2015

Stereoselective synthesis of 2-deoxy glycosides via anomeric O-alkylation

Danyang Zhu

University of Toledo

Follow this and additional works at: http://utdr.utoledo.edu/theses-dissertations

Recommended Citation

This Dissertation is brought to you for free and open access by The University of Toledo Digital Repository. It has been accepted for inclusion in Theses and Dissertations by an authorized administrator of The University of Toledo Digital Repository. For more information, please see the repository's About page.
A Dissertation

entitled

Stereoselective Synthesis of 2-Deoxy Glycosides via Anomeric O-Alkylation

by

Danyang Zhu

Submitted to the Graduate Faculty as partial fulfillment of the requirements for the

Doctor of Philosophy Degree in Chemistry

Dr. Jianglong Zhu, Committee Chair

Dr. Max Funk, Committee Member

Dr. Steven Sucheck, Committee Member

Dr. L. M. Viranga Tillekeratne, Committee Member

Dr. Patricia Komuniecki, Dean
College of Graduate Studies

The University of Toledo

August 2015
Copyright 2015, Danyang Zhu

This document is copyrighted material. Under copyright law, no parts of this document may be reproduced without the expressed permission of the author.
An Abstract of

Stereoselective Synthesis of 2-Deoxy-Glycosides via Anomeric O-Alkylation

by

Danyang Zhu

Submitted to the Graduate Faculty as partial fulfillment of the requirements for the Doctor of Philosophy Degree in Chemistry

The University of Toledo

August 2015

2-Deoxy sugars are an important class of carbohydrates which exist in a wide range of bioactive natural products and have been found to play vital role in biological activity of those natural molecules.\(^1\) Due to limited amounts of these molecules can be isolated from natural sources, it is critical to develop efficient tools for stereoselective synthesis of oligosaccharides in order to extensively study their structure and activity relationship for discovery of effective therapeutic agents. Despite a number of synthetic studies have been previously reported, stereoselective synthesis of 2-deoxy-glycosides still remains very challenging because of the lack of directing group at C-2 position. In this presentation, we have outlined an approach for direct synthesis of 2-deoxy-\(\beta\)-oligosaccharides involving \(O\)-alkylation of anomic alkoxides with challenging secondary triflates as electrophiles.\(^2\) We also found that a free hydroxyl group at C3 of the 2-deoxy-sugar-derived lactols is required to achieve synthetically efficient yields. Using this approach, 2-deoxy-\(\beta\)-tetrasaccharide has been obtained in excellent yields (Figure 1).

We also reported stereoselective synthesis of 2-deoxy \(\alpha\)-digitoxosides and \(\alpha\)-boivinosides via chelation-controlled anomic \(O\)-alkylation using anomic alkoxides
containing C3 axial alkoxides and sugar-derived secondary triflates.\(^3\) In this chelation-controlled anomeric O-alkylation, the axial anomeric alkoxides are locked which lead to the formation of α-glycosides. Using this approach, α-digitoxosides and α-boivinosides have been successfully obtained (Figure 2).

**Figure 1:** Synthesis of β-linked 2,6-tetrasaccharides using iterative anomeric O-alkylation

**Figure 2:** Synthesis of α-linked 2,6-trisaccharides using iterative chelation-controlled anomeric O-alkylation
Acknowledgement

The generous help and valuable contribution from many warm, caring people in the development and completion of this thesis and my Doctor of Philosophy program made my learning at The University of Toledo a rewarding experience.

First and foremost I am deeply indebted to my advisor, Dr. Jianglong Zhu, for his excellent guidance, extreme patience and effort during my graduate work with him. He not only guided and supported my research, but also offered helpful suggestions concerning my future career. I am indebted to him for all his concerns about me throughout these years. Words may not be sufficient to express my deep appreciation.

For this thesis, I am also equally appreciative to the members of my committee: Dr. Max Funk, Dr. Steven Sucheck and Dr. L. M. Viranga Tillekeratne. Their prompt feedback and valuable suggestions greatly enhanced the quality of the research and assured the timely completion the thesis.

I am also thankful for the friendship and help provided by current members of the Zhu group. Thank them for sharing with me their valuable experience on conducting research. Their experience made me avoid many hidden research difficulties.

I thank the Department of Chemistry and Biochemistry, The University of Toledo, for providing me with financial support and National Science Foundation (NSF) CHE-1213352 grant that supported the work described herein.

Finally, I would like to express my greatest thanks to my family members: my husband, Qinzhe Wang, and my parents, Genlin Zhu and Yaping Song for their
understanding, words of encouragement, support, sacrifices of time and love to assure the completion of the thesis.
Contents

1 Direct Synthesis of 2-Deoxy-β-Glycosides via Anomeric O-Alkylation with Secondary Electrophiles ................................................................. 1

1.1 Introduction ................................................................................................................................................. 1

1.1.1 Deoxy Sugars ............................................................................................................................................ 1
1.1.2 Occurrence of Deoxy Sugars ...................................................................................................................... 1
1.1.3 Antitumor Glycoconjugates ......................................................................................................................... 2

1.1.3.1 Anthracycline Antitumor Antibiotics ......................................................... 2
1.1.3.2 Aureolic Acid Antitumor Antibiotics ............................................................ 3
1.1.3.3 Angucycline Antibiotics ............................................................................... 4

1.2 Previous Synthesis of 2-Deoxy Glycosides ............................................................................................... 7

1.2.1 Traditional Method for Synthesis of Glycosides ......................................................... 7
1.2.2 Glycosylation Process with a Participating Group ................................................... 8
1.2.3 Direct Synthesis of 2-Deoxy Sugars ....................................................................................... 10

1.3 Results and Discussions ............................................................................................................................ 14

1.3.1 Research Strategy ................................................................................................................................. 14
1.3.2 Optimization of Synthesis of 2,6-Dideoxy-β-Glycosides ..................................... 16
1.3.3 Synthesis of Various 2,6-Dideoxy-β-Glycosides .................................................. 20
1.3.4 Synthesis of 2-Deoxy-β-Glycosides .................................................. 22
1.3.5 Synthesis of 2,3,6-Trideoxy-β-Glycosides and 2,4,6-Trideoxy-4-
azido-β-glycosides .................................................................................. 23
1.3.6 Synthesis of β linked 2,6-Dideoxy-Tri- and -Tetra-saccharides ...... 24
1.3.7 Conclusion .......................................................................................... 25

1.4 Experimentals ....................................................................................... 27
General Information.................................................................................... 27
1.4.1 Preparation of lactol donors .............................................................. 28
1.4.2 Preparation of sugar-derived triflutes: ............................................. 43
1.4.3 General procedure for preparation of O-linked 2-Deoxy β-
Glycosides: ............................................................................................... 54
1.4.4 Synthesis of trisaccharide 23 and tetrasaccharide 24.................... 69

2 Stereoselective Synthesis of α-Digitoxosides and α-Boivinosides via Chelation-
Controlled Anomeric O-Alkylation.......................................................... 171

2.1 Introduction ........................................................................................... 171

2.1.1 Anomeric O-Alkylation .................................................................... 172
2.1.2 Model Studies .................................................................................. 173
2.1.3 Chelation-Controlled Anomeric O-Alkylation ................................. 174

2.2 Results and Discussion ......................................................................... 176

2.2.1 Synthesis of α-D-Digitoxosides ....................................................... 176
2.2.2 Synthesis of 4-O-Benzyl-\(\text{D}\)-Boivinose and \(\alpha\text{-D}\)-Boivinosides........ 177

2.2.3 Conclusion ........................................................................................................ 179

2.3 Experimentals ........................................................................................................ 180

   General Information............................................................................................. 180

2.3.1 Synthesis of 4-\(O\)-\(p\)-methoxybenzyl-\(\text{D}\)-digitoxose .................. 181

2.3.2 Synthesis of \(\alpha\text{-D}\)-digitoxosides ............................................................. 182

2.3.3 Synthesis of 4-\(O\)-benzyl-\(\text{D}\)-boivinose..................................................... 189

2.3.4 Synthesis of \(\alpha\text{-D}\)-boivinosides ............................................................... 192

2.4 NMR of Selected Compounds ............................................................................. 194

3 References ................................................................................................................. 221
Lists of Tables

Chapter 1

Table 1. 1 Electrophile scope by Shair and co-workers via anomeric O-alkylation........ 15
Table 1. 2 Optimization of Synthesis of 2,6-Dideoxy-β-Glycosides............................ 17
Table 1. 3 Synthesis of Various 2,6-Dideoxy-β-glycosides ........................................ 21
Table 1. 4 Synthesis of 2,3,6-Trideoxy-β-Glycosides and 2,4,6-Trideoxy-4-azido-β-
glycosides.................................................................................................................. 24

Chapter 2

Table 2. 1 Synthesis of α-D-digitoxosides.................................................................... 177
Lists of Figures

Chapter 1

Figure 1. 1 Representative anthracycline antitumor antibiotics ........................................... 3
Figure 1. 2 Representative aureolic acid antitumor antibiotics .................................................. 4
Figure 1. 3 Representative angucycline antibiotics ................................................................. 5
Figure 1. 4 Traditional method for synthesis of glycosidic bond ............................................. 8
Figure 1. 5 Glycosylation process with a participating group ................................................... 9

Chapter 2

Figure 2. 1 The Structure of digitoxin .................................................................................. 171
Lists of Schemes

Chapter 1

Scheme 1. 1 Direct glycosylation by Takahashi and co-workers ............................................. 10
Scheme 1. 2 Direct glycosylation by Kim and co-workers ....................................................... 11
Scheme 1. 3 Direct glycosylation by Herzon and co-workers .................................................. 11
Scheme 1. 4 Direct glycosylation by Taylor and co-workers .................................................. 12
Scheme 1. 5 Direct glycosylation by Bennet and co-workers .................................................. 12
Scheme 1. 6 Direct glycosylation by Schmidt and co-workers via anomeric O-alkylation
.................................................................................................................................................... 14
Scheme 1. 7 Synthesis of complex glycosides via anomeric O-alkylation ......................... 16
Scheme 1. 8 Formation of Side Products Containing Aldehyde Functional Group .......... 18
Scheme 1. 9 Suppression of Anomeric Alkoxide Decomposition ........................................ 19
Scheme 1. 10 Synthesis of 2-Deoxy-β-Glycosides ................................................................. 22
Scheme 1. 11 Synthesis of β-linked 2,6-Dideoxy-Tri- and -Tetra-saccharides ............... 25

Chapter 2

Scheme 2. 1 Synthesis of complex glycosides via anomeric O-alkylation .................. 172
Scheme 2. 2 Synthesis of 4-O-p-methoxybenzyl-D-digitoxose ........................................... 173
Scheme 2. 3 Formation of α-linked disaccharide 8 ......................................................... 174
Scheme 2. 4 Synthesis of complex glycosides via chelation-controlled anomeric O-
alkylation .................................................................................................................................. 175
Scheme 2. 5 Synthesis of 4-O-benzyl-D-boivinose and α-D-boivinosides ................ 178
List of Abbreviations

[α] specific rotation
Ac acetyl
Ac₂O acetic anhydride
AcOH acetic acid
Bn benzyl
br broad
c concentration
calcd. calculated
cat. catalytic
CSA camphorsulfonic acid
δ chemical shift
d doublet
DIEA diisopropylethylamine
DMAP 4-(dimethylamino)pyridine
DMF N,N-dimethylformamide
DNA deoxyribonucleic acid
equiv. equivalent
Et ethyl
EtOAc ethyl acetate
FTIR fourier transform infrared spectroscopy
gm gram
h hour
HPLC high performance liquid chromatography
HRMS high resolution mass spectroscopy
HSQC heteronuclear single quantum coherence spectroscopy
Hz hertz
IC₅₀ inhibitory concentration 50%
LRMS low resolution mass spectroscopy
µg microgram
µL microliter
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>µmol</td>
<td>micromole</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>M</td>
<td>molar</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>min</td>
<td>minute</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
</tr>
<tr>
<td>mL</td>
<td>milliliter</td>
</tr>
<tr>
<td>mmol</td>
<td>millimole</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectroscopy</td>
</tr>
<tr>
<td>MS</td>
<td>molecular sieve</td>
</tr>
<tr>
<td>ng</td>
<td>nanogram</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NMP</td>
<td>N-methylpyrrolidone</td>
</tr>
<tr>
<td>ovrlp</td>
<td>overlapping</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PMB</td>
<td>para-methoxybenzyl</td>
</tr>
<tr>
<td>ppm</td>
<td>part per million</td>
</tr>
<tr>
<td>p-TsOH</td>
<td>para-toluenesulfonic acid</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>S_N2</td>
<td>nucleophilic substitution bimolecular</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>tertiary-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tertiary-butylidiphenylsilyl</td>
</tr>
<tr>
<td>'Bu</td>
<td>tertiary-butyl</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilyl</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl</td>
</tr>
</tbody>
</table>
Chapter 1

Direct Synthesis of 2-Deoxy-β-Glycosides via Anomeric O-Alkylation with Secondary Electrophiles

1.1 Introduction

1.1.1 Deoxy Sugars

Carbohydrates are not only essential building blocks of life, but also have been the focus of potential therapeutic drug targets. Imitating the glycome has resulted in the creation of many carbohydrate-based drugs, such as Acarbose for treating diabetes and Tamiflu for treating influenza. Among various types of sugars, 2-deoxy-glycosides are a class of carbohydrates in which the hydroxide group at C2 position is replaced by a hydrogen atom. For example, 2-deoxy-D-ribose is a well-known component of the sugar backbone of deoxyribonucleic acid (DNA). Besides, 2-deoxy sugars, especially, 2,6-dideoxy and 2,3,6-trideoxy sugars, widely exist in natural molecules with biological activity and are reported to play a significant role in their bioactivities.

1.1.2 Occurrence of Deoxy Sugars

These molecules including some secondary metabolites with important antitumor activities have been already applied in clinics as cancer therapeutics, such as well-known anthracycline antitumor antibiotics, aureolic acid family compounds, angucycline group antibiotics, avermectins, and endiyne antibiotics. The majority of these molecules are DNA intercalators, which inhibit DNA replication and RNA transcription.
Although the clinical application is limited due to toxic side effects caused by arresting cellular development, a hall-mark of anticancer drugs (i.e., cisplatin), these molecules are unique biological tools and are still attractive anticancer drugs, despite high toxicity.

1.1.3 Antitumor Glycoconjugates

1.1.3.1 Anthracycline Antitumor Antibiotics

In nature, 2-deoxy oligosaccharide subunits exist in a number of biologically active molecules. Anthracycline antitumor antibiotics, one group of natural products possessing a tetracyclic aglycone linked with 2-deoxy sugar subunits, are among the most effective and wildly used anticancer agents. 7-8
Figure 1. 1 Representative anthracycline antitumor antibiotics.

In this family, the typical members include daunomycin, adriamycin, rubomycin, marcellomycin, and aclacinomycin A (Figure 1.1). Antitumor activities of anthracycline antibiotics are attributed to intercalation of the pharmaceuticals into DNA. The intercalation of these molecules with DNA results in unwinding of RNA helix and formation of noncovalent complexes, which inhibit DNA replication and RNA transcription. Besides, it’s worth noting that anthracyclines containing longer carbohydrate chains have less side effects. For example, marcellomycin and aclacinomycin A are active, but both were found to be less toxic than daunomycin.

1.1.3.2 Aureolic Acid Antitumor Antibiotics

The aureolic acid antitumor antibiotics\textsuperscript{14-16} are composed of a large family of glycosylated tricyclic polyketides which possess very important antitumor activity produced by different streptomycete species. In this family, the typical members include mithramycin,\textsuperscript{17-18} chromomycin A\textsubscript{3},\textsuperscript{19} olivomycin A, chromocyclomycin,\textsuperscript{19} and UCH9\textsuperscript{20-21} (Figure 1.2). Structurally, they all contain a polycyclic chromophore and two 2-deoxy-oligosaccharides subunits with varying length. Because of effective biological activities, mithramycin, chromomycin A\textsubscript{3}, and olivomycin A all have already been applied in clinics as chemotherapeutic agents for treatment of cancer.
Figure 1. 2 Representative aureolic acid antitumor antibiotics.

In addition, recent structure-activity relationship (SAR) studies of aureolic acid analogues showed that 2-deoxy-oligosaccharide subunits of these molecules play a crucial role and slight modification of these oligosaccharides may lead to significant changes in their bioactivities.\textsuperscript{22}

1.1.3.3 Angucycline Antibiotics

The angucycline antibiotics (Figure 1.3) containing more than one hundred members are one family of the emerging natural antibiotics.\textsuperscript{10-11} Most of the angucyclines are glycosylated, belong to a class of extensional family, and show very interesting biological activity.

Aquayamycin\textsuperscript{23} inhibits tyrosine and dopamine $\beta$-hydroxylase,\textsuperscript{24} for example. Urdamycin A,\textsuperscript{25-26} a member of the urdamycin family, has potent bioactivities against gram-positive bacteria and murine leukemia L1210 stem cells. The angucycline PI-080 shows the property of inhibition of platelet aggregation and the aglycone was discovered
to have no activity, which demonstrate that sugars in the whole molecules play a very important role in biological activities. 

Landomycin A (Figure 1.3), a potent antitumor angucycline, possesses a broad-spectrum antitumor activity against a range of 60 cancer cell lines, which has attracted special interest as the most effective antitumor antibiotic among landomycin family.

![Angucycline Antibiotics](image)

**Figure 1.3 Representative angucycline antibiotics.**

The initial structure assignment of landomycin A was proposed by Rohr in 1990, and subsequently revised in 1994. Later, it was confirmed by Roush and his co-workers via synthetic research, and the first total synthesis of landomycin A was achieved by Yu and his co-workers in 2011. Structurally, landomycin A contains the longest hexasaccharides which are composed of two repeated trisaccharides (α-L-rhodinose-
(1→3)-β-D-olivose-(1→4)-β-D-olivose). Although landomycin A is known to inhibit DNA biosynthesis during the G1/S cell cycle progression, the specific mechanism of action on cancer cells is still not verified. Structure-activity relationship (SAR) studies indicate that the high cytotoxic activity of landomycin A is correlated with the length of the glycan chain. For instance, landomycin E (Figure 1.3) has significantly lower biology activity due to the truncation of glycosylated units.
1.2 Previous Synthesis of 2-Deoxy Glycosides

Because of their interesting biological characteristics, studies of the structure-activity relationship (SAR) of these natural molecules and their modified analogues may trigger the discovery of promising new therapies for cancer. Interesting structures and biological activities of these antitumor antibiotics have already led to abundant synthetic accomplishments and investigation of bioactivities. Plentiful analogues with less toxicity have been prepared, however, more efforts are needed. From another aspect, some special activity mechanisms of these molecules are not quite clear yet due to the fact that limited amounts of these molecules can be obtained from natural sources. Therefore, it is imperative to focus efforts on synthesis to obtain sufficient supplies of target molecules by developing facile methods for assembling 2-deoxy-sugars of these antitumor antibiotics.

1.2.1 Traditional Method for Synthesis of Glycosides

Preparation of sugar-derived donor and acceptor in advance is involved with traditional glycosylation. After that, the activation of sugar derived-donors by suitable electrophiles can be utilized for forming the new glucosidic bond via attack of sugar acceptors (Figure 1.4). The leaving group of the starting material donor first is activated by an electrophile (E⁺). Then an equilibrium is formed between donor bearing activated leaving group and an oxocarbenium ion intermediate. The hydroxide group of the acceptor acting as a nucleophile attacks the oxocarbenium ion carbon to construct the glycosidic linkage. It is worth noting that, due to sp² hybridization of the oxocabemium ion, the geometry of the carbocation is trigonal planar. Thus, both bottom (α-) and top (β-) faces of
the carbocation are available to be approached by nucleophiles to generate axial (α-) and equatorial (β-) linkages.

![Figure 1.4 Traditional method for synthesis of glycosidic bond](image)

**1.2.2 Glycosylation Process with a Participating Group**

In the synthesis of 2-deoxy-sugars, axial glycosylation is more favored due to the anomeric effect, while equatorial linkage is comparatively difficult and challenging. A common indirect approach involving participating group has been utilized for stereochemical control of glycosidation. Due to the absence of substitution of the C2 position in 2-deoxy-glycosides, a participating group has been introduced to govern which face will be attacked (Figure 1.5). The participating group Y, often a halogen, sulfur, or selenium, can exist in starting material donor or be introduced to glycal either several steps before construction of glycosidic bond or during the reaction. If the participating group Y occupies the axial position and blocks the β face, the α face would be available to be approached by the hydroxyl group of the acceptor to form an axial glycosidic bond. Alternatively, when the participating group Y is equatorial, construction of β glycosides is
more favored. Stereoselective 2-deoxy-\(\alpha\) or \(\beta\)-glycoside formation is achieved after subsequent removal of participating group.

\[ \text{Figure 1. 5 Glycosylation process with a participating group} \]

In general, application of neighboring group participation (NGP) may result in stereoselective formation of a \(\beta\)-glycosidic bond. Meanwhile, stereoselective \(\alpha\)-glycosylation can be achieved by anomeric effect. However, due to the absence of a directing neighboring group at the C2 position of 2-deoxy sugars, control of anomeric stereoselectivity becomes comparatively difficult and challenging in the key glycosylation reaction and mixtures of anomeric \(\alpha/\beta\) isomers are frequently obtained.\(^{38-39}\) Besides, their similar physical properties result in difficult separation of isomers. Although this problem may be solved by introduction of a participating group which will be removed after the glycosylation reaction, extra synthetic steps are required to achieve the final aim. In
addition, further reaction conditions needed to be screened to obtain a high \( \alpha/\beta \) ratio, nevertheless \( \alpha \) glycosylation is favored to be generated on account of the anomeric effect.

1.2.3 Direct Synthesis of 2-Deoxy Sugars

Examples of direct synthesis of glycosidic bonds in 2-deoxy sugars have been introduced in the literature. For instance, oxidative activation of sugar imidates were published by Takahashi and his co-workers for direct and stereoselective synthesis of \( \beta \) glycosidic bonds in 2-deoxy-glycosides (Scheme 1.1). Though satisfactory results were obtained using 4-\( O \)-benzylsulfonylloivosyl imidate and perbenzyolated digitoxosyl imidate, moderate selectivity was shown when amicetoxyl and oligosyl imidate were used in the reaction.\(^{40}\)

![Scheme 1.1 Direct glycosylation by Takahashi and co-workers](image)

In another example, Kim and co-workers reported a suitable donor, (2’-carboxy)benzyl 4,6-\( O \)-benzylidene-2-deoxyglucoside (Scheme 1.2), which can be utilized for direct synthesis of 2-deoxy-\( \beta \)-glycosides.\(^{41}\) However, 4,6-\( O \)-benzylidene protected donor was required to get high \( \beta \) selectivity.
Herzon and co-workers found that 2-deoxy- and 2,6-dideoxyglycosyl bromides may be used for synthesis of 2-deoxy-β- and 2,6-dideoxy-β-glycosides (Scheme 1.3).\textsuperscript{42} The glycosyl bromide donors can be prepared in excellent yield and purity and employed in highly β-selective glycosylation reactions. However, the high efficiency and β-selectivity requires one electron-withdrawing substituent in the 2,6-dideoxyglycosides.

Later, organoboron-catalyzed stereoselective formation of 2-deoxy-β-glycosidic linkages was reported by Taylor and coworkers.\textsuperscript{43} 2-Deoxy-β-glycosides were afforded
between corresponding glycosyl chloride donors and secondary alcohol derived acceptors in the presence of a borinic acid derived catalyst (Scheme 1.4).

![Scheme 1.4 Direct glycosylation by Taylor and co-workers](image)

Recently, Bennet and co-workers reported that hemiacetal lactols were first activated in the presence of potassium hexamethyldisilazane (KHMDS), tri-tert-butylpyrimidine (TTBP) and p-toluenesulfonic anhydride to form α-linked glycosyl tosylates which reacted through an $S_N2$ or $S_N2$-like mechanism (Scheme 1.5). After that, the nucleophilic acceptors attacked α-glycosyl tosylate intermediates to achieve β-anomers exclusively. It is worth noting that this work was published a few months after we reported our results in 2014.

![Scheme 1.5 Direct glycosylation by Bennet and co-workers](image)
So, development of an efficient and highly-selective approach for acquisition of 2-deoxy-β-glycoside is still very attractive in organic synthesis. In this dissertation, a direct and stereoselective approach, involving anomeric $O$-alkylation introduced afterwards, is developed to prepare 2-deoxy-β-glycosides.
1.3 Results and Discussion

1.3.1 Research Strategy

Schmidt and co-workers\textsuperscript{45} reported anomeric \textit{O}-alkylation, as an alternative to the traditional direct glycosylation method, and successfully employed this approach for stereoselective synthesis of \(\beta\)-linked glycoconjugates (Scheme 1.6). They carried out the glycosylation reaction with 2,3,4,6-tetra-\textit{O}-benzylglucose and secondary alkyl triflate in the presence of sodium hydride and 15-crown-5. The desired \(\beta\) anomer product was successfully obtained in 70\% yield.

\begin{equation}
\begin{array}{c}
\text{BnO} \quad \text{O} \quad \text{Bn} \quad \text{O} \quad \text{Bn} \quad \text{OH} \\
\text{BnO} \quad \text{O} \quad \text{Bn} \quad \text{O} \quad \text{Bn} \\
\text{NaH, 15-Crown-5, Toluene, r.t.} \\
\text{BnO} \quad \text{O} \quad \text{Bn} \quad \text{O} \quad \text{Bn} \\
\end{array}
\end{equation}

\textbf{Scheme 1. 6} Direct glycosylation by Schmidt and co-workers via anomeric \textit{O}-alkylation

In 1992, Shair and co-workers also applied anomeric \textit{O}-alkylation/arylation to synthesize 2-deoxy-\(\beta\)-glycosides. Treatment of lactols with sodium hydride in dioxane followed by addition of primary triflates as electrophiles generated the desired \(\beta\)-linked glycosides in high yield and high selectivity. However, they failed when more challenging secondary electrophiles and 2-deoxy-derived anomeric alkoxides were employed (Table 1.1).\textsuperscript{46}
It was believed that anomeric O-alkylation initially involved a rapid equilibrium after deprotonation of lactol. This equilibrium occurred between axial anomeric alkoxide 1 and its equatorial isomer 3 via an open intermediate 2. The equatorial alkoxide 3 is gauche to both electron lone pairs of the ring oxygen, which makes the equatorial alkoxide more reactive and nucleophilic in comparison to its axial isomer with a single gauche effect due to stronger lone-pair repulsion (Scheme 1.7). This phenomenon has been referred to as the kinetic anomeric effect, or the β-effect.46

Subsequently, selective O-alkylation is accomplished via more reactive equatorial anomeric alkoxide 3 attacking compatible electrophile to generate stereoselective product β-linked glycoside 4. By this approach, 2-deoxy sugars could be gained without a substituent at the C2 position.

