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UMI
1 MECHANISTIC STUDIES ON THE FORMATION OF GLYCOSYL IODIDES

2 SYNTHESIS OF AMINO SUGARS VIA GLYCOSYL IODIDES

By

Truc Ngoc Nguyen

A Thesis Submitted to the Faculty of the
DEPARTMENT OF CHEMISTRY
In Partial Fulfillment of the Requirements
For the Degree of
MASTER OF SCIENCE
In the Graduate College

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1998
STATEMENT BY AUTHOR

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Jacquelyn Gervay
Professor of Chemistry
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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIST OF FIGURES</td>
<td>5</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>7</td>
</tr>
<tr>
<td>LIST OF SCHEMES</td>
<td>8</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>10</td>
</tr>
<tr>
<td><strong>CHAPTER 1. MECHANISTIC STUDIES ON THE FORMATION OF GLYCOSYL IODIDES</strong></td>
<td></td>
</tr>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td></td>
</tr>
<tr>
<td>1.1 Overview</td>
<td>12</td>
</tr>
<tr>
<td>1.2 O-Glycosidation</td>
<td>13</td>
</tr>
<tr>
<td>1.3 Glycosyl Halides</td>
<td>14</td>
</tr>
<tr>
<td>1.4 Glycosyl Bromides and Chlorides</td>
<td>15</td>
</tr>
<tr>
<td>1.5 Glycosyl Iodides</td>
<td>20</td>
</tr>
<tr>
<td>1.6 Halide Ion Catalyzed Glycosidation</td>
<td>24</td>
</tr>
<tr>
<td><strong>RESULTS AND DISCUSSION</strong></td>
<td>26</td>
</tr>
<tr>
<td><strong>CONCLUSIONS</strong></td>
<td>40</td>
</tr>
<tr>
<td><strong>EXPERIMENTAL SECTION</strong></td>
<td>43</td>
</tr>
<tr>
<td><strong>CHAPTER 2. SYNTHESIS OF AMINO SUGARS VIA THE GLYCOSYL IODIDES</strong></td>
<td></td>
</tr>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td></td>
</tr>
<tr>
<td>2.1 Overview</td>
<td>51</td>
</tr>
<tr>
<td>2.2 1,6 Anhydro Sugars</td>
<td>52</td>
</tr>
<tr>
<td>2.3 Lewis Blood Group Antigenic Determinants</td>
<td>55</td>
</tr>
<tr>
<td><strong>RESULTS AND DISCUSSION</strong></td>
<td>60</td>
</tr>
<tr>
<td><strong>CONCLUSIONS</strong></td>
<td>75</td>
</tr>
<tr>
<td><strong>EXPERIMENTAL SECTION</strong></td>
<td>76</td>
</tr>
<tr>
<td><strong>APPENDIX</strong></td>
<td>91</td>
</tr>
<tr>
<td><strong>REFERENCES</strong></td>
<td>130</td>
</tr>
</tbody>
</table>
**LIST OF FIGURES**

| Figure 1.1 | Cell membranes of erythrocytes with carbohydrate and protein components | 12 |
| Figure 1.2 | First synthesis of an O-glycoside | 16 |
| Figure 1.3 | Preparation of α-D-glucopyranosyl bromide from the pentaacetates using HBr | 16 |
| Figure 1.4 | Methanolysis of α and β glucopyranosyl bromide: $k_2 >> k_1, k_4 >> k_4$ | 17 |
| Figure 1.5 | Reaction of diisopropylidene furanose with TMSBr | 18 |
| Figure 1.6 | Reaction of N-acetyl-tetra-O-acetyl-2-deoxy-β-D-glucosamine with TMSBr | 18 |
| Figure 1.7 | Reaction of a 1,2 trans pyranose with TMSBr | 18 |
| Figure 1.8 | Reaction of a 1,2 cis pyranose with TMSBr | 19 |
| Figure 1.9 | Preparation of glucosyl chlorides from glucose pentaacetates | 19 |
| Figure 1.10 | Formation of a glycosyl chloride from the chlorodiphenylphosphate | 20 |
| Figure 1.11 | Formation of glucosyl iodide using HI, CH₃COOH | 21 |
| Figure 1.12 | In situ formation of glucosyl iodide from glucosyl chloride with NaI | 22 |
| Figure 1.13 | *In situ* generation of glycosyl iodides from glycosyl phosphates in LiClO₄ | 23 |
| Figure 1.14 | α-Glycoside synthesis utilizing fucosyl iodides | 24 |
| Figure 1.15 | Halide catalyzed glycosidation from a glycosyl bromide | 25 |
| Figure 1.16 | First order rate plot for 1.1 | 30 |
| Figure 1.17 | First order rate plot for 1.2 | 30 |
| Figure 1.18 | First order rate plot for 1.3 | 31 |
| Figure 1.19 | Second order rate plot for 1.3 | 31 |
| Figure 1.20 | First order rate plot for 1.12 | 35 |
Figure 1.21 First order rate plot for 1.17 ................................................................. 39
Figure 1.22 Second order rate plot for 1.17 ................................................................. 39
Figure 2.1 Lewis x and Lewis a trisaccharides ......................................................... 51
Figure 2.2 Pyrolysis of starch to the 1,6-anhydroglucose and its ring opening under acidic conditions ................................................................. 52
Figure 2.3 Example of Paulsen's work towards the synthesis of α-glycosidically linked 2-amino sugars from the reactive β-glycosyl chloride ................................. 54
Figure 2.4 Paulsen's coupling of the β-glucosyl chloride with the 4-O-benzyl ether 1,6-anhydroglucopyranose ......................................................... 54
Figure 2.5 Paulsen's coupling of the β-galactosyl chloride to the 4-O-benzyl ether 1,6 anhydroglucopyranose ......................................................... 54
Figure 2.6 Synthesis of the 2,2,2-trichloroethyl glucopyranoside ................................ 57
Figure 2.7 Lemieux's work towards the synthesis of the disaccharide of Lewis x ......................................................... 58
Figure 2.8 Lemieux's synthesis of the trisaccharide of Lewis x: the coupling of fucosyl bromide ......................................................... 59
Figure 2.9 Proposed mechanism for acetoxy group participation in glycoside formation ......................................................... 67
LIST OF TABLES

Table 1.1 Reactivity of halides, catalysts, and alcohols in glycoside synthesis ..... 14
Table 1.2 Reaction of peracetylated glucose and galactose with 2.2 eq TMSI ..... 28
Table 1.3 Reaction of peracetylated glucose and galactose with 1.2 eq TMSI ..... 28
Table 1.4 Rate data for compounds 1.1, 1.2, 1.3 ............................................. 32
Table 1.5 Summary of NMR results of monosaccharides studied .................. 41
Table 1.6 Summary of NMR results of anhydro sugars studied .................... 42
Table 2.1 Blood group and related antigens expressed on O-linked cores .......... 56
Table 2.2 Results from reaction of galactosyl and fucosyl iodide to the glycosyl acceptor cholesterol .... 74
LIST OF SCHEMES

Scheme 1.1  Reactions of peracetylated glycopyranoses with TMSI in acetonitrile  . 27
Scheme 1.2  Proposed mechanism of glycosyl iodide formation from  .......... 29
             peracetylated sugars
Scheme 1.3  Proposed mechanism of glycosyl iodide formation from .......... 33
             sugars without C-2 participating groups
Scheme 1.4  Mechanism of iodide formation from α and β  ..................... 34
             1-O-acetyl-tetra-O-benzyl mannopyranoses
Scheme 1.5  Mechanism of iodide formation from 1,2-anhydroglucose .......... 37
Scheme 1.6  Proposed mechanism of iodide formation from 1,6-anhydroglucose .... 38
             with TMSI
Scheme 2.1  Preparation of the 1,6-anhydro-2-azido-2-deoxy-(3  ........................................... 60
             -D-glucopyranose
Scheme 2.2  Benzyl protection of 2.1 ................................................. 61
Scheme 2.3  Opening of the anhydro ring with TMSI  .................................. 61
Scheme 2.4  Reaction of 2.5 with allyl alcohol and with 1,6-anhydroglucose ...... 62
Scheme 2.5  Opening of the 1,6-anhydroglucose to the diacetate 2.9 ............. 63
Scheme 2.6  Coupling of the iodide 2.10 to the 1,6-anhydro glucose ............... 63
Scheme 2.7  Synthesis of a β-linked disaccharide 2.13 by the .................. 65
             Koenig-Knorr’s method
Scheme 2.8  t-Butyl-dimethylsilyl ether protection of 2.1  ......................... 66
Scheme 2.9  Orthoester formation from reaction of 3-silyl ether .......... 66
             1,6-anhydroglucose with tetra-O-benzoyl-galactosyl bromide
Scheme 2.10 Reaction of galactosyl iodide to 3-silyl protected glucose 2.17 ...... 68
Scheme 2.11 Generation of fucosyl iodide from the anomeric acetate 2.21 ........ 69
Scheme 2.12 Coupling of fucosyl iodide with diol 2.1  ............................. 70
Scheme 2.13 Coupling of fucosyl iodide to 4-O-benzyl 1,6-anhydroglucose 2.3 ...... 71
Scheme 2.14 Coupling of fucosyl iodide to 3-O-t-butyl-dimethylsilyl-1,6- ...... 72
             anhydroglucose 2.17
Scheme 2.15  Coupling of fucosyl iodide to β-gal(1→4)-1,6-anhydroglucose 2.13 ... 73
ABSTRACT

The synthesis of oligosaccharides remains a challenging task. In our studies, we applied glycosyl iodides to the synthesis of oligosaccharides. The mechanism of formation of glycosyl iodides from anomeric acetates of glucose, galactose and mannose, and 1,2 and 1,6 anhydro sugars were investigated by NMR. Glycosyl iodides were then applied in glycosidation studies and specifically in the synthesis of a precursor to the trisaccharide of Lewis x, a blood group antigen.
CHAPTER 1

MECHANISTIC STUDIES ON THE FORMATION OF GLYCOSYL IODIDES
INTRODUCTION

1.1 Overview

One of the major challenges in carbohydrate chemistry lies in the synthesis of complex oligosaccharides. The complex role of carbohydrate was not recognized until the beginning of the 1950s when the biological information these molecules carried became more clear to scientists.\textsuperscript{1,2} Carbohydrates have been found to be covalently linked to proteins (glycoproteins), lipids (glycolipids), or phospholipids (glycophospholipids), which in general are termed glycoconjugates. These are encountered in membranes (Fig. 1) with the carbohydrate portion extended from the membrane.\textsuperscript{1} The carbohydrate portion functions in intercellular recognition and interaction, and importantly in the immune system. Also, numerous antibiotics and natural products have carbohydrate units attached to them.\textsuperscript{3} Many of these are attached via the $O$-glycosidic bond.

![Figure 1.1](image)

Figure 1.1 Cell membranes of erythrocytes with carbohydrate and protein components

"There are no universal reaction conditions for oligosaccharide syntheses."\textsuperscript{1} Predictions in the stereochemistry and regioselectivity of the new linkage formed are not
always straightforward. In the synthesis of oligosaccharides, consideration in the regioselectivity and stereoselectivity of the product formed is important. Stereoselectivity involves the stereochemical outcome, α or β, of the linkage formed at the anomeric center. Much effort has been put into achieving one stereoisomer in the product formed. Usually both are obtained. This lowers the yields and also many times the separation of the two anomers is difficult. Regioselectivity is usually achieved by protection and deprotection of the nucleophilic portion of the glycosyl acceptor. In controlling the stereochemistry of the glycosidic linkage, several methods have been established including: 1) neighboring group participation, 2) in situ anomerization, and 3) adsorption onto heterogeneous catalyst. Conformation, steric influences, and the molecular sizes of the two reacting species are also significant.

1.2 O-Glycosidation

Many of the linkages between two sugars (in biological systems are through an oxygen atom at the anomic center via an O-glycosidic bond. The anomic center is the hemiacetal carbon atom. The reacting components are called the glycosyl donor and glycosyl acceptor, comparable to the nucleophile and electrophile in organic synthesis, respectively. The glycosyl acceptor is the alcohol (or its anion) in O-glycoside synthesis. The glycosyl donor consists of many variations.

A wide variety of synthetic methodologies in the preparation of glycosyl donors exist to effectively carry out the synthesis of glycosides and oligosaccharides (10-15 sugar units attached). Some of these donors of glycosyl halides, thioglycosides, and trichloroacetimidates. Many of these reactions employ catalysts such as heavy metal salts, Lewis acids, or phase-transfer catalysts to activate the glycosyl donor. Emphasis will be
focused on glycosyl halides and particularly on glycosyl iodides (in O-glycoside synthesis).

1.3 Glycosyl Halides

The identity of the leaving group attached to the anomeric carbon atom is a significant factor in glycoside synthesis. Table 1.1 charts the reactivity of halides, catalysts, and alcohols in the synthesis of oligosaccharides conducted in solvents of low polarity. With the R substituent on the glycosyl halide the same, the iodide is the most reactive (or least stable), then the bromide and lastly the chloride. Fluorides are actually the most stable (least reactive). However, the reaction conditions employed for glycosyl fluorides are different than those typically used for the other halides. The protecting group or substituent R also can influence the reactivity of the glycosyl halide dramatically. Electron donating groups increase the rate of halide displacement as opposed to electron withdrawing groups: benzyl glycosyl halides are more reactive than benzoyl which are slightly more reactive than acetyl.

<table>
<thead>
<tr>
<th>Halide</th>
<th>Catalyst</th>
<th>Alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂OR</td>
<td>Eu₄NBr / mol. sieve Hg(CN)₂ Hg(CN)₂ / HgBr₂ HgBr₂ / mol. sieve AgClO₄, AgCO₃ AgOTf, Ag₂CO₃</td>
<td>H₂O &gt; HOCH₃ &gt;&gt; HOCH₂R &gt; 6-OH</td>
</tr>
<tr>
<td>R = Bn &gt; Bz – Ac X = I &gt; Br &gt; Cl</td>
<td>6-OH &gt;&gt; 3-OH &gt; 2-OH &gt; 4-OH</td>
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</tbody>
</table>

Table 1.1 Reactivity of halides, catalysts, and alcohols in glycoside synthesis
The catalyst is regarded as the most important factor influencing the reaction. The catalysts range from tetraethylammonium bromide (Et₄NBr) being the mildest to silver triflate/silver carbonate being the most active. In accordance with the original procedure using Et₄NBr, a small amount of dimethylformamide is added.

In regards to the glycosyl acceptor (or alcohol), primary hydroxyl groups are more reactive than secondary which are more reactive than tertiary. Primary OH groups are considerably more reactive which causes the differences in reactivity of the α or β glycosyl halides to be smaller, decreasing the stereoselectivity. In such instances a milder catalyst must be selected. Secondary OH groups, which are important in saccharide linkages, are moderately nucleophilic and it is critical that reactive halides are used to obtain high selectivity.¹

1.4 Glycosyl Bromides and Chlorides

Of the glycosyl halides and donors, the bromide and chloride have been extensively studied in the synthesis of O-glycosides since glycosyl fluorides have too low an activity and glycosyl iodides were believed to be too unstable. The first synthesis of an O-glycoside dates back to 1879 and was carried out by Michael. This work involved the condensation of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl chloride with potassium phenoxides to obtain the aryl glycoside (Figure 1.2). Later, in 1901, Koenigs-Knorr and Fischer-Armstrong extended this approach to glycosylation of alcohols. In these reactions, hydrogen halide is liberated and must be removed to prevent side products. To get around this, silver oxide was added to the mixture as a hydrogen halide acceptor. However, it also
serves as a catalyst but this was not known until 30-40 years later. Later, further work and modifications of the Koenigs-Knorr method by other groups, Helferich, Isbell and Frush, Lemieux, and Zemplen brought a great depth of understanding of the theoretical aspects to this method.\textsuperscript{6}

![Figure 1.2 First synthesis of an O-glycoside](image1)

Tetra-\(O\)-acetyl-\(\alpha\)-D-glucopyranosyl bromide can be prepared from the pentaacetates using hydrogen bromide in glacial acetic acid (Figure 1.3).\textsuperscript{7} The \(\beta\)-glucopyranosyl bromide can be expected to form and convert to the thermodynamically more stable \(\alpha\)-anomer during the reaction and to undergo rapid hydrolysis during the isolation procedure. The bromide of tetra-\(O\)-benzoyl-\(\alpha\)-D-glucose is also prepared using this reagent.\textsuperscript{8}

![Figure 1.3 Preparation of \(\alpha\)-D-glucopyranosyl bromide from the pentaacetates using HBr](image2)

The synthesis and solvolysis of \(D\)-glucopyranosyl bromides from 1-\(p\)-nitrobenzoyl glucopyranoses having benzyl groups at the C-2 position with hydrogen bromide in dichloromethane were studied by Fletcher in 1968.\textsuperscript{9} The experimental studies were
performed and data obtained polarimetrically. Regardless of the anomeric configuration of the p-nitrobenzoyl used, the β-D-glucopyranosyl bromide was formed first. Equilibration to the more stable α-anomer was inversely related to the number of p-nitrobenzoyl groups present which seems to have a stabilizing effect on the β-anomer formed. From the methanolysis of the glucopyranosyl bromides (Figure 1.4). Fletcher observed that the β-bromo glucoside reacted faster than the α-bromide and that the major product was the methyl-α-D-glucopyranoside formed from the solvolysis of the β-D-glucopyranosyl bromides.

