DEVELOPMENT OF NEW METHODOLOGIES FOR FUNCTIONALIZING GLYCALS AND 1,2-CYCLOPROPANATED SUGARS, AND APPLICATIONS IN THE SYNTHESIS OF INHIBITORS OF ENZYMES IN THE *MYCOBACTERIA*

BY

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To my beloved mother Letekidan Tesfa and grandmother Thsigeweini G. Selasie

I declare that ***'Development of new catalytic methodologies for functionalizing glycals and 1,2-cyclopropanated sugars, and application in the synthesis of inhibitors of enzymes in the Mycobacteria'*** is my own work and that all sources that I have used or quoted have been indicated and acknowledged by means of complete references.

Henok Hadgu Kinfe

ABSTRACT

Tuberculosis (TB) is a contagious respiratory disease caused by *Mycobacterium tuberculosis*. Due to lack of an efficient and short term treatment of TB, the bacterium has become resistant to the first line antibiotics and the disease has ranked next to HIV/Aids. A low molecular weight thiol called mycothiol protects the bacteria from any foreign stress factors and secures its survival. Studies have shown that mycothiol-deficient bacteria are hypersensitive to external stresses and hence inhibition of the biosynthesis of mycothiol could be a drug lead against TB.

In this thesis, the aim is to develop strategies for the synthesis of compounds that will mimic biologically active compounds that are substrates for the enzymes of *Mycobacterium tuberculosis,* in particular a deacetylase implicated in the biosynthesis of mycothiol. The compounds to be synthesized are analogues of this enzyme's substrate with special emphasis on sulfoxide and sulfone containing analogues, which will be similar enough to be recognized by the deacetylase enzyme but different enough to inhibit its functioning.

In achieving our aims, new synthetic methodologies were developed for the synthesis of the building blocks of the target molecules. A key building block identified for the synthesis of the isosteres was a 1,2-cyclopropanated sugar, derivable from glucal. This led to an investigation and exploration of new methodologies for functionalizing glycals and 1,2-cyclopropanated sugars.

A recently developed catalytic oxidative halogenation reaction using hydrogen peroxide in the presence of WO_4^{2-} exchanged synthetic takovite has thus been developed as an environmentally benign method for transforming a range of acetylated and benzylated glycals into their corresponding halohydrins and halo-glycosides. The product distributions are highly dependent on the nucleophile and the halogenating agent used. However, application of this method to the opening of 1,2-cyclopropanated sugars was unsuccessful. An alternative method that could be applied to a wide range of substrates was then sought and a novel iodoacetoxylation protocol was developed, involving the use of ammonium iodide and hydrogen peroxide in $AcOH/Ac_2O/CH_3CN$ and affording excellent yields and stereoselectivity in favor of

α-manno acetate in all glycals tested, except for a per-*tert*-butyldiphenylsilylated glucal which gave the β-gluco isomer as major product. The iodoacetoxylation method was then applied to the synthesis of the key intermediate required for preparation of the target molecules, by opening 1,2-cyclopropanated sugars to give suitably protected 2-C-iodomethylglucopyranosyl acetate that could function as a glycosyl donor.

Model studies on manipulation of the iodomethyl side-chain were then carried out on cyclohexyl glucosides prepared by coupling the 2-C-iodomethylglucopyranosyl acetate with cyclohexanol. Nucleophilic substituton of the iodide by thiolate salts prepared *in situ* gave sulfides that were oxidized efficiently and selectively to the desired sulfoxides and sulfones using Oxone®.

Attention was then focused on preparation of the analogues of 1-(2'-acetamido-D-glucopyranosyl)-D-myo-inositol. A shorter, more efficient way of making the selectively protected *myo*-inositol derivative was investigated, involving selective *O*-acylation of a 1,2-diol derivative with camphanic acid chloride in the presence of triethylamine and DMAP followed by a base-assisted acyl migration from the 1β to 2α oxygen. Coupling of the pyranosyl acetate and a resolved penta-*O*-benzylated *myo*-inositol derivative afforded the desired glycoside. The resulting glycoside underwent further transformations towards the target analogues bearing the sulfinylated and sulfonylated side-chains.

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ABBREVIATIONS

Ac	Acetyl
AIBN	2,2'-Azobisisobutyronitrile
All	Allyl
Anal.	Analytical
aq	Aqueous
Ar	Aryl
ATP	Adenosine 5'-triphosphate
Bn	Benzyl
Boc	*t*-Butoxycarbonyl
br	Broad
Bz	Benzoyl
Calcd.	Calculated
CAN	Cerric ammonium nitrate
CoA	Coenzyme A
COSY	Correlation spectroscopy
d	Doublet
DBU	1,5-Diazabicyclo[5.4.0]undec-5-ene
dd	Doublet of doublets
ddd	Doublet of doublet of doublet (in NMR)
DCM	Dichloromethane
DDT	Dithiothreitol
DEPT	Distortionless Enhancement by Polarization Transfer
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulphoxide
DNP	2,4-Dinitrophenol
δ	Chemical shift in parts per million downfield from tetramethylsilane (in NMR)
EDCI	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

g	Gram(s)
Gal	Galactose
Glc	Glucose
GlcNAc	2-Acetamido-2-deoxyglucose
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOAt	1-Hydroxy-7-azabenzotriazole
HPLC	High performance liquid chromatography
HMQC	Heteronuclear multiple quantum coherence
Hz	Hertz
IR	Infrared
IUPAC	International union of pure and applied chemistry
J	Coupling constant
LAH	Lithium aluminum hydride
LG	Leaving group
LRFAB	Low resolution fast-atom bombardment
m	Multiplet
M	Moles per cubic decimeter
M^+	Molecular ion
Man	Mannose
MCPBA	*m*-Chloroperbenzoic acid
Me	Methyl
MHz	Mega hertz
min	Minute
mL	Milliliter
MNO	4-Methylmorpholine *N*-oxide
mmol	Millimole(s)
mp	Melting point
MS	Mass spectrometry
Multi.	Multiplicity
NBA	*N*-Bromoacetamide
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodosuccinimide

NMR	Nuclear magnetic resonance
p	*Para*
PG	Protecting group
Ph	Phenyl
Piv	Pivaloyl
ppm	Parts per million
Pr	Propyl
q	Quartet
R_f	Retention factor (in chromatography)
rt	Room temperature
s	Singlet
t	Triplet
S_N1	Unimolecular nucleophilic substitution
S_N2	Bimolecular nucleophilic substitution
TB	Tuberculosis
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
tert	Tertiary
Tf	Trifluoromethanesulphonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TPAP	Tetra-*n*-propylammonium ruthenate (VII)
WHO	World Health Organization
X	Halide(s)

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CHAPTER ONE

1. INTRODUCTION

Carbohydrates comprise the most abundant group of naturally occurring organic compounds. They are produced in billions of tons every year, of which 4 x 10^{14} kg alone is produced by plants *via* the process of photosynthesis.[1,2] Besides being produced by plants, carbohydrates are the major constituents of plant and the arthropod structures. Carbohydrate compounds such as cellulose, pectin and xylan make up the structures of plants while chitin, a polymer of 2-acetamido-2-deoxy-D-glucose, is the major constituent of the shells of insects, crabs and lobsters.[3]

Even though carbohydrate compounds such as cotton, sugar cane and honey were known to human kinds in early times, the basis of understanding the chemistry of carbohydrates was laid by Emil Fischer in the 1800's.[4,5,6] The easily available carbohydrates of the time were starch, cotton, cellulose, D-glucose and D-fructose having in common an empirical formula of $C_n(H_20)_m$. Thus, the substances were considered as compounds of hydrates of carbon and then termed 'carbohydrates'. However, the definition was found to be inconclusive with the advance of carbohydrate chemistry as carbohydrate compounds devoid of specific hydroxyl groups or having thiol or halogen or amino and other groups that are not governed by the general empirical formula were known. A general and more acceptable definition of carbohydrates was required and hence, the following definition was adopted by IUPAC in 1996:[5,6]

> "The generic term 'carbohydrate' includes monosaccharides, oligosaccharides and polysaccharides as well as substances derived from monosaccharides by reduction of the carbonyl group (alditols), by oxidation of one or more terminal groups to carboxylic acids, or by replacement of one or more hydroxy group(s) by a hydrogen atom, an amino group, a thiol group or similar heteroatomic groups. It also includes derivatives of these

> compounds. The term 'sugar' is frequently applied to monosaccharides and lower oligosaccharides."

Besides their roles in storage of energy and skeletal purposes, the importance of carbohydrates in the biological systems was unknown until 1960s. Interest in the field grew after the discovery of carbohydrate binding proteins (called lectins) from plants.[2] The finding alerted a number of scientists to the fact that carbohydrate compounds could have indispensable biological functions. Studies thereafter, showed that carbohydrates are the most prominently exposed class of molecules that decorate the surfaces of all living cells. These carbohydrates having flexible chains and many potential binding sites are involved in intercellular communications of biological systems such as cell-cell recognition.[7,8] Such interactions play important roles in biological processes such as fertilisation, embryogenesis, immune responses, nervous system development, hormone activities, maintenance and pathogenesis of tissues, viral and bacterial infections and cancer metastasis.[7,8,9]

There are a number of ways by which carbohydrates play crucial roles in preventing and combating diseases. Some of the examples are:[2]

a. disruption of infective pathways
b. triggering of immune response when administered as a vaccine
c. inhibition of enzymes
d. inhibition of interaction between carbohydrates and lectins to terminate disease progression

If success in the utilization of the potential of carbohydrates in the biological system is to be achieved, the issues of ease of obtaining the building blocks, development of new reaction methodologies and synthetic strategies have to be addressed. Even though quite a number of methodologies and successful synthesis of various complex carbohydrates have been reported in the literature, the subject still remains challenging as more and more new functions and needs for carbohydrates emerge from time to time.

Among the numerous types of carbohydrate transformations, we are interested in the conversion of glycals into 2-deoxy-2-halo-sugars with the view of applying the methodologies developed in the synthesis of potential inhibitors of the enzymes involved in the biosynthesis of mycothiol.

1.1 Mycothiol

1.1.1 Tuberculosis (TB)

Tuberculosis (TB) is a respiratory disease caused by the bacterium *Mycobacterium tuberculosis* or tubercle bacillus.*[9,10] The bacterium is a non-motile rod-shaped bacillus and can grow up to the size of 2 - 4 μm in length and 0.2 - 0.5 μm in width (Figure 1.1).[12,13] It is an obligate aerobe and grows successfully in oxygen rich tissues such as the lungs.[14]

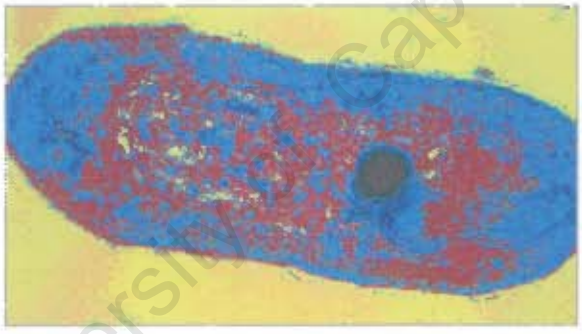


Figure 1.1. *Mycobacterium tuberculosis.*

TB has been identified as the second-largest death-causing infectious disease worldwide (the first being HIV/AIDS). WHO reports indicate that TB affects 1% of the world population of which 5 – 10% become sick or infectious. In 2004 TB claimed the lives of approximately 1.7 million people with estimated 8.8 million new cases.[14]

TB is spread through the air when a patient with pulmonary tuberculosis exhales, coughs or sneezes. Once inhaled, the bacteria can settle in the lungs and begin to grow and then circulate through the blood to other parts of the body such as the brain,

* *Mycobacterium bacteria* was first discovered in 1882 by Robert Koch. He received the Nobel Prize in Medicine in 1905 for his discovery of the bacteria.[11]

kidney and spine. However, TB in the non-respiratory organs is usually not infectious. Most people carry the TB bacilli without becoming sick but as immunity wanes due to aging, malnutrition or HIV/AIDS the chances of the bacteria to become active increase resulting in an outbreak. The symptoms of the TB disease include: a persistent cough that lasts for more than three weeks, coughing up blood, chest pain, localized bone pain, weakness or fatigue, weight loss, loss of appetite, fever and sweating at night.[14]

The first highly effective drugs for treating TB were discovered in the 1940s, long after the discovery of the bacteria in the late 19th century. Streptomycylic acid was the first drug to be discovered in 1944 followed by *p*-aminosalicyclate, commonly known as PAS (1946). The rest of the drugs that were introduced later include: isoniazid (1952), cycloserine (1955), kanamycine (1957), rifampicin (1965), ethionamide (1966), ethambutol (1968) and pyrazinamide (1970)[15] and some of them are shown in Figure 1.2.[10] The current TB treatment is a six month, four-drug combination which includes isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), and ethambutol (EMD). All drugs are administered in the initial two-month 'intensive phase', and then INH and RMP are continued during the four-month 'continuation phase'.[16] The shortcoming of the drugs is the need for a long duration of treatment and as a consequence many patients fail to comply with the treatment, especially when the symptoms subside as the drugs exert their effect and when the side effects become unbearable.[15,16] Failure of compliance results to unsuccessful treatment and worse, to the emergence of strains of *mycobacterium tuberculosis* (MDR-TB) that are resistant to all the first-line drugs.[17] Introduction of Directly Observed Treatment, Short-Course (DOTS) TB management systems have greatly improved the therapy by ensuring the best use of available drugs and compliance of patients to the full course of treatment.[18] Alternatively, improvements have been made by generating derivatives of improved activity from the existing drugs. One such example is rifapentine. It is a derivative of rifampicin and exhibits a better activity even though it lacks activity against rifampicin-resistant isolates.[19]

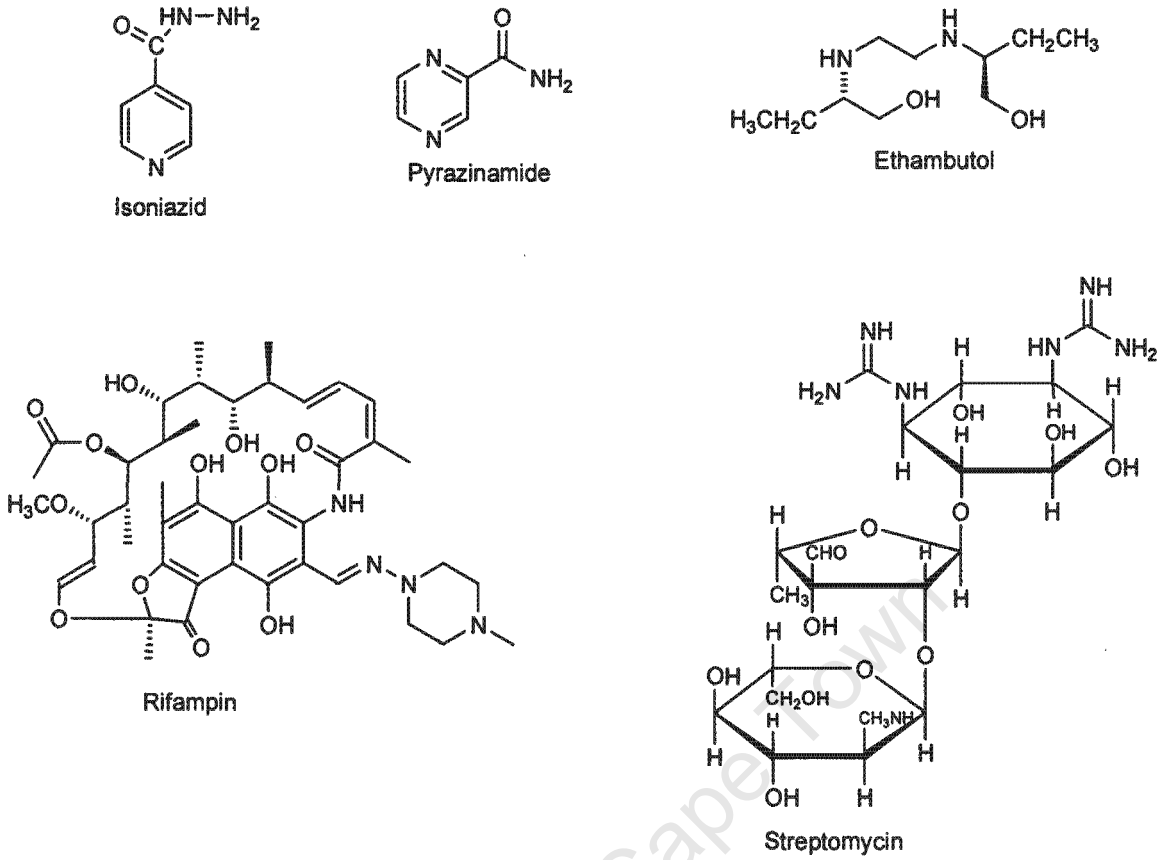


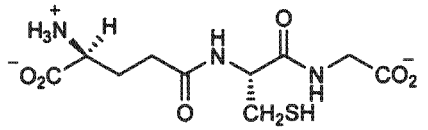
Figure 1.2. Structure of TB drugs.

The wide spread emergence of MDR-TB coupled with the synergy of TB with HIV, which is having a devastating impact in impoverished countries such as the African nations, where 31% of new TB cases were attributed to HIV co-infection, led the WHO to declare TB a 'global health emergency' in 1993.[20-23] Consequently, a search for anti-TB treatment has been a challenge and attracted researchers from all over the world. One of the approaches has been to try to expose the bacteria to harmful agents by inhibiting the biosynthesis of its defensive agents, usually low molecular weight thiols.

1.1.2 Low molecular weight thiols

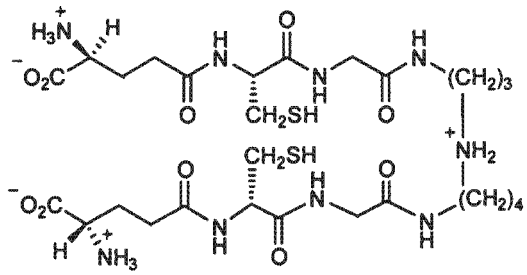
Low molecular weight thiols play critical roles in maintaining cellular redox potentials, protein thiol-disulfide ratios and protecting the cells against oxygen toxicity and other stress factors. A number of thiols have been identified that play such important roles (Figure 1.3).[24] The tripeptide glutathione **1** (γ-Glu-Cys-Gly) is

the most abundant thiol present in Eukaryotes and Gram-negative bacteria and renders the service required by the organisms. Conversely, glutathione is absent in actinomycetes, a subgroup of Gram-positive bacteria but instead an unusual low molecular weight thiol called 1-D-*myo*-inositol-2-(*N*-acetyl-L-cysteinyl)amino-2-deoxy-α-D-glucopyranoside is present in abundance.[25] The thiol was first isolated as a disulfide (MSSM, **20**) from *Streptomyces* sp. strain AJ9463 by Sakuda and co-workers[25a] and the MSSM was given a trivial name mycothione by Blanchard[26] though Newton and co-workers[27] disagreed with the nomenclature. Later Steenkamp and Spies[25b] isolated and identified the thiol from *Mycobacterium bovis* and gave it the trival name mycothiol (MSH, **4**). Newton *et al.* also managed to isolate mycothiol as the bimane derivative (MSmB) from *Streptomyces clavuligerus*.[25c] Mycothiol is obtained exclusively in actinomycetes and is present in high levels in *Mycobacterium tuberculosis*.[28] Hence, *Mycobacterium tuberculosis* is highly dependent on mycothiol for antioxidant and alkylating activity.

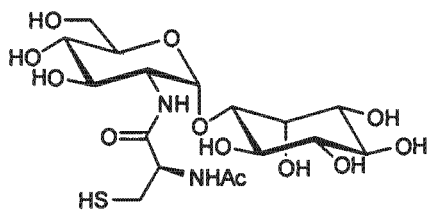


Glutathione (GSH, **1**)

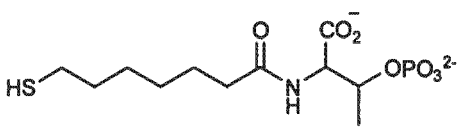
Coenzyme M (HSCoM, **2**)



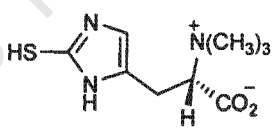
Trypanothione (TSH2, **3**)



Mycothiol (MSH, **4**)



Coenzyme B (HSCoB, **5**)



Ergothioneine (ESH, **6**)

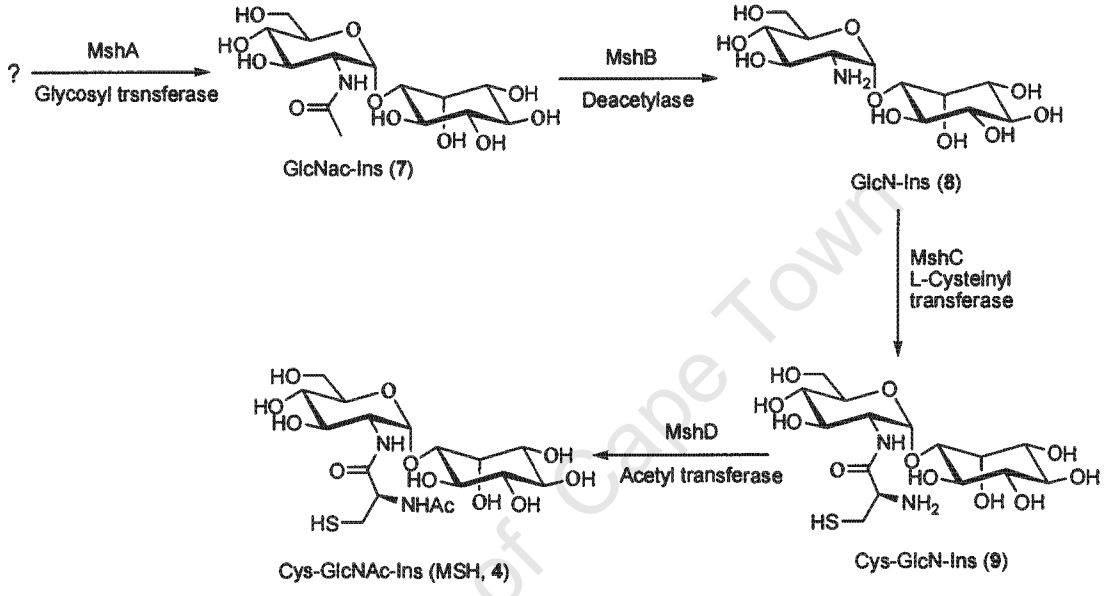
Figure 1.3. Major low molecular weight thiols.

Chemical analysis has shown the uniqueness of the structure of mycothiol among the low molecular weight thiols. Beside the *N*-acetyl cysteine moiety which is common to most of the low molecular weight thiols, mycothiol consists of a 2-deoxy-2-amino-glucose attached to a D-*myo*-inositol unit *via* an α (1→1) glycosidic bond.[25]

1.1.3 Biosynthesis of mycothiol

The biosynthetic pathway of MSH in *Mycobacterium bacteria* has been elucidated and involves four enzymatic reactions that are designated as MshA, MshB, MshC and MshD and are shown in Scheme 1.1.[29] The enzymes involved in the synthesis are encoded by genes *mshA*, *mshB*, *mshC* and *mshD*, respectively. The biosynthesis commences by the formation of the pseudodisaccharide 1-D-*myo*-inositol-2-*N*-acetamido-2-deoxy-α-D-glucopyranoside (GlcNAc-Ins) by the glycosyl transferase

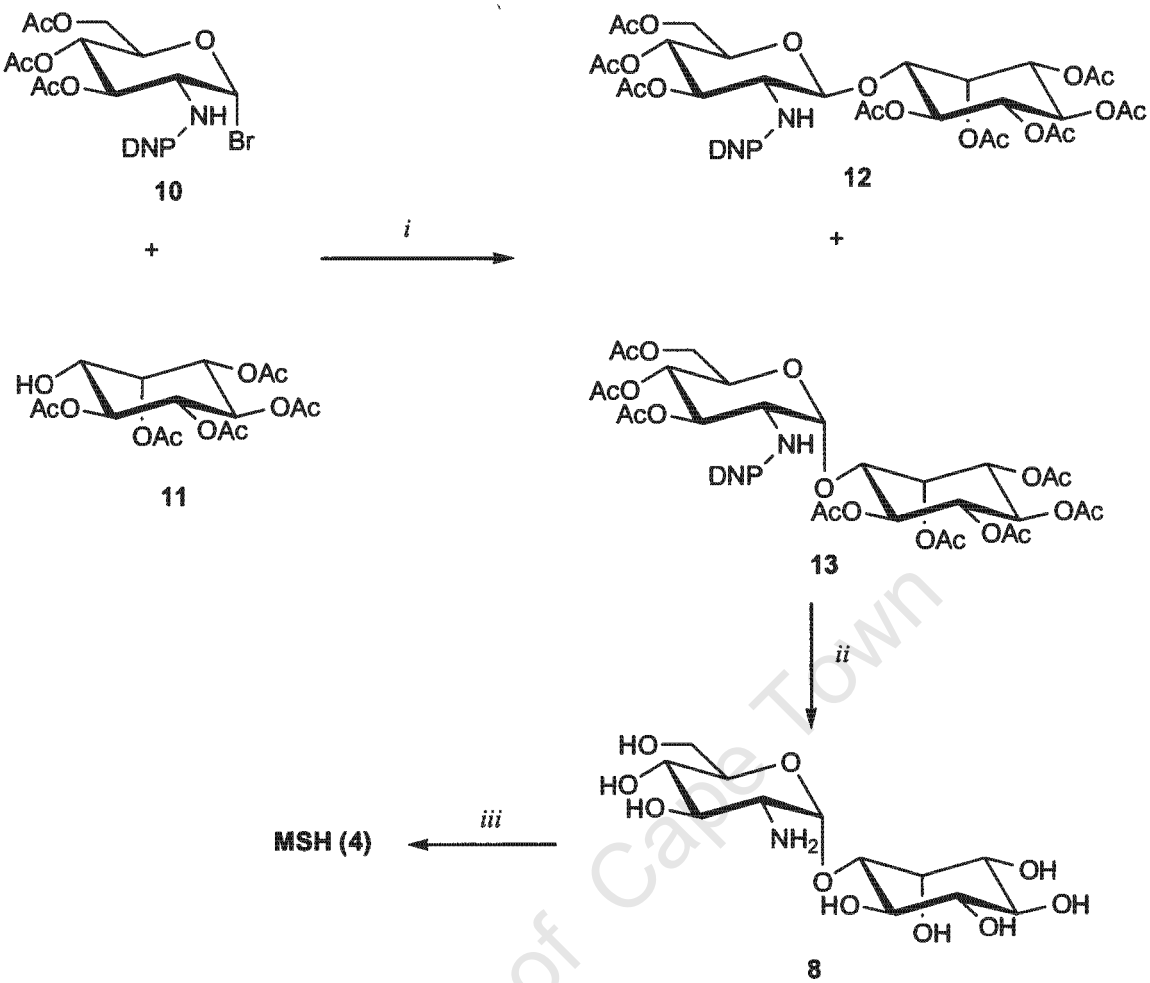
(MshA) from yet unidentified precursors.[30] *N*-deacetylation of GlcNAc-Ins by deacetylase (MshB) gives the free amine pseudodisaccharide 1-D-*myo*-inositol-2-amino-2-deoxy-α-D-glucopyranoside (GlcN-Ins)[31] which is then ligated with L-cysteine to give Cys-GlcN-Ins by L-cysteinyl transferase (MshC).[32] Transacetylation of Cys-GlcN-Ins by acetyl transferase (MshD) completes the synthesis by affording mycothiol.[33]



Scheme 1.1. Biosynthesis of mycothiol.

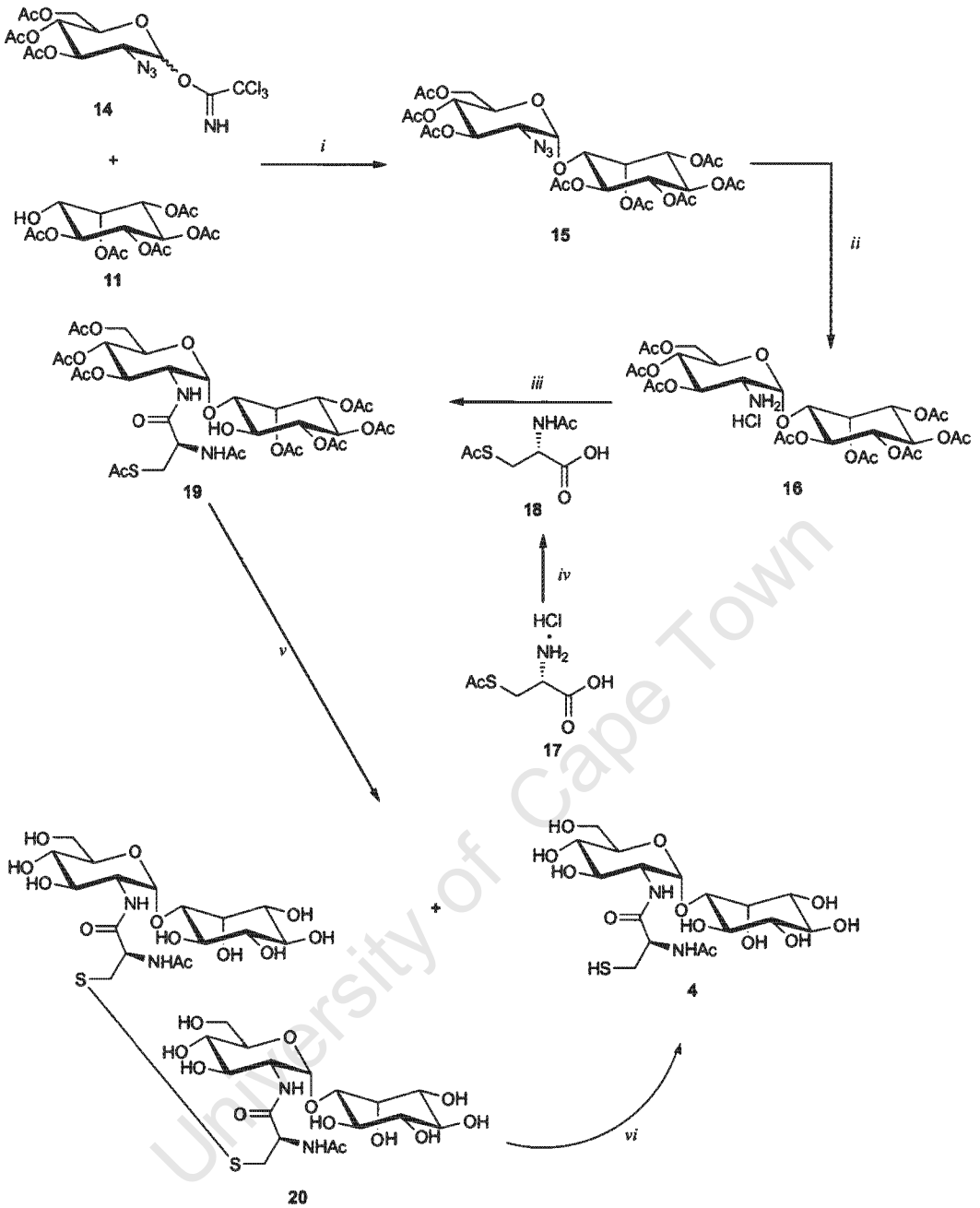
1.1.4 Chemical synthesis of mycothiol

A literature survey on the chemical synthesis of mycothiol reveals a number of reports on the synthesis of mycothiol derivatives. However, only two papers report the actual synthesis of mycothiol. The first total synthesis of mycothiol was reported by Steenkamp *et al.* in 2002.[34] The synthesis involves preparation of resolved and suitably protected *myo*-inositol **11** as a glycosyl acceptor (Scheme 1.2). Koenigs-Knorr glycosylation of **11** with glycosyl donor **10** gives a separable 1:1 mixture of α- and β-linked pseudosaccharides **12** and **13** as shown in Scheme 1.2. Deprotection of the protecting groups in **13** with anion exchange resin affords **8** which is then enzymaticaly ligated with L-cysteine to give mycothiol.



Scheme 1.2. *i*) AgOTf, 2,6-*tert*-dibutylpyridine, CH_2Cl_2, rt, 1 h, 78%; *ii*) Amberlite IRA400 (OH) resin, rt, 3 days, 85%; *iii*) Sodium phosphate, pH 7.5, DTT, Mg^{2+}, L-[^{35}S]cysteine, ATP, acetyl-*S*-CoA, partially purified enzyme.

The second report on the total synthesis of mycothiol was reported by Rosazza and Lee in 2004.[35] According to the report, pseudodisaccharide **15** is obtained by coupling of *myo*-inositol **11** with imidate **14** as depicted in Scheme 1.3. Reduction of the azide group in **15** followed by ligation of the resulting amino group gives **19**. Global deacetylation with $Mg(OMe)_2$ affords mycothiol **4** along with MSSM **20** in 40% and 29%, respectively. The yield of the mycothiol is boosted by reduction of the MSSM **20** with bis(2-mercaptoethyl)sulfone (BMS).



Scheme 1.3. *i*) TMSOTf, molecular sieves, 0°C, 1 h, 56%; *ii*) H_2, Pd/C, EtOAc, rt, 6 h, 86%; *iii*) HATU, HOAt, collidine, DMF, 0°C , 2 h to rt, 22 h, 25%; *iv*) NaOH, Ac_2O, H_2O, 0°C, 0.5 h, 84%; *v*) $Mg(OM)_2$, MeOH, rt, 2 h, 69%; *vi*) bis(2-mercaptoethyl)sulfone, H_2O, rt, 5 days, 100%.

The two reported protocols are basically the same except for the fact that in the former report the cysteine unit was introduced enzymatically. Unfortunately, though both methods reported the successful chemical synthesis of mycothiol, none of them is efficient for the synthesis of large quantities of MSH. Therefore, until a more efficient

synthetic protocol is developed, the recently reported protocol[36] for the isolation of milligram quantities of MSH from *Mycobacterium smegmatics* will have great contribution for further studies of mycothiol.[24]

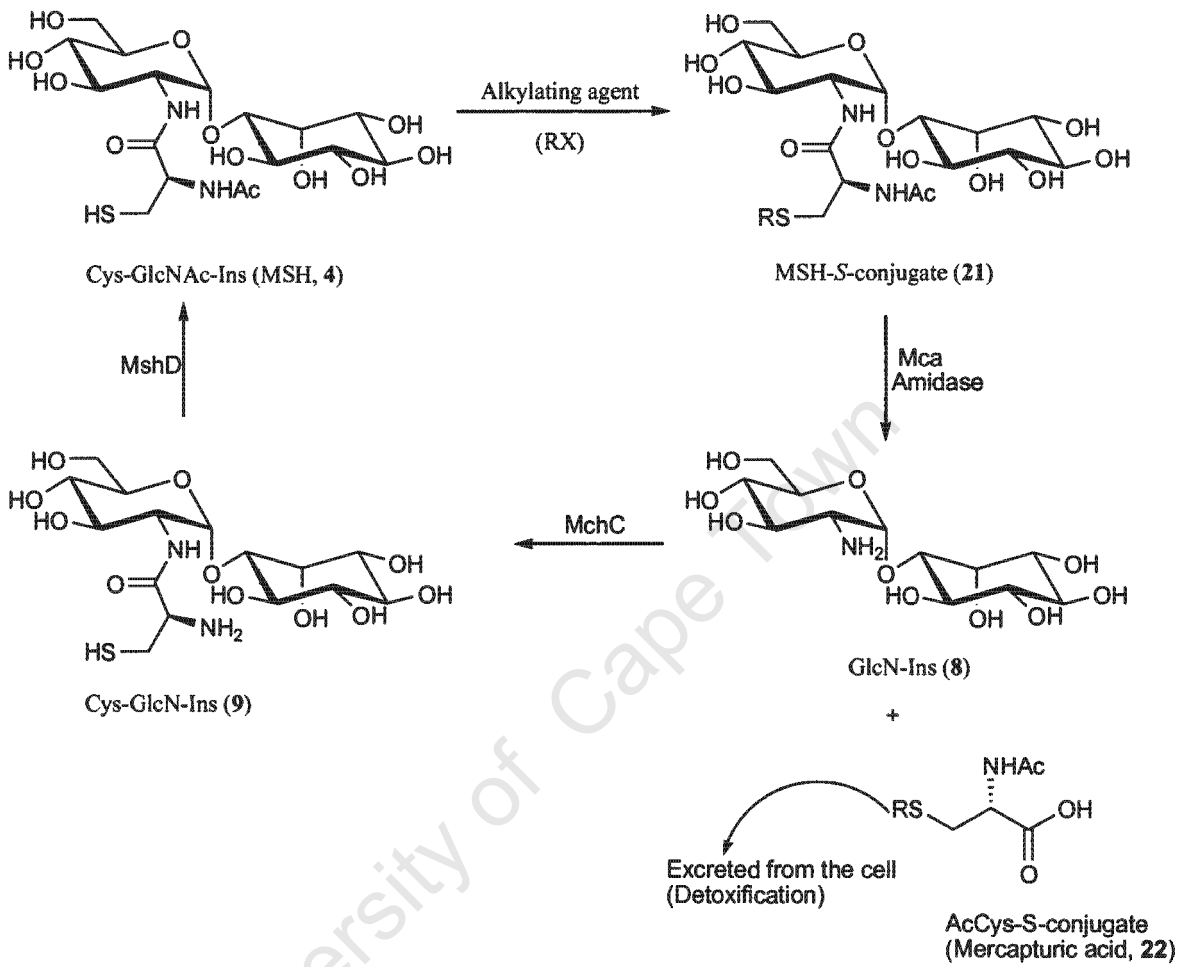
1.1.5 Mycothiol-dependent detoxification

Like its analogous glutathione, mycothiol plays a key role in protecting the cell and has been shown to participate in the detoxification of reactive oxygen (ROS) and nitrogen species (RNS) as well as in the neutralization of alkylating agents. Under oxidative stress, mycothiol responds by forming MSH disulfide (MSSM **20**). A corresponding MSH disulfide reductase (mycothione reductase) analogous of the glutathione and trypanothione reductases reduces the disulfide back into active MSH to maintain a reducing intracellular environment.[26,37,38] Blanchard *et al.* reported that mycothione reductase is similar to the flavoprotein disulfide oxidoreductases present in glutathione and trypanothione. Flavoprotein disulfide oxidoreductases are a class of flavoproteins that contain a redox-active disulfide involved in disulfide reduction.[37]

Mycothiol responds to nitrosative stress by detoxification of the RNS into harmless species, for instance, nitrates. The mycothiol reacts with the RNS such as $NO^{\bullet}$ to form the intermediate *S*-nitrosomycothiol (MSNO). A two-electron reduction of MSNO by *S*-nitrosomycothiol reductase results in the formation of the unstable *N*-hydroxysulfenamide which eventually leads to the formation and excretion of NO_3^- from the cell.[39]

A more general MSH-dependent scheme for the detoxification of alkylating agents is elucidated by Newton and co-workers and is depicted in Scheme 1.4.[40] The detoxification begins by formation of a mycothiol-*S*-conjugate **21** (MSR, where R is any alkylating agent) from the reaction of MSH and an alkylating agent. A key enzyme involved in the detoxification of alkylating agents is mycothiol *S*-conjugate amidase (Mca) which hydrolyzes the cysteinyl-glucosamine amide of the MSR **21**. The hydrolysis results in the formation of two products, namely: *N*-acetyl-cysteine-*S*-conjugate **22** (commonly known as mercapturic acid), which can be excreted from the cell, and GlcN-Ins **8**, which is retained in the cell and utilized for resynthesis of

mycothiol. The authors have shown the versatility of the Mca by reacting it with a broad range of mycothiol *S*-conjugates, including rifamycin and cerulenin.[40,41]



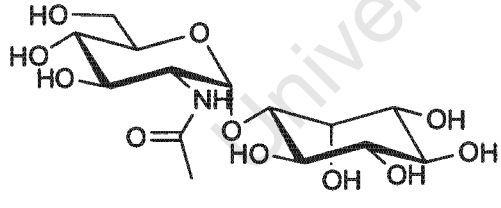
Scheme 1.4. Detoxification of alkylating agents (RX).

Studies have shown that MSH-deficient *mycobacterium smegmatis* mutants are hypersensitive to alkylating agents, free radicals and antibiotics. Hence, disruption of the enzymatic pathways of mycothiol biosynthesis and/or mycothiol-dependent detoxification by enzyme inhibitors may lower the level of MSH and leave the *M. tuberculosis* vulnerable to antibiotics and other stress factors allowing the development of new anti-tuberculars.[24,42]

1.1.6 Enzyme and substrate specificity study of MshB and Mca

Currently, a number of studies are underway to investigate inhibition of the biosynthesis of mycothiol by inhibiting some of the enzymes with analogues of mycothiol derivatives. However, the synthesis of analogues of mycothiol derivatives requires multiple reaction steps, resolution of diastereoisomers and a number of protection and deprotection steps. In order to resolve some of the problems, studies have been carried out to establish substrate specificity of the AcGI deacetylase and amidase enzymes.

Nicholas *et al.* synthesized diastereoisomers **7** and **23** containing either 1-D-*myo*-inositol or 1-L-*myo*-inositol (Figure 1.4) and investigated substrate specificity of the *Mycobacterium tuberculosis* enzyme AcGI deacetylase (MshB).[43] When both substrates were subjected to deacetylation with MshB under otherwise identical conditions, deacetylation of **7** was achieved in more than 60% yield but no detectable deacetylated product of **23** was observed even at relatively higher enzyme concentrations, thus establishing the specificity of the enzyme on the conformation of the *myo*-inositol. However, attempts have not yet been made to demonstrate the specificity of the enzyme with regards to the configuration of the glycosidic bond.



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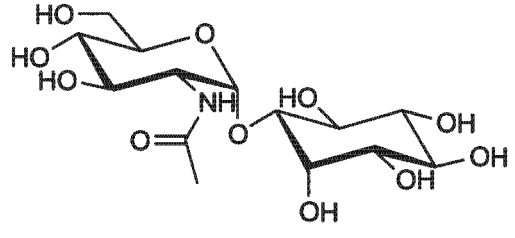


23

Figure 1.4. α-GlcNac-Ins D and L diastereoisomers

In a separate communication Bornemann and co-workers investigated the substrate specificity of the α-D-GI-L-cysteine ligase (MshC) on the configuration of the glycosidic bond and *myo*-inositol. The authors synthesized the compounds depicted in Figure 1.5.[44] Thus, treatment of α-D-GI **8** with a crude, undialysed, cell-free extract of *M. smegmatis* resulted in the MshC catalysed mixture of products, desacetyl mycothiol **27** and mycothiol **4** in a 1:4 ratio and 40% conversion. Ligation of α-L-GI

24 under the same conditions, however, displayed poor selectivity (Figure 1.6). Conversely, the β-coupled isomers **25** and **26** were inactive under identical conditions. The results demonstrated the substrate specificity of the enzyme on the glycosidic bond and the configuration of the *myo*-inositol.[34,44]

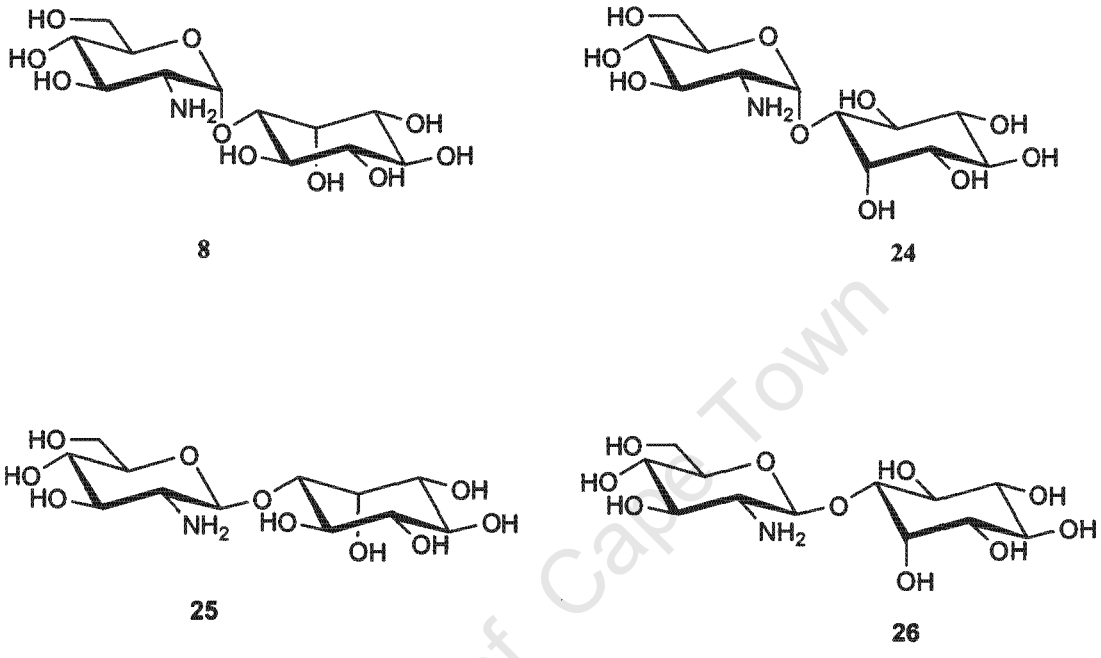


Figure 1.5. Diastereoisomers of Glc-Ins

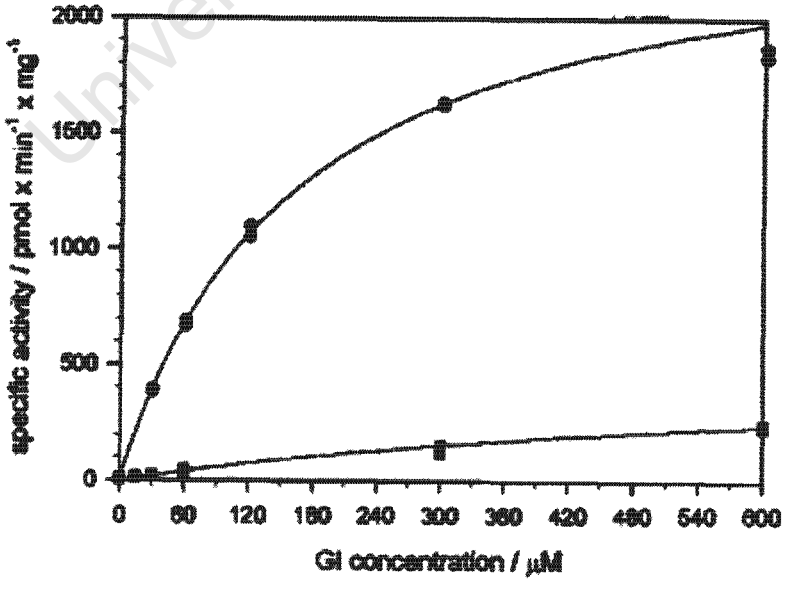
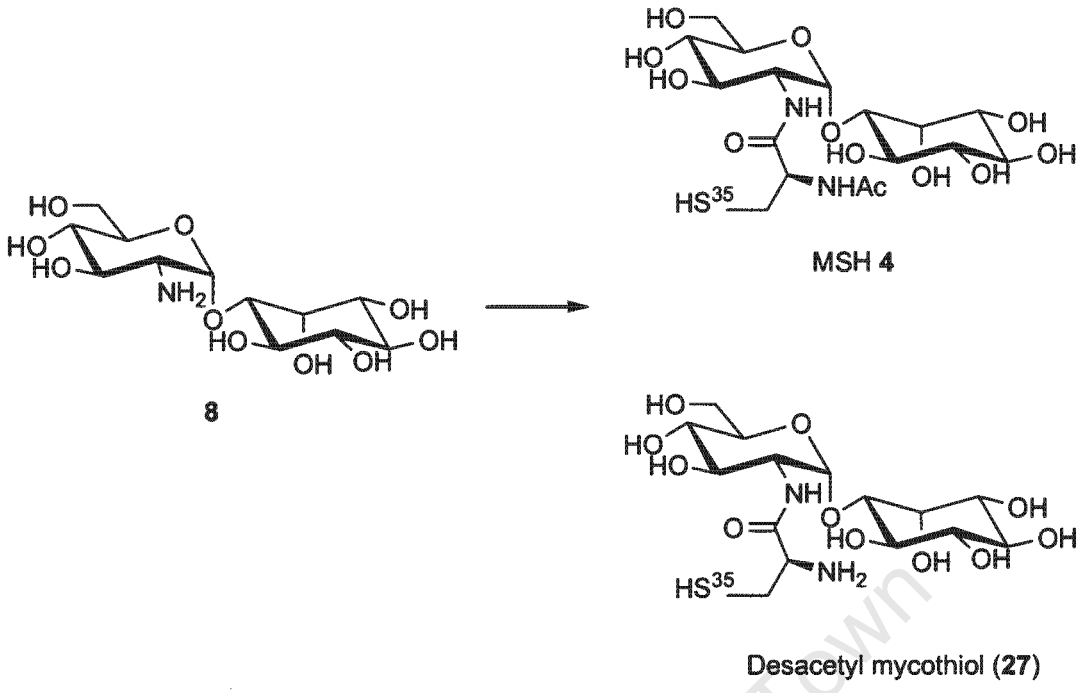


Figure 1.6. Dependence of the rate of product formation on the concentration of the α-D-Glc-Ins **8** (●) and α-L-Glc-Ins **24** (■)



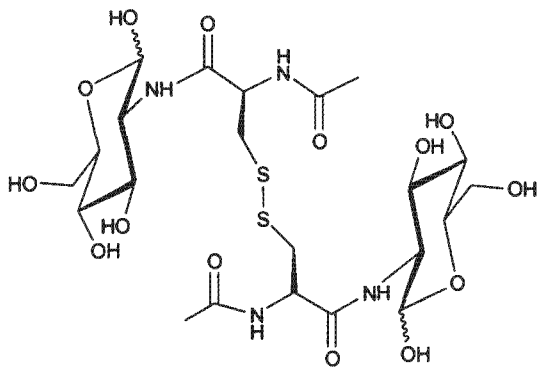
Scheme 1.5. Cell-free extract of *M. smegmatis* and ^{35}S-cysteine.

These results assist in the design of enzyme inhibitors that target the biosynthesis of mycothiol in the search of new TB drugs. Currently several groups are involved in synthesizing small molecules that function as substitute substrates for the enzymes in mycothiol biosynthesis.[29]

1.1.7 Synthetic carbohydrate based enzyme inhibitors in the biosynthesis of mycothiol

The current treatment of TB is based on antibiotics, but the importance of this method is fading out with the emergence of drug-resistant strains of TB. However, the rise in the number of MRD-TB strains has opened a new approach for the discovery of TB drugs. One of the potential approaches is inhibition of the biosynthesis of mycothiol and/or reducing the level of mycothiol in the cell with simple analogues of the natural substrates. The area is, however, in an early stage as only a few papers on the work are published so far. The earliest work was published by Blanchard and Patel where they synthesized des-*myo*-inositol-MSH disulfide **28** and investigated its potential as a possible inhibitor of the mycothione reductase.[37] The result indicated that the

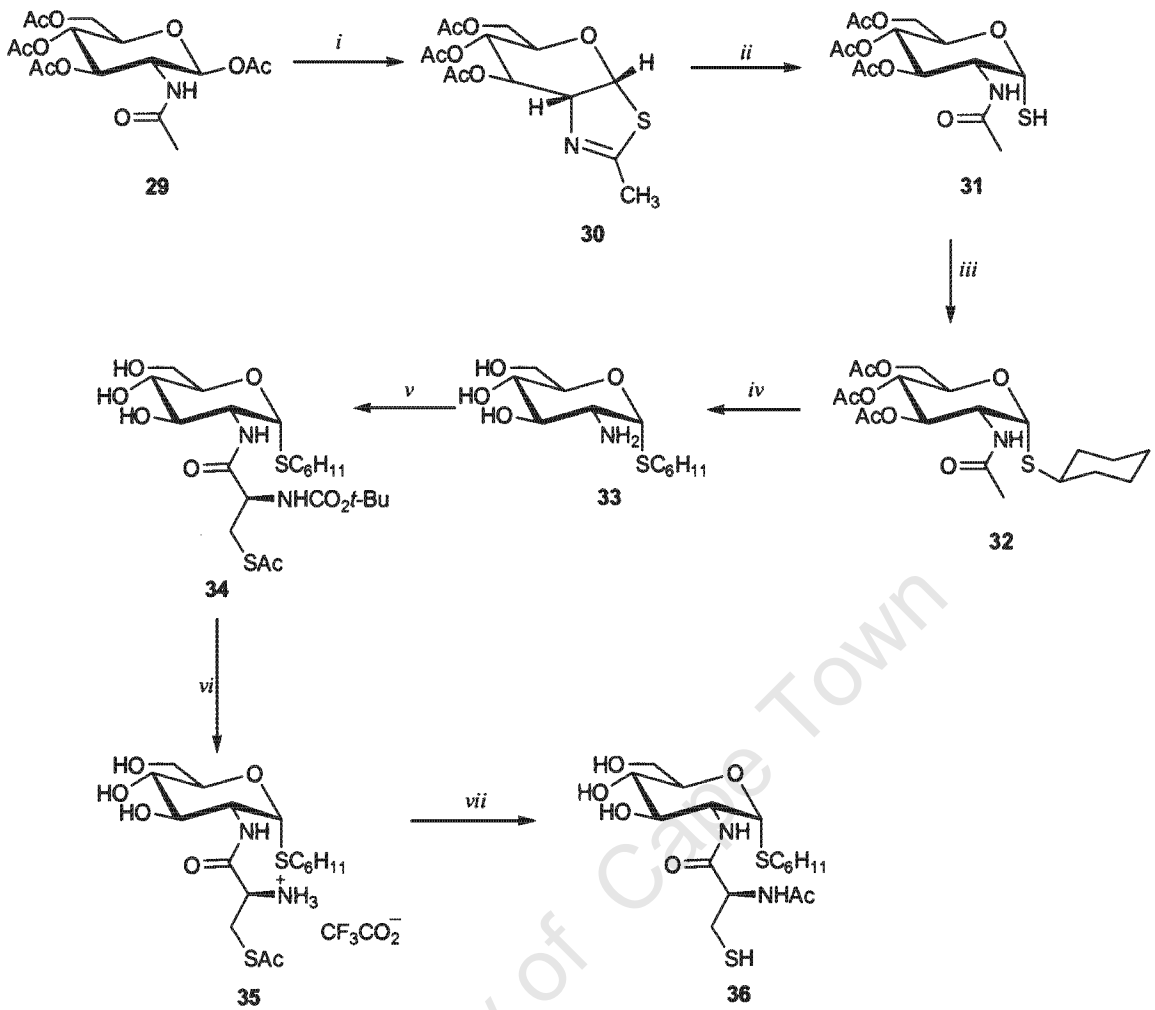
truncated disulfide substrate though it lacks the *myo*-inositol unit, provides sufficient features of the natural substrate to act as an active analogue of mycothiol.



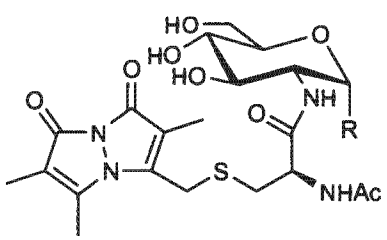
28

Figure 1.7. Des-*myo*-inositol-mycothiol disulfide.

The field remained dormant with no further reports until Knapp *et al.* reported the synthesis of a cyclohexyl thioglycoside **36** analogue of mycothiol.[42] The thioglycoside was synthesized as shown in Scheme 1.6. Treatment of the commercially available *N*-acetyl glucopyranose **29** with Lawesson's reagent followed by acid hydrolysis of the resulting thiazoline **30** provided the acetamido mercaptan **31**. Reaction of **31** with cyclohexene under conditions for free radical addition of anomeric mercaptans to alkenes gave the cyclohexyl thioglycoside **32**, exclusively. Hydrazinolysis of **32** followed by coupling of the resulting aminotriol **33** with *S*-acetyl-*N*-Boc-L-cysteine afforded **34** in good yield and high isomeric purity. Treatment of **34** with trifluoroacetic acid resulted in ammonium salt of **35** which upon basification with pyridine gave the mycothiol analogue **36** in good yield. In order to evaluate **36** as a possible substrate for *M. tuberculosis* mycothiol *S*-conjugate amidase, **36** was converted to its bimane derivative **37** (Figure 1.8). When **37** and **38** (a reference) were subjected to cleavage by the amidase enzyme, **37** displayed specific activity of 7500 nmol min-1-mg-protein as compared to 14200 nmol min-1-mg-protein for **38**, indicating **37** as a good substrates for Mca. In agreement with previous result, the results indicated that neither the glycosidic linking atom (O vs S) nor the inositol hydroxyls play a major role in enzyme binding.



Scheme 1.6. *i*) Lawesson's reagent, toluene, 80°C, 1.5 h, 100%; *ii*) TFA, wet MeOH, 100%; *iii*) C_6H_{10}, AIBN, $CHCl_3$, reflux, 79%; *iv*) $NH_2NH_2{\cdot}H_2O$, 120°C, 24 h, 84%; *v*) *N*-Boc-*S*-acetylcysteine, EDCI, DMF, 82%; *vi*) TFA; *vii*) (a) pyridine; (b) Sephadex, 100% (from **34**).

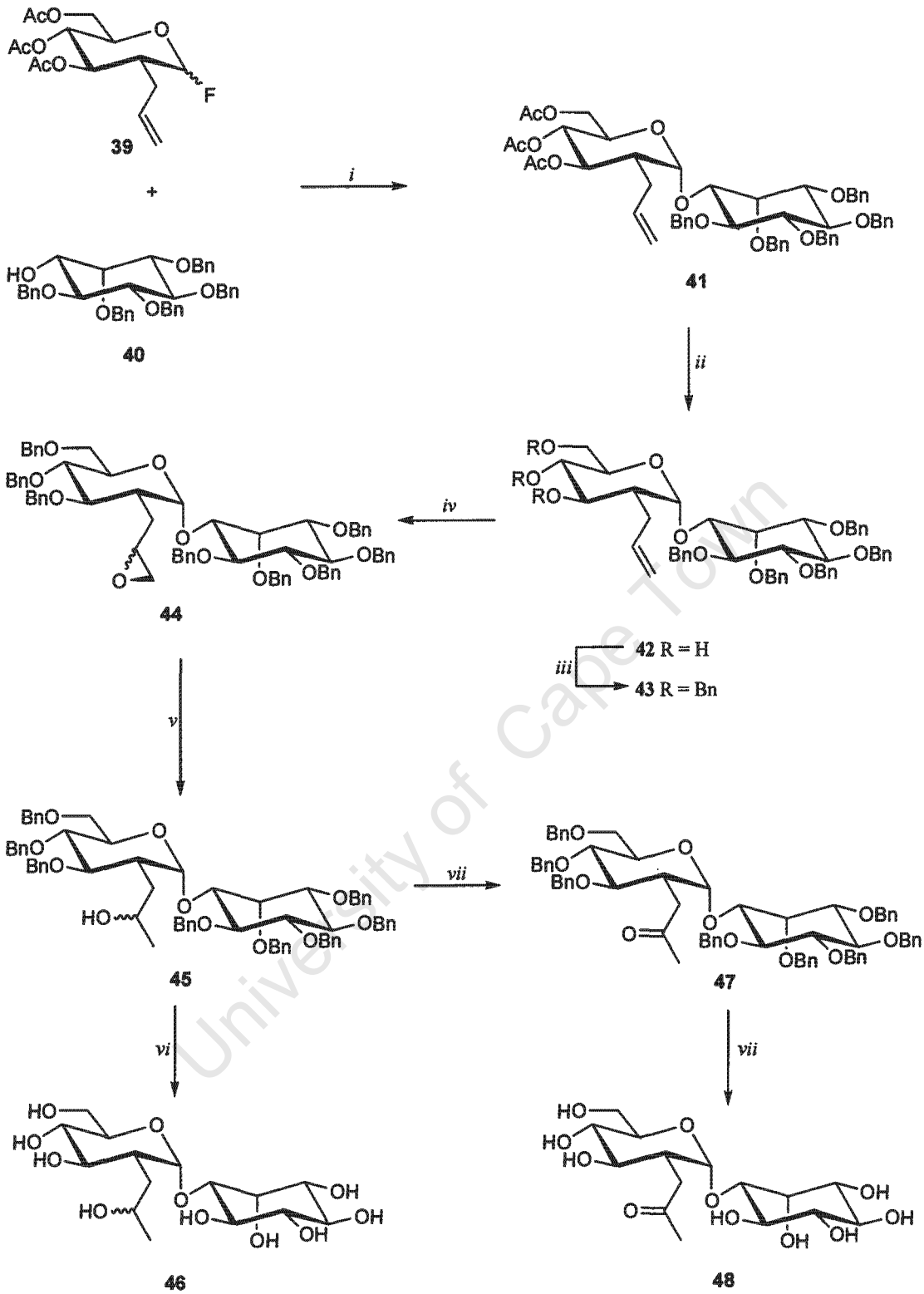


37 R = S-C_6H_{11}

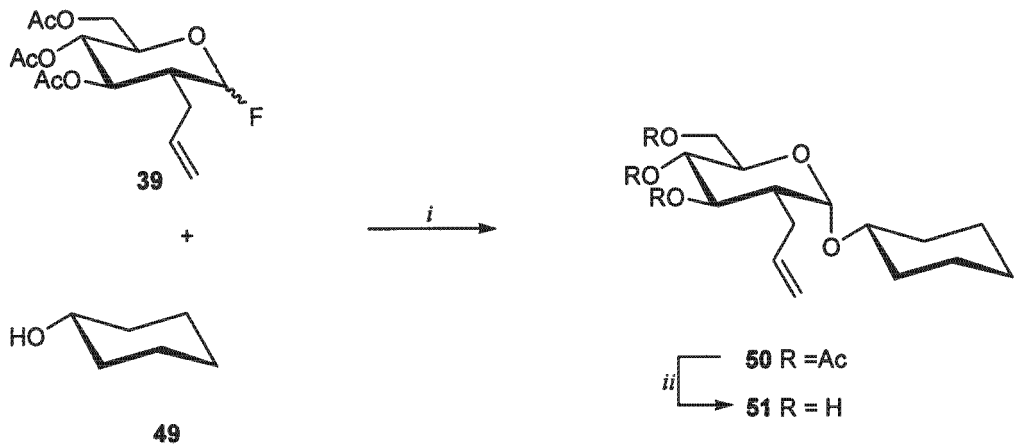
38 R = O-$C_6H_{11}O_5$

Figure 1.8. Bimane derivatives of mycothiol and analogue **36**.

Shortly after Knapp's report, Gammon *et al.* reported the synthesis of a number of C-2 modified glucosamine isosteres of AcGlc-In. Some of the synthesized analogues include: 1-*O*-[2'-deoxy-2'-C-(2''-hydroxypropyl)-α-D-glucopyranosyl]-D-*myo*-inositol **46**, 1-*O*-[2'-deoxy-2'-C-(2''-oxopropyl)-α-D-glucopyranosyl]-D-*myo*-inositol **48**, and cyclohexyl 2-C-allyl-2-deoxy-α-D-glucopyranoside **51**. Glycosides **46** and **48** were prepared by coupling of fluoride **39** with an enantiomerically pure *myo*-inositol **40** followed by epoxidation of the alkene to give **46** after debenzylation, and **48** was obtained after subsequent reduction and oxidation of **44** (Scheme 1.7). **51** was prepared by coupling of fluoride **39** with cyclohexanol followed by *Zemplén* deacetylation (Scheme 1.8). When the compounds were tested for their biological activity, they were found to be biologically active. However, even though the compounds did not inhibit the growth of *M. smegmatis* in *vitro,* a pronounced inhibition of incorporation of [^{3}H]inositol by whole cells into inositol containing metabolites was observed. The study has elegantly shown that mycothiol analogues can indeed effect the biosynthesis of mycothiol paving a new road for the design of new TB drugs.[45]



Scheme 1.7. *i*) $BF_3{\cdot}Et_2O$, 4Å molecular sieves, rt, 2 h (α:β = 8:1); *ii*) NaOMe, MeOH-CH_2Cl_2, rt, 1 h, 36% (from **40**); *iii*) NaH, BnBr, THF, reflux, 20 h, 94%; *iv*) MCPBA (70%), CH_2Cl_2, rt, 24 h, 83% (1:1); *v*) LAH, THF, 0°C, 1 h, 82% (1:1); *vi*) H_2, 10% Pd/C, EtOAc-MeOH, rt, 3 days, >90%; *vii*) TPAP, MNO, CH_2Cl_2, 4Å molecular sieves, rt, 25 min, 90%.



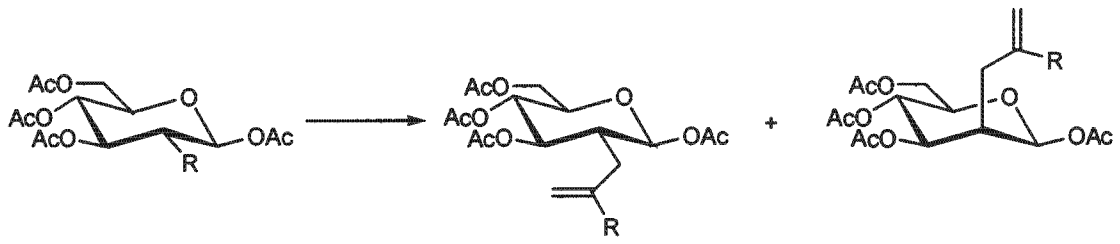
Scheme 1.8. *i*) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 4Å molecular sieves, rt, 18 h (α:β = 1:1); *ii*) NaOMe, $MeOH/CH_2Cl_2$, rt, 4 h, 99%.

From the abovementioned investigations and findings there is some evidence that synthetic analogues of the natural substrates can inhibit the enzymes involved in the biosynthesis or detoxification process of mycothiol and that preparation of larger numbers of carefully designed analogues are warranted. The analogues modified at the C-2 position of the sugar unit remain an important target, and justify the development of new synthetic methodologies for synthesis and manipulation of 2-deoxy sugars.

