitors such as **54** were synthesised in the Ganem group in the 1990s.[149] Subsequently, the amidrazone and the lactam oxime **55** and **56** were prepared and found to inhibit both α- and β-glycosidases.[150,151] Conjugation of the carbon nitrogen double bond of the hydroximolactam group with the endocyclic oxygen causes a distortion in the ring favouring the formation of a half chair conformation.[152] In this context glycotetrazole and imidazole derived compounds **57** and **58** were prepared which showed good β-glucosidase inhibition.[153,154] It was noted that if a triazole moiety is fused to the pseudo glycoside ring (i.e if the nitrogen atom adjacent to the anomeric carbon was replaced with a carbon) very weak inhibition ensues. This supports the hypothesis that the heteroatom attached to the anomeric carbon makes an important contribution to inhibitory activity via interaction with the carboxylate residues in the active site of the enzyme.[155]

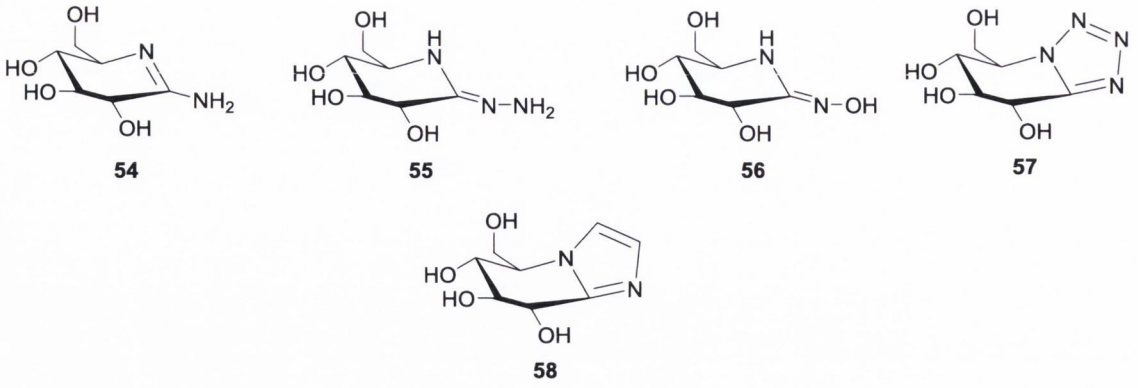


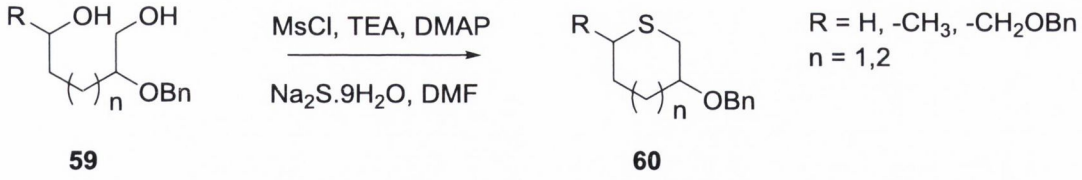
Figure 20 Rationally designed iminosugar structures incorporating flattened chair conformations

1.5 Synthetic routes to glycosidase inhibitors

1.5.1 Synthetic routes to thiosugar synthesis

A large number of efficient strategies exist for the synthesis of thiosugars. It is beyond the scope of this thesis to describe all of these in detail. Instead, a few recent and significant examples of thiosugar preparations will be discussed.

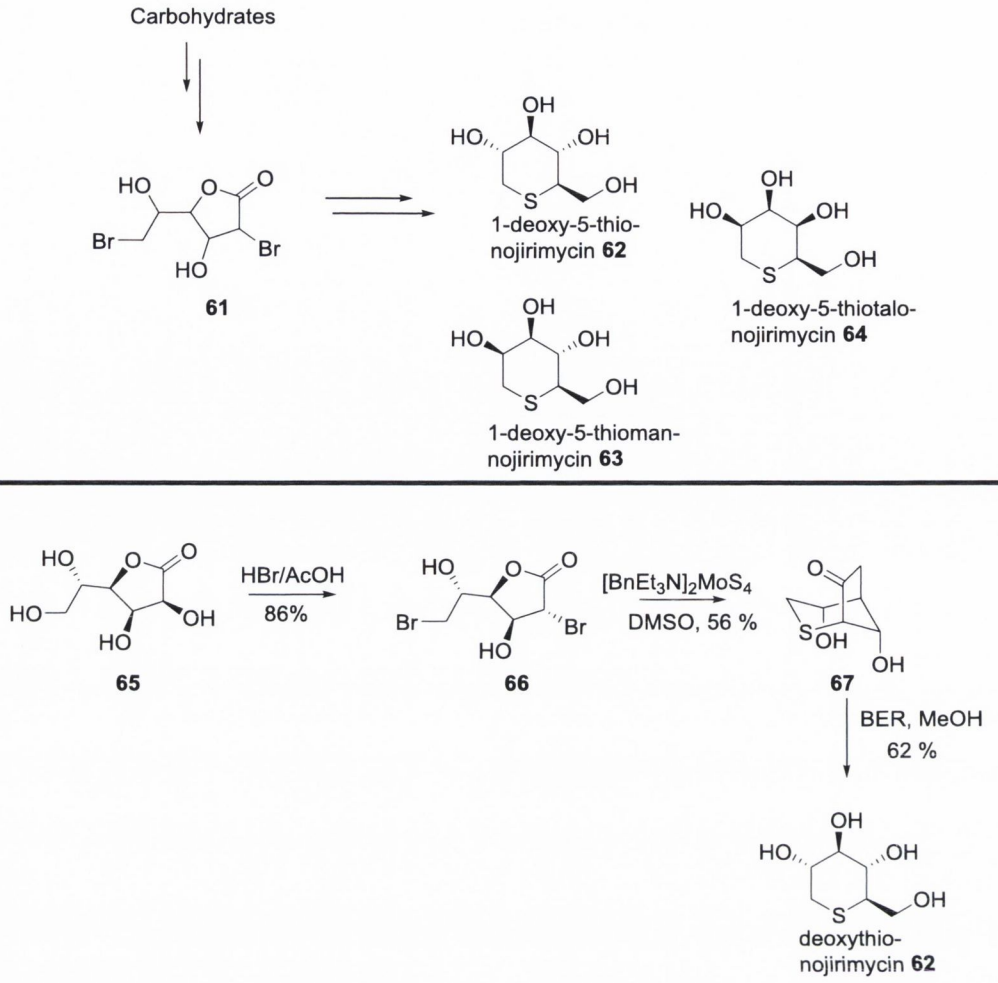
Very recently, Zhang *et al.*[156] described a synthesis of polyoxygenated tetrahydrothiopyranes and thiopines. From partially protected alditols, the preparation of the corresponding *xylo*, *ribo*, *manno*, *gluco*, *galacto*, and *fuco* tetrahydrothiopyrans proceeded in 'one pot' and with excellent yield (80-95 %). The requisite alditol starting material was prepared according to literature procedures. Thereafter, activation of the two hydroxyl groups by mesylation, followed by treatment with $Na_2S.9H_2O$ in DMF, afforded the desired compound (Scheme 1). While this procedure could be efficiently applied to the preparation of polyoxygenated thiosugars on a large scale, a limitation is the preparation of the requisite starting materials, which require a number of protecting group manipulations.



59 **60**

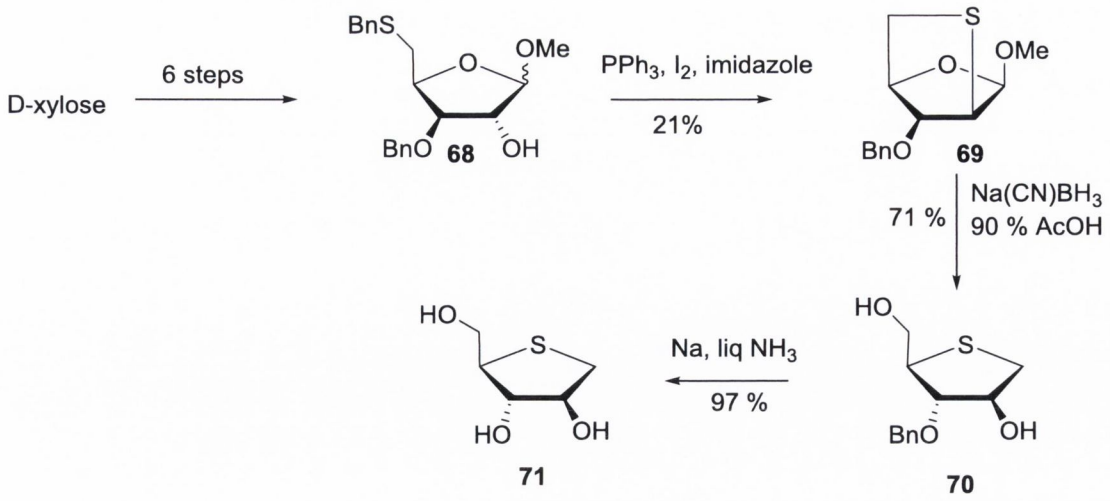
Scheme 1 Thiosugar synthesis designed by Zhang *et al.*[156]

Gunasundari *et al.*[157] have described an enantioselective and protecting group free strategy for the synthesis of 1-Deoxythionojirimycin **62**, 1-Deoxythiomannonojirimycin **63** and 1-Deoxy-5-thiotalonojirimycin **64**. The synthesis of **62** began from commercially available L-gluconic acid γ lactone **65**. Bromination with HBr in acetic acid yielded the dibromo species **66** which subsequently reacted with benzyltriethylammonium tetrathiomolybdate as a sulfur transfer agent to afford the desired deoxythiosugar in good yield. A similar synthesis of **63** and **64** was carried out starting from D-mannose and D-ribose respectively. In this case benzyltriethylammonium tetrathiomolybdate functions as an efficient sulfur transfer reagent. Further methods for the introduction of a thiol moiety in the synthesis of thiosugars have involved nucleophilic displacement of a good leaving group with different sources of sulfur including Na_2S,[158-160] KSAc,[161,162] NaSH,[163] NH_2CS,[120] and AcSH (Scheme 2).[164,165]



Scheme 2 (a) Route to deoxythionojirimycin, deoxythiomannonojirimycin and deoxythiotalonojirimycin **(b)** Synthesis of deoxythionojirimycin

Synthesis of the thioarabitol ring structure of salicinol and kotalanol was reported by Yuasa *et al.*[166] in 1994. From D-xylose various protecting group manipulations were carried out to yield methyl-3,5-thio-α- and -β-xylofuranosides. Both anomers were reacted under iodination conditions to implement an intramolecular cyclisation between 5-S and C-2. Simultaneous hydrolysis and reduction with $NaBH_3CN$ in aqueous acetic acid afforded the benzylated thiosugar analogue which was deprotected *via* Birch reduction. This synthetic route has been used by the Pinto group to prepare the thioarabitol ring structure in the synthesis of salicinol, kotalanol and related structural analogues (Scheme 3). [126,127,131,132]

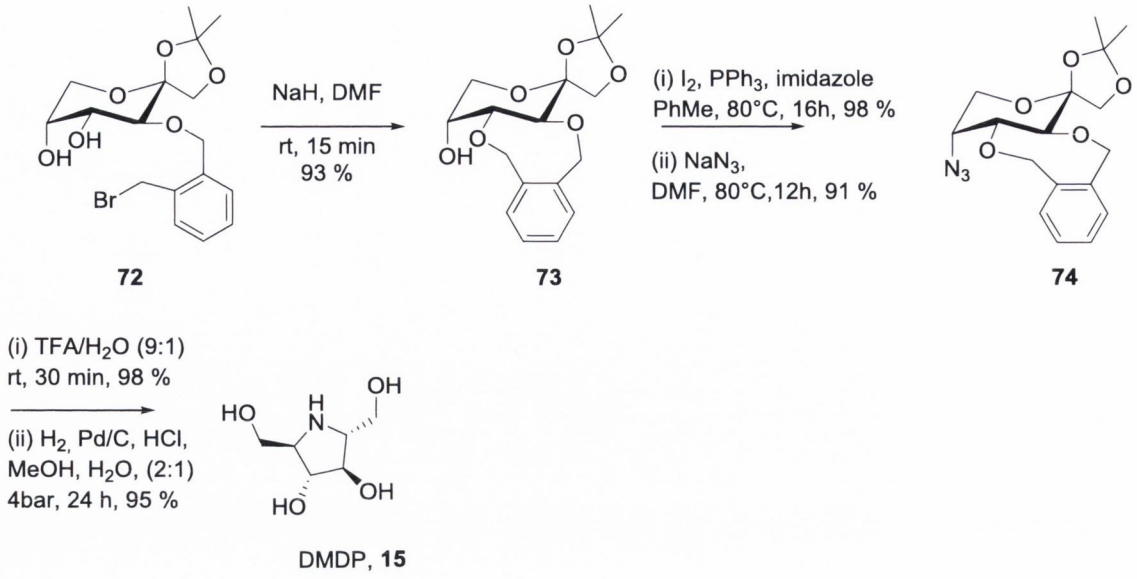


Scheme 3 Synthesis of thioarabitol ring structure of salicinol and kotalanol

1.5.2 Synthetic routes to azasugar synthesis

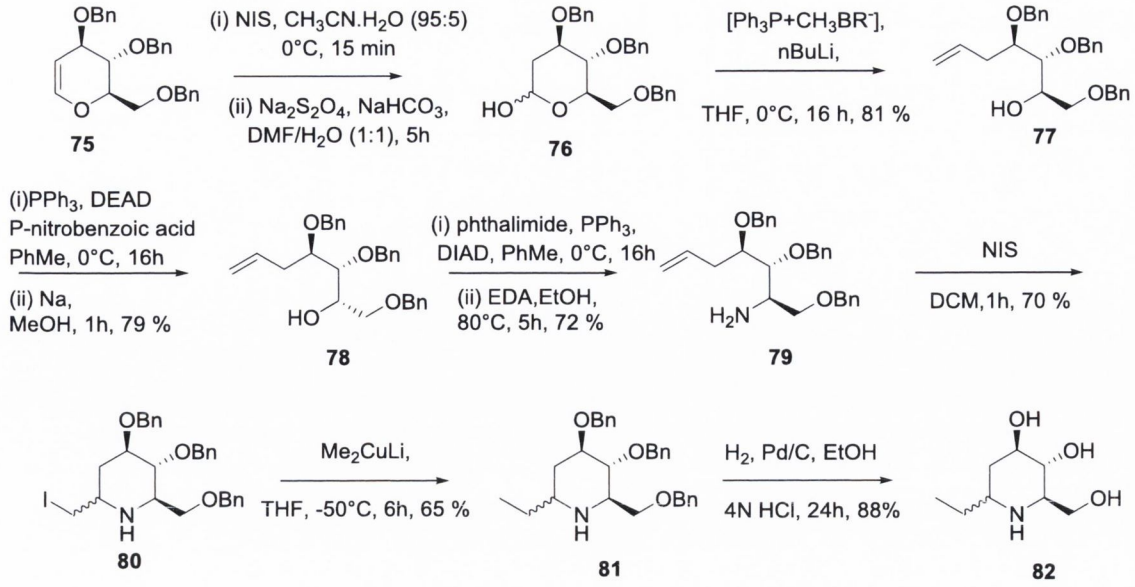
Given the enormous therapeutic potential of azasugars, the development of efficient synthetic methods for their preparation has become a key research topic within the carbohydrate chemistry community, with a large number of syntheses described. In this section three commonly employed techniques will be discussed, including reductive amination, Wittig and Horner-Wadsworth Emmons reactions, and protecting group free strategies.

Reductive amination has been used in the synthesis of natural pyrrolidine DMDP **15**. Fernandez and co-workers[167] developed an effective intramolecular benzyl protection/cyclisation reaction using the D-fructose derived 3-*O*-(2-bromomethyl)benzyl ether **72** to form alcohol **73**, which possesses an eight membered ring tethered between the C-3 and C-4 hydroxyl groups. The 5-OH group underwent a substitution to form azide **74**. Acidic hydrolysis removed the acetonide protecting group following which catalytic hydrogenation effected a one-pot reductive amination-cyclisation to yield **15** in 93 % yield (Scheme 4).



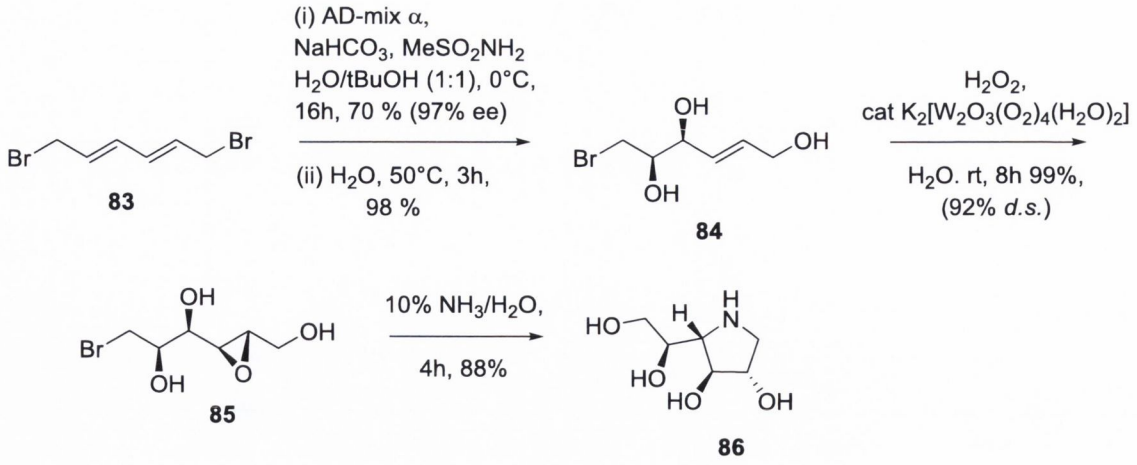
Scheme 4 Synthesis of DMDP **15**

Wittig and Horner-Wadsworth-Emmons (HWE) reactions have been used by several groups for the preparation of azasugars. As well as being successfully applied to the synthesis of piperidine and pyrrolidines, this methodology is also a versatile means by which to synthesise a variety of bicyclic iminosugars such as pyrrolizidines and indolizidines. In general the olefination reaction is used to extend a suitably protected pyrrolidine with an alkyl chain that is subsequently used for the generation of the second ring. Goujon *et al.*[168] have described an intramolecular electrophilic iodination of a terminal bond, followed by nucleophilic attack of an amine, to synthesise various α-1-*C*-substituted derivatives of fagomine as illustrated in Scheme 5. 3,4,6-Tri-*O*-benzyl-D-glucal **75** was treated with NIS. Following this the iodide was removed by treatment with sodium dithionite. The resultant 2-deoxy sugar **76** was converted into the D-*xylo* heptenitol **77** by subsequent Wittig methlylenation. Two consecutive mitsunobu reactions were carried out in order to install a phthalamido group with retention of configuration. Subsequent hydrolysis to the free amine **79** and an iodination/intramolecular cyclisation reaction furnished the iodo substitued azasugar **80**. Treatment with Me_2CuLi followed by hydrogenolysis of the benzyl groups furnished α-1-C-ethyl fagomine **82** (Scheme 5).



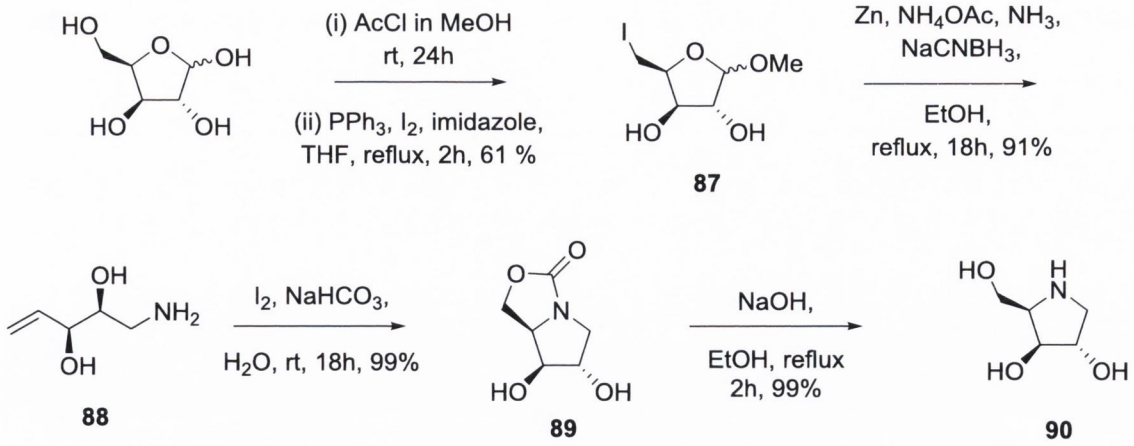
Scheme 5 Synthesis of α-1-C ethyl fagomine **82**

In recent years there has been a growth in environmental concern and awareness which has seen a development of more efficient and less hazardous chemical processes. In the synthesis of azasugars several groups have been exploring methodologies that allow for their synthesis without the need for protecting group. Two recent and notable examples include the work of Lindstöm and Dangerfield.[170] Lindström and co-workers completed an extremely efficient synthesis of a pyrrolidine in water starting from 1,6 dibromodiene **83**, itself prepared in one step from cost effective 1,5 hexadiene-3,4 diol. A modified Sharpless asymmetric dihydroxylation was carried out on **83**. The diol product was then selectively hydrolysed at the allylic position to afford triol **84** in 98 % yield. Epoxidation through the use of a dinuclear perxotungstate catalyst gave the requisite epoxide **85** in excellent yield (99 %) and diastereoselectivity (92% d.s). Nucleophilic displacement of the bromide in **85** by ammonia led to spontaneous intramolecular ring-opening of the epoxide to afford iminosugar **86** in an 88% yield. The total yield for this synthesis thus reaching an impressive 60% (Scheme 6).[169]



Scheme 6 Protecting group free synthesis of iminsugar **86**

Dangerfield *et al.*[170] have developed a protecting group free synthesis of pyrrolidines involving two novel reaction methodologies, the first being a zinc mediated ring opening reaction with *in-situ* reductive amination. The second novel reaction methodology involves the stereoselective formation of cyclic carbamates from alkenylamines. D-xylose was converted to its corresponding methyl iodoglycoside **87**. The zinc-mediated, ring opening reaction initially reported by Vasella was then utilised to form the glycosyl aldehyde upon which reductive amination ensued to afford **88**. Alkenylamine **88** was then treated with $NaHCO_3$ and iodine to form carbamate **89**. **89** was hydrolysed to give D-*xylo* pyrrolidine in excellent 97% yield. The full synthetic route could be carried out in an overall 57% over five synthetic steps (Scheme 7).



Scheme 7 Protecting group free synthesis of D-*xylo* pyrrolidine **90**

1.5.3 Remarks on developed routes to thiosugars and iminosugars

A vast amount of synthetic effort has yielded numerous elegant and efficient routes to both thiosguars and azasugars. Given the increasing understanding of the biological capabilities of glycosidase inhibitors it is imperative that continued improvements in their synthesis are made in order to expedite access to both novel and known therapeutic agents. The breadth of developed syntheses has become truly diverse however, a radical cyclisation involving a radical heteroatom has never been pursued for thio- or iminosugar preparation. It was anticipated that through this work a novel, general and efficient free radical based methodology could be established for the synthesis of potential glycosidase inhibitors. The following sections will discuss the advantages of radical chemistry in complex synthesis.

1.6 Radicals in synthesis

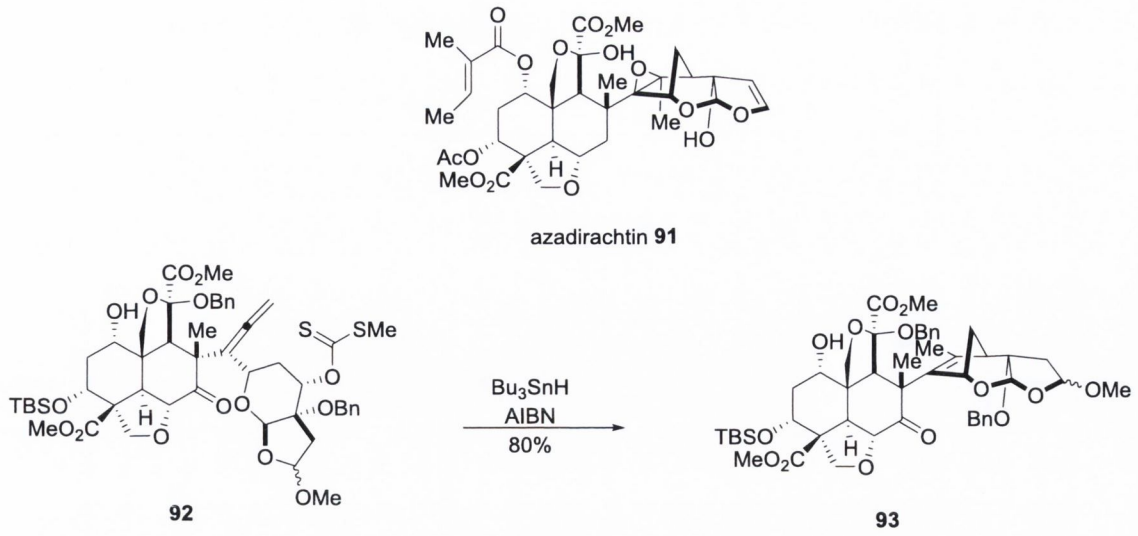
In recent years radical chemistry has developed into one of the most fundamental tools in organic synthesis. While once considered 'too reactive' for practical synthetic use, radicals have proven to be frequently more selective and predictable than ionic reactions and thus have become central to the development of new methodologies. As an extremely versatile strategy, radical processes hold many advantages over traditional ionic synthesis including tolerance of a wide range of protecting groups and mild reaction conditions.[171] Radical reactions are frequently carried out at neutral pH.[171] Radical cascades are capable

of constructing complex molecular architectures in a single step, rendering radical processes ideal for incorporation in natural product total synthesis.[172,173] Radical chemistry is also amenable to 'green chemistry', current research is moving away from tin-based methodologies and towards the use of environmentally benign reagents and aqueous solvents.[171]

Radical cyclisations are the most abundant category of radical transformation owing to the high degree of regio-, chemo- and stereoselectivity they infer. Radical reactions are also susceptible to the formation of 'unusual' ring sizes.[174] This could be due to their reactive nature, thus overcoming unfavourable entropic factors. Equally, radical trapping via a reagent or cascade process can prevent the newly formed ring from opening, as such, radical cyclisations have found much synthetic utility in natural product synthesis.

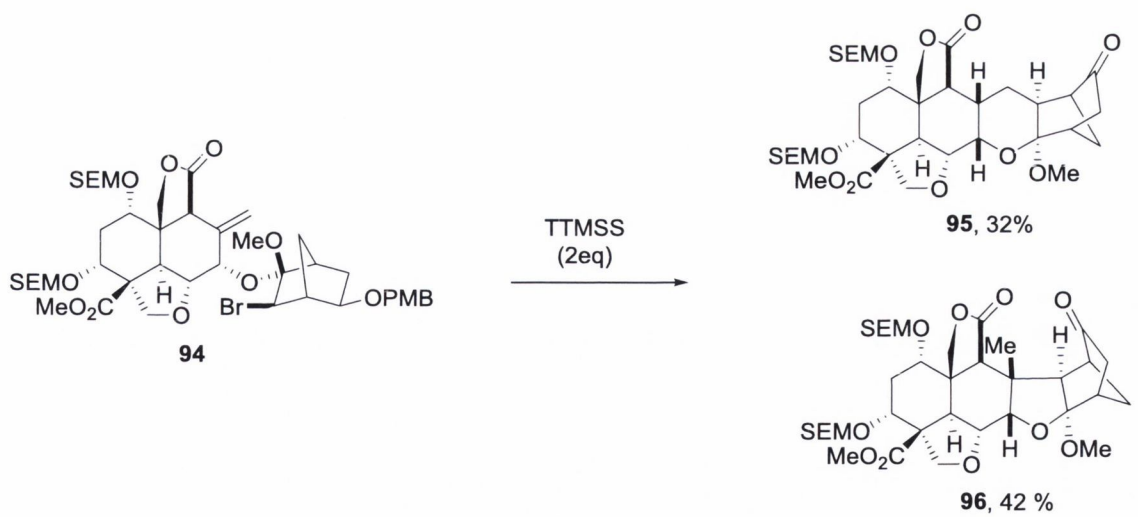
1.6.1 Radical chemistry applied to natural product chemistry

Azadirachtin, a naturally occurring highly oxidised tetranortriterpenoid contains 16 stereocentres, 7 of which are tetrasubstituted. As a result of its complex molecular structure and synthetic difficulties encountered in its preparation, the first synthesis of its structure was not published for over 22 years after the compound's discovery. The synthesis of azadirachtin was successfully achieved by the groups of Ley[175,176] and Nikolaou,[177-181] both of whom incorporated radical cyclisations as key steps. The first reported synthesis of azadirachtin, provided by the Ley group[175,176] involved a 5-*exo* cyclisation of xanthate **92** to give alkene **93** in an excellent 80% yield. The authors rationale for the high degree of stereoselectivity lies with the highly congested nature of the tertiary radical which prevents the approach of the hydrogen source. Thus, the *endo*-alkene is the favoured product as the more accessible, albeit thermodynamically disfavoured, primary radical accepts the hydrogen source. Following this landmark synthesis, Ley significantly quoted 'I would rank this as being one of the very toughest syntheses so far reported' thus illuminating the capability and reliability of radical chemistry to tackle the synthesis of the most complicated of molecular structures.



Scheme 8 5-*exo*-trig radical cyclisation utilized in Ley's synthesis of azasdirachtin **91**

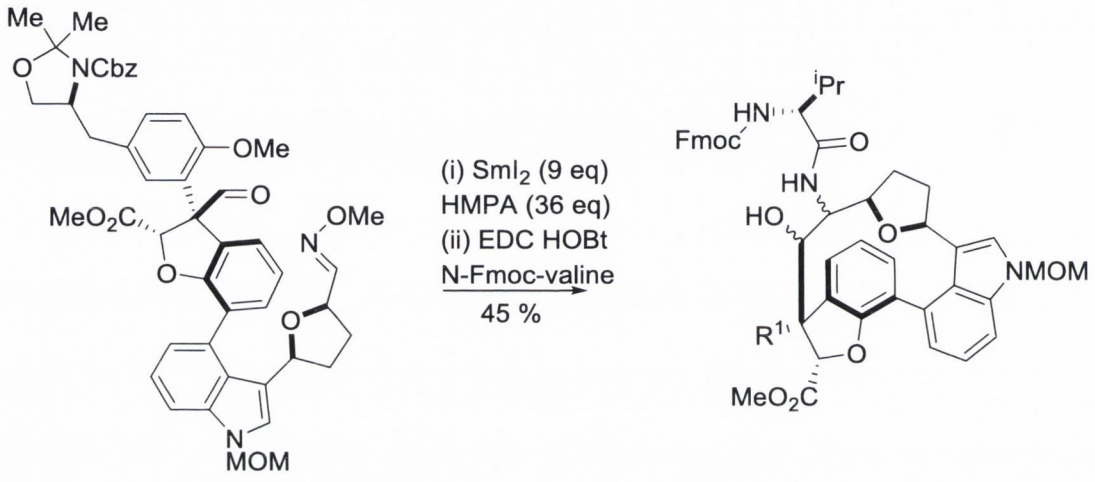
Nicolaou's approach to the synthesis of azadirachtin[177-181] involved a 5-*exo*-trig radical cyclisation in order to form the problematic C-8-C-14 bond (Scheme 9). While the radical reaction proceeded to give the desired product, the yield was a diminished 42% as a result of a competing 6-*endo*-trig cyclisation. In an analogues system with the absence of a THF ring, the desired 5-*exo*-trig cyclisation proceeded exclusively.



Scheme 9 5-*exo*-trig radical cyclisaiton in Nicalou's synthesis of azadirachtin **91**

Nikolaou has also employed radical chemistry for his synthesis of the marine natural product diazonamide A.[182] This reaction constituted one of the first examples of a

heteropinacol reaction leading to the formation of a macrocyclic ring. Treatment of **97** with an excess of samarium II iodide in the presence of HMPA resulted in reduction of aldehyde and oxime ether to give a diradical intermediate that underwent direct C-C bond formation. Excess samarium (II) iodide complex was also responsible for the cleavage of the N-O bond resulting in an amino alcohol that underwent peptide formation *in situ* (Scheme 10).



97 **98**

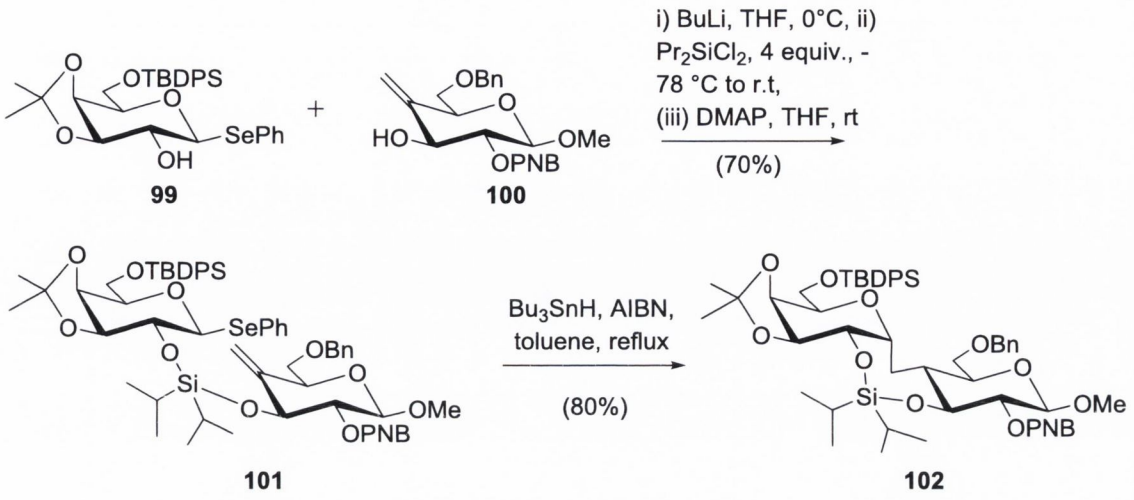
Scheme 10 Radical cyclisation in the synthesis of diazonamide A

1.6.2 Applications of free radicals in carbohydrate chemistry

In spite of its many advantages, free radical chemistry has seldom been employed in carbohydrate chemistry, notable exceptions including *C*-glycoside formation,[183] the formation of deoxy sugars,[184] and glycal formation.[185-187]

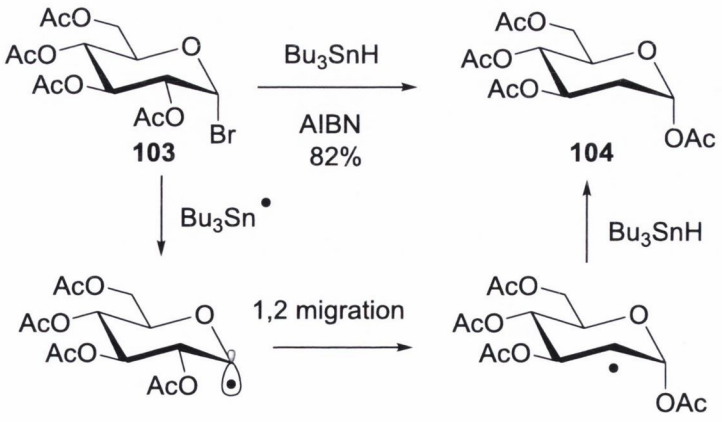
C-glycosides are sugar moieties in which the interglycosidic oxygen has been replaced by a methylene group. A number of *C*-glycosides have been isolated from natural sources and combined with their biological activities, their increased metabolic stability relative to *O*-glycosides makes this class of carbohydrate an attractive synthetic target.[4] A classic example of *C*-glycoside formation is the work by Sinäy and coworkers,[183] who reported the use of an 8- or 9-*endo*-trig radical cyclisation from two monosaccharides connected through a silicon tether for the formation of *C*-glycosides (Scheme 11). The radical reaction proceeds with significant selectivity. It was proposed that the radical adopts a

boat conformation thereby α-*C*-galactosylation is the sole reaction for geometrical reasons.



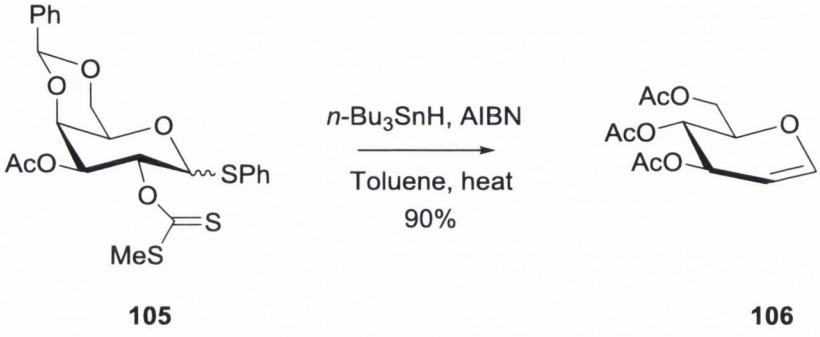
Scheme 11 Preparation of C-glycosides via radical cyclisation

2-deoxy sugars are important targets of natural product synthesis, however traditional methods for their formation are laborious, requiring glycal formation followed by solvomercuration and subsequent demercuration. Giese *et al.*[188] successfully applied the use of a radical migration to a glycosyl halide to directly convert it to a 2- deoxy sugar. The glycosyl radical is generated by halogen abstraction, the acyloxy group irreversibly migrates to the anomeric position and the rearranged radical is trapped thereafter by Bu_3SnH. While careful control of tin-hydride concentration is required to give good yields, this method has facilitated a general approach to 2-deoxy sugars (Scheme 12).



Scheme 12 Preparation of 2-deoxy sugars via radical halogen abstraction

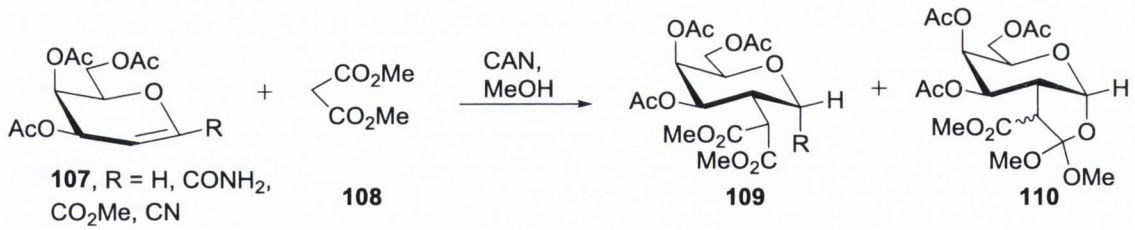
Barton-McCombie dehydroxylation conditions have also been successfully applied to the synthesis of deoxy sugars. Barton and coworkers have applied their successful synthetic methodology to radical chain deoxygenation, dehalogenation and deamination reactions.[185] Radical elimination has been utilised in carbohydrate chemistry to facilitate the synthesis of glycals. As carbon centred radicals are normally not prone to β-elimination, the process proceeds efficiently solely in the presence of weak β-bonds. Sinäy *et al.*[186] reported radical elimation from xanthate **105** to give glycal **106** in an excellent 90% yield (Scheme 13).



105 **106**

Scheme 13 Radical elimination for glycal formation

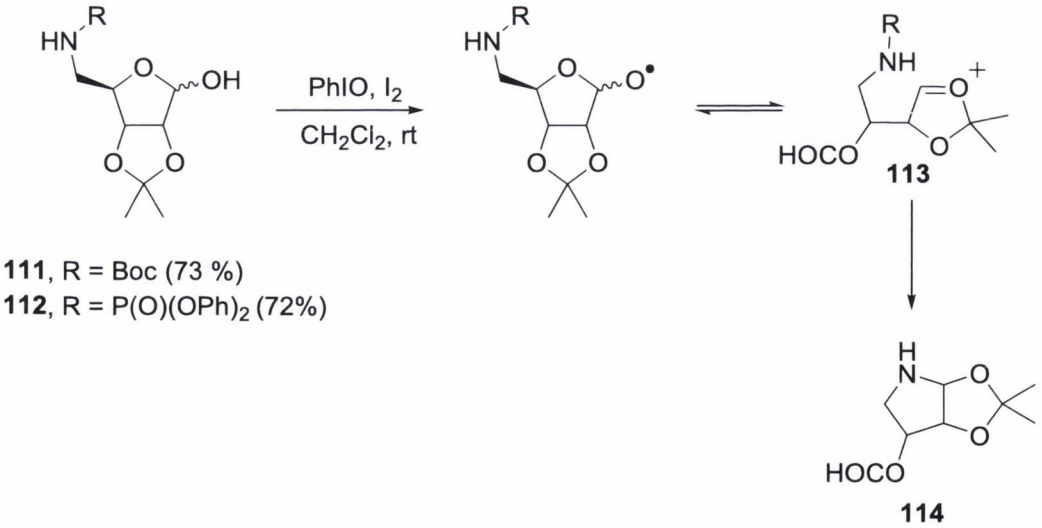
In this context, glycals can be further functionalised by radical methods, Linker *et al.*[189] have described ceric (IV) ammonium nitrate (CAN) mediated radical addition to afford methyl glycosides **109** or ortho esters **110** as the major product (Scheme 14). The product distribution depended strongly on the substitution pattern at the 1-position. Methyl glycosides are formed exclusively in the presence of a carboxamido group at C-1 or in the presence of unsubstituted glycals. However an ester or nitrile group yield ortho esters as predominant products. It has been postulated that the oxidation potential of the anomeric radical is directly correlated to the product distribution.



Scheme 14 Radical addition to glycals

1.6.2.1 Radical chemistry applied to the synthesis of glycosidase inhibitors

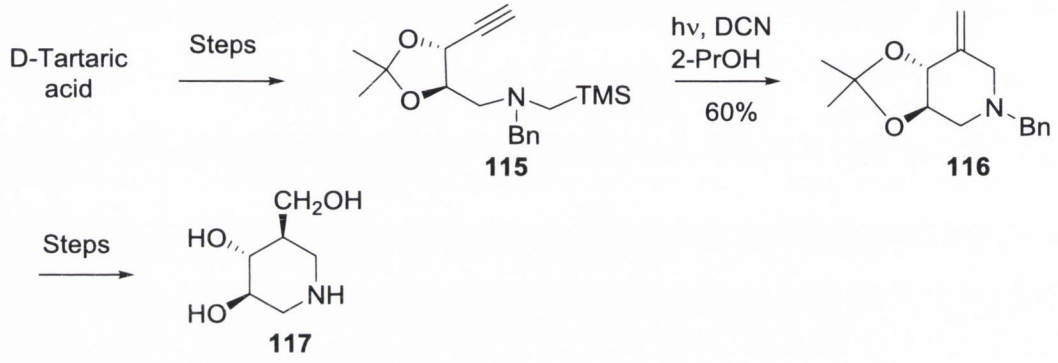
There are no examples in the literature of free radical chemistry being applied to the synthesis of thiosugars, however a small number of literature examples exist of free radical chemistry being applied to the synthesis of azasugars. Francisco *et al.*[190] reported the β-fragmentation of an anomeric alkoxy radical, the resultant carbon centred radical was oxidised to an oxonium ion suitable for intramolecular cyclisation by an amide to furnish the azasugar in good yield (Scheme 15). While the radical cyclisation proceeded in good yield the methodology involved the preparation of tedious starting materials as the protected amide functionality must be installed at the C-6 position prior to cyclisation. Complex iodo by-products were also formed through the use of hypervalent iodine reagents as initiators.



111, R = Boc (73 %)
112, R = P(O)(OPh)2 (72%)

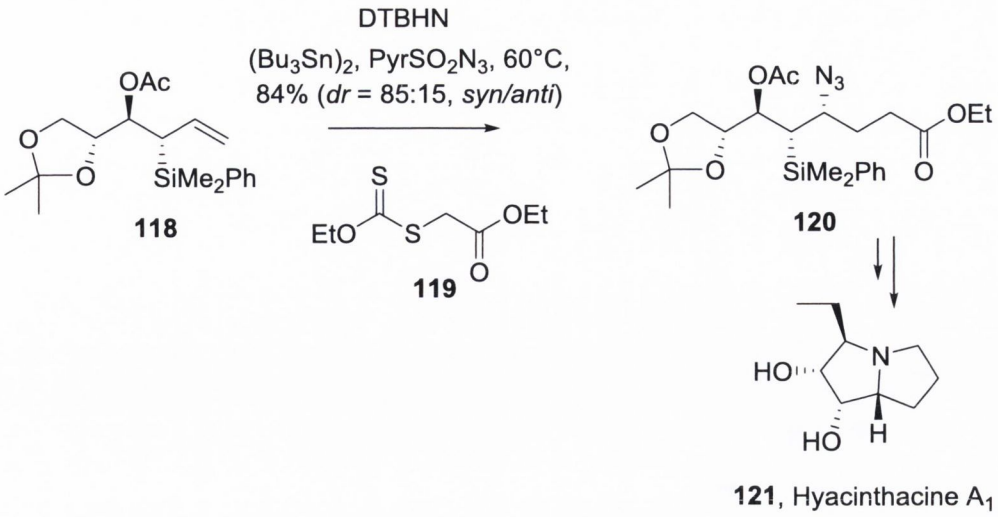
Scheme 15 Azasugar synthesis via β-fragmentation of an anomeric alkoxy radical

Pandey and co-workers[191] reported the synthesis of azasugars via intramolecular cyclisation of an α-trimethylsilylmethylamine radical cation, generated by photoinduced electron transfer (PET) onto an acetylene functionality (Scheme 16). The resultant alkene was converted to a secondary hydroxyl and the ensuing radical cyclisation from the carbon atom alpha to the nitrogen atom onto the terminal acetylene was efficient in furnishing the acetylene core **116**. Nevertheless, the synthesis of the requisite starting material posed a significant synthetic challenge and the use of toxic naphthalene resulted in a complex workup and limits applications in pharmaceutical production and biological testing.



Scheme 16 Azasugar synthesis via radical cyclisation

The synthesis of several bicyclic iminosugar structures has been achieved through the use of radical reactions. Chabaud *et al.*[192] have described an elegant synthesis of hyacinthacine A_1 **120** and its 3-epimer through the stereocontrolled carboazidation of chiral allylsilane **118** with xanthate **119**. C-Si bond oxidation and reduction of the azide, with ring closure, completed the total synthesis and established the absolute configuration of hyacinthacine A_1 **121** (Scheme 17). Chen *et al.*[193] applied radical cyclisation of acylsilanes in the synthesis of lentiginosine **45** and related indozoline alkaloids.



Scheme 17 Synthesis of Hyacinthacine A_1 via radical carboazidation

1.6.3 Thiol-ene click

In 2001 Sharpless and coworkers[194] characterised a novel ligation concept known as click chemistry. The umbrella of click chemistry includes several acclaimed reactions that encompass the characteristics of being;

1. High yielding with or without minimal by-products that are easily removed without chromatography.
2. Excellent regio- and stereospecificity
3. Compatibility with aqueous and aerobic conditions
4. Amenability to multiple reaction substrates

Processes that adhere to most or all of the above criteria include copper (I) catalysed azide-alkyne cyloaddition, hetero Diels-Alder reactions, nucleophilic ring opening of strained heterolytic electrophiles, synthesis of oxime ethers and hydrazones from carbonyls, epoxidation, dihydroxylation and aziridination. Since its establishment in synthetic chemistry, this powerful concept has been applied to the synthesis of biomedical libraries, dendrimer preparations, derivatization of cellular surfaces and cross linking of adhesives for metal substrates.[194-197] Owing to the tremendous applicability of click reactions extensive literature reports of its use continues to flourish ($\geq$1000 papers), thus highlighting the demand for additional click reaction processes.

At the beginning of the 20th century Posner described the hydrothiolation of alkenes,[198] its free-radical chain mechanism was later detailed by Kharasch and co-workers.[199] This versatile 'click' process, currently called 'thiol-ene coupling' (TEC) has undergone a renaissance in recent years and has found new applications in synthetic methodologies, biofunctionalisations and surface and polymer modifications.[200-203] The reaction is triggered by the formation of a thiyl radical, produced via light irradiation and/or the presence of a radical initiator. The thiyl radical adds across the 'ene' double bond in an anti-Markovnikov fashion to give an alkyl radical that via abstraction of a hydrogen radical from a further thiol molecule leads to the thioether product and a new thiyl radical, thus propagating the radical chain. (Figure 20) This reaction is separated from the Michael addition of thiols to electron deficient carbon-carbon bonds.

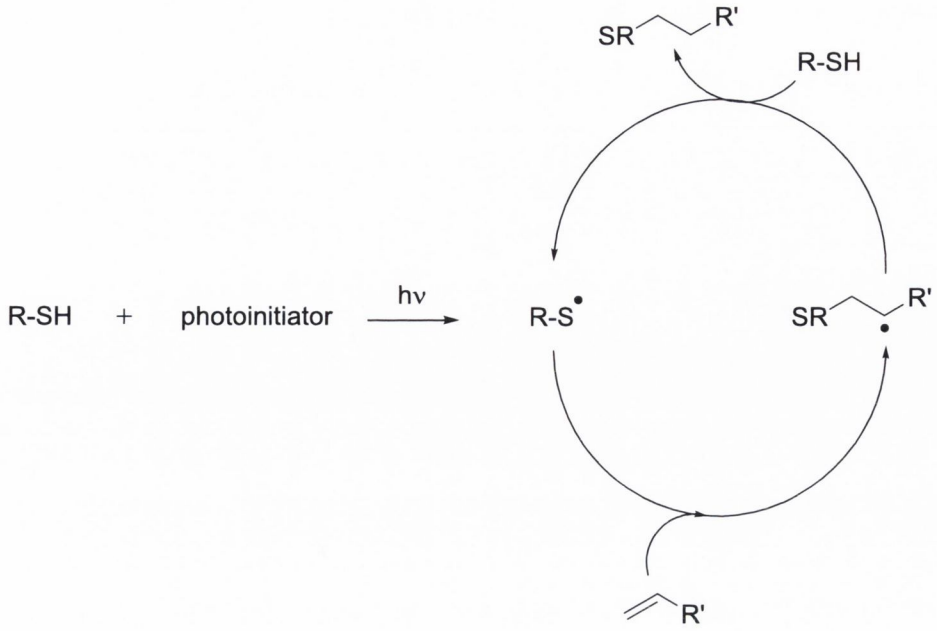
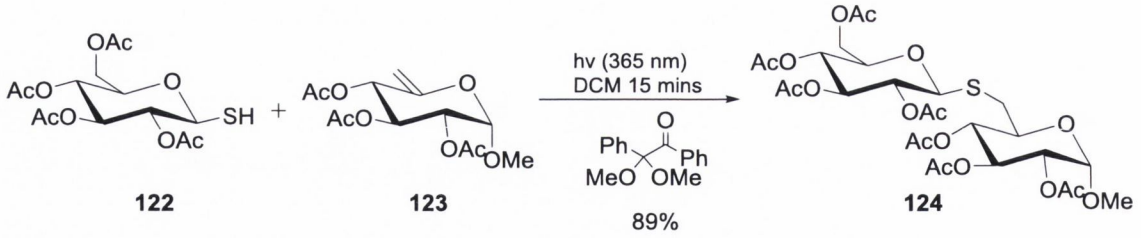


Figure 21 Thiol-ene click catalytic cycle

The click status of this reaction is affirmed by its high efficiency, compatibility with a wide array of functional groups and it's adaptability to aqueous conditions. In addition TEC reactions result in the formation of a robust thio-ether motif, stable to acidic, basic, oxidising and reducing conditions. While the tremendous scope of TEC reactions has come to light in recent years, it is only now beginning to be employed as a ligation tool in the realm of glycoscience. However, a number of innovative examples in literature exemplify the great potential of this synthetic method.[200-203]

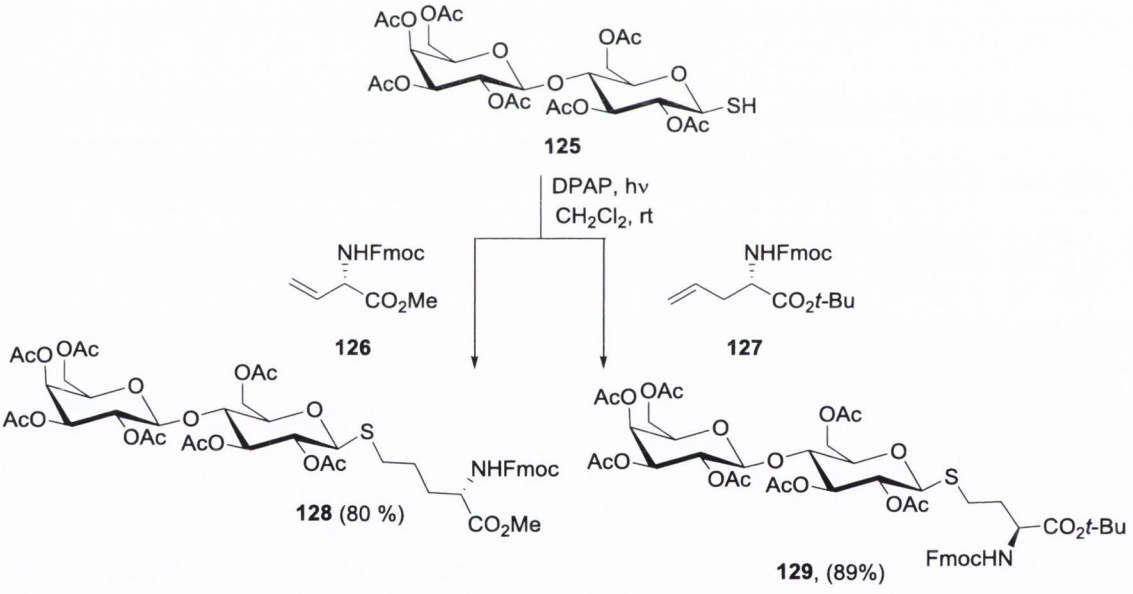
1.6.3.1 Intermolecular TEC reactions

Replacement of the oxygen atom in the interglycosidic linkage with a carbon or sulfur results in glycosyl motifs that are resistant to chemical and enzymatic degradation. These molecules by virtue of their stability have potential as probes for enzymatic studies and as therapeutics.[4] While several syntheses exist for the preparation of *S*-glycosides thiol-ene coupling as a ligation method it was not pursued until 2009.[204] Dondoni *et al.*[204] utilised TEC to good effect furnishing 1,6 thiodisaccharides in good yields and high diastereoselectivities via coupling of an anomeric thiyl radical couples to a carbohydrate based alkene. (Scheme 18)



Scheme 18 Thiodissacharide formation via TEC chemistry

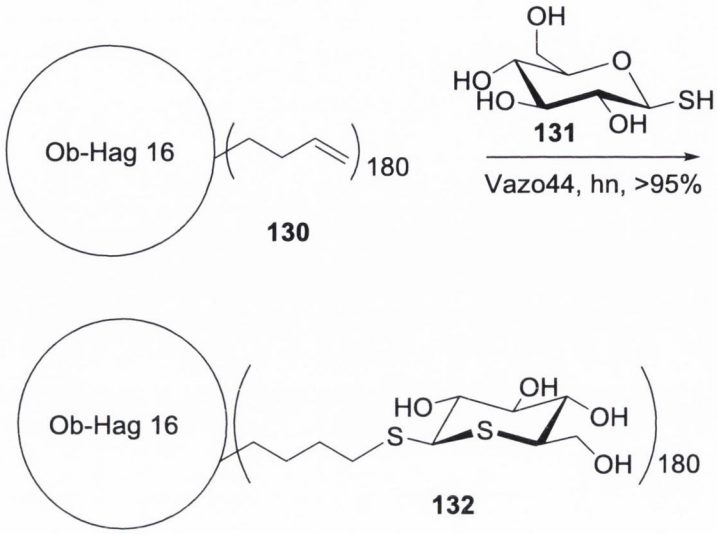
The classical preparation of *S*-glycosyl amino acids involved coupling a protected cysteine residue with an activated sugar derivative,[205] TEC has recently proven compatible for an efficient synthesis of such glycoconjugates.[206-209] Similar to *S*-disaccharides, *S*-linked glycopeptides exhibit stability towards *O*- and *N*-glycosidases which cleave the *O*- and *N*-glycosidic bonds of natural glycopeptides. The groups of Dondoni and Davis have both demonstrated the utility of TEC for *S*-linked glycopeptide synthesis through the coupling of glycosyl thiols with peptidic alkenes.[206-209]



Scheme 19 TEC applied to the synthesis of glycopeptides

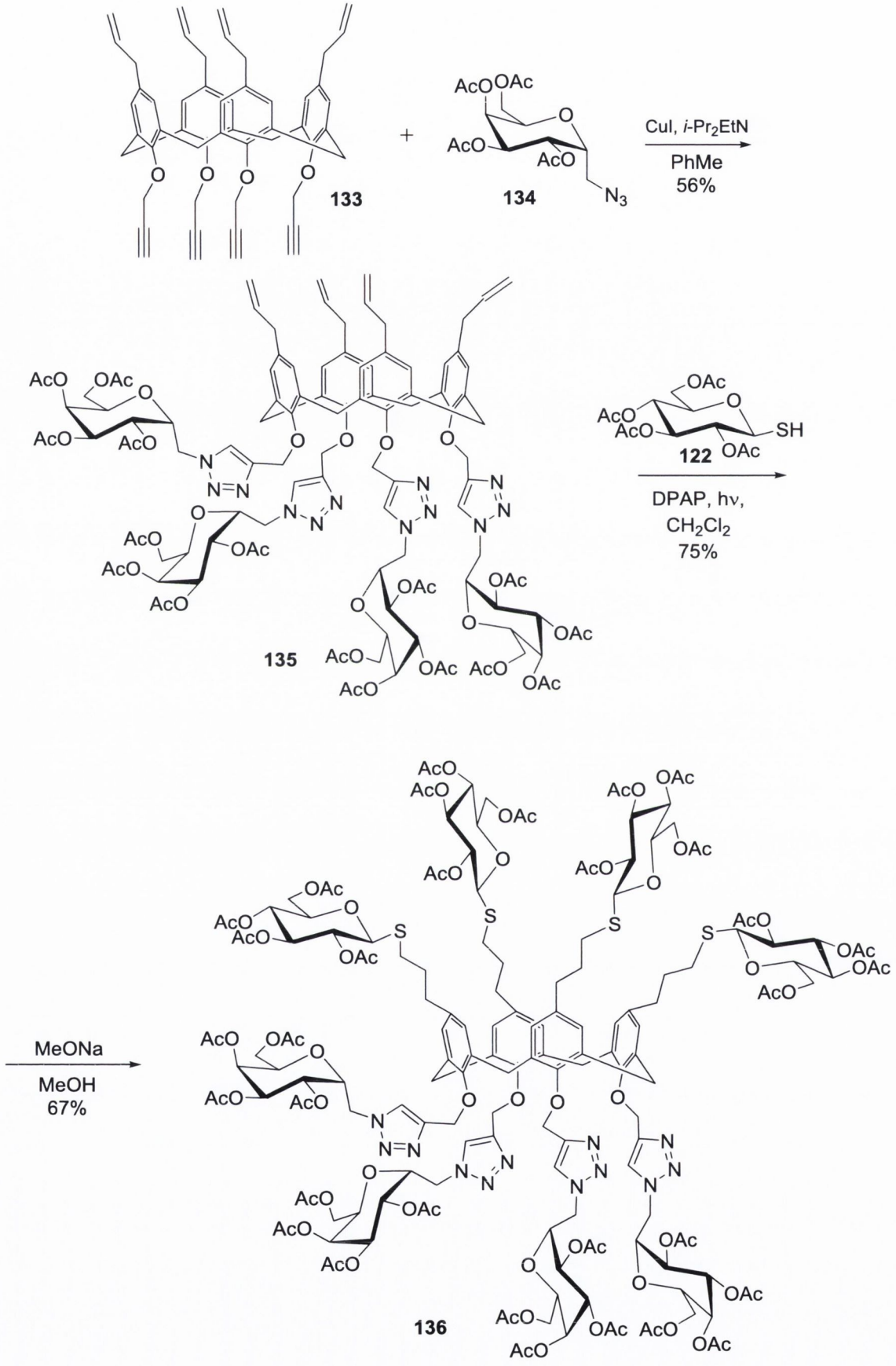
Davis and co-workers extended the methodology to incorporate ligation of a glycosyl thiol to a protein.[209] L-homoallylglycine (L-Hag) was site specifically introduced into a number of proteins using gene sequence design thus resulting in olefenic proteins for TEC conjugation. Reactions were carried out in aqueous solvents at room temperature in

the presence of water soluble initiator Vazo44. The *S*-linked protein glycoconjugates were obtained in excellent yield (Scheme 20).



Scheme 20 TEC for the conjugation of a glycosyl thiol to proteins

Cell surface protein-carbohydrate interactions are known to play a pivotal role in numerous biological processes.[4] It is also appreciated that the multitude of those weak interactions result in a strong adhesion (the glycoside cluster effect).[209,210] Accordingly this has prompted numerous of groups to develop syntheses of multivalent neoglycoconjugates with a wide range of different structures and valencies.[211] Of particular interest are glycoclusters anchored to calix[4]arenes and calix[4]resorcarenes, as a result of the starting materials ready availability, easy functionalization and tolerance to a wide range of reaction conditions.[212] Through development of such artificial systems it is anticipated that the glycoside-cluster effect can be probed with a view to preventing adhesion of pathogens to epithelial cells. As a number of bacteria exhibit various lectins capable of recognising different carbohydrate residues, and a single lectin is capable of interacting with various types of carbohydrates,[213] Dondoni *et al.*[214] established a dual scaffold around a calix[4]arene platform functionalised with alkene and alkyne moietys. A Cu (I) catalysed reaction between tetraallyl and tetra-*O*-propargyl functionalised calix[4]arene **133** with peracetylated α-linked galactosylmethyl azide **134** furnished calix[4]arene derivative **135** exhibiting the trizole linked glycocluster at the lower rim while the upper (alkene functionalised) rim remained unaltered. Photoinduced TEC of **135** with β-D-glucosyl thiol **122** gave, after deacetylation, product **136**.

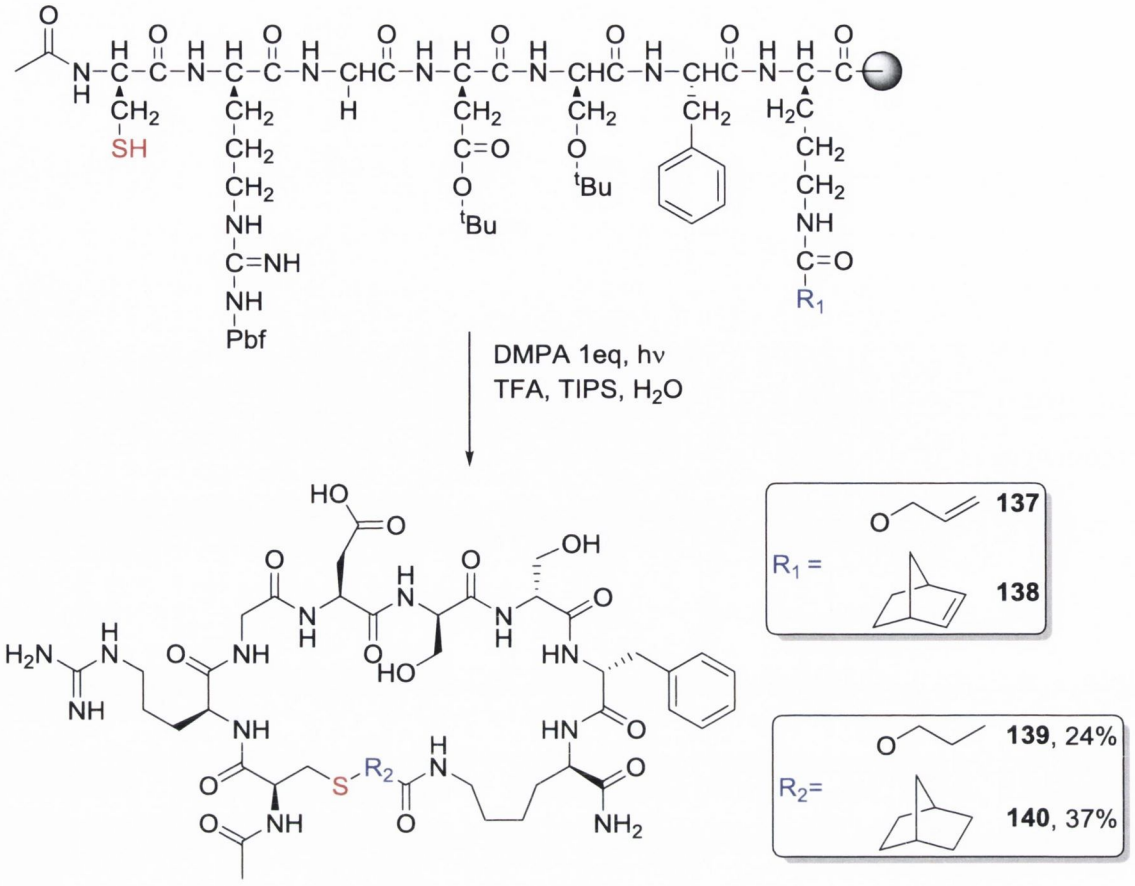


Scheme 21 Anchoring of glycoglusters to calix[4]arenes via TEC

136 contains two different tetravalent glycoclusters anchored to the same calix[4]arene scaffold, the upper rim being glucoconjugated and the lower containing *galacto* residues. This multivalent neoglycoconjugate is thus capable of recognition by different lectins.[215] It is noteworthy that copper 'click' reactions and TEC are orthogonal in the above approach, however if such a sequence is reversed it is likely that the thiyl radical would react with both alkene and alkyne (thiyl-yne coupling). The latter method in which two thiol fragments are added across a triple bond via free radical chain mechanism, has shown recent applicability in the synthesis of glycosylated peptides and glycoconjugates.[216,217]

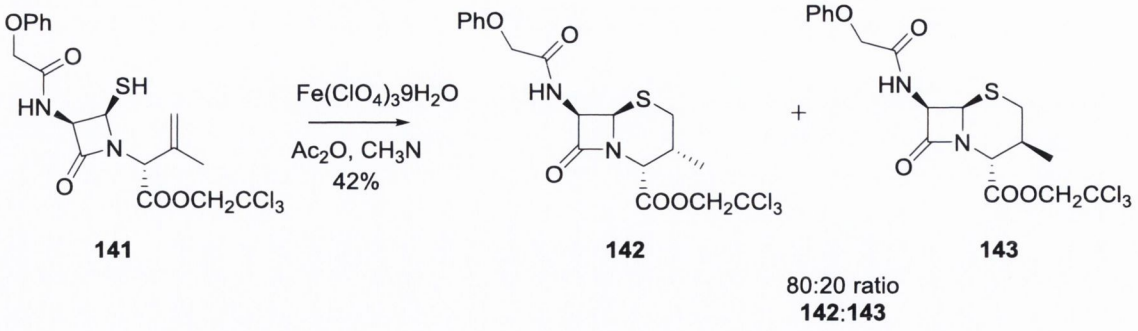
1.6.3.2 Intra-molecular Thiol-ene click

Despite intensive synthetic studies into the preparation of thiosugars the use of intramolecular thiyl radical cyclisation reactions has not previously been considered for the preparation of this class of potential therapeutics. While intermolecular TEC reactions have undergone a resurgence in recent years with innovative applications in the synthesis of glycoconjugates, intramolecular TEC cyclisations for the preparation of sulfur containing heterocycles are rare. Indeed only one example from the previous decade has been reported employing intramolecular TEC. Aimetti *et al.*[218] carried out TEC coupling between a cysteine moiety on a peptide chain to a pendant allyl group in order to furnish a peptide macrocycle. Cyclisations were intitated both photochemically and thermally and the authors noted that the use of a strained alkene (norborane) can be employed to achieve accelerated reaction rates with the reaction reaching completion within 20 minutes.



Scheme 22 Intramolecular TEC for the synthesis of cyclic peptides

In 1992 Cabri *et al.*[219] investigated iron promoated thiyl radical cyclisations to furnish β-lactam antibiotic analogues. In this sequence **141** is treated with stoichiometric amounts of Fe (III) salts to deliver a mixture of cephams **142** and **143** (80:20 ratio) (Scheme 23).



Scheme 23 Intramolecular TEC for the synthesis of β-lactam antibiotics

While intramolecular TEC has not been fully exploited as a synthetic method for the synthesis of sulfur heteorcycles it was anticipated that this method could lend itself to a rapid and facile route to thiosugar preparation.

1.6.4 Chemistry of iminyl radicals

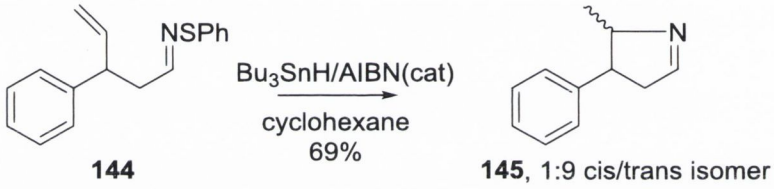
Nitrogen centered radicals hold excellent potential as useful synthetic intermediates, however their applicability has not yet been fully exploited. *N*-centred radicals include neutral, protonated and metal complexed aminyl radicals, iminyl and amidyl radicals. They are generally prepared via cleavage of an N-X bond, wherein X is a halogen (except fluorine), a nitrogen, sulfur or oxygen group. A second approach to the generation of *N*-centred radicals involves radical addition to an unsaturated nitrogen group such as a nitrile, imine, oxime, hydrazine or an azide. The work described in this thesis is concerned with the preparation and generation of glycosyl iminyl radicals.

Like its thiyl counterpart, the use of an iminyl radical in the preparation of iminosugars has never previously been reported. In fact iminyl radicals have been almost completely overlooked by synthetic organic chemists. The underlying reason for this, was a result of limited studies which indicated that these species were unreactive,[220-222] coupled with a lack of convenient methods for their generation. Contrary to the earlier impressions of iminyl radicals a number of recent reports have been published where intramolecular iminyl radical cyclisations have been employed for the synthesis of *N*-heterocycles.[223-225] The rate constant for iminyl radical cyclisations have been measured and have been found comparable to those of other intramolecular radical cyclisation processes therefore making it a synthetically useful process.[226,227]

Most of the earlier reported methods for iminyl radical preparation are based on non chain pyrolytic or photochemical reactions which are inappropriate for preparative work.[228-232] A noteworthy exception is the addition of a carbon centred radical to a nitrile leading to the generation of an iminyl radical.[233,234]

1.6.4.1 Iminyl radicals in *N*-heterocycle synthesis

Iminyl radicals are principally generated *via* cleavage of sulfenamines, oximes and hydroxamic acids. These species can be cleaved photochemically, through exposure to stannyl radicals or by electron transfer from a reducing agent or dissolving metal. Stannane chemistry was then applied to sulphenylimines owing to the highly thiophilic nature of stannyl radcials and the weakness of the N-S bond. This proved a powerful source of iminyl radicals, with sulphenylimines themselves readily available starting materials. Boivin and cowokers[235] have prepared pyrrolidine rings via cyclisation of sulfenylimies (Scheme 24). Bicyclic and spiro systems were also accessible via this synthetic approach.

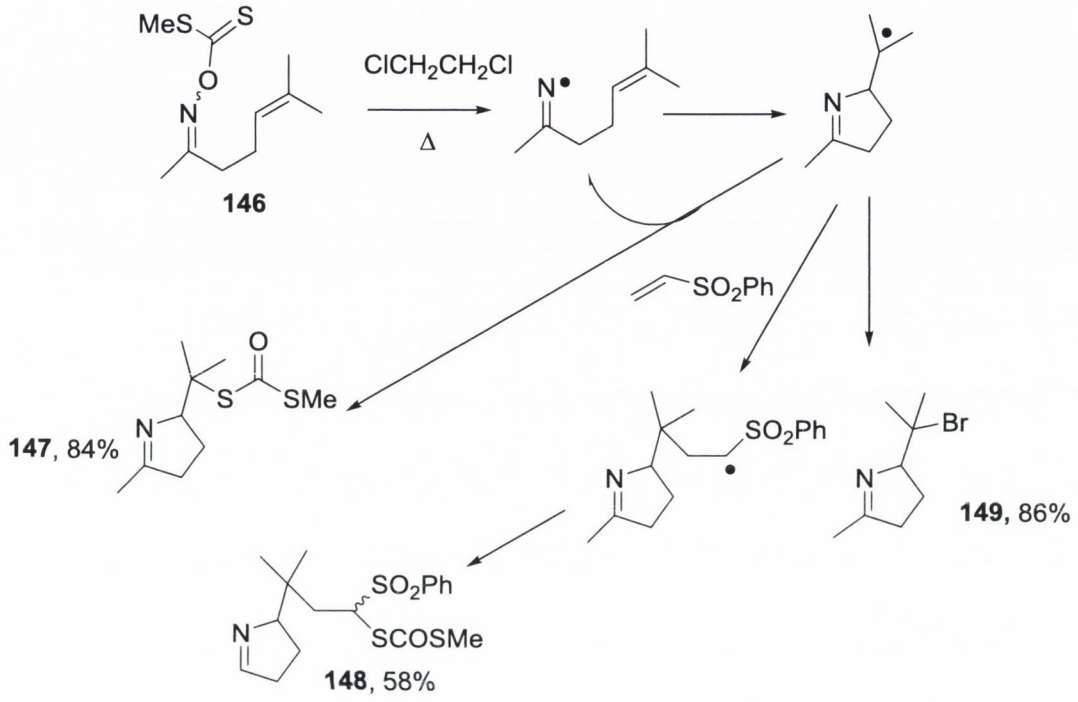


Scheme 24 Cylisation of iminyl radicals from sulfenamines

This synthetic work demonstrates the electrophilicity of iminyl radicals, unlike aminyl radicals which add sluggishly to an unactivated double bond and usually necessitate protonation or complexation with a transition metal. Newcomb and co-workers[236] have suggested that the carbon radical resulting from aminyl radical cyclisation is less nucleophilic, a direct result of the aminyl radical's requirement for protonation. This leads to limitations in further intermolecular addition of the *C*-centered radical to an electrophilic alkene. Iminyl radicals are not limited in this regard, they were found to be capable of implementing an intramolecular cyclisation and further capture of a primary, secondary and tertiary radical. [237]

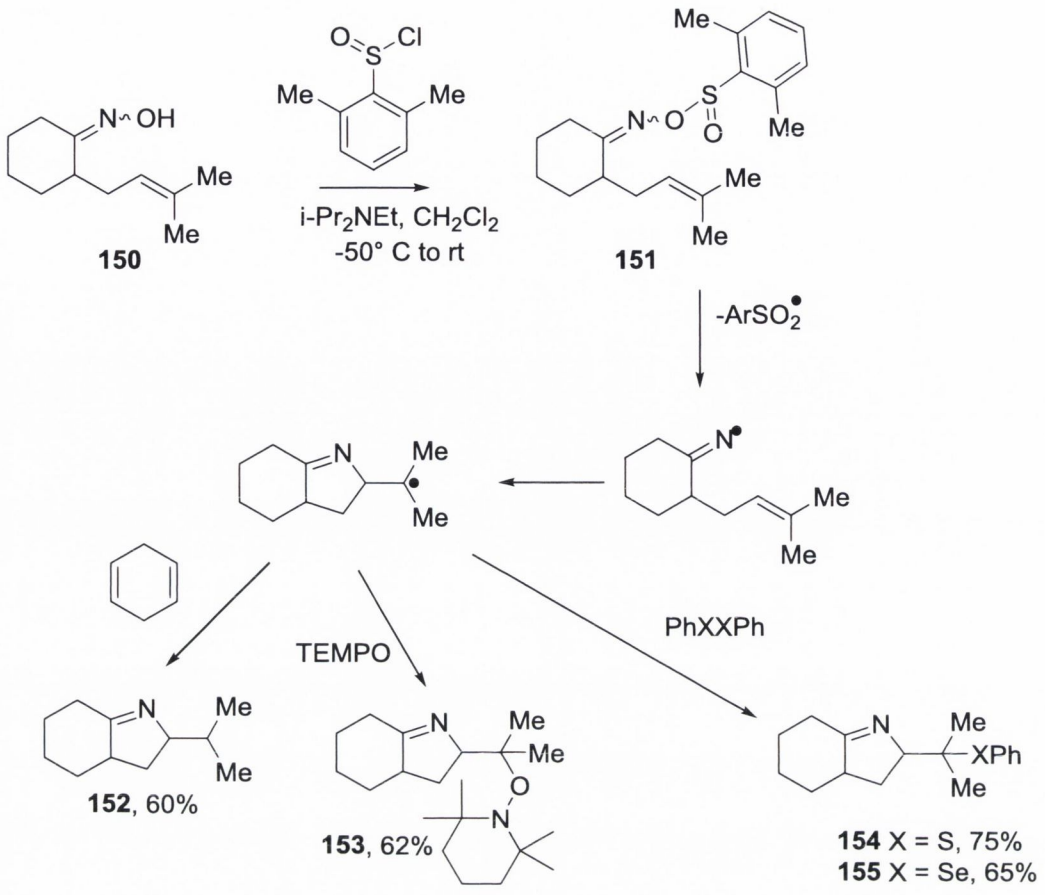
Xanthates derived from oximes are a source of iminyl radicals. They operate via a chain reaction (Scheme 25) Gagosz *et al.*[238] have shown oxime is converted to a xanthate via treatment with base, carbon disulphide and methyl iodide. This derivative is not purified, but upon gentle heating the iminyl radical is formed, cyclising to give the tertiary carbon radical species. Without an external radical trap, the alkyl radical reacts with the initial

xanthate starting material to furnish pyrrolenine dithiocarbonate **147**. If an electrophilic alkene such as phenyl vinyl sulfone is added to the reaction mixture prior to heating then **148** is formed via trapping of the alkyl radical. The intermediate radical may also be trapped with bromotrichloromethane to furnish bromopyrrolenine **149** (Scheme 25).



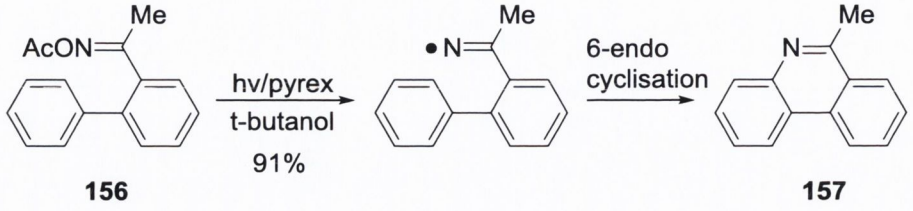
Scheme 25 Iminyl radical cyclisations initiated from xanthate **146**

Weinreb and co-workers[239] have demonstrated nitrogen radicals arising from thermal decomposition of sulfinates and trivalent phosphorus of oximes and hydroxamic acids can be intercepted by alkenes and the resultant alkyl radical captured by various radical traps. Sulfinite **151** is heated to generate an iminyl radical which undergoes intramolecular cyclisation to give an alkyl radical via H-atom transfer from cyclohexadiene. This results in the formation of pyrrolenine **152**. Capture with TEMPO provides **153**, sulphides and selenides were also formed via trapping with the appropriate trap.



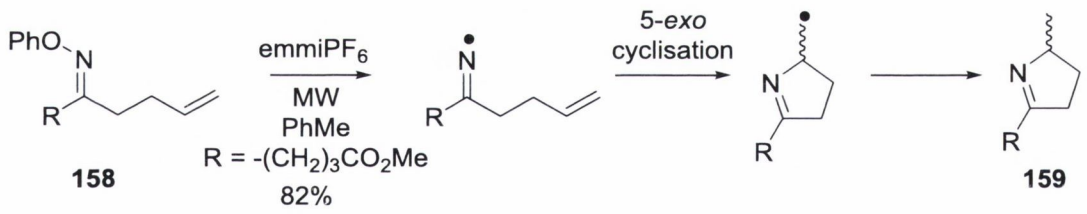
Scheme 26 Iminyl radical cyclisation and subsequent trapping

Rodriguez and co-workers[240] were the first to report an efficient photochemical approach for the generation of six membered heterocyclic rings through the use of acyloximes. The synthesis of phenanthridines via the photolysis of 2-phenylacetophenone *O*-acetyl oxime **156** in tert butanol proceeded in very high yield (Scheme 27). Further systems were examined in order to probe the scope of the methodology, such as irradiation of 2-vinylbenzaldehyde *O*-acetyloximes which also successfully underwent a 6-*endo* iminyl radical cyclisation.



Scheme 27 Iminyl radical formation from photochemical initiation of acyl oxime **156**

Walton and co-workers have recently pioneered a thermal route to iminyl radicals via oxime ethers.[241] Recent investigations revealed the N–O bond dissociation enthalpies (BDE) of *O*-phenyl oxime ethers [BDE (R_2C=N–OPh) = 140 kJ $mol^{-1}$for R = Me or Ph] were found to actually be lower than the O–O BDEs of dialkyl peroxides (159–167 kJ mol^{-1}).[242] Iminyl radical formation from oxime ether **158** was expected to initiate 5-*exo* ring closure to produce 3,4-dihydro[2H]pyrrolomethyl radicals that would subsequently yield the corresponding substituted dihydropyrrole **159** upon hydrogen abstraction from solvent. The phenoxyl radicals were also expected to abstract hydrogen from the solvent giving phenol as the main by-product. The authors found that under the optimised conditions alkenone *O*-phenyl oximes were irradiated in the microwave at 160° C dihydropyrrole derivatives were formed in high yield, scission of the weak N–O bond is favoured because of the resonance stabilisation of the released phenoxyl radical. Such 5-*exo*-cyclisations of pent-4-en-1-iminyl radicals are fast cyclisation processes and are thought to be only about a factor of five slower than the archetype hex-5-enyl radical cyclisations.[227,243] Further synthetic work by Walton and co-workers illustrated that 3-arylalkyliminyls yield aromatic heterocycles via a 5-*exo*-iminyl radical cyclisation using this methodology.



Scheme 28 Iminyl radical formation from thermolysis of oxime ether **158**

Inspired by the simplicity and ease of access in the methods described by Rodriguez[240] and Walton,[241] it was anticipated to apply their synthetic methodologies to the synthesis of azasugars. Iminyl radical intermediates from oxime esters can be observed by ESR spectroscopy, allowing for mechanisms to be mapped and the kinetics of cyclisation to be calculated. This would constitute the first example of an iminyl radical cyclisation to iminosugar preparation and would provide a rapid and versatile synthetic route to a library of known and novel glycosidase inhibitors.

1.7 Thesis overview

As evident from the preceding sections, the strong therapeutic potential of glycosidase inhibitors has generated huge interest in their synthesis. While several significant routes to both thio- and azasugars have been developed their syntheses have never been attempted via intramolecular cyclisation of a thiyl or iminyl radical. Radical reactions are a very attractive methodology capable of both photochemical or thermal initiation, excellent yields and atom economy, and tolerant of a wide range of substrates. Radical cyclisations have played a key role in the synthesis of many fundamental, complex natural products and it is thus believed that via a free radical based approach could provide an elegant synthetic route to glycosidase inhibitors with significant therapeutic potential.

Chapter 2 outlines the applications of intramolecular TEC cyclisation for the synthesis of thiosugars. Cyclisation of a thiyl radical onto a range of glycosyl alkenes furnished a small library of *C*-thiosugars. The prepared compounds will undergo biological evaluation for potential glycosidase inhibition.

Chapter 3 outlines synthetic efforts to iminosugar preparations via an iminyl radical cyclisation. Both thermal and photochemical routes to iminyl radical cyclisation were pursued and will be discussed in addition to the corresponding ESR data. A further potential application of iminyl radicals within carbohydrate chemistry was studied, namely the intermolecular iminyl radical capture of a peptidic alkene, this work will also be outlined in Chapter 3.

It was also of interest to investigate thiyl radical cyclisations onto oxime ethers, moieties that are known to function as excellent radical traps. In addition to complementing the work carried out in Chapter 2 wherein thiyl radical cyclisation onto alkenes was accomplished for *C*-thiosugar preparation, this work would expedite access to *N*-*O*-linked thiosugars. The presence of a basic group at the anomeric position of the sugar is known to increase inhibitory glycosidase activity, thus it was anticipated that this method would furnish a new class of thiosugars suitable for biological evaluation. This work is outlined in Chapter 4.

2.0 Results and Discussion

2.1 Intra-molecular thiyl radical cyclisations for the synthesis of thiosugars

As emphasised in section 1.3 the strong therapeutic potential of thiosugars and their analogues has generated significant interest in their synthesis. While several efficient synthetic routes to thiosugars have been developed,[126,127,131,132,156,157,166] the use of an intramolecular thiyl radical cyclisation for thiosugar preparation has not been investigated. As outlined in section 1.6.3 thiol-ene click (TEC) has proven to be an extremely versatile strategy in organic synthesis. Conditions are mild and tolerant of a wide array of solvent and protecting groups. Reactions can be initiated both photochemically and thermally, and the radical chain processes offer excellent atom economy and high yields.[200-203] It is therefore understandable that TEC has gained considerable popularity in recent years. TEC has proven compatible within carbohydrate chemistry,[204-209] section 1.6.3.1 details its application in intermolecular processes for the synthesis of *S*-linked glycosides and glycopeptides. The rationale behind this work was to employ thiyl radical cyclisations to provide an elegant, rapid and general approach to the synthesis of highly functionalised thiosugars and glycoconjugates. Subsequently pharmaceutically relevant analogs could be screened for potential inhibitory activity (Figure 22).

The aim of this investigation was to prepare open chain carbohydrate derivatives containing a free thiol moiety in a 1,4 or 1,5 relationship to an alkene component as the radical acceptor functionality. Investigation would then ensue to determine if these precursors could undergo intermolecular radical cyclisation reactions to give the desired thio-glycoconjugates.

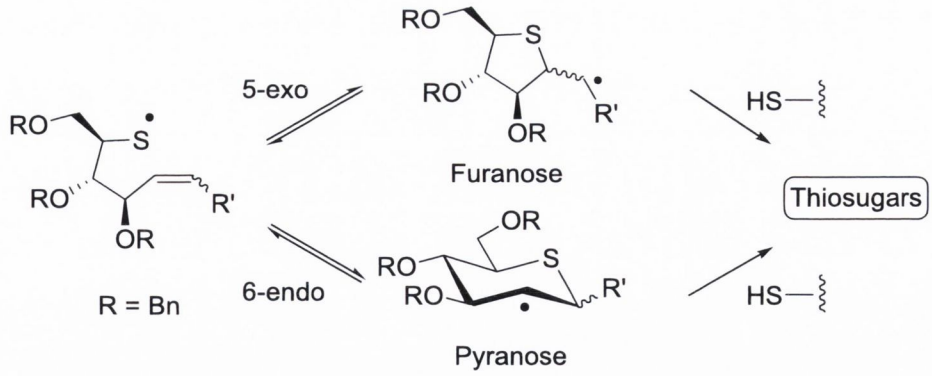


Figure 22 Proposed intermolecular thiyl radical cyclisation for thiosugar preparation

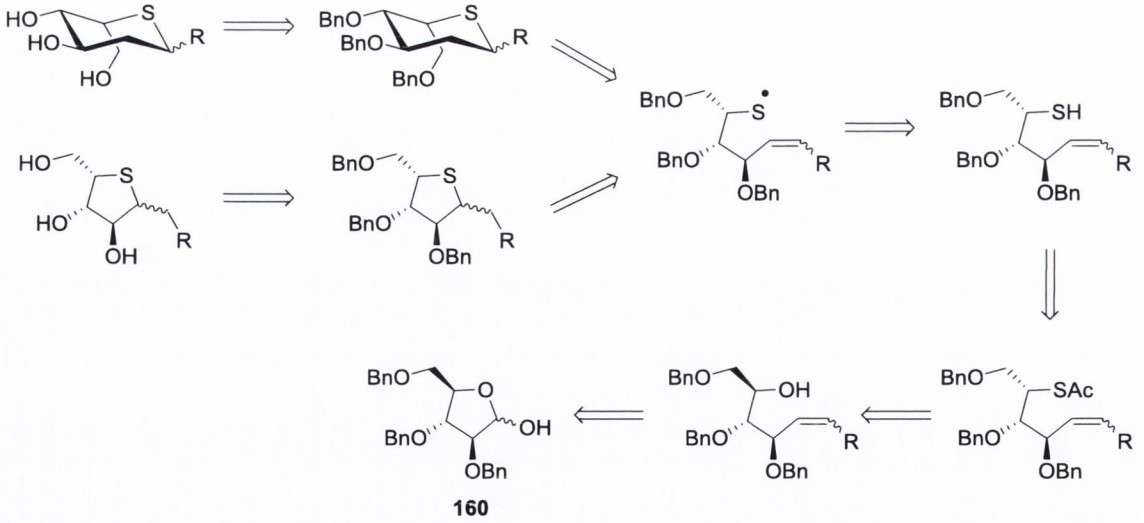
2.2 Proposed synthetic approach: Retrosynthetic analysis

The synthesis of thiosugar analogs was devised following a retrosynthetic approach. Several determining factors were taken into account in order to generate a sensible and efficient synthesis.

For ease of purification it was deemed desirable to deprotect the thiosugar in the final step. Hydrogenolysis of the benzyl groups could only be performed following ring closure as a prior deprotection would also reduce the alkene functionality. Sulfur is known to poison heavy metal catalysts used in hydrogenolysis[244] therefore alternative deprotection methods such as birch reduction/lewis acid deprotections were taken into consideration as potential methods for benzyl group removal. For practical reasons it was decided upon to synthesise and store the radical precursor as its associated thioester which could be deprotected to the free thiol immediately prior to use. This approach was implemented in order to avoid oxidation of the thiol group by adventitious oxygen during storage. Prior synthetic endeavours to install a thioacetate moiety from an alcohol, (discussed in detail in Chapter 4), indicated that triflate formation followed by displacement with potassium thioacetate gives rise to glycosyl thioesters in good yield. Employing this approach, the stereochemistry of the thioester would be inverted relative to the parent alcohol. Epimerisation at C-5 gives rise to carbohydrates (L-sugars), that are uncommon in nature thus it was rationalised that via this approach a small library of rare thiosugar analogs could be generated for biological screening.

Access to the hydroxyl group at C-5 with commitant installation of the alkene functionality was deemed possible via a Wittig reaction on a protected glycosyl hemiacetal. In order to introduce variability and flexibility to the synthetic sequence a range of different alkene functionalities could be introduced to the glycosyl hemiacetal from an array of phosphonium salts. While a late stage variation of the alkene moiety e.g. via cross metathesis, would allow for the large scale preparation of a common precursor and subsequent derivatisation, literature precedence suggested this route would not proceed efficiently.[245] Nolen *et al.* have detailed cross metathesis reactions on glycosyl alkenes,[245] however they have found the reaction necessitates the presence of a free allylic hydroxyl. This would not be compatible within our desired system. In addition the high cost of Grubbs catalyst and the potential for many competing side reactions[246] deemed this route unsatisfactory as a synthetic starting point.

