SYNTHESIS OF ANALOGUES OF MYCOTHIOL AS POSSIBLE INHIBITORS OF ENZYMES IN THE BIOSYNTHESIS OF MYCOTHIOL

BY

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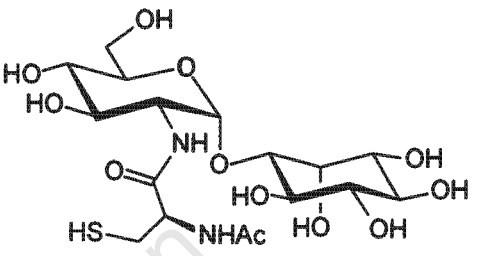
Abstract

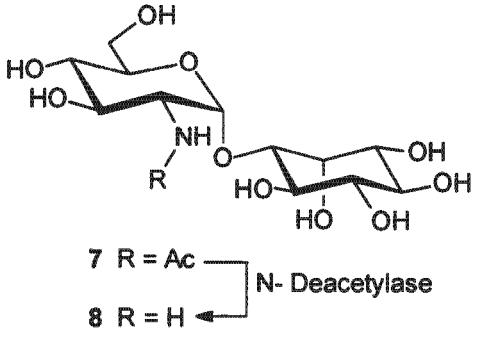
Mycobacterium tuberculosis is the causative agent of tuberculosis and is a leading pathogenic cause of death worldwide. The rise of mycobacterial resistance to common antituberculars such as isoniazid and rifampicin, along with the lethal alliance of HIV and *M. tuberculosis* co-infection, has led to 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.



Mycothiol

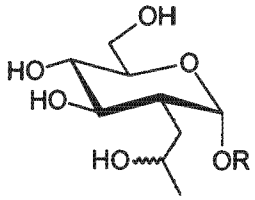
Deacetylation of 1-D-*myo*-inosityl-2-*N*-acetamido-2-deoxy-α-D-glucopyranoside (GlcNAc-Ins, **7**) to 1-D-*myo*-inosityl-2-amino-2-deoxy-α-D-glucopyranoside (GlcN-Ins, **8**) by a deacetylase enzyme (*MshB*) is believed to be an important step in the biosynthesis of mycothiol. With the possibility of 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.



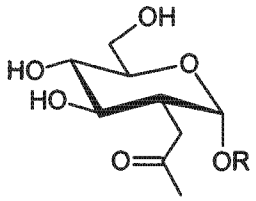
Stereoselective synthesis of C-2 alkyl glucosides was identified as a key challenge and methods for their synthesis have been extensively reviewed. Synthesis of the analogues proceeded *via* initial stereoselective introduction of the alkenyl group at C-2 of the sugars, either by lithium enolate-mediated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

Coupling of the 2-C-allyl glycosyl fluoride with the D-*myo*-inositol or cyclohexanol in the presence of $BF_3{\cdot}Et_2O$ as a catalyst gave 2-C-allyl-2-deoxy-glucosides as a mixture of anomers

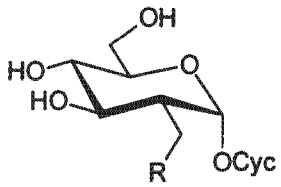
with good selectivity (α:β = 8:1) in the case of D-*myo*-inositol. Portions of these allylated compounds were further functionalized, including oxygenation, to afford a range of potential enzyme inhibitors (**51**, **52** and **57-61**) after deprotection.



51 R = D-Inositol
58 R = Cyclohexyl



52 R = D-Inositol
57 R = Cyclohexyl



59 R = CH_2
60 R = CH_3
61 R =

The 1-*O*-[2′-deoxy-2′-C-(2′′-hydroxypropyl)-α-D-glucopyranosyl]-D-*myo*-inositol **51**, 1-*O*-[2′-deoxy-2′-C-(2′′-oxopropyl)-α-D-glucopyranosyl]-D-*myo*-inositol **52** and cyclohexyl 2-C-allyl-2-deoxy-α-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.

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To my dearest mother, Jerminah Mudzunga. 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

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.[4,5]

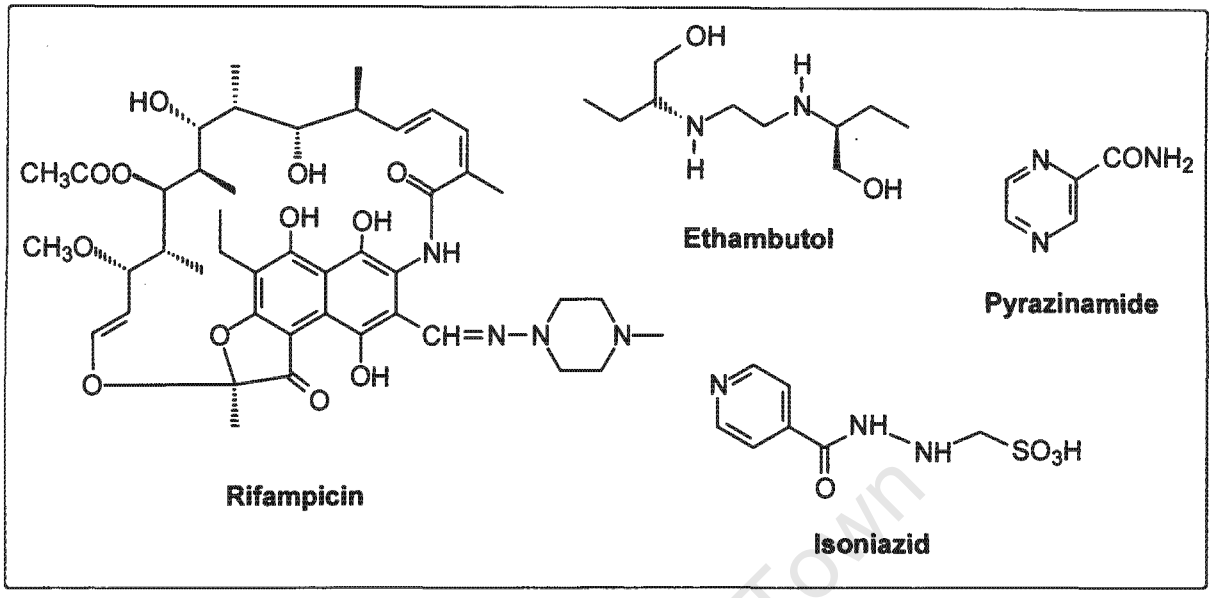


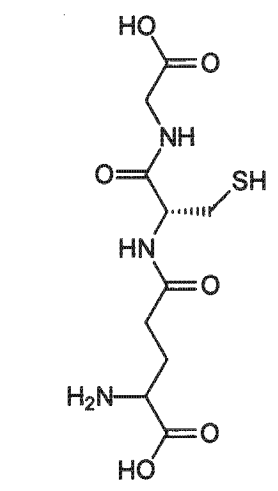
Figure 1 Drugs used to treat TB disease

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 (mrdTB) and synergism between Human Immunodeficiency Virus (HIV) and *M. tuberculosis* infection to an extent that the World Health Organization (WHO) has declared it a global health emergency.[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 *Mycobacterium tuberculosis*[9] has led to the view that mycothiol analogues are potential lead drugs for TB.

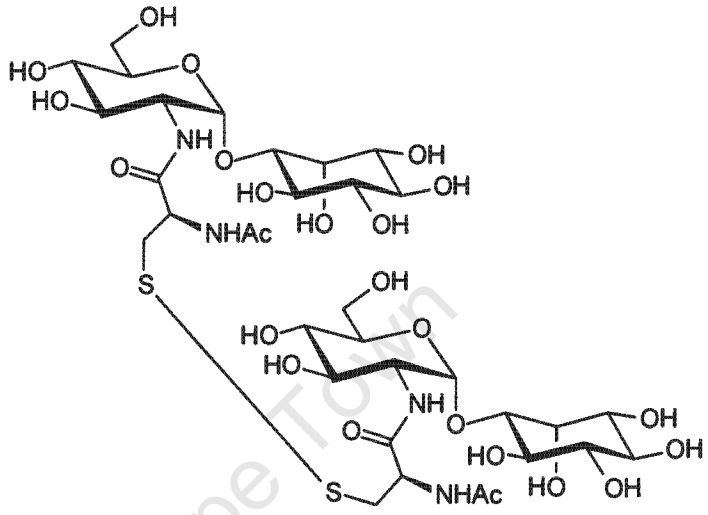
1.2 Mycothiol

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.[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 *N*-acetyl-L-cysteine linked to a *pseudo*-disaccharide composed of D-glucosamine and *myo*-inositol (Figure 2).[12]

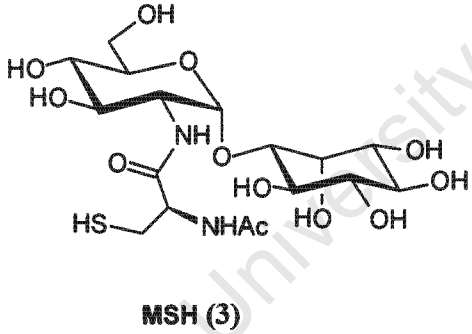
The systematic name of mycothiol[a] is 1-*O*-(2′-[*N*-acetyl-L-cysteinyl]amido-2′-deoxy-α-D-glucopyranosyl)-D-*myo*-inositol.[13] It was first isolated as the disulfide (MSSM, **2**) from *Streptomyces sp.* AJ9463[13] and as the bimane derivative (MSmB, **4**)[14] and free thiol from *M. bovis*, which allowed the demonstration of a mycothioldisulfide reductase activity, by analogy to glutathione reductase (Figure 2).[15]



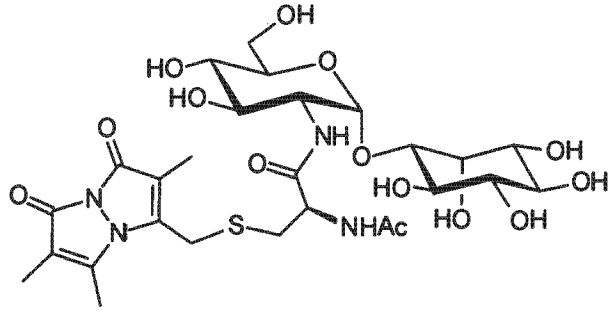
Glutathione (1)



MSSM (2)



MSH (3)



MSmB (4)

Figure 2 Glutathione **1**, mycothiol (**MSH, 3**), the symmetric disulfide (**MSSM, 2**), and mycothiol bimane (**MSmB, 4**)

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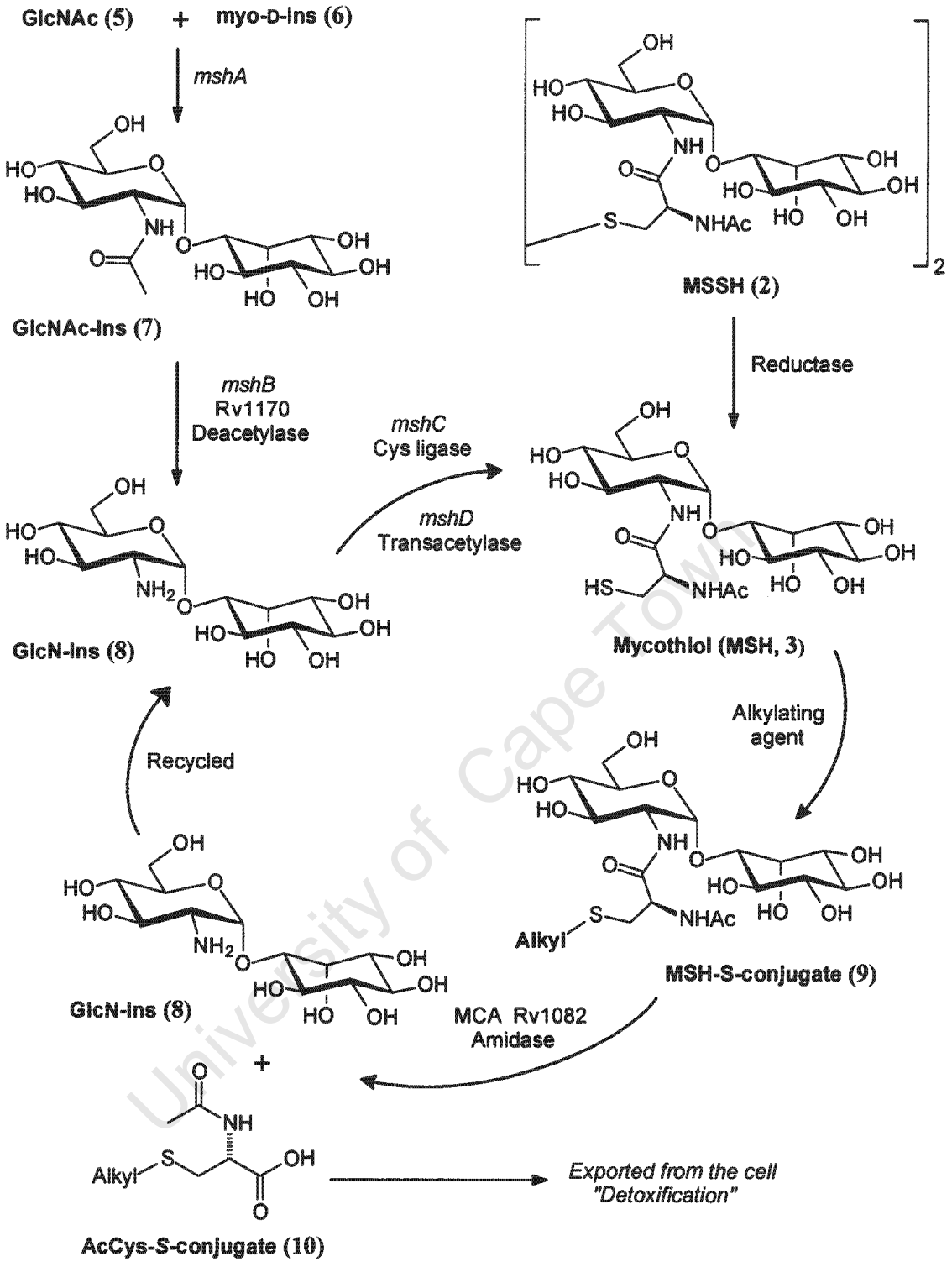
[a] **The trivial nomenclature for thiols**: There is ambiguity in the literature on nomenclature of these compounds. Ergothionine which has a genuine thione structure is not called ergothione, while glutathione, which has no thione, is called glutathione. If we are going to call the mycobacterial thiol 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.



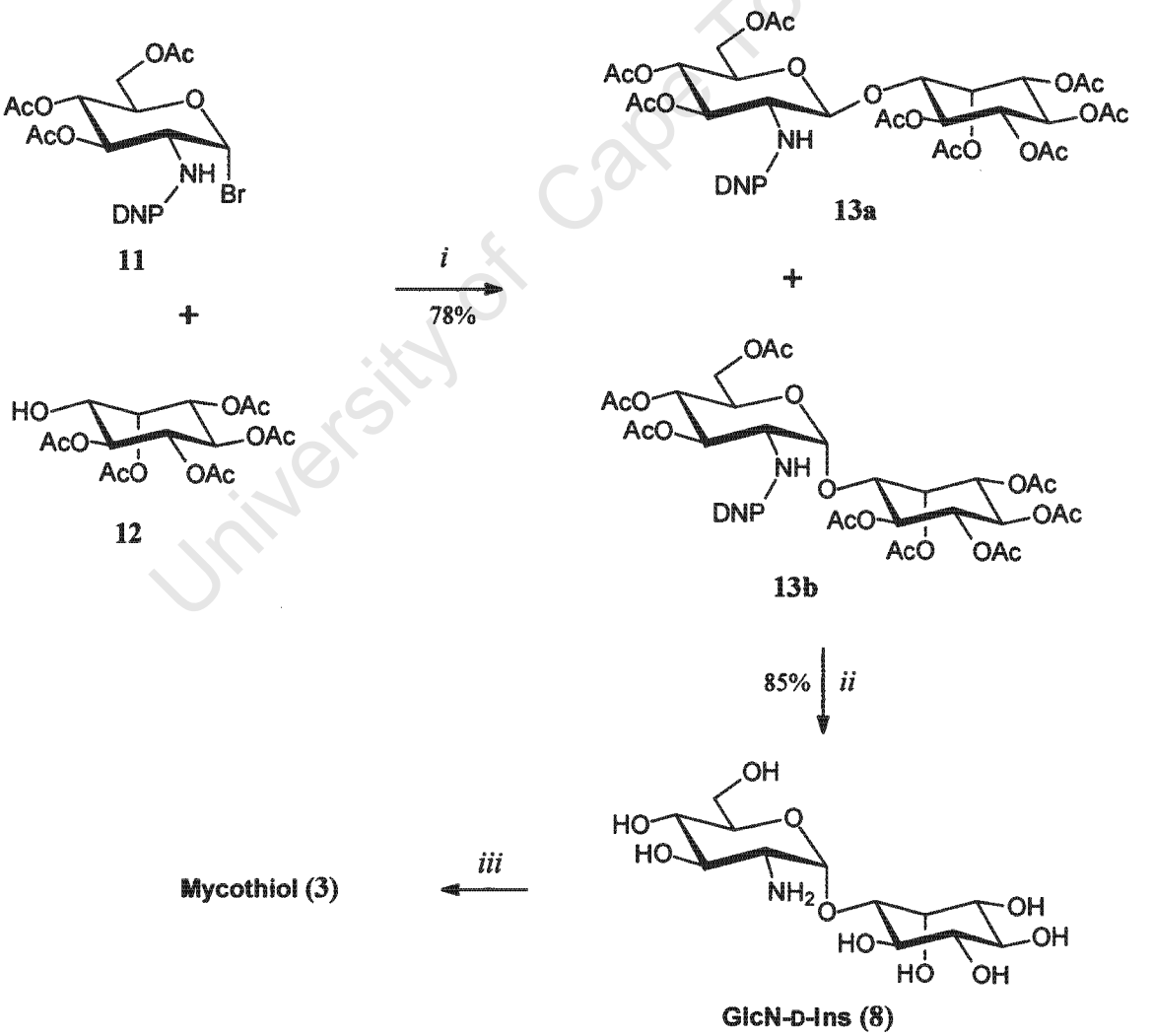
Scheme 1 Proposed biosynthetic pathways of mycothiol **3**

Two further pathways involving MSH **3** formalate hydrogenase have been elucidated (Scheme 1): (a) a reductase[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).[14] MCA cleaves the amide bond between cysteine and D-glucosamine-α-(1→1)-*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.[9] The detoxification enzyme mycothiol *S*-conjugate amidase (MCA)[14] and the mycothiol-disulfide reducing enzyme mycothione reductase[27] were the first mycothiol-related enzymes to be identified and characterized.

1.2.2 Chemical synthesis of mycothiol bimane

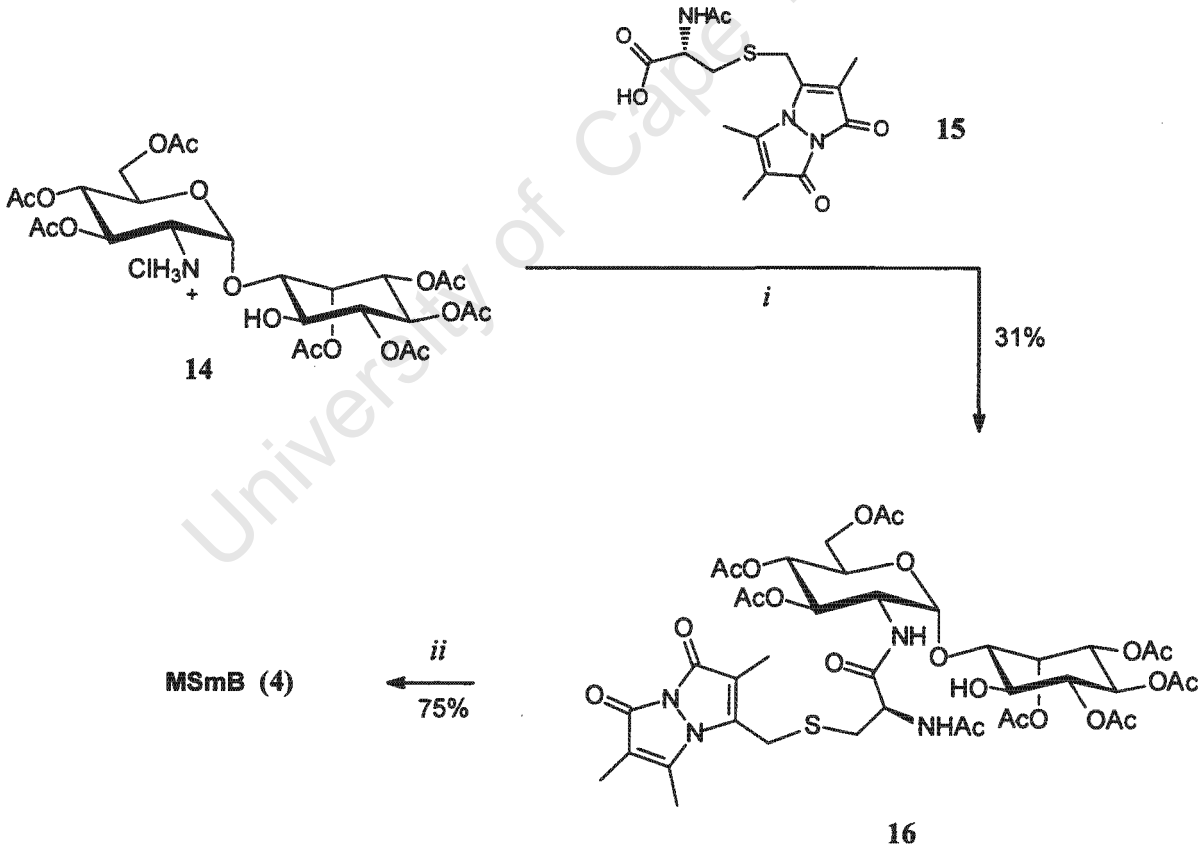
Sakuda *et al.*,[13] proposed the absolute stereochemistry of the three components of MSH **3** as D-glucosamine, L-cysteine, and D-*myo*-inositol. His experimental evidence for the stereochemical assignments of the glucosamine and cysteine was not provided in the paper. Steenkamp and co-workers reported the first synthesis of mycothiol *via* GlcN-D-Ins **8** (Scheme 2).[29]



Scheme 2 *Reagents and conditions*: *i*) AgOTf, 2,6-tert-dibutylpyridine, CH_2Cl_2, rt, 1 h; *ii*) Amberlite IR400 (OH) resin, rt, 3 days; *iii*) Sodium phosphate, pH 7.5, DTT, Mg^{2+}, L-[^{35}S]cysteine, ATP, acetyl-S-CoA, partially purified enzyme

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[19] 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.[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)[30] on the basis of comparisons of optical rotation and cd measurements with those from the bimane derivative of the natural material.



Scheme 3 *Reagents and conditions*: *i*) DEPC, iPr$_2$EtN, 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-cysteinyl 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-*myo*-inositol **7** or 1-L-*myo*-inositol **17** have been synthesized in order to establish substrate specificity of GlcNAc-α-Ins deacetylase from *M. tuberculosis* (Figure 3).[22]

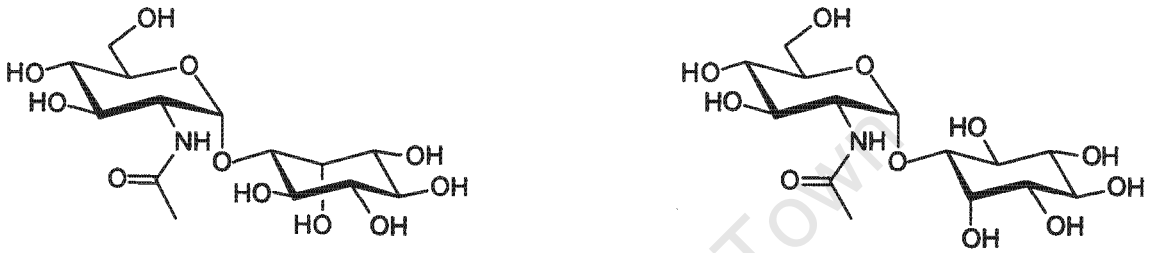
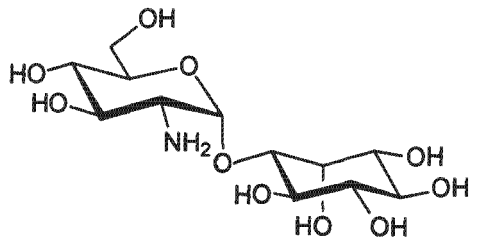


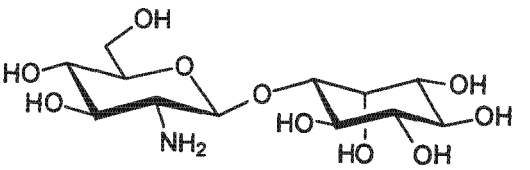
Figure 3 Two diastereomers of GlcNAc-α-Ins containing either 1-D-*myo*-inositol or 1-L-inositol

In order to establish substrate specificity of AcGI deacetylase from *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)-*myo*-D-Ins] were used as standards. Following derivatization of the standard solutions and the reaction mixtures with 6-aminoquinolyl-*N*-hydroxysuccinamidyl 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-contaning isomer **17** was observed under the same conditions.

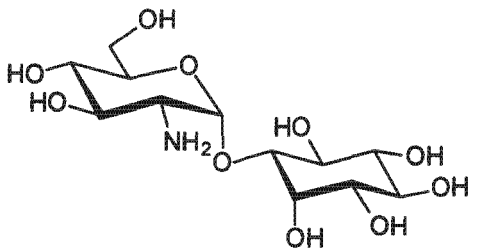
Further attempts of deacetylation of **17** were conducted, but even in the presence of relatively high enzyme concentrations, no cleavage products were detected, thereby establishing the 1-D-*myo*-inositol containing isomer **7** as the natural substrate of AcGI deacetylase.[22] These results are consistent with a separate study showing that D-GlcN-α-(1→1)-*myo*-L-Ins **17** was not a substrate for MSH biosynthesis by crude extracts of *Mycobacterium smegmatis*.[19,29]



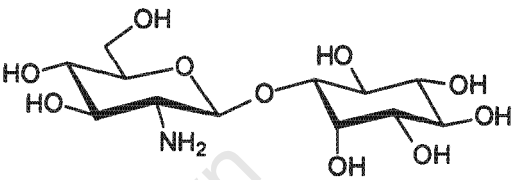
GlcN-α-D-Ins (8)



GlcN-β-D-Ins (18)



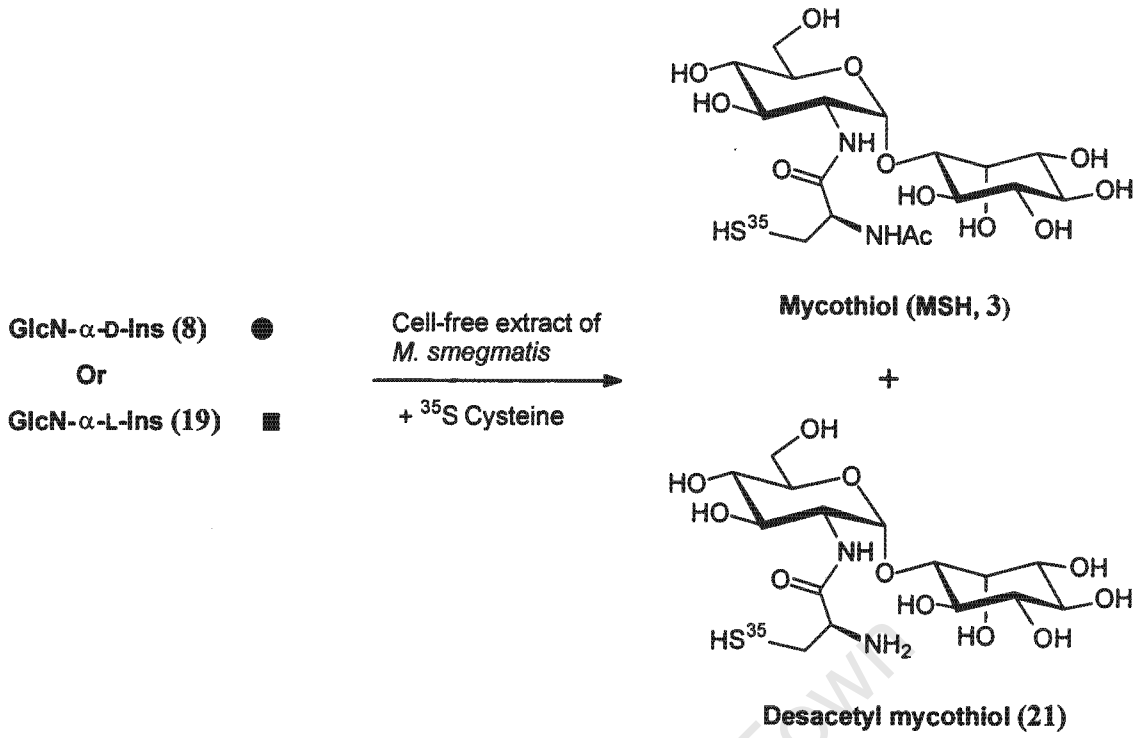
GlcN-α-L-Ins (19)



GlcN-β-L-Ins (20)

Figure 4 Four diastereomers of GlcN-Ins containing either 1-α/β-D-*myo*-inositol or 1-α/β-L-inositol

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 [^{35}S]-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_{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_{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*

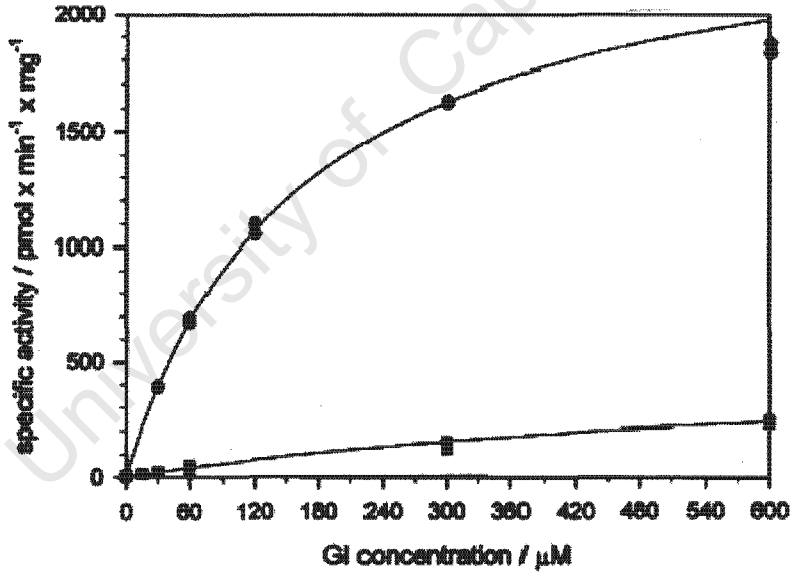


Figure 5 Dependence of the rate of product formation on the concentration of the two isomers of GlcN-α-D-Ins **8** (●) and GlcN-α-L-Ins **19** (■)[19,29]

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-workers[31-33] 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 IC_{50} 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]

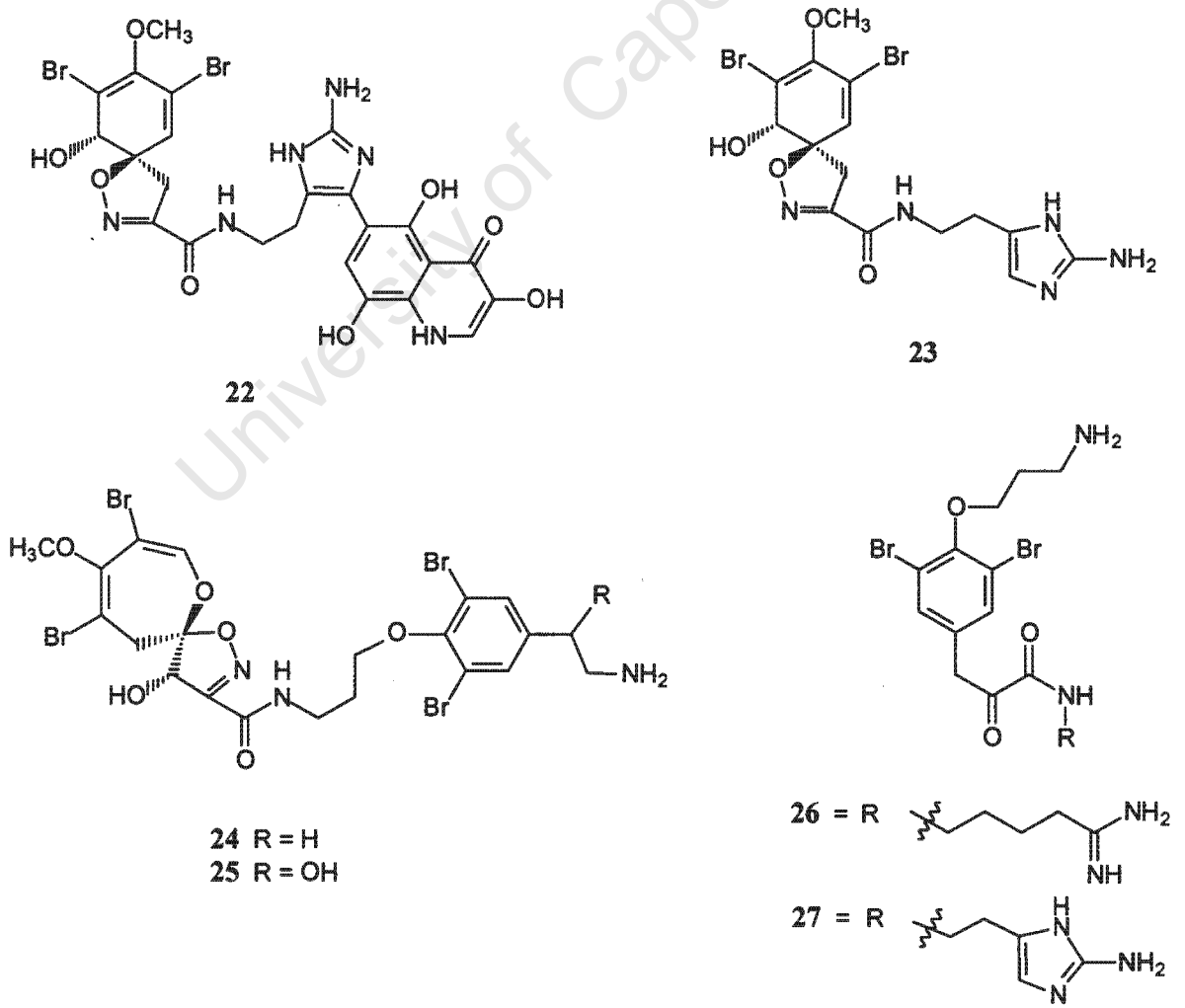
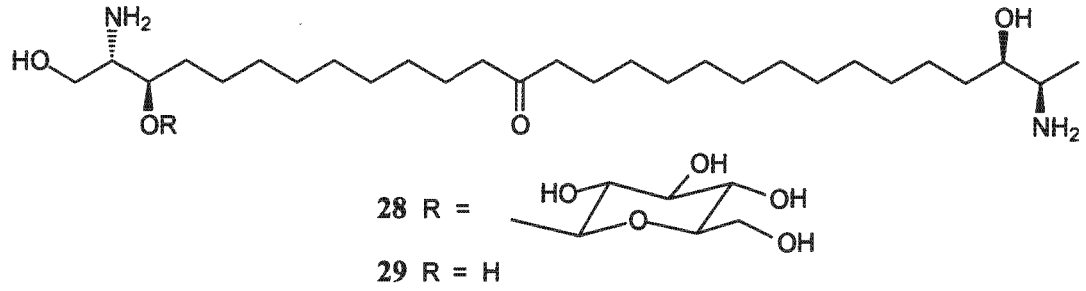


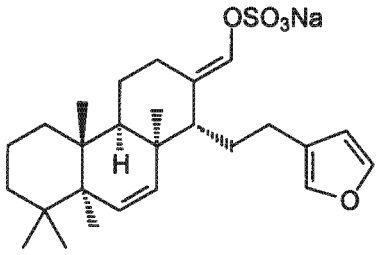
Figure 6 Bromotyrosine-derived natural products that inhibit mycothiol *S*-conjugate amidase

The α,ω-bis-aminohydroxy glycosphingolipid oceanapiside **28** (Figure 7) inhibited MCA at low micromolar concentration (Table 1). Like the substrate mycothiol 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_{50} values for natural product inhibitors of *M. tuberculosis* and *M. smegmatis* mycothiol *S*-conjugate amidase (MCA)[31,33]

Compound	Common name or first author	Organism	Genus and species	NCI collection no.	IC_{50} (μM)	
					M. tb	*M. smeg*
22	Nicholas et al.	Marine sponge	*Oceanapia sp.*	C2385	3	2
23	Pseudoceratine	Marine sponge	*Oceanapia sp.*	C2385	100	100
24	Psammaplysin A	Marine sponge	*Pseudoceratina sp.*	C16115	30	30
25	Psammaplysin B	Marine sponge	*Pseudoceratina sp.*	C16115	30	20
26	Nicholas et al.	Marine sponge	*Oceanapia sp.*	C2385	3	2
27	Litaudon and Guyot	Marine sponge	*Oceanapia sp.*	C2385	30	37
28	Oceanapiside	Marine sponge	*Oceanapia sp.*	C2523	10	0.5
29	Oceanapiside aglycon	Marine sponge	——	C2523	100	50
30	Suvanine	Marine sponge	*Coscinoderma mathewsi*	C16199	nt	60
31	Halisulfate	Marine sponge	*Coscinoderma mathewsi*	C16199	nt	40
32	Gliotoxin	Terrestrial fungus	*Mycena sp.*	F205435	50	50
33	Physcion	Terrestrial fungus	*Aspergillus sp.*	F205337	nt	50
34	1,3-Pyridinium polymers	Marine sponge	*Amphimedon sp.*	C2355	0.1	0.1
35	S,S-Dimethyl gliotoxin	Terrestrial fungus	*Aspergillus sp.*	F205337	70	nt





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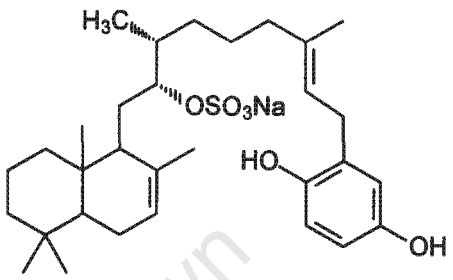

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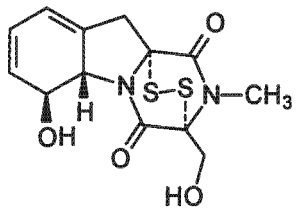

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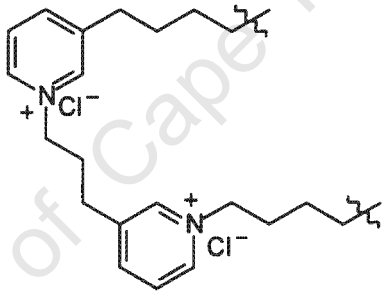

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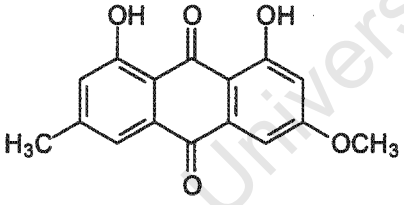

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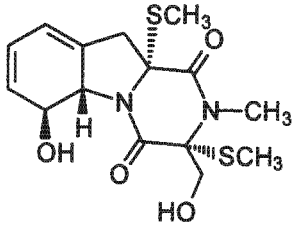

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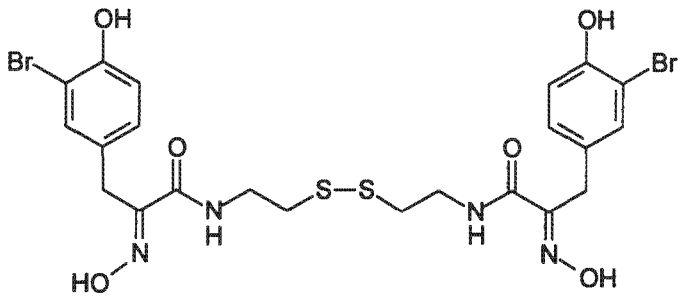
Figure 7 Natural products that inhibit mycothiol *S*-conjugate amidase

Other completely different classes of natural compound[33] 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.[34-37] Most recently, Nicolaou and co-workers[38,39] 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.[31]



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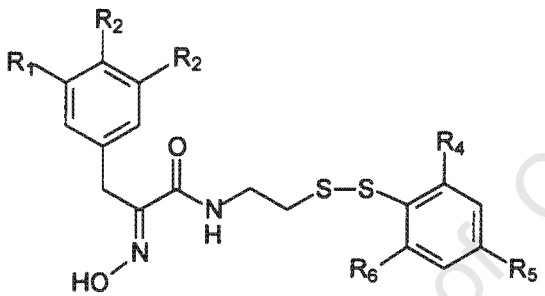

	R_1	R_2	R_3	R_4	R_5	R_6
37	Br	H	H	H	F	H
38	Br	H	H	H	H	CH_3
39	Br	H	H	CH_3	NH_2	H_1
40	F	H	F	H	F	H
41	F	H	F	H	NH_2	H
42	Cl	OH	H	H	F	H
43	Cl	OH	H	H	NH_2	H

Figure 8 Bromotyrosine-derived natural product and members of a synthetic library

Table 2 Inhibition of mycothiol *S*-conjugate amidase (MCA) from *M. tuberculosis* by synthetic and natural bromotyrosine-derived compounds[31]

Marine natural products			Sythetic library		
Compound	Common name or first author	IC_{50} (μM)	Compound	Common name or first author	IC_{50} (μM)
22	Nicholas et al.	2.0 ± 0.2	**37**	Nicolaou et al.	90 ± 4
23	Pseudoceratine	100 ± 21	**38**	Nicolaou et al.	65 ± 18
24	Psammaplysin A	20 ± 11	**39**	Nicolaou et al.	185 ± 62
25	Psammaplysin B	26 ± 12	**40**	Nicolaou et al.	2720 ± 640
26	Litaudon and Guyot	36 ± 3	**41**	Nicolaou et al.	450 ± 173
27	Nicholas et al.	2.8 ± 0.5	**42**	Nicolaou et al.	37 ± 10
36	Psammaplin A	2.8 ± 0.5	**43**	Nicolaou et al.	35 ± 11

By screening marine and fungal extracts, Bewley and co-workers[31-33] have identified 14 compounds encompassing several unrelated structural classes that inhibit MCA with micromolar IC_{50} values. Preliminary studies with psammaplysins A and B, oceanapiside, and the toxin gliotoxin demonstrate that these compounds inhibit growth of *M. smegmatis* (MC^2155) 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.[31]

Recently, Knapp and co-workers[40] have reported the synthesis of a simplified thioglycosidic analogue of mycothiol **44** (Figure 9).

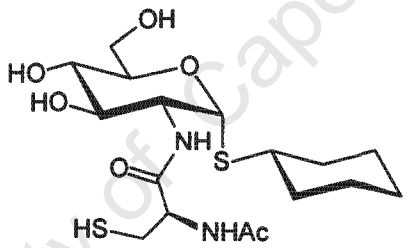

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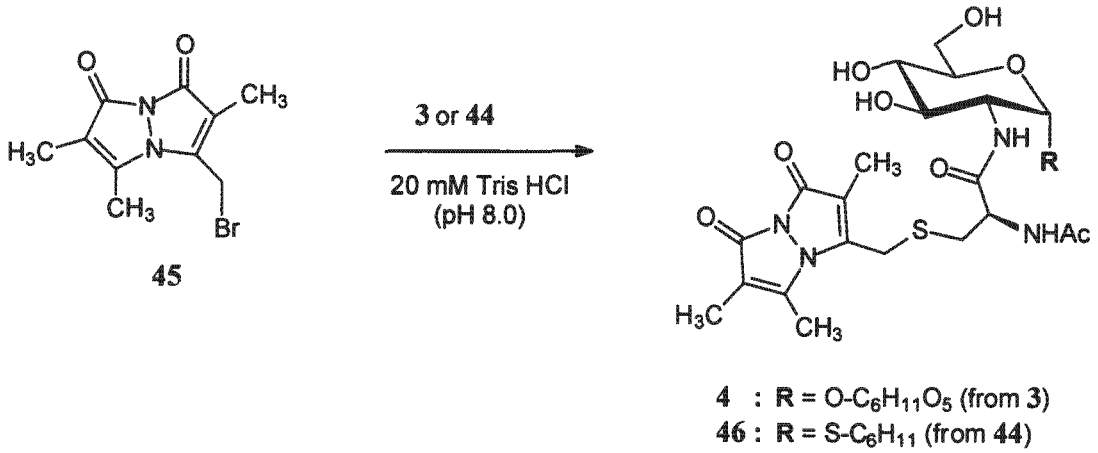
Figure 9 Simplified thioglycosidic analogue of mycothiol

In previous synthetic studies on MSH **3** and related compounds,[19,26,29,30,41] the preparation of a protected D-*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 *O*-glycosides,[42-44] so this approach to inhibitors design combines several possible advantages.



Scheme 5 Preparation of bimane derivative

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.

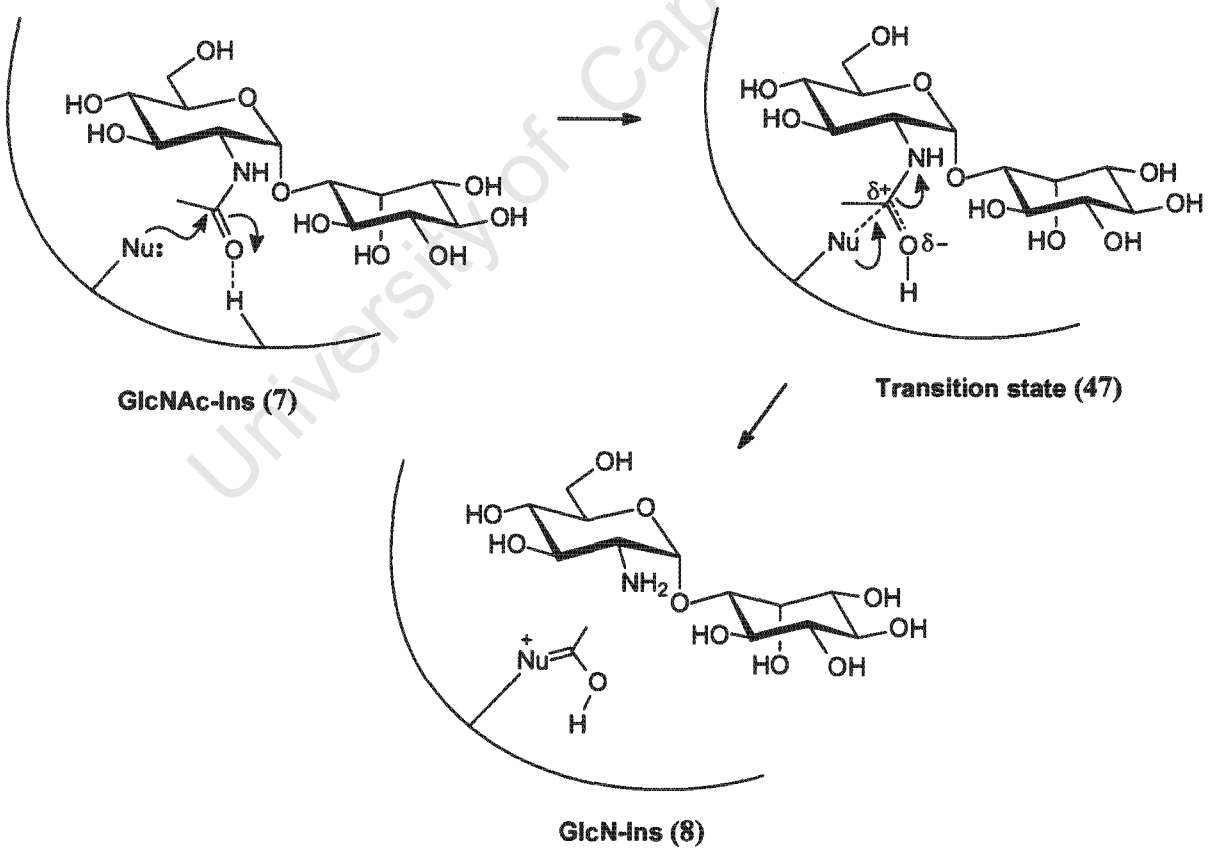
1-D-*myo*-inosityl-2-amino-2-deoxy-α-D-glucopyranoside (GlcN-Ins, **8**) is formed by deacetylation of 1-D-*myo*-inosityl 2-acetamino-2-deoxy-α-D-glucopyranoside (GlcNAc-Ins, **7**). A homologous deacetylase (1-D-*myo*-inosityl-2-acetamino-2-deoxy-α-D-glucopyranoside deacetylase, *mshB*) has

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 *Mycobaterium tuberculosis*.