1.2 Synthesis of 2-Deoxy-2-Halo-Sugars

2-Deoxy-2-halo-sugars are known to be of great biological interest, such as in exhibiting antitumor activity and as contrast agents in X-ray urology.[46] They have wide applications as key intermediates in the synthesis of deoxy-sugars which are components of structural units that have biological importance including inhibition in yeast fermentation, bacterial growth, D-glucose utilization in muscle, and tumor growth (anthracyclines, aureolic acids, calcicheamicin, esperamicins). These deoxy-sugars are obtained by catalytic reductive cleavage of the 2-deoxy-2-halo-sugars with hydrogen in the presence of Raney nickel and triethylamine or by free radical reduction with tributyltin hydride in the presence of AIBN.[47,48] The characteristic behaviour of halides as good leaving groups and radical precursors means that 2-deoxy-2-halo-sugars are easily transformed into other important intermediates in carbohydrate synthesis. An example that can be cited is the C-2 alkylation of tetra-*O*-

acetyl-2-deoxy-2-halo-pyranosyls **52b** and **53b** using methallyltributylstannane or allyltributylstannane and AIBN (Scheme 1.9).[49]



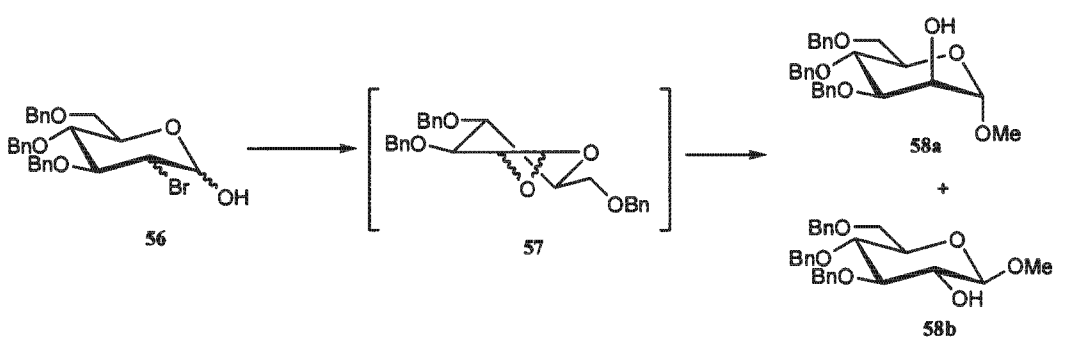
52b R = Br
53b R = I

54a R = H
55a R = CH_3

54b R = H
55b R = CH_3

Scheme 1.9. Methallyltributylstannane or allyltributylstannane, AIBN, benzene, reflux, 43 – 70% (**54a**:**54b** 9:1 and **55a**:**55b** 6:1 ratios).

Another example of the use of 2-deoxy-2-halo-sugars is in the synthesis of glycosides with a free hydroxyl group at the C-2 position for further elongation. It is usually achieved by *in situ* stereoselective epoxidation of glycals followed by regioselective opening of the epoxide. In spite of the fact that the classical glucal epoxidation methods are successful, there are a number of drawbacks associated with the method *i.e.* need for stoichiometric and expensive oxidants, and extremely dry reaction conditions.[50] Thus, halohydrins in the presence of a base have become preferable substrates for such transformations as demonstrated in Scheme 1.10.[50]



56 **57** **58a** **58b**

Scheme 1.10. Cs_2CO_3, MeOH, 5°C, 11% (**58a**) and 44% (**58b**).

More recently, Suárez *et al.* reported fragmentation of halohydrins with (diacetoxyiodo) benzene (DIB) in the presence of bromine to synthesise 1-deoxy-1-halo-1-bromo-alditols that are valuable intermediates in organic synthesis.[51]

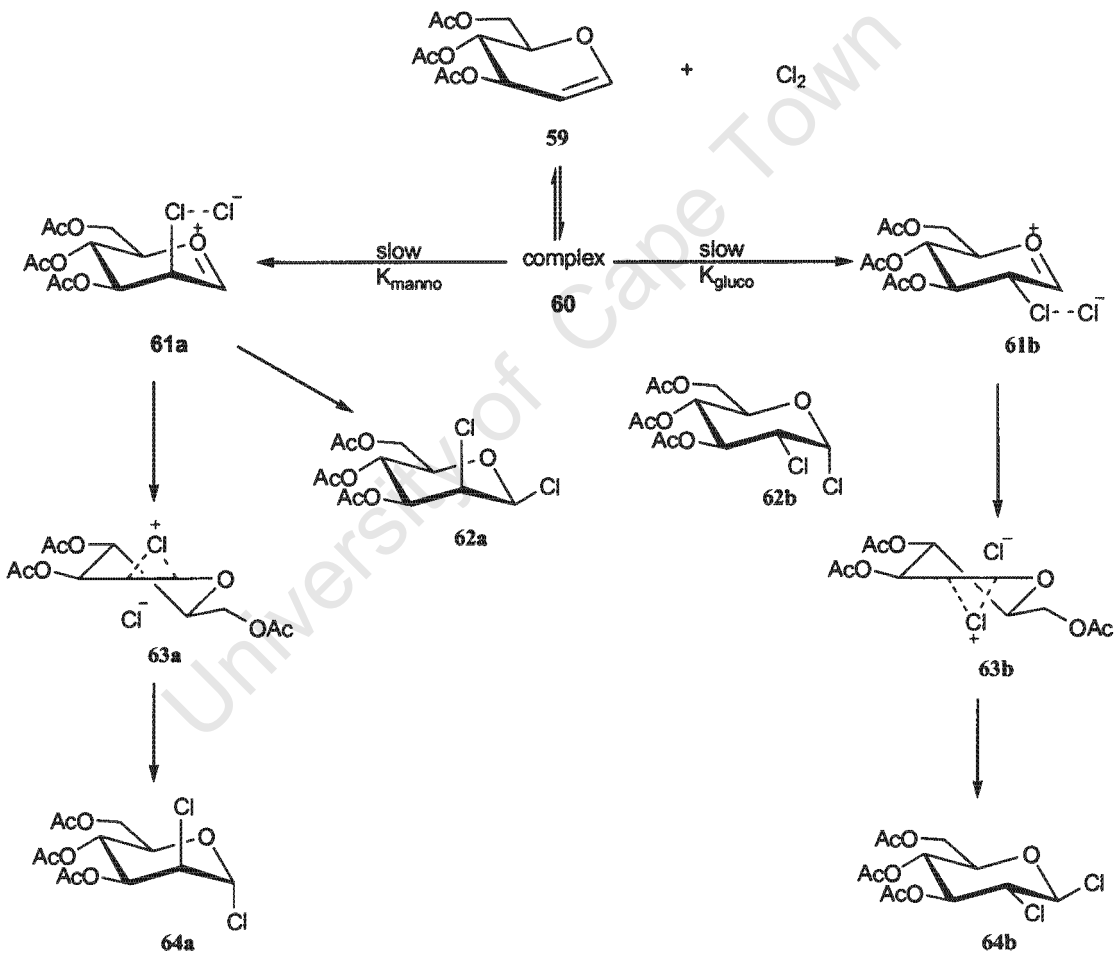
Owing to their versatile biological and synthetic applications, a number of methods have been developed for the synthesis of 2-deoxy-2-halo-sugars. The classical approach involves the displacement of a sulphonic ester group with a halide.[52,53] Methyltriphenoxyphosphonium iodide and iodotriphenoxyphosphonium iodide reagents have been employed in the iodination of hydroxyls in carbohydrates.[54,55] Selective replacement of primary hydroxyl groups by iodo groups in the presence of secondary hydroxyl groups was achieved using triphenylphosphine-*N*-iodosuccinimide[56] and triphenylphosphine-tetra iodomethane.[57] Selective conversion of hydroxyl groups into triflate esters followed by iodide ion displacement also results in deoxyiodo-sugars.[58] Garegg *et al.* reported two reagent systems consisting of triphenylphosphine, iodine and imidazole, and triphenylphosphine and 2,4,5-tri-iodoimidazole for converting primary and secondary hydroxyl groups into iodo groups with inversion of configuration.[59,60] They extended the method to synthesize bromodeoxy sugars using triphenylphosphine, tribromoimidazole and imidazole in toluene at elevated temperature.[61]

However, with realization that glycals undergo addition reactions similar to any other common alkenes and with characteristic regio- and stereo-selectivities due to the ring oxygen, they soon appeared as ideal precursors for the synthesis of 1,2-dihalo, 1,2-halohydrins, and 2-deoxy-2-halo-glycosides.

1.2.1 Halogenation of glycals

Halogenation of glycals provides 1,2-dihalide sugars. The first example on halogenation of glycals was reported by Fischer and co-workers.[62] In their communication, they reported that addition of chlorine to acetylated glucal **59** in carbon tetrachloride resulted to a crystalline product, which they named triacetyl glucal dichloride. Lemieux and Fraser-Reid revised the work and clarified the structure of the compound as 3,4,6-*tri*-*O*-acetyl-2-chloro-2-deoxy-α-D-

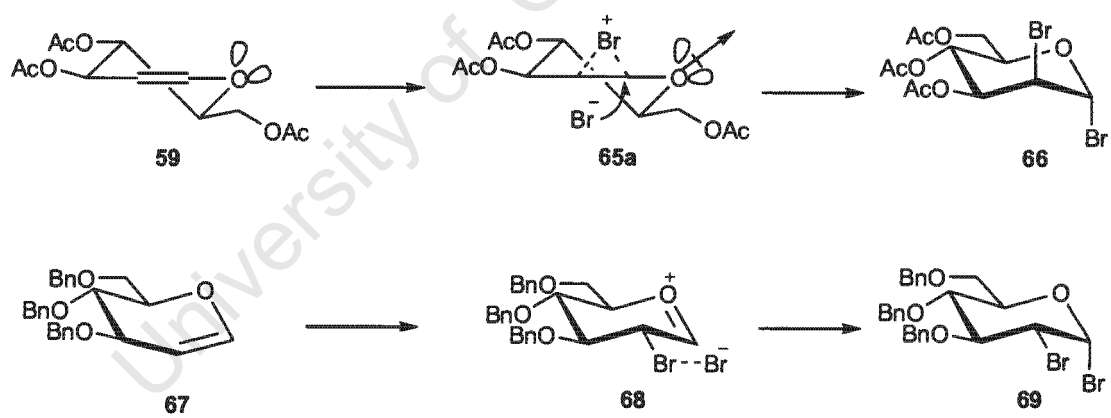
glucopyranosyl chloride (**62b**) and explained their results by proposing a general mechanism whereby a polar attack of a halogen on the olefinic bond results in the formation of oxocarbenium ion intermediate which upon attack by a halide ion give principally the products of the thermodynamic control.[63] Lefan and Weill reinvestigated the chlorination reaction using chloroform as the solvent and obtained 3,4,6-*tri*-*O*-acetyl-2-chloro-2-deoxy-α-D-mannopyranosyl chloride (**64a**) along with **62b**.[64] Contrary to the rationalization of the mechanism of chlorination by Lemieux and Fraser-Reid, Igarashi *et al.* demonstrated that the product distribution was not under thermodynamic control but kinetic control.[65]



Scheme 1.11. Chlorination of 3,4,6-tri-*O*-acetyl-D-glucal (**59**).

They stated that the reaction proceeds by molecular process whereby the halogen approaches perpendicular to the π-system of the enol ether from above or below the plane of the glucal. The resulting charge-transfer complex may rearrange in the rate-

determining step, to either oxocarbenium ions or halonium ions or *syn* ion pairs, which depending on their relative stabilities direct the course of the reaction. In line with their proposed mechanism, they reported that chlorination of 3,4,6-*tri*-*O*-acetyl-D-glucal afforded the four possible 1,2-dichlorides **62a**, **62b**, **64a**, and **64b** in variable ratios depending on the polarity of the solvent system and in some cases, on the concentration of the reaction mixture (Scheme 1.11).[65] In nonpolar solvents, *cis* dichlorides, **62a** and **62b** were predominantly obtained by the collapse of ion pairs **61a** and **61b** in which the chloride ion is associated on the same side of the original plane from which chlorine attack first occurred. Conversely, in polar solvents, *trans* dichlorides, **64a** and **64b** were predominantly obtained *via* free ions, **63a** and **63b**. The authors studied the reaction with various solvents of different polarity and concluded that with increasing solvent polarity, the proportion of *cis* dichlorides decreased and that of *trans* dichlorides increased. The trend was accounted on the fact that the charge separation is unfavourable in nonpolar solvents and favourable in polar solvents.



Scheme 1.12. Influence of protecting groups in bromination of D-glycals.

Besides the polarity of the solvent system, the product distribution from halogenation of glycals depends also on the source of the halogenating agent and the type of the protecting groups present in the glucal.[66] Boullanger and Descotes carried out bromination of 3,4,6-tri-*O*-acetyl-D-glucal (**59**) and 3,4,6-tri-*O*-benzyl-D-glucal (**67**) in the same solvent, carbon tetrachloride, in order to observe influence of protecting groups (Scheme 1.12).[66] Under identical reaction conditions, they found a completely different product distribution. Bromination of the benzylated glucal resulted in *cis*-

addition product **69** (α-D-*gluco*) as a major product while the acetylated glucal gave predominantly a *trans*-addition product **66** (α-D-*manno*).

Horton and Priebe rationalized the observation by electronic effects.[67] They found that the product distribution in the bromination of the glucals depended on the electron-withdrawing or –donating effect of the substituent at C-6. They interpreted the results in terms of the effect that the C-6 substituent may exert on the nonbonding electron pairs of the ring oxygen atom, which indirectly affects the stabilization of the oxocarbenium ion at C-1. A strongly electron-withdrawing substituent decreases the ability of the lone pair of electrons on the ring oxygen atom to stabilize the positive charge at the anomeric center, which thus favours the symmetrical bromonium ion intermediates such as **65a** and hence results in *trans* addition product. The preferential formation of β-bromonium ion **65a** might have resulted from the electrostatic effects *i.e* orientation of the net dipole moment of the compound. In contrast, a weak electron-withdrawing or a good electron-donating substituent at C-6 favours the formation of ion pairs or oxocarbenium ions and attack from below the molecular plane affords *syn* ion pair **68** and with the assistance from the anomeric effect leads to the *cis*-addition product **69**. However, in polar solvents, oxocarbenium ions are more favoured than *syn* ion pairs and hence α-*trans* addition products are expected if the bromine at C-2 is axial or α-*cis* product dominates if the bromine is in equatorial position at C-2. However, chlorination of the glucals was found to be unaffected by the C-6 substituent implying the reaction does depend on the source of the halogenating agent.[67]

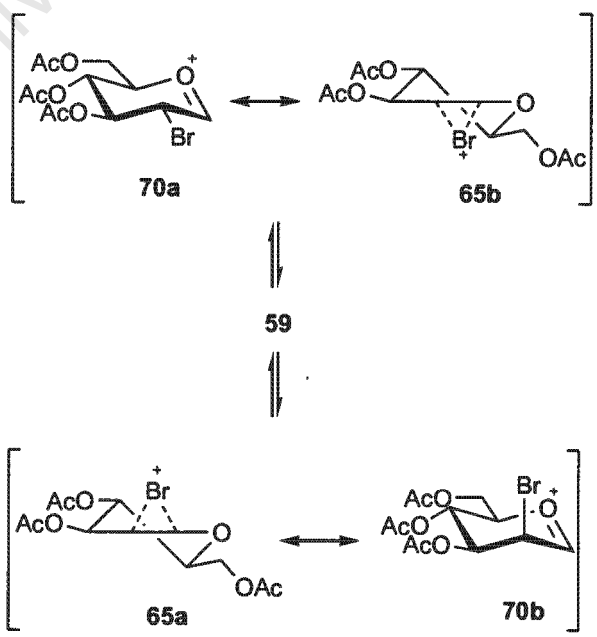
1.2.2 Haloalkoxylation, halohydroxylation and haloacetoxylation of glycals

1.2.2.1 Bromoalkoxylation and bromohydroxylation of glycals

There are different methods of synthesising 2-deoxy-2-bromo-glycosides. One of the classical methods involves treatment of a glucal with bromine and silver acetate in alcohol.[68] But later, Br^+-equivalent reagent, *N*-bromosuccinimide (NBS) was found to activate alkenes and Dalton and co-workers used it to transform a series of alkenes into *trans*-halohydrins.[69] Nine years later, Tatsuta *et al.* extended the method to include glycals and synthetic glycosides.[48] The authors reacted different glycals,

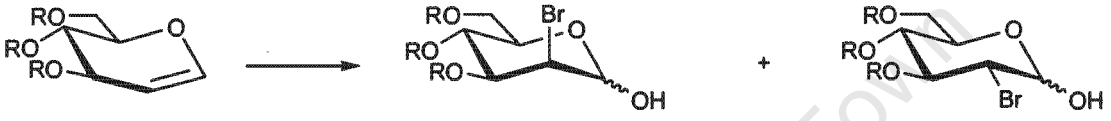
namely 3,4,6-tri-*O*-acetyl-D-glucal, 4-*O*-acetyl-1,5-anhydro-2,6-dideoxy-3-C-methyl-3-*O*-methyl-L-*ribo*-hex-1-enitol, and 3-acetamido-4,6-di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-D-*arabino*-hex-1-enitol, with 1.5 molar equivalents of several alcohols in the presence of NBS in acetonitrile to give mainly the corresponding 2-bromo-2-deoxy-α-glycosides. The majority of the yields of the reactions were in the range 78 – 97%. In contrast, the reaction of glucal **59** and methanol in the presence of NBS at 5°C resulted in a mixture of methyl α-D-manno- and β-D-gluco-pyranosides in 4:1 ratio. However, when the same reaction was carried out at room temperature, the ratio of the products was 2:1.[48]

The authors' account on the mechanism of the reaction is that the reaction proceeds *via* the formation of a cyclic bromonium ion intermediate **65a** in resonance with an oxocarbenium ion **70b** through the lone pairs of the ring oxygen.[48] The bromonium ion may undergo nucleophilic attack by the alcohol from below the molecular plane favoured by the anomeric effect and readily collapse to the *trans* addition product (Scheme 1.13). But in the case of methanol, additional intermediates **70a** and **65b** seem to appear that can lead to 2-bromo-β-D-glycopyranoside by equatorial attack of methanol. They hypothesised that the higher rate of reaction with methanol prevents complete equilibration of the *gluco*-cyclic ion **65b** to the more stable, *manno* bromonium ion **65a** as the reverse anomeric effect destabilizes the *gluco* bromonium ion **65b**.[48]



Scheme 1.13. Resonance structures of bromomethoxylation using NBS.

Another example of a brominating agent is *N*-bromoacetamide (NBA),[50,70] which reacts in a similar fashion to NBS. Spilling *et al.* reported that 3,4,6-tri-*O*-methyl-D-glucal (**71**) and 3,4,6-tri-*O*-benzyl-D-glucal (**67**) reacted with NBA in aqueous THF to give a diastereoisomeric mixture of methyl bromohydrins and benzyl bromohydrins in 84 and 100% yield, respectively (Scheme 1.14).[50] The authors attempted some variation in solvents (ether, THF, or CH_3CN) and source of Br^+ (NBA and NBS) and although the authors stated that the rate and yield of the reaction were affected, and to a lesser extent the product distribution, they did not comment on the comparison results.



67 R = Bn
71 R = Me

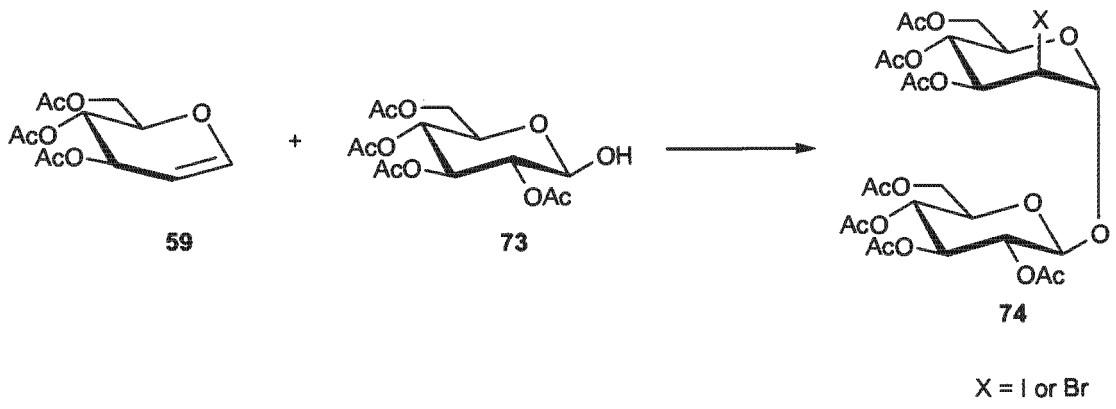
56a R = Bn
72a R = Me

56b R = Bn
72b R = Me

Scheme 1.14. NBA, H_2O/THF (1:9), 100% (**56a** and **56b**), 84% (**72a** and **72b**).

1.2.2.2 Iodoalkoxylation and iodohydroxylation of glycals

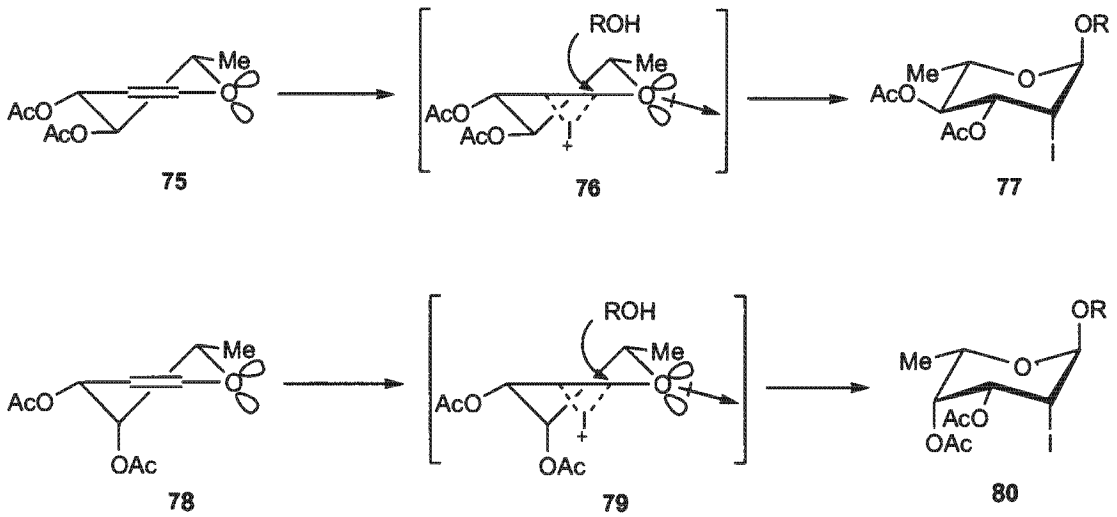
Lemieux and Levine discovered that the reaction of 3,4,6-tri-*O*-acetyl-D-glucal (**59**) with iodine and silver benzoate in dry benzene gives a 1:1 mixture of *trans*-addition products, namely 3,4,6-tri-*O*-acetyl-1-*O*-benzoyl-2-deoxy-2-iodo-β-D-glucopyranose and the α-D-*manno* stereoisomer.[71] The same authors extended the method to the preparation of glycosides by reacting acetylated glucal **59** in benzene with equimolar amounts of an alcohol, iodine, silver perchlorate and *sym*-collidine.[72] Due to the limited solubility of silver perchlorate in nonpolar solvents, they improved the method by use of preformed positive halogen complexes with *sym*-collidine instead of the silver perchlorate.[73] Accordingly, the authors managed to synthesise the non-reducing disaccharide **74** in quantitative yields (Scheme 1.15) by reacting acetylated glucal **59** with equimolar amounts of 2,3,4,6-tetra-*O*-acetyl-β-D-glucose (**73**) and iodonium or bromonium di-*sym*-collidine complexes dissolved in chloroform.



Scheme 1.15. Iodonium or bromonium di-*sym*-collidine perchlorate, CCl_4.

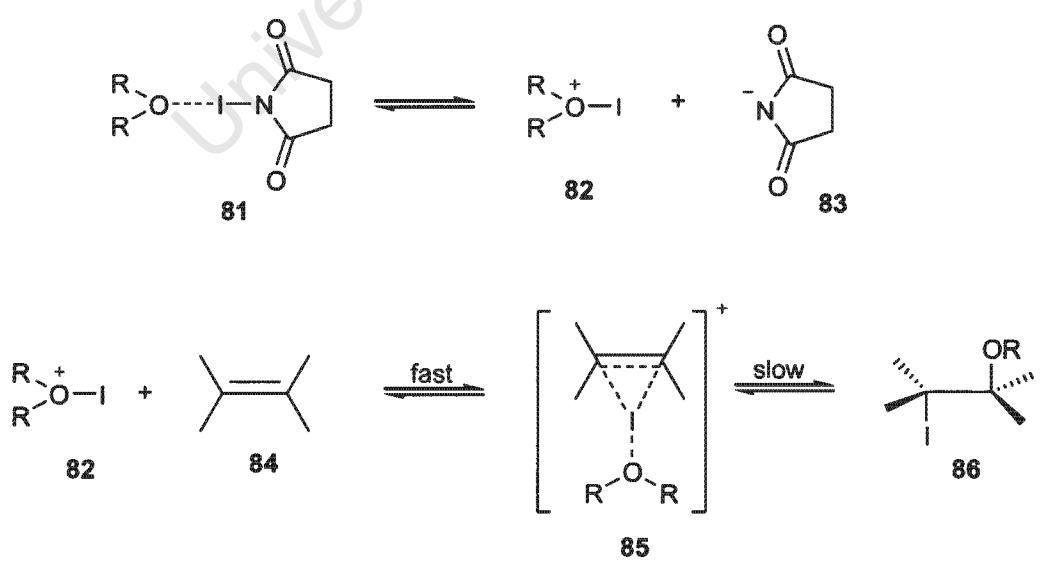
In the late seventies, Thiem came up with a simpler method of the same reaction.[74] He used *N*-iodosuccinimide (NIS) as a source of iodonium ion and reported, in a separate communication, the efficient synthesis of trisaccharide sequences of dihydroaclacinomycin A, an anthracycline antibiotic, and kijanimycin, a macrolide antibiotic, containing three 2,6-dideoxysugar with α-(1-4) and α-(1-3) linkages, respectively.[75]

Horton evaluated Thiem's method with the goal of exerting a higher degree of control on the product distribution by examining the influence of the solvent nature, the nucleophile and structure of the glycal.[76] When L-rhamnal diacetate **75** in acetonitrile was reacted with various alcohols in the presence of NIS, the ratio of resultant stereoisomers remain the same at 41:9. Similar results were obtained with other glycals, too.[76] These findings led to conclude that in acetonitrile electrophilic attack by iodonium ion seems to be irreversible and the ratio of the final products reflects the proportion of attack of iodonium ion from below or above the molecular plane. However, electrostatic effects *i.e.* the net dipole moment of the glycal influences the stereochemistry of the first step rather than steric effects. This conclusion can be deduced from the results of iodoalkoxylation of 3,4-di-*O*-acetyl-L-rhamnal **75** and 3,4-di-*O*-acetyl-L-fucal **78** (Scheme 1.16).[76] Both L-rhamnal **75** and L-fucal **78** in the preferred $^5H_4$ conformation have a negative pole below the plane despite opposite orientation of the C-4 substituent. Electrophilic attack is favoured from the same side of the dipole moment regardless of the steric hindrance by C-4 substituent, and hence leads to α-L-rhamnopyranose **77** *via* iodonium ion **76** and α-L-fucopyranoside **80** *via* iodonium ion **79**, respectively.[76]



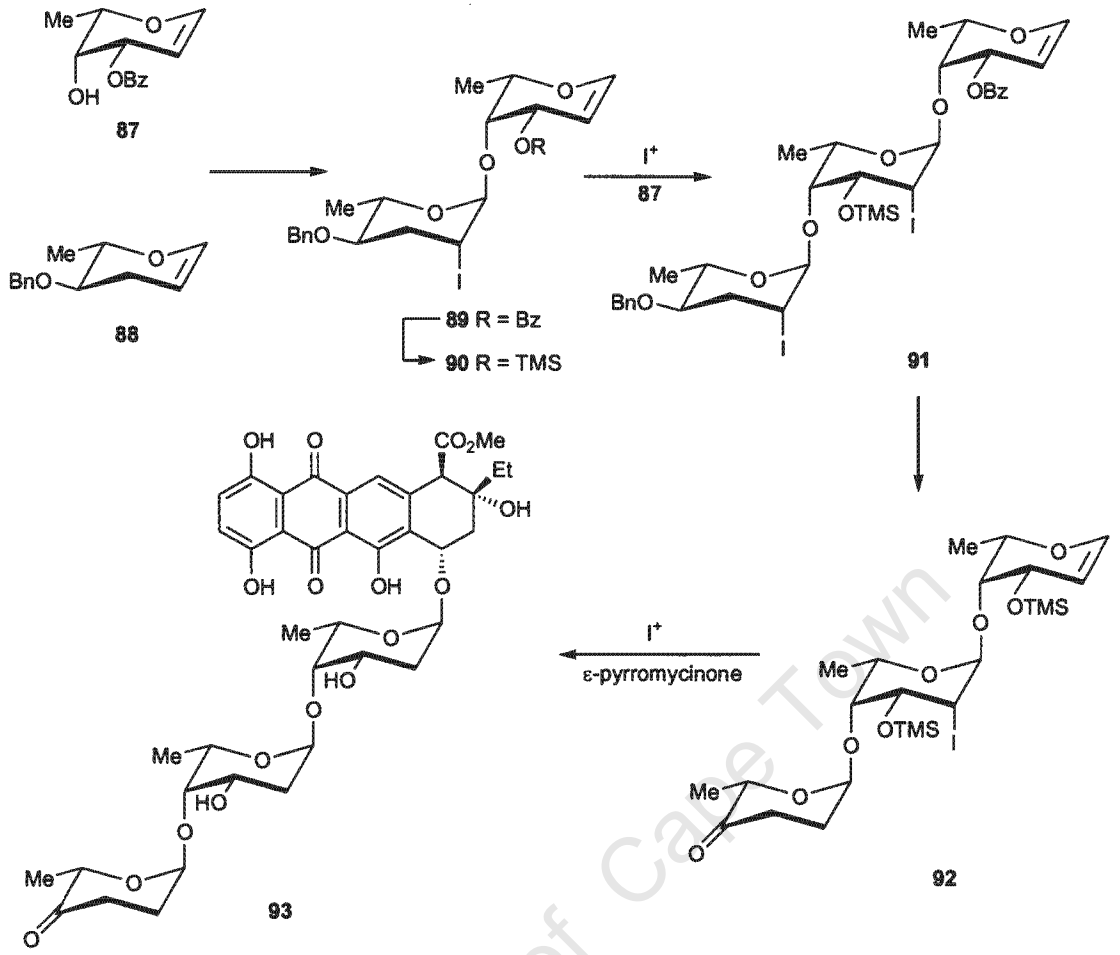
Scheme 1.16. NIS, CH_3CN, ROH.

On the other hand, when the reaction was carried out in methanol or THF, the final ratio of stereoisomers varied for the same substrates. In this case, it was concluded that either methanol or THF forms a complex with iodine, so that the first step will be fast and reversible, and then the complex collapses slowly to afford the final product (Scheme 1.17). In such a situation, the proportion of the stereoisomers will depend on the tendency for *trans*-diaxial opening of the cyclic iodonium ion, and by steric factors in the glycal and in the nucleophile.[76]



Scheme 1.17. NIS-promoted addition of an alcohol in oxygenated solvents.

Danishefsky has exploited the NIS-methodology in the synthesis of bulky polysaccharides.[77,78] He applied the concept of "armed-disarmed", developed by Fraser-Reid *et al.*,[79] to couple suitably protected glycals promoted by iodonium ion "I^+". Substrates with electron withdrawing protecting groups are considered as being 'disarmed' while the ones with electron donating groups being as 'armed'. Hence, the armed glycals are more reactive towards the halonium ions as compared to the disarmed glycals. Using the methodology, Danishefsky has successfully synthesised ciclumycin 0 (**93**),[77] an anthracycline antibiotic containing a trisaccharide with three α-(1-4) linked 2,6-dideoxy sugars and an α-linkage to the daunomycin aglycone (Scheme 1.18).[77] The armed glycal **88** is coupled with the disarmed glucal **87**. Since glycal **88** is more nucleophilic than **87**, the glycosyl donor is activated by "I^+" to generate a cyclic iodonium ion intermediate which is then attacked by the glycosyl acceptor to yield **89**. To reiterate the strategy, **89** was converted to **90** in order to enhance the nucleophilicity of the disaccharide so that it can act as a glycosyl donor. Coupling of **90** with **87** gave **91** which was converted to **92** in the same way. **92** was then coupled with ε-pyromycinone which after few steps afforded ciclumycin 0 (**93**).



Scheme 1.18. Synthesis of ciclumycin 0 (**93**).

The synthesis of iodohydrins from the direct reaction of olefins with aqueous iodine is not as simple as the synthesis of corresponding bromohydrins owing to the reversibility of the addition of the iodide to the double bond (Scheme 1.19).[80]

Scheme 1.19: Reversibility of iodination of olefins in aqueous medium.

The reversibility of the reaction poses a challenge for chemists to search for alternative methods. A number of methods have been developed to solve the problem and some of them are: iodination in the presence of iodide scavengers like mercuric oxide or silver oxide,[81] the combined reagent system of $H_5IO_6/NaHSO_3$ developed by

Ishii *et al.*,[82] ring opening of epoxides with elemental iodine in the presence of three pyridine containing macrocyclic diamides,[83] using NIS in a mixture of H_2O and DME at –20°C[84] and iodination in water in the presence of surfactants.[85] More recently, a mixture of molecular iodine and phenyliodine (III)bis(trifluoroacetate) in acetonitrile-water at –15°C reaction system reported for the transformation of acetylated glucal **59** and benzylated glucal **67** into their respective iodohydrins (Scheme 1.20).[86]

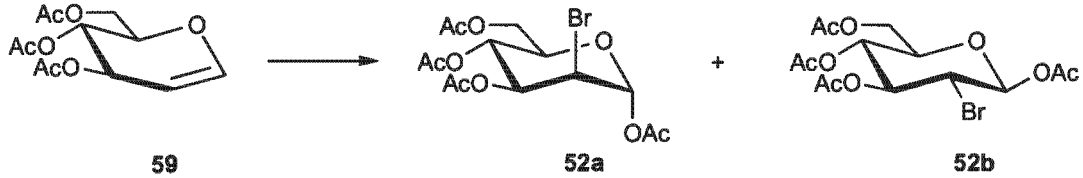
59 R = Ac
67 R = Bn

95a R = Ac
96a R = Bn

Scheme 1.20. I_2, $PhI(OCOCF_3)_2$, CH_3CN/H_2O (4:1), 78% (**95a**) and 66% (**96a**).

1.2.2.3 Haloacetoxylation of glycals

Another interesting class of 1,2-addition reaction of glycals is haloacetoxylation. The acetoxyhalides that can be obtained by this type of reactions can function as glycosyl donors in glycosylations and synthesis of 2-deoxy oligosaccharides.[87] A number of reagent systems have been developed for the synthesis of acetoxyhalides. Takiura *et al.* attempted to develop a method of obtaining 1-*O*-acetyl-2-deoxy-2-halopyranosyls *via* iodinolysis of C-2 mercurated peracetylated pyranosyl.



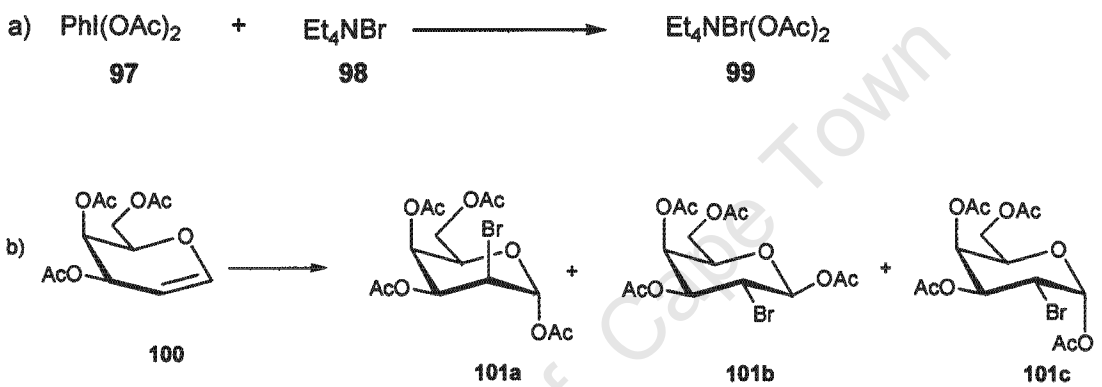
59 **52a** **52b**

Scheme 1.21. NBS, AcOH, rt, 3 h, 74% (2:1, α-*manno*:β-*gluco*).

However, since the 1-acetoxyl group is extremely labile, the yield of the desired product was very poor in such reaction conditions.[88] It was in early eighties that a successful attempt was made to introduce directly, at C-1 of a glycal derivative, an acetoxyl group. Treatment of the acetylated glucal **59** with NBS in the presence of

acetic acid afforded the 2-deoxy-2-brominated hexopyranosyl acetates **52a** and **52b** with a total yield of 74% (Scheme 1.21).[89]

An alternative method for the bromoacetoxylation of glycals is the iodine (III) initiated protocol developed by Kirschning and co-workers.[87] According to their procedure, galactal **100** is added to a solution of tetraethylammonium [di(acyloxy)bromate(I)] **99** prepared from the reaction of tetraethylammonium bromide **98** and (diacetoxyiodo)benzene **97** to afford 1-acetoxy-2-bromo-2-deoxy pyranoses **101a** - **c** in 74% overall yield (Scheme 1.22).



Scheme 1.22. Reagent **99**, DCM, rt, 2 h, 74%.

Kirschning *et al.* also developed phosphonium salts of diacetoxyiodine (I) **104** which are hypoiodite **105** equivalent, for promoting acetoxyiodination of glycals.[90] The reagents are prepared from corresponding phosphonium iodides **102** and diacetoxyiodobenzene **103** as shown in Scheme 1.23 (a). Iodoacetoxylation of galactal **106** promoted by diacetoxyiodine (I) **102b** in acetonitrile and toluene afforded a 3.5:1 ratio of α-*talo* **107a** and β-*galacto* **107b** in 67% and 74%, respectively [Scheme 1.23 (b)].

a) $R^1{}_3R^2PI$ + $PhI(OAc)_2$ ⟶ $R^1{}_3R^2PI(OAc)_2$ + PhI

102a-c **103** **104**

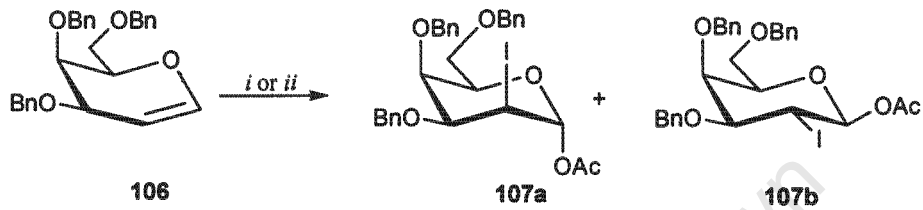
a $R^1 = R^2 = Ph$

b $R^1 = Ph$, $R^2 = Me$

c $R^1 = Ph$, $R^2 = NMePh$

["I - OAc"]

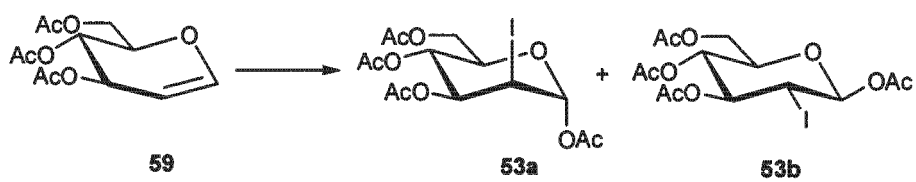
105

b) 

106 **107a** **107b**

Scheme 1.23. *i*) Reagent **102b**, MeCN, rt, 72 h, 67%; *ii*) reagent **102b**, toluene, rt, 72 h, 74% (3.5:1).

Studies of similar reactions but with NIS and AcOH have shown that the product distribution depends upon the reaction temperature. It was reported that a selectivity of up to 9:1 of α-*manno* to β-*gluco* could be obtained at reaction temperatures of as low as –78°C.[91,92] In contrast, a 1:1 ratio of α-*manno* to β-*gluco* can be achieved at reflux with toluene as solvent. Roush *et al.* came up with a novel CAN-NaI-HOAc reagent system that affords a better selectivity. Under these reagent systems glycals such as **59** quantitatively afforded 1-acetyl-2-iodopyranoses **53a** and **53b** in 92:8 ratio and 75% overall yield (Scheme 1.24).[92]



59 **53a** **53b**

Scheme 1.24. CAN, NaI, AcOH, MeCN, 0°C, 75% (92:8).

Though the aforementioned methodologies for the synthesis of 2-deoxy-2-halo-sugars are effective and find wide applications in organic synthesis, they are usually associated with high toxicity, expensive reagents and production of stoichiometric

CHAPTER TWO

2. RESULTS AND DISCUSSION

2.1 Preparation of Glycal Substrates

The work on functionalization of glycals began with the synthesis of glycals with different protecting group patterns. The glycals selected for the study were: 3,4,6-*tri*-*O*-acetyl-D-glucal (**59**), 3,4,6-*tri*-*O*-acetyl-D-galactal (**100**), 3,4,6-*tri*-*O*-benzyl-D-glucal (**67**), 3,4,6-*tri*-*O*-benzyl-D-galactal (**106**), 3,4-*di*-*O*-acetyl-6-*O*-*tert*-butyldiphenylsilyl-D-glucal (**114**), 3,4-*di*-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-D-glucal (**115**), 3,4,6-*tris*-*O*-*tert*-butyldiphenylsilyl-D-glucal (**116**) and 3-*O*-acetyl-4,6-*O*-benzylidene-D-glucal (**118**). They were chosen with a view to investigate the steric, electronic and conformational factors during their transformations. Besides the per-*O*-acetylated glycals, the rest were prepared using available literature procedures. As the main focus was on the derivatization of these glycals, no attempts were made to improve their yields and synthetic protocols.

Per-*O*-benzylated glycals **67** and **106** were prepared in *ca* 50% yield from their corresponding commercially available acetylated glycals after treatment with benzyl chloride in the presence of *t*-BuOH and *n*-Bu_4NHSO_4 in a mixture of benzene and 50% aq NaOH (Scheme 2.1).[94]

59 R^1 = H, R^2 = OAc

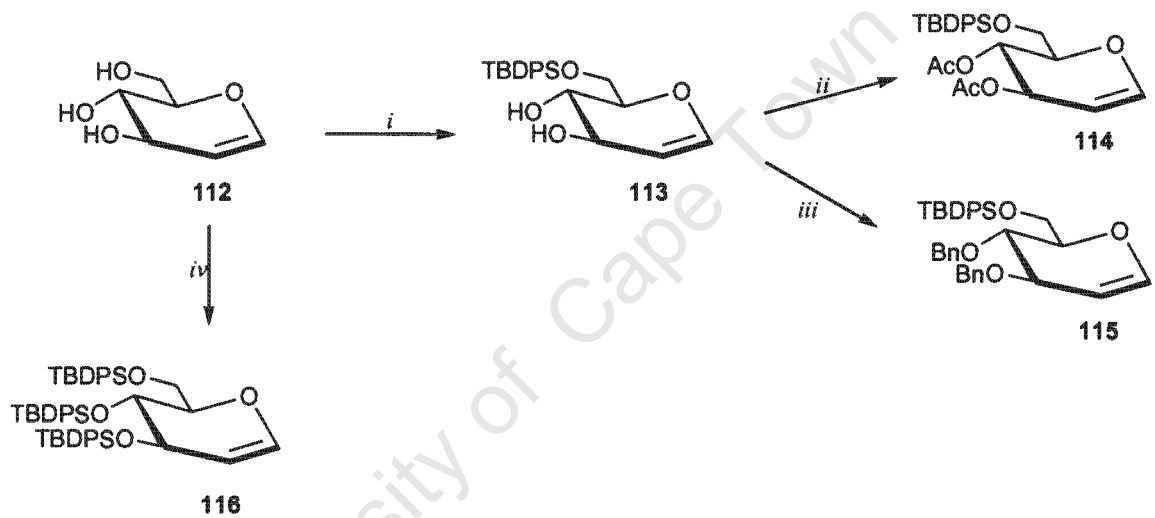
100 R^1 = OAc, R^2 = H

67 R^1 = H, R^2 = OBn

106 R^1 = OBn, R^2 = H

Scheme 2.1. BnCl, *t*-BuOH, *n*-Bu_4NHSO_4, benzene, 50% aq NaOH, 50°C, 6.5 h, 50% (**67**) and 54% (**106**).

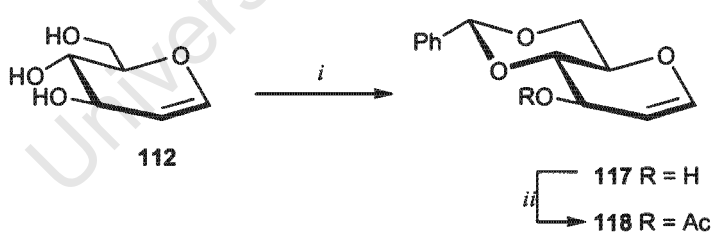
The silylated glucals were derived from glucal **112**. Exposure of glucal **112** in DMF to one equivalent of TBDPSCl in the presence of imidazole resulted in the selective silylation of the primary hydroxyl group to give mono-silylated glucal **113** in 66% yield (Scheme 2.2).[95,96] However, when three equivalents of TBDPSCl were used, per-*O*-silylated glucal **116** was produced in a yield of 85% (Scheme 2.2).[95] Treatment of a solution of glucal **113** with sodium hydride and benzyl bromide in the presence of TBAI afforded glucal **115** in 70% yield (Scheme 2.2).[95] Glucal **114** was obtained in 90% yield when a solution of diol **113** in dry dichloromethane was acetylated using acetic anhydride in the presence of DMAP and triethylamine (Scheme 2.2).[96]



Scheme 2.2. *i*) TBDPSCl (1.1 equiv.), imidazole, DMF, rt, 1 h, 66%; *ii*) Ac_2O, DMAP, Et_3N, DCM, rt, 1 h, 90%; *iii*) BnBr, NaH, *n*-Bu_4NI, THF, 0°C (2 h) to rt, overnight, 70%; *iv*) TBDPSCl (3.1 equiv.), imidazole, DMF, rt, overnight, 85%.

Unlike the ease of synthesis of the rest of the glycals, 4,6-*O*-benzylidene protected glycals are not readily available *via* simple acid catalysed benzylidenation of D-glucal on the account of the acid sensitivity of the enol ether functionality and the yields are usually low.[97] An alternative four step method has been reported which results in high yield of the desired glycal starting from the readily available starting material α-methyl glucopyranoside, and involving selective triflation and iodide displacement at C-2.[97] Since in our case the main focus was on the transformation of a benzylidene glucal, the quick low yielding acid catalyzed preparation was chosen. Therefore, D-glucal **112** was treated with benzaldehyde dimethylacetal and *p*-TsOH at room temperature.[98] The reaction resulted in a number of by-products as judged from TLC,

but after a tedious column chromatography, 4,6-*O*-benzylidene-D-glucal (**117**) was isolated as a white crystalline solid in 41% yield (Scheme 2.3). The structure of the product was established by comparing the NMR data with the reported values.[97] The ^{1}H NMR spectrum displayed aromatic signals indicating the presence of an aromatic group and the characteristic singlet signal of H-7 appeared at δ 5.60, which clearly indicated the presence of the benzylidene ring. The olefin functionality was confirmed from the appearance of a doublet of doublets signal of H-1 at δ_H 6.34, which is in the olefin range. The presence of the hydroxyl group was proved by the appearance of a D_2O exchangeable broad singlet at δ_H 2.25 integrating for one proton. The ^{13}C NMR spectrum also displayed the characteristic signals besides the aromatic peaks. The appearance of a signal at δ 144.2 corresponding to C-1 was an indication of the presence of a double bond between C-1 and C-2. Moreover, the characteristic C-7 signal appeared at δ 101.9 indicating the presence of a benzylidene ring. In accordance with other glucal derivatives, the C-2 signal appeared down field at δ 103.6 indicating a C-1 - C-2 double bond. Acetylation of the resulting glucal **117** with acetic anhydride in the presence of DMAP and triethylamine afforded glucal **118** in 80% yield (Scheme 2.3). The NMR spectra showed the characteristic acetoxy signals at δ_H 2.10, δ_C 170.6 and δ_C 21.0. The rest of the NMR spectra were in complete agreement with the reported literature.[97]



Scheme 2.3. *i*) benzaldehyde dimethylacetal, *p*-TsOH, DMF, rt, overnight, 41%; *ii*) Ac_2O, DMAP, Et_3N, DCM, rt, 1 h, 80%.

With this range of variously protected glycals in hand, attention turned to the investigation of alternative methods for their further functionalization.

2.2 Development of Catalytic Route to 2-Halo Sugars

Our first efforts were directed towards the synthesis of 2-deoxy-2-halo sugars from glycals in a stereoselective and environmentally-friendly manner. Synthesis of 2-deoxy-2-halo sugars is well documented, but generally involves the use of stoichiometric amounts of reagents which are either toxic or expensive and produce stoichiometric amounts of waste. Catalytic and environmental friendly methods of functionalizing glycals have received little attention in sugar chemistry.[99] The synthetic possibility of iodohydroxylation of organic substrates with halide salts in the presence of hydrogen peroxide and a catalyst have recently been highlighted.[100] *In situ* formation of reactive halogen compounds is one of the most promising approaches to overcome the safety and waste handling problems and although it has not been applied to carbohydrates, electrochemical haloalkoxylation and halohydroxylation of simple alkenes using common halide salts has been achieved.[99] However, taking into account the costs and the apparatus needed with electrochemistry, reactive halonium ions are better generated gradually in a chemical way. A classical example is the biohalogenation of alkenes by marine organisms.[101,102] These organisms use haloperoxidases, and in particular vanadium bromoperoxidase (V-BrPO) and FeHeme bromoperoxidase (FeHeme-BrPO) to catalyze oxidation of halides by hydrogen peroxide resulting in a concomitant halogenation of alkenes.[102] It has been demonstrated that man-made analogues used instead of enzymes resulted in almost comparable activities with improved long-term stabilities. Sels *et al.* reported tungstate exchanged on naturally occurring minerals such as hydrotalcite and takovite-like materials to be excellent mimic for haloperoxidases.[103,106] Our group has demonstrated the transformations of a series of cyclic enol ethers into their corresponding halo alcohols and ethers in high stereoselectivity and yields using oxidative halogenation with tungstate exchanged on takovite [(Na, Al)LDH-WO_4^{2-}]* (Figure 2.1) as shown in Scheme 2.4 with the intention of applying the method to the functionalization of glycals.[99] The protocol involved the treatment of a cyclic enol ether with ammonium halide salts and hydrogen peroxide in the presence of a tungstate exchanged takovite catalyst.

* LDH stands for layered double hydroxide which is a hydrotalcite-type of structure.[103,106]

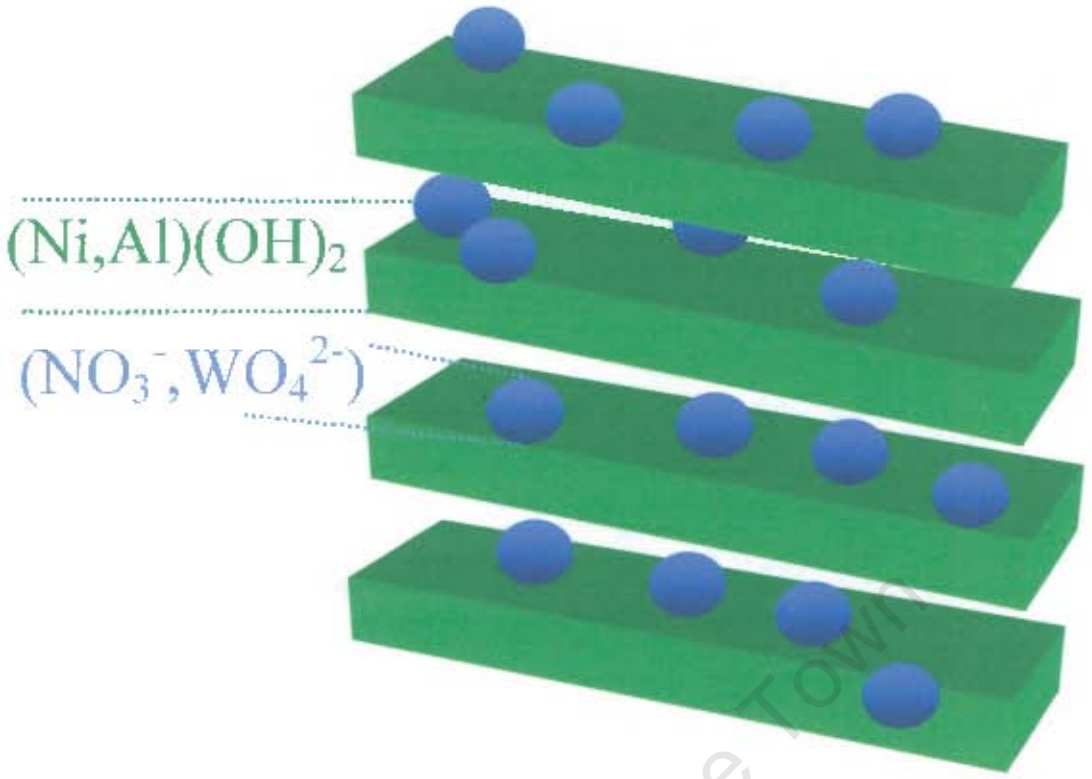
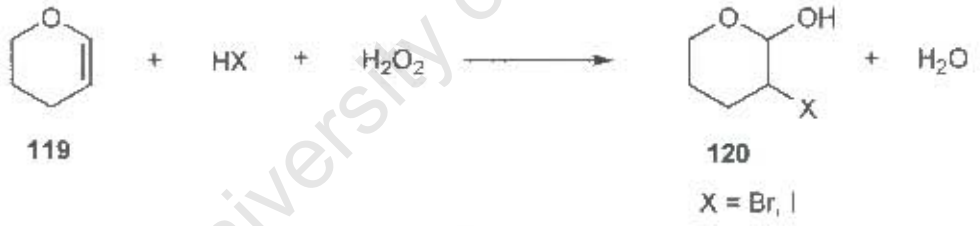


Figure 2.1. Microscopic representation of [(Na, Al) LDH-WO_4^{2-}].



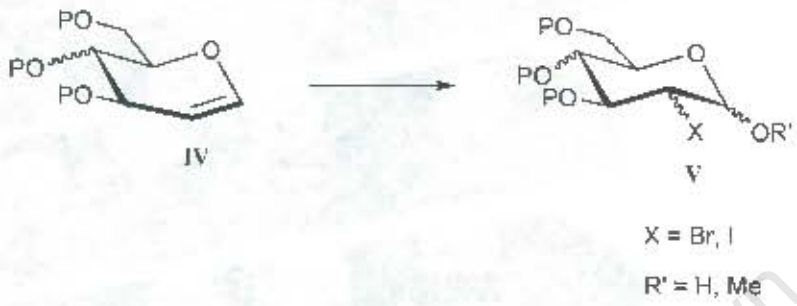
119 **120**

X = Br, I

Scheme 2.4. 0.25 - 1 mol% WO_4^{2-} on takovite, 20 - 35°C, 5 - 25 min, aq CH_3CN or THF, 90 - 97%.

Encouraged by the results, the protocol was successfully extended to the halofunctionalization of protected glycals, proceeding in most cases in high yield and with some synthetically useful stereoselectivities as shown in Scheme 2.5 and Table 2.1. The protocol involves treatment of a solution of a glycal, ammonium halide and catalytic amounts of the takovite catalyst in acetonitrile or methanol with periodic addition of hydrogen peroxide until TLC analysis of the reaction mixture shows disappearance of the starting material. It was found that when the hydrogen peroxide was added all at once, the progress of the reaction stopped and addition of more of the reagents was required for the reaction to go to completion. The resulting

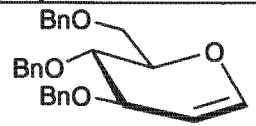
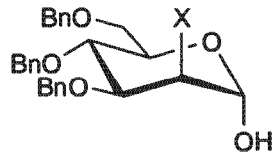
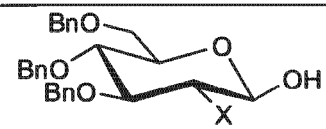
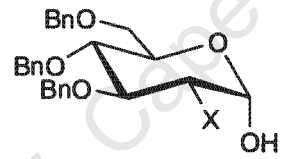
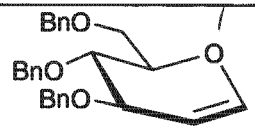
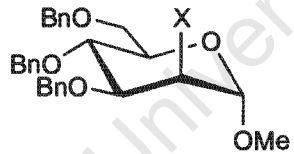
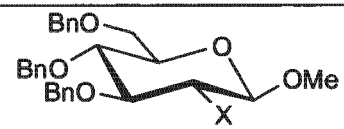
stereoisomeric products were chromatographically inseparable but their structures were confirmed by comparing characteristic signals in the ^{1}H NMR spectra with the literature reports and in most cases acetylating the mixture of halohydrins before further analysis using ^{1}H NMR .

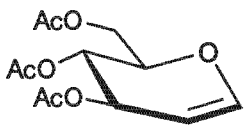
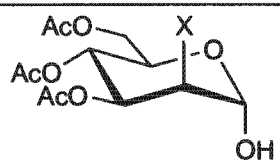
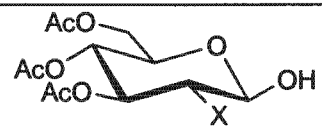
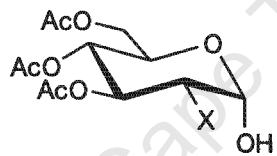
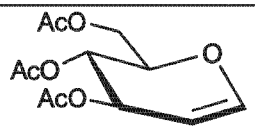
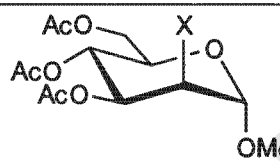
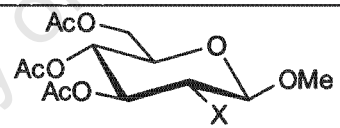


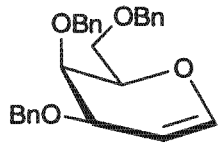
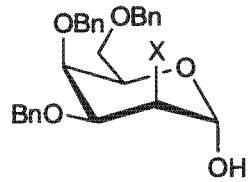
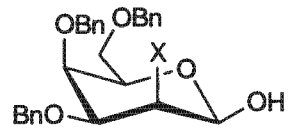
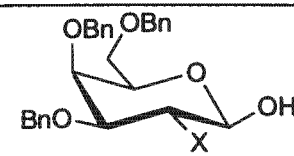
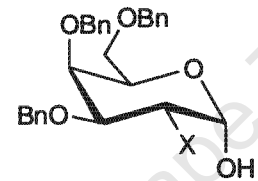
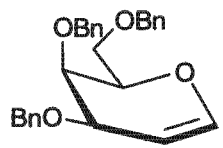
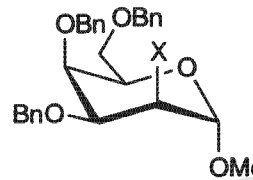
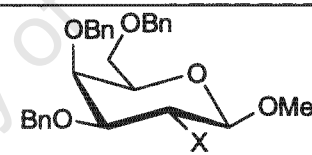
Scheme 2.5. NH_4X, 50% aq H_2O_2, 0.25 – 1 mol% WO_4^{2-} on takovite, aq CH_3CN or MeOH, 20 – 60°C, 2.5 – 5 h, 66 – 100%.

As it is evident from Table 2.1, the reaction proceeded in high yield but with relatively poor selectivity. The stereochemical outcomes were in agreement with results reported for other methods,[48,70,76,86] and were dependent to some extent on the halide used, the solvent and the nature of the protecting groups. The nature of protecting groups also had a significant effect on the rate of the reaction. Reactions of benzylated glucal or galactal proceeded to completion within 1.5 h at ambient temperatures while acetylated glucals required 2.5 – 5 h at 60°C, and in some cases did not go to completion. The higher reactivity of benzylated than acetylated glycals was consistent with the electron-donating and electron-withdrawing characters of the respective protecting groups. The particular role of the C-6 substituent has been discussed previously[67] in the context of studies on the bromination of benzylated or acetylated glycals, with the postulate that interaction of this group with the non-bonding electron pairs on the ring oxygen would affect their stabilizing role on the intermediate carbocation at C-1.

Table 2.1. Oxidative iodination and bromination of glycals.

Entry	Glycal	Products	Yield (%)	Stereochemistry
1	 **67**	 **56a** X = Br **96a** X = I  **56b** X = Br **96b** X = I  **56c** X = Br **96c** X = I  **56d** X = Br **96d** X = I	95 (**56**) 96 (**96**)	5:1:2:2 6:1:8:0
2	 **67**	 **121a** X = Br **122a** X = I  **121b** X = Br **122b** X = I	100 (**121**) 85 (**122**)	5:4 > 9:1

3	 **59**	 **123a** X = Br **95a** X = I  **123c** X = Br **95c** X = I	 **123b** X = Br **95b** X = I  **123d** X = Br **95d** X = I	67 (**123**) ~40 (**95**)	5:1:3:0 not determined[a]
4	 **59**	 **124a** X = Br **125a** X = I	 **124b** X = Br **125b** X = I	89 (**124**) 66 (**125**)	3:1 6:1

5	 **106**	 **126a** X = Br **127a** X = I  **126c** X = Br **127c** X = I	 **126b** X = Br **127b** X = I  **126d** X = Br **127d** X = I	97 (**126**) 97 (**127**)	1:1:0:0 not determined[a]
6	 **106**	 **128a** X = Br **129a** X = I	 **128b** X = Br **129b** X = I	81 (**128**) 92 (**129**)	1:1 8:2

[a] The NMR was too complex to be analysed.

When the reactions were carried out in acetonitrile, bromo- or iodohydrins were formed in excellent yields. In all cases the *manno*-products predominated, i.e., those resulting from top- or β-face addition of the halogen. This selectivity was lowest in the case of benzylated galactal (entry 5), reflecting the influence of the *pseudo*-axial C-4 substituent which presumably alters the conformation of the galactal ring and the orientation of its dipole, thereby influencing the preferred face of attack of the electrophile. With the limited data available, it is not possible to draw firm conclusions on the effects of protecting groups on the selectivity in that the reactions of the acetylated glucals were carried out at higher temperatures. However, in formation of bromohydrins (entries 1 and 3) from benzylated and acetylated glucals respectively, the *manno*:*gluco* ratio changed from 7:3 to 8:1, and the *trans*:*cis* ratio from 6:4 to 6:3. The selectivity towards the *manno*-configuration was most marked in the reactions using NH_4I (entry 1) with a *manno*:*gluco* ratio of 14:1, and a surprisingly high ratio (8:7) of *cis*:*trans*. This suggested that following the favoured β-face addition of the iodonium ion, the oxocarbenium ion was strongly stabilized with assistance from the electron-donating benzyl protecting group on C-6.

When reactions were carried out in the polar, nucleophilic solvent methanol, the methyl 2-deoxy-2-halo glycosides were obtained in good to excellent yields (entries 2, 4 and 6), even in the case of the less reactive acetylated glucal (entry 4). Interestingly, only the 1,2-*trans*-products were detected from the reaction. The reactions of benzylated or acetylated glucal using NH_4I (entries 2 and 4) were highly stereoselective, yielding predominantly the α-mannosides. However, in the NH_4Br based haloalkoxylation, even though the *trans* addition products were formed, the selectivity was poor. This halide-dependent stereochemistry agreed well with earlier work on haloalkoxylation of glycals and has been rationalized in terms of either a bridged halonium intermediate with the charge located at the halide or a carbocation-like intermediate bearing the charge at the anomeric carbon atom. In the iodonium case, only the bridged intermediate was formed on the β-face of the glycal giving a *manno-trans* addition almost exclusively. In the bromination, the intermediate bridged bromonium species is not as stable as with iodine and thus some carbocation was formed without preference to the α- or β-face of the glycal leading to a mixture of *gluco* and *manno-trans* addition products. The nature of solvent also affected which intermediate was more favoured. While the haloalkoxylation in methanol yielded

trans product, the halohydroxylation in acetonitrile where the nucleophile was water gave about an equimolar (in some cases) mixtures of *cis* and *trans* products. This could probably be due to the high solvation power of water which exerts a stabilizing effect on the carbocation intermediate **VI** leading to an almost equimolar isomer production (Figure 2.2).

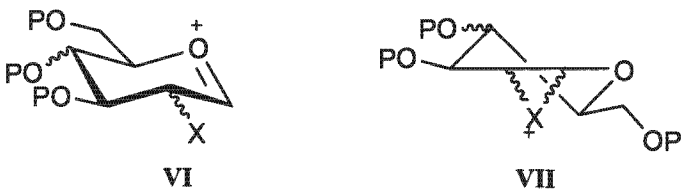
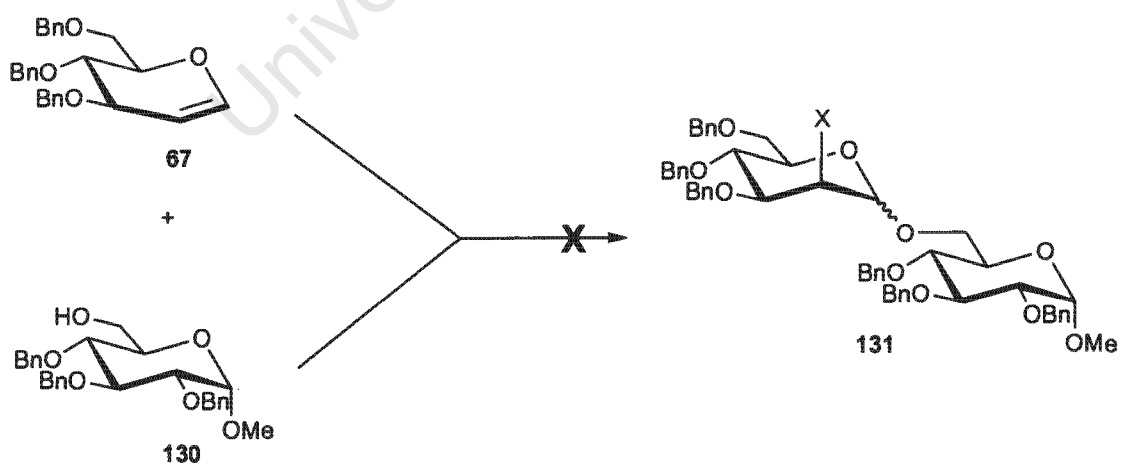


Figure 2.2. Possible intermediates in the oxidative halogenation reactions.

Encouraged by the excellent selectivity of α-glycosylation in methanol with NH_4I, attempts were made to effect glycosylation of a glycal with sugar glycosyl acceptors* under the oxidative halogenation conditions (eg. Scheme 2.6). Unfortunately, the reactions were unsuccessful and the products of the competing reaction, halohydrins, were obtained. Attempts were made using urea-hydrogen peroxide instead of aqueous H_2O_2 to no avail. Further investigations on the reactions were not carried out in view of the difficulty of maintaining an anhydrous environment.