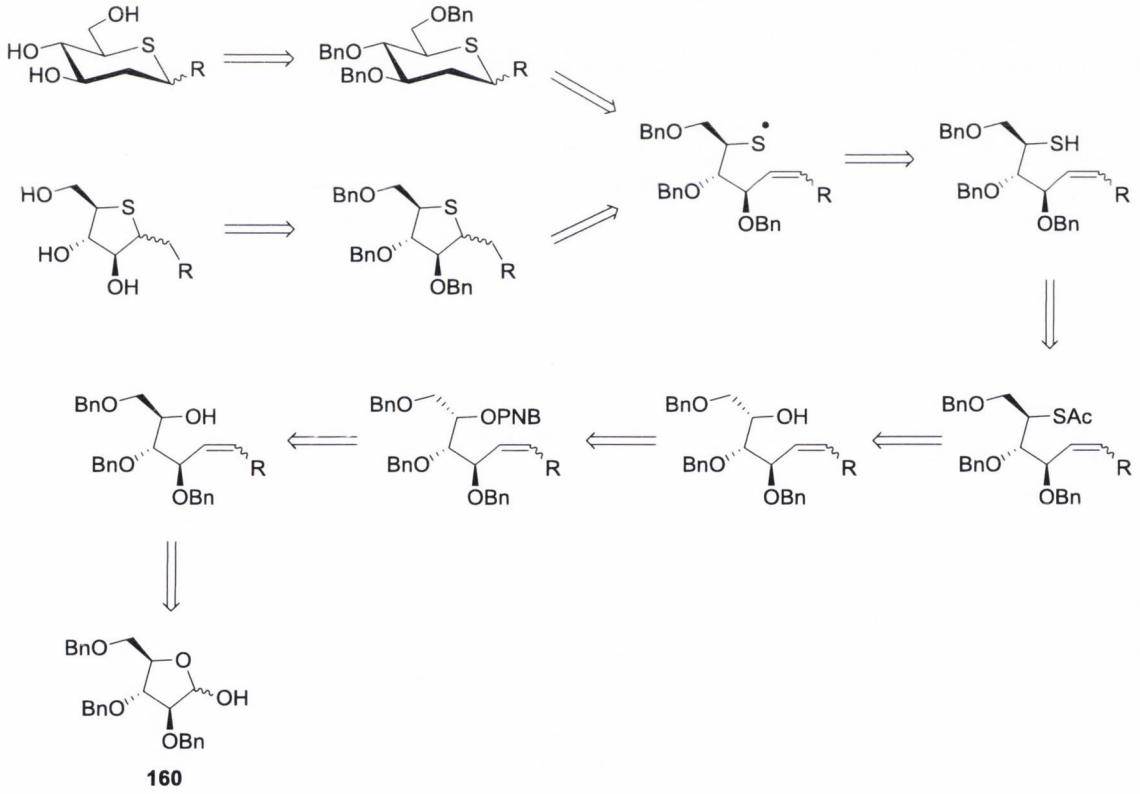
Orthogonal protecting groups of the hydroxyl and thiol groups were considered to be advantageous for a simplified purification of the thiol derivative. In order to achieve this, and based on work that will be discussed in Chapter 4, benzyl protecting groups were selected. Coupled with this, benzylated hemiacetals are cheap and commercially available starting materials. The proposed retrosynthetic analysis, as described, would give rise to thiosugar analogs in five synthetic steps. (Retrosynthesis A)



Scheme 29 Retrosynthesis A; approach to L-thiosugar analogs

2.2.1 Retrosynthetic route B: retention of configuration

Since the proposed methodology gives access to thiosugar analogs with inversion at C-5 it was also of interest to develop a synthetic pathway that would allow for retention of stereochemistry at this centre, thereby giving access to thiosugars stereochemically identical to the natural, commercially available starting material. Inspired by the work of Martin et al[247] a double inversion strategy was decided upon to introduce the thioacetate group with retention of configuration. The first inversion reaction could be carried out via Mitsunobu chemistry, installing a *p*-nitrobenzoic acid motif followed by hydrolysis to furnish the inverted alcohol. Triflation/displacement with potassium thioacetate could then ensue on the inverted alcohol to install the thioacetate. Subsequently, deprotection and radical cyclisation could yield the thiosugar product with an overall retention of configuration. (Retrosynthesis B)



Scheme 30 Retrosynthetis B; approach to D-thiosugars

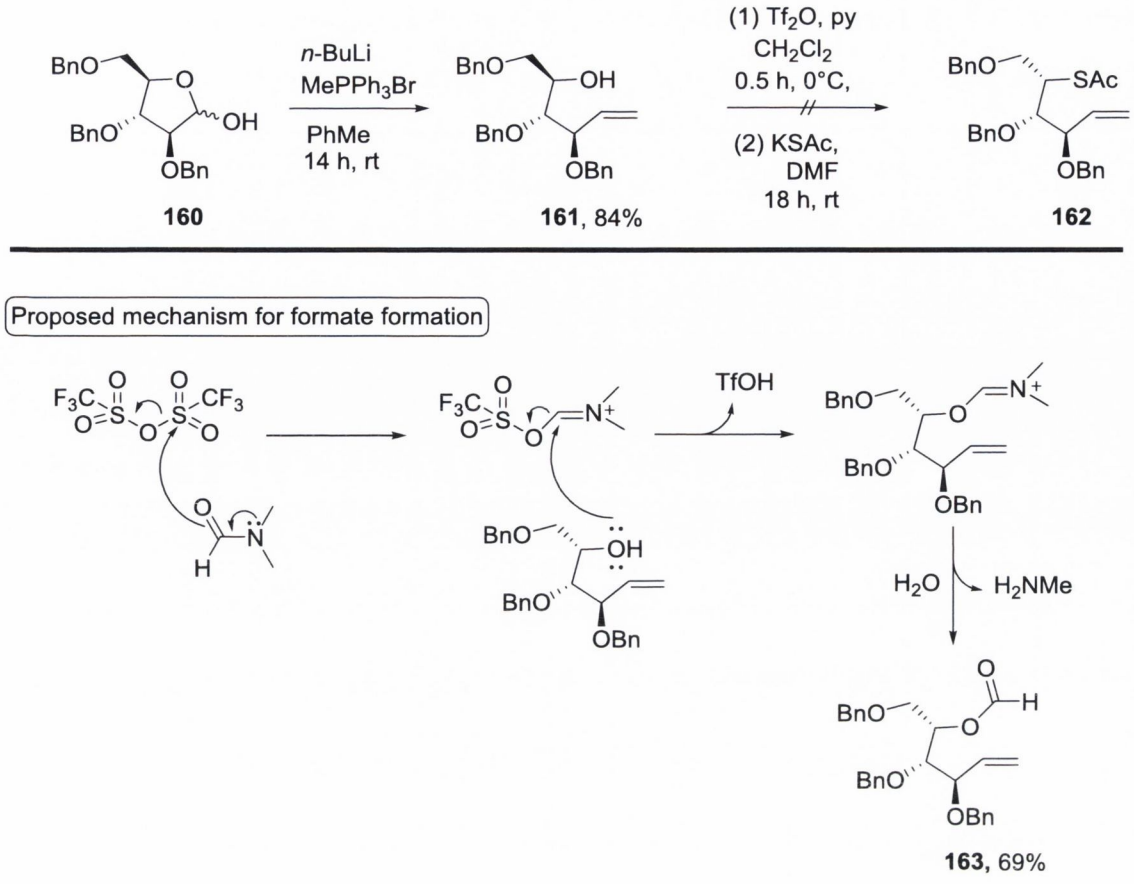
2.3 Choice of model system

As proof of concept the synthesis was carried out on a furanose sugar in the first instance. Chapter 4 details synthetic difficulties encountered with displacement reactions in pyranose systems and while S_N2 reactions are known to proceed more efficiently in 5 member systems it was reasoned that a furanose system would function as an excellent model from which to further develop the methodology. Epimerisation reactions at C-2 and low yields were observed upon Wittig methlyenation of ribose. These side reactions were not observed with an *arabino*-starting material, therefore tri-*O*-benzyl-arabinofuranose **160** was chosen as the starting material for the initial studies. A terminal alkene was initially studied for its ease of synthesis and characterisation, and in order to allow investigation of a 6-*endo* vs 5-*exo* system. A unique synthetic advantage of radical cyclisation strategies over classic synthetic ring closures is the ability to prepare both pyranose and furanose thiosugars from the same starting material.

2.4 Synthesis of singly inverted thiopyranose

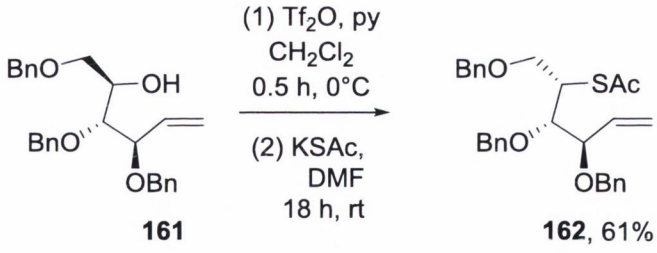
2.4.1 Synthesis of the thiol radical precursor

In order to introduce the terminal alkene suitable for the intramolecular radical cyclisation, Wittig methylenation was carried out on commercially available 2,3,4-tri-*O*-benzyl arabinofuranose.[248] The Wittig reaction furnished alkene **161** in good yield (84%). The reaction between **161**, triflic anhydride and pyridine afforded the desired intermediate. The solvent was evaporated and the mixture was directly treated with potassium thioacetate to afford the inverted thioacetate. Surprisingly, in the first instance, the sole product obtained from the reaction of the intermediate triflate was the formylated alcohol **163** (Scheme 31). It is presumed that excess triflic anhydride from the crude triflate mixture reacted with DMF used as the solvent in the subsequent displacement step to generate imminium triflate as a Vilsmeier-type reagent.[249,250]



Scheme 31 Attempted synthesis of thioacetate **162**

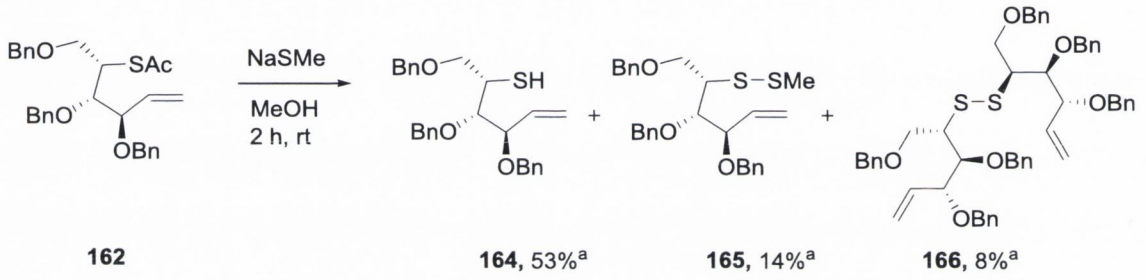
Gratifyingly the use of a cold aqueous work up followed by reaction with potassium thioacetate in DMF afforded the desired product **162** in a 61 % yield. (Scheme 32)



Scheme 32 Formation of thioacetate **162**

With thioacetate **162** in hand, our next aim was deprotection of the thioacetate to provide the free thiol. Tewari *et al.*[251] have reported the formation of thiols from thioacetates by the generation of HCl in situ using catalytic acetyl chloride in methanol. It was envisaged that this protocol would provide a viable option for the deprotection of the thioester and it

was also noted that the sole byproduct of the protocol was the volatile methyl acetate. Basic deprotection conditions of thioacetates are also commonly associated with disulphide formation. However, a sluggish reaction with multiple side products was observed upon an acidic deprotection of **162**. Deprotection with sodium thiomethoxide, a reagent that selectively removes thioacetates in the presence of acetates was next employed for thioacetate removal. While Wallace *et al.*[252] report it a versatile reagent which acts as a sacrificial reductant preventing thiol oxidation, this reaction in our hands was also unfortunately unsatisfactory. This reaction gave rise to the desired compound, albeit contaminated with two disulphide side products which could not be separated by chromatography (Scheme 33).



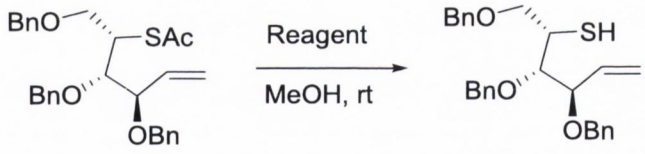
162 **164**, 53%[a] **165**, 14%[a] **166**, 8%[a]

Scheme 33 Deprotection of **162** in the presence of sodium thiomethoxide

[a] Determined by ^{1}H-NMR and mass spectroscopy

Reduction of the disulphide byproducts was primarily sought via sodium borohydride in methanol.[253] Interestingly only cleavage of the thiomethyl disulphide **165** was observed under these conditions. A more aggressive reaction, namely reduction using tributylphosphine,[254] was required to cleave the apparently stronger sugar-sugar disulphide bond in **166**.

Recent studies[255] have revealed that the presence of phosphine inhibits progression of a radical thiol-ene reaction and can result in desulfurisation, therefore we decided to explore an alternative route to thioacetate deprotection. Fresh degassed sodium methoxide was prepared and reaction in a 0.1 M NaOMe solution gave the desired compound **164** within five minutes with quantitative conversion. (Table 1)



162 **164**

Entry	Deprotection reagent	Time	Yield of Thiol[a]
1	AcCl, MeOH	24 h	21 %
2	NaSMe	2 h	53 %
3	Na, MeOH	0.08 h	≥ 99 %

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

Table 1 Deprotection of thioacetate **162** to furnish thiol **164**

2.4.2 Optimisation of radical thiol-ene cyclisation

With a route to the singly inverted thiosugar now firmly in hand we attempted to cyclise the resultant thiol by a radical thiol-ene reaction. We postulated that the presence of an unsubsituted terminal alkene should favour a 6-*endo* cyclisation over a 5-e*xo* ring closure. Three potential cyclised products could be formed upon initiation of the thiol, the kinetically favoured being two furanose products resulting from the 5-*exo* cyclisation. The thermodynamically favoured product on the other hand would result from a slower 6-*endo* cyclisation. (Figure 23)

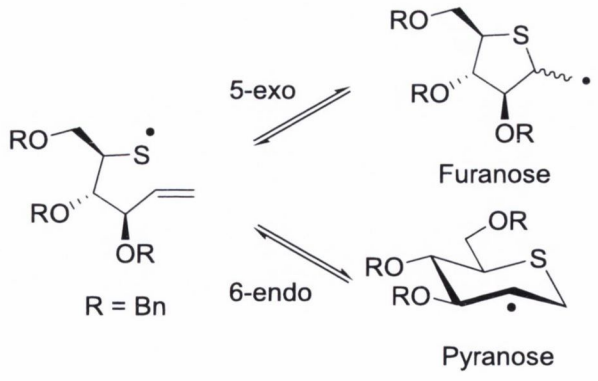
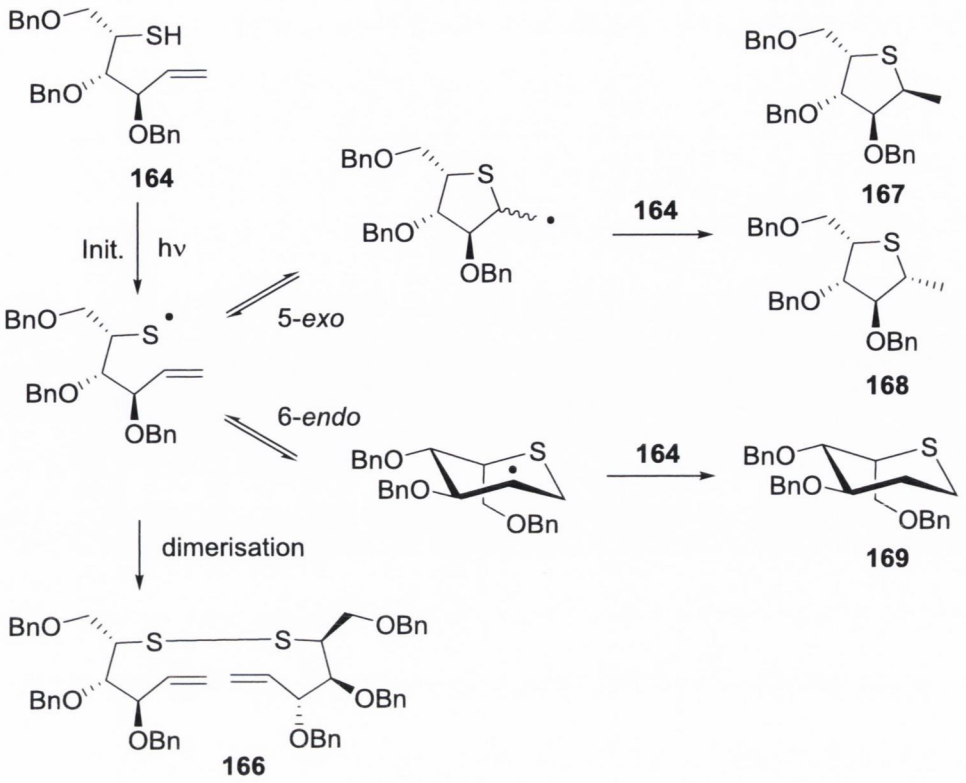


Figure 23 5-*exo* and 6-*endo* cyclisations can be employed to furnish furanose and pyranose thiosugars.

A number of crucial factors can determine the distribution of radical products, including the rate of hydrogen abstraction from the thiol and the relative stability of the resultant alkyl radical following the cyclisation reaction. Cramer[256] and Northrop[257] have studied the kinetics of intermolecular thiol-ene reactions and have suggested that the critical factor governing the overall kinetics of the thiol-ene polymerisation reaction is the ratio of the propagation rate to chain transfer rate. We assumed that the chain-transfer step is rate limiting for an intramolecular cyclisation and thus the overall process is first order with respect to the thiol concentration. Therefore, given the relative stability of the secondary alkyl radical formed upon 6-*endo* cyclisation it would be reasonable to assume the 6-*endo* product would dominate.

At the outset, we treated the thiol with a radical initiator 2,2-dimethoxy-2-phenyl acetophenone (DPAP) and a photosensitizer 4-methoxyacetophenone (MAP) at room temperature. Following irradiation for 1 h, four compounds were isolated thus the expected pyranose product **169** as the major component of the reaction mixture (64%), the two furanose products **167/168** at 8% and 6% respectively and the disulphide **166** (15%), presumably formed via dimerization of the thiyl radical.

A range of conditions were applied to fully investigate the radical reaction (Table 2). Attempts to use an alternative radical initiator 4,4-Azobis(4-cyanovaleric acid) (ACVA) photochemically gave unsatisfactory conversions. A thermal initiation of ACVA resulted in a further diminished yield. We anticipated that the formation of the disulphide could be minimised via dilution of the reaction mixture, and while a 5-fold dilution resulted in a drop in the yields of both the disulphide and 5-*exo* products, the yield of the 6-*endo* was not significantly increased. Degassing the reaction mixture under argon was then considered in order to remove any dissolved oxygen. This resulted in a further drop in the yield of disulphide and an increase in the amount of **169** formed. Combining both dilution and degassing of the system negated disulphide formation and led to an optimum conversion of the thiyl radical to the 6-*endo* cyclised product **169** (73 %) and 5-exo product **167/168** (9 %). (Table 2)

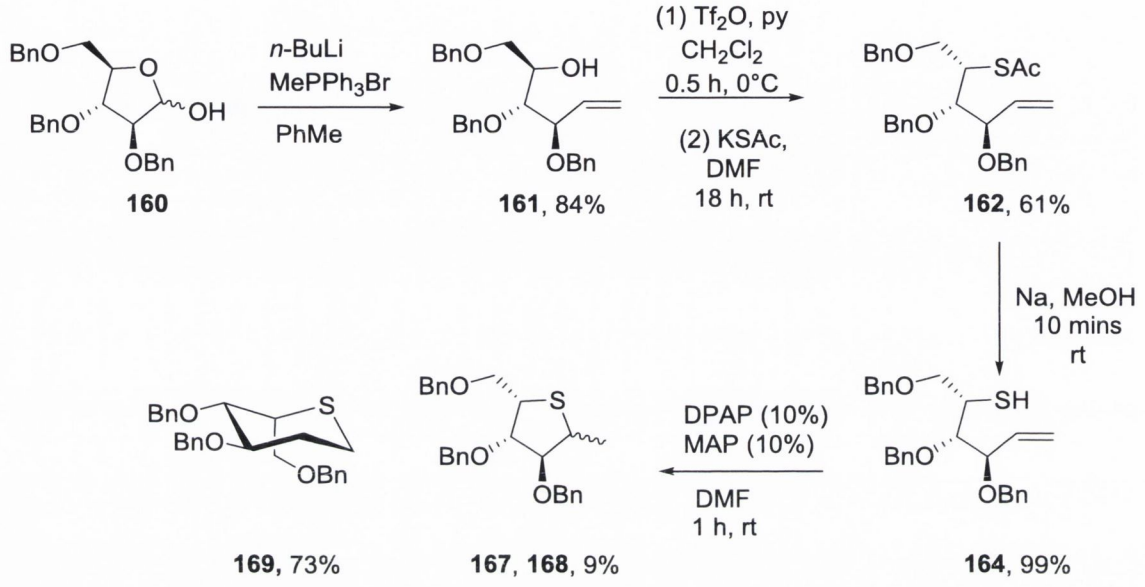


Entry	Initiator	Conditions[b]	Yield (%)[c]
1	DPAP (10%) MAP (10%)	hυ	**169** (64), **167** (8), **168** (6), **166** (10)
2	ACVA (10%) MAP (10%)	hυ	**169** (42), **167** (-), **168** (-), **166** (-)
3	ACVA (10%) MAP (10%)	hυ	**169** (45), **167** (-), **168** (-), **166** (-)
4	ACVA (10%) MAP (10%)	Δ	**169** (18), **167** (-), **168** (-), **166** (-)
5	DPAP (10%) MAP (10%)	hυ[d]	**169** (62), **167** (5), **168** (6), **166** (6)
6	DPAP (10%) MAP (10%)	hυ[e]	**169** (68), **167** (4), **168** (6), **166** (4)
7	DPAP (10%) MAP (10%)	hυ[d,e]	**169** (73), **167** (3), **168** (6), **166** (-)

[b] All reactions carried out in DMF at room temperature with UV irridation for 1h. [c] Isolated yields. [d] Reaction mixture diluted x 5. [e] Reaction mixture degassed with a stream of argon for 10 min.

Table 2 Optimisation of TEC cyclisation

This result constituted the first example of an intramolecular thiyl radical cyclisation to furnish a thiosugar (Scheme 34). Similar 1,2 dideoxythiosugar compounds have been reported starting from glycals, however the method for their synthesis does not lend itself to a versatile and flexible route.[258]

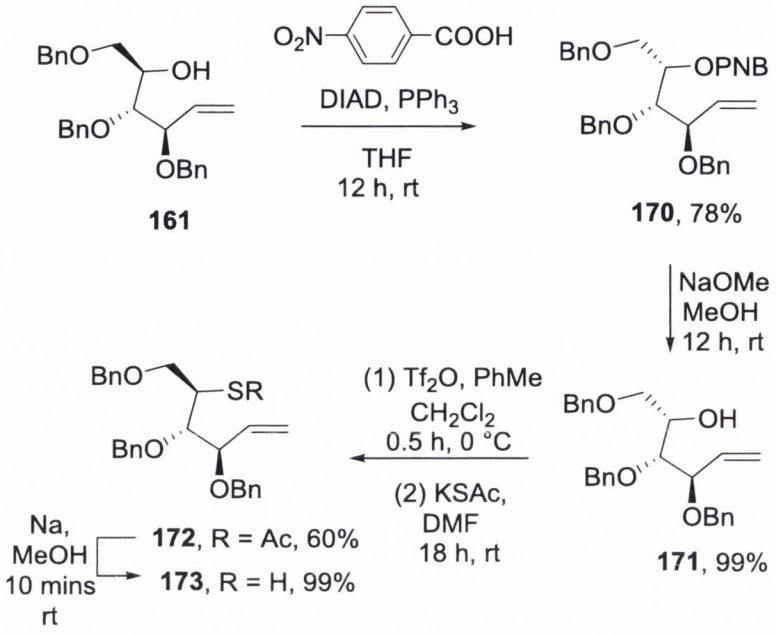


Scheme 34 Synthesis of *C*-thiosugars **167**, **168**, **169**

2.5 Synthesis of double inverted thiopyranose

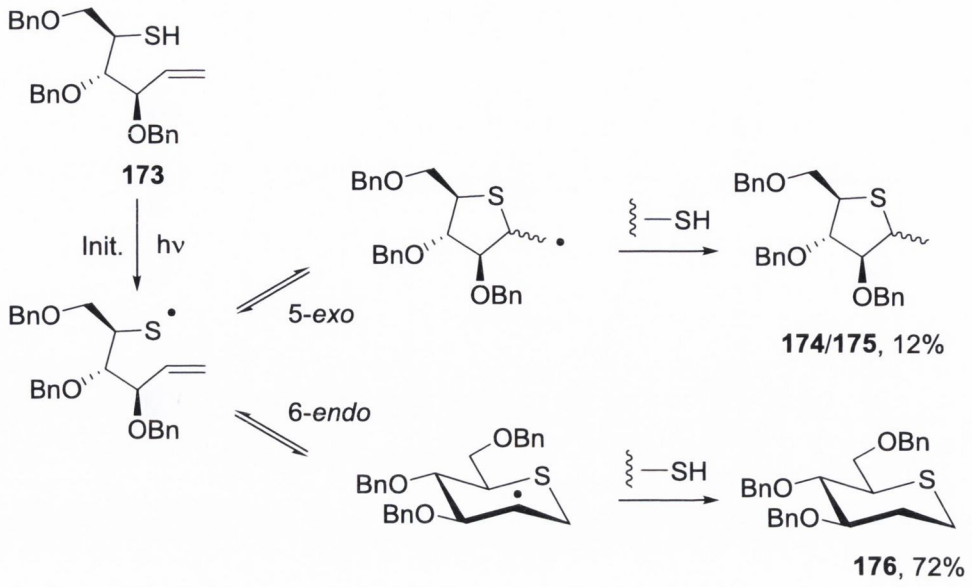
With the optimised conditions via radical thiol-ene to 1,2 di-deoxy thiosugars, we were also interested in developing a synthetic pathway that would allow for retention of configuration at C-5 in order to prepare the more common D-sugars. In order to install the thiol group while maintaining the conformation of the parent sugar a double inversion strategy was employed.[247] The first inversion was carried out by way of a Mitsunobu reaction with *p*-nitrobenzoic acid to furnish **170** in an excellent 78 % yield. On a scale of 1.00 g the reaction proceeded very smoothly. However upon scale up vast excess of reagents were required and up to 1 week was required for the reaction to reach completion. Large-scale reactions also led to difficulties in the purification of the reaction mixture, which initially led to unacceptable loss of material. However, by including a basic wash to remove residual *p*-nitrobenzoic acid and by suspending the reaction mixture in toluene overnight prior to column chromatography to crystallise unwanted triphenylphosphine oxide, sufficient yields of $\geq$ 60% could be obtained on a large scale.

170 was deprotected under basic conditions to afford **171** in excellent yield ≥ 99%. A thioacetate group was then installed as before via a triflation/thioacetate displacement, proceeding in a comparable 60% yield. The free thiol **173** was prepared in quantitative yield on treatment of **172** with freshly prepared degassed sodium methoxide.



Scheme 35 Synthesis of radical precursor **173** with retention of configuration at C-5

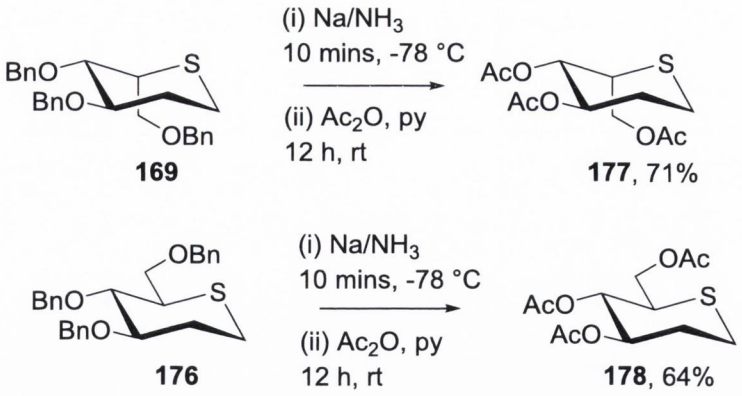
Having successfully optimised an intramolecular thiol ene reaction for the synthesis of **169** we next investigated the C-4 epimeric thiol **173** using the previously optimised reaction conditions. Gratifyingly the reaction proceeded to give the desired 6-*endo* product **176** in a 72% yield and the 5-*exo* products **174/175** in a combined yield of 12% (Scheme 36).



Scheme 36 Thiyl radical cyclisation starting from thiol **173**

2.6 Deprotection of thiosugars 177 and 178

As thiosugars potentially hold interesting biological activities in their deprotected form it was anticipated to remove the benzyl protecting groups from compounds **169** and **176**. It is believed that thiofuranosyl compounds **167**, **168**, **174** and **175** may also function as glucosidase inhibitors. However these compounds could not be debenzylated owing to insufficient material being generated from the synthesis. Further work on radical thiol-ene concentrated on the promotion of a 5-*exo* cyclisation. The results from this work will be discussed in the following sections. In the first instance, hydrogenation to remove the benzyl protecting group was applied using hydrogen over Pd/C. No reaction was observed presumably due to the sulphur moiety poisoning the palladium.[246] Repeating the reaction under a pressurised system equally did not give rise to the deprotected product. Acetic acid was added to the reaction in order to wash the catalyst surface and minimize thiol poisoning. This was also unsuccessful. Attention was then turned to a Birch reduction which cleanly removed the benzyl protecting groups from both thiosugars. The Birch reaction was quenched using acetic acid and methanol[259] and therefore a large excess of ammonium acetate was observed which could not be removed from the deprotected compound by chromatography. For ease of purification and characterisation both reaction mixtures were therefore acetylated. Compounds **177** and **178** will undergo biological testing as putative glucosidase inhibitors.[260]



Scheme 37 Deprotection/ Acetylation protocol for thiosugars **177** and **178**

2.7 Application of methodology to a pyranose system

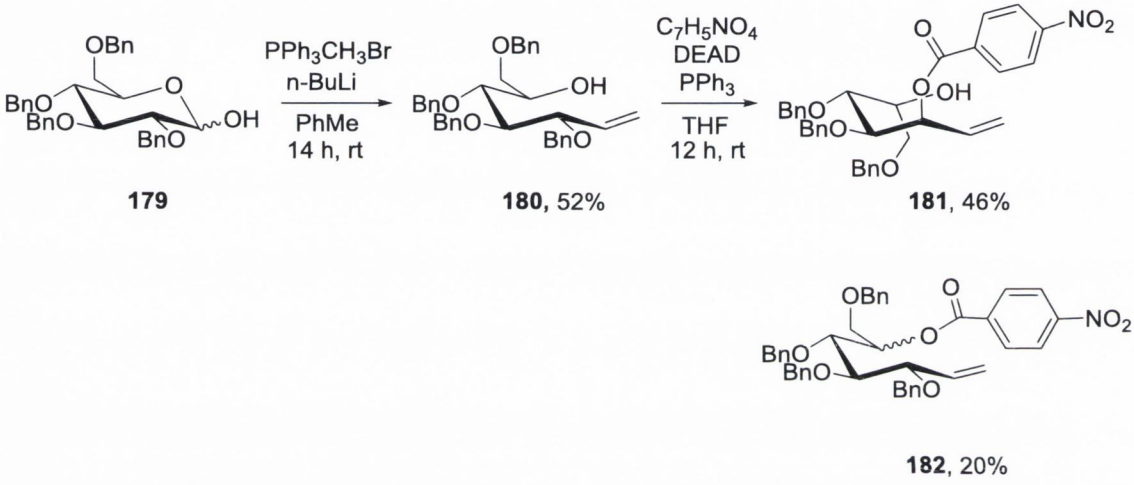
2.7.1 Towards the synthesis of thioseptanoses

Following the excellent results obtained in the radical thiol ene cyclisation of **164** and **173**, we were encouraged to evaluate our newly established methodology using different glycosyl thiols. It was initially decided to apply our synthetic strategy to a pyranose system. In the first instance this would allow investigation if the methodology could be extended to the synthesis of synthetically challenging thioseptanose sugars. While this area has been relatively unexplored Bozo *et al.*[261] have prepared D-thioglucoseptanosides via a Pummer rearrangement and compounds prepared were found to exhibit antithrombotic activity.

Because of ring strain, septanoses do not exist in great abundance naturally, however due to their enhanced conformational flexibility relative to pyranose sugars they may represent interesting candidates for glucosidase inhibition. Taking inspiration from the work of Martin *et al.*[247] our synthesis began from a D-*galacto* derivative. Previous synthetic endeavours, as discussed in Chapter 4, highlighted that displacement reactions using D-galactose proceed generally without complication while identical reactions on a D-gluco epimer are accompanied with complex inseparable mixtures.

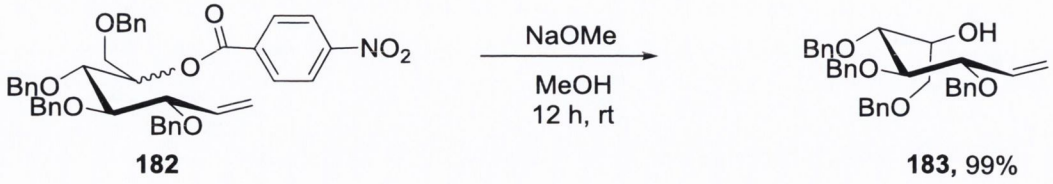
Wittig metheneylation, following Sinäys procedure[248] as before, afforded alkene **180** in 52 % yield from tetra-*O*-benzylgalactopyranose **179**. While this reaction proceeded within 24 h on the arabino system, the corresponding pyranose hemiacetal required 72 h

to reach completion. In the next step we applied Mitsunobu conditions in order to prepare the L-altro *p*-nitrobenzoate derivative. As before, Di-isopropylazodicarboxylate (DIAD) was employed for the transformation while DEAD was the reported Mitsunobu reagent in the literature protocol.[247] However, upon reaction we observed two distinct products, both with an identical correct mass by ESI^+. Detailed NMR analysis revealed them to be the expected epimerisation product and a rearrangement product with inversion of configuration and substitution of the PNB group at C-3 and inversion of configuration also at C-6 (Scheme 38).



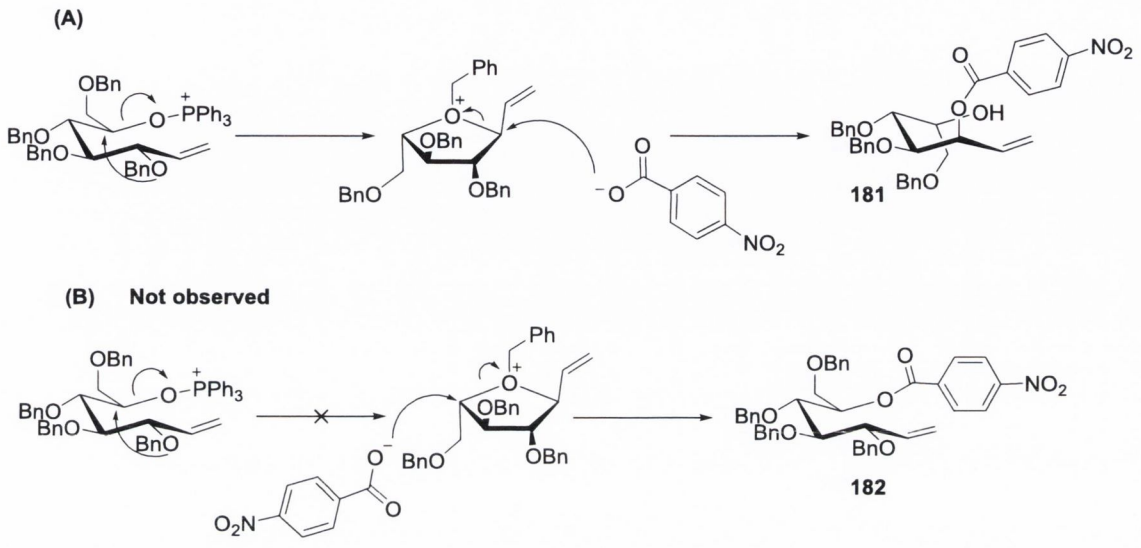
Scheme 38 Mitsunobu reaction leading to an unexpected epimerization

We tentatively proposed a mechanism for this rearrangement wherein the C-3 benzylic oxygen attacks the activated alcohol at C-6. The cyclic oxonium intermediate would be preferentially attacked at C-3 providing substitution of the PNB group at C-3 and also inversion of configuration at both C-3 and C-5. The mechanism could explain the observed stereochemical outcome of the rearrangement product of the reaction. However, in order to ascertain if **182** has the stereochemical structure of the SM or the expected Mitsunobu epimer, we hydrolysed the PNB group under basic conditions (Scheme 39).



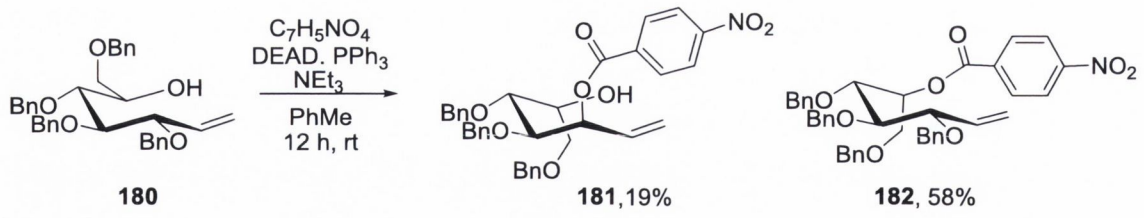
Scheme 39 Hydrolysis of benzoate **182** in order to ascertain stereochemistry of SM

The NMR of **183** was found to be identical to the starting material. It was therefore proposed that pathway B as depicted in Scheme 40 was not a competing process, possibly due to the increased reactivity of the allylic carbon at C-3.



Scheme 40 Proposed formation of **181** and **182**

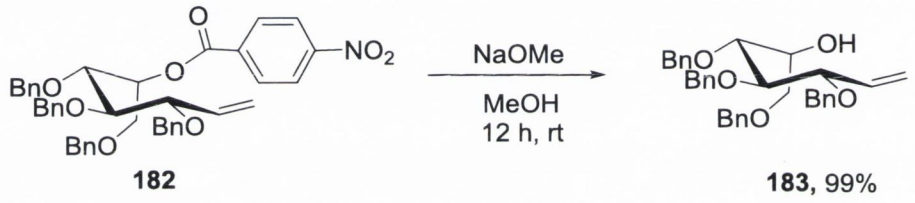
While this result was not obtained by Martin *et al.*[247] who performed the reaction on the same substrate, albeit employing the use of DEAD as opposed to DIAD, a literature search revealed that a similar result had been noted by Persky *et al.*[262] While in our hands the rearrangement product **181** constituted 46 % of the reaction mixture it was only uncovered by Persky *et al.*[262]as a minor side product (9:1 molar ratio). Instead they found this competing reaction dominant only in reactions with *gluco* and *manno* substrates with DEAD as the Mitsunobu reagent. Gratifyingly, their proposed mechanism for the rearrangement agrees with our presumed pathway, although their proposal also takes into account a further side product not observed by us. Persky *et al.*[262] reported that by changing the solvent and reactant ratio, the desired epimerisation could be promoted. Therefore toluene was substituted as solvent in place of the more polar THF in order to destabilise the protonated oxonium intermediate. Triethylamine was also added in order to increase the concentration of nucleophilic carboxylate, which led to a satisfactory 3:1 molar ratio of the desired compound to rearrangement product.



Scheme 41 Optimised Mitsunobu conditions to afford **182**

2.7.2 Attempt at thioacetate incorporation

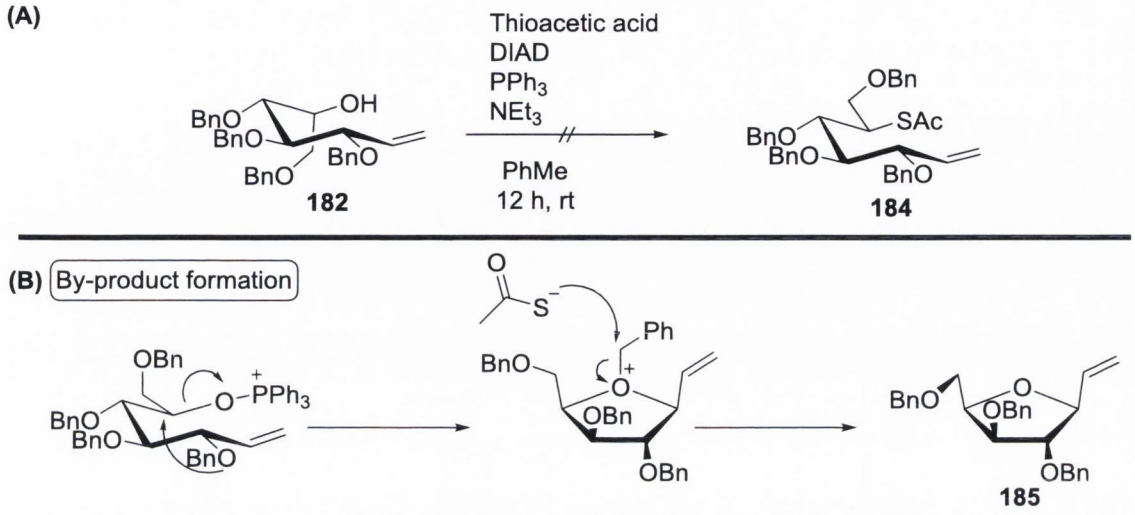
With **182** in hand we deprotected this substrate to the corresponding alcohol **183** in quantitative yield (Scheme 42).



Scheme 42 Hydrolysis of **182**

From previous synthetic endeavours we have learnt that the presence of a good leaving group in a 1,4 position to an ether leads to a rapid benzyloxy cyclisation to form a furan ring (see Chapter 4 for details). Therefore we anticipated that the use of thioacetic acid as the acidic nucleophle in a second Mitsunobu reaction could lend itself to the formation of the desired thioacetate. Applying the optimised conditions used for the synthesis of **182** in order to avoid a similar rearrangement reaction, unfortunately, led to no reaction being observed. We postulated that the presence of base led to disulphide formation of thioacetic acid. Therefore, the reaction was repeated in the absence of base, which again gave no reaction. Addition of base and changing the solvent from hydrophobic toluene to the original THF led to the observation of the unwanted furan ring **185**, presumably formed from C-3 benzyloxy cyclisation. We proposed that installation of a milder leaving group at the C-5 position could provide a viable option as it could prove less reactive to C-3 benzyloxy substitution. The tosylate of **183** was prepared via reaction with TsCl (2eq.) in NEt_3. With the tosylate in hand we attempted *in situ* installation of the

thioacetate via displacement of leaving group. However all attempts at tosylate displacement led to the undesired furan side product (Table 3).



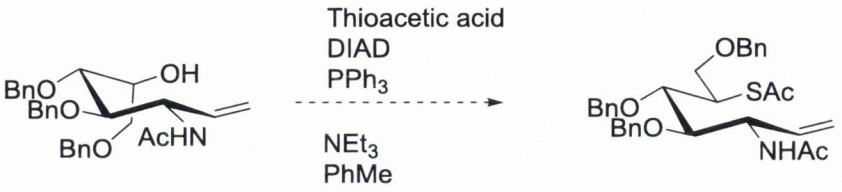
Scheme 43 (A) Attempted synthesis of thioester, (B) Proposed mechanism for byproduct **185** formation

Entry	Starting Material	Reactants	Base	Solvent	Isolated Product[a]
1	**183**	Thioacetic acid (4eq) DIAD (4eq) PPh_3 (3eq)	NEt_3 (5eq)	PhMe	No reaction
2	**183**	Thioacetic acid (4eq) DIAD (4eq) PPh_3 (3eq)	-	PhMe	No reaction
3	**183**	Thioacetic acid (4eq) DIAD (4eq) PPh_3 (3eq)	NEt_3 (5eq)	THF	**185** (43%)
4	**183**	(i) TsCl (2eq), NEt_3 (ii) KSAc, DMF	-	(i)NEt_3 (ii) DMF	**185** (64%)

[a]Determined by ^{1}H NMR Spectroscopy

Table 3 Attempts at thioacetate incorporation

Owing to the synthetic difficulties in installing the thioacetate group on the C-6 position of a pyranose ring this synthesis was temporarily abandoned. A possible solution to circumvent unwanted cyclisation reactions could be the application of this methodology to a glucosamine system as the *N*-acyl group at C-2 should negate any cyclisations (Scheme 44).



186 **187**

Scheme 44 Possible solution to incorporate thioacetate in a glycosyl pryanose system

2.8 Investigation of 5-*exo* ring closure reaction

In view of the excellent results obtained with a 6-*endo* ring closure on a furanose ring,[260] and the difficulties experienced in synthesising a pyranose precursor, we decided to turn our attention to the synthesis of thiofuranose derivatives. In so doing, we aimed to investigate if the stereochemistry of the ring closure could be controlled by stabilising the resultant alkyl radical following ring closure. It was initially envisaged to persue the synthesis of an analogous thiol containing an isopropyl alkene. It was proposed that in contrast to the system containing the terminal olefin, the 5-*exo* cyclisation should dominate over the 6-*endo* ring closure by virtue of the tertiary radical formed. The 5-*exo* radical cyclization process would also result in the formation of a new stereocentre at C-1 and we were interested in studying the diastereoselectivity of the radical cyclisation reaction process (Figure 24).

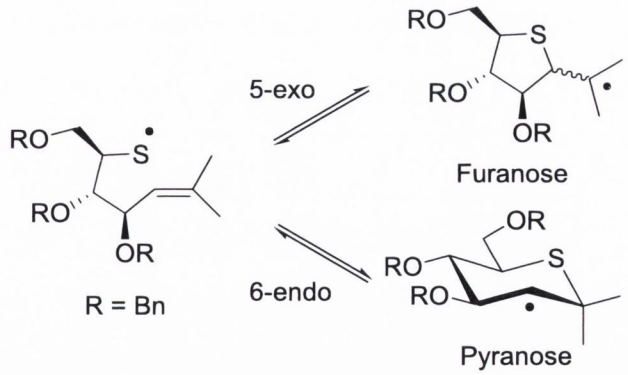
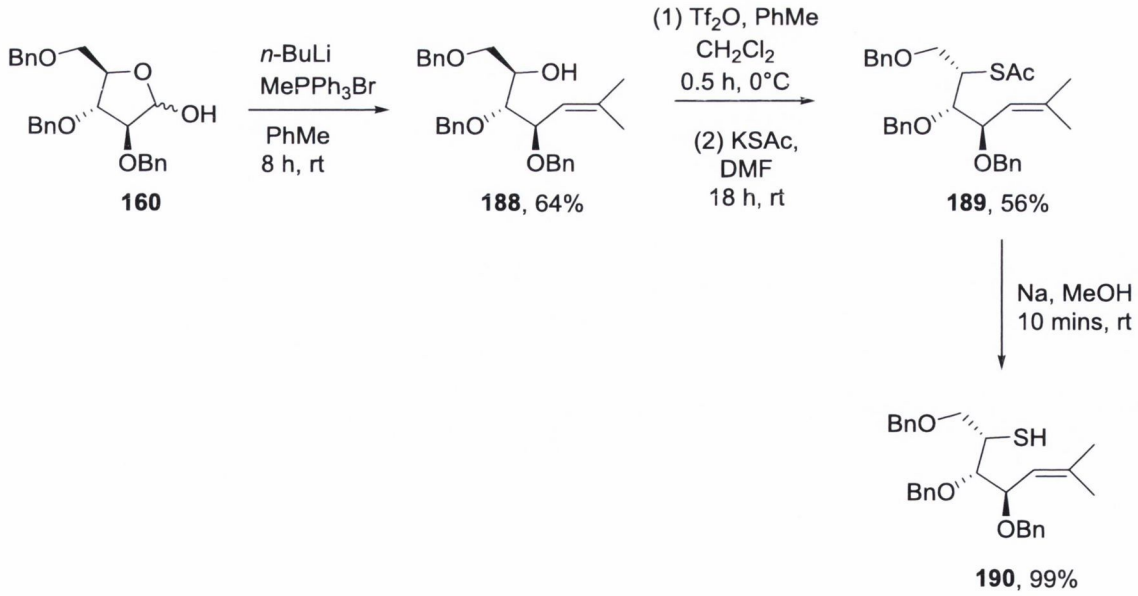


Figure 24 Proposed thiyl radical cyclisation onto an isopropyl functionalised alkene

2.8.1 Synthesis of an isopropyl analog

The synthesis commenced with the preparation of the isopropyl olefin **188**. Treatment of 2,3,4 tri-*O*-benzyl-D-arabinofuranose, **160,** with *n*-BuLi and isopropyltriphenylphosphonium iodide gave **188** in 64% yield. Sequential triflation/displacement with potassium thioacetate gave **188** in good yield, however this reaction was not always reproducible on larger scales as triflate elimation products were observed and necessitated a laborious separation from the desired thioacetate. With **189** in hand, basic hydrolysis ensued which gave **190** in excellent yield without complication (Scheme 45).



Scheme 45 Synthesis of an isopropyl alkene precursor

Detailed NMR studies on **189** clearly showed that a strong NOE correlation could be detected between the methyl group of the thioacetate (2.29 ppm) and the methyl groups of the isopropyl (1.80 and 1.61 ppm) (Figure 25). The result was confirmed by irradiating the isopropyl signals which correspondingly correlated with the thioacetate peak. This interaction suggests that the orientation of the compound could be primed for 5-*exo* attack. The same correlation was not noted for **190**, possibly due to the shorter length of the sugar chain.

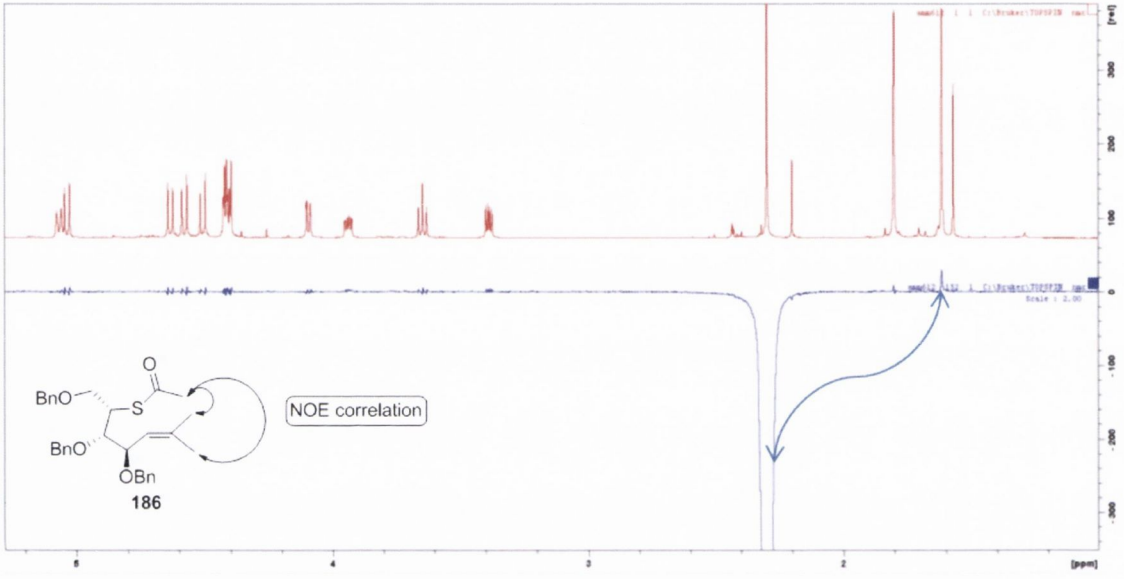
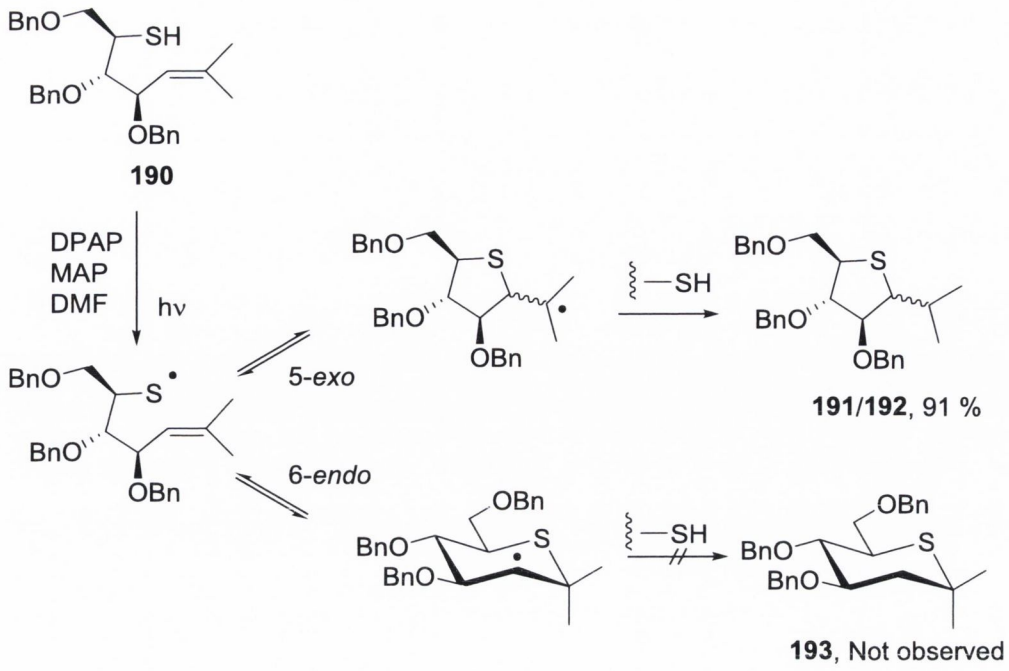


Figure 25 NOE correlation between isopropyl and methyl thioacetate peaks in **189**

With the desired precursor in hand, radical formation ensued through the use of DPAP and MAP as before. The reaction proceeded with almost quantitative conversion to yield only the 5-*exo* product as an inseparable mixture of diastereoisomers **191/192** (3:1, β:α). The diastereomeric ratio was determined by ^{1}H-NMR. The competing 6-*endo* product **193** was not observed under these conditions. This result constituted the first 5-*exo* thiyl radical cyclisation route to thiofuranosides and clearly demonstrated that 5-*exo*-trig radical cyclizations of a thiyl radical onto a substituted alkene could be used to prepare *C*-linked thiofuranosides in high yield (Scheme 46).



Scheme 46 5-*exo* cyclisation to yield thiofuranoses **191**/**192**

2.8.1.1 Rationalisation of the product distribution and diastereomeric ratio

Both the product distribution and the diastereomeric ratio of 5-*exo*-trig products observed for this reaction require comment. The distribution of products formed from the intramolecular thiyl-radical cyclisation depends on a number of factors including the relative stability of the alkyl radicals formed upon cyclisation and the rate of the radical chain transfer step (Figure 26). For the diastereomeric ratio of the 5-*exo* products, steric factors relating to the stereochemistry of the benzyl protected hydroxyl groups and the conformation of the transition state should be considered. As previously eluded to in Section 2.4.2, the major factor governing the overall kinetics of the thiol-ene polymerization reaction is the ratio of the propagation rate to the chain transfer rate.[256,257] For the intra-molecular process we assume that the chain transfer step is rate limiting and that the overall process is first order with respect to thiol concentration. It was anticipated that the 5-*exo*-trig products would dominate due to the relative stability of the tertiary alkyl radical that is formed upon 5-*exo* cyclisation. In terms of the diastereoselectivity of the radical reaction, there are two possible transition structures which can potentially be adopted upon reaction. Transition state A and Transition state B (Figure 26). Beckwith[263] and Houk[264] have reported that hex-5-enyl radical cyclisations normally proceed through

either a chair-like or boat-like transition state with the chair-like state predominating. Beckwith[263] proposed that the major product would arise from a conformation where the substituents could occupy quasi-equatorial orientations. Rajan Babu[265-267] has carried out detailed studies on the cyclisation of hex-5-enyl radicals derived from carbohydrates. His studies have concluded that in systems with a C_4 substituent present, the local allylic conformation dictates the choice between the "chair-like" and "boat-like" transition states and the conformation that results in the least allylic strain will dominate.[267] In the case of thiol **190**, formation of the chair-like transition structure **A** is favored since it minimizes steric interactions between the isopropyl group at C-1 and the benzyl protecting group at C-2 which results in the 1,2-trans product **191** as the major diastereoisomer (Figure 26). The 1,2-cis product **192** was the minor product. The formation of the new C1-C2 bond in both **191** and **192** was confirmed by the presence of the strong correlation between H-1 and H-2 in the COSY experiment. The relative stereochemistry of each diastereoisomer was determined by detailed analysis of coupling constants.

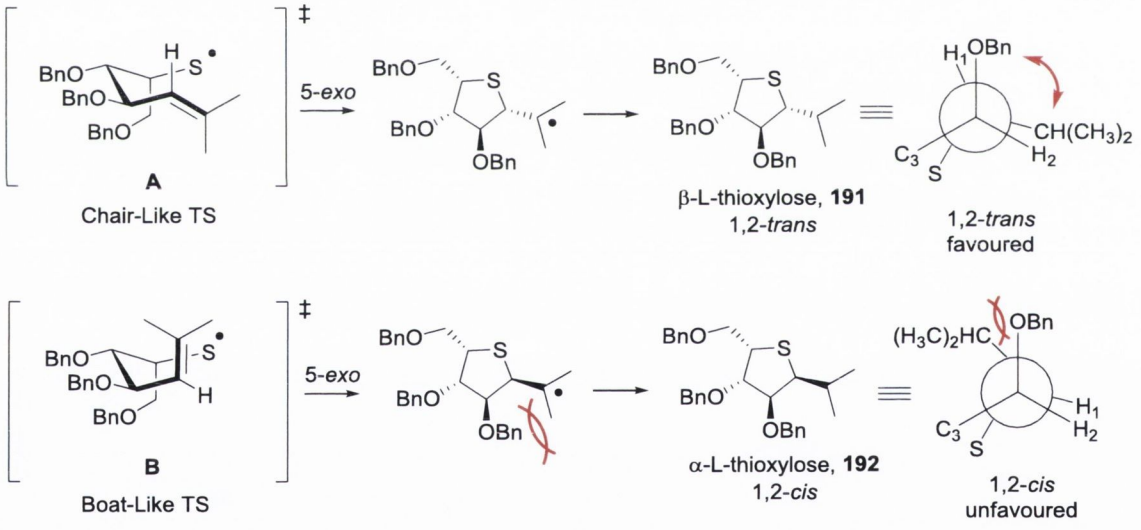


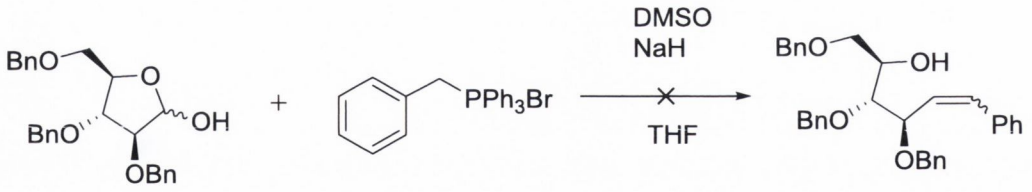
Figure 26 Transition state structures for thiyl radical derived from **190**.

2.8.2 Synthesis of a phenyl analog

2.8.2.1 Synthesis of phenyl substituted glycosyl alkene

Prompted by the discovery that the regioselectivity of the radical ring closure could be controlled by stabilising the alkyl radical, we decided to futher investigate the methodology. Addition of a phenyl ring on the alkene would additionally stabilise the resultant alkyl radical, allowing delocalisation into the aromatic ring and thus further promoting a 5-*exo* cyclisation.

Reaction of triphenylphosphine and benzyl bromide gave the desired Wittig salt on a large scale. Jung *et al.*[268] have described a procedure for the synthesis of a phenyl substituted alkene from the glycosyl hemiacetal of D-xylose, however application of the reported protocol to tri-*O*-benzyl-arabinofuranose gave no product. Extending the reaction time overnight led to a breakdown of the sugar with numerous products noted on TLC. The reaction was repeated using revised quantities of reagents however reaction did not proceed within the reported 2 h and a breakdown of material ensued when the reaction was left on overnight.

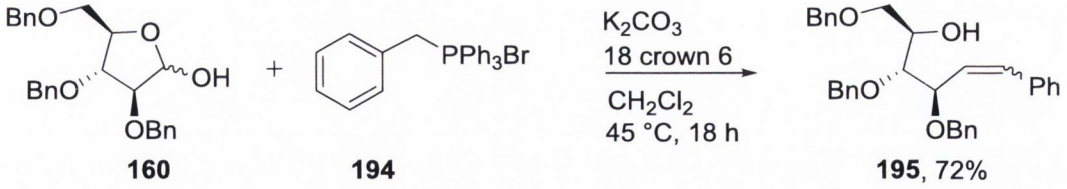


160 **194** **195**

Entry	Wittig salt	Base	Solvent	Reaction time	Product isolated
1	**194**	DMSO anion [DMSO (3 eq) NaH (7.6 eq)]	THF	2h	No reaction
2	**194**	DMSO anion [DMSO (3 eq) NaH (7.6 eq)]	THF	16 h	Breakdown
3	**194**	DMSO anion [DMSO (3 eq) NaH (3 eq)]	THF	2h	No reaction
4	**194**	K^tOBU	THF	8h	No reaction
5	**194**	K_2CO_3	CH_2Cl_2	16 h	**195,** 20%
6	**194**	K_2CO_3	CH_2Cl_2	16 h	**195,** 72 %

Table 4 Optimisation of phenyl substituted alkene synthesis

Attention was turned to ylide formation through the use of potassium *tert*-butoxide, this reaction was also unsuccessful. Whilst the ylide was formed, only starting material was isolated after the reaction. Finally we attempted olefin formation via the procedure described by Motoshima *et al.*[269] wherein potassium carbonate functions as the base and 18-crown-6 is added as a phase transfer catalyst. Gratifyingly, reaction with one equivalent of the base and Wittig salt yielded 20% of the desired compound. Increasing the molar ratio to three equivalents of base and Wittig salt gave an optimised yield of **195** of 72% (Scheme 47).



Scheme 47 Synthesis of alkene **195**

195 was obtained in a 1:1 molar ratio of cis:trans isomers which were inseperable by column chromatography. While this complicated NMR analysis of the compounds they could be easily separated via 1- and 2D TOCSY experiments. No further effort was made to separate the isomers. Upon cyclisation we expected only two isomers, the α- and β-furanosides.

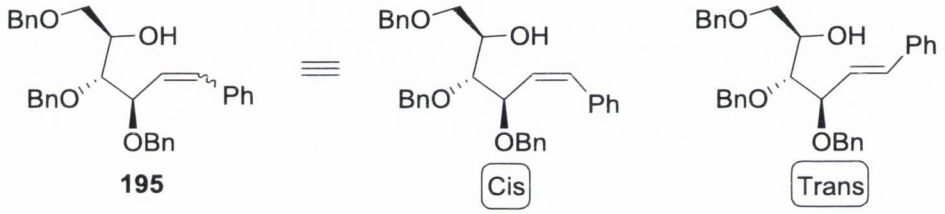
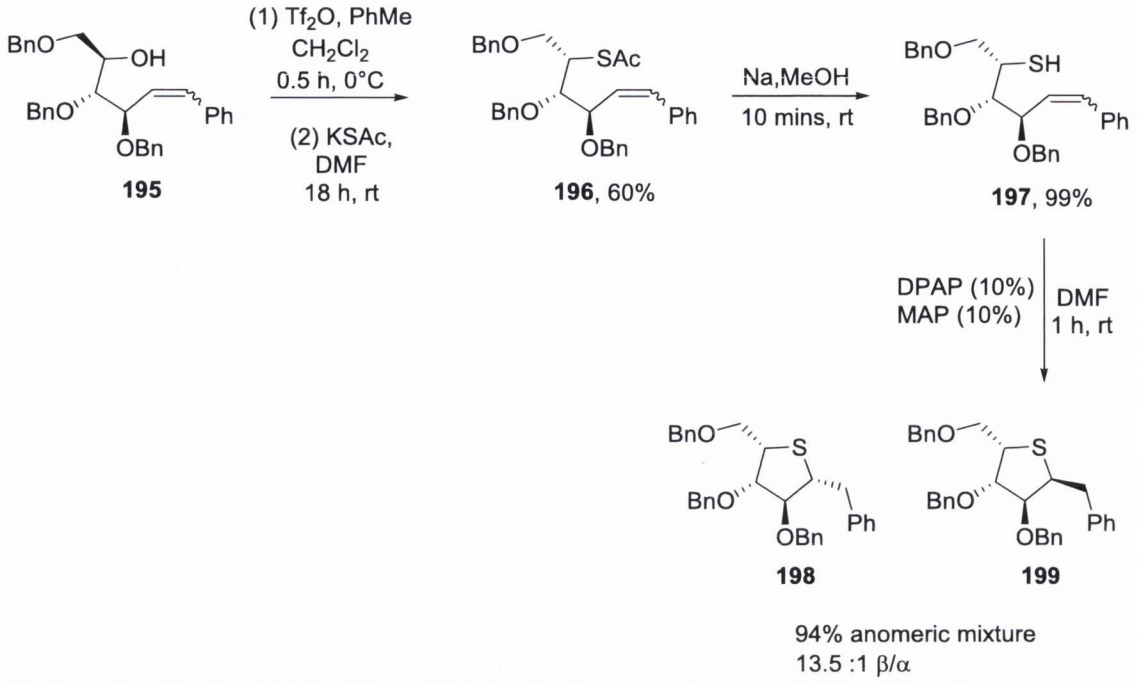


Figure 27 NMR analysis of alkene isomers (A) 1D TOCSY of cis isomer (B) 1D TOCSY of trans isomer and (C) ^{1}H NMR spectrum

2.8.2.2 Synthesis of thiofuranose derivative from phenyl glycosyl alkene 195

With alkene **195** in hand we then applied the developed synthetic protocol to furnish the corresponding thiyl radical precursor. Triflation of the free hydroxyl, followed by nucleophilic displacement with potassium thioacetate, afforded **196**. Basic hydrolysis yielded **197** in quantitative yield. Radical precursor **197** was thus treated with DPAP and MAP to initiate radical formation with concomitant cyclisation. To our delight, the reaction proceeded to give only an anomeric mixture of the expected furanoside **198/199**, and considerable stereoselectivity was noted with the α/β ratio an impressive 1:13.5 (Scheme 48).



Scheme 48 Synthesis of thiosugars **198** and **199**

We proposed a two-fold explanation for the observed diastereocontrol. The result firstly suggested that the formation of the chair-like transition structure C was highly favoured in order to minimize allylic strain. We further rationalised that an additional stabilising interaction must be participating in the stabilisation of transition state C. Thereafter we considered that a π-stacking interaction could be occuring in this system between the anomeric phenyl group and the C-6 OBn protecting group which occupy the same face of the sugar (Figure 28). This type of π-stacking promoted diastereoselectivity in intramolecular reactions has been reported by a number of groups.[270,271]

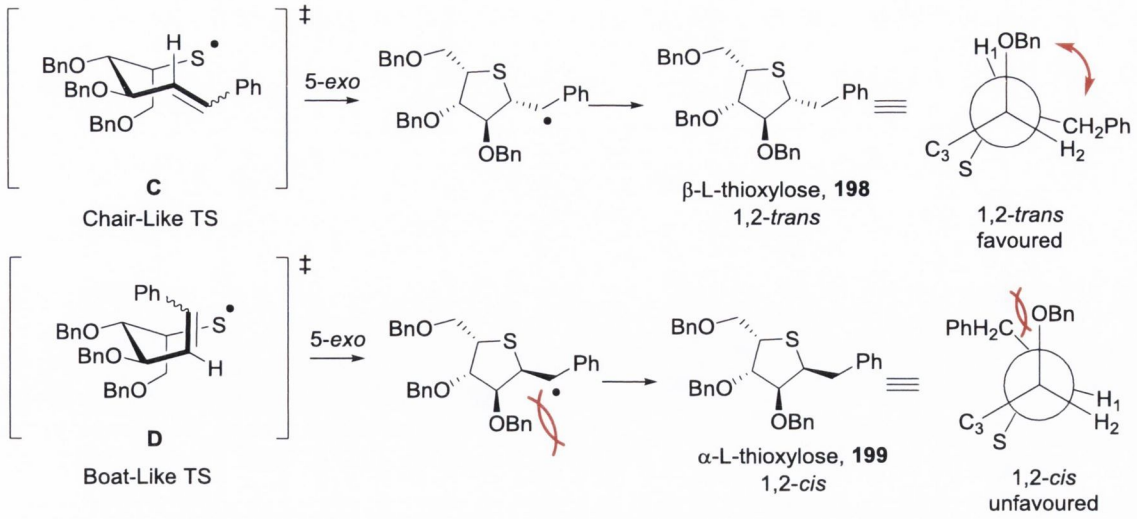
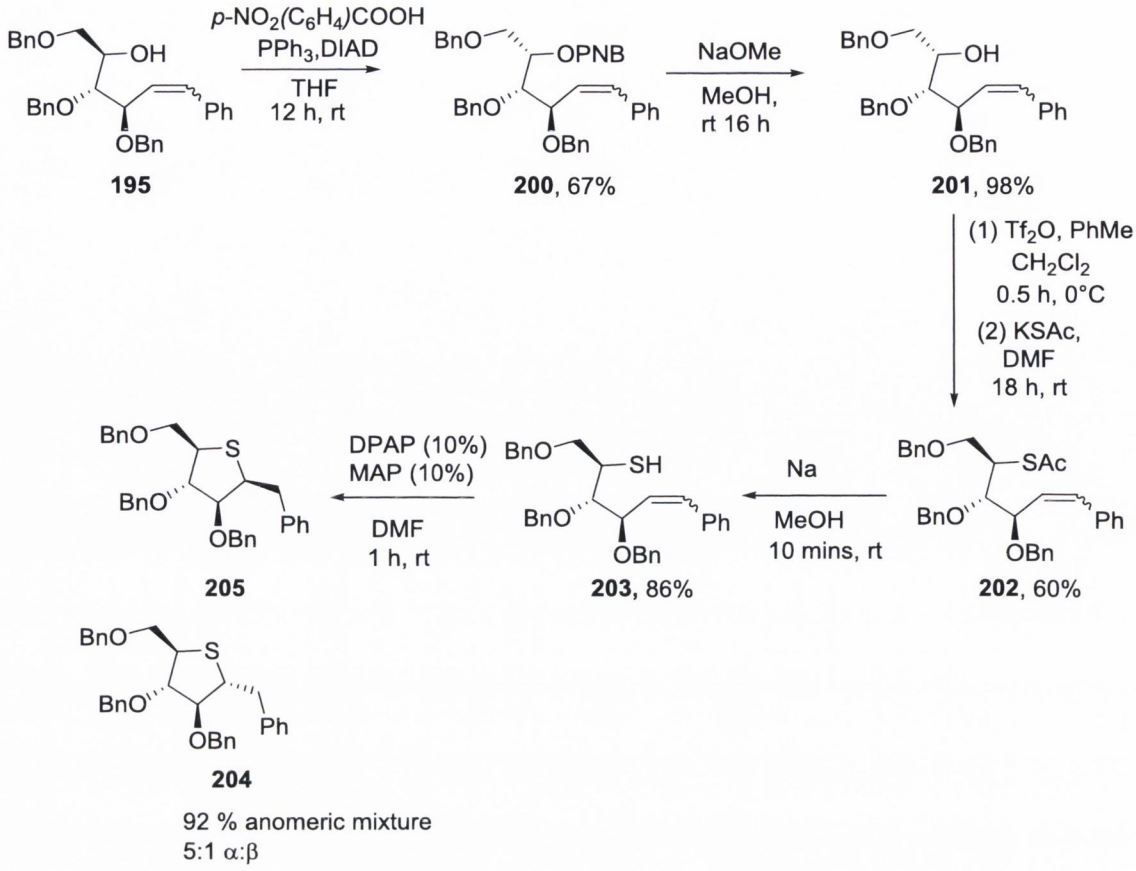


Figure 28 Transition state structure for the thiyl radical derived from **197**

2.8.2.3 Synthesis of a thiofuranose derivative with retained stereochemistry

Having obtained excellent diastereoselectivity by carrying out the thiyl radical cyclisation with a phenyl substituent on the alkene, we investigated if the same steric control could be afforded on an analog with the original *arabino*- conformation. This would ascertain what effect the orientation of the group at C-4 asserts on the stereochemistry of the product. Applying the developed protocol for the double inversion, **195** underwent Mitsunobu conditions with p-nitrobenzoic acid and DIAD to afford **200** in good yield. Hydrolysis of the p-nitrobenzoate group gave full conversion to the inverted alcohol **201,** after which triflation/displacement with potassium thioacetate provided **202,** which exhibited the original *arabino*-conformation. Hydrolysis of the thioacetate group gave the radical precursor **203** and initiation ensued upon treatment of **203** with 10 % DPAP and 10 % MAP. We observed that the anomeric mixture of furanosides **204** and **205** were obtained in 92% isolated yield and an anomeric ratio 5:1 α/β (Scheme 49).



Scheme 49 Synthesis of thiosugars **204** and **205**

This result confirms the proposed explanation for stereo-control in the preceding section and also suggests that the orientation of the group at C-4 plays a vital role in controlling the steroselectivity of the radical ring closure. In this system steric clashes exist between the bulky aromatic substituents at C-2 and C-3, therefore favouring the formation of a chair like transition state. This resulted in the formation of the α-anomer as the predominant product. In this case there would be no π-stacking interaction between the anomeric phenyl group and the C-6 OBn on the sugar ring and thus the diastereoselectivity was comparable to that of the isopropylidene example. This variation in diastereoselectivity strongly suggested that the stereochemistry at both C-2 and C-4 are important in determining the stereochemical outcome of the intra-molecular radical cyclization. This observation is consistent with observations reported by Beckwith and others for related systems.[263,264,266] It is also noteworthy that using a mixture of *E* and *Z* isomers in the starting material did not appear to affect the product distribution with both isomers the D- and L-sugar furnishing the 1,2-*trans* products **198** and **204** as the major product.

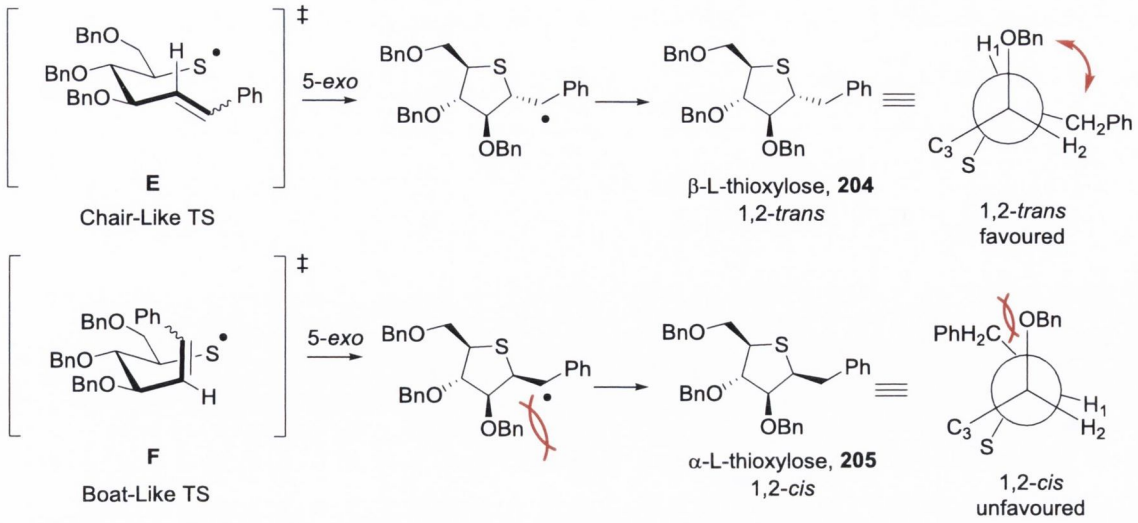


Figure 29 Transition state structure of thiyl radical from **203**

2.8.3 Extension of substrate scope

Encouraged by the excellent results obtained through thiyl radical cyclisations onto benzylic alkenes, we decided to extend the substrate scope further. We next turned our attention to the synthesis of a thiyl radical precursor with a benzoic acid motif conjugated to the alkene (Figure 30). This would allow for a study of the radical cyclisation onto an excellent Michael acceptor.[272] The subsequent benzoic acid functionalised thiosugar would function as a versatile synthetic 'handle', upon which a vast range of coupling reactions could be performed to yield very interesting biologically active products.

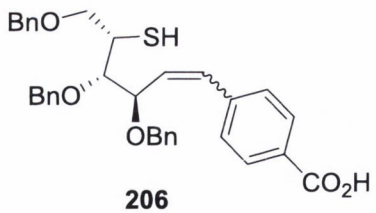
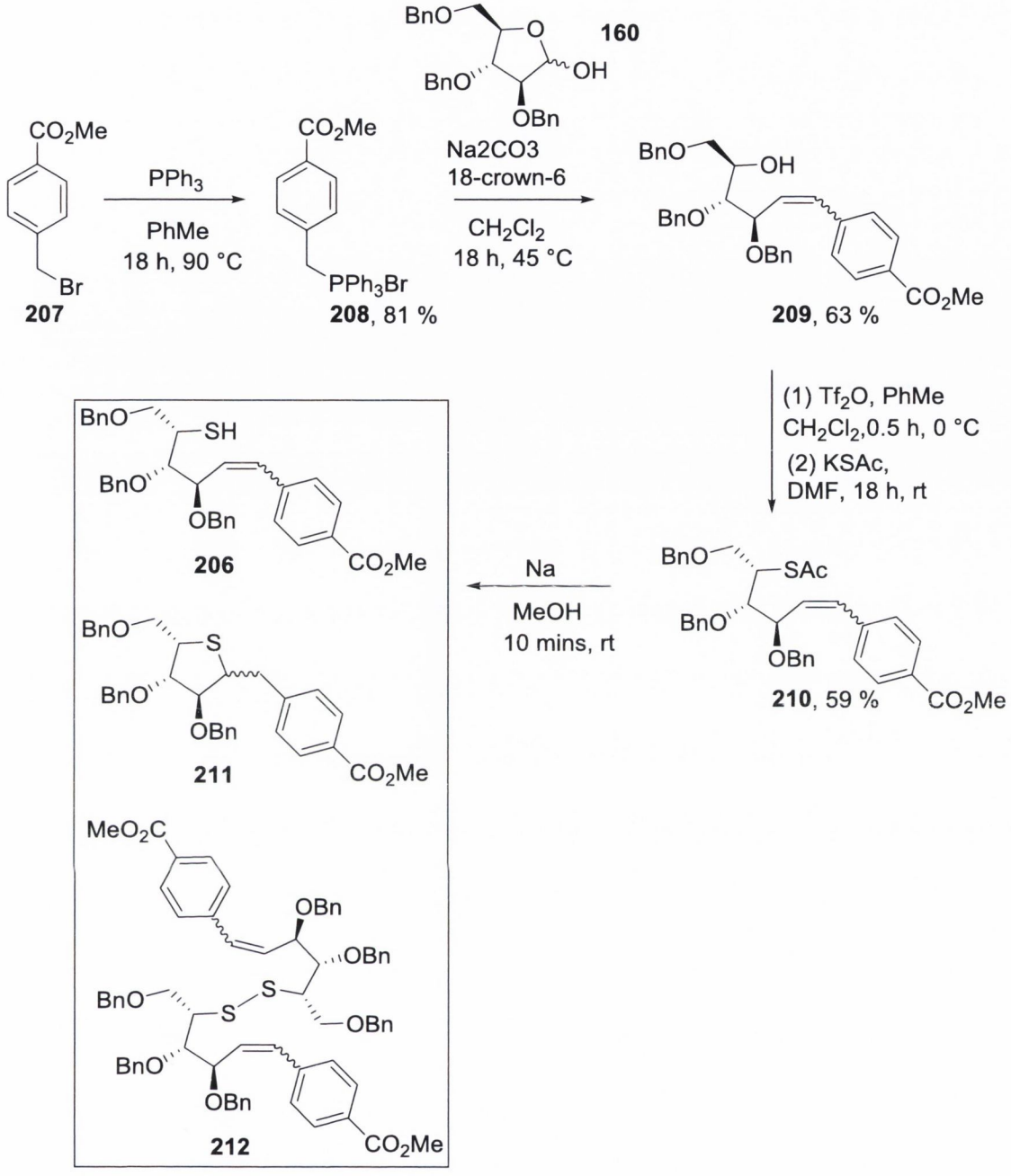


Figure 30 New synthetic target

We set out to synthesise the triphenylphosphonium Wittig salt from methyl 4-(bromomethyl) benzoate, which itself could be obtained economically from a commercial supplier. For practical reasons it was deemed sensible to carry out the synthesis on the

protected acid. As such the methyl benzoate alkene could be generated, and the developed synthetic methodology for the preparation of thiyl radical precursors applied. In order to avoid oxidative side reactions from the free thiol moiety, we aimed to deprotect the methyl benzoate to the free acid on the closed thiosugar ring following radical cyclisation.

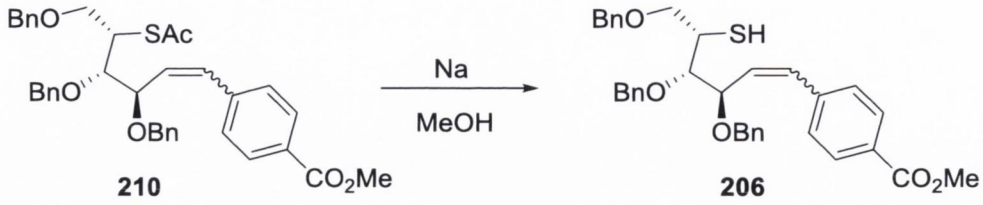
The synthesis began with the preparation of the Wittig salt. Triphenylphosphine and methyl 4-(bromomethyl) benzoate were refluxed in toluene overnight. The resultant salt was treated with Na_2CO_3 and 18-crown-6 in the presence of 2,3,4-tri-*O*-benzylarabinofuranose to yield the desired alkene **209** in a 1:1 ratio of isomers. As before, the isomers were not seperateable by column chromatography and necessitated the use of TOCSY spectra to characterise both compounds fully. With the alkene in hand, sequential triflation/displacement with potassium thioacetate was carried out to afford **210**. Basic hydrolysis of the thioacetate however did not proceed smoothly. **210** was initially treated with freshly prepared 0.1 M NaOMe which after five minutes gave three inseparable products **206**, **211** and **212** (Scheme 50).



Scheme 50 Byproducts isolated from basic hydrolysis of **210** in 0.1 M NaOH

We assumed the deprotection with concomitant cyclisation was a result of nucleophilic Michael addition of the thiol to the activated alkene. Similarily, the dimerised product **212** resulted from a further intra-molecular Michael addition. In order to circumvent the formation of **211** and **212** we attempted the deprotection of **210** at low temperature and with a 10-fold dilution of base. Optimised conditions were found at -10°C and in 0.01M NaOMe for 30 mins (Table 5). The crude reaction mixture appeared to decompose over time (~ two hours). Therefore, upon completion of the reaction, a rapid chromatography

ensued following which characterisation of the compound could be carried out. Unfortunately, owing to the short lifespan of **206** ^{13}C NMR could not be generated and the ^{13}C characterisation data had to be gleaned from the HSQC spectrum.



210 **206**

Entry	Temperature (°C)	NaOMe concentration (M)	Time (mins)	Yield of **206** (%)[a]
1	22	0.1	5	21
2	0	0.1	20	30
3	-10	0.1	20	56
4	-10	0.01	30	73

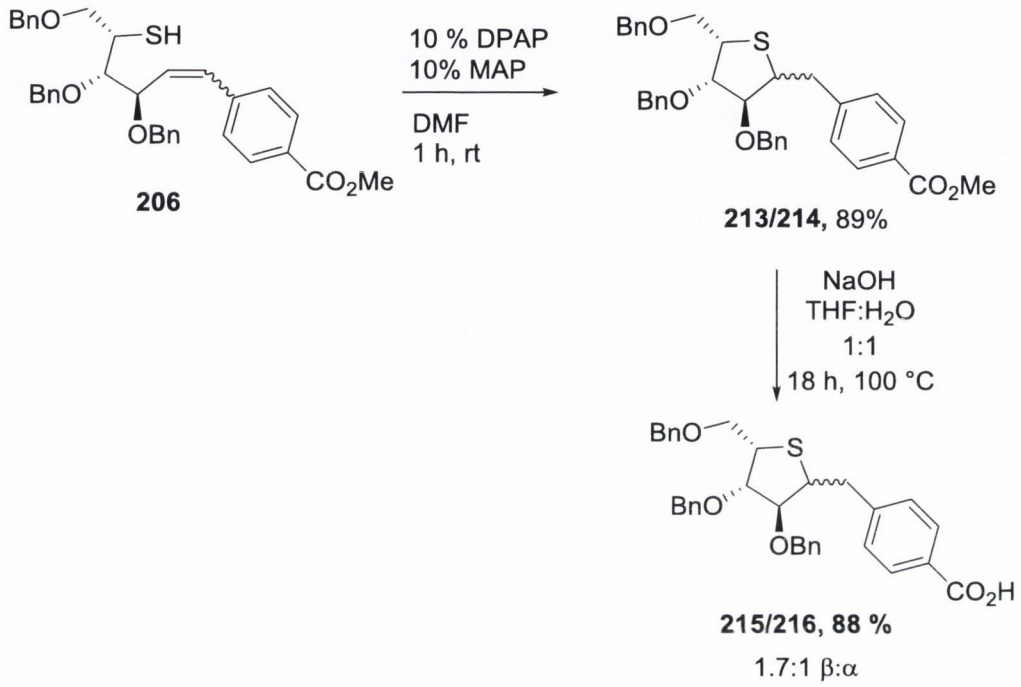
[a]Determined by ^{1}H NMR

Table 5 Optimisation of the deprotection of thioacetate **210**

Radical cyclisation of **206** gave the desired thiofurnaose isomers **213/214** as a 1.7:1 mixture of α/β in an excellent 89% yield. Interestingly the stereoselectivity of the radical cyclisation of **206** had drastically dropped compared to the phenyl thiofuranose analog **197** (13.5:1 α/β). It was reasoned that radicals, by their very nature, are soft species and as such react rapidly with activated alkenes, to give radicals that are highly stabilised by the extended conjugation. The superior kinetics of the radical reaction with **206** leads to a less selective reaction, and, as a result, thermodynamic factors such as steric clashes and π-stacking have less influence on the stereocontrol of the reaction.

With **213/214** in hand, we aimed to deprotect the methyl ester to afford the free acid. Applying the procedure of Niwayama *et al.*[273] did not lead to conversion within the specified time, instead increasing the concentration of NaOH tenfold and refluxing at 100°C overnight was necessary to reach full conversion and formation of **215/216** (Scheme 51). In the first instance the reaction mixture was purified through a plug of silica, however substantial loss of material resulted and the purified acid obtained appeared amorphous by NMR and therefore could not be fully characterised. Instead

215/216 could be characterised as the crude material which did not appear amorphous in nature, possibly due to less stacking of the aromatic rings. The benzoic acid thiofuranose **215/216** itself could function as an interesting glycosidase inhibitor, however we were also interested in investigating its potential as a synthetic 'handle' and as such it was our aim to synthesise a further functionalised glycoconjugate.



Scheme 51 Synthesis of thiofuranose benzoic acid derivatives **215/216**

2.8.4 Synthesis of a PEGylated fluorophore

2.8.4.1 Rationale for choice of linker and fluorophore

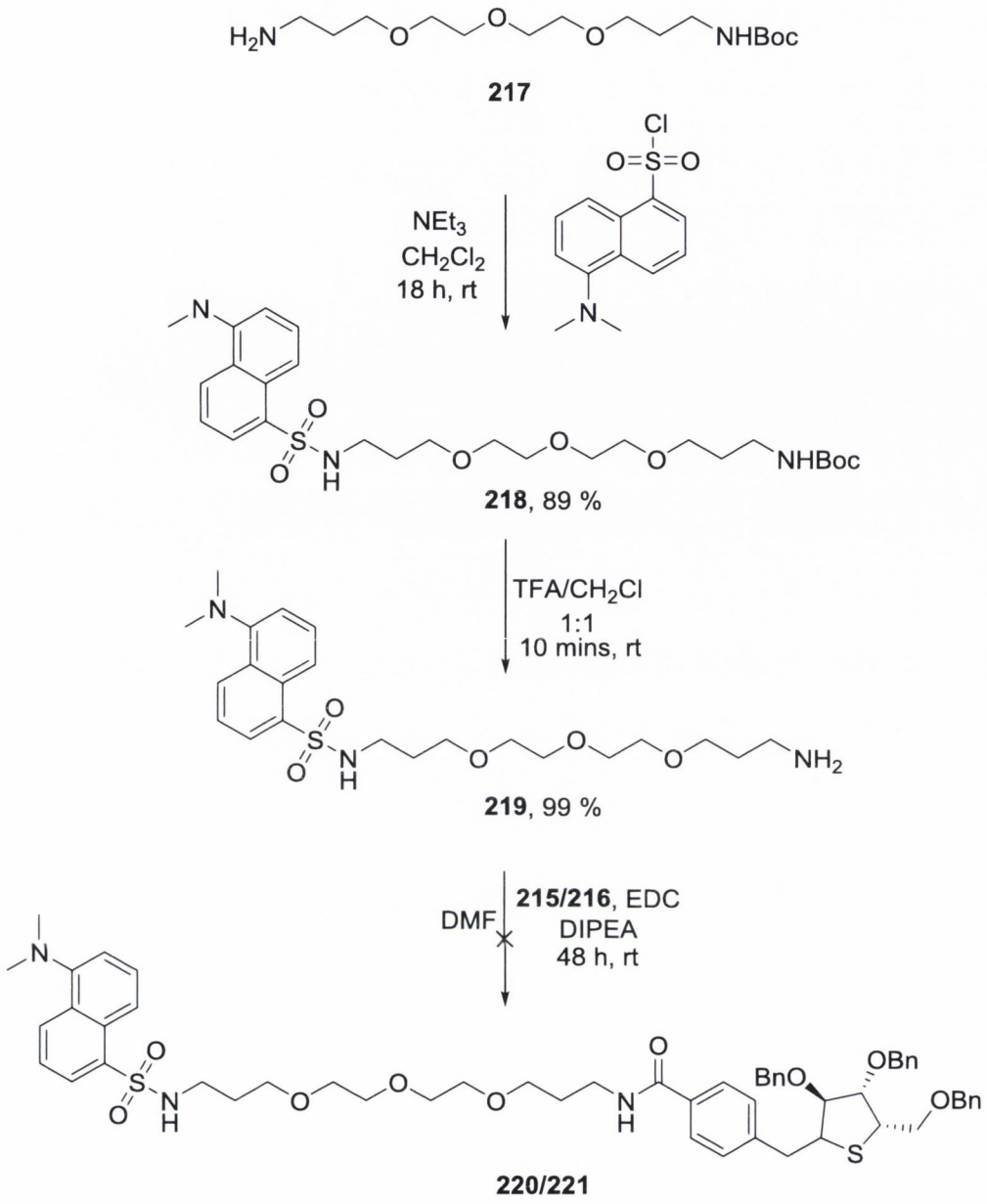
Recently many leading groups in the area of glucosidase inihibition have suggested that the inclusion of a hydrophobic group to an amino- or thiosugar structure can result in superior binding to the active site of the enzyme.[68,69,274-277] This effect can be attributed to a hydrophobic interaction between an aglycan group on the inhibitor's structure and a corresponding region in the enzyme pocket. Hermettor *et al.*[276] have fluorescently labelled derivatives of known glucosidase inhibitors and found an increase in the inhibitory activity, relative to the parent compounds' activity, by two folds of magnitude. Thereby these compounds are amongst the most potent reversible β-glycsoidase inhibitors

to date. We became interested in applying this strategy to our own system and thus decided to functionalise the acid moiety of **215/216** with a dansyl fluorophore coordinated through a PEG (polyethylene glycol) linker.