---

**Table 1.1 Electrophile scope by Shair and co-workers via anomeric O-alkylation**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>2-deoxy β-glycoside</th>
<th>Yield(β:α)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Electrophile 1" /></td>
<td><img src="image2.png" alt="2-deoxy β-glycoside 1" /></td>
<td>90%(20:1)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Electrophile 2" /></td>
<td>----</td>
<td>n/a</td>
</tr>
<tr>
<td>3</td>
<td><img src="image4.png" alt="Electrophile 3" /></td>
<td>----</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Numerous natural products, including the aforementioned antitumor antibiotics, contain 2-deoxy-β-sugars, especially 2,6-dideoxy-β-sugars possessing a 1→3 or 1→4 linkage. Therefore, it will be very attractive to explore a plan for more challenging secondary electrophiles in stereoselective anomeric O-alkylation.

1.3.2 Optimization of Synthesis of 2,6-Dideoxy-β-Glycosides

At the beginning, L-oliose-derived lactol 5a and D-olivose-derived C4-triflate 6a were selected to construct the desired disaccharides 7 via an anomeric O-alkylation reaction (Table 1.2). Not surprisingly, application of the same condition (sodium hydride, 1, 4-dioxane, RT) reported previously did not furnish detectable desired product 7 (entry 1, Table 1.2).
Table 1. Optimization of Synthesis of 2,6-Dideoxy-\(\beta\)-Glycosides

<table>
<thead>
<tr>
<th>entry</th>
<th>reaction condition</th>
<th>yield, (\beta/\alpha) ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a, NaH (2 eq.), 1,4-dioxane, RT, 24h</td>
<td>7, &lt;1%, ND</td>
</tr>
<tr>
<td>2</td>
<td>5a, NaH (2 eq.), 15-C-5 (1.5 eq.), toluene, RT, 24h</td>
<td>7, 51%, (\beta) only</td>
</tr>
<tr>
<td>3</td>
<td>5a, NaH (2 eq.), 15-C-5 (1.5 eq.), 1,4-dioxane, RT, 24h</td>
<td>7, 41%, (\beta) only</td>
</tr>
<tr>
<td>4</td>
<td>5b, NaH (3 eq.), 15-C-5 (1.5 eq.), 1,4-dioxane, RT, 24h</td>
<td>8, 81%, (\beta) only</td>
</tr>
<tr>
<td>5</td>
<td>5b, NaH (3 eq.), 15-C-5 (1.5 eq.), THF, RT, 24h</td>
<td>8, 70%, (\beta) only</td>
</tr>
<tr>
<td>6</td>
<td>5b, NaH (3 eq.), 15-C-5 (1.5 eq.), toluene, RT, 24h</td>
<td>8, 45%, (\beta) only</td>
</tr>
<tr>
<td>7</td>
<td>5b, NaH (3 eq.), 15-C-5 (30 mol%), 1,4-dioxane, RT, 24h</td>
<td>8, 22%, (\beta) only</td>
</tr>
<tr>
<td>8</td>
<td>5b, NaH (3 eq.), 15-C-5 (1.0 eq.), 1,4-dioxane, RT, 24h</td>
<td>8, 48%, (\beta) only</td>
</tr>
<tr>
<td>9</td>
<td>5b, KO(^{t})Bu (2 eq.), 18-C-6 (1.5 eq.), 1,4-dioxane, RT, 24h</td>
<td>8, &lt;1%, ND</td>
</tr>
</tbody>
</table>

It was very interesting that in toluene as solvent, addition of 15-crown-5\(^{47-48}\) known for chelation to sodium cation produced the desired \(\beta\) only disaccharide compound 7 with 51% yield (entry 2). Therefore, the reactivity of the anomeric alkoxide was accordingly enhanced due to relatively more exposure to the environment once 15-crown-5 chelated sodium ions.
The yield of glycosylation dropped to 41% when solvent was changed to 1,4-dioxane (entry 3). $^1$H-NMR spectroscopy of crude reaction mixtures indicated that a number of side products containing the aldehyde functional group were present, which may be due to decomposition of anomeric alkoxides $A$ (Scheme 1.8). Under basic conditions anomeric alkoxides $A$ may be opened to generate intermediate $B$ which probably undergoes further elimination to generate $E$ and $Z$ configurational isomers of mixture $C$. The $Z$-isomer of intermediate $C$ may undergo cyclization followed by coupling with secondary $D$-olivose-derived C4-triflate 6a to afford an undesired side product, while the $E$-isomer of intermediate $C$ remained in the reaction mixture.

Scheme 1.8 Formation of Side Products Containing Aldehyde Functional Group

Along this line, we hypothesized that suppression of anomeric alkoxide decomposition may result in the desired 2-deoxy-glycoside product with improved yield. This decomposition problem could be circumvented by employing modified lactols 5b bearing a free hydroxide group at the C3 position. Deprotonation of two hydroxide group
of donor 5b at C1 and C3 positions with excess sodium hydride (3.0 eq.) may form the corresponding anomeric alkoxides, dianions D which may reversibly be further opened to generate an aldehyde intermediate E (Scheme 1.9).

Scheme 1.9 Suppression of Anomeric Alkoxide Decomposition

However, because of lower acidity of the α-H in aldehyde E and poor leaving ability of sodium oxide anion, the following enolization-elimination of aldehyde E may be suppressed, which hopefully can increase the glycosylation reaction yield of desired product 8 (table 1.2). The other alkoxide at C3 position of donor 5b has been reported to be less nucleophilic compared with C1-anomeric alkoxide due to the aforementioned double electron-electron repulsion. It was very delightful that formation of desired 2-deoxy-glycoside product 8 was facilitated by treatment of lactol donor 5b with 3.0 equiv sodium hydride in 1,4-dioxane followed by addition of triflate 6a and 1.5 equiv 15-crown-5.

The desired β-only 2-deoxy-glycoside product 8 (entry 4, Table 1.2) was isolated in 81% yield after stirring 24 h at room temperature. This glycosylation yield decreased when THF or toluene were selected as solvent (entries 5 and 6, Table 1.2). Besides,
employment of less 15-crown-5 in the reaction also led to inferior yields (entries 7 and 8, Table 1.2). In addition, application of mild base, like KO'Bu and 18-C-6\(^9\), did not afford detectable desired product (entries 9, Table 1.2).

Therefore, a 2-deoxy-glycoside derived lactol bearing a hydroxyl group at the C3 position was first employed in an anomeric \(O\)-alkylation reaction to afford (1→4)-\(\beta\)-linked 2-deoxy-disaccharide with good yield and excellent anomeric selectivity. In addition, the free hydroxyl group at the C3 position in disaccharide 8 may be utilized directly in a following glycosylation reaction.

1.3.3 Synthesis of Various 2,6-Dideoxy-\(\beta\)-Glycosides

With this encouraging result, the reaction scope for preparation of various 2,6-dideoxy-\(\beta\)-oligosaccharides were investigated (Table 1.3). Thus we prepared other three 2,6-ddeoxy sugar-derived lactols (5c-e) containing a free hydroxyl group at the C3 position, four additional sugar-derived secondary triflates (6b-e), and one disaccharide-derived C3 triflate 6f.
Table 1. 3 Synthesis of Various 2,6-Dideoxy-β-glycosides\textsuperscript{a,b}

\begin{align*}
\text{Base; then triflate 6} \\
\text{reaction conditions} \\
\end{align*}

\begin{align*}
\text{5} \\
\text{9-18} \\
\end{align*}

\begin{align*}
\text{5c} \\
\text{5d} \\
\text{5e} \\
\text{5f} \\
\text{5g} \\
\text{5h} \\
\end{align*}

\begin{align*}
\text{Sodium hydride (2 eq.) was used.} \\
\end{align*}

\begin{align*}
\text{a General conditions: lactol 5 (1.0 eq.), sodium hydride (3.0 eq.), 1,4-dioxane, RT 10 min; then} \\
\text{triflate 6 (2.0 eq.), 15-C-5 (1.5 eq.), RT, 24 h.} \\
\text{b Isolated yield.} \\
\text{c Sodium hydride (2 eq.) was used.} \\
\end{align*}

Just like the examples shown in Table 1.3, under the optimized reaction conditions the 2-deoxy sugar-derived lactols (5b-e) were coupled with secondary triflates (6a-f) to obtain the desired β-linked oligosaccharides (9-16) with good to excellent yields and excellent anomeric selectivities. It is worth noting that this approach was successfully applied to the efficient preparation of a challenging β-glycoside.\textsuperscript{40, 50} In addition,
glycosylation of primary triflates 6g-h and lactol 5d were also carried out via anomeric O-alkylation. In the event, desired disaccharides 17 and 18 were obtained with comparable yields and anomeric selectivities as reported previously.\textsuperscript{46}

1.3.4 Synthesis of 2-Deoxy-β-Glycosides

The anomeric O-alkylation was next employed in the synthesis of 2-deoxy-β-glycoside (Scheme 1.10). Treatment of 2-dexoy-D-glucose-derived lactol 5f with sodium hydride, followed by secondary triflates 6b and 6d afforded the desired 2-deoxy-β-disaccharides 19 and 20 with 68% and 62% yield respectively.

![Scheme 1.10 Synthesis of 2-Deoxy-β-Glycosides](image)

Generally, the yield of glycosylation involving 2-deoxy-sugar-derived lactols 5f was slightly less than that involving 2,6-dideoxy sugar derived lactols (5b-e), which may be explained by the relatively lower reactivity of 2-deoxy-sugar-derived anomeric
alkoxides compared with 2,6-dideoxy-sugar-derived anomeric alkoxides due to an electronic effect.

1.3.5 Synthesis of 2,3,6-Trideoxy-β-Glycosides and 2,4,6-Trideoxy-4-azido-β-glycosides

Preparation of 2,3,6-trideoxy, 2,4,6-trideoxy-4-amino-β-glycosides from secondary triflates (Table 1.4) were also investigated via anomeric O-alkylation. We synthesized three 2,3,6-trideoxy-sugar-derived lactols 5g-I and one 2,4,6-trideoxy-4-β-azidosugar-derived lactol 5j. Just like the results shown in Table 1.3, the desired β-linked oligosaccharides (21-25) were obtained in good yields and excellent anomeric selectivities from lactol donors (5g-j) and secondary triflate 6 via anomeric O-alkylation under optimized reaction conditions.
Table 1. Synthesis of 2,3,6-Trideoxy-β-Glycosides and 2,4,6-Trideoxy-4-azido-β-glycosides\textsuperscript{a,b}

\[
\begin{align*}
\text{(PO)}_n & \xrightarrow{\text{Base; then triflate 6}} \text{(PO)}_n \\
5g-j & \quad \text{reaction conditions} \\
\end{align*}
\]

\begin{table}
\centering
\begin{tabular}{c}
\hline
$21$, \textsuperscript{c} 83\%, β only \\
$22$, \textsuperscript{c} 75\%, β only \\
$23$, \textsuperscript{c} 75\%, β only \\
$24$, 70\%, β only \\
$25$, 95\%, β only \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a} General conditions: lactol $5$ (1.0 eq.), sodium hydride (3 eq.), 1,4-dioxane, RT 10 min; then triflate $6$ (2.0 eq.), 15-C-5 (1.5 eq.), RT, 24 h. \textsuperscript{b} Isolated yield. \textsuperscript{c} Sodium hydride (2 eq.) was used.

1.3.6 Synthesis of β-linked 2,6-Dideoxy-Tri- and -Tetra-saccharides

In order to further demonstrate this approach for synthesis of 2-dexoy-oligosaccharides, a practical plan of synthesis of 2,6-dideoxy-trisaccharide $27$ and tetrascarharide $28$ possessing β-linkages was designed (Scheme 1.11). Disaccharide $8$, obtained from aforementioned lactol donor $5b$ and trifalte acceptor $6a$ via anomeric $O$-
alkylation, further underwent benzyl protection (82% yield), NBS-mediated anomic phenylsulfide oxidation (94% yield), and DDQ-mediated PMB deprotection (89% yield) to get a free hydroxyl at the C3 position of disaccharide lactol 26 which would be utilized as desired lactol donor for the next glycosylation. As we expected from previous experiences, this lactol donor 26 was coupled with C4-triflate acceptor 6d and dideoxy-derived C3-triflate 6f via anomic O-alkylation under optimized reaction conditions to smoothly afford 2-deoxy-trisaccharide 27 and tetrasaccharide 28 with 76% and 95% yield respectively.

![Scheme 1.11 Synthesis of β-linked 2,6-Dideoxy-Tri- and -Tetra-saccharides

Scheme 1.11 Synthesis of β-linked 2,6-Dideoxy-Tri- and -Tetra-saccharides\textsuperscript{a,b}

\textsuperscript{a} General conditions: lactol 5 (1.0 eq.), sodium hydride (3 eq.), 1,4-dioxane, RT 10 min; then triflate 6 (2.0 eq.), 15-C-5 (1.5 eq.), RT, 24 h. \textsuperscript{b} Isolated yield. \textsuperscript{c} Sodium hydride (2 eq.) was used.

1.3.7 Conclusion
In conclusion, an effective approach was developed for stereoselective synthesis of 2-deoxy-β-(1→3) and (1→4)-linked oligosaccharides via anomeric O-alkylation. In particular, secondary electrophiles were successfully applied in the glycosylation for formation of desired products. It is believed that this excellent anomeric stereoselectivity is controlled by a kinetic anomeric effect. The anomeric O-alkylation carried out under basic conditions is beneficial for the synthesis of acid-sensitive 2-deoxy-sugars. Natural molecules containing 2-deoxy-sugar subunits may be synthesized by this anomeric O-alkylation.
1.4 Experimental

General Information

Proton and carbon nuclear magnetic resonance spectra (\(^1\)H NMR and \(^{13}\)C NMR) were recorded on either Bruker 600 (\(^1\)H NMR-600 MHz; \(^{13}\)C NMR 150 MHz), INOVA 600 (\(^1\)H NMR-600 MHz; \(^{13}\)C NMR-150 MHz) or Varian VXR-400 (\(^1\)H NMR 400 MHz; \(^{13}\)C NMR 100 MHz) at ambient temperature with CDCl\(_3\) as the solvent unless otherwise stated. Chemical shifts are reported in parts per million relative to residual protic solvent internal standard CDCl\(_3\): \(^1\)H NMR at δ 7.26, \(^{13}\)C NMR at δ 77.36. Data for \(^1\)H NMR are reported as follows: chemical shift, integration, multiplicity (app = apparent, par obsc = partially obscure, ovrlp = overlapping, s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet) and coupling constants are in Hertz. All \(^{13}\)C NMR spectra were recorded with complete proton decoupling. Infrared spectra were recorded on a PerkinElmer FT-IR spectrophotometer. High resolution mass spectra (HRMS) were obtained on a Waters Acuity Premiere XE TOF LC-MS by electrospray ionization. Optical rotations were measured with Autopol-IV digital polarimeter; concentrations are expressed as g/100 mL.

All reagents and chemicals were purchased from Acros Organics, Sigma Aldrich, Fisher Scientific, Alfa Aesar, and Strem Chemicals and used without further purification. THF, methylene chloride, toluene, and diethyl ether were purified by passing through two packed columns of neutral alumina (Innovative Technology). Anhydrous DMF, and benzene were purchased from Acros Organics and Sigma-Aldrich and used without further drying. All reactions were carried out in oven-dried glassware under an argon atmosphere.
unless otherwise noted. Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash column chromatography was performed using 200-400 mesh silica gel (Scientific Absorbents, Inc.). Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated.

1.4.1 Preparation of lactol donors

![Reaction Scheme]

To a solution of glycosyl phenyl sulfide S1 (4.2 g, 10.0 mmol) in 150 mL acetone and 10mL water cooled at 0 °C was added N-Bromosuccinimide (2.7 g, 15.0 mmol). The resulting mixture was stirred at 0°C for 15 mins. Saturated sodium bicarbonate (50 mL) was added and acetone was removed under reduced pressure. The remaining aqueous mixture was extracted with ethyl acetate (3×100 mL). Combined extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude residue was purified by flash column chromatography (hexanes:EtOAc = 8:1 to 2:1) to furnish 3.1 g (95% yield) of lactol 5a as a mixture of anomers (α/β = 1.7/1) which is characterized below:

\[ \alpha \rho^{22} = -38.1^\circ \ (c = 1.0, \text{CHCl}_3) \]

\[ ^1H \text{ NMR (600 MHz, CDCl}_3) \delta \] 7.39 - 7.27 (m, 16 H), 5.33 (d, \( J = 2.8 \) Hz, 1 H), 4.99 - 4.93 (m, 2 H), 4.75 (dd, \( J = 1.5, 9.5 \) Hz, 1 H), 4.71 - 4.60 (m, 5 H), 4.05 - 3.95 (m, 2 H), 3.64 (ddd, \( J = 5.0, 8.6, 11.6 \) Hz, 1 H), 3.40 (dd, \( J = 6.2, 9.4 \) Hz, 1 H), 3.18 - 3.12 (m, 2 H), 2.84 (br. s., 1 H), 2.41 (ddd, \( J = 1.9, 5.0, 12.5 \) Hz, 1 H), 2.32 (ddd, \( J = 1.2, 5.0, 13.0 \) Hz, 1 H), 2.02 - 1.81 (m, 5 H), 1.79 - 1.60 (m, 5 H), 1.52 (s, 3 H), 1.35 - 1.00 (m, 14 H), 0.91 - 0.73 (m, 18 H), 0.74 (d, \( J = 6.3 \) Hz, 3 H)
Hz, 1 H), 2.18 (s, 1 H), 1.68 (ddd, $J = 3.6, 11.5, 13.0$ Hz, 1 H), 1.57 (dt, $J = 9.8, 12.1$ Hz, 1 H), 1.35 - 1.32 (m, 2 H), 1.29 (d, $J = 6.2$ Hz, 3 H)

$^{13}$C NMR (150 MHz, CDCl$_3$) δ 138.9, 138.8, 138.7, 138.6, 128.8, 128.7, 128.7, 128.4, 128.3, 128.1, 128.0, 127.9, 94.2, 92.3, 84.6, 83.7, 79.3, 77.6, 77.1, 75.6, 75.5, 72.1, 71.8, 71.8, 67.7, 38.7, 36.1, 31.3, 18.5, 18.5

FT-IR (thin film): 3400, 2246, 2087, 1637, 1454, 1264, 1207, 986, 902, 728 cm$^{-1}$.

ESIHRMS [M+Na]$^+$ calculated for C$_{20}$H$_{24}$O$_4$Na 351.1572, found 351.1567.

To a mixture of protected L-rhamnal S$_2$ (4.0 g, 10.6 mmol) and thiophenol (1.3 mL, 12.7 mmol) in 35 mL dry toluene cooled at 0 °C ReOCl$_3$(SMe$_2$)(OPPh$_3$) (69.0 mg, 0.11 mmol) was added. The resulting mixture was warmed to room temperature for 2 hours. The mixture was concentrated under vacuo and the crude residue was purified by flash column chromatography (hexanes:EtOAc = 50:1 to 20:1) to afford 4.88 g (95% yield) of glycosyl phenyl sulfide S$_3$ as a mixture of anomers. To a solution of this glycosyl phenyl sulfide (4.8 g, 10.0 mmol) in 150 mL acetone and 10 mL water cooled at 0 °C N-Bromosuccinimide (2.7 g, 15.0 mmol) was added. The resulting mixture was stirred at 0 °C for 15 mins. Saturated sodium bicarbonate (50 mL) was added and acetone was removed under reduced pressure. The remaining aqueous mixture was extracted with ethyl acetate
(3×100 mL). The combined extracts were washed with brine (100mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude residue was purified by flash column chromatography (hexanes:EtOAc = 20:1 to 10:1) to furnish 3.8 g (98% yield) of lactol S4 as a mixture of anomers. To a solution of this lactol (3.8 g, 9.9 mmol) in 33 mL THF cooled at 0 °C 1.0 M tetra-n-butylammonium fluoride (TBAF) in THF (14.8 mL, 14.8 mmol) was added, and the resulting mixture was stirred overnight. Saturated ammonium chloride (15 mL) was added and THF was removed under reduced pressure. The remaining aqueous mixture was extracted with ethyl acetate (3×100 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. The crude residue was purified by flash column chromatography (hexanes:EtOAc = 2:1 to 1:1) to furnish 1.9 g (81% yield) of lactol 5b as a mixture of anomers (α/β = 1.6/1) which is characterized below:

\[ \beta = -29.0^\circ \text{ (c = 1.0, CHCl}_3). \]

\textbf{H NMR (600 MHz, CDCl}_3) \delta 7.40 - 7.28 \text{ (m, 8 H), 5.29 (d, J = 3.1 Hz, 1 H), 4.80 - 4.68 \text{ (m, 4 H), 4.08 (ddd, J = 5.1, 8.8, 11.7 Hz, 1 H), 3.96 (qd, J = 6.3, 9.4 Hz, 1 H), 3.69 (ddd, J = 5.0, 8.7, 11.8 Hz, 1 H), 3.41 - 3.33 (m, 1 H), 2.99 (t, J = 9.1 Hz, 2 H), 2.24 (ddd, J = 2.0, 5.0, 12.5 Hz, 1 H), 2.17 (s, 1 H), 2.15 (ddd, J = 1.1, 5.1, 13.0 Hz, 1 H), 1.68 (ddd, J = 3.7, 11.7, 13.0 Hz, 1 H), 1.55 (dt, J = 9.6, 12.2 Hz, 1 H), 1.37 (d, J = 6.2 Hz, 2 H), 1.31 (d, J = 6.4 Hz, 3 H)

\textbf{C NMR (150 MHz, CDCl}_3) \delta 138.5, 138.4, 129.0, 129.0, 128.5, 128.4, 128.3, 128.2, 94.2, 92.2, 86.9, 86.0, 77.6, 77.1, 75.6, 75.4, 71.7, 71.2, 68.5, 67.5, 40.5, 38.0, 31.3, 18.6

\textbf{FT-IR (thin film):} 3401, 2091, 1638, 1453, 1248, 1109, 1075, 983, 924, 694 cm\(^{-1}\).
ESIHRMS $[M+Na]^+$ calculated for $\text{C}_{13}\text{H}_{18}\text{O}_4\text{Na}$ 261.1103, found 261.1116.

To a solution of alcohol $\text{S}5$ (6.4 g, 26 mmol) in 52.0 mL $N,N$-dimethylformamide cooled at 0 °C sodium hydride (936 mg, 39.0 mmol) was added portionwise. The resulting mixture was stirred at 0 °C for 1 h before benzyl bromide (3.74 mL, 31.5 mmol) was added. The reaction mixture was warmed up and stirred at ambient temperature overnight. The resulting mixture was diluted with EtOAc (150 mL), washed with water (4 × 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude residue was purified by flash column chromatography (hexanes:EtOAc = 10:1) to afford 7.5 g (86% yield) of glycal $\text{S}6$. To protected $\text{L}$-fucal $\text{S}6$ (7.5 g, 22.4 mmol) and thiophenol (3.0 mL, 29.1 mmol) in 68 mL dry toluene cooled at 0°C catalyst ReOCl$_3$(SMe$_2$)(OPPh$_3$) (145 mg, 0.22 mmol) was added. The resulting mixture was warmed to room temperature and stirred for 2 h. The mixture was concentrated under vacuo and the crude residue was purified by flash column chromatography (hexanes:EtOAc = 15:1) to afford 8.8 g (88% yield) of glycosyl phenyl sulfide $\text{S}7$ as a mixture of anomers. To a solution of this glycosyl phenyl sulfide $\text{S}7$ (2.0 g, 4.5 mmol) in 68 mL acetone and 4.5 mL water cooled at 0 °C was added $N$-Bromosuccinimide (1.2 g, 6.7 mmol). The resulting mixture was stirred at 0 °C for 15 min. Saturated sodium bicarbonate (20 mL) was added and acetone was removed under
reduced pressure. The remaining aqueous mixture was extracted with ethyl acetate (3×100 mL). Combined extracts were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude residue was purified by flash column chromatography (hexanes: EtOAc = 6:1) to furnish 1.5 g (95% yield) of lactol S8 as a mixture of anomers. To a solution of this lactol (400 mg, 1.1 mmol) in 3.8 mL THF cooled at 0 °C 1.0 M tetra-n-butylammonium fluoride (TBAF) was added in THF (1.7 mL, 1.7 mmol), and the resulting mixture was stirred overnight. Saturated ammonium chloride (2 mL) was added and THF was removed under reduced pressure. The remaining aqueous mixture was extracted with ethyl acetate (3×25 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. The crude residue was purified by flash column chromatography (hexanes: EtOAc = 2:1 to 1:1) to furnish 188 mg (89% yield) of lactol 5c as a mixture of anomers (α/β = 2.4/1) which is characterized below:

\[ [\alpha]_{D}^{23} = -89.0^\circ \ (c = 1.0, \text{CHCl}_3) \].

