The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.
SYNTHESIS OF ANALOGUES OF MYCOTHIOL AS POSSIBLE INHIBITORS OF ENZYMES IN THE BIOSYNTHESIS OF MYCOTHIOL

BY

THEOPHILUS THIVHULAWI MUDZUNGA

Thesis Presented for the Degree of
DOCTOR OF PHILOSOPHY

In the Department of Chemistry
UNIVERSITY OF CAPE TOWN

October 2003

Supervisors: Associate Professor David W. Gammon
Professor Roger Hunter
Abstract

*Mycobacterium tuberculosis* is the causative agent of tuberculosis and is a leading pathogenic cause of death worldwide. The rise of mycobacterial resistance to common antituberculars such as isoniazid and rifampicin, along with the lethal alliance of HIV and *M. tuberculosis* coinfection, has led to interest in developing novel, effective, non-toxic antituberculosis agents.

Mycothiol is a low-molecular weight thiol produced only by actinomycetes including *Mycobacterium tuberculosis* and is of significant importance because it is thought to protect these organisms against oxidative stress and function in the removal of exogenous electrophilic agents. The absence of mycothiol in mammalian cells suggests that the enzymes involved in the metabolism of mycothiol may be attractive drug targets.

Deacetylation of 1-D-β-myo-inosityl-2-N-acetamido-2-deoxy-α-D-glucopyranoside (GlcNAc-Ins, 7) to 1-D-β-myo-inosityl-2-amino-2-deoxy-α-D-glucopyranoside (GlcN-Ins, 8) by a deacetylase enzyme (*MshB*) is believed to be an important step in the biosynthesis of mycothiol. With the possibility of inhibition of this enzyme in mind, several new analogues representing isosteres of either GlcNAc-Ins 7 or the transition state in the deacetylation of GlcNAc-Ins 7 have been designed and synthesized, in which the nitrogen atom at C-2 is replaced by a methylene group.

Stereoselective synthesis of C-2 alkyl glucosides was identified as a key challenge and methods for their synthesis have been extensively reviewed. Synthesis of the analogues proceeded via initial stereoselective introduction of the alkenyl group at C-2 of the sugars, either by lithium enolate-mediated or free radical alklylation. The alkenyl glucosides where subsequently converted to glycosyl fluorides as suitable glycosyl donors. An enantiomerically pure, selectively protected D-β-myo-inositol glycosyl acceptor was prepared by a resolution of DL-1,2,4,5,6 penta-O-benzyl-myoinositol as its (S)-(−)-camphanate ester followed by hydrolysis.

Coupling of the 2-C-allyl glycosyl fluoride with the D-β-myo-inositol or cyclohexanol in the presence of BF₃·Et₂O as a catalyst gave 2-C-allyl-2-deoxy-glucosides as a mixture of anomers.
with good selectivity ($\alpha:\beta = 8:1$) in the case of $D$-myo-inositol. Portions of these allylated compounds were further functionalized, including oxygenation, to afford a range of potential enzyme inhibitors (51, 52 and 57-61) after deprotection.

![Structural diagrams for compounds 51, 52, and 59](image)

The 1-O-[2'-deoxy-2'-C-(2''-hydroxypropyl)-\(\alpha\)-D-glucopyranosyl]-D-myoinositol 51, 1-O-[2'-deoxy-2'-C-(2''-oxopropyl)-\(\alpha\)-D-glucopyranosyl]-D-myoinositol 52 and cyclohexyl 2-C-allyl-2-deoxy-\(\alpha\)-D-glucopyranoside 59 inhibit the incorporation of [\(^3\)H]inositol by whole cells of *Mycobacterium smegmatis* into a number of metabolites which contain inositol and these compounds represent the first examples of inhibitors of deacetylase enzyme (*mshB*) in the biosynthesis of mycothiol.
Acknowledgements

I would like to thank the following people for their contributions to the preparation of this thesis:

My supervisors, Associate Professor David W. Gammon and Professor Roger Hunter for their constant guidance, enthusiasm, and patient throughout the course of my PhD studies.

Associate Professor Daan J. Steenkamp (UCT) for biological activity experiments and useful discussions.

Professor James R. Bull, Associate Professor Kelly Chibale, and Dr Eugene Sickle for their helpful discussions.

Colleagues past and present in the Hunter/Gammon Research Group, Dr Philip Richards, Wolfgang Hinz, Seanette Wilson, Gareth Arnott, Dr Catherine Kaschula, Dr Comfort Nkambule, Henock Knife, Sophie Rees-Jones, Bernard Verblun, Dr JJ Nair, Sanjay Mahabir, Aklilu Kidane, Anthony Seymour, Dr Aloysius Nchinda, Divendren Patten, David van der Merwe, Hayley Haupt, Clare Muhanji, Mlandzeni Boyce, Linda Mbeki, Ludwe Sinuka and Pieter Levecque.

All my colleagues past and present in the Department of Chemistry.

Noel Hendricks, Pete Roberts, Dr Philip Boshoff, and John Hill (Kent mass spectroscopy, UK) for their analytical services.

The National Research Foundation and University of Cape Town for financial support. The financial assistance of the Department of Labour (DoL) towards this research is hereby acknowledged. Opinions expressed and conclusions arrived at, are those of the author and are not necessarily to be attributed to the DoL.

My family and friends for their constant support and encouragement during the ups and downs that this period has been filled with. Without them this might not have been!

To my dearest mother, Jerminah Mudzungu. Thank you for all the love, support, prayers and words of encouragement throughout my years of studies. You have been a great pillar of support!!
CONTENTS

1. INTRODUCTION 1
   1.1 Background 1
   1.2 Mycothiol 2
      1.2.1 Biosynthetic pathways to mycothiol 4
      1.2.2 Chemical synthesis of mycothiol bimane 6
      1.2.3 Enzyme and substrate specificity 8
      1.2.4 Inhibitors of mycothiol S-conjugate amidase (MCA) 10
   1.3 Aim of the project 16
   1.4 Design of inhibitors of the deacetylase enzyme 17
   1.5 Retrosynthetic analysis 21
   1.6 Review on the synthesis of C-2 branched sugars 22

2. RESULTS AND DISCUSSION 44
   2.1 Alkylation at C-2 of the sugars 44
      2.2.1 Lithium enolate alkylation 44
      2.2.2 Radical alkylation 53
   2.2 Synthesis of the glycosyl donor 61
   2.3 Synthesis of the glycosyl acceptor 67
   2.4 Glycosylation and side-chain functionalisation 73
      2.4.1 Synthesis of 2-C-alkylglucosides of 1-D-myo-inositol 73
      2.4.1 Synthesis of cyclohexyl 2-C-alkylglucosides 87
   2.5 Biological activities 99

3. CONCLUSION 101

4. EXPERIMENTAL 102

5. REFERENCES 175
CHAPTER 1

INTRODUCTION

1.1 Background

Tuberculosis (TB), is one of the most devastating infectious diseases in the world today\(^1\) and is caused by the microorganism called *Mycobacterium tuberculosis*. An estimated two billion people are infected with *M. tuberculosis*, and eight million new cases are reported and more than two million people die from the infection each year.\(^2\)^3

*Mycobacterium tuberculosis* is a gram-positive aerobic bacterium that divides every 16–20 hours. This is extremely slow compared to other bacteria which tend to have division times measured in minutes (for example, *E. coli* can divide roughly every 20 minutes). It is a small rod-like bacillus which can withstand weak disinfectants and can survive in a dry state for weeks but can only grow within a host organism.\(^4\)

*Mycobacterium* species, along with members of a related genus *Nocardia*, are identified microscopically by their staining characteristics. They retain certain stains after being treated with acidic solution, and are thus classified as acid-fast bacillus (AFB). In the most common staining technique, the Ziehl-Neelsen stain, AFB are stained a bright red which stands out clearly against a blue background. Acid-fast bacilli can also be visualized by fluorescent microscopy, and by auramine-rhodamine stain.\(^4\)

TB is transmitted from person to person through the aerosol route and usually from droplets coughed out by an infected person. The TB bacillus can affect several organs of the human body, including the brain, kidney, bones, and most commonly it affects lungs (Pulmonary Tuberculosis). The symptoms of TB include a low-grade fever, night sweats, fatigue, weight loss and a persistent cough.\(^4\)

TB is a treatable disease and drugs to treat susceptible strains of mycobacterium tuberculosis are not expensive. The most commonly used drugs are rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA), ethambutol (EMB) or streptomycin (SM) (Figure 1). However, diagnosis and treatment with current tools are complicated, require strict compliance by patients, as well as infrastructure that may not exist where the patients are found. Treatment is even more vulnerable
to dropouts, because it takes at least six months and can be difficult to get patients to complete the full course.\textsuperscript{4,5}

![Figure 1 Drugs used to treat TB disease](image)

After the discovery of antibiotics to treat TB in the 1950's, it has reemerged as a serious public health threat worldwide because of significant increase in multiple drug-resistant TB (MDR-TB) and synergism between Human Immunodeficiency Virus (HIV) and \textit{M. tuberculosis} infection to an extent that the World Health Organization (WHO) has declared it a global health emergency.\textsuperscript{6-8} HIV patients have weakened immune systems, making them more susceptible to secondary infectious and about one-third of HIV patients die from tuberculosis. Consequently, there is a continuing need for discovery of new antituberculars with novel modes of action. The significance of mycothiol for \textit{Mycobacterium tuberculosis}\textsuperscript{9} has led to the view that mycothiol analogues are potential lead drugs for TB.

### 1.2 Mycothiol

In eukaryotes and gram-negative prokaryotes, glutathione 1 (Figure 2), a low molecular mass thiol, plays an important role in defending the organism against oxidative stress and environmental toxins.\textsuperscript{10,11} Glutathione-dependent enzymes such as glutathione peroxidases and glutathione S-transferases protect the cell against oxidants and electrophiles. Actinomycetes like mycobacteria do not produce glutathione but instead synthesize mycothiol (MSH, 3), a thiol comprised of \textit{N}-acetyl-L-cysteine linked to a \textit{pseudo}-disaccharide composed of D-glucosamine and \textit{myo}-inositol (Figure 2).\textsuperscript{12}
The systematic name of mycothiol is 1-\textit{O-(2'-[\textit{N-acetyl-L-cysteinyl}amido-2'-deoxy-\textit{d}-glucopyranosyl]-d-\textit{myo}-inositol}.\textsuperscript{13} It was first isolated as the disulfide (MSSM, 2) from \textit{Streptomyces sp. AJ9463}\textsuperscript{13} and as the bimane derivative (MSmB, 4)\textsuperscript{14} and free thiol from \textit{M. bovis}, which allowed the demonstration of a mycothioldisulfide reductase activity, by analogy to glutathione reductase (Figure 2).\textsuperscript{15}

![Glutathione (1)](image1)

![MSSM (2)](image2)

![MSH (3)](image3)

![MSmB (4)](image4)

\textbf{Figure 2} Glutathione 1, mycothiol (MSH, 3), the symmetric disulfide (MSSM, 2), and mycothiol bimane (MSmB, 4)

\textsuperscript{a} \textbf{The trivial nomenclature for thiols}: There is ambiguity in the literature on nomenclature of these compounds. Ergothionine which has a genuine thione structure is not called ergothione, while glutathione, which has no thione, is called glutathione. If we are going to call the mycobacterial thiol mycothiol and its disulfide mycothione, then to be consistent we have to call glutathione glutathiol. But no one does. The problem is that thione is C=S and, therefore, whoever named this tripeptide did it incorrectly and the name stuck. So calling the oxidized forms mycothioldisulfide (MSSM) is preferable, and with glutathione we have the option to call GSSG either oxidized glutathione or glutathione disulfide.
Since mycobacteria lack glutathione, mycothiol serves functions analogous to glutathione in these organisms including protection against oxidants. For instance, *Mycobacterium smegmatis*, a fast-growing non-pathogenic relative of *M. tuberculosis*, is able to withstand up to 12 mM hydrogen peroxide without loss of viability whereas a chemically induced mutant and transposon mutants lacking mycothiol are killed by a hydrogen peroxide concentration of 1 mM.\(^{16,17}\) *M. smegmatis* is also remarkable in its ability to withstand millimolar concentrations of toxins such as monobromobimane, an alkylating agent that is lethal in much smaller amounts to cultured mammalian cells.\(^ {17}\) Mycothiol may thus play an important role in protecting *M. tuberculosis* against hostile environments such as that of the macrophages. Given the increasing need for new classes of antituberculars, MSH is of considerable contemporary interest, because of the pronounced structural differences between it and glutathione, and the role played by these thiol compounds in the detoxification of alkylating agents and other noxious chemicals.\(^ {17,18}\)

### 1.2.1 Biosynthetic pathways to mycothiol

In mycobacteria, biosynthesis of MSH is accomplished in four steps\(^ {19,20}\) by the protein products of genes termed *mshA-D* (Scheme 1)\(^ {21,22}\) and all these enzymes has been identified\(^ {9,23-25}\) and characterized\(^ {b}\). These include formation of the *pseudo*-disaccharide 1-D-*myo*-inosityl-2-N-acetamido-2-deoxy-α-D-glucopyranoside (GlcNAc-Ins, 7) by the putative glycosyl transferase *mshA*, followed by deacetylation of GlcNAc-Ins 7 by the enzyme 1-D-*myo*-inosityl-2-N-acetamido-2-deoxy-α-D-glucopyranoside deacetylase (*mshB* or AcGI deacetylase), to form the free amine 1-D-*myo*-inosityl-2-amino-2-deoxy-α-D-glucopyranoside (GlcN-Ins, 8).\(^ {9}\)

Transfer of cysteine to GlcN-Ins 8 by the cysteine transferase *mshC*\(^ {24}\) and then an acetate to GlcNCys-Ins 21 by the acetyl transferase *mshD*\(^ {23}\) completes MSH 3 biosynthesis.

---

\(^ {b}\) It is important in the aftermath of the elucidation of the complete *M. tuberculosis* genome to discern between annotation of a gene, based on work with mutants, as encoding an enzyme because one can detect accumulation of its substrate, and actual characterization of the enzyme. Thus the gene encoding *MshD* has been identified, but the enzyme is otherwise uncharacterized. It is also possible to characterize many properties of an enzyme without knowing its amino acid sequence and, therefore, the gene which encodes it. In fact, this used to be the case for most enzymes before all the advances in molecular biology.
Two further pathways involving MSH 3 formate hydrogenase have been elucidated (Scheme 1): (a) a reductase\textsuperscript{26-28} regenerates MSH 3 from the corresponding disulfide, mycothione (MSSM, 2), thus maintaining the reducing intracellular environment; (b) like glutathione 1, MSH 3 reacts with electrophiles and alkylating agents to form mycothiol-S-conjugates 9, which in turn serve as the substrate for mycothiol S-conjugate amidase (MCA).\textsuperscript{14} MCA cleaves the amide bond between cysteine and D-glucosamine-\(\alpha-(1\rightarrow1)\)-myo-D-inositol in MSH 3, thereby freeing N-acetyl-cysteine-
S-conjugates (also known as mercapturic acids) 10 for excretion from the cell, while GlcN-D-Ins 8 is retained intracellularly and is reused in MSH 3 biosynthesis. The detoxification enzyme mycothiol S-conjugate amidase (MCA) and the mycothiol-disulfide reducing enzyme mycothione reductase were the first mycothiol-related enzymes to be identified and characterized.

1.2.2 Chemical synthesis of mycothiol bimane

Sakuda et al., proposed the absolute stereochemistry of the three components of MSH 3 as D-glucosamine, L-cysteine, and D-my-o-inositol. His experimental evidence for the stereochemical assignments of the glucosamine and cysteine was not provided in the paper. Steenkamp and coworkers reported the first synthesis of mycothiol via GlcN-D-Ins 8 (Scheme 2).
Thus, coupling of 2,3,4,5,6-penta-O-acetyl-D-myo-inositol 12 with 3,4,6-tri-O-acetyl-2-deoxy-2-(2,4-dinitrophenylamino)-α-D-glucopyranosyl bromide 11 gave a mixture of α- and β-linked pseudo-disaccharides (13a and 13b, 1:1, respectively) in good yield. After separation of the anomers, the α-anomer 13b was treated with an anion exchange resin (IR400-OH) to give pseudo-disaccharide 8 in good yield. The final step of coupling the cysteine with GlcN-D-Ins 8 was achieved enzymatically to give mycothiol in good yield (Scheme 2). In these papers, the structure of the myo-inositol portion was depicted as 1-L while being referred to as 1-D.\textsuperscript{19,29}

The ambiguities surrounding the absolute stereochemistry of MSH were resolved with the total synthesis of the mycothiol bimane (MSmB, 4) which established the absolute stereochemistry of its three subunits as L-cysteine, D-glucosamine and 1-D-myo-inositol (Scheme 3)\textsuperscript{30} on the basis of comparisons of optical rotation and cd measurements with those from the bimane derivative of the natural material.

![Scheme 3](image_url)

Scheme 3 Reagents and conditions: i) DEPC, iPr₂EtN, DMF; ii) Mg(OMe)₂, MeOH

The synthesis of the bimane derivative was achieved by reaction of N-acetyl-L-cysteine with mono-bromobimane under basic conditions to give N-acetyl-L-cysteiny1 mono(reductant)bimane 15. Coupling of amine hydrochloride 14 with carboxylic acid 15 using Shioiri’s reagent diethylphosphoryl cyanide, DEPC) in the presence of diisopropylethylamine gave 16 in good
yield. Deacetylation was achieved in quantitative yields with Mg(OMe)_2 in methanol to give a final product 4 (Scheme 3).^{30}

### 1.2.3 Enzyme and substrate specificity

The two diastereomers of GlcNAc-α-Ins containing either 1-D-\textit{myo-}inositol 7 or 1-L-\textit{myo-}inositol 17 have been synthesized in order to establish substrate specificity of GlcNAc-α-Ins deacetylase from \textit{M. tuberculosis} (Figure 3).^{22}

![GlcNAc-α-D-Ins (7)](image1)

![GlcNAc-α-L-Ins (17)](image2)

**Figure 3** Two diastereomers of GlcNAc-α-Ins containing either 1-D-\textit{myo-}inositol or 1-L-inositol

In order to establish substrate specificity of AcGI deacetylase from \textit{M. tuberculosis}, solutions of 7 and 17 (30 and 100 μM) were incubated in the presence of 3.7 μg recombinant GlcNAc-α-Ins deacetylase. Quantitated solutions of 8 [D-GlcN-α-(1→1)-\textit{myo-}D-Ins] were used as standards. Following derivatization of the standard solutions and the reaction mixtures with 6-aminoquinolyl-N-hydroxysuccinimidyl carbamate, the extent of deacetylation was measured by fluorescence-detected HPLC. Deacetylation of the 30 and 100 μM solutions of 7 proceeded to 72% and 60%, respectively. In contrast, no detectable cleavage of the 1-L-inositol-containing isomer 17 was observed under the same conditions.

Further attempts of deacetylation of 17 were conducted, but even in the presence of relatively high enzyme concentrations, no cleavage products were detected, thereby establishing the 1-D-\textit{myo-}inositol containing isomer 7 as the natural substrate of AcGI deacetylase.^{22} These results are consistent with a separate study showing that D-GlcN-α-(1→1)-\textit{myo-}L-Ins 17 was not a substrate for MSH biosynthesis by crude extracts of \textit{Mycobacterium smegmatis}.^{19,29}
Thus compounds (8, 18-20) were synthesized (Figure 4) and these isomers were used to investigate the substrate specificity of the GlcN-α-D-Ins-L-cysteine ligase. A crude, cell-free extract of *M. smegmatis* catalyzed the conversion of GlcN-α-D-Ins 8 into a mixture of mycothiol 3 and desacetyl mycothiol 21 (1:4, 40% conversion) (Scheme 4). The products were quantified by [35S]-cysteine incorporation, and characterized as the bimane derivative 4. The GlcN-α-D-Ins-L-cysteine produced mycothiol 3 from GlcN-α-D-Ins 8 \( V_{\text{max}} \) (app) = 0.92 ± 0.02 nmol/min/mg, \( K_m \) (app) = 140 ± 9 μM, whereas GlcN-α-L-Ins 19 displayed poor binding \( V_{\text{max}} \) (app) = 0.51 ± 0.22 nmol/min/mg, \( K_m \) (app) = 2.69 ± 1.34 μM) (Figure 5). Incorporation of the β-coupled products (GlcN-β-D-Ins, 18 and GlcN-β-L-Ins, 20) into mycothiol was not detected under the same conditions, suggesting that these isomers were not the natural substrate for the MSH biosynthesis. 19,29
Scheme 4 The conversion of 8 or 19 to mycothiol catalyzed by a cell-free extract of *M. smegmatis*

![Chemical structures](image)

**Figure 5** Dependence of the rate of product formation on the concentration of the two isomers of GlcN-α-D-Ins 8 (●) and GlcN-α-L-Ins 19 (■)\(^{19,20}\)

### 1.2.4 Inhibitors of mycothiol S-conjugate amidase (MCA)

The unique structure of mycothiol suggests the possibility of designing inhibitors of the enzymes involved in mycothiol metabolism.\(^{26}\) Since MCA is unique to actinomycetes and shares no sequence homology to other known eukaryotic enzymes, it represents a novel target for new classes of antimycobacterials or co-drugs.\(^{31}\) Inhibition of homologous deacetylase and MCA
would result in disruption of MSH-dependent detoxification pathways at two distinct levels: biosynthesis and detoxification.³⁰

In the absence of a three-dimensional structure of MCA or an MCA homologue, Bewley and co-workers³¹-³³ chose to begin looking for MCA inhibitors by screening natural product extracts using a fluorescence-detected assay for inhibition of MCA activity on the substrate mycothiol bimane (MSmB, 4).

Three types of bromotyrosine-derived marine natural products containing a spirocyclic isoxazoline ring system inhibit MCA with IC₅₀ values ranging from ~1 to 100 μM (results summarized in Table 1).³¹,³³ These include spiro[4.6]decatrienes in compounds 22 and 23, spiro[4.6]undecatrienes present in psammaplysins A 24 and B 25 and the reduced bromophenyl oximinoamides in compounds 26 and 27 (Figure 6). Common to all of the bromotyrosine-derived compounds are a central amide group, an oxyimine to the carboxy side of the amide, and polar substituents to the amino side of the amide.³¹

Figure 6 Bromotyrosine-derived natural products that inhibit mycothiol S-conjugate amidase
The α,ω-bis-aminohydroxy glycosphingolipid oceanapiside 28 (Figure 7) inhibited MCA at low micromolar concentration (Table 1). Like the substrate myothiol bimane, oceanapiside contains a D-glucopyranoside unit. To determine whether the presence of the D-glucose unit in oceanapiside was essential for MCA inhibition, the pyranose from the C-3 hydroxyl of oceanapiside was removed to form the aglycon 29. Dose-response curves for compound 29 showed a 50- to 100-fold decrease in activity for the aglycon relative to oceanapiside, indicating that the presence of the D-glucoside in oceanapiside contributes favourably to MCA binding.33

**Table 1** Sources, taxonomic identities and IC<sub>50</sub> values for natural product inhibitors of *M. tuberculosis* and *M. smegmatis* myothiol S-conjugate amidase (MCA)<sup>31,33</sup>

<table>
<thead>
<tr>
<th>Compound</th>
<th>Common name or first author</th>
<th>Organism</th>
<th>Genus and species</th>
<th>NCI collection no.</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
<th>M. tb</th>
<th>M. smeg</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 Nicholas et al.</td>
<td>Pseudoceratina Marine sponge Oceanapia sp.</td>
<td>C2385</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Psammoplysarn A Marine sponge Oceanapia sp.</td>
<td>C2385</td>
<td>100</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Psammoplysarn B Marine sponge Pseudoceratina sp.</td>
<td>C16115</td>
<td>30</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Nicholas et al. Marine sponge Oceanapia sp.</td>
<td>C16115</td>
<td>30</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Litaudon and Guyot Marine sponge Oceanapia sp.</td>
<td>C2385</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>Oceanapiside Marine sponge Oceanapia sp.</td>
<td>C2385</td>
<td>30</td>
<td>37</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>Oceanapiside aglycon Marine sponge</td>
<td>C2523</td>
<td>10</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>Suvanine Marine sponge Coscinoderma mathewsi</td>
<td>C16199</td>
<td>nt</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Halisulfate Marine sponge Coscinoderma mathewsi</td>
<td>C16199</td>
<td>nt</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Gliotoxin Terrestrial fungus Mycena sp.</td>
<td>F205435</td>
<td>50</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>Physcion Terrestrial fungus Aspergillus sp.</td>
<td>F205337</td>
<td>nt</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>1,3-Pyridinium polymers Marine sponge Amphimedon sp.</td>
<td>C2355</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>SS-Dimethyl gliotoxin Terrestrial fungus Aspergillus sp.</td>
<td>F205337</td>
<td>70</td>
<td>nt</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 7 Natural products that inhibit mycothiol S-conjugate amidase

Other completely different classes of natural compounds that inhibit MCA (Table 1) in micromolar concentration are (Figure 7): the sulfated terpenes suvanine 30, halisulfate 1 31, a mixture of 1.3 pyridinium polymers 34, gliotoxin 32, S,S-dimethyl gliotoxin 35, and the anthraquinone physcion 33.

Consequently, a number of bromotyrosine-derived natural products have been synthesized. Most recently, Nicolaou and co-workers constructed a combinatorial library of asymmetric disulfide-containing compounds inspired by the disulfide-containing homodimer psammaplin A 36.
(Figure 8). To further elucidate the structural requirements for inhibition of MCA, members of this synthetic library (37-43) alongside various related natural products inhibitors have been screened and the efficacy of each compound is summarized in Table 2.  

![Figure 8 Bromotyrosine-derived natural product and members of a synthetic library](image)

<table>
<thead>
<tr>
<th>Marine natural products</th>
<th>IC\textsubscript{50} (\textmu M)</th>
<th>Synthetic library</th>
<th>IC\textsubscript{50} (\textmu M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound</td>
<td>Common name or first author</td>
<td></td>
<td>Compound</td>
</tr>
<tr>
<td>22</td>
<td>Nicholas et al.</td>
<td>2.0 ± 0.2</td>
<td>37</td>
</tr>
<tr>
<td>23</td>
<td>Pseudoceratine</td>
<td>100 ± 21</td>
<td>38</td>
</tr>
<tr>
<td>24</td>
<td>Psammaplysins A</td>
<td>20 ± 11</td>
<td>39</td>
</tr>
<tr>
<td>25</td>
<td>Psammaplysins B</td>
<td>26 ± 12</td>
<td>40</td>
</tr>
<tr>
<td>26</td>
<td>Litaudom and Guyot</td>
<td>36 ± 3</td>
<td>41</td>
</tr>
<tr>
<td>27</td>
<td>Nicholas et al.</td>
<td>2.8 ± 0.5</td>
<td>42</td>
</tr>
<tr>
<td>36</td>
<td>Psammapiolin A</td>
<td>2.8 ± 0.5</td>
<td>43</td>
</tr>
</tbody>
</table>

Table 2 Inhibition of mycothiol S-conjugate amidase (MCA) from \textit{M. tuberculosis} by synthetic and natural bromotyrosine-derived compounds  

By screening marine and fungal extracts, Bewley and co-workers\textsuperscript{31-33} have identified 14 compounds encompassing several unrelated structural classes that inhibit MCA with micromolar IC\textsubscript{50} values. Preliminary studies with psammaplysins A and B, oceanapiside, and the toxin gliotoxin demonstrate that these compounds inhibit growth of \textit{M. smegmatis} (MC\textsuperscript{2}155) in disk diffusion assays.
Enzyme inhibition assays using different inhibitors at various substrate concentration was conducted, and the mode of inhibition of *Mycobacterium tuberculosis* MCA for four of these compounds (24, 26, 28, 32) was then determined. Two types of bromotyrosine-derived natural products (24 and 26) were found to be competitive inhibitors of MCA. However, the oceanapiside 28 and the fungal metabolite gliotoxin 32 were found to be simple and mixed non-competitive inhibitors, respectively.

Structural features of the active natural products and modified analogues suggest that MCA is a metalloenzyme, and that the oximinoamide and spiro-isoxazoline amide groups present in the competitive inhibitors are substrate mimics. These finding are valuable in the design and synthesis of both natural products-inspired and substrate-based inhibitors of MCA.\textsuperscript{31}

Recently, Knapp and co-workers\textsuperscript{40} have reported the synthesis of a simplified thioglycosidic analogue of mycothiol 44 (Figure 9).

![Figure 9 Simplified thioglycosidic analogue of mycothiol](image)

In previous synthetic studies on MSH 3 and related compounds,\textsuperscript{19,26,29,30,41} the preparation of a protected D-\textit{myo}-inositol glycosylation acceptor has required several steps and a resolution, and both the inositol α-glycosylation and N-acylation steps have been problematic. These synthetic difficulties were avoided by a stripped-down version of the inositol ring that could be used as a component of inhibitors. Thioglycosides are generally more resistant to degradation by glycosidases than \textit{O}-glycosides,\textsuperscript{42-44} so this approach to inhibitors design combines several possible advantages.
Evaluation of 44 as a substrate for *M. tuberculosis* mycothiol S-conjugate amidase (MCA)\(^{14,30}\) was carried out by *S*-alkylation with bromobimane 45 (Scheme 5) under mildly basic conditions. The resulting bimane derivative 46 was subjected to cleavage by the amidase in parallel with mycothiol-bimane 4, while monitoring formation of cysteine-*S*-bimane product 10 by fluorescence-detected HPLC assay. Specific activities for 4 and 46 are 7500 and 14 200 nmol min\(^{-1}\) mg-protein\(^{-1}\), respectively, establishing 46 as a good substrate for this amidase. Neither the inositol hydroxyls nor the glycosidic linking atom (O vs S) plays a major role in enzyme binding.\(^{40}\) An earlier study\(^{26}\) had indicated that the inositol ring is not required for reduction of disulfides 2 by the *M. tuberculosis* mycothione reductase. The accumulated information thus suggests that 44, which dispenses with the inositol hydroxyls and the linking oxygen atom, can serve as a suitable foundation upon which to base inhibitor design.\(^{40}\)

### 1.3 Aim of the project

The absence of mycothiol (MSH) in mammalian cells suggests that the enzymes involved in the metabolism of MSH may be attractive antimycobacterial targets for either rational drug design or screening of libraries of inhibitory compounds.\(^{45}\) Although studies of MSH biosynthesis are still at an early stage, elements of the overall pathway have been described (Scheme 1).\(^{9,19,20}\) Moreover, direct measurement of intermediates in bacterial extracts that support the proposed biosynthetic pathway have been reported.\(^{20}\) It has been shown that 1-D-*myo*-inosityl-2-acetamino-2-deoxy-α-D-glucopyranoside (GlcNAc-Ins, 7) is an intermediate, and it is presumed that its formation is the first dedicated step in MSH biosynthesis.

1-D-*myo*-inosityl-2-amino-2-deoxy-α-D-glucopyranoside (GlcN-Ins, 8) is formed by deacetylation of 1-D-*myo*-inosityl 2-acetamino-2-deoxy-α-D-glucopyranoside (GlcNAc-Ins, 7). A homologous deacetylase (1-D-*myo*-inosityl-2-acetamino-2-deoxy-α-D-glucopyranoside deacetylase, *mshB*) has
been identified as the gene that encodes this deacetylase, and it appears that mshB is the key (rate limiting) enzyme in mycothiol biosynthesis.\(^9\)

The main objectives of this project were to design, synthesize and evaluate biological activities of a range of mycothiol analogues which might act as potential inhibitors of deacetylase enzyme (mshB) implicated in the conversion of GlcNAc-Ins 7 to GlcN-Ins 8, thereby preventing the production of mycothiol and hopefully the survival of *Mycobacterium tuberculosis*.

### 1.4 Design of inhibitors of deacetylase enzyme (mshB)

The conversion of GlcNAc-Ins 7 to GlcN-Ins 8 by a deacetylase enzyme (mshB) has been identified as a main control point in the mycothiol biosynthesis. Derivate 47 has been proposed as a transition state in the action of a deacetylase, resulting from a nucleophilic attack on the acetamide carbonyl group of GlcNAc-Ins 7 (Scheme 6).

![Scheme 6 Proposed general mechanism of N-deacetylation step](image)

Isosteres of the proposed transition state, which have been identified as potential inhibitors are sulfoximine 48, sulfone 49, phosphinic acid 50, and 2-C-hydroxypropyl derivatives 51, in which
the C-2 of the glucosamine unit has been modified, thus mimicking the transition state of the deacetylation of GlcNAc-Ins 7 (Figure 10).

![Sulfoximine (48)](image1)

![Sulfone (49)](image2)

![Phosphonic acid (50)](image3)

![2-C-hydroxypropyl (51)](image4)

**Figure 10** Isosteres of transition state of deacetylation of GlcNAc-Ins 7 as potential inhibitors of N-deacetylase step

The phosphinates and sulfoximines are slow, tight binding inhibitors of a number of ATP-dependent ligases, while hydroxyethylene isosteres were found to be very effective mimics of the transition state in hydrolytic enzymes, such as HIV protease.\(^{46,47}\)

The focus of this project centred on the synthesis and biological evaluation of 2-C-hydroxypropyl glucoside 51 and related compounds (52-62) (Figure 11 and 12). Compound 52 represents an isostere of 1-D-\textit{myo}-inositol-2-acetamido-2-deoxy-\(\alpha\)-D-glucopyranoside (GlcNAc-Ins, 7) in which the nitrogen atom is formally replaced with a methylene group (Figure 11), and could be a competitive binder or a substrate for the deacetylase enzyme. Compounds 53 to 56 (Figure 11) represent isosteres of GlcNAc-Ins 7 or the transition state of deacetylation of GlcNAc-Ins 7 in which the nitrogen atom at C-2 is replaced by a carbon atom. These analogous also contain an amine functionality at the carbon \(\alpha\)- to the carbonyl, as is found in mycothiol 3.
The synthesis of compounds 51 to 56 requires the preparation of a protected \( \text{D}-\text{myo}-\text{inositol} \) glycosylation acceptor. Previous reports on synthetic studies of MSH 3 and related compounds revealed that the synthesis of the protected \( \text{D}-\text{myo}-\text{inositol} \) acceptor is expensive, and requires several steps and a resolution of diastereomers. Thus, "stripped down" cyclohexyl glucosides (57-62), with features analogous to 51 to 56 were envisaged as potential inhibitors of deacetylase enzyme (mshB) in order to avoid these synthetic difficulties and to determine whether the inositol hydroxyls play any major role in the enzyme binding (Figure 12).
Figure 12 Potential inhibitors of the deacetylase step in which the inositol ring has been replaced with the cyclohexyl ring
1.5 Retrosynthetic analysis

The target compounds (51-62), shown in Figures 11 and 12, are very similar in structure. They all contain a C-2 alkyl group in the glucose portion of the pseudo-disaccharide, and an alpha-glycosidic bond with either 1-D-\textit{myo}-inositol or cyclohexanol.

![Chemical structures](image)

\textit{Scheme 7 Retrosynthetic analysis of target compounds}

The synthesis of target compounds (51-62) was envisaged according to the retrosynthetic analysis depicted on Scheme 7, identifying the key building blocks A to D as the initial targets. It was envisaged that cyclohexanol or protected \textit{myo}-inositol derivative C could be coupled with activated glycosyl donors A or B, which in turn were derivable from 2-deoxy-2-C-
alkenylglucoside D. 2-Deoxy-2-C-alkenylglucoside D could be obtained in a few reaction steps from mannose or glucose via radical- or lithium enolate-mediated alklylation.

Stereoselective alkylation at the C-2 position of the sugar was therefore identified as a key synthetic step in this project. An alkyl group offers two advantages in this approach: (a) they are non-participating groups and therefore, during the glycosylation step, the О-anomer was expected to be the major product; (b) an allyl group can easily be functionalized to give the desired functional groups by simple and familiar methods (Scheme 8). Thus it may be oxidized by the Wacker process to give a ketone which in turn can be easily reduced to the alcohol. Alternatively, it can hydrated to give a secondary alcohol which in turn can be oxidized to the ketone. Epoxidation followed by nucleophilic opening of the epoxide can give a secondary alcohol, which in turn can be oxidized to ketone. Cyclopropanation and hydrogenation of the alkene are also options for further manipulation of this side-chain.

![Scheme 8 Functional group interconversions on the C-2 side chain](image)

1.6 Review on the synthesis of C-2 branched sugars

The formation of carbon stereogenicity with good and preferably predictable stereocontrol is one of the most important objectives in organic chemistry. Synthesis of branched chain sugars remains an important challenge mainly because of the occurrence of such structural units in many natural products. Synthesis of 2-C-alkyl glycosides has been identified as a key challenge in the synthesis of analogues of mycothiol inhibitors in this project, and several methods for their synthesis are reviewed in the following sections.
1.6.1 Nucleophilic opening of carbohydrate epoxides

Sugar derivatives that possess three-membered oxygen-containing rings are called epoxides and are named as anhydro sugars. The more systematic term oxirane, is not often used since its introduction leads to nomenclature difficulties. Epoxides are frequently obtainable as stable compounds but are important synthetic intermediates because the three-membered rings are readily opened by various nucleophiles to yield a wide variety of modified sugars.\(^{51}\) Attack can in principle occur at either of the carbon atoms, and unsymmetrical epoxides can therefore give rise to mixtures of isomeric products (Scheme 9).\(^{52}\)

![Scheme 9 Nucleophilic opening of epoxide](image)

The nucleophilic opening of carbohydrate epoxides in carbon-carbon bond formation has received wide attention because it is a highly regioselective process as a result of conformational bias of the ring.\(^{53-68}\) Organocuprates\(^ {54}\) and Grignard\(^ {55}\) reagents are often used as nucleophiles, and in all cases, trans-diaxial ring opening occurs with inversion of configuration as expected for an S\(_{N}2\) reaction. In many cases, almost complete selectivity is observed, especially when the epoxide rings are fused in conformationally restricted derivatives such as trans-fused 4,6-O-benzylidene hexopyranosides (63 and 64) or 1,6-anhydropyranoses 65 (Figure 13).\(^ {52}\)

![Figure 13 Stereoselective opening of epoxides](image)

The regioselectivity of epoxide opening is determined by the conformation of the ring containing the epoxide group.\(^ {52,59-61}\) The pyranoid rings of 63, 64 and 65 adopt half-chair conformations, with nucleophilic attack occurring at C-2 for 63 and 65 and at C-3 for 64. This is in accordance with the Fürst-Plattner rule, which can be explained by consideration of the transition states in the ring opening reactions (Figure 13).\(^ {52}\)
Thus, treatment of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside 63 separately with allylmagnesium chloride and methallylmagnesium chloride gave the alcohols 66 and 67 in high yield with the expected D-altro configuration (Scheme 10).\(^{62}\) Swern oxidation of the alcohols 66 and 67, followed by epimerization, gave stable equatorial allyl groups (70 and 71), despite a report by Ferrier\(^{69}\) that the epimerization reaction was not possible.

![Chemical structures](image)

**Scheme 10 Reagents and conditions:** i) CH₂CRCH₂MgCl, THF, reflux; ii) Swern oxidation; iii) Et₃N, DMF

During the synthesis of Rosaramycin by Procter et al., 1,6:2,3-dianhydro-4-O-benzyl-β-D-mannopyranoside 65, readily obtained from 1,6-anhydro-β-D-mannopyranoside, was reacted with allylmagnesium chloride in ether to give 72 as a sole product (Scheme 11).\(^{60,61}\) The exclusive formation of 72 was expected, since the opening of the epoxide on the rigid 1,6-anhydro-β-D-hexopyranose derivative 65 with the pyranose ring locked into the \(^1\)C₄ configuration, is well known to generate *trans*-dialxial products. When THF was used as the solvent in the Grignard reaction on 65, only the chlorohydrin 73 was obtained (Scheme 11). It was not clear why the change of solvent in this reaction caused such a drastic change in the product. However, it was presumed that the position of the Schlenk equilibrium (solvent dependent) was an important factor. Methanolysis of 72 gave methyl-2-C-allyl-4-O-benzyl-2-deoxy-α-D-glucopyranoside 74 in good yield.
1.6.2 Radical alkylation

In recent years, the use of free-radical reactions has added very markedly to the range of efficient carbon-carbon bond-forming reactions available in organic synthesis, and great advantage has been taken of these new developments. These reactions have advantages such as high reaction rates, high functional group tolerance, and mild reaction conditions, being less prone to steric hindrance or polar effects, in view of less solvation of the radical species. They also exhibit high levels of regio- and stereo-selectivity.\(^{70}\)

One experimental problem encountered at the completion of the reaction is the removal of tin-containing material from the desired products. A number of solutions to this problem have been reported:\(^{71,72}\) (a) for reasonably polar compounds, partitioning the crude product between acetonitrile and pentane will generally remove the bulk of the tin-containing compounds; (b) stirring with aqueous KF will convert tin halides, etc. to stannyl fluorides, which are very insoluble and can be removed by filtration through basic alumina; (c) simple treatment of reaction mixtures containing tributylstannyl halides with \(\text{Me}_3\text{Al}\) or aqueous 1 M NaOH leads after filtration through silica gel to complete removal of tin residues. The \(\text{Me}_3\text{Al}\) method is particularly convenient for polar products and the NaOH method for non-polar products.

1.6.2.1 Intermolecular alkylation at the C-2 of the sugar

Glycosyl halides, in which the radical centre is the anomeric carbon atom, yield predominately \(\alpha\)-substituted products. This stereoselectivity is due to stereoelectronic effects that influence both the
radical configuration and the direction of attack on the radicals. However, the stereoselectivity at C-2 depends on the stereochemistry of the substituents at C-1 and C-3 (Figure 14). An anti-attack is favoured if the two substituents (C-1 and C-3) are cis to each other (75 and 76), while low selectivity is observed with trans substituents (77).

Figure 14 Stereoselective radical alkylation at C-2

 Allyltributylstannane and methallyltributylstannane are the most popular amongst those in the class of reagents belonging to the “fragmentation methods”. These reagents serve as both the precursor of the radical chain transfer agent as well as the radical trap. Three distinct steps occur in radical reactions: initiation, propagation and termination, and the accepted chain mechanism for alkylation with allyltributylstannane is shown in Scheme 12. Abstraction of X by the tributyltin radical is followed by addition of radical A to allyltributylstannane. Rapid β-fragmentation then provides the allylated product and the tributyl radical. Reduction is the most observed side reaction with substrates that possess poor solubility in toluene, and this can be minimized by employing benzene as a solvent.

\[
\begin{align*}
\text{Propagation} & \\
\text{Initiation} & \\
\text{Termination} & \\
\text{Scheme 12 Propagation step in intermolecular alkylation}
\end{align*}
\]
Giesen’s contributions to the development of fundamental aspects of radical chemistry as applied to carbohydrates are particularly notable. Thus, treatment of peracetylated 2-bromo sugar \(78b\) with allyltributylstannane and AIBN at 80 °C in benzene resulted in introduction of the allyl group into the C-2 position of the carbohydrate to give \(81a\) and \(81b\) (9:1, equatorial:axial, respectively) (Scheme 13). The predominance of equatorially alkylated product \(81a\) was due to the presence of equatorial substituents flanking the radical centre,\(^73\) and the major isomer could be isolated by crystallization.

![Scheme 13 Reagents and conditions: \(i\) Methallyltributylstannane or allyltributylstannane, AIBN, benzene, reflux](image)

The second example involves the alkylation of a peracetylated 2-iodo sugar during the synthesis of ketone isosteres of 2-N-acetomido-sugars (Scheme 13).\(^77\) Keck radical coupling of methallyltributylstannane with 2-iodo glucose analogue \(79\) or 2-iodo galactose analogue \(80\) afforded 2-methallylperacetylated sugars (\(82a\) and \(83a\)) as major products (ratios of equatorial:axial methallylation of 6:1 and 7:1, respectively). The predominance of the equatorial over the axial isomer is in accordance with the diastereoselectivity principles discussed above.

Another interesting example of intermolecular C-2 alkylation involves the generation of free radicals from acyloxy groups in the carbohydrate \(\alpha\)-acyloxy ketones.\(^69\) In carbohydrate chemistry, compounds containing carbon-halogen or carbon-mercury bonds, thionocarbonate esters of various kinds, nitro-compounds, isocyanides, and phenylthio-and phenylseleno-derivatives are all frequently used as radical precursors in the presence of AIBN as initiator. Ferrier et al.\(^69\) has reported the use of \(\alpha\)-acyloxy ketones as a source of free radicals when treated with AIBN. Thus, separate treatment of the highly functionalized D-arabino- and D-ribo-3-ulosides (\(84\) and \(85\)) with allyltributylstannane and AIBN afforded almost quantitative yields of 2-C-allyl-2-deoxy-D-arabino-derivative \(68\) with the C-2 substituent axial (Scheme 14).
Both epimers 84 and 85 gave the same product of allylation, indicating reaction by a common intermediate. Compound 68 could not be induced to isomerise, and its epimer 70 was not detected at any stage in the reaction. It was concluded that the α-keto radicals derived from 84 and 85 react under kinetic control to give a product with the allyl group in the axial orientation.

1.6.2.2 Intramolecular C-2 alkylation

Among the several methods used for the synthesis of C-branched sugars, the intermolecular addition of glycopyranoside radicals to olefins has been shown to be the most useful. However, intramolecular radical cyclization reactions for stereoselective C-C bond formation in sugars offer two major advantages in comparison with the intermolecular process: (a) more efficient C-C bond formation; and (b) higher stereoselectivity due to the exclusive formation of a cis ring junction.

The reaction is carried out in the presence of tributyltin hydride and a radical initiator (e.g. AIBN). The general mechanism for the formation of a carbon-carbon bond onto a double bond using tin radicals is illustrated (Scheme 15). The generated tributyltin radical abstracts X (where X is a halide, SPh, SePh, OC(S)SMe, etc.) to give a carbon radical, in which the driving force is the formation of the strong tributyltin-X bond. For the propagation step, the radical then attacks a double bond to form a new carbon-carbon bond and the new radical thus generated then abstracts a hydrogen from a new tributyltin hydride molecule to regenerate the tin radical (Scheme 15).
There is a competitive reaction involving the initial carbon radical and tributyltin hydride itself resulting in the reduction of RX. The formation of a new carbon-carbon bond only occurs if the rate of addition to the double bond is greater than that of reduction. To minimize the risk of reduction, the tributyltin hydride concentration is kept as low as possible by the slow dropwise addition of the reagent to the reaction mixture.