![Figure 1.4 Methanolysis of α and β glucopyranosyl bromides; k₂ >> k₁, k₃ >> k₄](image)

Glycosyl bromides have also been prepared from anomeric glycosyl acetates with trimethylsilyl bromide (TMSBr). The reaction involves starting with 100 mg glycosyl acetate, dissolving in 0.5 mL CDCl₃, cooling to 0°C, adding 1.5 eq TMSBr and monitoring the reaction at room temperature. After completion of the reaction, trimethylsilyl acetate and excess TMSBr are removed by vacuum distillation. Numerous furanosyl and pyranosyl acetates were treated under those conditions, and all gave
quantitative yields of the glycosyl bromide. Also, the 1,2:5,6-diisopropylidene furanose and a methyl 2-deoxy-α-glycoside reacted with TMSBr resulted in a 40% yield (Figure 1.5) and no reaction over 72 hour, respectively. \(N\)-Acetyl tetra-\(O\)-acetyl-2-deoxy-\(\beta\)-D-glucosamine was shown to be converted to only the \(\alpha\)-bromide in 2 hr in quantitative yield (Figure 1.6). A 1,2 trans acetyl-\(\beta\)-pyranose was shown to yield a mixture of anomers 9:1 \(\alpha\):\(\beta\) in 1 hour (Figure 1.7). A 1,2 cis acetyl-\(\beta\)-pyranose yielded the \(\alpha\)-bromide in 85% in 24 hr (Figure 1.8). The author did not go into much depth to explain the observation from this study.

![Figure 1.5 Reaction of diisopropylidene furanose with TMSBr](image)

![Figure 1.6 Reaction of \(N\)-acetyl-tetra-\(O\)-acetyl-2-deoxy-\(\beta\)-D-glucosamine with TMSBr](image)

![Figure 1.7 Reaction of a 1,2 trans pyranose with TMSBr](image)
Glycosyl chlorides are considerably more stable than glycosyl bromides, making isolation of the β-glycoside possible. Tetra-O-acetyl-α-D-glucopyranosyl chloride can be obtained by reaction of the peracetylated β-D-glucopyranose with titanium chloride (Figure 1.9). Also, reagents such as liquid hydrogen chloride, aluminum chloride and phosphorus pentachloride, hydrogen chloride and acetyl chloride and aluminum chloride have been used to prepare chloro glucosides. In all these reactions, the first product of reaction is probably the β-anomer. The β-chloro glucoside, in turn, must be prepared under kinetic control and in most cases starting from the β-peracetylated glucose. Treatment of the β-D-glucopyranose pentaacetate with titanium tetrachloride, or reaction of α-D-glucopyranosyl bromide with silver chloride are possible routes to the β-chlorides which can be stored under anhydrous conditions up to several weeks.

In a more recent study by C.H. Wong, glycosyl chlorides were prepared under basic conditions from their corresponding alcohols. The conditions employed treatment of the anomeric hydroxyls of various glucosides with one equivalent of n-butyllithium at 0°C followed by addition of one equivalent of chlorodiphenylphosphate, then warming to 25°C.
C and stirring for 15 hours. In 5 of the 6 examples only α-anomers were isolated, in >80% yield. The mechanism suggested by the author is that the reaction proceeds through the complex of glycosyl diphenylphosphate and lithium cation which then reacts with chloride to give α-glycosyl chloride (Figure 1.10).

**Figure 1.10** Formation of a glycosyl chloride from the chlorodiphenylphosphate

Glycosyl bromides and chlorides have been used effectively as glycosyl donors in glycosidation reactions using a promoter or activator. Stereochemistry can be achieved by neighboring group participation, in situ anomerization, or phase transfer catalysis.¹⁴

1.5 Glycosyl Iodides

The first known literature on the preparation of glycosyl iodides was in 1910 by Fischer and in 1929, Helferich reacted glycosyl bromides with sodium iodide in acetone.¹⁴ Since then, Fletcher et al. out of curiosity prepared glycosyl iodides (and glycosyl chloride) while studying the reactivity of tetrabenzoyl-α-D-glucosyl and α-D-mannosyl...
bromide.\textsuperscript{15} They prepared the iodide by treating \(\beta\)-D-glucopyranose pentabenzoate with hydrogen iodide in glacial acetic acid and by measuring the molecular rotation confirmed the product to be the \(\alpha\)-iodide as needle-like crystals after crystallization (Figure 1.11). The iodide decomposed spontaneously at room temperature. However, if stored carefully at -5\(^\circ\) C over sodium hydroxide, there was no sign of decomposition over the course of a month. They also did this with the mannose pentabenzoate and after 2 hours and after purification obtained the \(\alpha\)-iodide as an amorphous. They suggested that glycosyl iodides were too unstable to be of practical use.

\begin{center}
\textbf{Figure 1.11} Formation of a glucosyl iodide using HI, CH\(_3\)COOH
\end{center}

In 1974, Kronzer and Schuerch investigated the use of glycopyranosyl iodides in \(\alpha\)-glycoside synthesis, the first such comprehensive study of glycosyl iodides and their reactivity.\textsuperscript{16} Methanolyses and ethanolyses of benzylated glucosyl and galactosyl iodides were studied and high ratios of \(\alpha\)- to \(\beta\)-glycosides were obtained. They reasoned that the greater reactivity of the iodides might permit the use of equimolar of quantities of alcohol and halide which are desirable conditions for oligosaccharide synthesis. Glycosyl iodides were prepared \textit{in situ} from the corresponding glucosyl and galactosyl chlorides, using 3.7 to 4.0 equivalents of sodium iodide in acetonitrile in the presence of an acid acceptor, 2,6-lutidine (Figure 1.12).
Dichloromethane was also tried in two reactions and seemed to give good results in terms of yield and α to β ratio. They found acetone to give unsatisfactory results as solvent since impurities (not identified) were present. Addition of a limited amount of methanol (2 eq) led to high yields of glycosides having over 90% α-anomer. Results in reacting glycosyl iodides with propanol and cyclohexanol were inconclusive as to the α:β ratio. Conversely, using a large excess of methanol reduced the selectivity of the glycosides formed. Glucosyl and galactosyl bromides were reacted with sodium iodide and a large excess of alcohol. The ratios obtained from these studies were determined using nmr data. In summary, the authors concluded that there were clear indications that the yield and ratios of α- to β-anomers reflect differences in the rates of anomerisation of the halides (I > Br > Cl) prior to glycoside formation.

In the first preparation of glycosyl iodides using trimethylsilyl iodide, Thiem and Meyer converted peracetylated hexopyranoses and high yields to the corresponding glycosyl iodides. They also tried this on methyl glycosides and obtained similar results. Lactose octaacetate was also transformed to the iodide without affecting the interglycosidic linkage.

In recent work by Waldman and Schmid, glycosyl phosphates were converted in situ in lithium perchlorate (LiClO₄) to glycosyl iodides which were used for glycosidation. Concentrated solutions of lithium perchlorate in organic solvents were applied to stabilize polar or ionic intermediates. The procedures involved reacting glycosyl
phosphates with 6-O-deprotected glucose derivatives in solutions of LiClO₄ in CH₂Cl₂ in the presence of 1.5 equivalents of an iodide salt (Figure 1.13). The disaccharides formed in 40-63% yield with the α-anomers as the predominante products. They proposed that the reaction proceeds via initial attack of the iodide on the α-configured glycosyl phosphates to give the β-glycosyl iodide which then is activated by the LiClO₄ solution and attacked by the glycosyl acceptor to give predominantly the α anomer in most cases. The primary hydroxyls of a disaccharide were reacted with the β-tetrabenzyl glucosyl iodide to gave a 46% yield of only the α anomer.

![Figure 1.13](image-url) 

*Figure 1.13 In situ generation of glycosyl iodides from glycosyl phosphates in LiClO₄*

Hindsgaul investigated the glycosidation of fucosyl iodide starting from L-fucose. In his synthesis, L-fucose was silylated using trimethylsilyl chloride and upon addition of 1 eq. TMSI in CDCl₃, resulting in quantitative formation of fucosyl iodide in less than 30 min at r.t. Fucosyl iodides used in excess was added to the reaction mixture containing the alcohol acceptor (Figure 1.14). The product yields ranged between 45-90%. The unique aspects about the method are the ease of the protection and deprotection scheme. Starting from L-fucose, which is readily available, the hydroxyls are silylated using TMS-Cl. The
tetra-silylated derivative is used to generate the reactive fucosyl iodide used for coupling and is easily removed by adding methanol. The authors also claim that the purification step is greatly simplified due to the large differences in polarity between the unreacted acceptor and fucosylated product.

Figure 1.14 α-Glycoside synthesis utilizing fucosyl iodides

1.6 Halide Ion Catalyzed Glycosidation

The detailed and thorough investigation of the mechanism of reactions of glycosyl halides without C-2 participation with alcohols and their application to the synthesis of α-D-glycosides were discussed by Lemieux et al.\textsuperscript{20} From the stereochemistry of the product obtained, the mechanism was proposed to involved halide ion catalysis. This is the basis for many of the syntheses carried out in our studies with glycosyl iodides in the presence of tetrabutylammonium iodide to form α-glycosides.

In the investigation of the halide ion catalyzed mechanism, tetra-\textit{O}-benzyl-α-D-glucopyranosyl chloride and bromide were reacted with simple alcohols (Figure 1.15).
The characteristics of the mechanism confirm the presence of β-halide formation (even though in low concentration in solution) and its greater reactivity over that of the α-anomer. Early observations have shown that the anomic 3,4,6-tri-O-acetyl-D-glycopyranosyl chlorides tend to undergo acetolysis with inversion of the anomic center and that the β-anomer solvolyzes about 100 times more rapidly than the α-anomer. In consideration of the mechanism proposed, three criteria were envisaged for successful halide ion catalyzed glycosidation. They are as followd: a) the glycosidation must be carried out under conditions where the halide ion concentration is maintained in order to form the β-glycosyl halide faster than nucleophilic attack on the α-glycosyl halide,  b) the solvolyisis of the glycosyl halide must be fast enough that its reaction with the nucleophile does not require an activator or strongly polar solvents, and c) the reaction conditions should minimize byproduct formation.
RESULTS AND DISCUSSION

Glycosyl halides have been used in glycosidation reactions since the late 1800's. Glycosyl bromides and chlorides are the two most extensively studied due to ease of handling. On the other hand, the use of glycosyl iodides as intermediates in glycosidations has not been explored as much. Only a handful of literature examples have dealt with these intermediates. Among the potential problems or disadvantages of using glycosyl iodides is that they are very reactive which makes them difficult to handle and to isolate, and they undergo homolytic cleavage easily.

Our interest in glycosyl iodides stems from the fact that they are very reactive intermediates compared to the bromo and chloro glycosides. For example, it was postulated that glycosidation could be effected without the need to use promoters such as silver or mercury salts. Moreover, perhaps these can be used to effect glycosidation in a regio- and stereoselective or stereospecific manner. The mechanism of the formation of glycosyl iodides has not been directly investigated before. Indirect evidence from the stereochemical outcome of product formation has been used to postulate the existence of the β-anomer as an intermediate that is formed during the reaction.

In our initial studies, peracetylated α- and β-glucopyranose and β-galactopyranose were used. The glycosyl iodides were formed using trimethylsilyl iodide (TMSI) in acetonitrile-d3 with and without addition of sodium iodide. (Glycosyl iodides previously known were prepared by reaction of glycosyl bromides with sodium iodide. Similar to our method, groups such as Thiem and Meyer have produced α-D-glycosyl iodides.\textsuperscript{17} These reactions were done using 2.2 eq. of trimethylsilyl iodide (TMSI) and then later with only 1.2 eq. The results are summarized in Tables 1.2 and 1.3, respectively.
Scheme 1.1 Reactions of peracetylated glycopyranoses with TMSI in acetonitrile

The reaction completion times shown are approximate. The most significant aspect to notice is that in all cases, the \( \alpha: \beta \) ratio is greater in the reactions containing sodium iodide.

This observation showed that in the presence of a catalytic amount of \( \text{NaI} \), the reaction proceeded to the \( \alpha \)-iodide much faster, suggesting that equilibration favors the \( \alpha \)-iodide, a result of the anomeric effect. The differences in the reaction completion time for the peracetylated sugars were not significant enough to say whether the concentration of TMSI affected the rate of the reaction. The only obvious change was for the peracetylated-\( \beta \)-D-glucopyranose where the reaction was completed within 15 min using 2.2 eq TMSI and in one hour using 1.2 eq TMSI.

These initial studies indicated that the reaction would need to be slowed in order to observe the intermediate(s) formed using NMR. Thus, reaction conditions were modified and worked out to include dichloromethane as a solvent, a reaction temperature of \(-40^\circ \text{C}\), and one eq of TMSI.
<table>
<thead>
<tr>
<th>Peracetylated Glycopyranose</th>
<th>Conditions</th>
<th>Reaction time</th>
<th>Ratio α:β a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>2.2 eq TMSI, NaI</td>
<td>ND</td>
<td>------</td>
</tr>
<tr>
<td></td>
<td>2.2 eq TMSI</td>
<td>15 min</td>
<td>1:1</td>
</tr>
<tr>
<td>1.2</td>
<td>2.2 eq TMSI, NaI</td>
<td>20 min</td>
<td>all α</td>
</tr>
<tr>
<td></td>
<td>2.2 eq TMSI</td>
<td>10 min</td>
<td>1:1.2</td>
</tr>
<tr>
<td>1.3</td>
<td>2.2 eq TMSI, NaI</td>
<td>2 hr b</td>
<td>not significant amount of β</td>
</tr>
<tr>
<td></td>
<td>2.2 eq TMSI</td>
<td>1 hr</td>
<td>2:1</td>
</tr>
</tbody>
</table>

Table 1.2 Reaction of peracetylated glucose and galactose with 2.2 eq TMSI.

a ratio of anomers determined at time of completion of starting material
b more than 50% of starting material had reacted

<table>
<thead>
<tr>
<th>Peracetylated glycopyranose</th>
<th>Conditions</th>
<th>Reaction time a</th>
<th>Ratio α:β</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>1.2 eq TMSI, NaI</td>
<td>1 hr</td>
<td>22:1</td>
</tr>
<tr>
<td></td>
<td>1.2 eq TMSI</td>
<td>1 hr</td>
<td>2:1 d</td>
</tr>
<tr>
<td>1.2</td>
<td>1.2 eq TMSI, NaI</td>
<td>10 min</td>
<td>23:1</td>
</tr>
<tr>
<td></td>
<td>1.2 eq TMSI</td>
<td>10 min</td>
<td>2:1 e</td>
</tr>
<tr>
<td>1.3</td>
<td>1.2 eq TMSI, NaI</td>
<td>2 hr b</td>
<td>2.5:1</td>
</tr>
<tr>
<td></td>
<td>1.2 eq TMSI</td>
<td>1 hr c</td>
<td>------</td>
</tr>
</tbody>
</table>

Table 1.3 Reaction of peracetylated glucose and galactose with 1.2 eq TMSI

a approximate times reported; in all cases except where noted, more than 75% of the reaction has gone to completion
b final spectrum obtained. 65% of starting sugar unreacted
c 75% of starting material inreacted
d at 4 hr, α:β ratio 4:1
e at 22 min, α:β ratio 5:1
Scheme 1.2 Proposed mechanism of glycosyl iodide formation from peracetylated sugars.

Under these conditions, the peracetylated glucose and galactose were reacted and followed by NMR to near completion, except for the α-D-glucopyranose which took over four hours for half of the starting material to react. The results in each of these cases showed the β-iodide as the first species formed and over time it equilibrated to the thermodynamically more stable α-iodide species. In Scheme 1.2, a mechanism for the formation of the iodide is proposed. Starting with the β-peracetylated glucose 1.1 or galactose 1.2 the first step is silylation of the carbonyl oxygen at the anomeric position which through neighboring group participation (anchimeric assistance) by the 2-O-acetyl, forms a stabilized oxonium intermediate 1.1b or 1.2b. Iodide subsequently attacks to form the β-iodide 1.4 or 1.6 which then slowly equilibrates to the α anomer 1.5 or 1.7. In the case of the α-peracetylated glucose 1.3, the first step is silylation giving the α-trimethylsilylacetoxyxonium intermediate 1.3a. The lone pair of electrons from the ring oxygen facilitates displacement of the trimethylsilyl acetate forming the oxonium ion 1.3b which then is stabilized by
Figure 1.16 First order rate plot for 1.1.