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

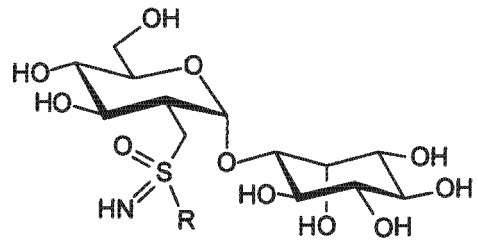
The conversion of GlcNAc-Ins **7** to GlcN-Ins **8** by a deacetylase enzyme (*mshB*) has been identified as a main control point in the mycothiol biosynthesis. Derivate **47** has been proposed as a transition state in the action of a deacetylase, resulting from a nucleophilic attack on the acetamide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



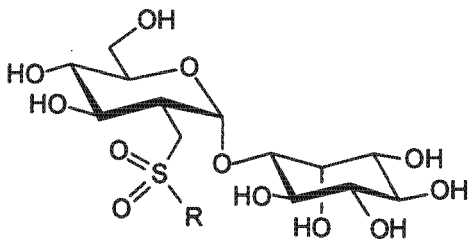
Scheme 6 Proposed general mechanism of *N*-deacetylation step

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

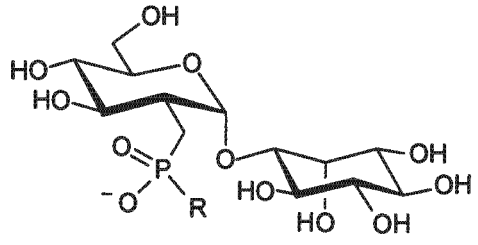
the C-2 of the glucosamine unit has been modified, thus mimicking the transition state of the deacetylation of GlcNAc-Ins 7 (Figure 10).



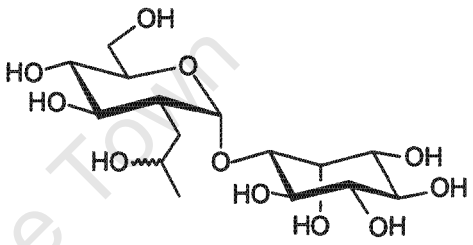
Sulfoximine (48)



Sulfone (49)



Phosphonic acid (50)

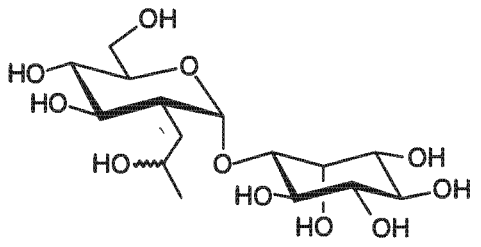


2-C-hydroxypropyl (51)

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-*myo*-inosityl-2-acetamido-2-deoxy-α-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 α- to the carbonyl, as is found in mycothiol **3**.



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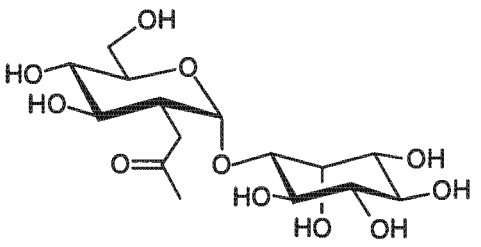

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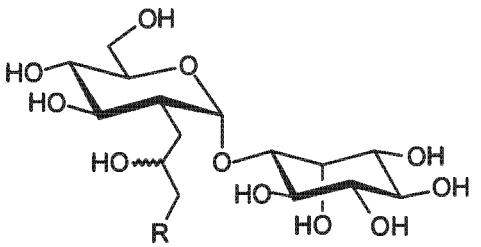

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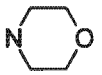

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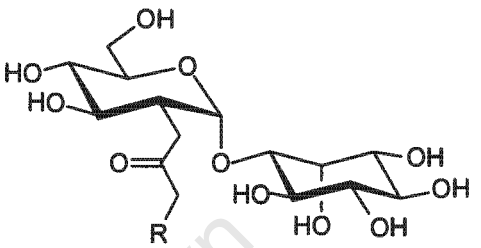

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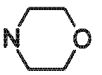
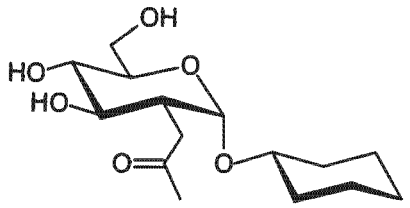


56 R =

Figure 11 Isosteres of GlcNAc-Ins 7 or the transition state of deacetylation of GlcNAc-Ins 7 as potential inhibitors of the deacetylase step

The synthesis of compounds **51** to **56** requires the preparation of a protected D-*myo*-inositol glycosylation acceptor. Previous reports on synthetic studies of MSH **3** and related compounds[19,26,29,30] revealed that the synthesis of the protected D-*myo*-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).



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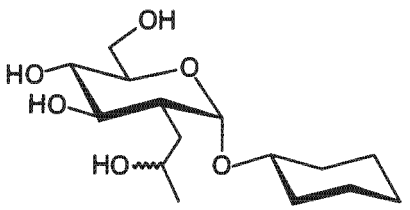

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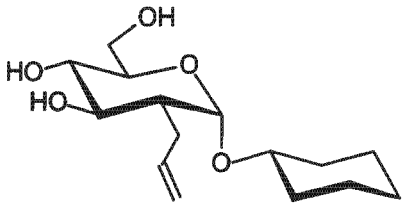

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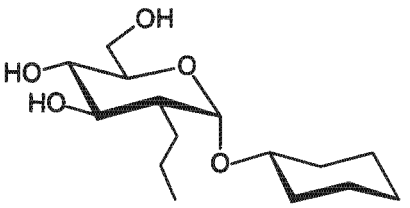

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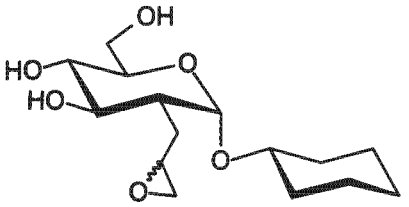

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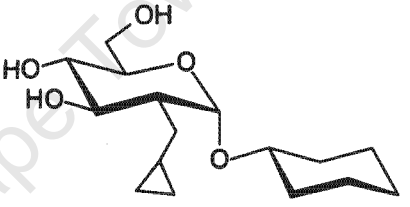
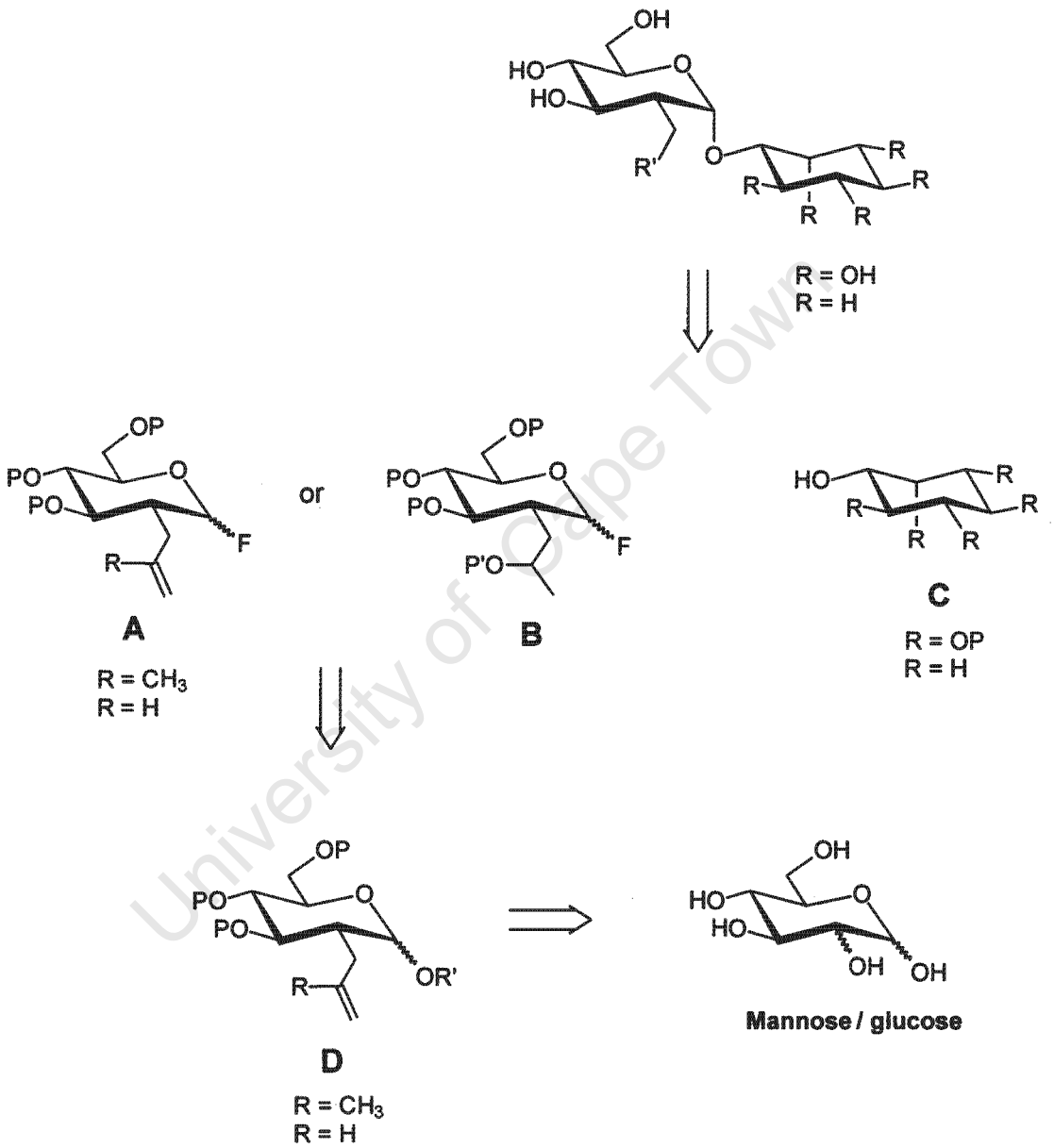


62

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-*myo*-inositol or cyclohexanol.

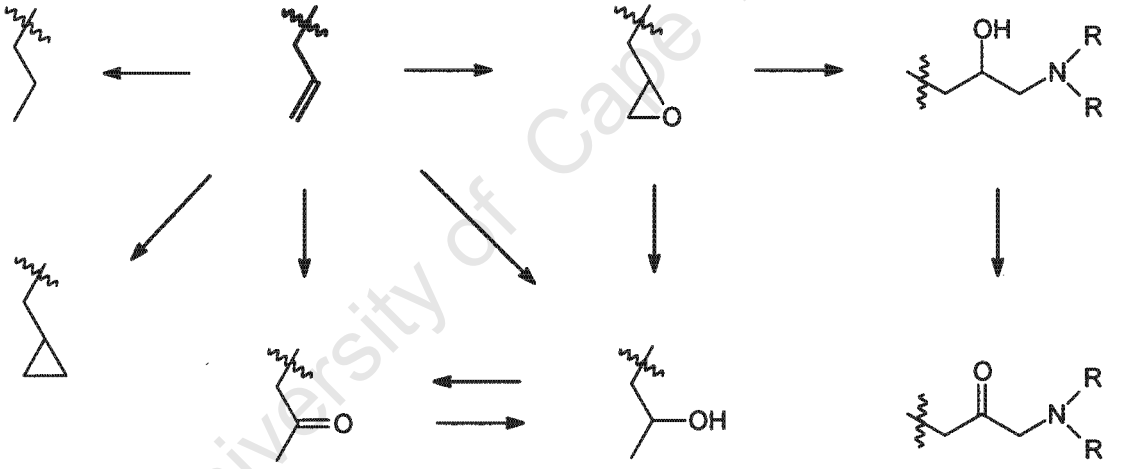


Scheme 7 Retrosynthetic analysis of target compounds

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 *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 alkylation.

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 α-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).[48,49] 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.



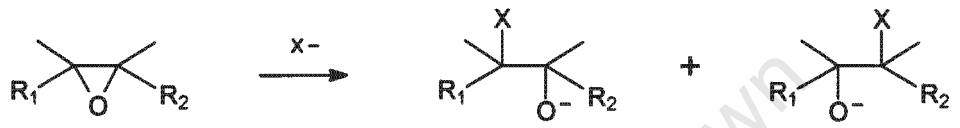
Scheme 8 Functional group interconversions on the C-2 side chain

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.[50] 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.

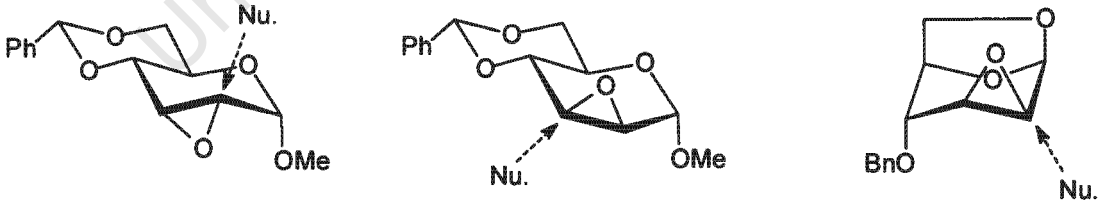
1.6.1 Nucleophilic opening of carbohydrate epoxides

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-mememred 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

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_N2 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]

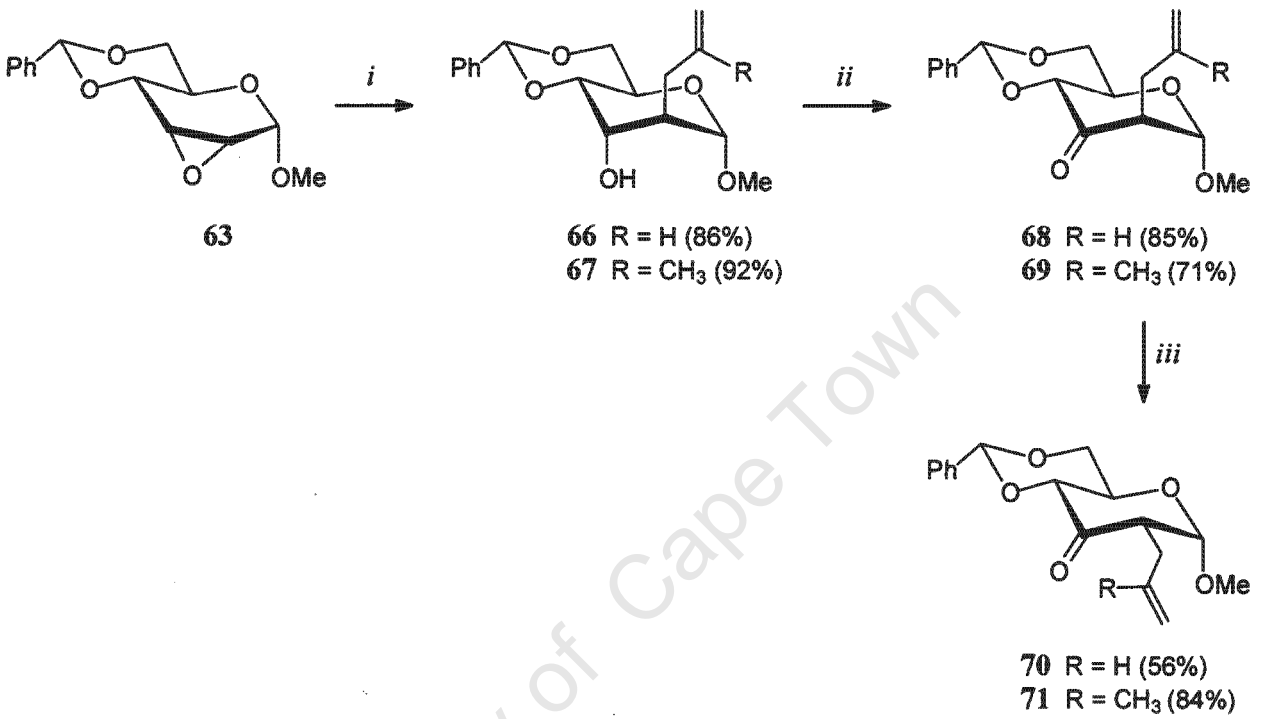


63 **64** **65**

Figure 13 Stereoselective opening of epoxides

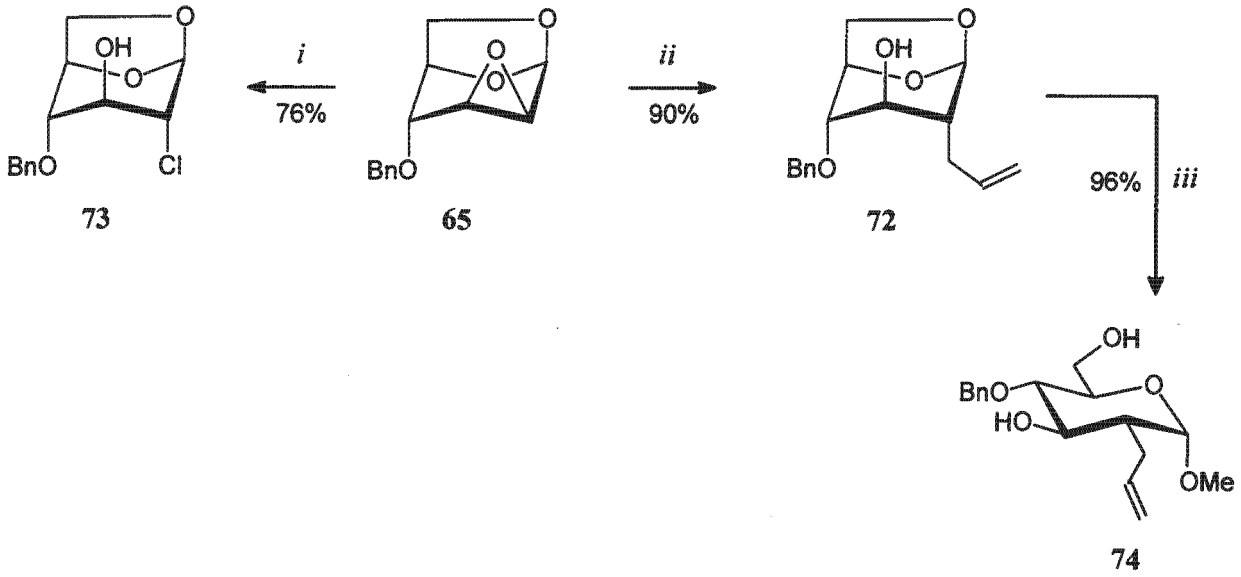
The regioselectivity of epoxide opening is determined by the conformation of the ring containing the epoxide group.[52,59-61] The pyranoid rings of **63**, **64** and **65** adopt half-chair conformations, with nucleophilic attack occurring at C-2 for **63** and **65** and at C-3 for **64**. This is 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.



Scheme 10 *Reagents and conditions*: *i*) CH_2CRCH_2MgCl, THF, reflux; *ii*) Swern oxidation; *iii*) Et_3N, 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 $^1C_4$ configuration, is well known to generate *trans*-diaxial 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.



Scheme 11 *Reagents and conditions*: *i*) C_3H_5MgCl, THF; *ii*) C_3H_5MgCl, Et_2O; *iii*) MeOH, HCl

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 Me_3Al or aqueous 1 M NaOH leads after filtration through silica gel to complete removal of tin residues. The Me_3Al 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 α-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**).[70,73-75]

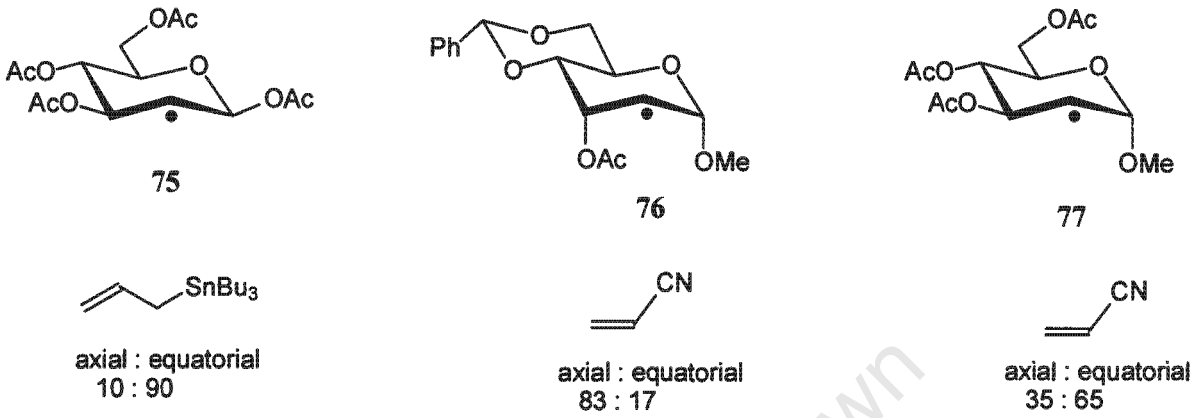
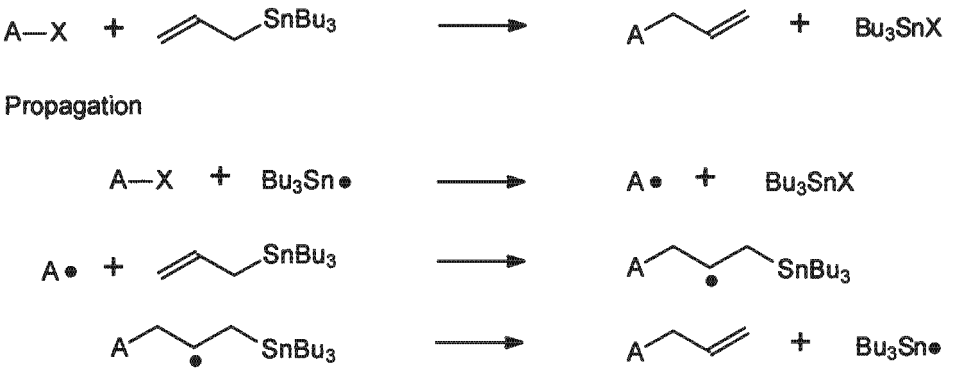


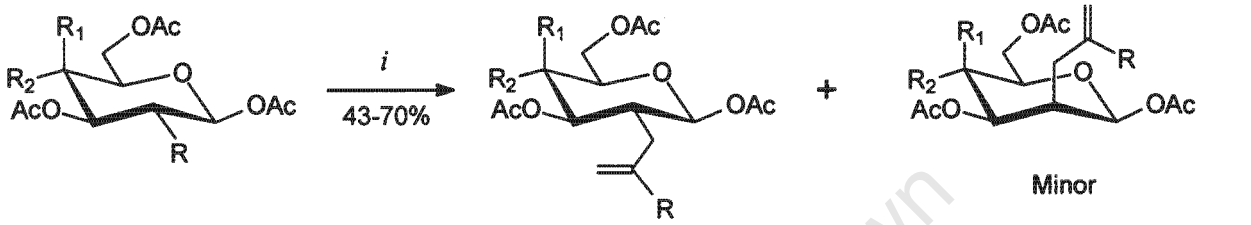
Figure 14 Stereoselective radical alkylation at C-2

Allyltributylstannane and methallyltributylstannane[71] 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.[76] Three distinct steps occur in radical reactions: initiation, propagation and termination, and the accepted chain mechanism for allylation 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.[70] 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.[71]



Scheme 12 Propagation step in intermolecular alkylation

Gieses'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.



78b R = Br, R_1 = H, R_2 = OAc
79 R = I, R_1 = H, R_2 = OAc
80 R = I, R_1 = OAc, R_2 = H

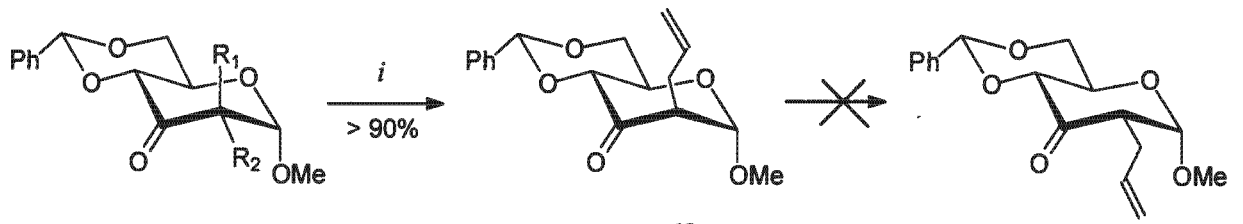
81a R = H, R_1 = H, R_2 = OAc
82a R = CH_3, R_1 = H, R_2 = OAc
83a R = CH_3, R_1 = OAc, R_2 = H

81b R = H, R_1 = H, R_2 = OAc
82b R = CH_3, R_1 = H, R_2 = OAc
83b R = CH_3, R_1 = OAc, R_2 = H

Scheme 13 *Reagents and conditions*: *i*) Methallyltributylstannane or allyltributylstannane, AIBN, benzene, reflux

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 α-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 α-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).



84 R_1 = OBz, R_2 = H
85 R_1 = H, R_2 = OBz

68

70

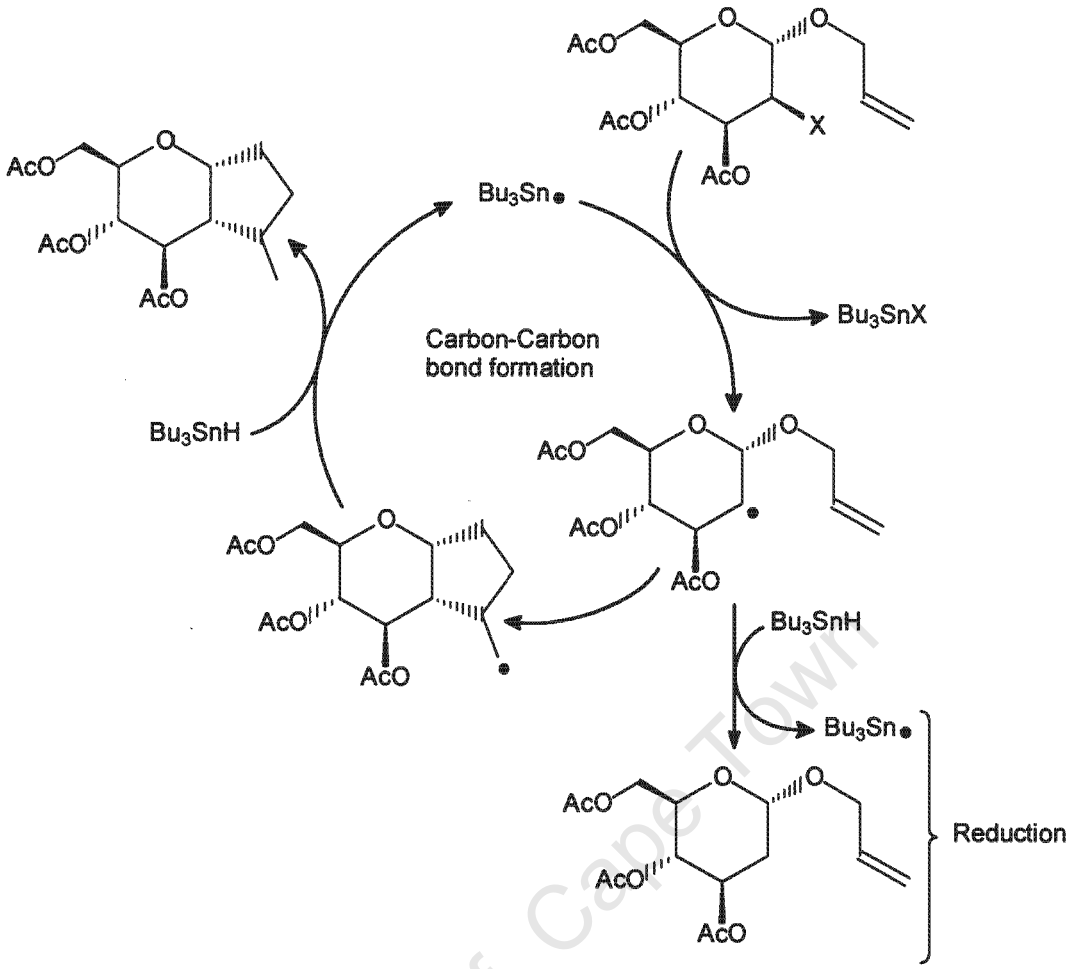
Scheme 14 *Reagents and conditions*: *i*) Allyltributylstannane, AIBN, benzene, reflux

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.[78]

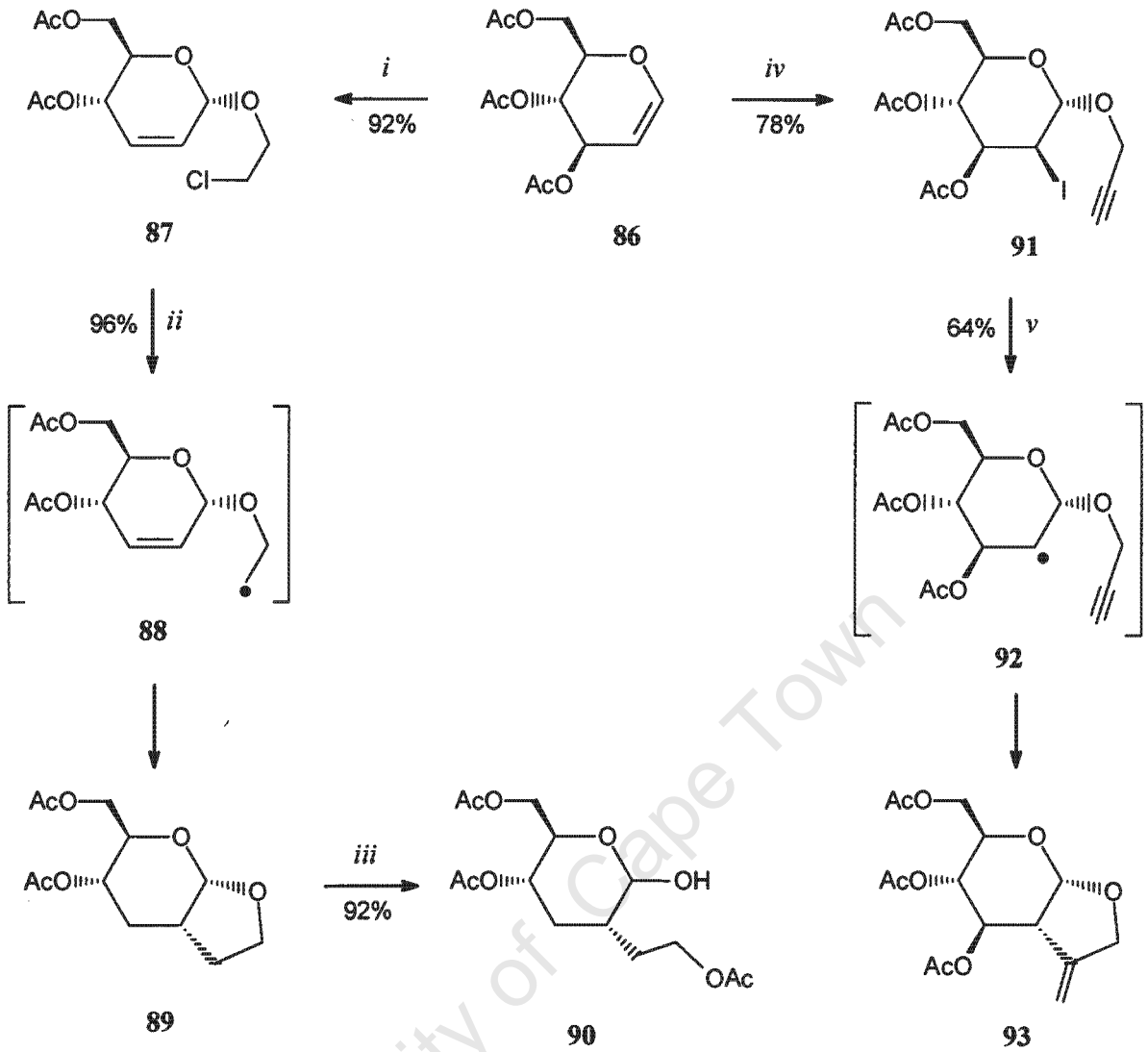
The reaction is carried out in the presence of tributyltin hydride and a radical initiator (e.g. AIBN). The general mechanism for the formation of a carbon-carbon bond onto a double bond using tin radicals is illustrated (Scheme 15).[70,79,80] The generated tributyltin radical abstracts X (where X is 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).



Scheme 15 Propagation step in intramolecular carbon-carbon bond formation

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.[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 *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 $CoCl_2$ to give compound **90** in good yield.



Scheme 16 *i*) $HOCH_2CH_2Cl$, $BF_3{\cdot}Et_2O$, toluene, rt; *ii*) *n*-Bu_3SnH, AIBN, toluene, reflux; *iii*) $CoCl_2$, MeCOCl, MeCN, 0 °C, then hydrolysis on silica gel; *iv*) $HOCH_2C{\equiv}CH$, NIS, MeCN, rt; *v*) *n*-Bu_3SnH, AIBN, toluene, reflux

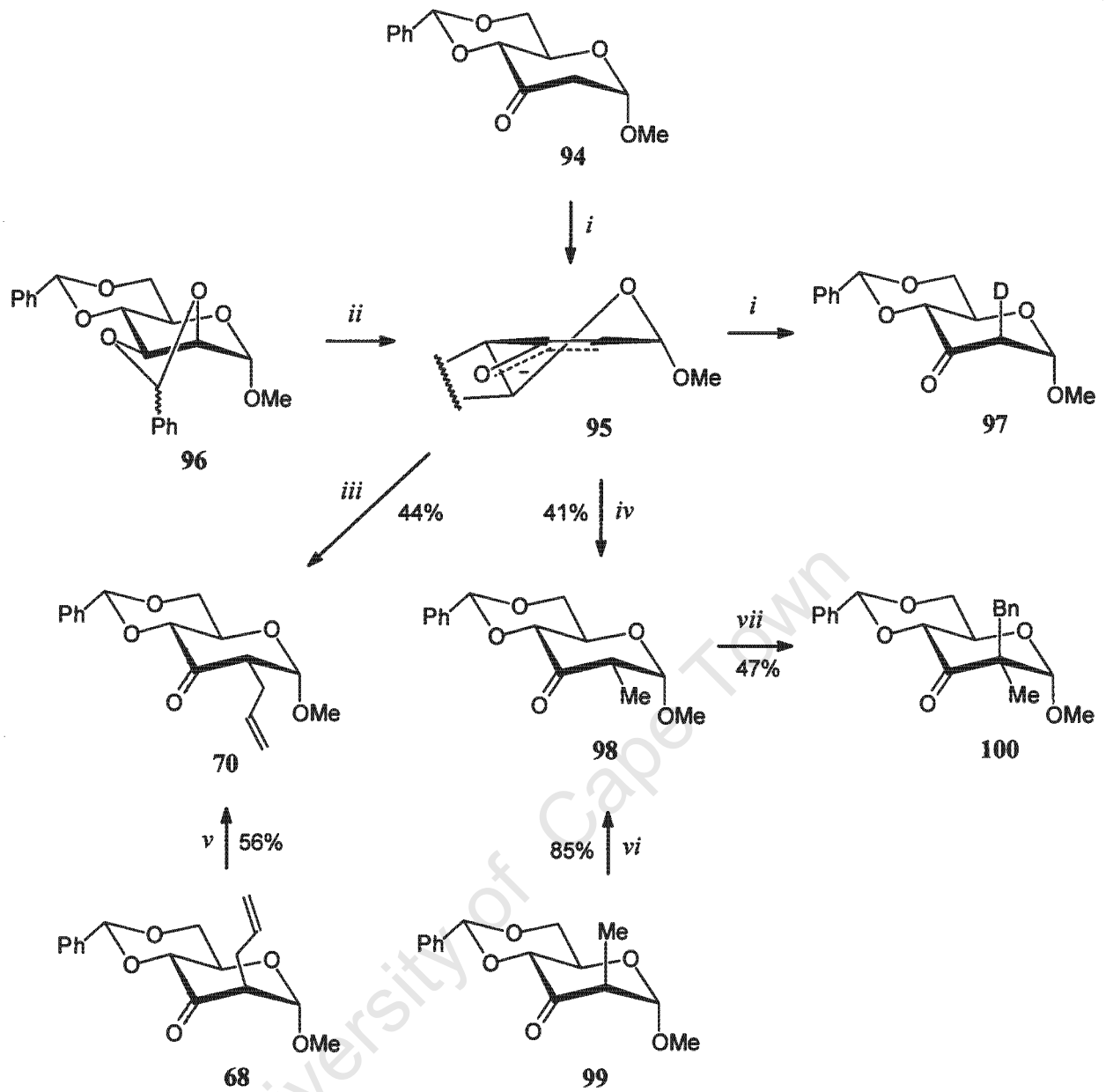
Other recent related work described complementary reactions in which the initial radical precursor X is centred on the pyranosidic ring (C-2) and the radical acceptor (C≡C) is located on the glycosidic side chain.[81] The radical precursor **91** was prepared, mainly as an α-isomer, by reaction of tri-*O*-acetyl-glucal **86** with propargylic alcohol in the presence of NIS (Scheme 16). The anticipated product **93** having a tetrahydrofuranyl 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 Bu_3SnH 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 Bu_3SnH, 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-hexopyranosid-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

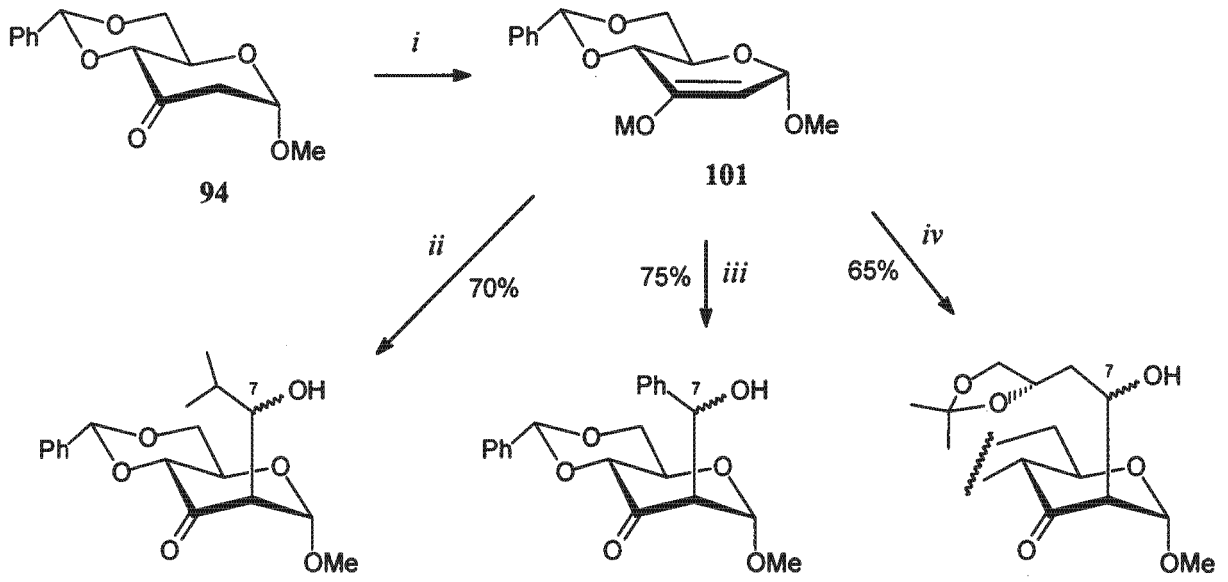
Alkylation of the same enolate **95** with allyl bromide or methyl bromide gives the 2-C-allyl-2-deoxy- or 2-deoxy-2-C-methylglycosides **70** or **98** (Scheme 17).[89] At first sight, the formation of the branched-chain sugars **70** and **98** with equatorial C-2 allyl or methyl groups appears to 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-altropyranosidse **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**[62] and **98**.[67]

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-erthryo-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-workers[90] 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*) $ZnCl_2$, isobutylraldehyde, −78 °C; *iii*) $ZnCl_2$, benzaldehyde, −78 °C; *iv*) $ZnCl_2$, 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 ($Ph_3P{=}CR_1R_2$). The reaction is easy to carry out and proceeds under mild conditions. When electron-withdrawing groups are present at the α-position (i.e. $=CO_2R_3$, CHO, SO_3R_3, 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

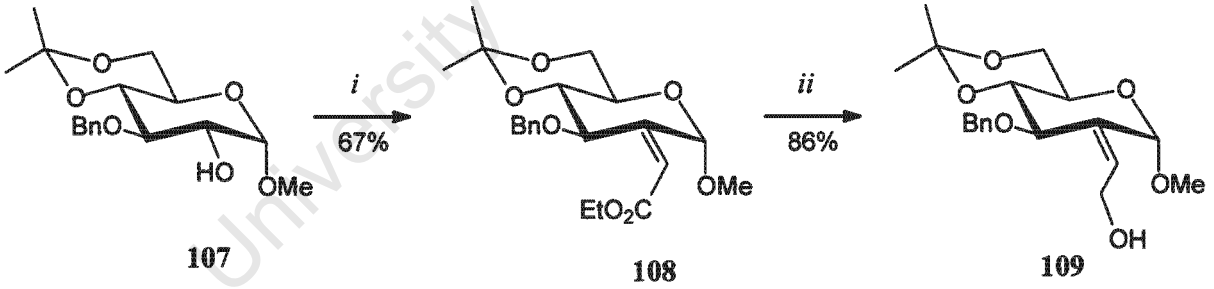
$Ph_3\overset{+}{P}-\bar{C}R_1R_2$ **(105)**

$(R_3O)_2P(O)\bar{C}R_1R_2$ **(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**, $R_1 = CO_2R_3$) and most phosphonate anions **106** give predominantly *E*-alkenes. On the other hand, non-stabilized ylides (e.g. **105**, R_1 and R_2 = 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 = H, $R_2 = CO_2Me$, $R_3 = CF_3CH_2$) 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]

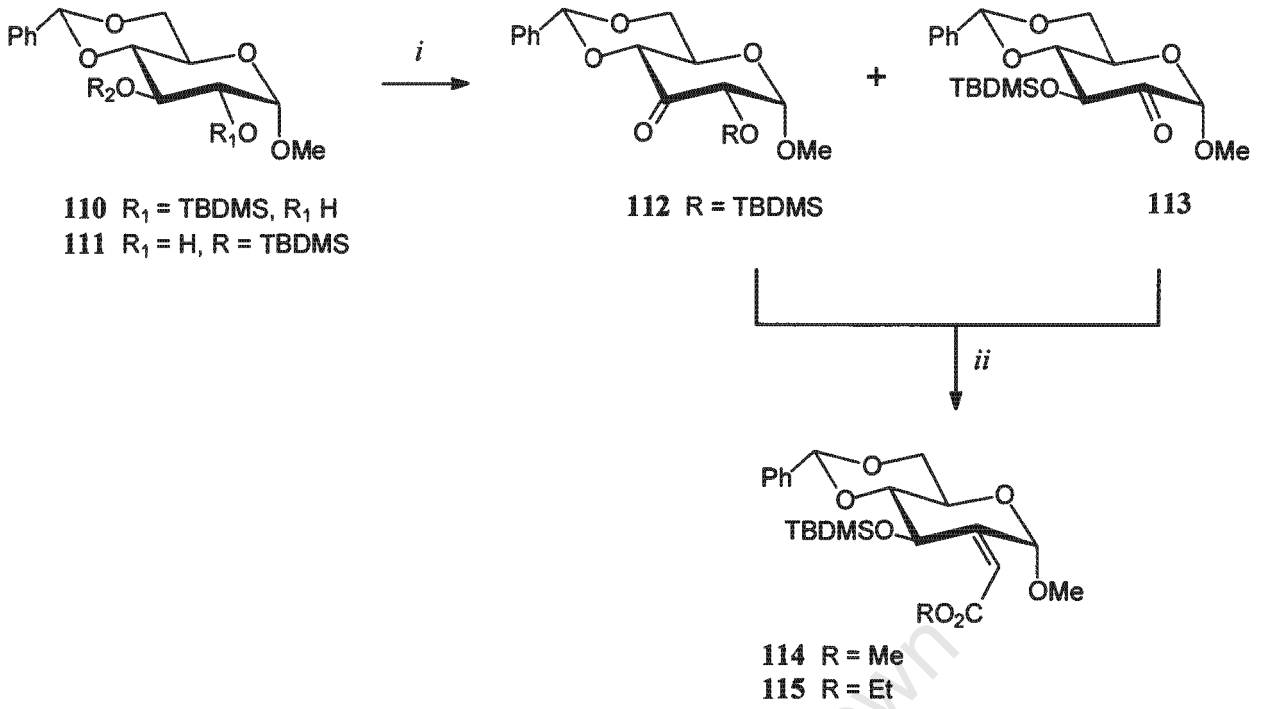
Wittig and related reagents have been extensively used with sugar derivatives such as uloses,[85,94-96] ketoses and particularly aldoses with which they have been successful in producing chain-extended sugars and related compounds. Thus, oxidation of readily available methyl-4,6-*O*-isopropylidene-α-D-glucopyranoside **107** gave the 2-ulose derivative which was subjected to two-carbon homologation using $Ph_3P{=}CHCO_2Et$ in refluxing acetonitrile to afford **108** (Scheme 19).[95] Reduction of **108** with LAH in ether at 0 °C produced the allylic alcohol **109**.