\(^1\)H NMR (600 MHz, CDCl\(_3\))  δ 7.41 - 7.33 (m, 7 H), 7.33 - 7.29 (m, 2 H), 5.36 (t, \(J = 2.1 \text{ Hz}, 1 \text{ H}\)), 4.85 - 4.79 (m, 2 H), 4.69 - 4.63 (m, 2 H), 4.14 (q, \(J = 6.5 \text{ Hz}, 1 \text{ H}\)), 4.08 (ddd, \(J = 3.2, 6.7, 10.1 \text{ Hz}, 1 \text{ H}\)), 3.74 - 3.66 (m, 1 H), 3.55 - 3.49 (m, 2 H), 3.41 (d, \(J = 3.3 \text{ Hz}, 1 \text{ H}\)), 2.07 - 2.01 (m, 1 H), 1.88 - 1.83 (m, 3 H), 1.63 (dt, \(J = 9.7, 12.1 \text{ Hz}, 1 \text{ H}\)), 1.33 (d, \(J = 6.6 \text{ Hz}, 2 \text{ H}\)), 1.27 - 1.22 (m, 4 H)

\(^{13}\)C NMR (150 MHz, CDCl\(_3\))  δ 138.6, 138.4, 128.9, 128.9, 128.5, 128.4, 128.4, 128.3, 128.3, 94.7, 92.6, 80.0, 78.7, 77.6, 77.1, 76.4, 76.1, 71.4, 69.5, 66.8, 66.0, 38.1, 34.3, 17.7, 17.7, 17.6

FT-IR (thin film): 3401, 2979, 2936, 2067, 1638, 1454, 1092, 1040, 962, 703 cm\(^{-1}\).
ESIHRMS [M+Na]^+ calculated for C_{13}H_{18}O_4Na 261.1103, found 261.1120.

To a solution of D-rhamnal S9\textsuperscript{54} (550 mg, 4.2 mmol) in 4 mL DMF was added imidazole (1.14 g, 17 mmol) and triisopropyl silyl chloride (2.3 mL, 10.5 mmol). The reaction mixture was stirred for 9 h before water was added. The mixture was extracted with ethyl acetate (3×25 mL) and the combined organic extracts were sequentially washed with water (2×25 mL), brine (25 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (hexane:EtOAc = 40:1 to 30:1) to afford 1.46 g (99% yield) of S10. Next, to a solution of S10 (1.08 g, 3.8 mmol) in 7 mL N,N-dimethylformamide cooled at 0 °C sodium hydride (268 mg, 6.7 mmol) was added portionwise. The resulting mixture was stirred at 0 °C for 45 min and para-methoxybenzyl chloride (770 µL, 5.7 mmol) was added. The reaction mixture was warmed up and stirred at ambient temperature for 8 h. Ice cold water was added and the resulting mixture was extracted with EtOAc (3×20 mL). The combined organic extracts were washed with water (2×20 mL), brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (hexane:EtOAc = 50:1 to 40:1) to afford 813 mg (53% yield) of protected
glycal **S11**. To a mixture of **S11** (710 mg, 1.75 mmol) and thiophenol (215 µL, 2.1 mmol) in 6 mL toluene cooled at 0 °C catalyst ReOCl$_3$(SMe$_2$)(OPPh$_3$) (14 mg, 0.021 mmol) was added. The resulting mixture was warmed to room temperature and stirred overnight. The mixture was concentrated under vacuo and crude residue was purified by flash column chromatography (toluene: methylene chloride = 25:1) to afford 840 mg (95% yield) of glycosyl phenyl sulfide **S12** as a mixture of anomers. Next, to a solution of **S12** (840 mg, 1.6 mmol) in 27 mL acetone and 1.6 mL water cooled at 0 °C **N**-bromosuccinimide (434 mg, 2.4 mmol) was added. The reaction mixture was stirred for 30 min at 0 °C before saturated sodium bicarbonate was added. The resulting mixture was extracted with ethyl acetate (4x10 mL), the combined layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography (hexanes:EtOAc= 10:1 to 7:1) to afford 637 mg (96% yield) of compound **S13**. To a solution of **S13** (637 mg, 1.5 mmol) in THF 5 mL cooled at 0 °C 1.0 M tetra-n-butylammonium fluoride was added in THF (2.3 mL, 2.3 mmol). The reaction mixture was stirred at ambient temperature for 24 h before sodium bicarbonate (189 mg, 2.25 mmol) was added. The resulting mixture was concentrated in vacuo and the residue was purified by flash column chromatography (hexane:EtOAc =3:1 with 1.5% methanol) to furnish 320 mg (80% yield) of **5d** as a mixture of anomers (α/β = 1.8/1) which is characterized below:

$$[\alpha]_D^{23} = 26.8^\circ \ (c = 2.0, \ CHCl_3).$$

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.31 - 7.26 (m, 3 H), 6.92 - 6.87 (m, 3 H), 5.33 - 5.28 (m, 1 H), 4.77 (ddd, $J = 2.0, 6.2, 9.6$ Hz, 1 H), 4.74 - 4.69 (m, 2 H), 4.65 - 4.58 (m, 2 H), 4.05 (dddd, $J = 2.9, 5.3, 8.7, 11.6$ Hz, 1 H), 3.95 (qd, $J = 6.3, 9.5$ Hz, 1 H), 3.80 (s, 5
H), 3.72 - 3.63 (m, 1 H), 3.41 - 3.33 (m, 1 H), 3.01 - 2.94 (m, 2 H), 2.68 (t, $J = 2.5$ Hz, 1 H), 2.29 - 2.19 (m, 2 H), 2.18 - 2.11 (m, 1 H), 1.71 - 1.63 (m, 2 H), 1.54 (dt, $J = 9.6$, 12.2 Hz, 1 H), 1.37 (d, $J = 6.2$ Hz, 2 H), 1.31 (d, $J = 6.2$ Hz, 3 H)

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 159.9, 159.8, 130.7, 130.5, 130.0, 129.9, 114.5, 114.4, 94.2, 92.3, 86.6, 85.7, 77.6, 77.1, 75.2, 75.1, 71.8, 71.2, 68.5, 67.6, 55.6, 40.5, 37.9, 18.7, 18.6

FT-IR (thin film): 3401, 2935, 2066, 1613, 1514, 1251, 1076, 987, 819, 731 cm$^{-1}$.

ESIHRMS [M+Na]$^+$ calculated for C$_{14}$H$_{20}$O$_5$Na 291.1208, found 291.1217.

To a mixture of protected fucal S15 (1.0 g, 2.8 mmol), prepared from S14 following a previously reported procedure for the preparation of its enantiomer, and thiophenol (342 µL, 3.3 mmol) in 9.5 mL dry toluene cooled at 0 °C ReOCl$_3$(SMe$_2$)(OPPh$_3$) (18.0 mg, 0.027 mmol) was added. The resulting mixture was warmed to room temperature for 2 h. The mixture was concentrated under vacuo and crude residue was purified by flash column chromatography (hexanes:EtOAc = 50:1 to 20:1) to afford 1.1 g (83% yield) of glycosyl phenyl sulfide S16 as a mixture of anomers. To a solution of this glycosyl phenylsulfide (1.1 g, 2.3 mmol) in 35 mL acetone and 2.3 mL water cooled at 0 °C N-bromosuccinimide (619 mg, 3.5 mmol) was added. The resulting mixture was stirred at 0 °C for 15 min.
Saturated sodium bicarbonate (20 mL) was added and acetone was removed under reduced pressure. The remaining aqueous mixture was extracted with ethyl acetate (3×40 mL). The combined extracts were washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude residue was purified by flash column chromatography (hexanes:EtOAc = 5:1 to 1:1) to furnish 887 mg (100% yield) of lactol S17. To a solution of this lactol (887 mg, 2.3 mmol) in 8.2 mL THF cooled at 0 °C 1.0 M tetra-n-butylammonium fluoride was added in THF (3.7 mL, 3.7 mmol), and the reaction mixture was stirred overnight. Saturated ammonium chloride (4 mL) was added and THF was removed under reduced pressure. The remaining aqueous mixture was extracted with ethyl acetate (3×50 mL). Combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. The crude residue was purified by flash column chromatography (hexanes:EtOAc = 1:1 to 1:2) to furnish 334 mg (54% yield) of lactol 5e as a mixture of anomers (α/β = 2.1/1) which is characterized below:

\[ [\alpha]_D^{23} = 79.5° \text{ (c = 2.0, CHCl}_3) \].

\(^1\text{H NMR (600 MHz, CDCl}_3\) δ 7.33 - 7.27 (m, 3 H), 6.89 (d, \(J = 8.4 \text{ Hz} \), 3 H), 5.36 (d, \(J = 2.8 \text{ Hz} \), 1 H), 4.80 - 4.74 (m, 2 H), 4.67 (dd, \(J = 2.1, 9.6 \text{ Hz} \), 1 H), 4.59 - 4.52 (m, 2 H), 4.17 - 4.10 (m, 1 H), 4.09 - 4.02 (m, 1 H), 3.80 (s, 5 H), 3.69 (td, \(J = 3.9, 12.0 \text{ Hz} \), 1 H), 3.51 (d, \(J = 2.9 \text{ Hz} \), 1 H), 3.40 (d, \(J = 3.3 \text{ Hz} \), 1 H), 2.06 - 2.01 (m, 1 H), 1.86 - 1.83 (m, 1 H), 1.83 - 1.78 (m, 1 H), 1.60 (dt, \(J = 9.7, 12.1 \text{ Hz} \), 1 H), 1.32 (d, \(J = 6.4 \text{ Hz} \), 2 H), 1.24 (d, \(J = 6.6 \text{ Hz} \), 4 H)

\(^{13}\text{C NMR (150 MHz, CDCl}_3\) δ 159.8, 159.8, 130.7, 130.6, 130.2, 130.1, 114.3, 94.7, 92.7, 79.6, 78.3, 77.6, 77.1, 76.0, 75.8, 71.5, 69.4, 66.9, 65.9, 55.6, 38.2, 34.3, 17.8, 17.7
FT-IR (thin film): 3401, 3057, 2936, 2547, 2059, 1890, 1513, 1428, 1034 cm$^{-1}$.

ESIHRMS [M+Na]$^+$ calculated for C$_{14}$H$_{20}$O$_5$Na 291.1208, found 291.1216.

A solution of methyl glycoside S18 (684 mg, 2.9 mmol) in 20 mL acetic acid and 4 mL H$_2$O was heated at 70 °C overnight. Saturated sodium bicarbonate (10 mL) was added and the remaining aqueous mixture was extracted with ethyl acetate (2×20 mL). The combined extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (hexanes:EtOAc = 1:1) to furnish 486 mg (75% yield) of lactol 5f as a mixture of anomers (α/β = 1.2/1) which is characterized below:

[α]$_D^{23}$ = -92.1° (c = 1.0, CHCl$_3$).

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.38 - 7.31 (m, 9 H), 7.31 - 7.27 (m, 2 H), 5.21 (d, $J$ = 2.6 Hz, 1 H), 4.83 - 4.78 (m, 1 H), 4.66 (d, $J$ = 11.7 Hz, 1 H), 4.63 (d, $J$ = 11.6 Hz, 1 H), 4.49 (d, $J$ = 6.1 Hz, 1 H), 4.47 (d, $J$ = 6.1 Hz, 1 H), 4.00 (qd, $J$ = 6.2, 9.0 Hz, 1 H), 3.50 (qd, $J$ = 6.1, 8.9 Hz, 1 H), 3.12 - 3.03 (m, 2 H), 2.25 - 2.18 (m, 1 H), 2.08 (s, 1 H), 2.03 - 1.96 (m, 2 H), 1.91 - 1.85 (m, 1 H), 1.85 - 1.77 (m, 1 H), 1.74 - 1.65 (m, 1 H), 1.54 - 1.41 (m, 2 H), 1.32 (d, $J$ = 6.2 Hz, 4 H), 1.28 - 1.22 (m, 3 H)

$^{13}$C NMR (150 MHz, CDCl$_3$) δ 138.8, 138.6, 128.7, 128.7, 128.1, 128.0, 128.0, 96.2, 91.2, 79.1, 78.4, 77.6, 77.1, 75.2, 71.6, 71.0, 68.4, 32.1, 29.6, 27.7, 23.4, 21.0, 18.7, 18.6
FT-IR (thin film): 3414, 2089, 1638, 1453, 1223, 1072, 955, 734, 697, 459 cm\(^{-1}\).

ESIHRMS [M+Na]\(^+\) calculated for C\(_{13}\)H\(_{18}\)O\(_3\)Na 245.1154, found 245.1179.

To a mixture of methyl glycoside S\(_{19}\)\(^{56}\) (741 mg, 5.1 mmol) and imidazole (690 mg, 10.1 mmol) in 5.1 mL N,N-dimethylformamide chlorotriisopropylsilane(1.63 mL, 7.6 mmol) was added dropwise. The resulting mixture was stirred at ambient temperature overnight. Water (50 mL) was added and the mixture was extracted with EtOAc (3×50 mL). The combined organic extracts were sequentially washed with water (30 mL) and brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude residue was purified by flash column chromatography (hexanes:EtOAc = 30:1) to furnish 1.0 g (65% yield) of protected methyl glycoside S\(_{20}\) as a mixture of anomers. To a mixture of S\(_{20}\) (1.0 mg, 3.3 mmol) and thiophenol (1.4 mL, 13.2 mmol) in 11 mL dichloromethane camphorsulfonic acid (307.2 mg, 1.32 mmol) was added. The resulting mixture was stirred at room temperature overnight. The acid was neutralized with triethylamine (0.2 mL, 1.32 mmol) and the mixture was concentrated under vacuo and the crude residue was purified by flash column chromatography (hexanes: dichloromethane = 2:1) to afford 605 mg (48% yield) of glycosyl phenyl sulfide S\(_{21}\) as a mixture of anomers. To a solution of this glycosyl phenyl sulfide (604 mg, 1.60 mmol) in 24 mL acetone and 1.6 mL water cooled at 0 °C N-
bromosuccinimide (423.6 mg, 2.4 mmol) was added. The resulting mixture was stirred at 0 °C for 15 min. Saturated sodium bicarbonate (20 mL) was added and acetone was removed under reduced pressure. The remaining aqueous mixture was extracted with ethyl acetate (3×30 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude residue was purified by flash column chromatography (hexanes:EtOAc = 10:1 to 3:1) to furnish 381 mg (83% yield) of lactol 5g as a mixture of anomers (α/β = 1.2/1) which is characterized below:

\[ \alpha \text{D}_22 = 37.0^\circ \ (c = 1.0, \text{CHCl}_3). \]

\[^1\text{H NMR (600 MHz, CDCl}_3\text{) } \delta \]

\[ 5.20 (d, J = 2.8 \text{ Hz}, 1 \text{ H}), \ 4.79 (d, J = 7.7 \text{ Hz}, 1 \text{ H}), \]

\[ 3.89 - 3.80 (m, 1 \text{ H}), \ 3.47 - 3.40 (m, 2 \text{ H}), \ 3.40 - 3.33 (m, 1 \text{ H}), \ 3.30 (\text{br. s.}, 1 \text{ H}), \ 2.76 (\text{br. s.}, 1 \text{ H}), \ 2.07 - 2.01 (m, 1 \text{ H}), \ 1.96 - 1.92 (m, 1 \text{ H}), \ 1.88 - 1.79 (m, 3 \text{ H}), \ 1.76 - 1.67 (m, 1 \text{ H}), \ 1.64 (\text{br. s.}, 1 \text{ H}), \ 1.57 - 1.44 (m, 2 \text{ H}), \ 1.31 (d, J = 6.1 \text{ Hz}, 4 \text{ H}), \ 1.24 (d, J = 6.2 \text{ Hz}, 3 \text{ H}), \ 1.06 (\text{br. s.}, 20 \text{ H}), \ 1.06 - 1.01 (m, 28 \text{ H}) \]

\[^{13}\text{C NMR (150 MHz, CDCl}_3\text{) } \delta \]

\[ 96.1, \ 91.2, \ 77.6, \ 77.1, \ 77.1, \ 73.5, \ 72.7, \ 70.5, \ 32.6, \ 32.1, \ 29.9, \ 28.0, \ 18.9, \ 18.8, \ 18.5, \ 18.5, \ 18.5, \ 18.4, \ 13.1, \ 13.0 \]

\[
\text{FT-IR (thin film): } 3400, \ 2975, \ 2248, \ 2090, \ 1638, \ 1463, \ 1067, \ 880, \ 796, \ 733 \text{ cm}^{-1}.
\]

\[
\text{ESIHRMS [M+Na]}^{+} \text{ calculated for C}_{15}\text{H}_{32}\text{O}_3\text{NaSi 311.2018, found 311.2011.}
\]

To a solution of glycosyl phenylsulfide S22\textsuperscript{57} (443 mg, 1.40 mmol) in 21 mL acetone and 1.4 mL water cooled at 0 °C N-bromosuccinimide (377 mg, 2.1 mmol) was added. The resulting mixture was stirred at 0 °C for 15 min. Saturated sodium bicarbonate
(5mL) was added and acetone was removed under reduced pressure. The remaining aqueous mixture was extracted with ethyl acetate (3×50 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude residue was purified by flash column chromatography (hexanes:EtOAc = 4:1 to 2:1) to furnish 201.5 mg (65% yield) of lactol 5h as a mixture of anomers (α/β = 1.3/1) which is characterized below:

\[ [\alpha]_D^{22} = 10.2^\circ (c = 1.0, \text{CHCl}_3). \]

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta 7.39 - 7.30 (m, 8 \text{ H}), 7.30 - 7.26 (m, 2 \text{ H}), 5.33 (\text{br. s.}, 1 \text{ H}), 4.78 - 4.71 (m, 1 \text{ H}), 4.68 (t, J = 11.6 \text{ Hz}, 2 \text{ H}), 4.44 (\text{dd}, J = 8.3, 12.1 \text{ Hz}, 2 \text{ H}), 4.18 (\text{dq}, J = 1.3, 6.5 \text{ Hz}, 1 \text{ H}), 3.65 (\text{dq}, J = 1.1, 6.5 \text{ Hz}, 1 \text{ H}), 3.52 - 3.41 (m, 1 \text{ H}), 3.33 - 3.27 (m, 1 \text{ H}), 3.22 - 3.17 (m, 1 \text{ H}), 3.00 (\text{br. s.}, 1 \text{ H}), 2.14 (\text{qd}, J = 3.3, 14.4 \text{ Hz}, 1 \text{ H}), 2.05 - 1.96 (m, 1 \text{ H}), 1.94 - 1.88 (m, 2 \text{ H}), 1.75 - 1.68 (m, 3 \text{ H}), 1.55 - 1.47 (m, 2 \text{ H}), 1.27 (d, J = 6.4 \text{ Hz}, 3 \text{ H}), 1.26 - 1.23 (m, 1 \text{ H}), 1.19 (d, J = 6.6 \text{ Hz}, 3 \text{ H}), 0.90 - 0.82 (m, 1 \text{ H})

\(^1\)C NMR (150 MHz, CDCl\(_3\)) \(\delta 138.9, 138.8, 128.6, 128.2, 128.2, 127.9, 96.6, 92.0, 77.6, 77.1, 74.5, 73.7, 72.6, 71.3, 71.1, 66.9, 28.1, 25.7, 24.3, 20.9, 17.7, 17.6

**FT-IR (thin film):** 3428, 2933, 2868, 1641, 1453, 1345, 1205, 1071, 736, 701 cm\(^{-1}\).

**ESI-HRMS [M+Na]** calculated for C\(_{13}\)H\(_{18}\)O\(_3\)Na 245.1154, found 245.1171.
To a mixture of this glycosyl phenyl sulfide $\textbf{S23}^{51}$ (1.28 g, 3.6 mmol) and pyridine (2.93 mL, 36.0 mmol) in 18 mL methylene chloride cooled at 0 °C triflic anhydride (1.21 mL, 7.2 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 30 min before being quenched with ice-water. The organic layer was separated and the aqueous layer was extracted with methylene chloride three times. The combined organic layers were washed sequentially with saturated copper sulfate three times and water three times, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford 1.75 g (100% yield) of crude triflate $\textbf{S24}$. To a solution of triflate $\textbf{S24}$ (1.75 g, 3.6 mmol) in 18 mL $N,N$-dimethylformamide sodium azide (2.34 g, 36 mmol) was added in one portion. The mixture was allowed to stir at room temperature for 3 h. The mixture was diluted with brine and extracted with EtOAc three times. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude residue was purified by flash column chromatography (hexanes: diethyl ether = 50:1) to obtain 1.20 g (88% yield) of compound $\textbf{S25}$. To a solution of this glycosyl phenylsulfide $\textbf{S25}$ (1.31 g, 2.97 mmol) in 45 mL acetone and 3 mL water cooled at 0 °C $N$-bromosuccinimide (0.79 g, 4.45 mmol) was added. The resulting mixture was stirred at 0 °C for 15 min. Saturated sodium bicarbonate (32 mL) was added and acetone was removed under reduced pressure. The remaining aqueous mixture was extracted with ethyl acetate three times. The combined extracts were
washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude residue was purified by flash column chromatography (hexanes:EtOAc = 10:1 to 5:1) to furnish 0.79 g (92% yield) of lactol S26 as a mixture of anomers. To a solution of this lactol (0.79 g, 2.73 mmol) in 10 mL THF cooled at 0 °C 1.0 M tetra-n-butylammonium fluoride was added in THF (4.1 mL, 4.1 mmol), and the reaction mixture was stirred for 4 h. Saturated ammonium chloride (8 mL) was added and THF was removed under reduced pressure. The remaining aqueous mixture was extracted with ethyl acetate three times. Combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. The crude residue was purified by flash column chromatography (hexanes:EtOAc = 2:1) to furnish 372 mg (79% yield) of lactol 5i as a mixture of anomers (α/β = 3.1/1) which is characterized below:

\[ \alpha \beta \] = 70.4° (c = 1.0, CHCl3).

\[ \text{H NMR (600 MHz, CDCl}_3\text{)} \delta 5.36 (\text{br. s., 1 H, } \alpha), 4.80 (\text{ddd, } J=9.6, 6.0, 1.8 \text{ Hz, 1 H, } \beta), 4.03 (\text{ddt, } J=11.5, 9.4, 4.6 \text{ Hz, 1 H, } \alpha), 3.83 - 3.92 (\text{m, 1 H, } \alpha), 3.67 (\text{ddt, } J=11.6, 9.3, 4.6 \text{ Hz, 1 H, } \beta), 3.30 (\text{dq, } J=9.7, 6.2 \text{ Hz, 1 H, } \beta), 2.98 (\text{d, } J=6.1 \text{ Hz, 1 H, } \beta), 2.90 - 2.97 (\text{ovrlp, 1 H, } \alpha \text{ and } \beta), 2.45 (\text{br. s., 1 H, } \alpha), 2.34 (\text{ddd, } J=12.6, 5.0, 2.0 \text{ Hz, 1 H, } \beta), 2.14 - 2.23 (\text{ovrlp, 2 H, } \alpha \text{ and 1 H, } \beta), 1.66 - 1.74 (\text{m, 1 H, } \alpha), 1.54 - 1.63 (\text{m,1 H, } \beta), 1.39 (\text{d, } J=6.2 \text{ Hz, 3 H, } \beta), 1.33 \text{ ppm (d, } J=6.2 \text{ Hz, 3 H, } \alpha).\]

\[ \text{C NMR (150 MHz, CDCl}_3\text{)} \delta 94.1, 92.3, 71.4, 71.2, 70.8, 70.3, 67.7, 66.9, 40.8, 38.1, 19.0, 18.9.\]

\[ \text{FT-IR (thin film): 3412, 2937, 2109, 1642, 1264, 1118, 1080, 991, 924, 826 cm}^{-1}.\]

\[ \text{ESI LRMS [M+Na]}^{+} \text{ calculated for } C_{13}H_{18}O_{3}Na 196.07, \text{ found 196.05.}\]
1.4.2 Preparation of sugar-derived triflates:

A mixture of fucal S27 (3.12 g, 24 mmol) and dibutyltin oxide (6.0 g, 24 mmol) in 144 mL dry toluene was refluxed for 2 h using a Dean-Stark apparatus to remove water. To the resulting mixture cooled to room temperature 4-methoxybenzyl chloride (PMBCl) (3.4 g, 21.6 mmol) and tetrabutylammonium bromide (TBABr) (8.5 g, 26.4 mmol) were added. The reaction mixture was heated at 100 °C overnight. The resulting mixture was cooled to room temperature, filtrated through a pad of celite, and concentrated. The crude residue was purified by flash column chromatography (hexanes:EtOAc = 10:1) to afford 4.88 g (81% yield) of protected fucal S28. To a mixture of S28 (2.94 g, 11.75 mmol) and thiophenol (2.4 mL, 23.5 mmol) in 35 mL dry toluene cooled at 0 °C ReOCl₃(SMe₂)(OPPh₃) (76 mg, 0.12 mmol) was added. The resulting mixture was slowly warmed to room temperature and stirred for 1 h. The mixture was concentrated under vacuo and the crude residue was purified by flash column chromatography (hexanes:EtOAc = 5:1) to afford 3.45 g (82% yield) of glycosyl phenylsulfide S29 which is characterized below:

\[ [\alpha]_{D}^{22} = 248.0^\circ \text{ (c = 1.0, CHCl}_3) \]
$^1$H NMR (600 MHz, CDCl$_3$) δ 7.47 - 7.41 (m, 2 H), 7.31 - 7.27 (m, 4 H), 7.25 - 7.21 (m, 1 H), 6.94 - 6.88 (m, 2 H), 5.71 (d, $J = 5.7$ Hz, 1 H), 4.59 - 4.51 (m, 2 H), 4.34 (q, $J = 6.5$ Hz, 1 H), 3.87 - 3.83 (m, 1 H), 3.83 - 3.80 (m, 4 H), 2.36 (ddd, $J = 5.9$, 12.1, 13.2 Hz, 1 H), 2.09 (dd, $J = 5.0$, 13.4 Hz, 1 H), 1.30 (d, $J = 6.6$ Hz, 3 H)

$^{13}$C NMR (150 MHz, CDCl$_3$) δ 159.8, 135.6, 131.1, 130.1, 129.8, 129.2, 127.2, 114.3, 84.3, 77.6, 77.1, 73.5, 70.2, 68.8, 67.1, 55.6, 31.1, 17.0

FT-IR (thin film): 3436, 2080, 1614, 1514, 1301, 1246, 1173, 818, 735, 690 cm$^{-1}$.

