Synthesis of Lipooligosaccharide Antigens from Mycobacteria

by

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Abstract

Lipooligosaccharides (LOSs) are one of the three major classes of glycolipids produced by mycobacteria. Over 15 LOSs have been isolated and characterized in the past three decades. However, there are only a small number of studies that have focused on the synthesis of LOSs molecules. In this thesis, I have developed a synthetic route to oligosaccharide fragments of LOS III from *Mycobacterium gastri*.

To achieve our purpose, eight different building blocks were designed and synthesized. The L-xylopyranosides were prepared via stannanylidene acetal, a key intermediate for the selective protection of the hydroxyl groups. Two synthesized D-glucopyranosides were then coupled into an α,α-trehalose in 49% yield, while the coupling between the 3,6-dideoxy sugar alkene and terminal olefin failed to give any desired product.

In the synthesis of the oligosaccharide target, a key intermediate pentasaccharide was prepared using a 2+1+2 strategy. Upon obtaining this pentasaccharide, two oligosaccharides, a nonasaccharide and an ocatasaccharide, were synthesized as key advanced intermediates to the LOS target.

Dedicated to my family who support me, especially my wife, Ying Chen, and all my friends.

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List of Abbreviations

$[\alpha]_D$	Specific rotation (sodium D line)
Å	Angstrom
Ac	Acetyl
Ac_2O	Acetic anhydride
AcOH	Acetic acid
AG	Arabinogalactan
All	Allyl
app	Apparent
Ar	Aromatic
Ara*f*	Arabinofuranose
aq.	Aqueous
atm	Atmosphere
Bn	Benzyl
br	Broad
BSP	1-benzenesulfinylpiperidine

Bu	Butyl
Bz	Benzoyl
°C	Degrees Celsius
calcd	Calculated
COSY	Correlation Spectroscopy
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
d	Doublet (NMR spectra)
DBU	Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIEPA	*N,N*-Diisopropylethylamine
DMAP	*N,N*-Dimethyl-4-amminopyridine
DMB	3,4-dimethoxybenzyl
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide

DNA	Deoxyribonucleic acid
DTBMP	2,6-Di-*tert*-butyl-4-methylpyridine
equiv. or eq.	Equivalent
ESI	Electrospray Ionization
Et	Ethyl
Et_3N	Triethylamine
EtOH	Ethanol
Fuc*p*	Fucopyranose
Gal*f*	Galactofuranose
Gal*p*	Galactopyranose
GlcNAc	*N*-Acetylglucosamine
Glc*p*	Glucopyranose
GLPs	Glycopeptidolipids
h	Hour(s)
HMBC	Heteronuclear Multiple Bond Coherence
HMQC	Heteronuclear Multiple Quantum Coherence
HRMS	High resolution mass spectrometry

HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
IAD	Intramolecular Aglycone Delivery
IBX	2-Iodoxybenzoic acid
J	Coupling constant
LAM	Lipoarabinomannan
Lev	Levulinoyl
LOS(s)	Lipooligosaccharide(s)
m	Multiplet (NMR spectra)
M	Molar
Me	Methyl
MeOH	Methanol
mg	Milligram(s)
MHz	Megahertz
min	Minute(s)
mL	Millilitre(s)
mol	Mole(s)

mmol	Millimole(s)
Ms	Methanesulfonyl (mesyl)
MS	Mass spectrometry
MurNAc	*N*-Acetylmuramic acid
NBS	*N*-Bromosuccinimide
ND	Not Determined
NIS	*N*-Iodosuccinimide
NMR	Nuclear Magnetic Resonance
NTM	Non-tuberculous mycobacteria
Ph	Phenyl
PGLs	Phenolic Glycolipids
PMB	*p*-Methoxybenzyl
PMP	*p*-Methoxyphenol
ppm	Parts per million
Pyr	Pyridine
q	Quartet (NMR spectra)
quant	Quantitative

R_f	Retention factor
Rha*p*	Rhamnopyranose
rt	Room temperature
s	Singlet (NMR spectra)
satd	Saturated
SM	Starting material
t	Triplet (NMR spectra)
TBAI	Tetra-*n*-butylammonium iodide
TBS, TBDMS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
Tf	Triflate, trifluoromethanesulfonate
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TMSI	Trimethylsilyl iodide
TNF-α	Tumor necrosis factor α

TOF	Time Of Flight
Tol	*p*-Tolyl
Troc	2,2,2-Trichloroethoxycarbonyl
Ts	*p*-Toluenesulfonyl
p-TsOH	*p*-Toluenesulfonic acid
Xyl*p*	Xylopyranose

Chapter 1: Introduction

1.1 Mycobacterial Disease

There are more than 120 different mycobacterial species, among which many are pathogenic in humans or animals.[1] These organisms can be classified into three groups based on the diseases they cause: *Mycobacterium tuberculosis* complex, *Mycobacterium leprae* and non-tuberculous mycobacteria (NTM).[2] Members of the *Mycobacterium tuberculosis* complex cause infections similar to what is referred to as tuberculosis in humans. *Mycobacterium leprae* causes leprosy, which is also called Hansen's disease, in humans. The non-tuberculous mycobacteria, which are also sometimes referred to as 'atypical mycobacteria', include all other mycobacterial organisms.

1.1.1 Tuberculosis

Tuberculosis is an ancient disease. Evidence of the disease has been found in DNA taken from Egyptian mummies, which has confirmed that this disease had infected people who lived more than 5000 years ago.[3,4] In 1882, a German physician, Robert Koch, announced the discovery of a microbe (Figure 1.1), which he called *Mycobacterium tuberculosis*, and showed that it caused pulmonary disease.[5] In the 19th and early 20th centuries, tuberculosis was a leading cause of death in Europe, resulting in nearly 25% of all deaths. Since that time, mortality from tuberculosis has decreased, through a combination of many factors such as improvement of public health, better living conditions, vaccination with the bacillus Calmette Guérin (BCG) vaccine,[6,7] and the discovery and use of anti-mycobacterial drugs. However, today tuberculosis still remains a leading cause of death in the world, especially in Africa, where HIV has supported the growth of

the tuberculosis epidemic. In addition, after many years treatment of tuberculosis by antibiotics, new strains that are resistant to many antibiotics are now common. Scientists are facing more challenges, not only for the treatment of multidrug resistant tuberculosis (MDR-TB), but also for the development of new diagnostic tools.

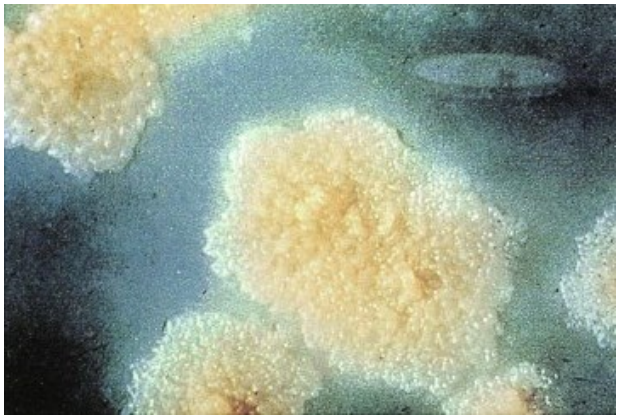


Figure 1.1. Mycobacterium tuberculosis colonies on Löwenstein-Jensen agar after 8 weeks of incubation.[8] Reprinted by permission from Elsevier.

1.1.2 Leprosy

Leprosy is a chronic disease of the skin and nervous tissues that is caused by *Mycobacterium leprae*.[9] Leprosy is also called Hansen's disease, after the Norwegian physician Gerhard Armauer Hansen, who identified the bacillus in patients in 1873.[10] Like tuberculosis, leprosy is an ancient disease. Reference to the disease goes back to 600 B.C.[11] and recent studies from skeletons in India provide evidence of the disease going back even earlier to 2000 B.C.[12] The disease can be treated by a multidrug therapy and deaths from the leprosy have decreased steadily since 1985.[9,13] In the beginning of the 21st century, disease rates are controlled to under one case per 10,000 population.[13]

1.1.3 Non-tuberculosis Mycobacteria (NTM) disease

There are many non-tuberculosis mycobacteria, some of which are not pathogenic, but others cause disease. One example is *Mycobacterium ulcerans.* Infection by this organism leads to Buruli ulcer. This disease mostly affects the skin, and may cause severe complications. Worldwide, it is the third most common mycobacterial disease after tuberculosis and leprosy.[2] The Buruli ulcer is generally found in Africa, the western Pacific region, Malaysia, Indonesia and South America.[14]

1.2 Mycobacterial Cell Wall Structure

Mycobacteria posses a complex, characteristic, hydrophobic cell wall, which is rich in lipids and carbohydrates.[15,16] The cell wall structure of mycobacteria, which is depicted in Figure 1.2, is responsible for many properties of the bacteria such as its acid-fastness, slow growth and the ability to influence the host immune response. In the following sections I will highlight some parts of this structure.

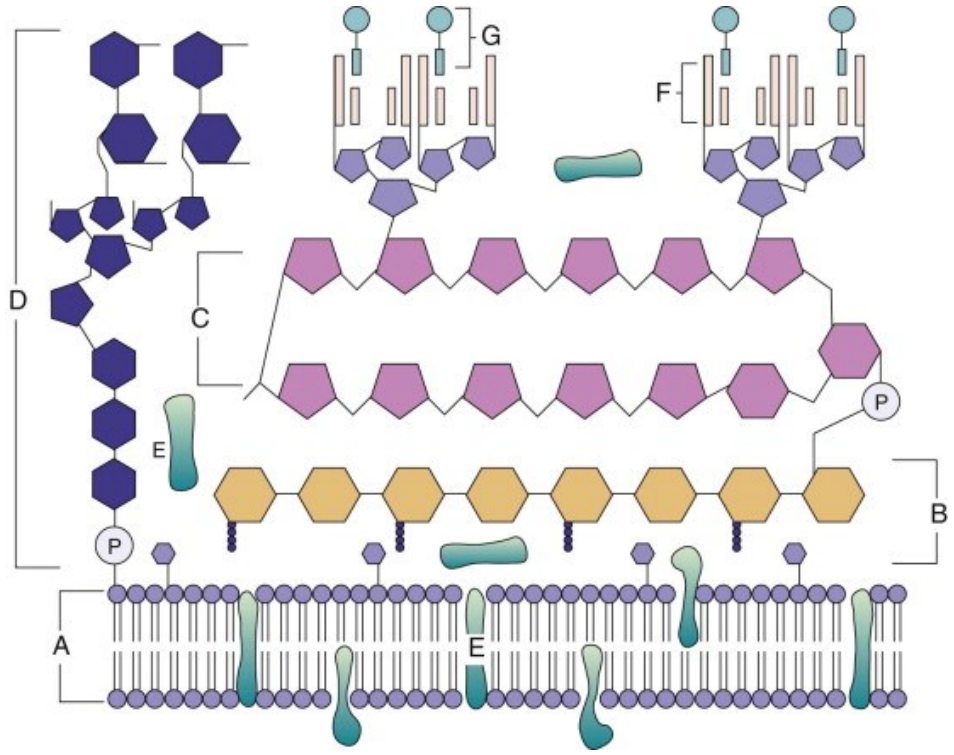


Figure 1.2. Mycobacteria Cell Wall Structure[17]

The components include the (A) plasma membrane, (B) peptidoglycan, (C) arabinogalactan, (D) lipoarabinomannan, (E) cell wall proteins, (F) mycolic acids, and (G) extractable glycolipids. Reprinted by permission from Elsevier.

1.2.1 Plasma Membrane

The plasma membrane is also called the cell membrane; it separates the inside of the cell from the outside environment. Its structure consists of phospholipid bilayer with associated proteins, which are responsible for transportation of nutrients (small organic molecules such as carbohydrates and amino acids) into the cell. The plasma membrane also acts as the attachment surface for extracellular structures (B, C, D, F, G shown in Figure 1.2).

1.2.2 Peptidoglycan

Peptidoglycan is an essential component of the cell wall and is found on the outside of the plasma membrane.[18] The peptidoglycan is a polymer consisting of carbohydrates and amino acids. The general structure is that the linear glycan strands are cross-linked by short peptides. The glycans are made of alternating N-acetylglucosamine (GlcNAc) and N-acetylmuramic acid (MurNAc) residues, which are connected by β-(1→4) linkages (Figure 1.3).

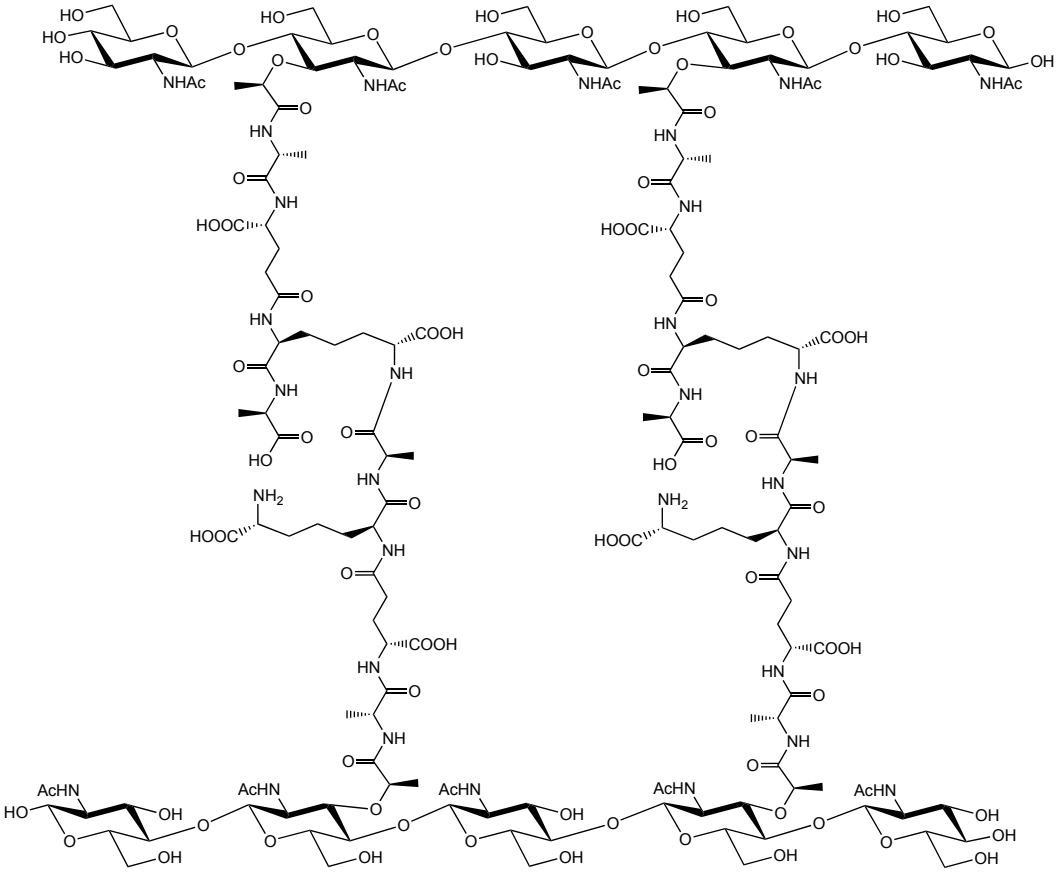


Figure 1.3. A Typical Structure of peptidoglycan (A1γ).

Peptidoglycans, depending on type of amino acids and way they are cross-linked to each other, vary from species to species. In Figure 1.3 is shown a most common type (A1γ), in which the peptide side chain consists of L-Ala-D-Glu-*m*-Dpm-D-Ala.[19] The peptides are cross-linked to each other directly through an amide bond between the *meso*-diaminopimelic acid (*m*-Dpm) and D-alanine. Mycobacterial cell wall peptidoglycan also has cross-links between two residues of *m*-Dpm.

As the peptidoglycan is an essential component of the bacterial cell wall, including mycobacteria, inhibition of peptidoglycan formation could inhibit the growth of the organism. Antibiotics such as penicillin inhibit the biosynthesis of peptidoglycan.[20] However, β-lactamase produced in mycobacteria,[21] as well as the nature of lipid-rich of the outer cell wall,[22-24] make mycobacteria resistant to penicillin.

1.2.3 Arabinogalactan (AG)

Arabinogalactan, which consists of arabinose and galactose solely in the furanose form, is the major structural component found in the cell wall of mycobacteria. The general structure is illustrated in Figure 1.4. The linear galactan backbone, which consists of ~30 D-galactofuranose (Gal*f*) residues polymerized via alternating β-(1→5) and β-(1→6) linkages, is attached to the peptidoglycan through a disaccharide phosphate moiety (α-L-Rha*p*-(1→4)-α-D-Glc*p*NAc-O-PO_3) link to the C-6 hydroxyl group of ~10−12% of the muramic acid residues.[25,26] Along this galactan chain are connected three arabinan chains, containing 22 D-arabinofuranose (Ara*f*) residues.[27] The arabinan consists of a

combination of α-(1→5), α-(1→3) and β-(1→2) linkages, with mycolic acids esterified at the non reducing end. The docosanasaccharide arabinan domain of mycobacteria arabinogalactan was synthesized independently by Lowary and Ito.[28,29]

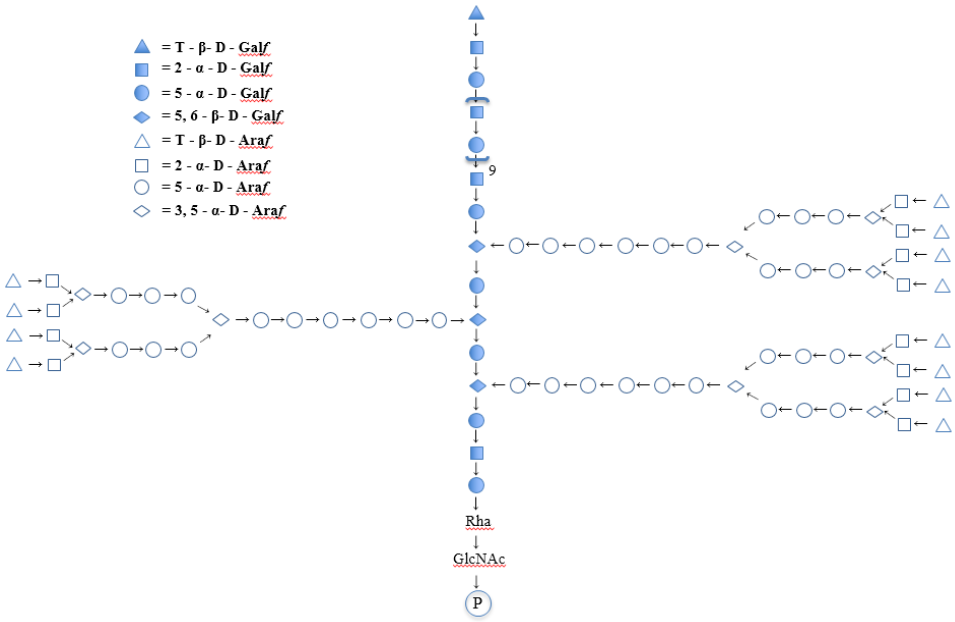


Figure 1.4. Structure of Arabinogalactan.

1.2.4 Lipoarabinomannan (LAM)

Lipoarabinomannan is another important cell wall molecule and it is responsible for the antigenic character of most pathogenic mycobacteria.[30] LAM is one of the virulence factors associated with *Mycobacterium tuberculosis*. It allows the bacteria to survive in the host by affecting host resistance and immune responses.[31] Depending on the capping moiety present at the arabinan chain termini, there are three types of LAM found so far: ManLAM, PILAM, and

AraLAM. ManLAM has capping moieties of mannose units.[32] On the other hand, in PILAM, the arabinan chain termini are capped with *myo*-inositol phosphate groups. Finally, AraMan does not have any capping moitifs.[33] The general LAM structure consists of an arabinan side chain (Figure 1.5),[34,35] which is attached to the α-(1→6)-linked mannopyranan core. The mannopyranan core is attached to the plasma membrane via a phosphatidylinositol lipid group. The arabinan side chain is more heterogeneous compared to the well defined arabinan domain structure in AG.[30,36]

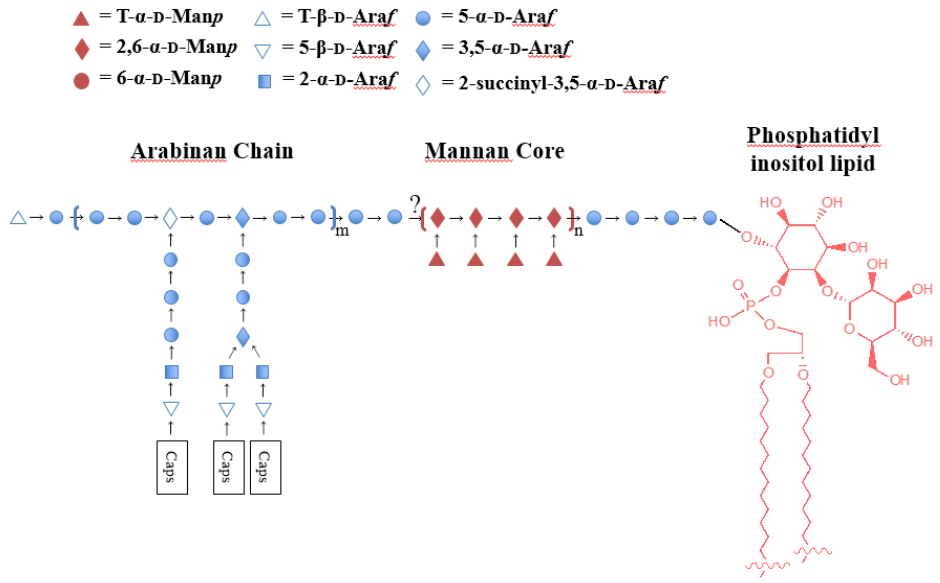


Figure 1.5. General Structure representation of Lipoarabinomannan.

1.2.5 Mycolic Acids

Mycolic acids are a family of long chain fatty acids found in mycobacteria and related organisms.[15,37,38] Stodola et al. isolated mycolic acids for the first time in 1938 from an extract of *Mycobacterium tuberculosis*.[39] Mycolic acids consist

of a long β-hydroxy chain with a short α-alkyl side chain. The number of carbons of mycolic acids found in mycobacteria varies from 60 to 90.[38]

The three main types of mycolic acid from mycobacteria are illustrated in Figure 1.6. Most of the mycolic acids from *Mycobacterium tuberculosis* are of the α-type, which has two degrees of unsaturation (cyclopropane rings, double bonds)[38]. Mycolates containing an α-methyl-branched methyl ether together with a cyclopropane ring (both *cis* and *trans*) are termed methoxy-mycolates. Keto-mycolates contain an α-methyl-branched ketone with a *cis* or *trans* cyclopropane ring possessing an adjacent methyl branch.

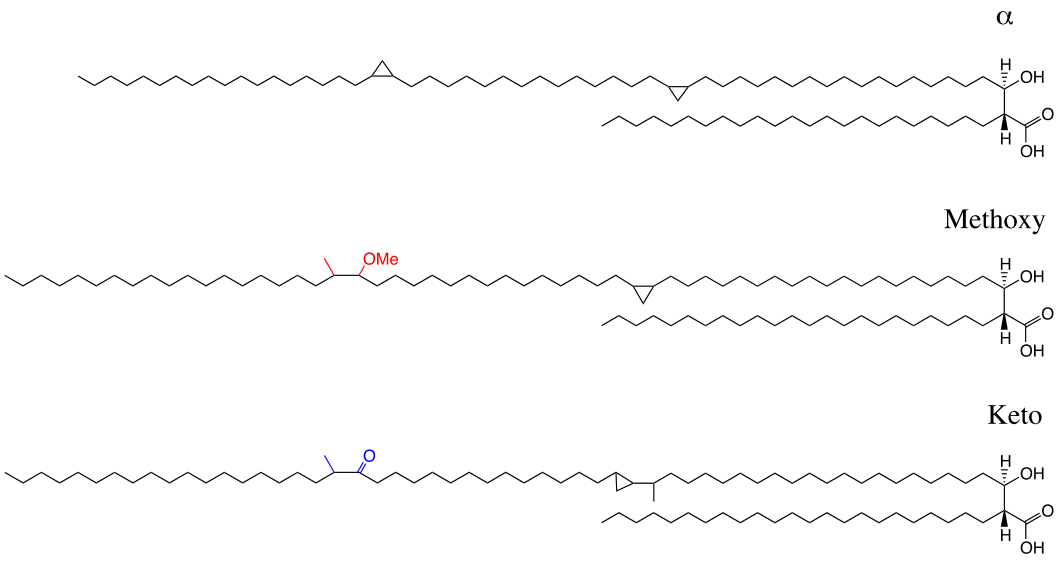


Figure 1.6. Structure of the three types of mycolic acids present in *Mycobacterium tuberculosis*.

1.2.6 Extractable Glycolipids

The extractable glycolipids, which are located at the outer layer of the mycobacterial cell wall, are a combination of different types of immunogenic glycoconjugates. The glycolipids are associated with the mycolic acids through their lipid portions by hydrophobic interactions. Three major classes of glycolipids, Phenolic Glycolipids (PGLs), Glycopeptidolipids (GPLs) and Lipooligosaccharides (LOSs), are found in the mycobacterial cell wall. The exact composition depends upon the species of mycobacteria.

1.2.6.1 Phenolic Glycolipids (PGLs)

PGLs consist of an oligosaccharide domain linked through a phenolic group to a lipid composed of phenolthiocerol, esterified to two mycocerosic acid groups. The oligosaccharide domain contains from one to four sugar residues, which are usually not very hydrophilic, consisting of deoxy sugars with multiple O-methyl groups. The structure of a PGL isolated from *Mycobacterium leprae* is shown in Figure 1.7.[40]

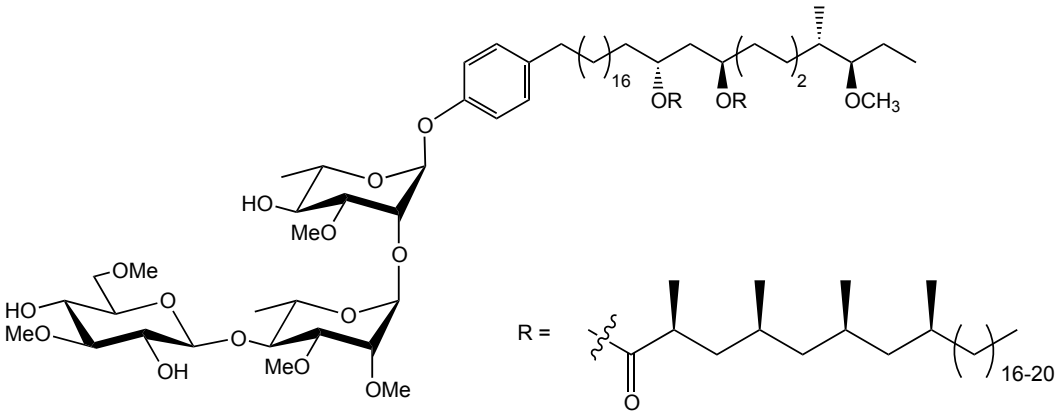


Figure 1.7. Structure of the major phenolic glycolipid isolated from *Mycobacterium leprae*.

1.2.6.2 Glycopeptidolipids (GPLs)

Glycopeptidolipids are the major cell surface antigens of the *Mycobacterium avium*, *Mycobacterium intracellulare*, *Mycobacterium scrofulaceum* complex (MAC) mycobacteria.[41] The C-terminus of the short peptide, D-Phe-D-*allo*-Thr-D-Ala-L-alaninol, is connected to a 3,4-di-*O*-methyl-L-rhamnose moiety; the N-terminus is linked to a fatty acid. The hydroxyl group of the D-*allo*-threonine residue carries an oligosaccharide substituent, with an α-L-rhamnopyranosyl-(1→2)-6-deoxy-L-talopyranose disaccharide as a core.[42-44] Structurally, GPLs can be subdivided into 31 distinct serotypes, which are related to the non-reducing terminus of the oligosaccharide attached to the *allo*-threonine residues.[45] The structure of nonspecific and serovar-specific GPLs isolated from *Mycobacterium avium* complex are shown in Figure 1.8.

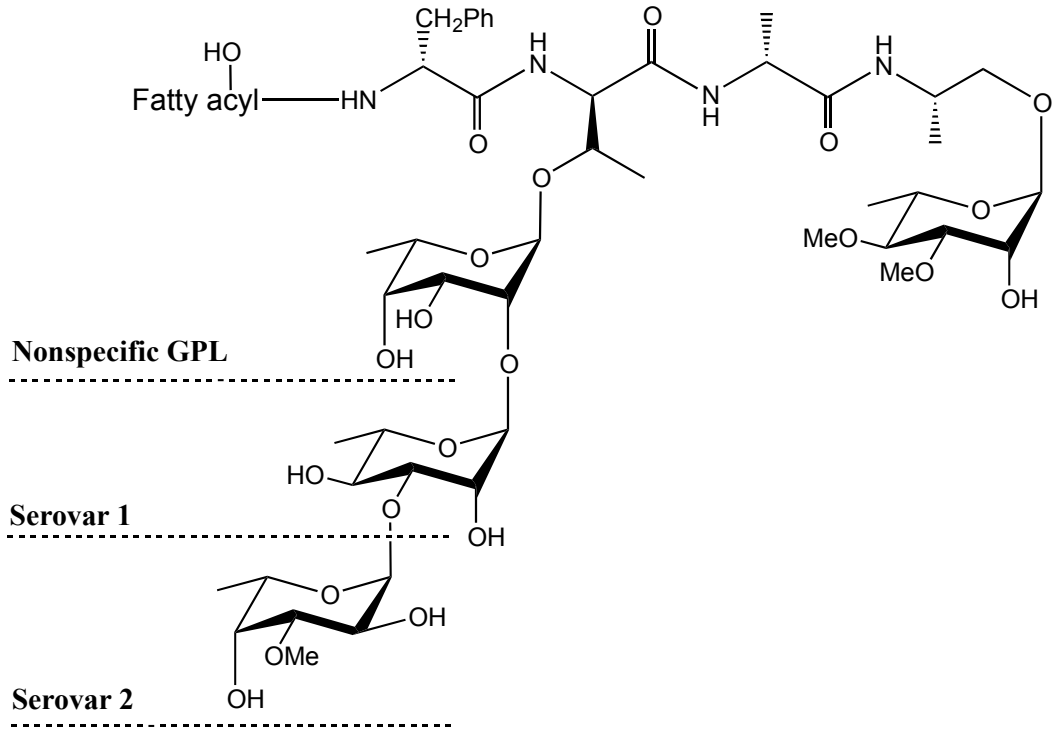


Figure 1.8. Structure of nonspecific and serovar-specific GPLs from *Mycobacterium avium*.

1.2.6.3 Lipooligosaccharides (LOSs)

Lipooligosaccharides are a broad class of important trehalose-containing glycolipids that are found in *Mycobacterium smegmatis*,[46] *Mycobacterium kansasii*,[47-49] *Mycobacterium gastri*.[48,50] *Mycobacterium malmoense*,[51] *Mycobacterium szulgai*,[52] *Mycobacterium gordonae*[53] and certain representatives of *Mycobacterium tuberculosis* complex.[54,55] My thesis work pertains to LOSs and thus the structure and biological function of these molecules will be discussed in more detail in the following sections.

1.3 Structure of Lipooligosaccharides from Mycobacteria

The first lipooligosaccharide was reported as a new class of glycolipid in 1983 when Saadat and Ballou were studying biosynthetic precursors of the 6-*O*-methylglucose lipopolysaccharides.[46] Since then, more than 15 lipooligosaccharides have been isolated and characterized. Structurally, they share a common trehalose core with the lipid groups attached solely on the trehalose moiety.[56] The structures of the non-reducing end of the oligosaccharides vary in different mycobacterial species, which results in antigenic specificity.

1.3.1 Lipooligosaccharides from *Mycobacterium smegmatis*

The first lipooligosaccharides isolated from *Mycobacterium smegmatis* were described as acidic oligosaccharides, given the presence of a pyruvate acetal (Figure 1.8). Acidic oligosaccharides B_1 is a tetrasaccharide, which also forms the core structure of acidic oligosaccharide A and B_2, consisting of 4,6-(1'-carboxyethylidene)-β-D-Glc*p*-(1→4)-β-D-Glc*p*-(1→6)-α-D-Glc*p*-(1↔1)-α-D-Glc*p* (Figure 1.9). The difference between the oligosaccharide A and B_2 is that the acidic oligosaccharide A has two pyruvate acetal groups, whereas oligosaccharide B_2 has a single one.

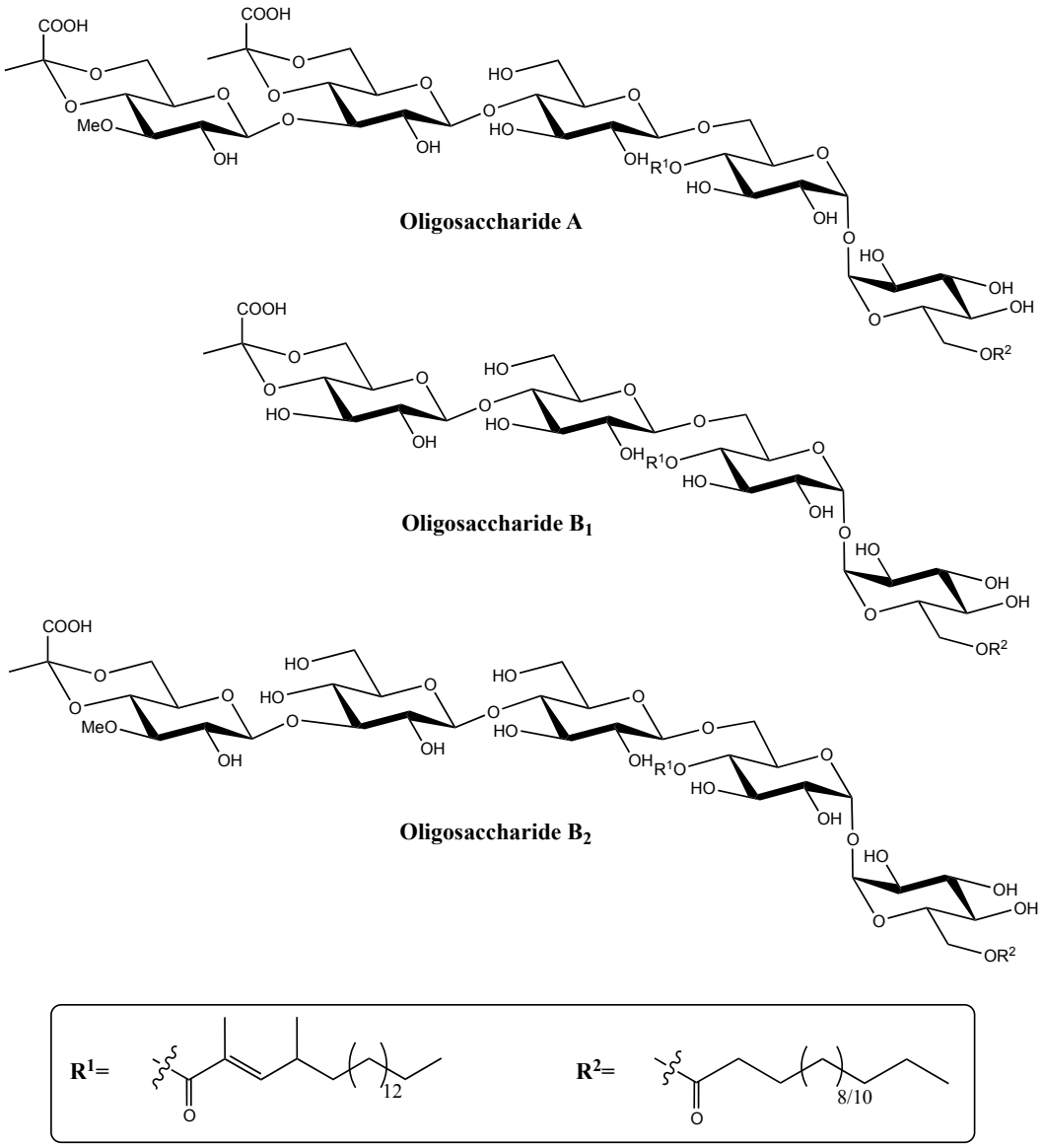


Figure 1.9. Structure of acidic oligosaccharides from *Mycobaterium smegmatis*.

Given the structural relationships between the oligosaccharides, the authors suggested that B_1 and B_2 are biosynthetic precursors to oligosaccharide A. However, the details of the biosynthetic pathway, as well as the enzymes that are responsible for the assembly of these structures, are still unknown.

The location and structure of the lipid was determined later.[57] First, all acyl groups are located on the trehalose moiety. Secondly, three fatty acids were identified. Analysis suggested that 60% of the lipooligosaccharide contained C_{14} and C_{22} fatty acids while 40% of the structure contained C_{16} and C_{22} fatty acids. The C_{14}, C_{16} and C_{22} fatty acids were identified as myristic acid, palmitic acid and 2,4-dimethyl-2-eicosenoic acid, respectively. The longer fatty acid is located on the C-4 hydroxyl group of internal glucose unit of the trehalose moiety, whereas the shorter acid is located on the C-6 hydroxyl group of terminal glucose unit of the trehalose moiety.

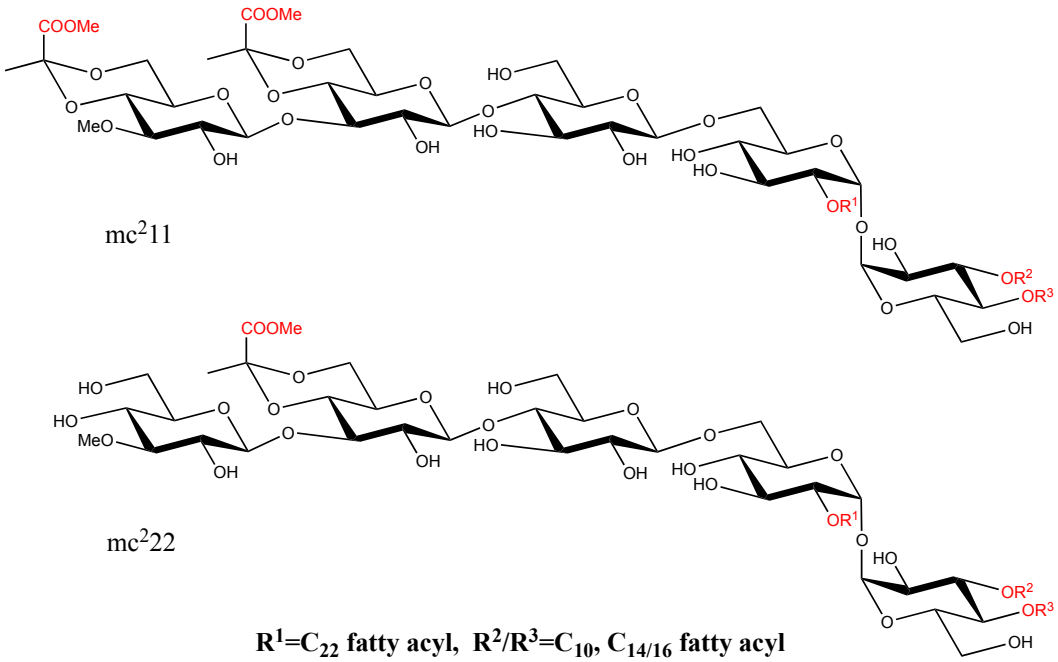


Figure 1.10. Structure of LOSs found in *Mycobacterium smegmatis* stains mc^{2}22 and mc^{2}11.

Brennan and coworkers have isolated lipooligosaccharides from *Mycobacterium smegmatis* strains mc^{2}22 and mc^{2}11.[58] These LOSs share the same pentasaccharide core as that found in the original pyruvylated glycolipids reported by Saadat and Ballou, but with a few differences (Figure 1.10). First, the pyruvate acetal group is methylated in both LOSs. Secondly, the location of acyl groups is different. The fatty acids of the LOSs from the mc^{2}22 and mc^{2}11 strains are located on the C-2 hydroxyl groups of the internal glucose unit of the trehalose moiety. On the other hand, the fatty acids are located on the C-3 and C-4 hydroxyl groups of the terminal glucose unit of trehalose moiety. Finally, in the mc^{2}22 LOS the C-3 hydroxyl group of the non-reducing terminus glucose unit is not methylated. In summary, to date, five LOSs have been reported from *Mycobacterium smegmatis*. These are listed in Table 1.1.

Table 1.1. Lipooligosaccharides from *Mycobacterium smegmatis.*

Name	Structure	Position of Acyl groups
Acidic oligosaccharide A	4,6-(1-carboxyethylidene)-3-*O*-Me-β-D-Glc*p*-(1→3)-4,6-(1-carboxyethylidene)-β-D-Glc*p*-(1→4)-β-D-Glc*p*-(1→6)-α-D-Glc*p*-(1↔1)-α-D-Glc*p*	Trehalose 4' and 6-hydroxyl groups
Acidic oligosaccharide B_1	4,6-(1-carboxyethylidene)-β-D-Glc*p*-(1→4)-β-D-Glc*p*-(1→6)-α-D-Glc*p*-(1↔1)-α-D-Glc*p*	ND
Acidic oligosaccharide B_2	3-*O*-Me-β-D-Glc*p*-(1→3)-4,6-(1-carboxyethylidene)-β-D-Glc*p*-(1→4)-β-D-Glc*p*-(1→6)-α-D-Glc*p*-(1↔1)-α-D-Glc*p*	ND
Lipooligosaccharide $mc^2$22	β-D-Glc*p*-(1→3)-4,6-(1-methoxycarboxyethylidene)-β-D-Glc*p*-(1→4)-β-D-Glc*p*-(1→6)-α-D-Glc*p*-(1↔1)-α-D-Glc*p*	Trehalose 2', 3 and 4 hydroxyl groups
Lipooligosaccharide $mc^2$11	4,6-(1-methoxycarboxyethylidene)-3-*O*-Me-β-D-Glc*p*-(1→3)-4,6-(1-methoxycarboxyethylidene)-β-D-Glc*p*-(1→4)-β-D-Glc*p*-(1→6)-α-D-Glc*p*-(1↔1)-α-D-Glc*p*	Trehalose 2', 3 and 4 hydroxyl groups

1.3.2 Lipooligosaccharides from *Mycobacterium kansasii*

Lipooligosaccharides from *Mycobacterium kansasii* are a large group of LOSs; to date, nine have been isolated and characterized. By using a combination of experimental techniques (e.g., acetolysis, partial acid cleavage, permethylation) and analytical methods, e.g., ^{1}H and ^{13}C NMR spectroscopy, electron ionization/mass spectroscopy (EI/MS), Brennan and co-workers revealed for the first time that the structure of these LOSs are composed of variable residues of xylose, 3-*O*-methyl-rhamnose, fucose, a novel N-acyl amino sugar, and a tetrasaccharide made up of glucose residues.[49,53,59] About a decade later, a more precise structure was determined by Gilleron and Puzo.[48] The core, the structure

of which was revealed to be β-D-Glc*p*-(1→3)-β-D-Glc*p*-(1→4)-α-D-Glc*p*-(1↔1)-α-D-Glc*p*, was shared by all LOSs found in *M. kansasii*. A structure of the most complex lipooligosaccharide LOS VIII was illustrated in Figure 1.11.

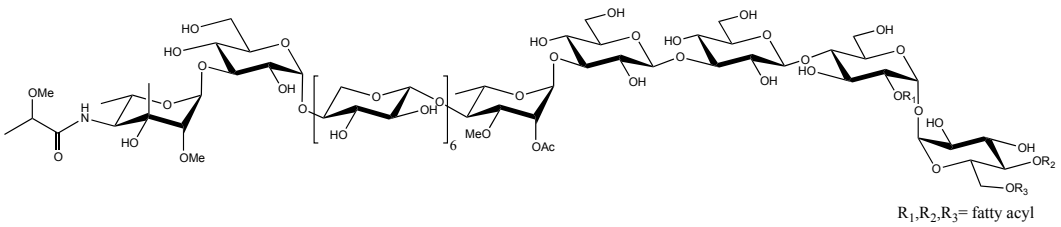


Figure 1.11. Structure of LOS VIII from *Mycobacterium kansasii.*

The LOS I' is the only one that does not contain a xylopyranose (Xyl*p*) unit (Table 1.2). In this case, a 2-*O*-Ac-3-*O*-Me-L-Rha*p* unit is attached to the tetrasaccharide core via an α-(1→3)-linkage.[48] LOS I has one L-Xyl*p* unit connected to the Rha*p* unit of LOS I' via a β-(1→4) glycosyl bond.[48]

Table 1.2. Lipooligosaccharides from *Mycobaterium kansasii.*

Names	Structure of Oligosaccharide	Position of Acyl groups
LOS I'	2-*O*-Ac-3-*O*-Me-α-L-Rha*p*-(1→3)-β-D-Glc*p*-(1→3)-β-D-Glc*p*-(1→4)-α-D-Glc*p*-(1↔1)-α-D-Glc*p*	ND
LOS I	β-L-Xyl*p*-(1→4)-2-*O*-Ac-3-*O*-Me-α-L-Rha*p*-(1→3)-β-D-Glc*p*-(1→3)-β-D-Glc*p*-(1→4)-α-D-Glc*p*-(1↔1)-α-D-Glc*p*	ND
LOS II, III	[β-L-Xyl*p*-(1→4)]$_2$-2-*O*-Ac-3-*O*-Me-α-L-Rha*p*-(1→3)-β-D-Glc*p*-(1→3)-β-D-Glc*p*-(1→4)-α-D-Glc*p*-(1↔1)-α-D-Glc*p*	ND
LOS IV, V, VI	α-KanNAcyl-(1→3)-α-D-Fuc*p*-(1→4)-[β-L-Xyl*p*-(1→4)]$_4$-2-*O*-Ac-3-*O*-Me-α-L-Rha*p*-(1→3)-β-D-Glc*p*-(1→3)-β-D-Glc*p*-(1→4)-α-D-Glc*p*-(1↔1)-α-D-Glc*p*	ND
LOS VII, VIII	α-KanNAcyl-(1→3)- α-D-Fuc*p*-(1→4)-[β-L-Xyl*p*-(1→4)]$_6$-2-*O*-Ac-3-*O*-Me-α-L-Rha*p*-(1→3)-β-D-Glc*p*-(1→3)-β-D-Glc*p*-(1→4)-α-D-Glc*p*-(1↔1)-α-D-Glc*p*	Trehalose 2', 4, 6-hydroxyl groups

LOS II and III share the same oligosaccharide core structure, which consists of one more L-Xyl*p* unit than LOS I, connected to the rhamnopyranose (Rha*p*) moiety via a β-(1→4) linkage. The differences between LOS II and III are probably due to a different number of acyl groups in the structure.[47] This also

applies to LOS IV, LOS V and LOS VI, which are all based on the same hexasaccharide structure found in LOS II and LOS III. In LOS IV–VI, however, this oligosaccharide is elongated by an additional tetrasaccharide with the structure α-KanNAcyl-(1→3)-α-D-Fuc*p*-(1→4)-β-L-Xyl*p*-(1→4)-β-L-Xyl*p*.[48] The novel KanNAcyl amino sugar was later determined to be 4,6-dideoxy-2-*O*-methyl-3-*C*-dimethyl-4-(2-methoxypropionamido)-L-mannopyranose (Figure 1.1),[59] and it was determined that this monosaccharide, as well as D-fucopyranose, are essential for the antigenicity of the LOS.[47] The LOS VII and VIII differ from LOS IV−VI on the size of the molecule. LOS VII and VIII are triskaidecasaccharide with two extra L-Xylp units than the LOS IV−VII.

One fatty acyl was found linked to the C-2 hydroxyl group of the penultimate α-Glc*p*, whereas one fatty acyl was determined to be on the C-4 hydroxyl group of the terminal Glc*p*. One addition fatty acyl was also found to be located on the C-6 hydroxyl group of the terminal Glc*p*.

1.3.3 Lipooligosaccharides from *Mycobacterium gastri*

Mycobacterium gastri is very closely related to *Mycobacterium kansasii*. The differentiation of the two species relies on the identification of the lipooligosaccharide antigens, which are different in the two species.

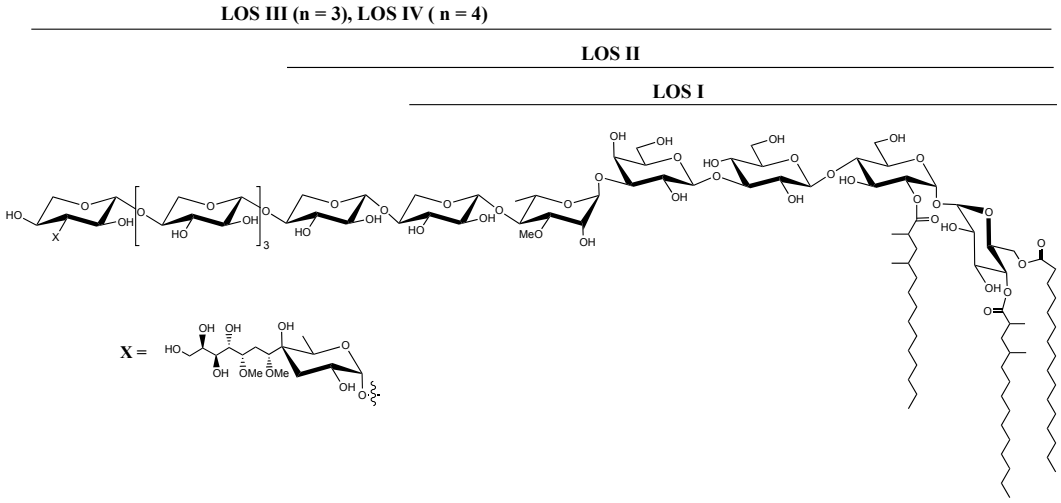


Figure 1.12. Structure of LOSs from *Mycobacterium gastri.*[*]

Four LOSs were isolated and identified from *M. gastri* by Puzo and coworkers in the mid-1990s.[48,50,60] The most simple LOS, called LOS I, consists of a Xyl*p*, a Rha*p*, a Gal*p*, and three Glc*p* units. LOS II differs from LOS I by the presence of an additional Xyl*p* unit. Both LOS I and LOS II lack the novel C4-branched-3,6-dideoxy-hexopyranose residue, which is found in the structure of LOS III and LOS IV. The LOS III and IV contain the same monosaccharide units, but differ from each other by the number of Xyl*p* units (Figure 1.12). The repeating Xyl*p* unit, like the one present in LOSs from *Mycobacterium kansasii*, was determined to be the L-series.[50]

The detailed stereochemistry of the novel C4-branched-3,6-dideoxy-hexopyranose residue was not revealed until 1997. This was made possible when

[*] The 3,6-dideoxy-4-*C*-branched galactopyranosyl residue may be the enantiomer of the configuration shown in this figure.

Prandi and coworkers assigned the structure through chemical synthesis of the monosaccharide.[61]

Table 1.3. Lipooligosaccharide from *Mycobaterium gastri.*[*]

Names	Structure of oligosaccharide	Position of Acyl groups
LOS I	β-L-Xyl*p*-(1→4)-3-*O*-Me-α-L-Rha*p*-(1→3)-β-D-Gal*p*-(1→3)-β-D-Glc*p*-(1→4)-α-D-Glc*p*-(1↔1)-α-D-Glc*p*	Trehalose 2', 4 and 6 hydroxyl groups.
LOS II	[β-L-Xyl*p*-(1→4)]$_2$-3-*O*-Me-α-L-Rha*p*-(1→3)-β-D-Gal*p*-(1→3)-β-D-Glc*p*-(1→4)-α-D-Glc*p*-(1↔1)-α-D-Glc*p*	Trehalose 2', 4 and 6 hydroxyl groups.
LOS III	3,6-dideoxy-5,7-di-*O*-methyl-4-*C*-[(*R*)-1-hydroxyethyl)]-D-*lyxo*-D-*allo*-undecopyranosyl-(1→3)-[β-L-Xyl*p*-(1→4)]$_5$-3-*O*-Me-α-L-Rha*p*-(1→3)-β-D-Gal*p*-(1→3)-β-D-Glc*p*-(1→4)-α-D-Glc*p*-(1↔1)-α-D-Glc*p*	Trehalose 2', 4 and 6 hydroxyl groups.
LOS IV	3,6-dideoxy-5,7-di-*O*-methyl-4-*C*-[(*R*)-1-hydroxyethyl)]-D-*lyxo*-D-*allo*-undecopyranosyl-(1→3)-[β-L-Xyl*p*-(1→4)]$_6$-3-*O*-Me-α-L-Rha*p*-(1→3)-β-D-Gal*p*-(1→3)-β-D-Glc*p*-(1→4)-α-D-Glc*p*-(1↔1)-α-D-Glc*p*	Trehalose 2', 4 and 6 hydroxyl groups.

The location of the fatty acyl groups, are the same in all four LOSs from *M. gastri*. Two of the fatty acyl groups are 2,4-dimethyltetradecanoic acids, and are located on the C-2 hydroxyl group of the penultimate α-Glc*p* unit and the C-4 hydroxyl group of the terminal α-Glc*p* unit. One additional fatty acid, palmitic

[*] The 3,6-dideoxy-*C*-4-branched galactopyranosyl residue may be the enantiomer of the configuration described in this table.

acid, is linked to the C-6 hydroxyl group of the terminal α-Glc*p* unit. The LOSs that have been identified in *Mycobacterium gastri* are listed in Table 1.3.

1.3.4 Lipooligosaccharides from *Mycobacterium marinum*

Recent research on *Mycobacterium marinum* has revealed a new class of lipooligosaccharide.[62-64] Like the LOSs isolated from *M. kansasii* and *M. gastri*, LOSs isolated from *M. marinum* share a same tetrasaccharide core containing four glucopyranose residues. LOS I from *M. marinum* has a Rha*p* residue attached to the C-3 hydroxyl group of the non-reducing end of this core domain (Figure 1.13).

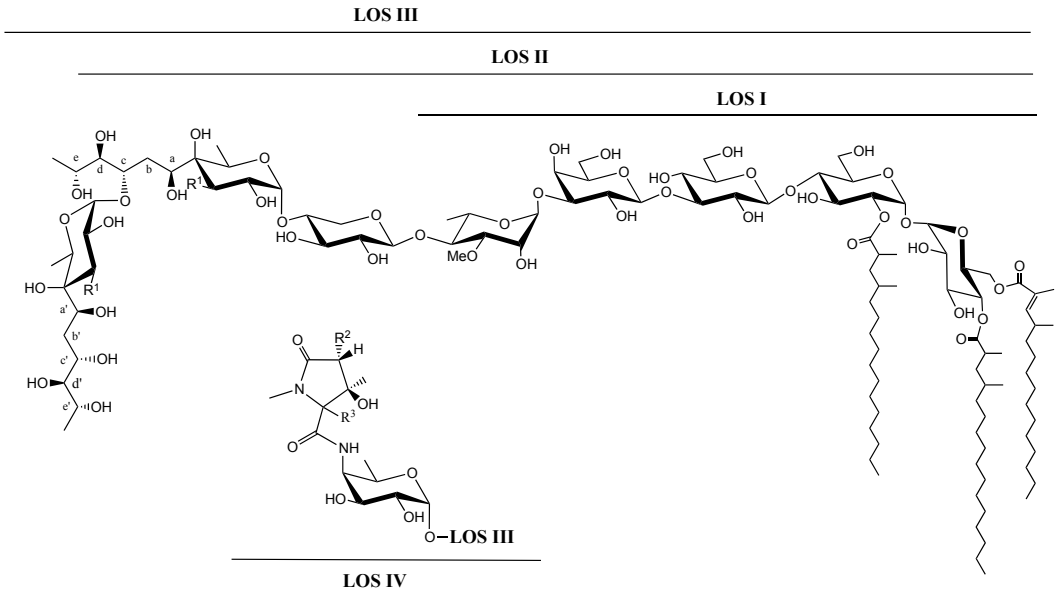


Figure 1.13. Structure of Lipooligosaccharides from *Mycobacterium marinum.*[64]

R^1= −H or –OH; R^2 = –H or –OCH_3; R^3 = –H or –COOH

Compared to LOS I, the structure of LOS II consists of two more sugar units. In LOS II, a 3,6-dideoxy-4-*C*-(D-*altro*-1,3,4,5-tetrahydroxyhexyl)-α-D-*xylo*-hex*p*-(1→4)-β-D-Xyl*p* disaccharide moiety is connected at the C-4 hydroxyl

group of the Rha*p* residue. The C-4 branched monosaccharide, which is called caryophyllose, is identical to a monosaccharide previously isolated from *Pseudomonas caryophylli*.[63,65,66] *Mycobacterium marium* LOS III contains an additional caryophyllose unit substituted on the OH-c position of the polyhydroxylated chain of the branched chain sugar by an α-(1→c) linkage.

The situation is complicated when it comes to LOS IV, which, in addition to the two caryophyllose moieties, has a unique α-4-amino-4, 6-dideoxy-Gal*p* moiety *N*-acylated by a 3-hydroxy-3-methylated-pyrrolidone group. The dideoxysugar residue is substituted on the OH-c' position of the terminal caryophyllose side chain of LOS III. Further study on the isolation and identification of LOSs revealed differences between neutral and acidic LOS IV, which have similar chromatographic behavior. These differences depend on the substitution and stereochemistry of the pyrrolidone residue (Figure 1.14).[64]

Through the use of a range of NMR spectroscopic experiments, the structure of the pyrrolidone termini was revealed to be as illustrated in Figure 1.14. In the neutral species, the major component Za, which accounts for 80% of total molecule, is a (2*S*, 3*S*, 4*R*)-3-hydroxy-4-methoxy-1,3-dimethyl-5-oxopyrrolidine-2-carboxylic acid group. The structure of the minor derivatives Zb, have the 2*S*, 3*S*- and 2*R*, 3*R*- configurations, and the methoxy group is substituted by a hydrogen atom. The structural difference between the neutral LOS IV terminal residue Za and acidic LOS IV terminal residue Zc is a carboxylic acid group at the C-2 position of the pyrrolidone ring. Two diastereoisomers (2*S*, 3*S*, 4*R*) and (2*R*, 3*S*, 4*R*) were determined.

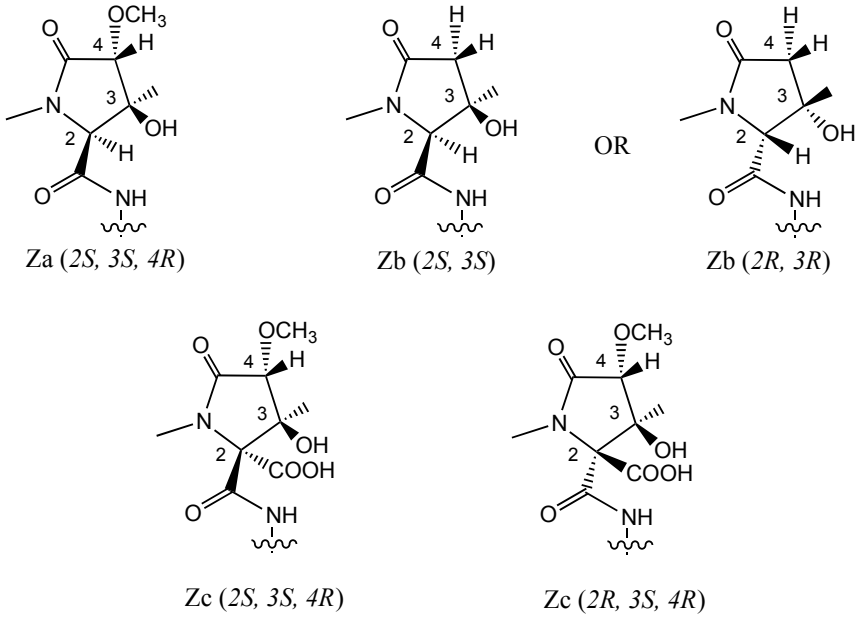


Figure 1.14. Structure of the substituted pyrrolidone residue

Za and Zb: from neutral LOS IV; Zc: from acidic LOS IV.

The identification and location of the fatty acids on the trehalose moiety were also studied.[67] In the original study, the type of acyl group was identified to be a 2,4-dimethyl-branched fatty acid chain.[64] More details were revealed in a later report, showing that the fatty acids are 2,4-dimethylhexadecanoic acid and 2,4-dimethyl-2-pentadecenoic acid. Furthermore, three hydroxyl groups of the trehalose moiety were esterified by fatty acids. The unsaturated 2,4-dimethyl-2-pentadecenoic acid substitutes the C-6 position of the terminal Glc*p* unit of trehalose moiety, whereas the saturated 2,4-dimethyl-2-pentadecenoic acid substitutes the C-4 and C-2 hydroxyl groups of the terminal and penultimate Glc*p* units, respectively.

1.3.5 Lipooligosaccharides from other mycobacterial species

There are other LOSs isolated and identified from mycobacteria different from those discussed above; these are listed in listed in Table 1.4. As described in the table, the structures of the molecules all have an acylated trehalose moiety as a common core, whereas differences are found at the non-reducing end of the oligosaccharide.

Mycobacterium malmoense has been shown to produce three LOSs, LOS I, II and III.[51] The lipooligosaccharides from *M. malmoense*, LOS I – LOS III, share a common trisaccharide core, α-L-Rha*p*-(1→3)-α-D-Glc*p*-(1↔1)-α-D-Glc*p*. *M. malmoense* LOS I and II also share a same tetrasaccharide residue, α-D-Man*p*-(1→3)-α-D-Man*p*-(1→2)-α-L-Rha*p*-(1→2)-3-*O*-Me-α-L-Rha*p*, at their non-reducing terminus. The difference is that the LOS I is a nonasaccharide, with a disaccharide unit, α-L-Rha*p*-(1→2)-α-L-Rha*p*, in the middle of shared non-reducing and reducing terminal; while the LOS II is a octasaccharide with a 3-*O*-Me-α-L-Rha*p* unit in the middle of shared carbohydrate residues.

LOS III has a unique pentasaccharide on the non-reducing terminal, which includes a D-Gal*f* unit, a rare monosaccharide residue found in mycobacterium LOSs.[51] The non-reducing terminal is consist of a pentasaccharide unit, D-Gal*f*-(1→2)-α-L-Rha*p*-(1→2)-[3-*O*-Me-α-L-Rha*p*-(1→2)]$_2$-α-L-Rha*p*.

Table 1.4. Lipooligosaccharides from other mycobacteria.

Species & Names	Structure of Oligosaccharide	Positions of Acyl Groups*
M. malmoense **LOS I**	α-D-Man*p*-(1→3)-α-D-Man*p*-(1→2)-α-L-Rha*p*-(1→2)-3-*O*-Me-α-L-Rha*p*-(1→2)-α-L-Rha*p*-(1→2)-α-L-Rha*p*-(1→3)-α-L-Rha*p*-(1→3)-α-D-Glc*p* (1↔1)-α-D-Glc*p*	Trehalose 3, 4 and 6 hydroxyl groups
M. malmoense **LOS II**	α-D-Man*p*-(1→3)-α-D-Man*p*-(1→2)-α-L-Rha*p*-(1→2)-[3-*O*-Me-α-L-Rha*p*-(1→2)]$_2$-α-L-Rha*p*-(1→3)-α-D-Glc*p* (1↔1)-α-D-Glc*p*	Trehalose 3, 4 and 6 hydroxyl groups
M. malmoense **LOS III**	D-Gal*f*-(1→2)-α-L-Rha*p*-(1→2)-[3-*O*-Me-α-L-Rha*p*-(1→2)]$_2$-α-L-Rha*p*-(1→3)-α-L-Rha*p*-(1→3)-α-D-Glc*p* (1↔1)-α-D-Glc*p*	Trehalose 3, 4 and 6 hydroxyl groups
M. szulgai **LOS 1**	α-L-2-*O*-Me-Fuc*p*-(1→3)-α-L-Rha*p*-(1→3)-β-L-Rha*p*-(1→3)-β-D-Glc*p* -(1→6)-α-D-Glc*p*-(1↔1)-α-D-2-*O*-Me-Glc*p*	Trehalose 3, 4 and 6 hydroxyl groups
M. linda	β-D-Glc*p* –(1→3)-α-L-Rhap-(1→3)-α-D-Glc*p* -(1↔1)-α-D-Glc*p*	Trehalose 3, 4 and 6 hydroxyl groups

Table 1.4.(continued) Lipooligosaccharides from other mycobacteria.

M. butyricum **LOS I**	4,6-(methyl-1-carboxyethylidene)-3-*O*-Me-β-D-Glc*p* – (1→3)-4,6-(methy-1-carboxyethylidene)-β-D-Glc*p* (1→4)-β-D-Glc*p* –(1→6)-α-D-Glc*p*-(1↔1)-α-D-Glc*p*	Trehalose 2', 3 and 4 hydroxyl groups
M. gordonae **990 LOS I**	α-L-Rha*p*-(1→2)-3-*O*-Me-α-L-Rha*p*-(1→3)-[β-D-Xyl*p*-(1→2)]-α-L-Rha*p*-(1→3)-β-D-Glc*p*-(1→3)- β-D-Glc*p*-(1→3)-α-L-Rha*p*-(1→3)-6-*O*-Me-α-D-Glc*p*-(1↔1)-α-D-Glc*p*	Trehalose 2, 3, 4 and 6 hydroxyl groups
M. gordonae **989 LOS I**	N-acyl-4-amino-4,6-dideoxy-2,3-*O*-Me-α-Gal*p*-(1→3)-2-*O*-Me-4-*O*-Acyl-α-L-Fuc*p*-(1→3)-β-D-Glc*p*-(1→3)-2-*O*-Me-α-L-Rha*p*-(1→3)-[β-D-Xyl*p*-(1→2)]-α-L-Rha*p*-(1→3)-β-D-Glc*p*-(1→3)-α-L-Rha*p*-(1→3)-6-*O*-Me-α-D-Glc*p*-(1↔1)-α-D-Glc*p*	Trehalose 2, 3, 4 and 6 hydroxyl groups
M. tuberculosis **Canetti LOS II**	N-acyl-4-amino-4,6-dideoxy-Galp-(1→4)-2-*O*-Me-α-L-Fucp-(1→3)-β-D-Glc*p*-(1→3)-2-*O*-Me-α-L-Rha*p*-(1→3)-2-*O*-Me-α-L-Rha*p*-(1→3)-β-D-Glc*p*-(1→3)-4-*O*-Me-α-L-Rha*p*-(1→3)-6-*O*-Me-α-D-Glc*p*-(1↔1)-α-D-Glc*p*	Trehalose 2, 3, 6 and 3,4,6 hydroxyl groups (2:3)
M. tuberculosis **H37Rv**	α-D-Glc*p*-(1↔1)-α-D-Glc*p*	Trehalose 2, 3 hydroxyl groups
M. fortuitum **biovar *fortuitum***	β-D-Glc*p*-(1→6)-α-D-Glc*p*-(1↔1)-α-D-Glc*p*	Trehalose 2', 2, 3 and 6 hydroxyl groups

The acyl groups, mainly 2-methyleicosanoic acid and 2,4-dimethylpentacosanoic acid, are located at the C-3, C-4 and C-6 hydroxyl groups of the terminal Glc*p* unit. The structure of LOS I from *Mycobacterium malmoense* is shown in Figure 1.15.

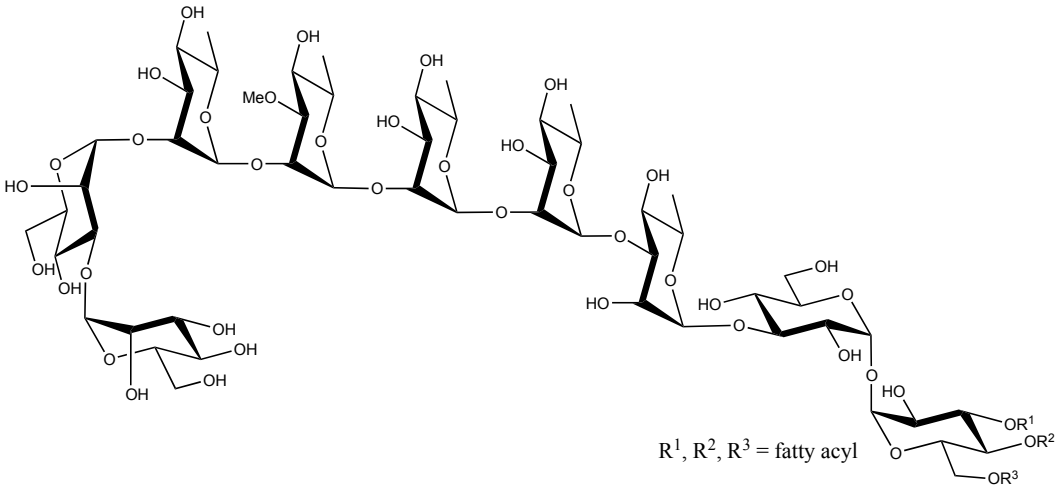


Figure 1.15. Structure of LOS I from *Mycobacterium malmoense.*

Six lipooligosaccharides, LOS 1–6, have been isolated from *Mycobacterium szulgai*.[52] LOS 1–3 were not antigenic but serological activities were observed for LOS 4, LOS 5 and LOS 6.[52] The structure of LOS 1 was studied and it showed to have a 2-*O*-methylated trehalose moiety. The structure also contains a 2-*O*-methylated-L-Fuc*p* unit, two L-Rha*p* units and one D-Glc*p* unit. The terminal Glc*p* unit is fully substituted by acyl groups. The structural details are shown both in Table 1.4 and Figure 1.16. The structure of LOS 4 was also been briefly studied, although the details are still unknown. An unidentified

sugar unit, which could possibly be an α-linked 6-deoxyhexose, is likely to be responsible for its antigenicity. Structural work on the other LOSs from *Mycobacterium szulgai* has not been reported.

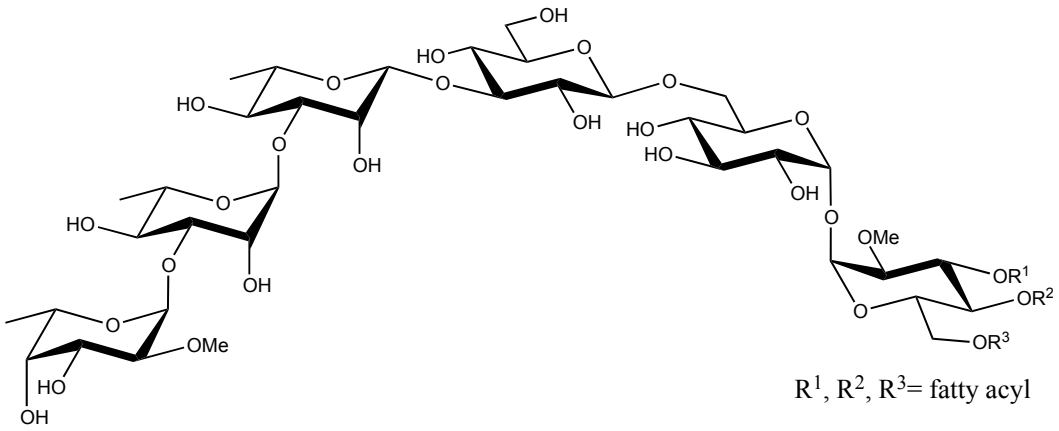
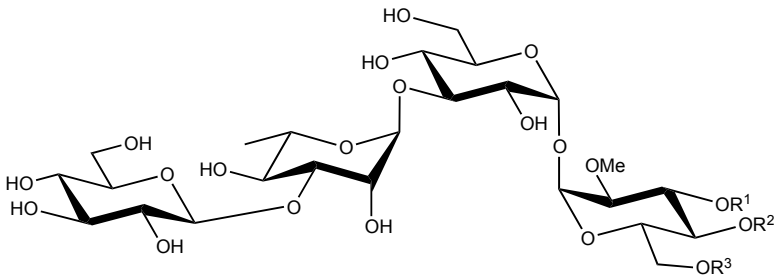


Figure 1.16. Structure of LOS 1 *from Mycobacterium szulgai.*

A variant of *Mycobacterium linda* produces a simple lipooligosaccharide.[56] The structure was determined to be β-D-Glc*p*-(1→3)-α-L-Rhap-(1→3)-α-D-Glc*p*-(1↔1)-α-D-Glc*p* (Figure 1.17). The fatty acyl esters, primarily 2,4-dimethyltetradecanoate, were substituted on the C-3, C-4, and C-6 hydroxyl groups of the terminal Glc*p* unit.



R^1, R^2, R^3 = fatty acyl

Figure 1.17. Structure of LOS from *Mycobacterium linda*.

A lipooligosaccharide isolated from *Mycobacterium butyricum* showed an identical structure to the pyruvated LOS found from *Mycobacterium smegmatis* strain mc^{2}11 (Figure 1.10).[58,68]

A number of lipooligosaccharides were isolated from two strains of *M. gordonae*. The structure of the major LOSs from two strains, *M. gordonae* 989 and 990 are listed in Table 1.4. As illustrated, the LOS I from *M. gordonae* 989 and 990 contain a branched β-D-Xyl*p*, β-D-3-*O*-Me-Xyl*p*, or α-D-Ara*f* unit at the C-2 hydroxyl group of the α-L-Rha*p* unit.[69] The major differences between the two LOSs are at the non-reducing end of the oligosaccharide. LOS I from *M. gordonae* 989 (shown in Figure 1.18) consists of a 4-amino-4,6-dideoxy sugar moiety, whose structure is still unknown, as well as a 2-*O*-Me-4-*O*-Ac-α-L-Fuc*p* moiety. LOS I from *M. gordonae* 990, on the other hand, has a α-L-Rhap-(1→2)-3-*O*-Me-α-L-Rhap moiety at its non-reducing terminal. The terminal Glc*p* unit of the trehalose is fully substituted by acyl groups.