107 **108** **109**

Scheme 19 *Reagents and conditions*: *i*) (a) TFAA, DMSO, Et_3N, DCM, −78 °C; (b) $Ph_3P{=}CHCO_2Et$, CH_3CN, reflux; *ii*) LAH, ether, 0 °C

In another example, silylation of methyl 4,6-*O*-benzylidene-α-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_2Cl_2) to give the ketones **112** and **113**. However, separate treatment of **112** and **113** with Wittig reagent ($Ph_3P{=}CHCO_2Me$, MeCN, reflux) led surprisingly to exclusive formation of the same C-2 olefin **114** in each case. Repeating the experiments with $Ph_3P{=}CHCO_2Et$ gave the same unexpected results, leading to formation of the olefin **115** from both **112** and **113**.[94]



110 R_1 = TBDMS, R_1 H
111 R_1 = H, R = TBDMS

112 R = TBDMS

113

114 R = Me
115 R = Et

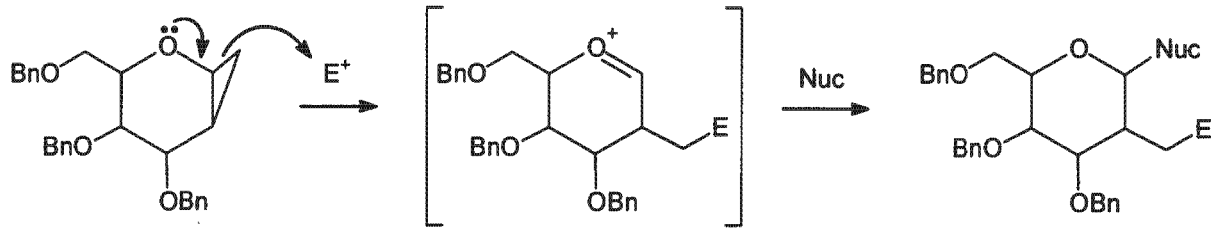
Scheme 20 *Reagents and conditions*: *i*) PCC, CH_2Cl_2; *ii*) $Ph_3P{=}CHCO_2R$, MeCN, reflux

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_3N, 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.[94]

1.6.5 Opening of 1,2 cyclopropanes

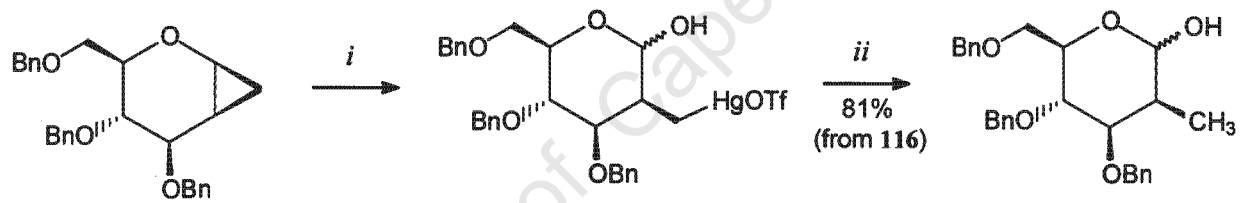
Cyclopropanes are versatile functional groups in organic synthesis, and cyclopropanation has recently been extended to carbohydrates where several methods have been developed for stereocontrolled cyclopropanation of glycals. In general, zinc-mediated cyclopropanation under modified Simmons-Smith conditions 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.[97]

Cyclopropanated carbohydrates are ideally suited for electrophilic ring opening and this has been extensively investigated.[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.[97]



Scheme 21 General mechanism for most cyclopropane ring-opening

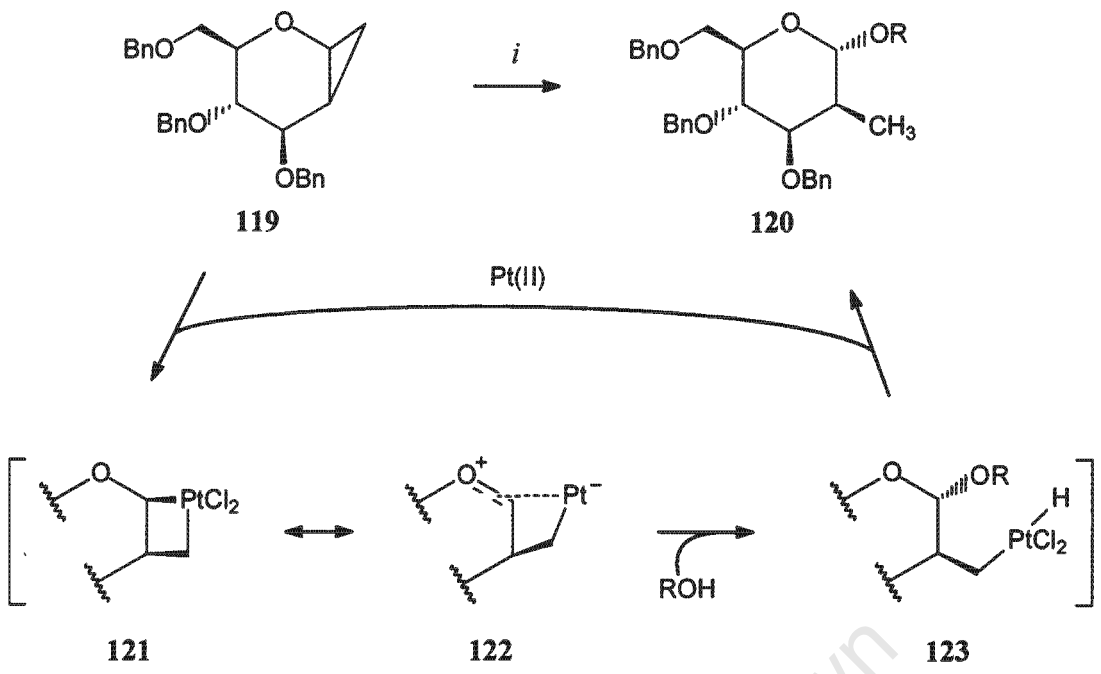
The use of mercury(II) ion to catalyze the opening of various cyclopropanes has been reported and Heathcock used this strategy in the reaction of cyclopropanated sugars and the synthesis of a 2-C-methyl glucal. Treatment of cyclopropane sugar **116** with mercuric trifluoroacetate in the presence of water provided the organomercurial **117** as a mixture of anomers (Scheme 22). Reductive cleavage of the organomercury intermediate with Bu_3SnH 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]



116 **117** **118**

Scheme 22 *Reagents and conditions*: *i*) $Hg(OTf)_2$, H_2O, THF, rt; *ii*) *n*-Bu_3SnH, AIBN, toluene, reflux

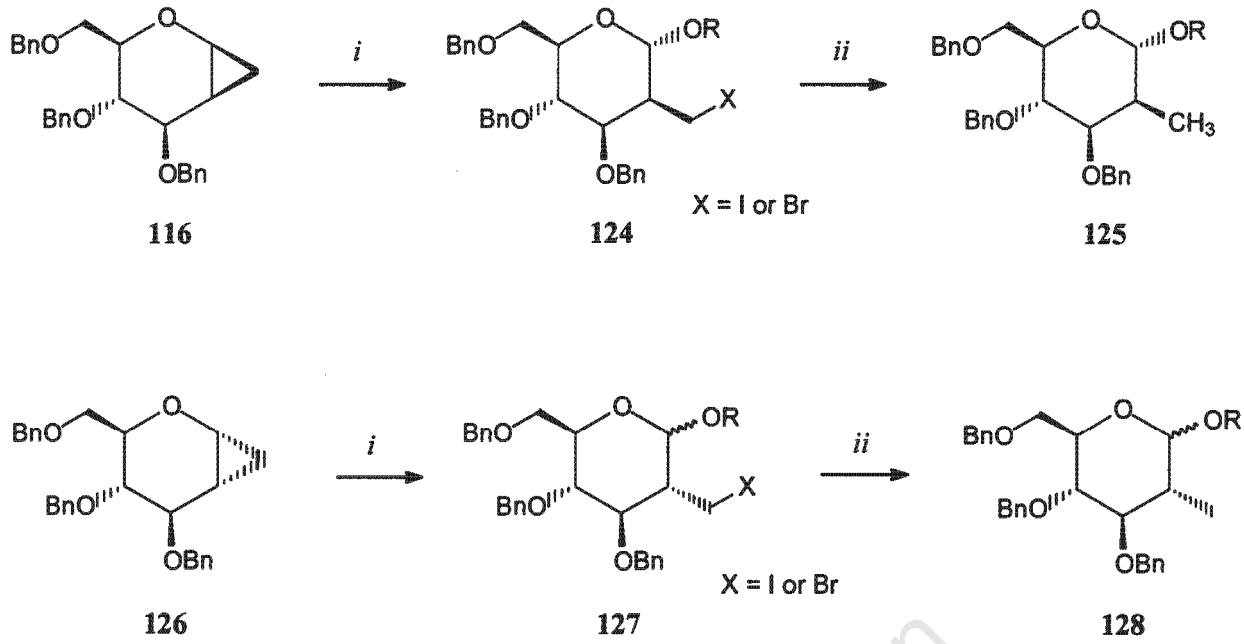
Another example of a metal-induced ring-opening, developed by Madsen, uses catalytic amounts of the platinum complex, Zeise's dimer $[Pt(C_2H_4)Cl_2]_2$ (Scheme 23).[97,98,100] The ring opening was achieved with a variety of alcohols to produce 2-C-branched methyl glycoside **120** and other more complex 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.



Scheme 23 *Reagents and conditions*: *i*) $[Pt(C_2H_4)Cl_2]_2$, ROH, CH_2Cl_2, rt

A suggested reaction sequence for the ring opening involves oxidative addition of the platinum to the cylcopropane to give a platinacyclobutane **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.

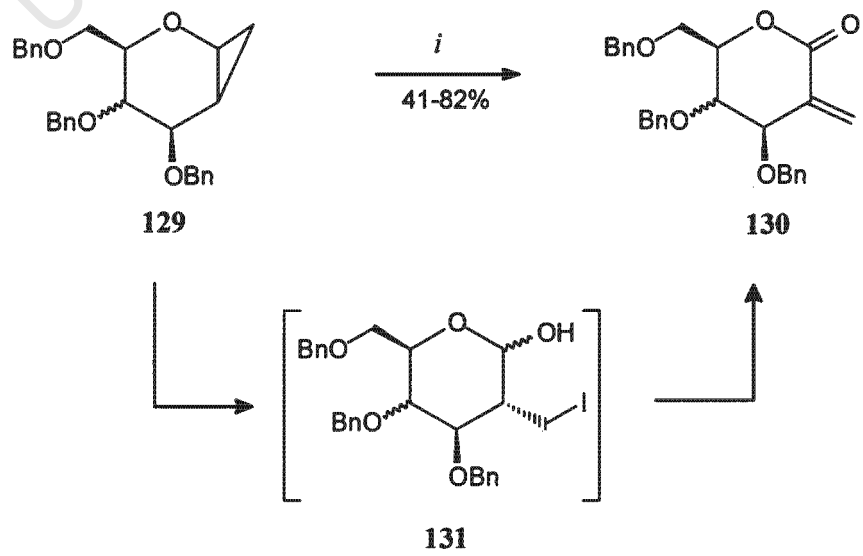
Another recently developed strategy for ring opening of the cyclopropane moiety was originally reported by Danishefsky and co-workers.[103,104] Both Ley[101] and Nagarajana[99] have reported on conversion of the diastereomeric cyclopropanes **116** and **126** using NBS as well as NIS (Scheme 24). Yields 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**.



Scheme 24 *Reagents and conditions*: *i*) NIS or NBS, ROH, rt; *ii*) *n*-Bu_3SnH, AIBN, toluene, reflux

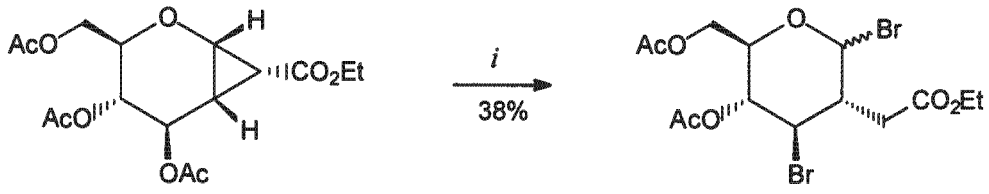
Nagarajana attributed this difference in reactivity and selectivity to an S_N2-type ring opening of the more sterically hindered **116** producing the more favoured α-glycosides, while formation of **128**, in which ring opening is unhindered, presumably involves an S_N1-type pathway.

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 α-methylidenevalerolactones **130** in acceptable yields.[105] This reaction was shown to proceed through the intermediate iodide **131**, which subsequently undergoes elimination and oxidation.



Scheme 25 *Reagents and conditions*: *i*) Dioxane-H_2O, [s-collidine]$_2I^+$ ClO_4^-

A final example of an electrophilic ring opening is illustrated in Scheme 26 using the ester-substituted cylcopropane **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]



132 **133**

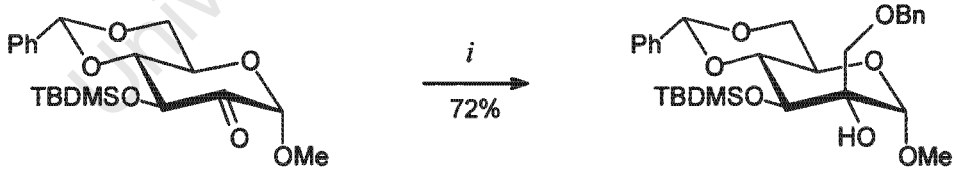
Scheme 26 *Reagents and conditions*: *i*) 30% HBr in AcOH

1.6.6 Others

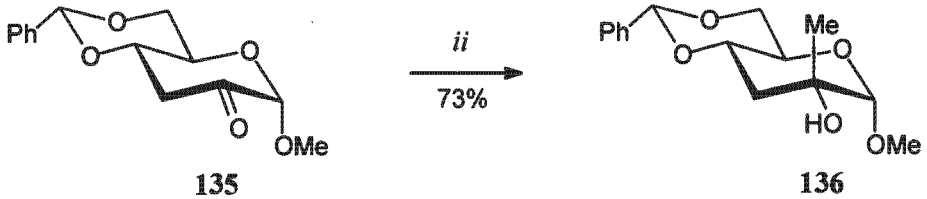
Several other methods for C-2 alkylation in carbohydrates derivatives have been reported and these include:

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 benzyloxymethyllithium gave **134** in good yield (Scheme 27).[107]



113 **134**



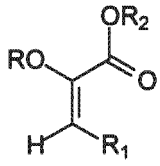
135 **136**

Scheme 27 *Reagents and conditions*: *i*) Bu_3SnCH_2OBn, *n*-BuLi, THF; *ii*) MeMgI, Et_2O

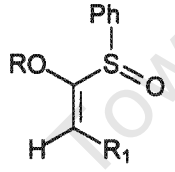
Similarly, treatment of ketone **135** with MeMgI gave **136** in good yield (Scheme 27).[108] The complete stereoselectivity was strongly influenced by the axial methoxy group.

1.6.6.2 C-2 Lithiation / Trapping

Direct lithiation at the α-vinylic position of functionally substituted acrylates has become a versatile tool in organic synthesis because the vinyllithium 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**.



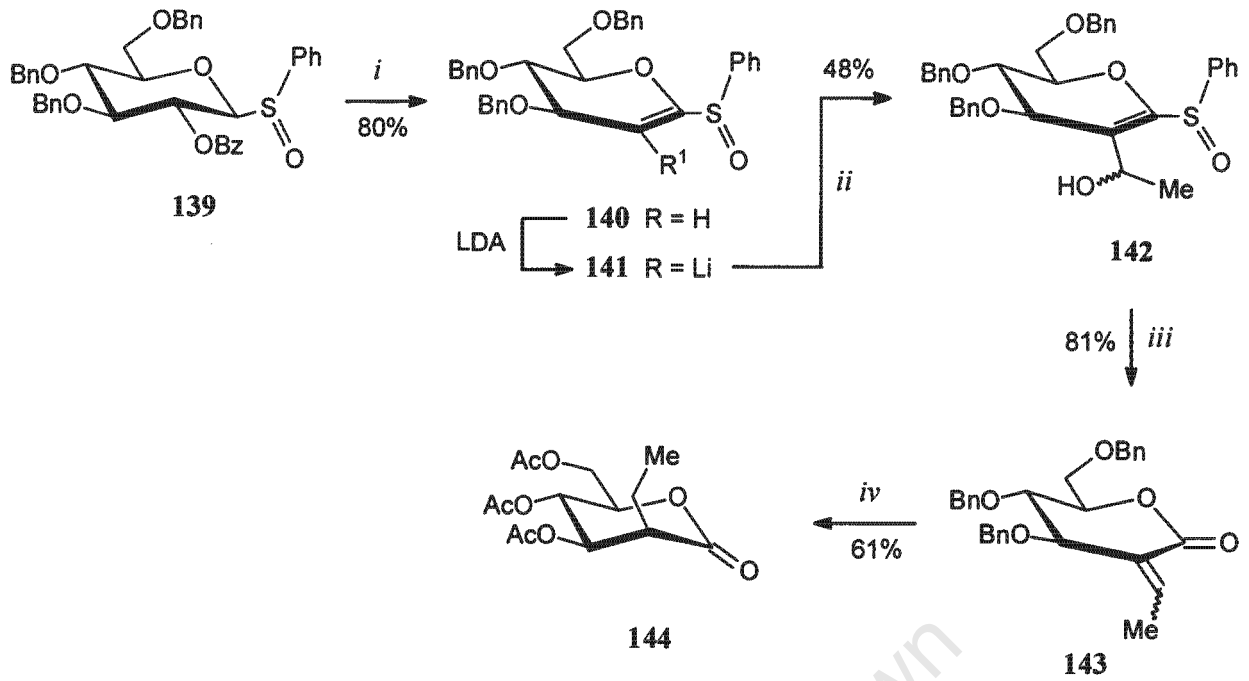
137 R_1 = H, Li



138 R_1 = H, Li

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.[111]

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.

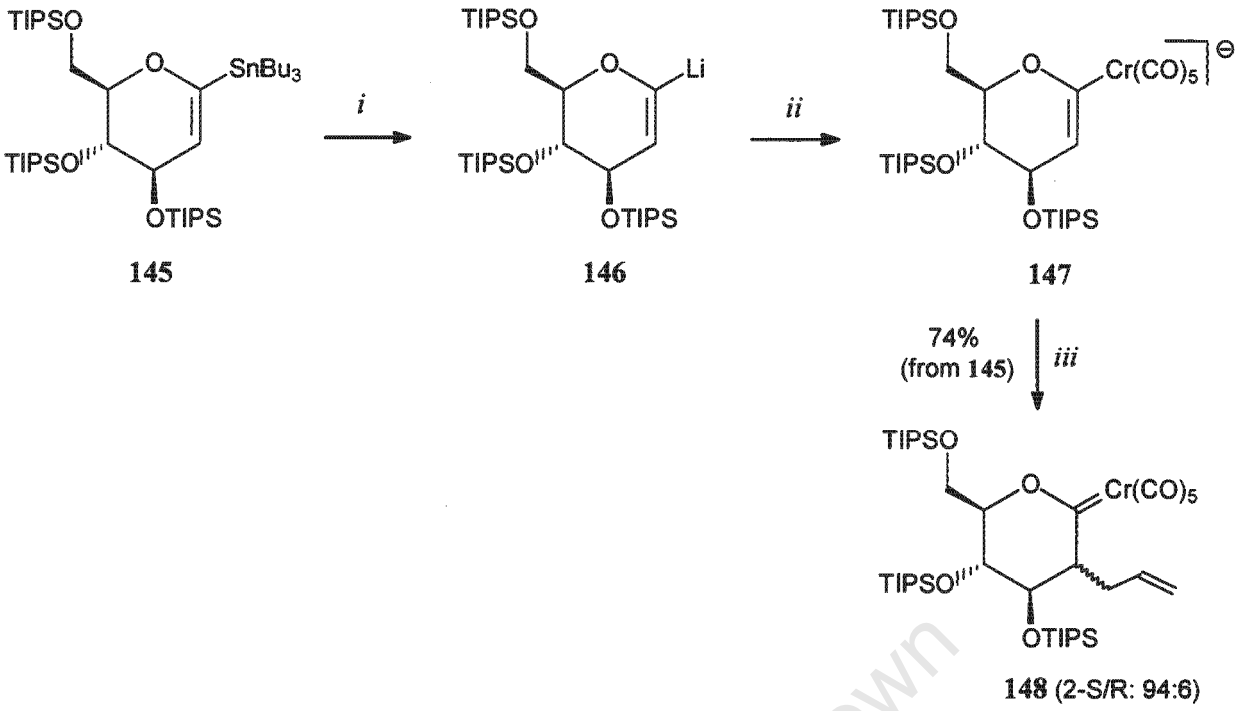


Scheme 28 *Reagents and conditions*: *i*) LDA, −80 °C; *ii*) MeCHO, −80 °C; *iii*) H^+; *iv*) (a) Pd / C, H_2; (b) Ac_2O, pyridine

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.[111]

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 $K_2M(CO)_5$-'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-lithioglucal **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 lithioglucal 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

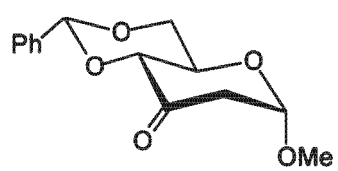
According to the retrosynthetic analysis depicted in Scheme 7 (Section 1.5), the synthesis of the target compounds was envisaged as beginning with the introduction of an alkenyl group at C-2 of glucose or mannose followed by its conversion to a suitable glycosyl donor *via* anomeric modification. Resolution 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.

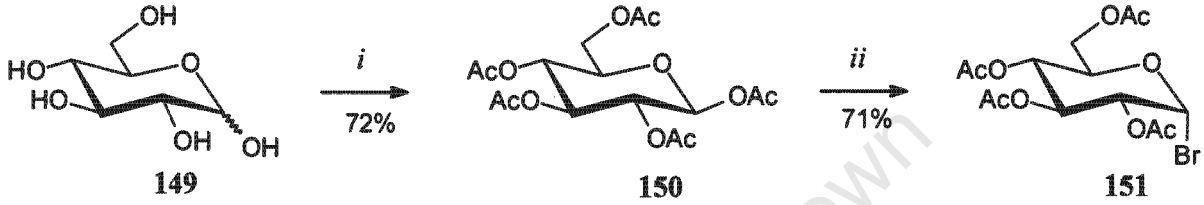


94

Figure 15

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 β-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 δ 5.70 for H-1 with a large vicinal diaxial[c] coupling ($J_{1,2}$ 8.1 Hz).



Scheme 30 *Reagents and conditions*: *i*) Ac_2O, NaOAc, reflux, 1 h; *ii*) HBr (30% in acetic acid), CH_2Cl_2, rt, 2 h

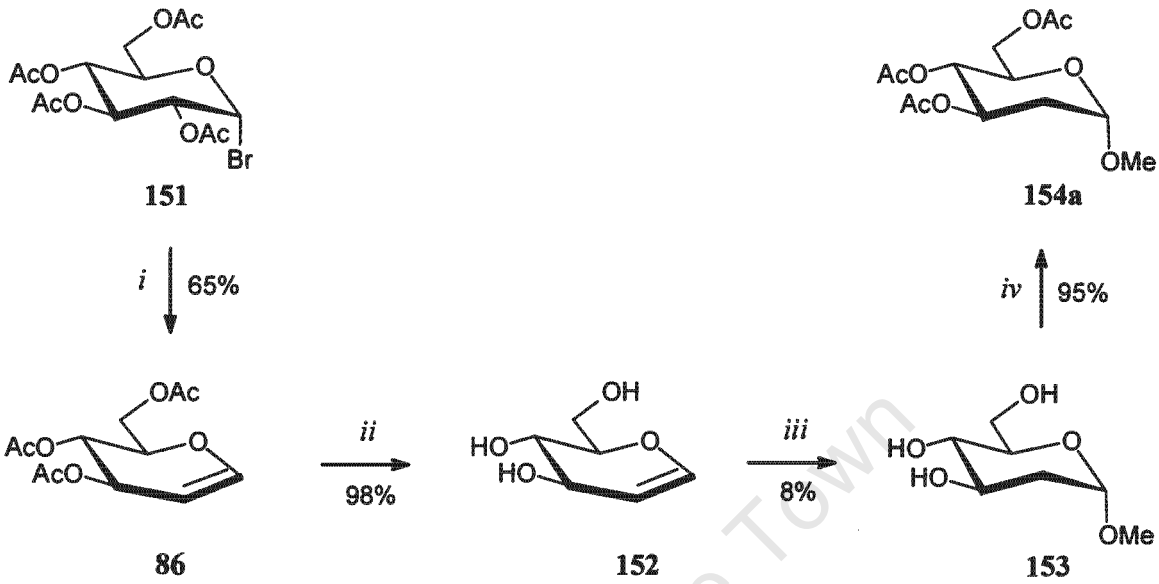
Treatment of **150** with 30% HBr in acetic acid at room temperature produced tetra-*O*-acetate-α-D-glucopyranosyl bromide **151** in excellent yield (Scheme 30).[114] The α-bromide is expected from the dominance of the anomeric effect.

The presence of bromide was supported by a downfield shift of the anomeric proton from δ 5.70 in **150** to δ 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 $(CP_2TiCl)_2$ 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 δ 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).

[c] 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).[118] 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.



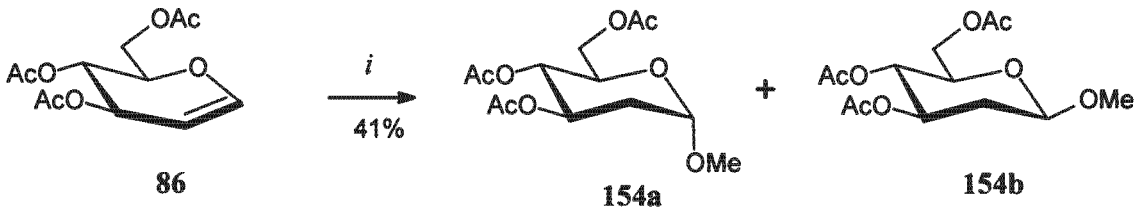
Scheme 31 *Reagents and conditions*: *i*) Zn, AcOH, rt, 2 h; *ii*) NaOMe, MeOH-CH_2Cl_2, rt, 18 h; *iii*) HCl (2.5% in MeOH), 60 °C, 1 h; *iv*) Ac_2O, pyridine, rt, 16 h

Treatment of **152** with 2.5% HCl in methanol gave methyl 2-deoxy-α-D-arabino-hexopyranoside **153** in poor yield (8%) (Scheme 4).[119] 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.[120] 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,[121] acetylated glucal **86** was subjected to direct treatment with methanol in the presence of cation exchange resin (AG

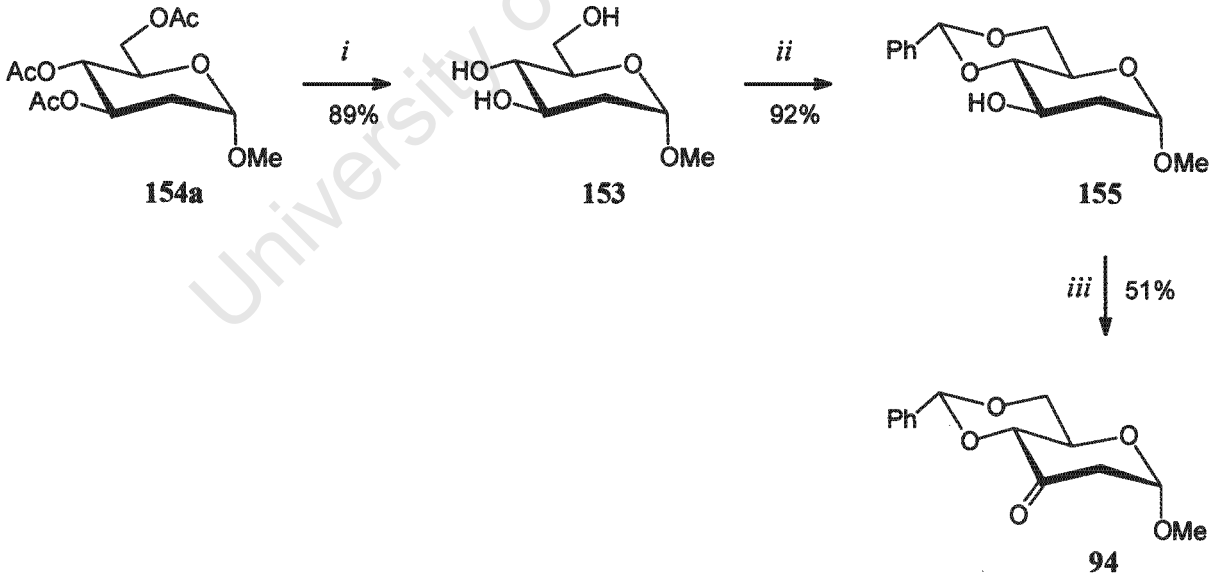
50W × 8 H^+, 50-100 mesh) and LiBr at room temperature to give an anomeric mixture of methyl tri-*O*-acetyl-2-deoxy-D-arabino-hexopyranosides **154a** and **154b** (2:1, by ^1H NMR) in a combined 41% yield (Scheme 32), accompanied by some unreacted starting material. The desired α-anomer **154a** was obtained after separation by column chromatography. Spectroscopic data of **154a** was in agreement with the literature values[121] and characterization was carried out as before.



86 **154a** **154b**

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.



154a **153** **155** **94**

Scheme 33 *Reagents and conditions*: *i*) NaOMe, MeOH-CH_2Cl_2, rt, 18 h; *ii*) Benzaldehyde, $ZnCl_2$, rt, 3 days, *iii*) Jones oxidation

Jones oxidation of **155** gave methyl 4,6-benzylidene-2-deoxy-α-D-erythro-hexopyranosid-3-ulose **94** in 51% yield (Scheme 33).[114] In this reaction the starting material and product had the same R_f value (tlc), making it difficult to judge the progress of the reaction. However, changing the reagent

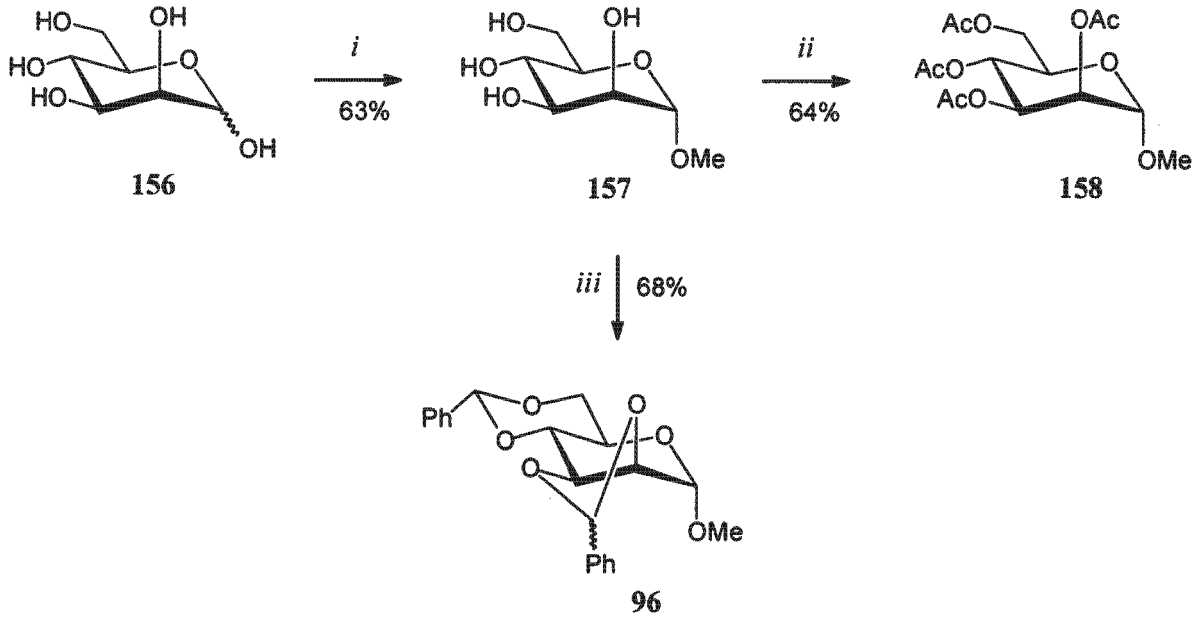
for visualizing components on the tlc plate from acidified ammonium ceric sulfate to acidified anisaldehyde revealed a colour difference, with the starting material showing up brown and the product green.

The ^{1}H NMR spectrum of **94** displayed a doublet at δ 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 ~90°. Thus, the signal for H-1 appeared as a doublet at δ 5.12 with a coupling constant $J_{1,2ax}$ of 4.3 Hz while the signal for H-2_{ax} appeared at δ 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 δ 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 δ 197.39 confirmed the formation of the ketone, with the corresponding disappearance of the signal at δ 65.90 for C-3 in alcohol **155**. In addition, its IR spectrum displayed an absorption at ν_{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-α-D-mannopyranoside, which can be readily prepared from commercially available methyl-α-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-α-D-mannopyranoside **158** in good yield (Scheme 34).[122] The stereochemistry at C-1 was assigned on the basis of a signal at δ 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).

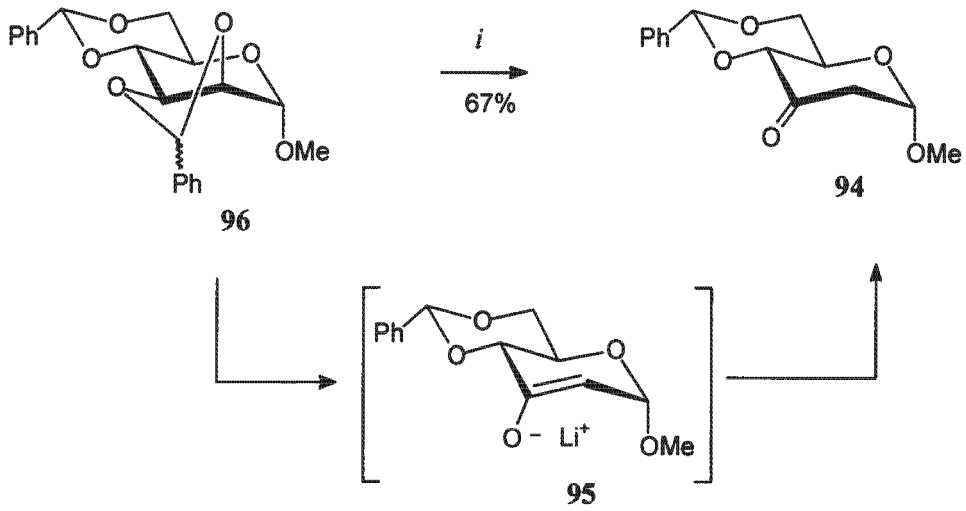


Scheme 34 *Reagents and conditions*: *i*) MeOH, Dowex-50 (H^+) resin, *ii*) Ac_2O, NaOAc, reflux, 30 min; *iii*) α,α-dimethoxytoluene, TsOH, DMF, 75 °C, 4 h (1:1)

Following the procedure of Horton,[123] compound **157** was then treated with α,α-dimethoxytoluene to give methyl dibenzylidene-α-D-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 δ 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 δ 5.01 (diastereomer **96a**) and δ 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 δ 4.14 for H-2 with a moderate axial-equatorial coupling constant ($J_{2,3}$ 5.6 Hz), thus showing no coupling with the anomeric proton.

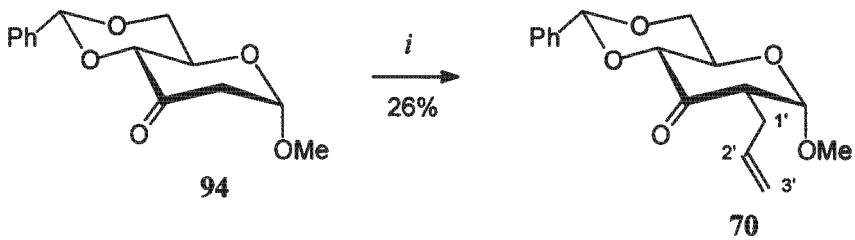
Treatment of the dibenzylidene acetals **96** with *n*-butyllithium at –30 °C followed by quenching with water gave ketone **94** in a moderate yield (Scheme 35). This highly regioselective elimination is thought to occur by preferential abstraction of the axial C-3 proton followed by anti-elimination 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.[123] The spectroscopic and analytical data of this compound were identical with those of material prepared previously.



Scheme 35 *Reagents and conditions*: *i*) (a) *n*-BuLi, THF, −30 °C, 1 h (b) H_2O

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[89] 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 δ 5.76 (m, H-2′), δ 2.59 (m, H-1′$_a$) and δ 2.22 (m, H-1′$_b$), while the ^{13}C NMR spectrum displayed corresponding signals at δ 134.90 (C-2′), 117.24 (C-3′) and 28.21 (C-1′).



Scheme 36 *Reagents and conditions*: *i*) (a) LDA, THF, −78 °C, 15 min (b) HMPA, allyl bromide, −40 °C, 11 h

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 δ 5.01 with a moderate axial-equatorial ($J_{1,2}$ 4.0 Hz)

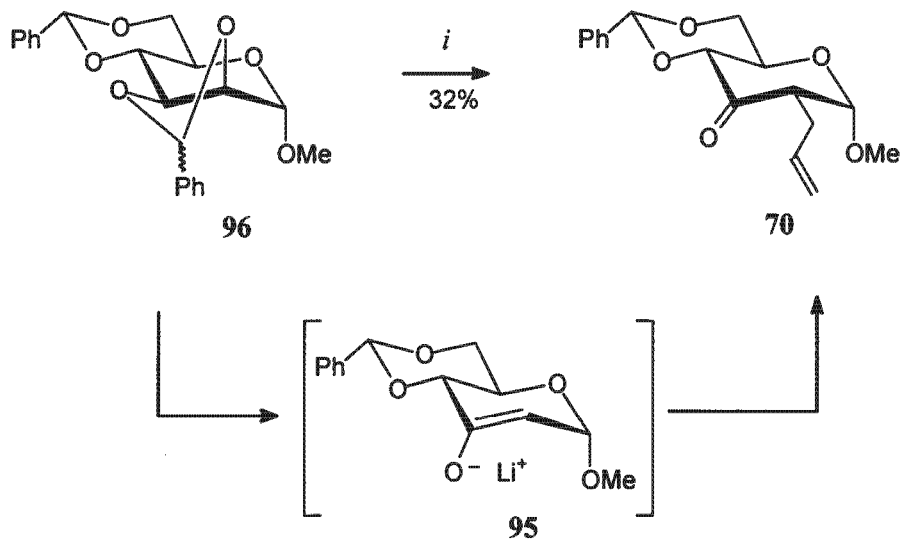
coupling constant, thus confirming the allyl group to be equatorial. In addition, the IR spectrum displayed an absorption at ν_{max} 1755 cm^{-1} (C=O).

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 °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 °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.

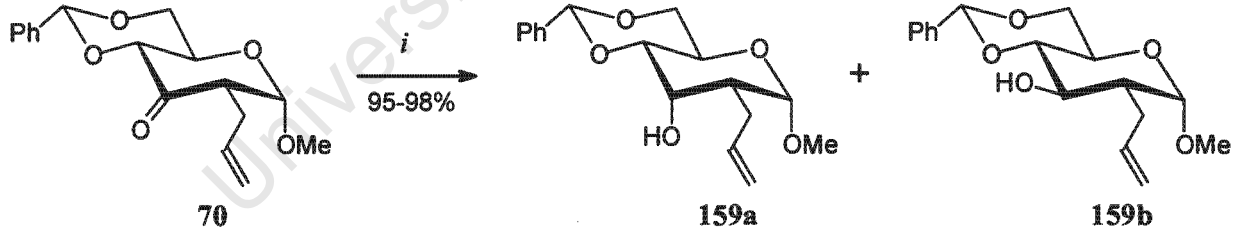
The characterization of the side products by NMR spectroscopy was unsuccessful and no conclusive assignment of the structures could be made. However, benzylidene, allylic and methoxy group signals were observed in both compounds (^{1}H NMR), which suggest that dialkylation and/or O-alkylation might have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

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 $NaBH_4$ 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*) $LiAlH_4$, THF, 0 °C, 2 h, 95% (**159a:159b** = 8:1); or *i*) $NaBH_4$, 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 ^{13}C 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 ($J_{4,5}$ 9.6 Hz) and moderate axial-equatorial ($J_{3,4}$ 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.[125-135] 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).

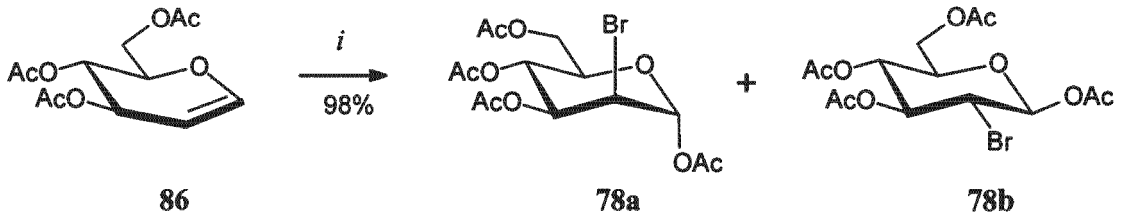
With the above aim in mind, 2-halo sugars with different anomeric groups were synthesized using literature procedures.

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).[125] The diastereomers were easily separated by column chromatography and the spectroscopic data of **78a** and **78b** were in agreement with the literature values.

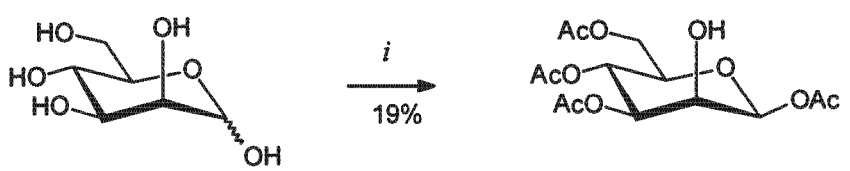


86 **78a** **78b**

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 δ 6.30 with a small equatorial-equatorial ($J_{1,2}$ 1.9 Hz) coupling constant while the signal for H-3 appeared at δ 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 δ 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 α-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 β-gluco-configuration.

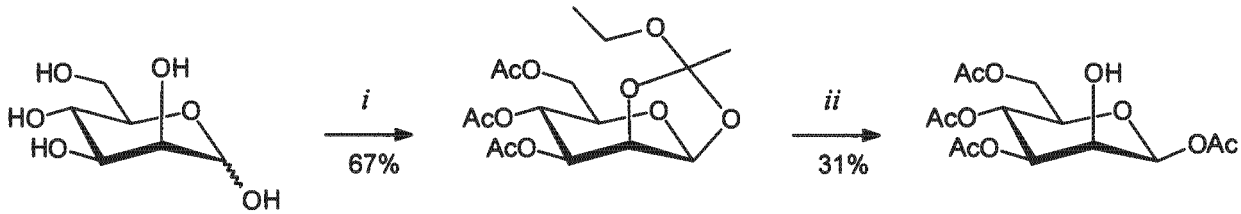
In a second approach, synthesis of the 2-bromo and 2-iodo tetraacetates was envisaged from selectively unprotected D-mannopyranose derivative **160** *via* formation of the 2-triflate and subsequent displacement by halide ion. Selectively unprotected sugar **160** could be obtained in a one-pot synthesis 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).[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).



156 **160**

Scheme 40 *Reagents and conditions*: *i*) (a) Ac_2O, $HClO_4$, 40-50 °C, 1 h (b) PBr_3, 20-25 °C (c) H_2O, 25 °C, 1.5 h (d) $NaOAc{\cdot}3H_2O$, 35-40 °C, 25 min

Thus, D-mannose **156** was acetylated and subjected to anomeric 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).[135] The orthoester **161** was then subjected to a controlled acetolysis to afford **160** in 31% yield (Scheme 41).[135]



156 **161** **160**

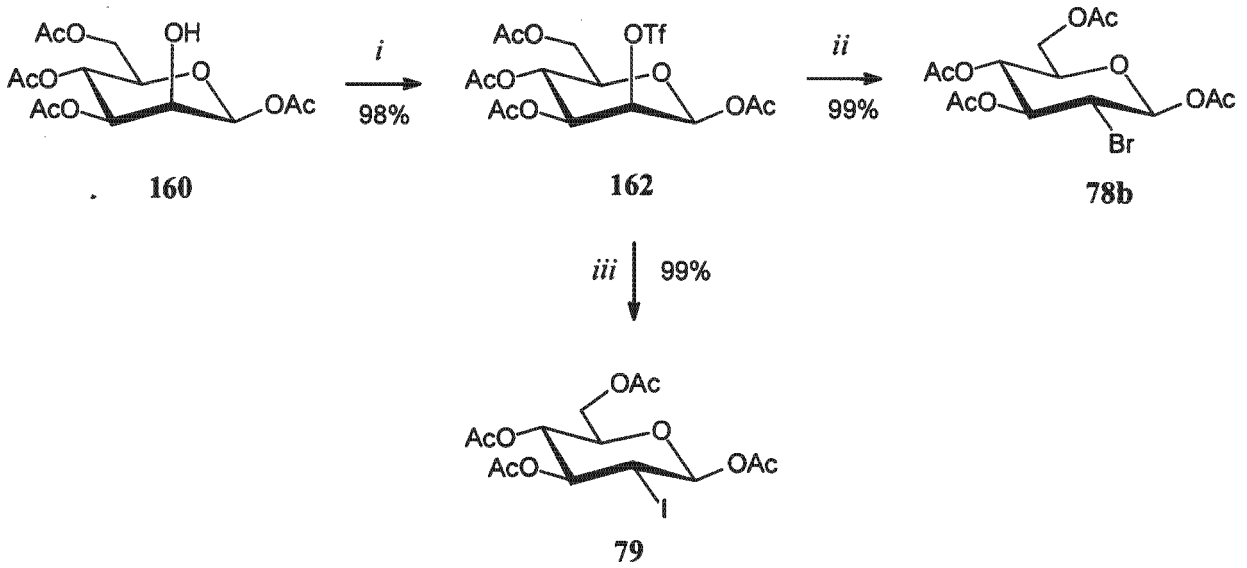
Scheme 41 *Reagents and conditions*: *i*) (a) Ac_2O, NaOAc, 100 °C, 1 h (b) HBr (30% in AcOH), CH_2Cl_2, rt, 3 h (c) lutidine, EtOH, CH_3CN, rt, 15 h; *ii*) 1 N HCl, acetone, rt, 10 min

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 ^1H 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 ^1H NMR spectrum. The signal at δ 5.78 for H-1 appeared as a doublet with a small equatorial-axial ($J_{1,2}$ 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 ($J_{3,4}$ 9.7 Hz) and a moderate axial-equatorial ($J_{1,2}$ 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).[127,135] A downfield shift of the H-2 signal in the ^1H NMR spectrum from δ 4.18 in **160** to δ 5.13 and a shift in the ^{13}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.

S_N2 displacement of the triflate in **162** by bromide ion in refluxing benzene gave 2-bromoglucose derivative **78b** in excellent yield after chromatography and with inversion of configuration (Scheme 42).[127] The spectroscopic and analytical data of **78b** were identical to those of material previously isolated.



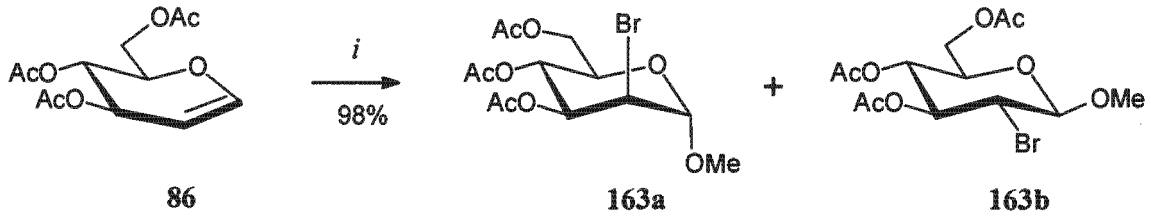
Scheme 42 *Reagents and conditions*: *i*) Triflic anhydride, pyridine, CH_2Cl_2, 0 °C to rt, 2 h; *ii*) Bu_4NBr, benzene, reflux, 2 h, *iii*) Bu_4NI, benzene, reflux, 2 h

Similar treatment of triflate **162** with tetrabutylammonium iodide gave 2-iodo pentaacetate **79** in excellent yield (Scheme 42).[127] 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 ^{13}C 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).[125,126] 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.