ESIHRMS [M+Na]$^+$ calculated for C$_{20}$H$_{24}$O$_4$Na 383.1293, found 383.1294.

To a mixture of this alcohol S29 (2.0 g, 5.6 mmol) in 31 mL methylene chloride and pyridine (4.53 mL, 55.6 mmol) cooled at 0 °C triflic anhydride (1.87 mL, 11.1 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 30 min and then quenched with ice water. The organic layer was separated and the aqueous layer was extracted with methylene chloride (3×150 mL). The combined organic layer was washed sequentially with saturated copper sulfate (3×100 mL) and water (3×100 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford 2.67 g (98% yield) of crude sugar derived triflate 6a:

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.40 (d, $J = 7.3$ Hz, 2 H), 7.33 - 7.27 (m, 5 H), 6.93 - 6.87 (m, 2 H), 5.69 (d, $J = 5.7$ Hz, 1 H), 5.03 (s, 1 H), 4.69 (d, $J = 11.6$ Hz, 1 H), 4.54 - 4.48 (m, 2 H), 3.94 - 3.88 (m, 1 H), 3.82 (s, 3 H), 2.37 (dt, $J = 5.8$, 13.0 Hz, 1 H), 2.15 (dd, $J = 4.9$, 13.7 Hz, 1 H), 1.55 (s, 1 H), 1.30 (d, $J = 6.6$ Hz, 3 H).

$^{13}$C NMR (150 MHz, CDCl$_3$) δ 159.8, 134.4, 131.5, 129.8, 129.4, 129.4, 127.8, 122.1, 119.9, 117.8, 114.3, 85.8, 84.1, 77.6, 77.1, 71.0, 70.9, 65.7, 55.6, 31.6, 17.2.
A mixture of L-fucal S30 (4.8 g, 36.9 mmol) and dibutyltin oxide (9.2 g, 36.9 mmol) in 222 mL dry toluene was refluxed for 2 h using a Dean-Stark apparatus to remove water. To the resulting mixture cooled to room temperature 4-Methoxybenzyl chloride (PMBCl) (5.2 g, 33.21 mmol) and tetrabutylammonium bromide (TBABr) (13.1 g, 40.6 mmol) were added. The reaction mixture was heated at 100 °C overnight. The remaining mixture was filtrated with celite, concentrated and purified by flash column chromatography (hexanes:EtOAc = 10:1) to afford 5.43 g (59% yield) of protected L-fucal S31. To a mixture of S31 (1.24 g, 5.0 mmol) in 14.9 mL dry toluene and thiophenol (1.02 mL, 9.91 mmol) cooled at 0 °C catalyst ReOCl₃(SMe₂)(OPPh₃) (32.2 mg, 0.05 mmol) was added. The resulting mixture was slowly warmed to room temperature for 1 h. The mixture was concentrated under vacuo and the crude residue was purified by flash column chromatography (hexanes:EtOAc = 4:1) to afford 1.63 g (91% yield) of α-glycosyl phenyl sulfide S32 which is characterized below:

\[ \alpha \] D²³ = -219.5° (c = 1.0, CHCl₃).

\(^1\text{H NMR (600 MHz, CDCl₃)}\) \(\delta\) 7.47 - 7.41 (m, 2 H), 7.31 - 7.27 (m, 4 H), 7.25 - 7.21 (m, 1 H), 6.94 - 6.88 (m, 2 H), 5.71 (d, J = 5.7 Hz, 1 H), 4.59 - 4.52 (m, 2 H), 4.34 (q, 1 H), 3.94 (s, 3 H), 3.85 (s, 3 H), 3.76 (s, 3 H), 3.56 (s, 3 H), 3.36 (s, 3 H), 2.11 (s, 3 H), 1.34 (t, J = 7.0 Hz, 3 H).
$J = 6.6 \text{ Hz}, 1 \text{ H}), 3.87 - 3.83 \text{ (m}, 1 \text{ H}), 3.83 - 3.80 \text{ (m}, 4 \text{ H}), 2.36 \text{ (ddd, } J = 5.9, 12.0, 13.3 \text{ Hz}, 1 \text{ H}), 2.09 \text{ (dd, } J = 4.9, 13.3 \text{ Hz}, 1 \text{ H}), 1.30 \text{ (d, } J = 6.6 \text{ Hz}, 3 \text{ H})$

$\text{^13C NMR (150 MHz, CDCl}_3) \delta 159.5, 135.3, 130.8, 129.8, 129.5, 128.9, 126.9, 114.0, 84.0, 77.3, 77.1, 76.8, 73.2, 69.9, 68.5, 66.8, 55.3, 30.7, 16.7$

$\text{FT-IR (thin film): 3452, 3018, 2067, 1613, 1514, 1248, 1092, 974, 754, 667 cm}^{-1}$.  

$\text{ESI-HRMS \{} [\text{M+Na}]^+ \text{ calculated for } \text{C}_{20}\text{H}_{24}\text{O}_4\text{SNa 383.1293, found 383.1325.}$

To a mixture of alcohol S32 (721 mg, 2.0 mmol) in 11 mL methylene chloride and pyridine (1.6 mL, 20.0 mmol) cooled at 0 °C triflic anhydride (0.68 mL, 4.0 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 30 min and quenched with ice-water. The organic layer was separated and the aqueous layer was extracted with methylene chloride (3×50 mL). The combined organic layers were washed sequentially with saturated copper sulfate (3×50 mL) and water (3×50 mL), dried over anhydrous sodium sulfate, filtered and concentrated, and the residue was purified by flash column chromatography (pure CH$_2$Cl$_2$) to afford 791 mg (80% yield) of sugar derived triflate 6b which is characterized below:

$\text{^1H NMR (600 MHz, CDCl}_3) \delta 7.42 - 7.38 \text{ (m}, 2 \text{ H}), 7.33 - 7.26 \text{ (m}, 5 \text{ H}), 6.93 - 6.89 \text{ (m}, 2 \text{ H}), 5.69 \text{ (d, } J = 5.7 \text{ Hz}, 1 \text{ H}), 5.05 - 5.00 \text{ (m}, 1 \text{ H}), 4.69 \text{ (d, } J = 11.6 \text{ Hz}, 1 \text{ H}), 4.54 - 4.48 \text{ (m}, 2 \text{ H}), 3.94 - 3.88 \text{ (m}, 1 \text{ H}), 3.82 \text{ (s, } 3 \text{ H}), 2.37 \text{ (ddd, } J = 5.8, 12.4, 13.5 \text{ Hz}, 1 \text{ H}), 2.15 \text{ (dd, } J = 5.0, 13.6 \text{ Hz}, 1 \text{ H}), 1.30 \text{ (d, } J = 6.6 \text{ Hz}, 3 \text{ H})$

$\text{^13C NMR (150 MHz, CDCl}_3) \delta 159.8, 134.4, 131.5, 130.3, 130.1, 129.8, 129.7, 129.4, 129.2, 129.1, 129.0, 127.8, 127.8, 122.1, 119.9, 117.8, 115.7, 114.3, 114.2, 114.2, 85.8, 84.1, 83.8, 77.6, 77.1, 71.0, 70.9, 65.7, 65.2, 65.1, 64.7, 55.6, 31.6, 17.2, 17.1.$
To a solution of protected fucal S31 (1.56 g, 6.23 mmol) in 14 mL methanol camphorsulfonic acid (58.0 mg, 0.24 mmol) was added. The resulting mixture was stirred at room temperature overnight and quenched with Et₃N (35 µL). The mixture was concentrated under vacuo and crude residue was purified by flash column chromatography (hexanes:EtOAc = 4:1) to afford 1.28 g (73% yield) of α-methyl glycoside S33 which is characterized below:

\[
[a]D^{23} = 220.9^\circ \ (c = 1.0, \text{CHCl}_3).
\]

\(^1\text{H NMR (600 MHz, CDCl}_3\) \): δ 7.28 - 7.26 (m, 1 H), 7.26 - 7.24 (m, 1 H), 6.90 - 6.86 (m, 2 H), 4.83 - 4.79 (m, 1 H), 4.55 - 4.48 (m, 2 H), 3.85 - 3.82 (m, 1 H), 3.81 (s, 4 H), 3.76 (d, \(J = 2.4\) Hz, 1 H), 3.31 (s, 3 H), 1.96 - 1.87 (m, 2 H), 1.60 (br. s., 3 H), 1.30 (d, \(J = 6.6\) Hz, 3 H), 1.25 (s, 2 H)

\(^{13}\text{C NMR (150 MHz, CDCl}_3\) \): δ 159.3, 130.1, 129.3, 113.9, 98.7, 77.3, 77.0, 76.8, 72.7, 69.8, 68.3, 65.3, 55.3, 54.8, 29.9, 29.7, 16.8

FT-IR (thin film): 3436, 2998, 2837, 2067, 1614, 1514, 1247, 916, 820, 734 cm⁻¹.

ESIHRMS [M+Na]⁺ calculated for C₁₅H₂₂O₅Na 305.1365, found 305.1371.

To a mixture of S33 (538 mg, 1.91 mmol) in 10 mL methylene chloride and pyridine (1.6 mL, 19.1 mmol) cooled at 0 °C triflic anhydride (0.64 mL, 3.81 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 30 min and quenched with ice-water. The organic layers were separated and the aqueous layer was extracted with
methylene chloride (3×15 mL). The combined organic layer was washed sequentially with saturated copper sulfate (3×15 mL) and water (3×15 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford 759 mg (96% yield) of triflate 6c. Triflate 6c was purified by flash column chromatography (pure CH$_2$Cl$_2$) and is characterized below:

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.30 - 7.27 (m, $J = 8.8$ Hz, 2 H), 6.90 - 6.86 (m, 2 H), 5.00 (d, $J = 2.4$ Hz, 1 H), 4.84 - 4.81 (m, 1 H), 4.66 (d, $J = 11.6$ Hz, 1 H), 4.48 - 4.44 (m, 1 H), 3.98 (q, $J = 6.6$ Hz, 1 H), 3.94 - 3.88 (m, 1 H), 3.82 - 3.79 (m, 4 H), 3.32 - 3.29 (m, 3 H), 1.97 (d, $J = 2.6$ Hz, 1 H), 1.96 (d, $J = 2.9$ Hz, 1 H), 1.56 (s, 1 H), 1.31 (d, $J = 6.6$ Hz, 3 H)

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 159.6, 129.8, 129.6, 122.1, 120.0, 117.8, 115.7, 114.2, 98.8, 86.3, 77.6, 77.1, 70.8, 70.3, 64.4, 55.6, 55.4, 30.9, 17.3.

A mixture of D-fucal S27 (2.6 g, 20.0 mmol) and dibutyltin oxide (5.0 g, 20.0 mmol) in 1201 mL dry toluene was refluxed for 2 h using a Dean-Stark apparatus to remove water. To the resulting mixture cooled to room temperature benzyl bromide (2.2 mL, 18.0 mmol) and tetrabutylammonium bromide (TBABr) (1.9 g, 6.0 mmol) were added. The reaction mixture was heated at 100 °C overnight. The remaining mixture was filtrated with
celite and concentrated. The crude residue was purified by flash column chromatography (hexanes:EtOAc = 10:1) to afford 3.2 g (73% yield) of protected D-fucal S34. To a mixture of S34 (3.2 g, 14.5 mmol) in 43 mL dry toluene and thiophenol (3.0 mL, 29.1 mmol) cooled at 0 °C catalyst ReOCl₃(SMe₂)(OPPh₃) (94.3 mg, 0.15 mmol) was added. The resulting mixture was warmed to room temperature for 1 h. The mixture was concentrated under vacuo and crude residue was purified by flash column chromatography (hexanes:EtOAc = 7:1) to afford 3.0 g (63% yield) of α-glycosyl phenyl sulfide S35 which is characterized below:

\[ [\alpha]_D^{23} = 259.2^\circ \text{ (c} = 1.0, \text{ CHCl}_3) \].

\(^1\text{H NMR (600 MHz, CDCl}_3\) \( \delta 7.43 - 7.47 \text{ (m, 2 H), 7.28 - 7.41 \text{ (m, 7 H), 7.22 - 7.26 \text{ (m, 1 H), 5.72 \text{ (d, J=5.5 Hz, 1 H), 4.64 \text{ (d, J=1.1 Hz, 2 H), 4.36 \text{ (qd, J=6.6, 0.6 Hz, 1 H), 3.86 - 3.95 \text{ (m, 1 H), 3.85 \text{ (d, J=2.8 Hz, 1 H), 2.39 \text{ (ddd, J=13.3, 12.0, 5.9 Hz, 1 H), 2.12 \text{ (ddt, J=13.3, 4.9, 1.1 Hz, 2 H), 1.32 ppm (d, J=6.6 Hz, 3 H)}}}

\(^{13}\text{C NMR (150 MHz, CDCl}_3\) \( \delta 138.2, 135.6, 131.2, 129.3, 129.0, 128.3, 128.1, 127.3, 84.4, 74.0, 70.6, 68.9, 67.3, 31.1, 17.0 \)

\text{FT-IR (thin film): 3435, 2087, 1638, 1479, 1371, 1096, 1058, 814, 735, 690 cm}^{-1}.

\text{ESIHRMS [M+Na]^+ calculated for } C_{19}H_{22}O_3SNa 353.1187, \text{ found 353.1199.}

To a mixture of alcohol S35 (3.0 g, 9.08 mmol) in 49 mL methylene chloride and pyridine (7.4 mL, 90.8 mmol) cooled at 0 °C triflic anhydride (3.1 mL, 18.16 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 30 min and quenched with ice-water. Organic layer was separated and aqueous layers were extracted with methylene chloride (3×150 mL). The combined organic layer was washed sequentially with saturated
copper sulfate (3×100 mL) and water (3×100 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to afford 3.63 g (86% yield) of triflate 6d. Triflate 6d was purified by flash column chromatography (pure CH2Cl2) and is characterized below:

**1H NMR (600 MHz, CDCl3)** δ 7.42 - 7.39 (m, 2 H), 7.39 (d, J = 4.6 Hz, 4 H), 7.37 - 7.26 (m, 5 H), 5.70 (d, J = 5.7 Hz, 1 H), 5.06 (s, 1 H), 4.77 (d, J = 12.1 Hz, 1 H), 4.59 (d, J = 12.1 Hz, 1 H), 4.52 (q, J = 6.6 Hz, 1 H), 3.96 - 3.90 (m, 1 H), 2.40 (dt, J = 5.9, 12.9 Hz, 1 H), 2.19 (d, J = 4.8 Hz, 1 H), 2.18 - 2.16 (m, 2 H), 1.57 (s, 1 H), 1.31 (d, J = 6.4 Hz, 3 H)

**13C NMR (150 MHz, CDCl3)** δ 137.1, 137.0, 134.1, 133.1, 131.9, 131.1, 129.1, 128.9, 128.6, 128.6, 128.1, 128.0, 127.8, 127.7, 127.7, 127.5, 121.7, 119.6, 117.5, 115.4, 85.4, 83.8, 83.7, 82.3, 77.3, 77.0, 76.8, 73.6, 72.6, 71.0, 71.0, 70.7, 65.4, 31.8, 31.2, 31.0, 17.4, 16.9.

To a mixture of diol S36 (548 mg, 1.5 mmol), potassium iodide (250 mg, 1.5 mmol), potassium carbonate (228 mg, 1.65 mmol), 2-aminoethyl diphenyl borinate (34 mg, 0.15 mmol) in 7.0 mL acetonitrile benzyl bromide (270 µL, 2.25 mmol) was added. The reaction mixture was stirred at 40 °C for 24 h, quenched with saturated sodium bicarbonate (10 mL) and diluted with brine (20 mL). The organic layer was separated and remaining aqueous layer was extracted with ethyl acetate (4×15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated, and the
residue was purified by flash column chromatography (hexane:EtOAc = 15:1 to 5:1) to afford 259 mg (39% yield) of S37 and 120 mg of recovered starting material S36 (50% yield based on recovered starting material). S37 is characterized below:

\[ [\alpha]^{23}_D = 13^\circ \ (c = 1, \ \text{CHCl}_3). \]

\[ ^1H \text{ NMR (600 MHz, CDCl}_3) \delta 7.57 - 7.49 \ (m, 2 \ H), 7.43 - 7.23 \ (m, 16 \ H), 5.06 \ (d, J = 9.7 \ Hz, 1 \ H), 4.75 - 4.69 \ (m, 1 \ H), 4.69 - 4.62 \ (m, 2 \ H), 4.51 \ (d, J = 11.7 \ Hz, 1 \ H), 4.34 \ (t, J = 2.8 \ Hz, 1 \ H), 3.93 - 3.84 \ (m, 1 \ H), 3.32 \ (dd, J = 2.9, 9.9 \ Hz, 1 \ H), 3.07 \ (dd, J = 2.7, 9.4 \ Hz, 1 \ H), 2.47 \ (s, 1 \ H), 1.34 - 1.21 \ (m, 3 \ H) \]

\[ ^13C \text{ NMR (150 MHz, CDCl}_3) \delta 137.8, 137.8, 134.2, 132.2, 129.1, 128.9, 128.5, 128.4, 128.4, 128.3, 127.7, 83.7, 79.8, 72.7, 71.5, 71.2, 66.1, 18.4 \]

\[ \text{FT-IR (thin film): 3487, 3061, 2974, 2893, 1583, 1496, 1477, 1454, 1205, 1089 cm}^{-1}. \]

\[ \text{ESIHRMS } [M+Na]^+ \text{ calculated for C}_{26}H_{28}NaO_4S \ 459.1606, \text{ found 459.1613.} \]

To a solution of S37 (306 mg, 0.69 mmol) in 3.5 mL dichloromethane and 730 µL of pyridine cooled at 0 °C triflic anhydride (0.47 mL, 2.76 mmol) was added. The resulting mixture was stirred at 0 °C for 3 h and quenched with water. The organic layer was separated and the remaining aqueous layer was extracted with dichloromethane (3X10 mL). The combined organic layers were washed sequentially with saturated copper sulfate (3X10 mL), water (2X10 mL), dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and the residue was purified by short flash column chromatography (dichloromethane) to afford 255 mg of triflate 6e and 44 mg of recovered alcohol S37.
(65% yield, 76% yield based on recovered starting material). Triflate 6e is characterized below:

^1^H NMR (600 MHz, CDCl$_3$) δ 7.56 - 7.47 (m, 2 H), 7.43 - 7.27 (m, 14 H), 5.38 (t, J = 2.4 Hz, 1 H), 4.93 (d, J = 9.9 Hz, 1 H), 4.74 (dd, J = 9.1, 11.3 Hz, 2 H), 4.63 (d, J = 11.4 Hz, 1 H), 4.41 (d, J = 11.6 Hz, 1 H), 3.79 (qd, J = 6.1, 9.4 Hz, 1 H), 3.38 (dd, J = 2.6, 9.7 Hz, 1 H), 3.11 (dd, J = 2.2, 9.4 Hz, 1 H), 1.24 (d, J = 6.2 Hz, 3 H)

^1^C NMR (150 MHz, CDCl$_3$) δ 136.7, 136.7, 133.2, 132.6, 129.3, 128.9, 128.9, 128.8, 128.7, 128.6, 128.2, 83.9, 83.6, 77.1, 74.4, 73.3, 72.4, 71.9, 18.2.

To a solution of S38 (1.76 g, 3.0 mmol) in 10 mL THF cooled to 0 °C tetrabutyl ammonium fluoride (6.1 mL, 1 M) was added. The reaction mixture was stirred at ambient temperature for 24 h and then heated at 40 °C for an additional 6 h before saturated sodium bicarbonate was added. THF was removed under reduced pressure and the remaining aqueous mixture was extracted with ethyl acetate (3×50 mL), and sequentially washed with water (2×50 mL) and brine (20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude residue was purified by flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) to obtain 1.35 g (94% yield) of alcohol S39 which is characterized below:

\[ [\alpha]_D^{23} = -29.5^\circ \] (c = 1.0, CHCl$_3$).
$^1$H NMR (600 MHz, CDCl$_3$) δ 7.26 - 7.23 (m, 2 H), 6.91 - 6.85 (m, 2 H), 5.22 (dd, $J = 1.9, 9.6$ Hz, 1 H), 4.83 (s, 1 H), 4.56 (d, $J = 11.2$ Hz, 1 H), 4.46 (d, $J = 11.2$ Hz, 1 H), 4.19 (q, $J = 3.1$ Hz, 1 H), 4.12 (dd, $J = 5.8, 7.1$ Hz, 1 H), 4.08 - 4.03 (m, 1 H), 3.81 (s, 3 H), 3.73 (qd, $J = 6.2, 9.5$ Hz, 1 H), 3.65 - 3.55 (m, 2 H), 3.35 (s, 3 H), 3.11 (dd, $J = 3.0, 9.4$ Hz, 1 H), 2.40 - 2.34 (m, 1 H), 2.21 - 2.13 (m, 1 H), 1.55 (tdd, $J = 2.7, 9.7, 13.6$ Hz, 1 H), 1.51 (s, 3 H), 1.32 (s, 3 H), 1.27 (d, $J = 5.9$ Hz, 3 H), 1.23 (d, $J = 6.2$ Hz, 3 H)

$^{13}$C NMR (150 MHz, CDCl$_3$) δ 159.9, 130.0, 114.3, 109.5, 98.3, 96.7, 80.3, 78.6, 77.9, 76.3, 71.6, 68.5, 65.0, 64.7, 55.6, 55.1, 37.3, 28.2, 26.8, 18.6, 18.0

FT-IR (thin film): 3476, 2978, 2936, 1607, 1508, 1456, 1378, 1259, 1140, 1088 cm$^{-1}$.

ESIHRMS [M+Na]$^+$ calculated for C$_{24}$H$_{36}$NaO$_9$ 491.2257, found 491.2252.