Figure 1.17 First order rate plot for 1.2
Figure 1.18  First order rate plot for 1.3

Figure 1.19  Second order rate plot for 1.3
anchimeric assistance leading to the intermediate 1.1b. Again, iodide attacks yielding the β anomer 1.4 which undergoes equilibration generating the α anomer 1.5. From the data obtained by integrating the peaks on the $^1$H NMR spectra, calculation of the concentration of starting material at each time measured was determined. From these values, a first order rate plot was graphed and a line drawn through the points. The first order plots for the β peracetylated glucose (Figure 1.16) and galactose (Figure 1.17) gave straight lines with root mean squares of 0.99 and a half life of about 17 and 8 min, respectively (Table 1.4). However, for the α-peracetylated glucose the half life is 1.3 hr (from the first order rate plot). The reaction was much slower suggesting that neighboring group participation can have significant influence on the rate of iodide formation. The kinetic plot for the α peracetylated glucose did not give linear lines in the first (Figure 1.18) or second (Figure 1.19) order plots indicating that both are competing processes. (NMR spectra can be found in Appendix A).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Rate ($k$)</th>
<th>$t_{1/2}$ (s)</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>$6.73 \times 10^{-4}$</td>
<td>$1.04 \times 10^3$</td>
<td>0.99</td>
</tr>
<tr>
<td>1.2</td>
<td>$1.42 \times 10^{-3}$</td>
<td>$4.94 \times 10^2$</td>
<td>0.99</td>
</tr>
<tr>
<td>1.3</td>
<td>$2.38 \times 10^{-5}$</td>
<td>$2.88 \times 10^4$</td>
<td>0.96</td>
</tr>
<tr>
<td>1.3</td>
<td>$3.25 \times 10^{-5}$</td>
<td>not determined</td>
<td>0.98</td>
</tr>
</tbody>
</table>

**Table 1.4** Rate data for compounds 1.1, 1.2, 1.3.

In order to understand the effect of the C-2 participating group on the rate of formation of the iodide, α and β 1-O-acetyl-tetra-O-benzyl-glucopyranoses (1.8 and 1.9) were studied (Scheme 1.3). The same experimental conditions were applied to the substrate as for the peracetylated sugars (1.3 and 1.1). The results obtained showed a
reversal in reactivity between the α and β tetra-O-benzyl glucopyranoses (1.8 and 1.9) as opposed to the peracetylated sugars (1.3 and 1.1) described above. The α tetra-O-benzyl glucopyranose 1.8 reaction at -100° C was completed within 10 min. From the α anomeric acetate 1.8, silylation of the carbonyl oxygen occurs (the rate determining step)

\[
\begin{align*}
\text{BnO} & \quad \text{OBn} \\
\text{BnO} & \quad \text{OBn} \\
\text{BnO} & \quad \text{OAc} \\
\text{1.8} & \\
\end{align*}
\]

\[
\begin{align*}
\text{TMSI} & \quad \text{BnO} \\
\text{BnO} & \quad \text{OBn} \\
\text{BnO} & \quad \text{OBn} \\
\text{OBn} & \quad \text{OTMS} \\
\text{1.8a} & \\
\end{align*}
\]

\[
\begin{align*}
\text{BnO} & \quad \text{OBn} \\
\text{BnO} & \quad \text{OBn} \\
\text{BnO} & \quad \text{OBn} \\
\text{OBn} & \quad \text{I} \\
\text{1.10} & \\
\end{align*}
\]

\[
\begin{align*}
\text{BnO} & \quad \text{OBn} \\
\text{BnO} & \quad \text{OBn} \\
\text{BnO} & \quad \text{OBn} \\
\text{OBn} & \quad \text{OTMS} \\
\text{1.9a} & \\
\end{align*}
\]

\[
\begin{align*}
\text{BnO} & \quad \text{OBn} \\
\text{BnO} & \quad \text{OBn} \\
\text{BnO} & \quad \text{OBn} \\
\text{OBn} & \quad \text{I} \\
\text{1.11} & \\
\end{align*}
\]

Scheme 1.3 Proposed mechanism of glycosyl iodides formation from sugars without C-2 participating groups.

and iodide displaces trimethylsilyl acetate to generate the β-iodide 1.10. Subsequent nucleophilic attack by iodide produces the more stable α-anomer 1.11. Formation of the oxonium intermediate to obtain the α-iodide is not ruled out since the rate of going from the β to the α iodide was very rapid. In contrast, starting from the β-anomer 1.9, only the α-iodide 1.11 is observed at 10° C. Possible routes would be by way of the trimethylacetoxonium intermediate 1.9a or by way of the oxonium ion.
In summary, glycosyl iodides can be stereoselectively and quantitatively generated at low temperatures from anomeric acetates. In terms of reactivity of the three compounds studied, β-D-peracetylated galactose (1.2) reacts fastest, β-D-peracetylated glucose (1.1) is intermediate in reactivity and the α-D-peracetylated glucose (1.3) is least reactive. Studies by Hadd and Gervay have shown stereoselectivity and in certain cases stereospecificity in the synthesis of β C-, N-, and O- glycosides with stabilized anions starting from the α-iodides. When nonstabilized anions were used, elimination products were the major products.

Scheme 1.4 Mechanism of iodide formation from α and β 1-O-acetyl-tetra-O-benzyl mannopyranoses
Figure 1.20 First order rate plot for 1.12
Other systems were also studied. When $\alpha$ and $\beta$ 1-O-acetyl-tetra-O-benzyl-mannose in CD$_2$Cl$_2$ were reacted with 1 eq TMSI at -100° C, only the $\alpha$-iodo mannose (1.14) (singlet, $\delta$ 6.99) was observed in both cases (Scheme 1.4). For the $\beta$-acetate (1.13), the reaction was complete within the time it took to take the first spectrum. The stereochemistry at the C-2 position must have an overriding effect over the reverse anomeric effect because if explained by the reverse anomeric effect, the $\alpha$-acetate (1.12) should react faster. Iodide formation in the $\beta$-acetate (1.13) can occur from the $\beta$-acetoxonium 1.13a or oxonium intermediate. In the case of the $\alpha$-acetate 1.12, whether the $\beta$-iodide is formed first and quickly equilibrates to the $\alpha$ anomer 1.14 by way of the acetoxonium intermediate 1.12a is not known since the $\beta$-iodide was not observed. If formed, it equilibrates within the NMR time scale or perhaps only a minute amount is formed and not observable in the NMR. A competing process between oxonium formation and iodide displacement of trimethylsilyl acetate might be happening. The first order rate plot gave a root mean square of 0.986 at approximately 25% completion (Figure 1.20). To confirm that the $\beta$-iodides were not formed during the reaction, we tried to generate the $\beta$-iodide by adding 2 eq of tetrabutylammonium iodide at -90° C so that if concentration was a factor, we could possibly the $\beta$-iodide forming. However, within 3 min before the first scan, the reaction was again complete and only the $\alpha$-iodide 1.14 was present. This same scheme was also tested on $\alpha$-1-O-acetyl-tetra-O-benzyl galactose using 1 eq of Bu$_4$NI at room temperature. At 0, -10, and -20° C, there was no sign of $\beta$-iodide. To do this type of experiment is quite tricky because to see the $\beta$-iodide low temperature is needed in order to slow down the rate. Nonetheless, at low temperatures, from the stable $\alpha$-anomer the $\beta$-iodide might not be formed. Furthermore, if the temperature was increased, increases in the rate of equilibration to the $\alpha$-iodide would occur.
Other systems that were investigated were 1,2- and 1,6-anhydroglucose derivatives 1.15 and 1.17. Interest in the opening of anhydro rings using TMSI was that coupling or chemistry can first be done at the anomeric position while temporarily keeping the 2-O or 6-O position protected as a silyl ether. Silyl ethers can be removed with weak acids. After removal, the hydroxyl can in turn serve as a glycosyl acceptor in further synthesis. NMR results for 1,2 anhydro-tri-O-benzyl-glucopyranose (1.15) showed that this ring system is very reactive and that within the time of the first scan, the reaction had gone completion giving only the α-iodide 1.16 (Scheme 1.5).

![Scheme 1.5 Mechanism of iodide formation from 1,2-anhydroglucose](image)

Most of the 1,6-anhydro-2-azido-3,4-di-O-benzyl-2-deoxy-glucopyranose (1.17) at 25° C had reacted within 10 min. At -5° C only the α-anomer 1.18 (d, δ 6.85, J = 3.9 Hz) was formed (Scheme 1.6). Either by silylation of the oxygen of the 1,6-anhydro ring and direct attack of iodide or by the oxonium intermediate, the α-iodide 1.18 is formed. First and second order kinetic plots were made. Neither produced a straight line (Figures 1.21 and 1.22). Perhaps an equilibrium between the starting material 1.17 and the iodide 1.18 is set up.
Scheme 1.6 Proposed mechanism of iodide formation from 1,6-anhydroglucose with TMSI
Figure 1.21 First order rate plot for 1.17

Figure 1.22 Second order rate plot for 1.17
CONCLUSIONS

Tables 1.5 and 1.6 summarize the results for each of the monosaccharides studied. The reactivities of the 1-\textit{O}-acetyl-tetra-\textit{O}-benzylglycopyranoses studied are as follows: the mannose \textit{\beta}-acetate 1.13 was most reactive, the mannose \textit{\alpha}-acetate of 1.12 was more reactive than the \textit{\alpha}-acetate of glucose 1.8, and the glucose \textit{\beta}-acetate 1.9 was least reactive. The studies showed the effect of participation at the C-2 center, and the effect of axial substituents (galactose and mannose) on the rate of reactivity. The alleviation of ring strain in the 1,2 anhydro system makes these very reactive to iodide formation.

An interesting experiment to consider performing in order to further explore and confirm the mechanism occurring in the formation of the iodide of mannose would be to start with 3,4,6-tri-\textit{O}-acetyl-2-\textit{O}-benzyl-mannopyranose in order to slow the reaction rate. Perhaps if the \textit{\beta}-iodide is formed, the equilibration to the \textit{\alpha} anomer is slow enough and the \textit{\beta}-iodide in large enough concentration that the reaction can be followed by NMR. Another point that needs confirmation is whether a true equilibrium is present for the 1,6-anhydro ring. Following the reaction by TLC shows the starting material always present in some amount. Even after adding one or two equivalent more of TMSI, the reaction does not appear to go to completion. Further experiment is needed.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Monosaccharide</th>
<th>Temperature 0 °C</th>
<th>Completion Time</th>
<th>Product Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td><img src="image1" alt="Monosaccharide Structure" /></td>
<td>-40</td>
<td>30 min</td>
<td>24:1 β:α</td>
</tr>
<tr>
<td>1.2</td>
<td><img src="image2" alt="Monosaccharide Structure" /></td>
<td>-40</td>
<td>15 min</td>
<td>30:1 β:α</td>
</tr>
<tr>
<td>1.3</td>
<td><img src="image3" alt="Monosaccharide Structure" /></td>
<td>-40</td>
<td>~ 16 hr</td>
<td>26:1 β:α (62% SM unreacted)</td>
</tr>
<tr>
<td>1.8</td>
<td><img src="image4" alt="Monosaccharide Structure" /></td>
<td>-100</td>
<td>&lt; 3 min</td>
<td>36:1 β:α</td>
</tr>
<tr>
<td>1.9</td>
<td><img src="image5" alt="Monosaccharide Structure" /></td>
<td>10</td>
<td>30 min</td>
<td>100% α quantitative</td>
</tr>
<tr>
<td>1.13</td>
<td><img src="image6" alt="Monosaccharide Structure" /></td>
<td>-100</td>
<td>&lt; 5 min</td>
<td>100% α quantitative</td>
</tr>
<tr>
<td>1.12</td>
<td><img src="image7" alt="Monosaccharide Structure" /></td>
<td>-80</td>
<td>25 min</td>
<td>100% α quantitative</td>
</tr>
</tbody>
</table>

Table 1.5 Summary of NMR results of monosaccharides studied
<table>
<thead>
<tr>
<th>Entry</th>
<th>Monosaccharide</th>
<th>Temperature °C</th>
<th>Completion Time</th>
<th>Product Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.15</td>
<td><img src="image" alt="Monosaccharide Structure" /></td>
<td>-100</td>
<td>&lt; 5 min</td>
<td>100% α quantitative</td>
</tr>
<tr>
<td>1.17</td>
<td><img src="image" alt="Monosaccharide Structure" /></td>
<td>-5</td>
<td>&gt; 4 hr</td>
<td>100% α 29% SM unreacted</td>
</tr>
</tbody>
</table>

Table 1.6 Summary of NMR results of anhydro sugars studied.
EXPERIMENTAL SECTION

Starting materials and reagents were purchased from commercial suppliers and used without further purification. Solvents were dried by distillation before use. Dichloromethane and acetonitrile were distilled from calcium hydride under argon atmosphere.

Proton and carbon nuclear magnetic spectra were recorded on either a Bruker AM 250 or Varian Unity 300 spectrometer. Chemical shifts are recorded in ppm relative to the residual solvent peak. $^1$H NMR data are reported in the order of chemical shift, multiplicity ($s$ = singlet, $d$ = doublet, $q$ = quartet, $m$ = multiplet, $br$ = broad), number of protons, coupling constant in Hz, and proton assignment when known.

General procedure for the formation of glycosyl iodides. Each of the protected anomeric acetates and anhydro sugars (Tables 1.5 and 1.6) were dissolved in dichloromethane-$d_2$ in varying concentrations and placed in an NMR tube. The samples were cooled to the temperature at which the spectrometer was set and one eq of iodonitrtrimethylsilane (from Geleste) was added. The reaction was followed by NMR spectroscopy on the Varian 300 instrument.

Formation of the iodo-glucose and galactose acetate. The $\alpha$ and $\beta$ peracetylated glucose (1.3 and 1.1) and $\beta$-galactose (1.2) (from Aldrich) were dissolved in dichloromethane-$d_2$ in 0.26 M concentration. To this, 1 equivalent of TMSI (from Geleste Inc.) was added directly into a NMR tube and the reaction was followed by NMR spectroscopy using a Bruker 250 instrument. These reactions were performed at ambient temperature. Variable temperature experiments were performed on the Varian 300 instruments.
2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl iodide (1.4). \(^1\)H-NMR (CD\(_2\)Cl\(_2\)):
\(\delta\) 5.82 (d, 1 H, \(J = 9.3\) Hz, H-1), 5.28 (t, 1 H, \(J = 9.1\) Hz), 5.13 (m, 2 H), 4.20 (dd, 1 H, \(J = 12.6\) & 4.8 Hz), 4.09 (dd, 1 H, \(J = 10.2\) & 2.3 Hz), 3.74-3.81 (m, 1 H, H-5), 2.01 (s, 3 H), 2.00 (s, 3 H), 1.94 (s, 3 H), 1.92 (s, 3 H); \(^1\)C NMR: \(\delta\) 170.22, 169.68, 169.12, 168.72, 77.75 (C-1), 74.99, 71.50, 67.52, 61.56, 56.58, 20.50, 20.41, 20.28 (2 carbons).

2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl iodide (1.5). \(^1\)H-NMR: \(\delta\) 6.98 (d, 1 H, \(J = 4.1\) Hz, H-1), 5.39 (dd, 1 H, \(J = 16.3\) & 9.8 Hz), 5.15 (t, 1 H, \(J = 10.0\) Hz), 4.29 (dd, 1 H, \(J = 12.8\) & 4.3 Hz), 4.18 (dd, 1 H, \(J = 9.9\) & 4.2 Hz), 4.04 (m, 2 H), 2.03 (s, 3 H), 2.01 (s, 3 H), 1.99 (s, 3 H), 1.96 (s, 3 H); \(^1\)C NMR: \(\delta\) 170.15, 169.56, 169.35, 169.22, 74.98 (C-1), 73.74, 71.50, 70.09, 66.71, 60.80, 20.52, 20.33, 20.28 (2 carbons).

2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl iodide (1.6). \(^1\)H-NMR: \(\delta\) 5.81 (d, 1 H, \(J = 9.5\) Hz, H-1), 5.50 (t, 1 H, \(J = 9.8\) Hz, H-2), 5.45 (d, 1 H, \(J = 3.3\) Hz, H-4), 4.95 (dd, 1 H, \(J = 9.9\) & 3.3 Hz, H-3), 4.10 (m, 2 H), 4.00 (dd, 1 H, \(J = 12.5\) & 6.43 Hz), 2.16 (s, 3 H), 2.05 (s, 3 H), 2.02 (s, 3 H), 1.94 (s, 3 H); \(^1\)C NMR: \(\delta\) 170.53, 170.40, 170.06, 169.19, 77.24, 72.29, 70.66, 67.53, 61.72, 57.68, 21.01, 20.66-20.77 (3 carbons).

2,3,4,6-Tetra-O-acetyl-α-D-galactopyranosyl iodide (1.7). \(^1\)H-NMR: \(\delta\) 7.10 (d, 1 H, \(J = 4.2\) Hz, H-1), 5.47 (dd, 1 H), 5.24 (dd, 1 H, \(J = 10.5\) & 3.3 Hz), 4.35 (dd, 1 H, \(J = 10.5\) & 4.2 Hz), 4.06-4.27 (m, 3 H), 2.13 (s, 3 H), 2.08 (s, 3 H), 2.03 (s, 3 H),
1.97 (s, 3 H); $^{13}$C NMR: $\delta$ 170.48, 170.05-170.21 (3 carbons), 76.30, 74.22, 70.01, 67.83, 66.97, 61.17, 21.06, 20.71-20.76 (3 carbons).