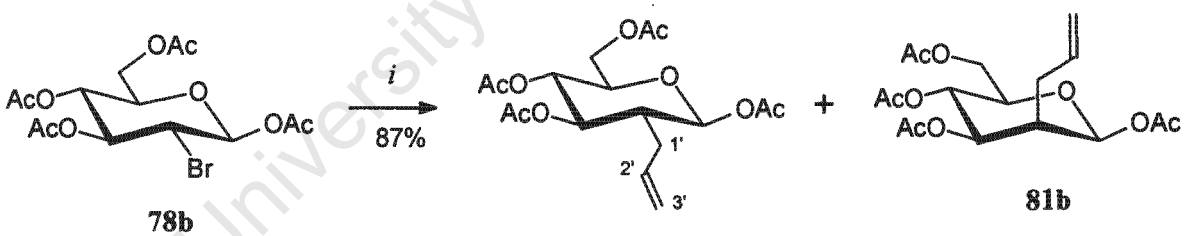


86 **163a** **163b**

Scheme 43 *Reagents and conditions*: *i*) NBS, MeOH, 0 °C, 3 h (**163a:163b** = 2:1)

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 ^{1}H 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.



78b **81a** **81b**

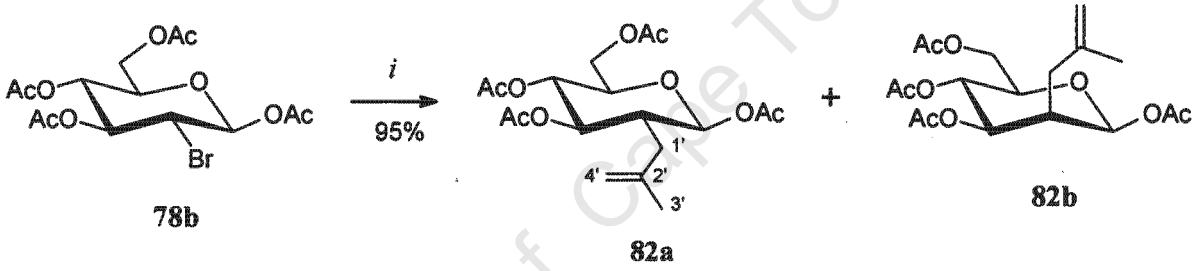
Scheme 44 *Reagents and conditions*: *i*) Allyltributylstannane, AIBN, benzene, reflux, 16 h (**81a:81b** = 9:1)

The spectroscopic data of **81a** and **81b** was consistent with the structures and literature values. For the desired major diastereomer **81a**, the ^{1}H NMR spectrum displayed a diagnostic signal at δ 5.76-5.65 (m) for H-2′ while the ^{13}C 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 ^{1}H NMR spectrum of the major diastereomer **81a** displayed a doublet at δ 5.56 for H-1 with a large diaxial ($J_{1,2}$ 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 δ 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 methallyltributylstananne[137] 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).[77] 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.

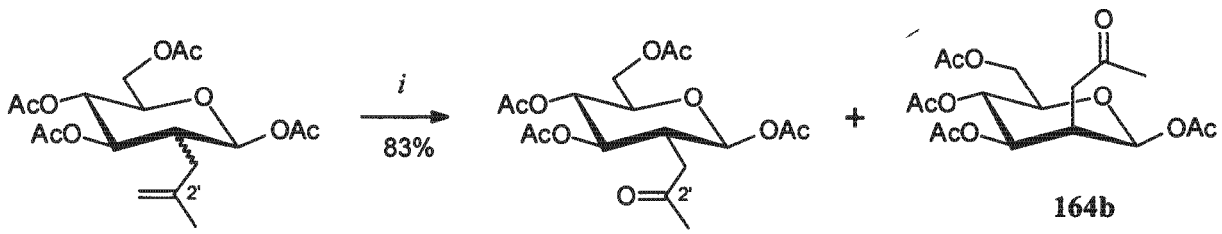


Scheme 45 *Reagents and conditions*: *i*) Methallyltributylstannane, AIBN, benzene, reflux, 16 h (**82a:82b** = 7:1)

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 δ 4.67 (J_{gem} 1.1 Hz) for H-4′$_a$, a doublet at δ 4.63 (J_{gem} 1.1 Hz) for H-4′$_b$ and a broad singlet for the adjacent methyl group at δ 1.73, for the methallyl group. In addition, the ^{13}C NMR spectrum displayed signals at δ 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 δ 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 δ 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[138] of the mixture of **82a** and **82b** followed by reduction with DMS gave a mixture of 2-oxopropyl glucopyranoside **164a** and 2-oxopropyl mannopyranoside **164b** (7:1, by ^{1}H NMR) in excellent yield (Scheme 46).[77] As before, separation of diastereomers by column chromatography was unsuccessful, but crystallization from diethyl ether afforded **164a** as a single diastereomer in 48% yield.

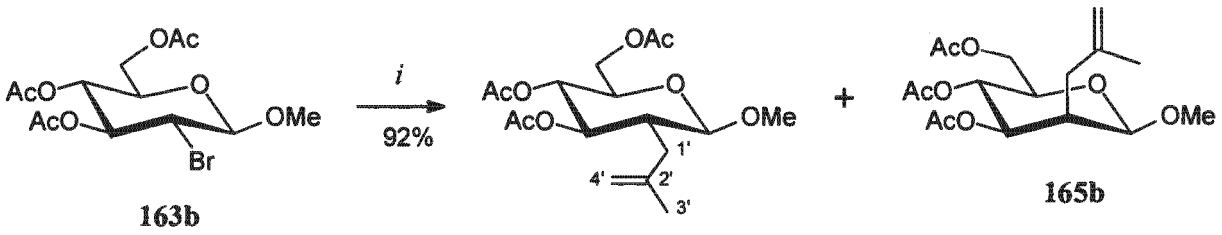


82a / 82b **164a** **164b**

Scheme 46 *Reagents and conditions*: *i*) (a) O_3, CH_2Cl_2-MeOH (10:1), −78 °C, 40 min; (b) DMS, −78 °C to rt, 20 h (**164a:164b** = 7:1)

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

A similar methallylation[77] reaction was then carried out on methyl 2-bromo triacetate **163b**, giving a mixture of methyl 2-C-methallyl glucopyranoside **165a** and methyl 2-C-methallyl mannopyranoside **165b** (5:1, by ^{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.[70] However, several attempts to separate the diastereomers by column chromatography or crystallization were unsuccessful.

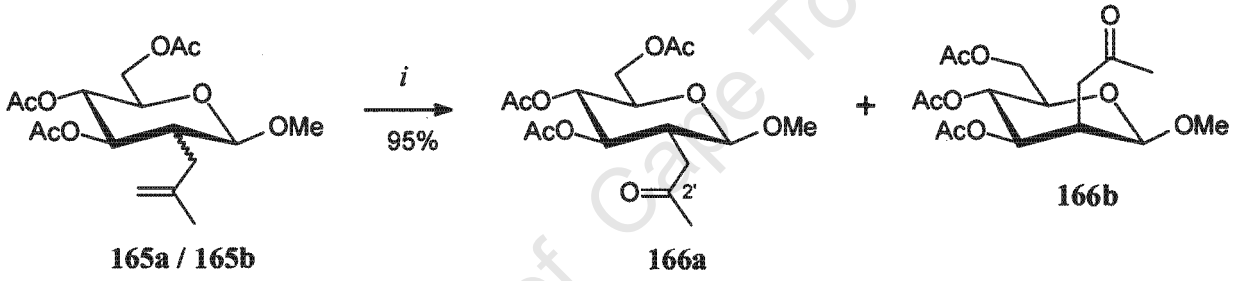


163b **165a** **165b**

Scheme 47 *Reagents and conditions*: *i*) Methallyltributylstannane, AIBN, benzene, reflux, 2 h (**165a:165b** = 5:1)

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.



165a / 165b **166a** **166b**

Scheme 48 *Reagents and conditions*: *i*) (a) O_3, CH_2Cl_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.

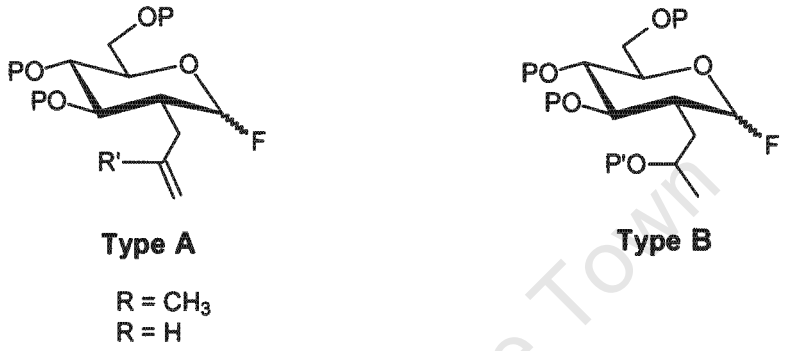
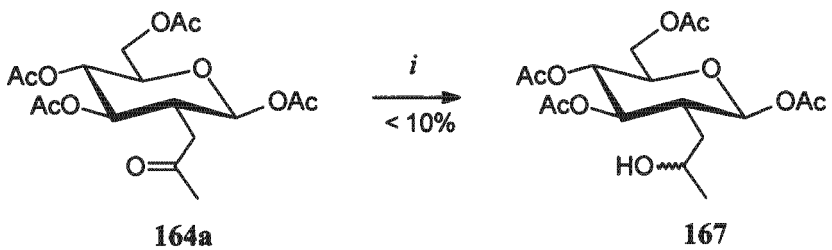


Figure 16 Envisaged glycosyl donors

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 anomeric position.

Thus, reduction of **164a** with $NaBH_4$ 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** (^{1}H NMR).

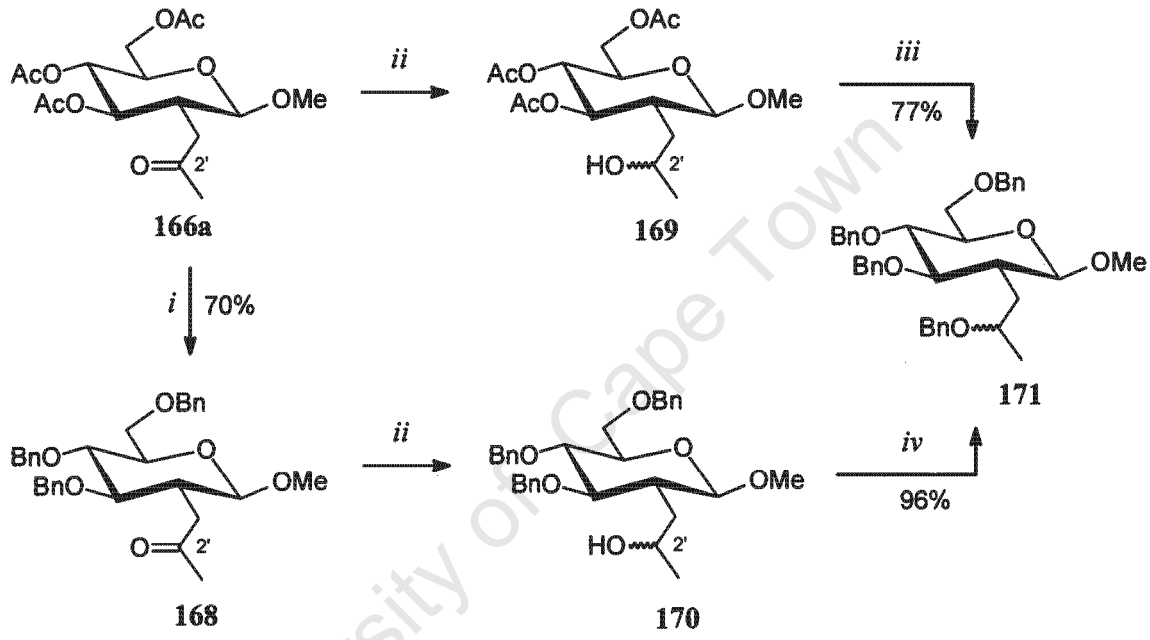


Scheme 49 *Reagents and conditions*: *i*) $NaBH_4$, THF-MeOH, −20 °C, 2 h

Since there was some evidence for instability of anomeric 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 anomeric position. Benzylated analogue **168**, which is compatible with several reducing agents, was prepared in a one-pot synthesis[139] 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 δ 7.40-7.18 (15 H, m) for the aromatic protons while the ^{13}C NMR spectrum displayed a diagnostic signal at δ 207.83 confirming retention of the carbonyl group at C-2′. In addition, the IR spectrum displayed an absorption at ν_{max} 1705 cm^{-1} for the carbonyl group.



Scheme 50 *Reagents and conditions*: *i*) NaOH (50%), $[CH_3(CH_2)_3]_4N(HSO_4)$, $(CH_3)_3COH$, BnCl, benzene, 50 °C, 24 h; *ii*) See Table 2; *iii*) (a) NaOMe, MeOH-CH_2Cl_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**

Entry	Ketone	Ruducing agent (equiv)[ref]	Solvent	Temp (time)	Alcohol (yield%)	Ratio
1	**166**	$NaBH_4$ (10)[140]	THF-MeOH	–30 °C (2 h)	**169** (99%)	2 : 1
2	**166**	K-Selectride® (2)[141,142]	THF	–78 °C (2 h)	----	----
3	**166**	$Zn(BH_4)_2$ (2)[143,144]	Et_2O	0 – 25 °C (18 h)	**169** (75%)	1 : 1
4	**166**	$NaBH_4$-$CeCl_3$[145,146]	THF-MeOH	–30 °C (2.5 h)	**169** (78%)	1.2 : 1
5	**166**	$LiAlH(O\text{-}t\text{-}Bu)_3$[147-149]	THF	0 – 25 °C (22 h)	**169** (69%)	1 : 1.3
6	**168**	$LiAlH_4$ (1.2)[141,142]	THF	–78 °C (20 min)	**170** (98%)	1.2 : 1
7	**168**	DibalH (1.2)[141,142]	Toluene	–78 °C (15 min)	**170** (99%)	1.7 : 1
8	**168**	L-Selectride® (2)[141,142]	THF	–78 °C (15 min)	----	----
9	**168**	CBS[150]	Toluene-THF	40 °C (15 min)	**170** (99%)	2 : 1

Interestingly, the best selectivity (2:1) was obtained with both $NaBH_4$ 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 ^{1}H 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 ^{13}C 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**.

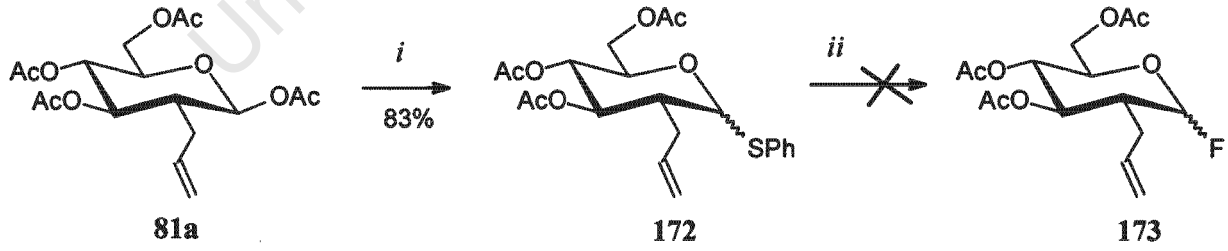
For major diastereomer **170a**, the ^{1}H NMR spectrum displayed a diagnostic signal at δ 3.87 (m) for H-2′ while a doublet at δ 1.13 (3 H, *J* 6.3 Hz) for the methyl protons confirmed reduction of the carbonyl group. In addition, the ^{13}C NMR spectrum displayed a new signal at δ 67.14 for C-2′ and 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 anomeric leaving groups and activation methods for effective glycosylation have been developed.[152] In our synthesis, glycosyl fluorides were preferred over bromide, chloride, imidates, etc., because of their higher thermal and chemical stability, ease of synthesis,[152-155] and extensive glycosylation with inositol derivatives.[156-158] Having such favourable synthetic attributes has led to the development of a number of synthetic methods for their preparation.[152] However in this work, only two methods were investigated, namely preparation of glycosyl fluorides from phenyl thioglycosides with DAST-NBS[153] and fluorination of the free anomeric hydroxyl with DAST.[154,155]

In the thioglycoside approach, 2-C-allyl pentaacetate **81a** was treated with $PhSSiMe_3$[159] in the presence of $BF_3{\cdot}Et_2O$[160] 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 ($J_{1,2}$ 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 ($J_{1,2}$ 10.8 Hz) coupling constant.



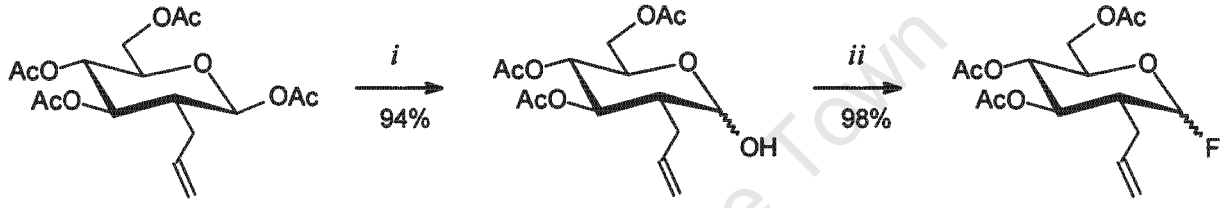
81a **172** **173**

Scheme 51 *Reagents and conditions*: *i*) $PhSSiMe_3$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C to rt, 18 h (α:β = 2:1); *ii*) DAST, NBS, CH_2Cl_2, 0 °C, 1 h

Thioglycoside **172** was treated with DAST in the presence of NBS with the intention of replacing the –SPh with fluoride (Scheme 51).[153] However, the isolated polar product displayed aromatic signals in both the ^1H and ^{13}C 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 anomeric hydroxyl.

Thus in an alternative approach, selective deacetylation of **81a** with hydrazine acetate[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 anomeric 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.



81a **174** **173**

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[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.

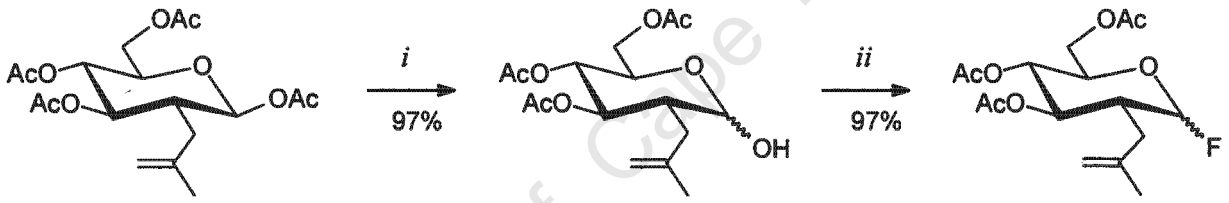
The configurations of anomers were determined from their H-1 coupling constants. Thus for the α-anomer, the ^{1}H NMR spectrum displayed a doublet of doublets at δ 5.66-5.52 for H-1 with a very large fluorine-H-1 coupling ($J_{1,F}$ 51.0 Hz) and a moderate axial-equatorial ($J_{1,2}$ 2.6 Hz) coupling 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 anomeric 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 δ 111.56 ($J_{1,F}$ 214.0 Hz) for C-1. In addition, the ^{19}F NMR displayed a broad doublet at δ –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 (α:β = 6:1, by ^1H 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 δ 95.66 for C-1 (β-anomer) and δ 92.93 (α-anomer), thus differentiating the configuration of anomers.[d]



82a **175** **176**

Scheme 53 *Reagents and conditions*: *i*) Hydrazine acetate, DMF, 60 °C, 1 h (α:β = 6:1); *ii*) DAST, THF, rt, 30 min (α:β = 2:1)

Fluorination of **175** with DAST[154,155] gave methallyl fluoride **176** as a mixture of anomers (α:β = 2:1, by ^1H 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, ^1H 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.

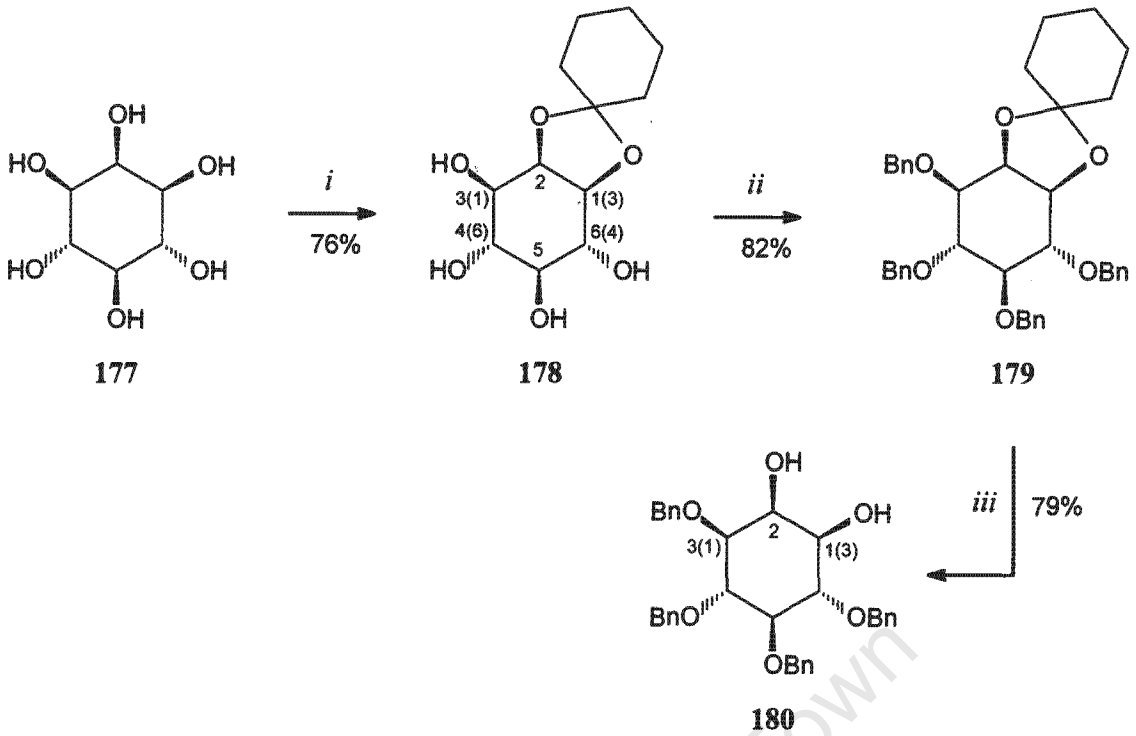
[d] In the ^{13}C NMR spectroscopy of glucopyranoses, an anomeric carbon bearing an α-substituent generally resonates upfield to one bearing a β-substituent.(162)

2.3 Synthesis of the glycosyl acceptor

A protected and enantiomerically pure D-*myo*-inositol derivative with a free hydroxyl group at C-1 was required as glycosyl acceptor in our synthesis. *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.[29,156,158,163-174] A range of methods for the preparation of enantiomerically pure derivative of *myo*-inositol such as *trans*-acetalization of *myo*-inositol with D-camphor dimethyl ketal as the chiral reagent,[167,170] the use of monnosacharides as asymmetrical agents in resolving racemic alcohols,[156-158] and the use of (−)-menthol chloroformate to resolve 2:3,4:5-cyclohexylidene has been reported.[165] The most practical route in our experience was *via* a resolution of 1,2,4,5,6 pentabenzyl DL-*myo*-inositol with (S)-(−)-camphanic chloride followed by hydrolysis of the ester to give free alcohol at C-1.

To prepare the benzylated DL-*myo*-inositol, a procedure by Massy[174] which involves eight reaction steps from *myo*-inositol was followed. Thus, *myo*-inositol **177** was treated with cyclohexanone and TsOH (10%) at reflux to give racemic cyclohexylidene-DL-*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[175] (mp 179-180 °C).

Global benzylation of **178** with benzyl bromide in the presence of NaH gave racemic cyclohexylidene tetrabenzyl-*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.

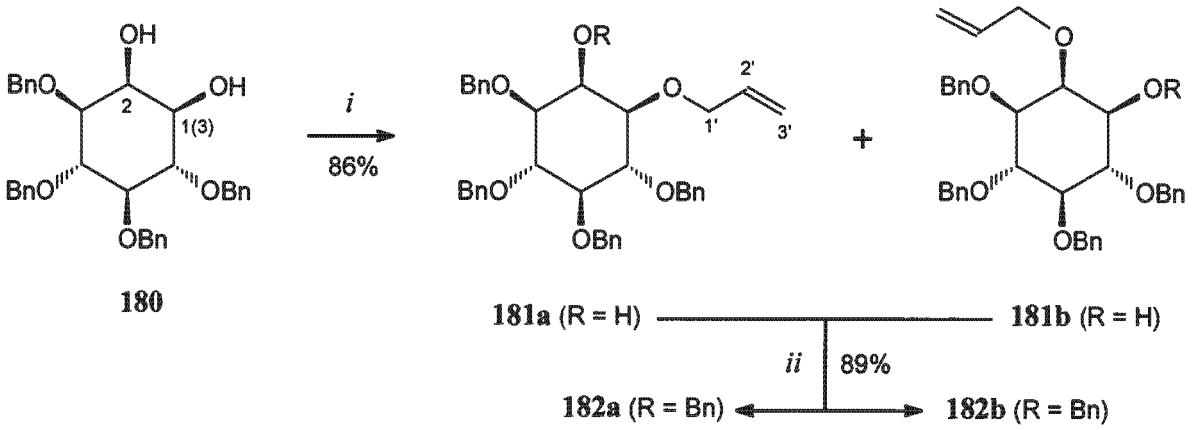


Scheme 54 *Reagents and conditions*: *i*) Cyclohexanone, TsOH (10% in DMF), DMF, toluene, reflux, 12 h; *ii*) BnBr, NaH, THF, reflux, 18 h; *iii*) AcOH (80%), 90-100 °C, 2 h

Acidic hydrolysis of **179** with 80% acetic acid gave racemic tetrabenzyl-*myo*-inositol **180** in 79% yield (Scheme 54). Its melting point and spectroscopic data were in agreement with the literature values. The absence of cyclohexylidene 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 ν_{max} 3570 cm^{-1} (OH).

Stannylidene-mediated regioselective allylation of the diol **180** gave a racemic mixture of allyl ethers **181a** and **181b** (≈ 10:1, by ^{13}C NMR)[e] 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 δ 3.47 in **180** to δ 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 ν_{max} 3573 cm^{-1} (OH).

[e] Severe signal overlap in the ^{1}H NMR made a comparison of integrals difficult.

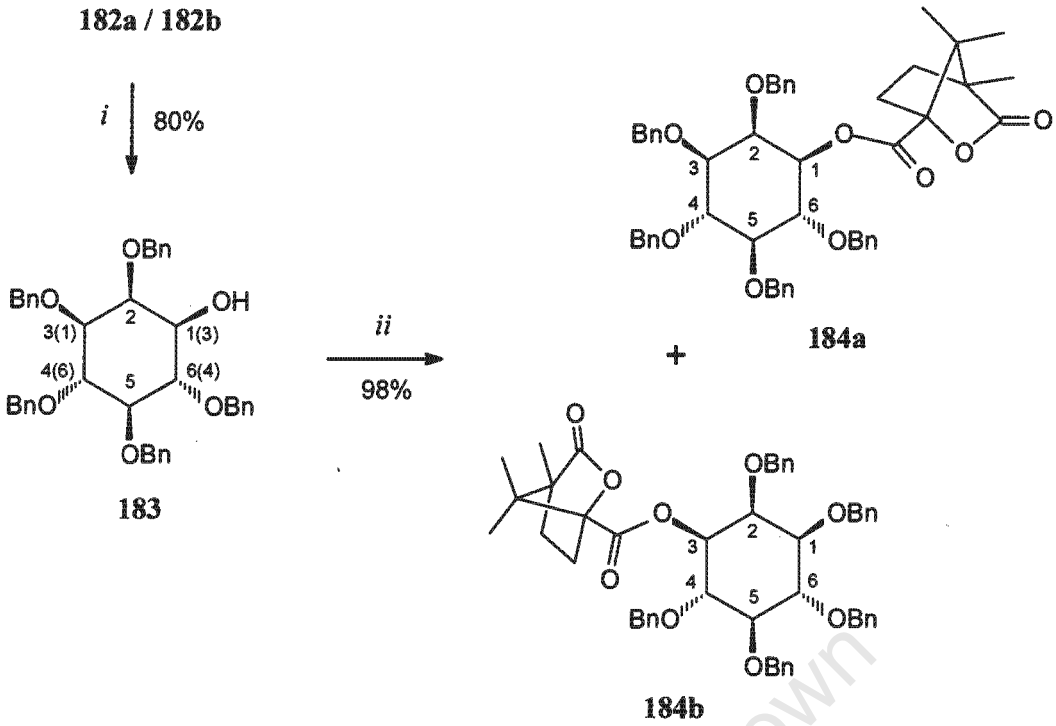


Scheme 55 *Reagents and conditions*: *i*) (a) Bu_2SnO, toluene, reflux, 2 h (b) Allyl bromide, DMF, 70 °C, 5 h (**181a:181b** = 10:1); *ii*) BnBr, NaH, THF, reflux, 3 h (**182a:182b** ≈ 10:1)

Benzylation of the mixture of alcohols **181a** and **181b** with benzyl bromide in the presence of NaH gave racemic allyl pentabenzyl-*myo*-inositol **182a** and **182b** (≈ 10:1, ^{13}C NMR)[e] 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 **182a** and **182b** with $PdCl_2$ in ethanol gave racemic pentabenzyl-*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 ν_{max} 3560 cm^{-1} for hydroxyl.

[e] Severe signal overlap in the ^1H NMR made a comparison of integrals difficult.



Scheme 56 *Reagents and conditions*: *i*) $PdCl_2$, EtOH-MeOH, rt, 5 h; *ii*) Camphanic acid chloride, Et_3N, DMAP, CH_2Cl_2, rt, 28 h

Having successfully synthesized the protected DL-*myo*-inositol derivative **183** with a free hydroxyl group at C-1, the next step involved its resolution as a camphanate ester. Thus, esterification[166] of racemic alcohol **183** with camphanic acid chloride, Et_3N 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** = $[\alpha]_D$ +9.8° and **184b** = $[\alpha]_D$ −15.3°).

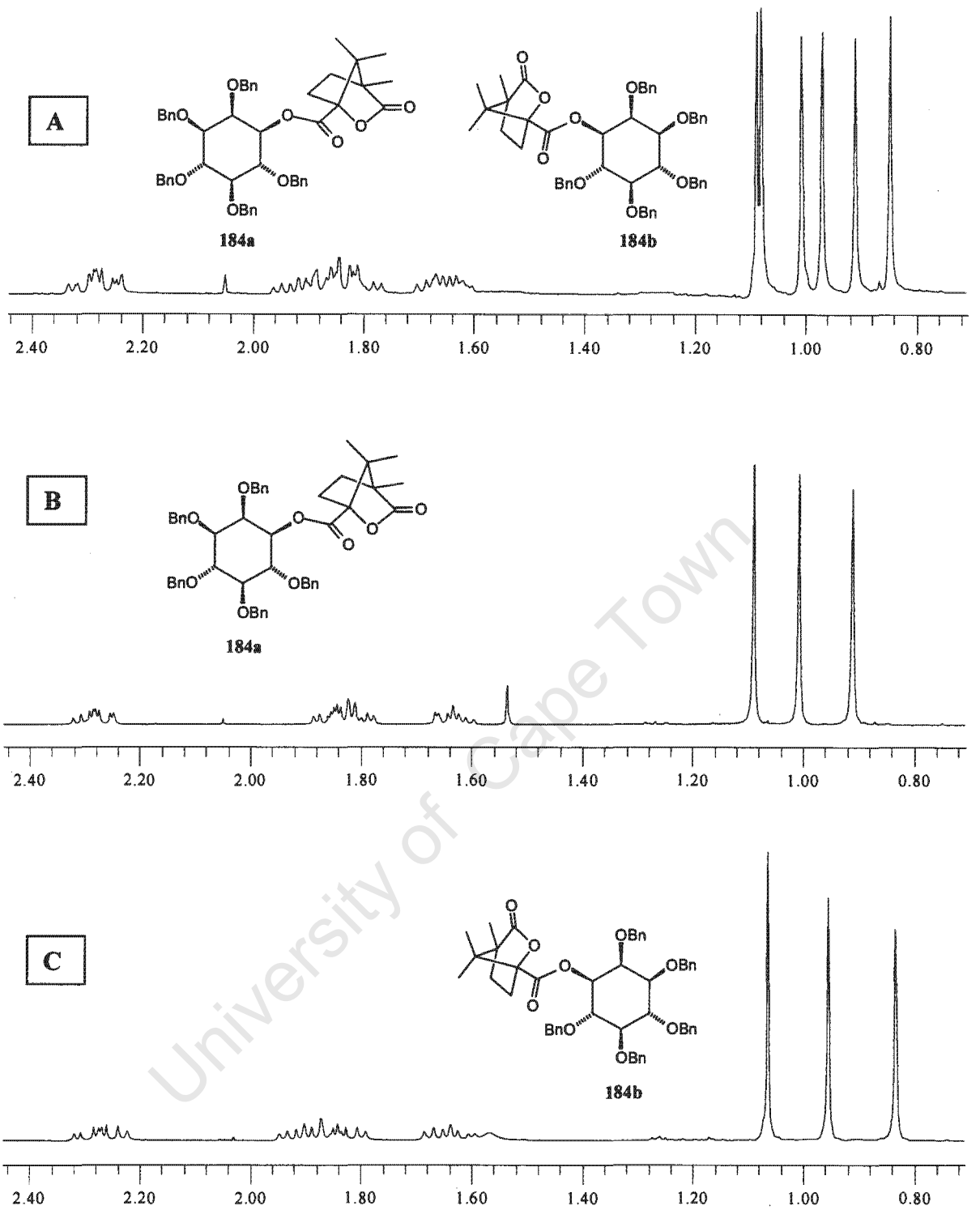
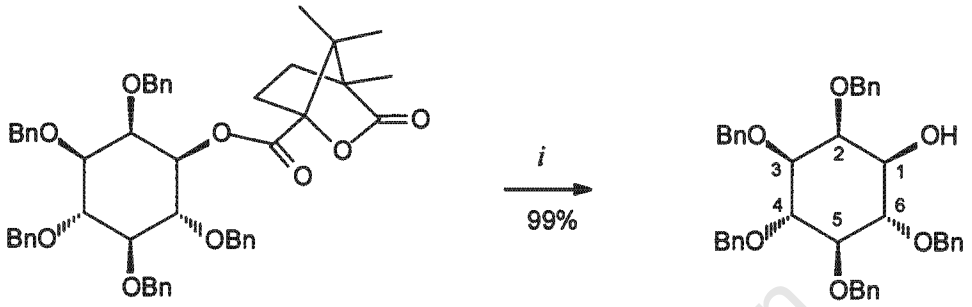


Figure 17 ^{1}H NMR expansions of methyl proton region of inositol camphanate esters: (a) mixture of diastereomers (b) diastereomer with D-enantiomer **184a** and (c) diastereomer with L-enantiomer **184b**

The ^{1}H 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 ^{1}H NMR spectrum), while the ^{13}C 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 ν_{max} 1781, 1718 cm^{-1} (C=O).

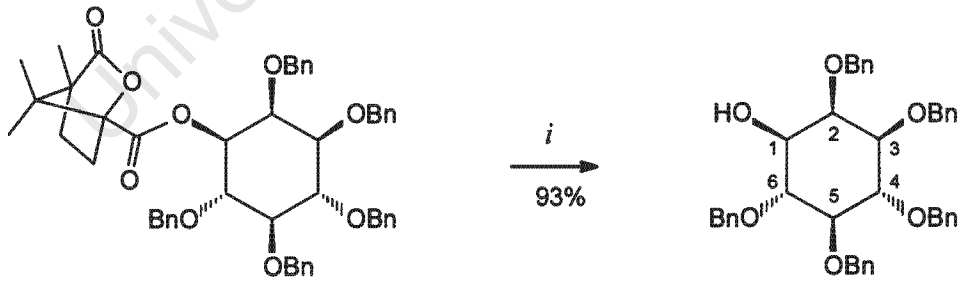
For the other diastereomer **184b** containing the L-inositol, the ^{1}H NMR spectrum displayed diagnostic signals at δ 1.08, 0.97, 0.85 (9 H, 3 s) for the methyl protons (see Figure 17c for the ^{1}H NMR spectrum) while the ^{13}C NMR spectrum displayed signals at δ 177.89 and 167.46 for the camphanoyl carbonyl groups. In addition, the IR spectrum displayed an absorption at ν_{max} 1785, 1722 cm^{-1} (C=O).



184a **185**

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-*myo*-inositol **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° and −8.0°, confirming that they were the D- and L- isomers respectively.[173]



184b **186**

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 anomeric 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 anomeric 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.[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-*myo*-inositol (51-56)

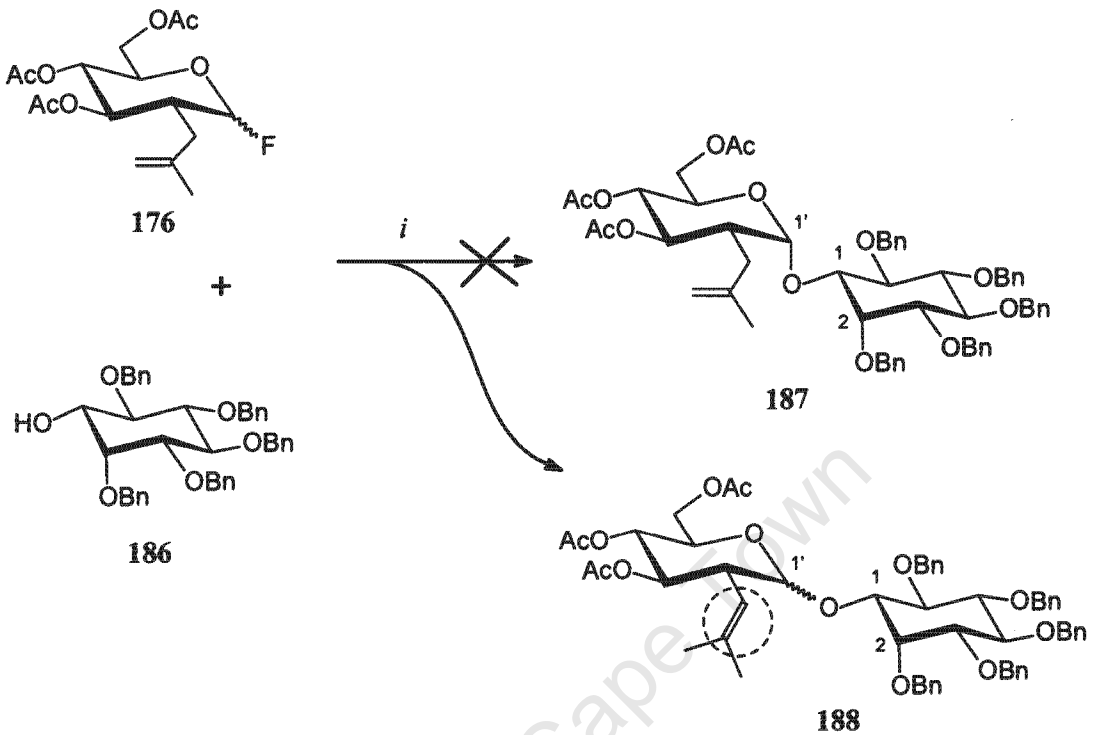
A model glycosylation reaction using L-inositol[f] **186** as the acceptor with **176** as the donor and promoted by $BF_3{\cdot}Et_2O$[157,176] gave *pseudo*-disaccharide **188** (60%, $\alpha{:}\beta \approx 99{:}1$, by ^{13}C NMR)[g] with the desired α-selectivity (Scheme 59). Unfortunately, undesired 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, $ZnCl_2$,

[f] L-inositol was used to save D-inositol

[g] In the ^1H 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.

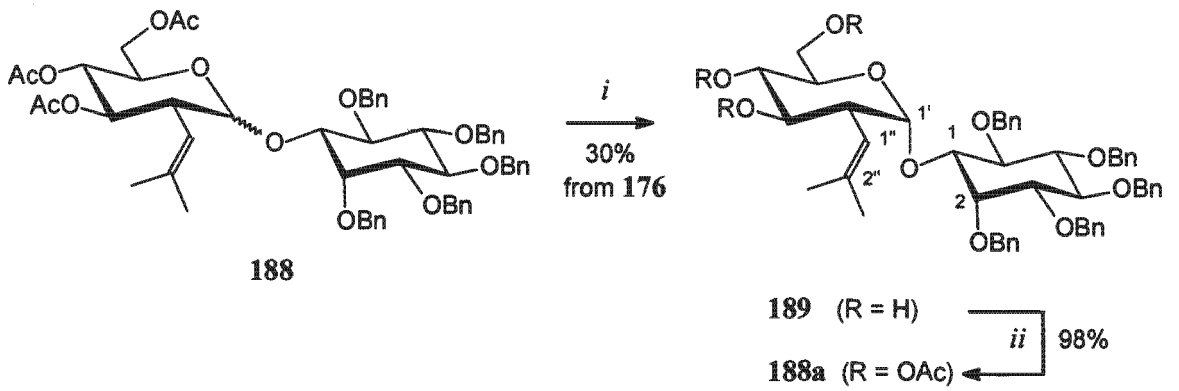
CH_2Cl_2, rt) were used with and without a base (2,4 lutidine), but again no reaction was observed (tlc) after two days.



Scheme 59 *Reagents and conditions*: *i*) $BF_3{\cdot}Et_2O$, ms, CH_2Cl_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 ^1H 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 ^1H and ^{13}C NMR spectra. The ^1H 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.



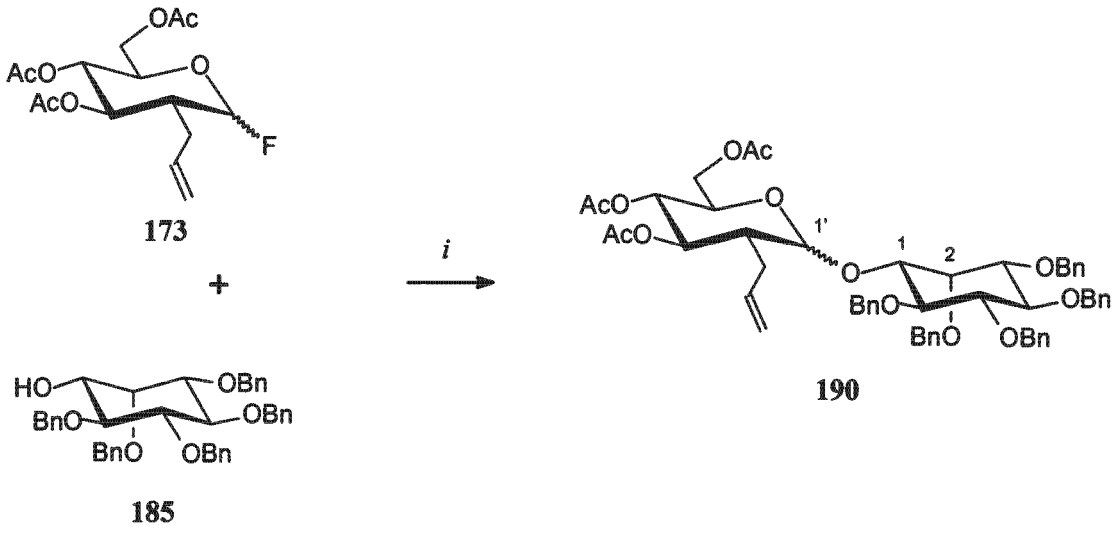
Scheme 60 *Reagents and conditions*: *i*) NaOMe, MeOH-CH_2Cl_2, rt, 2 h; *ii*) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1 h

The stereochemistry of **189** at C-1′ was determined from the coupling constant value for H-1′. Thus the ^{1}H NMR spectrum displayed a doublet at δ 5.22 for H-1′ with a moderate axial-equatorial ($J_{1',2'}$ 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 acetoxy signals were evident in both ^{1}H and ^{13}C NMR spectra. The ^{1}H 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 ^{13}C 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 $BF_3{\cdot}Et_2O$[157,176] as a promoter gave 2-C-allyl *pseudo*-disaccharide **190** as an inseparable mixture of anomers (α:β ≈ 8:1, by ^{13}C NMR)[g] as an oil (Scheme 61). Once again, the donor, acceptor and the product displayed the same R_f 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**.

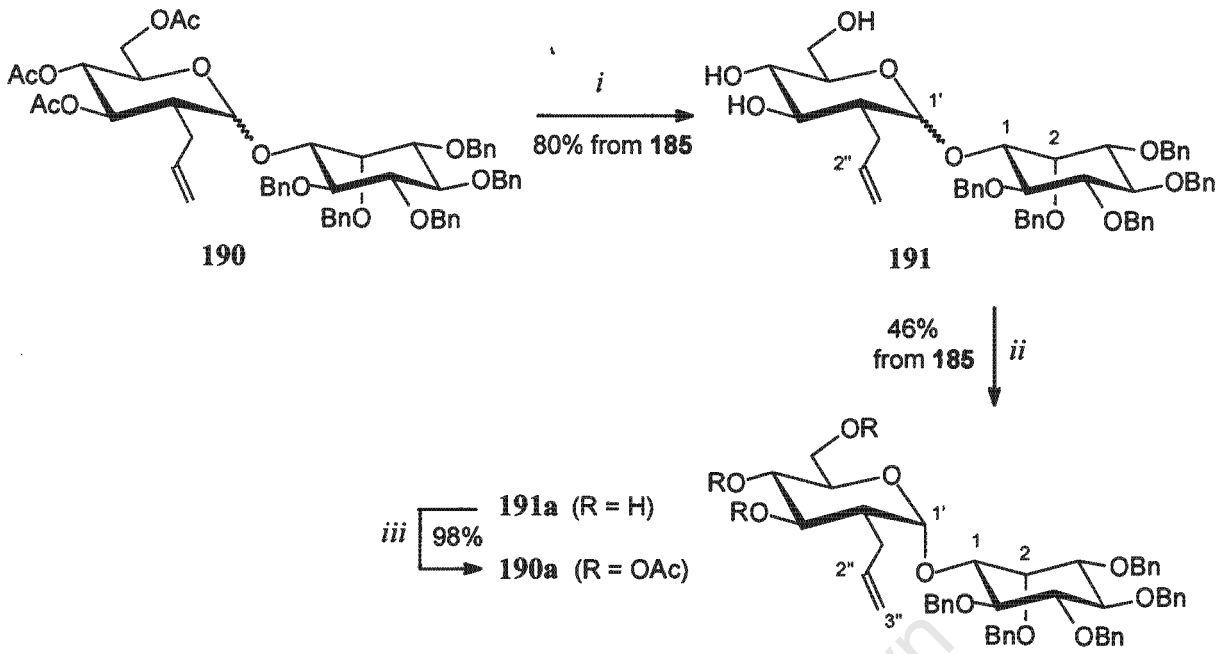
[g] In the ^{1}H NMR spectrum, the signal for H-1 in the β-anomer was not resolved from the benzylic and other protons, making a comparison of integrals difficult.



Scheme 61 *Reagents and conditions*: *i*) $BF_3{\cdot}Et_2O$, ms, CH_2Cl_2, 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 ^1H 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.