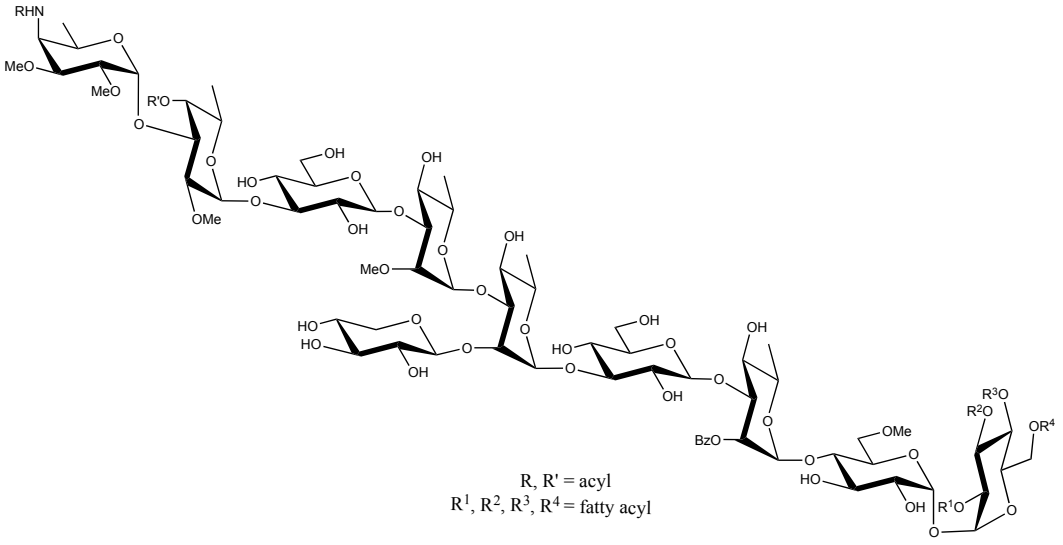


Figure 1.18. Structure of LOS I from *Mycobacterium gordonae* 989.

Generally, LOSs are rarely found from *Mycobacterium tuberculosis*. However, some exceptions that have been reported. *Mycobacterium tuberculosis* Canetti produces two lipooligosaccharides.[54] The non-antigenic LOS I is a simpler molecule, which lacks a unique 4-amino-4,6-dideoxy sugar unit and a 2-*O*-Me-L-Fuc*p* unit, whereas LOS II (shown in Figure 1.19) consists of the novel amino sugar moiety that was found to be highly antigenic. The structure of the unique terminal amino sugar is still unknown after two decades since Brennan and coworkers' work.[69] However, serological studies strongly suggest that a unique amino sugar is responsible for its antigenicity. The fatty acids are substituted at the 2,3,6 and 3,4,6 hydroxyl groups of the terminal Glc*p* unit in proportions of 2:3. *M. tuberculosis* H37Rv produces the simplest LOSs, which only have trehalose in their structure.[55] Two fatty acids are found substituted at the C-2 and C-3 hydroxyl groups of one of the Glc*p* units.

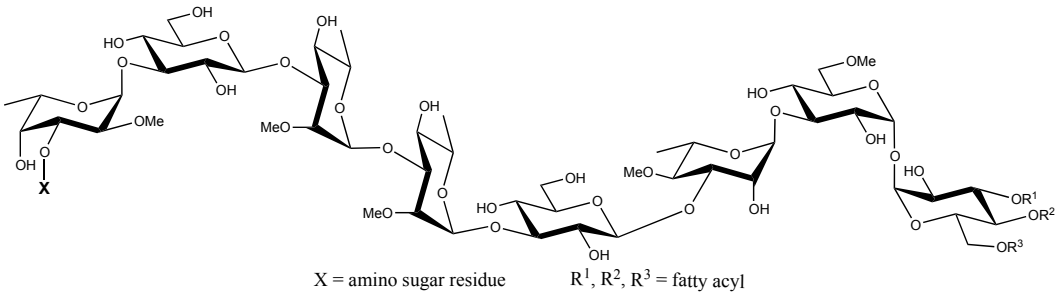


Figure 1.19. Structure of antigenic LOS II from *Mycobacterium tuberculosis* Canetti.

Another antigenic LOS was found from *Mycobacterium fortuitum*, biovar *fortuitum*.[70] The structure of the major LOS consists of three Glc*p* units (Table 1.4). The fatty acids are located at 2'- and 2,3,6- hydroxyl groups of terminal trehalose.

1.4 Biological Function of Lipooligosaccharides

Lipooligosaccharides, as a new type of glycolipid, have attracted the interest of scientists. However, the biological function of LOSs remains a mystery even after 30 years since their initial discovery.[67]

Initially, Brennan and co-workers suggested a connection between colony morphology in *Mycobacterium kansasii* and lipooligosaccharides. The rough variants of *M. kansasii*, which are pathogenic and cause chronic infection in mice,[71] lack the ability to produce LOSs. On the other hand, the smooth variants, which do produce LOSs, could be cleared by the immune system of infected

animals.[72] However, it was later reported that there is no correlation between colony morphology and lipooligosaccharide production in *Mycobacterium tuberculosis* complex.[73] Both rough and smooth variant from *M. tuberculosis* were found to produce LOSs.

A recent study showed that, in addition to phenolic glycolipids (PGL), LOSs from *Mycobacterium marinum* can also inhibit tumor necrosis factor α (TNF-α) response in lipopolysaccharide-stimulated human macrophages.[63] TNF-α is cytokine, which is produced upon macrophage activation stimulation by various molecules, including lipopolysaccharide.[74] The ability of LOSs to inhibit the TNF-α response, in combination with the fact that the loss of the TNF-α signaling could lead to progression of *Mycobacterium marinum* infection,[75] suggests that LOS plays an important immunomodulatory role in the pathogenicity of this organism.

In a study of LOS biosynthesis in *M. marinum*, an unexpected correlation was found between the LOS production and cell surface protein release.[76] The LOS mutants do not affect the production and translocation of these proteins, but it was shown that these proteins and the cell surface of the LOS mutants have a stronger attachment.

In addition, the most extended lipooligosaccharide, LOS IV, from *M. marinum*, plays a role in the virulence of the organism. A LOS IV deficient mutant showed a stronger ability to infect zebrafish embryos compared to the wild type species.[76] In particular, the absence of LOS IV in *M. marimum* mutant

prevents the bacterium from entering the macrophage.[62] This was also confirmed by a study on mutants that cannot produce higher order lipooligosaccharides (such as LOS IV). These mutants enter the macrophage less efficiently than the wild type strain.[77] However, an inverse correlation between the production of higher order lipooligosaccharides in other *M. marinum* mutants and efficiency in entering the macrophage has been observed.[78]

In addition, there are many studies that report the antigenicity of mycobacterial LOSs. For example, it was demonstrated that novel carbohydrate moieties at the non-reducing end of LOSs from *M. kansasii* and *M.gastri* were responsible for the antigenicity.[48,50,60]

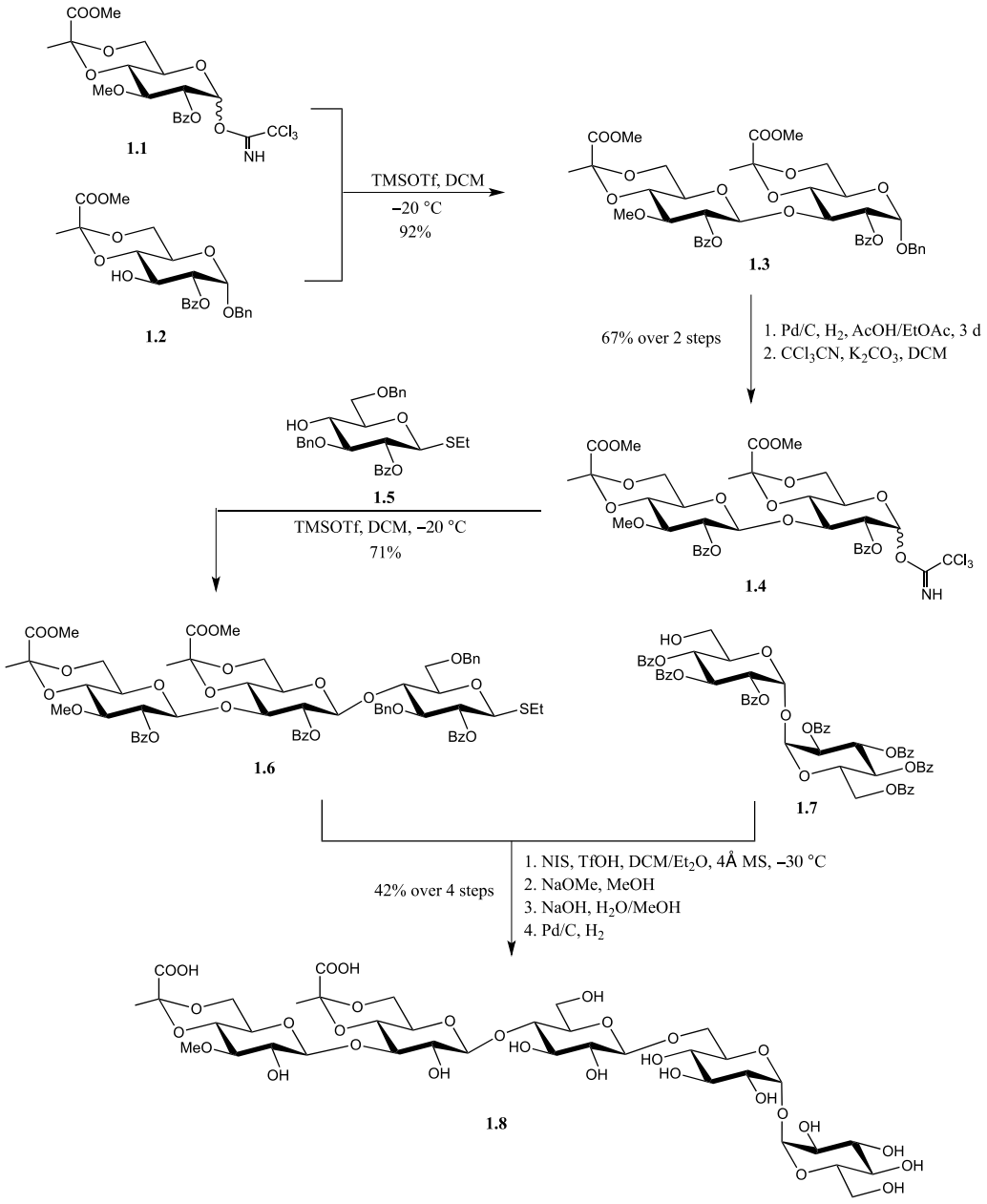
Overall, there is still not a clear picture about the biological function of these structurally interesting molecules.

1.5 Synthetic Work Towards the Preparation of Mycobacterial Lipooligosaccharides

Mycobacterial lipooligosaccharides are generally complex oligosaccharides with fatty acyl groups on the terminal trehalose moiety. To the best of my knowledge, there have been no total syntheses of any mycobacterial lipooligosaccharide. However, a few papers have reported syntheses of the oligosaccharide core, as well as unique sugar units of the LOSs.

1.5.1 Synthesis of a lipooligosaccharide pentasaccharide from *Mycobacterium smegmatis*

Ziegler and coworkers reported the first synthetic work focused on LOSs from *M. smegmatis* in 1993 (Scheme 1.1).[79] The synthesis started by glycosylation between the methylated pyruvate glycosyl trichloroacetimidate donor **1.1** and acceptor **1.2**, which produced a 92% yield of disaccharide **1.3**. This disaccharide was then treated with Pd/C under 1 atm H_2 gas, followed by the preparation of trichloroacetimidate with CCl_3CN in the presence of K_2CO_3 to give the disaccharide donor **1.4** in 67% yield over two steps. Glycosylation of the previously prepared acceptor **1.5** with donor **1.4** yielded trisaccharide **1.6** in 71% yield. The thioglycoside was then activated by *N*-iodosuccinimide (NIS) and trifluoromethanesulfonic acid (TfOH) in a glycosylation with the trehalose acceptor **1.7** to give a 64% yield of the expected pentasaccharide. The final deprotection steps, which involved deprotection of benzoate esters, hydrolysis of the methyl ester of the pyruvate acetals, and hydrogenation of the benzyl ether, gave 66% yield of deprotected pentasaccharide **1.8**.



Scheme 1.1. Synthesis of pentasaccharide **1.8** by Ziegler and coworkers.[79]

1.5.2 Synthesis of C-4 branched sugar from *Mycobacterium gastri*

The structures of LOS III and IV from *M. gastri* contain a unique C-4 branched 3,6-dideoxy sugar moiety. The general structure of the side chain was

determined to be a 2,3-dimethoxy-4,5,6,7-tetrahydroxyheptyl chain. However, the detailed stereochemistry was not determined until Prandi and coworkers chemically synthesized this monosaccharide. In previous work,[48,60] the relative configurations of C-9 and C-10; C-10 and C-11; and C-11 and C-12 were determined to be *syn*-, *anti*-, and *syn*-, respectively (Figure 1.13). The relative configuration between C-7 and C-9 was unknown. In addition, the 3,6-dideoxy glycoside stereochemistry of the cyclic ring was known, but the absolute configuration (D or L) was not. To identify the complete structure with the relative configurations of C-7 and C-9, the authors synthesized four diastereoisomers differing in the stereochemistry at C-7 and C-9.

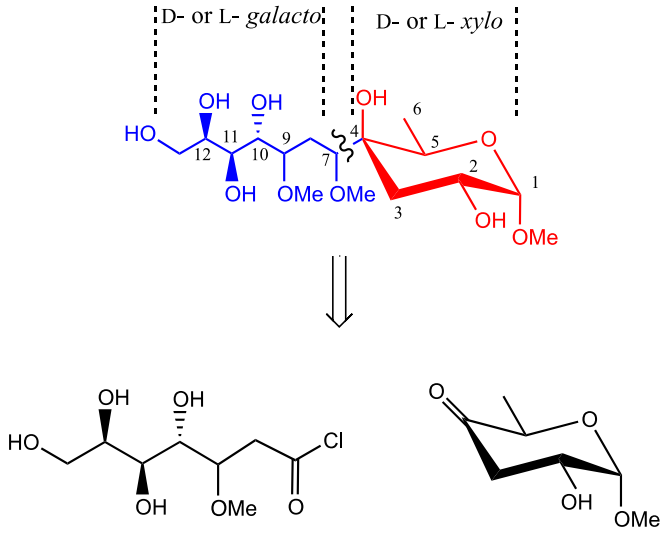
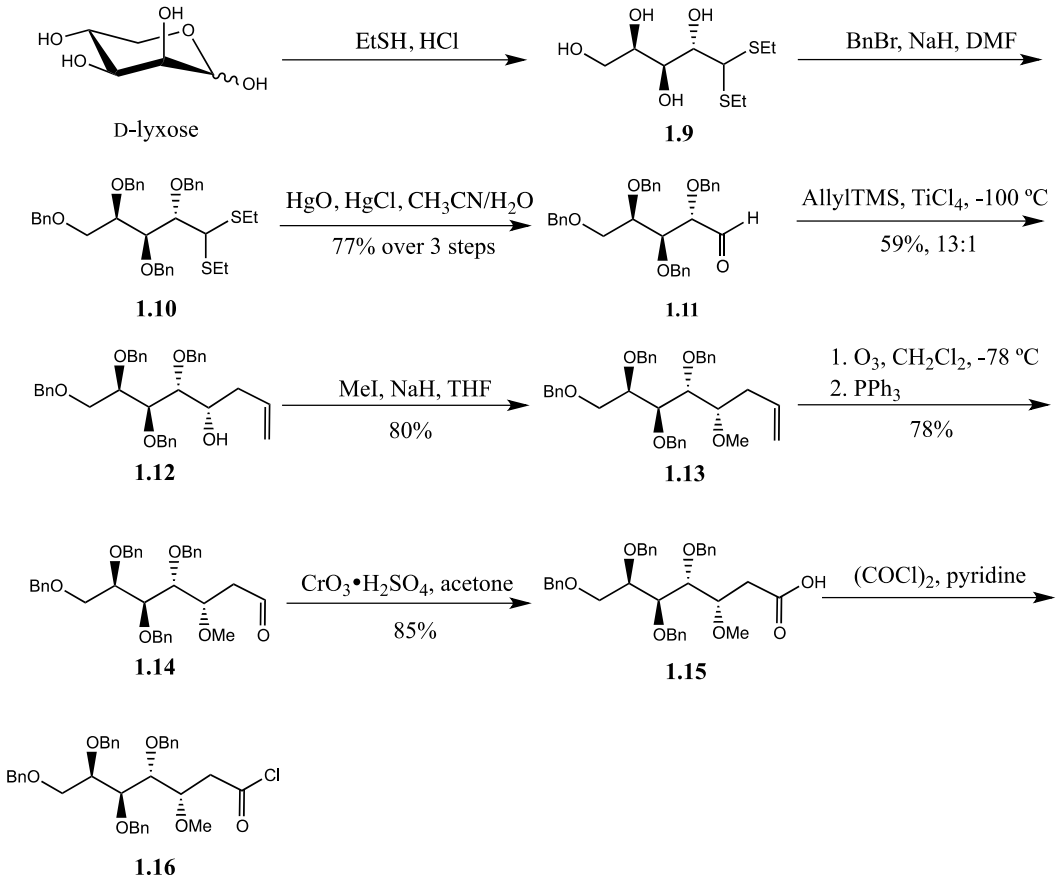


Figure 1.20. Retrosynthetic analysis of the C-4 branched sugar.[61]

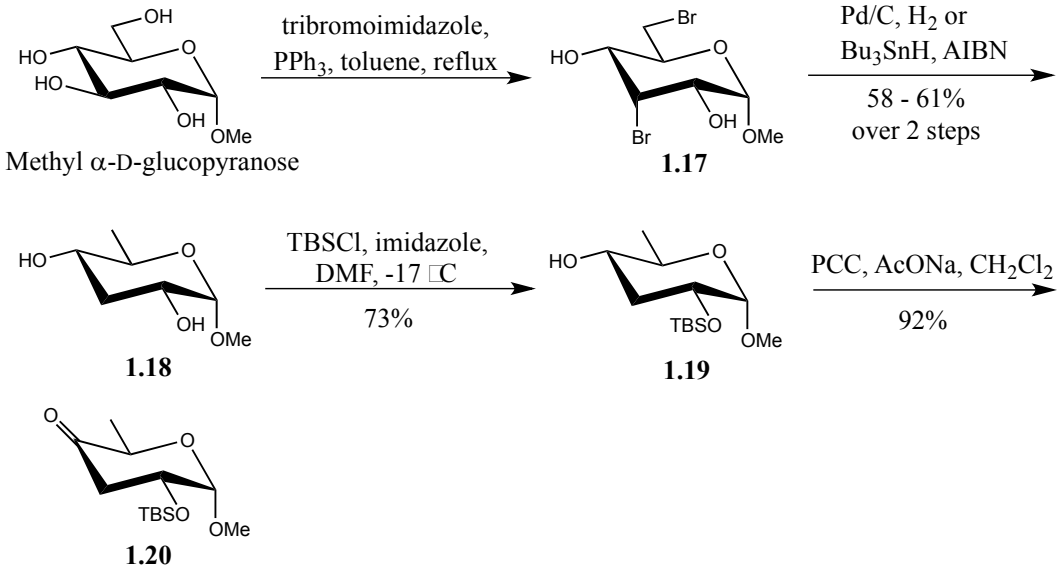
The synthesis of these compounds is shown in Schemes 1.2–1.4. An obvious disconnection is between C-4 and C-7 (Figure 1.20). Formation of this carbon–carbon bond was conducted by a coupling reaction between an acyl chloride and a cyclic ketone promoted by samarium diiodide.

The seven-backbone-carbon acid chloride was prepared from optically pure D-lyxose (Scheme 1.2). First, the perbenzylated aldehyde **1.11** was prepared in 77% yield in three steps. This involved formation of diethyldithioacetal derivative, benzylation and hydrolysis of the dithioacetal. The aldehyde was then treated with allyltrimethylsilane and titanium tetrachloride at –100 °C to yield 59% of homoallylic alcohol **1.12**. Methylation of the hydroxyl group followed by ozonolysis gave the *galacto*-configured aldehyde **1.14** in good (62% over two steps) yield. Treatment **1.14** with Jones reagent produced carboxylic acid **1.15** in 85% yield.



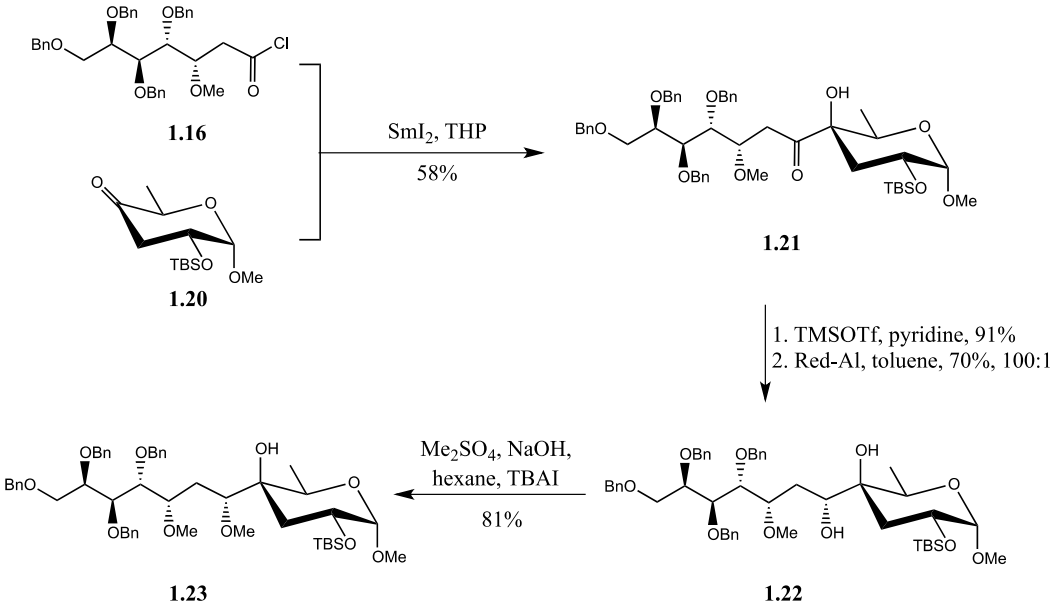
Scheme 1.2. Synthesis of acyl chloride **1.16**.[61]

The synthesis of the 3,6-dideoxysugars from 3,6-dideoxy-3,6-dibromo-glycosides was reported previously by Garegg.[80] Dibromination of methyl α-D-glucopyranoside followed by reduction gave the 3,6-dideoxy sugar **1.18** in ~60% yield. Next, the C-2 hydroxyl group was selectively protected as a *tert*-butyldimethylsilyl ether. The C-4 hydroxyl group was then oxidized to ketone **1.20** by pyridinium chlorochromate (Scheme 1.3).



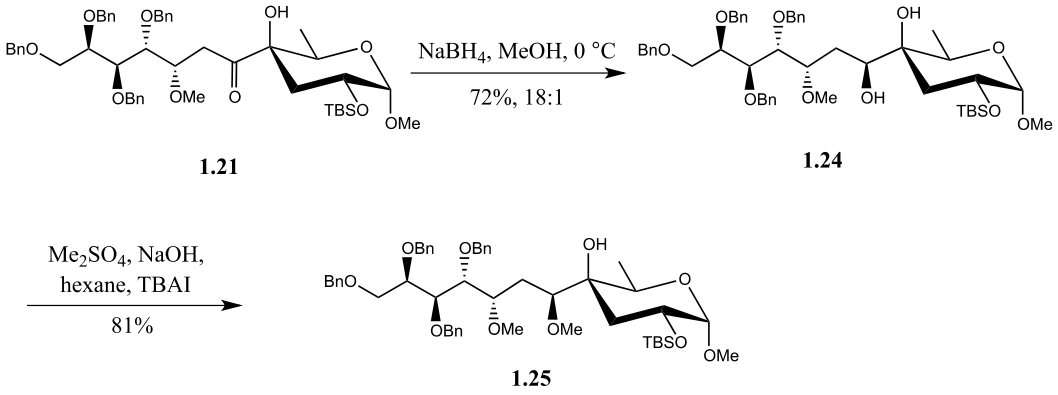
Scheme 1.3. Synthesis of ketone **1.20**.[61]

Coupling between ketone **1.20** and freshly made acyl chloride **1.16** was conducted using two equivalents of samarium diiodide to give α-hydroxy ketone **1.21** in 58% yield and 5:1 diastereoselectivity. Asymmetric reduction of the α-hydroxy ketone **1.21**, after protection of the hydroxyl group with a trimethylsilyl group, gave a good yield of diol **1.22** in excellent selectivity. Selective methylation of the secondary hydroxyl group occurred under phase-transfer conditions with dimethyl sulfate to give the desired C-4 branched sugar **1.23** in 81% yield.



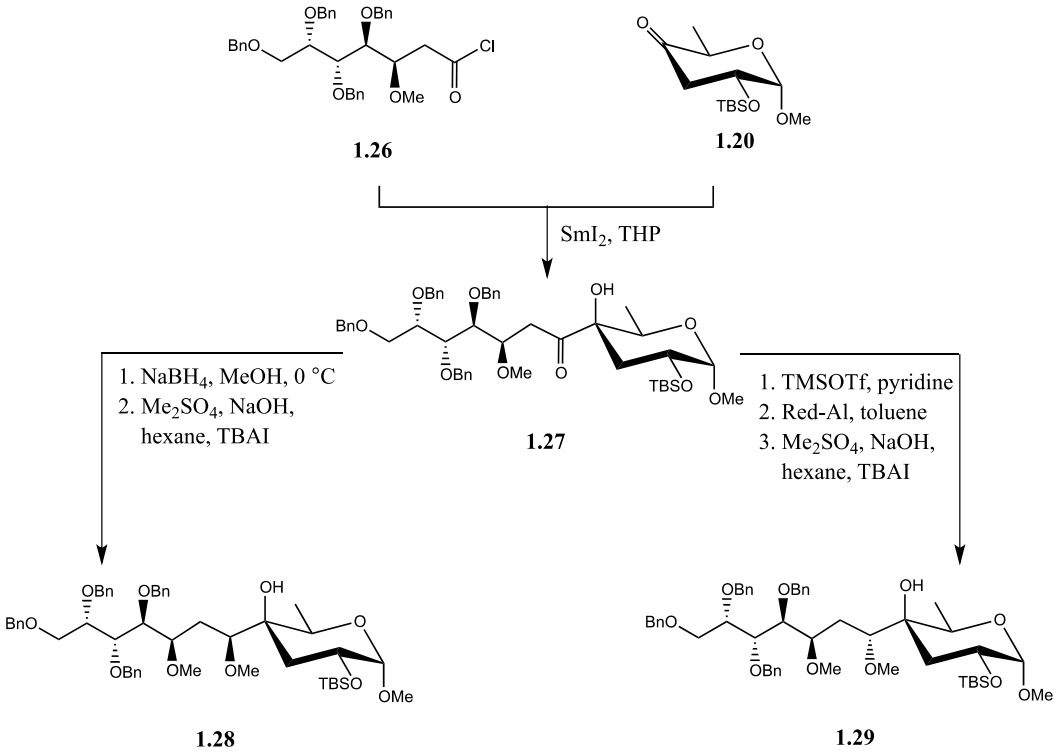
Scheme 1.4. Synthesis of C-4 branched sugar **1.23**.[61]

The synthesis of the other three diastereoisomers is illustrated in Scheme 1.5−1.6. The α-hydroxy-ketone **1.21** was reduced to 7,9-*anti*-4,7-diol, in a yield of 72% and 18:1 selectivity. Selective methylation gave an 81% of diastereoisomer **1.25** (Scheme 1.5).



Scheme 1.5. Synthesis diastereoisomer **1.25**.[61]

Starting from **1.26**, the enantiomer of **1.16**, the two other diastereoisomers were prepared in similar yields (Scheme 1.6).[61] After construction of the C4 and C7 bond, the α-hydroxy-ketone **1.27** was then treated with $NaBH_4$ and Red-Al to give 7,9-*syn* and 7,9-*anti* diols, respectively, which were methylated selectively on the secondary hydroxyl group to give diastereoisomers **1.28** and **1.29**. Exact yield for these reactions were not reported.



Scheme 1.6. Synthesis of diastereoisomers **1.28** and **1.29**.[61]

1.5.3 Synthesis of partial lipooligosaccharide of *Mycobacterium gordonae* strain 989

The latest synthetic work on mycobacterial LOSs was reported by Mukherjee and Misra in 2008.[81] They synthesized a heptasaccharide motif found in the LOS of *Mycobacterium gordonae* 989 (Figure 1.21).

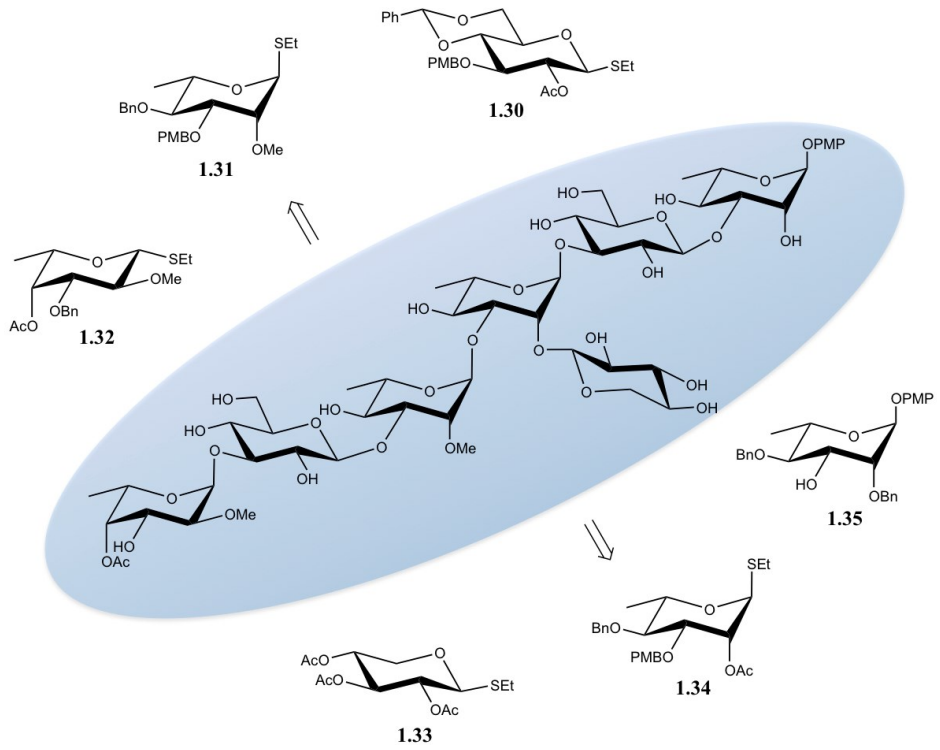
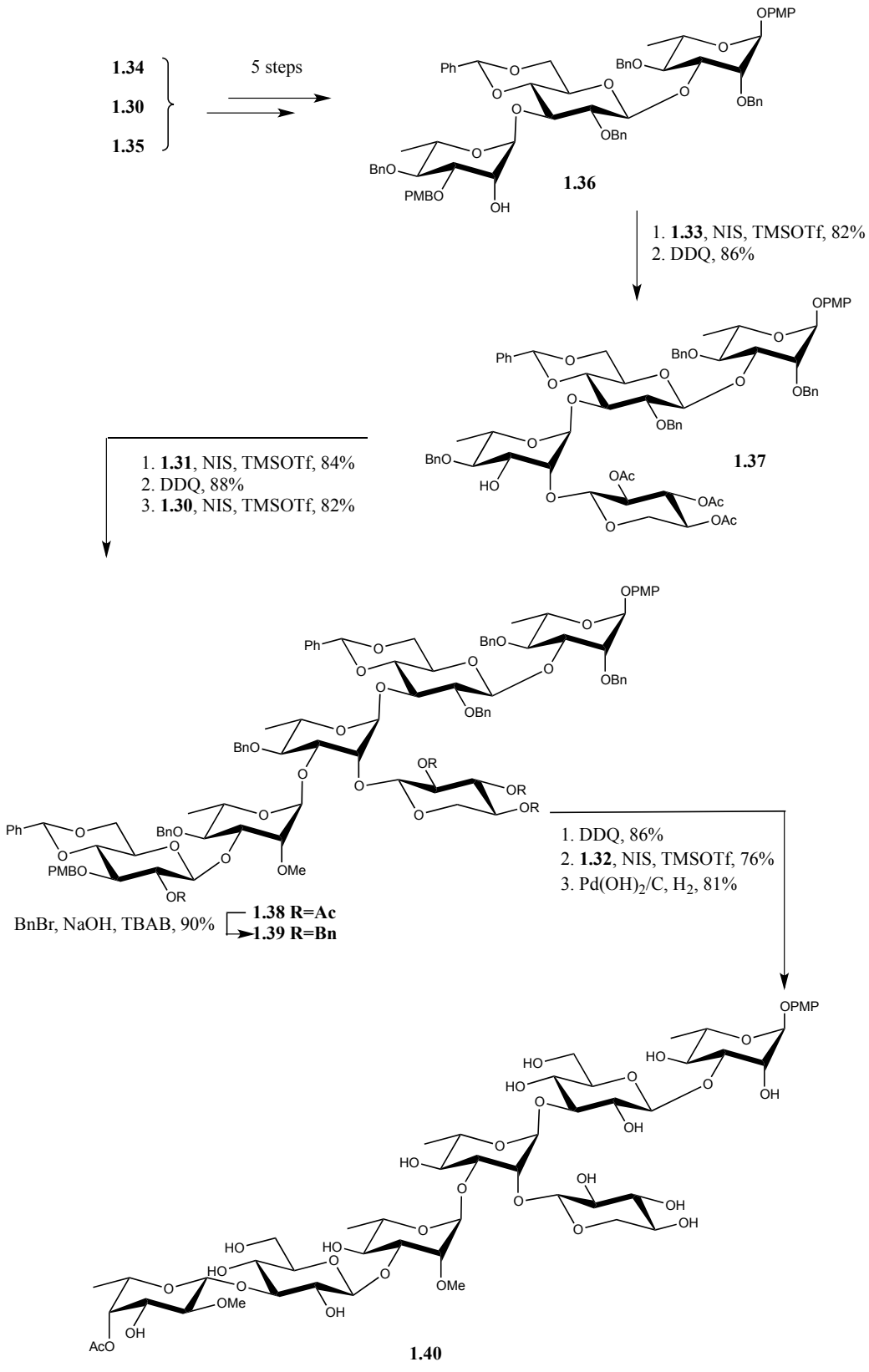


Figure 1.21. Construction building blocks for heptasaccharide antigen of the LOS from *Mycobacterium gordonae* 989.[81]

The heptasaccharide was constructed by using six building blocks (Figure 1.21). The general route used is shown in Scheme 1.7. After trisaccharide **1.36** was obtained from two glycosylations with building blocks **1.34**, **1.30** and **1.35**, the D-Xyl*p* unit (**1.33**) was installed at the C-2 position and a third Rha*p* unit (**1.31**) was installed at the C-3 position.



Scheme 1.7. Synthesis of pentasaccharide antigen **1.34**.[81]

Before the installation of the last sugar moiety, a 4-*O*-acetyl-L-Fuc*p* residue **1.32**, all of the acetate protecting groups were converted to benzyl ethers. This allowed the acetate on the Fuc*p* moiety to be preserved during the final deprotection stage. Finally, hydrogenolysis using $Pd(OH)_2/C$ under hydrogen gas gave the target molecule in 81% yield.

1.6 Overview of Thesis Research

In this thesis, I describe my work focused on the synthesis of a complete lipooligosaccharide antigen from *Mycobacterium gastri*, LOS III, including the preparation of necessary building blocks as well as incorporation of the building blocks into oligosaccharides. The target molecule is shown in Figure 1.12. Unfortunately, due to an error in the drawing of the target molecule at very beginning of my research, the oligosaccharide I have prepared is an isomer of the natural compound. The glycosidic bond between D-Gal*p* and D-Glc*p* should be β-(1→3) linkage, rather than the synthesized β-(1→4) linkage.

The native structure is illustrated in Figure 1.22A. To simplify this project, two modifications are made on our target molecule. Firstly, fatty acyl groups are replaced by fatty alkyl groups. Secondly, only one type of fatty alkyl group is used in the target molecule. The LOS III analogue with the β-(1→4) linkage between D-Galp and D-Glcp, as well as the simplifications described above, is shown in Figure 1.22B.

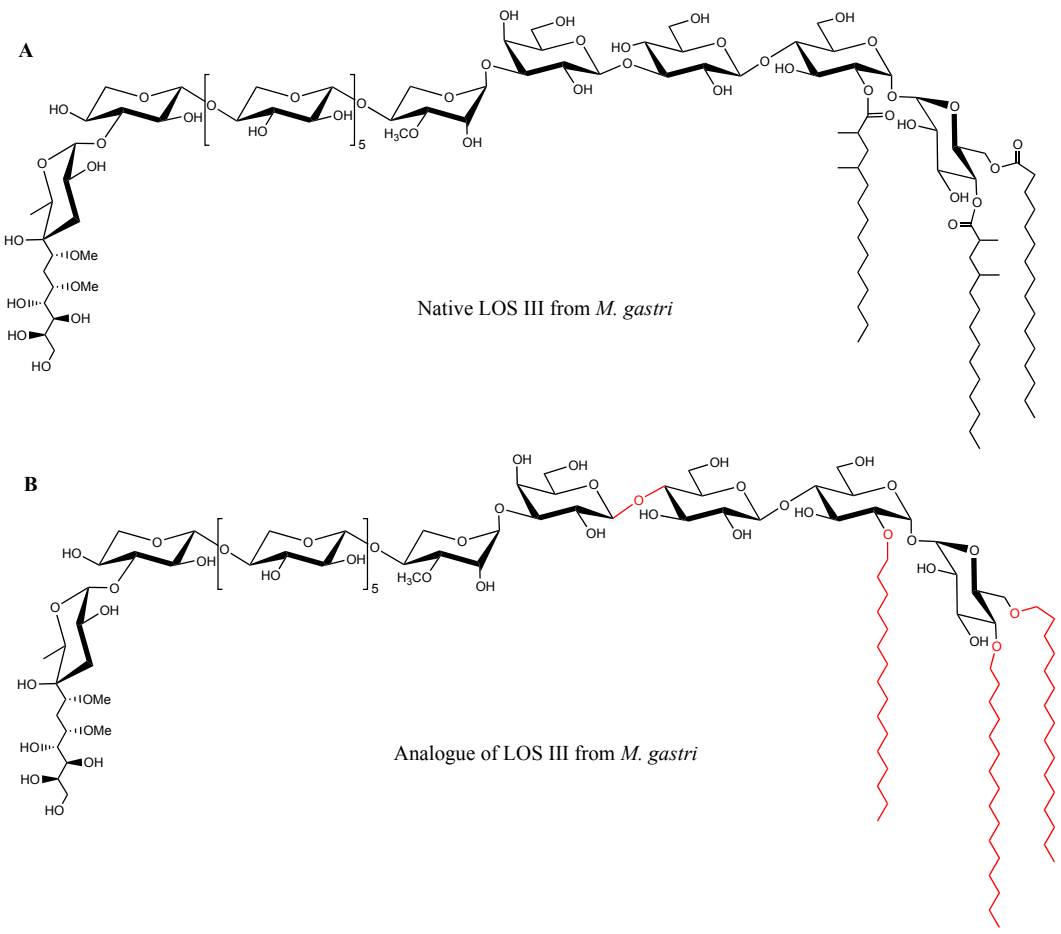


Figure 1.22. LOS III and its analogue from *M. gastri*.

In Chapter 2, a retrosynthetic analysis of the target is described. In addition, the design and synthesis of eight building blocks will be presented. Challenges in synthesizing some building blocks will be discussed. For example, protecting group manipulation on L-xylose is very important to build the oligosaccharide backbone. Another challenge is the synthesis of asymmetric substituted trehalose building block. Finally, attempts to synthesize the C-4 branched sugar by both known and new routes will be described.

In Chapter 3, nonasaccharide and octasaccharide fragments of the target molecule were synthesized from the building blocks described in Chapter 2.

In Chapter 4, I will summarize the work I have done and discuss directions of this research for the future.

Chapter 2: Synthesis of Designed Building Blocks for Lipooligosaccharide Antigen (LOS) Assembly

2.1 Introduction

As outlined in Chapter 1, my synthetic target is Lipooligosaccharide (LOS) III analogue from *Mycobacterium gastri* (Figure 2.1). This molecule contains a number of structurally unusual carbohydrate moieties that I anticipated would lead to synthetic challenges. Among these are a 3-*O*-methyl-L-rhamnopyranose moiety and a 3,6-dideoxy-C-4-branched D-galactopyranoside residue, which is very rarely found in nature. In addition, while D-xylose is widespread in animals and plants, L-xylopyranose is much less common. Finally, the asymmetrically-substituted trehalose glycolipid, the common backbone structure of all LOS antigens, is also unusual.

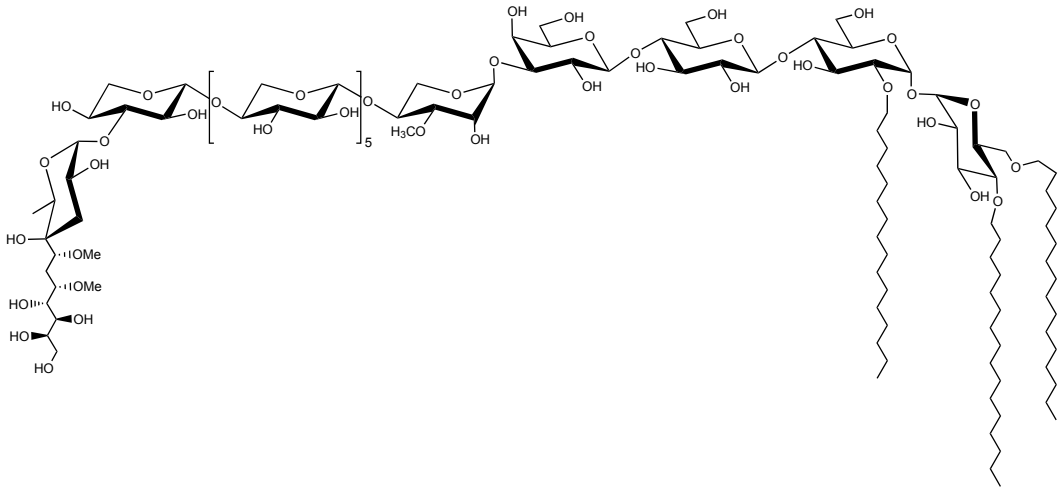


Figure 2.1. Structure of LOS III analogue from *Mycobacterium gastri* chosen for synthesis.*

* The 3,6-dideoxy-4-*C*-branched galactopyranosyl residue may be the enantiomer of the configuration shown in this figure.

2.2 Retrosynthetic Analysis of LOS III

Analysis of the glycosidic linkages of LOS III provided me a practical strategy for its total synthesis (Figure 2.2). Most of the monosaccharide residues are connected via 1,2-*trans*-linkages, which require a participating group, e.g., a benzoyl (Bz) ester, at O-2 to give the desired stereochemistry. The 3,6-dideoxy sugar is connected to the L-xylose moiety via an α-(1→3) linkage. A non-participating protecting group on O-2 of the 3,6-dideoxy sugar is therefore needed to install this 1,2-*cis* α-linkage. The asymmetrically-substituted trehalose moiety is a disaccharide with an α,α-(1↔1) linkage, which could be assembled from two selectively protected glucopyranose residues containing non-participating groups at O-2.

The lipid groups on LOS III are connected to the oligosaccharide via ester linkages. This complicates the choice of protecting groups for the synthesis. As discussed before, esters (e.g., benzoyl groups) are essential for the formation of 1,2-*trans*-glycosidic linkages. However, the acyl lipid groups would be removed during the final deprotection steps to remove the benzoate esters, which requires a strong base such as sodium methoxide. To prevent this, all of the benzoyl esters need to be converted to, for example, benzyl ethers prior to installation of the asymmetrically-substituted trehalose moiety in which the fatty acyl groups are present. However this approach opens up another problem: it can be difficult to remove large number of benzyl groups from complex glycans at the end of a synthesis. To circumvent this problem, I chose to replace the fatty ester linkages with long-chain alkyl groups of the same length (See **2.1** and **2.2**).

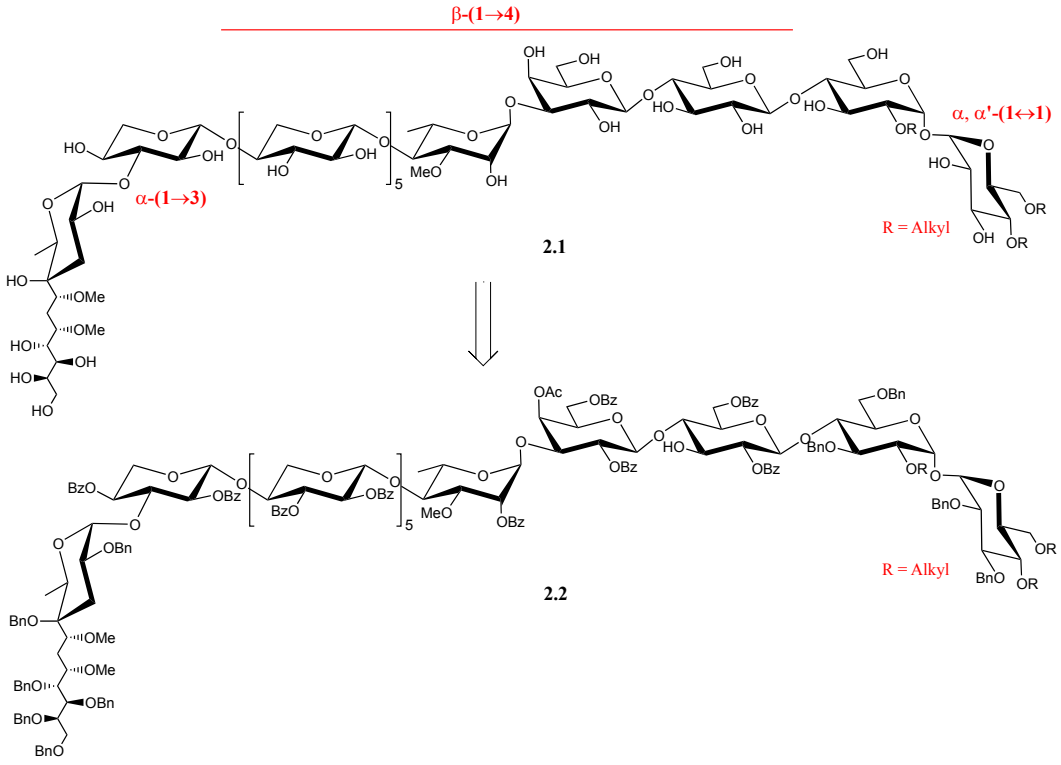


Figure 2.2. Glycosidic linkage analysis.

From the glycosidic linkage analysis, the fully protected target oligosaccharide could be designed as compound **2.2**, which has a) a benzyl (Bn) group at O-2 of the 3,6-dideoxy sugar; b) Bz groups on all xylose residues, as well as the rhamnose and lactose moieties; c) a benzyl group on O-2 of both trehalose glucose residues. The designed target oligosaccharide can then be cut into three major fragments: 1) a 3,6-dideoxy-4-C-branched sugar moiety **2.3** (Figure 2.3); 2) an asymmetrically-protected trehalose moiety **2.4**; 3) a nonasaccharide **2.5** that contains the xylose, rhamnose and lactose residues.

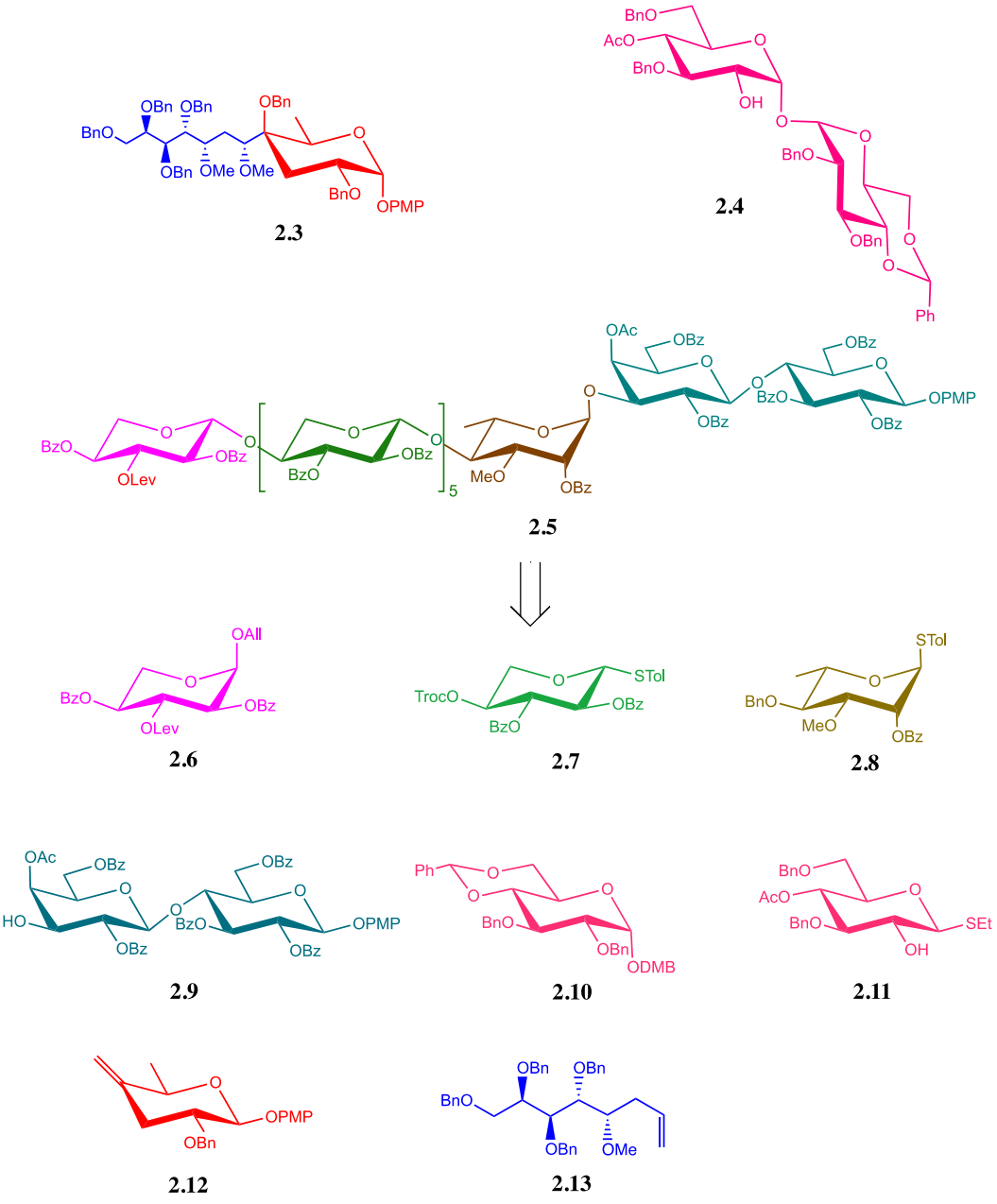
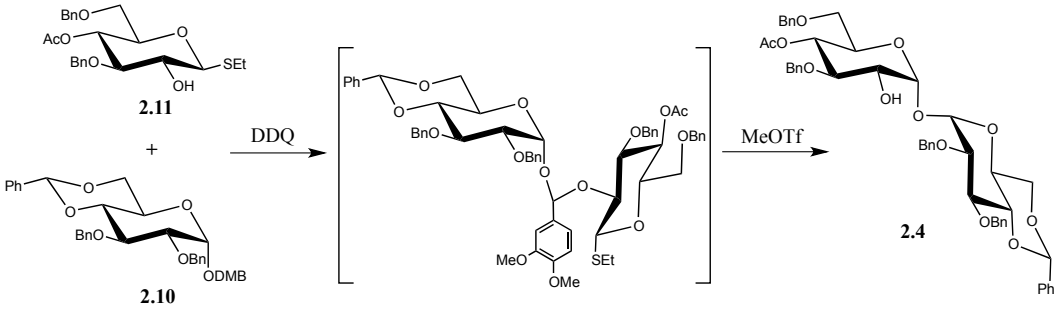


Figure 2.3. Retrosynthetic analysis of LOS III.

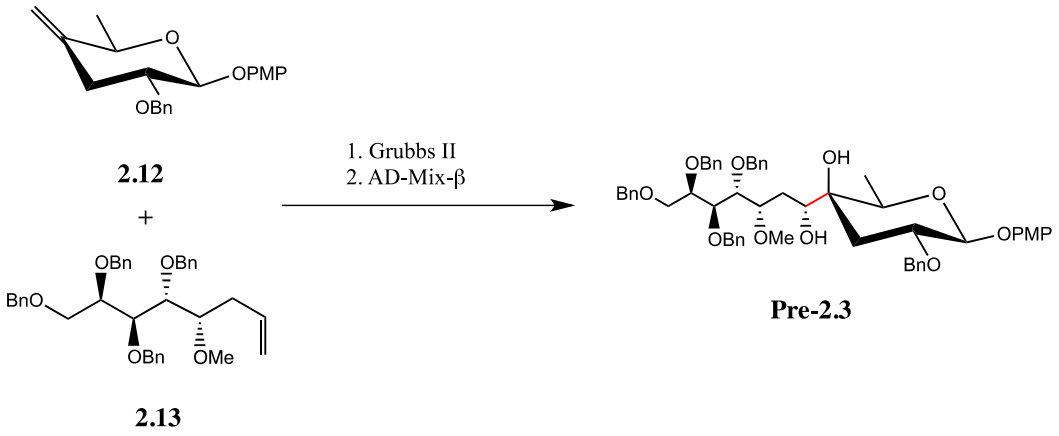
Based on the glycosidic linkage analysis, the three major fragments can be further cut into eight building blocks: **2.6**–**2.13**. Benzoyl groups are used as a neighboring participating group at O-2 in building blocks **2.6**–**2.9** to facilitate the formation of the 1,2-*trans*-(β)-linkages. For O-3 of **2.6**, O-4 of **2.7** and O-4 of **2.8**, groups that are orthogonal to benzoyl esters are required. For these residues, levulinoyl (Lev), 2,2,2-trichloroethoxycarbonyl (Troc) and Bn groups, respectively, were chosen. Selective deprotection of these groups on the growing oligosaccharide will lead to a glycosyl acceptor for the subsequent glycosylation.

Synthesis of asymmetrically-substituted trehalose derivatives has been a challenging problem.[82-88] One approach is to start with commercially available trehalose. However, differentiating the secondary hydroxyl groups is difficult due to their similar chemical properties. Another approach is to construct the α,α-(1↔1)-linkage, which leads to side products such as β,α and α,β trehalose derivatives.[89] To circumvent this problem, Bertozzi and coworkers have developed a method for constructing the α,α-(1↔1) glycosidic bond using Intramolecular Aglycone Delivery (IAD).[90-92] In this approach, a 3,4-dimethoxybenzyl (DMB) group at the anomeric position of building block **2.10** is employed as a precursor for the formation of a mixed acetal intermediate. The C-2 hydroxyl group of building block **2.11** is not protected, as it will form the mixed acetal together with building block **2.10** (Scheme 2.1). Subsequent activation of the mixed acetal will lead to the α,α-(1↔1) glycosidic linkage.



Scheme 2.1. Construction of α,α-(1↔1) glycosidic bond via Intramolecular Aglycone Delivery.

The 3,6-dideoxy-4-C-branched sugar moiety contains two fragments, the 3,6-dideoxysugar residues and a polyhydroxylated alkyl side chain. I envisioned that the C–C bond could be formed by coupling olefins **2.12** and **2.13** via Grubbs cross metathesis using the Grubbs II catalyst, followed by Sharpless asymmetric dihydroxylation using AD-Mix-β catalyst (Scheme 2.2).

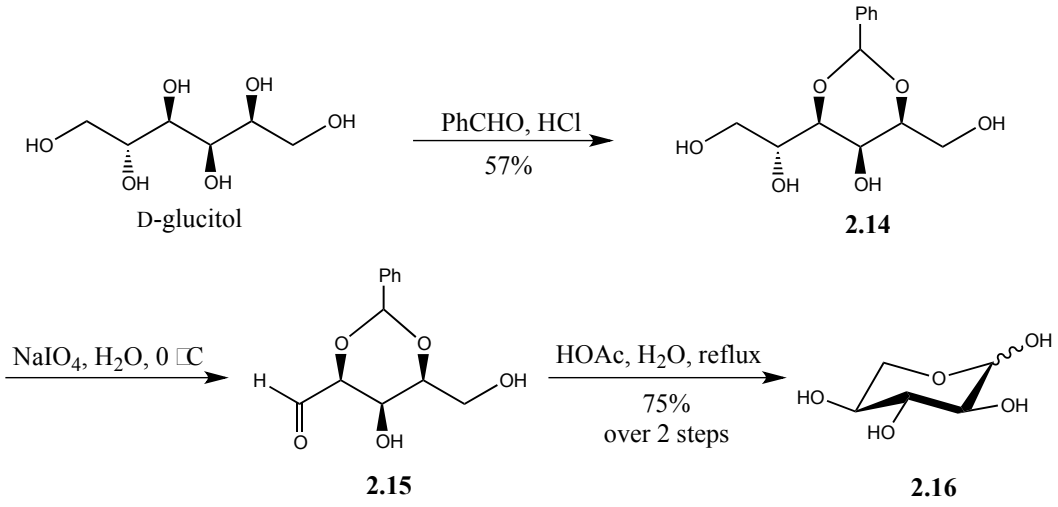


Scheme 2.2. C-C bond formation via Grubbs cross metathesis.

2.3 Synthesis of Xylose Building Blocks

2.3.1 Synthesis of L-xylose

L-Xylose is rare in nature. Thus, commercially available L-xylose is very expensive. For example, the Sigma Aldrich price for L-xylose is $9.30/gram, which is almost 40 times more expensive than D-xylose ($0.25/g). The synthesis of L-xylose from other inexpensive starting materials was therefore essential. This monosaccharide was synthesized for the first time from L-gulonate by Fischer and Ruff.[93] A more practical and scaleable method (Scheme 2.3) involves first the formation of a benzylidene acetal derivative of inexpensive D-glucitol. This intermediate is then oxidized with either lead tetraacetate,[94] sodium meta-periodate[95] or periodic acid.[96] Finally, acid hydrolysis of the benzylidene acetal affords the product.



Scheme 2.3. Synthesis of L-xylose.

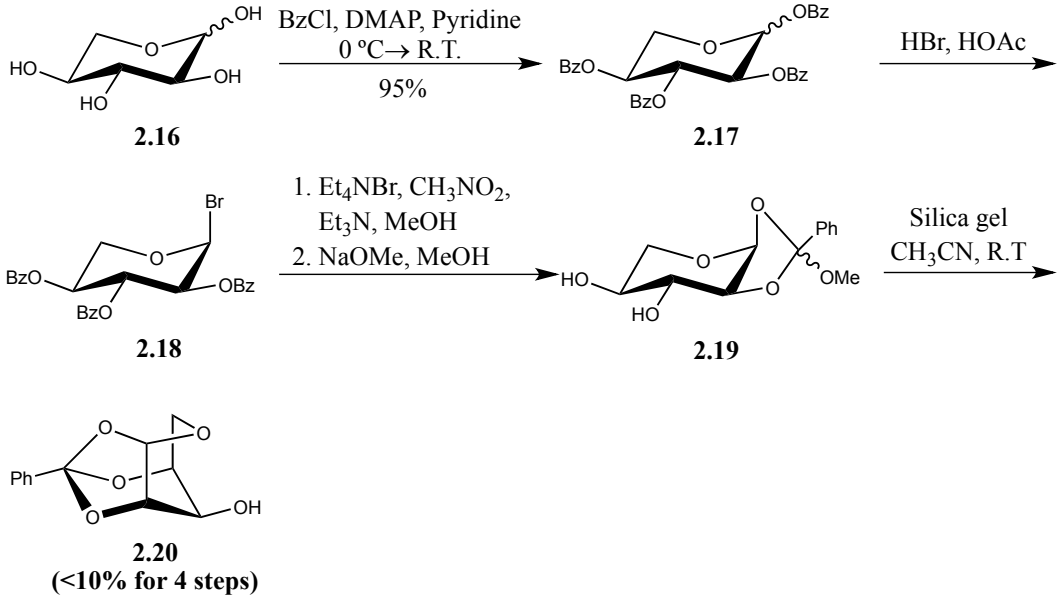
Following the literature procedure,[95] the synthesis of L-xylose started with the formation of 2,4-*O*-benzylidene-D-glucitol (**2.14**) from D-glucitol by reaction with benzaldehyde and HCl. The procedure was done several times and the yield varied from 55–60%, which is in line with the reported yield, 58%. Oxidation of the acetal intermediate by sodium metaperiodate in water, followed by acid hydrolysis of the benzylidene group with aqueous acetic acid at reflux, gave L-xylose. After crystallization from ethanol, L-xylose (**2.16)** was obtained in 75% yield from **2.14**.

2.3.2 Preliminary study on the selective protection of xylopyranosides

The key issue in synthesizing building blocks **2.6** and **2.7** is to protect selectively one of the hydroxyl groups on a xylopyranose derivative. Generally, primary hydroxyl groups assist the differentiation of hydroxyl groups on hexoses. For example, formation of a 4,6-*O*-benzylidene acetal derivative followed by acetal ring opening can lead to the selective protection of either the C-4 or C-6 hydroxyl group, depending upon the conditions used.[97,98] However, xylopyranose, a pentose, has no primary hydroxyl group in its structure. In addition, hydroxyl groups with a 1,2-*trans* relationships on a pyranose ring, which is the case for xylopyranose, can be difficult to differentiate. This is different from 1,2-*cis* diols in pyranose rings, which can be more easily selectively functionalized. For instance, formation of an orthoester of a pyranose 1,2-*cis* diol, followed by

treatment with acid, results in selective acylation of the axial hydroxyl group. The lack of a primary hydroxyl group and the all *trans* relationship between the secondary hydroxyl groups makes xylopyranose rings difficult to functionalize selectively.

At the beginning of my research, a then recently published paper had described a method for selective protection of D-xylose using 1,2,4-tricyclic orthoesters as intermediates.[99] Use of this approach would allow the C-4 hydroxyl group to be protected and then, after cleavage of the orthoester, the addition of other groups.

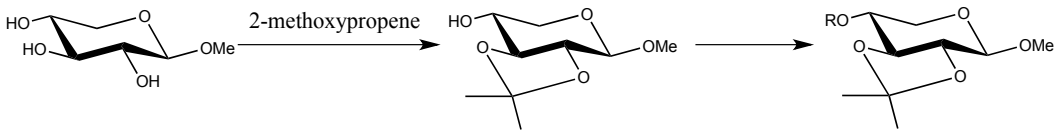


Scheme 2.4. Synthesis of tricyclic orthoester **2.20**.

My attempt to implement this route is shown in Scheme 2.4. Compound **2.17** can be synthesized from L-xylose via reaction with benzoyl chloride in pyridine in excellent (95%) yield. Treatment of **2.17** with hydrogen bromide in

acetic acid yielded the unstable glycosyl bromide **2.18**,[100] which was carried to the next step without purification. Next, **2.19** was obtained over two steps: formation of the 1,2-orthoester and deprotection of the benzoate esters with sodium methoxide.[101] This unstable intermediate was treated with silica gel, which acted as an acid, to facilitate the formation of the 1,2,4-tricyclic orthoester **2.20**.[99] However, due to the instability of these intermediates, the yield for the four-step reaction sequence was only about 10% overall in my hands. Obviously, this is not an efficient route for generating protected xylose intermediates.

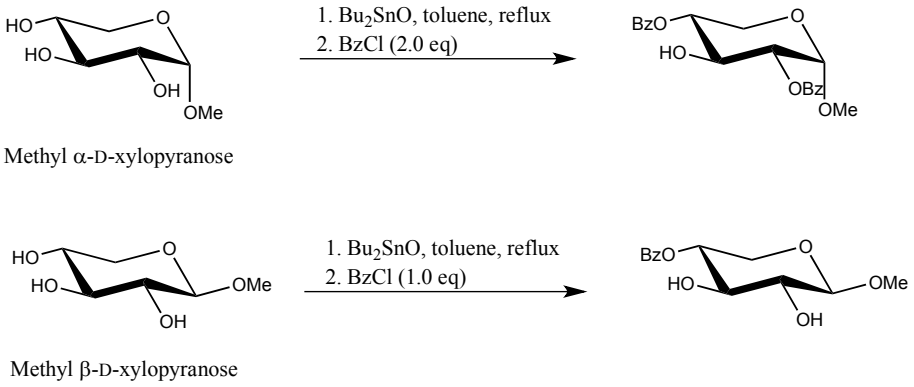
An alternate strategy is to protect a β-D-xylopyranosides using either 2,2-dimethoxypropane or 2-methoxypropene and a suitable acid catalyst to generate the 2,3-*O*-isopropylidene-β-D-xylopyranoside derivative (Scheme 2.5).[102,103] The C-4 hydroxyl group can then be protected and the acetal cleaved. Unfortunately, in my hands, this strategy provided unreproducible results and therefore the approach turned out to be impractical.



Scheme 2.5. Alternate strategy to 4-*O*-protected xylopyranose derivatives via a 2,3-isopropylidene acetal intermediate.

I then turned my attention to a paper published by Ralph and coworkers, which reported selective protection strategies for D-xylopyranosides using di-*n*-butyltin oxide.[104] In their work, summarized in Scheme 2.6, when an alkyl α-D-xylopranoside is treated with di-*n*-butyltin oxide, followed by the addition of 2.0

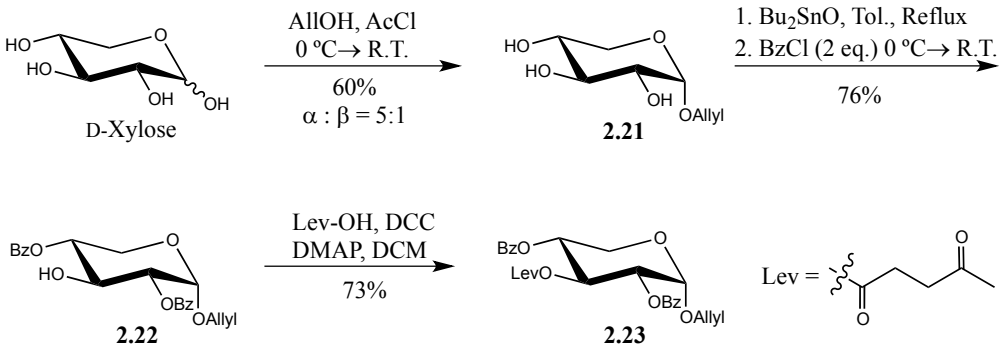
equivalents of benzoyl chloride, the C-2 and C-4 hydroxyl groups are protected as benzoate esters, leaving the C-3 hydroxyl group free. Further protection of this hydroxyl group could give one of the required building blocks, **2.6**. In contrast, when a β-D-xylopranoside is treated with di-*n*-butyltin oxide, followed by the addition 1.0 equivalents of benzoyl chloride, the C-4 hydroxyl group is selectively protected as a benzoate ester. This would allow me to access the other building block, **2.7**. The yields for both reactions were reported to be very good.



Scheme 2.6. Protecting group manipulation on xylopyranosides by using *n*-Bu_2SnO.

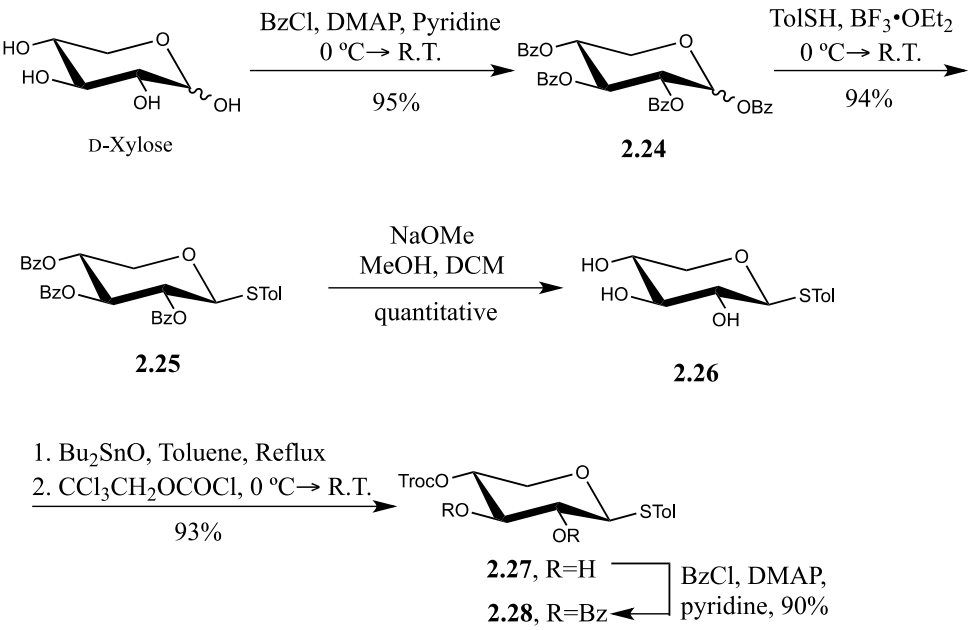
Due to the price of L-xylose, inexpensive D-xylose was used to do some preliminary studies to demonstrate the feasibility of the method. As depicted in Scheme 2.7, allyl α-D-xylopyranoside (**2.21**) can be synthesized by Fischer glycosylation by treating D-xylose with a solution of acetyl chloride and allyl alcohol. The product was obtained in 60% as an α,β mixture (α:β ≈ 6:1). The α-isomer could be crystallized from methanol, leading to a 50% yield of the desired α-glycoside from D-xylose. Glycoside **2.21** was then heated with di-*n*-butyltin oxide in toluene with azeotropic removal of water using a Dean–Stark apparatus.

The resulting stannylidene acetal was then treated with 2.0 equivalents of benzoyl chloride at 0 °C, leading to the formation of allyl 2,4-di-*O*-benzoyl-α-D-xylopyranoside (**2.22**) in 76% yield. A Lev ester, which can be removed using conditions orthogonal to Bz esters, was then introduced to the C-4 hydroxyl group using standard conditions (levulinic acid and dicyclohexylcarbodiimide, DCC).



Scheme 2.7. Synthesis of building block **2.23** from D-xylose.

To selectively protect the C-4 hydroxyl group of xylose, as required for the preparation of **2.7**, an alkyl β-D-xylopranoside was synthesized. As depicted in Scheme 2.8, benzoylation of D-xylose in pyridine containing a catalytic amount of DMAP gave perbenzyolated D-xylose, **2.24**, in excellent yield (95%). The corresponding β-thioglycoside **2.25** could be obtained from **2.24** in 94% yield by reaction with *p*-thiocresol in the presence of BF_3•OEt_2.[105] Debenzoylation of **2.25** with sodium methoxide in methanol gave a quantitative yield of β-thioglycoside triol **2.26**, which could be selectively protected at the C4 hydroxyl group by treatment with di-*n*-butyltin oxide in toluene, followed by addition of 1.0 equivalent of a suitable reagent.



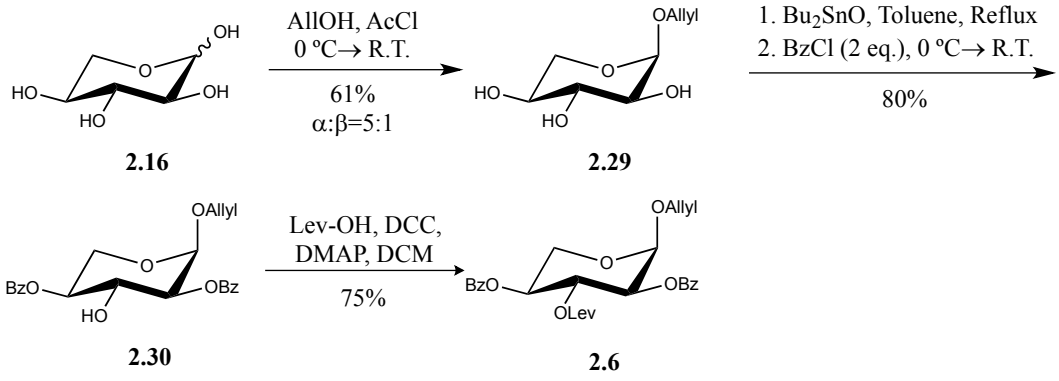
Scheme 2.8. Selective protection of the C-4 hydroxyl group on D-xylopyranosides.

A 2,2,2-trichloroethylcarbonate (Troc) group could be introduced to the C-4 hydroxyl group in excellent yield and could be removed easily in the presence of benzoyl esters (see Chapter 3). As depicted in Scheme 2.8, the Troc group was introduced in 93% yield by application of the standard protocol, resulting in the formation of **2.27**. The D-xylose building block **2.28** could be obtained in 90% yield after benzoylation.

2.3.3 Synthesis of L-xylose-based building block 2.6

After the preliminary study on selective installation of protecting groups on D-xylopyranoside derivatives, the synthesis of the L-xylopyranoside building blocks was straightforward. Starting from L-xylose (**2.16**), obtained as described above, allyl α-L-xylopyranoside (**2.29**, Scheme 2.7) could be synthesized via

Fischer glycosylation in acidic allyl alcohol. With the triol **2.29** in hand, the 2,4-di-*O*-benzoylated derivative, **2.30**, could be synthesized via the stannylidene acetal in 80% yield (Scheme 2.9). At this point, the C-3 hydroxyl group in **2.30** could be protected as a Lev ester via Steglich esterification with levulinic acid to give compound **2.6** in 75% yield.