Alian de Mesmaeker has reported an efficient and stereoselective synthesis of the α-2-C-allyl pyranose unit by radical cyclization.\textsuperscript{78,81} The work described simple ring closures involving 2-haloethyl substituents bonded to O-1 of 2,3-dideoxy hex-2-enopyranosyl compound 87 to give product 89 having a tetrahydrofuranyl ring \textit{cis}-fused at C-1 and C-2 in good yield (Scheme 16). The crucial final ring scission of the bicyclic acetal 89 was performed with acetyl chloride in the presence of a catalytic amount of CoCl\textsubscript{2} to give compound 90 in good yield.
Scheme 16 i) HOCH₂CH₂Cl, BF₃·Et₂O, toluene, rt; ii) n-Bu₃SnH, AIBN, toluene, reflux; iii) CoCl₂, MeCOCl, MeCN, 0 °C, then hydrolysis on silica gel; iv) HOCH₂C≡CH, NIS, MeCN, rt; v) n-Bu₃SnH, AIBN, toluene, reflux

Other recent related work described complementary reactions in which the initial radical precursor X is centred on the pyranosidic ring (C-2) and the radical acceptor (C≡C) is located on the glycosidic side chain.⁸¹ The radical precursor 91 was prepared, mainly as an α-isomer, by reaction of tri-O-acetyl-glucal 86 with propargylic alcohol in the presence of NIS (Scheme 16). The anticipated product 93 having a tetrahydrofuran ring cis-fused at C-1 and C-2 was isolated in good yield following radical cyclization. The reduced product resulting from reduction of the initial radical 92 by Bu₃SnH was not detected with the 5-exo product. However 6-exo cyclization using a longer tether did produce the reduced compound even at low concentration (0.01M) of Bu₃SnH, as a result of the well-known slower cyclization rate compared to the 5-exo mode. Several other examples of C-2 radical cyclizations have also been reported.⁸⁰,⁸²-⁸⁷
1.6.3 Carbohydrate enolates in C-2 alkylations

1.6.3.1 Reaction of lithium enolates with electrophilic reagents

Ketones possessing at least one α-hydrogen atom adjacent to the carbonyl group can readily form enolates, which behave as ambident nucleophilic reagents. Ketone-enolate alkylation has been widely used for carbon-carbon bond formation in organic synthesis. However, owing to their instability, carbohydrate-derived ketone enolates have not been extensively studied.\(^{52}\)

The polyoxygenated structure of fully protected glycosuloses would be anticipated to be more susceptible to base-catalyzed deprotonation. This has been verified with methyl 4,6-O-benzylidene-2-deoxy-α-D-erythro-hexopyanosid-3-ulose \(94\), which undergoes deuterium exchange at the C-2 axial position to give \(97\) by way of enolate \(95\), 1000 times faster than 4-\(t\)-butylcyclohexanone undergoes analogous exchange (Scheme 17).\(^{88}\) The reaction is also in keeping with the general view that, in the kinetically controlled steps, electrophiles (in these case \(D^+\)), react with carbon from a direction orthogonal to the plane of the enolates which in this case is from the stereoelectronically favoured β-face to give products with the electrophiles axial.\(^{48}\)
Scheme 17 Reagents and conditions: i) D_2O/MeOD, K_2CO_3, THF; ii) n-BuLi, THF, -30 °C; iii) Allyl bromide, HMPA, THF, -30 °C; iv) Methyl bromide, HMPA, THF, -30 °C; v) Et_3N, DMF; vi) NaOMe, MeOH, 0 °C; vii) (a) LDA, THF, -78 °C; (b) Benzyl bromide, HMPA, THF, -20 °C

Alkylation of the same enolate 95 with allyl bromide or methyl bromide gives the 2-C-allyl-2-deoxy- or 2-deoxy-2-C-methylglycosides 70 or 98 (Scheme 17). At first sight, the formation of the branched-chain sugars 70 and 98 with equatorial C-2 allyl or methyl groups appears to contravene the rule of orthogonal attack at the enolate carbon. However these isomers are probably derived by base-catalyzed epimerization of the first-formed axially-alkylated 68 or 99, compounds that have been independently prepared by oxidation of the 3-hydroxyl group in methyl 4,6-O-benzylidene-2-C-allyl-2-deoxy-α-D-altropyranoside 66 or methyl 4,6-O-benzylidene-2-deoxy-2-C-methyl-α-D-altropyranoside, and have been found to isomerize rapidly in a basic medium to give 70 and 98.
Isomerizations of this type are possible with most α-monosubstituted ketones because of the availability of the base sensitive hydrogen atom alpha to the carbonyl, but when such hydrogen atoms are not present, products of axial C-alkylation arise.52 Thus, treatment of 98 with benzyl bromide under the condition given in Scheme 17 gives the branched-chain sugar derivative 100, in which the incoming alkyl group occupies the axial position.89 Isomerization of glycosulose derivatives has been used on many occasions as a means of obtaining rare sugar derivatives.56,62,67

1.6.3.2 Aldol condensation

In aldol reactions, the α-carbon of one aldehyde or ketone molecule adds to the carbonyl carbon of another. Aldol reactions in carbohydrate ketones have been the subject of interest in the hope of developing a convergent strategy for the efficient preparation of arrays with multiple contiguous chiral centres as an alternative to a linear strategy. Methyl 4,6-O-benzylidene-2-deoxy-α-D-erythryo-hexopyranosid-3-ulose 94 is a readily prepared keto-sugar and it has been established that the methoxy group of 94 is remarkably resistant to base-catalyzed β-elimination, as illustrated by its monoalkylation to give the products 70 and 98 (vide supra) and even dialkylation to give 100 (Scheme 17).90

The preferred trajectory for electrophilic attack on enolate 95 is from the β-face, since the anomeric methoxy group impedes attack from the α-face. Hence, an aldol condensation would be expected to give the C-2 axial adduct as the product of kinetic control. Fraser-Reid and co-workers90 have used benzaldehyde, isobutyraldehyde, and a 2-deoxy tetrose, to determine the facial selectivity preferences of the enolate 101 (Scheme 18).
Scheme 18 Reagents and conditions: i) Sodium or potassium bis(trimethylsilyl) amide, −40 °C; ii) ZnCl₂, isobutylraldehyde, −78 °C; iii) ZnCl₂, benzaldehyde, −78 °C; iv) ZnCl₂, 3-(S)-3,4-dihydroxy-3,4-O-isopropylidene butyraldehyde, −78 °C

The aldol products 102-104 were obtained in good yields as the only isomers, in which β-face attack was observed exclusively. It was also noteworthy under the reaction conditions that in situ C-2 epimerization did not occur, as happened in the aforementioned alkylation.⁸⁹ Several other examples of aldol condensation at C-2 have been reported.⁹¹-⁹³

1.6.4 Wittig reactions

The Wittig reaction and its variations are useful methods for producing carbon-carbon double bonds from carbon-oxygen double bonds of aldehydes and ketones. It is accomplished by using nucleophilic carbon available in triphenylphosphorane ylides 105, called triphenylphosphoranes (Ph₃P=CR₁R₂). The reaction is easy to carry out and proceeds under mild conditions. When electron-withdrawing groups are present at the α-position (i.e. =CO₂R₃, CHO, SO₃R₃, etc.), the ylides are more stable, and easier to work with, but they are really only suitable for reactions with aldehydes. Valuable alterations to these ylides come in the form of reagents prepared from phosphonate esters, which possess a more nucleophilic carbon atom in the derived anion 106 because the negative charge cannot be attenuated by delocalization into

\[
\text{Ph₃P}^+\text{CR₁R₂} (105)
\]
\[
(R₂O)_2 P(O)\text{CR₁R₂} (106)
\]
the \(d\)-orbitals of the phosphorus atom.\(^{48}\)

When these ylides are used to convert aldehydes or ketones to alkenes, the reaction is referred to as the Horner-Wadsworth-Emmons reaction. Some control may be exerted over \(E\)- and \(Z\)-selectivity in these reactions by the choice of ylides, solvent and ylide counterion. As a general rule, stabilized ylides (e.g. 105, \(R_1 = \text{CO}_2\text{R}_3\)) and most phosphonate anions 106 give predominantly \(E\)-alkenes. On the other hand, non-stabilized ylides (e.g. 105, \(R_1\) and \(R_2 = \text{H}\) or alkyl substituents), under salt-free conditions in polar, non-protic solvent, give \(Z\)-alkenes in reactions with aldehydes. The anions (e.g. 106, \(R_1 = \text{H}, R_2 = \text{CO}_2\text{Me}, R_3 = \text{CF}_3\text{CH}_2\)) generated from esters of bis(trifluoroethyl)phosphonoacetate by potassium hexamethyldisilazide in the presence of 18-crown-6-ether in THF also give \(Z\)-alkenes in reactions with aldehydes.\(^{48}\)

Wittig and related reagents have been extensively used with sugar derivatives such as uloses,\(^{85,94-96}\) ketoses and particularly aldoses with which they have been successful in producing chain-extended sugars and related compounds. Thus, oxidation of readily available methyl-4,6-\(O\)-isopropylidene-\(\alpha\)-d-glycopyranoside 107 gave the 2-uloside derivative which was subjected to two-carbon homologation using \(\text{Ph}_3\text{P} = \text{CHCO}_2\text{Et}\) in refluxing acetonitrile to afford 108 (Scheme 19).\(^{95}\) Reduction of 108 with LAH in ether at 0 °C produced the allylic alcohol 109.

![Scheme 19](image)

Scheme 19 Reagents and conditions: i) (a) TFAA, DMSO, Et\(_3\)N, DCM, −78 °C; (b) Ph\(_3\)P = CHCO\(_2\)Et, CH\(_3\)CN, reflux; ii) LAH, ether, 0 °C

In another example, silylation of methyl 4,6-\(O\)-benzylidene-\(\alpha\)-d-glucopyranoside with TBDMSCl gave a 3:1 mixture of 110 and 111 respectively (Scheme 20). These two ethers were separated chromatographically and oxidized (PCC, CH\(_2\)Cl\(_2\)) to give the ketones 112 and 113. However, separate treatment of 112 and 113 with Wittig reagent (Ph\(_3\)P = CHCO\(_2\)Me, MeCN, reflux) led surprisingly to exclusive formation of the same C-2 olefin 114 in each case. Repeating the experiments with Ph\(_3\)P = CHCO\(_2\)Et gave the same unexpected results, leading to formation of the olefin 115 from both 112 and 113.\(^{94}\)
The explanation put forward for these observations was that the ketones 112 and 113 equilibrated under the basic conditions of the Wittig reaction, and that the C-2 ketone 113 was the major component of the mixture. However, when this was checked by treating 112 with triethylamine (Et$_3$N, MeCN, reflux, 6 h), 112 was found to be the major component of the mixture being present in a 4:1 ratio with 113. It therefore appeared that the effect that caused the exclusive formation of the C-2 olefin was kinetic in nature. Thus, under conditions of the Wittig reaction, an equilibrium between 112 and 113 is established with 112 as the major component. However, 113 reacts with the Wittig reagent at a faster rate than 112 as the carbonyl group of 113 is less hindered.\textsuperscript{94}

### 1.6.5 Opening of 1,2 cyclopropanes

Cyclopropanes are versatile functional groups in organic synthesis, and cyclopropanation has recently been extended to carbohydrates where several methods have been developed for stereocontrolled cyclopropanation of glycols. In general, zinc-mediated cyclopropanation under modified Simmons-Smith conditions takes place from the same face of the glycal double bond as the C-3 substituent, while cyclopropanation with metal carbenes or dihalocarbenes occurs from the opposite face.\textsuperscript{97}

Cyclopropanated carbohydrates are ideally suited for electrophilic ring opening and this has been extensively investigated.\textsuperscript{97-106} The reaction sequence that applies to the majority of the ring-openings reported is illustrated in Scheme 21, in which the formation of an oxocarbenium ion intermediate leads to nucleophilic attack and formation of substituted sugars.\textsuperscript{97}
Scheme 21 General mechanism for most cyclopropane ring-opening

The use of mercury(II) ion to catalyze the opening of various cyclopropanes has been reported and Heathcock used this strategy in the reaction of cyclopropanated sugars and the synthesis of a 2-C-methyl glucal. Treatment of cyclopropane sugar 116 with mercuric trifluoroacetate in the presence of water provided the organomercurial 117 as a mixture of anomers (Scheme 22). Reductive cleavage of the organomercury intermediate with Bu₃SnH produced the 2-C-methyl 118 in a combined 81% yield. With methanol as a solvent the, the methyl glucosides were obtained in an α:β ratio of 10:1.¹⁰²

Scheme 22 Reagents and conditions: i) Hg(OTf)₂, H₂O, THF, rt; ii) n-Bu₃SnH, AIBN, toluene, reflux

Another example of a metal-induced ring-opening, developed by Madsen, uses catalytic amounts of the platinum complex, Zeise's dimer [Pt(C₅H₅)Cl₂]₂ (Scheme 23).⁹⁷,⁹⁸,¹⁰⁶ The ring opening was achieved with a variety of alcohols to produce 2-C-branched methyl glycoside 120 and other more complex disaccharides. Yields range from 50-97% and very high diastereoselectivities can be obtained at the anomeric centre. The α-glycoside, favoured by the anomeric effect, was the major product regardless of the stereochemistry of the starting cyclopropane.
A suggested reaction sequence for the ring opening involves oxidative addition of the platinum to the cyclopropane to give a platincyclobutane 121 (Scheme 23). Polarization of the carbon-platinum bond provides a stabilized oxocarbenium ion 122, which undergoes nucleophilic attack with the alcohol. Subsequent reductive elimination produces the 2-C-branched glycoside 120 and regenerates the Pt(II) catalyst.

Another recently developed strategy for ring opening of the cyclopropane moiety was originally reported by Danishefsky and co-workers.\textsuperscript{103,104} Both Ley\textsuperscript{101} and Nagarajana\textsuperscript{99} have reported on conversion of the diastereomeric cyclopropanes 116 and 126 using NBS as well as NIS (Scheme 24). Yields of up to 72% and a stereospecific selection for the α-anomer were reported in the slow forming of 125. However, conversion of 126 to 128 occurred rapidly, giving a mixture of anomers 128.
Nagarajana attributed this difference in reactivity and selectivity to an $S_N2$-type ring opening of the more sterically hindered 116 producing the more favoured $\alpha$-glycosides, while formation of 128, in which ring opening is unhindered, presumably involves an $S_N1$-type pathway.

Several other variations of this ring opening strategy have been reported (Scheme 25). Reaction of the cyclopropanated sugars 129 with iodonium bis(s-collidine) perchlorate in dioxane-water leads to the formation of the $\alpha$-methylidenevalerolactones 130 in acceptable yields.\textsuperscript{105} This reaction was shown to proceed through the intermediate iodide 131, which subsequently undergoes elimination and oxidation.
A final example of an electrophilic ring opening is illustrated in Scheme 26 using the ester-substituted cyclopropane 132. The pyranosyl bromide 133 was isolated in 38% yield with a 13:1 (β:α) selectivity, although bromide substitution of the C-3 acetate also occurred.106

Scheme 26 Reagents and conditions: i) 30% HBr in AcOH

1.6.6 Others

Several other methods for C-2 alkylation in carbohydrates derivatives have been reported and these include:

1.6.6.1 Nucleophilic attack at the carbonyl group

A wide variety of nucleophilic reagents have been used to add to a carbohydrate C-2 carbonyl group as a means of synthesizing branched-chain sugars.107-110 Thus, treatment of 113 with excess benzylloxymethyl lithium gave 134 in good yield (Scheme 27).107

Scheme 27 Reagents and conditions: i) Bu3SnCH2OBn, n-BuLi, THF; ii) MeMgl, Et2O
Similarly, treatment of ketone 135 with MeMgI gave 136 in good yield (Scheme 27). The complete stereoselectivity was strongly influenced by the axial methoxy group.

1.6.6.2 C-2 Lithiation / Trapping

Direct lithiation at the α-vinylc position of functionally substituted acrylates has become a versatile tool in organic synthesis because the vinylolithium intermediate is compatible with a variety of other substituents. This approach to the generation of highly reactive intermediates bearing various functional groups has also been extended to direct β-lithiation of α-alkoxy acrylates 137.

Replacement of the carboxylate group by a phenylsulfinyl group (138) as the promoting moiety for β-lithiation has greatly extended the versatility of this methodology because substitution of this group is easily achieved. This methodology has been exhibited in the synthesis of C-2 branched sugars derived from glucose.

The required glucal derivatives were obtained from phenyl tetra-O-benzyl-1-thio-β-D-glucopyranoside. Oxidation with m-CPBA afforded sulfoxide 139, with chirality at the sulfur atom (Scheme 28). Treatment of 139 with LDA provided the phenylsulfinyl glucal 140 via elimination, in good yields, which with a second equivalent of base led cleanly to vinylic lithiation at C-2 to give 141. Reaction of the latter with an aldehyde (MeCHO) gave a mixture of diastereomers 142 in good yield.
Scheme 28 Reagents and conditions: i) LDA, −80 °C; ii) MeCHO, −80 °C; iii) H⁺; iv) (a) Pd / C, H2; (b) Ac₂O, pyridine

Convenient formation of 2-alkylidene lactone 143 was achieved by formal thermal hydroxyl group migration at C-1 with subsequent phenylsulfenic acid elimination. Hydrogenation of the ethylidene lactone with Pd/C as a catalyst occurred exclusively from the less hindered side. Concomitant debenzylation and subsequent acetylation afforded the 2-ethyl-branched lactone 144 with the "manno"-configuration.⁷⁻¹¹

1.6.6.3 Metal glycosylidenes

Different synthetic methods have been developed for the introduction of the ‘Fischer-type carbene functionality’ into a carbohydrates skeleton. The K₂M(CO)₅⁻"dianion’ approach (M = Cr, Mo, W) provides access to metal iminoglycosylidenes. Sugar-derived propynols have been applied to the synthesis of vinylcarbene complexes, which undergo stereoselective C-C bond formation at C-2 in the carbohydrate backbone. The reaction of 1-lithiogluca 146, prepared via transmetalation of the corresponding 1-stannylated glucals 145, with group 6 metal carbonyls is controlled by the substitution pattern of the carbonyl complex (Scheme 29). With a ligand combining good leaving group and good donor properties such as triphenylphosphine or tetrahydrofuran, the lithiogluca adds at the metal to generate vinyl chromate 147 which behaves like an enolate-type pentacarbonyl chromium intermediate.
Scheme 29 Reagents and conditions: i) n-BuLi, -78 °C; ii) Cr(CO)₅THF; iii) Allyl iodide

Enolates such as 147 are valuable intermediates which can be trapped by various electrophiles. Alkylation with allyl iodide resulted in the formation of 2-C-allyl complex 148 in good yield and with excellent diastereoselectivity.¹¹²
CHAPTER 2

RESULTS AND DISCUSSION

According to the retrosynthetic analysis depicted in Scheme 7 (Section 1.5), the synthesis of the target compounds was envisaged as beginning with the introduction of an alkenyl group at C-2 of glucose or mannose followed by its conversion to a suitable glycosyl donor via anomic modification. Resolution of selectively protected *myo*-inositol was then anticipated to provide the correct isomer (d-enantiomer) having a free hydroxyl group at C-1 as a glycosyl acceptor. This could be coupled with the donor with subsequent transformation of the alkenyl group to the desired functional groups. Finally, the biological activities of these analogues would be evaluated.

2.1 Alkylation at C-2 of the sugars

Alkylation at C-2 of the sugar was identified as one of the key challenges in our synthesis of analogues of biosynthetic intermediates of mycothiol. This area has received significant attention in the past few years (see the review on C-2 alkylation of the sugars, Section 1.6). Allyl or methallyl groups were preferred because they can be easily transformed to the desired functional groups present in the target compounds, and two synthetic routes for the introduction of alkenyl groups were investigated, namely, lithium enolate-mediated and free-radical alkylation.

2.1.1 Lithium-enolate alkylation

Methyl 4,6-**O**-benzylidene-2-deoxy-α-D-erythro-hexopyranosid-3-ulose 94 (Figure 15) was identified as a suitable precursor for lithium enolate-mediated alkylation at C-2, and following the literature procedures, two synthetic routes to this starting material were investigated.

![Figure 15](image-url)
2.1.1.1 Synthesis of 94 from tri-\(O\)-acetyl-D-glucal (86)

Tri-\(O\)-acetyl-D-glucal 86 is available commercially, or can be prepared on a large scale from D-glucose 149 by a well-established procedure. Thus, treatment of 149 with acetic anhydride in the presence of sodium acetate as a catalyst afforded \(\beta\)-D-glucopyranose pentaacetate 150 in good yield (Scheme 30).\(^{113}\) The spectroscopic data for 150 was consistent with the assigned structure, with the stereochemistry at C-1 confirmed by a doublet in the \(^1\)H NMR spectrum at \(\delta\) 5.70 for H-1 with a large vicinal diaxial\(^6\) coupling (\(J_{1,2}\) 8.1 Hz).

\[
\text{Scheme 30 Reagents and conditions: } i) \text{Ac}_2\text{O}, \text{NaOAc, reflux, 1 h;} \text{ ii) HBr (30\% in acetic acid), CH}_2\text{Cl}_2, \text{rt, 2 h.}
\]

Treatment of 150 with 30\% HBr in acetic acid at room temperature produced tetra-\(O\)-acetate-\(\alpha\)-D-glucopyranosyl bromide 151 in excellent yield (Scheme 30).\(^{114}\) The \(\alpha\)-bromide is expected from the dominance of the anomeric effect.

The presence of bromide was supported by a downfield shift of the anomeric proton from \(\delta\) 5.70 in 150 to \(\delta\) 6.60 in 151. The stereochemistry at C-1 was assigned on the basis of a moderate axial-equatorial coupling constant (\(J_{1,2}\) 4.0 Hz) for H-1. Compound 151 was found to be unstable at room temperature, and was therefore used immediately in the next step.

Reductive elimination of bromide and the neighboring acetate from 151 with zinc dust in acetic acid at room temperature gave triacetyl glucal 86 in 65\% yield (Scheme 31).\(^{115}\) The use of vitamin B-12 as well as \((\text{CP}_2\text{TiCl})_2\) as a reductive catalyst has been reported.\(^{116,117}\) However, zinc was preferred because it is cheap and readily available. The anomeric proton signal of 86 at \(\delta\) 6.43 displayed a long-range allylic coupling with H-3, and therefore appeared as a doublet of doublets (\(J_{1,2}\) 6.3 Hz, \(J_{1,3}\) 1.4 Hz).

---

\(^6\) In pyranoid ring, the coupling constant (\(J\)) value for the equatorial-equatorial is generally less than the equatorial-axial, which in turn is less than the axial-axial value.
Zemplén deacetylation of 86 gave the polar D-glucal 152 in quantitative yield (Scheme 31). The absence of acetoxy group signals in the $^1$H NMR spectrum as well as the retention of the enol ether functionality as evident by the $^1$H and $^{13}$C NMR spectra supported the assigned structure.

Scheme 31 Reagents and conditions: i) Zn, AcOH, rt, 2 h; ii) NaOMe, MeOH-CH$_2$Cl$_2$, rt, 18 h; iii) HCl (2.5% in MeOH), 60 °C, 1 h; iv) Ac$_2$O, pyridine, rt, 16 h

Treatment of 152 with 2.5% HCl in methanol gave methyl 2-deoxy-α-D-arabino-hexopyranoside 153 in poor yield (8%) (Scheme 4). The low yield was presumably due to competing reactions as judged by tlc analysis of the product mixture, which is consistent with reports that facile conversion to furan derivatives is possible when this reaction is carried out under mild conditions. Unprotected glycoside 153 gave poorly resolved NMR spectra, and was acetylated to produce the fully characterizable methyl tri-O-acetyl-2-deoxy-α-D-arabino-hexopyranoside 154a in excellent yield (Scheme 31).

The presence of three acetoxy groups and the anomeric methoxy group in 154a were evident from the $^1$H NMR spectrum. The α-stereochemistry of 154a at C-1 was confirmed by the absence of a large diaxial coupling constant for H-1 in the $^1$H NMR spectrum. Furthermore, the $^1$H NMR spectrum displayed signals at δ 2.27-2.20 (ddd, $J$ 12.9, 5.4, 1.2 Hz) for the equatorial H-2 and δ 1.84-1.75 (ddd, $J$ 12.9, 11.7, 3.6 Hz) for the axial H-2, thus confirming that C-2 was deoxygenated.

Since the hygroscopic character of D-glucal 152 seemed to contribute to the poor yield in the glycosylation, the order of events was changed. Using a procedure of Sabesan, acetylated glucal 86 was subjected to direct treatment with methanol in the presence of cation exchange resin (AG
50W × 8 H⁺, 50-100 mesh) and LiBr at room temperature to give an anomeric mixture of methyl tri-O-acetyl-2-deoxy-D-arabino-hexopyranosides 154a and 154b (2:1, by ¹H NMR) in a combined 41% yield (Scheme 32), accompanied by some unreacted starting material. The desired α-anomer 154a was obtained after separation by column chromatography. Spectroscopic data of 154a was in agreement with the literature values¹²¹ and characterization was carried out as before.

**Scheme 32 Reagents and conditions:** i) LiBr, AG50W-X8 (H⁺), ms, MeOH, rt, 18 h (154a:154b = 2:1)

Zemplén deacetylation of 154a at room temperature afforded methyl glycoside 153 which upon subsequent treatment with freshly distilled benzaldehyde in the presence of zinc chloride for 3 days gave methyl 4,6-benzylidene-2-deoxy-α-D-arabino-hexopyranoside 155 in excellent overall yield (Scheme 33).¹¹⁹ The ¹H NMR spectrum of 155 displayed diagnostic signals at δ 7.50-7.35 (5 H, m) for the aromatic protons and a singlet at δ 5.55 for the benzylic proton.

**Scheme 33 Reagents and conditions:** i) NaOMe, MeOH-CH₂Cl₂, rt, 18 h; ii) Benzaldehyde, ZnCl₂, rt, 3 days, iii) Jones oxidation

Jones oxidation of 155 gave methyl 4,6-benzylidene-2-deoxy-α-D-erythro-hexopyranosid-3-uloside 94 in 51% yield (Scheme 33).¹¹⁴ In this reaction the starting material and product had the same Rf value (tlc), making it difficult to judge the progress of the reaction. However, changing the reagent
for visualizing components on the tlc plate from acidified ammonium ceric sulfate to acidified anisaldehyde revealed a colour difference, with the starting material showing up brown and the product green.

The $^1$H NMR spectrum of 94 displayed a doublet at $\delta$ 4.28 for H-4 with a large diaxial coupling constant $J_{4,5}$ of 9.9 Hz, thus confirming the absence of a proton at C-3. Particularly noteworthy was the absence of coupling between H-1 and H-2$_{eq}$ indicating the H$_1$-C$_1$-C$_2$-H$_{2eq}$ torsion angle to be $\sim$90°. Thus, the signal for H-1 appeared as a doublet at $\delta$ 5.12 with a coupling constant $J_{1,2ax}$ of 4.3 Hz while the signal for H-2$_{ax}$ appeared at $\delta$ 2.81 as a doublet of doublets ($J_{2,2}$ 14.5, $J_{1,2}$ 4.3 Hz) and that for H-2$_{eq}$ at $\delta$ 2.64 as a doublet ($J_{2,2}$ 14.5 Hz) due to geminal coupling.

The $^{13}$C NMR spectrum of 94 was also useful for assigning the structure. A new signal at $\delta$ 197.39 confirmed the formation of the ketone, with the corresponding disappearance of the signal at $\delta$ 65.90 for C-3 in alcohol 155. In addition, its IR spectrum displayed an absorption at $\nu_{max}$ 1750 cm$^{-1}$ for the (C=O) stretch.

2.1.1.2 Synthesis of 94 from D-mannose (156)

An alternative route to the synthesis of the desired 3-ulose was via base-induced decomposition of the benzylidene acetal of methyl-$\alpha$-D-mannopyranoside, which can be readily prepared from commercially available methyl-$\alpha$-D-mannopyranoside 157. Compound 157 could however, also be prepared on a large scale by treatment of D-mannose 156 with methanol and an acidic ion-exchange resin (Dowex-50, H$^+$, 50-100 mesh), giving 157 in 63% yield (Scheme 34).122

For characterization purposes, a portion of 157 was acetylated with acetic anhydride in the presence of sodium acetate as a catalyst to produce methyl tetra-O-acetyl-$\alpha$-D-mannopyranoside 158 in good yield (Scheme 34).122 The stereochemistry at C-1 was assigned on the basis of a signal at $\delta$ 4.68 in the $^1$H NMR spectrum for H-1 which appeared as a doublet with a small equatorial-equatorial coupling constant ($J_{1,2}$ 1.7 Hz).
Following the procedure of Horton,\textsuperscript{123} compound 157 was then treated with \(\alpha\),\(\alpha\)-dimethoxytoluene to give methyl dibenzylidene-\(\alpha\)-\(\delta\)-mannopyranoside 96 in moderate yield (Scheme 34). The \(^1\)H NMR spectrum confirmed that the product was a mixture of diastereomers which could be fractionally recrystallized from propyl alcohol to give a single diastereomer in good yield. Concentration of the mother liquor followed by recrystallization from ethanol gave the other diastereomer.

The \(^1\)H NMR spectrum for both diastereomers displayed diagnostic signals at \(\delta\) 7.59-7.34 (10 H, m) which integrated for two phenyl groups. Furthermore, the \(^1\)H NMR spectrum for both diastereomers displayed singlets for H-1 at \(\delta\) 5.01 (diastereomer 96a) and \(\delta\) 5.08 (diastereomer 96b), indicating a zero (or very small) coupling between H-2 and H-1 (equatorial-equatorial). In addition, diastereomer 96a revealed a doublet at \(\delta\) 4.14 for H-2 with a moderate axial-equatorial coupling constant \((J_{2,3} 5.6\text{ Hz})\), thus showing no coupling with the anomeric proton.

Treatment of the dibenzylidene acetals 96 with \(n\)-butyllithium at \(-30^\circ\text{C}\) followed by quenching with water gave ketone 94 in a moderate yield (Scheme 35). This highly regioselective elimination is thought to occur by preferential abstraction of the axial C-3 proton followed by anti-elimination of the axial C-2 substituent to generate the enolate anion 95 with the release of benzaldehyde; the enolate then rearranging to the ketone after protonation.\textsuperscript{123} The spectroscopic and analytical data of this compound were identical with those of material prepared previously.
Ketone 94 was obtained in seven steps from D-glucose 149 via tri-O-acetyl-D-glucal 86 (67% overall yield), and in only three steps from D-mannose 156 (66% overall yield). As a result, synthesis of 94 from D-mannose was preferred on the basis of short synthetic route over that from tri-O-acetyl glucal.

With ketone 94 in hand, attention turned to the possibility of stereoselective alkylation at C-2. Treatment of 94 with LDA at −78 °C in THF, followed by addition of an excess of allyl bromide in the presence of HMPA at low temperature gave benzylidene-2-C-allyl-2-deoxy-α-D-ribo-hexopyranosid-3-ulose 70 in 26% yield, although tlc showed the reaction to be incomplete (Scheme 36). The $^1$H NMR spectrum displayed diagnostic signals for the allyl side-chain at $\delta$ 5.76 (m, H-2'), $\delta$ 2.59 (m, H-1'a) and $\delta$ 2.22 (m, H-1'b), while the $^{13}$C NMR spectrum displayed corresponding signals at $\delta$ 134.90 (C-2'), 117.24 (C-3') and 28.21 (C-1').

The stereochemistry of 70 at the C-2 position was determined from the $^1$H NMR coupling constant for H-1, which appeared as a doublet at $\delta$ 5.01 with a moderate axial-equatorial ($J_{1,2}$ 4.0 Hz)
coupling constant, thus confirming the allyl group to be equatorial. In addition, the IR spectrum displayed an absorption at $v_{\text{max}}$ 1755 cm$^{-1}$ (C=O).

The poor yield (26%) and the incompleteness of the reaction prompted us to carry out an investigation of factors influencing this reaction. The number of equivalents of allyl bromide and LDA were varied as was the temperature. Although the use of HMPA was undesirable, it was unavoidable for this reaction because no reaction was observed (tlc) in its absence. This was rationalized on the basis that HMPA, as a polar aprotic and ion-solvating agent, could stabilize the polar transition-state.$^{124}$

After a number of reactions, it was discovered that the reaction rate was temperature dependent. There was no reaction at $-78 ^\circ$C after 10 hours while a total decomposition was observed (tlc) when the reaction was left at room temperature. In all cases, tlc revealed the presence of starting material and three new products. After separation by column chromatography, the most polar product was identified as 70. The highest yield (32%) of the desired product 70 was obtained when the reaction mixture was left at $-20 ^\circ$C for 2 hours with 1.2 equivalents of LDA and 2.5 equivalents of allyl bromide. In the event of leaving the reaction mixture longer than two hours, the reaction went to completion but the side products (less polar products) were isolated as major components.

The characterization of the side products by NMR spectroscopy was unsuccessful and no conclusive assignment of the structures could be made. However, benzylidene, allylic and methoxy group signals were observed in both compounds ($^1$H NMR), which suggest that dialkylation and/or O-alkylation might have occurred.

In a slightly different method reported by Chaupler,$^{89}$ a mixture of dibenzylidene acetals 96 was treated with $n$-butyllithium followed by trapping of the enolate intermediate 95 with allyl bromide in the presence of HMPA to give 70 in 32% yield (Scheme 37). The characterization of 70 was carried out as before and was in agreement with the structure.
Scheme 37 Reagents and conditions: i) (a) n-BuLi, THF, −30 °C, 15 min (b) HMPA, allyl bromide, −30 °C, 12 h

Reduction of 70 with NaBH₄ at low temperature gave exclusively the undesired axial epimer 159a in excellent yield (Scheme 38) while reduction with LAH gave a mixture of diastereomers 159a and 159b (8:1, by ¹H NMR), also in excellent yield (Scheme 38). The predominance of axial hydroxyl group was explained by the fact that the C-2 equatorial allyl substituent and the axial C-1 methoxy group causes unfavourable steric interactions with the incoming hydride from an axial trajectory (same face), resulting in preferred β-face attack to the undesired epimer.⁹⁰

Scheme 38 Reagents and conditions: i) LiAlH₄, THF, 0 °C, 2 h, 95% (159a:159b = 8:1); or i) NaBH₄, THF-MeOH, −20 to 0 °C, 2 h, 98% (159a only)

The structures of 159a and 159b were supported firstly by the absence of carbonyl absorptions in the IR spectra. In addition, the ¹³C NMR spectrum of 159a displayed a new signal at δ 67.57 (C-3) and a corresponding disappearance of the signal at δ 198.26 for C-3 in 70.

The stereochemistry at C-3 in 159a was determined from the coupling constant for H-4. The ¹H NMR spectrum displayed a signal at δ 3.55 for H-4 which appeared as a doublet of doublets with a large diaxial (J₄,5 9.6 Hz) and moderate axial-equatorial (J₃,4 2.8 Hz) coupling constant, thus confirming the axial epimer.
The fact that C-2 alkylation via the enolate proceeded in poor yield and that reduction of 3-keto-2-C-allyl-2-deoxy-α-D-glucoside 70 favoured the undesired axial epimer with even the least sterically demanding hydride reducing agents, led to abandonment of this synthetic route. Attention was turned instead to stereoselective C-2 alkylation by a free-radical method.

2.1.2 Radical alkylation

In carbohydrate chemistry, compounds containing carbon-halogen or carbon-mercury bonds, thionocarbonate esters of various kinds, nitro-compounds, isocyanides, and phenylthio-and phenylseleno-derivatives are used as radical precursors in the presence of AIBN as initiator. However, carbon-halogen derivatives are the most frequently used because they are readily available. Consequently, the carbon-halogen derivatives were chosen as suitable precursors and the focus turned to the synthesis of different 2-halo sugars.

2.1.2.1 Synthesis of 2-halo sugars

Several methods have been reported for the synthesis of 2-halo sugars. A particular consideration in our synthesis was the requirement for introduction of an equatorial alkyl group at C-2 and the observation from the literature that stereoselectivity in intermolecular radical alkylation at C-2 depends on the configuration of the substituents at C-1 and C-3 of the 2-halo sugar, rather than on the orientation of the halogen. Equatorial alkylation is favoured when both C-1 and C-3 substituents are equatorial (see the review on C-2 intermolecular radical alkylation, Section 1.6.2.1).

With the above aim in mind, 2-halo sugars with different anomic groups were synthesized using literature procedures.

2.1.2.1(a) Synthesis of tetra-O-acetyl-2-bromo/iodo-2-deoxy-β-D-glucopyranose (78b and 79)

From the range of reported approaches to 2-bromo or 2-iodo sugars, two synthetic methods were investigated: (a) from tri-O-acetyl glucal 86 and (b) from mannose 156 via 2-hydroxy mannopyranose 160.

In the first method, tri-O-acetyl glucal 86 was treated with NBS and acetic acid to produce a mixture of tetra-O-acetyl-2-bromo-α-D-mannopyranose 78a and tetra-O-acetyl-2-bromo-β-D-
glucopyranose 78b (2:1, by \( ^1\)H NMR) in excellent combined yield (Scheme 39).\textsuperscript{125} The diastereomers were easily separated by column chromatography and the spectroscopic data of 78a and 78b were in agreement with the literature values.

![Diagram](image_url)

**Scheme 39** Reagents and conditions: i) NBS, AcOH, rt, 4 h (78a:78b = 2:1)

The stereochemical assignments at C-1 and C-2 of 78a were made from the coupling constants for H-1, H-2 and H-3 in the \( ^1\)H NMR spectrum. H-1 appeared as a doublet at \( \delta \) 6.30 with a small equatorial-equatorial (\( J_{1,2} \) 1.9 Hz) coupling constant while the signal for H-3 appeared at \( \delta \) 5.18 as a doublet of doublets with a large diaxial (\( J_{3,4} \) 9.7 Hz) and moderate axial-equatorial (\( J_{2,3} \) 4.0 Hz) coupling constants. H-2 appeared as a doublet of doublets at \( \delta \) 4.42 with moderate axial-equatorial (\( J_{2,3} \) 4.0 Hz) and small equatorial-equatorial (\( J_{1,2} \) 1.9 Hz) coupling constants, thus confirming the \( \alpha \)-mannopyranose diastereomer 78a. The stereochemistry of 78b at C-1 and C-2 was also determined from the \( ^1\)H NMR coupling constants for H-1, H-2 and H-3, which all exhibited large axial-axial couplings consistent with the \( \beta \)-gluco-configuration.

In a second approach, synthesis of the 2-bromo and 2-iodo tetraacetates was envisaged from selectively unprotected \( D \)-mannopyranose derivative 160 via formation of the 2-triflate and subsequent displacement by halide ion. Selectively unprotected sugar 160 could be obtained in a one-pot synthesis by a direct acetylation of mannose 156, followed by anomeric bromination using phosphorus tribromide and acetyl migration in an overall yield of 19\% (Scheme 40).\textsuperscript{136} Control of temperature was found to be crucial in this reaction. However, yields were very low and difficult to reproduce, attention turned to the synthesis of the same compound via the orthoester 161 (Scheme 41).

![Diagram](image_url)

**Scheme 40** Reagents and conditions: i) (a) \( \text{Ac}_2\text{O}, \text{HClO}_4, 40-50 \degree\text{C}, 1 \text{ h} \) (b) \( \text{PBr}_3, 20-25 \degree\text{C} \) (c) \( \text{H}_2\text{O}, 25 \degree\text{C}, 1.5 \text{ h} \) (d) \( \text{NaOAc-3H}_2\text{O}, 35-40 \degree\text{C}, 25 \text{ min} \)
Thus, D-mannose 156 was acetylated and subjected to anomic bromination using 30% HBr in acetic acid. Treatment of the crude product with anhydrous ethanol and lutidine gave the orthoester 161 as a crystalline material in 67% yield from mannose (Scheme 41). The orthoester 161 was then subjected to a controlled acetolysis to afford 160 in 31% yield (Scheme 41).

![Scheme 41 Reagents and conditions: i) (a) Ac₂O, NaOAc, 100 °C, 1 h (b) HBr (30% in AcOH), CH₂Cl₂, rt, 3 h (c) lutidine, EtOH, CH₃CN, rt, 15 h; ii) 1 N HCl, acetone, rt, 10 min](image)

The spectroscopic and analytical data for 160 were consistent with the literature values and the downfield shifts for H-3, H-4, and H-6 compared to H-2 confirmed H-2 as unacetylated. The ^1^H NMR spectrum displayed signals for 4 acetoxy groups and the IR spectrum displayed an absorption at ν_max 3450 cm⁻¹ (OH).

The stereochemistry of 160 at C-1 and C-2 was determined from the coupling constants for H-1 and H-3 in the ^1^H NMR spectrum. The signal at δ 5.78 for H-1 appeared as a doublet with a small equatorial-axial (J₁₂ 1.2 Hz) coupling constant, while the signal at δ 5.02 for H-3 appeared as a doublet of doublets with a large diaxial (J₃₄ 9.7 Hz) and a moderate axial-equatorial (J₁₂ 2.8 Hz) coupling constant, thus confirming the β-mannopyranoside 160.

Compound 160 was treated with triflic anhydride in dichloromethane at low temperature to give triflate 162 in excellent yield (Scheme 42). A downfield shift of the H-2 signal in the ^1^H NMR spectrum from δ 4.18 in 160 to δ 5.13 and a shift in the ^1^C NMR spectrum of C-2 from δ 68.44 in 160 to δ 81.21 confirmed the presence of the triflate at C-2.

S₉,₂ displacement of the triflate in 162 by bromide ion in refluxing benzene gave 2-bromogluco derivative 78b in excellent yield after chromatography and with inversion of configuration (Scheme 42). The spectroscopic and analytical data of 78b were identical to those of material previously isolated.
Scheme 42 Reagents and conditions: i) Triflic anhydride, pyridine, CH₂Cl₂, 0 °C to rt, 2 h; ii) Bu₄NBr, benzene, reflux, 2 h; iii) Bu₃NI, benzene, reflux, 2 h

Similar treatment of triflate 162 with tetrabutylammonium iodide gave 2-ido pentaacetate 79 in excellent yield (Scheme 42). An upfield shift of the H-2 signal in the ¹H NMR spectrum from δ 5.13 in 162 to δ 3.98 and a shift in the ¹³C NMR spectrum of C-2 from δ 81.21 in 162 to δ 25.68 confirmed the displacement of triflate with iodide.

The stereochemistry of 79 at C-2 was determined from the ¹H NMR coupling constants for H-1, H-2 and H-3, which all exhibited large axial-axial couplings consistent with the β-gluco-configuration.

2.1.2.1(b) Synthesis of methyl 3,4,6-tri-O-acetyl-2-bromo-2-deoxy-β-D-glucopyranoside (163b)

The 2-halo sugars were also synthesized as methyl glycosides as alternative substrates for subsequent radical alkylation reactions. Thus, treatment of tri-O-acetyl glucal 86 with NBS in methanol led to a mixture containing methyl tri-O-acetyl-2-bromo-α-D-mannopyranoside 163a and methyl tri-O-acetyl-2-bromo-β-D-glucopyranoside 163b (2:1, by ¹H NMR) in excellent yield (Scheme 43). Crystallization of the mixture with methanol gave the minor diastereomer 163b as crystals and column chromatography of the mother liquor afforded 163a. The spectroscopic data of 163a and 163b were in agreement with those reported in the literature, and the stereochemistry at C-1 and C-2 was assigned by analogy to 78a and 78b above.
2.1.3 Synthesis of 2-C allyl and methallyl sugars

After synthesizing a range of 2-halo sugars as precursors for intermolecular radical alkylation, the stage was set for establishing conditions for efficient and stereoselective alkylation at C-2. Using a procedure by Giese, 73 2-bromo tetraacetate 78b was refluxed with allyltributylstannane in benzene in the presence of AIBN to give a mixture of 2-C-allyl glucopyranose 81a and 2-C-allyl mannopyranose 81b (9:1, by 1H NMR) in 87% yield (Scheme 44). Repeating the reaction with 2-iodo tetraacetate 79 gave the same mixture but in 42% yield. The equatorially alkylated product predominated as predicted due to the presence of equatorial substituents at C-1 and C-3 (see the review on C-2 intermolecular radical alkylation of sugars, Section 1.6.2.1). Fractional crystallization of the mixture from diethyl ether-pentane afforded the desired major diastereomer 81a in 42% yield.

The spectroscopic data of 81a and 81b was consistent with the structures and literature values. For the desired major diastereomer 81a, the 1H NMR spectrum displayed a diagnostic signal at δ 5.76-5.65 (m) for H-2′ while the 13C NMR spectrum displayed signals at δ 133.58 (C-2′), 117.85 (C-3′) and 31.06 (C-1′) typical for an allyl moiety. The diagnostic signals for minor diastereomer 81b were analogous to those in 81a.

The key issue of the stereochemistry of diastereomers 81a and 81b at C-2 was determined from the coupling constants for H-1 in these compounds. The 1H NMR spectrum of the major diastereomer 81a displayed a doublet at δ 5.56 for H-1 with a large diaxial (J1,2 8.8 Hz) coupling...
constant, thus confirming an equatorial orientation of the allyl group. The $^1$H NMR spectrum for the minor diastereomer **81b** displayed a doublet at $\delta$ 5.90 for H-1 with a moderate equatorial-axial ($J_{1,2}$ 2.4 Hz) coupling constant consistent with an axial orientation of the allyl group at C-2.

Having successfully synthesized the C-2 allyl glucopyranose, attention turned to the synthesis of methallyl glucopyranoses in a similar manner. Treatment of 2-bromo tetraacetate **78b** with methallyltributylstannane in the presence of AIBN produced a mixture of 2-C-methallyl glucopyranose **82a** and 2-C-methallyl mannopyranose **82b** (7:1, by $^1$H NMR) in excellent yield (Scheme 45). Once again, the predominance of the equatorial methallyl diastereomer was noted. Attempts to separate the diastereomers by column chromatography were unsuccessful, but the desired major diastereomer **82a** crystallized slowly on standing at low temperature and recrystallization from petroleum ether afforded a single diastereomer **82a** in 48% yield.

![Scheme 45](image)

**Scheme 45 Reagents and conditions: i) Methallyltributylstannane, AIBN, benzene, reflux, 16 h (82a:82b = 7:1)**

The presence of the methallyl group was evident in both $^1$H and $^{13}$C NMR spectra. The $^1$H NMR spectrum for the major diastereomer **82a** displayed a diagnostic doublet at $\delta$ 4.67 ($J_{\text{gem}}$ 1.1 Hz) for H-4', a doublet at $\delta$ 4.63 ($J_{\text{gem}}$ 1.1 Hz) for H-4, and a broad singlet for the adjacent methyl group at $\delta$ 1.73, for the methallyl group. In addition, the $^{13}$C NMR spectrum displayed signals at $\delta$ 142.34 (C-2'), 112.22 (C-4'), 37.07 (C-1') and 21.65 (C-3') for the methallyl group. The diagnostic signals for the minor diastereomer **82b** were analogous to those in **82a**.

As before, the stereochemistry of diastereomers **82a** and **82b** at C-2 was determined from the coupling constant for H-1. The $^1$H NMR spectrum for the major diastereomer **82a** displayed a doublet at $\delta$ 5.55 for H-1 with a large diaxial ($J_{1,2}$ 9.0 Hz) coupling constant, thus confirming the equatorial orientation of the methallyl group, while the $^1$H NMR spectrum for the minor diastereomer **82b** displayed a corresponding doublet at $\delta$ 5.84 with a moderate equatorial-axial ($J_{1,2}$ 2.4 Hz) coupling constant, thus confirming the axial orientation of the methallyl group.
Ozonolysis\textsuperscript{138} of the mixture of \textbf{82a} and \textbf{82b} followed by reduction with DMS gave a mixture of 2-oxopropyl glucopyranoside \textbf{164a} and 2-oxopropyl mannopyranoside \textbf{164b} (7:1, by \textsuperscript{1}H NMR) in excellent yield (Scheme 46).\textsuperscript{77} As before, separation of diastereomers by column chromatography was unsuccessful, but crystallization from diethyl ether afforded \textbf{164a} as a single diastereomer in 48% yield.

![Scheme 46 Reagents and Conditions](image)

The \textsuperscript{1}H NMR spectrum of \textbf{164a} displayed a diagnostic signal at \(\delta 2.04\) (3 H, s) for the \(\alpha\)-keto methyl group. The downfield shift of these protons from \(\delta 1.73\) in \textbf{82a} confirmed the presence of a carbonyl group at C-2'. The \textsuperscript{13}C NMR spectrum provided further confirmation with a new signal at \(\delta 204.94\) for C-2' having shifted from \(\delta 142.34\) for C-2' in \textbf{82a}.

