UNIVERSITY OF CAPE TOWN

STEREOSELECTIVE SYNTHESIS OF 2-*C*-ALKYLGLUCOSIDES, POTENTIAL INHIBITORS OF MYCOBACTERIAL MshB AND RELATED ENZYMES

By

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SUPERVISOR: **Assoc. Prof. DAVID W. GAMMON**

DEDICATION

I would like to dedicate this work to my mother, ***Mrs Marie Jeanne Ngwanda Diansobo.***

DECLARATION

I declare that **"Stereoselective synthesis of phenylthio-2-*C*-alkylglucosides as potential inhibitors of mycobacterial MshB and related enzymes"** is my own work and that all sources that I have used or quoted have been indicated and acknowledged by means of complete references.

ABSTRACT

Tuberculosis (TB) is one of the world's most deadly diseases and kills approximately 1.7 million people each year. The developing resistance of TB to the two most common anti-TB drugs (isoniazid and rifampicin) proves the urgency of the current situation. The MshB reducing agent exclusively in the actinomycetes is used as a model for the development of new anti-TB drugs. It was shown that the stereoselectivity synthesis of C-2 alkyl glucoside gave a key intermediate for the suitable synthesis of glycosyl donors. In addition, we achieved the preparation of D-inositol derivative chirally pure and having the hydroxyl at the 1-position. However, the attempted glycosylation reaction failed to give the desired product.

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I wish to extend my thanks to the following people:

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To all colleagues, who always found the time to help me and encourage me in the lab.

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To my immediate family: My parents (Ernest Ngumbu Bata and Marie Jeanne Ngwanda Diansobo), my brother (Ernest Ngumbu Gombo) and my sisters (Mamie Ngumbu Kipela and Renate Ngumbu Sona).

ABBREVIATIONS

Ac	Acetyl
AcCysSR	Mercapturic acid
Ac_2O	Acetic anhydride
AcOH	Acetic acid
AIBN	2,2′-Azobisisobutyronitrile
All	Allyl
br	Broad
Bn	Benzyl
BnBr	Benzylbromide
^{13}C NMR	Carbon nuclear magnetic resonance
Calcd	Calculated
$(CD_3)_2SO$	Deuterodimethylsulfoxide
Cosy	Correlation spectroscopy
DBU	1,5-Diazobicyclo[5.4.0]undec-5-ene
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
ESI	Electrospray ionisation
Et	Ethyl
EtOAc	Ethyl acetate
FT-IR	Fourrier Transform Infrared
g	Gram (s)
Glc	Glucose
GlcNAc	2-Acetamido-2-deoxyglucose
GSH	Glutathione
GSSG	Glutathione disulfide
h	Hour(s)
^{1}H NMR	Proton nuclear magnetic resonance

HSQC	Heteronuclear single quantum coherence
Hz	Hertz
IC_{50}	50% Inhibitor Concentration
IR	Infrared
J	Coupling constant
m	Multiplets
Me	Methyl
min	Minute(s)
mL	Milliliter
mmol	Millimole(s)
mp	Melting point
Ms	Mass spectroscopy
MSH	Mycoyhiol
MsmB	Mycothiol bimane
MSSM	Mycothiol disulfide
m/Z	Mass to charge ratio
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
P	Protecting group
Ph	Phenyl
ppm	Parts per million
R_f	Retention factor (in chromatography)
rt	Room temperature
TB	Tuberculosis
THF	Tetrahydrofurane
TLC	Thin layer chromatography
UV	Ultraviolet
WHO	World Health Organisation
X	Halide(s)

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CHAPTER 1

INTRODUCTION

1.1. TUBERCULOSIS

Tuberculosis (TB) is a major health threat and often a deadly infectious disease caused mainly by the pathogenic bacterium *Mycobacterium tuberculosis*. Other *Mycobacteria* such as *M. bovis*, *M. africanum*, *M. cannetti*, and *M. microti* also cause tuberculosis, but these species are less common.[1] *Mycobacterium tuberculosis* is a small bacillus that can withstand weak disinfectants, can survive in a dry state for weeks and is rich in lipids such as mycolic acid, which is likely responsible for the resistance to the medical treatment and is a key virulence factor.

M. tuberculosis, which requires oxygen to grow, is classified as acid-fast gram positive due to high lipid content in its walls. It divides every 15-20 hours which is extremely slow compared to other bacteria, which tend to have division times measured in minutes (*E. coli* can divide roughly every 20 minutes).[2] Tuberculosis is spread through the air when people who have TB cough, sneeze or spit, and usually attacks the lungs, but can also affect the central nervous system, the lymphatic system, the circulatory system, the genitourinary system, the gastrointestinal system, bones, joints, and even the skin. The World Health Organisation (WHO) estimates 4.3% of the newly and previously treated TB cases are multi-drug-resistant (MDR), meaning these strains are resistant to at

least two of the best anti-TB drugs, isoniazid (INH) and rifampicin, making successful treatment of the disease difficult. Extensively drug-resistant TB (XDR-TB) is also resistant to three or more of the six classes of second-line drugs including amino glycosides (e.g. kanamycin), fluoroquinolones (e.g. ciprofloxacin), thioamides (e.g. ethionamide), cycloserine and *p*-aminosalicylic acid (Fig. 1).[3,4,5]

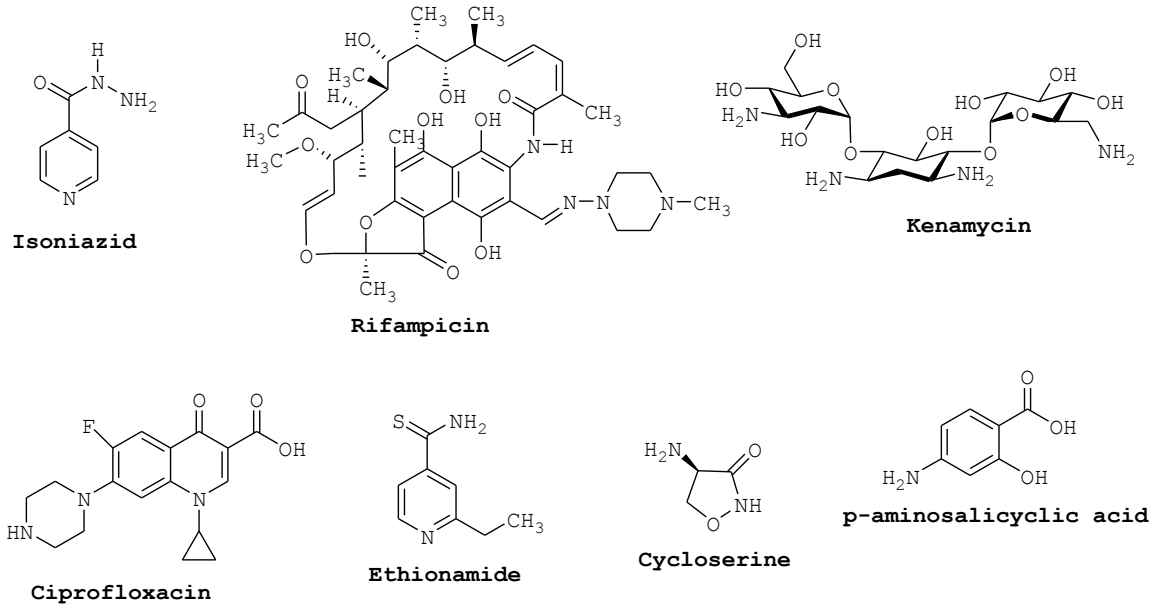


Figure 1. Drugs used for TB treatment.

The third-line anti-TB drugs (Fig. 2) are either not effective (e.g. clarithromycin), or their efficacy has not been proven (e.g. linezolid, R207910). Rifabutin is a drug that is effective, but is not included on the WHO list because for most developing countries, it is impractically expensive.[5] These observations suggest a better understanding

of the organism's defence is critical to battling infections.[6,7]

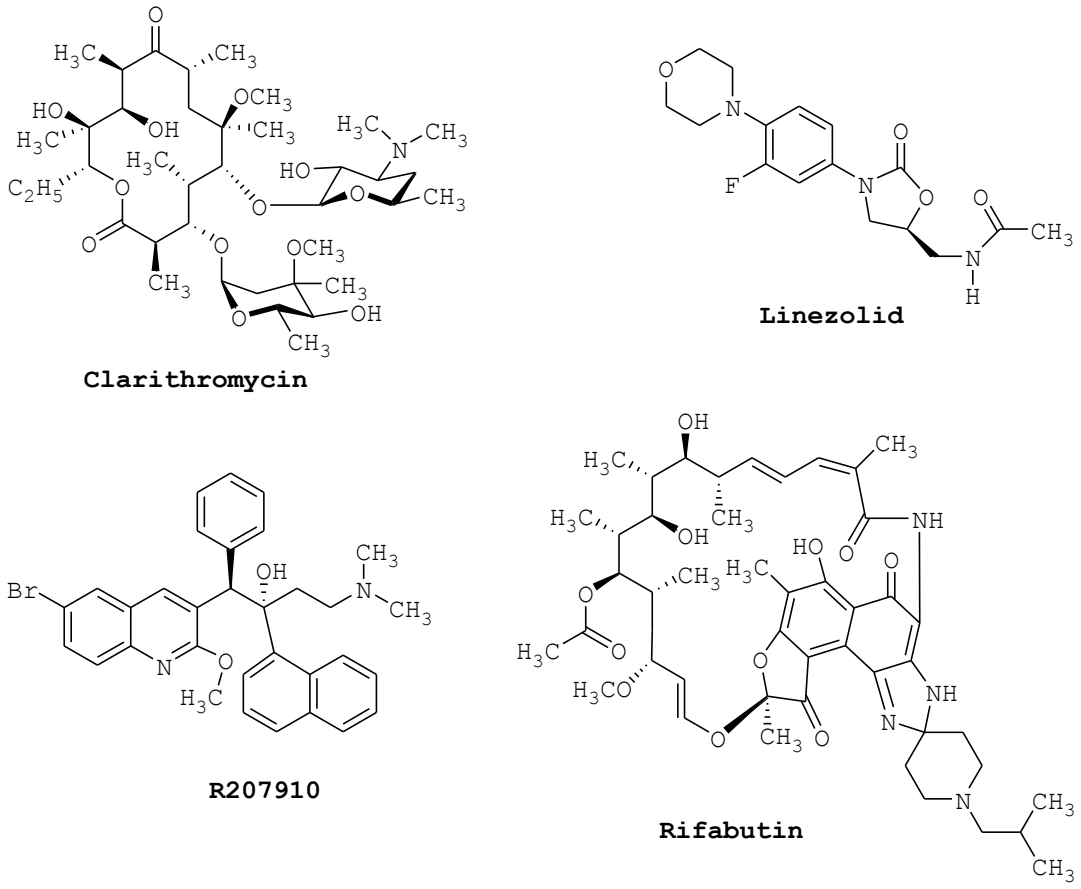


Figure 2. The third-line anti-TB drugs.

1.2. MYCOTHIOL

Mycothiol (MSH) is a low molecular weight thiol found in most *Actinomycetes* including *Mycobacterium tuberculosis*, the TB causative agent. MSH has functional similarities to glutathione (GSH) (Fig. 3), the dominant thiol in eukaryotes and many bacteria.

In the *Actinomycetes*, MSH acts as the thiol redox buffer to

form mycothiol disulfide (MSSM). This is similar to the role of glutathione (GSH) in eukaryotes and Gram-negative bacteria, where it reduces toxic oxidants (e.g. hydrogen peroxide, nitric oxide) to form the symmetrical disulfide (GSSG) to help maintain a reducing intracellular environment in the eukaryote.[8] MSH was first isolated as the disulfide (MSSM) from *Streptomyces* sp. AJ9463 and then as the free sulfhydryl (MSH) from *M. bovis* and as its bimane derivative (MSmB) from *S. clavuligerus*.[9,10]

MSH plays a significant role in the detoxification of thiol-reactive substances, such as formaldehyde, antibiotics and various electrophiles including alkylating agents with which it reacts to form sulphides. Mycothiol S-conjugate amidase (Mca) has been shown to be a zinc metalloenzyme[11] and cleaves the glucosaminyl-amide bond of the mycothiol S-conjugate by hydrolysis to release GlcN-Ins, used to resynthesize the MSH and a mercapturic acid (AcCysSR) (Fig. 3) which is excreted from the cell. The disruption of mycothiol metabolic pathways or Mca is fatal to *M. tuberculosis*, so they are excellent potential targets for the drug design and the development of new treatments.[12,13]

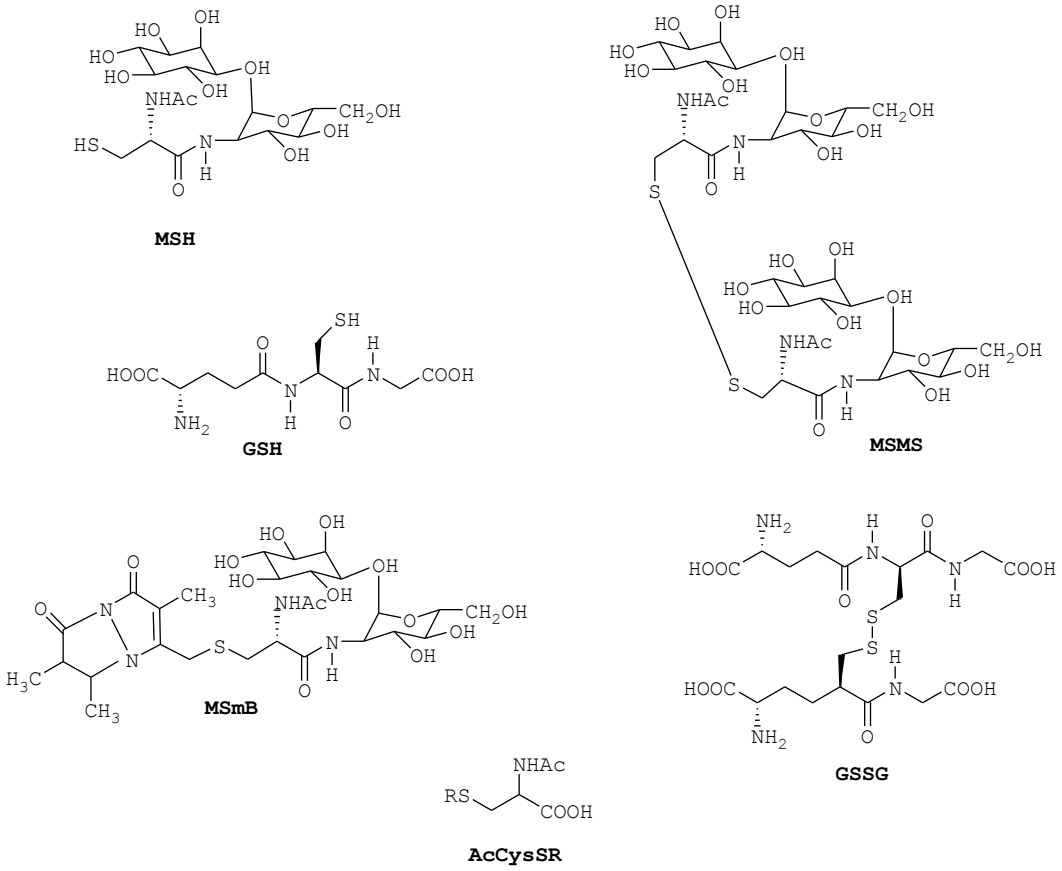


Figure 3. MSH, GSH), MsmB, MSSM, GSSG and AcCysSR.

1.3. BIOSYNTHESIS OF MYCOTHIOL

The biosynthetic pathway of MSH (Fig. 4) starts by action of inositol-1-phosphate synthase (Ino-1) on glucose-6-phosphate to obtain 1L-Ins-1-P, which is glycosylated by UDP-GlcNAc under catalysis of MshA, followed by removal of the phosphate group by the phosphatase MshA2. *N*-Deacetylation is then achieved by the enzyme MshB and this is followed by ligation to L-cysteine involving the ligase MshC, and then *N*-acetylation by acetyl CoA with MshD to produce MSH. MshB is

one of the key enzymes in mycothiol biosynthesis.

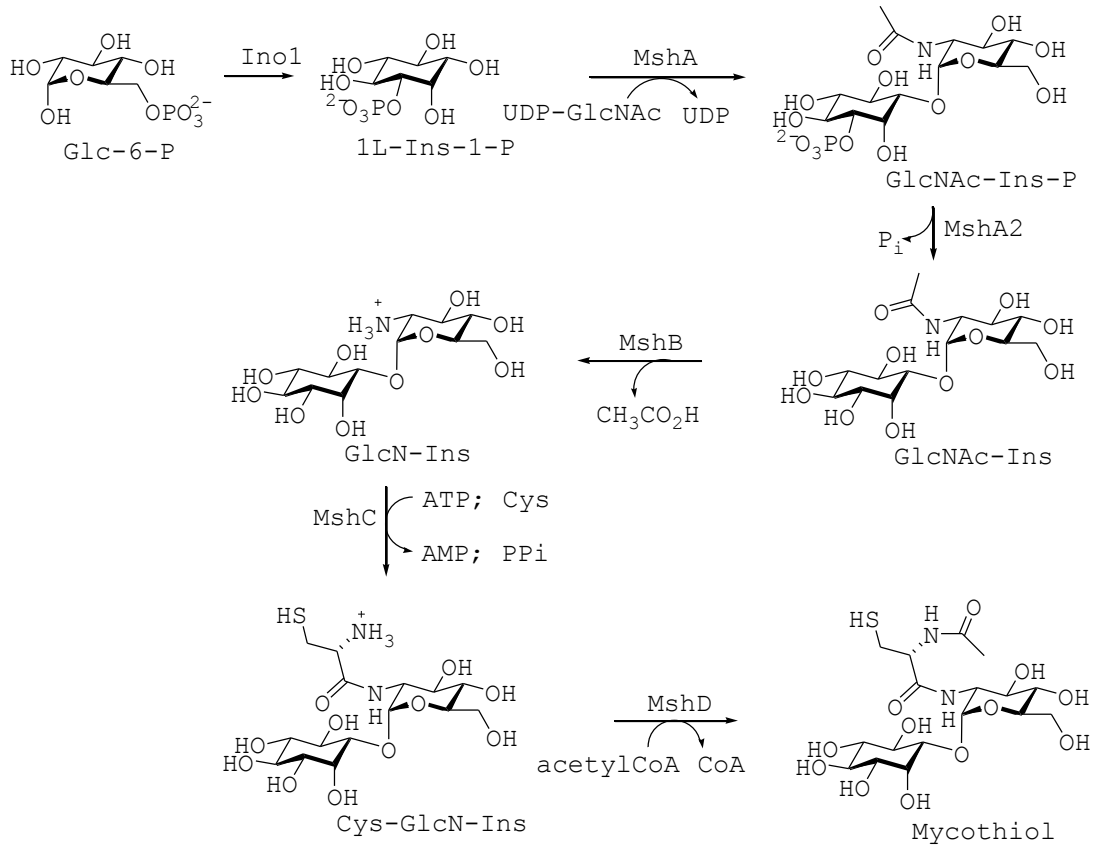


Figure 4. Biosynthetic pathway for synthesis of MSH.

Although it has been shown that while disruption of MshB in *M. smegmatis* resulted in decreased production of mycothiol (5–10 % of the parent strain mc^2155), it did not abolish mycothiol synthesis completely.[14] Subsequently, It was found that the MshB ortholog mycothiol amide hydrolase can be utilised in mycothiol biosynthesis by providing *N*-acetylglucosaminylinositol deacetylation activity in the absence of MshB.[15,16]

1.4. The enzyme MshB

In the biosynthesis of mycothiol, the deacetylase (MshB) is a zinc metalloprotein that catalyses hydrolysis of the precursor GlcNAc-Ins to yield the free amino sugar GlcN-Ins and corresponds to gene Rv1170 (with a molecular mass of 33,400 Da) of *M. tuberculosis*. The deacetylase activity is completely dependent on the presence of the divalent metal cation. The analysis of the X-ray crystal structure of MshB reveals a protein that folds in a manner resembling lactate dehydrogenase in the N-terminal domain and a C-terminal domain consisting of two β-sheets and two α-helices.[17(a)] The active site Zn^{2+} cation is coordinated to three amino acid side-chains (His-13, Asp-16, His-147) and two water molecules. One water molecule would be displaced upon binding of the substrate to allow coordination (and further polarisation) of the substrate carbonyl by the zinc cation; the other is proposed to be the nucleophilic water (Fig. 5), assisted by the general base carboxylate of Asp-15. In addition, the Zn^{2+} provides electrophilic assistance in the hydrolysis, and the His-144 imidazole could form a hydrogen bond to the oxyanion of the tetrahedral intermediate. Proton transfer to the substrate nitrogen accompanies collapse of the tetrahedral intermediate with cleavage of the N-C bond to liberate the GlcN-Ins product.