In addition to its potential biological activity as a glucosidasae inhibitor in its own right, a dansyl tagged thiosugar could be directly investigated in a biological system and allow for mapping of the enzyme active site. Dansyl chloride was selected initially as the fluorophore of choice as it is widely applied to investigate protein sequencing and, as one of the simplest naphthalene fluorophores, it could function as an excellent starting point for the development of more exotic derivatives. We anticipated to link the dansyl moiety to the sugar unit via a PEG linker. Oligoethylene glycol chains have frequently been applied as spacer arms between ligands and fluorescent tags and will bestow structural flexibility to the sugar-fluorophore system.[278,279]

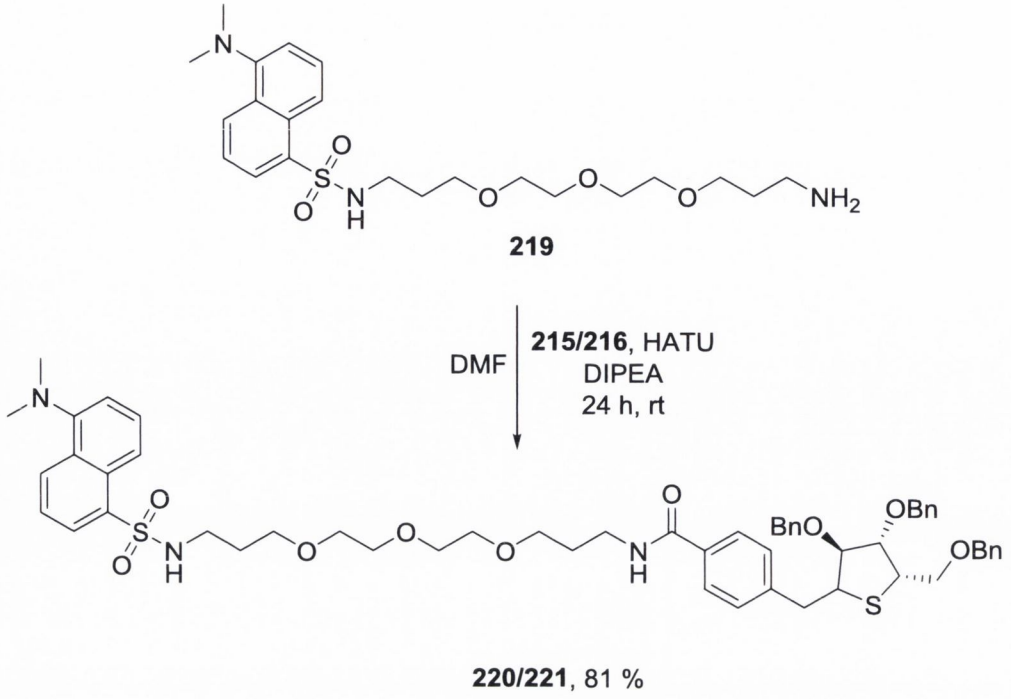
2.8.4.2 Synthesis of Dansyl functionalised thiosugar

A sample of mono-BOC-PEG-NH_2 217 was obtained from a co-worker in the lab, Ms Lyn Markey. This was coupled with dansyl chloride in the presence of triethylamine which gave the desired fluorophore-linker 218 in an 89% yield. The BOC group was removed quantitatively by stirring under a 1:1 mixture of TFA/CH_2Cl_2 and we attempted to directly couple the crude free amine 219 to 215/216 in the presence of EDC (*N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride) and DIPEA (*N*,*N*-Diisopropylethylamine). EDC was initially assessed as a coupling reagent in this system owing to its low cost and the solubility of its urea based by-products in water. Suprisingly no product was obtained from this reaction, addition of excess base and coupling reagent saw no conversion (Scheme 52).



Scheme 52 Attempted synthesis of Dansyl tagged thiosugar **220/221**

HATU (*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate), one of the most successful and reactive coupling reagents, synthesised by Carpino et al in 1993,[280] was next employed and full conversion to **220/221** was noted within 24 hours (Scheme 53).



Scheme 53 Synthesis of dansyl tagged thiosugar **220/221**

2.8.5 Conclusions on 5-exo ring closure

Our attempts to control the stereoselectivity of the thiyl radical cyclisation have revealed that by stabilisation of the resultant alkyl radical, a 5-*exo* cyclisation can be achieved with no competing 6-*endo* product observed. Significantly, we proved that the presence of tertiary alkyl or secondary aromatic group on an *arabino* glycal will give only the corresponding furanose products. We have also demonstrated that the use of a benzyl protecting group also contributed to stereo-control of the reaction via π-π stacking and steric blocking. The substrate scope for thiyl radical cyclisations has also been realised and the benzoic acid conjugated thiosugar **215/216** has proved a very useful synthetic 'handle' upon which a vast array of amide couplings could be carried.[281]

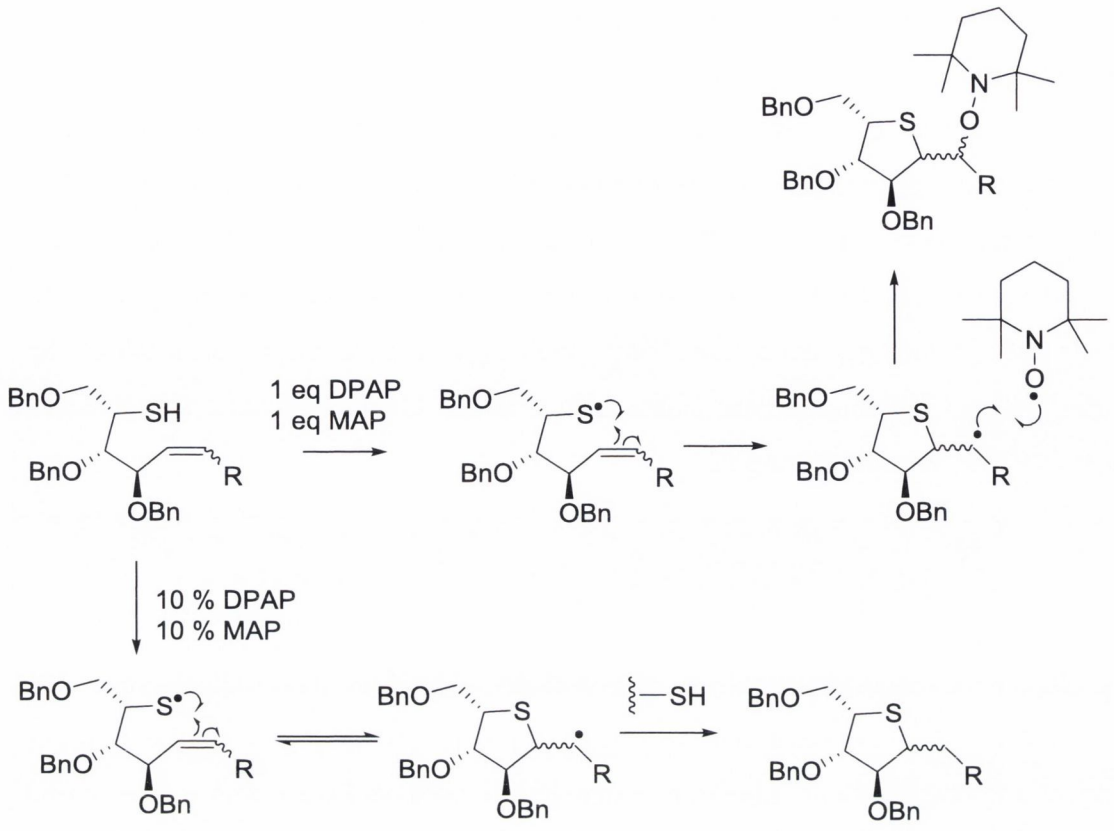
2.9 Thiyl radical cyclisation with *in-situ* TEMPO trapping

In order to further investigate the scope of our newly developed thiyl radical cyclisation we became interested in the possibility of trapping the alkyl radical with TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy radical) following cyclisation. This would allow for the synthesis of synthetically useful hydroxylamines which could be orthogonally

deprotected under reducing conditions (Zn/AcOH) to hydroxylate the sugar ring,[282] equally the hydroxylamine moiety could be oxidised (mCBPA) to yield the corresponding carbonyl.[283] Literature precedence has demonstrated that radical cyclisation followed by TEMPO trapping can proceed with excellent yield and ee, and can be reliably used to generate natural product analogs.[282,284,285] As far as this author is aware, no prior example of an intra-molecular thiol-ene reaction followed by inter-molecular trapping with TEMPO exists. It must be added that TEMPO may react with the thiyl radical before the cyclisation occurs, although it was anticipated that the kinetics of radical cyclisation would exceed that of radical trapping.

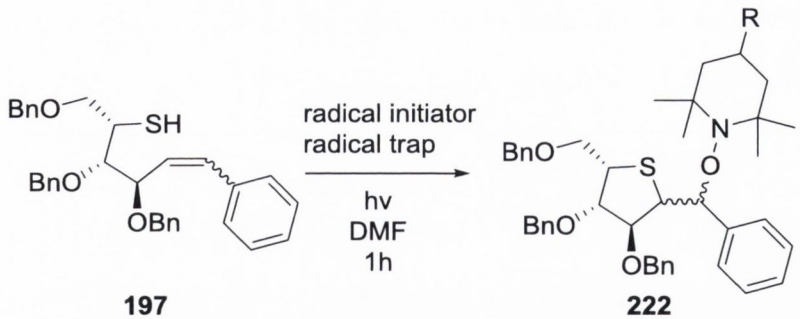
2.9.1 Attempts at TEMPO trapping from radical precursor 197

Owing to the excellent diastereoselectivity and high yields of the thiyl radical cyclisation of **197,** we decided to use this system as a starting point with which to optimise TEMPO trapping of the alkyl radical. Literature examples of cyclisations involving *C*-centered radicals require portion-wise addition of TEMPO over numerous hours.[282] However as the kinetics of intra-molecular thiol-ene exceed that of *C*-centred radical cyclisation's, slow addition of TEMPO was not feasible. Instead, we anticipated to evaluate the domino process in 'one pot'. Unlike the thiol-ene radical chain cycle as described in Section 1.6.3.1, radical cyclisation followed by TEMPO trapping would necessitate the use of stoichiometric rather than catalytic amounts of radical initiator. We wished to inhibit propagation of the reaction, which would lead only to the cyclised thiosugar, and instead collectively carry out hydrogen atom abstraction (HAT) on all thiols in the reaction mixture. This would result in a simultaneous radical cyclisation of all the thiyl radicals and the furnished alkyl radical could then be trapped with TEMPO (Scheme 54).



Scheme 54 Proposed thiyl radical cyclisation with TEMPO trapping

Inspired by the work of Han *et al.*[286] in which TEMPO itself is used to initiate radical formation via HAT, we treated **197** with 3 eq of TEMPO at 80°C under argon (Entry 1, Table 6). Disappointingly, no reaction was observed. Presumably this is due to the higher BDE of the thiol moiety relative to the oxime (BDE 83 $kJmol^{-1}$) utilised by Han *et al.*[286] We then revisited the use of DPAP/ MAP as a radical initiation system. In order to test our hypothesis that a full equivalent of radical initiator was needed in order to facilitate TEMPO trapping as a competing process, we carried out the reaction in the presence of catalytic DPAP and MAP (10%) and a full equivalent of TEMPO. Unsurprisingly, an unsatisfactory yield of 7% was obtained. Increasing the initiator loading to 1 eq saw a marked increase in yield as expected to 21%. Literature examples illustrate that excess TEMPO is often required to secure high yields of radical trapped products.[284-286] Therefore, we increased loadings of TEMPO to 3 eq which resulted in a corresponding increase in the yield of product to 68%. In order to investigate if the yield could be further increased, the reaction was carried out in the presence of 5 eq of TEMPO which gave our highest conversion of 70 %.



197 **222**

R = H, OH

Entry	Thiol **197** loading (eq)	Radical Initiator	Initiator loading (eq)	Radical trap	Radical trap loading (eq)	Yield of **222** (%)[a]
1	1	TEMPO	3	-	-	No reaction
2	1	DPAP, MAP	0.1	TEMPO	1	7
3	1	DPAP, MAP	1	TEMPO	1	21
4	1	DPAP, MAP	1	TEMPO	3	68
5	1	DPAP, MAP	1	TEMPO	5	70
6	1	ACVA	1	TEMPO	5	8
7	1	ACVA	3	TEMPO	15	10
8	1	ACVA	3	4HT	15	Trace
9	1	DPAP, MAP	1	4HT	5	Trace

[a]Determined by ^{1}H NMR

Table 6 Attempts at radical cyclisation of **197** with TEMPO trapping

Difficulties arose however upon purification of **222**. It became apparent that residual TEMPO and methyl benzoate, presumably formed as a by-product of DPAP initiation, were co-eluting with the desired product **222** upon column chromatography. Despite being a volatile solvent, methyl benzoate could not be removed by evaporation, distillation or co-evaporation with chloroform. We believed the difficulty in removing methyl benzoate arises from its potential π-stacking between the aromatic rings of **222**. Huang *et al.*[287] have utilised methylbut-2-ene as a radical trap for excess TEMPO however applying this radical scavenger to our system was surprisingly unsuccessful.

Following numerous column chromatography purfications, in a range of different solvent conditions, residual TEMPO was eventually successfully removed from **222**. However throughout this laborious process methyl benzoate could not be removed despite running at a retardation factor (R_f) of 0.2 lower than that of **222**. Preperative TLC was also attempted in an effort to remove this by-product which unfortunately was also unsuccessful.

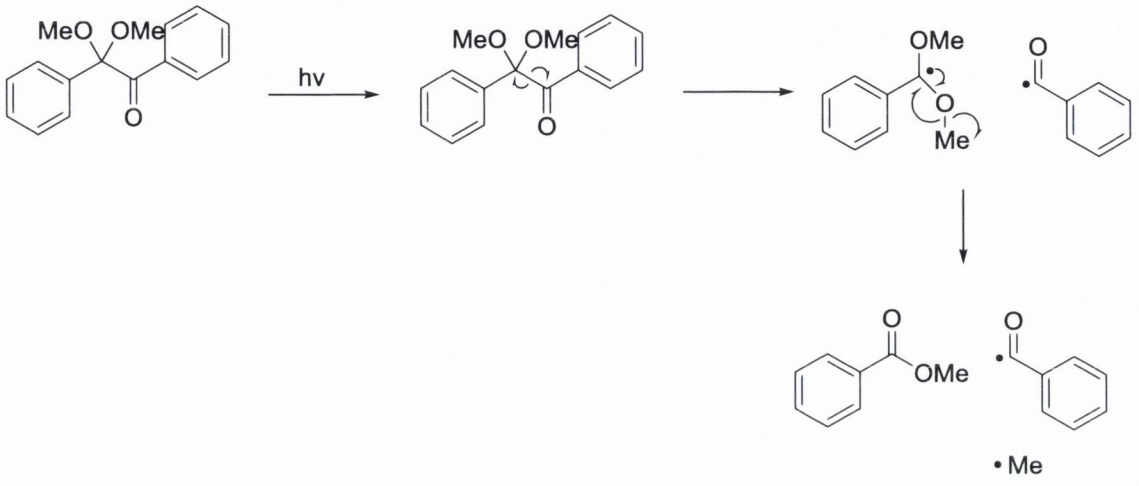


Figure 31 Formation of methyl benzoate through DPAP initiation

Despite the presence of by-products, initial characterisation of **222** was carried out, proving **222** was unequivocally formed with complete diastereoselectivity, only one product was isolated from the reaction mixture. Further characterisation is needed to unambiguously assign the absolute configuration of **222**.

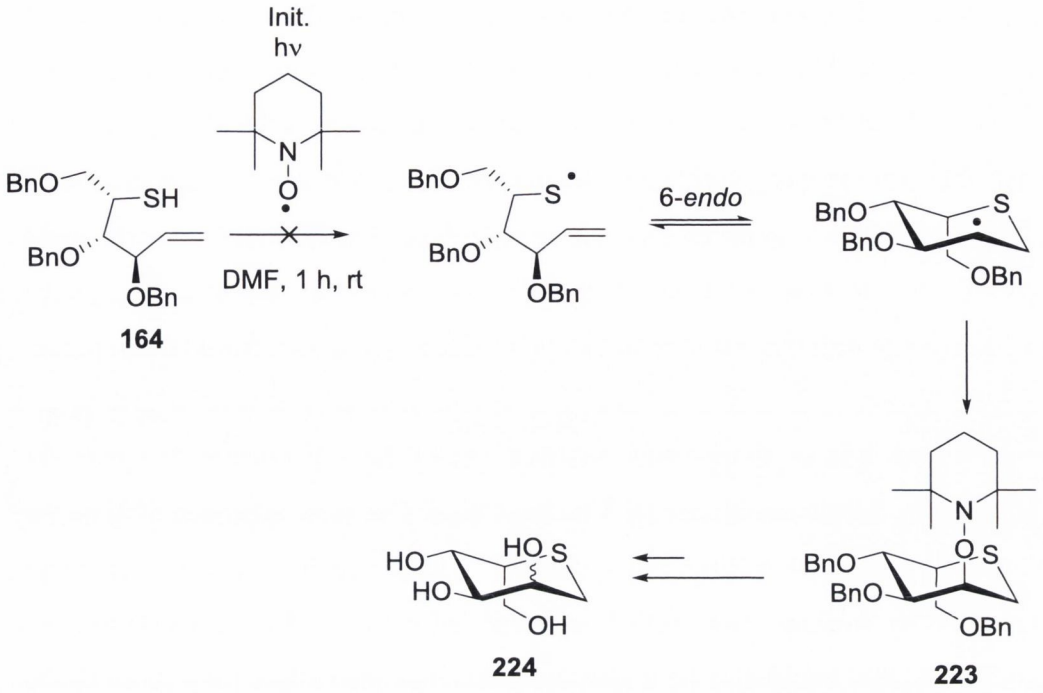
In order to circumvent the problematic purification of methyl benzoate from **222** we decided to attempt the radical cyclisation reaction using ACVA as the radical initiator. Despite giving low yields for the radical cyclisation of **165** we anticipated the use of a water soluble initiator would greatly expedite purification. However a very unsatisfactory yield of 8% was obtained when ACVA was substituted in place of DPAP. We then increased initiator loadings to 3 eq and that of TEMPO to 15 eq, which gave only a disappointing 10% conversion. Owing to the impractical yields obtained through the use of ACVA and TEMPO we turned our attention to the use of 4-hydroxy-TEMPO (4HT) as a radical trap. 4HT unlike the analogous TEMPO is water soluble and can be easily removed via an aqueous work up. The 4HT glycosyl trapped product should also exhibit a

different R_f to that of **222** owing the free para hydroxyl group on the TEMPO motif, and therefore may be seperatable from methyl benzoate. Unfortuately however, reaction of 4HT using both DPAP/MAP and ACVA as radical initiators gave no conversion. Astonishingly only the starting thiol was recovered from the reaction. From mass spectrum analysis (ESI^+) we observed the addition product of 4HT to the benzaldehyde radical of DPAP, therefore we proposed that 4HT, as a superior radical scavenger to TEMPO, reacts directly with the initiator and so precludes any reaction from taking place.

Given time constraints and an inopportune malfunction of the UV reactor, this work is now being persued by fellow researcher Dr Vincent Corcé. Our next approach to obtain a clean sample of **222** will involve Birch reduction of **197** after which methyl benzoate can be cleanly removed by workup. Zinc/AcOH mediated reduction of the hydroxylamine to the corresponding alcohol could also be undertaken, this may also allow for a more facile removal of the residual methyl benzoate.[282] Characterisation of the TEMPO trapped analog and a full assignment of **222** configuration will be carried out.

2.9.2 Future Work

While 1,2 di-deoxy thiopyranoses may possess interesting biological activities, we also aimed to develop a route to 1-deoxythiosugars, as they more closely resemble natural thiosugar analogs while still maintaining metabolic stability as *C*-glycosides.[4] We postulated that synthesis of these compounds could be accomplished via 6-*endo* radical cyclisation with concomitant TEMPO trapping of the secondary C-2 radical (Scheme 55). In tandem with the work described in the previous section we treated **164** with our optimised conditions of DPAP (1 eq) in conjuction with TEMPO (1 eq). Disappointingly, only starting material was uncovered. It was deduced however that the UV reactor had malfunctioned and as such it is not obvious if the reaction did not proceed owing to inherent mechanistic reasons or simply a breakdown in equipment. My colleague Dr Vincent Corcé will continue this work pending replacement of the UV reactor.



Scheme 55 Proposed synthesis of 1-deoxythiosugars

In this work we have demonstrated for the first time that thiyl radical cyclisations can be employed for the synthesis of thiosugars. We have employed both 6-*endo* and 5-*exo* thiyl radical cyclisations for the synthesis of thiopyranose[260] and thiofuranose[281] products. The synthetic utility of the methodology was demonstrated through the preparation of a number of novel *C*-linked thiosugars. The methodology was proven robust and diastereoselective, allowing rapid access to thiofuranose derivatives with high yields under carefully controlled conditions. Future applications of this work will a reinvestigation of 7-*endo* thiyl radical cyclisations. Thiyl radical cyclisation onto a terminal alkene followed by TEMPO trapping to furnish 1-deoxy thiosugars is also of considerable interest.

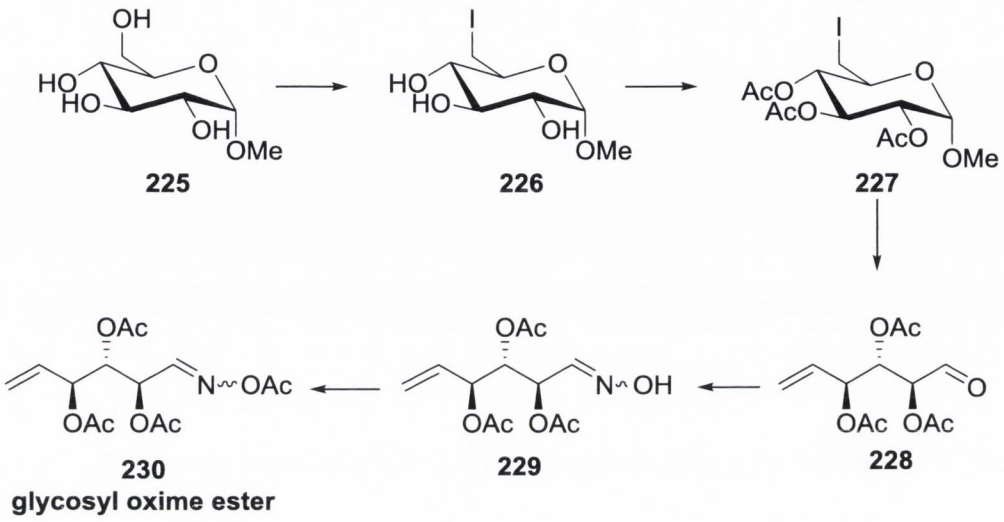
3.1 Intramolecular iminyl radical cyclisations for the synthesis of iminosugars

As discussed in Section 1.3, certain iminosugars are potent inhibitors of glycosidases, holding enormous therapeutic potential for the treatment of a range of different diseases. Accordingly, like their thio-counterparts, much effort has been expended over the past decades in the development of novel and versatile methodologies for their synthesis. Despite an extensive number of synthetic approaches, an iminyl radical cyclisation has never previously been investigated as a synthetic strategy towards azasugar synthesis. Recent developments in the initiation and application of iminyl radicals for the synthesis of *N*-heterocycles have proven their reliability and reactivity.[235-243] As emphasised in Section 1.6, current research in radical chemistry is moving away from tin-based methodologies and towards the use of environmentally benign reagents. In this context it was envisaged that photochemical and thermal initiation routes would be applied to iminyl radical production for azasugar synthesis. It was anticipated that the free radical based methodology would allow rapid access to a range of biologically active glycosidase inhibitors for biological evaluation.

3.1.1 Proposed synthetic route

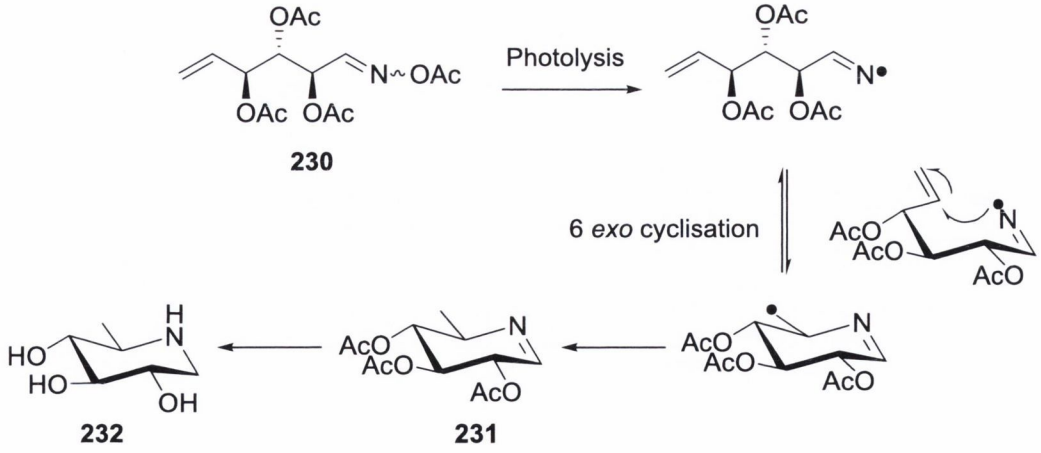
It was of interest to design a synthetic strategy that could incorporate two modes of initiation, photochemical and thermal. As discussed in Section 1.6.4.1, the photochemical approach to iminyl radical generation as described by Alonso *et al*[240] requires acyloximes as the requisite radical precursor. The thermal approach to iminyl radical generation, as described by Walton and co-workers,[241] and as discussed in the same section, requires an oxime ether as the iminyl radical precursor. The use of a photochemical approach was investiagted in the first instance, thereby making our initial synthetic target a glycosyl oxime ester. The initially proposed synthetic route is outlined in Scheme 56. It was reasoned that the glycosyl oxime ester could be synthesised from commercially available α-methoxy hexoses in five synthetic steps. Preparation of the iodide **226** followed by zinc mediated fragmentation of methyl 6-deoxy-6-iodo hexapyranoside **227**, as reported by Madsen and co-workers[288] would give access to aldehyde **228**. **228** is a useful synthetic handle from which either an oxime ester (for photochemically initiated iminyl radical generation) or an oxime ether (for thermally initiated iminyl radical generation) could be

prepared. In the case of the former, it was anticipatated that treatment with hydroxylamine hydrochloride to give oxime **229** followed by treatment with acyl chloride would provide the requisite oxime ester (Scheme 56).



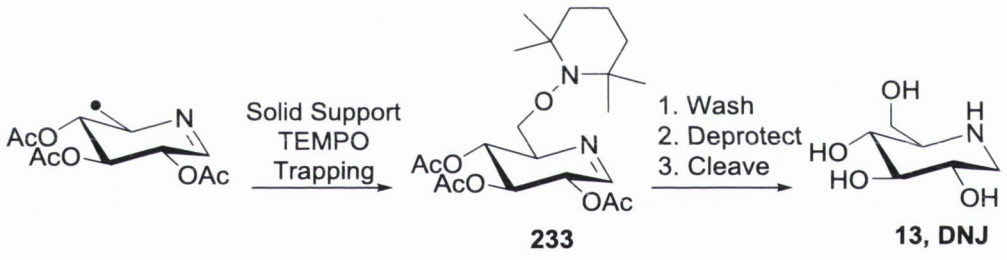
Scheme 56: Proposed synthesis of iminyl radical precursor

Homolytic cleavage of the weak oxime ester (N-O) bond of **230** upon photochemical irradiation would generate an iminyl radical, which upon cyclisation would furnish a methylene radical. Subsequent quenching of the methylene radical by a suitable solvent, followed by deprotection, would furnish an azasugar (Scheme 57).



Scheme 57 Propsed iminyl radical generation and cyclisation to furnish azasugar

Furthermore, in order to fully explore the synthetic possibilities available through the use of a radical cyclisation, sequential trapping of the methyl radical with a radical trap was attempted. Through the use of different trapping agents, variation would be afforded at the 6-position of the sugar. Of particular initial interest was the use of TEMPO as a trapping agent. This would allow for reintroduction of the hydroxyl moiety at the C-6 position in one step, thus giving access to the native polyhydroxylated carbohydrate skeleton. Through the use of a solid supported radical trap, purification of the final product would be greatly simplified requiring only to be washed, deprotected and cleaved from the resin. Purification and isolation of deprotected azasugars requires considerable effort, often coupled with significant loss of material. Via this methodology, a significant problem commonly encountered with iminosugar preparation could be circumvented. Use of TEMPO as a radical trap also allows for re-installation of a hydroxyl moiety at C-6. Using this methodology, key iminosugars such as 1-DNJ, 1-DMJ and various structural analogs could be prepared (Scheme 58).



Scheme 58 Trapping of methyl radical with solid supported radical trap

ESR spectroscopy is a technique that can be used to study free radical reactions in detail. Formation of the methylene and iminyl radical could potentially be observed using ESR spectroscopy. Through use of this technique it was anticipated that the kinetics of the free-radical cyclisation process could be studied, which would prove useful in optimising the synthetic process. It was assumed that the radical cyclisation would occur 6-*exo*-trig, as favoured by Baldwin's guidelines for cyclisation reactions,[290] since the competing 7-*endo*-trig is highly unfavoured. Stereocontrol of 6-*exo* and 5-*exo* trig radical cyclisation reactions have been reported.[171] It was expected in this case that the natural R stereochemistry would be installed at C-5 following cyclisation owing to the thermodynamic stability of the product. In order to further ascertain if the protecting

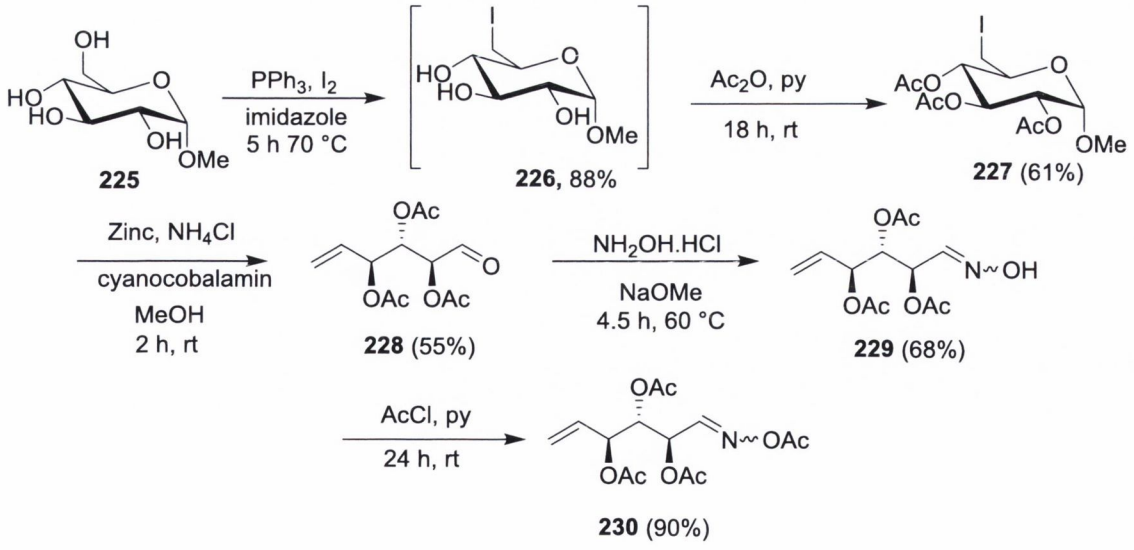
group at C-4 imparts an influence over the stereocontrol of the radical cyclisation it was decided to investigate the effect of varying the hydroxyl protecting groups on the sugar ring.

This methodology differs from the synthetic route utilised for thiosugar synthesis in that the alkene is formed at the C-5 position and cyclisation takes place from the anomeric position. It was anticipated that the synthetic route outlined in scheme 57 could be attempted in the first instance in order to generate known iminosugars such as DNJ, **13**.

3.2 Photochemical route to iminosugar synthesis

3.2.1 Synthesis of oxime esters as iminyl radical precursors

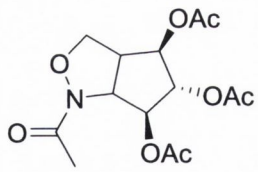
The initial objective of this work was the synthesis of glycosyl oxime esters as photochemical precursors of iminyl radicals. It was decided to synthesise these precursors with both arming and disarming protecting groups in order to probe their reactivity, and also to investigate if altering the protecting group could impact upon the diastereoselectivity of the radical reaction and the rate of the subsequent radical ring closure. For ease of synthesis and characterisation, the synthesis of an acetylated precursor was first considered as shown in Scheme 59.



Scheme 59 Synthesis of acetylated glycosyl oxime ester **230**

The peracetylated iodo sugar **227** was synthesised by treating α-methoxy-D-glucopyranoside with iodine, PPh_3 and imidazole.[288] The resultant intermediate was not isolated but further reacted with acetic anhydride and pyridine to furnish **227** in a 61% yield. The next step in our synthesis involved the zinc mediated fragmentation of **227**. Such fragmentations of methyl 6-deoxy 6-halo hexapyranosides have been reported in literature, the first example from Bernet and Vasella in 1979.[291,292] The resultant 5,6 dideoxyhex-5-enoses thus generated are very useful chiral synthons that have found many applications within carbohydrate chemistry.[170, 293-297] Despite its synthetic utility, the reductive fragmentation of ω-haloglycosides continues to pose significant experimental difficulties. The original protocol calls for reflux with acid-washed zinc powder in aqueous solvent.[291,292] While still a widely used protocol, the yields are reported to be moderate owing to the instability of 5,6 dideoxydex-5-enoses at reflux and formation of multiple by-products. Skaanderup *et al.*[288] carried out a thorough investigation on this reaction and reported optimised conditions involving sonication of the iodoglycoside in the presence of zinc in a mixture of THF/H_2O. However, in our hands, fragmentation of **227** under these conditions gave rise to numerous inseparable by-products. Other reported procedures in the literature suggest use of a better leaving group to increase yields of the fragmentation reaction,[294] and the use of cyanocobalamin (Vit B_{12}) at room temperature has also been reported.[298] Application of the latter procedure, wherein the iodo sugar **227** was stirred in alcoholic solution at room temperature in the presence of zinc and cyanocobalamin (vitamin B_{12}), gratifyingly gave **228** in a 55% yield within 3 hours. With **228** in hand, treatment with hydroxylamine hydrochloride and sodium methoxide produced oxime **229**[289] as a 3:2 mixture of E/Z isomers, with subsequent acetylation giving the oxime ester **230** in a 90% yield. The oxime ester isomers were not separated as it was reasoned that upon photolysis only a single iminyl radical product would be formed.

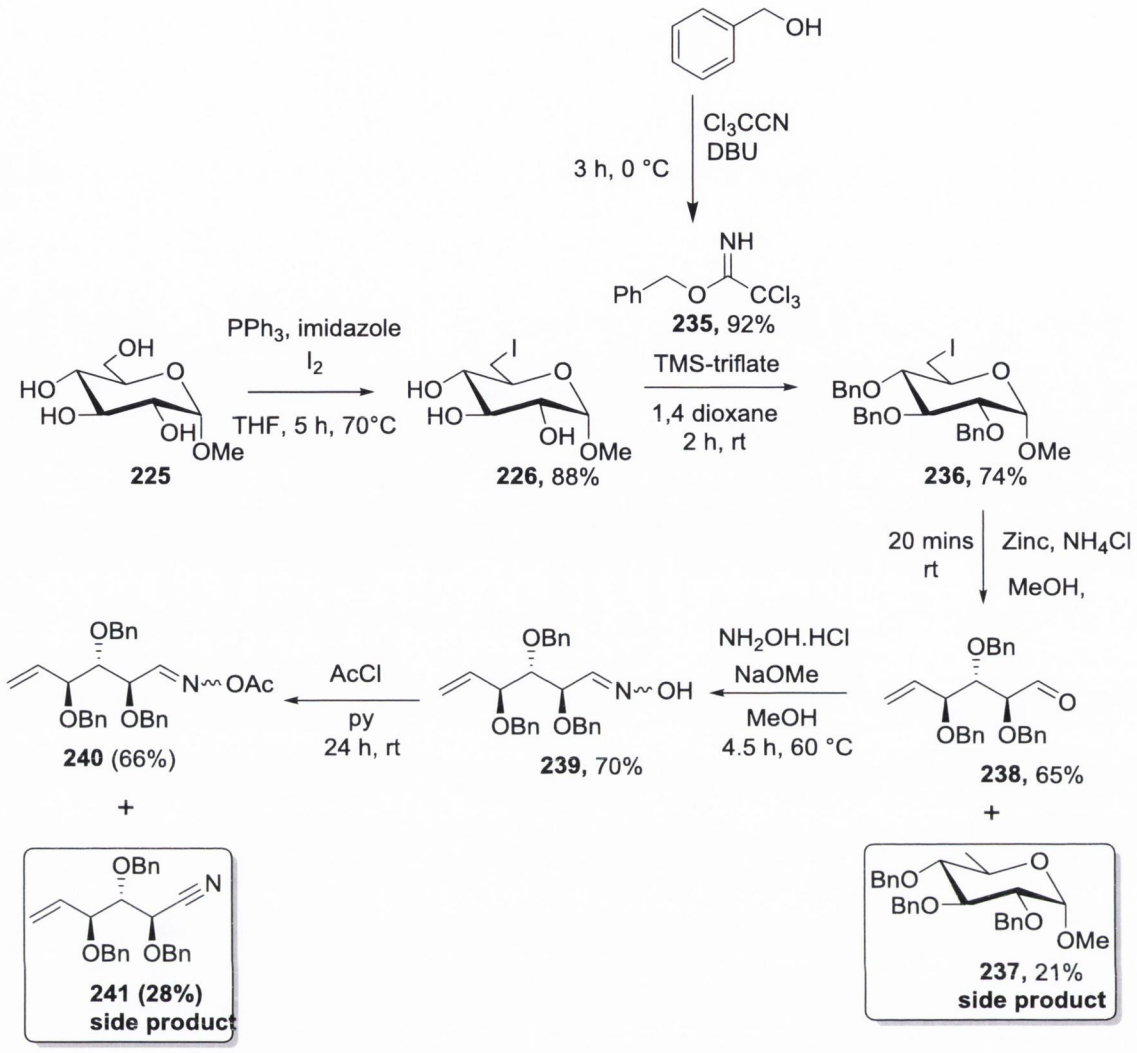
While this synthetic route gave rise to the desired iminyl radical precursor in moderate yield on a small scale, when the synthesis was attempted on a multigram scale formation of a by-product lowered the overall yield significantly. An intramolecular nitrone-alkene cycloaddition was noted upon oxime formation from **229** to yield bicycle **234**.[299] Reactions of this kind have been previously noted, and shortening the reaction time was successful in minimising the formation of **234**.



234

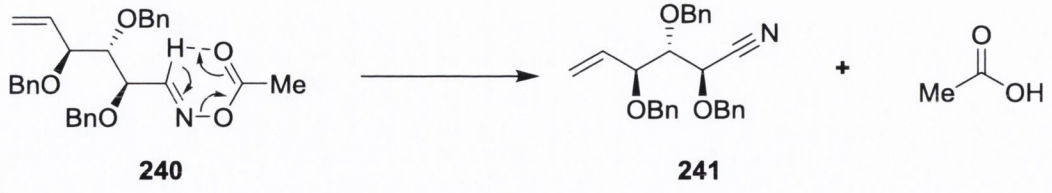
Figure 32 By-product **234** formed via intramolecular nitrone alkene cycloaddition

Attention was then turned to the synthesis of benzylated precursors as shown in Scheme 60. α-Methoxy-D-glucopyranoside **225** was treated with I_2, PPh_3 and imidazole to furnish iodo sugar **226**. An acidic benzylation procedure was sought next in order to install an arming protecting group on the glycosyl hydroxyl groups. An acidic route was considered for installation of the protecting group as benzylation under basic conditions would eliminate the primary iodo group. Treatment of **226** with benzyltrichloroacetimidate **235**,[300] itself synthesised from benzyl alcohol, gave **236** in good yield. The protocol described by Kleban et al[298] was applied to facilitate zinc mediated fragmentation of **236**. This reaction proved quite problematic on the benzylated substrate, presenting itself acutely time sensitive and accompanied with the presence of a 6-deoxy by product **237**, presumable formed via zinc mediated reduction of **236**.[291,292] However, careful monitoring of the reaction over 20 minutes gave **238** in 65% yield. Oxime formation[289] proceeded in good yield in the presence of hydroxylamine hydrochloride and sodium methoxide to afford **239** in a 7:3 mixture of E/Z isomers, while subsequent esterification of **239** led to the formation of the desired compound **240** and nitrile side product **241**.



Scheme 60 Synthesis of benzylated glycosyl oxime ester **240**

The ratio of **240** to **241** did not change upon variation of the acetylation conditions. It was proposed that the nitrile had formed through dehydration of the alkoxime ester (Scheme 61). Acetic anhydride is the most widely used reagent for effecting the dehydration of such species, although acetyl chloride,[301] thionyl chloride,[302] ethyl chloroformate[303] and benzoyl chloride[304] among others have also been implicated in the formation of nitriles.



Scheme 61 Decomposition of aldoxime **240** into nitrile **241** and acetic acid

Interestingly, a nitrile side product was not observed upon preparation of **230**, suggesting that the nature of the protecting group (arming or disarming) impacts upon the strength of the oxime (N-O) bond.

3.2.2 ESR Spectroscopy of glycosyl oxime esters

As part of this project it was anticipated that EPR spectroscopy would be carried out in order to observe iminyl radicals produced and to probe the kinetics of the subsequent cyclisation. It is known that superior spectra are obtained by using resonance stabilised oxime esters[305] (Figure 33). Photolysis of such compounds leads to the formation of stabilised radicals for which strong EPR spectra can be observed.

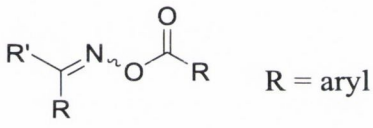
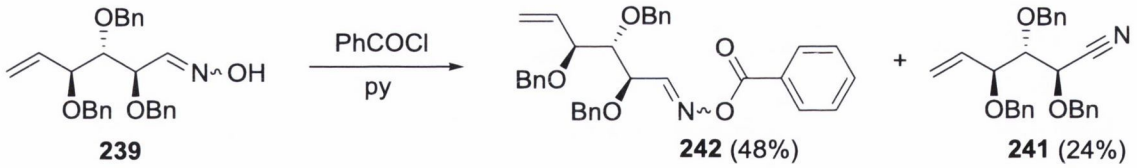


Figure 33 Resonance stabilised oxime ether

In this context, a glycosyl oxime ester containing a benzoyl ester was synthesised from **239** using benzoyl chloride and pyridine (Scheme 62). The nitrile degradation product **241** was again observed in a 24% yield.



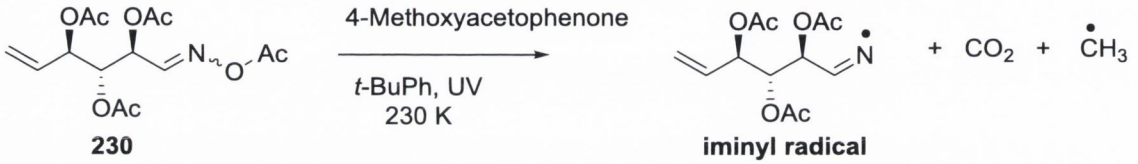
Scheme 62 Synthesis of glycosyl oxime ester **242**

With both of the oxime ester radical precursors **230, 240** and **242** in hand, we were interested in determining the ability of these compounds to act as precursors for iminyl radicals and to carry out intramolecular cyclisation reactions. In the first instance, we submitted these compounds for EPR studies in order to study their behaviour on

photolysis and to investigate if any of the expected free-radical intermediates could be observed and characterised.

EPR spectroscopic studies were carried out on compounds **230**, **240** and **242** by irradiating the samples with UV light from a 500 W super pressure Hg arc lamp within a 9 GHz EPR spectrometer. All EPR spectroscopy was carried out by our collaborator, Professor John Walton, at the University of St Andrews. 4-methoxyacetophenone (MAP) was added as a photosensitiser for all oxime esters in order to improve the signal strength.

3.2.2.1 Photolysis *O*-Acyl oxime ester 230



Scheme 63 Photolysis of glycosyl oxime ester **230**

Photolysis of **230** at 230K unfortunately did not provide spectral evidence of the iminyl radical. Nevetheless the central 2 lines from the Me radical quartet (a(3H) = 22.8 G) can be observed, albeit weakly (Figure 8). This suggests some dissociation did take place. Absence of the iminyl radical in the spectra could be due to the instability of the glycosyl radical product formed upon photolysis, owing to the absence of resonance stabilisation. This can result in the radical being too short lived to be observed.

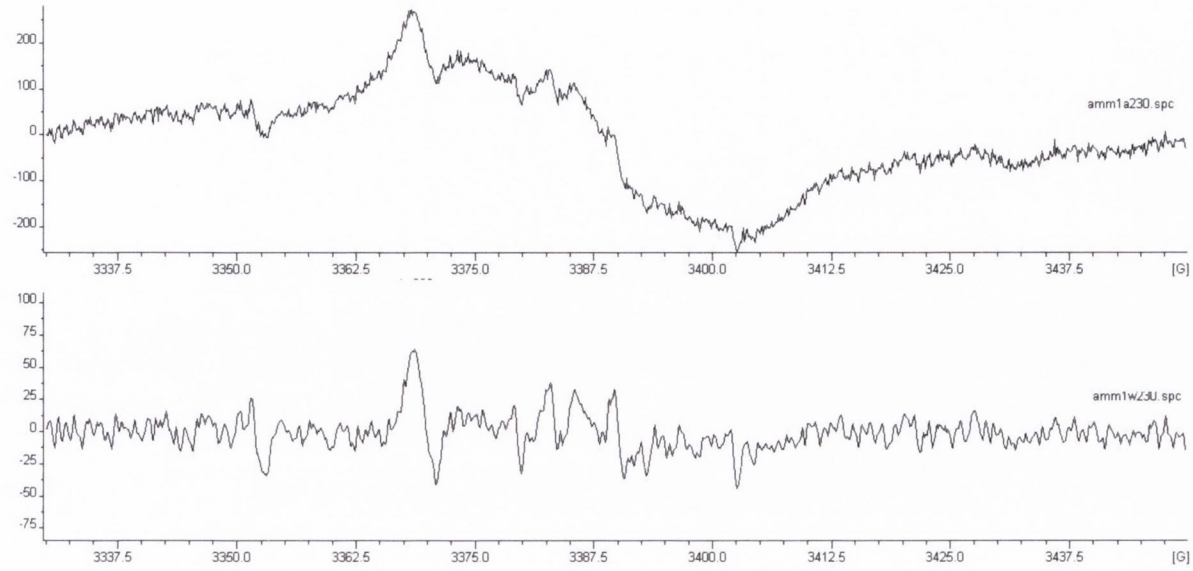
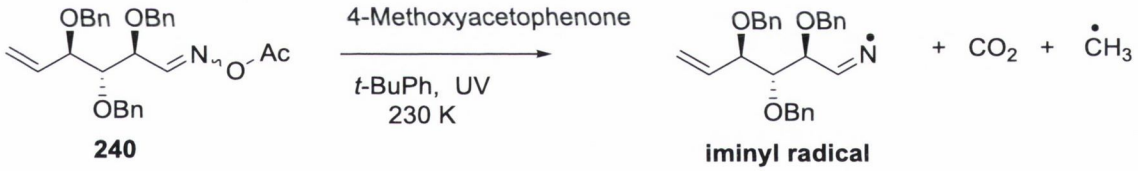


Figure 34 EPR spectra from **230** at 230K. Top: raw spectrum (25 scans accumulated). Bottom: Spectrum after digitally removing the broad central feature.

3.2.2.2 Photolysis *O*-Acyl oxime ester 240



Scheme 64 Photolysis of glycosyl oxime ester **240**

Photolysis of **240** at 230K provided spectroscopic evidence of the Me radical (marked M) and the expected iminyl radical (Figure 9). The bottom panel of Figure 35 shows a computer simulation with the following parameters:

Iminyl: a(N) = 10.0 G, a (1H) = 80.2 G
Me: a(3H) = 22.8 G

It was deduced that other lines in the spectra most likely correspond to the iminoxyl radical which could have formed from a trace of the oxime present as an impurity. As iminoxyls are persistent radicals, a tiny trace of oxime, not visible by NMR, can be deprotonated by any radical in solution thus leading to generation of an iminoxyl radical.

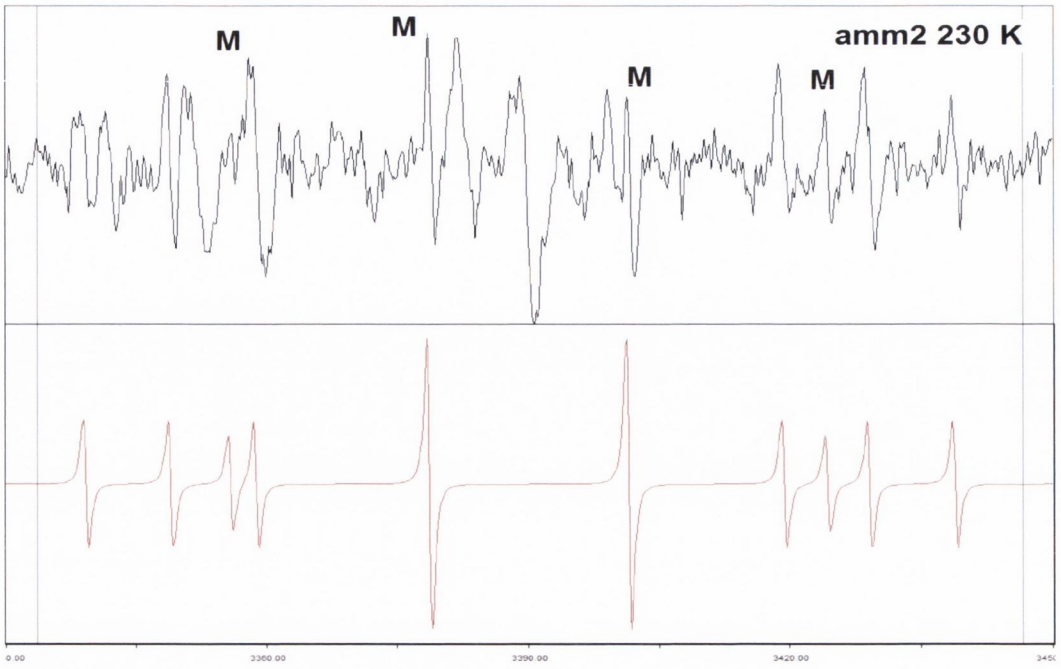
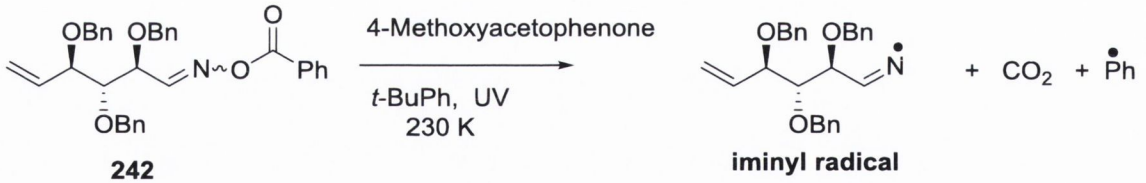


Figure 35 EPR spectra from **240** at 230K. **Top:** spectrum (25 scans accumulated) after digital removal of central feature. **Bottom**: computer simulation for Me and iminyl radicals.

3.2.2.3 Photolysis *O*-Benzoyl oxime ester 242



Scheme 65 Photolysis of glycosyl oxime ester **242**

Photolysis of **242** at 230K provided the expected iminyl radical which can be clearly distinguished in the wings of the spectrum (Figure 10). The top panel shows 10 scans accumulated of **242** compared with 25 scans for **240,** proving dissociation was considerably more efficient with a resonance stabilized oxime ester. The released Ph radical can't be observed by EPR in solution, which is expected owing to its high reactivity as a sigma-radical. It is proposed that other lines in the spectrum could be derived from a cyclohexadienyl radical generated when the phenyl radical adds to the

PhBu-t solvent *meta* to the *t*-Bu substituent.[306-309] It is possible that the *para*-isomer of the cyclohexadienyl is also present to a minor extent. Because this addition happens solely in the presence of sigma radicals the observation of the cyclohexadienyl is good evidence that the phenyl radical was also generated in this system.

The simulation in Figure 10 was obtained with:

Iminyl: a(N) = 10.0, a(1H) = 80.2 G

Cyclohexadienyl: a(1H) = 35.6, a(1H) = 12.5, a(1H) = 9.8, a(1H) = 8.2, a(1H) = 3.3 G.

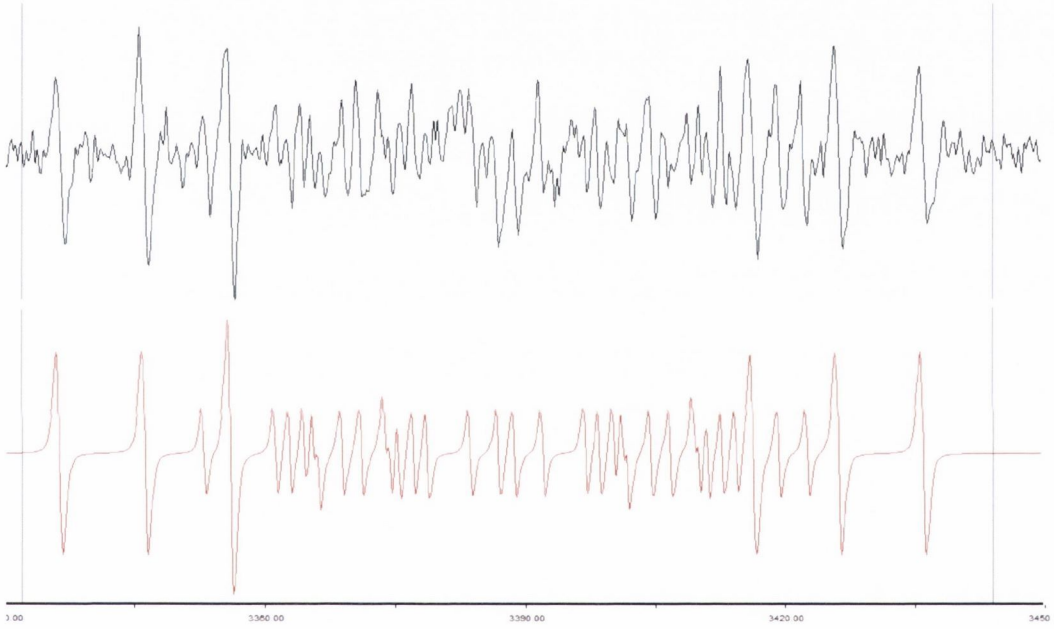


Figure 36 EPR spectra from **242** at 230K. Top: spectrum (10 scans accumulated) after digital removal of central feature. Bottom computer simulation for iminyl radical and cyclohexadienyl radical.

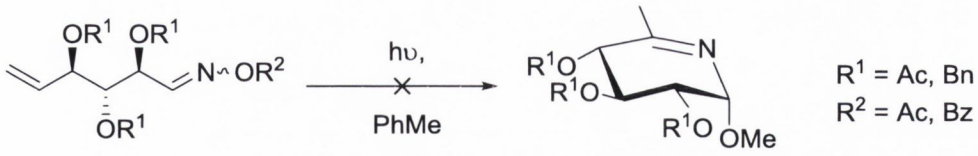
It is assumed that cyclisation of the iminyl radicals would take place in the 6-*exo* mode. Spectra were too weak to observe this at higher temperatures required for ring closure, however, even if the spectra had been strong, it is unlikely a 6-*exo* ring closure could be observed by EPR spectroscopy as the process is too slow at accessible temperatures. Comparatively 5-*exo* ring closures can be observed but these require shorter chain oxime esters.[310]

The generated EPR spectra provided good evidence that the expected N-O bond scission does take place on UV irradiation of *O*-acyl and *O*-benzoyl oxime esters. However it was noted that stronger EPR spectra could be accessed from oxime esters with an aryl group conjugated with the C=N bond, of the type: Ar(R)C=NOC(O)Me where R is the unsaturated chain and Ar = Ph or 4-MeOPh *etc* [305] as this would allow for delocalisation of the iminyl radical leading to a longer lifetime and thus stronger spectra.

With the EPR spectral studies completed, we set out to investigate the behaviour of these compounds under photolysis conditions on a preparative scale. A number of test reactions were carried out to determine the product distribution of the iminyl radical reactions and to identify if any of the desired iminosugars could be isolated.

3.2.3 Initial reactions of oxime esters under photolytic and thermolytic conditions

Photolysis of **230, 240** and **242** was attempted with a 125 W UV lamp with the aim of achieving homolytic cleavage and intramolecular cyclisation. The results are shown in Table 7.



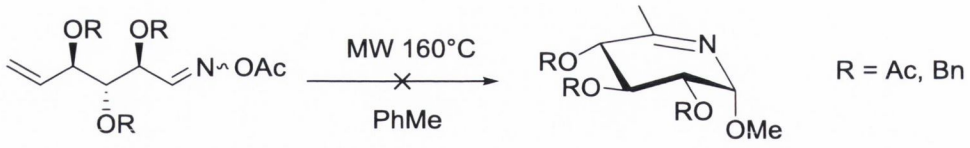
Entry	Starting material	Photosensitiser	Photosensitiser loading	Reaction Time	Observed reaction
1	**230**	-	-	8 hours	-
2	**240**	-	-	8hours	-
3	**242**	-	-	8 hours	-
4	**230**	PMAP	10%	3hours	-
5	**230**	PMAP	30%	4hours	-

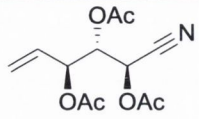
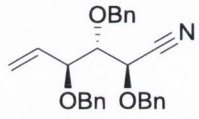
All reactions carried out in PhMe (0.13M) at room temperature

Table 7. Reaction of glycosyl oxime esters under 125 W UV source

Unfortunately even in the presence of the photosensitiser PMAP the UV lamp was not powerful enough to cleave the oxime ester (N-O) bond, in all cases no reaction was observed. The use of a photochemically initated iminyl radical precursor for azasugar synthesis was thus suspended pending the acquisition of a stronger UV source.

A thermal cleavage of the oxime ester bond was then considered. It has been found in practice that oxime esters are generally unsuitable for the production of iminyl radicals. Nevertheless, Portela-Cubillo *et al.*[311] have observed 6-*endo* cyclisations at high temperatures through the use of indoalkanone *O*-acetyl oximes to afford pyrridoindoles. While the reaction is almost certainly not driven by the formation of iminyl radicals and instead most likely proceeds via a rearrangement/elimination sequence, we were interested to ascertain if a cyclisation could be observed upon heating oxime esters **230** and **240** at high temperatures. As expected however, exposing **230** and **240** to elevated temperatures and pressures resulted in the formation of nitriles **243** and **241**. These results are in agreement with the findings of Ambrose and Brady,[312] such that oxime esters which are heated alone or in an aprotic solvent are decomposed quantitatively into nitriles and acid.



Entry	Starting Material	Reaction Time	Observed Product	Yield(%)
1	**230**	15 minutes	 **243**	42%
2	**240**	15 minutes	 **242**	61%

All reactions were carried out in a 350MW microwave at 160°C in PhMe (0.13M)

Table 8 Reaction of glycosyl oxime ester upon microwave irradiation

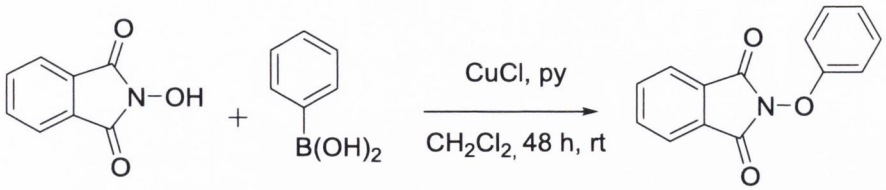
3.3 Thermal route to iminosugar synthesis

3.3.1 Synthesis of glycosyl oxime ethers

While oxime esters proved unsuitable for thermal generation of azasugars it has been shown by Ingold and coworkers[242] that oxime ethers are appropriate for this route. Clean N-O bond homolysis has been observed through the use of a phenyl oxime ether. Microwave promoted reactions were also deemed to be superior, as conventional sealed tube thermolyses reactions of *O*-phenyl oxime ethers required long reaction times, and gave rise to multiple products and low yields. Thermolysis of *O*-phenyl oxime ethers gives rise to iminyl radicals and phenoxy radicals, the latter was found to abstract hydrogen from the solvent giving phenol as the major by-product.

Oxime ethers are formed from aldehydes or ketones by condensation with the relevant hydroxylamine. In order to obtain an *O*-phenyl oxime ether the preparation of the corresponding hydroxylamine, *O*-phenyl hydroxylamine, was approached via conditions

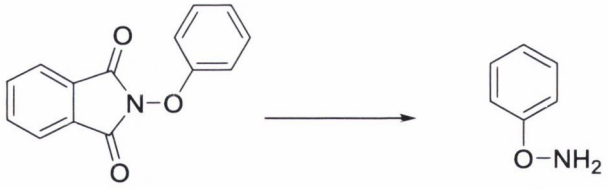
developed by Petrassi et al.[313] *N*-hydroxyphthalamide **244** and phenylboronic acid **245** were cross coupled using a copper(I) salt to yield phthalamide **246** (Scheme 66).



244 **245** **246**, 74%

Scheme 66 Cross coupling of *N*-hydroxy phthalamide and phenyl boronic acid

Subsequent deprotection was then attempted using $NaBH_4$ in a 6:1 isopropanol: water mixture followed by acidic hydrolysis.[314] Deprotection via this method gave the hydroxylamine product, **247**, in a very poor 8% yield. An EDA deprotection of the phthalimide was also considered (Table 9). While the reaction appeared to proceed quantitatively by TLC, upon purification only a 20% yield of the product was attained. Attempts to isolate the compound as an HCl salt were equally unsuccessful and resulted in considerable decomposition products. Thus it was considered more efficient to purchase *O*-phenyl hydroxylamine hydrochloride from a commercial source.

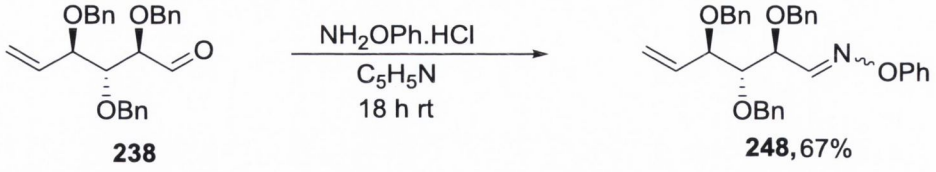


246 **247**

Entry	Conditions	Temp (°C)	Solvent	Reaction time (h)	Yield (%)
1	$NaBH_4$ (5eq), acetic acid (pH 5)	(i) rt (ii) 80	6:1 *i*Pr-OH/H_2O	(i) 24 (ii) 2	8
2	EDA (1.1 eq)	70	MeOH	1	20

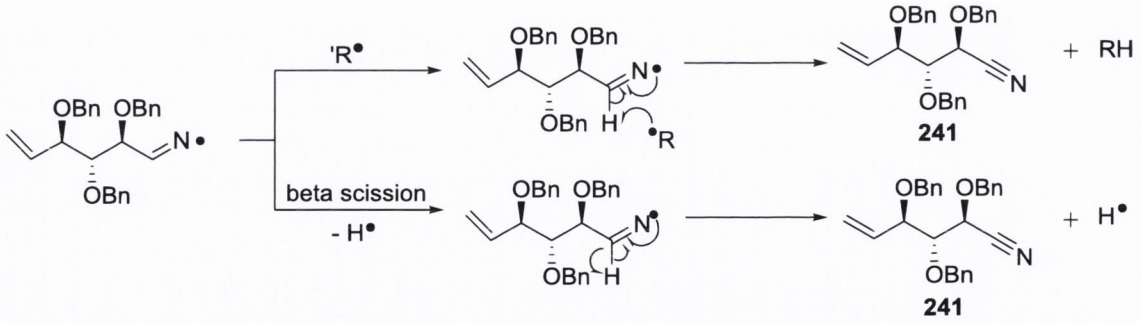
Table 9 Deprotection of phthalimide **246** to yield oxyamine **247**

Coupling of aldehyde **238** with *O*-phenyl hydroxylamine hydrochloride gave oxime ether **248** in a satisfactory 67% yield (Scheme 67).

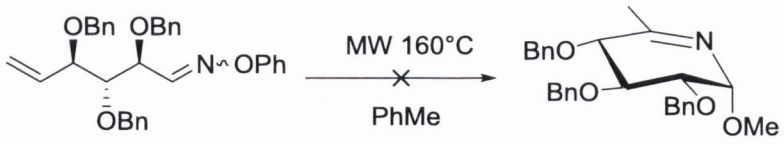


Scheme 67 Synthesis of glycosyl oxime ether

The protocol developed by Walton et al[224] for the thermolysis of oxime ethers was then applied to **248**. A dilute solution of **248** was heated to 160 °C in the microwave in order to initiate radical formation. Unfortunately under these conditions nitrile **241** was the major product obtained. None of the desired products arising from intramolecular cyclisation were observed. Phenol was observed in the reaction mixture suggesting that iminyl radical formation was successful. It is proposed that this transformation is a result of H-1 atom abstraction by radicals present in solution. Upon formation, the reactive iminyl radical could readily abstract a proton from the solvent, toluene, forming an imine intermediate. Subsequent abstraction of H-1 by persistent radicals present in solution (methyl radical of toluene or phenoxy radical) could deliver the nitrile product (Scheme 68). Kinetic studies on 6-*exo* ring closure have been reported to be a hundred fold slower than that of 5-*exo*.[226] A delayed cyclisation could thus account for the interaction of the iminyl radical with other species present in solution. β scission from the imine is unlikely to lead to the nitrile product owing to the inherent instability of the H· radical (Scheme 68).



Scheme 68 Suggested pathways for nitrile formation

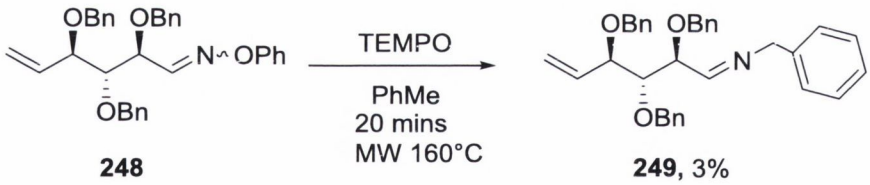


Entry	Starting material	Solvent[a]	Radical trap	Temp (°C) MW	Product isolated	Yield (%)
1	**248**	PhMe	None	160	**241**	72
2	**248**	PhMe	TEMPO	160	**241**	80
3	**248**	DCE	None	120	**241**	83
4	**248**	DMF	None	160	**241**	78

All reactions were carried out for 15 minutes in a 350 MW microwave [a] Concentration (0.13M)

Table 10 Thermolysis of oxime ethers

Varying the thermolytic conditions, as shown in Table 3, did not allow for cyclisation to take place. Interestingly however, when TEMPO was added as a radical trap, trace amounts of imine **249** was obtained. **249** was presumably formed via addition of the iminyl radical to the methyl radical of toluene, proving unequivocally that the iminyl radical is formed during microwave irradiation but also suggesting that the presence of TEMPO could prolong the lifetime of the iminyl radical (Scheme 69).



Scheme 69 Addition of toluene to iminyl radical

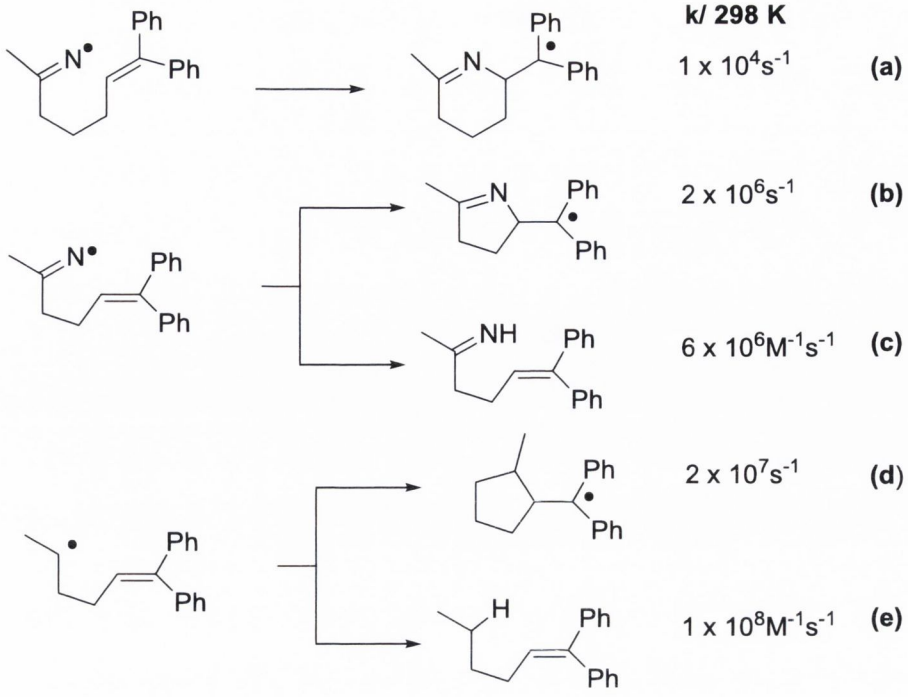
3.3.1.1 Further methods for iminyl radical formation

As piperidine azasugars could not be recovered from thermolysis of *O*-phenyl oximes, various other methods were screened for the generation of iminyl radicals and subsequent intramolecular cyclisation. Weinreb *et al.*[239] reported a methodology for effecting iminyl radical/ olefin cyclisations from oximes, wherin the cylisations are initiated by diethyl

chlorophosphite, while Zard et al[315] have shown that a one electron transfer reaction converts an oxime ester into a radical anion that rapidly collapses to an iminyl radical and carboxylate anion. However application of both described methodologies to our system led to the sole formation of nitrile **241** presumably formed via the imine by H-1 abstraction from radicals in solution.

3.3.2 Conclusions on thermolytic cleavage of 248

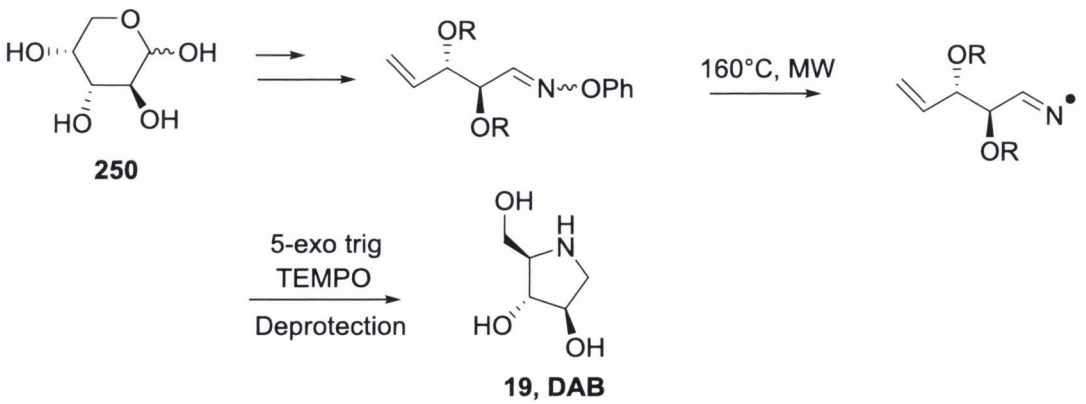
The preparation of photochemical and thermally initiated precursors of glycosyl iminyl radicals was achieved. However any attempt at a 6-*endo* intramolecular radical cyclisation has been unsuccessful owing to the competitive formation of the nitrile side product. It was therefore considered to apply the synthetic route of piperidine azasugars to that of pyrrolidines. It was also envisaged that a 5-*exo* cyclisation, being thermodynamically and kinetically more favourable than 6-*exo* would proceed more efficiently.[226] Rate constants have been measured and recorded for *C*- and *N*- radical cyclisation processes (Scheme 70). Kinetics of 6-*endo* radical cyclisations have been noted to be a factor of 100 slower than the analogues 5-*exo* system. 5-*exo* ring closure proceeds only a factor of 10 slower than archetype hex-5-enyl radical cyclisation.[226] In addition H-atom abstraction by iminyls is comparatively slow, signifying the synthetic utility of this process. It is assumed from kinetic data that for a 5-*exo* iminyl radical system, cyclisation onto the terminal alkene would occur prior to interacting with radical species present in solution, thus providing a cleaner reaction.



Scheme 70 Rate constants for radical cyclisation.
H-atom abstraction in (c) and (e) from PhSH.

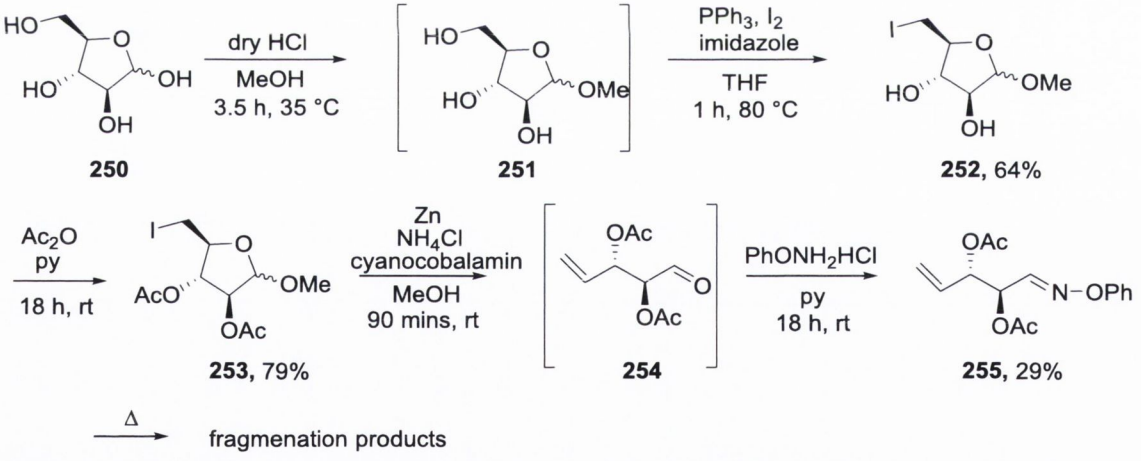
3.4 Synthesis of pyrrolidine oxime ethers

DAB, **19**, a naturally occurring azasugar which exhibits potent anti-HIV activity[32,75] was decided upon as an initial synthetic target following a 5-*exo* iminyl radical cyclisation. The proposed route via a microwave promoted oxime ether thermolysis was devised starting from commercially available D-arabinose (Scheme 71).



Scheme 71 Proposed route to DAB via a microwave promoted oxime ether thermolysis

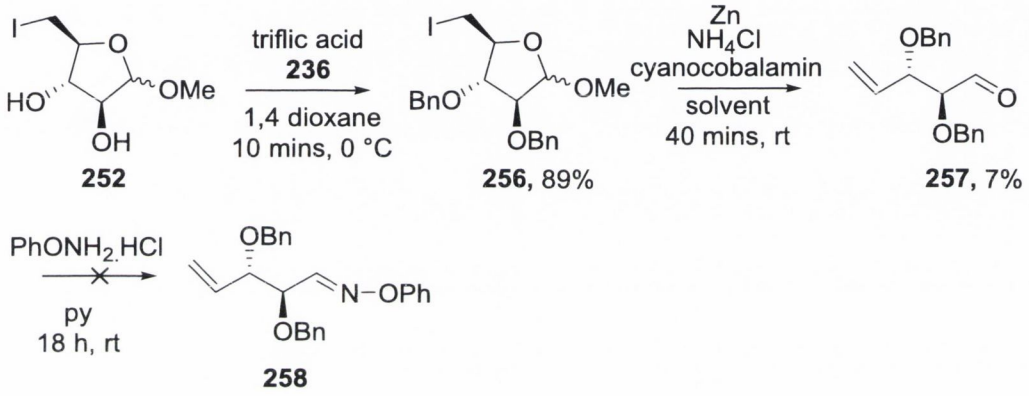
D-Arabinose, **250,** was treated under Fischer glycosylation conditions in order to introduce a methoxy group at the anomeric position[316] (Scheme 72). This acetal intermediate was iodinated according to conditions reported by Madsen *et al.*[288] Iodo furanose **252,** was acetylated to afford **253,** following which, zinc mediated reductive elimination of **253** was used in order to generate aldehyde **254**.[298] However the instability of the liberated aldehyde prevented purification and characterisation. Owing to its short life span (approximately 3 hours), *in situ* trapping of the aldehyde with a nucleophile has been reported. Thus it was reasoned that *O*-phenyl hydroxylamine hydrochloride could be used to trap the aldehyde and deliver the radical precursor in one pot. The sole product from the reaction was partially deprotected oxime ether **255**, obtained in a combined yield for the two steps, of 29%. Unfortunately this radical precursor proved equally unstable and fragmented upon microwave irradiation at the high temperatures required for oxime ether thermolysis. Mass spectrum analysis of the product showed a small amount of the corresponding nitrile. No peak corresponding to the desired cyclised product was observed.



Scheme 72 Attempted synthesis of DAB, **19**

As acetyl protected arabinose proved unsuitable for the proposed synthesis of **19** it was reasoned that applying benzyl protecting groups could lead to the formation of a more robust precursor. Iodo furanose **252** was treated with benzyl trichloroacetimidate and TMS-triflate (Scheme 73), while this reaction proceeded in excellent yields with pyranose iodo sugars, when applied to the corresponding furanoses an incomplete reaction with

multiple side products was noted. Benzylation of **252** was then carried out using triflic acid in place of TMS-triflate this allowed conversion within ten minutes with an 89% yield. **256** was ring opened under Kleban conditions[298] as before, giving aldehyde **257**. It was noted that **257** was marginally more stable than the acetylated analogue, as purification and characterisation could be carried out, however a considerable amount of product loss was noted upon purification. While the reaction had appeared to proceed quantitatively by TLC analysis, only 7% of clean aldehyde was recovered following column chromatography. Coupling of the aldehyde **257** with *O*-phenyl hydroxylamine hydrochloride was ineffective rendering multiple fragmentation products.



Scheme 73 Attempted synthesis of DAB via a benzylated precursor

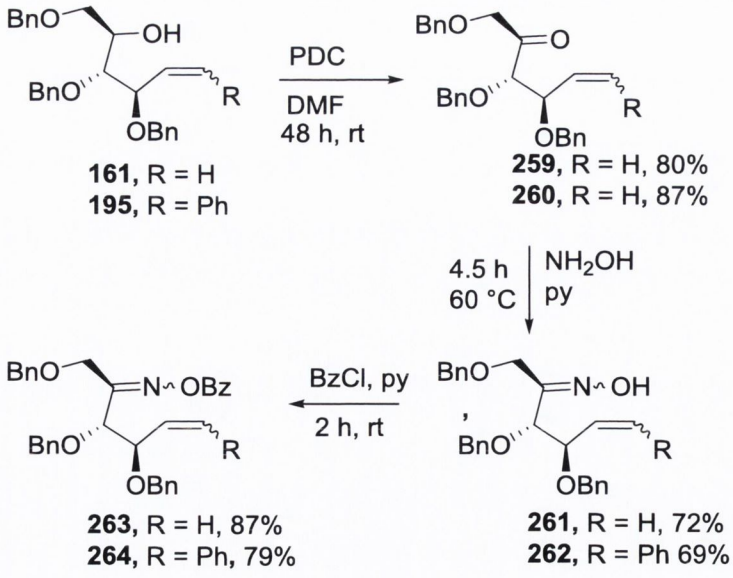
3.4.1 Concluding remarks on the attempted synthesis of aldoxime ethers

Given the synthetic difficulties encountered in the synthesis of *arabino* aldoxime ethers, this synthesis was abandoned. It was deduced that functionalization of the imine carbon is imperative to the stability of the iminyl radical and also to prevent formation of the unwanted nitrile by-product. In this context it was therefore decided to attempt iminyl radical formation and cyclisation via a complementary synthetic route to that already outlined for thiosugar synthesis. In this route, the oxime ether is installed at the C-5 position while the alkene radical acceptor is present at the anomeric position. Owing to the inherent structure of the parent sugar the imine carbon is thus already functionalised with a CH_2OBn, negating the possibility of nitrile formation.

3.5 Synthesis of pyranose and furanose ketoxime ethers and esters for iminyl radical development

3.5.1 Synthesis of furanose C-5 oxime esters for ESR evaluation

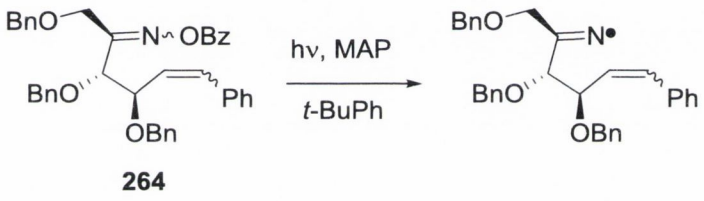
In a similar approach to the synthetic route developed to *C*-thiosugars as outlined in Chapter 2, synthesis of a glycosyl iminyl radical precursor began with Wittig methylenation on benzylated glycosyl hemiacetal. With *arabino* alkene **161** in hand from previous synthetic work, oxidation of the secondary alcohol at C-5 ensued. Initial attempts utilising PDC as an oxidising reagent in CH_2Cl_2 gave unsatisfactory conversions (31-38%) to the desired ketone **259**.[318] Repeating the reaction in a 1:1 mixture of CH_2Cl_2:DMF gave rise to a superior conversion (55%) owing to the increased solubility of the dichromate in DMF. In order to further enhance the conversion of the oxidation reaction DMF was utilised as the sole solvent giving an excellent overall conversion of 80% to ketone **259**. Coupling of hydroxylamine hydrochloride with **259** necessitated the use of reflux in order to reach completion, benzoylation of the oxime, **261**, gave the desired oxime ester **263** in 87% yield. With the aim of introducing variability at the anomeric position an oxime ester was also generated from phenyl alkene **161**. The synthesis successfully proceeded without incident to yield the desired oxime esters **264** (Scheme 74).



Scheme 74 Synthesis of ketoxime esters **263** and **264**

Once again, with the oxime esters in hand, we were interested in testing these samples under ESR conditions in order to determine if the iminyl radical or indeed the cyclised species could be observed. 5-*exo*-trig iminyl radical ring closures are conducive to the visualisation of both the iminyl and cyclised radical by ESR.[310] It was therefore anticipated that the 5-*exo* oxime esters, particularly **264**, which is capable of resonance stabilisation of the alkyl radical would generate strong EPR spectra from which the kinetics of the cyclisation reaction could be studied. Samples were analysed by Professor John Walton at the University of St. Andrews, the results from which are shown below.

3.5.1.1 EPR data from photolysis of 264



264

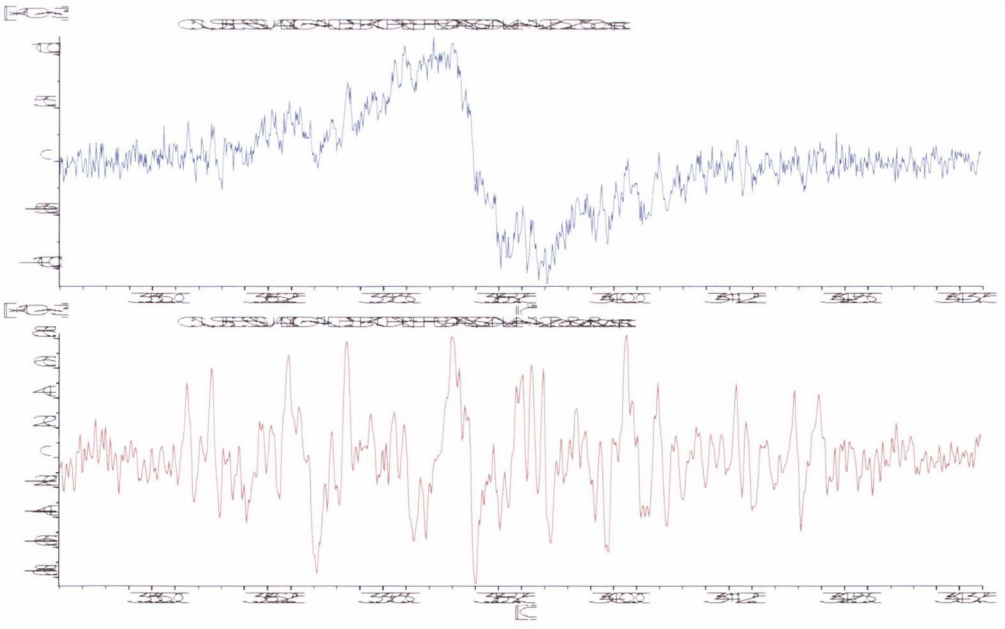


Figure 37 Top: Raw spectrum on photolysis of **264** with MAP in *t*-BuPh at 230 K. Bottom: After adding together 3 sets of scans like the one on top and then digitally removing the broad central feature.

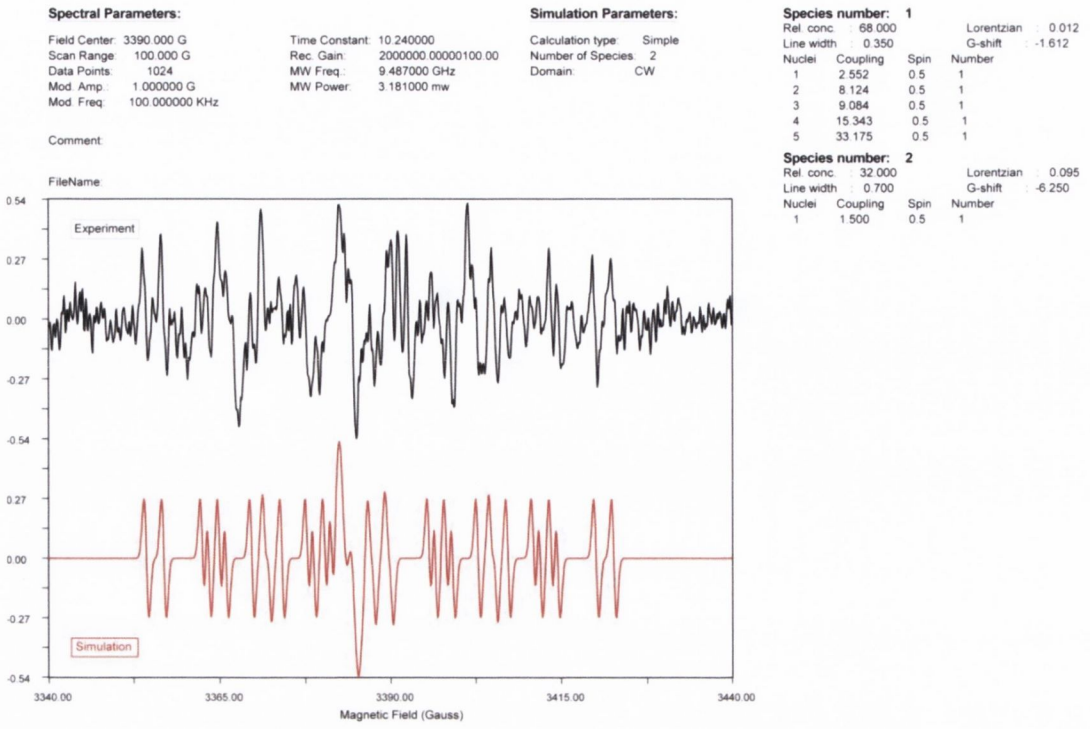
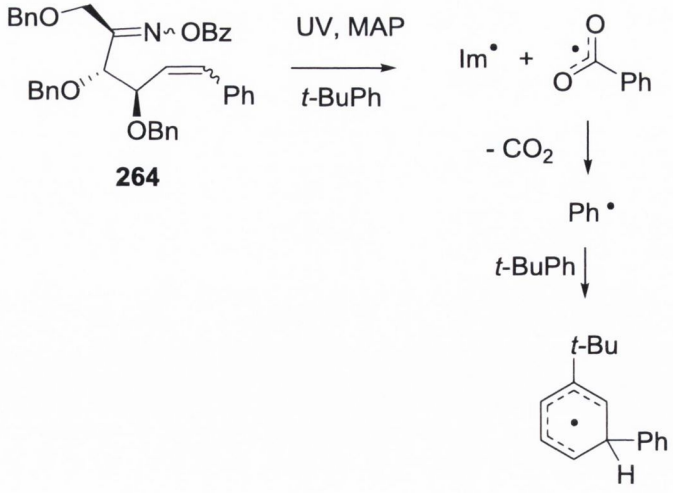


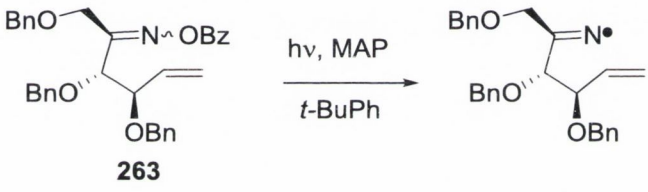
Figure 38 Top: EPR spectra from **264**. Bottom: Computer simulation of iminyl and cyclohexadienyl radical with parameters shown above right.

The simulation shown in Figure 38 identifies the main species present is the cyclohexadienyl radical. Presumably this is formed upon photolysis upon which the benzyloxyl radical which loses CO_2 to give the phenyl radical. The latter, a sigma radical adds *meta* to the *t*-BuPh solvent to give the cyclohexadienyl radical (Scheme 75). While other signals are present in the spectrum the large number of lines from the cyclohexadienyl radical obscures them and thus negating the possibility of characterisation.



Scheme 75 Formation of cyclohexadienyl radical

3.5.1.2 EPR data from photolysis of 263



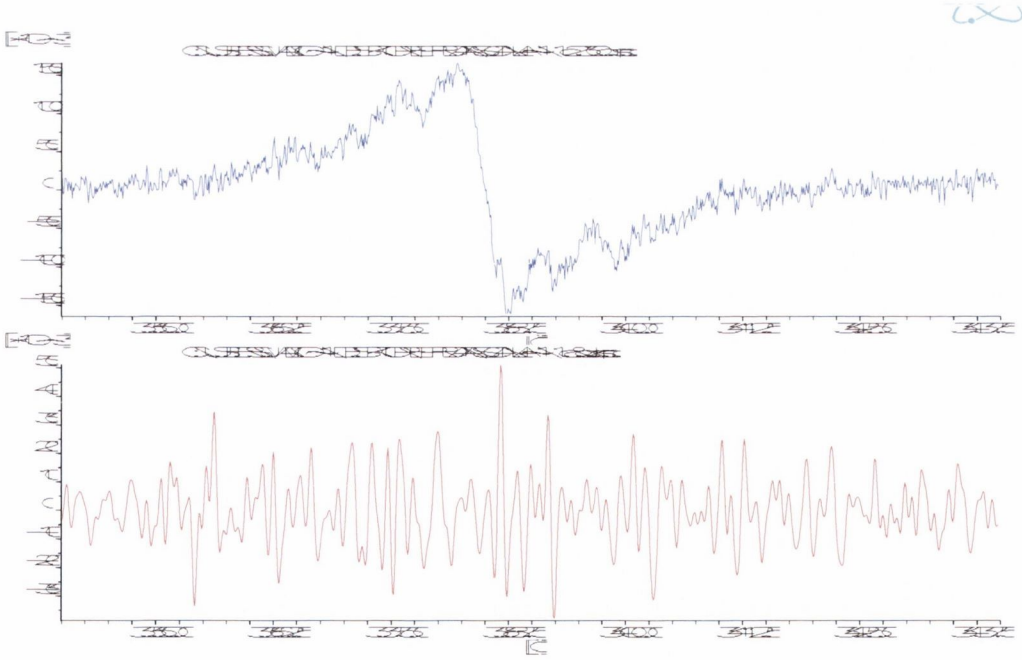


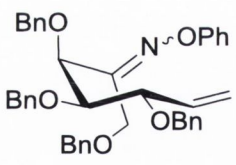
Figure 39 Top: Raw EPR spectra of **263.** Bottom**:** After adding together 3 sets of scans like the one on top and then digitally removing the broad central feature.

Unfortunately irradiation of oxime ester **263** yielded similarly disappointing results. Evidence of an iminyl or alkyl radical was obscured by the cyclohexadienyl radical, presumably formed *via* addition of the sigma radical to the tert butyl benzene solvent as before. For **263** and **264**, the strength of the generated iminyl radical signal is diminutive in comparison with the signal from the cyclohexadienyl radical. It was accordingly deduced that substitution of the imine carbon did not provide the requisite stabilisation necessary to prolong the lifespan of the iminyl radical. Substitution of the imine carbon with an aromatic motif would represent the most prudent choice in order to obtain strong EPR spectra. Delocalisation of the iminyl radical could then ensue resulting in stabilisation and increasing the possibility of obtaining good spectroscopic results.