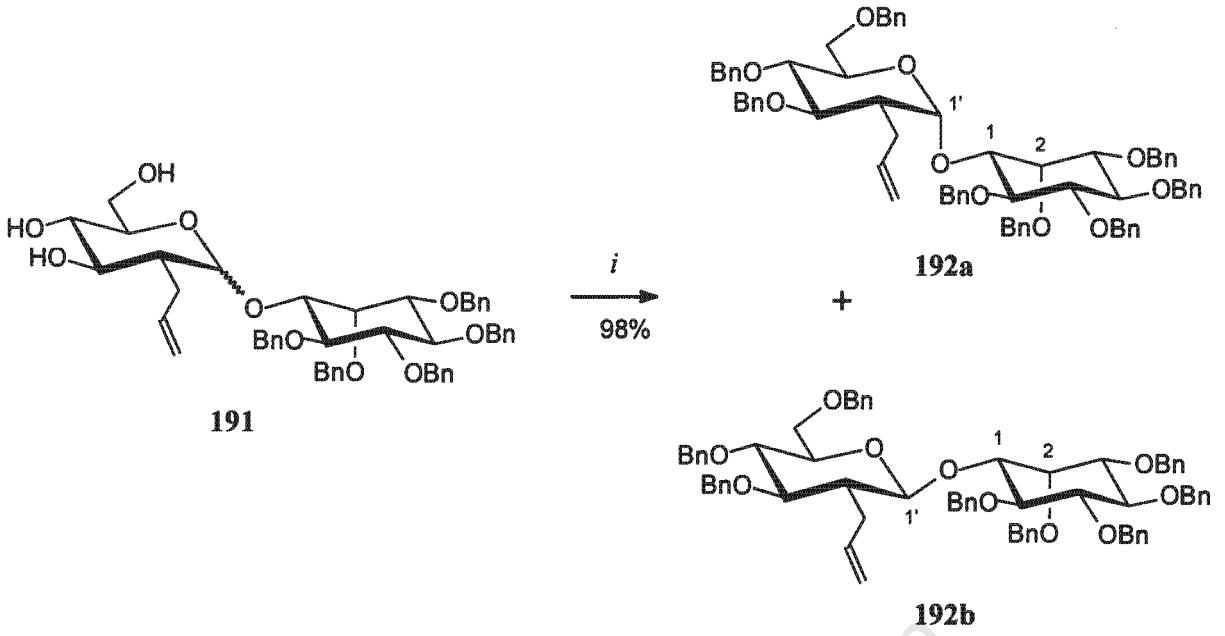
Since compound **190** was inseparable from unreacted inositol derivative **185**, the mixture was subjected to *Zemplén* deacetylation to give the separable pentabenzyl *pseudo*-disaccharide **191** as a mixture of anomers (α:β ≈ 8:1, by ^{13}C NMR) in 80% yield from **185** (Scheme 62). A careful separation of the anomers by silica column chromatography gave α-anomer **191a** in 56% yield from the acceptor **185**. The ^1H 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-CH_2Cl_2, rt, 2 h (α:β ≈ 8:1); *ii*) Separation of anomers; *iii*) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 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, $J_{1',2'}$ 3.2 Hz) for H-1′, δ 3.65 (dd, *J* 9.6, 2.0 Hz) for H-1 while the ^{13}C 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 ^{13}C 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 β-anomer appearing at δ 103.88 and the α-anomer appearing at δ 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.

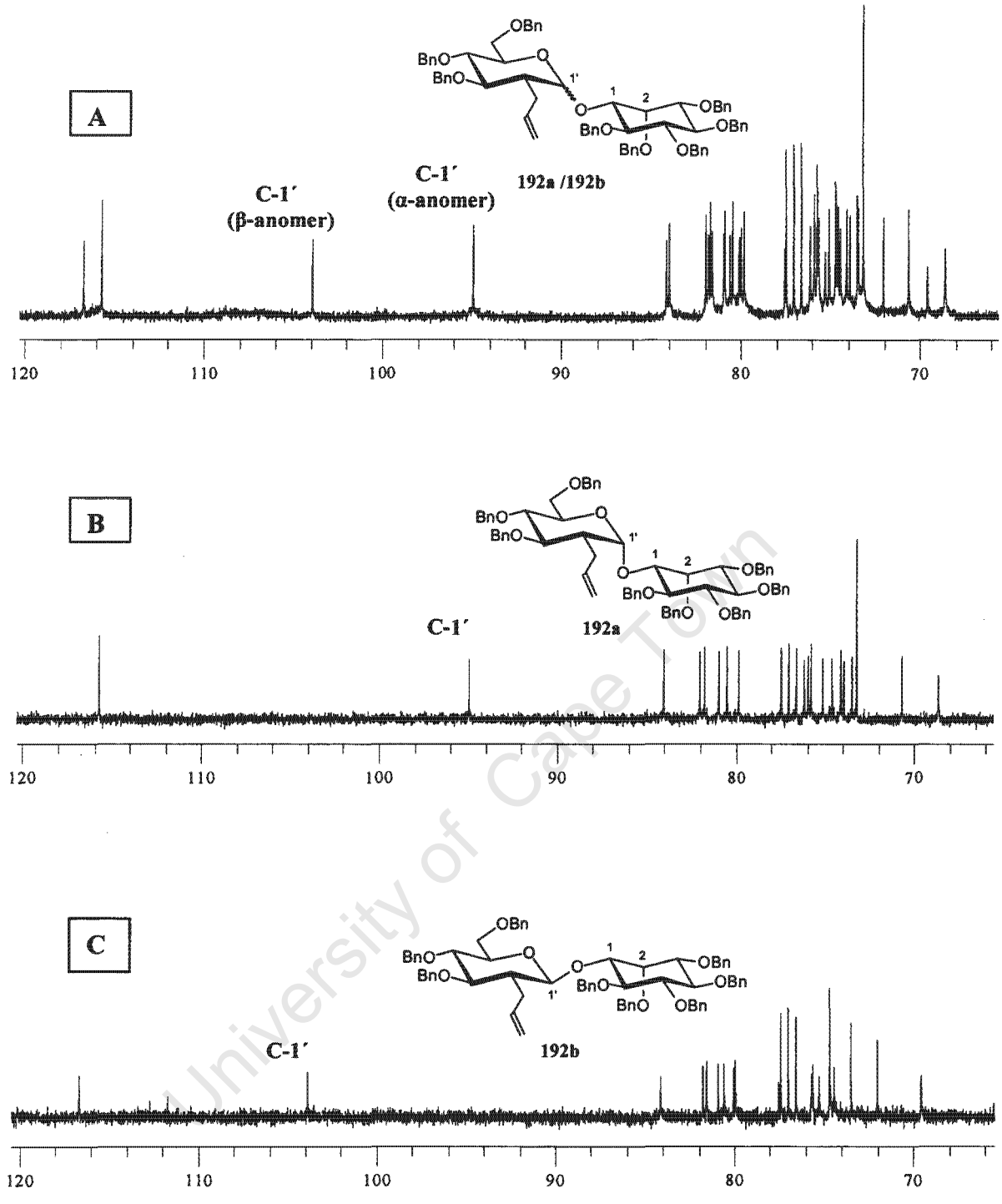
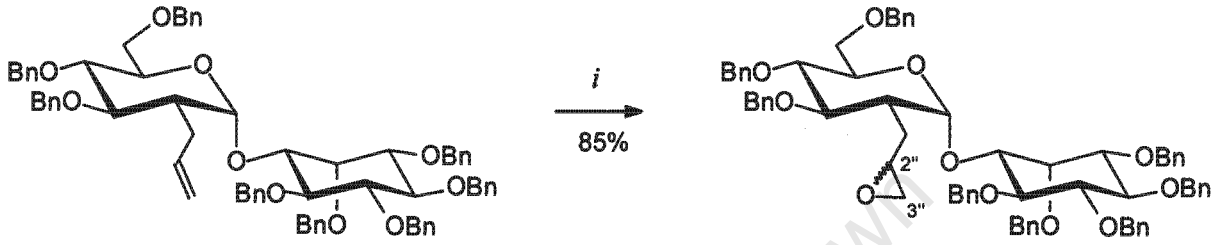


Figure 18 ^{13}C NMR expansions of anomeric region of **192a** and **192b**. (a) mixture of anomers (b) α-anomer **192a** (c) β-anomer **192b**

The ^{1}H NMR spectrum for **192a** displayed a signal for H-1′ at δ 5.09 which appeared as a doublet with a moderate axial-equatorial ($J_{1',2'}$ 3.3 Hz) coupling constant, thus confirming the α-anomer. In contrast, the ^{1}H NMR spectrum for **192b** displayed a signal for H-1′ at δ 4.72 which appeared as a doublet with a large diaxial ($J_{1',2'}$ 8.1 Hz) coupling constant, thus confirming the β-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 $LiAlH_4$ used for the regioselective opening of epoxide, compared with the acetate groups in **190a**. Hence, treatment of **192a** with *m*-CPBA[177,178] 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)



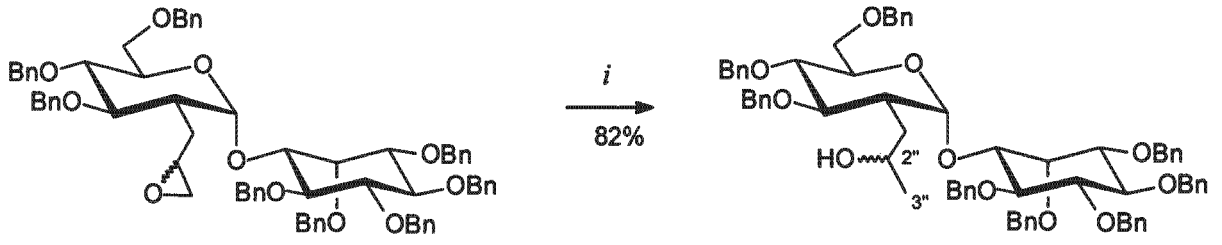
192a **193**

Scheme 64 *Reagents and conditions*: *i*) *m*-CPBA (70%), CH_2Cl_2, 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 ^{13}C 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 ^{13}C 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[179,180] of epoxide **193** with $LiAlH_4$ 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 ^{13}C NMR spectra.

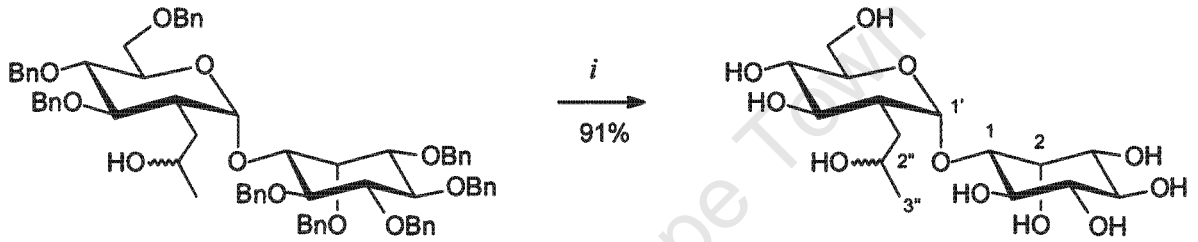


193 **194**

Scheme 65 *Reagents and conditions*: *i*) $LiAlH_4$, THF, 0 °C, 2 h (1:1)

Thus for diastereomer **194a**, the ^{1}H NMR spectrum displayed diagnostic signals at δ 3.79 (m) for H-2′′ and at δ 0.93 (3 H, d, *J* 6.0 Hz) for the adjacent methyl protons. The ^{13}C NMR spectrum displayed signals at δ 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 ν_{max} 3465 cm^{-1} (OH).

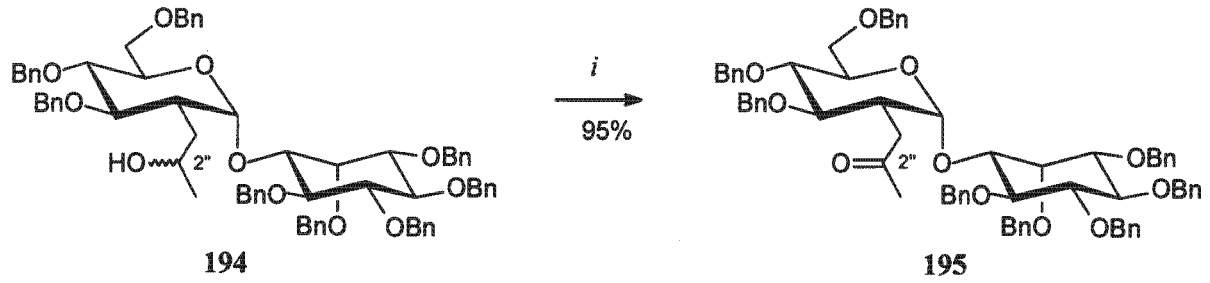
Global debenzylation of **194** with Pd/C under an atmospheric hydrogen pressure gave the target compound as an inseparable mixture (1:1, by ^{1}H NMR) of alcohols **51** in 90% yield (Scheme 66). The completion of reaction was ensured by periodic addition of further equivalents of Pd/C over an 18 h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



Scheme 66 *Reagents and conditions*: *i*) H_2, 10% Pd/C, MeOH-EtOAc, rt, 3 days (1:1)

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 δ 5.09 (d, $J_{1',2'}$ 3.3 Hz) for H-1′, a broad singlet at δ 4.24 for H-2 and a doublet at δ 1.20 (3 H, *J* 6.0 Hz) for the methyl protons. The ^{13}C NMR spectrum displayed signals at δ 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.

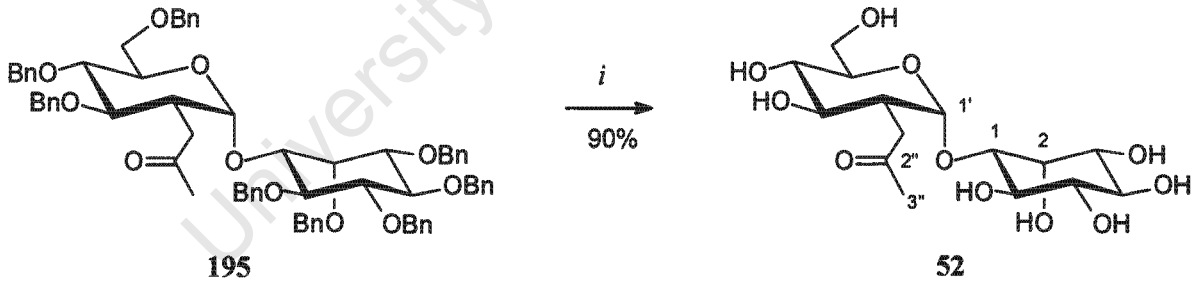
In order to synthesize the 2-keto target compound **52**, the diasteromeric mixture of alcohols **194** was oxidized with TPAP using NMO as co-oxidant,[181] to give ketone **195** in 95% yield (Scheme 67). This was adopted as the reagent of choice for all further oxidations, owing to the mild reaction conditions and ease of work-up.



Scheme 67 *Reagents and conditions*: *i*) TPAP, NMO, CH_2Cl_2, ms, 30 min

The ^{1}H NMR spectrum displayed a diagnostic signal at δ 1.61 (3 H, s) for the methyl group. The downfield shift of these protons from δ 0.93 and δ 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 δ 207.77 for C-2′′ having shifted from δ 66.92 and 66.39 for C-2′′ in **194**. In addition, the IR spectrum displayed a new absorption at ν_{max} 1712 cm^{-1} (C=O).

Global debenzylation 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.



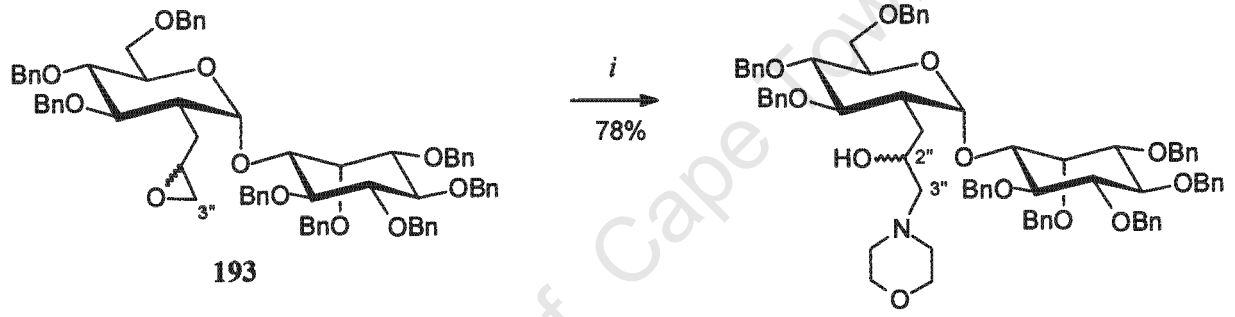
Scheme 68 *Reagents and conditions*: *i*) H_2, 10% Pd/C, MeOH-EtOAc-H_2O, rt, 8 days

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 δ 4.84 ($J_{1',2'}$ 3.3 Hz) for H-1′, a triplet at δ 3.87 (J 2.6 Hz) for H-2 and a singlet at δ 2.01 (3 H) for the methyl protons. The ^{13}C NMR spectrum displayed signals at δ 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 α- 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.

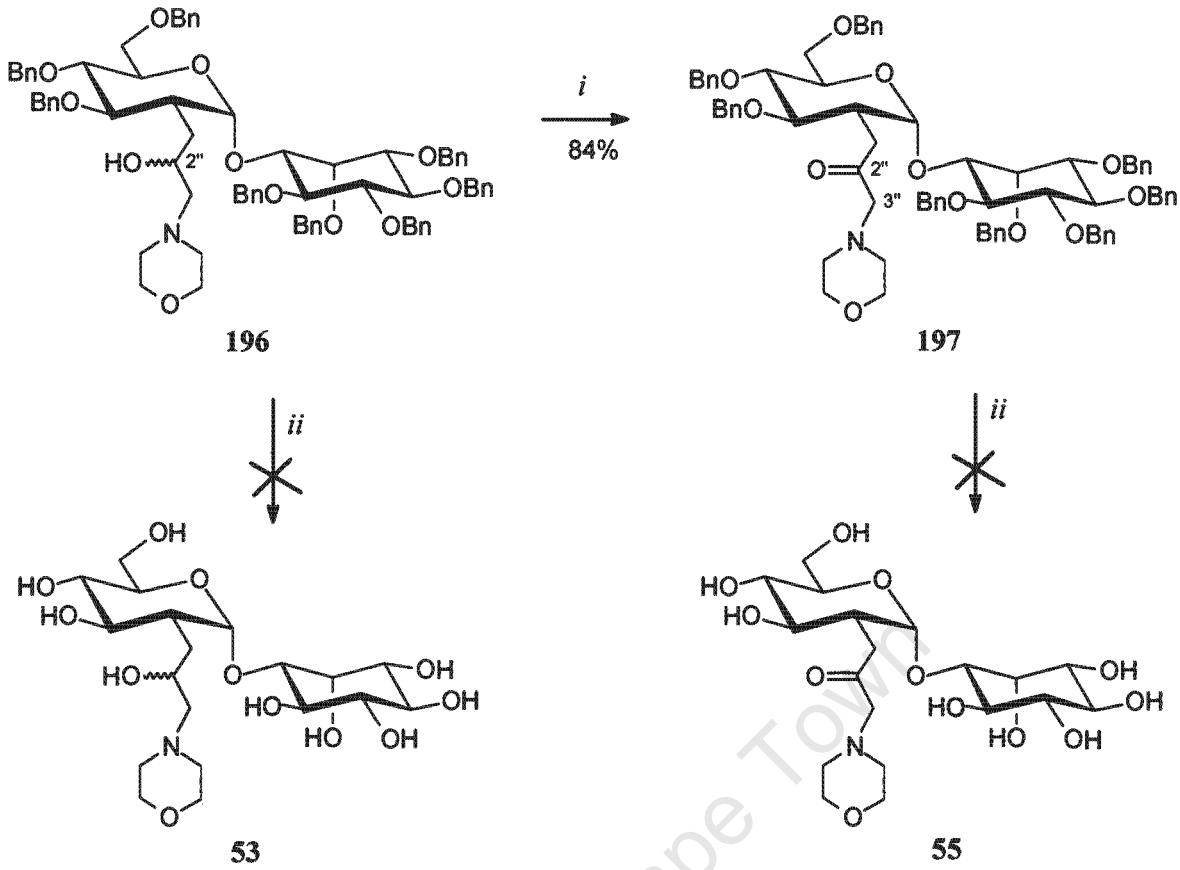
Thus S_N2 nucleophilic opening of the epoxide **193** with morpholine[182] occurred in a regioselective manner to give an inseparable mixture (1:1, by ^{1}H NMR) of diastereomeric morpholino alcohols **196** in 78% yield (Scheme 69), arising from nucleophilic attack at C-3′′. The presence of the secondary alcohol and morpholine moieties was clearly evident from both ^{1}H and ^{13}C NMR spectra.



Scheme 69 *Reagents and conditions*: *i*) Morpholine, EtOH, reflux, 1 h (1:1)

Thus for diastereomeric **196a**, the ^{13}C NMR spectrum displayed diagnostic signals at δ 66.76 (-N(CH_2CH_2)$_2$O-), 66.37 (C-2′′), 64.63 (C-3′′) and 53.34 for -N(CH_2CH_2)$_2$O-. The diagnostic signals for diastereomer **196b** were analogous to those in **196a**. In addition, the IR spectrum displayed a new absorption at ν_{max} 3625 cm^{-1} (OH).

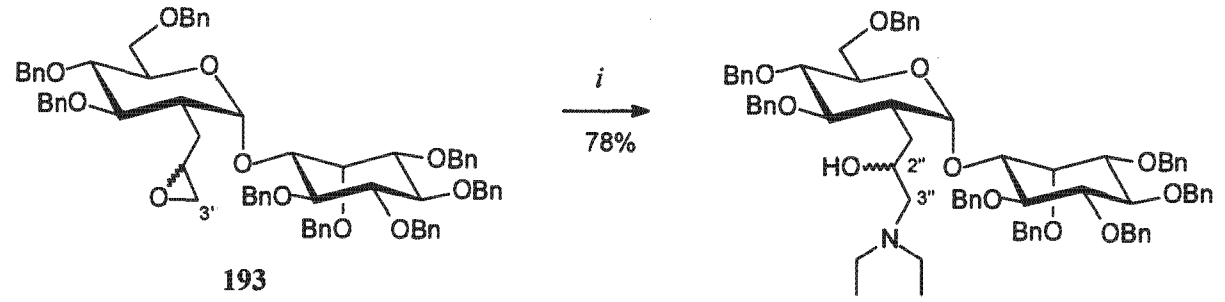
Further evidence for the diastereomeric mixture of **196** was provided by oxidising **196** with TPAP using NMO as co-oxidant,[181] to give ketone **197** in 84% yield (Scheme 70) as a single component. The ^{1}H NMR spectrum for **197** displayed a diagnostic diastereotopic AB doublet set at δ 2.68 (*J* 17.0 Hz) for H-3′′$_a$ and at δ 2.56 (*J* 17.0 Hz) for H-3′′$_b$. The ^{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_{max} 1723 cm^{-1} (C=O).



Scheme 70 *Reagents and conditions*: *i*) TPAP, NMO, CH_2Cl_2, ms, 30 min; *ii*) H_2, 10% Pd/C, MeOH-EtOAc-H_2O, 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 ^{1}H 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 diethylamine[182] to produce an inseparable diastereomeric mixture (1:1, by ^{1}H 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 ^{1}H and ^{13}C NMR spectra.

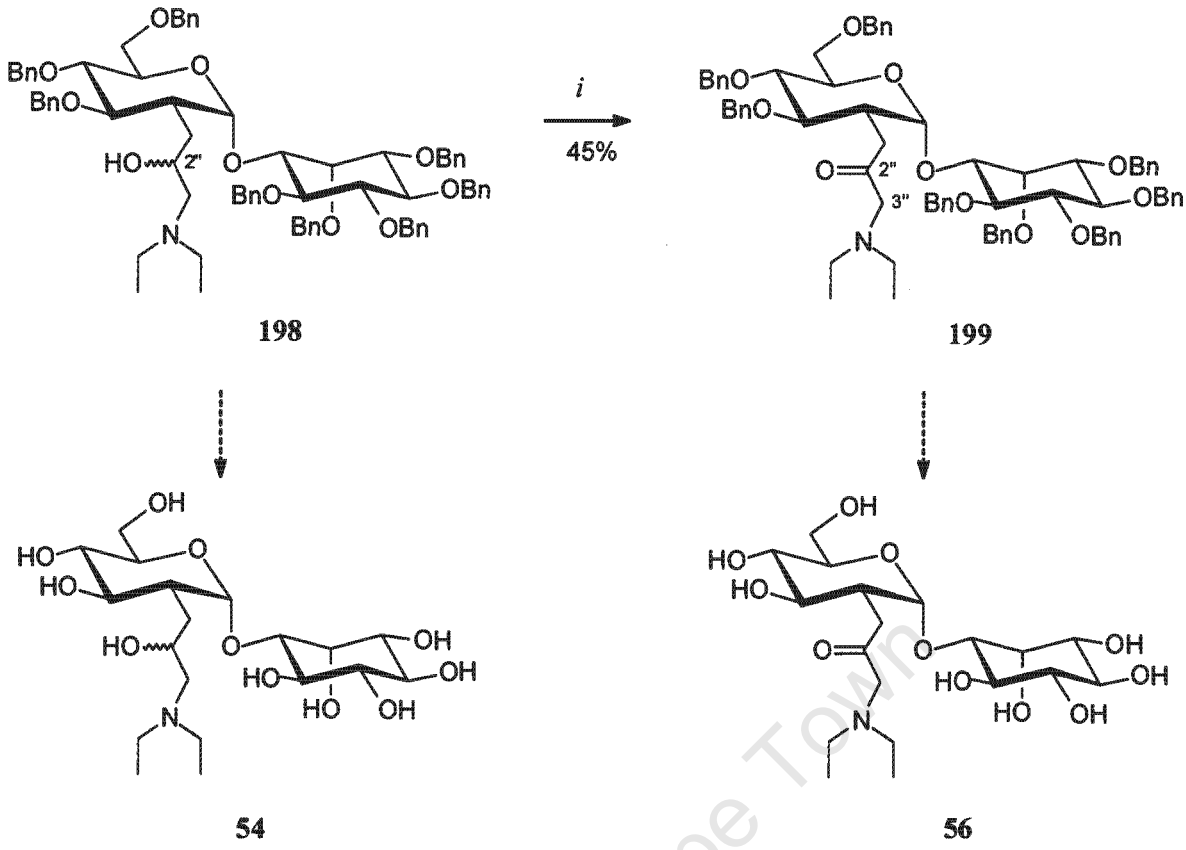


193 198

Scheme 71 *Reagents and conditions*: *i*) diethylamine, ethanol, reflux, 2 h (1:1)

Thus for diastereomer **198a**, the ^{1}H NMR spectrum displayed a diagnostic triplet at δ 0.94 (6 H, *J* 7.1 Hz) for -N(CH_2CH_3)$_2$. The ^{13}C NMR spectrum displayed diagnostic signals at δ 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 ν_{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 ν_{max} 3620 cm^{-1} in the IR spectrum. The ^{1}H NMR spectrum also displayed a diagnostic pair of AB doublets at δ 2.76 (*J* 16.5 Hz) for H-3′′$_a$ and a doublet at δ 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 δ 210.36 (C-2′′) confirmed formation of the ketone, which had shifted from δ 67.34 and 64.41 for C-2′′ in **198**. In addition, the IR spectrum displayed an absorption at ν_{max} 1718 cm^{-1} for the carbonyl group.



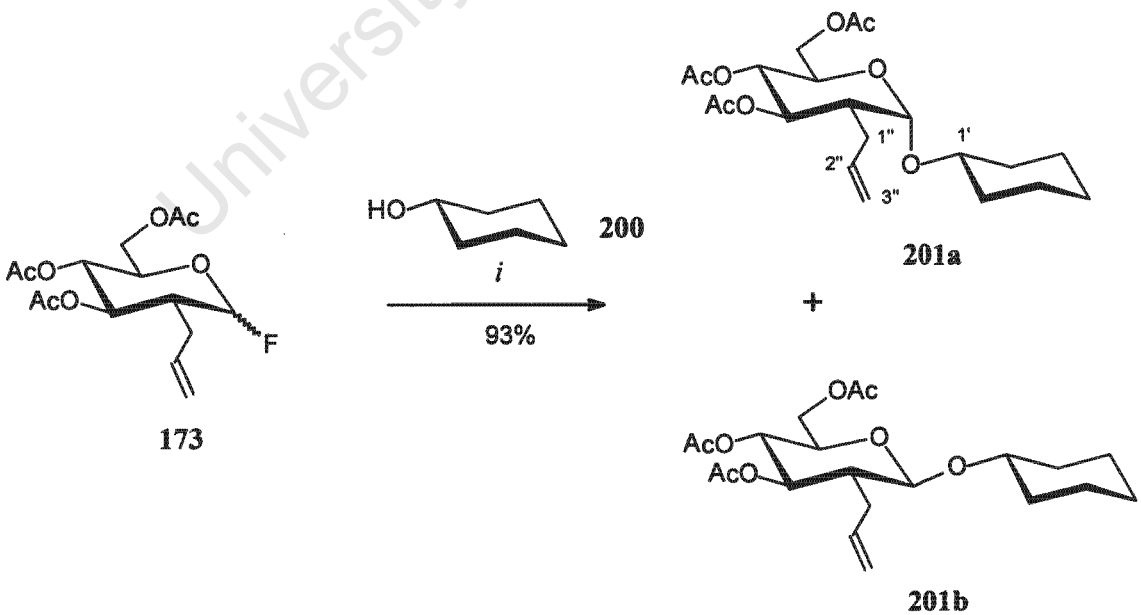
Scheme 72 *Reagents and conditions*: *i*) TPAP, NMO, CH_2Cl_2, ms, 18 h

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-*myo*-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 $BF_3{\cdot}Et_2O$[176,183] gave cyclohexyl 2-C-allyl glucopyranoside (**201a** and **201b**) as a mixture of anomers (α:β ≈ 1:1, by ^{13}C NMR)[h] 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 ^1H 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*) $BF_3{\cdot}Et_2O$, CH_2Cl_2, ms, 18 h (**201a:201b** = 1:1)

[h] In the ^1H NMR spectrum, the signal for H-1 in the β-anomer was not resolved from other protons, making a comparison of integrals difficult.

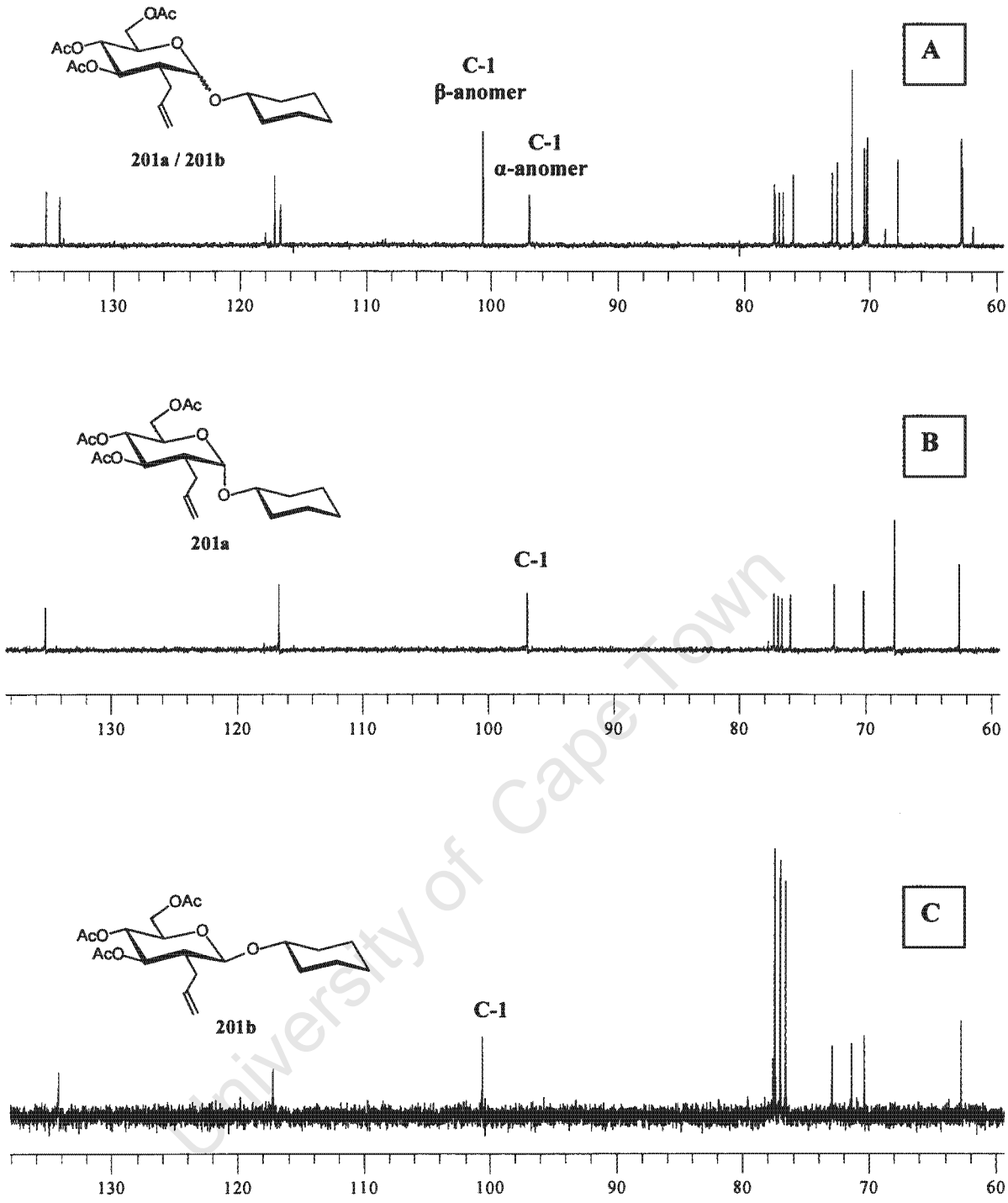
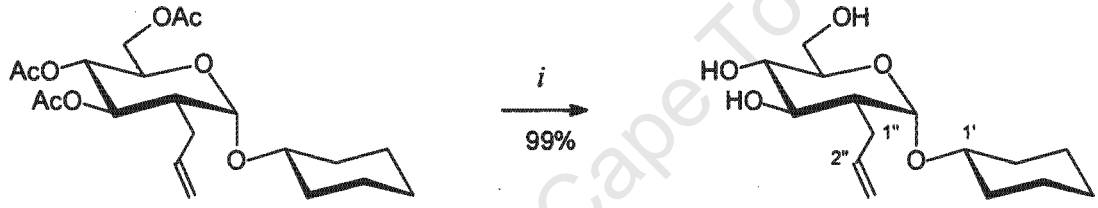


Figure 19 ^{13}C NMR expansions of anomeric region of **201a** and **201b**. (a) mixture of anomers (b) α-anomer **201a** (c) β-anomer **201b**

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 α-anomer **201a**, the ^{1}H NMR spectrum displayed diagnostic signals at δ 5.73-5.63 (m) for H-2′′ and δ 3.54-3.47 (m) for H-1′ while the ^{13}C NMR spectrum displayed diagnostic signals at δ 135.25 (C-2′′), 96.84 (C-1) and 75.95 (C-1′). The diagnostic signals for β-anomer **201b** were analogous to those in α-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.

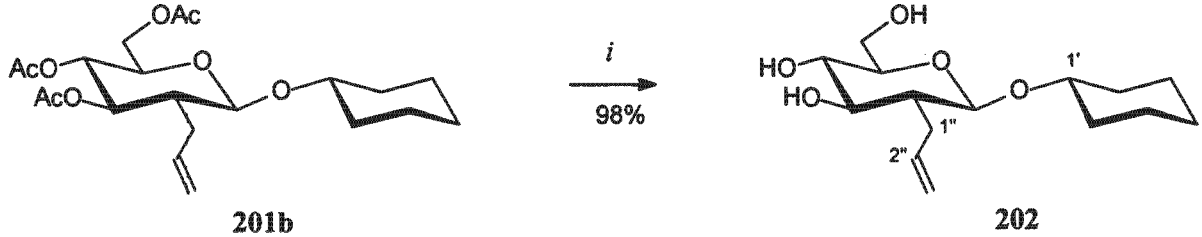
Zemplén deacetylation of **201a** gave the target compound **59** in 99% yield (Scheme 74). The ^{1}H NMR spectrum of **59** displayed signals at δ 5.86-5.76 (m) for H-2′′, δ 4.87 (d, $J_{1,2}$ 3.2 Hz) for H-1 and at δ 3.58 (m) for H-1′ while the ^{13}C NMR spectrum displayed signals at δ 136.84 (C-2′′), 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.



201a **59**

Scheme 74 *Reagents and conditions*: *i*) NaOMe, MeOH-CH_2Cl_2, rt, 4 h

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′).

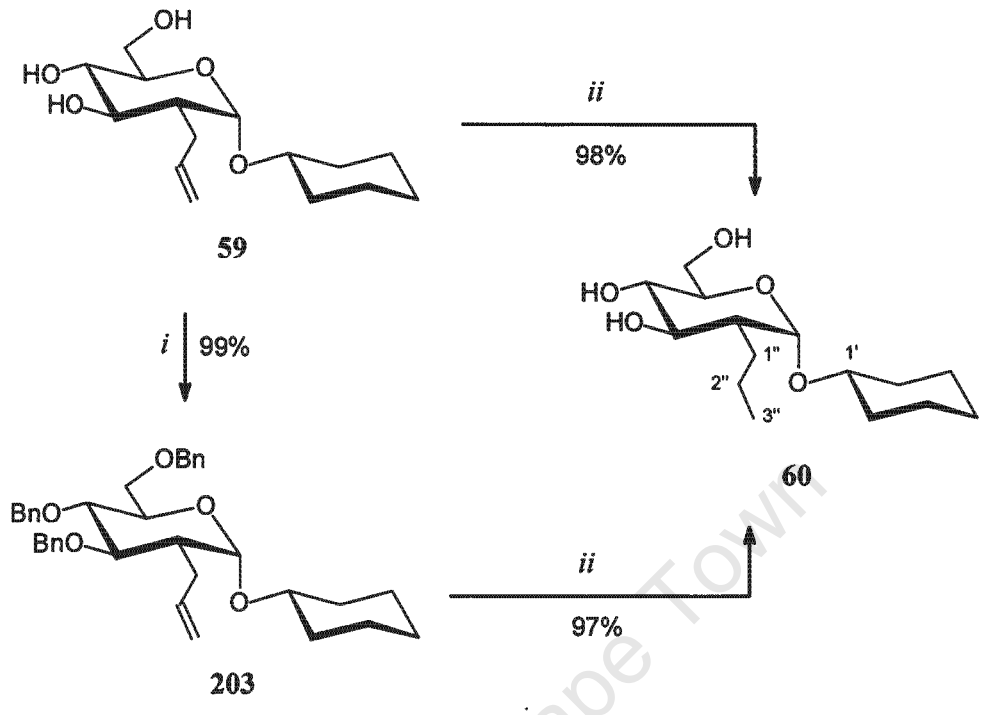


201b **202**

Scheme 75 *Reagents and conditions*: *i*) NaOMe, MeOH-CH_2Cl_2, rt, 2 h

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

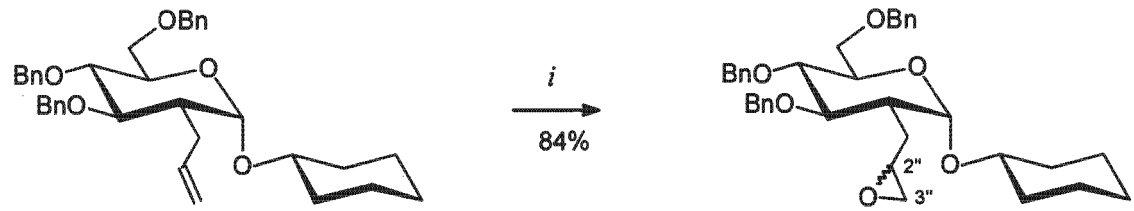
and C-6 from δ 72.82, δ 72.15 and δ 61.87 respectively in **59** to δ 81.38 (C-3), δ 79.97 (C-4) and 68.98 (C-6) confirmed the presence of benzyl groups in **203**.



Scheme 76 *Reagents and conditions*: *i*) BnBr, NaH, THF, reflux, 18 h; *ii*) H_2, Pd/C, MeOH, rt, 18 h

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 δ 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 δ 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.

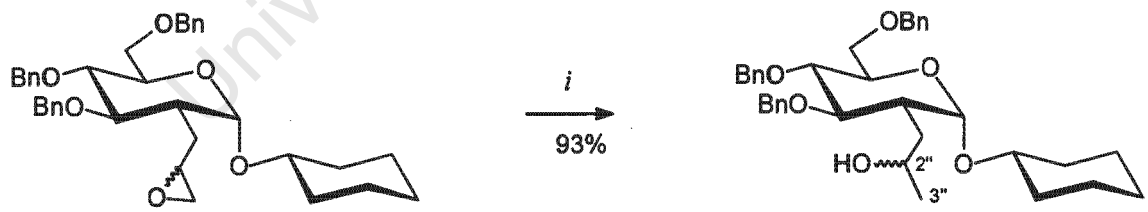


203 **204**

Scheme 77 *Reagents and conditions*: *i*) *m*-CPBA, CH_2Cl_2, rt, 26 h (1:1)

Doubling of signals in the NMR spectrum of the mixture **204** made assignments difficult, however the epoxide signals were evident from both ^1H and ^{13}C NMR spectra. Thus for the diastereomer **204a**, the ^1H NMR spectrum displayed signals at δ 3.01-2.94 (m) for H-2′′, a doublet of doublets at δ 2.68 (*J* 5.0, 4.2 Hz) for H-3′′$_a$ and a doublet of doublets at δ 2.47 (*J* 5.0, 2.6 Hz) for H-3′′$_b$. The ^{13}C NMR spectrum displayed signals at δ 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 $LiAlH_4$ in THF gave an inseparable diastereomeric mixture (1:1, by ^1H NMR) of secondary alcohols **205** in 93% yield (Scheme 78). The ^1H NMR spectrum of **205a** displayed a doublet at δ 1.15 (3 H, *J* 6.0 Hz) for the methyl protons while the ^{13}C NMR spectrum displayed diagnostic signals at δ 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 ν_{max} 3426 cm^{-1} (OH).

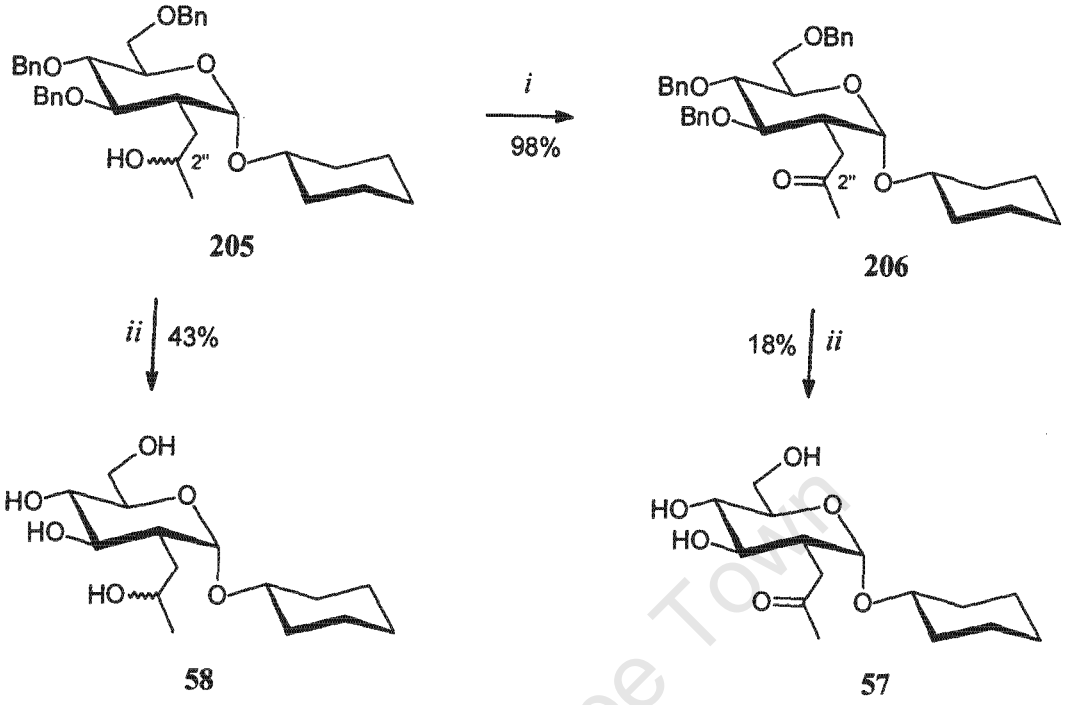


204 **205**

Scheme 78 *Reagents and conditions*: *i*) $LiAlH_4$, THF, 0 °C, 2 h (1:1)

Treatment of the diastereomic 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 ^1H NMR spectrum displayed a doublet of doublets at δ 2.66 (*J* 16.2, 3.4 Hz) for H-1′′$_a$ and a singlet at δ 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 δ 207.77 for the C-2′′ carbonyl group, having shifted from δ

65.96 and 66.39 for C-2′′ in **205**. In addition, the IR spectrum displayed a new absorption at ν_{max} 1714 cm^{-1} for the carbonyl group.



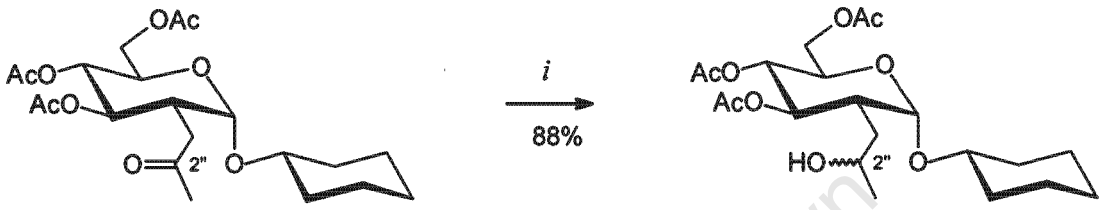
Scheme 79 *Reagents and conditions*: *i*) TPAP, NMO, ms, CH_2Cl_2, rt, 1 h; *ii*) H_2, Pd/C, MeOH-EtOAc, rt, 7 days (**57**), 4 days (**58**)

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 $PdCl_2$ and $CuCl_2$ under an atmospheric oxygen pressure in DMF-water[184,185] for 4 days gave ketone **207** in 50% yield (Scheme 80). In the case where only a catalytic quantity of $PdCl_2$ 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 ^1H 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.

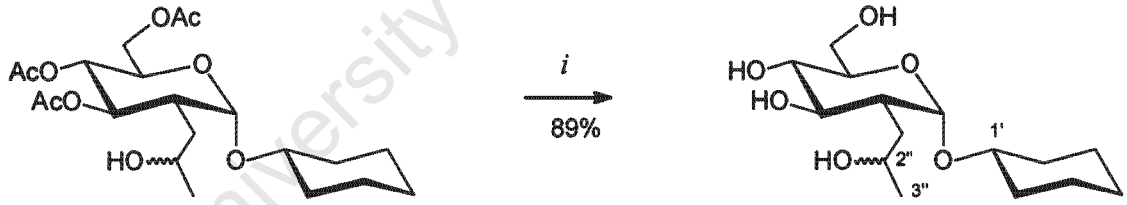
The ^{1}H NMR spectrum of **208a** displayed important signals at δ 3.85-3.77 (m) for H-2′′ and at δ 1.17 (3 H, d, *J* 6.0 Hz) for the methyl protons. The ^{13}C NMR spectrum displayed a new signal at δ 66.74 (C-2′′) confirming the reduction of the carbonyl group, which had shifted from δ 206.43 for 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).