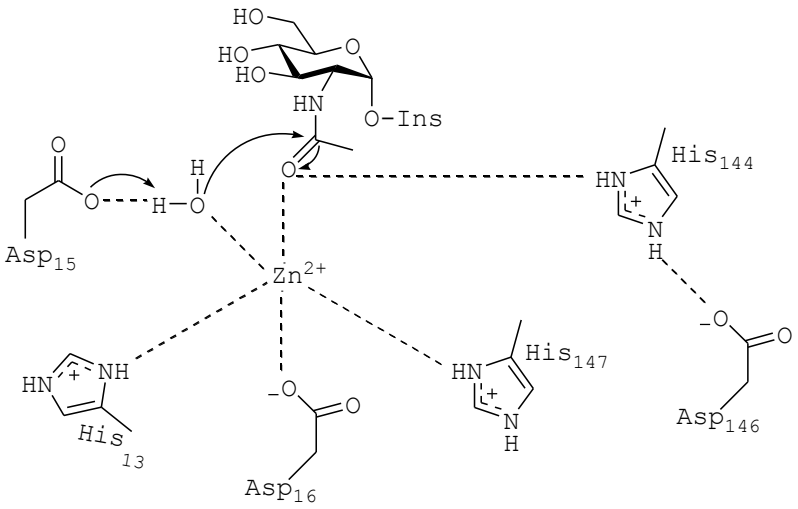


Figure 5. Catalytic mechanism of MshB.[16]

1.5. The enzyme Mca.

Mca (Fig. 6) is a zinc-dependent *N*-acyl hydrolase and reported to be closely related to MshB (e.g. 42% sequence identity between Mca and MshB). This extensive sequence homology has contributed to the construction of a model of the catalytic domain of mycothiol *S*-conjugate amidase, based on the structure of MshB.[16,17(a)] From *M. Segmatis*, Mca was purified and sequenced.[16] The corresponding gene Rv1082 was then identified in *M. tuberculosis*.

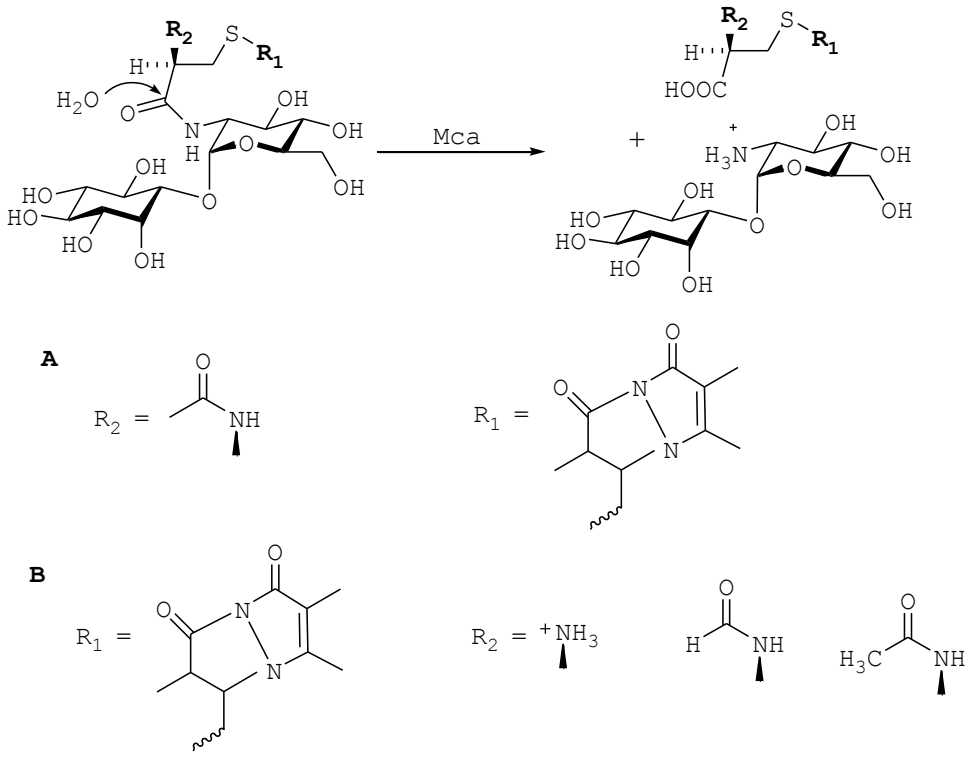


Figure 6. Substrate specificity of *M. tuberculosis* MSH S-conjugate amidase (Mca).[17(b)]

1.6. Inhibitors of Mca and MshB

Metaferia *et al.*,[18] reported the synthesis and evaluation of novel substrate mimic inhibitors of Mca, built upon a quinic acid-derived scaffold by incorporating a quinic acid template to replace the inositol ring of MSH and then produce a variety of analogs. It was also identified that natural products[11,19,20] and synthetic compounds[18,21] inhibit Mca, with sub- to low micromolar IC_{50} values. This demonstrated that a series of bromotyrosine-derived molecules, which include spiroisoxaline and linear oximinoamide-containing bromotyrosine derived, glycosylated sphingolipid as well as tricyclic piperazine-containing toxins (Fig. 7) are

competitive inhibitors of not only Mca, but also the homologous biosynthetic enzyme deacetylase MshB. These compounds were screened against Mca, using bioassay-guided fractionation. It was found that Oceanapiside **C** and gliotoxin **D** were non-competitive inhibitors of Mca, whereas spiro-isoxazolin **A** and bromotyrosine alkaloid **B** compete with the MsmB for Mca activity. In support, the potent competitive activity may be attributed by the possible chelation of Mca, which contains a zinc cation with the oximinoamides, the amino-alcohols, or the dithiadioxopiperazines moieties.[22]

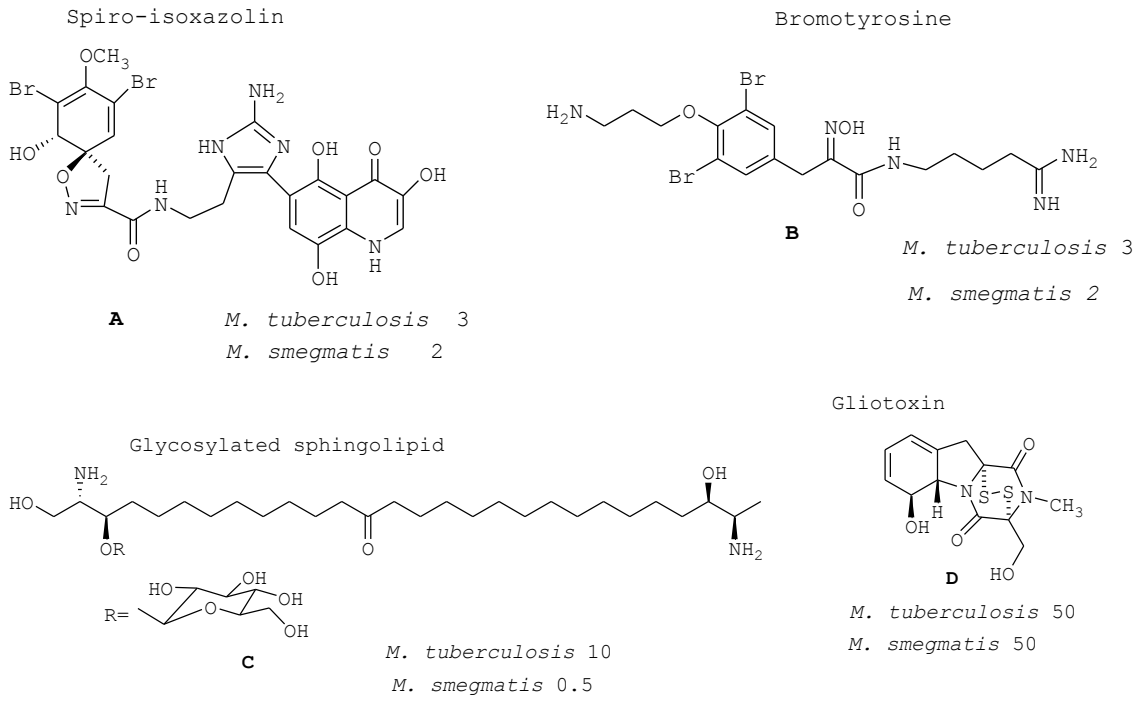
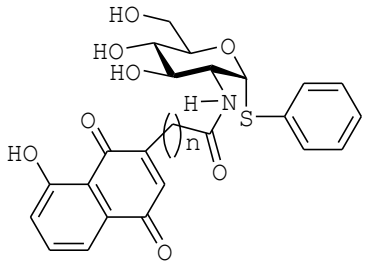


Figure 7. Natural and Synthetic Mca inhibitors. IC_{50} values are given in µM.[11,16]

Recently, the introduction of phenylthio group (Table 1) to replace the inositol moiety present in GlcNAc-Ins by the

Gammon group,[23] led to a series of potent inhibitors of Mca and MshB. These incorporated naphthoquinones tethered to the amino group were synthesised using the approach of Salmon-chemin *et al*.[24]

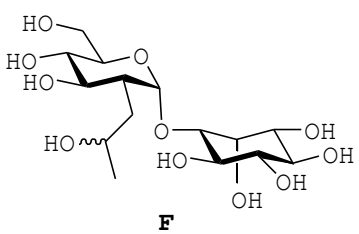
Table 1. Inhibition of Mca and MshB by substituted naphthoquinones: percentage inhibitor was determined at substrate and inhibitor concentrations of 250 µM each for Mca and 500 µM each for MshB.



E

Substrate	Mca	MshB
n = 2	28.8	57.4
n = 3	37.8	81.6
n = 4	23.2	81.4
n = 5	44.5	94.8

The same group also postulated that isosteres of substrates of MshB, in which the NH residue of the glucosamine unit is replaced by a non-hydrosable hydrocarbon side-chain, can serve as inhibitors of MshB. This led to synthesis of compounds **F** and **G** (Fig. 8) which were reported to inhibit MSH biosynthesis maximally at 200µg/ml in *M. smegmatis*.[10]



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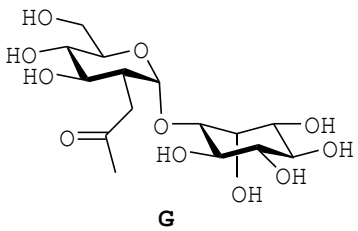


G

Figure 8. Synthetic nonreacting analogs of the substrate (GlcNAc-Ins) for the MshB.

These results have confirmed that 2-*C*-alkylated glucosides have potential as inhibitors of enzymes implicated in the biosynthesis of mycothiol. During the synthesis of **F** and **G** the two key synthetic challenges encountered were (i) the regio- and stereoselective introduction of alkyl substituents at *C*-2 of glucose, and (ii) achieving selective formation of α-glucosides from derivatives of these 2-*C*-alkylated compounds which have been suitably activated at *C*-1. This project has focussed mainly on the first of these challenges, by exploring an alternative strategy for efficient, stereoselective formation of 2-*C*-allylglucosides, where the allyl group is a precursor for preparation of further side-chain-modified glucosides.

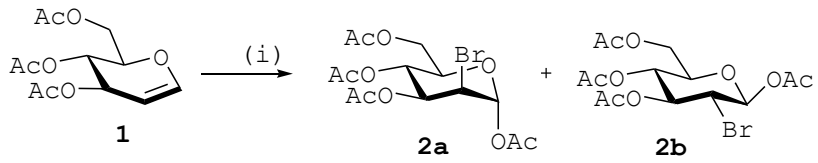
1.7. SELECTED METHODS FOR THE SYNTHESIS OF C-2 BRANCHED–CHAIN SUGARS

2-Deoxy-2-*C*-alkylated sugars are a sub-set of "branched-chain sugars", where either a hetero-atom substituent (typically O or N) or one of the hydrogens on the carbon skeleton of the sugar has been substituted by an alkyl groups. The synthetic approaches to this broad class of compounds have been comprehensively reviewed (J. Yoshimura, *Adv. Carbohydr. Chem. Biochem.*, **1984**, 42, 69) and specific approaches to the 2-deoxy-2-*C*-allyl sugars have been more recently highlighted by Mudzunga *et al.*[10,31] The key findings in this later work are summarized here, and two other general approaches in the recent literature are evaluated, one involving radical-mediated additions to glycols, and the other the use of anhydro-sugars as templates for regio- and stereoselective

modifications of sugars.

1.7.1. Alkylation by radical addition

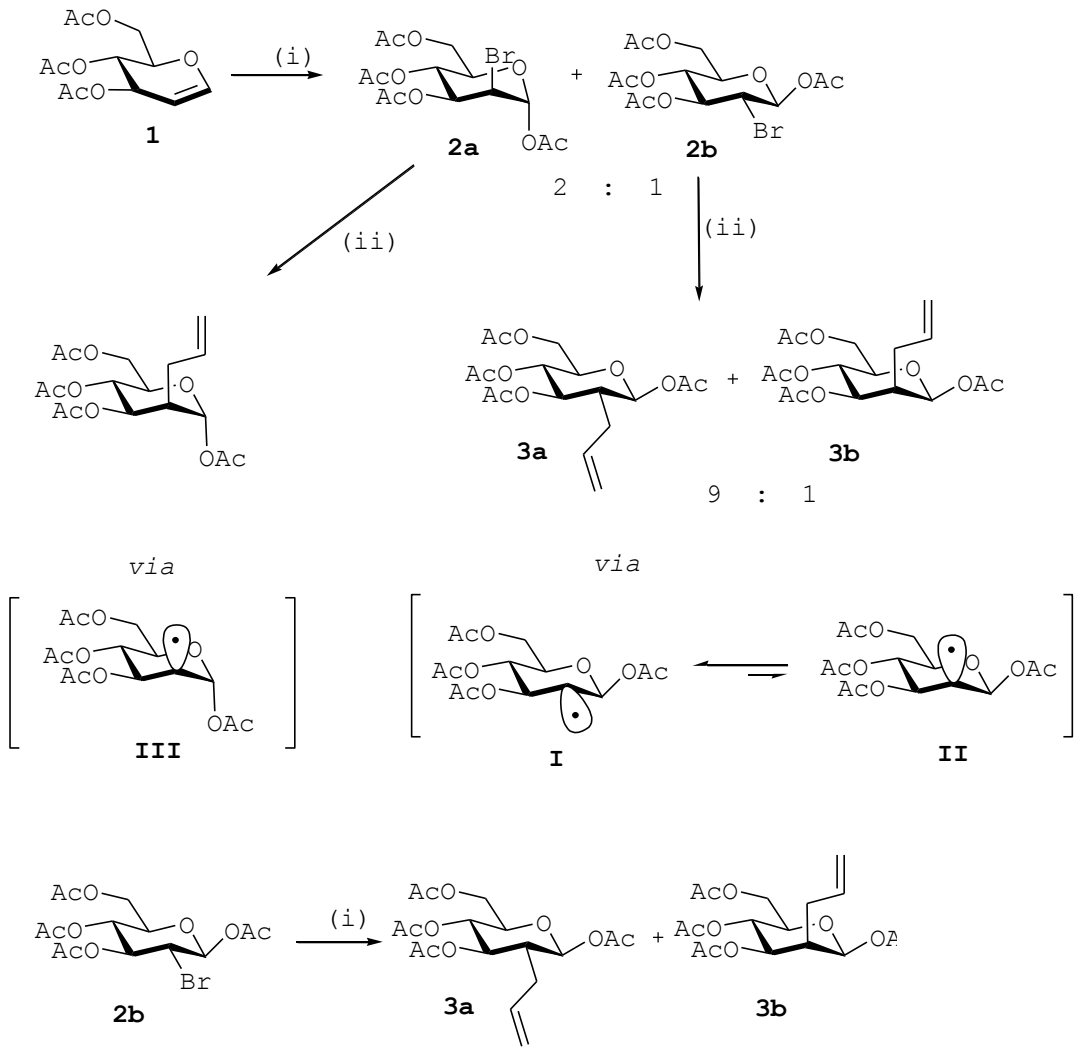
Mudzunga *et al.*,[10] demonstrated the C-2 alkylation *via* 2-bromoglucosides. The bromination at C-2 was achieved by treating the readily available D-glucal **1** with NBS in acetic acid to give a mixture of 2 isomers, 2-bromomannoside **2a** and 2-bromoglucoside **2b** in good yield (98%), in a ratio of 2:1 (Scheme 1).



Scheme 1. Reagents and conditions: (i) NBS, AcOH, rt, 4h.

Radical-mediated substitution at C-2 of the minor isomer **2b** with allyltributylstannane and the radical initiator azobisisobutyronitrile (AIBN) gave a mixture of two separable isomers (2-*C*-allylglucoside **3a** and 2-*C*-allylmannoside **3b**) in 87% yield in a ratio of 9:1 (Scheme 2). The fractional crystallization of the mixture from diethyl ether-pentane afforded the desired major isomer **3a** in 42% yield. The alkylation of the major isomer **2a** leads selectively to the undesired 2-*C*-allylmannoside **3b.** The stereoselectivity of radical substitution at C-2 appears to depend on the orientation of the substituent at C-1 and its influence on the preferred orientation of the intermediate radical at *C*-2.

(See scheme below). These results suggest that orientation of the radical *trans* to the substituent at C-1 is favoured; i.e. radical intermediate **I** arising from **2b,** and radical intermediate **III** arising from **2a** (see Scheme below).[25]

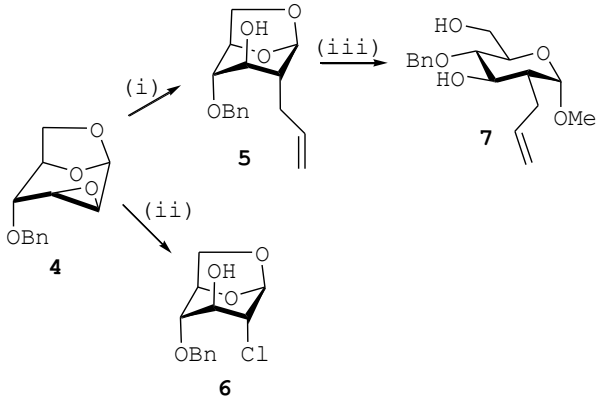


Scheme 2. Reagents and conditions: (i) NBS, AcOH, rt, 4h, (ii) Allyltributylstannane, AIBN, Benzene, reflux, 16h.

It was clear from these results that the efficiency of the

overall approach would be improved by a more selective route to **2b,** and although this was investigated further it required a rather more lengthy synthetic route.[31] An alternative way of ensuring the desired 1,2-*trans* orientation of the intermediate radical is to prepare this from 1,6-anydro-sugars, and this is evaluated below and forms the basis for this project.

1.7.2. NUCLEOPHILIC OPENING OF 2,3-ANHYDRO SUGARS



Scheme 3. Reagents and conditions: (i) C_3H_5MgCl, Et_2O, (90%); (ii) C_3H_5MgCl, THF, (76%); (iii) MeOH, HCl, (96%).