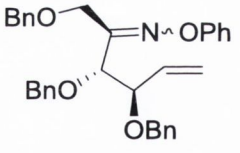
3.5.2 Synthesis of ketoxime oxime ethers and thermolytic studies

Following EPR studies, synthetic work ensued to prepare and investigate the behaviour of the corresponding furanose oxime ethers under thermolytic conditions. It was anticipated that the desired iminosugars could be synthesised and isolated on a preparative scale via 5-*exo* iminyl radical cyclisations.

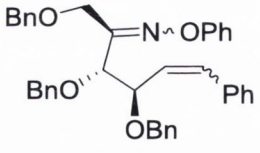
In order to assess thermolytic iminyl radical formation from ketoxime ethers the synthesis of 3 initial representative examples were considered (Scheme 76).



265



266

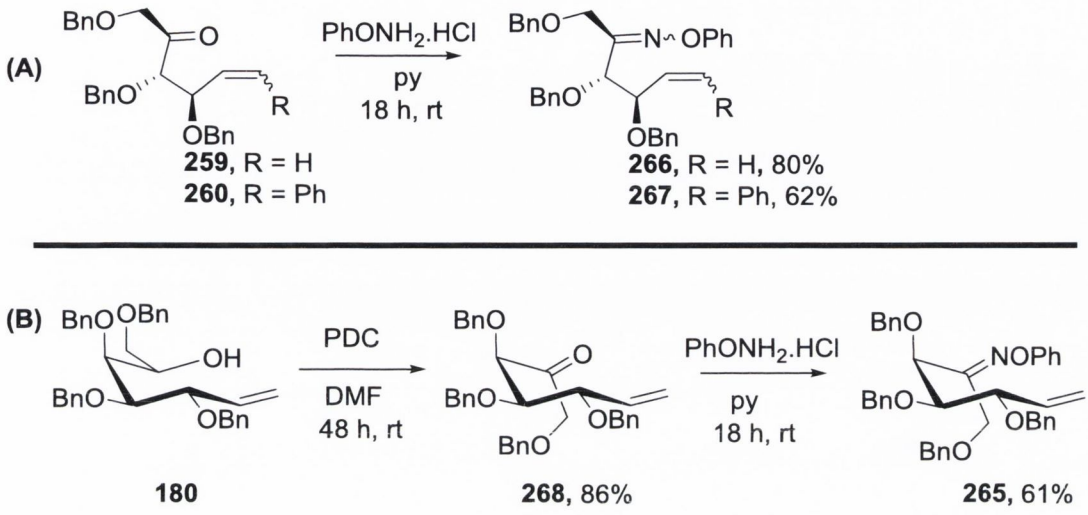


267

Scheme 76 Ketoxime ethers for initial thermolytic dissociation studies

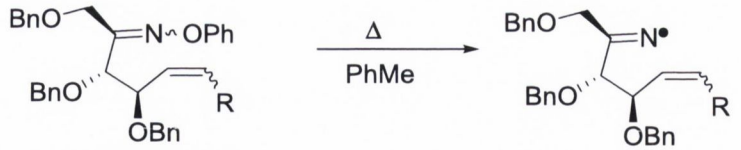
With the intention of evaluating 6-*exo* radical cyclisation, ketoxime ether **265** was synthesised from alcohol **180**. Simultaneously, it was decided upon that preparation of **266** would allow for an investigation of the analogous 5-*exo* radical cyclisation. In order to further extend the study, it was anticipated that resonance stabilisation of the cyclised alkyl radical, as would be provided by **267**, constituted an excellent starting point from

which to optimise the radical cyclisation. The oxime ethers were synthesised from their parent aldehydes by condensation with *O*-phenyl hydroxylamine hydrochloride (Scheme 77).

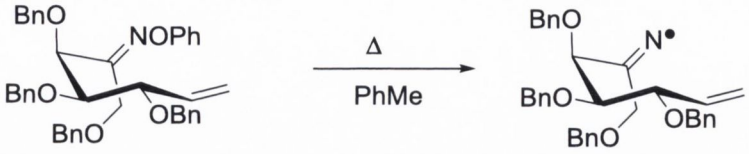


Scheme 77 synthesis of oxime ethers **265**, **266** and **267**

Studies on thermolytic dissociation of the ketoxime ether to form an iminyl radical began with exposing **267** to 160°C in the microwave for 15 minutes, according to the conditions described by Portela Cubillo *et al.*[224] Unfortunately, much charred residue was obtained following the reaction, although the presence of phenol was noted proving an iminyl radical intermediate had been formed. Following this, individual samples of **267** were heated in the microwave at varying temperatures in order to assess the temperature required for clean iminyl radical formation. Unfortunately varying times and temperature did not yield a successful radical cyclisation. No reaction was noted below 110°C. Reaction at this temperature for fifteen minutes resulted in a small amount of fragmentation accompanied by a large amount of unreacted starting material. Increasing reaction times at 110°C led only to decomposition while longer reaction times at 100°C saw unreacted starting material. Short reactions at 120°C gave charred residue. Similar reactions with oxime ethers **265** and **266** gave similarly disappointing results (Table 11).



266, R = H
267, R = Ph



265

Entry	Oxime ether	Time (min)	Temperature (°C)	Result[a]
1	**267**	15	160	Fragmentation
2	**267**	15	60	No reaction
3	**267**	15	70	No reaction
4	**267**	15	80	No reaction
5	**267**	15	90	No reaction
6	**267**	15	100	No reaction
7	**267**	15	110	Small amount fragmentation
8	**267**	30	110	Fragmentation
9	**267**	40	100	No reaction
10	**267**	10	120	Fragmentation
11	**265**	15	110	Small amount of fragmentation
12	**266**	15	110	Small amount of fragmentation

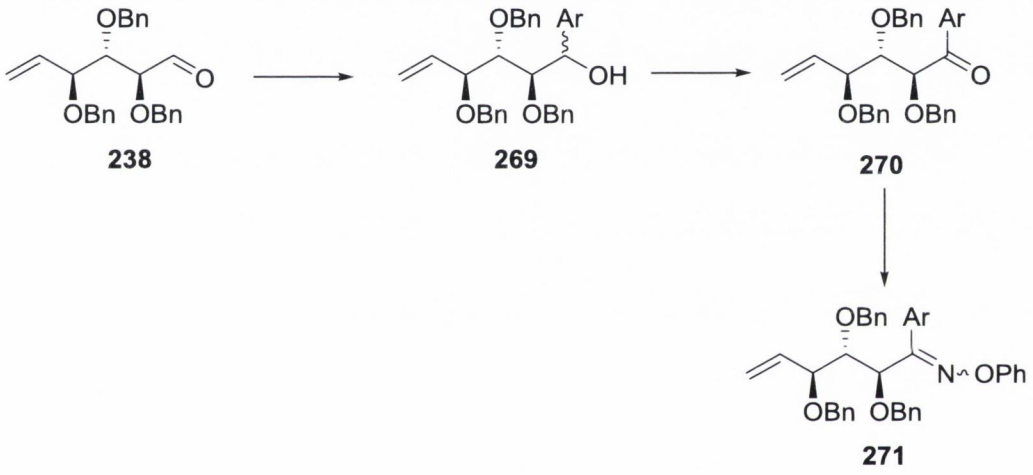
[a]Results visualised by TLC and ^{1}H NMR analysis. All reactions carried out in 350MW microwave

Table 11 Thermolysis of oxime ethers **265**, **266** and **267**

3.5.3 Conclusions on synthetic attempts at an intramolecular iminyl radical cyclisation

Regrettably owing to significant synthetic difficulties and challenges associated with the initiation and reactivity of the iminyl radicals, we were unable to replicate the successful

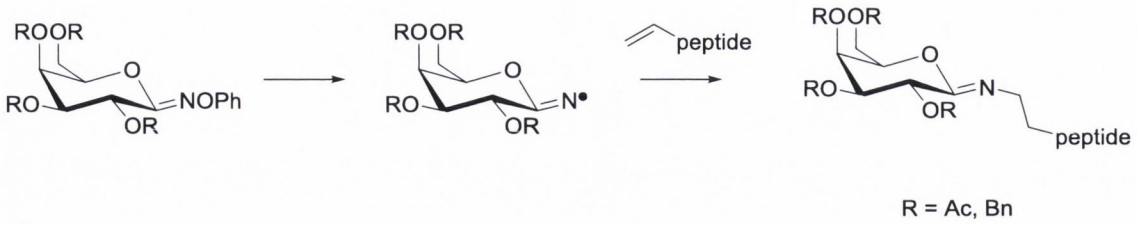
results obtained through a thiyl radical chain cycle in the iminyl radical system. Alkyl substitution at the imine carbon was insufficient to stabilise the short lived iminyl radical therefore potential future work that could be engaged on this project could involve the conjugation of an aryl substituent on the imine carbon. This could conceivably be implemented by carrying out a Grignard reaction with an aromatic magnesium bromide on aldehyde **238** followed by subsequent oxidation and condensation to form the desired oxime ether (Scheme 78). Further methods for iminyl radical generation could be investigated, a photochemical system for light induced iminyl radical formation is also extremely appealing; equally the use of other nitrogen containing radicals could be explored.



Scheme 78 Potential route for synthesis of a resonance stabilised oxime ether **271**

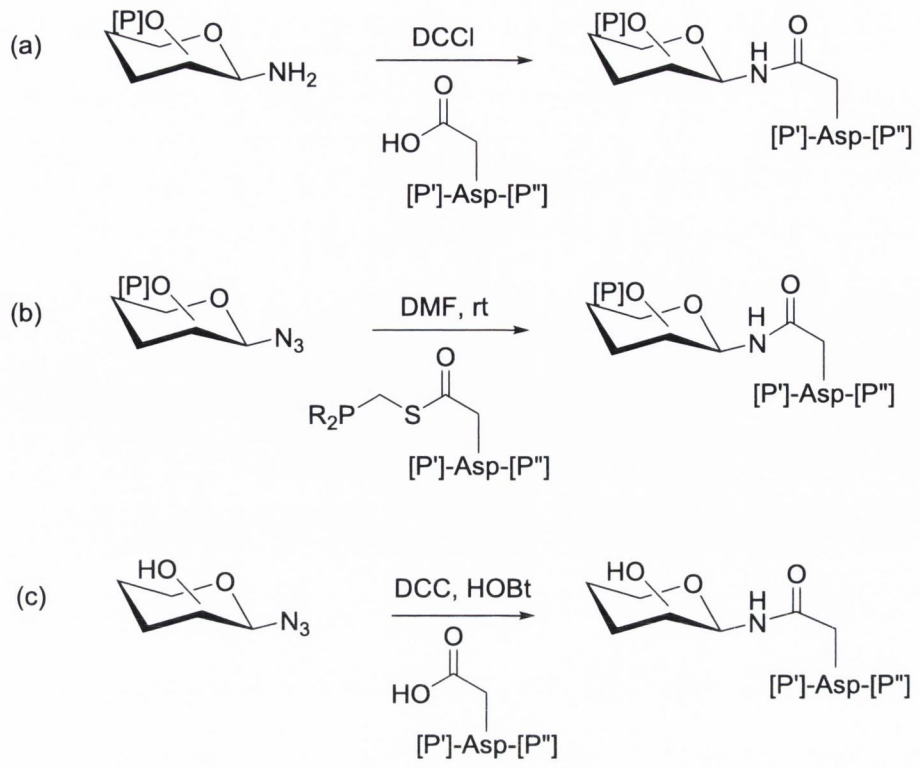
3.6 Glycosyl iminyl radicals in the synthesis of *N*-linked glycopeptides

As part of our study on the generation of glycosyl iminyl radicals an intermolecular radical addition of an anomeric iminyl radical to a peptide based alkene was envisaged. This would provide a novel, concise route to *N*-linked glycopeptides (Scheme 79).



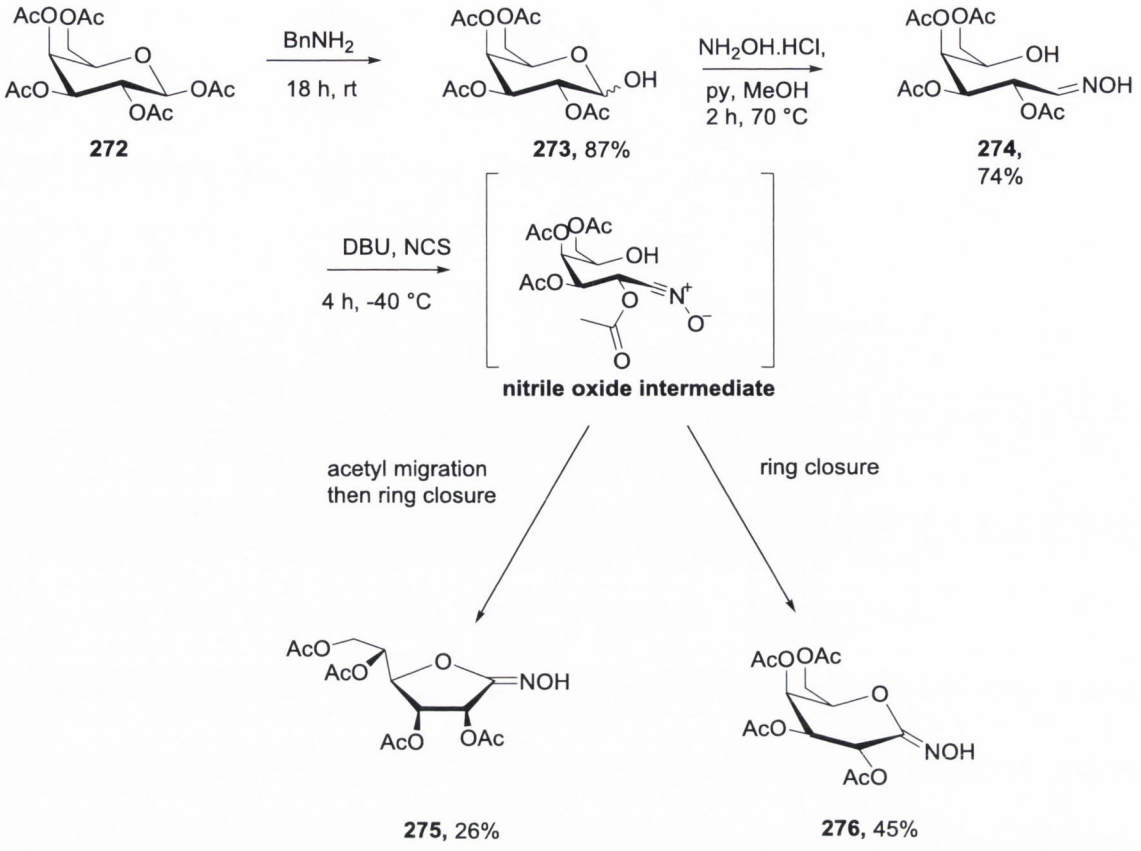
Scheme 79 Proposed route to *N*-linked glycopeptide via intermolecular iminyl radical trapping

The most commonly employed route to *N*-linked glycan synthesis is the reaction of a protected or deprotected glycan with a suitably protected Asp derivative.[319] Staudinger reactions of glycosyl azides with Asp side carboxylates in the presence of triphenylphosphine have also been successful for peptide ligation to *N*-linked sugar units[320] (Scheme 80). However, a nitrogen centred radical route to *N*-linked glycopeptide synthesis has not yet been investigated. Indeed, intermolecular additions of nitrogen radicals are relatively uncommon. Nitrogen radicals with electrophilic character, particularly amidyls and sulfoamidyls have a propensity for allylic hydrogen abstraction thus complicating intermolecular addition. Thiyl radicals on the other hand, as discussed in section 1.6 undergo rapid intermolecular alkene and alkyne addition and have been utilised in the synthesis of *S*-glycopeptides.[206-209]



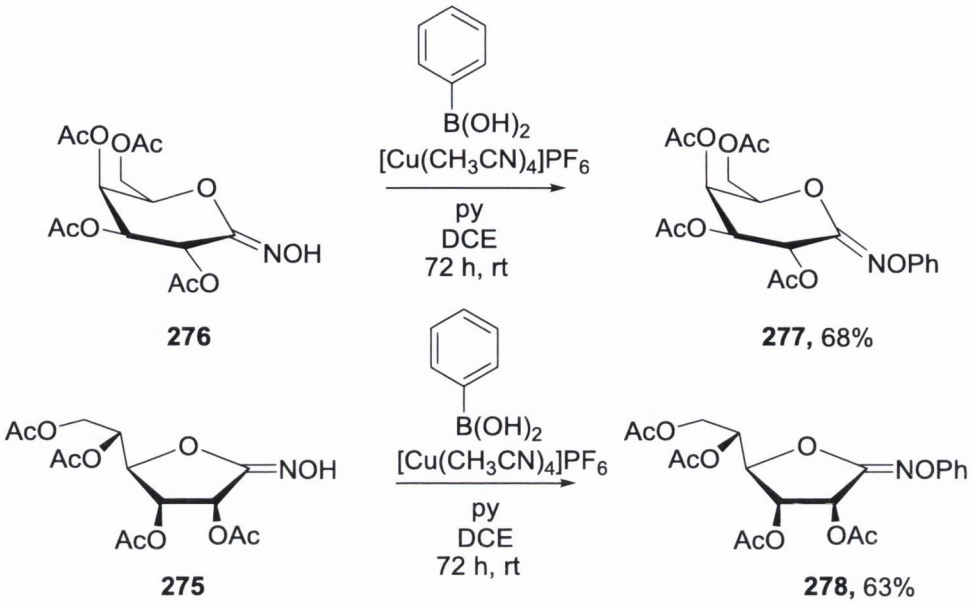
Scheme 80 Commonly employed techniques for *N*-linked glycopeptide synthesis

A microwave assisted thermolysis of an oxime ether was considered in the first instance as an accessible approach to the desired anomeric iminyl radical. Commercially available β-penta-acetylated galactopryanoside was hydrolysed to its corresponding lactol **273**, and subsequently was treated with hydroxylamine hydrochloride and pyridine to afford **274**. With an oxime installed at the anomeric position oxidative ring closure was applied in the presence of DBU and NCS in CH_2Cl_2 at -40°C to afford oxime **276** and oximinolactone 1,4 lactam oxime **275**. This NCS-mediated oxidative ring closure has been reported as being problematic, providing variable yields, acute temperature sensitivity, while also being accompanied by the formation of an 1,4 lactam oxime. Vasella *et al.*[321] have proposed formation of the oximinolactone as a byproduct results from the presence of the carbonyl group at C-2 which may reversibly capture the presumed nitrile oxide intermediate, delaying ring closure, and enabling acetyl migration to be a competitive process. In our hands **275** and **276** were seperable by column chromatography, therefore we continued the synthesis towards an exocyclic oxime ether on both the pyrano, **276,** and furano, **275**, systems (Scheme 81).



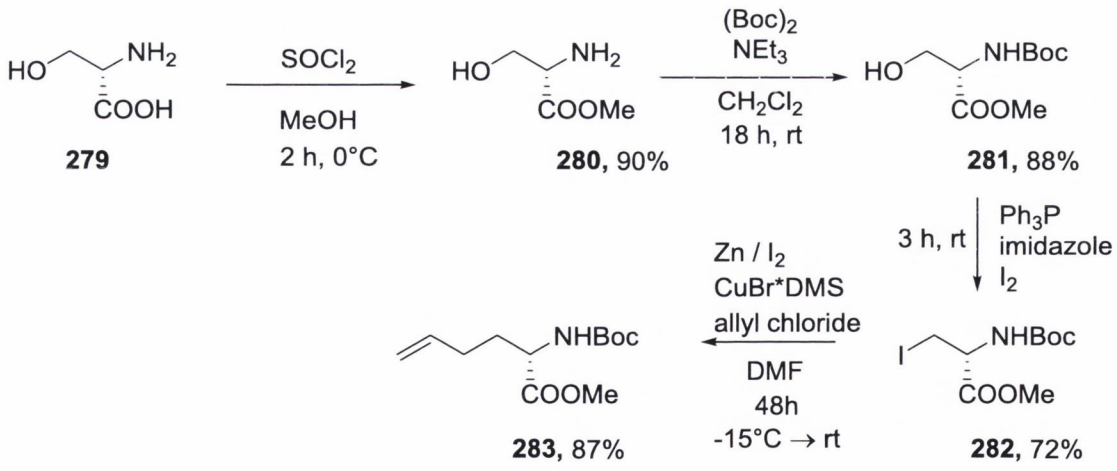
Scheme 81 Rationalisation of the oxidative ring closure

In order to synthesise the requisite *O*-phenyl oxime ether for thermolytic iminyl radical generation, inspiration was taken from the work of Petrassi *et al.*[313] We decided to apply a copper (I) mediated coupling of **275** and **276** with phenyl boronic acid in the presence of pyridine to furnish **277** and **278**. Disappointingly conversion was noted as poor 13% and 18% yields for **277** and **278**, the yields could not be increased upon by increasing the reagent loadings or temperature of the reaction. However a change of the copper catalyst from CuCl to tetrakis (acetonitrile)copper (I) hexaflurorphosphate proved an excellent choice as the latter salt, a superior source of copper (I), increased the yields of oxime ether synthesis to 68% and 63% for **277** and **278** respectively (Scheme 82).



Scheme 82 Synthesis of oxime ethers **277** and **278**

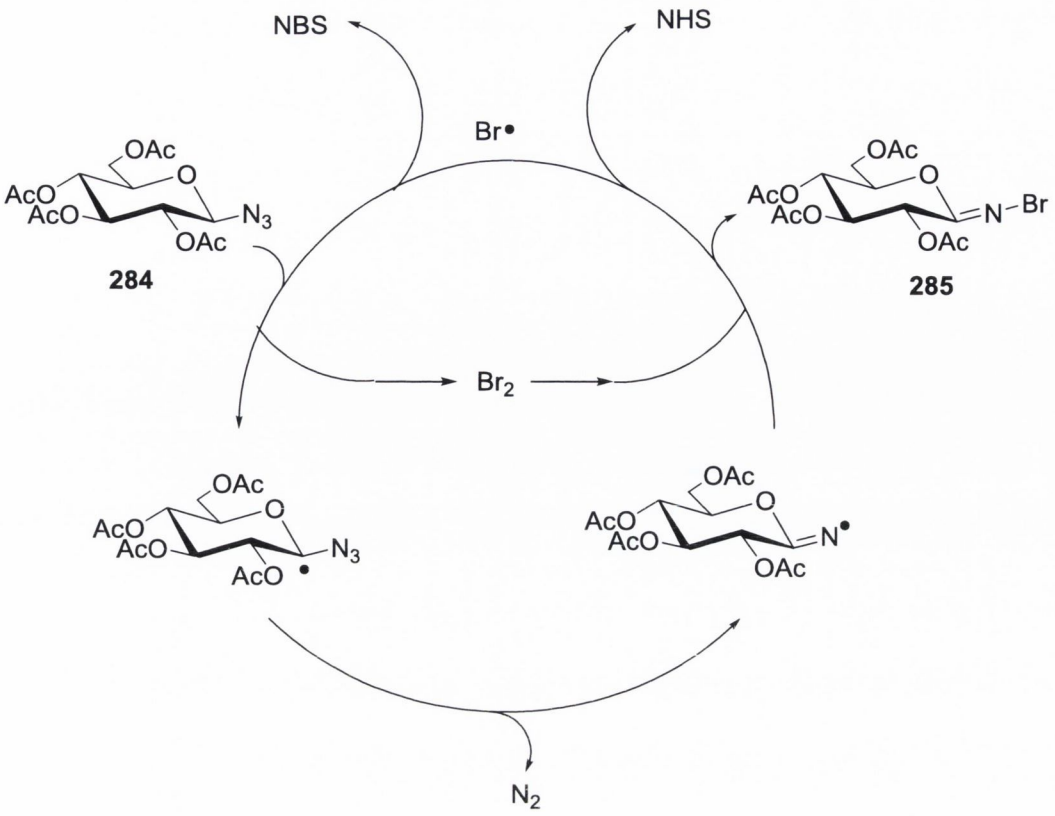
With the preparation of oxime ethers **277** and **278** complete, attention was then turned to the synthesis of a suitable peptidic alkene as a radical trap. Rodriguez *et al*[322] have established a route to but-3-enylglycine **283** via transmetallation of organozinc reagents with $CuBr.SMe_2$ in the presence of allyl chloride. Thus applying the reported conditions starting from L-serine, **279**, allylated compound **283** was isolated (Scheme 83).



Scheme 83 Synthesis of but-3-enylglycine **283**

With all requisite precursors in hand, microwave irridation of both compounds was pursued in toluene. Previous studies on the thermolysis of oxime ethers had seen N-O bond cleavage at 160°C which is in accordance with the findings of Walton and co-workers.[224] However at 160°C no reaction was observed on either precursor. A temperature of 180°C was required to cleave the N-O bond in both cases. Following the thermolysis analysis of the crude reaction mixture did not present a major radical degradation pathway, instead many fragments were observed. Mass spectroscopy results showed phenol had formed from the thermolysis of both oxime ethers proving that iminyl radical formation had taken place. In the case of pyranose oxime ether **277**, microwave irridation was found to have formed trace amounts of its lactone. Lactone formation is a known known degradation product of an iminyl radical, formed via hydrolysis of the imine after abstraction of a hydrogen atom by the iminyl radical. All attempted trappings of the iminyl radical with alkene **283** were unsuccessful, a mixture of inseparable fragments of the oxime ethers were recovered alongside unreacted alkene. This suggests that upon N-O bond cleavage the electron deficient nature of the peracetylated sugar could not stabilise the iminyl radical long enough for intermolecular attack to take place.

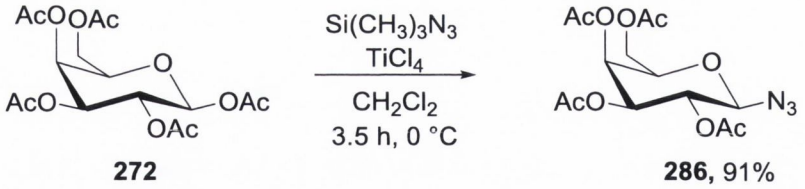
As far as this author is aware only one example of an anomeric iminyl radical exists in the literature. Reported by Praly *et al.*[323] a method for the synthesis of bromoimines via intermolecular attack of a glycosyl iminyl radical was achieved using NBS as both initiator and radical trap. Initiation of the radical reaction was mediated by use of a 60 W Tungsten lamp (Scheme 84).



Scheme 84 Synthesis of N-bromoimines reported by Praly *et al.*[323]

It was decided upon to attempt iminyl radical generation from an anomeric azide in a parallel fashion, substituting ACVA in place of NBS as a radical initiator. The β anomeric azide **286** was synthesised in an excellent 91% yield in 1 step from β-penta-acetyl galactopyranoside according to conditions reported by Virginie *et al.*[324] (Scheme 85). Interestingly the α-anomeric azide can be synthesised exclusively via radical methods, by the radical azidation of an anomeric xanthate.

Disappointingly, upon reaction it was found that ACVA was not capable of abstracting the requisite anomeric H-atom on **286** to deliver the iminyl radical. The azide remained unreacted even in the presence of a 5 equivalent excess of ACVA at 40°C.

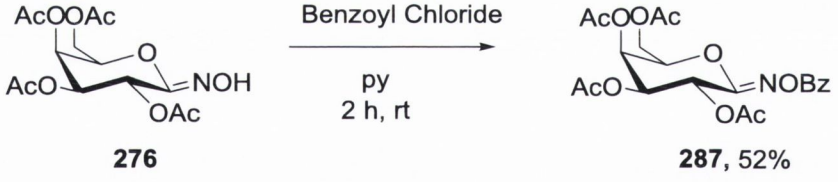


272 **286**, 91%

Scheme 85 Synthesis of β-azido-galactopyranoside **286**

Furthermore, attempts to replicate the results obtained by Praly *et al.*[323] using NBS to initiate radical formation in the presence of a 50 and 150W lamp source were futile, homolysis of NBS was not observed, presumably the light source used was not high-energy enough to cleave the succinimyl-bromine bond.

In order to fully examine anomeric iminyl radical formation, oxime ester **287** was synthesised from oxime **276** (Scheme 86) and was sent for ESR evaluation. It was anticipated that information on the stability and localisation of the iminyl radical could be yielded. Unfortunately owing to an inopportune breakdown of equipment, **287** was found to have decomposed prior to ESR evaluation.



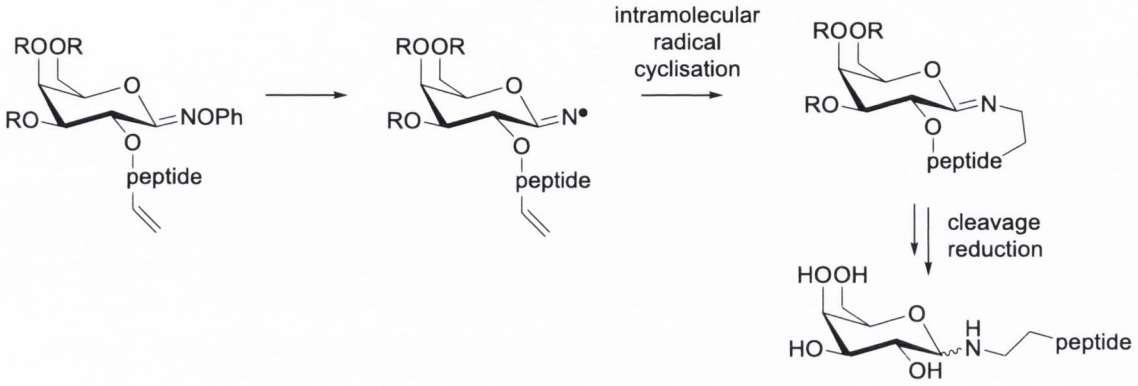
276 **287**, 52%

Scheme 86 Synthesis of oxime ester **287** for ESR analysis

3.6.1 Concluding remarks on *N*-linked glycopeptide synthesis

As iminyl radicals are noted for their excellent reactivity in intramolecular systems, a more efficient synthesis may be achieved via an intermolecular iminyl radical cyclisation onto a peptide alkene tethered on the 2-position. Cleavage of the peptide moiety from the 2-position would furnish an *N*-linked glycopeptide species (Scheme 87). Additionally, it must be considered that further nitrogen containing radicals could be considered with the aim of investigating a radical method for *N*-linked glycopeptide synthesis. This would

initially involve tuning of the nucleophilic/ electrophilic nature of the radical and its trap in order to elucidate a compatible pairing.



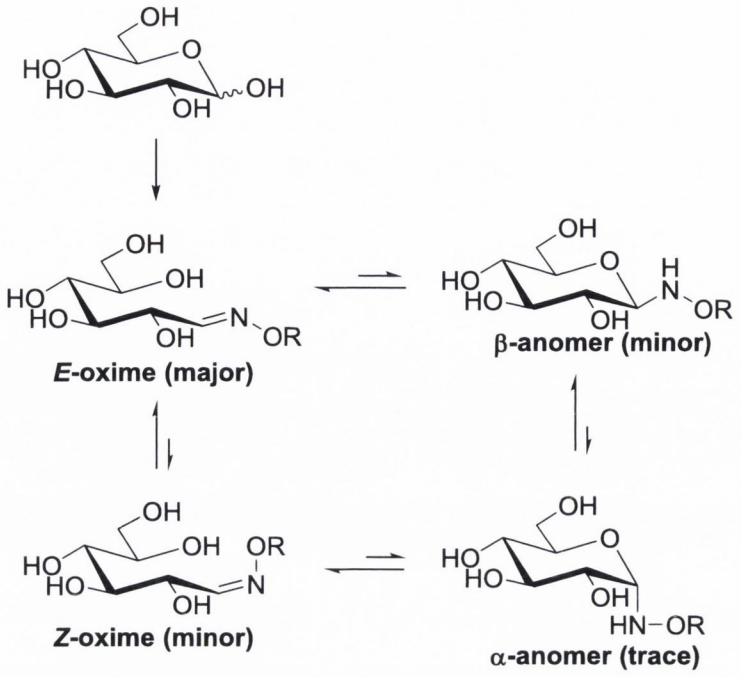
Scheme 87 Possible synthesis of *N*-linked glycopeptide via intramolecular iminyl radical cyclisation

4.0 Synthesis of oxyaminoglycans as potential glycosidase inhibitors

4.1 Oxime ligation as a tool for glycoconjugation

Carbohydrates in which one of the oxygen atoms has been replaced by a nitrogen atom constitutes a large and varied class of compounds in glycobiology known as glycosylamines. These compounds, as mentioned in section 1.2.1.3 are very abundant in nature, the most common being 2-amino-2deoxy D-glucopyranose and its *N*-acetylated derivative. Compounds in which the ring oxygen has been replaced by a nitrogen gives rise to compounds such as nojirimycin **10**, their synthesis was attempted in chapter 2. This Chapter will be concerned primarily with a class of compound in which the interglycosidic oxygen has been replaced with a nitrogen containing functionality, namely an aminooxy group.

As alluded to in section 1.2.1.3, glycosylamines are specific competitive inhibitors of α- and β-glycosides. **28**, containing an amino group in the interglycosidic linkage has the highest reported binding affinity for a carbohydrate binding protein.[14] However, only a few examples of such 'pseudo-sugars' containing nitrogen in the interglycosidic linkage have been reported in the literature, those which do appear however show very promising results. [40-42, 137, 325, 326] In this context we were interested in studying the use of an oxime linkage to ligate various derivatives via the hemiacetal functionality at the anomeric position of the sugar. Carbohydrate oxime ligation has been applied to neo-glycopeptides,[327] solution-phase tagging,[328] microarrays,[329] nanoparticles[330] and solid supports[331] and has proved a robust and powerful tool for rapid functionalization of glycoconjugates. By exploiting the unique availability of the hemiacetal functionality at the reducing end of glycan's, selective oxime ligation can be carried out at the anomeric position in the absence of protecting groups.[332-334] Carbohydrate oximes and oxime ethers are known to exist in several ring chain tautomeric forms, the open chain *E* and *Z* forms generally predominate over the pyranose α- and β-form although the distribution of tautomeric forms is dependent on the individual monosaccharide unit.[335-337] (Scheme 87) The unusual N-O interglycosidic linkage has been observed in the antitumour antibiotic esperamycin A_1[338] and calicheamicin γ_1[339] with the N-O moiety suggested as playing a crucial conformational role for minor groove DNA binding.

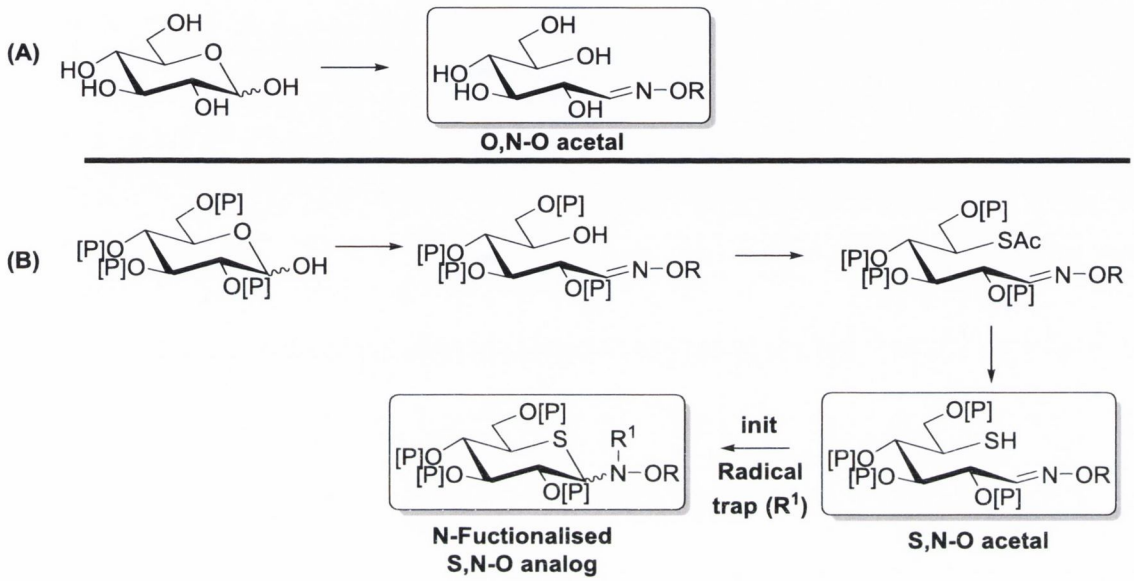


Scheme 87 Tautomeric forms of glucose oxime ethers

4.1.1 Proposed synthesis of O/N-O and S/N-O acetals as potential glycosidase inhibitors

In addition to studying its utility as a ligation tool it was also of interest to investigate the use of an oxime as a radical trap for thiyl radicals. As discussed in Chapter 2, the intramolecular thiyl radical cyclisation reaction offers an efficient methodology for accessing thiosugars.[260, 281] Since oximes have previously been used as efficient radical traps for iminyl radical cyclizations[340] we were interested in applying this strategy to thiyl radicals. Thus, in the first instance an oxime would be installed at the anomeric position of the sugar, giving an open chain reactant with the hydroxyl at C-5 available for further modification. Installation of a thioacetate would then ensue, followed by deprotection to give the free thiol. Thereafter, generation of a thiyl radical which could undergo a 6-*exo* radical cyclisation would generate an aminyl radical for further functionalization, thus expediting access to a novel class of highly functionalised glycoconjugates for biological evaluation. Thiyl radical cyclisation onto oximes has not previously been studied for the synthesis of thiosugars or indeed any sulphur containing heterocycles. Through this work it was anticipated to synthesise a range of substituted hydroxylamines and to carry out their condensation with a glycosyl hemiacetal. Conjugation with deprotected glucose

would be carried out primarily, in order to optimise the reaction conditions required for conjugation. This rapid one step transformation would give rise to oxygen analogs with potentially interesting biological activities. It was also reasoned that attaining such analogs would allow for an insightful comparison of the biological activities of both *O/NO* and *S/NO* acetals.



Scheme 88 Synthetic approach to the synthesis of (A) *O,N-O* acetals and (B) synthetic approach to *S,N-O* acetals and aminyl radical functionalised SNO analog.

There is literature precedence to support the hypothesis that oxime linked thiosugars should have interesting biological activities. [40-42, 137, 325, 326] Thiosugars are known glucosidase inhibitors and the presence of a basic group (eg –NHR,-NHOR) at C-1 is known to increase inhibitory activity by increasing the interaction with the carboxyl groups within the active site of the enzyme. While *N*-linked thiosugars are a relatively unexplored class of compounds, the research group of Mario Pinto have developed several *S/N* acetal analogs. Andrews *et al.*[137] reported the synthesis of an S/N acetal analogue of methyl maltoside which was found to exhibit glucoamylase inhibition with a *K*i of 4 μM (Figure 1), this is a significant value as 1-deoxynojirimycin offers considerably less inhibition of glucoamylase at a *K*i of 96 μM. The group have also synthesised 4-thiogalactofuranosyl-containing disaccharides with nitrogen in the interglycosidic linkage[341] and 1,2- and 1,3-*N*-Linked disaccharides of 5-thio-D-mannopyranose as potential inhibitors of the mannosidase I and mannosidase II enzymes.[326] The bioactivity of these few literature compounds suggested that there was

considerable potential for new glycosidase inhibitors to be developed within this chemical space.

4.1.2 Stability and anomeric configurations of O/N and S/N acetals

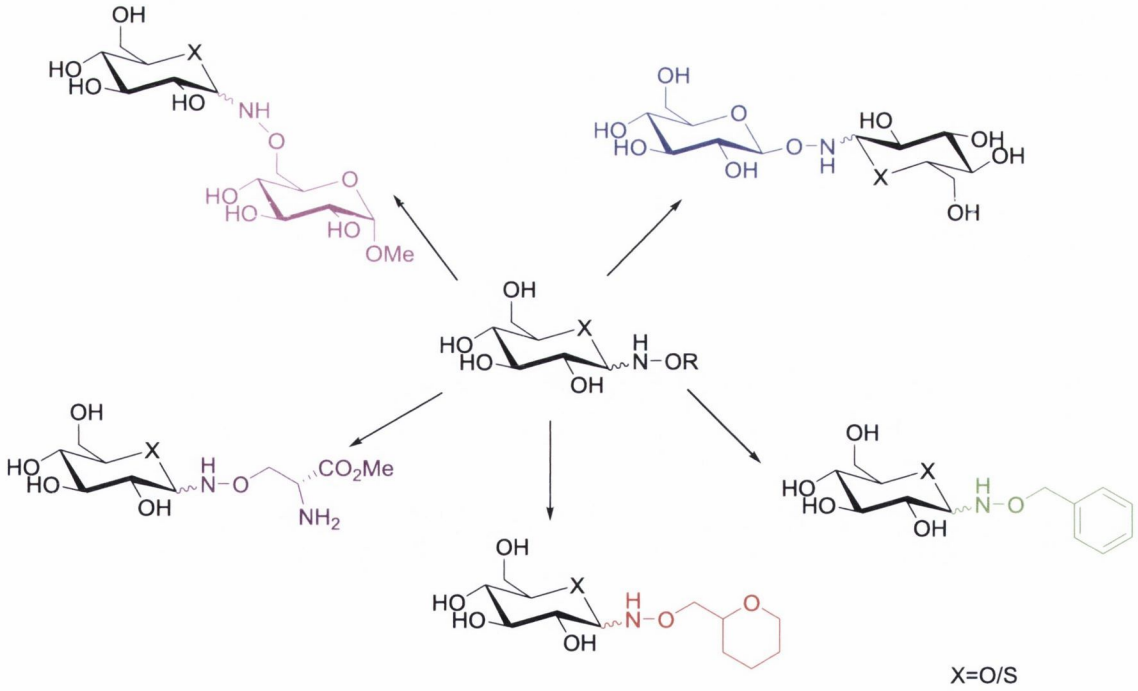
A commonly observed problem with the preparation of glycosylamines is their propensity for hydrolysis. *N*-alkyl galactosylamine has a half-life of 20 minutes at pH 7).[342] Far more resistant to hydrolysis are *N*-aryl glycosylamines. Nevertheless, basic inhibitors were found to bind 10^2-$10^{3.5}$ more tightly to the glycosidase active site than their neutral counterparts.[343] *N*-alkylation, while leading to a more hydrolysable substrate greatly enhanced the binding of inhibitors to β glycosidases from E-coli.[344] Conversely, *N*-arylation and *N*-acylation significantly lowered binding, owing to the reduced basicity of the glycosyl nitrogen.[343] While *O/N* acetals are known to suffer from rapid hydrolysis, *S/N* acetals have been reported to be "quite stable at 25 °C".[345] Indeed, analogs synthesised by Pinto and co-workers were stable to hydrolysis after several weeks in D_2O.[137] Comparatively, glycosyl oximes are known to be slightly more stable to hydrolysis than their corresponding glycoyslamine counterparts, they can be hydrolysed in acidic water at pH<4.[346] Since *S/NO* acetals have never previously been synthesised, knowledge of their stability has not been documented. However, it was presumed that they would exhibit greater stability than their *O/NO* counterparts.

Glycosyl amines are known to mutarotate (ie form an equilibrium mixture of α and β anomers) rapidly in solution. Thereby complicating the assignment of the anomeric orientation required for inhibition. β-glucosylamine, which is unique as a glycosylamine which does not mutarotate in solution was found to inhibit both α and β glucosidases. For an *O/N* acetal, when an equilibrium exists between α and β anomers, the latter is presumed to be more stable thermodynamically, owing to steric effects. The preference for the β-orientation is not in agreement with the anomeric effect, which operates for systems in which an electronegative substituent is present at the anomeric position, and favours the formation of the α anomer.[347] When glycosylamines are protonated, as they are assumed to be upon enzyme binding, the "reverse anomeric effect"[348] has been suggested as a rationale for the increased preference for the β orientation, although this has been disputed by several groups.[349] In contrast to *O/N* acetals, *S/N* acetals have been reported to contain significant proportions of the axial anomer. The difference has been

attributed to reduced steric effects, coupled with enhanced *exo* and *endo*-anomeric orbital interactions with *S/N* acetals compared to their *O/N* counterparts.[347] While *O*-glycosyl oximes are known to preferentially exist in the open chain configuration a comparative study of the orientation of the *S/N-O* and *O/N-O* acetals was anticipated through this work.

4.1.3 Proposed synthetic targets

In order to access a broad range of oxime linked glycans for potential biological studies, routes to glycan, aglycan and peptidic hydroxylamines were considered for conjugation to glycosyl hemiacetals, from which both *O/N-O* and *S/N-O* acetals could be prepared. Thereafter, attempted aminyl radical trapping via a thiyl radical cyclisation would be investigated. This would allow for analysis of aglycan and glycan based oximes and comparison of the inhibitory activities of a derivative with oxygen or sulphur as the enocyclic heteroatom in the nonreducing sugar unit. In this chapter the synthesis of synthetic hydroxylamines will be discussed initially, followed by an examination of their conjugation to glucose, and concluding with the preparation of the corresponding thiosugar targets.

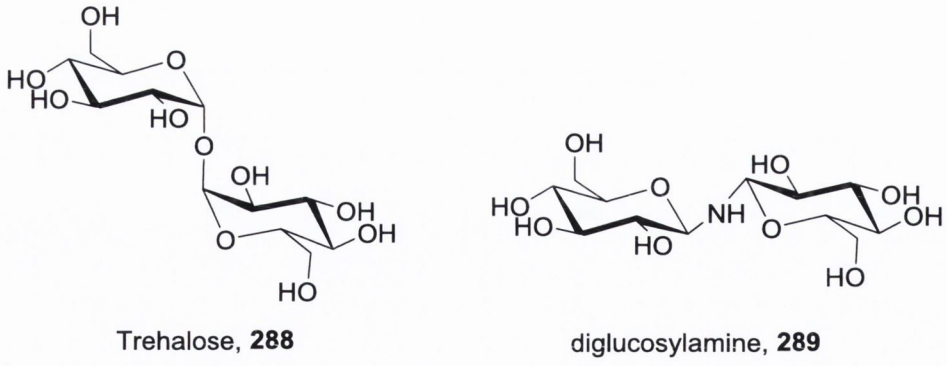


Scheme 89 S/N-O and O/N-O synthetic targets as potential glycosidase inhibitors

4.2 Preparation of synthetic hydroxylamines

4.2.1 Synthesis of 1-oxyaminoglucose

The first synthetic hydroxylamine target prepared was 1-oxyaminoglucose. Through its conjugation with a glycosyl hemiacetal, the synthesis of a 1,1 oxyamino linked disaccharide is thus facilitated. Naturally occurring 1,1 disaccharides are present in nature which exhibit interesting biological activities. Among them, trehalose, **288,** an α,α-1,1 disaccharide which exhibits mild glucosidase inhibiton.[350] It has found widespread use in the food and cosmetics industry owing to its high water retention capactity.[351] An analogues 1,1-di-β-glucopyranosylamine, **289**, has been prepared, which contains a nitrogen in the interglycosidic linkage in place of an oxygen, and has been found to exhibit significantly enhanced glucosidase inhibition.[352] Thus it was of considerable interest to prepare both an *O/NO* and *S/NO* oxyamino analogues for biological evaluation. Several reported methods exist for the synthesis of thiotrehalose,[353] a sugar in which the endocyclic heteroatom is oxygen and the glycosidic heteroatom is sulfur. Such analogs hold greater chemical and enzymatic stability than their *O*-linked isosteres, however the synthesis of a 5-thio trehalo-analog has not been described. Therefore, analogs of this type would constitute the first synthesis of an exciting novel group of potential enzyme inhibitors.

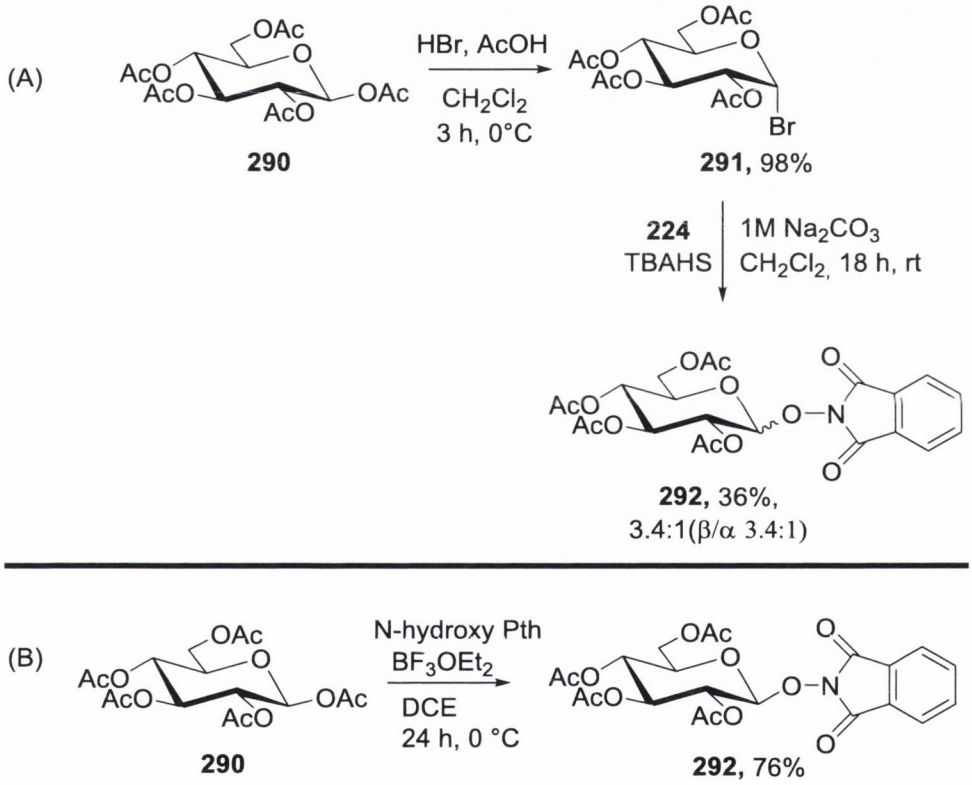


Trehalose, **288** diglucosylamine, **289**

Figure 39 Structure of trehalose **288** and diglucosylamine **289**

The synthetic route to desired hydroxylamines was designed by incorporation of a hydroxyphthalimido group at the desired ligation position, followed by hydrazine deprotection to expose the required hydroxylamine. The synthesis of the intermediate

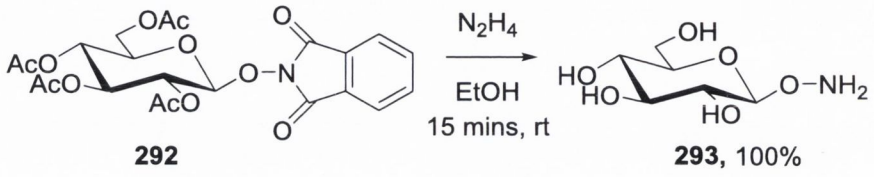
phthalimide necessary for a 1-oxyamino glucose was considered via two routes described in the literature. Firstly the route described by Roy and coworkers[354] was undertaken which involved formation of an anomeric bromide **291** followed by nucleophilic displacement with *N*-hydroxyphthalimide in a phase transfer catalysed reaction, this gave **292** in a 36% overall yield as a mixture of α and β anomers. The synthesis of **292** was also attempted via the method described by Oscarson and co-workers[355] in which pentaacetylated glucose was treated with *N*-hydroxyphthalimide in the presence of boron trifluoride-diethyletherate in order to initiate glycosylation. This gave solely the β-configured product in a 76% yield. The major β-anomer was utilized for further synthesis.



Scheme 90 (A) Synthesis of **292** via phase transfer catalysis
(B) synthesis of **292** via glycosylation reaction

With **292** in hand two deprotection routes were sought, one in which the anomeric phthalimide is selectively deprotected to the hydroxylamine in the presence of the acetate groups and another in which the compound is globally deprotected. Conjugation of the deprotected hydroxylamine with glucose would give rise to the deprotected *O/N-O* disaccharide in 3 synthetic steps (Section 4.5), while the analog with only the phthalimido

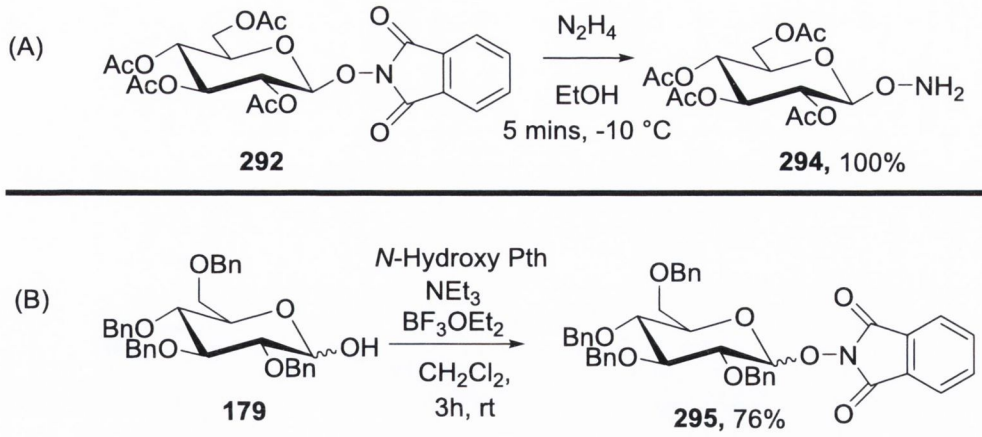
deprotected would give an analog suitable for further thioacetate incorporation (Section 4.4.1). Global deprotection of **292** was assessed in the first instance. Hydrazine monohydrate was deemed the most efficient reagent to remove the phthalimido group (Scheme 91). However, the resultant hydroxylamine was found to be unstable to chromatographic conditions, thereafter for all cases the hydroxylamine was characterized as its parent phthalimide and thereafter deprotected and coupled directly in one pot.



292 **293**, 100%

Scheme 91 Hydrolysis of phthalimide **292** to give hydroxylamine **293**

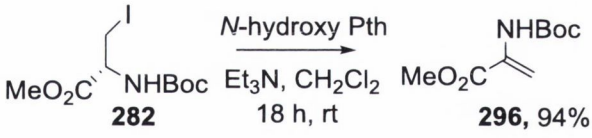
A second deprotection of **292** was then investigated wherein the phthalimido group would be deprotected to the hydroxylamine in the presence of the acetate groups. Such an analog could then be reacted with a protected glucose hemiacetal and the thio moiety installed *in situ* for the preparation of the *S/NO* disaccharide. The synthesis began with the attempted removal of the phthalimido group of **292** in the presence of the acetate protecting groups. (Scheme 92) An initial test reaction using a 1:1 ratio of **292** and hydrazine monohydrate in EtOH for ten minutes showed the formation of the desired product **294** but also the presence of analogs in which the acetate protecting groups were partially deprotected. We anticipated that reducing the reaction time and lowering the reaction temperature would allow for a selective removal of the phthalimide group in the presence of the acetate protecting groups. The reaction was then repeated using a 1:1 ratio of **292** and hydrazine monohydrate for 5 minutes at -10 °C, this gave full conversion to the desired compound **294**. However upon NMR analysis in $CDCl_3$ intamolecular acetyl migration ensued onto the anomeric hydroxylamine resulting in a complex mixture of products. Therefore the synthesis of a benzyl protected glycosyl phtalimide **295** was considered as it allowed for orthogonal deprotection of the phthalimide without migration of the protecting groups (Scheme 92).



Scheme 92 (A) Attempted selective phthalimido deprotection to yield **294**
(B) Synthesis of benzylated phthalimide **295**

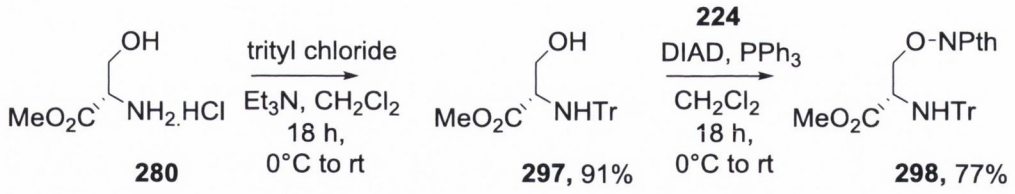
4.2.2 Synthesis of oxyamino serine

Attention was next turned to the preparation of an amino acid containing hydroxylamine reagent. Oxime ligation is an established method for glycopeptide synthesis however ligation is usually carried out on polypeptide chains. In the first instance the synthesis was approached via nucleophilic displacement of iodoserine serine by *N*-hydroxyphthalimide. However this resulted in β-elimination, and the formation of didehydroalanine **296** (Scheme 93).



Scheme 93 Formation of didehydroalanine **296** (Route A)

β-elimination reactions to yield didehydroalanine derivatives are well documented,[356] however the use of *N*-trityl protecting groups have been shown to protect the α centre of amino acids from base promoted racemization.[357] Thus the reaction route to the peptide based hydroxylamine was revaluated (route B) as shown in Scheme 94.

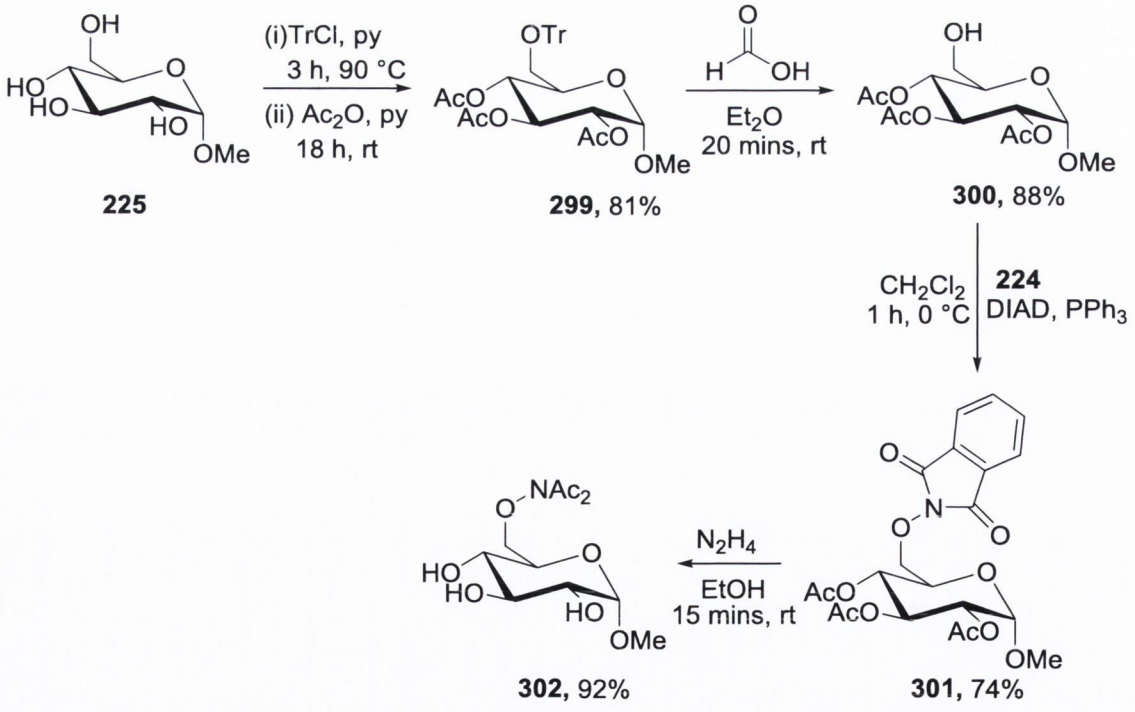


Scheme 94 synthesis of oxyamino serine **298** (Route B)

Tritylation of the amino group of **280** to yield **297**, followed by a mild mitsunobu reaction afforded **298**. (Scheme 94) The analog was stored as the phthalimide for later deprotection of the phthalimido group and conjugation with a glycosyl hemiacetal.

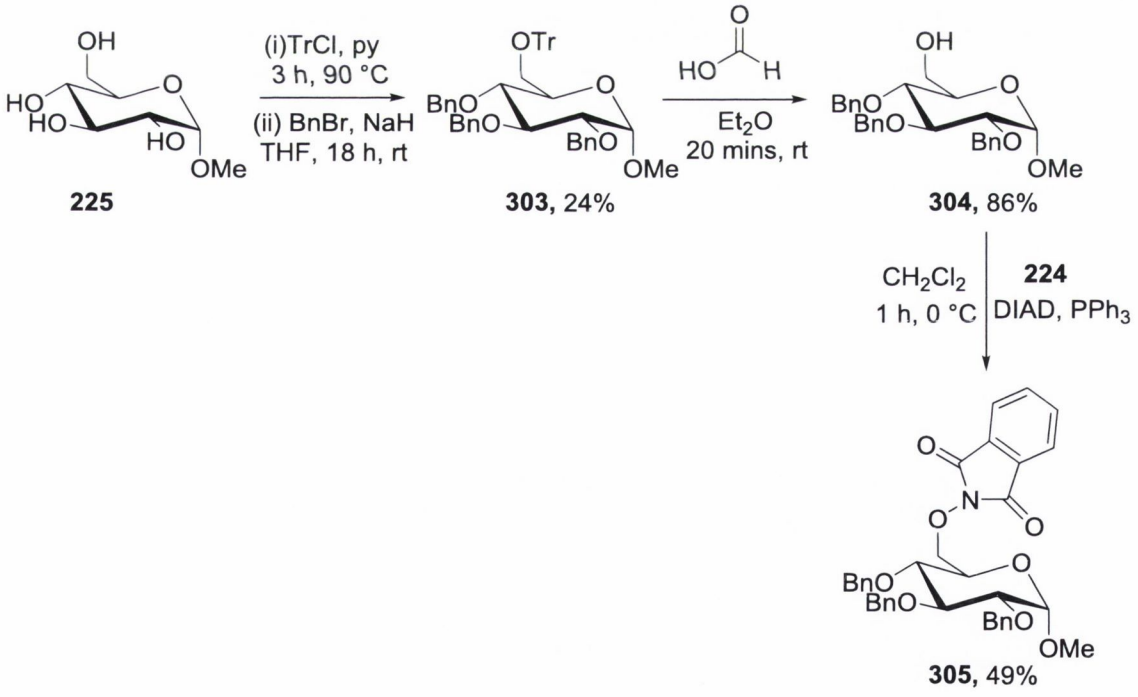
4.2.3 Synthesis of 1,6 oxyamine linked thiosugar disaccharides

In order to further assess the capacity of the methodology for disaccharide formation it was decided upon to synthesise a 1,6 oxyamine glycosidic linkage via synthesis of an unusual 6-gluco-oxyamine. The synthesis of the desired hydroxylamine was initially attempted via the approach shown in Scheme 95.



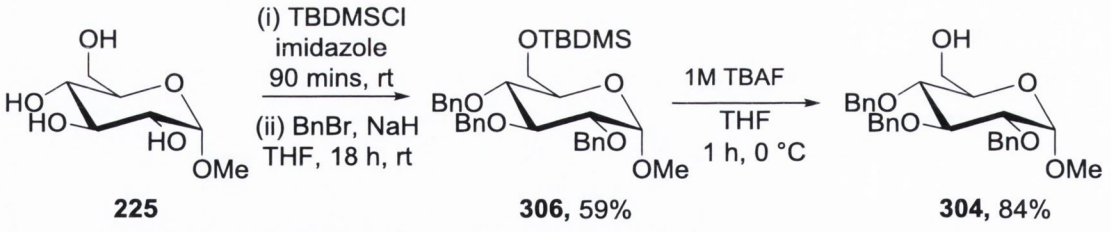
Scheme 95 Attempted synthesis of oxyamine linked 1,6 disaccharide (Route A)

Tritylation of the 6-hydroxyl of α-methoxy-glucopyranoside and acetylation of the intermediate gave **299** in an 81% yield. Removal of the trityl group was initially attempted in formic acid/Et_2O which gave rise to the 6-formate ester as the predominant product. Presumably this formed via esterification with excess formic acid. It was anticipated that this side product could be simply hydrolysed to the desired alcohol **300** in refluxing methanol. Disappointingly this gave rise to migration of the acetate groups. Trityl removal was thereafter attempted via the use of formic acid/dry Et_2O which gave **300** in an excellent 88% yield, the 6-formate ester and migration products were not observed. From **300** a Mitsunobu reaction with *N*-hydroxy phthalimide gave **301** in a 74% yield. In order to ascertain that acetyl migration would not occur upon hydrazine deprotection a test reaction ensued on a small scale. Disappointingly, the reactive primary oxyamine intermediate underwent rapid acetyl migration and the subsequent aliphatic diamide **302** could not be deprotected. In order to circumvent acetyl migration the use of an orthogonal protecting group was again considered. Thus the synthesis of the 6-oxyamine was revised as shown in scheme 96. (Route B)



Scheme 96 Synthesis of 6-phthalimido glucose **305** (Route B)

α-methoxyglucopyranoside **225** was trityl protected and per-benzylated by treatment with BnBr and NaH albeit in a poor 24% yield. Formic acid removal of the trityl group was efficient with an 86% yield and the ensuing Mitsunobu reaction gave **305,** albeit contaminated mixture with a side product of the reaction DICH (reduced di-isopropyl azodicarboxylate). However, unsatisfied with the overall yield, and in order to make this reaction sequence more efficient and suitable to scale up, a smaller primary hydroxyl protecting group was considered to prevent steric congestion on the sugar ring. α-methoxyglucopyranoside was TBS protected and benzylated giving the fully protected glycoside in 59% yield (Scheme 97, route C). A TBAF deprotection of the TBS-group gave **304** in an 84% yield, in order to avoid contamination by Mitsunobu byproducts, tosylation of the hydroxyl followed by an S_N2 displacement with *N*-hydroxy phthalimide was endeavoured. This was unsuccessful however, giving only trace amounts of the desired product and unreacted tosylate. A Mitsunobu reaction was then attempted employing the use of *N*-hydroxysuccinimide as the product was envisaged to run at a lower R_f thus potentially facilitating easier purification. However, despite the addition of excess reagent and triethylamine to the Mitsunobu reaction mixture **304** was unaffected. It was reasoned thereafter that DICH however should not impede upon the coupling reaction and as it is structurally related to the byproduct obtained from hydrazine deprotection, **305** was stored as the crude phthalimide for deprotection and subsequent conjugation.



225 **306,** 59% **304,** 84%

Scheme 97 Revised synthesis of **304** (Route C)

4.3 Preparation of oximes

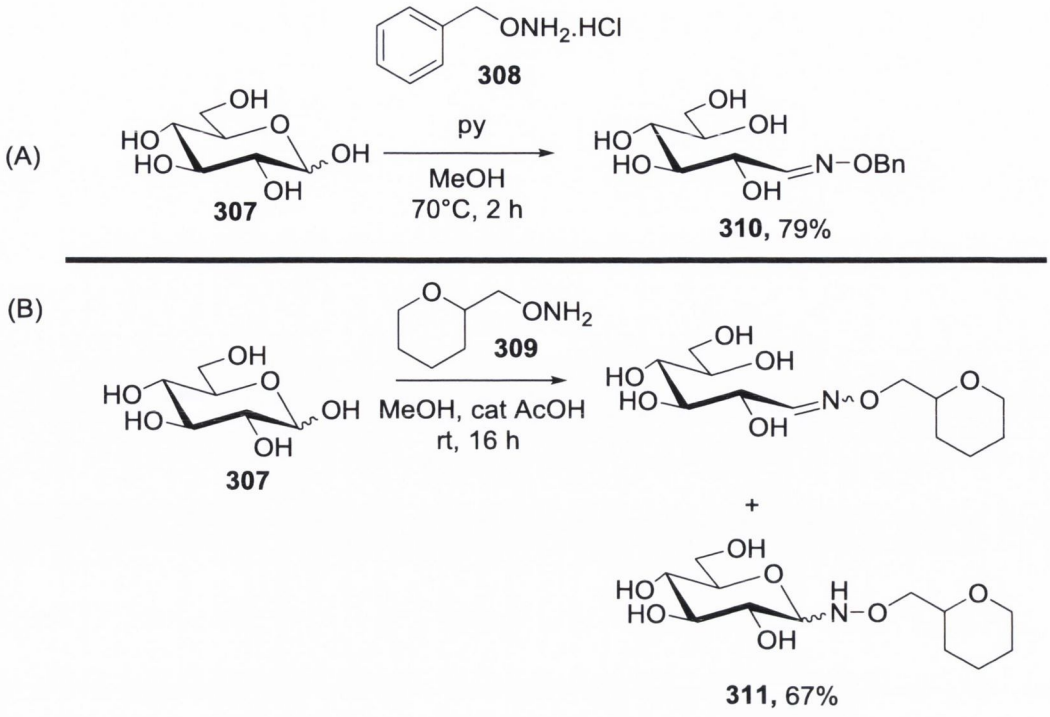
With the synthetic hydroxylamines in hand, two commercially available hydroxylamines, *O*-benzyl hydroxylamine hydrochloride **308** and *O*-(tetrahydro-2*H*-pyran-2-yl) hydroxylamine were obtained from a commercial supplier. In the first instance direct

coupling with glucose was approached for the synthesis of *O/N-O* acetals. Following this, the preparation of *S/N-O* acetals was attempted.

The application of reducing glycans as electrophiles in oxime formation is complicated by the 'dynamic masking' of the "aldehyde" tautomer as a cyclic pyranose (and furanose) hemiacetals (over 99.9%).[358] Thus oxime ligation on a hemiacetal functionality is not as straightforward as for an open chain aldehyde. Equally mutarotation of the resultant oxime can occur, catalysed by acid or base which leads to conformational heterogeneity of the glycoconjugate. For this project our interests lay in obtaining open chain acyclic oximes in order to gain access to the free C-5 OH for further structural modification of the newly exposed hydroxyl group. Conversely, it has been reported that the use of an oxymethylamino group allows for the preservation of the pyranose cyclic form of the sugar.[359]

4.3.1 Synthesis of aglycan derived hydroxylamine glycosides

O-benzyl hydroxylamine hydrochloride **308** was condensed directly with glucose in the presence of pyridine to deliver the desired 'open chain' oxime **310** as a mixture of isomers in excellent yield. Only the open chain oximes were visible by NMR analysis. Comparatively *O*-(tetrahydro-2*H*-pyran-2-yl) hydroxylamine was coupled with glucose under oxyamine ligation conditions described by Jensen and coworkers.[330] The reported mildly acidic conditions gave **311** as a 4:1:0.5 mixture of *E*/*Z*/β pyranose ring structure. A coupling constant of $J_{1,2} = 7.1$ Hz was noted for the anomeric position of the closed ring, thus confirming the β orientation. This result is in accordance with the related work carried out by Jensen and co-workers for an oxime ligation.[330] Oxime couplings have been reported to proceed with modest reaction rates at acidic pH but have been reported to react poorly in neutral pH.[330]

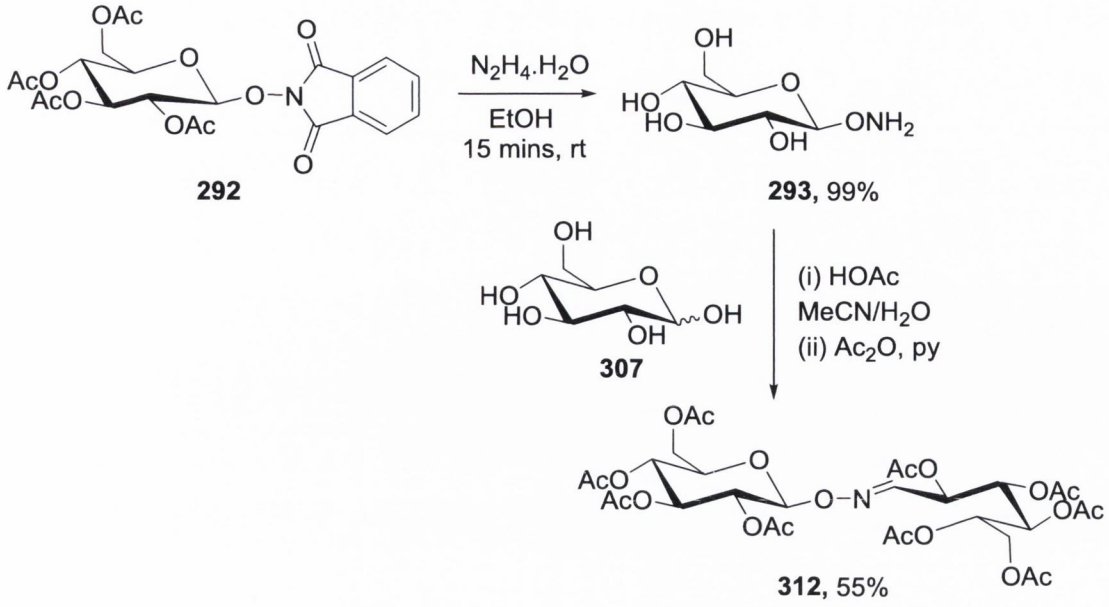


Scheme 98 (A) Synthesis of benzyl oxyamine **310**

(B) Sytnthesis of aglycan oxyamine **311**

4.3.2 Synthesis of 1,1 oxyamine linked disaccharide

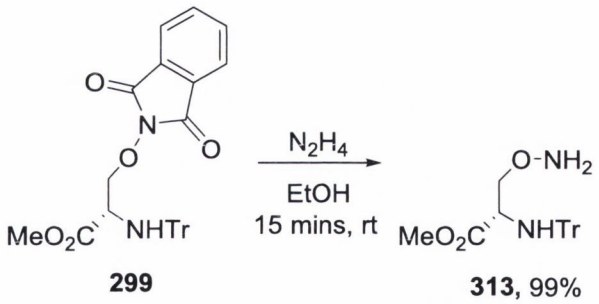
Phthalimide **292** was deprotected through reaction with hydrazine hydrate and the resultant *O*-glucohydroxylamine was coupled directly with glucose under mildly acidic conditions as previously described.[330] In the first instance no reaction was observed, it was established thereafter that residual hydrazine was present in the reaction mixture and was thus competing for conjugation with glucose. Due care was then taken to remove all residual hydrazine under vacuum. The reaction was repeated and for ease of characterisation and purification the crude reaction mixture was acetylated, gratifyingly giving **312** in an overall 55% yield in a 4:1 mixture of *E/Z* isomers (Scheme 99).



Scheme 99 Synthesis of oxyamine linked 1,1 disaccharide **312**

4.3.3 Attempted oxime ligation from oxyamine serine 313

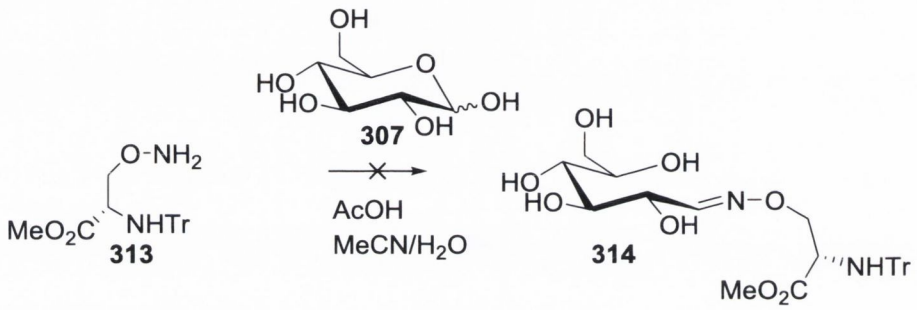
The peptidic phthalimide **299**, the synthesis of which was describes earlier in Section 4.2.2 was hydrolysed to an oxyamine following reaction with hydrazine hydrate.



Scheme 100 Synthesis of oxyamine **313**

Oxyamine **313** was thereafter directly condensed with glucose under the previously utilised mildly acidic conditions. Unfortunately no reaction ensued. A number of attempts were made to promote the condensation reaction through lengthening of the reaction time, addition of excess acid and gentle heating (Table 12) although no reaction could be observed under any of the conditions investigated. Surprisingly trityl removal

was not observed under the aforementioned conditions. A possible reason for the lack of reactivity of **313** could be due to the bulky trityl group which could be sterically blocking the oxyamine. Therefore future work on this conjugation could involve removal of the trityl group from **299**, possibly through the use of ytterbium triflate, a reported effective method for tritylamine deprotection. The resultant amino group could then be BOC protected or indeed coupled to a further amino acid to yield a less sterically congested analog for oxyamine coupling.



Entry	Eq of glucose	Eq of oxyamine	Acid utilised (pH)	Temp (°C)	Reaction time (h)	Result[a]
1	1	1	AcOH pH4	20	24	No reaction
2	1	2	AcOH pH4	50	48	No reaction
3	1	2	AcOH to pH3	50	48	No reaction
4	1	3	HCl to pH4	50	48	No reaction

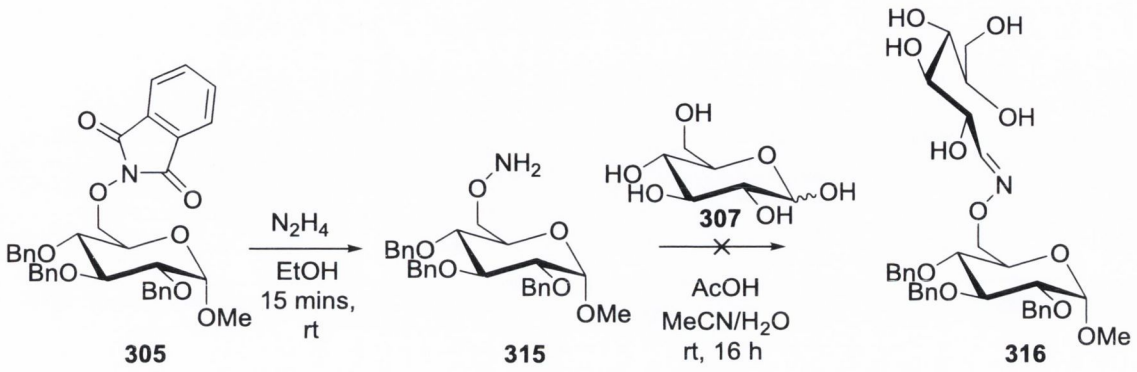
[a]Reactions were monitored by TLC and ^{1}H NMR analysis

Table 12 Attempted coupling of oxyamine **313** with **307**

4.3.4 Attempted synthesis of 1,6 oxyamine linked disaccharide

Simultaneously, phthalimide **305** was deprotected to the corresponding oxyamine through hydrazine hydrate hydrolysis. Regrettably, conjugation of this oxyamine proved equally ineffective. No reaction could be observed following the addition of surplus acid, heat or time, starting materials appeared unaltered by NMR analysis. Since attempting this work however, Thygsen and coworkers have reported the catalysis of oxime ligation on a

carbohydrate hemiacetal, through the use of aniline as a nucleophilic catalyst.[360] Up to 20-fold increases in overall reaction rates were described for formerly sluggish oxime couplings. Therefore, future workings on this project could conceivably include the use of an aniline catalysis to facilitate the condensation reaction.



Scheme 101 Attempted coupling of oxyamine **315** with glucose

4.3.5 Conclusions on oxime conjugation

Oxime conjugation was successfully implemented for the synthesis of oximes **310**, **311**, and **312**. Further work is necessitated to optimise ligation conditions for **314** and **316**. Ligation of oxyamines to glucose, in addition to being a rapid method of extrapolating the necessary oxime conjugation conditions, allowed for the synthesis of potentially biologically active glycosidase inhibitors. Oximes **310**, **311** and **312** are also dynamic synthetic intermediates capable of oxidative ring closure, as outlined in section 3.6 to provide pyranose oximes. Such compounds have previously been noted as excellent glycosidase inhibitors owing to their conformational resemblance to the putative transition state structure of the glycosidase enzymes substrate in the enymes active site.[149-155]

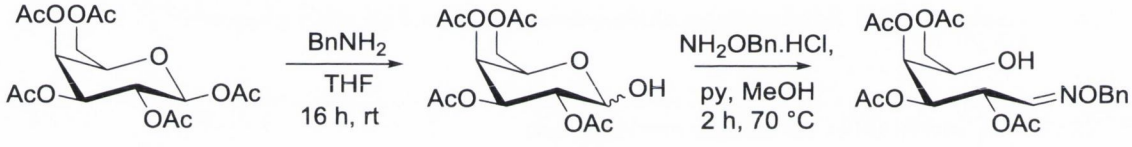
4.4 Synthesis of *S/N-O* acetals

The synthesis of the *S/NO* acetals was approached from two distinct routes. The first (Route A) involves oxime ligation, on a protected glycosyl hemiacetal with thiol incorporation *in situ*. The second (Route B) involves an oxyamine conjugation onto commercially available thioglucose. Thus, highly functionalised glycoconjugates could be

accessed in three synthetic steps, complementary to the synthesis of the corresponding oxygen analogs. However, this proposal is restricted by the high cost or tedious preparation of thioglucose.

4.4.1 Route A for the preparation of oxyamine linked thiosugars

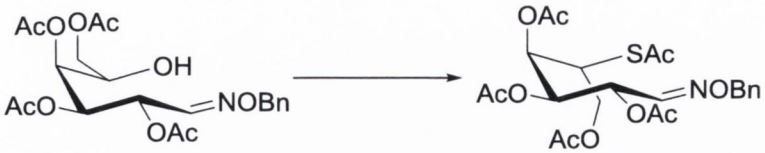
Route A was initially undertaken for the preparation of *SNO* analogs. Galactose was utilised as the glycosyl starting material, as initial attempts of displacement reactions with glucose proceeded with complex mixtures of inseperable byproducts. This is in accordance with the findings of Persky[262] and Martin[247] for displacement reactions at C-5 of glucose.



Scheme 102 Synthesis of oxime **317**

Commercially available β-penta-acetylated galactopyranoside **272** was treated with benzylamine in order to hydrolyse the anomeric acetate and deliver hemiacetal **273** which was treated with *O*-benzyl hydroxylamine hydrochloride and pyridine to afford oxime **317**. As this work was carried out prior to the developed of the synthesis outlined in chapter 2, a Mitsunobu reaction using thioacetic acid as the acidic nucleophile was considered in the first instance as an accessible approach to the desired 5-thio product. However while this reaction did result in formation of the thioacetate, the product was found to run at an identical R_f to a byproduct of the Mitsunobu reaction namely diisopropoxycarbonylhydrazine (DICH) (Table 13). Numerous acidic work ups and various chromatography procedures were attempted in order to remove the hydrazine side product, however these proved unsuccessful. Di-*tert*-butylazodicarboxylate (DTBAB) was then considered as an alternative azadicarboxylate reagent in the Mitsunobu reaction. It has been reported that treatment of DTBAB in an acidic work up will lead to formation of gaseous and water soluble by-products, thus avoiding a tedious purification.[361] However upon application of DTBAB no reaction was observed. Mesylation of alcohol

317 followed by displacement with potassium thioacetate was considered, however high temperatures and long reaction times could not implement the displacement of the mesylate. The use of an excellent leaving group, a triflate, was examined, gratifyingly reaction of the secondary triflate afforded the thioacetate **318** in a 46% yield.



317 **318**

Entry	Starting Materials	Reaction Conditions	Reagents[a]	Observed Product
1	**317**	Mitsunobu conditions	PPh_3, thioacetic acid, DIAD, THF	**318** contaminated with DICH
2	**317**	Mitsunobu conditions	PPh_3, thioacetic acid, DIAD. THF	No reaction
3	**317**	Mesylation and displacement by KSAc	(i)MsCl, py (ii)KSAc, DMF	Mesylate
4	**317**	Triflation and displacement by KSAc	(i) Tf_2O, py (ii) KSAc, DMF	**318** (46%)

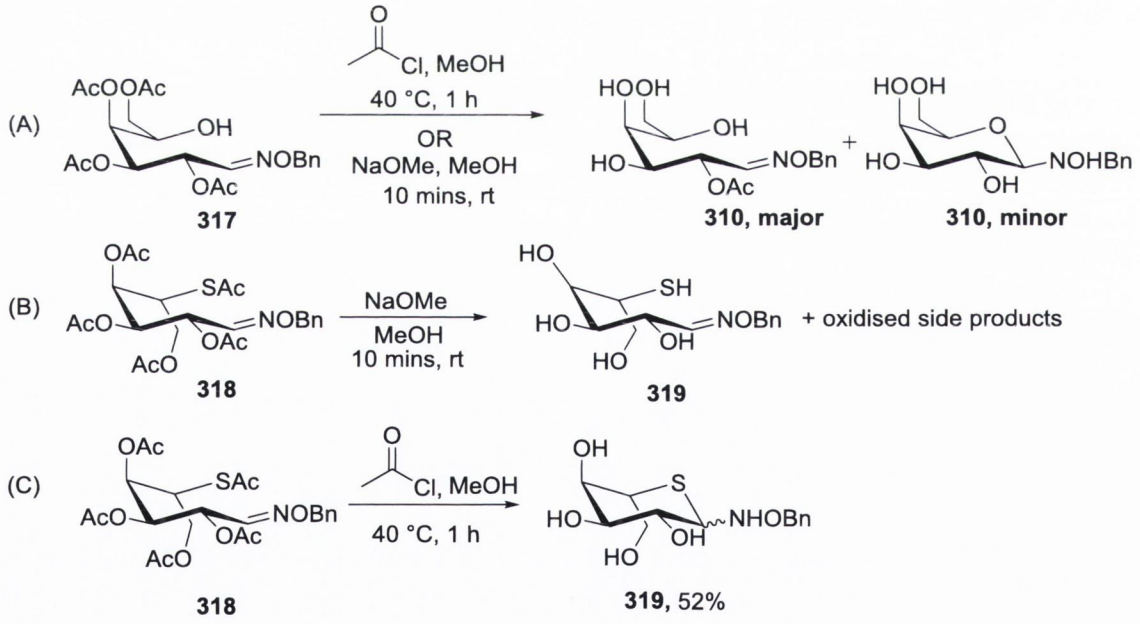
[a]All reactions carried out at room temperature

Table 13 Insertion of thiol at C-5

While the thioacetate was obtained in average yield it was noted that neighbouring group participation had occurred during the two step transformation resulting in 10% formation of the primary thioacetate. Migration could unfortunately not be prevented by carrying out the reaction at lower temperature, in addition both compounds were inseparable by column chromatography. Nevertheless the synthesis was continued in the first instance, it was anticipated that both compounds could be separated later in the synthesis.

Various deprotection methods were compared in order to investigate if the thioacetate could be selectively cleaved in the presence of the acetate groups. It has been reported that sodium thio-methoxide can remove a thioacetate in the presence of acetate groups[252] however application of this method to the deprotection of **318** led to a mixture of

deprotected products. Basic deprotection conditions were also investigated, treatment with ethyl diamine, sodium methoxide and sodium in methanol were found to be unsatisfactory, large excesses of reagents were needed to complete the deprotection, in addition the deprotected product was contaminated with a mixture of oxidised by-products. Deprotection was then investigated under acidic conditions incorporating the use of catalytic acetyl chloride which efficiently deprotected the thioacetate group with no observable disulphide formation. Surprisingly, only the ring closed thiosugar **319** was obtained, acidic conditions appeared to promote ring closure and subsequent anomerisation. Interestingly, when oxime **317** was deprotected under acidic and basic conditions only trace ring closure was observed (Scheme 103), differences in reactivity could be due to the increased nucleophilicity of the thiol relative to the alcohol. From NMR analysis is was deduced that the α anomer (coupling) was the predominant product formed (2.5/1 α:β) with H-1 exhibiting a coupling constant of $J_{1,2}$ = 9.2 Hz. No hydrolysis of the compound was noted after several weeks.

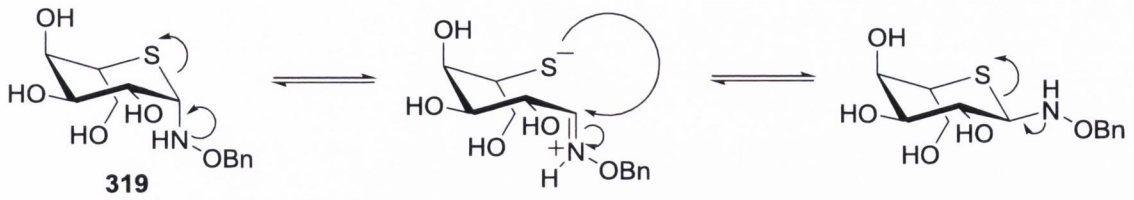


Scheme 103 Acidic and basic deprotection of O and S acetates

4.4.1.1 Anomerisation of 319

Owing to the fact that no appreciable hydrolysis of **319** was noted in aqueous solution, anomerisation is presumed to take place via endocyclic C-S bond cleavage to give an

intermediate iminium ion. Thereafter intra-molecular nucleophilic attack of the thiolate anion occurs preferentially to nucleophilic attack by water.



Scheme 104 Proposed mechanism for anomerisation

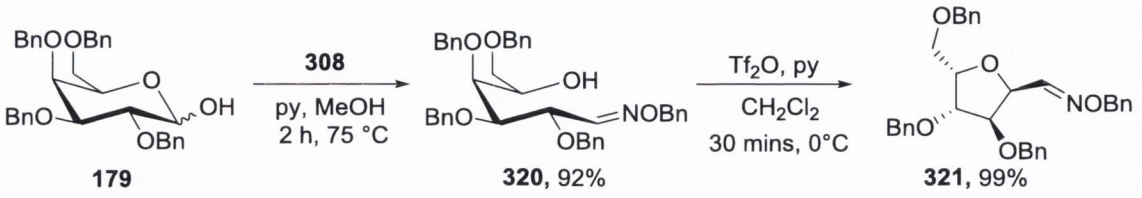
The anomerisation observed is in accordance with results obtained by Pinto and coworkers in their synthesis of *N*-linked thiosugars.[137] Studies into the lifetime of aliphatic imminium ions $CF_3CH_2N^+(CH_3)=CH_2$ in aqueous solution, which formed during the solvolysis of the corresponding thiol $CF_3CH_2N(CH_3)CH_2SC_6H_4\text{-}COO^-$ revealed the lifetime of the imminium ion to be 5.5 x 10^{-8}s.[362] The relative rate of the diffusion controlled reaction of the nucleophilic RS- leaving group versus the solvent water was deemed to be $k_{RS^-}/k_{water} = 280$.[362]

4.4.2 Investigation into a compatible protecting group strategy

While the described synthesis successfully provided access to the desired class of oxyamine linked thiosugars the protecting group strategy utilized was inherently flawed. This was due to the formation of a structural isomer through acetyl migration, separation of the two isomers was futile via chromatographic procedures at all stages of the synthesis. In order to improve the synthetic route acetyl protecting groups were reasoned as not ideal for practical use within this methodology and attention was therefore turned to the use of a non-migrateable protecting group.

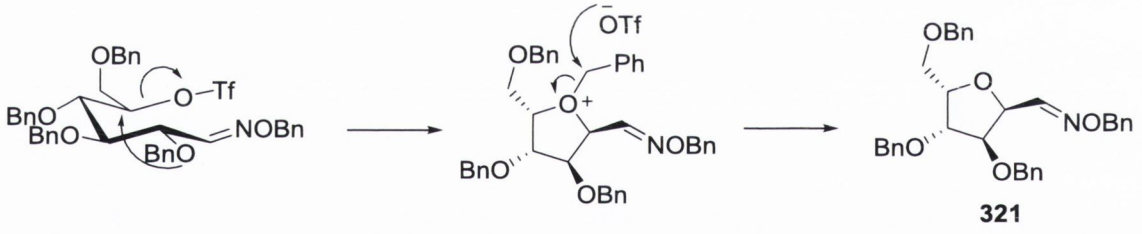
Benzyl protecting groups were first selected as a potential protecting group strategy within this methodology. Firstly, commercially available 2,3,4,6 tetra-*O*-benzyl-α-D-galactopyranoside **179** was treated with *O*-benzyl hydroxylamine hydrochloride **308** to give oxime **320** in a 92% yield. Mitsunobu chemistry did not lend itself to incorporation

of the thioacetate moiety into the molecule thus **320** was treated with triflic anhydride and pyridine in order to form the triflate in the 5 position, which could then be displaced by potassium thioacetate. Unexpectedly, implementing triflation reaction conditions led to formation of furanoside **321** in quantitative yield, this by-product was also found to form in near quantitative yield within 5 minutes at -15°C.