A similar methallylation\textsuperscript{77} reaction was then carried out on methyl 2-bromo triacetate \textbf{163b}, giving a mixture of methyl 2-C-methallyl glucopyranoside \textbf{165a} and methyl 2-C-methallyl mannopyranoside \textbf{165b} (5:1, by \textsuperscript{1}H NMR) in excellent yield (Scheme 47). The predominance of the equatorial methallyl diastereomer was again in accordance with the trend reported by Giese and co-workers.\textsuperscript{70} However, several attempts to separate the diastereomers by column chromatography or crystallization were unsuccessful.

![Scheme 47 Reagents and Conditions](image)
The spectroscopic data of 165a and 165b was consistent with the assigned structures and the presence of the methallyl group was evident in both the $^1$H and $^{13}$C NMR spectra. The stereochemistry of the diastereomers at C-2 was assigned by analogy to that in 82a and 82b above.

Ozonolysis$^{77,138}$ of compound 165a and 165b followed by reduction with dimethyl sulfide (DMS) gave a mixture of methyl 2-oxopropyl glucopyranoside 166a and methyl 2-oxopropyl mannopyranoside 166b (5:1, by $^1$H NMR) in excellent yield (Scheme 48). Attempts to separate the diastereomers by column chromatography were unsuccessful but crystallization was achieved after azeotropic distillation with ethanol followed by petroleum ether. A careful recrystallization from ethyl acetate-petroleum ether at room temperature afforded major diastereomer 166a in 48% yield, while column chromatography of the mother liquor followed by recrystallization afforded the minor diastereomer 166b as crystals.

Scheme 48 Reagents and conditions: i) (a) $\text{O}_3$, CH$_2$Cl$_2$-MeOH (10:1), $-78$ °C, 40 min (b) DMS, $-78$ °C to rt, 20 h (166a:166b = 5:1)

The spectroscopic data of 166a and 166b supported the assigned structures and configurational assignments were made by analogy to that of 164a just mentioned.
2.2 Synthesis of the glycosyl donor

According to the retrosynthetic analysis in Scheme 7, two types of glycosyl donor were envisaged as suitable precursors for glycosylation (Figure 16): (a) glycosyl donors of type A, bearing the alkenyl group, and (b) glycosyl donors of type B, with an oxygenated side-chain. In a quest to synthesize a suitable donor that would promote good stereoselectivity during glycosylation, both types were investigated.

![Diagram of type A and type B glycosyl donors]

**Figure 16** Envisaged glycosyl donors

In order to synthesize the glycosyl donor of type B, stereoselective reduction of ketone (164a or 166a) and protection of the resulting alcohol was required before activation at the anomic position.

Thus, reduction of 164a with NaBH₄ was initially tried but proved to be problematic (Scheme 49) with tlc of the reaction mixture indicating the formation of several products with only traces of the desired product 167 (**H NMR**).

![Diagram of 164a and 167 with reaction arrow]

**Scheme 49** Reagents and conditions: i) NaBH₄, THF-MeOH, −20 °C, 2 h

Since there was some evidence for instability of anomic acetate in the presence of hydride reducing agents, attention turned to the possibility of stereoselective reduction of compound 166a, bearing a methoxy group at the anomic position. Benzylated analogue 168, which is compatible with several reducing agents, was prepared in a one-pot synthesis from acetylated methyl 2-
oxopropyl glucopyranoside 166a by treatment with NaOH (50%), tert-butyl alcohol, tetra-n-butylammonium hydrogen sulphate and benzyl bromide at 50 °C, yielding 168 in 70% yield (Scheme 50).

The $^1$H NMR spectrum of 168 displayed diagnostic signals at $\delta$ 7.40-7.18 (15 H, m) for the aromatic protons while the $^{13}$C NMR spectrum displayed a diagnostic signal at $\delta$ 207.83 confirming retention of the carbonyl group at C-2'. In addition, the IR spectrum displayed an absorption at $\nu_{\text{max}}$ 1705 cm$^{-1}$ for the carbonyl group.

Scheme 50 Reagents and conditions: i) NaOH (50%), [CH$_3$(_CH$_2$)$_3$]$_4$N(HSO$_4$), (CH$_3$)$_3$COH, BnCl, benzene, 50 °C, 24 h; ii) See Table 2; iii) (a) NaOMe, MeOH-CH$_2$Cl$_2$, rt, 5 h (b) BnBr, NaH, THF, reflux, 4 h; iv) BnBr, NaH, THF, reflux, 5 h

Ketone 166a and its benzylated analogue 168, were then exposed to a variety of reducing agents and conditions (Table 3) producing the alcohols (169 and 170) in good to excellent yields, but generally with moderate to poor selectivity as judged by $^1$H NMR spectroscopy of the product mixtures (Scheme 50).
Table 3: Results of the reduction of ketones 166a and 166b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Reducing agent (equiv)¹⁰⁴</th>
<th>Solvent</th>
<th>Temp (time)</th>
<th>Alcohol (yield%)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>166</td>
<td>NaBH₄ (10)¹⁰⁰</td>
<td>THF-MeOH</td>
<td>−30 °C (2 h)</td>
<td>169 (99%)</td>
<td>2 : 1</td>
</tr>
<tr>
<td>2</td>
<td>166</td>
<td>K-Selectride® (2)¹⁴¹,¹⁴²</td>
<td>THF</td>
<td>−78 °C (2 h)</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>3</td>
<td>166</td>
<td>Zn(BH₄)₂ (2)¹⁴³,¹⁴⁴</td>
<td>Et₂O</td>
<td>0 − 25 °C (18 h)</td>
<td>169 (75%)</td>
<td>1 : 1</td>
</tr>
<tr>
<td>4</td>
<td>166</td>
<td>NaBH₄-CeCl₃¹⁴⁵,¹⁴⁶</td>
<td>THF-MeOH</td>
<td>−30 °C (2.5 h)</td>
<td>169 (78%)</td>
<td>1.2 : 1</td>
</tr>
<tr>
<td>5</td>
<td>166</td>
<td>LiAlH₄(O-t-Bu)₂¹⁴⁷,¹⁴⁸</td>
<td>THF</td>
<td>−30 °C (2.0 min)</td>
<td>170 (98%)</td>
<td>1.2 : 1</td>
</tr>
<tr>
<td>6</td>
<td>168</td>
<td>LiAlH₄ (1.2)¹⁴¹,¹⁴²</td>
<td>THF</td>
<td>−78 °C (20 min)</td>
<td>170 (99%)</td>
<td>1.7 : 1</td>
</tr>
<tr>
<td>7</td>
<td>168</td>
<td>DibalH (1.2)¹⁴¹,¹⁴²</td>
<td>Toluene</td>
<td>−78 °C (15 min)</td>
<td>170 (99%)</td>
<td>----</td>
</tr>
<tr>
<td>8</td>
<td>168</td>
<td>L-Selectride® (2)¹⁴¹,¹⁴²</td>
<td>THF</td>
<td>−78 °C (15 min)</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>9</td>
<td>168</td>
<td>CBS¹⁵⁰</td>
<td>Toluene-THF</td>
<td>40 °C (15 min)</td>
<td>170 (99%)</td>
<td>2 : 1</td>
</tr>
</tbody>
</table>

Interestingly, the best selectivity (2:1) was obtained with both NaBH₄ and CBS (Oxazaborolidine-catalysts, B-H-4),¹⁵⁰,¹⁵¹ the former representing a substrate-controlled process and the latter presumably via a combination of reagent- and substrate-control in the reduction. While these preliminary results appear to suggest that the chiral environment is too remote from the carbonyl group to direct the reduction, it may be that deprotection of one or other of the ring hydroxyl groups could encourage a chelation-controlled reduction. Varying the protecting groups did not seem to have a marked effect on the selectivity, although consistently higher yields of the alcohol were observed in reactions of the benzylated ketone 168.

The spectroscopic data of alcohols 169 and 170 supported the assigned structures. For compound 169a, the ¹H NMR spectrum displayed a diagnostic signal at δ 3.78 (m) for H-2' while the signal for the methyl protons appeared as a doublet at δ 1.12 (3 H, J 6.4 Hz), thus confirming reduction had taken place. In addition, the ¹³C NMR spectrum of 169a displayed a new signal at δ 67.01 for C-2' and a corresponding disappearance of the signal at δ 206.08 for C-2' in 166. The diagnostic signals for diastereomer 169b were analogous to those in 169a.

For major diastereomer 170a, the ¹H NMR spectrum displayed a diagnostic signal at δ 3.87 (m) for H-2' while a doublet at δ 1.13 (3 H, J 6.3 Hz) for the methyl protons confirmed reduction of the carbonyl group. In addition, the ¹³C NMR spectrum displayed a new signal at δ 67.14 for C-2' and a corresponding disappearance of the signal at δ 207.83 for C-2' found in 168. The diagnostic signals for diastereomer 170b were analogous to those in 170a. No attempt was made to determine the absolute configuration at C-2' for the diastereomers.

Not only was there no evidence of stereoselective reduction under any of these reaction conditions, but the isomeric mixtures were inseparable and attempts to achieve separation via derivatization...
(as esters or ethers 171) also failed (Scheme 50). As a result, further work in this series was discontinued. Attention was rather focused on the preparation of glycosyl donor of type A with the alkenyl side-chains (81a and 82a), with a view to glycosylating these compounds and subsequently modifying the alkenyl groups.

Over the years, several anomic leaving groups and activation methods for effective glycosylation have been developed. In our synthesis, glycosyl fluorides were preferred over bromide, chloride, imidates, etc., because of their higher thermal and chemical stability, ease of synthesis, and extensive glycosylation with inositol derivatives. Having such favourable synthetic attributes has led to the development of a number of synthetic methods for their preparation. However in this work, only two methods were investigated, namely preparation of glycosyl fluorides from phenyl thioglycosides with DAST-NBS and fluorination of the free anomic hydroxyl with DAST.

In the thioglycoside approach, 2-C-allyl pentaacetate 81a was treated with PhSSiMe3 in the presence of BF3·Et2O to give an inseparable mixture (α:β = 2:1, by 1H NMR) of thioglycosides 172 in 83% yield (Scheme 51). The 1H NMR spectrum of 172 displayed diagnostic signals at δ 7.54-7.38 (5 H, m) for the phenyl group. The configurations of the anomers were distinguished by the coupling constant of H-1. Thus for the α-anomer, the 1H NMR spectrum displayed a doublet for H-1 at δ 5.45 with a moderate axial-equatorial (J1,2 4.8 Hz) coupling constant while for the β-anomer, the 1H NMR spectrum displayed a doublet at δ 4.54 with a large diaxial (J1,2 10.8 Hz) coupling constant.

![Scheme 51 Reagents and conditions: i) PhSSiMe3, BF3·Et2O, CH2Cl2, 0 °C to rt, 18 h (α:β = 2:1); ii) DAST, NBS, CH2Cl2, 0 °C, 1 h](image-url)

Thioglycoside 172 was treated with DAST in the presence of NBS with the intention of replacing the −SPh with fluoride (Scheme 51). However, the isolated polar product displayed aromatic signals in both the 1H and 13C NMR spectra, while the allylic signal for H-2′ at δ 5.80 was absent. It was concluded that bromination at the allyl double bond might have occurred, so in order
to avoid the use of NBS or NIS, the thioglycoside approach was abandoned in favour of direct fluorination of free anomic hydroxyl.

Thus in an alternative approach, selective deacetylation of 81a with hydrazine acetate\textsuperscript{161} in DMF gave 2-C-allyl triacetate 174 (α:β = 2:1, by $^1$H NMR) in excellent yield (Scheme 52). The $^1$H and $^{13}$C NMR spectra of 174 revealed the presence of only three acetoxy groups and the stereochemistry of the anomers was evident by $^1$H NMR coupling constants of anomic protons. Thus for the α-anomer, the $^1$H NMR spectrum displayed a broad singlet at δ 5.24 for H-1 while for the β-anomer, the $^1$H NMR spectrum displayed a doublet at δ 4.67 with a large diaxial ($J_{1,2} 8.4$ Hz) coupling constant.

Scheme 52 Reagents and conditions: i) Hydrazine acetate, DMF, 60 °C, 1 h (α:β = 2:1); ii) DAST, THF, rt, 30 min (α:β = 2:1)

Treatment of 174 with excess DAST\textsuperscript{154,155} gave fluoride 173 as an inseparable mixture of anomers (α:β = 2:1, by $^1$H NMR) in excellent yield (Scheme 52), however separation of the anomers was not necessary for the next step in the sequence. The spectroscopic data of 173 was in agreement with the assigned structure, and the presence of fluorine and the allyl group was confirmed by $^{19}$F, $^1$H and $^{13}$C NMR spectra.

The configurations of anomers were determined from their H-1 coupling constants. Thus for the α-anomer, the $^1$H NMR spectrum displayed a doublet of doublets at δ 5.66-5.52 for H-1 with a very large fluorine-H-1 coupling ($J_{1,F} 51.0$ Hz) and a moderate axial-equatorial ($J_{1,2} 2.6$ Hz) coupling constant. Fluorine-carbon coupling was also observed in the $^{13}$C NMR spectrum, which displayed a diagnostic doublet at δ 110.07 ($J_{1,F} 223.0$ Hz) for C-1. In addition, the $^{19}$F NMR spectrum displayed a diagnostic doublet of doublets at δ -146.59 for the anomic fluorine with a fluorine-H-1 coupling constant $J_{1,F}$ of 51.0 Hz and a fluorine-H-2 coupling constant $J_{2,F}$ of 29.75 Hz.

For the β-anomer, the $^1$H NMR spectrum displayed a signal for H-1 at δ 5.28-5.14 which appeared as a doublet of doublets with a very large fluorine-H-1 coupling ($J_{1,F} 51.2$ Hz) and a large diaxial ($J_{1,2} 7.2$ Hz) coupling constant. Fluorine-carbon coupling was also observed in the $^{13}$C NMR
spectrum which displayed a diagnostic doublet at $\delta$ 111.56 ($J_{1,F}$ 214.0 Hz) for C-1. In addition, the $^{19}$F NMR displayed a broad doublet at $\delta$ -133.55 for fluorine with a fluorine-H-1 coupling constant $J_{1,F}$ of 51.2 Hz.

Armed with the above results, attention then turned to the synthesis of the methallyl glycosyl donor. Compound 82a was selectively deacetylated as before with hydrazine acetate$^{161}$ to afford the alcohol 175 as an inseparable mixture of anomers ($\alpha:\beta = 6:1$, by $^1$H NMR) in good yield (Scheme 53).

The NMR spectroscopy of 175 revealed the presence of only three acetoxy groups, and the $^{13}$C NMR and HSQC spectra were more useful in assigning the configurations of the anomers. The $^{13}$C NMR spectrum displayed signals at $\delta$ 95.66 for C-1 ($\beta$-anomer) and $\delta$ 92.93 ($\alpha$-anomer), thus differentiating the configuration of anomers.$^4$

![Scheme 53 Reagents and conditions: i) Hydrazine acetate, DMF, 60 °C, 1 h ($\alpha:\beta = 6:1$); ii) DAST, THF, rt, 30 min ($\alpha:\beta = 2:1$)](image)

Fluorination of 175 with DAST$^{154,155}$ gave methallyl fluoride 176 as a mixture of anomers ($\alpha:\beta = 2:1$, by $^1$H NMR) in excellent yield (Scheme 53). Separation of anomers was achieved by column chromatography, but was not necessary for the next step in the sequence. The spectroscopic data of 176 was in agreement with the assigned structure and the presence of fluoride and methallyl was confirmed by $^{19}$F, $^1$H and $^{13}$C NMR spectra. The configuration of each anomer was determined from coupling constant for H-1 by analogy to that in 173 above.

---

$^4$ In the $^{13}$C NMR spectroscopy of glucopyranoses, an anomic carbon bearing an $\alpha$-substituent generally resonates upfield to one bearing a $\beta$-substituent.$^{(162)}$
2.3 Synthesis of the glycosyl acceptor

A protected and enantiomerically pure D-\textit{myo}-inositol derivative with a free hydroxyl group at C-1 was required as glycosyl acceptor in our synthesis. \textit{Myo}-inositol chemistry has received a great deal of attention in recent years, particularly with regard to the preparation of regioselectively substituted and enantiomerically pure derivatives.\textsuperscript{29,156,158,163-174} A range of methods for the preparation of enantiomerically pure derivative of \textit{myo}-inositol such as \textit{trans}-acetalization of \textit{myo}-inositol with D-camphor dimethyl ketal as the chiral reagent,\textsuperscript{167,170} the use of monosaccharides as asymmetrical agents in resolving racemic alcohols,\textsuperscript{156-158} and the use of (−)-menthol chloroformate to resolve 2:3,4:5-cyclohexylidene has been reported.\textsuperscript{165} The most practical route in our experience was \textit{via} a resolution of 1,2,4,5,6 pentabenzyl \textit{DL-myo}-inositol with (S)-(−)-camphamic chloride followed by hydrolysis of the ester to give free alcohol at C-1.

To prepare the benzylated DL-\textit{myo}-inositol, a procedure by Massy\textsuperscript{174} which involves eight reaction steps from \textit{myo}-inositol was followed. Thus, \textit{myo}-inositol 177 was treated with cyclohexanone and TsOH (10%) at reflux to give racemic cyclohexylidene-DL-\textit{myo}-inositol 178 in 76\% yield (Scheme 54). The spectroscopic data for 178 was consistent with the assigned structure and the melting point (mp 180 °C) was in agreement with the literature value\textsuperscript{175} (mp 179-180 °C).

Global benzyla
tion of 178 with benzyl bromide in the presence of NaH gave racemic cyclohexylidene tetrabenzyl-\textit{myo}-inositol 179 in 82\% yield (Scheme 54). Its $^1$H NMR spectrum displayed signals at δ 7.40-7.26 (20 H, m) for the benzylic protons and δ 1.84-1.43 (10 H, m) for the cyclohexyl methylene protons.
Scheme 54 Reagents and conditions: i) Cyclohexanone, TsOH (10% in DMF), DMF, toluene, reflux, 12 h; ii) BnBr, NaH, THF, reflux, 18 h; iii) AcOH (80%), 90-100 °C, 2 h

Acidic hydrolysis of 179 with 80% acetic acid gave racemic tetrabenzyl-myoinositol 180 in 79% yield (Scheme 54). Its melting point and spectroscopic data were in agreement with the literature values. The absence of cyclohexyldiene signals from both $^1$H and $^{13}$C NMR spectra of 180 confirmed the assigned structure. In addition, the IR spectrum displayed an absorption at $\nu_{max}$ 3570 cm$^{-1}$ (OH).

Stannyldiene-mediated regioselective allylation of the diol 180 gave a racemic mixture of allyl ethers 181a and 181b ($\approx$ 10:1, by $^{13}$C NMR) in good yield (Scheme 55) although separation of these isomers by column chromatography was unsuccessful. The regioselectivity was confirmed by the upfield shift of H-1 from $\delta$ 3.47 in 180 to $\delta$ 3.33 ppm. The allylic signals were evident from both $^1$H and $^{13}$C NMR spectra and in addition, the IR spectrum displayed an absorption at $\nu_{max}$ 3573 cm$^{-1}$ (OH).

* Severe signal overlap in the $^1$H NMR made a comparison of integrals difficult.
Scheme 55 Reagents and conditions: \( i \) (a) \( \text{Bu}_2\text{SnO}, \) toluene, reflux, 2 h \( \) (b) Allyl bromide, DMF, 70 °C, 5 h \( \) \( (181\text{a}:181\text{b} = 10:1) \); \( ii \) \( \text{BnBr}, \) NaH, THF, reflux, 3 h \( (182\text{a}:182\text{b} \approx 10:1) \)

Benzylaion of the mixture of alcohols \( 181\text{a} \) and \( 181\text{b} \) with benzyl bromide in the presence of NaH gave racemic allyl pentabenzyl-\textit{myo}-inositol \( 182\text{a} \) and \( 182\text{b} \) \( (\approx 10:1, \) \( ^{13}\text{C} \) NMR)\(^c \) in 89% yield (Scheme 55). The spectroscopic data was in agreement with the structure, and the absence of hydroxyl absorption in the IR spectrum confirmed the assigned structures.

Deallylation of \( 182\text{a} \) and \( 182\text{b} \) with \( \text{PdCl}_2 \) in ethanol gave racemic pentabenzyl-\textit{myo}-inositol \( 183 \) in good yield after separation of regioisomers by recrystallization from petroleum ether (Scheme 56). The spectroscopic data of \( 183 \) supported the assigned structure and the melting point of 88-89 °C was recorded which was in agreement with the literature value of 86-88 °C. In addition, the IR spectrum displayed an absorption at \( \nu_{\text{max}} \) 3560 cm\(^{-1} \) for hydroxyl.

\(^c \) Severe signal overlap in the \( ^1\text{H} \) NMR made a comparison of integrals difficult.
Scheme 56 Reagents and conditions: i) PdCl₂, EtOH-MeOH, rt, 5 h; ii) Camphanic acid chloride, Et₃N, DMAP, CH₂Cl₂, rt, 28 h

Having successfully synthesized the protected DL-myoinositol derivative 183 with a free hydroxyl group at C-1, the next step involved its resolution as a camphanate ester. Thus, esterification¹⁶⁶ of racemic alcohol 183 with camphanic acid chloride, Et₃N and DMAP (catalytic) gave a mixture of diastereomeric esters 184a and 184b (Scheme 56) in high yield (see Figure 17a for the ¹H NMR spectrum of the mixture of diastereomer). Careful gravity chromatography conducted on silica gel gave partial separation of 184a (47%) and 184b (47%), each >95% pure based on the relative integration of the camphanoyl methyl peaks in each ¹H NMR spectrum (see Figure 17b and 17c for the ¹H NMR of separated enantiomers). These diastereomers gave different melting points (184a = 147-149 °C and 184b = 161-163 °C) and optical rotations with opposite signs (184a = [α]D +9.8° and 184b = [α]D −15.3°).
Figure 17 ¹H NMR expansions of methyl proton region of inositol camphanate esters: (a) mixture of diastereomers (b) diastereomer with D-enantiomer 184a and (c) diastereomer with L-enantiomer 184b

The ¹H NMR spectrum for the diastereomer 184a containing the D-inositol displayed diagnostic signals at δ 1.09, 1.01, 0.91 (9 H, 3 s) for the camphanoyl methyl protons (see Figure 17b for ¹H NMR spectrum), while the ¹³C NMR spectrum displayed signals at δ 177.87 and 167.26 for the camphanoyl carbonyl groups. In addition, the IR spectrum displayed an absorption at νmax 1781, 1718 cm⁻¹ (C=O).
For the other diastereomer 184b containing the L-inositol, the $^1$H NMR spectrum displayed diagnostic signals at $\delta$ 1.08, 0.97, 0.85 (9 H, 3 s) for the methyl protons (see Figure 17c for the $^1$H NMR spectrum) while the $^{13}$C NMR spectrum displayed signals at $\delta$ 177.89 and 167.46 for the camphanoyl carbonyl groups. In addition, the IR spectrum displayed an absorption at $\nu_{\text{max}}$ 1785, 1722 cm$^{-1}$ (C=O).

![Chemical structure](image)

Scheme 57 Reagents and conditions: i) KOH, EtOH, reflux, 2 h

Basic hydrolysis$^{166}$ of the ester 184a with KOH at reflux afforded the desired alcohol 185 in near quantitative yield (Scheme 57). The spectroscopic data for 185 supported the assigned structure. Similarly, basic hydrolysis$^{166}$ of the ester 184b with KOH in ethanol gave pentabenzyl-L-myoinositol 186 in excellent yield (Scheme 58), whose spectroscopic data was also consistent with assigned the structure. The measured optical rotations for 185 and 186 were $+7.1^\circ$ and $-8.0^\circ$, confirming that they were the D- and L- isomers respectively.$^{173}$

![Chemical structure](image)

Scheme 58 Reagents and conditions: i) KOH, EtOH, reflux, 2 h
2.4 Glycosylation and side-chain functionalization

The term "glycosylation" describes the formation of a chemical bond between the anomic position of a sugar unit and a suitable nucleophile, such as an alcohol, thiol amine or one of a variety of carbon nucleophiles. The nucleophile is classified as the glycosyl acceptor, and the sugar bearing the activated electrophile animeric carbon as the glycosyl donor. From a synthetic standpoint, an effective $O$-glycosylation reaction generally involves high chemical regioselectivity and stereoselectivity. The former is easily realized by selective protection of the hydroxyl groups of the glycosyl acceptor as well as by the unique reactivity of the anomic carbon. The anomeric stereoselectivity is highly influenced by neighboring group (participating or non-participating group) effects in the glycosyl donor, as well as the activating agent, the solvent and the anomeric effect.\textsuperscript{152}

Having successfully synthesized glycosyl fluorides of type A (173 and 176) and the glycosyl acceptor, the next challenge was to develop a stereoselective glycosylation reaction to give a desired alpha-anomer.

2.4.1 Synthesis of 2-C-alkylglucosides of 1-D-\textit{myo}-inositol (51-56)

A model glycosylation reaction using L-inositol\textsuperscript{1} 186 as the acceptor with 176 as the donor and promoted by BF$_3$-Et$_2$O\textsuperscript{157,176} gave pseudo-disaccharide 188 (60%, $\alpha:\beta \approx 99:1$, by $^{13}$C NMR)\textsuperscript{8} with the desired $\alpha$-selectivity (Scheme 59). Unfortunately, undesired isomerisation of the side chain double bond occurred, presumably due to HF protonating the double bond to give the tertiary carbocation, which then eliminated to the more stable olefin. The donor, acceptor and the product displayed the same $R_f$ value, making it difficult to judge the progress of the reaction. However, the coupling reaction was evident by the appearance on tlc of a new UV-active product spot that was also revealed by anisaldehyde spray. Compound 176 was UV-inactive and showed up as a dark spot on the anisaldehyde spray, whereas compound 186 was UV-active and didn’t show up clearly with anisaldehyde spray.

These disappointing but interesting results encouraged us to conduct the same reaction in the presence of triethylamine. It was hoped that the addition of a base may prevent the C=C migration by trapping HF produced during the reaction. Unfortunately, no reaction was observed (tlc) after two days at room temperature. In another attempt, a different reaction conditions (AgOTf, ZnCl$_2$, \footnote{L-inositol was used to save D-inositol} \footnote{In the $^1$H NMR spectrum, the signal for H-1 in the $\beta$-anomer was not resolved from the benzylic and other protons, making a comparison of integrals difficult.}}
CH$_2$Cl$_2$, rt) were used with and without a base (2,4 lutidine), but again no reaction was observed (tlc) after two days.

Scheme 59 Reagents and conditions: i) BF$_3$·Et$_2$O, ms, CH$_2$Cl$_2$, rt, 2 h (α:β > 99:1)

The predominance of the α-anomer was as expected on stereoelectronic grounds and in view of the presence of a non-participating methallyl group at C-2. The unreacted starting material 186, which was inseparable from the product, complicated the NMR spectrum, although the diagnostic signals of the products were evident in both $^1$H and $^{13}$C NMR spectra. A signal at δ 5.29 for H-1’ appearing as a doublet with a moderate axial-equatorial ($J_{1,2'}$ 3.6 Hz) coupling constant, confirmed the formation of the α-anomer.

In order to separate the product 188 from the unreacted acceptor 186, the mixture was subjected to Zemplén deacetylation to give α-linked pseudo-disaccharide 189 (30% from 176) (Scheme 60) after separation. The spectroscopic data was consistent with the assigned structure and benzylic signals were evident from both $^1$H and $^{13}$C NMR spectra. The $^1$H NMR spectrum displayed signals at δ 5.17 (dt, J 10.2, 1.2 Hz) for H-1’’, δ 4.00 (t, J 2.2 Hz) for H-2, δ 2.61-2.53 (td, J 10.2, 3.6 Hz) for H-2’, and δ 1.53 (d, J 1.2 Hz) and δ 1.45 (d, J 1.2 Hz) for the six methyl protons. The $^{13}$C NMR spectrum displayed signals at δ 138.15 (C-2’’), 119.95 (C-1’’), 100.45 (C-1’), and 25.86 and 18.08 (2 C) for the methyl carbons.
Scheme 60 Reagents and conditions: i) NaOMe, MeOH-CH₂Cl₂, rt, 2 h; ii) Ac₂O, Et₃N, DMAP, CH₂Cl₂, rt, 1 h

The stereochemistry of 189 at C-1' was determined from the coupling constant value for H-1'. Thus the ¹H NMR spectrum displayed a doublet at δ 5.22 for H-1' with a moderate axial-equatorial (J₁₂ 3.6 Hz) coupling constant, thereby confirming the α-anomer.

For characterization purposes, compound 189 was reacetylated to produce fully protected pseudo-disaccharide 188a in 98% yield (Scheme 60). The acetoxyl signals were evident in both ¹H and ¹³C NMR spectra. The ¹H NMR spectrum displayed signals at δ 5.28 (d, J 3.6 Hz) for H-1', δ 5.12-5.10 (d, br, J 10.4 Hz) for H-1'', δ 3.64 (dd, J 9.6, 2.2 Hz) for H-1, δ 2.82 (td, J 10.4, 3.6 Hz) for H-2', and δ 1.42 and 1.41 (6 H, 2 s) for the methyl protons. The ¹³C NMR spectrum displayed signals at δ 119.56 (C-1''), 100.56 (C-1'), and δ 25.77 and 18.05 for the methyl carbons.

The failure to obtain the 2'''-methyl-3'''-propenylglucoside 187 prompted a modified approach utilizing 2-C-allyl glycosyl fluoride 173. Thus, treatment of acceptor 185 with donor 173 and BF₃·Et₂O¹⁵⁷,¹⁷⁶ as a promoter gave 2-C-allyl pseudo-disaccharide 190 as an inseparable mixture of anomers (α:β ≈ 8:1, by ¹³C NMR)⁸ as an oil (Scheme 61). Once again, the donor, acceptor and the product displayed the same Rₜ value, making it difficult to monitor the progress of the reaction. However, anisaldehyde spray differentiated the UV-active product from the UV-active acceptor 185.

---

¹³C NMR spectrum, the signal for H-1 in the β-anomer was not resolved from the benzylic and other protons, making a comparison of integrals difficult.
Scheme 61 Reagents and conditions: i) BF₃·Et₂O, ms, CH₂Cl₂, rt, 2 h (α:β ≈ 8:1)

As before, the α-anomer predominated, and anomers were distinguishable in the $^{13}$C NMR spectrum with C-1' of the β-anomer appearing at δ 103.86 and that of the α-anomer appearing at δ 95.34. In addition, the $^1$H NMR spectrum of 190 displayed a signal at δ 5.02 which appeared as a doublet with a moderate axial-equatorial ($J_{1',2'}$ 3.2 Hz) coupling constant, thus confirming an α-configuration.

Since compound 190 was inseparable from unreacted inositol derivative 185, the mixture was subjected to Zemplén deacetylation to give the separable pentabenzyl pseudo-disaccharide 191 as a mixture of anomers (α:β ≈ 8:1, by $^{13}$C NMR) in 80% yield from 185 (Scheme 62). A careful separation of the anomers by silica column chromatography gave α-anomer 191a in 56% yield from the acceptor 185. The $^1$H NMR spectrum of 191a displayed signals at δ 7.38-7.28 (25 H, m) for the aromatic protons and at δ 5.85 (m) for H-2''.
Scheme 62 Reagents and conditions: i) NaOMe, MeOH-CH₂Cl₂, rt, 2 h (α:β = 8:1); ii) Separation of anomers; iii) Ac₂O, Et₃N, DMAP, CH₂Cl₂, rt, 1 h

For characterization purposes, compound 191a was reacetylated to produce the pseudo-disaccharide triacetate 190a in 98% yield (Scheme 62). The ¹H NMR spectrum of 190a displayed signals at δ 5.71 (m) for H-2′′, δ 5.02 (d, J₁₁₂: 3.2 Hz) for H-1′, δ 3.65 (dd, J 9.6, 2.0 Hz) for H-1 while the ¹³C NMR spectrum displayed signals at δ 116.07 (C-3′′), 95.35 (C-1′) and 74.70 (C-1). In addition, the presence of acetoxy groups was evident in both ¹H and ¹³C NMR spectra.

At this point, it was discovered that the anomers could best be separated from one another as fully benzylated derivatives. Thus, the mixture of anomers 191 was treated with benzyl bromide in the presence of NaH to produce a mixture of fully benzylated pseudo-disaccharides 192a and 192b in 98% yield (Scheme 63).
Scheme 63 Reagents and conditions: i) BnBr, NaH, THF, reflux, 18 h (192a:192b = 8:1)

Once again, $^{13}$C NMR spectroscopy was useful for assigning the anomers, with the $\beta$-anomer appearing at $\delta$ 103.88 and the $\alpha$-anomer appearing at $\delta$ 94.82 (see Figure 18a for the $^{13}$C NMR spectrum of mixture of anomers). The anomers were separated by careful silica-gel column chromatography and the $^{13}$C NMR spectra differentiated compound 192a and 192b (see Figure 18b and 18c for $^{13}$C NMR spectrum of separated anomers). Benzyl (40 H, m) and allyl signals were evident from both $^1$H and $^{13}$C NMR spectra of separated anomers.
Figure 18 $^{13}$C NMR expansions of anomeric region of 192a and 192b. (a) mixture of anomers (b) $\alpha$-anomer 192a (c) $\beta$-anomer 192b

The $^1$H NMR spectrum for 192a displayed a signal for H-1' at $\delta$ 5.09 which appeared as a doublet with a moderate axial-equatorial ($J_{1',2'}$ 3.3 Hz) coupling constant, thus confirming the $\alpha$-anomer. In contrast, the $^1$H NMR spectrum for 192b displayed a signal for H-1' at $\delta$ 4.72 which appeared as a doublet with a large diaxial ($J_{1',2'}$ 8.1 Hz) coupling constant, thus confirming the $\beta$-anomer.

The most practical route to the oxygenated alkyl side-chains was envisaged to be via epoxidation of olefin followed by reduction to the secondary alcohol and oxidation as required. Benzyl
protecting groups would be compatible with the LiAlH₄ used for the regioselective opening of epoxide, compared with the acetate groups in 190a. Hence, treatment of 192a with m-CPBA was attempted, and although the reaction was slow, completion was ensured by periodic addition of equivalents of m-CPBA to eventually give an inseparable diastereomeric mixture (1:1, by ¹H NMR) of epoxides 193 in 85% yield (Scheme 64). The facial selectivity was similar to that of the carbonyl group used to access the secondary alcohol via reduction and described previously (Page 62-63).

![Diagram](image)

**Scheme 64 Reagents and conditions: i) m-CPBA (70%), CH₂Cl₂, rt, 24 h (1:1)**

Although doubling of signals in the NMR spectrum of the mixture made assignments difficult, the epoxide signals were clearly identifiable in both ¹H and ¹³C NMR spectra. Thus for diastereomer 193a, the ¹H NMR spectrum displayed diagnostic signals at δ 2.97 (m) for H-2″, δ 2.50 (dd, J 5.0, 4.2 Hz) for H-3″a and δ 2.04 (dd, J 5.0, 2.6 Hz) for H-3″b. Its ¹³C NMR spectrum displayed signals at δ 52.22 (C-2″) and 46.61 (C-3″) which were diagnostic for an epoxide moiety. The diagnostic signals for diastereomer 193b were analogous to those in 193a.

Regioselective reductive opening of epoxide 193 with LiAlH₄ in THF gave an inseparable mixture (1:1, by ¹H NMR) of secondary alcohols 194 in 82% yield (Scheme 65). The presence of the secondary alcohol was evident from both ¹H and ¹³C NMR spectra.

![Diagram](image)

**Scheme 65 Reagents and conditions: i) LiAlH₄, THF, 0 °C, 2 h (1:1)**
Thus for diastereomer 194a, the $^1$H NMR spectrum displayed diagnostic signals at $\delta$ 3.79 (m) for H-2$'$ and at $\delta$ 0.93 (3 H, d, J 6.0 Hz) for the adjacent methyl protons. The $^{13}$C NMR spectrum displayed signals at $\delta$ 66.92 (C-2$''$) and 23.73 (C-3$''$) characteristic of a 2-hydroxypropyl group. The diagnostic signals for diastereomer 194b were analogous to those in 193a. In addition, the IR spectrum displayed a new absorption at $\nu_{\text{max}}$ 3465 cm$^{-1}$ (OH).

Global debenzylation of 194 with Pd/C under an atmospheric hydrogen pressure gave the target compound as an inseparable mixture (1:1, by $^1$H NMR) of alcohols 51 in 90% yield (Scheme 66). The completion of reaction was ensured by periodic addition of further equivalents of Pd/C over an 18 h period.

![Scheme 66 Reagents and conditions: i) H$_2$, 10% Pd/C, MeOH-EtOAc, rt, 3 days (1:1)](image)

The spectroscopic data of 51 was consistent with the assigned structure. Once again, the doubling of signals made the assignments difficult, but the absence of benzylic signals was evident from both $^1$H and $^{13}$C NMR spectra. Thus for diastereomer 51a, the $^1$H NMR spectrum displayed a doublet at $\delta$ 5.09 (d, $J_1,2'$ 3.3 Hz) for H-1$'$, a broad singlet at $\delta$ 4.24 for H-2 and a doublet at $\delta$ 1.20 (3 H, J 6.0 Hz) for the methyl protons. The $^{13}$C NMR spectrum displayed signals at $\delta$ 95.62 (C-1$'$), 67.78 (C-2), 66.63 (C-2$''$) and 22.25 (C-3$''$). The diastereomer 51b was assigned by analogy to 51a. The mass spectrum of 51 was obtained using FAB (negative) techniques displaying a molecular ion at 383 corresponding to the (M-H)$^-$ molecular ion.

In order to synthesize the 2-keto target compound 52, the diastereomeric mixture of alcohols 194 was oxidized with TPAP using NMO as co-oxidant,$^{181}$ to give ketone 195 in 95% yield (Scheme 67). This was adopted as the reagent of choice for all further oxidations, owing to the mild reaction conditions and ease of work-up.
Scheme 67 Reagents and conditions: i) TPAP, NMO, CH$_2$Cl$_2$, ms, 30 min

The $^1$H NMR spectrum displayed a diagnostic signal at $\delta$ 1.61 (3 H, s) for the methyl group. The downfield shift of these protons from $\delta$ 0.93 and $\delta$ 0.88 in 194 supported the presence of a carbonyl group at C-2''. The $^{13}$C NMR spectrum provided further confirmation with a new signal at $\delta$ 207.77 for C-2'' having shifted from $\delta$ 66.92 and 66.39 for C-2'' in 194. In addition, the IR spectrum displayed a new absorption at $\nu_{\text{max}}$ 1712 cm$^{-1}$ (C=O).

Global debenzylolation of 195 with Pd/C under an atmospheric hydrogen pressure afforded the 2-keto target compound 52 in 90% yield as a hydroscopic solid (Scheme 68). The completion of reaction was ensured by periodic addition of further equivalents of Pd/C over a 48 h interval. Compound 52 dissolves well in a mixture of water and methanol, as a result, isolation of the product was ensured by freeze-drying of the aqueous mixture.

Scheme 68 Reagents and conditions: i) H$_2$, 10% Pd/C, MeOH-EtOAc-H$_2$O, rt, 8 days

Significant overlapping of signals in the $^1$H NMR spectrum made the characterization difficult, but the absence of aromatic signals was evident from both $^1$H and $^{13}$C NMR spectra. The $^1$H NMR spectrum displayed a doublet at $\delta$ 4.84 ($J_{1',2}$: 3.3 Hz) for H-1', a triplet at $\delta$ 3.87 ($J$ 2.6 Hz) for H-2 and a singlet at $\delta$ 2.01 (3 H) for the methyl protons. The $^{13}$C NMR spectrum displayed signals at $\delta$ 214.54 (C-2''), 95.02 (C-1'), 67.96 (C-2) and 29.54 (C-3''). Mass spectroscopy of 52 was particularly difficult as no molecular ion was visualised in EI, FAB and CI techniques.

Having successfully completed the synthesis of target compounds 51 and 52, attention turned to the synthesis of analogues containing an amine functionality at the carbon $\alpha$- to the carbonyl (53-
56), as found in mycothiol 3. The epoxide 193, is a strategic synthetic intermediate because of the three-membered ring, which can be opened by various nucleophiles to yield a wide range of analogues. Morpholine and diethylamine were selected for nucleophilic regioselective ring opening study because they were readily available and could be characterized easily by NMR spectroscopy.

Thus SN2 nucleophilic opening of the epoxide 193 with morpholine\textsuperscript{182} occurred in a regioselective manner to give an inseparable mixture (1:1, by \textsuperscript{1}H NMR) of diastereomeric morpholino alcohols 196 in 78\% yield (Scheme 69), arising from nucleophilic attack at C-3'''. The presence of the secondary alcohol and morpholine moieties was clearly evident from both \textsuperscript{1}H and \textsuperscript{13}C NMR spectra.

![Scheme 69 Reagents and conditions: i) Morpholine, EtOH, reflux, 1 h (1:1)](image)

Thus for diastereomeric 196a, the \textsuperscript{13}C NMR spectrum displayed diagnostic signals at δ 66.76 (-N(CH\textsubscript{2}CH\textsubscript{2})\textsubscript{2}O-), 66.37 (C-2'''), 64.63 (C-3''') and 53.34 for -N(CH\textsubscript{2}CH\textsubscript{2})\textsubscript{2}O-. The diagnostic signals for diastereomer 196b were analogous to those in 196a. In addition, the IR spectrum displayed a new absorption at ν\textsubscript{max} 3625 cm\textsuperscript{-1} (OH).

Further evidence for the diastereomeric mixture of 196 was provided by oxidising 196 with TPAP using NMO as co-oxidant,\textsuperscript{181} to give ketone 197 in 84\% yield (Scheme 70) as a single component. The \textsuperscript{1}H NMR spectrum for 197 displayed a diagnostic diastereotopic AB doublet set at δ 2.68 (J 17.0 Hz) for H-3''a and at δ 2.56 (J 17.0 Hz) for H-3''b. The \textsuperscript{13}C NMR spectrum was more useful in assigning the structure. A new signal at δ 207.55 (C-2''') confirmed formation of the ketone, which had shifted from δ 66.37 and 64.17 for C-2'' in 196. In addition, the IR spectrum displayed a new absorption at ν\textsubscript{max} 1723 cm\textsuperscript{-1} (C=O).
Scheme 70 Reagents and conditions: i) TPAP, NMO, CH₂Cl₂, ms, 30 min; ii) H₂, 10% Pd/C, MeOH-EtOAc-H₂O, 25-35 °C, 10 days

Global debenzylation of 196 and 197 with Pd/C under hydrogen pressure of 1 atm gave fully deprotected 53 and 55 in low conversion after two weeks (by tlc and ¹H NMR) (Scheme 70). Increasing the reaction temperature from 25 °C to 35 °C with periodic addition of further equivalents of Pd/C over a 48 h period made no difference. Tlc showed total consumption of starting material but revealed several products intermediate spots. It was suspected that the presence of nitrogen was interfering in chemisorption. Further investigation on these compounds was precluded by time constraints and unavailability of material.

Similarly, in order to synthesize the diethylamino-containing target compounds 54 and 56, the epoxide 193 was reacted with diethylamine¹⁶² to produce an inseparable diastereomeric mixture (1:1, by ¹H NMR) of diethylamino alcohols 198 in 78% yield (Scheme 71), arising from nucleophilic attack at C-3′′. The presence of a secondary hydroxyl and a diethylamino group at C-3′′ was evident from both ¹H and ¹³C NMR spectra.
Thus for diastereomer 198a, the $^1$H NMR spectrum displayed a diagnostic triplet at $\delta$ 0.94 (6 H, $J$ 7.1 Hz) for $-N(CH_2CH_3)_2$. The $^{13}$C NMR spectrum displayed diagnostic signals at $\delta$ 67.34 (C-2'''), 59.87 (C-3'''), 46.22 for $-N(CH_2CH_3)_2$ and 11.53 for $-N(CH_2CH_3)_2$. The diagnostic signals for diastereomer 198b were analogous to those in 198a. In addition, the IR spectra displayed an absorption at $v_{\text{max}}$ 3620 cm$^{-1}$ (OH).

Compound 198 was subjected to TPAP oxidation$^{181}$ to give ketone 199 in 45% yield (Scheme 72). Oxidation was observed to have taken place by loss of the C-2''' proton in the $^1$H NMR spectrum as well as the hydroxyl stretch frequency at $v_{\text{max}}$ 3620 cm$^{-1}$ in the IR spectrum. The $^1$H NMR spectrum also displayed a diagnostic pair of AB doublets at $\delta$ 2.76 ($J$ 16.5 Hz) for H-3''', and a doublet at $\delta$ 2.66 ($J$ 16.5 Hz) for H-3'''b. The $^{13}$C NMR spectrum was also very useful in assigning the structure. A new signal at $\delta$ 210.36 (C-2''') confirmed formation of the ketone, which had shifted from $\delta$ 67.34 and 64.41 for C-2''' in 198. In addition, the IR spectrum displayed an absorption at $v_{\text{max}}$ 1718 cm$^{-1}$ for the carbonyl group.
Scheme 72 Reagents and conditions: i) TPAP, NMO, CH₂Cl₂, ms, 18 h

Time constraints and insufficient material prevented the final debenzylation of 198 and 199 into target compounds 54 and 56 respectively (Scheme 72). However, it was demonstrated that the epoxide was a strategic intermediate, suitable for generation of a range of amino-alcohols or amino-ketones as long as the problem of debenzylation can be solved.
2.4.2 Synthesis of cyclohexyl 2-C alkylglucosides (57-62)

Cyclohexanol 200 is readily available, inexpensive and was identified as an appropriate replacement of D-mylo-inositol as the glycosyl acceptor as discussed in Section 1.4. It was envisaged that glycosylation of acceptor with the glycosyl fluoride 173 followed by functionalization of the allyl group would lead to the synthesis of target compounds (57-62). Thus, coupling of fluoride 173 with excess cyclohexanol 200 in the presence of BF$_3$·Et$_2$O$^{176,183}$ gave cyclohexyl 2-C-allyl glucopyranoside (201a and 201b) as a mixture of anomers (α:β ≈ 1:1, by $^{13}$C NMR) in 93% yield (Scheme 73). The poor selectivity was noted, however a study to improve stereoselectivity was not undertaken due to time constraints.

The presence of excess acceptor 200 made the separation of anomers by column chromatography problematic and doubling of signals in the $^1$H NMR spectrum of the mixture made the assignments difficult. The $^{13}$C NMR spectrum was useful for assigning the configuration and ratio of the anomers, with the β-anomer carbon appearing at δ 100.58 and the α-anomer appearing at δ 96.84 (see Figure 19a for the $^{13}$C NMR spectrum of mixture of anomers). Fortunately, crystallization of the residue from pentane at low temperature afforded the crystalline β-anomer 201b in 36% yield and purification of the residual mother liquor by column chromatography afforded the α-anomer 201a (42%) as an oil (see figure 19b and 19c for $^{13}$C NMR spectra of separate anomers).