$\alpha$-1-O-Acetyl-2,3,4,6-tetra-O-benzyl-$\alpha$-D-glucopyranose (1.8) and $\beta$-1-O-acetyl-2,3,4,6-tetra-O-benzyl-$\beta$-D-glucopyranose (1.9). 2,3,4,6-tetra-O-benzy-glucopyranose (1 g, 1.8mmol) was dissolved in 5 mL pyridine (0.37 M) and 0.2 mL (2.8 mmol, 1.6 eq) of acetyl chloride was added dropwise to the mixture. (Be cautious when adding in the acetyl chloride since pyridine reacts violently with acetyl chloride.) The mixture was refluxed for approximately one hr and quenched with ethyl acetate and washed once with H$_2$O. The crude material was purified by flash chromatography using a 5:1 hexane/ethyl acetate solution to obtain a 55% overall yield of a 1:4 mixture of the $\alpha$ and $\beta$ anomers (1.8 and 1.9), respectively. The procedure above was like that of Charette and others$^{22}$ but instead of benzoylation of the sugar, an acylation at the anomeric position was performed. The anomers were purified by HPLC (Waters, Millipore HPLC) using a 6:1 hexane/ethyl acetate + 9% acetone solvent system.

$\alpha$-1-O-acetyl-2,3,4,6-tetra-O-benzyl-$\alpha$-D-glucopyranose (1.8). $^1$H NMR: $\delta$
7.17-7.32 (m, 20 H), 6.29 (d, 1 H, $J = 3.6$ Hz, H-1), 4.92 (d, 1 H, $J = 11.0$ Hz), 4.84 (d, 1 H, $J = 10.9$ Hz), 4.80 (d, 1 H, $J = 11.0$ Hz), 4.69 (d, 1 H, $J = 11.4$ Hz), 4.64 (d, 1 H, $J = 11.4$ Hz), 4.56 (d, 1 H, $J = 10.9$ Hz), 4.54 (d, 1 H, $J = 11.9$ Hz), 4.46 (d, 1 H, $J = 11.9$ Hz), 3.95-3.83 (m, 2 H), 3.60-3.76 (m, 4 H), 2.12 (s, 3 H).

$\beta$-1-O-acetyl-2,3,4,6-tetra-O-benzyl-$\beta$-D-glucopyranose (1.9). $^1$H NMR: $\delta$
7.16-7.35 (m, 20 H), 5.59 (d, 1 H, $J = 8.0$ Hz), 4.77-4.92 (m, 5 H), 4.56 (d, 2 H, $J = 12.5$ Hz), 4.48 (d, 1 H, $J = 11.8$ Hz), 3.52-3.72 (m, 6 H), 2.06 (s, 3 H).
Preparation of \(\alpha,\beta-2,3,4,6\text{-tetra-O-benzyl glucopyranosyl iodide (1.10 & 1.11).}\) The same procedure to form 1.4-1.7 was used except for the concentration: 0.0127 M of the \(\alpha\) and \(\beta\) 1-O-acetyl-2,3,4,6-tetra-O-benzyl glucose in CD\(_2\)Cl\(_2\). The reaction was then followed by NMR at temperatures from -100° up to 10° C on the Varian Unity 300 instrument.

\[2,3,4,6\text{-Tetra-O-benzyl-\(\beta\)-D-glucopyranosyl iodide (1.10).}\] \(^1\)H NMR: (-100°C, CD\(_2\)Cl\(_2\)) \(\delta\) 6.99-7.70 (m, 20 H), 5.61 (d, 1 H, \(J = 9.0\) Hz, H-1), 4.32-5.00 (m, 8 H), 3.39-3.85 (m, 6 H).

\[2,3,4,6\text{-Tetra-O-benzyl-\(\alpha\)-D-glucopyranosyl iodide (1.11).}\] \(^1\)H NMR: \(\delta\) 7.19-7.40 (m, 20 H), 6.96 (d, 1 H, \(J = 3.7\) Hz, H-1), 4.94 (d, 1 H, \(J = 10.9\) Hz), 4.85 (d, 1 H, \(J = 10.9\) Hz), 4.79 (d, 1 H, \(J = 10.9\) Hz), 4.71 (d, 1 H, \(J = 11.5\) Hz), 4.60 (d, 1 H, \(J = 11.5\) Hz), 4.56 (d, 1 H, \(J = 10.9\) Hz), 4.53 (d, 1 H, \(J = 11.8\) Hz), 4.49 (d, 1 H, \(J = 11.8\) Hz), 3.63-3.89 (m, 5 H), 2.81 (dd, 1 H, \(J = 8.8\) and 3.9 Hz).

\[1\text{-O-acetyl-2,3,4,6-tetra-O-benzyl-\(\alpha,\beta\)-D-mannopyranose (1.12 & 1.13).}\] Prepared according to procedure for 1.8 and 1.9. To a solution of 2,3,4,6-tetra-O-benzyl-D-mannopyranose (3.0 g, 5.55 mmol. Toronto Research) cooled to 0° C in 10 mL CH\(_2\)Cl\(_2\) was added pyridine (2.24 mL, 27.7 mmol) followed by acetyl chloride (1.57 mL, 22.2 mmol). After stirring for 4 hr, the mixture was diluted in CH\(_2\)Cl\(_2\), extracted with 2 M H\(_2\)SO\(_4\) followed by brine, and dried over sodium sulfate. The oil was chromatographed using hexane/ethyl acetate to yield 2.9 g (89%) with the \(\alpha\) anomer as the major product.
(1.12). \( R_f = 0.16 \) (4:1 hexane/ethyl acetate). \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 7.44-7.21 (m, 20 H), 6.17 (d, 1 H, \( J = 2.0 \) Hz, H-1), 4.90 (d, 1 H, \( J = 10.8 \) Hz), 4.75 (s, 2 H), 4.65 (s, 2 H), 4.61 (m, 3 H), 4.04 (t, 1 H, \( J = 9.5 \) Hz), 3.92-3.67 (m, 5 H), 2.05 (s, 3 H).

(1.13). \( R_f = 0.13 \) (4:1 hexane/ethyl acetate). \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 7.45-7.16 (m, 20 H), 5.56 (d, 1 H, \( J = 0.6 \) Hz, H-1), 4.86 (d, 1 H, \( J = 10.9 \) Hz), 4.83 (s, 1 H), 4.65-4.47 (m, 6 H), 3.96-3.87 (m, 2 H), 3.72 (d, 2 H, \( J = 3.3 \) Hz), 3.63 (dd, 1 H, \( J = 9.3 \) & 2.9 Hz), 3.54-3.49 (m, 1 H), 2.09 (s, 3 H).

Preparation of \( \alpha \)-2,3,4,6-tetra-O-Benzyl-mannopyranosyl iodide. (1.14). Tetra-O-benzyl-mannopyranosyl iodide was prepared following the general procedure. The mannose \( \alpha \)-acetate (1.12), 37 mg, 0.064 mmol) was dissolved in approximately 0.5 mL CD\(_2\)Cl\(_2\) in an NMR tube and was cooled to -60° C in a dry ice acetone bath. One eq of trimethylsilyl iodide (9.04 µL) was added and the tube was placed into the NMR instrument which was taken down to -80° C. Within three min the first spectrum was obtained. The reaction was followed over 2. When the sample was removed from the instrument there appeared to be some white precipitate in the solution. The same procedure was carried out for the \( \beta \)-acetate (1.13, 11.5 mg, 0.02 mmol) using 1 equivalent trimethylsilyl iodide (2.8 µL) in 0.5 mL CD\(_2\)Cl\(_2\).

In the experiment with addition of tetrabutylammonium iodide, the temperature of the instrument was taken to -90° C. The 1-O-acetate of mannose (1.12, 61.3 mg, 0.11 mmol) was dissolved in CD\(_2\)Cl\(_2\) with 2 equivalent tetrabutylammonium iodide cooled to -98° C in methanol liquid nitrogen bath. TMSI (15 µL, 1 equivalent) was added and the reaction followed by NMR; within 3 min the first spectrum was obtained.
2,3,4,6-Tetra-O-benzyl-\(\alpha\)-D-mannopyranosyl iodide (1.14). \(^1\)H NMR (250 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 7.38-7.22 (m, 20 H), 6.99 (s, 1 H, H-1), 4.89 (d, 1 H, \(J = 10.8\) Hz), 4.71 (d, 1 H, \(J = 11.9\) Hz), 4.66-4.55 (m, 5 H), 4.48 (d, 1 H, \(J = 12.0\) Hz), 4.40 (dd, 1 H, \(J = 9.6, 3.1\) Hz), 4.10-4.03 (m, 2 H), 3.82 (dd, 1 H, \(J = 11.2, 4.2\) Hz), 3.67-3.58 (m, 2 H).

1,2-Anhydro-3,4,6-tri-O-benzyl-\(\alpha\)-D-glucopyranose (1.15). To a solution of 3,4,6 tri-O-benzyl-D-glucal (100 mg, 0.24 mmol) in dichloromethane (1 mL) cooled to \(0^\circ\)C was added dimethyldioxirane (4.8 mL, 0.24 mmol). The solution was stirred for 20 min and the solvent was removed \(\text{in vacuo}\) to yield the product as a white solid. \(^1\)H NMR (250 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 7.35-7.22 (m, 15 H), 4.98-4.49 (m, 6 H), 3.83 (d, 1 H, \(J = 7.7\) Hz), 3.81-3.58 (m, 5 H), 3.08 (d, 1 H, \(J = 2.3\) Hz, H-1).

Procedure for treatment of the 1,2-anhydro-3,4,6-tri-O-benzyl-\(\alpha\)-D-glucopyranose (1.15) with trimethylsilyl iodide. To a solution of the 1,2 anhydro glucose (52.1 mg, 0.12 mmol) in 0.5 mL CD\(_2\)Cl\(_2\) in an NMR tube cooled to \(-100^\circ\)C in a diethyl ether dry ice bath was added TMSI (17.2 \(\mu\)L, 1 equivalent). The tube was inserted into the NMR instrument set to \(-100^\circ\)C and the reaction followed.

3,4,6-Tri-O-benzyl-2-O-trimethylsilyl-\(\alpha\)-D-glucopyranosyl iodide (1.16). \(^1\)H NMR (250 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 7.36-7.23 (m, 15 H), 6.98 (d, 1 H, \(J = 3.8\) Hz, H-1), 4.85 (d, 2 H, \(J = 11.5\) Hz), 4.63-4.66 (m, 4 H), 3.84-3.66 (m, 5 H), 2.81 (dd, 1 H, \(J = 3.8, 8.5\) Hz, H-2), 0.09 (s, 9 H).
1,6-Anhydro-2-azido-3,4-di-O-benzyl-2-deoxy-glucopyranose (1.17). Procedure of Beau. Prepared from 200 mg (1.07 mmol) of 1,6-anhydro-β-D-glucopyranose (1.17) dissolved in dimethylformamide with a mild base Ba(OH)$_2$ (202 mg, 1.18 mmol) and benzyl bromide (509 μL, 4.28 mmol). The reaction was left to stir overnight. A mixture of the di- and mono-protected sugars was obtained. Product obtained as light yellow oil (230 mg, 59%). $R_f = 0.43$ (2:1 hexane/ethyl acetate). $^1$H NMR (250 MHz, CDCl$_3$) δ 7.41-7.34 (m, 10 H), 5.54 (s, 1 H, H-1), 4.67-4.52 (m, 4 H), 4.05 (d, 1 H, $J = 7.3$ Hz, H-6exo), 3.76 (d, 1 H, $J = 6.1$ Hz, H-6endo), 3.72 (s, 1 H, H-3), 3.43 (s, 1 H, H-4), 3.32 (s, 1 H, H-2).

Procedure for treatment of 1,6-anhydro-2-azido-3,4-di-O-benzyl-2-deoxy-glucopyranose (1.17) with trimethylsilyl iodide. To a solution of the 1,6 anhydro glucose (1.17, 39.1 mg, 0.11 mmol) in 0.5 mL CD$_2$Cl$_2$ in an NMR tube kept cold in an ice bath was added TMSI (15.2 μL, 1 equivalent). The tube was inserted into the NMR instrument set at -5° C and the reaction monitored.

2-Azido-3,4,-di-O-benzyl-2-deoxy-6-O-trimethylsilyl-α-D-glucopyranosyl iodide (1.18). $^1$H NMR (250 MHz, CD$_2$Cl$_2$) δ 7.41-7.33 (m, 10 H), 6.85 (d, 1 H, $J = 3.9$ Hz, H-1), 4.95-4.87 (m, 3 H), 4.75 (d, 1 H, $J = 9.3$ Hz), 3.98-3.90 (m, 3 H), 3.82 (d, 1 H, $J = 1.3$ Hz), 3.77 (m, 1 H), 3.06 (m, 1 H, H-2), 0.14 (s, 9H).
CHAPTER 2

SYNTHESIS OF AMINO SUGARS VIA GLYCOSYL IODIDES
INTRODUCTION

2.1 Overview

The purpose of our study involves the synthesis of amino oligosaccharides utilizing glycosyl iodides as glycosyl donors and 1,6-anhydro systems as glycosyl acceptors. The initial synthesis performed led us towards targeting the trisaccharides of Lewis x and Lewis a, and other blood group antigens (Figure 2.1).

![Lewis x trisaccharide](image1)

![Lewis a trisaccharide](image2)

**Figure 2.1** Lewis x and Lewis a trisaccharides

The mechanistic studies performed in Chapter 1 showed that the 1,6-anhydro ring can be opened using trimethylsilyl iodide allowing for extension of nucleophiles at the two ends. Also, we wanted to take advantage of the fact that only two positions, the O-3 and O-4 hydroxyls, required protection and deprotection. Normally, extensive protection and deprotection strategies are necessary. The azide at the 2 position can be reduced to give the amine. This work involves utilization of glycosyl iodides in the effort to synthesize...
complex oligosaccharides. We envision that these compounds can be used as inhibitors of GalCer/gp120 binding.

2.2 1,6-Anhydro Sugars

1,6-Anhydro sugars and especially 1,6-anhydroglucose are a group of compounds of great potential use as building blocks due to their rigid structure that exists in a $\alpha$-D conformation and because they are relatively stable in alkaline media. A number of workers have utilized 1,6-anhydro sugars in their syntheses of oligosaccharides. These 1,6-anhydro sugars are readily available by pyrolysis of starch.\textsuperscript{15} The anhydro bond can be hydrolyzed by strong acid (Figure 2.2).