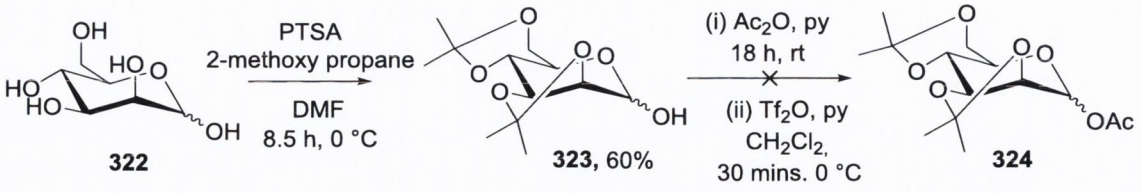
Scheme 106 Formation of furanoside **321** from benzylated precursor **320**

It was thereafter noted that reactions of this sort have been observed previously in carbohydrate chemistry, Gray *et al.*[363] described the ability of the benzyloxy group to ring close when in a 1,4 relationship to a reacting group, resulting in debenzoylation and the formation of tetrahydrofuran ring derivatives. This process has in many cases been observed as an unanticipated, undesired side reaction.[153, 364, 365]



Scheme 107 Cylisation of benxyloxy to give furanose **321**

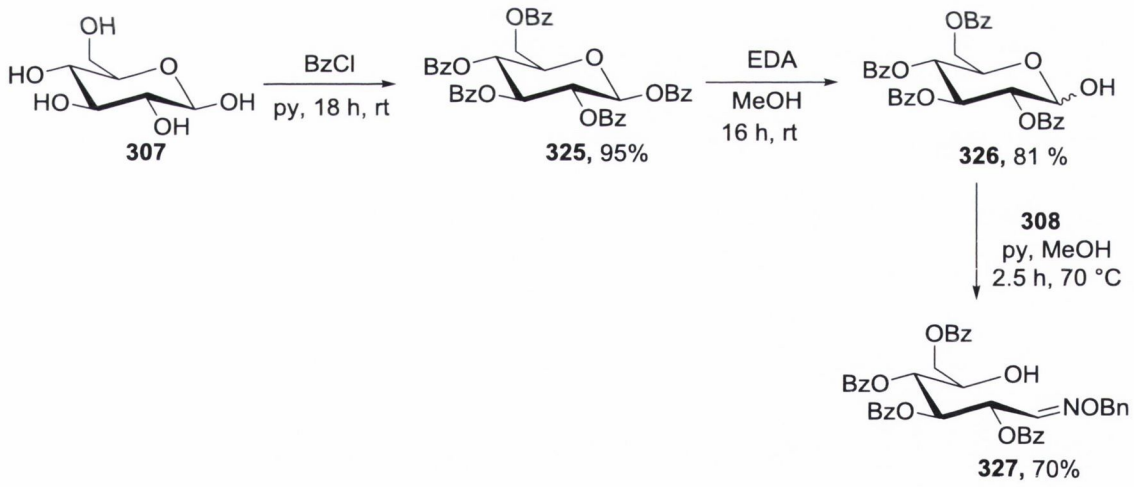
Since ether protecting groups proved unsuitable for the formation of *N*-linked thiosugars acetonide protecting groups were considered as an alternative as they are stable to the reaction conditions required for acetate deprotection, are easily installed and unlike ethereal protecting groups they would not undergo a cyclisation side reaction upon triflation.



Scheme 108 Proposed synthesis of acetonide protected thiosugar

Mannose, **322,** was protected as a di-acetonide according to the method reported by Cocinera *et al*[366] (Scheme 108) The stability of this di-acetonide to triflation reaction conditions was in question therefore prior to oxime formation **323** was acetylated and exposed to the triflation reaction conditions which resulted in the removal of the protecting groups. Acetonide protecting groups were therefore also deemed to be unsuitable for the formation of oxyamine linked thiosugars.

As acetyl, benzyl and acetonide protecting groups had all proven problematic with the proposed synthetic sequence benzoyl protecting groups were considered (Scheme 109). Benzoyl esters are less prone to migration than their acetyl analogs and are also stable to the mild acidic conditions required to cleave thioacetates. Glucose was perbenzoylated by treatment with benzoyl chloride and pyridine giving **325** in a 95% yield. The anomeric ester was hydrolysed by treatment with EDA to give **326**. Oxime formation was then investigated **326** was reacted with *O*-benzyl hydroxylamine hydrochloride this reaction proceeded with a 70% yield, albeit with a 20% impurity due to ester migration.

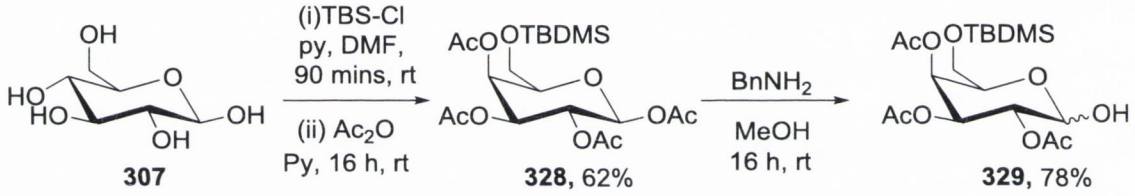


Scheme 109 Use of benzoyl protecting group in thiosugar synthesis

As protecting group migration could not be circumvented through the use of benzoyl esters, their use within this methodology was abandoned. It was thereafter considered to install a nonmigrateable protecting group on the primary position in order to avoid intramolecular transformations. The protecting groups on the 2, 3 and 4 position would remain non-ethereal thus negating the possibility of a 1,4 ring closure reaction.

4.4.3 Synthesis of a mixed TBS/acetyl protecting group system

A *Tert*-butyldimethylsilyl (TBS) group was considered as a suitable protecting group for use on the primary position, in order to avoid migration. In addition acetyl protecting groups would be installed at positions 2, 3 and 4 thus circumventing ring closure reactions associated with ethereal protecting groups. The TBS group should not impede upon the rate of the subsequent displacement reaction. It was decided to take advantage of the increased reactivity of the primary glycosyl hydroxyl group to investigate if both protections could be carried out in one pot. Glucose was treated with TBS-Cl in pyridine and the resultant crude mixture was acetylated, gratifyingly only the desired compound **328** was isolated in a 62% yield. Benzylamine deprotection of the anomeric acetate proceeded smoothly giving **329** in a 78% yield.



Scheme 110 Synthesis of **329**

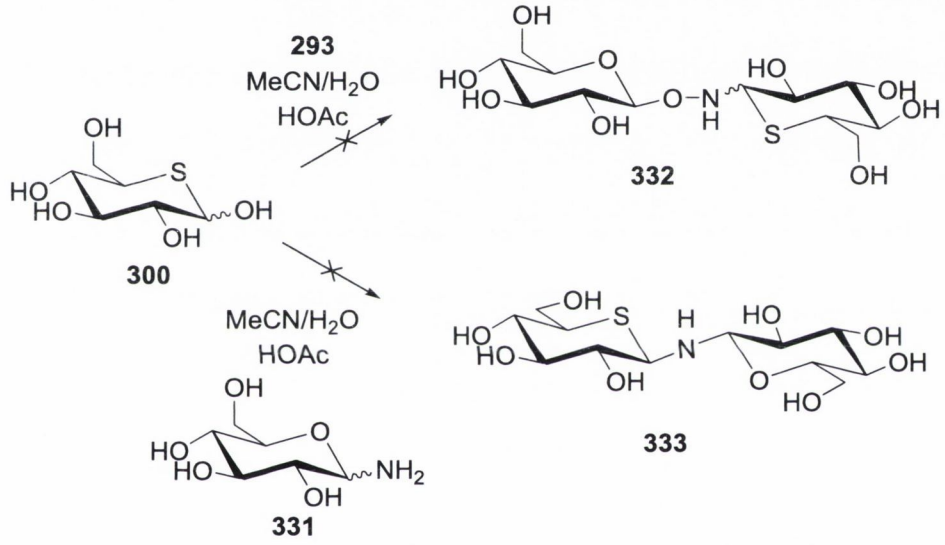
4.4.4 Conclusions on synthetic attempts at oxyamine thiosugar synthesis

Owing to significant synthetic difficulties encountered and time constraints within the project, this work was not continued beyond these preliminary studies. Future applications of this work will involve coupling of glycosyl hemiacetal **329** with oxyamines under the developed conditions. Thereafter thioacetate incorporation, deprotection and radical substitution can be thoroughly examined.

4.5 Protecting group free synthesis of oxyamine linked thiosugars (Route B)

Simultaneous to the previously described route to oxyamine linked thiosugars a second pathway involving the direct condensation of thioglucose with **293** was of interest. Via

this method oxyamine conjugation could be carried out in 3 synthetic steps, in the absence of protecting groups, and under aqueous conditions. Thioglucose **330** was obtained from a commercial source. The condensation of thioglucose with **293** was undertaken in order to obtain a thiogluco-oxyamine liked disaccharide. Under the acidic conditions previously utilized for oxime conjugation no reaction was observed. Higher concentrations of acid or higher reaction temperatures led to a breakdown of material. Similar results were observed following the attempted coupling of thioglucose and commercially available glucopyranosyl amine **331**. Amadori rearrangements have been noted in glycosylamines under higher concentrations of acid[137] therefore the synthesis was temporarily suspended.



Scheme 111 Attempted synthesis of amine and oxyamine linked 1,1-thiodisaccharides (Route B)

4.6 Conclusions

Through this work the first synthesis of a 1,1-oxyamine-linked disaccharide was reported. A pathway to *S/N-O* acetals has been established which involved a full study on the protecting group strategy required within this methodology. The preparation of these compounds remains challenging but the potential biological activity of these compounds renders further study a viable option. Further applications of this work will involve coupling of oxyamines **314** and **316** to glucose in order to elucidate the reaction conditions required. As the standard reported acidic conditions for oxime formation were inefficient in facilitating the desired coupling reaction, attention could be turned to incorporating the use of aniline as a nucleophilic catalyst as described by Thygsen and co-workers.[360] In addition Pinto and co-workers have described the application of mercuric salts to promote the formation of the imine intermediate,[326] this approach could also be considered within this synthesis. The synthesis of a nonmigrateable glycosyl oxime precursor has been established. It is anticipated that with this precursor in hand problems associated with protecting group participations can be circumvented and thus access to *SNO* acetals will be expedited. Additionally, following the successful synthesis of *C*-thiosugars, described in Chapter 2, the synthesis could also be attempted on a tribenzylated glycosylfuranose substrate.

5.0 General experimental data

Unless otherwise stated; infrared spectra (IR) were recorded on a Perkin Elmer spectrometer. A Bruker Advance 400 spectrometer, ^{1}H (400.13 MHz) and ^{13}C (100.61 MHz) and a Bruker Ultrashield (600 MHz) spectrometer were employed for ^{1}H (600.13 MHz) and ^{13}C (150.90 MHz) NMR spectra. Resonances δ, are in ppm units downfield from an internal reference in $CDCl_3$ or MeOD. Mass spectrometry analysis was performed with a Q-Tof Premier Waters Maldi-quadrupole time-of-flight (Q-Tof) mass spectrometer equipped with Z-spray electrospray ionization (ESI) and matrix assisted laser desorption ionisation (MALDI) sources. Optical rotation measurements were recorded using a Rudolf Research Analytical Autopol IV instrument and are quoted in units of 10^{-1}deg cm^2 g^{-1}. Silica gel Florisil (200 mesh; Aldrich) was used for column chromatography. All UV reactions were carried out in a Luzchem photoreactor, LZC-EDU (110 V/ 60 Hz) containing 10 UV lamps. Analytical thin-layer chromatography was performed using Merck 60 F_{254} silica gel (pre-coated sheets, 0.2 mm thick, 20 cm x 20 cm) and visualised by UV irradiation or molybdenum staining. Toluene, methylene chloride (CH_2Cl_2), Tetrahydrofuran (THF) and diethyl ether were dried over 4 Å molecular sieves. Methanol (MeOH) and isopropyl alcohol (^{i}PrOH) were dried over activated 3Å molecular sieves. Dimethylformamide (DMF) was used dry from sure sealed bottles. Other reagents were purchased from an industrial supplier and used without further purification.

5.1 Experimental data for Chapter 2

5.1.1 General Procedure for the synthesis of thioesters

Sugar-OH (1 eq) in dry CH_2Cl_2 (0.5 mmol/ mL) was added to an oven dried RBF equipped with a Teflon stirring bar. The reaction mixture was cooled to 0° C and pyridine (2.5 eq) was added, followed by the dropwise addition of triflic anhydride (1.2 eq). The solution was stirred at 0 °C for 30 minutes. The reaction mixture was diluted in CH_2Cl_2 and washed with cold $NaHCO_3$, water, and brine. The organic layer was dried over magnesium sulphate and concentrated *in vacuo*. The crude triflate was dried under high vacuum and re-suspended in dry DMF. KSAc (5 eq) was added in one portion and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was diluted in ether and washed with brine, the ethereal layer was dried over magnesium sulphate and concentrated *in vacuo*. Reaction mixture was purification by column chromatography.

5.1.2 General Procedure for Thioacetate hydrolysis

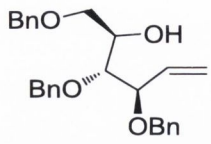
To a degassed solution of sugar-thioacetate (1 eq) in MeOH was added freshly prepared NaOMe (0.1 M soln), after having been stirred for 10 minutes the reaction mixture was quenched by the addition of Dowex H^+ ion exchange resin until pH neutral. The resin was removed by filtration, washed with MeOH and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography.

5.1.3 General Procedure for Radical Cyclisation

Sugar-Thiol (1 eq) was dissolved in dry DMF (0.03 mmol/ mL) and the solution was degassed under argon. 2,2-Dimethoxy-2-phenyl-acetophenone (DPAP) (0.1 eq) and 4-Methoxyacetophenone (MAP) (0.1 eq) were added in one portion and the resultant solution was irradiated under UV for 1 h without agitation. DMF was removed *in vacuo* and the crude reaction mixture was purified by column chromatography.

5.1.4 Synthesis of singly and doubly inverted thiopyranoses

5.1.4.1 (3*R*,4*R*,5*R*)-5-Hydroxy-3,4,6-tribenzyloxy-1-hexene (161)[367]

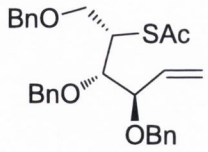


To a suspension of methyltriphenylphosponium bromide (7.61 g, 21.4 mmol) in dry toluene (15 mL) was added dropwise a 1.6 M solution of butyllithium in hexane (13.3 mL, 21.4 mmol) at 0 °C under N_2 and the reaction mixture was stirred for 2 hours at room temperature. A suspension of 2,3,4-tri-*O*-benzyl-α-D-arabinofuranose **160** (3.00 g, 7.14 mmol) in dry toluene (10 mL) was added and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with acetone (5 mL), the mixture was diluted with ether (100 mL) and extracted with water (50 mL). The aqueous phase was extracted with ether (50 mL), the organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (10:1 Hexane/ Ethyl Acetate) to afford **161** (2.51 g, 6.00 mmol, 84%) as a colourless oil.

δ_H (600 MHz, $CDCl_3$): 7.40-7.20 (15H, m, Ar-H), 5.99 (1H, ddd, $J_{2,1}$ = 16.9 Hz, $J_{2,1'}$ = 8.6 Hz, $J_{2,3}$ = 7.5 Hz, H-2), 5.38 (2H, app dd, $J_{1,2}$ = 16.9 Hz, $J_{1',2}$ = 8.6 Hz, H-1 and H-1'), 4.69 – 4.53 (5H, m, CH_2), 4.40 (1H, d, J = 12.0 Hz, CH_2), 4.12 (1H, dd, $J_{3,2}$ = 7.5 Hz, $J_{3,4}$ = 3.8 Hz, H-3), 4.05 (1H, m, H-5), 3.66 (1H, dd, $J_{4,5}$ = 6.9 Hz, $J_{4,3}$ = 3.8 Hz, H-4), 3.63 (2H, app bd, $J_{6,5}$ = 4.3 Hz, H-6 and H-6'), 2.87 (1H, d, $J_{OH,5}$ = 4.9 Hz, OH).

HRMS (*m/z* ESI+): Calcd for $C_{27}H_{30}O_4$ [M + Na]$^+$441.2042 Found 441.2048.

5.1.4.2 (3*R*,4*R*,5*S*)-5-Thioacetate-3,4,6-tribenzyloxy-1-hexene (162)



General procedure for the synthesis of thioesters was carried out to yield **162**. Purification by column chromatography (12:1 Hexane/ Ethyl Acetate) yielded **162** (348 mg, 0.73 mmol, 61%) as a yellow oil.

δ_H (600 MHz, $CDCl_3$): 7.37-7.27 (15H, m, Ar-H), 5.75 (1H, ddd, $J_{2,1}$ = 17.2 Hz, $J_{2,1'}$ = 10.2 Hz, $J_{2,3}$ = 7.6 Hz, H-2), 5.35 (1H, ddd, $J_{1,1'}$ = 1.5 Hz, $J_{1,2}$ = 10.2 Hz, $J_{1',2}$ = 17.2 Hz, H-1 and H-1'), 4.90 (1H, d, J = 11.6 Hz, CH_2), 4.50 (2H, d, J = 11.9 Hz, CH_2), 4.42 (1H, d, J = 11.6 Hz, CH_2), 4.41 (2H, d, J = 11.7 Hz, CH_2), 4.11 (1H, app t, $J_{3,2}$ = $J_{3,4}$ = 7.8 Hz, H-3), 4.07 (1H, dd, $J_{4,3}$ = 7.0 Hz, $J_{4,5}$ = 2.0 Hz, H-4), 3.98 (1H, ddd, $J_{5,4}$ = 2.0 Hz, $J_{5,6}$ = 5.2 Hz, $J_{5,6'}$ = 9.7 Hz, H-5), 3.70 (1H, app t, $J_{6,5}$ = $J_{6,6'}$ = 9.8 Hz, H-6), 3.41 (1H, dd, $J_{6',5}$ = 5.2 Hz, $J_{6',6}$ = 9.7 Hz, H-6'), 2.33 (3H, s, S-Ac).

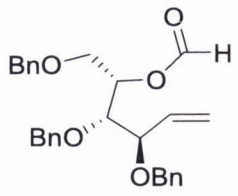
δ_C (150 MHz, $CDCl_3$): 194.6 (C=O), 138.8, 138.4, 138.1 (q-C), 134.7 (C-2), 128.3, 128.3, 128.2, 128.2, 127.7, 127.6, 127.6, 127.4, 127.3, (Ar-C), 119.8 (C-1), 84.0 (C-3), 79.4 (C-4), 75.2, 72.9, 70.7 (CH_2), 69.7 (C-6), 45.4 (C-5), 30.4 (CH_3).

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): -26 °

ν_{max} (film)/cm^{-1}: 1725 (C=O), 1101 (C-O).

HRMS (*m/z* -ESI): Calcd for $C_{29}H_{32}O_4S$ [M + Na]$^+$ 499.1919 Found 499.1907.

5.1.4.3 (3*R*,4*R*,5*S*)-5-para-Nitro-benzoyl-3,4,6-tribenzyloxy-1-hexene (163)



To a stirred solution of **161** (500 mg, 1.19 mmol) in dry CH_2Cl_2 (10 mL) at 0° C was added pyridine (0.24 mL, 2.86 mmol), followed by the dropwise addition of triflic anhydride (0.21 mL, 1.30 mmol). The solution was stirred at 0 °C for 30 minutes. The solvent was concentrated *in vacuo*, the crude triflate was dried under high vacuum and re-suspended in dry DMF (2 mL). KSAc (680 mg, 5.9 mmol) was added in one portion and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was diluted in ether (50 mL) and washed with brine (5 x 50 mL), the ethereal layer was dried over magnesium sulphate and concentrated *in vacuo*. Purification by column chromatography (12:1 Hexane/ Ethyl Acetate) yielded **163** (367 mg, 0.82 mmol, 69%) as a yellow oil.

δ_H (600 MHz, $CDCl_3$): 7.91 (1H, s, OCOH), 7.41-7.28 (15H, m, Ar-H), 5.94 (1H, ddd, $J_{2,1}$ = 10.8 Hz, $J_{2,1'}$ = 17.6 Hz, $J_{2,3}$ = 7.9 Hz, H-2), 5.39 (1H, app d, $J_{1,2}$ = 10.8 Hz, H-1), 5.35 (1H, app d, $J_{1',2}$ = 17.6 Hz, H-1'), 5.30 (1H, m, H-5), 4.75 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.67 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.65 (1H, d, J = 12.1 Hz, Bn-CH_2), 4.52 (2H, d, J = 11.4 Hz, Bn-CH_2), 4.36 (1H, d, J = 12.1 Hz, Bn-CH_2), 3.97 (1H, dd, $J_{3,2}$ = 7.9 Hz, $J_{3,4}$ = 4.9 Hz, H-3), 3.86 (1H, app t, $J_{4,3} = J_{4,5}$ = 4.9 Hz, H-4), 3.82 (2H, m, H-6 and H-6').

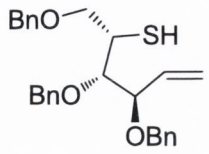
δ_C (150 MHz, $CDCl_3$): 160.3 (OCOH), 137.9, 137.8, 137.7 (q-Ar), 134.9 (C-2), 128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 127.6, 127.5, 127.5 (Ar-C), 119.5 (C-1), 80.1 (C-4), 80.0 (C-3 and C-5), 75.0, 73.0, 70.3 (Bn-CH_2), 67.8 (C-6).

ν_{max} (film)/cm^{-1}: 1725 (C=O), 1101 (C-O).

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): -28 °

HRMS (*m/z* -ESI): Calcd for $C_{28}H_{30}O_5$ $[M+Na]^+$ 469.1991 Found 469.2004.

5.1.4.4 (3*R*,4*R*,5*S*)-5-Thio-3,4,6-tribenzyloxy-1-hexene (164)



General procedure for the hydrolysis of thioesters was carried out to yield **164**. The residue was purified by column chromatography (12:1 Hexane/ EtOAc) to give **164** (270 mg, 0.62 mmol, 99 %) as a colourless oil.

δ_H (600 MHz, $CDCl_3$): 7.38-7.23 (15H, m, Ar-H), 5.75 (1H, m, H-2), 5.44 (1H, app d, $J_{1,2}$ = 17.3 Hz, H-1), 5.35 (1H, app d, $J_{1',2}$ = 10.3 Hz, H-1'), 4.98 (1H, d, J = 11.6 Hz, CH_2), 4.59 (2H, d, J = 10.5 Hz, CH_2), 4.41 (3H, m, CH_2), 4.29 (1H, app t, $J_{3,2} = J_{3,4}$ = 7.8 Hz, H-3), 3.93 (1H, app d, $J_{4,3}$ = 7.8 Hz, H-4), 3.52 (2H, m, H-6 and H-6'), 3.05 (1H, m, H-5), 1.69 (1H, d, $J_{SH,5}$ = 10.7 Hz, SH).

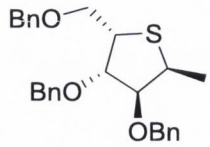
δ_C (150 MHz, $CDCl_3$): 139.0, 138.6, 138.0 (q-C), 135.0 (C-2), 128.4, 128.2, 128.2, 127.8, 127.7, 127.7, 127.7, 127.4, 127.4 (Ar-C), 119.9 (C-1), 84.7 (C-3), 79.2 (C-4), 75.1, 73.0 (CH_2), 73.0 (C-6), 71.2 (CH_2), 40.6 (C-5).

ν_{max} (film)/cm^{-1}: 1901 (C-O).

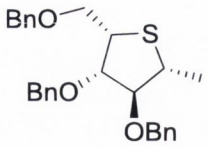
$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): -31 °

HRMS (*m/z* ESI^+): Calcd for $C_{27}H_{30}O_3S$ [M + Na]$^+$ 457.1813 Found 457.1385.

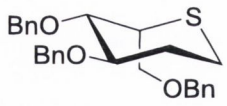
5.1.4.5 Radical cyclisation reaction of 165



167



168



169

The general procedure for the synthesis of thiosugars was carried out to yield **167**, **168,** and **169**. The crude reaction mixture was purified by column chromatography (10:1 Hexane/Ethyl Acetate) to yield **167** and **168** (6 mg, 13.8 μL, 9%) as a colourless oil and **169** (48 mg, 0.11 mmol, 73%) as a colourless oil.

Data for 167

δ_H (600 MHz, $CDCl_3$): 7.36-7.27 (15H, m, Ar-H), 4.63-4.54 (6H, m, Bn-CH_2), 4.17 (1H, app t, $J_{3,2} = J_{3,4} = 6.2$ Hz, H-3), 3.89 (1H, dd, $J_{5,4} = 6.1$ Hz, $J_{5,5'} = 9.3$ Hz, H-5), 3.81 (1H, app t, $J_{2,1} = J_{2,3} = 6.2$ Hz, H-2), 3.71 (1H, m, H-4), 3.62 (1H, dd, $J_{5',4} = 6.5$ Hz, $J_{5',5} = 9.3$ Hz, H-5'), 3.32 (1H, m, H-1), 1.37 (3H, d, $J_{Me,1} = 6.8$ Hz, CH_3).

δ_C (150 MHz, $CDCl_3$): 138.3, 138.2, 137.9 (q-C), 128.4, 128.4, 128.4, 128.3, 128.3, 127.8, 127.7, 127.7, 127.6 (Ar-C), 88.5 (C-2), 86.4 (C-3), 73.2, 72.7, 72.6 (CH_2), 69.3 (C-5), 45.5 (C-4), 42.0 (C-1), 21.1 (CH_3).

ν_{max} (film)/cm^{-1}: 1054 (C-O)

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): -22°

HRMS (*m/z* ESI^+): Calcd for $C_{27}H_{30}O_3S$ [M + Na]$^+$457.1813 Found 457.1831.

Data for 168

δ_H (600 MHz, $CDCl_3$): 7.36-7.27 (15H, m, Ar-H), 4.74 (1H, d, J = 12.3 Hz, CH_2), 4.60 (4H, m, CH_2), 4.48 (1H,d, J = 12.2 Hz, CH_2), 4.17 (1H, app t, $J_{3,2} = J_{3,4}$ = 4.2 Hz, H-3), 3.96 (1H, m, H-4), 3.88 (1H, m, H-5), 3.84 (1H, app s, H-2), 3.73 (1H, m, H-1), 3.61 (1H, dd, $J_{5',4}$ = 6.2 Hz, $J_{5',5}$ = 9.1 Hz, H-5), 1.32 (3H, d, $J_{Me,1}$ = 6.8 Hz, CH_3).

δ_C (150 MHz, $CDCl_3$): 138.3, 138.2, 138.1 (q-C), 128.4, 128.4, 128.3, 128.3, 127.8, 127.8, 127.8, 127.7, 127.5 (Ar-C), 85.0 (C-3), 84.9 (C-2), 72.9, 72.8, 72.2 (CH_2), 70.8 (C-5), 47.9 (C-4), 42.9 (C-1), 15.8 (CH_3)).

ν_{max} (film)/cm^{-1}: 1054 (C-O).

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): -22°

HRMS (*m/z* -ESI): Calcd for $C_{27}H_{30}O_3S$ [M + Na]$^+$457.1813 Found 457.1831.

Data for 169

δ_H (600 MHz, $CDCl_3$): 7.35-7.25 (15H, m, Ar-H), 4.56 (2H, d, J = 6.3 Hz, Bn-CH_2), 4.48 (4H, m, Bn-CH_2), 3.77 (1H, app d, $J_{4,3}$= 5.2 Hz, H-4), 3.63 – 3.50 (4H, m, H-3, H-5, H-6 and H-6'), 2.90 (1H, m, H-1), 2.40 (1H, m, H-1'), 2.15 (1H, m, H-2), 1.96 (1H, m, H-2').

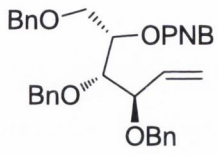
δ_C (150 MHz, $CDCl_3$): 138.5, 138.3, 138.1 (q-C), 128.2, 128.2, 128.1, 127.7, 127.7, 127.7, 127.6, 127.5, 127.4, (Ar-C), 73.4 (C-4), 73.4 (C-3), 73.0, 72.7, 71.2 (Bn-CH_2) 69.4 (C-6), 41.1 (C-5), 27.8 (C-2), 22.5 (C-1).

ν_{max} (film)/cm^{-1}: 1054 (C-O)

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): -17°C

HRMS (*m/z* ESI$^+$): Calcd for $C_{27}H_{30}O_3S$ [M + Na]$^+$457.1813 Found 457.1829.

5.4.1.6 (3*R*,4*R*,5*S*)-5-para-Nitro-benzoyl-3,4,6-tribenzyloxy-1-hexene (170)



To a stirred solution of **161** (2.65 g, 6.30 mmol) in dry THF (10 mL) was added 4-nitrobenzoic acid (4.23 g, 25.2 mmol), and PPh_3 (4.95 g, 18.9 mmol). The reaction mixture was cooled to 0° C and DIAD (5.00 mL, 25.2 mmol) was added dropwise under N_2. After having been stirred for 12 h at room temperature the reaction mixture was concentrated *in vacuo* and the residue purified by column chromatography (15:1 Hexane/ Ethyl Acetate) to afford **170** (2.78 g, 4.91 mmol, 78%) as a colourless oil.

δ_H (600 MHz, $CDCl_3$): 8.27 (2H, d, J = 9.0 Hz, C<u>H</u>CNO$_2$), 8.13 (2H, d, J = 9.0 Hz, C<u>H</u>CHCNO$_2$) 7.36-7.22 (15H, m, Ar-H), 5.90 (1H, ddd, $J_{2,1}$ = 10.3 Hz, $J_{2,1'}$ = 17.4 Hz, $J_{2,3}$ = 7.5 Hz, H-2), 5.53 (1H, m, H-5), 5.33 (1H, app d, $J_{1,2}$ = 10.7 Hz, H-1), 5.26 (1H, app d, $J_{1',2}$ = 17.3 Hz, H-1'), 4.86 (1H, d, J = 11.3 Hz, CH_2), 4.64 (2H, d, J = 11.6 Hz, CH_2), 4.49 (1H, d, J = 12.0 Hz, CH_2), 4.40 (1H, d, J = 12.0 Hz, CH_2), 4.34 (1H, d, J = 11.3 Hz, CH_2), 4.04 (1H, m, H-3), 3.93 (1H, app t, $J_{4,3}$ = $J_{4,5}$= 5.1 Hz, H-4), 3.73 (1H, dd, $J_{6,5}$ = 4.9 Hz, $J_{6,6'}$ = 10.4 Hz, H-6), 3.63 (1H, dd, $J_{6',5}$ = 5.7 Hz, $J_{6,6'}$ = 10.4 Hz, H-6').

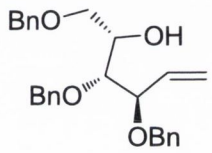
δ_C (150 MHz, $CDCl_3$): 163.9 (C=O), 150.4 (CNO_2), 138.1, 137.8, 137.7 (q-C), 135.5 (<u>C</u>COOCH), 134.7 (C-2), 130.7 (<u>C</u>HCHCNO$_2$), 128.2, 128.2, 128.1, 127.9, 127.8, 127.8, 127.6, 127.5, 127.5 (Ar-C), 123.3 (<u>C</u>HCNO$_2$), 119.3 (C-1), 80.5 (C-3), 79.6 (C-4), 75.1 (CH_2), 74.0 (C-5), 73.0, 70.6 (CH_2), 67.8 (C-6).

ν_{max} (film)/cm^{-1}: 1725 (C=O), 1101 (C-O)

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): -41 °

HRMS (*m/z* ESI^+): Calcd for $C_{34}H_{33}NO_7$ $[M+Na]^+$ 590.2155 Found 590.21214.

5.1.4.7 (3*R*,4*R*,5*S*)-5-Hydroxy-3,4,6-tribenzyloxy-1-hexene (171)



To a stirred solution of **170** (1.00 g, 1.76 mmol) in MeOH (10 mL) was added NaOMe (10 mg, 0.18 mmol). The solution was stirred at room temperature for 12 h and neutralised with Dowex H^+ ion exchange resin. The resin was removed by filtration, washed with MeOH and concentrated *in vacuo*. The residue was purified by chromatrography (10:1 Hexane/ Ethyl Acetate) to give **171** (728 mg, 1.75 mmol, 99%) as a colourless oil.

δ_H (600 MHz, $CDCl_3$): 7.40-7.36 (15H, m, Ar-H), 5.89 (1H, ddd, $J_{2,1}$ = 10.3 Hz, $J_{2,1'}$ = 17.6 Hz, $J_{2,3}$ = 7.7 Hz, H-2), 5.38 (2H, m, H-1 and H-1'), 4.89 (1H, d, J = 11.5 Hz, CH_2), 4.65 (1H, d, J = 11.7 Hz, CH_2), 4.58 (1H, d, J = 11.3 Hz, CH_2), 4.47 (2H, m, CH_2), 4.41 (1H, d, J = 11.7, CH_2), 4.13 (1H, app t, $J_{3,2}$ = $J_{3,4}$= 7.1 Hz, H-3), 3.95 (1H, m, H-5), 3.64 (1H, dd, $J_{4,3}$ = 7.1 Hz, $J_{4,5}$= 2.4 Hz, H-4), 3.46 (2H, m, H-6 and H-6'), 2.47 (1H, bs, OH).

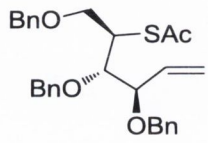
δ_C (150 MHz, $CDCl_3$): 138.4, 138.3, 138.1 (q-C), 135.3 (C-2), 128.4, 128.4, 128.3, 127.9, 127.8, 127.8, 127.7, 127.7, 127.5 (Ar-C), 119.4 (C-1), 82.2 (C-3), 80.6 (C-4), 75.1, 73.4 (CH_2), 71.4 (C-6), 70.7 (CH_2), 70.1 (C-5).

ν_{max} (film)/cm^{-1}: 3396 (OH), 1063 (C-O).

$[\alpha]_D^{20}$(c = 0.1, $CHCl_3$): -8 °

HRMS (*m/z* ESI$^+$): Calcd for $C_{27}H_{30}O_4$ [M + Na]$^+$ 441.2042 Found 441.2052.

5.1.4.8 (3*R*,4*R*,5*R*)-5-Thioacetate-3,4,6-tribenzyloxy-1-hexene (172)



General procedure for the synthesis of thioesters was carried out to prepare **172**. The residue was purified by chromatography (15:1 Hexane/ Ethyl Acetate) to afford 1**72** (68.2 mg, 0.14 mmol, 60%) as a colourless oil ;

δ_H (600 MHz, $CDCl_3$): 7.37 – 7.25 (15H, m, Ar-H), 5.94 (1H, ddd, $J_{2,1}$ = 9.7 Hz, $J_{2,1'}$ = 17.5 Hz, $J_{2,3}$ = 7.8 Hz, H-2), 5.36 (1H, dd, $J_{1,1'}$ = 1.5 Hz, $J_{1,2}$ = 10.2 Hz, H-1), 5.28 (1H, app d, $J_{1',2}$ = 17.5 Hz, H-1'), 4.76 (1H, d, J = 11.6 Hz, CH_2). 4.66 (1H, d, J = 11.5 Hz, CH_2), 4.60 (1H, d, J = 11.6 Hz, CH_2), 4.47 (1H, d, J = 11.7 Hz, CH_2), 4.42 (1H, d, J = 11.7 Hz, CH_2), 4.33 (1H, d, J = 11.5 Hz, CH_2), 4.19 (1H, dt, $J_{5,4}$ = 4.8 Hz, $J_{5,6}$ = 6.3 Hz, H-5), 4.05 (1H, dd, $J_{3,2}$ = 8.2 Hz, $J_{3,4}$ = 4.8 Hz, H-3), 3.80 (1H, app t, $J_{4,3}$ = $J_{4,5}$ = 4.8 Hz, H-4), 3.65 (2H, m, H-6 and H-6'), 2.33 (3H, s, SAc).

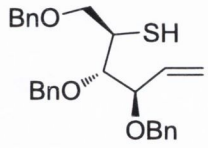
δ_C (150 MHz, $CDCl_3$): 195.5 (C=O), 138.2, 138.1, 137.9 (*q*-C), 135.3 (C-2), 128.2, 128.2, 128.1, 128.1, 128.0, 127.8, 127.8, 127.5, 127.4 (Ar-C), 119.4 (C-1), 81.7 (C-4), 81.7 (C-3), 74.7, 72.5, 70.0 (CH_2), 68.4 (C-6), 44.8 (C-5), 30.2 (CH_3).

ν_{max} (film)/cm^{-1}: 1726 (C=O), 1097 (C-O)

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): +68 °

HRMS (*m/z* ESI^+): Calcd for $C_{29}H_{32}O_4S$ [M + Na]$^+$499.1919 Found 499.1912.

5.1.4.9 (3*R*,4*R*,5*R*)-5-Thio-3,4,6-tribenzyloxy-1-hexene (173)



General procedure for the hydrolysis of thioacetates was carried out to prepare **173.** The residue was purified by column chromatography (12:1 Hexane/ Ethyl Acetate) to yield **173** (63 mg, 0.14 mmol, 99%) as a colourless oil.

δ_H (600 MHz, $CDCl_3$): 7.37-7.27 (15H, m, Ar-H), 5.94 (1H, ddd, $J_{2,1}$ = 10.7 Hz, $J_{2,1'}$ = 17.2 Hz, $J_{2,3}$ = 7.7 Hz, H-2), 5.35 (2H, m, H-1), 4.73 (1H, d, *J* = 11.4 Hz, CH_2), 4.63 (1H, d, *J* = 12.1 Hz, CH_2), 4.60 (1H, d, *J* = 11.3 Hz, CH_2), 4.51 (1H, d, *J* = 12.0 Hz, CH_2), 4.49 (1H, d, *J* = 12.0 Hz, CH_2), 4.36 (1H, d, *J* = 11.8 Hz, CH_2), 4.32 (1H, dd, $J_{3,2}$ = 7.7 Hz, $J_{3,4}$ = 4.0 Hz, H-3), 3.86 (1H, dd, $J_{6,5}$ = 4.6 Hz, $J_{6,6'}$ = 9.5 Hz, H-6), 3.69 (1H, dd, $J_{6',5}$ = 4.0 Hz, $J_{6',6}$ = 9.5 Hz, H-6'), 3.64 (1H, dd, $J_{4,3}$ = 4.0 Hz, $J_{4,5}$ = 7.8 Hz, H-4), 3.32 (1H, m, H-5), 1.86 (1H, d, $J_{SH,5}$ = 9.3 Hz, SH).

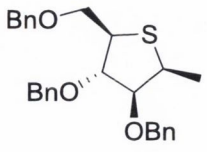
δ_C (150 MHz, $CDCl_3$): 138.9, 138.1, 137.9 (q-C), 135.9 (C-2), 128.2, 128.1, 128.1, 128.1, 127.9, 127.6, 127.6, 127.5, 127.4 (Ar-C), 118.8 (C-1), 84.1 (C-4), 80.4 (C-3), 75.3, 72.9 (CH_2), 71.4 (C-6), 70.6 (CH_2), 40.4 (C-5).

ν_{max} (film)/cm^{-1}: 1084 (C-O).

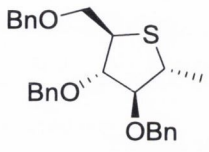
$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): +16°

HRMS (*m/z* ESI^+): Calcd for $C_{27}H_{30}O_3S$ [M + Na]$^+$457.1813 Found 457.1827.

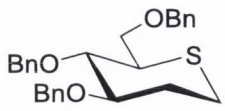
5.1.4.10 Radical Cyclization Reaction of 173



174



175



176

General procedure for the synthesis of thiosugars was carried out to yield **174, 175** and **176.** The residue was purified by column chromatography (10:1 Hexane/ Ethyl Acetate) to yield **174/175** (8 mg ,0.15mmol, 12%) as a colourless oil and **176** (47 mg, 0.15 mmol, 72%) as a colourless oil.

Data for 174

δ_H (600 MHz, $CDCl_3$): 7.41-7.23 (15H, m, Ar-H), 4.73 - 4.43 (6H, m, Bn-CH_2), 4.06 (1H, m, H-3), 3.81 (1H, dd, J = 7.5 Hz, J = 6.2 Hz, H-2), 3.65 (2H, m, H-5), 3.53 (1H, m, H-4), 3.37 (1H, m, H-1), 1.36 (3H, d, $J_{Me,1}$ = 6.9 Hz, CH_3).

δ_C (150 MHz, $CDCl_3$): 138.1, 138.0, 137.9 (q-C), 128.2, 128.2, 128.1, 127.7, 127.6, 127.6, 127.5, 127.5, 127.4 (Ar-C), 91.7 (C-2), 87.0 (C-3), 73.0, 72.8 (CH_2), 72.5 (C-5), 71.8 (CH_2), 47.1 (C-4), 42.4 (C-1), 19.7 (CH_3).

ν_{max} (film)/cm^{-1}: 1720, 1620 (C=O).

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): +26 °

HRMS (*m/z* ESI^+): Calcd for $C_{27}H_{30}O_3S$[M + Na]$^+$ 457.1813 Found 457.1823.

Data for 175

δ_H (600 MHz, $CDCl_3$): 7.41-7.23 (15H, m, Ar-H), 4.73 - 4.43 (6H, m, Bn-CH_2), 4.14 (1H, app t, $J_{3,2} = J_{3,4} = 4.1$ Hz, H-3), 3.97 (1H, app t, $J_{2,1} = J_{2,3} = 4.1$ Hz, H-2), 3.68 (2H, m, H-5), 3.64 (1H, m, H-1), 3.54 (1H, m, H-4), 1.35 (3H, d, $J_{Me,1} = 6.8$ Hz, CH_3).

δ_C (150 MHz, $CDCl_3$): (150 MHz, $CDCl_3$) δ 138.1, 138.0, 137.9 (q-C), 128.2, 128.2, 128.1, 127.7, 127.6, 127.6, 127.5, 127.4, 127.3 (Ar-C), 86.4 (C-2), 83.6 (C-3), 72.9 (CH_2), 72.5 (C-5), 72.4, 71.6 (CH_2), 48.7 (C-4), 41.9 (C-1), 16.1 (CH_3).

ν_{max} (film)/cm^{-1}: 1031 (C-O).

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): +26 °

HRMS (*m/z* ESI^+): Calcd for $C_{27}H_{30}O_3S[M + Na]^+$ 457.1813 Found 457.1823.

Data for 176

δ_H (600 MHz, $CDCl_3$): δ 7.39-7.20 (15H, m, Ar-H), 4.89 (1H, d, J = 10.8 Hz, Bn-CH_2), 4.67 (2H, app s, Bn-CH_2), 4.57 (1H, d, J = 10.8 Hz, Bn-CH_2), 4.54 (2H, app s, Bn-CH_2), 3.81 (1H, dd, $J_{6,5} = 5.7$ Hz, $J_{6,6} = 9.6$ Hz, H-6), 3.77 (1H, dd, $J_{6',5} = 3.6$ Hz, $J_{6',6} = 9.6$ Hz, H-6'), 3.69 (1H, app t, $J_{4,3 = 4,5} = 8.9$ Hz, H-4), 3.41 (1H, ddd, $J_{3,2} = 4.2$ Hz, $J_{3,2'} = 4.6$ Hz, $J_{3,4} = 8.9$ Hz, H-3), 3.03 (1H, ddd, $J_{5,4} = 8.9$ Hz, $J_{5,6} = 5.7$ Hz, $J_{5,6'} = 3.6$ Hz, H-5), 2.65-2.55 (2H, m, H-1 and H-1'), 2.46 (1H, m, H-2), 1.90 (1H, m, H-2').

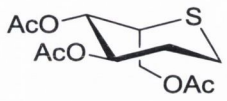
δ_C (150 MHz, $CDCl_3$): 138.5, 138.3 137.9 (q-C), 128.2, 128.2, 128.2, 127.9, 127.6, 127.6, 127.5, 127.5, 127.4 (Ar-C), 82.4 (C-3), 81.2 (C-4), 75.2, 73.1, 72.2 (CH_2), 69.1 (C-6), 46.6 (C-5), 33.8 (C-2), 25.9 (C-1).

ν_{max} (film)/cm^{-1}: 1031 (C-O) cm^{-1}

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): +23 °

HRMS (*m/z* ESI^+): Calcd for $C_{27}H_{30}O_3S[M + Na]^+$ 457.1813 Found 457.1825.

5.1.4.11 Birch Reduction of 169 (177)



Ammonia (~20 mL) was condensed in a flame-dried three-necked flask at -78 °C. Sodium metal was added portionwise until a dark blue colour was obtained. **169** (15 mg, 0.03 mmol) was added in dry THF (5 mL) and the reaction mixture was stirred for 10 minutes at -78 °C. The reaction was quenched with MeOH (2 mL) and AcOH (0.5 mL) and the reaction mixture was warmed to room temperature. The crude reaction mixutre was suspended in pyridine (5 mL) and acetic anhydride (5 mL) added, after being stirred at room temperature for 12 h, the mixture was diluted in EtOAc (50 mL) and washed the saturated aqueous $CuSO_4$ (5 x 50 mL) and brine (50 mL). The organic extract was dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (3:1 Hexane/Ethyl Acetate) to yield **177** (6 mg, 0.2 mmol, 71%) as a colourless oil.

δ_H (600 MHz, $CDCl_3$): δ 5.20 (1H, dd, $J_{4,3}$ = 7.7 Hz, $J_{4,5}$= 3.9 Hz, H-4), 5.06 (1H, app dt, $J_{3,2}$ = 7.7 Hz, $J_{3,4}$= 3.9 Hz, H-3), 4.29 (1H, m H-6 and H-6'), 3.47 (1H, m, H-5), 2.72 (2H, m, H-2 and H-2'), 2.29 (1H, m, H-1), 2.13, 2.12, 2.10 (3H, m, CH_3), 2.03 (1H, m, H-1').

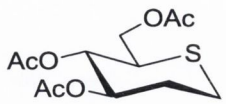
δ_C (150 MHz, $CDCl_3$): 170.4, 169.7, 169.5 (C=O), 69.6 (C-4), 68.6 (C-3), 62.1 (C-6), 39.9 (C-5), 30.0 (C-1), 22.7 (C-2), 20.8, 20.7, 20.7 (CH_3).

ν_{max} (film)/cm^{-1}: 1702, 1685 (C=O)

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): -2°

HRMS (*m/z* ESI^+): Calcd for $C_{12}H_{18}O_6S$ [M + Na]$^+$ 313.0722 Found 313.0716.

5.1.4.12 Birch Reduction of 176 (178)



Procedure as described for **177** to yield **178** (5 mg, 0.02 mmol, 64 %) as a colourless oil.

δ_H (600 MHz, $CDCl_3$): 5.18 (1H, app t, $J_{4,3} = J_{4,5} = 9.4$ Hz, H-4), 4.84 (1H, ddd, $J_{3,2} = 4.5$ Hz, $J_{3,2'} = 5.0$ Hz, $J_{3,4} = 11.3$ Hz, H-3), 4.32 (1H, dd, $J_{6,5} = 5.9$ Hz, $J_{6,6'} = 12.0$ Hz, H-6), 4.16 (1H, dd, $J_{6,5} = 3.9$ Hz, $J_{6',6} = 12.0$ Hz, H-6) 3.20 (1H, ddd, $J_{5,4} = 9.4$ Hz, $J_{5,6} = 3.5$ Hz, $J_{5,6'} = 5.9$ Hz, H-5), 2.76 (1H, m, H-2), 2.66 (1H, app dt, $J_{2,1} = J_{2,3} = 4.5$ Hz, $J_{2,2'} = 14.2$ Hz, H-2'), 2.43 (1H, m, H-1), 2.10, 2.07, 2.05 (3H, s, CH_3), 1.98 (1H, m, H-1').

δ_C (150 MHz, $CDCl_3$): 170.6, 169.6, 169.7 (C=O), 73.3 (C-3), 72.1 (C-4), 62.3 (C-6), 43.9 (C-5), 33.3 (C-1), 25.3 (C-2), 20.8, 20.5, 20.5 (CH_3).

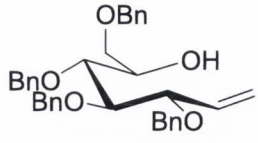
ν_{max} (film)/cm^{-1}: 1650 (C=O).

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): +58°

HRMS (*m/z* ESI^+): Calcd for $C_{12}H_{18}O_6S$ [M + Na]$^+$ 313.0722 Found 313.0716.

5.1.5 Application of the methodology to a pyranose system

5.1.5.1 3,4,5,7-Tetra-*O*-benzyl-1,2,dideoxy-*D*-galacto-hep-1-entiol (180)[247]

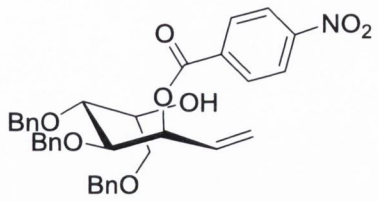


To a suspension of methyltriphenylphosponium bromide (7.10 g, 19.9 mmol) in dry toluene (15 mL) was added dropwise a 1.6 M solution of butyllithium in hexane (12.4 mL, 19.2 mmol) at 0 °C under N_2 and the reaction mixture was stirred for 2 hours at room temperature. A suspension of 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranose **179** (3.58 g, 6.62 mmol) in dry toluene (10 mL) was added and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with acetone (20 mL), the mixture was diluted with ether (100 mL) and extracted with water (50 mL x 2). The aqueous phase was extracted with ether (50 mL), the organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (10:1 Hexane/ Ethyl Acetate) to afford **180** (1.85g, 3.44 mmol, 52%) as a colourless oil.

δ_H (600 MHz, $CDCl_3$): 7.41-7.18 (15H, m, Ar-H), 5.90 (1H, ddd, $J_{2,1}$ = 10.4, $J_{2,1}$ = 17.4 Hz, $J_{2,3}$ = 7.8 Hz, H-2), 5.34 (1H, app d, $J_{1',2}$ = 17.4 Hz, H-1'), 5.33 (1H, app d, $J_{1,2}$ = 10.4 Hz, H-1), 4.79 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.77 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.68 (1H, d, J = 12.1 Hz, Bn-CH_2), 4.52 (1H, d, J = 12.1 Hz, Bn-CH_2), 4.48-4.37 (4H, m, Bn-CH_2), 4.15 (1H, m, H-6), 4.11 (1H, dd, $J_{3,2}$ = 7.8 Hz, $J_{3,4}$ = 4.5 Hz, H-3), 3.84 (2H, m, H-4 and H-5), 3.56 (1H, dd, $J_{7,6}$ = 5.1 Hz, $J_{7,7'}$ = 9.1 Hz, H-7), 3.51 (1H, dd, $J_{7',6}$ = 6.4 Hz, $J_{7',7}$ = 9.1 Hz, H-7'), 3.05 (1H, d, $J_{OH,6}$ = 5.8 Hz, OH).

HRMS (*m/z* -ESI): Calcd for $C_{35}H_{38}O_5$ [M + Na]$^+$ 561.2617 Found 561.2622.

5.1.5.2 4,5,6,7-Tetra-*O*-benzyl-1,2-dideoxy-2-*O*-(4nitrobenzoyl)-L-altro-hep-1-enitol (181)



Procedure as for **170** to yield **181** (1.08 g, 1.5 mmol, 46%) as a yellow oil and **182** (473 mg, 0.68 mmol, 20%) as a yellow oil.

Data for 181

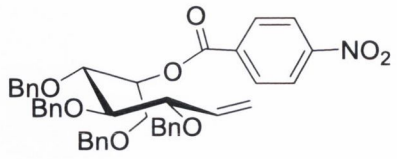
δ_H (600 MHz, $CDCl_3$): 8.26 (2H, d, J = 8.8 Hz, *m*-C_6H_4), 8.10 (2H, d, J = 8.8 Hz, *o*-C_6H_4), 7.40-7.28 (18H, m, Ar-H), 6.11 (1H, ddd, $J_{2,1}$ = 17.2 Hz, $J_{2,1'}$ = 10.6 Hz, $J_{2,3}$ = 7.3 Hz, H-2), 5.99 (1H, dd, $J_{3,2}$ = 7.3 Hz, $J_{3,4}$ = 2.7 Hz, H-3), 5.35 (2H, m, H-1), 4.83 (1H, d, J = 11.5 Hz, Bn-CH_2), 4.80 (1H, d, J = 11.5 Hz, Bn-CH_2), 4.79 (1H, d, J = 11.7 Hz, BnCH_2), 4.72 (1H, d, J = 11.7 Hz, Bn-CH_2), 4.71 (1H, d, J = 11.5 Hz, Bn-CH_2), 4.67 (1H, d, J = 11.5 Hz, Bn-CH_2), 4.54 (1H, d, J = 12.3 Hz, Bn-CH_2), 4.50 (1H, d, J = 12.3 Hz, Bn-CH_2), 4.11 (2H, m, H-4 and H-6), 3.89 (1H, dd, J = 3.5 Hz, J = 7.4 Hz, H-5), 3.84 (1H, dd, $J_{7,6}$ = 4.1 Hz, $J_{7,7'}$ = 10.7 Hz, H-7), 3.77 (1H, dd, $J_{7',6}$ = 5.9 Hz, $J_{7',7}$ = 10.7 Hz, H-7').

δ_C (150 MHz, $CDCl_3$): 163.5 (C=O), 150.4 (CCOO), 138.5, 138.2, 138.0, 137.9 (q-Ar), 135.7 (CNO2), 132.2 (C-2), 130.6 (o-C_6H_4), 128.3, 128.3, 128.2, 128.2, 127.9, 127.9, 127.7, 127.6, 127.6, 127.6, 127.5, 127.4 (Ar-C), 123.4 (p-C_6H_4), 119.7 (C-1), 80.2 (C-6), 78.8 (C-5), 78.8 (C-4), 77.4 (C-3), 73.7, 73.2, 72.6 (Bn-CH_2), 70.0 (C-7).

ν_{max} (film)/cm^{-1}: 2922, 1320, 920 (C-O).

HRMS (*m/z* -ESI): Calcd for $C_{42}H_{41}NO_8$ [M + Na]$^+$ 710.2730 Found 710.2722.

5.1.5.3 3,4,5,7-Tetra-*O*-benzyl-1,2-dideoxy-6-*O*-(4nitrobenzoyl)-L-altro-hep-1-enitol (182)[247]

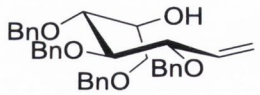


To a stirred solution of **180** (2.00 g, 3.71 mmol) in dry toluene (40 mL) was added 4-nitrobenzoic acid (2.48 g, 14.9 mmol), and PPh_3 (2.91 g, 11.1 mmol). To this reaction mixture was added triethylamine (1.52 mL, 11.1 mmol). The reaction mixture was cooled to 0° C and DIAD (2.95 mL, 14.9 mmol) was added dropwise under N_2. After having been stirred for 12 h at room temperature the reaction mixture was concentrated *in vacuo* and the residue purified by column chromatography (15:1 Hexane/ Ethyl Acetate) to afford **182** (1.47 g, 2.15 mmol, 58%) as a yellow oil and **181** (413 mg, 0.60 mmol, 19%) as a yellow oil.

δ_H (600 MHz, $CDCl_3$): 8.27 (2H, d, J = 8.8 Hz, m-C_6H_4), 8.11 (2H, d, J = 8.8 Hz, *o*-C_6H_4), 7.39-7.22 (20H, m, Ar-H), 5.96 (1H, ddd, $J_{2,1}$ = 17.4 Hz, $J_{2,1'}$ = 10.7 Hz, $J_{2,3}$ = 7.4 Hz, H-2), 5.84 (1H, app dt, $J_{6,5}$ = 3.8 Hz, $J_{6,7}$ = 6.7 Hz, H-6), 5.40 (1H, app d, $J_{1,2}$ = 17.4 Hz, H-1), 5.38 (1H, app d, $J_{1',2}$ = 10.7 Hz, H-1'), 4.83 (1H, d, J = 11.1 Hz, Bn-CH_2), 4.76 (1H, d, J = 11.5 Bn-CH_2), 4.65 (1H, d, J = 12.1 Hz, Bn-CH_2), 4.64 (1H, d, J = 11.5 Hz, Bn-CH_2), 4.53 (1H, d, J = 12.1 Hz, Bn-CH_2), 4.50 (1H, d, J = 11.5 Hz, Bn-CH_2), 4.42 (1H, d, J = 11.5 Hz, Bn-CH_2), 4.37 (1H, d, J = 11.1 Hz, Bn-CH_2), 4.16 (1H, dd, $J_{3,2}$ = 7.4 Hz, $J_{3,4}$ = 5.3 Hz, H-3), 4.11 (1H, dd, $J_{5,4}$ = 5.4 Hz, $J_{5,6}$ = 3.2 Hz, H-5), 3.94 (2H, m, H-7 and H-7'), 3.78 (1H, app t, $J_{4,3}$ = $J_{4,5}$ = 5.2 Hz, H-4).

HRMS (*m/z* ESI$^+$): Calcd for $C_{42}H_{41}NO_8$ [M + Na]$^+$ 710.2730 Found 710.2733.

5.1.5.4 3,4,5,7-Tetra-*O*-benzyl-L-idose-hep-1-enitol (183)[247]

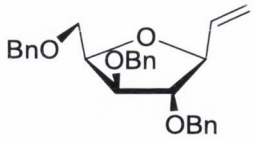


Procedure as described for **171** to yield **183.** Purification by column chromatography (10:1 Hexane/Ethyl Acetate) afforded **183** (445 mg, 0.83 mmol, 99%) as a colourless oil.

δ_H (600 MHz, $CDCl_3$): 7.38 - 7.19 (20H, m, Ar-H), 5.92 (1H, ddd, $J_{2,1'}$ = 17.2 Hz, $J_{2,1}$ = 10.6 Hz, $J_{2,3}$ = 7.9 Hz, H-2), 5.37 (1H, dd, $J_{1',1}$ = 0.9 Hz, $J_{1',2}$ = 17.2 Hz, H-1'), 5.34 (1H, dd, $J_{1',1}$ = 0.9 Hz, $J_{1,2}$ = 10.6 Hz, H-1), 4.81 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.74 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.67 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.55 (1H, d, J = 12.1 Hz, Bn-CH_2), 4.51 (1H, d, J = 12.1 Hz, BnCH_2), 4.50 (2H, s, Bn-CH_2), 4.41 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.16 (2H, m, H-3 and H-6), 3.82 (2H, m, H-4 and H-5), 3.69 (1H, dd, $J_{7,6}$ = 2.9 Hz, $J_{7,7'}$=10.0 Hz, H-7), 3.64 (1H, dd, $J_{7',6}$ = 6.4 Hz, $J_{7,7'}$=10.0 Hz, H-7').

HRMS (*m/z* -ESI): Calcd for $C_{29}H_{32}O_4$ [M + Na]$^+$ 561.2617 Found 561.2643.

5.1.5.5 2,3,4-Tri-*O*-benzyl-1-vinyl-xylofuranose (185)[262]



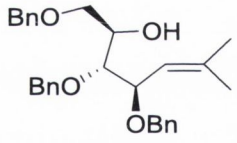
To a stirred solution of **183** (2.00 g, 3.71 mmol) in dry THF (40 mL) was added thioacetic acid (1.00 mL, 14.9 mmol), and PPh_3 (2.91 g, 11.1 mmol). To this reaction mixture was added triethylamine (1.52 mL, 11.1 mmol). The reaction mixture was cooled to 0° C and DIAD (2.95 mL, 14.9 mmol) was added dropwise under N_2. After having been stirred for 16 h at room temperature the reaction mixture was concentrated *in vacuo* and the residue purified by column chromatography (15:1 Hexane/ Ethyl Acetate) to afford **185** (687 mg, 1.59 mmol, 43%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 7.19-7.06 (15H, m, Ar-H), 5.78 (1H, ddd, $J_{6,7}$ = 17.2 Hz, $J_{6,7'}$ = 10.5 Hz, $J_{6,1}$ = 7.4 Hz, H-6), 5.49 (2H, m, H-7 and H-7'), 4.66 (1H, d, J = 12.0 Hz, Bn-CH_2), 4.63 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.36 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.58 (1H, d, J = 12.0 Hz, Bn-CH_2), 4.55 (1H, d, J = 11.7 Hz, Bn-CH_2), 4.53 (1H, d, J = 11.7 Hz, Bn-CH_2), 4.44 (1H, dd, $J_{1,6}$ = 7.4 Hz, $J_{1,2}$ = 5.0 Hz, H-1), 4.04 (1H, dd, $J_{2,1}$ = 5.0 Hz, $J_{2,3}$ = 7.2 Hz, H-2), 3.56 (1H, dd, $J_{3,2}$ = 7.2 Hz, $J_{3,4}$ = 3.7 Hz, H-3), 3.50 (2H, m, H-5), 3.46 (1H, m, H-4).

HRMS (*m/z* ESI^+): Calcd for $C_{28}H_{31}O_4$ [M + H]$^+$ 431.2222 Found 431.2228.

5.1.6 Investigation of 5-*exo* thiyl radical ring closures

5.1.6.1 (3*R*,4*R*,5*R*)-5-Hydroxy-3,4,6-tribenzyloxy-hex-1-isopropyl-ene (188)



To a suspension of isopropyltriphenylphosponium iodide (3.08 g, 7.15 mmol) in dry toluene (30 mL) was added dropwise a 1.6 M solution of butyllithium in hexane (4.31 mL, 6.90 mmol) at 0 °C under N_2 and the reaction mixture was stirred for 30 mins at room temperature. A suspension of 2,3,4-tri-*O*-benzyl-α-D-arabinofuranose **160** (1.00 g, 2.38 mmol) in dry toluene (10 mL) was added and the reaction mixture was stirred for 6 h at room temperature. The reaction mixture was quenched with acetone (5 mL), the mixture was diluted with ether and extracted with water (50 mL). The aqueous phase was extracted with ether (50 mL), the organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (10:1 Hexane/ Ethyl Acetate) to afford **188** (674 mg, 1.51 mmol, 64%) as a colourless oil.

δ_H (600 MHz, $CDCl_3$): 7.42-7.28 (15H, m, Ar-H), 5.34 (1H, bd, $J_{2,1}$ = 9.1 Hz, H-2), 4.68 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.62 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.60 (1H, d, J = 11.1 Hz, Bn-CH_2), 4.53 (2H, app s, Bn-CH_2), 4.35 (1H, dd, $J_{3,2}$ = 9.1 Hz, $J_{3,4}$ = 4.5 Hz, H-3), 4.34 (1H, d, J = 11.1 Hz, Bn-CH_2), 4.01 (1H, m, H-5), 3.60 (3H, m, H-4, H-6 and H-6'), 2.96 (1H, bs, OH), 1.80 (3H, s, CH_3), 1.57 (3H, s, CH_3).

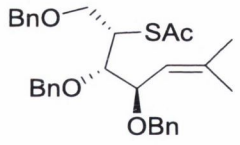
δ_C (150 MHz, $CDCl_3$): 138.2, 138.1, 138.1 (q-Ar), 137.9 (C-1), 128.2, 128.2, 128.1, 128.0, 127.8, 127.7, 127.5, 127.5, 127.4 (Ar-C), 121.9 (C-2), 80.9 (C-4), 75.1 (C-3), 74.1 (Bn-CH_2), 73.3 (Bn-CH_2), 71.0 (C-6), 70.5 (C-5), 69.8 (Bn-CH_2), 26.1 (CH_3), 18.5 (CH_3).

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): +17.1 °

ν_{max} (film)/cm^{-1}: 1180 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{29}H_{34}O_4$ [M + Na]$^+$ 469.2355 Found 469.2370.

5.1.6.2 (3*R*,4*R*,5*S*)-5-thioacetate-3,4,6-tribenzyloxy-hex-1-isopropylene(189)



General procedure for the synthesis of thioesters was carried out to prepare **189**. Purified by column chromatography (Hexane/EtOAc, 10:1, R_f= 0.42) afforded **189** as a colourless oil. (426 mg, 0.85 mmol, 56 %) ;

δ_H (600 MHz, $CDCl_3$): 7.36-7.26 (15H, m, Ar-H), 5.06 (1H, dt, $J_{2,CH3}$ = 1.1 Hz, $J_{2,3}$ = 10.0 Hz, H-2), 5.03 (1H, d, J =11.5 Hz, Bn-CH_2), 4.62 (1H, d, J = 11.5 Hz, Bn-CH_2), 4.57 (1H, d, J = 11.3 Hz, Bn-CH_2),

4.50 (1H, d, J = 11.3 Hz, Bn-CH_2), 4.40 (1H, dd, $J_{3,2}$ = 10.0 Hz, $J_{3,4}$ = 8.5 Hz, H-3), 4.39 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.38 (1H, d, J = 11.3 Hz, Bn-CH_2), 4.08 (1H, dd, $J_{4,3}$ = 8.5 Hz, $J_{4,5}$ = 1.5 Hz, H-4), 3.93 (1H, ddd, $J_{5,4}$ = 1.5 Hz, $J_{5,6}$ = 5.3 Hz, $J_{5,6'}$ = 10.2 Hz, H-5), 3.64 (1H, app t, $J_{6',5}$ = $J_{6',6}$ = 10.2 Hz, H-6'), 3.38 (1H, dd, $J_{6,5}$ = 5.3 Hz, $J_{6,6'}$ = 10.2 Hz, H-6), 2.29 (3H, s, SCH_3), 1.80 (3H, d, $J_{CH3,2}$ = 1.1 Hz, CH_3), 1.61 (3H, d, $J_{CH3,2}$ = 1.1 Hz, CH_3).

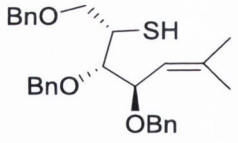
δ_C (150 MHz, $CDCl_3$): 194.8 (C=O), 139.2 (C-1), 139.1, 138.9, 138.1 (q-Ar), 128.3, 128.2, 128.2, 127.7, 127.7, 127.6, 127.6, 127.3, 127.3 (Ar-C), 121.7 (C-2), 79.9 (C-4), 79.6 (C-3), 75.6, 72.3, 70.1 (Bn-CH_2), 70.1 (C-6), 45.6 (C-5), 30.6 (SCH_3), 26.2, 18.5 (CH_3).

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): -45.8 °

ν_{max} (film)/cm^{-1}: 1785 (C=O), 1150 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{31}H_{36}O_4S$ [M + Na]$^+$ 527.2232 Found 527.2220.

5.1.6.3 (3*R*,4*R*,5*S*)-5-Thio-3,4,6-tribenzyloxy-1-isopropyl-ene (190)



General procedure for the hydrolysis of thioesters was carried out to prepare **190**. Purified by column chromatography (Hexane/EtOAc, 15:1, R_f= 0.20) afforded **190** as a colourless oil. (388 mg, 0.84 mmol, 99 %) ;

δ_H (600 MHz, $CDCl_3$): 7.40-7.25 (15H, m, Ar-H), 5.08 (2H, m, H-2 and Bn-CH_2), 4.60 (3H, m, H-3 and Bn-CH_2 x 2), 4.41 (3H, m, Bn-CH_2 x 3), 3.96 (1H, dd, $J_{4,3}$ = 8.6 Hz, $J_{4,3}$ = 2.2 Hz, H-4), 3.54 (2H,

m, H-6 and H-6'), 3.02 (1H, dddd, $J_{5,4}$ = 2.2 Hz, $J_{5,SH}$ = 10.8 Hz, $J_{5,6}$ = 6.0 Hz, $J_{5,6'}$ = 8.1 Hz, H-5), 1.83 (1H, d, $J_{CH3,2}$ = 1.4 Hz, CH_3), 1.80 (1H, d, $J_{CH3,2}$ = 1.4 Hz, CH_3), 1.72 (1H, d, $J_{SH,5}$ = 10.8 Hz, SH).

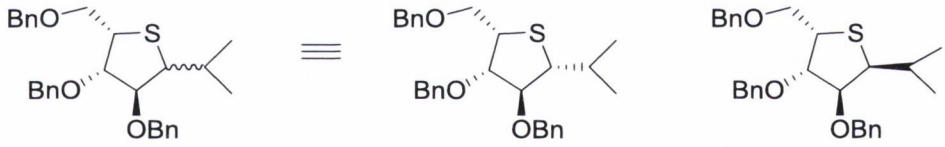
δ_C (150 MHz, $CDCl_3$): 139.2, 139.1, 139.1 (q-Ar), 138.0 (C-1), 128.4, 128.2, 128.2, 127.8, 127.7, 127.7, 127.3, 127.4 (Ar-C), 122.1 (C-2), 79.7 (C-4), 79.5 (C-3), 75.4 (Bn-CH_2), 73.3 (C-6), 72.9 (Bn-CH_2), 70.4 (Bn-CH_2), 41.5 (C-5), 26.3, 19.1 (CH_3).

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): -36.8 °

ν_{max} (film)/cm^{-1}: 1022 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{29}H_{34}O_3S$ [M + Na]$^+$ 485.2126 Found 485.2138.

5.1.6.4 2,3,4-Tri-*O*-benzyl-1-isopropyl-L-xylofuranoside (190/191)



190/191 **190** **191**

General procedure for radical cyclisation was carried out to prepare **190/191** as a mixture of diastereoisomers (3:1, β:α). Purification by column chromatography (Hexane/EtOAc, 15:1, R_f= 0.22) furnished the mixture of isomers **190/191** as a colourless oil. (351 mg, 0.76 mmol, 91 %) ;

Data for α anomer 191

δ_H (600 MHz, $CDCl_3$): 7.37-7.25 (15H, m, Ar-H), 4.63 (1H, d, *J* = 11.9 Hz, Bn-CH_2), 4.56 (4H, m, 4 x Bn-CH_2), 4.34 (1H, d, *J* = 11.6 Hz, Bn-CH_2), 4.21 (1H, dd, $J_{3,2}$ = 3.8 Hz, $J_{3,4}$ = 2.0 Hz, H-3), 3.97 (1H, m, H-4), 3.86 (2H, m, H-2 and H-5), 3.63 (1H, app dd,

$J_{5,4}$ = 5.8 Hz, $J_{5,5'}$ = 9.2 Hz, H-5), 3.39 (1H, dd, $J_{1,CH(CH3)2}$ = 10.9 Hz, $J_{1,2}$ = 3.1 Hz, H-1), 2.09 (1H, m, C<u>H</u>$(CH_3)_2$), 0.99 (3H, d, $J_{CH3,CH(CH3)2}$ = 6.7 Hz, CH_3), 0.81 (3H, d, $J_{CH3,CH(CH3)2}$ = 6.5 Hz, CH_3).

δ_C (150 MHz, $CDCl_3$): 138.2, 138.2, 137.9 (q-Ar), 128.4, 128.3, 128.3, 127.9, 127.9, 127.7, 127.6, 127.6, 127.6 (Ar-C), 83.2 (C-2), 81.9 (C-3), 73.3, 72.9, 71.8 (Bn-CH_2), 69.0 (C-5), 58.6 (C-1), 48.5 (C-4), 29.2 ($CH(CH_3)_2$), 23.2 (CH_3), 21.1 (CH_3).

ν_{max} (film)/cm^{-1}: 1130 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{29}H_{34}O_3S$ [M + Na]$^+$ 485.2126 Found 485.2140.

Data for β anomer 190

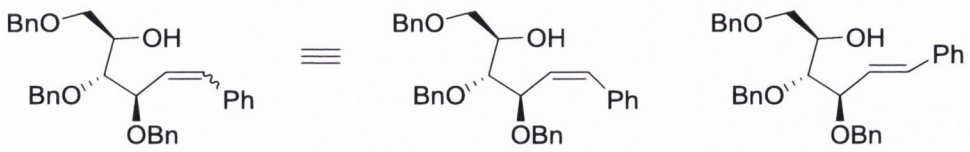
δ_H (600 MHz, $CDCl_3$): 7.38-7.27 (15H, m, Ar-H), 4.73 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.62 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.57 (4H, m, 4 x Bn-CH_2), 4.57 (1H, app t, $J_{3,4}$ = $J_{3,2}$ = 5.4 Hz, H-3), 3.95 (1H, app t, $J_{2,1}$ = $J_{2,3}$ = 5.4 Hz, H-2), 3.86 (1H, dd, $J_{5,4}$ = 6.7 Hz, $J_{5,5'}$ = 9.6 Hz, H-5), 3.68 (1H, m, H-4), 33.57 (1H, dd, $J_{5',4}$ = 6.9 Hz, $J_{5',5}$ = 9.6 Hz, H-5'), 3.11 (1H, dd, $J_{1,CH(CH3)2}$ = 7.5 Hz, $J_{1,2}$ = 5.4 Hz, H-1), 1.94 (1H, m, C<u>H</u>$(CH_3)_2$), 0.94 (3H, d, $J_{CH3,CH(CH3)2}$ = 7.1 Hz, CH_3), 0.93 (3H, d, $J_{CH3,CH(CH3)2}$ = 6.7 Hz, CH_3).

δ_C (150 MHz, $CDCl_3$): 138.3, 138.3, 137.9 (q-Ar), 128.4, 128.4, 128.4, 128.3, 128.3, 127.9, 127.8, 127.8, 127.7 (Ar-C), 85.2 (C-3), 84.8 (C-2), 73.3, 72.6, 72.2 (Bn-CH_2), 70.4 (C-5), 55.6 (C-1), 45.1 (C-4), 31.9 (C<u>H</u>$(CH_3)_2$), 21.6, 20.0 (CH_3).

ν_{max} (film)/cm^{-1}: 1130 (C-O) cm^{-1}

HRMS (*m/z* ES^+): Calcd for $C_{29}H_{34}O_3S$ [M + Na]$^+$ 485.2126 Found 485.2140.

5.1.6.5 (3*R*,4*R*,5*R*)-5-Hydroxy-3,4,6-tribenzyloxy-hex-1-styrene (195)



2,3,4-tri-*O*-benzyl-α-D-arabinofuranose **160** (1.00 g, 2.38 mmol), benzyl triphenylphosphonium bromide (2.77 g, 7.14 mmol), potassium carbonate (1.08 g, 7.85 mmol) and 18-crown-6 (377 mg, 1.43 mmol) were added to an oven dried RBF. The reaction mixture was solubilised in dry CH_2Cl_2 (50 mL) under argon and refluxed at 45°C overnight. The reaction mixture was diluted in CH_2Cl_2 (50 mL) and washed with water (50 mL x 2) and brine (50 mL). The organic layer was dried over magnesium sulphate and the solvent was removed *in vacuo*. Purification by column chromatography (Hexane/EtOAc 10:1) afforded **195** as a mixture of isomers (1:1, E:Z) as a colourless oil. (847 mg, 1.71 mmol, 72 %)

Data for *E* isomer

δ_H (600 MHz, $CDCl_3$): 7.41-7.08 (20H, m, Ar-H), 6.62 (1H, d, $J_{1,2}$ = 16.5 Hz, H-1), 6.33 (1H, dd, $J_{2,1}$ = 16.5 Hz, $J_{2,3}$ = 7.8 Hz, H-2), 4.68-4.42 (6H, m, Bn-CH_2), 4.29 (1H, dd, $J_{3,2}$ = 7.8 Hz, $J_{3,4}$ = 3.7 Hz, H-3), 4.10 (1H, m, H-5), 3.71 (1H, dd, $J_{4,5}$ = 3.7 Hz, $J_{4,5}$ = 6.7 Hz, H-4), 3.66 (2H, m, H-6 and H-6'), 2.85 (1H, d, $J_{OH,5}$ = 5.5 Hz, OH).

δ_C (150 MHz, $CDCl_3$): 138.1, 138.1, 137.9 (q-Ar), 136.5 (q-Ph), 133.6 (C-1), 128.7, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 127.9, 127.7, 127.7, 127.7 (Ar-C), 127.6 (C-2), 126.6 (C-1), 81.1 (C-4), 79.8 (C-3), 74.3, 73.4 (Bn-CH_2), 71.0 (C-6), 70.7 (Bn-CH_2), 70.4 (C-5).

ν_{max} (film)/cm^{-1}: 1180 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{33}H_{34}O_4$ [M + Na]$^+$ 517.2355 Found 517.2347.

Data for *Z* isomer

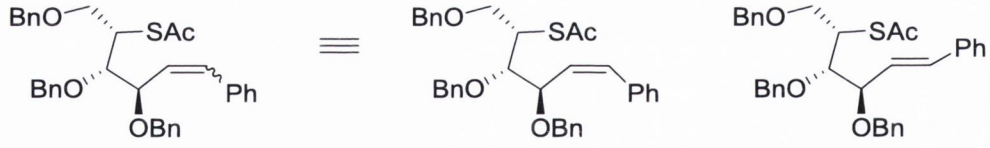
δ_H (600 MHz, $CDCl_3$): 7.41-7.08 (20H, m, Ar-H), 6.84 (1H, d, $J_{1,2}$ = 12.1 Hz, H-1), 5.95 (1H, dd, $J_{2,1}$ = 12.1 Hz, $J_{2,3}$ = 9.5 Hz, H-2), 4.72 (1H, dd, $J_{3,2}$ = 9.5 Hz, $J_{3,4}$ = 3.1 Hz, H-3), 4.68-4.42 (6H, m, Bn-CH_2), 4.12 (1H, m, H-5), 3.75 (1H, dd, $J_{4,3}$ = 3.1 Hz, $J_{4,5}$ = 6.7 Hz, H-4), 3.58 (1H, dd, $J_{6,5}$ = 5.4 Hz, $J_{6,6'}$ = 9.7 Hz, H-6), 3.49 (1 H, dd, $J_{6',5}$ = 4.1 Hz, $J_{6',6}$ = 9.7 Hz, H-6'), 2.90 (1H, d, $J_{OH,5}$ = 5.8 Hz, OH).

δ_C (150 MHz, $CDCl_3$): 138.1, 138.0 137.6 (q-Ar), 136.4 (q-Ph), 133.9 (C-1), 129.5 (C-2), 128.6, 128.4, 128.4, 128.3, 128.2, 128.2, 128.2, 127.9, 127.7, 127.7, 127.3, 126.6 (Ar-C), 80.8 (C-4), 74.0 (Bn-CH_2), 73.4, (C-3 and Bn-CH_2), 71.2 (C-6), 70.5 (C-5), 70.2 (Bn-CH_2).

ν_{max} (film)/cm^{-1}: 1180 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{33}H_{34}O_4$ [M + Na]$^+$ 517.2355 Found 517.2347.

5.1.6.6 (3*R*,4*R*,5*S*)-5-Thioacetate-3,4,6-tribenzyloxy-hex-1-styrene (196)



General procedure for the synthesis of thioesters was carried out to prepare **196** as a mixture of isomers (1:1 E:Z). Purification by column chromatography (Hexane/EtOAc, 12:1) furnished **196** as a colourless oil. (566 mg, 1.03 mmol, 60 %)

Data for *E* isomer

δ_H (600 MHz, $CDCl_3$): 7.45-7.23 (20H, m, Ar-H), 6.65 (1H, d, $J_{1,2}$ = 16.2 Hz, H-1), 6.14 (1H, dd, $J_{2,1}$ = 16.2 Hz, $J_{2,3}$ = 7.7 Hz, H-2), 5.01 (1H, d, *J*

= 11.3 Hz, CH_2), 4.69 (3H, m, Bn-CH_2), 4.53 (2H, m, Bn-CH_2), 4.31 (1H, app t, $J_{3,2} = J_{3,4} = 7.7$ Hz, H-3), 4.17 (1H, m, H-4), 4.08 (1H, ddd, $J_{5,4} = 2.3$ Hz, $J_{5,6} = 5.1$ Hz, $J_{5,6'} = 9.7$ Hz, H-5), 3.69 (1H, app t, $J_{6,5} = J_{6,6'} = 9.7$ Hz, H-6), 3.46 (1H, dd, $J_{6',5} = 5.1$ Hz, $J_{6'6} = 9.7$ Hz, H-6'), 2.32 (3H, s, SOC$\underline{H}_3$).

δ_C (150 MHz, $CDCl_3$): 194.7 (C=O), 138.7, 138.4, 138.1 (q-Ar), 136.6 (q-Ph), 134.3 (C-1), 128.5, 128.3, 128.2, 128.2, 128.1, 127.9, 127.8, 127.7, 127.7, 127.4, 127.4, 127.2 (Ar-C), 125.9 (C-2), 83.3 (C-3), 80.1 (C-4), 75.1, 72.7, 70.9 (CH_2), 69.9 (C-6), 45.6 (C-5), 30.9 (SCO$\underline{C}H_3$).

ν_{max} (film)/cm^{-1}: 1782 (C=O), 1110 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{35}H_{36}O_4S$ [M + Na]$^+$ 575.2232 Found 575.2261.

Data for *Z* isomer

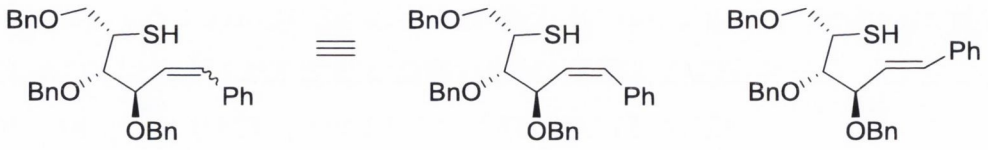
δ_H (600 MHz, $CDCl_3$): 7.45-7.23 (20H, m, Ar-H), 6.80 (1H, d, $J_{1,2} = 12.1$ Hz, H-1), 5.63 (1H, dd, $J_{2,1} = 12.1$ Hz, $J_{2,3} = 10.8$ Hz, H-2), 4.91 (1H, d, $J = 11.4$ Hz, Bn-CH_2), 4.69 (2H, m, Bn-CH_2), 4.51 (1H, d, $J = 12.4$ Hz, Bn-CH_2), 4.43 (2H, m, Bn-CH_2), 4.85 (1H, dd, $J_{3,2} = 10.8$ Hz, $J_{3,4} = 7.1$ Hz, H-3), 4.17 (1H, dd, $J_{4,3} = 7.1$ Hz, $J_{4,5} = 2.3$ Hz, H-4), 4.05 (1H, ddd, $J_{5,4} = 2.3$ Hz, $J_{5,6} = 4.9$ Hz, $J_{5,6'} = 9.4$ Hz, H-5), 3.63 (1H, app t, $J_{6',5} = J_{6',6} = 9.4$ Hz, H-6'), 3.39 (1H, dd, $J_{6,5} = 4.9$ Hz, $J_{6,6'} = 9.4$ Hz, H-6), 2.08 (3H, s, SCOC$\underline{H}_3$).

δ_C (150 MHz, $CDCl_3$): 194.4 (C=O), 138.6, 138.3, 138.0 (q-Ar), 136.4 (q-Ph), 134.1 (C-1), 128.7 (C-2), 128.6, 128.3, 128.2, 128.2, 127.9, 127.7, 127.7, 127.6, 127.4, 127.4, 127.2, 126.7 (Ar-C), 79.6 (C-4), 77.2 (C-3), 75.2, 72.7, 70.5 (CH_2), 69.8 (C-6), 45.3 (C-5), 30.4 (SCO$\underline{C}H_3$).

ν_{max} (film)/cm^{-1}: 1782 (C=O), 1110 (C-O).

HRMS (*m/z* ES$^+$): Calcd for $C_{35}H_{36}O_4S$ [M + Na]$^+$ 575.2232 Found 575.2261.

5.1.6.7 (3*R*,4*R*,5*S*)-5-Thio-3,4,6-tribenzyloxy-hex-1-styrene (197)



General procedure for the hydrolysis of thioesters was carried out to prepare **197** as a mixture of isomers (1:1, E:Z). Purification by column chromatography (Hexane/EtOAc, 15:1) furnished **197** as a colourless oil. (520 mg, 1.02 mmol, 99 %)

Data for *E* isomer

δ_H (600 MHz, $CDCl_3$): 7.50-7.13 (20H, m, Ar-H), 6.78 (1H, d, $J_{1,2}$ = 16.0 Hz, H-1), 6.15 (1H, dd, $J_{2,1}$ = 16.0 Hz, $J_{2,3}$ = 8.5 Hz, H-2), 5.07 (1H, d, J = 11.2 Hz, Bn-CH_2), 4.97 (1H, d, J = 11.2 Hz, Bn-CH_2), 4.68 (3H, d, J = 11.5 Hz, Bn-CH_2), 4.51 (1H, d, J = 11.5 Hz, Bn-CH_2), 4.50 (1H, app t, $J_{3,2}$ = $J_{3,4}$ = 8.5 Hz, H-3), 4.06 (1H, dd, $J_{4,3}$ = 8.5 Hz, $J_{4,5}$ = 2.3 Hz, H-4), 3.59 (1H, app t, $J_{6,5}$ = $J_{6,6'}$ = 9.3 Hz, H-6), 3.53 (1H, dd, $J_{6',5}$ = 5.0 Hz, $J_{6',6}$ = 9.3 Hz, H-6'), 3.09 (1H, dddd, $J_{5,4}$ = 2.3 Hz, $J_{5,6}$ = 5.0 Hz, $J_{5,6'}$ = 9.3 Hz, $J_{5,SH}$ = 10.5 Hz, H-5), 1.76 (1H, d, $J_{SH,5}$ = 10.5 Hz, SH).

δ_C (150 MHz, $CDCl_3$): 138.9, 138.6, 137.9 (q-Ar), 136.5 (q-Ph), 134.6 (C-1), 128.9, 128.6, 128.4, 128.3, 128.2, 128.2, 128.1, 127.9, 127.8, 127.8, 127.7, 127.5 (Ar-C), 126.1 (C-2), 84.1 (C-3), 79.5 (C-4), 75.6, 75.3 (Bn-CH_2), 72.9 (C-6), 70.9 ($BnCH_2$), 41.3 (C-5).

ν_{max} (film)/cm^{-1}: 1154 (C-O).

HRMS (*m/z* ES$^+$): Calcd for $C_{33}H_{34}O_3S$ [M + Na]$^+$ 533.2126 Found 533.2120.

Data for *Z* isomer

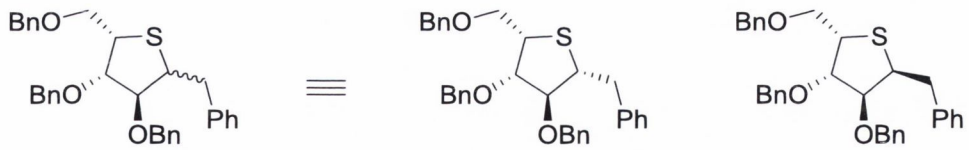
δ_H (600 MHz, $CDCl_3$): 7.50-7.13 (20H, m, Ar-H), 6.68 (1H, d, $J_{1,2}$ = 11.9 Hz, H-1), 5.68 (1H, dd, $J_{2,1}$ = 11.9 Hz, $J_{2,3}$ = 10.1 Hz, H-2), 4.86 (1 H, dd, $J_{3,2}$ = 10.1 Hz, $J_{3,4}$ = 6.9 Hz, H-3), 4.57 (1 H, d, J = 11.6 Hz, Bn-CH_2), 4.45 (2H, d, J = 12.1 Hz, Bn-CH_2), 4.43 (1H, d, J = 10.9 Hz, Bn-CH_2), 4.37 (1H, d, J = 10.9 Hz, Bn-CH_2), 4.27 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.01 (1H, dd, $J_{4,3}$ = 6.9 Hz, $J_{4,5}$ = 3.3 Hz, H-4), 3.50 (1H, app t, $J_{6,5}$ = $J_{6,6'}$ = 9.1 Hz, H-6), 3.44 (1H, dd, $J_{6',5}$ = 4.9 Hz, $J_{6',6}$ = 9.1 Hz, H-6'), 3.21 (1H, dddd, $J_{5,4}$ = 3.3 Hz, $J_{5,6}$ = 9.1 Hz, $J_{5,6'}$ = 4.9 Hz, $J_{5,SH}$ = 10.0 Hz, H-5), 1.78 (1H, d, $J_{SH,5}$ = 10.0 Hz).

δ_C (150 MHz, $CDCl_3$): 138.8, 138.3, 137.9 (q-Ar), 136.3 (q-Ph), 134.7 (C-1), 129.0 (C-2), 128.9, 128.6, 128.4, 128.3, 128.3, 128.2, 128.1, 127.9, 127.9, 127.8, 127.8, 127.4 (Ar-C), 80.7 (C-4), 76.3 (C-3), 72.9 (Bn-CH_2), 72.8 (C-6), 72.7, 70.3 (Bn-CH_2), 41.3 (C-5).

ν_{max} (film)/cm^{-1}: 1154 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{33}H_{34}O_3S$ [M + Na]$^+$ 533.2126 Found 533.2120.

5.1.6.8 2,3,5-Tri-*O*-benzyl-1-benzyl-L-xylofuranoside (198/199)



198/199 **198** **199**

General procedure for radical cyclisation was carried out to prepare **198/199** as a mixture of isomers (13.5:1, β:α). Purification by column chromatography (Hexane/EtOAc, 15:1, R_f= 0.22) furnished **198/199** as a colourless oil. (351 mg, 0.96 mmol, 94 %)

Data for β anomer 198

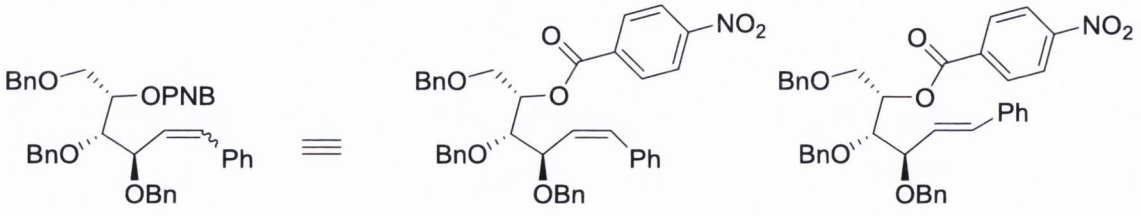
δ_H (600 MHz, $CDCl_3$): 7.41-7.12 (20H, m, Ar-H), 4.59 (2H, s, Bn-CH_2), 4.56 (2H, d, J = 8.9 Hz, Bn-CH_2), 4.46 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.42 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.16 (1H, app t, $J_{3,2} = J_{3,4}$ = 5.1 Hz, H-3), 3.94 (1H, app t, $J_{2,1} = J_{2,3}$ = 5.1 Hz, H-2), 3.87 (1H, dd, $J_{5,4}$ = 6.6 Hz, $J_{5,5'}$ = 9.3 Hz, H-5), 3.78 (1H, m, H-4), 3.61 (1H, dd, $J_{5',4}$ = 6.1 Hz, $J_{5',5}$ = 9.3 Hz, H-5'), 3.57 (1H, ddd, $J_{1,C\underline{H}2Ph}$ = 8.3 Hz, $J_{1,1C\underline{H}2Ph'}$ = 7.1 Hz, $J_{1,2}$ = 5.1 Hz, H-1), 3.10 (1H, dd, $J_{C\underline{H}2Ph,CH2Ph'}$ = 13.4 Hz, $J_{C\underline{H}2Ph,1}$ = 8.3 Hz, CH_2Ph), 2.88 (1H, dd, $J_{C\underline{H}2Ph',CH2Ph}$ = 13.4 Hz, $J_{C\underline{H}2Ph',1}$ = 7.1 Hz, CH_2Ph').

δ_C (150 MHz, $CDCl_3$): 139.5, 138.1, 137.9 (q-Ar), 137.9 (q-Ph), 128.9, 128.3, 128.3, 128.2, 128.2, 127.7, 127.6, 127.6, 127.5, 127.4, 126.8, 126.2 (Ar-C), 85.5 (C-2), 84.8 (C-3), 73.4, 72.5, 71.8 (Bn-CH_2), 69.7 (C-5), 50.2 (C-1), 46.8 (C-4), 42.0 ($\underline{C}H_2$Ph).

ν_{max} (film)/cm^{-1}: 1185 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{33}H_{34}O_3S$ [M + Na]$^+$ 533.2126 Found 533.2130.

5.1.6.9 (3*R*,4*R*,5*S*)-5-Para-nitro-benzyl-3,4,6-tribenzyloxy-hex-1-styrene (200)



To a stirred solution of **195** (608 mg, 1.2 mmol) in dry THF (10 mL) was added 4-nitrobenzoic acid (801 mg, 4.8 mmol), and PPh_3 (968 mg, 3.7 mmol). The reaction mixture was cooled to 0° C and DIAD (0.94 mL, 4.8 mmol) was added dropwise under N_2. After having been stirred for 12 h at room temperature the reaction mixture was concentrated *in vacuo* and the residue purified by column chromatography (15:1 Hexane/

Ethyl Acetate) to afford **200** (517 mg, 0.80 mmol, 67%) as a mixture of isomers (1:1, E:Z) and as a colourless oil.