In the synthesis of rosaramycin by Procter *et al.*,[26] 1,6:2,3-dianhydro-4-*O*-benzyl-β-D-mannopyranose **4** was reacted with allylmagnesium chloride in ether to give **5** as a sole product in 90% yield (Scheme 3). The exclusive formation of **5** was expected, since the opening of the epoxide on the rigid 1,6-anhydro-β-D-hexopyranose framework proceeds preferentially *via* a trans-diaxial transition state. Subsequent methanolysis of **5** gave the glucoside **7.** However, when tetrahydrofuran

(THF) was used as the solvent in the Grignard reaction on **4**, only the chlorohydrin **6** was formed. It is not clear why the change of solvent in this reaction caused such a dramatic change in the product, but the authors suggest the position of the Schlenk equilibrium,[27] which is solvent-dependent and takes place in solutions of Grignard reagents played a significant role.

$$2RMgX \rightleftharpoons MgX_2 + MgR_2$$

The Schlenk equilibrium is an equilibrium between two equivalents of an alkyl or aryl magnesium halide on the left of the equation, with one equivalent of the dialkyl or diarylmagnesium compound and a magnesium halide salt on the right side. Organomagnesium halides in solution also form dimers and higher oligomers, especially at high concentration, and the high concentration of chloride ions together with the possible co-ordination of Mg to the epoxide oxygen, could lead to the nucleophilic opening of the epoxide by chloride ions. In support of this proposal, it has been noted that the difference in the Schlenk equilibrium in Et_2O and THF can be due to the increased coordination number of magnesium halide in THF (e.g. $MgX_2.nTHF$, $n \geq 3$).[28]

1.7.3. RADICAL ALLYLATION OF 1,6-ANHYDRO SUGARS

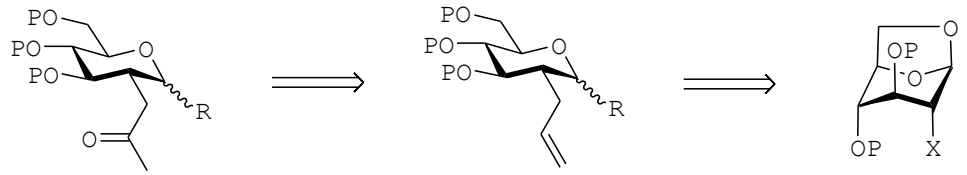
Leteux *et al.*,[29] demonstrated the regioselective introduction of an axial allyl group onto an 1,6-anhydro sugar, which was prepared from an electrophile-mediated intramolecular cyclisation of the D-glucal **1**. The formation of *C*-allyl product was favoured, by the preference of the

allylstannane to add to the less hindered face of the carbon-centered radical and tendency to enter in an orientation *syn* to the β oxygen atom in conformationally locked six-membered rings bearing oxygen substituents adjacent to the radical centre.[30] This section will be discussed later in Chapter 2.

1.8. AIMS AND OBJECTIVE

The objective of this work was to synthesize the 2-*C*-allylglycosides **H**, which are key synthetic intermediates for the preparations of analogues of mycothiol and its biosynthetic precursors (Scheme 4). These analogues have already been shown to inhibit enzymes involved in the biosynthesis of mycothiol in mycobacteria, and have been identified as possible new drug leads for a disease like TB.[10] It was recognized that an allyl group is a useful substituent at C-2 because it can be easily transformed to give a range of analogues. A key challenge, therefore, was to find improved methods for stereoselective alkylation at C-2. In particular, the objective was to explore the use of 2-deoxy-2-halo-1,6-anhydroglucose derivatives **I** (Scheme 4). Since these exist in the $^{1}C_{4}$ conformation in which all substituents are axially oriented, they have the potential for high stereoselectivity in reactions at the ring carbons, and in particular would allow for generation of the desired intermediate with a radical at C-2 oriented *trans* to the substituent at C-1. Once the substitution has taken place, the glucose derivative, in its normal $^{4}C_{1}$ conformation, can be obtained by selective opening of the 1,6-anhydro ring. A further objective was to attempt further functionalization of

the allyl side-chain, by exploring conditions for the direct conversion to the 2-oxopropyl-substituted derivative **J**.



J **H** **I**

R = -SPh, $-OC(=NH)CCl_3$
P = Protecting group

Scheme 4. Key synthetic intermediates.

CHAPTER 2

RESULTS AND DISCUSSION

In the biosynthesis of mycothiol, the de-*N*-acetylation of **8** (Fig. 9) is catalysed by the enzyme MshB. Compounds such as **9**, an analogue of the natural substrate, where the NH of the acetamido group has been replaced by a methylene group, have been shown to be inhibitors of MshB.[10] In addition, phenyl-2-acetamidothioglucoside **10** has recently been shown to be a substrate for MshB, thus demonstrating that the D-inositol unit may not be necessary for binding in the active site of the enzyme.[23] These observations have led to renewed interest in preparing relatively simple potential inhibitors of MshB such as **11**. A major problem in the earlier preparation of **9** was the poor stereoselectivity in the key C-2 alkylation, carried out on a 2-deoxy-2-haloglucoside.[31]

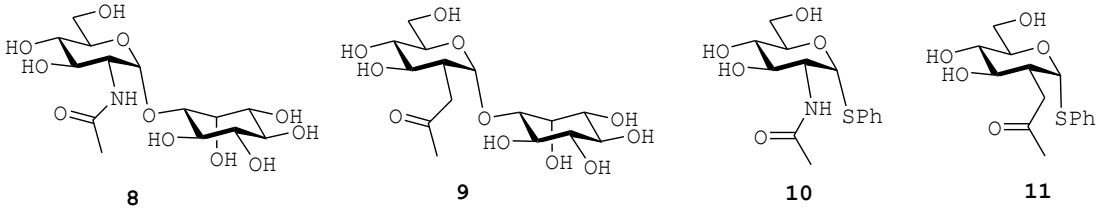
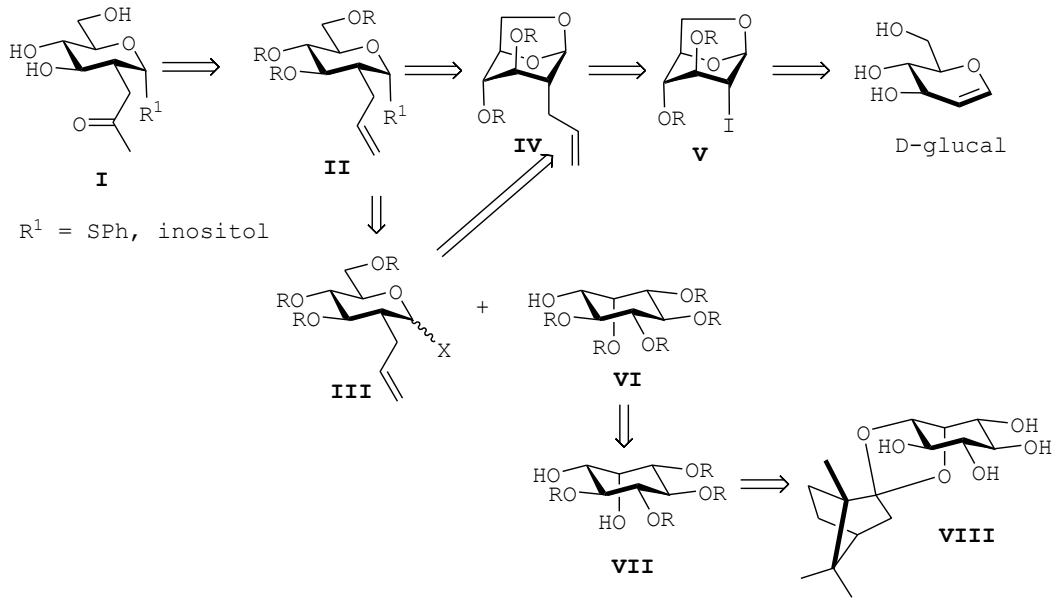


Figure 9. Potential inhibitors of MshB.

It was therefore recognized that in order to prepare desired analogues such as **9** and **11**, it would be necessary to find a more efficient and highly stereoselective method for alkylation at C-2, and that it might be possible to use the inverted conformation of 1,6-anhydroglucose derivatives to direct alkylation at C-2 from the lower (α-) face of the molecule. A retrosynthetic analysis of the problem, showing

the proposed use of 1,6-anhydroglucose derivatives is shown in Scheme 5.



Scheme 5. Retrosynthetic analysis.

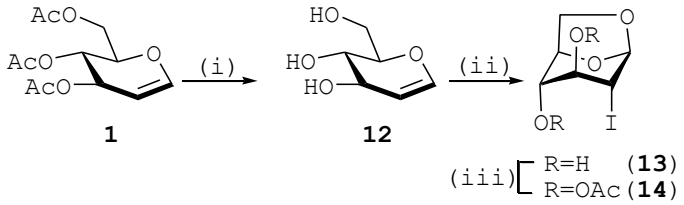
It was thought that the target 2-(2′-oxopropyl)glucosides **I** could be formed from the corresponding 2-*C*-allyl glucosides **II**, either by direct regioselective oxidation (e.g. Wacker) or by indirect methods used previously. The 2-*C*-allyl glucosides **II** could in turn be prepared from the anomerically activated glucosyl donor **III**, which could be made from the 1,6-anhydro-2-*C*-allylglucose **IV** by, for example, acetolysis. The stereoselective formation of the axially 2-allylated derivative would be achieved by radical-mediated allylation of the 2-iodo-derivative **V**, which can be prepared from D-glucal by the method of Leteux *et al.*[29] It was also recognized that it might be possible to achieve the formation of glucoside **II** directly from the 1,6-anhydro precursor **IV** by opening with an appropriate nucleophile under Lewis acid or

other catalysis. For preparation of the inositol glycosides, the selectively protected 1-D-inositol derivative **VI** could be obtained from the diol **VII** by selective allylation of the equatorial hydroxyl group, followed by protection of the axial hydroxyl and selective de-*O*-allylation. The resolved diol **VII** can be obtained from the known *S*-camphor acetal **VIII** by protection (e.g. benzylation) of the four hydroxyl groups, followed by hydrolysis of the acetal.

2.1. STEREOSELECTIVE SYNTHESIS OF 2-*C*-ALLYL GLUCOSE AND CONVERSION TO SUITABLE GLYCOSYL DONORS

2.1.1. PREPARATION OF 2-DEOXY-2-IODO-1,6-ANHYDROGLUCOSE 14 AS KEY SYNTHETIC INTERMEDIATE

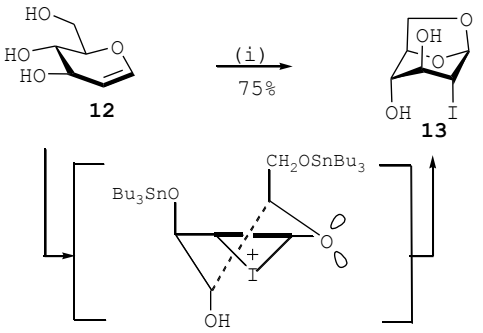
The proposed synthetic route (Scheme 6) required preparation of 2-deoxy-2-iodo-1,6-anhydroglucose **14** as the possible precursor for a stereoselective free radical allylation from the bottom face. The method chosen was that of Leteux *et al.*[29]



Scheme 6. Reagents and conditions: (i) Et_3N-MeOH-H_2O, rt, (67%); (ii) $(Bu_3Sn)_2O$, I_2, acetonitrile, reflux, 3 h, (75%); (iii) Ac_2O, pyridine, rt, (61%)

D-Glucal **12** was first prepared in 67% yield from the commercially-available acetylated D-glucal **1**, by deacetylation using a mixture of MeOH:H_2O:Et_3N. These mildly

basic conditions appear to be preferable to the Zemplén conditions[32] (sodium methoxide in methanol) in ensuring survival of the sensitive glucal formed in the reaction. Presumably the esters are removed by methanolysis under these conditions. The 2-iodo-1,6-anhydroglucoside **13** was then formed by treating D-glucal **12** sequentially with $(Bu_3Sn)_2O$ and I_2. A single product was formed, and the structure of **13** confirmed by analysis of the NMR spectra and comparison with literature data.[29] The ^1H NMR spectrum showed a one-proton singlet for H-1 at δ 5.61 ppm. Unexpectedly, there was no observable coupling between H-1 and H-2, and modelling showed that the H_1-C_1-C_2-H_2 dihedral angle is close to 90° which supports the data according to the Karplus equation. The formation of **13** is understood to involve initial formation of a 3,6-di-*O*-tributylstannyl glucal, followed by formation of an intermediate iodonium species (scheme 7), with attack of the iodine from the α-face being favoured due to the steric bulk of the tributylstannyl ethers at C-3 and C-6 on the β-face. The increased nucleophilicity of the oxygen atom at C_6 in its stannyl ether form then allows for an intramolecular attack at C-1, leading to the 2-iodo-1,6-anhydroglucose **13**.



Scheme 7. Mechanism of 1,6-iodocyclisation.

In order to allow further selective reaction at C-2, compound

13 was acetylated to give di-acetate **14** in 61% yield. Its structure was confirmed by analysis of the NMR spectra and comparison with the literature data.[29] The ^{1}H NMR spectrum still showed the one-proton singlet for H-1 at δ 5.70 ppm but included two new three-proton singlets at δ 2.21 and δ 2.12 ppm assignable to the two acetate groups (Fig. 10). In addition, the signals for H-3 and H-4 have been shifted significantly downfield to δ 5.16 and δ 4.74 ppm, consistent with acetylation of the free hydroxyl groups at these positions in **13**.

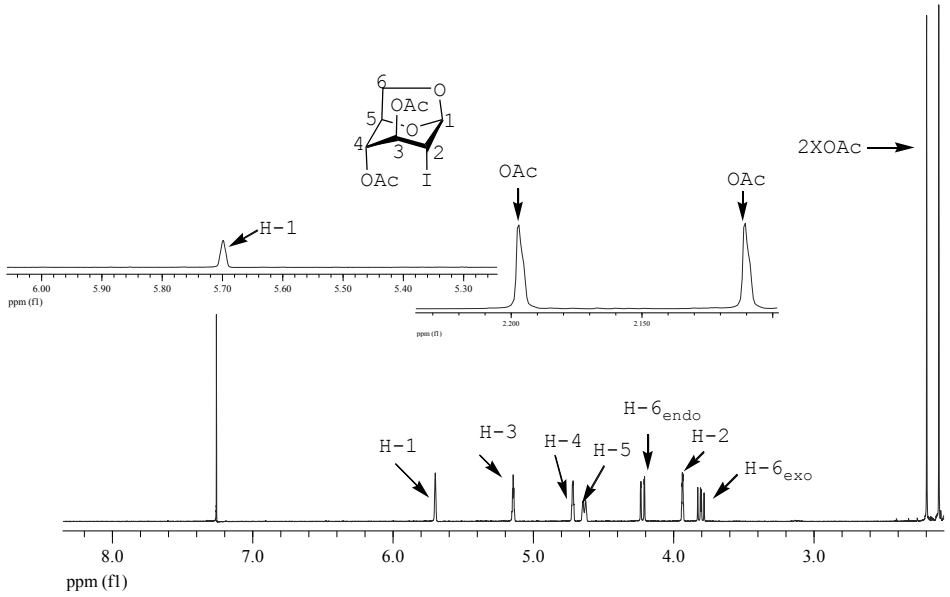
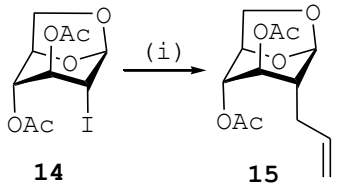


Figure 10. ^{1}H NMR spectrum of **14** in $CDCl_3$.

2.1.2. STEREOSELECTIVE ALKYLATION AT C-2 OF THE GLUCOSE DERIVATIVE 14



14 **15**

Scheme 8. Reagents and conditions: (i) 1,1'-azobis(cyclohexanecarbonitrile), allyltributylstannane, dry toluene, reflux, 3 h, (79%)

The conversion of **14** to **15** was successfully achieved by radical-mediated substitution of the iodo group at *C*-2 with an allyl group, using allyltributylstannane and a radical initiator. A single product was formed and the structure confirmed by analysis of the NMR spectra and comparison with literature data.[29] The ^{1}H NMR spectrum (Fig. 11) displayed a one-proton singlet for H-1 at δ 5.42 ppm, while the presence of the allyl group attached to C-2 was deduced by presence of a multiplet at δ 5.83 ppm for H-2', multiplets at δ 5.15 ppm for H-3'$_a$, and δ 5.12 ppm for H-3'$_b$, a multiplet at δ 2.32 ppm for H-1', and an upfield triplet at δ 1.82 ppm for H-2. When Leteux *et al.*,[29] used benzene as the solvent, **15** was formed in 65% yield. To avoid the toxicity of the benzene, we utilized toluene as the solvent which gave a higher yield of 79%.

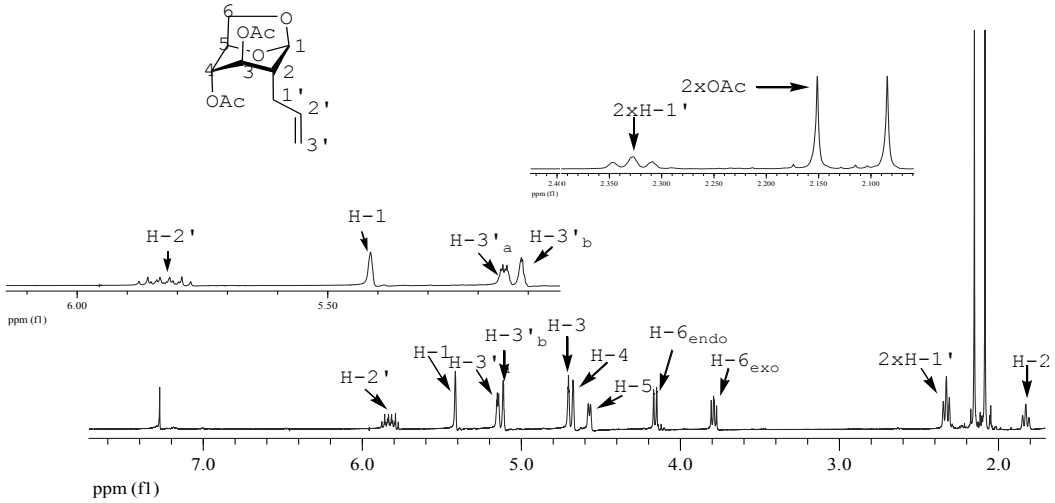
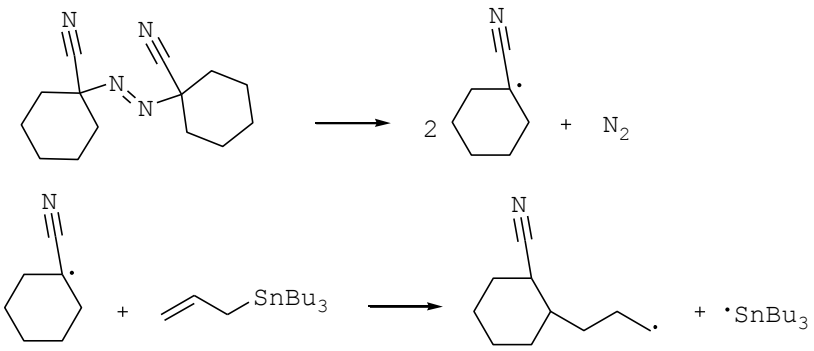


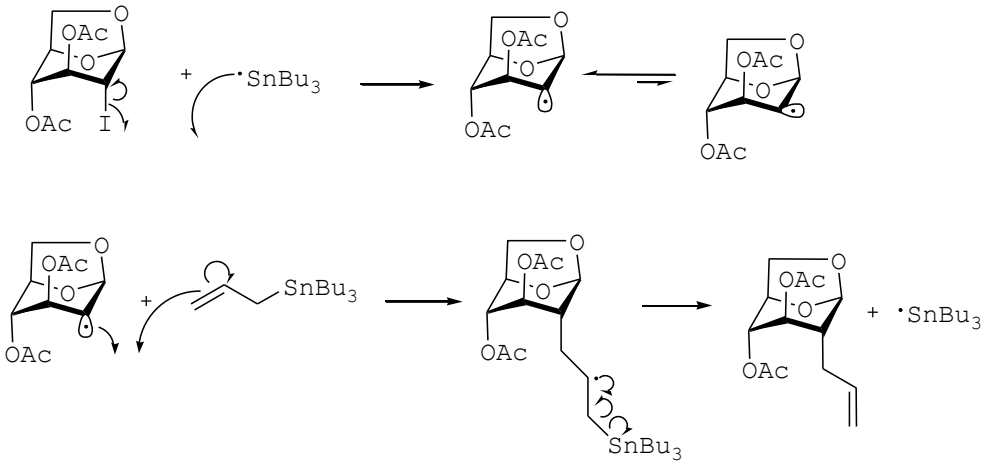
Figure 11. ^{1}H NMR spectrum of **15** in $CDCl_3$.