![Figure 2.2: Pyrolysis of starch to 1,6-anhydroglucose and its ring opening under acidic conditions](image)

The relative reactivities of the various hydroxyl groups toward tosylation are: $\text{OH-2e} > \text{OH-3e} > \text{OH-2a} > \text{OH-4a} > \text{OH-4e} > \text{OH-3a}$. The reactivities with acetyl chloride follow a quite different order, namely, $\text{OH-2e} > \text{OH-4a} > \text{OH-3e} > \text{OH-2a} > \text{OH-3a} > \text{OH-4e}$.\textsuperscript{26} The hydroxyls can be functionalized in many different ways and various conditions without affecting the 1,6 anhydro ring.
1,6-anhydro sugars have been used successfully and effectively in glycoside synthesis. One example is Paulsen's work towards the synthesis of α-glycosidically linked amino sugars utilizing the 1,6 anhydro sugar in his coupling procedure.\textsuperscript{27,28,29,30} The coupling was done using glycosyl bromides as intermediates. He uses the azido group as a "blocking group" for amino groups so that the C-2 substituent does not exert a neighboring group effect. His synthesis started with 2-azido 1,6-anhydro sugars and involved opening the ring by acetolysis to the diacetate in 64% yield (Figure 2.3, step a). The diacetate next is treated with HBr in dichloromethane generating the α-bromide in 82% yield (step b). \textit{In situ} anomerization using tetraethylammonium chloride generated the reactive β-glucosyl chloride (step c) which was then reacted with 1,6 anhydro-3-O-benzyl-glucose to give a 55% yield of a 1→4 linked disaccharide mixture containing 80% of the α-form (step d). He also effected glycosidation of the β-glucosyl chloride with 1,6 anhydro-4-O-benzyl-glucose, in this case obtaining a 36% yield of the 1→3 linked disaccharide containing 80% of the α-glucoside (Figure 2.4). In his synthesis of D-galactosamine, Paulsen reacted β-galactosyl chloride under the conditions described above to the 1,6 anhydro-4-O-benzyl-glucose, generating the α-glycoside in 66% yield in an α:β ratio of 10:1 (Figure 2.5).
**Figure 2.3** Example of Paulsen's work towards the synthesis of α-glycosidically linked 2-amino sugars from the reactive β-glycosyl chloride

**Figure 2.4** Paulsen's coupling of the β-glucosyl chloride with the 4-0-benzyl ether 1,6-anhydroglucopyranose

**Figure 2.5** Paulsen's coupling of the β-galactosyl chloride to the 4-0-benzyl ether 1,6-anhydroglucopyranose
2.3 Lewis Blood Group Antigenic Determinants

On serum, cell membrane and mucins, various O-glycosylation based glycoproteins are found. The role and function of many of these glycoproteins are still largely unknown. Table 2.1 shows the list of blood group and related antigens that are expressed on O-linked cores and among the Lewis blood groups there are Lewis x, the sialic derivative of Lewis x, y, a, and b. There is evidence that Lewis b antigens are involved in the attachment to human gastrointestinal epithelium of *Helicobacter pylori* and *Clostridium difficile* toxin A which are the suggested causative agents of gastric ulcers and pseudomembranous colitis, respectively. Lewis y has been identified as an important epitope for eliciting antibodies against colon and liver adenocarcinoma cell lines. These oligosaccharide based blood groups, and the Lewis blood group antigens are of great importance in understanding diseases such as cancer, HIV, and bacterial and viral infections.
Table 2.1 Blood group and related antigens expressed on O-linked cores
The first chemical synthesis of the Lewis a blood group was by Lemieux in 1974. Lemieux had synthesized trisaccharides of Lewis a and Lewis b by the halide ion catalyzed reaction from the glycosyl bromide.\(^{32,33}\) The 2,2,2-trichloroethyl group was used to block the anomeric hydroxyl of glucose (Figure 2.6). In his syntheses of Lewis a, 2-acetamido-2-deoxy-4-\(\text{-}\alpha\text{-fucopyranosyl}\)-3-\(\text{-}\beta\text{-galactopyranosyl}\)-D-glucose, the galactose moiety is coupled to 2,2,2-trichloroethyl 2-acetamido-4,6-\(\text{-}\beta\text{-benzylidene-2-deoxy-\beta-D-glucopyranose}\) by the Helferich method utilizing mercuric cyanide (Figure 2.7). The benzylidene protecting group is removed under acid conditions. Acetylation is then performed to protect the primary hydroxyl of the 6-OH and this intermediate is coupled to the \(\beta\text{-fucosyl bromide}\) which is generated \textit{in situ} from the \(\alpha\text{-fucosyl bromide}\) (Figure 2.8). The coupling conditions consisted of reacting 2 eq of the fucosyl bromide in the presence of Hunig's base with methylene chloride-dimethylformamide (5:1) as solvent, and gave a crystalline product in 83\% yield.

\[\text{Et}_4\text{NCl} \quad \text{NaHCO}_3\]

\[\text{AcHN} \quad \text{AcHN} \quad \text{AcHN} \]

\[\text{CCI}_3\text{CH}_2\text{OH} \quad \text{CF}_3\text{SO}_3\text{H}\]

\[2,2,2\text{-trichloroethyl}\]

\[2\text{-acetamido-3,4,6\text{-tri-O-acetyl-2-deoxy-\beta-D-glucopyranose}}\]

\textbf{Figure 2.6} Synthesis of the 2,2,2-trichloroethyl glucopyranoside
Figure 2.7 Lemieux's work towards the synthesis of the disaccharide of Lewis x
Figure 2.8 Lemieux's synthesis of the trisaccharide of Lewis x: coupling of fucosyl bromide

As shown above, the first synthesis of Lewis x by Lemieux is quite complicated utilizing numerous protection and deprotection methods especially in the synthesis of the disaccharide portion, though once that was prepared, addition of fucose was done in one step from the bromide fucoside. Since then, much study has been done towards the synthesis of Lewis x and other blood group antigens. Here, we present our route towards the synthesis of Lewis x and variations of Lewis x utilizing glycosyl iodide chemistry.
RESULTS AND DISCUSSION

From the NMR experiments performed thus far, we took interest in the 1,6-anhydro system as a means to get into oligomers by extending the chain through 1→6 linkages. By opening the ring using TMSI, the glucosyl iodide is formed and can act as a glycosyl donor. The silyl group at the 6-O position can be removed under mild acidic conditions and further coupling to another glycosyl iodide can be done, leading to an extended chain. Also, only two positions require contention for protection: the hydroxyls at the 3 and 4 positions. Furthermore, the azide at the 2 position acts as a temporary protection allowing for generation of amino sugars. The 1,6-anhydro-2-azido-2-deoxy-D-glucopyranose (2.1) can be prepared in 3 steps starting from tri-O-acetyl glucal following the work of Veyrieres and Beau (Scheme 2.1). Intramolecular iodocyclization catalyzed by formation of a tin ether leads to an iodo derivative. Reaction with sodium azide gives substitution with retention of configuration leading to 2.1. The 2,3-epoxide is the postulated intermediate.

Scheme 2.1 Preparation of 1,6-anhydro-2-azido-2-deoxy-β-D-glucopyranose (2.1)
Benzyl protection (Scheme 2.2) produced the desired compound 2.2 for ring opening with TMSI (Scheme 2.3). In the protection step, the C-3 and C-4 monosubstituted products were also obtained in a 33:1 ratio of the 4-OBn to 3-OBn.

Scheme 2.2 Benzyl protection of 2.1

The dibenzyl protected 1,6-anhydro sugar 2.2 was then reacted with TMSI forming the 6-O-trimethylsilyl-α-D-glucopyranosyl iodide 2.5. From 2.5, displacement of the iodide by allyl alcohol in benzene with tetrabutylammonium iodide, 2,6-di-i-butylpyridine and subsequent acid workup afforded the α-linked allyl glycoside 2.6 (Scheme 2.4). The reaction was performed both at room temperature and under reflux giving 18 and 13% yield, respectively. In the reaction performed at room temperature and left overnight, 21% of a disaccharide linked α-(1→6) formed from the reaction of 2.6 with another iodide donor. Realizing that the dimer could be formed, we decided to couple the
azido diol 2.1 to the iodide 2.5 under the same conditions as the previous reaction with the allyl alcohol (Scheme 2.4.).

Scheme 2.4 Reaction of 2.5 with allyl alcohol and with 1.6-anhydro glucose

The disaccharide 2.8 was isolated in 12% yield. At this point, the low yields needed to be addressed. Following the reaction by TLC in the first step of the reaction (formation of the iodide from 2.2) showed the spot corresponding to the starting material was always present even after addition of more TMSI. Thus, it was prudent that this step be optimized. To circumvent this problem, we decided to generate the iodide intermediate from the diacetate 2.9. The diacetate can be prepared from the dibenzyl sugar 2.2 in a solution of acetic anhydride/trifluoroacetic acid (9:1 v:v); (Scheme 2.5) in 86% yield. The
diacetate was treated with TMSI and then used to couple 2.1 affording the α-(1→4) linked disaccharide 2.11 in 16% yield (Scheme 2.6). One major factor that perhaps is contributing to the low yield might be the low solubility of the diol 2.1 in methylene chloride. So we performed the reaction in acetonitrile. The iodide of the peracetylated glucose was reacted with 2.1 in acetonitrile with refluxing and left to react overnight. Unfortunately, no product was obtained and about 60% of the diol was recovered.

Scheme 2.5 Opening of the 1.6-anhydro glucose to the diacetate 2.9

Scheme 2.6 Coupling of the iodide 2.10 to the 1.6-anhydro glucose

In an effort to incorporate glycosyl iodides in the synthesis of biologically significant molecules, we directed attention to the synthesis of the trisaccharides of Lewis x and Lewis a. The difference between Lewis x and Lewis a is the position of the galactose and fucose components which are reversed. To accomplish this, the strategy would be to start with the 1,6-anhydro-glucopyranose without any protection at the 3-O and 4-O position and then add on galactose then fucose or vice versa. We suspected that the 4-O
position would be less hindered than the 3-O position which on glycosidation hopefully would yield the 1→4 linkage preferrably. We hypothesized steric hindrance at 4-O would be less because in the benzylation reaction previously performed, the predominant monobenzylation product was from benzylation at the 4-O position. Galactose is attached β to the glucose and fucose has an α linkage to glucose in Lewis x and Lewis a. Our original intention was to synthesize these compounds employing glycosyl iodide chemistry exclusively. However, along the way we realized that the α-iodides were not reactive enough to undergo \( \text{S}_2 \) displacement to give the opposite stereochemistry, the β-glycoside. Instead, to obtain the β linkage, neighboring group participation was employed. The Koenigs-Knorr method (condensation of acylglycosyl halides with alcohols) using glycosyl halides and metal salts as catalyst was applied. The fucose would be attached in an α-linkage and this would be carried out using the conditions and methods of the glycosyl iodides. In situ anomerization of the α-iodide with tetrabutylammonium iodide generates the more reactive β-anomer which reacts with the glycosyl acceptor by \( \text{S}_2 \) or ion pair intermediate to yield the β-glycoside.

In summary, the approach taken for β-(1→4) linkage of galactose to glucose was by way of the Koenigs-Knorr method using silver triflate as promoter (Scheme 2.7). Conditions comprised of reacting 1-bromo-tetra-O-benzoyl-α-D-galactopyranose (2.12) with the diol 2.1 in methylene chloride, in the presence of silver triflate, with 2,6-di-\( \alpha \)-butylpyridine as the proton acceptor. The β-galactose-(1→4)-glucopyranoside 2.13 was isolated in 20% yield from the recovered diol. Connectivity of the C-H bonds was acquired by an HMQC experiment. An HMBC experiment was performed to verify that the linkage was at the 4-O position. Not all the 3-bond couplings were observed, but the peak from C-1 of galactose to H-4 of glucose was present, verifying the connectivity.
Scheme 2.7 Synthesis of β-linked disaccharide 2.13 by the Koenigs-Knorr method

The reaction was performed a second time to try to improve the yield. Knowing that the diol is not very soluble in CH$_2$Cl$_2$, we decided to try running the reaction in a more polar solvent. The diol is completely soluble in tetrahydrofuran (THF), but tetrabutylammonium iodide is not very soluble and so a cosolvent of THF/CH$_2$Cl$_2$ was used (Scheme 2.7). In this case, a mild base as proton acceptor was not added. After one h, from TLC it looked like all the galactose bromide 2.12 was gone. After column purification, numerous products were isolated along with the desired β-(1→4) product 2.13, one of them being the β-(1→3) disaccharide 2.14. Also, 2.15 with an α-linkage of galactose at the 4 position of glucose was obtained in 10% yield. Lastly, 10% of the doubly glycosylated compound 2.16 was obtained. As can be seen from the yields of the three minor components there does not seem to be much regio- or stereoselectivity. Letting the reaction go overnight might have increased the yield since it was run for only one h.
From the results obtained in the previous reaction where all the different combinations of product were obtained with the azido diol and from results of the fucosyl studies (described later), we ascertained that protecting groups were necessary. Therefore the \( t \)-butyl-dimethylsilyl ether protecting group was incorporated (Scheme 2.8).

\[
\begin{align*}
\text{OH} & \quad \text{N}_3 \\
\text{OTBS} & \quad \text{N}_3
\end{align*}
\]

Scheme 2.8 \( t \)-Butyl-dimethylsilyl ether protection of 2.1

This protecting group was chosen because it is stable to hydrolysis and can be removed using tetrabutylammonium fluoride without affecting other portions of the molecule, especially the glycosidic bond. Coupling of galactose to the 3-\( O-t \)-butyl-dimethylsilyl protected 1,6-anhydro-glucose by the Koenigs-Knorr method in methylene chloride, silver triflate, and Hunig's base was performed (Scheme 2.9). Instead of the desired \( \beta(1 \rightarrow 4) \) 2.13, the orthoester 2.19 was obtained. The reaction yielded 85% of the orthoester.
which was characterized by NMR. The anomeric proton chemical shift was 6.29 ppm with a small doublet \( J = 5.1 \text{ Hz} \) which is both unusual for it being either the \( \alpha \) or \( \beta \) anomer. A \(^{13}\text{C}\) shift \( \delta \) 120.6 ppm provided further evidence for the orthoester. At first we thought that the silyl protecting group was affecting the conformation and so was showing lots of differences in the proton spectrum. Therefore, the protecting group was removed. After deprotection in tetrabutylammonium fluoride, the spectrum was not that of the \( \beta \) linkage disaccharide 2.13. Orthoesters are often byproducts in oligosaccharide synthesis. Orthoester formation can be reversed in acidic conditions to the acetoxy intermediate which can with another alcohol at the anomeric position to give the \( \beta \) glycoside (Figure 2.9). In this case, Hunig’s base might have been too strong a base (usually s-collidine or tetramethylurea is used) and so once the orthoester formed, the medium was not acidic enough to rearrange the orthoester to the \( \beta \)-glucoside.

Figure 2.9 Proposed mechanism for acetoxy group participation in glycoside formation

Coupling of the tetra-\( O \)-benzyl-D-galactopyranosyl iodide with 3-\( O \)-silyl ether 1,6-anhydro-D-glucopyranose 2.17 in methylene chloride was tetrabutylammonium iodide and
Hunig's base produced the \( \alpha-(1\rightarrow4) \) linked disaccharide 2.20 (Scheme 2.10). This was not the desired stereochemistry for synthesis of Lewis a and Lewis x, but it was interesting that at room temperature the reaction proceeded in 34% yield.

**Scheme 2.10** Reaction of galactosyl iodide to 3-silyl protected glucose 2.17

Fucosyl iodides were reacted with a number of different glycosyl acceptors. Fucosyl iodides are the most reactive of all the glycoside iodides studied in Chapter 1. Normally, on thin layer chromatography plates, the iodides are identified from the yellow spot that appears above that of the anomeric acetate after dipping the plate into a molybdenum stain. However, when spotting a solution of the fucosyl iodide on TLC plates, after development a yellow spot is not seen but a dark intense spot that cospots with the OH of fucose is observed from its reaction on the plate, suggesting that fucosyl iodides are extremely reactive. The fast reaction makes it difficult to monitor the reaction by TLC requiring careful handling to avoid moisture. Fucosyl iodides are prepared from the 1-\( O \)-acetyl-2,3,4-tri-\( O \)-benzyl-\( \alpha,\beta \)-fucopyranose with TMSI in methylene chloride (Scheme 2.11). The solution is azeotroped with toluene to a brown oil and resuspended in \( \text{CH}_2\text{Cl}_2 \) for the coupling reactions. Then, the \( \alpha \)-iodo-fucoside under halide ion catalyzed conditions was reacted with a number of nucleophiles (Schemes 2.12-2.15).
The first attempt was to couple the fucosyl iodide \textbf{2.23} to the disaccharide \textbf{2.13}. 1.5 equivalent of the 1-O-acetate fucose was used in excess to the nucleophile and the reaction was left for 26 h at room temperature. Unfortunately, this first attempt proved futile perhaps due to moisture entering when rotovaping off the solvent.

\begin{center}
\begin{tabular}{c}
\textbf{Scheme 2.11} Generation of fucosyl iodide from the anomeric acetate \textbf{2.21} \\
\end{tabular}
\end{center}

We next tried coupling 2 eq of fucosyl iodide to the diol \textbf{2.1} to see whether the trisaccharide would be formed (Scheme 2.12). The major product isolated (23\% yield) was the disaccharide $\beta$-D-fucosyl-(1→4)-$\beta$-D-glucose \textbf{2.24}. This result was unexpected, since under these conditions, the $\alpha$-glycoside should have been the product. formed. Generation of the $\beta$-iodide \textit{in situ} should yield the $\alpha$-glycoside by nucleophilic displacement. We suspected that the stereochemistry of the diol might be hindering the $\beta$-iodide from entering and that the $\alpha$-iodide is reactive enough to undergo direct displacement or through an ion-pair oxonium intermediate forming the $\beta$-glycoside. Another explanation though might be that fucose is an L sugar and that the sugar might come together better with the $\alpha$-iodide than the $\beta$-iodide.\textsuperscript{1}
Scheme 2.12 Coupling of fucosyl iodide with diol 2.1

The synthesis of the trisaccharide was repeated taking the disaccharide 2.24 from above and subjecting it to 2 eq of fucosyl iodide (Scheme 2.12). The reaction was run at room temperature for 2 h and there was no sign of product seen on TLC; the reaction was refluxed at 70°C and left stirring overnight. The next day, TLC showed a dark spot above that of the acetylated fucose which was characterized as the trehalose of fucose 2.25. Unfortunately, none of the targeted trisaccharide was isolated. After knowing that trehalose was being formed, we reevaluated reactions performed before and realized that that was often a byproduct.
The reaction of fucosyl iodide with the diol 2.1 was repeated using an excess of iodide, and a cosolvent, tetrahydrofuran/methylene chloride (1:1 v/v), to solublize the diol (Scheme 2.12). The reaction was left stirring at room temperature for 28 h. The reaction after purification yielded 13% of the β-anomer of a 1→4 linked disaccharide 2.24 and also 1% of β-fuc-(1→4)-[α-fuc-(1→3)] trisaccharide 2.27. The formation of an α-linkage at the 3-O position was strong evidence that the diol possessed a different conformation than its monoprotected derivative. These low yields are indicative that the coupling at the 3-O position of 1,6-anhydro-glucose may be difficult and would require heating the reaction mixture.