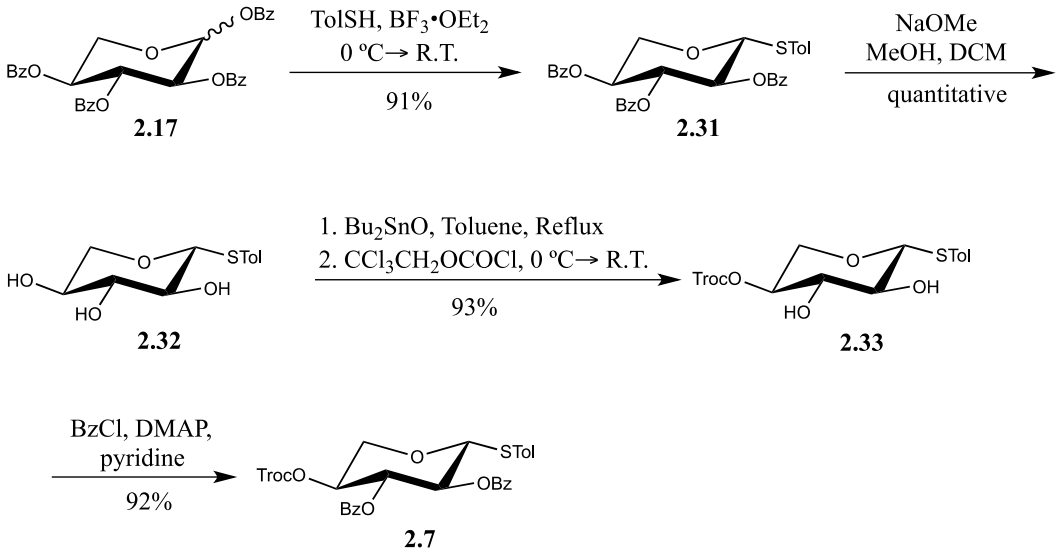


2.16 **2.29** **2.30** **2.6**

Scheme 2.9. Synthesis of building block **2.6**.

2.3.4 Synthesis of L-xylose-based building block 2.7

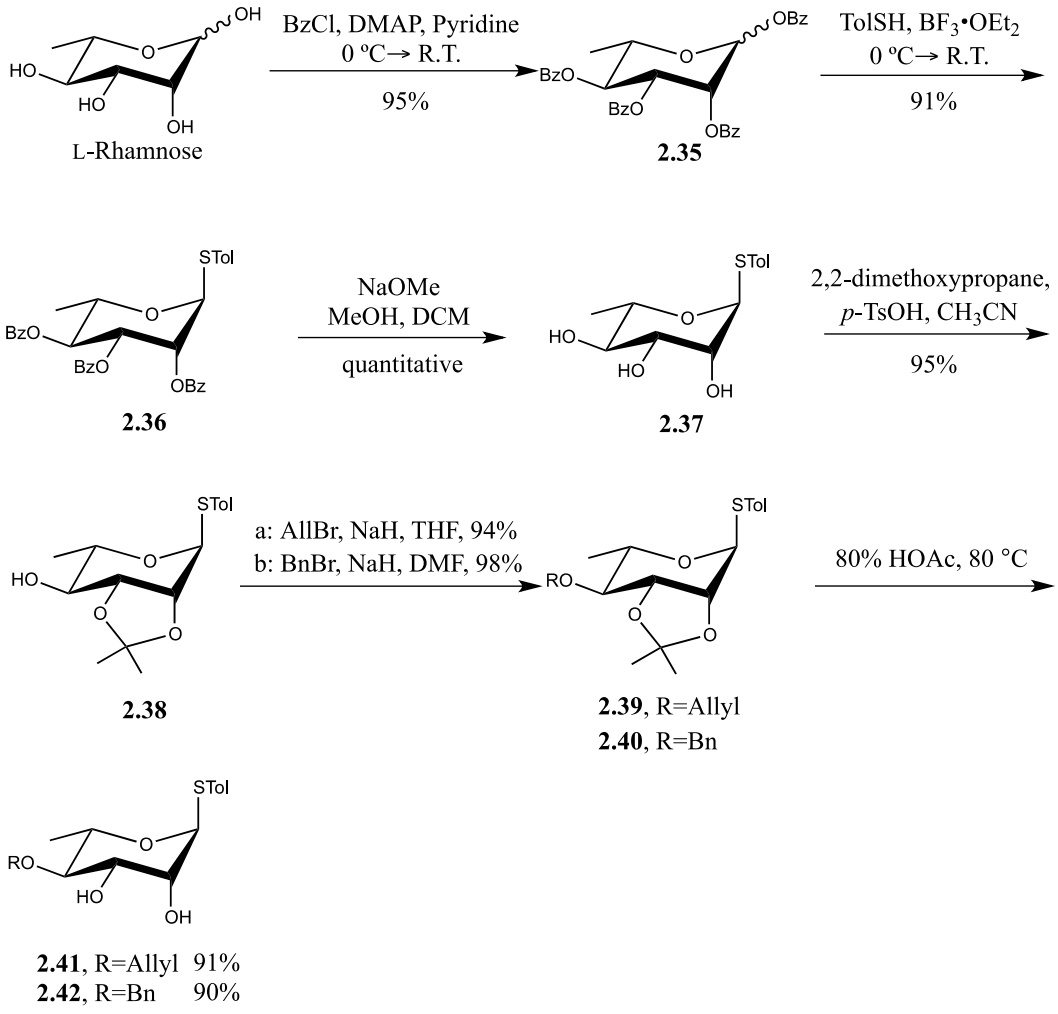
As outlined in Scheme 2.10, the synthesis of L-xylose-derived building block **2.7** started from previously synthesized perbenzoylated L-xylose derivative **2.17**. The corresponding β-thioglycoside **2.31** can be obtained in 91% yield from **2.17** by coupling with *p*-thiocresol in the presence of BF_3•OEt_2. Debenzoylation of **2.31** with sodium methoxide in methanol gave triol **2.32** in quantitative yield. Treatment of **2.32** with di-*n*-butyltin oxide followed by addition of 1.0 equivalent of 2,2,2-trichloroethyl chloroformate lead to a 93% yield of the O-4 protected L-xylose derivative **2.33**, which was then benzoylated to give **2.7** in 92% yield.



Scheme 2.10. Synthesis of building block **2.7**.

2.4 Synthesis of L-Rhamnose Building Block 2.8

I next turned my attention to the preparation of building block **2.8**, which was needed for the installation of the rhamnose moiety. As described in the next chapter, two different O4 protecting groups were explored in the glycosylation reactions. Hence two different derivatives, one with an allyl ether at this position and the other with a benzyl ether at this position, were prepared. The preparation of these compounds first required the synthesis of either intermediate **2.41** or **2.42** (Scheme 2.11). The α-thioglycoside **2.36** can be easily synthesized from L-rhamnose, by perbenzoylation followed by coupling of the resulting product with *p*-thiocresol in the presence of BF_3•OEt_2. The product can be isolated after column chromatography in 86% yield over the two steps.



Scheme 2.11. Synthesis of L-rhamnose intermediates **2.41** and **2.42**.

Deprotection of all the benzoyl groups of **2.36** gave a quantitative yield of triol **2.37**, which was converted to the 2,3-*O*-isopropylidene intermediate **2.38** by reaction with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid in acetonitrile. The reaction gave intermediate **2.38** in 95% yield.

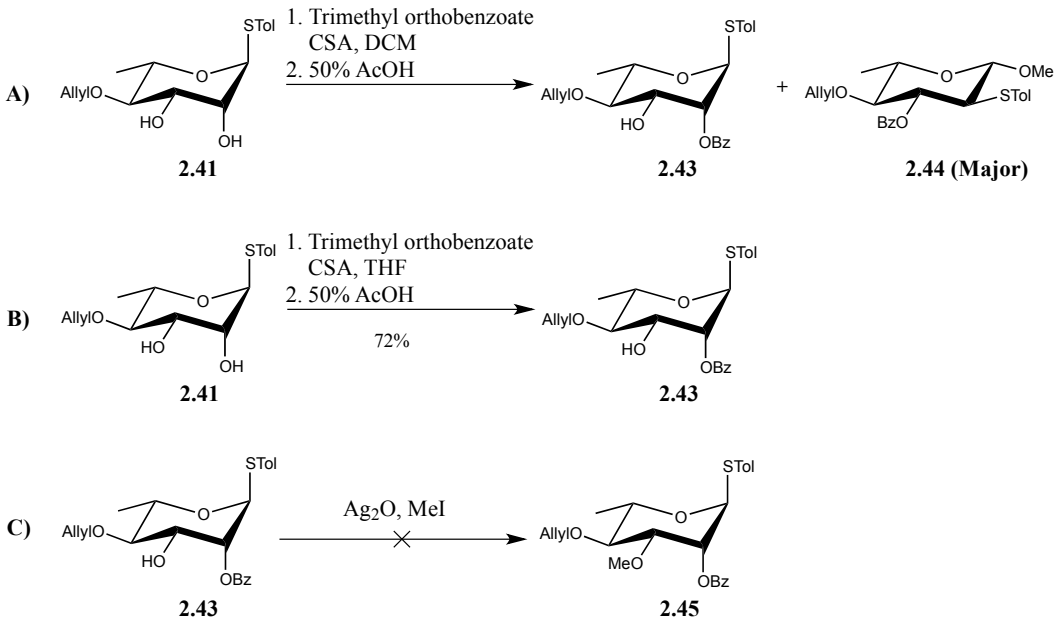
In theory, the stereochemistry of major product should be the α-isomer. However, evidence from ^{1}H NMR spectroscopy cannot distinguish the α-isomer

from the β-isomer. The dihedral angle between H-1 and H-2 is ~60° in both isomers. Therefore, according to Karplus relationship, the coupling constants of both the α and β anomer would be similar. Therefore, it is difficult to determine the stereochemistry of anomeric position using the $^{3}J_{H\text{-}1,H\text{-}2}$. The $^{1}J_{C\text{-}1,H\text{-}1}$ was then measured. As described by Bock and coworkers,[106,107] the $^{1}J_{C\text{-}1,H\text{-}1}$ of O-glycosides varies from 166–172 Hz for hexopyranosides with axial aglycones and 158–164 for hexopyranosides with equatorial aglycones. Although the $^{1}H/^{13}C$ coupled HSQC experiment was not performed on compound **2.36**, I have analyzed the $^{1}J_{C\text{-}1,H\text{-}1}$ constant within **2.38**. This analysis showed that the $^{1}J_{C\text{-}1,H\text{-}1}$ value is 169 Hz, consistent with it and its precursors being α-glycosides.

Next, the hydroxyl group in **2.38** was protected as two different ethers using the appropriate alkyl halide and sodium hydride as the base. The 4-*O*-allyl-protected intermediate **2.39** and 4-*O*-benzyl protected intermediate **2.40** were obtained in yields of 94% and 98%, respectively. The two intermediates, **2.39** and **2.40**, were treated with 80% acetic acid at 80 °C to give diol **2.41** (91% yield) and diol **2.42** (90% yield), respectively.

With the two diol intermediates in hand, I studied their conversion to the corresponding 3-*O*-methyl ether. First, diol **2.41** was treated with triethylorthobenzoate under acidic conditions in dichloromethane, followed by 50% aqueous acetic acid (Scheme 2.12A). The major product isolated was the migration product **2.44**. The problem was resolved by changing the solvent from dichloromethane to THF as described previously (Scheme 2.12B).[108] The 2-*O*-benzoyl-α-L-rhamnopyranoside derivative **2.43** was obtained in 72% yield under

these conditions. Unfortunately, methylation of **2.43** using Ag_2O as the base failed due to benzoate migration from O-2 (axial) to O-3 (equatorial) (Scheme 2.12C).

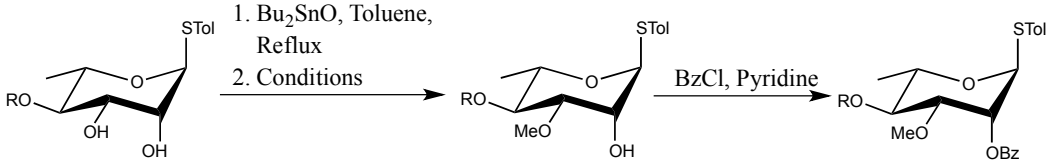


Scheme 2.12. Attempted synthesis of L-rhamnose building blocks via orthoester intermediates.

An alternate route to the target was selective methylation of the C-3 hydroxyl group by reaction first with di-*n*-butyltin oxide and then methyl iodide. In reactions of this type with thioglycoside substrates, cesium fluoride is usually added. This additive can activate alkyl halides through the interaction of the cesium cation with the halogen atom of the alkyl halide. In addition, the fluorine anion can also interact with the tin by forming a penta-coordinate complex to activate the stannylidene acetal.[109] However in this case, the addition of cesium fluoride did not give any desired product until I increased the amount of methyl iodide from 1.5 equivalents (Entry 1 and 2). By using 5.0 equivalents of methyl iodide at 36 °C, the desired product could be isolated in 20% yield (entry 3).

Further increasing the amount of methyl iodide to 10.0 equivalents and raising the reaction temperature to 60 °C led to higher yields (50%, entry 4). Further increasing the amount of methyl iodide and reaction temperature gave a similar result (entry 5). The optimized reaction conditions were to heat 20.0 equivalents of methyl iodide to 55 °C with the stannylidene acetal derived from **2.41** or **2.42**. Under these conditions, both compound **2.46** and compound **2.47,** yield the product in 73% yield.

Table 2.1. Optimization of the selective methylation on C3 hydroxyl group of **2.41** and **2.42**.



2.41, R=Allyl
2.42, R=Bn

2.46, R=Allyl
2.47, R=Bn

2.45, R=Allyl 94%
2.8, R=Bn 90%

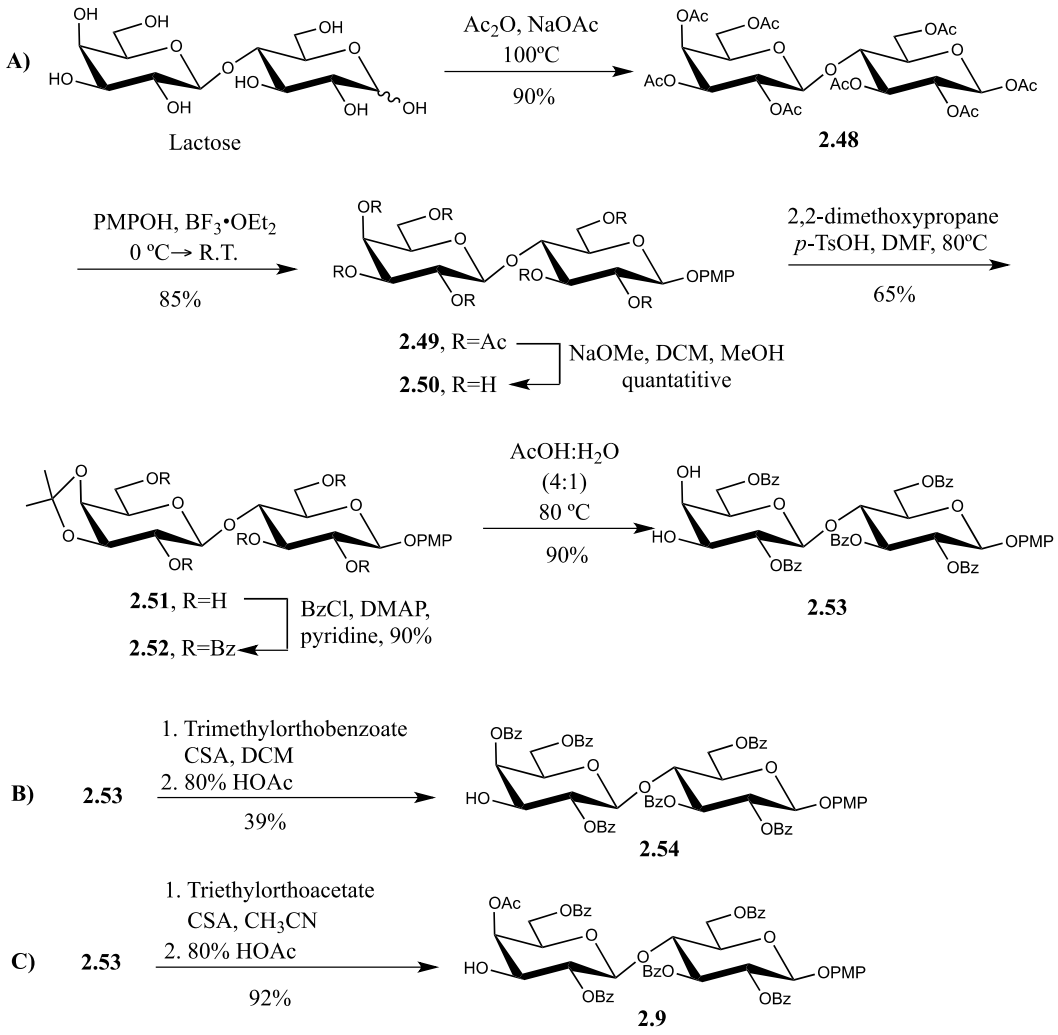
Entry	R	MeI	Temp.(°C)	Results
1	Allyl	1.5 eq	36	No Reaction
2	Allyl	5.0 eq	36	20%
3	Allyl	10.0 eq	60	50%
4	Allyl	20.0 eq	70	50%
5	Allyl	20.0 eq	55	73%
6	Bn	20.0 eq	55	73%

Finally, the benzoylation reaction worked very well on both **2.46** and **2.47**. The reactions gave the desired building blocks **2.45** and **2.8** in 94% and 90% yield, respectively.

2.5 Synthesis of Lactose Building Block 2.9

The synthesis of building block **2.9** is illustrated in Scheme 2.13. β- lactose octaacetate (**2.48**) was obtained in 90% yield by reacting lactose with 1.0 equivalent of sodium acetate in acetic anhydride at 100 °C.[110] Subsequent treatment of **2.48** and *p*-methoxyphenol with BF_3•OEt_2 at 0 °C yielded the *p*-methoxyphenyl β-D-lactoside derivative **2.49** in 85% yield. Deacetylation of **2.49** with sodium methoxide in dichloromethane and methanol gave **2.50** as a white solid.

The C-3 and C-4 hydroxyl groups on the galactosyl residue were protected as an isopropylidene acetal using 2,2-dimethoxypropane and a catalytic amount of *p*-TsOH in DMF at 80 °C. The product, **2.51**, was obtained in 65% yield. The remaining hydroxyl groups were benzoylated with benzoyl chloride in pyridine to afford compound **2.52** in 90% yield. Hydrolysis of the isopropylidene acetal with aqueous 80% acetic acid at 80 °C gave diol **2.53** in 90% yield. This diol was then treated with triethylorthobenzoate or triethylorthoacetate under acidic conditions followed by regioseletive opening of 3,4-orthoester ring.[111] This series of transformations led to compounds **2.54** and **2.9**, in 39% and 92% yield, respectively. Compound **2.54** was synthesized as my initial target. However the low yield in the preparation of **2.54**, as well as a failure of a glycosylation using **2.54** as an acceptor (see Chapter 3), led me to prepare acceptor **2.9**.



Scheme 2.13. Synthesis of building blocks **2.9** and **2.54**.

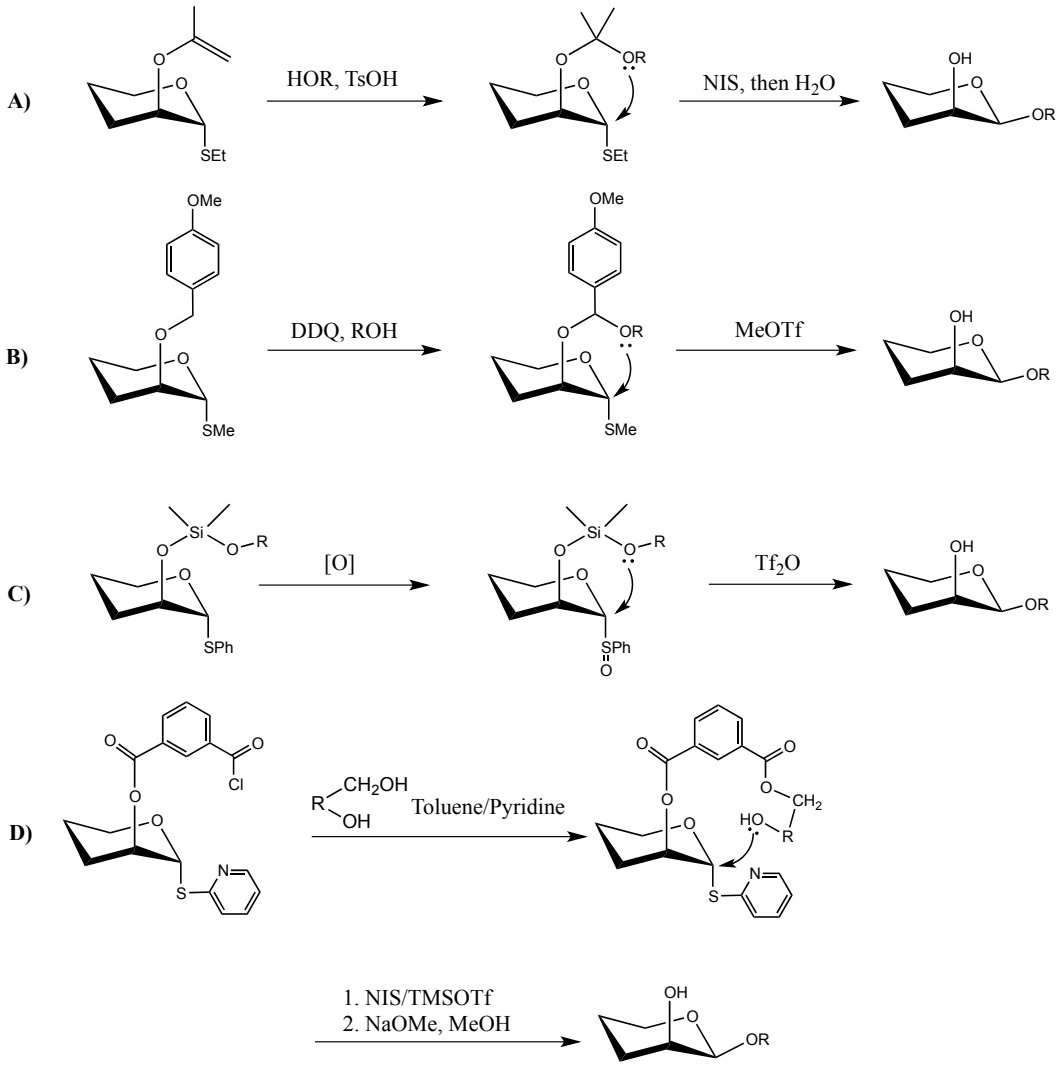
2.6 Synthesis of Asymmetrically-substituted Trehalose Building Blocks

2.6.1 Intramolecular aglycone delivery (IAD)

The structure of LOS III contains an asymmetrically-substituted trehalose moiety. Generally, there are two approaches to molecules of this type. Studies on

the direct modification of commercially-available trehalose have been reported by many groups.[92,112-116] However, due to the symmetry of the trehalose molecule, carrying out regioselective transformations can lead to poor results. Another approach involves the formation of the α,α-(1↔1) glycosidic linkage from two suitably protected glucopyranose residues. Direct formation of an α-(1↔1) glycosidic bond from two glycopyranose residues often gives a poor yield of the desired α,α-trehalose, due to the formation of α,β- and β,α-trehalose side products.[84,85,117,118]

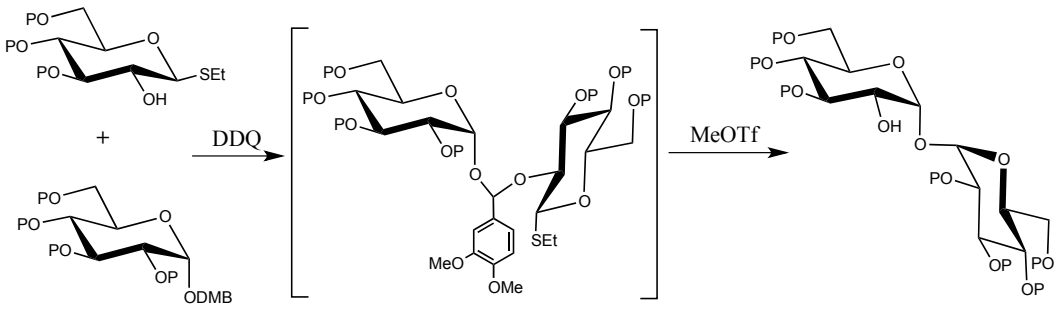
Recently, the synthesis of asymmetrically-substituted trehalose derivatives was accomplished by using the Intramolecular Aglycone Delivery method,[90,91] which was first introduced for the synthesis of β-mannosides by Hindsgual in 1991.[91,119] This approach involves two steps as shown in Scheme 2.14. The first step is the formation of a mixed acetal between the aglyconic alcohol and O-2 of the glycosyl donor to generate a species where the two components are tethered together. In the second step, the tethered intermediate is treated with an activating agent, which results in the delivery of the aglycone via a proposed concerted process leading to the formation of the desired glycosidic linkage. Various mixed acetal groups have been used as tether groups to temporarily connect the donor and the alcohol (Scheme 2.14 A&B).[119-123] However, other tethering groups such as mixed dialkoxysilane,[124] *m*-xylylene and isophthaloyl[125] have also been reported (Scheme 2.14 C&D).



Scheme 2.14. Examples of intramolecular aglycone delivery approaches.

Bertozzi and coworkers have applied the Intramolecular Aglycone Delivery approach to the preparation of trehalose derivatives.[90-92] In this work, either a 3,4-dimethoxybenzyl (DMB) α-glucopyranoside (shown in Scheme 2.15) or 4-methoxybenzyl (PMB) α-glucopyranoside was used as the coupling partner. Similar to Ito's methodology for β-mannoside synthesis (Scheme 2.14B), the reaction involves the formation of a mixed acetal followed by intramolecular

aglycone delivery upon activation of a thioglycoside by methyl trifluoromethanesulfonate (MeOTf).



Scheme 2.15. Bertozzi's Intramolecular Aglycone Delivery route to trehalose.

The use of the Intramolecular Aglycone Delivery method should provide an efficient way to prepare the asymmetrically-substituted trehalose derivative present in the LOS III structure. The alkyl groups in the target are located on O-2, O-4' and O-6' of the trehalose. In designing suitable building blocks for use in the reaction, **2.10** and **2.11** (Figure 2.4), I decided that O-4' and O-6' could be protected by a benzylidene acetal, while O-2 could be left as a free hydroxyl group for the formation of the mixed acetal. The acetate group is designed to protect O-4 of one residue of the trehalose, to allow for further glycosylation after deprotection.

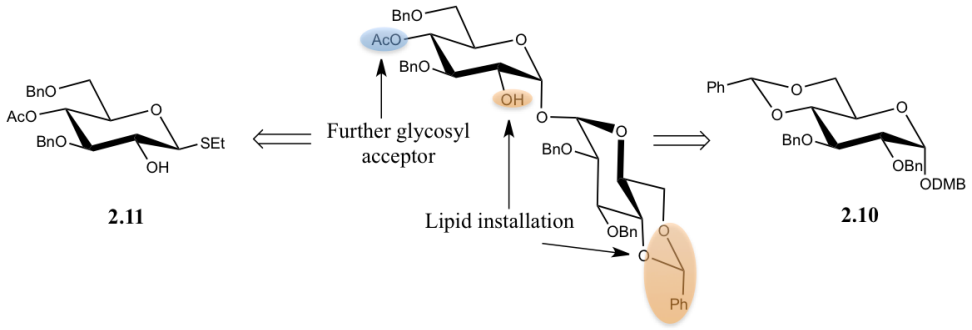
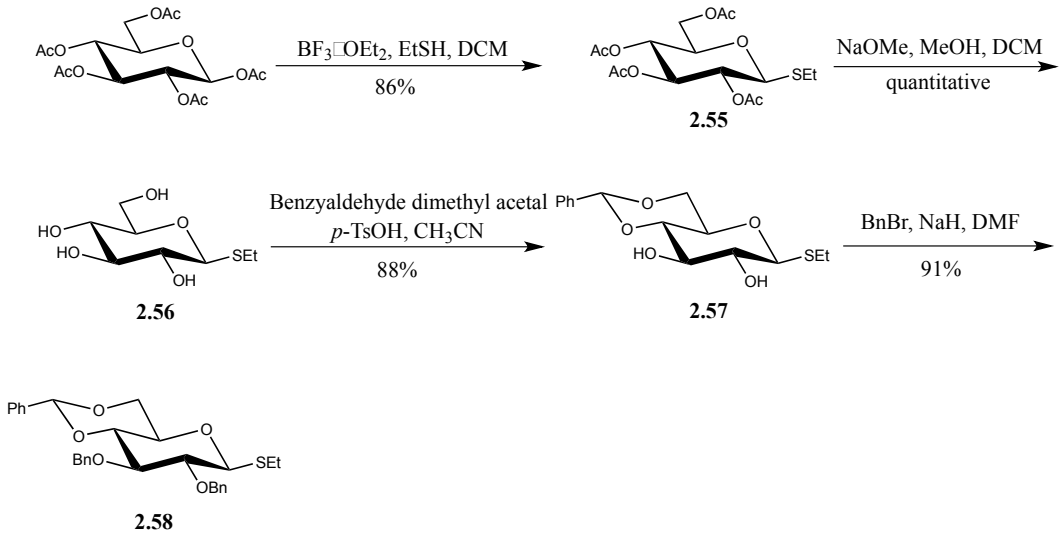


Figure 2.4. Design of building blocks for desired trehalose moiety.

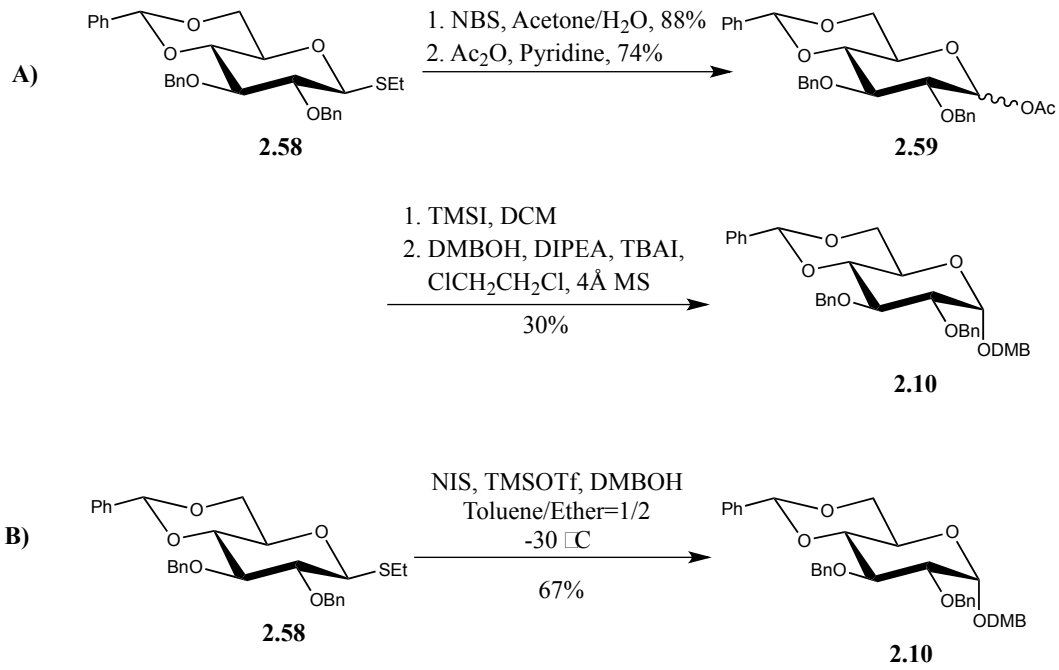
*2.6.1.1 Synthesis of building block **2.10***

The synthesis of building block **2.10** started with β-D-glucose pentaacetate (Scheme 2.16). First, the peracetylated thioglycoside **2.55** was obtained in 86% yield by coupling β-D-glucose pentaacetate with ethanethiol in the presence of BF_3•OEt_2. Deacetylation gave a quantitative yield of thioglycoside **2.56**. The C-4 and C-6 hydroxyl groups were then protected as a benzylidene acetal, which was produced by treating **2.56** with benzaldehyde dimethyl acetal in acidic acetonitrile. The product, **2.57**, was obtained in 88% yield. Subsequent treatment of this diol with benzyl bromide and sodium hydride in DMF gave **2.58**, a precursor for synthesizing **2.10**, in 91% yield.



Scheme 2.16. Synthesis of precursor **2.58** required for accessing building block **2.10**.

3,4-Dimethoxybenzyl α-D-glucopyranoside (**2.10**) was synthesized from **2.58** as described in the literature (Scheme 2.17A).[91,126] The approach involves derivative **2.59** and the *in situ* formation of a glycosyl iodide intermediate. The yield and stereoselectivity of this reaction was reported to be very good. In my case, however, the synthesis of this compound was unsuccessful. First, I hydrolyzed the thioglycoside moiety in **2.58** using NBS in acetone and water, which gave a good yield (88%) of the product. Next, formation of glycosyl acetate **2.59** gave a 74% yield of the product. The final step, which involves *in situ* formation of glycosyl iodide and treatment with 3,4-dimethoxybenzyl alcohol, was problematic, giving only 30% yield of the product. Separation of desired product from impurities was also a challenge.



Scheme 2.17. Synthesis of building block **2.10**.

Given this failure, I considered a more direct approach for converting **2.58** into **2.10**, based on an analysis of the literature. Previously, thioglycoside **2.58** was shown to be α-selective in glycosylations using 1-benzenesulfinylpiperidine (BSP)/ trifluoromethanesulfonic anhydride (Tf_2O) as the promoter.[127] In addition, the use of ether as solvent or co-solvent has been shown to increase the α selectivity in reactions of this type.[128,129] Keeping all these factors in mind, I tested the glycosylation of 3,4-dimethoxybenzyl alcohol with thioglycoside **2.58** (Scheme 2.17B) using N-iodosuccinimide (NIS)/ trimethylsilyl trifluoromethanesulfonate (TMSOTf), as the promoter instead of BSP/Tf_2O. Fortunately, I was able to isolate 67% of the desired α-glucopyranoside and so I chose this as the best approach for synthesizing the compound.

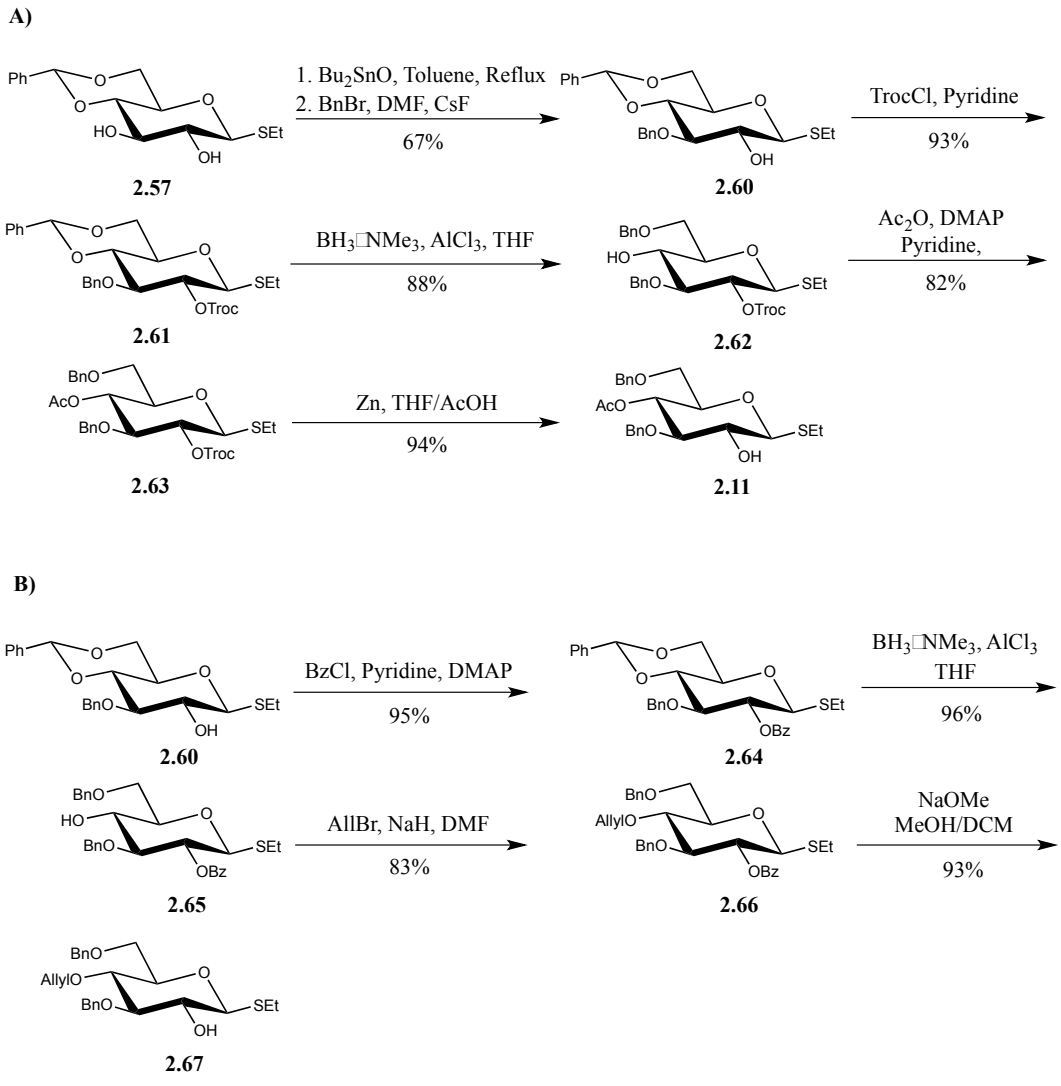
*2.6.1.2 Synthesis of building block **2.11** and its analogue **2.67***

Building block **2.11** could be synthesized from diol **2.57** (Scheme 2.18A). Heating **2.57** and di-*n*-butyltin oxide in toluene at reflux for four hours followed by the addition of benzyl bromide with cesium fluoride in DMF, led to selective benzylation of the C-3 hydroxyl group to give **2.60** in 67% yield. Subsequent installation of the Troc group gave the fully protected β-thioglucoside **2.61**. Selective reductive opening of the 4,6-benzylidene acetal with borane trimethylamine complex and aluminum chloride in THF resulted in the formation of a 6-*O*-benzylated intermediate **2.62** in 88% yield. Acetylation of the C-4 hydroxyl group in **2.62** gave an 82% yield of **2.63**. Finally, the Troc group was removed by treatment of **2.63** with activated Zn in THF and acetic acid to give **2.11** in 94% yield.

I also synthesized **2.67** (Scheme 2.18B) because there was a possibility that the acetate group on O-4 of building block **2.11** could be cleaved when I installed the long chain alkyl groups on the trehalose. The need for an alkyl group, which is stable to basic alkylation conditions, instead of a base labile ester, prompted me to explore the use of an allyl group to protect the C-4 hydroxyl group.

Compound **2.67** was prepared via a similar reaction scheme to **2.11** (Scheme 2.18B). The hydroxyl group on **2.60** was easily protected as a benzoyl ester to give compound **2.64** in 95% yield. Regioselective opening of the 4,6-

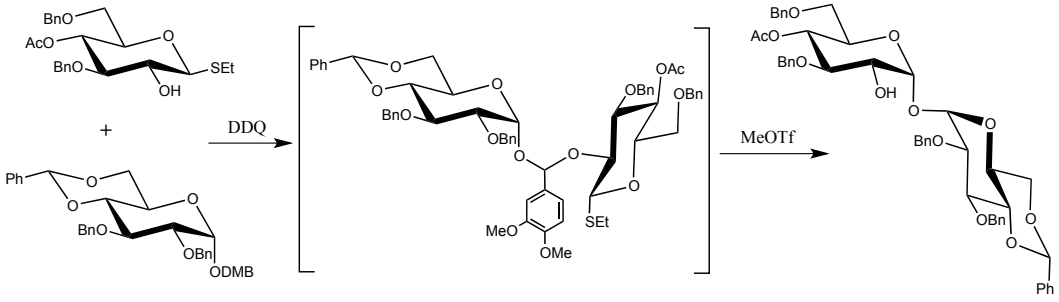
benzylidene acetal by treating **2.64** with borane trimethylamine complex and aluminum chloride gave compound **2.65** in 96% yield. The hydroxyl group was then protected with an allyl group using allyl bromide and sodium hydride affording an 83% yield of **2.66**. Finally, the benzoate ester in **2.66** was removed with sodium methoxide in methanol and dichloromethane to give **2.67** in 93% yield.



Scheme 2.18. Synthesis of building blocks **2.11** and **2.67**.

2.6.1.3 Attempted formation of the α,α-(1↔1) glycosidic bond via IAD

Based on the literature,[91] the procedure for making the α,α-(1↔1) glycosidic bond from **2.10** and **2.11** involves using the oxidizing reagent 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to oxidize the methylene group on the 3,4-dimethoxybenzyl moiety in **2.10** to a cation, which is then trapped by the acceptor alcohol, **2.11**. This intermediate is then treated with methyl trifluoromethanesulfonate (MeOTf) to produce the disaccharide (Scheme 2.19).



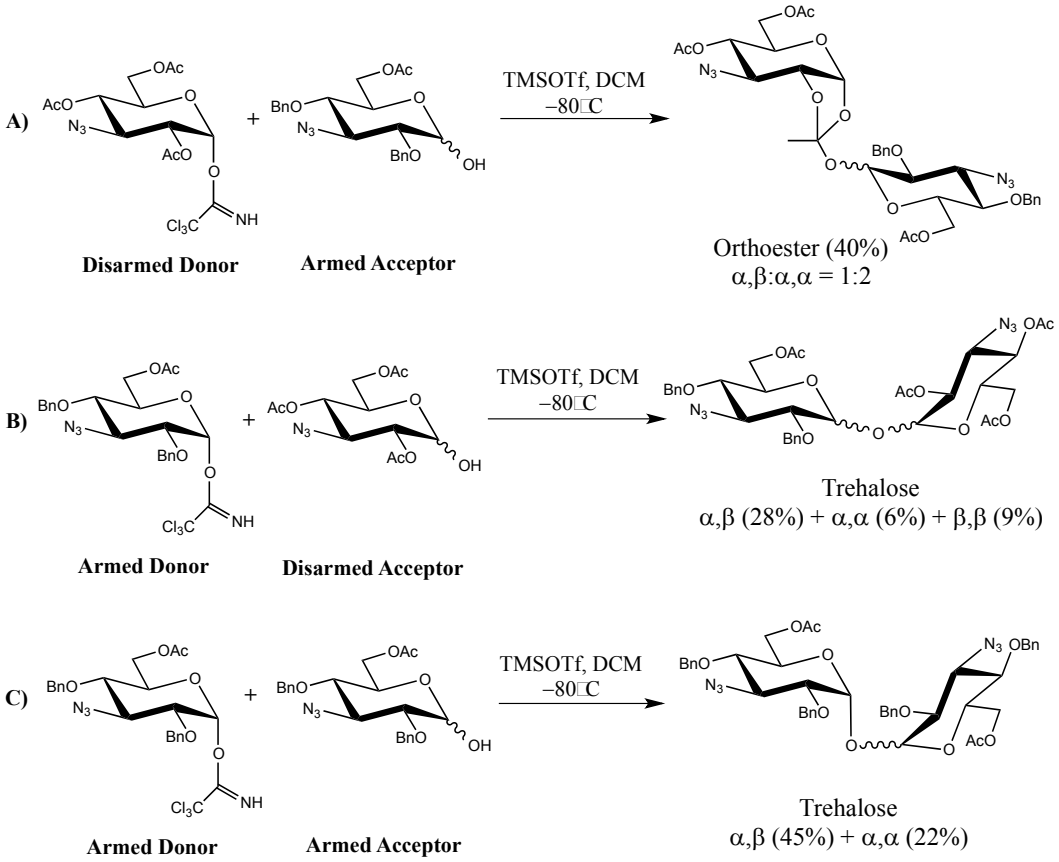
Scheme 2.19. Attempted formation of the α,α-(1↔1)-glycosidic bond in trehalose derivative **2.4** via Intramolecular Aglycone Delivery.

After many attempts, using both acceptors **2.11** and **2.67**, I abandoned this approach due to the following reasons. First, the reactions were not reproducible. Although sometimes the product was obtained, in other cases it was not. Second, the product was difficult to purify, a problem described previously for this reaction.[90] All these problems led me to an alternate strategy: direct glycosylation for the formation of the α,α-(1↔1)-glycosidic bond.

2.6.2 Direct Glycosylation

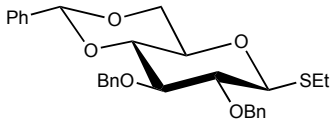
In the past twenty years, there have been several papers published regarding the formation of α,α-(1↔1)-glycosidic bonds via direct glycosylation involving different donors such as trichloroacetimidates[85,118] and glycosyl sulfates.[117] Posner and coworkers have even studied the possibility of dimerization of two free sugar moieties by using 4Å molecular sieves and TMSOTf as the promoter.[84] Those studies showed positive results for the formation of α,α-trehalose. However, as discussed before, direct glycosylation can give α,β and β,β isomers as side products. This problem cannot be avoided, but can be reduced by optimizing reaction conditions. The glycosyl donors and acceptors used in these papers are simple carbohydrates, not the more complex ones needed to synthesize asymmetricalally-substituted trehalose.

Recently, Palmer and coworkers systematically studied the formation of (1↔1)-glycosidic bonds, using more complex donors and acceptors, including those that are disarmed, armed and superarmed.[89] They found that the use of a disarmed donor and disarmed acceptor resulted in the formation of orthoesters in 40% yield (Scheme 2.20A). Glycosylation between an armed donor and disarmed acceptor only gave 43% of products with a (1↔1)-glycosidic bond and only 6% was the α,α-isomer (Scheme 2.20B). Glycosylation between an armed donor and an armed acceptor gave a mixture of α,β- and α,α-isomeric products in a 2:1 ratio (Scheme 2.20C).

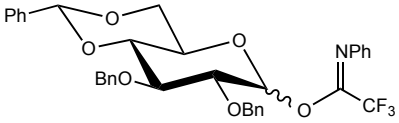


Scheme 2.20. Studies on direct glycosylation leading to (1↔1)-glycosidic bonds using armed and disarmed donors and acceptors.

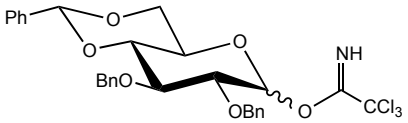
These results, as well as my experience on the nature of glycosyl donors and acceptors, helped me to design a donor and an acceptor for the formation of α,α-trehalose, via direct glycosylation. As I discussed in section 2.6.1.1, the 4,6-*O*-benzylidene derivatives, a series of compounds with arming protecting groups, acted as very good α-selective donors. Therefore, I decided to explore 4,6-*O*-benzylidene derivatives **2.58**, **2.68** and **2.69** as the glycosyl donors (Figure 2.5). In my designed scheme, a silyl group was introduced to the C-2 hydroxyl group of the glycosyl acceptor.



2.58



2.69

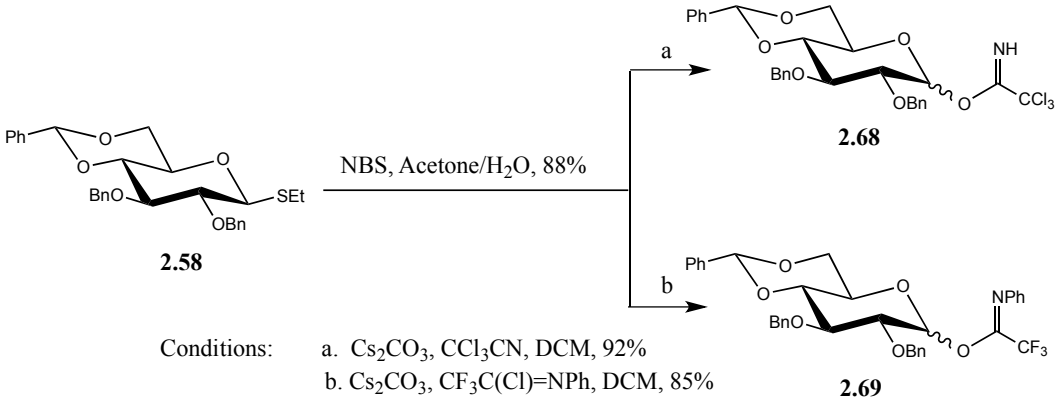


2.68

Figure 2.5. Designed donors for direct glycosylation leading to (1↔1)-glycosidic bonds.

2.6.2.1 Synthesis of the donors for direct glycosylation

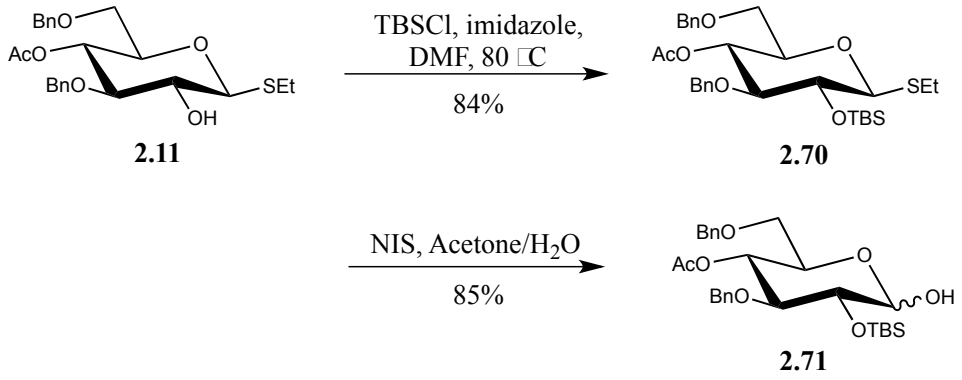
The synthesis of the glycosyl donors for use in the direct glycosylation was very straightforward (Scheme 2.21). Thioglycoside **2.58** had already been synthesized (section 2.6.1.1, Scheme 2.16). Starting from **2.58**, hydrolysis of thioglycoside using NBS in wet acetone gave the hemiacetal in 88% yield. The hemiacetal was then converted into the corresponding trichloroacetimidate or *N*-phenyl-trifluoroacetimidate using Cs_2CO_3 and trichloroacetonitrile or 2,2,2-trifluoro-*N*-phenylethanimidoyl chloride, respectively, to give donor **2.68** (92%) and **2.69** (85%) which could be used without column chromatography purification.



Scheme 2.21. Synthesis of donors for direct glycosylation.

2.6.2.2 Synthesis of the acceptor for direct glycosylation

The glycosyl acceptor could be prepared from the previously synthesized alcohol **2.11**, used for the intramolecular aglycone delivery methodology (Scheme 2.22). Fully protected thioglycoside **2.70** could be obtained from **2.11** by treatment with *tert*-butyldimethylsilyl chloride (TBSCl) and imidazole in DMF at 80 °C. The reaction took two days to complete and the product could be isolated in 84% yield. The hydrolysis of thioglycoside using NBS in acetone/water resulted in very low yield of product. However, changing the oxidizing reagent from NBS to NIS gave much better yield. The glycosyl acceptor **2.71** was isolated in 85% yield when the latter conditions were used.



Scheme 2.22. Synthesis of acceptor for direct glycosylation.

2.6.2.3 Formation of α,α-trehalose via direct glycosylation

With glycosyl donors **2.58**, **2.68**, **2.69** and glycosyl acceptor **2.71** in hand, I studied their coupling (Table 2.2). First, donor **2.68** and acceptor **2.71** were treated with 0.1 eq of TMSOTf in dichloromethane at –78 °C. The reaction gave the desired α,α isomer **2.72** in 42% yield (Entry 1). Changing the solvent from dichloromethane to diethyl ether and reducing the amount of acid increased the yield of the desired isomer **2.72** to 49% (Entry 2). Activation of the *N*-phenyl trifluoroacetimidate donor **2.69** requires higher temperature (–10 °C) than the trichloroacetimidate donor **79**. The reaction was slow compared with using donor **2.68** and the use of prolonged reaction times resulted in more hydrolyzed donor. With **2.69**, the yield of the desired product was 37% (Entry 3). Thioglycoside **2.58** was also tested as a donor in this reaction using diethyl ether at –78 °C. However, the yield was only 22%, presumably due to the poor solubility of **2.58** in this solvent at low temperature. In summary, glycosylation between trichloroacetimidate **2.68** and alcohol **2.71** in dichloromethane at –78 °C to –40 °C with 0.05 eq of TMSOTf gave best yield of desired product **2.72** (49%).

Although this is a modest yield of the product, the relative ease by which the molecule could be assembled made it my preferred approach. Given the lack of time, further work to improve the yield of the reaction was not pursued.

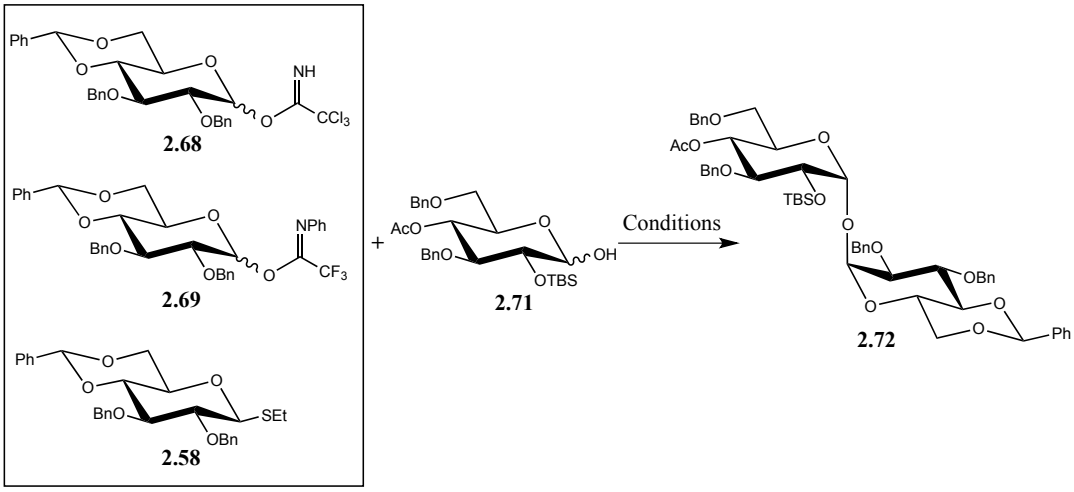


Table 2.2. Optimization of direct glycosylation for the synthesis of α,α-trehalose.

Entry	Donor	Solvent	TMSOTf	Temperature (°C)	Yield of **2.72**
1	**2.68**	Dichloromethane	0.1 eq	–78 → –40	42%
2	**2.68**	Ether	0.05 eq	−78 → –40	49%
3	**2.69**	Dichloromethane	0.1 eq	–10	37%
4	**2.58**	1:5 Toluene–Ether	0.05 eq	−78 → −40	22%

2.7 Synthesis of C-4 Branched Sugar Building Blocks

2.7.1 Analysis of C-4 branched sugar building blocks

The relative configuration of the 3,6-dideoxy-4-C branched chain sugar in LOS-III was proven by Prandi and coworkers in 1997 through chemical

synthesis.[61] The key step in their synthesis was the coupling of a 3,6-dideoxy ketone and a polyoxygenated acid chloride with samarium diiodide (Figure 2.6A). However, the yield for the final coupling reaction was not very good. Therefore, I proposed another strategy that involved making the C–C bond via cross metathesis using Grubbs II catalyst from two alkenes and then dihydroxylation (Figure 2.6B).

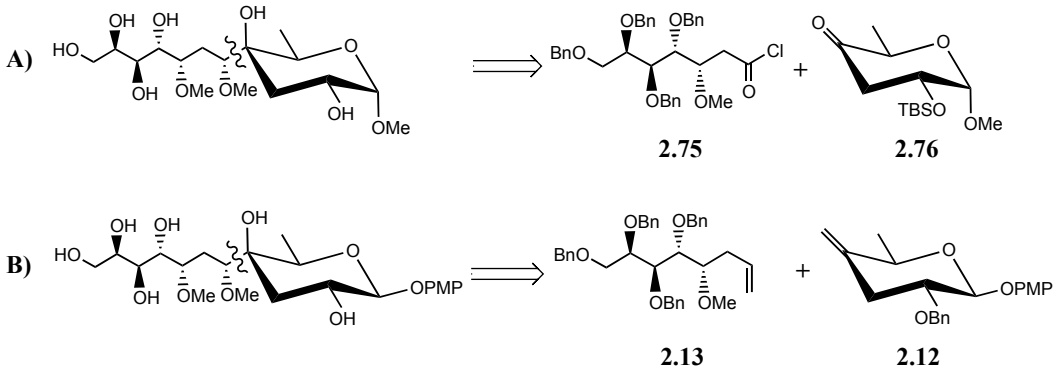
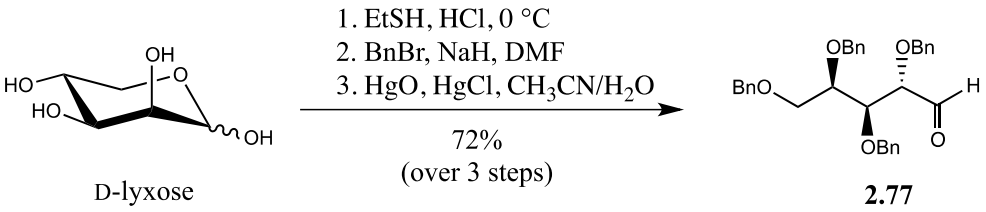


Figure 2.6. Retrosynthetic analysis of C-4 branched-chain sugar.

2.7.2 Synthesis of side chain precursor

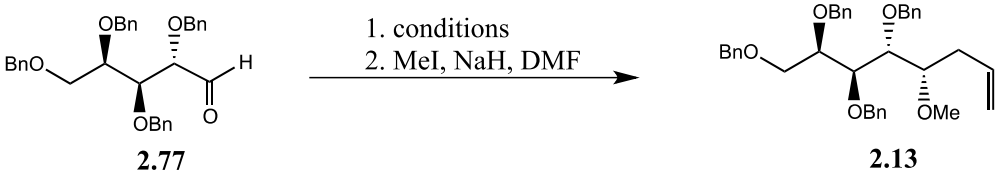
The side chain precursor, alkene **2.13** (Figure 2.6), has been synthesized before.[61] Following the literature procedure,[130,131] the perbenzylated aldehyde **2.77** could be synthesized from D-lyxose, as compound **2.77** and this monosaccharide share the same absolute stereochemistry. In my hands, this three-step reaction sequence gave **2.77** in 72% yield (Scheme 2.23).



Scheme 2.23 Synthesis of aldehyde **2.77**.

I next studied the asymmetric allylation of **2.77** using different reagents (Table 2.3). First, allyltrimethylsilane and $TiCl_4$ were tested as described in the literature (Entry 1). Despite many attempts, I could not repeat the published result and no product was isolated. Use of allyltributyltin, a more reactive allylation reagent, and $TiCl_4$ at –78 °C gave about a 30% yield of the product (Entry 2). Repeating this reaction at a low temperature, –97 °C, gave slightly better results (Entry 3 *vs*. Entry 2). After methylation of the hydroxyl group, a 44% yield of the desired isomer **2.13** was isolated, which was shown to be pure by ^1H NMR spectroscopic analysis.

Table 2.3. Asymmetric allylation of **2.77**.



Entry	Reagent	Temp (°C)	Yield	d.r.
1	$TiCl_4$/AllylTMS	–97	22%	N/A
2	$TiCl_4$/Allyltributyltin	–78	30%	N/A
3	$TiCl_4$/Allyltributyltin	–97	44%[a]	3:1
4	$ZnCl_2$/Allylmagnesium bromide	0	64%[a]	1:3
5	(–)-Ipc_2BAllyl (1.1 eq)	–78	55%[a]	6:1

a. Yield over two steps, for two isomers.

The diastereoselectivity of this reaction was ~3:1 with the desired isomer as the major product. This is much lower than the reported 13:1 ratio of desired to undesired products. Therefore, I explored other reagents. The use of allylmagnesium bromide and $ZnCl_2$, a procedurally simpler approach, surprisingly gave 64% of the allylation product. However, further investigation of the selectivity of the product using ^1H NMR spectroscopy showed that the reaction proceeded with opposite diastereoselectivity. Finally, asymmetric allylation using a chiral boron allylation reagent, (–)-Ipc_2BAllyl, gave a satisfactory yield and diastereoselectivity of the product: 55% yield and 6:1 desired to undesired products. These stereoisomeric homoallylic alcohols were not separable by chromatography. Therefore, the yields indicated in Table 2.3 below are yields for both isomers. Methylation of these alcohols using sodium hydride and methyl iodide gave two separable methyl ether derivatives from which the desired isomer, **2.13**, could be isolated. In the case of the reaction with (–)-Ipc_2BAllyl, **2.13** was obtained in 47% overall yield from **2.77**.

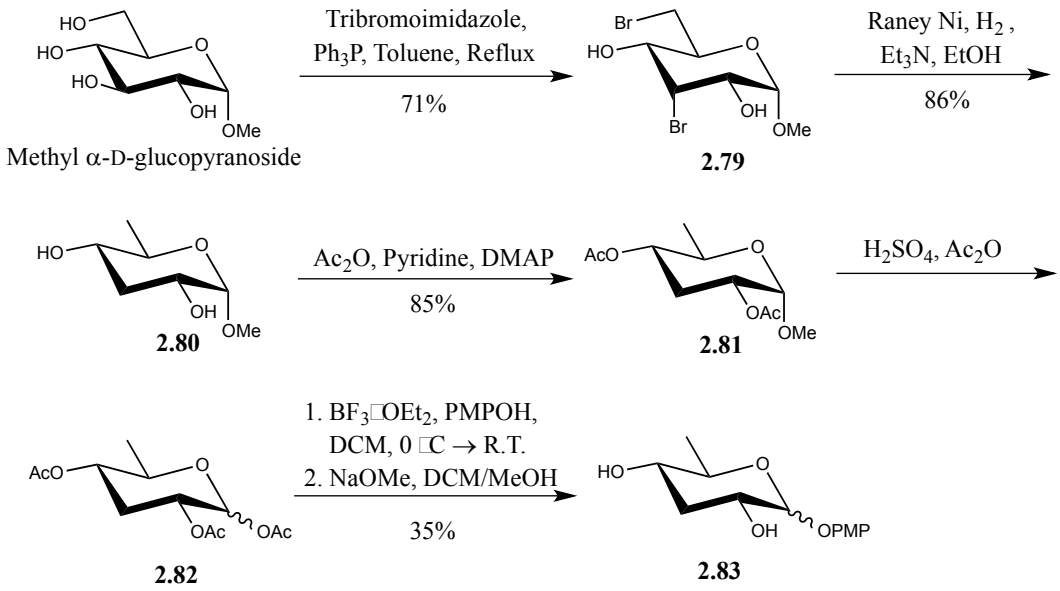
2.7.3 Synthesis of the 3,6-dideoxy sugar alkene

The synthesis of 3,6-dideoxy derivative was another challenge and required a protecting group on the anomeric position that: a) could be easily removed when needed and b) had no impact on the series of modification on the sugar moiety needed to functionalize it to generate the target alkene. I considered a protecting group like a 4-methoxyphenyl (PMP) glycoside as the best choice

because it is stable to many reaction conditions, both basic or acidic. In addition, unlike a thioglycoside, which could poison the transition metal catalyst, the PMP group will not have such effect on any catalyst. Two approaches, differing in the point at which the PMP group was introduced, were studied.

2.7.3.1 Installation of the PMP group at a late stage

In this approach, a published synthetic route was used to prepare 3,6-dideoxy sugar glycoside **2.80** (Scheme 2.24).[80] Starting from commercially-available methyl α-D-glucopyranoside, bromination at C3 and C6 was achieved by treatment with tribromoimidazole and Ph_3P in toluene at reflux to give the 3,6-dibromo derivative **2.79** in 71% yield. This compound was then treated with Raney Ni under H_2 to afford, in 86% yield, the 3,6-dideoxy derivative **2.80**. The two hydroxyl groups were then protected with acetyl groups to give intermediate **2.81** in 85% yield.



Scheme 2.24. Synthesis of 3,6-dideoxy sugar by installing the PMP glycoside at a late stage.

Acetolysis of **2.81** was attempted to give the 1,2,4-tri-*O*-acetyl-3,6-dideoxy sugar **2.82**. However, the yield of this reaction was not good and many side products were obtained. Nevertheless, the α-isomer of **2.82** could be isolated, which was treated with PMPOH in the presence of Lewis acid $BF_3 \bullet OEt_2$. Due to the similarity of polarity between the product and starting material, the reaction was difficult to monitor by TLC. Therefore, the reaction was stopped after four hours and the resulting mixture was treated with sodium methoxide to yield **2.83** in a 35% yield over the two steps. At this point, TLC showed that the installation of PMP group was incomplete. The first step, which involves the 4-methoxyphenol glycoside formation, was performed under similar conditions overnight. However this did not resolve this problem, but did result in an increase

in the amount of the α isomer. After deacetylation, the unprotected 3,6-dideoxy sugar **2.83** was isolated as an α/β mixture.

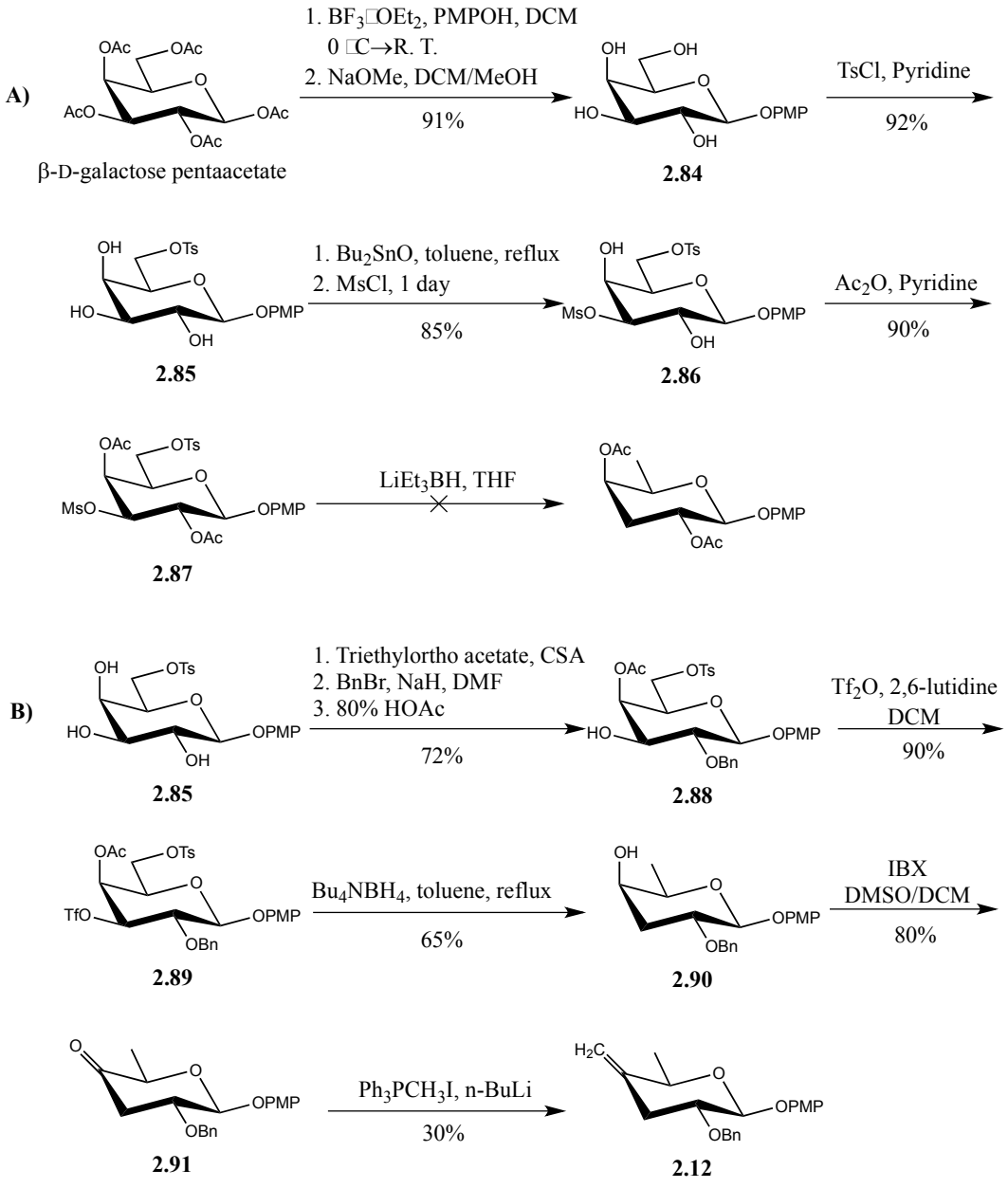
It turns out that the installation of the PMP group at a late stage is not very efficient. The limitations are a) the acetolysis of methyl glycoside giving multiple products; b) the installation of PMP group not being complete and giving a mixture of two products. The presence of an α,β mixture will complicate product separation and characterization. Therefore, I investigated installing the PMP group at an early stage.

2.7.3.2 Installation of the PMP group at an early stage

Starting from β-D-galactopyranose pentaacetate, 4-methoxyphenyl β-D-galactopyranoside (**2.84)** could be synthesized, in 91% overall yield, via coupling with 4-methoxyphenol in the presence of $BF_3 \bullet OEt_2$ followed by deacetylation (Scheme 2.25A). The tosyl (Ts) group was then introduced to the primary hydroxyl group selectively to give the triol intermediate **2.85**, in 92% yield.

My plan was to introduce another sulfonate group to the C3 hydroxyl group, so that the sulfonates could be reduced by a hydride source in a single step. Similar to the installation of an ester group to the C-3 hydroxyl group on galactopyranose derivatives, a methanesulfonate moiety could also be introduced via formation of a stannylidene acetal.[132] Thus, triol **2.85** was treated with *n*-Bu_2SnO followed by addition of mesyl chloride, resulting in the conversion, in 85%

yield, of the C-3 hydroxyl group into a mesylate (Ms). Next, acetylation gave 90% yield of compound **2.87**.



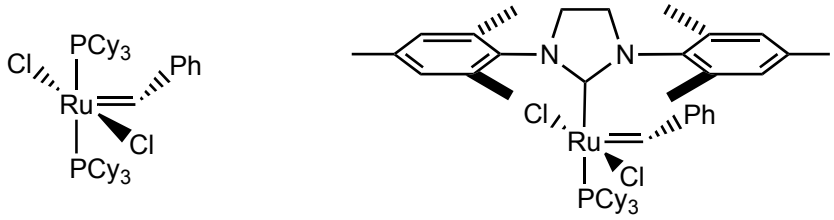
Scheme 2.25 Synthesis of the 3,6-dideoxy sugar by installing the PMP glycoside at an early stage.

With a route to **2.87** developed, I investigated its deoxygenation. Unfortunately, reduction using $LiEt_3BH$ showed many side products by analytical TLC.[133] Because substitution reactions on secondary centers of pyranose rings are slow compared to primary centers, the use of a more reactive leaving group, trifluoromethanesulfonate (triflate, Tf) in this case, was a possible solution. Therefore, triol **2.85** was treated with Tf_2O after the formation of stannylidene acetal; however, no triflated product was isolated.

To install the triflate, I investigated a different route (Scheme 2.25B). I first protected the C-3, C-4 diol in **2.85** as an orthoacetate. Orthoesters are acid labile but stable to basic conditions. Without purification by chromatography on silica gel, a weak acid, the intermediate was treated with benzyl bromide and sodium hydride in DMF. The crude product was then treated with aqueous 80% acetic acid to selectively open the orthoester ring to yield the desired 4-*O*-acetylated product **2.88** in 72% yield from **2.85**. Compound **2.88** was then treated with Tf_2O in the presence of 2,6-lutidine to give a 90% yield of **2.89**. Compound **2.89** could be deoxygenated by *n*-Bu_4NBH_4 to give 3,6-dideoxy derivative **2.90** in 65% yield.[134] The hydroxyl group of the 3,6-dideoxy derivative was then oxidized, in 80% yield, to the corresponding ketone (**2.91**) by using 2-iodoxybenzoic acid. The ketone was treated with methyltriphenylphosphonium iodide and *n*-butyl lithium to yield the 1,1-disubstituted alkene **2.12** in 30% yield.

2.7.4 Cross metathesis coupling reaction

With the two coupling partners in hand, I tested the olefin cross metathesis. The Grubbs catalysts (Grubbs I and Grubbs II, Figure 2.7) have been widely used in olefin metathesis including ring-closing metathesis and cross metathesis.[135-137]



Grubbs I **Grubbs II**

Figure 2.7. Structures of Grubbs 1st and 2nd generation catalysts.

In 2003, Grubbs and coworkers provided a general model for predicting the outcome of an olefin cross-metathesis reaction.[138] Olefins were classified as one of four types, which are shown in Table 2.4. The olefin cross metathesis partner **2.13** is a terminal olefin, which would rapidly homodimerize when using either the Grubbs I and Grubbs II catalysts. So, the Grubbs I catalyst is not able to catalyze the olefin metathesis reaction to produce a 1,1-disubstituted olefin **2.12**. However, my prediction was that the Grubbs II catalyst could do so.