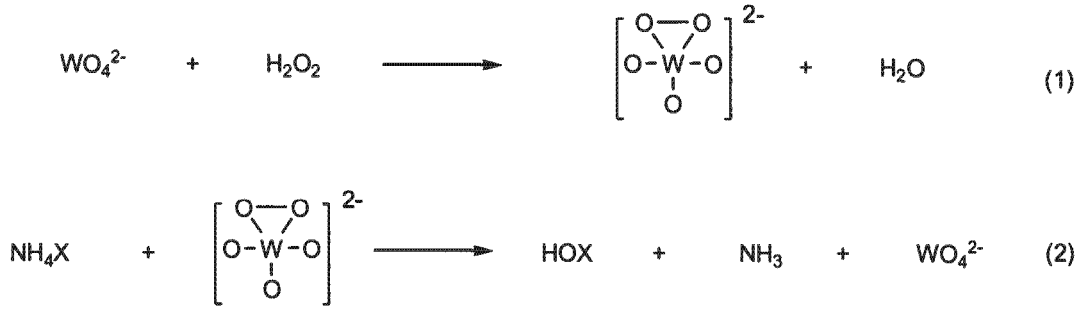


Scheme 2.6. NH_4X, 50% aq H_2O_2, 0.25 – 1 mol% WO_4^{2-} on takovite, rt, CH_3CN.

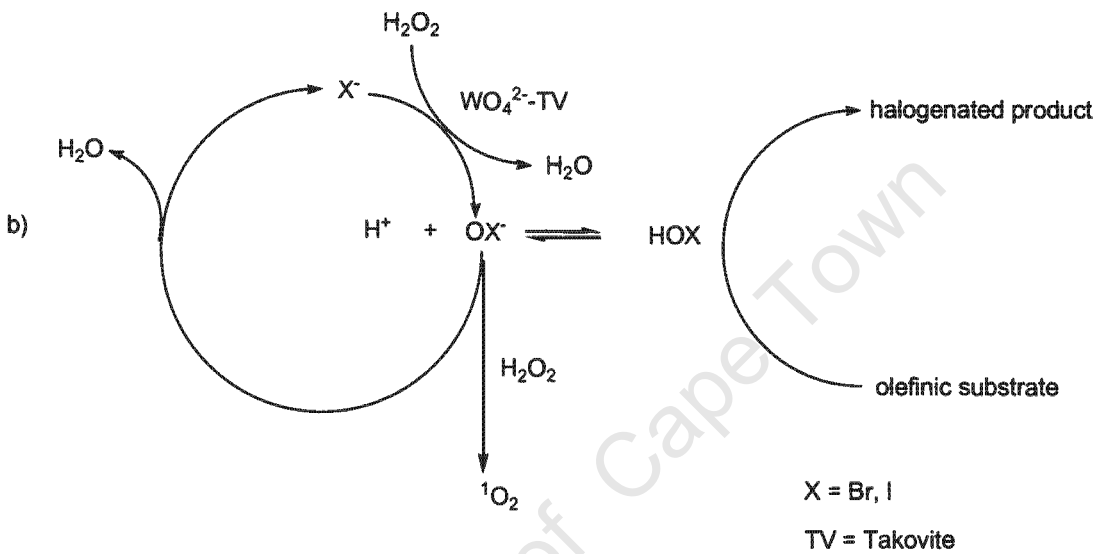
* Glycosyl acceptor **130** was prepared following reported procedure.[105]

The mechanism for the oxidative halogenation is shown in Scheme 2.7. The catalytic oxyhalogenation cycle has been fully elucidated[99] and appears to be similar to that of the vanadium-containing haloperoxidases.[102] The reaction begins with formation of a peroxotungstate complex (1) which oxidizes the halide to the hypohalite anion. The anion equilibrates with its conjugate acid and the corresponding dihalide, the ratio depending on the pH, the halide concentration and the solvent. The hypohalous acid reacts with the olefin and yields, after solvolysis, either the halohydrins or haloalkoxylated products depending on the nucleophile used. Had it been possible for the X^+ to remain associated with the surfaces of the takovite, better stereoselectivity would have been expected. The proton for the hypohalite anion-hypohalous acid equilibrium is donated by the weak acid, NH_4^+ (2). If the oxidative halogenation is not buffered properly, the equilibrium shifts toward the hypohalite anions which rapidly react with a new molecule of H_2O_2 to produce $^1O_2$ and water. This explains why periodic addition of the H_2O_2 was required in the protocol.

a)



b)



Scheme 2.7. Catalytic oxyhalogenation cycle using the tungstate exchanged takovite.

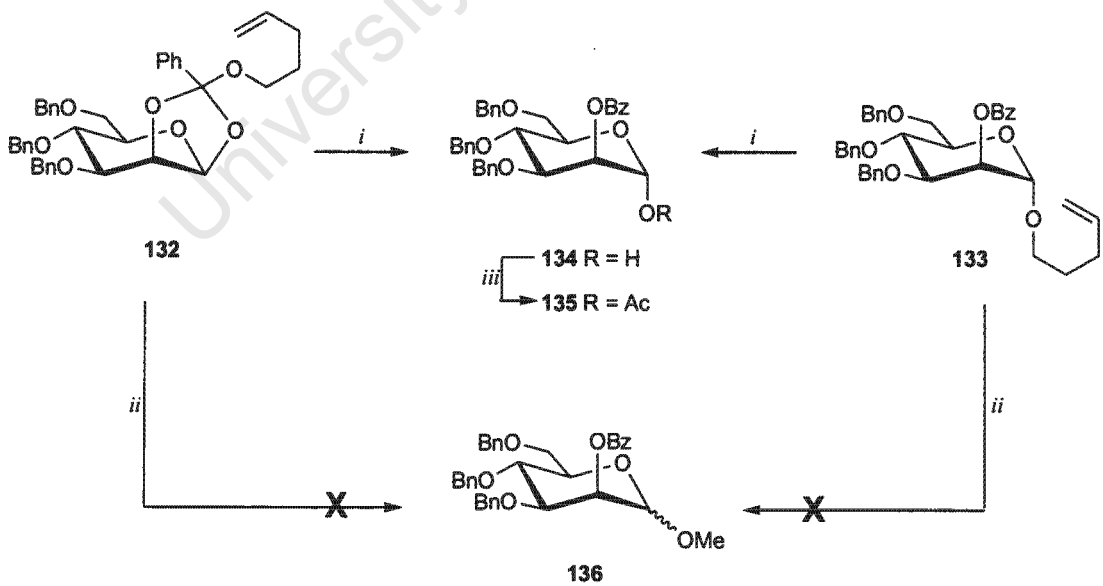
In summary, the methodology using takovite catalyst provides high yields of 2-halo sugars from glycals, but with moderate selectivities with either iodide or bromide as source of the halogen. However, with methanol as solvent and ammonium iodide as halogen source, methyl 2-deoxy-2-iodo-D-glycosides are produced in high yields and excellent selectivities towards the 1,2-*trans* addition products.

2.3 Application of Takovite Catalyst in Activation of Pentenyl Glycosides and Orthoesters

A further application of the method described above was considered in investigating its potential for deprotection and/or activation of pentenyl orthoesters and glycosides which are routinely activated with halonium ions to afford anomeric hydroxyls or glycosides depending on the nucleophile used.[79,107,108] Since the protocol developed

above also generates halonium ions, attempts were made to activate both a pentenyl orthoester **132** and glycoside **133**.* When a solution of orthoester **132** in THF was treated with NH_4I and 50% aq H_2O_2 in the presence of the takovite catalyst at 60°C, the free sugar **134** was obtained almost exclusively in 82% yield (Scheme 2.8). The product was identified after acetylation to give the known compound **135** with the NMR data in complete agreement with the reported values.[107] The opening of the orthoester group was confirmed by the absence of the characteristic signal of the quaternary carbon in orthoester **132** at δ_C 122.2 and absence of any *n*-pentenyl signals in both the ^1H and ^{13}C NMR spectra. When the reaction was carried out in methanol in the hope of obtaining methyl glycoside **136**, protected mannose **134** was again obtained in excellent yield, although the ^1H NMR spectrum showed traces of the β-anomer (Scheme 2.8).

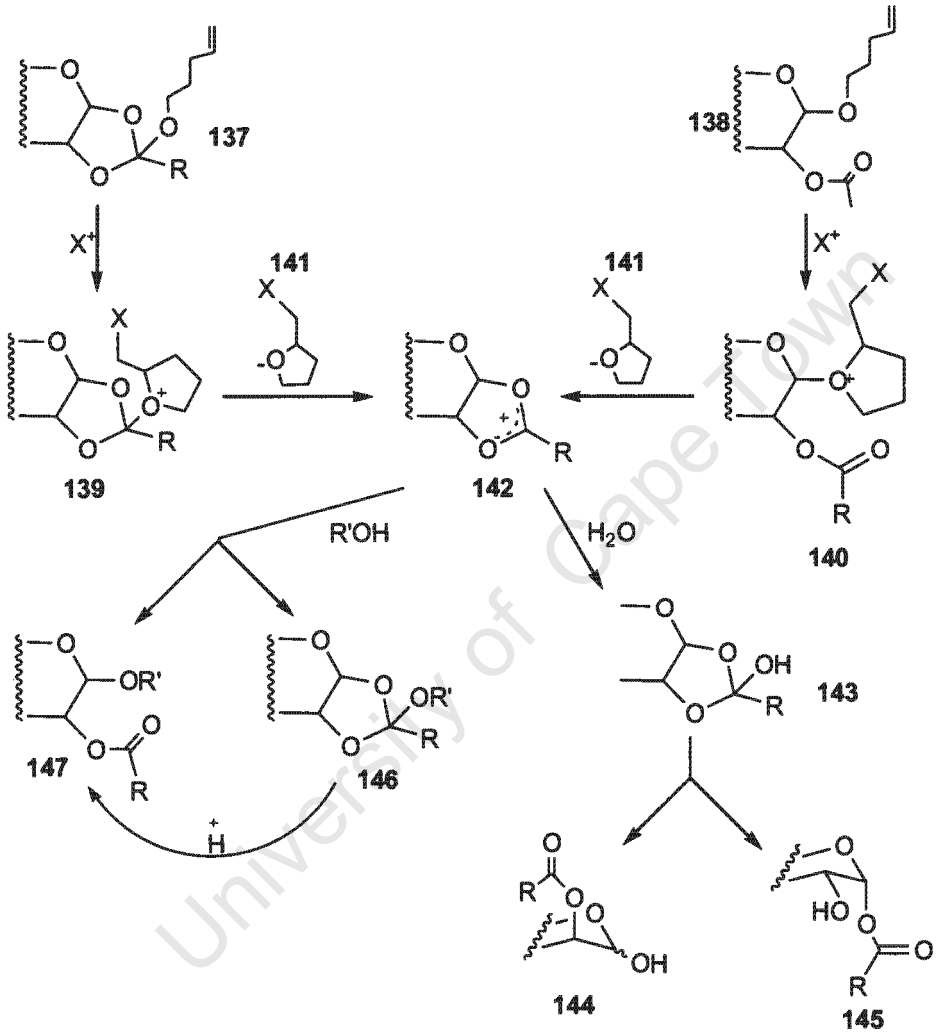
Under similar conditions *n*-pentenyl glycoside **133** also gave mannose **134** in 90% yield accompanied by traces of the β-anomer (Scheme 2.8). The product was confirmed in a similar way as the product from orthoester **132**. As shown in Scheme 2.8, synthesis of methyl glycosides **136** could not be achieved under the specified reaction conditions, presumably due to the presence of water accompanying the H_2O_2 and also as a by-product of the reaction.



Scheme 2.8. *i*) NH_4I, 50% aq H_2O_2, 0.25 – 1 mol% WO_4^{2-} on takovite, THF, 60°C, ~6 h, 82% (from **132**) and 90% (from **133**); *ii*) NH_4I, 50% aq H_2O_2, 0.25 – 1 mol% WO_4^{2-} on takovite, 60°C, MeOH; *iii*) Ac_2O, DMAP, Et_3N, DCM, rt, 30 min, 76%.

* Orthoester **132** and *n*-pentenyl glycoside **133** were prepared following literature procedures.[79,105,107]

The results were comparable with previously reported results.[107] However, the activation was highly dependent on the electrophilic promoter and solvent used. When the activation of both the orthoester and *n*-pentenyl glycosides were attempted using NH_4Br, the reaction resulted in poor conversion (<< 50%) even after long reaction time, while similar reactions in acetonitrile with either NH_4Br or NH_4I were also unsuccessful.



Scheme 2.9. Possible mechanism of the activation of orthoester and *n*-pentenyl glycosides.

In agreement with the mechanism proposed by Fraser-Reid *et al.*, the reaction using the NH_4I-H_2O_2-takovite catalytic system seems to have gone *via* the formation of the crucial intermediate **142** (Scheme 2.9).[79,107,108] Electrophilic attack on the *n*-pentenyloxy moiety of **137** and **138** provides furanylium ions **139** and **140**, respectively. Ejection of the non-nucleophilic halomethylfuran **141** from both

furanylium ions **139** and **140**, results in cationic intermediate **142**. In the presence of water, this crucial intermediate **142** produces orthoacid **143**, which is unstable and rearranges to the hydroxyl esters **144** or **145**. In an anhydrous environment and with alcohol present, orthoester **146** is formed and rearranges to glycoside **147** or alternatively glycoside **147** is produced directly from intermediate **142**. The high susceptibility of intermediate **142** to attack by water explains why a methyl glycoside was not obtained when orthoester **132** and *n*-pentenyl glycoside **133** were subjected to the NH_4I-H_2O_2-takovite catalyst system (Scheme 2.8). The formation of the 2-*O*-benzoyl-mannose **134** (Scheme 2.8) is also in line with King's principle that a *manno* orthoacid gives 2-*O*-acyl-mannose while a *gluco* analogue provides 2-hydroxy glycosyl acetate.[107,109] As a final alternative, water may have attacked at the anomeric center of intermediate **142** from the bottom face of the molecule as the top face would be shielded by anchimeric assistance by the benzoyl group, thus resulting in the observed excellent α-selectivity as compared to results obtained using *N*-halosuccinamide.[107]

The abovementioned results have demonstrated that the NH_4I-H_2O_2-takovite catalytic system is able to activate *n*-pentenyl glycosides and orthoesters and as a result it can be used as an alternative to the existing *n*-pentenyl glycoside and orthoester deprotection techniques. However, it lacks applicability in the activation of these substrates as glycosyl donors during glycosylation.

2.4 Development of an Alternative Method for Direct Haloacetoxylation of Glycals and 1,2-Cyclopropanated Sugars

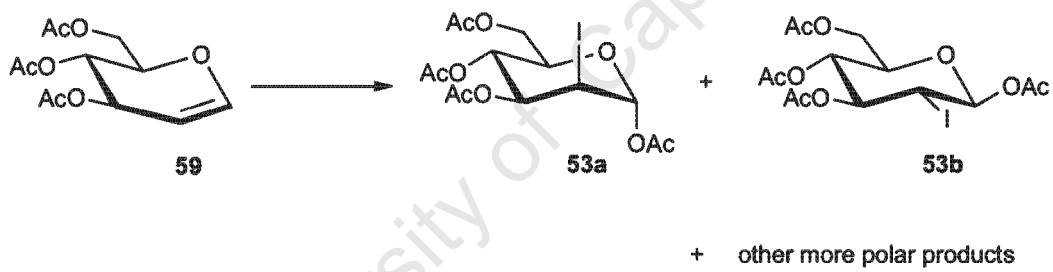
In contemplating the outcomes of the investigation of alternative routes to halohydrins from glycals, the usefulness of this methodology in synthesis of glycosides and oligosaccharides was critically evaluated. It was realized that if the 2-haloglycoses are to be used as potential glycosyl donors, their method of preparation would have to be highly stereoselective, thus obviating the need for difficult separations. In addition, it was likely that an additional step would be required to activate the anomeric substituent. Iodoacetoxylation – or haloacetoxylation in general – of glycals is known to provide ready access with quite good stereoselectivity to the required haloacetates,

and attention turned to the possibility of developing alternative, efficient methods to achieve this transformation.

2.4.1 Haloacetoxylation of glycals

Tri-*O*-acetyl-D-glucal (**59**) was chosen as a model substrate to establish optimal conditions because of its readily availability and the challenge of its lower reactivity towards electrophiles.

In our first attempts at direct oxidative halogenation, acetylated glucal **59** was treated with 3 equivalents of NH_4I and 50% aq H_2O_2 in acetic acid, using conditions reported to achieve easy iodination of phenol.[110,111] The desired 2-iodoacetates were formed but accompanied by significant amounts of the corresponding iodohydrins as judged from the TLC of the reaction mixture (Scheme 2.10).

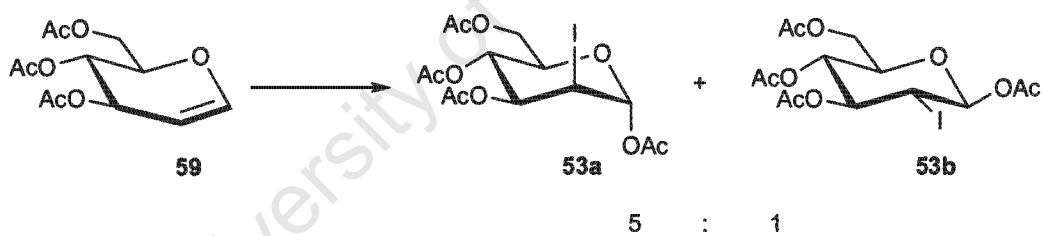


Scheme 2.10. NH_4I, 50% aq H_2O_2, AcOH, rt, 1.5 h.

As the presence of water from the hydrogen peroxide reagent was inevitable, a water scavenger was needed in the reaction mixture. So acetic anhydride was the first option to intercept the water and thereby produce more acetic acid that could also take part in the reaction. Accordingly, iodoacetoxylation in the presence of acetic anhydride at room temperature furnished exclusively the 2-iodoacetates **53a** and **53b**. In order to improve the stereoselectivity of the products, reactions were attempted at 0°C in consideration that low temperatures generally favour high stereoselectivities. However, lowering the temperature below room temperature resulted in freezing of the reaction mixture, thus impeding the reaction from proceeding. The method was therefore modified by introducing acetonitrile as a co-solvent in order to lower the freezing point of the mixture even though cooling below 0°C led to unacceptably slow

reactions. Attempts were also made to lower the number of equivalents of the reagents needed. It was found that an optimum 1.2 equivalents of both NH_4I and hydrogen peroxide was required for the reaction to go to completion without affecting the reaction time or yield. The reaction proceeded very slowly with decomposition and generation of side products when the amount of acetic acid was reduced to stiochiometric quantities. NaI was also evaluated as an iodide source instead of NH_4I: while an improved stereoselectivity of 7:1 in favour of α-*manno* isomer was observed, the yield (64% overall) was inferior and the ^{1}H NMR spectrum of the reaction products provided evidence for further unidentified products.

Under optimized reaction conditions a 0.15 M solution of glucal **59** in $AcOH/CH_3CN$ (1:1) reacted with 1.2 equivalents of NH_4I, 50% aq H_2O_2 and Ac_2O at 0°C to afford, exclusively, separable mixtures of iodoacetates **53a** and **53b** in an overall yield of 85% and a ratio of 5:1 as judged from a crude ^{1}H NMR spectrum (Scheme 2.11). No halohydrins or other side products were evident in the ^{1}H NMR spectrum of the crude product.



Scheme 2.11. NH_4I, 50% aq H_2O_2, AcOH, Ac_2O, rt, 1.5 h, 85%.

The spectroscopic data of the products were in agreement with the literature values.[112,113] The proton and carbon NMR spectra exhibited the characteristic signals indicating the presence of four acetyl groups. The stereochemistry of the products were assigned on the bases of the relative coupling constants of the anomeric protons. The anomeric proton of the iodoacetate **53a** appeared as a doublet at δ 6.36 with 1.2 Hz coupling constant confirming α-configuration whereas in the case of iodoacetate **53b** it appeared as a doublet at δ 5.87 but with a *J* value of 9.6 Hz, a clear indication of a β-anomer.

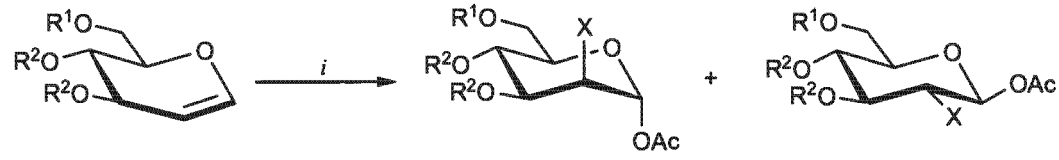
Similarly, glucals **67** (entry 2), **114** (entry 3) and **115** (entry 4) were transformed into their corresponding iodoacetates in excellent yield and with high α-*manno* selectivity (Scheme 2.12 and Table 2.2). The spectroscopic data of iodoacetates **148a** and **148b** were consistent with the reported literature data.[100] However, the structures of novel iodoacetates **149a**, **149b**, **150a** and **150b** were formulated on the basis of their corresponding ^{1}H and ^{13}C NMR spectra with the aid of a COSY and HMQC spectra.

The ^{1}H NMR spectrum of iodoacetate **149a** displayed among others a multiplet in the aromatic region integrating for ten protons, a doublet (J = 1.5 Hz) at δ 6.45 due to the H-1, doublet of doublets (J = 4.2 and 9.6 Hz) at δ 4.60 due to H-3, doublet of doublets (J = 1.5 and 4.2 Hz) at δ 4.52 due to the H-2 and characteristic three singlets at δ 2.12, 2.09 and 1.93 corresponding to the three acetoxy groups, and a diagnostic singlet at δ 1.08 integrating for the three methyl groups of the TBDPS group. This was supported by the ^{13}C NMR spectrum that showed the characteristic signals such as the three carbonyl signals at δ 170.0, 169.0 and 168.2, C-1 at δ 95.0, CH_3CSi at δ 26.7, three methyl signals at δ 20.9, 20.8 and 20.5 corresponding to the three acetoxy groups, and a signal of the *tertiary* carbon of the silyl group at δ 19.2. Similarly, the characteristic signals of iodoacetate **149b** included a doublet at δ_H 5.87 (J = 9.3 Hz) due to H-1, a triplet at δ_H 5.12 (J = 9.3 Hz) due to H-3, doublet of doublets at δ_H 3.98 (J = 9.3 and 11.0 Hz) due to H-2, three singlet acetoxy signals at δ_H 2.18, 2.09 and 1.89, and the presence of the silyl group was confirmed by the singlet signal that appeared at δ_H 1.04 with an integration of nine protons.

The signals of the ^{13}C NMR spectrum were analogous to the spectrum of iodoacetate **149a** but with a slight shift of the signal of C-1 to δ 94.0. The two stereoisomers, iodoacetates **149a** and **149b**, were distinguished by comparison of the signals (coupling constant and multiplicity) for H-1, H-2 and H-3. The small coupling constant of H-1 in iodoacetate **149a** was due to the diequatorial coupling of H-1 and H-2. However, in iodoacetate **149b**, the coupling was due to an axial-equatorial coupling that resulted in a larger coupling constant. The appearance of H-2 as a perfect doublet of doublets supported the equatorial orientation of H-2 in iodoacetate **149a** whereas the AB type of doublet of doublets was a confirmation of an axially oriented H-2 in iodoacetate **149b**. The signals of H-3 in both cases further supported the assignment of the respective stereoisomers. Due to unequal coupling (e-a and a-a)

in the case of iodoacetate **149a**, H-3 appeared as a doublet of doublets whereas in iodoacetate **149b** a diaxial coupling with both H-2 and H-4 favoured a triplet signal of H-3. The structures of iodoacetates **150a** and **150b** were assigned in the same way. The presence of an acetyl group was confirmed by the appearance of singlet signals at δ_H 2.01 (integrating for three protons) and δ_C 168.5 for iodoacetate **150a**; δ_H 2.19 (integrating for three protons) and δ_C 168.8 for iodoacetate **150b**.

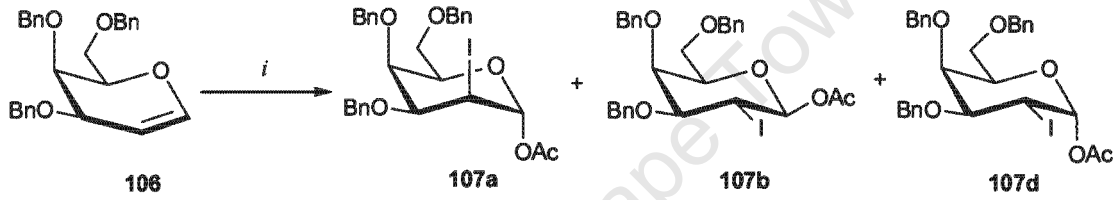
a)



	R^1	R^2
59	Ac	Ac
67	Bn	Bn
114	TBDPS	Ac
115	TBDPS	Bn
116	TBDPS	TBDPS

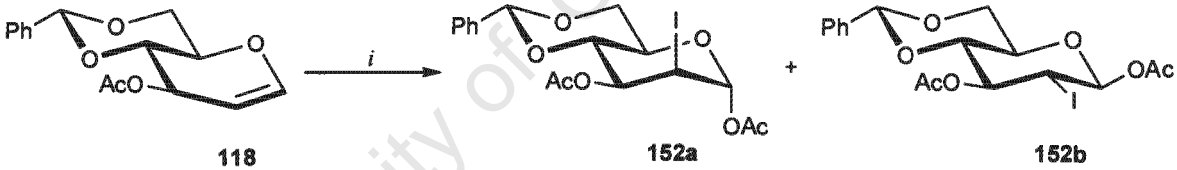
	R^1	R^2	X
53a,b	Ac	Ac	I
148a,b	Bn	Bn	I
149a,b	TBDPS	Ac	I
150a,b	TBDPS	Bn	I
151a,b	TBDPS	TBDPS	I
52a.b	Ac	Ac	Br
167a,b	TBDPS	Bn	Br

b)



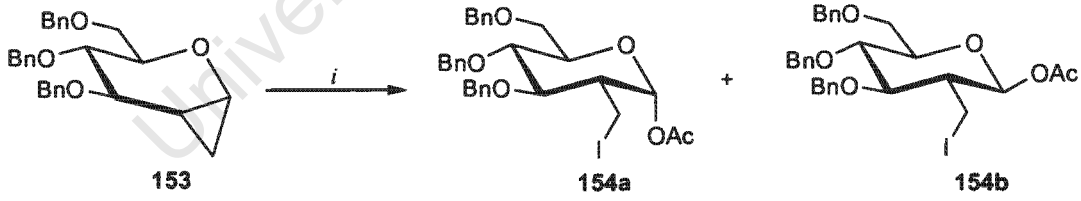
106 **107a** **107b** **107d**

c)



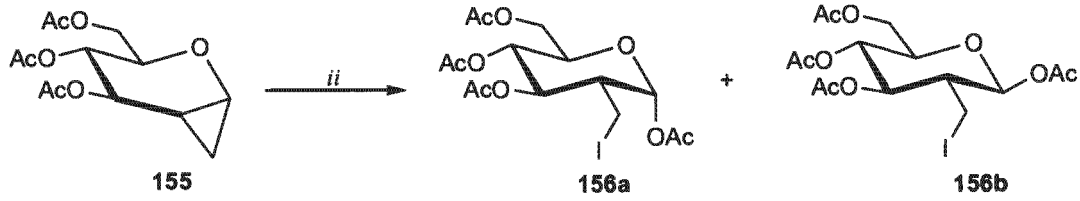
118 **152a** **152b**

d)



153 **154a** **154b**

e)



155 **156a** **156b**

Scheme 2.12. *i)* NH_4X, 50% H_2O_2, Ac_2O, $AcOH/CH_3CN$ (1:1), 0°C (for iodoacetoxylation) or 60°C (for bromoacetoxylation), 25 min – 2 h, refere to Table 2.2 for yields and stereoselectivity; *ii)* NH_4I, 50% aq H_2O_2, Ac_2O, $AcOH/CH_3CN$ (1:1), 60°C, overnight, 96% (2:1, α:β).

Table 2.2. Yields and selectivities in the iodoacetoxylation of protected glycals and cyclopropanated sugars (see Scheme 2.12).

Entry	Substrate	Products	Yield (%)	Ratio
1	**59**	**53a, 53b**	85	83:17
2	**67**	**148a, 148b**	100	91:9
3	**114**	**149a, 149b**	100	93:7
4	**115**	**150a, 150b**	95	93:7
5	**116**	**151a, 151b**	94	17:83
6	**118**	**152a, 152b**	86	44:56
7	**106**	**107a, 107b, 107d**	96	15:1:4
8	**153**	**154a, 154b**	100	3:2
9	**155**	**156a, 156b**	96	3:7
10	**59**	**52a, 52b**	82	5:3
11	**115**	**167a, 167b**	70	3:1

Only the 1,2-*trans* addition products were detected in reactions of the glucals, and in accordance with previous findings the α-*manno* products predominated except in the case of the per-*O*-silylated derivative (entry 5). Selectivity in favour of the *gluco*-isomer in per-*O*-silylated glucal **116** has been explained in terms of the preference in this glycal for the $^{5}H_{4}$ conformation, which minimizes steric interactions of the bulky silyl groups but also restricts access of the electrophile to the β-face of the glucal (Scheme 2.13).[114] Besides the steric factor, the orientation of the net dipole moment that is facing downward favors the formation of an α-halonium ion intermediate and thus results in favour of a *gluco* stereoisomer product.

Scheme 2.13. Conformation of glucal **116**.

The product distribution in the reaction of benzylated galactal **106** (entry 7) was similar to previously reported results with the *talo*-isomer **107a** as the major product, and a significant proportion of the α-*gluco*-isomer **107d** resulting from 1,2-*cis* addition (Scheme 2.12).[90,91]

The selectivities and yields compare very favourably with reported methods, with those obtained with benzyl or silyl protecting groups being the best yet reported, and the reaction conditions are tolerant of a range of protecting groups. The selectivity towards 2-deoxy-2-iodomannopyranosyl acetate increases noticeably from entries 1 - 3, corresponding *inter alia* to changes in the substituent at C-6 from acetyl to benzyl to *tert*-butyldiphenylsilyl. This difference in selectivity could be due to the electron-donating and electron-withdrawing nature of the protecting groups. Electron-donating groups enhance the electron density of the ring oxygen, thereby increasing both the anomeric and reverse anomeric effects. Thus, the electrophilic iodonium ion is directed preferentially to the electron rich face of the glycal. Therefore, as *tert*-butyldiphenylsilyl has more electron-donating character than benzyl and acetyl groups due to stronger hyperconjugation, the electron density enhancement on the ring oxygen is more pronounced, thus affording better selectivity. The same argument applies to the higher selectivity of benzyl protected substrate over acetylated ones.

Interestingly, formation of iodoacetate **151b** using NIS in AcOH required heating at 100°C for 10 min[114] whereas the reaction proceeded at room temperature within 2 h using our method. Iodoacetoxylation of per–*O*-benzylated–D-galactal **106** using the NIS/AcOH protocol afforded β-*galacto*- and α-*talo*-isomers in a ratio of 87:13 (β-*galacto*:α-*talo*).[91] Conversely, our method afforded a ratio of 15:1:4 (α-*talo*:β-*galacto*:α-*galacto*) in excellent yield, which is relatively better than the 3:1 (α-*talo*:β-*galacto*) ratio in 67 - 74% yield reported by Kirschning and co-workers[90] establishing the superiority of our method for the synthesis of α-*talo*-isomer **107a**.

To evaluate the scope and limitations of the method, glucal **118** (entry 6) was converted into the corresponding inseparable iodoacetates, **152a** and **152b** in an almost 1:1 ratio and excellent yield. The benzylidene group survived the reaction conditions indicating the mildness of the method. No side products were evident in the proton NMR spectrum of the crude product. The presence of the benzylidene ring

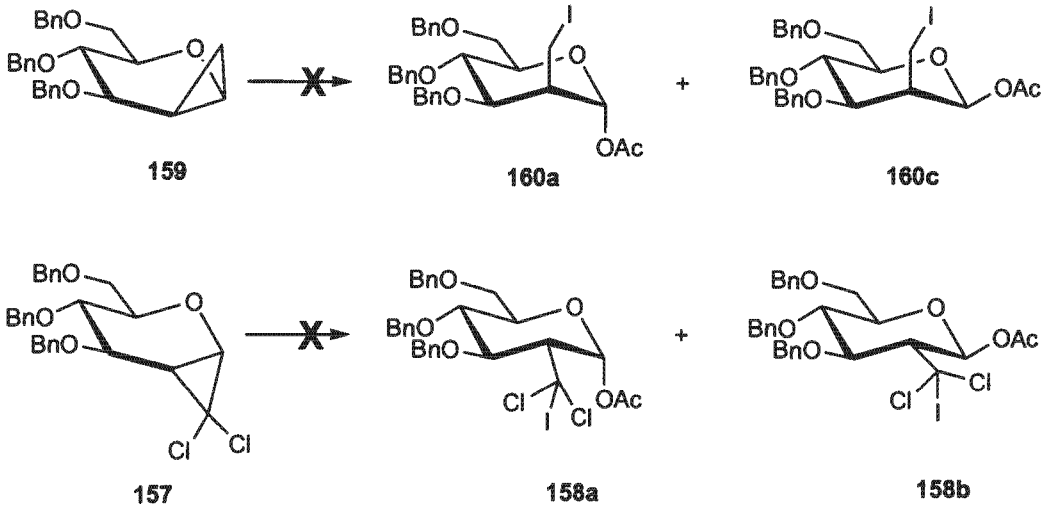
was confirmed by the appearance of the characteristic signals at δ_H 5.61 and δ_C 102.1 together with the aromatic peaks in the NMR spectra of iodoacetate **152a**. This characteristic signal overlapped with the signals of H-3 in the ^{1}H NMR spectrum of iodoacetate **152b**, however, it was clearly evident in the ^{13}C NMR spectrum at δ 101.6. The addition of one acetyl group to the substrate was also proved by the presence of three diagnostic signals at δ_H 2.17, 2.16 and 2.14 (of the mixture of **152a** and **152b**) with an integration of six protons, and δ_C 169.9, 169.1 and 168.3. The poor selectivity of the reaction is no doubt due to the conformational restrictions imposed by the *trans*-fused benzylidene acetal.

Table 2.3. ^{1}H Chemical shifts (δ, ppm) of H-1, H-2 and H-3, multiplicities and coupling constants (*J*, Hz) for the products listed in Table 2.2 at 25°C in $CDCl_3$

Products	H-1			H-2			H-3		
	δ	Mult.	*J* (Hz)	δ	Mult.	*J* (Hz)	δ	Mult.	*J* (Hz)
53a	6.36	d	1.2	4.51	dd	1.6 and 4.4	4.56	dd	4.4 and 9.6
53b	5.87	d	9.6	3.99	dd	9.6 and 10.8	5.34	dd	8.8 and 11.2
148a	6.41	d	2.0	4.46	dd	1.6 and 4.0	3.23	dd	4.0 and 8.0
148b	5.82	d	9.6						
149a	6.45	d	1.5	4.52	dd	1.5 and 4.2	4.60	dd	4.2 and 9.6
149b	5.87	d	9.3	3.98	dd	9.3 and 11.0	5.12	t	9.3
150a	6.45	d	1.6	4.48	dd	1.6 and 4.4	3.25	m	
150b	5.84	d	9.6	4.00	dd	9.6 and 10.4	3.78	dd	9.0 and 10.4
151b	6.54	d	6.9						
107a	6.51	d	2.4	4.32	ddd	0.8, 2.4 and 4.4	3.51	dd	2.4 and 4.4
107b	6.34	d	3.6						
107d	5.82	d	9.6						
152a	6.40	d	1.0	4.69	dd	1.3 and 4.4	4.51	dd	4.6 and 9.7
152b	5.98	d	9.3						
167a	6.40	d	1.6	3.90					
167b	5.78	d	8.8	3.80	dd	8.8 and 10.0			
52a	6.29	d	2.0	4.42	dd	1.6 and 3.7	5.18	dd	3.7 and 9.7
52b	5.81	d	9.2	3.89	dd	9.2 and 10.8	5.33	dd	9.0 and 10.6
154a	6.36	d	3.6	2.24	tt	3.4 and 10.8			
154b	5.59	d	8.4						
156a	6.39	d	3.6	2.40	tt	3.6 and 10.8			
156b	5.65	d	8.8		m				

2.4.2 Iodoacetoxylation of 1,2-cyclopropanated sugars

In view of the success of the above methodology for haloacetoxylation of glycals, it was of interest to explore the extension of this to the cyclopropanated sugars. It is well established[115,116] that cyclopropanated sugars undergo regioselective electrophilic opening to give either the C-2 alkylated hexoses or the ring expanded oxepins (see full discussion on page 67). However, there are no reports of haloacetoxylation and this was accordingly investigated further. In this context, cyclopropanes **153**, **155**, **157**, and **159** were chosen for investigation. Iodoacetoxylation of the dichlorocyclopropane **157** was unsuccessful under both mild (stirring at room temerature) and vigorous (stirring at 50 - 60°C) reaction conditions on the account of the deactivating effect of the chlorides (Scheme 2.14). However, treatment of cyclopropanated sugar **153** with NH_4I/H_2O_2 in $AcOH/MeCN/Ac_2O$ at room temperature resulted in regioselective ring opening to furnish a mixture of iodoacetates **154a** and **154b** in a total yield of 100% and a 3:2 ratio. The reaction was rapid and went to completion in 25 min. The structures were assigned on the basis of analytical results and NMR spectroscopic data (see page 71). Similarly, the acetylated analogue **155** underwent regioselective ring opening at 60°C to afford 96% yield of iodoacetates **156a** and **156b** in a ratio of 3:7 (Scheme 2.12). Regioselective ring opening of benzylated cyclopropanated sugar **159** was unsuccessful even at temperatures as high as 60°C (Scheme 2.14). The starting material was recovered intact after workup. This was in accordance with the results reported by Nagarajan.[117a]



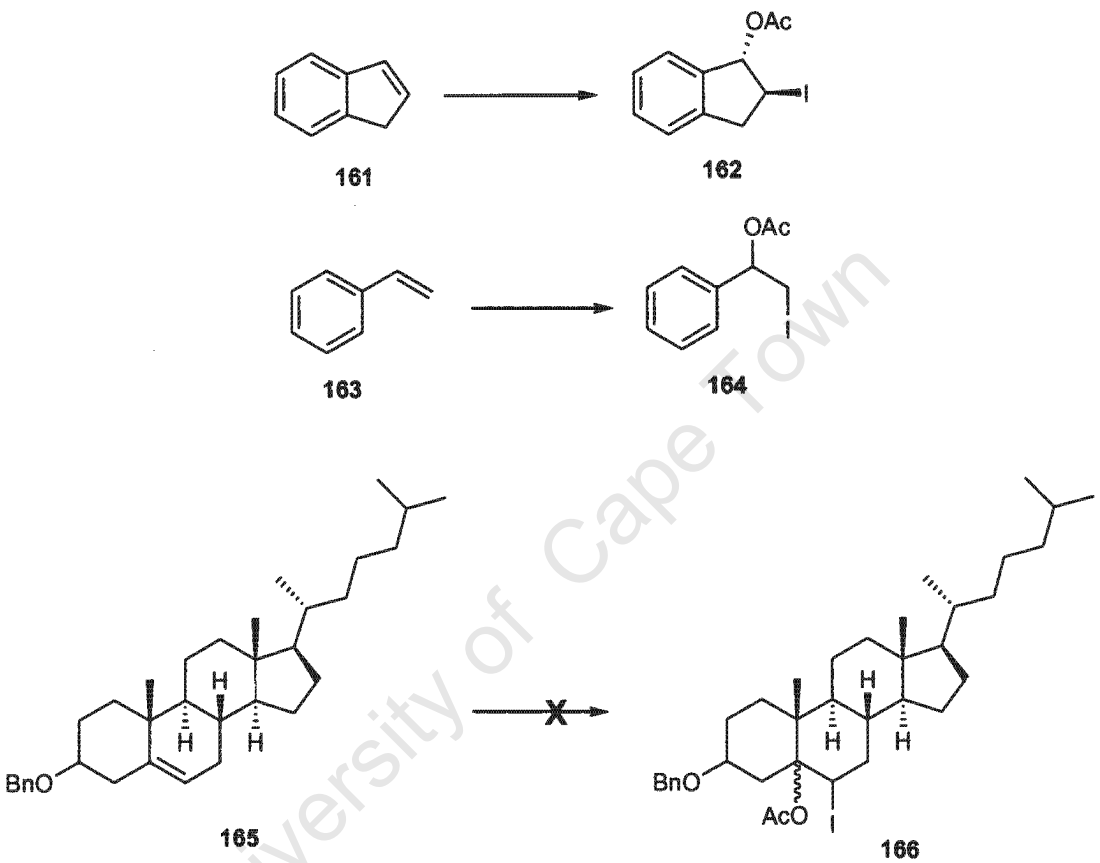
Scheme 2.14. NH_4I, 50% aq H_2O_2, Ac_2O, $AcOH/CH_3CN$ (1:1), rt - 60°C, overnight.

Nagarajan *et al.* reported that the β-isomer was less reactive than the corresponding α-isomer towards NIS based ring opening in the presence of water or methanol. They accounted for the sluggish of the ring opening of β-cyclopropanes due to steric hindrance of the incoming electrophile. Thus, the resistance of the β-cyclopropane to undergo iodoacetoxylation under our reaction conditions suggested that the ring opening of cyclopropanes not only depends on steric effects and nature of solvent but also on the source of the halonium ion.

2.4.3 Iodoacetoxylation of miscellaneous alkenes

The generality of the iodoacetoxylation methodology was further examined by the reaction of relatively electron-poor olefins, such as indene (**161**), styrene (**163**) and cholesterol (**165**). Iodoacetoxylation of **161** furnished *trans*-1-acetoxy-2-iodo-indane (**162**) in 90% yield (Scheme 2.15). The spectroscopic data were in complete agreement with reported values.[118] The diagnostic signals at δ_H 2.10 and δ_C 170.2 and 20.8 were the indicators of the presence of an acetyl group in the product. Similarly, iodoacetoxylation of styrene (**163**) afforded 1-acetoxy-2-iodo-1-phenylethane (**164**) in 67% yield (Scheme 2.15). The NMR spectrum was in agreement with the literature reports.[119] The characteristic acetyl group signals appeared at δ_H 2.13 and δ_C 169.6 and 20.9. Both olefins were converted into their corresponding 1,2-*trans* iodoacetates according to Markovnikov's rule without any traces of 1,2-*cis* iodoacetate products

establishing the high stereoselectivity of the method. However, attempted iodoacetoxylation of cholesterol was unsuccesful both under mild (stirring at room temperature) and more vigorous conditions (heating at 50 - 60°C) (Scheme 2.15). At high temeprature the starting material was destroyed without yielding a major product.

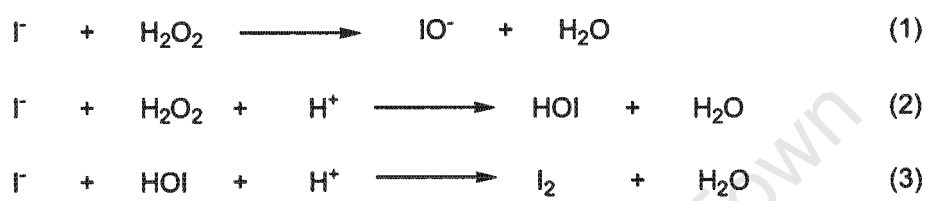


Scheme 2.15. NH_4I, 50% aq H_2O_2, Ac_2O, AcOH/CH_3CN (1:1), rt, 1 h, 90% (**162**) and 67% (**164**).

The possibility of using this methodology for bromoacetoxylation reactions was demonstrated by replacement of NH_4I with NH_4Br in reactions of glycals **59** and **115**, albeit that the bromoacetoxylation is less stereoselective and less reactive. The reaction needed to be heated to 60°C to go to completion. The NMR data of bromoacetates **52a** and **52b** were found to be in complete agreement with the already reported results.[47] The structure and stereochemistry of bromoacetates **167a** and **167b** were formulated on the basis of ^1H and ^{13}C NMR spectra in the same way iodoacetates **150a** and **150b** were analyzed.

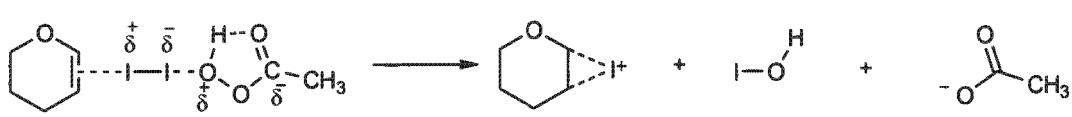
2.4.4 Mechanism of the iodoacetoxylation reaction

Concerning the proposed mechanism of the reaction, the appearance of a brown/yellow color in the reaction solutions upon addition of H_2O_2 to the other reactants suggests the presence of molecular iodine, formed either by reaction of I^- with H_2O_2 under acidic conditions (Scheme 2.16)[120,121] or by reaction of I^- with peracetic acid, generated upon addition of H_2O_2 to acetic anhydride in the presence of acetic acid.[122]



Scheme 2.16. Iodine clock reaction.

It is possible that an initial and rapid formation of a π-complex between the olefin and I_2 is followed by rate-determining abstraction of I^- by the peracetic acid (Scheme 2.17).[122] The preferential formation of β-iodonium ion might have resulted from the electrostatic effects *i.e* orientation of the net dipole moment of the compound. The high degree of stereoselectivity in solvolysis of the resulting iodonium species and the fact that in the absence of acetic anhydride the iodoacetates predominate over iodohydrins suggests that acetic acid attacks the iodonium species directly. The presence of an excess of acetic anhydride ensures that the concentration of water in the reaction mixture is minimized, allowing for successful addition of the acetate or acetic acid to the cyclic iodonium species.

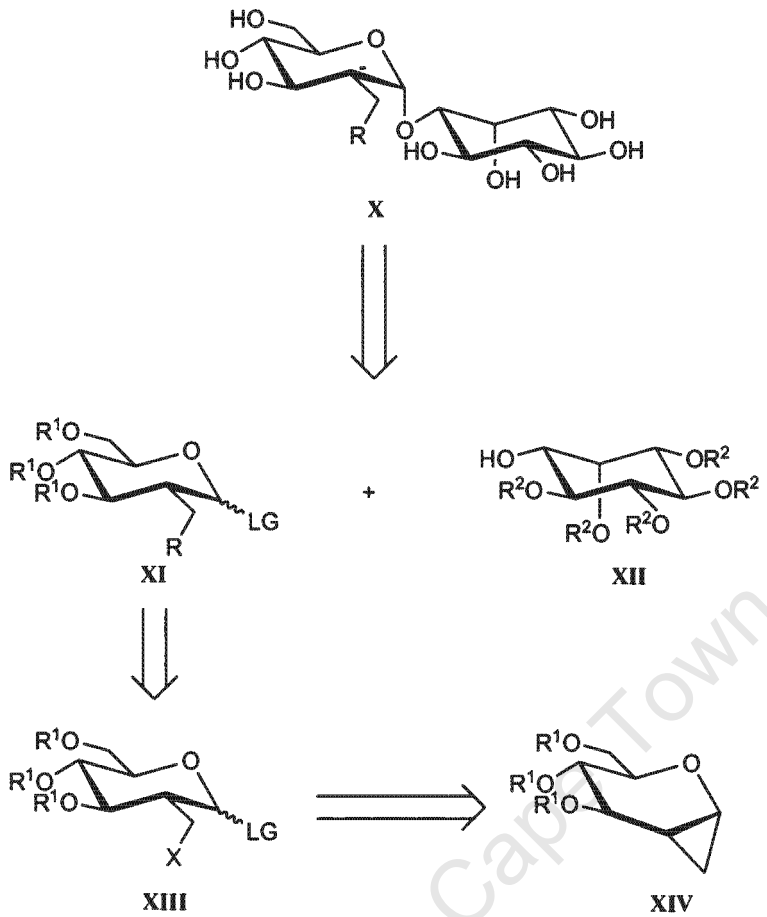


Scheme 2.17. Proposed transition-state of the iodoacetoxylation reaction.

In the case of the bromoacetoxylation, a relatively poor selectivity was observed implying that the path followed was different from the iodoacetoxylation reaction. In the iodoacetoxylation of the glycals, a β-iodonium ion intermediate was evident from the ratio of the products obtained except in the case of the per-*O*-silylated glycal. Conversely, in the bromoacetoxylation reaction two competing routes seem to take part, namely, *via* either a bromonium or oxocarbonium ion intermediates. This observation was in line with previously reported results.

2.5 Towards the Synthesis of Isosteres of Intermediates in the Biosynthesis of Mycothiol

As stated in the general introduction, one of the objectives of this work was to prepare a new family of isosteres of a key biosynthetic intermediate in the production of mycothiol in the *Mycobacteria*. The synthetic target is represented by structure **X** in the retrosynthetic scheme shown below (Scheme 2.18). This was envisaged to arise from glycosyl donor **XI**, bearing the functionalized side chain at C-2 and the appropriately protected inositol unit **XII**. Based on the methodologies described in the earlier part of this thesis, the 2-*C*-halomethyl compound **XIII**, derivable from cyclopropanated sugar **XIV**, was identified as the desired precursor, while the inositol derivative **XII** would be prepared by modification of existing methods. Some of the crucial issues identified for attention were: (a) the choice of LG in glycosyl donor, (b) the timing of the introduction of the R group by displacement of halide X (e.g. before or after glycosylation), (c) the impact of substituents X on the stereoselectivity of the glycosylation step and (d) protecting group strategies.



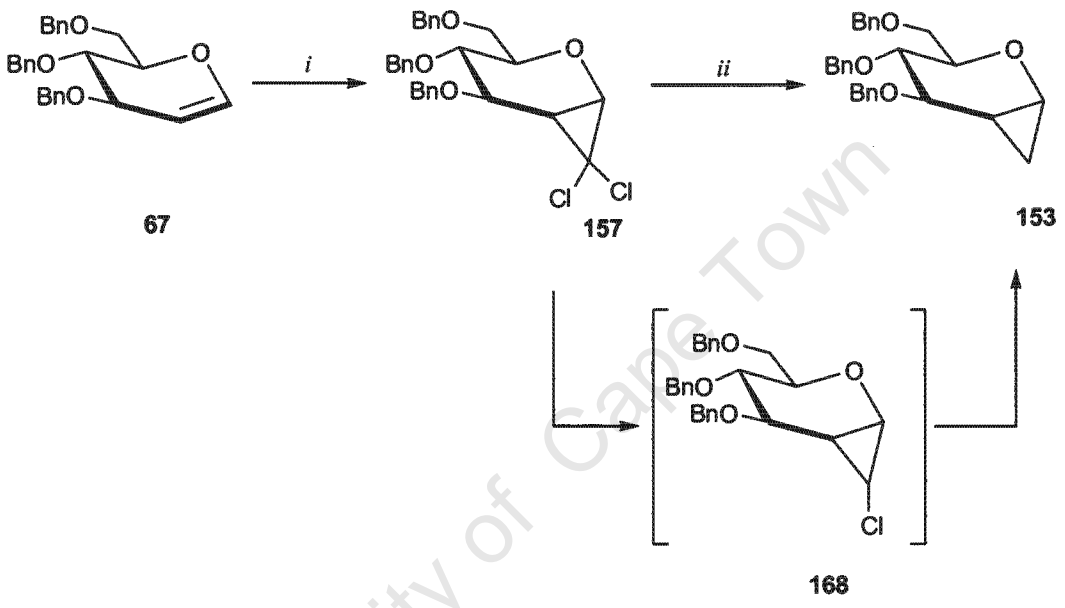
Scheme 2.18. Retrosynthetic analysis of target compounds.

2.5.1 Benzyl protecting group strategy

2.5.1.1 Preparation of benzylated glycosyl donor

The target compounds depicted in Scheme 2.18 contain a 2-*C* branched sugar moiety and it was recognized that these compounds could be fashioned from the versatile chiral building block **XIV**. 1,2-Cyclopropanated sugars have found widespread applications in organic synthesis.[115,116] The high reactivity of strained cyclopropanes in conjunction with the inherent optical purity of sugars makes cyclopropanated carbohydrates indispensable chiral building blocks. Due to the resemblance of cyclopropyl to an olefinic functionality and assistance from the lone pair of electrons on the pyran ring oxygen atom, 1,2-cyclopropanated sugars undergo regioselective ring opening to afford 2-*C* branched and C-1 functionalized sugar derivatives.[117]

When halonium ions are employed as electrophiles to open the ring, the 2-*C* branch is introduced stereoselectively and with functionality which allows further elaboration of the side chain. Through previously established synthetic pathways, cyclopropanated sugar **153** could be prepared in enantiomerically pure form from benzylated D-glucal **67**.[117] Thus, treatment of glucal **67** with chloroform and 50% aq sodium hydroxide in the presence of benzyltriethylammonium chloride as a phase transfer catalyst furnished dichlorocyclopropane **157** in 73% yield (Scheme 2.19).[117]



Scheme 2.19. *i*) $CHCl_3$, 50% aq NaOH, $BnEt_3NCl$, 35°C, 4 h, 73%; *ii*) LAH, THF, rt, 8 days, 75%.

^{1}H NMR spectrum of the crude product revealed the presence of a single isomer of the dichlorocyclopropane **157**. This selectivity is probably due to the orientation of the benzyl substituent at C-3 in glucal **67** which shields one of the two diastereotopic faces of the glucal and induces the cyclopropanation to proceed across the more accessible α–face. The stereochemistry of dichlorocyclopropane **157** was established on the basis of the *J* values associated with H-2 and H-1 in the ^{1}H NMR spectrum. ^{1}H NMR studies of cyclopropanes have shown that the 1,2-*cis* coupling ($J \sim 8$ Hz) is larger than the 1,2-*trans* coupling ($J \sim 4$ Hz).[123-125] In accordance with these reports, H-1 of dichlorocyclopropane **157** appeared as a doublet with a *J* value of 8.0 Hz and a doublet of doublets signal was detected for H-2 with *J* values of 8.0 and 3.9 Hz. The relatively larger coupling constant between H-1 and H-2 indicated that they are *cis* to

each other while the smaller coupling constant between H-2 and H-3 is consistent with *trans*-orientation of these protons in a pyran ring whose conformation is distorted from the normal chair due to the fused cyclopropane ring at C-1 - C-2. The spectroscopic data of **2** were also found to be consistent to that reported by Nagarajan *et al.*.[117]

Reductive dehalogenation of the dichlorocyclopropane **157** with lithium aluminum hydride in dry THF provided the non-halogenated cyclopropane **153** in 75% yield (Scheme 2.19).[117] Comparison of the ^{1}H NMR spectra of dichlorocyclopropane **2** and cyclopropane **153** confirmed the complete dehalogenation. The signal for H-2 at δ_H 0.90 appeared as a multiplet and had moved upfield compared to the corresponding H-2 in dichlorocyclopropane **157** where it appeared as a doublet of doublets at *ca* δ_H 2.0. Furthermore, a multiplet at δ_H 0.70 that integrated for two protons was assigned to the protons attached to C-7. Moreover, all the spectroscopic data were consistent with those recorded in the literature.[117]

It is noted, however, that the dehalogenation reaction did not proceed as smoothly as reported by Nagarajan[117] even though the same reaction scale and conditions were followed. According to the reported methodology, the reaction proceeded to completion within 2 h but in our case took considerably longer. TLC analysis of the reaction mixture after 2 h revealed the disappearance of the dichlorocyclopropane and formation of a new product. The reaction was then quenched by decomposing excess lithium aluminum hydride with saturated aqueous sodium sulphate solution and the resulting white solid removed by filtration and washed several times with hot ethyl acetate. The filtrate was concentrated and the residue chromatographed on silica gel, to give the desired product, cyclopropane **153** together with, surprisingly, a significant proportion of mono-chlorocyclopropanated intermediate **168**,* having the same R_f

* Compound **168** is not included in the experimental section and its mp and NMR data are as follows: mp 62 – 65°C (ethyl acetate/petroleum ether); δ_H ($CDCl_3$, 400 MHz): 7.35 – 7.26 (m, 15H, 3 x Ph), 4.95 (d, 1H, J = 11.6 Hz, CH_2Ph), 4.80 (d, 1H, J = 11.60 Hz, CH_2Ph), 4.69 (d, 1H, J = 12.0 Hz, CH_2Ph), 4.62 (d, 1H, J = 11.2 Hz, CH_2Ph), 4.57 (d, 1H, J = 12.0 Hz, CH_2Ph), 4.48 (d, 1H, J = 12.0 Hz, CH_2Ph), 3.98 – 3.91 (m, 2H, H-3 and H-5), 3.85 (dd, 1H, J = 6.8 and 9.6 Hz, H-4), 3.67 (dd, 1H, J = 5.0 and 7.4 Hz, H-1), 3.61 (d, 2H, J = 4.0 Hz, H-6_a and H-6_b), 3.15 (dd, 1H, J = 5.0 and 8.2 Hz, H-7), 1.31 (dt, 1H, J = 4.9 and 7.8 Hz, H-2); δ_C ($CDCl_3$, 100 MHz): 138.5, 138.2, 138.1, 128.3, 128.2, 128.0,

values on TLC. The mixture was therefore subjected to further treatment with lithium aluminum hydride in THF, monitoring by ^{1}H NMR of portions of the reaction mixture removed at various intervals. The extent of dehalogenation was evident from the disappearance of a signal for H-7 in mono-halogenated cyclopropane **168**, which appeared at δ 3.15 as a doublet of doublets. The reaction was complete after 8 days, and standard work up followed by column chromatography provided the desired non-halogenated cyclopropane **153**. The NMR spectra of the product were in agreement with those reported in the literature.[117]

Before adopting NMR to monitor the progress of the reaction, the mixture was subjected to iodoacetoxylation (will be discussed in detail later) in the hope that the different reactivity of the two compounds and isolation of resulting products would assist in fully identifying the unexpected product **168**. Iodoacetoxylation was monitored by TLC, and after 25 min a new product had formed while starting material was still present. After a further 15 h there was no change to this product distribution. The reaction was then quenched and the two compounds with different R_f values were separated by column chromatography on silica gel. The structure of the unreacted compound was then established with the help of NMR spectroscopy (*i.e* ^{1}H and ^{13}C NMR, COSY, HMQC), from which it was found to be mono-chloro cyclopropane **168**. H-2 resonated around δ_H 1.20 and appeared as doublets of a triplet confirming that H-2 was coupled with three protons, namely, H-1, H-3 and H-7 and this was supported by the COSY spectrum. Doublet of doublets signals each integrating for one proton at δ_H 3.67 and 3.15 due to the H-1 and H-7, respectively, were also confirmations of the assigned structure of the compound. The observed stereoselective reduction could be due to the attack of the LAH from the less hindered (exo) face of the cyclopropyl ring.

Having established conditions for obtaining the desired cyclopropanated glucal **153**, it was available for further manipulation. A number of useful strategies for regioselective electrophilic opening of the cyclopropyl ring have been reported. Examples include the use of mercury (II) salts,[126,127] Zeise's dimer (a platinum

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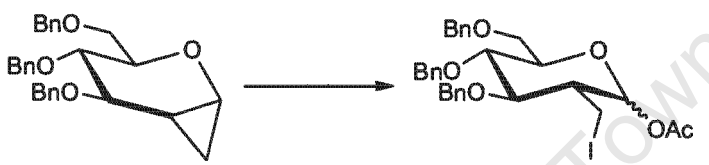
127.7, 127.6, 127.5 (3 x Ph), 80.4, 76.7, 75.8, 74.1, 73.1, 71.4, 70.6 (C-3, C-4, C-5, C-6 and 3 x CH_2Ph), 50.2 (C-1), 36.1 (C-7), 21.2 (C-2).

complex),[128] NIS or NBS, iodonium di(*s*-collidine)perchlorate,[117,129-132] and 30% HBr in acetic acid.[133] However, in our experience, the most effective and convenient method was the protocol developed by our group, which makes use of ammonium iodide and hydrogen peroxide in glacial acetic acid.[134] Besides being eco-friendly, the method provides an anomeric acetate that can be activated for glycosylation. Thus, using conditions reported to achieve efficient iodoacetoxylation of glycals,[134] a solution of cyclopropane **153** in a 1:1 mixture of AcOH/CH_3CN was treated with NH_4I, 50% aq H_2O_2 and Ac_2O to furnish 2-*C* iodomethylacetate **154** as a 3:2 mixture of diastereoisomers, epimeric at C-1, in a yield of 100% (Scheme 2.20).



153 **154**

Scheme 2.20. NH_4I, 50% aq H_2O_2, Ac_2O, AcOH/CH_3CN (1:1), rt, 25 min, 100%.

NMR spectroscopy was again used to establish the structure of the product. The anomeric protons resonated in the appropriate downfield region[1] at δ_H 6.36 and 5.59 and appeared as doublets confirming the opening of the cyclopropyl ring. The smaller coupling constant (J = 3.6 Hz) of the signal at δ_H 6.36 compared to the larger coupling constant (J = 8.4 Hz) of the signal at δ_H 5.59, showed that the former was an α-anomer and the latter was a β-anomer. The other ^{1}H NMR signals that indicated the opening of the ring were those due to H-7_a and H-7_b. They appeared as doublets of doublets in the regions between δ_H 2.60 and 3.80, which was further downfield than the protons of the multiplet at δ_H 0.70 for C-7 in the corresponding cyclopropanated compound **153**. The presence of the acetoxy groups was confirmed by the appearance of two singlets at δ_H 2.14 and 2.10 which corresponded to the acetoxy methyl groups in the β- and α- epimers, respectively. The ^{13}C NMR spectrum provided further confirmation of the assigned structure, showing the carbonyl signals of the acetoxy groups at δ 168.8 and 168.7 and the signals of the methyls of the acetoxy groups resonating at δ 20.8 and 20.7. The presence of the acetate groups was also confirmed from the IR spectrum which showed a strong signal at 1759 cm^{-1}. The significant downfield shift of the anomeric carbons to δ_C 94.9 and 93.6 (C-1β and C-1α,

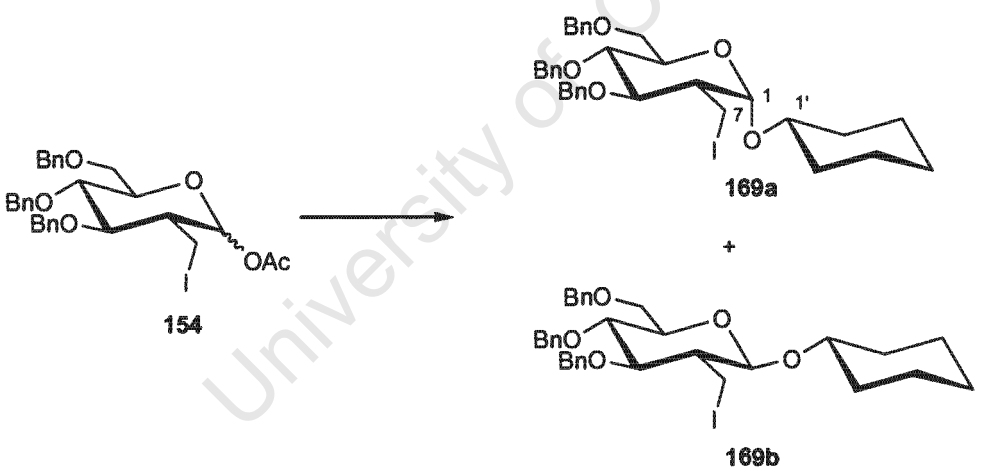
respectively) also confirmed the opening of the cyclopropyl ring.[1] The C-2 and C-7 of the α-anomer of iodoacetate **154** resonated at δ_C 46.6 and 0.6, respectively while the corresponding carbons in the β-anomer appeared at δ_C 45.0 and 4.1, respectively. The further confirmation was obtained from the DEPT spectrum of iodoacetate **154**, it showed that the carbon attached to iodine was a methylene and not a methine group, indicating that ring opening had taken place as opposed to ring expansion.

2.5.1.2 Glycosylation of cyclohexanol with benzylated glycosyl donor

With the 2-*C*-iodomethyl compound **154** in hand, the next steps for preparation of the target analogues called for stereoselective glycosylation of glycosyl acceptors such as cyclohexanol and *myo*-inositol. Anomeric acetates can function as effective leaving groups and thus allowing for direct glycosylation in the presence of Lewis acid activating agents such as $BF_3{\cdot}Et_2O$, $SnCl_4$ and TMSOTf.[1] The stereocontrolling element of a glycosylation reaction is mainly the presence or absence of a participating group at the C-2 position, such as 2-*O*-acyl, 2-*O*-benzoyl, 2-*N*-acyl, 2-*N*-phthaloyl or halide.[2,90] In the presence of such groups at C-2 of a glycosyl donor, the glycosylation proceeds *via* a neighboring group participation and 1,2-*trans* glycoside is formed. However, in the absence of a neighboring group effect other factors such as strength of the promoter, temperature and solvent come into play and a mixture of 1,2-*trans* and 1,2-*cis* glycosides are produced.[1,2] It was thus expected that the iodomethyl group at C-2 in **154** would be non-participatory and that 1,2-*cis* glycosides would predominate due to the anomeric effect.

In the first model studies, the glycosylation of iodoacetate **154** with cyclohexanol was attempted. Thus, when a solution of iodoacetate **154** and cyclohexanol in dichloromethane containing 4Å molecular sieves was treated with $BF_3{\cdot}Et_2O$, glycosides **169a** and **169b** were obtained in 74% combined yield and 2.6:1 ratio (Scheme 2.21).[135] The products were separated by column chromatography and their identities established by NMR studies and analytical methods. In the case of glycoside **169a**, the presence of the cyclohexyl methylene groups was evident from the signals in both the ^1H and ^{13}C NMR spectra. They appeared in the region of δ_H 1.97 – 1.25 and δ_C 33.4 - 23.8. However, the signals of H-1' and C-1' appeared further downfield in both the ^1H and ^{13}C NMR spectra. The ^1H NMR spectrum displayed additional

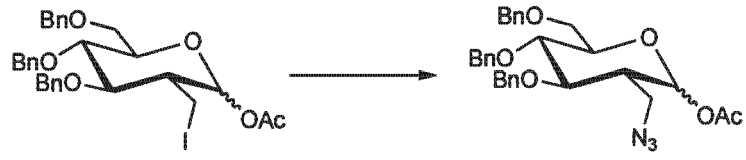
diagnostic signals at δ 5.22 (d) for H-1, δ 3.52 (dd) for H-7_a, δ 3.06 (AB type of dd) for H-7_b, and δ 2.19 (tt) for H-2. The signals of the corresponding carbons were displayed at δ 97.9 for C-1, 48.6 for C-2 and 3.3 for C-7. The diagnostic signals for the β-anomer were analogous to those in α-anomer. The stereochemistry of the α-anomer and β-anomer at the anomeric center was determined by comparing the coupling constants of the H-1 protons from the ^{1}H NMR spectrum and the relative shift of the respective carbons in the ^{13}C NMR spectrum. The H-1 of glycoside **169a** appeared as a doublet at δ 5.22 with a moderate axial-equatorial coupling constant of 3.3 Hz while the corresponding proton in glycoside **169b** appeared upfield at δ 4.45 as a doublet with a large diaxial coupling constant of 8.0 Hz, thus confirming glycoside **169a** was the α-anomer and glycoside **169b** the β-anomer. The anomeric carbon of glycoside **169b** resonated at δ_C 101.4 while the C-1 of glycoside **169a** appeared further upfield at δ_C 97.9, thus affirming the assigned anomeric configuration. This was in accordance to the report that in glycosides the C-1 of the β-anomer appears downfield relative to the corresponding α-anomer.[1]



Scheme 2.21. Cyclohexanol, $BF_3{\cdot}Et_2O$, 4Å molecular sieves, CH_2Cl_2, 0°C – rt, 1 h, 54% (**169a**) and 20% (**169b**).