While we were unsuccessful in obtaining the trisaccharide, we had determined that the 3-O position was so hindered that fucosyl iodide did not react. This led us to react 2 eq of fucosyl iodide with the 4-O-benzyl protected 1,6-anhydro sugar 2.3 (Scheme 2.13). The reaction yielded the desired product, α-L-fucosyl-(1→3)-anhydro-glucose 2.26, in 61% yield. The results proved positive; however, one benzyl group at the 4 position is much smaller than the sugars that are being added and so comparison would not be accurate.

![Scheme 2.13 Coupling of fucosyl iodide to 4-O-benzyl 1,6-anhydro glucose 2.3](image-url)
Towards the synthesis of Lewis a, the fucose is attached through the 4-O position of glucose. The galactose portion is linked at the 3-O of NAc-glucosamine. Fucose was attached onto the 4-O position starting from the 1,6-anhydro-2-azido-2-deoxy-3-\(O\)\(-\text{r-butyl-dimethylsilyl-}\)D-glucopyranose 2.17 and reacted under familiar conditions using 1.5 eq of fucose acetate. The desired product \(\alpha\)-fuc-(1\(\rightarrow\)4) glucose 2.28 was obtained in 67\% yield (Scheme 2.14). Deprotection of the disaccharide in a TBAF, THF solution\textsuperscript{39} afforded a greater than 99\% yield of the free hydroxyl 2.29. The disaccharide 2.29 was then used in the next stage to couple galactose at the 3-O position of glucose by the Koenigs-Knorr method. Disappointingly, the trisaccharide was not successfully obtained.

In the final attempt to synthesize the trisaccharide of Lewis x, 2 eq of fucosyl iodide was added to a flask containing the \(\beta\)-gal\((1\rightarrow4)\)-1,6-anhydroglucose 2.13 (Scheme 2.15). When generating the fucosyl iodide the reaction flask was cooled to -30\(^{\circ}\) C in an ethanol/dry ice bath. After removing methylene chloride from the mixture, toluene was added and again removed under vacuum. The reaction was left stirring for 2 days after which the reaction was stopped and extracted with sodium thiosulfate and water. TLC showed at least two new spots and other spots corresponding to the trehalose, the 1-O-acetyl and 1-OH of fucose, and the starting disaccharide. With so many spots, purification was difficult. Characterization of one of the new spots showed that this was the desired
trisaccharide. Unfortunately, the yield was very low; less than 20 mg (15%) was obtained starting from 129 mg of the disaccharide (Scheme 2.15).

Scheme 2.15 Coupling of fucosyl iodide to β-gal(1→4)-1,6-anhydroglucose 2.13

Optimization of the yield is needed. The conditions are not optimal. From the work of Michael Hadd, in our lab, change of solvent from dichloromethane to benzene and also performing the reaction under reflux may lead to improve yields.

Among these reactions, we wanted to understand whether tetrahydrofuran (THF), a more polar solvent, would affect the stereochemistry of the glycosides formed and/or the yields. It has been known that THF can add to the anomeric center. In an attempt to answer this question, cholesterol was used as an alternative to the diol. Cholesterol was coupled to the iodo fucopyranoside or galactopyranoside. The results are summarized in Table 2.10. The iodo-galactoside yielded the α glycosidic linkage in both cases, with and without Hunig’s base (entries 1 and 2). The iodo-fucoside produced a 4:1 α:β ratio of glycoside (entry 3). In this case, the α linkage was formed as opposed to the previous reaction where the iodo fucose reacted with the diol generating the only product isolated with a β-linkage. Again, this is highly suggestive that the conformation of the diol is having some effect on the stereochemical outcome of the fucose addition. Whether this is
particular to just fucose or to L sugars in general would be interesting to determine. Also, whether D sugars are affected by the conformation of the diol would be another area to explore.

![Diagram of cholesterol and glycosyl acceptor](image)

**Table 2.2.** Results from reaction of galactosyl and fucosyl iodide to the glycosyl acceptor cholesterol

<table>
<thead>
<tr>
<th>Entry</th>
<th>Glycosyl Donor</th>
<th>Conditions-base used</th>
<th>Linkage Formed(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\alpha)-iodo tetra-O-Bn-galactopyranoside</td>
<td>Hunig's base</td>
<td>(\alpha^b)</td>
</tr>
<tr>
<td>2</td>
<td>(\alpha)-iodo tetra-O-Bn-galactopyranoside</td>
<td>none</td>
<td>(\alpha)</td>
</tr>
<tr>
<td>3</td>
<td>(\alpha)-iodo tetra-O-Bn-fucopyranoside</td>
<td>Hunig's base</td>
<td>4:1 (\alpha:\beta^c)</td>
</tr>
</tbody>
</table>

\(^a\) yields were not determined

\(^b\) possibly some minor amount of \(\beta\)-linkage obtained; did not attempt to purify

\(^c\) ratio obtained from NMR integration
CONCLUSION

The synthesis of a trisaccharide Lewis x precursor has been achieved by applying glycosyl iodide chemistry to incorporate the fucosyl portion of the target molecule. However, the yield obtained was extremely low. Eventually, variations of trisaccharide besides the Lewis x and Lewis a and of oligosaccharides are of interest to synthesize in order to assay these compounds for biological activity towards inhibiting HIV/host cell entry events.

Optimization of the yields is critical in an effort to apply glycosyl iodides to synthesis of oligosaccharides. Also, a continuous effort to achieve high stereochemistry in these syntheses is needed. Both of these factors are issues which our group are currently addressing. Incorporation of glycosyl iodides to solid phase chemistry is another approach where we want to apply this chemistry. Much of this work on glycosyl iodides is still in the preliminary stage and much chemistry is yet to be learned in the process.
EXPERIMENTAL SECTION

Starting materials and reagents purchased from suppliers were used without further purification. Chemicals were obtained from the following suppliers: trimethylsilyl iodide, Fluka; tetrabutylammonium iodide, silver triflate, Hunig's base, 2,6-di-tert-butylpyridine, Aldrich. Solvents were dried by distillation prior to use. Dichloromethane and toluene were dried over calcium hydride, and tetrahydrofuran was dried over sodium/benzophenone. All reactions were performed under argon or nitrogen atmosphere.

Thin layer chromatography was performed using silica gel 60 F254 plates. Flash column chromatography was performed using silica gel 60 (230-400 mesh ASTM). Proton and carbon nuclear magnetic resonance spectra were recorded on either a Bruker AM 250 or a Varian Unity 300 spectrometer. Chemical shifts are reported in the order of chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad), the coupling constant in hertz (Hz) and the number of protons. Infrared spectra were recorded using a Nicolet 510P FT-IR spectrometer. Specific rotations were determined using an Autopol III polarimeter. Mass spectrometry was performed by the University of Arizona Mass Spectrometry Facility.

General procedure for the formation of glycosyl iodides. The reaction flask containing ground molecular sieves and a magnetic stirrer was either oven or flame dried prior to use (this is particularly important when working with fucosyl acetates since the fucosyl iodides are extremely reactive). The acetylated sugar was then weighed out in a dry box. The 1-O-acetyl monosaccharide was diluted in dichloromethane and added to the flask. The solution was cooled to below 0°C was stirred for at least 15 min. Trimethylsilyl iodide was added and the solution allowed to sit for 30 min to 1 h. Before transferring to an already stirring solution containing the glycosyl acceptor or alcohol, the

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iodide solution was evaporated with 0.5-1 mL toluene two times to remove trimethylsilyl acetate formed during the reaction. Evaporation was done by pulling a vacuum through a needle line connected to the reaction flask. The dried solution was then redissolved in dichloromethane and syringed into the flask containing the acceptor alcohol for coupling.

1,6-Anhydro-2-azido-2-deoxy-glucopyranose (2.1). These were prepared in four steps according to the procedure by Beau and Veyrieres. Product obtained as a white solid. $R_f = 0.31$ (5:2 toluene/methanol), 0.06 (1:1 hexane/ethyl acetate). $^1$H NMR (250 MHz, DMSO) $\delta$ 5.39 (d, 1H, $J = 4.2$ Hz, -OH), 5.36 (s, 1 H, H-1), 5.26 (d, 1 H, $J = 3.9$ Hz, -OH), 4.42 (dd, 1 H, $J = 5.8$ Hz, H-5), 3.93 (d, 1 H, $J = 7.0$ Hz, H-6exo), 3.56-3.50 (m, 2 H, H-3 and H-6endo), 3.40 (br s, 1 H, H-4), 3.01 (br s, 1 H, H-2). IR (CH$_2$Cl$_2$) 2105 cm$^{-1}$ N$_3$.

1,6-Anhydro-2-azido-3,4-di-O-benzyl-2-deoxy-glucopyranose (2.2). Procedure employed according to work by Beau. Prepared from 200 mg (1.07 mmol) of 1,6-anhydro-ß-D-glucopyranose dissolved in DMF with a mild base Ba(OH)$_2$ (202 mg, 1.18 mmol) and BnBr (509 µL, 4.28 mmol). The reaction was left to stir overnight. A mixture of the di- and mono-protected sugars was obtained. Product obtained as light yellow oil (230 mg, 59%). $R_f = 0.43$ (2:1 hexane/ethyl acetate). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.41-7.34 (m, 10 H), 5.54 (s, 1 H, H-1), 4.67-4.52 (m, 4 H), 4.05 (d, 1 H, $J = 7.3$ Hz, H-6exo), 3.76 (d, 1 H, $J = 6.1$ Hz, H-6endo), 3.72 (s, 1 H, H-3), 3.43 (s, 1 H, H-4), 3.32 (s, 1 H, H-2).

1,6-Anhydro-2-azido-4-O-benzyl-2-deoxy-glucopyranose (2.3). Product obtained as white solid. $R_f = 0.17$ (2:1 hexane/ethyl acetate). $^1$H NMR (250 MHz,
1,6-Anhydro-2-azido-3-O-benzyl-2-deoxy-glucopyranose (2.4). Product obtained as white solid. R<sub>f</sub> = 0.31 (2:1 hexane/ethyl acetate). H NMR (250 MHz, CDCl<sub>3</sub>) δ 7.27-7.17 (m, 5 H), 5.59 (d, 1 H, J = 3.0 Hz, H-1), 4.58 (s, 1 H, OH), 4.39 (m, 1 H, H-5), 3.62-3.53 (m, 3 H), 3.33 (t, 1 H, J = 3.0 Hz, H-4), 3.07 (m, 1 H, H-2).

Allyl 2-azido-3,4-di-O-benzyl-2-deoxy-α-D-glucopyranoside (2.6). To a solution of dibenzyl 1,6-anhydro-glucose 2.2 (50 mg, 0.13 mmol) in 0.7 mL CD<sub>2</sub>Cl<sub>2</sub> cooled to 0° C was added 19 μL (0.13 mmol) of trimethylsilyl iodide (TMSI). The solvent was removed in vacuo, resuspended in dichloromethane, and transferred into an already stirring solution of allyl alcohol (13.3 μL, 0.19 mmol), tetrabutylammonium iodide (48 mg, 0.13 mmol), and 2-6-di-t-butylpyridine (32 μL, 0.14 mmol) in 2 mL benzene. The solution was left to react overnight at room temperature, then diluted in dichloromethane and evaporated in vacuo to an oil. The crude oil was chromatographed using 2:1 hexane/ethyl acetate to yield 9.6 mg (18%) of white solid 2.6 as the major product. R<sub>f</sub> = 0.23 (2:1 hexane/ethyl acetate). H NMR (250 MHz, CDCl<sub>3</sub>) δ 7.36-7.28 (m, 10 H), 5.90 (m, 1 H, H-2'), 5.32 (dd, 1 H, J = 17.2 & 1.5 Hz, H-3' allyl), 5.22 (dd, 1 H, J = 10.4 & 1.3Hz, H-3"allyl), 4.93 (d, 1 H, J = 3.6 Hz, H-1), 4.88 (s, 2 H), 4.86 (d, 1 H, J = 10.0 Hz), 4.17 (m, 1 H, J = 12.8, 6.6 & 1.3 Hz, H-5), 4.09-3.98 (m, 2 H), 3.76-3.71 (m, 3 H), 3.64 (t, 1 H, J = 8.7 Hz, H-3), 3.35 (dd, 1 H, J = 10.2 & 3.6 Hz, H-2), 1.64
O-(2-Azido-3,4-di-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→6)-1-O-allyl α-D-2-azido-3,4-di-O-benzyl-glucopyranoside (2.7). Product obtained as a white solid (2.5 mg, 21% based on yield of 2.6). 1H NMR (250 MHz, CDCl₃) δ 7.35-7.28 (m, 20 H), 5.88 (m, 1 H, J = 5.5 Hz, H-2'allyl), 5.33 (dd, 1 H, J = 19.0 & 1.5 Hz, H-3'allyl), 5.21 (dd, 1 H, J = 9.9 & 1.3 Hz, H-3'allyl), 4.98 (d, 1 H, J = 3.5 Hz, H-7), 4.93 (d, 1 H, J = 4.1 Hz, H-1), 4.90-4.83 (m, 6 H), 4.65-4.59 (m, 2 H), 4.18 (dd, 1 H, J = 13.8 & 1.5 Hz, H-1'allyl), 4.06-3.81 (m, 5 H), 3.68-3.57 (m, 7 H), 3.39 (dd, 1 H, J = 9.6 & 3.2 Hz), 3.30 (dd, 1 H, J = 10.0 & 3.5 Hz). IR (CH₂Cl₂) 2112 cm⁻¹, N₃. HRFABMS calcd for C₄₃H₄₈O₉N₆: 792.3483, found: 791.2571 (M-H)+.

O-(2-Azido-3,4-di-O-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-1,6-anhydro-2-azido-2-deoxy-glucopyranoside (2.8). Method above for compound 2.6 was employed. To a stirring solution of 1,6-anhydro-2-azido-2-deoxy-glucopyranose (80 mg, 0.43 mmol), tetrabutylammonium iodide (105 mg, 0.28 mmol), and 2,6-di-t-butylpyridine (70 µL, 0.31 mmol) in 2 mL benzene was added the iodide sugar (2.5, 109 mg, 0.28 mmol of 2-azido-3,4-di-O-benzyl-2-deoxy-1,6-anhydro glucopyranose) and 44.5 µL (0.31 mmol) of TMSI. The reaction was refluxed for 45 min. Solids were filtered and the solution was extracted with sodium thiosulfate, saturated sodium chloride, and water. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The crude material was chromatographed using 1:1 hexane/ethyl acetate to yield 18.5 mg (12%) of 2.8 as a white solid. Rf = 0.43 (1:1 toluene/acetone). 1H NMR (250 MHz, CDCl₃) δ 7.36-7.27 (m, 10 H), 5.44 (s, 1 H, H-1'), 5.06 (d, 1 H, J = 3.6 Hz, H-1), 4.88-4.84 (m,
3 H), 4.66 (t, 1 H, J = 3.5 Hz, H-5'), 4.64 (d, 1 H, J = 11.1 Hz), 4.10 (t, 1 H, J = 10.1 Hz), 4.02-3.95 (m, 3 H), 3.78 (dd, 1 H, J = 11.9 & 2.2 Hz), 3.76-3.68 (m, 2 H), 3.60-3.52 (m, 3 H), 3.41 (dd, 1 H, J = 10.4 & 3.7 Hz, H-2), 3.19 (d, 1 H, J = 3.9 Hz, H-2'), 2.83 (br s, 1 H, 3-OH), 1.79 (br s, 1 H, 6-OH). IR (CH$_2$Cl$_2$) 2100 cm$^{-1}$. N3.

1,6-Di-O-acetyl-3,4-di-O-benzyl-2-azido-α-D-glucopyranose (2.9). Reaction of 3,4-di-O-benzyl-1.6-anhydro-2-azido glucopyranose (2.2, 64.7 mg, 0.17 mmol) in 3 mL of an acetic anhydride-trifluoroacetic acid solution (9:1 v/v) for 1 h at room temperature followed by addition of 5 mL methanol to quench the reaction gave 2.9 as a white solid (68.5 mg, 86%). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.34-7.20 (m, 10 H), 6.17 (d, 1 H, J = 3.6, H-1), 4.86 (d, 2 H, J = 1.4 Hz), 4.82 (d, 1 H, J = 10.7 Hz), 4.20 (d, 2 H, J = 3.0 Hz), 3.95-3.85 (m, 2 H), 3.62-3.51 (m, 2 H), 2.10 (s, 3 H), 1.98 (s, 3 H).