To a mixture of S39 (360 mg, 0.77 mmol) and pyridine (0.63 mL, 7.7 mmol) in 3.9 mL methylene chloride cooled at 0 °C triflic anhydride (0.26 mL, 1.54 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 30 min and quenched with water. The organic layer was separated and the aqueous layer was extracted with methylene chloride (3×20 mL). The combined organic extracts were washed sequentially with saturated copper sulfate (3×20 mL) and water (2×20 mL), dried over anhydrous sodium sulfate, filtered, concentrated in vacuo. The residue was purified by flash column chromatography (dichloromethane) to furnish 342 mg (74% yield) of triflate 6f. Triflate 6f is characterized below:

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.27 (s, 1 H), 7.26 (s, 1 H), 6.87 (d, $J = 8.4$ Hz, 2 H), 5.39 (d, $J = 2.8$ Hz, 1 H), 5.15 (dd, $J = 1.6, 9.4$ Hz, 1 H), 4.83 (s, 1 H), 4.71 (d, $J = 11.2$ Hz, 1 H), 3.70 (s, 3 H), 3.65 (d, $J = 7.7$ Hz, 1 H), 3.40 (q, $J = 3.1$ Hz, 1 H), 3.12 - 3.07 (m, 1 H), 2.40 - 2.34 (m, 1 H), 2.18 - 2.13 (m, 1 H), 1.55 (tdd, $J = 2.7, 9.7, 13.6$ Hz, 1 H), 1.51 (s, 3 H), 1.32 (s, 3 H), 1.27 (d, $J = 5.9$ Hz, 3 H), 1.23 (d, $J = 6.2$ Hz, 3 H)
**1.4.3 General procedure for preparation of O-linked 2-Deoxy β-Glycosides:**

To a solution of lactol donor 5a (32.8 mg, 0.1 mmol) in 0.8 mL 1,4-dioxane NaH (60% dispersion in mineral oil, 8.0 mg, 0.2 mmol) was added and the resulting mixture was stirred for 10 min. A solution of triflate acceptor 6a (98.5 mg, 0.2 mmol) in 0.4 mL 1,4-dioxane was added followed by addition of 15-crown-5 (30 µL, 0.15 mmol). The reaction mixture was stirred at room temperature for 24 h. The crude reaction mixture was purified by preparative thin layer chromatography (toluene:EtOAc = 20:1) to furnish 27.3 mg (41% yield) of 2-deoxy β-glycoside 7 which is characterized below:

\[ [\alpha]_D^{23} = 307.8^\circ \ (c = 1.0, \text{CHCl}_3). \]

\(^1\text{H NMR (600 MHz, CDCl}_3\) δ 7.49 - 7.44 (m, 2 H), 7.40 - 7.33 (m, 8 H), 7.33 - 7.28 (m, 5 H), 7.27 (d, \(J = 1.7\) Hz, 1 H), 7.25 (s, 1 H), 6.88 (d, \(J = 8.6\) Hz, 2 H), 5.60 (d, \(J = 5.3\) Hz, 1 H), 4.94 (d, \(J = 11.0\) Hz, 1 H), 4.80 - 4.74 (m, 1 H), 4.66 (d, \(J = 10.8\) Hz, 1 H), 4.37 (d, \(J = 11.4\) Hz, 1 H), 4.10 - 4.05 (m, 2 H), 3.80 (s, 4 H), 3.79 - 3.75 (m, 1 H), 3.69 (s, 9 H), 3.58 - 3.54 (m, 2 H), 3.35 (s, 3 H), 3.15 (dd, \(J = 2.6, 9.4\) Hz, 1 H), 2.37 - 2.31 (m, 1 H), 1.80 (ddd, \(J = 2.4, 9.7, 14.7\) Hz, 1 H), 1.33 (s, 3 H), 1.24 (d, \(J = 5.3\) Hz, 3 H), 1.22 - 1.18 (m, 3 H)

\(^{13}\text{C NMR (150 MHz, CDCl}_3\) δ 159.9, 130.6, 130.5, 129.1, 129.0, 128.9, 122.0, 119.9, 117.8, 115.7, 114.3, 114.2, 114.2, 109.7, 98.2, 96.4, 84.6, 79.3, 78.4, 77.6, 77.1, 77.1, 76.9, 76.4, 72.2, 69.4, 67.4, 64.4, 55.6, 55.3, 55.2, 37.0, 28.1, 26.7, 18.3, 18.0, 17.8.
4.65 - 4.62 (m, 1 H), 4.61 (d, \( J = 11.0 \text{ Hz} \), 1 H), 4.56 (d, \( J = 11.7 \text{ Hz} \), 1 H), 4.46 (d, \( J = 11.0 \text{ Hz} \), 1 H), 4.19 (dd, \( J = 6.2, 9.2 \text{ Hz} \), 1 H), 3.89 - 3.84 (m, 1 H), 3.81 - 3.75 (m, 3 H), 3.54 (ddd, \( J = 5.0, 8.7, 11.6 \text{ Hz} \), 1 H), 3.39 (t, \( J = 9.2 \text{ Hz} \), 1 H), 3.32 - 3.24 (m, 1 H), 3.12 (t, \( J = 8.9 \text{ Hz} \), 1 H), 2.46 (dd, \( J = 4.8, 13.2 \text{ Hz} \), 1 H), 2.34 - 2.26 (m, 1 H), 2.08 - 1.99 (m, 1 H), 1.63 (br. s., 1 H), 1.60 - 1.51 (m, 1 H), 1.31 (dd, \( J = 6.2, 10.6 \text{ Hz} \), 7 H)

\(^{13}\text{C NMR (150 MHz, CDCl}_3\) \( \delta 159.6, 138.8, 138.8, 135.4, 131.6, 131.5, 130.7, 129.6, 129.3, 128.8, 128.8, 128.7, 128.5, 128.1, 128.0, 127.9, 127.4, 114.2, 100.7, 84.2, 84.0, 82.1, 79.9, 77.8, 77.6, 77.1, 75.6, 71.8, 71.6, 71.4, 68.4, 55.6, 37.5, 36.7, 18.5, 18.2

\text{FT-IR (thin film): } 3435, 2965, 2931, 2060, 1809, 1639, 1514, 1249, 819, 694 \text{ cm}^{-1}.

\text{ESIHRMS [M+Na]}^+ \text{ calculated for C}_{40}\text{H}_{46}\text{O}_{7}\text{NaS 693.2862, found 693.2886.}

To a solution of lactol donor 5b (23.8 mg, 0.1 mmol) in 0.8 mL 1, 4-dioxane NaH (60 % dispersion in mineral oil, 12.0 mg, 0.3 mmol) was added and the resulting mixture was stirred for 10 min. A solution of triflate acceptor 6a (98.5 mg, 0.2 mmol) in 0.4 mL 1, 4-dioxane was added followed by addition of 15-crown-5 (30 µL, 0.15 mmol). The reaction mixture was stirred at room temperature for 24 h. The crude reaction mixture was purified by preparative thin layer chromatography (toluene:EtOAc = 5:1) to furnish 47 mg (81 % yield) of 2-deoxy β-glycoside 8 which is characterized below:

\([\alpha]_D^{23} = 126.2^\circ \ (c = 1.0, \text{ CHCl}_3)\).
$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.45 - 7.42 (m, 2 H), 7.40 - 7.34 (m, 4 H), 7.34 - 7.27 (m, 4 H), 7.26 - 7.21 (m, 3 H), 6.91 - 6.87 (m, 2 H), 5.56 (d, $J$ = 5.3 Hz, 1 H), 4.82 (dd, $J$ = 1.8, 9.7 Hz, 1 H), 4.77 (d, $J$ = 11.4 Hz, 1 H), 4.68 (d, $J$ = 11.4 Hz, 1 H), 4.57 (d, $J$ = 11.0 Hz, 1 H), 4.47 (d, $J$ = 11.0 Hz, 1 H), 4.19 - 4.12 (m, 1 H), 3.86 - 3.81 (m, 1 H), 3.81 (s, 3 H), 3.68 - 3.57 (m, 2 H), 3.38 (t, $J$ = 9.2 Hz, 1 H), 3.30 - 3.23 (m, 1 H), 2.97 (t, $J$ = 8.9 Hz, 1 H), 2.44 - 2.39 (m, 1 H), 2.16 (ddd, $J$ = 1.9, 5.0, 12.3 Hz, 1 H), 2.11 - 2.04 (m, 1 H), 2.00 (ddd, $J$ = 5.6, 11.8, 13.3 Hz, 1 H), 1.60 (br. s., 1 H), 1.55 (dt, $J$ = 9.7, 12.0 Hz, 2 H), 1.33 (d, $J$ = 6.2 Hz, 3 H), 1.29 (d, $J$ = 6.2 Hz, 4 H), 1.27 - 1.23 (m, 1 H)

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 159.7, 138.5, 135.5, 131.6, 130.6, 129.7, 129.3, 129.3, 129.1, 128.5, 128.3, 127.4, 114.3, 100.5, 86.4, 84.1, 81.9, 77.6, 77.6, 77.1, 75.5, 71.8, 71.6, 71.3, 68.4, 55.6, 39.4, 36.7, 18.6, 18.3

FT-IR (thin film): 3435, 2929, 2067, 1643, 1513, 1249, 1093, 1029, 738, 699 cm$^{-1}$.

ESIHRMS [M+Na]$^+$ calculated for C$_{33}$H$_{40}$O$_7$NaS 603.2392, found 603.2385.

2-Deoxy $\beta$-glycoside 9 was prepared following the general procedure described for preparation of 8. The crude reaction mixture was purified by preparative thin layer chromatography (toluene:EtOAc = 5:1) to furnish 80% yield of 2-deoxy $\beta$-glycoside 9 which is characterized below:

$[\alpha]_D^{23} = -97.3^\circ$ (c = 1.0, CHCl$_3$).
\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.46 - 7.41 (m, 2 H), 7.40 - 7.34 (m, 4 H), 7.34 - 7.27 (m, 4 H), 7.26 - 7.21 (m, 3 H), 6.89 (d, \(J = 8.6\) Hz, 2 H), 5.57 (d, \(J = 5.3\) Hz, 1 H), 4.82 (dd, \(J = 1.7, 9.5\) Hz, 1 H), 4.77 (d, \(J = 11.4\) Hz, 1 H), 4.68 (d, \(J = 11.4\) Hz, 1 H), 4.57 (d, \(J = 11.0\) Hz, 1 H), 4.47 (d, \(J = 11.2\) Hz, 1 H), 4.20 - 4.12 (m, 1 H), 3.87 - 3.82 (m, 1 H), 3.81 (s, 3 H), 3.62 (t, \(J = 12.4\) Hz, 1 H), 3.38 (t, \(J = 9.2\) Hz, 1 H), 3.27 (qd, \(J = 6.2, 9.2\) Hz, 1 H), 2.97 (t, \(J = 8.9\) Hz, 1 H), 2.42 (dd, \(J = 4.8, 13.0\) Hz, 1 H), 2.16 (ddd, \(J = 1.7, 5.0, 12.3\) Hz, 1 H), 2.09 (br. s., 1 H), 2.01 (ddd, \(J = 5.6, 11.9, 13.2\) Hz, 1 H), 1.59 - 1.52 (m, 1 H), 1.33 (d, \(J = 6.2\) Hz, 3 H), 1.30 (d, \(J = 6.2\) Hz, 3 H), 1.28 - 1.23 (m, 1 H), 0.94 - 0.81 (m, 1 H)

\(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 159.7, 138.5, 135.5, 131.6, 130.6, 129.7, 129.3, 129.0, 129.0, 128.5, 128.3, 127.4, 114.3, 100.5, 86.4, 84.1, 81.9, 77.6, 77.6, 77.1, 75.5, 71.8, 71.6, 71.3, 68.4, 55.6, 39.4, 36.7, 18.6, 18.3

FT-IR (thin film): 3435, 2957, 2067, 1730, 1638, 1513, 1247, 1068, 821, 736 cm\(^{-1}\).

ESIHRMS [M+Na]\(^+\) calculated for C\(_{33}\)H\(_{40}\)O\(_7\)NaS 603.2392, found 603.2392.

2-Deoxy \(\beta\)-glycoside 10 was prepared following the general procedure described for preparation of 8. The crude reaction mixture was purified by preparative thin layer chromatography (hexanes: EtOAc = 2:1 with 2% MeOH) to furnish 72% yield of 2-deoxy \(\beta\)-glycoside 10 which is characterized below:
$[\alpha]D^{22} = 192.6^\circ$ ($c = 0.4$, CHCl$_3$).

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.40 - 7.34 (m, 4 H), 7.34 - 7.30 (m, 1 H), 7.30 - 7.27 (m, 2 H), 6.87 - 6.83 (m, 2 H), 4.80 - 4.76 (m, 1 H), 4.75 (dd, $J = 2.0$, 9.5 Hz, 1 H), 4.72 - 4.66 (m, 3 H), 4.53 (d, $J = 11.0$ Hz, 1 H), 3.85 (ddd, $J = 5.2$, 8.6, 11.3 Hz, 1 H), 3.81 - 3.78 (m, 3 H), 3.71 - 3.61 (m, 2 H), 3.31 - 3.24 (m, 5 H), 2.99 (t, $J = 8.9$ Hz, 1 H), 2.23 (ddd, $J = 2.0$, 5.0, 12.5 Hz, 1 H), 2.21 - 2.17 (m, 1 H), 2.10 (br. s., 1 H), 1.65 (ddd, $J = 3.7$, 11.4, 13.2 Hz, 1 H), 1.62 - 1.60 (m, 1 H), 1.36 (d, $J = 6.2$ Hz, 3 H), 1.32 - 1.28 (m, 1 H), 1.27 (d, $J = 6.4$ Hz, 3 H), 1.25 (br. s., 1 H)

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 159.0, 138.2, 131.2, 129.1, 128.7, 128.2, 128.0, 127.9, 113.7, 100.3, 98.2, 86.0, 83.2, 77.3, 77.0, 76.8, 75.5, 75.2, 71.8, 71.5, 71.1, 66.7, 55.3, 54.5, 39.1, 35.8, 18.5, 18.3

FT-IR (thin film): 3428, 2933, 2094, 1639, 1514, 1365, 1247, 1099, 1063, 695 cm$^{-1}$.

ESIHRMS [M+Na]$^+$ calculated for C$_{28}$H$_{38}$O$_8$Na 525.2464, found 525.2440.

2-Deoxy β-glycoside 11 was prepared following the general procedure described for preparation of 8. The crude reaction mixture was purified by preparative thin layer chromatography (toluene:EtOAc = 5:1) to furnish 88% yield of 2-deoxy β-glycoside 11 which is characterized below:

$[\alpha]D^{22} = 32.6^\circ$ ($c = 1.0$, CHCl$_3$).
**1H NMR (600 MHz, CDCl₃)** δ 7.56 - 7.48 (m, 4 H), 7.40 - 7.26 (m, 16 H), 7.26 - 7.23 (m, 1 H), 4.98 (d, J = 10.1 Hz, 1 H), 4.86 (dd, J = 1.8, 9.7 Hz, 1 H), 4.78 - 4.73 (m, 1 H), 4.71 (s, 1 H), 4.70 (s, 2 H), 4.69 - 4.65 (m, 1 H), 4.63 (d, J = 9.9 Hz, 1 H), 3.91 (t, J = 8.9 Hz, 1 H), 3.52 (ddd, J = 5.0, 8.6, 11.8 Hz, 1 H), 3.42 - 3.35 (m, 2 H), 3.25 - 3.17 (m, 2 H), 2.95 (t, J = 9.0 Hz, 1 H), 2.15 (ddd, J = 1.8, 5.0, 12.4 Hz, 1 H), 2.04 (d, J = 10.5 Hz, 1 H), 1.62 - 1.54 (m, 2 H), 1.35 (d, J = 6.1 Hz, 3 H), 1.30 - 1.24 (m, 4 H)

**13C NMR (150 MHz, CDCl₃)** δ 138.8, 138.4, 138.0, 134.0, 132.4, 129.1, 129.1, 129.0, 128.7, 128.5, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 100.7, 87.4, 86.5, 84.4, 83.7, 79.9, 77.6, 77.1, 75.9, 75.7, 75.6, 75.4, 71.6, 71.4, 39.9, 18.7, 18.5

FT-IR (thin film): 3435, 2912, 2079, 1730, 1642, 1454, 1265, 1065, 736, 699 cm⁻¹.


2-Deoxy β-glycoside 12 was prepared following the general procedure described for preparation of 8 except the use of 2 equiv. of NaH. The crude reaction mixture was purified by preparative thin layer chromatography (toluene:EtOAc = 10:1) to furnish 65% yield of 2-deoxy β-glycoside 12 which is characterized below:

[α]D²³ = 241.4° (c = 1.0, CHCl₃).

**1H NMR (600 MHz, CDCl₃)** δ 7.45 - 7.42 (m, 2 H), 7.40 - 7.34 (m, 7 H), 7.34 - 7.27 (m, 7 H), 7.25 - 7.22 (m, 1 H), 5.57 (d, J = 5.3 Hz, 1 H), 4.85 (d, J = 11.7 Hz, 1 H),
$^1$H NMR (600 MHz, CDCl$_3$) δ 7.45 - 7.41 (m, 2 H), 7.39 - 7.36 (m, 2 H), 7.36 - 7.32 (m, 2 H), 7.31 - 7.26 (m, 6 H), 7.25 - 7.21 (m, 1 H), 6.92 - 6.88 (m, 2 H), 5.56 (dd, $J = 1.9$, 5.6 Hz, 1 H), 4.79 (d, $J = 11.6$ Hz, 1 H), 4.74 (dd, $J = 2.1$, 9.6 Hz, 1 H), 4.71 (d, $J = 11.2$ Hz, 1 H), 4.64 (d, $J = 11.6$ Hz, 1 H), 4.58 (d, $J = 11.2$ Hz, 1 H), 4.24 - 4.17 (m, 1 H), 4.70 (dd, $J = 1.8$, 9.7 Hz, 1 H), 4.67 - 4.63 (m, 1 H), 4.61 (d, $J = 11.7$ Hz, 1 H), 4.58 - 4.55 (m, 1 H), 4.20 - 4.14 (m, 1 H), 3.87 (ddd, $J = 5.0$, 8.8, 11.7 Hz, 1 H), 3.61 - 3.54 (m, 1 H), 3.43 - 3.38 (m, 2 H), 3.37 (d, $J = 3.5$ Hz, 1 H), 2.44 (ddd, $J = 0.8$, 4.9, 13.3 Hz, 1 H), 2.06 - 1.99 (m, 1 H), 1.96 (ddd, $J = 1.5$, 4.8, 11.7 Hz, 1 H), 1.89 (d, $J = 10.8$ Hz, 1 H), 1.67 - 1.60 (m, 1 H), 1.59 (s, 1 H), 1.34 (d, $J = 6.2$ Hz, 3 H), 1.28 (d, $J = 6.6$ Hz, 3 H)

$^{13}$C NMR (150 MHz, CDCl$_3$) δ 138.4, 138.2, 135.2, 131.2, 131.2, 129.0, 128.9, 128.7, 128.6, 128.5, 128.0, 128.0, 127.9, 127.8, 127.1, 100.9, 83.8, 81.9, 78.6, 77.7, 77.3, 77.0, 76.8, 75.8, 71.9, 70.7, 69.3, 68.2, 36.4, 36.4, 18.1, 17.2

FT-IR (thin film): 3435, 2094, 1640, 1265, 1095, 1063, 907, 732, 701, 464 cm$^{-1}$.

ESIHRMS [M+Na]$^+$ calculated for C$_{32}$H$_{58}$O$_6$NaS 573.2287, found 573.2297.

2-Deoxy β-glycoside 13 was prepared following the general procedure described for preparation of 8. The crude reaction mixture was purified by preparative thin layer chromatography (toluene:EtOAc = 5:1 with 0.5% MeOH) to furnish 87% yield of 2-deoxy β-glycoside 13 which is characterized below:

[$\alpha$]$_D$$^{23}$ = 196.2° (c = 1.0, CHCl$_3$).

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.45 - 7.41 (m, 2 H), 7.39 - 7.36 (m, 2 H), 7.36 - 7.32 (m, 2 H), 7.31 - 7.26 (m, 6 H), 7.25 - 7.21 (m, 1 H), 6.92 - 6.88 (m, 2 H), 5.56 (dd, $J = 1.9$, 5.6 Hz, 1 H), 4.79 (d, $J = 11.6$ Hz, 1 H), 4.74 (dd, $J = 2.1$, 9.6 Hz, 1 H), 4.71 (d, $J = 11.2$ Hz, 1 H), 4.64 (d, $J = 11.6$ Hz, 1 H), 4.58 (d, $J = 11.2$ Hz, 1 H), 4.24 - 4.17 (m, 1 H), 4.70 (dd, $J = 1.8$, 9.7 Hz, 1 H), 4.67 - 4.63 (m, 1 H), 4.61 (d, $J = 11.7$ Hz, 1 H), 4.58 - 4.55 (m, 1 H), 4.20 - 4.14 (m, 1 H), 3.87 (ddd, $J = 5.0$, 8.8, 11.7 Hz, 1 H), 3.61 - 3.54 (m, 1 H), 3.43 - 3.38 (m, 2 H), 3.37 (d, $J = 3.5$ Hz, 1 H), 2.44 (ddd, $J = 0.8$, 4.9, 13.3 Hz, 1 H), 2.06 - 1.99 (m, 1 H), 1.96 (ddd, $J = 1.5$, 4.8, 11.7 Hz, 1 H), 1.89 (d, $J = 10.8$ Hz, 1 H), 1.67 - 1.60 (m, 1 H), 1.59 (s, 1 H), 1.34 (d, $J = 6.2$ Hz, 3 H), 1.28 (d, $J = 6.6$ Hz, 3 H)
3.89 (dd, J = 4.8, 8.1, 11.0 Hz, 1 H), 3.81 (s, 3 H), 3.63 (dd, J = 5.1, 8.7, 11.8 Hz, 1 H), 3.33 (dd, J = 8.3, 9.2 Hz, 1 H), 3.26 (qd, J = 6.2, 9.2 Hz, 1 H), 2.96 (t, J = 9.0 Hz, 1 H), 2.38 (dd, J = 2.0, 4.8, 13.7 Hz, 1 H), 2.24 (dd, J = 2.1, 5.0, 12.5 Hz, 1 H), 2.09 (dd, J = 5.7, 11.0, 13.6 Hz, 1 H), 1.60 (dt, J = 9.7, 12.2 Hz, 2 H), 1.32 (d, J = 6.1 Hz, 3 H), 1.31 - 1.29 (m, 1 H), 1.27 (d, J = 6.4 Hz, 3 H)

$^{13}$C NMR (150 MHz, CDCl$_3$) δ 159.9, 139.1, 135.5, 131.5, 131.5, 130.6, 130.0, 129.2, 128.6, 127.9, 127.4, 114.5, 100.7, 85.9, 83.8, 83.7, 77.6, 77.1, 76.5, 75.2, 72.5, 71.9, 71.3, 68.3, 55.6, 39.4, 36.6, 18.7, 18.5

FT-IR (thin film): 3435, 2090, 1642, 1514, 1365, 1248, 1216, 1067, 1028, 749 cm$^{-1}$.

ESIHRMS [M+Na]$^+$ calculated for C$_{33}$H$_{40}$O$_7$NaS 603.2392, found 603.2399.

2-Deoxy β-glycoside 14 was prepared following the general procedure described for preparation of 8 except the use of 2 equiv. of NaH. The crude reaction mixture was purified by preparative thin layer chromatography (toluene:EtOAc = 5:1) to furnish 59% yield of 2-deoxy β-glycoside 14 which is characterized below:

$[\alpha]_D^{23} = 123.1^\circ$ (c = 1.0, CHCl$_3$).

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.45 - 7.42 (m, 2 H), 7.42 - 7.37 (m, 2 H), 7.34 - 7.26 (m, 7 H), 7.25 - 7.20 (m, 1 H), 6.89 - 6.86 (m, 2 H), 5.56 (dd, J = 2.0, 5.7 Hz, 1 H), 4.82 (d, J = 11.4 Hz, 1 H), 4.79 (d, J = 11.4 Hz, 1 H), 4.66 - 4.61 (m, 2 H), 4.53 (d, J =
11.4 Hz, 1 H), 4.20 (qd, J = 6.2, 9.1 Hz, 1 H), 3.92 (dd, J = 4.8, 7.8, 10.7 Hz, 1 H), 3.81 - 3.78 (m, 3 H), 3.66 - 3.58 (m, 1 H), 3.40 - 3.32 (m, 3 H), 2.37 (dd, J = 2.2, 4.8, 13.6 Hz, 1 H), 2.09 (dd, J = 5.7, 10.8, 13.6 Hz, 1 H), 1.99 (dd, J = 1.7, 4.5, 12.0 Hz, 1 H), 1.96 - 1.88 (m, 1 H), 1.68 (dt, J = 9.9, 12.1 Hz, 1 H), 1.28 (dd, J = 3.2, 6.3 Hz, 6 H)

\(^1\text{H} \text{NMR (500 MHz, CDCl}_3\text{)} \delta 7.57 - 7.53 (m, 2 H), 7.45 - 7.41 (m, 2 H), 7.41 - 7.27 (m, 14 H), 6.94 - 6.89 (m, 2 H), 5.10 (d, J = 10.5 Hz, 1 H), 5.02 (d, J = 10.1 Hz, 1 H), 4.89 (dd, J = 1.7, 9.6 Hz, 1 H), 4.70 (d, J = 11.0 Hz, 1 H), 4.63 (d, J = 9.9 Hz, 1 H), 4.61 - 4.55 (m, 3 H), 3.97 (t, J = 9.0 Hz, 1 H), 3.81 (s, 3 H), 3.53 - 3.46 (m, 2 H), 3.45 - 3.38 (m,

\[^{13}\text{C NMR (150 MHz, CDCl}_3\text{)} \delta 159.7, 139.2, 135.5, 131.4, 130.8, 129.9, 129.2, 128.6, 127.9, 127.7, 127.3, 114.3, 101.1, 83.7, 83.4, 78.6, 77.6, 77.1, 76.6, 75.9, 72.5, 71.4, 69.3, 68.3, 55.6, 36.7, 36.5, 18.5, 17.7

\text{FT-IR (thin film):} 3435, 2952, 2090, 1642, 1514, 1454, 1248, 1065, 738, 698 cm\(^{-1}\).

\text{ESIHRMS [M+Na]}^+ \text{calculated for C}_{33}\text{H}_{40}\text{O}_{7}\text{NaS} 603.2392, \text{found 603.2392.}

2-Deoxy β-glycoside 15 was prepared following the general procedure described for preparation of 8. The crude reaction mixture was purified by preparative thin layer chromatography (toluene:EtOAc = 5:1) to furnish 90% yield of 2-deoxy β-glycoside 15 which is characterized below:

\[^{[\alpha]}\text{D}_{23} = 2.1^\circ\ (c = 1.0, \text{CHCl}_3).\]

\(^1\text{H NMR (600 MHz, CDCl}_3\text{)} \delta 7.57 - 7.53 (m, 2 H), 7.45 - 7.41 (m, 2 H), 7.41 - 7.27 (m, 14 H), 6.94 - 6.89 (m, 2 H), 5.10 (d, J = 10.5 Hz, 1 H), 5.02 (d, J = 10.1 Hz, 1 H), 4.89 (dd, J = 1.7, 9.6 Hz, 1 H), 4.70 (d, J = 11.0 Hz, 1 H), 4.63 (d, J = 9.9 Hz, 1 H), 4.61 - 4.55 (m, 3 H), 3.97 (t, J = 9.0 Hz, 1 H), 3.81 (s, 3 H), 3.53 - 3.46 (m, 2 H), 3.45 - 3.38 (m,
1H), 3.24 - 3.18 (m, 1 H), 3.16 (t, J = 9.2 Hz, 1 H), 2.93 (t, J = 8.9 Hz, 1 H), 2.14 (ddd, J = 1.7, 5.0, 12.3 Hz, 1 H), 1.59 (dt, J = 9.8, 12.1 Hz, 1 H), 1.35 (d, J = 6.1 Hz, 3 H), 1.30 (d, J = 6.1 Hz, 3 H), 1.29 - 1.23 (m, 1 H)

13C NMR (150 MHz, CDCl3) δ 159.8, 138.8, 138.0, 134.2, 132.0, 130.5, 130.0, 129.3, 128.9, 128.8, 128.7, 128.5, 128.4, 128.0, 127.8, 114.4, 100.3, 87.7, 86.1, 83.4, 82.1, 81.8, 77.6, 77.1, 75.8, 75.7, 75.3, 75.2, 71.5, 71.4, 55.6, 39.8, 18.6, 18.6

FT-IR (thin film): 3435, 2090, 1643, 1513, 1453, 1248, 1216, 1064, 1028, 748 cm⁻¹.

