University of Alberta

2,3-Aziridino Ribofuranosyl Donors in Glycoside Bond Synthesis

by

Md. Faiaz Ahmed

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of

Master of Science

Department of Chemistry

©Md. Faiaz Ahmed
Spring 2013
Edmonton, Alberta

Permission is hereby granted to the University of Alberta Libraries to reproduce single copies of this thesis and to lend or sell such copies for private, scholarly or scientific research purposes only. Where the thesis is converted to, or otherwise made available in digital form, the University of Alberta will advise potential users of the thesis of these terms.

The author reserves all other publication and other rights in association with the copyright in the thesis and, except as herein before provided, neither the thesis nor any substantial portion thereof may be printed or otherwise reproduced in any material form whatsoever without the author’s prior written permission.
Dedicated to my Family Members
Abstract

The number of biologically important events mediated by carbohydrates has generated great interest in the synthesis of oligosaccharides and the development of new methods for glycosidic bond formation. I have developed a glycosylation method where glycosyl donors containing a three-membered epoxide ring are used. These species are highly selective glycosyl donors and the glycoside bonds formed are cis to the epoxide moiety. In this project, I have extended this work to substrates in which the epoxide ring is replaced with an aziridine moiety. For this purpose, I synthesized two aziridine-containing donors \(N\)-acetyl-2,3-aziridino-5-\(O\)-benzoyl-2,3-dideoxy-D-ribofuranose (1) and \(N\)-acetyl-2,3-aziridino-5-\(O\)-benzoyl-2,3-dideoxy-\(\beta\)-D-ribofuranosyl trichloroacetimidate (2).

A seven step route was developed for the synthesis of hemiacetal (1) starting from D-arabinose and one step is required to synthesize trichloroacetimidate (2) from 1. Glycosylation of a range of alcohol acceptors with donor 1 using dimethylsulfide and trifluoromethanesulfonic acid anhydride (Gin glycoslylation) gave products in good yields and with moderate \(\alpha:\beta\) selectivity. Glycosylation of these alcohols with 2 promoted by trimethylsilyl trifluoromethanesulfonate proceed with slightly better selectivity. I also investigated the effect of diethyl ether on glycosylation reactions with donor 2.
Acknowledgement

I wish to thank my advisor, Professor Todd L. Lowary, for his constant encouragement and support during the research. The research project and scientific independence he gave me made a comprehensive training for my future career. His kindness made the years in his research group truly enjoyable.

I also want to thank crystallographer Dr. Robert McDonald for his help with X-ray analysis of crystals. I thank Mark Miskolzie, Ami, NupurDabral and all of the staff at the Chemistry Department for their continuous support during my study at University of Alberta.

I am eternally grateful to all of past and present members of the Lowary group for help and advice during my research. I would like to thank my M.Phil advisor Professor Wahab Khan and all of my friends in the chemistry department, U of A for their constant support and encouragement.

And very special thank to my family members for their endless love and encouragement, without them I am not sure if I would ever been able to finish this endeavor.
Contents

Chapter 1

1.1. Biological and Chemical Background on Carbohydrates .........................1

1.2. General Aspects of Glycosidic Bond Synthesis ..................................3

   1.2.1. Formation of Glycosidic Bonds .............................................3

   1.2.2. Anomeric Effect .....................................................................4

1.3. Methods for Glycosidic Bonds Synthesis ............................................7

   1.3.1. Koenigs-Knorr and Related Methods .......................................9

   1.3.2. Thioglycosides and Related Donors .......................................12

   1.3.3. Sulfoxide Methodology ..........................................................15

   1.3.4. Trichloroacetimidate and Related Donors ...............................16

   1.3.5. Gin Glycosylation Method .......................................................19

   1.3.6. n-Pentenyl Glycoside Methodology ......................................20

   1.3.7. Glycosylation with Glycals ....................................................22

1.4. Factors Controlling Stereochemistry and Rate of Glycosylation Reaction...23

   1.4.1. Factors Controlling the Stereochemistry and Rate of Glycosylation

           Reaction, Donor .....................................................................23

           1.4.1.1. Protecting Group on the Donors .....................................23

   1.4.2. Solvent Effect ......................................................................26
Chapter 2: Results and Discussion

2.1. Research Aims and Strategy

2.2. Synthesis of Donors 1 and 2

2.2.1. Synthesis of N-acetyl-2,3-aziridino-5-O-benzoyl-2,3-dideoxy-D-ribofuranose (1)

2.3. Synthesis of N-acetyl-2,3-aziridino-5-O-benzoyl-2,3-dideoxy-β-D-ribofuranosyltrichloroacetimidate (2)

2.4. Method for Establishing Anomeric Stereochemistry

2.5. Stereoselectivity of Donors 1 and 2 in Glycosylation Reactions

2.5.1. Glycosylation Reactions with Hemiacetal 1

2.6. Conclusion

2.7. Bibliography

Chapter 3: Future Work

3.0. Future Work

Chapter 4: Experimental
**List of Tables**

2-1. Glycosylation of alcohols 20–27 with N-acetyl-2,3-aziridino-5-O benzoyl-2,3-dideoxy-D-ribofuranose (1)…………………………………………………………51

2-2. Glycosylation of alcohols 20–27 with N-acetyl-2,3-aziridino-5-O benzoyl-2,3-dideoxy-β-D-ribofuranosyltrichloroacetimidate (2)……………………………………………..55
List of Figures

1-1. General glycosylation reaction.........................................................3

1-2. α and β glycosides...........................................................................4

1-3. General mechanism of glycosylation reaction....................................4

1-4. Anomeric center...............................................................................5

1-5. Endo anomeric effect.......................................................................6

1-6. Exo anomeric effect.........................................................................6

1-7. Categories of glycosylation mechanisms...........................................7

1-8. Categories of glycosyl donors...........................................................8

1-9. Examples of glycosyl donors.............................................................8

1-10. Conversion of one donor into another.............................................9

1-11. Glycosidic bonds............................................................................9

1-12. Koenings–Knorr glycosylation method...........................................10

1-13. Preparation of glycosyl bromide....................................................10

1-14. Synthesis of glycosyl fluoride........................................................11

1-15. Glycosyl fluorides as a glycosyl donor...........................................11

1-16. Conversion of a thioglycosides into other glycosyl donors...............12

1-17. Preparation of thioglycosides........................................................13
1-18. Chemical structures of IDCP, BSP and DMTST

1-19. Preparation of glycosidic bonds using thioglycosides and a general mechanism

1-20. Synthesis of phenylseleno glycosides and their reactions with alcohols

1-21. Preparation of glycosylsulfoxides

1-22. Glycosylation reaction of glycosylsulfoxide donors

1-23. Synthesis of trichloroacetimidate donors

1-24. Selective synthesis of trichloroacetimidate

1-25. Synthesis of thermodynamic and kinetic trichloroacetimidates

1-26. Reaction of trichloroacetimidate and its mechanism

1-27. Gin glycosylation

1-28. Example of Gin glycosylation

1-29. Synthesis of n-pentenyl glycoside

1-30. Mechanism of n-pentenyl glycoside activation

1-31. Rearrangement of orthoester

1-32. Strategy of glycosylation with glycal XI

1-33. Example of glycosylation with glycal

1-34. Neighboring group participation

1-35. Effect of C-2 group on formation of an oxocarbenium ion
1-36. Formation of oxocarbenium ions ................................................. 25
1-37. Polar aprotic solvent effect on glycoside synthesis ..................... 27
1-38. Ether solvent effect on glycosylation reaction .............................. 27
1-39. Relative reactivity of glycosyl acceptors ................................... 28
1-40. Effect of bulky groups on glycosylation ..................................... 29
1-41. Relative reactivity of glucose amides ....................................... 29
1-42. Mechanism of β-arabinofuranosides synthesis via 2, 3-anhydrosugar .... 32
1-43. Synthesis of β-arabinofuranoside ............................................ 33
2-1. Glycosyl donor targets 1 and 2 .................................................. 39
2-2. General strategy to targets and predicted decomposition pathway with thioglycoside substrates ......................................................... 40
2-3. Thermal ellipsoid plot (20% probability) of compound 7 ................ 42
2-4. Thermal ellipsoid plot (20% probability) of compound 19 ............. 47
2-5. List of acceptors studied (20–27) and possible products (28–35) .... 49
2-6. Plausible mechanism of the Gin glycosylation ............................. 52
2-7. Proposed negative steric interactions between the aziridine moiety in V and acceptor alcohols ......................................................... 53
2-8. Proposed pathway for reactions involving imidate donors .............. 56
3-1. Thioglycosyl donors .................................................................. 58
List of Schemes

1-1. Use of $N$-phenyl trifluoroacetimidates as donors........................................19

1-2. Thioglycosides and sulfoxides in glycoside bond synthesis.........................30

1-3. Synthesis of $\beta$-arabinofuranoside and regioselective opening of epoxide moiety..............................................................30

1-4. Synthesis of $\alpha$-arabinofurnoside and regioselective opening of epoxide moiety..............................................................31

2-1. Initial attempts to synthesize an aziridine-containing precursor to 1 and 2...........................................................................41

2-2. Second attempt to synthesize an aziridine-containing precursor to 1 and 2...........................................................................44

2-3. Attempted synthesis of 1 from PMP glycoside 18.......................................45

2-4. Successful synthesis of 1.............................................................................46

2-5. Synthesis of 2 from 1.................................................................................48

2-6. Gin glycosylation reaction of donor 1 with alcohols 20–27 .........................50

2-7. Glycosylation reactions with trichloroacetimidate donor 2.........................54
List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>aq.</td>
<td>Aqueous</td>
</tr>
<tr>
<td>BSP</td>
<td>1-benzenesulfinyl piperidine</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzoyl</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>TBAHS</td>
<td>tetra-butylammonium hydrogen sulfate</td>
</tr>
<tr>
<td>DTBMP</td>
<td>2,6-di-tert-butyl-4-methylpyridine</td>
</tr>
<tr>
<td>TTBP</td>
<td>2,4,6-tri-tert-butyl-pyrimidine</td>
</tr>
<tr>
<td>Cat.</td>
<td>Catalyst</td>
</tr>
<tr>
<td>Cbz</td>
<td>Carbobenzyloxy</td>
</tr>
<tr>
<td>CAN</td>
<td>Ceric ammonium nitrate</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>DFT</td>
<td>Density functional theory</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0.]undec-7-ene</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5, 6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DIAD</td>
<td>Diisopropylazodicarboxylate</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-Diisopropylethylamine</td>
</tr>
<tr>
<td>DMDO</td>
<td>3,3-Dimethylidioxirane</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N'-Dimethylformamide</td>
</tr>
<tr>
<td>DMTST</td>
<td>Dimethyl (methylthio)sulfoniumtriflate</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>h</td>
<td>Hour</td>
</tr>
<tr>
<td>IDCP</td>
<td>Iodoniumdicollidinepechlorate</td>
</tr>
<tr>
<td>NIS</td>
<td>N-Iodosuccinimide</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>MsCl</td>
<td>Methanesulfonyl chloride</td>
</tr>
<tr>
<td>MTr</td>
<td>(p-Methoxyphenyl) diphenylmethyl</td>
</tr>
<tr>
<td>min</td>
<td>Minute</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>q</td>
<td>Quartet</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>AgOTf</td>
<td>Silver trifluoromethanesulfonate</td>
</tr>
<tr>
<td>satd.</td>
<td>Saturated</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>Tf</td>
<td>Trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>Tf₂O</td>
<td>Trifluoromethanesulfonic acid anhydride</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TMSOTf</td>
<td>Trimethylsilyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>TMANO</td>
<td>TrimethylamineN-oxide</td>
</tr>
<tr>
<td>TsCl</td>
<td>4-Toluenesulfonyl chloride</td>
</tr>
</tbody>
</table>
Chapter 1

1.1. Biological and Chemical Background on Carbohydrates

Oligosaccharides are components of many natural products involved in an enormous number of biological processes, and particularly associated with tremendous diagnostic and therapeutic potential.\(^1\) It is well known that complex oligosaccharides in the form of glycolipids and glycoproteins are present in the membranes of the human cells.\(^1\) These molecules can mediate a large number of diverse and important biological functions. Due to their complexity, many functions of oligosaccharides in biological systems still remain unknown. In the last few decades major scientific effort has focused upon those carbohydrates associated with diseases involved in cancer, cardiovascular disease, and bacterial, viral, and parasitic infections.\(^2\) The main reason for this effort is to try to understand structural and conformational preferences of carbohydrate molecules, and mechanistic pathways for pathogenesis that could lead to producing effective tools for the prevention, diagnosis, and treatment of these diseases.\(^2\) The biological roles of carbohydrate molecules depend on many factors. Biological properties of biopolymers such as nucleic acids, peptides and proteins depend on the sequence of amino acids or nucleotides, whereas the situation is more complex in case of carbohydrates. For carbohydrate molecules, biological function not only depends on the sequence of the monomeric structures but also on the stereochemistry of glycosidic linkages, the functional groups and ring stereochemistry. All these factors have made the construction of oligosaccharides challenging. Therefore, the development and testing of new synthetic methodologies must be investigated in order to meet these synthetic
In mid-1980s and 1990s approaches were developed that significantly shortened oligosaccharide assembly by minimizing the use of protecting groups among the glycosylation steps. Notable among these approaches are Nicolaou’s concept of selective donor activation, the armed–disarmed technique of Fraser-Reid, the active–latent concept of Roy and Boons, Danishefsky’s glycal assembly methodology, Ogawa’s and Ito’s orthogonal approach, and finally, programmable strategies developed by Wong and Ley. These innovations have allowed chemists to synthesize complex oligosaccharides that were practically inaccessible previously. One example is the total synthesis of the complex tumor antigens of the Globo-series, in particular Globo-H, by Danishefsky, Schmidt, Boons, Wong, and Seeberger. However, these syntheses still remain very complex. Only highly skilled chemists can accomplish these targets. Moreover, the syntheses of each target still requires careful manipulation of protecting groups, optimization of conditions and careful design of synthetic strategies.