Scheme 73 Reagents and conditions:  i) BF$_3$·Et$_2$O, CH$_2$Cl$_2$, ms, 18 h (201a:201b = 1:1)

---

$^b$ In the $^1$H NMR spectrum, the signal for H-1 in the β-anomer was not resolved from other protons, making a comparison of integrals difficult.
Figure 19 $^{13}$C NMR expansions of anomic region of 201a and 201b. (a) mixture of anomers (b) $\alpha$-anomer 201a (c) $\beta$-anomer 201b

The spectroscopic data of 201a and 201b was consistent with the assigned structure and cyclohexyl methylene signals were evident from both $^1$H and $^{13}$C NMR spectra. Thus for $\alpha$-anomer 201a, the $^1$H NMR spectrum displayed diagnostic signals at $\delta$ 5.73-5.63 (m) for H-2'' and $\delta$ 3.54-3.47 (m) for H-1' while the $^{13}$C NMR spectrum displayed diagnostic signals at $\delta$ 135.25 (C-2''), 96.84 (C-1) and 75.95 (C-1'). The diagnostic signals for $\beta$-anomer 201b were analogous to those in $\alpha$-anomer 201a.
The stereochemistry of 201a and 201b at C-1 was determined from the coupling constant for H-1. The $^1$H NMR spectrum of 201a displayed a doublet at δ 4.92 for H-1 with a moderate axial-equatorial ($J_{1,2}$ 3.6 Hz) coupling constant, thus confirming the α-anomer. By comparison, the $^1$H NMR spectrum of 201b displayed a doublet at δ 4.39 for H-1 with a large diaxial ($J_{1,2}$ 8.1 Hz) coupling constant, thus confirming the β-anomer.

Zemplén deacetylation of 201a gave the target compound 59 in 99% yield (Scheme 74). The $^1$H NMR spectrum of 59 displayed signals at δ 5.86-5.76 (m) for H-2', δ 4.87 (d, $J_{1,2}$ 3.2 Hz) for H-1 and at δ 3.58 (m) for H-1' while the $^{13}$C NMR spectrum displayed signals at δ 136.84 (C-2'), 96.65 (C-1) and 74.62 (C-1'). The absence of acetoxy groups was clear from both $^1$H and $^{13}$C NMR spectra. Accurate mass determination using FAB techniques displayed a molecular ion at 309.168001, corresponding to the M+Na molecular ion.

\[
\begin{align*}
\text{Scheme 74 Reagents and conditions:} & \quad i) \text{NaOMe, MeOH-CH}_2\text{Cl}_2, \text{rt, 4 h} \\
201a & \quad \xrightarrow{i} \quad 99\% \\
\end{align*}
\]

Similarly, Zemplén deacetylation of 201b at room temperature gave 202 in 98% yield as crystals (Scheme 75). The absence of acetoxy groups was evident from both $^1$H and $^{13}$C NMR spectra. The $^1$H NMR spectrum of 202 displayed signals at δ 5.97-5.87 (m) for H-2', δ 4.41 (d, $J_{1,2}$ 8.8 Hz) for H-1 and at δ 3.71 (m) for H-1' while the $^{13}$C NMR spectrum displayed signals at δ 135.34 (C-2'), 100.48 (C-1) and 76.32 (C-1').

\[
\begin{align*}
\text{Scheme 75 Reagents and conditions:} & \quad i) \text{NaOMe, MeOH-CH}_2\text{Cl}_2, \text{rt, 2 h} \\
201b & \quad \xrightarrow{i} \quad 98\% \\
202 & \\
\end{align*}
\]

Benzylation of 59 with benzyl bromide in the presence of NaH afforded the fully benzylated sugar 203 in excellent yield (Scheme 76) as an oil. The $^1$H NMR spectrum of 202 displayed signals at δ 7.41-7.19 (15 H, m), characteristic of the benzylic phenyl groups. A downfield shift of C-3, C-4
and C-6 from $\delta$ 72.82, $\delta$ 72.15 and $\delta$ 61.87 respectively in 59 to $\delta$ 81.38 (C-3), $\delta$ 79.97 (C-4) and 68.98 (C-6) confirmed the presence of benzyl groups in 203.

![Scheme 76 Reagents and conditions: i) BnBr, NaH, THF, reflux, 18 h; ii) H$_2$, Pd/C, MeOH, rt, 18 h](image)

Synthesis of C-2 propyl glucoside target compound 60 was achieved in high yield from either unprotected 59 or protected 203 allyl glucoside by separate treatment with Pd/C under an atmospheric hydrogen pressure (Scheme 76). The formation of product 60 was confirmed by the disappearance of allylic H-2'' at about $\delta$ 5.80 and by the presence of propyl group signals in the high field region in the $^1$H NMR. The $^1$H NMR spectrum of 60 displayed a triplet at $\delta$ 0.92 (3 H, $J$ 7.2 Hz) for the methyl protons while the $^{13}$C NMR spectrum displayed signals at 29.44 (C-1'''), 19.89 (C-2''') and 13.59 (C-3''') diagnostic for a propyl group. Accurate mass determination using FAB techniques displayed a molecular ion at 311.182957, corresponding to the M+Na molecular ion.

Epoxidation of the olefin in benzylated glucoside 203 followed by regioselective reductive opening of the epoxide ring with LiAlH$_4$ to give the secondary alcohol, which could be oxidised, was envisaged as the most practical route for introducing an oxygenated alkyl side-chain. Thus, treatment of 203 with m-CPBA$^{177,178}$ gave an inseparable diastereomeric mixture (1:1, by $^1$H NMR) of epoxides 204 in 84% yield (Scheme 77). The reaction was slow and required periodic addition of further equivalents of m-CPBA.
Doubling of signals in the NMR spectrum of the mixture 204 made assignments difficult, however the epoxide signals were evident from both $^1$H and $^{13}$C NMR spectra. Thus for the diastereomer 204a, the $^1$H NMR spectrum displayed signals at $\delta$ 3.01-2.94 (m) for H-2", a doublet of doublets at $\delta$ 2.68 ($J$ 5.0, 4.2 Hz) for H-3", and a doublet of doublets at $\delta$ 2.47 ($J$ 5.0, 2.6 Hz) for H-3". The $^{13}$C NMR spectrum displayed signals at $\delta$ 50.69 (C-2") and 47.93 (C-3") which were typical for an epoxide moiety. The diagnostic signals for diastereomer 204b were analogous to those in 204a.

Regioselective reductive opening$^{179,180}$ of epoxide 204 with LiAlH₄ in THF gave an inseparable diastereomeric mixture (1:1, by $^1$H NMR) of secondary alcohols 205 in 93% yield (Scheme 78). The $^1$H NMR spectrum of 205a displayed a doublet at $\delta$ 1.15 (3 H, $J$ 6.0 Hz) for the methyl protons while the $^{13}$C NMR spectrum displayed diagnostic signals at $\delta$ 65.96 (C-2") and 24.28 (C-3"). The diagnostic signals for diastereomer 205b were analogous to those in 205a. In addition, the IR spectrum displayed an absorption at $\nu_{max}$ 3426 cm$^{-1}$ (OH).

Treatment of the diastereomeric mixture of alcohols 205 with TPAP using NMO as co-oxidant,$^{181}$ gave ketone 206 as a crystalline solid in 93% yield (Scheme 79). Its $^1$H NMR spectrum displayed a doublet of doublets at $\delta$ 2.66 ($J$ 16.2, 3.4 Hz) for H-1", and a singlet at $\delta$ 2.05 (3 H) for the methyl protons, thus confirming the absence of protons at C-2". The $^{13}$C NMR spectrum provided further confirmation with a new signal at $\delta$ 207.77 for the C-2" carbonyl group, having shifted from $\delta$
65.96 and 66.39 for C-2⁻ in 205. In addition, the IR spectrum displayed a new absorption at $\nu_{\text{max}}$ 1714 cm⁻¹ for the carbonyl group.

Scheme 79 Reagents and conditions: i) TPAP, NMO, ms, CH₂Cl₂, rt, 1 h; ii) H₂, Pd/C, MeOH-EtOAc, rt, 7 days (57), 4 days (58)

Global debenzylation of 205 and 206 with Pd/C under an atmospheric hydrogen pressure gave target compounds 58 and 57 respectively in poor yields after column chromatography (Scheme 79). Reactions were incomplete after 4 days and addition of further equivalents of Pd/C did not make a difference. Debenzylation proved to be a general problem in our synthetic strategy and consequently, it was envisaged that synthesis of the same target compounds (58 and 57) might be achieved via Wacker oxidation of acetylated olefin 201a followed by reduction to the secondary alcohol.

To this end, treatment of 201a with excess PdCl₂ and CuCl₂ under an atmospheric oxygen pressure in DMF-water¹⁸⁴,¹⁸⁵ for 4 days gave ketone 207 in 50% yield (Scheme 80). In the case where only a catalytic quantity of PdCl₂ was used, the reaction didn't go to completion and only a trace of 207 was isolated after 8 days. The reaction outcome was confirmed by the absence of allyl group signals in the $^1$H and $^{13}$C NMR spectra of 207.
and product had the same R_f value (tlc), however, visualization of components on the tlc plate by acidified anisaldehyde spray revealed a colour difference.

The ^1H NMR spectrum of 208a displayed important signals at δ 3.85-3.77 (m) for H-2'' and at δ 1.17 (3 H, d, J 6.0 Hz) for the methyl protons. The ^13C NMR spectrum displayed a new signal at δ 66.74 (C-2'') confirming the reduction of the carbonyl group, which had shifted from δ 206.43 for C-2'' in 207. The diagnostic signals for diastereomer 208b were analogous to those in 208a. In addition, the IR spectrum displayed an absorption at ν_max 3467 cm^{-1} (OH).

![Chemical structure of 207 and 208](image)

**Scheme 82 Reagents and conditions:** i) NaBH₄, THF-MeOH, -20 °C, 2 h (1:1)

The diastereomeric mixture of alcohols 208 was exposed to Zemplén deacetylation conditions followed by neutralization of the solution with Amberlite IR-120 H⁺ resin to give an inseparable mixture of diastereomers 58 in 89% yield (Scheme 83).

![Chemical structure of 208 and 58](image)

**Scheme 83 Reagents and conditions:** i) NaOMe, MeOH-CH₂Cl₂, rt, 18 h (1:1)

The absence of acetoxy groups in the ^1H and ^13C NMR supported a successful deacetylation. For diastereomer 58a, the ^1H NMR spectrum displayed signals at δ 4.90 (d, J 3.3 Hz) for H-1, δ 3.92 (m) for H-2'' and δ 1.16 (3 H, d, J 6.0 Hz) for the methyl group while the ^13C NMR spectrum displayed signals at δ 99.07 (C-1), 75.78 (C-1''), 67.32 (C-2'') and 23.54 (C-3''). The other diastereomer 58b was assigned by analogy to 58a. Accurate mass determination using FAB techniques displayed a molecular ion at 327.177488, corresponding to the M+Na molecular ion.

Synthesis of the epoxide target compound was envisaged to be very tricky. It was important to choose an appropriate protecting group that would be removed regioselectively without opening
the epoxide ring. Benzylated epoxide 204 was ruled out, in view of chemoselectivity problems envisaged in the debenzylation step. Acetate ester protecting groups were chosen as appropriate because only a catalytic amount of sodium methoxide was required for deprotection.

The epoxide was prepared by treating compound 201a with \textit{m}-CPBA\textsuperscript{177,178} to give an inseparable diastereomeric mixture (1:1, by \textsuperscript{1}H NMR) of epoxides 209 in 91\% yield as an oil (Scheme 84). Although doubling of signals in the NMR spectroscopy of the mixture made assignments difficult, the epoxide signals were evident from both \textsuperscript{1}H and \textsuperscript{13}C NMR spectra. Thus for diastereomer 209a, the \textsuperscript{1}H NMR spectrum displayed important signals at \(\delta\) 2.82 (m) for H-2''', \(\delta\) 2.66 (t, \(J\) 5.0 Hz) for H-3'''\textsubscript{a}, and \(\delta\) 2.36 (dd, \(J\) 5.0, 2.6 Hz) for H-3'''\textsubscript{b}. The \textsuperscript{13}C NMR spectrum displayed signals at \(\delta\) 49.97 (C-2'') and 47.53 (C-3'') which were diagnostic for the epoxide moiety. The diagnostic signals for diastereomer 209b were analogous to those in 209a.

![Scheme 84 Reagents and conditions: i) m-CPBA, CH\textsubscript{2}Cl\textsubscript{2}, rt, 24 h (1:1)]

Catalytic deacetylation of diastereomeric mixture of epoxides 209 under \textit{Zemplén} conditions followed by dilution of the solution with water gave an inseparable diastereomeric mixture (4:1, by \textsuperscript{1}H NMR) of epoxides 61 in 50\% yield after column chromatography, together with an inseparable diastereomeric mixture (1:1, by \textsuperscript{1}H NMR) of 210 (Scheme 85). The latter was not expected and arose from the intramolecular opening of the epoxide 209 at C-3''. An attempt to neutralize the solution with Amberlite IR-120 H\textsuperscript{+} resin led to total decomposition of the desired product (tlc).
Given our experience to date, the presence of epoxide signals was clearly discernible from both $^1$H and $^{13}$C NMR spectra but only one of the epoxide diastereomers could be characterized by NMR. Thus, the $^1$H NMR spectrum of 61a displayed signals at $\delta$ 5.04 (d, $J_{1,2}$ 3.2 Hz) for H-1, $\delta$ 3.07-3.00 (m) for H-2', $\delta$ 2.77 (dd, $J$ 5.0, 4.0 Hz) for H-3'-a and $\delta$ 2.51 (d, $J$ 5.0, 2.8 Hz) for 3'-b while its $^{13}$C NMR spectrum displayed signals at $\delta$ 96.88 (C-1), 74.51 (C-1'), 50.42 (C-2') and 47.51 (C-3'). Accurate mass determination using FAB techniques displayed a molecular ion at 325.162227, corresponding to the M+Na molecular ion.

The spectra for 210 were complicated due to overlapping signals, but evidence from $^1$H and $^{13}$C NMR and the accurate mass spectra led to the tentative assignment of the structure. The $^1$H NMR spectrum of 210a displayed signals at $\delta$ 5.15 (d, $J_{1,2}$ 3.0 Hz) for H-1, and $\delta$ 4.11 (m) for H-2'. The $^{13}$C NMR spectrum displayed signals at $\delta$ 97.75 (C-1), 81.96 (C-1'), 81.05 (C-2'), 65.66 (C-3'). The diastereomer 210b was assigned by analogy to 210a.

The final target in this work was the synthesis of the cyclopropanated compound 62. Cyclopropanated carbohydrates have been considered difficult to work with as a number of protection and deprotection reactions can be necessary. Cyclopropanated carbohydrates are ideally suited for electrophilic ring opening and it was important to have suitable protecting groups that could be removed selectively without opening of the cyclopropane ring. In our synthesis, benzyl protecting groups were not desirable because cyclopropane ring might open up during hydrogenation.
This left us with acetylated sugar as in 201a but several attempts to cyclopropane 201a using modified Simmons-Smith reaction conditions\textsuperscript{186-188} were unfortunately unsuccessful (Scheme 86). The reactions were conducted in different solvents (e.g. toluene, Et\textsubscript{2}O, hexane, CH\textsubscript{2}Cl\textsubscript{2}) and at different temperatures (0 °C, rt, 70 °C) without success. Increasing the equivalents of Et\textsubscript{2}Zn and CH\textsubscript{2}I\textsubscript{2} (> 10 eq) made no difference.

In all cases, the reaction did proceed in low conversion to a more polar product. This was isolated, but NMR revealed the retention of the allyl group.

These disappointing results prompted a model study on cyclopropanation. Following a procedure by Hoberg,\textsuperscript{186} benzylated glucal 212 was reacted under modified Simmons-Smith reaction conditions [Et\textsubscript{2}Zn, 1 M in toluene] (6 eq), CH\textsubscript{2}I\textsubscript{2} (6 eq), Et\textsubscript{2}O, rt, 6 h] to give known cyclopropanated sugar 116 in excellent yield (Scheme 87). The spectroscopic data for 116 was in agreement with the literature values.\textsuperscript{102}

However, cyclopropanation of 159a under similar conditions was unsuccessful (Scheme 88) and once more the isolated polar product (tlc) revealed the presence of olefinic signals (NMR). A possible reason for the reactivity difference was due to the greater nucleophilicity of the glucal double bond compared to that in 159a.
Scheme 88 Reagents and conditions: i) Et₂Zn, CH₂I₂, Et₂O, rt, 6 h

Time constraints and unavailability of material prevented further investigations of this reaction, and no concrete explanation could be put forward for the failure of cyclopropanation of the 2-C allyl sugars. However, undesired benzyl protecting groups are reported to be preferred during the cyclopropanation of sugars, and a number of reports have also suggested that other protecting groups such as OAc and TIPS are problematic.¹⁸⁶,¹⁸⁹
2.5 Biological activities

Having successfully synthesized some of the target compounds (51, 52, 57–61), the next phase of the project was to determine the biological activity of these compounds. Unfortunately, the biological testing of these compounds is still underway and full details of their activities are not yet available.

However, preliminary results suggest that 1-O-[2′-deoxy-2′-C-(2′′-hydroxypropyl)-α-D-glucopyranosyl]-D-myoinositol 51, 1-O-[2′-deoxy-2′-C-(2′′-oxopropyl)-α-D-glucopyranosyl]-D-myoinositol 52 and cyclohexyl 2-C-allyl-2-deoxy-α-D-glucopyranoside 59 are biologically active.

While compounds 51 and 52 do not inhibit the growth of Mycobacterium smegmatis in vitro, a pronounced inhibition of incorporation of [3H]inositol by whole cells into inositol containing metabolites was observed (Figure 20). The experiments involved monitoring the uptake of [3H]inositol by M. smegmatis as shown in details in Figure 20.

![Figure 20](image-url)

**Figure 20.** Effect of 51 on the incorporation of [3H]inositol into acid soluble metabolites of Mycobacterium smegmatis: M. smegmatis was grown in Middlebrook medium containing 5% glycerol. [3H]Inositol was added when the culture reached an absorbance of 0.44 at 600 nm. Cells were incubated for 3.5 h in the presence of two different amounts of 51 and was then harvested and sonicated in 0.25 M HClO4 to obtain the acid soluble fraction, which was chromatographed on a Vydac 201HS54 octadecylsilane column. Following injection of the sample the column was eluted for 5 min at 100%A, then for 25 min with a linear gradient to 70%B and for 5 min with a linear gradient to 100%B (A: 0.1% TFA, B: 0.1% TFA in a 6:4 (v/v) mixture of acetonitrile and water. The flow rate was 0.8 ml/min and 0.5 min fractions were collected and counted. The traces represent a radiolabel recovered in the eluate for a control culture lacking inhibitor (solid line), and for cultures labeled in the presence of 20 μg/ml (Broken line) or 200 μg/ml (dotted line) 51.

---

Footnote: Full results are shown for 51 and 52. At the time of writing the tests on 59 had not been fully completed, although indications were that the activities were similar to 51 and 52.
Of the three radiolabeled peaks in the HPLC trace, the peak eluting at 4 - 5.5 min was found to contain inositol monophosphate as determined by coelution with an authentic standard on a Partisil SAX10 anion exchange column, while the peak eluting at 7 - 9 min contains mycothiol as determined by reaction with sulfhydryl reagents and coelution with authentic mycothiol as the 7-diethylamino-3-(4'-maleimidyl-phenyl)-4-methylcoumarin derivative. The [3H]inositol labeled compound(s) eluting at 15.5 - 17 min have not as yet been characterised, but incorporation of radiolabel into this fraction was maximally inhibited at 20 µg/ml of 51 (Figure 21). At this level of the inhibitor the transport of radiolabel into the organisms was unaffected as compared to a control which lacked inhibitors.

![Figure 21. Comparison of the radiolabel recovered in the three major HPLC peaks after incubation of M. smegmatis in the presence of two different levels of 51 and 52. (MSH = mycothiol).](image)

It is evident, therefore, that 51 and 52 inhibit the incorporation of [3H]inositol into a number of metabolites which contain inositol. The identification of these metabolites, more detailed enzymological studies and an evaluation of the effects of 51 and 52 on the susceptibility of mycobacteria to various stresses will be of much interest.

In addition, there is some evidence that inhibitors containing D-myo-inositol undergo some hydrolysis during the assay, presumably catalyzed by glycosidases present in M. smegmatis. This needs to be clarified further, but hints at the need to develop more stable analogues in the ongoing work.
CONCLUSION

An effective and simple synthetic strategy has been developed for the synthesis of 2-deoxy-2-C-alkylglucosides as analogues of biosynthetic intermediates of mycothiol. C-2 alkylation of the sugars has been achieved in high yields and with good stereoselectivities by free-radical methodology, whereas lithium enolate-mediated alkylation gave the desired alkylated compound in poor yield and with the additional problem that reduction of ketone gave predominantly the undesired axial epimer.

Synthesis of glycosyl donors bearing an alkenyl side-chain has been achieved in high yields and these proved effective as glycosylating agents in reactions with enantiomerically pure myo-inositol derivative, giving high α- selectivities. The most practical route for the introduction of the oxygenated alkyl side-chain proved to be via epoxidation of the olefin of benzylated glucosides followed by regioselective reductive opening and oxidation as required. The epoxides were also shown to be valuable strategic intermediates for generating a range of additional analogues.

Final deprotection of some benzylated analogues has been problematic but an alternative synthetic strategy using acetyl protecting groups allowed for efficient final deprotection to give the desired target compounds in good yields. Evaluation of the biological activity of the target compounds is still in progress, but preliminarily results have shown that 51, 52 and 59 inhibit the incorporation of [³H]inositol by whole cells of Mycobacterium smegmatis into a number of metabolites which contain inositol.
CHAPTER 4

EXPERIMENTAL

4.1 General Procedures

**Preparative:** All solvents were freshly distilled. Diethyl ether and tetrahydrofuran were distilled under nitrogen and dried over sodium wire with benzophenone. Toluene and benzene were distilled over sodium under nitrogen. Dichloromethane was distilled over phosphorus pentoxide and the condensor was fitted with drying tube. Other solvents were purified according to standard procedures.\(^{190}\)

Reactions were monitored by thin layer chromatography (t.lc) using aluminum-backed precoated Merck silica gel 60 F254 plates and were visualized with a combination of ultraviolet, iodine vapour and either anisaldehyde or ceric ammonium sulfate solutions and then heated at 150 °C. Column chromatography was performed using Merck silica gel 60 (70-230 mesh) or on isolute\(^{®}\) C18 column. Work-up typically involved threefold extraction with an organic solvent. All reagents were purchased from Aldrich or Merck.

**Analytical:** Melting points were determined using a Reichert-Jung Thermovar hot-plate microscope and are uncorrected. Optical rotations were obtained using a Perkin Elmer 141 polarimeter at 20 °C. The concentration \(c\) refers to g/100 ml. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer in chloroform.

Nuclear Magnetic Resonance spectra were recorded on a Varian Unity 400 (100 MHz for \(^{13}\)C, 376.3 MHz for \(^{19}\)F) or Varian Mercury 300 MHz (75 MHz for \(^{13}\)C) and were carried out in d-chloroform unless otherwise stated. Chemical shifts (\(\delta\)) were recorded using residual chloroform (\(\delta\) 7.24 in \(^1\)H NMR and \(\delta\) 77.00 in \(^{13}\)C NMR) or tetramethylsilane as an internal standard (\(\delta\) 0.00). For D\(_2\)O, dioxane (\(\delta\) 3.75 in \(^1\)H NMR and \(\delta\) 67.19 in \(^{13}\)C NMR) was used as an internal standard. For CD\(_3\)OD, the residual methanol peak (\(\delta\) 3.31 in \(^1\)H NMR and \(\delta\) 49.00 in \(^{13}\)C NMR) was used as an internal standard. All chemical shifts are reported in ppm. Mass spectroscopy was performed at Cape Technikon or Kent mass-spectroscopy unit using a VG70-SEQ micromass spectrometer.
1,2,3,4,6-Penta-\(O\)-acetyl-\(\beta\)-D-glucopyranose (150)

A suspension of anhydrous sodium acetate (40.0 g, 0.49 mol) and D-glucose (80 g, 0.44 mol) in acetic anhydride (560 ml, 5.94 mol) was heated at reflux for 1 h. The clear solution was allowed to cool to room temperature and then poured into crushed ice (160 ml). After standing for 3 h with occasional stirring, the crystalline material was filtered, washed several times with cold water and dried over phosphorus pentoxide to afford compound 150 (120.23 g, 72%) as white crystals; mp 131-132 °C (from ethanol) (lit.,\(^{113}\) 132 °C); \(\delta_H\) (300 MHz; CDCl\(_3\)) 5.70 (1 H, d, J 8.1 Hz, H-1), 5.24 (1 H, t, J 9.5 Hz, H-3), 5.15-5.08 (2 H, m, H-2, H-4), 4.26 (1 H, dd, J 12.5, 4.7 Hz, H-6\(_a\)), 4.10 (1 H, dd, J 12.5, 2.3 Hz, H-6\(_b\)), 3.85-3.79 (1 H, m, H-5), 2.09, 2.07, 2.01, 2.00, 1.99 (15 H, 5 s, 5 \(\times\) COOCH\(_3\)); \(\delta_C\) (75 MHz; CDCl\(_3\)) 170.53, 170.02, 169.32, 169.17, 168.88 (5 \(\times\) COOCH\(_3\)), 91.71 (C-1), 72.79 (C-5), 72.74 (C-3), 70.26 (C-2), 67.79 (C-4), 61.46 (C-6), 20.74, 20.63, 20.51, 20.50, 20.50 (C-5 \(\times\) COOCH\(_3\)).

2,3,4,6-Tetra-\(O\)-acetyl-\(\alpha\)-D-glucopyranosyl bromide (151)

To a solution of 150 (23.0 g, 58.92 mmol) in CH\(_2\)Cl\(_2\) (24 ml) was added HBr in acetic acid (30%, 23 ml, 388.2 mmol). The round-bottomed flask was tightly stoppered and kept at room temperature for 2 h. Azeotrop istic distillation with toluene (300 ml x 3) and diethyl ether (80 ml \(\times\) 2) resulted in a white slurry, which was dissolved in dry diethyl ether (200 ml) and diluted with petroleum ether (300 ml). The semi-crystalline material was left at 0 °C for 18 h and filtered to give compound 151 (17.26 g, 71%) as crystals; mp 87-89 °C (diethyl ether-petroleum ether) (lit.,\(^{191}\) 88-89 °C); \(\delta_H\) (300 MHz; CDCl\(_3\)) 6.60 (1 H, d, J 4.0 Hz, H-1), 5.55 (1 H, t, J 9.6 Hz, H-3), 5.15 (1 H, dd, J 10.2, 9.6 Hz, H-4), 4.83 (1 H, dd, J 9.9, 4.0 Hz, H-2), 4.32 (1 H, dd, J 12.0, 4.2 Hz, H-6\(_a\)), 4.28 (1 H, m, H-5), 4.12 (1 H, dd, J 12.0, 1.9 Hz, H-6\(_b\)), 2.09, 2.08, 2.04, 2.02 (12 H, 4 s, 4 \(\times\) COOCH\(_3\)); \(\delta_C\) (75 MHz; CDCl\(_3\)) 170.44, 169.78, 169.74, 169.41 (4 \(\times\) COOCH\(_3\)), 86.55 (C-1), 72.15 (C-5), 70.62 (C-2), 70.19 (C-3), 67.22 (C-4), 60.97 (C-6), 20.61, 20.59, 20.56, 20.50 (4 \(\times\) COOCH\(_3\)).
3,4,6-Tri-O-acetyl-D-glucal (86)

A mixture of 151 (12.56 g, 30.54 mmol) and zinc dust (25g) in acetic acid (50%, 126 ml) was stirred vigorously at room temperature for 2 h. The zinc dust was then filtered off and the filtrate evaporated. Water (126 ml) was added to the syrup, which was extracted with diethyl ether, washed successively with saturated NaHCO₃ and water, then dried over MgSO₄ and concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (3:7) as eluent afforded compound 86 (5.39 g, 65%) as crystals; mp 53-54 °C (from ethanol) (lit.,¹¹⁵ 54-55 °C); δH (400 MHz; CDCl₃) 6.43 (1 H, dd, J 6.3, 1.4 Hz, H-1), 5.31 (1 H, m, H-3), 5.19 (1 H, dd, J 7.4, 5.8 Hz, H-4), 4.81 (1 H, ddd, J 6.3, 3.6, 0.4 Hz, H-2), 4.36 (1 H, dd, J 11.9, 5.4 Hz, H-6a), 4.22 (1 H, m, H-5), 4.17 (1 H, dd, J 11.9, 3.2 Hz, H-6b), 2.06, 2.04, 2.01 (9 H, 3 s, 3 × COOCH₃); δC (100 MHz; CDCl₃) 170.52, 170.34, 169.51 (3 × COOCH₃), 145.62 (C-1), 99.00 (C-2), 73.97 (C-5), 67.43 (C-3), 67.24 (C-4), 61.38 (C-6), 20.94, 20.74, 20.67 (3 × COOCH₃).
Methyl 2-deoxy-3,4,6-tri-O-acetyl-α-D-arabino-hexopyranoside (154a)

A solution of 86 (4.47 g, 16.41 mmol) in acetonitrile (44.7 ml) containing anhydrous lithium bromide (4.87 g, 2.18 mmol), dry methanol (15 ml, 370.78 mmol), 3 Å molecular sieves (1.63 g) and an acid resin (AG 50W-X8 (H⁺ form, 50-100 mesh, 7.2 g) was stirred at room temperature for 18 h. [The acid resin was prepared by washing commercial AG 50W-X8 (H⁺ form, 50-100 mesh resin, 20.0 g) with water (3 x 40 ml) until the filtrates were colourless and then with reagent grade acetonitrile (10 x 25 ml). The resin was then dried over phosphorus pentoxide in a desiccator under vacuum (0.2 mmHg) for 24 h to give dry resin (14 g)]. The resin and molecular sieves were filtered off, the filtrate was neutralized with triethylamine and solvent removed by evaporation under reduced pressure. The residue was dissolved in dichloromethane, successively washed with water, ice-cold 1 M HCl and saturated NaHCO₃, then dried over MgSO₄ and concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (1:4, then 3:7) as eluent afforded compound 154a (1.30 g, 26%) as an oil, its β-anomer 154b (730 mg, 15%) as an oil and starting material 86 (681 mg, 15%); δH (300 MHz; CDCl₃) 5.33-5.24 (1 H, m, H-3), 4.98 (1 H, t, J 9.8 Hz, H-4), 4.83 (1 H, d (br), J 3.0 Hz, H-1), 4.29 (1 H, dd, J 12.2, 4.7 Hz, H-6a), 4.06 (1 H, dd, J 12.2, 2.3 Hz, H-6b), 3.93 (1 H, m, H-5), 3.34 (3 H, s, -OMe), 2.27-2.20 (1 H, ddd, J 12.9, 5.4, 1.2 Hz, H-2α), 2.08, 2.02, 1.99 (9 H, 3 s, 3 × COOCH₃), 1.84-1.75 (1 H, ddd, J 12.9, 11.7, 3.6 Hz, H-2β); δC (75 MHz; CDCl₃) 170.70, 169.12, 169.87 (3 × COOCH₃), 98.05 (C-1), 69.37 (C-4), 69.07 (C-3), 67.75 (C-5), 62.44 (C-6), 54.86 (C-OMe), 34.92 (C-2), 20.91, 20.70, 20.68 (3 × COOCH₃).
Methyl 2-deoxy-α-D-arabino-hexopyranoside (153)

1. From 86

(i) Methanolic sodium methoxide (1 M, 11 ml, 11 mmol) was added dropwise to a solution of 86 (6.10 g, 22.40 mmol) in CH₂Cl₂-MeOH (3:5, 40 ml). The solution was stirred at room temperature for 18 h and then neutralized with Amberlite IR-120 H⁺ resin. After filtration to remove the resin, the solvent was evaporated to dryness and purified by column chromatography using methanol-ethyl acetate (1:4) as eluent to afford D-glucal 152 (3.22 g, 98 %) as hygroscopic crystals; mp 54-55 °C (from ethyl acetate) (lit., 118 58-60 °C). (ii) A solution of D-glucal 152 (3.22 g, 22.03 mmol) in 2.5% HCl in methanol (83 ml) was heated at 60 °C for 1 h. The solution was neutralized with silver carbonate, treated with charcoal and then filtered through celite. The solvent was evaporated and the resulting residue purified by column chromatography using methanol-ethyl acetate (1:4) as eluent to afford compound 153 (330 mg, 8%) as crystals. For characterization, a portion of this compound was acetylated as follows:

Acetic anhydride (2 ml, 21.19 mmol) was added to a solution of 153 (100 mg, 0.56 mmol) in pyridine (3 ml) and the reaction mixture was left at room temperature. After 16 h, 1 M HCl was added and the solution extracted with ethyl acetate. The ethyl acetate phase was washed successively with water and saturated NaHCO₃, then dried over MgSO₄ and concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (3:7) as eluent gave the acetylated compound 154a (162 mg, 95%) as an oil.

2. From 154a

Methanolic sodium methoxide (1 M, 1.92 ml, 1.92 mmol) was added dropwise to a solution of 154a (1.17 g, 3.84 mmol) in CH₂Cl₂-MeOH (7:15 ml). The solution was stirred at room temperature for 18 h and then neutralized with Amberlite IR-120 H⁺ resin. After filtration of resin, the solvent was evaporated to dryness and purified by column chromatography using methanol-ethyl acetate (1:4) as eluent to afford compound 153 (612 mg, 89 %) as crystals; mp 85-88 °C (from ethanol) (lit., 119 90-92 °C).
Methyl 4,6-\(O\)-benzylidene-2-deoxy-\(\alpha\)-D-arabino-hexopyranoside (155)

A mixture of 153 (360 mg, 2.02 mmol) and finely powdered anhydrous zinc chloride (0.33 g, 2.42 mmol) in freshly distilled benzaldehyde (1.5 ml, 14.78 mmol) was stirred vigorously at room temperature for 3 days. Water was added, and the mixture then extracted with ethyl acetate. The ethyl acetate was dried over MgSO\(_4\) and concentrated. The resulting residue was purified by column chromatography using ethyl acetate-petroleum ether (3:7) as eluent to afford compound 155 (493 mg, 92\%) as crystals; mp 147-150 °C (from ethanol) (lit.,\(^{192}\) 151-152 °C, lit.,\(^{119}\) 137-139 °C); \(\delta\)\(_H\) (400 MHz; CDCl\(_3\)) 7.50-7.35 (5 H, m, aromatic H), 5.55 (1 H, s, PhCH\(-\)), 4.78 (1 H, d, \(J\) 3.6 Hz, H-1), 4.24 (1 H, dd, \(J\) 9.2, 3.6 Hz, H-6\(_a\)), 4.18-4.12 (1 H, m, H-3), 3.81-3.67 (2 H, m, H-5, H-6\(_b\)), 3.45 (1 H, t, \(J\) 9.0 Hz, H-4), 3.33 (3 H, s, -OMe), 2.47 (s (br), -OH), 2.23-2.18 (1 H, m, H-2\(_{ax}\)), 1.80-1.73 (1 H, m, H-2\(_{eq}\)); \(\delta\)\(_C\) (100 MHz; CDCl\(_3\)) 137.36, 129.22, 128.33, 126.26 (aromatic C), 102.05 (C-PhCH\(-\)), 99.08 (C-1), 83.91 (C-4), 69.08 (C-6), 65.90 (C-3), 62.52 (C-5), 54.83 (C-OMe), 37.29 (C-2).

Methyl-\(\alpha\)-D-mannopyranoside (157)

A solution of D-mannose (40.0 g, 222.02 mmol) in methanol (200 ml) was heated at reflux for 40 min. Methanol-equilibrated Dowex-50 (H\(^+\)) resin (25 g, prepared by soaking Dowex-50, X-8, 50-100 mesh, for 18 h in each of six successive portions of absolute methanol and finally filtered under vacuum until damp-dry and then stored slightly moist with methanol in a closed container) was added and the mixture was refluxed for a further 3 h. The solution was immediately decanted from the ion exchange resin and the resin washed with methanol. The solvent was evaporated and the resulting crystalline slurry refrigerated for 20 h. The thick crystalline slurry was filtered and washed several times with \(n\)-propanol to afford compound 157 (27.01 g, 63\%) as crystals; mp 189-191 °C (\(n\)-propanol) (lit.,\(^{122}\) 190-192 °C); A portion of this compound was acetylated for characterization as described below.
Methyl 2,3,4,6-tetra-\(O\)-acetyl-\(\alpha\)-D-mannopyranoside (158)

A mixture of compound 157 (1.05 g, 5.40 mmol), anhydrous NaOAc (0.5 g) and acetic anhydride (12 ml) was heated at 100 °C for 30 min. The reaction mixture was cooled to room temperature, water added, and the mixture extracted with CH\(_2\)Cl\(_2\). The CH\(_2\)Cl\(_2\) was dried over MgSO\(_4\), and concentrated. Purification was achieved by column chromatography using ethyl acetate-petroleum ether (3:7) as mobile phase. Crystallization was effected by addition of ethanol-water and leaving the solution at 0 °C for 18 h. Filtration afforded compound 158 (1.26 g, 64%) as crystals; mp 62-64 °C (from ethanol) (lit.,\(^{122}\) 63-64 °C); \(\delta_H\) (400 MHz; CDCl\(_3\)) 5.30 (1 H, dd, \(J\) 10.2, 3.4 Hz, H-3), 5.24 (1 H, t, \(J\) 10.0 Hz, H-4), 5.20 (1 H, dd, \(J\) 3.4, 1.7 Hz, H-2), 4.68 (1 H, d, \(J\) 1.7 Hz, H-1), 4.25 (1 H, dd, \(J\) 12.3, 5.4 Hz, H-6\(_a\)), 4.09 (1 H, dd, \(J\) 12.3, 2.4 Hz, H-6\(_b\)), 3.95-3.91 (1 H, m, H-5), 3.37 (3 H, s, -OME), 2.12, 2.07, 2.00, 1.95 (12 H, 4 s, 4 × COOCH\(_3\))\(^{2}\); \(\delta_C\) (100 MHz; CDCl\(_3\)) 170.58, 169.98, 169.82, 169.68 (4 × COOCH\(_3\)), 98.59 (C-1), 69.52 (C-2), 69.04 (C-3), 68.40 (C-5), 66.20 (C-4), 62.52 (C-6), 55.26 (C-OMe), 20.82, 20.64, 20.63, 20.62 (4 × COOCH\(_3\)).
Methyl 2,3:4,6-di-O-benzylidene-α-D-mannopyranoside (96)

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{Ph} & \quad \text{O} \\
\end{align*}
\]

α,α-Dimethoxytoluene (46 g, 302.46 mmol) and anhydrous p-toluenesulfonyl acid (0.5 g, 2.63 mmol) was added to a solution of 157 (25.0 g, 128.74 mmol) in DMF (150 ml), and the solution was heated at 75 °C for 4 h. The mixture was poured with vigorous stirring into ice-water (500 ml) containing sodium hydrogen carbonate (25 g). The resulting gum-like crystalline product was filtered and re-suspended into ice-water, filtered again and washed with water. The product was dried under vacuum over phosphorus pentoxide to afford compound 96 (32.7 g, 68%) as crystals. The product, sufficiently pure for the following step, appeared from its 1H NMR spectrum to be a mixture of diastereomers at the carbon atom of the 2,3-acetal.

Recrystallization from n-propanol gave 96a as a single diastereomer; mp 176-179 °C (n-propanol) (lit., 182 180-182 °C, lit., 193 188 °C); δH (300 MHz; CDCl₃) 7.58-7.35 (10 H, m, aromatic H), 6.29 (1 H, s, PhCH-), 5.64 (1 H, s, PhCH'-), 5.01 (1 H, s, H-1), 4.62 (1 H, dd, J 7.5, 5.6 Hz, H-3), 4.36 (1 H, m, H-6a), 4.14 (1 H, d, J 5.6 Hz, H-2), 3.93-3.81 (3 H, m, H-4, H-5, H-6b), 3.40 (3 H, s, -OMe); δC (75 MHz; CDCl₃) 138.63, 137.17, 129.11, 129.10, 128.37, 128.22, 126.30, 126.05 (aromatic C), 103.00 (PhCH-), 102.04 (PhCH'-), 98.87 (C-1), 77.52 (C-5), 75.57 (C-3), 75.34 (C-2), 68.93 (C-6), 60.33 (C-4), 55.18 (C-OMe); HREIMS: m/z 370.14159 (M)+. Calcd for C₂₁H₂₂O₆ 370.14164.

Recrystallization of the mother liquor from ethanol gave the other diastereomer 96b; 105-107 °C (from ethanol) (lit., 193 106-107 °C); δH (400 MHz; CDCl₃) 7.59-7.34 (10 H, m, aromatic H), 5.97 (1 H, s, PhCH-), 5.52 (1 H, s, PhCH'-), 5.08 (1 H, s, H-1), 4.48 (1 H, t, J 6.6 Hz, H-3), 4.35-4.26 (2 H, m, H-2, H-6a), 3.87-3.71 (3 H, m, H-4, H-5, H-6b), 3.43 (3 H, s, -OMe); δC (100 MHz; CDCl₃) 137.49, 137.33, 129.63, 129.24, 128.66, 128.40, 126.76, 126.48 (aromatic C), 104.34 (d, J 3.8 Hz, PhCH-), 102.02 (d, J 3.8 Hz, PhCH'-), 98.97 (d, J 3.8 Hz, C-1), 80.76 (C-5), 78.58 (C-2), 74.38 (C-3), 68.12 (C-6), 60.60 (C-4), 55.34 (C-OMe); HREIMS: m/z 370.14159 (M)+. Calcd for C₂₁H₂₂O₆ 370.14164.
Methyl 4,6-O-benzylidene-2-deoxy-α-D-erythro-hexopyranosid-3-ulose (94)

\[ \text{Ph} \]
\[ \text{O} \]
\[ \text{O} \]
\[ \text{OMe} \]

1. From 96

A solution of a mixture of diastereomers 96 (5.0 g, 13.49 mmol) in THF (100 ml) was cooled down to −40 °C, and n-butyllithium in hexane (2.5 M, 12.5 ml, 31.25 mmol) was added dropwise, keeping the temperature below −30 °C for 1 h. The progress of the reaction was monitored by tlc; plates were developed with diethyl ether-petroleum ether (1:1) and heated for 20 min at 130 °C before being sprayed with ceric ammonium sulphate in sulphuric acid. The heating step was required for removal of 1-phenyl-1-pentanol (from addition of butyllithium to benzaldehyde), whose \( R_f \) value was the same as that of the starting material. The solution was poured with vigorous stirring into cold saturated ammonium chloride and without separating the layers, THF was evaporated in vacuo at a temperature below 30 °C. The remaining aqueous slurry was refrigerated for 18 h, and the crystalline compound filtered off and washed with water. The product was recrystallized from ethanol and washed with cold petroleum ether to afford compound 94 (2.37 g, 67%) as crystals; mp 169-170 °C (from ethanol) (lit., 123 170-171 °C).

2. From 155

Dry pyridine (3.3 ml, 40.8 mmol) was added to chromium trioxide (0.18 g, 1.8 mmol) at 0 °C. After stirring for 15 min, a solution of 155 (120 mg, 0.45 mmol) in dry pyridine (2 ml) was added. The resulting mixture was allowed to warm to room temperature during 1 h and then heated at 90 °C for another 1 h. The black solution was filtered, washed with ethyl acetate and then evaporated to dryness. The residue was taken up in dry benzene and solvent was evaporated. The resulting light brown solid was purified by column chromatography using ethyl acetate-petroleum ether (3:7) as eluent to afford compound 94 (61 mg, 51%) as crystals; mp 169-170 °C (from ethanol) (lit., 192 177-178 °C); \( \nu_{\text{max}}/\text{cm}^{-1} \) 1750 (C=O); \( \delta_H \) (300 MHz; CDCl\textsubscript{3}) 7.50-7.34 (5 H, m, aromatic H), 5.56 (1 H, s, PhCH\textsubscript{2}), 5.12 (1 H, d, J 4.3 Hz, H-1), 4.35 (1 H, dd, J 10.1, 4.5 Hz, H-6\textsubscript{a}), 4.28 (1 H, d, J 9.9 Hz, H-4), 4.13 (1 H, m, H-5), 3.90 (1 H, t, J 10.1 Hz, H-6\textsubscript{b}), 3.36 (3 H, s, -OMe), 2.81 (1 H, dd, J 14.5, 4.3 Hz, H-2\textsubscript{ax}), 2.64 (1 H, d, J 14.5 Hz, H-2\textsubscript{eq}); \( \delta_C \) (75 MHz; CDCl\textsubscript{3}) 197.39 (C-3), 136.57, 129.23, 129.22, 126.37 (aromatic C), 102.08 (C-1), 100.57 (C-PhCH\textsubscript{2}), 83.07 (C-4), 69.42 (C-6), 65.06 (C-5), 54.93 (C-OMe), 46.38 (C-2); HREIMS: \( m/z \) 264.10017 (M\textsuperscript{+}). Calcd for C\textsubscript{14}H\textsubscript{16}O\textsubscript{5} 264.09977.
Methyl 4,6-O-benzylidene-2-C-allyl-2-deoxy-α-D-ribo-hexopyranosid-3-ulse (70)

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{OMe}
\end{align*}
\]

1. General procedure for alkylation via enolate:
Diisopropylamine was added to THF (10 ml) at −78 °C and, after 2 minutes, n-butyllithium in hexane (2.5 M) was added dropwise. The reaction mixture was allowed to stand for 15 minutes and a solution of 94 (200 mg, 0.76 mmol) in THF (5 ml) was then added. After 15 minutes, HMPA (2 ml) was added followed by allyl bromide, and the reaction was left, varying the temperature and time for each run. A solution of saturated ammonium chloride was then added, the slurry extracted with dichloromethane, and the organic phase dried over MgSO₄ and concentrated. TLC showed the presence of starting material and three new products. Separation was achieved by column chromatography using ethyl acetate-petroleum ether (1:4) as eluent with the most polar product identified as compound 70.