ESIHRMS [M+Na]+ calculated for C₄₀H₄₆O₈NaS 709.2811, found 709.2820.

2-Deoxy β-glycoside 16 was prepared following the general procedure described for preparation of 8. The crude reaction mixture was purified by preparative thin layer chromatography (toluene:EtOAc = 5:1) to furnish 96% yield of 2-deoxy β-glycoside 16 which is characterized below:

[α]D²³ = 5.1° (c = 1.0, CHCl₃).

1H NMR (600 MHz, CDCl3) δ 7.36 - 7.32 (m, 2 H), 7.32 - 7.27 (m, 3 H), 6.93 - 6.89 (m, 2 H), 6.87 - 6.84 (m, 2 H), 4.95 (d, J = 10.5 Hz, 1 H), 4.87 - 4.82 (m, 2 H), 4.73 (d, J = 11.2 Hz, 1 H), 4.64 - 4.58 (m, 3 H), 4.51 (d, J = 10.3 Hz, 1 H), 4.13 (dd, J = 5.7, 7.3 Hz, 1 H), 4.07 (d, J = 5.5 Hz, 1 H), 4.02 (ddd, J = 5.1, 8.5, 11.6 Hz, 1 H), 3.82 - 3.80 (m, 4 H), 3.80 (s, 3 H), 3.71 - 3.65 (m, 1 H), 3.65 - 3.60 (m, 2 H), 3.60 - 3.54 (m, 2 H), 3.35 (s,
3 H), 3.34 - 3.30 (m, 1 H), 3.29 - 3.24 (m, 1 H), 3.05 - 2.96 (m, 2 H), 2.26 (ddd, J = 1.3, 5.1, 12.1 Hz, 1 H), 2.14 (ddd, J = 1.8, 5.0, 12.5 Hz, 1 H), 2.11 (br. s., 1 H), 1.69 - 1.56 (m, 4 H), 1.48 (s, 3 H), 1.44 (dt, J = 10.1, 11.9 Hz, 1 H), 1.40 - 1.37 (m, 3 H), 1.35 - 1.32 (m, 3 H), 1.26 (d, J = 6.1 Hz, 7 H)

\(^{13}\text{C NMR (150 MHz, CDCl}_3\) \(\delta\): 159.9, 159.5, 131.3, 130.6, 130.4, 130.0, 129.0, 114.5, 114.3, 113.9, 109.6, 98.2, 98.1, 96.2, 86.1, 82.0, 78.9, 77.7, 77.6, 77.1, 76.8, 76.4, 75.2, 74.5, 71.7, 71.5, 65.4, 64.6, 55.6, 55.1, 39.8, 36.9, 28.1, 26.8, 18.8, 18.6, 17.8

**FT-IR (thin film):** 3436, 2934, 2065, 1732, 1613, 1514, 1371, 1087, 756, 476 cm\(^{-1}\).

**ESIHRMS [M+Na]**\(^+\) calculated for C\(_{38}\)H\(_{54}\)O\(_{13}\)Na 741.3462, found 741.3485.

![Structure](image)

2-Deoxy \(\beta\)-glycoside 17 was prepared following the general procedure described for preparation of 8 except the use of 2 equiv. of NaH. The crude reaction mixture was purified by preparative thin layer chromatography (hexanes:EtOAc = 10:1) to furnish 83\% yield of 2-deoxy \(\beta\)-glycoside 17 which is characterized below:

\([\alpha]_D^{23} = 145.0^\circ\) (c = 1.0, CHCl\(_3\)).

\(^1\text{H NMR (600 MHz, CDCl}_3\) \(\delta\): 7.46 - 7.42 (m, 2 H), 7.39 - 7.35 (m, 3 H), 7.35 - 7.31 (m, 6 H), 7.31 - 7.27 (m, 4 H), 7.25 - 7.21 (m, 1 H), 5.58 (d, J = 5.1 Hz, 1 H), 4.81 (dd, J = 1.9, 9.4 Hz, 1 H), 4.66 (d, J = 11.4 Hz, 1 H), 4.62 (d, J = 11.7 Hz, 1 H), 4.56 (d, J = 11.4 Hz, 1 H), 4.47 (d, J = 11.6 Hz, 1 H), 4.16 (qd, J = 6.2, 9.4 Hz, 1 H), 3.86 (ddd, J =
4.9, 8.8, 11.7 Hz, 1 H), 3.43 (t, J = 9.2 Hz, 1 H), 3.37 (qd, J = 6.1, 8.9 Hz, 1 H), 3.04 (ddd, J = 4.5, 9.0, 10.5 Hz, 1 H), 2.48 - 2.41 (m, 1 H), 2.22 - 2.15 (m, 1 H), 2.04 (ddd, J = 5.7, 11.8, 13.3 Hz, 1 H), 1.91 - 1.85 (m, 1 H), 1.48 (ddt, J = 4.0, 9.4, 13.4 Hz, 1 H), 1.39 (ddd, J = 4.1, 10.6, 12.6 Hz, 1 H), 1.30 (d, J = 6.2 Hz, 3 H), 1.28 (d, J = 6.2 Hz, 3 H)

\[^{13}\text{C NMR (150 MHz, CDCl}_3\] δ 138.4, 138.3, 135.2, 131.2, 128.9, 128.5, 128.4, 127.8, 127.7, 127.6, 127.1, 102.3, 83.8, 81.4, 78.5, 77.7, 77.3, 77.1, 76.8, 74.5, 71.8, 71.3, 68.2, 36.4, 30.7, 27.8, 18.4, 18.0

FT-IR (thin film): 3943, 3435, 3056, 2873, 2092, 1642, 1265, 1068, 746, 477 cm\(^{-1}\).

ESIHRMS [M+Na]\(^+\) calculated for C\(_{32}\)H\(_{38}\)O\(_5\)NaS 557.2338, found 557.2341.

2-Deoxy β-glycoside 18 was prepared following the general procedure described for preparation of 8 except the use of 2 equiv. of NaH. The crude reaction mixture was purified by preparative thin layer chromatography (hexanes:EtOAc = 10:1) to furnish 75% yield of 2-deoxy β-glycoside 18 which is characterized below:

\([\alpha]_D^{23} = 72.4^\circ \ (c = 1.0, \text{CHCl}_3)\).

\[^1\text{H NMR (600 MHz, CDCl}_3\] δ 7.45 - 7.42 (m, 2 H), 7.38 - 7.32 (m, 5 H), 7.32 - 7.27 (m, 4 H), 7.25 - 7.21 (m, 1 H), 5.57 (d, J = 5.3 Hz, 1 H), 4.79 (dd, J = 1.9, 9.3 Hz, 1 H), 4.65 (d, J = 11.6 Hz, 1 H), 4.57 (d, J = 11.6 Hz, 1 H), 4.18 - 4.12 (m, 1 H), 3.85 (ddd, J = 4.9, 8.8, 11.7 Hz, 1 H), 3.42 (d, J = 9.4 Hz, 1 H), 3.39 (td, J = 4.3, 10.2 Hz, 1 H), 3.27 - 3.20 (m, 1 H), 2.43 (ddd, J = 1.1, 4.8, 13.3 Hz, 1 H), 2.07 - 1.97 (m, 2 H), 1.87 - 1.81 (m,
1H, 1.54 - 1.35 (m, 4 H), 1.31 (d, J = 6.2 Hz, 3 H), 1.25 (d, J = 6.2 Hz, 5 H), 1.06 (s, 25 H)

13C NMR (150 MHz, CDCl3) δ 138.7, 135.6, 131.6, 129.2, 128.8, 128.1, 128.0, 127.4, 102.7, 84.2, 81.9, 78.0, 77.6, 77.1, 76.7, 73.0, 72.1, 68.6, 36.7, 32.5, 31.4, 18.9, 18.5, 18.5, 18.3, 13.0

FT-IR (thin film): 3434, 2945, 2866, 2067, 1731, 1642, 1455, 1067, 737, 456 cm⁻¹


2-Deoxy β-glycoside 19 was prepared following the general procedure described for preparation of 8 except the use of 2 equiv. of NaH. The crude reaction mixture was purified by preparative thin layer chromatography (toluene:EtOAc = 10:1) to furnish 75% yield of 2-deoxy β-glycoside 19 which is characterized below:

[α]D22 = -110.0° (c = 1.0, CHCl3).

1H NMR (600 MHz, CDCl3) δ 7.47 - 7.42 (m, 2 H), 7.40 - 7.36 (m, 2 H), 7.36 - 7.31 (m, 5 H), 7.31 - 7.26 (m, 4 H), 7.25 - 7.20 (m, 1 H), 6.85 - 6.82 (m, 2 H), 5.55 (dd, J = 2.7, 5.6 Hz, 1 H), 5.29 (s, 4 H), 4.78 (d, J = 11.0 Hz, 1 H), 4.72 - 4.67 (m, 2 H), 4.58 - 4.54 (m, 1 H), 4.46 - 4.41 (m, 1 H), 4.20 (qd, J = 6.2, 9.0 Hz, 1 H), 3.93 (ddd, J = 4.7, 7.5, 10.4 Hz, 1 H), 3.82 - 3.80 (m, 1 H), 3.79 - 3.76 (m, 3 H), 3.55 (dq, J = 1.3, 6.4 Hz, 1 H), 3.38 (dd, J = 7.7, 9.0 Hz, 1 H), 3.19 - 3.15 (m, 1 H), 2.35 - 2.29 (m, 1 H), 2.15 (qd, J = 3.2,
14.2 Hz, 1 H), 2.09 (ddd, $J = 5.8, 10.4, 13.7$ Hz, 1 H), 1.81 (ddt, $J = 4.0, 9.7, 13.4$ Hz, 1 H), 1.68 - 1.65 (m, 1 H), 1.65 - 1.62 (m, 1 H), 1.47 (ddt, $J = 2.7, 4.1, 14.1$ Hz, 1 H), 1.29 (d, $J = 6.2$ Hz, 3 H), 1.26 (d, $J = 6.4$ Hz, 3 H)

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 159.1, 138.8, 135.4, 131.1, 131.1, 129.5, 129.2, 128.9, 128.3, 128.3, 127.9, 127.7, 127.5, 126.9, 113.6, 102.8, 83.3, 82.5, 77.3, 77.1, 76.9, 76.1, 74.1, 72.5, 72.0, 70.8, 68.2, 55.3, 53.5, 36.0, 26.1, 25.5, 18.3, 17.6

FT-IR (thin film): 3435, 2088, 1642, 1513, 1247, 1079, 1027, 739, 692, 465 cm$^{-1}$.

ESIHRMS [M+Na]$^+$ calculated for C$_{33}$H$_{40}$O$_6$NaS 587.2443, found 587.2457.

2-Deoxy β-glycoside 20 was prepared following the general procedure described for preparation of 8. The crude reaction mixture was purified by preparative thin layer chromatography (toluene:EtOAc = 4:1) to furnish 70% yield of 2-deoxy β-glycoside 20 which is characterized below:

$[\alpha]_D^{23} = 91.8^\circ$ (c = 1.0, CHCl$_3$).

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.45 - 7.41 (m, 2 H), 7.39 - 7.32 (m, 4 H), 7.31 - 7.27 (m, 3 H), 7.25 - 7.21 (m, 1 H), 5.56 (dd, $J = 1.7, 5.6$ Hz, 1 H), 4.75 (d, $J = 11.4$ Hz, 1 H), 4.70 - 4.66 (m, 1 H), 4.66 - 4.62 (m, 1 H), 4.22 (qd, $J = 6.2, 9.2$ Hz, 1 H), 3.89 (ddd, $J = 4.9, 8.1, 11.1$ Hz, 1 H), 3.58 (ddd, $J = 5.0, 9.3, 11.7$ Hz, 1 H), 3.36 - 3.31 (m, 1 H), 3.13 (qd, $J = 6.1, 9.7$ Hz, 1 H), 2.94 - 2.88 (m, 1 H), 2.40 (ddd, $J = 1.9, 4.9, 13.6$ Hz, 1 H), 2.27
(ddd, \( J = 2.0, 5.0, 12.7 \) Hz, 1 H), 2.18 (br. s., 1 H), 2.12 - 2.04 (m, 1 H), 1.63 (dt, \( J = 9.7, 12.2 \) Hz, 1 H), 1.31 (d, \( J = 6.2 \) Hz, 3 H), 1.27 (d, \( J = 6.4 \) Hz, 3 H)

\(^{13}\text{C NMR (150 MHz, CDCl}_3\) \( \delta \) 138.6, 135.1, 131.1, 128.9, 128.3, 127.6, 127.5, 127.1, 100.1, 83.5, 83.5, 77.2, 77.0, 76.8, 75.9, 72.0, 71.0, 70.5, 70.2, 67.9, 39.4, 36.2, 18.6, 18.1

\textbf{FT-IR (thin film)}: 3435, 2104, 1642, 1454, 1366, 1266, 1067, 1027, 975, 738 cm\(^{-1}\).

\textbf{ESIHRMS [M+Na]\(^+\) calculated for C\(_{25}\)H\(_{31}\)N\(_{3}\)O\(_{5}\)NaS 508.1882, found 508.1859.

\[
\begin{array}{cc}
\text{N}_3 & \text{Me} \\
\text{HO} & \text{PMBO} \\
\text{O} & \text{Me} \\
\text{O} & \text{Me} \\
\text{OMe} & \text{Me}
\end{array}
\]

2-Deoxy \( \beta \)-glycoside 21 was prepared following the general procedure described for preparation of 8. The crude reaction mixture was purified by preparative thin layer chromatography (toluene:EtOAc = 5:1 with 1% MeOH) to furnish 96% yield of 2-deoxy \( \beta \)-glycoside 21 which is characterized below:

\[\{\alpha\}^D_{23} = -27.4^\circ \ (c = 1.0, \text{CHCl}_3).\]

\(^1\text{H NMR (600 MHz, CDCl}_3\) \( \delta \) 7.34 - 7.30 (m, 2 H), 6.87 - 6.83 (m, 2 H), 4.92 (d, \( J = 10.3 \) Hz, 1 H), 4.87 - 4.82 (m, 2 H), 4.58 - 4.53 (m, 1 H), 4.50 (d, \( J = 10.5 \) Hz, 1 H), 4.13 (dd, \( J = 5.6, 7.2 \) Hz, 1 H), 4.07 (d, \( J = 5.7 \) Hz, 1 H), 4.02 (ddd, \( J = 5.2, 8.6, 11.7 \) Hz, 1 H), 3.80 (s, 3 H), 3.66 - 3.54 (m, 4 H), 3.35 (s, 3 H), 3.30 - 3.24 (m, 1 H), 3.24 - 3.19 (m, 1 H), 3.03 (t, \( J = 8.9 \) Hz, 1 H), 2.94 (t, \( J = 9.4 \) Hz, 1 H), 2.37 (br. s., 1 H), 2.25 (ddd, \( J = 18.6, 18.1, 18.0 \) Hz, 3 H), 1.31 (d, \( J = 6.2 \) Hz, 3 H), 1.27 (d, \( J = 6.4 \) Hz, 3 H)
1.5, 5.3, 12.2 Hz, 1 H), 2.20 - 2.14 (m, 1 H), 1.64 (dt, $J = 9.9, 12.1$ Hz, 1 H), 1.48 (s, 3 H), 1.47 - 1.41 (m, 1 H), 1.39 (d, $J = 6.2$ Hz, 3 H), 1.33 (s, 3 H), 1.27 (d, $J = 3.5$ Hz, 3 H), 1.26 (d, $J = 3.5$ Hz, 3 H)

$^{13}$C NMR (150 MHz, CDCl$_3$) δ 159.5, 131.2, 130.3, 113.9, 109.6, 98.1, 96.0, 82.0, 78.9, 77.7, 77.6, 77.1, 76.9, 76.4, 74.6, 71.5, 71.2, 71.0, 70.7, 64.6, 55.6, 55.1, 40.1, 36.8, 28.1, 26.8, 19.0, 18.5, 17.8

FT-IR (thin film): 3448, 2935, 2106, 1731, 1613, 1514, 1363, 1248, 860, 738 cm$^{-1}$.

ESIHRMS [M+Na]$^+$ calculated for C$_{30}$H$_{45}$N$_3$O$_{11}$Na 646.2952, found 646.2956.

1.4.4 Synthesis of trisaccharide 23 and tetrasaccharide 24

To a solution of alcohol 8 (208 mg, 0.36 mmol) in 1.0 mL $N,N$-dimethylformamide cooled at 0 °C sodium hydride (17 mg, 0.72 mmol) was added. The resulting mixture was stirred at 0 °C for 1 h and benzyl bromide (51 µL, 0.43 mmol) was added. The reaction mixture was warmed up and stirred at ambient temperature overnight. The resulting mixture was diluted with EtOAc (50 mL), washed with water (3×10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude residue was
purified by flash column chromatography (toluene: EtOAc = 80:1) to obtain 197 mg (82% yield) of compound 7. To a solution of glycosyl phenylsulfide 7 (171 mg, 0.25 mmol) in 3.75 mL acetone and 0.25 mL water cooled at 0 °C N-bromosuccinimide (68.0 mg, 0.38 mmol) was added. The resulting mixture was stirred at 0 °C for 30 min. Saturated sodium bicarbonate (2.0 mL) was added and acetone was removed under reduced pressure. The remaining aqueous mixture was extracted with ethyl acetate (3×20 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude residue was purified by flash column chromatography (toluene:EtOAc = 10:1) to furnish 136 mg (94% yield) of lactol S38 as a mixture of anomers. To a solution of lactol S40 (143 mg, 0.24 mmol) in 2.5 mL dichloromethane and 0.4 mL pH 7.0 buffer 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (112 mg, 0.49 mmol) was added. The reaction mixture was stirred at ambient temperature for 4 h. Saturated sodium bicarbonate (2 mL) was added and the remaining mixture was extracted with dichloromethane (3×20 mL). The combined extracts were washed with brine (2 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude residue was purified by flash column chromatography (hexanes:EtOAc = 3:1) to furnish 100 mg (89% yield) of lactol 22 as a mixture of anomers (α/β = 1.9/1) which is characterized below:

\[ \alpha \text{D}_{23}^2 = 29.2^\circ \text{ (c = 1.0, CHCl}_3). \]

\(^1\text{H NMR (600 MHz, CDCl}_3) \delta 7.37 - 7.32 (m, 11 H), 7.32 - 7.27 (m, 4 H), 5.32 - 5.28 (m, 1 H), 4.94 (d, \text{J} = 10.8 \text{ Hz, 2 H}), 4.83 - 4.79 (m, 1 H), 4.78 - 4.73 (m, 2 H), 4.70 - 4.67 (m, 2 H), 4.66 (d, \text{J} = 11.0 \text{ Hz, 2 H}), 4.64 - 4.60 (m, 2 H), 4.11 - 4.04 (m, 1 H), 3.95 (qd, \text{J} = 6.2, 9.7 \text{ Hz, 1 H}), 3.72 - 3.66 (m, 1 H), 3.66 - 3.59 (m, 2 H), 3.42 - 3.34 (m, 2 H), 3.05 - 2.93 (m, 2 H), 2.57 - 2.44 (m, 1 H), 1.98 - 1.76 (m, 2 H), 1.65 - 1.46 (m, 4 H), 1.41 - 1.20 (m, 2 H), 0.95 - 0.75 (m, 2 H). \]
3.30 (br. s., 1 H), 3.28 - 3.23 (m, 2 H), 3.23 (br. s., 1 H), 3.16 - 3.10 (m, 2 H), 2.94 (br. s., 1 H), 2.75 (s, 3 H), 2.33 - 2.25 (m, 2 H), 2.22 - 2.15 (m, 1 H), 1.75 (br. s., 2 H), 1.73 - 1.67 (m, 2 H), 1.67 - 1.63 (m, 1 H), 1.55 (dt, J = 9.7, 12.1 Hz, 1 H), 1.34 - 1.29 (m, 6 H), 1.26 (d, J = 6.2 Hz, 4 H)

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 177.6, 138.3, 138.3, 138.3, 138.2, 128.5, 128.4, 128.1, 127.8, 127.8, 127.8, 127.7, 98.3, 97.9, 93.9, 91.8, 83.4, 83.3, 83.3, 81.9, 79.3, 79.3, 77.3, 77.1, 76.8, 75.3, 75.3, 71.8, 71.7, 71.6, 71.6, 70.7, 70.2, 67.0, 66.1, 40.4, 37.7, 36.7, 36.4, 29.6, 18.1

FT-IR (thin film): 3413, 2091, 1638, 1497, 1453, 1364, 1265, 696 cm$^{-1}$.

ESIHRMS [M+Na]$^+$ calculated for C$_{26}$H$_{34}$O$_7$Na 481.2202, found 481.2202.

2-Deoxy trisaccharide 23 was prepared from lactol 22 and triflate 6d following the general procedure described for preparation of 8. The crude reaction mixture was purified by preparative thin layer chromatography (toluene:EtOAc = 5:1) to furnish 76% yield of 2-deoxy $\beta$-glycoside 23 which is characterized below:

$[\alpha]_D^{23} = 102^\circ$ (c = 1.0, CHCl$_3$).

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.48 - 7.42 (m, 3 H), 7.40 - 7.22 (m, 31 H), 5.56 (dd, J = 1.9, 5.6 Hz, 1 H), 4.94 (d, J = 10.8 Hz, 2 H), 4.79 (d, J = 11.6 Hz, 2 H), 4.74 - 4.62 (m, 10 H), 4.22 (qd, J = 6.2, 9.2 Hz, 2 H), 3.90 (ddd, J = 4.9, 8.0, 11.0 Hz, 2 H), 3.63 (ddd, J = 5.0, 8.6, 11.4 Hz, 4 H), 3.41 - 3.33 (m, 3 H), 3.28 - 3.22 (m, 4 H), 3.13 (t, J = 9.0 Hz,
2.38 (ddd, $J = 1.9, 4.8, 13.6$ Hz, 2 H), 2.30 - 2.23 (m, 3 H), 2.09 (ddd, $J = 5.7, 11.0, 13.6$ Hz, 2 H), 1.73 - 1.56 (m, 7 H), 1.39 (dd, $J = 6.8, 8.3$ Hz, 1 H), 1.34 - 1.17 (m, 20 H).

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 139.1, 138.6, 138.6, 135.5, 131.5, 129.3, 129.2, 128.8, 128.6, 128.4, 128.1, 128.0, 127.9, 127.8, 127.4, 100.6, 98.4, 83.8, 83.7, 83.6, 79.6, 77.6, 77.1, 76.4, 75.6, 72.5, 72.1, 72.0, 70.9, 70.5, 68.3, 39.5, 36.7, 36.6, 30.0, 18.5, 18.5, 18.4

FT-IR (thin film): 3942, 3435, 2932, 2105, 1642, 1454, 1265, 1068, 908, 735 cm$^{-1}$.

ESIHRMS [M+Na]$^+$ calculated for C$_{45}$H$_{54}$O$_9$NaS 793.3386, found 793.3372.

2-Deoxy trisaccharide 24 was prepared from lactol 22 and triflate 6f following the general procedure described for preparation of 8. The crude reaction mixture was purified by preparative thin layer chromatography (toluene:EtOAc = 5:1 with 1% MeOH) to furnish 96% yield of 2-deoxy $\beta$-glycoside 23 which is characterized below:

$[\alpha]_D^{23} = -37.7^\circ$ (c = 1.0, CHCl$_3$).

$^{1}$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.38 - 7.32 (m, 9 H), 7.32 - 7.27 (m, 2 H), 6.88 - 6.83 (m, 2 H), 4.95 (dd, $J = 6.2, 10.6$ Hz, 2 H), 4.88 - 4.83 (m, 2 H), 4.76 (dd, $J = 1.8, 10.1$ Hz, 1 H), 4.71 - 4.62 (m, 3 H), 4.61 (dd, $J = 1.7, 9.6$ Hz, 1 H), 4.51 (d, $J = 10.5$ Hz, 1 H), 4.14 (dd, $J = 5.7, 7.3$ Hz, 1 H), 4.07 (d, $J = 5.5$ Hz, 1 H), 4.03 (ddd, $J = 5.2, 8.6, 11.6$ Hz, 1 H), 3.72 - 3.61 (m, 4 H), 3.61 - 3.55 (m, 2 H), 3.43 - 3.37 (m, 1 H), 3.36 (s, 3 H), 3.33 -
3.29 (m, 1 H), 3.29 - 3.25 (m, 2 H), 3.21 (br. s., 1 H), 3.13 (t, \( J = 9.0 \) Hz, 1 H), 3.03 (t, \( J = 8.9 \) Hz, 1 H), 2.32 - 2.24 (m, 2 H), 2.21 - 2.15 (m, 1 H), 1.76 - 1.68 (m, 1 H), 1.67 - 1.58 (m, 4 H), 1.49 (s, 3 H), 1.48 - 1.41 (m, 1 H), 1.35 - 1.31 (m, 9 H), 1.31 - 1.28 (m, 1 H), 1.28 - 1.25 (m, 7 H)

\(^{13}\text{C NMR} (150 \text{ MHz, CDCl}_3) \delta 159.5, 138.6, 138.6, 131.3, 130.4, 128.8, 128.8, 128.4, 128.1, 128.1, 128.0, 113.9, 109.6, 98.6, 98.2, 98.1, 96.1, 83.6, 82.6, 82.0, 79.7, 78.9, 77.7, 77.6, 77.1, 76.8, 76.4, 75.6, 74.5, 72.1, 72.0, 71.5, 70.8, 70.8, 64.6, 55.6, 55.1, 39.9, 36.9, 36.8, 28.1, 26.8, 18.6, 18.5, 18.4, 17.8

\text{FT-IR (thin film)}: 3435, 2934, 2068, 1613, 1514, 1453, 1371, 1247, 1092, 737 cm\(^{-1}\).