These challenges have stimulated synthetic chemists to develop new methods for the stereoselective synthesis of glycosidic bonds. As a result, a number of new strategies have been developed and applied successfully in complex oligosaccharide synthesis. Among this work is Gin’s dehydrative glycosylation method, Lowary’s work on small ring strategies for furanosides, solid phase automated synthetic strategies of Seeberger, Hung’s work on synthesis via regioselective one-pot protection, Gervay-Hague’s glycosyl iodide approach in oligosaccharide synthesis and Boons’ strategy for stereoselective 1,2-cis-glycosylations.
1.2. General Aspects of Glycosidic Bond Synthesis

1.2.1. Formation of Glycosidic Bonds

The bond connecting a carbohydrate residue to another species is referred to as a glycoside bond. The usual method by which glycoside bonds are synthesized is shown in Figure 1-1. This bond is formed by the substitution of a leaving group (LG) at the anomeric position of a carbohydrate residue by an alcohol (ROH). The glycosyl moiety is referred to as the Donor and the alcohol is known as the Acceptor. The glycosylation reaction is generally performed in the presence of an appropriate activator (such as TMSOTf or NIS/AgOTf), which facilitates cleavage of the leaving group to generate a positively charged intermediate. Nucleophilic attack at the anomeric center of this intermediate, either from the top or from the bottom face of the ring, gives the glycoside product. The OR group at the anomeric center in a glycoside is referred to as the aglycone.

\[
\text{Donor} \quad \text{Acceptor} \quad \text{Activator} \quad \text{Glycoside}
\]

\( P = \text{Protecting group} \)

Stereoselectivity in glycosylation is one of the major challenges of this reaction. The anomeric carbon on the glycosyl donor is a stereogenic center. Thus, two diastereomers, referred to as α or β glycosides, are formed. The thermodynamically favored product is the axial (usually α) glycoside due to the anomeric effect (discussed later). The stereoselectivity of the reaction can be controlled using various conditions as discussed later.
The general mechanism for glycosylation reaction is represented in Figure 1-3. The donor’s leaving group is chemoselectively activated by an activator, often a Lewis acid, to generate an oxocarbenium ion that can react with an acceptor alcohol, as a result forming glycosidic bond.

1.2.2. Anomeric Effect

The anomeric effect, or the Edward–Lemieux effect, is a stereoelectronic effect that describes the tendency to form gauche conformations around the C–Y bond in an O(5)–C(1)–Y(1)–C system (shown in Figure 1-4), where Y is an electronegative heteroatom with electron lone pair. In carbohydrates, the Y–C bond of interest is the one that connects the anomeric carbon with aglycone. In pyranoses, when Y is an electronegative heteroatom, this group prefers to adopt
an axial orientation instead of the less hindered equatorial orientation due to the anomeric effect. This effect was initially described by J. T. Edward in 1955 in pyranose rings.\textsuperscript{29b} There are two types of anomeric effect, the \textit{endo}-anomeric effect and the \textit{exo}-anomeric effect.\textsuperscript{29a}

\begin{center}
\includegraphics[width=0.5\textwidth]{figure1.png}
\end{center}

\textbf{Figure 1-4:} Anomeric center

Stabilization by the \textit{endo} and \textit{exo} anomeric effects can be explained as shown in Figures 1-5 and 1-6 (where Y is replaced by an O(1) atom) respectively. In the \textit{endo} anomeric effect, when the C1–O1 bond is axial, interactions occur between the anti bonding orbital of this bond and one of the lone pairs of the ring oxygen. Both are in the same plane. This interaction provides some double bond character to the O5–C1 bond. Thus, this bond becomes shorter and stronger, and the C1–O1 bond becomes longer. On the other hand, this type of orbital overlap is impossible when the C1–O1 bond is in an equatorial position because anti bonding orbital and oxygen lone pairs are in different planes. Therefore, the β-isomer is less stable. An alternative way of looking at this effect involves dipole–dipole repulsion between the lone pairs of the ring oxygen and the oxygen on the β-glycosidic bond, which disfavors the β-anomer. On the other hand, in the case of the α-anomer these dipoles are opposed.
Another anomeric effect is the exo-anomeric effect, which involves rotation around the C(1)–O(1)-R as shown in Figure 1-6. In this case, one of the lone pairs of the aglycon oxygen atom interacts with the antibonding orbital of the C1–O5 bond. In both axial and equatorial anomers, the oxygen lone pairs and O(5)-C(1) anti bonding orbitals are on the same plane. Therefore, both axial and equatorial glycosides have an exo-anomeric effect. Because the equatorial (β)-glycoside lacks an endo-anomeric effect, the exo-anomeric effect is more important for the equatorial glycoside.
1.3. Methods for Glycosidic Bonds Synthesis

Several methods are available to synthesize glycoside bonds. Generally, glycoside bond formation requires a leaving group in either the donor or the acceptor. The departure of the leaving group is usually activated by the use of specific promoters. The majority of glycosidic bonds syntheses involve one of three ionic mechanisms A, B and C (Figure 1-7). Strategy A involves $S_N$2 displacement of the leaving group by a nucleophile. In strategy B, a leaving group in the acceptor is displaced by a donor nucleophile in an $S_N$2 manner. This strategy is less popular in glycoside bond formation. In the third mechanistic strategy, C, the alcohol nucleophile attacks an electrophilic anomeric center that is generated in situ from an appropriate donor species. Nowadays the most used approach is strategy C and the discussion below will focus on this approach.

![Figure 1-7: Categories of glycosylation mechanisms](image)

To synthesize a glycoside bond, one needs a suitable donor. Modern glycosyl donors have the following characteristics: mild activation conditions, high stability toward the protecting group manipulations and a versatile accessibility (reacts with most of alcohols). Glycosyl donors can be classified according to the nature
of the leaving group: O-glycosyl derivatives, S-glycosyl derivatives and X-glycosyl derivatives as shown in Figure 1-8. Among them, O-glycosyl derivatives and S-derivatives are more frequently used as glycosyl donors compared to X-glycosyl derivatives.

![Figure 1-8: Categories of glycosyl donors](nan)

Some examples of glycosyl donors are shown in Figure 1-9. Among them, the most commonly used glycosyl donors are imidates and thioglycosides. Acetate, sulfoxide and selenoglycoside donors are also used in some extent in glycosylation reactions.

![Figure 1-9: Examples of glycosyl donors](nan)
In many cases, one donor can be converted to another using the appropriate reagents. For example, a glycosyl acetate can be easily converted into a glycosyl bromide using PBr_3 in dichloromethane (Figure 1-10).

![Figure 1-10: Conversion of one donor into another](image)

There are two types of O-glycosidic bonds with respect to the stereochemistry between the groups at O1 and O2, 1,2-cis and 1,2-trans. Examples of these glycosidic linkages are shown in Figure 1-11.

![Figure 1-11: Glycosidic bonds](image)

### 1.3.1. Koenigs–Knorr and Related Methods

Wilhelm Koenigs and Edward Knorr first treated acetobromoglucose with alcohol in presence of Ag_2CO_3. That’s why the substitution reaction of the glycosyl bromide with an alcohol to produce a glycosidic linkage is known as the Koenigs–Knorr reaction. It is the oldest glycosylation procedure. It was first
successfully performed in 1901 by Hermann Emil Fisher\cite{30(c)} and until mid-1980s commonly-used method for the synthesis of glycosidic bonds. Initially, insoluble activators such as Ag₂CO₃ and Ag₂O were used.\cite{30(b)} In the early of the 1960s homogenous promoters such as HgBr₂ and Hg(CN)₂, a method often called the Helferich reaction, were exploited.\cite{30(d)} It is now more common to use AgOTf as the activator. One example is shown in Figure 1-12. Glycosylation of the alcohol I with bromide II gave disaccharide III in the presence of AgOTf in 82% yield.\cite{30(a), 31}

\[ \text{II} \xrightarrow{\text{AgOTf, DCM}} \text{III} \]

Figure 1-12: Koenigs–Knorr glycosylation method

The mannose bromide can be synthesized from the fully acetylated sugar. The reaction of acetylated mannose with PBr₃/H₂O produced the glycosyl bromide in 85% yield (Figure 1-13).\cite{32(a)}

\[ \text{I} \xrightarrow{\text{PBr₃, H₂O, DCM}} \text{Br} \]

Figure 1-13: Preparation of glycosyl bromide

The instability of glycosyl halides the needs for the disposal of toxic metal promoter waste and the requirement of equimolar amounts of the activator have made this methodology less popular. So, other alternative methods have been of
great interest. In 1981, Mukaiyama and co-workers first used glycosyl fluorides as a donor for the synthesis of glycosidic bonds.\textsuperscript{32} One of the notable advantages of glycosyl fluorides as a donor is their high thermal and chemical stability compared to the corresponding iodides, bromides or chlorides, which makes them good alternatives to the Koenigs–Knorr method. These glycosyl fluorides can be synthesized from hemiacetals by the treatment with diethylaminosulfur trifluoride or by treatment of anomic acetates with HF/Pyr as shown in Figure 1-14.\textsuperscript{32(b)}

![Figure 1-14: Synthesis of glycosyl fluoride](image)

Mukaiyama and co-workers used the fluorophilic activator SnCl\textsubscript{2}–AgClO\textsubscript{4} in glycosylation reactions of glycosyl fluorides. After that report, a number of fluorophilic activators have been reported to be effective in O-glycosylation reactions such as TMSOTf (Hashimoto, 1984),\textsuperscript{32(c)} F\textsubscript{3}B–OEt\textsubscript{2} (Kunz, 1985),\textsuperscript{32(d)} Cp\textsubscript{2}ZrCl\textsubscript{2}–AgClO\textsubscript{4} (Matsumoto, 1988),\textsuperscript{32(e)} La(ClO\textsubscript{4})\textsubscript{3} (Kim, 1995)\textsuperscript{32(f)} and LiClO\textsubscript{4} (Waldmann, 1995)\textsuperscript{32(g)}.

![Figure 1-15: Glycosyl fluorides as a glycosyl donor](image)
1.3.2. Thioglycosides and Related Donors

Thioglycosides are one of the most popular glycosyl donors. The success of thioglycosides arises from the lack of reactivity of the anomeric sulfur-containing group toward a range of conditions used to activate other glycosyl donors, and during protection and deprotection of sugar functional group. Moreover, thioglycosides are hydrolytically more stable compared to glycosyl halides. Thioglycosides can be converted into other types of donor, making them a versatile class of compounds.\textsuperscript{33}

![Conversion of thioglycosides into other glycosyl donors](image)

**Figure 1-16**: Conversion of thioglycosides into other glycosyl donors

The synthesis of simple alkyl and aryl thioglycosides is straightforward and can be performed using commercially available materials on a large scale. For example, phenyl thioglycosides can be prepared readily from the corresponding anomeric acetates by the treatment with thiophenol in the presence of BF$_3$·OEt$_2$.\textsuperscript{34}
Activation of thioglycosides can be performed by many promoters. Examples include $N$-iodosuccinimide (NIS)/trifluoromethanesulfonic acid (TfOH), methyl trifluoromethanesulfonate (MeOTf), phenylselenyltriflate (PhSeOTf), dimethylthiomethylsulfoniumtriflate (DMTST) and iodonium di-sym-collidine perchlorate (IDCP). Recently, it has been reported that sulfoniumtriflate species, generated by diphenylsulfoxide–Tf$_2$O (Ph$_2$SO–Tf$_2$O), or 1-benzenesulfinyl piperidine–triflic anhydride (BSP–Tf$_2$O), can activate thioglycosides.

There are many examples of glycosylation reactions using thioglycosides as glycosyl donors. One example, involving sulfonium triflate activation, is shown in Figure 1-19 with a general reaction mechanism. Here a methyl thioglycoside is used as the donor. Upon activation with dimethyl disulfide and triflic anhydride in the presence of an alcohol, the expected disaccharide was produced in 93% yield. A general mechanism of thioglycoside is shown in Figure 1-19. Activation of the thioglycoside generates an oxacarbeniumion, which is attacked by the nucleophile at the carbocation center to produce a glycosidic bond.
Other types of glycosyl donors that behave similarly to thioglycosides are selenoglycosides. Phenyl selenoglycosides are versatile donors and are more reactive compared to thioglycoside. Selective activation of selenoglycosides over thioglycosides is possible and, together with their inertness under conditions in which glycosyl halides and glycosyl trichloroacetimidates (see below) can be activated, makes them attractive donor in glycoside bond synthesis. Phenylseleno glycosides can be synthesized easily by the reaction of sugar acetates with phenylselenol in the presence of BF₃·OEt₂. Phenylseleno glycosides can be activated using AgOTf or NIS/TfOH resulting in the formation of glycosidic bonds.

Figure 1-19: Preparation of glycosidic bonds using thioglycosides and a general mechanism
1.3.3. Sulfoxide Methodology

Another powerful method for glycosylation is the use of glycosylsulfoxides. Glycosylsulfoxides can be prepared easily by the oxidation reaction of thioglycosides with several oxidizing agents such as m-chloroperbenzoic acid (m-CPBA) or magnesium monoperoxyphthalate (MMPP).\textsuperscript{37,38}

The activation of glycosylsulfoxides involves the use of the promoter triflic anhydride (Tf\textsubscript{2}O) or trimethylsilyl triflates in a stoichiometric amount. Sulfoxide glycosylations are always carried out in the presence of a hindered base such as DTBMP or TTBP, which acts as an acid scavenger. The strength of this method is that it is very efficient with rather unreactive nucleophiles, and the activation conditions are mild leading to the potential for chemoselectivity. In some cases, the reactions can be done even at −100 °C. One example is shown below, where the glycoside is synthesized at very low temperature even with an acceptor containing an less reactive alcohol.\textsuperscript{38,39}
1.3.4. Trichloroacetimidates and Related Donors

Trichloroacetimidates are among the most useful and popular glycosyl donors in carbohydrate chemistry. This donor is easy to make from commercially available reagents and easy to activate. This method was developed by Schmidt in 1980, and avoids the use of heavy metal reagents as activators. The glycosyl donor can be prepared easily from the reaction of hemiacetals with trichloroacetonitrile in presence of base and the products are stable enough to store for a short period of time.40

![Figure 1-23: Synthesis of trichloroacetimidate donors]

The anomeric stereochemistry of the trichloroacetimidate is crucial to the stereocontrol of the glycosylation. Generally, the α-trichloroacetimidate gives the β-glycoside and vice-versa. The α-trichloroacetimidate can be exclusively synthesized using a strong base (NaH, KOH or 1,8-diazabicyclo[5.4.0.]undec-7-ene), whereas a weak base such as K₂CO₃ is used to synthesize the β-isomer as
shown in Figure 1-24. The β-trichloroacetimidate is a kinetic product and is produced in the reaction system very rapidly. This may be due to repulsions of lone pair electrons on the two oxygens attached to the anomeric center (the ring oxygen and glycosidic oxygen), thus making β-alkoxide more reactive. In contrast, the α-trichloroacetimidate is the thermodynamic product. The β-isomer slowly isomerizes to the α-product through anomerization of the alkoxide, as shown in Figure 1-25.