Table 2.4. Olefin types in cross metathesis reactions.[138]

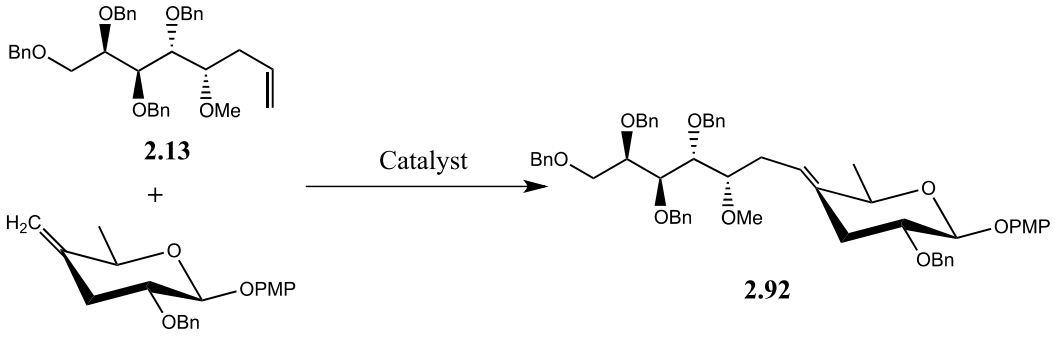
Olefin Type	Grubbs I catalyst	Grubbs II Catalyst
Type I Rapid homodimerization	**Terminal olefins (e.g., 2.13)**	**Terminal olefins (e.g., 2.13)**
Type II Slow homodimerization	Styrene, 2° allylic alcohols, vinyl boronates, etc.	Styenes (large ortho substituent), vinyl ketones, unprotected 3° allylic alcohols, vinyl epoxides, etc.
Type III No homodimerization	vinyl siloxanes	**1,1-disubstituted olefins (e.g., 2.12)**
Type IV Inert to cross metathesis	**1,1-disubstituted olefins (e.g., 2.12)**	Vinyl nitro olefins, trisubstituted allyl alcohols (protetected)

The initial reaction was performed using cross metathesis partners **2.13** and **2.12** with the Grubbs II catalyst (Table 2.5). Unfortunately, the 1,1-disubstituted olefin **2.12** was not reactive enough with a catalyst loading of either 5 mol% or 20 mol% (Entries 1 and 2). Only the homodimerized product of olefin **2.13** was isolated. The reason may be the steric hindrance in the 1,1-disubstituted olefin **2.12**, arising from the methyl group at C5 of the pyranose ring.

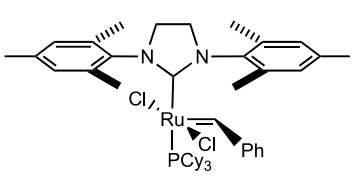
A recent published paper described the more reactive Hoveyda–Grubbs catalyst (catalyst B, Table 2.5), which could catalyze cross metathesis reaction on 1,1-disubstituted olefins.[139] Due to the steric hindrance from the methyl group, however, the reaction using catalyst B did not give any promising results (Table 2.5, Entry 3). The 1,1-disubstituted olefin **2.12** was also inert to the catalyst, resulting in dimerization of the terminal olefin **2.13**. Thus, the formation of C=C bond of the C4-branched sugar via cross metathesis was unsuccessful. Given time

limitations, I did not have the opportunity to explore the preparation of this compound further.

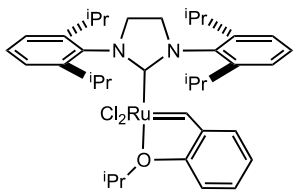
Table 2.5. Cross metathesis with different olefin metathesis catalysts.



Catalyst **A**



Catalyst **B**



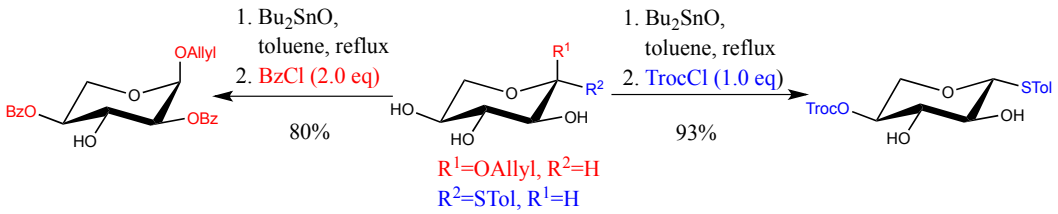
Entry	Catalyst	Olefin **2.13**	Olefin **2.12**	Desired Product
1	**A** (5 mol %)	2.0 eq	1.0 eq	No
2	**A (**20 mol %)	2.0 eq	1.0 eq	No
3	**B** (10 mol %)	2.0 eq	1.0 eq	No

2.8 Summary

In this chapter, I described approaches for preparing building blocks required for the synthesis of lipooligosaccharide (LOS) antigens from

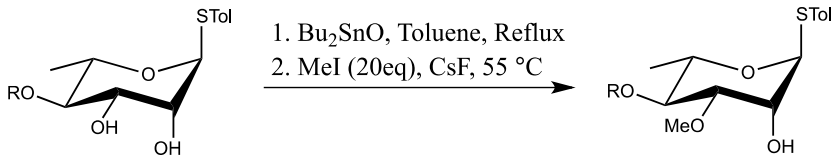
Mycobacterium gastri. Based on my retrosynthetic analysis, the target molecule LOS III from *Mycobacterium gastri* could be composited using eight different building blocks.

The key steps for synthesis of L-xylose building blocks **2.6** and **2.7** were the stannylidene-mediated protection of a xylopyranoside derivative (Scheme 2.26). The 2,4-*O*-di-benzoyl derivative could be obtained from allyl α-L-xylopyranoside in 80% yield and the 4-*O*-Troc derivative could be obtained from *p*-toluyl 1-thio-β-L-xylopyranoside in 93% yield. Both reactions are an efficient way to prepare 2,4-*O*-di-protected and 4-*O*-protected xylopyranoside derivatives. It is notable that the use of the electrophile was limited to acyl and carbonate groups. Attempts to use an alkyl halide as the electrophile failed.



Scheme 2.26. Key steps in the preparation of building blocks **2.6** and **2.7**.

The synthesis of the L-rhamnose building blocks was successful. Two analogues, containing a methyl group on O-3 and either an allyl group or a benzyl group on O-4 were synthesized. The 3-*O*-methyl group was introduced via formation of a stannylene acetal, followed by addition of methyl iodide (Scheme 2.27).

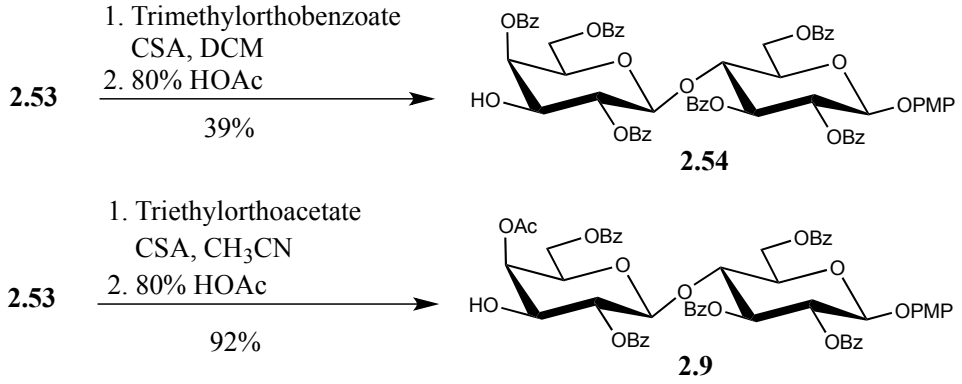


2.41, R=Allyl
2.42, R=Bn

2.46, R=Allyl
2.47, R=Bn

Scheme 2.27. Key steps in the synthesis of rhamnose building blocks.

The synthesis of lactose building block was also successful. The key step for the synthesis of lactose building block was selective protection the C-4 hydroxyl group on the galactose moiety (Scheme 2.28). This was achieved by treating diol **2.53** with trimethylorthobenzoate or triethylorthoacetate, leading to the formation of an orthoacetate. Acid catalyzed ring opening led to the formation of products containing acyl protecting groups on O-4.

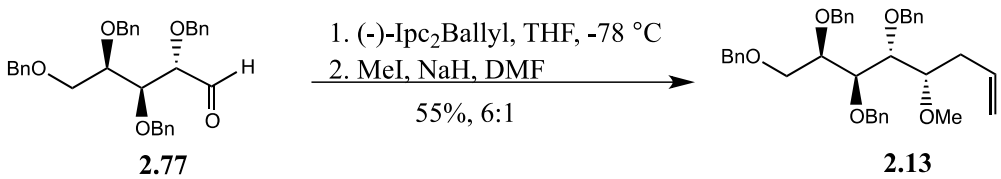


Scheme 2.28. Key steps in the synthesis of lactose building blocks **2.54** and **2.9**.

Although the intramolecular aglycone delivery (IAD) methodology had previously demonstrated success in the synthesis of α,α-trehalose, in my hands

this approach was problematic. In particular, the synthesis of the required DMB-α-glycoside was a multistep, time-consuming and low efficiency process. Moreover, the coupling reaction between the two synthesized building blocks gave poor yield and stereoselectivity. These discoveries led me to a different strategy. Direct glycosylation of two differentially-substituted glucose residues usually would give four possible stereoisomers as products: α,α, α,β, β,α and β,β. However, due to the role of anomeric effect, the β isomer only contributes a small portion to the products, especially the β,β isomer. Furthermore, the fact that one of the coupling partners is a 4,6-*O*-benzylidene protected glucose derivative made me confident in the effeciency of a direct glycosylation for the preparation of an α,α-trehalose building block.[127] In fact, the desired product could be obtained in 49% yield when I used a trichloroacetimidate as the donor.

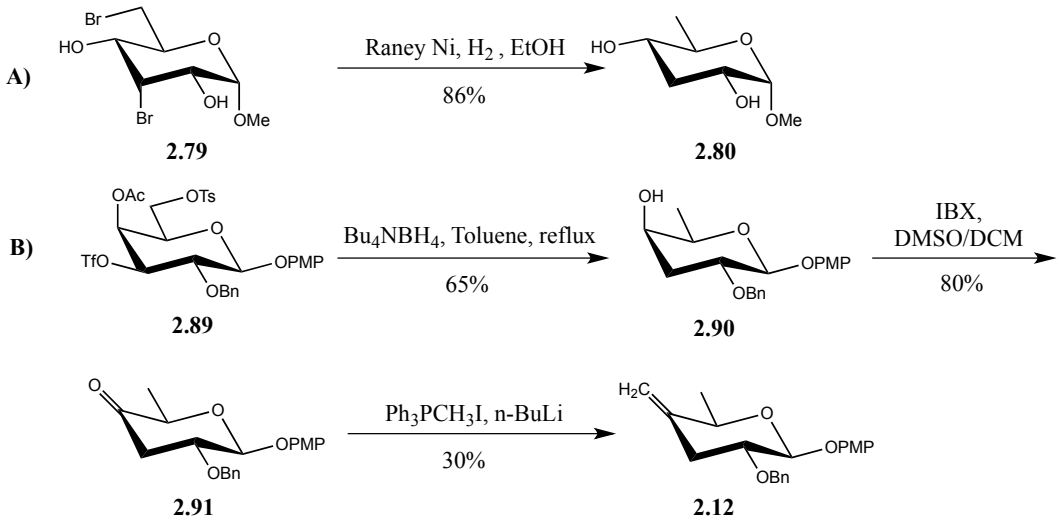
The synthesis of 3,6-dideoxy-4-C-branched sugar moiety was planned to be achieved through the olefin cross metathesis of two alkenes. Two olefin partners were synthesized successfully. The polyoxygenated olefin **2.13** was synthesized from L-lyxose. The key step was the asymmetric allylation of aldehyde **2.77**. After many experiments, the best result was 55% with 6:1 diastereoselectivity when using (–)-Ipc$_2$BAllyl at –78 °C (Scheme 2.29).



2.77 **2.13**

Scheme 2.29. Asymmetric allylation of **2.77**.

Two different approaches were explored for the synthesis of the 3,6-dideoxysugar alkene. The deoxygenation was successful both from 3,6-dibromo derivative **2.79** (Scheme 2.30A) and 3-*O*-triflyl-6-*O*-tosyl derivative **2.89** (Scheme 2.30B). The latter reaction was the key step for the preparation of 3,6-dideoxy derivative. The reaction could be conducted with tetrabutylammonium borohydride in toluene at reflux. After oxidation of alcohol **2.90** to ketone **2.91**, the olefin **2.12** was synthesized via a Wittig reaction.



Scheme 2.30. Key steps in the preparation of olefin **2.12**.

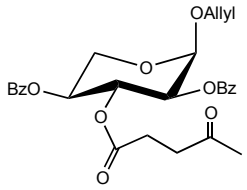
After I successfully synthesized the two olefin partners for the cross metathesis, the reaction was explored using two different catalyst, the Grubbs II catalyst and a modified Hoveyda–Grubbs catalyst. However, both were unsuccessful, likely due to the steric hindrance of the methyl group of the pyranose ring.

With all building blocks, except the branched chain-sugar synthesized, the coupling of the different building blocks into oligosaccharides was carried out. This will be discussed in the next chapter.

2.9 Experimental

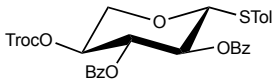
General methods for chemical synthesis: All reagents were purchased from commercial sources and were used without further purification unless noted. Reaction solvents were purified by successive passage through columns of alumina and copper under an argon atmosphere. All reactions were carried out under positive pressure of argon at room temperature unless specified and were monitored by TLC on silica gel 60-F254 (0.25 mm, Silicycle, Quebec, Canada). Visualization of the reaction components was achieved using UV fluorescence (254 nm) and/or by charring with a solution of H_2SO_4 in ethanol. Organic solvents were evaporated under reduced pressure at < 50 °C unless noted. The products were purified by column chromatography on silica gel (230–400 mesh, Silicycle, Quebec, Canada). The ratio between silica gel and crude product ranged from 100:1 to 20:1 (w/w). The yields reported are after purification. Optical rotations were measured on Perkin–Elmer 241 polarimeter at ambient temperature and are in units of degree•mL/(g•dm). ^{1}H NMR spectra were recorded at 400, 500 or 600 MHz and chemical shifts were referenced to $CHCl_3$ (7.26 ppm), CHD_2OD (3.30 ppm), HOD (4.79 ppm), CHD_2SOCD_3 (2.49 ppm). ^{13}C NMR spectra were recorded at 125 MHz and chemical shifts were referenced to $CDCl_3$ (77.06 ppm),

CD_3OD (49.0 ppm) and $(CD_3)SO$ (39.5 ppm). Assignments of NMR spectra were based on two-dimensional experiments (^1H–^1H COSY, HMQC or HSQC and HMBC) and the stereochemistry of the anomeric centers of the pyranose rings were confirmed by measuring $^1J_{C\text{-}1,H\text{-}1}$ via coupled HMQC or HSQC experiments if necessary. The monosaccharide residues in the disaccharide is labeled by a and b starting from the non-reducing end to the reducing end. Electrospray mass spectra were recorded on Agilent Technologies 6220 TOF.



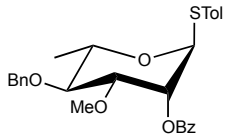
Allyl 2,4-di-*O*-benzoyl-3-*O*-levulinoyl-α-L-xylopyranoside (2.6). To a solution of **2.30** (3.26 g, 8.2 mmol) and levulinic acid (1.7 mL, 16.3 mmol) in CH_2Cl_2 (80 mL) was added DCC (3.36 g, 16.3 mmol) and DMAP (100 mg). The reaction mixture was stirred at room temperature for 4 h at which point the TLC showed completion of the reaction. CH_3OH was then added to the reaction mixture and then it was concentrated. The crude residue was purified by chromatography (5:1 hexanes–EtOAc) to yield **2.6** (3.05 g, 75%) as a colorless foam. R_f 0.29 (3:1 hexanes–EtOAc); $[\alpha]_D$ –62.4 (*c* 3.3, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.07–8.01 (m, 4H, Ar), 7.61–7.57 (m, 2H, Ar), 7.49–7.44 (m, 4H, Ar), 5.94 (app t, *J* = 9.9 Hz, 1H, H-2), 5.88–5.80 (m, 1H, CH_2=C<u>H</u>CH_2O), 5.32–5.23 (m, 3H, C<u>H</u>$_2$=CHCH_2O, H-4, H-1), 5.16–5.12 (m, 2H, C<u>H</u>$_2$=CHCH_2O, H-3), 4.24 (ddt, *J* = 13.2, 5.1, 1.5 Hz, 1H, CH_2=CHC<u>H</u>$_2O$), 4.05–4.01 (m, 2H, CH_2=CHC<u>H</u>$_2O$, H-5), 3.82 (app t, *J* = 10.8 Hz, 1H, H-5'), 2.56–2.53 (m, 2H, C<u>H</u>$_2$), 2.45–2.42 (m, 2H,

C<u>H</u>$_2$), 1.94 (s, 3H, C<u>H</u>$_3$).; ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 205.4 (C=O), 171.9 (C=O), 165.8 (C=O), 165.6 (C=O), 133.4 (Ar), 133.3 (Ar), 130.0 (CH_2=<u>C</u>HCH_2O), 129.9 (Ar), 129.23 (Ar), 129.21 (Ar), 128.50 (Ar), 128.48 (Ar), 117.7 (<u>C</u>H_2=CHCH_2O), 95.2 (C-1), 71.7 (C-3), 70.1 (C-4), 69.6 (C-2), 68.70 (CH_2=CH<u>C</u>H_2O), 58.7 (C-5), 37.9 (Lev <u>C</u>H_2), 28.1 (Lev <u>C</u>H_2); HRMS (ESI) calcd for $(M+Na)^+$ $C_{27}H_{28}O_9Na$: 519.1626. Found: 519.1620.



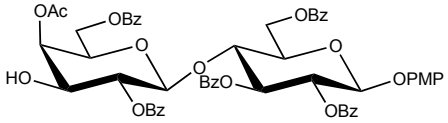
***p*-Tolyl 2,3-di-*O*-benzoyl-4-*O*-(2,2,2-trichloroethoxycarbonyl)-1-thio-β-L-xylopyranoside (2.7).** To a solution of **2.33** (7.34 g, 17.0 mmol) in pyridine (170 mL) was added benzoyl chloride (5.2 mL, 41.0 mmol) and DMAP (100 mg) with stirring and cooling at 0 °C. Upon addition of benzoyl chloride, the reaction mixture was stirred for 30 min before it was removed from the ice bath and then stirred overnight at which point TLC showed completion of the reaction. The mixture was diluted with EtOAc and ice was added. The pyridine was removed under reduced pressure and the resulting syrup was extracted with EtOAc. The organic extract was then washed with 1M HCl, a satd aq solution of $NaHCO_3$ and brine. The organic extract was dried (Na_2SO_4), filtered, concentrated and the resulting crude product was purified by chromatography (10:1 hexanes–EtOAc) to give **2.7** (10.0 g, 92%) as a white foam. R_f 0.5 (4:1 hexane–EtOAc); $[\alpha]_D$ +3.0 (*c* 1.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.08–8.06 (m, 4H, Ar), 7.58–7.53 (m, 2H, Ar), 7.44–7.39 (m, 6H, Ar), 7.13–7.11 (m, 2H, Ar), 5.61 (app t, *J* = 6.2

Hz, 1H, H-3), 5.41 (app t, J = 5.9 Hz, 1H, H-2), 5.19 (d, J = 5.7 Hz, 1H, H-1), 5.03 (app td, J = 6.2, 3.8 Hz, 1H, H-4), 4.72 (s, 2H, $Cl_3CC\underline{H}_2O$), 4.61 (dd, J = 12.6, 3.7 Hz, 1H, H-5), 3.85 (dd, J = 12.5, 6.1 Hz, 1H, H-5'), 2.33 (s, 3H, $ArC\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 165.1 (ArC=O), 165.0 (ArC=O), 153.2 (C=O), 138.5 (Ar), 133.7 (Ar), 133.4 (Ar), 133.1 (Ar), 130.14 (Ar), 130.07 (Ar), 129.9 (Ar), 129.3 (Ar), 129.2 (Ar), 128.8 (Ar), 128.6 (Ar), 128.5 (Ar), 94.1 ($Cl_3\underline{C}$), 86.5 (C-1), 77.0 ($Cl_3C\underline{C}H_2O$), 72.1 (C-4), 69.9 (C-3), 69.6 (C-2), 62.5 (C-5), 21.2 ($Ar\underline{C}H_3$); HRMS (ESI) calcd for $(M+Na)^+$ $C_{29}H_{25}{}^{35}Cl_3O_8SNa$: 661.0228. Found: 661.0228.



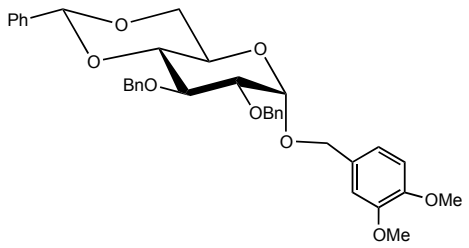
***p*-Tolyl 4-*O*-benzyl-2-*O*-benzoyl-3-*O*-methyl-1-thio-α-L-rhamnopyranoside (2.8).** To a solution of **2.47** (2.15 g, 5.7 mmol) in CH_2Cl_2 (50 mL) and pyridine (5 mL) was added benzoyl chloride (1.0 mL, 8.6 mmol) and DMAP (10 mg) with cooling and stirring. The solution was stirred for 4 h at which point TLC showed completion of the reaction. The reaction mixture was diluted with EtOAc and ice was added. The organic extract was washed with 1M HCl, water and brine. The organic extract was dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (15:1 hexanes–EtOAc) to yield **2.8** (2.48 g, 90%) as a colorless oil. R_f 0.26 (10:1 hexanes–EtOAc); $[\alpha]_D$ –119.4 (*c* 2.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.06–8.04 (m, 2H, Ar), 7.69 (tt, J = 7.5, 1.3 Hz, 1H, Ar), 7.60–7.52 (m, 2H, Ar), 7.48–7.44 (m, 2H, Ar), 7.40–7.30 (m, 5H, Ar), 7.13–

7.11 (m, 2H, Ar), 5.81 (dd, J = 3.2, 1.7 Hz, 1H, H-2), 5.47 (d, J = 1.4 Hz, 1H, H-1), 4.94 (d, J = 11.0 Hz, 1H, PhC$\underline{H}_2$), 4.69 (d, J = 11.0 Hz, 1H, PhC$\underline{H}_2$), 4.31 (ddq, J = 9.4, 6.2, 0.5 Hz, 1H, H-5), 3.77 (dd, J = 9.2, 3.2 Hz, 1H, H-3), 3.56 (app t, J = 9.4 Hz, 1H, H-4), 3.49 (s, 3H, OC$\underline{H}_3$), 2.32 (s, 3H, ArC$\underline{H}_3$), 1.39 (d, J = 6.2 Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 165.7 (C=O), 138.5 (Ar), 137.9 (Ar), 133.2 (Ar), 132.3 (2C, Ar), 130.2 (Ar), 129.9 (Ar), 129.9 (Ar), 128.4 (Ar), 128.39 (Ar), 128.1 (Ar), 127.7 (Ar), 86.6 (C-1), 80.8 (C-3), 80.3 (C-4), 75.4 (Ph$\underline{C}H_2$), 70.7 (C-2), 68.9 (C-5), 57.5 (O$\underline{C}H_3$), 21.1 (Ar$\underline{C}H_3$), 18.1 (C-6); HRMS (ESI) calcd for $(M + Na)^+$ $C_{28}H_{30}O_5SNa$: 501.1706. Found: 501.1701.



***p*-Methoxyphenyl 4-*O*-acetyl-2,6-di-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (2.9).** To a solution of **2.53** (146.7 mg, 0.15 mmol) in CH_3CN (3 mL) was added trimethyl orthoacetate (0.56 mL, 3.0 mmol) and camphorsulfonic acid (CSA) (5 mg) with stirring. The reaction mixture was stirred for 3 h and Et_3N was added when TLC showed complete consumption of the starting material. The mixture was concentrated to a syrup that was dissolved in 80% aqueous acetic acid (3 mL). This solution was stirred for 30 min at room temperature and the concentrated, with the residual solvent being co-evaporated with toluene. The crude product was purified by chromatography (4:1 hexanes–EtOAc) to give **2.9** (139.9 mg, 92%) as a white

foam. R_f 0.43 (1:1 hexanes–EtOAc); $[\alpha]_D$ +25.1 (*c* 4.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.06–8.03 (m, 6H, Ar), 7.98–7.95 (m, 4H, Ar), 7.61–7.33 (m, 15H, Ar), 6.87 (d, *J* = 8.9 Hz, 2H, Ar), 6.64 (d, *J* = 9.0 Hz, 2H, Ar), 5.78 (app t, *J* = 9.4 Hz, 1H, H-3b), 5.68 (dd, *J* = 9.4, 8.0 Hz, 1H, H-2b), 5.26 (d, *J* = 3.3 Hz, 1H, H-4a), 5.20 (dd, *J* = 9.6, 8.2 Hz, 1H, H-2a), 5.12 (d, *J* = 7.8 Hz, 1H, H-1b), 4.71–4.66 (m, 2H, H-1a, H-6b), 4.53 (dd, *J* = 11.8, 5.9 Hz, 1H, H-6b'), 4.22 (app t, *J* = 9.4 Hz, 1H, H-4b), 3.99–3.96 (m, 1H, H-5b), 3.88 (ddd, *J* = 9.8, 6.1, 3.7 Hz, 1H, H-3a), 3.79 (dd, *J* = 11.0, 6.2 Hz, 1H, H-6a), 3.70–3.68 (m, 4H, $OC\underline{H}_3$, H-5a), 3.57 (dd, *J* = 11.0, 6.8 Hz, 1H, H-6a'), 2.72 (d, *J* = 6.3 Hz, 1H, O<u>H</u>-3a), 2.01 (s, 3H, $C\underline{H}_3C{=}O$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 170.6 (C=O), 166.4 (C=O), 165.9 (C=O), 165.7 (C=O), 165.4 (C=O), 165.2 (C=O), 155.7 (Ar), 151.0 (Ar), 133.5 (Ar), 133.44 (Ar), 133.36 (Ar), 133.29 (Ar), 133.25 (Ar), 129.88 (Ar), 129.84 (Ar), 129.82 (Ar), 129.78 (Ar), 129.62 (Ar), 129.59 (Ar), 129.55 (Ar), 129.52 (Ar), 129.2 (Ar), 128.9 (Ar), 128.7 (Ar), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 128.3, 118.9 (Ar), 114.4 (Ar), 100.7 (C-1b), 100.5 (C-1a), 75.9 (C-4b), 73.5 (C-2a), 73.2 (C-5b), 72.7 (C-3b), 71.6 (C-2b), 71.5 (C-3a), 71.3 (C-5a), 69.4 (C-4a), 62.8 (C-6b), 61.4 (C-6a), 55.6 ($O\underline{C}H_3$), 20.6 ($\underline{C}H_3C{=}O$); HRMS (ESI) calcd for $(M + Na)^+$ $C_{56}H_{50}O_{18}Na$: 1033.2889. Found: 1033.2880.

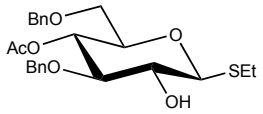


3,4-dimethoxybenzyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (2.10).

Method A:[91,126] To a solution of **2.59** (905.6 mg, 1.85 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added iodotrimethylsilane (0.3 mL, 2.0 mmol) and the reaction mixture was allowed to stir for 1 h. The solvent was then evaporated and the resulting oil was dissolved in toluene and evaporated (4 times). The residue was dissolved with CH_2Cl_2 and the resulting solution was added to a stirring solution of *n*-Bu_4NI (1.36 g, 3.70 mmol), 3,4-dimethoxybenzyl alcohol (0.5 mL, 3.4 mmol), DIEA (0.7 mL, 4.0 mmol) and 4 Å molecular sieves in CH_2Cl_2 (10 mL). The reaction mixture was heated at reflux for 16 h, at which time the solvent was evaporated. The resulting oil was purified by chromatography (6:1 hexanes–EtOAc) to yield **2.10** (596.9 mg, 30%) as a colorless oil.

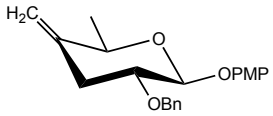
Method B: To a solution of **2.58** (749.3 mg, 1.5 mmol), 3,4-dimethoxybenzyl chloride (0.27 mL, 1.9 mmol) and 4Å molecular sieves (600 mg) in toluene (5 mL) and ether (15 mL) was added NIS (410.4 mg, 1.8 mmol) at room temperature with stirring. The mixture was allowed to stir for 10 min before it was cooled to –30 °C. The mixture was added 0.1 M TMSOTf in ether (0.7 mL, 0.07 mmol) and the color turned dark red immediately. The reaction mixture was stirred for 30 min. When TLC showed completion of the reaction, Et_3N was added. The reaction mixture was then washed with a satd aq solution of $Na_2S_2O_3$, water and brine. The

organic extract was dried (Na_2SO_4), filtered, concentrated and the crude residue was purified by chromatography (6:1 hexanes–EtOAc) to give **2.10** (611.6 mg, 67%) as a white foam. R_f 0.38 (2:1 hexanes–EtOAc); $[\alpha]_D$ +34.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.51–7.49 (m, 2H, Ar), 7.40–7.36 (m, 5H, Ar), 7.32–7.24 (m, 8H, Ar), 6.96–6.93 (m, 2H, Ar), 6.84 (d, *J* = 8.0 Hz, 1H, Ar), 5.56 (s, 1H, benzylidene C<u>H</u>), 4.93 (d, *J* = 11.3 Hz, 1H, PhC<u>H</u>$_2$), 4.85 (d, *J* = 11.1 Hz, 1H, PhC<u>H</u>$_2$), 4.84 (d, *J* = 3.7 Hz, 1H, H-1), 4.74 (d, *J* = 12.0 Hz, 1H, PhC<u>H</u>$_2$), 4.69 (d, *J* = 12.1 Hz, 1H, PhC<u>H</u>$_2$), 4.57 (d, *J* = 12.0 Hz, 1H, PhC<u>H</u>$_2$), 4.53 (d, *J* = 12.1 Hz, 1H, PhC<u>H</u>$_2$), 4.26 (dd, *J* = 10.2, 4.9 Hz, 1H, H-6), 4.11 (app t, *J* = 9.3 Hz, 1H, H-3), 3.98–3.90 (m, 4H, H-5, OC<u>H</u>$_3$), 3.81 (s, 3H, OC<u>H</u>$_3$), 3.72 (app t, *J* = 10.3 Hz, 1H, H-6), 3.63 (app t, *J* = 9.4 Hz, 1H, H-4), 3.56 (dd, *J* = 9.3, 3.8 Hz, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 149.1 (Ar), 149.0 (Ar), 138.9 (Ar), 138.2 (Ar), 137.5 (Ar), 129.3 (Ar), 129.0 (Ar), 128.36 (Ar), 128.33 (Ar), 128.27 (Ar), 128.0 (Ar), 127.77 (Ar), 127.76 (Ar), 127.6 (Ar), 126.1 (Ar), 121.4 (Ar), 111.8 (Ar), 110.9 (Ar), 101.3 (Ph<u>C</u>H), 95.9 (C-1), 82.3 (C-4), 79.3 (C-2), 78.8 (C-3), 75.4 (Ph<u>C</u>H$_2$), 73.4 (Ph<u>C</u>H$_2$), 69.2 (Ph<u>C</u>H$_2$), 69.0 (C-6), 62.7 (C-5), 56.0 (O<u>C</u>H$_3$), 55.9 (O<u>C</u>H$_3$); HRMS (ESI) calcd for $(M + Na)^+$ $C_{36}H_{38}O_8Na$: 621.2459. Found: 621.2455.

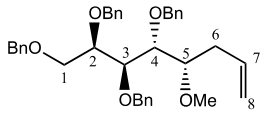


Ethyl 4-*O*-acetyl-3,6-di-*O*-benzyl-1-thio-β-D-glucopyranoside (2.11).

To a solution of **2.63** (5.05 g, 8.1 mmol) in THF (60 mL) and acetic acid (15 mL) was added zinc powder with vigorous stirring. The reaction mixture was stirred for 30 min at which point TLC showed completion of the reaction. The mixture was filtered through a pad of Celite and the filtrate was co-evaporated with toluene. The residue was dissolved in EtOAc and the organic solution was washed with a satd aq solution of $NaHCO_3$, water and brine. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting syrup was purified by chromatography (6:1 hexanes–EtOAc) to yield **2.11** (3.41 g, 94%) as a white foam. R_f 0.45 (2:1 hexanes–EtOAc); $[\alpha]_D$ –38.5 (*c* 3.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.29–7.20 (m, 10H, Ar), 4.94 (app t, *J* = 9.4 Hz, 1H, H-4), 4.79 (d, *J* = 11.8 Hz, 1H, $PhCH_2$), 4.66 (d, *J* = 11.8 Hz, 1H, $PhCH_2$), 4.47, 4.45 (ABq, *J* = 12.1 Hz, 2H, $PhC\underline{H}_2$), 4.29 (d, *J* = 9.4 Hz, 1H, H-1), 3.55–3.47 (m, 5H, H-2, H-3, H-5, H-6, H-6'), 2.74–2.63 (m, 2H, SCH_2CH_3), 2.39 (d, *J* = 1.9 Hz, 1H, OH-2), 1.82 (s, 3H, $C\underline{H}_3C$=O), 1.27 (t, *J* = 7.4 Hz, 3H, $SCH_2C\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 169.8 (C=O), 138.3 (Ar), 137.9 (Ar), 128.4 (Ar), 128.3 (Ar), 127.81 (Ar), 127.78 (Ar), 127.71 (Ar), 127.65 (Ar), 86.1 (C-1), 82.9 (C-3), 77.8 (C-5), 74.5 ($Ph\underline{C}H_2$), 73.6 ($Ph\underline{C}H_2$), 73.0 (C-2), 70.6 (C-4), 69.8 (C-6), 24.3 ($\underline{C}H_3C$=O), 20.8 ($S\underline{C}H_2CH_3$), 15.4 ($SCH_2\underline{C}H_3$); HRMS (ESI) calcd for $(M + Na)^+$ $C_{24}H_{30}O_6SNa$: 469.1655. Found: 469.1647.



4-Methoxyphenol 2-*O*-benzyl-3,6-dideoxy-4-deoxy-4-C-methylene-β-D-*erythro*-hexopyranosid-4-ulose (2.12). To a solution of methyltriphenylphosphonium iodide (1.21 g, 3 mmol) in ether (15 mL) was added a 2.5 M solution of n-BuLi (1.0 mL, 2.5 mmol) dropwise with stirring and cooling at –78 °C. The reaction mixture was stirred for 1 h at –40 °C. A solution of ketone **2.91** (912.1 mg, 2.7 mmol) in ether was added to the reaction mixture dropwise at –40 °C. The reaction mixture was slowly warmed to 0 °C and stirred for 30 min at that temperature. The reaction mixture was filtered and the filtrate was extracted with water. The organic extract was dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (12:1, hexanes–EtOAc) to give **2.12** (260.2 mg, 30%) as light yellow syrup. R_f 0.26 (10:1, hexanes–EtOAc); $[\alpha]_D$ –19.5 (*c* 2.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.39–7.27 (m, 5H, Ar), 7.06–7.04 (m, 2H, Ar), 6.86–6.84 (m, 2H, Ar), 5.06 (d, *J* = 6.8 Hz, 1H, H-1), 4.90–4.87 (m, 3H, $=CH_2$, $PhCH_2$), 4.74 (d, *J* = 11.9 Hz, 1H, $PhCH_2$), 4.15 (q, *J* = 6.3 Hz, 1H, H-5), 3.79 (s, 3H, $OC\underline{H}_3$), 3.62 (ddd, *J* = 10.1, 6.6, 5.5 Hz, 1H, H-2), 2.83 (dd, *J* = 13.8, 5.4 Hz, 1H, H-3), 2.39 (ddt, *J* = 13.8, 10.2, 1.9 Hz, 1H, H-3), 1.39 (d, *J* = 6.4 Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 155.0 (Ar), 151.5 (Ar), 144.1 (Ar), 138.6 ($CH_2=\underline{C}$), 128.4 (Ar), 127.8 (Ar), 127.6 (Ar), 118.2 (Ar), 114.5 (Ar), 109.6 ($\underline{C}H_2=C$), 103.3 (C-1), 77.0 (C-2), 72.6 ($Ph\underline{C}H_2$), 72.3 (C-5), 55.7 ($O\underline{C}H_3$), 37.3 (C-3), 18.0 (C-6); HRMS (ESI) calcd for $(M+Na)^+$ $C_{21}H_{24}O_4Na$: 363.1567. Found: 363.1559.

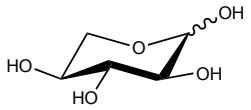


6,7,8-trideoxy-5-*O*-methyl-1, 2, 3, 4-tetra-*O*-benzyl-D-*galacto*-oct-7-enitol (2.13).

General method using $TiCl_4$: To a solution of aldehyde **2.77** (550.0 mg, 1.1 mmol) and allyltrimethylsilane (860 μL, 5.5 mmol) in CH_2Cl_2 (10 mL) was added $TiCl_4$ (140 μL, 1.3 mmol) at –97 °C. The reaction mixture was stirred for 30 min, diluted with CH_2Cl_2 and then an aqueous solution of $NaHCO_3$ was added before it was brought to room temperature. The reaction mixture was washed with water and brine before the organic layer was dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (7:1 hexanes–EtOAc) to give a diastereomeric mixture of products (22%).

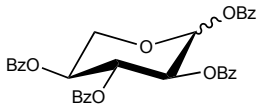
Use of (–)-Ipc_2BAllyl: To a solution of aldehyde **2.77** (500 mg, 1.0 mmol) in Et_2O (10 mL) was added (–)-Ipc_2BAllyl dropwise at –78 °C. The reaction mixture was stirred at –78 °C for 1 h and then warmed to room temperature and treated with 3M NaOH (0.7 mL) followed by 30% H_2O_2 (0.35 mL). The reaction mixture was then heated at reflux for 1 h, cooled to room temperature and extracted with EtOAc. The organic extract was washed with water and brine before being dried (Na_2SO_4), filtered and concentrated. The crude product was dried under high vacuum overnight. The dried product was dissolved in DMF (10 mL) and then treated with 60% NaH dispersion in mineral oil (80 mg, 2.0 mmol) followed by addition of CH_3I (79 μL, 1.3 mmol). The reaction mixture was stirred at room temperature for 1 h and upon completion of the reaction as determined by TLC,

the mixture was diluted with EtOAc. The organic liquid was washed with water and brine before being dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (15:1 hexanes–EtOAc) to give **2.13** (261.3 mg, 47%) and its diastereomer (45.8 mg, 8%) both as light yellow oils. Data for the major isomer **2.13**: R_f 0.38 (6:1 hexanes–EtOAc); $[\alpha]_D$ −9.5 (*c* 1.9, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.38–7.26 (m, 20H, Ar), 5.86–5.78 (m, 1H, H-7), 5.09 (app t, *J* = 1.3 Hz, 1H, H-8), 5.08–5.06 (m, 1H, H-8'), 4.80 (d, *J* = 12.0 Hz, 1H, $PhCH_2$), 4.72 (d, *J* = 11.6 Hz, 1H, $PhCH_2$), 4.66–4.59 (m, 4H, $PhCH_2$), 4.51–4.45 (m, 2H, $PhCH_2$), 4.03 (app dt, *J* = 5.6, 3.2 Hz, 1H, H-2), 3.97 (dd, *J* = 7.0, 3.2 Hz, 1H, H-3), 3.82 (dd, *J* = 7.0, 3.3 Hz, 1H, H-4), 3.75 (dd, *J* = 10.0, 5.9 Hz, 1H, H-1), 3.70 (dd, *J* = 10.0, 5.3 Hz, 1H, H-5), 3.61 (ddd, *J* = 7.2, 6.1, 3.3 Hz, 1H, H-5'), 3.42 (s, 3H, $OC\underline{H}_3$), 2.55–2.49 (m, 1H, H-6), 2.43 (dtt, *J* = 14.4, 7.2, 1.2 Hz, 1H, H-6'); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 139.0 (Ar), 138.8 (Ar), 138.7 (Ar), 138.3 (Ar), 135.1 (C-7), 128.4 (Ar), 128.3 (Ar), 128.25 (Ar), 128.24 (Ar), 127.9 (Ar), 127.8 (Ar), 127.72 (Ar), 127.68 (Ar), 127.59 (Ar), 127.54 (Ar), 127.42 (Ar), 127.39 (Ar), 117.2 (C-8), 80.3 (C-5), 79.7 (C-4), 78.5 (C-3), 78.2 (C-2), 74.0 ($Ph\underline{C}H_2$), 73.9 ($Ph\underline{C}H_2$), 73.3 ($Ph\underline{C}H_2$), 72.5 ($Ph\underline{C}H_2$), 70.7 (C-1), 57.6 ($O\underline{C}H_3$), 34.6 (C-6); HRMS (ESI) calcd for $(M + Na)^+$ $C_{37}H_{42}O_5Na$: 589.2924. Found: 589.2912.



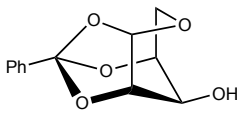
L-xylopyranose (2.16).[95] To a solution of D-glucitol (250 g, 1.37 mol) in water (250 mL) and 37% hydrochloric acid (25 mL), benzaldehyde (140 mL, 1.38 mol) was added with efficient stirring under argon. The reaction mixture was stirred at room temperature before it was stored at 0 °C overnight. Water was added to the reaction mixture with stirring to facilitate filtration. After filtration, the solid was washed with cold water, absolute ethanol and hexanes. The product was re-dissolved in pre-heated water containing sodium carbonate (25 g) to neutralize the remaining acidity. After filtration to remove insoluble impurities, the solution was brought to 0 °C and crystals. The crystals were filtered and washed with cold water, absolute ethanol and hexanes. The product was collected and dried under vacuum, giving **2.14** (210 g, 57%) as a colorless solid. To a suspension of **2.14** (50 g, 0.19 mol) in water (100 mL) was added sodium metaperiodate (43.3 g, 0.4 mol) with stirring and cooling in an ice-bath at 0 °C. After 15 min, the reaction mixture was brought to room temperature and kept stirring for another 15 min. Inorganic salts were precipitated by addition of absolute ethanol (150 mL) and then filtered by vacuum filtration. The salts were washed absolute ethanol (100 mL) and the filtrate was concentrated to thick syrup, containing 2,4-*O*-benzylidene-L-xylose (**2.15)**. The above concentrated solution of **2.15** was then diluted with acetic acid (10 mL) and water (200 mL). The solution was brought to a boil in an open flask. Upon completion of hydrolysis, as determined by TLC analysis, the solution was concentrated under reduced pressure. The resulting

syrup was dissolved in absolute ethanol and α-L-xylose was allowed to crystallize at room temperate and later in the refrigerator at +4 °C. The crystalline solid was removed by filtration, washed with cold absolute ethanol and hexanes and dried under vacuum to give L-xylose **2.16** (23 g, 75%) as colorless crystals. $[\alpha]_D$ –18.1 (*c* 1.9, H_2O); ^1H NMR (500 MHz, D_2O, δ_H) 5.22 (d, *J* = 3.7 Hz, H-1α), 4.60 (d, *J* = 7.9 Hz, H-1β), 3.96 (dd, *J* = 11.5, 5.5 Hz, H-5β), 3.73–3.61 (m, H-5β, H-5α, H-4α, H-3α), 3.55 (dd, *J* = 9.4, 3.7 Hz, H-2α), 3.46 (app t, *J* = 9.3 Hz, H-3β), 3.35 (t, *J* = 11.1 Hz, H-5β), 3.25 (dd, *J* = 9.3, 7.9 Hz, H-2β). ^{13}C NMR (125 MHz, D_2O, δ_H) 96.7 (C-1β), 92.3 (C-1α), 75.9 (C-3β), 74.1 (C-2β), 72.9 (C-3α), 71.5 (C-2α), 69.4 (C-4α), 69.3 (C-4β), 65.2 (C-5β), 60.97 (C-5α); HRMS (ESI) calcd for $(M + Na)^+$ $C_5H_{10}O_5Na$: 173.0420. Found: 172.0422.



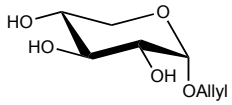
1,2,3,4-tetra-*O*-benzoyl-L-xylopyranose (2.17). To a solution of **2.16** (1.5 g, 10 mmol) in pyridine (20 mL) was added benzoyl chloride (7.0 mL, 60 mmol) and DMAP (10 mg) with stirring and cooling at 0 °C. After 30 min, the reaction mixture was brought to room temperature and kept stirring for 12 h. At that point, TLC showed the completion of the reaction and CH_3OH (20 mL) was added to quench the excess benzoyl chloride. The pyridine was removed by evaporation under reduced pressure and the residue was diluted with CH_2Cl_2. The organic solution was washed with 1M HCl, a satd aq solution of $NaHCO_3$ and brine. The organic extract was dried (Na_2SO_4), filtered, concentrated and the resulting crude product was purified by chromatography (15:1 hexanes–EtOAc) to yield **20** (5.4 g,

95%) as a white foam. R_f 0.63 (2:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H): 8.18–7.90 (m, 7H, Ar), 7.66–7.31 (m, 10H, Ar), 6.78 (d, *J* = 3.6 Hz, 0.58H, H-1α), 6.38 (d, *J* = 4.5 Hz, 0.42H, H-1β), 6.29 (app t, *J* = 9.8 Hz, 0.58H, H-3α), 5.84 (app t, *J* = 6.0 Hz, 0.42H, H-3β), 5.64 (m, 1H, H-2β, H-2α), 5.56 (dt, *J* = 10.1, 5.6 Hz, 0.58H, H-4α), 5.41 (dt, *J* = 5.7, 3.8 Hz, 0.42H, H-4β), 4.59 (dd, *J* = 12.6, 3.6 Hz, 0.42H, H-5β), 4.32 (dd, *J* = 11.3, 5.7 Hz, 0.58H, H-5α), 4.06 (app t, *J* = 11.1 Hz, 0.58H, H-5α), 4.01 (dd, *J* = 12.4, 5.4 Hz, 0.42H, H-5β); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C): 92.2 (C-1β), 90.3 (C-1α), 70.3 (C-2α), 70.0 (C-3α), 69.5 (C-4α,) 69.1 (C-2β), 68.5 (C-3β), 68.1 (C-4β), 61.8 (C-5β), 61.3 (C-5α); HRMS (ESI) calcd for $(M + NH_4)^+$ $C_{33}H_{26}O_9NH_4$: 584.1915. Found: 584.1908.



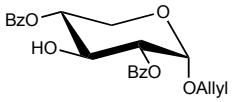
α-L-xylopyranose 1,2,4-orthobenzoate (2.20).[99] To a solution of **2.17** (5.4g, 9.5 mmol) in CH_2Cl_2 (50 mL) was added HBr•HOAc (2.7 mL, 15 mmol) under argon. The reaction mixture was sealed with a septum and allowed to stir overnight. During the reaction, a white solid precipitated from the solution. The reaction mixture was filtered and the solid was washed with acetic acid. The solid was collected and dried under high vacuum. Without further purification, a solution of **2.18** in nitromethane (25 mL) was treated with Et_3N (5 mL) and CH_3OH (0.5 mL). The reaction mixture was allowed to stand at 37 °C for 2 days before $CHCl_3$ was added. The organic extract was washed with water, a satd aq solution of $NaHCO_3$ and brine. The organic extract was dried (Na_2SO_4), filtered and concentrated

under reduced pressure at < 40 °C. The resulting dark brown residue was dissolved in CH_3OH and then treated with 1M $NaOCH_3$ solution in CH_3OH (1 mL). The reaction mixture was allowed to stir for 2 h before water was added. The residue was extracted with $CHCl_3$ (4 × 15 mL). The organic extract was washed with water (3 × 10 mL) and brine (10 mL). The organic extract was dried (Na_2SO_4), filtered and concentrated to a syrup. The residue was added to hexanes (20 mL). The mixture was shaken well and allowed to stand for 5 h before the hexane was decanted. The residue **2.19** was dried under vacuum for 2 h. To a solution of **2.19** in CH_3CN (50 mL) was added silica gel (10 g). The reaction mixture was stirred at room temperature for 12 h before it was filtered through a short pad of Celite. The solvent was evaporated under reduced pressure and the resulting crude product was purified by chromatography (2:1 CH_2Cl_2–EtOAc) to yield **2.20** (210 mg, 9%) as a colorless solid. R_f 0.31 (1:1 CH_2Cl_2–EtOAc). The obtained data matched that reported previously.[140]



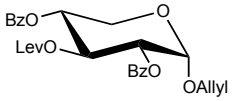
Allyl α-D-xylopyranoside (2.21).[141,142] To a solution of D-xylose (50 g, 0.33 mol) in allyl alcohol (200 mL) was added acetyl chloride (50 mL) dropwise with stirring at 0 °C. Upon completion of the addition of acetyl chloride, the reaction mixture was brought to room temperature and was allowed to stir for 15 h. Then, solid $NaHCO_3$ (20 g) was added slowly and the solution was stirred for 30 min. The remaining salt was filtered and the filtrate was concentrated to a syrup. The crude residue was purified by chromatography (1:4 hexanes–acetone) to yield

2.21 (11.6 g, 61%, α:β 5:1). Crystallization from EtOAc yielded **2.21** (9.5 g, 50%) as a white crystalline material. R_f 0.46 (1:4 hexanes–acetone); $[\alpha]_D$ +150.3 (*c* 1.3, CH_3OH); ^1H NMR (500 MHz, CD_3OD, δ_H) 5.97 (dddd, *J* = 16.9, 11.0, 5.6 Hz, 1H, CH_2=C<u>H</u>CH_2O), 5.34 (dd, *J* = 17.3, 1.6 Hz, 1H, C<u>H</u>$_2$=CHCH_2O), 5.18 (dd, *J* = 10.5, 1.2 Hz, 1H, C<u>H</u>$_2$=CHCH_2O), 4.78 (d, *J* = 3.7 Hz, 1H, H-1), 4.19 (dd, *J* = 13.0, 5.2 Hz, 1H, CH_2=CHC<u>H</u>$_2O$), 4.02 (dd, *J* = 13.0, 6.0 Hz, 1H, CH_2=CHC<u>H</u>$_2O$), 3.63–3.45 (m, 4H, H-3, H-4, H-5 × 2), 3.39 (dd, *J* = 9.5, 3.7 Hz, 1H, H-2); ^{13}C NMR (125 MHz, CD_3OD, δ_H): 135.6 (CH_2=<u>C</u>HCH_2O), 117.5 (<u>C</u>H$_2$=CHCH_2O), 99.5 (C-1), 75.2 (C-3), 73.6 (C-2), 71.5 (C-4), 69.4 (CH_2=CH<u>C</u>H$_2O$), 63.08 (C-5). The ^1H NMR and ^{13}C NMR data matched that reported.[141,142]



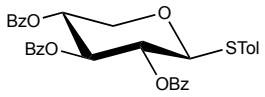
Allyl 2,4-di-*O*-benzoyl-α-D-xylopyranoside (2.22). To a solution of **2.21** (950.8 mg, 5.0 mmol) in toluene (80 mL) was added *n*-Bu_2SnO (1.37 g, 5.5 mmol). The mixture was stirred at reflux for 4 h with the azeotropic removal of water (Dean–Stark trap). The resulting solution was cooled under argon in an ice-water bath and stirred while the benzoyl chloride (1.3 mL, 11 mmol) was added via a syringe. The reaction mixture was allowed to stir for 2 h at which point the TLC showed completion of the reaction and then CH_3OH was added. The mixture concentrated to a syrup and the resulting crude residue was purified by chromatography (2:1 hexanes–EtOAc) to give **2.22** (1.52 g, 76%) as a light yellow syrup. R_f 0.34 (3:1 hexanes–EtOAc); $[\alpha]_D$ +70.8 (*c* 4.7, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H)

8.10–8.03 (m, 4H, Ar), 7.58–7.54 (m, 2H), 7.45–7.40 (m, 4H, Ar), 5.89–5.82 (m, 1H, CH_2=C<u>H</u>CH_2O), 5.31 (app dq, *J* = 17.2, 1.6 Hz, 1H, C<u>H</u>$_2$=$CHCH_2O$), 5.21–5.14 (m, 3H, H-4, H-1, C<u>H</u>$_2$=$CHCH_2O$), 5.07 (dd, *J* = 9.7, 3.6 Hz, 1H, H-2), 4.47 (app t, *J* = 9.4 Hz, 1H, H-3), 4.23 (ddt, *J* = 13.3, 5.1, 1.5 Hz, 1H, CH_2=CHC<u>H</u>$_2O$), 4.02 (ddt, *J* = 13.3, 5.9, 1.4 Hz, 1H, CH_2=CHC<u>H</u>$_2O$), 3.96 (dd, *J* = 10.9, 5.8 Hz, 1H, H-5), 3.78 (app t, *J* = 10.7 Hz, 1H, H-5); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.3 (C=O), 166.2 (C=O), 133.48 (CH_2=<u>C</u>HCH_2O), 133.35 (Ar), 133.31 (Ar), 129.9 (Ar), 129.8 (Ar), 129.5 (Ar), 129.4 (Ar), 128.5 (2C, Ar), 117.5 (<u>C</u>H_2=$CHCH_2O$), 95.4 (C-1), 73.9 (C-2), 72.4 (C-4), 69.7 (C-3), 68.6 (CH_2=CH<u>C</u>H_2O), 58.8 (C-5); HRMS (ESI) calcd for $(M+Na)^+$ $C_{22}H_{22}O_7Na$: 421.1258. Found: 421.1259.



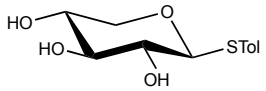
Allyl 2,4-di-*O*-benzoyl-3-*O*-levulinoyl-α-D-xylopyranoside (2.23). To a solution of **2.22** (1.38 g, 3.5 mmol) and levulinic acid (0.7 mL, 7 mmol) in CH_2Cl_2 (35 mL) was added DCC (1.44 g, 7 mmol) and DMAP (35 mg). The reaction mixture was stirred at room temperature for 4 h at which point the TLC showed completion of the reaction. CH_3OH was then added to the reaction mixture and then it was evaporated. The crude residue was purified by chromatography (5:1 hexanes–EtOAc) to yield **2.23** (1.27 g, 73%) as a colorless foam. R_f 0.28 (3:1 hexanes–EtOAc); $[\alpha]_D$ +64.3 (*c* 2.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.04–7.97 (m, 4H, Ar), 7.56–7.51 (m, 2H, Ar), 7.44–7.39 (m, 4H, Ar), 5.91 (app t, *J* = 9.9 Hz, 1H, Ar, H-2), 5.83–5.76 (m, 1H, CH_2=C<u>H</u>CH_2O),

5.28–5.21 (m, 3H, C<u>H</u>$_2$=CHCH$_2$O, H-4, H-1), 5.13–5.08 (m, 2H, C<u>H</u>$_2$=CHCH$_2$O, H-3), 4.20 (ddt, *J* = 13.3, 5.0, 1.5 Hz, 1H, CH$_2$=CHC<u>H</u>$_2$O), 4.02–3.96 (m, 2H, CH$_2$=CHC<u>H</u>$_2$O, H-5), 3.79 (app t, *J* = 10.8 Hz, 1H, H-5'), 2.51–2.48 (m, 2H, C<u>H</u>$_2$), 2.40–2.37 (m, 2H, CH$_2$), 1.88 (s, 3H, C<u>H</u>$_3$); ^{13}C NMR (125 MHz, CD$_3$OD, δ_C) 205.1 (C=O), 171.7 (C=O), 165.5 (C=O), 165.3 (C=O), 133.2 (Ar), 133.2 (Ar), 129.8 (CH$_2$=<u>C</u>HCH$_2$O), 129.7 (Ar), 129.05 (Ar), 129.04 (Ar), 128.31 (Ar), 128.29 (Ar), 117.4 (<u>C</u>H$_2$=CHCH$_2$O), 95.0 (C-1), 71.5 (C-3), 69.9 (C-4), 69.4 (C-2), 68.4 (CH$_2$=CH<u>C</u>H$_2$O), 58.5 (C-5), 37.7 (Lev <u>C</u>H$_2$), 27.9 (Lev <u>C</u>H$_2$); HRMS (ESI) calcd for (M+NH$_4$)$^+$ $C_{27}H_{28}O_9NH_4$: 514.2072. Found: 514.2077.

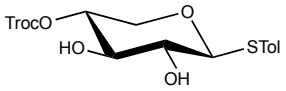


***p*-Tolyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-xylopyranoside (2.25).** To a solution of **2.24**[143] (5.67 g, 10.0 mmol) and *p*-thiocresol (2.53 g, 18.0 mmol) in CH_2Cl_2 (50 mL) was added BF_3•OEt_2 (2.5 mL, 20.0 mmol) slowly via a syringe with stirring and cooling at 0 °C. After the addition of BF_3•OEt_2, the reaction mixture was allowed to stir for 4 h at 0 °C. When TLC showed completion of reaction, the mixture was diluted with CH_2Cl_2 and ice was added. The organic liquid was washed with water and brine. The organic phase was dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (8:1, hexanes–EtOAc) to yield **2.25** (5.33 g, 94%) as a colorless foam. R_f 0.46 (4:1, hexanes–EtOAc); $[\alpha]_D$ −21.3 (*c* 1.9, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 8.05−7.99 (m, 6H, Ar), 7.56−7.34 (m, 12H, Ar), 7.16−7.14 (m, 2H, Ar), 5.77 (app t, *J* = 6.9 Hz, 1H, H-3), 5.44 (app t, *J* = 6.6 Hz, 1H, H-2), 5.30 (m, H-4), 5.20 (d, *J* = 6.4 Hz, 1H,

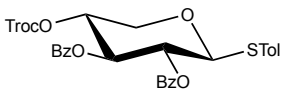
H-1), 4.69 (dd, J = 12.2, 4.1 Hz, 1H, H-5), 3.80 (dd, J = 12.2, 6.8 Hz, 1H, H-5'), 2.36 (s, 3H, ArC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 165.7 (C=O), 165.4 (C=O), 164.1 (C=O), 134.0 (Ar), 133.7 (Ar), 133.5 (Ar), 133.3 (Ar), 130.2 (Ar), 130.1 (Ar), 129.79 (Ar), 129.76 (Ar), 129.0 (Ar), 128.8 (Ar), 128.7 (Ar), 128.5v, 128.4 (Ar), 91.4 (C-1), 71.3 C (C-3), 69.9 (C-2), 69.8 (C-4), 69.4 (C-5), 17.8 (Ar$\underline{C}H_3$); HRMS (ESI) calcd for $(M+Na)^+$ $C_{33}H_{28}O_7SNa$: 591.1448. Found: 591.1441.



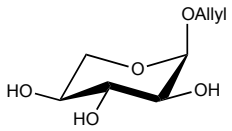
***p*-Tolyl 1-thio-β-D-xylopyronoside (2.26).**[144] A solution of **2.25** (7.2 g, 12.7 mmol) in CH_2Cl_2 (60 mL) and CH_3OH (60 mL) was treated with 1M $NaOCH_3$ in CH_3OH (3.8 mL). After stirring for 4 h, TLC showed completion of the reaction. The reaction mixture was neutralized with Amberlite IR-120 H^+ resin, filtered and concentrated. The crude residue was purified by chromatography (15:1 CH_2Cl_2–CH_3OH) to give **2.26** (3.24 g, quantitative) as a white foam. R_f 0.35 (10:1 CH_2Cl_2–CH_3OH); $[\alpha]_D$ –63.8 (*c* 0.9, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD, δ_H) 7.41–7.39 (m, 2H, Ar), 7.13–7.11 (m, 2H, Ar), 4.45 (d, J = 9.3 Hz, 1H, H-1), 3.91 (dd, J = 11.3, 5.2 Hz, 1H, H-5), 3.44 (ddd, J = 10.0, 8.9, 5.2 Hz, 1H, H-4), 3.33 (d, J = 8.6 Hz, 1H, H-3), 3.20–3.14 (m, 2H, H-5, H-2), 2.30 (s, 3H, ArC$\underline{H}_3$); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 139.0 (Ar), 133.9 (Ar), 130.8 (Ar), 130.5 (Ar), 90.4 (C-1), 79.3 (C-3), 73.6 (C-2), 70.9 (C-4), 70.5 (C-5), 21.1 (Ar$\underline{C}H_3$); HRMS (ESI) calcd for $(M + Na)^+$ $C_{12}H_{16}O_4SNa$: 279.0662. Found: 279.0664.



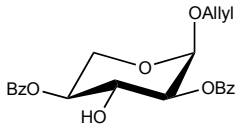
***p*-Tolyl 4-*O*-(2,2,2-trichloroethoxycarbonyl)-1-thio-β-D-xylopyranoside (2.27).** To a solution of **2.26** (512.6 mg, 2.0 mmol) in toluene (30 mL) was added *n*-Bu_2SnO (522.8 mg, 2.2 mmol). The mixture was stirred at reflux for 4 h, with the azeotropic removal of water (Dean–Stark trap). The resulting solution was cooled under argon in an ice-water bath and stirred while 2,2,2-trichloroethyl chloroformate (0.28 mL, 2.1 mmol) was added via syringe. The reaction mixture was allowed for 30 min when TLC showed completion of the reaction. The mixture was concentrated to a syrup and the resulting crude residue was purified by chromatography (2:1 hexanes–EtOAc) to give **2.27** (806.4 mg, 93%) as a white foam. R_f 0.51 (1:1 hexanes–EtOAc); $[\alpha]_D$ –31.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.44–7.42 (m, 2H, Ar), 7.16–7.14 (m, 2H, Ar), 4.81, 4.72 (ABq, *J* = 11.8 Hz, 2H, $Cl_3CC\underline{H}_2O$), 4.72 (ddd, *J* = 10.1, 9.3, 5.4, 1H, H-4), 4.43 (d, *J* = 9.4 Hz, 1H, H-1), 4.23 (dd, *J* = 11.4, 5.4 Hz, 1H, H-5), 3.79 (app dt, *J* = 8.9, 3.1 Hz, 1H, H-3), 3.41–3.34 (m, 2H, H-5, H-2), 2.81 (d, *J* = 3.2 Hz, 1H, O<u>H</u>-3), 2.67 (d, *J* = 2.6 Hz, 1H, O<u>H</u>-2), 2.36 (s, 3H, Ar$C\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 153.5 (C=O), 139.1 (Ar), 133.9 (Ar), 130.0 (Ar), 126.9 (Ar), 94.2 (Cl_3C), 88.7 (C-1), 77.1 ($Cl_3C\underline{C}H_2O$), 75.2 (C-3), 75.0 (C-4), 71.9 (C-2), 66.3 (C-5), 21.2 (Ar$\underline{C}H_3$); HRMS (ESI) calcd for $(M+Na)^+$ $C_{15}H_{17}{}^{35}Cl_3O_6SNa$: 452.9704. Found: 452.9704.



***p*-Tolyl 2,3-di-*O*-benzoyl-4-*O*-(2,2,2-trichloroethoxycarbonyl)-1-thio-β-D-xylopyranoside (2.28).** To a solution of **2.27** (802.5 mg, 1.86 mmol) in pyridine (20 mL) was added benzoyl chloride (0.6 mL, 4.5 mmol) and DMAP (10 mg) with stirring and cooling at 0 °C. Upon addition of benzoyl chloride, the reaction mixture was stirred for 30 min before it was removed from the ice bath. The reaction mixture was stirred for 6 h at which point TLC showed completion of the reaction. The mixture was diluted with EtOAc and ice was added. The pyridine and water was removed under redeced pressure and the resulting syrup was extracted with EtOAc. The organic extract was then washed with 1M HCl, a satd aq solution of $NaHCO_3$ and brine. The organic extract was dried (Na_2SO_4), filtered, concentrated and the resulting crude product was purified by chromatography (10:1 hexanes–EtOAc) to give **2.28** (1.07 g, 90%) as a white foam. R_f 0.5 (4:1 hexanes–EtOAc); $[\alpha]_D$ –3.6 (*c* 0.7, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.08–8.06 (m, 4H, Ar), 7.58–7.53 (m, 2H, Ar), 7.45–7.39 (m, 6H, Ar), 7.13–7.11 (m, 2H, Ar), 5.60 (app t, *J* = 6.2 Hz, 1H, H-3), 5.41 (app t, *J* = 5.9 Hz, 1H, H-2), 5.19 (d, *J* = 5.7 Hz, 1H, H-1), 5.02 (app dt, *J* = 6.2, 3.9 Hz, 1H, H-4), 4.72 (s, 2H, $Cl_3CC\underline{H}_2O$), 4.61 (dd, *J* = 12.6, 3.7 Hz, 1H, H-5), 3.85 (dd, *J* = 12.6, 6.2 Hz, 1H, H-5'), 2.34 (s, 3H, $ArC\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 165.1 (ArC=O), 164.9 (ArC=O), 153.2 (C=O), 138.5 (Ar), 133.7 (Ar), 133.4 (Ar), 133.1 (Ar), 130.13 (Ar), 130.07 (Ar), 129.9 (Ar), 129.3 (Ar), 129.2 (Ar), 128.8 (Ar), 128.6 (Ar), 128.5 (Ar), 94.1 ($Cl_3\underline{C}$), 86.5 (C-1), 77.0 ($Cl_3C\underline{C}H_2O$), 72.1 (C-4), 69.9 (C-3), 69.6 (C-2), 62.5 (C-5), 21.2 ($Ar\underline{C}H_3$); HRMS (ESI) calcd for $(M+Na)^+$ $C_{29}H_{25}{}^{35}Cl_3O_8SNa$: 661.0228. Found: 661.0228.

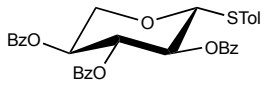


Allyl α-L-xylopyranoside (2.29). The preparation of **2.29** was performed followed the procedure described in the preparation of **2.21**. The compound **2.29** was obtained in 61% (α:β 5:1). Data for the α isomer: R_f 0.23 (10:1, CH_2Cl_2:CH_3OH); $[\alpha]_D$ −146.9 (*c* 0.8, CH_3OH). The ^1H NMR and ^{13}C NMR data were identical to that of **2.21**. HRMS (ESI) calcd for $(M+Na)^+$ $C_8H_{14}O_5Na$: 213.0733. Found: 213.0732.



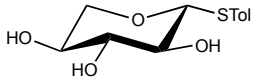
Allyl 2,4-di-*O*-benzoyl-α-L-xylopyranoside (2.30). To a solution of **2.29** (2.56 g, 13.5 mmol) in toluene (150 mL) was added *n*-Bu_2SnO (3.69 g, 14.8 mmol). The mixture was stirred at reflux for 4 h with the azeotropic removal of water (Dean–Stark trap). The resulting solution was cooled under argon in an ice-water bath and stirred while the benzoyl chloride (3.1 mL, 27.0 mmol) was added via a syringe. The reaction mixture was allowed to stir for 2 h at which point the TLC showed completion of the reaction and then CH_3OH was added. The mixture concentrated to a syrup and the resulting crude residue was purified by chromatography (2:1 hexanes–EtOAc) to give **2.30** (4.3 g, 80%) as a light yellow syrup. R_f 0.34 (3:1 hexanes–EtOAc); $[\alpha]_D$ –78.3 (*c* 2.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.11–8.05 (m, 4H, Ar), 7.61–7.57 (m, 2H, Ar), 7.48–7.44 (m,

4H, Ar), 5.86 (dddd, J = 17.2, 10.5, 5.9, 5.1 Hz, 1H, CH_2=C<u>H</u>CH_2O), 5.34–5.29 (m, 1H, C<u>H</u>$_2$=CHCH_2O), 5.23-5.15 (m, 3H, H-4, H-1, C<u>H</u>$_2$=CHCH_2O), 5.07 (dd, J = 9.8, 3.7 Hz, 1H, H-2), 4.47 (app t, J = 9.5 Hz, 1H, H-3), 4.24 (ddt, J = 13.3, 5.1, 1.5 Hz, 1H, CH_2=CHC<u>H</u>$_2O$), 4.03 (ddt, J = 13.3, 5.9, 1.4 Hz, 1H, CH_2=CHC<u>H</u>$_2O$), 3.97 (dd, J = 10.9, 5.9 Hz, 1H, H-5), 3.81–3.77 (app t, J = 10.9 Hz, 1H, H-5'); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 166.3 (C=O), 166.2 (C=O), 133.5 (CH_2=<u>C</u>HCH_2O), 133.42 (Ar), 133.37 (Ar), 129.91 (Ar), 129.85 (Ar), 129.6 (Ar), 129.5 (Ar), 128.5 (2C, Ar), 117.6 (<u>C</u>H$_2$=CHCH_2O), 95.4 (C-1), 74.0 (C-2), 72.5 (C-4), 69.8 (C-3), 68.7 (CH_2=CH<u>C</u>H$_2O$), 58.8 (C-5). HRMS (ESI) calcd for $(M+Na)^+$ $C_{22}H_{22}O_7Na$: 421.1258. Found: 421.1257.



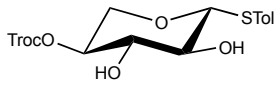
***p*-Tolyl 2,3,4-tri-*O*-benzoyl-1-thio-β-L-xylopyranoside (2.31).** To a solution of **2.17** (11.3 g, 19.9 mmol) and *p*-thiocresol (4.2 g, 33.8 mmol) in CH_2Cl_2 (200 mL) was added BF_3•OEt_2 (6.2 mL, 50.0 mmol) slowly via a syringe with stirring and cooling at 0 °C. After the addition of BF_3•OEt_2, the reaction mixture was allowed to stir for 4 h at 0 °C. When TLC showed completion of reaction, the solution was diluted with CH_2Cl_2 and ice was added. The organic liquid was washed with water and brine. The organic phase was dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (8:1, hexanes–EtOAc) to yield **2.31** (10.8 g, 95%) as a colorless foam. R_f 0.46 (4:1, hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.05−7.99 (m, 5H, Ar), 7.55−7.34 (m, 12H, Ar), 7.15−7.13 (m, 2H, Ar), 5.79 (app t, J = 6.9 Hz, 1H, H-3), 5.46 (app t, J

= 6.6 Hz, 1H, H-2), 5.30 (app dt, *J* = 6.9, 4.1 Hz, 1H, H-4), 5.21 (d, *J* = 6.4 Hz, 1H, H-1), 4.69 (dd, *J* = 12.2, 4.1 Hz, 1H, H-5), 3.80 (dd, *J* = 12.2, 6.8 Hz, 1H, H-5'), 2.35 (s, 3H, ArC$\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$, δ_H) 165.5 (C=O), 165.3 (C=O), 165.1 (C=O), 138.5 (Ar), 133.42 (Ar), 133.37 (Ar), 133.32 (3C, Ar), 129.99 (Ar), 129.93 (Ar), 129.90 (Ar), 129.82 (Ar), 129.3 (Ar), 129.2 (Ar), 129.06 (Ar), 128.99 (Ar), 128.45 (Ar), 128.42 (Ar), 128.39 (Ar), 86.7 (C-1), 70.8 (C-3), 70.1 (C-2), 68.8 (C-4), 63.8 (C-5), 21.2 (Ar$\underline{C}H_3$); HRMS (ESI) calcd for $(M+Na)^+$ $C_{33}H_{28}O_7SNa$: 591.1448. Found: 591.1443.

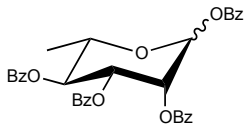


***p*-Tolyl 1-thio-β-L-xylopyranoside (2.32).** A solution of **2.31** (2.84 g, 5.0 mmol) in CH_2Cl_2 (60 mL) and CH_3OH (60 mL) was treated with 1M $NaOCH_3$ in CH_3OH (1.5 mL). After stirring for 3 h, TLC showed completion of the reaction. The reaction mixture was neutralized by the addition of Amberlite IR-120 H^+ resin, filtered and concentrated. The crude residue was purified by chromatography (15:1 CH_2Cl_2–CH_3OH) to give **2.32** (1.26 g, quantitative) as a white foam. R_f 0.34 (10:1 CH_2Cl_2–CH_3OH); $[\alpha]_D$ +68.9 (*c* 1.0, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD, δ_H) 7.40–7.38 (m, 2H, Ar), 7.11–7.08 (m, 2H, Ar), 4.45 (d, *J* = 9.3 Hz, 1H, H-1), 3.90 (dd, *J* = 11.3, 5.2 Hz, 1H, H-5), 3.43 (ddd, *J* = 10.1, 8.8, 5.2 Hz, 1H, H-4), 3.32 (app t, *J* = 8.6 Hz, 1H, H-3), 3.18 (dd, *J* = 11.3, 10.2 Hz, 1H, H-5'), 3.16 (dd, *J* = 9.3, 8.5 Hz, 1H, H-2), 2.29 (s, 3H, ArC$\underline{H}_3$); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 139.0 (Ar), 134.0 (Ar), 130.8 (Ar), 130.5 (Ar), 90.3 (C-1), 79.2 (C-3), 73.6 (C-2),

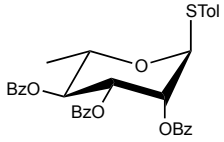
70.9 (C-4), 70.4 (C-5), 21.0 (Ar<u>C</u>H$_3$); HRMS (ESI) calcd for (M + Na)$^+$ $C_{12}H_{16}O_4SNa$: 279.0662. Found: 279.0657.