The results of the above glycosylation reaction confirmed that the anomeric acetates of compound **154** could be activated for effective *O*-glycosylation and that the iodide remained intact under such reaction conditions. However, no definite conclusion could be drawn on whether the iodide provided any anchimeric assistance during glycosylation. To investigate this further, the iodide in iodoacetate **154** was

substituted with a non-participatory azido group in order to observe if there would be any change in the distribution of products during subsequent glycosylation. Thus, treatment of a solution of iodoacetate **154** in DMF with sodium azide provided azidoacetate **170** in a yield of 97% (Scheme 2.22).[136] The ^{1}H NMR spectrum of the product was similar to the starting material.



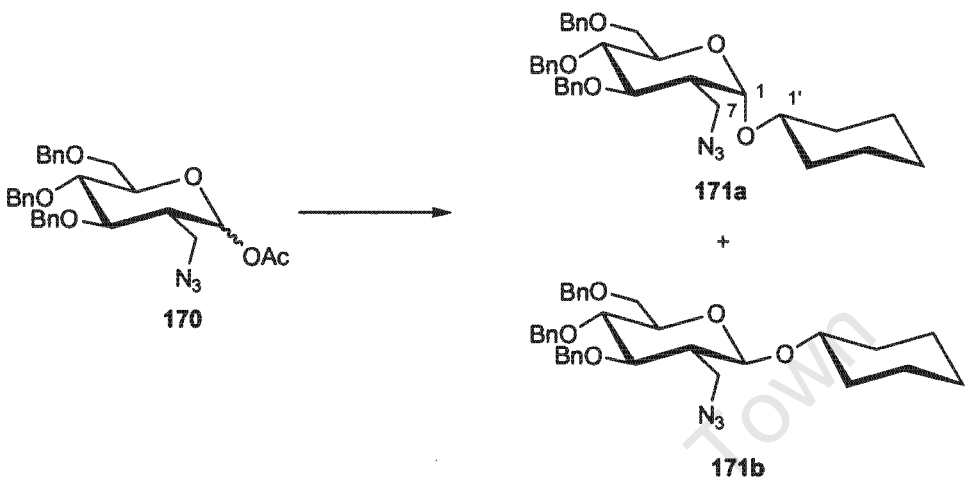
154 **170**

Scheme 2.22. NaN_3, DMF, rt, 4 h, 97%.

The substitution of the iodide by the azide was confirmed by two observations: firstly, comparison of the ^{13}C NMR signals for C-7 in iodoacetate **154** and azidoacetate **170** showed a downfield shift to δ 49.4 (for the α-anomer) and 47.6 (for the β-anomer) from δ 4.1 (for the α-anomer) and 0.6 (for the β-anomer) in iodoacetate **154**; secondly, the characteristic azide group stretches were observed at 2104 and 1144 cm^{-1} in the IR spectrum.[137]

A 1:2 anomeric mixture of azidoacetates **170** was then combined with cyclohexanol in dichloromethane in the presence of 4Å molecular sieves and $BF_3{\cdot}Et_2O$ as promoter.[135] The reaction furnished separable ~2:1 mixtures of glycosides **171a** and **171b** in a combined yield of 87% (Scheme 2.23). As before, the structures of the products were established with the help of NMR spectroscopy and elemental analysis. The presence of the cyclohexyl groups was indicated by the appearance of the methylene signals in the region of δ_H 1.90 – 1.20 and δ_C 34.0 – 23.0. In the ^{1}H NMR spectrum of glycoside **171a,** the anomeric proton appeared as a doublet with a coupling constant of 3.6 Hz, thus confirming the α-anomer. The other diagnostic signals that correspond to H-7_a, H-7_b, and H-2 appeared at δ 3.61 (dd), 3.26 (AB type dd) and 2.09 (tt), respectively, as established by COSY and HMQC. The ^{13}C NMR spectrum of glycoside **171a** displayed the signal of C-1 at 95.9 which suggested that the configuration at the anomeric center was α. C-1' of the cyclohexyl group resonated at δ 77.5 confirming the formation of the glycosidic bond with the sugar donor. C-2 and C-7 showed no

significant shift and appeared at δ 46.5 and 50.1, respectively. The diagnostic signals of glycoside **171b** were analogous to those in glycoside **171a** and its structure was established in the same way. These results confirm that the iodide group does not appear to provide anchimeric assistance, and suggest that glycosylation occurs predominantly *via* an S_N2-type of mechanism.

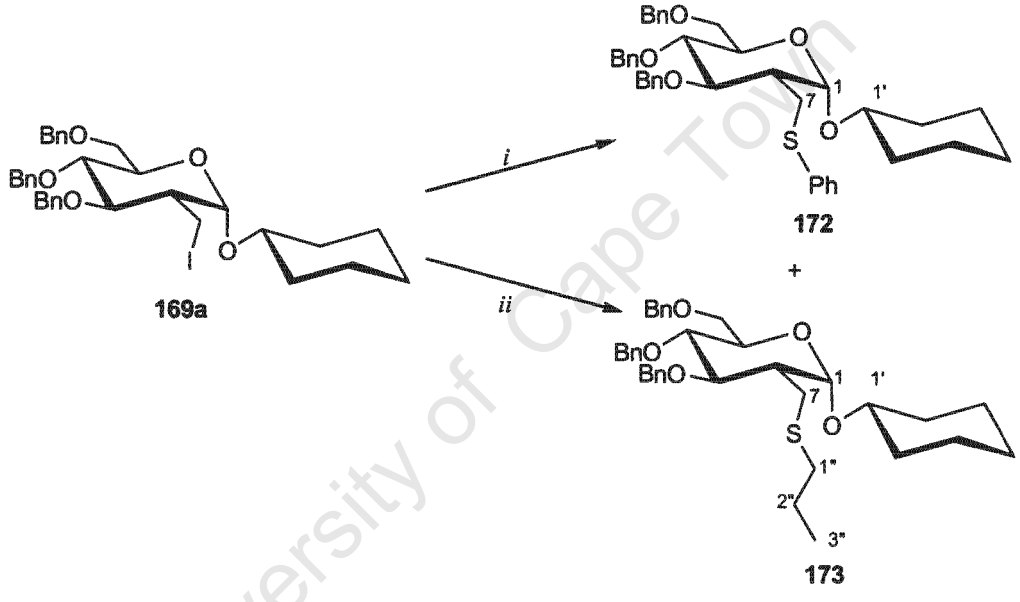


Scheme 2.23. Cyclohexanol, $BF_3{\cdot}Et_2O$, 4Å molecular sieves, CH_2Cl_2, 0°C – rt, 5 h, 57% (**171a**) and 30% (**171b**).

2.5.1.3 Manipulation of the C-2 iodomethyl group to provide sulfide, sulfoxide, and sulfone analogues

After successful glycosylation, our focus turned to investigate introduction of sulfoxide and sulphone functionalities in the side chain, and establishing deprotection strategies with these in place. The preparation of these intermediates entailed thiolation at C-7 in iodide **169a** and several thiolation methods were investigated. In a first attempt, a solution of iodide **169a** in dichloromethane was treated with phenolthiolate salt prepared *in situ* from thiophenol and triethylamine in dichloromethane.[138] Even though the reaction furnished 85% yield of the desired product after stirring overnight, a large excess of reagents was required and as a consequence the workup was not easy due to the repellent smell of the thiophenol. Besides a concern for the stoichiometry of the reagents, attempts at using 1-propanethiol instead of thiophenol were unsuccessful disproving the generality of the protocol. Consideration was thus given to an alternative approach. The use of a thiol with sodium hydride as reported by Stasik *et al.* allowed easy thiolation of iodide

169a.[139] When a solution of iodide **169a** in THF was added to equimolar solution of thiophenol and sodium hydride in a 1:1 mixture of THF and DMSO, sulfide **172** was instantly obtained in 84% yield (Scheme 2.24).[139] The presence of an additional aromatic group in sulfide **172** was confirmed from the ^{1}H NMR spectrum as the integration of the aromatic signals corresponded to 20 protons. The diagnostic signals such as the H-1, H-2, H-7_a and H-7_b did not shift significantly and appeared at δ_H 5.25 (d), 2.10 (tt), 3.38 (dd) and 2.80 (AB type dd), respectively. But the signal of C-7 in the ^{13}C NMR spectrum shifted downfield to δ 30.8 as compared to the corresponding C-7 in iodide **169a** and suggested the substitution of the iodide.



Scheme 2.24. *i*) PhSH, NaH, DMSO/THF (1:1), rt, 5 min, 84%; *ii*) *n*-PrSH, NaH, DMSO/THF (1:1), rt, 5 min, 92%.

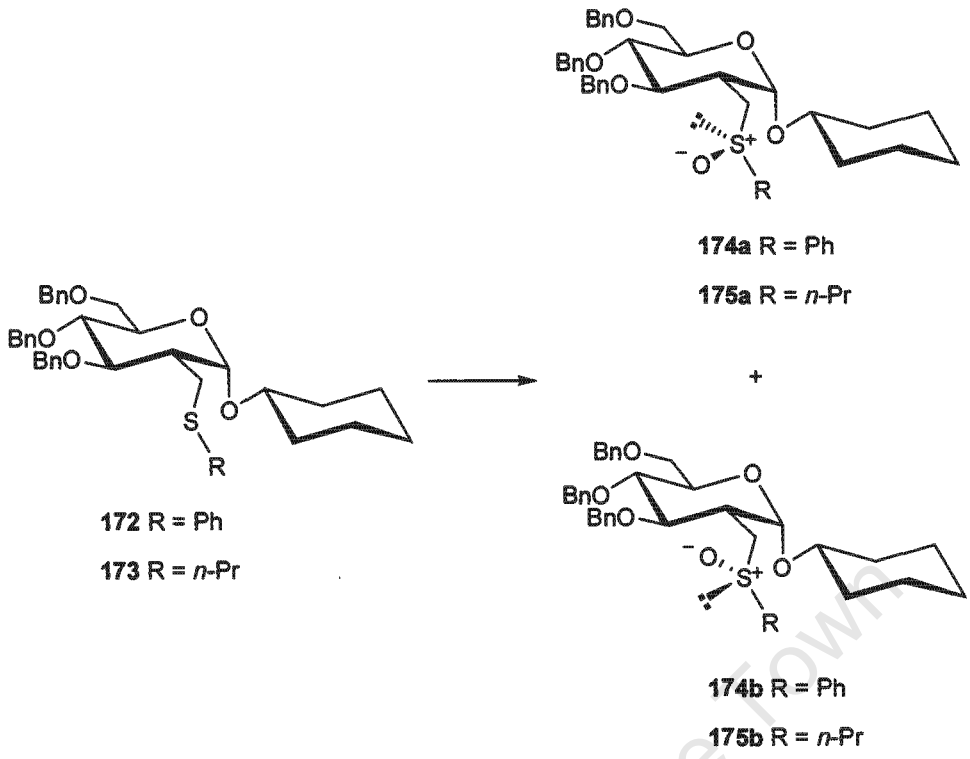
When a solution of iodide **169a** in THF was added to a solution of 1-propanethiol and sodium hydride in a 1:1 mixture of THF and DMSO, sulfide **173** was also produced in a yield of 92% (Scheme 2.24).

The signals of the *n*-propyl group in both ^{1}H and ^{13}C NMR spectra with the aid of 2D NMR studies were helpful in confirming the structure of the compound. The H-1" peaks overlapped with H-7_b signals and resonated in the region of δ_H 2.51 – 2.38; the methylene protons of H-2" appeared in the region δ_H 1.93 – 1.16 along with the cyclohexyl signals. The methyl group of the *n*-propyl group appeared distinctively at

δ_H 0.96 as a perfect triplet. The corresponding carbon signals appeared at 34.5, 23.1 and 13.6, respectively. As was the case in sulfide **172**, the C-7 in sulfide **173** resonated at δ_C 29.8 confirming the substitution of the iodide.

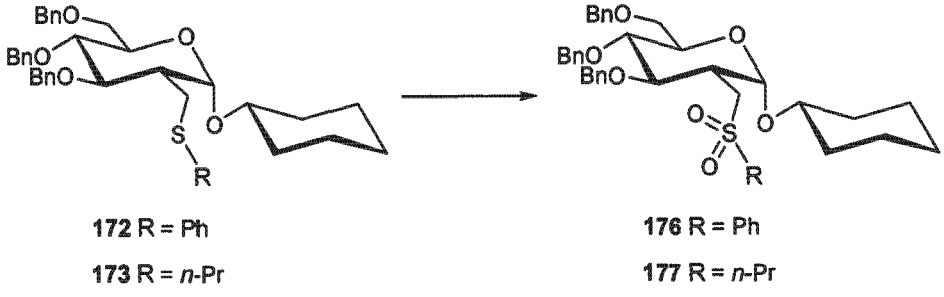
With the sulfides in hand, it was possible to synthesize the corresponding sulphoxides and sulphones. Sulphoxides and sulphones are prepared by oxidation of the corresponding sulphides and several synthetic protocols have been reported for effective oxidation. Hydrogen peroxide (aqueous),[140] urea-hydrogen peroxide,[141] hydrogen peroxide with trirutile-type solid oxide ($LiNbMoO_6$),[142] *m*-chloroperbenzoic acid,[143] OXONE®* in the presence of wet alumina,[144,145] and *tert*-butylhydroperoxide[145] with or without alumina are some of the reagents reported to achieve transformation of alkyl- and arylsulfides to corresponding sulphoxides and sulphones. Even though most of these protocols are efficient, they suffer major drawbacks associated with toxicity and problems during workup. Among the different methodologies reported, the method reported by Greenhalgh[144a] was found to be operationally convenient due to simple workup and control of addition of the required stoichiometric amount of the reagents. Reaction of sulfide **172** with one equivalent of OXONE® supported with wet alumina in dichloromethane at 32°C afforded inseparable diastereomeric mixture of sulphoxides **174a** and **174b** (*ca* 1:1) (the assignment is tentative) in a total yield of 75% (Scheme 2.25).[144] Attempts to separate the two diastereoisomers with column chromatography and recrystallization were unsuccessful. However, ^{1}H NMR examination of the mixture enabled the respective isomeric components to be distinguished by comparison of the chemical shifts of the signals for the H-1 protons. The H-1 of one of the diastereoisomers appeared as a doublet at δ_H 5.22 while the H-1 of the other isomer appeared at δ_H 5.12 as a doublet. Both signals had the same coupling constant of 3.2 Hz. The C-1 and C-2s were also distinguishable in the ^{13}C NMR spectrum. The C-1s resonated at δ 96.9 and 96.2 while the C-2 peaks appeared at δ 42.7 and 41.3. The presence of the sulphoxide functionality was confirmed when the IR spectrum of the diastereoisomers displayed a signal at 1028.[137,144c] In the same way, sulphoxide **175** was obtained as a 3:7 mixture of diastereoisomers in a yield of 82% (Scheme 2.25). The diagnostic signals obtained in the NMR and IR spectra were analogous to sulphoxide **174**.

* OXONE® is a 2:1:1 mixture of $KHSO_5$ (the active ingredient), $KHSO_4$ and K_2SO_4.



Scheme 2.25. Al_2O_3, H_2O, OXONE®, CH_2Cl_2, 32°C, 7 h, 75% (**174**) and 82% (**175**).

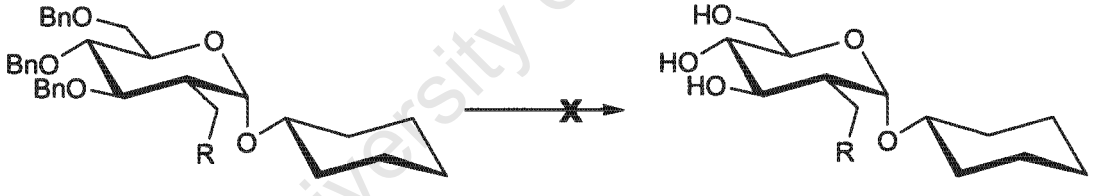
When sulfides **172** and **173** were treated with excess OXONE® for a longer reaction time under otherwise similar conditions to those used in the synthesis of sulphoxides, sulphones **176** and **177** were obtained in excellent yields, presumably *via* the corresponding sulphoxides (Scheme 2.26).[144] The structures of the products were established with the aid of ^1H and ^{13}C NMR spectroscopy along with COSY and HMQC spectra. The presence of the sulphone functionalities were confirmed by IR analysis. The appearance of absorptions at 1306 and 1124 cm^{-1} for sulphone **176** and 1309 and 1127 cm^{-1} for sulphone **177** confirmed the presence of sulphones.[137,144c]



Scheme 2.26. Al_2O_3, H_2O, OXONE®, CH_2Cl_2, 32°C, overnight, 95% (**176**) and 100% (**177**).

It is known that the wet alumina serves as a medium of the oxidation. The OXONE® is dispersed on the surface of the alumina adsorbent creating contact between the active ingredient ($KHSO_5$) and the sulfide. As judged from the results obtained, the extent of oxidation depends on the stoichiometry of the reaction, with the use of excess equivalents of OXONE® resulting in the formation of sulphones. Chiosis and co-workers reported that excessive wetting of the alumina favours formation of sulphoxides over sulphones.[144,145] Hence, prior to use, activation of the alumina at 120°C for 48 h was recommended.

During the planning stages of this synthesis, the task of achieving a global debenzylation of intermediates **174 - 177** was probably not considered as being too difficult. Although sulphur in the oxidation state II is usually not compatible with cleavage of benzyl protecting groups by palladium catalyzed hydrogenolysis, hydrogenolysis in the presence of sulphoxides and sulphones are routinely carried out in organic synthesis.[146] Unfortunately, however, the seemingly straightforward debenzylation reaction in intermediates **174 - 177** proved to be the most difficult step in the synthesis towards the target molecules (Scheme 2.27).



174 R = PhS(O)

175 R = *n*-PrS(O)

176 R = $PhS(O_2)$

177 R = *n*-$PrS(O_2)$

178 R = PhS(O)

179a R = *n*-PrS(O)

180 R = $PhS(O_2)$

181a R = *n*-$PrS(O_2)$

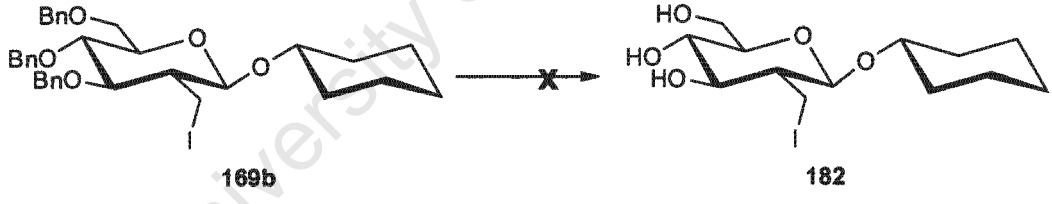
Scheme 2.27. 10% Pd/C, EtOH, rt, 1 – 5 bar, two weeks.

Several hydrogenolysis attempts under a balloon filled with a hydrogen gas led solely to recovery of starting material. However, when the same reaction was carried out at pressures as high as 5 bar, a relatively less polar product (judged from TLC) was formed, which presumably resulted from hydrogenation of the aromatic rings. Besides

hydrogenolysis, catalytic transfer hydrogenation attempts were made without any success. Some of the attempts include utilizing palladium on carbon and formic acid[147] or ammonium formate[148] as sources of hydrogen and palladium hydroxide on carbon and cyclohexene.[149] Another failed attempt involved the use of BBr_3 to cleave the benzyl groups.[150] Birch reduction was considered but a survey of the existing literature showed the incompatibility of the method with sulphoxides and sulphones.[151]

2.5.1.4 Timing of debenzylation in the reaction sequence

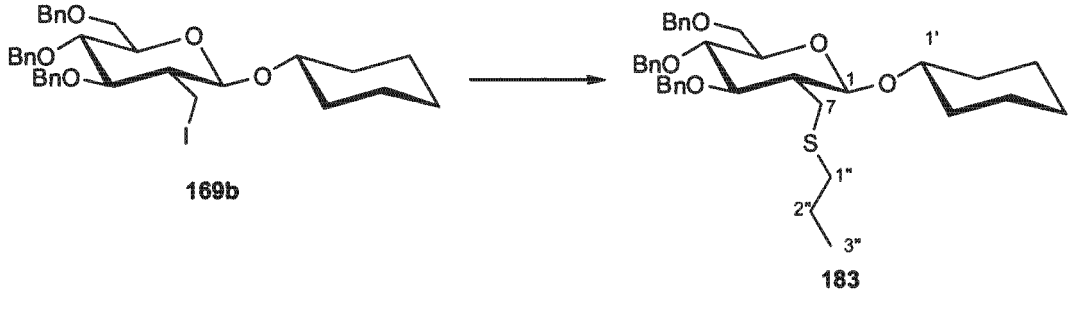
The failure to deprotect the benzyl groups at the final step led us to investigate the timing of the deprotection prior to oxidation of the sulfides and replace the benzyls with milder protecting groups. The β-glycoside **169b** was identified as a useful precursor. However, hydrogenolysis of glycoside **169b** itself was not successful. Prolonged treatment with hydrogen over palladium on activated carbon gave several products with the brown colour of the ensuing solution suggesting the possible displacement of the iodide in **169b** (Scheme 2.28).[146a]



169b **182**

Scheme 2.28. 10% Pd/C, EtOH, H_2, 1 bar, two weeks.

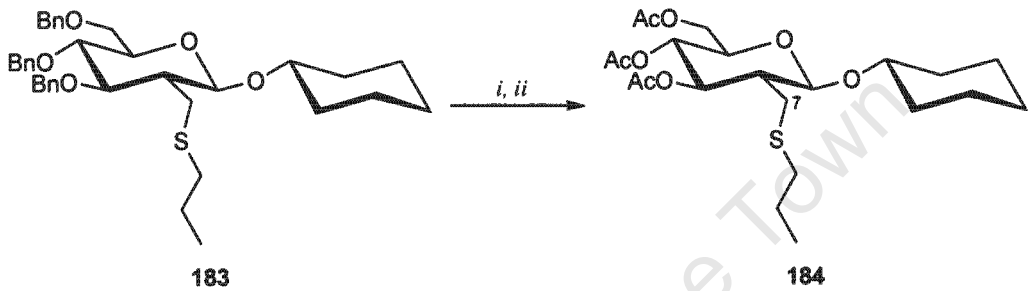
It appeared, therefore, that the only remaining option was to attempt removal of the benzyl groups from sulfide **183,** prepared as shown in Scheme 2.29.



169b **183**

Scheme 2.29. *n*-PrSH, NaH, DMSO:THF (1:1), rt, 5 min, 100%.

An attempt at hydrogenolysis of sulfide **183** was unsuccessful, presumably due to poisoning of the palladium catalyst by the sulphide.[146] This led to consideration of cleavage of the benzyl ethers by Birch reduction even though carbon-sulfur bonds are reportedly easily reduced[152] under these conditions. Thus, when a solution of sulfide **183** in dry THF was exposed to a blue solution of calcium in liquid ammonia,[151] the benzyl groups were removed to give, after treatment of the crude products with acetic anhydride in pyridine in the presence of DMAP, the acetylated compound **184** in a yield of 55% (Scheme 2.30).



183 **184**

Scheme 2.30. *i*) Ca, NH_3, reflux, 20 min; *ii*) Ac_2O, DMAP, pyridine, rt, overnight, 55% (over 2 steps).

The survival of the *n*-propyl group was confirmed from ^1H and ^{13}C NMR spectra. The signals of H-1"s and H-2"s appeared as multiplets in the region of δ_H 2.50 – 2.38 and 1.62 – 1.50, respectively, whereas the H-3"s were revealed at δ_H 0.96 as a symmetrical triplet. The signals of the corresponding carbons appeared at δ_C 35.9, 24.0 and 13.3, respectively. Additional confirmation was the signal of C-7 that appeared at δ_C 29.3 without a significant shift as compared to the signal observed in sulfide **183** (δ_C 29.7). The presence of the three acetoxy groups and the cyclohexyl moiety were evident in both ^1H and ^{13}C NMR spectra of sulfide **184**.

These model studies therefore demonstrated that chemoselective removal of benzyl protecting groups in the presence of a sulphide was possible using the Birch reduction. Before investigating further the compatibility of deacetylation of the acetyl protecting groups in the presence of sulfoxides and sulfones, the successful debenzylation findings prompted us to consider alternative route to the synthesis of acetylated glycosides such as **184** using acetylated glycosyl donors.

2.5.2 Acetyl protecting group strategy

2.5.2.1 Synthesis of acetylated 1,2-cyclopropanated sugar

As is the case with the benzylated glycosyl donor **153** (Scheme 2.19), 1,2-cyclopropanated glucose **155** (Figure 2.3) was identified as an ideal starting material for the synthesis of sulfide **184**.

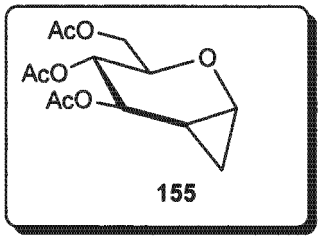
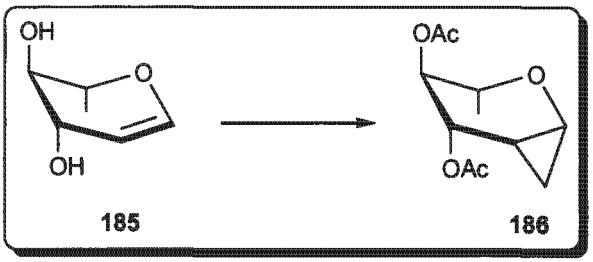


Figure 2.3. Acetylated 1,2-cyclopropanated sugar.

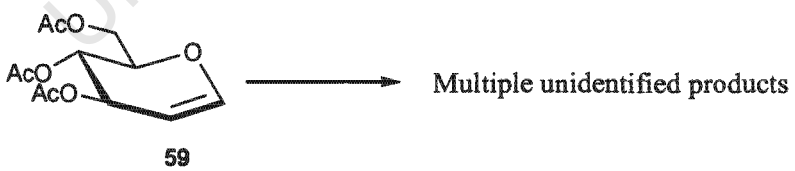
The most common methods of preparing cyclopropanated sugars are: the Simmons-Smith reaction,[117,153,154] dihalocarbene cyclopropanation[117,155,156] and diazocyclopropanation.[133,157,158] The Simmons-Smith cyclopropanation involves treating a glycal with CH_2I_2/Zn/CuCl activated with acetyl chloride. The method was later modified by Furukawa in which diethyl zinc was employed instead of Zn/Cu.[159] Under those conditions a cyclopropane *syn* to the oxygen of the C-3 of the respective glycal is formed. On the other hand, the dihalocarbene cyclopropanation of glycals affords a cyclopropane with a stereochemistry opposite to that of the Simmons-Smith cyclopropanation. The dihalocarbene which adds to the double bond is generated from the reaction of chloroform and aqueous NaOH solution in the presence of a phase transfer catalyst (see page 68). Dehalogenated cyclopropane is obtained upon reduction with LAH (see page 69). Although cyclopropanation of glycals with a wide range of protecting groups has been successful under the Simmons-Smith condition, attempts at direct cyclopropanation of corresponding per-*O*-acetylated glycals are messy and very low yielding.[115,116,154] The best yield recorded is 38% and contrary to the expectations, the stereochemistry of the product formed was *trans* to the acetoxy group at C-3 of the glucal.[160] The problem associated with acetyl protecting groups has been solved by using partially protected substrates and quenching the

cyclopropanation reaction with acetic anhydride to afford acetylated product (Scheme 2.31).[154]



Scheme 2.31. *i*) Et_2Zn, CH_2I_2, Et_2O, 0°C for 4 h and then reflux for 6 h (8.7:1, β:α); *ii*) Ac_2O, rt, 12 h, 85%.

Since no direct or indirect method has been reported to adequately alleviate the problems associated with synthesis of fully acetylated glycals, we settled for the 38% yield using the Furukawa modified method as reported by Lorica. However, following the procedure reported by Furukawa,[154,159] treatment of a solution of glucal **59** in diethyl ether with diethyl zinc in the presence of diiodomethane unfortunately resulted in progressive decomposition to an intractable mixture of products as judged from the TLC of the reaction mixture (Scheme 2.32). Attempts to separate the products were not successful and the method was abandoned. An indirect synthetic methodology was then considered, based upon selective debenzylation of benzylated cyclopropanated glucose **157**, followed by acetylation of the resulting triol.

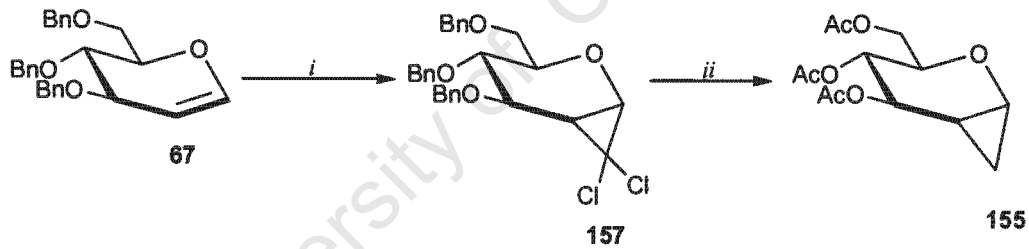


59

Scheme 2.32. Et_2Zn, CH_2I_2, Et_2O, rt, 1 h.

The synthesis therefore began with benzylated glucal **67**, which, as discussed earlier, undergoes direct dichlorocyclopropanation using the method reported by Nagarajan and co-workers[117] to provide dichlorocyclopropane **157** in 73% yield. Once the dichlorocyclopropane intermediate was obtained, there were two routes that could possibly lead to the desired product **155**. The first option was to simultaneously

remove the benzyl groups and chlorides and then acetylate the resulting triol; the second possibility was to first carry out dehalogenation using LAH to yield cyclopropane **153** (Scheme 2.19) followed by global debenzylation and then acetylation of the resulting triol. The first option was attractive for two reasons: firstly, it would avoid the difficulties of dehalogenation experienced during the synthesis of cyclopropane **153** and secondly, it was one step shorter than the second option. Thus, the dichlorocyclopropanated sugar **157** was treated with calcium dissolved in liquid ammonia, using the conditions reported to cleave *O*-benzyl protecting groups.[151] After ten minutes of reflux in ammonia, the formation of a more polar, non-UV active product was evident from TLC. In agreement with the results reported earlier, longer reaction time resulted in formation of a number of by-products. After quenching of the reaction by careful addition of ammonium chloride and evaporation of the ammonia, acetylation of the crude product using acetic anhydride and DMAP in pyridine afforded the desired product **155** as a low-viscosity oil in 60% yield (over two steps, Scheme 2.33).



Scheme 2.33. *i*) $CHCl_3$, 50% aq NaOH, $BnEt_3NCl$, 35°C, 4 h, 73%; *ii*) (a) Ca, NH_3, reflux, 10 min; (b) Ac_2O, DMAP, pyridine, rt, overnight, 60%.

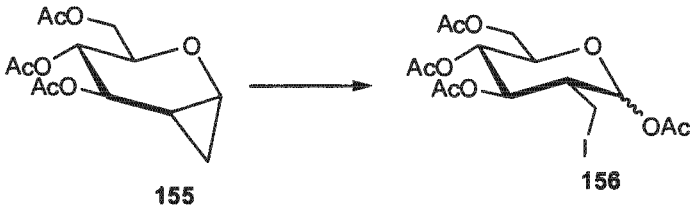
Our experience was contrary to that of Lorica *et al.*[160] who reported the state of the product as solid and established the structure of the compound mainly on the basis of IR analysis, with incomplete NMR data provided. A thorough NMR analysis was therefore required to establish the structure of acetylated cyclopropane **155**. The ^{13}C NMR spectrum showed the expected 13 signals. In the ^{1}H NMR spectrum, the multiplicity of the H-2 signal increased and the signal moved further upfield relative to the corresponding H-2 in dichlorocyclopropane **157**, resonating at around δ 0.98. The triplet of doublet of doublets at δ 0.86 integrating for two protons was assigned to the protons attached to C-7, thus confirming complete dehalogenation. The complete

dehalogenation was also supported by the appearance of the C-2 and C-7 signals upfield at δ_C 13.7 and 11.1, respectively. The signal of H-3 appeared as a doublet of doublets with coupling constants of 3.0 and 6.3 Hz. The small coupling constant was assigned to $J_{2,3}$ as evidenced from the H-4 signal that appeared as doublet of doublets with 4.5 and 6.3 Hz coupling constants and it suggested a diaxial arrangement and thus confirmed the presence of the cyclopropyl group (typical of cyclopropanes).[123-125] In addition, H-1 appeared at δ 3.62 as a doublet of a triplet with *J* values of 3.0 and 6.0 Hz confirming that the cyclopropyl group was intact during the reduction. The presence of the three acetoxy groups was confirmed from both the ^{1}H and ^{13}C NMR spectra. The methyls of the acetoxy groups displayed singlet peaks at δ 2.09, 2.08 and 2.07 in the ^{1}H NMR spectrum and at δ 21.0, 20.8 and 20.7 in the ^{13}C NMR spectrum. The diagnostic carbonyl signals of the acetoxy groups were also displayed at δ_C 170.6, 169.8 and 169.7.

2.5.2.2 Preparation and glycosylation of acetylated glycosyl donor

After synthesizing cyclopropanated sugar **155** in a reasonable yield, the attention turned to regioselective opening of the cyclopropyl ring of the compound. Thus, when cyclopropane **155** was treated with ammonium iodide, hydrogen peroxide and acetic anhydride in a 1:1 solution of AcOH/CH_3CN at 50°C, iodoacetate **156** was obtained in 96% yield as a 3:7 mixture of anomers (α:β).[134] Since compounds such as cyclopropane **155** with a leaving group at C-3 (acetyl groups) undergo ring expansion upon treatment with a Lewis acid and a nucleophile,[154] there were fears that we might encounter ring expansion rather than regioselective ring opening. Fortunately, the reaction resulted in exclusive ring opening of the cyclopropyl ring. This was confirmed by the appearance of two anomeric doublets of the α- and β-anomers at δ_H 6.38 and 5.65, respectively. And the respective anomeric carbons resonated at δ_C 92.8 and 94.7, thus confirming the anomeric assignment. The signals of C-2 moved downfield to δ_C 45.4 (α-anomer) and 43.4 (β-anomer) while the signals of C-7 shifted further upfield to δ_C 0.43 (β-anomer) and -2.0 (α-anomer). These relative shifts of C-2 and C-7 were consistent to the signals obtained in the ^{13}C NMR spectrum of iodoacetate **154**. The DEPT spectrum showed that C-7 was a methylene and not a methine, once again confirming the opening of the ring. In addition, ^{1}H and ^{13}C NMR

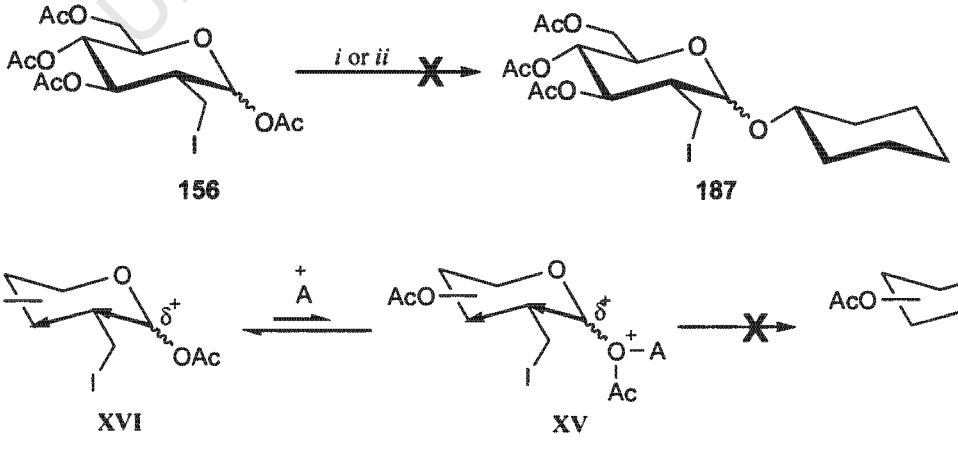
spectra showed the presence of four acetoxy groups on each isomer indicating the addition of an acetate group at the anomeric center.



155 **156**

Scheme 2.34. NH_4I, 50% aq H_2O_2, Ac_2O, AcOH/CH_3CN (1:1), 60°C, overnight, 96% (3:7 of α:β ratio).

Having iodoacetate **156** in hand, our focus turned towards the synthesis of cyclohexyl glycosides with **156** acting as a glycosyl donor. However, exposure of glycosyl donor **156** to cyclohexanol and $BF_3{\cdot}Et_2O$ (excess) in dichloromethane led to the recovery of the starting material. The reaction was unsuccessful even when strong Lewis acid promoters, such as TMSOTf in dichloromethane as well as diethyl ether, were employed (Scheme 2.35). The failure of the glycosylation reaction is probably a consequence of the deactivating effect of the acetate protecting groups. The action of the Lewis acid on the glycosyl donor **156** results in the build-up of a positive charge around the anomeric center of intermediate **XV** in the transition state. The electron withdrawing effect through induction by the acetyl protecting groups destabilizes the partial positive charge in intermediate **XV** and thus, the equilibrium shifts to the reverse direction (Scheme 2.35).[2,161]



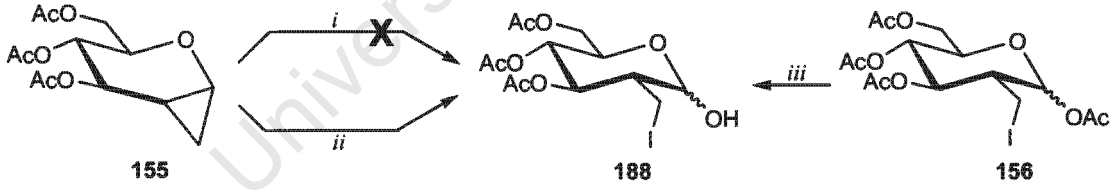
156 **187**

XVI **XV** **XVII**

Scheme 2.35. *i*) Cyclohexanol, $BF_3{\cdot}Et_2O$, 4Å molecular sieves, CH_2Cl_2, rt; *ii*) cyclohexanol, TMSOTf, 4Å molecular sieves, CH_2Cl_2 or Et_2O, rt.

Consideration was therefore given to an alternative approach, based upon the reports that selective hydrolysis of an anomeric acetate group can be achieved[162] allowing for transformation of the anomeric oxygen into a better leaving group.

Other than acetates there are a number of anomeric functionalities that could be displaced selectively during glycosylation reaction by a glycosyl acceptor. A commonly used leaving group is the anomeric trichloroacetimidate due to its high reactivity under quite mild activating conditions.[163] It is prepared by reaction of the anomeric hydroxyl group with trichloroacetonitrile in the presence of a base. Thus, in our case, in order to obtain a free hydroxyl group at the anomeric center, anomeric deacetylation was carried out on iodoacetate **156** to yield **188** in 70% yield as a 3:2 (α:β) mixture of anomers (Scheme 2.36).[162] Alternatively, hydroxyl **188** could be prepared by opening of the cyclopropyl ring in cyclopropane **155** with halonium electrophiles and water as a nucleophile. Since we had some experience with derivatization of glycals to halohydrins using catalytic methods (refere to section 2.2), attempts were made to promote opening of the cyclopropyl ring with ammonium iodide and hydrogen peroxide in acetonitrile in the presence of a takovite catalyst using the conditions reported for halohydroxylation of glycals.[99] However, the reaction was unsuccessful even at temperatures as high as 60°C (Scheme 2.36).



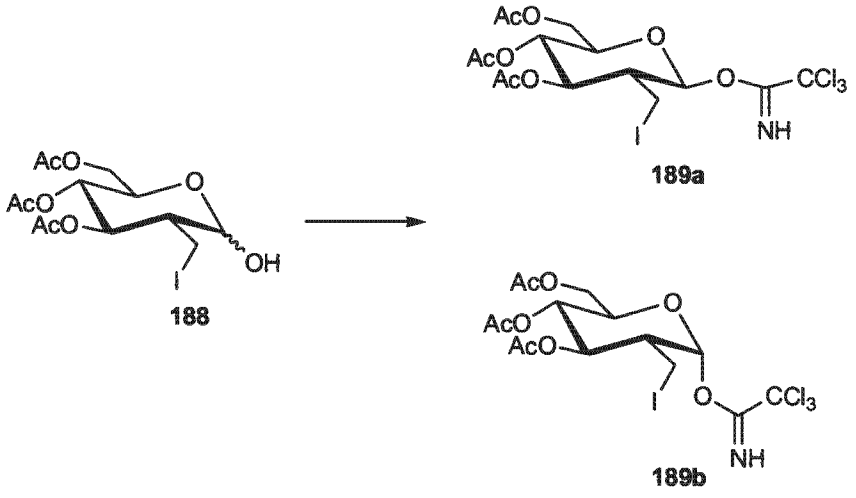
Scheme 2.36. *i*) NH_4I, 50% aq H_2O_2, takovite catalyst, CH_3CN, rt - 60°C, overnight; *ii*) NIS, dioxane/water (2:1), 60°C, overnight, 90%; (*iii*) Hydrazine acetate, DMF, 1 h, 50°C, 70% (3:2, α:β).

However, when cyclopropane **155** was treated with NIS in a 2:1 solution of dioxane/water at 60°C, hydroxyl **188** was obtained in excellent yield (Scheme 2.36).[117a] The ^{1}H NMR spectrum of the compound displayed characteristic features that supported the assignment of the structure. H-1 of the α-anomer appeared at δ 5.48 as a triplet with a coupling constant of 3.6 Hz. A COSY spectrum showed a

correlation of H-1 with H-2 and the hydroxyl group, thus it appeared as a triplet. In a D_2O wash ^1H NMR spectrum, H-1 appeared as a doublet at δ 5.47 with a *J* value of 3.2 Hz confirming α configuration of the hydroxyl group at the anomeric center. Similarly, H-1 of the β-anomer resonated at δ 4.78 and appeared as a doublet of doublets with *J* values of 5.4 and 7.8 Hz. After a D_2O wash, the ^1H NMR spectrum displayed H-1 as a doublet with 8.0 Hz coupling constant, once again confirming the assigned configuration. Comparison of the chemical shifts of the anomeric protons in iodoacetate **156** and hydroxyl **188**, showed that the signals in **188** moved further upfield, indicating the replacement of the acetate group by a hydroxyl group. The signal of the hydroxyl group of the α-anomer appeared distinctively at δ_H 3.72 as a doublet of doublets having *J* values of 1.5 and 4.1 Hz. The peak disappeared in a D_2O wash ^1H NMR spectrum. The ^{13}C NMR spectra was consistent with that of compounds obtained by opening of a cyclopropyl ring. The signals of C-1, C-2 and C-7 appeared at δ 97.4 (C-1β), 93.8 (C-1α), 46.9 (C-2α), 45.3 (C-2β), 3.3 (C-7β), and 0.8 (C-7α). Further more, the signals of the acetoxy groups in the ^1H and ^{13}C NMR spectra supported the assigned structure.

After successfully synthesizing hydroxyl **188**, the stage was set for the synthesis of the glycosyl donor, imidate **189**. A literature survey showed that there were different methods of preparing anomeric acetimidate. The general protocol involved treatment of a free anomeric hemi-acetal with trichloroacetonitrile under basic conditions to furnish the desired anomeric acetimidate. However, depending on the strength of the base used in the reaction, either the α- or β-anomer of the acetimidate could be obtained.[163,164]

Thus, when a solution of hydroxyl **188** in dry dichloromethane was treated with trichloroacetonitrile and freshly dried and powdered potassium carbonate, separable mixtures of β-and α-glycosyl trichloroacetimidates **189a** and **189b** were obtained in yields of 47% and 18%, respectively (Scheme 2.37).[164a]

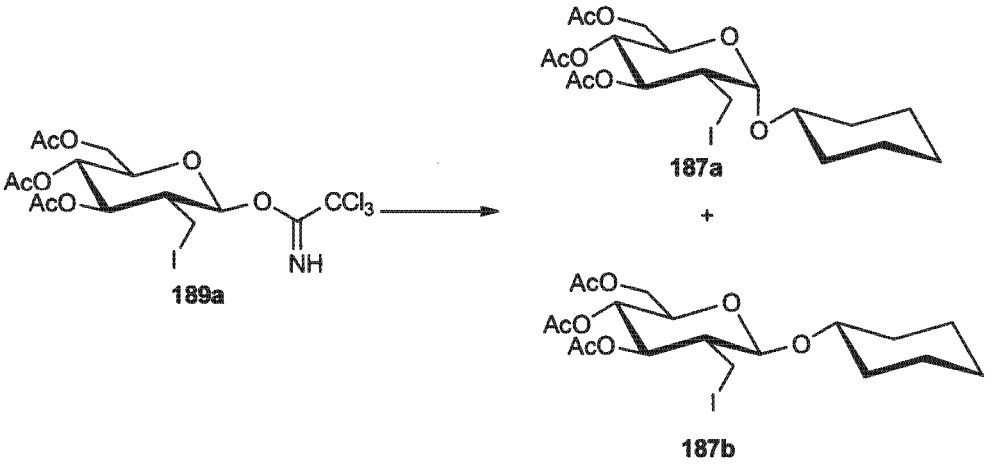


Scheme 2.37. Trichloroacetonitrile, K_2CO_3, CH_2Cl_2, rt, 2 h, 47% (**189a**) and 18% (**189b**).

The compounds were analyzed with the help of NMR spectroscopy. The characteristic singlet NH peaks of the α-and β-anomers appeared at δ_H 8.80 and 8.75, respectively. Anomeric signals moved downfield and appeared as doublets at δ_H 6.60 (H-1 of **189b**) and 5.82 (H-1 of **189a**). The ^{13}C NMR spectrum was also helpful in confirming the structure of the acetimidates by showing the signal of the *C*=NH peak in both the α- and β-anomers at δ_C 160.1 and 160.3, respectively.[164b]

It has been reported that a lack of a participating group at the C-2 position of a donor and the use of non-polar solvents, low temperature and mild activator favour the process of glycosylation to proceed *via* an S_N2-type mechanism; thus, α-trichloroacetimidate donors give a predominance of β-glycosides and β-trichloroacetimidates favour α-products.[1,2] Based on these precedents, we carried out a glycosylation reaction of β–trichloroacetimidate **189a** with cyclohexanol in dichloromethane using $BF_3{\cdot}Et_2O$ as an activator.[165] The reaction proceeded nicely, but unexpectedly gave the β-glycoside as a major product (Scheme 2.38).

Glycosylation of the α–trichloroacetimidate **189b** with cyclohexanol using conditions (TMSOTf as promoter, diethyl ether as solvent) that favour an S_N1-type mechanism[166] was also attempted in order to obtain a higher yield of α-glycoside **187a**. However, this reaction also resulted in formation of the β-glycoside as major product.

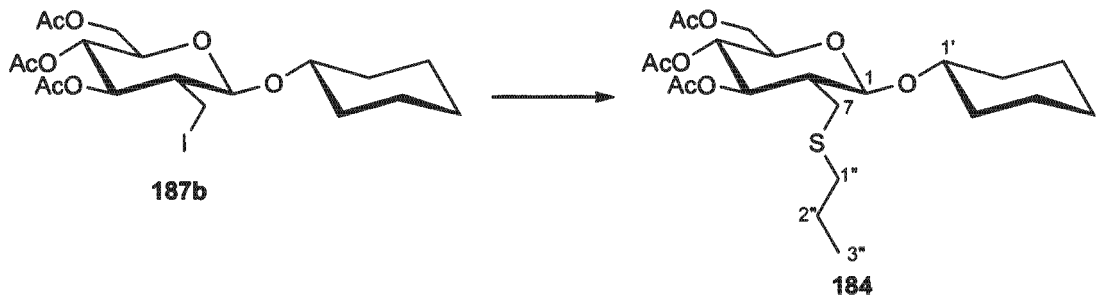


Scheme 2.38. Cyclohexanol, $BF_3{\cdot}Et_2O$, 4Å molecular sieves, CH_2Cl_2, 0°C - rt, 3 h, 35% (**187a**) and 53% (**187b**).

Once again, ^1H and ^{13}C NMR spectra were useful for assigning the structures of the anomers. The anomeric carbon of the β-anomer appeared at δ_C 101.5 while that of the α-anomer appeared at δ_C 97.9. The ^1H NMR spectrum for glycoside **187a** displayed a doublet for the anomeric proton at δ 5.23 with $J_{1,2}$ = 3.6 Hz, while the ^1H NMR spectrum of glycoside **187b** displayed a corresponding doublet for H-1 at δ 4.54 with a large diaxial *J* value of 8.0 Hz, thus confirming the β-anomer. Acetoxy and methylene signals of the acetyl and the cyclohexyl groups were evident from both ^1H and ^{13}C NMR spectra of the separated anomers.

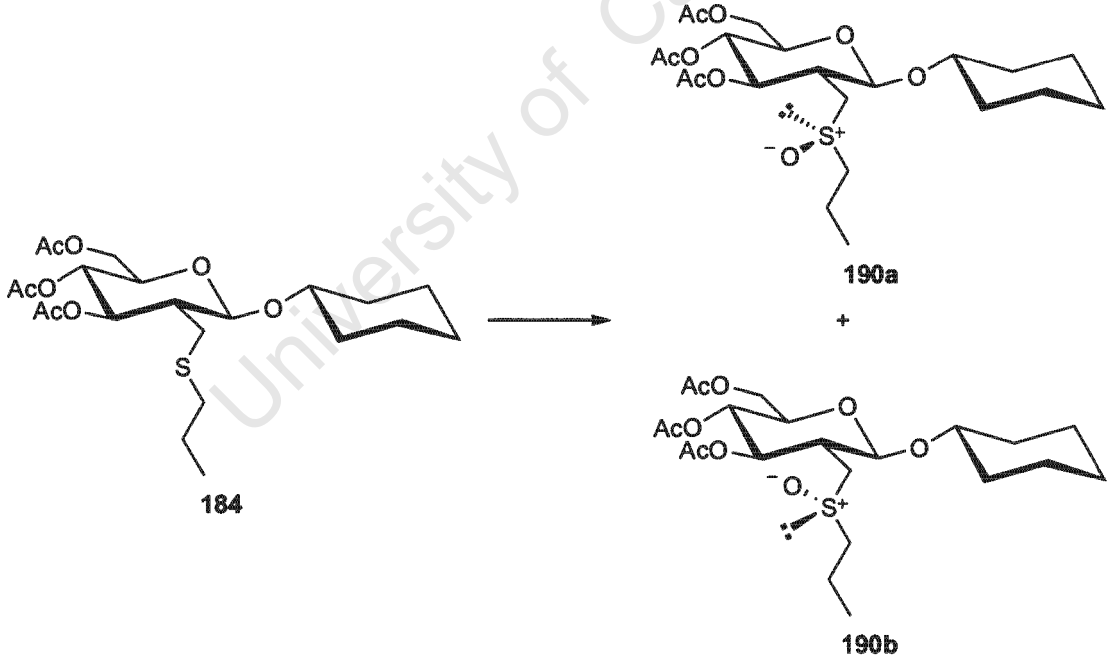
2.5.2.3 Manipulation of the C-2 iodomethyl group in acetylated glycosides

The 2-iodomethylglucoside **187b** proved a useful model substrate for evaluating methodology for introducing sulfide, sulfoxide and sulfone functionalities in the side chain. Thus, substitution of the iodide in glycoside **187b** with *n*-propanethiolate ion gave sulfide **184** in 80% yield, under conditions employed in synthesizing sulfide **173** (Scheme 2.39). The low yield relative to the benzylated analogue appeared to be due to the losses as a result of partial deacetylation during the workup of the reaction. The spectroscopic data of the compound was found to be identical to the one obtained according to Scheme 2.30.



Scheme 2.39. *n*-PrSH, NaH, DMSO/THF (1:1), rt, 5 min, 80%.

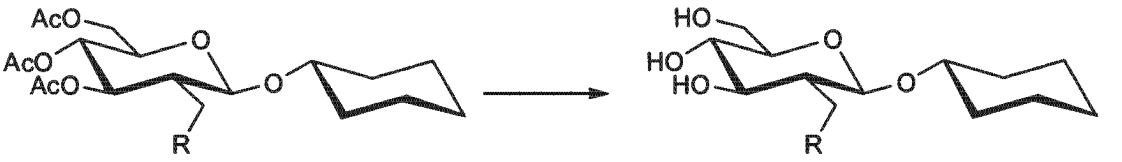
Selective oxidation of sulfide **184** using conditions employed to achieve intermediate **174** furnished an equimolar ratio of inseparable diastereoisomeric mixtures of sulfoxides **190a** and **190b** in a yield of 90% (Scheme 2.40). The spectroscopic data were consistent with the assigned structure. The presence of a sulphoxide function was confirmed from the IR spectrum of sulfoxides **190a** and **190b** that showed a band at 1029 cm^{-1}.[137,144c]



Scheme 2.40. Al_2O_3, H_2O, OXONE®, CH_2Cl_2, 32°C, 4 h, 90%.

Exposure of sulfoxides **190a** and **190b** to *Zemplén* deacetylation[1] resulted in the formation of a diastereoisomeric mixture of target sulfoxides **179b** in excellent yield (Scheme 2.41). Although the ^1H NMR spectrum seemed complex, the presence of the

n-propyl group was evident in the spectrum. The sulfoxides were confirmed from the appearance of IR bands at 1032 cm^{-1}.

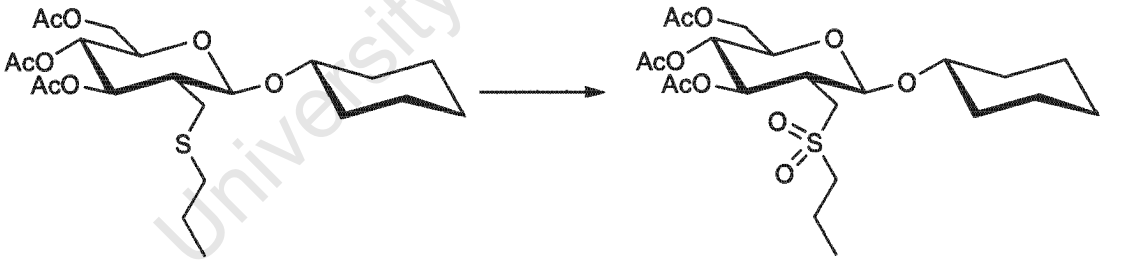


190 (**a** and **b**) R = *n*-PrS(O) **179b** R = *n*-PrS(O)

191 R = *n*-PrS(O_2) **181b** R = *n*-PrS(O_2)

Scheme 2.41. NaOMe, MeOH, rt, 10 min, 96% (**179b**) and 98% (**181b**).

In a similar fashion, sulfide **184** was oxidized with excess OXONE® to give sulphone **191** in 100% yield (Scheme 2.42). The spectroscopic and analytical data were consistent with the assigned structure and the acetoxy, cyclohexyl and propyl signals were evident from both ^{1}H and ^{13}C NMR spectra. In addition, the IR spectrum displayed signals at 1315 and 1132 cm^{-1}, confirming the presence of the sulphone function.[137,144c]



184 **191**

Scheme 2.42. Al_2O_3, H_2O, OXONE®, CH_2Cl_2, 32°C, 4 h, 100%.

Global deacetylation of sulphone **191**, using *Zemplén* procedure, gave the target compound **181b** in a yield of 98% (Scheme 2.41). The structure of the compound was established with the help of NMR spectroscopy and IR.

The model studies demonstrated that acetyl protecting groups were compatible with the desired synthetic transformations, and suggested that the required isosteres

incorporating the inositol unit as aglycone could be easily synthesized by coupling an appropriate acetylated glycosyl donor and acceptor and then carrying out the sequence of transformations described above. The focus then shifted to the synthesis of suitably protected *myo*-inositol glycosyl acceptors in order to complete the synthesis of the target compounds.

2.5.3 Synthesis of the glycosyl acceptor, selectively protected *myo-inositol*

As discussed earlier and shown in the retrosynthetic analysis (Scheme 2.18 on page 67), the next challenge involved preparation of a selectively protected and resolved inositol unit **XII** as acceptor for the glycosylation step. The resolved *myo*-inositol derivatives shown in Figure 2.4 were identified as potential glycosyl acceptors for the synthesis of target compounds depicted in Scheme 2.18. The protocol for the synthesis of glycosyl acceptors **40** and **11** is well documented.[34,35,167] However the synthetic route reported for the synthesis of **11** was unsatisfactory due to its reported low yields and an attempt to improve the method is described below, together with an efficient route to glycosyl acceptor **192**.

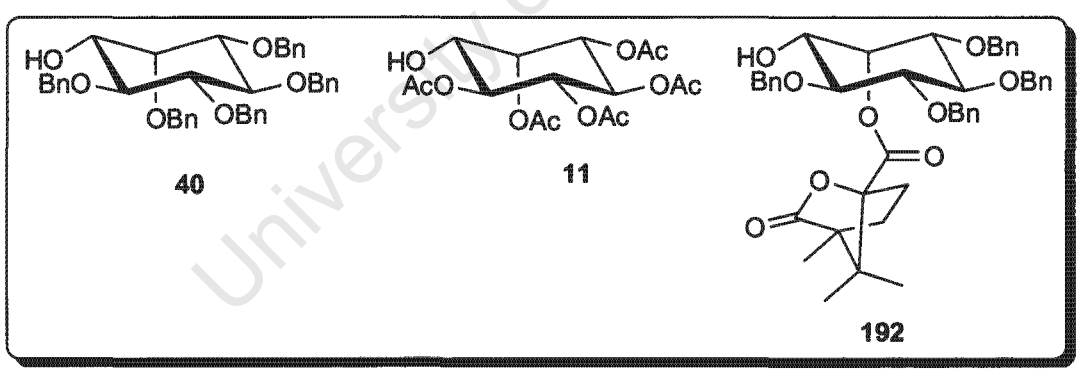


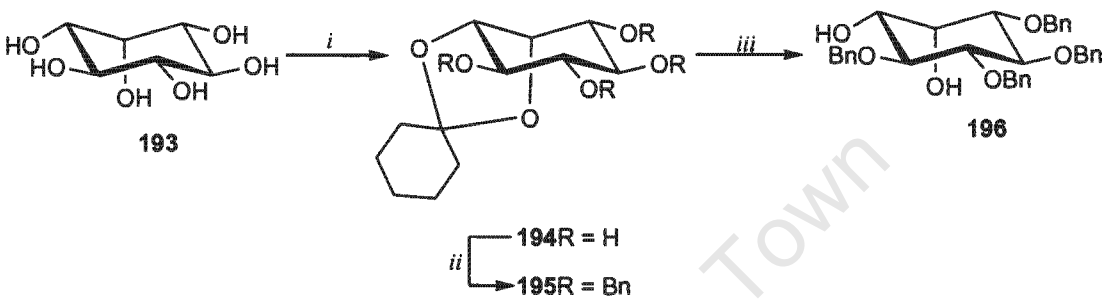
Figure 2.4. Selected *myo*-inositol glycosyl acceptors.

2.5.3.1 Synthesis of penta-*O*-benzylated inositol derivative

According to the reported methodology,[167] the synthesis of enantiomerically pure D-*myo*-inositol derivative **40** commenced with the protection of the *cis*-1,2-diol of **193** (a racemic mixture of D- and L-isomers) as an acetal. Thus, treatment of commercially available *myo*-inositol **193** with cyclohexanone and TsOH in DMF under the

conditions of Massy[167] resulted in the formation of cyclohexylidene-DL-*myo*-inositol **194** in 80% yield. The structure of **194** was confirmed by comparing the spectroscopic and analytical data with the literature values and was in complete agreement.[183,184]

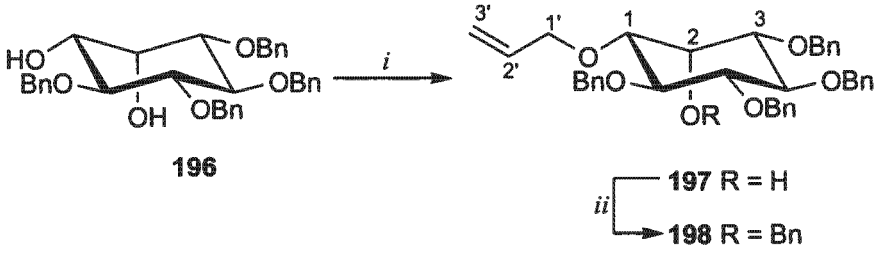
Global benzylation of acetal **194** with benzyl bromide in the presence of sodium hydride furnished tetra-*O*-benzylated **195** in a yield of 78%. The analytical data were in complete agreement with the literature.[167]



Scheme 2.43. *i*) Cyclohexanone, 10% TsOH in DMF, DMF, toluene, reflux, 12 h, 80%; *ii*) BnBr, NaH, TBAI, THF, reflux, 16 h, 78%; *iii*) 80% aq AcOH, 100°C, 2 h, 80%.

Exposure of acetal **195** to acid hydrolysis using 80% aq acetic acid at 100°C resulted in formation of diol **196** in 80% yield (Scheme 2.43). Once again, the analytical and spectroscopic data were in agreement with the literature values with the absence of the characteristic cyclohexyl methylene signals in the ^{1}H and ^{13}C NMR spectra.[167,53]

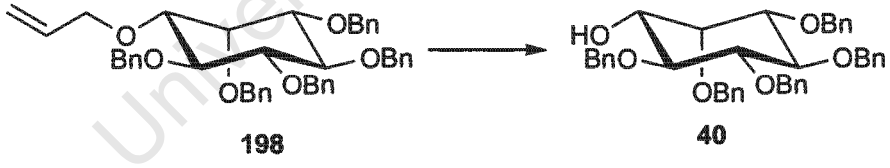
When a solution of the diol **196** in dry toluene was exposed to dibutyltin oxide, a stannylene acetal was formed which, after treatment with allyl bromide in DMF, gave regioselectively the allyl ether **197** in a yield of 85% (Scheme 2.44). The allylic group was identified by signals in the ^{1}H NMR spectrum for the protons attached to C-1', C-2' and C-3' at δ 4.21 – 4.18, 6.00 - 5.90, and 5.35 – 5.10, respectively. The corresponding ^{13}C NMR signals appeared at δ 67.7, 134.7 and 117.4, respectively. The regioselective protection was confirmed by the slight upfield shift of the signal of H-1 from around δ 3.47 in diol **196** to δ 3.43 while the signal of H-2 showed no significant change in chemical shift.



Scheme 2.44. *i*) (a) Bu_2SnO, toluene, reflux, 2 h; (b) Allyl bromide, DMF, 70°C, 5 h, 85%; *ii*) BnBr, NaH, THF, reflux, 3 h, 89%.

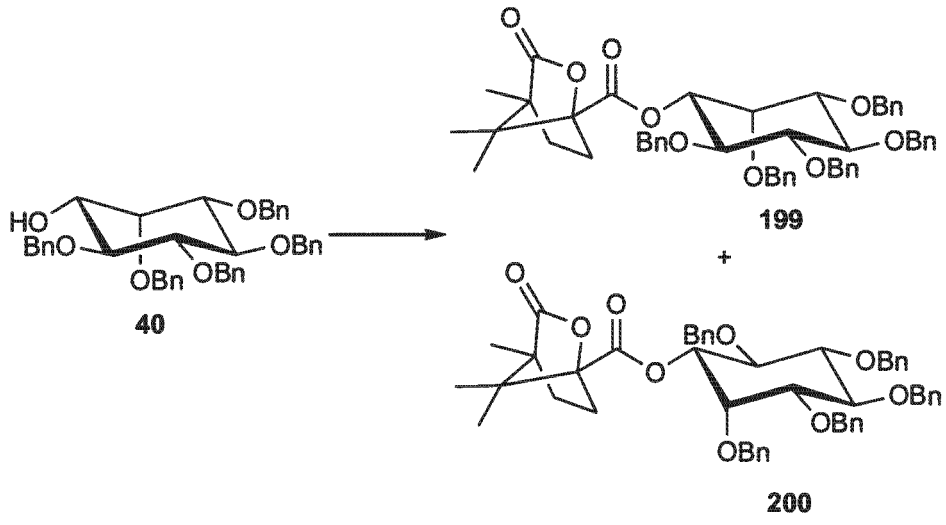
Benzylation of **197** using benzyl bromide in the presence of sodium hydride furnished allyl penta-*O*-benzyl-*myo*-inositol **198** in a yield of 89% (Scheme 2.44). The spectroscopic and analytical data were consistent to that reported in the literature.[167]

The action of palladium(II)chloride to a solution of allyl ether **198** in ethanol/methanol (1:1) resulted in deallylation to give penta-*O*-benzyl-*myo*-inositol **40** (racemic mixture) in 80% yield (Scheme 2.45). The deallylation was confirmed when the signals of the allylic group observed in allyl ether **198** were absent in the ^1H and ^{13}C NMR spectra of **40**. The signal of H-1 moved slightly downfield from δ 3.38 in **198** to 3.52 (overlapped with other signals) in **40**, clearly indicative of the deallylation of the allyl group. The spectroscopic data were consistent to the reported values.



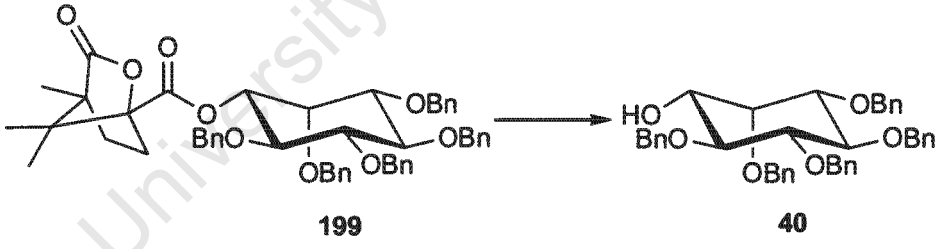
Scheme 2.45. $PdCl_2$, EtOH/MeOH (1:1), rt, 3 h, 80%.