The preferred formation of an axial C-C bond can be explained, as shown in Scheme 9, by the abstraction of the iodine atom from the bottom side, and the preferred orientation of the intermediate radical *anti* to the oxygen substituents on C-1 and C-3. This would lead to direct the addition of the allyl group from the axial orientation (which is also the less hindered side).

Initiation



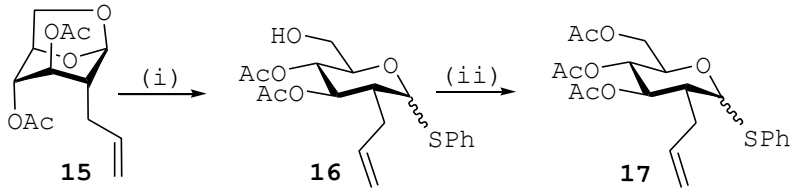
Propagation



Scheme 9. Free-radical mechanism.

2.1.3. DIRECT FORMATION OF GLYCOSIDES FROM 1,6-ANHYDRO DERIVATIVE 15

In order to achieve the objective of forming glycosides of the 2-*C*-allyl sugars, it was necessary to evaluate whether 1,6-anhydroglucose derivative **15** could act as a glycosyl donor itself, or would need to be converted to a suitable donor first.



Scheme 10. Reagents and conditions: (i) TMSOTf, PhSTMS, DCM, rt; (ii) Ac_2O, pyridine, rt, (47%).

Direct formation of phenylthioglucoside **16** was first attempted by treating **15** with phenylthiotrimethylsilane

(PhSTMS) in the presence of trimethylsilyl triflate (TMSOTf) in dichloromethane at room temperature.[33] Complete conversion of the starting material was observed, and after work up the crude product was acetylated to afford **17** in 47% yield from **15**. The ^{1}H NMR spectrum of **17** confirmed the opening of the 1,6-anhydro ring and the presence of a mixture of anomers by the appearance of two doublets at δ 5.36 and 4.45 ppm for H-1 in the α- and β-anomers respectively (α:β = 1:0.6). The appearance of downfield signals at δ 7.45-7.19 ppm corresponding to five aromatic protons confirmed the presence of the phenyl group. The ^{13}C NMR also confirmed the presence of the phenyl group, with carbon resonances at δ 131.8, 128.9, 128.8, 127.3 ppm for the α-anomer and δ 132.3, 129.1, 129.0, 127.7 ppm for the β-anomer.

The molecular ion (m/z 422.14) was detected in the electron impact mass spectrum and fragments were observed corresponding to loss of the anomeric substituent (m/z 109.01), loss of one molecule of acetic acid (m/z 60.02) and further loss of one molecule of acetic acid (m/z 60.02). Figure 11 shows a possible fragmentation pattern to account for the observed ions.

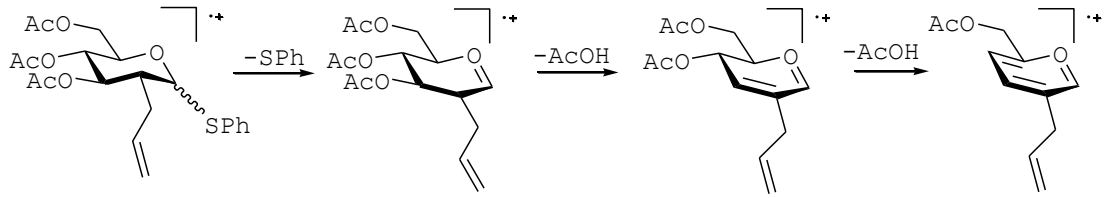
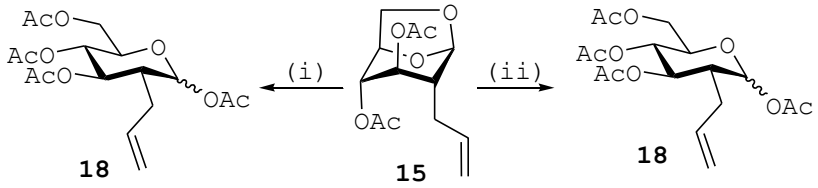


Figure 12. Tentative assignment of observed fragment ions in the EI-MS of **17**.

2.1.4. PREPARATION OF GLYCOSYL DONORS

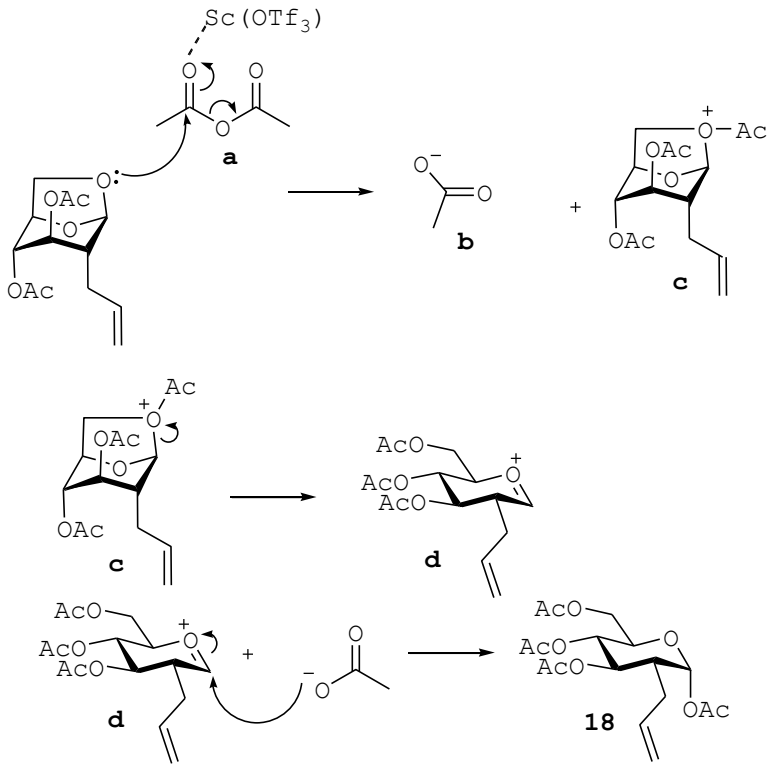
Mudzunga *et al.*,[31] have described a route to analogues of mycothiol, which involved the preparation of a glycosyl fluoride as glycosyl donor. This was achieved by anomeric deprotection of **3a**, followed by conversion of the resultant alcohol to fluoride. Although the reaction was successful, it resulted in an inseparable mixture of isomers.[10] It was therefore interesting to explore the use of other glycosyl donors, and the acetolysis reaction was investigated with a view to providing glycosyl acetates that could be used themselves as glycosyl donors, or easily converted to other ones.



Scheme 11. Reagents and conditions; (i) Ac_2O, $Sc(OTf)_3$, DCM, rt, (60%); (ii) TESOTf, Ac_2O, rt, (32%).

The acetolysis of **15** was first conducted at room temperature in Ac_2O with scandium(III) triflate $Sc(OTf)_3$ as initiator. A mixture of anomers was formed in 60% yield. The ^1H NMR spectrum provided evidence that the α-anomer of **18** was the major product, showing a doublet for H-1 at δ 6.16 ppm with a small coupling constant (J = 3 Hz). The β-anomer was present in only trace amounts. The ^{13}C NMR spectrum displayed signals at δ 170.6, δ 170.4, δ 169.7 and δ 168.8 ppm for the carbonyl carbons in the four acetyl groups of the major isomer. Lee *et*

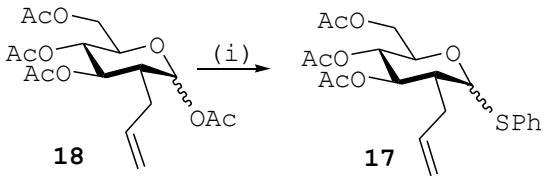
al.,[35] reported that the mechanism of the acetolysis reaction involves the Lewis acid $Sc(OTf)_3$ activating the Ac_2O to form a polarised complex (**a**, Scheme 12). The oxygen atom at C-6, then attacks the carbon bearing the activated oxygen to form a positively charged intermediate (**c**) and its counter ion (**b**). The highly unstable species (**c**) immediately undergoes cleavage of the 1,6-anhydro ring to form carbenium ion (**d**) and the latter is attacked by the acetate ion to form **18**.



Scheme 12. Proposed mechanism of acetolysis of **18** by using $Sc(OTf)_3$.

Alternatively, Zottola *et al.*[36] proposed a method using triethylsilyl triflate (TESOTf). Treatment of **15** with Ac_2O and TESOTf at 0 °C also gave **18** but in low yield (32%) and

the ^{1}H NMR spectrum again showed the predominant formation of the α-glucoside. TLC-monitoring of the reaction indicated a clean conversion of starting material to the product, but it appears that losses occurred during work-up and in the time available it was decided not to attempt to optimize the reaction conditions. The mechanism of the reaction is assumed to be similar to that catalysed by $Sc(OTf)_3$.
Another approach to the synthesis of **17** that could now be attempted, involves treatment of glycosyl acetate **18** with thiophenol in the presence of a Lewis catalyst (Scheme 13).



18 **17**

Scheme 13. Reagents and conditions: (i) $BF_3.OEt_2$, PhSH, DCM, rt, (76%).

Glycosyl acetate **18** was therefore treated with thiophenol (PHSH) in the presence of Lewis acid $BF_3.Et_2O$[37] to give a mixture of anomers **17** (α:β = 1:0.7) in 76% yield . The ^{1}H NMR spectrum (Fig. 13) was consistent with that obtained earlier (see section 2.1.3) and confirmed the assigned structures. The presence of the two anomers was evident from a doublet at δ 5.36 ppm ($J_{1,2}$ = 4.9 Hz) for H-1 in the α-glycoside and a doublet at δ 4.45 ppm ($J_{1,2}$ = 10.9 Hz) for H-1 in the β-glycoside. A multiplet at δ 7.45-7.19 ppm indicated the presence of phenyl protons. The ^{13}C NMR spectrum was also consistent with that reported in section 2.1.3.

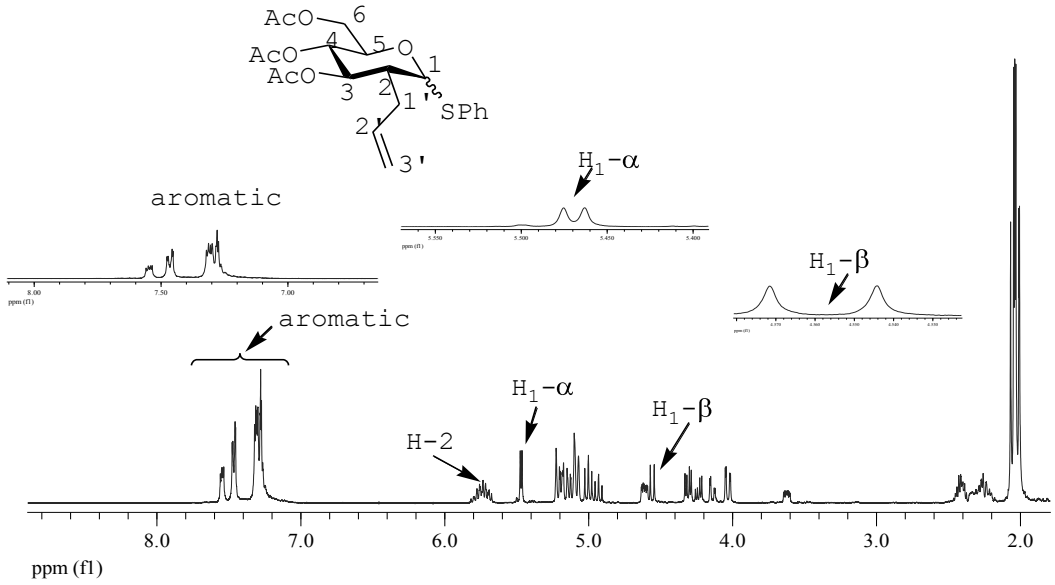
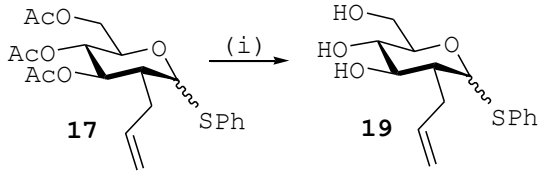


Figure 13. ^{1}H NMR spectrum of **17** in $CDCl_3$.

It was interesting to note that in the synthesis of phenylthioglucoside **17**, the method *via* direct opening of 1,6-anhydro derivative **15** gave the product in similar yield (46%) to the indirect method *via* glycosyl acetate **18.** However, the former (direct) is not favoured because it involved a complex separation of by-product after the first step, whereas no purification is required in the second approach.



Scheme 14. Reagents and conditions: (i) MeOH, NaOMe, rt, (59%).

Zemplén deactylation[32] of **17** afforded **19** as a mixture of isomers (α:β = 1:0.1) in 59% yield. The absence of acetyl signals in ^{1}H NMR and ^{13}C NMR spectra supported successful deacetylation. In addition, the IR spectrum showed an absorption band at ν_{max}/cm^{-1} 3369, confirming the presence of OH groups. The EI mass spectrum of **19** confirmed the assigned structure and a proposed fragmentation pattern is given in Figure 14. The molecular ion (m/z 295.99) was detected and fragments were observed corresponding to the expected loss of the anomeric substituent (m/e 187.10) and further loss of one molecule of water (m/e 169.09).

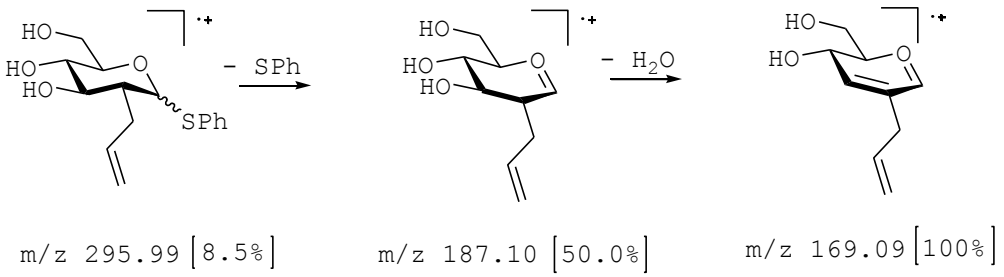
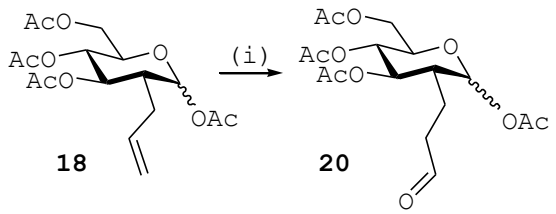


Figure 14. Assignment of observed fragment ions in the EI-MS of **19**.

2.1.5. ATTEMPTED FORMATION OF KETONE BY WACKER OXIDATION

With the objective of forming the target 2-(2'-oxopropyl) glucosides **I** (Scheme 5), compounds **18** and **17** were subjected to Wacker oxidation, with the different anomeric substituents in these compounds allowing for investigation of the possible influence of the anomeric substituents on the reaction outcome.

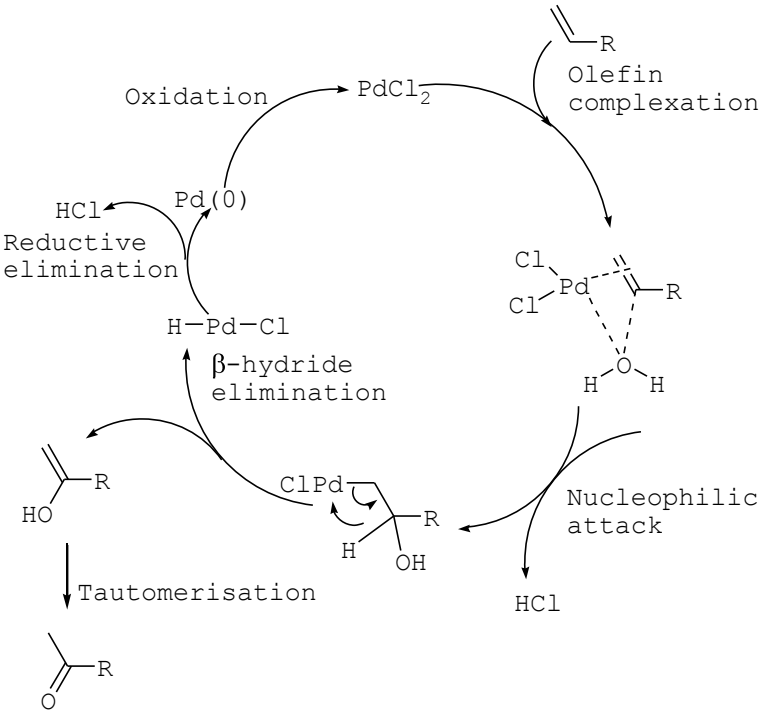


Scheme 15. Reagents and conditions: (i) $PdCl_2$ (Cat), CuCl (1eq), O_2, rt, (91%).

In the first instance, glycosyl acetate **18** (present predominantly as α-anomers) was treated under Wacker oxidation conditions to unexpectedly give aldehyde **20** as a mixture of anomers in 91% yield. Instead of the expected upfield methyl singlet for the methyl ketone protons, the ^{1}H NMR spectrum displayed a downfield triplet at δ 9.73 ppm with a coupling constant J = 0.3 Hz, consistent with the presence of an aldehyde proton coupled to adjacent methylene hydrogens. Attempts to separate the major α-product and traces of β-product by column chromatography were unsuccessful. The structure of the α-product was confirmed by analysis of the ^{1}H NMR spectrum which displayed the disappearance of signals for the allyl group and presence of a doublet at δ 6.23 ppm (J = 3.2 Hz), confirming the axial orientation of the acetate group at C-1. The ^{13}C NMR spectrum displayed signals at δ 204.9 ppm for the aldehyde carbonyl group, and δ 170.7, 170.6, 169.5, and 168.9 ppm for 4 acetyl carbonyl carbons.

Wacker oxidation of terminal alkenes usually leads selectively to methyl ketones and the proposed mechanism is typical of palladium olefin chemistry (Scheme 16).[39] The addition of the Pd(II) species to the olefin results in formation of the Pd-π-complex; this is followed by attack of

water to form the β-hydroxylated alkyl palladium intermediate, which then undergoes β-hydride elimination to give the hydroxyvinyl species which tautomerizes to the ketone. The reduced palladium is reoxidized by Cu (II) and ultimately by atmospheric oxygen.



Regeneration of Pd(II):

$$Pd(0) + 2CuCl \longrightarrow PdCl_2 + 2CuCl$$

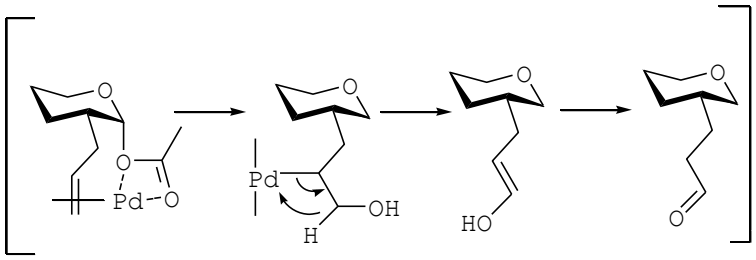
Regeneration of Cu(II):

$$CuCl + O_2 \longrightarrow CuCl_2 + H_2O$$

Scheme 16. Mechanism of wacker oxidation of terminal alkene leading to methyl ketone.

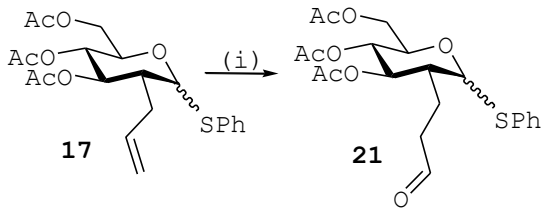
The selective formation of the aldehyde in this case could be attributed to the coordination of one or both acetate oxygens at C-1 and other substituents to the palladium π-complex,

forcing water to attack the terminal carbon by an anti-Markovnikov hydration, followed by β-hydride elimination to eventually give the aldehyde[38] (Scheme 17).



Scheme 17. Mechanism of wacker oxidation of terminal alkene leading to aldehyde.