2. From 96
A solution of n-butyllithium in hexane (2.5 M, 0.5 ml, 1.25 mmol) was added dropwise to a solution of 96 (202 mg, 0.54 mmol) in THF (9 ml) at −30 °C. After stirring for 15 minutes, HMPA (0.9 ml) was added followed by allyl bromide (0.1 ml, 1.15 mmol). The mixture was maintained at a temperature below −30 °C for 12 hours. The reaction was stopped by the addition of cold saturated NH₄Cl, extracted with CH₂Cl₂, and the organic phase dried over MgSO₄ and concentrated, whereupon TLC indicated the presence of some starting material. The brown oil was purified by column chromatography using ethyl acetate-petroleum ether (1:9) as eluent to give unreacted starting material 96 (113 mg, 56%) and desired compound 70 (52 mg, 32%) as crystals; mp 158-159 °C (from ethanol) (lit., 89 158-159 °C); ν<sub>max</sub>/cm<sup>-1</sup> 1755 (C=O); δ<sub>H</sub> (400 MHz; CDCl₃) 7.56-7.34 (5 H, m, aromatic H), 5.76 (1 H, m, H-2'), 5.58 (1 H, s, PhCH<sub>2</sub>), 5.14-5.05 (2 H, m, H-3<sup>"</sup> m, H-3<sup>"</sup> b), 5.01 (1 H, d, J 4.0 Hz, H-1), 4.38 (1 H, dd, J 10.3, 4.8 Hz, H-6<sup>a</sup>), 4.29 (1 H, dd, J 9.6, 1.2 Hz, H-4), 4.11 (1 H, m, H-5), 3.93 (1 H, t, J 10.3 Hz, H-6<sup>b</sup>), 3.38 (3 H, s, -OMe), 2.81 (1 H, m, H-2), 2.59 (1 H, m, H-1'), 2.22 (1 H, m, H-1'); δ<sub>C</sub> (100 MHz; CDCl₃) 198.26 (C-3), 136.66 (aromatic C), 134.90 (C-2'), 129.24, 128.25, 126.41 (aromatic C), 117.24 (C-3'), 103.18 (C-1), 102.05 (C-PhCH<sub>2</sub>), 83.16 (C-4), 69.61 (C-6), 66.02 (C-5), 55.26 (C-OMe), 53.54 (C-2), 28.21 (C-1'); HREIMS: <sup>m/z</sup> 304.12926 (M)<sup>+</sup>. Calcd for C<sub>17</sub>H<sub>26</sub>O<sub>5</sub> 304.13107.
Methyl 4,6-\(\text{-}\text{O-benzylidene-2-C-allyl-2-deoxy-\(\alpha\)-D-allopyranoside\) (159a)}}

1. Reduction of 70 with LAH

To a solution of lithium aluminium hydride (5 mg, 0.13 mmol) in THF (1 ml) at 0 °C was added dropwise a solution of 70 (20 mg, 0.065 mmol) in THF (1 ml). After 2 h, water was added to decompose excess lithium aluminium hydride, the slurry extracted with ethyl acetate, which was dried over MgSO\(_4\) and concentrated to afford a mixture of C-3 diastereomers (19 mg, 95%, \(\alpha\)-allo 159\(\alpha\):\(\alpha\)-gluco 159b = 8:1 by \(^1\text{H-NMR\) as crystals. Recrystallization from petroleum ether afforded a single diastereomer 159\(\alpha\).

2. Reduction of 70 with NaBH\(_4\)

NaBH\(_4\) (0.2 g, 5.49 mmol) was added portion-wise to a solution of 70 (167 mg, 0.55 mmol) in THF-MeOH (3.6 ml) at –20 °C. The reaction mixture was allowed to reach 0 °C within 2 h, quenched with saturated NaHCO\(_3\), extracted with CH\(_2\)Cl\(_2\), dried over MgSO\(_4\) and concentrated to give a single diastereomer 159\(\alpha\) (166 mg, 98%) as crystals; mp 124-125 °C (from petroleum ether); \([\alpha]_D^0 +73.4^\circ\) (c 1.2, CHCl\(_3\)); \(v_{\text{max}}/\text{cm}^{-1}\) 3018 (OH); \(\delta_\text{H}\) (400 MHz; CDCl\(_3\)) 7.55-7.31 (5 H, m, aromatic H), 5.78 (1 H, m, H-2’), 5.60 (1 H, s, PhCH-), 5.18-5.06 (2 H, m, H-3’\(a\), H-3’\(b\)), 4.63 (1 H, d, J 3.4 Hz, H-1), 4.35 (1 H, dd, J 10.1, 5.2 Hz, 6\(a\)), 4.14 (1 H, m, H-5), 4.06 (1 H, m, H-3), 3.77 (1 H, t, J 10.1 Hz, H-6\(a\)), 3.55 (1 H, dd, J 9.6, 2.8 Hz, H-4), 3.41 (3 H, s, -OMe), 2.76 (d (br), J 7.8 Hz, -OH), 2.37 (2 H, m, H-1’\(a\), H-1’\(b\)), 1.91 (1 H, m, H-2); \(\delta_\text{C}\) (75 MHz; CDCl\(_3\)) 137.38 (aromatic C), 135.05 (C-2’), 129.02, 128.21, 126.27 (aromatic C), 117.41 (C-3’), 102.01 (C-PhCH-), 101.37 (C-1), 80.52 (C-4), 69.42 (C-6), 67.56 (C-3), 58.24 (C-5), 55.81 (C-OMe), 43.22 (C-2), 31.53 (C-1’); HREIMS: \(m/z\) 306.14587 (M\(^+\)). Calcd for C\(_{17}\)H\(_{22}\)O\(_5\) 306.14672.
3,4,6-Tri-O-acetyl-1,2-O-(1-ethoxyethylidene)-β-D-mannopyranose (161)

A mixture of D-mannose (10.0 g, 55.5 mmol), anhydrous NaOAc (5 g, 60.95 mmol) and acetic anhydride (70 ml) was heated at 100 °C for 1 h. The solvent was evaporated in vacuo, water was added, and the mixture extracted with CH₂Cl₂, dried over MgSO₄ and concentrated. The resulting syrup was dissolved in CH₂Cl₂ (25 ml) and HBr in acetic acid (30%, 27 ml) was added. After stirring for 3 h at room temperature, tlc indicated the completion of reaction to give 2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl bromide. The solution was diluted with CH₂Cl₂, successively washed with ice-water (× 5), 1% NaHCO₃, ice-water, dried over MgSO₄ and concentrated. The resultant syrup was dissolved in acetonitrile (10 ml) and treated with anhydrous EtOH (15 ml) and 2.6-lutidine (14 ml). After 15 h at room temperature the solution was diluted with CH₂Cl₂, washed with water, dried over MgSO₄ and concentrated. The semi-solid material was crystallized from ethanol to afford compound 161 (14.40 g, 67%) as crystals; mp 93-95 °C (from ethanol) (lit.,¹³⁵ 101-103 °C); δH (300 MHz; CDCl₃) 5.46 (1 H, d, J 2.6 Hz, H-1), 5.28 (1 H, t, J 9.8 Hz, H-4), 5.13 (1 H, dd, J 9.8, 4.0 Hz, H-3), 4.58 (1 H, dd, J 4.0, 2.6 Hz, H-2), 4.22 (1 H, dd, J 12.1, 4.6 Hz, H-6a), 4.13 (1 H, dd, J 12.1, 2.8 Hz, H-6b), 3.66 (1 H, m, H-5), 3.59-3.49 (2 H, m, -OCH₂CH₃), 2.10, 1.05, 2.03 (9 H, 3 s, 3 × COOCH₃), 1.73 (3 H, s, -O₃CCH₃), 1.17 (3 H, t, J 7.1 Hz, -OCH₂CH₃); δC (75 MHz; CDCl₃) 170.61, 170.35, 169.39 (3 × COOCH₃), 124.21 (C-O₃CCH₃), 97.37 (C-1), 76.34 (C-2), 71.39 (C-5), 70.62 (C-3), 65.61 (C-4), 62.39 (C-6), 58.15 (C-OCH₂CH₃), 24.62 (C-O₂CCH₃), 20.71, 20.67, 20.62 (3 × COOCH₃), 15.03 (C-OCH₂CH₃); HREIMS: m/z 361.11159 (M-CH₃)⁺. Calcd. for C₁₅H₂₁O₁₀ 361.11347 (M-CH₃)⁺.
1,3,4,6-Tetra-O-acetyl-β-D-mannopyranose (160)

1. From D-mannose

A small amount of D-mannose (53 mg) was added to acetic anhydride (26 ml) followed by 3 drops of 70% perchloric acid to give a yellow solution. Bulk D-mannose (6.65 g, 36.93 mmol) was then added portion-wise with continuous stirring during 20 min, with the internal temperature being kept at 40-50 °C. The mixture was kept at room temperature for 1 h, then cooled down to 15 °C and phosphorus tribromide (4.4 ml) added dropwise, the internal temperature being kept at 20-25 °C. Water (2.4 ml) was then added and the mixture was kept at room temperature for 1.5 h. A solution of sodium acetate trihydrate (20 g) in water (25 ml) at 5 °C was slowly added (the internal temperature being kept at 35-40 °C) and the resulting yellow solution was kept at this temperature for 25 min. The solution was then poured onto ice-water and extracted with CH₂Cl₂ (× 3). The dichloromethane extracts were combined, successively washed with cold water, saturated NaHCO₃, cold water and dried over MgSO₄. The filtrate was evaporated to dryness and the residue was crystallized from diethyl ether to afford compound 160 (2.40 g, 19%) as crystals.

2. From orthoester 161

A solution of 161 (11.0 g, 29.23 mmol) in acetone (66 ml) was treated with 1 N HCl (7 ml) at room temperature for 10 min and the solvent was evaporated at less than 20 °C at 20 mmHg. The residue was dissolved in CH₂Cl₂, washed with water, and the CH₂Cl₂ phase dried over MgSO₄ and concentrated. The resulting syrup crystallized upon addition of diethyl ether to afford compound 160 (3.12 g, 31%) as crystals; mp 165-166 °C (from ethanol) (lit., 164-165 °C, lit., 164-166 °C); ν<sub>max</sub>/cm⁻¹ 3450 (OH); δ<sub>H</sub> (300 MHz; CDCl₃) 5.78 (1 H, d, J 1.2 Hz, H-1), 5.37 (1 H, t, J 9.7 Hz, H-4), 5.02 (1 H, dd, J 9.7, 2.8 Hz, H-3), 4.29 (1 H, dd, J 12.5, 4.9 Hz, H-6a), 4.18 (1 H, t (br), J 2.8 Hz, H-2), 4.12 (1 H, dd, J 12.5, 2.4 Hz, H-6b), 3.76 (1 H, m, H-5), 2.30 (d, J 3.6 Hz, -OH), 2.16, 2.10, 2.07, 2.03 (12 H, 4 s, 4 × COOCH₃); δ<sub>C</sub> (75 MHz; CDCl₃) 170.66, 170.03, 169.49, 168.43 (4 × COOCH₃), 91.66 (C-1), 73.13 (C-5), 72.81 (C-3), 68.44 (C-2), 65.25 (C-4), 61.94 (C-6), 20.82, 20.74, 20.69, 20.61 (4 × COOCH₃); HREIMS: m/z 331.10273 (M-OH)<sup>+</sup>. Calcd for C₁₄H₁₉O₉ 331.10291 (M-OH)<sup>+</sup>.
To a mixture of 160 (450 mg, 1.29 mmol) and pyridine (0.27 ml, 3.4 mmol) in CH₂Cl₂ (10 ml) was added trifluoromethanesulfonic anhydride (0.24 ml, 1.4 mmol) dropwise at 0 °C. The mixture was allowed to warm to room temperature over a period of 2 h. The reaction mixture was then poured into cold saturated NaHCO₃ (150 ml) and extracted with CH₂Cl₂ (× 3). The combined organic layers were washed with 1% HCl and dried over MgSO₄. Evaporation of the solvent afforded compound 162 (609 mg, 98%) as crystals; mp 119-121 °C (from ethanol) (lit.,¹²⁷ 118-119 °C); δH (300 MHz; CDCl₃) 5.90 (1 H, d, J 0.9 Hz, H-1), 5.29 (1 H, t, J 9.8 Hz, H-4), 5.18 (1 H, dd, J 9.8, 2.8 Hz, H-3), 5.13 (1 H, d (br), J 2.8 Hz, H-2), 4.24 (1 H, dd, J 12.4, 4.9 Hz, H-6b), 4.17 (1 H, dd, J 12.4, 2.8 Hz, H-6b), 3.82 (1 H, m, H-5), 2.16, 2.10, 2.09, 2.06 (12 H, 4 s, 4 × COOCH₃); δC (75 MHz; CDCl₃) 170.57, 169.79, 169.10, 167.92 (4 × COOCH₃), 89.12 (C-1), 81.21 (C-2), 73.58 (C-5), 69.62 (C-3), 64.63 (C-4), 61.68 (C-6), 20.64, 20.51, 20.42, 20.38 (4 × COOCH₃); HREIMS: m/z 421.04004 (M-C₂H₃O₂)⁺. Calcd for C₁₃H₁₆O₁₀F₃S 421.04163 (M-C₂H₃O₂)⁺.
1,3,4,6-Tetra-O-acetyl-2-bromo-2-deoxy-\(\alpha\)-D-mannopyranose (78a) and 1,3,4,6-Tetra-O-acetyl-2-bromo-2-deoxy-\(\beta\)-D-glucopyranose (78b)

1. From triflate 162
To a solution of 162 (3.66 g, 7.62 mmol) in benzene (100 ml) was added tetrabutylammonium bromide (4.8 g, 15.0 mmol) and the solution heated at reflux for 2 h. After cooling to room temperature, benzene was evaporated under reduced pressure. The residue was purified by column chromatography using ethyl acetate-petroleum ether (1:1) as eluent to afford compound 78b (3.10 g, 99%) as crystals.

1. From tri-O-acetyl D-glucal 86
A solution of 86 (1.0 g, 3.67 mmol) in acetic acid (10 ml) was stirred at room temperature in the presence of NBS (0.8 g, 4.49 mmol). After 4 h, the reaction was neutralized with a cold solution of 10% sodium hydroxide and extracted with diethyl ether. The organic layer was dried over MgSO₄, the solvent evaporated and the resulting mixture of diastereomers (\(\alpha\)-manno 78a: \(\beta\)-gluco 78b = 2:1 by \(^1\)H-NMR) separated by column chromatography using ethyl acetate-petroleum ether (3:7) as eluent to afford, successively, compound 78b (501 mg, 33%) as crystals, and compound 78a (980 mg, 65%) as an oil.

**Diastereomer 78a:** \(\delta\)H (300 MHz; CDCl₃) 6.30 (1 H, d, J 1.9 Hz, H-1), 5.47 (1 H, t, J 9.7 Hz, H-4), 5.18 (1 H, dd, J 9.7, 4.0 Hz, H-3), 4.42 (1 H, dd, J 4.0, 1.9 Hz, H-2), 4.22 (1 H, dd, J 12.1, 4.6 Hz, H-6b), 4.16-4.04 (2 H, m, H-5, H-6b), 2.15, 2.10, 2.09, 2.05 (12 H, 4 s, 4 \(\times\) COOCH₃); \(\delta\)C (75 MHz; CDCl₃) 170.63, 170.01, 169.22, 168.07 (4 \(\times\) COOCH₃), 93.19 (C-1), 71.32 (C-5), 68.81 (C-3), 65.66 (C-4), 61.88 (C-6), 47.80 (C-2), 20.81, 20.70, 20.64, 20.56 (4 \(\times\) COOCH₃).

**Diastereomer 78b:** mp 96-97 °C (from ethanol) (lit.,\(^{125,127}\) 95-96 °C); \(\delta\)H (300 MHz; CDCl₃) 5.80 (1 H, d, J 9.0 Hz, H-1), 5.33 (1 H, dd, J 10.5, 9.1 Hz, H-3), 5.01 (1 H, dd, J 10.0, 9.1 Hz, H-4), 4.30 (1 H, dd, J 12.6, 4.5 Hz, H-6a), 4.09 (1 H, dd, J 12.6, 2.4 Hz, H-6b), 3.89 (1 H, dd, J 10.5, 9.0 Hz, H-2), 3.87 (1 H, m, H-5), 2.16, 2.08, 2.06, 2.01 (12 H, 4 s, 4 \(\times\) COOCH₃); \(\delta\)C (75 MHz; CDCl₃) 170.47, 169.54, 169.43, 168.52 (4 \(\times\) COOCH₃), 93.17 (C-1), 74.43 (C-3), 72.92 (C-5), 68.59 (C-4), 61.41 (C-6), 47.56 (C-2), 20.63, 20.50, 20.49, 20.48 (4 \(\times\) COOCH₃).
To a solution of 162 (501 mg, 1.04 mmol) in benzene (25 ml) was added tetrabutylammonium iodide (0.76 g, 2.08 mmol) and the solution heated at reflux for 2 h. After cooling to room temperature, benzene was evaporated under reduced pressure. The residue was purified by column chromatography using ethyl acetate-petroleum ether (1:1) as eluent to afford compound 79 (473 mg, 99%) as crystals; mp 114-115 °C (from ethanol) (lit.,127 113-114 °C); δH (300 MHz; CDCl3) 5.86 (1 H, d, J 9.5 Hz, H-1), 5.33 (1 H, dd, J 11.1, 9.0 Hz, H-3), 4.99 (1 H, dd, J 10.2, 9.0 Hz, H-4), 4.31 (1 H, dd, J 12.6, 4.5 Hz, H-6a), 4.08 (1 H, dd, J 12.6, 2.2 Hz, H-6b), 3.98 (1 H, dd, J 11.1, 9.5 Hz, H-2), 3.87 (1 H, m, H-5), 2.15, 2.08, 2.06, 2.01 (12 H, 4 s, 4 × COOCH3); δC (75 MHz; CDCl3) 170.50, 170.49, 169.46, 169.45 (4 × COOCH3), 93.96 (C-1), 75.24 (C-3), 73.01 (C-5), 68.51 (C-4), 61.47 (C-6), 25.68 (C-2), 20.65, 20.64, 20.63, 20.51 (4 × COOCH3); HREIMS: m/z 358.01073 (M)+. Calcd for C14H19O9I 458.00738.
Methyl 3,4,6-tri-O-acetyl-2-bromo-2-deoxy-α-D-mannopyranoside (163a) and Methyl 3,4,6-tri-O-acetyl-2-bromo-2-deoxy-β-D-glucopyranoside (163b)

A solution of 86 (2.50 g, 9.18 mmol) in methanol (25 ml) was stirred at 0 °C for 3 h in the presence of NBS (2.2 g, 12.36 mmol). The solution was diluted with water and extracted with diethyl ether. The organic layer was washed successively with a 10% aqueous solution of Na₂S₂O₃ and water, then dried over MgSO₄. Evaporation of solvent gave a mixture of diastereomers (3.45 g, 98%, α-manno 163a:β-gluco 163b = 2:1 by ¹H-NMR). The residue was crystallized from methanol, yielding a single diastereomer 163b (880 mg, 25%) as crystals.

**Diastereomer 163b:** mp 137-138 °C (from methanol) (lit. 125 136-137 °C); δ_H (300 MHz; CDCl₃) 5.28 (1 H, dd, J 10.5, 9.2 Hz, H-3), 4.98 (1 H, dd, J 10.2, 9.2 Hz, H-4), 4.48 (1 H, d, J 8.4 Hz, H-1), 4.29 (1 H, dd, J 12.3, 4.8 Hz, H-6a), 4.13 (1 H, dd, J 12.3, 2.4 Hz, H-6b), 3.77 (1 H, dd, J 10.5, 8.4 Hz, H-2), 3.72 (1 H, m, H-5), 3.57 (3 H, s, -OMe) 2.08, 2.07, 2.01 (9 H, 3 s, 3 × COOCH₃); δ_C (75 MHz; CDCl₃) 170.56, 169.76, 169.43 (3 × COOCH₃), 103.32 (C-1), 74.68 (C-3), 71.94 (C-5), 69.23 (C-4), 61.85 (C-6), 57.57 (C-OMe), 49.29 (C-2), 20.66, 20.55, 20.52 (3 × COOCH₃).

Column chromatography of the mother liquor using ethyl acetate-petroleum ether (3:7) afforded the other diastereomer 163a as an oil; δ_H (300 MHz; CDCl₃) 5.38 (1 H, t, J 9.8 Hz, H-4), 5.19 (1 H, dd, J 9.8, 4.0 Hz, H-3), 4.95 (1 H, d, J 1.1 Hz, H-1), 4.42 (1 H, dd, J 4.0, 1.1 Hz, H-2), 4.23 (1 H, dd, J 12.3, 5.1 Hz, H-6a), 4.14 (1 H, dd, J 12.3, 2.7 Hz, H-6b), 3.97 (1 H, m, H-5), 3.40 (3 H, s, -OMe), 2.08, 2.06, 2.03 (9 H, 3 s, 3 × COOCH₃); δ_C (75 MHz; CDCl₃) 170.62, 169.90, 169.39 (3 × COOCH₃), 100.91 (C-1), 69.18 (C-5), 68.94 (C-3), 66.17 (C-4), 62.28 (C-6), 55.49 (C-OMe), 49.26 (C-2), 20.71, 20.64, 20.57 (3 × COOCH₃).
A solution of 78b (530 mg, 1.29 mmol) and allyltributylstannane (1.2 ml, 3.87 mmol) in benzene (5 ml) was degassed at room temperature for 30 min and then heated to reflux for 10 min. A solution of AIBN (37 mg, 0.19 mmol) in anhydrous benzene (2 ml) was added dropwise through a pressure-compensating dropping funnel and the heating was continued for 16 h. The reaction mixture was then cooled to room temperature, the solvent evaporated, and the residue dissolved in acetonitrile and washed with pentane (× 5). The acetonitrile phase was concentrated under reduced pressure and the crude product purified by column chromatography using ethyl acetate-petroleum ether (3:7) as eluent to afford an inseparable mixture of diastereomers (421 mg, 87%, β-glucopyranosyl 81a:β-manno 81b = 9:1 by 1H-NMR). Fractional crystallization from diethyl ether-pentane afforded a single diastereomer 81a (201 mg, 42%) as crystals; mp 99-100 °C (from diethyl ether-pentane) (lit.,73 89-90 °C); δH (400 MHz; CDCl3) 5.76-5.65 (1 H, m, H-2'), 5.56 (1 H, d, J 8.8 Hz, H-1), 5.10-4.93 (4 H, m, H-3, H-4, H-3', H-3''), 4.29 (1 H, dd, J 12.4, 4.4 Hz, H-6a), 4.05 (1 H, dd, J 12.4, 2.0 Hz, H-6a), 3.73 (1 H, m, H-5), 2.17-2.09 (3 H, m, H-2, H-1', H-1''), 2.11, 2.05, 2.01, 1.99 (12 H, 4 s, 4 × COOCH3); δC (100 MHz; CDCl3) 170.81, 170.31, 169.97, 169.04 (4 × COOCH3), 133.58 (C-2'), 117.85 (C-3'), 93.58 (C-1), 72.60 (C-3), 72.55 (C-5), 69.31 (C-4), 62.02 (C-6), 44.00 (C-2), 31.06 (C-1'), 21.04, 20.86, 20.83, 20.76 (4 × COOCH3); HREIMS: m/z 329.12403 (M- C2H3O)+. Calcd for C15H21O8 329.12364 (M-C2H3O)+.
1,3,4,6-Tetra-\(\text{O}\)-acetyl-2-deoxy-2-C-methallyl-\(\beta\)-D-glucopyranose (82a) and 1,3,4,6-Tetra-\(\text{O}\)-acetyl-2-deoxy-2-C-methallyl-\(\beta\)-D-mannopyranose (82b)

A solution of 78b (502 mg, 1.22 mmol) and methallyltributylstannane (1.25 ml, 3.62 mmol) in benzene (10 ml) was degassed at room temperature for 30 min and then heated to reflux for 10 min. A solution of AIBN (27 mg, 0.14 mmol) in anhydrous benzene (2 ml) was added dropwise through a pressure-compensating dropping funnel and the heating was continued for 16 h. The reaction mixture was cooled to room temperature, the solvent evaporated, and the residue dissolved in acetonitrile and washed with pentane (× 5). The acetonitrile phase was concentrated under reduced pressure and the crude product was purified by column chromatography using ethyl acetate-petroleum ether (3:7) as eluent to afford an inseparable mixture of diastereomers (450 mg, 95%, \(\beta\)-gluco 82a: \(\beta\)-manno 82b = 7:1 by \(^1\)H-NMR). The glucopyranose diastereomer crystallized slowly on standing at low temperature and recrystallization from petroleum ether afforded a single diastereomer 82a (228 mg, 48%).

**Diastereomer 82a** (\(\beta\)-gluco): mp 62-64 °C (from petroleum ether); \([\alpha]_D^{16.15°}\) (c 1.3, CHCl\(_3\)); \(\delta\)H (300 MHz; CDCl\(_3\)) 5.55 (1 H, d, J 9.0 Hz, H-1), 5.06-4.96 (2 H, m, H-3, H-4), 4.67 (1 H, d, J 1.1 Hz, H-4\(\prime\)a), 4.63 (1 H, d, J 1.1 Hz, H-4\(\prime\)b), 4.31 (1 H, dd, J 12.4, 4.5 Hz, H-6\(\prime\)b), 4.06 (1 H, dd, J 12.4, 2.2 Hz, H-6\(\prime\)a), 3.76 (1 H, m, H-5), 2.27 (1 H, m, H-2), 2.01 (2 H, d, J 6.6 Hz, H-1\(\prime\)a, H-1\(\prime\)b), 2.08, 2.07, 2.00, 1.98 (12 H, 4 s, 4 × COOCH\(_3\)), 1.73 (3 H, s (br), H-3\(\prime\)); \(\delta\)C (75 MHz; CDCl\(_3\)) 170.64, 170.25, 169.82, 168.96 (4 × COOCH\(_3\)), 142.34 (C-2\(\prime\)), 112.22 (C-4\(\prime\)), 94.43 (C-1), 74.04 (C-3), 72.48 (C-5), 69.08 (C-4), 61.94 (C-6), 42.10 (C-2), 37.07 (C-1\(\prime\)), 21.65 (C-3\(\prime\)), 20.86, 20.71, 20.62, 20.61 (4 × COOCH\(_3\)); HRFABMS: \(m/z\) 409.147246 (M+Na)+. Calcd for C\(_{18}\)H\(_{26}\)O\(_9\)Na 409.147444 (M+Na)+.

**Diastereomer 82b** (\(\beta\)-manno): \(\delta\)H (300 MHz; CDCl\(_3\)) 5.84 (1 H, d, J 2.4 Hz, H-1), 4.72 (1 H, s (br), H-4\(\prime\)a), 4.65 (1 H, s (br), H-4\(\prime\)b), 1.65 (3 H, s, H-3\(\prime\)); \(\delta\)C (75 MHz; CDCl\(_3\)) 170.47, 170.09, 169.68, 168.81 (4 × COOCH\(_3\)), 142.90 (C-2\(\prime\)), 111.95 (C-4\(\prime\)), 92.41 (C-1), 72.75 (C-3), 71.08 (C-5), 65.69 (C-4), 62.40 (C-6), 38.16 (C-2), 31.26 (C-1\(\prime\)), 22.15 (C-3\(\prime\)), 20.76, 20.60, 20.56, 20.47 (4 × COOCH\(_3\)); HRFABMS: \(m/z\) 409.147246 (M+Na)+. Calcd for C\(_{18}\)H\(_{26}\)O\(_9\)Na 409.147444 (M+Na)+.
1,3,4,6-Tetra-O-acetyl-2-deoxy-2-C-(2'-oxopropyl)-β-D-glucopyranoside (164a)

A solution of a mixture of diastereomers 82a and 82b (320 mg, 0.83 mmol) in CH₂Cl₂-MeOH (0.1 M, 10:1, 8 ml) was allowed to stir at room temperature for 10 min, cooled to −78 °C and then purged with oxygen for 5 min. A stream of ozone was then passed through the solution until a blue colour persisted (≈ 40 min), indicating that the solution was saturated with ozone. The reaction mixture was then purged with nitrogen for 20 min. To the clear solution was added, dimethyl sulfide (2 ml) and the solution was allowed to warm to room temperature over 20 h. The reaction mixture was diluted with CH₂Cl₂, washed with 10% HCl (× 3), and the CH₂Cl₂ phase dried over MgSO₄ and concentrated. The resulting clear oil was purified by column chromatography using ethyl acetate-petroleum ether (1:1) to give a mixture of diastereomers (268 mg, 83%, β-gluco 164a;β-manno 164b = 7:1 by ¹H-NMR). The residue was crystallized from diethyl ether, yielding a single diastereomer 164a (155 mg, 48%) as crystals; mp 122-124 °C (from diethyl ether); [α]D +13.86° (c 1.5, CHCl₃); νmax/cm⁻¹ 1752 (C=O); δH (400 MHz; CDCl₃) 5.62 (1 H, d, J 9.2 Hz, H-1), 5.03 (1 H, dd, J 10.8, 9.3 Hz, H-3), 4.96 (1 H, t, J 9.3 Hz, H-4), 4.23 (1 H, dd, J 12.4, 4.4 Hz, H-6a), 4.00 (1 H, dd, J 12.4, 2.4 Hz, H-6b), 3.72 (1 H, m, H-5), 2.48 (1 H, m, H-2), 2.34 (2 H, d, J 5.6 Hz, H-1'a, H-1'b), 2.04 (3 H, s, H-3'), 2.01, 2.00, 1.94, 1.93 (12 H, 4 s, 4 × COOCH₃); δC (100 MHz; CDCl₃) 204.94 (C-2''), 170.59, 170.36, 169.62, 168.81 (4 × COOCH₃), 93.58 (C-1), 73.35 (C-3), 72.63 (C-5), 68.82 (C-4), 61.81 (C-6), 41.24 (C-2), 40.71 (C-1''), 29.79 (C-3''), 20.76, 20.67, 20.57, 20.54 (4 × COOCH₃); HREIMS: m/z 345.11735 (M-C₄H₃O)⁺. Calcd for C₁₅H₂₁O₉ 345.11856 (M-C₂H₃O)⁺.
Methyl 3,4,6-tri-O-acetyl-2-deoxy-2-C-methallyl-β-D-glucopyranoside (165a) and Methyl 3,4,6-tri-O-acetyl-2-deoxy-2-C-methallyl-β-D-mannopyranoside (165b)

A solution of 163b (2.57 g, 6.70 mmol) and methallyltributylstannane (6.9 ml, 19.9 mmol) in benzene (100 ml) was degassed at room temperature for 30 min and then heated to reflux for 10 min. A solution of AIBN (135 mg, 0.7 mmol) in anhydrous benzene (12 ml) was added drop-wise through a pressure-compensating dropping funnel and the heating was continued for 2 h. The reaction mixture was cooled to room temperature, the solvent evaporated, and the residue dissolved in acetonitrile and washed with pentane (∗5). The acetonitrile phase was concentrated under reduced pressure and the crude product was purified by column chromatography using ethyl acetate-petroleum ether (3:7) as a mobile phase to afford an inseparable mixture of diastereomers (2.22 g, 92%, β-gluco 165a:β-manno 165b = 5:1 by 1H-NMR) as an oil.

**Diastereomer 165a** (β-gluco): δH (300 MHz; CDCl3) 5.04-4.92 (2 H, m, H-3, H-4), 4.65 (1 H, d, J 1.0 Hz, H-4'), 4.63 (1 H, d, J 1.0 Hz, H-4''), 4.29 (1 H, dd, J 12.2, 4.8 Hz, H-6a), 4.15 (1 H, d, J 8.1, H-1), 4.11 (1 H, dd, J 12.2, 2.4 Hz, H-6b), 3.64 (1 H, m, H-5), 3.49 (3 H, s, -OMe), 2.36-2.04 (3 H, m, H-2, H-1', H-1''), 2.07, 1.99, 1.93 (9 H, 3 s, 3 × COOCH3), 1.72 (3 H, d, J 0.6 Hz, H-3'); δC (75 MHz; CDCl3) 170.75, 170.44, 169.89 (3 × COOCH3), 143.01 (C-2'), 111.74 (C-4'), 104.38 (C-1), 74.57 (C-3), 71.57 (C-5), 69.93 (C-4), 62.47 (C-6), 57.03 (C-OMe), 43.53 (C-2), 37.35 (C-1'), 22.01 (C-3'), 20.74, 20.67, 20.66 (3 × COOCH3); HRFABMS: m/z 381.151969 (M+Na)+. Calcd for C17H26O9Na 381.152529 (M+Na)+.

**Diastereomer 165b** (β-manno): δH (300 MHz; CDCl3) 5.13 (1 H, t, J 8.4 Hz, H-4), 5.02 (1 H, m, H-3), 4.74 (1 H, s (br), H-4'), 4.70 (1 H, s (br), H-4''), 4.51 (1 H, d, J 2.4 Hz, H-1), 4.26-4.31 (2 H, m, H-6a, H-6b), 3.68 (1 H, m, H-5), 3.46 (3 H, s, -OMe), 2.58-1.89 (3 H, m, H-2, H-1', H-1''), 2.08, 2.04, 2.00 (9 H, 3 s, 3 × COOCH3), 1.70 (3 H, s, H-3'); δC (75 MHz; CDCl3) 170.75, 170.44, 169.89 (3 × COOCH3), 144.10 (C-2'), 111.36 (C-4'), 101.97 (C-1), 72.54 (C-5), 72.22 (C-3), 66.52 (C-4), 62.93 (C-6) 56.79 (C-OMe), 40.07 (C-2), 31.15 (C-1'), 22.47 (C-3'), 20.74, 20.67, 20.66 (3 × COOCH3); HRFABMS: m/z 381.151969 (M+Na)+. Calcd for C17H26O9Na 381.152529 (M+Na)+.
Methyl 3,4,6-tri-O-acetyl-2-deoxy-2-C-(2'-oxopropyl)-β-D-glucopyranoside (166a) and
Methyl 3,4,6-tri-O-acetyl-2-deoxy-2-C-(2'-oxopropyl)-β-D-mannopyranoside (166b)

A solution of mixture of diastereomers 165a and 165b (1.35 g, 3.77 mmol) in CH₂Cl₂-MeOH (0.1 M, 10:1, 30 ml) was allowed to stir at room temperature for 10 min, cooled to −78 °C and then purged with oxygen for 5 min. A stream of ozone was then passed through the solution until a blue colour persisted (≈ 40 min), indicating that the solution was saturated with ozone. The reaction mixture was then purged with nitrogen for 20 min. To the clear solution was added, dimethyl sulfide (5 ml) and the solution was allowed to warm to room temperature over 20 h. The reaction mixture was diluted with CH₂Cl₂, washed with 10% HCl (× 3), and the CH₂Cl₂ phase dried over MgSO₄, and concentrated. The resulting clear oil was purified by column chromatography using ethyl acetate-petroleum ether (2:3) as eluent to give a mixture of diastereomers (1.30 g, 95%, β-gluco 166a; β-manno 166b = 5:1 by ¹H-NMR) as oil. Crystallization was achieved by azeotropic distillation with ethanol and then with petroleum ether. Recrystallization from ethyl acetate-petroleum ether afforded the desired single diastereomer 166a (640 mg, 47%) as crystals; mp 87-88 °C (from ethyl acetate and petroleum ether); [α]D +3.18° (c 1.1, CHCl₃); νmax/cm⁻¹ 1748 (C=O); δH (400 MHz; CDCl₃) 5.08 (1 H, dd, J 11.0, 9.2 Hz, H-3), 4.99 (1 H, t, J 9.2 Hz, H-4), 4.44 (1 H, d, J 8.8 Hz, H-1), 4.29 (1 H, dd, J 12.4, 4.8 Hz, H-6a), 4.12 (1 H, dd, J 12.4, 2.4 Hz, H-6b), 3.67 (1 H, m, H-5), 3.46 (3 H, s, -OMe), 2.52 (1 H, dd, J 16.6, 5.8 Hz, H-1′), 2.43 (1 H, dd, J 16.6, 5.4 Hz, H-1′b), 2.29 (1 H, m, H-2), 2.11 (3 H, s, H-3'), 2.07, 2.00, 1.99 (9 H, 3 s, 3 × COOCH₃); δC (75 MHz; CDCl₃) 206.08 (C-2'), 170.66, 170.41, 169.67 (3 × COOCH₃), 103.18 (C-1), 73.43 (C-3), 71.74 (C-5), 69.61 (C-4), 62.27 (C-6), 57.02 (C-OMe), 42.94 (C-2), 40.89 (C-1'), 29.78 (C-3'), 20.68, 20.59, 20.53 (3 × COOCH₃); HRFABMS: m/z 383.131842 (M+Na)^+. Calcd for C₁₆H₂₄O₉Na 383.131795 (M+Na)^+.

Column chromatography of the mother liquor using ethyl acetate-petroleum ether (2:3) afforded the other diastereomer 166b (73 mg, 10%) as crystals; mp 125-127 °C (from ethyl acetate and petroleum ether); [α]D −37.8° (c 1.0, CHCl₃); νmax/cm⁻¹ 1748 (C=O); δH (300 MHz; CDCl₃) 5.12 (1 H, dd, J 9.7, 5.2 Hz, H-3), 5.01 (1 H, t, J 9.7 Hz, H-4), 4.51 (1 H, d, J 2.1 Hz, H-1), 4.26 (1 H, dd, J 12.3, 5.1 Hz, H-6a), 4.12 (1 H, dd, J 12.3, 2.7 Hz, H-6b), 3.59 (1 H, m, H-5), 3.45 (3 H, s, -OMe), 3.11 (1 H, m, H-2), 2.85 (1 H, dd, J 17.4, 5.7 Hz, H-1′), 2.49 (1 H, dd, J 17.4, 5.8 Hz, H-1′b), 2.18
Methyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-(2′-oxopropyl)-β-D-glucopyranoside (168)

To a solution of 166a (500 mg, 1.39 mmol) in benzene (10 ml), was added NaOH (50%) (5.7 ml), tert-butyl alcohol (1 ml) and tetra-n-butylammonium hydrogen sulphate (0.1 g, 0.0276 mmol). The mixture was warmed at 50 °C for 10 min, and benzyl chloride (2 ml, 16.56 mmol) in benzene (1 ml) was added slowly while the temperature was maintained at 50 °C. After 7 h, NaOH (50%, 1 ml) and benzyl chloride (1 ml, 6 mmol) in benzene (0.5 ml) were added again. After 24 h, the solution was cooled, diluted with water and extracted with ethyl acetate. The ethyl acetate phase was washed once with water, then dried over MgSO₄ and concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (1:9, then 1:4) afforded compound 168 (490 mg, 70%) as crystals; mp 70 °C (from diethyl ether and petroleum ether); [α]D +3.9° (c 1.0, CHCl₃); νmax/cm⁻¹ 1705 (C=O); δH (400 MHz; CDCl₃) 7.40-7.18 (15 H, m, aromatic H), 4.92-4.56 (6 H, m, 3 × PhCH₂-), 4.27 (1 H, d, J 8.4 Hz, H-1), 3.78 (2 H, d, J 3.2 Hz, H-6ₐ, H-6ₖ), 3.67 (1 H, t, J 9.0 Hz, H-4), 3.54 (1 H, dd, J 10.8, 9.0 Hz, H-3), 3.51 (1 H, m, H-5), 3.46 (3 H, s, -OMe), 2.56 (1 H, dd, J 15.9, 5.2 Hz, H-1′ₐ), 2.48 (1 H, dd, J 15.9, 6.2 Hz, H-1′ₖ), 2.20 (1 H, m, H-2), 2.06 (3 H, s, H-3′); δC (100 MHz; CDCl₃) 207.83 (C-2′), 138.38, 138.37, 138.23, 128.59, 128.57, 128.50, 128.00, 127.95, 127.93, 127.90, 127.88, 127.74 (aromatic C), 103.81 (C-1), 82.49 (C-3), 80.11 (C-4), 75.33 (C-5), 74.95, 74.82, 73.68 (3 × PhCH₂-), 69.12 (C-6), 56.91 (C-OMe), 45.08 (C-2), 42.06 (C-1′), 29.70 (C-3′); HRFABMS: m/z 527.240137 (M+Na)⁺. Calcd for C₃₃H₃₈O₆Na 527.240945 (M+Na)⁺.
Methyl 3,4,6-tri-O-acetyl-2-deoxy-2-C-(2'′-hydroxypropyl)-β-D-glucopyranoside (169)

1. Reduction of 166a with NaBH₄

NaBH₄ (0.2 g, 5.5 mmol) was added portion-wise to a solution of 166a (200 mg, 0.55 mmol) in THF-MeOH (3:5 ml) at −30 °C. After 2 h, the reaction was quenched with saturated NaHCO₃, extracted with CH₂Cl₂, dried over MgSO₄ and concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (1:1) afforded an inseparable mixture of diastereomers 169 (190 mg, 95%, 2:1 by ¹H-NMR) as an oil.

2. Reduction of 166a with Zn(BH₄)₂

To a solution of 166a (50 mg, 0.14 mmol) in diethyl ether (1 ml) at 0 °C was added Zn(BH₄)₂ (2 ml, 6.4 mmol). After 18 h at 0 °C, water was added and the stirring was continued for 30 min. The mixture was extracted with ethyl acetate, dried over MgSO₄ and concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (1:1) afforded an inseparable mixture of diastereomers 169 (39 mg, 77%, 1:1 by ¹H-NMR) as an oil.

3. Reduction of 166a with NaBH₄-CeCl₂

A solution of 166a (50 mg, 0.14 mmol) and ceric chloride (52 mg, 0.14 mmol) in THF-MeOH (1:2 ml) was cooled to −30 °C. After 30 min NaBH₄ (6.0 mg, 0.165 mmol) was added and the reaction mixture was left at −30 °C for 3 h. Water was added, the mixture extracted with ethyl acetate, and the ethyl acetate phase washed with saturated NaCl, dried over MgSO₄ and concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (1:1) afforded an inseparable mixture of diastereomers 169 (40 mg, 79%, 1.2:1 by ¹H-NMR) as an oil.

4. Reduction of 166a with LiAlH(O-t-Bu)₃

A solution of LAH (11 mg, 0.29 mmol) in THF (1 ml) was cooled to 0 °C followed by the addition of t-BuOH (0.08 ml, 0.8 mmol). After 2 h at 0 °C, a solution of 166a (50 mg, 0.14 mmol) in THF (1 ml) was added dropwise. After 2 h, water was added, the mixture extracted with ethyl acetate, and the ethyl acetate phase dried over MgSO₄ and concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (1:1) afforded an inseparable mixture of diastereomers 169 (35 mg, 69%, 1.3:1 by ¹H-NMR) as an oil; v_max/cm⁻¹ 3480 (br) (OH).
Diastereomer 169a: δ\textsubscript{H} (400 MHz; CDCl\textsubscript{3}) 5.03 (1 H, dd, J 11.0 Hz, 9.3 Hz, H-3), 4.92 (1 H, t, J 9.3 Hz, H-4), 4.30-4.25 (2 H, m, H-1, H-6\textsubscript{a}), 4.09 (1 H, dd, J 12.4, 2.4 Hz, H-6\textsubscript{b}), 3.78 (1 H, m, H-2'), 3.63 (1 H, m, H-5), 3.52 (3 H, s, -OMe), 2.05, 2.02, 1.98 (9 H, 3 s, 3 × COOCH\textsubscript{3}), 1.19 (1 H, m, H-2), 1.44 (2 H, m, H-1', H-1'), 1.12 (3 H, d, J 6.4 Hz, H-3'); δ\textsubscript{C} (100 MHz; CDCl\textsubscript{3}) 170.94, 170.78, 169.85 (3 × COOCH\textsubscript{3}), 104.39 (C-1), 74.56 (C-3), 71.86 (C-5), 69.87 (C-4), 67.01 (C-2'), 62.41 (C-6), 57.18 (C-OMe), 44.46 (C-2), 36.80 (C-1'), 24.21 (C-3'), 20.85, 20.81, 20.73 (3 × COOCH\textsubscript{3}); HRFABMS: m/z 385.147331 (M+Na). Calcd for C\textsubscript{16}H\textsubscript{26}O\textsubscript{9}Na 385.147446 (M+Na).

Diastereomer 169b: δ\textsubscript{H} (400 MHz; CDCl\textsubscript{3}) 5.03 (1 H, dd, J 11.0 Hz, 9.3 Hz, H-3), 4.92 (1 H, t, J 9.3 Hz, H-4), 4.30-4.25 (2 H, m, H-1, H-6\textsubscript{a}), 4.09 (1 H, dd, J 12.4, 2.4 Hz, H-6\textsubscript{b}), 3.93 (1 H, m, H-2'), 3.63 (1 H, m, H-5), 3.50 (3 H, s, -OMe), 2.05, 2.01, 1.98 (9 H, 3 s, 3 × COOCH\textsubscript{3}), 1.19 (1 H, m, H-2), 1.44 (2 H, m, H-1', H-1'), 1.11 (3 H, d, J 6.0 Hz, H-3'); δ\textsubscript{C} (100 MHz; CDCl\textsubscript{3}) 170.94, 170.78, 169.85 (3 × COOCH\textsubscript{3}), 104.77 (C-1), 73.93 (C-3), 71.77 (C-5), 69.98 (C-4), 65.05 (C-2'), 62.47 (C-6), 57.09 (C-OMe), 42.53 (C-2), 36.88 (C-1'), 23.71 (C-3'), 20.85, 20.81, 20.73 (3 × COOCH\textsubscript{3}); HRFABMS: m/z 385.147331 (M+Na). Calcd for C\textsubscript{16}H\textsubscript{26}O\textsubscript{9}Na 385.147446 (M+Na).
Methyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-(2'-hydroxypropyl)-β-D-glucopyranoside (170)

1. Reduction of 168 with LAH

To a solution of LAH (3.0 mg, 0.078 mmol) in THF (1 ml) at -78 °C was added a solution of 168 (33 mg, 0.065 mmol) in THF (1 ml) dropwise. After 1 h, water was added to decompose excess LAH, the slurry extracted with ethyl acetate, and the ethyl acetate phase dried over MgSO₄ and concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (2:3) afforded an inseparable mixture of diastereomers 170 (32 mg, 97%, 1:1 by ¹H-NMR) as an oil.

2. Reduction of 168 with DIBALH

DIBALH (1 M in toluene, 0.1 ml, 0.1 mmol) was added to a solution of 168 (40 mg, 0.079 mmol) in toluene (2 ml) at -78 °C. After stirring for 15 min, 1 M NaOH was added, the solution extracted with CH₂Cl₂, and the CH₂Cl₂ phase dried over MgSO₄ and concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (2:3) afforded an inseparable mixture of diastereomers 170 (39 mg, 97%, 1:1 by ¹H-NMR) as an oil.

3. Reduction of 168 with CBS

A solution of BH₃·Me₂S (2 M in toluene, 1.05 ml, 2.1 mmol) in THF (2 ml) was stirred for 5 min at room temperature. Diphenylprolinol (25 mg, 0.099 mmol) was added and the reaction mixture was heated at 40 °C for 12 h. A solution of 168 (101 mg, 0.20 mmol) in THF (2 ml) was added dropwise while the temperature was maintained at 40 °C. After 15 min, the solution was cooled to room temperature, quenched with MeOH, followed by 1 M HCl. The mixture was extracted with ethyl acetate, and the ethyl acetate washed once with saturated NaCl, then dried over MgSO₄ and concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (2:3) afforded an inseparable mixture of diastereomers 170 (97 mg, 96%, 2:1 by ¹H-NMR) as an oil; νmax/cm⁻¹ 3455 (OH).