The racemic *myo*-inositol derivative **40** was then resolved as camphanate esters.[167] Esterification of racemic alcohol **40** with (S)-(-)-camphanic chloride in the presence of triethylamine and DMAP furnished a 1:1 mixture of separable diastereoisomeric camphanate esters **199** and **200** in excellent yield (Scheme 2.46). The diastereoisomeric mixtures were separated by careful silica gel column chromatography and had $[\alpha]_D$'s, melting points, and ^1H and ^{13}C NMR data in full agreement with those reported in the literature.[167]



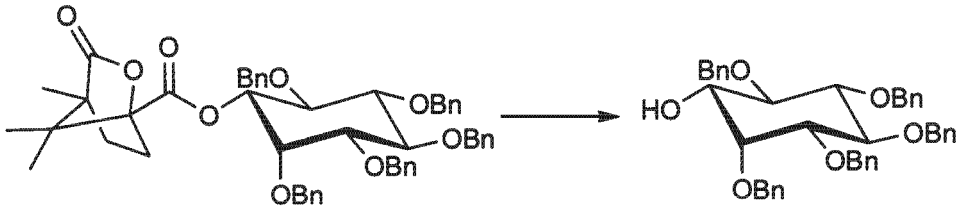
Scheme 2.46. (S)-(-)-Camphanic chloride, Et_3N, DMAP, CH_2Cl_2, rt, 2 h, 43% (**199**) and 46% (**200**).

Hydrolysis of the camphanate ester in **199** was achieved by treatment with powdered potassium hydroxide in absolute ethanol under reflux (Scheme 2.47),[168] to give the desired alcohol **40** (D-isomer) in excellent yield. The characteristic camphanate signals were absent in the ^1H and ^{13}C NMR spectra of **40** and the signal for H-1 had moved upfield from δ 4.98 in **199** to around δ 3.51 in **40**.



Scheme 2.47. KOH, EtOH, reflux, 2 h, 98%.

Under similar reaction conditions camphanate ester **200** was de-esterified to furnish **201** in excellent yield (Scheme 2.48). The spectroscopic data were similar to that of **40** while the optical rotation of +7.1° for D-isomer **40** and -8.0° for L-isomer **201** confirmed their enantiomeric relationship.[169] The spectroscopic data of both isomers were consistent to that reported in the literature.[167]

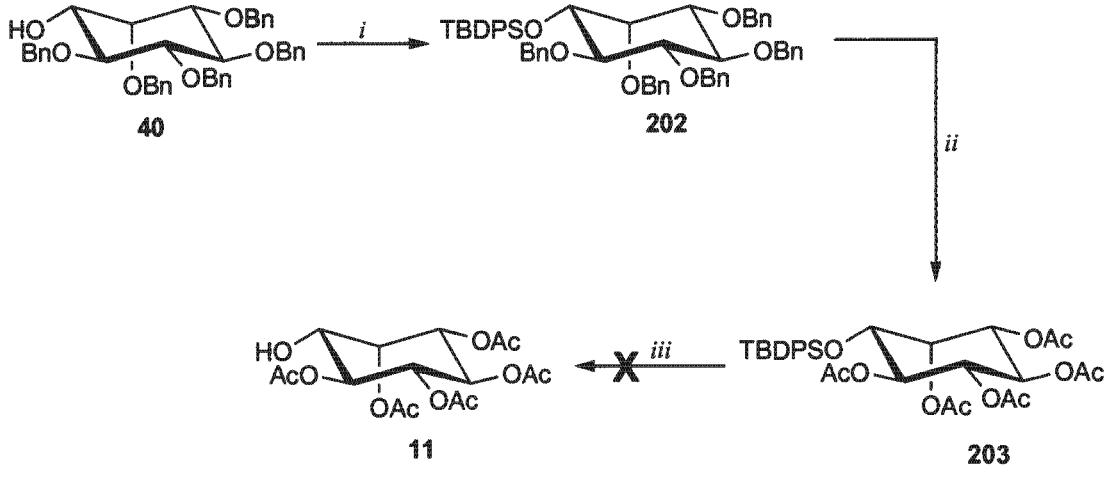


200 **201**

Scheme 2.48. KOH, EtOH, reflux, 2 h, 97%.

2.5.3.2 Attempts towards the synthesis of penta-*O*-acetylated inositol derivative

The reported synthesis of penta-*O*-acetylated *myo*-inositol **11** commences from the commercially available *myo*-inositol **193** by treating it with 1-ethoxycyclohexene to give mixtures of *myo*-inositol biscyclohexylidene ketals. The poor selectivity of this step results in a very low yield (23%) of the desired product which is required for further derivatization to yield the target compound **11**.[34,35] Although this sequence leads to the desired product, the low yields were discouraging considering the quantity of **11** needed for our synthesis, and an alternative route which utilized the readily-available resolved *myo*-inositol derivative **40**[167]seemed attractive. We first considered protecting the 1-OH in **40** with a silyl group with a view to then removing the benzyl groups, acetylating and finally desilylating under acidic conditions. The hydroxyl group on compound **40** was, therefore, silylated using TBDPS chloride in the presence of imidazole to furnish silylated *myo*-inositol **202** in 84% yield (Scheme 2.49).[170] The presence of the TBDPS was confirmed from its diagnostic peaks in both the ^{1}H and ^{13}C NMR spectra. The integration of the aromatic signals in the ^{1}H NMR spectrum corresponded to 35 protons, indicative of the additional two phenyl rings to silylated *myo*-inositol **202** while the characteristic singlet for the *tert*-butyl group at δ_H 1.12 provided further evidence for the presence of the silyl group.



Scheme 2.49. *i*) TBDPSCl, Imidazole, DMF, 0°C – rt, overnight, 84%; *ii*) (a) 10% Pd/C, ethanol, rt, 3 days; (b) Ac_2O, DMAP, Et_3N, DCM, rt, 1 h, 89%; *iii*) TBAF or HF in acetonitrile or ammonium fluoride in methanol, rt.

The ^{13}C NMR spectrum supported the assignment by displaying signals at δ_C 27.2 and 19.3 which corresponded to the carbons of the methyl groups and the tertiary carbon attached to silicon, respectively. In addition, the signal for H-1 moved further upfield from around δ 3.50 in **40** to 3.07 in **202**, a clear indication of the protection of the hydroxyl with an electron donating group. Compound **202** was then subjected to hydrogenolysis followed immediately by acetylation to yield penta-*O*-acetylated *myo*-inositol **203** in 89% yield (Scheme 2.49). It is worth mentioning that although the benzyl groups at C-3, C-4, C-5 and C-6 were readily cleaved, the benzyl group at C-2 proved difficult to remove as evidenced from the ^1H NMR spectrum analysis of an intermediate taken during debenzylation. Thus, periodic addition of further equivalents of Pd/C was required during hydrogenolysis over a period of 48 h until TLC showed completion of the reaction. The complete debenzylation was confirmed from the analysis of the ^1H and ^{13}C NMR of **203**. The survival of the TBDPS group was evident from the ^1H NMR spectrum that displayed a multiplet at δ 7.74 – 7.32 with an integration of ten protons and a singlet at δ 0.99 integrating for nine protons. These signals corresponded to the two phenyl rings and three methyls in the TBDPS protecting group of **203**. In the ^{13}C NMR spectra the diagnostic signals of the TBDPS group appeared at δ 26.6 (Me_3C-Si) and 19.2 (Me_3C-Si). The presence of five acetoxy groups in **203** was also confirmed from both ^1H and ^{13}C NMR spectral analysis. Five singlet peaks each integrating for three protons appeared at δ 2.20, 1.95, 1.94, 1.92

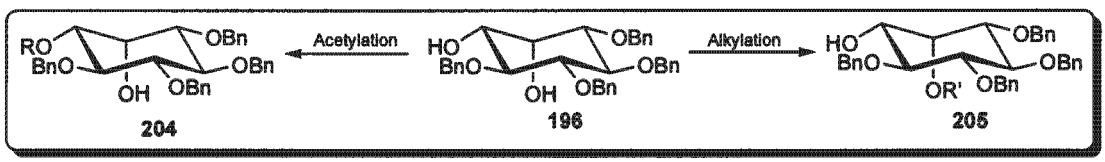
and 1.53 in the ^{1}H NMR spectrum of **203**, and the ^{13}C NMR spectrum of **203** displayed the characteristic signals of the acetate groups, *i.e* the carbonyl carbons resonated at δ 170.0, 169.9, 169.8, 169.7 and 169.6 and the methyl signals appeared at δ 20.9, 20.53, 20.50, 20.48, and 20.46.

All that remained was to selectively cleave the TBDPS in order to obtain the desired compound **11**. The first choice of desilylating agent was TBAF but when **203** was treated with this reagent,[171] the TBDPS group in **203** was cleaved but resulted in multiple products and no single major product could be isolated. The result was perhaps not too surprising as it is well documented that under basic conditions acyl protecting groups on an inositol ring are able to undergo migration and result in formation of several regioisomers.[172,173] The fluoride ion is sufficiently basic to cause acyl migration.[172] It was necessary, therefore, to consider protocols that cleave TBDPS under acidic conditions. HF in acetonitrile[174] is one such method, but in our hands treatment of a solution of silyl **203** in acetonitrile with HF (diluted in acetonitrile) led only to the recovery of starting material after workup. Attempts at higher temperatures and addition of concentrated HF solution resulted in hydrolysis of the acetates. A further attempt using ammonium fluoride in methanol under reflux[175] resulted in hydrolysis of the acetates in **203** rather than cleavage of the silyl group. With this result, we focused on a route that avoids use of the acetylated glycosyl acceptor in our synthesis towards the target compounds depicted in Scheme 2.18.

2.5.3.3 Synthesis of camphanated inositol derivative 192 *via* base assisted 1→2 acyl migration

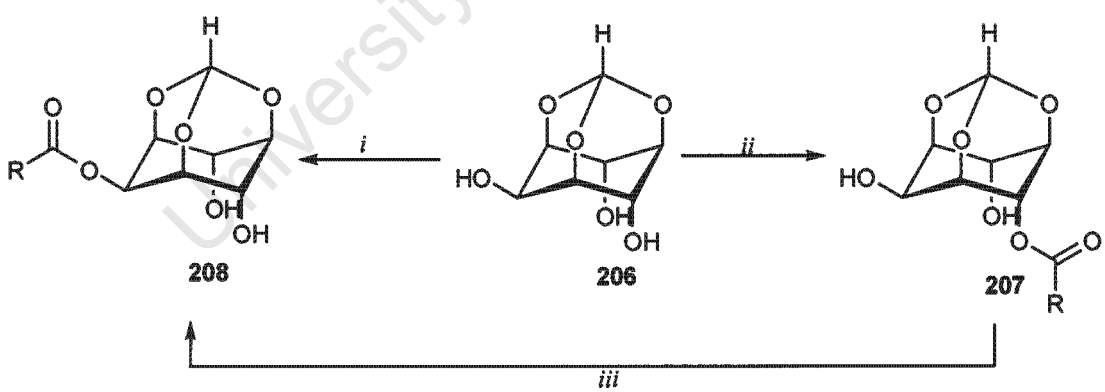
As mentioned above and reported in the literature, selective derivatization and resolution of racemic *myo*-inositols requires lengthy reaction sequences.[34,35,167] Thus, the search for better synthetic methodologies for the selective protection of the six secondary hydroxyl groups present in *myo*-inositol has drawn the attention of several research groups since the middle of the twentieth century. The selective protection of the *cis*-vicinal diols of **196** (Scheme 2.50), for instance, could be cited as one of the earliest achievements.[176] Regioselective acylation and alkylation of *cis*-1,2 diols of tetra-*O*-benzyl *myo*-inositol diol **196** was pioneered by Angyal and co-workers in 1965.[176] They reported that the diol undergoes regioselective acylation and

sulphonylation at the equatorial hydroxyl group (exclusively at this postion on reaction with tosyl chloride), but regioselective alkylation at the axial hydroxyl group with alkylating agents such as dihydropyran and benzyloxymethyl chloride (Scheme 2.50). Similar regioselectivities in reactions of *trans*-1,3-diol of tetra-*O*-benzyl *myo*-inositol were reported by Fraser-Reid and co-workers.[177,178]



Scheme 2.50. Selective acylation and alkylation of diol **196**.

Depending on the reaction conditions employed, regioselective acylation of either an equatorial or axial hydroxyl group was also achieved on orthoester *myo*-inositol **206** (Scheme 2.51).[179] Benzoylation of the orthoformate **206** with one equivalent of each of sodium hydride and benzoyl chloride in DMF gave the axial 4-*O*-benzoate **207**, while the use of two equivalents of sodium hydride and one equivalent of benzoyl chloride gave the equatorial 2-*O*-benzoate **208** (Scheme 2.51).

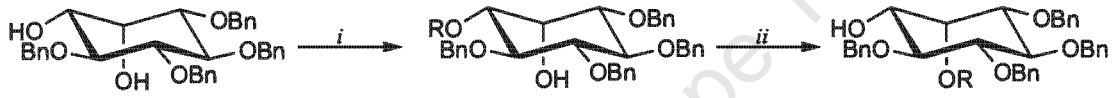


Scheme 2.51. *i*) DMF, NaH (2 equiv.), RCOCl (R = Me, Ph), 5 min, 85 – 97%; *ii*) DMF, NaH (1 equiv.), RCOCl (R = Me, Ph), 5 min, 86 – 89%; *iii*) DMF, NaH (1 equiv.), 5 min, 90 – 96%.

The authors accounted for this observation by rationalizing that in the presence of excess base isomerization takes place and an acyl group migrates intramolecularly from an axial position to an equatorial position. This is in agreement with previous

results that demonstrated the migration of acyl groups on inositol ring under basic conditions.[173]

Based on these findings we decided to investigate the synthesis of camphanate **192** from *cis*-1,2-diol **196**. Before we started working on camphanate ester of the diol, we revisited the selective acylation of Angyal with benzoyl and pivaloyl chlorides. Thus, treatment of a solution of the *myo*-inositol 1,2-diol **196** in dichloromethane with one equivalent of benzoyl chloride, triethylamine and DMAP led exclusively to the equatorial ester **209** in a yield of 82% after workup with ice-cold aqueous ammonium chloride solution (Scheme 2.52). In a similar fashion, pivaloyl **210** was also prepared in 83% yield (Scheme 2.52). The structures of the compounds were established using NMR and analytical techniques.



196 **209** R = Bz **211** R = Bz

210 R = Piv **212** R = Piv

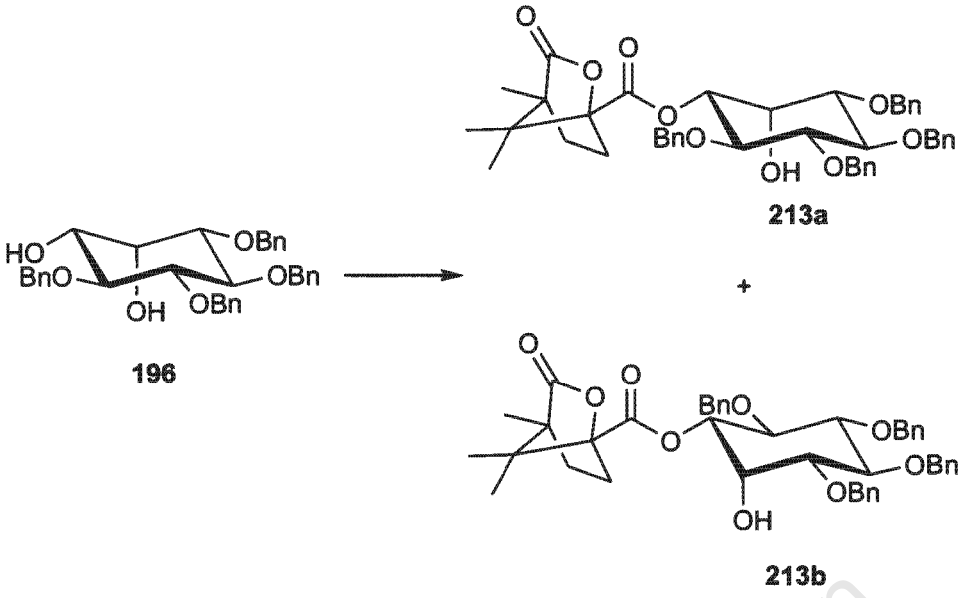
Scheme 2.52. *i)* RCOCl (1 equiv., R = Bz, Piv), Et_3N, DMAP, DCM, 0°C - rt, 24 h, 82% (**209**) and 83% (**210**); *ii*) DBU, CH_3CN, rt, 1 h, 67% (**211**) and 96% (**212**).*

Once 1-*O*-acyl derivatives of **196** were synthesized successfully, optimized acyl migration conditions were sought. A series of bases were investigated including: triethylamine, DMAP, sodium hydride, DBU, and *t*-BuOK in aprotic solvents (dichloromethane and acetonitrile) with water and without water.[173,176] In accordance with previous reports, addition of water resulted in hydrolysis of the acyl group.[173] With triethylamine and DMAP migration was not achieved and the starting material was recovered. No conclusive result could be obtained from the action of sodium hydride as TLC of the reaction mixture showed hydrolysis of the acyl group, which could have taken place on the TLC plate itself. Further investigation of this was not, however, carried out as it was discovered that the use of DBU as base resulted in a clean migration. This was achieved by stirring a solution of 1-*O*-benzoate **209** in

* HPLC analysis of the reaction mixture at equilibrium showed a 1:1 and 64:36 ratios of **211**:**209** and **212**:**210**, respectively. And the yields were calculated by consideration of the recovered starting material.

acetonitrile with one equivalent of DBU at room temperature for 1 h. Addition of further equivalents of DBU and longer reaction times had no effect in driving the migration forward. The reaction was quenched after 1 h by addition of ice-cold aqueous ammonium chloride solution to prevent base assisted hydrolysis of the acyl group. The more polar 2-*O*-benzoate **211** was isolated from the less polar unreacted 1-*O*-benzoate **209** in 67% yield using column chromatography on silica gel. Similarly, treatment of 1-*O*-pivaloate **210** with DBU in acetonitrile afforded 2-*O*-pivaloate **212** in 96% yield (Scheme 2.52). When *t*-BuOK was used as a base for the migration, the reaction took longer (>24 h) to reach the same equilibrium ratio for the C1/C2 regioisomers and appreciable hydrolysis was also observed during the migration.

Excited with these results, our attention turned to effect a similar migration of camphanate esters of a *myo*-inositol derivative. Thus, under these optimized reaction conditions, a diastereoisomeric mixture of camphanate esters **213a** and **213b** was obtained in 75% yield when diol **196** was treated with (S)-(-)-camphanic acid chloride in the presence of triethylamine and DMAP in dichloromethane (Scheme 2.53). Minor products which correspond to 2-*O*-camphanate **192** and **214** were also detected on TLC of the reaction mixture. The ^{1}H NMR spectrum displayed diagnostic signals at δ 1.11, 1.10, 1.08, 1.00, 0.97 and 0.90 for the methyl groups of the camphanate moieties in each diastereoisomers of **213a** and **213b**. The integration of these methyl signals confirmed the presence of one camphanate group on each diastereoisomer. The chemical shifts of H-1 and H-2 also gave evidence as to which hydroxyl group in diol **196** was being esterified. Comparisons of the chemical shifts of H-1 and H-2 in the camphanate ester **213a** and diol **196**, for instance, showed that H-1 moved downfield from δ 3.49 in diol **196** to around δ_H 4.90 (overlapped with benzylic signals) in **213a** but the signal of H-2 displayed no significant shift and appeared in both compounds around δ 4.20. Thus, the downfield shift of the signal of H-1 and the unaffected signal of H-2 clearly confirmed that selective esterification of the equatorial hydroxyl had taken place.

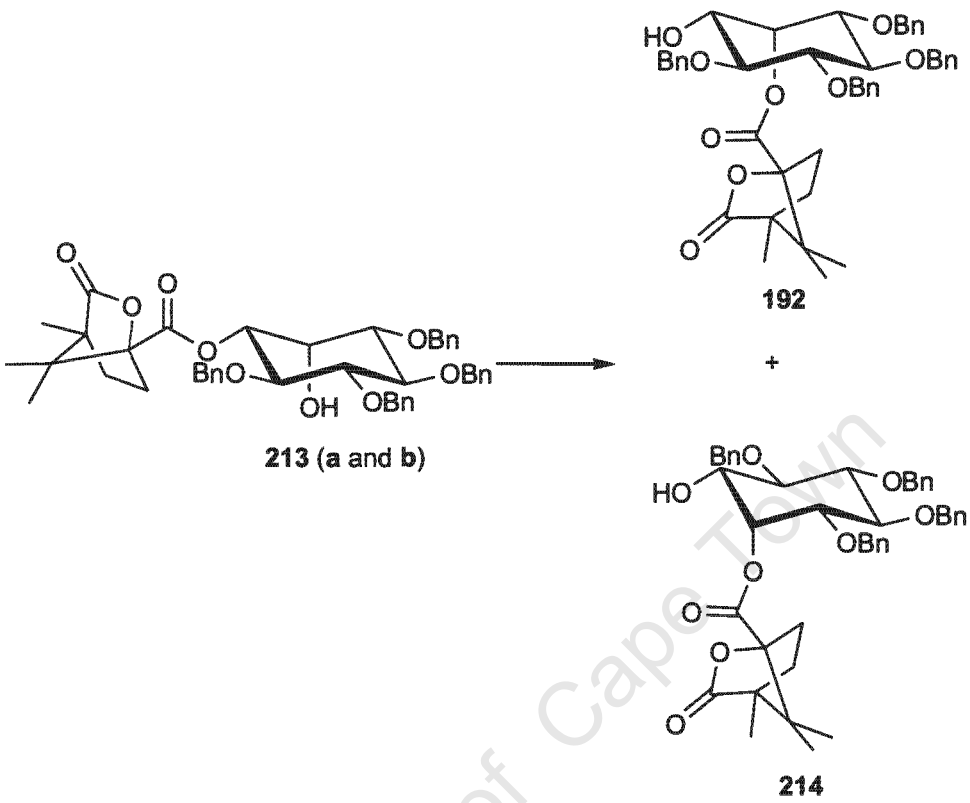


Scheme 2.53. (S)-(-)-Camphanic acid chloride, Et_3N, DMAP, CH_2Cl_2, 0°C - rt, 10 min, 75%.

1→2 Migration of the camphanate ester from an equatorial position to an axial position in **213a** and **213b** was achieved upon treatment with DBU, under conditions used to effect migration of the benzoyl group in **209** (Scheme 2.54). Gratifyingly, the diastereoisomers were chromatographically separable and the D-isomer **192** and the L-isomer **214** were obtained in 54% and 47% yields, respectively. In addition 30% of the starting material was recovered which was subjected for further acyl migration. NMR spectra were helpful in establishing the structures of the compounds and the D and L configurations were assigned on the basis of their optical rotation.

The ^{1}H NMR spectrum of 2-*O*-camphanate **192** showed a significant downfield shift of the H-2 signal from δ 4.32 in **213** (**a** and **b**) to δ 5.84 whereas the H-1 signal shifted further upfield from around δ 4.90 in **213** (**a** and **b**) to δ 3.57 proving the migration of the camphanate group from the 1β to 2α oxygen. The camphanate group in **192** was evident from ^{1}H NMR spectrum which displayed the signals of the three methyl groups of the camphanate moiety at δ 1.11, 0.94 and 0.93 as singlets. The diagnostic signals for **214** were analogous to those of **192**. The observed 1→2 migration from an equatorial position to an axial position is considered unusual and generally unfavourable in a chair conformation due to the 1,3-diaxial steric strain. However, our findings, which have shown that both sterically demanding and non-demanding acyl groups were able to migrate to the axial position, suggest that it is not the 1,3-diaxial

steric strain but other factors that come into play in preference of the migration to either an axial or equatorial position.

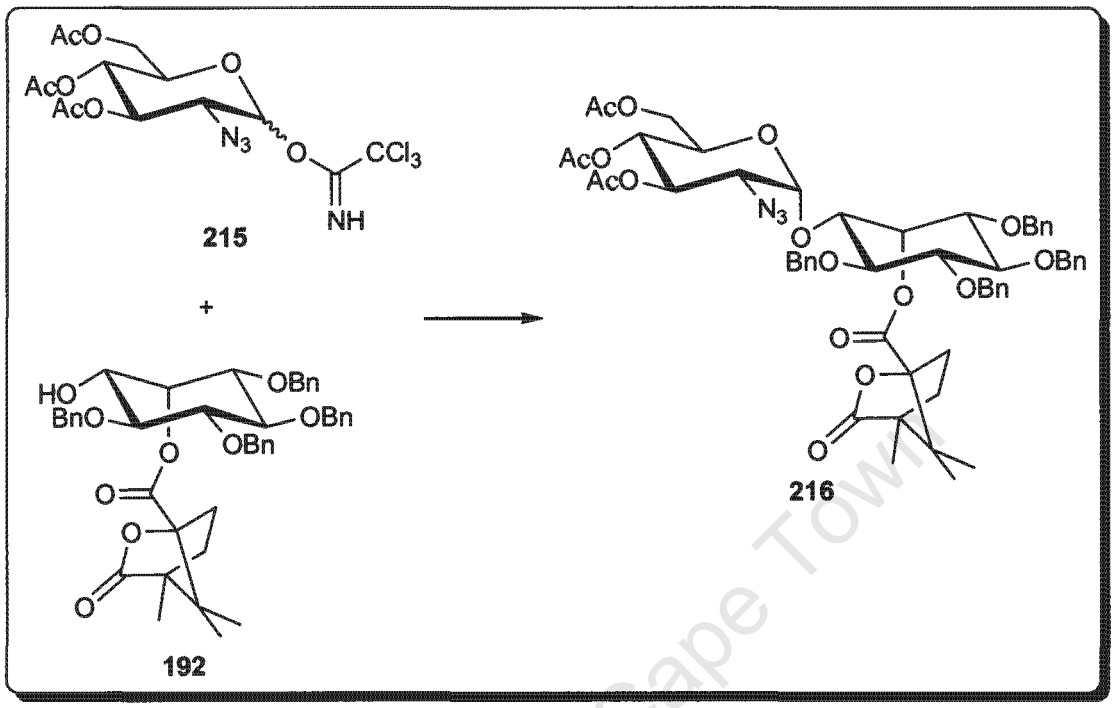


Scheme 2.54. DBU, acetonitrile, rt, 1 h, 54% (**192**) and 47% (**214**).*

These regioselective acylation and acyl migration protocols shorten the synthetic pathways for preparation of the resolved glycosyl 1-OH acceptor, such as **40**. The protocol provides dual functions in *myo*-inositol chemistry: on one hand it provides a suitably protected glycosyl acceptor with a free hydroxyl group at the C-1 position of a *myo*-inositol, while on the other hand access is provided to resolution of the racemic mixtures. Unfortunately, due to time constraints we did not use **192** and **214** in our synthesis of mycothiol analogues, although the resolved glycosyl acceptor **192** has been used in a parallel project. It has been reported that glycosylation of the glycosyl acceptor **192** with imidate **215** resulted in the exclusive formation of α-glycoside **216** (Scheme 2.55), showing the superiority over the corresponding glycosyl acceptor **40** which results in formation of mixtures of α-and β-anomers.[180] The excellent

* The yields were calculated by taking the recovered starting material under consideration.

stereoselectivity of the glycosyl acceptor **192** could be attributed to the bulkiness of its axially oriented camphanate group at 2-*O* position.



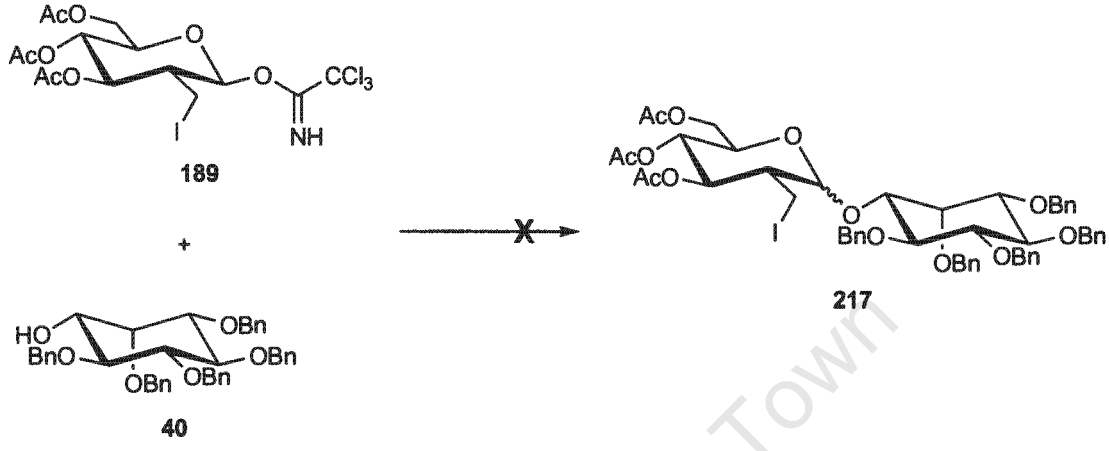
Scheme 2.55. TMSOTf, 4Å molecular sieves, CH_2Cl_2, 0°C - rt, 2 h, 53%.

2.5.4 Synthesis of isosteres containing *myo*-inositol derivative

In the first phase of this investigation cyclohexyl glycosides were used to explore the type of protecting groups and timing of their deprotection in order to obtain the target molecules respresented in the retrosynthetic analysis (Scheme 2.18). After solving the challenges associated with introduction and removal of protecting groups, the focus then shifted in the second phase to the synthesis of suitably protected *myo*-inositol derivatives that can be used as glycosyl acceptors.

Having both acetylated and benzylated glycosyl donors, and benzylated *myo*-inositol acceptors in hand, our next challenges were therefore to develop a stereoselective glycosylation reaction to obtain predominantly the α-anomer, and to achieve further functionalization of the C-2 side chain.

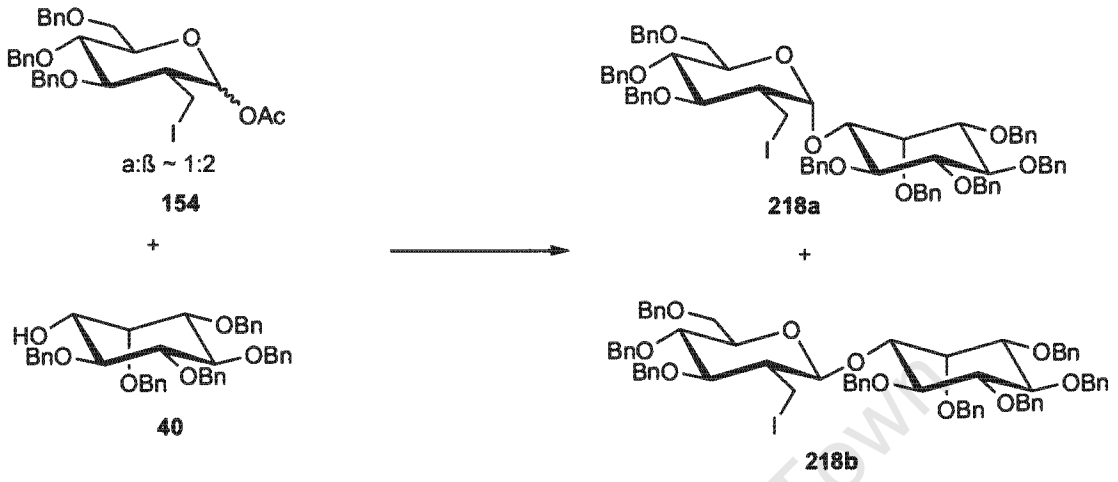
Attempted glycosylations using imidate **189** and *myo*-inositol **40** were unsuccessful resulting to the decomposition of the imidate (Scheme 2.56). This is possible due to the deactivating effects of the acetyl protecting groups in the donor, and the steric hinderance of the 2° alcohol on the *myo*-inositol group.



Scheme 2.56. $BF_3{\cdot}Et_2O$/TMSOTf, 4Å molecular sieves, DCM/Et_2O, 0°C – rt.

Having established that benzyl groups could be cleaved in the presence of sulfides using calcium dissolved in ammonia, the perbenzylated glycoside **218a** was identified as a viable target. Thus, glycosides **218a** and **218b** were obtained in 65% and 16% yields, respectively, by glycosylation of benzylated glycosyl donor **154** and acceptor **40** in the presence of 4Å molecular sieves using $BF_3{\cdot}Et_2O$ as an activator and DCM as a solvent (Scheme 2.57). The diastereoisomers were separated by column chromatography on silica gel and their structures were established with the help of NMR spectroscopy and analytical data. The ^{1}H NMR spectrum of **218a** showed aromatic peaks with an integration of 40 protons that correspond to the 8 phenyl groups. The anomeric proton appeared at δ_H 5.21 with a J value of 3.0 Hz indicating α-anomer. The ^{1}H NMR spectrum of **218b** was analogous to that of **218a** but the H-1 signal overlapped with the benzylic proton signals making it difficult to compare the J values. However, the anomeric assignment was confirmed by comparison of the chemical shifts of the C-1s. In line with previous results, the signal of the β-anomer appeared relatively downfield at δ_C 104.2 as compared to the signal of the α-anomer which appeared at δ_C 96.3 confirming the assigned structures. Another pattern that has been observed on those kinds of compounds is that the H-2 signal of the α-anomer

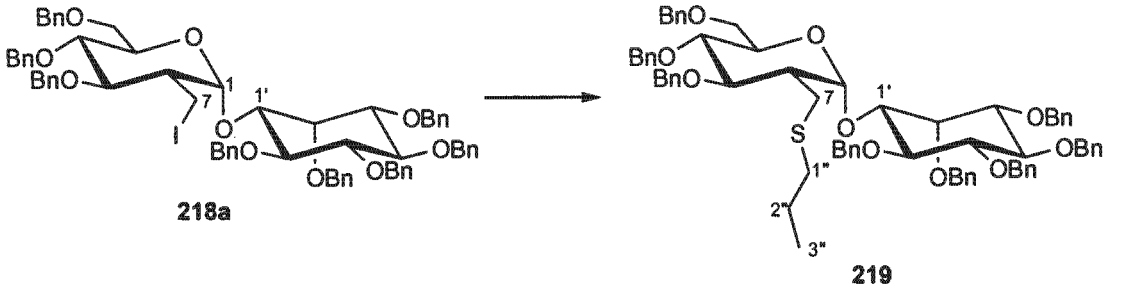
appears downfield relative to the β-anomer and accordingly, in glycosides **218a** and **218b** the signals of H-2 appeared in the region of δ_H 2.31 – 1.96 and δ_H 1.39 – 1.28, respectively, supporting the assigned stereochemistry.



Scheme 2.57. $BF_3{\cdot}Et_2O$, 4Å molecular sieves, DCM, 0°C – rt, 1 h, 65% (**218a**) and 16% (**218b**).

The stereochemical outcome of the reaction suggested that the iodo-substituent did not provide anchimeric assistance during glycosylation. Improvement of the stereoselectivity of the glycosylation reaction was attempted by using TMSOTf as an activator in DCM, but the outcome was decomposition of the glycosyl donor while leaving the glycosyl acceptor intact. No reaction took place when diethyl ether was used as solvent, with starting materials fully recovered. The use of $BF_3{\cdot}Et_2O$ in DCM seemed therefore to provide the best results.

After the successful glycosylation, the next step was the introduction of thiols. Following the procedure described for the thiolation of cyclohexyl glycoside **169a**, thiolation of glycoside **218a** afforded compound **219** in 92% yield. The thiolation was confirmed by the appearance of the characteristic signals of the *n*-propyl group in the region of δ_H 2.40 – 2.32 for H-1", δ_H 1.56 – 1.45 for H-2" and at δ_H 0.92 for H-3". The corresponding signals in the ^{13}C NMR spectrum appeared at δ_C 34.0, 28.5 and 22.7, respectively.



Scheme 2.58. *n*-PrSH, NaH, DMSO/THF, rt, 5 min, 92%.

At this stage of the project the small amount of the propylthio-derivative **219** and its precursors available regrettably prevented the successful completion of this sequence, and it was judged that in the time available it would not be feasible to repeat the sequence to obtain more material. However, we were satisfied that the possibility of successful debenzylation had been demonstrated earlier on the cyclohexyl glycosides **183**, and that this could be carried out at various levels of oxidation of the sulfur as desired. Although this sequence has the disadvantage of providing mixtures of α- and β-glycosides, it nevertheless remains an attractive route to a wide range of sulfur-containing analogues of mycothiol. One attractive possibility is to produce analogues with a sulfur atom replacing the methyl group at the 3" position in the side-chain. This would mimic the position of the thiol in the cysteinyl unit in mycothiol, and the compounds may inhibit the mycothione reductase enzyme in the biosynthetic sequence.

CHAPTER THREE

3. CONCLUSION

During the course of the project towards the synthesis of enzyme inhibitors of the *mycobacterium*:

A new catalytic system that involves oxidative halogenation with commercially available hydrogen peroxide in the presence of a WO_4^{2-} exchanged synthetic takovite has been developed for halohydroxylation and haloalkoxylation of glycals. The iodoalkoxylation was found to be more stereoselective and high yielding as compared to the corresponding bromoalkoxylation and halohydroxylation. Benzylated glycals were more reactive than the corresponding acetylated glycals and this has been accounted for by the electron donating and withdrawing nature of the protecting groups. In addition to the functionalization of glycals, the catalytic method has been extended to function as an alternative deprotection protocol of *n*-pentenyl and ortho ester glycosides.

A simple, cost effective and environmentally benign protocol for iodoacetoxylation of glycals to the corresponding iodoacetates using a combination of NH_4I, hydrogen peroxide and $Ac_2O/AcOH/CH_3CN$ has been developed. The reaction is efficient, highly stereoselective and compatible with a range of protecting groups. The application of the method has been extended to include simple alkenes such as styrene and indene. The cyclopropyl group of both benzylated and acetylated 1,2-cyclopropanated sugars underwent regioselective ring opening under the iodoacetoxylation reaction conditions. To the best of our knowledge, this is the first example of opening the cyclopropyl ring into an iodoacetate.

An indirect, efficient and high yielding, method for the synthesis of per-acetylated 1,2-cyclopropanated sugar **155** has been established. Even though the compound was reported already, it had never been characterized fully. Hence, we have provided a full characterization of the compound.

In order to prepare *myo*-inositol containing isosteres, penta-*O*-benzylated *myo*-inositol **40** was prepared successfully following Massy's protocol with slight modifications. Attempts to synthesize penta-*O*-acetylated *myo*-inositol **11** were unsuccessful owing to the difficulty of cleaving the TBDPS group. However, regioselective 1-O-acylation of diol **194** followed by 1→2 acyl migration using DBU in acetonitrile provided the enantiomerically resolved novel camphanated *myo*-inositols **190** and **212**, which can be used as glycosyl acceptors. Among other things, the advantages of this strategy over the classical synthesis of *myo*-inositols **40** and **11** are the shorter synthetic sequences and early resolution of the D and L enantiomers.

An effective and simple synthetic strategy has been established for the synthesis of isosteres **108** and **109** (Figure 1.9) using cyclohexyl β-glycosides for model studies. Compound **154** proved to be an excellent choice of glycosyl donor and couples with enantiomerically pure *myo*-inositol derivative in high yield and a seemingly S_N2 type of reaction. The C-2 iodomethyl group in **154** has been amenable for further transformations allowing the introduction of sulfides and azides to generate valuable analogues. The use of benzyl protecting groups throughout the synthesis posed problems as the groups were resistant to deprotection at the final stages. However, exchange of the benzyl groups with acetates at the early stage of the synthesis allowed successful deprotection to afford the desired products.

This work has developed new methodologies allowing for the successful synthesis of isosteres involved in the biosynthesis of mycothiol at a later stage. Once the isosteres are synthesized, they will be evaluated as enzyme inhibitors.

CHAPTER FOUR

4. EXPERIMENTAL SECTION

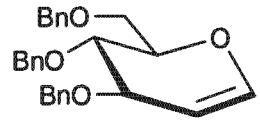
All the solvents used were freshly distilled. Dichloromethane was distilled over phosphorous pentoxide in a condenser fitted with a drying tube containing calcium chloride. Diethyl ether and THF were distilled under argon and dried over sodium wire in the presence of benzophenone. Other solvents were dried by appropriate techniques. All reagents were purchased from either Aldrich or Merck.

All reactions were monitored by thin layer chromatography (TLC) on aluminum-backed Merck silica gel 60 F_{254} plates using an ascending technique. The plates were visualized by spraying with ceric ammonium sulphate in 8 M sulphuric acid or a 1:1 solution of 5% *p*-anisaldehyde in ethanol and 10% sulphuric acid in ethanol baking at 150°C. Gravity column chromatography was done on Merck silica gel 60 (70 – 230 mesh).

Melting points were determined using a Reichert-Jung Thermovar hot-stage microscope and are uncorrected. Optical rotations were determined on a Perkin-Elmer 141 polarimeter in chloroform solutions unless otherwise stated. The concentration *c* refers to g/100 mL. Infrared spectra were recorded in using a Perkin-Elmer Spectrum One FT-IR spectrometer.

All proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded, unless otherwise specified, as deuteriochloroform solutions using tetramethylsilane as an internal standard on a Varian Mercury spectrometer 300 MHz or a Varian Unity spectrometer 400 MHz. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on the same instruments at 75 or 100 MHz using tetramethylsilane as an internal standard. All chemical shifts are reported in ppm. Elemental analysis for C, H, N and S were carried out using a Thermo Flash 1112 Series CHNS-O analyser. Low resolution FAB mass spectra were recorded on a VG70 SEQ micromass spectrometer, Mass Spectrometry Service, School of Chemistry, University of Witwatersrand.

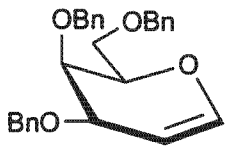
3,4,6-Tri-O-benzyl-D-glucal (67):



67

To a solution of 3,4,6-tri-*O*-acetyl-D-glucal (2.7 g, 9.91 mmol) in benzene (20 mL), 50% aq NaOH (20 mL), *t*-BuOH (0.5 mL, 5.22 mmol), and *n*-Bu_4NHSO_4 (640 mg, 2.01 mmol) were added. The reaction mixture was warmed to 50°C and a solution of benzyl chloride in benzene (400μL, 1:1 (v/v) BnCl-benzene) was then added dropwise at 10 minutes interval over 4.5 h. After stirring at 50°C for an additional 2 h, the reaction mixture was allowed to cool to room temperature and the layers were separated. The aqueous layer was extracted with benzene and the combined organic phases were washed with water and dried over $MgSO_4$. After filtration, the solvent was evaporated and the solid residue was recrystallized from ethanol to give **67** (2.1 g, 50%); mp 52 – 55°C (lit.,[94] 53 - 55°C); δ_H ($CDCl_3$, 400 MHz): 7.36 – 7.16 (m, 15H, 3 x Ph), 6.42 (dd, 1H, J = 1.3 and 6.2 Hz, H-1), 4.87 (dd, 1H, J = 2.7 and 6.2 Hz, H-2), 4.82 (d, 1H, J = 11.4 Hz, CH_2Ph), 4.67 – 4.49 (m, 5H, CH_2Ph), 4.22 – 4.19 (m, 1H, H-3), 4.08 – 4.04 (m, 1H, H-5), 3.87 – 3.74 (m, 3H, H-4, H-6_a and H-6_b); δ_C ($CDCl_3$, 100 MHz): 144.7 (C-1), 138.4, 138.2, 138.0, 128.4, 127.9, 127.7, 127.6 (3 x Ph), 99.9 (C-2), 77.4 (C-3), 75.7 (C-5), 74.4 (C-4), 73.7, 73.5, 70.4 (3 x CH_2Ph), 68.6 (C-6). The spectroscopic data were in agreement with the reported data.[94]

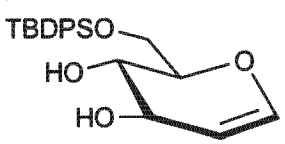
3,4,6-Tri-O-benzyl-D-galactal (106):



106

Following the procedure for the preparation of benzylated glucal **67**, galactal **106** was obtained from 3,4,6-tri-*O*-acetyl-D-galactal in 54% yield as a white solid; mp 54°C (lit.,[94] 52 – 54°C); δ_H ($CDCl_3$, 400 MHz): 7.38 – 7.20 (m, 15H, 3 x Ph), 6.36 (dd, 1H, J = 1.5 and 6.2 Hz, H-1), 4.88 – 4.83 (m, 2H, H-2 and CH_2Ph), 4.67 – 4.39 (m, 5H, CH_2Ph), 4.21 – 4.16 (m, 2H, H-3 and H-5), 3.95 – 3.94 (m, 1H, H-4), 3.80 – 3.76 (m, 1H, H-6_a), 3.68 – 3.64 (m, 1H, H-6_b); δ_C ($CDCl_3$, 100 MHz): 144.1 (C-1), 138.5, 138.4, 138.0, 128.3, 128.2, 128.1, 127.8, 127.7, 127.5, 127.4 (3 x Ph), 99.9 (C-2), 75.7 (C-3), 73.4, 73.3 (2 x CH_2Ph), 71.4 (C-4), 70.9 (CH_2Ph), 70.8 (C-5), 68.4 (C-6). The spectroscopic data were in agreement with the reported data.[94]

6-O-tert-Butyldiphenylsilyl-D-glucal (113):

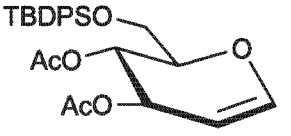


113

To a solution of D-glucal (230 mg, 1.57 mmol) and imidazole (214 mg, 3.14 mmol) in dry DMF (3 mL) at 0°C, *tert*-butyldiphenylsilyl chloride (490 µL, 1.89 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 1 h. It was then diluted with water and the aqueous phase was extracted with diethyl ether. The combined organic layers were washed with water and dried over $MgSO_4$. After filtration, the solvent was evaporated and the crude product was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 2:8) to afford the silylated glucal **113** (797 mg, 66%) as a colorless oil; δ_H ($CDCl_3$, 400 MHz): 7.70 – 7.67 (m, 4H, Ph), 7.44 – 7.35 (m, 6H, Ph), 6.30 (dd, 1H, J = 1.8 and 6.2 Hz, H-1), 4.71 (dd, 1H, J = 2.2 and 6.2 Hz, H-2), 4.26 (br s, 1H, OH), 4.00 (s, 2H), 3.97 (s, 2H),

2.88 (br s, 1H, OH), 2.28 (m, 1H), 1.06 (s, 9H, Me_3C-Si); δ_C ($CDCl_3$, 100 MHz): 144.4 (C-1), 135.6, 133.0, 129.8, 127.7, 102.3 (C-2), 77.1, 71.5, 69.7, 63.6, 26.7 (Me_3C-Si), 19.2 (Me_3C-Si). The spectroscopic data were in agreement with the reported data.[95,96]

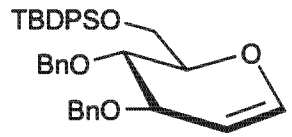
3,4-Di-O-acetyl-6-O-tert-butyldiphenylsilyl-D-glucal (114):



114

To a solution of glucal **113** (200 mg, 0.52 mmol) in dry dichloromethane (3 mL), acetic anhydride (300 µL, 3.12 mmol), triethylamine (300 µL, 2.08 mmol), and catalytic amount of DMAP were added at 0°C and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dichloromethane and then poured onto ice-water with stirring. The organic layer was separated and washed successively with water and brine, dried over $MgSO_4$, filtered and then concentrated on the rotary evaporator. The resulting residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 1:9) to give the title compound (219 mg, 90%) as a colorless oil; δ_H ($CDCl_3$, 400 MHz): 7.70 – 7.36 (m, 10H, 2 x Ph), 6.45 (dd, 1H, J = 1.2 and 6.0 Hz, H-1), 5.38 (dd, 1H, J = 5.4 and 7.0 Hz, H-4), 5.33 – 5.30 (m, 1H, H-3), 4.78 (dd, 1H, J = 3.2 and 6.1 Hz, H-2), 4.19 – 4.14 (m, 1H, H-5), 3.85 (dd, 2H, J = 2.4 and 4.8 Hz, H-6_a and H-6_b), 2.02, 1.98 (2s, 6H, 2 x CH_3CO_2), 1.06 (s, 9H, Me_3C-Si); δ_C ($CDCl_3$, 75 MHz): 170.4, 169.4 (2 x CH_3CO_2), 146.0 (C-1), 135.6, 133.2, 133.1, 129.7, 127.7, 127.6 (2 x Ph), 98.2 (C-2), 76.5 (C-5), 67.5, 67.4, 61.6 (C-6), 26.7 (Me_3C-Si), 21.0, 20.8 (2 x CH_3CO_2), 19.2 (Me_3C-Si). The spectroscopic data were in agreement with the reported data.[96]

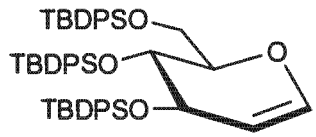
3,4-Di-O-benzyl-6-O-tert-butyldiphenylsilyl-D-glucal (115):



115

A solution of silylated glucal **113** in dry THF (1 mL) at 0°C was treated with NaH (52 mg of 60% dispersion in mineral oil, 1.30 mmol) and the reaction mixture was stirred at 0°C for 2 h. *n*-Bu_4NI (38 mg, 0.10 mmol) and a solution of benzyl bromide in THF (200 μL in 500 μL of THF, 1.58 mmol) were added and then the reaction mixture was allowed to warm to room temperature. After overnight stirring, the reaction mixture was cooled to 0°C and water was carefully added. The aqueous layer was extracted with diethyl ether and the combined organic phases were washed with water, dried over $MgSO_4$, filtered, and concentrated to dryness. The resulting crude product was purified by column chromatography on silica gel to afford glucal **115** in 70% yield as a colorless oil; δ_H ($CDCl_3$, 300 MHz): 7.73 – 7.26 (m, 20H, 4 x Ph), 6.42 (dd, 1H, J = 1.5 and 7.2 Hz, H-1), 4.95 – 4.58 (m, 5H), 4.27 – 4.24 (m, 1H), 4.08 – 3.94 (m, 4H), 1.09 (s, 9H, Me_3C-Si); δ_C ($CDCl_3$, 75 MHz): 144.8 (C-1), 138.4, 135.8, 135.6, 133.2, 129.6, 128.4, 127.8, 127.7, 127.6 (4 x Ph), 99.6 (C-2), 77.4, 75.9, 74.2, 73.8, 70.6, 62.2 (C-3, C-4, C-5, C-6 and 2 x CH_2Ph), 26.8 (Me_3C-Si), 19.3 (Me_3C-Si). The spectroscopic data were in agreement with the reported data.[95]

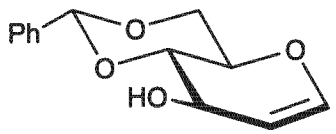
3,4,6-Tris-O-tert-butyldiphenylsilyl-D-glucal (116):



116

To a solution of D-glucal (319 mg, 2.18 mmol) and imidazole (979 mg, 14.38 mmol) in DMF (5 mL), *tert*-butyldiphenylsilyl chloride (1.76 mL, 6.76 mmol) was added dropwise at 0°C. After stirring at room temperature overnight, the reaction mixture was diluted with water. The aqueous layer was extracted with diethyl ether and the combined organic phases were washed with water, dried over $MgSO_4$, filtered and evaporated. Chromatography on silica gel (ethyl acetate/petroleum ether, 1:99) afforded glucal **116** (1.6 g, 85%) as a colorless oil; δ_H ($CDCl_3$, 300 MHz): 7.75 – 7.17 (m, 30H, 6 x Ph), 6.29 (d, 1H, J = 6.6 Hz, H-1), 4.44 (ddd, 1H, J = 1.8, 3.6 and 5.4 Hz, H-2), 4.29 – 4.25 (m, 1H, H-5), 4.18 (dd, 1H, J = 8.2 and 11.2 Hz, H-6_a), 3.98 (q, 1H, J = 1.8 and 3.6 Hz, H-4), 3.75 (dd, 1H, J = 3.3 and 11.4 Hz, H-6_b), 3.74 (m, 1H, H-3), 1.04, 0.94, 0.75 (3s, 27H, 3 x Me_3C-Si); δ_C ($CDCl_3$, 75 MHz): 143.0 (C-1), 135.8, 135.7, 135.6, 135.5, 135.3, 134.8, 133.9, 133.8, 133.7, 133.6, 133.4, 133.2, 129.6, 129.4, 127.3 (6 x Ph), 100.2 (C-2), 79.8, 70.4, 64.8, 62.5 (C-3, C-4, C-5 and C-6), 29.92, 29.89, 26.7 (3 x Me_3C-Si), 19.21, 19.19, 18.8 (3 x Me_3C-Si). The spectroscopic data were in agreement with the reported data.[95]

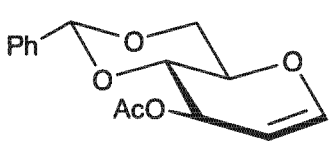
4,6-O-Benzylidene-D-glucal (117):



117

A solution of D-Glucal (100 mg, 0.68 mmol) in dry DMF (1 mL) was treated with benzaldehyde dimethylacetal (120 μL, 1.03 mmol) and catalytic amount of *p*-toluenesulphonic acid monohydrate and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then poured into ice-cold saturated aqueous $NaHCO_3$ with vigorous stirring. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water, dried over $MgSO_4$, filtered and concentrated to dryness. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 1:9) to obtain the title compound **117** (65 mg, 41%) as a white crystalline solid; mp 130 – 135°C (lit.[97] 134 – 138°C); δ_H ($CDCl_3$, 400 MHz): 7.53 – 7.37 (m, 5H, Ph), 6.34 (dd, 1H, J = 1.8 and 6.2 Hz, H-1), 5.60 (s, 1H, H-7), 4.78 (dd, 1H, J = 2.0 and 6.2 Hz, H-2), 4.52 (dt, 1H, J = 2.0 and 7.2 Hz, H-3), 4.37 (dd, 1H, J = 5.2 and 10.4 Hz, H-6_a), 3.95 – 3.89 (m, 1H, H-6_b), 3.84 – 3.78 (m, 2H, H-4 and H-5), 2.25 (br s, 1H, OH); δ_C ($CDCl_3$, 75 MHz): 144.2 (C-1), 137.1, 130.8, 129.3, 128.8, 128.4, 126.2 (Ph), 103.6 (C-2), 101.9 (C-7), 80.8, 68.4, 68.2, 66.7 (C-3, C-4, C-5 and C-6). The spectroscopic data were in agreement with the reported data.[97]

3-O-Acetyl-4,6-O-benzylidene-D-glucal (118):



118

To a solution of alcohol **117** (100 mg, 0.43 mmol) in dry dichloromethane (2 mL), triethylamine (250 μL, 1.71 mmol), acetic anhydride (250 μL, 2.58 mmol), and DMAP (2.29 mg, 0.02 mmol) were added. After stirring for 1 hr, the mixture was

diluted with dichloromethane, washed with brine, and the organic layer dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 3:7) to give **118** (95 mg, 80%) as a white crystalline solid; mp 134 – 137°C (lit.,[97] mp 140 – 141°C); δ_H ($CDCl_3$, 400 MHz): 7.50 – 7.35 (m, 5H, Ph), 6.39 (dd, 1H, J = 1.4 and 6.0 Hz, H-1), 5.59 (s, 1H, H-7), 5.55 – 5.52 (m, 1H, H-3), 4.81 (dd, 1H, J = 2.2 and 6.2 Hz, H-2), 4.41 – 4.37 (m, 1H, H-6_a), 4.06 – 3.82 (m, 3H, H-4, H-5 and H-6_b), 2.10 (s, 3H, CH_3CO_2); δ_C ($CDCl_3$, 100 MHz): 170.6 (CH_3CO_2), 145.3 (C-1), 136.8, 136.7, 129.1, 128.2, 126.1 (Ph), 101.5 (C-7), 100.7 (C-2), 76.9, 70.5, 68.8, 68.2 (C-3, C-4, C-5 and C-6), 21.0 (CH_3CO_2). The spectroscopic data were in agreement with the reported data.[97]

Typical procedure for the oxidative hydroxy and methoxyhalogenation of glycals using WO_4^{2-}-TV

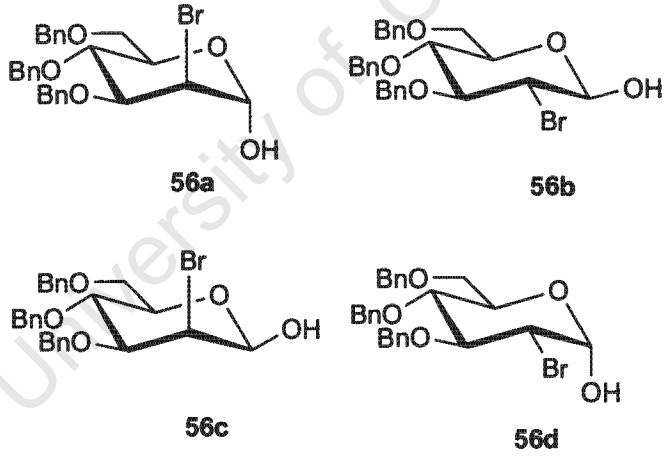
Method (a): *Benzylated glucal or galactal:* To a mixture of WO_4^{2-}-TV (4 mg, 0.002 mmol, W) and benzylated glucal **67** or galactal **106** (100 mg, 0.24 mmol) in aqueous acetonitrile or methanol (3 – 5 mL) containing ammonium bromide or ammonium iodide (1.5 – 6 equivs.) at room temperature, was added hydrogen peroxide in portions of 0.22 mmol (or 20 μL of 50% aqueous solution) every 5 minutes until complete conversion as judged by TLC. The catalyst was then removed by filtration or centrifugation and the filtrate partitioned between ice-water and diethyl ether. The organic layer was separated, washed successively with 0.1 M solution of sodium thiosulfate and water, dried over $MgSO_4$, and concentrated. The resulting crude products were purified on a column of silica eluting with mixtures of ethyl acetate and petroleum ether. Some of the halohydrins obtained were acetylated for ease of identification.

Method (b): *Acetylated glucal:* To a mixture of WO_4^{2-}-TV (4 mg, 0.002 mmol, W) and acetylated glycal **59** (100 mg, 0.37 mmol) in aqueous acetonitrile or methanol (3 – 5 mL) containing ammonium bromide or ammonium iodide (1.5 – 6 equivs.) at 60°C was added hydrogen peroxide in portions of 0.22 mmol (or 20 μL of 50% aqueous solution) every 5 minutes until complete conversion as judged by TLC. The catalyst was then removed by filtration or centrifugation and the filtrate partitioned

between ice-water and diethyl ether. The organic layer was separated, washed successively with 0.1 M solution of sodium thiosulfate and water, dried over $MgSO_4$, and concentrated. The mixtures of isomers were then separated on a column of silica eluting with mixtures of ethyl acetate and petroleum ether.

General Acylation Conditions of the Halohydrins: To a solution of the product of halohydroxylation (0.15 mmol) in dichloromethane were added acetic anhydride (0.60 mmol), triethylamine (0.60 mmol) and catalytic amount of DMAP. The solution was stirred at room temperature until completion (monitored by TLC). The solution was diluted with dichloromethane, washed with water and dried over $MgSO_4$. The residue was then purified by flash column chromatography on silica eluting with mixtures of ethyl acetate and petroleum ether.