Data for *E* anomer

δ_H (600 MHz, $CDCl_3$): 8.17 (2H, d, J = 9.0 Hz, Ar-H), 8.08 (2H, d, J = 9.0 Hz, Ar-H), 7.38-7.21 (15H, m, Ar-H), 7.10 (5H, m, Ar-H), 6.54 (1H, d, $J_{1,2}$ = 16.2 Hz, H-1), 6.24 (1H, dd, $J_{2,1}$ = 16.2 Hz, $J_{2,3}$ = 7.5 Hz, H-2), 5.62 (1H, app dd, $J_{5,6}$ = 4.9 Hz, $J_{5,6'}$ = 10.3 Hz, H-5), 4.86 (1H, d, J = 11.4 Hz, Bn-CH_2), 4.68 (1H, d, J = 11.4 Hz, Bn-CH_2), 4.69 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.51 (1H, d, J = 12.1 Hz, Bn-CH_2), 4.42 (1H, d, J = 12.1 Hz, Bn-CH_2), 4.40 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.21 (1H, dd, $J_{3,2}$ = 7.5 Hz, $J_{3,4}$ = 5.1 Hz, H-3), 4.01 (1H, app t, $J_{4,3}$ = $J_{4,5}$ = 5.1 Hz, H-4), 3..76 (1H, dd, $J_{6,5}$ = 4.9 Hz, $J_{6,6'}$ = 10.3 Hz, H-6), 3.68 (1H, dd, $J_{6',5}$ = 5.8 Hz, $J_{6',6}$ = 10.3 Hz, H-6').

δ_C (150 MHz, $CDCl_3$): 163.8 (C=O), 150.4 (OCOCCH), 138.1, 137.9, 137.8 (q-Ar), 136.2 (q-Ph), 135.5 (CNO_2), 133.5 (C-1), 130.8, 128.6, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.7, 127.7 (Ar-C), 126.1 (C-2), 123.4 (Ar-C), 79.9 (C-4), 79.8 (C-3), 75.1 (Bn-CH_2), 73.7 (C-5), 73.2, 70.7 (Bn-CH_2), 68.0 (C-6).

ν_{max} (film)/cm^{-1}: 1725, 1643 (C=O), 1067 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{40}H_{37}NO_7$ [M + Na]$^+$ 666.2468 Found 666.2458.

Data for *Z* anomer

δ_H (600 MHz, $CDCl_3$): 8.32 (2H, d, J = 8.7 Hz, Ar-H), 8.25 (2H, d, J = 8.7 Hz, Ar-H), 7.36-7.21 (15H, m, Ar-H), 7.10 (5H, m, Ar-H), 6.83 (1H, d, J = 12.3 Hz, H-1), 5.85 (1H, dd, $J_{2,1}$ = 12.3 Hz, $J_{2,3}$ = 9.9 Hz, H-2), 5.57 (1H, m, H-5), 4.87 (1H, d, J = 11.5 Hz, Bn-CH_2), 4.69 (1H, d, J = 11.5 Hz, Bn-CH_2), 4.68 (1H, dd, $J_{3,2}$ = 9.9 Hz, $J_{3,4}$ = 3.9 Hz, H-3), 4.67 (1H, d, J = 12.2 Hz, Bn-

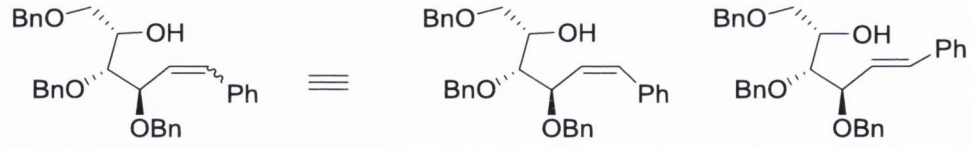
CH_2), 4.42 (1H, d, J = 12.2 Hz, Bn-CH_2), 4.34 (1H, d, J = 11.7 Hz, Bn-CH_2), 4.26 (1H, d, J = 11.7 Hz, Bn-CH_2), 4.11 (1H, dd, $J_{4,3}$ = 3.9 Hz, $J_{4,5}$ = 6.0 Hz, H-4), 3.68 (1H, dd, $J_{6,5}$ = 4.1 Hz, $J_{6,6'}$ = 11.0 Hz, H-6), 3.46 (1H, dd, $J_{6',5}$ = 4.9 Hz, $J_{6',6}$ = 11.0 Hz, H-6').

δ_C (150 MHz, $CDCl_3$): 165.3 (C=O), 150.6 (OCOCCH), 138.0, 137.8, 137.5 (q-Ar), 136.2 (q-Ph), 135.5 (CNO_2), 134.3 (C-1), 130.7 (Ar-C), 129.1 (C-2), 129.2, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.2, 123.4 (Ar-C), 80.5 (C-4), 75.5 (Bn-CH_2), 74.8 (C-5), 73.1 (Bn-CH_2), 72.9 (C-3), 69.9 (Bn-CH_2), 67.9 (C-6).

ν_{max} (film)/cm^{-1}: 1725, 1643 (C=O), 1067 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{40}H_{37}NO_7$ [M + Na]$^+$ 666.2468 Found 666.2458.

5.1.6.10 (3*R*,4*R*,5*S*)-5-Hydroxy-3,4,6-tribenzyloxy-hex-1-styrene (201)



To a stirred solution of the glycosyl *p*-nitrobenzoate **200** (500 mg, 0.78 mmol) in MeOH (10 mL) was added NaOMe (4 mg, 0.08 mmol). The solution was stirred at room temperature for 12 h and neutralised with Dowex H^+ ion exchange resin. The resin was removed by filtration, washed with MeOH and concentrated *in vacuo.* The residue was purified by chromatrography (10:1 Hexane/ Ethyl Acetate) to give **201** (378 mg, 0.76 mmol, 98%) as a mixture of isomers (1:1, E:Z) and as a colourless oil.

Data for *E* anomer

δ_H (600 MHz, $CDCl_3$): 7.46 (2H, m, Ar-H), 7.40-7.30 (18H, m, Ar-H), 6.71 (1H, d, $J_{1,2}$ = 16.3 Hz, H-1), 6.23 (1H, dd, $J_{2,1}$ = 16.3 Hz, $J_{2,3}$ = 8.2

Hz, H-2), 4.96 (1H, d, J = 11.3 Hz, Bn-CH_2), 4.74 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.67 (1H, d, J = 11.3 Hz, Bn-CH_2), 4.51 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.49 (1H, d, J = 11.7 Hz, Bn-CH_2), 4.48 (1H, d, J = 11.7 Hz, Bn-CH_2), 4.34 (1H, app t, $J_{3,2} = J_{3,4}$ = 8.2 Hz, H-3), 4.02 (1H, m, H-5), 3.75 (1H, dd, $J_{4,3}$ = 8.2 Hz, $J_{4,5}$ = 2.6 Hz, H-4), 3.52 (1H, dd, $J_{6,5}$ = 6.2 Hz, $J_{6,6'}$ = 9.3 Hz, H-6), 3.49 (1H, dd, $J_{6',5}$ = 6.1 Hz, $J_{6',6}$ = 9.3 Hz, H-6'), 2.56 (1H, d, $J_{OH,5}$ = 6.9 Hz, OH).

δ_C (150 MHz, $CDCl_3$): 138.3, 138.3, 137.9, 136.3 (q-Ar), 134.1 (C-1), 128.6, 128.3, 128.3, 128.3, 128.3, 127.9, 127.9, 127.9, 127.7, 127.7, 127.5 (Ar-C), 126.5 (C-2), 126.5 (Ar-C), 81.9 (C-3), 80.7 (C-4), 75.2, 73.3 (Bn-CH_2), 71.3 (C-6), 70.8 (Bn-CH_2), 70.2 (C-5).

ν_{max} (film)/cm^{-1}: 2968 (OH), 1021 (C-O).

HRMS (m/z ES^+): Calcd for $C_{33}H_{34}O_4$ [M + Na]$^+$ 517.2355 Found 517.2350.

Data for *Z* anomer

δ_H (600 MHz, $CDCl_3$): 7.39-7.28 (15H, m, Ar-H), 7.23 (3H, m, Ar-H), 7.09 (2H, m, Ar-H), 6.88 (1H, d, $J_{1,2}$ = 11.7 Hz, H-1), 5.75 (1H, dd, $J_{2,1}$ = 11.7 Hz, $J_{2,3}$ = 10.2 Hz, H-2), 4.92 (1H, d, J = 11.4 Hz, Bn-CH_2), 4.71 (1H, dd, $J_{3,2}$ = 10.2 Hz, $J_{3,4}$ = 6.3 Hz, H-3), 4.62 (1H, d, J = 11.4 Hz, Bn-CH_2), 4.55 (1H, d, J = 11.7 Hz, Bn-CH_2), 4.51 (1H, d, J = 12.1 Hz, Bn-CH_2), 4.43 (1H, d, J = 12.1 Hz, Bn-CH_2), 4.16 (1H, d, J = 11.7 Hz, Bn-CH_2), 4.05 (1H, m, H-5), 3.79 (1H, dd, $J_{4,3}$ = 6.3 Hz, $J_{4,5}$ = 3.0 Hz, H-4), 3.45 (1H, dd, $J_{6,5}$ = 5.9 Hz, $J_{6,6'}$ = 9.6 Hz, H-6), 3.42 (1H, dd, $J_{6',5}$ = 5.8 Hz, $J_{6,6'}$ = 9.6 Hz, H-6'), 2.58 (1H, d, $J_{OH,5}$ = 6.9 Hz, OH).

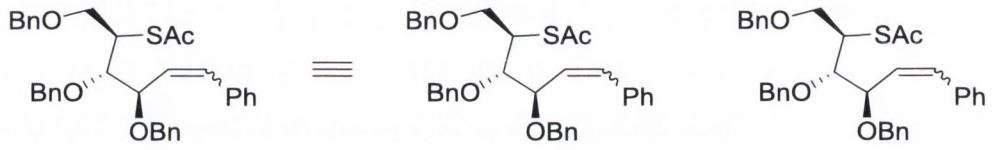
δ_C (150 MHz, $CDCl_3$): 138.3, 138.0, 138.0, 136.4 (q-Ar), 134.6 (C-1), 128.9 (C-2), 128.9, 128.4, 128.3, 128.3, 128.3, 128.2, 128.1, 127.8, 127.7,

127.6, 127.4, 128.3 (Ar-C), 80.7 (C-4), 75.4 (C-3), 75.4 (Bn-CH_2), 73.3 (Bn-CH_2), 71.1 (C-6), 70.2 (Bn-CH_2), 70.1 (C-5).

ν_{max} (film)/cm^{-1}: 2968 (OH), 1021 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{33}H_{34}O_4$ [M + Na]$^+$ 517.2355 Found 517.2350.

5.1.6.11 (3*R*,4*R*,5*R*)-5-Thioacetate-3,4,6-tribenzyloxy-hex-1-styrene (202)



General procedure for the synthesis of thioesters was carried out to prepare **202** as a mixture of isomers (1:1 E:Z). Purification by column chromatography (Hexane/EtOAc, 12:1) furnished **202** as a colourless oil. (252 mg, 0.46 mmol, 60 %).

Data for *E* anomer

δ_H (600 MHz, $CDCl_3$): 7.41-7.15 (20H, m, Ar-H), 6.56 (1H, d, $J_{1,2}$ = 16.0 Hz, H-1), 6.29 (1H, dd, $J_{2,1}$ = 16.0 Hz, $J_{2,3}$ = 8.3 Hz, H-2), 4.78 (1H, d, J = 11.1 Hz, Bn-CH_2), 4.73 (1H, d, J = 11.1 Hz, Bn-CH_2), 4.66 (1H, d, J = 12.1 Hz, Bn-CH_2), 4.48 (1H, d, J = 12.1 Hz, Bn-CH_2), 4.43 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.38 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.23 (1H, dd, $J_{3,2}$ = 8.3 Hz, $J_{3,4}$ = 5.4 Hz, H-3), 3.90 (1H, app t, $J_{4,3}$ = $J_{4,5}$ = 5.4 Hz, H-4), 3.69 (3H, m, H-5, H-6 and H-6') 2.31 (3H, s, SCH_3).

δ_C (150 MHz, $CDCl_3$): 195.2 (C=O), 138.2, 138.0, 137.9, 136.3 (q-Ar), 134.0 (C-1), 128.6, 128.5, 128.2, 128.1, 128.1 128.0, 127.9, 127.8, 127.4, 127.4, 127.3, 127.3 (Ar-C), 126.7 (C-2), 81.7 (C-4), 81.4 (C-3), 74.7, 72.8, 70.4 (Bn-CH_2), 68.8 (C-6), 44.7 (C-5), 30.4 (SCH_3).

ν_{max} (film)/cm^{-1}: 1680 (C=O)

HRMS (*m/z* ES$^+$): Calcd for $C_{35}H_{36}O_4S$ [M + Na]$^+$ 575.2232 Found 575.2230.

Data for *Z* anomer

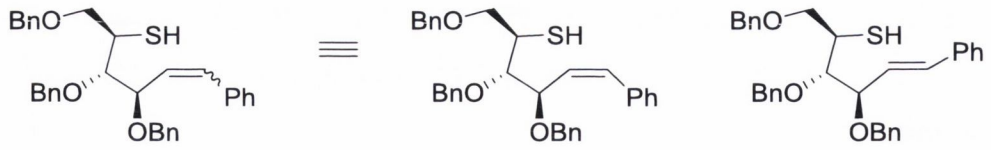
δ_H (600 MHz, $CDCl_3$): 7.41-7.17 (18H, m, Ar-H), 7.09 (2H, m, Ar-H), 6.82 (1H, d, $J_{1,2}$ = 11.9 Hz, H-1), 5.92 (1H, dd, $J_{2,1}$ = 11.9 Hz, $J_{2,3}$ = 9.6 Hz, H-2), 4.70 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.65 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.59 (1H, dd, $J_{3,2}$ = 9.6 Hz, $J_{3,4}$ = 3.7 Hz, H-3), 4.59 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.35 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.32 (1H, m, H-5), 4.27 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.18 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.02 (1H, dd, $J_{4,3}$ = 3.7 Hz, $J_{4,5}$ = 5.9 Hz, H-4), 3.57 (1H, dd, $J_{6,5}$ = 6.1 Hz, $J_{6,6'}$ = 10.2 Hz, H-6), 3.28 (1H, dd, $J_{6',5}$ = 6.8 Hz, $J_{6',6}$ = 10.2 Hz, H-6'), 2.31 (3H, s, SCH_3).

δ_C (150 MHz, $CDCl_3$): 195.7 (C=O), 137.8, 137.5, 137.5, 136.4 (q-Ar), 133.5 (C-1), 129.9 (C-2), 128.7, 128.6, 128.2, 128.1, 128.1, 128.1, 128.0, 127.9, 127.5, 127.3, 127.3, 126.5 (Ar-C), 80.1 (C-4), 74.1 (Bn-CH_2), 73.0 (C-3), 72.9, 70.0 (Bn-CH_2), 69.0 (C-6), 44.2 (C-5), 30.4 (SCH_3).

ν_{max} (film)/cm^{-1}: 1680 (C=O).

HRMS (*m/z* ES$^+$): Calcd for $C_{35}H_{36}O_4S$ [M + Na]$^+$ 575.2232 Found 575.2230.

5.6.1.12 (3*R*,4*R*,5*R*)-5-Thio-3,4,6-tribenzyloxy-hex-1-styrene (203)



General procedure for the hydrolysis of thioesters was carried out to prepare **203** as a mixture of isomers (1:1 E:Z). Purification by column chromatography (Hexane/EtOAc, 15:1) furnished **203** as a colourless oil. (201 mg, 0.39 mmol, 86 %)

Data for *E* anomer

δ_H (600 MHz, $CDCl_3$): 7.42-7.23 (20H, m, Ar-H), 6.64 (1H, d, $J_{1,2}$ = 16.3 Hz, H-1), 6.28 (1H, dd, $J_{2,1}$ = 16.3 Hz, $J_{2,3}$ = 8.1 Hz, H-2), 4.73 (2H, d, J = 11.4 Hz, Bn-CH_2), 4.69 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.64 (2H, d, J = 11.4 Hz, Bn-CH_2), 4.51 (1H, dd, $J_{3,2}$ = 8.1 Hz, $J_{3,4}$ = 3.9 Hz, H-3), 4.40 (1H, d, J = 11.6 Hz, Bn-CH_2), 3.90 (1H, dd, $J_{4,3}$ = 3.9 Hz, $J_{4,5}$ = 9.6 Hz, H-4), 3.72 (2H, m, H-6 and H-6'), 3.36 (1H, m, H-5), 1.88 (1H, d, $J_{SH,5}$ = 9.3 Hz, SH).

δ_C (150 MHz, $CDCl_3$): 138.3, 138.0, 137.9, 136.9 (q-Ar), 133.4 (C-1), 128.9, 128.7, 128.6, 128.4, 128.3, 128.3, 128.3, 127.9, 127.8, 127.7, 127.6, 127.3 (Ar-C), 126.6 (C-2), 84.1 (C-4), 80.1 (C-3), 75.6, 75.5 (Bn-CH_2), 71.5 (C-6), 70.6 (Bn-CH_2), 40.7 (C-5).

ν_{max} (film)/cm^{-1}: 1174 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{33}H_{34}O_3S$ [M + Na]$^+$ 533.2126 Found 533.2119.

Data for *Z* anomer

δ_H (600 MHz, $CDCl_3$): 7.35-7.19 (17H, m, Ar-H), 7.15 (3H, m, Ar-H), 6.98 (2H, d, J = 7.6 Hz, Ar-H), 6.73 (1H, d, $J_{1,2}$ = 12.0 Hz, H-1), 5.83 (1H, d, $J_{2,1}$ = 12.0 Hz, $J_{2,3}$ = 9.8 Hz, H-2), 4.92 (1H, dd, $J_{3,2}$ = 9.8

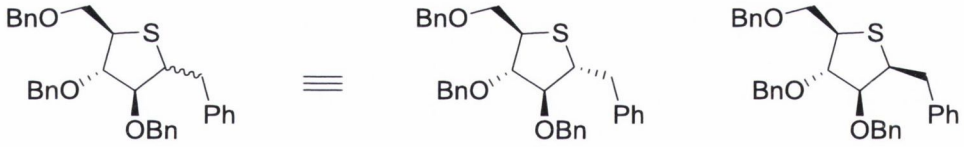
Hz, $J_{3,4}$ = 2.4 Hz, H-3), 4.59 (1H, d, J = 12.2 Hz, Bn-CH_2), 4.50 (4H, m, Bn-CH_2 x 4), 4.15 (1H, d, J = 12.2 Hz, Bn-CH_2), 3.94 (1H, dd, $J_{5,4}$ = 4.3 Hz, $J_{6,6'}$ = 9.4 Hz, H-6), 3.74 (1H, dd, $J_{4,3}$ = 2.4 Hz, $J_{4,5}$ = 9.0 Hz, H-4), 3.59 (1H, dd, $J_{6',5}$ = 3.3 Hz, $J_{6,6'}$ = 9.4 Hz, H-6'), 3.35 (1H, dddd, $J_{5,SH}$ = 9.2 Hz, $J_{5,4}$ = 9.0 Hz, $J_{5,6}$ = 4.3 Hz, $J_{5,6'}$ = 3.3 Hz, H-5), 1.65 (1H, d, $J_{SH,5}$ = 9.2 Hz, SH).

δ_C (150 MHz, $CDCl_3$): 138.3, 138.2, 138.0, 136.5 (q-Ar), 133.6 (C-1), 130.5 (C-2), 128.9, 128.6, 128.44, 128.4, 128.3, 128.3, 128.3127.8, 127.7, 127.7, 127.6, 127.5 (Ar-C), 84.8 (C-4), 73.1, 73.0 (Bn-CH_2), 72.5 (C-3), 71.2 (C-6), 70.1 (Bn-CH_2), 40.6 (C-5).

ν_{max} (film)/cm^{-1}: 1074 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{33}H_{34}O_3S$ [M + Na]$^+$ 533.2126 Found 533.2119.

5.1.6.13 2,3,5-Tri-*O*-benzyl-1-benzyl-D-arabinofuranoside (204/205)



204/205 **204** **205**

General procedure for radical cyclisation was carried out to prepare **204/205** as a mixture of isomers (5:1, α/β). Purification by column chromatography (Hexane/EtOAc, 15:1) furnished **204/205** as a colourless oil. (182 mg, 0.36 mmol, 92 %).

Data for α anomer 204

δ_H (600 MHz, $CDCl_3$): 7.37-7.16 (20H, m, Ar-H), 4.65 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.61 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.54 (2H, d, J = 12.1 Hz, Bn-CH_2), 4.51 (2H, d, J = 12.4 Hz, Bn-CH_2), 4.13 (1H, app t, $J_{3,2}$ = $J_{3,4}$ = 4.7 Hz, H-3), 3.96 (1H, app t, $J_{2,1}$ = $J_{2,3}$

= 4.7 Hz, H-2), 3.67 (1H, dd, $J_{5,4}$ = 8.1 Hz, $J_{5,5'}$ = 9.3 Hz, H-5), 3.60 (2H, m, H-1 and H-4), 3.51 (1H, dd, $J_{5',4}$ = 6.4 Hz, $J_{5',5}$ = 9.3 Hz, H-5'), 3.21 (1H, dd, $J_{C\underline{H}2Ph,C\underline{H}2Ph'}$ = 13.7 Hz, $J_{C\underline{H}2Ph,1}$ = 6.3 Hz, C$\underline{H}_2$Ph), 2.81 (1H, dd, $J_{C\underline{H}2Ph',C\underline{H}2Ph}$ = 13.7 Hz, $J_{C\underline{H}2Ph',1}$ = 8.6 Hz, H-1').

δ_C (150 MHz, $CDCl_3$): 139.4 (q-Ph), 138.1, 138.1, 137.9 (q-Ar), 128.9, 128.9, 128.4, 128.4, 128.4, 128.3, 128.3, 127.8, 127.8, 127.7, 127.7, 127.7 (Ar-C), 88.9 (C-2), 86.9 (C-3), 73.0 (Bn-CH_2), 72.4 (C-5), 72.3, 72.2 (Bn-CH_2), 50.4 (C-1), 48.3 (C-4), 41.3 ($\underline{C}H_2$Ph).

ν_{max} (film)/cm^{-1}: 1100, 1093 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{33}H_{34}O_3S$ [M + Na]$^+$ 533.2126 Found 533.2132.

Data for β anomer 205

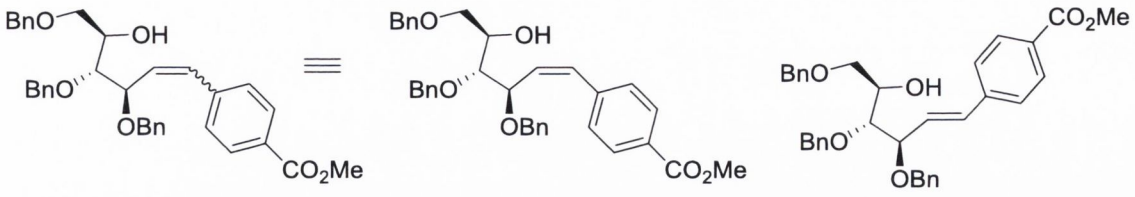
δ_H (600 MHz, $CDCl_3$): 7.39-7.17 (20H, m, Ar-H), 4.67-4.44 (5H, m, Bn-CH_2), 4.36 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.23 (1H, app t, $J_{3,2}$ = $J_{3,4}$ = 2.8 Hz, H-3), 3.93 (1H, app t, $J_{2,1}$ = 2.8 Hz, $J_{2,3}$ = 2.8 Hz, H-2), 3.88 (1H, m, H-1), 3.69 (1H, m, H-5), 3.61 (1H, m, H-4), 3.53 (1H, m, H-5'), 3.15 (1H, dd, $J_{C\underline{H}2Ph,C\underline{H}2Ph'}$ = 13.8 Hz, $J_{C\underline{H}2Ph,1}$ = 6.5 Hz, C$\underline{H}_2$Ph), 2.91 (1H, dd, $J_{C\underline{H}2Ph',C\underline{H}2Ph}$ = 13.8 Hz, $J_{C\underline{H}2Ph',1}$ = 8.7 Hz, H-C$\underline{H}_2$Ph').

δ_C (150 MHz, $CDCl_3$): 140.0 (q-Ph), 138.2, 138.0, 137.8 (q-Ar), 128.9, 128.4, 128.4, 127.9, 127.8, 127.6, 127.6, 127.6, 127.6, 126.4, 126.4, 126.4, 126.4 (Ar-C), 85.3 (C-2), 83.4 (C-3), 73.0 (Bn-CH_2), 72.5 (C-5), 71.7, 71.6 (Bn-CH_2), 51.2 (C-1), 49.7 (C-4), 36.1 ($\underline{C}H_2$Ph).

ν_{max} (film)/cm^{-1}: 1100, 1093 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{33}H_{34}O_3S$ [M + Na]$^+$ 533.2126 Found 533.2132.

5.1.6.14 (3*R*,4*R*,5*R*)-5-Hydroxy-3,4,6-tribenzyloxy-hex-1-vinylbenzoate-4-Methyl (209)



2,3,4-tri-*O*-benzyl-α-D-arabinofuranose **160** (1.00 g, 2.38 mmol), methylbenzoate triphenylphosphonium bromide (3.18 g, 7.14 mmol), potassium carbonate (1.08 g, 7.85 mmol) and 18-crown-6 (377 mg, 1.43 mmol) were added to an oven dried RBF. The reaction mixture was solubilised in dry CH_2Cl_2 (50 mL) under argon and refluxed at 45°C overnight. The reaction mixture was diluted in CH_2Cl_2 (50 mL) and washed with water (50 mL x 2) and brine (50 mL). The organic layer was dried over magnesium sulphate and the solvent was removed *in vacuo*. Purification by column chromatography (Hexane/EtOAc 10:1) afforded **209** as a mixture of isomers (1:1, E:Z) as a colourless oil. (828 mg, 1.49 mmol, 63 %)

Data for *E* anomer

δ_H (600 MHz, $CDCl_3$): 8.02 (2H, d, J = 8.5 Hz, Ar-H), 7.42-7.19 (17H, m, Ar-H), 6.64 (1H, d, $J_{1,2}$ = 16.2 Hz, H-1), 6.41 (1H, dd, $J_{2,1}$ = 16.2 Hz, $J_{2,3}$ = 7.3 Hz, H-2), 4.72-4.40 (6H, m, Bn-CH_2), 4.31 (1H, dd, $J_{3,2}$ = 7.7 Hz, $J_{3,4}$ = 3.9 Hz, H-3), 4.08 (1H, m, H-5), 3.70 (1H, dd, $J_{4,3}$ = 3.9 Hz, $J_{4,5}$ = 6.8 Hz, H-4), 3.66 (2H, m, H-6 and H-6') 2.78 (1H, bd, J = 5.2 Hz, OH).

δ_C (150 MHz, $CDCl_3$): 140.8 (q-CO_2Me), 137.9, 137.7, 137.6, 137.3 (q-Ar), 132.2 (C-1), 131.5 (C-2), 129.8, 128.6, 128.4, 128.3, 128.2, 128.2, 128.1, 127.8, 127.7, 127.6, 127.6 (Ar-C), 80.8 (C-4), 79.4 (C-3), 74.2, 73.4, 71.1 (Bn-CH_2), 70.8 (C-6), 70.4 (C-5), 52.0 (CO_2Me).

ν_{max} (film)/cm^{-1}: 3453 (OH), 1733 (C=O) 1021 (C-O) .

HRMS (*m/z* ES^+): Calcd for $C_{35}H_{36}O_6$ [M + Na]$^+$ 575.2510 Found 575.2413.

Data for *Z* anomer

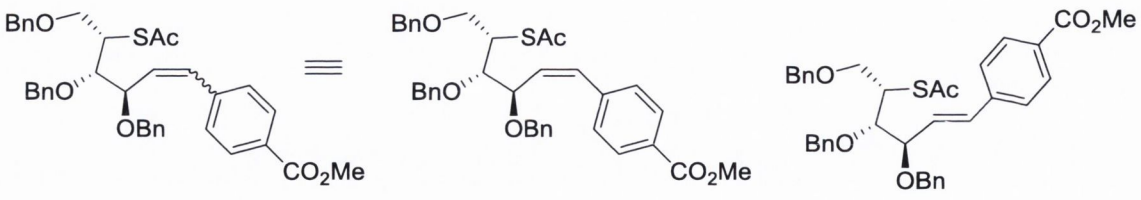
δ_H (600 MHz, $CDCl_3$): 7.88 (2H, d, J = 8.3 Hz, Ar-H), 7.34-7.14 (15H, m, Ar-H), 6.76 (1H, d, $J_{1,2}$ = 12.1 Hz, H-1), 5.98 (1H, dd, $J_{2,1}$ = 12.1 Hz, $J_{2,3}$ = 9.9 Hz, H-2), 4.63 (1H, dd, $J_{3,2}$ = 9.9 Hz, $J_{3,4}$ = 3.0 Hz, H-3), 4.55 (3H, d, J = 11.2 Hz, Bn-CH2), 4.46 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.41 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.17 (1H, d, J = 11.2 Hz, Bn-CH_2), 4.07 (1H, m, H-5), 3.90 (3H, s, CO_2CH_3), 3.68 (1H, dd, $J_{4,3}$ = 3.0 Hz, $J_{4,5}$ = 7.0 Hz, H-4), 3.55 (1H, dd, $J_{6,5}$ = 5.5 Hz, $J_{6,6'}$ = 9.9 Hz, H-6), 3.47 (1H, dd, $J_{6',5}$ = 4.2 Hz, $J_{6',6}$ = 9.9 Hz, H-6'), 2.83 (1H, d, $J_{OH,5}$ = 5.7 Hz, OH).

δ_C (150 MHz, $CDCl_3$): 140.8 (q-CO_2Me), 137.9, 137.7, 137.6, 137.3 (q-Ar), 132.7 (C-1), 129.6 (C-2), 129.5, 129.1, 128.6, 128.4, 128.3, 128.3, 128.2, 128.1, 127.8, 127.6, 127.6 (Ar-C), 80.5 (C-4), 78.3 (Bn-CH_2), 73.4 (C-3), 73.4 (Bn-CH_2), 71.03 (C-6), 70.5 (Bn-CH_2), 70.3 (C-5), 52.0 (CO_2Me).

ν_{max} (film)/cm^{-1}: 3453 (OH), 1733 (C=O) 1021 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{35}H_{36}O_6$ [M + Na]$^+$ 575.2510 Found 575.2413.

5.1.6.15 (3*R*,4*R*,5*S*)-5-Thioacetate-3,4,6-tribenzyloxy-hex-1-vinylbenzoate-Methyl (210)



General procedure for the synthesis of thioesters was carried out to prepare **210** as a mixture of isomers (1:1 E:Z). Purification by column chromatography (Hexane/EtOAc, 12:1) furnished **210** as a colourless oil. (539 mg, 0.88 mmol, 59 %).

Data for *E* anomer

δ_H (600 MHz, $CDCl_3$): 8.02 (2H, d, J = 8.1 Hz, Ar-H), 7.44 (2H, d, J = 8.1 Hz, Ar-H), 7.37-7.24 (15 H, m, Ar-H), 6.64 (1H, d, $J_{1,2}$ 16.1 Hz, H-1), 6.23 (1H, dd, $J_{2,1}$ = 16.1 Hz, $J_{2,3}$ = 4.5 Hz, H-2), 4.94 (1H, d, J = 10.9 Hz, Bn-CH_2), 4.93 (1H, d, J = 11.3 Hz, Bn-CH_2), 4.65 (1H, d, J = 11.3 Hz, Bn-CH_2), 4.63 (1H, d, J = 10.9 Hz, Bn-CH_2), 4.49 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.40 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.29 (1H, app t, $J_{3,2} = J_{3,4}$ = 7.4 Hz, H-3), 4.13 (1H, dd, $J_{4,3}$ = 7.4 Hz, $J_{4,5}$ = 2.1 Hz, H-4), 4.03 (1H, m, H-5), 3.94 (3H, s, CO_2Me), 3.64 (1H, app t, $J_{6,5} = J_{6,6'}$ = 9.7 Hz, H-6), 3.41 (1H, dd, $J_{6',5}$ = 5.6 Hz, $J_{6',6}$ = 9.7 Hz, H-6'), 2.29 (3H, s, SCH_3).

δ_C (150 MHz, $CDCl_3$): 194.7 (C=O), 140.9 (q-CO_2Me), 138.6, 138.6, 138.3, 137.9 (q-Ar), 132.7 (C-1), 129.9 (Ar-C), 128.9 (C-2), 128.7, 128.4, 128.3, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 126.5 (Ar-C), 82.7 (C-3), 79.9 (C-4), 75.4, 75.1, 70.7 (Bn-CH_2), 69.9 (C-6), 52.1 (CO_2Me), 45.1 (C-5), 30.6 (SCH_3).

ν_{max} (film)/cm^{-1}: 1740, 1680 (C=O), 1027 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{37}H_{38}O_6S$ [M + Na]$^+$ 633.2287 Found 633.2298.

Data for *Z* anomer

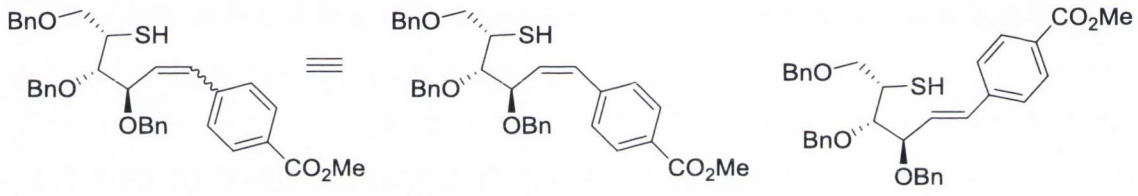
δ_H (600 MHz, $CDCl_3$): 7.90 (2H, d, J = 8.2 Hz, Ar-H), 7.36-7.25 (14H, m, Ar-H), 7.22 (1H, m, Ar-H), 6.76 (1H, d, $J_{1,2}$ = 12.3 Hz, H-1), 5.69 (1H, app t, $J_{2,1} = J_{2,3}$ = 12.3 Hz, H-2), 4.75 (1H, m, H-3), 4.64 (2H, m, Bn-CH_2), 4.47 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.46 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.39 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.38 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.14 (1H, dd, $J_{4,3}$ = 4.9 Hz, $J_{4,5}$ = 2.4 Hz, H-4), 3.94 (3H, s, CO_2Me), 3.98 (1H, m, H-5), 3.59 (1H, app t, $J_{6,5} = J_{6,6'}$ = 9.7 Hz, H-6), 3.36 (1H, dd, $J_{6',5}$ = 5.1 Hz, $J_{6',6}$ = 9.7 Hz, H-6'), 2.06 (3H, s, SCH_3).

δ_C (150 MHz, $CDCl_3$): 194.4 (C=O), 140.9 (q-CO_2Me), 138.6, 138.6, 138.3, 137.9 (q-Ar), 133.5 (C-1), 130.5 (C-2), 129.5, 128.7, 128.4, 128.4, 128.4, 128.3, 128.3, 127.8, 127.7, 127.6, 127.5 (Ar-C), 79.4 (C-4), 76.9 (C-3), 72.8, 72.7, 71.3 (Bn-CH_2), 69.9 (C-6), 52.1 (CO_2Me), 45.4 (C-5), 30.4 (SCH_3).

ν_{max} (film)/cm^{-1}: 1740, 1680 (C=O), 1027 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{37}H_{38}O_6S$ [M + Na]$^+$ 633.2287 Found 633.2298.

5.1.6.16 (3*R*,4*R*,5*S*)-5-Thio-3,4,6-tribenzyloxy-hex-1-vinylbenzoate-4-Methyl (206)



To a degassed solution of **210** (530 mg, 0.87 mmol) in MeOH was added freshly prepared NaOMe (0.01 M soln) at -10°C, after having been stirred for 30 minutes the reaction mixture was quenched by the addition of Dowex H^+ ion exchange resin until pH neutral. The resin was removed by filtration, washed with MeOH and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (20:1 Hexane/ Ethyl Acetate) to afford **206** as a colourless oil (366 mg, 0.64 mmol, 73 %).

Data for *E* anomer

δ_H (600 MHz, $CDCl_3$): 8.03 (2H, d, J = 8.3 Hz, Ar-H), 7.47 (2H, t, J = 7.2 Hz, Ar-H), 7.40-7.15 (15H, m, Ar-H), 6.78 (1H, d, $J_{1,2}$ = 16.1 Hz, H-1), 6.26 (1H, dd, $J_{2,1}$ = 16.1 Hz, $J_{2,3}$ = 8.2 Hz, H-2), 4.67 - 4.63 (4H, m, Bn-CH_2), 4.49 (1H, app t, $J_{3,2} = J_{3,4}$ = 8.2 Hz, H-3), 4.36 (1H, d, J = 12.2 Hz, Bn-CH_2), 4.27 (1H, d, J = 12.2 Hz, Bn-CH_2), 4.05 (1H, dd, $J_{4,3}$ = 8.2 Hz, $J_{4,5}$ = 2.3 Hz, H-4), 3.56 (2H, m, H-6 and H-6'), 3.06 (1H, m, H-5), 3.94 (3H, s, CO_2Me), 1.75 (1H, d, $J_{5,SH}$ = 10.6 Hz, SH).

δ_C (150 MHz, $CDCl_3$): 191.5 (C=O), 139.0 (q-CO_2Me), 138.7, 138.3, 138.0, 136.3 (q-Ar), 133.4 (C-1), 130.1, 129.6 (Ar-C), 129.4 (C-2), 128.4, 128.4, 128.3, 128.3, 128.2, 127.8, 127.7, 127.6, 127.6 (Ar-C), 83.7 (C-3), 79.5 (C-4), 75.3, 75.1 (Bn-CH_2), 72.8 (C-6), 72.5 (Bn-CH_2), 52.4 (CO_2Me), 41.1 (C-5).

ν_{max} (film)/cm^{-1}: 1039 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{35}H_{36}O_5S$ [M + Na]$^+$ 591.2181 Found 591.2192.

Data for *Z* anomer

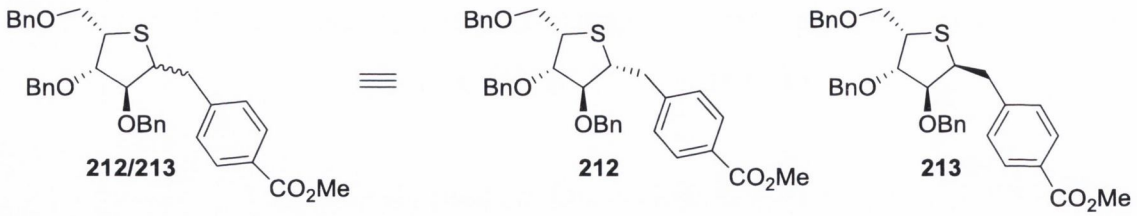
δ_H (600 MHz, $CDCl_3$): 7.96 (2H, d, J = 8.1 Hz, Ar-H), 7.40-7.15 (17H, m, Ar-H), 6.83 (1H, d, $J_{1,2}$ = 12.4 Hz, H-1), 5.75 (1H, app t, $J_{2,1} = J_{2,3}$ = 12.4 Hz, H-2), 5.03 (1H, d, J = 12.2 Hz, Bn-CH_2), 4.95 (1H, d, J =12.2 Hz, Bn-CH_2), 4.83 (1H, dd, $J_{3,2}$ = 12.4 Hz, $J_{3,4}$ = 6.9 Hz, H-3), 4.67 - 4.63 (4H, m, Bn-CH_2), 4.01 (1H, dd, $J_{4,3}$ = 6.9 Hz, $J_{4,5}$ = 3.1 Hz, H-4), 3.46 (2H, m, H-6 and H-6'), 3.15 (1H, m, H-5), 3.94 (3H, s, CO_2Me).

δ_C (150 MHz, $CDCl_3$): 192.3 (C=O), 140.9 (q-CO_2Me), 138.3, 137.9, 134.9, 134.3 (q-Ar), 133.4 (C-1), 130.6 (C-2), 129.8, 129.7, 129.4, 128.7, 128.4, 128.3, 128.1, 128.1, 127.8, 127.5, 126.8 (Ar-C), 80.3 (C-4), 76.3 (C-3), 73.2, 72.8 (Bn-CH_2), 72.8 (C-6), 72.6 (Bn-CH_2), 51.9 (CO_2Me), 41.1 (C-5).

ν_{max} (film)/cm^{-1}: 1039 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{35}H_{36}O_5S$ [M + Na]$^+$ 591.2181 Found 591.2192.

5.1.6.17 2,3,5-Tri-*O*-benzyl-1-(4-methylbenzoate)-L-xylofuranoside (212/213)



General procedure for radical cyclisation was carried out to prepare **212/213** as a mixture of isomers (5:1, α/β). Purification by column chromatography (Hexane/EtOAc, 15:1) furnished **212/213** as a colourless oil. (81 mg, 0.14 mmol, 89 %).

Data for α anomer 213

δ_H (600 MHz, $CDCl_3$): 7.94 (4H, m, C_2H_4), 7.39-7.22 (15H, m, Ar-H), 4.62 (1H, d, J =11.9 Hz, Bn-CH_2), 4.59 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.52 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.51(1H, d, J = 11.6 Hz, Bn-CH_2), 4.42 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.34 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.18 (1H, app t, $J_{3,2} = J_{3,4}$ = 3.5 Hz, H-3), 3.94 (2H, m, H-2 and H-4), 3.92 (3H, s, CO_2Me), 3.84 (1H, app t, $J_{5,4} = J_{5,5'}$ = 8.6 Hz, H-5), 3.78 (1H, m, H-1), 3.56 (1H, dd, $J_{5',5}$ = 8.6 Hz, $J_{5',4}$ = 6.8 Hz, H-5'), 3.09 (1H, dd, $J_{C\underline{H}2Ar,C\underline{H}2Ar'}$ = 13.3 Hz, $J_{C\underline{H}2Ar,1}$ = 7.2 Hz, C$\underline{H}_2$Ar), 3.01 (1H, dd, $J_{C\underline{H}2Ar',C\underline{H}2Ar}$ = 13.3 Hz, $J_{C\underline{H}2Ar',1}$ = 8.8 Hz, C$\underline{H}_2$Ar').

δ_C (150 MHz, $CDCl_3$): 166.0 (C=O), 145.0, 137.9, 137.8, 137.8, 137.5 (q-Ar), 130.3, 128.9, 128.9, 128.8, 128.5, 128.4, 127.7, 127.3, 127.1, 126.9, 126.8, (Ar-C), 83.6 (C-2), 81.7 (C-3), 72.8, 72.6, 71.9 (Bn-CH_2), 69.8 (C-5), 52.2 ($CO_2\underline{Me}$), 50.2 (C-1), 46.8 (C-4), 36.3 ($\underline{C}H_2Ar$).

ν_{max} (film)/cm^{-1}: 1762 (C=O), 1050 (C-O) cm^{-1}

HRMS (*m/z* ES^+): Calcd for $C_{35}H_{36}O_5S$ [M + Na]$^+$ 575.2410 Found 575.2400.

Data for β anomer 212

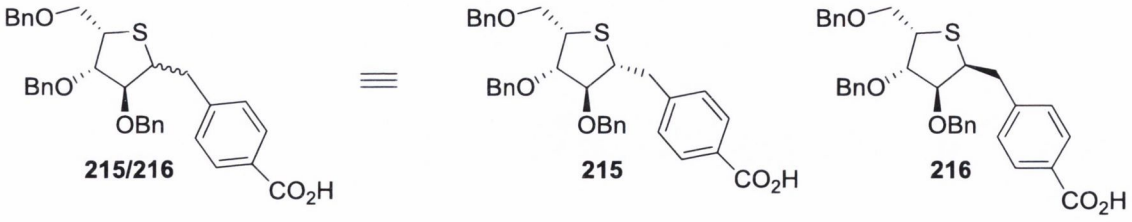
δ_H (600 MHz, $CDCl_3$): 7.37-7.23 (17H, m, Ar-H), 7.17 (1H, d, J = 8.3 Hz, Ar-H), 7.13 (1H, m, Ar-H), 4.58 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.57 (2H, d, J = 12.2 Hz, Bn-CH_2), 4.53 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.52 (2H, d, J = 11.5 Hz, Bn-CH_2), 4.18 (1H, app t, $J_{3,2} = J_{3,4}$ = 4.8 Hz, H-3), 3.91 (1H, app t, $J_{2,1} = J_{2,3}$ = 4.8 Hz, H-2), 3.86 (1H, dd, $J_{5,4}$ = 6.9 Hz, $J_{5,5'}$ = 9.4 Hz, H-5), 3.79 (1H, m, H-4), 3.62 (1H, dd, $J_{5',4}$ = 5.6 Hz, $J_{5',5}$ = 9.4 Hz, H-5'), 3.61 (3H, s, CO_2Me), 3.54 (1H, m, H-1), 3.15 (1H, dd, $J_{C\underline{H}2Ar,1}$ = 6.7 Hz, $J_{C\underline{H}2Ar,C\underline{H}2Ar'}$ = 13.5 Hz, C$\underline{H}_2$Ar), 2.91 (1H, dd, $J_{C\underline{H}2Ar',1}$ = 8.2 Hz, $J_{C\underline{H}2Ar',C\underline{H}2Ar}$ = 13.5 Hz, C$\underline{H}_2$Ar').

δ_C (150 MHz, $CDCl_3$): 166.6 (C=O), 145.1, 137.8, 137.7, 137.6, 137.5 (q-Ar), 130.3, 128.9, 128.9, 128.7, 127.9, 127.6, 127.4, 127.4, 127.3, 127.3, 126.9 (Ar-C), 85.1 (C-2), 84.7 (C-3), 73.4, 72.2, 71.6 (Bn-CH_2), 68.9 (C-5), 52.1 ($CO_2\underline{Me}$), 49.7 (C-1), 48.5 (C-4), 41.7 ($\underline{C}H_2Ar$).

ν_{max} (film)/cm^{-1}: 1762 (C=O), 1050 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{35}H_{36}O_5S$ [M + Na]$^+$ 591.2181 Found 591.2194.

5.1.6.18 2,3,5-Tri-*O*-benzyl-1-(4-benzoicacid)-L-xylofuranoside (215/216)



212/213 (80 mg, 0.14 mmol) was dissolved in THF (1mL) and water (10 mL) added. To this mixture was added dropwise with stirring NaOH (2.5 M, 3.5 mmol) aqueous solution. The reaction mixture was heated to 100°C overnight. The reaction mixture was acidified

with 1 M HCl at 0°C until pH neutral, saturated with NaCl (50 mL) and extracted with ethyl acetate (25 mL x 4). The crude reaction mixture was dried over magnesium sulphate, concentrated in vacuo and used directly in the following step. **215/216** (69 mg, 0.12 mmol, 88 %).

Data for α anomer 216

δ_H (600 MHz, $CDCl_3$): 8.03 (2H, m, C_2H_4), 7.41-7.22 (17H, m, Ar-H), 4.61 (2H, m, Bn-CH_2), 4.54 (4H, m, Bn-CH_2), 4.21 (1H, m, H-3), 3.92 (2H, m, H-1 and H-4), 3.88 (1H, app t, $J_{5,4} = J_{5,5'} = 8.6$ Hz, H-5), 3.82 (1H, m, H-2), 3.61 (1H, dd, $J_{5,4} = 6.3$ Hz, $J_{5,5'} = 8.6$ Hz, H-5'), 3.12 (1H, dd, $J_{CH2Ar,CH2Ar'} = 13.5$ Hz, $J_{CH2Ar,1} = 6.9$ Hz, $\underline{C}H_2Ar$), 3.04 (1H, dd, $J_{C\underline{H}2Ar',C\underline{H}2Ar} = 13.5$ Hz, $J_{C\underline{H}2Ar',1} = 8.6$ Hz, $C\underline{H}_2Ar'$).

δ_C (150 MHz, $CDCl_3$): 171.6 (C=O), 146.4 ($\underline{C}CO_2H$), 137.9, 137.8, 137.7, 137.6 (q-Ar), 130.2, 128.8, 128.4, 128.3, 127.8, 127.8, 127.7, 127.7, 127.5, 127.5, 127.4 (Ar-C), 83.5 (C-2), 81.7 (C-3), 73.2, 72.8, 71.9 (Bn-CH_2), 67.8 (C-5), 50.3 (C-1), 48.5 (C-4), 36.3 ($\underline{C}H_2Ar$).

ν_{max} (film)/cm^{-1}: 1710 (CO_2H), 1041 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{34}H_{34}O_5S$ [M + Na]$^+$ 577.2025 Found 577.2038.

Data for β anomer 215

δ_H (600 MHz, $CDCl_3$): 7.41-7.22 (17H, m, Ar-H), 7.21 (1H, d, J = 8.2 Hz, Ar-H), 7.16 (1H, m, Ar-H), 4.81 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.60 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.59 (1H, d, J = 11.5 Hz, Bn-CH_2), 4.52 (1H, d, J = 11.5 Hz, Bn-CH_2), 4.44 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.36 (1H, d, J = 11.8 Hz, BnCH_2), 4.20 (1H, app t, $J_{3,2} = J_{3,4} = 4.8$ Hz, H-3), 3.94 (1H, app t, $J_{2,1} = J_{2,3} = 4.8$ Hz, H-2), 3.89 (1H, dd, $J_{5,4} = 6.7$ Hz, $J_{5,5'} = 9.3$ Hz, H-5), 3.82 (1H, m, H-4), 3.65 (1H, dd, $J_{5',4} = 6.1$ Hz, $J_{5',5} = 9.3$

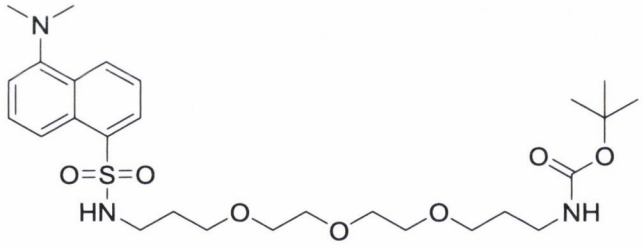
Hz, H-5'), 3.58 (1H, m, H-1), 3.18 (1H, dd, $J_{CH2Ar,1}$ = 7.8 Hz, $J_{CH2Ar,CH2Ar'}$ = 13.8 Hz, CH_2Ar), 2.94 (1H, dd, $J_{CH2Ar',1}$ = 8.4 Hz, $J_{CH2Ar',CH2Ar}$ = 13.8 Hz, CH_2Ar').

δ_C (150 MHz, $CDCl_3$): 171.5 (C=O), 145.9 (CCO_2H), 137.9, 137.7, 137.7, 137.6 (q-Ar), 129.0, 128.8, 128.4, 128.4, 128.3, 128.3, 127.7, 127.7, 127.7, 127.7, 127.5, 127.7 (Ar-C), 85.4 (C-2), 84.6 (C-3), 73.2, 72.6, 71.9 (Bn-CH_2), 69.6 (C-5), 49.7 (C-1), 46.9 (C-4), 41.6 (CH_2Ar).

ν_{max} (film)/cm^{-1}: 1710 (CO_2H), 1041 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{34}H_{34}O_5S$ [M + Na]$^+$ 577.2025 Found 577.2038.

5.1.6.19 Dansyl-PEG-BOC (218)



To a solution of dansyl chloride (259 mg, 0.96 mmol) and BOC-PEG-amine (85 mg, 0.32 mmol) in dry CH_2Cl_2 (10 mL) was added triethylamine (0.13 mL, 0.96 mmol). The reaction mixture was stirred at room temperature overnight, upon completion the solvent was removed *in vacuo* and the residue purified by column chromatography (EtOAc/ Hexane 3:1) to afford **218** as a colourless oil (472 mg, 0.85 mmol, 89%)

δ_H (600 MHz, $CDCl_3$): 8.57 (1H, app s, Ar-H), 8.36 (1H, bd, J = 6.7 Hz, Ar-H), 8.27 (1H, d, J = 7.4 Hz, Ar-H), 7.59 (1H, t, J = 8.4 Hz, Ar-H), 7.55 (1H, t, J = 7.9 Hz, Ar-H), 7.23 (1H, app s, Ar-H), 5.73 (1H, app s, NH), 4.99 (1H, app s, NH), 3.67 (2H, m, CH_2), 3.64 (4H, m, CH_2), 3.54 (2H, app t, J = 5.9 Hz, CH_2), 3.52 (2H, m, CH_2), 3.46 (2H, t, J = 5.9 Hz, CH_2), 3.23 (2H, m,

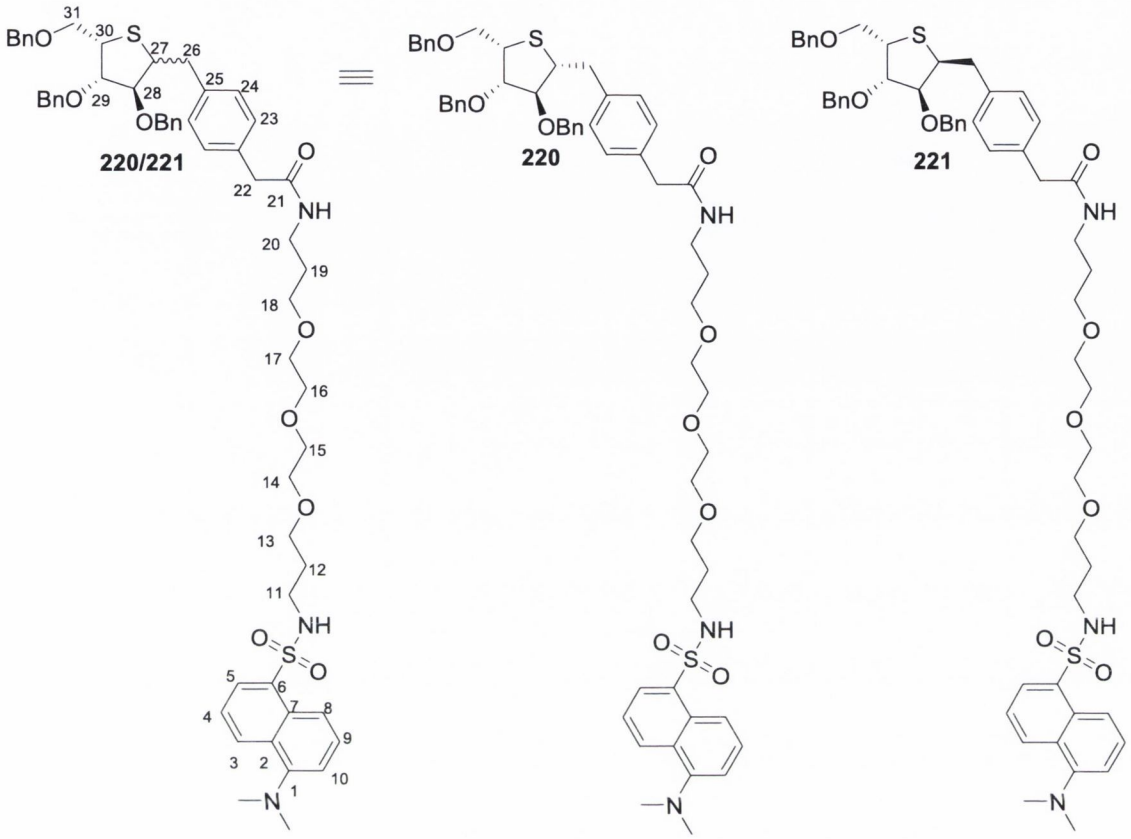
CH_2), 3.07 (2H, q, J = 5.9 Hz, CH_2), 2.93 (6H, s, NMe_2), 1.77 (2H, quintet, J = 5.9 Hz, CH_2), 1.67 (2H, quintet, J = 6.0 Hz, CH_2), 1.44 (9H, s, BOC-CH_3).

δ_C (150 MHz, $CDCl_3$): 155.9 (C=O), 135.0, 129.9 (q-Ar), 129.9, 129.6, 129.6, (Ar-C), 129.4, 127.9 (q-Ar), 127.9, 123.1, 115.1 (Ar-C), 78.7 (CMe3), 70.5, 70.4, 70.1, 69.9, 69.8, 69.4 (CH_2), 45.3 (NMe_2), 42.1, 38.4, 29.4, 28.5 (CH_2), 28.3 (BOC-CH_3).

ν_{max} (film)/cm^{-1}: 3082 (Aromatic C-H), 1629 (HN=O), 1150 (S=O).

HRMS (*m/z* ES^+): Calcd for $C_{27}H_{43}N_3O_7S$ [M + Na]$^+$ 576.2719 Found 576.2717.

5.1.6.20 2,3,5-Tri-*O*-benzyl-1-(4-benzoicacid-PEG-DANSYL)-L-xylofuranoside (220/221)



To a solution of **218** (66 mg, 0.12 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (1 mL) the reaction mixture was allowed to stir for ten minutes at room temperature. The solvent was removed *in vacuo* and co-evaporated with DIPEA (0.02 mL,1.2 mmol). The resultant residue was dissolved in dry DMF (1 mL) under argon and **215/216** (55 mg, 0.1 mmol) added. To the reaction mixture was added O-(7-Azabenzotriazole-1-yl)-N,N,N,N'-tetramethyluronium hexafluorophosphate (HATU, 57 mg, 0.15 mmol) and DIPEA (35 µL,0.2 mmol). The reaction mixture was left to stir overnight at room temperature under argon. The solvent was removed in vacuo and the residue purified by column chromatography (EtOAc/Hexane 4:1) to yield **220/221** as a yellow oil (80 mg, 0.08 mmol, 81%).

Data for α anomer 221

δ_H (600 MHz, $CDCl_3$): 8.52 (1H, d, $J_{3,4}$ = 8.6 Hz, H-3), 8.35 (1H, d, $J_{8,9}$ = 8.6 Hz, H-8), 8.24 (1H, d, $J_{5,4}$ = 8.6 Hz, H-5), 7.68 (2H, t, $J_{23,24}$ = 6.8

Hz, H-23), 7.55 (1H, t, $J_{9,8} = J_{9,10} = 8.6$ Hz, H-9), 7.52 (1H, t, $J_{4,3} = J_{4,5} = 8.6$ Hz, H-4), 7.40-7.22 (14H, m, Ar-H), 7.21 (1H, d, $J = 8.6$ Hz, H-10), 7.16 (1H, d, $J = 7.9$ Hz, Bn-Ar-H), 7.12 (2H, d, $J_{24,23} = 6.8$ Hz, H-24), 7.03 (1H, t, $J = 5.3$ Hz, CONH), 5.81 (1H, t, $J = 5.7$ Hz, $NHSO_2$), 4.61 (1H, d, $J = 11.9$ Hz, Bn-CH_2), 4.58 (1H, d, $J = 11.9$ Hz, Bn-CH_2), 4.56 (1H, d, $J = 11.6$ Hz, Bn-CH_2), 4.54 - 4.48 (3H, m, Bn-CH_2), 4.17 (1H, app t, $J_{29,28} = J_{29,30} = 5.1$ Hz, H-29), 3.93 (1H, app t, $J_{28,27} = J_{28,29} = 5.1$ Hz, H-28), 3.87 (1H, dd, $J_{31,30} = 6.8$ Hz, $J_{31,31'} = 9.3$ Hz, H-31), 3.78 (1H, m, H-30), 3.62-3.60 (1H, m, H-31', H-14 (x2), H-15 (x2), H-16 (x2), H-18 (x2), H-20 (x2)), 3.52 (1H, m, H-27), 3.43 (2H, m, H-17), 3.39 (2H, t, $J = 5.9$ Hz, H-13), 3.13 (1H, dd, $J_{26,27} = 6.7$ Hz, $J_{26,26'} = 13.7$ Hz, H-26), 3.02 (2H, q, $J = 5.9$ Hz, H-11), 2.92 (6H, s, NMe_2), 2.86 (1H, dd, $J_{26,27} = 8.6$ Hz, $J_{26,26'} = 13.7$ Hz, H-26'), 1.89 (2H, m, H-19 (x2)), 1.62 (2H, quintet, $J = 5.8$ Hz, H-12 (x2)).

δ_C (150 MHz, $CDCl_3$): 167.4 (C-21), 151.3 (C-1), 143.1 (C-25), 138.2, 137.9, 137.9 (q-Bn-Ar), 135.1 (C-6), 132.8 (C-22), 129.9 (C-3), 129.7 (C-2), 129.5 (C-5), 129.0 (C-24) 128.5, 128.4, 128.4 (Ar-C), 128.2 (C-9), 127.8, 127.8, 127.8 (Ar-C), 127.1 (C-23), 119.5 (C-7), 119.5 (C-8), 115.3 (C-10), 113.5 (C-4), 85.8 (C-28), 84.7 (C-29), 73.3, 72.7, 72.1 (Bn-CH_2), 70.5 (C-15), 70.4 (C-16), 70.2 (C-18), 70.1 (C-14), 69.9 (C-13), 69.8 (C-17), 69.7 (C-31), 50.0 (C-27), 46.9 (C-30), 45.5 (NMe_2), 42.1 (C-11), 41.6 (C-26), 38.4 (C-20), 29.0 (C-19), 28.6 (C-12).

ν_{max} (film)/cm^{-1}: 3059 (Aromatic C-H), 1692 (HN=O), 1045 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{56}H_{67}N_3O_9S_2$ [M + Na]$^+$ 1012.4217 Found 1012.4225.

Data for β anomer 220

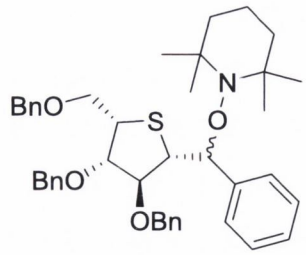
δ_H (600 MHz, $CDCl_3$): 8.52 (1H, d, $J_{3,4}$ = 8.6 Hz, H-3), 8.35 (1H, d, $J_{8,9}$ = 8.6 Hz, H-8), 8.24 (1H, d, $J_{5,4}$ = 8.6 Hz, H-5), 7.67 (2H, t, $J_{23,24}$ = 6.8 Hz, H-23), 7.55 (1H, t, $J_{9,8} = J_{9,10}$ = 8.6 Hz, H-9), 7.52 (1H, t, $J_{4,3} = J_{4,5}$ = 8.6 Hz, H-4), 7.40 – 7.22 (15H, m, Ar-H), 7.21 (1H, d, $J_{10,9}$ = 8.6 Hz, H-10), 7.18 (2H, d, $J_{24,23}$ = 6.8 Hz, H-24), 7.03 (1H, t, $J_{NH,20}$ = 5.3 Hz, CONH), 5.81 (1H, t, $J_{NH,11}$ = 5.7 Hz, $NHSO_2$), 4.54-4.48 (4H, m, Bn-CH_2), 4.41 (1H, d, J = 12.6 Hz, Bn-CH_2), 4.39 (1H, d, J = 12.6 Hz, Bn-CH_2), 4.16 (1H, app t, $J_{29,28} = J_{29,30}$ = 4.3 Hz, H-29), 3.98 (1H, m, H-30), 3.92 (1H, app t, $J_{28,27} = J_{28,29}$ = 4.3 Hz, H-28), 3.86 (1H, m, H-27), 3.82 (1H, dd, $J_{31,30}$ = 5.9 Hz, $J_{31,31'}$ = 10.1 Hz, H-31), 3.68 (1H, dd, $J_{31',30}$ = 5.2 Hz, $J_{31',31}$ = 10.1 Hz, H-31'), 3.66 (10H, m, H-14 (x2), H-15 9x2), H-16 (x2), H-18 (x2), H-20 (x2)), 3.43 (2H, m, H-17 (x2)), 3.39 (2H, t, J = 5.9 Hz, H-13), 3.07 (1H, dd, $J_{26,27}$ = 6.7 Hz, $J_{26,26'}$ = 13.8 Hz, H-26), 3.02 (2H, q, J = 5.9 Hz, H-11), 2.96 (1H, d, $J_{26,27}$ = 8.1 Hz, $J_{26',26}$ = 13.8 Hz, H-26'), 2.92 (6H, s, NMe_2), 1.89 (2H, m, H-19 (x2)), 1.62 (2H, quintet, J = 5.8 Hz, H-12 (x2)).

δ_C (150 MHz, $CDCl_3$): 167.4 (C-21), 151.3 (C-1), 143.6 (C-25), 138.2, 137.9, 137.9 (q-Bn-Ar), 135.1 (C-6), 132.7 (C-22), 129.9 (C-3), 129.7 (C-2), 129.5 (C-5), 128.6, 128.5, 128.4 (Ar-C), 128.3 (C-24), 128.2 (C-9), 127.9, 127.8, 127.8 (Ar-C), 127.1 (C-23), 119.5 (C-7), 119.5 (C-8), 115.3 (C-10), 113.5 (C-4), 83.7 (C-28), 81.8 (C-29), 73.3, 72.8, 72.0 (Bn-CH_2), 70.5 (C-15), 70.4 (C-16), 70.2 (C-18), 70.1 (C-14), 69.9 (C-13), 69.8 (C-17), 69.1 (C-31), 50.6 (C-27), 48.6 (C-30), 45.5 (NMe_2), 42.1 (C-11), 36.1 (C-26), 38.4 (C-20), 29.0 (C-19), 28.6 (C-12).

ν_{max} (film)/cm^{-1}: 3059 (Aromatic C-H), 1692 (HN=O), 1045 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{56}H_{67}N_3O_9S_2$ [M + Na]$^+$ 1012.4217 Found 1012.4225.

5.6.1.21 2,3,6-Tri-*O*-benzyl-1-benzyl-6-TEMPO-L-xylofuranoside (222)



197 (43 mg, 0.08 mmol) was dissolved in dry DMF (1 mL) and the solution was degassed under argon. 2,2-Dimethoxy-2-phenyl-acetophenone (DPAP) (22 mg, 0.08 mmol) and 4-Methoxyacetophenone (22 mg, 0.8 mmol) and TEMPO (62 mg, 0.4 mmol) were added in one portion and the resultant solution was irradiated under UV for 1 h without agitation. DMF was removed *in vacuo* and the crude reaction mixture was purified by column chromatography (30:1 Hexane/Ethyl Acetate) to afford **222** (37 mg, 0.06 mmol, 70%) as a single isomer.

δ_H (600 MHz, $CDCl_3$): 7.68-7.51 (20H, m, Ar-H), 5.02 (1H, d, $J_{6,1}$ = 5.0 Hz, H-6), 4.86 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.65 (1H, d, J = 11.4 Hz, Bn-CH_2), 4.57 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.51 (3H, m, Bn-CH_2), 4.25 (2H, m, H-2 and H-3), 3.71 (1H, t, $J_{1,6} = J_{1,2}$ = 5.0 Hz, H-1), 3.49 (1H, dd, $J_{5,4}$ = 3.1 Hz, $J_{5,5'}$ = 10.2 Hz, H-5), 3.45 (1H, dd, $J_{5',4}$ = 5.7 Hz, $J_{5',5}$ = 10.2 Hz, H-5'), 2.31 (1H, m, H-4), 1.40-1.23 (6H, m, CH_2 TEMPO), 0.89 (12H, m, CH_3 TEMPO)

δ_C (150 MHz, $CDCl_3$): 138.5, 138.2, 137.6, 137.4 (q-Ar), 129.9, 129.9, 129.6, 129.6, 129.3, 128.3, 128.2, 127.8, 127.5, 127.5, 127.3, 126.9 (Ar-C), 82.6 (C-4), 82.5 (C-3), 78.4, 77.6, 77.1 (Bn-CH_2), 68.1 (C-5), 59.5 (C-6), 50.1 (C-1), 49.4 (C-4), 29.7 (CH_2 TEMPO), 20.1 (q-C TEMPO), 14.2 (CH_3 TEMPO)

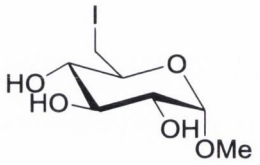
ν_{max} (film)/cm^{-1}: 3080 (Aromatic C-H), 1040 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{42}H_{51}NO_4S$ [M + Na]$^+$ 688.3436 Found 688.3442.

5.2 Experimental data for chapter 3

5.2.1 Synthesis of aldoxime ethers and esters

5.2.1.1 Methyl-6-deoxy-6-iodo-α-D-glucopyranoside 226[288]

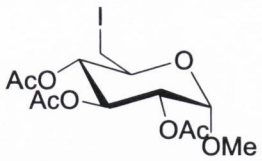


Methyl-α-D-glucopyranoside **225** (3.00 g, 15.4 mmole), PPh_3 (6.08g, 23.2 mmol) and imidazole (2.04 g, 30 mmol) were dissolved in THF (50 mL) and the reaction mixture was heated to reflux (70°C) for 2 hours. Iodine (5.88 g, 23.2 mmol) in THF (10 mL) was added dropwise to the reaction mixture, a colour change from colourless to brown was noted and the appearance of a white precipitate (imidazole hydroiodide) was observed. The reaction mixture was heated at reflux for a further 3 hours, the progression of the reaction was monitored by TLC (EtOAc/THF, 4:1), upon completion the reaction mixture was cooled to room temperature, filtered and concentrated to a yellow syrup. The crude reaction mixture was dissolved in EtOAc (200 mL) and extracted with water (5 x 25 mL). The combined aqueous extracts were concentrated to give **226** (4.11 g, 13.5 mmol 88%) as a white solid.

δ_H (400 MHz, MeOD): 4.68 (1H, d, $J_{1,2}$ = 3.7 Hz, H-1), 3.62 (2H, m, H-6 and H-3), 3.45 (3H, s, OMe), 3.41 (2H, m, H-5 and H-2) 3.30 (1H, m, H-6'), 3.14 (1H, dd, J = 9.2 Hz, J = 8.8 Hz, H-4) ;

HRMS (*m/z* ES+): Calcd for $C_7H_{13}O_5I$ [M + Na]$^+$ 326.9705 Found 326.9712.

5.2.1.2 Methyl-2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside 227[288]

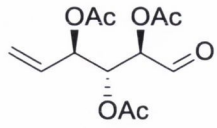


Methyl-α-D-glucopyranoside **225** (3.00 g, 15.4 mmole), PPh_3 (6.08g, 23.2 mmol) and imidazole (2.04 g, 30 mmol) were dissolved in THF (50 mL) and the reaction mixture was heated to reflux (70°C) for 2 hours. Iodine (5.88 g, 23.2 mmol) in THF (10 mL) was added dropwise to the reaction mixture, a colour change from colourless to brown was noted and the appearance of a white precipitate (imidazole hydroiodide) was observed. The reaction mixture was heated at reflux for a further 3 hours, the progression of the reaction was monitored by TLC (EtOAc/THF, 4:1), upon completion the reaction mixture was cooled to room temperature, filtered and concentrated to a yellow syrup. The crude reaction mixture was dissolved in EtOAc (200 mL) and extracted with water (5 x 25 mL). The combined aqueous extracts were concentrated. The crude iodo compound was treated with pyridine (50 mL) and acetic anhydride (50 mL) and stirred overnight at room temperature. The solution was concentrated and purified by column chromatography (Hexane/Ethyl Acetate, 5:1), crystallisation from hexane furnished the iodoglycoside **227** (6.80 g, 9.39 mmol, 61%) as a white crystalline solid;

δ_H (400 MHz, $CDCl_3$): 5.48 (1H, App t, $J_{3,2} = J_{3,4} = 9.7$ Hz, H-3), 4.98 (1H, d, $J_{1,2} = 3.5$ Hz, H-1), 4.89 (2H, m, H-2 and H-4), 3.81 (1H, m, H-5), 3.50 (3H, s, OMe), 3.32 (1H, dd, $J_{6,6'} = 10.8$ Hz, $J_{6,5} = 2.8$ Hz, H-6), 3.16 (1H, dd, $J_{6',6} = 10.8$ Hz, $J_{6',5} = 2.8$ Hz, H-6'), 2.10, 2.08, 2.03 (3H, s, CH_3).

HRMS (*m/z* ES+): Calcd for $C_{13}H_{19}IO_8$ [M + Na]$^+$ 453.0022 Found 453.0029.

5.2.1.3 2,3,4-Tri-*O*-acetyl-5,6-dideoxy-D-*xylo*-5-hexenose 228[298]

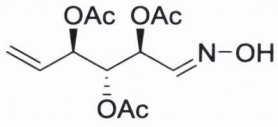


Activated zinc dust (457 mg, 6.99 mmol), NH_4Cl (374 mg, 6.99 mmol) and catalytic cyanocobalamin were stirred at room temperature in MeOH (15 mL) for 15 minutes. **227** (300 mg, 0.70 mmol) was added to the suspension in MeOH (3 mL) and the resultant mixture stirred at room temperature for 2 hours. The reaction was monitored by TLC (Ethyl Acetate/Hexane 7:3). The mixture was filtered and washed with MeOH (2 x 20 mL). The filtrate was evaporated, the residue dissolved in EtOAc (60 mL) and washed with water and brine (3 x 30 mL). Organic extracts were combined and dried over $MgSO_4$. The residue was concentrated *in vacuo*. Purification by column chromatography (Hexane/Ethyl Acetate 1:1) gave **228** (105 mg, 0.38 mmol, 55%) as a yellow oil;

δ_H (400 MHz, $CDCl_3$): 9.50 (1H, app s, H-1), 5.77 (1H, m, H-5), 5.54 (2H, m, H-3 and H-4), 5.42 (1H, dd, $J_{6,5}$ = 17.2 Hz, $J_{6,6'}$ = 2.0 Hz, H-6), 5.37 (1H, m, H-6'), 5.28 (1H, app d, $J_{2,3}$ = 3.0 Hz, H-2), 2.24, 2.11, 2.08 (3H, s, CH_3)

HRMS (*m/z* ES+): Calcd for $C_{12}H_{16}O_7$ [M + H]$^+$ 273.0972 Found 273.0974.

5.2.1.4 2,3,4-Tri-*O*-acetyl-5,6-dideoxy-D-*xylo*-5-hexenose oxime 229[289]



Sodium methoxide (84 mg, 1.56 mmol) was dissolved in MeOH (60 mL) and heated to 60 °C. Hydroxylamine hydrochloride (216 mg, 3.12 mmol) was added and the mixture stirred for ten minutes. **228** (105 mg, 0.39 mmol) was added in MeOH (5 mL) and the mixture was stirred at 60 °C for 4.5 hours. The reaction was monitored by TLC (Hexane/Ethyl Acetate, 7:3). The mixture was concentrated, dissolved in Ethyl Acetate

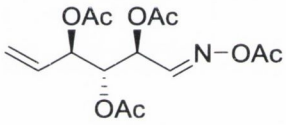
(60 mL) and washed with water (3 x 30 mL) and brine (3 x 30 mL). Purification by column chromatography (Hexane/Ethyl Acetate 1:1) gave **229** (76 mg, 265 mmol, 68%) as a yellow oil in a 6:4 mixture of *E/Z* isomers. Data given for major *E* isomer;

δ_H (400 MHz, $CDCl_3$): 8.13 (1H, br s, OH), 7.52 (1H, d, $J_{1,2}$ = 5.9 Hz, H-1), 5.77 (1H, m, H-5), 5.60 (1H, m, H-4), 5.50 (1H, m, H-6), 5.35 (2H, m, H-6' and H-3) 5.41 (1H, dd, $J_{2,1}$ = 5.9 Hz, $J_{2,3}$ = 4.9 Hz, H-2), 2.13, 2.12, 2.11 (3H, s, CH_3) ;

HRMS (*m/z* ES+): Calcd for $C_{12}H_{17}NO_7$ [M + Na]$^+$ 310.0903 Found 310.0899.

.

5.2.1.5 2,3,4-Tri-*O*-acetyl-5,6-dideoxy-D-*xylo*-hexanose-*O*-acetyl-oxime ester (230)



229 (76 mg, 0.26 mmol) was dissolved in pyridine (5 mL) and acetic anhydride (5 mL) and stirred at room temperature for 24 hours. The solvent was evaporated to a crude yellow oil that was purified by column chromatography (Hexane/Ethyl Acetate 1:1) to give **230** (78 mg, 0.23 mmol, 90%) as a colourless oil in a 6:4 mixture of *E/Z* isomers. Data given for major *E* isomer;

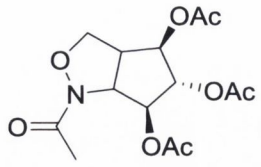
δ_H (600 MHz, $CDCl_3$): 7.60 (1H, d, $J_{1,2}$ = 5.9 Hz, H-1), 5.77 (1H, m, H-5) 5.68 (1H, m, H-4), 5.50 (1H, app t, $J_{2,1}$ = $J_{3,2}$ = 5.9 Hz, H-2), 5.40 (3H, m, H-3, H-6 and H-6'), 2.17, 2.17, 2.13, 2.11 (3 H, s, CH_3)

δ_C (150 MHz, $CDCl_3$): 172.2, 171.1, 170.4, 170.3 (C=O), 152.8 (C-1), 131.2 (C-5), 120.9 (C-6), 72.3 (C-4), 71.5 (C-2), 69.1 (C-3), 20.8, 20.6, 20.5, 19.3 (CH_3)

ν_{max} (film)/cm^{-1}: 1742 (C=O), 857 (N-O) cm^{-1}

HRMS (*m/z* ES^+): Calcd for $C_{14}H_{19}NO_8$ [M + Na]$^+$ 352.1009 Found 352.1008.

5.2.6 3,4,5-tri-*O*-acetyl-6-deoxy-α-D-glucopyranoside (234)[299]

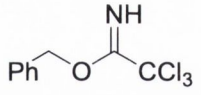


Sodium methoxide (1.13 g, 20.9 mmol) was dissolved in MeOH (150 mL) and heated to 60 °C. Hydroxylamine hydrochloride (2.9 g, 41.8 mmoles) was added and the mixture stirred for ten minutes. **228** (1.42 g, 5.22 mmol) was added in MeOH (20 mL) and the mixture was stirred at 60 °C for 4.5 hours. The reaction was monitored by TLC (Hexane / Ethyl Acetate 7:3). The mixture was evaporated to dryness, dissolved in ethyl acetate (60 mL), washed with water (3 x 30 mL) and brine (3 x 30 mL), dried over $MgSO_4$ and evaporated to dryness. The residue was suspended in pyridine (25 mL) and acetic anhydride (25 mL) and stirred at room temperature for 24 hours. The solvent was evaporated giving a crude yellow oil that was purified by column chromatography (Hexane/ Ethyl Acetate 50:50) to give **234** (550 mg, 1.67 mmol, 32%) as an orange waxy solid;

δ_H (400 MHz, $CDCl_3$): 5.44 (1H, t, $J_{3,2}$ = 8.8 Hz, H-3), 5.20 (1H, dd, $J_{2,1}$ = 6.0 Hz, $J_{2,3}$ = 8.8 Hz, H-2), 5.02 (1H, dd, $J_{4,3}$ = 8.8 Hz, $J_{4,5}$= 7.4 Hz, H-4), 4.91 (1H, dd, $J_{1,2}$= 6.0 Hz, $J_{1,5}$= 10 Hz, H-1), 4.40 (1H, d, $J_{6,6'}$ = 9.1 Hz, H-6'), 3.68 (1H, dd, $J_{6',6}$ = 9.1 Hz, $J_{6,5}$ = 6.5 Hz, H-6) 3.02 (1H, ddd, $J_{5,1}$ =10.0 Hz, $J_{5,4}$ = 7.4 Hz, $J_{5,6}$ = 6.5 Hz, H-5) 2.77, 2.11, 2.07, 2.06 (3H, s, CH_3).

HRMS (*m/z* ES^+): Calcd for $C_{14}H_{19}NO_8$ [M + Na]$^+$ 352.1008 Found 352.1002.

5.2.7 2,2,2-Trichloro-acetimidic acid benzyl ester 235[300]

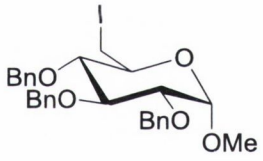


Benzyl Alcohol (2.51 mL, 24.3 mmol) and trichloroacetonitrile (12 mL, 120 mmol) were added to DCM (25 mL). The solution was cooled in an icebath and DBU (0.37 mL, 2.5 mmol) was added dropwise, a colour change from colourless to deep brown was observed as the solution was left to warm to room temperature for 3 hours with continuous stirring. The reaction was monitored by TLC (Pet ether/Ethyl acetate, 9:1). The solution was concentrated under vacuum and purified by column chromatography (Pet ether/ Ethyl acetate 9:1) to give **235** (5.60 g, 22.35 mmol, 92%) as a colourless oil

δ_H (400 MHz, $CDCl_3$): 8.49 (1H, s, NH), 7.5 (5H, m, Ar-H), 5.42 (2H, s, CH_2).

HRMS (*m/z* ES+): Calcd for $C_9H_8Cl_3NO$ [M + Na]$^+$ 273.9569 Found 273.9570.

5.2.8 3,4,5-tri-*O*-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside 236[288]

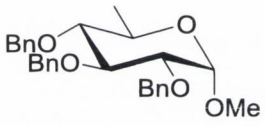


226 (493 mg, 1.62 mmol) was co-evaporated with toluene (20 mL x 3) and dried under high vacuum for 1 hour. **226** was dissolved in dry 1,4-dioxane (10 mL) under N_2 and **235** (1.6 g, 12.8 mmol) was added. The suspension was stirred for 1 hour over 4Å flame dried molecular sieves, the solution was cooled to 0°C and TMS-triflate (0.1 mL) was added. The reaction was stirred for two hours at room temperature and monitored by TLC (Hexane/Ethyl acetate 5:1) .Triethylamine (1 mL) was added to quench the reaction, the reaction mixture was diluted in DCM (10 mL) and the mixture filtered to remove molecular sieves. The filtrate was concentrated and the crude oil was purified by column chromatography (Hexane/Ethyl Acetate 8:1) to give **236** (688 mg, 1.18 mmol, 74%) as a colourless oil

δ_H (400 MHz, $CDCl_3$): 7.40-7.17 (15 H, m, Ar-H), 5.02-4.70 (6H, m, 3 x CH_2), 4.65 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1) 4.05 (1H, t, $J_{3,2}$ = 9.5 Hz, $J_{3,4}$ = 9.0 Hz, H-3), 3.59 (1H, dd, $J_{2,1}$ = 3.5 Hz, $J_{2,3}$ = 9.5 Hz, H-2), 3.48 (1H, m, H-5), 3.47 (1H, m, H-6), 3.45 (3H, s, OMe), 3.37 (1H, t, $J_{4,3}$ = 9.0 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 3.29 (1H, dd, $J_{6',5}$ = 6.5 Hz, $J_{6,6'}$ = 10.5 Hz, H-6')

HRMS (*m/z* ES+): Calcd for $C_{28}H_{31}O_5I$ [M + Na]$^+$ 597.1114 Found 597.1125.

5.2.9 3,4,5-tri-*O*-acetyl-6-deoxy-α-D-glucopyranoside (237)[291]



Activated zinc dust (2.22 g, 34.8 mmol), NH_4Cl (1.84 g, 34.8 mmol) and catalytic cyanocobalamin were stirred at room temperature in MeOH (30 mL) for 15 minutes. **236** (2.00 g, 3.48 mmol) was added to the suspension in MeOH (5 mL) and the resultant mixture stirred at room temperature for 2 hours. The reaction was monitored by TLC (Ethyl Acetate/Hexane 7:3). The mixture was filtered and washed with MeOH (2 x 100 mL). The filtrate was evaporated, the residue dissolved in EtOAc (60 mL) and washed with water and brine (3 x 50 mL). Organic extracts were dried over $MgSO_4$ and evaporated to give a crude yellow oil. Purification by column chromatography (Hexane/Ethyl Acetate 1:1) gave **237** (686 mg, 1.53 mmol, 44%) as a yellow oil and **238** (304 mg, 0.73 mmol, 21%) as a yellow oil;

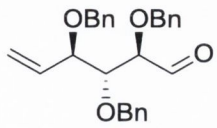
Data for 237

δ_H (400 MHz, $CDCl_3$): 7.40-7.20 (15H, m, Ar-H), 5.01 (1H, d, J = 10.9 Hz, Bn-CH_2), 4.92 (1H, d, J = 11.1 Hz, Bn-CH_2), 4.85 (1H, d, J = 10.5 Hz, Bn-CH_2), 4.82 (1H, d, J = 10.9 Hz, Bn-CH_2), 4.70 (1H, d, J = 10.5 Hz, Bn-CH_2) 4.62 (1H, d, J = 11.1 Hz, Bn-CH_2), 4.56 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1), 3.98 (1H, dd, $J_{3,2}$ = 9.5 Hz, $J_{3,4}$ = 9.2 Hz, H-3), 3.76 (1H, m, H-5), 3.55 (1H, dd, $J_{2,1}$

= 3.6 Hz, $J_{2,3}$ = 9.5 Hz, H-2), 3.40 (3H, s, OMe), 3.15 (1H, dd, $J_{4,3}$ = 9.2 Hz, $J_{4,5}$ = 9.8 Hz, H-4), 1.27 (3H, m, CH_3).

HRMS (*m/z* ES+): Calcd for $C_{28}H_{32}O_5$ [M + Na]$^+$ 471.2147 Found 471.2148.

5.2.10 2,3,4-Tri-*O*-benzyl-5,6-dideoxy-D-*xylo*-5-hexenose 238[298]

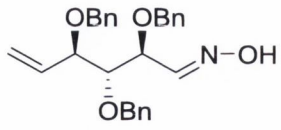


Activated zinc (274 mg, 4.18 mmol), NH_4Cl (187 mg, 3.49 mmol) and catalytic cyanocobalamin were stirred at room temperature in MeOH (15 mL) for 15 minutes. A solution of **236** (200 mg, 0.35 mmol) in MeOH (3 mL) was added to the suspension and the resultant mixture stirred at room temperature for 20 minutes. The reaction was monitored by TLC (Hexane/Ethyl Acetate, 5:1). Upon completion the mixture was filtered and washed with MeOH (2 x 20 mL). The filtrate was evaporated, the residue dissolved in EtOAc (60 mL) and washed with water and brine (3 x 30 mL). Organic extracts were dried over $MgSO_4$ and evaporated to give a crude yellow oil. Purification by column chromatography (Hexane/Ethyl Acetate 8:1) gave **238** (93 mg, 0.23 mmol, 65%) as a yellow oil;

δ_H (400 MHz, $CDCl_3$): 9.69 (1H, app s, H-1), 7.35-7.33 (15H, m, Ar-H), 5.86 (1H, m, H-5), 5.30 (2H, m, H-6 and H-6'), 4.80-4.40 (6H, m, 3 x Bn-CH_2), 4.20 (1H, m, H-4), 3.93 (1H, dd, , $J_{2,1}$ = 0.8 Hz, $J_{2,3}$ = 4.5 Hz H-2), 3.85 (1H, dd, $J_{3,2}$ = 4.5 Hz, $J_{3,4}$ = 4.5 Hz, H-3)

HRMS (*m/z* ES+): Calcd for $C_{27}H_{28}O_4$ [M + Na]$^+$ 439.1878 Found 439.1885.

5.2.11 2,3,4-Tri-*O*-benzyl-5,6-dideoxy-D-*xylo*-5-hexenose oxime 239[289]



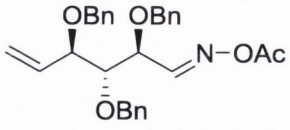
Procedure as described for **229** to afford **239**. Purification by column chromatography (10:1 Hexane/Ethyl Acetate) gave **239** (61 mg, 14.0 μmol, 70%) as a yellow oil in a 7:3 mixture of *E/Z* isomers.

Data given for major *E* isomer;

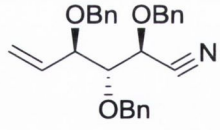
δ_H (400 MHz, $CDCl_3$): 8.77 (1H, br s, OH), 7.51 (1H, d, $J_{1,2}$ = 7.7 Hz, H-1), 7.4-7.3 (15H, m, Ar-H), 5.75 (1H, m, H-5), 5.27 (2H, m, H-6 and H-6'), 4.80-4.60 (6H, m, CH_2), 4.18 (2H, m, H-2 and H-4), 3.62 (1H, m, H-3),

HRMS (*m/z* ES+): Calcd for $C_{27}H_{29}NO_4$ [M + Na]$^+$ 431.1994 Found 454.2003.

5.2.12 2,3,4-Tri-*O*-benzyl-5,6-dideoxy-D-*xylo*-5-hexenose-*O*-acetyl-oxime ester 240 and 2,3,4-Tri-*O*-benzyl-5,6-dideoxy-D-*xylo* nitrile 241



240



241

Procedure as described for **230** to afford **240** and **241**. Purification by column chromatography (Hexane/ Ethyl Acetate 70:30) gave **240** (44 mg, 0.09 mmol, 66%) as a colourless oil in a 7:3 mixture of *E/Z* isomers and **241** (28 mg, 0.04 mmol, 28%) as a colourless oil;

Data for 240, major *E* isomer;

δ_H (600 MHz, $CDCl_3$): 7.69 (1H, d, $J_{1,2}$ = 8.1 Hz, H-1), 7.37-7.29 (15H, m, Ar-H), 5.78 (1H, m, H-5), 5.28 (2H, m, H-6 and H-6'), 4.86 (1H, d, *J*

= 11.8 Hz, CH_2), 4.70 (1H, d, J = 11.8 Hz, CH_2), 4.63 (1H, d, J = 11.9 Hz, CH_2), 4.59 (1H, d, J = 11.9 Hz CH_2), 4.43 (1H, d, J = 9.5 Hz, CH_2), 4.40 (1H, d, J = 9.5 Hz, CH_2), 4.32 (1H, dd, $J_{2,1}$ = 8.1 Hz, $J_{2,3}$ = 4.1 Hz, H-2), 4.27 (1H, dd, $J_{4,3}$ = 6.4 Hz, $J_{4,5}$ = 1.2 Hz, H-4), 3.66 (1H, dd, $J_{3,2}$ = 4.1 Hz, $J_{3,4}$ = 6.4 Hz, H-3), 2.15 (3H, s, CH_3) ;

δ_C (150 MHz, $CDCl_3$): 168.3 (C=O), 157.5 (C-1), 138.2, 137.8, 137.1 (q-Ar), 134.5 (C-6), 129.1, 129.0, 128.6, 128.4, 128.3, 127.9, 127.6, 126.5, 126.4 (Ar-C), 119.2 (C-5), 81.8 (C-3), 81.2 (C-4), 75.8 (C-2), 74.8, 71.9, 70.8 (CH_2), 19.6 (CH_3) ;

ν_{max} (film)/cm^{-1}: 1769 (C=O), 1453 (C=C aromatic), 910 (N-O), 733 (C-H aromatic) cm^{-1}

HRMS (*m/z* ES^+): Calcd for $C_{29}H_{31}NO_5$ [M + Na]$^+$ 496.2100 Found 496.2121.

Data for 241

δ_H (600 MHz, $CDCl_3$): 7.35-7.31 (15H, m, Ar-H), 5.83 (1H, m, H-5), 5.31 (2H, m, H-6 and H-6') 4.82, 4.61, 4.53 (6H, m, Bn-CH_2), 4.47 (1H, d, $J_{2,3}$ = 5.5 Hz, H-2) 4.18 (1H, m, H-4), 3.75 (1H, dd, $J_{3,2}$ = 5.5 Hz, $J_{3,4}$ = 4.5 Hz, H-3)

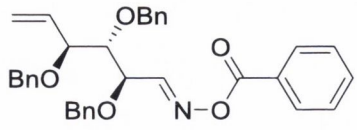
δ_C (150 MHz, $CDCl_3$): 152.9 (-C≡N), 137.6, 137.5, 135.7 (Ar-C), 134.2 (C-5), 128.6, 128.6, 128.4, 128.3, 128.3, 128.2, 127.9, 127.8, 127.7 (Ar-C), 120.2 (C-6), 81.2 (C-3), 80.2 (C-4), 75.9, 72.8, 70.8 (CH_2) 69.5 (C-2);

ν_{max} (film)/cm^{-1}: 2913 (C≡N), 1455 (C=C aromatic), 733 (C-H aromatic) cm^{-1}

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): -10.0°

HRMS (*m/z* ES^+): Calcd for $C_{27}H_{27}NO_3$ [M + Na]$^+$ 436.2001 Found 436.1827.