***p*-Tolyl 4-*O*-(2,2,2-trichloroethoxycarbonyl)-1-thio-β-L-xylopyranoside (2.33).** To a solution of **2.32** (2.61 g, 10.2 mmol) in toluene (120 mL) was added *n*-Bu_2SnO (2.79 g, 11.2 mmol). The mixture was stirred at reflux for 4 h with the azeotropic removal of water (Dean–Stark trap). The resulting solution was cooled under argon in an ice-water bath and stirred while the 2,2,2-trichloroethyl chloroformate (1.5 mL, 11 mmol) was added via a syringe. The reaction mixture was allowed to stir for 30 min when TLC showed completion of the reaction and then CH_3OH was added. The mixture concentrated to a syrup and the resulting crude residue was purified by chromatography (2:1 hexanes–EtOAc) to give **2.33** (4.09 g, 93%) as a white foam. R_f 0.52 (1:1 hexanes–EtOAc); $[\alpha]_D$ +34.0 (*c* 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.44–7.41 (m, 2H, Ar), 7.16−7.14 (m, 2H, Ar), 4.81, 4.72 (ABq, *J* = 11.8 Hz, 2H, $Cl_3CC\underline{H}_2O$), 4.74−4.70 (m, 1H, H-4), 4.43 (d, *J* = 9.4 Hz, 1H, H-1), 4.21 (dd, *J* = 11.4, 5.4 Hz, 1H, H-5), 3.78 (app dt, *J* = 8.9, 2.0 Hz, 1H, H-3), 3.39–3.35 (m, 2H, H-5', H-2), 2.80 (d, *J* = 2.7 Hz, O<u>H</u>-3), 2.66 (d, *J* = 2.2 Hz, O<u>H</u>-2), 2.34 (s, 3H, Ar$C\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ) 153.5 (C=O), 139.1 (Ar), 133.9 (Ar), 130.(Ar), 126.9 (Ar), 94.2 (Cl_3C), 88.7 (C-1), 77.1 ($\underline{C}H_2O$), 75.2 (C-3), 75.1 (C-4), 71.9 (C-2), 66.3 (C-5), 21.2 (Ar$\underline{C}H_3$); HRMS (ESI) calcd for (M + Na)$^+$ $C_{15}H_{17}{}^{35}Cl_3O_6SNa$: 452.9704. Found: 452.9700.

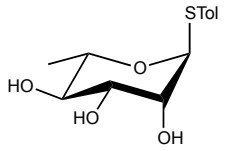


1,2,3,4-tetra-*O*-benzoyl-L-rhamnopyranose (2.35). To a solution of L-rhamnose (16.42 g, 0.1 mol) in dry pyridine (100 mL) was added benzoyl chloride (70 mL, 0.6 mol) dropwise and DMAP (200 mg) with stirring and cooling at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before it was removed from the ice bath. The reaction mixture was stirred for 12 h at which point TLC showed completion of the reaction. Excess benzoyl chloride was quenched by the addition of CH_3OH and the mixture was concentrated by azeotropic removal of pyridine with toluene. The residue was dissolved in CH_2Cl_2 and the organic extract was washed with 1M HCl, water and brine. The organic extract was dried (Na_2SO_4), filtered and concentrated. The resulting crude product was purified by chromatography (10:1 hexanes–EtOAc) to give **2.35** (55.2 g, 95%, α:$\beta \approx 8$:1) as a white foam. The ^1H and ^{13}C NMR spectrum were identical to the reported data.[145]

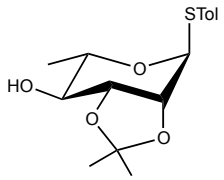


***p*-Tolyl 2,3,4-tri-*O*-benzoyl-1-thio-α-L-rhamnopyranoside (2.36).** To a solution of **2.35** (6.1, 10.4 mmol) and *p*-thiocresol (1.8 g, 14.5 mmol) in CH_2Cl_2 (50 mL) was added $BF_3 \bullet OEt_2$ (1.9 mL, 15 mmol) slowly at 0 °C with stirring. The reaction mixture stirred for 30 min before it was removed from the ice bath. The solution was stirred for 3 h at room temperature at which point TLC showed completion of the reaction. The reaction mixture was diluted with CH_2Cl_2 and ice was added.

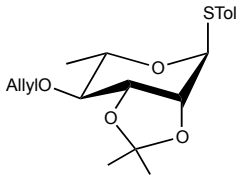
The organic layer was washed with a sat aq $NaHCO_3$ solution and brine, before being dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (10:1 hexane–EtOAc) to give **2.36** (5.5 g, 91%, α only) as a white foam. The ^1H NMR spectrum was identical to the reported data.[146]



***p*-Tolyl 1-thio-α-L-rhamnopyranoside (2.37).**[147] To a solution of **2.36** (28.1 g, 48.2 mmol) in CH_2Cl_2 (100 mL) and CH_3OH (100 mL) was added $NaOCH_3$ (0.1 eq). The mixture was stirred for 4 h at which point TLC showed completion of the reaction. The basicity of the solution was neutralized by the addition of Amberlite IR-120 H^+ resin, which was then filtered. The filtrate was concentrated to a syrup and the resulting crude residue was purified by chromatography (10:1 CH_2Cl_2–CH_3OH) to give **2.37** (13.0 g, quantitative) as a white foam. R_f 0.39 (10:1 CH_2Cl_2–CH_3OH); $[\alpha]_D$ –270.9 (*c* 1.0, CH_3OH); ^1H NMR (500 MHz, CD_3OD, δ_H) 7.35–7.33 (m, 2H, Ar), 7.14–7.12 (m, 2H, Ar), 5.29 (d, *J* = 1.5 Hz, 1H, H-1), 4.06 (dd, *J* = 3.4, 1.5 Hz, 1H, H-2), 4.07–4.02 (m, 1H, H-5), 3.64 (dd, *J* = 9.5, 3.4 Hz, 1H, H-3), 3.44 (app t, *J* = 9.4 Hz, 1H, H-4), 2.31 (s, 3H, ArC$\underline{H}_3$), 1.26 (d, *J* = 6.2 Hz, 3H, H-6); ^{13}C NMR (125 MHz, CD_3OD δ_C): 138.8 (Ar), 133.23 (Ar), 132.2 (Ar), 130.78 (Ar), 90.5 (C-1), 74.2 (C-4), 73.8 (C-2), 72.9 (C-3), 70.9 (C-5), 21.1 (Ar$\underline{C}H_3$), 17.8 (C-6); HRMS (ESI) calcd for $(M + Na)^+$ $C_{13}H_{18}O_4SNa$: 293.0818. Found: 293.0817.

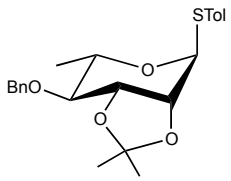


p-Tolyl 2,3-*O*-isopropylidene-1-thio-α-L-rhamnopyranoside (2.38). To a solution of **2.37 (**24.1 g, 89.2 mmol) and 2,2-dimethoxypropane (120 mL, 98 mmol) in acetonitrile (200 mL) was added *p*-TsOH (1.5 g, 8.9 mmol) at room temperature. The solution was stirred for 4 h at which point TLC showed completion of the reaction. The mixture was neutralized by the addition of Et_3N and concentrated to a syrup. The crude residue was purified by chromatography (4:1 hexanes–EtOAc) to yield **2.38** (26.2 g, 95%) as a colorless foam. R_f 0.45 (2:1 hexanes–EtOAc); $[\alpha]_D$ –216.6 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$ δ_H) 7.38–7.35 (m, 2H, Ar), 7.14–7.12 (m, 2H, Ar), 5.67 (d, *J* = 0.7 Hz, 1H, H-1), 4.34 (dd, *J* = 5.5, 0.8 Hz, 1H, H-2), 4.12–4.06 (m, 2H, H-3, H-5), 3.46 (dd, *J* = 9.7, 7.6 Hz, 1H, H-4), 2.33 (s, 3H, ArC$\underline{H}_3$), 1.53 (s, 3H, isopropylidene C$\underline{H}_3$), 1.37 (s, 3H, isopropylidene C$\underline{H}_3$), 1.24 (d, *J* = 6.2 Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$ δ_C): 137.9 (Ar), 132.6 (Ar), 129.9 (Ar), 129.6 (Ar), 109.8 (isopropylidene C), 84.1 (C-1), 78.5 (C-3), 76.6 (C-2), 75.3 (C-4), 66.9 (C-5), 28.2 (isopropylidene $\underline{C}H_3$), 26.4 (isopropylidene $\underline{C}H_3$), 21.2 (Ar$\underline{C}H_3$), 17.1 (C-6); HRMS (ESI) calcd for $(M + Na)^+$ $C_{16}H_{22}O_4SNa$: 333.1131. Found: 333.1129.



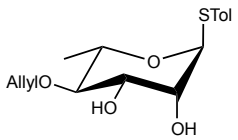
***p*-Tolyl 4-*O*-allyl-2,3-*O*-isopropylidene-1-thio-α-L-rhamnopyranoside (2.39).** To a solution of **2.38** (931.2 mg, 3.0 mmol) in THF (10 mL) was added allyl bromide (0.4 mL, 4.0 mmol). Sodium hydride (100 mg, 4.0 mmol) was then added slowly with stirring and cooling at 0 °C. The reaction mixture was stirred for 12 h until TLC showed the completion of the reaction. The mixture was diluted with EtOAc and ice was added. The organic extract was washed with water and brine and then dried (Na_2SO_4), filtered and concentrated. The resulting crude residue was purified by chromatography (15:1 hexanes–EtOAc) to give **2.39** (982.0 mg, 94%) as a white foam. R_f 0.41 (10:1 hexanes–EtOAc); $[\alpha]_D$ – 222.0 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.37–7.34 (m, 2H, Ar), 7.13–7.11 (m, 2H, Ar), 5.93 (dddd, *J* = 17.2, 10.4, 6.0, 5.4 Hz, 1H, CH_2=C<u>H</u>CH_2O), 5.65 (d, *J* = 0.7 Hz, 1H, H-1), 5.29 (dq, *J* = 17.2, 1.7 Hz, 1H, C<u>H</u>$_2$=CHCH_2O), 5.18 (ddt, *J* = 10.4, 1.8, 1.3 Hz, 1H, C<u>H</u>$_2$=CHCH_2O), 4.36 (dddd, *J* = 12.7, 5.4, 1.6, 1.3 Hz, 1H, CH_2=CHC<u>H</u>$_2$O), 4.32 (dd, *J* = 5.6, 0.9 Hz, 1H, H-2), 4.22 (dd, *J* = 7.2, 5.7 Hz, 1H, H-3), 4.15–4.09 (m, 2H, CH_2=CHC<u>H</u>$_2$O, H-5), 3.22 (dd, *J* = 9.8, 7.2 Hz, 1H, H-4), 2.33 (s, 3H, ArC<u>H</u>$_3$), 1.53 (s, 3H, isopropylidene C<u>H</u>$_3$), 1.36 (s, 3H, isopropylidene C<u>H</u>$_3$), 1.23 (d, *J* = 6.2 Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 137.8 (Ar), 135.0 (CH_2=<u>C</u>HCH_2O), 132.5 (Ar), 129.83 (Ar), 129.76 (Ar), 117.1 (<u>C</u>H$_2$=CHCH_2O), 109.4 (isopropylidene C), 84.2 (C-1), 81.4 (C-4), 78.4 (C-3), 76.7 (C-2), 72.3 (CH_2=CH<u>C</u>H$_2$O), 66.2 (C-5), 28.1

(isopropylidene $\underline{C}H_3$), 26.5 (isopropylidene $\underline{C}H_3$), 21.2 (Ar$\underline{C}H_3$), 17.7 (C-6); HRMS (ESI) calcd for $(M + Na)^+$ $C_{19}H_{26}O_4SNa$: 373.1444. Found: 373.1446.



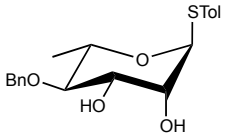
***p*-Tolyl 4-*O*-benzyl-2,3-*O*-isopropylidene-1-thio-α-L-rhamnopyranoside (2.40).** To a solution of **2.38** (2.03 g, 6.6 mmol) in DMF (15 mL) was added benzyl bromide (1.0 mL, 8.6 mmol) and sodium hydride (520 mg, 13.2 mmol) with stirring and cooling to 0 °C. The reaction mixture was stirred for 4 h at which point TLC showed completion of the reaction. The reaction mixture was then diluted with EtOAc and ice was added. The organic extract was washed with water and brine and then dried (Na_2SO_4), filtered and concentrated. The resulting crude residue was purified by chromatography (15:1 hexanes–EtOAc) to give **2.40** (2.59 g, 98%) as a white foam. R_f 0.37 (10:1 hexanes–EtOAc); $[\alpha]_D$ –211.3 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.40–7.29 (m, 7H, Ar), 7.15–7.12 (m, 2H, Ar), 5.69 (d, *J* = 0.6 Hz, 1H, H-1), 4.94 (d, *J* = 11.6 Hz, 1H, PhC$\underline{H}_2$), 4.66 (d, *J* = 11.6 Hz, 1H, PhC$\underline{H}_2$), 4.37 (dd, *J* = 5.7, 0.8 Hz, 1H, H-2), 4.33 (app t, *J* = 6.3 Hz, 1H, H-3), 4.18 (ddq, *J* = 9.8, 6.2, 0.4 Hz, 1H, H-5), 3.32 (dd, *J* = 9.8, 7.0 Hz, 1H, H-4), 2.35 (s, 3H, ArC$\underline{H}_3$), 1.53 (s, 3H, isopropylidene C$\underline{H}_3$), 1.40 (s, 3H, isopropylidene C$\underline{H}_3$), 1.26 (d, *J* = 6.2 Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.3 (Ar), 137.8 (Ar), 132.5 (Ar), 129.8 (Ar), 129.8 (Ar), 128.3 (Ar), 128.0 (Ar), 127.7 (Ar), 109.4 (isopropylidene C), 84.2 (C-1), 81.5 (C-4), 78.5 (C-3), 76.7 (C-2), 73.1 (Ph$\underline{C}H_2$), 66.17 (C-5), 28.09 (isopropylidene C$\underline{H}_3$), 26.5

(isopropylidene C<u>H</u>$_3$), 21.2 (Ar<u>C</u>H$_3$), 17.8 (C-6); HRMS (ESI) calcd for (M + Na)$^+$ $C_{23}H_{28}O_4SNa$: 423.1601. Found: 423.1593.

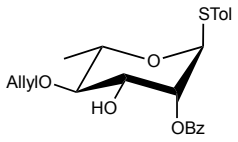


***p*-Tolyl 4-*O*-allyl-1-thio-α-L-rhamnopyranoside (2.41).** Two methods were used to synthesize **2.41**. **Method A**: To a solution of **2.39** (932.0 mg, 2.7 mmol) in CH_3OH (27 mL) was added *p*-TsOH (100 mg, 0.54 mmol) with stirring. The mixture was stirred for 24 h at which point TLC showed completion of the reaction. The reaction mixture was neutralized by the addition of Et_3N and concentrated to dryness. The crude residue was purified by chromatography (2:1 hexanes–EtOAc) to give **2.41** (746.1 mg, 90%) as a white foam. **Method B**: A solution of **2.39** (5.21 g, 14.9 mmol) in acetic acid (120 mL) and water (30 mL) was stirred at 80 °C. The solution was allowed to stir for 1 h at which point TLC showed completion of the reaction. The solvent was co-evaporated with toluene. The resulting crude product was purified by chromatography (2:1 hexanes–EtOAc) to give **2.41** (4.20 g, 91%) as a white foam. R_f 0.55 (1:1 hexanes–EtOAc); $[\alpha]_D$ – 253.5 (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.36–7.33 (m, 2H, Ar), 7.12–7.10 (m, 2H, Ar), 5.96 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H, CH_2=C<u>H</u>CH_2O), 5.39 (dd, *J* = 1.6, 0.5 Hz, 1H, H-1), 5.32 (dq, *J* = 17.2, 1.6 Hz, 1H, C<u>H</u>$_2$=CHCH_2O), 5.22 (ddt, *J* = 10.4, 1.7, 1.2 Hz, 1H, C<u>H</u>$_2$=CHCH_2O), 4.23 (dt, *J* = 5.7, 1.4 Hz, 2H, CH_2=CHC<u>H</u>$_2$O), 4.20 (dd, *J* = 3.3 1.5 Hz, H-2) 4.18 (ddq, *J* = 9.5, 6.3, 0.5 Hz, 1H, H-5), 3.90 (dd, *J* = 9.1, 3.4 Hz, 1H, H-3), 3.31 (app t, *J* = 9.3

Hz, 1H, H-4), 2.60–2.20 (br, 2H, OH-2, OH-3), 2.33 (s, 3H, ArCH$_3$), 1.32 (d, J = 6.3 Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 137.7 (Ar), 134.7 (CH_2=CHCH$_2$O), 132.2 (Ar), 130.3 (Ar), 129.9 (Ar), 117.6 (CH$_2$=CHCH$_2$O), 87.9 (C-1), 81.8 (C-4), 74.0 (CH_2=CHCH$_2$O), 72.6 (C-2), 71.8 (C-3), 68.6 (C-5), 21.2 (ArCH$_3$), 17.9 (C-6); HRMS (ESI) calcd for $(M + Na)^+$ $C_{16}H_{22}O_4SNa$: 333.1131. Found: 333.1132.

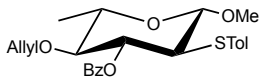


***p*-Tolyl 4-*O*-benzyl-1-thio-α-L-rhamnopyranoside (2.42).** A solution of **2.40** (2.73 g, 6.8 mmol) in acetic acid (55 mL) and water (15 mL) was heated at 80 °C with stirring. The solution was stirred for 4 h at which point TLC showed completion of the reaction. The solvent was evaporated under reduced pressure and the resulting crude product was purified by chromatography to yield **2.42** (2.21 g, 90%) as a white foam. R_f 0.43 (1:1 hexanes–EtOAc); $[\alpha]_D$ –238.1 (*c* 3.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.38–7.30 (m, 7H, Ar), 7.13–7.10 (m, 2H, Ar), 5.40 (d, J = 1.2 Hz, 1H, H-1), 4.76 (s, 2H, PhCH$_2$), 4.24 (dq, J = 9.3, 6.2 Hz, 1H, H-5), 4.17 (dd, J = 3.3, 1.5 Hz, 1H, H-2), 3.94 (dd, J = 9.1, 3.3 Hz, 1H, H-3), 3.42 (app t, J = 9.3 Hz, 1H, H-4), 2.33 (s, 3H, ArCH$_3$), 1.36 (d, J = 6.3 Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C): 138.2 (Ar), 137.7 (Ar), 132.1 (Ar), 130.3 (Ar), 129.9 (Ar), 128.7 (Ar), 128.1 (Ar), 129.0 (Ar), 87.8 (C-1), 81.9 (C-4), 75.1 (PhCH$_2$), 72.6 (C-2), 71.9 (C-3), 68.6 (C-5), 21.1 (ArCH$_3$), 17.9 (C-6); HRMS (ESI) calcd for $(M + Na)^+$ $C_{20}H_{24}O_4SNa$: 383.1288. Found: 383.1289.



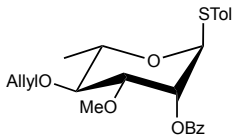
***p*-Tolyl 4-*O*-allyl-2-*O*-benzoyl-1-thio-α-L-rhamnopyranoside (2.43).** To a solution of **2.41** (439.5 mg, 1.4 mmol) in THF (28 mL) was added trimethyl orthobenzoate (0.37 mL, 2.2 mmol) and CSA (33 mg) with stirring. The reaction mixture was stirred for 3 h at which point TLC showed complete consumption of the starting material and then Et_3N was added. The mixture was concentrated to give a syrup that was dissolved in 80% aqueous acetic acid (28 mL) and stirred for 30 min at room temperature. The mixture was then concentrated and the residue solvent was co-evaporated with toluene. The crude product was purified by chromatography (8:1 hexanes–EtOAc) to give **2.43** (417.9 mg, 72%) as a colorless syrup. R_f 0.45 (4:1 hexanes–EtOAc); $[\alpha]_D$ –115.1 (*c* 1.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.06–8.03 (m, 2H, Ar), 7.60–7.57 (m, 1H, Ar), 7.47–7.44 (m, 2H, Ar), 7.39–7.37 (m, 2H, Ar), 7.13–7.11 (m, 2H, Ar), 5.98 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H, CH_2=C<u>H</u>CH_2O), 5.63 (dd, *J* = 3.4, 1.6 Hz, 1H, H-2), 5.47 (dd, *J* = 1.6, 0.5 Hz, 1H, H-1), 5.33 (dq, *J* = 17.2, 1.6 Hz, 1H, C<u>H</u>$_2$=CHCH_2O), 5.22 (ddt, *J* = 10.4, 1.7, 1.2 Hz, 1H, C<u>H</u>$_2$=CHCH_2O), 4.34 (ddt, *J* = 12.5, 5.8, 1.4 Hz, 1H, CH_2=CHC<u>H</u>$_2$O), 4.29–4.24 (m, 2H, CH_2=CHC<u>H</u>$_2$O, H-5), 4.18 (dd, *J* = 9.3, 3.3 Hz, 1H, H-3), 3.44 (app t, *J* = 9.4 Hz, 1H, H-4), 2.32 (s, 3H, ArC<u>H</u>$_3$), 1.40 (d, *J* = 6.2 Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.1 (C=O), 138.0 (Ar), 134.7 (CH_2=<u>C</u>HCH_2O), 133.4 (Ar), 132.4 (Ar), 130.0 (Ar), 129.9 (Ar), 129.8 (Ar), 129.7 (Ar), 128.5 (Ar), 117.4 (<u>C</u>H$_2$=CHCH_2O), 86.4 (C-1),

82.0 (C-4), 74.7 (C-2), 74.1 (CH_2=CH<u>C</u>H_2O), 70.9 (C-3), 68.8 (C-5), 21.1 (Ar<u>C</u>H_3), 18.0 (C-6). HRMS (ESI) calcd for $(M+Na)^+$ $C_{23}H_{26}O_5SNa$: 437.1393. Found: 437.1386.



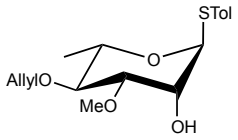
Methyl 4-*O*-allyl-3-*O*-benzoyl-2-deoxy-2-*p*-thiotolyl-α-L-rhamnopyranoside (2.44). To a solution of **2.41 (**310.4 mg, 1 mmol) in CH_2Cl_2 (20 mL) was added trimethyl orthobenzoate (0.22 mL, 1.3 mmol) with stirring. The reaction mixture was stirred for 24 h at which point TLC showed full consumption of the starting material. The reaction mixture was concentrated to a syrup, which was dissolved in acidic acid (10 mL) and water (10 mL) with stirring. The reaction mixture was stirred for 1 h and the solvent was co-evaporated with toluene. The resulting crude product was purified by chromatography (10:1 hexanes–EtOAc) to give **2.44** (305.1 mg, 71%) as a white foam. R_f 0.24 (10:1 hexanes–EtOAc); $[\alpha]_D$ –91.7 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.06–8.04 (m, 2H, Ar), 7.59–7.56 (m, 1H, Ar), 7.46–7.41 (m, 4H, Ar), 7.03–7.01 (m, 2H, Ar), 5.68 (ddt, *J* = 17.1, 10.4, 6.1 Hz, 1H, CH_2=C<u>H</u>CH_2O), 5.35 (dd, *J* = 11.2, 8.9 Hz, 1H, H-3), 5.06 (dd, *J* = 17.2, 1.4 Hz, 1H, C<u>H$_2$</u>=CHCH_2O), 4.99 (dd, *J* = 10.3, 0.7 Hz, 1H, C<u>H$_2$</u>=CHCH_2O), 4.12 (d, *J* = 8.7 Hz, 1H, H-1), 4.00 (dq, *J* = 11.1, 6.0 Hz, 2H, CH_2=CHC<u>H$_2$</u>O), 3.53 (s, 3H, OC<u>H$_3$</u>), 3.38 (dq, *J* = 9.4, 6.2 Hz, 1H, H-5), 3.19 (app t, *J* = 9.1 Hz, 1H, H-4), 3.02 (dd, *J* = 11.2, 8.7 Hz, 1H, H-2), 2.27 (s, 3H, ArC<u>H$_3$</u>), 1.33 (d, *J* = 6.2 Hz, 3H, H-6); ^{13}C NMR (126 MHz, CDCl3, δ_C): 165.7 (Ar), 138.4 (Ar), 134.9 (Ar), 134.2 (Ar), 133.0 (CH_2=<u>C</u>HCH_2O), 130.1 (Ar),

129.8 (Ar), 129.5 (Ar), 128.4 (Ar), 128.3 (Ar), 117.6 ($\underline{C}H_2$=CHCH$_2$O), 102.7 (C-1), 82.8 (C-4), 75.0 (C-3), 73.8 (CH$_2$=CH$\underline{C}$H$_2$O), 71.0 (C-5), 57.0 (O$\underline{C}$H$_3$), 54.3 (C-2), 21.1 (Ar$\underline{C}$H$_3$), 17.9 (C-6); HRMS (ESI) calcd for $(M + Na)^+$ $C_{24}H_{28}O_5SNa$: 451.1550. Found: 451.1551.



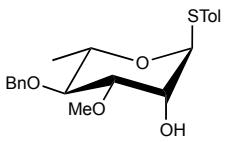
***p*-Tolyl 4-*O*-allyl-2-*O*-benzoyl-3-*O*-methyl-1-thio-α-L-rhamnopyranoside (2.45).** To a solution of **2.46** (329 mg, 1.0 mmol) in pyridine (10 mL) was added benzoyl chloride (0.2 mL, 1.5 mmol) and DMAP (10 mg) with cooling and stirring. The reaction mixture was stirred for 4 h at which point TLC showed completion of the reaction. The reaction mixture was diluted with EtOAc and ice was added. The organic extract was washed with 1M aqueous HCl, water and brine. The organic extract was dried (Na_2SO_4), filtered and concentrated and the crude residue was purified by chromatography (12:1 hexanes–EtOAc) to yield **2.45** (408.1 mg, 94%) as a colorless oil. R_f 0.65 (4:1 hexanes–EtOAc); $[\alpha]_D$ –100.6 (*c* 3.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.07–8.04 (m, 2H, Ar), 7.59–7.56 (m, 1H, Ar), 7.47–7.43 (m, 2H, Ar), 7.40–7.38 (m, 2H, Ar), 7.14–7.12 (m, 2H, Ar), 5.98 (dddd, *J* = 17.2, 10.4, 5.9, 5.5 Hz, 1H, CH$_2$=C$\underline{H}$CH$_2$O), 5.80 (dd, *J* = 3.2, 1.7 Hz, 1H, H-2), 5.48 (dd, *J* = 1.7, 0.4 Hz, 1H, H-1), 5.32 (dq, *J* = 17.2, 1.7 Hz, 1H, C$\underline{H}_2$=CHCH$_2$O), 5.20 (ddt, *J* = 10.4, 1.9, 1.2 Hz, 1H, C$\underline{H}_2$=CHCH$_2$O), 4.41 (ddt, *J* = 12.5, 5.5, 1.4 Hz, 1H, CH$_2$=CHC$\underline{H}_2$O), 4.28 (ddq, *J* = 9.5, 6.2, 0.6 Hz, 1H, H-5), 4.18 (ddt, *J* = 12.5, 6.0, 1.4 Hz, 1H, CH$_2$=CHC$\underline{H}_2$O), 3.71 (dd, *J* =

9.2, 3.2 Hz, 1H, H-3), 3.47 (s, 3H, OC$\underline{H}_3$), 3.45 (app t, J = 9.3 Hz, H-4), 2.33 (s, 3H, ArC$\underline{H}_3$), 1.41 (d, J = 6.2 Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 165.7 (C=O), 137.9 (Ar), 135.1 (CH_2=$\underline{C}$HCH_2O), 133.2 (Ar), 132.3 (2C, Ar), 130.2 (Ar), 129.88 (Ar), 129.87 (Ar), 128.4 (Ar), 116.8 ($\underline{C}H_2$=CHCH_2O), 86.5 (C-1), 80.5 (C-3), 80.4 (C-4), 74.3 (CH_2=CH$\underline{C}H_2O$), 70.8 (C-2), 68.9 (C-5), 57.6 (O$\underline{C}H_3$), 21.1 (Ar$\underline{C}H_3$), 18.0 (C-6); HRMS (ESI) calcd for $(M + Na)^+$ $C_{24}H_{28}O_5SNa$: 451.1550. Found: 451.1546.



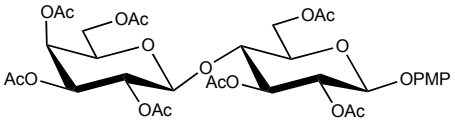
***p*-Tolyl 4-*O*-allyl-3-*O*-methyl-1-thio-α-L-rhamnopyranoside (2.46).** To a solution of **2.41** (968.0 mg, 3.2 mmol) in toluene (50 mL) was added *n*-Bu_2SnO (853.9 mg, 3.4 mmol). The mixture was heated at reflux for 4 h, with the azeotropic removal of water (Dean–Stark trap). The resulting solution was cooled under argon to 60 °C. To the solution was added CsF (516.7 mg, 3.4 mmol) and methyl iodide (3.8 mL, 60 mmol). The reaction mixture was stirred for 2 days at 60 °C in a round bottom flask equipped with a reflux condenser. Upon completion of the reaction, the mixture was diluted with EtOAc (50 mL) and filtered. The filtrate was washed with water and then brine. The organic extract was dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (4:1 hexanes–EtOAc) to give **2.46** (733.5 mg, 73%) as a colorless oil. R_f 0.56 (1:1 hexanes–EtOAc); $[\alpha]_D$ −251.1 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.36–7.34 (m, 2H, Ar), 7.11 (m, 2H, Ar), 5.94 (ddt, J =

17.2, 10.4, 5.7 Hz, 1H, CH_2=C<u>H</u>CH_2O), 5.45 (d, *J* = 1.3 Hz, 1H, H-1), 5.29 (dq, *J* = 17.2, 1.6 Hz, 1H, C<u>H</u>$_2$=$CHCH_2O$), 5.17 (dq, *J* = 10.4, 1.4 Hz, 1H, C<u>H</u>$_2$=$CHCH_2O$), 4.32 (ddt, *J* = 12.4, 5.5, 1.3 Hz, 1H, CH_2=CHC<u>H</u>$_2O$), 4.28−4.27 (m, 1H, H-2), 4.18–4.10 (m, 2H, H-5, CH_2=CHC<u>H</u>$_2O$), 3.51 (s, 3H, OC<u>H</u>$_3$) 3.50 (dd, *J* = 9.0, 3.3 Hz, 1H, H-3), 3.31 (t, *J* = 9.3 Hz, 1H, H-4), 2.55 (d, *J* = 2.3 Hz, 1H, OH-2), 2.33 (s, 3H, ArC<u>H</u>$_3$), 1.30 (d, *J* = 6.2 Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 137.6 (Ar), 135.0 (CH_2=C<u>H</u>CH_2O), 132.1 (Ar), 130.4 (Ar), 129.9 (Ar), 116.9 (CH_2=<u>C</u>HCH_2O), 87.5 (C-1), 81.8 ((C-3), 80.0 (C-4), 74.1 (CH_2=CHC<u>H</u>$_2O$), 69.5 (C-2), 68.6 (C-5), 57.6 (O<u>C</u>H_3), 21.1 (Ar<u>C</u>H_3), 17.8 (C-6); HRMS (ESI) calcd for $(M + Na)^+$ $C_{17}H_{24}O_4SNa$: 347.1288. Found: 347.1291.



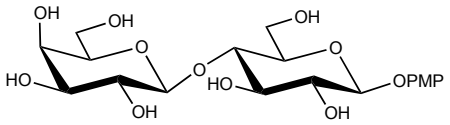
***p*-Tolyl 4-*O*-benzyl-3-*O*-methyl-1-thio-α-L-rhamnopyranoside (2.47).** To a solution of **2.42** (3.57 g, 9.9 mmol) in toluene (130 mL) was added *n*-Bu_2SnO (2.72 g, 10.9 mmol). The mixture was heated at reflux for 4 h, with the azeotropic removal of water (Dean–Stark trap). The resulting solution was cooled under argon to 60 °C. To the solution was added CsF (1.68 g, 10.9 mmol) and methyl iodide (12 mL, 0.2 mol). The reaction mixture was stirred for 2 days at 60 °C using a reflux condenser. Upon completion of the reaction, the mixture was diluted with EtOAc (150 mL) and filtered. The filtrate was washed with water and brine. The organic extract was dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (8:1 hexanes–EtOAc) to give **2.47**

(2.70 g, 73%) as a colorless oil. R_f 0.48 (2:1 hexanes–EtOAc); $[\alpha]_D$ –240.4 (*c* 2.3, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.37–7.30 (m, 7H, Ar), 7.12 (d, *J* = 7.9 Hz, 2H, Ar), 5.48 (d, *J* = 0.9 Hz, 1H, H-1), 4.87 (d, *J* = 11.1 Hz, 1H, PhC$\underline{H}_2$), 4.65 (d, *J* = 11.1 Hz, 1H, PhC$\underline{H}_2$), 4.31 (dd, *J* = 3.1, 0.9 Hz, 1H, H-2), 4.21 (dq, *J* = 9.5, 6.2 Hz, 1H, H-5), 3.59 (dd, *J* = 9.0, 3.3 Hz, 1H, H-3), 3.52 (s, 3H, OC$\underline{H}_3$), 3.45 (app t, *J* = 9.3 Hz, 1H, H-4), 2.78–2.59 (broad, 1H, O$\underline{H}$-2), 2.33 (s, 3H, ArC$\underline{H}_3$), 1.31 (d, *J* = 6.2 Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.5 (Ar), 137.6 (Ar), 132.1 (Ar), 130.3 (Ar), 129.9 (Ar), 128.4 (Ar), 128.0 (Ar), 127.8 (Ar), 87.5 (C-1), 82.0 (C-3), 80.1 (C-4), 75.3 (Ph$\underline{C}H_2$), 69.4 (C-2), 68.5 (C-5), 57.5 (O$\underline{C}H_3$), 21.1 (Ar$\underline{C}H_3$), 17.8 (C-6); HRMS (ESI) calcd for $(M + Na)^+$ $C_{21}H_{26}O_4SNa$: 397.1444. Found: 397.1443.

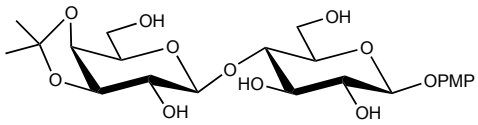


***p*-Methoxyphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-aceyl-β-D-glucopyranoside (2.49).** β-Lactose octaacetate **(2.48)** could be synthesized from lactose as described by Hudson and Johnson.[148] The ^1H NMR spectrum was identical to the reported data.[149] To a solution of **2.48** (17.4 g, 25.6 mmol) and *p*-methoxyphenol (4.3 g, 38.4 mmol) in CH_2Cl_2 (100 mL) was added BF_3•OEt_2 (6.3 mL, 51.2 mmol) slowly via a syringe with stirring and cooling at 0 °C. The reaction mixture was stirred for 30 min before it was removed from the ice bath. The mixture was then stirred for 4 h at room temperature. The mixture was diluted with CH_2Cl_2 and ice was added. The organic extract was washed with

water, a satd aq solution of $NaHCO_3$ and brine. The organic extract was dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (2:1 hexanes–EtOAc) to give **59** (16.23 g, 85%) as a white foam. R_f 0.26 (1:1 hexanes–EtOAc); $[\alpha]_D$ –16.3 (*c* 1.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 6.94–6.92 (m, 2H, Ar), 6.82–6.80 (m, 2H, Ar), 5.36 (d, *J* = 3.3 Hz, 1H, H-4a), 5.26 (app t, *J* = 9.1 Hz, 1H, H-3b), 5.16–5.10 (m, 2H, H-2b, H-2a), 4.97 (dd, *J* = 10.4, 3.5 Hz, 1H, H-3a), 4.92 (d, *J* = 7.8 Hz, 1H, H-1a), 4.52–4.49 (m, 2H, H-1b, H-6a), 4.17–4.10 (m, 3H, H-6b, H-6a', H-6b'), 3.91–3.86 (m, 2H, H-5a, H-4b), 3.79–3.76 (m, 3H, $OC\underline{H}_3$), 3.72 (ddd, *J* = 9.7, 5.6, 1.9 Hz, 1H, H-5b), 2.16 (s, 3H, $C\underline{H}_3C{=}O$), 2.10 (s, 3H, $C\underline{H}_3C{=}O$), 2.07 (s, 3H, $C\underline{H}_3C{=}O$), 2.07 (s, 3H, $C\underline{H}_3C{=}O$), 2.06 (s, 3H, $C\underline{H}_3C{=}O$), 2.05 (s, 3H, $C\underline{H}_3C{=}O$), 1.96 (s, 3H, $C\underline{H}_3C{=}O$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_H) 170.33 (C=O), 170.29 (C=O), 170.1 (C=O), 170.0 (C=O), 169.7 (C=O), 169.6 (C=O), 169.1 (C=O), 155.8 (Ar), 150.9 (Ar), 118.7 (Ar), 114.6 (Ar), 101.10 (C-1b), 100.0 (C-1a), 76.8 (C-4b), 72.9 (C-3b), 72.7 (C-5b), 71.6 (C-2a), 71.0 (C-3a), 70.8 (C-5a), 69.1 (C-2b), 66.6 (C-4a), 62.0 (C-6a), 60.8 (C-6b), 55.7 ($O\underline{C}H_3$), 20.8 ($\underline{C}H_3C{=}O$), 20.8 ($\underline{C}H_3C{=}O$), 20.7 ($\underline{C}H_3C{=}O$), 20.6 ($\underline{C}H_3C{=}O$), 20.6 ($\underline{C}H_3C{=}O$), 20.5 ($\underline{C}H_3C{=}O$); HRMS (ESI) calcd for $(M + Na)^+$ $C_{33}H_{42}O_{19}Na$: 765.2216. Found: 765.2197.

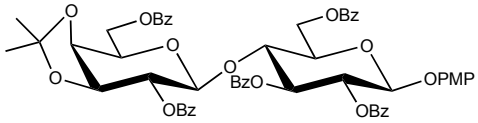


***p*-Methoxyphenyl β-D-galactopyranosyl-(1→4)-β-D-glucopyranoside (2.50).** To a solution of **2.49** (1.09 g, 1.5 mmol) in CH_2Cl_2 (15 mL) and CH_3OH (15 mL) was added a 1M solution of $NaOCH_3$ in CH_3OH (0.6 mL). The reaction mixture was stirred for 12 h. During the reaction, a white solid precipitated from the solution. Upon completion of the reaction, TLC showed no product in the solution. The reaction mixture was filtered and the recovered white solid was washed with room temperature CH_2Cl_2 and CH_3OH. The solid was dissolved in water and the solution was lyophilized to yield **2.50** (672.0 mg, quantitative) as a white foam. $[\alpha]_D$ –18.2 (*c* 0.9, DMSO); ^{1}H NMR (500 MHz, DMSO-d_6, δ_H) 6.98–6.96 (m, 2H, Ar), 6.85–6.83 (m, 2H, Ar), 4.79 (d, J = 7.8 Hz, 1H, H-1a), 4.22 (d, J = 7.1 Hz, 1H, H-1b), 3.74 (dd, J = 11.6, 1.5 Hz, 1H, H-6a), 3.69 (s, 3H), 3.63–3.60 (m, 2H, H-6a', H-5b), 3.54–3.33 (m, 6H, H-4b, H6b, H-6b', H-5a, H-4b, H-3a), 3.32–3.29 (m, 3H, H-3b, H-4a, H-2b), 3.25 (app t, J = 8.3 Hz, 1H, H-2a); ^{13}C NMR (125 MHz, DMSO-d_6, δ_C) 154.3 (Ar), 151.3 (Ar), 117.6 (Ar), 114.5 (Ar), 103.8 (C-1b), 101.0 (C-1a), 80.2, 75.5, 74.9, 74.8, 73.2, 73.0, 70.5, 68.1, 60.4, 60.2, 55.3 ($O\underline{C}H_3$); HRMS (ESI) calcd for $(M + Na)^+$ $C_{19}H_{28}O_{12}Na$: 471.1473. Found: 471.1471.



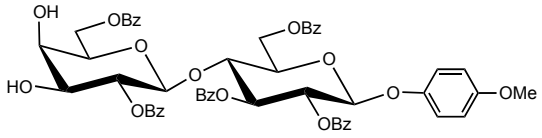
***p*-Methoxyphenyl 3,4-*O*-isopropylidene-β-D-galactopyranosyl-(1→4)-β-D-glucopyranoside (2.51).** To a solution of 2,2-dimethoxypropane (5 mL) in DMF (5 mL) was added **2.50** (448.4 mg, 1.0 mmol). The emulsion was stirred at 80 °C and *p*-TsOH was added until the solution became clear and pH paper indicated the pH of solution was ~1. The reaction mixture stirred for 4 h at 80 °C and then Et_3N was added after cooling. The solvent was co-evaporated with toluene under high vacuum. The crude residue was dissolved in CH_3OH and the mixture was heated at reflux for 2 h. The mixture was then cooled, concentrated and the crude residue was purified by chromatography (15:1 CH_2Cl_2–CH_3OH) to yield **2.51** (294 mg, 65%) as a white solid. R_f 0.39 (10:1 CH_2Cl_2–CH_3OH); $[\alpha]_D$ –4.0 (*c* 1.3, CH_3OH); ^1H NMR (500 MHz, CD_3OD, δ_H) 7.04–7.01 (m, 2H, Ar), 6.83–6.81 (m, 2H, Ar), 4.80 (d, *J* = 7.8 Hz, 1H, H-1b), 4.39 (d, *J* = 8.2 Hz, 1H, H-1a), 4.19 (dd, *J* = 5.5, 2.1 Hz, 1H, H-4a), 4.05 (dd, *J* = 7.2, 5.5 Hz, 1H, H-3a), 3.95 (ddd, *J* = 7.7, 4.5, 2.2 Hz, 1H, H-5a), 3.89 (dd, *J* = 12.2, 2.5 Hz, 1H, H-6b), 3.84 (dd, *J* = 12.1, 3.9 Hz, 1H, H-6b'), 3.80 (dd, *J* = 11.6, 7.8 Hz, 1H, H-6a), 3.80 (dd, *J* = 11.6, 4.5 Hz, 1H, H-6a'), 3.74 (s, 3H, ArOC$\underline{H}_3$), 3.65 (app t, *J* = 9.0 Hz, 1H, H-4b), 3.61 (app t, *J* = 8.6 Hz, 1H, H-3b), 3.52 (ddd, *J* = 9.3, 3.8, 2.6 Hz, 1H, H-5b), 3.48 (app t, *J* = 8.7 Hz, 1H, H-2b), 3.46 (app t, *J* = 7.8 Hz, H-2a), 1.47 (s, 3H, isopropylidene C$\underline{H}_3$), 1.32 (s, 3H, isopropylidene C$\underline{H}_3$); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 156.7 (Ar), 153.1 (Ar), 119.3 (Ar), 115.5 (Ar), 111.1 (isopropylidene C), 104.1 (C-1a), 103.2 (C-1b), 80.9 (C-3a), 80.6 (C-4b), 76.5 (C-5b), 76.2 (C-3b), 75.4 (C-5a),

75.1 (C-4a), 74.7 (C-2a), 74.45 (C-2b), 62.42 (C-6b), 61.71 (C-6a), 56.05 (ArO<u>C</u>H$_3$), 28.40 (isopropylidene <u>C</u>H$_3$), 26.50 (isopropylidene <u>C</u>H$_3$); HRMS (ESI) calcd for $(M + Na)^+$ $C_{22}H_{32}O_{12}Na$: 511.1786. Found: 511.1780.



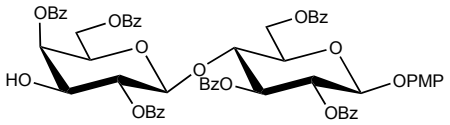
***p*-Methoxyphenyl 2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (2.52).** To a solution of **2.51** (2.05 g, 4.2 mmol) in pyridine (40 mL) was added benzoyl chloride (3.4 mL, 27.3 mmol) and DMAP (100 mg) slowly with stirring and cooling at 0 °C. The reaction mixture was stirred for 30 min before it was removed from the ice bath. The mixture was stirred for 12 h at which point TLC showed completion of the reaction. The solution was diluted with CH_3OH and the solvent was co-evaporated with toluene. The resulting syrup was dissolved with CH_2Cl_2 and the organic extract was washed with 1M HCl, water and brine. The organic extract was dried (Na_2SO_4), filtered and concentrated and the resulting syrup was purified by chromatography (4:1 hexanes–EtOAc) to yield **2.52** (3.81 g, 90%) as a white foam. R_f 0.67 (1:1 hexanes–EtOAc); $[\alpha]_D$ +49.0 (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.11–7.93 (m, 10H, Ar), 7.62–7.29 (m, 15H, Ar), 6.86–6.84 (m, 2H, Ar), 6.64–6.62 (m, 2H), 5.78 (app t, *J* = 9.3 Hz, 1H, H-3b), 5.65 (dd, *J* = 9.5, 7.7 Hz, 1H, H-2b), 5.16 (app t, *J* = 7.3 Hz, 1H, H-2a), 5.09 (d, *J* = 7.7 Hz, 1H, H-1b), 4.65 (dd, *J* = 11.9, 2.1 Hz, 1H, H-6a), 4.63 (d, *J* = 7.6 Hz, 1H, H-1a), 4.49 (dd, *J* = 11.9, 5.5 Hz, 1H, H-6a'), 4.28–4.21 (m, 3H, H-6b, H-3a,

H-4b), 4.10 (dd, *J* = 5.6, 2.2 Hz, 1H, H-4a), 3.95 (ddd, *J* = 9.8, 5.5, 2.0 Hz, 1H, H-5a), 3.85 (ddd, *J* = 7.3, 4.9, 2.2 Hz, 1H, H-5b), 3.72 (dd, *J* = 11.5, 7.4, Hz, 1H, H-6b'), 3.70 (s, 3H, OC$\underline{H}_3$), 1.54 (s, 3H, isopropylidene C$\underline{H}_3$), 1.26 (s, 3H, isopropylidene C$\underline{H}_3$). ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.0 (C=O), 165.81 (C=O), 165.6 (C=O), 165.2 (C=O), 164.9 (C=O), 155.6 (Ar), 151.0 (Ar), 133.6 (Ar), 133.4 (Ar), 133.23 (Ar), 133.16 (Ar), 133.0 (Ar), 130.2 (Ar), 129.86 (Ar), 129.84 (Ar), 129.82 (Ar), 129.80 (Ar), 129.76 (Ar), 129.57 (Ar), 129.54 (2C, Ar), 129.32 (Ar), 129.26 (Ar), 128.7 (Ar), 128.49 (Ar), 128.42 (Ar), 128.40 (Ar), 128.38 (Ar), 128.2 (Ar), 110.9 (isopropylidene C), 100.6 (C-1b), 100.3 (C-1a), 77.0 (C-3a), 75.6 (C-4b), 73.6 (C-2a), 73.2 (C-4a), 73.2 (C-5a), 72.6 (C-3b), 71.8 (C-2b), 71.4 (C-5b), 62.9 (C-6a), 62.8 (C-6b), 55.5 (OC$\underline{H}_3$), 27.4 (isopropylidene $\underline{C}H_3$), 26.2 (isopropylidene $\underline{C}H_3$); HRMS (ESI) calcd for $(M + Na)^+$ $C_{57}H_{52}O_{17}Na$: 1031.3097. Found: 1031.3087.



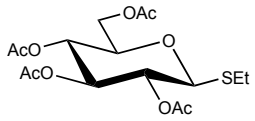
***p*-Methoxyphenyl 2,6-di-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (2.53).** A solution of **2.52** (3.23 g, 3.2 mmol) in acetic acid (25 mL) and water (5 mL) was stirred at 80 °C for 4 h at which point TLC showed completion of the reaction. The solvent was co-evaporated with toluene and the resulting syrup was dissolved the CH_2Cl_2 and then washed with a satd solution of $NaHCO_3$, water and brine. The organic extract was dried (Na_2SO_4), filtered and concentrated. The crude product was purified by

chromatography (1:1 hexanes–EtOAc) to yield **2.53** (2.78 g, 90%) as a white foam. R_f 0.23 (1:1 hexanes–EtOAc); $[\alpha]_D$ +40.6 (*c* 0.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.07–7.92 (m, 10H, Ar), 7.60–7.38 (m, 15H, Ar), 6.88–6.84 (m, 2H, Ar), 6.65–6.62 (m, 2H, Ar), 5.72 (app t, *J* = 9.2 Hz, 1H, H-3b), 5.65 (dd, *J* = 9.6, 7.7 Hz, 1H, H-2b), 5.30 (dd, *J* = 9.7, 7.9 Hz, 1H, H-2a), 5.06 (d, *J* = 7.7 Hz, 1H, H-1b), 4.63 (d, *J* = 7.8 Hz, 1H, H-1a), 4.63 (d, *J* = 11.9, 2.0 Hz, 1H, H-6b), 4.53 (dd, *J* = 11.9, 6.0 Hz, 1H, H-6b'), 4.18 (dd, *J* = 9.7, 9.0 Hz, 1H, H-4b), 4.07 (dd, *J* = 11.3, 6.5 Hz, 1H, H-6a), 3.94 (ddd, *J* = 9.8, 5.9, 2.1 Hz, 1H, H-5b), 3.84–3.82 (m, 1H, H-4a), 3.72 (ddd, *J* = 9.8, 7.9, 3.5 Hz, 1H, H-3a), 3.69 (s, 3H, OC<u>H</u>$_3$), 3.62 (dd, *J* = 11.3, 6.5 Hz, 1H, H-6a'), 3.55–3.53 (m, 1H, H-5a), 3.34 (d, *J* = 7.8 Hz, 1H, O<u>H</u>-3a), 2.93 (d, *J* = 6.1 Hz, 1H, O<u>H</u>-4a); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.6 (C=O), 166.2 (C=O), 165.9 (C=O), 165.8 (C=O), 165.3 (C=O), 155.7 (Ar), 151.0 (Ar), 133.5 (Ar), 133.4 (Ar), 133.3 (3C, Ar), 130.0 (Ar), 129.9 (Ar), 129.8 (Ar), 129.7 (3C, Ar), 129.6 (2C, Ar), 129.3 (Ar), 129.1 (Ar), 128.7 (Ar), 128.6 (Ar), 128.5 (Ar), 128.4 (Ar), 118.9 (Ar), 114.4 (Ar), 100.9 (C-1a), 100.6 (C-1b), 76.3 (C-4b), 73.9 (C-2a), 73.3 (C-5b), 73.0 (C-3b), 72.7 (C-3a), 72.6 (C-5a), 71.6 (C-2b), 68.5 (C-4a), 62.9 (C-6b), 61.9 (C-6a), 55.6 (O<u>C</u>H$_3$); HRMS (ESI) calcd for $(M + Na)^+$ $C_{54}H_{48}O_{17}Na$: 991.2784. Found: 991.2773.



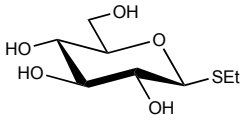
***p*-Methoxyphenyl 2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (2.54).** To a solution of **2.53** (146.0 mg, 0.15 mmol) in CH_3CN (3 mL) was added trimethyl orthobenzoate (0.5 mL, 3.0 mmol) and CSA (5 mg) with stirring. The reaction mixture was stirred for 3 h at which point TLC showed completion of the reaction. Et_3N was added and the mixture was concentrated to give a syrup that was dissolved in 80% aqueous acetic acid (3 mL). The solution was stirred for 30 min at room temperature and the mixture was then concentrated and the residual solvent being co-evaporated with toluene. The crude product was purified by chromatography (4:1 hexanes–EtOAc) to give **2.54** (109.3 mg, 68%) as a white foam. R_f 0.53 (1:1 hexanes–EtOAc); $[\alpha]_D$ +10.3 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.07–7.92 (m, 12H, Ar), 7.64–7.29 (m, 16H, Ar), 7.08–7.05 (m, 2H, Ar), 6.91–6.87 (m, 2H, Ar), 6.67–6.64 (m, 2H, Ar), 5.80 (app t, *J* = 9.4 Hz, 1H, H-3b), 5.71 (dd, *J* = 9.8, 7.8 Hz, 1H, H-2b), 5.52 (d, *J* = 3.4 Hz, 1H, H-4a), 5.33 (dd, *J* = 10.0, 7.8 Hz, 1H, H-2a), 5.13 (d, *J* = 7.8 Hz, 1H, H-1b), 4.77 (d, *J* = 7.8 Hz, 1H, H-1a), 4.70 (dd, *J* = 11.9, 2.0 Hz, 1H, H-6b), 4.58 (dd, *J* = 11.9, 5.9 Hz, 1H, H-6b'), 4.24 (app t, *J* = 9.5 Hz, 1H, H-4b), 4.01–3.97 (m, 2H, H-5b, H-3a), 3.81–3.77 (m, 2H, H-5a, H-6a), 3.70 (s, 3H, OC<u>H</u>$_3$), 3.52 (dd, *J* = 13.3, 9.0 Hz, 1H, H-6a'), 2.70 (d, *J* = 6.6 Hz, 1H, O<u>H</u>-3a); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.5 (C=O), 166.0 (C=O), 165.9 (C=O), 165.7 (C=O), 165.5 (C=O), 165.2 (C=O), 155.7 (Ar), 151.0 (Ar), 133.6 (Ar), 133.5 (Ar), 133.44 (Ar), 133.40 (Ar), 133.3 (Ar), 133.14 (Ar), 130.10 (Ar), 129.89 (Ar),

129.83 (Ar), 129.7 (Ar), 129.6 (Ar), 129.60 (Ar), 129.55 (Ar), 129.52 (Ar), 129.2 (Ar), 128.92 (Ar), 128.91 (Ar), 128.68 (Ar), 128.60 (Ar), 128.59 (Ar), 128.54 (Ar), 128.4 (Ar), 128.1 (Ar), 118.9 (Ar), 114.4 (Ar), 100.73 (C-1b), 100.68 (C-1A), 76.2 (C-4B), 73.8 (C-2a), 73.3 (C-5b), 72.82 (C-3a), 71.87 (C-3b), 71.7 (C-2b), 71.6 (C-5a), 70.1 (C-4a), 62.9 (C-6b), 61.6 (C-6a), 55.6 ($O\underline{C}H_3$); HRMS (ESI) calcd for $(M + Na)^+$ $C_{61}H_{52}O_{18}Na$: 1095.3046. Found: 1095.3040.

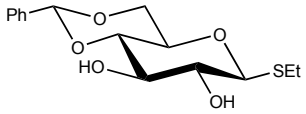


Ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (2.55).[150] To a solution of commercially available 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranoside (3.90 g 10 mmol) and ethanethiol (1.1 g, 15 mol) in CH_2Cl_2 (50 mL) was added BF_3•OEt_2 (3.1 mL, 25 mmol) slowly with stirring and cooling at 0 °C. After addition of BF_3•OEt_2, the reaction mixture was allowed to stir for 30 min before it was removed from the ice bath. The mixture was stirred for 3 h at which point TLC showed completion of the reaction. The reaction mixture was diluted with CH_2Cl_2 and then ice was added. The organic extract was washed with water, a satd aq solution of $NaHCO_3$ and brine. The organic extract was dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (4:1 hexanes–EtOAc) to give **2.55** (3.38 g, 86%) as a white foam. R_f 0.31 (2:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 5.21 (app t, J = 9.4 Hz, 1H, H-3), 5.07 (app t, J = 9.8 Hz, 1H, H-4), 5.03 (app t, J = 9.7 Hz, 1H, H-2), 4.49 (d, J = 10.1 Hz, 1H, H-1), 4.23 (dd, J = 12.3, 5.0 Hz, 1H, H-6), 4.13 (dd, J = 12.3, 2.2

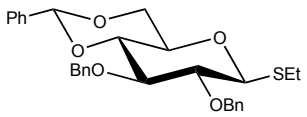
Hz, 1H, H-6'), 3.70 (ddd, J = 10.0, 4.9, 2.3 Hz, 1H, H-5), 2.76–2.64 (m, 2H, SC$\underline{H}_2$CH$_3$), 2.07 (s, 3H, C$\underline{H}_3$C=O), 2.05 (s, 3H, C$\underline{H}_3$C=O), 2.02 (s, 3H, C$\underline{H}_3$C=O), 2.00 (s, 3H, C$\underline{H}_3$C=O), 1.26 (t, J = 7.4 Hz, 3H, SCH$_2$C$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_H) 170.7 (C=O), 170.2 (C=O), 169.4 (C=O), 169.4 (C=O), 83.6 (C-1), 75.9 (C-5), 74.0 (C-3), 69.9 (C-2), 68.4 (C-4), 62.2 (C-6), 24.2 (S$\underline{C}$H$_2$CH$_3$), 20.76 ($\underline{C}$H$_3$C=O), 20.75 ($\underline{C}$H$_3$C=O), 20.65 ($\underline{C}$H$_3$C=O), 20.62 ($\underline{C}$H$_3$C=O), 14.9 (SCH$_2\underline{C}$H$_3$).



Ethyl 1-thio-β-D-glucopyranoside (2.56).[151] To a solution of **2.55** (3.92 g, 10 mmol) in CH_2Cl_2 (50 mL) and CH_3OH (50 mL) was added 1M $NaOCH_3$ in CH_3OH (4 mL). The reaction mixture was stirred for 4 h at which point TLC showed completion of the reaction. The solution was neutralized by the addition of Amberlite IR-120 H^+ resin, filtered and concentrated. The resulting crude residue was purified by chromatography (15:1 CH_2Cl_2–CH_3OH) to give **2.56** (2.24 g, quantitative) as a white foam. R_f 0.21 (10:1 CH_2Cl_2–CH_3OH); ^{1}H NMR (500 MHz, CD_3OD, δ_H) 4.36 (d, J = 9.7 Hz, 1H, H-1), 3.84 (dd, J = 12.0, 2.0 Hz, 1H, H-6), 3.64 (dd, J = 12.0, 5.4 Hz, 1H, H-6), 3.36–3.26 (m, 3H, H-3, H-4, H-5), 3.19 (dd, J = 9.7, 8.6 Hz, 1H, H-2), 2.78–2.68 (m, 2H, SC$\underline{H}_2$CH$_3$), 1.27 (t, J = 7.4 Hz, 3H, SCH$_2$C$\underline{H}_3$); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 86.9 (C-1), 82.0 (C-5), 79.6 (C-3), 74.3 (C-2), 71.5 (C-4), 62.9 (C-6), 24.8 (S$\underline{C}$H$_2$CH$_3$), 15.4 (SCH$_2\underline{C}$H$_3$).

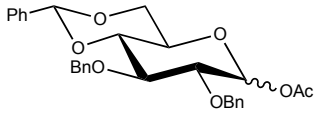


Ethyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (2.57).[152] To a solution of **2.56** (2.24 g, 10 mmol) and benzaldehyde dimethyl acetal (3.0 mL, 20 mmol) in CH_3CN (80 mL) was added *p*TsOH (190.2 mg, 1 mmol) with stirring. The reaction mixture was allowed to stir at room temperature and the reaction was monitored by TLC. When TLC showed completion of the reaction, Et_3N was added and the solution was concentrated. The crude residue was purified by chromatography (3:2 hexanes–EtOAc) to yield **2.57** (2.75 g, 88%) as a white foam. R_f 0.23 (1:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.50–7.47 (m, 2H, Ar), 7.39–7.35 (m, 3H, Ar), 5.53 (s, 1H), 4.44 (d, J = 9.8 Hz, 1H, H-1), 4.34 (dd, J = 10.5, 4.9 Hz, 1H, H-6), 3.81 (app dt, J = 8.8, 2.1 Hz, 1H, H-3), 3.75 (app t, J = 10.2 Hz, 1H, H-6'), 3.55 (app t, J = 9.3 Hz, 1H, H-4), 3.51–3.46 (m, 2H, H-2, H-5), 3.03 (d, J = 2.4 Hz, 1H, O<u>H</u>-3), 2.79–2.71 (m, 3H, OH-2, S<u>C</u>H$_2$CH$_3$), 1.32 (t, J = 7.5 Hz, 3H, SCH$_2$C<u>H</u>$_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 136.9 (Ar), 129.3 (Ar), 128.4 (Ar), 126.3 (Ar), 101.9 (benzylidene <u>C</u>H), 86.5 (C-1), 80.4 (C-4), 74.6 (C-3), 73.2 (C-5), 70.5 (C-2), 68.6 (C-6), 24.7 (S<u>C</u>H$_2$CH$_3$), 15.3 (SCH$_2$<u>C</u>H$_3$); HRMS (ESI) calcd for $(M + Na)^+$ $C_{15}H_{20}O_5SNa$: 335.0924. Found: 335.0919.

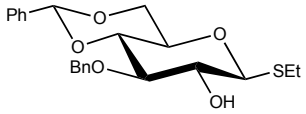


Ethyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (2.58).[153] To a solution of **2.57** (917.0 g, 2.9 mmol) and benzyl bromide (0.9 mL, 7.6 mmol) in DMF (15 mL) was added 60% NaH dispersion in mineral oil (352.5 mg, 8.8 mmol) with stirring and cooling at 0 °C. The reaction mixture was stirred for 30 min before it was removed from the ice bath. The mixture was stirred for 2 h at which point TLC showed completion of the reaction. The mixture was then diluted with EtOAc and CH_3OH was added. The organic extract was washed with water and brine. The organic extract was dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (15:1 hexanes–EtOAc) to give **2.58** (1.31 g, 91%) as a white foam. R_f 0.31 (10:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.52–7.30 (m, 15H, Ar), 5.60 (s, 1H, benzylidene C<u>H</u>), 4.97 (d, *J* = 11.3 Hz, 1H, PhC<u>H</u>$_2$), 4.91 (d, *J* = 10.2 Hz, 1H, PhC<u>H</u>$_2$), 4.84 (d, *J* = 10.2 Hz, 1H, PhC<u>H</u>$_2$), 4.83 (d, *J* = 11.3 Hz, 1H, PhC<u>H</u>$_2$), 4.59 (d, *J* = 9.8 Hz, 1H, H-1), 4.38 (dd, *J* = 10.5, 5.0 Hz, 1H, H-6), 3.83 (dd, *J* = 9.3, 8.4 Hz, 1H, H-3), 3.80 (app t, *J* = 10.3 Hz, 1H, H-6), 3.74 (app t, *J* = 9.3 Hz, 1H, H-4), 3.51–3.45 (m, 2H, H-2, H-5), 2.84−2.72 (m, 2H, SC<u>H</u>$_2$CH$_3$), 1.34 (t, *J* = 7.4 Hz, 3H, SCH$_2$C<u>H</u>$_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.4 (Ar), 138.0 (Ar), 137.3 (Ar), 129.0 (Ar), 128.4 (2C, Ar), 128.3 (Ar), 128.3 (Ar), 128.1 (Ar), 127.9 (Ar), 127.7 (Ar), 126.0 (Ar), 101.1 (benzylidene <u>C</u>H), 85.9 (C-1), 82.8 (C-3), 81.7 (C-2), 81.3 (C-4), 76.0 (Ph<u>C</u>H$_2$), 75.2 (Ph<u>C</u>H$_2$), 70.3 (C-5), 68.8 (C-6), 25.2

($S\underline{C}H_2CH_3$), 15.1 ($SCH_2\underline{C}H_3$); HRMS (ESI) calcd for $(M + Na)^+$ $C_{29}H_{32}O_5SNa$: 515.1863. Found: 515.1856.

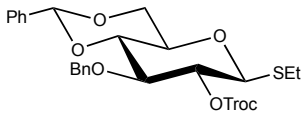


1-*O*-Acetyl-2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranose (2.59). To a solution of **2.58** (1.39 g, 2.8 mmol) in acetone (20 mL) and H_2O (5 mL) was added NBS (2.5 g, 14.0 mmol) with stirring and cooling at 0 °C. The reaction mixture was stirred for 15 min at which point TLC showed completion of the reaction. The reaction mixture was extracted with EtOAc. The organic extract was washed with a satd solution of $Na_2S_2O_3$, water and brine and then dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (6:1 hexanes–EtOAc) to yield the corresponding hemiacetal (1.12 g, 88%) as a colorless foam. R_f 0.28 (4:1 hexanes–EtOAc). The ^{1}H NMR spectrum was identical to the reported data.[154] To a solution of the hemiacetal (1.12 g, 2.5 mmol) in CH_2Cl_2 (25 mL) and pyridine (2 mL) was added Ac_2O (0.5 mL, 5.6 mmol) and DMAP (10 mg). The reaction mixture was stirred for 2 h and then diluted with CH_2Cl_2 and water was added. The organic extract was washed with 1M HCl, water and brine, before being dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (10:1 hexanes–EtOAc) to yield **2.59** (905.6 mg, 74%) as a colorless foam (α:β ≈ 1:1). R_f 0.56 (4:1 hexanes–EtOAc). The ^{1}H NMR and ^{13}C NMR spectrum were identical to the reported data.[154]



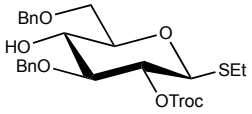
Ethyl 3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (2.60).[155,156] To a solution of **2.57** (2.75 g, 8.8 mmol) in toluene (100 mL) was added *n*-Bu_2SnO (2.24 g, 9.0 mmol). The mixture was stirred at reflux for 4 h, with the azeotropic removal of water (Dean–Stark trap). The resulting solution was cooled under argon to room temperature and the solvent was evaporated under reduced pressure. The resulting syrup was dissolved in DMF (40 mL) and to the solution was added CsF (1.37 g, 9.0 mmol) and benzyl bromide (1.1 mL, 9.0 mmol). The reaction mixture was stirred for 2 days at room temperature. Upon completion of the reaction, the mixture was diluted with EtOAc and filtered. The organic extract was washed with water and brine and then dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (5:1 hexanes–EtOAc) to give **2.60** (2.36 g, 66%) as a white foam. R_f 0.44 (2:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.50–7.47 (m, 2H, Ar), 7.41–7.27 (m, 8H, Ar), 5.58 (s, 1H, benzylidene C<u>H</u>), 4.97 (d, J = 11.6 Hz, 1H, PhC<u>H</u>$_2$), 4.82 (d, J = 11.6 Hz, 1H, PhC<u>H</u>$_2$), 4.47 (d, J = 9.7 Hz, 1H, H-1), 4.36 (dd, J = 10.5, 5.0 Hz, 1H, H-6), 3.78 (app t, J = 10.3 Hz, 1H, H-6), 3.72 (app t, J = 9.0 Hz, 1H, H-4), 3.68 (app t, J = 8.5 Hz, 1H, H-3), 3.59 (ddd, J = 9.8, 8.1, 1.8 Hz, 1H, H-2), 3.50 (ddd, J = 10.0, 9.0, 5.0 Hz, 1H, H-5), 2.80–2.70 (m, 2H, SC<u>H</u>$_2$CH$_3$), 2.51 (d, J = 2.0 Hz, 1H, O<u>H</u>-2), 1.32 (t, J = 7.4 Hz, 3H, SCH$_2$C<u>H</u>$_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C): 138.4 (Ar), 137.3 (Ar), 129.1 (Ar), 128.5 (Ar), 128.3 (Ar), 128.1 (Ar), 127.9 (Ar),

126.1 (Ar), 101.3 (benzylidene CH), 86.7 (C-1), 81.6 (C-3), 81.3 (C-4), 74.8 ($PhCH_2$), 73.1 (C-2), 70.9 (C-5), 68.7 (C-6), 24.6 (SCH_2CH_3), 15.3 (SCH_2CH_3).



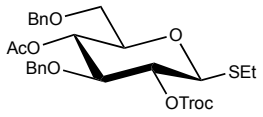
Ethyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2,2,2-trichloroethoxycarbonyl)-1-thio-β-D-glucopyranoside (2.61). To a solution of **2.60** (2.36 g, 5.9 mmol) in pyridine (60 mL) was added 2,2,2-trichloroethyl chloroformate (0.83 mL, 6.0 mmol) and DMAP (30 mg) with stirring and cooling. The reaction mixture was allowed to stir overnight and TLC showed completion of the reaction. The solvent was co-evaporated with toluene. The residue was dissolved in EtOAc and the organic extract was washed with 1M HCl, water and brine. The organic extract was dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (15:1 hexanes–EtOAc) to yield **2.61** (3.15 g, 93%) as a white foam. R_f 0.63 (4:1 hexanes–EtOAc); $[\alpha]_D$ –28.6 (*c* 1.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.46–7.44 (m, 2H, Ar), 7.37–7.33 (m, 3H, Ar), 7.27–7.23 (m, 5H, Ar), 5.54 (s, 1H, benzylidene CH), 4.88 (d, J = 11.7 Hz, 1H, $PhCH_2$), 4.85 (dd, J = 10.1, 8.7 Hz, 1H, H-2), 4.81, 4.70 (ABq, J = 11.8 Hz, 2H, Cl_3CCH_2O), 4.71 (d, J = 11.7 Hz, 1H, $PhCH_2$), 4.51 (d, J = 10.1 Hz, 1H, H-1), 4.33 (dd, J = 10.5, 5.0 Hz, 1H, H-6), 3.81 (app t, J = 9.0 Hz, 1H, H-3), 3.74 (app t, J = 10.3 Hz, 1H, H-6), 3.73 (app t, J = 9.3 Hz, 1H, H-4), 3.45 (ddd, J = 10.0, 9.3, 5.1 Hz, 1H, H-5), 2.69 (m, 2H, SCH_2CH_3), 1.24 (d, J = 7.5 Hz, 3H, SCH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 153.4 (C=O), 137.9 (Ar), 137.0 (Ar), 129.1 (Ar), 128.36

(Ar), 128.34 (Ar), 127.88 (Ar), 127.85 (Ar), 127.81 (Ar), 126.0 (Ar), 101.3 (benzylidene CH), 94.3 ($Cl_3\underline{C}CH_2O$), 84.0 (C-1), 81.4 (C-4), 79.4 (C-3), 77.1 ($Cl_3C\underline{C}H_2O$), 76.7 (C-2), 74.7 ($Ph\underline{C}H_2$), 70.7 (C-5), 68.6 (C-6), 24.4 ($S\underline{C}H_2CH_3$), 14.9 ($SCH_2\underline{C}H_3$); HRMS (ESI) calcd for $(M + Na)^+$ $C_{25}H_{27}{}^{35}Cl_3O_7SNa$: 599.0435. Found: 599.0433.



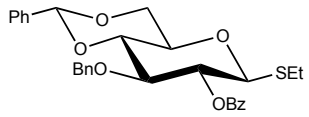
Ethyl 3,6-di-*O*-benzyl-2-*O*-(2,2,2-trichloroethoxycarbonyl)-1-thio-β-D-glucopyranoside (2.62). To a solution of **2.61** (3.15g, 5.5 mmol) and $BH_3{\bullet}NMe_3$ (1.60 g, 21.8 mmol) in THF (55 mL) and water (0.6 mL) was added $AlCl_3$ (4.36 g, 32.7 mmol) portionwise with stirring and cooling at 0 °C. The reaction mixture was stirred for 30 min before it was removed from the ice bath. The reaction mixture was then stirred for 4 h at room temperature. The mixture was diluted with EtOAc and ice was added. The organic extract was washed with 1M HCl, water and brine before being dried (Na_2SO_4), filtered and concentrated. The resulting syrup was purified by chromatography (6:1 hexanes–EtOAc) to give **2.62** (2.78 g, 88%) as a white foam. R_f 0.29 (4:1 hexanes–EtOAc); $[\alpha]_D$ –17.4 (*c* 1.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.36–7.28 (m, 10H, Ar), 4.83–4.75 (m, 5H, H-2, $PhC\underline{H}_2$, $Cl_3CC\underline{H}_2O$), 4.60, 4.52 (ABq, *J* = 12.0 Hz, 2H, $PhC\underline{H}_2$), 4.47 (d, *J* = 10.1 Hz, 1H, H-1), 3.77–3.73 (m, 3H, H-4, H-6, H-6'), 3.61 (app t, *J* = 9.0 Hz, 1H, H-3), 3.50 (dd, *J* = 9.6, 4.7 Hz, 1H, H-5), 2.74–2.67 (m, 3H, O<u>H</u>-4, $SC\underline{H}_2CH_3$), 1.25 (t, *J* = 7.5 Hz, 3H, $SCH_2C\underline{H}_3$); ^{13}C NMR (500 MHz, $CDCl_3$, δ_C)

153.4 (C=O), 138.1 (Ar), 137.6 (Ar), 128.6 (Ar), 128.5 (Ar), 127.96 (Ar), 127.94 (Ar), 127.8 (2×Ar), 94.3 ($Cl_3\underline{C}CH_2O$), 83.33 (C-1), 83.28 (C-3), 78.1 (C-5), 76.9 (C-2), 76.5 (C-2), 75.0 ($Ph\underline{C}H_2$), 73.8 ($Ph\underline{C}H_2$), 72.3 (C-4), 70.4 (C-6), 24.3 ($S\underline{C}H_2CH_3$), 14.9 ($SCH_2\underline{C}H_3$); HRMS (ESI) calcd for $(M + Na)^+$ $C_{25}H_{29}{}^{35}Cl_3O_7SNa$: 601.0592. Found: 601.0596.



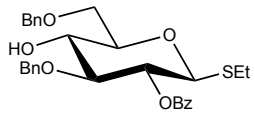
Ethyl 4-*O*-acetyl-3,6-di-*O*-benzyl-2-*O*-(2,2,2-trichloroethoxycarbonyl)-1-thio-β-D-glucopyranoside (2.63). To a solution of **2.62** (5.73 g, 9.9 mmol) in pyridine (60 mL) was added acetic anhydride (1.4 mL, 14.8 mmol) and DMAP (100 mg) with stirring and cooling at 0 °C. The reaction mixture was stirred for 1.5 h at room temperature at which point TLC showed completion of the reaction. The solvent was co-evaporated with toluene and the residue was dissolved with EtOAc. The organic extract was washed with 1M HCl, water and brine before being dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (10:1 hexanes–EtOAc) to yield **2.63** (5.05 g, 82%) as a white foam. R_f 0.58 (4:1 hexanes–EtOAc); $[\alpha]_D$ –9.2 (*c* 1.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.36–7.26 (m, 10H, Ar), 5.11 (app t, J = 9.5 Hz, 1H, H-4), 4.92 (dd, J = 10.0, 9.1 Hz, 1H, H-2), 4.85, 4.79 (ABq, J = 15.0 Hz, 2H, $PhC\underline{H}_2$), 4.75, 4.66 (ABq, J = 11.7 Hz, 2H, $PhC\underline{H}_2$), 4.54 (s, 2H, $Cl_3CC\underline{H}_2$), 4.52 (d, J = 10.1, 1H, H-1), 3.80 (t, J = 9.2 Hz, 1H, H-3), 3.61−3.53 (m, 3H, H-5, H-6, H-6'), 2.79−2.67 (m, 2H, $SC\underline{H}_2CH_3$), 1.89 (s, 3H, $C\underline{H}_3C$=O), 1.32–1.29 (m, 3H, SCH_2CH_3); ^{13}C

NMR (125 MHz, $CDCl_3$, δ_C) 169.5 ($CH_3C=O$), 153.2 (C=O), 137.8 (Ar), 137.7 (Ar), 128.4 (Ar), 128.3 (Ar), 127.88 (Ar), 127.85 (Ar), 127.77 (Ar), 127.68 (Ar), 94.3 ($Cl_3\underline{C}$), 83.3 (C-1), 81.2 (C-3), 77.9 (C-5), 77.1 ($Cl_3C\underline{C}H_2$), 76.9 (C-2), 74.6 ($Ph\underline{C}H_2$), 73.7 ($Ph\underline{C}H_2$), 70.7 (C-4), 69.7 (C-6), 24.3 ($S\underline{C}H_2CH_3$), 20.8 ($\underline{C}H_3C=O$), 14.9 ($SCH_2\underline{C}H_3$); HRMS (ESI) calcd for $(M + Na)^+$ $C_{27}H_{31}{}^{35}Cl_3O_8SNa$: 643.0697. Found: 643.0693.