207 **208**

Scheme 82 *Reagents and conditions*: *i*) $NaBH_4$, 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).



208 **58**

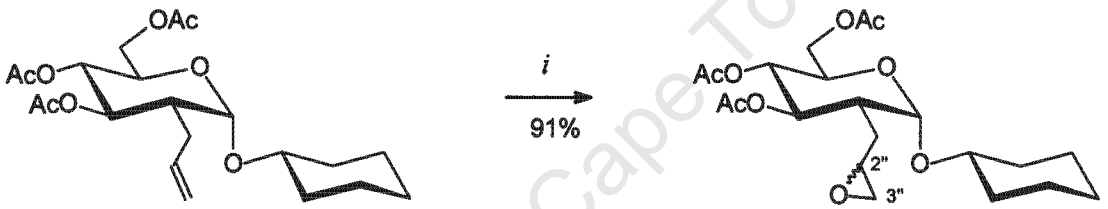
Scheme 83 *Reagents and conditions*: *i*) NaOMe, MeOH-CH_2Cl_2, rt, 18 h (1:1)

The absence of acetoxy groups in the ^{1}H and ^{13}C NMR supported a successful deacetylation. For diastereomer **58a**, the ^{1}H 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 ^{13}C 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.

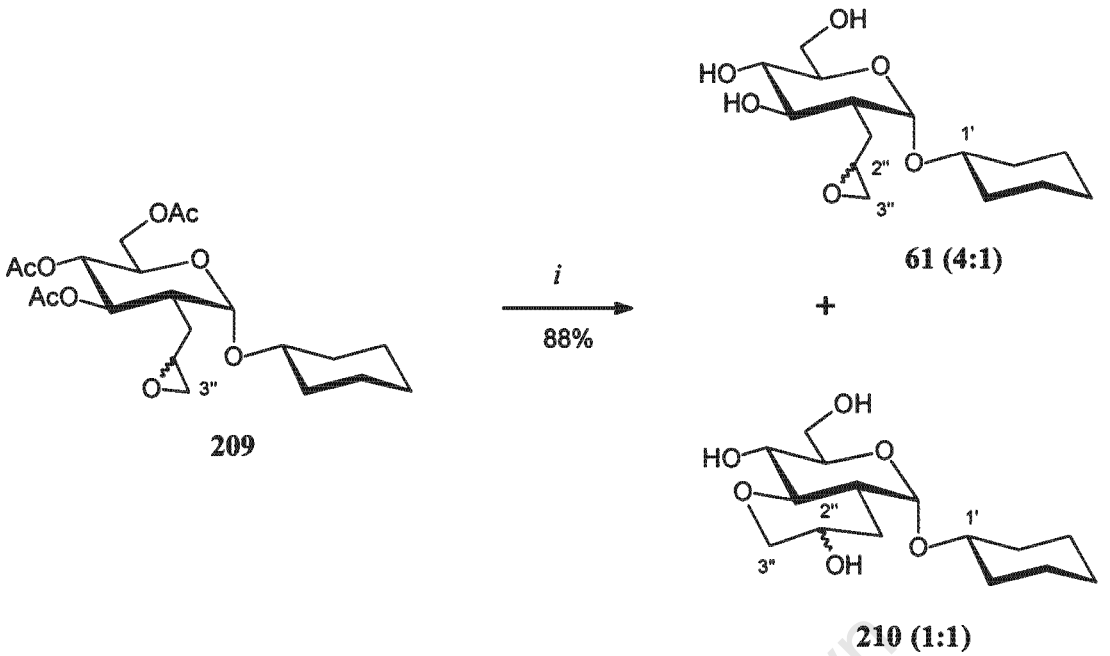
The epoxide was prepared by treating compound **201a** with *m*-CPBA[177,178] to give an inseparable diastereomeric mixture (1:1, by ^{1}H NMR) of epoxides **209** in 91% yield as an oil (Scheme 84). Although doubling of signals in the NMR spectroscopy of the mixture made assignments difficult, the epoxide signals were evident from both ^{1}H and ^{13}C NMR spectra. Thus for diastereomer **209a**, the ^{1}H NMR spectrum displayed important signals at δ 2.82 (m) for H-2′′, δ 2.66 (t, *J* 5.0 Hz) for H-3′′$_a$ and δ 2.36 (dd, *J* 5.0, 2.6 Hz) for H-3′′$_b$. The ^{13}C NMR spectrum displayed signals at δ 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**.



201a **209**

Scheme 84 *Reagents and conditions*: *i*) *m*-CPBA, CH_2Cl_2, rt, 24 h (1:1)

Catalytic deacetylation of diastereomeric mixture of epoxides **209** under *Zemplén* conditions followed by dilution of the solution with water gave an inseparable diastereomeric mixture (4:1, by ^{1}H NMR) of epoxides **61** in 50% yield after column chromatography, together with an inseparable diastereomeric mixture (1:1, by ^{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^+ resin led to total decomposition of the desired product (tlc).



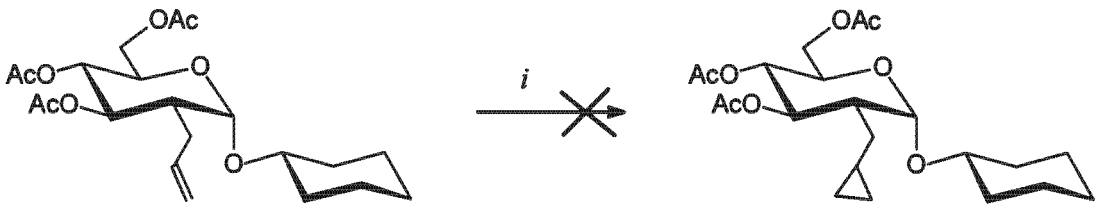
Scheme 85 *Reagents and conditions*: *i*) NaOMe, MeOH-CH_2Cl_2, rt, 6 h

Given our experience to date, the presence of epoxide signals was clearly discernible from both ^1H and ^{13}C NMR spectra but only one of the epoxide diastereomers could be characterized by NMR. Thus, the ^1H NMR spectrum of **61a** displayed signals at δ 5.04 (d, $J_{1,2}$ 3.2 Hz) for H-1, δ 3.07-3.00 (m) for H-2′′, δ 2.77 (dd, *J* 5.0, 4.0 Hz) for H-3′′$_a$ and δ 2.51 (d, *J* 5.0, 2.8 Hz) for 3′′$_b$ while its ^{13}C NMR spectrum displayed signals at δ 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 ^1H and ^{13}C NMR and the accurate mass spectra led to the tentative assignment of the structure. The ^1H NMR spectrum of **210a** displayed signals at δ 5.15 (d, $J_{1,2}$ 3.0 Hz) for H-1, and δ 4.11 (m) for H-2′′. The ^{13}C NMR spectrum displayed signals at δ 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 cylopropanated 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 cyclopropanate **201a** using modified Simmons-Smith reaction conditions[186-188] were unfortunately unsuccessful (Scheme 86). The reactions were conducted in different solvents (e.g toluene, Et_2O, hexane, CH_2Cl_2) and at different temperatures (0 °C, rt, 70 °C) without success. Increasing the equivalents of Et_2Zn and CH_2I_2 (> 10 eq) made no difference.

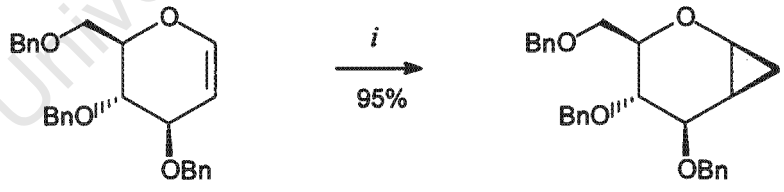


201a **211**

Scheme 86 *Reagents and conditions*: *i*) Et_2Zn, CH_2I_2

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.

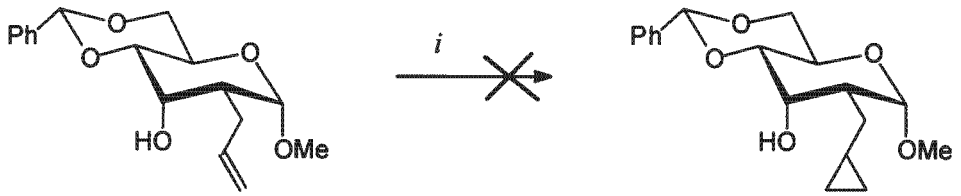
These disappointing results prompted a model study on cyclcopropation. Following a procedure by Hoberg,[186] benzylated glucal **212** was reacted under modified Simmons-Smith reaction conditions [Et_2Zn, 1 M in toluene) (6 eq), CH_2I_2 (6 eq), Et_2O, rt, 6 h] to give known cyclopropanated sugar **116** in excellent yield (Scheme 87). The spectroscopic data for **116** was in agreement with the literature values.[102]



212 **116**

Scheme 87 *Reagents and conditions*: *i*) Et_2Zn, CH_2I_2, Et_2O, rt, 6 h

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**



159a **62**

Scheme 88 *Reagents and conditions*: *i*) Et_2Zn, CH_2I_2, Et_2O, 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, undisered 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-*myo*-inositol **51**, 1-*O*-[2′-deoxy-2′-C-(2′′-oxopropyl)-α-D-glucopyranosyl]-D-*myo*-inositol **52** and cyclohexyl 2-C-allyl-2-deoxy-α-D-glucopyranoside **59** are biologically active.[i] While compounds **51** and **52** do not inhibit the growth of *Mycobacterium smegmatis* in *vitro*, a pronounced inhibition of incorporation of [^{3}H]inositol by whole cells into inositol containing metabolites was observed (Figure 20). The experiments involved monitoring the uptake of [^{3}H]inositol by *M. smegmatis* as shown in details in Figure 20.

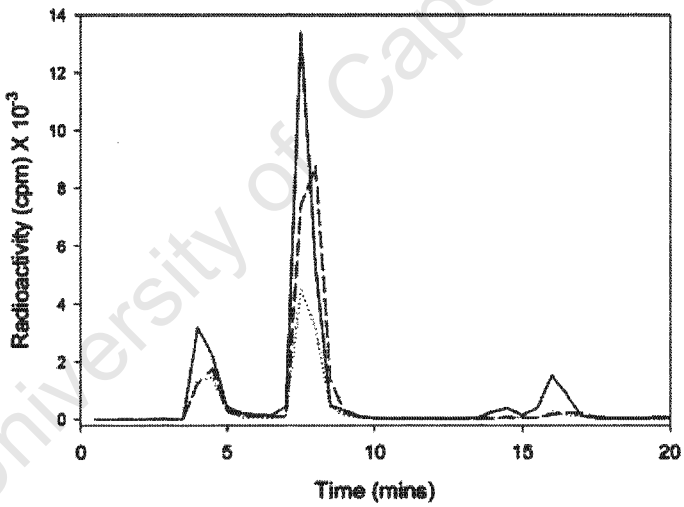
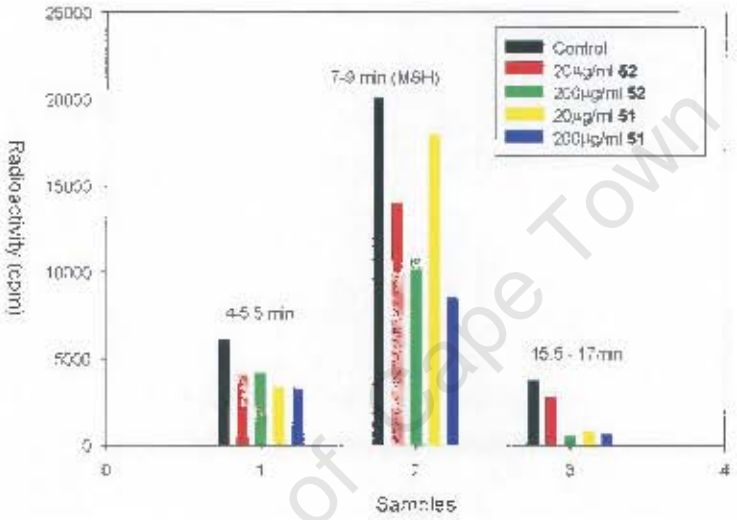


Figure 20. Effect of **51** on the incorporation of [^{3}H]inositol into acid soluble metabolites of *Mycobacterium smegmatis*: *M. smegmatis* was grown in Middle brook medium containing 5% glycerol. [^{3}H]Inositol was added when the culture reached an absorbance of 0.44 at 600 nm. Cells were incubated for 3.5 h in the presence of two different amounts of **51** and was then harvested and sonicated in 0.25 M $HClO_4$ to obtain the acid soluble fraction, which was chromatographed on a Vydac 201HS54 octadecilesilane 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**.

[i] 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 [^{3}H]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.



Figire 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).

It is evident, therefore, that **51** and **52** inhibit the incorporation of [^{3}H]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 [^{3}H]inositol by whole cells of *Mycobacterium smegmatis* into a number of metabolites which contain inositol.

CHAPTER 4

EXPERIMENTAL

4.1 General Procedures

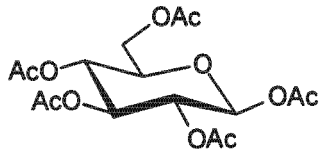
Preparative: All solvents were freshly distilled. Diethyl ether and tetrahydrofuran were distilled under nitrogen and dried over sodium wire with benzophenone. Toluene and benzene were distilled over sodium under nitrogen. Dichloromethane was distilled over phosphorus pentoxide and the condensor was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

Reactions were monitored by thin layer chromatography (tlc) 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.

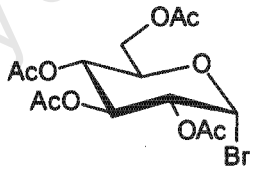
Nuclear Magnetic Resonance spectra were recorded on a Varian Unity 400 (100 MHz for ^{13}C, 376.3 MHz for ^{19}F) or Varian Mercury 300 MHz (75 MHz for ^{13}C) and were carried out in d-chloroform unless otherwise stated. Chemical shifts (δ) were recorded using residual chloroform (δ 7.24 in ^{1}H NMR and δ 77.00 in ^{13}C NMR) or tetramethylsilane as an internal standard (δ 0.00). For D_2O, dioxane (δ 3.75 in ^{1}H NMR and δ 67.19 in ^{13}C NMR) was used as an internal standard. For CD_3OD, the residual methanol peak (δ 3.31 in ^{1}H NMR and δ 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-β-D-glucopyranose (150)



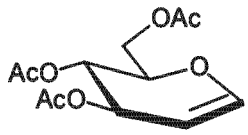
A suspension of anhydrous sodium acetate (40.0 g, 0.49 mol) and D-glucose (80 g, 0.44 mol) in acetic anhydride (560 ml, 5.94 mol) was heated at reflux for 1 h. The clear solution was allowed to cool to room temperature and then poured into crushed ice (160 ml). After standing for 3 h with occasional 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); δ_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 × $COOCH_3$); δ_C (75 MHz; $CDCl_3$) 170.53, 170.02, 169.32, 169.17, 168.88 (5 × $COOCH_3$), 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 × $COOCH_3$).

2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (151)



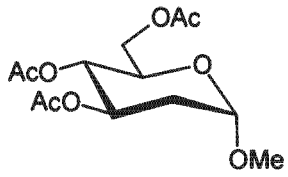
To a solution of **150** (23.0 g, 58.92 mmol) in CH_2Cl_2 (24 ml) was added HBr in acetic acid (30%, 23 ml, 388.2 mmol). The round-bottomed flask was tightly stoppered and kept at room temperature for 2 h. Azeotropic distillation with toluene (300 ml x 3) and diethyl ether (80 ml × 2) resulted in a white 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); δ_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 × $COOCH_3$); δ_C (75 MHz; $CDCl_3$) 170.44, 169.78, 169.74, 169.41 (4 × $COOCH_3$), 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 × $COOCH_3$).

3,4,6-Tri-*O*-acetyl-D-glucal (86)



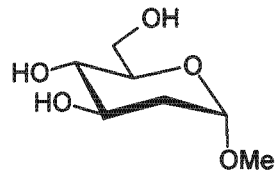
A mixture of **151** (12.56 g, 30.54 mmol) and zinc dust (25g) in acetic acid (50%, 126 ml) was stirred vigorously at room temperature for 2 h. The zinc dust was then filtered off and the filtrate evaporated. Water (126 ml) was added to the syrup, which was extracted with diethyl ether, washed successively with saturated $NaHCO_3$ and water, then dried over $MgSO_4$ 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); δ_H (400 MHz; $CDCl_3$) 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-6_a), 4.22 (1 H, m, H-5), 4.17 (1 H, dd, *J* 11.9, 3.2 Hz, H-6_b), 2.06, 2.04, 2.01 (9 H, 3 s, 3 × $COOCH_3$); δ_C (100 MHz; $CDCl_3$) 170.52, 170.34, 169.51 (3 × $COOCH_3$), 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 × $COOCH_3$).

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 $NaHCO_3$, then dried over $MgSO_4$ 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%); δ_H (300 MHz; $CDCl_3$) 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-6_a), 4.06 (1 H, dd, *J* 12.2, 2.3 Hz, H-6_b), 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-2_{eq}), 2.08, 2.02, 1.99 (9 H, 3 s, 3 × $COOCH_3$), 1.84-1.75 (1 H, ddd, *J* 12.9, 11.7, 3.6 Hz, H-2_{ax}); δ_C (75 MHz; $CDCl_3$) 170.70, 169.12, 169.87 (3 × $COOCH_3$), 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 × $COOCH_3$).

Methyl 2-deoxy-α-D-arabino-hexopyranoside (153)



1. From **86**

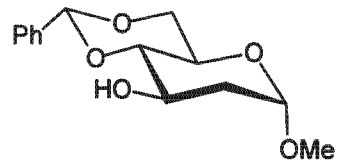
(i) Methanolic sodium methoxide (1 M, 11 ml, 11 mmol) was added dropwise to a solution of **86** (6.10 g, 22.40 mmol) in CH_2Cl_2-MeOH (3:5, 40 ml). The solution was stirred at room temperature for 18 h and then neutralized with Amberlite IR-120 H^+ resin. After filtration to remove the resin, the solvent 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 $NaHCO_3$, then dried over $MgSO_4$ 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**

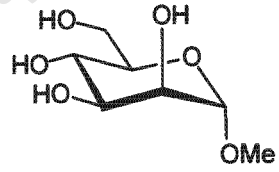
Methanolic sodium methoxide (1 M, 1.92 ml, 1.92 mmol) was added dropwise to a solution of **154a** (1.17 g, 3.84 mmol) in CH_2Cl_2-MeOH (7:15 ml). The solution was stirred at room temperature for 18 h and then neutralized with Amberlite IR-120 H^+ resin. After filtration of resin, the solvent was evaporated 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-α-D-arabino-hexopyranoside (155)



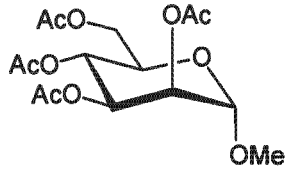
A mixture of **153** (360 mg, 2.02 mmol) and finely powdered anhydrous zinc chloride (0.33 g, 2.42 mmol) in freshly distilled benzaldehyde (1.5 ml, 14.78 mmol) was stirred vigorously at room temperature for 3 days. Water was added, and the mixture then extracted with ethyl acetate. The ethyl acetate 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); δ_H (400 MHz; $CDCl_3$) 7.50-7.35 (5 H, m, aromatic H), 5.55 (1 H, s, PhC*H*-), 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_{eq}), 1.80-1.73 (1 H, m, H-2_{ax}); δ_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-α-D-mannopyranoside (157)



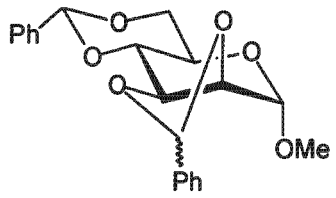
A solution of D-mannose (40.0 g, 222.02 mmol) in methanol (200 ml) was heated at reflux for 40 min. Methanol-equilibrated Dowex-50 (H^+) resin (25 g, *prepared by soaking Dowex-50, X-8, 50-100 mesh, for 18 h in each of six successive portions of absolute methanol and finally filtered under vacuum until 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-α-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_2Cl_2. The CH_2Cl_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); δ_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 × $COOCH_3$); δ_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)

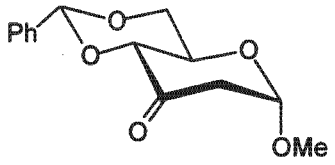


α,α-Dimethoxytoluene (46 g, 302.46 mmol) and anhydrous *p*-toluenesulfonic acid (0.5 g, 2.63 mmol) was added to a solution of **157** (25.0 g, 128.74 mmol) in DMF (150 ml), and the solution was heated at 75 °C for 4 h. The mixture was poured with vigorous stirring into ice-water (500 ml) containing sodium 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 ^{1}H 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.,[123] 180-182 °C, lit.,[193] 188 °C); δ_H (300 MHz; $CDCl_3$) 7.58-7.35 (10 H, m, aromatic H), 6.29 (1 H, s, PhC*H*-), 5.64 (1 H, s, PhC*H*′-), 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-6_a), 4.14 (1 H, d, *J* 5.6 Hz, H-2), 3.93-3.81 (3 H, m, H-4, H-5, H-6_b), 3.40 (3 H, s, -OMe); δ_C (75 MHz; $CDCl_3$) 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 $C_{21}H_{22}O_6$ 370.14164.

Recrystallization of the mother liquor from ethanol gave the other diastereomer **96b**; 105-107 °C (from ethanol) (lit.,[193] 106-107 °C); δ_H (400 MHz; $CDCl_3$) 7.59-7.34 (10 H, m, aromatic H), 5.97 (1 H, s, PhC*H*-), 5.52 (1 H, s, PhC*H*′-), 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-6_a), 3.87-3.71 (3 H, m, H-4, H-5, H-6_b), 3.43 (3 H, s, -OMe); δ_C (100 MHz; $CDCl_3$) 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 $C_{21}H_{22}O_6$ 370.14164.

Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-erythro-hexopyranosid-3-ulose (94)



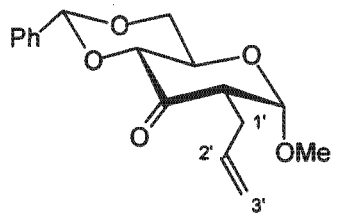
1. From **96**

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-pheny-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); ν_{max}/cm^{-1} 1750 (C=O); δ_H (300 MHz; $CDCl_3$) 7.50-7.34 (5 H, m, aromatic H), 5.56 (1 H, s, PhC*H*-), 5.12 (1 H, d, *J* 4.3 Hz, H-1), 4.35 (1 H, dd, *J* 10.1, 4.5 Hz, H-6_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_b), 3.36 (3 H, s, -OMe), 2.81 (1 H, dd, *J* 14.5, 4.3 Hz, H-2_{ax}), 2.64 (1 H, d, *J* 14.5 Hz, H-2_{eq}); δ_C (75 MHz; $CDCl_3$) 197.39 (C-3), 136.57, 129.23, 129.22, 126.37 (aromatic C), 102.08 (C-1), 100.57 (C-PhCH-), 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 $(M)^+$. Calcd for $C_{14}H_{16}O_5$ 264.09977.

Methyl 4,6-*O*-benzylidene-2-C-allyl-2-deoxy-α-D-ribo-hexopyranosid-3-ulose (70)



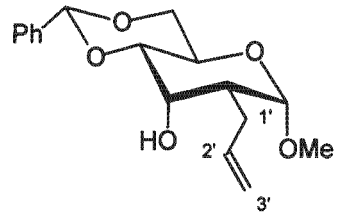
1. General procedure for alkylation via enolate:

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 min and a solution of **94** (200 mg, 0.76 mmol) in THF (5 ml) was then added. After 15 min, 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 $MgSO_4$ 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 min, 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 h. The reaction was stopped by the addition of cold saturated NH_4Cl, extracted with CH_2Cl_2, and the organic phase dried over $MgSO_4$ 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_{max}/cm^{-1} 1755 (C=O); δ_H (400 MHz; $CDCl_3$) 7.56-7.34 (5 H, m, aromatic H), 5.76 (1 H, m, H-2′), 5.58 (1 H, s, PhC*H*-), 5.14-5.05 (2 H, m, H-3′$_a$, H-3′$_b$), 5.01 (1 H, d, *J* 4.0 Hz, H-1), 4.38 (1 H, dd, *J* 10.3, 4.8 Hz, H-6$_a$), 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$_b$), 3.38 (3 H, s, -OMe), 2.81 (1 H, m, H-2), 2.59 (1 H, m, H-1′$_a$), 2.22 (1 H, m, H-1′$_b$); δ_C (100 MHz; $CDCl_3$) 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-Ph*C*H-), 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: *m/z* 304.12926 $(M)^+$. Calcd for $C_{17}H_{20}O_5$ 304.13107.

Methyl 4,6-*O*-benzylidene-2-C-allyl-2-deoxy-α-D-allopyranoside (159a)



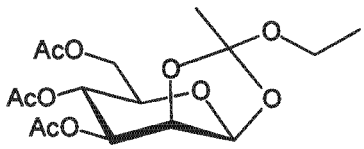
1. Reduction of **70** *with LAH*

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%, α-allo **159a**:α-gluco **159b** = 8:1 by ^{1}H-NMR) as crystals. Recrystallization from petroleum ether afforded a single diastereomer **159a.**

2. Reduction of **70** *with* $NaBH_4$

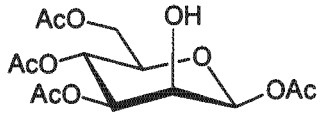
$NaBH_4$ (0.2 g, 5.49 mmol) was added portion-wise to a solution of **70** (167 mg, 0.55 mmol) in THF-MeOH (3:6 ml) at –20 °C. The reaction mixture was allowed to reach 0 °C within 2 h, quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated to give a single diastereomer **159a** (166 mg, 98%) as crystals; mp 124-125 °C (from petroleum ether); $[\alpha]_D$ +73.4° (*c* 1.2, $CHCl_3$); ν_{max}/cm^{-1} 3018 (OH); δ_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, PhC*H*-), 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$_b$), 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); δ_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-Ph*C*H-), 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 CH_2Cl_2, dried over $MgSO_4$ and concentrated. The resulting syrup was dissolved in CH_2Cl_2 (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 CH_2Cl_2, successively washed with ice-water (× 5), 1% $NaHCO_3$, ice-water, dried over $MgSO_4$ 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 CH_2Cl_2, washed with water, dried over $MgSO_4$ 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); δ_H (300 MHz; $CDCl_3$) 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-6_a), 4.13 (1 H, dd, *J* 12.1, 2.8 Hz, H-6_b), 3.66 (1 H, m, H-5), 3.59-3.49 (2 H, m, -OCH_2CH$_3$), 2.10, 1.05, 2.03 (9 H, 3 s, 3 × COOCH_3), 1.73 (3 H, s, -O$_3$CCH_3), 1.17 (3 H, t, *J* 7.1 Hz, -OCH$_2$CH_3); δ_C (75 MHz; $CDCl_3$) 170.61, 170.35, 169.39 (3 × *C*OOCH$_3$), 124.21 (C-O$_3$*C*CH$_3$), 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-O*C*H$_2$CH$_3$), 24.62 (C-O$_3$C*C*H$_3$), 20.71, 20.67, 20.62 (3 × COO*C*H$_3$), 15.03 (C-OCH$_2$*C*H$_3$); HREIMS: *m/z* 361.11159 (M-CH$_3$)$^+$. Calcd. for $C_{15}H_{21}O_{10}$ 361.11347 (M-CH$_3$)$^+$.

1,3,4,6-Tetra-*O*-acetyl-β-D-mannopyranose (160)



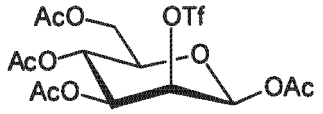
1. From D-mannose

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 CH_2Cl_2 (× 3). The dichloromethane extracts were combined, successively washed with cold water, saturated $NaHCO_3$, cold water and dried over $MgSO_4$. 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**

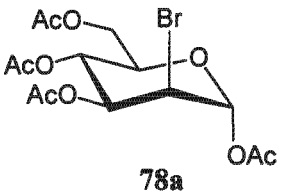
A solution of **161** (11.0 g, 29.23 mmol) in acetone (66 ml) was treated with 1 N HCl (7 ml) at room temperature for 10 min and the solvent was evaporated at less than 20 °C at 20 mmHg. The residue was dissolved in CH_2Cl_2, washed with water, and the CH_2Cl_2 phase dried over $MgSO_4$ and concentrated. 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.,[136] 164-165 °C, lit.,[135] 164-166 °C); ν_{max}/cm^{-1} 3450 (OH); δ_H (300 MHz; $CDCl_3$) 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-6_a), 4.18 (1 H, t (br), *J* 2.8 Hz, H-2), 4.12 (1 H, dd, *J* 12.5, 2.4 Hz, H-6_b), 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 × $COOCH_3$); δ_C (75 MHz; $CDCl_3$) 170.66, 170.03, 169.49, 168.43 (4 × *C*$OOCH_3$), 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 × $COOCH_3$); HREIMS: *m/z* 331.10273 $(M\text{-}OH)^+$. Calcd for $C_{14}H_{19}O_9$ 331.10291 $(M\text{-}OH)^+$.

1,3,4,6-Tetra-*O*-acetyl-2-*O*-(trifluoromethanesulfonyl)-β-D-mannopyranose (162)

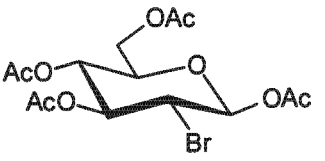


To a mixture of **160** (450 mg, 1.29 mmol) and pyridine (0.27 ml, 3.4 mmol) in CH_2Cl_2 (10 ml) was added trifluoromethanesulfonic anhydride (0.24 ml, 1.4 mmol) dropwise at 0 °C. The mixture was allowed to warm to room temperature over a period of 2 h. The reaction mixture was then poured into cold saturated $NaHCO_3$ (150 ml) and extracted with CH_2Cl_2 (× 3). The combined organic layers were washed with 1% HCl and dried over $MgSO_4$. Evaporation of the solvent afforded compound **162** (609 mg, 98%) as crystals; mp 119-121 °C (from ethanol) (lit.,[127] 118-119 °C); δ_H (300 MHz; $CDCl_3$) 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-6_a), 4.17 (1 H, dd, *J* 12.4, 2.8 Hz, H-6_b), 3.82 (1 H, m, H-5), 2.16, 2.10, 2.09, 2.06 (12 H, 4 s, 4 × $COOCH_3$); δ_C (75 MHz; $CDCl_3$) 170.57, 169.79, 169.10, 167.92 (4 × $COOCH_3$), 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 × $COOCH_3$); HREIMS: *m/z* 421.04004 $(M\text{-}C_2H_3O_2)^+$. Calcd for $C_{13}H_{16}O_{10}F_3S$ 421.04163 $(M\text{-}C_2H_3O_2)^+$.

1,3,4,6-Tetra-*O*-acetyl-2-bromo-2-deoxy-α-D-mannopyranose (78a) and 1,3,4,6-Tetra-*O*-acetyl-2-bromo-2-deoxy-β-D-glucopyranose (78b)



78a



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.

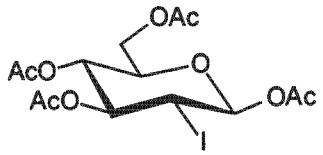
1. From tri-O-acetyl D-glucal **86**

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 $MgSO_4$, the solvent evaporated and the resulting mixture of diastereomers (α-manno **78a**:β-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**: δ_H (300 MHz; $CDCl_3$) 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-6_a), 4.16-4.04 (2 H, m, H-5, H-6_b), 2.15, 2.10, 2.09, 2.05 (12 H, 4 s, 4 × $COOCH_3$); δ_C (75 MHz; $CDCl_3$) 170.63, 170.01, 169.22, 168.07 (4 × $COOCH_3$), 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 × $COOCH_3$).

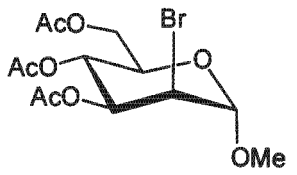
Diastereomer **78b**: mp 96-97 °C (from ethanol) (lit.,[125,127] 95-96 °C); δ_H (300 MHz; $CDCl_3$) 5.80 (1 H, d, *J* 9.0 Hz, H-1), 5.33 (1 H, dd, *J* 10.5, 9.1 Hz, H-3), 5.01 (1 H, dd, *J* 10.0, 9.1 Hz, H-4), 4.30 (1 H, dd, *J* 12.6, 4.5 Hz, H-6_a), 4.09 (1 H, dd, *J* 12.6, 2.4 Hz, H-6_b), 3.89 (1 H, 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 × $COOCH_3$); δ_C (75 MHz; $CDCl_3$) 170.47, 169.54, 169.43, 168.52 (4 × $COOCH_3$), 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 × $COOCH_3$).

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-iodo-β-D-glucopyranose (79)

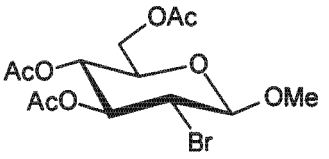


To a solution of **162** (501 mg, 1.04 mmol) in benzene (25 ml) was added tetrabutylammonium iodide (0.76 g, 2.08 mmol) and the solution heated at reflux for 2 h. After cooling to room temperature, benzene was evaporated under reduced pressure. The residue was purified by column chromatography using 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); δ_H (300 MHz; $CDCl_3$) 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-6_a), 4.08 (1 H, dd, *J* 12.6, 2.2 Hz, H-6_b), 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 × $COOCH_3$); δ_C (75 MHz; $CDCl_3$) 170.50, 170.49, 169.46, 169.45 (4 × $COOCH_3$), 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 × $COOCH_3$); HREIMS: *m/z* 358.01073 $(M)^+$. Calcd for $C_{14}H_{19}O_9I$ 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)



163a



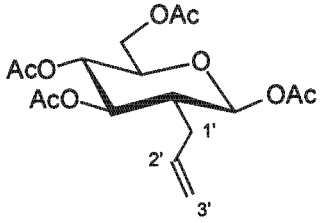
163b

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 $Na_2S_2O_3$ and water, then dried over $MgSO_4$. Evaporation of solvent gave a mixture of diastereomers (3.45 g, 98%, α-manno **163a**:β-gluco **163b** = 2:1 by ^{1}H-NMR). The residue was crystallised 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; $CDCl_3$) 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-6_a), 4.13 (1 H, dd, *J* 12.3, 2.4 Hz, H-6_b), 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 × $COOCH_3$); δ_C (75 MHz; $CDCl_3$) 170.56, 169.76, 169.43 (3 × *C*$OOCH_3$), 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 × $COOCH_3$).

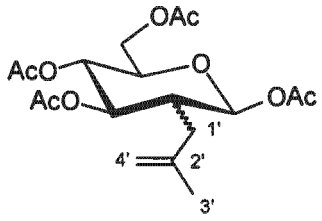
Column chromatography of the mother liquor using ethyl acetate-petroleum ether (3:7) afforded the other diasteromer **163a** as an oil; δ_H (300 MHz; $CDCl_3$) 5.38 (1 H, t, *J* 9.8 Hz, H-4), 5.19 (1 H, dd, *J* 9.8, 4.0 Hz, H-3), 4.95 (1 H, d, *J* 1.1 Hz, H-1), 4.42 (1 H, dd, *J* 4.0, 1.1 Hz, H-2), 4.23 (1 H, dd, *J* 12.3, 5.1 Hz, H-6_a), 4.14 (1 H, dd, *J* 12.3, 2.7 Hz, H-6_b), 3.97 (1 H, m, H-5), 3.40 (3 H, s, -OMe), 2.08, 2.06, 2.03 (9 H, 3 s, 3 × $COOCH_3$); δ_C (75 MHz; $CDCl_3$) 170.62, 169.90, 169.39 (3 × *C*$OOCH_3$), 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 × $COOCH_3$).

1,3,4,6-Tetra-*O*-acetyl-2-C-allyl-2-deoxy-β-D-glucopyranose (81a)



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-gluco **81a**:β-manno **81b** = 9:1 by ^{1}H-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); δ_H (400 MHz; $CDCl_3$) 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′$_a$, H-3′$_b$), 4.29 (1 H, dd, *J* 12.4, 4.4 Hz, H-6$_a$), 4.05 (1 H, dd, *J* 12.4, 2.0 Hz, H-6$_a$), 3.73 (1 H, m, H-5), 2.17-2.09 (3 H, m, H-2, H-1′$_a$, H-1′$_b$), 2.11, 2.05, 2.01, 1.99 (12 H, 4 s, 4 × $COOCH_3$); δ_C (100 MHz; $CDCl_3$) 170.81, 170.31, 169.97, 169.04 (4 × *C*$OOCH_3$), 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 × $COOCH_3$); HREIMS: *m/z* 329.12403 (M- C_2H_3O)$^+$. Calcd for $C_{15}H_{21}O_8$ 329.12364 (M-C_2H_3O)$^+$.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-C-methallyl-β-D-glucopyranose (82a) and 1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-C-methallyl-β-D-mannopyranose (82b)

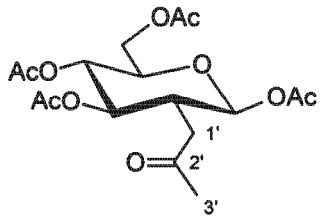


A solution of **78b** (502 mg, 1.22 mmol) and methallyltributylstannane (1.25 ml, 3.62 mmol) in benzene (10 ml) was degassed at room temperature for 30 min and then heated to reflux for 10 min. A solution of AIBN (27 mg, 0.14 mmol) in anhydrous benzene (2 ml) was added dropwise through a pressure-compensating 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%, β-gluco **82a**:β-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** (β-gluco): mp 62-64 °C (from petroleum ether); $[\alpha]_D$ +16.15° (*c* 1.3, $CHCl_3$); δ_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′$_a$), 4.63 (1 H, d, *J* 1.1 Hz, H-4′$_b$), 4.31 (1 H, dd, *J* 12.4, 4.5 Hz, H-6$_a$), 4.06 (1 H, dd, *J* 12.4, 2.2 Hz, H-6$_b$), 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′$_a$, H-1′$_b$), 2.08, 2.07, 2.00, 1.98 (12 H, 4 s, 4 × $COOCH_3$), 1.73 (3 H, s (br), H-3′); δ_C (75 MHz; $CDCl_3$) 170.64, 170.25, 169.82, 168.96 (4 × *C*$OOCH_3$), 142.34 (C-2′), 112.22 (C-4′), 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′), 21.65 (C-3′), 20.86, 20.71, 20.62, 20.61 (4 × $COOCH_3$); HRFABMS: *m/z* 409.147246 $(M+Na)^+$. Calcd for $C_{18}H_{26}O_9Na$ 409.147444 $(M+Na)^-$.

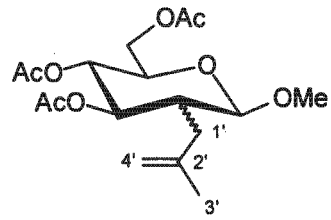
Diastereomer **82b** (β-manno): δ_H (300 MHz; $CDCl_3$) 5.84 (1 H, d, *J* 2.4 Hz, H-1), 4.72 (1 H, s (br), H-4′$_a$), 4.65 (1 H, s (br), H-4′$_b$), 1.65 (3 H, s, H-3′); δ_C (75 MHz; $CDCl_3$) 170.47, 170.09, 169.68, 168.81 (4 × *C*$OOCH_3$), 142.90 (C-2′), 111.95 (C-4′), 92.41 (C-1), 72.75 (C-3), 71.08 (C-5), 65.69 (C-4), 62.40 (C-6), 38.16 (C-2), 31.26 (C-1′), 22.15 (C-3′), 20.76, 20.60, 20.56, 20.47 (4 × $COOCH_3$); HRFABMS: *m/z* 409.147246 $(M+Na)^+$. Calcd for $C_{18}H_{26}O_9Na$ 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 CH_2Cl_2-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 CH_2Cl_2, washed with 10% HCl (× 3), and the CH_2Cl_2 phase dried over $MgSO_4$ 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 ^{1}H-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); $[\alpha]_D$ +13.86° (*c* 1.5, $CHCl_3$); ν_{max}/cm^{-1} 1752 (C=O); δ_H (400 MHz; $CDCl_3$) 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-6_a), 4.00 (1 H, dd, *J* 12.4, 2.4 Hz, H-6_b), 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 × $COOCH_3$); δ_C (100 MHz; $CDCl_3$) 204.94 (C-2′), 170.59, 170.36, 169.62, 168.81 (4 × *C*$OOCH_3$), 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 × $COOCH_3$); HREIMS: *m/z* 345.11735 $(M-C_2H_3O)^+$. Calcd for $C_{15}H_{21}O_9$ 345.11856 $(M-C_2H_3O)^+$.

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)

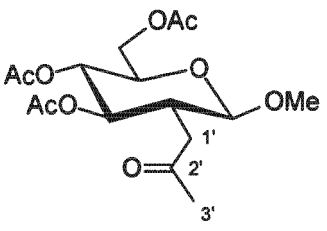


A solution of **163b** (2.57 g, 6.70 mmol) and methallyltributylstannane (6.9 ml, 19.9 mmol) in benzene (100 ml) was degassed at room temperature for 30 min and then heated to reflux for 10 min. A solution of AIBN (135 mg, 0.7 mmol) in anhydrous benzene (12 ml) was added drop-wise through a pressure-compensating 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 ^{1}H-NMR) as an oil.

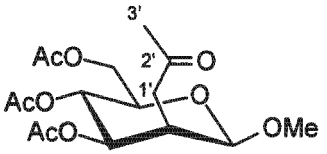
Diastereomer **165a** (β-gluco): δ_H (300 MHz; $CDCl_3$) 5.04-4.92 (2 H, m, H-3, H-4), 4.65 (1 H, d, *J* 1.0 Hz, H-4′$_a$), 4.63 (1 H, d, *J* 1.0 Hz, H-4′$_b$), 4.29 (1 H, dd, *J* 12.2, 4.8 Hz, H-6$_a$), 4.15 (1 H, d, *J* 8.1, H-1), 4.11 (1 H, dd, *J* 12.2, 2.4 Hz, H-6$_b$), 3.64 (1 H, m, H-5), 3.49 (3 H, s, -OMe), 2.36-2.04 (3 H, m, H-2, H-1′$_a$, H-1′$_b$), 2.07, 1.99, 1.93 (9 H, 3 s, 3 × $COOCH_3$), 1.72 (3 H, d, *J* 0.6 Hz, H-3′); δ_C (75 MHz; $CDCl_3$) 170.75, 170.44, 169.89 (3 × *C*$OOCH_3$), 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 × $COOCH_3$); HRFABMS: *m/z* 381.151969 $(M+Na)^+$. Calcd for $C_{17}H_{26}O_8Na$ 381.152529 $(M+Na)^+$.

Diastereomer **165b** (β-manno): δ_H (300 MHz; $CDCl_3$) 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′$_a$), 4.70 (1 H, s (br), H-4′$_b$), 4.51 (1 H, d, *J* 2.4 Hz, H-1), 4.26-4.31 (2 H, m, H-6$_a$, H-6$_b$), 3.68 (1 H, m, H-5), 3.46 (3 H, s, -OMe), 2.58-1.89 (3 H, m, H-2, H-1′$_a$, H-1′$_b$), 2.08, 2.04, 2.00 (9 H, 3 s, 3 × $COOCH_3$), 1.70 (3 H, s, H-3′); δ_C (75 MHz; $CDCl_3$) 170.75, 170.44, 169.89 (3 × *C*$OOCH_3$), 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 × $COOCH_3$); HRFABMS: *m/z* 381.151969 $(M+Na)^+$. Calcd for $C_{17}H_{26}O_8Na$ 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)



166a



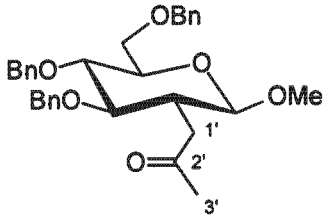
166b

A solution of mixture of diastereomers **165a** and **165b** (1.35 g, 3.77 mmol) in CH_2Cl_2-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 CH_2Cl_2, washed with 10% HCl (× 3), and the CH_2Cl_2 phase dried over $MgSO_4$, 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 ^{1}H-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); $[\alpha]_D$ +3.18° (*c* 1.1, $CHCl_3$); ν_{max}/cm^{-1} 1748 (C=O); δ_H (400 MHz; $CDCl_3$) 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-6_a), 4.12 (1 H, dd, *J* 12.4, 2.4 Hz, H-6_b), 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′$_a$), 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 × $COOCH_3$); δ_C (75 MHz; $CDCl_3$) 206.08 (C-2′), 170.66, 170.41, 169.67 (3 × $COOCH_3$), 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 × $COOCH_3$); HRFABMS: *m/z* 383.131842 $(M+Na)^+$. Calcd for $C_{16}H_{24}O_9Na$ 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); $[\alpha]_D$ −37.8° (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 1748 (C=O); δ_H (300 MHz; $CDCl_3$) 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-6_a), 4.12 (1 H, dd, *J* 12.3, 2.7 Hz, H-6_b), 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′$_a$), 2.49 (1 H, dd, *J* 17.4, 5.8 Hz, H-1′$_b$), 2.18

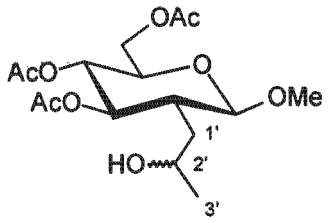
(3 H, s, H-3′), 2.09, 2.02, 1.95 (9 H, 3 s, 3 × $COOCH_3$); δ_C (75 MHz; $CDCl_3$) 206.52 (C-2′), 170.63, 169.81, 169.70 (3 × $COOCH_3$), 101.71 (C-1), 72.28 (C-5), 71.78 (C-3), 66.46 (C-4), 62.56 (C-6), 56.93 (C-OMe), 38.65 (C-2), 36.04 (C-1′), 30.48 (C-3′), 20.73, 20.67, 20.66 (3 × $COOCH_3$); HRFABMS: *m/z* 383.131842 $(M+Na)^+$. Calcd for $C_{16}H_{24}O_9Na$ 383.131795 $(M+Na)^+$.

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 $MgSO_4$ 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); $[\alpha]_D$ +3.9° (*c* 1.0, $CHCl_3$); ν_{max}/cm^{-1} 1705 (C=O); δ_H (400 MHz; $CDCl_3$) 7.40-7.18 (15 H, m, aromatic H), 4.92-4.56 (6 H, m, 3 × $PhCH_2$-), 4.27 (1 H, d, *J* 8.4 Hz, H-1), 3.78 (2 H, d, *J* 3.2 Hz, $H\text{-}6_a$, $H\text{-}6_b$), 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, $H\text{-}1'_a$), 2.48 (1 H, dd, *J* 15.9, 6.2 Hz, $H\text{-}1'_b$), 2.20 (1 H, m, H-2), 2.06 (3 H, s, H-3′); δ_C (100 MHz; $CDCl_3$) 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 × $PhCH_2$-), 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 $C_{31}H_{36}O_6Na$ 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* $NaBH_4$

$NaBH_4$ (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 $NaHCO_3$, extracted with CH_2Cl_2, dried over $MgSO_4$ 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 ^{1}H-NMR) as an oil.