5.2.13 2,3,4-Tri-*O*-benzyl-5,6-dideoxy-D-*xylo*-5-hexenose-*O*-benzoyl-oxime ester (242)



239 (190 mg, 0.44 mmol) was dissolved in pyridine (25 mL) and the solution was cooled to 0°C. Benzoyl chloride (0.06 mL, 0.57 mmol) was added dropwise to the cooled solution and the mixture was stirred for 2 hours under nitrogen. The reaction mixture was monitored by TLC (Hexane/Ethyl Acetate 5:1). Diethyl ether (25 mL) was added and the reaction mixture was washed with 1M HCl solution (3 x 25 mL) and sat. $NaHCO_3$ (25 mL). The organic extracts were combined, dried over $MgSO_4$ and purified by column chromatography (Hexane/EtOAc 8:1) to give **242** (113 mg, 0.21 mmol, 48 %) as a yellow oil in a 7:3 mixture of *E/Z* isomers.

Data given for major *E* isomer;

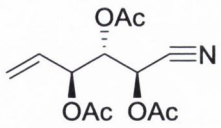
δ_H (600 MHz, $CDCl_3$): 8.17-8.05 (2H, m, Ar-H), 7.83 (1H, d, $J_{1,2}$ = 8.4 Hz, H-1), 7.69-7.30 (18H, m, Ar-H), 5.81 (1H, m, H-5), 5.32 (2H, m, H-6 and H-6'), 4.89, 4.73, 4.67, 4.65, 4.45, 4.45 (6H, s, Bn-CH_2), 4.41 (1H, m, H-2), 4.29 (1H, dd, $J_{4,3}$ = 6.3 Hz, $J_{4,5}$ = 5.2 Hz, H-4), 3.73 (1H, dd, $J_{3,4}$ = 6.3 Hz, $J_{3,2}$ = 4.1 Hz, H-3).

δ_C (150 MHz, $CDCl_3$): 163.0 (C=O), 158.1 (C-1), 138.2, 137.8, 137.1, 134.6, 133.7, 133.5, 130.2, 129.8, 128.7, 128.5, 128.4, 128.4, 128.3, 128.1, 128.0, 128.0, 127.9, 127.9, 127.7, 127.5, 127.5, 127.5, 127.3, 127.3 (Ar-C), 134.6 (C-5), 119.9 (C-6), 82.3 (C-3), 81.9 (C-4), 75.9 (C-2), 74.7, 71.5, 70.7 (Ph-CH_2) ;

ν_{max} (film)/cm^{-1}: 1747 (C=O), 1452 (C=C aromatic).

HRMS (*m/z* ES^+): Calcd for $C_{34}H_{33}NO_5$ [M + Na]$^+$ 558.2256 Found 558.2228.

5.2.14 2,3,4-Tri-*O*-acetyl-5,6-dideoxy-D-*xylo*-nitrile (243)



230 (46 mg, 0.14 mmol) was dissolved in dry toluene (3 mL) and the solution was transferred to a microwave vial charged with a magnetic stirrer bar and heated in the microwave at 160°C for 15 minutes. The reaction was monitored by TLC (Hexane/ EtOAc 1:1) the solvent was evaporated and the resulting yellow oil was purified by chromatography (Hexane/EtOAc 1:1) to give **243** (7.5 mg, 0.06 mmol, 42%) as a colourless oil;

δ_H (400 MHz, $CDCl_3$): 5.76 (1H, m, H-5), 5.55 (1H, m, H-4), 5.64 (1H, d, $J_{2,3}$ = 5.2 Hz, H-2), 5.38, (3H, m, H-3, H-6 and H-6'), 2.19, 2.19, 2.18 (9H, s CH_3).

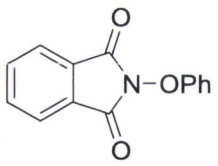
δ_C (100 MHz, $CDCl_3$): 169.4, 169.3, 168.4 (C=O), 149.9 (C≡N), 130.6 (C-5), 120.6 (C-6), 70.8 (C-3) 69.9 (C-2) 59.1 (C-4), 20.8, 20.5 20.1 (CH_3).

ν_{max} (film)/cm^{-1}: 2932 (C≡N), 1743 (C=O) cm^{-1}

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): +46.0

HRMS (*m/z* ES^+): Calcd for $C_{12}H_{15}NO_6$ [M + H]$^+$ 270.0978 Found 270.0967.

5.2.15 *N*-phenyloxyphthalamide (242)[313]

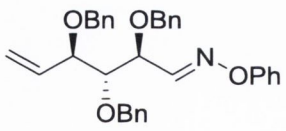


N-hydroxypthalamide (163 mg, 1.00 mmol,) CuCl (99 mg, 1.00 mmol) and phenylboronic acid (244 mg, 2.00 mmol) were stirred in DCM (5 mL), pyridine (90 μL, 1.1 mmol) was added and a colour change from green to deep brown was noted. 4Å Molecular sieves were added and a stopper loosely applied such that the reaction was open to the atmosphere, the reaction mixture was stirred for 48 hours at room temperature, the progression of the reaction was monitored by TLC (Hexane/EtOAc 4:1). The reaction mixture was filtered to remove the molecular sieves and the solvent removed to afford a crude green solid that was purified by column chromatography (Hexane/EtOAc 4:1) to give **17** (178 mg, 0.74 mmol, 74% yield) as a white crystalline solid.

δ_H (400 MHz, $CDCl_3$): 7.92-7.96 (3H, m, Ar-H), 7.82-7.87 (2H, m, Ar-H), 7.33-7.37 (2H, m, Ar-H), 7.13-7.19 (2H, m, Ar-H)

HRMS (*m/z* ES^+); Calcd for $C_{14}H_9NO_3$ [M + H]$^+$ 240.0661 Found 240.0658.

5.2.16 2,3,4-Tri-*O*-benzyl-5,6-dideoxy-D-*xylo*-*O*-phenyl oxime ether (248)



238 (93 mg, 0.34 mmol) was dissolved in dry pyridine (20 mL). *O*-phenyl hydroxylamine hydrochloride (50 mg, 0.34 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction was monitored by TLC (Hexane/EtOAc 5:1), upon completion the reaction mixture was filtered and the solvent removed under vacuum, the crude reaction mixture was dissolved in EtOAc (50 mL) and washed with a

mixture of water and brine (3 x 30 mL). The organic extracts were combined and dried over $MgSO_4$ the reaction mixture was purified by column chromatography (Hexane/EtOAc 8:1) to give **248** (116 mg, 0.23 mmol, 67%) a yellow oil as a 7:3 mixture of *E/Z* isomers.

Data given for major *E* isomer

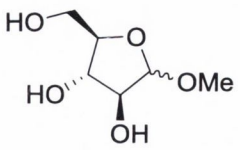
δ_H (600 MHz, $CDCl_3$): 7.67 (1H, d, $J_{1,2}$ = 8.4 Hz, H-1) 7.38 (15H, m, Ar-H), 7.11 (5H, m, Ar-H), 5.88 (1H, m, H-5), 5.38 (2H, m, H-6 and H-6'), 4.87 (1H, J = 11.6 Hz, Bn-CH_2), 4.77 (1H, J = 11.5 Hz, Bn-CH_2), 4.69 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.66 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.64 (1H, d, J = 11.5 Hz, Bn-CH_2), 4.42 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.31 (1H, m, H-2), 3.89 (1H, m, H-4), 3.68 (1H, dd, J = 5.7 Hz, J = 4.8 Hz, H-3).

δ_C (150 MHz, $CDCl_3$): 152.2 (C-1), 138.0, 138.0, 137.9, 137.7 (q-Ar), 135.5, 135.3 (Ar-C), 134.8 (C-5), 129.6, 129.3, 129.2, 129.0, 128.4, 128.3, 127.8 (Ar-C), 119.5 (C-6) 82.4 (C-3), 81.1 (C-2), 76.4 (C-4), 74.9, 71.5, 70.9 (Bn-CH_2).

ν_{max} (film)/cm^{-1}: 1041 (C-*O*-C) cm^{-1}

HRMS (*m/z* ES^+); Calcd for $C_{33}H_{33}NO_4$ [M + Na]$^+$ 530.2307 Found 530.2313.

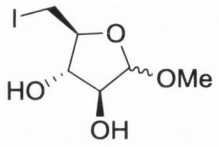
5.2.17 Methyl-5-deoxy-5-iodo-D-arabinofuranose (251)[316]



D-arabinose (3.50 g, 23.2 mmol) was dissolved in dry MeOH (100 mL), 2M HCl in dioxane (10 mL, 5.8 mmole) was added dropwise to a cooled solution of the sugar and the solution was left to warm to room temperature for one hour and heated to 35°C for 3 hours. The progession of the reaction was followed by TLC (5% MeOH in EtOAc). The

solution was cooled to 0°C and pyridine (10 mL) was added dropwise. The yellow solution was concentrated *in vacuo* to give a yellow syrup that was dried under high vacuum. This intermediate was used directly, without purification, in the following iodination step.

5.2.18 Methyl-5-deoxy-5-iodo-D-arabinofuranose (252)[288]

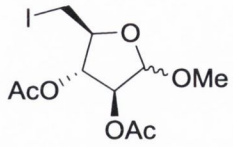


251 (1.00 g, 6 mmol), PPh_3 (2.39 g, 9.14 mmol) and imidazole (830 mg, 12.19 mmol) were dissolved in dry THF (50 mL). The reaction mixture was heated to 70° C, iodine (2.31 g, 9.14 mmol) in THF (2 mL) was added dropwise and the solution was refluxed for 1 hour. The progression of the reaction was followed by TLC (EtOAc). The reaction mixture was cooled, filtered and concentrated, the residue was dissolved in EtOAc (50 mL) and washed with water (5 x 50 mL). The organic extracts were combined, dried over $MgSO_4$ concentrated and purified by chromatography (EtOAc/THF 4:1) to give **252** (1.05 g, 64%) as a yellow syrup in a 6:4 ratio of α/β anomers;

δ_H (400 MHz, $CDCl_3$): 4.93 (0.6H, d, $J_{1,2}$ = 1.1 Hz, H-1 α), 4.85 (0.4H, d, $J_{1,2}$ = 4.7 Hz, H-1 β), 4.15 (1H, m, H-2), 4.11 (1H, m, H-4), 3.9 (1H, app s, H-3), 3.4 (3H, s, OMe), 3.39-3.33 (2H, m, H5 and H5')

HRMS (*m/z* ES+): Calcd for $C_6H_{11}IO_4$ [M + Na]$^+$ 296.9600 Found 296.9594.

5.2.19 Methyl-2,3-di-*O*-acetyl-5-deoxy-5-iodo-D-arabinofuranose (253)[288]

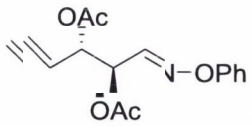


252 (1.00 g, 3.66 mmol) was dissolved in pyridine (25 mL). Acetic anhydride (25 mL) was added portionwise and the reaction was stirred at room temperature for 18 h. The progression of the reaction was followed using TLC (1:1 Hexane/ EtOAc). Upon completion the reaction mixture was concentrated and purified by column chromatography 2:1 Hexane/EtOAc to give **253** (1.03g, 2.89 mmol, 79%) as a yellow syrup ;

δ_H (400 MHz, $CDCl_3$): 5.11 (1H, app d, $J_{2,1}$ = 1.7 Hz, H-2), 4.98 (1H, app s, H-1), 4.90 (1H, ddd, $J_{3,5}$ = 0.7 Hz, $J_{3,2}$ = 1.7 Hz, $J_{3,4}$ = 5.3 Hz, H-3), 4.11 (1H, m, H-4), 3.54 (1H, m, H-5), 3.53 (1H, m, H-5'), 3.43 (3H, s, OMe), 2.13 (3H, s, CH_3), 2.13 (3H, s, CH_3).

HRMS (*m/z* ES+): Calcd for $C_{10}H_{15}IO_6$ [M + Na]$^+$ 380.9811 Found 380.9816.

5.2.20 2,3-di-*O*-acetyl-1,4,5-trideoxy-1-phenyloxime-D-arabino-pent-5-ene (255)



NH_4Cl (190 mg, 3.56 mmol), zinc (233 mg, 3.56 mmol) and catalytic cyanocobalamin were stirred in MeOH (20 mL) for 15 minutes. **254** (127 mg, 0.36 mmol) in MeOH (3 mL) was added in one addition and the solution was stirred at room temperature for 90 minutes. The progression of the reaction was monitored by TLC (1:1 Hexane/EtOAc). Upon completion the reaction mixture was filtered and concentrated. The residue was dissolved in EtOAc (50 mL) and extracted (3 x 30 mL) of water and brine. The organic extracts dried over $MgSO_4$ and concentrated to a yellow oil. This intermediate was

dissolved in dry pyridine (25 mL) and *O*-phenyl hydroxylamine hydrochloride (19 mg, 0.08 mmol) was added in one portion. The reaction mixture was stirred under nitrogen at room temperature overnight. The progression of the reaction was monitored by TLC (1:1 EtOAc/ Hexane). Upon completion the reaction mixture was poured into distilled water (40 mL) and extracted with ethyl acetate (3 x 30 mL). The organic extracts were combined and washed with saturated copper sulphate solution until all pyridine was consumed. The organic extracts were dried over $MgSO_4$ and purified by column chromatography 3:1 Hexane: EtOAc to give **255** as a colourless oil (30 mg, 0.10 mmol, 29% over 2 steps)

Data for major *E* isomer

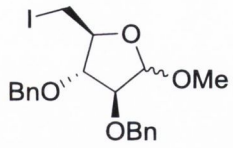
δ_H (400 MHz, $CDCl_3$): 7.80 (1H, d, $J_{1,2}$ = 4.9 Hz, H-1), 7.31 (2H, t, J = 7.5 Hz, o-Ar), 7.18 (2H d, J = 7.5 Hz, m-Ar), 7.00 (1H, t, J = 7.5 Hz, p-Ar), 5.94 (1H, ddd, $J_{4,5}$ = 16.7 Hz, $J_{4,5'}$ = 9.1 Hz, $J_{4,3}$ = 6.7 Hz, H-4), 5.53 (1H, dd, $J_{3,4}$ = 6.7 Hz, $J_{3,2}$ = 5.2 Hz, H-3), 5.42 (2H, m, H-5 and H-5'), 4.59 (1H, dd, $J_{2,3}$ = 5.2 Hz, $J_{2,1}$ = 4.9 Hz, H-2), 2.15 (6H, s, CH_3).

δ_C (100 MHz, $CDCl_3$): 169.6 (C-1), 158.5, 158.3 (C=O), 134.9 (q-C), 131.3 (C-4), 128.9 (Ar-C), 122.3 (Ar-C), 119.7 (Ar-C), 114.2 (C-5), 74.7 (C-3), 70.2 (C-2), 20.6, 20.4 (CH_3)

ν_{max} (film)/cm^{-1}: 1744 (C=O) 1162 (C-O).

HRMS (*m/z* ES+): Calcd for $C_{15}H_{17}NO_5$ $[M + Na]^+$ 314.1004 Found 314.1009.

5.2.21 Methyl 2,3-di-*O*-benzyl-5-deoxy-5-iodo-D-arabinofuranose 256[288]



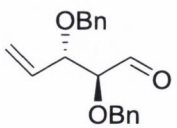
252 (300 mg, 1.09 mmol) and benzyltrichloroacetimidate **236** (720 mg, 2.8 mmol) were dissolved in dry dioxane (25 mL). The solution was cooled to 0°C and catalytic triflic acid (5 drops) was added. The reaction mixture was stirred for 10 minutes and diluted with diethyl ether (20 mL), ice cold $NaHCO_3$ (20 mL) was added dropwise, the resultant precipitate was filtered, the organic layer was separated and dried over $MgSO_4$. The crude reaction mixture was concentrated and purified by column chromatography (Hexane/Ethyl Acetate 9:1) to give **256** (440 mg, 2.49 mmol, 89%) as a yellow oil in a 6:4 mixture of α/β.

Data given for major α anomer.

δ_H (400 MHz, $CDCl_3$): 7.40-7.32 (10H, m, Ar-H), 4.99 (1H, app s, H-1), 4.75 - 4.47 (4H, m, Bn-CH_2) 4.05 (2H, m, H-2 and H-4), 3.82 (1H, dd, $J_{3,2}$ = 2.9 Hz, $J_{3,4}$ = 5.9 Hz, H-3), 3.41 (3H, s, OMe), 3.39 (1H, dd, $J_{5,4}$ = 5.2 Hz, $J_{5,5'}$ = 10.2 Hz, H-5), 3.3 (1H, dd, $J_{5',4}$ = 5.9 Hz, $J_{5',5}$ = 10.3 Hz, H-5').

HRMS (*m/z* ES+): Calcd for $C_{20}H_{23}IO_4$ [M + Na]$^+$ 477.0539 Found 477.0538.

5.2.22 Synthesis of 2,3,4-Tri-*O*-benzyl-5,6-dideoxy-D-*arabino*-furanose 257[298]



NH_4Cl (909 mg, 17.0 mmol), zinc (1.11 g, 17.0 mmol) and catalytic cyanocobalamin were stirred in MeOH (50 mL) for 15 minutes. **256** (440 mg, 1.7 mmol) in MeOH (3 mL) was added in one addition and the solution was stirred at room temperature for 40

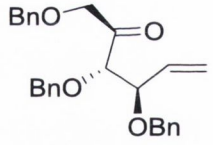
minutes. The progression of the reaction was monitored by TLC (Hexane/EtOAc 9:1). Upon completion the reaction mixture was filtered and concentrated. The residue was dissolved in EtOAc (50 mL) and washed (3 x 30 mL) of water and brine. The organic extracts dried over $MgSO_4$ and concentrated to a yellow oil that was purified by column chromatography (Hexane/ Ethyl Acetate 9:1) to give **257** (21 mg, 0.12 mmol, 7%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$): 9.72 (1H, d, $J_{1,2}$ = 1.4 Hz, H-1), 7.37-7.26 (10H, m, Ar-H), 5.96 (1H, m, H-4), 5.38 (2H, m, H-5), 4.78 (1H, d, J = 12.3 Hz, Bn-CH_2), 4.67 (1H, d, J = 12.8 Hz, Bn-CH_2), 4.64 (1H, d, J = 12.8 Hz, Bn-CH_2), 4.38 (1H, d, J = 12.3 Hz, Bn-CH_2), 4.19 (1H, dd, $J_{3,2}$ = 4.3 Hz, $J_{3,4}$ = 7.4 Hz, H-3), 3.8 (1H, dd, $J_{2,1}$ = 1.4 Hz, $J_{2,3}$ = 4.3 Hz, H-2) ;

HRMS (*m/z* ES+): Calcd for $C_{19}H_{20}O_3$ [M + Na]$^+$ 319.1310 Found 319.1312.

5.2.2 Ketoxime oxime and ether synthesis

5.2.2.1 3,4,6-Tri-*O*-benzyl-1,2,5-trideoxy-D-arabino-hex-1-en-5-one (259)[318]



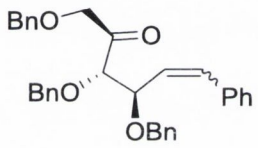
To the stirred mixture of compound **161** (500 mg, 0.92 mmol) and 4Å molecular sieves (100 mg) in A 1:1 mixture of CH_2Cl_2/ DMF (15 mL), PDC (400 mg, 1.8 mmol) was added under ice-salt bath. CH_2Cl_2 (15 mL) was then poured into the mixture after stirring for 48 h at room temperature. The resulting mixture was filtered through Celite, evaporated to dryness. The residue was purified by column chromatography on silica gel (Hexanes/EtOAc 8:1 to 3:1) to provide **259** (306 mg, 0.74 mmol, 80%) as a golden syrup

δ_H (400 MHz, $CDCl_3$): 7.38-7.23 (15H, m, Ar-H), 5.92 (1H, ddd, $J_{2,1}$ = 10.2 Hz, $J_{2,1'}$ = 16.7 Hz, $J_{2,3}$ = 7.8 Hz, H-2), 5.35 (2H, m, H-1 and H-1'),

4.61 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.60 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.53 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.52 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.45 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.36 (2H, d, J = 6.4 Hz, H-6), 4.30 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.20 (1H, dd, $J_{3,2}$ = 7.8 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 4.02 (1H, d, $J_{4,3}$ = 3.5 Hz, H-4)

HRMS (*m/z* ES+): Calcd for $C_{27}H_{28}O_4$ [M + Na]$^+$ 439.1885 Found 439.1901.

5.2.2.2 1-Phenyl-3,4,6-Tri-*O*-benzyl-1,2,5-trideoxy-D-arabino-hex-1-en-5-one (260)



Procedure as described for **259** to afford **260**. Purification by column chromatography (60:40 EtOAc/Hexane) gave **260** (3.14 g, 6.38 mmol, 87%) as a white solid

Data for *E* isomer

δ_H (600 MHz, $CDCl_3$): 7.39-7.24 (20H, m, Ar-H), 6.61 (1H, d, $J_{1,2}$ = 16.3 Hz, H-1), 6.25 (1H, dd, $J_{2,1}$ = 16.3 Hz, $J_{2,3}$ = 8.2 Hz, H-2), 4.67 (1H, d, J = 12.2 Hz, Bn-CH_2), 4.63 (1H, d, J = 12.4 Hz, Bn-CH_2), 4.52 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.51 (1H, d, J = 12.2 Hz, Bn-CH_2), 4.45 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.43 (1H, d, $J_{6,6'}$ = 18.1 Hz, H-6), 4.38 (1H, dd, $J_{3,2}$ = 8.2 Hz, $J_{3,4}$ = 3.6 Hz, H-3), 4.36 (1H, d, $J_{6',6}$ = 18.1 Hz, H-6'), 4.06 (1H, d, $J_{4,3}$ = 3.6 Hz, H-4).

δ_C (150 MHz, $CDCl_3$): 207.6 (C-5), 137.5, 137.4, 136.7 (q-Bn), 136.1 (q-Ph), 134.4 (C-1), 128.6, 128.5, 128.4, 128.4, 128.4, 128.2, 128.2, 128.1, 127.9, 127.9, 127.8 126.7 (Ar-C), 125.4 (C-2), 86.0 (C-4), 80.6 (C-3), 74.6 (C-6), 74.6, 73.3, 70.9 (Bn-CH_2).

ν_{max} (film)/cm^{-1}: 1712 (C=O), 1405 (C=C aromatic).

HRMS (*m/z* ES^+): Calcd for $C_{33}H_{32}O_4$ [M + Na]$^+$ 515.2198 Found 515.2187.

Data for *Z* isomer

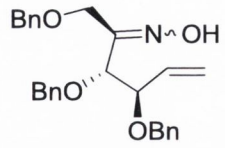
δ_H (600 MHz, $CDCl_3$): 7.35-7.16 (18 H, m, Ar-H), 7.03 (2H, d, J = 7.2 Hz, Ar-H), 6.82 (1H, d, $J_{1,2}$ = 11.9 Hz, H-1), 5.86 (1H, dd, $J_{2,1}$ = 11.9 Hz, $J_{2,3}$ = 9.6 Hz, H-2), 4.80 (1H, dd, $J_{3,2}$ = 9.6 Hz, $J_{3,4}$ = 3.4 Hz, H-3), 4.68 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.55 (1H, d, J = 11.9 Hz, Bn-CH_2), 4.52 (1H, d, J = 11.7 Hz, Bn-CH_2), 4.46 (1H, d, J = 12.0 Hz, Bn-CH_2), 4.34 (1H, d, J = 12.0 Hz, Bn-CH_2), 4.26 (1H, d, $J_{6,6'}$ = 17.8 Hz, H-6), 4.22 (1H, d, $J_{6',6}$ = 17.8 Hz, H-6'), 4.21 (1H, d, $J_{4,3}$ = 3.4 Hz, H-4), 4.13 (1H, d, J =11.7 Hz, Bn-CH_2).

δ_C (150 MHz, $CDCl_3$): 207.2 (C-5), 137.4, 137.3, 136.9 (q-Bn), 136.1 (q-Ph), 13.4.4 (C-1), 128.7 128.5, 128.4, 128.4, 128.3, 128.3, 128.2 (Ar-C), 128.2 (C-2), 128.1, 127.9, 127.8, 127.6, 127.5 (Ar-C), 85.5 (C-4), 74.5 (C-6), 74.4 (C-3), 74.1, 73.2, 70.4 (Bn-CH_2).

ν_{max} (film)/cm^{-1}: 1712 (C=O), 1405 (C=C aromatic).

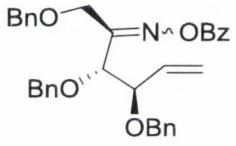
HRMS (*m/z* ES^+): Calcd for $C_{33}H_{32}O_4$ [M + Na]$^+$ 515.2198 Found 515.2187.

5.2.2.3 3,4,6-Tri-*O*-benzyl-1,2,5-Tri-deoxy-D-arabino-hex-1-en-5-oxime (261)



Procedure as described for **229** to afford **261**. Purification by column chromatography (15:1 Hexane/Ethyl Acetate) gave **261** (220 mg, 0.53 mmol, 72%) as a yellow oil as a mixture of isomers. Owing to considerable overlap on the NMR spectrum this compound could not be characterised and was used directly in the next step.

5.2.2.4 3,4,6-Tri-*O*-benzyl-1,2,5-tri-deoxy-D-arabino-hex-1-en-5-benzoyl oxime ester (263)



Procedure as described for **224** to afford **263**. Purification by column chromatography (30:1 Hexane/Ethyl Acetate) gave **263** (237 mg, 0.44 mmol, 87%) as a colourless oil and in a 1:1 mixture of isomers.

Data for *E* oxime isomer

δ_H (600 MHz, $CDCl_3$): 7.64 (1H, m, Bz-Ar-H), 7.47 (2H, m, Bz-H), 7.42-7.26 (17H, m, Ar-H), 5.93 (1H, ddd, $J_{2,1} = 10.2$ Hz, $J_{2,1'} = 17.6$ Hz, $J_{2,3} = 7.3$ Hz, H-2), 5.37 (1H, app d, $J_{1,2} = 10.2$ Hz, H-1), 5.35 (1H, app d, $J_{1',2} = 17.6$ Hz, H-1'), 5.02 (1H, d, $J_{4,3} = 6.6$ Hz, H-4), 4.78 (1H, d, $J = 11.3$ Hz, Bn-CH_2), 4.71 (1H, d, $J = 12.1$ Hz, Bn-CH_2), 4.61 (1H, d, $J = 11.6$ Hz, Bn-CH_2), 4.58 (2H, m, Bn-CH_2), 4.52 (1H, d, $J_{6,6'} = 12.4$ Hz, H-6), 4.47 (1H, d, $J = 12.1$ Hz, Bn-CH_2), 4.41 (1H, d, $J_{6',6} = 12.4$ Hz, H-6), 4.35 (1H, dd, $J_{3,2} = 7.3$ Hz, $J_{3,4} = 6.6$ Hz, H-3),

δ_C (150 MHz, $CDCl_3$): 164.5 (C=O), 163.1 (C-5), 138.0 (q-Bz Ar), 137.5, 137.3, 137.2 (q-Ar), 134.4 (C-2), 133.5, 129.7, 128.7, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.7 (Ar-C), 119.7 (C-1), 81.3 (C-3), 77.8 (C-4), 73.5, 72.8, 70.9 (Bn-CH_2), 67.7 (C-6).

ν_{max} (film)/cm^{-1}: 1749 (C=O), 1422 (C=C aromatic).

HRMS (*m/z* ES^+): Calcd for $C_{34}H_{33}NO_5$ [M + Na]$^+$ 558.2256 Found 558.2268.

Data for *Z* oxime isomer

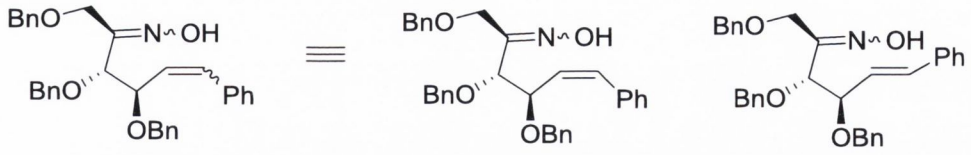
δ_H (600 MHz, $CDCl_3$): 8.04 (2H, d, J = 7.9 Hz, Bz-H), 7.96 (2H, d, J = 7.9 Hz, Bz-H), 7.42-7.26 (16H, m, Ar-H), 5.85 (1H, ddd, $J_{2,1}$ = 17.7 Hz, $J_{2,1'}$ = 9.8 Hz, $J_{2,3}$ = 7.5 Hz, H-2), 5.33 (1H, app d, $J_{1,2}$ = 17.7 Hz, H-1), 5.29 (1H, app d, $J_{1',2}$ = 9.8 Hz, H-1'), 4.72 (2H, d, J = 11.8 Hz, Bn-CH_2), 4.59 (3H, m, Bn-CH_2), 4.58 (1H, d, $J_{4,3}$ = 6.4 Hz, H-4), 4.49 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.48 (1H, d, J = 12.1 Hz, Bn-CH_2), 4.36 (1H, dd, $J_{3,2}$ = 7.5 Hz, $J_{3,4}$ = 6.4 Hz, H-3), 4.46 (1H, d, $J_{6,6'}$ = 13.2 Hz, H-6), 4.38 (1H, d, $J_{6',6}$ = 13.2 Hz, H-6')

δ_C (150 MHz, $CDCl_3$): 164.9 (C=O), 163.3 (C-5), 138.2 (q-Bz), 137.7, 137.3, 137.1 (q-Ar), 133.6 (C-2), 133.4, 129.6, 128.6, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5 (Ar-C), 119.7 (C-1), 82.0 (C-3), 81.7 (C-4), 73.8, 73.2, 71.3 (Bn-CH_2), 63.4 (C-6).

ν_{max} (film)/cm^{-1}: 1749 (C=O), 1422 (C=C aromatic).

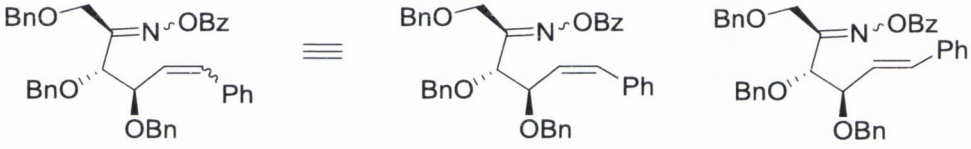
HRMS (*m/z* ES^+): Calcd for $C_{34}H_{33}NO_5$ [M + Na]$^+$ 558.2256 Found 558.2268.

5.2.2.5 1-Phenyl-3,4,6-Tri-*O*-benzyl-1,2,5-trideoxy-D-arabino-hex-1-en-5-oxime (262)



Procedure as described for **229** to afford **262**. Purification by column chromatography (18:1 Hexane/Ethyl Acetate) gave **262** (820 mg, 1.61 mmol, 69%) as a yellow oil as a mixture of isomers. Owing to considerable overlap on the NMR spectrum this compound could not be characterised and was used directly in the next step.

5.2.2.6 1-Phenyl-3,4,6-Tri-*O*-benzyl-1,2,5-trideoxy-D-arabino-hex-1-en-5-benzoyl oxime ester (264)



Procedure as described for **224** to afford **264**. Purification by column chromatography (30:1 Hexane/Ethyl Acetate) gave **263** (776 mg, 1.27 mmol, 79%) as a colourless oil and in a 1:1 mixture of isomers.

Data for *E* isomer

δ_H (600 MHz, $CDCl_3$): 7.41-7.20 (25H, m, Ar-H), 6.73 (1H, d, $J_{1,2}$ = 16.5 Hz, H-1), 6.03 (1H, dd, $J_{2,1}$ = 16.5 Hz, $J_{2,3}$ = 6.4 Hz, H-2), 5.37 (1H, d, $J_{4,3}$ = 6.1 Hz, H-4), 4.96 (1H, dd, $J_{3,2}$ = 6.4 Hz, $J_{3,4}$ = 6.1 Hz, H-3), 4.73 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.57 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.55 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.46 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.44 (2H, m, Bn-CH_2), 4.36 (1H, d, $J_{6,6'}$ = 13.4 Hz, C-6), 4.21 (1H, d, $J_{6',6}$ = 13.4 Hz, C-6)

δ_C (150 MHz, $CDCl_3$): 165.3 (C=O), 164.9 (C-5), 158.8 (q-Ph), 138.6 (q-Bz), 137.8, 137.7, 137.5 (q-Ar), 135.1 (C-1), 133.1, 128.6, 128.5, 128.5,

128.5, 128.4 (Ar-C), 127.9 (C-2), 128.0, 128.1, 128.0, 127.7, 127.6, 127.6, 125.4, 125.4, 125.2 (Ar-C), 80.1 (C-4), 76.3 (C-3), 75.1, 73.7, 73.1 (Bn-CH_2), 62.1 (C-6).

ν_{max} (film)/cm^{-1}: 1728 (C=O), 1120 (C-*O*-C aromatic).

HRMS (*m/z* ES^+): Calcd for $C_{33}H_{32}O_4$ [M + Na]$^+$ 634.2569 Found 634.2561.

Data for *Z* isomer

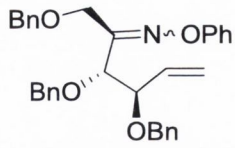
δ_H (600 MHz, $CDCl_3$): 7.57 (5H, m, Bz-Ar), 7.41-7.20 (20H, m, Ar-C), 6.87 (1H, d, $J_{1,2}$ = 11.9 Hz, H-1), 5.94 (1H, dd, $J_{2,1}$ = 11.9 Hz, $J_{2,3}$ = 6.8 Hz, H-2), 4.88 (1H, d, $J_{4,3}$ = 6.2 Hz, H-4), 4.67 (1H, d, J = 11.4 Hz, Bn-CH_2), 4.65 (1H, d, J = 11.3 Hz, Bn-CH_2), 4.59 (2H, m, Bn-CH_2), 4.51 (1H, dd, $J_{3,2}$ = 6.8 Hz, $J_{3,4}$ = 6.2 Hz, H-3), 4.38 (1H, d, J = 12.9 Hz, H-6), 4.36 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.31 (1H, d, J = 12.9 Hz, H-6') 4.29 (1H, d, J = 11.8 Hz, Bn-CH_2),

δ_C (150 MHz, $CDCl_3$): 165.8 (C=O), 165.0 (C-5), 158.4 (q-Ph), 138.8 (q-Bz Ar), 138.5, 137.7, 137.2 (q-Ar), 135.2 (C-1), 129.5, 129.4, 129.1, 128.6, 128.5, 128.5, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 128.1, 128.0, 127.4 (Ar-C), 125.6 (C-2), 80.2 (C-4), 77.1 (C-3), 74.8, 73.2, 72.9 (Bn-CH_2), 63.6 (C-6).

ν_{max} (film)/cm^{-1}: 1728 (C=O), 1120 (C-*O*-C aromatic).

HRMS (*m/z* ES^+): Calcd for $C_{33}H_{32}O_4$ [M + Na]$^+$ 634.2569 Found 634.2561.

5.2.2.7 3,4,6-Tri-*O*-benzyl-1,2,5-trideoxy-D-galacto-hex-1-en-6-phenyloxime (266)



Procedure as described for **248** to afford **266**. Purification by column chromatography (10:1 Hexane/Ethyl Acetate) gave **266** (300 mg, 0.59 mmol, 80%) as a colourless oil.

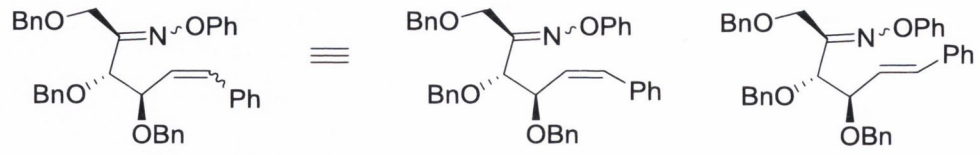
δ_H (600 MHz, $CDCl_3$): 7.40-7.24 (15H, m, Ar-H), 7.18-7.05 (5H, m, Ar-H), 5.85 (1H, ddd, $J_{2,1}$ = 17.4 Hz, $J_{2,1'}$ = 10.3 Hz, $J_{2,3}$ = 6.1 Hz, H-2), 5.31 (1H, app d, $J_{1,2}$ = 17.4 Hz, H-1), 5.27 (1H, app d, $J_{1',2}$ = 10.3 Hz, H-1'), 5.13 (1H, d, $J_{4,3}$ = 6.1 Hz, H-4), 4.68 (1H, d, J = 12.5 Hz, Bn-CH_2), 4.64 (1H, d, J = 11.4 Hz, Bn-CH_2), 4.51 (5H, m, Bn-CH_2), 4.31 (1H, d, $J_{6',6}$ = 13.1 Hz, H-6'), 4.29 (1H, app t, $J_{3,2} = J_{3,4}$ = 6.1 Hz, H-3).

δ_C (150 MHz, $CDCl_3$): 159.2 (C-5), 159.1 (q-Ph), 158.6 (q-OPh) 138.1, 138.0, 137.9 (q-Ar), 134.9 (C-2), 129.2, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 128.1, 127.8, 126.7, 126.5, 126.1, 125.9, 125.4 (Ar-C), 122.5 (p-Ph), 119.5 (o-Ph), 114.9 (C-1), 81.3 (C-3 and C-4), 73.8, 73.5, 72.1 (Bn-CH_2), 63.5 (C-6).

ν_{max} (film)/cm^{-1}: 1609 (C=C), 1093 (C-*O*-C)

HRMS (*m/z* ES+): Calcd for $C_{33}H_{33}NO_4$ [M + Na]$^+$ 530.2307 Found 530.2292

5.2.2.8 1-Phenyl-3,4,6-Tri-*O*-benzyl-1,2,5-trideoxy-D-arabino-hex-1-en-5-phenyl oxime (267)



Procedure as described for **248** to afford **267**. Purification by column chromatography (30:1 Hexane/Ethyl Acetate) gave **267** (1.24 g, 0.21 mmol, 62 %) as a colourless oil and in a 1:1 mixture of isomers.

Data for *E* isomer

δ_H (600 MHz, $CDCl_3$): 7.42-7.03 (25H, m, Ar-H), 6.61 (1H, d, $J_{1,2}$ = 16.3 Hz, H-1), 6.25 (1H, dd, $J_{2,1}$ = 16.3 Hz, $J_{2,3}$ = 7.2 Hz, H-2), 5.17 (1H, d, $J_{4,3}$ = 4.0 Hz, H-4), 4.84 (1H, dd, $J_{3,2}$ = 7.2 Hz, $J_{3,4}$ = 4.0 Hz, H-3), 4.54 (1H, d, $J_{6,6'}$ = 12.8 Hz, H-6), 4.34 (1H, d, $J_{6',6}$ = 12.8 Hz, H-6'), 4.72-4.60 (6H, m, Bn-CH_2).

δ_C (150 MHz, $CDCl_3$): 159.6 (C-5), 159.1 (q-Ph), 158.4 (q-OPh) 138.6, 138.4, 138.3 (q-Ar), 134.9 (C-1), 129.2, 128.7, 128.6, 128.6, 128.4, 128.2, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 127.5 127.3, 127.1 (Ar-C), 125.3 (C-2), 78.4 (C-4), 75.1 (C-3), 73.2, 72.8, 72.6 (Bn-CH_2), 62.3 (C-6)

ν_{max} (film)/cm^{-1}: 1425 (C=C aromatic), 1032 (C-*O*-C).

HRMS (*m/z* ES^+): Calcd for $C_{39}H_{37}NO_4$ [M + Na]$^+$ 606.2620 Found 606.2008.

Data for *Z* isomer

δ_H (600 MHz, $CDCl_3$): 7.42-7.03 (25H, m, Ar-H), 6.80 (1H, d, $J_{1,2}$ = 11.7 Hz, H-1), 5.84 (1H, d, $J_{2,1}$ = 11.7 Hz, $J_{2,3}$ = 9.8 Hz, H-2), 4.88 (1H, dd, $J_{3,2}$ = 9.8 Hz, $J_{3,4}$ = 5.9 Hz, H-3), 4.85 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.68 (1H, d, J = 12.2 Hz, Bn-CH_2), 4.64 (1H, d,

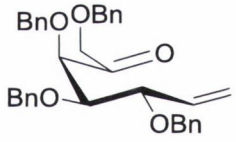
$J_{4,5}$ = 6.0 Hz, H-4), 4.61 (1H, d, J = 12.2 Hz, Bn-CH_2), 4.55 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.53 (2H, m, Bn-CH_2), 4.42 (1H, d, $J_{6,6'}$ = 13.8 Hz, H-6), 4.15 (1H, d, $J_{6',6}$ = 13.8 Hz, H-6'),

δ_C (150 MHz, $CDCl_3$): 162.3 (C-5), 158.8 (q-Ph), 158.1 (q-OPh), 138.4, 138.1, 137.8 (q-Ar), 134.3 (C-1), 129.8, 128.6, 128.5, 128.4, 128.4, 128.3, 128.2, 128.2, 128.2, 128.2 (Ar-C), 127.8 (C-2), 127.4 127.1, 126.0 (Ar-C), 122.1 (p-Ph), 114.8 (o-Ph), 81.2 (C-4), 80.6 (C-3), 74.6, 72.3, 72.4 (Bn-CH_2), 63.9 (C-6).

ν_{max} (film)/cm^{-1}: 1425 (C=C aromatic), 1032 (C-*O*-C).

HRMS (*m/z* ES^+): Calcd for $C_{39}H_{37}NO_4$ [M + Na]$^+$ 606.2620 Found 606.2008.

5.2.2.9 3,4,5,7-Tetra-*O*-benzyl-1,2,6-trideoxy-D-galacto-hept-1-en-6-one (268)[368]



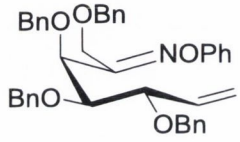
Procedure as described for **259** to afford **268**. Purification by column chromatography (10:1 Hexane/Ethyl Acetate) gave **268** (312 mg, 0.58 mmol, 86%) as a white solid.

δ_H (400 MHz, $CDCl_3$): 7.35 – 7.16 (20H, m, Ar-H), 5.85 (1H, ddd, $J_{2,1}$ = 9.4 Hz, $J_{2,1}$ = 17.5 Hz, $J_{2,3}$ = 7.3 Hz, H-2), 5.37 (1H, app d, $J_{1',2}$ = 17.5 Hz, H-1'), 5.30 (1H, app d, $J_{1,2}$ = 9.4 Hz, H-1), 4.73 (1H, d, J = 11.2 Hz, Bn-CH_2), 4.60 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.58 (1H, d, J = 11.2 Hz, Bn-CH_2), 4.47 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.43 (1H, d, J = 11.8 Hz, H-7), 4.38 (1H, d, J = 11.1 Hz, Bn-CH_2), 4.37 (1H, d, J = 11.1 Hz, Bn-CH_2), 4.35 (2H,

m, Bn-CH_2), 4.25 (1H, d, J = 18.4 Hz, H-7), 4.18 (1H, d. $J_{5,4}$ = 4.5 Hz, H-5), 4.11 (1H, app t, $J_{3,2} = J_{3,4}$ = 7.3 Hz, H-3), 3.90 (1H, dd, $J_{4,3}$ = 7.3 Hz, $J_{4,5}$ = 4.5 Hz, H-4).

HRMS (*m/z* ES+): Calcd for $C_{35}H_{36}O_5$ [M + Na]$^+$ 599.2460 Found 559.2469

5.2.2.10 3,4,5,7-Tetra-*O*-benzyl-1,2,6-trideoxy-D-galacto-hept-1-en-6-phenyloxime (265)



Procedure as described for **230** to afford **265**. Purification by column chromatography (10:1 Hexane/Ethyl Acetate) gave **265** (154 mg, 0.25 mmol, 61%) as a white solid.

δ_H (600 MHz, $CDCl_3$): 7.36-7.18 (14 H, m, Ar-H), 7.06 (1H, t, J = 7.3 Hz, p-Ph), 6.01 (1H, ddd, $J_{2,1}$ = 10.7 Hz, $J_{2,1'}$ = 17.6 Hz, $J_{2,3}$ = 7.9 Hz, H-2), 5.40 (1H, app d, $J_{1',2}$ = 17.6 Hz, H-1'), 5.32 (1H, app d, $J_{1,2}$ = 10.7 Hz, H-1), 4.72 (1H, d, J = 11.2 Hz, Bn-CH_2), 4.67 (1H, d, $J_{5,4}$ = 8.3 Hz, H-5), 4.68 (1H, d, J = 12.2 Hz, Bn-CH_2), 4.59 (1H, d, J = 11.5 Hz, Bn-CH_2), 4.56 (1H, d, J = 11.2 Hz, Bn-CH_2), 4.55 (2H, s, Bn-CH_2), 4.47 (1H, d, $J_{7,7'}$ = 13.3 Hz, H-7), 4.35 (1H, d, J = 12.2 Hz, Bn-CH_2), 4.33 (1H, d, J = 11.5 Hz, Bn-CH_2), 4.26 (1H, d, $J_{7',7}$ = 13.3 Hz, H-7'), 4.23 (1H, dd, $J_{3,2}$ = 7.9 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 4.03 (1H, dd, $J_{4,3}$ = 3.5 Hz, $J_{4,5}$ = 8.3 Hz, H-4).

δ_C (150 MHz, $CDCl_3$): 159.8 (C-6), 159.1 (q-Ph), 138.5, 138.3, 137.9, 137.9 (q-Bn), 136.1 (C-2), 129.2, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 127.4 (Ar-C), 122.3 (p-Ph),

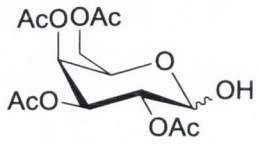
118.5 (C-1), 115.1 (o-Ph), 82.5 (C-4), 80.4 (C-3), 78.1 (C-5), 74.6, 73.6, 71.5, 70.6 (Bn-CH_2), 63.5 (C-7).

ν_{max} (film)/cm^{-1}: 1089 (C-*O*-C)

HRMS (*m/z* ES+): Calcd for $C_{41}H_{41}NO_5$ [M + Na]$^+$ 350.2882 Found 650.2893.

5.2.3 *N*-linked glycopeptide synthesis

5.2.3.1 2,3,4,6-tetra-*O*-acetyl-D-galactopyranoside (273)[369]

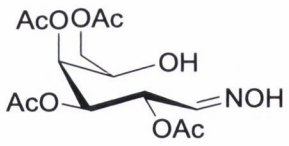


Penta-acetylated-β-galactopyranoside **272** (4.00 g, 10.2 mmol) was dissolved in THF (50 mL), benzylamine (2.24 mL, 20.5 mmol) was added and the resultant solution was stirred at room temperature overnight. The progression of the reaction was monitored by TLC (3:1 EtOAc/Hexane). Upon completion the solution was concentrated, diluted in DCM (50 mL) and washed with ice cold 1M HCl (2 x 30 mL), saturated $NaHCO_3$ (2 x 30 mL) brine (30 mL) and water (30 mL). The organic extract were dried over $MgSO_4$ and purified by column chromatography (60:40 EtOAc/Hexane) to give **273** (3.14 g, 9.02 mmol, 87%) as a white solid

δ_H (400 MHz, $CDCl_3$): 5.53 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1), 5.49 (1H, dd, $J_{4,3}$ = 3.3 Hz, $J_{4,5}$ = 1.3 Hz, H-4), 5.43 (1H, dd, $J_{3,2}$ = 10.8 Hz, $J_{3,4}$ = 3.3 Hz, H-3), 5.17 (1H, dd, $J_{2,1}$ = 3.6 Hz, $J_{2,3}$ = 10.8 Hz, H-2), 4.49 (1H, dd, $J_{5,4}$ = 1.3 Hz, $J_{5,6}$ = 6.7 Hz, H-5), 4.12 (2H, m, H-6), 2.17, 2.12, 2.07, 2.01 (3H, s, CH_3) ;

HRMS (*m/z* ES+): Calcd for $C_{14}H_{20}O_{10}$ [M + Na]$^+$ 371.0954 Found 371.0952.

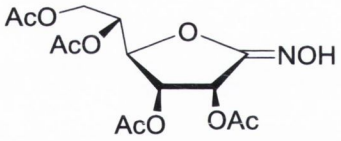
5.2.3.2 2,3,4,6-Tetra-*O*-acetyl-1-deoxy-D-galacto-hept-1-oxime (274)[321]



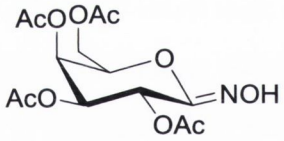
Hydroxylamine hydrochloride (289 mg, 4.16 mmol) and **273** (1 g, 2.77 mmol) were dissolved in MeOH (30 mL). Pyridine (0.63 mL, 7.69 mmol) was added and the solution was stirred at reflux (70°C) for 2 hours. The progression of the reaction was monitored by TLC (3:1 Hexane/EtOAc). Upon completion the reaction mixture was concentrated and the residue was dissolved in EtOAc (20 mL) and washed with water (2 x 30 mL) and brine (10 mL), dried ($MgSO_4$) filtered and concentrated. The residue was purified by column chromatography 1:1 Hexane/EtOAc to give **274** (762 mg, 74%) as a mixture of isomers. Used directly in the next step without further purification.

5.2.3.4 2,3,4,6-Tetra-*O*-Acetyl-1-deoxy-1-oxime-D-galactopyranoisde (276)[321]

2,3,5,6-Tetra-*O*-Acetyl-1-deoxy-1-oxime-D-galactofuranoisde (275)[321]



275



276

DBU (0.33 mL) was added to oxime **274** (720 mg, 1.9 mmol) and NCS (29 mg, 2.21 mmol) in CH_2Cl_2 (50 mL) at -45°C. The reaction mixture was left to stir at -45°C for 1 hour in such a way that the temperature did not exceed -40 °C. After 1 hour the reaction was allowed to warm to room temperature gradually over 3 hours. Distilled water (10 mL) was added portionwise to quench the reaction, EtOAc (50 mL) was added and the organic layer was separated. The organic layer was washed with water (2 x 20 mL) and brine (50 mL), dried ($MgSO_4$) filtered and concentrated. The resultant residue was

purified by chromatography 2:1 EtOAc/Hexane to give **276** (319 mg, 45%) as a white solid and **275** (182 mg 26%) as a colourless oil.

Data for 275

δ_H (400 MHz, $CDCl_3$): 5.87 (1H, d, $J_{2,3}$ = 3.1 Hz, H-2), 5.43 (1H, td, $J_{5,4}$ = 4.2 Hz, $J_{5,6}$ = 6.4 Hz, $J_{5,6'}$ = 5.2 Hz, H-5), 5.24 (1H, app t, $J_{3,2} = J_{3,4}$ = 3.1 Hz, C-3), 4.67 (1H, dd, $J_{4,3}$ = 3.1 Hz, $J_{4,5}$ = 4.2 Hz, H-4), 4.38 (1H, dd, $J_{6,5}$ = 6.4 Hz, $J_{6,6'}$ = 12.0 Hz, H-6), 4.26 (1H, dd, $J_{6'5}$ = 5.2 Hz, $J_{6',6}$ = 12.0 Hz, H-6'), 2.17, 2.16, 2.15, 2.13, 2.08 (3H, s, CH_3)

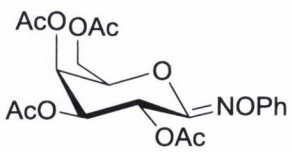
HRMS (*m/z* ES^+); Calcd for $C_{14}H_{19}NO_{10}$ [M + Na]$^+$ 384.0907 Found 384.0921.

Data for 276

δ_H (400 MHz, $CDCl_3$): 5.67 (1H, d, $J_{2,3}$ = 9.4 Hz, H-2), 5.56 (1H, dd, $J_{4,5}$ = 1.6 Hz, $J_{4,3}$ = 3.2 Hz, H-4), 5.24 (1H, dd, $J_{3,2}$ = 9.4 Hz, $J_{3,4}$ = 3.2 Hz, H-3), 4.47 (1H, td, $J_{5,4}$ = 1.6 Hz, $J_{5,6}$ = 6.7 Hz, H-5), 4.25 (2H, dd, $J_{6,6'}$ = 10.9 Hz, $J_{5,6}$ = 6.7 Hz, H-6), 2.14, 2.08, 2.04, 2.0 (CH_3)

HRMS (*m/z* ES^+); Calcd for $C_{14}H_{19}NO_{10}$ [M + Na]$^+$ 384.0907 Found 384.0918.

5.2.3.5 2,3,4,6-Tetra-*O*-Acetyl-1deoxy-1-phenyloxime-D-galactopyranoisde (277)



276 (100 mg, 0.23 mmol), $[Cu(CH_3CN)_4]PF_6$ (86 mg, 0.23 mmol), phenyl boronic acid (65 mg, 0.46 mmol) were dissolved in dry DCE (15 mL). 4A molecular sieves and pyridine (20 μL, 0.25 mmol) were added, a stopper was loosely applied so that the

reaction was open to the atmosphere and left to stir for 72 hours. The progression of the reaction was followed by TLC (2:1 Hexane/ EtOAC). Upon completion the reaction mixture was concentrated and purified by column chromatography 2:1 EtOAc/Hexane to give **277** (68 mg, 0.16 mmol, 68%) as a colourless oil.

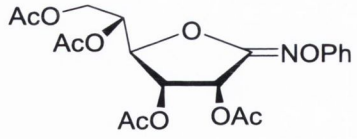
δ_H (400 MHz, $CDCl_3$): 7.31 (2H, m, Ar-H), 7.15 (2H, d, J = 9.0 Hz, Ar-H), 7.03 (2H, t, J = 6.7 Hz) 5.85 (1H, d, $J_{2,3}$ = 9.7 Hz, H-2), 5.68 (1H, dd, $J_{4,5}$ = 1.6 Hz, $J_{4,3}$ = 3.0 Hz, H-4), 5.36 (1H, dd, $J_{3,4}$ = 3.1 Hz, $J_{3,2}$ = 9.7 Hz, H-3), 4.59 (1H, td, $J_{5,4}$ = 1.1 Hz, $J_{5,6}$ = 6.4 Hz, H-5), 4.39 (1H, dd, $J_{6,5}$ = 6.4 Hz, $J_{6,6'}$ = 11.5, H-6), 4.3 (1H, dd, $J_{6'5}$ = 6.9 Hz, $J_{6'6}$ = 11.3 Hz, H-6'), 2.21 (3H, s, CH_3), 2.19 (6H, s, CH_3), 2.16 (3H, s, CH_3)

δ_C (100 MHz, $CDCl_3$): 170.0, 169.6, 169.6, 169.4 (C=O), 159.0 (q-OPh), 149.8 (C=N), 129.2, 127.5, 122.2 (Ar-C), 75.0 (C-5), 69.7 (C-3), 66.0 (C-4), 65.1 (C-2), 60.7 (C-6).

ν_{max} (film)/cm^{-1}: 1736 (C=O), 1022 (C-O).

HRMS (*m/z* ES^+); Calcd for $C_{20}H_{23}NO_{10}$ [M + Na]$^+$ 460.1220 Found 460.1202

5.2.3.6 2,3,5,6-Tetra-*O*-Acetyl-1-deoxy-1-phenyloxime-D-galactofuranoisde (278)



Procedure as described for **277** to afford **278.** Purification by column chromatography 2:1 EtOAc/Hexane to give **278** (44 mg, 0.1 mmol, 63%) as a colourless oil.

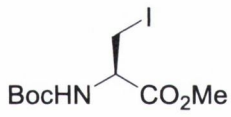
δ_H (400 MHz, $CDCl_3$): 7.32 – 7.03 (5H, m, Ar-H), 5.95 (1H, d, $J_{2,3}$ = 3.2Hz, H-2), 5.45 (1H, dt, $J_{5,4}$ = 4.5 Hz, $J_{5,6}$ = 6.5 Hz, H-5), 5.29 (1H, app t, $J_{3,2} = J_{3,4}$ = 4.5 Hz, H-3), 4.70 (1H, app t, $J_{4,3} = J_{4,5}$ = 4.5 Hz, H-4), 4.45 (1H, dd, $J_{6,5}$ = 6.7 Hz, $J_{6,6'}$ = 12.1 Hz, H-6), 4.32 (1H, dd, $J_{6',5}$ = 6.5 Hz, $J_{6'6}$ = 12.1 Hz, H-6'), 2.21 (3H, s, CH_3), 2.19 (6H, s, CH_3), 2.16 (3H, s, CH_3)

δ_C (100 MHz, $CDCl_3$): 169.9, 169.7, 169.0, 169.0 (C=O), 159.2 (C=N), 155.4 (q-Ar), 129.2, 122.3, 114.3 (Ar-C), 84.5 (C-4), 75.2 (C-3), 72.6 (C-2), 69.1 (C-5), 62.1 (C-6).

ν_{max} (film)/cm^{-1}: 1741 (C=O), 1048 (C-O)

HRMS (*m/z* ES^+); Calcd for $C_{20}H_{23}NO_{10}$ [M + Na]$^+$ 460.1220 Found 460.1208.

5.2.3.7 Iodoserine-Boc-NH-Methy-Ester (282)[322]

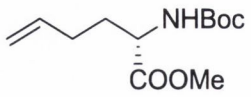


281 (2.00g, 0.009 mmol), PPh_3 (2.99 g, 0.011 mmol) and imidazole (0.78 g, 0.011 mmol) were dissolved in CH_2Cl_2 (50 mL). Iodine (2.89 g, 0.011 mmol) was added portionwise. The reaction was left to stir over ice for 1 h and allowed to warm to room temperature over a further 2 h. Upon completion (TLC) the reaction mixture was filtered, concentrated and suspended in diethyl ether (100 mL) overnight. The reaction mixture was filtered and concentrated *in vacuo*. Purification by column chromatography (10:1 Hexane/Diethyl Ether) gave **282** (1.72 g, 0.48 mmol, 48%) as a yellow crystalline solid.

δ_H (400 MHz, $CDCl_3$): 5.39 (1H, d, J = 7.1 Hz, NH), 4.54 (1H, dt, J = 3.2 Hz, J = 7.1 Hz, C<u>H</u>CH_2I), 3.81 (3H, s, CO_2<u>Me</u>), 1.47 (9H, s, BOC-CH_3)

HRMS (*m/z* ESI+): Calcd for $C_9H_{16}INO_4$ [M + Na]$^+$ 352.0022 Found 352.0031.

5.2.3.8 (S)-methyl 2-((tert-butoxycarbonyl)amino)hex-5-enoate (283)[322]

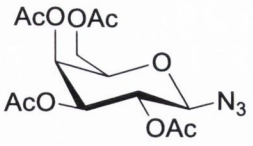


Zinc dust (0.300 g, 4.56 mmol) was added to iodine (0.012 g, 0.047 mmol) in a 3 neck round bottomed flask and heated under vacuum with a heat gun for 10 min. The flask was flushed with nitrogen and evacuated 3 times. *N*-(*tert*-Butoxycarbonyl)-3-iodo-L-alanine methyl ester **282** (0.500 g, 1.52 mmol) was dissolved in dry DMF (5 mL) and added to the zinc slurry at 0 ^{0}C. The reaction mixture was stirred at room temperature for 1 h. Whilst the zinc insertion reaction was in progress, CuBr_DMS(0.041 g, 0.20 mmol) was placed in a 3 way flask and gently dried under vacuum with a heat gun until a colour change from white to green. Dry DMF (4 mL) and allyl chloride (0.151 g, 1.98 mmol) were added and the reaction cooled to -15^{0}C. Once zinc insertion was complete, stirring of the reaction mixture was ceased to allow the zinc to settle and the supernatant was removed and added dropwise to the electrophile and Cu catalyst. The cold bath was removed and the reaction mixture was stirred at room temperature for 2 days. EtOAc (100 mL) was added and the reaction was stirred for 15 min. The reaction mixture was washed with 1 M $Na_2S_2O_3$ (100 mL), water (2 x 100 mL) and brine (100 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by column chromatography (95:5 hexane:ether) to furnish **283** as a yellow oil (143 mg, 0.59 mmol, 39%).

δ_H (400 MHz, $CDCl_3$): 5.84 – 5.68 (1H, m, $CH_2C\underline{H}$), 5.10 – 4.93 (2H, m, $C\underline{H_2}CH$), 4.30 (1H, m, $C\underline{H}NHBoc$), 3.72 (3H, s, OCH_3), 2.10 (2H, m, CH_2), 1.97 – 1.56 (4H, m, CH_2, CH_2), 1.42 (9H, s, $C(C\underline{H_3})_3$);

HRMS (*m/z* ES^+); Calcd. For $C_{12}H_{21}NO_4$ $[M + Na]^+$ 266.1368, Found 266.1371.

5.2.3.9 1-azido-2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranoside (286)[324]

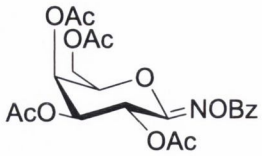


Penta-acetylated-β-galactopyranoside **272** (1.00 g, 2.56 mmol) was dissolved in dry DCM (60 mL) over 4A molecular sieves.The reaction mixture was cooled to 0°C and azidotrimethylsilane (0.37 mL, 2.82 mmol) was added dropwise. Stannic chloride (0.24 mL, 2 mmol) was added dropwise and the reaction mixture was left to stir under nitrogen for 3.5 hours The progression of the reaction was followed by TLC (3:1 Ethyl Acetate/ Hexane). The reaction mixture was added dropwise to distilled water (50 mL) and the organic layer was separated and washed with water (30 mL). The organic extracts were dried ($MgSO_4$) filtered, concentrated and purified by column chromatography 3:1 EtOAc/Hexane to give **36** (868 mg, 2.32 mmol, 91%) as a white solid.

δ_H (400 MHz, $CDCl_3$): 5.45 (1H, dd, $J_{4,3}$ = 3.3 Hz, $J_{4,5}$ = 1.2 Hz, H-4) 5.19 (1H, dd, $J_{2,1}$ = 9.3 Hz, $J_{2,3}$ = 10.3 Hz, H-2), 5.06 (1H, dd, $J_{3,2}$ = 10.3 Hz, $J_{3,4}$ = 3.3 Hz, H-3), 4.62 (1H, d, $J_{1,2}$ = 9.3 Hz, H-1), 4.21 (2H, m, H-6) 4.04 (1H, dt, $J_{5,4}$ = 1.2 Hz, $J_{5,6}$ = 7.0 Hz, H-5), 2.20, 2.12, 2.09, 2.02 (3H, s, CH_3)

HRMS (*m/z* ES+): Calcd. For $C_{14}H_{19}N_3O_9$ $[M + Na]^+$ 396.1019, Found 396.1027.

5.2.3.10 1-Benzoyloxime-ester-2,3,4,6-Tetra-*O*-acetyl-galactopyranoside (287)



276 (100 mg, 0.27 mmol) was dissolved in pyridine (10 mL). The solution was cooled to 0°C and benzoyl chloride (0.04 mL, 0.35 mmol) was added dropwise. The reaction was stirred at room temperature for 2 hours. The reaction mixture was diluted in diethyl ether (25 mL) and washed with 1M HCl (3 x 30 mL) and $NaHCO_3$ (3 x 30 mL), dried ($MgSO_4$). The reaction mixture was purified by chromatography 1:1 EtOAc/Hexane to give **287** (65 mg, 0.14 mmol, 52%).

Date given for major *E* isomer

δ_H (600 MHz, $CDCl_3$): 8.08 (2H, d, J = 7.8 Hz, o-Ar), 7.60 (1H, t, J = 7.6 Hz, p-Ar), 7.47 (2H, t, J = 7.6 Hz, m-Ar) 5.78 (1H, d, $J_{2,3}$ = 9.6 Hz, H-2), 5.67 (1H, dd, $J_{4,3}$ = 3.4 Hz, $J_{4,5}$ = 1.29 Hz, H-4), 5.43 (1H, dd, $J_{3,2}$ = 9.6 Hz, $J_{3,4}$ = 3.4 Hz, H-3), 4.68 (1H, dt, $J_{5,4}$ = 1.2 Hz, $J_{5,6}$ = 7.2 Hz, H-5), 4.37 (1H, dd, $J_{6,5}$ = 7.2 Hz, $J_{6,6'}$ = 11.6 Hz, H-6), 4.27 (1H, dd, $J_{6',5}$ = 7.1 Hz, $J_{6',6}$ = 11.6 Hz, H-6'), 2.21 2.20, 2.08, 2.09 (3H, s, CH_3)

δ_C (150 MHz, $CDCl_3$): 170.0, 169.6, 169.5, 169.5 (C=O), 162.9 (C=O, Bz), 156.2 (C=N), 133.7 (q-Ar), 129.9, 128.4, 128.2 (Ar-C), 75.4 (C-2), 69.5 (C-4), 65.8 (C-5), 65.5 (C-3), 60.9 (C-6), 20.6, 20.4, 20.3, 20.3 (CH_3)

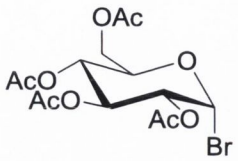
ν_{max} (film)/cm^{-1}: 1738 (C=O), 1020 (C-O)

HRMS (*m/z* ES^+); Calcd for $C_{21}H_{23}NO_{11}$ [M + Na]$^+$ 488.1169 Found 488.1158.

5.3 Experimental data Chapter 4

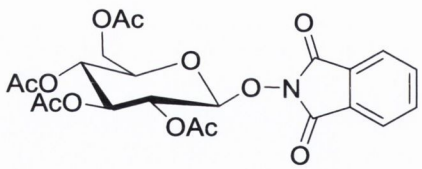
5.3.1 Synthesis of hydroxylamines

5.3.1.1 1-Bromo-2,3,4,6-Tetra-*O*-Acetyl-α-D-glucopyranoside (291)[354]



290 (1.00 g, 2.5 mmol) was dissolved in CH_2Cl_2 (20 mL) and the reaction mixture was cooled to 0 °C. Hydrogen bromide in glacial acetic acid (3.8 mL, 65 mmol) was added dropwise and the reaction mixture was left to stir for 3 h at room temperature. Upon completion (TLC) the reaction was quenched via dropwise addition to ice (50 mL). The mixture was stirred for 10 minutes, the organic layer was separated and the aqueous extracts extracted with CH_2Cl_2 (50 mL). The organic extracts were combined and washed with $NaHCO_3$ (100 mL x 3), water (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated to give **291** (1.00 g, 2.43 mmol, 98%) which was used directly in the next step without further purification.

5.3.1.2 1-*N*-hydroxy-pthalimide-2,3,4,6-tetra-*O*-acetyl-D-glucopyranoside (292)



Method A[354]

291 (0.95 g, 2.3 mmol) was dissolved in CH_2Cl_2 (30 mL). *N*-hydroxy-pthalimide (1.88 g, 11.5 mmol) was added followed by TBAHS (786 mg, 2.3 mmol) in a 1M solution of Na_2CO_3 at 0 °C. The reaction mixture was stirred vigorously for 18 h and allowed to warm to room temperature. Upon completion CH_2Cl_2 (50 mL) was added, the organic layer was separated and washed with water (6 x 50 mL) to remove all traces of bromine. The organic layer was then washed with brine (2 x 50 mL), dried ($MgSO_4$) and

concentrated *in vacuo*. Purification by column chromatography gave **292** (406 mg, 0.82 mmol, 36%) as a white solid in a 3.4 :1 mixture of β/α anomers.

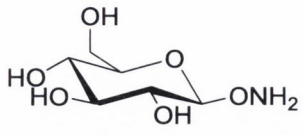
Method B[355]

290 (500 mg, 1.3 mmol) and *N*-hydroxy-pthalimide (815 mg, 5.0 mmol) were added to a flame dried round bottom flask containing activated 4Å molecular sieves. Dry CH_2Cl_2 (50 mL) was added and the reaction mixture was cooled to 0°C. BF_3OEt_2 (3.2 mL, 26 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 24 h. Upon completion (TLC), CH_2Cl_2 (50 mL) was added, the molecular sieves were filtered and the filtrate was washed with $NaHCO_3$ (100 mL x 2) and water (100 mL). The aqueous extracts were washed with CH_2Cl_2 (50 mL), the organic extracts were combined, dried ($MgSO_4$) and concentrated. Purification by chromatography (3:2 Hexane/ EtOAc) gave **292** (487 mg, 76%) as a white crystalline solid and as solely the β anomer.

δ_H (400 MHz, $CDCl_3$): 7.89 (1H, d, J = 3.0 Hz, Ar-H), 7.87 (1H, d, J = 3.0 Hz, Ar-H), 7.81 (1H, d, J = 3.2 Hz, Ar-H), 7.79 (1H, d, J = 3.2 Hz, Ar-H), 5.31 (3H, m, H-2, H-3 and H-4), 5.13 (1H, d, $J_{1,2}$ = 6.1 Hz, H-1), 4.37 (1H, dd, $J_{6,5}$ = 4.9 Hz, $J_{6,6'}$ = 12.4 Hz, H-6), 4.17 (1H, dd, $J_{6',5}$ = 2.9 Hz, $J_{6',6}$ = 12.4 Hz, H-6'), 3.79 (1H, ddd, $J_{5,4}$ = 2.7 Hz, $J_{5,6}$ = 2.9 Hz, $J_{5,6'}$ = 4.9 Hz, H-5) 2.21, 2.08, 2.06, 2.05 (CH_3).

HRMS (*m/z* ESI+): Calcd for $C_{22}H_{23}NO_{10}$ [M + Na]$^+$ 516.1118 Found 516.1131

5.3.1.3 1-hydroxylamine-α-D-glucopyranoside (293)[355]



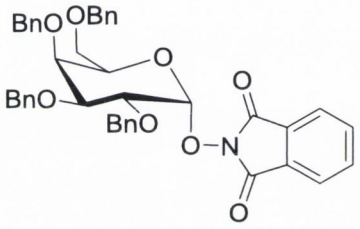
292 (222 mg, 0.45 mmol) was dissolved in EtOH (30 mL), hydrazine monohydrate (0.15 mL, 3.15 mmol) was added dropwise. The reaction mixture was left to stir at room temperature for 16 h. Upon completion (TLC) the reaction mixture was concentrated and

dried under vacuum to remove unreacted hydrazine. The crude reaction mixture **293** was used directly in the next step.

δ_H (400 MHz, D_2O): 4.43 (1H, d, $J_{1,2}$ = 8.1 Hz, H-1), 3.82 (1H, app d, $J_{6,6'}$ = 12.2 Hz, H-6), 3.6 (1H, dd, $J_{6',5}$ = 6.0 Hz, $J_{6',6}$ = 12.2 Hz, H-6), 3.42-3.15 (4H, m, H-2, H-3, H-4 and H-5)

HRMS (*m/z* ESI+): Calcd for $C_6H_{13}NO_6$ [M + Na]$^+$ 218.0641 Found 218.0651

5.3.1.4 1-*N*-hydroxy-pthalimide-2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranoside (295)[370]



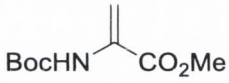
179 (1.00 g, 1.85 mmol), *N*-hydroxy pthalimide (302 mg, 1.85 mmol) and NEt_3 (0.25 mL, 1.85 mmol) were added to a flame dried round bottom flask containing activated 4Å molecular sieves. Dry CH_2Cl_2 (50 mL) was added and the reaction mixture was cooled to 0°C. BF_3OEt_2 (0.91 mL, 7.4 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 3 h at room temperature. Upon completion (TLC), CH_2Cl_2 (50 mL) was added, the molecular sieves were filtered and the filtrate was washed with $NaHCO_3$ (100 mL x 2) and water (100 mL). The aqueous extracts were washed with DCM (50 mL), the organic extracts were combined, dried ($MgSO_4$) and concentrated. Purification by chromatography 7:3 (Hexane/ Ethyl Acetate) gave **295** (696 mg, 1.02 mmol 76%) as a white crystalline solid and as solely the α anomer.

δ_H (400 MHz, $CDCl_3$): 7.86-7.73 (4H, m, Ar-H), 7.79-7.76 (20H, m, Ar-H), 5.72 (1H, d, $J_{1,2}$ = 3.9 Hz, H-1), 5.15 (1H, d, J = 11.1 Hz, Bn-CH_2), 5.04 (1H, d, J = 11.8 Hz, Bn-CH_2), 5.01 (1H, dd, $J_{3,2}$ = 7.6 Hz, $J_{3,4}$ = 6.1 Hz, H-3), 4.98 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.90 (1H, d, J = 11.5 Hz, Bn-CH_2), 4.84 (1H, d, J = 11.7 Hz, Bn-CH_2), 4.67 (1H, d, J = 11.1 Hz, Bn-CH_2), 4.62

(1H, d, J = 11.7 Hz, Bn-CH_2), 4.55 (1H, d, J = 11.5 Hz, Bn-CH_2), 4.34 (1H, dd, $J_{2,1}$ = 3.9 Hz, $J_{2,3}$ = 7.6 Hz, H-2), 4.21 (2H, m, H-4 and H-5), 3.68 (1H, dd, $J_{6,5}$ = 7.9 Hz, $J_{6,6'}$ = 9.1 Hz, H-6), 3.60 (1H, dd, $J_{6',5}$ = 5.9 Hz, $J_{6',6}$ = 9.1 Hz, H-6')

HRMS (*m/z* ESI+): Calcd for $C_{42}H_{39}NO_8$ [M + Na]$^+$ 708.2573 Found 708.2590.

5.3.1.5 Didehydroalanine (296)[356]

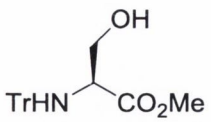


282 (441 mg, 1.34 mmol) and *N*-hydoxy pthalimide (200 mg, 1.22 mmol) were dissolved in CH_2Cl_2 (20 mL). Triethylamine (0.26 mL, 1.83 mmol) was added and the reaction was left to stir for 18 h at room temperature. The reaction mixture was filtered and partitioned between CH_2Cl_2 (50 mL) and water (50 mL). The organic layer was washed with $NaHCO_3$ (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (3:1 Hexane/Ethyl Acetate) gave **296** (253 mg, 1.25 mmol, 94%) as a white solid.

δ_H (400 MHz, $CDCl_3$): 6.18 (1H, bs, C=C<u>H</u>), 5.75 (1H, d, J = 1.6 Hz, C=C<u>H</u>), 3.85 (3H, bs, CO_2<u>Me</u>), 1.51 (9H, s, Boc-C<u>H</u>$_3$)

HRMS (*m/z* ESI+): Calcd for $C_9H_{15}NO_4$ [M + Na]$^+$ 224.0899 Found 224.0881.

5.3.1.6 Serine-Trityl-NH-Methyl ester (297)[357]



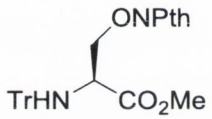
To a suspension of **280** (5.00 g, 32.3 mmol) in CH_2Cl_2 (60 mL) at 0 °C, under a blanket of nitrogen, was added dropwise triethylamine (9.0 mL, 64.5 mmol) and trityl chloride (9.00 g, 32.3 mmol) in CH_2Cl_2 (70 mL). The reaction mixture was stirred at room temperature for 18 h under nitrogen. Upon completion (TLC) the reaction mixture was

filtered and concentrated *in vacuo*. The reaction mixture was diluted in diethyl ether (150 mL) and washed with $NaHCO_3$ (100 mL), 10% citric acid (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated. Purification by column chromatography (5:1 Hexane/Ethyl Acetate) gave **297** (10.6 g, 29.3 mmol, 91%) as a white foamy solid.

δ_H (400 MHz, $CDCl_3$): 7.53-7.51 (6H, m, Ar-H), 7.32-7.28 (5H, m, Ar-H), 7.24-7.21 (4H, m, Ar-H), 3.78 (1H, m, $CHCH_2OH$), 3.64-3.55 (2H, m, $C\underline{H_2}OH$), 3.32 (3H, s, O<u>Me</u>), 3.21 (1H, d, J = 10.1 Hz, NH)

HRMS (*m/z* ESI+): Calcd for $C_9H_{15}NO_4$ [M + H]$^+$ 104.0473 Found 104.0462.

5.3.1.7 *N*-oxypthalimide-serine-Trityl-NH-Methyl Ester (298)[371]

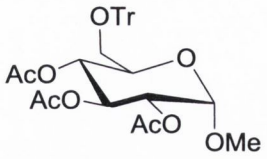


297 (3.00 g, 8.3 mmol), PPh_3 (2.35 g, 8.97 mmol) and *N*-hydroxy-pthalimide (1.97 g, 12.1 mmol) were dissolved in toluene (70 mL). The reaction mixture was stirred for 10 minutes under a blanket of nitrogen. DIAD (1.77 mL, 8.97 mmol) was added dropwise at 0 °C and the reaction mixture was allowed to warm to room temperature over 18 h. Upon completion (TLC) the reaction mixture was concentrated *in vacuo* and purified by column chromatography (15:1 Hexane/ Ethyl Acetate) to give **298** (549 mg, 6.4 mmol, 77%) as a white solid.

δ_H (400 MHz, $CDCl_3$): 7.85 (2H, m, Ar-H), 7.77 (2H, m, Ar-H), 7.57 (6H, d, J = 7.8 Hz, Ar-H), 7.28 (6H, t, J = 7.8 Hz, Ar-H), 7.21 (3H, t, J = 7.3 Hz, Ar-H), 4.51 (1H, dd, J = 4.1 Hz, J = 9.4 Hz, $C\underline{H_2}OPth$), 4.16 (1H, dd, J = 5.9 Hz, J = 9.4 Hz, $C\underline{H_2}OPth$), 3.73 (1H, m, $C\underline{H}CH_2OPth$), 3.37 (1H, s, O<u>Me</u>), 3.14 (1H, d, J = 10.0 Hz, N<u>H</u>).

HRMS (*m/z* ESI+): Calcd for $C_{31}H_{26}N_2O_5$ [M + Na]$^+$ 529.1739 Found 529.1743.

5.3.1.8 1-Methyl-2,3,4-Tri-*O*-Acetyl-6-Trityl-α-D-glucopyranoside (299)[372]

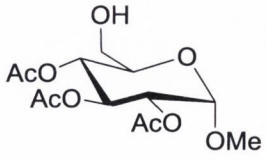


225 (3.00 g, 15.4 mmol) and trityl chloride (4.69 g, 16.8 mmol) were dissolved in pyridine (50 mL) and stirred for 3 h at 90 °C. The mixture was concentrated *in vacuo*, diluted in CH_2Cl_2 (150 mL) and washed with water (150 mL). The organic phase was dried, filtered and concentrated *in vacuo*. The crude product was acetylated by treatment with acetic anhydride (30 mL) and pyridine (30 mL) at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (3:1 Hexane/Ethyl Acetate) to give **299** (4.10 g, 12.7 mmol, 81%)

δ_H (400 MHz, $CDCl_3$): 7.48 (6H, m, Ar-H), 7.27 (9H, m, Ar-H), 5.48 (1H, app t, $J_{4,3} = J_{4,5} = 10.4$ Hz, H-4), 5.09 (1H, app t, $J_{3,2} = J_{3,4} = 10.4$ Hz, H-3), 5.04 (1H, d, $J_{1,2} = 3.2$ Hz, H-1), 4.97 (1H, dd, $J_{2,1} = 3.2$ Hz, $J_{2,3} = 10.4$ Hz, H-2), 3.93 (1H, ddd, $J_{5,4} = 10.4$ Hz, $J_{5,6} = 2.3$ Hz, $J_{5,6'} = 5.2$ Hz, H-5), 3.49 (3H, s, OMe), 3.22 (1H, dd, $J_{6,5} = 2.3$ Hz, $J_{6,6'} = 10.3$ Hz, H-6), 3.15 (1H, dd, $J_{6',5} = 5.2$ Hz, $J_{6',6} = 10.3$ Hz, H-6'), 2.11 (6H, s, CH_3), 2.02 (3H, s, CH_3)

HRMS (*m/z* ESI+): Calcd for $C_{32}H_{34}O_9$ [M + Na]$^+$ 585.2101 Found 585.2109.

5.3.1.9 Methyl-2,3,4-Tri-*O*-Acetyl-α-D-glucopyranoside (300)[373]



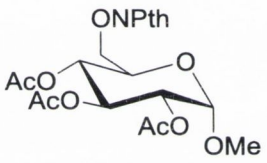
299 (200 mg, 0.36 mmol) was dissolved in dry Et_2O (5 mL), formic acid (5 mL) was added dropwise and the solution was stirred at room temperature for 20 minutes. The

reaction mixture was concentrated *in vacuo* and purified by column chromatography (5:1 Hexane/ Ethyl Acetate) to give **300** (101 mg, 0.31 mmol, 88%)

δ_H (400 MHz, $CDCl_3$): 5.53 (H, app t, $J_{4,3} = J_{4,5} = 9.9$ Hz, H-4), 5.02 (1H, app t, $J_{3,2} = J_{3,4} = 9.9$ Hz, H-3), 4.96 (1H, d, $J_{1,2} = 3.2$ Hz, H-1), 4.87 (1H, dd, $J_{2,1} = 3.2$ Hz, $J_{2,3} = 9.9$ Hz, H-2), 3.79 (1H, ddd, $J_{5,4} = 9.9$ Hz, $J_{5,6} = 2.9$ Hz, $J_{5,6'} = 3.7$ Hz, H-5), 3.73 (1H, app d, $J_{6,6'} = 12.8$ Hz, H-6), 3.58 (1H, dd, $J_{6',5} = 3.7$ Hz, $J_{6',6} = 12.8$ Hz, H-6'), 3.41 (1H, s, OMe), 2.09, 2.06, 2.02 (3H, s, CH_3).

HRMS (*m/z* ESI+): Calcd for $C_{13}H_{20}O_9$ [M + Na]$^+$ 343.1005 Found 343.1014.

5.3.1.10 1-Methyl-2,3,4-Tri-*O*-Acetyl-6-oxypthalimide-α-D-glucopyranoside (301)



300 (100 mg, 0.30 mmol), PPh_3 (204 mg, 0.78 mmol) and *N*-hydroxy-pthalimide (127 mg, 0.78 mmol), were dissolved in dry THF (3 mL). The solution was cooled to 0°C and DIAD (0.12 mL, 0.78 mmol) was added dropwise. The reaction was stirred for 1 h at 0 °C under nitrogen. Upon completion (TLC) the reaction mixture was concentrated, diluted in Et_2O (50 mL) and washed with water (2 x 100 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification by column chromatography (3:1 Hexane/Ethyl Acetate) gave **301** (673 mg, 0.22 mmol, 74%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$): 7.87 (2H, m, Ar-H), 7.78 (2H, m, Ar-H), 5.53 (1H, dd, $J_{4,3} = 9.4$ Hz, $J_{4,5} = 10.0$ Hz, H-4), 5.25 (1H, dd, $J_{3,4} = 9.4$ Hz, $J_{3,2} = 10.3$ Hz, H-3), 4.99 (1H, d, $J_{1,2} = 3.8$ Hz, H-1), 4.95 (1H, dd, $J_{2,1} = 3.8$ Hz, $J_{2,3} = 10.3$ Hz, H-2), 4.39 (1H, dd, $J_{6,5} = 5.7$ Hz, $J_{6,6'} = 11.0$ Hz, H-6), 4.30 (1H, dd, $J_{6',5} = 1.9$ Hz, $J_{6',6} = 11.0$ Hz, H-6'), 4.22 (1H, ddd, $J_{5,4} = 10.0$ Hz, $J_{5,6} = 5.7$ Hz, $J_{5,6'} =$

1.9 Hz, H-5), 3.43 (3H, s, OMe), 2.19, 2.10, 2.09 (3H, s, CH_3)

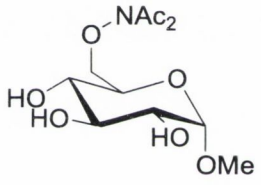
δ_C (100 MHz, $CDCl_3$): δ 170.2, 170.1, 169.7 (C=O), 163.1 (NCO), 134.6, 128.9, 123.6 (Ar-C), 96.8 (C-1), 76.2 (C-6), 70.7 (C-2), 70.2 (C-4), 68.6 (C-3), 67.7 (C-5), 55.9 (OMe), 20.7, 20.7, 20.7 (CH_3)

ν_{max} (film)/cm^{-1}: 1741 (C=O), 1660 (N-C=O).

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): -22.0°

HRMS (*m/z* ESI+): Calcd for $C_{13}H_{19}O_8$ [M + Na]$^+$ 326.0978 Found 326.0962.

5.3.1.11 1-Methyl-6-di-*N*-acetyl-α-D-glucopyranoside (302)



Procedure as described for **293** to afford **302**. Upon completion of the reaction mass spectroscopy analysis indicated the formation of the di-amide species. The crude reaction mixture was purified via a short plug of silica (Ethyl Acetate) to yield **302** (296 mg, 1.01 mmol, 92%) as a white foam.

δ_H (400 MHz, MeOD): 4.62 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1), 3.60 (1H, dd, $J_{4,3}$ = 7.8 Hz, $J_{4,5}$ = 6.4 Hz, H-4), 3.51 (3H, s, OMe), 3.49 (2H, m, H-2 and H-3), 3.46 (1H, ddd, $J_{5,4}$ = 6.4 Hz, $J_{5,6}$ = 5.5 Hz, $J_{5,6'}$ = 7.2 Hz, H-5), 3.37 (2H, m, H-6), 2.08, 2.06 (CH_3).

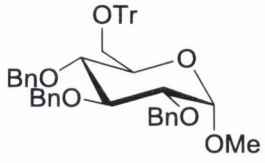
δ_C (100 MHz, MeOD): 168.7, 168.5 (N-C=O), 100.2 (C-1), 74.2 (C-3), 73.1 (C-2), 72.4 (C-4), 71.3 (C-5), 62.9 (C-6), 54.1 (OMe)

ν_{max} (film)/cm^{-1}: 3455 (OH), 1651 (N-C=O).

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): 35.0°

HRMS (*m/z* ESI+): Calcd for $C_{11}H_{19}NO_8$ [M + Na]$^+$ 316.1008 Found 316.1016.

5.3.1.12 1-Methyl-2,3,4-Tri-*O*-benzyl-6-*O*-Trityl-α-D-glucopyranoside (303)[374]

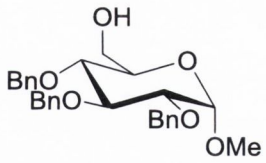


225 (3.00 g, 15.4 mmol) and trityl chloride (4.69g, 16.8 mmol) were dissolved in pyridine (50 mL) and stirred for 3 h at 90 °C. The mixture was concentrated *in vacuo*, diluted in CH_2Cl_2 (150 mL) and washed with water (150 mL). The organic phase was dried, filtered and concentrated *in vacuo*. The crude product suspended in dry DMF (10 mL) under nitrogen and BnBr (8 mL, 67.3 mmol) was added. The reaction mixture was cooled to 0 °C and NaH (2.69 g, 67.3 mmol) was added portionwise. The suspension was left to stir for 18 h at room temperature. Upon completion (TLC) water (10 mL) was added and the aqueous extracts were extracted with ethyl acetate (5 x 50 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo.* Purification by column chromatography (15:1 Hexane/Ethyl Acetate) gave **303** (1.65 g, 3.69 mmol, 24%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$): 7.22-7.07 (30H, m, Ar-H), 5.03 (1H, d, J = 10.8 Hz, Bn-CH_2), 4.92 (1H, d, J = 12.5 Hz, Bn-CH_2), 4.88 (1H, d, J = 10.8 Hz, Bn-CH_2), 4.82 (3H, m, Bn-CH_2), 4.36 (1H, d, $J_{6,6'}$ = 10.6 Hz, H-6), 4.04 (1H, app t, $J_{4,3} = J_{4,5}$ = 8.9 Hz, H-4), 3.88 (1H, m, H-5), 3.70 (2H, m, H-1 and H-2), 3.57 (1H, app d, $J_{6',6}$ = 10.6 Hz, H-6'), 3.51 (1H, s, OMe), 3.26 (1H, dd, $J_{3,2}$ = 4.7 Hz, $J_{3,4}$ = 8.9 Hz, H-3).

HRMS (*m/z* ESI+): Calcd for $C_{28}H_{31}O_5$ [M + Na]$^+$ 470.2069 Found 470.2078.

5.3.1.13 1-Methyl-2,3,4-Tri-*O*-benzyl-α-D-glucopyranoside (304)[374]

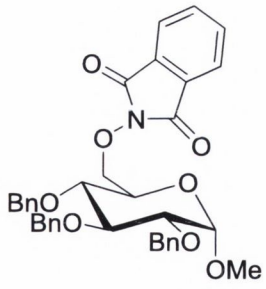


Procedure as for **300** to yield **304.** Purification by column chromatography (8:1 Hexane/ Ethyl Acetate) gave **304** (812 mg, 1.75 mmol, 86%) as a white solid.

δ_H (400 MHz, $CDCl_3$): 7.40-7.28 (15H, m, Ar-H), 5.03 (1H, d, J = 11.0 Hz, Bn-CH_2), 4.92 (1H, d, J = 11.3 Hz, Bn-CH_2), 4.88 (1H, d, J = 11.3 Hz, Bn-CH_2), 4.82 (1H, d, J = 11.0 Hz, Bn-CH_2), 4.70 (1H, d, J = 10.7 Hz, Bn-CH_2), 4.67 (1H, d, J = 10.7 Hz, Bn-CH_2), 4.59 (1H, d, $J_{1,2}$ = 3.7 Hz, H-1), 4.04 (1H, app t, $J_{4,3}$ = $J_{4,5}$ = 9.6 Hz, H-3), 3.80-3.66 (2H, m, H-4 and H-5), 3.57-3.51 (2H, m, H-5 and H-6), 3.40 (3H, s, OMe).

HRMS (*m/z* ESI+): Calcd for $C_{28}H_{32}O_6$ [M + Na]$^+$ 487.2097 Found 487.2078.

5.3.1.14 1-Methyl-2,3,4-Tri-*O*-benzyl-6-oxypthalimide-α-D-glucopyranoside (305)



Procedure as for **301** to yield **305.** Purification by column chromatography (12:1 Hexane/ Ethyl Acetate) gave **305** (120 mg, 0.19 mmol, 49%) as a white solid.

δ_H (400 MHz, $CDCl_3$): 7.84 (2H, m, Ar-H), 7.77 (2H, m, Ar-H), 7.39-7.29 (15H, m, Ar-H), 5.04 - 4.99 (3H, m, Bn-CH_2), 4.93 (1H, d, J = 11.3

Hz, Bn-CH_2), 4.84 (1H, d, J = 11.6 Hz, Bn-CH_2), 4.70 (1H, d, J = 11.3 Hz, Bn-CH_2), 4.44 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1), 4.17 (1H, m, H-5), 4.06 (1H, t, $J_{4,3} = J_{4,5}$ = 8.9 Hz, H-4), 3.89 (3H, m, H-6, H-6' and H-3), 3.64 (1H, dd, $J_{2,1}$ = 3.6 Hz, $J_{2,3}$ = 9.3 Hz, H-2), 3.43 (3H, s, OMe)

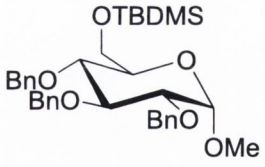
δ_C (100 MHz, $CDCl_3$): 170.2 (N=CO), 138.5, 138.4, 138.2, 134.5 (q-Ar), 128.7, 128.6, 128.6, 128.4, 128.4, 128.3, 128.2, 128.0, 127.6, 127.4, 127.3 (Ar-C), 91.4 (C-1), 83.1 (C-2), 77.8 (C-6), 76.1, 75.9, 75.7 (Bn-CH_2), 71.8 (C-4), 70.5 (C-3), 68.7 (C-5), 56.1 (OMe)

ν_{max} (film)/cm^{-1}: 1657 (N-C=O), 1580 (C=C).

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): -12.0°

HRMS (*m/z* ESI+): Calcd for $C_{36}H_{35}NO$ [M + Na]$^+$ 632.2260 Found 632.2254.