Figure 1-24: Selective synthesis of trichloroacetimidate

Figure 1-25: Synthesis of thermodynamic and kinetic trichloroacetimidates
Trichloroacetimidates can be activated by Lewis acid catalysts such as TMSOTf, F₃B-Et₂O, AgOTf or ZnCl₂ leading to the desired glycosides in an irreversible manner. The proton released from acceptor is trapped by the trichloroacetimidate leaving group to generate an amide, which provides the driving force for glycosylation reaction.⁴⁰

![Figure 1-26: Reaction of trichloroacetimidate and its mechanism](image)

Sometimes trichloroacetimidates groups may not be suitable donors for glycosylation. An alternative in such cases may be the N-phenyltrifluoroacetimidate (Scheme 1-1).⁴² One example is shown below where trifluoroacetimidate (VII) was synthesized from IV and V using K₂CO₃ as a basic catalyst. Reaction of the primary sugar alcohol IV with the imidate gave disaccharide (VIII) in 80% yield.
1.3.5. Gin Glycosylation Method

This dehydrative methodology was described by the American chemist David Gin in 2001. This methodology involves in situ activation of hydroxyl groups to construct the glycosidic linkage. The hydroxy group of the hemiacetal is activated by the combination of a dialkyl sulfide (R₂S, usually (CH₃)₂S), and triflic anhydride (Tf₂O) reagents at low temperature. An intermediate is formed in situ from dialkyl sulfide and triflic anhydride. Then, addition of sugar hemiacetal (IX) to the reaction system produces glycosyl oxasulfonium intermediate (X) via expulsion of trifluoromethanesulfinic acid (CF₃SO₂H). The sulfonium ion is a good leaving group and generate oxacarbonium ion. This intermediate reacts with the acceptor to form the glycosidic bond.⁴³
This combination tolerates the primary acceptors of carbohydrate and non-carbohydrate with high percentage of yields and selectivity. In case of secondary carbohydrate acceptors moderate yields are obtained, as shown in Figure 1-28. Here, the hemiacetal underwent reaction with a secondary carbohydrate alcohol to give a disaccharide in 65% yield.43

1.3.6. n-Pentenyl Glycoside Methodology

The pentenyl glycoside donor was first introduced by Fraser-Reid in 1992. Pentenyl glycosides can be synthesized from glycoside halides (glycosyl bromides or glycosyl chlorides) and n-pentenol by activation with AgOTf or by using the Fischer glycosylation method.44
The pentenyl glycoside can be activated by many iodonium ion generating species such as ICDP or NIS/TfOH. The activation steps involve electrophilic addition of the iodonium ion to the double bond of the aglycone to form a halonium ion. Then, nucleophilic attack by the anomeric oxygen followed by expulsion of the pentenyl chain produces the oxocarbenium ion. Trapping the ion by an acceptor gives the desired glycosidic bond.

Sometimes, during the synthesis of n-pentenyl glycoside some 1,2-orthoester may be produced. The orthoester can be converted into n-pentenyl glycoside through rearrangement in the presence of a strong Lewis acid such as TMSOTf. Then n-pentenyl glycoside can be used as a glycosyl donor.
1.3.7. Glycosylation with Glycals

In the 1960s Lemieux and co-workers first used glycal as a donor in oligosaccharide synthesis. Since then, glycals have been used by Thiem and Danishefsky to synthesize glycosidic bonds. The use of glycals as donors in oligosaccharide bond synthesis is attractive because C-2 functionalizations of the donors are achieved in this strategies. Glycals can be used in two different ways to form glycosidic bonds. The first is in situ activation of glycal forming \( \text{XII} \)

![Figure 1-32: Strategy of glycosylation with glycal XII](image)

followed by reaction with an acceptor to give the glycosidic bond \( \text{XV} \) allowing subsequent functionalization (E) at C-2. The second approach makes a glycosyl donor through different types of reactions such as azidonitration or epoxidation, then reaction with the acceptor generates glycosidic linkage. For example, glycals can be converted into 1,2-halonium sugar species, which may react with several glycosyl acceptors. These halonium derivatives have a tendency to give the \( \alpha \)-glycosidic bond. A major disadvantage of the methodology is that an additional step is required to re-functionalize C-2.\(^{47,48}\)
1.4. Factors Controlling Stereochemistry and Rate of Glycosylation Reaction

Generally, the stereoselective preparation of 1,2-cis glycosides is more demanding than 1,2-trans-glycosides. The structure of the donor and acceptor, the position and type of the protecting groups, the stereochemistry of the leaving group, the type of leaving group, the solvent, activator, temperature, and pressure have a great influence on stereochemistry and rate of glycosylation reaction.

1.4.1. Factors Controlling the Stereochemistry and Rate of Glycosylation Reactions, Donor

The donor has major influence on the stereochemistry and rate of a glycosylation reaction. These are discussed in the following sections.

1.4.1.1. Protecting Group on the Donors

The most powerful impact on stereoselectivity and rate of glycosylation is the choice of protecting groups O-2 of the donor. The protecting group at C-2 is a
very important player to synthesize selectively 1,2-trans glycosides. Controlling the selectivity of the reaction by participation of a protecting group is known as neighboring group participation. Ester groups such as acetate, chloroacetate, benzoate, and pivaloate have an influential effect to form 1,2-trans glycosidic bond. These types of neighboring groups stabilize the oxocarbenium ion by delocalizing the positive charge. As a result, the acceptor can only attack from the opposite direction to construct a 1,2-trans linkage as shown in Figure 1-34. Without neighboring group participation, in the case of a benzyl ether group the reaction outcome depends on thermodynamic stability as shown in Figure 1-34.

![Figure 1-34: Neighboring group participation](image-url)

Based on the C-2 substituent, glycosyl donors are classified into two categories: armed and disarmed. Glycosyl donors with an electron donating group at C-2 such as benzyl (Bn) or methyl (CH₃) group are armed donors and those with electron withdrawing ester or amide groups are disarmed. The protecting group at C-2 also influences the rate of glycosylation. In a glycosylation reaction, the rate determining step is the formation of an oxocarbenium ion that reacts with acceptor to give the glycosidic bond. The rate depends on how fast the
oxocarbenium ion forms and its stability. Disarming group (benzoyl/acetyl) at C-2 destabilizes the partial positive charge at anomeric center making the formation of oxocarbenium ion a slower process. Armed (e.g., benzyl) groups enhance the release of the leaving group and stabilize the oxocarbenium ion.\textsuperscript{51}

![Figure 1-35: Effect of C-2 group on formation of oxocarbenium ion](image1)

Similarly 4,6-benzylidene or 4,6-silyl protecting groups also lower the rate of a glycosylation reaction. The effect is proposed to arise because the protecting group inhibits the flattening of the ring in oxocarbenium ion, which is required in oxocarbenium intermediate as shown in Figure 1-36. As a result, formation oxocarbenium ion \textbf{III} is faster compared to \textbf{I}, which contains a 4,6-benzylidene protecting group.\textsuperscript{52}

![Figure 1-36: Formation of oxocarbenium ions](image2)
1.4.2. Solvent Effects

The solvent has a significant influence on the selectivity of a glycosylation reaction especially in the case of the donors without a participating group at O-2. Anhydrous solvents are required to avoid competition from water. Solvents of low polarity such as dichloromethane (CH$_2$Cl$_2$) or either (CH$_3$CH$_2$OCH$_2$CH$_3$) are frequently used. Sometimes polar aprotic solvents such as acetonitrile (CH$_3$CN) or nitromethane (CH$_3$NO$_3$) are used. In general, polar aprotic solvents such as acetonitrile and nitromethane increase the amount of β-glycoside formation via the reduction of electrostatic repulsion between the electron lone pair on a ring oxygen and on a oxygen in a nucleophile. Moreover if the reaction is performed in acetonitrile, the molecules of the solvent exclusively make a bond from the axial orientation of oxocarbenium ion to give an α-nitrilium-ion species as shown in Figure 1-37. As a result the oxocarbenium ion is stabilized by dispersion of the positive charge on the face. So, nucleophilic attack occurs from the equatorial (β) position, which leading to β-glycosidic product formation. Both reduction of electrostatic repulsion and stabilization effect favors the formation of β-glycoside. On the other hand formation of such species from the equatorial (β) position is very slow though the complex β-nitrilium-nitrile is thermodynamically more stable due to the reverse anomeric effect. This factor leads to the generation of some amount the α-glycosidic product.$^{49}$
Less polar aprotic solvents such as diethyl ether, dichloromethane, tetrahydrofuran or toluene enhance the formation of thermodynamic α-glycosides. Ether solvent coordinates from the equatorial position to produce a thermodynamically favorable β-oxonium intermediate as shown in Figure 1-38. In this case the β-oxonium intermediate is more stable than the α-oxonium because of the reverse anomeric effect. The presence of a positive charge on the exocyclic oxygen favors the acceptor coming from axial position because of dipolar effects. So, the formation of a α-glycoside is favorable.49

Figure 1-38: Ether solvent effect on glycosylation reaction
1.4.3. Acceptor Structure

The structure of the glycosyl acceptor also influences the rate and stereoselectivity of glycosylation reaction, although this has been less studied. The influencing factors are degree of the alcohols (general reactivity 1º>2º>3º) and its spatial arrangement (axial or equatorial), conformation of the sugar ring (C₄ or C₁) and the presence of protecting groups adjacent to the alcohol moiety. In general, the more reactive nucleophile shows less stereoselectivity. Because the reaction occurs faster, hence it is hard to control the selectivity. Electron withdrawing groups adjacent to the alcohol moiety decrease the reaction rate and yield compared to electron donating groups. For example, acyl (Ac) protected sugars are less reactive than those with alkyl (Bn) protected (Figure 1-39). The electron withdrawing acyl groups reduce the nucleophilicity of the acceptors.

![Figure 1-39: Relative reactivity of glycosyl acceptors](image)

Steric demand is another factor in glycosylation reactions. Sugars with bulky protecting group adjacent to the hydroxyl group of acceptor are less reactive. For example the sterically demanding t-butyl diphenylsilyl (OTBDPS) group at C-6 in pyranoside reduces the yield of a (1→4) glycosylation reaction to a large extent.
Moreover, the C-4 hydroxyl group is usually the least reactive, particularly in N-acetyl-glucosamine derivatives. What is the exact reason it isn’t clear yet. Some relative reactivities are shown in Figure 1-41. The doubly acyl protected glucosyl acceptor is much more reactive than single acyl protected.⁵⁴

1.4.4. Use of Conformationally-Restricted Donors

Conformationally restricted donors are more selective than flexible donors. The concept of the approach is the production of a rigid intermediate than can be preferentially attached by alcohol with high stereocontrol. Most of the work in this area has been focused mainly on synthesis of β-arabinofuranoside and α-galactofuranoside derivatives. Lowary and co-workers first reported conformationally restricted furanosyl donors that were based upon a 2,3-anhydrosugar scaffold. They used thioglycosides and glycosylsulfoxides as
donors. These donors undergo glycosylation reactions with high stereoselectivity, where newly glycosidic bonds formed cis to the epoxide moiety. Here, a total of two steps are involved: The first is the glycosylation of an alcohol with a 2,3-anhydro glycosyl donor. The second is a regioselective opening of the epoxide moiety with a lithium alkoxide in the presence of (-)-sparteine.55,56,57

As example of the synthesis β-arabinofuranoside is shown in Scheme 1-3. Glycosylation of p-tolyl 2,3-anhydro-5-O-benzoyl-1-thio-α-D-lyxofuranoside (IV) with primary alcohol III in the presence of NIS/AgOTf activator system produced β-glycosidic bond selectively, in 79% yield. Then, opening of the epoxide moiety with LiOBn in presence of (-)-sparteine gave the β-arabinofuranoside in 83% yield.58,59

Scheme 1-3: Synthesis of β-arabinofuranoside and regioselective opening of epoxide moiety
The reaction can also be applied to α-arabinofuranosides (Scheme 1-4). Glycosylation of ρ-polyl 2,3-anhydro-5-O-benzoyl-1-thio-β-D-ribofuranoside (IV) with primary alcohol III in presence of NIS/AgOTf activator system produced α-glycosidic bond selectively, which in 82% yield, Then opening of the epoxide moiety with LiOBn in presence of (−)-sparteine gave the α-arabinofuranoside in 84% yield.52,57

![Scheme 1-4: Synthesis of α-arabinofuranoside and regioselective opening of epoxide moiety](image)

Due to a lack of mechanistic investigation, the origin of the stereoselectivity of thioglycoside donors is unclear. DFT calculations and experimental results suggest that an α-glycosyltriflate intermediate is formed in situ and this triflate intermediate is a key to the observed high stereocontrol as shown in Figure 1-42. Then, the intermediate reacts with the acceptor alcohol in S_N2-like manner.52
Although the method involves two separate steps, the overall transformation yield of this methodology is comparable to other routes for the preparation of β-arabinofuranosides. However, the approach requires rather harsh conditions and sometimes regioselective opening of epoxide gives two regioisomers rather than one.

Donors with a silyl acetal or siloxane spanning C-3 and C-5 in arabinofuranose rings can be played a vital role for stereoselectivity. The conformations of the oxocarbenium ion intermediates of these donors in which, the alcohols could approach in such a direction to give stereoselectively 1,2-cis-glycoside. This attack occurs bases on the “inside attack rule” and DFT calculations support this hypothesis. This is a powerful and efficient technique to achieve β-arabinofuranosides with high stereoselectivity.\(^{57}\)
Figure 1-43: Synthesis of β-arabinofuranoside
1.5. Bibliography


57. Akihiro, I.; Lowary, T. L. *Trends in Glycoscience and Glycotechnology* 2011, 23 (131), 134-152.


Chapter 2: Results and Discussion

2.1. Research Aims and Strategy

The goal of this thesis was to explore the ability of furanose derivatives incorporating an aziridine moiety spanning C-2 and C-3 (e.g., 1 and 2, Figure 2-1) to act as stereoselective glycosylating agents. To the best of our knowledge, there have been no previous reports on the use of such species as glycosylating agents. If these species can be used to produce glycosides in high selectivity, then they may find application in the synthesis of furanoseaminosugars, through subsequent transformation of the aziridine ring (e.g., nucleophilic opening).

![Figure 2-1: Glycosyl donor targets 1 and 2](image)

In developing a route to these species, I envisioned an approach (Figure 2-2) starting from \(\beta\)-arabinose (3) and proceeding through a key azidosugar intermediate (4), which possesses a leaving group at C-2. In our earlier studies on 2,3-anhydrosugar donors, I had employed thioglycoside and sulfoxide donors.\(^1\)\(^-\)\(^3\) However, based on this work, I knew that use of a thioglycoside (X = SR) in this approach would likely lead to decomposition of 4 via displacement of the C-2 leaving group by neighboring group participation of the sulfur atom.\(^4\)\(^-\)\(^6\) We therefore chose instead to carry out the synthesis with an oxygen-containing group at C1 (X = OR) and initially investigated donors other than
thioglycosides (i.e., 1 and 2). Should these donors prove to be highly stereoselective, an alternate route to targets containing a thioglycoside moiety could be investigated.