Mudzunga *et al*,[31] described the attempted regioselective formation of ketone from **18** under Wacker oxidation, by running the reaction under oxygen in a balloon. The unexpected aldehyde **20** resulted by carrying out the reaction under atmospheric oxygen.



Scheme 18. Reagents and conditions: (i) $PdCl_2$, CuCl, O_2, rt, (88%).

The phenylthioglycoside **17** was then also treated under the same Wacker oxidation conditions, and also gave an aldehyde **21** as a mixture of anomers in 87% yield (α:β = 0.2:1). The structure was confirmed by analysis of the NMR spectra. Once

again, the singlet expected for the methyl ketone was not visible in the ^{1}H NMR spectrum of **21** while two triplets at δ 9.73 and δ 9.76 ppm corresponding to the aldehyde proton signal in the α- and β- anomers respectively. The ^{13}C NMR displayed only one aldehyde carbonyl carbon resonance at δ 200.6 ppm.

The molecular ion (m/z 438.13) was not detected, however fragments were observed corresponding to the loss of the anomeric substituent (m/z 109.01), loss of one molecule of acetic acid (m/z 60.02) as well as loss of one molecule of acetic acid (m/z 60.02) (Fig. 15).

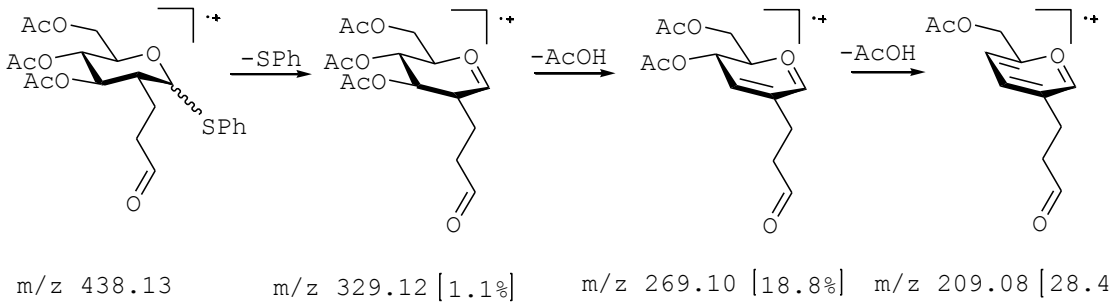
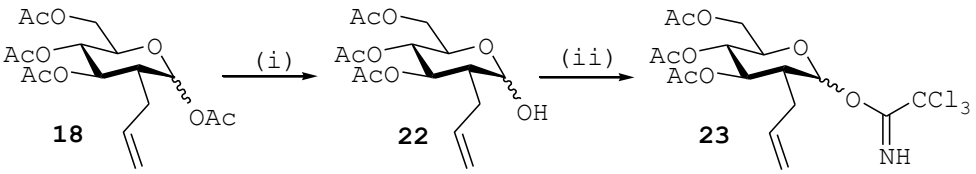


Figure 15. Assignment of observed fragment ions in the EI-MS of **21**.

2.1.6. PREPARATION OF AN ALTERNATIVE GLYCOSYL DONOR FROM 2-C-ALLYL DERIVATIVE 18

The failure to achieve a high selectivity using glycosyl acetate **18** led to an attempt to convert **18** to an alternative glycosyl donor. Although glycosyl fluorides had been previously prepared, it was of interest to investigate the formation of trichloroacetimidate derivative **23** and its reaction with the protected inositol acceptor. Glycosyl

trichloroacetimidates are a class of donor with many advantages: they offer controlled access to α- or β- imidates by choice of the base and are thermally stable up to room temperature.[40,41] The formation of trichloroacetimidates requires sugars with selectively unprotected anomeric hydroxyl groups, so the important first step in our approach was the regioselective anomeric deacetylation of **18.**



Scheme 19. Reagents and conditions: (i) Piperidine, THF, rt,(63%); (ii) CCl_3CN, K_2CO_3, DCM, rt, (93%).

The approach of Rowell and Feather,[41] using piperidine in THF was applied for regioselective deacetylation of **18** to give a mixture of anomers **22** (α:β = 0.2:1) in 63% yield. The ^{1}H NMR spectrum showed the disappearance of the acetyl group at the anomeric centre and the appearance of a broad peak at δ 3.09 ppm corresponding to the hydroxyl proton. A broad peak at δ 5.24 ppm and a doublet at δ 4.68 ppm (J = 8.2 Hz) were assigned to H-1 of the α- and β-anomers respectively, and were in agreement with the literature.[10] For the selective α-glycosylation reaction, it was necessary to synthesize the β-imidate. This can be achieved with a nonparticipating group at C-2, K_2CO_3 as a base in nonpolar solvent and at low temperature. Compound **22** was thus treated with CCl_3CN in the presence of K_2CO_3 to afford a mixture of imidates **23** with an unexpected major α-product (α:β = 1:0.1) in 92% crude yield.

The ^{1}H NMR spectrum (Fig. 16) displayed two singlets at δ 8.65 ppm (NH- α) and at δ 8.67 ppm (NH- β), which confirmed the formation of the imidates.[40,42,43] In addition, a doublet at δ 5.72 ppm with a coupling of J = 7.9 Hz and a doublet at δ 4.66 ppm with a coupling of J = 8.6 Hz were assigned to H-1 of the α- and β-anomers respectively, although a coupling of 7.9 Hz is admittedly high for an α-linked sugar. The ^{13}C NMR spectrum displayed two signals at δ 160.4 and 160.7 ppm (C=NH) for the two anomers.

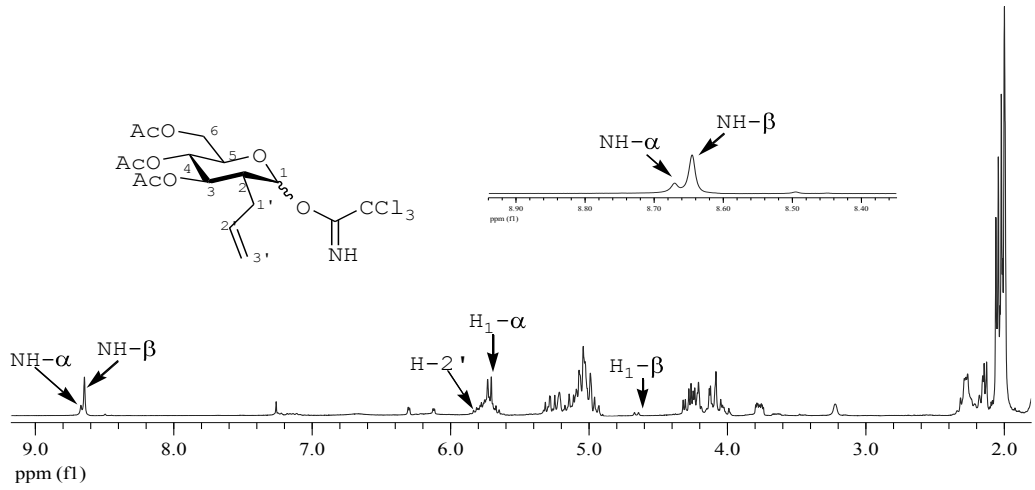


Figure 16. ^{1}H NMR spectrum of **23** in $CDCl_3$

Although the molecular ion (m/z 473.04) was not detected (Fig. 17), fragments were observed corresponding to the loss of the anomeric substituent (m/z 162.40), the loss of one molecule of acetic acid (m/z 60.02) and a further loss of one molecule of acetic acid (m/z 60.02).

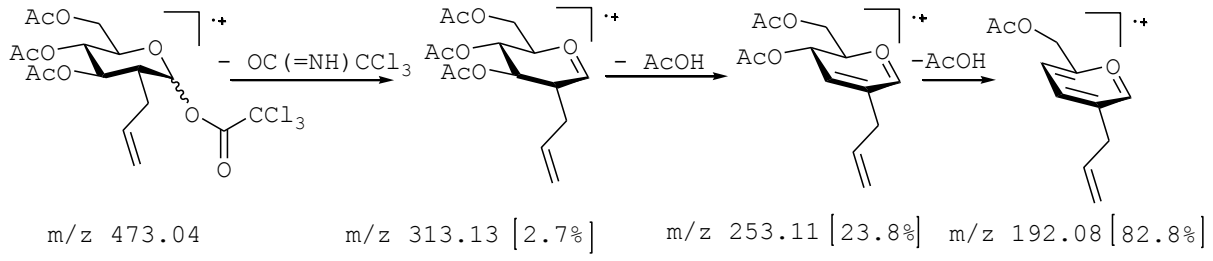
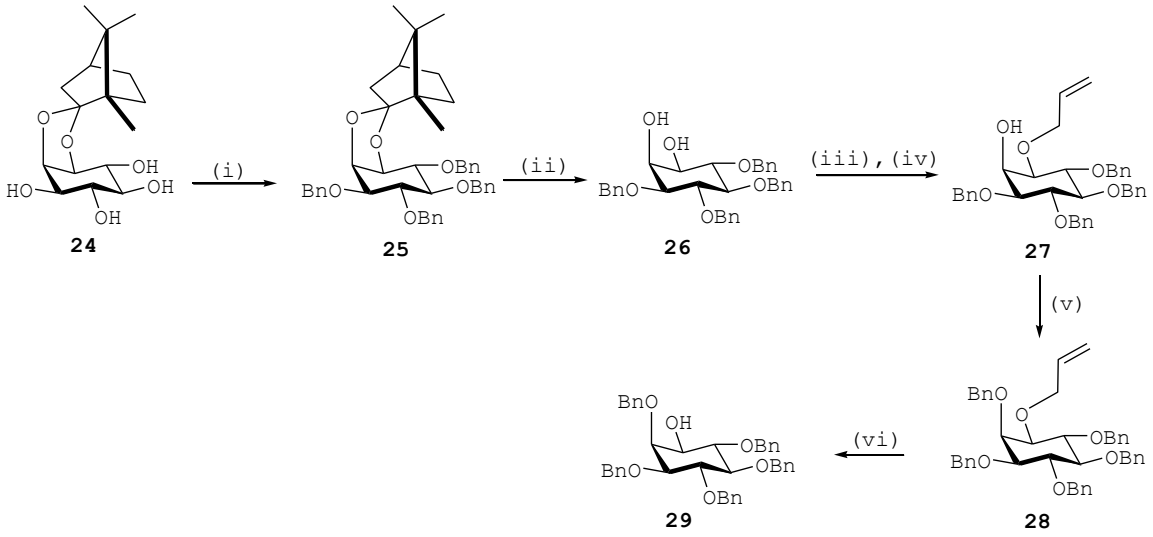


Figure 17. Assignment of observed fragment ions in the EI-MS of **23**.

2.2. SYNTHESIS OF GLYCOSYL ACCEPTOR

Although the phenyl-2-*C*-allyl-1-thioglucoside **19** is a potential inhibitor of MshB,[10] it was decided also to attempt the synthesis of a derivative that more closely resembles the natural substrate, i.e. one that includes the inositol unit as the aglycone. To achieve this it was necessary to prepare the selectively protected D-inositol derivative **29** (Scheme 20) which (a) is chirally pure, and (b) has the hydroxyl group at the 1-position available to be glycosylated.

We were fortunate to obtain a sample of the (*S*)-camphor acetal **24** from Professor Stefan Oscarson (University College Dublin).[44] The preparation of the selectively protected derivative was then carried out using the procedure described below,[31,44] involving selective preparation of the diol **26** by benzylation of **24** to give fully protected camphor acetal **25**, followed by acidic hydrolysis. Diol **26** was then subjected to regioselective allylation of the equatorial hydroxyl group, subsequent benzylation of the axial hydroxyl and finally cleavage of the allylic ether to give the desired inositol derivative **29**.



Scheme 20. Reagents and conditions: (i) NaH, BnBr, THF, (37%); (ii) 80% AcOH, (87%); (iii) Bu_2SnO, toluene, reflux, 2 h; (iv) Allyl bromide, CsF, DMF, (65%); (v) BnBr, NaH, THF, (90%); (vi) $PdCl_2$, EtOH-MeOH, (94%).

The diol **26** was selectively prepared from the starting material **24** by a sequence involving benzylation followed by hydrolysis.[45,46] Benzylation of **24** was achieved using BnBr with NaH in THF to give the fully protected product **25** in low yield (37%). Unfortunately, we were not able to explain the low yield. The derivative **25** was then subjected to acidic hydrolysis (aqueous 80% AcOH) to give diol **26** in 87% yield. The structure was confirmed by analysis of the ^{1}H NMR spectrum and comparison with the literature[46] with the key evidence being the disappearance of signals associated with the camphor acetal and the appearance of two sharp singlets corresponding to the two hydroxyl protons. The H-1 and H-2 protons shifted respectively from δ 3.72 to δ 3.44-3.51 ppm and from δ 4.33 to δ 4.20 ppm. In addition, the IR spectrum showed absorption at ν_{max}/cm^{-1} 3400, confirming the presence of

OH groups. Regiospecific allylation of diol **26** was achieved by treating it sequentially with Bu_2SnO and allyl bromide, to give the 2-hydroxy product **27** in 65% yield. The analysis of ^1H NMR spectrum (Fig. 18) showed the presence of one allyl moiety with a small coupling of J = 2.4 Hz between H-1 and H-2 and a large coupling of J = 9.5 Hz between H-1 and H-6 confirming the axial orientation of the H-1. A multiplet at δ 6.02-5.92 ppm for H-2′, a doublet of doublets at δ 5.32 ppm and 5.22 ppm respectively for H-3′$_a$ and H-3′$_b$, two upfield signals for H-1′$_a$ and H-1′$_b$ at δ 4.22-4.21 ppm compared with the literature values.[44,47] The proton signals for H-1 shifted from in between δ 3.51-3.44 ppm to δ 3.33 ppm and the one corresponding to the hydroxyl proton was visible at δ 2.53 ppm in the spectrum of **27**. In addition, the IR spectrum showed absorption at ν_{max}/cm^{-1} 3400, confirming the presence of an OH group.

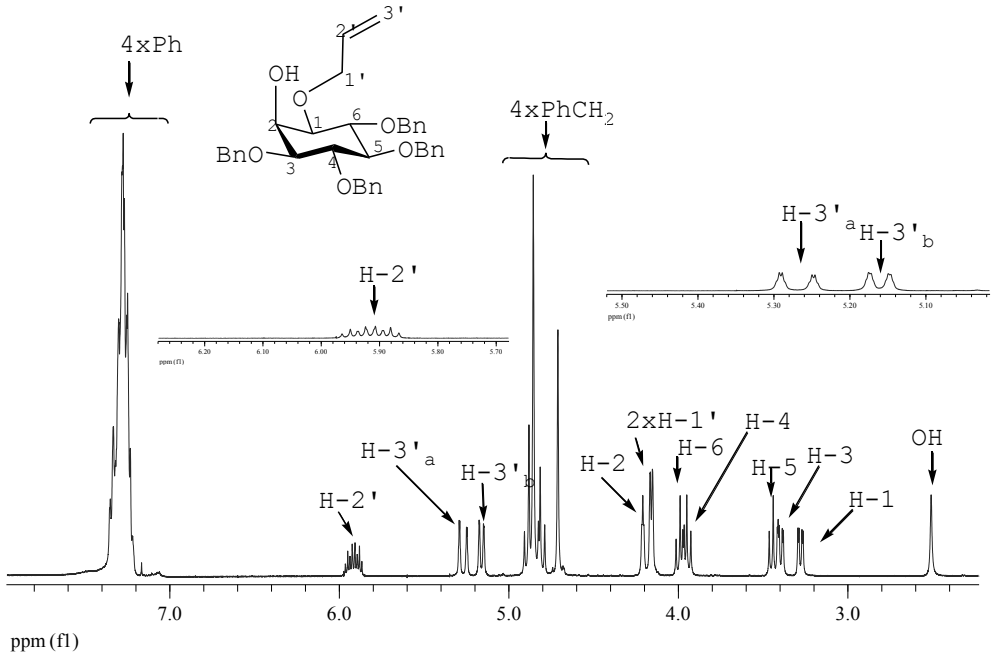


Figure 18. ^1H NMR spectrum of **27** in $CDCl_3$.

The allylation mechanism involves the formation of dibultylstannylidene acetals with enhancement of the nucleophilicity of the OH groups in the Sn acetal. Selective allylation at the equatorial position was favoured over the axial because of the steric hindrance from the benzyl ether groups.

Benzylation of **27** then afforded the fully protected derivative **28** in a good yield (90%) and its structure was assigned from ^{1}H and ^{13}C NMR spectra. The most obvious indication was the disappearance of the signal for the hydroxyl proton present in the spectrum of **27**. A downfield shift of the signal for H-2 was also observed after benzylation. Similar effects were noted for the corresponding signals in the ^{13}C NMR.

The selective removal of the allyl protecting group was performed with $PdCl_2$ in a mixture of ethanol and methanol to give the alcohol **29** in 95% yield.[48(a),(b)] The ^{1}H NMR spectrum showed the disappearance of signals of the allyl moiety and the appearance of a doublet at δ 2.23 ppm for the OH group. The NMR spectral data for **29** was also in agreement with that published in the literature.[44,47] In addition, the IR spectrum showed absorption at ν_{max}/cm^{-1} 3457 cm^{-1}, confirming the presence of an OH group (Fig. 19).

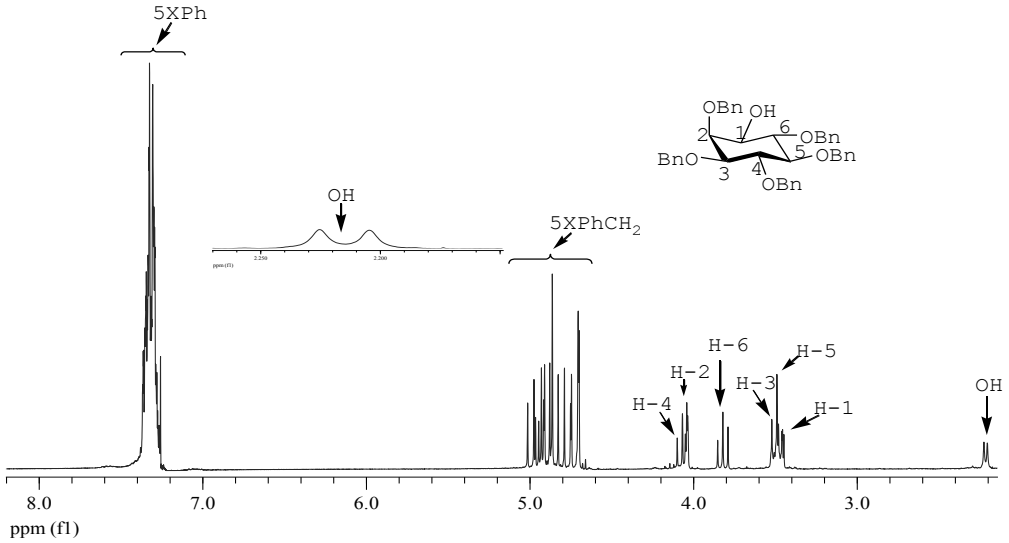
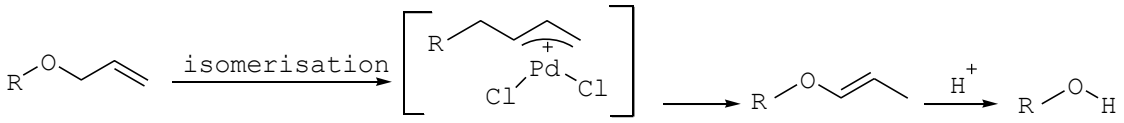
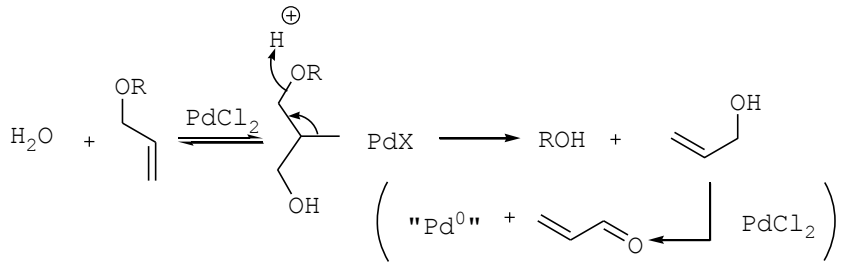


Figure 19. ^{1}H NMR spectrum of **29** in $CDCl_3$.