Ethyl 3-*O*-benzyl-2-*O*-benzoyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (2.64). To a solution of **2.60** (2.72 g, 6.8 mmol) in CH_2Cl_2 (40 mL) and pyridine (20 mL) was added benzoyl chloride (1.2 mL, 10 mmol) and DMAP (100 mg) with stirring and cooling at 0 °C. The reaction mixture was stirred 8 h at which point TLC showed completion of the reaction. The solvent was co-evaporated with toluene and the residue was dissolved in EtOAc. The organic extract was washed with 1M HCl, water and brine before being dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (10:1 hexanes–EtOAc) to yield **2.64** (3.26 g, 95%) as a white foam. R_f 0.47 (4:1 hexanes–EtOAc); $[\alpha]_D$ +17.5 (*c* 0.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.01–8.00 (m, 2H, Ar), 7.61–7.58 (m, 1H, Ar), 7.52–7.50 (m, 2H, Ar), 7.47–7.44 (m, 2H, Ar), 7.43–7.38 (m, 3H, Ar), 7.15–7.13 (m, 3H, Ar), 7.10–7.06 (m, 2H, Ar), 5.62 (s, 1H, benzylidene C$\underline{H}$), 5.34 (dd, *J* = 9.8, 8.7 Hz, 1H, H-2), 4.83 (d, *J* = 11.9 Hz, 1H, PhC$\underline{H}_2$), 4.70 (d, *J* = 12.0 Hz, 1H, PhC$\underline{H}_2$), 4.62 (d, *J* = 10.1 Hz, 1H, H-1), 4.41

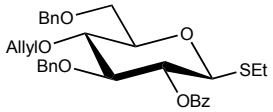
(dd, J = 10.6, 5.0 Hz, 1H, H-6), 3.92-3.81 (m, 3H, H-3, H-4, H-6), 3.56 (app dt, J = 9.6, 4.9 Hz, 1H, H-5), 2.76–2.68 (m, 2H, $SC\underline{H}_2CH_3$), 1.22 (t, J = 7.5 Hz, 3H, $SCH_2C\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 165.2 (C=O), 137.8 (Ar), 137.2 (Ar), 133.2 (Ar), 130.0 (Ar), 129.8 (Ar), 129.1 (Ar), 128.4 (Ar), 128.3 (Ar), 128.2 (Ar), 128.1 (Ar), 127.6 (Ar), 126.1 (Ar), 101.4 (benzylidene $\underline{C}$H), 84.4 (C-1), 81.7 (C-4), 79.3 (C-3), 74.2 ($Ph\underline{C}H_2$), 72.0 (C-2), 70.8 (C-5), 68.7 (C-6), 24.1 ($S\underline{C}H_2CH_3$), 14.9 ($SCH_2\underline{C}H_3$). HRMS (ESI) calcd for $(M + Na)^+$ $C_{29}H_{30}O_6SNa$: 529.1655. Found: 529.1650.



Ethyl 3,6-di-*O*-benzyl-2-*O*-benzoyl-1-thio-β-D-glucopyranoside (2.65).

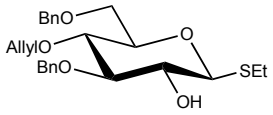
To a solution of **2.64** (3.2 g, 6.3 mmol) and $BH_3{\bullet}NMe_3$ (1.85 g, 25.2 mmol) in THF (65 mL) and water (0.6 mL) was added $AlCl_3$ (5.04 g, 37.8 mmol) portionwise with cooling and stirring. The reaction mixture was stirred for 4 h at room temperature before being diluted with EtOAc and then ice was added. The organic extract was washed with 1M HCl, water and brine. The organic extract was dried (Na_2SO_4), filtered and concentrated and the resulting syrup was purified by chromatography (6:1 hexanes–EtOAc) to give **2.65** (3.08 g, 96%) as a white foam. R_f 0.5 (2:1 hexanes–EtOAc); $[\alpha]_D$ +1.9 (*c* 1.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.08–8.05 (m, 2H, Ar), 7.61–7.58 (m, 1H, Ar), 7.49–7.45 (m, 2H, Ar), 7.39–7.30 (m, 6H, Ar), 7.22–7.18 (m, 4H, Ar), 5.31 (dd, J = 10.0, 9.1 Hz, 1H, H-2), 4.75, 4.73 (ABq, J = 11.5 Hz, 2H, $PhC\underline{H}_2$), 4.63, 4.60 (ABq, J = 12.0 Hz, 2H,

PhC<u>H</u>$_2$), 4.58 (d, J = 10.0 Hz, 1H, H-1), 3.84–3.80 (m, 3H, H-4, H-6, H-6'), 3.72 (app t, J = 9.0 Hz, 1H, H-3), 3.59 (app dt, J = 9.5, 4.7 Hz, 1H, H-5), 2.93 (d, J = 2.6 Hz, 1H, O<u>H</u>-4), 2.78–2.68 (m, 2H, SC<u>H</u>$_2$CH$_3$), 1.25 (t, J = 7.5 Hz, 3H, SCH$_2$C<u>H</u>$_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 165.3 (C=O), 137.9 (Ar), 137.7 (Ar), 133.2 (Ar), 129.83 (Ar), 129.81 (Ar), 128.43 (Ar), 128.38 (Ar), 128.33 (Ar), 127.9 (Ar), 127.79 (Ar), 127.71 (Ar), 83.6 (C-1), 83.5 (C-3), 78.3 (C-5), 74.6 (Ph<u>C</u>H$_2$), 73.7 (Ph<u>C</u>H$_2$), 72.2 (C-4), 72.0 (C-2), 70.4 (C-6), 23.9 (S<u>C</u>H$_2$CH$_3$), 14.9 (SCH$_2$<u>C</u>H$_3$); HRMS (ESI) calcd for (M + Na)$^+$ $C_{29}H_{32}O_6SNa$: 531.1812. Found: 531.1800.



Ethyl 4-*O*-allyl-3,6-di-*O*-benzyl-2-*O*-benzoyl-1-thio-β-D-glucopyranoside (2.66). To a solution of **2.65** (2.90 g, 5.7 mmol) and allyl bromide (0.7 mL, 8.3 mmol) in DMF (20 mL) was added 60% NaH dispersion in mineral oil (274.0 mg, 6.8 mmol) with stirring and cooling at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. When the TLC showed full consumption of the starting material, the mixture was diluted with EtOAc and ice was added. The organic extract was washed with water and brine before being dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (10:1 hexanes–EtOAc) to yield **2.66** (2.60 g, 83%) as a colorless oil. R_f 0.39 (4:1 hexanes–EtOAc); $[\alpha]_D$ +42.7 (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.03–8.01 (m, 2H, Ar), 7.59–7.55 (m, 1H, Ar), 7.44 (t, J = 7.8 Hz, 2H,

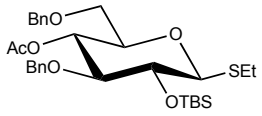
Ar), 7.36–7.29 (m, 5H, Ar), 7.15−7.12 (m, 5H, Ar), 5.85 (app dt, *J* = 11.2, 5.9 Hz, 1H, CH_2=C<u>H</u>CH_2O), 5.27 (app t, *J* = 9.6 Hz, 1H, H-2), 5.20 (dq, *J* = 17.2, 1.6 Hz, 1H, C<u>H</u>$_2$=$CHCH_2O$), 5.13 (dq, *J* = 10.4, 1.4 Hz, 1H, C<u>H</u>$_2$=$CHCH_2O$), 4.73 (d, *J* = 11.1 Hz, 1H, PhC<u>H</u>$_2$), 4.66 (d, *J* = 12.8 Hz, 1H, PhC<u>H</u>$_2$), 4.65 (d, *J* = 11.1 Hz, 1H, PhC<u>H</u>$_2$), 4.59 (d, *J* = 12.1 Hz, 1H, PhC<u>H</u>$_2$), 4.52 (d, *J* = 10.0 Hz, 1H, H-1), 4.29 (dd, *J* = 12.3, 5.7 Hz, 1H, CH_2=CHC<u>H</u>$_2$O), 4.10 (dd, *J* = 12.3, 5.7 Hz, 1H, CH_2=CHC<u>H</u>$_2$O), 3.81–3.73 (m, 3H, H-3, H-6, H-6'), 3.63 (app t, *J* = 9.4 Hz, 1H, H-4), 3.53 (dd, *J* = 9.8, 2.7 Hz, 1H, H-5), 2.77–2.67 (m, 2H, SC<u>H</u>$_2CH_3$), 1.24 (t, *J* = 7.5 Hz, 3H, SCH_2C<u>H</u>$_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 165.3 (C=O), 138.3 (CH_2=<u>C</u>HCH_2O), 137.9 (Ar), 134.6 (Ar), 133.1 (Ar), 130.0 (Ar), 129.9 (Ar), 128.41 (Ar), 128.38 (Ar), 128.3 (Ar), 128.0 (Ar), 127.72 (Ar), 127.65 (Ar), 127.62 (Ar), 117.1 (<u>C</u>H_2=$CHCH_2O$), 84.1 (C-3), 83.5 (C-1), 79.7 (C-5), 77.8 (C-4), 75.2 (Ph<u>C</u>H_2), 73.9 (Ph<u>C</u>H_2), 73.6 (CH_2=CH<u>C</u>H_2O), 72.4 (C-2), 69.0 (C-6), 23.9 (S<u>C</u>H_2CH_3), 15.0 (SCH_2<u>C</u>H_3); HRMS (ESI) calcd for $(M + Na)^+$ $C_{32}H_{36}O_6SNa$: 571.2125. Found: 571.2123.



Ethyl 4-*O*-allyl-3,6-di-*O*-benzyl-1-thio-β-D-glucopyranoside (2.67).

To a solution of **2.66** (2.50 g, 4.6 mmol) in CH_2Cl_2 (25 mL) and CH_3OH (25 mL) was added 1M $NaOCH_3$ in CH_3OH (0.5 mL). The reaction mixture was stirred overnight at which point TLC showed completion of the reaction. The reaction mixture was neutralized by the addition of Amberlite IR-120 H^+ resin, filtered and

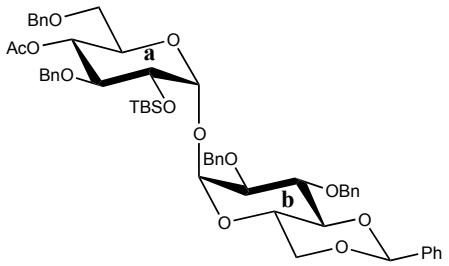
concentrated. The resulting syrup was purified by chromatography (8:1 hexanes–EtOAc) to yield **2.67** (1.88 g, 93%) as a white solid. R_f 0.58 (4:1 hexanes–EtOAc); $[\alpha]_D$ –8.3 (*c* 2.3, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.40–7.27 (m, 10H, Ar), 5.84 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H, CH_2=C<u>H</u>CH_2O), 5.19 (dq, *J* = 17.2, 1.6 Hz, 1H, C<u>H</u>$_2$=CHCH_2O), 5.12 (dq, *J* = 10.4, 1.4 Hz, 1H, C<u>H</u>$_2$=CHCH_2O), 4.90, 4.85 (ABq, *J* = 11.3 Hz, 2H, PhC<u>H</u>$_2$), 4.63, 4.55 (ABq, *J* = 12.1 Hz, 2H, PhC<u>H</u>$_2$), 4.32–4.28 (m, 2H, H-1, CH_2=CHC<u>H</u>$_2O$), 4.07 (ddt, *J* = 12.2, 5.7, 1.3 Hz, 1H, CH_2=CHC<u>H</u>$_2O$), 3.76 (dd, *J* = 11.0, 1.4 Hz, 1H, H-6), 3.70 (dd, *J* = 11.0, 4.1 Hz, 1H, H-6'), 3.52–3.45 (m, 4H, H-2, H-3, H-4, H-5), 2.79–2.68 (m, 2H, SC<u>H</u>$_2CH_3$), 2.38 (brs, 1H, O<u>H</u>-2), 1.32 (t, *J* = 7.4 Hz, 3H, SCH_2C<u>H</u>$_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.6 (Ar), 138.3 (CH_2=<u>C</u>HCH_2O), 134.7 (Ar), 128.5 (Ar), 128.4 (Ar), 128.0 (Ar), 127.8 (Ar), 127.7 (Ar), 127.6 (Ar), 117.0 (<u>C</u>H$_2$=CHCH_2O), 86.1 (C-1), 85.92, 79.57, 77.40, 75.2 (Ph<u>C</u>H$_2$), 73.9 (CH_2=CH<u>C</u>H$_2O$), 73.5 (Ph<u>C</u>H$_2$), 73.16, 69.1 (C-6), 24.3 (S<u>C</u>H$_2CH_3$), 15.5 (SCH_2<u>C</u>H$_3$). HRMS (ESI) calcd for $(M + Na)^+$ $C_{25}H_{32}O_5SNa$: 467.1863. Found: 467.1855.



Ethyl 4-*O*-allyl-3,6-di-*O*-benzyl-2-*O*-*tert*-butyldimethylsilyl-1-thio-β-D-glucopyranoside (2.70).

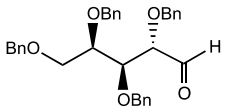
To a solution of **2.11** (3.32 g, 7.4 mmol) and TBSCl (1.68 g, 11.1 mmol) in DMF (10 mL) was added imidazole (1.26 g, 18.5 mmol). The reaction mixture was stirred at 80 °C overnight at which point TLC showed completion of the reaction.

The reaction mixture was diluted with EtOAc and then washed with water and brine. The organic phase was dried (Na_2SO_4), filtered and concentrated and the crude residue was purified by chromatography (10:1 hexanes–EtOAc) to give **2.70** (3.50 g, 84%) as a colorless foam. R_f 0.6 (4:1 hexanes–EtOAc); $[\alpha]_D$ –63.3 (*c* 1.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.31–7.19 (m, 10H, Ar), 4.98 (app t, *J* = 9.3 Hz, 1H, H-4), 4.74 (d, *J* = 11.7 Hz, 1H, PhC$\underline{H}_2$), 4.60 (d, *J* = 11.6 Hz, 1H, PhC$\underline{H}_2$), 4.49, 4.46 (ABq, *J* = 11.8 Hz, 2H, PhC$\underline{H}_2$), 4.36 (d, *J* = 9.2 Hz, 1H, H-1), 3.57–3.46 (m, 5H, H-2, H-3, H-6, H-6', H-5), 2.74–2.60 (m, 2H, SC$\underline{H}_2CH_3$), 1.71 (s, 3H, C$\underline{H}_3$C=O), 1.27 (t, *J* = 7.4 Hz, 3H, $SCH_2C\underline{H}_3$), 0.88 (s, 9H, SiC(C$\underline{H}_3)_3$), 0.13 (s, 3H, SiC$\underline{H}_3$), –0.02 (s, 3H, SiC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 169.9 (C=O), 138.4 (Ar), 138.0 (Ar), 128.4 (Ar), 128.3 (Ar), 127.8 (Ar), 127.7 (Ar), 127.4 (Ar), 127.2 (Ar), 86.5 (C-1), 85.0 (C-5), 77.6 (C-3), 75.2 (Ph$\underline{C}H_2$), 74.0 (C-4), 73.7 (Ph$\underline{C}H_2$), 71.8 (C-2), 70.3 (C-6), 26.2 (SiC($\underline{C}H_3)_3$), 24.9 ($S\underline{C}H_2CH_3$), 20.8 ($\underline{C}H_3$C=O), 18.2 (Si$\underline{C}(CH_3)_3$), 15.1 ($SCH_2\underline{C}H_3$), –3.5 (Si$\underline{C}H_3$), –3.9 (Si$\underline{C}H_3$); HRMS (ESI) calcd for $(M + Na)^+$ $C_{30}H_{44}O_6SSiNa$: 583.2520. Found: 583.2512.



4-*O*-acetyl-3,6-di-*O*-benzyl-2-*O*-*tert*-butyldimethylsilyl-α-D-glucopyranosyl-(1↔1')-2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (2.72). The hemiacetal was synthesized as previously described for the preparation of **2.59**. To a solution of the hemiacetal (742.0 mg, 1.7 mmol) and CCl_3CN (0.3 mL, 3.3 mmol) in CH_2Cl_2 (15 mL) was added Cs_2CO_3 (592.9 mg, 1.8 mmol) at room temperature. The reaction mixture was stirred for 2 h at which point the TLC showed completion of the reaction. The reaction mixture was then filtered through a pad of Celite. The filtrate was concentrated and dried under high vacuum to yield **2.68** as a yellow foam. The product was used without further purification. To a solution of crude **2.68**, **2.71** (441.2 mg, 0.9 mmol) and 4Å molecular sieves in dry ether (20 mL) was treated with 0.1 M solution of TMSOTf in ether (0.9 mL) at −78 °C. The reaction mixture was slowed warmed to −40 °C and monitored by TLC. After 1 h, when the TLC showed full consumption of acceptor, the reaction mixture was neutralized with Et_3N and filtered through a pad of Celite. The filtrate was then concentrated to a syrup. The crude residue was then purified by chromatography (6:1, hexanes−EtOAc) to yield **2.72** (393.0 mg, 49%) as a colorless foam. R_f 0.38 (4:1, hexanes−EtOAc); $[\alpha]_D$ +43.7 (*c* 1.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.50–7.21 (m, 25H, Ar), 5.56 (s, 1H, benzylidene C<u>H</u>), 5.26 (d, *J* = 3.7 Hz, 1H, H-1b), 5.08–5.03 (m, 2H, H-1a, H-4a), 4.97 (d, *J* =

11.3 Hz, PhC$\underline{H}_2$), 4.87–4.80 (m, 3H, PhC$\underline{H}_2$), 4.72 (d, *J* = 11.8 Hz, 1H, PhC$\underline{H}_2$), 4.63 (d, *J* = 11.8 Hz, 1H, PhC$\underline{H}_2$), 4.45, 4.41 (ABq, *J* = 11.9 Hz, 2H, PhC$\underline{H}_2$), 4.26 (dd, *J* = 10.3, 4.8 Hz, 1H, H-6b), 4.21–4.15 (m, 3H, H-5a, H-5b, H-3b), 3.86 (app t, *J* = 9.1 Hz, 1H, H-3a), 3.81 (dd, *J* = 9.4, 3.4 Hz, 1H, H-2a), 3.71 (app t, *J* = 10.3 Hz, 1H, H-6b'), 3.67 (app t, *J* = 9.4 Hz, 1H, H-4b), 3.63 (dd, *J* = 9.4, 3.7 Hz, 1H, H-2b), 3.26 (dd, *J* = 10.7, 2.6 Hz, 1H, H-6a), 3.18 (dd, *J* = 10.7, 5.0 Hz, 1H, H-6a'), 1.76 (s, 3H, C$\underline{H}_3$C=O), 0.94 (s, 9H, SiC(C$\underline{H}_3$)$_3$), 0.08 (s, 3H, SiC$\underline{H}_3$), 0.07 (s, 3H, SiC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 169.7 (C=O), 138.9 (Ar), 138.8 (Ar), 138.2 (Ar), 137.9 (Ar), 137.6 (Ar), 129.0 (Ar), 128.31 (Ar), 128.30 (Ar), 128.27 (Ar), 128.26 (Ar), 128.23 (Ar), 128.0 (Ar), 127.9 (Ar), 127.63 (Ar), 127.61 (Ar), 127.56 (Ar), 127.5 (Ar), 127.4 (Ar), 127.3 (Ar), 126.3 (Ar), 101.7 (benzylidene $\underline{C}$H), 95.0 (C-1a), 93.4 (C-1b), 82.7 (C-4b), 79.6 (C-3a), 78.9 (C-3a), 78.3 (C-3b), 75.4 (Ph$\underline{C}H_2$), 75.0 (Ph$\underline{C}H_2$), 73.8 (Ph$\underline{C}H_2$), 73.7 (Ph$\underline{C}H_2$), 73.1 (C-2a), 70.8 (C-4a), 69.24 (C-5a), 69.20 (C-6b), 68.6 (C-6a), 63.0 (C-5b), 26.2 (SiC($\underline{C}H_3$)$_3$), 20.9 ($\underline{C}H_3$C=O), 18.1 (Si$\underline{C}$(CH$_3$)$_3$), -4.12 (Si$\underline{C}H_3$), -4.78 (Si$\underline{C}H_3$); HRMS (ESI) calcd for $(M+Na)^+$ $C_{55}H_{66}O_{12}SiNa$: 969.4216. Found: 969.4209.

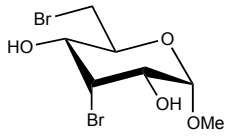


2,3,4,5-tetra-*O*-benzyl-D-lyxose (2.77). A solution of D-lyxose (1.5 g, 10 mmol) in concentrated HCl (37%, 10 mL) was treated with EtSH (1.6 mL, 22 mmol) and stirred until TLC showed complete consumption of the starting material. The reaction mixture was then poured into ice water and the acid was neutralized by

the addition of solid $NaHCO_3$. The mixture was filtered and the filtrate was concentrated to dryness. The compound was dried by co-evaporation with toluene three times. To a solution of the dried product in DMF (100 mL) was added 60% NaH dispersion in mineral oil (3.2 g, 80 mmol) portionwise with stirring and cooling at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before BnBr (6.2 mL, 52 mol) was added carefully. The reaction mixture was stirred for 30 min before it was removed from the ice bath. After stirring for 6 h, the reaction mixture was diluted with EtOAc and ice was added slowly. The organic liquid was washed with water and brine before being dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (12:1 hexanes–EtOAc) to give the diethyl dithioacetal (5.46 g, 89%) as a white foam. R_f 0.28 (10:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.42–7.33 (m, 20H), 5.13 (d, J = 11.2 Hz, 1H), 4.81 (m, J = 6.0 Hz, 3H), 4.64 (d, J = 7.2 Hz, 1H), 4.58–4.53 (m, 3H), 4.36 (d, J = 2.3 Hz, 1H), 4.30–4.28 (m, 1H), 4.16–4.13 (m, 2H), 3.82–3.75 (m, 2H), 2.86–2.67 (m, 4H), 1.31 (dd, J = 14.9, 5.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 138.8, 138.44, 138.38, 138.1, 128.29, 128.25, 128.17, 128.12, 127.8, 127.68, 127.65, 127.54, 127.47, 127.4, 127.3, 82.5, 79.4, 77.6, 74.4, 74.4, 73.3, 72.7, 72.0, 70.4, 53.7, 26.7, 25.0, 14.6, 14.3; HRMS (ESI) calcd for $(M + Na)^+$ $C_{37}H_{44}O_4S_2Na$: 639.2573. Found: 639.2563.

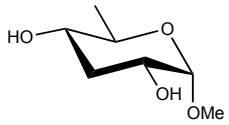
To a solution of the diethyl dithioacetal (5.46 g, 8.9 mmol) in CH_3CN (80 mL) and H_2O (20 mL) was added $HgCl_2$ (4.83 g, 17.8 mmol) and HgO (2.31 g, 10.7 mmol) with stirring. The reaction mixture was heated at reflux for 4 h. When TLC showed completion of the reaction, the reaction mixture was cooled and

filtered through a pad of Celite. The filter cake was washed with hexanes–CH_2Cl_2 (1:1). The organic phase was washed with 5M ammonium acetate, water and brine before being dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (10:1 hexane–EtOAc) to give the aldehyde **2.77** (3.68 g, 81%) as a light yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$, δ_C) 9.70 (d, J = 1.5 Hz, 1H, HC=O), 7.38–7.26 (m, 20H, Ar), 4.70−4.66 (m, 3H, PhCH_2), 4.62 (d, J = 11.5 Hz, 1H, PhCH_2), 4.58 (d, J = 11.8 Hz, 1H, PhCH_2), 4.53–4.47 (m, 3H, PhCH_2), 4.10 (dd, J = 3.5, 1.5 Hz, 1H, H-2), 4.08 (dd, J = 4.9, 3.5 Hz, 1H, H-3), 3.94–3.92 (m, 1H, H-4), 3.80–3.76 (m, 2H, H-5, H-5'); ^{13}C NMR (150 MHz, $CDCl_3$, δ_C) 201.3 (C=O), 138.10 (Ar), 138.08 (Ar), 137.7 (Ar), 137.35 (Ar), 128.44 (Ar), 128.36 (Ar), 128.34 (Ar), 128.32 (Ar), 128.05 (Ar), 128.04 (Ar), 127.92 (Ar), 127.87 (Ar), 127.79 (Ar), 127.71 (Ar), 127.68 (Ar), 127.63 (Ar), 83.8 (C-2), 80.0 (C-3), 78.4 (C-4), 73.6 (PhCH$_2$), 73.3 (PhCH$_2$), 73.0 (PhCH$_2$), 72.8 (PhCH$_2$), 69.9 (C-5). HRMS (ESI) calcd for $(M + Na)^+$ $C_{33}H_{34}O_5Na$: 533.2298. Found: 533.2298.



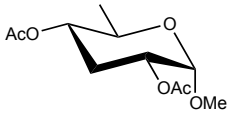
Methyl 3,6-dibromo-3,6-dideoxy-α-D-allopyranoside (2.79). A mixture of methyl α-D-glucopyranoside (1.94 g, 10.0 mmol), tribromoimidazole (6.10 g, 20.0 mmol) and triphenylphosphine (10.58 g, 40 mmol) in toluene (400 mL) was stirred for 1 h at 75 °C and then heated at 110 °C for 4 h. After cooling to room temperature, the product was stirred for 10 min with a satd aq soln of $NaHCO_3$

(400 mL). Iodine was then added portionwise until the organic phase remained purple. The mixture was stirred for 30 min the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried (Na_2SO_4), filtered and concentrated and the resulting crude residue was purified by chromatography (3:2 toluene–EtOAc) to yield **2.79** (2.27 g, 71%) as a colorless foam. R_f 0.33 (1:1 toluene–EtOAc); $[\alpha]_D$ +84.7 (*c* 2.1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, δ_C) 4.82 (app t, *J* = 3.9 Hz, 1H, H-3), 4.78 (d, *J* = 4.3 Hz, 1H, H-1), 3.95 (ddd, *J* = 9.3, 6.3, 2.4 Hz, 1H, H-5), 3.89 (app dt, *J* = 11.9, 4.3 Hz, 1H, H-2), 3.77 (dd, *J* = 11.1, 2.4 Hz, 1H, H-6), 3.62 (dd, *J* = 11.1, 6.3 Hz, 1H, H-6'), 3.59−3.55 (m, 1H, H-4), 3.48 (s, 3H, OC<u>H</u>$_3$), 2.74 (d, *J* = 11.9 Hz, 1H, O<u>H</u>-2), 2.26 (d, *J* = 10.7 Hz, 1H, O<u>H</u>-4); ^{13}C NMR (150 MHz, $CDCl_3$, δ_C) 98.9 (C-1), 68.1 (C-4), 67.9 (C-5), 67.0 (C-2), 62.8 (C-3), 56.1 (O<u>C</u>H$_3$), 32.9 (C-6); HRMS (ESI) calcd for $(M + Na)^+$ $C_7H_{12}{}^{79}Br_2O_4Na$: 340.8995. Found: 340.8992.



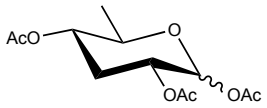
Methyl 3,6-dideoxy-α-D-*ribo*-hexopyranoside (2.80). To a solution of 2.79 (2.42 g, 7.6 mmol) in CH_3OH (30 mL) was added Raney Ni (slurry in water) and Et_3N (7 mL). The reaction mixture was degassed 3 times before it was stirred under a H_2 gas balloon. The reaction mixture was stirred for 4 h at which point the TLC showed completion of the reaction. The reaction mixture was then filtered through a pad of Celite and the filtrate was concentrated. The crude residue was purified by chromatography (15:1 CH_2Cl_2–CH_3OH) to yield **2.80** as a colorless solid. R_f

0.4 (10:1 CH_2Cl_2–CH_3OH); $[\alpha]_D$ +156.1 (*c* 2.5, CH_3OH); ^1H NMR (500 MHz, CD_3OD, δ_H): 4.49 (d, *J* = 3.5 Hz, 1H, H-1), 3.62 (ddd, *J* = 12.1, 4.7, 3.6 Hz, 1H, H-2), 3.44 (dq, *J* = 9.3, 6.2 Hz, 1H, H-5), 3.39 (s, 3H), 3.16 (ddd, *J* = 11.3, 9.4, 4.6 Hz, 1H, H-4), 2.00 (app dt, *J* = 11.5, 4.6 Hz, 1H, H-3), 1.71 (app q, *J* = 11.7 Hz, 1H, H-3), 1.18 (d, *J* = 6.2 Hz, 3H, H-6); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 100.3 (C-1), 71.8 (C-2), 69.6 (C-4), 68.7 (C-5), 55.3 ($O\underline{C}H_3$), 37.1 (C-3), 17.8 (C-6); HRMS (ESI) calcd for $(M+Na)^+$ $C_7H_{14}O_4Na$: 185.0784. Found: 185.0785.



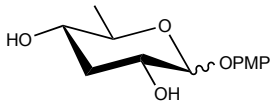
Methyl 2,4-di-*O*-acetyl-3,6-dideoxy-α-D-*ribo*-hexopyranoside (2.81). To a solution of **2.80** (2.22 g, 13.7 mmol) in CH_2Cl_2 (60 mL) and pyridine (10 mL) was added acetic anhydride (3.3 mL, 34.8 mmol) and DMAP (50 mg) with stirring and cooling at 0 °C. The reaction mixture was stirred 4 h at which point TLC showed completion of the reaction. The solvent was co-evaporated with toluene and the residue was dissolved in EtOAc. The organic extract was washed with 1M HCl, water and brine before being dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (4:1 hexanes–EtOAc) to yield **2.81** (2.87 g, 85%) as a white foam. R_f 0.56 (2:1 hexanes–EtOAc); $[\alpha]_D$ +153.7 (*c* 4.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 4.84 (ddd, *J* = 12.4, 4.9, 3.5 Hz, 1H, H-2), 4.75 (d, *J* = 3.5 Hz, 1H, H-1), 4.56 (ddd, *J* = 11.4, 9.8, 4.8 Hz, 1H, H-4), 3.76 (dq, *J* = 9.7, 6.2 Hz, 1H, H-5), 3.41 (s, 3H, $OC\underline{H}_3$), 2.20 (dt, *J* = 10.8, 5.2 Hz, 1H, H-3_{eq}), 2.07 (s, 3H, $C\underline{H}_3C$=O), 2.05 (s, 3H, $C\underline{H}_3C$=O), 1.90

(app dt, J = 12.4, 11.4 Hz, 1H, H-3_{ax}), 1.16 (d, J = 6.3 Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 170.2 ($CH_3\underline{C}$=O), 169.9 ($CH_3\underline{C}$=O), 96.1 (C-1), 71.6 (C-4), 68.6 (C-2), 65.6 (C-5), 55.0 (O$\underline{C}H_3$), 29.4 (C-3), 21.1 ($\underline{C}H_3$C=O), 21.0 ($\underline{C}H_3$C=O), 17.3 (C-6); HRMS (ESI) calcd for $(M+Na)^+$ $C_{11}H_{18}O_6Na$: 269.0096. Found: 269.0095.



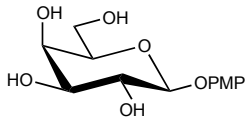
1,2,4-tri-*O*-acetyl-3,6-dideoxy-D-*ribo*-hexopyranose (2.82). To a solution of **2.81** (1.39 g, 5.6 mmol) in CH_2Cl_2 (18 mL), Ac_2O (18 mL) and AcOH (18 mL) was added H_2SO_4 (3.5 mL) dropwise at 0 °C. The reaction mixture was stirred for 20 h at room temperature before being poured into ice-water and then continuing to stir for 30 min. The mixture was extracted with CH_2Cl_2 twice and the combined organic extracts were washed with a satd aq soln of $NaHCO_3$, water and brine. The organic extract was dried (Na_2SO_4), filtered and concentrated and the resulting residue was purified by chromatography on 4:1 hexanes–EtOAc) to yield **2.82** (541 mg, 35%) as a white foam. The α anomer could be isolated as a single isomer. Data for α-anomer: R_f 0.47 (2:1 hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 6.17 (d, J = 3.4 Hz, 1H, H-1), 5.00 (ddd, J = 12.4, 5.0, 3.5 Hz, 1H, H-2), 4.62 (ddd, J = 11.4, 9.9, 4.7 Hz, 1H, H-4), 3.87 (dq, J = 9.8, 6.1 Hz, 1H, H-5), 2.30 (app ddt, J = 11.4, 4.9, 0.9 Hz, 1H, H-3), 2.16 (s, 3H, C$\underline{H}_3$C=O), 2.07 (s, 3H, C$\underline{H}_3$C=O), 2.01 (s, 3H, C$\underline{H}_3$C=O), 1.90 (app dt, J = 12.4, 11.5 Hz, 1H, H-3'), 1.17 (d, J = 6.2 Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 169.72 (C=O), 169.70 (C=O), 169.3 (C=O), 88.7 (C-1), 71.0 (C-4), 68.3 (C-5), 67.0 (C-2), 29.4

(C-3), 21.03 (<u>C</u>H$_3$C=O), 21.02 (<u>C</u>H$_3$C=O), 20.8 (<u>C</u>H$_3$C=O), 17.4 (C-6). HRMS (ESI) calcd for $(M + Na)^+$ $C_{12}H_{18}O_7Na$: 297.0945. Found: 297.0949.



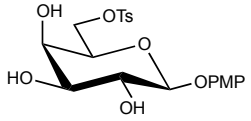
***p*-Methoxyphenyl 3,6-dideoxy-D-*ribo*-hexopyranoside (2.83).** To a solution of 2.82 (126.0 mg, 0.46 mmol) and *p*-methoxyphenol (85.6 mg, 0.69 mmol) in CH_2Cl_2 (5 mL) was added BF_3•OEt_2 (0.15 mL, 1.2 mmol) slowly via a syringe with stirring and cooling. The reaction mixture was stirred for 30 min before it was removed from the ice bath. The mixture was then stirred for overnight at room temperature. The mixture was diluted with CH_2Cl_2 and ice was added. The organic extract was washed with water, a satd aq solution of $NaHCO_3$ and brine. The organic extract was dried (Na_2SO_4), filtered and concentrated. The crude residue was dried and dissolved in CH_2Cl_2 (2 mL) and CH_3OH (2 mL). To the solution was added a 1.0 M solution of $NaOCH_3$ in CH_3OH (0.1 mL). The reaction mixture was allowed to stir for 2 h at room temperature at which point the starting material was completely consumed. The reaction mixture was neutralized by IR-120 H^+ resin. After filtration, the filtrate was concentrated and the crude residue was purified by chromatography (50:1 CH_2Cl_2–CH_3OH) to give α:β mixture (1:1) of **2.83** (39.2 mg, 35%) as a white foam. R_f 0.40 (30:1 CH_2Cl_2–CH_3OH); ^{1}H NMR (400 MHz, CD_3OD, δ_H) 7.06−6.97 (m, 2H, Ar), 6.85−6.80 (m, 2H, Ar), 5.18 (d, J = 3.5 Hz, 0.45H, H-1α), 4.68 (d, J = 7.6 Hz, 1H, 0.55H, H-1β), 3.79−3.71 (m, 3.45H, H-2α, OC<u>H</u>$_3$), 3.65−3.55 (m, 1H, H-5α, H-2β), 3.40−3.34 (m, 0.55H, H-5β), 3.30−3.22 (m, 1H, H-4α, H-4β), 2.32 (app dt, J = 12.3, 4.8 Hz,

0.55H, H-3β), 2.13 (app dt, J = 11.6, 4.6 Hz, 0.45H, H-3α), 1.92 (app q, J = 11.7 Hz, 0.45H, H-3α), 1.52 (app q, J = 11.7 Hz, 0.55H, H-3β), 1.27 (d, J = 6.1 Hz, 1.65H, H-6β), 1.17 (d, J = 6.2 Hz, 1.35H, H-6α); ^{13}C NMR (100 MHz, CD_3OD, δ_C) 156.6 (Ar), 156.5 (Ar), 153.1 (Ar), 152.7 (Ar), 119.4 (Ar), 119.1 (Ar), 115.54 (Ar), 115.45 (Ar), 105.3 (C-1β), 98.9 (C-1α), 77.3 (C-5β), 71.7 (C-4α), 71.3 (C-4β), 70.4 (C-5α), 69.5 (C-2β), 68.6 (C-2α), 56.1 (OCH_3), 40.6 (C-3β), 36.9 (C-3α), 18.1 (C-6β), 17.9 (C-6α); HRMS (ESI) calcd for $(M + Na)^+$ $C_{13}H_{18}O_5Na$: 277.1046. Found: 277.1046.



4-Methoxyphenol β-D-galactopyranoside (2.84).[157] To a solution of 1,2,3,4,5-penta-*O*-acetyl-β-D-galactopyranose (19.5 g, 50 mmol) and 4-methoxyphenol (PMPOH) (7.4 g, 60 mmol) in CH_2Cl_2 (150 mL) was added BF_3•OEt_2 (8.0 mL, 65 mmol) via a syringe with stirring and cooling at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and then ice was added. The organic extract was washed with a satd aq soln of $NaHCO_3$, water and brine before being dried (Na_2SO_4), filtered and concentrated. The crude residue was dried under high vacuum for 4 h and then dissolved in CH_2Cl_2 (100 mL) and CH_3OH (100 mL). To the mixture was added a 5.0M solution of $NaOCH_3$ in CH_3OH (4 mL). The reaction mixture was stirred at room temperature for 4 h and was then neutralized by the addition of Amberlite IR-120 H^+ resin and finally filtered and concentrated. The resulting crude residue was recrystallized from absolute ethanol to give **2.84** as a colorless

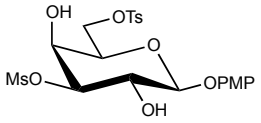
needle (13.0 g, 91%). ^{1}H NMR (500 MHz, CD_3OD, δ_H) 7.06–7.04 (m, 2H, Ar), 6.83–6.81 (m, 2H, Ar), 4.71 (d, *J* = 7.8 Hz, 1H, H-1), 3.88 (dd, *J* = 3.4, 0.8 Hz, 1H, H-4), 3.79–3.72 (m, 6H, H-6, H-6', H-2, OC<u>H</u>$_3$), 3.62 (ddd, *J* = 6.7, 5.5, 1.1 Hz, 1H, H-5), 3.54 (dd, *J* = 9.7, 3.4 Hz, 1H, H-3); ^{13}C NMR (125 MHz, CD_3OD, δ_C): 156.6 (Ar), 153.3 (Ar), 119.3 (Ar), 115.4 (Ar), 104.1 (C-1), 76.9 (C-5), 74.9 (C-3), 72.4 (C-2), 70.2 (C-4), 62.4 (C-6), 56.1 (O<u>C</u>H$_3$); HRMS (ESI) calcd for $(M + Na)^+$ $C_{13}H_{18}O_7Na$: 309.0945. Found: 309.0943.



4-Methoxyphenol 6-*O*-*p*-toluenesulfonyl-β-D-galactopyranoside (2.85).

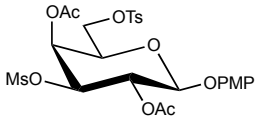
To a solution of **2.84** (4.1 g, 14 mmol) in pyridine (100 mL) was added TsCl (3.0 g, 16 mmol) portionwise with stirring and cooling at 0 °C. The reaction mixture was stirred for 1 h before it was removed from the ice bath. The reaction mixture was stirred overnight and then CH_3OH was added when TLC showed completion of the reaction. The solvent was co-evaporated with toluene and the resulting crude residue was purified by chromatography (15:1 CH_2Cl_2–CH_3OH) to yield **2.85** (5.80 g, 92%) as a white foam. R_f 0.4 (10:1 CH_2Cl_2–CH_3OH); $[\alpha]_D$ −62.9 (*c* 0.8, CH_3OH); ^{1}H NMR (500 MHz, CD_3OD, δ_H) 7.73–7.71 (m, 2H), 7.30–7.28 (m, 2H), 6.99–6.97 (m, 2H), 6.82–6.80 (m, 2H), 4.66 (d, *J* = 7.8 Hz, 1H, H-1), 4.25 (dd, *J* = 10.5, 3.9 Hz, 1H, H-6), 4.19 (dd, *J* = 10.5, 7.9 Hz, 1H, H-6'), 3.86 (ddd, *J* = 7.9, 3.9, 1.1 Hz, 1H, H-5), 3.80 (dd, *J* = 3.4, 0.9 Hz, 1H, H-4), 3.75 (s, 3H), OC<u>H</u>$_3$), 3.69 (dd, *J* = 9.8, 7.8 Hz, 1H, H-2), 3.53 (dd, *J* = 9.7, 3.4 Hz, 1H, H-3),

2.37 (s, 3H, $ArCH_3$); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 155.2 (Ar), 151.6 (Ar), 145.1 (Ar), 132.7 (Ar), 129.6 (Ar), 127.6 (Ar), 117.8 (Ar), 114.0 (Ar), 102.1 (C-1), 73.0 (C-3), 72.5 (C-5), 70.6 (C-2), 69.5 (C-6), 68.6 (C-4), 54.7 ($O\underline{C}H_3$), 20.2 ($Ar\underline{C}H_3$); HRMS (ESI) calcd for $(M + Na)^+$ $C_{20}H_{24}O_9SNa$: 463.1033. Found: 463.1025.



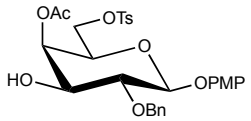
4-Methoxyphenol 3-*O*-methanesulfonyl-6-*O*-*p*-toluenesulfonyl-β-D-galactopyranoside (2.86). To a solution of **2.85** (4.96 g, 11.3 mmol) in toluene (110 mL) was added *n*-Bu_2SnO (2.99 g, 12.0 mmol). The mixture was stirred at reflux for 4 h, with the azeotropic removal of water (Dean–Stark trap). The resulting solution was cooled under argon to 0 °C and MsCl (0.93 m, 12.0 mmol) was added. The reaction mixture was stirred overnight at room temperature and then the mixture was diluted with EtOAc (150 mL) and filtered. The filtrate was washed with water and brine before being dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (1:1 hexanes–EtOAc) to give **2.86** (4.96 g, 85%) as a white foam. R_f 0.21 (1:1 hexanes–EtOAc);$[\alpha]_D$ –28.4 (*c* 0.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.76–7.73 (m, 2H, Ar), 7.29–7.27 (m, 2H, Ar), 7.00–6.95 (m, 2H, Ar), 6.84–6.80 (m, 2H, Ar), 4.72 (d, *J* = 7.7 Hz, 1H, H-1), 4.58 (dd, *J* = 9.9, 3.3 Hz, 1H, H-3), 4.27 (dd, *J* = 10.5, 5.6 Hz, 1H, H-6), 4.22–4.18 (m, 2H, H-6', H-4), 4.11–4.07 (m, 1H, H-2), 3.88–3.85 (m, 1H, H-5), 3.77 (s, 3H, $OC\underline{H}_3$), 3.18 (s, 3H, $C\underline{H}_3SO_2$), 3.00 (d, *J* =

3.2 Hz, 1H, O<u>H</u>-2), 2.90 (d, *J* = 4.6 Hz, 1H, O<u>H</u>-4), 2.41 (s, 3H, ArC<u>H</u>$_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 155.9 (Ar), 150.8 (Ar), 145.3 (Ar), 132.3 (Ar), 130.0 (Ar), 128.0 (Ar), 118.8 (Ar), 114.7 (Ar), 102.3 (C-1), 82.1 (C-3), 71.9 (C-5) 69.0 (C-2), 67.8 (C-4), 67.6 (C-6), 55.7 (OCH_3), 38.6 (<u>C</u>H$_3$), 21.7 (Ar<u>C</u>H$_3$); HRMS (ESI) calcd for $(M + Na)^+$ $C_{21}H_{26}O_{11}S_2Na$: 541.0809. Found: 541.0799.



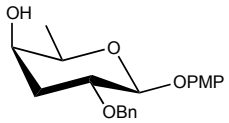
4-Methoxyphenol 2,4-di-*O*-acetyl-3-*O*-methanesulfonyl-6-*O*-*p*-toluenesulfonyl-β-D-galactopyranoside (2.87). To a solution of **2.86** (4.96 g, 9.6 mmol) in pyridine (30 mL) and CH_2Cl_2 (60 mL) was added Ac_2O (2.4 mL, 25.0 mmol) dropwise via a syringe with cooling and stirring. The reaction mixture was stirred overnight at room temperature before CH_3OH was added. The solvent was co-evaporated with toluene and the resulting syrup was purified by chromatography (2:1 hexanes–EtOAc) to yield **2.87** (5.18 g, 90%) as a colorless solid. R_f 0.40 (1:1 hexanes–EtOAc); $[\alpha]_D$ –18.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.77–7.76 (m, 2H, Ar), 7.33 (m, 2H, Ar), 6.94–6.91 (m, 2H, Ar), 6.84–6.81 (m, 2H, Ar), 5.55 (dd, *J* = 3.6, 0.8 Hz, 1H, H-4), 5.42 (dd, *J* = 10.2, 7.9 Hz, 1H, H-2), 4.95 (d, *J* = 8.0 Hz, 1H, H-1), 4.91 (dd, *J* = 10.2, 3.6 Hz, 1H, H-3), 4.16–4.08 (m, 2H, H-6, H-6'), 4.07–4.04 (m, 1H, H-5), 3.79 (s, 3H, OC<u>H</u>$_3$), 3.06 (s, 3H, C<u>H</u>$_3$SO$_2$), 2.45 (s, 3H, ArC<u>H</u>$_3$), 2.14 (s, 3H, C<u>H</u>$_3$C=O), 2.11 (s, 3H, C<u>H</u>$_3$C=O); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 169.8 (C=O), 169.4 (C=O), 155.9 (Ar), 150.8 (Ar), 145.4 (Ar), 132.2 (Ar), 130.0 (Ar), 128.1 (Ar), 118.6 (Ar), 114.7

(Ar), 100.5 (C-1), 75.9 (C-3), 70.7 (C-5), 68.5 (C-2), 67.3 (C-4), 66.0 (C-6), 55.7 ($O\underline{C}H_3$), 39.0 ($\underline{C}H_3SO_2$), 21.7 ($Ar\underline{C}H_3$), 20.8 ($\underline{C}H_3C{=}O$), 20.6 ($\underline{C}H_3C{=}O$); HRMS (ESI) calcd for $(M + Na)^+$ $C_{25}H_{30}O_{13}S_2Na$: 625.1020. Found: 625.1008.



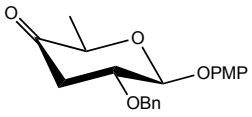
4-Methoxyphenol 3-*O*-acetyl-2-*O*-benzyl-6-*O*-*p*-toluenesulfonyl-β-D-galactopyranoside (2.88). To a solution of **2.85** (11.0 g, 25 mmol) and triethylorthoacetate (6.5 mL, 35 mmol) in CH_3CN (200 mL) was added CSA (400 mg) with stirring. The reaction mixture was stirred for 2 h at which point TLC showed complete consumption of the starting material. Et_3N was added and the mixture was concentrated to a syrup that was dried under high vacuum for 2 h. Without further purification the crude product was dissolved in DMF (50 mL) and then BnBr (3.6 mL, 30 mmol) was added 60% NaH dispersion in mineral oil (2.0 g, 50 mmol) with stirring and cooling at 0 °C. The reaction mixture was allowed to stir for 1 h at which point TLC showed no starting material remained. The solution was then diluted with EtOAc and ice was added. The organic extract was washed with water and brine before being dried (Na_2SO_4), filtered and concentrated. The crude residue was dissolved in 80% HOAc in water (100 mL) and TLC showed conversion of the starting material to product within 30 min. The solvent was co-evaporated with toluene and the residue was diluted with EtOAc. The organic extract was washed with a satd aq soln of $NaHCO_3$, water and brine before being dried (Na_2SO_4), filtered and concentrated. The resulting

syrup was purified by chromatography (3:2 hexanes–EtOAc) to give **2.88** (10.31 g, 72%) as a white foam. R_f 0.3 (1:1 hexanes–EtOAc); $[\alpha]_D$ –24.8 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.76–7.74 (m, 2H, Ar), 7.36–7.28 (m, 7H, Ar), 7.00–6.98 (m, 2H, Ar), 6.85–6.82 (m, 2H, Ar), 5.33 (dd, *J* = 3.5, 1.0 Hz, 1H, H-4), 5.05 (d, *J* = 11.2 Hz, 1H, PhC$\underline{H}_2$), 4.86 (d, *J* = 7.7 Hz, 1H, H-1), 4.76 (d, *J* = 11.2 Hz, 1H, PhCH_2), 4.11 (dd, *J* = 6.2, 2.6 Hz, 2H, H-6, H-6'), 3.95 (app dt, *J* = 6.2, 1.1 Hz, 1H, H-5), 3.82 (app dt, *J* = 9.7, 3.2 Hz, 1H, H-3), 3.80 (s, 3H, OC$\underline{H}_3$), 3.72 (dd, *J* = 9.7, 7.7 Hz, 1H, H-2), 2.42 (s, 3H, ArC$\underline{H}_3$), 2.36 (d, *J* = 2.9 Hz, 1H, OH-3), 2.06 (s, 3H, C$\underline{H}_3$C=O). ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 170.6 (C=O), 155.7 (Ar), 151.1 (Ar), 145.2 (Ar), 137.9 (Ar), 132.5 (Ar), 123.0 (Ar), 128.6 (Ar), 128.2 (Ar), 128.1 (Ar), 128.0 (Ar), 118.4 (Ar), 114.7 (Ar), 102.7 (C-1), 78.7 (C-2), 75.1 (Ph$\underline{C}H_2$), 71.7 (C-3), 71.3 (C-5), 68.8 (C-4), 67.1 (C-6), 55.7 (O$\underline{C}H_3$), 21.7 (Ar$\underline{C}H_3$), 20.7 ($\underline{C}H_3$C=O); HRMS (ESI) calcd for $(M + Na)^+$ $C_{29}H_{32}O_{10}SNa$: 595.1608. Found: 595.1605.



4-Methoxyphenol 3,6-di-deoxy-2-O-benzyl-β-D-galactopyranoside (2.90). To a solution of **2.88** (1.89 g, 3.3 mmol) and 2,6-lutidine (0.6 mL, 5.3 mmol) in CH_2Cl_2 (20 mL) was added Tf_2O (0.8 mL, 4.6 mmol) dropwise via a syringe at –20 °C. The reaction mixture was allowed to stir for 30 min before it was brought to 0 °C. The mixture was then stirred for 2 h at 0 °C. The reaction mixture was diluted with CH_2Cl_2 and then water was added. The organic phase was washed

with water and brine. The organic phase was dried (Na_2SO_4), filtered and concentrated. The crude product **2.89** was used in next step without further purification. The light yellow foam was dissolved in toluene (35 mL) and *n*-Bu_4NBH_4 (2.55 g, 9.9 mmol) was added. The reaction mixture was stirred at 80 °C for 2 h. When TLC showed full consumption of starting material, the reaction mixture was cooled to room temperature and water was added. The organic extract was washed with water and brine and then dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (5:1, toluene–EtOAc) to yield **2.90** (737.0 mg, 65%) as a white foam. R_f 0.23 (3:1, toluene–EtOAc); $[\alpha]_D$ −21.0 (*c* 2.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.37–7.26 (m, 5H, Ar), 7.05–7.02 (m, 2H, Ar), 6.86–6.83 (m, 2H, Ar), 4.92–4.89 (m, 2H, H-1, PhC<u>H</u>$_2$), 4.73 (d, *J* = 11.7 Hz, 1H, PhC<u>H</u>$_2$), 3.83–3.71 (m, 6H, H-2, H-5, OC<u>H</u>$_3$, H-4), 2.41 (ddd, *J* = 13.8, 5.4, 3.2 Hz, 1H, H-3), 1.93 (d, *J* = 8.5 Hz, 1H, O<u>H</u>-4), 1.73 (ddd, *J* = 13.8, 11.6, 3.0 Hz, 1H, H-3), 1.30 (t, *J* = 4.5 Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 155.2 (Ar), 151.4 (Ar), 138.5 (Ar), 128.4 (Ar), 127.8 (Ar), 127.7 (Ar), 118.4 (Ar), 114.6 (Ar), 104.6 (C-1), 73.9 (C-5), 73.2 (Ph<u>C</u>H$_2$), 72.6 (C-2), 69.0 (C-4), 55.7 (O<u>C</u>H$_3$), 37.2 (C-3), 16.6 (C-6); HRMS (ESI) calcd for $(M+Na)^+$ $C_{20}H_{24}O_5Na$: 367.1516. Found: 367.1510.



4-Methoxyphenol 2-*O*-benzyl-3,6-dideoxy-β-D-*erythro*-hexopyranosid-4-ulose (2.91). To a solution of **2.90** (1.15 g, 3.3 mmol) in CH_2Cl_2 (24 mL) was added a solution of 2-iodoxybenzoic acid (IBX) (1.40 g 5.0 mmol) in DMSO (12 mL).

The reaction mixture was stirred overnight at which point TLC showed complete consumption of the starting material The reaction mixture was diluted with EtOAc and the organic phase was washed with water and brine, before being dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (7:1 hexanes–EtOAc) to yield **2.91** (912.1 mg, 80%) as a colorless syrup. R_f 0.38 (4:1 hexanes–EtOAc). $[\alpha]_D$ –2.2 (*c* 0.9, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.37–7.29 (m, 5H, Ar), 7.04–7.00 (m, 2H, Ar), 6.87–6.84 (m, 2H, Ar), 5.42 (d, *J* = 4.0 Hz, 1H, H-1), 4.71, 4.68 (ABq, *J* = 10.0 Hz, 2H, PhC$\underline{H}_2$), 4.21 (q, *J* = 6.9 Hz, 1H, H-5), 4.12 (ddd, *J* = 5.7, 4.9, 4.0 Hz, 1H, H-2), 3.79 (s, 3H, OC$\underline{H}_3$), 3.03 (dd, *J* = 16.3, 4.9 Hz, 1H, H-3), 2.68 (dd, *J* = 16.4, 5.8 Hz, 1H, H-3), 1.35 (d, *J* = 6.9 Hz, 3H, H-6); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 207.5 (C-4), 155.2 (Ar), 150.8 (Ar), 137.5 (Ar), 128.6 (Ar), 128.0 (Ar), 127.8 (Ar), 117.9 (Ar), 114.7 (Ar), 99.8 (C-1), 76.0 (C-2), 75.9 (C-5), 71.8 (Ph$\underline{C}H_2$), 55.7 (O$\underline{C}H_3$), 40.3 (C-3), 17.0 (C-6); HRMS (ESI) calcd for $(M+Na)^+$ $C_{20}H_{22}O_5Na$: 365.1359. Found: 365.1352.

Chapter 3: Incorporation of Building Blocks into the Lipooligosaccharide Target

After I had synthesized the eight designed building blocks, I started to assemble them into the desired oligosaccharide. Depending on the connectivity of these glycosidic bonds, different strategies were proposed and tested. In this chapter, I will discuss my strategies, as well as their implementation.

3.1 Synthetic Strategy for Octasaccharide and Nonasaccharide

My initial plan was to first synthesize the nonasaccharide **3.1** (Figure 3.1), corresponding to the middle portion of my target molecule. The detailed retrosynthetic analysis of **3.1** is shown in Figure 3.1A. The nonasaccharide could be synthesized by glycosylation of two fragments, disaccharide **3.4** and pentasaccharide **3.3**. Disaccharide **3.4** has the C3 hydroxyl group on the non-reducing end protected by a levulinoyl (Lev) group. The key intermediate, pentasaccharide **3.3**, consists of two L-xylose units, an L-rhamnose residue and a lactose moiety. The pentasaccharide could be synthesized by coupling between a disaccharide donor **3.5** and a trisaccharide acceptor **3.6**. The disaccharide **3.5** has the C4 hydroxyl group on the non-reducing end protected by Troc group. Trisaccharide **3.6** could be obtained from glycosylation between an L-rhamnose donor and a lactose acceptor.

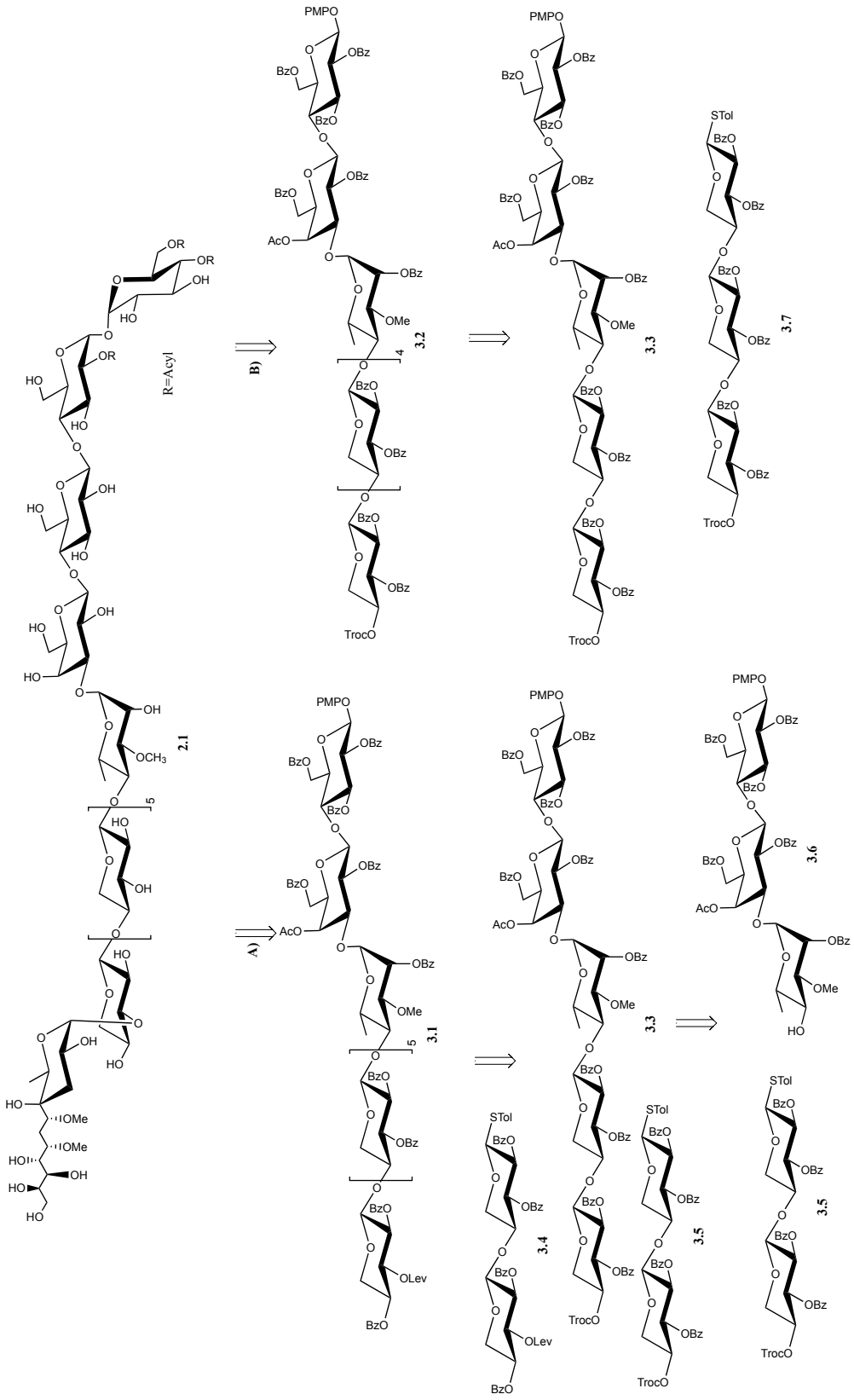


Figure 3.1. Retrosynthetic Analysis.

In the course of carrying out the assembly of the target, I anticipated that this strategy might not be efficient in the later stages of the synthesis. In particular, I envisioned that there would be difficulties in installing the 3,6-dideoxy sugar residue in good yield. As described in Chapter 2, the synthesis of this 3,6-dideoxy sugar turned out to be problematic; therefore, it is as precious as the synthetic nonasaccharide. The formation of the α-(1,2-*cis*)-glycosidic bond between the 3,6-dideoxy sugar and the nonasaccharide could lead to an α/β mixture, which could mean the loss of two precious synthesized molecules. Therefore, I modified my original strategy to one in which octasaccharide **3.2**, shown in Figure 3.1B, containing only five L-xylose moieties would be synthesized first. I envisioned this would require the preparation of three fragment oligosaccharides, disaccharide **3.5** and trisaccharides **3.7** and trisaccharide acceptor **3.6** (Figure 3.1). With the octasaccharide **3.2** in hand, the final decasaccharide target could be prepared by the introduction of a donor derived from disaccharide **3.8** (Figure 3.2). In the key step of introducing a disaccharide derived from **3.8** to octasaccharide **3.2**, the glycosylation stereocontrol would be controlled by the benzoate protecting group on O-2 of the L-xylose moiety, leading to 1,2-*trans*-glycoside formation. The synthesis of **3.8** could come from the coupling of **3.9** and **2.30** (Figure 3.2).

In the sections below, both of these approaches, involving either an advanced nonasaccharide or octasaccharide intermediate, are described.

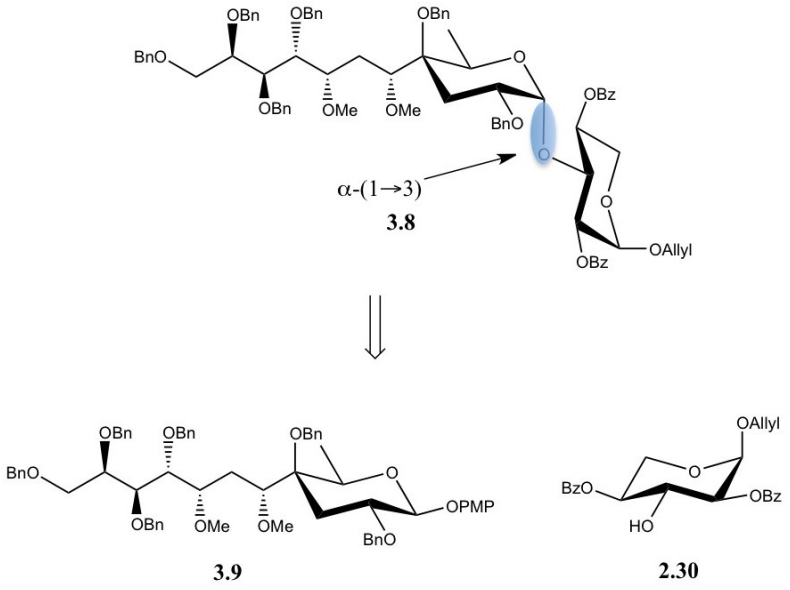


Figure 3.2. Retrosynthetic analysis for α-(1→3) linkage formation.

3.2 Synthesis of disaccharides from xylose building blocks

3.2.1 Synthesis of L-xylose donor and acceptor

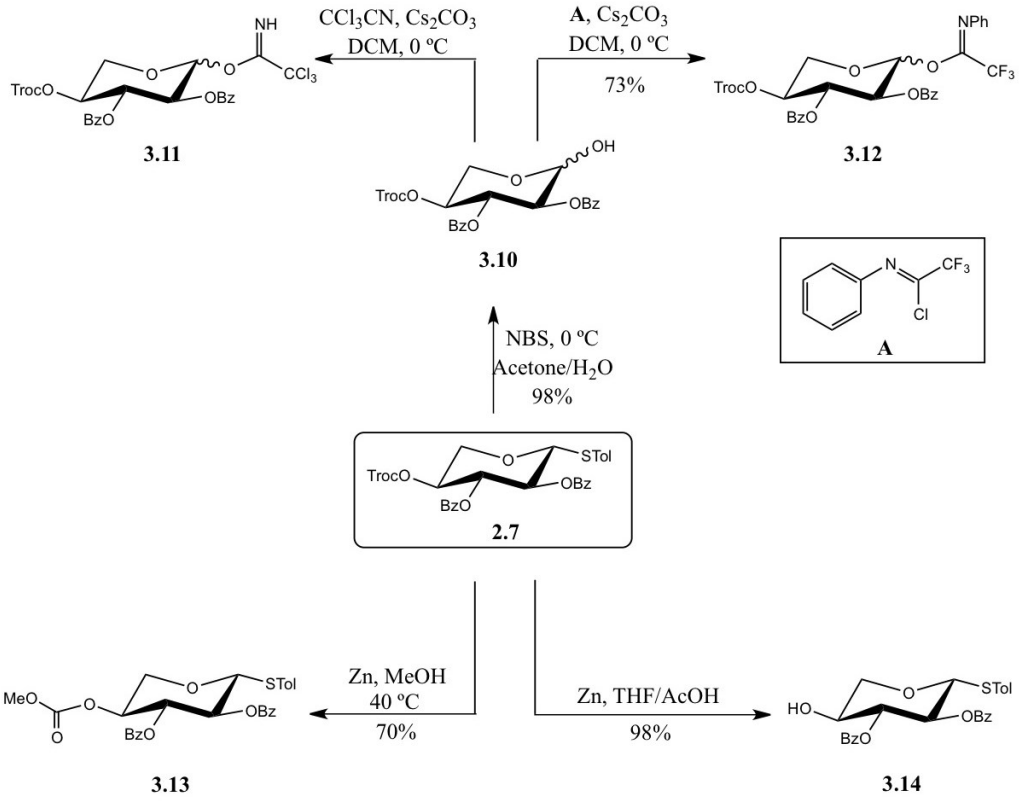
To synthesize disaccharides **3.4** and **3.5**, appropriate glycosyl donors and acceptors needed to be prepared first. In Chapter 2, I described the preparation of thioglycoside **2.7** (Scheme 3.1). My general strategy for the preparation of **3.5** was to couple two equivalents of this species together. However, because **3.5** is

also a thioglycoside, it was necessary to convert a portion of **2.7** into another glycosyl donor before it was coupled with a thioglycoside acceptor. This is necessary as chemoselective activation of one thioglycoside over another is problematic and many side-products were expected. Therefore, monosaccharide **2.7** was converted to two different glycosyl imidate donors. Trichloroacetimidates were introduced as a glycosyl donors by Schmidt in 1980,[158] and became popular in oligosaccharide synthesis. More recently, Yu and co-workers developed a new type of glycosyl imidate, *N*-phenyl trifluoroacetimidates, and applied them to oligosaccharide synthesis.[159-161] These *N*-phenyl trifluoroacetimidates are more stable and less reactive, giving them advantages over trichloroacetimidates in some reactions.

To synthesize the required trichloroacetimidate and *N*-phenyl trifluoroacetimidate derivatives, thioglycoside **2.7** was first hydrolyzed by *N*-bromosuccinimide in acetone and water. As depicted in Scheme 3.1, hemiacetal **3.10** was obtained in 98% yield. The hemiacetal was then converted to trichloroacetimidate **3.11** and *N*-phenyl trifluoroacetimidate **3.12**, respectively, as detailed below.

In the preparation of the trichloroacetimidate, both Cs_2CO_3 and DBU were used as bases. When Cs_2CO_3 was used, the reaction mixture was just filtered through Celite to remove insoluble salts. The crude imidate was used immediately after drying under high vacuum. If DBU was used, the mixture was concentrated and quickly purified by flash chromatography. The imidates produced by either method gave similar results in the glycosylations. The *N*-phenyl

trifluoroacetimidate donor **3.12** can be easily prepared by stirring hemiacetal **3.10** and trifluoro-*N*-phenylacetimidoyl chloride in the presence of Cs_2CO_3.



Scheme 3.1. Synthesis of glycosyl acceptor and donors from xylose building block **2.7**.

Preparation of the acceptor needed for the glycosylation required the removal of the Troc group, which can be selectively cleaved in the presence of benzoate esters using zinc dust. In an initial series of studies, the Troc group was converted to methyl carbonate derivative **3.13** in 70% yield. Presumably, this occurs by displacement of the trichloroethyl group by the solvent. This side reaction could be avoided by changing the solvent from methanol to a 4:1 mixture

of THF and acetic acid. Under these conditions, the reaction was completed within 15 min at room temperature, leading to the isolation of glycosyl acceptor **3.14** in 98% yield.

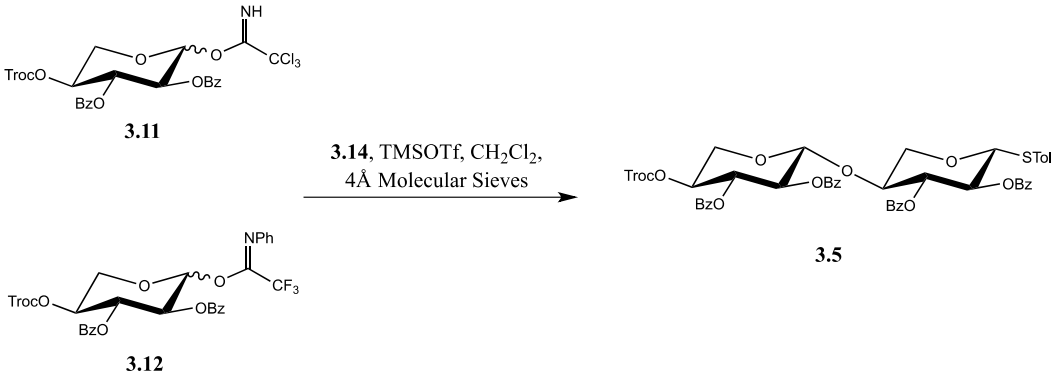
3.2.2 Synthesis of L-xylose disaccharide 3.5

With the glycosyl donors and acceptors synthesized, I tested glycosylation reaction conditions for the preparation of the xylose disaccharide **3.5**.

When I performed the glycosylation using tricholoroacetimidate **3.11** and acceptor **3.14** for the first time, only 32% of the desired product was isolated (Entry 1, Table 3.1). Generally, there are two major reasons that can lead to low yields in glycosylation reactions using trichloroacetimidate donors: a) rearrangement of the trichloroacetimidate during the glycosylation to the *N*-glycosyl-trichloroacetamide derivative;[162-165] b) when thioglycosides are used as acceptors, intermolecular sulfur transfer from acceptor to donor.[166,167] In my case, both reactions were observed, with the rearrangement being the more serious problem. Reducing the amount of Lewis acid promoter used in the reaction minimized the rearrangement of the trichloroacetimidate into the corresponding *N*-glycosyl-trichloroacetamide derivative. When the amount of TMSOTf was reduced from 0.15 eq to 0.05 eq relative to acceptor **3.14**, the yield of the glycosylation increased to 77%. Further changes to the reaction conditions did not give a better yield of the desired product. I also investigated the reaction of the

more stable *N*-phenyl trifluoroacetimidate donor **3.12** with acceptor **3.14** at room temperature; however, disaccharide **3.5** was only obtained in a 46% yield.

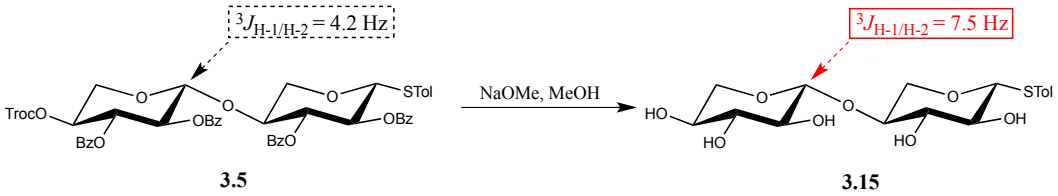
Table 3.1. Preparation of xylose disaccharide.



Entry	Donor	Acceptor	TMSOTf	Temperature	Yield
1	**3.11** (2.0 eq)	**3.14**	0.15 eq	–20 °C	32%
2	**3.11** (2.0 eq)	**3.14**	0.05 eq	–20 °C	77%
3	**3.12** (1.2 eq)	**3.14**	0.05 eq	R.T.	46%

To confirm that the desired β-linkage was obtained, ^{1}H NMR spectroscopic analysis was used to determine the stereochemistry of the newly formed glycosidic linkage. The NMR spectrum showed that the $^{3}J_{H,H}$ value for H-1 of the non-reducing sugar residue is only 4.2 Hz, which is much lower than the coupling constant expected for a 1,2-*trans* glycoside with the xylopyranose stereochemisty. The pyranose form of a pentose, such as L-xylose, would be expected to have a more flexible ring conformation than a hexopyranose due to

lack of a hydroxymethyl group at C-5.[168] Thus, I postulated that steric congestion between the bulky aglycone moiety (the reducing-end residue) and the benzoate group on O-2 on the non-reducing end moiety could lead to this xylopyranoside ring adopting a conformation other than the regular $^{1}C_{4}$ conformation. According to previous Molecular Mechanics calculations,[168] the lowest energy ring conformation of β-D-xylopyranose is $^{4}C_{1}$, while the second lowest energy conformation is $^{2}S_{O}$. However, the energy gap between the two conformations is only 2.6 kcal/mol. Alternatively, a mixture of conformations that are equilibrating fast on the NMR time scale could be present. Both of these situations could result in an unexpected coupling constant between H-1 and H-2. Indeed, the $^{3}J_{H1,H2}$ I observed (4.2 Hz) matches that calculated for the $^{2}S_{O}$ conformation of β-D-xylopyranose (4.5 Hz).[168] To confirm that the disaccharide **3.5** had the correct glycosidic stereochemistry at the non-reducing residue, all of the protecting groups were removed by treatment with sodium methoxide in methanol. ^{1}H NMR spectroscopic analysis of the deprotected product **3.15** showed that the $^{3}J_{H,H}$ value for H-1 of the non-reducing end moiety is 7.5 Hz, consistent with a 1,2-*trans* linkage. Thus, I am confident that the glycosylation produced the desired β-glycoside.