![Chemical structure](image)

**Figure 2-2:** General strategy to targets and predicted decomposition pathway with thioglycoside substrates

### 2.2. Synthesis of donors 1 and 2

#### 2.2.1. Synthesis of N-acetyl-2,3-aziridino-5-O-benzoyl-2,3-dideoxy-D-ribofuranose (1)

The initial approach we attempted for the synthesis of 1 is shown in Scheme 2-1 and started from 3, D-arabinose (3). Fischer glycosylation of 3 with allyl alcohol gave the α-glycoside isomer 6 in 55% yield. The α-anomeric stereochemistry was determined from the $^{13}$C NMR spectrum, which showed the resonance for C-1 was at 108.6 ppm, which is much higher than that expected for the β-isomer.$^7$ The second step was to introduce an epoxide moiety. Thus, allylfuranoside 6 was reacted with diisopropylazodicarboxylate, triphenylphosphine, and benzoic acid to provide, in a single step, 2,3-anhydro-D-lyxofuranoside (7) in 82% yield. The formation of 2,3-epoxide moiety was clear from the marked up field chemical shift of signals for C-2 and C-3 in the $^{13}$C NMR spectrum, which appeared at 56.3
ppm (C-2) and 54.1 ppm (C-3). These are very similar to those published previously by our group for other 2,3-anhydro-\(\alpha\)-D-lyxofuranosides.

![Scheme 2-1](image)

**Scheme 2-1**: Initial attempts to synthesize an aziridine-containing precursor to 1 and 2

Further confirmation of the structure of 7 could be obtained from a single crystal X-ray diffraction study, which unambiguously showed that the epoxide moiety is *trans* to the allyl group at the anomeric center and *cis* to the benzyolated hydroxymethyl group at C-4 (Figure 2-3).
Opening of the epoxide in 7 was performed using NaN$_3$ and NH$_4$Cl in EtOH and H$_2$O. The reaction was quite sluggish and it was necessary to heat the mixture at reflux for 48 h. Even after these long reaction times, the product, 8, was obtained together with 9% recovered starting material 7. This reaction gave exclusively one regioisomer 8 in 85% yield. A sharp strong peak at 2107 cm$^{-1}$ in the IR spectrum confirmed the presence of the azido group in the molecule.

The regioselectivity of the reaction was confirmed by the $^{13}$C NMR spectrum of 8. The resonance for C-2 appeared at 80.9 ppm for C-2 and that for C-3, as expected, at lower chemical shift, 67.5 ppm. In addition, the coupling constants for H-2 ($J = 1.0$ and 6.0 Hz) and H-3 ($J = 3.5$ and 7.0 Hz) were consistent with a product possessing the arabinofuranose stereochemistry. The regioselectivity observed in the epoxide opening was expected based on previous work on the nucleophilic opening of 2,3-anhydro-furanosides.$^9$ In 2,3-anhydro-$\alpha$-lyxofuranosides, nucleophilic attack at C-3 would be preferred because the $\alpha$-
allyl group at C-1 hinders C-2 attack. Another rationale for this stereoselectivity is that the partial positive charge that develops on C-3 in the $S_N2$ transition state is favorable compared to C-2, because of the latter carbon’s closer proximity to the electron withdrawing anomeric center (C-1).

With the alcohol 8 in hand, mesylation of the alcohol was performed using methanesulfonyl chloride and pyridine to give 9 in 78% yield. The next step was to reduce the azide to the amine, which we expected would lead to the formation of the aziridine moiety upon treatment with base. Our first attempt to do this involved the use of a Staudinger reaction followed by treatment with triethylamine. The Staudinger reaction and base treatment did not proceed cleanly. Acetylation using acetic anhydride and pyridine was used to facilitate purification of the product. This process led to the isolation of the acetamidosugar 10 in low (20%) yield.

From this observation it was decided that a more stable tosyl leaving group would be more suitable to make the aziridine ring. To test this hypothesis, tosylation of 8 gave 11 in 79% yield (Scheme 2-2). Then, reduction of the azide in 11 under hydrogenation conditions with Pd/C catalysis and then treatment with Et$_3$N followed by acetylation provided aziridine 12 in 61% overall yield. Although this process was successful in producing the aziridine, it also reduced the double bond of the allyl group. Hence, we explored the use of another group at anomeric centre, which was not susceptible to reduction by hydrogenation. For this purpose, we chose a $p$-methoxyphenyl (PMP) alglycone.
The route to a PMP glycoside derivative is shown in Scheme 2-3. First, Fischer glycosylation of the \( \alpha \)-arabinose (3) with methanol followed by treatment with benzoyl chloride and pyridine provided compound 13 in 56% yield. The anomic stereochemistry was confirmed by \( ^{13} \text{C} \) NMR spectroscopy; the C-1 resonance appeared at 106.9 ppm, which was similar to the literature value.\(^\text{10}\) Glycosylation of 4-methoxyphenol with 13 using BF\(_3\)-OEt\(_2\) in dichloromethane, followed by debenzylation gave desired product 14 in 87% yield. The \( \alpha \)-anomeric stereochemistry was determined from the \( ^{13} \text{C} \) NMR spectrum, which showed the resonance for C-1 was at 108.8 ppm, the value is almost similar to the C-1 of 6.

Mitsunobu reaction of 14 as described earlier for the synthesis of 7 provided epoxide 15 in 82% yield. The formation of 2,3-epoxide group was determined by the chemical shift of the signals for C-2 and C-3 in the \( ^{13} \text{C} \) NMR spectrum, which appeared at 56.3 ppm (C-2) and 54.5 ppm (C-3), which are similar to other related compounds prepared previously.\(^\text{11}\) Treatment of 15 with Na\( \text{N}_3 \) and NH\(_4\)Cl, and then tosylation of the product 16 gave tosylate 17 in good overall yield. The
NMR data for 17 were analogous to those for 9, thus indicating the product possessed the arabinofuranose stereochemistry. As has been successful in the case of allyl glycoside 11, reduction of the azide by catalytic hydrogenation, followed by treatment with triethylamine and finally acetylation resulted in compound 18 containing an aziridine ring moiety. All that remained was the removal of the PMP group in 18, which would lead to the formation of 1. Unfortunately, our attempts to do thus under standard conditions using ceric ammonium nitrate (CAN) and water led to extensive decomposition of the compound. None of the desired compound could be identified. The same problems happened when using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dichloromethane to cleave the PMP group.

Scheme 2-3: Attempted synthesis of 1 from PMP glycoside 18
After failing to remove the 4-methoxyphenyl group in 18, we returned to the route involving the allyl glycoside 11. In this case, reduction of azide using the Staudinger reaction, followed by treatment with triethylamine and finally acetylation produced aziridine 19 in 79% yield. In the $^{13}$C NMR spectrum of 19, the chemical shift of signals for C-2 and C-3 appeared at 42.6 ppm and 40.5 ppm, respectively, which is the clear indication of aziridine ring formation.

![Scheme 2-4: Successful synthesis of 1](image)

Fortunately, compound 19 was crystalline and single crystal X-ray diffraction study unambiguously showed (Figure 2-4) that the aziridine moiety is cis to the allyl group at anomic centre and trans to the benzoyl protecting group at C-5.
The final step in the synthesis of 1 is involved cleavage of the allyl glycoside in 19. Reaction of 19 in presence of palladium(II) chloride in methanol and dichloromethane gave decomposition of the starting material. This cleavage was achieved by first rearrangement of the allyl ether to the vinyl ether in presence of (1,5-cyclooctadiene)bis(methylidiphenylphosphine)iridium(I) hexafluorophosphate catalyst and H₂. Next, treatment with trimethylamine N-oxide (TMANO) and osmium tetraoxide resulted in cleavage of the vinyl ether to gave the expected hemiacetal (1) donor in 98% yield over the two steps (α: β 1.0:7.0).

2.3. Synthesis of N-acetyl-2,3-aziridino-5-O-benzoyl-2,3-dideoxy-β-D-ribofuranosyltrichloroacetimidate (2): The reaction of 1 with trichloroacetonitrile in the presence of DBU at room temperature produced 2 in an excellent 98% yield (Scheme 2-5). The outcome of the reaction was
selectively β. This selectivity is confirmed by $^3J_{\text{H1,H2}}$ coupling constant, which is zero.

Scheme 2-5: Synthesis of 2 from 1

Trichloroacetimidate 2 is surprisingly stable. We monitored the stability by $^1$H NMR spectroscopy. Surprisingly, the donor was stable for five days at −18 °C followed by for another five days at 2 °C. More surprisingly, it was stable even after five days at room temperature.

2.4. Method for Establishing Anomeric Stereochemistry

With 1 and 2 in hand, we were ready to explore their ability to serve as glycosyl donors. However, before doing that, we needed an unambiguous method for establishing anomeric stereochemistry in the products. Previous papers from our group reported that value of the $J_{C1-H1}$ is the only known reliable method for determining the stereochemistry at the anomeric center in 2,3-anhydro-D-furanosides. In these studies, $J_{C1-H1}$ was shown to fall between 163 and 169 Hz when H-1 is trans to the oxirane ring. When H-1 is cis to the epoxide moiety $J_{C1-H1}$ ranged between 174 and 178 Hz.

To determine if this trend was also observed in 2,3-aziridino-glycoisdes, we measured the values of the $^1J_{C1,H1}$ in 18 and 19. Because we had an X-ray structure for 19, we were absolutely sure of the relative stereochemistry between
the aziridine and the anomeric substituent. The similarities in NMR spectra between 18 and 19, as well as the route by which the compound was synthesized, allowed us to conclude that 18 also has a trans-relationship between the C-1–H-1 bond and the aziridine group. For both 18 and 19, the \( ^1J_{C1,H1} \) value was 169.1 Hz, which is consistent with the trends observed in the corresponding epoxide-functionalized compounds. As described below, in the other glycoside product, where H-1 is cis to the aziridine moiety, the \( ^1J_{C1,H1} \) value was \(~175\) Hz. Thus, it appears that the trends in \( ^1J_{C1,H1} \) magnitudes established in the epoxide series, also apply for these aziridinated substrates.

2.5. Stereoselectivity of Donors 1 and 2 in Glycosylation Reactions

After successfully synthesizing the desired donors 1 and 2, they were used in glycosylation reactions with a range of alcohols to produce glycosidic linkages. Various alcohol acceptors were used including aliphatic primary, secondary and tertiary alcohols, as well as primary and secondary sugar alcohols (Figure 2-5)

![Figure 2-5: List of acceptors studied (20–27) and possible products (28–35)](nan)
### 2.5.1. Glycosylation Reactions with Hemiacetal 1

I first explored glycosylation of hemiacetal 1 with alcohols (20–27, Scheme 2-6). In situ activation of this donor was performed using the Gin glycosylation protocol. In this reaction, the hemiacetal is activated by the use of trifluoromethanesulfonic anhydride (1.5 equiv) and dimethyl sulfide in dichloromethane in the presence of the acid scavenger 2,4,6-tri-tert-butyl-pyridine (TTBP) at –45 °C under an argon atmosphere. The resulting solution is stirred for 1 h at this temperature, followed by 0 °C for 15 min and finally another 15 min at 23 °C. Then, a solution of alcohol in dichloromethane is then added dropwise. The reaction mixture is then stirred again for 12 h at room temperature.

![Scheme 2-6: Gin glycosylation reaction of donor 1 with alcohols 20-27](image)

As illustrated in Table 2-1, under these conditions, 1 was able to efficiently glycosylate a number of the glycosides in good yields. All of the simple alcohols were glycosylated as was the primary carbohydrate alcohol 22. In contrast, neither of the secondary carbohydrate alcohols (24 or 25) led to a product. In these cases, we observed unreacted donor under the above mentioned conditions. When an increased the amount of activating system (trifluoromethanesulfonic anhydride and dimethyl sulfide), a baseline spot on TLC...
was observed. Although the yields were generally good, the $\alpha:\beta$ stereoselectivities were modest. The best results were obtained with benzyl alcohol (20), which gave the product in a 2.6:1.0 $\alpha:\beta$ ratio. With the more sterically encumbered tertiary alcohols 26 and 27, the selectivities were lower (~1.5:1 $\alpha:\beta$). In general, the glycosylation selectivity decreases as the size of the acceptor alcohol increases. In all cases, the anomeric stereochemistry was done by measurement of the $^{1}J_{C1,H1}$ values of the purified products. For all of the $\alpha$-glycosides, this value ranged from 167.4–169.1 Hz and for all of the $\beta$-glycosides this value was between 174.5 Hz and 177.2 Hz.

Table 2-1: Glycosylation of alcohols 20–27 with N-acetyl-2,3-aziridino-5-O-benzoyl-2,3-dideoxy-D-ribofuranose (1).\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acceptor</th>
<th>Product</th>
<th>Yield (%)</th>
<th>$\alpha:\beta$ Ratio(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>28</td>
<td>81</td>
<td>2.6:1.0</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>29</td>
<td>74</td>
<td>1.8:1.0</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>30</td>
<td>85</td>
<td>2.4:1.0</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>31</td>
<td>78</td>
<td>1.7:1.0</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>32</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>33</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>34</td>
<td>78</td>
<td>1.6:1.0</td>
</tr>
<tr>
<td>8</td>
<td>27</td>
<td>35</td>
<td>76</td>
<td>1.3:1.0</td>
</tr>
</tbody>
</table>

\(^a\)Ti$_2$O, TTBP, \((\text{CH}_3)_{2}S\), dichloromethane, rt, 12 h

\(^b\)Ratio determined by the integration anomeric H in the $^{1}$H NMR spectrum of the crude products.

see Figure 2-5 for structures of products.
A plausible mechanism for the Gin glycosylation is presented in Figure 2-6. The first step involves in situ generation of thiosulfonium intermediate I, which then reacts with the hemiacetal (II) to generate an anomeric oxosulfonium intermediate III via expulsion of trifluoromethanesulfinic acid (CF$_3$SO$_2$H)$_2$. Release of dimethylsulfoxide from III then leads to the formation an oxacarbenium ion pair IV.

![Figure 2-6: Plausible mechanism of the Gin glycosylation](image)

In the absence of an alcohol (or other "good" nucleophile), this oxocarbenium ion pair is in equilibrium with the corresponding glycosyltriflate intermediate V and VI. After the addition of a nucleophile (the acceptor alcohol) an S$_n$2-like displacement of triflate anion from the anomeric centre in V and VI, leads to glycosides. Previous work on 2,3-anhydrosugar glycosyl triflates suggests that
the β-triflate V should be more stable than VI. Hence, if this reaction manifold is operating, the favored product should be the α-glycoside VII.

The results presented in Table 2-1 can be rationalized based on the pathway shown in Figure 2-7. With the less hindered alcohols, modest α-selectivity results, which could be the result of a direct S\textsubscript{N}2-like displacement between the acceptor and triflate V. The formation of the β-isomer could arise from the reaction between triflate VI and the alcohol. Alternatively, oxocarbenium ion pair IV could be the immediate precursor to both glycosides. Direct attack on to IV from the top face (giving the β-glycoside) would be expected to be favored for steric reasons. The decreasing α-selectivity seen as the steric bulk of the alcohols increases could arise due to steric hindrance between the acetylated azidirine moiety in V and the nucleophile (Figure 2-7). This would lead to an increase in reaction through intermediates IV or VI.