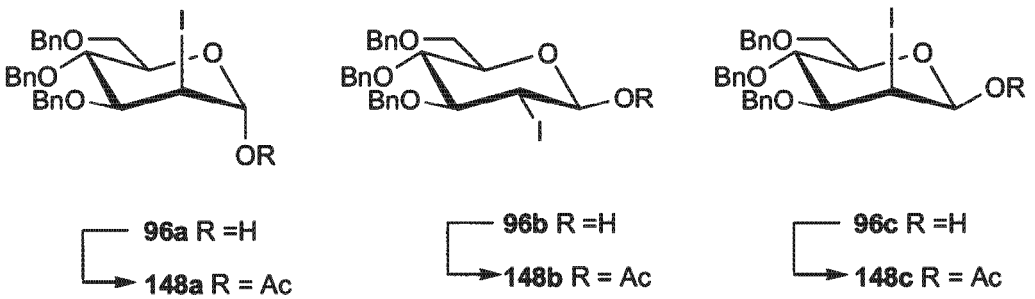
3,4,6-Tri-O-benzyl-2-bromo-2-deoxymanno and glycopyranosyls (56a, 56b, 56c and 56d):



Hydroxybromination of 3,4,6-tri-*O*-benzyl-D-glucal (**67**) using method A gave a mixture of bromohydrins **56a-d** as an oil in 95% yield and 5:2:2:1 ratio; δ_H ($CDCl_3$, 300 MHz): 7.42 – 7.16 (m 15H, 3 x Ph), 5.46 (d, 0.5H, J = 1.5 Hz, H-1 of **56a**), 5.35 (d, 0.2H, J = 3.0 Hz, H-1 of **56c**), 5.29 (d, 0.1H, J = 3.2 Hz, H-1 of **56d**), 4.99 – 4.44 (m, 6.2H), 4.37 (dd, 0.5H, J = 1.6 and 3.7 Hz), 4.19 – 3.48 (m, 5.5H), 1.26 (br s, OH); δ_C ($CDCl_3$, 75 MHz): 138.2, 138.0, 137.9, 137.6, 137.2, 133.0, 128.4, 128.1, 128.0, 127.8, 96.9, 94.7, 93.0, 91.8, 85.3, 81.5, 79.6, 75.8, 75.1, 74.9, 74.1, 73.5, 73.4, 71.7,

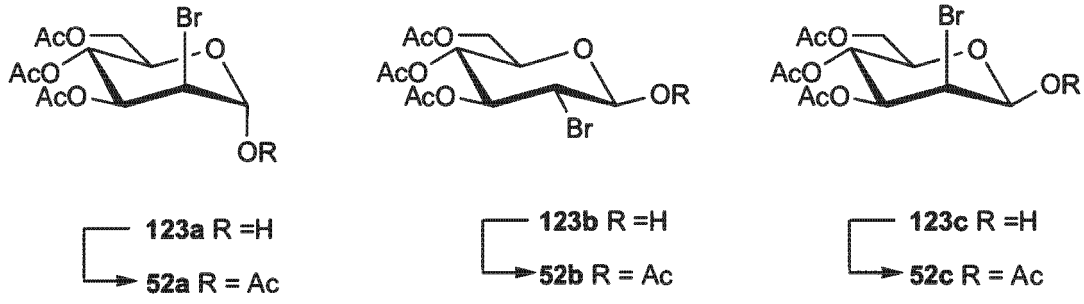
71.2, 70.8, 69.5, 68.9, 68.6, 58.9, 54.8, 52.2, 33.9, 30.3, 29.7. The spectroscopic data were in agreement with the reported data.[50]

3,4,6-Tri-O-benzyl-2-deoxy-2-iodo-manno and glycopyranosyls (96a, 96b and 96c):



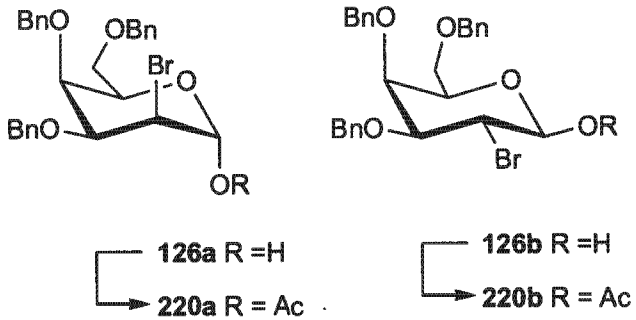
Hydroxyiodination of 3,4,6-tri-*O*-benzyl-D-glucal (**67**) using method A gave a mixture of iodohydrins **96a-c** as an oil in 96% yield. Acetylation of the iodohydrins using the general conditions and purification by column chromatography on silica gel (ethyl acetate/petroleum ether, 1:9) afforded separable iodoacetates **148a** (24%), **148b** (4%) and **148c** (32%) as colorless gums and white crystals, respectively. The NMR data for **148a** and **148b** matched those reported below by iodoacetoxylation of benzylated glucal. NMR data for **148c** is as follows: δ_H ($CDCl_3$, 400 MHz): 7.35 – 7.26 (m, 15H, 3 x Ph), 4.94 (d, 1H, J = 1.5 Hz, H-1), 4.86 – 4.80 (m, 7H, H-2 and 3 x CH_2Ph), 3.95 (t, J = 9.2 Hz, H-4), 3.79 – 3.58 (m, 3H, H-5, H-6_a and H-6_b), 3.13 (dd, 1H, J = 4.1 and 8.8 Hz, H-3), 2.16 (s, 3H, CH_3CO_2); δ_C ($CDCl_3$, 75 MHz): 169.0 (CH_3CO_2), 138.4, 138.3, 137.4, 128.7, 128.6, 128.5, 128.3, 128.2, 128.0, 127.8 (3 x Ph), 91.5 (C-1), 79.3 (C-3), 75.5, 75.4, 73.7, 71.03, 70.98, 68.8 (C-6), 36.2 (C-2), 21.3 (CH_3CO_2). The spectroscopic data were in agreement with the reported data.[100]

3,4,6-Tri-O-acetyl-2-bromo-2-deoxy-manno and glycopyranosyls (123a, 123b and 123c):



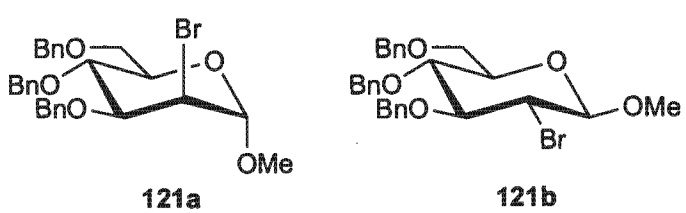
Bromohydroxylation of 3,4,6-tri-*O*-acetyl-D-glucal (**59**) using the general method B followed by acetylation under the standard conditions afforded after column chromatography on silica gel (ethyl acetate/petroleum ether, 1:9) a mixture of bromoacetates **52a** and **52c**, and pure **52b** in a ratio of 5:1:3 and combined yield of 60% as an oil. The NMR data of **52b** matched those reported below by bromoacetoxylation of acetylated glucal. However, the NMR data of the mixture of **52a** and **52c** is as follows: δ_H ($CDCl_3$, 400 MHz): 6.30 (d, 0.6H, J = 2.0 Hz, H-1 of **52a**), 5.72 (d, 0.4H, J = 1.2 Hz, H-1 of **52c**), 5.49 – 5.28 (m, 1H, H-4), 5.19 (dd, 0.6H, J = 4.0 and 9.6 Hz, H-3 of **52a**), 4.99 (dd, 0.4H, J = 4.0 and 9.6 Hz, H-3 of **52c**), 4.58 (dd, 0.4H, J = 1.2 and 3.6 Hz, H-2 of **52c**), 4.42 (dd, 0.6H, J = 1.6 and 4.0 Hz, H-2 of **52a**), 4.26 – 4.06 (m, 2.6H, H-5 of **52a**, H-6_a and H-6_b), 3.82 – 3.78 (m, 0.4H, H-5 of **52c**), 2.16, 2.15, 2.10, 2.09, 2.08 (x 2), 2.05 (x 2) (8s, 12H, 4 x CH_3CO_2 of each isomer); δ_C ($CDCl_3$, 75 MHz): 170.8, 170.2 (x 2), 170.1, 169.5, 169.4, 168.7, 168.3, 93.4 (C-1 of **52a**), 90.2 (C-1 of **52c**), 74.0, 71.5, 71.3, 69.4, 69.1, 69.0, 66.5, 65.9, 65.7, 62.6, 62.1, 51.0, 50.3, 48.0, 21.0, 20.98, 20.96, 20.92, 20.85, 20.83, 20.77. The spectroscopic data were in agreement with the reported data.[112,113]

3,4,6-Tri-O-benzyl-2-bromo-2-deoxy-talo and galactopyranosyls (126a and 126b):



Bromohydroxylation 3,4,6-tri-*O*-benzyl-D-galactal using method A followed by acetylation afforded inseparable bromoacetates **219a** and **219b** in excellent yield and a ratio of almost 1:1; δ_H ($CDCl_3$, 300 MHz): 7.47 – 7.24 (m, 15H, 3 x Ph), 6.33 (d, 0.57H, J = 3.5 Hz, H-1 of **220a**), 5.75 (d, 0.43H, J = 9.2 Hz, H-1 of **220b**), 5.00 – 3.49 (m, 12H, H-2, H-3, H-4, H-5, H-6_a, H-6_b and 3 x CH_2Ph), 2.14, 2.13 (2s, 3H, CH_3CO_2); δ_C ($CDCl_3$, 75 MHz): 169.0, 168.9 (CH_3CO_2), 138.1, 137.7, 137.6, 137.2, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7 (3 x Ph), 94.0 (C-1 of **220a**), 91.9 (C-1 of **220b**), 82.5, 78.8, 75.1, 74.8, 74.6, 74.4, 73.6, 73.5, 73.2, 73.0, 71.9, 68.1, 67.7, 50.8, 48.8, 20.8 (CH_3CO_2). The spectroscopic data were in agreement with the reported data.[91]

Methyl 3,4,6-tri-O-benzyl -2-bromo-2-deoxy-α-D-manno and β-D-glucopyranosides (121a and 121b):

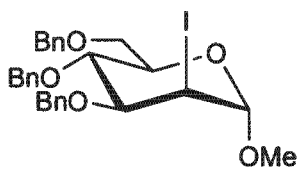


121a **121b**

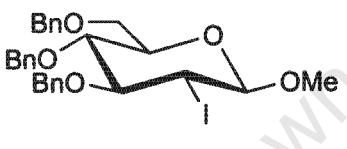
Methoxybromination of benzylated glucal **67** using method A gave inseparable methyl glycosides **121a** and **121b** in a ratio of 5:4 (α-*manno*:β-*gluco*) and 100% yield as colorless oil; δ_H ($CDCl_3$, 300 MHz): 7.41 – 7.20 (m, 15H, 3 x Ph), 5.30 (s, 0.6H, H-1 of **121a**), 5.00 (d, 0.4H, J = 10.4 Hz, H-1 of **121b**), 4.89 – 4.39 (m, 6H, 3 x CH_2Ph), 3.98 – 3.63 (m, 5.6H), 3.59 (s, 1.2H, OMe of **121b**), 3.55 – 3.51 (m, 0.4H, H-5 of

121b), 3.37 (s, 1.8H, OMe of **121a**); δ_C ($CDCl_3$, 100 MHz): 138.3, 138.2, 137.8, 137.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5 (3 x Ph), 103.4 (C-1 of **121b**), 101.0 (C-1 of **121a**), 85.5, 79.1, 76.0, 75.2, 75.1, 74.5, 73.6, 73.4, 71.9, 71.2, 68.9, 68.5, 57.3, 55.1, 53.0, 51.2. The spectroscopic data were in agreement with the reported data.[61,181]

Methyl 3,4,6-tri-O-benzyl-2-deoxy-2-iodo-α-D-manno and β-D-glucopyranosides (122a and 122b):



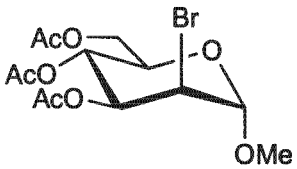
122a



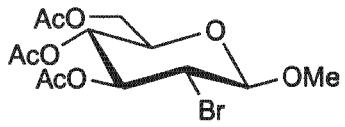
122b

Methoxyiodination of 3,4,6-tri-*O*-benzyl-D-glucal (**67**) using method A afforded inseparable methyl glycosides **122a** and **122b** as an oil in 85% yield and 9:1 ratio in favour of **122a**; δ_H ($CDCl_3$, 300 MHz): 7.48 – 7.16 (m, 15H, 3 x Ph), 5.14 (d, 0.9H, J = 0.8 Hz, H-1 of **122a**), 5.99 (d, 0.1H, J = 9.6 Hz, H-1 of **122b**), 5.04 – 4.46 (m, 6H), 3.98 – 3.60 (m, 5H), 3.57 (s, 0.3H, OMe of **122b**), 3.53 (ddd, 0.1H, J = 2.5, 4.0 and 9.5 Hz, H-5 of **122b**), 3.37 (s, 2.7H, OMe of **122a**), 3.33 (dd, 0.9H, J = 4.1 and 8.0 Hz, H-5 of **122a**); δ_C ($CDCl_3$, 75 MHz): 138.4, 138.3, 137.7, 128.4, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4 (3 x Ph), 104.1 (C-1 of **122b**), 102.4 (C-1 of **122a**), 85.8, 79.6, 76.9, 75.9, 75.5, 75.2, 75.1, 74.9, 73.5, 73.4, 72.0, 70.9, 69.0, 68.5, 57.2, 55.0, 33.2, 32.6. The spectroscopic data were in agreement with the reported data.[60]

Methyl 3,4,6-tri-O-acetyl-2-bromo-2-deoxy-α-D-manno and β-D-glucopyranosides (124a and 124b):



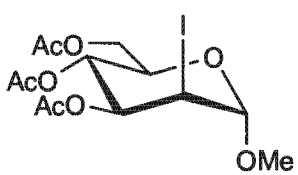
124a



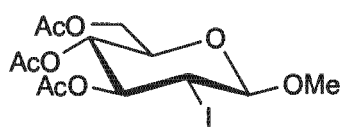
124b

Methoxybromination of acetylated glucal **59** using method B afforded inseparable methyl glycosides **124a** and **124b** in a ratio of 3:1 (α-*manno*:β-*gluco*) and 89% yield as an oil; δ_H ($CDCl_3$, 300 MHz): 5.36 (t, 0.75H, J = 9.9 Hz, H-4 of **124a**), 5.25 (dd, 0.25H, J = 9.3 and 10.6 Hz, H-3 of **124b**), 5.16 (dd, 0.75H, J = 4.0 and 9.8 Hz, H-3 of **124a**), 4.94 (dd, 0.25H, J = 9.2 and 10.0 Hz, H-4 of **124b**), 4.93 (d, 0.75H, J = 1.5 Hz, H-1 of **124a**), 4.46 (d, 0.25H, J = 8.4 Hz, H-1 of **124b**), 4.40 (dd, 0.75H, J = 1.5 and 4.0 Hz, H-2 of **124a**), 4.29 – 4.07 (m, 2H, H-6_a and H-6_b), 3.98 – 3.92 (m, 1H, H-5), 3.74 (dd, 0.25H, J = 8.6 and 10.6 Hz, H-2 of **124b**), 3.54 (s, 0.75H, OMe of **124b**), 3.38 (s, 2.25H, OMe of **124a**), 2.06, 2.05, 2.04, 2.01, 2.00, 1.98 (6s, 9H, 3 x CH_3CO_2 of each isomer); δ_C ($CDCl_3$, 100 MHz): 170.6, 170.5, 169.8, 169.7, 169.4, 103.2 (C-1 of **124b**), 100.8 (C-1 of **124a**), 74.6, 71.8, 69.1, 68.9, 66.1, 62.2, 61.8, 57.5, 55.4, 49.2, 20.6, 20.5, 20.4 (3 x CH_3CO_2). The spectroscopic data were in agreement with the reported data.[47,48]

Methyl 3,4,6-tri-O-acetyl-2-deoxy-2-iodo-α-D-manno and β-D-glucopyranosides (125a and 125b):



125a

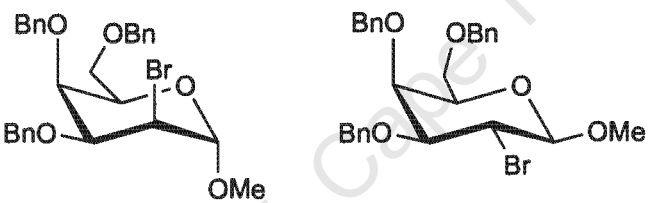


125b

Methoxyiodination of acetylated glucal **59** using method B gave an inseparable mixture of methyl glycosides **125a** and **125b** in a ratio of 6:1 (α-*manno*:β-*gluco*) and 66% yield as an oil; δ_H ($CDCl_3$, 300 MHz): 5.32 (t, 0.86H, J = 9.6 Hz, H-4 of **125a**),

5.25 (dd, 0.14H, J = 9.0 and 11.0 Hz, H-3 of **125b**), 5.04 (d, 0.86H, J = 0.8 Hz, H-1 of **125a**), 4.92 (t, 0.14H, J = 9.6 Hz, H-4 of **125b**), 4.58 (dd, 0.86H, J = 4.4 and 9.2 Hz, H-3 of **125a**), 4.51 – 4.48 (m, 3.14H, H-1 of **125b**, H-2, H-6_a, and H-6_b), 3.96 (ddd, 0.86H, J = 2.4, 5.2 and 10.0 Hz, H-5 of **125a**), 3.71 (ddd, 0.14H, J = 2.4, 4.8 and 10.0 Hz, H-5 of **125b**), 3.52 (s, 0.42H, OMe of **125b**), 3.37 (s, 2.58H, OMe of **125a**), 2.09, 2.07, 2.04, 2.01, 1.96 (5s, 9H, CH_3CO_2); δ_C ($CDCl_3$, 100 MHz): 170.6, 169.7, 169.4 (3 x CH_3CO_2), 103.9 (C-1 of **125b**), 102.3 (C-1 of **125a**), 75.5, 71.3, 71.2, 69.2, 69.0, 67.5, 62.9, 57.5, 55.3, 29.2, 27.9, 20.8, 20.7, 20.6, 20.5. The spectroscopic data were in agreement with the reported data.[76]

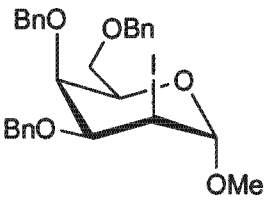
Methyl 3,4,6-tri-O-benzyl-2-bromo-2-deoxy-α-D-talo and β-D-galactopyranosides (128a and 128b):



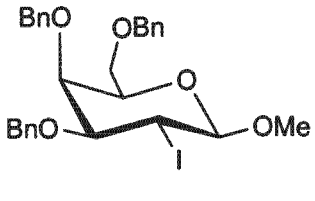
128a **128b**

Methoxybromination of benzylated galactal **106** using method A afforded inseparable methyl glycosides **128a** and **128b** in an approximately 1:1 ratio (α-*talo*:β-*galacto*) and 81% yield as an oil: δ_H ($CDCl_3$, 400 MHz): 7.44 – 7.24 (m, 15H, 3 x Ph), 4.89 (d, 0.5H, J = 11.2 Hz, CH_2Ph), 4.87 (d, 0.5H, J = 11.6 Hz, CH_2Ph), 4.85 (d, 0.5H, J = 3.6 Hz, H-1 of **128a**), 4.73 (m, 1H, CH_2Ph), 4.71 (m, 1H, CH_2Ph), 4.63 – 4.40 (m, 3H, CH_2Ph), 4.39 (d, 0.5H, J = 8.4 Hz, H-1 of **128b**), 4.20 (dd, 0.5H, J = 8.4 and 10.8 Hz, H-2 of **128b**), 3.98 (t, 0.5H, J = 6.6 Hz, H-5 of **128a**), 3.92 – 3.88 (m, 2H, H-2, H-3, H-6_a and H-6_b of **128a**), 3.88 – 3.37 (m, 4H, OMe, H-5, H-3, H-4 and H-6_a and H-6_b of **128b**), 3.55 (dd, 0.5H, J = 1.8 and 6.6 Hz, H-4 of **128a**), 3.42 (s, 1.5H, OMe of **128a**); δ_C ($CDCl_3$, 100 MHz): 138.5, 138.1, 138.0, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.6, 104.1 (C-1 of **128b**), 100.3 (C-1 of **128a**), 83.2 (C-3 of **128b**), 79.0 (C-3 of **128a**), 75.5, 75.2, 74.8, 74.0, 73.8, 73.7, 73.5, 73.4, 69.8 (C-6 of **128a**), 69.1, 68.7 (C-6 of **128b**), 57.2 (C-2 of **128b**), 56.0 (OMe of **128a**), 52.9 (OMe of **128b**), 50.7 (C-2 of **128a**). The spectroscopic data were in agreement with the reported data.[182]

Methyl 3,4,6-tri-O-benzyl-2-deoxy-2-iodo-α-D-talo and β-D-galactopyranosides (129a and 129b):



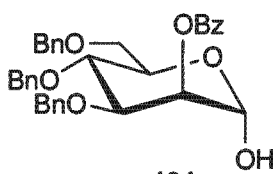
129a



129b

Methoxyiodination of benzylated galactal **106** using method A afforded inseparable methyl glycosides **129a** and **129b** in 8:2 ratio (α-*talo*:β-*galacto*) and 92% yield as a colorless oil; δ_H ($CDCl_3$, 400 MHz): 7.48 – 7.22 (m, 15H, 3 x Ph), 5.24 (d, 0.8H, J = 1.5 Hz, H-1 of **129a**), 5.05 (d, 0.8H, J = 11.8 Hz), 4.87 (dd, 0.4H, J = 9.0 and 11.8 Hz), 4.77 – 4.41 (m, 5H), 4.35 (ddd, 0.8H, J = 1.0, 1.7 and 4.4 Hz), 4.30 (dd, 0.2H, J = 8.9 and 11.2 Hz), 4.21 – 4.17 (m, 0.2H), 4.05 (dt, 0.8H, J = 2.0 and 6.2 Hz), 3.95 – 3.92 (m, 0.8H), 3.83 (d, 0.2H, J = 2.6 Hz), 3.80 (dd, 0.2H, J = 7.1 and 10.1 Hz), 3.74 – 3.66 (m, 1.6H), 3.64 – 3.61 (m, 0.4H), 3.56 – 3.49 (m, 1.4H), 3.36 (s, 2.4H, OMe); δ_C ($CDCl_3$, 100 MHz): 138.8, 138.2, 137.8, 128.4, 128.3, 128.1, 127.7, 127.6, 127.3, 104.8 (C-1 of **129b**), 103.4 (C-1 of **129a**), 83.8, 74.6, 74.0, 73.9, 73.6, 73.5, 73.3, 73.2, 73.1, 73.0, 72.8, 70.9, 70.7, 70.6, 69.4, 68.5, 57.0, 55.3, 33.0, 24.3.

2-O-Benzoyl-3,4,6-tri-O-benzyl-D-mannopyranose (134):



134

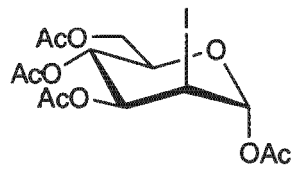
To a mixture of WO_4^{2-}-Tv (8 mg, 0.004 mmol W) and *n*-pentenyl glycoside **133** (150 mg, 0.24 mmol) or *n*-pentenyl orthoester **132** (150 mg, 0.24 mmol) in THF (5 mL) containing ammonium iodide (174 mg, 1.20 mmol) at 60°C, was added hydrogen peroxide in portions (20 μL of 50% aqueous solution) every 3 minutes until TLC indicated the full disappearance of starting material. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was then taken up in

ethyl acetate, washed successively with 10% $Na_2S_2O_3$, water and brine, and dried over $MgSO_4$. The crude product was purified by column chromatography to give mono-benzoate **134** in 82 - 90% yield as an oil; δ_H ($CDCl_3$, 300 MHz): 8.07 (d, 2H, J = 8.1 Hz, *ortho* protons from benzoate), 7.51 – 7.12 (m, 18H, 4 x Ph), 5.62 (dd, 1H, J = 2.1 and 2.9 Hz, H-2), 5.35 (s, 1H, H-1), 4.91 – 4.50 (m, 6H, 3 x CH_2Ph), 4.16 (dd, 1H, J = 3.2 and 9.3 Hz, H-3), 4.14 - 4.09 (m, 1H, H-5), 3.95 (t, 1H, J = 9.6 Hz, H-4), 3.82 – 3.76 (m, 2H, H-6_a and H-6_b), 3.37 (br s, OH); δ_C ($CDCl_3$, 75 MHz): 165.7 (PhCO_2), 138.3, 138.2, 138.0, 133.1, 129.9, 128.4, 128.3, 128.0, 127.7, 127.6 (4 x Ph), 92.6 (C-1), 77.7, 75.1, 74.5, 73.5, 71.6, 71.5, 69.5, 69.4. Acetylation of **134** under the general acetylation protocol described for the halohydrins resulted in formation of 1-*O*-acetyl-2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranose (**135**) in 76% yield as an oil; ($CDCl_3$, 300 MHz): 8.06 (d, 2H, J = 7.4 Hz, *ortho* protons from benzoate), 7.70 – 7.10 (m, 18H, 4 x Ph), 6.24 (d, 1H, J = 2.1 Hz, H-1), 5.61 (t, 1H, J = 2.6 Hz, H-2), 4.91 – 4.52 (m, 6H), 4.21 – 4.15 (m, 1H), 4.09 (dd, 1H, J = 3.0 and 9.1 Hz), 3.94 – 3.87 (m, 2H), 3.80 – 3.74 (m, 1H), 2.10 (s, 3H, CH_3CO_2). The spectroscopic data were in agreement with the reported data.[107]

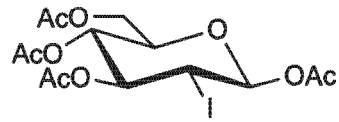
General procedure for the iodoacetoxylation of glycals

To a solution of a glycal (0.37 mmol) in AcOH/CH_3CN (1:1, 2 mL) was added NH_4I (0.44 mmol) and Ac_2O (0.5 μL) and the resulting reaction mixture was allowed to cool to 0°C. 50% aq H_2O_2 (0.44 mmol) was added and the solution was stirred for 1 h at 0°C, when TLC showed the reaction was complete. A 0.1 M sodium thiosulphate was then added until the brownish color disappeared, and the solution was cooled in an ice-water bath before adding 10% aq NaOH until the solution became slightly basic. The resultant mixture was extracted with ethyl acetate, and the combined organic phases were washed successively with water, 10% sodium thiosulfate and brine, dried over $MgSO_4$ and concentrated. The diastereoisomers were separated by column chromatography on silica gel using a mixture of ethyl acetate and petroleum ether as eluent.

1,3,4,6-Tetra-O-acetyl-2-deoxy-2-iodo-α-D-mannopyranose **(53a) and** ***1,3,4,6-tetra-O-acetyl-2-deoxy-2-iodo-β-D-glucopyranose*** **(53b):**



53a



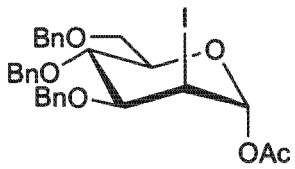
53b

Iodoacetoxylation of acetylated glucal **59** afforded separable iodoacetates **53a** and **53b** in a ratio of 83:17 and combined yield of 85% as colorless oils;

Diastereomer **53a**: δ_H ($CDCl_3$, 400 MHz): 6.36 (d, 1H, J = 1.2 Hz, H-1), 5.42 (t, 1H, J = 9.6 Hz, H-4), 4.56 (dd, 1H, J = 4.4 and 9.6 Hz, H-3), 4.51 (dd, 1H, J = 1.6 and 4.4 Hz, H-2), 4.22 – 4.07 (m, 3H, H-5, H-6_a and H-6_b), 2.14, 2.09, 2.08, 2.05 (4s, 12H, 4 x CH_3CO_2); δ_C ($CDCl_3$, 100 MHz): 170.6, 169.8, 169.2, 168.1 (4 x CH_3CO_2), 94.7 (C-1), 71.4, 68.6, 67.1, 61.8 (C-3, C-4, C-5 and C-6), 27.1 (C-2), 20.8, 20.7, 20.6, 20.5 (4 x CH_3CO_2).

Diastereomer **53b**: δ_H ($CDCl_3$, 400 MHz): 5.87 (d, 1H, J = 9.6 Hz, H-1), 5.34 (dd, 1H, J = 8.8 and 11.2 Hz, H-3), 5.01 (t, 1H, J = 9.4 Hz, H-4), 4.32 (dd, 1H, J = 4.4 and 12.4 Hz, H-6_a), 4.10 (dd, 1H, J = 2.2 and 12.6 Hz, H-6_b), 3.99 (dd, 1H, J = 9.6 and 10.8 Hz, H-2), 3.90 – 3.86 (m, 1H, H-5), 2.17, 2.10, 2.08, 2.02 (4s, 12H, 4 x CH_3CO_2); δ_C ($CDCl_3$, 100 MHz): 170.5, 169.5, 169.4, 168.5 (4 x CH_3CO_2), 94.0 (C-1), 75.2 (C-3), 73.0 (C-5), 68.5 (C-4), 61.5 (C-6), 25.7 (C-2), 20.7, 20.6 (x 2), 20.5 (4 x CH_3CO_2). The spectroscopic data were in agreement with the reported data.[112,113]

1-O-Acetyl-3,4,6-tri-O-benzyl-2-deoxy-2-iodo-α-D-mannopyranose (148a) and 1-O-acetyl-3,4,6-tri-O-benzyl-2-deoxy-2-iodo-β-D-glucopyranose (148b):



148a

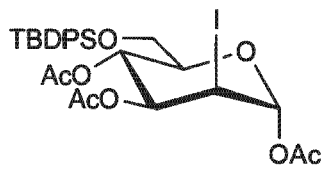
148b

Iodoacetoxylation of benzylated glucal **67** gave separable iodoacetates **148a** and **148b** in 100% combined yield and 91:1 ratio (α-*manno*:β-*gluco*) as colorless oil and white crystals, respectively;

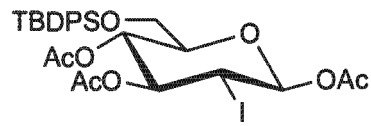
Diastereomer **148a**: δ_H ($CDCl_3$, 400 MHz): 7.41 – 7.18 (m, 15H, 3 x Ph), 6.41 (d, 1H, J = 2.0 Hz, H-1), 4.87 (d, 1H, J = 10.8 Hz, CH_2Ph), 4.71 (dd, 2H, J = 2.4 and 11.6 Hz, CH_2Ph), 4.54 (d, 3H, J = 10.8 Hz, CH_2Ph), 4.46 (dd, 1H, J = 1.6 and 4.0 Hz, H-2), 4.01 (dd, 1H, J = 8.0 and 9.6 Hz, H-4), 3.97 – 3.94 (m, 1H, H-5), 3.79 (dd, 1H, J = 4.2 and 11.0 Hz, H-6_a), 3.69 (dd, 1H, J = 1.6 and 11.2 Hz, H-6_b), 3.23 (dd, 1H, J = 4.0 and 8.0 Hz, H-3), 2.04 (s, 3H, C$H_3$$CO_2$); δ_C ($CDCl_3$, 100 MHz): 168.5 ($CH_3$$CO_2$), 138.3, 138.1, 137.4, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.6 (3 x Ph), 95.6 (C-1), 76.2, 75.5, 75.4, 74.9, 73.6, 71.1 (C-3, C-4, C-5 and 3 x CH_2Ph), 68.7 (C-6), 31.0 (C-2), 20.8 ($CH_3$$CO_2$).

Diastereomer **148b**: mp 90 – 95°C (lit.,[100] reported as oil); δ_H ($CDCl_3$, 400 MHz): 7.42 – 7.14 (m, 15H, 3 x Ph), 5.82 (d, 1H, J = 9.6 Hz, H-1), 4.97 (d, 1H, J = 10.4 Hz, CH_2Ph), 4.87 (d, 1H, J = 10.4 Hz, CH_2Ph), 4.79 (d, 1H, J = 10.8 Hz, CH_2Ph), 4.62 (d, 1H, J = 11.8 Hz, CH_2Ph), 4.56 (d, 1H, J = 10.8 Hz, CH_2Ph), 4.48 (d, 1H, J = 11.8 Hz, CH_2Ph), 4.02 – 3.59 (m, 6H, H-2, H-3, H-4, H-5, H-6_a and H-6_b), 2.16 (s, 3H, C$H_3$$CO_2$); δ_C ($CDCl_3$, 100 MHz): 168.9 ($CH_3$$CO_2$), 137.7, 128.4, 128.0, 127.9, 127.7 (3 x Ph), 94.3 (C-1), 85.5, 78.9, 75.9, 75.6, 75.0, 73.6, 67.9 (C-3, C-4, C-5, C-6 and 3 x CH_2Ph), 29.7 (C-2), 20.8 ($CH_3$$CO_2$). The spectroscopic data were in agreement with the reported data.[100]

1,3,4-Tri-*O*-acetyl-2-deoxy-2-iodo-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranose (149a) and 1,3,4-tri-*O*-acetyl-2-deoxy-2-iodo-6-O-*tert*-butyldiphenylsilyl-β-D-glucopyranose (149b):



149a



149b

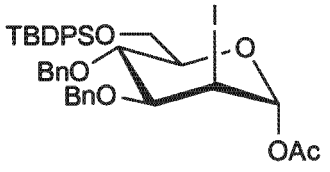
Iodoacetoxylation of silylated glucal **114** afforded separable iodoacetates **149a** and **149b** as crystalline white solids in a combined yield of 100% and 93:7 ratio (α-*manno*:β-*gluco*);

Diastereomer **149a**: mp 153 – 155°C; $[\alpha]_D$ = +31.9 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz): 7.77 - 7.34 (m, 10H, 2 x Ph), 6.45 (d, 1H, *J* = 1.5 Hz, H-1), 5.63 (t, 1H, *J* = 9.6 Hz, H-4), 4.60 (dd, 1H, *J* = 4.2 and 9.6 Hz, H-3), 4.52 (dd, 1H, *J* = 1.5 and 4.2 Hz, H-2), 3.98 - 3.92 (m, 1H, H-5), 3.72 (d, 2H, *J* = 2.7 Hz, H-6_a and H-6_b), 2.12, 2.09, 1.93 (3s, 9H, 3 x CH_3CO_2), 1.08 (s, 9H, Me_3C-Si); δ_C ($CDCl_3$, 100 MHz): 170.0, 169.0, 168.2 (3 x CH_3CO_2), 135.8, 135.7, 133.2, 133.1, 129.7, 129.6, 127.6 (2 x Ph), 95.0 (C-1), 74.0 (C-5), 69.2 (C-3), 67.1 (C-4), 62.0 (C-6), 27.3 (C-2), 26.7 (Me_3C-Si), 20.9, 20.8, 20.5 (3 x CH_3CO_2), 19.2 (Me_3C-Si). IR ($CHCl_3$): 1751 cm^{-1}. Anal. Calcd for $C_{28}H_{35}IO_8Si$: C, 51.38; H, 5.39. Found: C, 51.42; H, 5.31. LRFAB MS calcd for $C_{28}H_{35}IO_8Si$ $[M - OOAc]^+$ 595.6, found 594.8.

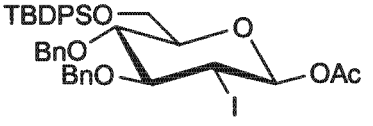
Diastereomer **149b**: mp 149 – 156°C; $[\alpha]_D$ = +44.0 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz): 7.67 – 7.33 (m, 10H, 2 x Ph), 5.87 (d, 1 H, *J* = 9.3 Hz, H-1), 5.30 (dd, 1H, *J* = 9.3 and 11.2 Hz, H-4), 5.12 (t, 1H, *J* = 9.3 Hz, H-3), 3.98 (dd, 1H, *J* = 9.3 and 11.0 Hz, H-2), 3.80 – 3.65 (m, 3H, H-5, H-6_a and H-6_b), 2.18, 2.09, 1.89 (3s, 9H, CH_3CO_2), 1.04 (s, 9H, Me_3C-Si); δ_C ($CDCl_3$, 100 MHz): 169.6, 169.3, 168.4 (3 x CH_3CO_2), 135.7, 135.6, 133.1, 129.7, 129.7, 127.7, 127.6, 127.5 (2 x Ph), 94.0 (C-1), 75.7, 75.4, 68.8, 62.2 (C-3, C-4, C-5 and C-6), 29.7 (C-2), 26.7 (Me_3C-Si), 20.7, 20.6, 20.5 (3 x CH_3CO_2), 19.2 (Me_3C-Si); IR ($CHCl_3$): 1759 cm^{-1}. Anal. Calcd for

$C_{28}H_{35}IO_8Si$: C, 51.38; H, 5.39. Found: C, 51.50; H, 5.55. LRFAB MS calcd for $C_{28}H_{35}IO_8Si$ $[M - 7H]^+$ 647.6, found 647.2.

1-*O*-Acetyl-3,4-di-*O*-benzyl-2-deoxy-2-iodo-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranose (150a) and 1-*O*-acetyl-3,4-di-*O*-benzyl-2-deoxy-2-iodo-6-*O*-*tert*-butyldiphenylsilyl-β-D-glucopyranose (150b):



150a



150b

Iodoacetoxylation of glucal **115** afforded separable iodoacetates **150a** and **150b** in 95% combined yield and 93:7 ratio (α-*manno*:β-*gluco*) as colorless oils;

Diastereomer **150a**: $[\alpha]_D$ = +55.2 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.77 – 7.18 (m, 20H, 4 x Ph), 6.45 (d, 1H, *J* = 1.6 Hz, H-1), 4.97 (d, 1H, *J* = 10.4 Hz, C*H*$_2$Ph), 4.74 (d, 1H, *J* = 11.6 Hz, C*H*$_2$Ph), 4.65 (d, 1H, *J* = 10.4 Hz, C*H*$_2$Ph), 4.57 (d, 1H, *J* = 11.6 Hz, C*H*$_2$Ph), 4.48 (dd, 1H, *J* = 1.6 and 4.4 Hz, H-2), 4.26 (t, 1H, *J* = 9.4 Hz, H-4), 3.40 (dd, 1H, *J* = 3.2 and 11.6 Hz, H-6_a), 3.88 – 3.82 (m, 2H, H-5 and H-6_b), 3.25 (m, 1H, H-3), 2.01 (s, 3H, C*H*$_3$CO$_2$), 1.11 (s, 9H, *Me*$_3$C-Si); δ_C ($CDCl_3$, 100 MHz): 168.5 (CH_3CO_2), 135.9, 135.7, 129.6, 129.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5 (4 x Ph), 95.8 (C-1), 75.6, 75.5, 75.4, 75.1, 71.2 (C-3, C-4, C-5, and 2 x *C*H$_2$Ph), 62.2 (C-6), 31.2 (C-2), 26.9 (*Me*$_3$C-Si), 20.8 (*C*H$_3$CO$_2$), 19.3 (Me$_3$*C*-Si). IR ($CHCl_3$): 1750 cm^{-1}. Anal. Calcd for $C_{38}H_{43}IO_6Si$: C, 60.80; H, 5.77. Found: C, 61.14; H, 5.94. LRFAB MS calcd for $C_{38}H_{43}IO_6Si$ $[M - 2H]^+$ 748.7, found 747.9.

Diastereomer **150b**: $[\alpha]_D$ = +25.3 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.70 – 7.21 (m, 20H, 4 x Ph), 5.84 (d, 1H, *J* = 9.6 Hz, H-1), 4.98 (d, 1H, *J* = 10.4 Hz, C*H*$_2$Ph), 4.91 (d, 1H, *J* = 4.2 Hz, C*H*$_2$Ph), 4.89 (d, 1H, *J* = 4.2 Hz, C*H*$_2$Ph), 4.77 (d, 1H, *J* = 10.4 Hz, C*H*$_2$Ph), 4.00 (dd, 1H, *J* = 9.6 and 10.4 Hz, H-2), 3.95 (m, 2H, H-6_a and H-6_b), 3.87 (t, 1H, *J* = 9.0 Hz, H-4), 3.78 (dd, 1H, *J* = 9.0 and 10.4 Hz, H-3), 3.53 – 3.49 (m, 1H, H-5), 2.19 (s, 3H, C*H*$_3$CO$_2$), 1.05 (s, 9H, *Me*$_3$C-Si); δ_C ($CDCl_3$, 100 MHz):

168.8 (CH_3CO_2), 135.9, 135.5, 129.6, 126.5, 128.5, 128.4, 128.2, 128.0, 127.9, 127.7, 127.6, 127.5 (4 x Ph), 94.4 (C-1), 85.4 (C-3), 78.9 (C-4), 76.6 (C-5), 75.8, 75.1 (2 x CH_2Ph), 62.0 (C-6), 30.5 (C-2), 26.8 (Me_3C-Si), 20.7 (CH_3CO_2), 19.3 (Me_3C-Si). IR ($CHCl_3$): 1760 cm^{-1}. Anal. Calcd for $C_{38}H_{43}IO_6Si$: C, 60.80; H, 5.77. Found: C, 61.18; H, 5.75. LRFAB MS calcd for $C_{38}H_{43}IO_6Si$ $[M - H]^+$ 750.7, found 749.0.

1-O-Acetyl-2-deoxy-2-iodo-3,4,6-tri-O-tert-butyldiphenylsilyl-β-D-glucopyranose (151b):

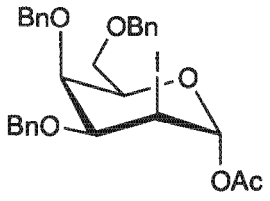
151b

Iodoacetoxylation of persilylated glucal **116** gave a pure crystalline form of iodoacetate **151b** and **151a** along with inseparable impurities (which made it difficult to interpret its NMR spectrum) in a combined 94% yield (estimated from NMR) and a ratio of 17:83 (α-*manno*:β-*gluco* estimated from the ratio of the acetoxy signals in the ^1H NMR of the crude product);*

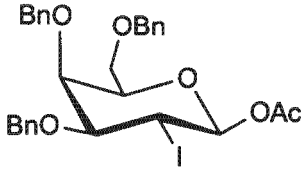
Diastereomer **151b**: mp 153°C (No lit. report); δ_H ($CDCl_3$, 300 MHz): 7.59 – 7.14 (m, 30H, 6 x Ph), 6.54 (d, 1H, J = 6.9 Hz, H-1), 4.48 (d, 1H, J = 3.3 Hz), 4.22 (dd, 1H, J = 4.5 and 8.4 Hz), 3.89 (d, 1H, J = 6.6 Hz), 3.83 (dd, 1H, J = 8.4 and 10.5 Hz), 3.70 (d, 1H, J = 2.7 Hz), 3.18 (dd, 1H, J = 4.5 and 10.8 Hz), 2.07 (s, 3H, CH_3CO_2), 1.04, 0.95, 0.81 (3s, 27H, 3 x Me_3C-Si); δ_C ($CDCl_3$, 100 MHz): 169.1 (CH_3CO_2), 136.1, 136.0, 135.9, 135.8, 135.6, 133.8, 133.6, 132.9, 132.7, 132.6, 132.3, 130.0, 129.9, 129.8, 129.7, 129.4, 127.8, 127.7, 127.6, 127.5 (6 x Ph), 94.3 (C-1), 82.8, 77.1, 70.8, 65.5 (C-3, C-4, C-5 and C-6), 27.0, 26.8, 26.7 (3 x Me_3C-Si), 24.8 (C-2), 21.0 (CH_3CO_2), 19.1, 19.0, 18.8 (3 x Me_3C-Si). Anal. Calcd for $C_{56}H_{67}IO_6Si_3$: C, 64.22; H, 6.45. Found: C, 64.86; H, 6.44. The spectroscopic data were in agreement with the reported data.[114]

* In line with the literature report the NMR of **151a** was complex and was not analyzed.[114]

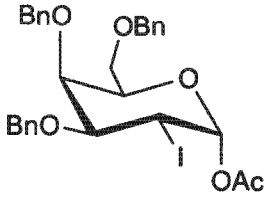
1-O-Acetyl-3,4,6-tri-O-benzyl-2-deoxy-2-iodo-α-D-talopyranose (107a), 1-O-acetyl-3,4,6-tri-O-benzyl-2-deoxy-2-iodo-β-D- and α-D-galactopyranoses (107b and 107d):



107a



107b



107d

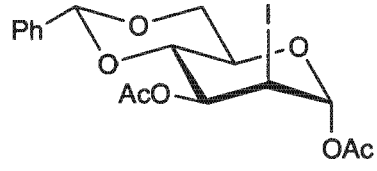
Iodoacetoxylation of benzylated galactal **106** gave iodoacetates **107a**, and a mixture of **107b** and **107d** in a combined yield of 96% and a ratio of 15:1:4 (α-*talo*:β-*galacto*:α-*galacto*) as colorless oils;

Diastereomer **107a**: δ_H ($CDCl_3$, 400 MHz): 7.43 – 7.25 (m, 15H, 3 x Ph), 6.51 (d, 1H, J = 2.4 Hz, H-1), 5.03 (d, 1H, J = 11.6 Hz, CH_2Ph), 4.76 (d, 1H, J = 11.2 Hz, CH_2Ph), 4.59 (d, 1H, J = 11.6 Hz, CH_2Ph), 4.54 (t, 2H, J = 12.2 Hz, CH_2Ph), 4.43 (d, 1H, J = 11.6 Hz, CH_2Ph), 4.32 (ddd, 1H, J = 0.8, 2.4, and 4.4 Hz, H-2), 4.20 (dt, 1H, J = 2.4 and 6.4 Hz, H-5), 4.01 (bt, 1H, J = 2.4 Hz, H-4), 3.72 (d, 2H, J = 6.4 Hz, H-6_a and H-6_b), 3.51 (dd, 1H, J = 2.4 and 4.4 Hz, H-3), 2.06 (s, 3H, CH_3CO_2); δ_C ($CDCl_3$, 75 MHz): 168.5 (CH_3CO_2), 138.4, 137.9, 137.3, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.4, 127.3 (3 x Ph), 95.9 (C-1), 73.6, 73.51, 73.48, 73.4, 73.0, 71.0 (C-3, C-4, C-5, 3 x CH_2Ph), 68.5 (C-6), 22.4 (C-2), 20.8 (CH_3CO_2);

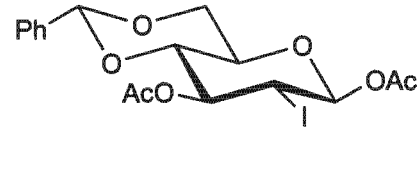
Diastereomers **107b** and **107d**: δ_H ($CDCl_3$, 300 MHz): 7.46 – 7.25 (m, 15H, 3 x Ph), 6.34 (d, 0.8H, J = 3.6 Hz, H-1 of **107d**), 5.82 (d, 0.2H, J = 9.6 Hz, H-1 of **107b**), 4.87 (d, 0.8H, J = 11.2 Hz, CH_2Ph), 4.85 (d, 0.2H, J = 11.6 Hz, CH_2Ph), 4.72 (d, 0.2H, 11.0 Hz, CH_2Ph), 4.67 (d, 0.8H, J = 11.6 Hz, CH_2Ph), 4.66 (d, 0.2H, J = 11.0 Hz, CH_2Ph), 4.55 (d, 0.2H, J = 11.6 Hz, CH_2Ph), 4.52 (d, 0.8H, J = 11.2 Hz, CH_2Ph), 4.46 (d, 0.2H, J = 12.0 Hz, CH_2Ph), 4.40 (d, 0.2H, J = 11.6 Hz, CH_2Ph), 4.39 (d, 0.8H, J = 11.6 Hz, CH_2Ph), 4.07 (br t, 0.8H, J = 6.8 Hz), 3.99 (br s 0.8H), 3.88 – 3.85 (m, 1.2H), 3.75 (dd, 0.8H, J = 5.4 and 7.8 Hz), 3.65 – 3.55 (m, 3.2H), 3.51 (dd, 0.8H, J = 5.2 and 9.2 Hz), 2.14 (s, 2.4H, CH_3CO_2), 2.12 (s, 0.6H, CH_3CO_2); δ_C ($CDCl_3$, 75 MHz): 169.3 (CH_3CO_2), 169.0 (CH_3CO_2), 138.2, 138.1, 137.7, 137.1, 137.4, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7 (3 x Ph), 94.9 (C-1 of **107b**), 92.8 (C-1

of **107d**), 83.3, 78.9, 75.0, 74.7, 74.0, 73.8, 73.6, 72.8, 72.6, 72.4, 68.1 (C-3, C-4, C-5, C-6 and 3 x CH_2Ph), 29.7 (C-2 of **107b**), 28.1 (C-2 of **107d**), 21.1 (CH_3CO_2), 20.8 (CH_3CO_2). The spectroscopic data were in agreement with the reported data.[90,91]

1,3-Di-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-iodo-α-D-manno and β-D-glucopyranoses (152a and 152b):



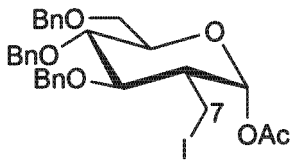
152a



152b

Iodoacetoxylation of the benzylidene glucal **118** afforded a chromatographically inseparable oil comprising **152a** and **152b** in 86% yield and 56:44 ratio (α-*manno*:β-*gluco*); $[\alpha]_D$ = +14.9 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz): 7.49 – 7.34 (m, 5H, Ph), 6.40 (d, 0.56H, *J* = 1.0 Hz, H-1 of **152a**), 5.98 (d, 0.44H, *J* = 9.3 Hz, H-1 of **152b**), 5.61 (s, 0.56H, H-7 of **152a**), 5.53 – 5.47 (m, 0.88H, H-3 and H-7 of **152b**), 4.69 (dd, 0.56H, *J* = 1.3 and 4.4 Hz, H-2 of **152a**), 4.51 (dd, 0.56H, *J* = 4.6 and 9.7 Hz, H-3 of **152a**), 4.38 – 3.56 (m, 4.44H), 2.17, 2.16, 2.14 (3s, 6H, CH_3CO_2); δ_C ($CDCl_3$, 75 MHz): 169.9, 169.1, 168.3 (CH_3CO_2), 136.8, 136.6, 130.8, 129.2, 129.2, 128.8, 128.3, 128.2, 126.2, 126.1 (Ph), 102.1 (C-7 of **152a**), 101.6 (C-7 of **152b**), 95.7 (C-1 of **152a**), 94.4 (C-1 of **152b**), 79.4, 76.6, 73.7, 68.4, 68.2, 67.6, 67.5, 66.8, 30.4, 29.2, 21.1, 20.9, 20.8, 20.6. Anal. Calcd for $C_{17}H_{19}IO_7$: C, 44.17; H, 4.14. Found: C, 44.77; H, 3.98. LRFAB MS calcd for $C_{17}H_{19}IO_7$ $[M - 2H]^+$ 460.2, found 460.0.

1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-iodomethyl-α- and -β-D-glucopyranoses (154a and 154b):

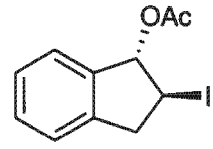


154a

154b

Iodoacetoxylation of cyclopropanated sugar **153** afforded a chromatographically inseparable oil containing **154a** and **154b** in 100% yield and 2:3 ratio (α:β); $[\alpha]_D$ = +33.2 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.35 – 7.16 (m, 15H, 3 x Ph), 6.36 (d, 0.44H, *J* = 3.6 Hz, H-1 of **154a**), 5.59 (d, 0.56H, *J* = 8.4 Hz, H-1 of **154b**), 4.99 (d, 0.56H, *J* = 10.8 Hz), 4.95 (d, 0.44H, *J* = 11.2 Hz), 4.84 – 4.58 (m, 4H), 4.50 (dd, 1H, *J* = 4.4 and 12.0 Hz), 3.89 – 3.65 (m, 4.4H), 3.60 (ddd, 0.56H, *J* = 2.0, 3.2 and 9.6 Hz), 3.54 (dd, 0.56H, *J* = 3.0 and 10.2 Hz), 3.46 (dd, 0.44H, *J* = 3.6 and 10.0 Hz), 3.28 (dd, 0.56H, *J* = 3.0 and 10.2 Hz), 2.85 (dd, 0.44H, *J* = 10.2 and 11.0 Hz), 2.24 (tt, 0.44H, *J* = 3.4 and 10.8 Hz, H-2 of **154a**), 2.14 (s, 1.68H, CH_3CO_2 of **154b**), 2.10 (s, 1.32H, CH_3CO_2 of **154a**), 1.56 – 1.50 (m, 0.56H, H-2 of **154b**); δ_C ($CDCl_3$, 100 MHz): 168.8 (CH_3CO_2), 168.7 (CH_3CO_2), 138.1, 137.8, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6 (Ph), 94.9 (C-1 of **154b**), 93.6 (C-1 of **154a**), 81.3, 80.7, 78.8, 78.4, 75.5, 75.4, 74.8, 74.6, 73.6, 73.5, 73.3, 68.1, 46.6 (C-2 of **154a**), 45.0 (C-2 of **154b**), 20.8 (CH_3CO_2 of **154b**), 20.7 (CH_3CO_2 of **154a**), 4.1 (C-7 of **154a**), 0.6 (C-7 of **154b**). IR ($CHCl_3$): 1759 cm^{-1}. Anal. Calcd for $C_{30}H_{33}IO_6$: C, 58.45; H, 5.40. Found: C, 57.99; H, 5.28. LRFAB MS calcd for $C_{30}H_{33}IO_6$ $[M-3H]^+$ 613.5, found 612.9.

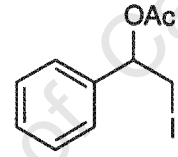
Trans-1-acetoxy-2-iodo-indane (162):



162

Iodoacetoxylation of indene (**162**) gave indane derivative **162** in 90% yield as colorless oil; δ_H ($CDCl_3$, 400 MHz): 7.42 – 7.26 (m, 4H, Ph), 6.39 (d, 1H, J = 3.6 Hz), 4.48 (ddd, 1H, J = 3.6, 4.4, and 6.8 Hz), 3.74 (dd, 1H, J = 6.8 and 16.8 Hz), 3.33 (dd, 1H, J = 4.4 and 17.2 Hz), 2.10 (s, 3H, CH_3CO_2); δ_C ($CDCl_3$, 100 MHz): 170.2 (CH_3CO_2), 141.9, 138.5, 129.4, 127.4, 125.6, 124.6, 85.5, 43.2, 24.0, 20.8 (CH_3CO_2). The spectroscopic data were in agreement with the reported data.[118]

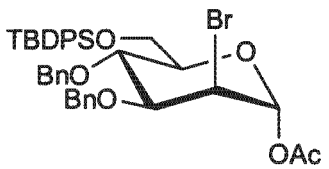
1-Acetoxy-2-iodo-1-phenylethane (164):



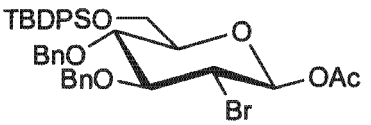
164

Iodoacetoxylation of styrene (**163**) afforded phenylethane **164** in 67% yield as colorless oil; δ_H ($CDCl_3$, 300 MHz): 7.37 – 7.35 (m, 5H, Ph), 5.89 (dd, 1H, J = 5.7 and 7.5 Hz), 3.48 (d, 1H, J = 3.0 Hz), 3.46 (d, 1H, J = 1.2 Hz), 2.13 (s, 3H, CH_3CO_2); δ_C ($CDCl_3$, 100 MHz): 169.6 (CH_3CO_2), 138.4, 128.6, 128.5, 126.3, 75.0, 20.9 (CH_3CO_2), 7.7. The spectroscopic data were in agreement with the reported data.[119]

1-*O*-Acetyl-3,4-di-*O*-benzyl-2-bromo-2-deoxy-6-*O*-*tert*-butyldiphenylsilyl-α-D-mannopyranose (167a) and 1-*O*-acetyl-3,4-di-*O*-benzyl-2-bromo-2-deoxy-6-*O*-*tert*-butyldiphenylsilyl-β-D-glucopyranose (167b):



167a



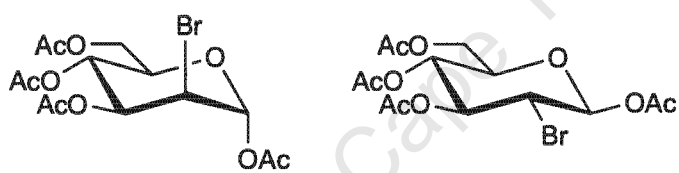
167b

To a solution of glucal **115** (488 mg, 0.86 mmol) in AcOH/CH_3CN (1:1, 24 mL), NH_4Br (102 mg, 1.04 mmol), Ac_2O (0.9 mL), and 50% aq H_2O_2 (60 μL, 1.04 mmol) were added. After stirring at room temperature for 4 h, the reaction mixture was diluted with 0.1 M sodium thiosulfate solution. The solution was then allowed to cool to 0°C and 10% aq NaOH was added until the solution became slightly basic. The resultant mixture was extracted with ethyl acetate and the combined organic phases were washed successively with water and brine, dried over $MgSO_4$ and concentrated to dryness. Separation of the product mixture by column chromatography on silica gel (ethyl acetate/petroleum ether, 1:9) afforded colorless oils of **167a** and **167b** (424 mg, 70% combined yield) in a 1:3 ratio;

Diastereomer **167a**: $[\alpha]_D$ = +21.8 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.79 – 7.23 (m, 20H, 4 x Ph), 6.40 (d, 1H, *J* = 1.6 Hz, H-1), 5.00 (d, 1H, *J* = 10.8 Hz, C*H*$_2$Ph), 4.79 (d, 1H, *J* = 12.0 Hz, C*H*$_2$Ph), 4.68 (t, 2H, *J* = 11.4 Hz, C*H*$_2$Ph), 4.38 (dd, 1H, *J* = 1.8 and 3.8 Hz), 4.35 (t, 1H, *J* = 9.4 Hz), 4.05 (dd, 1H, *J* = 3.2 and 11.6 Hz), 3.96 (dd, 1H, *J* = 3.8 and 9.0 Hz), 3.90 (dd, 1H, *J* = 1.6 and 11.2 Hz, H-2), 3.85 – 3.75 (m, 1H, H-5), 2.04 (s, 3H, C*H*$_3$CO$_2$), 1.13 (s, 9H, *Me*$_3$C-Si); δ_C ($CDCl_3$, 100 MHz): 168.3 (CH$_3$*C*O$_2$), 138.2, 137.4, 135.8, 135.5, 133.6, 132.9, 129.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.6, 127.5 (4 x Ph), 94.2 (C-1), 76.7, 75.4, 75.3, 73.7, 71.3, 62.1 (C-3, C-4, C-5, C-6 and 2 x *C*H$_2$Ph), 49.8 (C-2), 26.7 (*Me*$_3$C-Si), 20.7 (CH$_3$CO$_2$), 19.2 (Me$_3$*C*-Si). Anal. Calcd for $C_{38}H_{43}BrO_6Si$: C, 64.85; H, 6.16. Found: C, 64.88; H, 6.34. LRFAB MS calcd for $C_{38}H_{43}BrO_6Si$ $[M]^+$ 703.7, found 703.1.

Diastereomer **167b**: $[\alpha]_D$ = +28.4 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.71 – 7.22 (m, 20H, 4 x Ph), 5.78 (d, 1H, *J* = 8.8 Hz, H-1), 5.01 (d, 2H, *J* = 10.4 Hz, C*H*$_2$Ph), 4.93 – 4.88 (m, 2H, C*H*$_2$Ph), 3.96 – 3.86 (m, 4H), 3.80 (dd, 1H, *J* = 8.8 and 10.0 Hz, H-2), 3.53 (dt, 1H, *J* = 2.4 and 9.6 Hz, H-5), 2.21 (s, 3H, C*H*$_3$CO$_2$), 1.07 (s, 9H, *Me*$_3$C-Si); δ_C ($CDCl_3$, 75 MHz): 168.9 (CH_3CO_2), 137.8, 135.9, 135.6, 133.5, 132.9, 129.7, 129.6, 128.5, 127.7 , 127.5 (4 x Ph), 93.6 (C-1), 85.1, 78.5, 76.5, 76.3, 75.2 (C-3, C-4, C-5 and 2 x *C*H$_2$Ph), 62.1 (C-6), 51.4 (C-2), 26.8 (*Me*$_3$C-Si), 20.8 (*C*H$_3$CO$_2$), 19.3 (Me$_3$*C*-Si). Anal. Calcd for $C_{38}H_{43}BrO_6Si$: C, 64.85; H, 6.16. Found: C, 64.95; H, 6.03. LRFAB MS calcd for $C_{38}H_{43}BrO_6Si$ $[M]^+$ 703.7, found 703.0.

1,3,4,6-Tetra-O-acetyl-2-bromo-2-deoxy-α-D-mannopyranose (52a) and 1,3,4,6-tetra-O-acetyl-2-bromo-2-deoxy-β-D-glucopyranose (52b):



52a **52b**

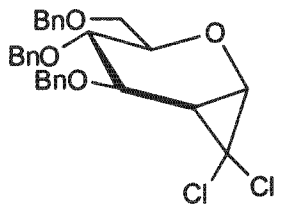
Using the procedure described above for the synthesis of **167a** and **167b**, bromoacetoxylation of acetylated glucal **59** at 60°C afforded separable bromoacetates **52a** and **52b** in a 5:3 ratio and 82% combined yield as colorless oils;

Diastereomer **52a**: δ_H ($CDCl_3$, 300 MHz): 6.29 (d, 1H, *J* = 2.0 Hz, H-1), 5.46 (t, 1H, *J* = 9.9 Hz, H-4), 5.18 (dd, 1H, *J* = 3.7 and 9.7 Hz, H-3), 4.42 (dd, 1H, *J* = 1.6 and 3.7 Hz, H-2), 4.21 – 4.05 (m, 3H, H-5, H-6$_a$ and H-6$_b$), 2.15, 2.09, 2.08, 2.05 (4s, 12H, 4 x C*H*$_3$CO$_2$); δ_C ($CDCl_3$, 75 MHz): 170.6, 170.0, 169.2, 168.0 (4 x CH_3CO_2), 93.2 (C-1), 71.3 (C-5), 68.8 (C-3), 65.6 (C-4), 61.9 (C-6), 47.8 (C-2), 20.8, 20.7, 20.6, 20.5 (4 x *C*H$_3$CO$_2$).

Diastereomer **52b**: δ_H ($CDCl_3$, 400 MHz): 5.81 (d, 1H, *J* = 9.2 Hz, H-1), 5.33 (dd, 1H, *J* = 9.0 and 10.6 Hz, H-3), 5.02 (t, 1H, *J* = 9.6 Hz, H-4), 4.31 (dd, 1H, *J* = 4.6 and 12.6 Hz, H-6$_a$), 4.10 (dd, 1H, *J* = 2.0 and 12.4 Hz, H-6$_b$), 3.89 (dd, 1H, *J* = 9.2 and 10.8 Hz, H-2), 3.87 (m, 1H, H-5), 2.17, 2.09, 2.07, 2.02 (4s, 12H, 4 x C*H*$_3$CO$_2$); δ_C

($CDCl_3$, 100 MHz): 170.4, 169.5, 169.4, 168.5 (4 x CH_3CO_2), 93.2 (C-1), 74.4 (C-3), 72.9 (C-5), 68.6 (C-4), 61.4 (C-6), 47.5 (C-2), 20.8, 20.7, 20.6, 20.5 (4 x CH_3CO_2). The spectroscopic data were in agreement with the reported data.[112,113]

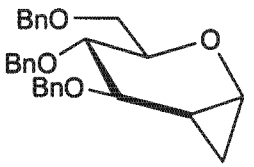
3,4,6-Tri-O-benzyl-1,5-anhydro-2-deoxy-1,2-C-dichloromethylene-D-glycero-D-gulo-hexitol (157):



157

50% aq NaOH (125 mL) was added to a vigorously stirred solution of glucal **67** (1.6 g, 3.84 mmol) in chloroform (10 mL) containing benzyltriethylammonium chloride (20 mg, 0.088 mmol). After stirring at 35°C for 4 h, the reaction mixture was diluted with water and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered and evaporated *in vacuo*. Chromatography on silica gel (ethyl acetate/petroleum ether, 3:97) of the residue and recrystallization from petroleum ether gave **157** (1.4 g, 73%) as a colorless solid; mp 60 - 65°C (lit.,[117] 62 – 63°C); δ_H ($CDCl_3$, 400 MHz): 7.50 – 7.20 (m, 15H, 3 x Ph), 4.93 – 4.40 (m, 6H, 3 x CH_2Ph), 3.89 (d, 1H, J = 8.1 Hz), 3.84 – 3.64 (m, 3H), 3.61 – 3.42 (m, 2H), 1.78 (dd, 1H, J = 4.2 and 8.0 Hz); δ_C ($CDCl_3$, 100 MHz): 138.3, 138.1, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6 (3 x Ph), 79.9, 77.4, 75.2, 74.5, 73.3, 71.8, 70.2, 61.8, 58.9, 34.3. The spectroscopic data were in agreement with the reported data.[117]

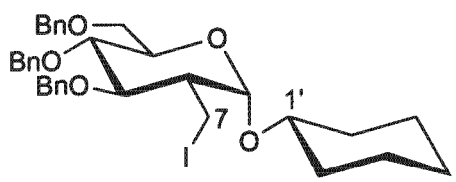
3,4,6-Tri-O-benzyl-1,5-anhydro-2-deoxy-1,2-C-methylene-D-glycero-D-gulo-hexitol (153):



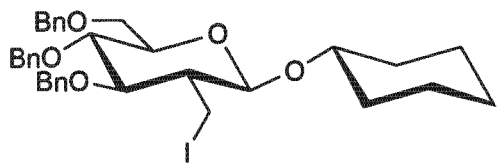
153

To a vigorously stirring suspension of lithium aluminum hydride (280 mg, 7.36 mmol) in dry THF (4 mL) was added a solution of the dichlorocyclopropane **157** (400 mg, 0.80 mmol) in dry THF (10 mL). After 8 days of stirring at room temperature, the reaction mixture was allowed to cool to 0°C and quenched by careful addition of saturated aqueous sodium sulphate. The white salts were filtered over a celite bed and washed several times with hot ethyl acetate. The filtrate was dried over $MgSO_4$ and evaporated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 1:9) to obtain **153** (258 mg, 75%) as a colorless syrup; δ_H ($CDCl_3$, 300 MHz): 7.41 – 7.23 (m, 15H, 3 x Ph), 4.83 – 4.55 (m, 6H, 3 x C*H*$_2$Ph), 3.82 – 3.52 (m, 6H, H-1, H-3, H-4, H-5, H-6_a and H-6_b), 1.01 – 0.90 (m, 1H, H-2), 0.78 – 0.68 (m, 2H, H-7_a and H-7_b); δ_C ($CDCl_3$, 75 MHz): 138.8, 138.6, 138.5, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8 (3 x Ph), 80.3, 77.7, 77.2, 73.7, 73.4, 71.3, 70.3 (C-3, C-4, C-5, C-6, and 3 x *C*H$_2$Ph), 49.9 (C-1), 15.1 (C-2), 11.7 (C-7). The spectroscopic data were in agreement with the reported data.[117]

Cyclohexyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-iodomethyl-α-D-glucopyranoside (169a) and cyclohexyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-iodomethyl-β-D-glucopyranoside (169b):



169a



169b

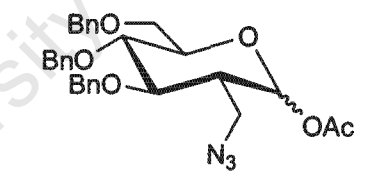
The glycosy donor **154** (425 mg, 0.69 mmol) and cyclohexanol (364 μL, 3.44 mmol) were dissolved in dry dichloromethane (3 mL) under an atmosphere of nitrogen and stirred together with 4Å molecular sieves at room temperature for 1 h. The mixture was cooled down to 0°C and then treated dropwise with $BF_3{\cdot}Et_2O$ (1 mL of 48% BF_3 solution in diethylether, 8.02 mmol). After stirring at room temperature for 1 h, Et_3N (0.7 mL) was added and the solids removed by filtration through a celite® bed. The solution was then diluted with water (10 mL) and the aqueous phase was extracted with dichloromethane. The combined organic phases were successively washed with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 1:9) to yield the glycoside **169a** (244 mg, 54%) as a syrup and **169b** (91 mg, 20%) as a white solid;

Diastereomer **169a**: $[\alpha]_D$ = +84.9 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz): 7.40 - 7.17 (m, 15H, 3 x Ph), 5.22 (d, 1H, *J* = 3.3 Hz, H-1), 4.94 (d, 1H, *J* = 11.4 Hz, C*H*$_2$Ph), 4.81 (d, 1H, *J* = 10.8 Hz, C*H*$_2$Ph), 4.63 (d, 1H, *J* = 11.1 Hz, C*H*$_2$Ph), 4.56 (d, 1H, *J* = 10.8 Hz, C*H*$_2$Ph), 4.54 (d, 1H, *J* = 12.2 Hz, C*H*$_2$Ph), 4.52 (d, 1H, *J* = 12.2 Hz, C*H*$_2$Ph), 3.93 (ddd, 1H, *J* = 1.8, 3.3 and 9.3 Hz, H-5), 3.83 (dd, 1H, *J* = 3.6 and 10.2 Hz, H-6$_a$), 3.74 – 3.63 (m, 4H, H-3, H-4, H-6$_b$ and H-1'), 3.52 (dd, 1H, *J* = 3.3 and 9.3 Hz, H-7$_a$), 3.06 (dd, 1H, *J* = 9.3 and 11.4 Hz, H-7$_b$), 2.19 (tt, 1H, *J* = 3.3 and 11.1 Hz, H-2), 1.97 – 1.25 (m, 10H, 5 x CH_2 of the cyclohexyl group); δ_C ($CDCl_3$, 75 MHz): 138.1, 138.0, 128.4, 128.3, 127.8, 127.7, 127.6 (3 x Ph), 97.9 (C-1), 81.3, 79.2, 75.3, 75.2, 74.8, 73.5, 71.1 (C-3, C-4, C-5, C-1' and 3 x *C*H$_2$Ph), 68.7 (C-6), 48.6 (C-2), 33.4, 31.7, 25.6, 24.0, 23.8 (cyclohexyl group), 3.3 (C-7). Anal. Calcd for $C_{34}H_{41}IO_5$:

C, 62.14; H, 6.24. Found: C, 62.31; H, 6.34. LRFAB MS calcd for $C_{34}H_{41}IO_5$ [M - H]$^+$ 655.6, found 655.1.

Diastereomer **169b**: $[\alpha]_D$ = +15.7 (*c* 1.0, $CHCl_3$); mp 96 – 98°C δ_H ($CDCl_3$, 400 MHz): 7.40 – 7.20 (m, 15H, 3 x Ph), 4.98 (d, 1H, *J* = 10.9 Hz, C*H*$_2$Ph), 4.85 (d, 1H, *J* = 10.9 Hz, C*H*$_2$Ph), 4.80 (d, 1H, *J* = 10.9 Hz, C*H*$_2$Ph), 4.64 (d, 1H, *J* = 12.2 Hz, C*H*$_2$Ph), 4.62 (d, 1H, *J* = 10.9 Hz, C*H*$_2$Ph), 4.58 (d, 1H, *J* = 12.2 Hz, C*H*$_2$Ph), 4.45 (d, 1H, *J* = 8.0 Hz, H-1), 3.80 – 3.42 (m, 8H, H-3, H-4, H-5, H-6$_a$, H-6$_b$, H-7$_a$, H-7$_b$ and H-1'), 2.10 – 1.10 (m, 11H, H-2 and cyclohexyl group); δ_C ($CDCl_3$, 100 MHz): 138.5, 138.4, 138.1, 128.5, 128.3, 127.9, 127.8, 127.7, 115.5 (3 x Ph), 101.4 (C-1), 81.9, 79.8, 77.2, 75.4, 75.0, 74.8, 73.4, 69.1 (C-3, C-4, C-5, C-6, C-1' and 3 x *C*H$_2$Ph), 46.3 (C-2), 33.7, 33.2, 25.6, 24.1, 24.0 (cyclohexyl group), 7.5 (C-7). Anal. Calcd for $C_{34}H_{41}IO_5$: C, 62.14; H, 6.24. Found: C, 61.78; H, 6.22. LRFAB MS calcd for $C_{34}H_{41}IO_5$ [M - H]$^+$ 655.6, found 655.0.