O-(6-O-Acetyl-2-azido-2-deoxy-3,4-di-O-benzyl-α-D-glucopyranosyl)-(1→4) 1,6-anhydro-glucopyranose (2.11). To a solution of 1,6-di-O-acetyl-3,4-di-O-benzyl-2-azido-glucopyranose (68.5 mg, 0.15 mmol) in 1 mL CH$_2$Cl$_2$ cooled to 0° C was added 22.8 µL (0.16 mmol) of trimethylsilyl iodide and the reaction mixture allowed sit for 1 h. The solvent was then removed in vacuo, and 1 mL toluene was added and again removed in vacuo. The resulting oil was diluted in CH$_2$Cl$_2$ and transferred to a previously stirring solution of 1,6-anhydro-2-azido-2-deoxy-glucopyranose (2.1, 41 mg, 0.22 mmol), tetrabutylammonium iodide (54 mg, 0.15 mmol), and 2,6-di-t-butylpyridine (36 µL, 0.16 mmol) in 1 mL CH$_2$Cl$_2$. The reaction was refluxed for 4 h. Extraction of the mixture was performed using saturated sodium thiosulfate, copper sulfate solution, and water. The residue was concentrated and chromatographed using a gradient 6:1 hexane/ethyl acetate to 1:1 hexane/ethyl acetate as eluent. 14.3 mg (16%) of the
disaccharide was obtained as yellowish oil containing white solids. Rf = 0.10 (1:1 hexane/ethyl acetate). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.36-7.25 (m, 10 H), 5.29 (br s, 1 H, H-1'), 4.93-4.78 (m, 4 H), 4.60-4.54 (m, 2 H), 4.36-3.99 (m, 4 H), 3.95 (br s, 1 H), 3.58-3.36 (m, 5 H), 3.07 (br s, 1 H), 2.02 (s, 3 H, CH$_3$). $^{13}$C NMR (250 MHz, CD$_2$Cl$_2$) $\delta$ 170.84, 138.42, 128.76-128.17, 96.48, 92.45, 83.31, 80.29, 78.54, 77.71, 75.74, 75.65, 75.30, 73.68, 69.71, 67.96, 64.42, 63.06, 20.97. IR (CH$_2$Cl$_2$) 750, 1260, 1750, 2100 cm$^{-1}$. N$_3$. MS calcd for C$_{28}$H$_{32}$O$_9$N$_6$ 596.2231.

(Note: MS did not show a molecular ion peak. Further experimentation is needed.)

$^{2,3,4,6}$-Tetra-O-benzoyl-$\alpha$-D-galactopyranosyl bromide (2.12). Procedure of Fletcher.$^{15}$ To a solution containing penta-O-benzoyl-galactopyranose in CH$_2$Cl$_2$ was added HBr in acetic acid at room temperature. After 15 min stirring at r.t., the mixture was placed in the refrigerator and left overnight. The next day, the organic layer was washed three times with 10% Na$_2$S$_2$O$_3$, three times with saturated NaH$_2$CO$_3$, and once with deionized water. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo to yield white solids in 94% yield. $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 8.06-7.21 (m, 20 H), 6.96 (d, 1 H, $J$ = 3.9 Hz, H-1), 6.10 (d, 1 H, $J$ = 3.4 Hz, H-4), 6.04 (dd, 1 H, $J$ = 10.4 & 3.4 Hz, H-3), 5.65 (dd, 1 H, $J$ = 10.3 & 4.0 Hz, H-2), 4.90 (t, 1 H, $J$ = 6.2 Hz, H-5), 4.62 (dd, 1 H, $J$ = 11.4 & 6.7 Hz, H-6endo), 4.44 (dd, 1 H, $J$ = 11.5 & 6.1 Hz, H-6exo).

$^{2,3,4,6}$-Tetra-O-benzoyl-$\beta$-D-galactopyranosyl (1$\rightarrow$4) 1,6-anhydro-glucopyranose (2.13). Method of Igarashi $^{36}$, Takeo $^{38}$, and Hanessian$^{37}$. The diol was dried under P$_2$O$_5$ overnight before use. To a solution of 1,6-anhydro-2-azido-2-deoxy-glucopyranose (72 mg, 0.39 mmol), silver triflate (118 mg, 0.46 mmole), and 2-6-di-r-
butylpyridine (216 μL, 0.96 mmol) in 2 mL dichloromethane cooled to -25 °C was added the bromo 2,3,4,6-tetra-O-benzoyl-galactopyranoside (2.12. 303 mg, 0.46 mmol) in CH₂Cl₂. The reaction flask was kept foiled and left to react at -25 to 0 °C for 3 h. Afterward, the mixture was diluted, filtered through Celite and concentrated in vacuo. Separation by chromatography using 3:1 hexane/ethyl acetate afforded 28 mg (20% from the recovered diol) of the disaccharide as a clear oil. ¹H NMR (250 MHz, CD₂Cl₂) δ 8.12-7.25 (m, 20 H), 6.00 (d, 1 H, = 3.3 Hz, H-4), 5.85 (dd, 1 H, J = 10.4 & 7.9 Hz, H-2), 5.63 (dd, 1 H, J = 10.5 & 3.4 Hz, H-3), 5.27 (s, 1 H, H-1'), 5.05 (d, 1 H, J = 7.89 Hz, H-1), 4.67 (dd, 1 H, J = 11.2 & 4.2 Hz, H-6exo or endo), 4.57-4.43 (m, 2 H, H-6 and H-5), 4.36 (d, 1 H, J = 5.3 Hz, H-5'), 3.94 (t, 1 H, J = 4.7 Hz, H-3'), 3.77 (d, 1 H, J = 4.7 Hz, H-6'exo), 3.67-3.51 (m, 3 H), 3.26 (d, 1 H, J = 6.0 Hz, H-2'). ¹³C NMR (250 MHz, CD₂Cl₂) δ 166.38, 165.88, 165.70, 165.48, 134.11, 133.76, 130.28-128.71, 102.32, 102.01, 85.32, 76.63, 72.58, 72.38, 71.93, 70.09, 68.56, 67.40, 64.93, 63.09. IR (CH₂Cl₂) 2103, 1719, 1265, 706 cm⁻¹. HRFABMS (matrix: glycerin:thioglycerin) calc for C₃₀H₃₅O₁₃N₃, 765.2170, found 766.2250 (M-H)⁻.

2,3,4,6-Tetra-O-benzoyl-β-D-galactopyranosyl (1→3) 1,6-anhydro-glucopyranose (2.14). 158 mg (10%) of 2.14 obtained as a yellow oil. ¹H NMR (250 MHz, CDCl₃) δ 8.10-7.16 (m, 20 H), 5.98 (d, 1 H, J = 2.9 Hz, H-4), 5.81 (dd, 1 H, J = 10.4 & 8.0 Hz, H-2), 5.62 (dd, 1 H, J = 10.5 & 3.4 Hz, H-3), 5.28 (s, 1 H, H-1'), 4.91 (d, 1 H, J = 8.0 Hz, H-1), 4.58-4.36 (m, 4 H), 3.95 (d, 1 H, J = 7.5 Hz), 3.82-3.73 (m, 2 H), 3.65 (q, 1 H, J = 4.6 Hz), 3.62 (dd, 1 H, J = 5.4 & 2.0 Hz), 3.25 (d, 1 H, J = 4.7 Hz, H-2'), 2.70 (br s, 1 H, OH).
2,3,4,6-Tetra-O-benzoyl-α-D-galactopyranosyl (1→4) 1,6-anhydro-glucopyranose (2.15). 161 mg (10%) of 2.15 obtained as a yellow oil. $^1$H NMR (250 MHz, C$_6$D$_6$) δ 8.15-7.95 (m, 8 H), 7.08-6.72 (m, 12 H), 6.51 (dd, 1 H, $J = 10.8$ & 3.3 Hz, H-3), 6.18 (d, 1 H, $J = 3.2$ Hz, H-4), 6.11 (dd, 1 H, $J = 10.8$ & 3.7 Hz, H-2), 5.76 (d, 1 H, $J = 3.7$ Hz, H-1), 5.23 (s, 1 H, H-1'), 4.84-4.80 (m, 2 H), 4.66 (d, 1 H, $J = 5.3$ Hz, H-5'), 4.27 (s, 1 H). 4.09 (d, 1 H, $J = 8.5$ Hz), 3.67 (br s, 1 H, H-3'), 3.58 (d, 1 H, $J = 7.4$ Hz), 3.24-3.18 (m, 2 H), 2.61 (s, 1 H, OH).

$O$-(2,3,4,6-Tetra-O-benzoyl-β-D-galactopyranosyl)-(1→4)-$O$-[(2,3,4,6-tetra-O-benzoyl-β-D-galactopyranosyl)-(1→3)]-1,6-anhydro-2-azido-2-deoxy-β-D-glucopyranoside (2.16). Product 2.16 obtained as a white solid in 10% yield. $R_f$ = 0.64 (9.4:0.6 methylene chloride/ethyl acetate). $^1$H NMR (250 MHz, CDCl$_3$) δ 8.09-7.21 (m, 40 H), 5.93 (d, 1 H, $J = 4.0$ Hz, H-4'), 5.91 (d, 1 H, $J = 4.3$ Hz, H-1''), 5.83 (dd, 1 H, $J = 10.4$ & 7.9 Hz, H-2''), 5.69 (dd, 1 H, $J = 10.4$ & 7.9 Hz, H-2''), 5.56 (dd, 1 H, $J = 10.4$ & 3.4 Hz, H-3''), 5.48 (dd, 1 H, $J = 10.5$ & 3.4 Hz, H-3''), 5.21 (s, 1 H, H-1), 5.01 (d, 1 H, $J = 7.9$ Hz, H-1'), 4.70 (d, 1 H, $J = 8.0$ Hz, H-1''), 4.65-4.59 (m, 2 H, H-6'b, H-6''b). 4.52-4.43 (m, 2 H, H-6'a, H-6''a). 4.38-4.32 (m, 3 H, H-5'). 4.13 (d, 1 H, $J = 7.1$ Hz), 4.07 (d, 1 H, $J = 7.1$ Hz), 4.06 (d, 1 H, $J = 7.7$ Hz), 3.97 (s, 1 H), 3.51 (s, 1 H, $J = 7.4$. 13.3 Hz), 2.84 (s, 1 H, H-2). $^{13}$C NMR (250 MHz, CDCl$_3$) δ 166.01, 165.88, 165.46, 165.34, 165.06, 164.82, 133.49, 133.22, 133.13, 130.07, 130.00, 129.84-128.25. 101.76, 101.5, 99.9, 76.71, 73.97, 71.67, 71.41, 71.13, 69.67, 69.27, 68.33, 68.16, 64.42, 62.11, 61.89, 60.34, 58.56.

3-O-t-Butyl-di-methylsilyl and 4-O-t-butyl-di-methylsilyl 1,6-anhydro-2-azido-2-deoxy-β-D-glucopyranose (2.17 & 2.18). To a solution of the
unprotected 1,6-anhydro sugar (1 g, 5.4 mmol), imidazole (15 mg, 0.05%), and triethylamine (2.24 mL, 16.05 mmol) in 30 mL (0.18 M) dimethylformamide with molecular sieves was added t-butyldimethylsilyl chloride (886 mg, 5.88 mmol). The reaction was left to stir for 9 h at room temperature. Dimethylformamide was evaporated as much as possible in vacuo and the residue chromatographed using a 4:1 hexane/ethyl acetate as eluent. A mixture of 2.17 and 2.18 was obtained (594 mg, 37%). Rf (2.17) = 0.39 (2:1 hexane/ethyl acetate). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 5.42 (s, 1 H, H-1), 4.51 (d, H-1, $J = 5.6$ Hz, H-5), 4.26 (d, 1 H, $J = 7.05$ Hz, H-6exo), 3.84 (t, H-1, $J = 1.5$ Hz, H-3), 3.75 (t, 1 H, $J = 6.3$ Hz, H-6endo), 3.47 (br s, 1 H, H-4), 3.35 (s, 1 H, H-2), 2.60 (br s, 1 H, 4-OH), 0.88 (s, 9 H), 0.10 (d, 6 H, 2.4 Hz). $^{13}$C NMR (250 MHz, CDCl$_3$) $\delta$ 100.00, 76.15, 71.94, 71.06, 64.85, 62.33, 25.58, 17.60, -5.10, -5.24. Rf (2.18) = 0.36 (2:1 hexane/ethyl acetate). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 5.48 (s, 1 H, H-1), 4.42 (d, 1 H, $J = 5.08$ Hz, H-5), 4.02 (d, 1 H, $J = 7.5$ Hz, H-6exo), 3.74 (br s, 1 H, H-3), 3.70 (dd, 1 H, $J = 7.5$ & 5.3 Hz, H-6endo), 3.64 (s, 1 H, H-4), 3.11 (s, 1 H, H-2), 2.36 (br s, 1 H, 3-OH), 0.89 (s, 9 H), 0.11 (d, 6 H, $J = 1.2$ Hz).

$O$-(1,6-Anhydro-2-azido-2-deoxy-3-hydroxy-glucopyranosyl)-3,4,6-tri-$O$-benzoyl-$\alpha$-galactosyl orthoester (2.19). To a solution of the 3-O-silyl protected anhydro sugar 2.17 (60 mg, 0.20 mmol), silver triflate (76.2 mg, 0.30 mmol), and Hunig's base (108 $\mu$L, 0.23 mmol) in CH$_2$Cl$_2$ cooled to -25° C in an acetone dry ice bath was added the tetra-$O$-benzoyl-galactosyl bromide (2.12, 197.2 mg, 0.30 mmol). The reaction flask was covered with aluminum foil and stirred for 3 h at -25° C after which it was left to warm to r.t. overnight. The reaction mixture was then diluted in CH$_2$Cl$_2$ and filtered through Celite. Purification of the residual oil yielded 148 mg (85%) of the
protected product as a light yellow oil. \( R_f = 0.50 \) (2:1) hexane/ethyl acetate. Deprotection of the silyl ether using TBAF in THF yielded 2.19. \( ^1\text{H NMR (250 MHz, CDCl}_3 \) \( \delta \) 7.98-7.90 (m, 8 H), 7.47-7.34 (m, 12 H), 6.29 (d, 1 H, \( J = 5.1 \) Hz, H-1), 5.80-5.77 (m, 1 H), 5.50 (dd, 1 H, \( J = 6.2 \) & 4.1 Hz), 5.41, (s, 1 H, H-1'), 4.86 (t, 1 H, \( J = 5.1 \) Hz), 4.56 (dd, 1 H, \( J = 10.8 \) & 6.3 Hz), 4.54 (d, 1 H, \( J = 6.0 \) Hz), 4.45 (dd, 1 H, \( J = 7.7 \), 5.6 & 2.7 Hz), 4.36 (dd, 1 H, \( J = 10.8 \) & 5.4 Hz), 3.83 (m, 1 H), 3.81 (d, 1 H, \( J = 4.2 \) Hz), 3.59 (dd, 1 H, \( J = 5.4 \) & 5.2 Hz), 3.48 (d, 1 H, \( J = 2.8 \) Hz), 3.17 (d, 1 H, \( J = 3.6 \) Hz), 2.39 (d, 1H, \( J = 5.7 \) Hz). \( ^1\text{C NMR (250 MHz, CDCl}_3 \) \( \delta \) 165.90, 165.20, 135.61, 133.56, 133.40, 133.12, 130.04-129.71, 128.80-128.29, 126.24, 120.55, 100.36, 98.47, 74.97, 73.37, 72.18, 71.13, 70.25, 69.01, 66.34, 64.68, 62.29, 61.31, 25.41, 17.56, -5.34, -5.41.