We next explored the glycosylation of the trichloracetimidate donor 2. These reactions involved the addition of a solution of 2 dissolved in dichloromethane to a stirring solution of the alcohol in dichloromethane at –25 °C. A solution of activator TMSOTf in dichloromethane was added dropwise to the reaction.
mixture over a period of 5 min. The resulting mixture was stirred at this
temperature for 15 min, then another 15 min at –20 °C, and at last warmed very
slowly to –5 °C over a period of 1 h. We also explored adding ether solvent on
the selectivity of the glycosylation reaction for some acceptors.

Scheme 2-7: Glycosylation reactions with trichloroacetimidate donor 2

The data for these glycosylation reactions is shown in Table 2-2. Overall the
trends observed in reactions with 1 are also observed with 2. These
glycosylations are modestly α-selective, and, as the steric hindrance on the
alcohol increases, the selectivity decreases. When comparing the two donors,
the use of the imidate donor generally gives better α-selectivity than the
hemiacetal. Finally, when a small amount of ether is added to the reaction
solvent, the α-selectivity increases further (Table 2-2, compare Entries 1 and 9,
Entries 2 and 10, and Entries 7 and 11).
Table 2-2. Glycosylation of alcohols 20–27 with N-acetyl-2,3-aziridino-5-O-benzoyl-2,3-dideoxy-β-D-ribofuranosyltrichloroacetimidate.

| Entry | Solvent   | Acceptor | Product | Yield (%) | α:β ratio  
|-------|-----------|----------|---------|-----------|-------------
| 1     | CH₂Cl₂    | 20       | 28      | 67        | 2.2:1.0     
| 2     | CH₂Cl₂    | 21       | 29      | 72        | 2.8:1.0     
| 3     | CH₂Cl₂    | 22       | 30      | 72        | 4.8:1.0     
| 4     | CH₂Cl₂    | 23       | 31      | 62        | 2.8:1.0     
| 5     | CH₂Cl₂    | 24       | 32      | ---       | ---         
| 6     | CH₂Cl₂    | 25       | 33      | ---       | ---         
| 7     | CH₂Cl₂    | 26       | 34      | 71        | 1.2:1.0     
| 8     | CH₂Cl₂    | 27       | 35      | 70        | 1.6:1.0     
| 9     | 9:1 CH₂Cl₂-Et₂O | 20 | 28 | 68 | 4.0:1.0 |
| 10    | 9:1 CH₂Cl₂-Et₂O | 21 | 29 | 69 | 3.6:1.0 |
| 11    | 9:1 CH₂Cl₂-Et₂O | 26 | 34 | 75 | 1.8:1.0 |

*a*TMSOTf, Sol., 4 Å MS, -25 to -5 °C, 1 h.

*b*Ratio determined by the integration of anomeric H crude products.

We propose that the mechanism of the reaction involves a pathway as shown in Figure 2-8. Activation of the imidate IX by the TMSOTf leads to intermediate X, which can proceed down one of two pathways. Direct SN₂-like displacement on X by the alcohol will lead directly to the α-glycoside XI. On the other hand, X can also dissociate into an oxocarbenium ion XII, which can react with alcohols to generate a mixture of α and β glycosides XIV. The increase in α-selectivity in the presence of diethyl ether can be rationalized by the formation of adduct XIII, which would lead to the increase amount of attack cis to the aziridine. Similar to what was proposed for the reactions involving hemiacetal 1, we speculate that as...
the steric hindrance on the alcohol increases, direct S\textsubscript{N}2 attack on intermediates such as \textbf{X} and \textbf{XIII} become disfavored and that the reaction proceeds through species such as ion \textbf{XII}, which is anticipated to be less \(\alpha\)-selective.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2-8.png}
\caption{Proposed pathway for reactions involving imidate donors}
\end{figure}

\textbf{2.6. Conclusion}

In summary, we describe here the synthesis of two aziridine-containing glycosylating agents, hemiacetal \textbf{1} and trichloroacetimidate \textbf{2}, from D-arabinose. The former is obtained in seven steps and the latter in one additional step. When the ability of these compounds to glycosylate alcohols was studied, the major products were those in which the newly formed glycosidic bond was \textit{cis} to the aziridine moiety. Trichloroacetimidate \textbf{2} provides the products with marginally better stereoselectivity than \textbf{1}, and the addition of ether to the reaction mixture further enhances this selectivity.

** A version of this Chapter 2 has been submitted for publication in \textit{Tetrahedron}, January 04, 2013.
2.7. Bibliography

3.0. Future Work

The experimental results suggest that these species behave analogously to the epoxide-containing (2,3-anhydrosugar) donors we have previously investigated. However, the stereoselectivities with the aziridine substrates were generally lower. We attribute this to the need for a protecting group on the aziridine nitrogen. The steric bulk of this group hinders the approach of the nucleophile into an electrophilic intermediate (e.g., page 53) from the face cis to the aziridine moiety. In the epoxide series, a protecting group is not necessary. Further refinement of this reaction through the use of other donor types (e.g., thioglycosides, sulfoxides shown in Figure 3-1, or other nitrogen protecting groups could enhance the $\alpha$-selectivity. However, the selectivities observed here, and the limitation that secondary carbohydrate alcohols cannot be glycosylated by these species, suggest these donors have limited future application in the synthesis of complex glycans.

![Figure 3-1: Thioglycosyl donors](image-url)
Chapter 4: Experimental

4.1. Experimental

**General Procedure:** Starting materials and reagents used in reactions were purchased from commercial sources, Sigma–Aldrich and Fluka, and were used without further purification, unless stated otherwise. Solvents used in reactions were purified by passage through columns of alumina and copper under argon pressure. Unless noted differently, all reactions were carried out under a positive pressure of argon or nitrogen and were monitored by TLC on silica gel G-25 UV<sub>254</sub> (0.25 mm, E. Merck). Spots were detected under UV light or by charring with 10% H<sub>2</sub>SO<sub>4</sub> in ethanol or charring with a solution of anisaldehyde in ethanol, acetic acid and H<sub>2</sub>SO<sub>4</sub>. Solvents were evaporated under reduced pressure and below 60 °C (bath), and organic solutions of crude products were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Column chromatography was performed on Silica Gel 60(40–60 µM) and the ratio between silica gel and crude product ranged from 100 to 50:1 (w/w). Optical rotations were measured at 21±2 °C at the sodium D line (589 nm) on Perkin–Elmer polarimeter and are in units of deg.mL/(dm.g). <sup>1</sup>H NMR spectra were recorded at 400 or 500 MHz and <sup>13</sup>C NMR spectra at 100 or 125 MHz. <sup>1</sup>H chemical shifts were referenced to TMS (0.0 ppm, CDCl<sub>3</sub>) or internal CD<sub>3</sub>OD (3.31 ppm, CD<sub>3</sub>OD). <sup>13</sup>C chemical shifts were referenced to CDCl<sub>3</sub> (77.00 ppm, CDCl<sub>3</sub>) or CD<sub>3</sub>OD (49.15 ppm, CD<sub>3</sub>OD). Peaks assignments were made by 2D-NMR (gCOSY, gHSQC and gHMBC) experiments. IR spectra were obtained as film made by application of a solution of the compound in CHCl<sub>3</sub> to an NaCl plate followed by evaporation of the solvent. Electrospray mass spectra were recorded on samples suspended in mixtures of THF and CH<sub>3</sub>OH.
with added NaCl. All acceptors were either commercially available or prepared as previously reported. Product yields from glycosylation reactions are shown in Tables 2-1 and 2-2 (Result and Discussion section).

Allyl α-D-arabinofuranoside (6): D-arabinose (10.01 g, 66.65 mmol) was dissolved in dried allyl alcohol and then 63 mL (1.06 M) hydrogen chloride (this solution was prepared by adding dropwise acetyl chloride to ice cold and rapidly stirring allyl alcohol) was added. The reaction mixture was stirred at room temperature under argon for 6 h and then the remaining acid was neutralized by adding pyridine (65 mL). The residue was extracted with 150 mL EtOAc. The organic portion was washed with satd. aq. NaHCO₃, filtered, dried, and the organic layer was concentrated under reduced pressure followed by column chromatography (EtOAc–CH₃OH, 99:1) gave compound 6 (6.97 g, 55%) as a colorless syrup: Rₜ 0.35 (EtOAc–CH₃OH, 99:0.5); [α]D+100.3 (c 3.3,CH₃OH); ¹H NMR (500 MHz, CD₃OD, δₜ) 5.96–5.88 (m, 1 H, CH=CH₂), 5.28 (ddd, 1 H, J = 2.0, 3.5, 17.0 Hz, CH=CH₂), 5.14 (ddd, 1 H, J = 1.5, 3.5, 10.5 Hz, CH=CH₂), 4.89 (d, 1 H, J = 2.0 Hz, H-1), 4.20 (dddd, 1 H, J = 1.5, 1.5, 4.5, 13.0 Hz, OCH₂CH=CH₂), 4.02–3.96 (m, 2 H, H-2, OCH₂CH=CH₂), 3.93 (ddd, 1 H, J = 3.5, 5.5, 6.5 Hz, H-4), 3.83 (dd, 1 H, J = 3.5, 6.5 Hz, H-3), 3.74 (dd, 1 H, J = 3.5, 12.0 Hz, H-5), 3.62 (dd, 1 H, J = 5.5, 12.0 Hz, H-5); ¹³C NMR (125.7 MHz, CDCl₃, δₚ) 135.7 (CH=CH₂), 117.1 (CH=CH₂), 108.6 (C-1), 85.4 (C-4), 83.63 (C-2), 78.7 (C-3), 69.2 (OCH₂CH=CH₂),
63.0 (C-5). HRMS (ESI) calcd for (M+Na) C₈H₁₄O₅ + Na: 213.0746, found 213.0735.

**Allyl 2,3-anhydro-5-O-benzoyl-α-D-lyxofuranoside (7):** To a solution of 6 (3.14 g, 16.51 mmol) in THF (180 mL), triphenylphosphine (10.73 g, 40.76 mmol) and benzoic acid (3.04 g, 24.46 mmol) were added. The resulting mixture was then cooled to 0 °C and diisopropylazodicarboxylate (3.86 mL, 19.51 mmol) was added dropwise over a period of 10 min. The reaction mixture was allowed to stir at room temperature for 2 h under an argon atmosphere. The solution was subsequently concentrated under reduced pressure to yield a crude oil from which most of the triphenylphosphine oxide precipitated upon trituration with cold diethyl ether. The triphenylphosphine oxide was filtered off and the filtrate was concentrated. The resulting residue was purified by silica gel chromatography (hexanes-EtOAc, 7:1) to obtain compound 7 (3.7 g, 82%) as a white solid: Rf 0.62 (hexanes–EtOAc, 4:1); [α]D +41.2 (c 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃, δH) 8.12–8.03 (m, 2 H, Ar), 7.62–7.52 (m, 1H, Ar), 7.51–7.40 (m, 2 H, Ar), 5.99–5.83 (m, 1H, CH=CH₂), 5.31 (ddd, 1 H, J = 1.6, 3.2, 17.1 Hz, CH=CH₂), 5.22 (ddd, 1 H, J = 1.6, 2.8, 10.3 Hz, CH=CH₂), 5.15 (s, 1 H, H-1), 4.55 (dd, 1 H, J = 6.0, 11.5Hz, H-5), 4.50 (dd, 1 H, J = 6.0, 11.5 Hz, H-5), 4.36 (dd, 1 H, J = 5.6, 6.0 Hz, H-4), 4.27 (dddd, 1 H, J = 1.2, 1.2, 5.2, 12.8 Hz, OCH₂CH=CH₂), 3.96 (dd, 1 H, J = 1.2, 2.8 Hz, OCH₂CH=CH₂), 3.83 (dd, 1 H, J = 0.8, 2.8 Hz, H-2), 3.73 (d, 1 H, J = 2.8 Hz, H-3); ¹³C NMR (125.3 MHz, CDCl₃, δC) 166.2 (C=O),
133.7 (CH=CH₂), 133.1 (Ar-C), 129.7 (Ar-C), 129.7 (Ar-C), 128.3 (Ar-C), 117.7 (CH=CH₂), 100.5 (C-1), 74.0 (C-4), 69.0 (OCH₂CH=CH₂), 62.8 (C-5), 56.3 (C-2), 54.1 (C-3). HRMS (ESI) calcd for (M+Na) C₁₅H₁₆O₅ + Na: 299.1563, found 299.1560.

**Allyl 3-azido-5-O-benzoyl-3-deoxy-α-D-arabinofuranoside (8):** To a solution of compound 7 (2.09 g, 9.49 mmol) in EtOH–H₂O (9:1, 95 mL) was added NaN₃ (3.67 g, 56.5 mmol) and NH₄Cl (5.03 g, 94.1 mmol). The reaction mixture was heated at reflux for 48 h, cooled to room temperature and extracted with EtOAc (2x50 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and the solvent was removed under reduced pressure. The product was purified by silica column chromatography (5:1, hexanes–EtOAc) to yield 8 (2.57g, 85%, 9% starting material 7 was also recovered) as a colorless syrup: Rᵣ 0.25 (5:1, hexanes–EtOAc); [α]₀D +100.6 (c 1.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃, δ_H) 8.12–8.03 (m, 2H, Ar), 7.62–7.52 (m, 1H, Ar), 7.51–7.40 (m, 2H, Ar), 5.94–5.86 (m, 1H, CH=CH₂), 5.31 (ddd, 1H, J = 1.6, 3.2, 17.1 Hz, CH=CH₂), 5.22 (ddd, 1H, J = 1.6, 2.8, 10.3 Hz, CH=CH₂), 5.05 (d, 1H, J = 1.5 Hz, H-1), 4.58 (dd, 1H, J = 4.0, 12.0 Hz, H-5), 4.50 (dd, 1H, J = 4.5, 12.0 Hz, H-5), 4.35–4.20 (m, 3H, 2 x OCH₂CH=CH₂), 4.05 (ddd, 1H, J = 1.0, 6.0, 13.0 Hz, H-2), 3.80 (dd, 1H, J = 3.5, 7.0 Hz, H-3), 3.12 (br, 1H); ¹³C NMR (125.3 MHz, CDCl₃, δ_C) 166.4 (C=O), 133.6 (CH=CH₂), 133.4 (Ar-C), 129.8 (Ar-C), 129.7 (Ar-C), 128.5 (Ar-C), 117.7 (CH=CH₂), 106.8 (C-1), 80.9 (C-2), 79.1 (C-4), 68.5 (OCH₂CH=CH₂), 67.5 (C-3),
63.8 (C-5); IR (film) 3467 (br), 3061, 2956, 2107 (N=N=N), 1723 (C=O), 1275 (C–O). HRMS (ESI) calcd for (M+Na) C_{15}H_{17}N_{3}O_{5}+ Na: 342.1066, found 342.1056.