\text{ESIHRMS [M+Na]}^+ \text{ calculated for C}_{50}\text{H}_{68}\text{O}_{15}\text{Na} 931.4456, \text{ found 931.4449.}

1.5 NMR of Selected Compounds

\(^1\text{HNMR} (\text{CDCl}_3, \text{600MHz})\)
Chemical Shift (ppm)

Me
BnO
OH
5h
Chemical Shift (ppm)

S33

Me

HO

OPMB

O

Me

S

H

O

M

P

M

B
Chemical Shift (ppm)

S37
[Image of a chemical structure with labels BnO, Me, SPh, and TfO, along with a spectrum showing chemical shifts (ppm)].
Chemical Shift (ppm)
$^1\text{H} - ^{13}\text{C}$ HSQC Spectrum of

![Chemical Structure](image)

F2 Chemical Shift (ppm)

- 56
- 64
- 72
- 80
- 88
- 96
- 104

F1 Chemical Shift (ppm)

- 5.0
- 4.5
- 4.0
- 3.5
- 3.0
$^1H - ^13C$ HSQC Spectrum of

![Chemical Structure](image)

---

119
$^{1}H - ^{13}C$ HSQC Spectrum of

![Structure](image)

F1 Chemical Shift (ppm)
5.5 5.0 4.5 4.0 3.5 3.0
F2 Chemical Shift (ppm)
56 64 72 80 88 96 104
$^1$H – $^{13}$C HSQC Spectrum of

![Chemical Structure](image)

F1 Chemical Shift (ppm) | F2 Chemical Shift (ppm)
------------------------|------------------------
56                      | 5.5
64                      | 5.0
72                      | 4.5
80                      | 4.0
88                      | 3.5
96                      | 3.0
$^1H - ^13C$ HSQC Spectrum of compound 10

![Chemical Structure](image)

$F_1$ Chemical Shift (ppm)
4.5 4.0 3.5 3.0

$F_2$ Chemical Shift (ppm)
48 56 64 72 80 88 96

128
$^1$H–$^{13}$C HSQC Spectrum of

\[ \text{11} \]

\[
\begin{array}{c}
\text{Me} \\
\text{BnO} \\
\text{HO} \\
\text{Me} \\
\text{BnO} \\
\text{SPh}
\end{array}
\]
$^1\text{H} - ^{13}\text{C}$ HSQC Spectrum of

![Chemical Structure](image)
$^1$H–$^{13}$C HSQC Spectrum of

$^{13}$C Chemical Shift (ppm)

F1 Chemical Shift (ppm)

$^{13}$C–$^1$H HSQC Spectrum of

$^{13}$C Chemical Shift (ppm)

F1 Chemical Shift (ppm)
$^{1}H - ^{13}C$ HSQC Spectrum of

![Chemical Structure Image]

15
$^1$H – $^{13}$C HSQC Spectrum of

16

F1 Chemical Shift (ppm)

5.0 4.5 4.0 3.5 3.0

F2 Chemical Shift (ppm)

56 64 72 80 88 96
$^{1}H - ^{13}C$ HSQC Spectrum of

\[
\begin{array}{c}
\text{O} \\
\text{BnO} \\
\text{Me} \\
\text{O} \\
\text{O} \\
\text{BnO} \\
\text{Me} \\
\text{SPh} \\
\text{BnO}
\end{array}
\]

F2 Chemical Shift (ppm)

65
70
75
80
85
90
95
100

F1 Chemical Shift (ppm)

5.5 5.0 4.5 4.0 3.5 3.0

5.5 5.0 4.5 4.0 3.5 3.0 3.0 3.0
The diagram shows a chemical structure labeled as 18. The chemical shift scale is on the x-axis ranging from 7.0 to 1.0 in ppm.
$^{1}H - ^{13}C$ HSQC Spectrum of

18

F2 Chemical Shift (ppm)

F1 Chemical Shift (ppm)
$^1$H – $^{13}$C HSQC Spectrum of

![Chemical Structure](image)

**F1 Chemical Shift (ppm)**
- 5.5
- 5.0
- 4.5
- 4.0
- 3.5

**F2 Chemical Shift (ppm)**
- 56
- 64
- 72
- 80
- 88
- 96
- 104
$^1$H – $^{13}$C HSQC Spectrum of

![Chemical Structure](image)

F1 Chemical Shift (ppm)

F2 Chemical Shift (ppm)
Chemical Shift (ppm)

21

[Chemical structure diagram]
$^1$H – $^{13}$C HSQC Spectrum of

![Chemical Structure](image)

F1 Chemical Shift (ppm)

F2 Chemical Shift (ppm)
$^{1}H - ^{13}C$ HSQC Spectrum of

\[
\text{Me} \quad \text{BnO} \quad \text{Me} \quad \text{BnO} \quad \text{OH}
\]

\[
\text{Me} \quad \text{O} \quad \text{O} \quad \text{Me} \quad \text{O} \quad \text{H}
\]

22
\[ ^1H - ^13C \text{ HSQC Spectrum of} \]

\[
\begin{array}{c}
\text{Me} \\
\text{BnO} \\
\text{BnO} \\
\text{Me} \\
\text{Me} \\
\text{O} \\
\text{PMBO} \\
\text{O} \\
\text{Me} \\
\text{Me} \\
\text{O} \\
\text{O} \\
\text{Me} \\
\text{O} \\
\text{O} \\
\text{Me} \\
\text{Me} \\
\text{P} \\
\text{M} \\
\text{B} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{Me} \\
\text{Me} \\
\text{O} \\
\text{O} \\
\text{Me} \\
\text{O} \\
\text{O} \\
\end{array}
\]

24
Chapter 2

Stereoselective Synthesis of α-Digoxosides and α-Boivinosides via Chelation-Controlled Anomeric O-Alkylation

2.1 Introduction

Cardiac glycosides, a large family of chemical substances, are found in some plants and animal species. The plants possessing cardiac glycosides have been applied therapeutically for more than 1500 years, as diuretics, emetics, abovtificients, antineoplastics, and heart tonics. Digitoxin, a naturally occurring cardiac glycoside, was isolated from digitalis and had been employed to cure cardiac arrhythmias and congestive heart failure since the 1700’s. It is known that digitoxin acts as the inhibitor of Na⁺/K⁺-ATPase which increases the concentration of sodium ion intracellularly. Additionally, digitoxin has shown significant antiproliferative activity against breast cancer, MCF-7 (GI₅₀=13.8 nM).
Structurally, digitoxin (Figure 2.1) is composed of two moieties, an aglycon consisting of a steroid core and an unsaturated lactone, and the other part possessing three 2,6-dideoxy sugars with β-linkages. After direct preparation of 2,6-dideoxy-β-(1→3)-and (1→4)-linked glycosides via anomeric O-alkylation using secondary triflates, which was discussed in Chapter 1, we thought that the same approach might be applied for direct synthesis of β-linked digitoxosides in digitoxin.

2.1.1 Anomeric O-Alkylation

Anomeric O-alkylation (Scheme 2.1) initially involved a rapid equilibrium after deprotonation of lactol. This equilibrium is formed between axial anomeric alkoxide 1 and its equatorial isomer 3 via an open intermediate 2. The two electron-electron repulsions resulted from the equatorial alkoxide 3 gauche to both electron lone pairs of the ring oxygen make the equatorial alkoxide more reactive and nucleophilic compared to its axial isomer with a single gauche interaction.

Scheme 2. 1 Synthesis of complex glycosides via anomeric O-alkylation
2.1.2 Model Studies

Initially, the donor possessing a C3 axial hydroxyl group was synthesized for model investigation. The known compound digitoxosyl phenylsulfide 4\textsuperscript{6f} was chosen for the preparation of the partially protected 2,6-dideoxy glycoside, 4-\textit{O}-\textit{p}-methoxybenzyl-\textit{D}-digitoxose 6 containing C3 axial OH group in two steps (Scheme 2.2). Thus, oxidation of glycosyl phenylsulfide 4 by \textit{N}-bromosuccinimide resulted in the corresponding intermediate lactol 5. After that, desilylation of lactol 5 was facilitated by treatment with tetra-n-butylammonium fluoride (TBAF) to give the 4-\textit{O}-\textit{p}-methoxybenzyl-\textit{D}-digitoxose 6 in 89\% yield over two steps.

![Scheme 2.2 Synthesis of 4-\textit{O}-\textit{p}-methoxybenzyl-\textit{D}-digitoxose](image)

With digitoxose 6 in hand, we devised a model investigation for stereoselective synthesis of \(\beta\text{-D}-\text{digitoxoside} \) via anomeric \(\text{O}\)-alkylation using secondary triflate 7\textsubscript{a}\textsuperscript{2} as electrophile. After the optimization based on our previous attempts, we found that 2.5 equivalents of sodium hydride and 1.5 equivalents of 15-crown-5 was optimal for this anomeric \(\text{O}\)-alkylation reaction. However, we did not detect the desired \(\beta\)-linked disaccharide. Instead, \(\alpha\)-linked disaccharide 8 (Scheme 2.3) was produced in 84\% yield. At the same time, the corresponding product of C3-\textit{O}-alkylation was not detected, probably because the C3 alkoxide is less nucleophile than the C1 anomeric alkoxide.\textsuperscript{2,46}
2.1.3 Chelation-Controlled Anomeric O-Alkylation

It is worth noting that the lactol donor 6 we chose for modeling purposes contains a C3 axial hydroxyl substituent. Accordingly, an explanatory hypothesis, chelation-controlled anomeric O-alkylation (Scheme 2.4), is proposed. We assumed that 2-deoxy glycoside-derived equatorial anomeric alkoxides 9 possessing C3 axial alkoxide should undergo anomerization via opened intermediate 10 to form mostly the corresponding axial anomeric alkoxides 11 due to a potential chelation effect.\textsuperscript{64-67} This chelation interaction may lock in an axial configuration of the anomeric alkoxides, which may result in corresponding \( \alpha \)-linked disaccharides 13 after glycosylation with suitable secondary electrophiles. Besides, the anomeric C1 alkoxides are more nucleophilic than C3 alkoxides on account of electron-electron repulsion (12).\textsuperscript{2,46} In addition, our previous experiments indicated that C3 alkoxide may help to inhibit the elimination of opened intermediate 10.\textsuperscript{2}
Scheme 2. 4 Synthesis of complex glycosides via chelation-controlled anomeric O-alkylation.

The α-linked 2,6-dideoxy-L-ribo-hexose possessing a C3-axial hydroxyl group (L-digitoxose) exists in several naturally occurring antibiotics, such as kijanimicin,\textsuperscript{68} antlermicin,\textsuperscript{69} and the teronolides.\textsuperscript{70} Therefore, we explored the stereoselective synthesis of α-digitoxosides and α-boivinosides via chelation-controlled anomeric O-alkylation.
2.2 Results and Discussion

2.2.1 Synthesis of α-D-Digitoxosides

Based on the success in synthesis of α-linked disaccharide 8, we started an investigation of chelation-controlled anomeric O-alkylation employing different glycoside-derived triflates 7b-f as electrophiles. In Table 2.1, under the optimized reaction conditions, the desired α-digitoxosides 14-17 were afforded by utilizing lactol donor 6 with secondary triflates 7b-d, and a disaccharide-derived 7e via chelation-controlled anomeric O-alkylation. The corresponding products 14-17 were successfully prepared in good to excellent yields and excellent anomeric selectivities respectively (Table 2.1). In addition, diacetone-D-galactose-derived primary triflate 7f employed in this glycosylation reaction generated desired digitoxoside 18 in 95% yield but moderate anomeric selectivity (α/β=7/1). It is worth noting that these discoveries complement our results reported previously.
Table 2. 

**Synthesis of α-D-digitoxosides.**

<table>
<thead>
<tr>
<th>Reaction Details</th>
<th>Product Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. General conditions: lactol 6 (1.0 eq.), sodium hydride (2.5 eq.), 1,4-dioxane, RT 10 min; then triflate 7 (2.0 eq.), 15-C-5 (1.5 eq.), RT, 24 h.</td>
<td>![Reaction Diagram]</td>
</tr>
<tr>
<td>Isolated yield.</td>
<td><strong>8, 14-18</strong></td>
</tr>
</tbody>
</table>

---

**2.2.2 Synthesis of 4-O-Benzyl-α-Boivinose and α-β-Boivinosides**

A second partially protected 2,6-dideoxy glycoside, 4-O-benzyl-α-boivinose 22 possessing C3 axial hydroxyl group, was prepared (Scheme 2.5). Accordingly, the hydroxyl group of readily available compound 19 was subjected to O-benzylation. After that, the allylic sulfide of compound 19 underwent oxidation by m-chloropenroxybenzoic acid to form compounds 8, 14, 15, 16, 17, and 18. The isolated yields are as follows:

- **8, α only, 84%**
- **14, α only, 86%**
- **15, α only, 95%**
- **16, α only, 85%**
- **17, α only, 89%**
- **18, α/β (7/1), 95%**

---

In general, lactol 6 (1.0 eq.), sodium hydride (2.5 eq.), 1,4-dioxane, RT 10 min; then triflate 7 (2.0 eq.), 15-C-5 (1.5 eq.), RT, 24 h. Isolated yield.
acid to form the corresponding anomeric sulfoxide, which underwent [2,3]-sigmatropic rearrangement\textsuperscript{72-73} and subsequent aminolysis of the sulenate to give 4-\textit{O}-benzyl-6-deoxy-\textit{D}-gulal 20 in 82\% yield in two steps (Scheme 2.5).

\textbf{Scheme 2. 5 Synthesis of 4-\textit{O}-benzyl-\textit{D}-boivinose and \textit{\textalpha}-\textit{D}-boivinosides.}

(a) lactol 22 (1.0 eq.), sodium hydride (2.5 eq.), 1,4-dioxane, RT 10 min; then triflate 7a or 7b (2.0 eq.), 15-C-5 (1.5 eq.), RT, 24 h.

Compound 20 was first subjected to TBS-ether protection, followed by thioglycosylation via Re(V)-catalyst\textsuperscript{74} in the presence of thiophenol to afford compound 21 in excellent yield. After that, N-bromosuccinimide-mediated oxidation of the glycosyl phenylsulfide of 21 provided the corresponding lactol in 83\% yield. This lactol was subjected to TBAF-mediated desilylation to generate the desired lactol donor, 4-\textit{O}-benzyl-\textit{D}-boivinose 22 in 78\% yield (Scheme 2.5).
Under the optimized reaction conditions as mentioned previously, chelation-controlled anomeric O-alkylation between 4-O-benzyl-D-boivinose 22 and secondary triflates 7a and 7b afforded the corresponding desired α-boivinosides 23 and 24 in synthetically useful yields and excellent anomeric selectivities, respectively. Besides, the stereochemistry and $^4C_1$ configuration of α-boivinosides 23 and 24 were absolutely confirmed by NMR spectrum analysis. α-Boivinosides 23 and 24 containing three axial substitutes and one equatorial substituent adopted a $^4C_1$ (25) configuration rather than $^1C_4$ (26) configuration, which may be due to an intramolecular hydrogen-bond (Scheme 2.5). Furthermore, the existence of an intramolecular hydrogen bond in 25 was determined by IR spectroscopy in which the hydroxyl absorption band was very weak in intensity and reduced in frequency. A similar intramolecular hydrogen bond effect was also detected in α-digitoxisides 13-18.

2.2.3 Conclusion

In summary, we have described stereoselective syntheses of α-digitoxosides and α-boivinosides via chelation-controlled anomeric O-alkylation. The axial anomeric alkoxides are locked via chelation-control, which leads to the formation of α-glycosides in this anomeric O-alkylation. This new approach may be applied in preparing digitoxin analogs possessing α-linked digitoxosides.
2.3 Experimental

General Information

Proton and carbon nuclear magnetic resonance spectra (\(^1\)H NMR and \(^{13}\)C NMR) were recorded on either Bruker 600 (\(^1\)H NMR-600 MHz; \(^{13}\)C NMR 150 MHz) or INOVA 600 (\(^1\)H NMR-600 MHz; \(^{13}\)C NMR-150 MHz) or Varian VXR-400 (\(^1\)H NMR 400 MHz; \(^{13}\)C NMR 100 MHz) at ambient temperature with CDCl\(_3\) as the solvent unless otherwise stated. Chemical shifts are reported in parts per million relative to residual protic solvent internal standard CDCl\(_3\): \(^1\)H NMR at \(\delta\) 7.26, \(^{13}\)C NMR at \(\delta\) 77.36. Data for \(^1\)H NMR are reported as follows: chemical shift, integration, multiplicity (app = apparent, par obsc = partially obscure, ovrlp = overlapping, s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet) and coupling constants in Hertz. All \(^{13}\)C NMR spectra were recorded with complete proton decoupling. Infrared spectra were recorded on a PerkinElmer FT-IR spectrophotometer. High resolution mass spectra (HRMS) were obtained on a Waters Acuity Premiere XE TOF LC-MS by electrospray ionization. Optical rotations were measured with Autopol-IV digital polarimeter; concentrations are expressed as g/100 mL.

All reagents and chemicals were purchased from Acros Organics, Sigma Aldrich, Fisher Scientific, Alfa Aesar, and Strem Chemicals and used without further purification. THF, methylene chloride, toluene, and diethyl ether were purified by passing through two packed columns of neutral alumina (Innovative Technology). Anhydrous DMF, and benzene were purchased from Acros Organics and Sigma-Aldrich and used without further drying. All reactions were carried out in oven-dried glassware under an argon atmosphere.
unless otherwise noted. Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash column chromatography was performed using 200-400 mesh silica gel (Scientific Absorbents, Inc.). Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated.

2.3.1 Synthesis of 4-\textit{O}-\textit{p}-methoxybenzyl-D-digitoxose

\begin{center}
\includegraphics[width=\textwidth]{synthesis_diagram}
\end{center}

To a solution of 4\textsuperscript{61} (726 mg, 1.5 mmol) in 23 mL acetone and 1.5 mL water cooled at 0 °C was added \textit{N}-Bromosuccinimide (407 mg, 2.3 mmol). The resulting mixture was stirred at 0 °C for 15 minutes. Saturated sodium bicarbonate (10 mL) was added and acetone was removed under reduced pressure. The remaining aqueous mixture was extracted with ethyl acetate (3 x 20 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude residue was purified by flash column chromatography (Hexanes: ethyl acetate = 10:1 to 5:1) to furnish 573 mg of lactol 5 as a mixture of anomers. To a solution of this lactol (573 mg, 1.5 mmol) in 5 mL THF cooled at 0 °C was added 1.0 M tetra-n-butylammonium fluoride (TBAF) in THF (2.3 mL, 2.3 mmol) and the reaction was stirred overnight. Saturated ammonium chloride (2.5 mL) was added and THF was removed under reduced pressure. The remaining aqueous mixture was extracted with ethyl acetate (3 x 40 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered, and
concentrated. The crude residue was purified by flash column chromatography (Hexanes: ethyl acetate = 5:1 to 1:1) to furnish 364 mg (89% yield for two steps) of 4-O-p-methoxybenzyl-D-digitoxose 6 as a mixture of anomers (α/β = 1.7/1).

\[ [\alpha]_D^{23} = 57.2^\circ (c = 0.5, \text{CHCl}_3). \]

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta 7.27 - 7.26 (m, 1 \text{ H}), 7.26 - 7.23 (m, 3 \text{ H}), 6.91 - 6.89 (m, 2 \text{ H}), 6.89 (d, J = 2.6 \text{ Hz}, 2 \text{ H}), 5.17 - 5.07 (m, 3 \text{ H}), 4.56 (t, J = 10.9 \text{ Hz}, 2 \text{ H}), 4.51 (d, J = 11.2 \text{ Hz}, 1 \text{ H}), 4.49 - 4.45 (m, 1 \text{ H}), 4.26 (d, J = 2.8 \text{ Hz}, 1 \text{ H}), 4.18 (d, J = 2.9 \text{ Hz}, 1 \text{ H}), 4.12 (qd, J = 6.1, 9.7 \text{ Hz}, 1 \text{ H}), 3.84 (dd, J = 6.2, 9.4 \text{ Hz}, 1 \text{ H}), 3.82 - 3.80 (m, 6 \text{ H}), 3.14 - 3.09 (m, 2 \text{ H}), 2.95 (br. s., 1 \text{ H}), 2.43 (br. s., 1 \text{ H}), 2.26 - 2.18 (m, 2 \text{ H}), 1.80 (dd, J = 2.5, 14.6 \text{ Hz}, 1 \text{ H}), 1.61 - 1.54 (m, 1 \text{ H}), 1.27 (dd, J = 6.2, 10.1 \text{ Hz}, 7 \text{ H}).

\(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta 159.9, 159.9, 130.0, 129.8, 129.8, 114.3, 114.3, 92.2, 92.0, 80.2, 80.1, 77.6, 77.1, 71.8, 71.7, 68.6, 65.9, 64.9, 61.9, 55.6, 38.2, 34.8, 18.6, 18.5.

FT-IR (thin film): 3411, 2932, 1612, 1514, 1454, 1249, 1088, 1032, 819, 523 cm\(^{-1}\).

ESI-LRMS [M+Na]\(^+\) calculated for C\(_{14}\)H\(_{20}\)NaO\(_5\) 291.12, found 291.25.

2.3.2 Synthesis of α-D-digitoxosides
General procedure for stereoselective anomeric O-alkylation: To a solution of
4-O-p-Methoxybenzyl-D-digitoxose 6 (25.6 mg, 0.1 mmol) in 0.8 mL 1, 4-dioxane was
added sodium hydride (60% dispersion in mineral oil, 10.0 mg, 0.25 mmol) and the
resulting mixture was stirred for 10 minutes. A solution of triflate acceptor 7a (92.5 mg,
0.2 mmol) in 0.4 mL 1, 4-dioxane was added followed by addition of 15-crown-5 (30 µL,
0.15 mmol). The reaction mixture was stirred at room temperature for 24 hours. The crude
reaction mixture was purified by preparative thin layer chromatography (hexanes: ethyl
acetate = 3:1) to furnish 46 mg (84% yield) of phenyl 2,6-dideoxy-4-O-p-methoxybenzyl-
α-D-ribo-hexapyranosyl-(1→4)-3-O-benzyl-2,6-dideoxy-1-thio-α-D-arabino-
hexopyranoside 13.

\[ \alpha \] D \text{22} = 197.4° (c = 1.0, CHCl\textsubscript{3}).

\textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}) δ 7.46 - 7.41 (m, 2 H), 7.38 - 7.33 (m, 2 H), 7.30 (d,
J = 7.3 Hz, 4 H), 7.29 - 7.27 (m, 3 H), 7.26 - 7.22 (m, 1 H), 6.90 - 6.86 (m, 2 H), 5.57 (d,
J = 5.3 Hz, 1 H), 5.37 (d, J = 4.0 Hz, 1 H), 4.65 (d, J = 7.5 Hz, 1 H), 4.63 (d, J = 7.5 Hz, 1
H), 4.50 (d, J = 11.6 Hz, 1 H), 4.48 (d, J = 11.4 Hz, 1 H), 4.23 - 4.12 (m, 3 H), 3.89 (ddd,
J = 4.8, 8.7, 11.6 Hz, 1 H), 3.80 (s, 3 H), 3.38 (t, J = 9.1 Hz, 1 H), 3.04 (dd, J = 2.8, 9.6
Hz, 2 H), 2.49 - 2.42 (m, 1 H), 2.15 - 2.09 (m, 1 H), 2.03 (ddd, J = 5.7, 11.6, 13.3 Hz, 1 H),
1.76 (td, J = 3.9, 14.7 Hz, 1 H), 1.32 (d, J = 6.2 Hz, 3 H), 1.25 (d, J = 6.2 Hz, 3 H).

\textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}) δ 159.6, 138.4, 135.3, 131.5, 130.3, 129.9, 129.3,
128.8, 128.1, 127.9, 127.4, 114.1, 98.9, 84.0, 82.2, 79.8, 78.4, 77.6, 77.1, 71.6, 70.7, 68.0,
64.2, 63.2, 55.6, 36.4, 35.6, 18.7, 18.1.

FT-IR (thin film): 3534, 2932, 1731, 1612, 1513, 1439, 1248, 1093, 739, 697 cm\textsuperscript{-1}. 

1.
ESI-LRMS [M+Na]$^+$ calculated for C$_{33}$H$_{40}$NaO$_7$S 603.24, found 603.37.

14 was prepared according to the general procedure. The crude reaction mixture was purified by preparative thin layer chromatography (hexanes: ethyl acetate = 3:1) to furnish 86% yield of phenyl 2,6-dideoxy-4-0-p-methoxybenzyl-α-D-ribo-hexopyranosyl-(1→4)-3-O-p-methoxybenzyl-2,6-dideoxy-1-thio-α-L-arabino-hexopyranoside 14.

$[^{[α}]D]_{22}^0$ = - 44.6° (c = 1.0, CHCl$_3$).