1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-azidomethyl-α- and –β-D-glucopyranose (170):

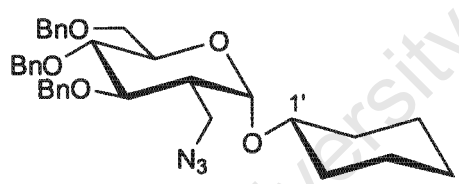


170

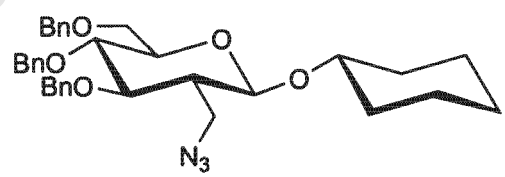
To a solution of **154** (600 mg, 0.97 mmol) in dry DMF (10 mL), sodium azide (189 mg, 2.91 mmol) was added and the reaction mixture was stirred at room temperature for 4 h. The solution was then reduced to half the volume *in vacuo*, water was added and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed successively with 25% aqueous sodium thiosulfate solution and brine and dried over $MgSO_4$. After filtration and evaporation of the solvent *in vacuo*, the colorless syrup obtained was purified by flash chromatography on silica gel to give the desired azido sugar **170** (500 mg, 97%) as colorless syrup in a ratio of 3:7 (α:β); $[\alpha]_D$ = +69.2 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.46 – 7.07 (m, 15H, 3 x Ph), 6.27 (d, 0.33H, *J* = 3.2 Hz, H-1 of α-anomer), 5.65 (d, 0.67H, *J* = 9.2 Hz, H-1 of β-

anomer), 4.98 – 4.90 (m, 1H, CH_2Ph), 4.83 – 4.75 (m, 1H, CH_2Ph), 4.69 – 4.46 (m, 4H, CH_2Ph), 3.86 – 3.58 (m, 5.33H, H-3, H-4, H-5 of α-anomer, H-6_a, H-6_b, H-7_a of α-anomer, and H-7_b of β-anomer), 3.54 (ddd, 0.67H, J = 2.0, 3.2 and 9.4 Hz, H-5 of β-anomer), 3.45 (dd, 0.67H, J = 2.8 and 12.4 Hz, H-7_a of β-anomer), 3.17 (dd, 0.33H, J = 9.6 and 12.4 Hz, H-7_b of α-anomer), 2.28 – 2.18 (m, 0.33H, H-2 of α-anomer), 2.14 (s, 2.01H, CH_3CO$_2$ of β-anomer), 2.11 (s, 0.99H, CH_3CO$_2$ of α-anomer), 1.99 – 1.93 (m, 0.67H, H-2 of β-anomer); δ_C ($CDCl_3$, 100 MHz): 169.3 (CH_3CO_2), 138.3, 138.2, 138.1, 128.7, 128,6, 128.2, 128.1, 128.0, 127.9 (3 x Ph), 92.4 (C-1β), 91.9 (C-1α), 79.3, 79.2, 78.6, 75.8, 75.5, 75.4, 75.2, 74.9, 73.9, 73.8, 73.6, 70.9, 68.5, 49.4 (C-7 of α-anomer), 47.6 (C-7 of β-anomer), 46.0 (C-2 of β-anomer), 45.0 (C-2 of α-anomer), 21.2, 21.1 (CH_3CO_2). IR ($CHCl_3$): 2104 and 1144 cm^{-1}. Anal. Calcd for $C_{30}H_{33}N_3O_6$: C, 67.78; H, 6.26; N, 7.90. Found: C, 66.77; H, 6.27; N, 7.49. LRFAB MS calcd for $C_{30}H_{33}N_3O_6$ $[M - H]^+$ 530.6, found 530.0.

Cyclohexyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-azidomethyl-α-D-glucopyranoside (171a) and cyclohexyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-azidomethyl-β-D-glucopyranoside (171b):



171a



171b

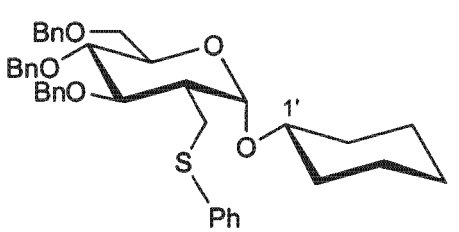
Following the glycosylation protocol for the synthesis of glycoside **169**, glycosylation of glycosyl donor **170** (200 mg, 0.38 mmol) of 1:2 α:β anomeric ratio and cyclohexanol afforded glycoside **171a** (124 mg, 57%) and **171b** (65 mg, 30%) as colorless syrups;

Diastereomer **171a**: $[\alpha]_D$ = +91.8 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.37 – 7.16 (m, 15H, 3 x Ph), 5.07 (d, 1H, J = 3.6 Hz, H-1), 4.89 (d, 1H, J = 11.2, CH_2Ph), 4.78 (d, 1H, J = 10.8 Hz, CH_2Ph), 4.67 (d, 1H, J = 12.0 Hz, CH_2Ph), 4.54 (m, 3H, CH_2Ph), 3.91 – 3.87 (m, 1H, H-5), 3.80 (dd, 1H, J = 3.8 and 10.6 Hz, H-6_a), 3.71 – 3.65 (m, 4H, H-3, H-4, H-6_b and H-1'), 3.61 (dd, 1H, J = 4.0 and 11.6 Hz, H-7_a), 3.26 (dd, 1H,

J = 10.4 and 11.6 Hz, H-7_b), 2.09 (tt, 1H, J = 3.6 and 10.4 Hz, H-2), 1.90 – 1.20 (m, 10H, 5 x CH_2 of the cyclohexyl group); δ_C ($CDCl_3$, 100 MHz): 138.5, 138.4, 138.3, 128.7, 128.6, 128.1, 128.0, 127.8 (3 x Ph), 95.9 (C-1), 80.0 (C-3), 79.4 (C-4), 77.5 (C-1'), 75.4, 75.1, 73.8 (3 x CH_2Ph), 71.2 (C-5), 69.0 (C-6), 50.1 (C-7), 46.5 (C-2), 33.6, 31.6, 25.9, 24.3, 24.0 (cyclohexyl group). IR ($CHCl_3$): 2104 and 1130 cm^{-1}. Anal. Calcd for $C_{34}H_{41}N_3O_5$: C, 71.43; H, 7.23; N, 7.35. Found: C, 71.50; H, 7.33; N, 7.06. LRFAB MS calcd for $C_{34}H_{41}N_3O_5$ $[M - H]^+$ 570.7, found 570.1.

Diastereomer **171b**: $[\alpha]_D$ = +26.3 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.50 – 7.07 (m, 15H, 3 x Ph), 4.93 (d, 1H, J = 11.2 Hz, CH_2Ph), 4.81 (d, 1H, J = 10.8 Hz, CH_2Ph), 4.68 – 4.56 (m, 4H, CH_2Ph), 4.52 (d, 1H, J = 8.8 Hz, H-1), 3.80 – 3.39 (m, 8H, H-3, H-4, H-5, H-6_a, H-6_b, H-7_a, H-7_b, and H-1'), 2.04 – 1.16 (m, 11H, H-2 and cyclohexyl protons); δ_C ($CDCl_3$, 100 MHz): 138.4, 138.2, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 113.2 (3 x Ph), 98.6 (C-1), 80.0, 79.4, 75.21, 75.18, 75.0, 74.7, 73.5 (C-3, C-4, C-5, C-1' and 3 x CH_2Ph), 69.2 (C-6), 47.9 (C-7), 47.4 (C-2), 33.7, 31.8, 25.7, 24.2, 24.0 (cyclohexyl). IR ($CHCl_3$): 2102 and 1121 cm^{-1}. Anal. Calcd for $C_{34}H_{41}N_3O_5$: C, 71.43; H, 7.23; N, 7.35. Found: C, 71.42; H, 7.26; N, 7.17. LRFAB MS calcd for $C_{34}H_{41}N_3O_5$ $[M - H]^+$ 570.7, found 570.0.

Cyclohexyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-phenylthiomethyl-α-D-glucopyranoside (172):

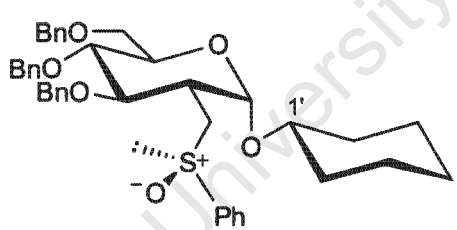


172

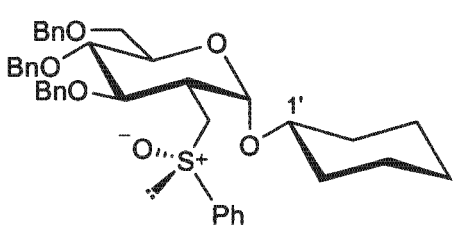
To a solution of thiophenol (170 μL, 1.62 mmol) in THF:DMSO (1:1, 20 mL), sodium hydride (60% dispersion on oil, 39 mg, 1.62 mmol) was added and the mixture was vigorously stirred at room temperature for 30 min. A solution of **169a** (900 mg, 1.35 mmol) in THF (2 mL) was then added and after 5 min stirring of the reaction mixture, methanol (3 mL) was added dropwise and the resulting clear

solution was concentrated *in vacuo* at 50°C. The solution was directly submitted to silica gel chromatography (ethyl acetate/petroleum ether, 2:8) to give the desired sulphide **172** (724 mg, 84%) as a colorless solid; mp 84 - 86°C; $[\alpha]_D$ = +55.2 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.38 – 7.11 (m, 20H, 4 x Ph), 5.25 (d, 1H, *J* = 4.4 Hz, H-1), 4.94 (d, 1H, *J* = 15.2 Hz, C*H*$_2$Ph), 4.78 (d, 1H, *J* = 14.2 Hz, C*H*$_2$Ph), 4.66 (d, 1H, *J* = 15.2 Hz, C*H*$_2$Ph), 4.65 (d, 1H, *J* = 16.2 Hz, C*H*$_2$Ph), 4.52 (d, 1H, *J* = 14.2 Hz, C*H*$_2$Ph), 4.49 (d, 1H, *J* = 16.2 Hz, C*H*$_2$Ph), 3.91 (qd, 1H, *J* = 2.4, 4.4 and 12.4 Hz, H-5), 3.81 – 3.54 (m, 5H, H-3, H-4, H-6$_a$, H-6$_b$ and H-1'), 3.38 (dd, 1H, *J* = 4.0 and 17.6 Hz, H-7$_a$), 2.80 (dd, 1H, *J* = 15.0 and 17.6 Hz, H-7$_b$), 2.10 (tt, 1H, *J* = 4.4 and 14.8 Hz, H-2), 1.90 – 1.12 (m, 10H, cyclohexyl protons); δ_C ($CDCl_3$, 75 MHz): 138.5, 138.2, 138.1, 136.5, 128.9, 128.4, 128.3, 127.9, 127.7, 127.6, 125.5 (4 x Ph), 96.3 (C-1), 81.0, 79.8, 75.33, 75.27, 74.8, 73.5, 70.9 (C-3, C-4, C-5, C-1' and 3 x Ph), 68.8 (C-6), 45.6 (C-2), 33.4, 31.5, 30.8 (C-7), 25.7, 24.0, 23.8. Anal. Calcd for $C_{40}H_{46}O_5S$: C, 75.20; H, 7.26; S, 5.02. Found: C, 74.89; H, 7.12; S, 5.04. LRFAB MS calcd for $C_{40}H_{46}O_5S$ $[M]^+$ 638.9, found 638.2.

Cyclohexyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-phenylsulfinylmethyl-α-D-glucopyranoside (174):



174a

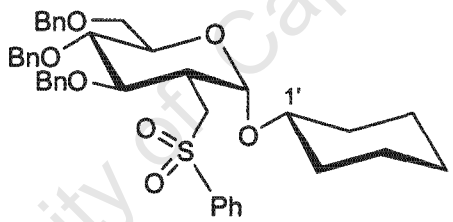


174b

The sulphide **172** (686 mg, 1.07 mmol) was added to a vigorously stirring suspension of wet alumina (2.8 g wetted with 300 μL of water) and OXONE® (690 mg, 1.12 mmol). The reaction mixture was stirred at 32°C for 7 h. After allowing the mixture to cool to room temperature, it was filtered to remove the adsorbent. Evaporation of the solvent and flash-chromatographic purification on silica gel (ethyl acetate/petroleum ether, 1:1) afforded a mixture of the title sulphoxides (525 mg, 75%) as white crystals in 43:57 ratio (assignment is tentative); mp 104 – 106°C; $[\alpha]_D$ = +61.5 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.81 – 6.97 (m, 20H, 4 x Ph), 5.22 (d, 0.43H, *J* = 3.2 Hz, H-1

of **174a**), 5.12 (d, 0.57H, J = 3.2 Hz, H-1 of **174b**), 4.99 – 4.42 (m, 6H, 3 x CH_2Ph), 3.93 – 3.86 (m, 1H, H-5), 3.83 – 3.51 (m, 5H, H-3, H-4, H-6_a, H-6_b and H-1'), 3.01 – 2.83 (m, 1.57H, H-7_a of **174b**, H-7_b of **174b**, and H-7_a of **174a**), 2.72 (dd, 0.43H, J = 9.6 and 13.2 Hz, H-7_b of **174a**), 2.36 – 2.22 (m, 1H, H-2), 1.96 – 1.12 (m, 10H, cyclohexyl protons); δ_C ($CDCl_3$, 100 MHz): 138.3, 138.1, 131.0, 130.8, 129.1, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 124.2, 124.1, 96.9 (C-1 of **174a**), 96.2 (C-1 of **174b**), 80.4, 80.0, 79.8, 79.7, 75.1, 74.9, 74.8, 74.7, 73.5, 71.0 (C-5), 68.8 (C-6), 56.1 (C-1'), 42.7 (C-2 of **174a**), 41.3 (C-2 of **174b**), 33.4, 31.6, 31.5, 25.6, 24.1, 23.9. IR ($CHCl_3$): 1028 cm^{-1}. Anal. Calcd for $C_{40}H_{46}O_6S$: C, 73.36; H, 7.08; S, 4.90. Found: C, 73.36; H, 7.10; S, 4.94. LRFAB MS calcd for $C_{40}H_{46}O_6S$ $[M + H]^+$ 655.8, found 655.1.

Cyclohexyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-phenylsulfonylmethyl-α-D-glucopyranoside (176):

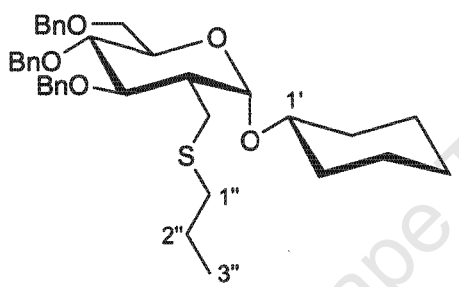


176

The sulphide **172** (155 mg, 0.24 mmol) was added to a vigorously stirring suspension of wet alumina (650 mg wetted with 70 μL of water) and OXONE® (1.19 g, 1.92 mmol) and the reaction mixture was stirred at 32°C overnight. After allowing the mixture to cool to room temperature, it was filtered to remove the adsorbent. Evaporation of the solvent and flash-chromatographic purification on silica gel (ethyl acetate/petroleum ether, 2:8) gave sulfone **176** (153 mg, 95%) as a colorless oil; $[\alpha]_D$ = +56.2 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz): 7.95 – 6.97 (m, 20H, 4 x Ph), 5.40 (d, 1H, J = 3.0 Hz, H-1), 4.88 (d, 1H, J = 11.4 Hz, CH_2Ph), 4.70 (d, 1H, J = 11.1 Hz, CH_2Ph), 4.68 (d, 1H, J = 12.0 Hz, CH_2Ph), 4.54 – 4.46 (m, 3H, CH_2Ph), 3.89 (ddd, 1H, J = 1.8, 3.0 and 9.3 Hz, H-5), 3.80 (dd, 1H, J = 3.8 and 10.8 Hz, H-6_a), 3.72 – 3.50 (m, 4H, H-3, H-4, H-6_b, and H-1'), 3.27 (d, 2H, J = 6.6 Hz, H-7_a and H-7_b), 2.33 – 2.20 (m, 1H, H-2), 2.02 – 1.04 (m, 10H, cyclohexyl protons); δ_C ($CDCl_3$, 75 MHz):

139.4, 138.1, 137.9, 133.5, 129.2, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 127.4 (4 x Ph), 95.9 (C-1), 79.7, 79.0, 75.9 (C-1'), 74.72, 74.66, 73.5, 70.7 (C-5), 68.6 (C-6), 53.3 (C-7), 41.6 (C-2), 33.4, 31.4, 25.6, 24.1, 23.9 (cyclohexyl group). IR ($CHCl_3$): 1306 and 1124 cm^{-1}. Anal. Calcd for $C_{40}H_{46}O_7S$: C, 71.61; H, 6.91; S, 4.78. Found: C, 71.11; H, 7.23; S, 4.99. LRFAB MS calcd for $C_{40}H_{46}O_7S$ $[M - H]^+$ 669.8, found 669.1.

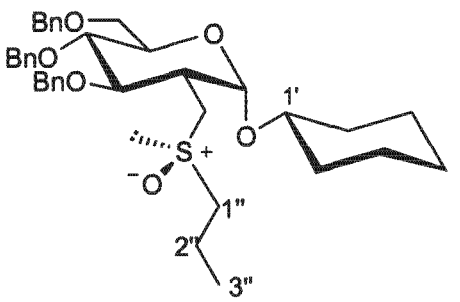
Cyclohexyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-(*n*-propylthiomethyl)-α-D-glucopyranoside (173):



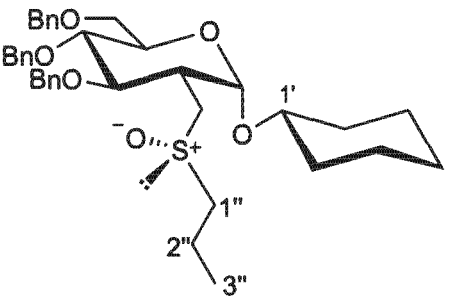
173

Following the procedure for the synthesis of sulfide **172**, treatment of **169a** (120 mg, 0.18 mmol) with 1-propanethiol in the presence of NaH afforded sulfide **173** (100 mg, 92%) as colorless oil; $[\alpha]_D$ = +93.8 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.37 – 7.16 (m, 15H, 3 x Ph), 5.24 (d, 1H, *J* = 3.2 Hz, H-1), 4.90 (d, 1H, *J* = 11.2 Hz, C*H*$_2$Ph), 4.79 (d, 1H, *J* = 10.8 Hz, C*H*$_2$Ph), 4.67 (d, 1H, *J* = 12.0 Hz, C*H*$_2$Ph), 4.62 (d, 1H, *J* = 11.2 Hz, C*H*$_2$Ph), 4.54 (d, 1H, *J* = 10.8 Hz, C*H*$_2$Ph), 4.52 (d, 1H, *J* = 12.0 Hz, C*H*$_2$Ph), 3.94 – 3.89 (m, 1H, H-5), 3.80 (dd, 1H, *J* = 3.6 and 10.8 Hz, H-6$_a$), 3.71 – 3.55 (m, 4H, H-3, H-4, H-6$_b$ and H-1'), 2.85 (dd, 1H, *J* = 3.2 and 13.2 Hz, H-7$_a$), 2.51 – 2.38 (m, 3H, H-7$_b$ and H-1"), 2.08 – 1.97 (m, 1H, H-2), 1.93 – 1.16 (m, 12H, H-2" and 5 x CH_2 of the cyclohexyl protons), 0.96 (t, 3H, *J* = 7.4 Hz, H-3"); δ_C ($CDCl_3$, 100 MHz): 138.8, 138.5, 138.4, 128.6, 128.5, 128.1, 128.0, 127.9, 127.8 (3 x Ph), 96.7 (C-1), 81.4, 80.1, 75.6 (x 2), 75.1, 73.7 (C-3, C-4, C-1' and 3 x *C*H$_2$Ph), 71.2 (C-5), 69.2 (C-6), 46.4 (C-2), 34.5 (C-1"), 33.7, 31.7, 29.8 (C-7), 25.9, 24.2, 24.0, 23.1 (C-2"), 13.6 (C-3"). Anal. Calcd for $C_{37}H_{48}O_5S$: C, 73.47; H, 8.00; S, 5.30. Found: C, 74.01; H, 7.87; S, 5.30. LRFAB MS calcd for $C_{37}H_{48}O_5S$ $[M - H]^+$ 603.8, found 603.0.

Cyclohexyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-(*n*-propylsulfinylmethyl)-α-D-glucopyranoside (175):



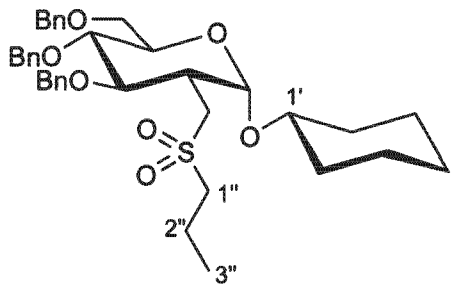
175a



175b

Following the procedure described for the synthesis of **174**, oxidation of sulphide **173** (100 mg, 0.16 mmol) gave inseparable mixture of sulfoxides **175a** and **175b** (81 mg, 82%) as white solids in a ratio of 33:67 (the assignment is tentative); mp 118 – 119°C; $[\alpha]_D$ = +82.2 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.49 – 7.07 (m, 15H, 3 x Ph), 5.20 (d, 0.67H, *J* = 3.2 Hz, H-1 of **175b**), 5.12 (d, 0.33H, *J* = 3.6 Hz, H-1 of **175a**), 4.95 (d, 1H, 11.6 Hz, C*H*$_2$Ph), 4.77 (d, 1H, *J* = 10.8 Hz, C*H*$_2$Ph), 4.70 – 4.48 (m, 4H, C*H*$_2$Ph), 3.95 – 3.85 (m, 1H, H-5), 3.84 – 3.53 (m, 5H, H-3, H-4, H-6_a, H-6_b, and H-1'), 2.89 – 2.70 (m, 2H, H-7_a and H-7_b), 2.66 – 2.37 (m, 2.67H, H-2, H-1''), 2.26 – 2.15 (m, 0.33H, H-2), 1.94 – 1.14 (m, 12H, H-2'', and cyclohexyl protons), 1.05 – 0.97 (m, 3H, H-3''); δ_C ($CDCl_3$, 75 MHz): 138.4, 138.2, 138.1, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 96.8 (C-1 of **175a**), 96.2 (C-1 of **175b**), 80.4, 80.0, 79.9, 79.8, 75.7, 75.3, 75.1, 74.9, 74.8, 73.5, 71.2, 71.1, 68.8, 68.6, 55.0, 54.7, 51.3, 50.9, 42.9, 40.9, 33.4, 31.4, 29.7, 25.6, 24.1, 24.0, 23.9, 23.8, 16.1, 16.0, 13.3. IR ($CHCl_3$): 1026 cm^{-1}. Anal. Calcd for $C_{37}H_{48}O_6S$: C, 71.58; H, 7.79; S, 5.16. Found: C, 71.53; H, 7.37; S, 4.94. LRFAB MS calcd for $C_{37}H_{48}O_6S$ $[M + H]^+$ 621.8 or $[M - H]^+$ 619.8, found 621.1 and 619.2, respectively.

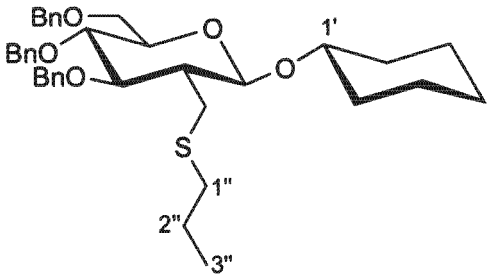
Cyclohexyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-(*n*-propylsulfonylmethyl)-α-D-glucopyranoside (177):



177

Oxidation of sulphide **173** (100 mg, 0.16 mmol) as described for the synthesis of **176** afforded sulfone **177** (102 mg, 100%) as white crystals; mp 122 – 125°C; $[\alpha]_D$ = +91.8 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.55 – 7.08 (m, 15H, 3 x Ph), 5.34 (d, 1H, *J* = 3.6 Hz, H-1), 4.99 (d, 1H, *J* = 11.6 Hz, C*H*$_2$Ph), 4.79 (d, 1H, *J* = 10.8 Hz, C*H*$_2$Ph), 4.69 (d, 1H, *J* = 11.6 Hz, C*H*$_2$Ph), 4.59 (d, 1H, *J* = 10.8 Hz, C*H*$_2$Ph), 4.56 (d, 1H, *J* = 11.6 Hz, C*H*$_2$Ph), 4.54 (d, 1H, *J* = 12.0 Hz, C*H*$_2$Ph), 3.91 (ddd, 1H, *J* = 1.8, 3.0 and 9.8 Hz, H-5), 3.86 – 3.55 (m, 5H, H-3, H-4, H-6_a, H-6_b and H-1'), 3.09 (dd, 1H, *J* = 2.0 and 14.2 Hz, H-7_a), 3.00 (dd, 1H, *J* = 10.0 and 14.2 Hz, H-7_b), 2.82 (t, 2H, *J* = 8.5 Hz, H-1"), 2.38 – 2.31 (m, 1H, H-2), 1.98 – 1.14 (m, 12H, H-2" and 5 x CH_2 of the cyclohexyl protons), 0.96 (t, 3H, *J* = 7.6 Hz, H-3"); δ_C ($CDCl_3$, 100 MHz): 138.1, 138.0, 137.9, 128.6, 128.4, 127.9, 127.8, 127.7 (3 x Ph), 96.1 (C-1), 80.0, 79.1, 76.0, 75.2, 74.8, 73.6, 70.9, 68.6, 54.6, 49.7, 41.5 (C-2), 33.4, 31.5, 25.6, 24.1, 23.9, 15.8, 13.0 (C-3"). IR ($CHCl_3$): 1309 and 1127 cm^{-1}. Anal. Calcd for $C_{37}H_{48}O_7S$: C, 69.78; H, 7.60; S, 5.04. Found: C, 70.56; H, 7.68; S, 5.25. LRFAB MS calcd for $C_{37}H_{48}O_7S$ $[M - H]^+$ 635.8, found 635.0.

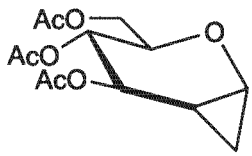
Cyclohexyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-(*n*-propylthiomethyl)-β-D-glucopyranoside (183):



183

Thiolation of **169b** (650 mg, 0.99 mmol) using the same conditions described for the synthesis of **173** gave **183** (599 mg, 100%) as white solids; mp 65 – 67°C (from ethanol); $[\alpha]_D$ = +6.2 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.36 – 7.20 (m, 15H, 3 x Ph), 4.93 (d, 1H, *J* = 11.0 Hz, C*H*$_2$Ph), 4.81 (d, 1H, *J* = 10.8 Hz, C*H*$_2$Ph), 4.79 (d, 1H, *J* = 10.8 Hz, C*H*$_2$Ph), 4.66 – 4.55 (m, 4H, H-1, 3 x C*H*$_2$Ph), 4.84 – 3.50 (m, 5H, H-3, H-4, H-6$_a$, H-6$_b$ and H-1'), 3.45 (ddd, 1H, *J* = 2.1, 4.9 and 9.7 Hz, H-5), 2.97 (dd, 1H, *J* = 3.5 and 12.0 Hz, H-7$_a$), 2.86 (dd, 1H, *J* = 3.3 and 12.0 Hz, H-7$_b$), 2.46 (dt, 2H, *J* = 1.1 and 7.3 Hz, H-1''), 2.20 – 1.15 (m, 13H, H-2, 5 x CH_2 of the cyclohexyl protons, H-2''), 0.97 (t, 3H, *J* = 7.3 Hz, H-3''); δ_C ($CDCl_3$, 100 MHz): 138.8, 138.3, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5 (3 x Ph), 99.8 (C-1), 80.9, 80.0, 75.01, 74.99, 74.9, 74.6, 73.4, 69.4, 47.5 (C-2), 35.9 (C-1''), 33.8, 32.0, 29.7 (C-7), 25.7, 24.2, 24.1, 23.0 (C-2''), 13.4 (C-3''). Anal. calcd for $C_{37}H_{48}O_5S$: C, 73.47; H, 8.00; S, 5.30. Found: C, 73.62; H, 7.78; S, 5.83.

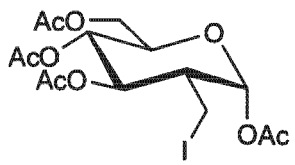
3,4,6-Tri-O-acetyl-1,5-anhydro-2-deoxy-1,2-C-methylene-D-glycero-D-gulo-hexitol (155):



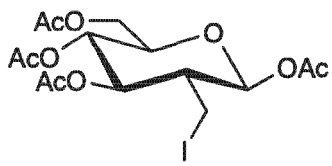
155

A solution of dichlorocyclopropane **157** (300 mg, 0.60 mmol) in dry THF (1 mL) was added dropwise to a stirred solution of calcium metal (60 mg, 1.50 mmol) in pre-dried liquid ammonia (~10 mL) at -78°C and the reaction mixture was stirred under reflux for 10 min. The blue color was discharged by careful addition of ammonium chloride and the ammonia was allowed to evaporate at room temperature. The solid residue was then dispersed in pyridine (10 mL) and treated with acetic anhydride (5 ml) and catalytic amount of DMAP. After stirring overnight at room temperature, the reaction was quenched by addition of water and the aqueous phase was extracted several times with ethyl acetate. The combined organic phases were then washed with 1N aq HCl solution, followed by water and then dried over $MgSO_4$. After filtration, the solvent was evaporated *in vacuo* and the residue purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 1:9) to give the title compound **155** (103 mg, 60%) as a low viscous oil; $[\alpha]_D$ = +26.6 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz): 4.95 (dd, 1H, *J* = 3.0 and 6.3 Hz, H-3), 4.83 (dd, 1H, *J* = 4.5 and 6.3 Hz, H-4), 4.51 (dd, 1H, *J* = 7.5 and 12.0 Hz, H-6_a), 4.14 (dd, 1H, *J* = 4.1 and 12.0 Hz, H-6_b), 3.88 – 3.83 (m, 1H, H-5), 3.62 (dt, 1H, *J* = 3.0 and 6.0 Hz, H-1), 2.09, 2.08, 2.04 (3s, 9H, 3 x CH_3CO_2), 1.02 – 0.93 (m, 1H, H-2), 0.86 (tdd, 2H, *J* = 4.6, 10.1, and 12.3 Hz, H-7_a and H-7_b); δ_C ($CDCl_3$, 75 MHz): 170.6, 169.8, 169.7 (3 x CH_3CO_2), 73.7 (C-5), 70.2 (C-3), 69.6 (C-4), 62.4 (C-6), 48.8 (C-1), 21.0, 20.8, 20.7 (3 x CH_3CO_2), 13.7 (C-2), 11.1 (C-7). Anal. calcd for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34. Found: C, 54.68; H, 6.21.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-*C*-iodomethyl-α and -β-D-glucopyranoses (156a and 156b):



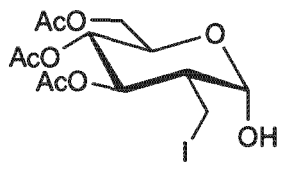
156a



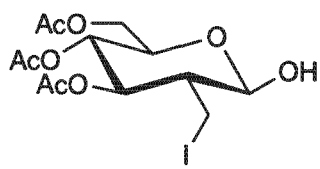
156b

Following the procedure described for the general iodoacetoxylation of glycals, the cyclopropyl ring in **155** (70 mg, 0.24 mmol) was opened at 60°C and overnight stirring to give inseparable mixture of **156a** and **156b** (109 mg, 96%) as colorless oil and 3:7 anomeric ratio; $[\alpha]_D$ = +16.1 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 6.39 (d, 0.3H, *J* = 3.6 Hz, H-1 of **156a**), 5.65 (d, 0.7H, *J* = 8.8 Hz, H-1 of **156b**), 5.28 – 5.16 (m, 1H, H-3), 5.12 – 4.99 (m, 1H, H-4), 4.35 – 4.24 (m, 1H, H-6_a), 4.11 – 3.96 (m, 1.3H, H-6_b and H-5 of **156a**), 3.87 – 3.78 (m, 0.7H, H-5 of **156b**), 3.22 (dd, 0.7H, *J* = 3.3 and 10.9 Hz, H-7_a of **156b**), 3.16 – 3.07 (m, 1H, H-7_b of **156b** and H-7_a of **156a**), 2.87 (t, 0.3H, *J* = 10.6 Hz, H-7_b of **156a**), 2.40 (tt, 0.3H, *J* = 3.6 and 10.8 Hz, H-2 of **156a**), 2.16, 2.15, 2.07, 2.06, 2.02, 2.01 (6s, 12H, CH_3CO_2), 1.85 – 1.75 (m, 0.7H, H-2 of **156b**); δ_C ($CDCl_3$, 100 MHz): 170.5, 170.4, 169.8, 169.6, 169.5, 168.4, 168.3, 94.7 (C-1 of **156b**), 92.8 (C-1 of **156a**), 72.8, 72.4, 72.0, 69.8, 69.0, 68.3 (C-3, C-4 and C-5), 61.7 (C-6), 45.4 (C-2 of **156a**), 43.4 (C-2 of **156b**), 20.8, 20.7, 20.6, 20.5 (CH_3CO_2), 0.43 (C-7 of **156b**), -2.0 (C-7 of **156a**). Anal. calcd for $C_{15}H_{21}IO_9$: C, 38.15; H, 4.48. Found: C, 38.55; H, 4.86.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-*C*-iodomethyl-α and -β-D-glucopyranoses (188a and 188b):



188a



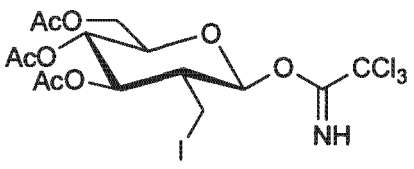
188b

Method (a). To a solution of **156** (100 mg, 0.21 mmol) in DMF (2 mL) at 50°C was added hydrazine acetate (24 mg, 0.26 mmol) and the resulting reaction mixture was stirred for 1 h at 50°C. The solution was allowed to cool to room temperature and diluted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 2:8) to give an inseparable mixture of anomers of **188a** and **188b** (63 mg, 70%) (3:2, α:β) as colorless oil.

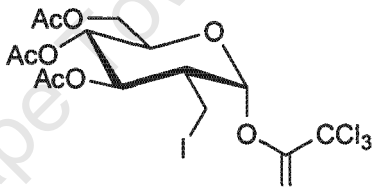
Method (b). A solution of cyclopropanated sugar **155** (320 mg, 0.68 mmol) in dioxane/water (2:1, 7 mL) was treated with NIS (186 mg, 0.83 mmol) and stirred overnight at 60°C. The reaction mixture was then concentrated to half its volume *in vacuo.* The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed successively with 25% aq sodium thiosulfate and water, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by flash chromatography to give **188a** and **188b** (263 mg, 90%) in 8:2 anomeric ratio (α:β) as a white gum; $[\alpha]_D$ = +92.6 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 5.48 (t, 0.8H, *J* = 3.6 Hz, H-1 of **188a**), 5.19 (dd, 0.8H, *J* = 9.2 and 11.2 Hz, H-3 of **188a**), 5.17 (dd, 0.2H, *J* = 8.8 and 10.8 Hz, H-3 of **188b**), 5.03 (dd, 0.2H, *J* = 8.8 and 10.0 Hz, H-4 of **188b**), 4.95 (t, 0.8H, *J* = 9.6 Hz, H-4 of **188a**), 4.78 (dd, 0.2H, *J* = 5.4 and 7.8 Hz, H-1 of **188b**), 4.27 – 4.04 (m, 3H, H-5 of **188a**, H-6_a, H-6_b and OH of **188b**), 3.74 (ddd, 0.2H, *J* = 2.4, 4.8 and 10.1 Hz, H-5 of **188b**), 3.72 (dd, 0.8H, *J* = 1.5 and 4.1 Hz, OH of **188a**), 3.44 (dd, 0.2H, *J* = 3.2 and 10.6 Hz, H-7_a of **188b**), 3.17 (dd, 0.2H, *J* = 2.8 and 10.5 Hz, H-7_b of **188b**), 3.09 (m, 1.6H, H-7_a and H-7_b of **188a**), 2.22 (m, 0.8H, H-2 of **188a**), 2.06, 2.05, 2.03, 2.01, 2.00, 1.99 (6s, 9H, CH_3CO_2), 1.49 (tdd, 0.2H, *J* = 2.9, 8.0 and 10.9 Hz, H-2 of **188b**); δ_C ($CDCl_3$, 100 MHz): 170.9, 170.8, 170.6, 170.0,

169.9 (CH_3CO_2), 97.4 (C-1β), 93.8 (C-1 of **188a**), 73.0 (C-3 of **188b**), 71.1 (C-3 of **188a**), 71.6 (C-5 of **188b**), 69.7 (C-4 of **188b**), 69.1 (C-4 of **188a**), 67.7 (C-5 of **188a**), 62.4 (C-6 of **188b**), 62.3 (C-6 of **188a**), 46.9 (C-2 of **188a**), 45.3 (C-2 of **188b**), 21.0, 20.72, 20.71, 20.6 (CH_3CO_2), 3.3 (C-7 of **188b**), 0.8 (C-7 of **188a**). A D_2O wash ^1H NMR spectrum showed among others δ 5.47 (d, 0.8H, J = 3.2 Hz, H-1 of **188a**) and δ 4.76 (d, 0.2 H, J = 8.0 Hz, H-1 of **188b**). Anal. calcd for $C_{13}H_{19}IO_8$: C, 36.30; H, 4.45. Found: C, 36.48; H, 4.65.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-*C*-iodomethyl-α-D-glucopyranosyl trichloroimidate (189b) and 3,4,6-tri-*O*-acetyl-2-deoxy-2-*C*-iodomethyl-β-D-glucopyranosyl trichloroimidate (189a):



189a



189b

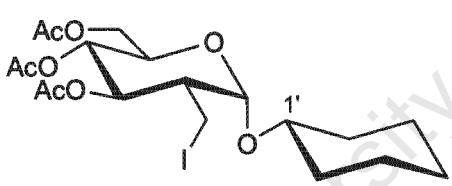
To a solution of **188a** and **188b** (90 mg, 0.21 mmol) in dry dichloromethane (2 mL), trichloroacetonitrile (120 μL, 1.06 mmol) and freshly dried and powdered potassium carbonate (120 mg, 0.86 mmol) were added and the reaction mixture was stirred at room temperature for 2 h. The mixture was diluted by adding dry dichloromethane and the potassium carbonate was removed by filtration. The solution was evaporated and purification of the residue by flash chromatography on silica gel (ethyl acetate/petroleum ether, 3:7) gave the α-glucosyl trichloroacetimidate **189b** (22 mg, 18%) as a syrup and the β-glucosyl trichloroacetimidate **189a** (57 mg, 47%) as white crystals after crystallization from diethyl ether/petroleum ether;

Diastereomer **189a**: mp 111°C, $[\alpha]_D$ = +54.1 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz): 8.75 (s, 1H, N*H*), 5.82 (d, 1H, J = 8.4 Hz, H-1), 5.28 (dd, 1H, J = 8.9 and 10.4 Hz, H-3), 5.15 (dd, 1H, J = 9.0 and 9.7 Hz, H-4), 4.34 (dd, 1H, J = 4.6 and 12.4 Hz, H-6_a), 4.13 (dd, 1H, J = 2.4 and 12.4 Hz, H-6_b), 3.88 (ddd, 1H, J = 2.4, 4.5 and 9.8 Hz, H-5), 3.42 (dd, 1H, J = 3.3 and 10.9 Hz, H-7_a), 3.20 (dd, 1H, J = 2.7 and 10.9 Hz, H-7_b), 2.07, 2.06, 2.03 (3s, 9H, 3 x CH_3CO_2), 1.95 (m, 1H, H-2); δ_C ($CDCl_3$, 75 MHz):

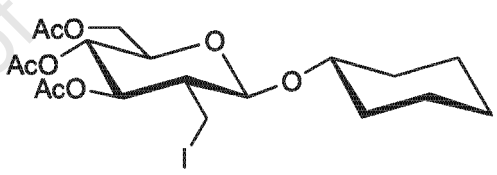
170.6, 169.9, 169.7 (3 x CH_3CO_2), 160.3 (*C*=NH), 98.6 (C-1), 72.6 (C-3), 72.5 (C-5), 69.1 (C-4), 61.9 (C-6), 43.8 (C-2), 20.7, 20.65, 20.6 (3 x CH_3CO_2), 1.2 (C-7). Anal. calcd for $C_{15}H_{19}Cl_3INO_8$: C, 31.36; H, 3.33; N, 2.44. Found: C, 31.61; H, 3.55; N, 2.12.

Diastereomer **189b**: δ_H ($CDCl_3$, 400 MHz): 8.80 (s, 1H, N*H*), 6.60 (d, 1H, J = 3.4 Hz, H-1), 5.25 (dd, 1H, J = 9.3 and 11.1 Hz, H-3), 5.09 (t, 1H, J = 9.6 Hz, H-4), 4.31 – 4.26 (m, 1H, H-6_a), 4.14 – 4.07 (m, 2H, H-5 and H-6_b), 3.19 (dd, 1H, J = 4.1 and 10.2 Hz, H-7_a), 3.06 (t, 1H, J = 10.8 Hz, H-7_b), 2.51 (tt, 1H, J = 3.8 and 11.2 Hz, H-2), 2.08, 2.06, 2.03 (3s, 9H, 3 x CH_3CO_2); δ_C ($CDCl_3$, 100 MHz): 170.5, 170.3, 169.6 (3 x CH_3CO_2), 160.1 (*C*=NH), 96.9 (C-1), 72.0 (C-3), 70.3 (C-5), 68.2 (C-4), 61.6 (C-6), 46.4 (C-2), 20.7, 20.6, 20.5 (3 x CH_3CO_2), -1.9 (C-7).

Cyclohexyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*C*-iodomethyl-α-D-glucopyranoside (187a) and cyclohexyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*C*-iodomethyl-β-D-glucopyranoside (187b):



187a



187b

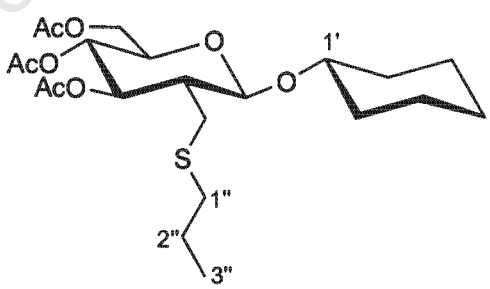
To a solution of **189a** (100 mg, 0.18 mmol) and cyclohexanol (93 µL, 0.87 mmol) in dry dichloromethane (3 mL) containing 4Å molecular sieves under nitrogen, $BF_3{\cdot}Et_2O$ (100 µL of 48% solution of BF_3 in diethyl ether , 0.88 mmol) was added dropwise at 0°C. After stirring at room temperature for 3 h, the reaction was quenched by addition of solid $NaHCO_3$. The mixture was then filtered over a celite bed and concentrated. The residue was purified by column chromatography (ethyl acetate/petroleum ether, 1:9) to yield a syrup of **187a** (32 mg, 35%) and **187b** (49 mg, 53%);

Diastereomer **187a**: $[\alpha]_D$ = +103.8 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 5.23 (d, 1H, J = 3.6 Hz, H-1), 5.16 (dd, 1H, J = 9.2 and 11.2 Hz, H-3), 4.95 (t, 1H, J = 9.6 Hz, H-4), 4.26 (dd, 1H, J = 5.2 and 12.8 Hz, H-6_a), 4.11 – 4.04 (m, 2H, H-5 and H-6_b), 3.66

– 3.56 (m, 1H, H-1'), 3.12 – 3.01 (m, 2H, H-7_a and H-7_b), 2.25 (tt, 1H, J = 3.8 and 10.8 Hz, H-2), 2.08, 2.05, 2.01 (3s, 9H, 3 x CH_3CO_2), 1.99 – 1.09 (m, 10H, cyclohexyl); δ_C ($CDCl_3$, 100 MHz): 170.7, 170.6, 169.8 (3 x CH_3CO_2), 97.9 (C-1), 76.5 (C-1'), 72.5 (C-3), 69.3 (C-4), 67.3 (C-5), 62.4 (C-6), 47.1 (C-2), 35.6, 33.4, 31.8, 25.6, 25.5 (cyclohexyl), 20.8, 20.7, 20.6 (3 x CH_3CO_2), 0.8 (C-7). Anal. calcd for $C_{19}H_{29}IO_8$: C, 44.54; H, 5.71. Found: C, 44.11; H, 5.63.

Diastereomer **187b**: $[\alpha]_D$ = +23.6 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 5.21 (dd, 1H, J = 8.8 and 10.8 Hz, H-3), 5.04 (dd, 1H, J = 8.8 and 10.0 Hz, H-4), 4.54 (d, 1H, J = 8.0 Hz, H-1), 4.29 (dd, 1H, J = 5.0 and 12.2 Hz, H-6_a), 4.09 (dd, 1H, J = 2.4 and 12.0 Hz, H-6_b), 3.73 – 3.64 (m, 2H, H-5 and H-1'), 3.45 (dd, 1H, J = 3.0 and 10.6 Hz, H-7_a), 3.16 (dd, 1H, J = 2.8 and 10.4 Hz, H-7_b), 2.06, 2.04, 2.02 (3s, 9H, 3 x CH_3CO_2), 2.00 – 1.14 (m, 11H, H-2 and cyclohexyl); δ_C ($CDCl_3$, 100 MHz): 170.0, 169.91, 169.89 (3 x CH_3CO_2), 101.5 (C-1), 77.8 (C-1'), 73.3 (C-3), 71.4 (C-5), 70.1 (C-4), 62.6 (C-6), 44.4 (C-2), 33.5, 32.1, 25.6, 24.1, 24.0 (cyclohexyl carbons), 20.8 (x 2), 20.7 (3 x CH_3CO_2), 3.9 (C-7). Anal. calcd for $C_{19}H_{29}IO_8$: C, 44.54; H, 5.71. Found: C, 44.31; H, 5.75.

Cyclohexyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*C*-(*n*-propylthiomethyl)-β-D-glucopyranoside (184):



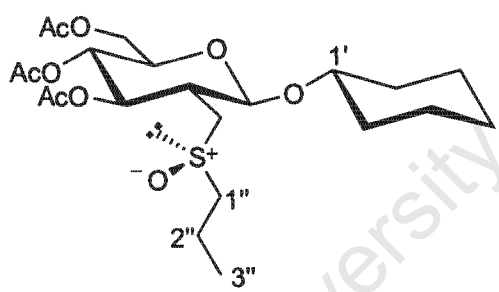
184

Method (a). Thiolation of **187b** (70 mg, 0.14 mmol) using conditions described for the preparation of **173** afforded **184** (52 mg, 80%) as a white solid;

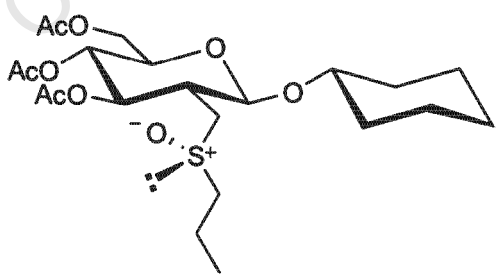
Method (b). Reaction of sulphide **183** (300 mg, 0.50 mmol) under the Birch reduction described for the synthesis of acetylated cyclopropanated sugar **155** gave **184** (126

mg, 55%) as a white solid; mp 116 - 118°C (from ethanol); $[\alpha]_D$ = -1.7 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 5.29 (dd, 1H, *J* = 9.0 and 11.1 Hz, H-3), 4.96 (t, 1H, *J* = 9.6 Hz, H-4), 4.60 (d, 1H, *J* = 8.8 Hz, H-1), 4.28 (dd, 1H, *J* = 5.2 and 12.0 Hz, H-6_a), 4.08 (dd, 1H, *J* = 2.5 and 12.1 Hz, H-6_b), 3.70 – 3.60 (m, 2H, H-5 and H-1'), 2.79 (dd, 1H, *J* = 4.5 and 13.1 Hz, H-7_a), 2.58 (dd, 1H, *J* = 3.2 and 13.1 Hz, H-7_b), 2.50 – 2.38 (m, 2H, H-1''), 2.20 – 2.07 (m, 1H, H-2), 2.06, 2.03, 2.00 (3s, 9H, 3 x CH_3CO_2), 1.96 – 1.69 (m, 4H, cyclohexyl protons), 1.62 – 1.50 (m, 2H, H-2''), 1.46 – 1.18 (m, 6H, cyclohexyl), 0.96 (t, 3H, *J* = 7.3 Hz, H-3''); δ_C ($CDCl_3$, 100 MHz): 170.7, 170.31, 170.29 (3 x CH_3CO_2), 99.9 (C-1), 77.7 (C-5), 72.4 (C-3), 71.3 (C-1'), 70.3 (C-4), 62.6 (C-6), 45.9 (C-2), 35.9 (C-1''), 33.5, 31.8, 29.3 (C-7), 25.6, 24.0, 22.9, 20.8, 20.73, 20.7 (3 x CH_3CO_2), 13.3 (C-3''). Anal. calcd for $C_{22}H_{36}O_8S$: C, 57.37; H, 7.88; S, 6.96. Found: C, 57.38; H, 8.01; S, 6.74.

Cyclohexyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*C*-(*n*-propylsulfinylmethyl)-β-D-glucopyranosides (190):



190a

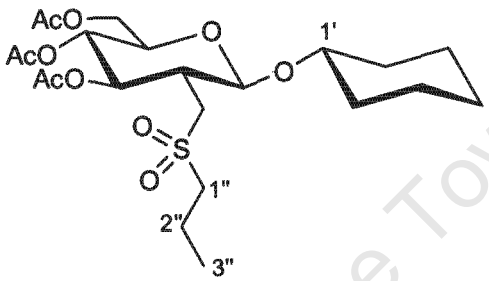


190b

On carrying out the OXONE® oxidation on sulphide **184** (50 mg, 0.11 mmol) as mentioned for the preparation of sulfoxide **175** gave an inseparable mixture of sulfoxides **190** (47 mg, 90%) as white solids; mp 125 – 128°C; $[\alpha]_D$ = -10.3 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz): 6.25 – 5.05 (m, 1H, H-3), 5.02 – 4.91 (m, 1H, H-4), 4.62 (d, 0.5H, *J* = 8.6 Hz, H-1 of **190a**), 4.55 (d, 0.5H, *J* = 8.6 Hz, H-1 of **190b**), 4.28 (dd, 1H, *J* = 4.6 and 12.2 Hz, H-6_a), 4.09 (dd, 1H, *J* = 2.5 and 12.1 Hz, H-6_b), 3.72 – 3.60 (m, 2H, H-1' and H-5), 2.91 – 2.51 (m, 4H, H-7_a, H-7_b, and H-1''), 2.37 – 2.15 (m, 1H, H-2), 2.06, 2.04, 2.00 (3s, 9H, 3 x CH_3CO_2), 1.98 – 1.15 (m, 12H, H-2'' and 5 x CH_2 of the cyclohexyl protons), 1.07 (t, 3H, *J* = 7.4 Hz, H-3''); δ_C ($CDCl_3$, 100 MHz): 170.6, 170.5, 170.4 (3 x CH_3CO_2), 100.1 (C-1), 78.0 (C-5), 77.9 (C-5), 73.6

(C-3), 73.3 (C-3), 71.8 (C-1'), 71.6 (C-1'), 69.7 (C-4), 69.6 (C-4), 62.4 (C-6), 54.7 (C-1''), 54.4 (C-1''), 51.7 (C-7), 51.5 (C-7), 43.1 (C-2), 42.0 (C-2), 33.5, 33.4, 31.7, 31.6, 25.5, 24.0, 23.9 (cyclohexyl group), 20.9, 20.7, 20.6 (3 x CH_3CO_2), 15.9 (C-2''), 13.4 (C-3''). IR ($CHCl_3$): 1029 cm^{-1}. Anal. calcd for $C_{22}H_{36}O_9S$: C, 55.44; H, 7.61; S, 6.73. Found: C, 55.48; H, 7.87; S, 6.79.

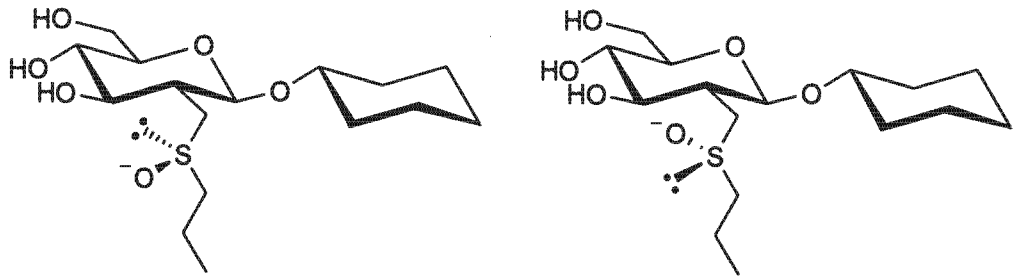
Cyclohexyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*C*-(*n*-propylsulfonylmethyl)-β-D-glucopyranoside (191):



191

Using the procedure described for **177**, oxidation of **184** (50 mg, 0.11 mmol) afforded sulfone **191** (54 mg, 100%) as white solids; mp 157 – 161°C; $[\alpha]_D$ = -16.1 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz): 5.20 (dd, 1H, *J* = 9.0 and 11.1 Hz, H-3), 5.01 (dd, 1H, *J* = 9.1 and 9.9 Hz, H-4), 4.61 (d, 1H, *J* = 8.8 Hz, H-1), 4.28 (dd, 1H, *J* = 5.1 and 12.2 Hz, H-6_a), 4.10 (dd, 1H, *J* = 2.5 and 12.2 Hz, H-6_b), 3.72 – 3.63 (m, 2H, H-5 and H-1'), 3.18 (dd, 1H, *J* = 3.3 and 14.8 Hz, H-7_a), 3.05 (dd, 1H, *J* = 5.2 and 15.0 Hz, H-7_b), 3.04 – 2.87 (m, 2H, H-1''), 2.47 – 2.38 (m, 1H, H-2), 2.07 (x 2), 2.01 (3s, 9H, 3 x CH_3CO_2), 1.98 – 1.08 (m, 12H, H-2'' and 5 x CH_2 of the cyclohexyl protons), 1.07 (t, 3H, *J* = 7.4 Hz, H-3''); δ_C ($CDCl_3$, 100 MHz): 171.0, 170.6, 169.6 (3 x CH_3CO_2), 99.4 (C-1), 77.9 (C-5), 73.0 (C-3), 71.8 (C-1'), 69.6 (C-4), 62.4 (C-6), 55.4 (C-1''), 50.9 (C-7), 42.5 (C-2), 33.5, 31.7, 25.4, 24.1, 24.0, 20.8, 20.7, 20.6 (3 x CH_3CO_2), 15.5 (C-2''), 13.1 (C-3''). IR ($CHCl_3$): 1315 and 1132 cm^{-1}. Anal. calcd for $C_{22}H_{36}O_{10}S$: C, 53.64; H, 7.37; S, 6.51. Found: C, 54.02; H, 7.56; S, 6.58.

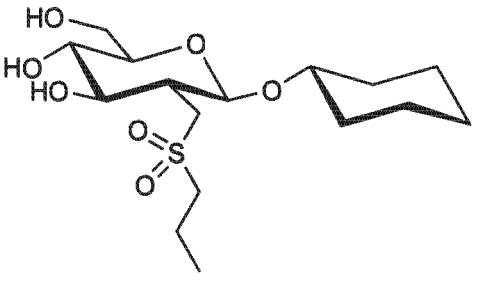
Cyclohexyl 2-deoxy-2-*C*-(*n*-propylsulfinylmethyl)-β-D-glucopyranoside (179b):



179b

Sulfoxide **190** (50 mg, 0.11 mmol) was added to a freshly prepared solution of NaOMe in MeOH (1 mL, 0.011 mmol, 0.01 M) and stirred for 30 min at room temperature. The reaction mixture was then neutralized by addition of Amberlite IR 120 (H+) resin. After 20 min of stirring, the resin was filtered off and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography (ethyl acetate/methanol, 95:5) to give inseparable mixtures of **179b** (37 mg, 96%) as white solids; mp 180 – 184°C; $[\alpha]_D$ = +0.3 (*c* 0.4, MeOH); δ_H (CD_3OD, 400 MHz): 4.58 (d, 1H, *J* = 8.5 Hz), 3.86 (dd, 1H, *J* = 1.6 and 11.8 Hz), 3.81 – 3.72 (m, 1H), 3.71 – 3.66 (m, 1H), 3.42 – 3.34 (m, 1H), 3.28 – 3.24 (m, 1H), 3.11 – 2.98 (m, 1H), 2.95 – 2.82 (m, 1H), 2.73 – 2.63 (m, 1H), 1.98 – 1.68 (m, 7H), 1.56 – 1.47 (m, 1H), 1.45 – 1.15 (m, 7H), 1.10 (t, 3H, *J* = 7.4 Hz); δ_C (CD_3OD, 100 MHz): 101.7, 101.2, 77.9, 77.8, 76.2, 75.9, 72.8, 72.7, 62.91, 62.87, 55.5, 54.4, 52.7, 52.6, 45.7, 45.4, 34.7, 32.7, 26.8, 25.1, 25.0, 24.9, 24.8, 17.3, 17.1, 13.5. IR (MeOH): 1032 cm^{-1}. Anal. calcd for $C_{16}H_{30}O_6S$: C, 54.83; H, 8.63; S, 9.15. Found: C, 54.48; H, 8.72, S, 10.27.

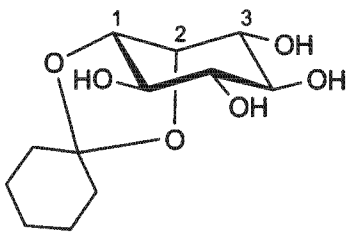
Cyclohexyl 2-deoxy-2-*C*-(*n*-propylsulfonylmethyl)-β-D-glucopyranoside (181b):



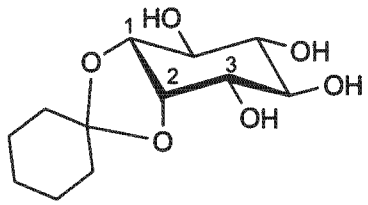
181b

Using the *Zemplén* deacetylation method described above for the preparation of **179b**, deacetylation of sulfone **191** (100 mg, 0.20 mmol) gave **181b** (72 mg, 98%) as white solids; mp 178 – 180 (from methanol); $[\alpha]_D$ = +0.2 (*c* 0.4, MeOH); δ_H (CD_3OD, 300 MHz): 4.66 (d, 1H, *J* = 8.7 Hz), 3.86 (dd, 1H, *J* = 1.8 and 11.8 Hz), 3.82 – 3.64 (m, 2H), 3.55 – 3.45 (m, 1H), 3.28 – 3.23 (m, 2H), 3.15 (dt, 2H, *J* = 4.1 and 7.4 Hz), 2.06 – 1.90 (m, 4H), 1.85 (dd, 2H, *J* = 7.4 and 15.9 Hz), 1.80 – 1.69 (m, 2H), 1.08 (t, 3H, *J* = 7.5 Hz); δ_C (CD_3OD, 75 MHz): 100.7, 77.9 (x 2), 75.6, 72.9, 62.8, 56.8, 52.1, 49.8, 46.1, 34.8, 32.7, 26.8, 25.2, 25.1, 16.8, 13.4. IR (MeOH): 1315 and 1122 cm^{-1}. Anal. calcd for $C_{16}H_{30}O_7S$: C, 52.44; H, 8.25; S, 8.75. Found: C, 52.84; H, 8.56; S, 9.01.

1,2-O-Cyclohexylidene-DL-myo-inositol (194):



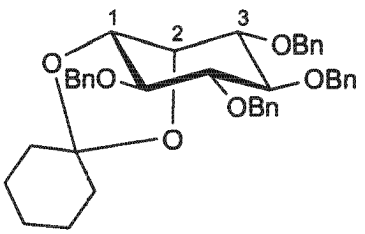
194 (D-isomer)



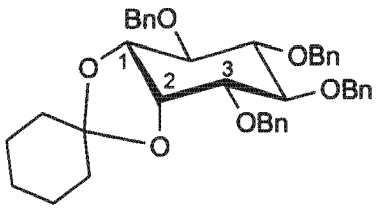
194 (L-isomer)

A suspension of *myo*-inositol **193** (10 g, 55.50 mmol) and cycohexanone (87 mL, 0.76 mmol) in DMF (98 mL) and toluene (21 mL) was stirred under reflux with a *Dean-Stark* separator filled with toluene. *p*-TsOH (10% in DMF, 10 mL) in 2 mL aliquots was added to the refluxing mixture at 2 h interval. The reaction mixture turned to a pale clear yellow solution after 12 h and was refluxed for a further 24 h. The mixture was then evaporated *in vacuo* to leave a viscous yellow oil that was taken up in ethanol (200 mL) and stored at 0°C overnight to crystallize. The resulting crystals were collected by filtration and re-crystallized from ethanol to give white crystals of cyclohexylidene **194** (11.6 g, 80%); mp 179 – 181°C (lit.,[183] 179 - 180°C, lit.,[184] 181 – 183°C); δ_H (DMSO-d_6, 300 MHz): 4.78 (d, 1H, J = 4.8 Hz), 4.73 (d, 1H, J = 5.2 Hz), 4.68 (d, 1H, J = 4.1 Hz), 4.62 (d, 1H, J = 4.3 Hz), 4.16 (dd, 1H, J = 4.0 and 5.2 Hz), 3.79 (dd, 1H, J = 5.3 and 7.3 Hz), 3.51 – 3.25 (m, 3H), 2.90 (dt, 1H, J = 4.1 and 9.4 Hz), 1.70 – 1.20 (m, 10H); δ_C (DMSO-d_6, 100 MHz): 108.4, 78.7, 75.9, 75.0, 74.2, 72.2, 69.9, 37.5, 34.8, 24.6, 23.6, 23.2. The spectroscopic data were in agreement with the reported data.[53]

1,4,5,6-Tetra-O-benzyl-2,3-O-cyclohexylidene-DL-myo-inositol (195):



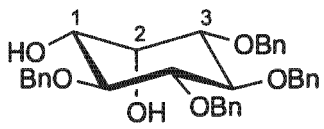
195 (D-isomer)



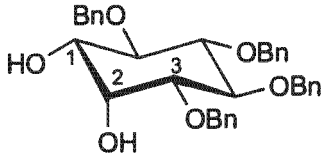
195 (L-isomer)

To a suspension of 1,2-*O*-cyclohexylidene-*myo*-inositol **194** (2 g, 7.68 mmol) in THF (43 mL), NaH (60% dispersed in mineral oil, 2.14 g, 46.08 mmol) was added at 0°C. After 30 min stirring, catalytic amount of TBAI was added followed by slow addition of benzyl bromide (5.43 mL, 46.14 mmol) and the reaction mixture was then stirred under reflux for 16 h. The excess NaH was quenched by careful addition of methanol followed by water. The organic solvent was evaporated *in vacuo* and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and filtered. After evaporation of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 5:95 → 3:7) to afford the title compound **195** (3.7 g, 78%) as a syrup; δ_H ($CDCl_3$, 400 MHz): 7.53 – 7.16 (m, 20H, 4 x Ph), 4.99 – 4.69 (m, 8H, 4 x C*H*$_2$Ph), 4.31 (dd, 1H, J = 3.8 and 5.8 Hz, H-2), 4.12 (dd, 1H, J = 6.0 and 6.8 Hz, H-1), 3.94 (t, 1H, J = 8.2 Hz, H-4), 3.84 (dd, 1H, J = 6.8 and 9.6 Hz, H-6), 3.72 (dd, 1H, J = 3.8 and 8.6 Hz, H-3), 3.43 (dd, 1H, J = 8.4 and 9.6 Hz, H-5), 1.93 – 1.15 (m, 10H, cyclohexylidene protons); δ_C ($CDCl_3$, 100 MHz): 138.7, 138.6, 138.4, 128.3, 128.2, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4 (4 x Ph), 110.4 (quaternary C of cyclohexylidene), 82.9 (C-6), 82.2 (C-5), 81.0 (C-4), 78.8 (C-1), 77.3 (C-3), 75.2, 75.0 (2 x *C*H$_2$Ph), 74.0 (C-2), 73.9, 73.1 (2 x *C*H$_2$Ph), 37.4, 35.0, 25.1, 23.9, 23.7 (cyclohexyl carbons). The spectroscopic data were in agreement with the reported data.[53,183]

1,4,5,6-Tetra-O-benzyl-DL-myo-inositol (196):



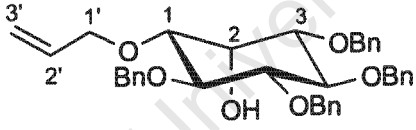
196 (D-isomer)



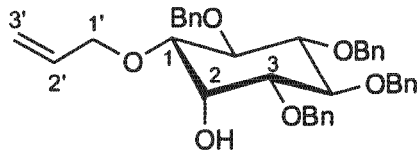
196 (L-isomer)

A mixture of the cyclohexylidene inositol **195** (2.36 g, 3.80 mmol) and 80% aq acetic acid (43 mL) was heated at 100°C for 2 h. The solvent was then evaporated under vacuum and crystallization from a mixture of toluene (6 mL) and hexane (19 mL) afforded diol **196** (1.6 g, 80%) as white crystals; mp 126 - 127°C (lit.,[167] 127 – 128°C); δ_H ($CDCl_3$, 400 MHz): 7.47 – 7.14 (m, 20H, 4 x Ph), 5.04 – 4.60 (m, 8H, 4 x CH_2Ph), 4.20 (t, 1H, J = 2.8 Hz, H-2), 3.99 (t, 1H, J = 9.4 Hz, H-4), 3.85 (t, 1H, J = 9.4 Hz, H-6), 3.53 – 3.44 (m, 3H, H-5, H-1 and H-3), 2.57 (br s, OH), 2.50 (br s, OH); δ_C ($CDCl_3$, 100 MHz): 138.7, 138.6, 137.8, 128.6, 128.5, 128.4, 127.9, 127.8, 127.6 (4 x Ph), 83.2 (C-5), 81.7 (C-4), 81.4 (C-6), 80.1 (C-3), 75.9, 75.7, 75.6, 72.8 (4 x CH_2Ph), 71.8 (C-1), 69.2 (C-2).

1-O-Allyl-3,4,5,6-tetra-O-benzyl-DL-myo-inositol (197):



197 (D-isomer)

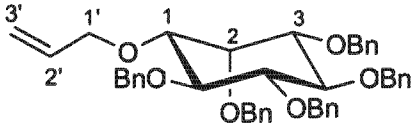


197 (L-isomer)

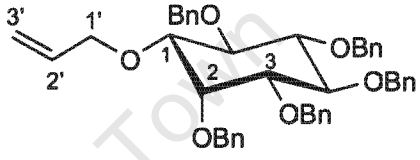
A suspension of **196** (15 g, 27.74 mmol) and dibutyltin oxide (8.3 g, 33.30 mmol), in toluene (131 mL) was refluxed under a *Dean-Stark* separator filled with toluene. After 2 h of refluxing, the solvent was evaporated *in vacuo*. The remaining stannane was dissolved in DMF (78 mL) and allyl bromide (7.25 mL, 83.24 mmol) was added and the reaction mixture was heated to 70°C for 5 h. The solvent was removed and the residue purified by flash chromatography to obtain allyl **197** (13.7 g, 85%) as a colorless oil; δ_H ($CDCl_3$, 400 MHz): 7.41 – 7.22 (m, 20H, 4 x Ph), 6.00 – 5.90 (m, 1H, H-2'), 5.30 (qd, 1H, J = 1.6, 3.2 and 17.2 Hz, H-3'$_a$), 5.20 (qd, 1H, J = 1.2, 2.8 and

10.4 Hz, H-3'$_b$), 4.94 – 4.71 (m, 8H, 4 x CH_2Ph), 4.24 (t, 1H, J = 2.6 Hz, H-2), 4.21 – 4.18 (m, 2H, H-1'$_a$ and H-1'$_b$), 4.01 (t, 1H, J = 9.6 Hz, H-4), 3.97 (t, 1H, J = 9.6 Hz, H-6), 3.46 (t, 1H, J = 9.6 Hz, H-5), 3.43 (dd, 1H, J = 2.8 and 9.6 Hz, H-1), 3.31 (dd, 1H, J = 2.8 and 9.6 Hz, H-3), 2.48 (br s, OH); δ_C ($CDCl_3$, 75 MHz): 138.8, 138.7, 138.0 (Ph), 134.7 (C-2'), 128.4, 128.3, 128.0, 127.8, 127.5 (Ph), 117.4 (C-3'), 83.1 (C-5), 81.20 (C-4), 81.17 (C-6), 79.9 (C-1), 79.6 (C-3), 77.4, 77.0, 76.6, 75.9 (4 x CH_2Ph), 71.9 (C-2), 67.7 (C-1').