**Allyl 3-azido-5-O-benzoyl-3-deoxy-2-O-methanesulfonyl-α-D-arabinofuranoside (9):** A solution of compound 8 (2.21 g, 6.91 mmol) dissolved in dichloromethane (20.7 mL) and pyridine (3.5 mL) was treated with methanesulfonyl chloride (0.84 mL, 0.83 mmol) at 0 °C, and then the reaction mixture was stirred for 2 h at room temperature under an argon atmosphere. The reaction mixture was quenched by the addition of a small piece of ice and then diluted with dichloromethane (18 mL). The organic layer was washed with a satd. aq. NaHCO₃ solution and then water. The crude solution was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (8:1, hexanes–EtOAc) to yield 9 (2.13 g, 78%) as a colorless syrup: R, 0.25 (5:1, hexanes–EtOAc); [α]D +86.2 (c 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃, δH) 8.14 (d, 2 H, J = 7.7 Hz, Ar), 7.65 (t, 1 H, J = 7.4 Hz, Ar), 7.53 (t, 2 H, J = 7.4 Hz, Ar), 5.99–81 (m, 1 H, CH=CH₂), 5.39 (dd, 1 H, J = 17.2, 0.9 Hz, CH=CH₂), 5.33–5.27 (m, 2H, H₂-2, CH=CH₂), 5.07 (s, 1H, H-1), 4.73–4.67 (m, 1H, H-5), 4.62–4.56 (m, 1H, H-5), 4.37–4.27 (m, 2H, H-4, OCH₂CH=CH₂), 4.19–4.07 (m, 2H, H-3, OCH₂CH=CH₂), 3.11 (s, 3 H, CH₃); ¹³C NMR (125.3 MHz, CDCl₃, δC) 166.3 (C=O),133.6 (CH=CH₂), 133.2 (Ar-C), 129.9 (Ar-C), 129.5 (Ar-C), 128.7 (Ar-C), 118.4 (CH=CH₂), 104.2 (C-1), 86.7 (C-2), 79.4 (C-4), 68.7
(O\textsubscript{2}C\textsubscript{2}H\textsubscript{2}CH=CH\textsubscript{2}) , 66.1 (C-3), 63.1 (C-5), 38.5 (CH\textsubscript{3}); IR (film) 3072, 2939, 2112 (N=N=N), 1723 (C=O), 1274 (C-O). HRMS (ESI) calcd for (M+Na) C\textsubscript{16}H\textsubscript{19}N\textsubscript{3}O\textsubscript{7}S + Na: 420.0943, found 420.0811.

**Allyl 3-acetoamide-3-deoxy-\alpha-D-arabinofuranoside (10):**

To a solution of azide 9 (2.01 g, 5.03 mmol) in THF (4.7 mL), water (0.4 mL) and triphenylphosphine (2.74 g, 1.05 mmol) were added. The resulting mixture was stirred for 20 h at room temperature. The solution then dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under high vacuum resulting in a colorless crude oil. Without further purification, DMF (21 mL) and triethylamine (0.81 mL) were added to the crude product at room temperature. The reaction mixture was stirred 100 °C for 20 h and then cooled to room temperature. Pyridine (24 mL) and acetic anhydride (4.2 mL) were then added to the mixture cooled at 0 °C. After stirring for 4 h at room temperature, the mixture was extracted with EtOAc (3 x 30 mL). The organic phases were combined, washed with a satd. aq. NaHCO\textsubscript{3} solution and then water. The organic layer was dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, filtered, and the solvent was evaporated under reduced pressure.\textsuperscript{7} The residue was purified by silica gel column chromatography (1:1, hexanes–EtOAc) to get 10 (0.401 g, 1.73 mmol, 20%) as a white solid: R\textsubscript{f} 0.19 (1:1, hexanes–EtOAc); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}, δ\textsubscript{H}) 6.39 (d, 1 H, J = 8.5 Hz, NH), 5.94-5.84 (m, 1 H, CH=CH\textsubscript{2}), 5.26 (ddd, 1 H, J = 1.5, 3.5, 17.0 Hz, CH=CH\textsubscript{2}), 5.20 (ddd, 1 H, J = 1.0, 2.5, 10.5 Hz, CH=CH\textsubscript{2}), 5.05 (s, 1 H, H-1), 4.35 (dd, 1 H, J = 3.0, 8.5 Hz, H-3), 4.20 (ddddd, 1 H, J = 1.5, 1.5, 5.5, 13.0
Hz, OCH$_2$CH=CH$_2$), 4.04-3.99 (m, 2 H, H-4, OCH$_2$CH=CH$_2$), 3.95 (s, 1 H, H-2), 3.80-3.84 (m, 2 H, H-5), 2.01 (s, 3 H, CH$_3$); $^{13}$C NMR (125.3 MHz, CDCl$_3$, δc) 169.8 (C=O), 133.8 (CH=CH$_2$), 117.6 (CH=CH$_2$), 107.3 (C-1), 85.8 (C-4), 78.8 (C-2), 67.9 (OCH$_2$CH=CH$_2$), 62.3 (C-5), 57.1 (C-3), 24.0 (CH$_3$); HRMS (ESI) calcd for (M+Na) C$_{10}$H$_{17}$NO$_5$+ Na: 254.1004, found 254.1004.

**Allyl 3-azido-5-O-benzoyl-3-deoxy-2-O-p-toluenesulfonyl-α-D-arabinofuranoside (11):** A solution of compound 8 (2.41 g, 7.54 mmol) dissolved in dichloromethane (28 mL) and pyridine (4.5 mL) was treated at 0 °C with p-toluenesulfonyl chloride (5.34 g, 28.08 mmol), and the reaction mixture was stirred for 50 h at room temperature under argon. The reaction mixture was quenched by the addition of a small piece of ice and then diluted with dichloromethane (22 mL). The organic layer was washed with a satd. aq. NaHCO$_3$ solution and then water. The crude solution was dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (7:1, hexanes–EtOAc) to yield 11 (2.81 g, 79%) as an oil: Rf 0.35 (7:1, hexanes–EtOAc); [α]$_D$ +86.2 (c 1.0, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$, δH) 8.10–8.04 (m, 2 H, Ar), 7.82–7.77 (m, 2 H, Ar), 7.61–7.56 (m, 1 H, Ar), 7.49–7.40 (m, 2 H, Ar), 7.35 (d, 2 H, J = 8.0 Hz, Ar), 5.57–5.55 (m, 1 H, CH=CH$_2$), 5.25 (ddd, 1 H, J = 1.5, 3.5, 17.0 Hz, CH=CH$_2$), 5.18 (ddd, 1 H, J = 1.0, 2.5, 11.5 Hz, CH=CH$_2$), 5.08 (s, 1 H, H-1), 4.78 (d, 1 H, J = 2.5 Hz, H-2), 4.55 (dd, 1 H, J = 4.0, 12.0 Hz, H-5), 4.46 (dd, 1 H, J = 4.0, 12.0 Hz, H-5), 4.18
(ddd, 1 H, J = 4.0, 4.0, 7.0 Hz, H-4), 4.12 (ddddd, 1 H, J = 1.5, 1.5, 5.0, 13.0 Hz, OCH₂CH=CH₂), 3.96 (dd, 1 H, J = 3.0, 6.5 Hz, H-3), 3.94 (dddd, 1 H, J = 1.5, 1.5, 6.5, 13.0 Hz, OCH₂CH=CH₂), 2.94 (s, 3 H, CH₃); \[^{13}\text{C} \text{NMR} \; (125.3 \text{ MHz, CDCl}_3, \delta_c) \; 166.1 \; (\text{C}=\text{O}), \; 145.7 \; (\text{Ar}), \; 133.4 \; (\text{C}=\text{CH}_2), \; 133.1, \; 132.6, \; 130.2, \; 129.8, \; 129.3, \; 128.5, \; 128.1, \; 118.0 \; (\text{CH}=\text{CH}_2), \; 104.1 \; (\text{C}-1), \; 87.4 \; (\text{C}-2), \; 79.3 \; (\text{C}-4), \; 68.2 \; (\text{OCH}_2\text{CH}=\text{CH}_2), \; 65.9 \; (\text{C}-3), \; 62.9 \; (\text{C}-5), \; 21.7 \; (\text{CH}_3); \; \text{IR (film) 3060, 2946, 2111 (N}=\text{N}=\text{N)}, \; 1724 \; (\text{C}=\text{O}), \; 1273 \; (\text{C–O}). \; \text{HRMS (ESI) calcd for (M+Na) C}_{22}\text{H}_{23}\text{N}_3\text{O}_{7}\text{S } + \text{ Na: 496.1153, found 496.1151.}

**Methyl 2,3,5-tri-O-benzoyl-α-D-arabinofuranoside (13):** D-Arabinose (10.06 g, 67.04 mmol) was dissolved in dried methanol and then 63 mL (1.06 M) methanolic hydrogen chloride (this solution was prepared by adding acetyl chloride dropwise to ice cold and rapidly stirring methanol) was added. This reaction mixture was stirred at room temperature under argon for 5 h and then neutralized by the addition of pyridine (75 mL). The mixture was concentrated to give oil color syrup free of methanol (achieved by evaporating the reaction residue three times with dichloromethane). Without purification, benzoyl chloride (29 mL, 249.99 mmol) was added at 0 ºC and then the reaction mixture was stirred at room temperature for 12 h. The reaction was quenched by the addition of water (5 mL) and diluted with dichloromethane (170 mL). After several of washes with water, 1 M HCl and satd. aq. NaHCO₃, the organic layer was dried over MgSO₄. The solution was concentrated to colorless syrup and recrystallized from ethanol to obtain **13**
(18.31 g, 57%) as a white crystalline solid: R\textsubscript{f} 0.48 (hexanes–EtOAc, 10:1); [\alpha]D\textsubscript{p} – 17.7 (c 1.2, CHCl\textsubscript{3}); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}, \delta\textsubscript{H}) 8.10–8.05 (m, 4 H), 8.03–7.90 (m, 2 H), 7.62–7.55 (m, 2 H), 7.54–7.48 (m, 1 H), 7.47–7.43 (m, 2 H), 7.42–7.37 (m, 2 H), 7.33–7.27 (m, 2 H), 5.61–5.59 (m, 1 H, H-3), 5.54–5.52 (m, 1 H, H-2), 5.19 (s, 1 H, H-1), 4.86 (dd, 1 H, J = 11.9, 3.5 Hz, H-5), 4.71 (dd, 1 H, J = 11.9, 3.5 Hz, H-5), 4.63–4.54 (m, 1 H), 3.50 (s, 3 H, CH\textsubscript{3}); \textsuperscript{13}C NMR (125.3 MHz, CDCl\textsubscript{3}, \delta\textsubscript{C}) 166.2 (C=O), 165.8 (C=O), 165.5 (C=O), 133.5 (Ar-C), 133.4 (Ar-C), 133.0 (Ar-C), 130.0 (Ar-C), 129.9 (Ar-C), 129.8 (Ar-C), 129.1 (Ar-C), 129.0 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 128.3 (Ar-C), 106.9 (C-1), 82.2 (C-2), 80.9 (C-4), 78.0 (C-3), 63.7 (C-5), 55.0 (OCH\textsubscript{3}); HRMS (ESI) calcd for (M+Na) C\textsubscript{27}H\textsubscript{24}O\textsubscript{8} + Na: 499.1470, found 499.1301.

\textit{p-Methoxyphenyl \textalpha-d-arabinofuranoside (14):} To a solution of compound 13 (17.03 g, 35.73 mmol) in dichloromethane (260 mL) was added 4-methoxyphenol (5.75 g, 46.37 mmol). The solution was cooled at 0 °C under an argon atmosphere and after 20 min F\textsubscript{3}B.Et\textsubscript{2}O (13.58 mL, 107.01 mmol) was added dropwise.\textsuperscript{9} The reaction mixture was stirred for 7 h at room temperature and then diluted with dichloromethane and carefully washed with satd. aq. NaHCO\textsubscript{3}. After washing with water, the organic layer was dried and concentrated to colorless liquid residue. Without further purification, the residue was dissolved in methanol-dichloromethane (1:1, 280 mL) and then 0.1 M NaOCH\textsubscript{3} in methanol (10 mL) was added. After stirring for 5 h at room
temperature, the reaction mixture was neutralized by the addition of Amberlite IR-120 H+ resin. The solution was filtered and then filtrate was concentrated to give a crude residue that was purified by silica gel column chromatography (99:1, EtOAc–CH3OH) to obtain 14 (7.89 g, 87%) as a colorless syrup: Rf 0.21 (hexanes–EtOAc, 1:10); 1H NMR (498.1 MHz, CDCl3, δH) 7.02–6.92 (m, 2 H, Ar), 6.86–6.75 (m, 2 H, Ar), 5.38 (d, J = 2.0 Hz, H-1), 4.19 (dd, J = 2, 4 Hz, H-2), 4.08–4.00 (m, 1 H, H-4), 3.95 (dd, 1 H, J = 4.0, 10.5 Hz, H-3), 3.76 (dd, 1 H, J = 3.5, 12.0 Hz, H-5), 3.64 (dd, 1 H, J = 5.0, 12.0 Hz, H-5), 3.71 (s, 3 H, OCH3); 13C NMR (125.3 MHz, CDCl3, δc) 156.4 (Ar), 152.4 (Ar), 119.3 (Ar), 115.5 (Ar), 108.8 (C-1), 86.0 (C-4), 83.8 (C-2), 78.3 (C-3), 62.8 (C-5), 56.1 (OCH3). HRMS (ESI) calcd for (M+Na) C12H16O6 + Na: 279.0946, found 279.0941.

p-Methoxyphenyl 2,3-anhydro-5-O-benzoyl-α-D-lyxofuranoside (15): The compound was prepared from 14 (4.59 g, 17.94 mmol), benzoic acid (3.29 g, 5.7 mmol), triphenyphosphine (14.91 g, 56.82 mmol) and diisopropylazodicarboxylate (8.97 mL, 44.87 mmol) in THF (267.0 mL) according to the procedure described for the preparation of 7. The compound was purified by chromatography (hexanes–EtOAc, 10:1) to provide 15 (8.13 g, 82%) as a white solid: Rf 0.35 (hexanes–EtOAc, 10:1); [α]D +100.4 (c 0.7 g, CHCl3); 1H NMR (498.1 MHz, CDCl3, δH) 8.08–8.06 (m, 2 H, Ar), 7.63–7.53 (m, 1 H, Ar), 7.49–7.40 (m, 2 H, Ar), 7.05–6.95 (m, 2 H, Ar), 6.88–6.75 (m, 2 H, Ar), 5.65 (s, 1 H, H-1), 4.63–4.41 (m, 3 H, H-4, H-5), 3.94
(d, 1 H, \( J = 2.8 \) Hz, H-3), 3.91 (d, 1 H, \( J = 2.8 \) Hz, H-2), 3.77 (s, 3 H, OCH\(_3\)); \(^{13}\)C NMR (125.3 MHz, CDCl\(_3\), \( \delta_C \)) 166.2 (C=O), 155.2 (Ar-C), 150.6 (Ar-C), 133.2 (Ar-C), 129.8 (Ar-C), 128.4 (Ar-C), 118.1 (Ar-C), 114.7 (Ar-C), 100.5 (C-1), 74.6 (C-4), 62.7 (C-5), 56.3 (C-2), 55.7 (OCH\(_3\)), 54.5 (C-3). HRMS (ESI) calcd for (M+Na) C\(_{19}\)H\(_{18}\)O\(_6\) + Na: 365.1102, found 365.1041.