2. Reduction of **166a** *with* $Zn(BH_4)_2$

To a solution of **166a** (50 mg, 0.14 mmol) in diethyl ether (1 ml) at 0 °C was added $Zn(BH_4)_2$ (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 $MgSO_4$ 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 ^{1}H-NMR) as an oil.

3. Reduction of **166a** *with* $NaBH_4$-$CeCl_2$

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 $NaBH_4$ (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 $MgSO_4$ 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 ^{1}H-NMR) as an oil.

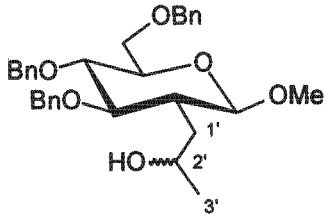
4. Reduction of **166a** *with* $LiAlH(O\text{-}^tBu)_3$

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, then mixture extracted with ethyl acetate, and the ethyl acetate phase dried over $MgSO_4$ 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 ^{1}H-NMR) as an oil; ν_{max}/cm^{-1} 3480 (br) (OH).

Diastereomer **169a**: δ_H (400 MHz; $CDCl_3$) 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_a), 4.09 (1 H, dd, *J* 12.4, 2.4 Hz, H-6_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 × $COOCH_3$), 1.19 (1 H, m, H-2), 1.44 (2 H, m, H-1′$_a$, H-1′$_b$), 1.12 (3 H, d, *J* 6.4 Hz, H-3′); δ_C (100 MHz; $CDCl_3$) 170.94, 170.78, 169.85 (3 × *C*$OOCH_3$), 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 × $COOCH_3$); HRFABMS: *m/z* 385.147331 $(M+Na)^+$. Calcd for $C_{16}H_{26}O_9Na$ 385.147446 $(M+Na)^+$.

Diastereomer **169b**: δ_H (400 MHz; $CDCl_3$) 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_a,), 4.09 (1 H, dd, *J* 12.4, 2.4 Hz, H-6_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 × $COOCH_3$), 1.19 (1 H, m, H-2), 1.44 (2 H, m, H-1′$_a$, H-1′$_b$), 1.11 (3 H, d, *J* 6.0 Hz, H-3′); δ_C (100 MHz; $CDCl_3$) 170.94, 170.78, 169.85 (3 × *C*$OOCH_3$), 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 × $COOCH_3$); HRFABMS: *m/z* 385.147331 $(M+Na)^+$. Calcd for $C_{16}H_{26}O_9Na$ 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 $MgSO_4$ 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 ^{1}H-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 CH_2Cl_2, and the CH_2Cl_2 phase dried over $MgSO_4$ 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 ^{1}H-NMR) as an oil.

3. Reduction of **168** *with CBS*

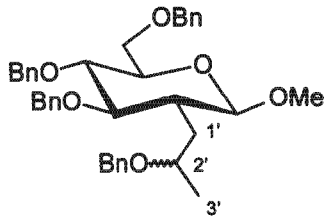
A solution of $BH_3{\cdot}Me_2S$ (2 M in toluene, 1.05 ml, 2.1 mmol) in THF (2 ml) was stirred for 5 min at room temperature. Diphenylprolinol (25 mg, 0.099 mmol) was added and the reaction mixture was heated at 40 °C for 12 h. A solution of **168** (101 mg, 0.20 mmol) in THF (2 ml) was added dropwise 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 $MgSO_4$ 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 ^{1}H-NMR) as an oil; ν_{max}/cm^{-1} 3455 (OH).

Diastereomer **170a**: δ_H (300 MHz; $CDCl_3$) 7.40-7.18 (15 H, m, aromatic H), 4.97-4.56 (6 H, m, 3 × PhC*H*$_2$-), 4.15 (1 H, d, *J* 8.7 Hz, H-1), 3.87 (1 H, m, H-2′), 3.75 (2 H, m, H-6$_a$, H-6$_b$), 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′$_a$, H-1′$_b$), 1.13 (3 H, d, *J* 6.3 Hz, H-3′); δ_C (75 MHz; $CDCl_3$) 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

C), 104.83 (C-1), 83.26 (C-3), 79.74 (C-4), 75.11, 75.00, 74.60, 73.53 (3 × PhCH$_2$-, C-5), 68.97 (C-6), 66.14 (C-2′), 56.72 (C-OMe), 44.32 (C-2), 37.41 (C-1′), 23.54 (C-3′); HRFABMS: *m/z* 529.256720 $(M+Na)^+$. Calcd for $C_{31}H_{38}O_6Na$ 529.256594 $(M+Na)^+$.

Diastereomer **170b**: δ_H (300 MHz; $CDCl_3$) 7.40-7.18 (15 H, m, aromatic H), 4.97-4.56 (6 H, m, 3 × PhC*H*$_2$-), 4.11 (1 H, d, *J* 8.4 Hz, H-1), 3.87 (1 H, m, H-2′), 3.75 (2 H, m, H-6$_a$, H-6$_b$), 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′$_a$, H-1′$_b$)), 1.12 (3 H, d, *J* 6.0 Hz, H-3′); δ_C (75 MHz; $CDCl_3$) 138.16, 137.99, 137.89, 128.46, 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 × 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 $C_{31}H_{38}O_6Na$ 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 CH_2Cl_2-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 $MgSO_4$ 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 ^{1}H-NMR) as crystals.

1. From **170**

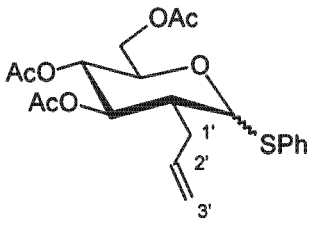
NaH (50%, 0.017 g, 0.37 mmol) was added to a solution of **170** (31 mg, 0.061 mmol) in THF (3 ml) at 0 °C. After 5 min, benzyl bromide was added and the reaction mixture was heated at reflux for 5 h. The solution was cooled down to room temperature and excess NaH was decomposed by the addition of MeOH followed by water. The THF was evaporated, and the water extracted with EtOAc which was washed with saturated NaCl, dried over $MgSO_4$ 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**: δ_H (400 MHz; $CDCl_3$) 7.38-7.19 (20 H, m, aromatic H), 4.91-4.45 (8 H, m, 4 × PhC*H*$_2$-), 4.10 (1 H, d, *J* 8.4 Hz, H-1), 3.83-3.71 (3 H, m, H-6$_a$, H-6$_b$, 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-1′$_a$, H-1′$_b$), 1.20 (3 H, d, *J* 6.0 Hz, H-3′); δ_C (100 MHz; $CDCl_3$) 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 × PhCH$_2$-), 74.55 (C-5), 73.45 (C-PhCH$_2$-), 73.29 (C-2′), 70.06 (C-PhCH$_2$-), 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 $(M\text{-}CH_3)^+$. Calcd for $C_{37}H_{41}O_6$ 581.29031 $(M\text{-}CH_3)^+$.

Diastereomer **171b**: δ_H (400 MHz; $CDCl_3$) 7.38-7.19 (20 H, m, aromatic H), 4.94-4.39 (8 H, m, 4 × PhC*H*$_2$-), 4.22 (1 H, d, *J* 8.0 Hz, H-1), 3.83-3.63 (4 H, m, H-6_a, H-6_b, 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′$_a$, H-1′$_b$), 1.18 (3 H, d, *J* 6.0 Hz, H-3′); δ_C (100 MHz; $CDCl_3$) 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 × PhCH_2-), 74.45 (C-5), 73.98, 73.43 (C-PhCH_2-, C-2′), 70.06 (C-PhCH_2-), 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 $(M\text{-}CH_3)^+$. Calcd for $C_{37}H_{41}O_6$ 581.29031 $(M\text{-}CH_3)^+$.

Phenyl 3,4,6-tri-*O*-acetyl-2-C-allyl-2-deoxy-1-thio-α/β-D-glucopyranoside (172)

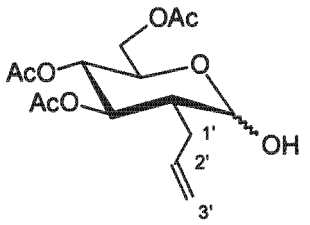


Boron trifluoride etherate (0.29 ml, 2.42 mmol) was added dropwise to a mixture of **81a** (150 mg, 0.40 mmol) and $PhSSiMe_3$ (0.31 ml, 1.61 mmol) in CH_2Cl_2 (5 ml) at 0 °C. The reaction was allowed to reach room temperature over 18 h. Saturated $NaHCO_3$ was added and the solution extracted with CH_2Cl_2, dried over $MgSO_4$ 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 ^{1}H-NMR) as an oil.

α-*Anomer*: δ_H (400 MHz; $CDCl_3$) 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′$_a$, H-3′$_b$), 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-6$_a$), 4.01 (1 H, dd, *J* 12.1, 2.4 Hz, H-6$_b$), 2.44-2.16 (3 H, m, H-2, H-1′$_a$, H-1′$_b$), 2.02, 2.01, 2.00 (9 H, 3 s, 3 × $COOCH_3$); δ_C (100 MHz; $CDCl_3$) 170.44, 170.13, 169.81 (3 × *C*$OOCH_3$), 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 × $COOCH_3$); HRFABMS: *m/z* 445.129696 $(M+Na)^+$. Calcd for $C_{21}H_{26}O_7SNa$ 445.129686 $(M+Na)^+$.

β-*Anomer*: δ_H (400 MHz; $CDCl_3$) 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′$_a$, H-3′$_b$), 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-6$_a$), 4.12 (1 H, dd, *J* 12.1, 2.2 Hz, H-6$_b$), 3.59 (1 H, m, H-5), 2.34-2.01 (3 H, m, H-2, H-1′$_a$, H-1′$_b$), 2.04, 1.98, 1.98 (9 H, 3 s, 3 × $COOCH_3$); δ_C (100 MHz; $CDCl_3$) 170.44, 170.06, 169.72 (3 × *C*$OOCH_3$), 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 × $COOCH_3$); HRFABMS: *m/z* 445.129696 $(M+Na)^+$. Calcd for $C_{21}H_{26}O_7SNa$ 445.129686 $(M+Na)^+$.

3,4,6-Tri-*O*-acetyl-2-C-allyl-2-deoxy-α/β-D-glucopyranose (174)

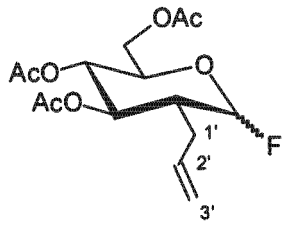


Hydrazine acetate (37 mg, 0.40 mmol) was added to a solution of **81a** (100 mg, 0.27 mmol) in DMF (3 ml) and the reaction was heated at 60 °C for 1 h. The solution was cooled and diluted with ethyl acetate, which was then washed with saturated NaCl (× 3), dried over $MgSO_4$ and concentrated. The resulting residue was purified by column chromatography using ethyl acetate-petroleum ether (2:3) as eluent to afford an inseparable mixture of anomers **174** (84 mg, 94%, α:β = 2:1 by ^{1}H-NMR) as an oil.

α-*Anomer*: δ_H (400 MHz; $CDCl_3$) 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-6$_a$), 4.10-4.06 (1 H, m, H-6$_a$), 2.76 (s (br), -OH), 2.17 (2 H, m, H-1′$_a$, H-1′$_b$), 2.08, 2.01, 2.01 (9 H, 3 s, 3 × $COOCH_3$), 2.01 (1 H, m, H-2); δ_C (100 MHz; $CDCl_3$) 173.62, 173.30, 172.81 (3 × *C*$OOCH_3$), 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 × $COOCH_3$); HRFABMS: *m/z* 353.120887 $(M+Na)^+$. Calcd for $C_{15}H_{22}O_8Na$ 353.121231 $(M+Na)^+$.

β-*Anomer*: δ_H (400 MHz; $CDCl_3$) 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-6$_a$, H-6$_b$), 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 × $COOCH_3$), 1.91 (1 H, m, H-2); δ_C (100 MHz; $CDCl_3$) 173.62, 173.30, 172.81 (3 × *C*$OOCH_3$), 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 × $COOCH_3$); HRFABMS: *m/z* 353.120887 $(M+Na)^+$. Calcd for $C_{15}H_{22}O_8Na$ 353.121231 $(M+Na)^+$.

3,4,6-Tri-*O*-acetyl-2-C-allyl-2-deoxy-α/β-D-glucopyranosyl fluoride (173)

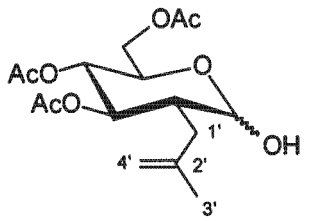


To a solution of **174** (123 mg, 0.37 mmol) in THF (3 ml) at 0 °C was added DAST (0.15 ml, 1.11 mmol) dropwise. After the addition, the ice-water bath was removed and the stirring was continued at room temperature for 30 min. The mixture was then cooled (0 °C) and excess DAST was quenched with methanol followed by saturated $NaHCO_3$. The solution was extracted with CH_2Cl_2, and the CH_2Cl_2 phase dried over $MgSO_4$ 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 ^{1}H-NMR) as an oil.

α-*Anomer*: δ_H (400 MHz; $CDCl_3$) 5.73 (1 H, m, H-2′), 5.66-5.52 (1 H, dd, $J_{1,F}$ 51.0 Hz, $J_{1,2}$ 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′$_b$), 4.30 (1 H, dd, *J* 12.2, 4.2 Hz, H-6$_a$), 4.14 (1 H, m, H-5), 4.10 (1 H, dd, *J* 12.2, 2.2 Hz, H-6$_b$), 2.23-2.00 (3 H, m, H-2, H-1′$_a$, H-1′$_b$), 2.08, 2.03, 2.02 (9 H, 3 s, 3 × $COOCH_3$); δ_C (100 MHz; $CDCl_3$) 173.38, 173.06, 172.59 (3 × *C*$OOCH_3$), 136.73 (C-2′), 120.78 (C-3′), 110.07 (d, $J_{1,F}$ 223.0 Hz, C-1), 74.09 (C-3), 72.93 (d, $J_{5,F}$ 3.8 Hz, C-5), 71.54 (C-4), 64.59 (C-6), 46.82 (d, $J_{2,F}$ 24.3 Hz, C-2), 34.06 (d, $J_{1',F}$ 2.3 Hz, C-1′), 23.49, 23.41, 23.40 (3 × $COOCH_3$); δ_F (376.3 MHz; $CDCl_3$) -146.59 (dd, $J_{1,F}$ 51.0 Hz, $J_{2,F}$ 29.75 Hz); HRFABMS: *m/z* 333.135369 $(M+H)^+$. Calcd for $C_{15}H_{21}FO_7$ 333.134955 $(M+H)^+$.

β-*Anomer*: δ_H (400 MHz; $CDCl_3$) 5.74 (1 H, m, H-2′), 5.28-5.14 (1 H, dd, $J_{1,F}$ 51.2 Hz, $J_{1,2}$ 7.2 Hz, H-1), 5.14-5.02 (4 H, m, H-3, H-4, H-3′$_a$, H-3′$_b$)), 4.26 (1 H, dd, *J* 12.0, 4.8 Hz, H-6$_a$), 4.18 (1 H, dd, *J* 12.0, 2.6 Hz, H-6$_b$), 3.77 (1 H, m, H-5), 2.32-2.00 (3 H, m, H-2, H-1′$_a$, H-1′$_b$), 2.08, 2.03, 2.02 (9 H, 3 s, 3 × $COOCH_3$); δ_C (100 MHz; $CDCl_3$) 173.38, 172.93, 172.46 (3 × *C*$OOCH_3$), 135.96 (C-2′), 121.19 (C-3′), 111.56 (d, $J_{1,F}$ 214.0 Hz, C-1), 74.76 (d, $J_{5,F}$ 4.5 Hz, C-5), 74.17 (d, $J_{3,F}$ 10.6 Hz, C-3), 71.77 (C-4), 65.15 (C-6), 47.52 (d, $J_{2,F}$ 22.0 Hz, C-2), 33.80 (d, $J_{1',F}$ 1.5 Hz, C-1′), 23.49, 23.41, 23.40 (3 × $COOCH_3$); δ_F (376.3 MHz; $CDCl_3$) -133.55 (d (br), $J_{1,F}$ 51.2 Hz); HRFABMS: *m/z* 333.135369 $(M+H)^+$. Calcd for $C_{15}H_{21}FO_7$ 333.134955 $(M+H)^+$.

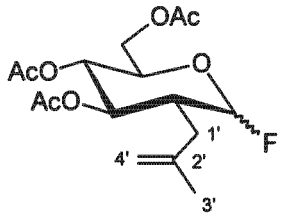
3,4,6-Tri-*O*-acetyl-2-deoxy-2-C-methallyl-α/β-D-glucopyranose (175)



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 (× 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%, α:β = 6:1 by ^{1}H-NMR) as an oil.

α-*Anomer*: δ_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′$_a$), 4.76 (1 H, s (br), H-4′$_b$), 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′$_a$, H-1′$_b$), 2.09, 2.02, 2.00 (9 H, 3 s, 3 × $COOCH_3$), 1.72 (3 H, s (br), H-3′); δ_C (100 MHz; $CDCl_3$) 170.70, 170.42, 169.92 (3 × *C*$OOCH_3$), 141.98 (C-2′), 112.54 (C-4′), 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′), 21.97 (C-3′), 20.67, 20.66, 20.65 (3 × $COOCH_3$); HRFABMS: *m/z* 367.136777 $(M+Na)^+$. Calcd for $C_{16}H_{24}O_8Na$ 367.136880 $(M+Na)^+$.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-C-methallyl-α/β-D-glucopyranosyl fluoride (176)

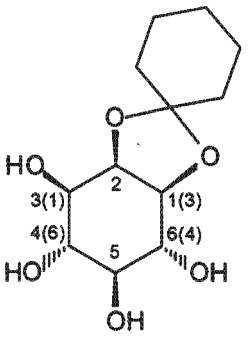


To a solution of **175** (157 mg, 0.45 mmol) in THF (5 ml) at 0 °C was added DAST (0.24 ml, 1.82 mmol) dropwise. After the addition the ice-water bath was removed and the stirring was continued at room temperature for 30 min. The mixture was cooled (0 °C) and the excess DAST was quenched with methanol followed by saturated $NaHCO_3$. The solution was extracted with CH_2Cl_2, and the CH_2Cl_2 phase dried over $MgSO_4$ 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 ^{1}H-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*: $[\alpha]_D$ +96.9° (*c* 3.3, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.58-5.45 (1 H, dd, $J_{1,F}$ 50.4 Hz, $J_{1,2}$ 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′$_a$), 4.73 (1 H, d, *J* 1.2 Hz, H-4′$_b$), 4.27 (1 H, dd, *J* 12.3, 4.2 Hz, H-6$_a$), 4.11 (1 H, m, H-5), 4.05 (1 H, dd, *J* 12.3, 2.0 Hz, H-6$_b$), 2.21-2.06 (3 H, m, H-2, H-1′$_a$, H-1′$_b$), 2.04, 1.97, 1.96 (9 H, 3 s, 3 × $COOCH_3$), 1.68 (3 H, s (br), H-3′); δ_C (100 MHz; $CDCl_3$) 170.72, 170.43, 169.96 (3 × *C*$OOCH_3$), 141.18 (C-2′), 113.62 (t, *J* 3.8 Hz, C-4′), 107.38 (dd, $J_{1,F}$ 222.3 Hz, C-1), 71.55 (C-3), 70.24 (d, $J_{5,F}$ 3.0 Hz, C-5), 68.90 (C-4), 61.93 (C-6), 42.17 (d, $J_{2,F}$ 24.3 Hz, C-2), 35.32 (C-1′), 22.20 (C-3′), 20.83, 20.80, 20.76 (3 × $COOCH_3$); δ_F (376.3 MHz; $CDCl_3$) -147.11 (dd, $J_{1,F}$ 50.4 Hz, $J_{2,F}$ 30.47 Hz); FABMS: *m/z* 369.1 $(M+Na)^+$. Calcd for $C_{16}H_{23}FO_7Na$ 369.1 $(M+Na)^+$.

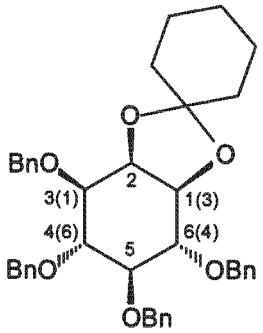
β-*Anomer*: $[\alpha]_D$ +70.5° (*c* 3.2, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 5.25-5.10 (1 H, dd, $J_{1,F}$ 51.6 Hz, $J_{1,2}$ 6.0 Hz, H-1), 5.05 (1 H, t, *J* 8.7 Hz, H-4), 4.96 (1 H, t, *J* 8.7 Hz, H-3), 4.74 (1 H, d, *J* 0.8 Hz, H-4′$_a$), 4.78 (1 H, d, *J* 0.8 Hz, H-4′$_b$), 4.24 (1 H, dd, *J* 12.2, 5.2 Hz, H-6$_a$), 4.18 (1 H, dd, *J* 12.2, 3.2 Hz, H-6$_b$), 3.81 (1 H, m, H-5), 2.30-2.12 (3 H, m, H-2, H-1′$_a$, H-1′$_b$), 2.06, 1.99, 1.96 (9 H, 3 s, 3 × $COOCH_3$), 1.72 (3 H, s (br), H-3′); δ_C (100 MHz; $CDCl_3$) 170.50, 170.07, 169.56 (3 × *C*$OOCH_3$), 141.59 (C-2′), 112.87 (C-4′), 109.32 (d, $J_{1,F}$ 215.5 Hz, C-1), 72.50 (d, $J_{3,F}$ 8.4 Hz, C-3), 71.93 (d, $J_{5,F}$ 4.5 Hz, C-5), 68.55 (C-4), 62.41 (C-6), 42.75 (d, $J_{2,F}$ 22.1 Hz, C-2), 36.89 (d, $J_{1',F}$ 2.3 Hz, C-1′), 21.76 (C-3′), 20.60, 20.56, 20.54 (3 × $COOCH_3$); δ_F (376.3 MHz; $CDCl_3$) 130.37 (d (br), $J_{1,F}$ 51.6 Hz); FABMS: *m/z* 369.1 $(M+Na)^+$. Calcd for $C_{16}H_{23}FO_7Na$ 369.1 $(M+Na)^+$.

1,2-*O*-Cyclohexylidene-DL-*myo*-inositol (178)



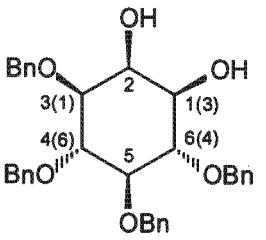
A cloudy mixture of *myo*-inositol (10.0 g, 55.5 mmol), cylohexanone (87.3 ml, 0.76 mol), TsOH (10% in DMF, 2.5 ml), DMF (98 ml) and toluene (21 ml) was heated to reflux with a *Dean-Stark* separator filled with toluene. Four additional portions of 10% TsOH solution (2.5 ml) were added at 2 h intervals. 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% Et_3N. 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 $C_{12}H_{20}O_6Na$ 283.1 $(M+Na)^+$.

1,4,5,6-Tetra-*O*-benzyl-2,3-*O*-cyclohexylidene-DL-*myo*-inositol (179)



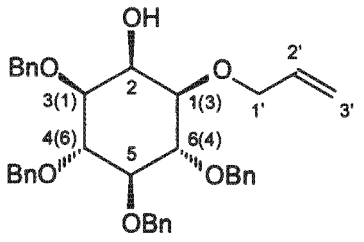
A portion of dry compound **178** (1.40 g, 5.38 mmol) in THF (30 ml) was cooled to 0 °C, and NaH (50%, 1.5 g, 32.3 mmol) was added portion-wise with stirring. After 30 min, benzyl bromide (3.8 ml, 32.3 mmol) was added slowly, then the ice-water bath removed and the heterogenous mixture heated at reflux 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 $MgSO_4$ 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; δ_H (300 MHz; $CDCl_3$) 7.40-7.26 (20 H, m, aromatic H), 4.94-4.74 (8 H, m, 4 × PhC*H*$_2$-), 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(CH_2)$_5$-, cyclohexylidene); δ_C (75 MHz; $CDCl_3$) 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, cyclohexylidene), 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 × PhCH_2-), 74.03 (C-2), 73.93, 73.11 (2 × PhCH_2-), 37.38, 35.04, 25.08, 23.94, 23.68 (5 × -CH_2-, cyclohexylidene); FABMS: *m/z* 619.2 $(M-H)^+$. Calcd for $C_{40}H_{43}O_6$ 619.3 $(M-H)^+$.

1,4,5,6-Tetra-*O*-benzyl-DL-*myo*-inositol (180)



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); ν_{max}/cm^{-1} 3570 (OH); δ_H (300 MHz; $CDCl_3$) 7.38-7.25 (20 H, m, aromatic H), 4.98-4.72 (8 H, m, 4 × PhC*H*$_2$-), 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); δ_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 × PhCH_2-), 71.77 (C-1(3)), 69.21 (C-2); FABMS: *m/z* 563.3 $(M+Na)^+$. Calcd for $C_{34}H_{36}O_6Na$ 563.2 $(M+Na)^+$.

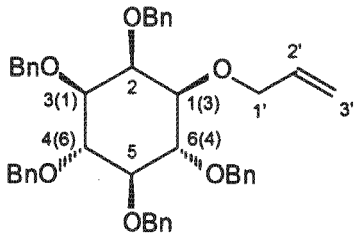
1-*O*-Allyl-3,4,5,6-tetra-*O*-benzyl-DL-*myo*-inositol (181a)



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 $NaHCO_3$ and saturated NaCl, before being dried over $MgSO_4$ 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 ^{13}C NMR) (1.60 g, 86%) as an oil; ν_{max}/cm^{-1} 3573 (OH);

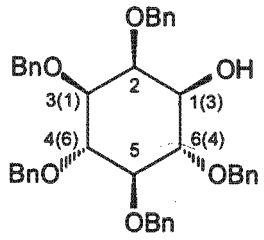
Diastereomer **181a**: δ_H (400 MHz; $CDCl_3$) 7.40-7.23 (20 H, m, aromatic H), 5.98 (1 H, m, H-2′), 5.35-5.20 (2 H, m, H-3′$_a$, H-3′$_b$), 4.96-4.73 (8 H, m, 4 × PhC*H*$_2$-), 4.26 (1 H, t, *J* 2.7 Hz, H-2), 4.23-4.20 (2 H, m, H-1′$_a$, H-1′$_b$), 4.03 (1 H, t, *J* 9.4 Hz, H-4(6)), 3.99 (1 H, t, *J* 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); δ_C (100 MHz; $CDCl_3$) 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 × PhCH_2-), 74.73 (C-2), 70.59 (C-1′); FABMS: *m/z* 603.2 $(M+Na)^+$. Calcd for $C_{37}H_{40}O_6Na$ 603.2 $(M+Na)^+$.

1-*O*-Allyl-2,3,4,5,6-penta-*O*-benzyl-DL-*myo*-inositol (182a)



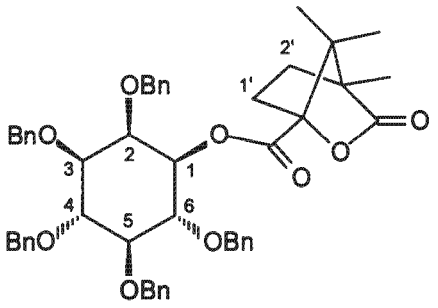
NaH (50%, 0.59 g, 12.27 mmol) was added to a solution of a mixture of **181a** and **181b** (1.15 g, 1.98 mmol) in THF (10 ml) at 0 °C. After 5 min, benzyl bromide was added and the reaction mixture heated to reflux for 3 h. Excess NaH was decomposed by the addition of MeOH followed by water. The THF was evaporated, and the aqueous phase extracted with EtOAc, which was then washed with saturated NaCl, dried over $MgSO_4$ 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; δ_H (300 MHz; $CDCl_3$) 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 × PhCH_2-), 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)); δ_C (75 MHz; $CDCl_3$) 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 × PhCH_2-), 74.01 (C-2), 72.73 (C-PhCH_2-), 71.57 (C-1′); FABMS: *m/z* 671.4 $(M+H)^+$. Calcd for $C_{44}H_{47}O_6$ 671.3 $(M+H)^+$.

1,2,4,5,6-Penta-*O*-benzyl-DL-*myo*-inositol (183)

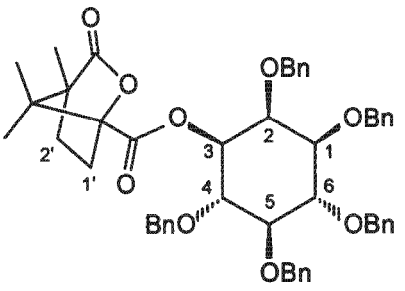


$PdCl_2$ (0.34 g, 1.89 mmol) was added to a solution of a mixture of **182a** and **182b** (7.0 g, 10.43 mmol) in EtOH-MeOH (1:1, 80 ml). The mixture was stirred for 5 h at room temperature, whereupon the solids were filtered through celite and solvent evaporated. Purification by column chromatography 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.,[174] 86-88 °C, lit.,[195] 92-94 °C); ν_{max}/cm^{-1} 3560 (OH); δ_H (400 MHz; $CDCl_3$) 7.38-7.29 (25 H, m, aromatic H), 5.03-4.72 (10 H, m, 5 × PhC*H*$_2$-), 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); δ_C (100 MHz; $CDCl_3$) 138.73, 138.71, 138.64, 138.60, 138.22, 128.42, 128.36, 128.32, 128.30, 128.27, 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 × Ph*C*H$_2$-), 72.40 (C-1(3)); FABMS: m/z 629.2 $(M-H)^+$. Calcd for $C_{41}H_{41}O_6$ 629.2 $(M-H)^+$.

2,3,4,5,6-Penta-*O*-benzyl-1-*O*-[(1S)-(−)-camphanoyl]-D-*myo*-inositol (184a) and 2,3,4,5,6-Penta-*O*-benzyl-1-*O*-[(1S)-(−)-camphanoyl]-L-*myo*-inositol (184b)



184a



184b

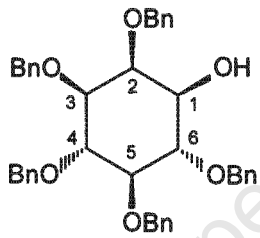
To a solution of **183** (3.12 g, 4.94 mmol) in CH_2Cl_2 (35 ml) was added (S)-(−)-camphanic acid chloride (1.39 g, 6.42 mmol), Et_3N (2.70 ml, 19.76 mmol) and DMAP (0.12 g, 0.98 mmol). The reaction mixture was left at room temperature for 28 h, then water was added, the mixture extracted with CH_2Cl_2, and the CH_2Cl_2 dried over $MgSO_4$ and concentrated. The resulting crystalline mixture of diastereomers was separated by chromatography on silica gel using Et_2O-CH_2Cl_2 (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); $[\alpha]_D$ +9.8° (*c* 2.9, $CHCl_3$); ν_{max}/cm^{-1} 1781, 1718 (C=O); δ_H (400 MHz; $CDCl_3$) 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 × PhCH_2-), 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 x -CH_3, camphanoyl); δ_C (100 MHz; $CDCl_3$) 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 × PhCH_2-, C-1, C-2), 54.71, 54.10 (2 C-quaternary C, campanoyl), 30.67, 28.85 (C-1′, C-2′), 16.68, 16.54, 9.58 (3 × -CH_3, camphanoyl); FABMS: *m/z* 895.0 $(M+Rb)^+$. Calcd for $C_{51}H_{54}O_6{}^{85}Rb$ 895.2 $(M+Rb)^+$.

Diastereomer **184b**: mp 161-163 °C (from ethyl acetate-petroleum ether); $[\alpha]_D$ −15.3° (*c* 2.5, $CHCl_3$); ν_{max}/cm^{-1} 1785, 1722 (C=O); δ_H (300 MHz; $CDCl_3$) 7.40-7.20 (25 H, m, aromatic H), 4.99-4.65 (10 H, m, 5 × PhCH_2-), 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-

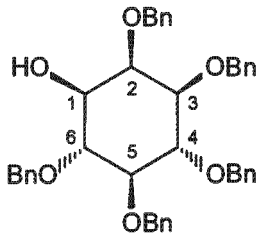
1.61 (1 H, m, H-2′$_b$), 1.08, 0.97, 0.85 (9 H, 3 s, 3 × -CH_3, camphanoyl); δ_C (75 MHz; $CDCl_3$) 177.89, 167.46 (2 × -C=O, camphanoyl), 138.59, 138.39, 138.35, 138.29,138.02, 128.42, 128.34, 128.32, 128.28, 128.26, 128.03, 128.00, 127.98, 127.80, 127.72, 127.70, 127.56, 127.50, 127.39, 127.19 (aromatic C), 90.84 (quaternary C, camphanoyl), 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, camphanoyl), 30.92, 28.94 (C-1′, C-2′), 16.62, 16.55, 9.61 (3 x -CH_3, camphanoyl); 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)



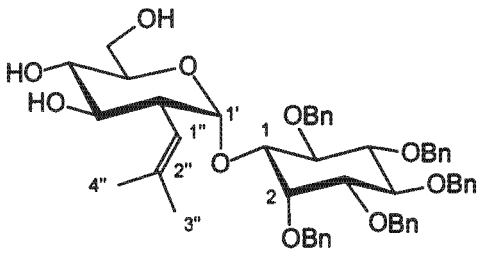
A mixture of **184a** (1.86 g, 2.29 mmol) and powdered potassium hydroxide (1.29 g, 22.99 mmol) in absolute ethanol (30 ml) was gently refluxed for 2 h. The solvent was evaporated, water then added and the mixture extracted with CH_2Cl_2, which was then dried over $MgSO_4$ and concentrated. The resulting 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; $[\alpha]_D$ +7.1° (*c* 1.0, $CHCl_3$) (lit.,[173] $[\alpha]_D$ +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 $C_{41}H_{42}O_6Na$ 653.287893 $(M+Na)^+$.

2,3,4,5,6-Penta-*O*-benzyl-L-*myo*-inositol (186)



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_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 **186** (1.38 g, 93%) as a gum; $[\alpha]_D$ −8.0° (*c* 1.0, $CHCl_3$) (lit.,[173] $[\alpha]_D$ −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 × PhC*H*$_2$-), 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 $C_{41}H_{42}O_6Na$ 653.287893 $(M+Na)^+$.

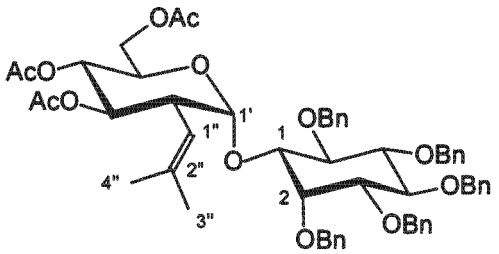
2,3,4,5,6-Penta-*O*-benzyl-1-*O*-[2′-C-(2′′-methylprop-1′′-enyl)-2′-deoxy-α-D-glucopyranosyl]-L-*myo*-inositol (189)



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 CH_2Cl_2 (10ml) 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). Et_3N (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 CH_2Cl_2. The CH_2Cl_2 phase was washed with saturated $NaHCO_3$ and water, then dried over $MgSO_4$ 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 ^{13}C-NMR) and unreacted acceptor **186**. The mixture was dissolved in CH_2Cl_2-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; $[\alpha]_D$ +43.2° (*c* 2.7, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 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 × PhC*H*$_2$-), 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′$_a$, H-6′$_b$), 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′′); δ_C (75 MHz; $CDCl_3$) 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 × PhCH_2-, 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

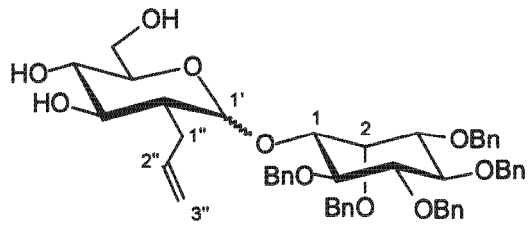
(C-3′′, C-4′′); HRFABMS: *m/z* 853.392986 $(M+Na)^+$. Calcd for $C_{51}H_{58}O_{10}Na$ 853.392746 $(M+Na)^+$.

2,3,4,5,6-Penta-*O*-benzyl-1-*O*-[3′,4′,5′-tri-*O*-acetyl-2′-C-(2′′-methylprop-1′′-enyl)-2′-deoxy-α-D-glucopyranosyl]-L-*myo*-inositol (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_2Cl_2 (3 ml) at room temperature. After 1 h, the reaction was stopped by the addition of water, and the mixture extracted with CH_2Cl_2, the CH_2Cl_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; $[\alpha]_D$ +35.4° (*c* 2.5, $CHCl_3$); δ_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 × PhC*H*$_2$-, 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 × $COOCH_3$), 1.42, 1.41 (6 H, 2 s, H-3′′, H-4′′); δ_C (100 MHz; $CDCl_3$) 170.73, 170.15, 169.95 (3 C-3 × *C*$OOCH_3$), 138.99, 138.88, 138.87, 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 × Ph*C*H_2-), 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 × $COOCH_3$), 18.05 (C-4′′); HRFABMS: *m/z* 979.422749 $(M+H)^+$. Calcd for $C_{57}H_{64}O_{13}$ 979.424439 $(M+H)^+$.

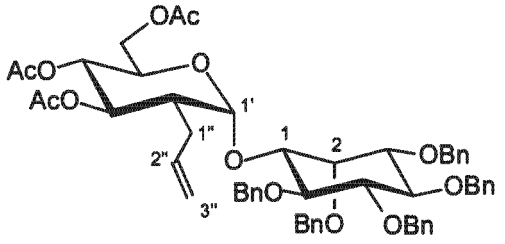
2,3,4,5,6-Penta-*O*-benzyl-1-*O*-(2′-C-allyl-2′-deoxy-α/β-D-glucopyranosyl)-D-*myo*-inositol (191)



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 CH_2Cl_2 (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). Et_3N (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 CH_2Cl_2. The CH_2Cl_2 extract was washed successively with saturated $NaHCO_3$ and water, then dried over $MgSO_4$ 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 ^{13}C-NMR) and unreacted acceptor **185**. The mixture was dissolved in CH_2Cl_2-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; $[\alpha]_D$ +34.1° (*c* 3.6, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 7.38-7.23 (25 H, m, aromatic H), 5.85 (1 H, m, H-2′′), 5.11-4.57 (13 H, m, 5 × PhC*H*$_2$-, 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′); δ_C (100 MHz; $CDCl_3$) 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 × PhCH_2-), 74.41, 74.28, 74.01, 73.47, 73.37 (2 × PhCH_2-, C-1, C-2,

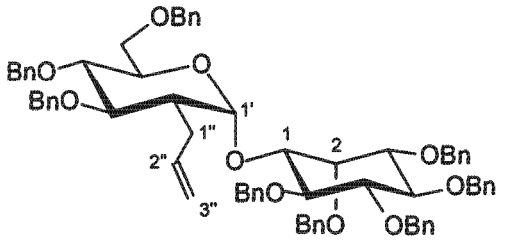
C-3′), 72.77 (C-4′), 70.85 (C-5′), 62.55 (C-6′), 45.71 (C-2′), 31.40 (C-1′′); FABMS: *m/z* 839.2 $(M+Na)^+$. Calcd for $C_{50}H_{56}O_{10}Na$ 839.3 $(M+Na)^+$.

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-*myo*-inositol (190a)

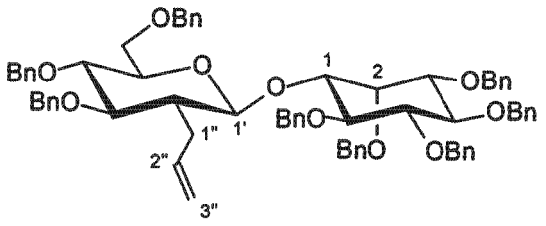


Triethylamine (0.1 ml, 0.72 mmol) was added slowly to a mixture of **191a** (110 mg, 0.13 mmol), acetic anhydride (0.25 ml, 2.6 mmol) and DMAP (5 mg, 0.04 mmol) in CH_2Cl_2 (5 ml) at room temperature. After 1 h, the reaction was stopped by the addition of water, and the mixture extracted with CH_2Cl_2, the CH_2Cl_2 phase dried over $MgSO_4$ and concentrated. Purification by column chromatography using ethyl acetate-petroleum ether (3:7) afforded compound **190a** (120 mg, 98%) as an oil; $[\alpha]_D$ +46.4° (*c* 2.2, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 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, PhC*H*H-), 5.02 (1 H, d, *J* 3.2 Hz, H-1′), 4.98-4.72 (11 H, m, 4 × PhCH_2-, H-4′, H-3′′$_a$, H-3′′$_b$), 4.58 (1 H, d, *J* 11.0 Hz, PhCH*H*-), 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 × $COOCH_3$); δ_C (100 MHz; $CDCl_3$) 170.69, 170.37, 170.01 (3 × *C*$OOCH_3$), 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, 127.69, 127.65, 127.55, 127.45, 127.29 (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 × Ph*C*H_2-), 74.70 (C-1), 74.49 (C-Ph*C*H_2-), 74.02 (C-2), 73.52 (C-Ph*C*H_2-), 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 × $COOCH_3$); HRFABMS: *m/z* 965.407457 $(M+Na)^+$. Calcd for $C_{56}H_{62}O_{13}Na$ 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-α-D-glucopyranosyl)-D-*myo*-inositol (192a) and 2,3,4,5,6-Penta-*O*-benzyl-1-*O*-(3′,4′,6′-tri-*O*-benzyl-2′-*C*-allyl-2′-deoxy-β-D-glucopyranosyl)-D-*myo*-inositol (192b)



192a



192b

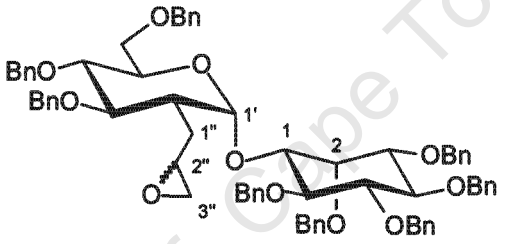
NaH (50%, 0.27 g, 5.60 mmol) was added to a solution of a mixture of anomers **191** (768 mg, 0.94 mmol) in THF (15 ml) at 0 °C. After 5 min, benzyl bromide (1.37 ml, 5.60 mmol) was added, the ice-water bath removed and the slurry heated at reflux for 18 h. The solution was then cooled and excess NaH quenched with methanol followed by water. The organic solvent was evaporated, the aqueous slurry extracted with CH_2Cl_2, and the CH_2Cl_2 phase washed with saturated NaCl, dried over $MgSO_4$ and concentrated. Separation of the anomers was acheived by column chromatography using ethyl acetate-petroleum ether (1:9) as eluent to afford the α-anomer **192a** (790 mg, 77%) as an oil, the β-anomer **192b** (120 mg, 10%) as an oil and a mixture of anomers (90 mg, 8%) (total yield 1.00 g , 98%).

α-*Anomer* **192a**: $[\alpha]_D$ +39.4° (*c* 2.7, $CHCl_3$); δ_H (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 × PhC*H*$_2$-, 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-6), 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′); δ_C (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 × PhCH_2-), 73.92 (C-1), 73.45 (C-2), 73.20, 73.19 (2 × 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 $C_{71}H_{74}O_{10}{}^{85}Rb$ 1171.4 $(M+Rb)^+$.

β-*Anomer* **192b**: $[\alpha]_D$ −4.3° (*c* 3.0, $CHCl_3$); δ_H (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 × PhC*H*$_2$-, H-3′′$_a$, H-3′′$_b$), 4.77-4.58 (6 H, m, 3 × 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′′$_a$, H-1′′$_b$), 2.04 (1 H, m, H-2′); δ_C (75 MHz; $CDCl_3$) 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, 128.12, 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 × Ph*C*H$_2$-), 74.42 (C-5′), 73.48, 72.01 (2 × Ph*C*H$_2$-), 69.56 (C-6′), 47.69 (C-2′), 30.86 (C-1′′); FABMS: *m/z* 1086.5 $(M)^+$. Calcd for $C_{71}H_{74}O_{10}$ 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)



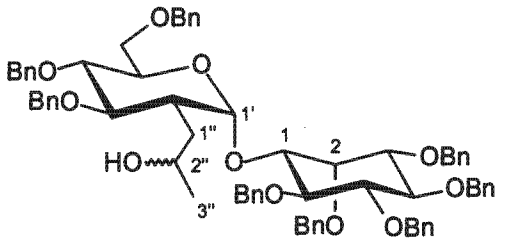
To a solution of **192a** (290 mg, 0.26 mmol) in CH_2Cl_2 (10 ml) at 0 °C was slowly added a solution of *m*-CPBA (70%, 0.14 g, 0.58 mmol) in CH_2Cl_2 (2.0 ml). (m-*CPBA was dissolved in* CH_2Cl_2, *dried with* $MgSO_4$, *filtered and concentrated before used*). The temperature was then raised to room temperature and after stirring for 5 h a further portion of the solution of *m*-CPBA (70%, 0.14 g, 0.58 mmol) in CH_2Cl_2 (1 ml) was added to the mixture at 0 °C. The reaction was stirred for 18 h at room temperature, saturated $Na_2S_2O_3$ then added, the mixture extracted with CH_2Cl_2, and the CH_2Cl_2 washed with saturated $NaHCO_3$, dried over $MgSO_4$ 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 ^{1}H-NMR) as an oil.

Diastereomer **193a**: δ_H (400 MHz; $CDCl_3$) 7.38-7.03 (40 H, m, aromatic H), 5.23-5.14 (2 H, m, PhC*H*H-, H-1′), 4.92-4.37 (15 H, m, 7 × PhC*H*$_2$-, PhCH*H*-), 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′′$_a$), 2.11 (1 H, m, H-2′), 2.04 (1 H, dd, *J* 5.0, 2.6 Hz, H-3′′$_b$), 1.74 (2 H, m, H-1′′$_a$, H-1′′$_b$); δ_C (100 MHz; $CDCl_3$) 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 × Ph*C*H$_2$-), 74.73, 74.46, 74.06, 73.68, 73.40, 73.39 (4 × Ph*C*H$_2$-, 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 $C_{71}H_{74}O_{11}Na$ 1125.5 $(M+Na)^+$.

Diastereomer **193b**: δ_H (400 MHz; $CDCl_3$) 7.38-7.03 (40 H, m, aromatic H), 5.23-5.14 (2 H, m, PhC*H*H-, H-1′), 4.92-4.37 (15 H, m, 7 × PhC*H*$_2$-, PhCH*H*-), 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′$_a$, H-6′$_b$), 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′′$_b$); δ_C (100 MHz; $CDCl_3$) 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 × Ph*C*H$_2$-), 74.68, 74.06, 73.89, 73.40, 73.39, 73.14 (4 × Ph*C*H$_2$-, 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 $C_{71}H_{74}O_{11}Na$ 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)

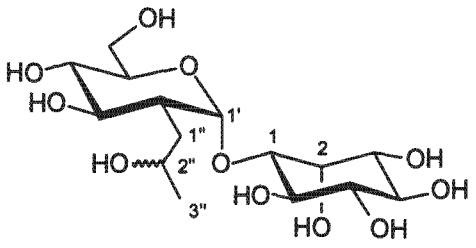


A solution of **193** (276 mg, 0.25 mmol) in THF (8 ml) was added dropwise to a solution of lithium aluminium hydride (0.1 g, 2.5 mmol) in THF (4 ml) at 0 °C. After 2 h at 0 °C, the excess LAH was quenched with water, extracted with ethyl acetate, dried over $MgSO_4$ and concentrated. Purification was 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 ^{1}H-NMR) as an oil; ν_{max}/cm^{-1} 3465 (OH).