Two possible mechanisms have been suggested for this deallylation. The first involves a two-step sequence, involving a Pd-mediated isomerisation of the double bond to the corresponding prop-1-enyl ether followed by H^+ catalysed hydrolysis (Scheme 21) and the second is based on anti-markovnikov hydropalladation followed by β-alkoxy cleavage (Scheme 22).



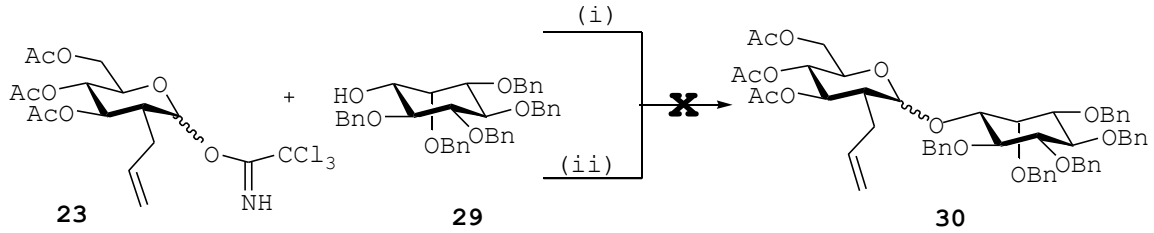
Scheme 21. Mechanism of deallylation via Pd-mediated isomerisation of the double bond.



Scheme 22. Mechanism of deallylation based on anti-markovnikov hydropalladation followed by β-alkoxy cleavage.[48(b)]

2.3. ATTEMPTED GLYCOSIDATION REACTION

Mudzunga[31] reported on the synthesis of the compound **30** in 80% yield with the α-anomer predominant, by treating **29** with the glycosyl fluoride in DCM using TMSOTf as activator. It was therefore of interesting to investigate the reactivity of glycosyl donors **23** and **17** and the stereochemical outcome of the glycosylation reaction with the acceptor **29**.

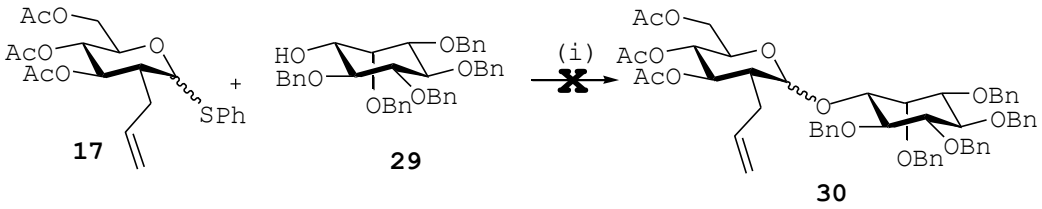


Scheme 23. Reagents and conditions: (i) TMSOTf, DCM, rt; (ii) $BF_3.OEt_2$, DCM, rt.

The glycosyl donor **23** was therefore reacted with the glycosyl acceptor **29** at room temperature to form glycoside **30** (Scheme

23). However, no reaction was observed and the starting materials were recovered. Repeating the reaction with $BF_3.OEt_2$ gave the same result, leading to the conclusion that the reaction was unsuccessful, presumably due to the low reactivity of the acceptor or the possible interaction of the double bond.[40]

We therefore turned our attention to the use of the thioglycoside as glycosyl donor. Thioglycosides are well known glycosyl donors, having the particular advantage of long shelf lives and stability under most protecting group transformations, which allows for highly functionalized derivatives to be made relatively easily.



Scheme 24. Reagents and conditions: (i) NBS, DCM, rt.[49]

The glycosylation reaction involving the acceptor **29** with the donor **17** was therefore attempted in dichloromethane using NBS to activate the thioglycoside. After 24 h, only the acceptor **29** was recovered. The NBS could have an effect on the double bond of the donor to afford a compound that we were unable to identify.

2.4. CONCLUSION

Part of the objectives of this project were achieved with the

successful preparation of 2-deoxy-2-C-allylglucoside **18** in five steps from D-glucal in 13.8% overall yield. This is comparable to the result of Mudzunga *et al.* who obtained the same compound in 13.9% overall yield in only two steps but involving two key separations.[31] The 2-*C*-allyl-1,6-anhydro-D-glucose derivative **15** could also be efficiently converted into the corresponding phenylthioglucoside **17**, either directly by treatment with TMS phenyl sulphide, or *via* glucosyl acetate **18**. Trichloroacetimidate donors were also prepared from glycosyl acetate **18**. The selectively protected inositol derivative **29** was prepared by a known procedure from chirally pure camphor acetal **24** in 18% overall yield. The attempted glycosylation reaction failed, suggesting that the glycosyl trichloroacetimidates and thiophenyl glycosides are not sufficiently reactive for coupling with the selectively protected inositol derivative, and that the successful glycosyl fluoride method be used in the future.[31]

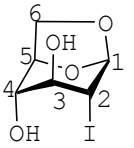
CHAPTER 3

EXPERIMENTAL

All reactions solvents were dried and distilled before use. Commercially available reagents were used without purification. Reactions were performed under an inert atmosphere of nitrogen in flame dried glassware, unless specified. Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck silica gel 60-F_{254} pre-coated plates and products visualized under UV or by wetting the plate with a solution of anisaldehyde and sulphuric acid in ethanol, followed by heating. Column chromatographies were performed on silica gel 60 and eluted with the mixture of light petroleum and ethyl acetate. Nuclear magnetic resonance spectra (^{1}H and ^{13}C) were recorded either on a Varian Mercury (300 MHz) or Varian Unity (400 MHz) at 25 °C in deuterated $CDCl_3$ or DMSO as the solvent. Chemical shifts are given in ppm relative to tetramethylsilane (TMS, δ = 0.00 ppm), which is used as internal standard. Assignments were confirmed by COSY and HSQC analysis. Coupling constants (*J*) are reported in Hertz (Hz). The spin multiplicities are indicated by the symbol s (singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet), and br (broad). Melting points were determined using a Reichert-Jung Thermovar hot-plate microscope and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer (in cm^{-1}). Mass spectra were recorded on a JEOL GC MATE II magnetic sector mass spectrometer and the base peaks are given, University of Cape Town. At University of Stellenbosch, mass spectra were recorded on a WATER API Q-TOF

Ultima (ESI+, 70 eV).

1,6-*Anhydro-2-deoxy-2-iodo-β-D-glucopyranose* (13)

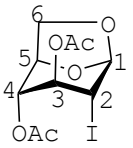


A solution of tri-O-acetyl-D-glucal **1** (10.0 g, 36.7 mmol) in 10:10:1 MeOH:H_2O:Et_3N (210 mL) was stirred for 5 h at room temperature and then concentrated. The residue was dried by repeated evaporations with EtOH, then kept overnight under vacuum in the presence of P_2O_5. The syrupy D-glucal (8.0 g) was treated with bis(tributyltin)oxide (13.2 g, 22.0 mmol) and activated, powdered 3 A° molecular sieves (22.0 g) in refluxing dry acetonitrile (175 mL) for 3 h. The mixture was cooled to 5 °C under Ar, and iodine (12.0 g, 47.3 mmol) was added in one portion. The dark-brown mixture was stirred for 15 min at 5 °C, then for 2 h at room temperature. TLC (1:1 toluene-acetone) showed complete conversion of D-glucal (R_f = 0.14) into a product with R_f = 0.45. The mixture was filtered through celite and concentrated. To the residue was added saturated aqueous sodium thiosulfate (100 mL) and hexane (100 mL), and the biphasic mixture was vigorously stirred for 3 h. The aqueous phase was then continuously extracted with EtOAc. The extracts were concentrated to give **13** (7.50 g, 75%, lit.[31]).

^{1}H NMR [400 MHz, $(CD_3)_2SO$]: δ 5.61 (s, 1H, H-1), 5.46 (d, $J_{3,OH}$ 4.2 Hz, 1H, O*H*-3), 5.36 (d, $J_{4,OH}$ 4.1 Hz, 1H, O*H*-4), 4.44 (m,

1H, H-5), 4.00 (d, $J_{6endo,6exo}$ 7.1 Hz, 1H, H-6_{endo}), 3.93 (m, 1H, H-3), 3.82 (m, 1H, H-2), 3.52 (dd, J 6.9 Hz, 1H, H-6_{exo}), 3.44 (m, 1H, H-4). ^{13}C NMR [100.6 MHz, $(CD_3)_2SO$]: δ 102.6 (C-1), 76.0 (C-5), 74.6 (C-3), 71.9 (C-4), 65.1 (C-6), 30.2 (C-2).

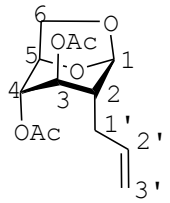
3,4-*Di*-*O*-*acetyl*-1,6-*Anhydro*-2-*deoxy*-2-*iodo*-β-*D*-*glucopyranose* (14)



Crude **13** (2.20 g, 8.09 mmol) was treated overnight at room temperature with pyridine (8 mL) and Ac_2O (5 mL). The mixture was cooled to 5 °C, then treated with MeOH (14 mL) and concentrated. Column chromatography (7:3 petroleum ether-EtOAc) of the residue gave **14** (1.75 g, 61%, mp 93-95 °C, lit.[31] mp 95 °C) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.70 (s, 1H, H-1), 5.16 (m, 1H, H-3), 4.74 (m, 1H, H-4), 4.65 (m, 1H, H-5), 4.24 (dd, $J_{5,6endo}$ 0.6 Hz, $J_{6endo,6exo}$ 7.7 Hz, 1H, H-6_{endo}), 3.94 (m, 1H, H-2), 3.82 (dd, $J_{5,6exo}$ 5.8 Hz, 1H, H-6_{exo}), 2.21, 2.12 (2s, 6H, 2 OAc).
^{13}C NMR (100.6 MHz, $CDCl_3$): δ 169.9, 168.9 (2 OAc), 102.8 (C-1), 73.5 (C-5), 73.1 (C-3), 70.4 (C-4), 65.6 (C-6), 21.5 (C-2), 21.1 (CH_3), 20.8 (CH_3).

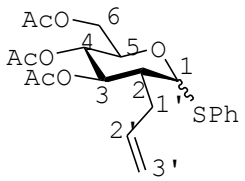
3,4-*Di*-*O*-*acetyl*-1,6-*anhydro*-2-*deoxy*-2-*C*-(2-*propenyl*)-β-*D*-*glucopyranose* (15)



A solution of **14** (2.0 g, 5.62 mmol) and 1,1'-azobis-cyclohexanecarbonitrile (0.30 g, 1.23 mmol) in dry toluene (90 mL) was degassed with Ar for 15 min. Allyltributylstannane (4.10 g, 12.4 mmol) was added under Ar and the mixture was heated under reflux for 3 h. TLC (7:3 petroleum ether-EtOAc) showed complete conversion of **14** (R_f = 0.31) into **15** (R_f = 0.37), a small amount of another spot (R_f = 0.22) and some polar products ($R_f \leq 0.1$). The solvent was evaporated, and a solution of the residue in acetonitrile (47 mL) was washed with petroleum ether (47 mL), and then concentrated. Column chromatography (7:3 petroleum ether-EtOAc) gave **15** (1.20 g, 79%, lit.[31]) as a green syrup.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83 (m, 1H, H-2′), 5.42 (s, 1H, H-1), 5.15 (m, 1H, H-3′$_a$), 5.12 (m, 1H, H-3′$_b$), 4.71 (m, 1H, H-3), 4.68 (m, 1H, H-4), 4.58 (m, 1H, H-5), 4.17 (dd, $J_{6endo,6exo}$ 7.6 Hz, 1H, H-6$_{endo}$), 3.80 (dd, $J_{5,6exo}$ 5.9 Hz, 1H, H-6$_{exo}$), 2.32 (m, 2H, H-1′), 2.16, 2.09 (2s, 6H, 2 OAc) and 1.82 (t, $J_{2,1'a}$ = $J_{2,1'b}$ 7.8 Hz, 1H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 169.7, 169.5 (2 OAc), 135.2 (C-2′), 117.5 (C-3′), 102.4 (C-1), 73.7 (C-4), 71.3 (C-3), 70.6 (C-5), 64.9 (C-6), 42.5 (C-2), 33.7 (C-1′), 21.1 (CH_3), 20.9 (CH_3).

***Phenyl*-3,4,6-*tri*-*O*-*acetyl*-2-*C*-*allyl*-2-*deoxy*-1-*thio*- α/β-*D*-*glucopyranoside* (17)**



1. To a solution **15** (0.160 g, 0.592 mmol) and PhSTMS (0.20 mL, 0.106 mmol) in CH_2Cl_2 (2 mL) at 0 °C under Ar was added TMSOTf (0.003 mL, 0.0166 mmol). The mixture was stirred at room temperature for 10 h, poured into aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed successively with brine and water, dried ($MgSO_4$) and evaporated. The residue was dissolved in dry tetrahydrofuran (THF)–MeOH (1:1; 2 mL) containing K_2CO_3 and the mixture was stirred for 10 min at room temperature. The mixture was diluted with EtOAc, washed successively with brine and water, dried (Na_2SO_4) and evaporated to give the crude **16** (0.190 g). The crude was directly treated overnight at room temperature with pyridine (0.6 mL) and Ac_2O (0.4 mL). The mixture was cooled to 5 °C, then treated with MeOH (0.8 mL), and concentrated. Column chromatography (7:3 petroleum ether-EtOAc) of the residue gave **17** (0.117 g, 47%, α:β = 1:0.6) as a colourless oil.

Phenyl-α-thioglucoside: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.19 (m, 5H, aromatic), 5.71-5.56 (m, 1H, H-2′), 5.36 (d, $J_{1,2}$ 4.9 Hz, 1H, H-1), 5.11-5.06 (m, 3H, H-3, H-3′$_a$, H-3′$_b$), 5.02 (dd, *J* 10.5 Hz, 9.0 Hz, H-4), 4.50 (m, 1H, H-5), 4.20 (dd, *J* 12.2 Hz, 2.4 Hz, 1H, H-6$_a$), 3.92 (dd, *J* 12.2 Hz, 2.2 Hz, 1H,

H-6_b), 2.24-2.05 (m, 3H, H-2, H-1'$_a$, H-1'$_b$), 1.93, 1.92, 1.91 (3s, 9H, 3 OAc). ^{13}C NMR (100.6 MHz, $CDCl_3$): 170.3, 170.0, 169.7 (3 OAc), 133.9 (C-2'), 132.6, 131.8, 128.8, 128.7 (aromatic C), 117.6 (C-3'), 87.9 (C-1), 75.3 (C-3), 69.9 (C-4), 68.7 (C-5), 62.3 (C-6), 44.8 (C-2), 32.8 (C-1'), 20.5 (*C*H_3), 20.5 (*C*H_3), 20.4 (*C*H_3). [M+Na] calcd for $C_{21}H_{26}O_7NaS$: 445.1; found 445.1.

Phenyl-β-thioglucoside: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.19 (m, 5H, aromatic), 5.69-5.78 (m, 1H, H-2'), 5.09-5.06 (m, 3H, H-3, H-3'$_a$, H-3'$_b$), 4.90 (dd, *J* 10.1 Hz, 9.3 Hz, 1H, H-4), 4.45 (d, $J_{1,2}$ 10.9 Hz, 1H, H-1), 4.20 (dd, *J* 12.3 Hz, 5.2 Hz, 1H, H-6_a), 4.13 (dd, *J* 12.3 Hz, 5.6 Hz, 1H, H-6_b), 3.93 (m, 1H, H-5), 2.35-2.26 (m, 3H, H-2, H-1'$_a$, H-1'$_b$), 1.95, 1.90, 1.89 (3s, 9H, 3 OAc). ^{13}C NMR (100.6 MHz, $CDCl_3$): 170.8, 169.9, 169.6 (3 OAc), 133.4 (C-2'), 132.3, 132.2, 131.2, 129.0 (aromatic C), 118.6 (C-3'), 86.3 (C-1), 73.0 (C-3), 69.7 (C-4), 62.5 (C-6), 60.1 (C-5), 43.7 (C-2), 31.9 (C-1'), 20.8 (*C*H_3), 20.6 (*C*H_3), 20.2 (*C*H_3). [M+Na] calcd for $C_{21}H_{26}O_7NaS$: 445.1; found 445.1.

2. Boron trifluoride etherate (0.023g, 0.186 mmol) was added to a stirred solution of **18** (0.11 g, 0.295 mmol) and thiophenol (0.05 mL, 0.487 mmol) in DCM (4 mL) at 0 °C under an atmosphere of Ar. The reaction mixture was allowed to equilibrate to room temperature. After 10 h, TLC (pet-ether/EtOAc, 1:1) indicated complete conversion of starting material. The reaction mixture was diluted with DCM (2 mL) and washed with satured aqueous sodium bicarbonate solution (2 × 1mL). The combined aqueous phases were re-extracted with

DCM (2 mL) and then the combined organic phases were dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was purified by column chromatography (7:3 petroleum ether-EtOAc) to give **17** (0.0596 g, 76%, α:β = 1:0.7) as a colourless oil.

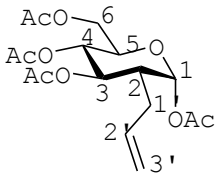
Phenyl-α-thioglucoside: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.19 (m, 5H, aromatic), 5.71-5.56 (m, 1H, H-2′), 5.36 (d, $J_{1,2}$ 4.9 Hz, 1H, H-1), 5.11-5.06 (m, 3H, H-3, H-3′$_a$, H-3′$_b$), 5.02 (dd, *J* 10.5 Hz, 9.0 Hz, H-4), 4.50 (m, 1H, H-5), 4.20 (dd, *J* 12.2 Hz, 2.4 Hz, 1H, H-6$_a$), 3.92 (dd, *J* 12.2 Hz, 2.2 Hz, 1H, H-6$_b$), 2.24-2.05 (m, 3H, H-2, H-1′$_a$, H-1′$_b$), 1.93, 1.92, 1.91 (3s, 9H, 3 OAc). ^{13}C NMR (100.6 MHz, $CDCl_3$): 170.3, 170.0, 169.7 (3 OAc), 133.9 (C-2′), 132.6, 131.8, 128.8, 128.7 (aromatic C), 117.6 (C-3′), 87.9 (C-1), 75.3 (C-3), 69.9 (C-4), 68.7 (C-5), 62.3 (C-6), 44.8 (C-2), 32.8 (C-1′), 20.5 (*C*H$_3$), 20.45 (*C*H$_3$), 20.41 (*C*H$_3$). [M+Na] calcd for $C_{21}H_{26}O_7NaS$: 445.1; found 445.1.

Phenyl-β-thioglucoside: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.19 (m, 5H, aromatic), 5.69-5.78 (m, 1H, H-2′), 5.09-5.06 (m, 3H, H-3, H-3′$_a$, H-3′$_b$), 4.90 (dd, *J* 10.1 Hz, 9.3 Hz, 1H, H-4), 4.45 (d, $J_{1,2}$ 10.9 Hz, 1H, H-1), 4.20 (dd, *J* 12.3 Hz, 5.2 Hz, 1H, H-6$_a$), 4.13 (dd, *J* 12.3 Hz, 5.6 Hz, 1H, H-6$_b$), 3.93 (m, 1H, H-5), 2.35-2.26 (m, 3H, H-2, H-1′$_a$, H-1′$_b$), 1.95, 1.90, 1.89 (3s, 9H, 3 OAc). ^{13}C NMR (100.6 MHz, $CDCl_3$): 170.8, 169.9, 169.6 (3 OAc), 133.4 (C-2′), 132.3, 132.2, 131.2, 129.0 (aromatic C), 118.6 (C-3′), 86.3 (C-1), 73.0 (C-3), 69.7 (C-4), 62.5 (C-6), 60.1 (C-5), 43.7 (C-2), 31.9 (C-1′), 20.8 (*C*H$_3$), 20.6 (*C*H$_3$), 20.2 (*C*H$_3$). [M+Na] calcd for

$C_{21}H_{26}O_7NaS$: 445.1; found 445.1.