\( p \)-Methoxyphenyl 3-azido-5-O-benzoyl-3-deoxy-\( \alpha \)-D-arabinofuranoside (16):

The compound 16 was prepared from 15 (8.01 g, 20.71 mmol) according to the procedure described for the preparation of 8. The compound was purified by silica gel chromatography (hexanes–EtOAc, 8:1) to obtain 16 (6.72 g, 75%) as silver color solid: R\(_f\) 0.21 (hexanes–EtOAc, 8:1); \([\alpha]_D^0 +157.1 \ (c 0.7, \text{CHCl}_3); \) \(^1\)H NMR (498.1 MHz, CDCl\(_3\), \( \delta_H \)) 8.09–8.03 (m, 2 H, Ar), 7.61–7.54 (m, 1 H, Ar), 7.48–7.41 (m, 2 H, Ar), 7.01–6.95 (m, 1 H, Ar), 6.85–6.79 (m, 1 H, Ar), 5.56 (d, 1 H, \( J = 1.8 \) Hz, H-1), 4.60 (dd, 1 H, \( J = 4.0, 12.0 \) Hz, H-5), 4.56–4.47 (m, 2 H, H-2, H-5), 4.40 (dt, 1 H, \( J = 4.0, 6.5 \) Hz, H-4), 3.92 (dd, 1 H, \( J = 3.5, 6.5 \) Hz, H-3), 3.76 (s, 3 H, OCH\(_3\)); \(^{13}\)C NMR (125.3 MHz, CDCl\(_3\), \( \delta_C \)) 166.2 (Ar-C), 155.2 (Ar-C), 150.1 (Ar-C), 133.4 (Ar-C), 129.7 (Ar-C), 129.5 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 118.0 (Ar-C), 114.7 (Ar-C), 106.5 (C-1), 81.2 (C-2), 79.8 (C-4), 67.2 (C-3), 63.6 (C-5), 55.7 (OCH\(_3\)); IR (film) 3466 (br), 2951, 2835, 2107 (N=N=N), 1722 (C=O), 1275. HRMS (ESI) calcd for (M+Na) C\(_{19}\)H\(_{19}\)N\(_3\)O\(_6\) + Na: 408.1273, found 408.1263.
**p-Methoxyphenyl 3-azido-5-O-benzoyl-3-deoxy-2-O-p-toluenesulfonyl-α-D-arabinofuranoside (17):** Compound 17 was prepared from 16 (6.01 g, 11.13 mmol) and according to the procedure described for the preparation of 11. The compound was purified by silica gel chromatography (hexanes–EtOAc, 9:1) to provide 17 (8.19 g, 97%) as a white solid: R<sub>f</sub> 0.56 (hexanes–EtOAc, 8:1); [α]<sub>D</sub> +164.3 (c 0.9, CHCl<sub>3</sub>); <sup>1</sup>H NMR (498.1 MHz, CDCl<sub>3</sub>, δ<sub>H</sub>) 8.08–8.04 (m, 2 H, Ar), 7.82–7.80 (m, 2 H, Ar), 7.62–7.57 (m, 1 H, Ar), 7.49–7.44 (m, 2 H, Ar), 7.34–7.31 (m, 2 H, Ar), 6.90–6.84 (m, 2 H, Ar), 6.82–6.76 (m, 2 H, Ar), 5.56 (s, 1 H, H-1), 4.99 (dd, 1 H, <i>J</i> = 0.5, 2.9 Hz, H-2), 4.56 (dd, 1 H, <i>J</i> = 4.0, 12.5 Hz, H-5), 4.56 (dd, 1 H, <i>J</i> = 4.0, 12.5 Hz, H-5), 4.32 (dt, 1 H, <i>J</i> = 3.5, 7.5 Hz, H-4), 4.07 (dd, 1 H, <i>J</i> = 3.0, 7.0 Hz, H-3), 3.76 (s, 3 H, CH<sub>3</sub>), 2.41 (s, 3 H, CH<sub>3</sub>); <sup>13</sup>C NMR (125.3 MHz, CDCl<sub>3</sub>, δ<sub>C</sub>) 166.1 (C=O), 155.5 (Ar-C), 149.4 (Ar-C), 145.9 (Ar-C), 133.4 (Ar-C), 132.4 (Ar-C), 130.2 (Ar-C), 129.8 (Ar-C), 129.3 (Ar-C), 128.5 (Ar-C), 128.1 (Ar-C), 118.2 (Ar-C), 114.6 (Ar-C), 104.2 (C-1), 87.5 (C-2), 79.8 (C-4), 65.8 (C-3), 62.7 (C-5), 55.6 (CH<sub>3</sub>), 21.7 (CH<sub>3</sub>); IR (film) 2954, 2835, 2112 (N=N=N), 1724 (C=O), 1214. HRMS (ESI) calcd for (M+Na) C<sub>26</sub>H<sub>25</sub>N<sub>3</sub>O<sub>8</sub>S + Na: 562.1361, found 562.1331.

**p-Methoxyphenyl N-acetyl-2,3-aziridino-5-O-benzoyl-2,3-dideoxy-α-D-ribofuranoside (18):** To a solution of azide 17 (3.12 g, 5.81 mmol) in EtOAc (58 mL) 10% Pd/C (253 mg) was added under Argon pressure. The resulting mixture was stirred for 4 h at room temperature under a H<sub>2</sub> pressure.<sup>10</sup> The solution then
filtered, dried over Na$_2$SO$_4$ and concentrated under high vacuum resulting in a colorless crude oil. Without further purification, DMF (30 mL) and triethylamine (1.1 mL) were added to the crude product at room temperature. The reaction mixture was stirred 100 °C for 20 h and then cooled to room temperature. Pyridine (34 mL) and acetic anhydride (5.9 mL) were then added to the mixture cooled at 0 °C. After stirring for 4 h at room temperature, the mixture was extracted with EtOAc (3x35 mL). The organic phases were combined, washed with a satd. aq. NaHCO$_3$ solution and then water. The organic layer was dried over anhydrous Na$_2$SO$_4$, filtered, and the solvent was evaporated under reduced pressure. The compound was purified by chromatography (hexanes–EtOAc, 2:1) to provide 18 (1.74 g, 76%) as a colorless liquid: $R_f$ 0.56 (hexanes–EtOAc, 8:1); $[\alpha]_D -69.8$ (c 0.7, CHCl$_3$); $^1$H NMR (498.1 MHz, CDCl$_3$, $\delta_H$) 8.02–7.89 (m, 2 H, Ar), 7.61–7.54 (m, 1 H, Ar), 7.47–7.42 (m, 2 H, Ar), 7.05–6.95 (m, 2 H, Ar), 6.88–6.75 (m, 2 H, Ar), 5.75 (d, 1 H, $J = 1.5$ Hz, H-1), 4.83 (dd, 1H, $J = 4.0$, 4.0 Hz, H-4), 4.58 (dd, 1H, $J = 4.0$, 12.5 Hz, H-5), 4.46 (dd, 1 H, $J = 4.0$, 12.5 Hz, H-5), 3.75 (s, 3 H, OCH$_3$), 3.62 (dd, 1 H, $J = 4.0$, 12.5 Hz, H-5), 3.40 (d, 1 H, $J = 4.0$ Hz, H-3), 2.31 (s, 3 H, acetate CH$_3$); $^{13}$C NMR (125.3 MHz, CDCl$_3$, $\delta_C$) 180.6 (C=O), 166.1 (C=O), 155.2 (Ar-C), 151.0 (Ar-C), 133.5 (Ar-C), 129.6 (Ar-C), 129.4 (Ar-C), 128.6 (Ar-C), 117.5 (Ar-C), 114.6 (Ar-C), 101.3 (C-1), 76.0 (C-4), 65.2 (C-5), 55.6 (CH$_3$), 42.9 (C-2), 40.4 (C-3), 24.0 (CH$_3$); $J_{C1-H1} = 169.1$ Hz. HRMS (ESI) calcd for (M+Na) C$_{21}$H$_{21}$NO$_6$ + Na: 406.1368, found 406.1360.
Allyl \textit{N}-acetyl-2,3-aziridino-5-\textit{O}-benzoyl-2,3-dideoxy-\textalpha-\textd-Ribofuranoside (19):

To a solution of azide 11 (2.09 g, 4.58 mmol) in THF (5.2 mL), water (0.41 mL) and triphenylphosphine (3.02 g, 11.49 mmol) were added. The resulting mixture was stirred for 20 h at room temperature. The solution then dried over Na$_2$SO$_4$ and concentrated under high vacuum resulting in a colorless crude oil. Without further purification, DMF (24 mL) and triethylamine (0.83 mL) were added to the crude product at room temperature. The reaction mixture was stirred 100 °C for 20 h and then cooled to room temperature. Pyridine (27 mL) and acetic anhydride (4.6 mL) were then added to the mixture cooled at 0 °C. After stirring for 4 h at room temperature, the mixture was extracted with EtOAc (3 x 30 mL). The organic phases were combined, washed with a satd. aq. NaHCO$_3$ solution and then water. The organic layer was dried over anhydrous Na$_2$SO$_4$, filtered, and the solvent was evaporated under reduced pressure.$^7$ The residue was purified by column chromatography (7:1, hexanes–EtOAc) to yield 19 (2.81 g, 79%) as a white solid: R$_f$ 0.35 (2:1, hexanes–EtOAc); \([\alpha]_D^{20} = -59.6$ (c 1.0, CHCl$_3$); \textit{H} NMR (500 MHz, CDCl$_3$, $\delta$) 8.01–8.04 (m, 2 H, Ar), 7.60–7.56 (m, 1 H, Ar), 7.47–7.41 (m, 2 H, Ar), 5.95-5.86 (m, 1 H, CH=CH$_2$), 5.65 (d, 1 H, $J = 1.5$ Hz, H-1), 5.3 (ddd, 1 H, $J = 1.5$, 3.5, 17.0 Hz, CH=CH$_2$), 5.19 (ddd, 1 H, $J = 1.0$, 2.5, 10.5 Hz, CH=CH$_2$), 4.71 (dd, 1 H, $J = 4.0$, 4.0 Hz, H-4), 4.5 (dd, 1 H, $J = 4.0$, 12.0 Hz, H-5), 4.38 (dd, 1 H, $J = 4.0$, 12.0 Hz, H-5), 4.32 (dddd, 1 H, $J = 1.5$, 1.5, 5.0, 13.0 Hz, OCH$_2$CH=CH$_2$), 4.15 (dddd, 1 H, $J = 1.5$, 1.5, 6.5, 13.0 Hz, OCH$_2$CH=CH$_2$), 3.4 (dd, 1 H, $J = 1.5$, 4.5 Hz, H-2), 3.3 (d, 1 H, $J = 4.0$ Hz, H-3), 3.22 (s, 3 H, CH$_3$); \textit{C} NMR (125.3 MHz, CDCl$_3$, $\delta$) 180.8
(C=O), 166.1 (C=O), 133.6 (Ar-C), 133.4 (CH=CH₂), 129.6 (Ar-C), 129.5 (Ar-C), 128.6 (Ar-C), 117.6 (CH=CH₂), 101.5 (C-1), 74.9 (C-4), 70.9 (OCH₂CH=CH₂), 65.2 (C-5), 42.6 (C-2), 40.5 (C-3), 24.0 (CH₃); \(J_{C1-H1} = 169.1\) Hz. HRMS (ESI) calcd for (M+Na) C₁₇H₁₉NO₅+ Na: 340.1160, found 340.1145.

**N-acetyl-2,3-aziridino-5-O-benzoyl-2,3-dideoxy-D-ribofuranose(1):**

\[\text{[Ir(COD)(PMePh₂)₂]PF₆} \ (0.12 \text{ g, 0.14 mmol)} \text{ in THF (24 mL) was stirred under a hydrogen atmosphere for 20 min at room temperature. The catalyst immediately lost its pink color and started to dissolve. The clear solution was injected carefully into 19 (1.4 g, 4.41 mmol) dissolved in THF (46.4 mL) and the reaction mixture was stirred overnight at room temperature under an argon atmosphere.}^{11}\ \text{Concentration of the mixture resulted in a colorless oil, which was dissolved in dichloromethane (58 mL). Anhydrous trimethylamine N-oxide (0.75 g, 6.7 mmol) and osmium tetra-oxide (11.8 mg) were added to the solution and the reaction mixture was stirred for another 12 h at room temperature. The reaction solution was then concentrated and purified by silica gel column chromatography (hexanes–EtOAc1:1) to afford 1 (1.19 g, 98%) as a colorless oil and as a mixture of isomers (α:β-1.0:7.0): R\(_f\) 0.21 (1:1, hexanes–EtOAc); \(^1\)H NMR (500 MHz, CDCl₃, \(δ_H\)) 8.11–8.08 (m, 2.38 H, Ar), 7.63–7.58 (m, 1.27 H, Ar), 7.51–7.46 (m, 2.42 H, Ar), 5.52 (d, 0.15 H, \(J = 1.0\) Hz, H-1α), 5.51 (s, 1 H, H-1β), 4.58–4.48 (m, 2.64 H), 4.44–4.35 (m, 1.24 H), 4.34–4.30 (m, 0.34 H), 3.44 (d, 1 H, \(J = 4.0\) Hz), 3.41 (dd, 0.17 H, \(J = 1.0, 4.0\) Hz), 3.38–3.34 (m, 1 H), 2.21 (s, 0.42 H, acetate CH₃α), 2.10 (s, 3 H, acetate CH₃β); \(^13\)C NMR (125.7 MHz, CDCl₃, \(δ_C\)) 180.8
(C=O), 179.7 (C=O), 166.3 (C=O), 166.0 (C=O), 133.5 (Ar-C), 133.4 (Ar-C), 129.7 (Ar-C), 129.6 (Ar-C), 129.4 (Ar-C), 128.6 (Ar-C), 128.6 (Ar-C), 128.5 (Ar-C), 97.9 (C-1α), 95.3 (C-1β), 74.9 (C-4β), 74.7 (C-4α), 65.3 (C-5β), 65.0 (C-5α), 43.6 (C-2β), 41.5 (C-2α), 40.9 (C-2α), 40.8 (C-2β), 23.9 (CH₃), 23.6 (CH₃). HRMS (ESI) calcd for (M+Na) C₁₄H₁₅NO₅⁺ Na: 300.0847, found 300.0845.