Diastereomer **194a**: δ_H (400 MHz; $CDCl_3$) 7.38-7.03 (40 H, m, aromatic H), 5.18 (1 H, d, *J* 12.0 Hz, PhC*H*H-), 5.09 (1 H, d, *J* 3.2 Hz, H-1′), 4.90-4.46 (14 H, m, 7 × PhC*H*$_2$-), 4.39 (1 H, d, *J* 12.0 Hz, PhCH*H*-), 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′′$_a$, H-1′′$_b$), 0.93 (3 H, d, *J* 6.0 Hz, H-3′′); δ_C (100 MHz; $CDCl_3$) 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 × PhCH_2-), 74.09, 73.87, 73.48, 73.39, 73.38 (3 × PhCH_2-, 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 $C_{71}H_{76}O_{11}Na$ 1127.5 $(M+Na)^+$.

Diastereomer **194b**: δ_H (400 MHz; $CDCl_3$) 7.38-7.03 (40 H, m, aromatic H), 5.14 (1 H, d, *J* 11.8 Hz, PhC*H*H-), 5.04 (1 H, d, *J* 3.2 Hz, H-1′), 4.90-4.46 (14 H, m, 7 × PhC*H*$_2$-), 4.42 (1 H, d, *J* 11.8 Hz, PhCH*H*-), 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′′); δ_C (100 MHz; $CDCl_3$) 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 × PhCH_2-), 74.09, 73.74, 73.48, 73.39, 73.13 (3 × PhCH_2-, 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 $C_{71}H_{76}O_{11}Na$ 1127.5 $(M+Na)^+$.

1-*O*-[2′-deoxy-2′-C-(2′′-hydroxypropyl)-α-D-glucopyranosyl]-D-*myo*-inositol (51)

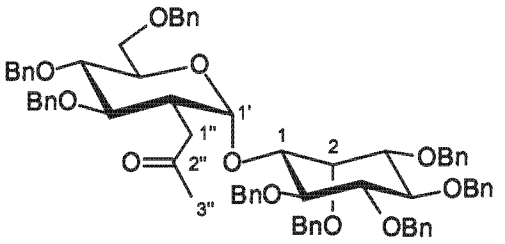


A solution of **194** (148 mg, 0.13 mmol) in ethyl acetate-methanol (4:6 ml) was stirred under H_2 (1 atm) at room temperature in the presence of 10% palladium on charcoal (300 mg) for 3 days. Three additional portions of 10% palladium on charcoal (200 mg) were added at 18 h interval. Tlc analysis (MeOH:EtOAc, 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 ^{1}H-NMR) as a hygroscopic solid.

Diastereomer **51a**: δ_H (300 MHz; D_2O) 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′$_b$, H-2′′), 1.90-1.62 (3 H, m, H-2′, H-1′′$_a$, H-1′′$_b$), 1.20 (3 H, d, *J* 6.0 Hz, H-3′′); δ_C (75 MHz; D_2O) 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 $(M-H)^-$. Calcd for $C_{15}H_{27}O_{11}$ 383.1 $(M-H)^-$.

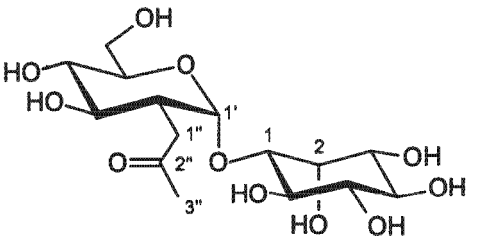
Diastereomer **51b**: δ_H (300 MHz; D_2O) 5.10 (1 H, d, *J* 3.3 Hz, H-1′), 4.23 (1 H, s (br), H-2), 4.00-3.27 (11 H, m, H-1, H-3, H-4, H-5, H-6, H-3′, H-4′, H-5′, H-6′$_a$, H-6′$_b$, H-2′′), 1.90-1.62 (3 H, m, H-2′, H-1′′$_a$, H-1′′$_b$), 1.20 (3 H, d, *J* 6.0 Hz, H-3′′); δ_C (75 MHz; D_2O) 95.34 (C-1′), 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 $(M-H)^-$. Calcd for $C_{15}H_{27}O_{11}$ 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-*myo*-inositol (195)



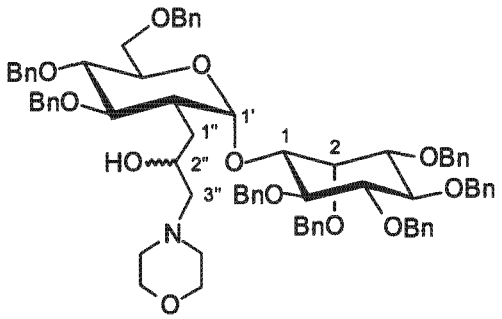
To a stirred solution of **194** (226 mg, 0.20 mmol) and activated molecular sieves 4Å (0.4 g) in CH_2Cl_2 (10 ml) was added NMO (39 mg, 0.29 mmol) at room temperature. After stirring for 5 min, TPAP (0.01 g, 0.028 mmol) was added and the stirring continued for 30 min. The solids were filtered through 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; $[\alpha]_D$ +38.5° (*c* 2.2, $CHCl_3$); ν_{max}/cm^{-1} 1712 (C=O); δ_H (400 MHz; $CDCl_3$) 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, PhC*H*H-), 4.89-4.67 (10 H, m, 5 × PhCH_2-), 4.64 (1 H, d, *J* 12.0 Hz, PhCH*H*-), 4.52 (1 H, d, *J* 11.4 Hz, PhC*H*H-), 4.49 (1 H, d, *J* 11.4 Hz, PhCH*H*-), 4.42 (1 H, d, *J* 12.0 Hz, PhC*H*H-), 4.41 (1 H, d, *J* 12.0 Hz, PhCH*H*-), 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; $CDCl_3$) 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 × PhCH_2-), 73.23 (C-1), 73.08, 73.07 (C-PhCH_2-, 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 $C_{71}H_{74}O_{11}Na$ 1125.5 $(M+Na)^+$.

1-*O*-[2′-deoxy-2′-C-(2′′-oxopropyl)-α-D-glucopyranosyl]-D-*myo*-inositol (52)



A solution of **195** (200 mg, 0.18 mmol) in ethyl acetate-methanol (5:7 ml) was stirred under H_2 (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; $[\alpha]_D$ +77.5° (*c* 1.4, H_2O); δ_H (300 MHz; D_2O) 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′′); δ_C (75 MHz; D_2O) 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-*myo*-inositol (196)



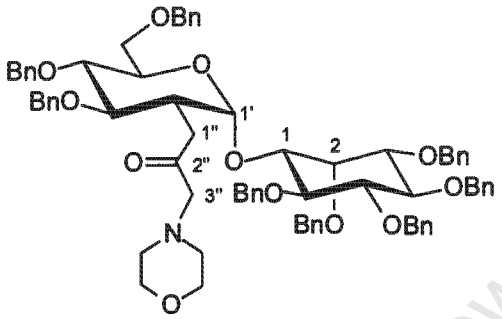
The mixture of **193** (482 mg, 0.44 mmol) and morpholine (1.5 ml, 17.2 mmol) in ethanol (10 ml) was refluxed for 1 h. The solvent was then evaporated, the residue was purified by column chromatography using ethyl acetate-petroleum ether (3:2) as eluent to afford an inseparable mixture of diastereomers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

Diastereomer **196a**: δ_H (300 MHz; $CDCl_3$) 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, PhC*H*H-), 5.06-4.77 (12 H, m, 6 × PhCH_2-), 4.71 (1 H, d, *J* 12.0 Hz, PhCH*H*-), 4.57 (1 H, d, *J* 12.0 Hz, PhC*H*H-), 4.47 (1 H, d, *J* 12.0 Hz, PhCH*H*-), 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(CH_2CH_2)$_2$O-, H-1, H-3, H-5, H-3′, H-4′, H-6′$_a$, H-6′$_b$, H-2′′), 2.46-1.51 (9 H, m, -N(CH_2CH_2)$_2$O-, H-2′, H-3′′$_a$, H-3′′$_b$, H-1′′$_a$, H-1′′$_b$); δ_C (75 MHz; $CDCl_3$) 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 × PhCH_2-), 73.89, 73.88 (C-PhCH_2-, C-1), 73.42 (C-2), 73.06, 72.89 (C-2 × PhCH_2-), 70.40 (C-5′), 68.53 (C-6′), 66.76 (2 C-N(CH_2CH_2)$_2$O-), 66.37 (C-2′′), 64.63 (C-3′′), 53.34 (2 C-N(CH_2CH_2)$_2$O-), 43.89 (C-2′), 32.29 (C-1′′); FABMS: *m/z* 1274.5 $(M+Rb)^+$. Calcd for $C_{75}H_{83}NO_{12}{}^{85}Rb$ 1274.5 $(M+Rb)^+$.

Diastereomer **196b**: δ_H (300 MHz; $CDCl_3$) 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, PhC*H*H-), 5.06-4.77 (12 H, m, 6 × PhCH_2-), 4.66 (1 H, d, *J* 11.1 Hz, PhCH*H*-), 4.56 (1 H, d, *J* 11.1 Hz, PhC*H*H-), 4.49 (1 H, d, *J* 12.3 Hz, PhCH*H*-), 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(CH_2CH_2)$_2$O-, H-1, H-3, H-5, H-3′, H-4′, H-6′$_a$, H-6′$_b$, H-2′′), 2.46-1.51 (9 H, m, -N(CH_2CH_2)$_2$O-, H-2′, H-3′′$_a$, H-3′′$_b$, H-1′′$_a$, H-1′′$_b$); δ_C (75 MHz; $CDCl_3$) 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 × PhCH_2-), 73.73 (C-1), 73.35 (C-2), 73.11, 73.04 (2 × PhCH_2-), 70.46 (C-5′), 68.50 (C-6′), 66.76 (2 C-N(CH_2CH_2)$_2$O-), 64.18, 64.17 (C-2′′, C-3′′), 53.49 (2 C- N(CH_2CH_2)$_2$O-

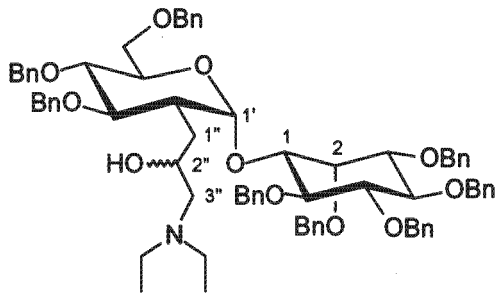
), 41.88 (C-2′), 31.36 (C-1′′); FABMS: *m/z* 1274.5 $(M+Rb)^+$. Calcd for $C_{75}H_{83}NO_{12}{}^{85}Rb$ 1274.5 $(M+Rb)^+$.

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 CH_2Cl_2 (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; $[\alpha]_D$ +42.6° (*c* 3.0, $CHCl_3$); ν_{max}/cm^{-1} 1723 (C=O); δ_H (300 MHz; $CDCl_3$) 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, PhCH*H*-), 4.95-4.71 (10 H, m, 5 × PhCH_2-), 4.68 (1 H, d, *J* 12.0 Hz, PhCH*H*-), 4.59 (1 H, d, *J* 11.6 Hz, PhCH*H*-), 4.53 (1 H, d, *J* 11.6 Hz, PhC*H*H-), 4.47 (1 H, d, *J* 12.0 Hz, PhC*H*H-), 4.46 (1 H, d, *J* 12.0 Hz, PhC*H*H-), 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(CH_2CH_2)$_2$O-, H-1, H-3, H-5, H-3′, H-4′, H-6′$_a$, H-6′$_b$), 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(CH_2CH_2)$_2$O-); δ_C (75 MHz; $CDCl_3$) 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 × PhCH_2-), 73.50, 73.19, 73.06, 73.05 (2 × PhCH_2-, C-1, C-2), 70.52 (C-5′), 68.46 (C-6′), 67.34 (C-3′′), 66.57 (2 C-N(CH_2CH_2)$_2$O-), 53.40 (2 C-N(CH_2CH_2)$_2$O-), 41.15 (C-2′), 37.54 (C-1′′); FABMS: *m/z* 1272.3 $(M+Rb)^+$. Calcd for $C_{75}H_{81}NO_{12}{}^{85}Rb$ 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)

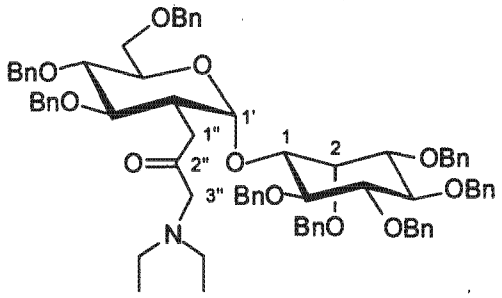


A mixture of **193** (165 mg, 0.15 mmol) and diethylamine (1.2 ml, 11.5 mmol) in ethanol (5 ml) was refluxed for 2 h. The solvent was then evaporated, the residue was purified by column chromatography using methanol-ethyl acetate (5:95) as eluent to afford an inseparable mixture of diastereomers **198**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

Diastereomer **198a**: δ_H (300 MHz; $CDCl_3$) 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 × PhC*H*$_2$), 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(C*H*$_2$CH$_3$)$_2$-, 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(CH$_2$C*H*$_3$)$_2$-); δ_C (75 MHz; $CDCl_3$) 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 × PhCH$_2$-), 73.96, 73.55, 73.05, 72.83 (2 × PhCH$_2$-, 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(*C*H$_2$CH$_3$)$_2$-), 44.39 (C-2′), 32.16 (C-1′′), 11.53 (2 C-N(CH$_2$*C*H$_3$)$_2$-); FABMS: *m/z* 1176.7 (M+H)$^+$. Calcd for $C_{75}H_{86}NO_{11}$ 1176.6 (M+H)$^+$.

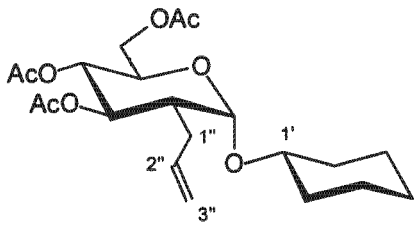
Diastereomer **198b**: δ_H (300 MHz; $CDCl_3$) 7.46-7.08 (40 H, m, aromatic H), 5.31 (1 H, d, *J* 3.3 Hz, H-1′), 5.19-4.41 (16 H, m, 8 × PhC*H*$_2$-), 4.34 (1 H, s (br), H-2), 4.25-4.09 (3 H, m, H-5′, H-4, H-6), 3.89-3.51 (8 H, m, H-1, H-3, H-5, H-2′′, H-3′, H-4′, H-6′$_a$, H-6′$_b$), 2.57-2.13 (5 H, m, -N(C*H*$_2$CH$_3$)$_2$-, 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(CH$_2$C*H*$_3$)$_2$-); δ_C (75 MHz; $CDCl_3$) 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 × PhCH$_2$-), 73.89, 73.44, 73.09, 72.96 (2 × PhCH$_2$-, 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(*C*H$_2$CH$_3$)$_2$-), 41.77 (C-2′), 31.03 (C-1′′), 11.50 (2 C-N(CH$_2$*C*H$_3$)$_2$-); FABMS: *m/z* 1176.7 (M+H)$^+$. Calcd for $C_{75}H_{86}NO_{11}$ 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-*myo*-inositol (199)

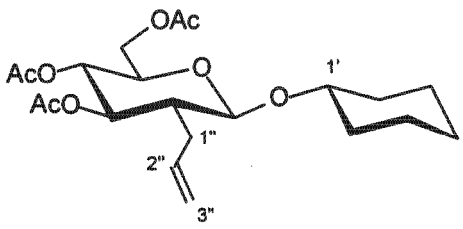


To a stirred solution of **198** (133 mg, 0.11 mmol) and activated molecular sieves 4Å (0.4 g) in CH_2Cl_2 (5 ml) was added NMO (23 mg, 0.17 mmol) at room temperature. After stirring for 5 min, TPAP (0.008 g, 0.023 mmol) was added and the stirring continued for 18 h. The solids were filtered through 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; $[\alpha]_D$ +29.3° (*c* 2.6, $CHCl_3$); ν_{max}/cm^{-1} 1718 (C=O); δ_H (300 MHz; $CDCl_3$) 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 × Ph*CH*$_2$-), 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′$_a$, 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(*CH*$_2$CH$_3$)$_2$, H-1′′$_b$, H-2′), 0.82 (6 H, t, *J* 7.2 Hz, -N(CH$_2$*CH*$_3$)$_2$); δ_C (75 MHz; $CDCl_3$) 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 × Ph*CH*$_2$-), 73.85, 73.61, 73.20, 73.19, 72.95 (3 × Ph*CH*$_2$-, C-1, C-2), 70.54 (C-5′), 68.56 (C-6′), 63.23 (C-3′′), 47.66 (2 C-N(*CH*$_2$CH$_3$)$_2$), 41.45 (C-2′), 37.29 (C-1′′), 11.64 (2 C-N(CH$_2$*CH*$_3$)$_2$); FABMS: *m/z* 1174.7 $(M+H)^+$. Calcd for $C_{75}H_{84}NO_{11}$ 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)



201a



201b

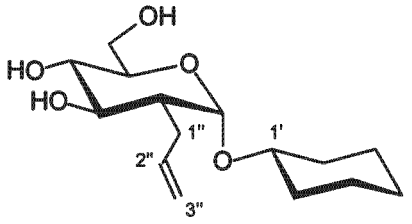
A mixture of fluoride **173** (550 mg, 1.65 mmol), cyclohexanol (2.62 ml, 24.84 mmol) and molecular sieves 4Å (1 g) in CH_2Cl_2 (13 ml) was stirred at room temperature for 1 h before boron trifluoride etherate (1.22 ml, 9.94 mmol) was added dropwise. The stirring was continued for 18 h, then Et_3N (1.1 ml) added and the solids removed by filtration. The filtrate was diluted with dichloromethane, and the CH_2Cl_2 phase washed sequentially with water, saturated $NaHCO_3$ and water, then dried over $MgSO_4$ 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 ^{13}C-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**: $[\alpha]_D$ +115.6° (*c* 2.6, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 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-6$_a$), 4.09-4.02 (2 H, m, H-5, H-6$_b$), 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 × $COOCH_3$), 1.99 (1 H, m, H-2), 1.87-1.19 (10 H, m, 5 × -CH_2-, cyclohexyl); δ_C (100 MHz; $CDCl_3$) 170.59, 170.42, 169.89 (3 × *C*$OOCH_3$), 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-CH_2-, cyclohexyl), 31.73 (C-1′′), 31.47, 25.48, 24.02, 23.79 (4 × -CH_2-, cyclohexyl), 20.70, 20.60, 20.59 (3 × $COOCH_3$); HRFABMS: *m/z* 435.199633 $(M+Na)^+$. Calcd for $C_{21}H_{32}O_8Na$ 435.199477 $(M+Na)^+$.

β-*Anomer* **201b**: mp 100 °C (from pentane); $[\alpha]_D$ +16.7° (*c* 1.7, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 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-6$_a$), 4.07 (1 H, dd, *J* 12.1, 2.6 Hz, H-6$_b$), 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 × $COOCH_3$), 2.03-1.21 (11 H, m, H-2, 5 × -CH_2-, cyclohexyl); δ_C (75 MHz; $CDCl_3$) 170.70,

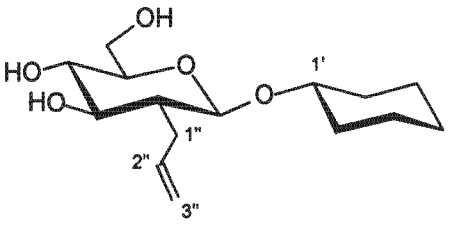
170.37, 169.84 (3 × *C*OOCH$_3$), 134.21 (C-2′′), 117.20 (C-3′′), 100.58 (C-1), 77.55 (C-1′), 72.90 (C-3), 71.34 (C-5), 70.34 (C-4), 62.68 (C-6), 45.24 (C-2), 33.57, 31.80 (2 × -CH$_2$-, cyclohexyl), 31.12 (C-1′′), 25.55, 24.08, 24.01 (3 × -CH$_2$-, cyclohexyl), 20.75, 20.72, 20.66 (3 × COO*C*H$_3$); HRFABMS: *m/z* 435.199633 $(M+Na)^+$. Calcd for $C_{21}H_{32}O_8Na$ 435.199477 $(M+Na)^+$.

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



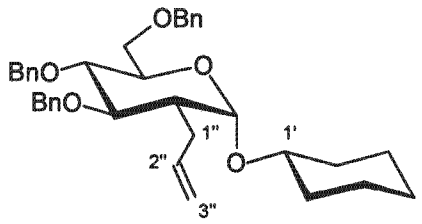
Methanolic NaOMe (0.2 M, 0.7 ml, 0.14 mmol) was added to a solution of **201a** (287 mg, 0.69 mmol) in CH_2Cl_2-MeOH (4:6 ml) at room temperature. After 4 h, the solution was neutralized with Amberlite IR-120 H^+ resin. The resin was removed by filtration, the solvent evaporated and the crystalline residue 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); $[\alpha]_D$ +120.8° (*c* 2.3, MeOH); δ_H (400 MHz; CD_3OD) 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-6$_a$), 3.69-3.63 (2 H, m, H-5, H-6$_b$), 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 × -CH$_2$-, cyclohexyl); δ_C (100 MHz; CD_3OD) 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-CH$_2$-, cyclohexyl), 31.56 (C-1′′), 31.45, 25.69, 23.88, 23.71 (4 × -CH$_2$-, cyclohexyl); HRFABMS: *m/z* 309.168001 $(M+Na)^+$. Calcd for $C_{15}H_{26}O_5Na$ 309.167784 $(M+Na)^+$.

Cyclohexyl 2-C-allyl-2-deoxy-β-D-glucopyranoside (202)



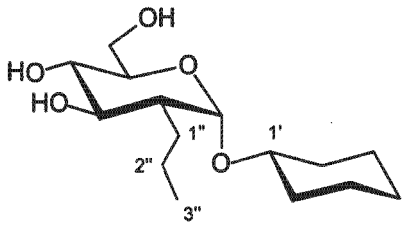
Methanolic NaOMe (0.2 M, 0.5 ml, 0.1 mmol) was added to a solution of **201b** (200 mg, 0.48 mmol) in CH_2Cl_2-MeOH (3:5 ml) at room temperature. After 2 h, the solution was neutralized with Amberlite IR-120 H^+ resin. The resin was removed by filtration, the solvent evaporated and the crystalline residue 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); $[\alpha]_D$ −35.4° (*c* 2.2, MeOH); δ_H (400 MHz; CD_3OD) 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-6$_a$), 3.71 (1 H, m, H-1′), 3.65 (1 H, dd, *J* 11.7, 5.4 Hz, H-6$_b$), 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 × -CH_2-, cyclohexyl); δ_C (100 MHz; CD_3OD) 135.34 (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 × -CH_2-, cyclohexyl), 30.39 (C-1′′), 25.65, 23.94, 23.84 (3 × -CH_2-, cyclohexyl); HRFABMS: *m/z* 309.168001 $(M+Na)^+$. Calcd for $C_{15}H_{26}O_5Na$ 309.167784 $(M+Na)^+$.

Cyclohexyl 3,4,6-tri-*O*-benzyl-2-C-allyl-2-deoxy-α-D-glucopyranoside (203)



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_2Cl_2, and the CH_2Cl_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; $[\alpha]_D$ +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′′$_a$, H-3′′$_b$), 4.96 (1 H, d, *J* 3.6 Hz, H-1), 4.93 (1 H, d, *J* 10.8 Hz, PhC*H*H-), 4.85 (1 H, d, *J* 10.8 Hz, PhC*H*H-), 4.70 (1 H, d, *J* 12.0 Hz, PhC*H*H-), 4.68 (1 H, d, *J* 10.8 Hz, PhCH*H*-), 4.57 (1 H, d, *J* 10.8 Hz, PhCH*H*-), 4.54 (1 H, d, *J* 12.0 Hz, PhCH*H*-), 3.99-3.94 (1 H, m, H-5), 3.83 (1 H, dd, *J* 10.6, 3.7 Hz, H-6$_a$), 3.78-3.67 (3 H, m, H-3, H-4, H-6$_b$), 3.59 (1 H, m, H-1′), 2.62-2.54 (1 H, m, H-1′′$_a$), 2.24-2.13 (1 H, m, H-1′′$_b$), 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-Ph*C*H$_2$-), 74.89 (C-1′), 74.78, 73.41 (2 × Ph*C*H$_2$-), 71.02 (C-5), 68.98 (C-6), 46.19 (C-2), 33.46 (C-*C*H$_2$-, cyclohexyl), 31.61 (C-1′′), 31.58, 25.68, 24.07, 23.85 (4 × -*C*H$_2$-, cyclohexyl); HRFABMS: *m/z* 579.308663 $(M+Na)^+$. Calcd for $C_{36}H_{44}O_5Na$ 579.308627 $(M+Na)^+$.

Cyclohexyl 2-deoxy-2-C-propyl-α-D-glucopyranoside (60)



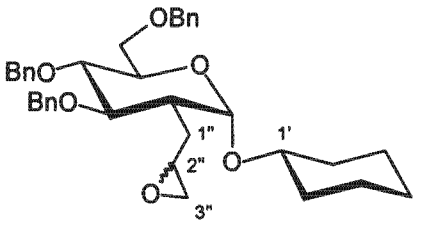
1. From **203**

A solution of **203** (279 mg, 0.50 mmol) in ethyl acetate-methanol (5:6 ml) was treated with H_2 (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 H_2 (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 °C (from ethyl acetate and petroleum ether); $[\alpha]_D$ +82.8° (*c* 2.3, MeOH); δ_H (400 MHz; CD_3OD) 4.92 (1 H, d, *J* 3.2 Hz, H-1), 3.77 (1 H, d (br), *J* 9.6 Hz, H-6_a), 3.69-3.60 (3 H, m, H-1′, H-5, H-6_b), 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 -CH_2-, cyclohexyl, -(CH_2)$_2CH_3$), 0.92 (3 H, t, *J* 7.2 Hz, H-3′′); δ_C (100 MHz; CD_3OD) 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 -CH_2-, cyclohexyl), 29.44 (C-1′′), 25.70, 23.75, 23.55 (3 x -CH_2-, cyclohexyl), 19.89 (C-2′′), 13.59 (C-3′′); HRFABMS: *m/z* 311.182957 $(M+Na)^+$. Calcd for $C_{15}H_{28}O_5Na$ 311.183433 $(M+Na)^+$.

Cyclohexyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(2′′,3′′-epoxypropyl)-α-D-glucopyranoside (204)

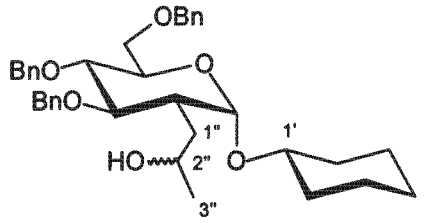


To a solution of **203** (780 mg, 1.40 mmol) in CH_2Cl_2 (15 ml) at 0 °C was slowly added a solution of *m*-CPBA (70%, 0.64 g, 2.59 mmol) in CH_2Cl_2 (4.0 ml) (m-*CPBA was dissolved in* CH_2Cl_2, *dried with* $MgSO_4$, *filtered and concentrated before used*). The temperature was raised to room temperature and after stirring for 18 h a further solution of *m*-CPBA (70%, 0.36 g, 1.47 mmol) in CH_2Cl_2 (3 ml) was added slowly to the mixture at 0 °C. The reaction was stirred for 8 h at room temperature, then saturated $Na_2S_2O_3$ was added, the solution extracted with CH_2Cl_2, and the CH_2Cl_2 washed with saturated $NaHCO_3$, dried over $MgSO_4$ 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 ^{1}H-NMR) as an oil.

Diastereomer **204a**: δ_H (400 MHz; $CDCl_3$) 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 × PhC*H*$_2$-), 3.96-3.89 (1 H, m, H-5), 3.79 (1 H, t, *J* 4.2 Hz, H-6$_a$), 3.75-3.65 (3 H, m, H-3, H-4, H-6$_b$), 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 × -CH_2-, cyclohexyl, H-1′′$_a$, H-1′′$_b$); δ_C (100 MHz; $CDCl_3$) 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 × Ph*C*H$_2$-, 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 × -CH_2-, cyclohexyl); HRFABMS: *m/z* 595.303894 $(M+Na)^+$. Calcd for $C_{36}H_{44}O_6Na$ 595.303542 $(M+Na)^+$.

Diastereomer **204b**: δ_C (400 MHz; $CDCl_3$) 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 × PhC*H*$_2$-), 3.96-3.89 (1 H, m, H-5), 3.82 (1 H, t, *J* 4.0 Hz, H-6$_a$), 3.75-3.65 (3 H, m, H-3, H-4, H-6$_b$), 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 × -CH_2-, cyclohexyl, H-1′′$_a$, H-1′′$_b$); δ_C (100 MHz; $CDCl_3$) 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 × Ph*C*H$_2$-, 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 × -CH_2-, cyclohexyl); HRFABMS: *m/z* 595.303894 $(M+Na)^+$. Calcd for $C_{36}H_{44}O_6Na$ 595.303542 $(M+Na)^+$.

Cyclohexyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(2′′-hydroxypropyl)-α-D-glucopyranoside (205)

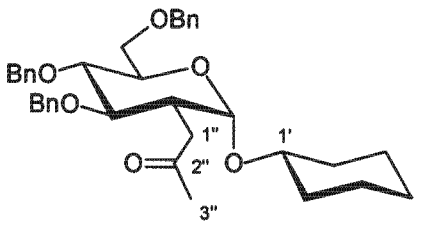


A solution of **204** (593 mg, 1.03 mmol) in THF (15 ml) was added dropwise to a solution of lithium aluminium hydride (0.39 g, 10.30 mmol) in THF (7 ml) at 0 °C. After 2 h at 0 °C, excess LAH was quenched with water, the aqueous mixture extracted with ethyl acetate, and the ethyl acetate phase dried over $MgSO_4$ 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 ^{1}H-NMR) as crystals; ν_{max}/cm^{-1} 3426 (br) (OH).

Diastereomer **205a**: δ_H (300 MHz; $CDCl_3$) 7.38-7.13 (15 H, m, aromatic H), 4.98-4.49 (6 H, m, 3 × PhCH_2-), 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-6_a, H-6_b, 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 × -CH_2-, cyclohexyl, H-1′′$_a$, H-1′′$_b$), 1.15 (3 H, d, *J* 6.0 Hz, H-3′′); δ_C (75 MHz; $CDCl_3$) 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 × PhCH_2-, 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 × -CH_2-, cyclohexyl), 24.28 (C-3′′), 24.08, 23.82 (2 × -CH_2-, cyclohexyl); HRFABMS: *m/z* 597.318376 $(M+Na)^+$. Calcd for $C_{36}H_{46}O_6Na$ 597.319191 $(M+Na)^+$.

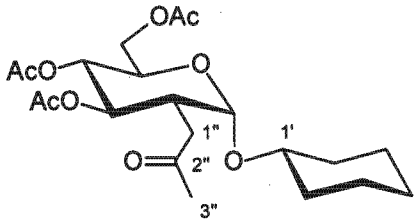
Diastereomer **205b**: δ_H (300 MHz; $CDCl_3$) 7.38-7.13 (15 H, m, aromatic H), 4.98-4.49 (6 H, m, 3 × PhCH_2-), 4.94 (1 H, d, *J* 3.6 Hz, H-1), 3.95-3.88 (1 H, m, H-5), 3.84-3.65 (5 H, m, H-3, H-4, H-6_a, H-6_b, H-2′′), 3.57 (1 H, m, H-1′), 2.49 (s (br), -OH), 2.09-1.94 (1 H, m, H-2), 1.89-1.19 (12 H, m, 5 × -CH_2-, cyclohexyl, H-1′′$_a$, H-1′′$_b$), 1.16 (3 H, d, *J* 6.0 Hz, H-3′′); δ_C (75 MHz; $CDCl_3$) 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 × PhCH_2-, 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 × -CH_2-, cyclohexyl), 23.59 (C-3′′); HRFABMS: *m/z* 597.318376 $(M+Na)^+$. Calcd for $C_{36}H_{46}O_6Na$ 597.319191 $(M+Na)^+$.

Cyclohexyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-C-(2′′-oxopropyl)-α-D-glucopyranoside (206)



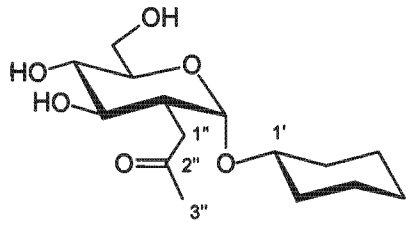
To a stirred solution of **205** (243 mg, 0.42 mmol) and activated molecular sieves 4Å (0.4 g) in CH_2Cl_2 (10 ml) was added NMO (0.08 mg, 0.63 mmol) at room temperature. After stirring for 5 min, TPAP (0.01 g, 0.028 mmol) was added and the stirring was continued for 1 h. The solids were filtered through 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); $[\alpha]_D$ +95.1° (*c* 2.2, $CHCl_3$); ν_{max}/cm^{-1} 1714 (C=O); δ_H (400 MHz; $CDCl_3$) 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, PhC*H*H-), 4.77 (1 H, d, *J* 10.8 Hz, PhC*H*H-), 4.67 (1 H, d, *J* 12.0 Hz, PhC*H*H-), 4.59 (1 H, d, *J* 11.4 Hz, PhCH*H*-), 4.55 (1 H, d, *J* 10.8 Hz, PhCH*H*-), 4.52 (1 H, d, *J* 12.0 Hz, PhCH*H*-), 3.91-3.87 (1 H, m, H-5), 3.80 (1 H, dd, *J* 10.7, 3.8 Hz, H-6_a), 3.69 (1 H, t, *J* 9.3 Hz, H-4), 3.67 (1 H, dd, *J* 10.7, 2.0 Hz, H-6_b), 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 × -CH_2-, cyclohexyl); δ_C (100 MHz; $CDCl_3$) 207.77 (C-2′′), 138.85, 138.45, 138.44, 128.61, 128.55, 128.54, 128.11, 128.110, 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 × Ph*C*H_2-), 74.92 (C-1′), 73.73 (C-Ph*C*H_2-), 71.26 (C-5), 69.17 (C-6), 42.17 (C-1′′), 42.10 (C-2), 33.62, 31.59 (2 × -CH_2-, cyclohexyl), 30.24 (C-3′′), 25.89, 24.24, 23.99 (3 × -CH_2-, cyclohexyl); HRFABMS: *m/z* 595.302843 $(M+Na)^+$. Calcd for $C_{36}H_{44}O_6Na$ 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_2O (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_2Cl_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_2Cl_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, $CHCl_3$); ν_{max}/cm^{-1} 1744 (C=O); δ_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′′$_a$), 2.54-2.45 (1 H, m, H-2), 2.37 (1 H, dd, *J* 17.0, 3.4 Hz, H-1′′$_b$), 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); δ_C (75 MHz; $CDCl_3$) 206.43 (C-2′′), 170.68, 170.69, 169.78 (3 × *C*$OOCH_3$), 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 $C_{21}H_{32}O_9Na$ 451.194392 $(M+Na)^+$.

Cyclohexyl 2-deoxy-2-C-(2′′-oxopropyl)-α-D-glucopyranoside (57)



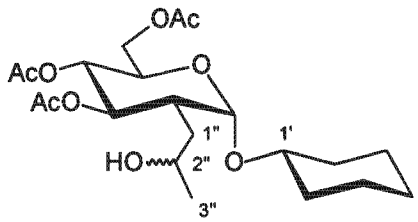
1. From **206**

A solution of **206** (211 mg, 0.37 mmol) in a mixture of ethyl acetate-methanol (4:6 ml) was treated with H_2 (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 CH_2Cl_2-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); $[\alpha]_D$ +128.8° (*c* 2.1, MeOH); δ_C (400 MHz; CD_3OD) 4.97 (1 H, d, *J* 3.6 Hz, H-1), 3.77 (1 H, dd, *J* 11.6, 2.4 Hz, H-6_a), 3.67 (1 H, dd, *J* 11.6, 5.6 Hz, H-6_b), 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′′$_a$), 2.58 (1 H, dd, *J* 17.9, 9.2 Hz, H-1′′$_b$), 2.14 (3 H, s, H-3′′), 2.12 (1 H, m, H-2), 1.87-1.19 (10 H, m, 5 × -CH_2-, cyclohexyl); δ_C (100 MHz; CD_3OD) 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 × -CH_2-, cyclohexyl), 29.12 (C-3′′), 25.63, 23.79, 23.59 (3 × -CH_2-, cyclohexyl); HRFABMS: *m/z* 325.162838 $(M+Na)^+$. Calcd for $C_{15}H_{26}O_6Na$ 325.162699 $(M+Na)^+$.

Cyclohexyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-C-(2′′-hydroxypropyl)-α-D-glucopyranoside (208)

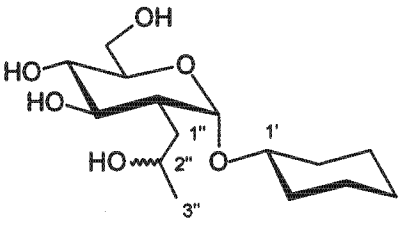


$NaBH_4$ (0.19 g, 5.02 mmol) was added portion-wise to a solution of compound **207** (200 mg, 0.47 mmol) in THF-MeOH (2:5 ml) at –20 °C and the reaction allowed to warm to 0 °C over 2 h. The solution was quenched with saturated $NaHCO_3$, extracted with CH_2Cl_2, and the CH_2Cl_2 dried over $MgSO_4$ 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 ^{1}H-NMR) as an oil; ν_{max}/cm^{-1} 3467 (br) (OH).

Diastereomer **208a**: δ_C (400 MHz; $CDCl_3$) 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-6_a), 4.08-4.03 (2 H, m, H-5, H-6_b), 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 × $COOCH_3$), 1.88-1.19 (12 H, m, 5 × -CH_2-, cyclohexyl, H-1′′$_a$, H-1′′$_b$), 1.17 (3 H, d, *J* 6.0 Hz, H-3′′); δ_C (100 MHz; $CDCl_3$) 170.61, 170.46, 169.91 (3 × *C*$OOCH_3$), 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 × -CH_2-, cyclohexyl), 24.03 (C-3′′), 24.03, 23.79 (2 × -CH_2-, cyclohexyl), 20.76, 20.61, 20.60 (3 × $COOCH_3$); HRFABMS: *m/z* 453.210259 $(M+Na)^+$. Calcd for $C_{21}H_{34}O_9Na$ 453.210041 $(M+Na)^+$.

Diastereomer **208b**: δ_H (400 MHz; $CDCl_3$) 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-6_a), 4.08-4.03 (2 H, m, H-5, H-6_b), 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 × $COOCH_3$), 1.88-1.19 (12 H, m, 5 × -CH_2-, cyclohexyl, H-1′′$_a$, H-1′′$_b$), 1.16 (3 H, d, *J* 6.0 Hz, H-3′′); δ_C (100 MHz; $CDCl_3$) 170.61, 170.46, 169.85 (3 × *C*$OOCH_3$), 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 × -CH_2-, cyclohexyl), 24.49 (C-3′′), 24.03, 23.79 (2 × -CH_2-, cyclohexyl), 20.76, 20.61, 20.60 (3 × $COOCH_3$); HRFABMS: *m/z* 453.210259 $(M+Na)^+$. Calcd for $C_{21}H_{34}O_9Na$ 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 H_2 (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 ^{1}H-NMR) as crystals.

2. From **208**

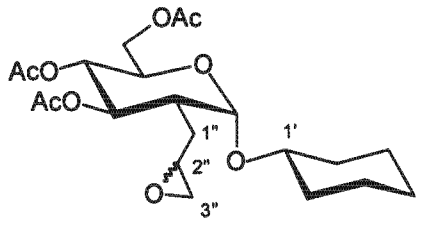
Methanolic sodium methoxide (0.2 M, 0.3 ml, 0.60 mmol) was added to a solution of **208** (155 mg, 0.36 mmol) in CH_2Cl_2-MeOH (3:5 ml) at room temperature. After 18 h, the solution was neutralized with Amberilite IR-120 H^+ resin, the solids were removed by filtration, the filtrate concentrated and the residue recrystallized from ethyl acetate-petroleum ether (4:1) to afford an inseparable mixture of diastereomers **58** (98 mg, 89%, 1:1 by ^{1}H-NMR).

Diastereomer **58a**: δ_H (300 MHz; CD_3OD) 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-6_a, H-6_b), 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 × -CH_2-, cyclohexyl, H-1′′$_a$, H-1′′$_b$), 1.16 (3 H, d, *J* 6.0 Hz, H-3′′); δ_C (75 MHz; CD_3OD) 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 × -CH_2-, cyclohexyl), 23.54 (C-3′′); HRFABMS: *m/z* 327.177488 $(M+Na)^+$. Calcd for $C_{15}H_{28}O_6Na$ 327.178348 $(M+Na)^+$.

Diastereomer **58b**: δ_H (300 MHz; CD_3OD) 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-6_a, H-6_b), 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 × -CH_2-, cyclohexyl, H-1′′$_a$, H-1′′$_b$), 1.17 (3 H, d, *J* 6.3 Hz, H-3′′); δ_C (75 MHz; CD_3OD) 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 × -CH_2-, cyclohexyl), 24.61 (C-3′′); HRFABMS: *m/z* 327.177488 $(M+Na)^+$. Calcd for $C_{15}H_{28}O_6Na$ 327.178348 $(M+Na)^+$.

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



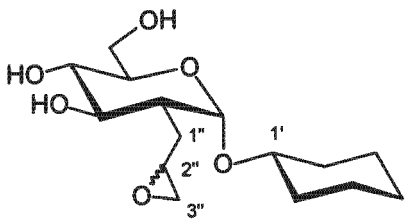
To a solution of **201a** (308 mg, 0.75 mmol) in CH_2Cl_2 (10 ml) at 0 °C was slowly added a solution of *m*-CPBA (70%, 0.32 g, 1.29 mmol) in CH_2Cl_2 (3.0 ml) (*m-CPBA was dissolved in CH_2Cl_2, dried with $MgSO_4$, filtered and concentrated before used*). The temperature was raised to room temperature and after stirring for 18 h, a further portion of *m*-CPBA (70%, 0.1 g, 0.40 mmol) in CH_2Cl_2 (2 ml) was added slowly to the mixture at 0 °C. The reaction was stirred for 6 h at room temperature, then saturated $Na_2S_2O_3$ added, the aqueous mixture extracted with CH_2Cl_2, and the CH_2Cl_2 washed with saturated $NaHCO_3$, dried over $MgSO_4$ 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 ^{1}H-NMR) as an oil.

Diastereomer **209a**: δ_H (400 MHz; $CDCl_3$) 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-6_a), 4.03-3.96 (2 H, m, H-5, H-6_b), 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 × $COOCH_3$), 1.82-1.10 (12 H, m, 5 × -CH_2-, cyclohexyl, H-1′′$_a$, H-1′′$_b$); δ_C (100 MHz; $CDCl_3$) 170.85, 170.83, 170.06 (3 × *C*$OOCH_3$), 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 × -CH_2-, cyclohexyl), 20.94, 20.78, 20.77 (3 × $COOCH_3$); HRFABMS: *m/z* 451.195037 $(M+Na)^+$. Calcd for $C_{21}H_{32}O_9Na$ 451.194392 $(M+Na)^+$.

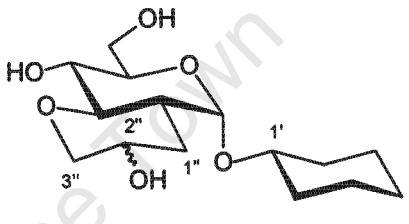
Diastereomer **209b**: δ_H (400 MHz; $CDCl_3$) 5.15 (1 H, dd, *J* 11.0, 9.5 Hz, H-3), 5.04 (1 H, d, *J* 3.2 Hz, H-1), 4.87 (1 H, t, *J* 9.5 Hz, H-4), 4.18-4.14 (1 H, m, H-6_a), 4.03-3.96 (2 H, m, H-5, H-6_b), 3.48 (1 H, m, H-1′), 2.82 (1 H, m, H-2′′), 2.62 (1 H, t, *J* 4.8 Hz, H-3′′$_a$), 2.31 (1 H, 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 × $COOCH_3$), 1.82-1.10 (12 H, m, 5 ×

-CH_2-, cyclohexyl, H-1′′$_a$, H-1′′$_b$); δ_C (100 MHz; $CDCl_3$) 170.75, 170.63, 170.11 (3 × *C*OOCH$_3$), 97.69 (C-1), 76.68 (C-1′), 72.48 (C-3), 70.29 (C-4), 67.79 (C-5), 62.68 (C-6), 51.06 (C-2′′), 46.82 (C-3′′), 43.89 (C-2), 33.51 (C-1′′), 31.52, 30.88, 25.71, 24.22, 24.00 (5 × -CH_2-, cyclohexyl), 20.94, 20.78, 20.77 (3 × COO*C*H$_3$); HRFABMS: *m/z* 451.195037 $(M+Na)^+$. Calcd for $C_{21}H_{32}O_9Na$ 451.194392 $(M+Na)^+$.

Cyclohexyl 2-deoxy-2-C-(2′′, 3′′-epoxypropyl)-α-D-glucopyranoside (61) and Cyclohexyl (2′′R), (2′′S)- 3,3′′-anhydro-2-deoxy-2-C-(2′′,3′′-dihydroxypropyl)-α-D-glucopyranoside (210)



61



210 (1:1)

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_2Cl_2-MeOH (3:5 ml) at room temperature. After 6 h, water was added (1 ml) and the solvent evaporated to dryness. Tlc indicate 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 mixtures of alcohols **210** (60 mg, 42%, 1:1 by ^{1}H-NMR) as crystals.

Diastereomer **61a**: δ_H (400 MHz; CD_3OD) 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′′$_a$), 2.51 (1 H, d, *J* 5.0, 2.8 Hz, H-3′′$_b$), 1.95-1.24 (13 H, m, 5 × -CH_2-, cyclohexyl, H-2, H-1′′$_a$, H-1′′$_b$); δ_C (100 MHz; CD_3OD) 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 × -CH_2-, cyclohexyl), 30.56 (C-1′′), 25.68, 23.95, 23.77 (3 × -CH_2-, cyclohexyl); HRFABMS: *m/z* 325.162227 $(M+Na)^+$. Calcd for $C_{15}H_{26}O_6Na$ 325.162699 $(M+Na)^+$.

Diastereomer **210a**: δ_H (300 MHz; CD_3OD) 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′′$_a$, H-3′′$_b$, 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′′$_a$, H-1′′$_b$); δ_C (75 MHz; CD_3OD) 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 × -

CH_2-, cyclohexyl), 29.71 (C-1′′), 26.82, 24.94, 24.76 (3 × -CH_2-, cyclohexyl); HRFABMS: *m/z* 325.162227 $(M+Na)^+$. Calcd for $C_{15}H_{26}O_6Na$ 325.162699 $(M+Na)^+$.

Diastereomer **210b:** δ_H (300 MHz; CD_3OD) 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-6$_a$, H-6$_b$), 2.05-1.30 (13 H, m, 5 x -CH_2-, cyclohexyl, H-2, H-1′′$_a$, H-1′′$_b$); δ_C (75 MHz; CD_3OD) 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 × -CH_2-, cyclohexyl), 29.14 (C-1′′), 26.82, 24.94, 24.76 (3 × -CH_2-, cyclohexyl); HRFABMS: *m/z* 325.162227 $(M+Na)^+$. Calcd for $C_{15}H_{26}O_6Na$ 325.162699 $(M+Na)^+$.

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