**Diastereomer 170a:** δH (300 MHz; CDCl₃) 7.40-7.18 (15 H, m, aromatic H), 4.97-4.56 (6 H, m, 3 × PhCH₂-), 4.15 (1 H, d, J 8.7 Hz, H-1), 3.87 (1 H, m, H-2'), 3.75 (2 H, m, H-6a, H-6b), 3.66 (1 H, t, J 9.4 Hz, H-4), 3.52 (3 H, s, -OMe), 3.46 (1 H, m, H-5), 3.33 (1 H, t, J 9.4 Hz, H-3'), 1.89 (1 H, m, H-2), 1.55 (2 H, m, H-1’, H-1”), 1.13 (3 H, d, J 6.3 Hz, H-3’); δC (75 MHz; CDCl₃) 138.14, 137.99, 137.89, 128.46, 128.42, 128.41, 128.33, 127.97, 127.81, 127.77, 127.76, 127.58 (aromatic
Diastereomer 170b: $\delta_H$ (300 MHz; CDCl$_3$) 7.40-7.18 (15 H, m, aromatic H), 4.97-4.56 (6 H, m, 3 $\times$ PhCH$_2$-), 4.11 (1 H, d, $J$ 8.4 Hz, H-1), 3.87 (1 H, m, H-2'), 3.75 (2 H, m, H-6a, H-6b), 3.65 (1 H, t, $J$ 9.4 Hz, H-4), 3.54 (3 H, s, -OMe), 3.46 (1 H, m, H-5), 3.33 (1 H, $t$, $J$ 9.4 Hz, H-3), 2.89 (1 H, m, H-2), 1.55 (2 H, m, H-1', H-1'b), 1.12 (3 H, d, $J$ 6.0 Hz, H-3'); $\delta_C$ (75 MHz; CDCl$_3$) 138.16, 137.99, 137.89, 128.41, 128.42, 128.41, 128.33, 127.97, 127.81, 127.77, 127.76, 127.58 (aromatic C), 104.93 (C-1), 83.52 (C-3), 79.74 (C-4), 75.18, 75.15, 74.64, 73.53 (3 $\times$ PhCH$_2$-, C-5), 68.89 (C-6), 67.66 (C-2'), 56.83 (C-OMe), 46.27 (C-2), 37.15 (C-1'), 23.74 (C-3'); HRFABMS: m/z 529.256720 (M+Na)$^+$. Calcd for C$_{31}$H$_{38}$O$_6$Na 529.256594 (M+Na)$^+$. 
Methyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-(2’-benzyloxypropyl)-β-D-glucopyranoside (171)

1. From 169

Methanolic NaOMe (0.2 M, 5 ml, 1.0 mmol) was added to a solution of 169 (500 mg, 1.38 mmol, 2:1) in CH₂Cl₂-MeOH (5:10 ml) at room temperature. After 5 h, the solution was neutralized with Amberlite IR-120 H⁺ resin. The resin was removed by filtration, the solvent was evaporated and the crystalline residue was passed through a silica column using methanol-ethyl acetate (3:17) as eluent. The dry product residue (294 mg, 1.24 mmol) in THF (15 ml) was cooled to 0 °C and NaH (0.36 g, 7.47 mmol) was added. After 15 min, benzyl bromide (0.86 ml, 7.47 mmol) was added and the reaction mixture was heated at reflux for 4 h. The solution was cooled to room temperature and excess NaH decomposed by the addition of MeOH followed by water. The solvent was evaporated, extracted with EtOAc, and the EtOAc phase washed with saturated NaCl, then dried over MgSO₄ and concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (1:9) as eluent afforded an inseparable mixture of diastereomers 171 (632 mg, 77% from 169, 2.1 by ¹H-NMR) as crystals.

1. From 170

NaH (50%, 0.017 g, 0.37 mmol) was added to a solution of 170 (31 mg, 0.061 mmol) in THF (3 ml) at 0 °C. After 5 min, benzyl bromide was added and the reaction mixture was heated at reflux for 5 h. The solution was cooled down to room temperature and excess NaH was decomposed by the addition of MeOH followed by water. The THF was evaporated, and the water extracted with EtOAc which was washed with saturated NaCl, dried over MgSO₄ and concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (1:4) as eluent afforded an inseparable mixture of diastereomers 171 (35 mg, 96%) as crystals.

Diastereomer 171a: δH (400 MHz; CDCl₃) 7.38-7.19 (20 H, m, aromatic H), 4.91-4.45 (8 H, m, 4 × PhCH₂), 4.10 (1 H, d, J 8.4 Hz, H-1), 3.83-3.71 (3 H, m, H-6ₐ, H-6₆, H-2’), 3.58 (1 H, dd, J 9.4, 8.6 Hz, H-4), 3.49-3.44 (2 H, m, H-3, H-5), 3.44 (3 H, s, -OMe), 1.99-1.53 (3 H, m, H-2, H-1ₐ, H-1ₐ), 1.20 (3 H, d, J 6.0 Hz, H-3’); δC (100 MHz; CDCl₃) 139.11, 138.47, 138.27, 138.19, 128.33, 128.30, 128.27, 128, 21, 128.15, 127.74, 127.70, 127.65, 127.62, 127.51, 127.49, 127.28, 127.16 (aromatic C), 105.19 (C-1), 83.57 (C-3), 79.86 (C-4); 75.15, 75.11 (2 × PhCH₂), 74.55 (C-5), 73.45 (C-PhCH₂⁻), 73.29 (C-2’), 70.06 (C-PhCH₂⁻), 69.20 (C-6), 56.50 (C-OMe), 44.40 (C-2),...
34.72 (C-1'), 19.66 (C-3'); HREIMS: m/z 581.29247 (M-CH₃)⁺. Calcd for C₃₇H₄₁O₆
581.29031 (M-CH₃)⁺.

Diastereomer 171b: δ_H (400 MHz; CDCl₃) 7.38-7.19 (20 H, m, aromatic H), 4.94-4.39 (8 H, m, 4 × PhCH₂-), 4.22 (1 H, d, J 8.0 Hz, H-1), 3.83-3.63 (4 H, m, H-6ₐ, H-6ₖ, H-4, H-2'), 3.49-3.44 (2 H, m, H-3, H-5), 3.47 (3 H, s, -OMe), 1.99-1.53 (3 H, m, H-2, H-1', H-1'B), 1.18 (3 H, d, J 6.0 Hz, H-3'); δ_C (100 MHz; CDCl₃) 139.11, 138.47, 138.27, 138.19, 128.33, 128.30, 128.27, 128, 21, 128.15, 127.74, 127. 70, 127.65, 127.62, 127.51, 127.42, 127.28, 127.16 (aromatic C), 105.13 (C-1), 83.29 (C-3), 79.56 (C-4), 75.11, 75.04 (2 × PhCH₂-), 74.45 (C-5), 73.98, 73.43 (C-PhCH₂-, C-2'), 70.06 (C-PhCH₂-), 69.26 (C-6), 56.63 (C-OMe), 44.22 (C-2), 35.35 (C-1'), 19.97 (C-3'); HREIMS: m/z 581.29247 (M-CH₃)⁺. Calcd for C₃₇H₄₁O₆ 581.29031 (M-CH₃)⁺.
Phenyl 3,4,6-tri-O-acetyl-2-C-allyl-2-deoxy-1-thio-α/β-D-glucopyranoside (172)

Boron trifluoride etherate (0.29 ml, 2.42 mmol) was added dropwise to a mixture of 81a (150 mg, 0.40 mmol) and PhSSiMe3 (0.31 ml, 1.61 mmol) in CH₂Cl₂ (5 ml) at 0 °C. The reaction was allowed to reach room temperature over 18 h. Saturated NaHCO₃ was added and the solution extracted with CH₂Cl₂, dried over MgSO₄ and concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (1:4) as eluent afforded an inseparable mixture of anomers 172 (141 mg, 83%, α:β = 2:1 by ¹H-NMR) as an oil.

α-Anomer: δH (400 MHz; CDCl₃) 7.54-7.38 (5 H, m, aromatic H), 5.71 (1 H, m, H-2'), 5.45 (1 H, d, J 4.8 Hz, H-1'), 5.21-5.05 (3 H, m, H-3, H-3′, H-3′), 4.98 (1 H, dd, 10.4, 8.8 Hz, H-4), 4.59 (1 H, m, H-5), 4.28 (1 H, dd, J 12.1, 5.0 Hz, H-6b), 4.01 (1 H, dd, J 12.1, 2.4 Hz, H-6b), 2.44-2.16 (3 H, m, H-2, H-1′, H-1″), 2.02, 2.01, 2.00 (9 H, 3 s, 3 × COOCH₃); δC (100 MHz; CDCl₃) 170.44, 170.13, 169.81 (3 × COOCH₃), 134.01 (C-2'), 132.71, 131.92, 128.93, 127.51 (aromatic C), 117.73 (C-3'), 88.02 (C-1), 72.44 (C-3), 69.99 (C-4), 68.78 (C-5), 62.37 (C-6), 44.93 (C-2), 32.94 (C-1'), 20.59, 20.55, 20.52 (3 × COOCH₃); HRFABMS: m/z 445.129696 (M+Na)⁺. Calcd for C₂₁H₂₆O₇SNa 445.129686 (M+Na)⁺.

β-Anomer: δH (400 MHz; CDCl₃) 7.54-7.38 (5 H, m, aromatic H), 5.77 (1 H, m, H-2'), 5.21-5.05 (3 H, m, H-3, H-3', H-3″), 4.91 (1 H, t, J 9.4 Hz, H-4), 4.54 (1 H, d, J 10.8 Hz, H-1'), 4.22 (1 H, dd, J 12.1, 5.6 Hz, H-6b), 4.12 (1 H, dd, J 12.1, 2.2 Hz, H-6b), 3.59 (1 H, m, H-5), 2.34-2.01 (3 H, m, H-2, H-1′, H-1″), 2.04, 1.98, 1.98 (9 H, 3 s, 3 × COOCH₃); δC (100 MHz; CDCl₃) 170.44, 170.06, 169.72 (3 × COOCH₃), 133.54 (C-2'), 132.49, 132.35, 128.79, 127.95 (aromatic C), 118.67 (C-3'), 86.38 (C-1), 75.29 (C-5), 72.17(C-3), 69.87 (C-4), 62.59 (C-6), 43.83 (C-2), 31.99 (C-1'), 20.59, 20.55, 20.52 (3 × COOCH₃); HRFABMS: m/z 445.129696 (M+Na)⁺. Calcd for C₂₁H₂₆O₇SNa 445.129686 (M+Na)⁺.
3,4,6-Tri-O-acetyl-2-C-allyl-2-deoxy-α/β-D-glucopyranose (174)

Hydrazine acetate (37 mg, 0.40 mmol) was added to a solution of 81a (100 mg, 0.27 mmol) in DMF (3 ml) and the reaction was heated at 60 °C for 1 h. The solution was cooled and diluted with ethyl acetate, which was then washed with saturated NaCl (× 3), dried over MgSO₄ and concentrated. The resulting residue was purified by column chromatography using ethyl acetate-petroleum ether (2:3) as eluent to afford an inseparable mixture of anomers 174 (84 mg, 94%, α:β = 2:1 by 1H-NMR) as an oil.

α-Anomer: δ_H (400 MHz; CDCl₃) 5.74 (1 H, m, H-2'), 5.29 (1 H, dd, J 11.2, 9.5 Hz, H-3), 5.24 (1 H, s (br), H-1), 5.11-5.01 (2 H, m, H-3'a, H-3'b), 4.97 (1 H, t, J 9.5 Hz, H-4), 4.27-4.21 (2 H, m, H-5, H-6a), 4.10-4.06 (1 H, m, H-6b), 2.76 (s (br), -OH), 2.17 (2 H, m, H-1', H-1'b), 2.08, 2.01, 2.01 (9 H, 3 s, 3 × COOCH₃), 2.01 (1 H, m, H-2); δ_C (100 MHz; CDCl₃) 173.62, 173.30, 172.81 (3 × COOCH₃), 137.86 (C-2'), 119.81 (C-3'), 95.91 (C-1), 74.74 (C-3), 72.79 (C-4), 70.65 (C-5), 65.38 (C-6), 47.02 (C-2), 34.81 (C-1'), 23.58, 23.57, 23.50 (3 × COOCH₃); HRFABMS: m/z 353.120887 (M+Na)⁺. Calcd for C₁₅H₂₂O₈Na 353.121231 (M+Na)⁺.

β-Anomer: δ_H (400 MHz; CDCl₃) 5.79 (1 H, m, H-2'), 5.29 (1 H, dd, J 11.2, 9.6 Hz, H-3), 5.11-4.93 (3 H, m, H-4, H-3'a, H-3'b), 4.67 (1 H, d, J 8.4 Hz, H-1), 4.27-4.06 (2 H, m, H-6a, H-6b), 3.66 (1 H, m, H-5), 3.23 (s (br), -OH), 2.28 (2 H, m, H-1'a, H-1'b), 2.07, 2.01, 2.00 (9 H, 3 s, 3 × COOCH₃), 1.91 (1 H, m, H-2); δ_C (100 MHz; CDCl₃) 173.62, 173.30, 172.81 (3 × COOCH₃), 136.72 (C-2'), 120.53 (C-3'), 99.51 (C-1), 75.39 (C-3), 74.63 (C-5), 72.71 (C-4), 65.32 (C-6), 49.30 (C-2), 33.91 (C-1'), 23.58, 23.57, 23.50 (3 × COOCH₃); HRFABMS: m/z 353.120887 (M+Na)⁺. Calcd for C₁₅H₂₂O₈Na 353.121231 (M+Na)⁺.
3,4,6-Tri-O-acetyl-2-C-allyl-2-deoxy-α/β-D-glucopyranosyl fluoride (173)

To a solution of 174 (123 mg, 0.37 mmol) in THF (3 ml) at 0 °C was added DAST (0.15 ml, 1.11 mmol) dropwise. After the addition, the ice-water bath was removed and the stirring was continued at room temperature for 30 min. The mixture was then cooled (0 °C) and excess DAST was quenched with methanol followed by saturated NaHCO₃. The solution was extracted with CH₂Cl₂, and the CH₂Cl₂ phase dried over MgSO₄ and concentrated. The resulting yellow syrup was purified by column chromatography using ethyl acetate-petroleum ether (1:4) as eluent to afford an inseparable mixture of anomers 173 (121 mg, 98%, α:β = 2:1 by ¹H-NMR) as an oil.

α-Anomer: δH (400 MHz; CDCl₃) 5.73 (1 H, m, H-2'), 5.66-5.52 (1 H, dd, J₁,F 51.0 Hz, J₁,₂ 2.6 Hz, H-1), 5.24 (1 H, dd, J 11.0, 9.4 Hz, H-3), 5.14-5.02 (3 H, m, H-4, H-3',ₐ, H-3',ₐ), 4.30 (1 H, dd, J 12.2, 4.2 Hz, H-6ₚ), 4.14 (1 H, m, H-5), 4.10 (1 H, dd, J 12.2, 2.2 Hz, H-6ₚ), 2.23-2.00 (3 H, m, H-2, H-1',ₐ, H-1',ₐ), 2.08, 2.03, 2.02 (9 H, 3 s, 3 × COOCH₃); δC (100 MHz; CDCl₃) 173.38, 173.06, 172.59 (3 × COOCH₃), 136.73 (C-2'), 120.78 (C-3'), 110.07 (d, J₁,F 223.0 Hz, C-1), 74.09 (C-3), 72.93 (d, J₅,F 3.8 Hz, C-5), 71.54 (C-4), 64.59 (C-6), 46.82 (d, J₂,F 24.3 Hz, C-2), 34.06 (d, J₁,F 2.3 Hz, C-1'), 23.49, 23.41, 23.40 (3 × COOCH₃); δF (376.3 MHz; CDCl₃) -146.59 (dd, J₁,F 51.0 Hz, J₂,F 29.75 Hz); HRFABMS: m/z 333.135369 (M+H)⁺. Calcd for C₁₅H₂₁FO₇ 333.134955 (M+H)⁺.

β-Anomer: δH (400 MHz; CDCl₃) 5.74 (1 H, m, H-2'), 5.28-5.14 (1 H, dd, J₁,F 51.2 Hz, J₁,₂ 7.2 Hz, H-1), 5.14-5.02 (4 H, m, H-3, H-4, H-3',ₐ, H-3',ₐ)), 4.26 (1 H, dd, J 12.0, 4.8 Hz, H-6ₚ), 4.18 (1 H, dd, J 12.0, 2.6 Hz, H-6ₚ), 3.77 (1 H, m, H-5), 2.32-2.00 (3 H, m, H-2, H-1',ₐ, H-1',ₐ), 2.08, 2.03, 2.02 (9 H, 3 s, 3 × COOCH₃); δC (100 MHz; CDCl₃) 173.38, 172.93, 172.46 (3 × COOCH₃), 135.96 (C-2'), 121.19 (C-3'), 111.56 (d, J₁,F 214.0 Hz, C-1), 74.76 (d, J₅,F 4.5 Hz, C-5), 74.17 (d, J₃,F 10.6 Hz, C-3), 71.77 (C-4), 65.15 (C-6), 47.52 (d, J₂,F 22.0 Hz, C-2), 33.80 (d, J₁,F 1.5 Hz, C-1'), 23.49, 23.41, 23.40 (3 × COOCH₃); δF (376.3 MHz; CDCl₃) -133.55 (d (br), J₁,F 51.2 Hz); HRFABMS: m/z 333.135369 (M+H)⁺. Calcd for C₁₅H₂₁FO₇ 333.134955 (M+H)⁺.
3,4,6-Tri-\(O\)-acetyl-2-deoxy-2-C-methallyl-\(\alpha/\beta\)-D-glucopyranose (175)

Hydrazine acetate (0.14 g, 1.61 mmol) was added to a solution of 82a (415 mg, 1.07 mmol) in DMF (8 ml) and the reaction was heated at 60 °C for 1 h. The solution was cooled, diluted with ethyl acetate, washed with saturated NaCl (\(\times\) 3), and the ethyl acetate phase separated, dried over MgSO\(_4\) and concentrated. The resulting residue was purified by column chromatography using ethyl acetate-petroleum ether (2:3) as eluent to afford an inseparable mixture of anomers 175 (359 mg, 97%, \(\alpha/\beta = 6:1\) by \(^1\)H-NMR) as an oil.

\(\alpha\)-Anomer: \(\delta_H\) (400 MHz; CDCl\(_3\)) 5.30 (1 H, dd, \(J\ 10.6, 9.5\ Hz\), H-3), 5.19 (1 H, t, \(J\ 3.2\ Hz\), H-1), 4.99 (1 H, t, \(J\ 9.5\ Hz\), H-4), 4.78 (1 H, s (br), H-4\(\prime\)\_a), 4.76 (1 H, s (br), H-4\(\prime\)\_b), 4.29-4.22 (2 H, m, H-5, H-6\_a), 4.07 (1 H, dd, \(J\ 12.0, 2.0\ Hz\), H-6\_b), 2.70 (d (br), \(J\ 3.6\ Hz\), -OH), 2.22-2.08 (3 H, m, H-2, H-1\(\prime\)\_a, H-1\(\prime\)\_b), 2.09, 2.02, 2.00 (9 H, 3 s, 3 \(\times\) COOCH\(_3\)), 1.72 (3 H, s (br), H-3\(\prime\)); \(\delta_C\) (100 MHz; CDCl\(_3\)) 170.70, 170.42, 169.92 (3 \(\times\) COOCH\(_3\)), 141.98 (C-2\(\prime\)), 112.54 (C-4\(\prime\)), 92.93 (C-1), 71.90 (C-3), 69.91 (C-4), 67.74 (C-5), 62.47 (C-6), 42.06 (C-2), 35.79 (C-1\(\prime\)), 21.97 (C-3\(\prime\)), 20.67, 20.66, 20.65 (3 \(\times\) COOCH\(_3\)); HRFABMS: \(m/z\) 367.136777 (M+Na\(^+\)). Calcd for C\(_{16}\)H\(_{24}\)O\(_8\)Na 367.136880 (M+Na\(^+\)).
3,4,6-Tri-O-acetyl-2-deoxy-2-C-methallyl-α/β-D-glucopyranosyl fluoride (176)

To a solution of 175 (157 mg, 0.45 mmol) in THF (5 ml) at 0 °C was added DAST (0.24 ml, 1.82 mmol) dropwise. After the addition the ice-water bath was removed and the stirring was continued at room temperature for 30 min. The mixture was cooled (0 °C) and the excess DAST was quenched with methanol followed by saturated NaHCO₃. The solution was extracted with CH₂Cl₂, and the CH₂Cl₂ phase dried over MgSO₄ and concentrated. The resulting yellow syrup was purified by column chromatography using ethyl acetate-petroleum ether (1:4) as eluent to afford compound 176 as a mixture of anomers (152 mg, 97%, α:β = 2:1 by ¹H-NMR). The mixture was separated by column chromatography using ethyl acetate-petroleum ether (1:9, then 1:4) as eluent to afford 176a (less polar product, α-anomer) as an oil and 176b (more polar product, β-anomer) as an oil.

**α-Anomer:** [α]D +96.9° (c 3.3, CHCl₃); δH (400 MHz; CDCl₃) 5.58-5.45 (1 H, dd, J1,F 50.4 Hz, J1,2 2.0 Hz, H-1), 5.18 (1 H, dd, J 10.4, 9.7 Hz, H-3), 5.02 (1 H, t, J 9.7 Hz, H-4), 4.78 (1 H, d, J 1.2 Hz, H-4′₂), 4.73 (1 H, d, J 1.2 Hz, H-4′₃), 4.27 (1 H, dd, J 12.3, 4.2 Hz, H-6₆), 4.11 (1 H, m, H-5), 4.05 (1 H, dd, J 12.3, 2.0 Hz, H-6₆), 2.21-2.06 (3 H, m, H-2, H-1′₆, H-1′₇), 2.04, 1.97, 1.96 (9 H, 3 s, 3 × COOCH₃), 1.68 (3 H, s (br), H-3′); δC (100 MHz; CDCl₃) 170.72, 170.43, 169.96 (3 × COOCH₃), 141.18 (C-2′), 113.62 (t, J 3.8 Hz, C-4′), 107.38 (dd, J1,F 222.3 Hz, C-1), 71.55 (C-3), 70.24 (d, J5,F 3.0 Hz, C-5), 68.90 (C-4), 61.93 (C-6), 42.17 (d, J2,F 24.3 Hz, C-2), 35.32 (C-1′), 22.20 (C-3′), 20.83, 20.80, 20.76 (3 × COOCH₃); δF (376.3 MHz; CDCl₃) -147.11 (dd, J1,F 50.4 Hz, J2,F 30.47 Hz); FABMS: m/z 369.1 (M+Na)+. Calcd for C₁₆H₂₃FO₇Na 369.1 (M+Na)+.

**β-Anomer:** [α]D +70.5° (c 3.2, CHCl₃); δH (400 MHz; CDCl₃) 5.25-5.10 (1 H, dd, J1,F 51.6 Hz, J1,2 6.0 Hz, H-1), 5.05 (1 H, t, J 8.7 Hz, H-4), 4.96 (1 H, t, J 8.7 Hz, H-3), 4.74 (1 H, d, J 0.8 Hz, H-4′₂), 4.78 (1 H, d, J 0.8 Hz, H-4′₃), 4.24 (1 H, dd, J 12.2, 5.2 Hz, H-6₆), 4.18 (1 H, dd, J 12.2, 3.2 Hz, H-6₆), 3.81 (1 H, m, H-5), 2.30-2.12 (3 H, m, H-2, H-1′₆, H-1′₇), 2.06, 1.99, 1.96 (9 H, 3 s, 3 × COOCH₃), 1.72 (3 H, s (br), H-3′); δC (100 MHz; CDCl₃) 170.50, 170.07, 169.56 (3 × COOCH₃), 141.59 (C-2′), 112.87 (C-4′), 109.32 (d, J1,F 215.5 Hz, C-1), 72.50 (d, J5,F 8.4 Hz, C-3), 71.93 (d, J5,F 4.5 Hz, C-5), 68.55 (C-4), 62.41 (C-6), 42.75 (d, J2,F 22.1 Hz, C-2), 36.89 (d, J1,F 2.3 Hz, C-1′), 21.76 (C-3′), 20.60, 20.56, 20.54 (3 × COOCH₃); δF (376.3 MHz; CDCl₃) 130.37 (d (br), J1,F 51.6 Hz); FABMS: m/z 369.1 (M+Na)+. Calcd for C₁₆H₂₃FO₇Na 369.1 (M+Na)+.
A cloudy mixture of myo-inositol (10.0 g, 55.5 mmol), cyclohexanone (87.3 ml, 0.76 mol), TsOH (10% in DMF, 2.5 ml), DMF (98 ml) and toluene (21 ml) was heated to reflux with a Dean-Stark separator filled with toluene. Four additional portions of 10% TsOH solution (2.5 ml) were added at 2 h intervals. After 12 h, water separation had ceased (9 ml). The clear, pale yellow mixture obtained was evaporated at 100 °C, diluted with absolute ethanol (200 ml) and stored in the cold room for 18 h. The resulting crystals were removed by filtration and washed with ethanol containing 0.1% Et₃N. After reacidification (0.2 g TsOH), the filtrate yielded similarly two further crops. The combined crystals were recrystallized from ethanol and washed several times with petroleum ether to afford compound 178 (11.0 g, 76%) as crystals; mp 178-180 °C (lit.,¹⁷⁵ 179-180 °C, lit.,¹⁹⁴ 181-183 °C); FABMS: $m/z$ 283.1 (M+Na)⁺. Calcd for C₁₂H₂₀O₅Na 283.1 (M+Na)⁺.
1,4,5,6-Tetra-O-benzyl-2,3-O-cyclohexyldene-DL-myoinositol (179)

A portion of dry compound 178 (1.40 g, 5.38 mmol) in THF (30 ml) was cooled to 0 °C, and NaH (50%, 1.5 g, 32.3 mmol) was added portion-wise with stirring. After 30 min, benzyl bromide (3.8 ml, 32.3 mmol) 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 methanol followed by water. The organic solvent was evaporated, and the aqueous mixture extracted with ethyl acetate, which was dried over MgSO₄ and concentrated under reduced pressure. Purification by column chromatography using ethyl acetate-petroleum ether (5:95, then 1:9) as eluent afforded compound 179 (2.75 g, 82%) as an oil; δH (300 MHz; CDCl₃) 7.40-7.26 (20 H, m, aromatic H), 4.94-4.74 (8 H, m, 4 × PhCH₂), 4.31 (1 H, dd, J 5.8, 3.8 Hz, H-2), 4.13 (1 H, dd, J 7.1, 5.8 Hz, H-1(3)), 3.95 (1 H, t, J 8.2 Hz, H-4(6)), 3.85 (1 H, dd, J 9.7, 7.1 Hz, H-6(4)), 3.72 (1 H, dd, J 8.2, 3.8 Hz, H-3(1)), 3.44 (1 H, dd, J 9.7, 8.2 Hz, H-5), 1.84-1.43 (10 H, m, -C(CH₂)₅-, cyclohexyldene); δC (75 MHz; CDCl₃) 138.71, 138.66, 138.62, 138.34, 128.34, 138.33, 128.32, 128.26, 128. 23, 127.96, 127.94, 127.91, 127.73, 127.58, 127.50, 127.45 (aromatic C), 110.44 (quaternary C, cyclohexyldiene), 82.89 (C-6(4)), 82.18 (C-5), 80.95 (C-4(6)), 78.79 (C-1(3)), 77.28 (C-3(1)), 75.17, 75.00 (2 × PhCH₂), 74.03 (C-2), 73.93, 73.11 (2 × PhCH₂-), 37.38, 35.04, 25.08, 23.94, 23.68 (5 × -CH₂-, cyclohexyldene); FABMS: m/z 619.2 (M-H)⁺. Calcd for C₄₀H₅₃O₆ 619.3 (M-H)⁺.
A mixture of 179 (2.75 g, 4.43 mmol) and AcOH (80%, 50ml) was heated at 90-100 °C for 2 h. The solvent was evaporated, toluene/hexane (1:3, 25 ml) was added and the slurry of crystals obtained was kept at low temperature for 18 h. The resulting crystals were filtrated, washed with toluene-petroleum ether (1:3) and dried under vacuum to afford compound 180 (1.90 g, 79%) as crystals; mp 126-127 °C (lit., \(^{174}\) 127-128 °C); \(\nu_{\text{max}}/\text{cm}^{-1}\) 3570 (OH); \(\delta_H\) (300 MHz; CDCl\(_3\)) 7.38-7.25 (20 H, m, aromatic H), 4.98-4.72 (8 H, m, \(4 \times \text{PhCH}_2\)), 4.20 (1 H, t, \(J 2.7\) Hz, H-2), 3.98 (1 H, t, \(J 9.5\) Hz, H-4(6)), 3.85 (1 H, t, \(J 9.5\) Hz, H-6(4)), 3.49 (1 H, t, \(J 9.5\) Hz, H-5), 3.49 (1 H, m, H-1(3)), 3.47 (1 H, dd, \(J 9.5, 2.7\) Hz, H-3(1)), 2.57 (s (br), -OH), 2.48 (s (br), -OH); \(\delta_C\) (75 MHz; CDCl\(_3\)) 138.65, 138.52, 138.51, 137.80, 128.54, 128.49, 128.36, 128.34, 127.93, 127.92, 127.91, 127.86, 127.83, 127.78, 127.58, 127.57 (aromatic C), 83.21 (C-5), 81.63 (C-4(6)), 81.33 (C-6(4)), 80.02 (C-3(1)), 75.89, 75.66, 75.56, 72.73 (\(4 \times \text{PhCH}_2\)), 71.77 (C-1(3)), 69.21 (C-2); FABMS: \(m/z\) 563.3 (M+Na\(^+\)). Calcd for C\(_{34}\)H\(_{36}\)O\(_6\)Na 563.2 (M+Na\(^+\)).
A mixture of 180 (1.72 g, 3.18 mmol) and dibutyltin oxide (98%, 0.95 g, 3.81 mmol) in toluene (15 ml) was refluxed under a Dean-Stark separator filled with toluene. After 2 h, the solvent was evaporated, DMF (9 ml) added followed by allyl bromide (0.83 ml, 9.53 mmol) and the reaction mixture heated at 70 °C for 5 h. The solvent was then concentrated, diluted with diethyl ether, and washed successively with saturated NaHCO₃ and saturated NaCl, before being dried over MgSO₄ and concentrated. The residue was purified by column chromatography using ethyl acetate-petroleum ether (1:4) as eluent to afford an inseparable mixture of allyl ethers (1-O-allyl 181a:2-O-allyl 181b ≈ 10:1 by ¹³C NMR) (1.60 g, 86%) as an oil; νmax/cm⁻¹ 3573 (OH);

_Diastereomer 181a:_ δH (400 MHz; CDCl₃) 7.40-7.23 (20 H, m, aromatic H), 5.98 (1 H, m, H-2'), 5.35-5.20 (2 H, m, H-3'a, H-3'b), 4.96-4.73 (8 H, m, 4 × PhCH₂), 4.26 (1 H, t, J 2.7 Hz, H-2), 4.23-4.20 (2 H, m, H-1'a, H-1'b), 4.03 (1 H, t, J 9.4 Hz, H-4(6)), 3.99 (1 H, t, J 9.4 Hz, H-6(4)), 3.49 (1 H, t, J 9.4 Hz, H-5), 3.45 (1 H, dd, J 9.4, 2.7 Hz, H-1(3)), 3.33 (1 H, dd, J 9.4, 2.7 Hz, H-3(1)), 2.55 (s (br), -OH); δC (100 MHz; CDCl₃) 141.68, 141.66, 141.64, 140.88 (aromatic C), 137.59 (C-2'), 131.32, 131.19, 131.18, 131.17, 130.91, 130.85, 130.54, 130.80, 130.72, 130.66, 130.40, 130.36 (aromatic C), 120.25 (C-3'), 86.03 (C-5), 84.08 (C-4(6)), 84.06 (C-6(4)), 82.81 (C-1(3)), 82.55 (C-3(1)), 78.78, 78.76, 78.74, 75.65 (4 × PhCH₂), 74.73 (C-2), 70.59 (C-1'); FABMS: m/z 603.2 (M+Na⁺). Calcd for C₃₇H₄₀O₆Na 603.2 (M+Na⁺).
NaH (50%, 0.59 g, 12.27 mmol) was added to a solution of a mixture of 181a and 181b (1.15 g, 1.98 mmol) in THF (10 ml) at 0 °C. After 5 min, benzyl bromide was added and the reaction mixture heated to reflux for 3 h. Excess NaH was decomposed by the addition of MeOH followed by water. The THF was evaporated, and the aqueous phase extracted with EtOAc, which was then washed with saturated NaCl, dried over MgSO₄ and concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (5:95, then 1:9) as eluent afforded a mixture of allyl ethers (principally 182a) (1.18 g, 89%) as an oil; δH (300 MHz; CDCl₃) 7.58-7.36 (25 H, m, aromatic H), 6.05 (1 H, m, H-2'), 5.46-5.26 (2 H, m, H-3'a, H-3'b), 5.06-4.71 (10 H, m, 5 × PhCH₂), 4.25-4.14 (5 H, m, H-2, H-4, H-6, H-1'a, H-1'b), 3.59 (1 H, t, J 9.8 Hz, H-5), 3.49 (1 H, dd, J 9.8, 2.3 Hz, H-1(3)), 3.38 (1 H, dd, J 9.8, 2.3 Hz, H-3(1)); δC (75 MHz; CDCl₃) 138.93, 138.86, 138.85, 138.83, 138.38 (aromatic C), 134.87 (C-2'), 128.28, 128.22, 128.21, 128.06, 128.02, 127.97, 127.92, 127.75, 127.69, 127.57, 127.49, 127.42, 127.39, 127.35, 127.26 (aromatic C), 116.55 (C-3'), 83.62 (C-5), 81.63 (C-4, C-6), 80.86 (C-1(3)), 80.67 (C-3(1)), 75.76, 75.74, 75.73, 74.29 (4 × PhCH₂), 74.01 (C-2), 72.73 (C-PhCH₂), 71.57 (C-1'); FABMS: m/z 671.4 (M+H). Calcd for C₄₄H₄₇O₆ 671.3 (M+H).
PdCl₂ (0.34 g, 1.89 mmol) was added to a solution of a mixture of 182a and 182b (7.0 g, 10.43 mmol) in EtOH-MeOH (1:1, 80 ml). The mixture was stirred for 5 h at room temperature, whereupon the solids were filtered through celite and solvent evaporated. Purification by column chromatography using ethyl acetate-petroleum ether (1:4) as eluent gave a syrup that crystallized from petroleum ether at low temperature to afford compound 183 (6.25 g, 80%) as crystals; mp 88-89 °C (from petroleum ether) (lit. ²⁷⁴ 86-88 °C, lit. ²⁹⁵ 92-94 °C); νmax/cm⁻¹ 3560 (OH); δH (400 MHz; CDCl₃) 7.38-7.29 (25 H, m, aromatic H), 5.03-4.72 (10 H, m, 5 × PhCH₂-), 4.09 (1 H, t, J 9.6 Hz, H-6(4)), 4.06 (1 H, t, J 2.4 Hz, H-2), 3.84 (1 H, t, J 9.6 Hz, H-4 (6)), 3.52 (1 H, m, H-1(3)), 3.51 (1 H, t, J 9.6 Hz, H-5), 3.49 (1 H, dd, J 9.6, 2.4 Hz, H-3(1)), 2.23 (d, J 6.4 Hz, -OH); δC (100 MHz; CDCl₃) 138.73, 138.71, 138.64, 138.60, 138.22, 128.42, 128.36, 128.32, 128.30, 128.27, 128.26, 127.99, 127.77, 127.73, 127.70, 127.62, 127.57, 127.53, 127.48 (aromatic C), 83.58 (C-5), 82.14 (C-4(6)), 81.73 (C-6(4)), 81.10 (C-3(1)), 77.12 (C-2), 75.79, 75.67, 75.44, 74.70, 72.94 (5 × PhCH₂-), 72.40 (C-1(3)); FABMS: m/z 629.2 (M-H)⁺. Calcd for C₄₁H₄₁O₆ 629.2 (M-H)⁺.
2,3,4,5,6-Penta-O-benzyl-1-O-[(1S)-(−)-camphanoyl]-D-myoinositol (184a) and 2,3,4,5,6-
Penta-O-benzyl-1-O-[(1S)-(−)-camphanoyl]-L-myoinositol (184b)

![Structural formulae of 184a and 184b](image)

To a solution of 183 (3.12 g, 4.94 mmol) in CH₂Cl₂ (35 ml) was added (S)-(−)-camphanic acid chloride (1.39 g, 6.42 mmol), Et₃N (2.70 ml, 19.76 mmol) and DMAP (0.12 g, 0.98 mmol). The reaction mixture was left at room temperature for 28 h, then water was added, the mixture extracted with CH₂Cl₂, and the CH₂Cl₂ dried over MgSO₄ and concentrated. The resulting crystalline mixture of diastereomers was separated by chromatography on silica gel using Et₂O-
CH₂Cl₂ (1:99) as eluent to afford 184a (1.89 g, 47%) as crystals, 184b (1.90 g, 47%) as crystals as well as a small amount of DL mixture (171 mg, 4%).

**Diastereomer 184a**: mp 147-149 °C (from ethyl acetate-petroleum ether); [α]D +9.8° (c 2.9, CHCl₃); νmax/cm⁻¹ 1781, 1718 (C=O); δH (400 MHz; CDCl₃) 7.40-7.21 (25 H, m, aromatic H), 4.98 (1 H, dd, J 9.8, 2.5 Hz, H-1), 4.94-4.66 (10 H, m, 5 × PhCH₂–), 4.18 (1 H, t, J 9.8 Hz, H-6), 4.14 (1 H, t, J 2.5 Hz, H-2), 4.11 (1 H, t, J 9.8 Hz, H-4), 3.58 (1 H, t, J 9.8 Hz, H-5), 3.58 (1 H, dd, J 9.8, 2.5 Hz, H-3), 2.32-2.25 (1 H, m, H-1′a), 1.88-1.77 (2 H, m, H-1′b, H-2′a), 1.66-1.59 (1 H, m, H-2′b), 1.09, 1.01, 0.91 (9 H, 3 s, 3 × -CH₃, camphanoyl); δC (100 MHz; CDCl₃) 177.87, 167.26 (2 × C=O, camphanoyl), 138.59, 138.40, 138.39, 138.26, 138.04, 128.36, 128.26, 128.25, 128.25, 128.18, 128.16, 128.15, 127.94, 127.73, 127.70, 127.69, 127.64, 127.49, 127.31, 127.19 (aromatic C), 90.77 (quaternary C, camphanoyl), 83.42 (C-5), 81.44 (C-4), 80.88 (C-3), 79.08 (C-6), 75.97, 75.84, 75.83, 75.16, 74.98, 74.97, 73.03 (5 × PhCH₂–, C-1, C-2), 54.71, 54.10 (2 C-quaternary C, camphanoyl), 30.67, 28.85 (C-1′, C-2′), 16.68, 16.54, 9.58 (3 × -CH₃, camphanoyl); FABMS: m/z 895.0 (M+Rb)⁺. Calcd for C₅₁H₃₄O₆⁸⁵Rb 895.2 (M+Rb)⁺.

**Diastereomer 184b**: mp 161-163 °C (from ethyl acetate-petroleum ether); [α]D -15.3° (c 2.5, CHCl₃); νmax/cm⁻¹ 1785, 1722 (C=O); δH (300 MHz; CDCl₃) 7.40-7.20 (25 H, m, aromatic H), 4.99-4.65 (10 H, m, 5 × PhCH₂–), 4.92 (1 H, dd, J 10.2, 2.2 Hz, H-3), 4.22 (1 H, t, J 2.2 Hz, H-2), 4.18 (1 H, dd, J 10.2, 9.5 Hz, H-4), 4.12 (1 H, t, J 9.5 Hz, H-6), 3.58 (1 H, t, J 9.5 Hz, H-5), 3.58 (1 H, dd, J 9.5, 2.2 Hz, H-1), 2.33-2.23 (1 H, m, H-1′a), 1.96-1.81 (2 H, m, H-1′b, H-2′b), 1.70-
1.61 (1 H, m, H-2_b), 1.08, 0.97, 0.85 (9 H, 3 s, 3 -CH_3, camphanyol); δ_C (75 MHz; CDCl_3) 177.89, 167.46 (2 -C=O, camphanyol), 138.59, 138.39, 138.35, 138.29, 138.02, 128.42, 128.34, 128.32, 128.28, 128.26, 128.03, 128.00, 127.98, 127.80, 127.72, 127.70, 127.56, 127.50, 127.39, 127.19 (aromatic C), 90.84 (quaternary C, camphanyol), 83.54 (C-5), 81.41 (C-6), 80.97 (C-1), 78.90 (C-4), 75.96, 75.89, 75.27, 75.26, 75.25, 74.68, 73.09 (5 × PhCH_2-), C-3, C-2), 54.77, 54.07 (2 C-quaternary, camphanyol), 30.92, 28.94 (C-1', C-2'), 16.62, 16.55, 9.61 (3 × -CH_3, camphanyol); EIMS: m/z 811.3 (M+H)^+. Calcd for C_{51}H_{55}O_{9} 811.3 (M+H)^+.

2,3,4,5,6-Penta-O-benzyl-d-myo-inositol (185)

![Chemical structure of 2,3,4,5,6-Penta-O-benzyl-d-myo-inositol](attachment:image)

A mixture of 184a (1.86 g, 2.29 mmol) and powdered potassium hydroxide (1.29 g, 22.99 mmol) in absolute ethanol (30 ml) was gently refluxed for 2 h. The solvent was evaporated, water then added and the mixture extracted with CH_2Cl_2, which was then dried over MgSO_4 and concentrated. The resulting residue was purified by column chromatography using ethyl acetate-petroleum ether (3:7) as eluent to afford compound 185 (1.43 g, 99%) as a gum; [α]_D +7.1° (c 1.0, CHCl_3) (lit., [α]_D +13.9° (c 0.3, CHCl_3); ν_{max}/cm^{-1} 3566 (OH); δ_H (400 MHz; CDCl_3) 7.38-7.26 (25 H, m, aromatic H), 5.01-4.67 (10 H, m, 5 × PhCH_2-), 4.07, (1 H, t, J 9.6 Hz, H-6), 4.04 (1 H, t, J 2.6 Hz, H-2), 3.82 (1 H, t, J 9.6 Hz, H-4), 3.50 (1 H, m, H-1), 3.49 (1 H, t, J 9.6, H-5), 3.47 (1 H, dd, J 9.6, 2.6 Hz, H-3), 2.23 (s (br), -OH); δ_C (100 MHz; CDCl_3) 138.91, 138.88, 128.81, 138.77, 138.40, 128.61, 128.55, 128.50, 128.47, 128.45, 128.19, 128.15, 127.96, 127.92, 127.89, 127.81, 127.75, 127.72, 127.68, 127.66 (aromatic C), 83.75 (C-5), 82.32 (C-4), 82.05 (C-6), 81.28 (C-3), 77.29 (C-2), 75.98, 75.87, 75.64, 74.89, 73.13 (5 × PhCH_2-), 72.57 (C-1); HRFABMS: m/z 653.288001 (M+Na)^+. Calcd for C_{41}H_{42}O_{8}Na 653.287893 (M+Na)^+. 
A mixture of 184b (1.90 g, 2.34 mmol) and powdered potassium hydroxide (1.32 g, 23.44 mmol) in absolute ethanol (30 ml) was gently refluxed for 2 h. The solution was concentrated, water then added and the mixture extracted into CH$_2$Cl$_2$, which was then dried over MgSO$_4$ and concentrated. The resulting residue was purified by column chromatography using ethyl acetate-petroleum ether (3:7) as eluent to afford compound 186 (1.38 g, 93%) as a gum; [α]$_D$ −8.0° (c 1.0, CHCl$_3$) (lit. [173] [α]$_D$ −13.5° (c 0.3, CHCl$_3$); ν$_{max}$/cm$^{-1}$ 3560 (OH); δ$_H$ (300 MHz; CDCl$_3$) 7.42-7.30 (25 H, m, aromatic H), 5.06-4.73 (10 H, m, 5 × PhCH$_2$), 4.11 (1 H, t, J 9.5 Hz, H-6), 4.07 (1 H, t, J 2.4 Hz, H-2), 3.87 (1 H, t, J 9.5 Hz, H-4), 3.55 (1 H, m, H-1), 3.53 (1 H, t, J 9.5 Hz, H-5), 3.50 (1 H, dd, J 9.5, 2.4 Hz, H-3), 2.28 (s (br), -OH); δ$_C$ (75 MHz; CDCl$_3$) 138.72, 138.70, 138.63, 138.59, 138.23, 128.44, 128.38, 128.33, 128.30, 128.29, 128.00, 127.98, 127.79, 127.75, 127.72, 127.64, 127.57, 127.55, 127.52, 127.49 (aromatic C), 83.56 (C-5), 82.13 (C-4), 81.86 (C-6), 81.09 (C-3), 77.09 (C-2), 75.81, 75.69, 75.46, 74.71, 72.94 (5 × PhCH$_2$), 72.38 (C-1); HRFABMS: m/z 653.287349 (M+Na)$^+$. Calcd for C$_{41}$H$_{42}$O$_6$Na 653.287893 (M+Na)$^+$. 
2,3,4,5,6-Penta-O-benzyl-1-O-[2'-C-(2''-methylprop-1''-enyl)-2'-deoxy-α-D-glucopyranosyl]-L-my-o-inositol (189)

A mixture of 176 (163 mg, 0.47 mmol) and 186 (355 mg, 0.56 mmol) was dried by co-evaporation with toluene (4 x 20 ml). The mixture was then dissolved in CH₂Cl₂ (10 ml) in a two-necked round bottom flask containing molecular sieves 4Å (1 g) and stirred at room temperature for 30 min before adding boron trifluoride etherate (0.29 ml, 2.35 mmol) dropwise. Stirring was continued for 2 h, whereupon the coupling reaction was evident by the appearance on tlc of a new UV-active product spot that was also revealed by anisaldehyde spray (176 was UV-inactive and showed up as a dark spot on the anisaldehyde spray, whereas 186 was UV-active and didn’t show up clearly with the anisaldehyde spray). Et₃N (0.2 ml) was added to the dark solution, and the solids removed by filtration. Water was then added to the brown filtrate, which was extracted with CH₂Cl₂. The CH₂Cl₂ phase was washed with saturated NaHCO₃ and water, then dried over MgSO₄ and concentrated. The brown residue was purified by column chromatography using ethyl acetate-petroleum ether (1:4) as eluent to give a mixture of anomers 188 (60%, α:β ≈ 99:1 by 13C-NMR) and unreacted acceptor 186. The mixture was dissolved in CH₂Cl₂-MeOH (4:5 ml), methanolic sodium methoxide (0.2 M, 4 ml, 0.8 mmol) added and the mixture stirred at room temperature for 2 h. The solution was neutralized with Amberlite IR-120 H⁺ resin, filtered and the filtrate concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (3:2) as eluent afforded a single α-anomer 189 (120 mg, 30% from 176) as an amorphous solid; [α]D +43.2° (c 2.7, CHCl₃); δH (300 MHz; CDCl₃) 7.50-7.16 (25 H, m, aromatic H), 5.22 (1 H, d, J 3.6 Hz, H-1'), 5.17 (1 H, dt, J 10.2, 1.2 Hz, H-1'''), 5.07-4.65 (10 H, m, 5 × PhCH₂-), 4.12-4.04 (2 H, m, H-4, H-6), 4.00 (1 H, t, J 2.2 Hz, H-2), 3.78 (2 H, d (br), J 3.6 Hz, H-6', H-6''), 3.73-3.51 (4 H, m, H-1', H-3', H-4', H-5'), 3.49 (1 H, t, J 9.2 Hz, H-5), 3.45 (1 H, dd, J 9.2, 2.2 Hz, H-3), 2.93 (s (br), -OH), 2.61-2.53 (1 H, td, J 10.2, 3.6 Hz, H-2''), 1.53 (3 H, d, J 1.2 Hz, H-3'''), 1.45 (3 H, d, J 1.2 Hz, H-4''), δc (75 MHz; CDCl₃) 139.10, 138.83, 138.79, 138.56, 138.27 (aromatic C), 138.15 (C-2''), 128.36, 128.25, 128.21, 128.19, 128.05, 127.95, 127.76, 127.72, 127.66, 127.52, 127.45, 127.39, 127.00, 126.84, 126.52 (aromatic C), 119.95 (C-1''), 100.45 (C-1'), 84.12 (C-5), 81.77 (C-4), 81.59 (C-6), 80.54 (C-3), 78.00 (C-2), 75.80, 75.77 75.69, 74.72, 74.63, 72.78 (5 × PhCH₂-, C-1), 72.58 (C-3'), 72.13 (C-4'), 71.54 (C-5'), 62.31 (C-6'), 46.56 (C-2'), 25.86, 18.08
(C-3'', C-4''); HRFABMS: m/z 853.392986 (M+Na)^+. Calcd for C_{51}H_{58}O_{10}Na 853.392746 (M+Na)^+.