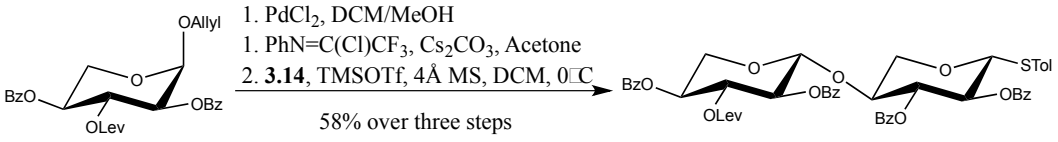


3.5 **3.15**

Scheme 3.2. Confirmation of stereochemistry on new-formed glycosidic bond in **3.5** through deprotection and ^{1}H NMR spectroscopic analysis.

3.2.3 Synthesis of disaccharide 3.4

Synthesis of the disaccharide **3.4** (Scheme 3.3) started from the hydrolysis of synthesized building block **2.6**, which was described in Chapter 2. The anomeric allyl group was cleaved by treatment with a catalytic amount of $PdCl_2$ in dichloromethane and methanol followed by formation of the corresponding *N*-phenyl trifluoroacetimidate. The latter intermediate was coupled with the L-xylose-derived acceptor **3.14** to yield the desired disaccharide **3.4** in a 58% yield over the three steps.



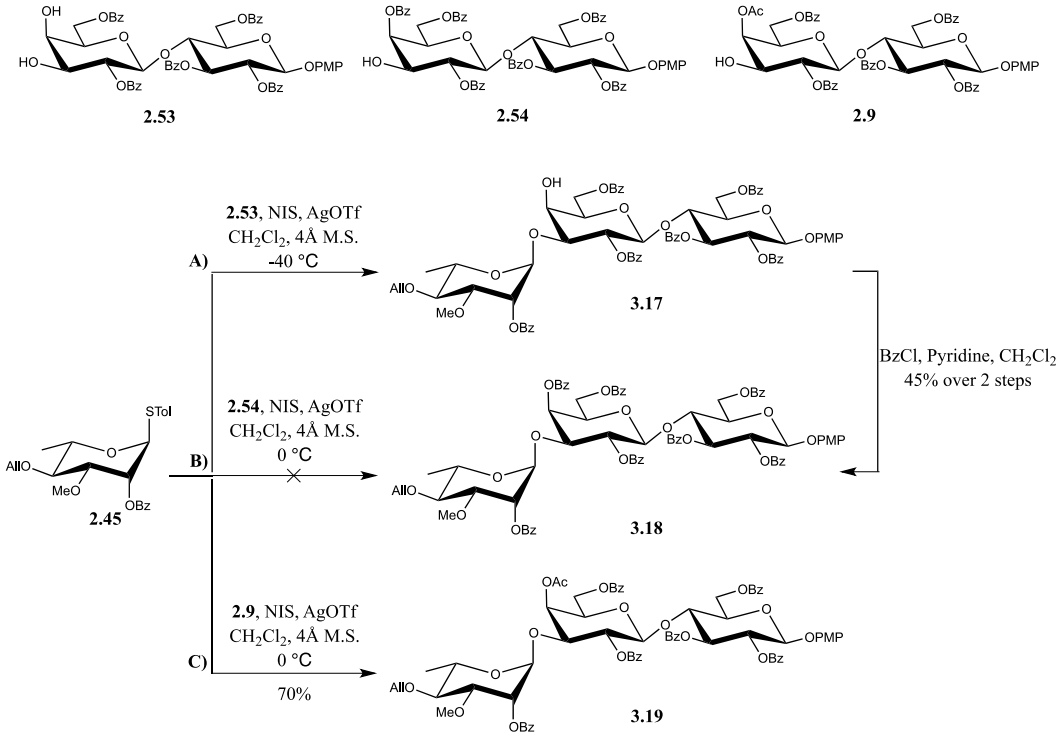
2.6 **3.4**

Scheme3.3. Synthesis of disaccharide **3.4**.

3.3 Synthesis of trisaccharide 3.6

To synthesize the trisaccharide with the L-rhamnose and lactose moieties, I first tested the glycosylation reaction between L-rhamnose donor **2.45** and lactose diol acceptor **2.53** (Scheme 3.4A). As the C-4 hydroxyl group on a galactose moiety is less nucleophilic than the C-3 hydroxyl group,[169-171] diol **2.53** can be used as a glycosyl acceptor. I expected that the (1→3) glycosidic bond would be obtained in preference to the (1→4)-linkage. The reaction was promoted by NIS and AgOTf at –40 °C. The product was difficult to purify due to the formation of a by-product (structure undetermined) that had similar polarity. Therefore, the C-4 hydroxyl group on the galactose residue of **3.17** was protected by a benzoyl ester. The fully protected trisaccharide **3.18** was obtained in a 45% over two steps. In analyzing the ^{1}H NMR spectra of **3.18**, the chemical shift of the H-4 of the galactopyranose residue was more downfield (5.58 ppm) than that of H-3 (4.02 ppm), thus confirming that benzoylation had occurred on the C-4 hydroxyl group. Therefore, glycosylation had occurred on the C-3 hydroxyl group.

To avoid potential separation issue and to increase the yield, two other lactose acceptors, prepared as described in Chapter 2, were investigated (Schemes 3.4B and C). In one of these (**2.54**), the C-4 hydroxyl group was protected as a benzoate ester; in the other (**2.9**), this group was protected as an acetate ester. The glycosylation between donor **2.45** and acceptor **2.54** failed to give any of the desired product. The acceptor appeared to be unreactive under these reaction conditions (Scheme 3.4B).



Scheme 3.4. Glycosylation using L-rhamnose donor **2.45**.

On the contrary, the glycosylation using acceptor **2.9** gave good results; the desired trisaccharide **3.19** could be isolated in 70% yield (Scheme 3.4C). The glycosylation resulted in the formation of an α-rhamnopyranosyl linkage. To confirm the stereochemistry of this linkage, a coupled HSQC experiment was performed on the trisaccharide product. The $^{1}J_{C\text{-}1,H\text{-}1}$ of the rhamnose residue in trisaccharide **3.18** was 172 Hz, which falls into the range expected for an α-linkage (Figure 3.3).[106,107]

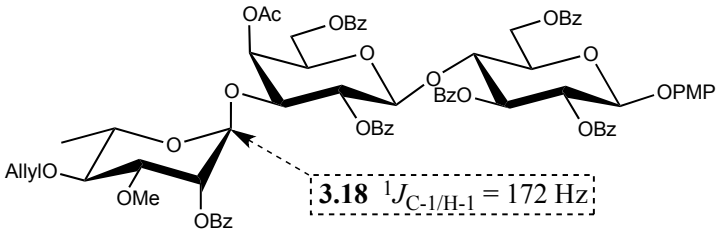
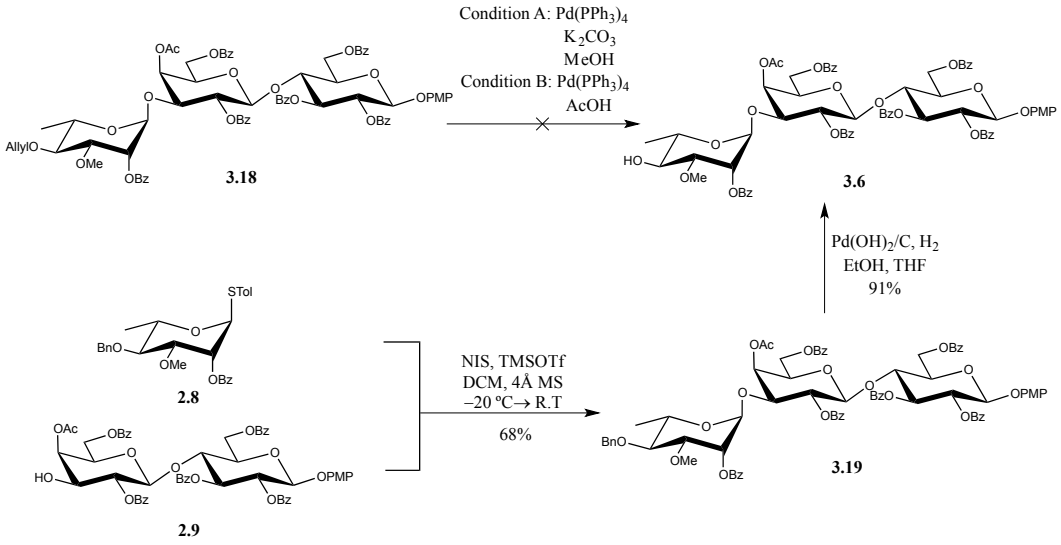


Figure 3.3. Confirmation of α-glycosidic linkage.

After synthesizing the rhamnopyranosyl–lactose trisaccharide, the protecting group on the C3 hydroxyl group of the rhamnopyranose moiety needed to be removed to prepare a glycosyl acceptor for the synthesis of the pentasaccharide. Thus, trisaccharide **3.18** was treated with $Pd(PPh_3)_4$ under both basic[172] and acidic[173] conditions to deprotect the allyl group (Scheme 3.5). When the trisaccharide was treated with palladium catalyst and K_2CO_3 in methanol (basic conditions) at room temperature overnight, TLC analysis showed no product was generated. The mixture was then heated at reflux for four hours and two new spots were observed by TLC while the starting material remained as the major product. The reaction led to a number of products by TLC analysis after 12 h stirring at reflux. This is presumably due to the basic conditions, which removed the benzoyl esters on the trisaccharide. This reaction was performed again using acidic conditions ($Pd(PPh_3)_4$ in acetic acid). This time, no product was formed after overnight stirring. Therefore, this approach was abandoned and I explored the use of an alternate substrate, in which the allyl glycoside was replaced with a benzyl glycoside. To achieve this, glycosylation between donor **2.8** and acceptor **2.9** (Scheme 3.5) gave trisaccharide **3.19** under similar conditions to those use for

the coupling of **2.45** and **2.9**. After optimization of the reaction, the trisaccharide product could be isolated in 68% yield by using the NIS and TMSOTf promoter system at –20 °C in dichloromethane as the solvent.



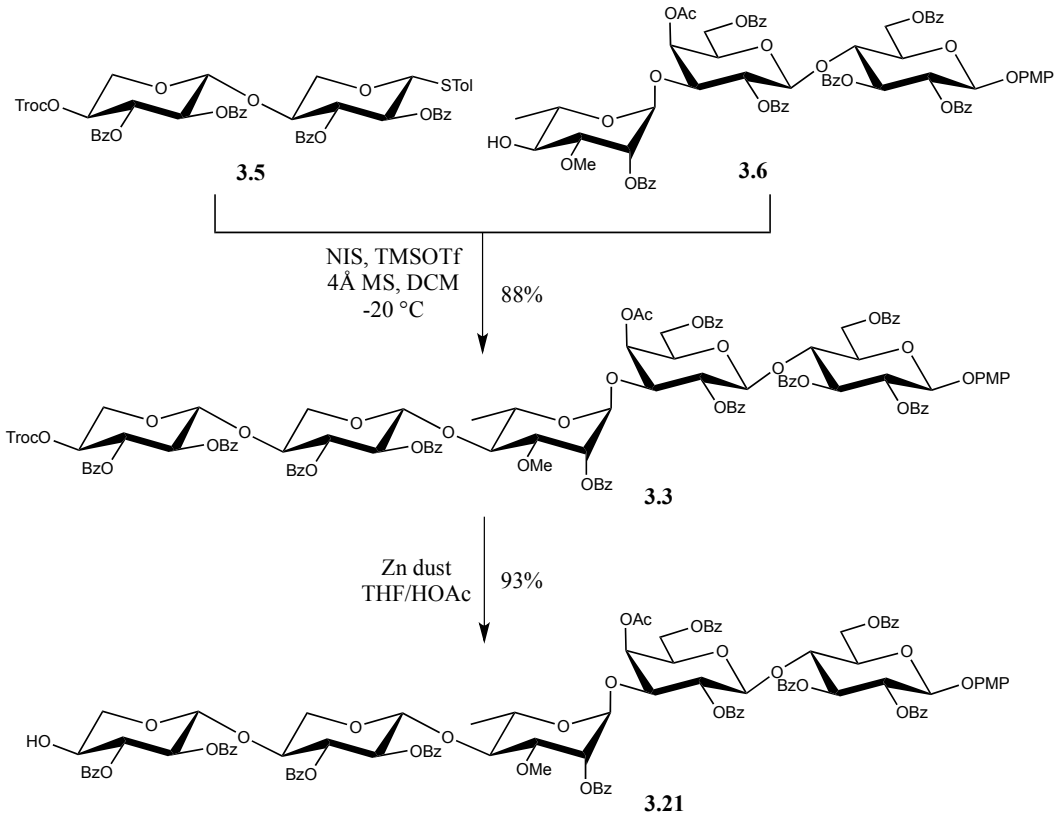
Scheme 3.5. Preparation of trisaccharide acceptor **3.6**.

Deprotection of the benzyl group on trisaccharide **3.19** was straightforward. The reaction was completed by hydrogenation using $Pd(OH)_2/C$ as a catalyst under H_2 gas. The reaction gave the trisaccharide acceptor **3.6** in an excellent yield (91%).

3.4 Synthesis of nonasaccharide 3.1

With the trisaccharide acceptor **3.6** in hand, I moved on to the glycosylation between the disaccharide donor **3.5** and the trisaccharide acceptor **3.6** (Scheme 3.6) to generate a pentasaccharide. The reaction was conducted using

NIS and TMSOTf as the promoter system at –20 °C. The glycosylation gave the product pentasaccharide **3.3** containing a β-linkage formed in a 88% yield.



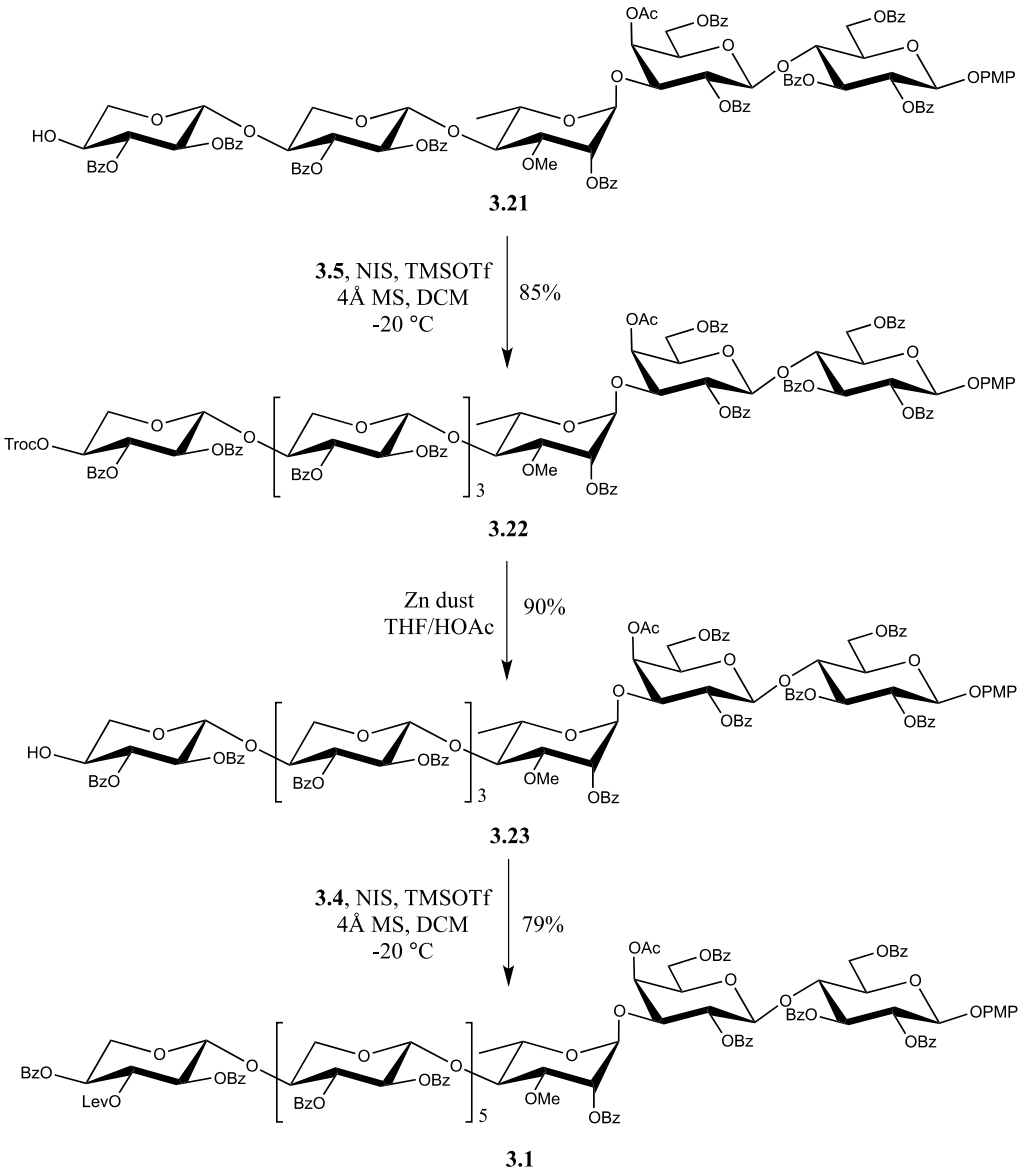
Scheme 3.6. Synthesis of the pentasaccharide acceptor **3.21**.

In the ^{1}H NMR spectrum of the product, the $^{3}J_{\text{H-1,H-2}}$ of the newly formed glycosidic bond was 4.3 Hz, similar to that observed for the disaccharide **3.5**. Thus, it appears that the conformational effects leading to a smaller than expected $^{3}J_{\text{H-1,H-2}}$ are present not only in small (disaccharide) fragments, but also large (pentasaccharide) fragments containing O-2 benzoylated β-xylopyranosides. After the glycosylation, the removal of the Troc group in the presence of the

benzoate esters was achieved using zinc dust in THF and acetic acid affording pentasaccharide acceptor **3.21** in 93% yield. Interestingly, the $^{3}J_{\text{H-1,H-2}}$ of the terminal β-xylopyranosyl residue in **3.21** is 5.9 Hz, which is also less than expected for a 1,2-*trans* linkage (See discussion above in section 3.3.2). This points to how subtle changes in ring substitution can lead to conformational changes in these rings.

The pentasaccharide was then converted to the heptasaccharide (Scheme 3.7). Glycosylation between the disaccharide donor **3.5** and the pentasaccharide acceptor **3.21** was performed using the NIS/TMSOTf promoter system. As observed in the formation of the pentasaccharide, the yield of this reaction was excellent; heptasaccharide **3.22** was obtained in 85% yield. Cleavage of the Troc group on **3.22** was achieved using zinc dust in THF and acetic acid, which provided the corresponding alcohol **3.23** in 90% yield.

The heptasaccharide could be further homologated by applying the glycosylation described above to **3.23**. Thus, the synthesis of the desired nonasaccharide **3.1** was performed using disaccharide donor **3.4** and heptasaccharide acceptor **3.23**, which gave a 79% yield of the desired product.



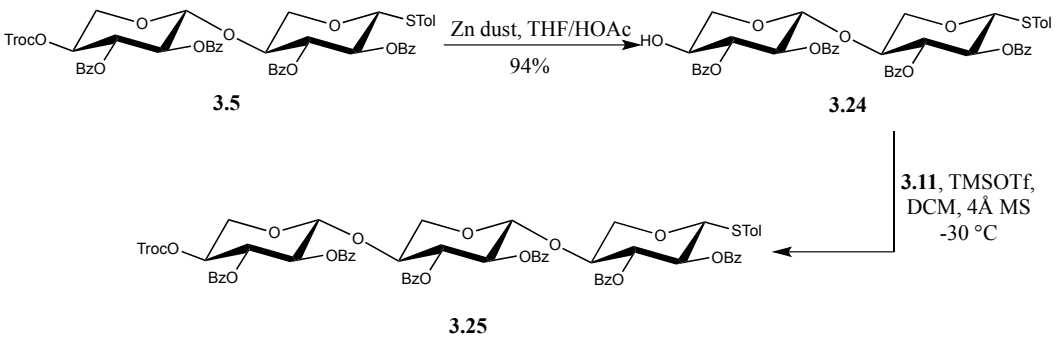
Scheme 3.7. Synthesis of nonasaccharide **3.1**.

3.5 Synthesis of octasaccharide 3.2

As I discussed earlier in this chapter, the target molecule has a 1,2-*cis*-α-linkage between the 3,6-dideoxy sugar and xylose residues. I had concerns about coupling this group to a nonasaccharide alcohol derived from **3.23** in good

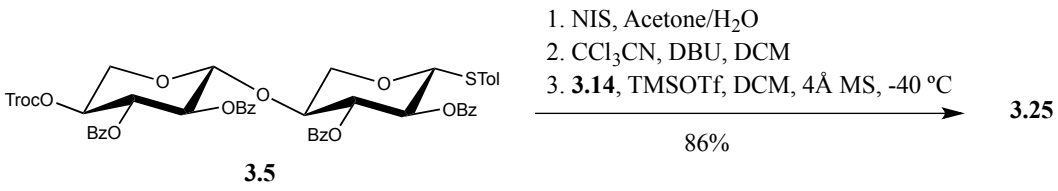
stereoselectivity. Therefore, I also explored an approach where this dideoxy sugar would be introduced as part of a disaccharide block, where the key glycosylation involved the formation of a 1,2-*trans* glycosidic bond (see Figure 3.2), which is a much more straightforward reaction. Use of this approach required octasaccharide **3.2** (See Figure 3.1), the synthesis of which is detailed below.

Synthesis of **3.2** required the preparation of a trisaccharide containing three xylopyranose moieties (**3.25**, Scheme 3.8). Two strategies to **3.25** were explored. One approach (Scheme 3.8) involved the synthesis of the trisaccharide from L-xylose donor **3.11** and disaccharide acceptor **3.24**. Acceptor **3.24** was obtained from disaccharide **3.5** by deprotecting the Troc group using zinc dust; the yield of this reaction was 94%. The next step, glycosylation between **3.24** and thioglycoside **3.11**, was not very successful due to a product separation issue. The product could not be purified by chromatography due to the formation of a by-product that showed similar polarity to the trisaccharide. Changing to a different eluent system also did not give good separation. Although the trisaccharide could be eventually purified by a three-step process: deprotection of the Troc group, purification of product, and then re-installation of the Troc group, this was a time consuming and inefficient process.



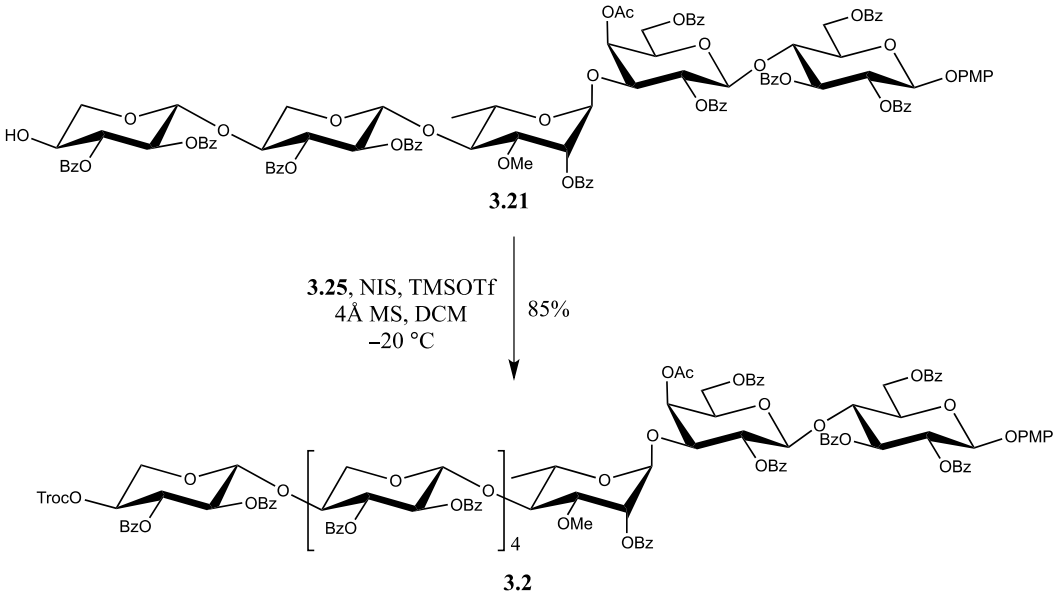
Scheme 3.8. Synthesis of trisaccharide **3.25** from disaccharide acceptor.

Another strategy for the synthesis of trisaccharide **3.25** involved a disaccharide donor and a monosaccharide acceptor (Scheme 3.9). First, disaccharide thioglycoside **3.5** was hydrolyzed with NIS in acetone and water. Then, the resulting hemiacetal was converted to the corresponding glycosyl trichloroacetimidate using CCl_3CN and DBU. Finally, the imidate donor and acceptor **3.13** were treated with TMSOTf in dichloromethane. In this case, the product could be purified by chromatography without any problems. Trisaccharide **3.25** was obtained in 86% yield.



Scheme 3.9. Synthesis of trisaccharide **3.25** from the disaccharide donor.

With trisaccharide **3.25** in hand, I synthesized octasaccharide **3.2** by coupling it with pentasaccharide acceptor **3.21** (Scheme 3.10). Thus, treatment of **3.21** and **3.25** with NIS and TMSOTf in dichloromethane for 30 min at –20 °C afforded octasaccharide **3.2** in 85% yield.

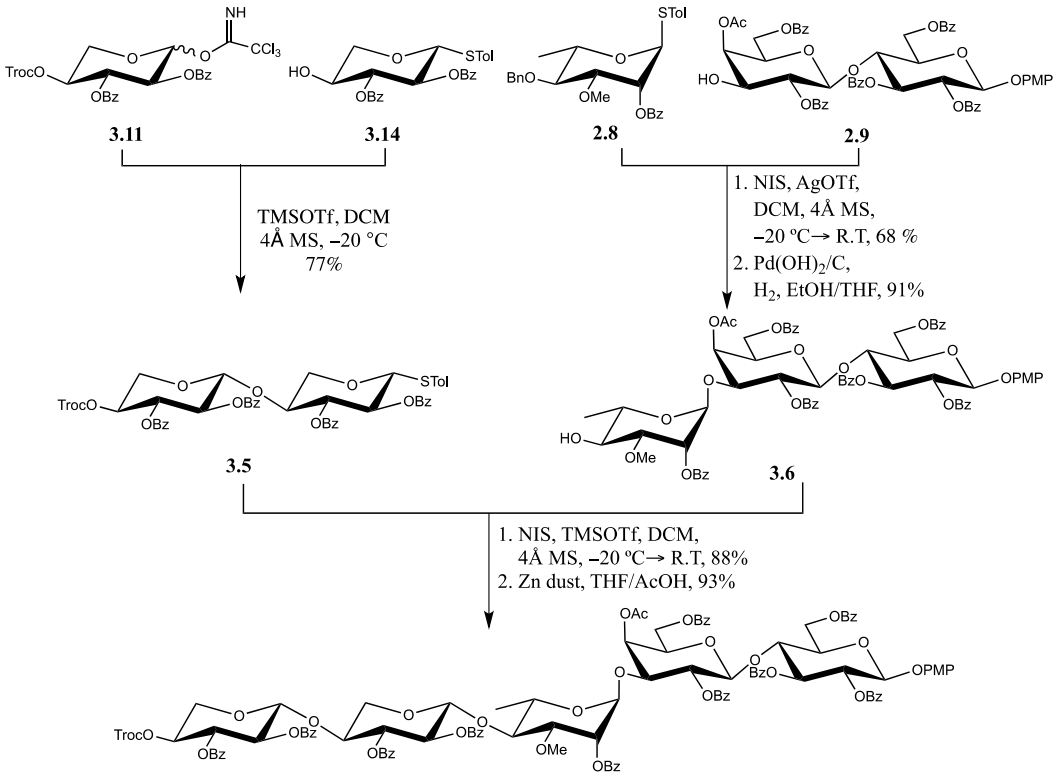


Scheme 3.10. Synthesis of octasaccharide **3.2**.

3.6 Summary

In this chapter, I have described synthetic routes to nonasaccharide **3.1** and octasaccharide **3.2**, key intermediates in the route designed for the synthesis of my lipooligosaccharide target molecule. The synthesis of both of these advanced intermediates involved the preparation of pentasaccharide intermediate **3.21**. To obtain this key intermediate, disaccharide donor **3.5** and trisaccharide acceptor **3.6** were prepared from previously synthesized donors and acceptors (Scheme 3.11).

In the synthesis of **3.5**, after optimization of the reaction condition, a 77% yield of the product could be isolated. While glycosylation between donor **2.8** and acceptor **2.9** could give trisaccharide **3.6** in 68%. Reaction of **3.5** and **3.6** promoted by TMSOTf, followed by cleavage of the Troc group, gave an 82% yield of the pentasaccharide **3.21**.



Scheme 3.11. Summary for the synthesis of pentasaccharide acceptor **3.21**.

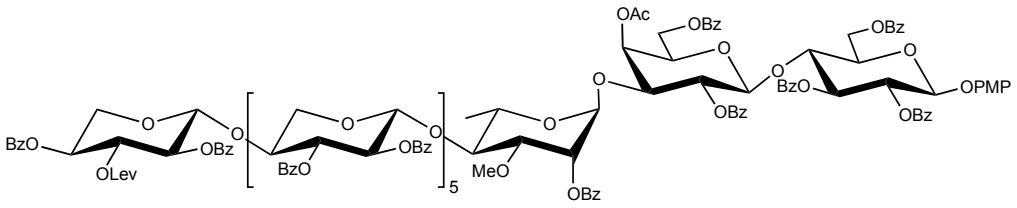
After the pentasaccharide acceptor was obtained, glycosylation between disaccharide **3.5** and pentasaccharide acceptor **3.21** yielded the heptasaccharide in 85% (Scheme 3.6). The resulting heptasaccharide acceptor was then coupled with

disaccharide donor **3.4** to give, in 79% overall yield, the desired nonasaccharide **3.1**. Alternatively, octasaccharide **3.1** could be synthesized from the trisaccharide donor and pentasaccharide acceptor **3.21** in 85% yield (Scheme 3.10). The octasaccharide will be used in assembling the final target by introducing a disaccharide containing a 3,6-dideoxy sugar and the asymmetrically substituted trehalose lipid moiety.

3.7 Experimental

General methods for chemical synthesis: All reagents were purchased from commercial sources and were used without further purification unless noted. Reaction solvents were purified by successive passage through columns of alumina and copper under an argon atmosphere. All reactions were carried out under positive pressure of argon at room temperature unless specified and were monitored by TLC on silica gel 60-F254 (0.25 mm, Silicycle, Quebec, Canada). Visualization of the reaction components was achieved using UV fluorescence (254 nm) and/or by charring with a solution of H_2SO_4 in ethanol. Organic solvents were evaporated under reduced pressure at < 50 °C unless noted. The products were purified by column chromatography on silica gel (230–400 mesh, Silicycle, Quebec, Canada). The ratio between silica gel and crude product ranged from 100:1 to 20:1 (w/w). The yields reported are after purification. Optical rotations were measured on Perkin–Elmer 241 polarimeter at ambient temperature and are in units of degree•mL/(g•dm). ^{1}H NMR spectra were recorded at 500 or 700 MHz and chemical shifts were referenced to $CHCl_3$ (7.26 ppm), CHD_2OD (3.30 ppm),

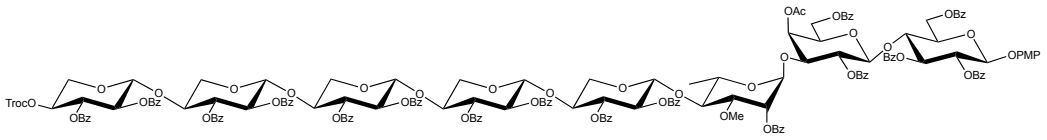
HDO (4.79 ppm). ^{13}C NMR spectra were recorded at 125 or 175 MHz and chemical shifts were referenced to $CDCl_3$ (77.06 ppm) or CD_3OD (49.0 ppm). Assignments of NMR spectra were based on two-dimensional experiments (^1H–^1H COSY, HMQC or HSQC, and HMBC) and stereochemistry of the anomeric centers of the pyranose rings were confirmed by measuring $^1J_{C\text{-}1,H\text{-}1}$ via coupled HMQC or HSQC experiments, if necessary. The monosaccharide residues in the disaccharide, trisaccharide, and pentasaccharide, are labeled by a, b, c, d and e starting from the non-reducing end to the reducing end. Electrospray mass spectra were recorded on Agilent Technologies 6220 TOF.



***p*-Methoxylphenyl 2,4-di-*O*-benzoyl-3-*O*-levulinyl-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranosyl-(1→4)-2-*O*-benzoyl-3-*O*-methyl-α-L-rhamnopyranosyl-(1→3)-4-*O*-acetyl-2,6-di-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (3.1).** To a solution of donor **3.4** (46.8 mg, 51.8 μmol), acceptor **3.23** (65.7 mg, 25.9 μmol) in dry CH_2Cl_2 (2 mL) was added 4Å molecular sieves. The suspension was stirred for 30 min before NIS (17.5 mg, 77.8 μmol) was

added at room temperature. The reaction mixture was stirred for 15 min and then it was treated with a 0.1 M solution of TMSOTf in CH_2Cl_2 (13 μL) at −20 °C. The reaction was stirred for 30 min at which point the TLC showed complete consumption of the acceptor. The reaction mixture was treated with Et_3N, filtered through a pad of Celite and the filtrate was concentrated. The crude residue was purified by chromatography (100:1, CH_2Cl_2–CH_3OH) to yield **3.1** (67.2 mg, 79%) as a white foam. R_f 0.43 (50:1, CH_2Cl_2–CH_3OH); $[\alpha]_D$ +14.2 (*c* 0.8, $CHCl_3$) ; ^1H NMR (700 MHz, $CDCl_3$, δ_H) 8.07−7.79 (m, 33H), 7.75−7.67 (m, 2H), 7.62−7.46 (m, 16H), 7.46−7.17 (m, 39H), 6.90−6.78 (m, 2H), 6.69-6.55 (m, 2H), 5.81 (app t, *J* = 9.4 Hz, 1H), 5.63 (dd, *J* = 9.7, 7.7 Hz ,1H), 5.53−5.35 (m, 5H), 5.29 (app t, *J* = 6.9 Hz, 1H), 5.26−5.21 (m, 1H), 5.19−5.14 (m, 1H), 5.14−4.98 (m, 5H), 4.90−4.82 (m, 1H), 4.77−4.74 (m, 2H), 4.67−4.59 (m, 3H), 4.47−4.38 (m, 3H), 4.25−4.18 (m, 1H), 4.00−3.77 (m, 6H), 3.77−3.66 (m, 4H), 3.66−3.56 (m, 2H), 3.54−3.32 (m, 5H), 3.30−3.24 (m, 2H), 3.15−2.89 (m, 6H), 2.59-2.51 (m, 2H), 2.48–2.38 (m, 2H), 2.04–1.94 (m, 3H), 1.05–0.94 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 205.6, 171.6, 169.5, 165.70, 165.68, 165.35, 165.34, 165.30, 165.29, 165.25 (3C), 165.19, 165.13, 164.98, 164.96, 164.90, 164.87 (2C), 164.84, 164.81, 155.68, 150.94, 133.45, 133.41, 133.40, 133.32, 133.27, 133.24 (2C), 133.21, 133.16, 133.06, 133.03 (3C), 129.87, 129.82, 129.78 (3C), 129.76 (2C), 129.73 (3C), 129.69 (2C) 129.68 (2C), 129.64 (2C), 129.62, 129.59 (3C), 129.56 (3C), 129.54, 129.51 (2C), 129.44, 129.36, 129.26 (2C), 129.23, 129.20 (2C), 129.13, 128.78, 128.66 (2C), 128.50 (2C), 128.46 (3C), 128.42 (4C), 128.36 (2C), 128.29 (2C), 128.27 (2C), 128.24 (3C), 128.21 (2C), 128.18 (2C), 118.93, 114.41,

100.79 (2C), 100.75, 100.69, 100.58, 100.55 (2C), 99.58, 99.08, 79.77, 77.77, 77.47, 77.26, 75.80, 75.70, 75.38, 75.26, 75.23, 74.33, 73.17, 72.67, 72.27, 72.09, 72.04 (2C), 71.99, 71.69 (2C), 71.66 (2C), 71.46, 71.40 (2C), 71.37 (2C), 71.31, 71.25 (2C), 71.23 (2C), 69.87, 69.54, 68.38, 68.22 (2C), 68.13, 62.51, 62.29, 62.24 (3C), 62.22 (2C), 61.45, 60.73, 56.91, 55.55, 37.77, 29.50, 27.84, 20.32, 17.58. HRMS (ESI) calcd for $(M+2Na)^{+2}$ $C_{189}H_{168}O_{61}Na_2$: 1729.4914. Found: 1729.4934. (+2 charge state)

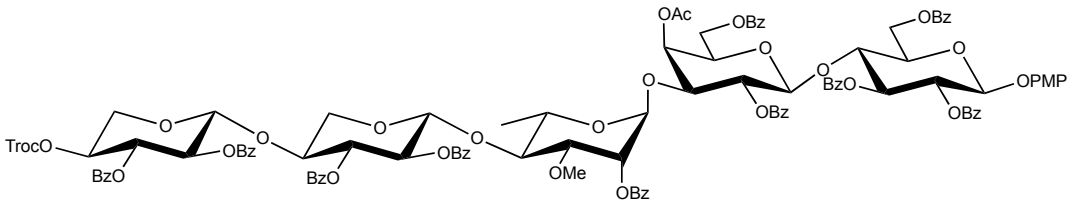


***p*-Methoxylphenyl 2,3-di-*O*-benzoyl-4-*O*-(2,2,2-trichloroethoxycarbonyl)-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranosyl-(1→4)-2-*O*-benzoyl-3-*O*-methyl-α-L-rhamnopyranosyl-(1→3)-4-*O*-acetyl-2,6-di-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (3.2).**

To a solution of donor **3.25** (162.8 mg, 124 μmmol), acceptor **3.21** (185.7 mg, 95 μmol) in dry CH_2Cl_2 (5 mL) was added 4Å molecular sieves. The suspension was stirred for 30 min before NIS (32.0 mg, 142.2 μmol) was added at room temperature. The reaction mixture was stirred for 15 min and then it was treated with a 0.1 M solution of TMSOTf in CH_2Cl_2 (48 μL) at –20 °C. The reaction was stirred for 30 min at which point the TLC showed complete consumption of glycosyl acceptor. The reaction mixture was then treated with Et_3N, filtered

through a pad of Celite and the filtrate was concentrated. The crude residue was purified by chromatography (7:1 toluene–EtOAc) to yield **3.2** (254.8 mg, 85%) as a white foam. R_f 0.28 (5:1 toluene–EtOAc); $[\alpha]_D$ +9.2 (*c* 2.3, $CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$, δ_H) 8.03–7.82 (m, 29H), 7.72–7.71 (m, 2H), 7.58–7.28 (m, 46H), 7.23–7.21 (m, 2H), 7.18–7.16 (m, 1H), 6.85–6.83 (m, 2H), 6.64–6.62 (m, 2H), 5.80 (app t, *J* = 9.4 Hz, 1H), 5.63 (dd, *J* = 9.7, 7.8 Hz, 1H), 5.48 (app t, *J* = 7.9 Hz, 1H), 5.45–5.38 (m, 5H), 5.22 (d, *J* = 3.9 Hz, 1H), 5.15 (dd, *J* = 8.2, 6.4 Hz, 1H), 5.10–5.01 (m, 6H), 4.77–4.76 (m, 2H), 4.73 (td, *J* = 5.9, 4.0 Hz, 1H), 4.68–4.62 (m, 5H), 4.59 (dd, *J* = 11.5, 1.6 Hz, 1H), 4.47–4.41 (m, 3H), 4.20 (app t, *J* = 9.4 Hz, 1H), 3.96–3.89 (m, 3H), 3.85 (dd, *J* = 12.8, 3.7 Hz, 1H), 3.80–3.75 (m, 3H), 3.70–3.67 (m, 5H), 3.58 (ddd, *J* = 7.2, 5.7, 5.4 Hz, 2H), 3.51–3.34 (m, 8H), 3.28 (dd, *J* = 12.0, 8.1 Hz, 1H), 3.06 (dd, *J* = 12.5, 8.6 Hz, 2H), 2.99 (dd, *J* = 12.5, 8.6 Hz, 1H), 2.93 (d, *J* = 6.2 Hz, 3H), 1.82 (s, 3H), 0.98 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$, δ_C) 169.5, 165.70, 165.68, 165.35, 165.34, 165.30, 165.25 (2C), 165.19, 165.12, 164.97, 164.96, 164.91, 164.88, 164.86, 164.82, 164.81, 155.69, 153.04, 150.95, 133.58, 133.51, 133.41, 133.31 (2C), 133.27, 133.24 (3C), 133.20, 133.17, 133.07, 133.03 (2C), 132.99, 129.95, 129.87, 129.82, 129.78, 129.76, 129.73 (2C), 129.69 (2C), 129.68, 129.66, 129.64, 129.61 (2C), 129.59 (2C), 129.56, 129.54, 129.51 (2C), 129.50, 129.44, 129.35, 129.26 (2C), 129.23, 129.18, 129.00, 128.79, 128.70, 128.66 (2C), 128.55 (2C), 128.52 (2C), 128.51, 128.43 (3C), 128.41 (3C), 128.36, 128.29, 128.27, 128.26, 128.21, 128.18, 118.9, 114.4, 100.78, 100.75, 100.69, 100.61, 100.55, 100.54, 99.6, 98.9, 94.1, 79.8, 77.8, 77.5, 76.9, 75.8, 75.69, 75.28, 75.26, 74.8, 73.2 (2C), 72.7 (2C), 72.3,

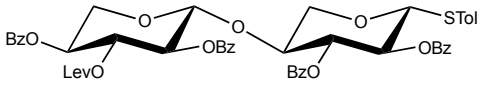
72.04 (3C), 72.00, 71.95 (2C), 71.69, 71.66, 71.5, 71.4 (2C), 71.34 (2C), 71.31, 71.26, 69.3, 68.9, 68.23, 68.22, 68.1, 62.5, 62.27, 62.24, 62.22, 62.21, 62.0, 61.47, 61.46, 59.9, 56.9, 55.6, 20.3, 17.6; HRMS (ESI) calcd for $(M+2Na)^{+2}$ $C_{168}H_{147}Cl_3O_{55}$: 1597.3778. Found: 1597.3829. (+2 charge state)



***p*-Methoxylphenyl 2,3-di-*O*-benzoyl-4-*O*-(2,2,2-trichloroethoxycarbonyl)-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranosyl-(1→4)-2-*O*-benzoyl-3-*O*-methyl-α-L-rhamnopyranosyl-(1→3)-4-*O*-acetyl-2,6-di-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (3.3).** To a solution of donor **3.5** (126.5 mg, 129.0 μmol), acceptor **3.6** (127.4 mg, 0.10 mmol) in dry CH_2Cl_2 (3 mL) was added 4Å molecular sieves. The suspension was stirred for 30 min before NIS (33.7 mg, 149.8 μmol) was added at room temperature. The reaction mixture was stirred for 15 min and then it was treated with a 0.1 M solution of TMSOTf in CH_2Cl_2 (50 μL) at –20 °C. The reaction was stirred for 30 min at which point the TLC showed complete consumption of the acceptor. The reaction mixture was treated with Et_3N, filtered through a pad of Celite and the filtrate was concentrated. The crude residue was purified by chromatography (10:1, toluene–EtOAc) to yield **3.20** (187.6 mg, 88%) as a white foam. R_f 0.60 (1:1, hexane–EtOAc); $[\alpha]_D$ +10.1

(*c* 0.7, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.04–7.90 (m, 18H, Ar), 7.74–7.73 (m, 2H, Ar), 7.59–7.27 (m, 30H, Ar), 6.85–6.83 (m, 2H, Ar), 6.64–6.62 (m, 2H, Ar), 5.80 (app t, *J* = 9.4 Hz, 1H, H-3e), 5.63 (dd, *J* = 9.6, 7.8 Hz, 1H, H-2e), 5.57 (app t, *J* = 7.7 Hz, 1H, H-3b), 5.47 (app t, *J* = 6.1 Hz, 1H, H-3a), 5.43 (dd, *J* = 10.0, 8.0 Hz, 1H, H-2d), 5.24 (d, *J* = 3.3 Hz, 1H, H-4d), 5.21 (dd, *J* = 8.0, 6.4 Hz, 1H, H-2b), 5.18 (dd, *J* = 6.0, 4.5 Hz, 1H, H-2a), 5.08 (d, *J* = 7.8 Hz, 1H, H-1e), 5.04 (app t, *J* = 2.5 Hz, 1H, H-2c), 4.89 (d, *J* = 4.3 Hz, 1H, H-1a), 4.84 (d, *J* = 6.3 Hz, 1H, H-1b), 4.79–4.76 (m, 2H, H-1c, H-4a), 4.70 (s, 2H, $Cl_3CC\underline{H}_2$-), 4.64 (d, *J* = 8.1 Hz, 1H, H-1d), 4.60 (dd, *J* = 11.8, 1.6 Hz, 1H, H-6e), 4.43 (dd, *J* = 11.9, 5.3 Hz, 1H, H-6e'), 4.20 (app t, *J* = 9.5 Hz, 1H, H-4e), 4.11–4.04 (m, 2H, H-5b, H-4b), 3.98–3.91 (m, 2H, H-5a, H-5e), 3.82–3.78 (m, 2H, H-6d, H-3d), 3.68 (s, 3H, $ArOC\underline{H}_3$), 3.64–3.59 (m, 2H, H-5d, H-5c), 3.52–3.38 (m, 5H, H-6d', H-5a', H-5b', H-4c, H-3c), 2.99 (s, 3H, $OC\underline{H}_3$), 1.86 (s, 3H, $C\underline{H}_3C$=O), 1.01 (d, *J* = 6.2 Hz, 3H, H-6c); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 169.5 (C=O), 165.73 (C=O), 165.72 (C=O), 165.5 (C=O), 165.3 (C=O), 165.21 (C=O), 165.17 (C=O), 165.0 (2C, C=O), 164.95 (C=O), 164.8 (C=O), 155.7 (Ar), 153.1 (C=O), 150.9 (Ar), 133.6 (Ar), 133.5 (Ar), 133.44 (Ar), 133.36 (Ar), 133.31 (Ar), 133.29 (Ar), 133.26 (Ar), 133.23 (Ar), 133.13 (Ar), 133.07 (Ar), 130.01 (Ar), 129.94 (Ar), 129.85 (Ar), 129.81 (Ar), 129.79 (2C, Ar), 129.71 (2C, Ar), 129.62 (2C, Ar), 129.59 (Ar), 129.57 (Ar), 129.54 (Ar), 129.49 (2C, Ar), 129.3 (Ar), 129.1 (Ar), 128.81 (Ar), 128.75 (Ar), 128.69 (2C, Ar), 128.53 (3C, Ar), 128.49 (Ar), 128.46 (Ar), 128.43 (Ar), 128.35 (Ar), 128.3 (Ar), 128.2 (Ar), 119.0 (Ar), 114.4 (Ar), 100.8 (C-1d), 100.7 (C-1e), 100.6 (C-1b), 99.6 (C-1c), 98.9 (C-1a), 94.1 ($\underline{C}Cl_3$-),

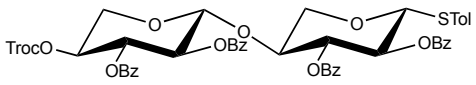
79.8 (C-4c), 77.8 (C-3d), 77.6 (C-3c), 77.0 ($CCl_3\underline{C}H_2$-), 75.8 (C-4e), 75.1 (C-4b), 73.2 (C-5e), 72.7 (C-3e), 72.3 (C-3b), 71.9 (C-4a), 71.71, 71.70, 71.65 (3C, C-2e, C-2b, C-5d), 71.4 (C-2d), 69.3 (C-2a), 68.8 (C-3a), 68.26, 68.23 (2C, C-2c, C-5c), 68.16 (C-4d), 62.5 (C-6e), 61.97 (C-5b), 61.5 (C-6d), 59.9 (C-5a), 57.0 ($O\underline{C}H_3$), 55.6 ($O\underline{C}H_3$), 20.4 ($\underline{C}H_3C$=O), 17.7 (C-6c); HRMS (ESI) calcd for (M+Na) $C_{111}H_{99}{}^{35}Cl_3O_{37}Na$: 2151.4823. Found: 2151.4809.



***p*-Tolyl 2,3-di-*O*-benzoyl-3-*O*-levulinyl-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranoside (3.4).** The preparation of glycosyl donor involves two steps: hydrolysis of **2.6** and synthesis of the corresponding N-phenyl trifluoroaceteimidate: To a solution **2.6** (1.23 g, 2.5 mmol) in CH_2Cl_2 (20 mL) and CH_3OH (5 mL) was added $PdCl_2$ (88.7 mg, 0.5 mmol) with stirring at room temperature. The reaction mixture was allowed to stir for overnight at which point the TLC showed completion of reaction. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated. The crude residue was purified by chromatography (2:1 hexanes–EtOAc) to give the corresponding hemiacetal (938.5 mg, 83%). Then, to this compound (800 mg, 1.8 mmol) and 2,2,2-trifluoro-N-phenylacetimidoyl chloride (0.4 mL, 2.6 mmol) in acetone (18 mL) was added Cs_2CO_3 (856.6 mg, 2.6 mmol) with stirring at room temperature. After stirring for 1 hour at room temperature, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated and the product N-phenyl

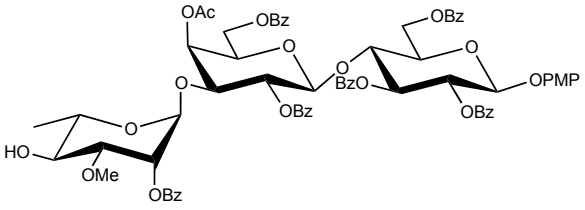
trifluoroaceteimidate was dried over high vacuum for 2 h. To a solution of the donor and acceptor **3.14** (538.9 mg, 1.2 mmol) in dry CH_2Cl_2 (30 mL) was added 4Å molecular sieves. The suspension was stirred for 30 min at room temperature before it was cooled to 0 °C. The reaction mixture was treated with a 0.1 M solution of TMSOTf in CH_2Cl_2 (0.58 mL) with stirring at 0 °C. After 30 min the reaction mixture was treated with Et_3N, after TLC showed complete consumption of the acceptor. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated. The crude residue was purified by chromatography (3:1, hexanes–EtOAc) to yield **3.4** (733.3 mg, 70%) over two steps as a white foam. R_f 0.29 (2:1 hexanes–EtOAc); $[\alpha]_D$ 21.8 (c 3.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.01–7.94 (m, 8H, Ar), 7.57–7.50 (m, 4H, Ar), 7.42–7.33 (m, 10H, Ar), 7.10–7.08 (m, 2H, Ar), 5.65 (app t, *J* = 8.3 Hz, 1H, H-3b), 5.35–5.29 (m, 2H, H-3a, H-2b), 5.08 (dd, *J* = 6.6, 5.0 Hz, 1H, H-2a), 4.92–4.84 (m, 3H, H-1b, H-4a, H-1a), 4.22 (dd, *J* =12.0, 4.8 Hz, 1H, H-5b), 4.05 (td, *J* = 8.5, 4.7 Hz, 1H, H-4b), 3.92 (dd, *J* = 12.3, 3.8 Hz, 1H, H-5a), 3.52 (dd, *J* = 11.9, 9.1 Hz, 1H, H-5b'), 3.34 (dd, *J* = 12.3, 6.4 Hz, 1H, H-5a), 2.59–2.56 (m, 2H, -C$\underline{H}_2$-), 2.47–2.45 (m, 2H, -C$\underline{H}_2$-), 2.32 (s, 3H, ArC$\underline{H}_3$), 2.02 (s, 3H, -C$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 205.7 (C=O), 171.6 (C=O), 165.5 (C=O), 165.4 (C=O), 165.3 (C=O), 165.0 (C=O), 138.4 (Ar), 133.47 (Ar), 133.43 (Ar), 133.32 (2C, Ar), 133.30 (Ar), 129.96 (Ar), 129.93 (Ar), 129.86 (Ar), 129.78 (Ar), 129.76 (Ar), 129.48 (Ar), 129.42 (Ar), 129.3 (Ar), 129.2 (Ar), 128.7 (Ar), 128.50 (Ar), 128.48 (Ar), 128.46 (Ar), 128.43 (Ar), 99.3 (C-1a), 87.0 (C-1b), 74.7 (C-4b), 73.4 (C-3b), 70.6 (C-2b), 69.9 (C-2a), 69.5 (C-3a), 68.3 (C-4a), 66.0 (C-5b), 60.7 (C-5a), 37.8 (-$\underline{C}H_2$), 29.6 (-$\underline{C}H_3$), 27.9

(-$\underline{C}H_2$), 21.2 (Ar$\underline{C}H_3$); HRMS (ESI) calcd for $(M+Na)^+$ $C_{50}H_{46}O_{14}SNa$: 925.2500. Found: 925.2486.



***p*-Tolyl 2,3-di-*O*-benzoyl-4-*O*-(2,2,2-trichloroethoxycarbonyl)-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranoside (3.5).** Hemiacetal **3.10** was first converted to trichloroacetimidate **3.11**. To a solution of **3.10** (6.62 g, 12.4 mmol) and CCl_3CN (8.7 mL, 86.8 mmol) in CH_2Cl_2 (120 mL) was added Cs_2CO_3 (16 g, 24.8 mmol) with stirring at room temperature. The reaction mixture was stirred for 4 h at which point the TLC showed completion of the reaction. The reaction mixture was then filtered through a pad of Celite and the filtrate was concentrated. The crude imidate was used without further purification. To a solution of donor **3.11** (1.18 g, 1.74 mmol) and acceptor **3.14** (404.1 mg, 0.87 mmol) was added 4Å molecular sieves. The suspension was stirred for 30 min before it was cooled to –20 °C. The reaction mixture was then treated with a 0.1 M solution of TMSOTf in CH_2Cl_2 (0.4 mL) at –20 °C. The reaction mixture was stirred for 30 min at which point the TLC showed fully consumption of acceptor **3.14**. The reaction mixture was then treated with Et_3N, filtered through a pad of Celite, and the filtrate was concentrated. The crude residue was purified by column chromatography (7:1, hexane–EtOAc) to yield **3.5** (660.3 mg, 77%) as a colorless foam. R_f 0.41 (4:1, hexanes–EtOAc); $[\alpha]_D$ +3.4 (*c* 1.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.03–7.93 (m, 8H, Ar), 7.57–7.51 (m, 4H, Ar), 7.45–7.37 (m, 8H, Ar), 7.34 (d, *J* = 8.1 Hz, 2H, Ar), 7.09 (d, *J* = 8.2 Hz, 2H, Ar), 5.64 (app t,

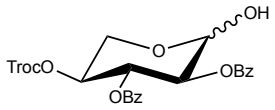
J = 8.0 Hz, 1H, H-3b), 5.48 (app t, J = 6.2 Hz, 1H, H-3a), 5.30 (app t, J = 8.1 Hz, 1H, H-2b), 5.18 (dd, J = 6.2, 4.5 Hz, 1H, H-2a), 4.92 (d, J = 8.1 Hz, 1H, H-1b), 4.91 (d, J = 4.2 Hz, 1H, H-1a), 4.77 (td, J = 5.8, 3.8 Hz, 1H, H-4a), 4.70, 4.66 (ABq, 2H, J_{AB} = 11.9 Hz, $Cl_3CC\underline{H}_2O$), 4.24 (dd, J = 12.2, 4.8 Hz, 1H, H-5b), 4.06 (td, J = 8.3, 4.8 Hz, 1H, H-4b), 3.93 (dd, J = 12.7, 3.6 Hz, 1H, H-5a), 3.51 (dd, J = 12.2, 8.7 Hz, 1H, H-5b'), 3.45 (dd, J = 12.7, 5.8 Hz, 1H, H-5a'), 2.32 (s, 3H, $ArC\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 165.4 (C=O), 165.2 (C=O), 165.0 (C=O), 164.9 (C=O), 153.1 (C=O), 138.5 (Ar), 133.6 (Ar), 133.5 (Ar), 133.4 (2C, Ar), 133.28 (Ar), 133.25 (Ar), 130.0 (Ar), 129.9 (Ar), 129.8 (2C, Ar), 129.43 (Ar), 129.36 (Ar), 129.0 (Ar), 128.7 (Ar), 128.59 (Ar), 128.56 (Ar), 128.54 (Ar), 128.44 (Ar), 128.38 (Ar), 99.10 (C-1a), 94.06 ($Cl_3\underline{C}$-), 86.9 (C-1b), 77.0 ($Cl_3C\underline{C}H_2O$-), 75.15 (C-4b), 73.23 (C-3b), 71.9 (C-4a), 70.5 (C-2b), 69.4 (C-2a), 68.9 (C-3a), 65.6 (C-5b), 59.9 (C-5a), 21.2 ($Ar\underline{C}H_3$); HRMS (ESI) calcd for $(M+Na)^+$ $C_{48}H_{41}{}^{35}Cl_3O_{14}SNa$: 1001.1175. Found: 1001.1176.



***p*-Methoxylphenyl 2-*O*-benzoyl-3-*O*-methyl-α-L-rhamnopyranosyl-(1→3)-4-*O*-acetyl-2,6-di-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (3.6).** To a solution of **3.19** (949.9 mg, 0.70 mmol) in EtOH (40 mL) and THF (10 mL) was added $Pd(OH)_2/C$ (20% Pd, 433.0 mg). The

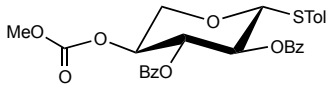
solution was degased under vacuum and refilled with hydrogen 3 times. The reaction mixture was then stirred under hydrogen overnight at which point TLC showed completion of reaction. The reaction mixture was filtered through a pad of Celite and concentrated. The crude residue was purified by chromatography (1:1, hexeans–EtOAc) to yield **3.6** (803.0 mg, 91%) as a colorless foam. R_f 0.24 (1:1, hexanes–EtOAc); $[\alpha]_D$ +44.6 (*c* 2.4, $CHCl_3$); ^1H NMR (500 MHz; $CDCl_3$, δ_H) 8.05–8.02 (m, 6H, Ar), 7.96–7.92 (m, 4H, Ar), 7.74–7.73 (m, 2H, Ar), 7.61–7.48 (m, 7H, Ar), 7.39–7.26 (m, 11H, Ar), 6.87–6.83 (m, 2H, Ar), 6.65–6.62 (m, 2H, Ar), 5.82 (app t, *J* = 9.4 Hz, 1H, H-3c), 5.65 (dd, *J* = 9.6, 7.8 Hz, 1H, H-2c), 5.48 (dd, *J* = 10.0, 8.0 Hz, 1H, H-2b), 5.32 (d, *J* = 3.2 Hz, 1H, H-4b), 5.12 (dd, *J* = 3.0, 1.8 Hz, 1H, H-2a), 5.09 (d, *J* = 7.8 Hz, 1H, H-1c), 4.87 (d, *J* = 1.5 Hz, 1H, H-1a), 4.67 (d, *J* = 8.0 Hz, 1H, H-1b), 4.60 (dd, *J* = 11.9, 1.8 Hz, 1H, H-6c), 4.45 (dd, *J* = 11.9, 5.4 Hz, 1H, H-6c'), 4.22 (app t, *J* = 9.5 Hz, 1H, H-4c), 3.95–3.91 (m, 2H, H-5c, H-3b), 3.82–3.76 (m, 2H, H-6b, H-5a), 3.70–3.67 (m, 4H, $OC\underline{H}_3$, H-5b), 3.60 (dd, *J* = 11.1, 6.8 Hz, 1H, H-6b'), 3.49 (app td, *J* = 9.5, 2.1 Hz, 1H, H-4a), 3.26 (dd, *J* = 9.5, 3.2 Hz, 1H, H-3a), 3.17 (s, 3H, $OC\underline{H}_3$), 2.24 (d, *J* = 2.4 Hz, 1H, O<u>H</u>-4a), 2.05 (s, 3H, $C\underline{H}_3C$=O), 1.27 (d, *J* = 6.2 Hz, 3H, H-6a); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 169.8 (C=O), 165.8 (C=O), 165.7 (C=O), 165.3 (C=O), 165.2 (C=O), 164.9 (C=O), 164.8 (C=O), 155.7 (Ar), 151.0 (Ar), 133.5 (Ar), 133.33 (Ar), 133.30 (Ar), 133.29 (Ar), 133.25 (Ar), 133.1 (Ar), 129.85 (Ar), 129.84 (Ar), 129.81 (Ar), 129.68 (Ar), 129.64 (Ar), 129.61 (Ar), 129.57 (Ar), 129.55 (Ar), 129.4 (Ar), 129.3 (Ar), 128.8 (Ar), 128.7 (Ar), 128.51 (Ar), 128.47 (Ar), 128.44 (Ar), 128.3 (Ar), 128.2 (Ar), 119.0 (Ar), 114.5 (Ar), 100.9 (C-1b), 100.7 (C-1c),

99.7 (C-1a), 79.0 (C-3a), 76.4 (C-3b), 75.9 (C-4c), 73.2 (C-5c), 72.7 (C-3c), 71.8 (C-2b), 71.7 (C-2c), 71.7 (C-4a), 71.6 (C-5b), 69.4 (C-5a), 68.4 (C-4b), 67.4 (C-2a), 62.6 (C-6c), 61.3 (C-6b), 57.0 (O<u>C</u>H$_3$), 55.6 (O<u>C</u>H$_3$), 20.7 (<u>C</u>H$_3$C=O), 17.7 (C-6a); HRMS (ESI) calcd for $(M+Na)^+$ $C_{70}H_{66}O_{23}Na$: 1297.3887. Found: 1297.3898.



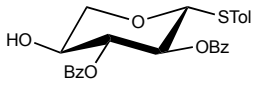
2,3-di-*O*-benzoyl-4-*O*-(2,2,2-trichloroethoxycarbonyl)-L-xylopyranoside (3.10). To a solution of **2.7** (6.21 g, 9.7 mmol) in acetone (80 mL) and water (20 mL) was added NBS (8.63 g, 48.5 mmol) at 0 °C with stirring. The reaction mixture was stirred for 20 min. The mixture was then diluted with EtOAc and the organic extract was washed with a saturated solution of $Na_2S_2O_3$, water and brine. The organic extract was dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by chromatography (6:1, hexanes–EtOAc) to yield **3.10** (7.93 g, 98%) as a white foam. R_f 0.30 (4:1, hexanes–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.04–8.00 (m, 4H, Ar), 7.58–7.54 (m, 2H, Ar), 7.45–7.40 (m, 4H, Ar), 6.09 (app t, J = 9.4 Hz, 0.67H, H-3α), 5.78 (app t, J = 8.5 Hz, 0.33H, H-3β), 5.66 (app t, J = 2.8 Hz, 0.67H, H-1α), 5.27–5.18 (m, 2H, H-2β, H-2α, H-4α, H-4β), 5.01 (app t, J = 6.6 Hz, 0.33H, H-1β), 4.76–4.69 (m, 4H, $Cl_3CC\underline{H}_2O$-(α,β)), 4.39 (dd, J = 12.0, 5.1 Hz, 0.33H, H-5β), 4.22 (app t, J = 10.7 Hz, 0.67H, H-5α), 4.04 (dd, J = 11.2, 5.6 Hz, 0.67H, H-5α'), 3.77–3.73 (m, 0.67H, H-5β', OH-1β), 3.05–

3.05 (d, J = 2.5 Hz, 0.67H, OH-1α); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 166.7 (ArC=O, β), 165.8 (ArC=O, α), 165.4 (ArC=O, α), 165.3 (ArC=O, β), 153.3 (C=O, α), 153.2 (C=O, β), 133.7 (Ar, β), 133.6 (Ar, β), 133.5 (Ar, α), 133.4 (Ar, α), 130.1 (Ar, β), 130.0 (Ar, α), 129.9 (Ar, β), 129.8 (Ar, α), 129.1 (Ar, α), 128.9 (Ar, α), 128.8 (Ar, β), 128.7 (Ar, β), 128.52 (Ar, β), 128.50 (Ar, α), 128.49 (Ar, β), 128.4 (Ar, α), 95.8 (C-1β), 94.1 (Cl_3C-, α), 94.0 (Cl_3C-, β), 90.6 (C-1α), 77.0 ($Cl_3CC\underline{H}_2O$-, β), 76.9 ($Cl_3CC\underline{H}_2O$-, α), 73.4 (C-4α), 73.00, 72.96 (C-2β, C-4β), 71.9 (C-2α), 70.8 (C-3β), 69.5 (C-3α), 62.0 (C-5β), 58.7 (C-5α); HRMS (ESI) calcd for $(M+Na)^+$ $C_{22}H_{19}{}^{35}Cl_3O_9Na$: 554.9987. Found: 554.9993.



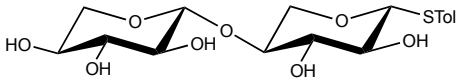
***p*-Tolyl 4-*O*-methoxycarbonyl-1-thio-β-L-xylopyranoside (3.13).** To a solution of **2.7** (2.22 g, 3.5 mmol) in CH_3OH was added active zinc powder with vigorous stirring at 40 °C. Upon consumption of starting material, the mixture was filtered and concentrated. The crude product was purified by chromatography (6:1, hexanes–EtOAc) to yield **3.13** (1.27 g, 70%) as a white foam. R_f 0.31 (4:1, hexanes–EtOAc); $[\alpha]_D$ –23.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.06–8.03 (m, 4H, Ar), 7.56–7.53 (m, 2H, Ar), 7.43–7.40 (m, 6H, Ar), 7.12 (d, J = 8.0 Hz, 2H, Ar), 5.63 (app t, J = 7.0 Hz, 1H, H-3), 5.41 (app t, J = 6.8 Hz, 1H, H-2), 5.12 (d, J = 6.7 Hz, 1H, H-1), 4.98 (td, J = 7.1, 4.2 Hz, 1H, H-4), 4.56 (dd, J = 12.2, 4.1 Hz, 1H, H-5), 3.75 (dd, J = 12,3, 7.4 Hz, H-5), 3.73 (s, 3H, $OC\underline{H}_3$), 2.30 (s, 3H, $ArC\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 165.1 (C=O), 165.0 (C=O),

154.8 (C=O), 138.4 (Ar), 133.5 (Ar), 133.3 (Ar), 133.2 (Ar), 130.0 (Ar), 129.95 (Ar), 129.8 (Ar), 129.2 (Ar), 129.0 (Ar), 128.9 (Ar), 128.4 (Ar), 128.36 (Ar), 86.6 (C-1), 71.5 (C-4), 70.9 (C-3), 69.9 (C-2), 63.7 (C-5), 55.1 ($OC\underline{H}_3$), 21.1 ($ArCH_3$); HRMS (ESI) calcd for $(M+Na)^+$ $C_{28}H_{26}O_8SNa$: 545.1241. Found: 545.1235.

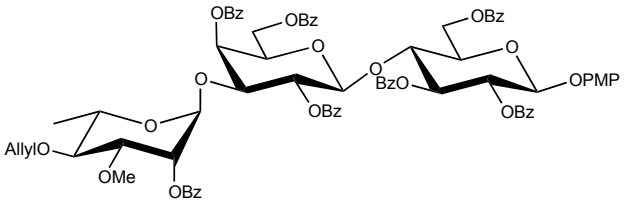


***p*-Tolyl 2,3-di-*O*-benzoyl-β-L-xylopyranoside (3.14).** To a solution of **2.7** (6.40 g, 10.0 mmol) in THF (100 mL) and AcOH (120 mL) was added Zn dust (63.0 g) with vigorous stirring at room temperature. The TLC indicated that the reaction was finished within 30 min. The reaction mixture was filtered and the filtrate was concentrated with azeotropic removal of AcOH with toluene. The resulting solid was dissolved with CH_2Cl_2 and the organic layer was washed with a saturated solution of $NaHCO_3$, water and then brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. The crude product was purified by chromatography on silica gel (4:1, hexanes–EtOAc) to yield **3.14** (4.57 g, 97%) as a white foam. R_f 0.36 (2:1, hexanes–EtOAc); $[\alpha]_D$ –54.6 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.04–7.99 (m, 4H, Ar), 7.56–7.53 (m, 2H, Ar), 7.43–7.39 (m, 6H, Ar), 7.13–7.11 (m, 2H, Ar), 5.41 (app t, J = 7.5 Hz, 1H, H-2), 5.32 (app t, J = 7.5 Hz, 1H, H-3), 5.01 (d, J = 7.5 Hz, 1H, H-1), 4.42 (dd, J = 12.0, 4.5 Hz, 1H, H-5), 3.99–4.01−3.96 (m, 1H, H-4), 3.58 (dd, J = 12.0, 8.0 Hz, 1H, H-5), 3.03 (d, J = 6.2 Hz, 1H, OH-4), 2.34 (s, 3H, $ArC\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 167.0 (C=O), 165.1 (C=O), 138.5 (Ar), 133.7 (Ar), 133.5 (Ar), 133.4 (Ar), 130.1 (Ar),

129.9 (Ar), 129.8 (Ar), 129.3 (Ar), 129.0 (Ar), 128.9 (Ar), 128.5 (Ar), 128.5 (Ar), 87.0 (C-1), 76.2 (C-3), 70.2 (C-2), 68.4 (C-4), 67.7 (C-5), 21.2 (Ar<u>C</u>H_3); HRMS (ESI) calcd for $(M+Na)^+$ $C_{26}H_{24}O_6SNa$: 487.1186. Found: 487.1183.



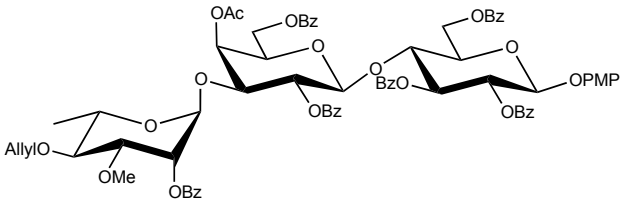
***p*-Tolyl β-L-xylopyranosyl-(1→4)-β-L-xylopyranoside (3.15).** To a solution of **3.5** (100.8 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) and CH_3OH (1 mL) was added a 1.0 M solution of $NaOCH_3$ in CH_3OH (0.05 mL). The reaction mixture was stirred for 2 h and then neutralized with IR-120 H^+ resin. The mixture was filtered, and concentrated. The residue was purified by column chromatography (8:1 CH_2Cl_2–CH_3OH) to give **3.15** (38.7 mg, 97%) as a colorless syrup. R_f 0.16 (8:1 CH_2Cl_2–CH_3OH); $[\alpha]_D$ +70.8 (*c* 2.3, CH_3OH); ^1H NMR (500 MHz, CD_3OD, δ_H) 7.41–7.40 (m, 2H, Ar), 7.13–7.11 (m, 2H, Ar), 4.46 (d, *J* = 9.2 Hz, 1H, H-1b), 4.30 (d, *J* = 7.6 Hz, 1H, H-1a), 4.06 (dd, *J* = 11.6, 5.1 Hz, 1H, H-5b), 3.87 (dd, *J* = 11.4, 5.4 Hz, 1H, H-5a), 3.59 (td, *J* = 9.3, 4.7 Hz, 1H, H-4b), 3.51–3.44 (m, 2H, H-4a, H-3b), 3.34–3.27 (m, 2H, H-5b', H-3a), 3.23–3.18 (m, 3H, H-2b, H-5a', H-2a), 2.31 (s, 3H, ArC<u>H</u>$_3$); ^{13}C NMR (125 MHz, CD_3OD, δ_C) 139.1 (Ar), 134.1 (Ar), 130.6 (Ar), 130.5 (Ar), 103.9 (C-1a), 90.1 (C-1b), 77.8 (C-4b), 77.6 (C-3a), 77.2 (C-3b), 74.3 (C-2a), 73.4 (C-2b), 71.0 (C-4b), 68.0 (C-5b), 67.1 (C-5a), 21.1 (Ar<u>C</u>H_3); HRMS (ESI) calcd for $(M+Na)^+$ $C_{17}H_{24}O_8SNa$: 411.1084. Found: 411.1081.