1,3,4,6,*Tetra-O-acetyl-2-C-allyl-2-deoxy-α-D-glucopyranoside*

(18)



1. A mixture of **15** (0.204 g, 0.755 mmol), scandium trifluoromethanesulfonate (0.50 mol %) and acetic anhydride (0.306 g, 3.0 mmol) was stirred at room temperature under nitrogen atmosphere. After 5.5 h, the reaction was complete, methanol was added to quench the excess of acetic anhydride, and the whole solution was kept stirring for another 0.5 h. The resulting mixture was concentrated under vacuum to remove methyl acetate and acetic acid, and the resulting mixture was dissolved in ethyl acetate and washed with aqueous bicarbonate solution (10 mL), water, as well as brine. The organic phase was dried over $MgSO_4$, filtered and concentrated under vacuum. Column chromatography (7:3 petroleum ether-EtOAc) gave **18** (0.167 g, 60%, mp 78-80 °C) as a white solid (not recrystallized).

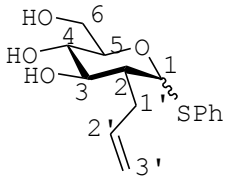
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.16 (d, $J_{1,2}$ 3.0 Hz, 1H, H-1), 5.74-5.64 (m, 1H, H-2′), 5.30 (dd, *J* 10.8 Hz, 9.6 Hz, 1H, H-3), 5.07-4.95 (m, 3H, H-3′$_a$, H-4, H-3′$_b$), 4.30 (dd, *J* 12.8 Hz, 4.6 Hz 1H, H-6$_a$), 4.02 (dd, *J* 12.8 Hz, 2.6 Hz, 1H, H-6$_b$), 4.03-4.01 (m, 1H, H-5), 2.22-2.17 (m, 3H, H-2, H-1′$_a$, H-1′ $_b$),

2.16, 2.08, 2.05, 2.04 (4s, 12H, 4 OAc). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.6, 170.5, 169.7, 168.8 (4 OAc), 134.0 (C-2′), 117.5 (C-3′), 91.7 (C-1), 71.9 (C-3), 69.8 (C-5), 69.2 (C-4), 62.0 (C-6), 43.1 (C-2), 31.7 (C-1′), 20.8 (*C*H_3), 20.74 (*C*H_3), 20.67 (*C*H_3), 20.6 (*C*H_3). [M+Na] calcd for $C_{17}H_{24}NaO_9$: 395.1; found 395.1.

2. The compound **15** (0.45 g, 1.66 mmol) was dissolved in Ac_2O and cooled to 0 °C with stirring under Ar. Two drops (~0.002-0.003 mL) of TESOTf are added to the solution. After 5 min, the reaction was complete. A solution of saturated sodium bicarbonate was then added and after being stirred for 30 min, the organic extracts are combined and washed with saturated sodium hydrogen carbonate solution followed by brine. The mixture was then dried over sodium sulphate, filtered and the solvents removed under pressure. Column chromatography (7:3 petroleum ether-EtOAc) gave **18** (0.20 g, 32%, mp 78-80 °C) as a white solid (not recrystallised).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.16 (d, $J_{1,2}$ 3.0 Hz, 1H, H-1), 5.74-5.64 (m, 1H, H-2′), 5.30 (dd, *J* 10.8 Hz, 9.6 Hz,1H, H-3), 5.07-4.95 (m, 3H, H-3′$_a$, H-4, H-3′$_b$), 4.30 (dd, *J* 12.8 Hz, 4.6 Hz 1H, H-6$_a$), 4.02 (dd, 12.8 Hz, 2.6 Hz, 1H, H-6$_b$), 4.03-4.01 (m, 1H, H-5), 2.22-2.17 (m, 3H, H-2, H-1′$_a$, H-1′ $_b$), 2.16, 2.08, 2.05, 2.04 (4s, 12H, 4 OAc). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.6, 170.5, 169.7, 168.8 (4 OAc), 134.0 (C-2′), 117.5 (C-3′), 91.7 (C-1), 71.9 (C-3), 69.8 (C-5), 69.2 (C-4), 62.0 (C-6), 43.1 (C-2), 31.7(C-1′), 20.8 (*C*H_3), 20.74 (*C*H_3), 20.67 (*C*H_3), 20.6 (*C*H_3). [M+Na] calcd for $C_{17}H_{24}NaO_9$: 395.1; found 395.1.

***Phenyl-2-C-allyl-2-deoxy-1-thio- α/β-D-glucopyranoside* (19)**



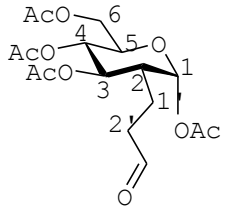
To a solution of **17** (0.120 g, 0.284 mmol) in MeOH (1.5 mL) was added NaOMe (0.20 g) and the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was quenched by addition of Amberlyst 15E-ion exchange resin, filtered, and the filtrate concentrated under reduced pressure. Column chromatography (1:1 petroleum ether-EtOAc) gave **19** (0.050 g, 59%, mp 85-87 °C, α:β = 1:0.1) as a white solid. Attempts were made to obtain HR-MS.

Phenyl-α-thioglucoside: ^{1}H NMR [400 MHz, $(CD_3)_2SO$]: δ 7.50-7.24 (m, 5H, aromatic) 5.91-5.72 (m, 1H, H-2′), 5.30 (d, $J_{1,2}$ 4.4 Hz, 1H, H-1), 5.13 (d, *J* 10.0 Hz, 1H, H_a-3′), 5.01 (d, *J* 16.9 Hz, 1H, H_b-3′), 4.89 (t, *J* 4.6 Hz, 2H, O*H*-3, O*H*-4), 4.35 (t, *J* 5.9 Hz, 1H, O*H*-6), 3.97-3.92 (m, 1H, H-3), 3.73-3.69 (m, 2H, H-1′$_a$, H-1′$_b$), 3.17-3.14 (m, 2H, H-4, H-5), 2.66-2.61 (m, 1H, H-6_a), 2.10-2.02 (m, 1H, H-6_b), 1.99-1.88 (m, 1H, H-2). ^{13}C NMR [100.6 MHz, $(CD_3)_2SO$]: δ 135.9 (C-2′), 131.8, 128.9, 128.8, 127.3 (aromatic C), 116.5 (C-3′), 88.5 (C-1), 74.4 (C-3), 72.6 (C-4), 71.3 (C-5), 60.7 (C-6), 46.6 (C-2), 32.6 (C-1′). ν_{max}/cm^{-1} 3369 (OH). [M+Na] calcd for $C_{15}H_{20}O_4NaS$: 297.1; found 297.1.

Phenyl-β-thioglucoside: ^{1}H NMR [400 MHz, $(CD_3)_2SO$]: δ 7.50-7.24 (m, 5H, aromatic), 5.87-5.77 (m, 1H, H-2′), 5.13 (d, *J*

10.0 Hz, 1H, H_a-3′), 5.01 (d, *J* 16.9 Hz, 1H, H_b-3′), 4.89 (t, *J* 4.6 Hz, 2H, O*H*-3, O*H*-4), 4.61 (d, $J_{1,2}$ 10.8 Hz, 1H, H-1), 4.35 (t, *J* 5.9 Hz, 1H, O*H*-6), 3.97-3.92 (m, 1H, H-3), 3.73-3.69 (m, 2H, H-1′$_a$, H-1′$_b$), 3.17-3.14 (m, 2H, H-4, H-5), 2.66-2.61 (m, 1H, H-6_a), 2.10-2.02 (m, 1H, H-6_b), 1.99-1.88 (m, 1H, H-2). ^{13}C NMR [100.6 MHz, $(CD_3)_2SO$]: δ 134.8 (C-2′), 132.3, 129.1, 129.0, 127.7 (aromatic C), 117.3 (C-3′), 85.3 (C-1), 73.6 (C-3), 72.6 (C-4), 70.9 (C-5), 61.1 (C-6), 45.7 (C-2), 31.2 (C-1′), ν_{max}/cm^{-1} 3369 (OH). [M+Na] calcd for $C_{15}H_{20}O_4NaS$: 297.1; found 297.1.

1,3,4,6,*Tetra-O-acetyl-2-deoxy-2-(3-oxopropyl)-α-D-glucopyranoside* (20)

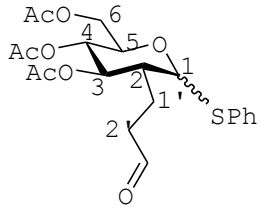


To a stirred solution of $PdCl_2$ (0.0180 g, 0.102 mmol) and CuCl (0.10 g, 1.01 mmol) in DMF and H_2O (7:1, 6 mL) under oxygen atmosphere was added **18** (0.210 g, 0.564 mmol). The resulting dark brown solution was stirred at room temperature for 12 h and then extracted with ether. The organic extract was dried over anhydrous $MgSO_4$ and evaporated under vacuum. Column chromatography (1:1 petroleum ether-EtOAc) to afford **20** (0.20 g, 91%, mp 92-93 °C) as a white solid.

***α*-anomer** : ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (t, *J* 0.8 Hz, 1H, C*H*O), 6.23 (d, $J_{1,2}$ 3.2 Hz, 1H, H-1), 5.20 (dd, *J* 11.4 Hz,

9.5 Hz, 1H, H-3), 5.12 (dd, *J* 10.0 Hz, 9.5 Hz, 1H, 1H, H-4), 4.26 (m, 1H, H-6_a), 4.07-4.01 (m, 2H, H-5, H-6_b), 2.76 (m, 1H, H-2), 2.46-2.37 (m, 2H, H-$1'_a$, H-$1'_b$), 2.21-2.16 (m, 2H, H-$2'_a$, H-$2'_b$), 2.14, 2.08, 2.02, 2.01 (4s, 12H, 4 OAc).
^{13}C NMR (100.6 MHz, $CDCl_3$): δ 204.9 (*C*HO), 170.7, 170.6, 169.5, 168.9 (4 OAc), 92.1 (C-1), 71.3 (C-3), 69.9 (C-5), 69.0 (C-4), 61.9 (C-6), 40.7 (C-1'), 38.9 (C-2) and 29.9 (C-2'), 20.8 (*C*H_3), 20.7 (*C*H_3), 20.6 (*C*H_3), 20.5 (*C*H_3). [M+Na] calcd for $C_{17}H_{24}NaO_{10}$: 411.1; found 411.1.

1,3,4,6,*Tetra-O-acetyl-2-deoxy-2-(3-oxopropyl)-α/β-D-glucopyranoside* (21)



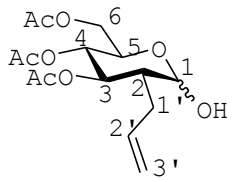
To a stirred solution of $PdCl_2$ (0.004 g, 0.0226 mmol) and CuCl (0.026 g, 0.263 mmol) in DMF and H_2O (7:1, 3.5 mL) under oxygen atmosphere was added **17** (0.110 g, 0.260 mmol). The resulting dark brown solution was stirred at room temperature for 12 h and then extracted with ether. The organic extract was dried over anhydrous $MgSO_4$ and evaporated under vacuum. Column chromatography (1:1 petroleum ether-EtOAc) to afford **21** (0.10 g, 88%, α:β = 0.2:1) as a colourless oil.

Phenyl-α-thioglucoside: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (t, *J* 1.2 Hz, 1H, C*H*O), 7.56-7.28 (m, 5H, aromatic), 5.78 (d, $J_{1,2}$ 5.2 Hz, 1H, H-1), 4.06-4.03 (m, 1H), 5.24-5.12 (m, 2H), 4.60-

4.57 (m, 1H), 4.03-4.02 (m, 2H), 3.76-3.71 (m, 1H), 2.99-2.91 (m, 1H), 2.78-2.72 (m, 2H), 2.09, 2.05, 2.02 (3s, 9H, 3 OAc). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 200.7 (CHO), 169.8, 169.7, 169.6 (3 OAc), 132.6, 132.4, 132.3, 131.7 (aromatic), 87.4 (C-1), 74.4, 72.9, 69.9, 62.4, 44.3, 42.6, 40.7, 20.7 (*C*H_3), 20.6 (*C*H_3), 20.6 (*C*H_3). [M+H] calcd for $C_{21}H_{26}O_8S$: 461.1; found 461.1.

Phenyl-β-thioglucoside: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (t, *J* 1.2 Hz, 1H, C*HO*), 7.56-7.28 (m, 5H, aromatic), 5.08-4.93 (m, 2H), 4.55 (d, $J_{1,2}$ 10.7 Hz, 1H, H-1), 4.72-4.14 (m, 1H), 3.69-3.64 (m, 1H), 2.72-2.34 (m, 3H), 2.09, 2.05, 2.02 (3s, 9H, 3 OAc), 1.82-1.81 (m, 1H), 1.65-1.53 (m, 2H), 2.08, 2.05, 2.01 (3s, 9H, 3 OAc). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 200.6 (CHO), 170.5, 170.4, 170.2 (3 OAc), 129.2, 129.1, 129.0, 128.2 (aromatic C), 86.8 (C-1), 75.7, 73.5, 69.6, 62.6, 43.6, 40.7, 39.5, 20.7 (*C*H_3), 20.6 (*C*H_3), 20.6 (*C*H_3). [M+H] calcd for $C_{21}H_{26}O_8S$: 461.1; found 461.1.

3,4,6-*Tetra-O-acetyl-2-C-allyl-2-deoxy - α/β-D-glucopyranoside* (22)



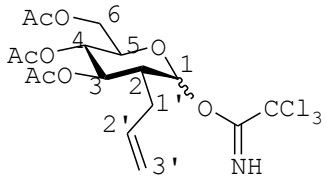
To a solution of **18** (0.18 g, 0.483 mmol) in THF (1.4 mL) was added piperidine (0.4 mL) with stirring. After 1 h at 25 °C, dissolution was complete and the solution stirred for an additional 1 h. The resulting mixture was poured into 200 mL

of ice-water and the aqueous solution extracted with dichloromethane (3 × 30 mL portions). The extracts were combined, washed successively with ice-cold, dilute hydrochloric acid solution, saturated aqueous sodium hydrogen carbonate and water, dried (sodium sulphate) and evaporated under reduced pressure to give **22** (0.10 g, 63 % crude, α:β = 1:0.2) as a colourless oil.

***α*-anomer**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.68 (m, 1H, H-2′), 5.30 (dd, *J* 11.1 Hz, 9.4 Hz, 1H, H-3), 5.24 (s, (br), 1H, H-1), 5.09-4.91 (m, 3H, H-3, H-3′$_a$, H-3′$_b$), 4.98 (t, *J* 9.7 Hz, 1H, H-4), 4.27-4.19 (m, 2H, H-5, H-6$_a$), 4.10-4.06 (m, 1H, H-6$_b$), 3.09 (s (br), O*H*), 2.16 (m, 2H, H-1′$_a$, H-1′$_b$), 2.07, 2.01, 2.01 (3s, 9H, 3 OAc), 1.89 (m, 1H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.8, 170.5, 170.0 (3 OAc), 135.0 (C-2′), 116.9 (C-3′), 92.9 (C-1), 71.9 (C-3), 69.9 (C-4), 67.7 (C-5), 62.5 (C-6) 44.2 (C-2), 32.0 (C-1′), 20.8 (*C*H$_3$), 20.7 (*C*H$_3$) and 20.6 (*C*H$_3$). [M+Na] calcd for $C_{15}H_{22}NaO_8$: 353.1; found 353.1.

β- anomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (m, 1H, H-2′), 5.30 (dd, *J* 11.1 Hz, 9.4 Hz, 1H, H-3), 5.11-4.93 (m, 3H, H-4, H-3′$_a$, H-3′$_b$), 4.68 (d, $J_{1,2}$ 8.2 Hz, 1H, H-1), 4.26-4.06 (m, 2H, H-6$_a$, H-6$_b$), 3.64 (m, 1H, H-5), 3.16 (s (br), OH), 2.28 (m, 2H, H-1′$_a$, H-1′$_b$), 2.1, 2.1, 2.0 (3s, 9H, 3 OAc), 1.9 (m, 2H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.8, 170.5, 169.9 (3 OAc), 133.9 (C-2′), 117.6 (C-3′), 96.6 (C-1), 72.6 (C-3), 71.7 (C-5), 69.9 (C-4), 62.5 (C-6), 46.4 (C-2), 31.0 (C-1′), 20.8 (*C*H$_3$), 20.7 (*C*H$_3$), 20.6 (*C*H$_3$). [M+Na] calcd for $C_{15}H_{22}NaO_8$: 353.1; found 353.1.

3,4,6-*Tetra-O-acetyl-2-C-allyl-2-deoxy- α/β-D-glucopyranosyl trichloroacetimidate* (23)



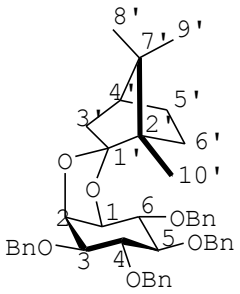
To crude of **22** (0.19 g, 0.575 mmol) and trichloroacetonitrile (0.21 mL, 2.09 mmol) in dry CH_2Cl_2 (3 mL), K_2CO_3 (0.210 g, 1.51 mmol) was added and the mixture stirred for 3 h at room temperature. The mixture was filtered and concentrated to give **23** (0.250 g, 93% crude, α:β = 1:0.1).

α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (s, 1H, CN*H*Cl_3), 5.81 (m, 1H, H-2′), 5.72 (d, $J_{1,2}$ 7.9 Hz, 1H, H-1), 5.30 (dd, *J* 10.9 Hz, 9.5Hz, 1H, H-3), 5.13 (dd, *J* 11.8 Hz, 9.5 Hz, 1H, H-4), 5.07-4.93 (m, 2H, H-3′$_a$, H-3′$_b$), 4.23 (m, 1H, H-6$_a$), 4.13 (dd, *J* 11.8 Hz, 2.7 Hz, 1H, H-5), 4.02 (m, 1H, H-6$_b$), 2.28 (m, 1H, H-2), 2.16-2.13 (m, 2H, H-1′$_a$, H-1′$_b$), 2.04, 2.02, 2.0 (3s, 9H, 3 OAc). ^{13}C NMR (100.6 MHz, $CDCl_3$) : δ 170.8, 170.6, 170.4 (3 OAc), 160.7 (*C*=NH), 133.9(*C*Cl_3), 132.9 (C-2′), 118.5 (C-3′), 97.1 (C-1), 71.9 (C-3), 69.4 (C-4), 67.7 (C-5), 62.1 (C-6), 44.4 (C-2), 30.6 (C-1′), 20.7 (*C*H_3), 20.6 (*C*H_3), 20.5 (*C*H_3). [M+H] calcd for $C_{17}H_{22}CCl_3NO_8$: 474.0; found 474.3.

β-anomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (s, 1H, CN*H*Cl_3), 5.68 (m, 1H, H-2′), 5.28 (dd, *J* 10.2 Hz, 9.6 Hz, 1H, H-3), 5.15 (m, 1H, H-4), 5.07-4.93 (m, 2H, H-3′$_a$, H-3′$_b$), 4.66 (d, $J_{1,2}$ 8.6 Hz, 1H, H-1), 4.30 (m, 1H, m, 1H, H-6$_a$), 4.13 (dd,

11.6 Hz, 10.4 Hz, 1H, H-5), 4.02 (m, 1H, H-6_b), 2.28 (m, 1H, H-2), 2.16-2.13 (m, 2H, H-$1'_a$, H-$1'_b$), 2.06, 2.03, 2.0 (3s, 9H, 3 OAc). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.1, 169.9, 169.8 (3 OAc), 160.4 (*C*=NH), 135.0 (C-2'), 133.9(*C*Cl_3), 116.9 (C-3'), 93.0 (C-1), 71.9 (C-3), 69.9 (C-4), 67.7 (C-5), 62.5 (C-6), 44.2 (C-2), 32.0 (C-1'), 20.7 (*C*H_3), 20.6 (*C*H_3), 20.5 (*C*H_3). [M+H] calcd for $C_{17}H_{22}CCl_3NO_8$: 474.0; found 474.3.