5.3.1.15 1-Methyl-2,3,4-Tri-*O*-benzyl-6-Tert-butyl-di-methyl-silyl-α-D-glucopyranoside (306)[375]



3Å molecular sieves were flame dried in a 50 mL RBF under nitrogen. **225** (3.00 g, 10.2 mmol) was solubilized in dry DMF (10 mL) and added via syringe to the RBF, imidazole (1.73 g, 25.5 mmol) was added in one portion and the solution was cooled to 0 °C. TDBMS-Cl (1.70 g, 11.3 mmol) was added in three portions, and left to stir for 90 minutes at room temperature. Upon completion (TLC) the reaction was quenched by the addition of $NaHCO_3$ (20 mL), the reaction mixture was diluted with CH_2Cl_2 (30 mL), filtered and the organic layer was separated. The aqueous layer was extracted with

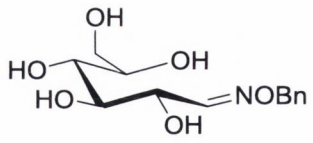
CH_2Cl_2 (50 mL) and the organic layer washed with water (5 x 30 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was suspended in dry DMF (10 mL) under nitrogen, and BnBr (4.33 mL, 36.5 mmol) was added. The reaction mixture was cooled to 0°C and NaH (1.46 g, 36.5 mmol) was added portionwise. The reaction mixture was allowed to warm to room temperature over 18 h. Upon completion (TLC) water (10 mL) was added and the aqueous extracts were extracted with ethyl acetate (5 x 50 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (15:1 Hexane/Ethyl Acetate) gave **306** (3.07 g, 5.30 mmol, 59%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$): 7.41-7.29 (15H, m, Ar-H), 5.02 (1H, d, J = 10.9 Hz, Bn-CH2), 4.93 (1H, d, J = 11.3 Hz, Bn-CH_2), 4.87 (1H, d, J = 10.9 Hz, Bn-CH_2), 4.82 (1H, d, J = 11.3 Hz, Bn-CH_2), 4.72 (1H, d, J = 12.2 Hz, Bn-CH_2), 4.65 (1H, d, J = 12.2 Hz, Bn-CH_2), 4.03 (1H, app t, $J_{4,3} = J_{4,5}$ = 9.7 Hz, H-4), 3.82 (2H, m, H-1 and H-5), 3.66 (1H, dd, $J_{2,1}$ = 2.4 Hz, $J_{2,3}$ = 10.6 Hz, H-2), 3.54 (3H, m, H-3, H-6 and H-6'), 3.40 (3H, s, OMe), 0.92 (9H, s, $SiMe_2C\underline{Me}_3$), 0.04 (6H, s, $Si\underline{Me}_2CMe_3$)

HRMS (*m/z* ESI+): Calcd for $C_{34}H_{46}O_6Si$ [M + Na]$^+$ 601.2961 Found 601.2986.

5.3.2 Synthesis of oxyamine linked glycoconjugates

5.3.2.1 1-benzyl-oxime-D-glucopyranoside (310)[330]



O-benzyl-hydroxylamine hydrochloride **308** (600 mg, 8.6 mmol) and **307** (1.00 g, 5.55 mmol) were solubilised in MeOH (50 mL), pyridine (1.25 mL, 15.5 mmol) was added dropwise and the reaction mixture was heated to 70°C for 2 hours. The progression of the reaction was monitored by TLC (Ethyl Acetate), upon completion the reaction mixture was concentrated *in vacuo* and purified by chromatography (8:1 Ethyl Acetate/Hexane) to

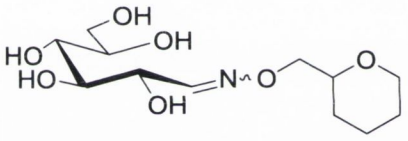
give **310** (1.25 g, 4.38 mmol, 79%) as a colourless syrup in a mixture of isomers (3:1 *E/Z*);

Data given for major *E* isomer

δ_H (400 MHz, D_2O): 7.49 (1H.d. $J_{1,2}$ = 7.0 Hz, H-1), 7.38-7.24 (5H, m, Ar-H), 5.06 (2H, s, Bn-CH_2), 4.31 (1H, dd, $J_{2,1}$ = 7.0 Hz, $J_{2,3}$ = 6.4 Hz, H-2), 3.87 (1H, dd, $J_{3,2}$ = 6.4 Hz, $J_{3,4}$ = 3.6 Hz, H-3), 3.77 (1H, dd, $J_{6,5}$ = 3.3 Hz, $J_{6,6'}$ = 10.9 Hz, H-6), 3.68 (1H, ddd, $J_{5,4}$ = 8.1 Hz, $J_{5,6}$ = 5.6 Hz, $J_{5,6'}$ = 3.3 Hz, H-5), 3.59 (1H, dd, $J_{6,6'}$ = 10.9 Hz, $J_{6,5}$ = 5.6 Hz, H-6'), 3.56 (1H, dd, $J_{4,5}$ = 8.1 Hz, $J_{4,3}$ = 3.6 Hz, H-4)

HRMS (*m/z* ESI+): Calcd for $C_{12}H_{17}NO_5$ [M + H]$^+$ 256.1179 Found 256.1191.

5.3.2.2 1-Tetrahydro-2H-pyran-2hyl-oxime-gluco-hexanose (311)



O-(tetrahydro-2H-pyran-2-hyl) hydroxylamine (195 mg, 1.67 mmol) was dissolved in acetonitrile (5 mL) and **307** (390 mg, 2.2 mmol) was added. Water (2.5 mL) was added to provide a clear solution, followed by addition of glacial acetic acid (150 µL). The reaction mixtures were stirred at RT for 16 h and then concentrated by rotary evaporation. Purification by column chromatography (4:1:0.5 Ethyl Acetate/Ethanol/water) gave **311** (328 mg, 1.19 mmol, 67%) as a yellow oil in a mixture of isomers (4:1:0.5 *E* oxime/Z oxime /β closed sugar)

Data given for major *E* isomer.

δ_H (400 MHz, D_2O): 7.56 (1H, d, $J_{1,2}$ = 6.7 Hz, H-1), 5.25 (1H, m, $CHCH_2ON$), 4.38 (1H, dd, $J_{2,1}$ = 6.7 Hz, $J_{2,3}$ = 3.4 Hz, H-2), 3.92 (3H, m, H-3, H-4 and $NOCH_2$), 3.81 (1H, dd, $J_{6,5}$ = 3.3 Hz, $J_{6,6'}$ = 10.4

Hz, H-6), 3.70 (1H, m, H-5), 3.62 (2H, m, H-6' , $NOCH_2$), 1.86-1.58 (8H, m, CH_2-pyran).

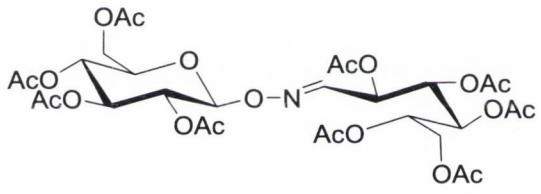
* Peak observed at 5.68 ppm (1H, dd, $J_{1,NH}$ = 10.1 Hz, $J_{1,2}$ = 7.1 Hz, H-1 β), corresponding to the closed beta-aminooxy linked sugar.

δ_C (100 MHz, D_2O): 154.3 (C-1), 100.3 ($\underline{C}HCH_2ON$), 71.4 (C-2), 71.3 (C-3 and C-4), 71.0 (C-6), 70.6 (C-5), 70.5 ($NO\underline{C}H_2$), 28.4, 28.2, 24.7, 18.9 (CH_2).

ν_{max} (film)/cm^{-1}: 3451 (OH), 1069 (C-O)

HRMS (*m/z* ESI+): Calcd for $C_{12}H_{23}NO_7$ [M + Na]$^+$ 316.1372 Found 316.1380.

5.3.2.3 1,1-oxyamino-2,3,4,6-*O*-acetyl-di-glucopyranoside (312)



294 (325 mg, 1.67 mmol) was dissolved in acetonitrile (5 mL) and **307** (390 mg, 2.2 mmol) was added. Water (2.5 mL) was added to provide a clear solution, followed by addition of glacial acetic acid (150 µL). The reaction mixtures were stirred at RT for 16 h. Mass spectroscopy analysis indicated the reaction was complete. The crude reaction mixture was concentrated *in vacuo* and dissolved in pyridine (5 mL) and acetic anhydride (5 mL) and stirred at RT for 18 h. The acetylated reaction mixture was concentrated *in vacuo* and purified by column chromatography (1:1 Hexane/ Ethyl Acetate) to give **312** (32 mg, 43 µmol, 55%) as a colourless oil in a 4:1 mixture of *E/Z* isomers.

Data given for major *E* isomer.

δ_H (400 MHz, $CDCl_3$): 6.21 (1H, dd, $J_{1,2}$ = 6.4 Hz, H-1), 5.25 (1H, dd, $J_{4',3'}$ = 3.1 Hz, $J_{4',5'}$ = 6.1 Hz, H-4'), 5.10 (1H, d, $J_{1',2'}$ = 3.2 Hz, H-1'), 4.96

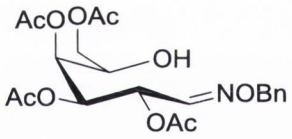
(2H, m, H-3 and H-4), 4.93 (1H, dd, $J_{3',2'}$ = 10.1 Hz, $J_{3',4'}$ = 3.1 Hz, H-3'), 4.27 (1H, dd, $J_{6a',5'}$ = 3.0 Hz, $J_{6a',6b'}$ = 12.1 Hz, H-6a'), 4.11 (1H, dd, $J_{6b',5}$ = 4.7 Hz, $J_{6'b,6'a}$ = 12.1 Hz, H-6b'), 4.07 (3H, m, H-5 and H-6a and H-6b), 3.09 (1H, m, H-2), 3.01 (1H, m, H-2'), 2.10, 2.09, 2.08, 2.07, 2.06, 2.06, 2.04, 2.03, 2.01, 2.00 (30H, s, CH_3).

δ_C (100 MHz, $CDCl_3$): 170.2, 170.2, 170.2, 170.1, 170.0, 169.8, 169.6, 169.6, 169.5, 169.4 (C=O), 156.4 (C-1), 102.7 (C-1'), 76.4 (C-3), 74.7 (C-2'), 74.0 (C-3'), 72.4 (C-4'), 72.1 (C-5), 68.9 (C-4), 63.9 (C-2), 63.8 (C-5'), 62.0 (C-6'), 61.9 (C-6), 20.8, 20.8, 20.7, 20.6, 20.6, 20.6, 20.5, 20.5, 20.4 (CH_3)

ν_{max} (film)/cm^{-1}: 1748 (C=O), 1074 (C-O).

HRMS (*m/z* ESI+): Calcd for $C_{30}H_{41}NO_{20}$ [M + Na]$^+$ 758.2120 Found 758.2111.

5.3.2.4 1,2-di-deoxy-*O*-benzyl-oxime ether-2,3,4,6-tetra-*O*-acetyl-galactopyranoside (317)



O-benzyl-hydroxylamine hydrochloride **308** (600 mg, 8.6 mmol) and **273** (2.00 g, 5.55 mmol) were solubilised in MeOH (50 mL), pyridine (1.25 mL, 15.5 mmol) was added dropwise and the reaction mixture was heated to 70°C for 2 hours. The progression of the reaction was monitored by TLC (EtOAc/Hexane 3:1), upon completion the reaction mixture was concentrated, the residue dissolved in EtOAc (50 mL) and extracted with water (2 x 30 mL) and brine (2 x 30 mL). The organic layer was dried over $MgSO_4$ and concentrated to a yellow oil that was purified by chromatography (4:1 Hexane/Ethyl Acetate) to give **317** (2.24 g, 5.16 mmol, 60%) as a colourless syrup in a mixture of isomers (3:1 *E/Z*);

Data given for major *E* isomer;

δ_H (400 MHz, $CDCl_3$): 7.40 (6H, m, Ar-H and H-1), 5.79 (1H, dd, J = 2.4 Hz, J = 5.7 Hz, H-2), 5.18 (2H, m, H-5 and H-3), 5.10 (2H, s, CH_2), 4.42 (1H, dd, $J_{6,5}$ = 5.2 Hz, $J_{6,6}$ = 11.7 Hz, H-6), 4.15 (1H, dd, $J_{6',5}$= 7.7 Hz, $J_{6',6}$= 11.7 Hz, H-6'), 3.80 (1H, app d, $J_{4,3}$ = $J_{4,5}$ = 9.07 Hz, H-4), 2.10, 2.07, 2.06 2.01 (3H, s, CH_3)

δ_C (100 MHz, $CDCl_3$): 170.9, 170.8, 170.3, 169.6 (C=O), 146.2 (q-Ar), 145.1 (C-1), 128.4, 128.0, 127.9 (Ar-C), 77.01 (Bn-CH_2), 75.2 (C-5), 69.7 (C-2), 68.6 (C-3), 67.8 (C-4), 62.9 (C-6), 21.1, 20.8, 20.8, 20.6 (CH_3) ;

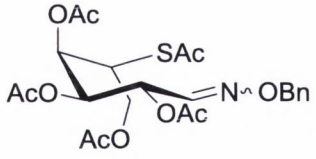
ν_{max} (film)/cm^{-1}: 3477 (OH), 1701, 1744 (C=O) cm^{-1}

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): -22.0°

HRMS (*m/z* ES^+); Calcd for $C_{21}H_{27}NO_{10}$ [M + Na]$^+$ 476.1533 Found 476.1547.

5.3.3 Synthesis of oxyamine linked thio-glycoconjugates

5.3.3.1 1,2-di-deoxy-*O*-benzyl-oxime ether-2,3,6-tri-*O*-acetyl-5-thioacetate-idopyranoside (318)



317 (141 mg, 0.31 mmol) was dissolved in dry CH_2Cl_2 (6 mL) under N_2. The reaction mixture was cooled to 0 °C, pyridine (0.06 mL, 0.74 mmol) was added followed by dropwise addition of triflic anhydride (0.06 mL, 0.37 mmol). The reaction mixture turned a deep yellow colour and was left to stir under nitrogen at 0°C for 2 hours. The reaction was monitored by TLC (1:1 Hexane/EtOAc) upon completion the reaction was quenched

by the addition of ice water (10 mL) and the aqueous layer extracted CH_2Cl_2 (2 x 20 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated to an orange oil. The triflate was dissolved in dry DMF (7 mL) and KSAc (71 mg, 0.62 mmol) added, the reaction was left to sir under nitrogen at room temperature for 12 hours. The progression of the reaction was monitored by TLC (Hexane/ Ethyl Acetate 1:1), upon completion diethyl ether (20 mL) was added to the reaction mixture and the organic layer was extracted with brine (3 x 30 mL), the aqueous layer was re-extracted with diethyl ether (2 x 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated to a yellow oil that was purified by chromatography (7:3 Hexane /Ethyl Acetate) to give thioacetate **318** (73 mg, 0.14 mmol, 46%) as a yellow oil in a mixture of isomers.

Data given for major *E* isomer

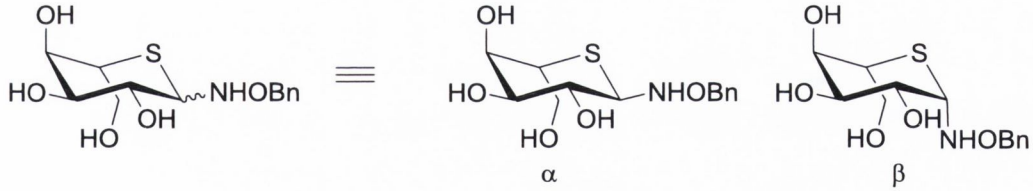
δ_H (600 MHz, $CDCl_3$): 7.42-7.31 (6H, m, Ar-H and H-1), 5.73 (1H, dd, $J_{2,1}$ = 2.3 Hz, $J_{2,3}$ = 9.0 Hz, H-2), 5.64 (1H, dd, $J_{3,2}$ = 9.0 Hz, $J_{3,4}$ = 2.7 Hz, H-3), 5.11 (2H, s, Bn-CH_2), 5.06 (1H, m, H-5), 4.29 (1H, m, H-6), 4.19 (1H, m, H-6'), 4.11 (1H, m, H-4), 2.40 (3H, s, SCOC$\underline{H}_3$), 2.11, 2.09, 2.04, 2.04 (3H, s, CH_3) ;

δ_C (150 MHz, $CDCl_3$): 170.6, 170.4, 170.0, 169.6, 169.4 (C=O), 143.8 (C-1), 135.7 (q-Ar), 128.5, 128.4, 128.2 (Ar-C), 76.5 (Bn-CH_2), 70.8 (C-3), 69.8 (C-5), 69.1 (C-2), 62.4 (C-6), 42.9 (C-4), 30.6 (SCO$\underline{C}H_3$), 20.8, 20.7, 20.7, 20.5 (CH_3) ;

ν_{max} (film)/cm^{-1}: 1701, 1744 (C=O) cm^{-1}

HRMS (*m/z* ES^+); Calcd for $C_{23}H_{29}NO_{10}S$ [M + Na]$^+$ 534.1410 Found 534.1420.

5.3.3.2 1-aminooxy-benzyl-5-thio-idopyranoside (319)



318 (73 mg, 0.16 mmol) was dissolved in MeOH (15 mL) and the solution was purged of oxygen for 30 minutes under argon. Acetyl chloride (4μL, 48 μmol) was added and the solution was heated to 40 °C for 1 h. Mass spectroscopy analysis indicated the reaction was complete. The reaction mixture was neutralised by the addition of Dowex OH^- resin until pH neutral, the resin was filtered, and the reaction mixture concentrated *in vacuo*. The reaction mixture was purified through a short plug of silica (Ethyl Acetate) to yield **319** (25 mg, 0.08 mmol, 52%) as a yellow oil. Anomerically pure early fractions were found to anomerise in D_2O, an equilibrium mixture of anomers (2.5:1 β/α) was obtained after 3 days.

Data for α anomer

δ_H (600 MHz, D_2O): 7.45-7.35 (5H, m, Ar-H), 5.16 (1H, d, J = 11.8 Hz, Bn-CH_2), 5.14 (1H, d, J = 11.8 Hz, Bn-CH_2), 4.85 (1H, d, $J_{1,2}$ = 9.2 Hz, H-1), 4.28 (1H, app t, $J_{2,1} = J_{2,3}$ = 9.2 Hz, H-2), 4.25 (1H, dd, $J_{4,3}$ = 3.7 Hz, $J_{4,5}$ = 1.4 Hz, H-4), 4.11 (1H, dd, $J_{3,2}$ = 9.2 Hz, $J_{3,4}$ = 3.7 Hz, H-3), 4.02 (1H, ddd, $J_{5,4}$ = 1.4 Hz, $J_{5,6}$ = 6.4 Hz, $J_{5,6'}$ = 8.9 Hz, H-5), 3.85 (1H, dd, $J_{6,5}$ = 6.4 Hz, $J_{6,6'}$ = 10.1 Hz, H-6), 3.78 (1H, dd, $J_{6',5}$ = 8.9 Hz, $J_{6',6}$ = 10.1 Hz, H-6').

δ_C (150 MHz, D_2O): 137.6 (C-1), 137.4 (q-Ar), 128.0, 127.9, 127.9 (Ar-C), 76.8 (Bn-CH_2), 72.9 (C-2), 71.2 (C-3), 69.0 (C-4), 68.9 (C-6), 40.9 (C-5).

ν_{max} (film)/cm^{-1}: 3361 (OH), 1071 (C-O).

HRMS (*m/z* ES^+): Calcd for $C_{13}H_{19}O_5S$ [M + Na]$^+$ 324.0882 Found 324.0890.

Data for β anomer

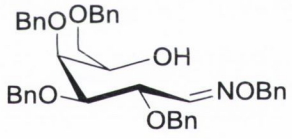
δ_H (600 MHz, D_2O): 7.45-7.35 (5H, m, Ar-H), 4.87 (2H, m, Bn-CH_2), 4.78 (1H, $J_{1,2}$ = 3.2 Hz, H-1), 4.37 (1H, dd, $J_{2,1}$ = 3.2 Hz, $J_{2,3}$ = 8.1 Hz, H-2), 4.25 (2H, m, H-3 and H-4), 4.07 (1H, m, H-5), 3.27 (2H, m, H-6 and H-6').

δ_C (150 MHz, D_2O): 137.5 (C-1), 137.4 (q-Ar), 127.9, 127.8, 127.7 (Ar-C), 77.2 (Bn-CH_2), 75.9 (C-2), 72.9 (C-3), 71.2 (C-4), 68.9 (C-6), 41.7 (C-5).

ν_{max} (film)/cm^{-1}: 3361 (OH), 1071 (C-O)

HRMS (*m/z* ES^+): Calcd for $C_{13}H_{19}O_5S$ [M + Na]$^+$ 324.0882 Found 324.0890.

5.3.3.3 2,3,4,6-tetra-*O*-benzyl-galacto-hex-1-*O*-benzyl-oxime ether (320)[376]



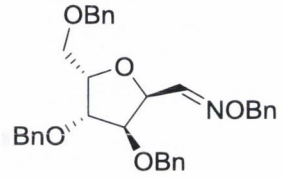
224 (200 mg, 2.86 mmol) and 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside **179** (1.00 g, 1.85 mmol) were solubilised in MeOH (50 mL), pyridine (0.42 mL, 5.18 mmol) was added dropwise and the reaction mixture was heated to 75°C for 2 hours. The progression of the reaction was monitored by TLC (Ethyl Acetate/Hexane, 3:1), upon completion the reaction mixture was concentrated, the residue dissolved in EtOAc (50 mL) and extracted with water (2 x 30 mL) and brine (2 x 30 mL). The organic layer was dried over $MgSO_4$ and concentrated to a yellow oil that was purified by chromatography (Ethyl Acetate/Hexane, 1:5) to give **320** (1.13 g, 2.03 mmol, 71 %) as a colourless syrup in a mixture of isomers; Data given for major *E* isomer;

δ_H (400 MHz, $CDCl_3$): δ 7.40 (1H, d, $J_{1,2}$ = 8.3 Hz, H-1), 7.39-7.26 (20H, m, Ar-H), 7.16 (5H, m, Ar-H), 5.11 (2H, s, NO-CH_2-Bn), 4.70-4.61

(8H, m, CH_2), 4.29 (1H, dd, $J_{2,3}$ = 3.3 Hz, $J_{2,1}$ = 8.3 Hz, H-2), 4.16 (1H, m, H-5), 3.86 (2H, m, H3 and H4), 3.55 (1H, dd, $J_{6,5}$ = 6.6 Hz, $J_{6,6}$ = 9.5 Hz, H-6), 3.50 (1H, dd, $J_{6,5}$ = 6.5 Hz, $J_{6,6}$ = 9.4 Hz, H-6')

HRMS (*m/z* ESI+): Calcd for $C_{41}H_{32}O_{11}$ [M + Na]$^+$ 723.1842 Found 723.1832.

5.3.3.4 1-ethyl-benzyl oxime ether, 2,3,5-tri-*O*-benzyl-α-D-ribofuranoside (321)



Procedure as described for **318** to yield **321**. Purification by column chromatography 5:1 (Hexane/Ethyl Acetate) gave **321** (63 mg, 0.12 mmol, 99%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$): 7.40-7.26 (21H, m, Ar-H and HC=N), 6.10 (1H, dd, $J_{1,CHN}$ = 6.5 Hz, $J_{1,2}$ = 6.9 Hz, H-1), 4.80 - 4.62 (6H, m, Bn-CH_2), 4.48 (1H, dd, $J_{2,1}$ = 6.9 Hz, $J_{2,3}$ = 4.2 Hz, H-2), 4.23 (1H, dd, $J_{5,4}$ = 5.1 Hz, $J_{5,5'}$ = 9.6 Hz, H-5), 4.16 (1H, m, H-5'), 3.99 (1H, m, H-3), 3.87 (1H, m, H-4).

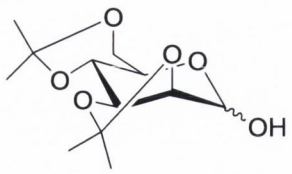
δ_C (100 MHz, $CDCl_3$): 159.1 (C=N), 138.2, 138.2, 138.1, 138.0 (q-Ar), 130.0, 129.9, 129.8, 129.7, 129.7, 129.1, 128.6, 128.5, 128.0, 127.6, 127.4, 127.2 (Ar-C), 100.3 (C-1), 81.2 (C-2), 78.6 (C-3), 77.2 (C-4), 76.5 (Bn-CH_2), 76.2 (C-5), 75.4, 74.2 (Bn-CH_2).

ν_{max} (film)/cm^{-1}: 1585 (C=C), 1061 (C-O).

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): 18 °

HRMS (*m/z* -ESI): Calcd for $C_{34}H_{35}NO_5$ $[M+Na]^+$ 560.2413 Found 560.2421.

5.3.3.5 2,3,4,6-Di-*O*-isopropylidine-α-D-mannopyranose (323)[366]

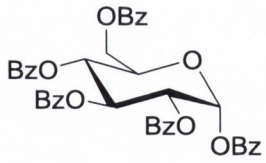


D-Mannose **322** (2.00 g, 11.11 mmol) was dissolved in dry DMF (15 mL), the solution was cooled to 0°C. Para toluene sulfonic acid (105 mg, 0.55 mmol) was added followed by 2-methoxy propane (4.09 mL, 33.33 mmol). The reaction mixture was left to stir at 0°C for 2.5h. TLC (EtOAc) indicated the reaction was not complete, a further equivalent of 2 methoxy propane (1.36 mL, 11.11 mmol) was added and the reaction was left to stir for a further 6h at 0°C. Upon completion, TLC (EtOAc), triethylamine (1 mL) was added to quench the reaction. Diethyl Ether (100 mL) was added and the organic extracts were washed with water (3 x 50 mL) and brine (2 x 50 mL), dried ($MgSO_4$) and concentrated. The crude product was recrystallised from hexane to give **323** (1.73 g, 6.67 mmol, 60%) as a white crystalline solid.

δ_H (400 MHz, $CDCl_3$): 5.45 (1H, d, $J_{1,2}$ = 3.1 Hz, H-1), 4.19-4.23 (2H, m, H-2 and H-3), 3.88 (1H, dd, $J_{5,6}$ = 4.4 Hz, $J_{6,6'}$ = 9.8 Hz, H-6'), 3.73-3.82 (3H, m, H-4, H-5, H-6), 2.70 (1H, d, J = 3.1 Hz, OH), 1.56, 1.53, 1.44, 1.37 (3H, s, CH_3)

HRMS (*m/z* ESI+): Calcd for $C_{12}H_{20}O_6$ [M + Na]$^+$ 283.1158 Found 283.114

5.3.3.6 1,2,3,4,6 Penta-*O*-benzoyl-α-D-glucopyranoside (325)[377]



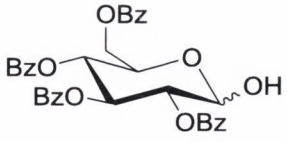
D-Glucose **307** (2.00 g, 11.11 mmol) was dissolved in dry pyridine (20 mL). The solution was stirred on ice for 5 minutes. Benzoyl chloride (9.00 mL, 77.7 mmol) was added dropwise at 0°C and the reaction mixture was left to stir for 18 h at room temperature. Upon completion, TLC (Hexane/EtOAc, 3:1) MeOH (60 mL) was added and a white precipitate formed that was filtered. The filtrate was concentrated and dissolved in CH_2Cl_2 (50 mL), the organic layer was washed with water (100 mL), 1 M HCl (100 mL), $NaHCO_3$ (100 mL) and brine (100 mL). The solvent was removed *in vacuo* and the crude reaction mixture was purified by chromatography (2:1 Hexane/EtOAc) to give **325** (7.41 g, 10.6 mmol, 95%) as a white crystalline solid in a 3:1 mixture of α/β anomers.

Data for α anomer

δ_H (400 MHz, $CDCl_3$): 8.21-7.34 (25H, m, Ar-H), 6.91 (1H, d, $J_{1,2}$ = 3.8 Hz, H-1), 6.37 (1H, app t, $J_{3,2} = J_{3,4}$ = 10.3 Hz, H-3), 5.92 (1H, app t, $J_{4,3} = J_{4,5}$ = 9.9 Hz, H-4), 5.73 (1H, dd, $J_{2,1}$ = 3.8 Hz, $J_{2,3}$ = 10.3 Hz, H-2), 4.68 (2H, m, H-5 and H-6), 4.53 (1H, dd, $J_{6,5}$ = 5.1 Hz, $J_{6,6}$ = 13.8 Hz, H-6).

HRMS (*m/z* ESI+): Calcd for $C_{41}H_{32}O_{11}$ [M + Na]$^+$ 723.1842 Found 723.1832

5.3.3.7 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranoside (326)[377]



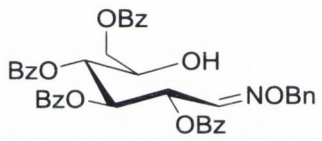
325 (5.81 g, 8.30 mmol) was dissolved in THF (30 mL). Ethylene diamine (0.4 mL, 9.0 mmol) was added dropwise and the solution was stirred for 16 h at room temperature.

Upon completion (TLC) the reaction mixture was concentrated *in vacuo* and purified by column chromatography (2:1 Hexane/ Ethyl Acetate) to give **326** (4.00 g, 6.72 mmol, 81%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 8.08-7.29 (20 H, m, Ar-H), 6.31 (1H, app t, J = 10.0 Hz, H-3), 5.80 (1H, d, $J_{1,2}$ = 3.1 Hz, H-1), 5.77 (1H, app t, J = 10.0 Hz, H-4), 5.35 (1H, dd, $J_{2,1}$ = 3.1 Hz, $J_{2,3}$ = 10.3, H-2), 4.68 (2H, m, H-5 and H-6), 4.47 (1H, dd, $J_{6,5}$ = 4.2 Hz, $J_{6,6}$ = 12.1 Hz, H-6)

HRMS (*m/z* ESI+): Calcd for $C_{34}H_{28}O_{10}$ [M + Na]$^+$ 619.1580 Found 619.1571.

5.3.3.8 1-benzyl-oxime-2,3,4,6-Tetra-*O*-benzoyl-D-glucopyranoside (327)[378]

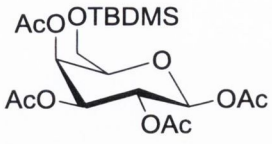


328 (120 mg, 0.20 mmol) was dissolved in MeOH (10 mL). *O*-benzyl hydroxylamine hydrochloride (50 mg, 0.31 mmol) and pyridine (0.045 mL, 0.56 mmol) were added and the reaction was heated to 70 °C for 2.5 h. Upon completion (TLC) the rection was cooled and concentrated *in vacuo.* The residue was diluted in Ethyl Acetate (30 mL) and washed with water (2 x 30 mL) and brine (30 mL), the organic layer was dried ($MgSO_4$) and purified by column chromatography (3:1 Hexane/Ethyl Acetate) to give **327** (98 mg, 0.14 mmol, 70%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$): 8.09-7.85 (6H, m, Ar-H and HC=NOBn), 7.62-7.26 (20H, m, Ar-H), 6.21 (1H, d, $J_{1,2}$ = 7.6 Hz, H-1), 6.11 (1H, app t, $J_{4,3}$ = $J_{4,5}$ = 6.4 Hz, H-4), 5.79 (1H, ddd, $J_{5,4}$ = 6.4 Hz, $J_{5,6}$ = 4.7 Hz, $J_{5,OH}$ = 6.0 Hz, H-5), 4.38 (1H, dd, $J_{3,2}$ = 8.1 Hz, $J_{3,4}$ = 6.4 Hz, H-3), 4.11 (1H, dd, $J_{2,1}$ = 7.6 Hz, $J_{2,3}$ = 8.1 Hz, H-2, 3.63 (1H, d, $J_{OH,5}$ = 6.0 Hz, OH).

HRMS (*m/z* ESI+): Calcd for $C_{41}H_{35}NO_{10}$ [M + Na]$^+$ 724.2159 Found 724.2171.

5.3.3.9 1,2,3,4-Tetra-*O*-Acetyl-6-Tert-butyl-di-methyl-silyl-β-D-glucopyranoside (328)



3Å molecular sieves were flame dried in a 50 mL RBF under nitrogen. **225** (3.00 g, 10.2 mmol) was solubilized in dry DMF (10 mL) and added via syringe to the RBF, imidazole (1.73 g, 25.5 mmol) was added in one portion and the solution was cooled to 0 °C. TDBMS-Cl (1.70 g, 11.3 mmol) was added in three portions, and left to stir for 90 minutes at room temperature. Upon completion (TLC) the reaction was quenched by the addition of $NaHCO_3$ (20 mL), the reaction mixture was diluted with CH_2Cl_2 (30 mL), filtered and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL) and the organic layer washed with water (5 x 30 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo.* The residue was suspended in pyridine (10 mL) and acetic anhydride (10 mL) was added. The reaction mixture was stirred at room temperature for 16 h. Upon completion the reaction mixture was poured into distilled water (40 mL) and extracted with ethyl acetate (3 x 30 mL). The organic extracts were combined and washed with saturated copper sulphate solution until all pyridine was consumed. The organic extracts were dried over $MgSO_4$ and purified by column chromatography (5:1 Hexane: EtOAc) to give **328** (2.92 g, 6.32 mmol, 62%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$): 5.72 (1H, d, $J_{1,2}$ = 7.9 Hz, H-1), 5.47 (1H, dd, $J_{4,3}$ = 9.6 Hz, $J_{4,5}$ = 2.3 Hz, H-4), 5.20 (1H, app t, $J_{3,2} = J_{3,4}$ = 9.6 Hz, H-3), 5.14 (1H, dd, $J_{2,1}$ = 7.9 Hz, $J_{2,3}$ = 9.6 Hz, H-2), 5.11 (1H, ddd, $J_{5,4}$ = 2.3 Hz, $J_{5,6}$ = 3.1 Hz, $J_{5,6'}$ = 6.2 Hz, H-5), 3.69 (1H, dd, $J_{6,5}$ = 6.2 Hz, $J_{6,6'}$ = 8.3 Hz, H-6), 3.66 (1H, dd, $J_{6,5}$ = 3.1 Hz, $J_{6',6}$ = 8.3 Hz, H-6'), 2.17, 2.10, 2.04, 2.04 (3H, s, CH_3), 0.89 (9H, s, $SiMe_2C\underline{Me}_3$), 0.04 (6H, s, $Si\underline{Me}_2CMe_3$).

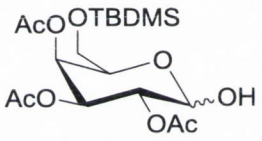
δ_C (100 MHz, $CDCl_3$): δ 170.5, 170.3, 169.7, 169.7 (C=O), 93.8 (C-1), 75.3 (C-4), 73.2 (C-2), 72.5 (C-3), 70.3 (C-5), 61.9 (C-6), 25.7 ($SiMe_2CMe_3$), 20.8, 20.8, 20.7, 20.7 (OAc CH_3), 18.3 (CMe_3), -5.4 (CH_3)

ν_{max} (film)/cm^{-1}: 1737 (C=O).

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): 52.0°

HRMS (*m/z* ESI+): Calcd for $C_{20}H_{34}O_{10}Si$ [M + Na]$^+$ 485.1819 Found 485.1801.

5.3.3.10 2,3,4-Tri-*O*-Acetyl-6-Tert-butyl-di-methyl-silyl-α-D-glucopyranoside (329)



Procedure as described for **272** to give **329.** Purification by column chromatography (8:1 Hexane/Ethyl Acetate) gave **329** (2.07 g, 4.93 mmol, 78%) as a yellow oil.

δ_H (400 MHz, $CDCl_3$): 5.45 (1H, app t, $J_{3,2} = J_{3,4} = 9.8$ Hz, H-3), 5.48 (1H, d, $J_{1,2} = 3.3$ Hz, H-1), 4.90 (1H, dd, $J_{2,1} = 3.3$ Hz, $J_{2,3} = 9.8$ Hz, H-2), 4.73 (1H, app d, $J_{4,3} = 9.8$ Hz, H-4), 4.15 (3H, m, H-5, H-6 and H-6'), 2.17, 2.16, 2.15 (CH_3), 0.90 (9H, s, $Si(CH_3)_2C\underline{Me}_3$), 0.06 (6H, s, $Si(C\underline{H}_3)_2CMe_3$).

δ_C (100 MHz, $CDCl_3$): δ 169.6, 169.4, 169.2 (C=O), 86.9 (C-1), 77.2 (C-4), 76.2 (C-2), 74.5 (C-3), 71.9 (C-5), 60.8 (C-6), 26.1 ($SiMe_2C\underline{Me}_3$), 20.6, 20.5 (CH_3 OAc), 17.8 ($\underline{C}Me_3$), -4.1 ($\underline{C}H_3$).

ν_{max} (film)/cm^{-1}: 3451 (OH), 1731 (C=O).

$[\alpha]_D^{20}$ (c = 0.1, $CHCl_3$): 36.0°

HRMS (*m/z* ESI+): Calcd for $C_{18}H_{32}O_9Si$ [M + Na]$^+$ 443.1713 Found 443.1702.

6.0 References

1. Horowitz, M. I.; Pigman, W. *The glycoconjugates*. Academic Press, New York. **1997-1982**, vol I-IV,
2. Hakamori, S. *Ann Rev Biochem*. **1981**, *50*, 733.
3. Li, Y, -T.; Li, S. –C. *Adv. Carbohydr. Chem. Biochem*. **1982**, *40*, 235.
4. Varki, A. *Glycobiology*. **1993**, *3*, 97.
5. Feizi, T.; Childs, R. A. *Biochem. J.* **1987**, *245*, 1.
6. Eurocarb www.eurocarbdb.org. Data correct as of 10/7/2013.
7. Consortium for functional Glycomics www.functionalglycomics.org. Data correct as of 9/11/2011
8. Human Disease Glycomics/Proteome Intiative www.hgpi.jp. Data correct as of 10/7/2013.
9. Capon, R. J.; MacLeod, J. K. *Chem. Commun*. **1987**, *15*, 1200.
10. Oishi, H.; Nato, J.; Suzuki, K.; Hayashi, T.; Okazaki, H.; Ando, K.; Sawada, M. *J. Antibiot*. **1982**, *35*, 391.
11. Slayden, R. A.; Lea, R.E.; Armour, J.W.; Cooper, A. M.; Orme, I. M, Brennan, P. J.; Besra, G. S. *Antimicrob. Agents. Chemother.* **1996**, *40*, 2813.
12. Kremer, L.; Douglas, J. D.; Baulard, A. R.; Morehouse, C.; Guy, M. R.; Alland, D.; Dover, L. G.; Lokey, J. H.; Jacobs, W. R.; Brennan, P. J.; Minnikin, D. E.; Besra, G. S. *J. Biol. Chem*. **2000**, *275*, 16857.
13. Jones, A. L.; Herber, D.; Rutter, A. J.; Dancer, J. E.; Horwood, J. L.; *J. Biochem*. **2000**, *347*, 205.
14. Barchi, J. J. Jr. *Curr. Pharm. Des*. **2000**, *6*, 485.
15. Goss, P. E.; Reid, C. L.; Bailey, D.; Dennis, J. W. *J. Am. Assoc. Cancer Res.* **1997**, *3*, 1077.
16. Markad, S. D.; Karanjule, N. S.; Sharma, T.; Sabharwal, S. G.; Dhavale, D. D. *Bioorg. Med. Chem.* **2006**, *14*, 5535.
17. Fan, J. –Q.; Ishii, S.; Asano, N.; Suzuki, Y. *Nat. Med*. **1999**, *5*, 112.
18. Mehta, A.; Zitzmann, N.; Rudd, P. M.; Black, J. M.; Dwek, R. A.; *FEBS Lett*. **1998**, *430*, 17.
19. Yoshikawa, M.; Murakami, T,; Shimada, H.; Matsuda, H.; Yamahara, J.; Tanabe, G.; Muraoka, O. *Tetrahedron Lett*. **1997**, *38*, 8367.

20. Yoshikawa, M.; Murakami, T.; Yashiro, K.; Matsuda, H. *Chem. Pharm. Bull.* **1998**, *46*, 1339.

21. Inouye, S.; Tsuruoka, T.; Niida, T. *J. Antibiot.* **1996**, *19*, 288.

22. Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645.

23. Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265

24. Asano, N.; Kato, A.; Watson, A. A.; *Mini Rev. Med Chem.* **2001**, *1*, 145.

25. Niwa, T.; Tsuroka, T.; Goi, H.; Kodoma, Y.; Itoth, J.; Inoue, S.; Yamodo, Y.; Niida, T.; Nobe, M.; Ogawa, Y. *J Antibiot.* **1984**, *37*, 1579.

26. Miyake, Y. Ebata, M. *Agric. Biol. Chem.* **1998**, *52*, 661.

27. Welter, A.; Jadot, J.; Dordenne, G.; Marlier, M.; Casimir, J. *Phytochemistry* **1976**, *15*, 747

28. Elbein, A. D.; Mitchell, M. Sanford, B, A.; Fellows, L. E.; Evans, S. V.; *J. Biol. Chem.* **1984**, *259*, 2409.

29. Wrodnigg, T. M.; *Monatsh. Chem.* **2002**, *133*, 393.

30. Wiglar, P. W. *J Bioenerg. Biomembr.* **1996**, *28*, 279.

31. Shibano, M.; Tsukamoto, D.; Masuda, A.; Tanaka, Y.; Kusano, G. *Chem. Pharm. Bull.* **2001**, *49*, 1362.

32. Henke, B. R.; Sparks, S. M.; *Mini Rev Med Chem.* **2006**, *6*, 845.

33. Stocker, B. L.; Dangerfield, E. M.; Win-Mason, A. L.; Haslett. G. W.; Timmer, M. S. M.; *Eur. J. Org. Chem.* **2010**, 1615.

34. Nash, R. J.; Bell, E. A.; Fleet, G. W. J.; Jones, R. H.; Williams, J. M. *Chem. Commun.* **1985**, *11*, 738.

35. Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, D. P.; Pyrce, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811.

36. Asano, N.; Kato, A.; Miyauchu, M.; Kizu, H.; Tomimari, T.; Matsui, K.; Nash, R. J.; Molyneux, R. J. *Eur. J. Biochem.* **1997**, *248*, 296.

37. Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 625.

38. Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 458.

39. Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 619.

40. Schmidt, D. D.; Frommer, W.; Junge, B.; Muller, L.; Wingender, W.; Truscheit, E.; Schafer, D. *Naturwissenchaften.* **1977**, *64*, 535.

41. (a) Murao, S.; Ohyama, K. *Agric. Biol. Chem.* **1975**, *39*, 2271.

(b) Murao, S.; Ohyama, K. Ogura, S. *Agric. Biol. Chem.* **1977**, *41*, 919.

(c) Murao, S.; Ohyama, K. *Agric. Biol. Chem.* **1979**, *43*, 679.

42. Ogura, H.; Hasegewa, A.; Suami, T. *Carbohydrates; Synthetic Methods and Applications in Medicinal Chemistry*. Eds. VCH, **1992**, 136.
43. Truscheit, E.; Frammer, W.; Junge, B.; Muller, L.; Schmidt, D. D.; Wingender, W. *Angew. Chem. Int. Ed.* **1981**, *20*, 744.
44. Van Den Broek, L. A. G. M.; Van den Witczak, Z. J.; Nieforth, K. A. *Carbohydrates in Drug Design.* **1997**, 471.
45. Pearson, M. S. M.; Mathé-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, *11*, 2159.
46. Tuomihehto, J.; Lindström, J.; Erikson, J. G.; Valle, T. T.; Hämäläinen, H.; Ilanne-Parikka, P.; Keinänen-Kiukaanniemi, S.; Laaksa, M.; Louheranta, A.; Rastas, M, Salminen, V.; Usuitupa, M. N. *Engl. J. Med*, **2001**, *344*, 1341.
47. Lyssenko, V.; Jansson, A.; Almgren, P.; Pulizzi, N.; Isomaa, B.; Tuomi, T.; Berglung, G.; Alshuler, D.; Nilsson, P.; Groop, L. N. *Engl. J. Med.* **2008**, *359*, 2220.
48. Mc Carthy, M. I. N. *Engl. J. Med.* **2010**, *363*, 2339.
49. Shaw, J. E.; Sicree, R. A.; Zimmet, P. Z. *Diabetes. Res. Clin. Pract.* **2010**, *87*, 4.
50. Gerich, J. E. *Arch. Intern. Med.* **2003**, *163*, 1306.
51. UK Prospective Diabetes Study Group. *Lancet*, **1998**, *352*, 837
52. UK Prospective Diabetes Study Group. *Lancet*, **1998**, *352*, 854.
53. Stratton, I. M. Adler, A. I.; Neil, H. A. W.; Matthws, D. R.; Manley, S. E.; Cull, C. A.; Hadden, D.; Turner, C.; Holmann, R. R. *Br. Med. J.* **2000**, *321*, 405.
54. Honefeld, M.; Cagaty, M, Petrowitsch, T.; Neuse, D.; Petzinna, D.; Rupp, M. *Eur. Heart. J.* **2004**, *25*, 10.
55. Charpentier, G. *Diabetes Metab. Res. Rev.* **2000**, *18*, S70.
56. Kato, A.; Kato, N.; Kano, E.; Adachi, I.; Ikeda, K.; Okamoto, T.; Banba, Y.; Ouchi, H.; Takahata, H.; Asano, N. *J. Med. Chem.* **2005**, *48*, 2035.
57. Junge, B.; Matzke, M, Stltefuss, J. *Handbook of Experimental Pharmacology*; Kulhmann, J., Puls, W., Eds., Springer-Verlag: New York, **1996**, *119*, 411.
58. Cauderoy, M.; Tappy, L.; Temler, E.; Jequier, E.; Hillebrand, I.; Felber, J. P. *Metabolism*. **1986**, *35*, 472.
59. Mador, Z.; Olefsky, *J. Am. J. Clin Nutr*. **1986**, *44*, 206.
60. Taylor, R. H.; Barker, H. M.; Bowey, E. A.; Canfield, J. E. *Gut*. **1986**, *27*, 1471.

61. Mooradian, A. D.; Turmann, J. E. *Drugs.* **1999**, *57*, 19.

62. Scott, L. J.; Spencer, C. M. *Drugs*. **2000**, *3*, 513.

63. Putter, J. *Enzyme Inhibitors.* Brodeck, E., Verlag Chemie, Weinhem Germany, **1980**, 139.

64. Joubert, P. H.; Venter, H. L.; Foukaridis, G. N. *Br. J. Clin. Pharmacol.* **1990**, *30*, 391.

65. Biscoff, H. *Eur. J. Clin. Invest.* **1994**, *24*, 3.

66. Scott, L. J.; Spencer, C. M. *Drugs*. **2000**, *3*, 521.

67. Samulitis, B. K.; Goda, T.; Lee, S. M. *Drugs, Exp. Clin. Res*. **1987**, *13*, 517.

68. Aerts, J. M.; Ottenhoff, R.; Powlson, A. S.; Grofhorst, A.; Van Eijk, M.; Dubbelhuis, P. F.; Aten, J.; Kuipers, F.; Serlie, M. J.; Wennekes, T.; Sehti, J. K.; O'Rehilly, S.; Overkleeft, H. S. *Diabetes.* **2007**, *56*, 1341.

69. Webbejesm, T.; Meijer, A. J. Groen, A. K.; Boot, R. G.; Groener, J. E.; Van Eijk, M.; Ottenhoff, R.; Bijl, N. Ghouharali, K.; Song, H.; O'Shea, T. J.; Liu, H.; Yew, N.; Copeland, D.; Van den Berg, R. J.; Van der Maro, G. A.; Overkleeft, H. S.; Aerts, J. M. *J. Med. Chem*. **2010**, *53*, 689.

70. Bijl, N.; Sokolovic, M.; Vrins, C.; Langeveld, M.; Moerland, P. D.; Ottenhoff, R.; Van Roomen, C. A. A. A.; Claessen, N.; Boot, R. G.; Aten, J.; Green, A. K. Aerts, J. M. F. G.; Van Eijk, M. *Hepatology*. **2009**, *50*, 1431.

71. Bietrix, F.; Lombardo, E.; Van Roomen, C. A. P. A.; Ottenhoff, R.; Vos, M.; Ronsen, P. C. N.; Verhoeven, A. J. Aerts, J. M.; Groen, A. K. *Arterioscler. Thromb. Vasc. Biol.* **2010**, *30*, 931.

72. Oikonomakus, N. G. *Curr. Protein. Pept. Sci*. **2002**, *3*, 561.

73. Somsák, L.; Nagy, V.; Hadady, Z.; Docso, T.; Gergely. P. *Curr. Pharm. Res.* **2003**, *9*, 1177.

74. Jacobsen, P.; Lundbeck, J. M.; Kristiansen, M.; Breiholt, J.; Demuth, H.; Pawlas, J.; Torres Candela, M. P.; Andersen, B.; Westergaard, N.; Lundgren, K.; Asano, N. *Bioorg. Med. Chem*. **2001**, *9*, 733.

75. Fosgerou, K.; Westergaard, N.; Quistaff, B.; Grunnet, N.; Kristiansen, M.; Lundgran, K. *Arch. Biochem. Biophys*. **2000**, *380*, 435.

76. Bichard, C. J. F.; Mitchell, E. P.; Wormold, M. R.; Watson, K. A.; Johnson, L. N. Zopraphos, S. E.; Koutro, D. D.; Oikonomakos, N. G.; Fleet, G. W. J. *Tetrahedron Lett*. **1995**. *36*, 2145.

77. Somsák, L.; C. R. *Chimie*. **2011**, *14*, 211.

78. Nagy, V.; Benltifa, M.; Vidal, S.; Berzényi, E. Teilhet, C. Czifrák, K. Batta, G. Docsa, T. Gergely, P. Somsák, L.; Praly, J. P. *Bioorg. Med. Chem.* **2009**, *17*, 5696.

79. Benltifa, M.; Hayes, J. M.; Vidal. S.; Gueyrard, D.; Goekjian, P. G.; Praly, J. P.; Kizilis, G.; Tiraidis, C.; Alexacou, K. M.; Chrysina, E. D.; Zographos, S. E. Leonidas, D. D.; Archontis, G.; Oikonomakos, N. G. *Bioorg. Med. Chem.* **2009**, *17*, 7368.

80. Dwek, R. A.; Butters, T. D.; Platt, F. M, Zitzmann, N. *Nat. Rev. Drug Discovery.* **2002**, *1*, 65.

81. Butters, T.; Dwek, R.; Platt, F. *Chem. Rev.* **2000**, *100*, 4683.

82. Butters, T.; Dwek, R.; Platt, F. *Tetrahedron: Asymmetry* **2000**, *11*, 113.

83. Bergeron, J. J.; Brenner, M. B.; Thomas, D. Y.; Williams, D. B. *Trends Biochem. Sci.* **1994**, *19*, 124.

84. Peterson, J. R., Ora, A.; Van, P. N.; Helenius, A. *Mol. Biol. Cell.* **1995**, *6*, 1173.

85. Werr, M.; Prange, R. *J. Virol.* **1998**, *72*, 778.

86. Chouhhi, A.; Urg, S.; Wychowski, C.; Dubikisson, J. *J Virol.* **1998**, *72*, 3851.

87. Mc Ginnes, L. W.; Morrison. T. G. *Virus Res*, **1998**, *53*, 175.

88. Platt, F. M.; Butters, T. D. *Exp. Rev. Mol. Med.* 2000. 1-17.

89. Fischl, M. A.; Resnick, L.; Coombs, R.; Kremer, A. B.; Pottage, J. C. Jr.; Fass, R. J.; Fife, K. H.; Powderly, W. G.; Collier, A. C.; Aspinall, R. L. *J. Aquir. Immune. Defic. Syndr.* **1994**,*7*, 139.

90. Chang, J.; Wang, L.; Ma, D. Qu, X.; Guo, H.; Xu, X.; Meso P. M.; Bourne, N.; Moriarity, R.; Gu, B.; Guo, J. –T.; Block, T. M. *Antimicrob. Agents. Chemother.* **2009**, *53*, 1501.

91. Greimel, P.; Spreitz, J.; Stutz, A. E.; Wrondnigg, T. M. *Current topics in medicinal chemistry.* **2003**, *3*, 513.

92. Fleet, G. W.; Karpas, A.; Dwek, R. A.; Fellows, L. E.; Tyms, A. S.; Petursson, S.; Namgoogng, S. K.; Ramsden, N. G.; Smith, P. W.; Son, J. C. *FEBS letters.* **1998**, *237*, 128.

93. Bridges, V. G.; Brenann, T. M.; Taylor, D. L.; Mc Pherson, M.; Tyms, A. S. *Antivir Res.* **1994**, *25*, 169.

94. Ouzounov, S.; Mehta, A.; Dwek, R. A.; Block, T. M.; Jordan, R. *Antivir. Res.* **2002**, 425.

95. Dennis, J. W.; Granovsky, M.; Warren, C. E. *Biochem. Biophys. Acta*. **1999**, *21*, 1473.

96. Parekh, R. B.; Dwek, R. A.; Sutton, B. J.; Fernandes, D. A.; Leung, A.; Stanworth, A.; Rademacher, T. A.; Mizuochi, T.; Taniguchi, T.; Matsuta, K.; Takeuchi, F.; Nagano, Y.; Miyamoto T.; Kobata, A. *Nature* **1985**, *316,* 452.

97. Barchi, J. J. *Curr. Pharm. Des*. **2000**, *6*, 485.

98. Micheal, J. P. *Nat. Prod. Rep*. **1997**, *14*, 619.

99. Shahean, P. E.; Stadler, W.; Elson, P.; Knox, J.; Winquist, E.; Bukowski, R. M. *Invest. New. Drugs*. **2005**, 23, 577.

100. Goss, P.; Reid, C. L.; Bailey, D.; Dennis, J. W. *Clin. Cancer Res*. **1997**, *3*, 1077

101. Zhang, L.; Sun, F.; Li, Y.; Sun, X.; Liu, Y.; Jung, L. –H.; Xhang, X, -S.; Ziao, J. *Med. Chem*. **2007**, *2*, 1594

102. Marchi, B.; Minutolo, A.; Grelli, S.; Cardona, F.; Cordero, F. M. Mastino, A.; Brandi, A. *Glycobiology*, **2010**, *20*, 500.

103. Padró, M.; Castillo, J. A.; Gómez, L.; Jogler, J.; Clápes, P.; De Bolós, C. *Glyconj. J*. **2010**, *27*, 277.

104. Wang, R. –J.; Yang, C. H.; Hu, M. –L. *J. Agric. Food Chem*. **2010**, *58*, 8988.

105. Wolfenden, R.; Lu, X.; Young, G. *J. Am. Chem. Soc*. **1998**, *120*, 6814.

106. Koshland Jr, D. E. *Biol. Rev*. **1953**, *28*, 416.

107. Davies, G. L.; Sinnott, M. L.; Withers, S. G. *Comprehensive biological catalysis. A mechanistic reference*. M. L. Sinnott, Academic Press, London, **1998**, *Volume I*, 119.

108. Sinnott, M. L. *Chem Rev*. **1990**, *90*, 1171.

109. Terwisscha van Scheltinga, A.C.; Armand, S.; Kalk, K.H.; Isogai, A.; Henrissat, B.; Dijkstra, B. *Biochemistry,* **1995**, *34*, 15619.

110. Macauley, M.S.; Whitworth, G.E.; Debowski, A.W.; Chin, D.; Vocadlo, D. *J. Biol. Chem*. **2005**, *280*, 25313.

111. Thompson, A.J.; Williams, R.J.; Hakki, Z.; Alonzi, D.S.; Wennekes, T.; Gloster, T.M.; Songsrirote, K.; Thomas-Oates, J.E.; Wrodnigg, T.M.; Spreitz, J. *Proc. Natl. Acad. Sci. U.S.A*. **2012**, *109*, 781.

112. Cantarel, B.L.; Coutinho, P.M.; Rancurel, C.; Bernard, T.; Lombard, V.; Henrissat, B. *Nucleic Acids Res*. **2008**, *37*, D233.

113. Gloster, T.M.; Turkenburg, J.P.; Potts, J.R.; Henrissat, B.; Davies, G. *J. Chem. Biol*. **2008**, *15*, 1058.

114. Kitamura, M.; Okuyama, M.; Tanzawa, F.; Mori, H.; Kitago, Y.; Watanabe, N.; Kimura, A.; Tanaka, I.; Yao, M. *J. Biol. Chem.* **2008**, *283*, 36328.

115. Okuyama, M.; Kitamura, M.; Hondoh, H.; Kang, M.S.; Mori, H.; Kimura, A.; Tanaka, I.; Yao, M. *J. Mol. Biol.* **2009**. *392*, 1232.

116. Davies, G, J.; Ducros, V. M. –A.; Varrot, A.; Zechel, D. L. *Biochem. Soc. Trans.* **2003**, *31*, 523.

117. Sabini, E.; Wilson, K. S.; Danielsen, S.; Schülein, M.; Davies, G. *J. Acta Crystallogr.* D. **2001**, *57*, 1344

118. Pauling, L. *Chem. Eng. News*. **1946**, *24,* 1375.

119. Laglerie, P.; Legler, G.; Yon, J. M. *Biochemie.* **1982**, *64*, 977.

120. Ermet, P.; Vasella, A. *Helv. Chim. Acta*. **1993**, *76*, 2687.

121. Selwood, D. L.; Carter, K.; Young, R. J.; Jandu, K. S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 991.

122. Yoshimura, Y.; Kuze, T.; Ueno, M.; Komiya, F.; Haraguchi, K.; Tanaka, H.; Kano, F.; Yamada, K.; Asami, K.; Kaneko, N.; Takahata, H. *Tetrahedron Lett.* **2006**, *47*, 591.

123. Hellman, B.; Lernmark, A.; Sehlin, J.; Taljedal, I. B.; Whistler, R. L. *Biochemical pharmacology.* **1973**, *22*, 29.

124. Yoshimura, Y.; Endo, M.; Sakata, S. *Tetrahedron Lett.* **1999**, *40*, 1937.

125. Kim, J. H.; Kim, S. H.; Hahn, E. W.; Song, C. W. *Science* (New York, N.Y.) **1978**, *200*, 206.

126. Mohan, S.; Pinto, B. M. *J. Carbohydrate Res*. **2007**, *342*, 1551.

127. Svansson, B. D.; Johnston, J. H.; Gu, J. H.; Patrick, B.; Pinto, B. M. *J. Am. Chem. Soc*. **2000**, *122*, 10769.

128. Kumar, N. S.; Pinto, B. M. *J. Org. Chem*. **2006**, *71*, 1262.

129. Weijia X.; Genzoh T.; Junji, A.; Toshio, M.; Kiyofumi, N.; Toshie, M.; Masayuki Y.; Xiaoming, W.; Osamu, M. *Bioorg. Med. Chem*. **2011**, *19*, 2015.

130. Eskandari, R.; Kuntz, D. A.; Rose, D. R.; Pinto, B. M. *Org. Lett*, **2010**, *12,* 1632.

131. Yuasa, H.; Takada, J.; Hashimoto, H. *Tetrahedron Lett*. **2000**, *41*, 6615.

132. Ghavami, A. Johnston, B. D.; Pinto, B. M. *J. Org. Chem*. **2001**, *66*, 2312.

133. Nasi, R.; Sim, L.; Rose, D. R.; Pinto, B. M. *Carbohydr. Res*. **2007**, *12*, 1888.

134. Ghavami, A.; Johnston, B. D.; Jensen, M. T.; Svensson,B.; Pinto, B. M. *J. Am. Chem. Soc*. **2001**, *123*, 6268.

135. Szczepina, M. G.; Johnston, B. D.; Yuan, Y.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 12458.

136. Siriwardena, A. H.; Chiaroni, A.; Riche, C.; Grierson, D. *J. Org. Chem.* **1992**, *57*, 5661.

137. Andrews, J. S.; Wiemar, T.; Frandsen, T. P.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc.* **1995**, *117*, 10799.

138. Jesperson, T. M.; Bols, M. *Tetrahedron* **1994**, *50*, 13449.

139. Jesperson, T. M; Dong, W.; Sierks, M. R.; Skrydstrup, T.; Lundt, I.; Bols, M. *Angew. Chem. Int. Ed.* **1994**, *33*, 1778.

140. Andersch, J.; Bols, M. *Chem. Eur. J.* **2001**, *7*, 3744.

141. Ichikawa, Y.; Igarashi, Y. *Tetrahedron Lett.* **1995**, *36*, 4585.

142. Ichikawa, Y.; Igarashi, Y.; Ichikawa, M.; Suhara, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3007.

143. Kim, Y. J.; Ichikawa, M.; Ichikawa, Y. *J. Org. Chem.* **2000**, *65*, 2599.

144. Namchuk, M. N.; Mc Carter, J. D.; Becalski, A.; Andrews, T.; Withers, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 1270.

145. Bols, M.; Hazell, R. G.; Thomsen, I. B. *Chem. Eur. J.* **1997**, *3*, 940.

146. Liang, X.; Bols, M. *J. Org. Chem.* **1999**, *64*, 8485.

147. Ernholt, B. V.; Thomsen, I. B.; Lohse, A. Plesner, I. W.; Jensen, K. B.; Hazell, R. G.; Liang, X. Jakobsen, A.; Bols, M. *Chem. Eur. J.* **2000**, *6*, 278.

148. Jensen, H. H.; Jensen, A.; Hazell, R.; Bols, M. *J. Chem. Soc., Perkin Trans.* **2002**, *1*, 1190.

149. Tong, M. K.; Papandreou, G.; Ganem, B. *J. Am. Chem. Soc.* **1990**, *112*, 6137.

150. Ganem, B.; Papandreou, G. *J. Am. Chem. Soc.* **1991**, *113*, 8984.

151. Papandreou, G.; Tong, M. K.; Ganem, B. *J. Am. Chem. Soc.* **1993**, *115*, 11682.

152. Hoos, R.; Naughton, A. B.; Thiel, W.; Vasella, A.; Weber, W.; Rupitz, K.; Withers, S. G. *Helv. Chim. Acta.* **1993**, *76*, 2666.

153. Ermet, P.; Vasella, A. *Helv. Chim. Acta.* **1991**, *74*, 2043.

154. Panday, N.; Vasella, A. *Synthesis* **1999**, 1459.

155. Heightman, T. D.; Locatelli, M.; Vasella, A. *Helv. Chim. Acta.* **1996**, *79*, 2190.

156. Zhang, J.; Niu, Y.; Cao, X.; Ye, X. -S. *Tetrahedron* **2012**, *68*, 4242.

157. Gunasundari, T.; Chandresekran, S. *J. Org. Chem.* **2010**, *19*, 6685.

158. Halila, S.; Benazza, M.; Demailly, G. *Tetrahedron Lett.* **2001**, *42*, 3307.

159. Benazza, M.; Halila, S.; Viot, C.; Danquigny, A.; Pierru, C.; Demailly, G. *Tetrahedron* **2004**, *60*, 2889.

160. Merrer, Y. L.; Fuzier, M.; Dosbaa, I.; Foglietti, M. J.; Depezay, J. C. *Tetrahedron* **1997**, *53*, 16731.

161. Cubero, I. I.; Lopez-Espinosa, M. T. P.; Richardson, A. C.; Suarez Ortega, M. D. *Carbohydr. Res.* **1993**, *242*, 109.

162. Chou, W. C.; Chen, L.; Fang, J. M.; Wong, C. H. *J. Am. Chem. Soc.* **1994**, *116*, 6191.

163. Robert, C. C.; Benazza, M.; Frechou, C.; Demailly, G. *Carbohydr. Res.* **1997**, *303*, 359.

164. Hashimoto, H.; Kawanishi, M.; Yuasa, H. *Carbohydr. Res.* **1996**, *282*, 207.

165. Cubero, I. I.; Lopez-Espinosa, M. T. P.; Asenjo, R. A.; Fernandez, A. R. *Carbohydr. Lett.* **1999**, *3*, 323.

166. Yuasa, H.; Kajimoto, T.; Wong, C. H. *Tetrahedron Lett.* **1994**, *35*, 8243.

167. Garca-Moreno, M. I.; Aguilar, M.; Mellet, C. O.; Fernández, J. M. G. *Org. Lett.* **2006**, *8*, 297.

168. Goujon, J. –Y.; Gueyrard, D.; Compain, P.; Martin, O. R.; Asano, N. *Tetrahedron: Asymmetry* **2003**, *14*, 1969.

169. Lindström, U. M.; Ding, R.; Hidestål, O. *Chem. Commun.* **2005**, 5, 1773.

170. Dangerfield, E. M.; Timmer, M. S. M.; Stocker, B. L. *Org. Lett.* **2009**, *11*, 535.

171. Renaud, P.; Sibi, M. P. *Radicals in Organic Synthesis;* **2001**, Wiley-VCH, Weinhem, Germany.

172. Mc Carroll, A. J.; Walton, J.C. *J. Chem. Soc., Perkin Trans 1.* **2001**, *24*, 3215.

173. Mc Carroll, A. J.; Walton, J.C. *Angew. Chem. Int. Ed.* **2001**, *40*, 2224.

174. Walton, J. C. *Radicals in Synthesis II: Complex Molecules*; **2006** Springer-Verlag: Berlin, 163–200.

175. Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Maslen, S. L.; Ley, S. V. *Angew. Chem. Int. Ed.* **2007**, *46*, 7629.

176. B. J.; Boyer, A.; Ayats, C.; Ley, S. V. *Angew. Chem. Int. Ed.* **2007**, *46*, 7633.

177. Nicolaou, K. C.; Sasmal, P. K.; Roecker, A. J.; Sun, X. W.; Mandal, S.; Converso, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3444.

178. Nicolaou, K. C.; Sasmal, P. K.; Koftis, T. V.; Converso, A.; Loizidou, E.; Kaiser, F.; Roecker, A. J.; Dellios, C. C.; Sun, X. W.; Petrovic, G. *Angew. Chem. Int. Ed.* **2005**, *44*, 3447.

179. Nicolaou, K. C.; Roecker, A. J.; Monenschein, H.; Guntupalli, P.; Follmann, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 3637.

180. Nicolaou, K. C.; Roecker, A. J.; Follmann, M.; Baati, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2107.

181. Nicolaou, K. C.; Follmann, M.; Roecker, A. J.; Hunt, K. W. *Angew. Chem. Int. Ed.* **2002**, *41*, 2103.

182. Nicolaou, K. C.; Snyder, S. A.; Giuseppone, N.; Huang, X. H.; Bella, M.; Reddy, M. V.; Rao, P. B.; Koumbis, A. E.; Giannakakou, P.; O' Brate, A. *J. Am. Chem. Soc.* **2004**, *126*, 10174.

183. Sinay, P. *Pure Appl. Chem.* **1998**, *2*, 407.

184. Gomez, A. M.; Moreno, E.; Valverde, S.; Lopez, J. C. *Eur. J. Org. Chem.* **2004**, *8*, 1830.

185. Lindström, U. M.; Ding, R.; Hidestål, O. *Chem. Commun.* **2005**, 13, 1773.

186. Marra, A.; Sinäy, P. *Carbohydr. Res.* **1987**, *187*, 35.

187. Calvo-Florez, F. G.; Hernandez-Mateo, F.; Garcia-Mendoza, P.; Isac-Garcia, I.; Perez-Alvarez, D. *Synlett* **1994**, *6*, 454.

188. Giese, B.; Groninger, K. S.; Witzel, T.; Karth, H. –G.; Sustmann, R. *Angew. Chem. Int. Ed.* **1987**, *26*, 233.

189. Gyóllai, V.; Schanzanbach, D.; Somá, L.; Linker, T. *Chem Commun.* **2002**, *12*, 1294.

190. Francisco, C. G.; Freire, R.; Gonzales, C. C.; Suarez, E. *Tetrahedron: Assymetry* **1997**, *12*, 1971.

191. Pandey, G.; Kapur, M.; Khan, M. I.; Gaitward, S. M. *Org. Biomol. Chem.* **2003**, *19*, 3321.

192. Chabaud, L.; Landais, Y.; Renaud, P. *Org. Lett.* **2005**, *7*, 2587.

193. Chen, M. –J.; Tsai, Y, -M. *Tetrahedron Lett.* **2007**, *48*, 6271.

194. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem.* **2001**, *113*, 2056; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.

195. Bock, V. D.; Hiemstra, H.; Van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, *1*, 51.

196. Binder, W. H. Kluger, C. *Curr. Org. Chem.* **2006**, *10*, 1791.

197. Dondoni, A. *Chem. Asian J.* **2007**, *2*, 700.

198. Posner, T. *Chem. Ber.* **1905**, *38*, 646

199. Kharasch, M. S.; Read, A. T.; Mayo, F. R. *Chem. Ind.* **1938**, *57*, 752.

200. Hoyle, C. E.; Bowman, C. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 1540.

201. Hoyle, C. E.; Lowe, A. B.; Bowman, C. N. *Chem. Soc. Rev.* **2010**, *39*, 1355.

202. Kade, M. J.; Burke, D. J.; Hawker, C. J. J. *Polym. Sci., Part A: Polym. Chem.* **2010**, *48*, 743.

203. Lowe, A. B. *Polym. Chem.* **2010**, *1*, 17.

204. Fiore, M.; Marra, A.; Dondoni, A. *J. Org. Chem.* **2009**, *74*, 4422.

205. Pachamuthu, K.; Schmidt, R. R. *Chem. Rev.* **2006**, *106*, 160.

206. Dondoni, A. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)***2010**, *51*, 709.

207. Fiore, M.; Lo Conte, M. Pacico, S.; Marra, A.; Dondoni, A. *Tetrahedron Lett.* **2011**, *52*, 444.

208. Floyd, N.; Vijayakrishnan, B.; Koeppe, J. R.; Davis, B. *J. Angew. Chem. Int. Ed.* **2009**, *48*, 7798.

209. Lee, Y. C.; Lee, R. T. *Acc. Chem. Res.* **1995**, *28*, 321.

210. Lundquist, J. J.; Toone, E. J. *Chem. Rev.* **2002**, *102*, 555.

211. Chabre, Y. M.; Roy, R. *Adv. Carbohydr. Chem. Biochem.* **2010**, *63*, 165.

212. Dondoni, A.; Marra, A. *Chem. Rev.* **2010**, *110,* 4949.

213. Pourceau, G.; Meyer, A.; Vasseur, J, -J.; Morvan, F. *J. Org. Chem.* **2009**, *74*, 1218.

214. Fiore, M.; Chambery, A.; Marra, A.; Dondoni, A. *Org. Biomol. Chem.* **2009**, *7*, 3910.

215. Ambrosi, M.; Cameron, N. R.; Davis, B. G. *Org. Biomol. Chem.* **2005**, *3*, 1593.

216. Hoogenboom, R. *Angew. Chem. Int. Ed.* **2010**, *49*, 3415.

217. Lowe, A. B.; Hoyle, C. E.; Bowman, C. *N. J. Mater. Chem.* **2010**, *20*, 4745.

218. Aimetti, A. A.; Shoemaker, R. K.; Lin, C. –C.; Anseth, K. S. *Chem. Commun.* **2010**, *46*, 4001.

219. Cabri, W.; Candiani, I.; Bedeschi, A. *Tetrahedron Letters*, **1992**, *33*, 4783.

220. Symons, M. C. R. *Tetrahedron* **1973**, *29*, 615.

221. Roberts, B. P.; Winter, J. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1353.

222. Griller, D.; Mendenhall, G. D.; Van Hoof, W.; Ingold, K. U. *J. Am. Chem. Soc.* **1974**, *96*, 6068.

223. Zard, S. Z. *Synlett* **1996**, *12*, 1148.

224. Portela-Cubillo, F.; Scott, J. S.; Walton, J. C. *J. Org. Chem.* **2008**, *14*, 2285.

225. Alonso, R.; Campos, P. J.; Rodriguez, M. A.; Sampedro, D. *J. Org. Chem.* **2008**, *6*, 2234.

226. Horner, J. H.; Musa, O. M.; Bouvier, A.; Newcomb, M. *J. Am. Chem. Soc.* **1998**, *120*, 7738.

227. Le Tadic-Biadatti, M. -H.; Callier-Dublanchet, A. –C.; Horner, J. H.; Quiclet-Sire, B.; Zard, S. Z.; Newcomb, M. *J. Org. Chem.* **1997**, *62*, 559.

228. Forrester, A. R., *'International Review of Science, Organic Chemistry Series Two: Free Radical Reactions'*, **1975,** *Vol. 10*, Chap. 5, Butterworths & Co., London.

229. Mc Nab J. *J. Chem. Soc., Chem. Commun.* **1980**, 10, *422.*

230. Hudson, R. F.; Record, K. A. F. *J. Chem. Soc., Chem. Commun.* **1976**, *14*, 539.

231. Hasebe, M.; Kogawa, K.; Tsuchiya, *Tetrahedron Lett.* **1984**, *25*, 3887.

232. Forrester, A. R., Gill, M.; Meyer, C. J.; Sadd, J. S.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. I.* **1979**, 606.

233. Beckwith, A. L. J.; O' Shea, D. M.; Gerba, S.; Westwood, S. W. *J. Chem. Soc., Chem. Commun.* **1987**, 666.

234. Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565.

235. Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron Lett.* **1990**, *31*, 3545.

236. Newcomb, M.; Deeb, T. M.; Marquardt, D. J. *Tetrahedron* **1990**, *46*, 2317.

237. Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron Lett.* **1991**, *32*, 4299.

238. Gagosz, F.; Zard, S. Z. *Synlett*, **1999**, *26* 1978.

239. Xichen, L.; Artman, G. D.; Stein, S.; Weinreb, S. M. *Tetrahedron* **2001**, *57,* 8779.

240. Alonso, R.; Campos, P. J.; Garcia, B.; Rodriguez, M. A. *Org. Lett.* **2008**, *8*, 3521.

241. Portela-Cubillo, F.; Scott, J. S.; Walton, J. C. *J. Chem. Commun.* **2007**, 4041.

242. Blake, J. A.; Pratt, D. A.; Lin, S.; Walton, J. C.; Mulder, P.; Ingold, K. U. *J. Org. Chem.* **2004**, *69*, 3112.

243. Fallis, A. G.; Brinza, I. M. *Tetrahedron.* **1997**, *53*, 17543.

244. Frankenburg, W. G.; Komarewsky, V. I.; Rideal Keightley, E. *Advances in Catalysis*, **1951**, *vol III*, Academic Press.

245. Nolen, E. G.; Kurish, A. J.; Wong, A. K.; Orlando, M. D. *Tetrahedron Lett.* **2003**, *44*, 2449.

246. Chatterjee, A. K.; Choi, T. -L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

247. Martin, O. R.; Saavedra, O. M.; Xie, F.; Liu, L.; Picasso, S.; Vogel, P.; Kizu, H.; Asano, N. *Bioorg. Med. Chem.* **2001**, *9*, 1269.

248. Lancelin, J. –H.; Pougney, J. –R.; Sinäy, P. *Carbohydr. Res.* **1985**, *136*, 369.

249. Matinez, A. G.; Alvarez, R. M.; Barcina, J. O.; Cerero, S. M.; Vilar, E. J.; Fraile, A. G.; Hanack, M.; Subramanian, L. R. *Chem. Commun.* **1990**, 1571.

250. Vedejs, E.; Engler, D. A.; Mullins, M. J. *J. Org. Chem.* **1977**, *42*, 3109.

251. N. Tewari, H. Nizar, A. Mane, V. George and M. Prasad, *Synth. Commun.* **2006**, *36*, 1911.

252. Wallace, O. B.; Springer, D. M. *Tetrahedron Lett.* **1998**, *39*, 2693.

253. Schlesinger, H. I.; Brown, H. C.; Finholt, A. E.; Gilbreath, J. R.; Hoekstra, H. R.; Hyde, E. K. *J. Am. Chem. Soc.* **1952**, *75*, 215.

254. Humphrey, R. E.; Potter, J. L. *Anal. Chem.* **1965**, *37*, 164.

255. Hoffmann, F. W.; Ess, R. J.; Simmons, T. C.; Hanzel, R. S. *J. Am. Chem. Soc.* **1956**, *78*, 6416.

256. Cramer, N. B.; Reddy, S. K.; O'Brien, A. K.; Bowman, C. N. *Macromolecules* **2003**, *36*, 7964.

257. Northrop, B. H.; Coffey, R. N. *J. Am. Chem. Soc.* **2012**, *134*, 13804.

258. Passacantilli, P.; Centore, C.; Ciliberti, E.; Piancatelli, G.; Leonelli, F. *Eur. J. Org. Chem.* **2006**, *14*, 3097.

259. Kwon, Y. –U.; Soucy, R. L.; Snyder, D. A.; Seeberger, P. H. *Chem. Eur. J.* **2005**, *11*, 2493.

260. Malone, A.; Scanlan, E. M. *Org. Lett.* **2013**, *15*, 504.

261. Bozó, E.; Gáti, T.; Demeter, Á.; Kuszmann, J. *Carb. Res.* **2002**, *337*, 1351.

262. Persky, R.; Albeck, A. *J. Org. Chem.* **2000**, *63*, 3775.

263. Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.

264. Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

265. RajanBabu, T. V. *J. Am. Chem. Soc.* **1987**, *109*, 609.

266. RajanBabu, T. V.; Fukunaga, T.; Reddy, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 1759.

267. RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139.

268. Kim, I. S.; Li, Q. R.; Dong, G. R.; Kim, Y. C.; Hong, Y. J.; Lee, M.; Chi, K, -W.; Oh, J. S.; Jung, Y. H. *Eur. J. Org. Chem.* **2010**, *8*, 15693.

269. Motoshima, K.; Ishikawa, M.; Hashimoto, Y.; Sugita, K. *Bioorg. Med. Chem.* **2011**, *19*, 3156.

270. Maddaluno, J. F.; Gresh, N.; Giessner-Prettre, C. *J. Org. Chem.* **1994**, *59*, 793.

271. Ruano, J. L. G.; Aleman, J.; Alonso, I.; Parra, A.; Marcos, V.; Aguirre, J. *Chem. Eur. J.* **2007**, *13*, 6179.

272. Yoshimi, Y.; Masuda, M.; Mizunashi, T.; Nishikawa, K.; Maeda, K.; Koshida, N.; Itou, T.; Morita, T.; Hatanaka, M. *Org. Lett.* **2009**, *11*, 4652.

273. Niwayama, S.; Cho, H. *Chem. Pharm. Bull (Tokyo).* **2009**, *57*, 508.

274. Panday. N.; Canac, Y.; Vasella, A. *Helv Chim Acta.* **2000**, *83*, 58.

275. Wrodnigg, T. M.; Withers, S.G.; Stutz, A. E. *Bioorg. Med. Chem. Lett.* **2001,** *11*, 1063.

276. Hermetter, A.; Scholze, H.; Stütz, A. E.; Withers, S. G.; Wrodnigg, T. M. *Bioorg. Med. Chem.* **2001**, *11*, 1339.

277. Popowycz, F.; Gerber-Lemaire, S.; Demange, R.; Rodriguez-Garcia, E.; Carmona-Asenjo, A. T.; Robina, I.; Vogel, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2489.

278. Schwabacher, A. W.; Lane, J. W.; Schiesher, M. W.; Leigh, K. M.; Johnson, C. W. *J. Org. Chem.* **1998**, *63*, 1727

279. Bertozzi, C. R.; Bednarski, M. *J. Org. Chem.* **1991**, *56*, 4326.

280. Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397.

281. Malone, A.; Scanlan, E. M. *J. Org. Chem.* **2013**, *78*, 10917

282. Boger, D. L.; Boyce, C. W. *J. Org. Chem.* **2000**, *65*, 4088. (b) Boger, D. L.; Mc Kie, J A. *J. Org. Chem.* **1997**, *62*, 8875.

283. Inokuchi, T.; Kowafuchi, H. *Tetrahedron* **2004**, *60*, 11969.

284. Bragd, P. L.; Besemer, A. C.; Van Bekkum, H. *Carb. Res.* **2000**, *328*, 355.

285. Mandal, M.; Yun, H.; Dudley, G. B.; Lin, S.; Tan, D. S.; Danishefsky, S. J. *J. Org. Chem.* **2005**, *70*, 10619.

286. Han, B.; Yang, X. –L.; Fang, R.; Yu, W.; Wang, C.; Duan, X. –Y.; Liu, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 8816.

287. Huang, L.; Teumelsan, N.; Huang, X. *Chem. Eur J.* **2006**, *12*, 5246.

288. Skaanderup, P. R.; Poulsen, C. S.; Hyldtoft, L.; Jørgensen, M. R.; Madsen, R. *Synthesis* **2002,** *12*, 1721.

289. Beer, D.; Vasella, A. *Helv. Chim. Acta.* **1985,** *68*, 2254.

290. Baldwin, J. E. *Chem. Commun.* **1976**, *18*, 734.

291. Bernet, B.; Vasella, A. *Helv. Chim. Acta.* **1979**, *62*, 1990.

292. Bernet, B.; Vasella, A. *Helv. Chim. Acta.* **1979**, *62*, 2400.

293. Dransfield, P. J.; Moutel, S.; Shipman, M.; Sik, V. *J. Chem. Soc., Perkin Trans. 1.* **1999**, 3349.

294. Ovaa, H.; Codee, J. D. C.; Lastdrager, B.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1999**, *40*, 5063.

295. Desire, J.; Prandi, J. *Tetrahedron Lett.* **1997**, *38*, 6189.

296. Hummer, W.; Dubois, E.; Gracza, T.; Jager, V. *Synthesis* **1997**, 634.

297. Grove, J. J. C.; Holzapfel, C. W. *Carbohydr. Lett.* **1997**, *2*, 329.

298. Kleban M; Kautz, U; Jörg, G; Hilgers P; Kugler, R; Dong, H-Q, Jäger V. *Synthesis* **2000**, *7*, 1027.

299. Ferrier, R. J.; Prasit, P.; Gainsford, G. J.; Page, Y. L. *J. Chem. Soc., Perkin Trans 1.* **1983**, 1629.

300. Jensen, HS; Limberg, G; Pederson C; *Carbohydrate Res.* **1997**, *302,* 109.

301. Lach, B. *Ber.* **1884**, *17*, 1571

302. Moureu, C. *Bull. Soc. Chim. France*, **1894**, *11* , 1067

303. Brady, L.; McHugh, G. P. *J. Chem. Soc.* **1923**, 1190

304. Restelli de Labriola, E.; Deulofeu, V. *J. Org. Chem.* **1947**, *12*, 726.

305. Portela-Cubillo, F.; Scanlan, E. M.; Scott, J. S.; Walton, J. C. *Chem. Commun.* **2008**, 4189.

306. Binmore, G. T.; Walton, J. C.; Adcock, W.; Clark, C. I.; Kristic, A. R. *Magn. Reson. Chem.* **1995**, *33*, 53.

307. Mangini, A.; Spagnolo, P.; Tossi, D.; Tiecco, M.; Zanirato, P. *Tetrahedron.* **1972**, *28*, 3485.

308. Testaferri, L.; Tiecco, P.; Spagnolo, P.; Zanirato, P.; Martelli, G. *J. Chem. Soc., Perkin. Trans 2.* **1976**, 662.

309. Griller, D.; Marriott, P. R.; Nonhebel, D. C.; Perkins, M. J.; Wong, P. C. *J. Am. Chem. Soc.* **1981**, *103*, 7761.

310. Portela-Cubillo, F.; Alonso-Ruiz, A.; Sampedro, D.; Walton, J. C. *J. Phys. Chem. A.* **2009**, *113*, 10005.

311. Portela-Cubillo, F.; Surgenor, B. A.; Aitken, R. A. Walton, J. C. *J. Org. Chem.* **2008**, *73*, 8124.

312. Ambrose, D.; Brady, O. L. *J. Chem. Soc.* **1950**, *15*, 1243.

313. Petrassi, M. H.; Sharpless B. K.; Kelly, J. W. *Org. Lett.* **2001**, *3,* 139.

314. Osby, J. O.; Martin, M. G. Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 2093.

315. Boivin, J.; Callier-Dublanchet. B.; Quiclet-Sire, A.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 6517.

316. Hansen, F. G.; Bundgaard, E.; Madsen, R. J. *J. Org. Chem.* **2005**, *70*, 10139.

317. Bernotas, R. C.; Papandreou, G.; Urbach, J.; Ganem, B. *Tetrahedron Lett.* **1990**, *31*, 3393.

318. Liu. Y.; Han, T. –X.; Yang, Z. –J.; Zhang, L. –R.; Zhang, L. –H. *Tetrahedron: Assymetry* **2007**, *18*, 2326.

319. Deras, I. L.; Takegawa, K.; Kondo, A.; Kato, I.; Lee, Y. C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1765,

320. Inazu, T.; Kobayashi, K. *Synlett* **1993**, 869.

321. Mohan, H.; Vasella, A. *Helv. Chim. Acta.* **2000**, *83*, 114.

322. Rodriguez, A.; Miller, D. D.; Jackson, R. F. W. *Org. Biomol. Chem.* **2003**, *1*, 973.

323. Praly, J. –P.; Senni, D.; Faure. R.; Descotes. G. *Tetrahedron.* **1995**, *51*, 1697.

324. Virginie, V.; Martin, J.; Jimÿnez-Barbero, J.; Chiara, J. L.; Vicent, C. *Chem. Eur. J.* **2004**, *10*, 4240.

325. Sánchez-Fernández, E. M.; Rísquez-Cuadro, R.; Aguilar-Moncayo, M.; García-Moreno, M. I.; Mellet, C. O.; Fernández, J. M. G. *Org. Lett.* **2009**, 15, 3306.

326. Johnston, B. D.; Pinto, M. P. *J. Org. Chem.,* **1998**, *63*, 5797.

327. Cervigni, S. E.; Dumy, P.; Mutter, M. *Angew. Chem. Int. Ed.* **1996**, *35*, 1230.

328. Hoerner, J. K.; Yaghoubi, S. S.; Syud, F. A.; Gambhir, S. S. *Bioconjugate Chem.* **2009**, *20*, 432.

329. Liu, Y.; Feizi, T.; Campanero-Rhodes, M. A.; Childs, R. A.; Zhang, Y.; Mulloy, B.; Evans, P. G.; Osborn, H. M. I.; Otto, D.; Crocker, P. R.; Chai, W. *Chem. Biol.* **2007**, *14*, 847.

330. Thygesen, M. B.; Sauer, J.; Jensen, K. J. *Chem. Eur. J.* **2009**, *15*, 1649.

331. Deguchi, K.; Miura, N.; Monde, K.; Kondo, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 91.

332. Singh, Y.; Renaudet, O.; Defrancq, E.; Dumuy, P. *Org. Lett.* **2005**, *7*, 1359.

333. Zatsepin, T. S.; Orestskaya, T. S. *Chem. Biodivers.* **2004**, *1*, 1401.

334. Carrasco, M. R.; Nguyen, M. J.; Burnell, D. R.; MacLaren, M. D.; Hengel, S. M. *Tetrahedron Lett.* **2002**, *43*, 5727.

335. Finch, P.; Merchant, Z. *J. Chem. Soc., Perkin Trans 1.* **1975**, *1*, 1682.

336. Hatanaka, Y.; Kempin, U.; Jong-Jip, P. *J. Org. Chem.* **2000**, *65*, 5639.

337. Ramsay, S. L.; Freeman, C.; Grace, P. B.; Redmond, J. W.; Mac- Leod, J. K. *Carbohydr. Res.* **2001**, *333*, 59.

338. Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K. I.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461.

339. Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464.

340. Bella, A. F.; Slawin, A. M. Z.; Walton, J. C. *J. Org. Chem.* **2004**, *69*, 5926.

341. Randell, K. D.; Johnston, B. D.; Pinto, M. B. *Carbohydr. Res.* **2000**, *326*, 145.

342. Phillips, D. C. *Proc. Nat. Acad. Sci. U. S. A.* **1967**, *57*, 484.

343. Legler, G. *Biochimica et Biophysica Acta.* **1978**, *524*, 94.

344. Legler, G.; Herrchen, M. *Carbohydr. Res.* **1985**, *116*, 95.

345. Van, E. S.; Whistler, R. L. *J. Org. Chem.* **1964**, *29*, 1087.

346. Kalro, J.; Raines, R. T. *Angew Chem, Int Ed. Engl.* **2008**, *47*, 7523.

347. Pinto, B. M.; Leung, R. Y. N. *The Anomeric effect and Associated Stereoelectronic Effects*. **1993**, Thatcher, G. R. J. (Ed.), American Chemical Society, Washington, D. C. Chapter 8.

348. Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2205.

349. Ratcliffe, A. J.; Fraser-Reid, B. *J. Chem. Soc., Perkin Trans. 1.* **1990**, 747.

350. Matsuura, H.; Askawa, C.; Kurimoto, M.; Mizutani, J. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 1576.

351. Higashiyama, T. *Pure Appl. Chem.* **2002,** 74, 1263.

352. Ogawa, S.; Sato, K.; Miyamoto, Y. *J. Chem. Soc., Perkin Trans 1.* **1993**, *6*, 691.

353. Morais, G. R.; Humphry, A. J.; Falconer, R. A. *Carbohydr. Res.* **2009**, *344*, 1039.

354. Cao, S.; Tropper, F. D.; Roy, R. *Tetrahedron* **1995**, *51*, 6679.

355. Anderson, M.; Oscarson, S. *Glycoconjugate. J.* **1992**, *9*, 122.

356. Wojciechowska, H.; Pawlowicz, R.; Andruszkiewicz, R.; Grzybowska, J. *Tetrahedron Lett.* **1978**, 4063.

357. Guthrie, R. D.; Nicolas, E. C. *J. Am. Chem. Soc.* **1981**, *103*, 4638.

358. Cordes, E. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1962**, *84*, 826.

359. Renaudet, O.; Dumy, P. *Tetrahedron* **2002**, *58*, 2127.

360. Thygesen, M. B.; Munch, H.; Sauer, J.; Clo, E.; Jørgensen, m. R.; Hindsgaul, O.; Jensen. K. *J. Org. Chem.* **2010**, *75,* 1752

361. Kiankarimi, M.; Lowe, R.; McCarthy J. R.; Whitten, J.P. *Tetrahedron Lett.* **1999**, *40*, 4497.

362. Eldin, S.; Digits, J. A.; Huang, S. –T.; Jencks, W. P. *J. Am. Chem. Soc.* **1995**, *117*, 6631.

363. Gray, G. R.; Hartman, F. C.; Barker, R. *J. Org. Chem.* **1965**, *30*, 2020.

364. Mootoo, D. R.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1986**, 1570.

365. Reed, L. A., III; Huang, J. T.; McGregor, M.; Goodman, L. *Carbohydr. Res.* **1994,** *254*, 133.

366. Cocinera, E.J.; Stanco-Kaposto, E.C.; Scanlan, E. M.; Gamblin, D. P.; Davis, B. G.; Simons, P. J. *Chem. Eur. J.* **2008**, *14*, 8947.

367. Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **2000**, *65*, 5785.

368. Reddy, S.; Kadigachalam, P.; Doddi, V. R.; Vankar, Y. D. *Tetrahedron Lett.* **2009**, *50*, 5872.

369. Himanen, J. A.; Pihko, P. M. *Eur. J. Org. Chem.* **2012**, *20*, 3765.

370. Lagnoux, D.; Darbre, T.; Schmitz, M. L.; Reymond, J. –L. *Chem. Eur. J.* **2005**, *13*, 3941.

371. Liu, F.; Thomas, J.; Burke, T. R. *Synthesis* **2008**, *15*, 2432.

372. Monrad, R. N.; Pipper, C. B.; Madsen, R. *Eur. J. Org. Chem.* **2009**, *20*, 3387.

373. Lou, Q.; Meng, Q.; Lao, Z.; Xuan, L.; Bai, J.; Hou, Q.; Hu, G.; Luo, R.; Tao, L.; Li, Z. *Molecules* **2012**, *17*, 884.

374. Dorgeret, B.; Khemtémourion, L.; Correia, I.; Soulier, J. –L.; Lequin, O.; Ongeri, S. *Eur. J. Med. Chem.* 2011, 12, 5959.

375. Lee, J. C.; Francis, S.; Dutta, D.; Gupta, V.; Yang, Y.; Zhu, J. –Y.; Tash, J. S.; Schönbrunn, E.; Georg, G. I. *J. Org. Chem.* **2012**, *77*, 3082.

376. Dickson, L. G.; Leroy, E.; Reymond, J. –L. *Org. Biomol. Chem.* **2004**, *2*, 1217.

377. Hartmann, M.; Betz, P.; Sun, Y.; Gorb, S. N.; Lindhorst, T. K.; Krueger, A. *Chem. Eur. J.* **2012**, *18*, 6485

378. Holzapfel, C. W.; Crous, R.; Grayling, H. F.; Verdoom, G. H. *Heterocycles* **1999**, *51*, 280.