\( O\)-(2,3,4,6-Tetra-O-benzyl-\( \alpha \)-D-galactopyranosyl)-(1→4)-1,6-anhydro-2-azido-2-deoxy-3-\( \alpha \)-butyl-dimethylsilyl-\( \beta \)-D-glucopyranoside (2.20). Product 2.20 obtained as a yellow oil and in 34% yield. \([\alpha]^{25}_D = +98.04^\circ\) (3.6 g/100 mL. CH\(_2\)Cl\(_2\)). \( ^1\text{H NMR (250 MHz, C}_6\text{D}_6 \) \( \delta \) 7.38-7.07 (m, 20 H), 5.50 (s, 1 H, H-1'). 5.06 (d, 1 H, \( J = 3.6 \) Hz), 4.98 (d, 1 H, \( J = 11.5 \) Hz), 4.90 (d, 1 H, \( J = 5.4 \) Hz, H-1), 4.85 (d, 1 H, \( J = 4.2 \) Hz), 4.76 (d, 1 H, \( J = 4.0 \) Hz), 4.71 (d, 1 H, \( J = 4.2 \) Hz), 4.58 (d, 1 H, \( J = 11.5 \) Hz), 4.47 (s, 2 H), 4.32 (t, 1 H, \( J = 6.1 \) Hz), 4.23 (dd, 1 H, \( J = 2.7 \), 10.2 Hz), 4.17-4.04 (m, 3 H), 3.93 (d, 1 H, \( J = 1.9 \) Hz), 3.67-3.53 (m, 2 H), 3.47-3.41 (m, 2 H), 2.86 (s, 1 H, H-2'), 0.89 (s, 9 H), -0.11 (d, 6 H, \( J = 1.6 \) Hz). \( ^1\text{C NMR (250 MHz, CDCl}_3 \) \( \delta \) 138.85, 138.52, 138.14, 128.29-127.35, 100.78 (\( J_C-H = 171.8 \) Hz), 79.58, 78.95, 76.25, 75.39, 74.87, 74.63, 73.24, 73.20, 73.00, 71.54, 70.21, 69.96, 64.56, 61.02, 25.52, 17.70, -5.28, -5.34. IR (CH\(_2\)Cl\(_2\)) 2098 cm\(^{-1}\), -N\(_3\). HRFABMS (in mNBA) calc for C\(_{46}\)H\(_{73}\)O\(_9\)N\(_3\)Si 823.3864, found 822.3777 (M-H)*.
1-O-Acetyl-2,3,4,6-tetra-O-benzyl-α,β-L-fucopyranose (2.21 & 2.22). To a solution of 2,3,4-tri-O-benzyl-L-fucopyranose (1 g, 2.30 mmol, Pfanstiehl) and pyridine (1.47 mL, 18.4 mmol) in 12 mL CH₂Cl₂ cooled in an ice bath was added acetyl chloride (327 µL, 4.60 mmol) and the reaction was left stirring for 3 h. The solution became orange-yellow and contained pyridinium chloride salts. The mixture was filtered through Celite, concentrated in vacuo, and chromatographed using 4:1 hexane/ethyl acetate. A mixture of α and β acetates (2.21 and 2.22) was obtained as a white solid in 95% yield (1.04 g). Rf = 0.22 (4:1 hexane/ethyl acetate). (2.19) ¹H NMR (250 MHz, CDCl₃) δ 7.39-7.25 (m, 15 H), 6.36 (d, 1 H, J = 3.7 Hz, H-1), 4.97 (d, 1 H, J = 11.5 Hz), 4.85 (d, 1 H, J = 11.9 Hz), 4.73 (d, 1 H, J = 11.9 Hz), 4.69 (m, 2H), 4.64 (d, 1 H, J = 11.5 Hz), 4.15 (dd, 1 H, J = 10.1 & 3.7 Hz, H-2), 3.93 (q, 1 H, J = 13.1 & 7.0 Hz, H-5), 3.87 (dd, 1 H, J = 10.1 & 2.8 Hz, H-3), 3.69 (m, 1 H, H-4), 2.10 (s, 3 H), 1.13 (d, 3 H, J = 6.5 Hz).

(2.20) ¹H NMR (250 MHz, CDCl₃) δ 7.39-7.25 (m, 15 H), 5.53 (s, 1 H, H-2), 2.02 (s, 3 H), 1.16 (d, 3 H, J = 6.5 Hz).

O-(2,3,4-tri-O-benzyl-β-L-fucosyl)-(1→4)-1,6-anhydro-2-azido-2-deoxy-β-D-glucopyranoside (2.24). To a solution containing the diol 2.1 (50 mg, 0.27 mmol), tetrabutylammonium iodide (97 mg, 0.27 mmol), and Hunig's base (51.2 µL, 0.29 mmol) in CH₂Cl₂/THF (2:1 v/v) was added 1.5 eq of fucosyl iodide. The reaction was left stirring for 28 h at r.t. The mixture was concentrated and chromatographed using a gradient system 4:1 to 2:1 to 1:1 hexane/ethyl acetate to yield (2.24, 20.5 mg, 1.3%) as a yellow oil. Also, 3.2 mg of the trisaccharide 2.27 was obtained. Rf = 0.08 (2:1 hexane/ethyl acetate). ¹H NMR (250 MHz, CD₂Cl₂) δ 7.41-7.27 (m, 15 H), 5.30 (s, 1 H, J = 6.5 Hz).
H-1'), 4.97 (d, 1 H, \( J = 11.1 \) Hz), 4.87 (m, 2 H), 4.76 (s, 2 H), 4.68 (d, 1 H, \( J = 4.7 \) Hz, H-5'), 4.62 (d, 1 H, \( J = 11.1 \) Hz), 4.49 (d, 1 H, \( J = 7.7 \) Hz, H-1'), 3.87 (d, 1 H, \( J = 7.4 \) Hz, H-6'endo), 3.78 (dd, 1 H, \( J = 9.6 \) & 7.8 Hz), 3.69 (m, 1 H, H-3'), 3.64-3.47 (m, 5 H), 3.20 (d, 1 H, \( J = 11.8 \) Hz), 1.47 (d, 1 H, \( J = 5.9 \) Hz, H-2), 2.76 (d, 1 H, \( J = 4.5 \) Hz, 3-OH), 1.47 (d, 1 H, \( J = 11.8 \) Hz). 13C NMR (250 MHz, CD2Cl2) \( \delta \) 128.73-128.01, 104.79, 101.80, 83.17, 83.03, 79.62, 77.65, 77.09, 75.73, 75.48, 73.13, 72.46, 71.01, 67.97, 65.05, 16.97. LRFABMS calc for C33H23O8N3 603, found 602.3 (M-H)+.

\( \alpha \)-Trehalose of fucose (2.25). \( R_f = 0.52 \) (2:1 hexane/ethyl acetate). Product 2.25 obtained as an oil. \( ^1H \) NMR (250 MHz, CDCl3) \( \delta \) 7.41 (m, 30 H), 5.22 (d, 2 H, \( J = 2.6 \) Hz), 4.95 (d, 2 H, \( J = 11.5 \) Hz), 4.80-4.59 (m, 12 H), 4.12 (dd, 2 H, \( J = 6.5 \) Hz), 4.06-4.00 (m, 4 H), 3.66 (s, 2 H), 1.02 (d, 6 H, \( J = 6.3 \) Hz). HRFABMS calcd for C54H46O10 850.4081, found 849.4019 (M-H)+, 851.4155 (M+H)+.

\( O-(2,3,4\text{-Tri-O-benzyl-}\alpha\text{-L-fucosyl})(1\rightarrow3)-1,6\text{-anhydro-2-azido-4-O-benzyl-glucopyranoside} \) (2.26). To a solution of 1-\( \alpha \)-acetyl-2,3,4-tri-O-benzyl-fucopyranose (2.21, 344 mg, 0.72 mmol) in 2 mL CH2Cl2 cooled to below 0° C was added TMSI (113 \( \mu \)L, 0.79 mmol). The mixture was reacted for 1 and concentrated in vacuo. Another evaporation was done using 1 mL toluene. The fucosyl iodide was transferred into a prepared solution containing 1,6-anhydro-2-azido-4-O-benzyl-2-deoxy-glucopyranose (2.3, 100 mg, 0.36 mmol), tetrabutylammonium iodide (266 mg, 0.72 mmol), and Hunig’s base (138 \( \mu \)L, 0.8 mmol) in CH2Cl2. The reaction was left stirring overnight at room temperature. The reaction mixture was diluted in CH2Cl2, filtered, and extracted. The resulting oil was chromatographed using 4:1 hexane/ethyl acetate to yield 152 mg (61%) of 2.26 as a yellow oil. The dimer 2.25 of fucose was also formed as a
minor byproduct. $^1$H NMR (250 MHz, C$_6$D$_6$) $\delta$ 7.49-7.01 (m, 20 H), 5.09 (s, 1 H, H-1'), 5.07 (d, 1 H, $J$ = 11.3 Hz), 4.92 (d, 1 H, $J$ = 3.6 Hz, H-1), 4.80 (d, 1 H, $J$ = 11.9 Hz), 4.65 (d, 2 H, $J$ = 13.2 Hz), 4.48 (d, 2 H, $J$ = 12.5 Hz), 4.42 (s, 1 H), 4.31 (d, 1 H, $J$ = 5.3 Hz), 4.17 (dd, 1 H, $J$ = 10.1 & 3.6 Hz), 4.06 (s, 1 H), 3.80 (dd, 1 H, $J$ = 10.0 & 2.7 Hz), 3.77 (d, 1 H, $J$ = 6.7 Hz), 3.65 (q, 1 H, $J$ = 12.8 & 6.4 Hz), 3.44-3.39 (m, 2 H), 3.15 (s, 1 H), 3.10 (s, 1 H), 1.03 (d, 3 H, $J$ = 6.4 Hz). $^{13}$C NMR (250 MHz, CDCl$_3$) $\delta$ 138.81, 138.65, 138.52, 137.49, 128.75-127.33, 100.56 ($J_{C-H} = 175.8$ Hz), 97.21 ($J_{C-H} = 171$ Hz), 78.75, 77.47, 76.37, 76.26, 74.91, 74.49, 73.94, 73.33, 73.11, 71.51, 67.54, 65.40, 59.25, 16.50. HRFABMS calc for C$_{40}$H$_{42}$O$_8$N$_3$ 693.3050, found 692.2991 (M-H)$^+$, 693.3035 (M+H)$^+$. O-(2,3,4-Tri-O-benzyl-$\beta$-L-fucopyranosyl)-(1$\rightarrow$4)-O-[(2,3,4-tri-O-benzyl-$\alpha$-L-fucopyranosyl)-(1$\rightarrow$3)]-1,6-anhydro-2-azido-2-deoxy-$\beta$-d-glucopyranoside (2.27). 3.2 mg of trisaccharide 2.27 was obtained as a yellow oil. R$_f$ = 0.37 (2:1 hexane/ethyl acetate). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.35-7.17 (m, 30 H), 5.47 (s, 1 H, H-1'), 5.06-4.56 (m, 13 H), 4.41 (d, 1 H, $J$ = 7.5, H-1'), 4.90-3.30 (m, 13 H), 1.09 (d, 3 H, $J$ = 6.3 Hz, CH$_3$), 1.02 (d, 3 H, $J$ = 6.5 Hz, CH$_3$). $^{13}$C NMR (250 MHz, CD$_2$Cl$_2$) $\delta$ 128.64-127.54, 103.74, 100.28, 98.02, 82.79, 79.08, 77.15, 76.43, 76.17, 75.58, 75.44, 75.06, 73.31, 73.16, 70.87, 67.91, 6563, 59.26, 16.94, 16.74. HRFABMS calc for C$_{60}$H$_{65}$O$_{12}$N$_3$ 1019.4568, found 1018.4474 (M-H)$^+$, 1020.4563 (M+H)$^+$. O-(2,3,4-Tri-O-benzyl-$\alpha$-D-fucosyl)-(1$\rightarrow$4)-1,6-anhydro-2-azido-2-deoxy-3-O-$t$-butyl-di-methylsilyl-$\beta$-D-glucopyranoside (2.28). R$_f$ = 0.61 (2:1 hexane/ethyl acetate). 82.3 mg (67%) of product obtained as clear oil. $[\alpha]^{25}_D$ = -189.92°
(2.6 g/100 mL, CH₂Cl₂). ¹H NMR (250 MHz, C₆D₆) δ 7.43-7.04 (m, 15 H), 5.45 (s, 1 H, H-1'), 6.05 (d, 1 H, J = 11.2 Hz), 4.88 (d, 1 H, J = 2.5 Hz, H-1'), 4.75 (d, 2 H, J = 11.7 Hz), 4.61-4.40 (m, 3 H), 4.35 (d, 1 H, J = 5.4 Hz, H-5'), 4.27 (s, 1 H), 4.23-4.11 (m, 4 H), 3.76 (d, 1 H, J = 6.9 Hz, H-6'endo), 3.44 (s, 1 H, H-3'), 3.11 (t, 1 H, J = 6.5 Hz, H-6'endo), 3.07 (s, 1 H, H-4'), 2.86 (s, 1 H, H-2'), 1.30 (d, 3 H, J = 6.5 Hz, CH₃), 0.89 (s, 9 H), 0.05 (d, 6 H, J = 3.4 Hz). ¹³C NMR (250 MHz, CDCl₃) δ 139.11, 138.96, 138.50, 128.54-127.38, 100.23 (J C-H = 183 Hz), 99.99 (J C-H = 166 Hz), 79.29, 79.06, 77.65, 76.71, 74.83, 74.39, 73.26, 73.20, 70.92, 67.33, 64.81, 61.65, 25.52, 17.66, 16.72, -5.03, -5.34. IR (CH₂Cl₂) 2098 cm⁻¹, -N₃. HRFABMS (in mNBA) calcd for C₃₉H₅₁O₈N₃Si 717.3445, found 716.3369 (M-H)+, 740.3358 (M+Na)+.

O-(2,3,4-Tri-O-benzyl-α-D-fucosyl)-(1→4)-1,6-anhydro-2-azido-2-deoxy-β-D-glucopyranoside (2.29). Removal of the silyl ether protecting group of 2.28 (67.6 mg, 0.09 mmol) in 0.72 mL THF (0.09 g/mL) cooled to 0°C was performed using typical cleavage procedure by addition of tetrabutylammonium fluoride (188 μL of 1.0 M solution in THF). The reaction was left stirring for 5 min at 0°C and then at r.t. for 40 min after which only one spot was observed by TLC. The mixture was concentrated in vacuo and chromatographed using 2:1 hexane:ethyl acetate yielding 57 mg (> 99%) of the product. ¹H NMR (250 MHz, CDCl₃) δ 7.41-7.24 (m, 15 H), 5.30 (s, 1 H, H-1'), 4.98 (d, 1 H, J = 11.4 Hz), 4.90-4.82 (m, 3 H, H-1', 2 PhH), 4.74 (d, 1 H, J = 11.82 Hz), 4.66-4.56 (m, 3 H, H-5', 2 PhH), 4.06 (m, 1 H), 3.95 (dd, 1 H, J = 10.2 & 2.7 Hz), 3.77 (br s, OH), 3.73-3.58 (m, 5 H), 3.24-3.20 (m, 2 H). ¹³C NMR (250 MHz, CDCl₃) δ 138.39, 138.01, 128.21-127.24, 101.66 (J C-H = 165.8 Hz), 99.14 (J C-H = 166.07 Hz), 84.77, 78.62, 77.30, 76.32, 76.18, 74.86, 73.57, 73.10, 72.25, 67.92, 67.60,
64.91, 16.53. HRFABMS calc for C$_{33}$H$_{37}$O$_8$N$_3$ 603.2580, found 602.2501 (M-H)$^+$, 604.2635 (M+H)$^+$.

$O$-($2,3,4$-Tri-$O$-benzyl-$\alpha$-$L$-fucosyl)-(1$\rightarrow$3)-$O$-[(2,3,4,6$\text{-}$tetra-$O$-benzoyl-$\beta$-$D$-galactopyranosyl)-(1$\rightarrow$4)]-1,6$\text{-}$anhydro-2$\text{-}$azido-2$\text{-}$deoxy$\text{-}$glucopyranoside (2.30). To a solution of 2.13 (129 mg, 0.169 mmol), tetrabutylammonium iodide (125 mg, 0.338 mmol), and Hunig’s base (50 µL, 0.338 mmol), in 1 mL CH$_2$Cl$_2$ was added 2 eq. fucosyl iodide (2.23, 161 mg, 0.335 mmol from 1-$O$-acetyl-tri-$O$-benzyl fucose) which was kept cooled at -58°C. The reaction was left stirring at r.t. for 2 days. After, the solution was filtered through Celite to remove molecular sieves, then diluted with CH$_2$Cl$_2$, and extracted with 10% sodium thiosulfate and water. The organic layer was dried with magnesium sulfate and filtered through Celite using a fritted funnel. Concentration of solution in vacuo resulted in brownish oil which was chromatographed using a 6:1 hexane/ethyl acetate system. 25 mg (15%) of 2.30 was obtained as an oil. R$_f$ = 0.32 (2:1 hexane/ethyl acetate). $^1$H NMR (250 MHz, CDCl$_3$) δ 8.05-7.18 (m, 35 H), 6.11 (dd, 1 H, $\jmath$ = 9.9 & 3.5 Hz, H-3), 6.03 (d, 1 H, $\jmath$ = 2.6 Hz, H-4), 5.64-5.67 (m, 2 H), 5.21 (s, 1 H), 4.95 (m, 2 H), 4.83 (d, 1 H, $\jmath$ = 5.2 Hz), 4.75-4.46 (m, 8 H), 4.40 (dd, 1 H $\jmath$ = 11.6 & 4.3 Hz), 3.95 (d, 1 H, $\jmath$ = 7.2 Hz), 3.99 (dd, 1 H, $\jmath$ = 10.0 & 3.7 Hz), 3.68-3.44 (m, 6 H), 3.04 (s, 1 H, H-2'), 0.68 (m, 3 H). $^{13}$C NMR (250 MHz, CDCl$_3$) δ 138.70, 138.46, 138.40, 133.59, 133.50, 133.27, 133.12, 129.95, 129.76, 129.70, 129.62, 128.65-127.43, 100.40, 98.15, 96.57, 77.21, 75.96, 74.84, 74.77, 74.56, 73.04, 72.87, 69.40, 69.29, 68.15, 68.01, 67.74, 64.50, 63.23, 56.82, 16.16. HRFABMS calc for C$_{67}$H$_{63}$O$_{17}$N$_3$ 1181.4157, found 1180.4073 (M-H)$^+$.
APPENDIX
NMR study done at -40°C
NMR study performed at -40°C.
NMR study done at -40°C
NMR study performed at -100°C


13. Hung, S-C.; Wong, C-H. "Synthesis of Glycosyl Chlorides with Acid-Labile