2,3,4,5,6-Penta-O-benzyl-1-O-[3',4',5'-tri-O-acetyl-2'-C-(2''-methylprop-1''-enyl)-2'-deoxy-\(\alpha\)-D-glucopyranosyl]-L-myoinositol (188a)

Triethylamine (0.1 ml, 0.72 mmol) was added dropwise to a mixture of 189 (70 mg, 0.084 mmol), acetic anhydride (0.2 ml, 2.12 mmol) and DMAP (3 mg, 0.024 mmol) in CH\(_2\)Cl\(_2\) (3 ml) at room temperature. After 1 h, the reaction was stopped by the addition of water, and the mixture extracted with CH\(_2\)Cl\(_2\), the CH\(_2\)Cl\(_2\) phase dried over MgSO\(_4\) and concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (3:7) as eluent afforded compound 188a (79 mg, 98%) as an oil; \([\alpha]_D^0 +35.4^\circ\) (c 2.5, CHCl\(_3\)); \(\delta_H\) (400 MHz; CDCl\(_3\)) 7.58-7.15 (25 H, m aromatic H), 5.35 (1 H, dd, \(J 11.0, 10.4\) Hz, H-3'), 5.28 (1 H, d, \(J 3.6\) Hz, H-1'), 5.12-5.10 (1 H, d (br), \(J 10.4\) Hz, H-1''), 5.05-4.66 (11 H, m, 5 \(\times\) PhCH\(_2\)H, H-4'), 4.21 (1 H, dd, \(J 12.2, 4.6\) Hz, H-6'a), 4.12 (1 H, t, \(J 9.6\) Hz, H-4), 4.09 (1 H, t, \(J 9.6\) Hz, H-6), 3.96 (1 H, s (br), H-2), 3.92-3.86 (2 H, m, H-5', H-6'b), 3.64 (1 H, dd, \(J 9.6, 2.2\) Hz, H-1), 3.50 (1 H, t, \(J 9.6\) Hz, H-5), 3.44 (1 H, dd, \(J 9.6, 2.2\) Hz, H-3), 2.82 (1 H, td, \(J 10.4, 3.6\) Hz, H-2'), 2.06, 2.05, 1.94 (9 H, 3 s, 3 \(\times\) COOCH\(_3\)), 1.42, 1.41 (6 H, 2 s, H-3'', H-4''); \(\delta_C\) (100 MHz; CDCl\(_3\)) 170.73, 170.15, 169.95 (3 C-3 \(\times\) COOCH\(_3\)), 138.99, 138.88, 138.72, 138.46 (aromatic C), 137.30 (C-2''), 128.54, 128.53, 128.46, 128.40, 128.39, 128.17, 127.86, 127.85, 127.82, 127.73, 127.67, 127.58, 127.56, 127.12, 126.67 (aromatic C), 119.56 (C-1''), 100.56 (C-1'), 84.43 (C-5), 81.76 (C-4), 81.67 (C-6), 81.22 (C-3), 77.16 (C-2), 76.73 (C-1), 75.95, 75.91, 74.75, 74.29, 73.24 (5 \(\times\) PhCH\(_2\)H), 71.64 (C-3'), 69.78 (C-4'), 68.36 (C-5'), 62.79 (C-6'), 45.20 (C-2'), 25.77 (C-3''), 20.88, 20.87, 20.75 (3 \(\times\) COOCH\(_3\)), 18.05 (C-4''); HRFABMS: m/z 979.422749 (M+H)^+. Calcd for C\(_{57}\)H\(_{64}\)O\(_{13}\) 979.424439 (M+H)^+. 
A mixture of 173 (1.0 g, 3.01 mmol) and 185 (1.13 g, 1.79 mmol) were dried by co-evaporation with toluene (4 x 20 ml). The mixture was then dissolved in CH₂Cl₂ (15 ml) in a two-necked flask containing molecular sieves 4Å (1.5 g) and stirred at room temperature for 30 min before boron trifluoride etherate (1.1 ml, 9.03 mmol) was added dropwise. Stirring was continued for 2 h, whereupon the coupling reaction was evident by the appearance on tlc of a new UV-active product that was also revealed by anisaldehyde spray (173 was UV-inactive and showed up as a dark spot on the anisaldehyde spray, whereas 185 was UV-active and didn’t show up clearly with the anisaldehyde spray). Et₃N (1.0 ml) was added to the dark solution, and the solids removed by filtration. Water was then added to the brown filtrate and the solution extracted with CH₂Cl₂. The CH₂Cl₂ extract was washed successively with saturated NaHCO₃ and water, then dried over MgSO₄ and concentrated. The brown residue was purified by column chromatography using ethyl acetate-petroleum ether (1:4) as eluent to give an inseparable mixture of anomers 190 (α:β ≈ 8:1 by ¹³C-NMR) and unreacted acceptor 185. The mixture was dissolved in CH₂Cl₂-MeOH (5:7 ml), methanolic sodium methoxide (0.2 M, 5 ml, 1 mmol) was added and the mixture stirred at room temperature for 2 h. The solution was then neutralized with Amberlite IR-120 H⁺ resin, filtered and the filtrate concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (3:2, then 7:3) as eluent afforded a mixture of anomers 191 (1.17 g, 80% from 185) as an amorphous solid. Separation of anomers was achieved by further column chromatography using ethyl acetate-petroleum ether (1:1) as eluent to afford a single α-anomer 191a as an amorphous solid; [α]₀ +34.1° (c 3.6, CHCl₃); δH (400 MHz; CDCl₃) 7.38-7.23 (25 H, m, aromatic H), 5.85 (1 H, m, H-2′′), 5.11-4.57 (13 H, m, 5 × PhCH₂, H-1′, H-3′′a, H-3′′b), 4.10 (1 H, t, J 9.6 Hz, H-4′), 4.06-401 (2 H, m, H-2, H-6), 3.82 (1 H, m, H-5′), 3.61-3.55 (4 H, m, H-1, H-3′, H-6′a, H-6′b), 3.53 (1 H, t, J 9.6 Hz, H-5), 3.47 (1 H, dd, J 9.6, 1.8 Hz, H-3), 3.36 (1 H, t, J 9.4 Hz, H-4′), 2.42 (1 H, m, H-1′′a), 2.23 (1 H, m, H-1′′b), 1.82 (1 H, m, H-2′); δC (100 MHz; CDCl₃) 138.98, 138.95, 138.88, 138.75, 138.41 (aromatic C), 136.96 (C-2′′′), 128.58, 128.55, 128.47, 128.44, 128.32, 128.12, 127.94, 127.93, 127.92, 127.84, 127.78, 127.68, 127.65, 127.50, 127.33 (aromatic C), 116.19 (C-3′′′), 95.49 (C-1′), 84.21 (C-5), 82.01 (C-3), 81.88 (C-4), 80.46 (C-6), 76.10, 75.93, 75.71 (3 × PhCH₂-), 74.41, 74.28, 74.01, 73.47, 73.37 (2 × PhCH₂-, C-1, C-2,
C-3′), 72.77 (C-4′), 70.85 (C-5′), 62.55 (C-6′), 45.71 (C-2′), 31.40 (C-1′); FABMS: m/z 839.2 (M+Na)⁺. Calcd for C₅₀H₅₆O₁₀Na 839.3 (M+Na)⁺.

2,3,4,5,6-Penta-O-benzyl-1-O-(3′,4′,6′-tri-O-acetyl-2′-C-allyl-2′-deoxy-α-D-glucopyranosyl)-D-myoinositol (190a)

Triethylamine (0.1 ml, 0.72 mmol) was added slowly to a mixture of 191a (110 mg, 0.13 mmol), acetic anhydride (0.25 ml, 2.6 mmol) and DMAP (5 mg, 0.04 mmol) in CH₂Cl₂ (5 ml) at room temperature. After 1 h, the reaction was stopped by the addition of water, and the mixture extracted with CH₂Cl₂, the CH₂Cl₂ phase dried over MgSO₄ and concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (3:7) afforded compound 190a (120 mg, 98%) as an oil; [α]D +46.4° (c 2.2, CHCl₃); δH (400 MHz; CDCl₃) 7.42-7.22 (25 H, m, aromatic H), 5.71 (1 H, m, H-2′), 5.31 (1 H, dd, J 10.4, 9.2 Hz, H-3′), 5.13 (1 H, d, J 11.0 Hz, PhCH₂-), 5.02 (1 H, d, J 3.2 Hz, H-1′), 4.98-4.72 (11 H, m, 4 × PhCH₂-), H-4′, H-3′⁻a, H-3′⁻b, 4.58 (1 H, d, J 11.0 Hz, PhCH₂-), 4.25 (1 H, m, H-5′), 4.13 (1 H, t, J 9.6 Hz, H-4), 4.08 (2 H, m, H-2, H-6), 3.92 (2 H, m, H-6⁻a, H-6⁻b), 3.65 (1 H, dd, J 9.6, 2.0 Hz, H-1), 3.54 (1 H, t, J 9.6 Hz, H-5), 3.48 (1 H, dd, J 9.6, 2.0 Hz, H-3), 2.35-2.10 (3 H, m, H-2′, H-1′⁻a, H-1′⁻b), 2.06, 1.99, 1.86 (9 H, 3 s, 3 × COOCH₃); δC (100 MHz; CDCl₃) 170.69, 170.37, 170.01 (3 × COOCH₃), 138.83, 138.79, 138.68, 138.67, 138.35 (aromatic C), 135.69 (C-2′⁻), 128.61, 128.50, 128.47, 128.38, 128.37, 128.24, 128.16, 127.94, 127.89, 127.78, 126.79, 126.75, 126.58, 126.58, 126.48, 126.39 (aromatic C), 116.07 (C-3′⁻), 95.35 (C-1'), 84.26 (C-5), 82.04 (C-3), 81.84 (C-4), 80.04 (C-6), 76.17, 76.02, 75.79 (3 × PhCH₂-), 74.70 (C-1), 74.49 (C-PhCH₂-), 74.02 (C-2), 73.52 (C-PhCH₂-), 72.39 (C-3'), 69.45 (C-4'), 67.70 (C-5'), 62.05 (C-6'), 44.16 (C-2'), 31.54 (C-1′⁻), 20.94, 20.88, 20.70 (3 × COOCH₃); HRFABMS: m/z 965.407457 (M+Na)⁺. Calcd for C₅₆H₆₂O₁₃Na 965.408790 (M+Na)⁺.
2,3,4,5,6-Penta-\(O\)-benzyl-1-\(O\)-(3',4',6'-tri-\(O\)-benzyl-2'-C-allyl-2'-deoxy-\(\alpha\)-D-glucopyranosyl)-D-\(\gamma\)-inositol (192a) and 2,3,4,5,6-Penta-\(O\)-benzyl-1-\(O\)-(3',4',6'-tri-\(O\)-benzyl-2'-C-allyl-2'-deoxy-\(\beta\)-D-glucopyranosyl)-D-\(\gamma\)-inositol (192b)

\[
\begin{align*}
\text{192a} & & \text{192b}
\end{align*}
\]

NaH (50%, 0.27 g, 5.60 mmol) was added to a solution of a mixture of anomers 191 (768 mg, 0.94 mmol) in THF (15 ml) at 0 °C. After 5 min, benzyl bromide (1.37 ml, 5.60 mmol) was added, the ice-water bath removed and the slurry heated at reflux for 18 h. The solution was then cooled and excess NaH quenched with methanol followed by water. The organic solvent was evaporated, the aqueous slurry extracted with CH\(_2\)Cl\(_2\), and the CH\(_2\)Cl\(_2\) phase washed with saturated NaCl, dried over MgSO\(_4\) and concentrated. Separation of the anomers was achieved by column chromatography using ethyl acetate-petroleum ether (1:9) as eluent to afford the \(\alpha\)-anomer 192a (790 mg, 77%) as an oil, the \(\beta\)-anomer 192b (120 mg, 10%) as an oil and a mixture of anomers (90 mg, 8%) (total yield 1.00 g, 98%).

\(\alpha\)-Anomer 192a: [\(\alpha\)]\(_D\) +39.4° (c 2.7, CHCl\(_3\)); \(\delta_{1H}\) (300 MHz; CDCl\(_3\)) 7.38-7.05 (40 H, m, aromatic H), 5.85 (1 H, m, H-2'''), 5.13-4.39 (18 H, m, 8 \(\times\) PhCH\(_2\)-, H-3'''a, H-3'''b), 5.09 (1 H, d, J 3.3 Hz, H-1'''), 4.18 (1 H, s (br), H-2'), 4.15 (1 H, m, H-5'), 4.12 (1 H, t, J 9.6 Hz, H-4'), 4.08 (1 H, t, J 9.6 Hz, H-5), 3.79-3.45 (6 H, m, H-1, H-3, H-3', H-4', H-6'a, H-6'b), 3.50 (1 H, t, J 9.6 Hz, H-5), 2.45 (1 H, m, H-1''a), 2.22 (1 H, m, H-1''b), 2.07 (1 H, m, H-2''), \(\delta_{13C}\) (75 MHz; CDCl\(_3\)) 138.95, 138.80, 138.79, 138.61, 138.48, 138.43, 138.31, 138.05 (aromatic C), 136.63 (C-2'''), 128.39, 128.30, 128.29, 128.28, 128.27, 128.26, 128.25, 128.23, 128.17, 128.13, 128.03, 127.99, 127.97, 127.90, 127.84, 127.81, 127.71, 127.62, 127.59, 127.46, 127.41, 127.37, 127.24, 127.10 (aromatic C), 115.69 (C-3'''), 94.92 (C-1'), 84.02 (C-5), 81.99 (C-3), 81.73 (C-4), 80.92 (C-3'), 80.46 (C-6), 79.81 (C-4'), 76.13, 75.91, 75.75, 75.09, 74.57, 74.09 (6 \(\times\) PhCH\(_2\)-), 73.92 (C-1), 73.45 (C-2), 73.20, 73.19 (2 \(\times\) PhCH\(_2\)-), 70.65 (C-5'), 68.61 (C-6'), 45.84 (C-2''), 30.69 (C-1''''); FABMS: \(m/z\) 1171.3 (M+Rb'). Calcd for C\(_{77}\)H\(_{106}\)O\(_{10}\)^{85}Rb 1171.4 (M+Rb').

\(\beta\)-Anomer 192b: [\(\alpha\)]\(_D\) -4.3° (c 3.0, CHCl\(_3\)); \(\delta_{1H}\) (300 MHz; CDCl\(_3\)) 7.43-7.28 (40 H, m, aromatic H), 5.96 (1 H, m, H-2'''), 5.09-4.86 (12 H, m, 5 \(\times\) PhCH\(_2\)-, H-3'''a, H-3'''b), 4.77-4.58 (6 H, m, 3 \(\times\) PhCH\(_2\)-), 4.72 (1 H, d, J 8.1 Hz, H-1'''), 4.51 (1 H, t, J 2.1 Hz, H-2'), 4.20 (1 H, t, J 9.6 Hz, H-4'), 4.17 (1 H, t, J 9.6 Hz, H-6), 3.80-3.49 (7 H, m, H-1, H-3, H-5', H-6'a, H-6'b, H-3'', H-4''), 3.62 (1
H, t, J 9.6 Hz, H-5), 2.49 (2 H, m, H-1''', H-1'''), 2.04 (1 H, m, H-2'); δC (75 MHz; CDCl3) 139.55, 138.87, 138.82, 138.65, 138.50, 138.44, 138.04, 138.01 (aromatic C), 135.78 (C-2'''), 128.38, 128.36, 128.35, 128.33, 128.22, 128.21, 128.20, 128.19, 128.12, 128.00, 127.98, 127.97, 127.80, 127.70, 127.60, 127.52, 127.46, 127.42, 127.41, 127.40, 127.36, 127.16, 127.07 (aromatic C), 116.67 (C-3'''), 103.88 (C-1'), 84.14 (C-5), 81.78 (C-3), 81.57 (C-4), 80.93 (C-6), 80.59 (C-3'), 80.06 (C-4'), 79.96 (C-1), 77.53 (C-2), 75.69, 75.62, 75.26, 74.68, 74.67, 74.66 (6 × PhCH2-), 74.42 (C-5'), 73.48, 72.01 (2 × PhCH2-), 69.56 (C-6'), 47.69 (C-2'), 30.86 (C-1'''); FABMS: m/z 1086.5 (M)+. Calcd for C71H74O10 1086.5.

**2,3,4,5,6-Penta-O-benzyl-1-O-[3',4',6'-tri-O-benzyl-2'-deoxy-2'-C-(2''',3'''-epoxypropyl)-α-D-glucopyranosyl]-D-myo-inositol (193)**

![Diagram of 2,3,4,5,6-Penta-O-benzyl-1-O-[3',4',6'-tri-O-benzyl-2'-deoxy-2'-C-(2''',3'''-epoxypropyl)-α-D-glucopyranosyl]-D-myo-inositol](attachment://diagram.png)

To a solution of 192a (290 mg, 0.26 mmol) in CH2Cl2 (10 ml) at 0 °C was slowly added a solution of m-CPBA (70%, 0.14 g, 0.58 mmol) in CH2Cl2 (2.0 ml). (m-CPBA was dissolved in CH2Cl2, dried with MgSO4, filtered and concentrated before used). The temperature was then raised to room temperature and after stirring for 5 h a further portion of the solution of m-CPBA (70%, 0.14 g, 0.58 mmol) in CH2Cl2 (1 ml) was added to the mixture at 0 °C. The reaction was stirred for 18 h at room temperature, saturated Na2S2O3 then added, the mixture extracted with CH2Cl2, and the CH2Cl2 washed with saturated NaHCO3, dried over MgSO4 and concentrated. The crude residue was purified by column chromatography using ethyl acetate-petroleum ether (1:4) as eluent to afford an inseparable mixture of diastereomers 193 (244 mg, 85%, 1:1 by 1H-NMR) as an oil.

**Diastereomer 193a:** δH (400 MHz; CDCl3) 7.38-7.03 (40 H, m, aromatic H), 5.23-5.14 (2 H, m, PhCHH-), 4.92-4.37 (15 H, m, 7 × PhCH2-, PhCHH-), 4.31 (1 H, s (br), H-2), 4.17 (1 H, m, H-5'), 4.13-4.02 (2 H, m, H-4, H-6), 4.82-3.46 (7 H, m, H-1, H-3, H-5, H-3', H-4', H-6'a, H-6'b), 2.97 (1 H, m, H-2'''), 2.50 (1 H, dd, J 5.0, 4.2 Hz, H-3'''), 2.11 (1 H, m, H-2'), 2.04 (1 H, dd, J 5.0, 2.6 Hz, H-3'''), 1.74 (2 H, m, H-1''', H-1'''), δC (100 MHz; CDCl3) 139.47-126.97 (aromatic C), 96.09 (C-1'), 84.24 (C-5), 82.10 (C-3), 81.96 (C-4), 80.59 (C-3'), 80.54 (C-6), 80.21 (C-4'), 76.22, 76.07, 75.92, 75.22 (4 × PhCH2-), 74.73, 74.46, 74.06, 73.68, 73.40, 73.39 (4 × PhCH2-, C-
1, C-2), 70.82 (C-5'), 68.67 (C-6'), 52.22 (C-2''), 46.61 (C-3''), 45.38 (C-2'), 30.25 (C-1''');
FABMS: m/z 1125.5 (M+Na)⁺. Calcd for C₇₁H₇₄O₁₁Na 1125.5 (M+Na)⁺.

Diastereomer 193b: \( \delta_H \) (400 MHz; CDCl₃) 7.38-7.03 (40 H, m, aromatic H), 5.23-5.14 (2 H, m, PhCH₂H, H-1'), 4.92-4.37 (15 H, m, 7 × PhCH₂-, PhCHH-), 4.28 (1 H, s (br), H-2), 4.13-4.02 (3 H, m, H-5', H-4, H-6), 3.82-3.46 (7 H, m, H-1, H-3, H-5, H-3', H-4', H-6', H-6′), 2.87 (1 H, m, H-2''), 2.40 (1 H, dd, J 5.0, 4.2 Hz, H-3''a'), 2.34 (1 H, dd, J 5.0, 2.6 Hz, H-3''b'), 2.04 (1 H, m, H-2'), 1.94 (2 H, m, H-1''a, H-1''b); \( \delta_C \) (100 MHz; CDCl₃) 139.47-126.97 (aromatic C), 94.92 (C-1'), 84.08 (C-5), 82.22 (C-3), 81.75 (C-4), 81.06 (C-3'), 80.75 (C-6), 79.78 (C-4'), 76.31, 76.07, 75.92, 75.08 (4 × PhCH₂-), 74.68, 74.06, 73.89, 73.40, 73.39, 73.14 (4 × PhCH₂-, C-1, C-2), 70.85 (C-5'), 68.75 (C-6'), 50.32 (C-2''), 46.80 (C-3''), 42.78 (C-2'), 29.55 (C-1''); FABMS: m/z 1125.5 (M+Na)⁺. Calcd for C₇₁H₇₄O₁₁Na 1125.5 (M+Na)⁺.
2,3,4,5,6-Penta-O-benzyl-1-O-[3',4',6'-tri-O-benzyl-2'-deoxy-2'-C-(2'-hydroxypropyl)-α-D-glucopyranosyl]-D-myo-inositol (194)

A solution of 193 (276 mg, 0.25 mmol) in THF (8 ml) was added dropwise to a solution of lithium aluminium hydride (0.1 g, 2.5 mmol) in THF (4 ml) at 0 °C. After 2 h at 0 °C, the excess LAH was quenched with water, extracted with ethyl acetate, dried over MgSO₄ and concentrated. Purification was achieved by column chromatography using ethyl acetate-petroleum ether (3:7) as eluent to afford an inseparable mixture of diastereomers 194 (226 mg, 82%, 1:1 by ¹H-NMR) as an oil; νₛₒₛ cm⁻¹ 3465 (OH).

**Diastereomer 194a**: δₜ (400 MHz; CDCl₃) 7.38-7.03 (40 H, m, aromatic H), 5.18 (1 H, d, J 12.0 Hz, PhCHH-), 5.09 (1 H, d, J 3.2 Hz, H-1’), 4.90-4.46 (14 H, m, 7 × PhCH₂H), 4.39 (1 H, d, J 12.0 Hz, PhCHH-), 4.22 (1 H, m, H-2), 4.13-3.98 (3 H, m, H-5’, H-4, H-6), 3.79 (1 H, m, H-2’”), 3.74-3.43 (7 H, m, H-1, H-3, H-5, H-3’, H-4’, H-6’a, H-6’b), 2.05 (1 H, m, H-2”), 1.67-1.41 (2 H, m, H-1’”, H-1’’b), 0.93 (3 H, d, J 6.0 Hz, H-3’’); δₜ (100 MHz; CDCl₃) 139.18-126.99 (aromatic C), 96.02 (C-1’), 84.10 (C-5), 82.14 (C-3), 81.81 (C-4), 81.63 (C-3’’), 80.66 (C-6), 80.16 (C-4’), 76.32, 76.06, 75.92, 75.44, 74.66 (5 × PhCH₂H), 74.09, 73.87, 73.48, 73.39, 73.38 (3 × PhCH₂H, C-1, C-2), 70.60 (C-5’), 68.72 (C-6’), 66.92 (C-2’”), 43.42 (C-2’), 37.12 (C-1’’), 23.73 (C-3’’); FABMS: m/z 1127.5 (M+Na⁺). Calcd for C₆₇H₇₆O₁₁Na 1127.5 (M+Na⁺).

**Diastereomer 194b**: δₜ (400 MHz; CDCl₃) 7.38-7.03 (40 H, m, aromatic H), 5.14 (1 H, d, J 11.8 Hz, PhCHH-), 5.04 (1 H, d, J 3.2 Hz, H-1’), 4.90-4.46 (14 H, m, 7 × PhCH₂H), 4.42 (1 H, d, J 11.8 Hz, PhCHH-), 4.22 (1 H, m, H-2), 4.13-3.98 (3 H, m, H-5’, H-4, H-6), 3.74 (1 H, m, H-2’”), 3.74-3.43 (7 H, m, H-1, H-3, H-5, H-3’, H-4’, H-6’a, H-6’b), 2.05 (1 H, m, H-2”), 1.67-1.41 (2 H, m, H-1”a, H-1’’b), 0.88 (3 H, d, J 6.0 Hz, H-3’’); δₜ (100 MHz; CDCl₃) 138.18-126.99 (aromatic C), 95.70 (C-1’), 84.05 (C-5), 82.19 (C-3), 81.72 (C-4), 80.80 (C-3’), 80.73 (C-6), 80.16 (C-4’), 76.32, 76.06, 75.92, 75.30, 74.66 (5 × PhCH₂H), 74.09, 73.74, 73.48, 73.39, 73.13 (3 × PhCH₂H, C-1, C-2), 70.86 (C-5’), 68.72 (C-6’), 66.39 (C-2’’), 43.36 (C-2’), 37.28 (C-1’’), 23.98 (C-3’’); FABMS: m/z 1127.5 (M+Na⁺). Calcd for C₆₇H₇₆O₁₁Na 1127.5 (M+Na⁺).
A solution of 194 (148 mg, 0.13 mmol) in ethyl acetate-methanol (4:6 ml) was stirred under H₂ (1 atm) at room temperature in the presence of 10% palladium on charcoal (300 mg) for 3 days. Three additional portions of 10% palladium on charcoal (200 mg) were added at 18 h interval. TLC analysis (MeOH:EtOAc, 3:2) showed the complete conversion of the starting material into the deprotected derivative. The catalyst was removed by filtration through celite, the celite washed with water-methanol (1:9) and the combined filtrates evaporated to dryness. The remaining residue was passed through a reverse phase isolute® C18 column using water-methanol (1:4) as eluent. The organic solvent was evaporated and the remaining aqueous solution freeze-dried to afford a mixture of diastereomers 51 (45 mg, 91%, 1:1 by ¹H-NMR) as a hygroscopic solid.

_Diastereomer 51a:_ δₜ (300 MHz; D₂O) 5.09 (1 H, d, J 3.3 Hz, H-1’), 4.24 (1 H, s (br), H-2), 4.00-3.27 (11 H, m, H-1, H-3, H-4, H-5, H-6, H-3’, H-4’, H-5’, H-6’ₐ, H-6’ₜ, H-2’), 1.90-1.62 (3 H, m, H-2’, H-1’ₐ, H-1’ₜ), 1.20 (3 H, d, J 6.0 Hz, H-3’’); δₜ (75 MHz; D₂O) 95.62 (C-1’), 74.58, 74.11, 72.09, 72.08, 71.74, 71.04, 71.03, 70.59 (C-1, C-3, C-4, C-5, C-6, C-3’, C-4’, C-5’), 67.78 (C-2), 66.63 (C-2’’), 60.59 (C-6’), 43.43 (C-2’), 35.59 (C-1’’), 22.25 (C-3’’); FABMS (negative): m/z 383.1 (M-H)⁻. Caled for C₁₈H₂₇O₁₁ 383.1 (M-H)⁻.

_Diastereomer 51b:_ δₜ (300 MHz; D₂O) 5.10 (1 H, d, J 3.3 Hz, H-1’), 4.23 (1 H, s (br), H-2), 4.00-3.27 (11 H, m, H-1, H-3, H-4, H-5, H-6, H-3’, H-4’, H-5’, H-6’ₐ, H-6’ₜ, H-2’), 1.90-1.62 (3 H, m, H-2’, H-1’ₐ, H-1’ₜ), 1.20 (3 H, d, J 6.0 Hz, H-3’’); δₜ (75 MHz; D₂O) 95.34 (C-1’), 74.40, 74.14, 72.25, 72.02, 71.74, 71.20, 71.08, 70.59 (C-1, C-3, C-4, C-5, C-6, C-3’, C-4’, C-5’), 67.94 (C-2), 65.01 (C-2’’), 60.59 (C-6’), 42.26 (C-2’), 35.67 (C-1’’), 22.74 (C-3’’); FABMS (negative): m/z 383.1 (M-H)⁻. Caled for C₁₈H₂₇O₁₁ 383.1 (M-H)⁻.
2,3,4,5,6-Penta-O-benzyl-1-O-[3',4',6'-tri-O-benzyl-2'-deoxy-2'-C-(2''-oxopropyl)-α-D-glucopyranosyl]-d-myoinositol (195)

To a stirred solution of 194 (226 mg, 0.20 mmol) and activated molecular sieves 4Å (0.4 g) in CH₂Cl₂ (10 ml) was added NMO (39 mg, 0.29 mmol) at room temperature. After stirring for 5 min, TPAP (0.01 g, 0.028 mmol) was added and the stirring continued for 30 min. The solids were filtered through celite and the filtrate concentrated. Purification of the black solution by column chromatography using ethyl acetate-petroleum ether (3:17) as eluent afforded compound 195 (210 mg, 95%) as an oil; [α]D +38.5° (c 2.2, CHCl₃); v_max/cm⁻¹ 1712 (C=O); δ_H (400 MHz; CDCl₃) 7.36-7.04 (40 H, m, aromatic H), 5.28 (1 H, d, J 3.6 Hz, H-1'), 5.08 (1 H, d, J 12.0 Hz, PhCHH-), 4.89-4.67 (10 H, m, 5 × PhCH₂-), 4.64 (1 H, d, J 12.0 Hz, PhCHH-), 4.52 (1 H, d, J 11.4 Hz, PhCHH-), 4.49 (1 H, d, J 11.4 Hz, PhCHH-), 4.42 (1 H, d, J 12.0 Hz, PhCHH-), 4.41 (1 H, d, J 12.0 Hz, PhCHH-), 4.17 (1 H, s (br), H-2), 4.09 (1 H, m, H-5'), 4.05 (1 H, t, J 9.4 Hz, H-4), 4.01 (1 H, t, J 9.4 Hz, H-6), 3.73-3.57 (5 H, m, H-1, H-3', H-4', H-6'a, H-6'b), 3.46 (1 H, t, J 9.4 Hz, H-5), 3.43 (1 H, m, H-3), 2.58 (1 H, dd, J 17.6, 3.2 Hz, H-1''a), 2.39 (1 H, m, H-2'), 2.31 (1 H, dd, J 17.6, 8.8 Hz, H-1''b), 1.61 (3 H, s, H-3'''); δ_C (100 MHz; CDCl₃) 207.77 (C-2''), 139.18-126.40 (aromatic C), 94.26 (C-1'), 83.87 (C-5), 81.84 (C-3), 81.66 (C-4), 80.54 (C-6), 79.92 (C-3'), 79.78 (C-4'), 76.22, 75.96, 75.76, 74.82, 74.52, 73.88, 73.50 (7 × PhCH₂-), 73.23 (C-1), 73.08, 73.07 (C-PhCH₂-, C-2), 70.53 (C-5'), 68.56 (C-6'), 41.19 (C-2'), 40.71 (C-1'''), 29.68 (C-3'''); FABMS: m/z 1125.7 (M+Na)^+. Calcd for C₇₁H₆₉O₂₁Na 1125.5 (M+Na)^+. 
1-O-[2′-deoxy-2′-C-(2′-oxopropyl)-α-D-glucopyranosyl]-D-myoinositol (52)

A solution of 195 (200 mg, 0.18 mmol) in ethyl acetate-methanol (5:7 ml) was stirred under H₂ (1 atm) at room temperature in the presence of 10% palladium on charcoal (300 mg) for 8 days. A few (7) drops of water were added after 24 h. Three additional portions of 10% palladium on charcoal (200 mg) and 5 drops of water were added at 48 h interval. Tlc analysis (MeOH:EtOAc, 3:2) showed the complete conversion of the starting material into the deprotected derivative. The catalyst was removed by filtration through celite, the celite washed with water-methanol (1:9) and the combined filtrates evaporated to dryness. The remaining residue was passed through a reverse phase isolute® C18 column using water-methanol (1:4) as an eluent. The organic solvent was evaporated and the remaining aqueous solution freeze-dried to afford compound 52 (62 mg, 90%) as a hygroscopic solid; [α]D +77.5° (c 1.4, H₂O); δH (300 MHz; D₂O) 4.84 (1 H, d, J 3.3 Hz, H-1′), 3.87 (1 H, t, J 2.6 Hz, H-2), 3.69 (1 H, m, H-5′), 3.57 (2 H, m, H-6′a, H-6′b), 3.51-3.04 (7 H, m, H-1, H-3, H-4, H-5, H-6, H-3′, H-4′), 2.70 (1 H, dd, J 17.9, 4.6 Hz, H-1′′a), 2.50 (1 H, dd, J 17.9, 8.3 Hz, H-1′′b), 2.05 (1 H, m, H-2′), 2.01 (3 H, s, H-3′′); δC (75 MHz; D₂O) 214.54 (C-2′′), 95.02 (C-1′), 74.58, 74.05, 71.95, 71.87, 71.49, 71.04, 70.93, 70.47 (C-1, C-3, C-4, C-5, C-6, C-3′, C-4′, C-5′), 67.96 (C-2), 60.47 (C-6′), 41.51 (C-2′), 41.15 (C-1′′), 29.54 (C-3′′).
2,3,4,5,6-Penta-O-benzyl-1-O-[3',4',6'-tri-O-benzyl-2'-deoxy-2'-C-(2''-hydroxy-3'''-morpholinopropyl)-α-D-glucopyranosyl]-D-myoinositol (196)

The mixture of 193 (482 mg, 0.44 mmol) and morpholine (1.5 ml, 17.2 mmol) in ethanol (10 ml) was refluxed for 1 h. The solvent was then evaporated, the residue was purified by column chromatography using ethyl acetate-petroleum ether (3:2) as eluent to afford an inseparable mixture of diastereomers 196 (410 mg, 78%, 1:1 by ¹H-NMR) as an oil; νmax/cm⁻¹ 3625 (OH).

**Diastereomer 196a:** δH (300 MHz; CDCl₃) 7.46-7.11 (40 H, m, aromatic H), 5.35 (1 H, d, J 3.3 Hz, H-1 ’), 5.24 (1 H, d, J 12.0 Hz, PhCHH-), 5.06-4.77 (12 H, m, 6 × PhCH₂-), 4.71 (1 H, d, J 12.0 Hz, PhCHH-), 4.57 (1 H, d, J 12.0 Hz, PhCHH-), 4.47 (1 H, d, J 12.0 Hz, PhCHH-), 4.38 (1 H, s (br), H-2), 4.27-4.11 (3 H, m, H-5', H-4, H-6), 3.90-3.54 (12 H, m, -N(CH₂CH₂)₂O-, H-1, H-3, H-5, H-3', H-4', H-6', H-6', H-2''), 2.46-1.51 (9 H, m, -N(CH₂CH₂)₂O-, H-2', H-3''', H-3''', H-1''', H-1'''', δC (75 MHz; CDCl₃) 139.41-126.49 (aromatic C), 96.35 (C-1'), 83.87 (C-5), 81.82 (C-3), 81.74 (C-4), 81.56 (C-3'), 80.43 (C-6), 79.81 (C-4'), 76.08, 75.83, 75.66, 74.99, 74.46 (5 × PhCH₂-), 73.89, 73.88 (C-PhCH₂-, C-1), 73.42 (C-2), 73.06, 72.89 (C-2 × PhCH₂-), 70.40 (C-5'), 68.53 (C-6'), 66.76 (2 C-N(CH₂CH₂)₂O-), 66.37 (C-2''), 64.63 (C-3''), 53.34 (2 C-N(CH₂CH₂)₂O-), 43.89 (C-2'), 32.29 (C-1''); FABMS: m/z 1274.5 (M+Rb)⁺. Calcd for C₇₅H₈₅NO₁₂₅⁸Rb 1274.5 (M+Rb)⁺.

**Diastereomer 196b:** δH (300 MHz; CDCl₃) 7.46-7.11 (40 H, m, aromatic H), 5.29 (1 H, d, J 3.0 Hz, H-1 ’), 5.22 (1 H, d, J 12.3 Hz, PhCHH-), 5.06-4.77 (12 H, m, 6 × PhCH₂-), 4.66 (1 H, d, J 11.1 Hz, PhCHH-), 4.56 (1 H, d, J 11.1 Hz, PhCHH-), 4.49 (1 H, d, J 12.3 Hz, PhCHH-), 4.35 (1 H, s (br), H-2), 4.27-4.11 (3 H, m, H-5’, H-4, H-6), 3.90-3.54 (12 H, m, -N(CH₂CH₂)₂O-, H-1, H-3, H-5, H-3’, H-4’, H-6’, H-6’, H-2’’), 2.46-1.51 (9 H, m, -N(CH₂CH₂)₂O-, H-2’, H-3’’, H-3’’, H-1’’, H-1’’’, δC (75 MHz; CDCl₃) 139.41-126.49 (aromatic C), 95.45 (C-1’), 83.84 (C-5), 81.82, 81.66 (2 C-3, C-4), 80.70 (C-3’), 80.43 (C-6), 79.80 (C-4’), 76.08, 75.83, 75.69, 74.81, 74.46, 73.88 (6 × PhCH₂-), 73.73 (C-1), 73.35 (C-2), 73.11, 73.04 (2 × PhCH₂-), 70.46 (C-5’), 68.50 (C-6’), 66.76 (2 C-N(CH₂CH₂)₂O-), 64.18, 64.17 (C-2’’, C-3’’'), 53.49 (2 C- N(CH₂CH₂)₂O-...
2,3,4,5,6-Penta-O-benzyl-1-O-[3′,4′,6′-tri-O-benzyl-2′-deoxy-2′-C-(3′′-morpholino-2′′-oxopropyl)-α-D-glucopyranosyl]-D-myo-inositol (197)

To the stirred solution of 196 (207 mg, 0.17 mmol) and activated molecular sieves 4Å (0.5 g) in CH₂Cl₂ (8 ml) was added NMO (30 mg, 0.25 mmol) at room temperature. After stirring for 5 min, TPAP (0.01 g, 0.028 mmol) was added and the stirring was continued for 30 min. The solids were filtered through celite and the filtrate concentrated. Purification of the black residue by column chromatography using ethyl acetate-petroleum ether (2:3) as eluent afforded compound 197 (173 mg, 84%) as a clear oil; [α]D +42.6° (c 3.0, CHCl₃); νmax/cm⁻¹ 1723 (C=O); δH (300 MHz; CDCl₃) 7.41-7.08 (40 H, m, aromatic H), 5.34 (1 H, d, J 3.3 Hz, H-1′), 5.16 (1 H, d, J 12.0 Hz, PhCHH-), 4.95-4.71 (10 H, m, 5 × PhCH₂⁻), 4.68 (1 H, d, J 12.0 Hz, PhCHH⁻), 4.59 (1 H, d, J 11.6 Hz, PhCHH⁻), 4.53 (1 H, d, J 11.6 Hz, PhCHH⁻), 4.47 (1 H, d, J 12.0 Hz, PhCHH⁻), 4.46 (1 H, d, J 12.0 Hz, PhCHH⁻), 4.24 (1 H, s (br), H-2), 4.15 (1 H, m, H-5′), 4.10 (1 H, t, J 10.0 Hz, H-4), 4.07 (1 H, t, J 10.0 Hz, H-6), 3.79-3.47 (11 H, m, -N(CH₂CH₂)₂O⁻, H-1, H-3, H-5, H-3′, H-4′, H-6′, H-6′'), 2.79 (1 H, dd, J 17.1, 2.7 Hz, H-1′′a), 2.68 (1 H, d, J 17.0 Hz, H-3′′a), 2.56 (1 H, d, J 17.0 Hz, H-3′′b), 2.43 (1 H, m, H-2′), 2.35 (1 H, dd, J 17.1, 8.7 Hz, H-1′′b), 2.14 (4 H, m, -N(CH₂CH₂)₂O⁻⁻); δC (75 MHz; CDCl₃) 207.55 (C-2′), 139.20-126.25 (aromatic C), 94.40 (C-1′), 83.81 (C-5), 81.76 (C-3), 81.61 (C-4), 80.50 (C-6), 80.05 (C-3′), 79.75 (C-4′), 76.20, 75.94, 75.73, 74.79, 74.47, 73.79 (6 × PhCH₂), 73.50, 73.19, 73.06, 73.05 (2 × PhCH₂, C-1, C-2), 70.52 (C-5′), 68.46 (C-6′), 67.34 (C-3′), 66.57 (2 C-N(CH₂CH₂)₂O⁻), 53.40 (2 C-N(CH₂CH₂)₂O⁻), 41.15 (C-2′), 37.54 (C-1′); FABMS: m/z 1272.3 (M+Rb)⁺. Calcd for C₇₅H₈₁NO₁₂³⁸⁵Rb 1272.4 (M+Rb)⁺.
2,3,4,5,6-Penta-O-benzyl-1-O-[3',4',6'-tri-O-benzyl-2'-deoxy-2'-C-(3''-diethylamino-2''-hydroxypropyl)-α-D-glucopyranosyl]-D-myo-inositol (198)

A mixture of 193 (165 mg, 0.15 mmol) and diethyamine (1.2 ml, 11.5 mmol) in ethanol (5 ml) was refluxed for 2 h. The solvent was then evaporated, the residue was purified by column chromatography using methanol-ethyl acetate (5:95) as eluent to afford an inseparable mixture of diastereomers 198 (138 mg, 78%, 1:1 by 1H-NMR) as an oil; νmax/cm⁻¹ 3620 (OH).

**Diastereomer 198a:** δH (300 MHz; CDCl₃) 7.46-7.08 (40 H, m, aromatic H), 5.36 (1 H, d, J 3.0 Hz, H-1”), 5.19-4.41 (16 H, m, 8 × PhCH₂), 4.40 (1 H, s (br), H-2), 4.25-4.09 (3 H, m, H-5’, H-4, H-6), 3.89-3.51 (8 H, m, H-1, H-3, H-5, H-2”, H-3”, H-4’, H-6’a, H-6’b), 2.57-2.15 (7 H, m, -N(CH₂CH₃)₂-, H-2”, H-3”’a, H-3”’b), 1.55 (2 H, m, H-1”’a, H-1”’b), 0.94 (6 H, t, J 7.1 Hz, -N(CH₂CH₃)₂-); δC (75 MHz; CDCl₃) 139.46-126.46 (aromatic C), 96.69 (C-1’), 83.97 (C-5), 81.86, 81.85 (C-3, C-4), 81.52 (C-3’), 80.36 (C-6), 80.02 (C-4’), 76.05, 75.83, 75.69, 74.98, 74.48, 73.97 (6 × PhCH₂-), 73.96, 73.55, 73.05, 72.83 (2 × PhCH₂-, C-1, C-2), 70.46 (C-5’), 68.61 (C-6’), 67.34 (C-2’’), 59.87 (C-3’’), 46.72 (2 C-N(CH₂CH₃)₂-), 44.39 (C-2’), 32.16 (C-1’’), 11.53 (2 C-N(CH₂CH₃)₂-); FABMS: m/z 1176.7 (M+H)+. Calcd for C₇₅H₇₆NO₁₁ 1176.6 (M+H)+.

**Diastereomer 198b:** δH (300 MHz; CDCl₃) 7.46-7.08 (40 H, m, aromatic H), 5.31 (1 H, d, J 3.3 Hz, H-1’”), 5.19-4.41 (16 H, m, 8 × PhCH₂), 4.34 (1 H, s (br), H-2), 4.25-4.09 (3 H, m, H-5’, H-4, H-6), 3.89-3.51 (8 H, m, H-1, H-3, H-5, H-2”, H-3”, H-4’, H-6’a, H-6’b), 2.57-2.13 (5 H, m, -N(CH₂CH₃)₂-, H-2”), 1.89-1.62 (4 H, m, H-1”’a, H-1”’b, H-3”’a, H-3”’b), 0.98 (6 H, t, J 7.1 Hz, -N(CH₂CH₃)₂-); δC (75 MHz; CDCl₃) 139.46-126.46 (aromatic C), 95.58 (C-1’), 83.94 (C-5), 81.85, 81.76 (C-3, C-4), 80.91 (C-3’), 80.42 (C-6), 79.81 (C-4’), 76.08, 75.85, 75.69, 74.77, 74.47, 74.25 (6 × PhCH₂-), 73.89, 73.44, 73.09, 72.96 (2 × PhCH₂-, C-1, C-2), 70.42 (C-5’), 68.61 (C-6’), 64.41 (C-2’’), 59.25 (C-3’’), 46.80 (2 C-N(CH₂CH₃)₂-), 41.77 (C-2’), 31.03 (C-1’’), 11.50 (2 C-N(CH₂CH₃)₂-); FABMS: m/z 1176.7 (M+H)+. Calcd for C₇₅H₇₆NO₁₁ 1176.6 (M+H)+.
2,3,4,5,6-Penta-O-benzyl-1-O-[3',4',6'-tri-O-benzyl-2'-deoxy-2'-C-(3''-diethylamino-2''-oxopropyl)-α-D-glucopyranosyl]-D-myoinositol (199)

To a stirred solution of 198 (133 mg, 0.11 mmol) and activated molecular sieves 4Å (0.4 g) in CH₂Cl₂ (5 ml) was added NMO (23 mg, 0.17 mmol) at room temperature. After stirring for 5 min, TPAP (0.008 g, 0.023 mmol) was added and the stirring continued for 18 h. The solids were filtered through celite and the filtrate concentrated. Purification of the black solution by column chromatography using ethyl acetate-petroleum ether (2:3, then 1:1) as eluent afforded compound 199 (59 mg, 45%) as a clear oil; [α]D +29.3° (c 2.6, CHCl₃); νmax/cm⁻¹ 1718 (C=O); δH (300 MHz; CDCl₃) 7.38-7.05 (40 H, m, aromatic H), 5.35 (1 H, d, J 2.7 Hz, H-1'), 5.12-4.37 (16 H, m, 8 × PhCH₂), 4.24 (1 H, s (br), H-2), 4.21-3.98 (3 H, m, H-5', H-4, H-6), 3.75-3.44 (7 H, m, H-1, H-3, H-5, H-3', H-4', H-6', H-6' b), 2.95 (1 H, m, H-1''a), 2.76 (1 H, d, J 16.5 Hz, H-3''a), 2.66 (1 H, d, 16.5 Hz, H-3''b), 2.44-2.19 (6 H, m, -N(CH₂CH₃)₂, H-1''b, H-2'), 0.82 (6 H, t, J 7.2 Hz, -N(CH₂CH₃)₂); δC (75 MHz; CDCl₃) 210.36 (C-2''), 139.20-126.41 (aromatic C), 94.52 (C-1'), 83.88 (C-5), 81.77 (C-3), 81.68 (C-4), 80.53 (C-6), 80.25 (C-3'), 79.79 (C-4'), 76.21, 75.98, 75.75, 74.95, 74.48 (5 × PhCH₂), 73.85, 73.61, 73.20, 73.19, 72.95 (3 × PhCH₂, C-1, C-2), 70.54 (C-5'), 68.56 (C-6'), 63.23 (C-3''), 47.66 (2 C-N(CH₂CH₃)₂), 41.45 (C-2''), 37.29 (C-1''), 11.64 (2 C-N(CH₂CH₃)₂); FABMS: m/z 1174.7 (M+H)⁺. Calcd for C₇₅H₇₆NO₁₁ 1174.6 (M+H)⁺.
Cyclohexyl 3,4,6-tri-O-acetyl-2-C-allyl-2-deoxy-α-D-glucopyranoside (201a) and 
Cyclohexyl 3,4,6-tri-O-acetyl-2-C-allyl-2-deoxy-β-D-glucopyranoside (201b)

\[
\begin{align*}
201a & \\
201b &
\end{align*}
\]

A mixture of fluoride 173 (550 mg, 1.65 mmol), cyclohexanol (2.62 ml, 24.84 mmol) and 
molecular sieves 4Å (1 g) in CH₂Cl₂ (13 ml) was stirred at room temperature for 1 h before boron 
trifluoride etherate (1.22 ml, 9.94 mmol) was added dropwise. The stirring was continued for 18 h, 
then Et₃N (1.1 ml) added and the solids removed by filtration. The filtrate was diluted with 
dichloromethane, and the CH₂Cl₂ phase washed sequentially with water, saturated NaHCO₃ and 
water, then dried over MgSO₄ and concentrated. Purification by column chromatography using 
ethyl acetate-petroleum ether (3:17) gave an inseparable mixture of anomers 201a and 201b (α:β, 
≈ 1:1 by ¹³C-NMR) as well as excess acceptor (cyclohexanol). The residue crystallized from 
pentane at low temperature to afford the β-anomer 201b (244 mg, 36%) as crystals. Purification of 
the mother liquor by column chromatography using ethyl acetate-petroleum ether (7:93) as eluent 
afforded α-anomer 201a (287 mg, 42 %) as an oil together with a mixture of anomers (105 mg, 
15%) (total yield 636 mg, 93%).