1-O-Allyl-2,3,4,5,6-penta-O-benzyl-DL-myo-inositol (198):



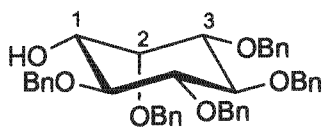
198 (D-isomer)



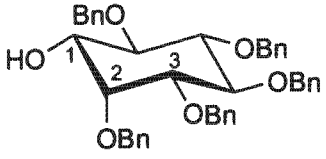
198 (L-isomer)

A solution of **197** (10.0 g, 17.22 mmol) in dry THF (87 mL) was cooled to 0°C and sodium hydride (60% dispersion on oil, 4.13 g, 0.10 mol) was carefully added. After stirring at 0°C for 5 min, benzyl bromide (4.05 mL, 34.44 mmol) was added to the reaction mixture and heated under reflux for 3 h. Excess sodium hydride was destroyed by adding methanol followed by water. The THF was then evaporated off and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine and dried over $MgSO_4$. After filtration, the solvent was evaporated and the crude product purified by column chromatography on silica gel (ethyl acetate/petroleum ether 1:9) to give the title benzylated compound **198** (10.3 g, 80%) as a colorless syrup; δ_H ($CDCl_3$, 300 MHz): 7.51 – 7.20 (m, 25H, 5 x Ph), 6.00 – 5.85 (m, 1H, H-2'), 5.37 – 5.15 (m, 2H, H-3'$_a$ and H-3'$_b$), 4.96 – 4.60 (m, 10H, 5 x CH_2Ph), 4.14 – 4.01 (m, 5H, H-2, H-4, H-6, H-1'$_a$ and H-1'$_b$), 3.47 (t, 1H, J = 9.3 Hz, H-5), 3.38 (dd, 1H, J = 2.1 and 9.9 Hz, H-1), 3.27 (dd, 1H, J = 2.4 and 9.9 Hz, H-3); δ_C ($CDCl_3$, 75 MHz): 139.0, 138.9, 138.4 (Ph), 134.9, (C-2'), 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.5, 127.4, 127.3 (Ph), 116.6 (C-3'), 83.7 (C-5), 81.7 (C-4 and C-6), 80.9 (C-1), 80.7 (C-3), 75.8 (x 3), 74.4 (CH_2Ph), 74.1 (C-2), 72.8 (CH_2Ph), 71.6 (C-1').

2,3,4,5,6-Penta-O-benzyl-DL-myo-inositol (40):



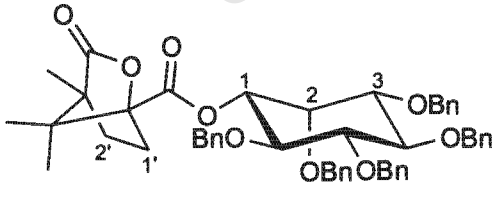
40 (D-isomer)



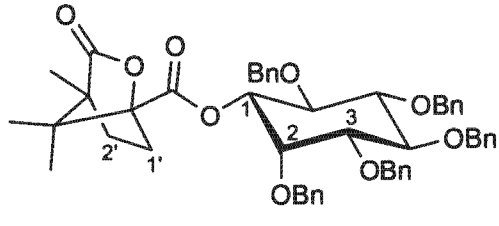
201 (L-isomer)

A suspension of **198** (6.5 g, 9.68 mmol) and palladium(II)chloride (370 mg, 2.06 mmol) in a solution of EtOH:MeOH (1:1, 80 mL) was stirred at room temperature for 3 h. The reaction mixture was filtered over a celite bed, washed with dichloromethane and the filtrate evaporated *in vacuo*. Flash chromatographic purification on silica gel (ethyl acetate/petroleum ether, 7:3) gave the desired deallylated product **40** (4.9 g, 80%) as colorless crystals; mp 89°C (from petroleum ether) (lit.,[167] 86 - 88°C, lit.,[184] 92 - 94°C); δ_H ($CDCl_3$, 300 MHz): 7.45 – 7.20 (m, 25H, 5 x Ph), 5.06 – 4.66 (m, 10H, 5 x CH_2Ph), 4.12 – 3.98 (m, 2H, H-2 and H-6), 3.83 (t, 1H, J = 9.4 Hz, H-4), 3.55 – 3.38 (m, 3H, H-1, H-5 and H-3), 2.22 (d, 1H, J = 6.3 Hz, OH); δ_C ($CDCl_3$, 75 MHz): 138.7, 138.6, 138.2, 128.5, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 127.5 (5 x Ph), 83.6 (C-5), 82.2 (C-4), 81.9 (C-6), 81.1 (C-3), 77.1 (C-2), 75.8, 75.7, 75.4, 74.7, 72.9 (5 x CH_2Ph), 72.4 (C-1).

2,3,4,5,6-Penta-O-benzyl-1-O-[(1S)-(-)-camphanoyl]-D-myo-inositol (199) and 2,3,4,5,6-penta-O-benzyl-1-O-[(1S)-(-)-camphanoyl]-L-myo-inositol (200):



199



200

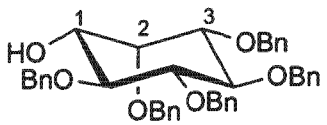
To a solution of **40** (racemic mixture) (5.4 g, 8.55 mmol) in dry dichloromethane (61 mL), (S)-(-)-camphanic acid chloride (2.41 g, 11.13 mmol), triethylamine (4.67 mL, 34.18 mmol) and DMAP (208 mg, 1.70 mmol) were added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was then diluted with

water and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the solvent was removed by evaporation. The white crystalline mixture of diastereoisomers was separated by column chromatography on silica gel (diethyl ether/dichloromethane, 1:99) to furnish **199** (2.9 g, 43%) and **200** (3.2 g, 46%) as white crystals;

Diastereomer **199**: mp 146 - 149°C (lit.,[53] 147 - 149°C); $[\alpha]_D$ +9.6 (*c* 1, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.41 – 7.22 (m, 25H, 5 x Ph), 4.98 (dd, 1H, *J* = 2.4 and 10.4 Hz, H-1), 4.95 – 4.65 (m, 10H, 5 x C*H*$_2$Ph), 4.18 (dd, 1H, *J* = 9.4 and 10.2 Hz, H-6), 4.14 (t, 1H, *J* = 2.4 Hz, H-2), 4.11 (t, 1H, *J* = 9.8 Hz, H-4), 3.61 – 3.55 (m, 2H, H-3 and H-5), 2.33 – 2.24 (m, 1H, H-1'$_a$), 1.90 – 1.76 (m, 2H, H-1'$_b$ and H-2'$_a$), 1.68 – 1.58 (m, 1H, H-2'$_b$), 1.09, 1.01, 0.91 (3s, 9H, 3 x C*H*$_3$ of the camphanoyl); δ_C ($CDCl_3$, 75 MHz): 177.9, 167.3 (2 x C=O of camphanoyl), 138.6, 138.4, 138.3, 138.1, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2 (5 x Ph), 90.8 (quaternary C of camphanoyl), 83.5 (C-5), 81.5 (C-4), 80.9 (C-3), 79.1 (C-6), 75.9, 75.2, 75.0 (x 2), 73.1 (5 x *C*H$_2$Ph, C-1 and C-2), 54.8, 54.2 (2 x quaternary C of camphanoyl), 30.7, 28.9 (C-1' and C-2'), 16.7, 16.6, 9.6 (3 x *C*H$_3$, camphanoyl).

Diastereomer **200**: mp 159 - 163 °C (lit.,[53] 161 - 163°C); $[\alpha]_D$ -15.7 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.45 – 7.10 (m, 25H, 5 x Ph), 4.99 – 4.64 (m, 11H, 5 x C*H*$_2$Ph and H-3), 4.22 (t, 1H, *J* = 2.4 Hz, H-2), 4.18 (dd, 1H, *J* = 9.2 and 10.4 Hz, H-4), 4.12 (t, 1H, *J* = 9.6 Hz, H-6), 3.61 – 3.55 (m, 2H, H-1 and H-5), 2.33 – 2.23 (m, 1H, H-1'$_a$), 1.96 – 1.80 (m, 2H, H-1'$_b$ and H-2'$_a$), 1.71 – 1.61 (m, 1H, H-2'$_b$), 1.08, 0.97, 0.84 (3s, 9H, 3 x –CH$_3$, camphanoyl); δ_C ($CDCl_3$, 100 MHz): 177.9, 167.5 (2 x C=O of camphanoyl), 138.6, 138.4, 138.2, 127.8, 127.6, 127.2 (5 x Ph), 90.8 (quaternary C of camphanoyl), 83.5 (C-5), 81.4 (C-6), 81.0 (C-1), 78.9 (C-4), 76.0, 75.9, 75.3 (x 2), 74.7, 73.1 (5 x *C*H$_2$Ph, C-3 and C-2), 54.8, 54.1 (2 x quaternary C of camphanoyl), 30.9, 28.9 (C-1' and C-2'), 16.6, 16.5, 9.6 (3 x *C*H$_3$ of camphanoyl).

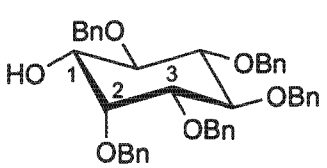
2,3,4,5,6-Penta-O-benzyl-D-myo-inositol (40):



40

A solution of **199** (1.5 g, 1.85 mmol) in absolute ethanol (24 mL) was treated with potassium hydroxide (1.04 g, 18.53 mmol) and stirred under reflux for 2 h. The solvent was then evaporated and the resulting residue was diluted with water. The aqueous phase was extracted with dichloromethane. The combined organic phases were dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether, 7:3) to give **40** (1.1 g, 98%) as a syrup; $[\alpha]_D$ +14.2 (*c* 1.0, $CHCl_3$) [lit.,[169] $[\alpha]_D$ +13.9 (*c* 0.3, $CHCl_3$)]; δ_H ($CDCl_3$, 400 MHz): 7.40 – 7.24 (m, 25H, 5 x Ph), 5.02 – 4.68 (m, 10H, 5 x CH_2Ph), 4.06 (t, 1H, J = 9.6 Hz, H-6), 4.04 (t, 1H, J = 2.4 Hz, H-2), 3.81 (t, 1H, J = 9.6 Hz, H-4), 3.51 (m, 1H, H-1), 3.50 (t, 1H, J = 9.6 Hz, H-5), 3.47 (dd, 1H, J = 9.6 and 2.6 Hz, H-3), 2.22 (br s, OH); δ_C ($CDCl_3$, 100 MHz): 138.9, 138.8, 138.7, 138.4, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6 (5 x Ph), 83.7 (C-5), 82.3 (C-4), 82.0 (C-6), 81.3 (C-3), 77.3 (C-2), 76.0, 75.9, 75.6, 74.9, 73.1 (5 x *C*H_2Ph), 72.6 (C-1).

2,3,4,5,6-Penta-O-benzyl-L-myo-inositol (201):

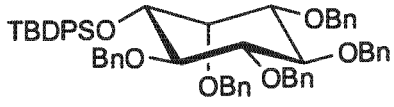


201

Under the same conditions as for the D-analogue, de-esterification of **200** (2.0 g, 2.47 mmol) yielded **201** (1.5 g, 97%) as a syrup; $[\alpha]_D$ -13.4 (*c* 1.0, $CHCl_3$), [lit.,[169] $[\alpha]_D$ -13.5 (*c* 0.3, $CHCl_3$)]; δ_H ($CDCl_3$, 400 MHz): 7.44 – 7.30 (m, 25H, 5 x Ph), 5.05 – 4.72 (m, 10H, 5 x CH_2Ph), 4.12 (t, 1H, J = 9.6 Hz, H-6), 4.06 (t, 1H, J = 2.4 Hz, H-2), 3.88

(t, 1H, J = 9.6 Hz, H-4), 3.55 (m, 1H, H-1), 3.52 (t, 1H, J = 9.6 Hz, H-5), 3.49 (dd, 1H, J = 9.6 and 2.4 Hz, H-3), 2.28 (br s, OH); δ_C ($CDCl_3$, 100 MHz): 138.7, 138.6, 138.5, 138.2, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4 (5 x Ph), 83.6 (C-5), 82.1 (C-4), 81.9 (C-6), 81.1 (C-3), 77.1 (C-2), 75.8, 75.7, 75.5, 74.7, 72.9 (5 x CH_2Ph), 72.4 (C-1).

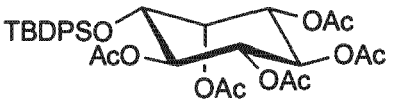
2,3,4,5,6-Penta-*O*-benzyl-1-*O*-*tert*-butyldiphenylsilyl-D-*myo*-inositol (202):



202

Alcohol **40** (1.3 g, 2.05 mmol) and imidazole (308 mg, 4.52 mmol) were dissolved in dry DMF (5 mL) and treated with *tert*-butyldiphenylsilyl chloride (590 µL, 2.26 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1 h before it was diluted with water. The aqueous phase was extracted with diethyl ether and the combined organic layers were washed with water and dried over $MgSO_4$. After filtration, the solvent was evaporated and the crude product was purified by column chromatography on silica gel using dichloromethane as eluent to afford *myo*-inositol **202** (1.5 g, 84%) as a colorless oil; $[\alpha]_D$ = +15.3 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.80 – 7.10 (m, 35H, 7 x Ph), 5.08 (d, 1H, J = 11.2 Hz, CH_2Ph), 4.97 (d, 1H, J = 11.2 Hz, CH_2Ph), 4.85 (m, 3H, CH_2Ph), 4.75 (d, 1H, J = 10.9 Hz, CH_2Ph), 4.67 (d, 1H, J = 11.4 Hz, CH_2Ph), 4.48 (d, 1H, J = 11.4 Hz, CH_2Ph), 4.20 – 4.10 (m, 3H, CH_2Ph and H-4), 3.98 (t, 1H, J = 9.5 Hz, H-6), 3.82 (dd, 1H, J = 2.2 and 9.8 Hz, H-3), 3.44 (t, 1H, J = 9.1 Hz, H-5), 3.33 (t, 1H, J = 2.0 Hz, H-2), 3.07 (dd, 1H, J = 2.0 and 9.8 Hz, H-1), 1.12 (s, 9H, Me_3C-Si); δ_C ($CDCl_3$, 100 MHz): 139.4, 139.2, 139.1, 138.8, 138.3, 136.5, 136.4, 136.1, 135.0, 133.2, 130.0, 129.8, 128.8, 128.7, 128.5, 128.3, 128.2, 128.0, 127.9, 127.6, 127.5, 127.4, 127.2, 127.1 (7 x Ph), 84.0 (C-5), 82.1 (C-4), 81.6 (C-6), 81.1 (C-1), 75.9, 75.7 (x 2), 75.6, 74.5, 74.2, 71.7 (C-2, C-3 and 5 x CH_2Ph), 27.2 (Me_3C-Si), 19.3 (Me_3C-Si). Anal. calcd for $C_{57}H_{60}O_6Si$: C, 78.77; H, 6.96. Found: C, 79.12; H, 6.84.

2,3,4,5,6-Penta-*O*-acetyl-1-*O*-*tert*-butyldiphenylsilyl-D-*myo*-inositol (203):



203

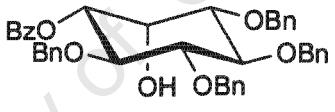
A suspension of **202** (1.2 g, 1.38 mmol) and 10% activated palladium on charcoal (122 mg, 0.11 mmol) in ethanol was stirred under a hydrogen atmosphere overnight at room temperature. Periodic addition of further equivalents of 10% activated palladium on charcoal was required over a period of 48 h interval until TLC showed completion of the reaction (approximately 3 days). The reaction mixture was filtered over a celite bed, washed with ethyl acetate and the filtrate evaporated *in vacuo*. The resulting residue was dissolved in dichloromethane (10 mL), acetic anhydride (6 mL), triethylamine (3 mL) and catalytic amount of DMAP were added and the reaction mixture was stirred at room temperature for 1 h. Water was then added and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed successively with water and brine, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 1:9) to give the desired product **203** (772 mg, 89%) as a colorless syrup; $[\alpha]_D$ = +1.0 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.76 – 7.34 (m, 10H, 2 x Ph), 5.50 (t, 1H, *J* = 9.8 Hz, H-6), 5.42 (t, 1H, *J* = 10.2 Hz, H-4), 5.35 (t, 1H, *J* = 2.8 Hz, H-2), 4.89 (t, 1H, *J* = 9.6 Hz, H-5), 4.70 (dd, 1H, *J* = 2.8 and 10.4 Hz, H-3), 3.93 (dd, 1H, *J* = 2.8 and 10.0 Hz, H-1), 2.20, 1.95, 1.94, 1.92, 1.53 (5s, 15H, 5 x CH_3CO_2), 0.99 (s, 9H, Me_3C-Si); δ_C ($CDCl_3$, 100 MHz): 170.0, 169.9, 169.8, 169.7, 169.6 (5 x CH_3CO_2), 136.4, 136.0, 135.7, 133.2, 131.6, 130.4, 129.9, 128.1, 127.7, 127.6 (2 x Ph), 72.4, 71.7, 70.7, 69.6, 69.5, 69.2 (C-1, C-2, C-3, C-4, C-5, C-6), 26.6 (Me_3C-Si), 20.9, 20.53, 20.50, 20.48, 20.46 (5 x CH_3CO_2), 19.2 (Me_3C-Si). Anal. calcd for $C_{32}H_{40}O_{11}Si$: C, 61.13; H, 6.41. Found: C, 61.30; H, 6.65.

Selective acylation of diol 196: A solution of diol **196** (0.93 mmol), triethylamine (1.11 mmol) and catalytic amount of DMAP in dry dichloromethane (5 mL) at 0°C was treated with the acylating agent (1.11 mmol) dropwise. The resulting reaction

mixture was stirred at room temperature until TLC analysis showed completion of the reaction. The reaction mixture was then diluted with dichloromethane and washed with ice-cold aq NH_4Cl. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography on silica gel using a mixture of ethyl acetate and petroleum ether as eluent to yield the desired mono-acylated products.

1→2 Acyl migration: To a solution of the substrate from the selective acylation in acetonitrile was added DBU (1 equiv.). After stirring for 1 h at room temperature, the reaction mixture was diluted with ice-cold aq NH_4Cl. The aqueous layer was extracted with dichloromethane. The combined organic phases were successively washed with water and brine, dried over $MgSO_4$, filtered and evaporated. The desired product was separated from the unreacted starting compound by column chromatography on silica gel using a mixture of ethyl acetate and petroleum ether as eluent.

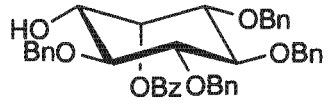
1-*O*-Benzoyl-3,4,5,6-tetra-*O*-benzyl-D/L-*myo*-inositol (209):



209

Using the selective acylation procedure, benzoylation of diol **196** (500 mg, 0.92 mmol) with benzoyl chloride afforded benzoate **209** (486 mg, 82%) as white crystals; mp 127 – 132°C; δ_H ($CDCl_3$, 300 MHz): 8.09 (d, 2H, J = 8.1 Hz, *ortho* protons from benzoate), 7.63 – 7.10 (m, 23H, 5 x Ph), 5.13 (dd, 1H, J = 2.0 and 10.4 Hz, H-1), 4.98 – 4.64 (m, 8H, 4 x CH_2Ph), 4.43 (br s, 1H, H-2), 4.27 (t, 1H, J = 10.3 Hz, H-6), 4.04 (t, 1H, J = 9.6 Hz, H-4), 3.68 – 3.56 (m, 2H, H-3 and H-5); δ_C ($CDCl_3$, 75 MHz): 165.9 (Ph*C*O_2), 138.5, 138.4, 138.0, 137.4, 133.2, 129.8, 129.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.6 (5 x Ph), 83.1, 81.1, 80.0, 79.0, 76.0 (x 2), 75.8, 73.4, 72.9, 67.9.

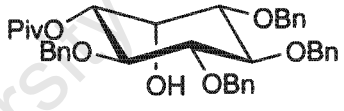
2-*O*-Benzoyl-3,4,5,6-tetra-*O*-benzyl-D/L-*myo*-inositol (211):



211

Using the general 1→2 acyl migration protocol on **209** (100 mg, 0.16 mmol), **211** (38 mg, 67%) was obtained as a syrup and 43 mg of the starting material was recovered (HPLC analysis of the reaction mixture at equilibrium showed a 50:50 ratio of **211**:**209**); δ_H ($CDCl_3$, 300 MHz): 8.04 (d, 2H, J = 7.5 Hz, *ortho* protons from benzoate), 7.71 – 7.02 (m, 23H, 5 x Ph), 5.95 (br s, 1H, H-2), 5.02 – 4.46 (m, 9H, H-1, 4 x CH_2Ph), 3.98 (t, 1H, J = 9.3 Hz, H-6), 3.88 (t, 1H, J = 9.3 Hz, H-4), 3.74 – 3.54 (m, 2H, H-3 and H-5); δ_C ($CDCl_3$, 75 MHz): 166.5 (PhCO_2), 138.5, 138.2, 137.6, 133.2, 129.9, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6 (5 x Ph), 83.2, 82.0, 81.4, 78.5, 76.2, 76.0, 75.6, 72.6, 70.4, 69.8.

3,4,5,6-Tetra-*O*-benzyl-1-*O*-pivaloyl-D/L-*myo*-inositol (210):



210

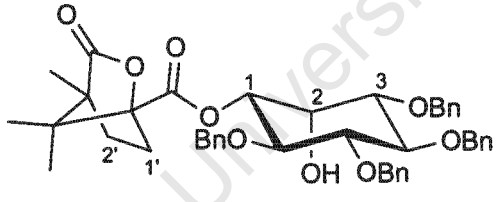
Pivaloylation of diol **196** (512 mg, 0.95 mmol) with pivaloyl chloride using the general procedure afforded pivaloate **210** (494 mg, 83%) as white crystals; mp 138 – 142°C); δ_H ($CDCl_3$, 300 MHz): 7.37 – 7.22 (m, 20H, 4 x Ph), 4.88 – 4.62 (m, 9H, H-1 and 4 x CH_2Ph), 4.32 (br s, 1H, H-2), 4.13 (t, 1H, J = 9.8 Hz, H-6), 3.98 (t, 1H, J = 9.3 Hz, H-4), 3.64 – 3.51 (m, 2H, H-3 and H-5), 2.48 (br s, OH), 1.24 (s, 9H, pivaloyl); δ_C ($CDCl_3$, 75 MHz): 178.0 (carbonyl of the pivaloyl), 138.5, 138.4, 138.3, 137.4, 128.5, 128.3, 128.0, 127.9, 127.8, 127.6, 127.5, 127.3 (4 x Ph), 83.1, 81.1, 80.0, 78.8, 75.9 (x 2), 75.5, 73.2, 72.8, 67.6, 38.9, 27.1.

3,4,5,6-Tetra-*O*-benzyl-2-*O*-pivaloyl-D/L-*myo*-inositol (212):

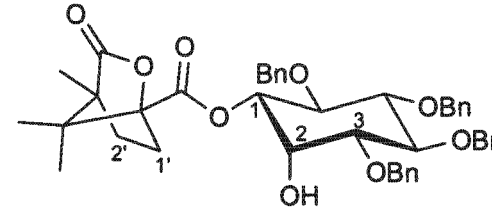
212

1→2 pivaloyl migration in **210** (100 mg, 0.16 mmol) using the general protocol afforded **212** (51 mg, 95%) as an oil and 47 mg of the starting material was recovered (HPLC analysis of the reaction mixture at equilibrium showed 64:37 ratio of **212**:**210**); δ_H ($CDCl_3$, 300 MHz): 7.63 – 7.31 (m, 20H, 4 x Ph), 5.88 (br s, 1H, H-2), 5.21 – 4.61 (m, 9H, H-1 and 4 x CH_2Ph), 4.20 – 3.60 (m, 4H, H-3, H-4, H-5 and H-6), 2.40 (br s, OH), 1.40 (s, 9H, pivaloyl); δ_C ($CDCl_3$, 75 MHz): 177.8 (carbonyl of the pivaloyl), 138.4, 138.2, 138.1, 137.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.5 (4 x Ph), 83.0, 81.8, 80.8, 78.5, 76.0, 75.8, 74.8, 71.7, 70.1, 65.5, 39.0, 27.2.

3,4,5,6-Tetra-O-benzyl-1-O-[(1S)-(-)-camphanoyl]-D and -L-*myo*-inositols (213a and 213b):



213a

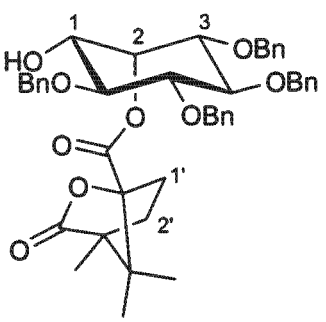


213b

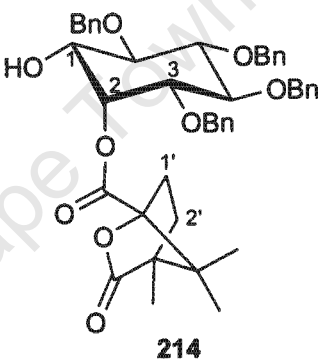
Mono-esterification of diol **196** (100 mg, 0.18 mmol) with camphanic acid chloride using the general procedure afforded chromatographically inseparable esters **213a** and **213b** (97 mg, 75%) as white gum; δ_H ($CDCl_3$, 300 MHz): 7.43 – 7.17 (m, 20H, 4 x Ph), 4.97 – 4.65 (m, 9H, H-1 and 4 x CH_2Ph), 4.32 (t, 0.5H, J = 2.7 Hz, H-2 of **213a**), 4.29 (t, 0.5H, J = 2.7 Hz, H-2 of **213b**), 4.15 (t, 0.5H, J = 9.8 Hz, H-6 of **213a**), 4.13 (t, 0.5H, J = 9.8 Hz, H-6 of **213b**), 3.97 (t, 0.5H, J = 9.6 Hz, H-4 of **213a**), 3.96 (t, 0.5H, J = 9.4 Hz, H-4 of **213b**), 3.61 – 3.51 (m, 2H, H-3 and H-5), 2.47 – 2.24 (m, 1H, H-1'$_a$), 2.04 (m, 2H, H-1'$_b$ and H-2'$_a$), 1.73 – 1.63 (m, 1H, H-2'$_b$), 1.60 (br s, OH),

1.11, 1.10, 1.08, 1.01, 0.98, 0.90 (6s, 9H, C*H*$_3$ of camphanoyl group); δ_C ($CDCl_3$, 100 MHz): 178.1, 177.8, 167.2, 167.0 (4 x C=O of camphanoyl), 138.5, 138.4, 138.2, 137.6, 137.5, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.6, 127.5, 127.3, 91.0, 83.02, 83.0, 81.12, 81.08, 80.0, 79.9, 78.5, 78.4, 75.96, 75.93, 75.9, 75.5, 75.4, 74.8, 74.7, 73.1, 73.0, 67.7, 67.4, 54.8, 54.7, 54.3, 54.2, 30.6, 30.5, 29.1, 28.8, 16.7, 16.6, 16.56, 16.47, 9.7, 9.6. Anal. calcd for $C_{44}H_{48}O_9$: C, 73.31; H, 6.71. Found C, 73.32; 6.67.

3,4,5,6-Tetra-O-benzyl-2-O-[(1S)-(-)-camphanoyl]-D-myo-inositol (192) and 3,4,5,6-tetra-O-benzyl-2-O-[(1S)-(-)-camphanoyl]-L-myo-inositol (214)



192



214

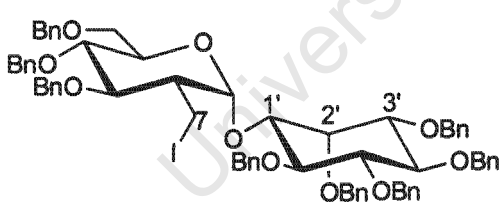
1→2 camphonyl migration on **213** (89 mg, 0.12 mmol) using the general protocol afforded separable diastereoisomers **192** (22 mg, 54%) and **214** (19 mg, 47%) as colorless oils;

Diastereomer **192**: $[\alpha]_D$ = -3.62 (*c* 2.5, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.37 – 7.24 (m, 20H, 4 x Ph), 5.84 (t, 1H, *J* = 2.8 Hz, H-2), 5.01 – 4.51 (m, 8H, 4 x *CH*$_2$Ph), 3.78 (t, 1H, *J* = 9.6 Hz, H-6), 3.76 (t, 1H, *J* = 9.6 Hz, H-4), 3.63 (dd, 1H, *J* = 2.2 and 10.2 Hz, H-1), 3.57 (dd, 1H, *J* = 2.6 and 9.8 Hz, H-3), 3.52 (t, 1H, *J* = 9.4 Hz, H-5), 2.46 – 2.36 (m, 1H, H-1'$_a$), 2.05 – 1.97 (m, 1H, H-1'$_b$), 1.94 – 1.84 (m, 1H, H-2'$_a$), 1.72 – 1.63 (m, 1H, H-2'$_b$), 1.59 (br s, OH), 1.11, 0.94, 0.935 (3s, 9H, 3 x C*H*$_3$ of camphanoyl group); δ_C ($CDCl_3$, 75 MHz): 178.2, 166.7 (2 x C=O of camphanoyl), 138.2, 137.4, 128.4, 128.2, 128.0, 127.9, 127.8, 127.6, 127.5, 127.3 (4 x Ph), 91.2 (quaternary carbon of camphanoyl), 82.9, 81.4, 80.9, 78.1, 75.73, 75.66, 75.3, 72.2, 70.5, 69.0 (C-1, C-2, C-3, C-4, C-5, C-6 and 4 x *C*H$_2$Ph), 54.8, 54.2 (2 x quaternary carbon of camphanoyl),

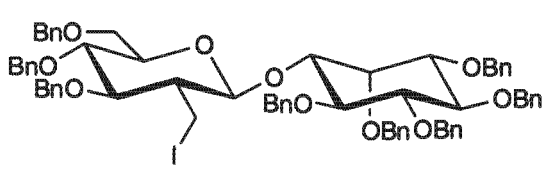
30.6, 28.8 (C-1' and C-2'), 16.40, 16.36, 9.6 (3 x CH_3 of camphanoyl). Anal. calcd for $C_{44}H_{48}O_9$: C, 73.31; H, 6.71. Found: C, 73.37; H, 6.70.

Diastereomer **214**: $[\alpha]_D$ = -12.8 (*c* 2.5, $CHCl_3$); δ_H ($CDCl_3$, 400 MHz): 7.37 – 7.24 (m, 20H, 4 x Ph) 5.82 (t, 1H, *J* = 2.8 Hz, H-2), 5.01 – 4.51 (m, 8H, 4 x CH_2Ph), 3.83 (t, 1H, *J* = 9.4 Hz, H-6), 3.72 – 3.48 (m, 4H, H-1, H-3, H-4 and H-5), 2.36 – 2.26 (m, 1H, H-1'$_a$), 2.06 – 1.95 (m, 1H, H-1'$_b$), 1.94 – 1.84 (m, 1H, H-2'$_a$), 1.74 – 1.62 (m, 1H, H-2'$_b$), 1.57 (br s, OH), 1.11, 1.04, 0.84 (3s, 9H, 3 x CH_3 of camphanoyl); δ_C ($CDCl_3$, 75 MHz): 178.1, 166.6 (2 x C=O of camphanoyl), 138.3, 138.2, 138.1, 137.3, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5 (4 x Ph), 91.2 (quaternary carbon of camphanoyl), 82.9, 81.7, 80.3, 77.9, 75.8, 75.7, 72.2, 70.4, 69.5 (C-1, C-2, C-3, C-4, C-5, C-6 and 4 x CH_2Ph), 54.7, 54.1 (2 x quaternary carbon of camphanoyl), 30.5, 28.8 (C-1' and C-2'), 16.6, 16.3, 9.56 (3 x CH_3 of camphanoyl). Anal. calcd for $C_{44}H_{48}O_9$: C, 73.31; H, 6.71. Found: C, 73.19; H, 6.74.

2',3',4',5',6'-Penta-*O*-benzyl-1'-*O*-(3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-iodomethyl-α-D-glucopyranosyl)-D-*myo*-inositol (218a) and 2',3',4',5',6'-penta-*O*-benzyl-1'-*O*-(3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-iodomethyl-β-D-glucopyranosyl)-D-*myo*-inositol (218b):



218a



218b

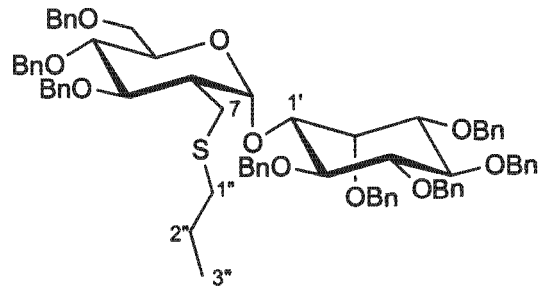
A mixture of acetate **154** (180 mg, 0.29 mmol) and **40** (203 mg, 0.32 mmol) was dried azeotropically with toluene. The mixture was then dissolved in dry dichloromethane (1 mL) containing 4Å molecular sieves and stirred at room temperature for 30 min. The reaction mixture was then allowed to cool to 0°C and treated by dropwise addition of $BF_3{\cdot}Et_2O$ (18 μL, 0.14 mmol). After 1 h stirring at room temperature, the reaction was quenched by addition of triethylamine (20 μL) and the solids removed by filtration. The filtrate was diluted with water and extracted with dichloromethane. The organic layer was washed successively with saturated $NaHCO_3$, water and brine, dried

over $MgSO_4$ and concentrated *in vacuo*. The brown residue was purified by column chromatography (ethyl acetate/petroleum ether, 1:9) to give **218a** (226 mg, 65%) and **218b** (57 mg, 16%) as colorless oils;

Diastereomer **218a**: $[\alpha]_D$ = +43.8 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz): 7.50 – 6.58 (M, 40H, 8 x Ph), 5.21 (d, 1H, *J* = 3.0 Hz, H-1), 5.21 (d, 1H, *J* = 11.3 Hz, C*H*$_2$Ph), 4.97 – 4.68 (m, 11H, C*H*$_2$Ph), 4.58 (t, 2H, *J* = 11.0 Hz, C*H*$_2$Ph), 4.43 (d, 1H, *J* = 11.1 Hz, C*H*$_2$Ph), 4.34 (d, 1H, *J* = 12.1 Hz, C*H*$_2$Ph), 4.30 (br s, 1H, H-2'), 4.17 – 3.98 (m, 3H), 3.72 – 3.40 (m, 8H), 3.03 (dd, 1H, *J* = 9.4 and 11.5 Hz, H-7$_b$), 2.31 – 1.96 (m, 1H, H-2); δ_C ($CDCl_3$, 75 MHz): 139.4, 138.6, 138.3, 138.2, 138.0, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 127.3, 127.2 (8 x Ph), 96.3 (C-1), 84.2, 82.0, 81.8, 80.6, 79.9, 79.2, 75.9, 75.8, 75.3, 75.2, 74.8, 74.6, 74.5, 74.1, 73.3, 73.1, 70.8, 68.2 (C-6), 49.4 (C-2), 2.7 (C-7). Anal. calcd for $C_{69}H_{71}IO_{10}$: C, 69.81; H, 6.03. Found: C, 69.83; H, 6.19.

Diastereomer **218b**: $[\alpha]_D$ = +7.6 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz): 7.35 – 7.21 (m, 40H, 3 x Ph), 5.10 – 4.63 (m, 12H), 4.61 – 4.54 (m, 3H), 4.51 – 4.98 (m, 2H), 4.96 – 4.84 (m, 1H), 4.13 – 3.92 (m, 2H), 3.72 – 3.49 (m, 10H), 1.39 – 1.28 (m, 1H, H-2); δ_C ($CDCl_3$, 75 MHz): 139.9, 139.3, 139.2, 139.1, 138.9, 138.7, 138.6, 138.2, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 127.4, 127.3 (8 x Ph), 104.2 (C-1), 84.2, 82.2, 81.8, 81.5, 81.1, 79.9, 76.0, 75.9, 75.7, 75.1, 74.9, 74.8, 73.8, 73.3, 72.5, 71.3, 70.4, 69.7, 47.7, 7.3. Anal. calcd for $C_{69}H_{71}IO_{10}$: C, 69.81; H, 6.03. Found: C, 69.86; H, 6.06.

2',3',4',5',6'-Penta-*O*-benzyl-1'-*O*-[3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-(*n*-propylthiomethyl)-α-D-glucopyranosyl]-D-*myo*-inositol (219):



220

Thiolation of **218a** (200 mg, 0.17 mmol) using the conditions described for the synthesis of sulfide **173** afforded **219** (176 mg, 92%) as a colorless oil; $[\alpha]_D$ = +56.4 (*c* 1.0, $CHCl_3$); δ_H ($CDCl_3$, 300 MHz): 7.47 – 6.98 (m, 40H, 8 x Ph), 5.30 (d, 1H, *J* = 2.5 Hz, H-1), 5.09 (d, 1H, *J* = 11.1 Hz, C*H*$_2$Ph), 4.94 – 4.71 (m, 11H, C*H*$_2$Ph), 4.59 (t, 2H, *J* = 11.0 Hz, C*H*$_2$Ph), 4.45 (d,1H, *J* = 11.0 Hz, C*H*$_2$Ph), 4.35 (d, 1H, *J* = 11.1 Hz, C*H*$_2$Ph), 4.25 (br s, 1H, H-2'), 4.16 – 3.97 (m, 3H), 3.73 – 3.62 (m, 3H), 3.52 – 3.42 (m, 4H), 2.81 (dd, 1H, *J* = 2.7 and 13.1 Hz, H-7_a), 2.51 (dd, 1H, *J* = 11.7 and 12.9 Hz, H-7_b), 2.40 – 2.32 (m, 2H, 2 x H-1"), 2.15 – 2.00 (m, 1H, H-2), 1.56 – 1.45 (m, 2H, 2 x H-2"), 0.92 (t, 3H, 3 x H-3"); δ_C ($CDCl_3$, 75 MHz): 139.4, 138.8, 138.6, 138.4, 138.3, 138.0, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 127.3, 127.1 (8 x Ph), 94.8 (C-1), 84.1, 81.8, 80.5, 80.1, 79.7, 76.0, 75.9, 75.8, 75.3, 74.6, 74.3, 73.9, 73.3, 72.9, 70.5, 68.4, 46.0 (C-2), 34.0 (C-1"), 28.5 (C-2"), 22.7 (C-3"), 13.4 (C-7). Anal. calcd for $C_{72}H_{78}O_{10}S$: C, 76.16; H, 6.92; S, 2.82. Found: C, 76.05; H, 6.88; S, 2.79.

REFERENCES

1. Lindhorst, T. K. *Essentials of Carbohydrate Chemistry and Biochemistry*; 2nd ed.; Wiley-VCH: Weinheim, 2003.
2. Osborn, H. M. I. *Carbohydrates;* Academic Press: 2003.
3. Pigman, W.; Horton, D. *The Carbohydrates: Chemistry and Biochemistry*; Academic Press: New York, 1972.
4. Collins, P.; Ferrier, R. *Monosaccharides: Their Chemistry and Their Roles in Natural Products*; John Wiley and Sons: Chichester, 1995.
5. http://www.chem.qmul.ac.uk/iupac/2carb/00n01.html#002.
6. http://www.chem.qmul.ac.uk/iupac/2carb.
7. Bucior, I.; Scheuking, S.; Engel, A.; Burger, M. M. *J. Biol. Chem.* **2004**, *165*, 529 - 537.
8. Haseley, S. R.; Vermeer, H. J.; Kamerling, J. P.; Vliegenthart, J. F. G. *Proc. Natl. Acad. Sci. Unit. States Am.* **2001**, *98*, 9419 - 9424 and references cited therein.
9. Boons, G. –J.; Hale, K. J. *Organic Synthesis with Carbohydrates*; Sheffield Academic Press: Sheffield, 2000.
10. http://textbookofbacteriology.net/tuberculosis.html.
11. http://almaz.com/nobel/nobel.html.
12. http://www.sanger.ac.uk/Projects/M_tuberculosis.
13. Zhang, Y.; Post-Martens, K.; Denkin, S. *Drug Discov. Today* **2006**, *11*, 21 - 27.
14. (a) http://www.tballiance.org;
    (b) http://www.who.int/health_topics/tuberculosis/en/.
15. Duncan, K. *Tuberculosis* **2003**, *83*, 201 - 207.
16. O'Brien, R. *The Global Alliance for TB Drug Development* **2001**, 1 - 51.
17. http://w3.whosea.org/en/Section10/Section2097/Section2106_10678.htm.
18. Benator, D.; Bhattacharya, M.; Bozeman, L.; Burman, W.; Cantazaro, A. *et al. Lancet* **2002**, *360*, 528 – 534.
19. Duncan, K.; Barry III, C. E. *Curr. Opin. Microbiol.* **2004**, *7*, 460 - 465.
20. Espinal, M. A. *Tuberculosis* **2003**, *83*, 44 - 51.

21. Corbett, E. L.; Watt, C. J.; Walker, N.; Maher, D.; Williams, B. G.; Raviglione, M. C.; Dye, C. *Arch. Intern. Med.* **2003**, *163*, 1009 - 1021.
22. Collins, F. M. C*rit. Rev.* **1993**, *19*, 1 - 16.
23. Cole, S. T.; Brosch, R.; Parkhill, J.; Garnier, T. *et al. Nature* **1998**, *393*, 537 - 544.
24. Hand, C. E.; Honek, J. F. *J. Nat. Prod.* **2005**, *68*, 293 - 308.
25. (a) Sakuda, S.; Zhou, Z. –Y.; Yamada, Y. *Biosci. Biotech. Biochem.* **1994**, *58*, 1347 – 1348; (b) Spies, H. S. C.; Steenkamp, D. J. *Eur. J. Biochem.* **1994**, *224*, 203 – 213; (c) Newton, C. A.; Bewley, T. J.; Dwyer, R.; Horn, Y.; Aharonowitz, G.; Cohen, G.; Davis, J.; Faulkner, D. J.; Fahey, R. C. *Eur. J. Biochem.* **1995**, *230*, 821 - 825.
26. Patel, M. P.; Blanchard, J. S. *Biochemistry* **1999**, *38*, 11827 - 11833.
27. Newton, G. L.; Fahey, R. C. *Arch. Microbiol.* **2002**, *178*, 388 - 394.
28. Newton, G. L.; Arnold, K.; Price, M. S.; Sherrill, C.; Delcardayre, S. B.; Aharonowitz, Y.; Cohen, G.; Davies, J.; Fahey, R. C.; Davis, C. *J. Bacteriol.* **1996**, *178*, 1990 - 1995.
29. Nicholas, G. M.; Bewley, C. A. *Curr. Med. Chem. Anti-Infective Agents* **2004**, *3*, 221 - 231.
30. Newton, G. L.; Koledin, T.; Gorovitz, B.; Rawat, M.; Fahey, R. C.; Av-Gay, Y. *J. Bacteriol.* **2003**, *185*, 3476 - 3479.
31. Newton, G. L.; Av-Gay, Y.; Fahey, R. C. *J. Bacteriol.* **2000**, *182*, 6958 - 6963.
32. Sareen, D.; Steffek, M.; Newton, G. L.; Fahey, R. C. *Biochemistry* **2002**, *41*, 6885 - 6890.
33. Koledin, T.; Newton, G. L.; Fahey, R. C. *Arch. Microbiol.* **2002**, *178*, 331 - 337.
34. Jardine, M. A.; Spies, H. S. C.; Nkambule, C. M.; Gammon, D. W.; Steenkamp, D. J. *Bioorg. Med. Chem.* **2002**, *10*, 875 - 881.
35. Lee, S.; Rosazza, J. P. N. *Org. Lett.* **2004**, *6*, 365 - 368.
36. Steenkamp, D. J.; Vogt, R. N. *Anal. Biochem.* **2004**, *325*, 21 - 27.
37. Patel, M. P.; Blanchard, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 11538 - 11539.
38. Patel, M. P.; Blanchard, J. S. *Biochemistry* **2001**, *40*, 5119 - 5126.
39. Vogt, R. N.; Steenkamp, D. J.; Zheng, R.; Blanchard, J. S. *Biochem. J.* **2003**, *374*, 657 - 666.

40. Newton, G. L.; Av-Gay, Y.; Fahey, R. C. *Biochemistry* **2000**, *39*, 10739 - 10746.

41. Steffek, M.; Newton, G. L.; Av-Gay, Y.; Fahey, R. C. *Biochemistry* **2003**, *42*, 12067 - 12076.

42. Knapp, S.; Gonzalez, S.; Myers, D. S.; Eckman, L. L.; Bewley, C. A. *Org. Lett.* **2002**, *4*, 4337 - 4339.

43. Nicholas, G. M.; Eckman, L. L.; Kováč, P.; Otero-Quintero, S.; Bewley, C. A. *Bioorg. Med. Chem.* **2003**, *11*, 2641 - 2647.

44. Bornemann, C.; Jardine, M. A.; Spies, H. S. C.; Steenkamp, D. J. *Biochem. J.* **1997**, *325*, 623 - 629.

45. Gammon, D. W.; Hunter, R.; Steenkamp, D. J.; Mudzunga, T. T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2045 - 2049.

46. Raymond, A. L.; Schroeder, E. F. *J. Am. Chem. Soc.* **1948**, *70*, 2785 - 2791.

47. Monneret, C.; Choay, P. *Carbohydr. Res.* **1981**, *96*, 299 - 305.

48. Tatsuta, K.; Fujimato, K.; Kinoshita, M. *Carbohydr. Res.* **1977**, *54*, 85 - 104.

49. Korth, H. –G.; Sustmann, R.; Giese, B.; Rückert, B.; Gröninger, K. S. *Chem. Ber.* **1990**, *123*, 1891 - 1898.

50. Marzabadi, C. H.; Spilling, C. D. *J. Org. Chem.* **1993**, *58*, 3761 - 3766.

51. González, C. C.; León, E. I; Riesco-Fagundo, C.; Suárez, E. *Tetrahedron Lett.* **2003**, *44*, 6347 - 6350.

52. (a) Oldham, J. W.; Rutherford, J. K. *J. Am. Chem. Soc.* **1932**, *54*, 366 – 378; (b) Tipson, R. S. *Adv. Carbohydr. Chem.* **1953**, *8*, 107 – 215; (c) Ball, D. H.; Parrish, F. W. *Adv. Carbohydr. Chem. Biochem.* **1969**, *24*, 139 - 197.

53. Submitted by Mudzunga T. T. in a thesis in fulfillment of the requirement for the degree of Doctor of Philosophy, University of Cape Town, **2003**.

54. Landauer, S. R.; Rydon, H. N. *J. Chem. Soc.* **1953**, 2224 - 2234.

55. Rydon, H. N. *J. Chem. Soc.* **1954**, 2281 - 2288.

56. Hanessian, S.; Ponpipom, M. M.; Lavalle, P. *Carbohydr. Res.* **1972**, *24*, 45 - 56.

57. Anisuzzaman, A. K.; Whistler, R. L. *Carbohydr. Res.* **1978**, *61*, 511 - 518.

58. Binkley, R. W.; Hehemann, D. G. *J. Org. Chem.* **1978**, *43*, 3244 - 3245.

59. Garegg, P. J.; Samuelsson, B. *J. Chem. Soc. Comm.* **1979**, 978 - 980.

60. (a) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc. Perkin Trans.* **1980**, *1*, 2866 – 2869; (b) Classon, B.; Liu, Z.; Samuelsson, B. *J. Org. Chem.* **1988**, *53*, 6126 - 6130.
61. Classon, B.; Garreg, P. J.; Samuelsson, B. *Can. J. Chem.* **1981**, *59*, 339 - 343.
62. Fischer, E.; Bergmann, M.; Schotte, H. *Chem. Ber.* **1920**, *53*, 509 - 547.
63. Lemieux, R. U.; Fraser-Reid, B. *Can. J. Chem.* **1965**, *43*, 1460 - 1475.
64. Lefan, M. S.; Weill, C. E. *J. Org. Chem.* **1965**, *30*, 954 - 955.
65. Igarashi, K.; Honma, T.; Imagawa, T. *J. Org. Chem.* **1970**, *35*, 610 - 616.
66. Boullanger, P.; Descotes, G. *Carbohydr. Res.* **1976**, *51*, 55 - 63.
67. Horton, D.; Priebe, W.; Varela, O. *J. Org. Chem.* **1986**, *51*, 3479 - 3485.
68. Lemieux, R. U.; Fraser-Reid, B. *Can. J. Chem.* **1964**, *42*, 532 - 538.
69. Dalton, D. R.; Dutta, V. P.; Jones, D. C. *J. Am. Chem. Soc.* **1968**, *90*, 5498 - 5501.
70. Kozlowski, J. S.; Marzabadi, C. H.; Rath, N. P.; Spilling, C. D. *Carbohydr. Res.* **1997**, *300*, 301 - 313.
71. Lemieux, R. U.; Levine, S. *Can. J. Chem.* **1962**, *40*, 1926 - 1932.
72. Lemieux, R. U.; Levine, S. *Can. J. Chem.* **1964**, *42*, 1473 - 1480.
73. Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2190 - 2198.
74. Thiem, J.; Karl, H.; Schwentner, J. *Synthesis* **1978**, 696 - 698.
75. Ernst, B.; Hart, G. W.; Sinaÿ, P. *Carbohydrates in Chemistry and Biology: Chemistry of Saccharides, Vol. I;* Wiley-VCH: Weinheim, 2000.
76. Horton, D.; Priebe, W.; Sznaidman, M. *Carbohydr. Res.* **1990**, *205*, 71 - 86.
77. Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656 - 6660.
78. Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1380 - 1419.
79. Fraser-Reid, B.; Udodong, U. E.; Wu, Z.; Ottosson, H.; Merritt, J. R.; Rao, C. S.; Roberts, C.; Madsen, R. *Synlett.* **1992**, 927 - 942.
80. Rodriguez, J.; Dulcere, J. –P. *Synthesis* **1993**, 1177 - 1205.
81. Cornforth, J. W.; Green, D. T. *J. Chem. Soc.* **1970**, 846 - 849.
82. Masuda, H.; Takase, K.; Nishio, M.; Hasegawa, A.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1994**, *59*, 5550 - 5555.
83. Sumrell, G.; Wimam, B. M.; Howell, R. G.; Harvey, M. C. *Can. J. Chem.* **1964**, *42*, 2710 - 2712.

84. Smietana, M.; Gouverneur, V.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 193 - 195.

85. Simona, C. Marco, C.; Giorgio, C. Marina, C.; Mario, M. *Eur. J. Org. Chem.* **2004**, 623 - 630.

86. De Corso, A. R.; Panunzi, B.; Tingoli, M. *Tetrahedron Lett.* **2001**, *42*, 7245 - 7247.

87. Hashem, M. A.; Jung, A.; Ries, M.; Kirschning, A. *Synlett.* **1998**, 195 - 197.

88. Honda, S.; Takiura, K. *Carbohydr. Res.* **1974**, *34*, 45 – 56.

89. Monneret, C.; Choay, P. *Carbohydr. Res.* **1981**, *96*, 299 - 305.

90. Kirschning, A.; Plumeier, C.; Rose, L. *Chem. Commun.* **1998**, 33 - 34.

91. Durham, T. B.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1871 - 1874.

92. Roush, W. R.; Narayan, S.; Bennett, C. E.; Briner, K. *Org. Lett.* **1999**, *1*, 895 - 897.

93. Tokutake, N.; Hiratake, J.; Katoh, M.; Irie, T.; Kato, H.; Oda, J. *Bioorg. Med. Chem.* **1998**, *6*, 1935 - 1953.

94. Chmielewski, M.; Fokt, I.; Grodner, J.; Grynkiewicz, G.; Szeja, W. *J. Carbohydr. Chem.* **1989**, *8*, 735 - 741.

95. Lellouche, J. –P.; Koeller, S. *J. Org. Chem.* **2001**, *66*, 693 - 696.

96. Bouillot, A.; Khac, D. D.; Fětizon, M.; Guir, F.; Memoria, Y. *Synthetic Commun.* **1993**, *23*, 2071 - 2081.

97. (a) Chambers, D. J.; Evans, G. R.; Fairbanks, A. J. *Tetrahedron Asymmetry* **2003**, *14*, 1767 - 1769; (b) Godage, H. Y.; Chambers, D. J.; Evans, G. R.; Fairbanks, A. *J. Org. Biomol. Chem.* **2003**, *1*, 3772 – 3786.

98. Evans, M. E. *Carbohydr. Res.* **1972**, *21*, 473 – 475.

99. Sels, B.; Levecque, P.; Brosius, R.; De Vos, D.; Jacobs, P.; Gammon, D. W.; Kinfe, H. H. *Adv. Synth. Catal.* **2005**, *347*, 93 - 104 and references cited therein.

100. Barluenga, J.; Marco-Arias, M.; Gonzáles-Bobes, F.; Ballesteros, A. *Chem. Eur.J.* **2004**, *10*, 1677 – 1682.

101. Franssen, M. C. R.; van der Plas, H. C. *Adv. Appl. Microbiol.* **1992**, *37*, 41 - 99.

102. Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, *93*, 1937 - 1944.

103. Sels, B.; De Vos, D.; Buntinx, M.; Pierard, F.; Kirsch-De Mesmaeker, F.; Jacobs, P. *Nature*, **1999**, *400*, 855 – 857.

104. De Vos, D. E.; Wahlen, J.; Sels, B. F.; Jacobs, P. A. *Synlett.* **2002**, 367 - 380.

105. Jaramillo, C.; Chiara, J. –L.; Martín-Lomas, M. *J. Org. Chem.* **1994**, *59*, 3135 – 3141.

106. Sels, B. F.; De Vos, D. E.; Jacobs, P. A. *J. Am. Chem. Soc.* **2001**, *123*, 8350 – 8359.

107. Mach, M.; Schlueter, U.; Mathew, F.; Fraser-Reid, B.; Hazen, K. C. *Tetrahedron* **2002**, *58*, 7345 - 7354.

108. Fraser-Reid, B.; Anilkumar, G.; Nair, L. G.; Radhakrishnan, K. V.; Lopez, J. C.; Gomez, A.; Uriel, C. *Aust. J. Chem.* **2002**, *55*, 123 - 130.

109. (a) King, J. F.; Allbutt, A. D. *Tetrahedron Lett.* **1967**, 49 - 54; (b) King, J. F.; Allbutt, A. D. *Can. J. Chem.* **1970**, *48*, 1754 - 1769.

110. Lubbecke, H.; Boldt, P. *Tetrahedron* **1978**, *34*, 1577 - 1579.

111. Sempere, C. J.; Nomen Ribe, R.; Serra Hosta, E.; Lopez Belmonte, L., ES Patent number WO 2004/014829 A1, 2004.

112. Binkley, R. W.; Ambrose, M. G.; Hehemann, D. W. *J. Carbohydr. Chem.* **1987**, *6*, 203 – 219.

113. Miljković, D.; Djurendić, E.; Vukojević, N.; Gaši, K.; Csanádi, J. *Carbohydr. Res.* **1992**, *233*, 251 - 253.

114. Chong, P. Y.; Roush, W. R. *Org. Lett.* **2002**, *4*, 4523 – 4526.

115. Cousins, G. S.; Hoberg, J. O. *Chem. Soc. Rev.* **2000**, *29*, 165 – 174.

116. Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321 – 347.

117. (a) Ramana, C. V.; Murali, R.; Nagarajan, M. *J. Org. Chem.* **1997**, *62*, 7694 – 7703; (b) Murali, R.; Ramana, C. V.; Nagarajan, M. *J. Chem. Soc., Chem. Commun.* **1995**, 217 – 218.

118. Monenschein, H.; Sourkouni-Argirusi, G.; Schubothe, K. M.; O'Hare, T.; Kirschning, A. *Org. Lett.* **1999**, *1*, 2101 – 2104.

119. Myint, Y. Y.; Pasha, M. A. *Synth. Commun.* **2004**, *34*, 4477 – 4482.

120. Copper, C. L.; Koubek, E. *J. Chem. Ed.* **1998**, *75*, 87 – 90.

121. Liebhafsky, H. A.; Mohammad, A. *J. Am. Chem. Soc.* **1933**, *55*, 3977 – 3988.

122. Ogata, Y.; Aoki, K. *J. Org. Chem.* **1966**, *31*, 1625 – 1629.

123. Graham, J. D.; Rogers, M. T. *J. Am. Chem. Soc.* **1962**, *84*, 2249 – 2252.

124. Wibero, K. B.; Barth, D. E.; Schertler, P. H. *J. Org. Chem.* **1973**, *38*, 378 – 381.

125. Williamson, K.; Lanford, C. A.; Nicholson, C. R. *J. Am. Chem. Soc.* **1964**, *86*, 762 – 765.

126. Collum, D. B.; Mohamadi, F.; Hallock, J. S. *J. Am. Chem. Soc.* **1983**, *105*, 6882 – 6889.

127. Collum, D. B.; Still, W. C.; Mohamadi, F. *J. Am. Chem. Soc.* **1986**, *108*, 2094 – 2096.

128. Beyer, J.; Madsen, R. *J. Am. Chem. Soc.* **1998**, *120*, 12137 – 12138.

129. Meng, D.; Bertinato, P.; Balong, A.; Su, D. –S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073 – 10092.

130. Fernandez-Megia, E.; Gourlaouen, S.; Ley, S. V.; Rowlands, G. J. *Synlett* **1998**, 991 – 994.

131. Ramana, C.; Nagarajan, M. *Synlett* **1997**, 763 – 764.

132. Ramana, C.; Nagarajan, M. *Carbohydr. Lett.* **1998**, *3*, 117 – 119.

133. Hoberg, J.; Claffey, D. J. *Tetrahedron Lett.* **1996**, *37*, 2533 – 2536.

134. Gammon, D. W.; Kinfe, H. H.; De Vos, D. E.; Jacobs, P. A.; Sels, B. F. *Tetrahedron Lett.* **2004**, *45*, 9533 – 9536.

135. Dahmén, J.; Frejd, T.; Grönberg, G.; Lave, T.; Magnusson, G.; Noori, G. *Carbohydr. Res.* **1983**, *116*, 303 – 307.

136. Fleet, G. W. J.; Smith, P. W. *Tetrahedron* **1987**, *43*, 971 – 978.

137. Gordon, A. J.; Ford, R. A. *The Chemist's Companion: A Handbook of Practical Data, Techniques, and References*; John Wiley and Sons: New York, 1972.

138. Lawson, D. D.; Getz, H. R.; Miller, D. A. *J. Org. Chem.* **1961**, *26*, 615 - 616.

139. Chaveriat, L.; Stasik, I.; Demailly, G.; Beaupère, D. *Carbohydr. Res.* **2004**, *339*, 1817 – 1821.

140. Sato, K.; Hydo, M.; Aoki, M.; Zheng, X.-Q.; Noyori, R. *Tetrahedron* **2001**, *57*, 2469 – 2476.

141. Varma, R. S.; Naicker, K. P. *Org. Lett.* **1999**, *1*, 189 – 191.

142. Choi, S.; Yang, J.-D.; Ji, M.; Choi, H.; Kee, M.; Ahn, K.-H.; Byeon, S.-H.; Baik, W.; Koo, S. *J. Org. Chem.* **2002**, *66*, 8192 – 8198.

143. Reutrakul, V.; Thongpaisanwong, T.; Tuchinda, P.; Kuhakam, C.; Pohmakotr, M. *J. Org. Chem.* **2004**, *69*, 6913 – 6915.

144. (a) Greenhalgh, R. P. *Synlett* **1992**, 235 – 236; (b) Ceccherelli, P.; Curin, M., Marcotullio, M. C.; Epifano, F.; Rosati, O. *Synlett* **1996**, 767 – 768; (c) Llauger, L.; He, H.; Chiosis, G. *Tetrahedron Lett.* **2004**, *45*, 9549 – 9552.

145. Kropp, P. J.; Breton, G. W.; Fields, J. D.; Tung, J. C.; Loomis, B. R. *J. Am. Chem. Soc.* **2000**, *122*, 4280 – 4285.

146. (a) Johnstone, R. A. W.; Wilby, A. H.; Entwistle, I. D. *Chem. Rev.* **1985**, *85*, 129 - 170; (b) Sung, Y.-E.; Chrzanowski, W.; Zolfaghari, A.; Jerkiewicz, G.; Wieckowski, A. *J. Am. Chem. Soc.* **1997**, *119*, 194 – 200.

147. Rao, V. S.; Perlin, A. S. *Carbohydr. Res.* **1980**, *83*, 175 – 177.

148. Bieg, T.; Szeja, W. *Synthesis* **1985**, 76 – 77.

149. Hanessian, S.; Liak, T. J.; Vanasse, B. *Synthesis* **1981**, 396 – 397.

150. Vickery, E. H.; Pahler, L. F.; Eisenbraun, E. J. *J. Org. Chem.* **1979**, *44*, 4444 – 4446.

151. Hwu, J. R.; Chua, V.; Schroeder, J. E.; Barrans, R. E.; Khoudary, Jr. K. P.; Wang, N.; Wetzel, J. M. *J. Org. Chem.* **1986**, *51*, 4731 – 4733.

152. Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis: Targets, Strategies,Methods*; Wiley-VCH: New York, 1996.

153. Boeckman, R. K.; Charette, Jr. A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 7553 – 7555.

154. Hoberg, J. O.; Bozell, J. J. *Tetrahedron Lett.* **1995**, *36*, 6831 – 6834.

155. Brimacombe, J. S.; Evans, M. E.; Forbes, E. J.; Foster, A. B.; Webber, J. M. *Carbohydr. Res.* **1967**, *4*, 239 – 243.

156. Weber, G. F.; Hall, S. S. *J. Org. Chem.* **1979**, *44*, 447 – 449.

157. Henry, K. J.; Fraser-Reid, B. *Tetrahedron Lett.* **1995**, *36*, 8901 – 8904.

158. Timmers, C. M.; Leeuwenburgh, M. A.; Verheijen, J. C.; Vandermarel, G. A.; van Boom, J. H. *Tetrahedron Asymmetry* **1996**, *7*, 49 – 52.

159. Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53 – 58.

160. Albano-Garcia, E. L.; Arbolario, E. M.; Lorica, R. G. *Nat. Appl. Sci. Bull.* **1979**, *31*, 61 – 74.

161. Fraser-Reid, B.; Wu, Z.; Udodong, U.; Ottosson, H. *J. Org. Chem.* **1990**, *55*,

6068 – 6070.

162. Excoffier, G.; Gagnaire, D.; Utille, J.-P. *Carbohydr. Res.* **1975**, *39*, 368 – 373.

163. Schmidt, R. R.; Michel, J. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 731 – 732.

164. (a) Schmidt, R. R.; Michel, J.; Roos, M. *Liebigs Ann. Chem.* **1984**, 1343 – 1357; (b) Schmidt, R. R.; Stumpp, M. *Liebigs Ann. Chem.* **1983**, 1249 – 1256; (c) Urban, F. J.; Moore, B. S.; Breitenbach, R. *Tetrahedron Lett.* **1990**, *31*, 4421 – 4424; (d) Patil, V. J. *Tetrahedron Lett.* **1996**, *37*, 1481 – 1484.

165. Schmidt, R. R.; Michel, J. *J. Carbohydr. Chem.* **1985**, *4*, 141 – 169.

166. Grundler, G.; Schmidt, R. R. *Liebigs Ann. Chem.* **1984**, 1826 – 1847.

167. Massy, D. J. R.; Wyss, P. *Helvetica Chimica Acta* **1990**, *73*, 1037 – 1057.

168. Vacca, J. P.; deSolms, S. J.; Huff, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 3478 – 3479.

169. Shvets, V. I.; Klyashchitskii, B. A.; Stepanov, A. E.; Evstigneeva, R. P. *Tetrahedron* **1973**, *29*, 331 – 340.

170. Alibés, R.; Bundle, D. R. *J. Org. Chem.* **1998**, *63*, 6288 – 6301.

171. Paquette, L. A.; Doherty, A. M.; Rayner, C. M. *J. Am. Chem. Soc.* **1992**, *114*, 3910 – 3926.

172. Danishefsky, S. J.; DeNinno, M. P.; Chen, S. *J. Am. Chem. Soc.* **1988**, *110*, 3929 – 3940.

173. Ahn, Y.-H.; Chang, Y.-T. *Chem. Eur. J.* **2004**, *10*, 3543 – 3547.

174. Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1989**, *111*, 2961 – 2980.

175. Zhang, W.; Robins, M. J. *Tetrahedron Lett.* **1992**, *33*, 1177 – 1180.

176. (a) Angyal, S. J.; Tate, M. E. *J. Chem. Soc.* **1965**, 6949 - 6955; (b) Angyal, S. J.; Gero, S. D. *J. Chem. Soc.* **1965**, 5255 – 5258; (c) Angyal, S. J.; Melrose, J. H. *J.Chem. Soc.* **1965**, 6494 – 6500; (d) Angyal, S. J.; Melrose, J. H. *J. Chem. Soc.* **1965**, 6501 – 6504.

177. Anilkumar, G.; Jia, Z. J.; Kraehmer, R.; Fraser-Reid, B. *J. Chem. Soc.; Perkin Trans. 1* **1999**, *24*, 3591 – 3596.

178. Fraser-Reid, B.; Anilkumar, G.; Nair, L. G.; Radhakrishnan, K. V.; Lopez, J. C.; Gomez, A.; Uriel, C. *Aust. J. Chem.* **2002**, *55*, 123 – 130.

179. Sureshan, K. M.; Shashidhar, M. S. *Tetrahedron Lett.* **2000**, *41*, 4185 – 4188.

180. Personal communication with Prof. David W. Gammon (University of Cape

Town, RSA).

181. Bellucci, G.; Chiappe, C.; D'Andrea, F.; Lo Moro, G. *Tetrahedron* **1997**, *53*, 3417 – 3424.

182. Boschi, A.; Chiappe, C.; De Rubertis, A.; Ruasse, M. F. *J. Org. Chem.* **2000**, *65*, 8470 – 8477.

183. Kiely, D. E.; Abruscato, G. J.; Baburao, V. *Carbohydr. Res.* **1974**, *34*, 307 – 313.

184. Angyal, S. J.; Irving, G. C.; Rutherford, D.; Tate, M. E. *J. Chem. Soc.* **1965**, 6662 – 6664.