***p*-Methoxylphenyl 4-*O*-allyl-2-*O*-benzoyl-3-*O*-methyl-α-L-rhamnopyranosyl-(1→3)-2,4,6-tri-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (3.17).** To a solution of donor **2.45** (340 mg, 0.79 mmol), acceptor **2.53** (639.5 mg, 0.66 mmol) in dry CH_2Cl_2 (15 mL) was added 4Å molecular sieves. The suspension was stirred for 30 min before NIS (222.7 mg, 0.99 mmol) was added at room temperature. The reaction mixture was stirred for 15 min and then it was treated with AgOTf (25.4 mg, 0.10 mmol) at –40 °C. The solution was stirred for 2 h at which point the TLC showed complete consumption of the acceptor. The reaction mixture was treated with Et_3N, filtered through a pad of Celite and the filtrate was concentrated. The product and by-product were not separable by column chromatography using hexane–EtOAc as eluent at this stage. The fractions containing product were concentrated then dried under high vacuum. To a solution of the crude product in pyridine (5 mL) was added benzoyl chloride (0.12 mL, 1.0 mmol) with stirring and cooling at 0 °C. The reaction mixture was stirred overnight before CH_3OH was added. The solvent was co-evaporated with toluene and the residue was purified by chromatography (12:1, toluene–EtOAc) to give **3.17** (410.0 mg, 45% over 2 steps) as a colorless foam. R_f 0.29 (8:1, toluene–EtOAc); $[\alpha]_D$ +32.2 (*c* 2.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.10–8.07 (m, 5H, Ar), 7.98–7.91 (m, 6H, Ar), 7.77–7.75 (m, 2H, Ar), 7.67–7.59 (m, 2H, Ar), 7.56–7.47 (m, 8H, Ar), 7.40–7.28 (m, 10H), 7.06–7.03 (m, 2H, Ar), 6.90–6.86 (m,

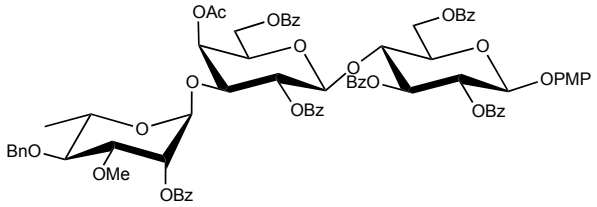
2H, Ar), 6.67–6.64 (m, 2H, Ar), 5.87–5.79 (m, 2H, H-3c, CH_2=C<u>H</u>CH_2O), 5.69 (dd, *J* = 9.7, 7.8 Hz, 1H, H-2c), 5.63 (dd, *J* = 10.0, 8.0 Hz, 1H, H-2b), 5.58 (d, *J* = 3.2 Hz, 1H, H-4b), 5.18–5.12 (m, 2H, C<u>H</u>$_2$=CHCH_2O, H-1c), 5.08 (app dq, *J* = 10.4, 1.5 Hz, 1H, C<u>H</u>$_2$=CHCH_2O), 5.05 (dd, *J* = 3.1, 1.9 Hz, 1H, H-2a), 4.88 (d, *J* = 1.8 Hz, 1H, H-1a), 4.75 (d, *J* = 7.9 Hz, 1H, H-1b), 4.63 (dd, *J* = 11.9, 1.9 Hz, 1H, H-6c), 4.50 (dd, *J* = 12.0, 5.4 Hz, 1H, H-6c'), 4.25 (app t, *J* = 9.5 Hz, 1H, H-4c), 4.19 (app ddt, J = 12.9, 5.2, 1.5 Hz, 1H, CH_2=CHC<u>H</u>$_2O$), 4.02–3.95 (m, 3H, H-3b, H-5c, CH_2=CHC<u>H</u>$_2O$), 3.88 (dd, *J* = 11.4, 5.7 Hz, 1H, H-6b), 3.80–3.77 (m, 1H, H-5b), 3.75–3.72 (m, 1H, H-5a), 3.70 (s, 3H, OC<u>H</u>$_3$), 3.48 (dd, *J* = 11.4, 7.1 Hz, 1H, H-6b'), 3.30 (dd, *J* = 9.4, 3.2 Hz, 1H, H-3a), 3.20 (app t, *J* = 9.4 Hz, 1H, H-4a), 2.99 (s, 3H, OC<u>H</u>$_3$), 1.18 (d, *J* = 6.2 Hz, 3H, H-6a); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 165.77 (C=O), 165.76 (C=O), 165.42 (C=O), 165.35 (C=O), 165.2 (C=O), 165.0 (C=O), 164.8 (C=O), 155.7 (Ar), 151.0 (Ar), 135.3 (CH_2=<u>C</u>HCH_2O), 134.6 (Ar), 133.7 (Ar), 133.5 (Ar), 133.4 (Ar), 133.30 (Ar), 133.28 (Ar), 133.1 (Ar), 133.0 (Ar), 130.6 (Ar), 130.22 (Ar), 130.16 (Ar), 129.9 (Ar), 129.8 (Ar), 129.7 (Ar), 129.62 (Ar), 129.61 (Ar), 129.55 (Ar), 129.33 (Ar), 129.27 (Ar), 129.1 (Ar), 128.91 (Ar), 128.89 (Ar), 128.68 (Ar), 128.65 (Ar), 128.52 (Ar), 128.50 (Ar), 128.47 (Ar), 128.42 (Ar), 128.16 (Ar), 128.12 (Ar), 119.0 (Ar), 116.2 (<u>C</u>H_2=CHCH_2O), 114.4 (Ar), 100.9 (C-1b), 100.8 (C-1c), 99.3 (C-1a), 79.2 (C-4a), 78.8 (C-3a), 77.1 (C-3b), 76.1 (C-4c), 73.3 (C-5c), 73.2 (CH_2=CH<u>C</u>H_2O), 72.8 (C-3c), 72.0 (C-5b), 71.8 (C-2b), 71.7 (C-2c), 68.95, 68.92, 68.86 (C-4b, C-2a, C-5b), 62.6 (C-6c), 61.7 (C-6b), 57.2 (O<u>C</u>H_3), 55.6 (O<u>C</u>H_3),

17.8 (C-6a); HRMS (ESI) calcd for $(M+Na)^+$ $C_{78}H_{72}O_{23}Na$: 1399.4357. Found: 1399.4338.



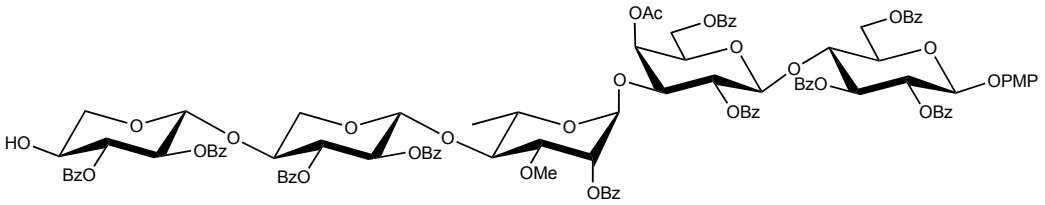
***p*-Methoxylphenyl 4-*O*-allyl-2-*O*-benzoyl-3-*O*-methyl-α-L-rhamnopyranosyl-(1→3)-4-*O*-acetyl-2,6-di-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (3.18).** To a solution of donor **2.45** (119.9 mg, 0.28 mmol), acceptor **2.9** (139.9 mg, 0.14 mmol) in dry CH_2Cl_2 (5 mL) was added 4Å molecular sieves. The suspension was stirred for 30 min before NIS (222.7 mg, 0.99 mmol) was added at room temperature. The reaction mixture was stirred for 15 min and then it was treated with AgOTf (5.4 mg, 0.02 mmol) at 0 °C. The reaction was stirred for 1 h at which point the TLC showed complete consumption of the acceptor. The reaction mixture was treated with Et_3N, filtered through a pad of Celite and the filtrate was concentrated. The crude residue was purified by chromatography (8:1, toluene–EtOAc) to yield **3.18** (127.7 mg, 70%) as a white foam. R_f 0.18 (8:1, toluene–EtOAc); $[\alpha]_D$ +40.5 (*c* 1.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.04–8.00 (m, 6H, Ar), 7.94–7.88 (m, 4H, Ar), 7.73–7.72 (m, 2H, Ar), 7.57–7.43 (m, 7H, Ar), 7.35–7.20 (m, 10H, Ar), 7.14–7.10 (m, 1H, Ar), 6.83–6.80 (m, 2H, Ar), 6.61–6.58 (m, 2H, Ar), 5.88–5.77 (m, 2H, CH_2=C<u>H</u>CH_2O, H-3c), 5.62 (dd, *J* = 9.6, 7.8 Hz, 1H, H-2c), 5.45 (dd, *J* = 10.0, 7.9 Hz, 1H, H-2b),

5.29 (d, J = 3.3 Hz, 1H, H-4b), 5.18 (app dq, J = 17.2, 1.7 Hz, 1H, C$\underline{H}_2$=CHCH$_2$O), 5.09–5.06 (m, 3H, C$\underline{H}_2$=CHCH$_2$O, H-2a, H-1c), 4.82 (d, J = 1.8 Hz, 1H, H-1a), 4.64 (d, J = 7.9 Hz, 1H, H-1b), 4.58 (dd, J = 11.9, 1.9 Hz, 1H, H-6c), 4.42 (dd, J = 11.9, 5.5 Hz, 1H, H-6c'), 4.24–4.18 (m, 2H, CH$_2$=CHC$\underline{H}_2$O, H-4c), 4.01 (ddt, J = 12.8, 6.0, 1.3 Hz, 1H, CH$_2$=CHC$\underline{H}_2$O), 3.91 (ddd, J = 9.9, 5.4, 1.9 Hz, 1H, H-5c), 3.86 (dd, J = 10.1, 3.4 Hz, 1H, H-3b), 3.82 (dd, J = 11.2, 5.9 Hz, 1H, H-6b), 3.70–3.62 (m, 5H, H-5a, OC$\underline{H}_3$, H-5b), 3.54 (dd, J = 11.3, 6.9 Hz, 1H, H-6b'), 3.35 (dd, J = 9.3, 3.2 Hz, 1H, H-3a), 3.20 (app t, J = 9.4 Hz, 1H, H-4a), 3.11 (s, 3H, OC$\underline{H}_3$), 2.01 (s, 3H, C$\underline{H}_3$C=O), 1.21 (d, J = 6.2 Hz, 3H, H-6a); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 169.7 (C=O), 165.7 (C=O × 2), 165.21 (C=O), 165.16 (C=O), 164.9 (C=O), 164.8 (C=O), 155.7 (Ar), 150.9 (Ar), 135.3 (CH$_2$=$\underline{C}$HCH$_2$O), 133.4 (Ar), 133.24 (Ar), 133.20 (Ar), 133.17 (Ar), 133.15 (Ar), 132.9 (Ar), 129.8 (Ar), 129.7 (Ar), 129.61 (Ar), 129.59 (Ar), 129.57 (Ar), 129.54 (Ar), 129.51 (Ar), 129.2 (Ar), 128.8 (Ar), 128.6 (Ar), 128.5 (Ar), 128.40 (Ar), 128.37 (Ar), 128.2 (Ar), 128.1 (Ar), 118.9 (Ar), 116.4 ($\underline{C}$H$_2$=CHCH$_2$O), 114.4 (Ar), 100.8 (C-1b), 100.7 (C-1c), 99.6 (C-1a), 79.3 (C-4a), 79.1 (C-3a), 77.0 (C-3b), 75.8 (C-4c), 73.6 (CH$_2$=CH$\underline{C}$H$_2$O), 73.2 (C-5c), 72.7 (C-3c), 71.7 (C-2c), 71.7 (C-2b), 71.6 (C-5b), 68.8 (2C, C-2a, C-5a), 68.4 (C-4b), 62.5 (C-6c), 61.4 (C-6b), 57.2 (O$\underline{C}$H$_3$), 55.5 (O$\underline{C}$H$_3$), 20.6 ($\underline{C}$H$_3$C=O), 17.9 (C-6a); HRMS (ESI) calcd for (M+Na)$^+$ $C_{73}H_{70}O_{23}Na$: 1337.4200. Found: 1337.4194.



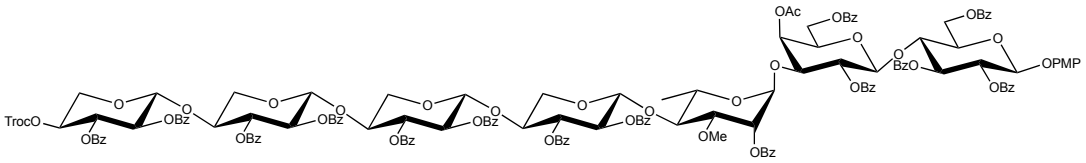
***p*-Methoxylphenyl 4-*O*-benzyl-2-*O*-benzoyl-3-*O*-methyl-α-L-rhamnopyranosyl-(1→3)-4-*O*-acetyl-2,6-di-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (3.19).** To a solution of donor **2.8** (2.00 g, 4.2 mmol), acceptor **2.9** (3.54 g, 3.5 mmol) in dry CH_2Cl_2 (80 mL) was added 4Å molecular sieves. The suspension was stirred for 30 min before NIS (1.02 g, 4.6 mmol) was added at room temperature. The reaction mixture was stirred for 15 min and then it was treated with a 0.1 M solution of TMSOTf in CH_2Cl_2 (0.18 mL) at –20 °C. The reaction was stirred for 30 min at which point the TLC showed complete consumption of glycosyl acceptor. The reaction mixture was treated with Et_3N, filtered through a pad of Celite and the filtrate was concentrated. The crude residue was purified by chromatography (3:1, hexanes–EtOAc) to yield **3.19** (3.26 g, 68%) as a white foam. R_f 0.27 (1:1, hexane–EtOAc); $[\alpha]_D$ +31.6 (*c* 3.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.07–8.03 (m, 6H, Ar), 7.97–7.92 (m, 4H, Ar), 7.78–7.76 (m, 2H, Ar), 7.59–7.49 (m, 7H, Ar), 7.39–7.25 (m, 16H, Ar), 6.87–6.84 (m, 2H, Ar), 6.65–6.61 (m, 2H, Ar), 5.82 (app t, *J* = 9.4 Hz, 1H, H-3c), 5.65 (dd, *J* = 9.7, 7.8 Hz, 1H, H-2c), 5.48 (dd, *J* = 10.1, 7.9 Hz, 1H, H-2b), 5.32 (dd, *J* = 3.3, 0.6 Hz, 1H, H-4b), 5.12 (dd, *J* = 3.2, 1.9 Hz, 1H, H-2a), 5.10 (d, *J* = 7.8 Hz, 1H, H-1c), 4.85 (d, *J* = 1.8 Hz, 1H, H-1a), 4.81 (d, *J* = 11.5 Hz, 1H, PhC$\underline{H}_2$), 4.67 (d, *J* = 7.9 Hz, 1H, H-1b), 4.61 (dd, *J* = 11.9, 1.9 Hz, 1H, H-6c), 4.58 (d, *J* = 11.5 Hz, 1H, PhC$\underline{H}_2$), 4.46 (dd, *J* = 12.0, 5.4 Hz, 1H, H-

6c'), 4.23 (app t, J = 9.5 Hz, 1H, H-4c), 3.94 (ddd, J = 9.9, 5.4, 2.0 Hz, 1H, H-5c), 3.89 (dd, J = 10.1, 3.4 Hz, 1H, H-3b), 3.84 (dd, J = 11.3, 5.9 Hz, 1H, H-6b), 3.76 (dq, J = 9.4, 6.1 Hz, 1H, H-5a), 3.69–3.65 (m, 4H, OC$\underline{H}_3$, H-5b), 3.56 (dd, J = 11.2, 6.9 Hz, 1H, H-6b'), 3.46 (dd, J = 9.3, 3.2 Hz, 1H, H-3a), 3.34 (app t, J = 9.4 Hz, 1H, H-4a), 3.15 (s, 3H, OC$\underline{H}_3$), 2.04 (s, 3H, C$\underline{H}_3$C=O), 1.20 (d, J = 6.2 Hz, 3H, H-6a); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 169.7 (C=O), 165.7 (2 × C=O), 165.3 (C=O), 165.2 (C=O), 165.0 (C=O), 164.9 (C=O), 155.7 (Ar), 151.0 (Ar), 138.6 (Ar), 133.4 (Ar), 133.30 (Ar), 133.28 (Ar), 133.25 (Ar), 133.22 (Ar), 133.0 (Ar), 129.84 (Ar), 129.81 (Ar), 129.79 (Ar), 129.7 (Ar), 129.64 (Ar), 129.63 (Ar), 129.61 (Ar), 129.59 (Ar), 129.55 (Ar), 129.3 (Ar), 128.8 (Ar), 128.7 (Ar), 128.50 (Ar), 128.45 (Ar), 128.42 (Ar), 128.3 (Ar), 128.21 (Ar), 128.20 (Ar), 128.0 (Ar), 127.5 (Ar), 119.0 (Ar), 114.4 (Ar), 100.9 (C-1b), 100.7 (C-1c), 99.7 (C-1a), 79.4 (C-3a), 79.2 (C-4a), 77.1 (C-3b), 75.8 (C-4c), 74.5 (Ph$\underline{C}H_2$), 73.2 (C-5c), 72.70 (C-3c), 71.7 (2C, C-5b, C-2c), 71.6 (C-2b), 68.8 (C-5a), 68.8 (C-2a), 68.4 (C-4b), 62.54 (C-6c), 61.46 (C-6b), 57.2 (O$\underline{C}H_3$), 55.6 (O$\underline{C}H_3$), 20.6 ($\underline{C}H_3$C=O), 17.9 (C-6a); HRMS (ESI) calcd for $(M+Na)^+$ $C_{77}H_{72}O_{23}Na$: 1387.4357. Found: 1387.4357.



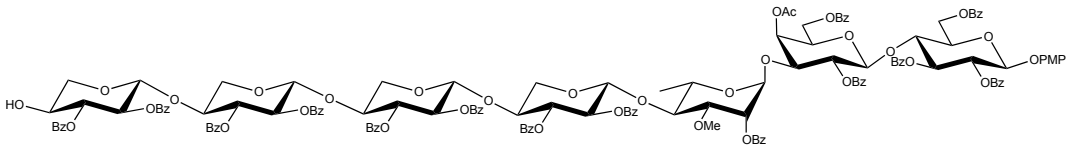
***p*-Methoxylphenyl 2,3-di-*O*-benzoyl-)-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranosyl-(1→4)-2-*O*-benzoyl-3-*O*-methyl-α-L-rhamnopyranosyl-(1→3)-4-*O*-acetyl-2,6-di-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (3.21).** To a solution of **3.3** (198.6 g, 88.0 μ mol) in THF (4 mL) and AcOH (0.5 mL) was added Zn dust (1.0 g) with vigorous stirring. The TLC indicated that the reaction was finished within 15 min. The reaction mixture was then filtered and the filtrate was concentrated with azeotropic removal of AcOH with toluene. The crude residue purified by chromatography on silica gel (3:2 hexanes–EtOAc) to yield **3.21** (4.57 g, 93%) as a white foam. R_f 0.32 (1:1 hexanes–EtOAc); [α [$_D$ +1.1 (*c* 1.2 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.04–7.90 (m, 16H, Ar), 7.74–7.72 (m, 2H, Ar), 7.59-7.46 (m, 11H, Ar), 7.42–7.24 (m, 19H, Ar), 7.18–7.15 (m, 2H, Ar), 6.85–6.83 (m, 2H, Ar), 6.64–6.62 (m, 2H, Ar), 5.80 (app t, *J* = 9.4 Hz, 1H, H-3e), 5.63 (dd, *J* = 9.7, 7.8 Hz, 1H, H-2e), 5.55 (dd, *J* = 8.2, 7.5 Hz, 1H, H-3b), 5.43 (dd, *J* = 10.0, 8.0 Hz, 1H, H-2d), 5.25–5.20 (m, 3H, H-4d, H-2a, H-2b), 5.16 (dd, *J* = 7.9, 7.0 Hz, 1H, H-3a), 5.08 (d, *J* = 7.8 Hz, 1H, H-1e), 5.03 (dd, *J* = 3.2, 2.1 Hz, 1H, H-2c), 4.81 (d, *J* = 6.4 Hz, 1H, H-1b), 4.78 (d, *J* = 1.9 Hz, 1H, H-1c), 4.77 (d, *J* = 5.9 Hz, 1H, H-1a), 4.64 (d, *J* = 8.0 Hz, 1H, H-1d), 4.60 (dd, *J* = 11.9, 1.9 Hz, 1H, H-6e), 4.43 (dd, *J* = 12.0, 5.4 Hz, 1H, H-6e'), 4.20 (app t, *J* = 9.5 Hz, 1H, H-4e),

4.04–4.00 (m, 2H, H-5b, H-4b), 3.94–3.91 (m, 1H, H-5e), 3.82–3.72 (m, 4H, H-6d, H-3d, H-4a, H-5a), 3.68 (s, 3H, OC$\underline{H}_3$), 3.62–3.58 (m, 2H, H-5d, H-5c), 3.50 (dd, *J* = 11.3, 7.0 Hz, 1H, H-6d'), 3.43 (app t, *J* = 9.1 Hz, 1H, H-4c), 3.39 (d, *J* = 3.2 Hz, 1H, H-3c), 3.36 (dd, *J* = 5.4, 3.6 Hz, 1H, H-5b'), 3.19 (dd, *J* = 13.3, 8.8 Hz, 1H, H-5a'), 2.96 (s, 3H, OC$\underline{H}_3$), 2.92 (d, *J* = 5.6 Hz, 1H, OH-4a), 1.83 (s, 3H, C$\underline{H}_3$C=O), 1.01 (d, *J* = 6.2 Hz, 3H, H-6c); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 169.6 (Ar), 167.0 (Ar), 165.74 (Ar), 165.71 (Ar), 165.5 (Ar), 165.3 (Ar), 165.21 (Ar), 165.20 (Ar), 165.0 (Ar), 164.95 (Ar), 164.86 (Ar), 155.7 (Ar), 151.0 (Ar), 133.6 (Ar), 133.43 (Ar), 133.35 (Ar), 133.29 (Ar), 133.27 (Ar), 133.23 (Ar), 133.18 (Ar), 133.10 (Ar), 133.07 (Ar), 130.0 (Ar), 129.83 (Ar), 129.80 (Ar), 129.77 (Ar), 129.70 (Ar), 129.67 (Ar), 129.61 (Ar), 129.57 (Ar), 129.52 (Ar), 129.51 (Ar), 129.45 (Ar), 129.2 (Ar), 129.14 (Ar), 129.06 (Ar), 128.83 (Ar), 128.79 (Ar), 128.7 (Ar), 128.52 (Ar), 128.51 (Ar), 128.45 (Ar), 128.43 (Ar), 128.40 (Ar), 128.33 (Ar), 128.26 (Ar), 128.25 (Ar), 128.21 (Ar), 119.0 (Ar), 114.4 (Ar), 100.8 (2C, C-1d, C-1a), 100.7 (C-1e), 100.6 (C-1b), 99.6 (C-1c), 79.8 (C-4c), 77.8 (C-3d), 77.5 (C-3c), 75.9, 75.8 (C-4b, C-4e), 75.3 (C-2b), 73.2 (C-5e), 72.7 (C-3e), 72.4 (C-3b), 71.70, 71.68 (C-2e, C-2d), 71.58 (C-5d), 71.4 (C-2b), 70.7 (C-2a), 68.3, 68.24 (2C), 68.18 (C-4d, C-2c, C-4a, C-5c), 64.4 (C-5a), 62.5 (C-6e), 62.4 (C-5a), 61.5 (C-6d), 57.0 (O$\underline{C}H_3$), 55.6 (O$\underline{C}H_3$), 20.4 ($\underline{C}H_3$C=O), 17.6 (C-6c); HRMS (ESI) calcd for $(M+2Na)^{+2}$ $C_{108}H_{98}O_{35}$: 1000.2837. Found: 1000.2821. (+2 charge state)



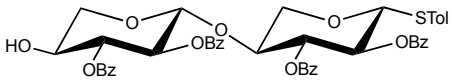
***p*-Methoxylphenyl 2,3-di-*O*-benzoyl-4-*O*-(2,2,2-trichloroethoxycarbonyl)-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranosyl-(1→4)-2-*O*-benzoyl-3-*O*-methyl-α-L-rhamnopyranosyl-(1→3)-4-*O*-acetyl-2,6-di-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (3.22).** To a solution of donor **3.5** (99.4 mg, 0.10 mmol), acceptor **3.21** (132.1 mg, 68 μmol) in dry CH_2Cl_2 (3 mL) was added 4Å molecular sieves. The suspension was stirred for 30 min before NIS (26.0 mg, 115.7 μmol) was added at room temperature. The reaction mixture was stirred for 15 min and then it was treated with a 0.1 M solution of TMSOTf in CH_2Cl_2 (34 μL) at −20 °C. The reaction was stirred for 30 min at which point the TLC showed complete consumption of the acceptor. The reaction mixture was treated with Et_3N, filtered through a pad of Celite and the filtrate was concentrated. The crude residue was purified by chromatography (2:1, hexanes–EtOAc) to yield **3.22** (161.5 mg, 85%) as a white foam. R_f 0.50 (1:1, hexanes–EtOAc); $[\alpha]_D$ +9.4 (*c* 1.9, $CHCl_3$); ^1H NMR (700 MHz, $CDCl_3$, δ_H) 8.01–7.83 (m, 25H, Ar), 7.71–7.70 (m, 2H, Ar), 7.57–7.23 (m, 43H, Ar), 6.84–6.82 (m, 2H, Ar), 6.62–6.60 (m, 2H, Ar), 5.79 (app t, *J* = 9.4 Hz, 1H), 5.62 (dd, *J* = 9.7, 7.8 Hz, 1H), 5.49–5.47 (m, 1H), 5.45–5.41 (m, 3H), 5.22 (d, *J* = 3.6 Hz, 1H), 5.15 (dd, *J* = 8.1, 6.4 Hz, 1H), 5.10 (dd, *J* = 8.2, 6.3 Hz, 1H), 5.08–5.05 (m, 3H), 5.01 (app t, *J* = 2.6 Hz, 1H), 4.77 (dd, *J* = 6.7,

2.7 Hz, 2H), 4.72 (td, *J* = 5.8, 4.0 Hz, 1H), 4.66–4.62 (m, 4H), 4.59–4.58 (m, 1H), 4.49 (d, *J* = 6.3 Hz, 1H), 4.42 (dd, *J* = 11.7, 5.3 Hz, 1H), 4.19 (app t, *J* = 9.4 Hz, 1H), 3.96–3.90 (m, 3H), 3.84 (dd, *J* = 12.9, 3.7 Hz, 1H), 3.79–3.75 (m, 3H), 3.71 (td, *J* = 8.2, 5.0 Hz, 1H), 3.66 (s, 3H), 3.61–3.56 (m, 2H), 3.50–3.44 (m, 3H), 3.41–3.38 (m, 1H), 3.37–3.34 (m, 2H), 3.28 (dd, *J* = 12.0, 8.0 Hz, 1H), 3.09–3.04 (m, 2H), 2.92 (s, 3H), 1.81 (s, 3H), 0.98 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$, δ_C) 169.5, 165.69, 165.68, 165.35, 165.33, 165.30, 165.24, 165.18, 165.13, 165.0 (2C), 164.91, 164.88, 164.82, 164.80, 155.7, 153.0, 150.9, 133.6, 133.5, 133.4, 133.31, 133.29, 133.27, 133.24 (2C), 133.20, 133.18, 133.17, 133.06, 133.03 (3C), 129.95, 129.87, 129.82, 129.79, 129.77, 129.75, 129.74, 129.69, 129.67, 129.66, 129.63, 129.60, 129.59 (2C), 129.55, 129.54, 129.52, 129.51, 129.44, 129.35, 129.27, 129.23, 129.19, 128.78, 128.70, 128.65 (2C), 128.54 (2C), 128.52 (2C), 128.50, 128.47, 128.43 (4C), 128.40, 128.37, 128.29, 128.27, 128.25, 128.24, 128.18, 118.9, 114.4, 100.80, 100.75, 100.69, 100.6, 100.5, 99.6, 98.8, 94.1, 79.8, 77.8, 77.5, 76.9, 75.8, 75.7, 75.3, 74.8, 73.2, 72.7, 72.7, 72.04, 71.99, 71.94, 71.69, 71.66, 71.44, 71.39, 71.35, 71.32, 69.27, 68.9, 68.23, 68.21, 68.1, 62.5, 62.3, 62.2, 62., 61.5, 60.4, 59.9, 56.9, 55.5, 20.3, 17.6. HRMS (ESI) calcd for $(M+2Na)^{+2}$ $C_{149}H_{131}Cl_3O_{49}$: 1427.3304. Found: 1427.3329. (+2 charge state)



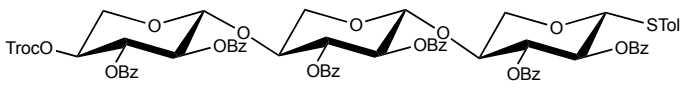
***p*-Methoxylphenyl 2,3-di-*O*-benzoyl-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranosyl-(1→4)-2-*O*-benzoyl-3-*O*-methyl-α-L-rhamnopyranosyl-(1→3)-4-*O*-acetyl-2,6-di-*O*-benzoyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (3.23).** To a solution of **3.22** (80 mg, 28.4 μmol) in THF (2.0 mL) and AcOH (0.5 mL) was added Zn dust (800.0 mg) with vigorous stirring. The TLC indicated that the reaction was finished within 30 min. The reaction mixture was filtered and the filtrate was concentrated with azeotropic removal of AcOH with toluene. The resulting solid was dissolved with CH_2Cl_2 and the organic liquid was washed with a saturated solution of $NaHCO_3$, water and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. The crude product was purified by chromatography on silica gel (3:2, hexanes–EtOAc) to yield **3.23** (67.5 mg, 90%) as a white foam. R_f 0.27 (1:1, hexanes–EtOAc); $[\alpha]_D$ +1.6 (*c* 1.9, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.02–7.84 (m, 25H), 7.72–7.71 (m, 2H), 7.57–7.46 (m, 14H), 7.42–7.22 (m, 29H), 6.85–6.83 (m, 2H), 6.64–6.62 (m, 2H), 5.80 (app t, *J* = 9.4 Hz, 1H), 5.63 (app t, *J* = 8.7 Hz, 1H), 5.48 (app t, *J* = 7.8 Hz, 1H), 5.45–5.40 (m, 3H), 5.22 (d, *J* = 2.7 Hz, 1H), 5.17–5.13 (m, 2H), 5.11–5.05 (m, 3H), 5.02–5.01 (m, 1H), 4.78–4.77 (m, 2H), 4.65–4.58 (m, 3H), 4.54 (d, *J* = 5.9 Hz, 1H), 4.47 (d, *J* = 6.4 Hz, 1H), 4.43 (dd, *J* = 11.8, 5.1 Hz, 1H), 4.20 (app t, *J* = 9.2 Hz, 1H), 3.96–3.90 (m, 3H), 3.80–3.68 (m, 9H), 3.64 (dd, *J* = 12.1, 4.3 Hz, 1H),

3.60–3.56 (m, 2H), 3.49 (dd, J = 11.2, 7.2 Hz, 1H), 3.47–3.34 (m, 4H), 3.29 (dd, J = 10.9, 7.6 Hz, 1H), 3.12–3.00 (m, 3H), 2.93 (s, 3H), 2.89 (d, J = 5.6 Hz, 1H), 1.83 (s, 3H), 0.98 (d, J = 5.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 169.5, 167.1, 165.73, 165.71, 165.38, 165.37, 165.29, 165.28, 165.21, 165.15, 165.0 (2C), 164.9, 164.83 (2C), 155.7, 151.0, 133.7, 133.5, 133.4, 133.34, 133.29, 133.26, 133.22, 133.20, 133.18, 133.14, 133.09, 133.06, 132.98, 129.99, 129.84, 129.80, 129.77, 129.75, 129.69 (2C), 129.64 (2C), 129.61 (2C), 129.58, 129.55 (2C), 129.52, 129.5, 129.28, 129.25 (2C), 129.13, 128.79, 128.77, 128.68, 128.57, 128.52 (2C), 128.45 (2C), 128.43, 128.39, 128.36, 128.31, 128.29, 128.26, 128.22, 128.20, 119.0, 114.4, 100.80, 100.77, 100.73, 100.71, 100.6 (2C), 99.6, 79.8, 77.8, 77.5, 75.8, 75.7, 75.53, 75.47, 75.36, 73.2, 72.7, 72.3, 72.13, 72.05, 71.70, 71.68, 71.5, 71.4, 71.3, 70.5, 68.4, 68.2, 68.2, 64.3, 62.5, 62.4, 62.31, 62.25, 61.5, 56.9, 55.6, 20.3, 17.6. HRMS (ESI) calcd for $(M+Na)^+$ $C_{146}H_{130}O_{47}Na$: 2657.7680. Found: 2657.7647.



***p*-Tolyl 2,3-di-*O*-benzoyl-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranoside (3.24).** To a solution of **3. 5** (49 mg, 48.4 μmol) in THF (2.0 mL) and AcOH (0.5 mL) was added Zn dust (500.0 mg) with vigorous stirring. The TLC indicated that the reaction was finished within 30 min. The reaction mixture was filtered and the filtrate was concentrated with azeotropic removal of AcOH with toluene. The resulting solid was dissolved with CH_2Cl_2 and the organic

liquid was washed with a saturated solution of $NaHCO_3$, water and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. The crude product was purified by chromatography on silica gel (2:1, hexanes–EtOAc) to yield **3.24** (36.6 mg, 94%) as a white foam. R_f 0.23 (2:1, hexanes–EtOAc); $[\alpha]_D$ –25.9 (*c* 0.7, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.01–7.93 (m, 8H, Ar), 7.56–7.50 (m, 4H, Ar), 7.42–7.37 (m, 8H, Ar), 7.33–7.32 (m, 2H, Ar), 7.09–7.07 (m, 2H, Ar), 5.63 (app t, *J* = 8.1 Hz, 1H, H-3b), 5.30 (app t, *J* = 8.3 Hz, 1H, H-2b), 5.25 (dd, *J* = 8.0, 6.0 Hz, 1H, H-2a), 5.18 (app t, *J* = 7.5 Hz, 1H, H-3a), 4.90 (d, *J* = 8.3 Hz, 1H, H-1b), 4.79 (d, *J* = 6.0 Hz, 1H, H-1a), 4.16 (dd, *J* = 12.1, 4.9 Hz, 1H, H-5b), 4.03 (td, *J* = 8.4, 4.8 Hz, 1H, H-4b), 3.75–3.69 (m, 2H, H-4a, H-5a), 3.47 (dd, *J* = 12.1, 8.9 Hz, 1H, H-5b'), 3.21–3.16 (m, 1H, H-5a), 2.95 (d, *J* = 5.5 Hz, 1H, OH-4a), 2.32 (s, 3H, Ar$C\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 167.1 (C=O), 165.5 (C=O), 165.2 (C=O), 165.0 (C=O), 138.4 (Ar), 133.7 (Ar), 133.5 (Ar), 133.3 (2C, Ar), 133.4 (Ar), 133.2 (Ar), 130.0 (Ar), 130.0 (Ar), 129.77 (Ar), 129.76 (Ar), 129.68 (Ar), 129.62 (Ar), 129.4 (Ar), 129.1 (Ar), 128.8 (Ar), 128.7 (Ar), 128.6 (Ar), 128.5 (Ar), 128.38 (Ar), 100.9 (C-1a), 87.0 (C-1b), 75.9 (C-4b), 75.4 (C-3a), 73.3 (C-3b), 70.7 (C-2a), 70.5 (C-2b), 68.4 (C-4a), 66.0 (C-5b), 64.4 (C-5a), 21.2 (Ar$\underline{C}H_3$); HRMS (ESI) calcd for $(M+Na)^+$ $C_{45}H_{40}O_{12}SNa$: 827.2133. Found: 827.2126.



***p*-Tolyl 2,3-di-*O*-benzoyl-4-O-(2,2,2-trichloroethoxycarbonyl)-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranosyl-(1→4)-2,3-di-*O*-benzoyl-β-L-xylopyranoside (3.25).** The preparation of glycosyl donor involves two steps: hydrolysis of thioglycoside **3.5** and synthesis of the corresponding trichloroacetimidate. First, to a solution of **3.5** (895 mg, 0.91 mmol) in acetone (8 mL) and water (2 mL) was added NBS (812.5 mg, 4.57 mmol) with stirring at 0 °C. The reaction mixture was concentrated after 30 min and purified by chromatography (4:1, hexanes–EtOAc) to give the corresponding hemiacetal. Then, to this compound in CH_2Cl_2 (10 mL) and CCl_3CN (0.4 mL, 4.39 mmol) was added DBU (13 μL, 86.9 μmol) with stirring at room temperature. After stirring for overnight at room temperature, the mixture was concentrated and the crude residue was partially purified by flash chromatography (7:1, hexanes–EtOAc). The product trichloroimidate was dried over high vacuum for 2 h. To a solution of the donor and acceptor **3.14** (252.3 mg, 0.54 mmol) in dry CH_2Cl_2 (15 mL) was added 4Å molecular sieves. The suspension was stirred for 30 min at room temperature before it was cooled to –40 °C. The reaction mixture was treated with a 0.1 M solution of TMSOTf in CH_2Cl_2 (270 μL) with stirring at –40 °C. After 30 min the reaction mixture was treated with Et_3N, after TLC showed complete consumption of the acceptor. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated. The crude residue was purified by chromatography (12:1, toluene–EtOAc) to yield **3.25** (613.8 mg, 86%) as a white foam. R_f 0.61 (5:1, toluene–EtOAc); $[\alpha]_D$ 1.7 (*c* 0.4, $CHCl_3$); ^{1}H NMR

(700 MHz, $CDCl_3$, δ_H) 8.00–7.97 (m, 4H, Ar), 7.94–7.91 (m, 7H, Ar), 7.57–7.50 (m, 6H, Ar), 7.45–7.37 (m, 11H, Ar), 7.32–7.27 (m, 4H), 7.08–7.06 (m, 2H, Ar), 5.59 (app t, *J* = 8.1 Hz, 1H, H-3c), 5.51 (app t, *J* = 8.1 Hz, 1H, H-3b), 5.44 (app t, *J* = 6.3 Hz, 1H, H-3a), 5.27 (app t, *J* = 8.2 Hz, 1H, H-2c), 5.15 (dd, *J* = 8.2, 6.4 Hz, 1H, H-2b), 5.10 (dd, *J* = 6.3, 4.6 Hz, 1H, H-2a), 4.88 (d, *J* = 8.3 Hz, 1H, H-1c), 4.75 (app td, *J* = 5.7, 4.0 Hz, 1H, H-4a), 4.73 (d, *J* = 6.3 Hz, 1H, H-1b), 4.69–4.65 (m, 3H, H-1a, $Cl_3CC\underline{H}_2$-), 4.12 (dd, *J* = 12.2, 4.8 Hz, 1H, H-5c), 3.97 (app td, *J* = 8.4, 4.9 Hz, 1H, H-4c), 3.87 (dd, *J* = 12.8, 3.7 Hz, 1H, H-5a), 3.81 (td, *J* = 8.2, 4.9 Hz, 1H, H-4b), 3.54 (dd, *J* = 12.5, 4.8 Hz, 1H, H-5b), 3.43 (dd, *J* = 12.2, 8.8 Hz, 1H, H-5c'), 3.38 (dd, *J* = 12.8, 5.8 Hz, 1H, H-5a'), 3.15 (dd, *J* = 12.5, 8.5 Hz, 1H, H-5b'), 2.31 (s, 3H, $ArC\underline{H}_3$); ^{13}C NMR (175 MHz, $CDCl_3$, δ_C) 165.4 (2C, C=O), 165.2 (C=O), 165.0 (C=O), 164.95 (C=O), 164.9 (C=O), 153.1 (C=O), 138.4 (Ar), 133.6 (Ar), 133.5 (Ar), 133.33 (Ar), 133.26 (Ar), 133.21 (Ar), 133.1 (Ar), 129.99 (Ar), 129.97 (Ar), 129.91 (Ar), 129.7 (Ar), 129.6 (Ar), 129.5 (Ar), 129.4 (Ar), 129.2 (Ar), 129.1 (Ar), 129.0 (Ar), 128.74 (Ar), 128.70 (Ar), 128.57 (Ar), 128.55 (Ar), 128.48 (Ar), 128.46 (Ar), 128.38 (Ar), 128.31 (Ar), 128.26 (Ar), 101.0 (C-1b), 98.9 (C-1a), 94.1 ($Cl_3\underline{C}$-), 86.9 (C-1c), 77.0 ($Cl_3C\underline{C}H_2O$-), 75.8 (C-4c), 74.9 (C-4b), 73.2 (C-3c), 72.1 (C-4a), 72.0 (C-3b), 71.5 (C-2b), 70.4 (C-2c), 69.3 (C-2a), 68.9 (C-3a), 65.9 (C-5c), 62.0 (C-5a), 59.9 (C-5b), 21.2 ($Ar\underline{C}H_3$); HRMS (ESI) calcd for $(M+Na)^+$ $C_{67}H_{57}{}^{35}Cl_3O_{20}SNa$: 1341.2122. Found: 1341.2149.

Chapter 4: Summary and Future Work

4.1 Summary

Lipooligosaccharides (LOSs), phenolic glycolipids (PGLs) and glycopeptidolipids (GPLs) are the three major classes of glycolipids produced by mycobacteria.[15] Many mycobacterial species produce LOSs, which have a more variable oligosaccharide structure compared to PGLs and GPLs.[40,41,174] Some structures of LOSs have been well established; for example, LOS I–VIII from *M. kansasii*,[47,48,59] LOS I–IV from *M. gastri*,[48,50,60] and LOS I–IV from *M. marinum*.[62-64] Some LOSs with novel carbohydrate residues on the non-reducing terminal showed high antigenicity.[48,50,60] In this thesis, I have described my studies on the design and synthesis of building blocks related to *M. gastri* LOSs (Chapter 2) and their incorporation into oligosaccharides (Chapter 3).

I have described the synthesis of building blocks for assembling the LOSs from *M. gastri*. The 4-*O*-substituted L-xylopyranose building block was prepared from a β-xylopyranose thioglycoside by formation of a stannylidene acetal followed by addition of 1.0 eq 2,2,2-trichloroethyl chloroformate (TrocCl). The 2,4-*O*-di-substituted L-xylopyranose building block was obtained from allyl α-xylopyranoside, also via formation of the same intermediate followed by addition of 2.0 eq BzCl.[104] The yields for both reactions were excellent.

I have described the synthesis of L-rhamnose and D-lactose building blocks, as well as several D-glucose building blocks for synthesis of the asymmetrically-substituted trehalose residue. Those syntheses, were for the most part straightforward, giving moderate to excellent yields of the products.

Assembling the synthesized D-glucose building blocks into α,α trehalose was a challenge. After an attempt to assemble this disaccharide by the intramolecular aglycon delivery (IAD) method failed, I turned my attention to the glycosylation using a donor armed with a 4,6-benzylidene acetal protecting group and an acceptor with 2-*O*-TBS protecting group. The α,α-trehalose was obtained in 49% yield as the major product in this reaction.

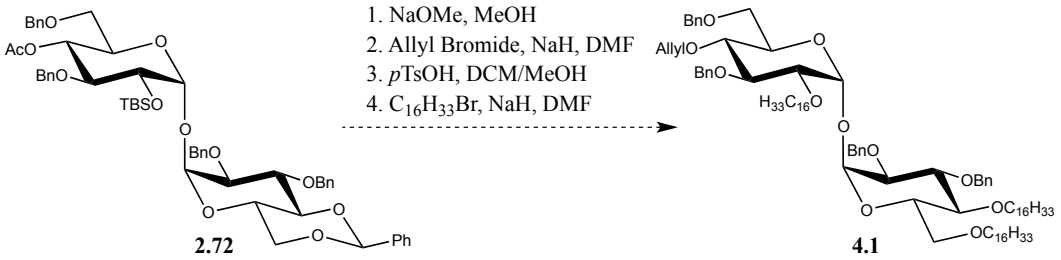
Another challenge was to make a C−C bond to facilitate the synthesis of the C-4 branched sugar. Two olefins were synthesized according to previous reports,[61,80,130,131,134] which I hoped could be coupled by cross metathesis. Unfortunately, the reaction only gave the dimerized product of the more reactive terminal olefin, likely due to the steric hindrance of C-6 methyl group in the cyclic olefin.[139]

The synthesized xylose, rhamnose and lactose building blocks were then assembled into oligosaccharides. Advanced intermediates for two different routes, an octasaccharide and a nonasaccharide, were synthesized in good yields.

4.2 Future Work

Due to the lack of time, I was unable to complete the total synthesis of the target. Therefore, there are a number of issues that should be resolved in the future.

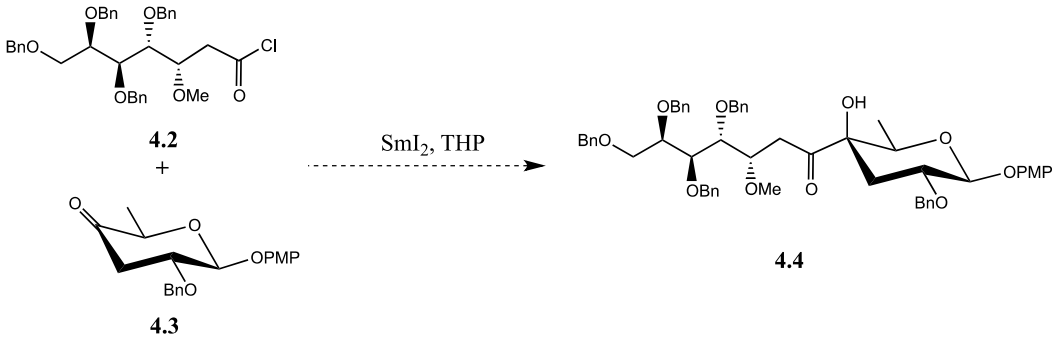
First, the protecting groups on the synthesized α,α-trehalose building block need to be removed, and then the alkyl lipids need to be installed. To achieve this, the acetyl protecting group on the C-4 hydroxyl needs to be replaced by a base-stable protecting group, for example, an allyl group. Then, the benzylidene acetal and TBS groups can be removed under acidic conditions. Finally the alkyl lipids can be installed to give compound **4.1** (Scheme 4.1). Subsequent cleavage of the allyl group in **4.1** would provide a compound ready to incorporate into the oligosaccharide target.



Scheme 4.1. Proposed scheme for the preparation of the lipid substituted trehalose **4.1**.

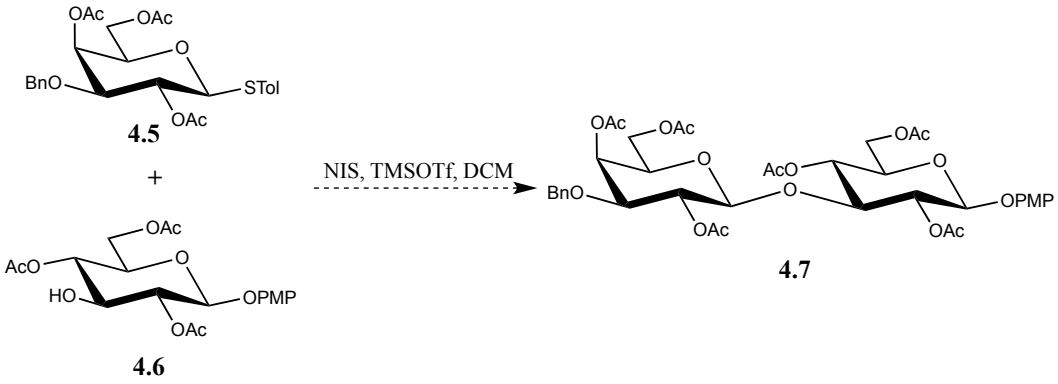
Second, a way to construct the C−C bond in the C-4 branched sugar needs to be identified. In Prandi's original paper, they made an α-methyl glycoside C-4 branched sugar by coupling the acyl chloride with a cyclic ketone by samarium diiodide. For future glycosylation, the methyl group is relatively difficult to remove and convert to a glycosyl donor without affecting other protecting groups. Hence, I selected a PMP group instead in developing the unsuccessful approach to this monosaccharide. To explore the possibility of using the Prandi method, a test

reaction should be performed with the β-glycoside using the same reaction conditions reported for the methyl glycoside (Scheme 4.2).



Scheme 4.2. Formation of C−C bond by SmI_2.

Finally, the mistake on the glycosidic linkage between the D-galactose and D-glucose residues need to be corrected. This β-(1→3) linkage could be obtained by glycosylation between donor **4.5** and acceptor **4.6** (Scheme 4.3).[175,176] Hydrogenation of the benzyl ether in **4.7** would provide a disaccharide alcohol that could then be converted to structures analogous to the octasaccharide or nonasaccharide targets described in Chapter 3.



Scheme 4.3. Proposed scheme for the synthesis of compound **4.7**.

Bibliography

(1) Tortoli, E. *FEMS Immunol. Med. Microbiol.* **2006**, *48*, 159–178.

(2) Wagner, D.; Young, L. S. *Infection* **2004**, *32*, 257–270.

(3) Nerlich, A. G.; Haas, C. J.; Zink, A.; Szeimies, U.; Hagedorn, H. G. *Lancet* **1997**, *350*, 1404.

(4) Crubézy, E.; Ludes, B.; Poveda, J. D.; Clayton, J.; Crouau-Roy, B.; Montagnon, D. *C. R. Acad. Sci. III, Sci. Vie* **1998**, *321*, 941–951.

(5) Daniel, T. M. *Int. J. Tuberc. Lung Dis.* **2005**, *9*, 1181–1182.

(6) Sakula, A. *Thorax* **1983**, *38*, 806–812.

(7) Daniel, T. M. *Int. J. Tuberc. Lung Dis.* **2005**, *9*, 944–945.

(8) Baron, E. J.; Peterson, L. R.; Finegold, S. M. *Bailey and Scott's Diagnostic Microbiology*; 13 ed.; Elsevier: St Louis, MO, 2014.

(9) Stearns, A. T. *Lepr. Rev.* **2002**, *73*, 215–224.

(10) Suzuki, K.; Akama, T.; Kawashima, A.; Yoshihara, A.; Yotsu, R. R.; Ishii, N. *J. Dermatol.* **2012**, *39*, 121–129.

(11) Zysk, K. G. *Religious Medicine: The History and Evolution of Indian Medicine*; 1st ed.; Transaction Publishers: New Brunswick, NJ, 1992.

(12) Robbins, G.; Tripathy, V. M.; Misra, V. N.; Mohanty, R. K.; Shinde, V. S.; Gray, K. M.; Schug, M. D. *PLoS ONE* **2009**, *4*, e5669.

(13) Britton, W. J.; Lockwood, D. N. *Lancet* **2004**, *363*, 1209–1219.

(14) Brown-Elliott, B. A.; Griffith, D. E.; Wallace, R. J., Jr. *Infect. Dis. Clin. North. Am.* **2002**, *16*, 187–220.

(15) Brennan, P. J.; Nikaido, H. *Annu. Rev. Biochem.* **1995**, *64*, 29–63.

(16) Etienne, G.; Laval, F.; Villeneuve, C.; Dinadayala, P.; Abouwarda, A.; Zerbib, D.; Galamba, A.; Daffé, M. *Microbiology* **2005**, *151*, 2075–2086.

(17) *Medical Microbiology*; Murray, P. R.; Rosenthal, K. S.; Pfaller, M. A., Eds.; 7 ed.; Elsevier: Philadelphia, PA, 2013.

(18) Vollmer, W.; Blanot, D.; de Pedro, M. A. *FEMS Microbiol. Rev.* **2008**, *32*, 149–167.

(19) Schleifer, K. H.; Kandler, O. *Bacteriol Rev* **1972**, *36*, 407–477.

(20) Sauvage, E.; Kerff, F.; Terrak, M.; Ayala, J. A.; Charlier, P. *FEMS Microbiol. Rev.* **2008**, *32*, 234–258.

(21) Kasik, J. *Am. Rev. Respir. Dis.* **1965**, 117–119.

(22) Jarlier, V.; Gutmann, L.; Nikaido, H. *Antimicrob. Agents Chemother.* **1991**, *35*, 1937–1939.

(23) Jarlier, V.; Nikaido, H. *J. Bacteriol.* **1990**, *172*, 1418–1423.

(24) Trias, J.; Jarlier, V.; Benz, R. *Science* **1992**, *258*, 1479–1481.

(25) McNeil, M.; Daffe, M.; Brennan, P. J. *J. Biol. Chem.* **1990**, *265*, 18200–18206.

(26) Misaki, A.; Nobuyo, S.; Azuma, I. *J. Biochem. (Tokyo)* **1974**, *76*, 15–27.

(27) Daffe, M.; Brennan, P. J.; McNeil, M. *J. Biol. Chem.* **1990**, *265*, 6734–6743.

(28) Joe, M.; Bai, Y.; Nacario, R. C.; Lowary, T. L. *J. Am. Chem. Soc.*

2007, *129*, 9885–9901.

(29) Ishiwata, A.; Ito, Y. *J. Am. Chem. Soc.* **2011**, *133*, 2275–2291.

(30) Briken, V.; Porcelli, S. A.; Besra, G. S.; Kremer, L. *Mol. Microbiol.* **2004**, *53*, 391–403.

(31) Guérardel, Y.; Maes, E.; Briken, V.; Chirat, F.; Leroy, Y.; Locht, C.; Strecker, G.; Kremer, L. *J. Biol. Chem.* **2003**, *278*, 36637–36651.

(32) Nigou, J.; Vercellone, A.; Puzo, G. *J. Mol. Biol.* **2000**, *299*, 1353–1362.

(33) Nigou, J.; Gilleron, M.; Puzo, G. *Biochimie* **2003**, *85*, 153–166.

(34) Cao, B.; Williams, S. J. *Nat. Prod. Rep.* **2010**, *27*, 919–947.

(35) Turnbull, W. B.; Stalford, S. A. *Org. Biomol. Chem.* **2012**, *10*, 5698–5706.

(36) Shi, L.; Berg, S.; Lee, A.; Spencer, J. S.; Zhang, J.; Vissa, V.; McNeil, M. R.; Khoo, K.-H.; Chatterjee, D. *J. Biol. Chem.* **2006**, *281*, 19512–19526.

(37) Takayama, K.; Wang, C.; Besra, G. S. *Clin. Microbiol. Rev.* **2005**, *18*, 81–101.

(38) Barry, C. E., III; Lee, R. E.; Mdluli, K.; Sampson, A. E.; Schroeder, B. G.; Slayden, R. A.; Yuan, Y. *Prog. Lipid Res.* **1998**, *37*, 143–179.

(39) Stodola, F. H.; Lesuk, A.; Anderson, R. J. *J. Biol. Chem.* **1938**, *126*, 505–513.

(40) Hunter, S. W.; Fujiwara, T.; Brennan, P. J. *J. Biol. Chem.* **1982**, *257*, 15072–15078.

(41) Schorey, J. S.; Sweet, L. *Glycobiology* **2008**, *18*, 832–841.

(42) Laneelle, G.; Asselineau, J. *Eur. J. Biochem.* **1968**, *5*, 487–491.

(43) Vilkas, E.; Lederer, E. *Tetrahedron Lett.* **1968**, *9*, 3089–3092.

(44) Chatterjee, D.; Khoo, K. H. *Cell. Mol. Life Sci.* **2001**, *58*, 2018–2042.

(45) Brennan, P. J.; Mayer, H.; Aspinall, G. O.; Nam Shin, J. E. *Eur. J. Biochem.* **1981**, *115*, 7–15.

(46) Saadat, S.; Ballou, C. E. *J. Biol. Chem.* **1983**, *258*, 1813–1818.

(47) Hunter, S. W.; Hunter, S. W.; Jardine, I.; Jardine, I.; Yanagihara, D. L.; Yanagihara, D. L.; Brennan, P. J.; Brennan, P. J. *Biochemistry* **1985**, *24*, 2798–2805.

(48) Gilleron, M.; Puzo, G. *Glycoconjugate J.* **1995**, *12*, 298–308.

(49) Hunter, S. W.; Murphy, R. C.; Clay, K.; Goren, M. B.; Brennan, P. J. *J. Biol. Chem.* **1983**, *258*, 10481–10487.

(50) Gilleron, M.; Vercauteren, J.; Puzo, G. *J. Biol. Chem.* **1993**, *268*, 3168–3179.

(51) McNeil, M.; Tsang, A. Y.; McClatchy, J. K.; Stewart, C.; Jardine, I.; Brennan, P. J. *J. Bacteriol.* **1987**, *169*, 3312–3320.

(52) Hunter, S. W.; Barr, V. L.; McNeil, M.; Jardine, I.; Brennan, P. J. *Biochemistry* **1988**, *27*, 1549–1556.

(53) Hunter, S. W.; Murphy, R. C.; Clay, K.; Goren, M. B.; Brennan, P. J. *J. Biol. Chem.* **1983**, *258*, 10481–10487.

(54) Daffé, M.; McNeil, M.; Brennan, P. J. *Biochemistry* **1991**, *30*, 378–388.

(55) Besra, G. S.; Bolton, R. C.; McNeil, M. R.; Ridell, M.; Simpson, K. E.; Glushka, J.; van Halbeek, H.; Brennan, P. J.; Minnikin, D. E. *Biochemistry* **1992**, *31*, 9832–9837.

(56) Camphausen, R. T.; McNeil, M.; Jardine, I.; Brennan, P. J. *J. Bacteriol.* **1987**, *169*, 5473–5480.

(57) Kamisango, K.-I.; Saadat, S.; Dell, A.; Ballou, C. E. *J. Biol. Chem.* **1985**, *260*, 4117–4121.

(58) Besra, G. S.; Khoo, K.-H.; Belisle, J. T.; McNeil, M. R.; Morris, H. R.; Dell, A.; Brennan, P. J. *Carbohydr. Res.* **1994**, *251*, 99–114.

(59) Hunter, S. W.; Fujiwara, T.; Murphy, R. C.; Brennan, P. J. *J. Biol. Chem.* **1984**, *259*, 9729–9734.

(60) Gilleron, M.; Vercauteren, J.; Puzo, G. *Biochemistry* **1994**, *33*, 1930–1937.

(61) Longépé, J.; Prandi, J.; Beau, J.-M. *Angew. Chem. Int. Ed.* **1997**, *36*, 72–75.

(62) Burguiere, A.; Hitchen, P.; Dover, L.; Kremer, L.; Ridell, M.; Alexander, D.; Liu, J.; Morris, H.; Minnikin, D.; Dell, A.; Besra, G. *J. Biol. Chem.* **2005**, *280*, 42124–42133.

(63) Rombouts, Y.; Burguière, A.; Maes, E.; Coddeville, B.; Elass, E.; Guérardel, Y.; Kremer, L. *J. Biol. Chem.* **2009**, *284*, 20975–20988.

(64) Rombouts, Y.; Elass, E.; Biot, C.; Maes, E.; Coddeville, B.; Burguière, A.; Tokarski, C.; Buisine, E.; Trivelli, X.; Kremer, L. *J. Am. Chem. Soc.* **2010**, *132*, 16073–16084.

(65) Adinolfi, M.; Corsaro, M. M.; De Castro, C.; Lanzetta, R.; Parrilli, M.; Evidente, A.; Lavermicocca, P. *Carbohydr. Res.* **1995**, *267*, 307–311.

(66) Adinolfi, M.; Corsaro, M. M.; De Castro, C.; Evidente, A.; Lanzetta, R.; Mangoni, L.; Parrilli, M. *Carbohydr. Res.* **1995**, *274*, 223–232.

(67) Rombouts, Y.; Alibaud, L.; Carrère-Kremer, S.; Maes, E.; Tokarski, C.; Elass, E.; Kremer, L.; Guérardel, Y. *J. Biol. Chem.* **2011**, *286*, 33678–33688.

(68) Khoo, K.-H.; Suzuki, R.; Morris, H. R.; Dell, A.; Brennan, P. J.; Besra, G. S. *Carbohydr. Res.* **1995**, *276*, 449–455.

(69) Besra, G. S.; McNeil, M. R.; Khoo, K.-H.; Dell, A.; Morris, H. R.; Brennan, P. J. *Biochemistry* **1993**, *32*, 12705–12714.

(70) Besra, G. S.; McNeil, M. R.; Brennan, P. J. *Biochemistry* **1992**, *31*, 6504–6509.

(71) Collins, F. M.; Cunningham, D. S. *Infect. Immun.* **1981**, *32*, 614–624.

(72) Belisle, J. T.; Brennan, P. J. *J. Bacteriol.* **1989**, *171*, 3465–3470.

(73) Lemassu, A.; Lévy-Frébault, V. V.; Laneelle, M. A.; Daffe, M. *J. Gen. Microbiol.* **1992**, *138*, 1535–1541.

(74) Mosser, D. M. *J. Leukocyte Biol.* **2003**, *73*, 209–212.

(75) Clay, H.; Volkman, H. E.; Ramakrishnan, L. *Immunity* **2008**, *29*, 283–294.

(76) van der Woude, A. D.; Sarkar, D.; Bhatt, A.; Sparrius, M.; Raadsen, S. A.; Boon, L.; Geurtsen, J.; van der Sar, A. M.; Luirink, J.; Houben,

E. N. *J. Biol. Chem.* **2012**, *287*, 20417–20429.

(77) Ren, H.; Dover, L. G.; Islam, S. T.; Alexander, D. C.; Chen, J. M.; Besra, G. S.; Liu, J. *Mol. Microbiol.* **2007**, *63*, 1345–1359.

(78) Alibaud, L.; Pawelczyk, J.; Gannoun-Zaki, L.; Singh, V. K.; Rombouts, Y.; Drancourt, M.; Dziadek, J.; Guerardel, Y.; Kremer, L. *J. Biol. Chem.* **2014**, *289*, 215–228.

(79) Ziegler, T.; Eckhardt, E.; Birault, V. *J. Org. Chem.* **1993**, *58*, 1090–1099.

(80) Classon, B.; Garegg, P.; Samuelsson, B. *Can. J. Chem.* **1981**, *59*, 339–343.

(81) Mukherjee, C.; Misra, A. K. *Glycoconjugate J.* **2008**, *25*, 611–624.

(82) Nishizawa, M.; Kodama, S.; Yamane, Y.; Kayano, K.; Hatakeyama, S.; Yamada, H. *Chem. Pharm. Bull.* **1994**, *42*, 982–984.

(83) Klemer, A.; Buhe, E. *Tetrahedron Lett.* **1969**, *10*, 1689–1691.

(84) Posner, G. H.; Posner, G. H.; Bull, D. S.; Bull, D. S. *Tetrahedron* **1996**, *37*, 6279–6282.

(85) Ronnow, T. E. C. L.; Meldal, M.; Bock, K. *Tetrahedron: Asymmetry* **1994**, *5*, 2109–2122.

(86) Ronnow, T. E. C. L.; Meldel, M.; Bock, K. *J. Carbohydr. Chem.* **1995**, *14*, 197–211.

(87) Joseph, A. A.; Verma, V. P.; Liu, X. Y.; Wu, C. H.; Dhurandhare, V. M.; Wang, C.-C. *Eur. J. Org. Chem.* **2012**, *2012*, 744–753.

(88) Joseph, A. A.; Chang, C.-W.; Wang, C.-C. *Chem. Commun. (Camb.)*

2013, *49*, 11497–11499.

(89) Anjum, S.; Vetter, N. D.; Rubin, J. E.; Palmer, D. R. J. *Tetrahedron* **2013**, *69*, 816–825.

(90) Leigh, C. D.; Bertozzi, C. R. *J. Org. Chem.* **2008**, *73*, 1008–1017.

(91) Pratt, M. R.; Pratt, M. R.; Leigh, C. D.; Leigh, C. D.; Bertozzi, C. R.; Bertozzi, C. R. *Org. Lett.* **2003**, *5*, 3185–3188.

(92) Lin, F. L.; van Halbeek, H.; Bertozzi, C. R. *Carbohydr. Res.* **2007**, *342*, 2014–2030.

(93) Fischer, E.; Ruff, O. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 2142–2147.

(94) Vargha, von, L. *Ber. dtsch. Chem. Ges. A/B* **2006**, *68*, 18–24.

(95) Ness, R. K. *Methods Carbohydr. Chem.* **1962**, 90.

(96) Dimant, E.; Banay, M. *J. Org. Chem.* **1960**, *25*, 475–476.

(97) Garegg, P. J.; Hultberg, H. *Carbohydr. Res.* **1981**, *93*, C10–C11.

(98) Lipták, A.; Imre, J.; Harangi, J.; Nánási, P.; Neszmélyi, A. *Tetrahedron* **1982**, *38*, 3721–3727.

(99) Liu, X.; Wada, R.; Boonyarattanakalin, S.; Castagner, B.; Seeberger, P. H. *Chem. Commun.* **2008**, 3510–3512.

(100) Fletcher, H. G. J.; Hudson, C. S. *J. Am. Chem. Soc.* **1947**, *69*, 921–924.

(101) Bochkov, A. F.; Betaneli, V. I.; Kochetkov, N. K. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1971**, 1291–1295.

(102) Barbat, J.; Gelas, J.; Horton, D. *Carbohydr. Res.* **1991**, *219*, 115–121.

(103) Naleway, J. J.; Raetz, C. R. H.; Anderson, L. *Carbohydr. Res.* **1988**,

179, 199–209.

(104) Helm, R. F.; Ralph, J.; Anderson, L. *J. Org. Chem.* **1991**, *56*, 7015–7021.

(105) Nilsson, M.; Svahn, C.-M.; Westman, J. *Tetrahedron* **1993**, *246*, 161–172.

(106) Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293.

(107) Bock, K.; Lundt, I.; Pedersen, C. *Tetrahedron Lett.* **1973**, *14*, 1037–1040.

(108) Auzanneau, F. I.; Bundle, D. R. *Carbohydr. Res.* **1991**, *212*, 13–24.

(109) Nagashima, N.; Ohno, M. *Chem. Lett.* **1987**, 141–144.

(110) Wolfrom, M. L.; Juliano, B. O. *J. Am. Chem. Soc.* **1960**, *82*, 1673–1677.

(111) King, J.; Allbutt, A. *Can. J. Chem.* **1970**, *48*, 1754–1769.

(112) Sarpe, V. A.; Kulkarni, S. S. *J. Org. Chem.* **2011**, *76*, 6866–6870.

(113) Hui, Y.; Chang, C.-W. T. *Org. Lett.* **2002**, *4*, 2245–2248.

(114) Guiard, J.; Collmann, A.; Gilleron, M.; Mori, L.; De Libero, G.; Prandi, J.; Puzo, G. *Angew. Chem. Int. Ed* **2008**, *47*, 9734–9738.

(115) Baer, H. H.; Radatus, B. *Carbohydr. Res.* **1984**, *128*, 165–174.

(116) Berndt, F.; Sajadi, M.; Ernsting, N. P.; Mahrwald, R. *Carbohydr. Res.* **2011**, *346*, 2960–2964.

(117) Cipolla, L.; Lay, L.; Nicotra, F.; Panza, L.; Russo, G. *Tetrahedron* **1994**, *35*, 8669–8670.

(118) Nicolaou, K. C.; van Delft, F. L.; Conley, S. R.; Mitchell, H. J.; Jin,

Z.; Rodríguez, R. M. *J. Am. Chem. Soc.* **1997**, *119*, 9057–9058.

(119) Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc.* **1991**, *113*, 9376–9377.

(120) Barresi, F.; Hindsgaul, O. *Synlett* **1992**, *1992*, 759–761.

(121) Ennis, S. C.; Fairbanks, A. J.; Tennant-Eyles, R. J.; Yeates, H. S. *Synlett* **1999**, *1999*, 1387–1390.

(122) Ito, Y.; Ando, H.; Wada, M.; Kawai, T.; Ohnish, Y.; Nakahara, Y. *Tetrahedron* **2001**, *57*, 4123–4132.

(123) Aloui, M.; Chambers, D. J.; Cumpstey, I.; Fairbanks, A. J.; Redgrave, A. J.; Seward, C. M. P. *Chem. Eur. J.* **2002**, *8*, 2608.

(124) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087–1088.

(125) Abdel-Rahman, A. A. H.; Ashry, El, E. S. H.; Schmidt, R. R. *Tetrahedron* **2002**, *337*, 195–206.

(126) Hadd, M. J.; Gervay, J. *Carbohydr. Res.* **1999**, *320*, 61–69.

(127) Bai, Y.; Lowary, T. L. *J. Org. Chem.* **2006**, *71*, 9672–9680.

(128) Eby, R.; Schuerch, C. *Tetrahedron* **1974**, *34*, 79–90.

(129) Demchenko, A.; Stauch, T.; Boons, G.-J. *Synlett* **1997**, *1997*, 818–820.

(130) Wolfrom, M.; Moody, F. *J. Am. Chem. Soc.* **1940**, *62*, 3465–3466.

(131) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553–3560.

(132) Bredenkamp, M. W.; Holzapfel, C. W.; Swanepoel, A. D. *Tetrahedron Lett.* **1990**, *31*, 2759–2762.

(133) Baer, H. H.; Astles, D. J. *Carbohydr. Res.* **1984**, *126*, 343–347.

(134) Sato, K.-I.; Hoshi, T.; Kajihara, Y. *Chem. Lett.* **1992**, *21*, 1469.

(135) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784.

(136) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450.

(137) Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043.

(138) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

(139) Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441–444.

(140) Seeberger, P. H. *Chem. Soc. Rev.* **2008**, *37*, 19–28.

(141) Jenkins, D. J.; Potter, B. V. *J. Chem. Soc., Perkin Trans. 1* **1998**, 41–50.

(142) Rosenberg, H.; Riley, A.; Marwood, R.; Correa, V.; Taylor, C.; Potter, BVL. *Carbohydr. Res.* **2001**, *332*, 53–66.

(143) Delany, J. J., III; Padykula, R. E.; Berchtold, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 1394–1397.

(144) Luning, B.; Norberg, T.; Tejbrant, J. *J. Carbohydr. Chem.* **1992**, *11*, 933–943.

(145) Zhang, H.; Sridhar Reddy, M.; Phoenix, S.; Deslongchamps, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1272–1275.

(146) Yu, C.-S.; Wang, H.-Y.; Chiang, L.-W.; Pei, K. *Synthesis* **2007**, *2007*, 1412–1420.

(147) Cumpstey, I.; Fairbanks, A. J.; Redgrave, A. J. *Tetrahedron* **2004**, *60*, 9061–9074.

(148) Hudson, C. S.; Johnson, J. M. *J. Am. Chem. Soc.* **1915**, *37*, 1270–1275.

(149) Hronowski, L. J. J.; Szarek, W. A.; Hay, G. W.; Krebs, A.; Depew, W. T. *Carbohydr. Res.* **1989**, *190*, 203–218.

(150) Weng, S.-S.; Lin, Y.-D.; Chen, C.-T. *Org. Lett.* **2006**, *8*, 5633–5636.

(151) Vic, G.; Hastings, J. J.; Howarth, O. W.; Crout, D. H. G. *Tetrahedron: Asymmetry* **1996**, *7*, 709–720.

(152) Michihata, N.; Kaneko, Y.; Kasai, Y.; Tanigawa, K.; Hirokane, T.; Higasa, S.; Yamada, H. *J. Org. Chem.* **2013**, *78*, 4319–4328.

(153) Kumar, A.; Geng, Y.; Schmidt, R. R. *Eur. J. Org. Chem.* **2012**, *2012*, 6846–6851.

(154) Moumé-Pymbock, M.; Furukawa, T.; Mondal, S.; Crich, D. *J. Am. Chem. Soc.* **2013**, *135*, 14249–14255.

(155) Rising, T. W.; Claridge, T. D.; Davies, N.; Gamblin, D. P.; Moir, J. W.; Fairbanks, A. J. *Carbohydr. Res.* **2006**, *341*, 1574–1596.

(156) Français, A.; Urban, D.; Beau, J.-M. *Angew. Chem. Int. Ed* **2007**, *46*, 8662–8665.

(157) McGill, N. W.; Williams, S. J. *J. Org. Chem.* **2009**, *74*, 9388–9398.

(158) Schmidt, R. R.; Michel, J. *Angew. Chem. Int. Ed.* **1980**, *19*, 731–732.

(159) Yu, B.; Tao, H. *J. Org. Chem.* **2002**, *67*, 9099–9102.

(160) Sun, J.; Han, X.; Yu, B. *Org. Lett.* **2005**, *7*, 1935–1938.

(161) Yang, X.; Fu, B.; Yu, B. *J. Am. Chem. Soc.* **2011**, *133*, 12433–12435.

(162) Larsen, K.; Olsen, C. E.; Motawia, M. S. *Carbohydr. Res.* **2008**, *343*,

383–387.

(163) Cramer, F.; Hennrich, N. *Chem. Ber.* **1961**, *94*, 976–989.

(164) Zhu, X.-X.; Cai, M.-S.; Zhou, R.-L. *Carbohydr. Res.* **1997**, *303*, 261–266.

(165) Shohda, K.-I.; Wada, T.; Sekine, M. *Nucleosides Nucleotides* **1998**, *17*, 2199–2210.

(166) Belot, F.; Jacquinet, J. C. *Carbohydr. Res.* **1996**, *290*, 79–86.

(167) Zhu, T.; Boons, G. J. *Carbohydr. Res.* **2000**, *329*, 709–715.

(168) Dowd, M. K.; Rockey, W. M.; French, A. D.; Reilly, P. J. *J. Carbohydr. Chem.* **2002**, *21*, 11–25.

(169) Baumann, H.; Erbing, B.; Jansson, P.-E.; Kenne, L. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2145–2151.

(170) Liu, B.; Roy, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 773–779.

(171) Schwardt, O.; Gao, G. P.; Visekruna, T.; Rabbani, S.; Gassmann, E.; Ernst, B. *J. Carbohydr. Chem.* **2004**, *23*, 1–26.

(172) Vutukuri, D. R.; Bharathi, P.; Yu, Z.; Rajasekaran, K.; Tran, M.-H.; Thayumanavan, S. *J. Org. Chem.* **2003**, *68*, 1146–1149.

(173) Nakayama, K.; Uoto, K.; Higashi, K.; Soga, T.; Kusama, T. *Chem. Pharm. Bull.* **1992**, *40*, 1718–1720.

(174) Watanabe, M.; Aoyagi, Y.; Ohta, A.; Minnikin, D. E. *Eur. J. Biochem.* **1997**, *248*, 93–98.

(175) Zhou, Y.; Rahm, M.; Wu, B.; Zhang, X.; Ren, B.; Dong, H. *J. Org. Chem.* **2013**, *78*, 11618–11622.

(176) Rabuka, D.; Hindsgaul, O. *Carbohydr. Res.* **2002**, *337*, 2127–2151.