α-Anomer 201a: [α]D +115.6° (c 2.6, CHCl₃); δH (400 MHz; CDCl₃) 5.73-5.63 (1 H, m, H-2′′), 
5.22 (1 H, dd, J 11.2, 9.2 Hz, H-3), 5.06-4.91 (3 H, m, H-4, H-3′′, a, H-3′′, b), 4.92 (1 H, d, J 3.6 Hz, 
H-1), 4.24 (1 H, dd, J 12.2, 4.6 Hz, H-6a), 4.09-4.02 (2 H, m, H-5, H-6b), 3.54-3.47 (1 H, m, H-1′), 
2.14-2.10 (2 H, m, H-1′′a, H-1′′b), 2.06, 2.00, 1.99 (9 H-3 × COOCH₃), 1.99 (1 H, m, H-2), 1.87-
1.19 (10 H, m, 5 × -CH₂-, cyclohexyl); δC (100 MHz; CDCl₃) 170.59, 170.42, 169.89 (3 × 
COOCH₃), 135.25 (C-2′′), 116.64 (C-3′′), 96.84 (C-1), 75.95 (C-1′), 72.45 (C-3), 70.11 (C-4), 
67.66 (C-5), 62.52 (C-6), 44.31 (C-2), 33.31 (C-CH₂-, cyclohexyl), 31.73 (C-1′′), 31.47, 25.48, 
24.02, 23.79 (4 × -CH₂-, cyclohexyl), 20.70, 20.60, 20.59 (3 × COOCH₃); HRFABMS: m/z 
435.199633 (M+Na)+. Calcd for C₂₁H₃₂O₈Na 435.199477 (M+Na)+.

β-Anomer 201b: mp 100 °C (from pentane); [α]D +16.7° (c 1.7, CHCl₃); δH (300 MHz; CDCl₃) 
5.84-5.70 (1 H, m, H-2′′), 5.06 (1 H, dd, J 10.8, 9.0 Hz, H-3), 5.02-4.89 (3 H, m, H-4, H-3′′, a, H- 
3′′, b), 4.39 (1 H, d, J 8.7 Hz, H-1), 4.25 (1 H, dd, J 12.1, 5.3 Hz, H-6a), 4.07 (1 H, dd, J 12.1, 2.6 
Hz, H-6b), 3.65-3.55 (2 H, m, H-5, H-1′), 2.25-2.21 (2 H, m, H-1′′a, H-1′′b), 2.05, 1.99, 1.99 (9 H, 
3 s, 3 × COOCH₃), 2.03-1.21 (11 H, m, H-2, 5 × -CH₂-, cyclohexyl); δC (75 MHz; CDCl₃) 170.70,
170.37, 169.84 (3 × COOCH₃), 134.21 (C-2'''), 117.20 (C-3'''), 100.58 (C-1), 77.55 (C-1''), 72.90 (C-3), 71.34 (C-5), 70.34 (C-4), 62.68 (C-6), 45.24 (C-2), 33.57, 31.80 (2 × -CH₂-, cyclohexyl), 31.12 (C-1'''), 25.55, 24.08, 24.01 (3 × -CH₂-, cyclohexyl), 20.75, 20.72, 20.66 (3 × COOCH₃); HRFABMS: m/z 435.199633 (M+Na)⁺. Calcd for C₂₁H₃₂O₈Na 435.199477 (M+Na)⁺.

**Cyclohexyl 2-C-allyl-2-deoxy-α-D-glucopyranoside (59)**

![Cyclohexyl 2-C-allyl-2-deoxy-α-D-glucopyranoside (59)](image_url)

Methanolic NaOMe (0.2 M, 0.7 ml, 0.14 mmol) was added to a solution of 201a (287 mg, 0.69 mmol) in CH₂Cl₂-MeOH (4:6 ml) at room temperature. After 4 h, the solution was neutralized with Amberlite IR-120 H⁺ resin. The resin was removed by filtration, the solvent evaporated and the crystalline residue chromatographed on silica using methanol-ethyl acetate (5:95) as eluent to afford compound 59 (196 mg, 99%) as crystals; mp 165-168 °C (from ethyl acetate and petroleum ether); [α]D +120.8° (c 2.3, MeOH); δH (400 MHz; CD₃OD) 5.86-5.76 (1 H, m, H-2'''), 5.07-4.98 (2 H, m, H-3'''a, H-3'''b), 4.87 (1 H, d, J 3.2 Hz, H-1), 3.77 (1 H, m, H-6a), 3.69-3.63 (2 H, m, H-5, H-6b), 3.58 (1 H, m, H-1'), 3.49 (1 H, dd, J 10.6, 9.1 Hz, H-3), 3.24 (1 H, t, J 9.1 Hz, H-4), 2.51 (1 H, m, H-1''a), 2.14-2.05 (1 H, m, H-1''b), 1.90-1.21 (11 H, m, H-2, 5 × -CH₂-, cyclohexyl); δC (100 MHz; CD₃OD) 136.84 (C-2'''), 115.38 (C-3'''), 96.65 (C-1), 74.62 (C-1''), 72.82 (C-3), 72.73 (C-5), 72.15 (C-4), 61.87 (C-6), 46.59 (C-2), 33.39 (C-CH₂-, cyclohexyl), 31.56 (C-1'''), 31.45, 25.69, 23.88, 23.71 (4 × -CH₂-, cyclohexyl); HRFABMS: m/z 309.168001 (M+Na)⁺. Calcd for C₁₅H₂₆O₅Na 309.167784 (M+Na)⁺.
Cyclohexyl 2-C-allyl-2-deoxy-β-D-glucopyranoside (202)

Methanolic NaOMe (0.2 M, 0.5 ml, 0.1 mmol) was added to a solution of 201b (200 mg, 0.48 mmol) in CH₂Cl₂-MeOH (3:5 ml) at room temperature. After 2 h, the solution was neutralized with Amberlite IR-120 H⁺ resin. The resin was removed by filtration, the solvent evaporated and the crystalline residue was chromatographed on silica using methanol-ethyl acetate (5:95) as eluent to afford compound 202 (135 mg, 98%) as crystals; mp 136-138 °C (from ethyl acetate and petroleum ether); [α]D −35.4° (c 2.2, MeOH); δH (400 MHz; CD₃OD) 5.97-5.87 (1 H, m, H-2′′′), 5.10-4.99 (2 H, m, H-3′′′a, H-3′′′b), 4.41 (1 H, d, J 8.8 Hz, H-1), 3.83 (1 H, dd, J 11.7, 2.4 Hz, H-6a), 3.71 (1 H, m, H-1′), 3.65 (1 H, dd, J 11.7, 5.4 Hz, H-6b), 3.33 (1 H, dd, J 10.8, 8.4 Hz, H-3), 3.22 (1 H, dd, J 9.6, 8.4 Hz, H-4), 3.18-3.13 (1 H, m, H-5), 2.38 (2 H, m, H-1′′′a, H-1′′′b), 1.93-1.21 (11 H, m, H-2, 5 × -CH₂-), cyclohexyl); δC (100 MHz; CD₃OD) 153.34 (C-2′′′), 116.06 (C-3′′′), 100.48 (C-1), 76.43 (C-5), 76.32 (C-1′), 73.80 (C-3), 71.97 (C-4), 61.89 (C-6), 47.32 (C-2), 33.59, 31.70 (2 × -CH₂-, cyclohexyl), 30.39 (C-1′′′), 25.65, 23.94, 23.84 (3 × -CH₂-, cyclohexyl); HRFABMS: m/z 309.168001 (M+Na)⁺. Calcd for C₁₅H₂₆O₅Na 309.167784 (M+Na)⁺.
Cyclohexyl 3,4,6-tri-O-benzyl-2-C-allyl-2-deoxy-α-D-glucopyranoside (203)

\[
\text{NaH (50\%, 0.57 g, 11.94 mmol) was added to a solution of 59 (570 mg, 1.99 mmol) in THF (15 ml) at 0 °C. After 5 min, benzyl bromide (1.42 ml, 11.94 mmol) was added, the ice-water bath removed and the mixture heated at reflux for 18 h. The solution was then cooled and excess NaH quenched with methanol followed by water. The organic solvent was evaporated, the aqueous mixture extracted with CH}_2\text{Cl}_2, \text{and the CH}_2\text{Cl}_2 washed with saturated NaCl, dried over MgSO}_4 and concentrated. Purification was achieved by column chromatography using ethyl acetate-petroleum ether (petroleum ether, then 5:95) as an eluent to afford compound 203 (1.10 g, 99%) as an oil; [α]_D +81.1° (c 2.9, CHCl}_3); δ_H (300 MHz; CDCl}_3) 7.41-7.19 (15 H, m, aromatic H), 5.89-5.75 (1 H, m, H-2′′), 5.14-5.02 (2 H, m, H-3′′, H-3′′′), 4.96 (1 H, d, J 3.6 Hz, H-1), 4.93 (1 H, d, J 10.8 Hz, PhCHH-), 4.85 (1 H, d, J 10.8 Hz, PhCHH-), 4.70 (1 H, d, J 12.0 Hz, PhCHH-), 4.68 (1 H, d, J 10.8 Hz, PhCHH-), 4.57 (1 H, d, J 10.8 Hz, PhCHH-), 4.54 (1 H, d, J 12.0 Hz, PhCHH-), 3.99-3.94 (1 H, m, H-5), 3.83 (1 H, dd, J 10.6, 3.7 Hz, H-6a), 3.78-3.67 (3 H, m, H-3, H-4, H-6b), 3.59 (1 H, m, H-1′), 2.62-2.54 (1 H, m, H-1′′), 2.24-2.13 (1 H, m, H-1′′′), 2.01-1.92 (1 H, m, H-2), 1.92-1.26 (10 H, m, 5 × -CH}_2-, cyclohexyl); δ_C (75 MHz; CDCl}_3) 138.63, 138.34, 138.17 (aromatic C), 136.49 (C-2′′), 128.32, 128.25, 128.12, 127.81, 127.77, 127.69, 127.58, 127.53, 127.49 (aromatic C), 116.18 (C-3′′), 96.83 (C-1), 81.38 (C-3), 79.97 (C-4), 75.27 (C-PhCH}_2-), 74.89 (C-1′), 74.78, 73.41 (2 × PhCH}_2-), 71.02 (C-5), 68.98 (C-6), 46.19 (C-2), 33.46 (C-CH}_2-, cyclohexyl), 31.61 (C-1′′), 31.58, 25.68, 24.07, 23.85 (4 × -CH}_2-, cyclohexyl); HRFABMS: m/z 579.308663 (M+Na)^+. Calcd for C}_36H}_44O}_5SNa 579.308627 (M+Na)^+.}
Cyclohexyl 2-deoxy-2-C-propyl-α-D-glucopyranoside (60)

1. From 203
A solution of 203 (279 mg, 0.50 mmol) in ethyl acetate-methanol (5:6 ml) was treated with H₂ (1 atm) at room temperature in the presence of 10% palladium on charcoal (400 mg) for 18 h. TLC analysis (ethyl acetate-petroleum ether, 4:1) showed the complete conversion of the starting material into the deprotected derivative. The catalyst was removed by filtration through celite, the celite washed with methanol and the combined filtrates evaporated to dryness. The remaining residue was passed through a reverse phase isolute® C18 column using methanol as an eluent to afford compound 60 (140 mg, 97%) as crystals.

2. From 202
A solution of 202 (201 mg, 0.70 mmol) in MeOH (10 ml) was treated with H₂ (1 atm) at room temperature in the presence of 10% palladium on charcoal (300 mg) for 18 h. The catalyst was removed by filtration through celite, the celite washed with methanol and the combined filtrates evaporated to dryness. The remaining residue was passed through a reverse phase isolute® C18 column using methanol as an eluent to afford compound 60 (198 mg, 98%) as crystals; mp 184-186 ºC (from ethyl acetate and petroleum ether); [α]D +82.8º (c 2.3, MeOH); δH (400 MHz; CD3OD) 4.92 (1 H, d, J 3.2 Hz, H-1), 3.77 (1 H, d (br), J 9.6 Hz, H-6a), 3.69-3.60 (3 H, m, H-1', H-5, H-6b), 3.46 (1 H, dd, J 10.4, 9.0 Hz, H-3), 3.22 (1 H, t, J 9.0 Hz, H-4), 1.87-1.25 (15 H, m, H-2, 5 x -CH₂-, cyclohexyl, -(CH₂)₂CH₃), 0.92 (3 H, t, J 7.2 Hz, H-3'); δC (100 MHz; CD3OD) 96.75 (C-1), 74.20 (C-1'), 73.32 (C-3), 72.54 (C-5), 72.14 (C-4), 61.91 (C-6), 46.23 (C-2), 33.34, 31.13 (2 x -CH₂-, cyclohexyl), 29.44 (C-1''), 25.70, 23.75, 23.55 (3 x -CH₂-, cyclohexyl), 19.89 (C-2''), 13.59 (C-3''); HRFABMS: m/z 311.182957 (M+Na)+. Calcd for C₁₅H₂₈O₃Na 311.183433 (M+Na)+.
Cyclohexyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-(2′′,3′′-epoxypropyl)-α-D-glucopyranoside (204)

To a solution of 203 (780 mg, 1.40 mmol) in CH₂Cl₂ (15 ml) at 0 °C was slowly added a solution of m-CPBA (70%, 0.64 g, 2.59 mmol) in CH₂Cl₂ (4.0 ml) (m-CPBA was dissolved in CH₂Cl₂, dried with MgSO₄, filtered and concentrated before used). The temperature was raised to room temperature and after stirring for 18 h a further solution of m-CPBA (70%, 0.36 g, 1.47 mmol) in CH₂Cl₂ (3 ml) was added slowly to the mixture at 0 °C. The reaction was stirred for 8 h at room temperature, then saturated Na₂S₂O₃ was added, the solution extracted with CH₂Cl₂, and the CH₂Cl₂ washed with saturated NaHCO₃, dried over MgSO₄ and concentrated. The crude residue was purified by column chromatography using ethyl acetate-petroleum ether (3:17) as eluent to afford an inseparable mixture of diastereomers 204 (673 mg, 84%, 1:1 by ¹H-NMR) as an oil.

**Diastereomer 204a:** δ_H (400 MHz; CDCl₃) 7.38-7.16 (15 H, m, aromatic H), 5.07 (1 H, d, J 2.8 Hz, H-1), 4.94-4.51 (6 H, m, 3 × PhCH₂-), 3.96-3.89 (1 H, m, H-5), 3.79 (1 H, t, J 4.2 Hz, H-6a), 3.75-3.65 (3 H, m, H-3, H-4, H-6b), 3.60 (1 H, m, H-1′), 3.01-2.94 (1 H, m, H-2′′), 2.68 (1 H, dd, J 5.0, 4.2 Hz, H-3′′a), 2.47 (1 H, dd, J 5.0, 2.6 Hz, H-3′′b), 2.08-1.99 (1 H, m, H-2), 1.95-1.22 (12 H, m, 5 × -CH₂-, cyclohexyl, H-1′′a, H-1′′b); δ_C (100 MHz; CDCl₃) 138.84-127.82 (aromatic C), 97.15 (C-1), 81.41 (C-3), 80.33 (C-4), 75.39, 75.07, 75.06, 73.73 (3 × PhCH₂-, C-1′), 71.34 (C-5), 69.17 (C-6), 50.69 (C-2′′), 47.93 (C-3′′), 43.95 (C-2), 33.73 (C-1′′), 31.72, 30.51, 25.91, 24.39, 24.17 (5 × -CH₂-, cyclohexyl); HRFABMS: m/z 595.303894 (M+Na)^+. Calcd for C₃₆H₄₄O₈Na 595.303542 (M+Na)^+.

**Diastereomer 204b:** δ_C (400 MHz; CDCl₃) 7.38-7.16 (15 H, m, aromatic H), 5.12 (1 H, d, J 3.2 Hz, H-1), 4.95-4.53 (6 H, m, 3 × PhCH₂-), 3.96-3.89 (1 H, m, H-5), 3.82 (1 H, t, J 4.0 Hz, H-6a), 3.75-3.65 (3 H, m, H-3, H-4, H-6b), 3.60 (1 H, m, H-1′), 3.00-2.94 (1 H, m, H-2′′), 2.75 (1 H, dd, J 5.2, 4.0 Hz, H-3′′a), 2.40 (1 H, dd, J 5.2, 2.8 Hz, H-3′′b), 2.08-1.99 (1 H, m, H-2), 1.95-1.22 (12 H, m, 5 × -CH₂-, cyclohexyl, H-1′′a, H-1′′b); δ_C (100 MHz; CDCl₃) 138.84-127.82 (aromatic C), 97.84 (C-1), 81.29 (C-3), 80.14 (C-4), 75.61, 75.50, 75.07, 73.73 (3 × PhCH₂-, C-1′), 71.28 (C-5), 69.17 (C-6), 51.72 (C-2′′), 47.00 (C-3′′), 45.75 (C-2), 33.73 (C-1′′), 31.65, 30.88, 25.95, 24.33, 24.11 (5 × -CH₂-, cyclohexyl); HRFABMS: m/z 595.303894 (M+Na)^+. Calcd for C₃₆H₄₄O₈Na 595.303542 (M+Na)^+.
Cyclohexyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-(2'-hydroxypropyl)-α-D-glucopyranoside (205)

A solution of 204 (593 mg, 1.03 mmol) in THF (15 ml) was added dropwise to a solution of lithium aluminium hydride (0.39 g, 10.30 mmol) in THF (7 ml) at 0 °C. After 2 h at 0 °C, excess LAH was quenched with water, the aqueous mixture extracted with ethyl acetate, and the ethyl acetate phase dried over MgSO₄ and concentrated. Purification was achieved by column chromatography using ethyl acetate-petroleum ether (1:4) as eluent to afford an inseparable mixture of diastereomers 205 (555 mg, 93%, 1:1 by ¹H-NMR) as crystals; ν_max/cm⁻¹ 3426 (br) (OH).

Diastereomer 205a: δ_H (300 MHz; CDCl₃) 7.38-7.13 (15 H, m, aromatic H), 4.98-4.49 (6 H, m, 3 × PhCH₂-), 4.94 (1 H, d, J 3.6 Hz, H-1'), 3.95-3.88 (1 H, m, H-5), 3.84-3.65 (5 H, m, H-3, H-4, H-6a, H-6b, H-2'”), 3.57 (1 H, m, H-1”), 2.49 (s, br, -OH), 2.09-1.94 (1 H, m, H-2), 1.89-1.19 (12 H, m, 5 × -CH₂-, cyclohexyl, H-1’”, H-1’’b), 1.15 (3 H, d, J 6.0 Hz, H-3’’); δ_C (75 MHz; CDCl₃) 138.29, 138.20, 138.12, 128.42, 128.39, 128.31, 127.83, 127.80, 127.77, 127.71, 127.65, 127.58 (aromatic C), 97.72 (C-1), 81.16 (C-3), 80.23 (C-4), 75.22, 74.77, 74.74, 73.47 (3 × PhCH₂-, C-1’), 71.05 (C-5), 68.88 (C-6), 65.96 (C-2’’), 43.55 (C-2), 37.51 (C-1’’), 33.40, 31.29, 25.64 (3 × -CH₂-, cyclohexyl), 24.28 (C-3’’), 24.08, 23.82 (2 × -CH₂-, cyclohexyl); HRFABMS: m/z 597.318376 (M+Na)⁺. Caled for C₃₆H₄₆O₆Na 597.319191 (M+Na)⁺.

Diastereomer 205b: δ_H (300 MHz; CDCl₃) 7.38-7.13 (15 H, m, aromatic H), 4.98-4.49 (6 H, m, 3 × PhCH₂-), 4.94 (1 H, d, J 3.6 Hz, H-1), 3.95-3.88 (1 H, m, H-5), 3.84-3.65 (5 H, m, H-3, H-4, H-6a, H-6b, H-2’”), 3.57 (1 H, m, H-1’), 2.49 (s, br, -OH), 2.09-1.94 (1 H, m, H-2), 1.89-1.19 (12 H, m, 5 × -CH₂-, cyclohexyl, H-1’”, H-1’’b), 1.16 (3 H, d, J 6.0 Hz, H-3’’); δ_C (75 MHz; CDCl₃) 138.39, 138.24, 138.12, 128.42, 128.38, 128.31, 127.83, 127.80, 127.77, 127.71, 127.65, 127.58 (aromatic C), 97.10 (C-1), 81.85 (C-3), 80.19 (C-4), 75.39, 74.82, 74.76, 73.48, (3 × PhCH₂-, C-1’), 70.93 (C-5), 68.91 (C-6), 66.39 (C-2’’), 43.27 (C-2), 37.35 (C-1’’), 33.44, 31.36, 25.67, 24.09, 23.85 (5 × -CH₂-, cyclohexyl), 23.59 (C-3’’); HRFABMS: m/z 597.318376 (M+Na)⁺. Caled for C₃₆H₄₆O₆Na 597.319191 (M+Na)⁺.
Cyclohexyl 3,4,6-tri-O-benzyl-2-deoxy-2-C-(2''-oxopropyl)-α-D-glucopyranoside (206)

To a stirred solution of 205 (243 mg, 0.42 mmol) and activated molecular sieves 4Å (0.4 g) in CH₂Cl₂ (10 ml) was added NMO (0.08 mg, 0.63 mmol) at room temperature. After stirring for 5 min, TPAP (0.01 g, 0.028 mmol) was added and the stirring was continued for 1 h. The solids were filtered through celite and the filtrate concentrated. Purification of the black residue by column chromatography using ethyl acetate-petroleum ether (1:4) as eluent afforded compound 206 (237 mg, 98%) as crystals; mp 94-95 °C (from petroleum ether); [α]_D^20 +95.1° (c 2.2, CHCl₃); νmax/cm⁻¹ 1714 (C=O); δ_H (400 MHz; CDCl₃) 7.38-7.15 (15 H, m, aromatic H), 5.04 (1 H, d, J 3.6 Hz, H-1), 4.93 (1 H, d, J 11.4 Hz, PhCH₂H-), 4.77 (1 H, d, J 10.8 Hz, PhCH₂H-), 4.67 (1 H, d, J 12.0 Hz, PhCH₂H-), 4.59 (1 H, d, J 11.4 Hz, PhCH₂H-), 4.55 (1 H, d, J 10.8 Hz, PhCH₂H-), 4.52 (1 H, m, H-5), 3.80 (1 H, dd, J 10.7, 3.8 Hz, H-6a), 3.69 (1 H, t, J 9.3 Hz, H-4), 3.67 (1 H, dd, J 10.7, 2.0 Hz, H-6b), 3.63 (1 H, dd, J 10.4, 9.3 Hz, H-3), 3.52 (1 H, m, H-1‘), 2.66 (1 H, dd, J 16.2, 3.4 Hz, H-1“a), 2.49-2.37 (2 H, m, H-2, H-1“b), 2.05 (3 H, s, H-3”), 1.84-1.17 (10 H, m, 5 × -CH₂-, cyclohexyl); δ_C (100 MHz; CDCl₃) 207.77 (C-2”), 138.85, 138.45, 138.44, 128.61, 128.55, 128.54, 128.11, 128.10, 128.06, 127.92, 127.91, 127.79 (aromatic C), 96.78 (C-1), 80.85 (C-3), 80.25 (C-4), 75.17, 75.02 (2 × PhCH₂-), 74.92 (C-1”), 73.73 (C-PhCH₂-), 71.26 (C-5), 69.17 (C-6), 42.17 (C-1“), 42.10 (C-2), 33.62, 31.59 (2 × -CH₂-, cyclohexyl), 30.24 (C-3”), 25.89, 24.24, 23.99 (3 × -CH₂-, cyclohexyl); HRFABMS: m/z 595.302843 (M+Na)*. Calcd for C₅₆H₄₄O₆Na 595.303542 (M+Na)*.
Cyclohexyl 3,4,6-tri-O-acetyl-2-deoxy-2-C-(2''-oxopropyl)-α-D-glucopyranoside (207)

A mixture of PdCl$_2$ (1.79 g, 10.10 mmol) and CuCl$_2$ (3.5 g, 26.03 mmol) in DMF-H$_2$O (1:7, 15 ml) was stirred at room temperature under an atmosphere of oxygen (balloon) for 2 h. A solution of 201a (1.05 g, 2.54 mmol) in CH$_2$Cl$_2$-DMF (3:3 ml) was added dropwise and stirring was continued for 4 days under an atmosphere of oxygen. The reaction was stopped by the addition of a solution of 3 M HCl, extracted with CH$_2$Cl$_2$, dried over MgSO$_4$ and concentrated. Purification by column chromatography using ethyl acetate-petroleum ether afforded compound 207 (550 mg, 50%) as crystals; mp 72-73 °C (from petroleum ether); $[\alpha]_D$ +131.9° (c 2.9, CHCl$_3$); $\nu_{\text{max}}$/cm$^{-1}$ 1744 (C=O); $\delta_H$ (300 MHz; CDCl$_3$) 5.14 (1 H, dd, $J$ 11.0, 9.6 Hz, H-3), 5.08 (1 H, d, $J$ 3.3 Hz, H-1), 4.95 (1 H, t, $J$ 9.6 Hz, H-4), 4.22 (1 H, dd, $J$ 12.0, 5.0 Hz, H-6$_a$), 4.05 (1 H, dd, $J$ 12.0, 2.6 Hz, H-6$_b$), 4.02 (1 H, m, H-5), 3.47 (1 H, m, H-1''), 2.60 (1 H, dd, $J$ 17.0, 9.0 Hz, H-1''), 2.54-2.45 (1 H, m, H-2), 2.37 (1 H, dd, $J$ 17.0, 3.4 Hz, H-1'''), 2.09 (3 H, s, H-3''), 2.05, 1.98, 1.97 (9 H, 3 s, 3 × COOCH$_3$), 1.84-1.15 (10 H, m, 5 × -CH$_2$-, cyclohexyl); $\delta_C$ (75 MHz; CDCl$_3$) 206.43 (C-2''), 170.68, 170.69, 169.78 (3 × COOCH$_3$), 96.16 (C-1), 75.65 (C-1''), 71.99 (C-3), 69.85 (C-4), 67.48 (C-5), 62.43 (C-6), 41.36 (C-1'''), 40.03 (C-2), 33.28, 31.32 (2 × -CH$_2$-, cyclohexyl), 30.13 (C-3'''), 25.48, 24.01, 23.76 (3 × -CH$_2$-, cyclohexyl), 20.73, 20.66, 20.63 (3 × COOCH$_3$); HRFABMS: m/z 451.194600 (M+Na)$^+$. Calcd for C$_{21}$H$_{32}$O$_9$Na 451.194392 (M+Na)$^+$. 
Cyclohexyl 2-deoxy-2-C-(2'-oxopropyl)-α-D-glucopyranoside (57)

1. From 206

A solution of 206 (211 mg, 0.37 mmol) in a mixture of ethyl acetate-methanol (4:6 ml) was treated with H₂ (1 atm) at room temperature in the presence of 10% palladium on charcoal (300 mg) for 7 days. During this time interval, three additional portions of 10% palladium on charcoal (100 mg) were added at 48 h intervals. After 7 days, tlc analysis (MeOH:EtOAc, 5:95) showed the incomplete conversion of the starting material into the deprotected derivative. The catalyst was removed by filtration through celite, washed with methanol and evaporated to dryness. The remaining residue was purified by column chromatography using methanol-ethyl acetate (3:95) as eluent to afford compound 57, (20 mg, 18%) as crystals.

2. From 207

A methanolic sodium methoxide (0.2 M, 0.2 ml, 0.04 mmol) was added to a solution of 207 (200 mg, 0.47 mmol) in CH₂Cl₂-MeOH (4:5 ml) at room temperature. After 18 h, water (1.7 ml) was added and the solvent evaporated. Co-evaporation with methanol (∗× 2) gave a crystalline residue that was recrystallized from ethyl acetate-petroleum ether (4:1) to afford compound 57 (120 mg, 84%) as crystals; mp 151-154 °C (from ethyl acetate and petroleum ether); [α]D⁺128.8° (c 2.1, MeOH); δC (400 MHz; CD₃OD) 4.97 (1 H, d, J 3.6 Hz, H-1), 3.77 (1 H, dd, J 11.6, 2.4 Hz, H-6α), 3.67 (1 H, dd, J 11.6, 5.6 Hz, H-6β), 3.65-3.60 (1 H, m, H-5), 3.55 (1 H, m, H-1'), 3.44 (1 H, dd, J 10.8, 8.8 Hz, H-3), 3.26 (1 H, dd, J 10.0, 8.8 Hz, H-4), 2.84 (1 H, dd, J 17.9, 4.2 Hz, H-1''α), 2.58 (1 H, dd, J 17.9, 9.2 Hz, H-1''β), 2.14 (3 H, s, H-3''), 2.12 (1 H, m, H-2), 1.87-1.19 (10 H, m, 5 × -CH₂-, cyclohexyl); δC (100 MHz; CD₃OD) 209.81 (C-2'''), 96.44 (C-1), 74.38 (C-1'), 72.68 (C-5), 72.37 (C-3), 71.98 (C-4), 61.81 (C-6), 42.39 (C-2), 41.52 (C-1''), 33.26, 31.09 (2 × -CH₂-, cyclohexyl), 29.12 (C-3''), 25.63, 23.79, 23.59 (3 × -CH₂-, cyclohexyl); HRFABMS: m/z 325.162838 (M+Na). Calcd for C₁₅H₂₆O₆Na 325.162699 (M+Na).
Cyclohexyl 3,4,6-tri-O-acetyl-2-deoxy-2-C-(2''-hydroxypropyl)-α-D-glucopyranoside (208)

\[
\begin{align*}
\text{NaBH}_4 (0.19 \text{ g}, 5.02 \text{ mmol}) \text{ was added portion-wise to a solution of compound 207 (200 mg, 0.47 mmol) in THF-MeOH (2:5 ml) at } -20 \degree \text{C and the reaction allowed to warm to 0 } \text{C over 2 h. The solution was quenched with saturated NaHCO}_3, \text{ extracted with CH}_2\text{Cl}_2, \text{ and the CH}_2\text{Cl}_2 dried over MgSO}_4 \text{ and concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (3:7) afforded an inseparable mixture of diastereomers 208 (178 mg, 88\%, 1:1 by 'H-NMR) as an oil; v}_\text{max/cm}^{-1} = 3467 (\text{br} \text{ OH}).
\end{align*}
\]

**Diastereomer 208a:** δC (400 MHz; CDCl3) 5.19 (1 H, dd, J 11.2, 8.9 Hz, H-3), 5.05 (1 H, d, J 3.6 Hz, H-1), 4.93 (1 H, dd, J 10.2, 8.9 Hz, H-4), 4.22 (1 H, t, J 4.4 Hz, H-6a), 4.08-4.03 (2 H, m, H-5, H-6b), 3.85-3.77 (1 H, m, H-2'''), 3.57-3.50 (1 H, m, H-1''), 2.07 (1 H, m, H-2), 2.06, 2.01, 2.00 (9 H, 3 s, 3 × COOCH3), 1.88-1.19 (12 H, m, 5 × -CH2-, cyclohexyl, H-1''''a, H-1''''b), 1.17 (3 H, d, J 6.0 Hz, H-3'''); δC (100 MHz; CDCl3) 170.61, 170.46, 169.91 (3 × COOCH3), 97.51 (C-1), 75.90 (C-1''), 72.97 (C-3), 70.14 (C-4), 67.47 (C-5), 66.74 (C-2'''), 62.49 (C-6), 42.44 (C-2), 36.94 (C-1'''), 33.30, 31.34, 25.48 (3 × -CH2-, cyclohexyl), 24.03 (C-3'''), 24.03, 23.79 (2 × -CH2-, cyclohexyl), 20.76, 20.61, 20.60 (3 × COOCH3); HRFABMS: m/z 453.210259 (M+Na)+. Calcd for C21H34O9Na 453.210041 (M+Na)+.

**Diastereomer 208b:** δH (400 MHz; CDCl3) 5.22 (1 H, dd, J 11.2, 9.3 Hz, H-3), 5.08 (1 H, d, J 3.6 Hz, H-1), 4.95 (1 H, dd, J 10.4, 9.3 Hz, H-4), 4.25 (1 H, t, J 4.4 Hz, H-6a), 4.08-4.03 (2 H, m, H-5, H-6b), 3.85-3.77 (1 H, m, H-2'''), 3.57-3.50 (1 H, m, H-1''), 2.27-2.19 (1 H, m, H-2), 2.06, 2.01, 2.00 (9 H, 3 s, 3 × COOCH3), 1.88-1.19 (12 H, m, 5 × -CH2-, cyclohexyl, H-1''''a, H-1''''b), 1.16 (3 H, d, J 6.0 Hz, H-3'''); δC (100 MHz; CDCl3) 170.61, 170.46, 169.85 (3 × COOCH3), 96.61 (C-1), 75.67 (C-1''), 72.43 (C-3), 70.14 (C-4), 67.57 (C-5), 64.49 (C-2'''), 62.49 (C-6), 40.89 (C-2), 36.28 (C-1'''), 33.30, 31.34, 25.48 (3 × -CH2-, cyclohexyl), 24.49 (C-3'''), 24.03, 23.79 (2 × -CH2-, cyclohexyl), 20.76, 20.61, 20.60 (3 × COOCH3); HRFABMS: m/z 453.210259 (M+Na)+. Calcd for C21H34O9Na 453.210041 (M+Na)+.
Cyclohexyl 2-deoxy-2-C-(2''-hydroxypropyl)-α-D-glucopyranoside (58)

1. From 205

A solution of 205 (214 mg, 0.42 mmol) in a mixture of ethyl acetate-methanol (5:6 ml) was treated with H₂ (1 atm) at room temperature in the presence of 10% palladium on charcoal (300 mg) for 4 days. During this period, two additional portions of 10% palladium on charcoal (100 mg) were added at 24 h interval. After 4 days tlc analysis (MeOH:EtOAc, 1:9) showed complete conversion of the starting material into the deprotected derivative. The catalyst was removed by filtration through celite, the celite washed with methanol and the combined filtrates evaporated to dryness. The remaining solids were purified by column chromatography using methanol-ethyl acetate (5:95) as an eluent to afford an inseparable mixture of diastereomers 58 (55 mg, 43%, 1:1 by ¹H-NMR) as crystals.

2. From 208

Methanolic sodium methoxide (0.2 M, 0.3 ml, 0.60 mmol) was added to a solution of 208 (155 mg, 0.36 mmol) in CH₂Cl₂-MeOH (3:5 ml) at room temperature. After 18 h, the solution was neutralized with Amberlite IR-120 H⁺ resin, the solids were removed by filtration, the filtrate concentrated and the residue recrystallized from ethyl acetate-petroleum ether (4:1) to afford an inseparable mixture of diastereomers 58 (98 mg, 89%, 1:1 by ¹H-NMR).

Diastereomer 58a: δH (300 MHz; CD₃OD) 4.90 (1 H, d, J 3.3 Hz, H-1), 3.92 (1 H, m, H-2''), 3.81-3.57 (4 H, m, H-1', H-5, H-6ₐ, H-6ₐ), 3.52 (1 H, dd, J 10.1, 9.0 Hz, H-3), 3.26 (1 H, t, J 9.0 Hz, H-4), 1.89-1.24 (13 H, m, H-2, 5 × -CH₂-, cyclohexyl, H-1''ₐ, H-1''ₐ), 1.16 (3 H, d, J 6.0 Hz, H-3''); δC (75 MHz; CD₃OD) 99.07 (C-1), 75.78 (C-1'), 74.67 (C-3), 73.77 (C-5), 73.25 (C-4), 67.32 (C-2''), 63.05 (C-6), 44.95 (C-2), 38.46 (C-1'''), 34.56, 32.33, 26.89, 25.06, 24.86 (5 × -CH₂-, cyclohexyl), 23.54 (C-3'''); HRFABMS: m/z 327.177488 (M+Na)⁺. Calcd for C₁₅H₂₉O₆Na 327.178348 (M+Na)⁺.

Diastereomer 58b: δH (300 MHz; CD₃OD) 4.96 (1 H, d, J 3.6 Hz, H-1), 3.83 (1 H, m, H-2''), 3.82-3.57 (4 H, m, H-1', H-5, H-6ₐ, H-6ₐ), 3.50 (1 H, dd, J 10.8, 9.1 Hz, H-3), 3.27 (1 H, t, J 9.1 Hz, H-4), 1.89-1.24 (13 H, m, H-2, 5 × -CH₂-, cyclohexyl, H-1''ₐ, H-1''ₐ), 1.17 (3 H, d, J 6.3 Hz, H-3''); δC (75 MHz; CD₃OD) 98.49 (C-1), 75.46 (C-1'), 74.50 (C-3), 73.77 (C-5), 73.25 (C-4),
66.30 (C-2′′′), 63.05 (C-6), 44.87 (C-2), 38.87 (C-1′′′), 34.52, 32.33, 26.87, 24.98, 24.79 (5 × -CH₂-, cyclohexyl), 24.61 (C-3′′′); HRFABMS: m/z 327.177488 (M+Na)⁺. Calcd for C₁₅H₂₉O₆Na 327.178348 (M+Na)⁺.

Cyclohexyl 3,4,6-tri-O-acetyl-2-deoxy-2-C-(2′′′, 3′′′-epoxypropyl)-α-D-glucopyranoside (209)

\[
\text{AcO} \quad \text{O} \\
\text{O} \quad \text{AcO} \\
\text{O} \quad \text{O} \\
1' \quad 1'' \\
2' \\
3''
\]

To a solution of 201a (308 mg, 0.75 mmol) in CH₂Cl₂ (10 ml) at 0 °C was slowly added a solution of m-CPBA (70%, 0.32 g, 1.29 mmol) in CH₂Cl₂ (3.0 ml) (m-CPBA was dissolved in CH₂Cl₂, dried with MgSO₄, filtered and concentrated before used). The temperature was raised to room temperature and after stirring for 18 h, a further portion of m-CPBA (70%, 0.1 g, 0.40 mmol) in CH₂Cl₂ (2 ml) was added slowly to the mixture at 0 °C. The reaction was stirred for 6 h at room temperature, then saturated Na₂S₂O₃ added, the aqueous mixture extracted with CH₂Cl₂, and the CH₂Cl₂ washed with saturated NaHCO₃, dried over MgSO₄ and concentrated. The crude residue was purified by column chromatography using ethyl acetate-petroleum ether (1:4) as eluent to afford an inseparable mixture of diastereomers 209 (292 g, 91%, 1:1 by ¹H-NMR) as an oil.

**Diastereomer 209a:** δH (400 MHz; CDCl₃) 5.15 (1 H, dd, J 11.0, 9.4 Hz, H-3), 5.00 (1 H, d, J 3.2 Hz, H-1), 4.86 (1 H, t, J 9.4 Hz, H-4), 4.18-4.14 (1 H, m, H-6a), 4.03-3.96 (2 H, m, H-5, H-6b), 3.48 (1 H, m, H-1′), 2.82 (1 H, m, H-2′′), 2.66 (1 H, t, J 5.0 Hz, H-3′′a), 2.36 (1 H, dd, J 5.0, 2.6 Hz, H-3′′b), 2.07 (1 H, m, H-2), 1.98, 1.93, 1.92 (9 H, 3 s, 3 × COOCH₃), 1.82-1.10 (12 H, m, 5 × -CH₂-, cyclohexyl, H-1′′′a, H-1′′′b); δC (100 MHz; CDCl₃) 170.85, 170.83, 170.06 (3 × COOCH₃), 96.94 (C-1), 75.99 (C-1′), 72.41 (C-3), 70.23 (C-4), 67.85 (C-5), 62.66 (C-6), 49.97 (C-2′′), 47.53 (C-3′′), 42.39 (C-2), 33.51 (C-1′′), 31.56, 30.69, 25.66, 24.27, 24.04 (5 × -CH₂-, cyclohexyl), 20.94, 20.78, 20.77 (3 × COOCH₃); HRFABMS: m/z 451.195037 (M+Na)⁺. Calcd for C₂₁H₃₂O₉Na 451.194392 (M+Na)⁺.

**Diastereomer 209b:** δH (400 MHz; CDCl₃) 5.15 (1 H, dd, J 11.0, 9.5 Hz, H-3), 5.04 (1 H, d, J 3.2 Hz, H-1), 4.87 (1 H, t, J 9.5 Hz, H-4), 4.18-4.14 (1 H, m, H-6a), 4.03-3.96 (2 H, m, H-5, H-6b), 3.48 (1 H, m, H-1′), 2.82 (1 H, m, H-2′′), 2.62 (1 H, t, J 4.8 Hz, H-3′′a), 2.31 (1 H, dd, J 4.8, 2.6 Hz, H-3′′b), 2.07 (1 H, m, H-2), 1.98, 1.93, 1.92 (9 H, 3 s, 3 × COOCH₃), 1.82-1.10 (12 H, m, 5 ×
1.1 was (l, 1.1, 3\'' prime, 3'' prime-epoxypropyl)-\(\alpha\)-D-glucopyranoside (61) and Cyclohexyl (2''R), (2''S)-3,3'''-anhydro-2-deoxy-2-C-(2''',3'''-dihydroxypropyl)-\(\alpha\)-D-glucopyranoside (210) at room temperature.

Methanolic sodium methoxide (0.2 M, 0.3 ml, 0.06 mmol) was added to a solution of 209 (200 mg, 0.47 mmol) in CH\(_2\)Cl\(_2\)-MeOH (3:5 ml) at room temperature. After 6 h, water was added (1 ml) and the solvent evaporated to dryness. TLC indicated the formation of two products and separation was achieved by column chromatography using methanol-ethyl acetate (3:97) to obtain a diastereomeric mixture of epoxides 61 (71 mg, 50%, 4:1 by \(^1\)H-NMR) as an oil and a diastereomeric mixture of alcohols 210 (60 mg, 42%, 1:1 by \(^1\)H-NMR) as crystals.

**Diastereomer 61a:** \(\delta_H\) (400 MHz; CD\(_3\)OD) 5.04 (1 H, d, \(J\) 3.2 Hz, H-1'), 3.80-3.60 (4 H, m, H-1', H-5, H-6\(_a\), H-6\(_b\)), 3.50 (1 H, dd, \(J\) 10.8, 8.8 Hz, H-3), 3.26 (1 H, dd, \(J\) 9.2, 8.8 Hz, H-4), 3.07-3.00 (1 H, m, H-2''), 2.77 (1 H, dd, \(J\) 5.0, 4.0 Hz, H-3''), 2.51 (1 H, d, \(J\) 5.0, 2.8 Hz, H-3'''), 1.95-1.24 (13 H, m, 5 x -CH\(_2\)-, cyclohexyl, H-2, H-1''), H-1''), \(\delta_C\) (100 MHz; CD\(_3\)OD) 96.88 (C-1), 74.51 (C-1'), 72.77 (C-3), 72.71 (C-5), 72.01 (C-4), 61.84 (C-6), 50.42 (C-2'''), 47.51 (C-3'''), 44.07 (C-2), 33.40, 31.27 (2 x -CH\(_2\)-, cyclohexyl), 30.56 (C-1''), 25.68, 23.95, 23.77 (3 x -CH\(_2\)-, cyclohexyl); HRFABMS: \(m/z\) 325.162227 (M+Na). Calcd for C\(_{15}\)H\(_{26}\)O\(_8\)Na 325.162699 (M+Na).

**Diastereomer 210a:** \(\delta_H\) (300 MHz; CD\(_3\)OD) 5.15 (1 H, d, \(J\) 3.0 Hz, H-1'), 4.11 (1 H, m, H-2''), 3.84-3.42 (8 H, m, H-1', H-3, H-3''), H-3''), H-4, H-5, H-6\(_a\), H-6\(_b\)), 2.05-1.30 (13 H, m, 5 x -CH\(_2\)-, cyclohexyl, H-2, H-1''), H-1''), \(\delta_C\) (75 MHz; CD\(_3\)OD) 97.75 (C-1), 81.05 (C-1'), 80.40 (C-2'''), 76.33 (C-3), 74.93 (C-4), 72.63 (C-5), 65.66 (C-3''), 62.32 (C-6), 47.92 (C-2), 34.50, 32.58 (2 x -
CH₂-, cyclohexyl), 29.71 (C-1'), 26.82, 24.94, 24.76 (3 × -CH₂-, cyclohexyl); HRFABMS: m/z 325.162227 (M+Na)⁺. Calcd for C₁₅H₂₆O₆Na 325.162699 (M+Na)⁺.

**Diastereomer 210b:** \( \delta_H \) (300 MHz; CD₃OD) 5.14 (1 H, d, \( J \) 3.0 Hz, H-1), 4.11 (1 H, m, H-2'''), 3.84-3.42 (8 H, m, H-1', H-3, H-3''a, H-3''b, H-4, H-5, H-6a, H-6b), 2.05-1.30 (13 H, m, 5 × -CH₂-, cyclohexyl, H-2, H-1''a, H-1''b); \( \delta_C \) (75 MHz; CD₃OD) 97.87 (C-1), 81.96 (C-1'), 80.15 (C-2'''), 76.33 (C-3), 74.83 (C-4), 72.52 (C-5), 65.84 (C-3'''), 62.35 (C-6), 46.65 (C-2), 34.50, 32.58 (2 × -CH₂-, cyclohexyl), 29.14 (C-1''), 26.82, 24.94, 24.76 (3 × -CH₂-, cyclohexyl); HRFABMS: m/z 325.162227 (M+Na)⁺. Calcd for C₁₅H₂₆O₆Na 325.162699 (M+Na)⁺.
REFERENCES


(52) Collins, P.; Ferrier, R. Monosaccharides: Their Chemistry and Their Roles in Natural Products; John Wiley and Sons Ltd: Chichester, 1995, 189-341.


(84) Rekař, E. D.; Rubinstenn, G.; Mallet, J.-M.; Sinaý, P.; Müller, S. N.; Giese, B. *Synlett* 1998, 831-834.


(86) Ferrier, R. J.; Petersen, P. M. *Tetrahedron* 1990, 46, 1-11.