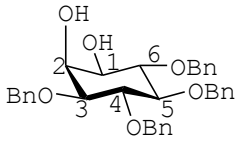
3,4,5,6-*Tetra-O-benzyl*-2,3-O-*(D*-1,7,7-*trimethyl*[2.2.1]*bicyclohept-2-ylidene)-myo-inositol* (25)



A portion of **24** (0.30 g, 0.954 mmol) in THF (4 mL) was cooled to 0 °C and NaH (60%, 0.530 g, 22.1 mmol) was added portion wise with stirring. After 30 min, benzylbromide (0.7 mL) was added slowly, then the ice water bath removed and the heterogeneous mixture heated at reflux for 18 h. The clear solution was cooled to 0 °C and the excess NaH quenched with the methanol (7 mL) and followed by water (7 mL). The organic solvent was evaporated and the aqueous mixture extracted with EtOAc, which was dried over $MgSO_4$ and concentrated under reduced pressure. Column chromatography (19:1 petroleum ether-EtOAc) gave **25** (0.230 g, 36% yield) as a green oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.25 (m, 20H, 4 × Ph), 4.98-4.60 (m, 8H, 4 × PhC*H*$_2$), 4.33 (t, $J_{2,3}$ 5.1 Hz, 1H, H-2), 3.89 (t, $J_{6,1}$ 8.1 Hz, 1H, H-6), 3.82 (dd, $J_{3,4}$ 7.2 Hz, 1H, H-3), 3.79 (dd, $J_{4,5}$ 10.0 Hz, 1H, H-4), 3.72 (dd, $J_{1,2}$ 3.7 Hz, 1H, H-1), 3.46 (t, $J_{5,6}$ 9.2 Hz, 1H, H-5), 2.07-1.08 (m, 7H, 2 × H-3′, H-4′, 2 × H-5′, 2 × H-6′), 0.91 (s, 3H, Me-9′), δ 0.88 (s, 6H, Me-10′, Me-8′). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 138.9, 138.8, 138.7, 138.5, 128.4, 128.3, 128.3, 128.2, 128.0, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.5 (aromatic C), 117.7 (C-1′), 83.3, 82.2, 80.8, 77.4, 76.3 (*C*H inositol), 75.1(Ph*C*H$_2$), 74.9 (*C*H inositol) 73.9, 73.8, 72.5 (3 × Ph*C*H$_2$), 51.6 (C-7′), 48.0 (C-2′), 45.3 (*C*H-4′), 45.0 (*C*H$_2$-3′), 29.9, 27.1 (*C*H$_2$-6′,5′), 20.7, 20.4, 10.2 (Me-10′, 9′, 8′).

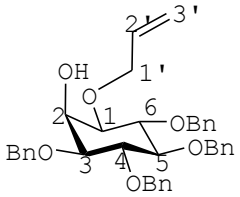
3,4,5,6-*Tetra-O-benzyl-myo-inositol* (26)



The compound **25** (0.230 g, 0.341 mmol) was suspended in aqueous 80% acetic acid (10 mL). The suspension was then stirred at 100 °C for 2 h. When the reaction was complete (TLC, 4:1 hexane-ether), the solvents were evaporated under reduced pressure. The residue was dissolved in petroleum-ether, then allowed to crystallize to give **26** (0.160 g, 87% yield, mp 127-129 °C) as a white solid; (lit[50] mp 127-128 °C, lit[51] mp 127 °C, crystallized from the crude reaction mixture).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.25 (m, 20H, 4 × Ph), 4.93-4.71 (m, 8H, 4 × PhC*H*$_2$), 4.22 (t, $J_{1,2}$ 2.7 Hz, 1H, H-2), 3.98 (t, $J_{4,5}$ 9.5 Hz, 1H, H-4), 3.85 (t, $J_{6,5}$ 9.5 Hz, 1H, H-6), 3.48 (t, $J_{4,5}$ 9.5 Hz, 1H, H-5), 3.48 (m, 1H, H-1), 3.47 (t, $J_{4,5}$ 9.5 Hz, 2.7 Hz, 1H, H-3), 2.53 (s (br), 1H, -O*H*), 1.64 (s (br), 1H, O*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 138.7, 138.6, 138.6, 137.8, 128.7, 128.6, 128.5, 128.4, 128.4, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 127.6 (aromatic C), 83.3 (C-5), 81.7 (C-4), 81.4 (C-6), 80.1 (C-3), 75.9, 75.7, 75.6, 72.8 (4 × Ph*C*H$_2$), 71.8 (C-1), 69.2 (C-2). ν_{max}/cm^{-1} 3400 (OH).

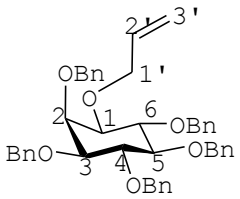
1-*O-Allyl*-3,4,5,6-*tetra-O-benzyl-D-myo-inositol* (27)



The diol **26** (0.20 g, 0.370 mmol) and Bu_2SnO (0.10 g, 0.402 mmol) were dissolved in toluene (4 mL) and heated at reflux for 2 h. The reaction mixture was then cooled to room temperature and concentrated. The residue was dissolved in DMF (2 mL) and allyl bromide (0.038 mL, 0.439 mmol) was added. The mixture was cooled to 0 °C before cesium fluoride (0.160 g, 1.05 mmol) was added and the mixture was allowed to attain room temperature and stirred over night. The mixture was diluted with EtOAc and washed with water. The organic layer was filtered through a silica plug and concentrated. Column chromatography (4:1 petroleum ether-EtOAc) gave **27** (0.130 g, 65%) as a colourless oil.[31]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.29 (m, 20H, 4 × Ph), 6.02-5.92 (m, 1H, H-2′), 5.32 (dd, *J* 17.2 Hz, 1.4 Hz, 1H, H-3′$_a$), 5.22 (dd, *J* 10.4 Hz, 1.3 Hz, 1H, H-3′$_b$), 4.95-4.77 (m, 8H, 4 × PhC*H*$_2$), 4.26 (t, $J_{2,1}$=$J_{2,3}$ 2.4 Hz, 1H, H-2), 4.22-4.21 (m, 2H, H-1′$_a$, H-1′$_b$), 4.03 (t, $J_{6,5}$ 9.5 Hz, 1H, H-6), 3.99 (t, $J_{4,5}$ 9.5 Hz, 1H, H-4), 3.48 (t, $J_{5,6}$ 9.4 Hz, 1H, H-5), 3.45 (dd, *J* 9.5 Hz, 2.6 Hz, 1H, H-3), 3.33 (dd, *J* 9.5 Hz, 2.6 Hz, 1H, H-1), 2.53 (s (br), 1H, O*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 138.8, 138.7, 137.9 (aromatic C), 134.7 (C-2′), 128.5, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.8, 127.5, 127.4 (aromatic C), 117.3 (C-3′), 83.1 (C-6), 81.2 (C-4), 79.9 (C-3), 79.6 (C-1), 77.4, 77.0, 76.6, 72.7 (4 × Ph*C*H$_2$), 72.8 (C-5), 71.8 (C-1′), 67.7 (C-2). ν_{max}/cm^{-1} 3400 (OH).

1-*O-Allyl*-2,3,4,5,6-*penta-O-benzyl-D-myo-inositol* (28)

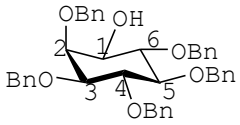


A solution of compound **27** (0.20 g, 0.344 mmol) in THF (2 mL) was added dropwise to 60% NaH (0.0840 g, 3.50 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C, then benzyl bromide (0.06 mL, 0.504 mmol) was added and the reaction mixture heated at reflux for 3 h. The reaction was quenched with MeOH (5 mL) followed by water (5 mL). The methanol was evaporated, and the aqueous phase extracted with EtOAc, which

was then washed with saturated NaCl and dried over $MgSO_4$. Column chromatography (19:1 petroleum ether-EtOAc) gave **28** (0.180 g, 90%) as a green oil.[31]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.28 (m, 25H, 5 × Ph), 6.03-5.90 (m, 1H, H-2′), 5.35 (dd, *J* 17.2 Hz, 1.7 Hz, 1H, H-3′$_a$), 5.22 (dd, *J* 10.4 Hz, 1.6 Hz, 1H, H-3′$_b$), 4.99-4.65 (m, 10H, 5 × PhC*H*$_2$), 4.14-4.07 (m, 5H, H-2, H-4, H-6, H-1′$_a$, H-1′$_b$), 3.52 (t, *J* 9.4 Hz, 1H, H-5), 3.43 (dd, *J* 9.8 Hz, 1.9 Hz, 1H, H-3), 3.31 (dd, *J* 9.8 Hz, 1.9 Hz, 1H, H-1). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 139.2, 139.1, 139.1, 138.8, 138.8, 138.6, 138.6, 138.5 (aromatic C), 134.9 (C-2′), 128.5, 128.4, 128.3, 128.2, 128.2, 128.0, 127.9, 127.7, 127.6, 127.6, 127.6, 127.5 (aromatic C), 116.6 (C-3′), 83.7 (C-5), 81.7 (C-4), 81.7 (C-6), 80.9 (C-3), 80.7 (C-1), 74.4, 75.8, 76.6, 77.0 (4 × Ph*C*H$_2$), 74.1 (C-2), 72.8 (Ph*C*H$_2$), 71.6 (C-1′).

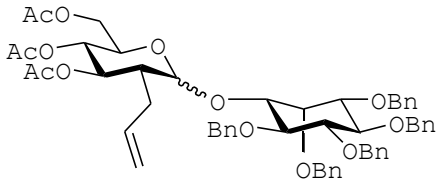
2,3,4,5,6-*penta-O-benzyl-D-myo-inositol* (29)



$PdCl_2$ (0.0034 g, 0.0192 mmol) was added to a solution of **28** (70 mg, 0.104 mmol) in EtOH-MeOH (1:1, 8 mL). The mixture was stirred for 5 h at room temperature, whereupon the solids were filtered through celite and solvent evaporated. Column chromatography (4:1 petroleum ether-EtOAc) gave **29** (69 mg, 95%, mp 90-92 ^{o}C; lit[47] mp 92-94 ^{0}C) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.25 (m, 25H, 5 × Ph), 5.02-4.07 (m, 10H, 5 × PhC*H*$_2$), 4.09 (t, *J* 9.5 Hz, 1H, H-4), 4.05 (t, *J* 2.4 Hz, 1H, H-2), 3.81 (t, *J* 9.5 Hz, 1H, H-6), 3.51 (m, 1H, H-3), 3.48 (t, *J* 9.5 Hz, 1H, H-5), 3.45 (dd, *J* 9.5 Hz, 2.4 Hz, 1H, H-1), 2.23 (d, *J* 6.4 Hz, 1H, O*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 138.8, 138.7, 138.7, 138.3, 128.8, 128.7, 128.5, 128.4, 128.4, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.6 (aromatic C), 83.6 (C-5), 82.2 (C-6), 81.9 (C-4), 81.2 (C-1), 77.4 (C-2), 72.4 (C-1′), 75.8, 75.7, 75.5, 74.7, 73.0 (5 × Ph*C*H$_2$). ν_{max}/cm^{-1} 3457 (OH).

***Attempted preparation of* 1-*O*-(3,4,6,*tri*-*O*-acetyl-2-*C*-allyl-2-deoxy-α/β-*D*-glucopyranosyl)-2,3,4,5,6-*penta*-*O*-benzyl-*D*-*myo*-*inositol* (30)**



A) A solution of **23** (0.030 g, 0.063 mmol) and **29** (0.060 g, 0.095 mmol) in dry CH_2Cl_2 (2 ml) was stirred with dried molecular sieves (4 A$^{\circ}$, 0.125 g) under nitrogen for 15 min, and then two drops of TMSOTf was added dropwise. After 24 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with satd aq $NaHCO_3$ (1.5 mL). The organic layer was dried over Na_2SO_4 and concentrated. No reaction was observed and we recovered the starting materials.

B) A solution of **23** (0.370 g, 0.78 mmol) and **29** (0.150 g, 0.24 mmol) was dissolved at 0 °C in dry CH_2Cl_2 (3 mL). $BF_3.OEt_2$ (2 drops) was added and the mixture was stirred for 14 h at room temperature. The mixture was diluted with DCM (30 ml), washed with saturated aqueous $NaHCO_3$ (2 × 30 mL), brine (1 × 30 mL) and dried ($MgSO_4$). No reaction was observed and we recovered the starting materials.

C) A solution of **17** (0.090 g, 0.21 mmol) and **29** (0.150 g, 0.24 mmol) in dry CH_2Cl_2 (4 mL) was stirred with dried molecular sieves (4 Å, 0.180 g) under nitrogen. The mixture was allowed to stir for 15 min, before recrystallized *N*-bromosuccinimide (0.150 g, 0.84 mmol) was added. After 24 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL) followed by filtration by successive washes with saturated aqueous $NaHCO_3$ (10 mL), water and brine. Drying ($MgSO_4$), filtration and evaporation under reduced pressure. Purification was carried out by preparative layer chromatography (Pet-ether/EtOAc: 3/2) to give a product that we were unable to identifier.

CHAPTER 4

REFERENCES

1. Kumar, V.; Abbas, A.K.; Fausto, N.; Mitchell, R.N. *Robbins Basic Pathology* (8th Ed.). Elsevier. **2007**, 516-522.

2. Murray, P.R.; Rosenthal, K.S.; Pfaller, M.A. *Medical Microbiology*. Elsevier. **2005**, 5, 963.

3. Zignol, M.; Hosseini, M.S.; Wright, A.; Weezenbeek, C.L.; Nunn, P.; Watt, C.J. Global incidence of multidrug-resistant tuberculosis. *J. Infect. Dis*. **2006**, 194, 479-485.

4. World Health Organisation (WHO). Global tuberculosis control-surveillance, planning, financing WHO Report. **2006**.

5. Emergence of Mycobacterium tuberculosis with extensive resistance to second-line drugs-worldwide, 2000-2004. **2006**, 55, 301-305. http://www.cdc.gov

6. Barry, C.E III.; Duncan, K. *Drug Discovery Today*. **2004**, 1, 491-496.

7. Xie, Z.; Siddiqi, N.; Rubin, E.J. *Antimicrob. Agent Chemother*. **2005**, 49, 4778-4780.

8. Fahey, R.C. *Annu. Rev. Microbiol*. **2001**, 55, 333-356.

9. Sakuda, S.; Zhou, Z.Y.; Yamanda, Y. *Biosci. Biotech. Biochem*. **1994**, 58, 1347-1348.

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

11. Nicholas, G.M.; Eckman, L.L.; Newton, G.L.; Fahey, R.C.; Ray, S.; Bewley, C.A. *Bioorg. Med. Chem*. **2003**, 11, 601-608.

12. Newton, G.L.; Av-Gay, Y.; Fahey, R.C. *Biochemistry* **2000**, 39, 10739-10476.

13. Park, J.H.; Roe, J.H. *Mol. Microbiol*. **2008**, 68, 861-870.

14. Rawat, M.; Kovacevic, S.; Jacobe. H.B.; Av-Gay, Y. *Microbiology*. **2003**, 149, 1341-1349.

15. Newton, G.L.; Fahey, R.C. *Arch. Microbiol*. **2002**, 178, 388-394.

16. Jothivasan, V.K.; Hamilton, C.J. *Nat. Prod. Rep*. **2008**, 25, 1091-1117.

17. (a) Maynes, J.T.; Garen, C.; Cherney, M.M.; Newton, G.; Arad, D.; Av-Gay, Y.; Fahey, R.C.; James, M.N.G. *J. Biol. Chem*. **2003**, 278, 47166-47170.

(b) Newto, G.L.; Buchmeler, N.; Fahey, R.C. *Microbiol. Mol. Biol. Rev*. **2008**, 72, 471-494.

18. Metaferia, B.B.; Ray, S.; Smith, J.A.; Bewley, C.A. *Bioorg. Med. Chem. Lett*. **2007**, 17, 444-447.

19. Nicholas, G.M.; Newton, G.L.; Fahey, R.C.; Bewley, C.A. *Org. Lett*. **2001**, 3, 1543-1545.

20. Fetterolf, B.J.; Bewley, C.A. *Bioorg. Med. Chem. Lett*. **2004**, 14, 3785-3788.

21. Nicholas, G.M.; Eckman, L.L.; Ray, S.; Hughes, R.O.; Pfefferkorn, J.A.; Barluenga, S.; Nicolaou, K.C.; Bewley, C. A. *Bioorg. Med. Chem. Lett*. **2002**, 12, 2487-2490.

22. Metaferia, B.B.; Fetterolf, B.J.; Shazad-ul-Hussan, S.; Moravec, M.; Smith, J.A.; Ray, S.; Gutierrez-Lugo, M.T.; Bewley, C.A. *J. Med. Chem*. **2007**, 50, 6326-6336.

23. Gammon, D.W.; Steenkamp, D.J.; Mavumengwana, V.; Marakalala, M.J.; Mudzunga, T.T.; Hunter, R.; Munyololo, M. *Bioorg. Med. Chem*. **2010**, 18, 2501-2514.

24. Salmon-Chemin, L.; Buisine, E.; Yardly, V.; Kohler, S.; Debreux, M.A.; Landry, V.; Sergheraert, C.; Croft, S.L.; Krauth-Siegel, L.; Daviuod-Charvet, E. *J. Med. Chem*. **2001**, 44, 548-565.

25. Giese, B.; Gröninger, K. *Tetrahedron Lett.* **1984**, 25, 2743-2746.

26. Procter, G.; Genin, D.; Challenger, S. *Carbohydr. Res.* **1990**, 202, 81-92.

27. Schlenk, W.; Schlenk, W.Jr. *Chem. Ber.* **1929**, 62, 920.

28. Tammiku-Taul, J.; Burk, P.; Tuulmets, A. *J. Phys. Chem. A.* **2004**, 108, 133-139.

29. Leteux, C; Veyrière, A; Robert, F. *Carbohydr. Res.* **1993**, 242, 119-30.

30. Keck, G.E.; Enholm, E.J.; Yates, J.B.; Wiley, M.R. *Tetrahedron*. **1985**, 41, 4079-4094.

31. Mudzunga, T.T. PhD thesis, University of Cape Town. **2003**.

32. Zemplén, G.; Pacsu, E. *Ber. Dtsch. Chem. Ges*. **1929**, 62, 1613-1614.

33. Wang. L.; Sakari, N.; Kuzuhara, H. *J. Chem. Soc. Perkin. Trans 1*. **1990**, 1677.

34. Kochetkov, N.K.; Chiz, O.S. *Adv. Carbohydr. Chem. Biochem*. **1966**, 41, 39-93.

35. Lee, J.C.; Tai, C.A.; Hung, S.C. *Tetrahedron Lett.* **2002**, 43 851-855.

36. Zottola, M.; Rao. B.V; Fraser-Reid, B. *J. Chem. Soc., Chem. Comm.* **1991**, 969-970.

37. Tennant-Eyles, R.J.; Davis, B.G.; Fairbanks, A.J. *Tetrahedron: Asymmetry*. **2003**, 114, 201-1210.

38. Muzart, J. *Tetrahedron* **2007**, 63, 7505-7521.

39. Tsuji, T. "Palladium Reagents and Catalysts", First Edition **2004**, Wiley, 29-35.

40. Schmidt, M.S.; Wittman, V. *Carbohydr. Res.* **2008**, 343, 1612-1623.

41. Rowell, R.M.; Feather, M.S. *Carbohydr. Res.* **1967**, 4, 486-

491.

42. Tran, A.T.; Deydier, S.; Bonnaffé, D.; Le Narvor, C. *Tetrahedron Lett*. **2008**, 49, 2163-2165.

43. Ning, J.; Hung, L.; Kong, F. *Carbohydr. Res*. **2002**, 337, 1159-1164.

44. Slättegård, R. PhD thesis, Stockholm University. **2007**.

45. Pietrusiewicz, K.M.; Salamonczyk, G.M.; Bruzik, K.S. *Tetrahadron* **1992**, 48, 5523-5542.

46. Bruzik, K.S.; Salamończyk, M. *Carbohydr. Res*. **1989**, 195, 67-63.

47. Gigg, R.; Warren, C.D. *J. Chem. Soc. (C)*. **1969**, 2367-2371.

48. (a) Hiromi M.; Tatsuya M.; Fumiyuki, O. *J. Org. Chem*. **2004**, 69, 4482-4486.

(b) lnstitut de Chimie Moleculaire d' Orsay, Laboratoire des Réactions Organiques Selectives, associé au CNRS. Brit. 420, Université Paris-Sud, 91405 Orsay (France). *Tetrehadron*. **1997**, 53, 13509-13556.

49. Nicolaou, K.C.; Seitz, S.P.; Papahatjis, D.P. *J. Am. Chem. Soc*. **1983**, 105, 2430-2434.

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

51. Angyal, S.J.; Tate, M.E. *J. Chem. Soc*. **1965**, 6949-6955.