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.45 - 7.41 (m, 2 H), 7.32 - 7.27 (m, 6 H), 7.25 - 7.21 (m, 1 H), 6.91 - 6.87 (m, 2 H), 6.83 - 6.79 (m, 2 H), 5.56 (d, $J = 4.4$ Hz, 1 H), 5.00 (d, $J = 3.7$ Hz, 1 H), 4.67 (d, $J = 11.4$ Hz, 1 H), 4.51 (s, 2 H), 4.46 (d, $J = 11.4$ Hz, 1 H), 4.42 - 4.35 (m, 1 H), 4.25 - 4.20 (m, 1 H), 4.20 - 4.15 (m, 1 H), 3.83 - 3.81 (m, 3 H), 3.81 - 3.76 (m, 2 H), 3.75 (s, 3 H), 3.36 (t, $J = 9.0$ Hz, 1 H), 3.25 (d, $J = 8.4$ Hz, 1 H), 3.02 (dd, $J = 2.9, 9.9$ Hz, 1 H), 2.43 (ddd, $J = 1.6, 4.7, 13.5$ Hz, 1 H), 2.21 - 2.15 (m, 1 H), 2.02 (ddd, $J = 5.7, 11.1, 13.5$ Hz, 1 H), 1.83 (td, $J = 3.6, 14.6$ Hz, 1 H), 1.25 (d, $J = 6.4$ Hz, 3 H), 0.99 (d, $J = 6.2$ Hz, 3 H).

$^{13}$C NMR (150 MHz, CDCl$_3$) δ 159.6, 159.5, 135.3, 131.4, 130.7, 130.5, 130.3, 129.8, 129.2, 127.4, 114.2, 114.1, 114.0, 98.1, 83.7, 81.7, 79.9, 77.6, 77.1, 75.7, 71.6, 70.5, 68.9, 64.4, 63.1, 55.6, 55.5, 36.4, 35.7, 18.6, 18.0.

FT-IR (thin film): 3515, 2933, 1731, 1612, 1513, 1248, 1084, 1032, 820, 691 cm$^{-1}$.
ESI-LRMS [M+Na]$^+$ calculated for C$_{34}$H$_{42}$NaO$_8$S 633.25, found 633.05.

15 was prepared according to the general procedure. The crude reaction mixture was purified by preparative thin layer chromatography (hexanes: ethyl acetate = 2:1) to furnish 95% yield of phenyl 2,6-dideoxy-4-$O$-p-methoxybenzyl-$a$-d-ribo-hexapyranosyl-(1→3)-2,4-di-$O$-benzyl-6-deoxy-1-thio-$\beta$-d-glucopyranoside 15.

[$\alpha$]$_D^{25}$ = 69.6° ($c$ = 1.0, CHCl$_3$).

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.56 (d, $J$ = 7.0 Hz, 2 H), 7.53 - 7.49 (m, 2 H), 7.38 - 7.26 (m, 11 H), 7.26 - 7.22 (m, 3 H), 6.90 (d, $J$ = 8.6 Hz, 2 H), 5.36 (d, $J$ = 3.9 Hz, 1 H), 4.97 (d, $J$ = 9.7 Hz, 1 H), 4.77 (d, $J$ = 9.7 Hz, 1 H), 4.74 - 4.67 (m, 3 H), 4.63 (d, $J$ = 11.4 Hz, 1 H), 4.44 (d, $J$ = 11.2 Hz, 1 H), 4.33 - 4.25 (m, 1 H), 4.16 (dd, $J$ = 2.8, 5.5 Hz, 1 H), 3.87 (t, $J$ = 9.2 Hz, 1 H), 3.82 (s, 3 H), 3.47 - 3.39 (m, 2 H), 3.29 (t, $J$ = 9.4 Hz, 1 H), 3.08 (d, $J$ = 5.9 Hz, 1 H), 3.00 (dd, $J$ = 2.8, 9.7 Hz, 1 H), 2.13 (dd, $J$ = 2.9, 14.5 Hz, 1 H), 1.74 (td, $J$ = 3.8, 14.6 Hz, 1 H), 1.38 (d, $J$ = 6.2 Hz, 3 H), 0.86 (d, $J$ = 6.1 Hz, 3 H).

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 159.5, 138.0, 137.9, 134.3, 131.9, 130.6, 129.6, 129.2, 129.1, 128.8, 128.4, 128.2, 127.9, 127.9, 127.7, 114.0, 97.6, 88.1, 85.3, 80.1, 80.0, 79.7, 77.6, 77.1, 75.7, 75.6, 75.3, 70.8, 64.3, 62.6, 55.6, 35.5, 18.4, 17.9.

FT-IR (thin film): 3525, 2909, 1732, 1612, 1454, 1248, 1001, 916, 751, 700 cm$^{-1}$.

ESI-LRMS [M+Na]$^+$ calculated for C$_{40}$H$_{46}$NaO$_8$S 709.28, found 709.35.
was prepared according to the general procedure. The crude reaction mixture was purified by preparative thin layer chromatography (hexanes: ethyl acetate = 2:1) to furnish 85% yield of methyl 2,6-dideoxy-4-<i>O</i>-methoxybenzyl-<i>a</i>-<i>d</i>-ribo-hexapyranosyl-(1→4)-3-<i>O</i>-methoxybenzyl-2,6-dideoxy-<i>a</i>-<i>L</i>-arabino-hexopyranoside 16.

[<i>α</i>]<sub>D</sub><sup>22</sup> = 42.8° (c = 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.28 (dd, <i>J</i> = 2.2, 8.6 Hz, 4 H), 6.90 - 6.86 (m, 2 H), 6.80 - 6.76 (m, 2 H), 4.99 (d, <i>J</i> = 3.7 Hz, 1 H), 4.71 (d, <i>J</i> = 2.8 Hz, 1 H), 4.65 (d, <i>J</i> = 11.4 Hz, 1 H), 4.50 - 4.42 (m, 3 H), 4.40 - 4.33 (m, 1 H), 4.19 - 4.13 (m, 1 H), 3.80 (s, 3 H), 3.80 - 3.74 (m, 2 H), 3.74 - 3.73 (m, 3 H), 3.73 - 3.66 (m, 1 H), 3.32 (dd, <i>J</i> = 5.2, 8.9 Hz, 2 H), 3.29 (s, 3 H), 2.99 (dd, <i>J</i> = 2.8, 9.8 Hz, 1 H), 2.32 - 2.25 (m, 1 H), 2.18 - 2.12 (m, 1 H), 1.80 (td, <i>J</i> = 3.6, 14.4 Hz, 1 H), 1.61 (dd, <i>J</i> = 3.7, 11.2, 13.0 Hz, 1 H), 1.25 (d, <i>J</i> = 6.2 Hz, 3 H), 0.95 - 0.91 (m, 3 H).

<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 159.5, 159.4, 130.7, 130.6, 130.4, 129.8, 114.0, 114.0, 98.4, 98.1, 81.9, 80.0, 77.6, 77.1, 75.4, 71.4, 70.5, 67.5, 64.5, 63.1, 55.6, 55.5, 54.9, 35.8, 35.6, 18.7, 17.9.

<sup>FT</sup>-IR (thin film): 3468, 2934, 2836, 1613, 1514, 1248, 1129, 1049, 820, 735 cm<sup>-1</sup>.

ESI-LRMS [M+Na]<sup>+</sup> calculated for C<sub>29</sub>H<sub>40</sub>NaO<sub>9</sub> 555.26, found 555.12.
17 was prepared according to the general procedure. The crude reaction mixture was purified by preparative thin layer chromatography (toluene: ethyl acetate = 5:1 with 1% methanol) to furnish 89% yield of methyl 2,6-dideoxy-4-\textit{O}-\textit{p}-methoxybenzyl-\textit{α}-\textit{d}-\textit{ribo}-hexapyranosyl-(1→3)-4-\textit{O}-\textit{p}-methoxybenzyl-2,6-dideoxy-β-\textit{d}-\textit{arabino}-hexopyranosyl-(1→4)-6-deoxy-2,3-\textit{O}-isopropylidene-\textit{α}-\textit{L}-mannopyranoside 17.

[\alpha]_D^{25} = 29.3° (c = 1.0, CHCl₃).

$^1$H NMR (600 MHz, CDCl₃) δ 7.30 - 7.26 (m, 2 H), 7.23 - 7.19 (m, 2 H), 6.89 - 6.84 (m, 4 H), 5.09 (d, $J = 3.7$ Hz, 1 H), 4.89 (dd, $J = 1.7$, 9.7 Hz, 1 H), 4.84 (s, 1 H), 4.69 (d, $J = 10.6$ Hz, 1 H), 4.65 (d, $J = 11.6$ Hz, 1 H), 4.57 (d, $J = 10.6$ Hz, 1 H), 4.47 (d, $J = 11.6$ Hz, 1 H), 4.16 - 4.12 (m, 2 H), 4.12 - 4.07 (m, 1 H), 4.07 - 4.04 (m, 1 H), 3.82 - 3.80 (m, 3 H), 3.79 (s, 3 H), 3.69 (ddd, $J = 5.3$, 8.8, 11.8 Hz, 1 H), 3.65 - 3.55 (m, 3 H), 3.35 (s, 3 H), 3.29 - 3.20 (m, 2 H), 3.08 - 3.01 (m, 2 H), 2.27 (ddd, $J = 1.7$, 5.2, 12.2 Hz, 1 H), 2.15 - 2.09 (m, 1 H), 1.81 (td, $J = 3.6$, 14.5 Hz, 1 H), 1.60 (dt, $J = 9.7$, 12.0 Hz, 2 H), 1.48 (s, 3 H), 1.33 (s, 3 H), 1.28 - 1.23 (m, 10 H).

$^{13}$C NMR (150 MHz, CDCl₃) δ 159.6, 130.7, 130.4, 129.9, 129.7, 114.2, 114.1, 109.5, 99.9, 98.2, 98.0, 84.1, 80.3, 79.7, 78.8, 77.6, 77.1, 76.4, 75.2, 71.5, 70.6, 64.5, 64.3, 63.1, 55.6, 55.6, 55.1, 39.5, 36.1, 28.1, 26.8, 18.5, 18.3, 17.8.

FT-IR (thin film): 3531, 2934, 2837, 1733, 1612, 1514, 1248, 861, 821, 756 cm$^{-1}$.

ESI-MS [M+Na]$^+$ calculated for C$_{38}$H$_{54}$NaO$_{13}$ 741.35, found 741.55.
18 was prepared according to the general procedure. The crude reaction mixture was purified by preparative thin layer chromatography (hexanes: ethyl acetate = 1:1 with 1% methanol) to furnish 95% yield of 2,6-dideoxy-4-O-p-methoxybenzyl-D-ribo-hexapyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranoside 18 as a mixture of anomers (α/β = 7/1). The α-anomer can be further separated from its β-isomer and the α-anomer was characterized:

\[ [\alpha]D^{25} = 31.5^\circ \ (c = 0.5, \text{CHCl}_3). \]

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta 7.31 - 7.27 (m, J = 8.4 \text{ Hz, 2 H}), 6.91 - 6.84 (m, J = 8.4 \text{ Hz, 2 H}), 5.51 (d, J = 5.0 \text{ Hz, 1 H}), 4.90 (d, J = 3.5 \text{ Hz, 1 H}), 4.66 (d, J = 11.6 \text{ Hz, 1 H}), 4.60 (dd, J = 2.4, 7.9 \text{ Hz, 1 H}), 4.46 (d, J = 11.6 \text{ Hz, 1 H}), 4.30 (dd, J = 2.4, 5.0 \text{ Hz, 1 H}), 4.24 (dd, J = 1.7, 7.9 \text{ Hz, 1 H}), 4.14 (d, J = 2.9 \text{ Hz, 1 H}), 4.09 - 4.03 (m, 1 H), 3.99 - 3.94 (m, 1 H), 3.84 - 3.81 (m, 1 H), 3.8 (s, 3 H), 3.61 (dd, J = 6.5, 10.2 \text{ Hz, 1 H}), 3.03 (dd, J = 2.8, 9.7 \text{ Hz, 1 H}), 2.17 (dd, J = 3.2, 14.6 \text{ Hz, 1 H}), 1.81 (td, J = 3.5, 14.7 \text{ Hz, 1 H}), 1.51 (s, 3 H), 1.43 (s, 3 H), 1.32 (d, J = 9.2 \text{ Hz, 7 H}), 1.26 (d, J = 6.4 \text{ Hz, 4 H}).

\(^1^3\)C NMR (150 MHz, CDCl\(_3\)) \(\delta 159.6, 130.5, 129.9, 114.1, 109.7, 108.9, 97.4, 96.6, 79.7, 77.6, 77.1, 71.3, 71.0, 70.9, 70.4, 66.2, 66.1, 64.4, 63.0, 55.6, 35.6, 26.4, 26.3, 25.2, 24.9, 18.4.
**FT-IR (thin film):** 3525, 2987, 2933, 1612, 1514, 1382, 1250, 1071, 1005, 865 cm\(^{-1}\).

**ESI-LRMS [M+Na]** calculated for C\(_{26}H_{38}NaO_{10}\) 533.24, found 533.35.

### 2.3.3 Synthesis of 4-O-benzyl-D-boivinose

![Chemical structure of 4-O-benzyl-D-boivinose synthesis](image)

To a solution of known phenyl 2,3,6-trideoxy-1-thio-\(\alpha\)-D-threo-hex-2-enopyranoside 19\(^{11}\) (1.110 g, 5.0 mmol) in DMF (20 mL) cooled at 0 °C was added benzyl bromide (0.71 mL, 9 mmol) and sodium hydride (60 % dispersion in mineral oil, 300 mg, 7.5 mmol) in 4 portions over 20 minutes. The reaction mixture was then stirred for 1 h at 0 °C before being warmed up to room temperature and stirred for 2 h until the consumption of starting material. The reaction mixture was diluted with ethyl acetate and water and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (3 times). The organic fractions were combined and washed with water, brine and dried over anhydrous Na\(_2\)SO\(_4\) then filtered, concentrated, and purified by flash column chromatography (Hexanes: ethyl acetate = 100: 1 to 15: 1) to afford 1.51 g (97 %) of...
corresponding phenyl 4-\(O\)-benzyl 2,3,6-trideoxy-1-thio-\(\alpha\)-D-threo-hex-2-enopyranoside.

To a solution of this phenyl 4-\(O\)-benzyl 2,3,6-trideoxy-1-thio-\(\alpha\)-D-threo-hex-2-enopyranoside (1.56 g, 5.0 mmol) in 60 mL anhydrous CH\(_2\)Cl\(_2\) cooled at -78 °C was added a solution of \(m\)-chloroperbenzoic acid (90% pure) (958 mg, 5 mmol) in 35 mL CH\(_2\)Cl\(_2\). The resulting mixture was stirred at -78 °C for 20 minutes before being diluted with CH\(_2\)Cl\(_2\) (300 mL). The organic solution was washed with saturated NaHCO\(_3\) solution, dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated. The crude product was azeotroped by toluene three times and dissolved in 50 mL anhydrous THF. To this solution was added diethylamine (2.5 mL) and the resulting mixture was stirred overnight. The reaction mixture was concentrated and the residue was purified by flash column chromatography (hexanes: ethyl acetate = 5:1 to 4:1) to afford 902 mg (82%) of 4-\(O\)-benzyl-D-gulal 20.

To a solution of 4-\(O\)-benzyl-D-gulal 20 (440 mg, 2.0 mmol) in 1 mL DMF was added imidazole (272 mg, 4.0 mmol). The resulting mixture was cooled to 0°C, tert-butyldimethylsilyl chloride (452 mg, 3.0 mmol) was added, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with water and extracted with ethyl acetate (3 times). The organic fractions were combined and washed with water and brine, dried over anhydrous Na\(_2\)SO\(_4\), filtered, concentrated, and purified by flash column chromatography (Hexanes: ethyl acetate = 50:1 to 25:1) to afford 608 mg (91%) of 4-\(O\)-benzyl-3-\(O\)-tert-butyldimethylsilyl-D-gulal. To a mixture of this 4-\(O\)-benzyl-3-\(O\)-tert-butyldimethylsilyl-D-gulal (922 mg, 2.76 mmol) and thiophenol (0.348 ml, 3.31 mmol) in 6.9 mL toluene cooled at 0 °C was added 1 mol% catalyst ReOCl\(_3\)(SMe\(_2\))(OPPh\(_3\)) (18 mg, 0.028 mmol), and the resulting mixture was stirred at
ambient temperature for 2 h. After a pinch of solid Na₂CO₃ was added, the reaction mixture was concentrated and purified flash column chromatography (hexanes: ethyl acetate = 50:1 to 10:1) to afford 1.213 g (98%) of phenyl 4-O-benzyl-3-O-tert-butyldimethylsilyl-2,6-dideoxy-1-thio-D-xylo-hexapyranoside 21 as an anomeric mixture (α/β = 1/1.6).

To a solution of phenyl 4-O-benzyl-3-O-tert-butyldimethylsilyl-2,6-dideoxy-1-thio-D-xylo-hexapyranoside 21 (1.10 g, 2.49 mmol) in 39.5 mL acetone/water (15/1, v/v) cooled at 0 °C was added N-bromosuccinimide (665 mg, 3.74 mmol), and the resulting mixture was stirred at 0 °C for 30 minutes before saturated NaHCO₃ was added. Acetone was removed under reduced pressure, the remaining aqueous mixture was extracted with ethyl acetate (3 times). The organic extracts were combined and washed with brine, dried over anhydrous Na₂SO₄, filtered, concentrated, and purified by flash column chromatography (hexanes: ethyl acetate = 8:1 to 4:1) to afford 724 mg (83%) of 4-O-benzyl-3-O-tert-butyldimethylsilyl-D-boivinose. To a solution of this 4-O-benzyl-3-O-tert-butyldimethylsilyl-D-boivinose (657 mg, 1.86 mmol) in 16 mL THF cooled at 0 °C 1.0 M tetra-n-butylammonium fluoride (2.8 mL, 2.8 mmol) was added, the reaction mixture was warmed up to room temperature and stirred for 4 hours. Saturated ammonium chloride (2.5 mL) was added, after THF was removed under reduced pressure, the aqueous mixture was extracted with ethyl acetate (3 times). The combined organic extracts were washed with water and brine, dried over anhydrous Na₂SO₄, filtered, concentrated, and purified by flash column chromatography (Hexanes: ethyl acetate = 5:1 to 1:2) to afford 346 mg (78%) of 4-O-Benzyl-D-boivinose 22.

\[ [\alpha]D^{23} = 75.3^\circ \text{ (c = 0.5, CHCl}_3) \].
$^1$H NMR (600 MHz, CDCl$_3$): δ = 7.27 - 7.40 (ovrlp, 5 H, α and β), 5.34 (br. s., 1 H, α ), 5.06 - 5.15 (br. s., 1 H, β ), 4.61 - 4.69 (ovrlp, 1 H, α and β), 4.51 - 4.60 (ovrlp, 1 H, α and β), 4.41 - 4.49 (br., 1 H, α), 4.20 - 4.25 (br. s., 1 H, β ), 4.05 (br. s., 1 H, α ), 3.32 - 3.43 (ovrlp, 2 H, α), 3.23 - 3.28 (br. s., 1 H, α), 3.04 - 3.12 (ovrlp, 2 H, α), 2.16 (d, J=14.5 Hz, 1 H, α), 1.84 (ovrlp, 1 H, α and 2H, β), 1.59 (ovrlp, 1 H, α and β), 1.24 - 1.29 (br. d., 3 H, β), 1.17 - 1.24 ppm (br. d, 3 H, α).

$^{13}$C NMR (150 MHz, CDCl$_3$): δ = 138.4, 128.7, 128.4, 128.4, 128.2, 93.2, 92.6, 73.3, 69.4, 66.7, 65.7, 61.9, 36.6, 30.9, 17.1, 17.0 ppm.

FT-IR (thin film): 3379, 2976, 2933, 1454, 1167, 1086, 989, 906, 734, 700 cm$^{-1}$.

ESI-LRMS [M+Na]$^+$ calculated C$_{13}$H$_{18}$O$_4$Na, 261.11, found 261.25.

2.3.4 Synthesis of α-D-boivinosides

![23]

23 was prepared according to the general procedure. The crude reaction mixture was purified by preparative thin layer chromatography (toluene: ethyl acetate = 20:1) to furnish 59% yield of phenyl 2,6-dideoxy-4-O-benzyl-α-D-xylo-hexapyranosyl-(1→4)-3-O-benzyl-2,6-dideoxy-1-thio-α-D-arabino-hexopyranoside 23.

$[\alpha]_D^{22} = 174.7^\circ$ (c = 1.0, CHCl$_3$).

$^1$H NMR (600 MHz, CDCl$_3$) δ 7.46 - 7.42 (m, 2 H), 7.37 - 7.32 (m, 6 H), 7.32 - 7.27 (m, 6 H), 7.26 - 7.22 (m, 1 H), 5.59 (d, J = 4.8 Hz, 1 H), 5.48 (d, J = 3.3 Hz, 1 H),
4.65 (dd, J = 9.6, 11.6 Hz, 2 H), 4.54 (d, J = 12.1 Hz, 1 H), 4.50 (d, J = 11.6 Hz, 1 H), 4.34 (dq, J = 1.3, 6.5 Hz, 1 H), 4.17 (qd, J = 6.2, 9.2 Hz, 1 H), 3.99 (dd, J = 3.6, 8.2 Hz, 1 H), 3.86 (ddd, J = 4.8, 8.5, 11.5 Hz, 1 H), 3.44 (d, J = 8.6 Hz, 1 H), 3.41 (t, J = 9.0 Hz, 1 H), 3.25 - 3.20 (m, 1 H), 2.47 (ddd, J = 1.3, 4.8, 13.4 Hz, 1 H), 2.14 (td, J = 3.7, 14.5 Hz, 1 H), 2.04 (ddd, J = 5.7, 11.7, 13.4 Hz, 1 H), 1.79 (td, J = 1.6, 14.5 Hz, 1 H), 1.31 (d, J = 6.2 Hz, 3 H), 1.19 (d, J = 6.6 Hz, 3 H).

$^{13}$C NMR (150 MHz, CDCl$_3$) δ 138.4, 138.2, 135.2, 131.4, 129.3, 128.8, 128.7, 128.4, 128.2, 128.1, 127.9, 127.5, 100.1, 83.9, 82.2, 78.3, 77.6, 77.6, 77.1, 73.2, 71.5, 68.0, 65.2, 62.5, 36.2, 31.1, 18.7, 16.9.

FT-IR (thin film): 3524, 3062, 2973, 2933, 1732, 1454, 1094, 1043, 738, 698 cm$^{-1}$.

ESI-LRMS [M+Na]$^{+}$ calculated for C$_{32}$H$_{38}$NaO$_{6}$S 573.23, found 573.05.

24 was prepared according to the general procedure. The crude reaction mixture was purified by preparative thin layer chromatography (toluene: ethyl acetate = 5:1) to furnish 53% yield of phenyl 2,6-dideoxy-4-O-benzyl-$\alpha$-D-xylo-hexapyranosyl-(1→4)-3-O-p-methoxybenzyl-2,6-dideoxy-1-thio-$\alpha$-L-arabino-hexopyranoside 24.

$[^{\alpha}]D^{22}$ = 47.4° (c = 1.0, CHCl$_3$).

$^{1}$H NMR (600 MHz, CDCl$_3$) δ 7.47 - 7.42 (m, 2 H), 7.35 - 7.32 (m, 4 H), 7.32 - 7.27 (m, 4 H), 7.26 - 7.22 (m, 1 H), 6.87 - 6.82 (m, 2 H), 5.58 (d, J = 5.1 Hz, 1 H), 5.10 (d,
$J = 3.1 \text{ Hz, 1 H)}$, 4.63 (d, $J = 12.1 \text{ Hz, 1 H}$), 4.57 - 4.49 (m, 3 H), 4.39 (d, $J = 10.6 \text{ Hz, 1 H}$), 4.20 (qd, $J = 6.3$, 9.4 Hz, 1 H), 4.03 - 3.96 (m, 1 H), 3.79 (s, 3 H), 3.76 (ddd, $J = 4.7$, 8.9, 11.3 Hz, 1 H), 3.72 (d, $J = 9.7 \text{ Hz, 1 H}$), 3.42 (t, $J = 9.1 \text{ Hz, 1 H}$), 3.13 - 3.08 (m, 1 H), 2.50 (dd, $J = 4.7$, 13.3 Hz, 1 H), 2.17 (td, $J = 3.5$, 14.3 Hz, 1 H), 2.04 (ddd, $J = 5.7$, 11.4, 13.4 Hz, 1 H), 1.86 - 1.79 (m, 1 H), 1.27 - 1.23 (m, 3 H), 0.83 (d, $J = 6.4 \text{ Hz, 3 H}$).

$\text{^{13}C NMR (150 MHz, CDCl}_3\delta 159.4, 138.3, 135.0, 131.1, 130.2, 129.8, 129.0, 128.3, 128.0, 127.7, 127.1, 113.7, 98.4, 83.5, 80.2, 77.4, 77.3, 77.1, 76.8, 75.5, 72.7, 70.9, 68.7, 64.9, 62.0, 55.3, 36.0, 30.5, 18.4, 16.2}$.

FT-IR (thin film): 3510, 3057, 2934, 1612, 1514, 1249, 1084, 1039, 737, 701 cm$^{-1}$.

ESI-LRMS [M+Na]$^+$ calculated for C$_{33}$H$_{40}$NaO$_7$S 603.24, found 603.05.

2.4 NMR of Selected Compounds

$\text{^1H NMR (CDCl}_3, 600MHz)$
$^{1}H - ^{13}C$ HSQC Spectrum of
$^1$H - $^{13}$C HSQC Spectrum of

$^{13}$C NMR Spectroscopy
$^1$H - $^{13}$C HSQC Spectrum of

![Chemical Structure](image)

203
$^1$H - $^{13}$C HSQC Spectrum of 16
$^1\text{H} - ^{13}\text{C}$ HSQC Spectrum of

![Chemical Structure](image)

F2 Chemical Shift (ppm)

F1 Chemical Shift (ppm)
$^1$H - $^{13}$C HSQC Spectrum of

{structure_image}

213
$^1$H - $^{13}$C HSQC Spectrum of

23
Chemical Shift (ppm)
\(^1\text{H} - ^{13}\text{C} \) HSQC Spectrum of

![Chemical Structure](image)

24
References


221