**N-acetyl-2,3-aziridino-5-O-benzoyl-2,3-dideoxy-β-D-ribofuranosyl**

**trichloroacetimidate (2):** To a stirring solution of 1 (0.51 g, 1.82 mmol) and trichloroacetonitrile (1.26 mL, 12.6 mmol) in dichloromethane (18.0 mL) cooled to 0 °C was added a solution of DBU (13.48 µL, 0.09 mmol) in dichloromethane (0.6 mL) over a period of 5 min. The reaction mixture then warmed to room temperature over 10 min and was stirred for 2 h at room temperature. The solution then concentrated at room temperature under reduced pressure, and the residue was purified by silica gel flash chromatography (6:4, hexanes–EtOAc with 0.5% Et₃N, Rᵣ 0.28) to give trichloroacetimidate 2 (0.74 g, 98%) as an amorphous white solid: [α]D₉⁻25.1 (c 0.6, CHCl₃); ¹H NMR (500 MHz, CDCl₃, δH) 8.68 (s, 1 H), 8.08–8.06 (m, 2 H, Ar), 7.63–8.59 (m, 1 H, Ar), 7.50–7.46 (m, 2 H, Ar), 6.56 (s, 1 H, H-1), 4.73 (dd, 1 H, J = 6.0, 7.0 Hz, H-4), 4.53 (dd, 1 H, J = 7.0, 12.5 Hz, H-5), 4.49 (dd, 1 H, J = 6.0, 11.5 Hz, H-5), 3.65 (d, 1 H, J = 4.0 Hz, H-2), 3.61 (dd, 1 H, J = 4.0 Hz, H-3), 2.22 (s, 3 H, CH₃); ¹³C NMR (125.7 MHz, CDCl₃, δc) 176.4 (C=O), 163.5 (C=O), 158.2 (C=NH), 130.8 (Ar), 127.2 (Ar), 126.8 (Ar), 125.9 (Ar), 95.9
(C-1), 89.0 (CCl₃), 74.9 (C-4), 62.8 (C-5), 40.5 (C-2), 39.2 (C-3), 22.1 (CH₃); \( J_{\text{C1-H1}} \) = 183.1 Hz. HRMS (ESI) calcd for (M+Na) \( \text{C}_{16}\text{H}_{15}\text{Cl}_3\text{N}_2\text{O}_5+ \text{Na} \): 442.9943, found 442.9943.

**General Procedure for Glycosylation Reactions**

**Method A: Glycosylation with hemiacetal 1 using (CH₃)₂S and Tf₂O (Gin Glycosylation\(^{13}\))**

To a stirring solution of \( N \)-acetyl-2,3-aziridino-5-\( O \)-benzoyl-2,3-dideoxy-\( \delta \)-ribofuranose (1, 35 mg, 0.13 mmol), 2,4,6-tri-\( \text{tert} \)-butylpyridine (140.33 mg, 0.57 mmol) and dimethylsulfide (18.64 \( \mu \)L, 0.31 mmol) in dichloromethane (1.8 mL) was added trifluoromethanesulfonic acid anhydride (31.85 \( \mu \)L, 0.19 mmol, 1.5 eq.) at -45 °C under an argon atmosphere. The resulting solution was stirred for 1 h at this temperature, followed by 15 min at 0 °C and finally another 15 min at room temperature. A solution of an alcohol (20 to 27, 0.19 mmol, 1.5 equiv) in dichloromethane (0.44 mL) was then added dropwise. The reaction mixture then stirred for 12 h at room temperature, and diluted with dichloromethane (20 mL). The diluted solution was washed with a saturated aqueous NaHCO₃ and water. The organic layer was dried, filtered, and concentrated. The crude residue was purified by chromatography to afford the products shown in Table 1 (Results and Discussion section)
Method B: Glycosylation with imidate 2 by TMSOTf in dichloromethane

To a stirring solution of an alcohol (20 to 27, 0.1 mmol, 0.8 equiv) in dichloromethane (1.0 mL) at −25 °C containing 4 Å molecular sieves (10 mg) was added a solution of trichloroacetimidate 2 (50 mg, 0.12 mmol) dissolved in dichloromethane (1.0 mL). A solution of TMSOTf (0.05 equiv) in dichloromethane (0.16 mL) was added dropwise to the reaction mixture over a period of 5 min. The resulting mixture was stirred at this temperature for 15 min, then another 15 min at −20 °C, and finally warmed slowly to −5 °C over 1 h. After quenching the acid by the addition of Et$_3$N, the reaction mixture was diluted with dichloromethane (3 mL) and filtered through Celite. The filtrate was concentrated under reduced pressure to give a crude residue that was purified by column chromatography to afford products shown in Table 2 (Results and Discussion section).

Method C: Glycosylation with imidate 2 by TMSOTf in dichloromethane with 10% diethyl ether

The donor 2 (50 mg, 0.12 mmol) was dissolved in dichloromethane (1.0 mL) and then added to a solution of alcohol (20, 21 and 26) dissolved in dichloromethane (1.0 mL) and diethyl ether (0.1 mL) containing 4 Å molecular sieves (10 mg, stirred already for 10 min) at −25 °C. At this temperature, a solution of TMSOTf (0.05 eq.) in dichloromethane (0.16 mL) was added dropwise over 5 min. The resulting mixture was stirred for 15 min followed by another 15 min at −20 °C, and at last warmed slowly to -5 °C over 1 h. The reaction mixture then quenched by the addition of Et$_3$N (0.56 µL), diluted with dichloromethane (3 mL)
and filtered through Celite. The filtrate was concentrated to give a crude residue that was purified by column chromatography to afford the products shown in Table 2 (Results and Discussion section).

*Benzyl N-acetyl-2,3-aziridino-5-O-benzoyl-2,3-dideoxy-α-D-ribofuranoside (28α):* The compound was isolated after silica gel chromatography (hexanes–EtOAc, 3:1) as a colorless oil: R$_f$ 0.26 (hexanes–EtOAc, 2:1); $^1$H NMR (500 MHz, CDCl$_3$, δ$_H$) 8.07–8.03 (m, 2 H, Ar), 7.62–7.58 (m, 1 H, Ar), 7.46–7.42 (m, 2 H, Ar), 7.26–7.22 (m, 5 H, Ar), 5.39 (d, 1 H, J = 1.5 Hz, H-1), 4.87 (d, 1 H, J = 12.0 Hz, PhCH$_2$), 4.76 (dd, 1 H, J = 4.0, 4.0 Hz, H-4), 4.59 (d, 1 H, J = 12.0 Hz, PhCH$_2$), 4.52 (dd, 1 H, J = 4.0, 12.0 Hz, H-5), 4.39 (dd, 1 H, J = 4.0, 12.0 Hz, H-5), 3.78 (dd, 1 H, J = 1.0, 3.5 Hz, H-2), 3.78 (d, 1 H, J = 4.0 Hz, H-3), 2.15 (s, 3 H, acetate CH$_3$); $^{13}$C NMR (125.7 MHz, CDCl$_3$, δ$_C$) 180.7 (C=O), 166.0 (C=O), 136.9 (Ar-C), 133.4 (Ar-C), 129.5 (Ar-C), 129.4 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 128.0 (Ar-C), 127.9 (Ar-C), 101.1 (C-1), 74.7 (C-4), 71.6 (OCH$_2$), 65.2 (C-5), 42.5 (C-2), 40.4 (C-3), 24.1 (CH$_3$); $^J_{C1-H1}$ = 168.3 Hz. HRMS (ESI) calcd for (M+Na) C$_{21}$H$_{15}$NO$_5$+Na: 390.1316, found 390.1314.
Benzyl \( N\)-acetyl-2,3-aziridino-5-\( O\)-benzoyl-2,3-dideoxy-\( \beta\)-\( D\)-ribofuranoside (28\( \beta\)): The compound was isolated after chromatography (hexanes–EtOAc, 3:1) as a colorless oil: \( R_f \) 0.28 (hexanes–EtOAc, 2:1); \(^1\)H NMR (500 MHz, CDCl\(_3\), \( \delta_H \)) 8.10–8.05 (m, 2 H, Ar), 7.61–7.54 (m, 1 H, Ar), 7.49–7.40 (m, 2 H, Ar), 7.38–7.31 (m, 5 H), 5.29 (s, 1 H, H-1), 4.78 (d, 1 H, \( J = 11.5 \) Hz, PhCH\(_2\)), 4.63 (dd, 1 H, \( J = 6.5, 6.5 \) Hz, H-4), 4.56 (d, 1 H, \( J = 11.5 \) Hz, PhCH\(_2\)), 4.51 (dd, 1 H, \( J = 6.0, 11.5 \) Hz, H-5), 4.48 (dd, 1 H, \( J = 6.5, 11.5 \) Hz, H-5), 3.46 (d, 1 H, \( J = 3.5 \) Hz, H-2), 3.42 (d, 1 H, \( J = 4.0 \) Hz, H-3), 2.16 (s, 3 H, acetate CH\(_3\)); \(^{13}\)C NMR (125.7 MHz, CDCl\(_3\), \( \delta_C \)) 179.2 (C=O), 166.1 (C=O), 136.7 (Ar-C), 133.2 (Ar-C), 129.7 (Ar-C), 129.6 (Ar-C), 128.5 (Ar-C), 128.4 (Ar-C), 128.2 (Ar-C), 128.0 (Ar-C), 100.2 (C-1), 75.0 (C-4), 70.2 (OCH\(_2\)), 64.8 (C-5), 42.8 (C-2), 40.7 (C-3), 23.7 (CH\(_3\)); \( J_{C1-H1} = 175.1 \) Hz. HRMS (ESI) calcd for (M+Na) \( C_{21}H_{11}NO_5+Na \): 390.1316, found 390.1314.

\( n\)-Octyl \( N\)-acetyl-2,3-aziridino-5-\( O\)-benzoyl-2,3-dideoxy-\( \alpha\)-\( D\)-ribofuranoside (29\( \alpha\)): The compound was isolated after silica gel column chromatography (4:1, hexanes–EtOAc) as a colorless oil: \( R_f \) 0.40 (3:1, hexanes–EtOAc); \(^1\)H NMR (500 MHz, CDCl\(_3\), \( \delta_H \)) 8.09–8.01 (m, 2 H, Ar), 7.65–7.52 (m, 1 H, Ar), 7.51–7.40 (m, 2 H, Ar), 5.34 (d, 1 H, \( J = 1.5 \) Hz, H-1), 4.76 (dd, 1
H, J = 4.0, 4.0 Hz, H-4), 4.53 (dd, 1 H, J = 4.0, 12.0 Hz, H-5), 4.40 (dd, 1 H, J = 4.0, 12.0 Hz, H-5), 3.81 (dd, 1 H, J = 6.5, 7.0, 9.5 Hz, octyl OCH$_2$), 3.53 (ddd, 1 H, J = 6.5, 7.0, 9.0 Hz, octyl OCH$_2$), 3.42 (dd, 1 H, J = 1.5, 4.5 Hz, H-2), 3.31 (d, 1 H, J = 4.0 Hz, H-3), 2.23 (s, 3 H, acetate CH$_3$), 1.71–1.58 (m, 4 H, octyl CH$_2$), 1.42–1.18 (m, 8 H, octyl CH$_2$), 0.95 (t, 3 H, J = 6.8 Hz, octyl CH$_3$); $^{13}$C NMR (125.7 MHz, CDCl$_3$, $\delta_C$) 180.8 (C=O), 166.1 (C=O), 133.4 (Ar-C), 129.6 (Ar-C), 129.5 (Ar-C), 128.6 (Ar-C), 102.5 (C-1), 74.3 (C-4), 70.8 (octyl OCH$_2$), 65.3 (C-5), 42.6 (C-2), 40.3 (C-3), 31.8(octyl-CH$_2$), 29.7(octyl-CH$_2$), 29.6 (octyl-CH$_2$), 29.5 (octyl-CH$_2$), 25.9 (octyl-CH$_2$), 24.1 (acetate-CH$_3$), 14.1 (octyl-CH$_3$); J$_{C1-H1}$ = 169.0 Hz. HRMS (ESI) calcd for (M+Na) C$_{22}$H$_{31}$NO$_5$+Na: 412.2099, found 412.2093.

**$n$-Octyl N-acetyl-2,3-aziridino-5-o-benzoyl-2,3-dideoxy-β-D-ribofuranoside (29β):** The compound was isolated after chromatography (4:1, hexanes–EtOAc) as a colorless oil: R$_f$ 0.43 (3:1, hexanes–EtOAc); $^1$H NMR (500 MHz, CDCl$_3$, $\delta_H$) 8.12–8.03 (m, 2 H, Ar), 7.62–7.55 (m, 1 H, Ar), 7.51–7.46 (m, 2 H, Ar), 5.17 (s, 1 H, H-1), 4.60 (dd, 1 H, J = 6.0, 6.5 Hz, H-4), 4.45 (d, 2 H, J = 6.5 Hz, H-5), 3.75 (ddd, 1 H, J = 6.5, 7.0, 9.5 Hz, octyl OCH$_2$), 3.47 (ddd, 1 H, J = 6.5, 7.0, 9.0 Hz, octyl OCH$_2$), 3.43 (d, 1 H, J = 3.5 Hz, H-2), 3.36 (d, 1 H, J = 3.5 Hz, H-3), 2.18 (s, 3 H, acetate CH$_3$), 1.64–1.50 (m, 4 H, octyl CH$_2$), 1.20–1.14 (m, 8 H, octyl CH$_2$), 0.91 (t, 3 H, J = 7.0 Hz, octyl CH$_3$); $^{13}$C NMR (125.7 MHz, CDCl$_3$, $\delta_C$) 179.2 (C=O), 166.1 (C=O), 133.2 (Ar-C), 129.7 (Ar-C), 129.6 (Ar-C), 128.4 (Ar-C), 100.9 (C-1), 74.6 (C-4), 68.9 (octyl-OCH$_2$), 64.9 (C-5),
42.6 (C-2), 40.7 (C-3), 31.8 (octyl-CH₂), 29.7 (octyl-CH₂), 29.5 (octyl-CH₂), 29.3 (octyl-CH₂), 26.1 (octyl-CH₂), 23.7 (acetate-CH₃), 14.1 (octyl-CH₃); J_{C1-H1} = 177.0 Hz. HRMS (ESI) calcd for (M+Na) C_{22}H_{31}NO₅+Na: 412.2099, found 412.2093.

**Methyl 5-O-(N-acetyl-2,3-aziridino-5-O-benzoyl-2,3-dideoxy-α-D-ribofuranosyl)-2,3-anhydro-α-D-lyxofuranoside (30α):** The compound was isolated after silica gel column chromatography (3:1, hexanes–EtOAc) as white solid: R_{f} 0.19 (3:2, hexanes–EtOAc); \(^1\)H NMR (500 MHz, CDCl₃, \(\delta_H\)) 8.09–8.01 (m, 2 H, Ar), 7.65–7.52 (m, 1 H, Ar), 7.51–7.40 (m, 2 H, Ar), 5.43 (d, 1 H, \(J = 1.5\) Hz, H-1'), 4.93 (s, 1 H, H-1), 4.76 (dd, 1 H, \(J = 4.0, 4.0\) Hz, H-4'), 4.55 (dd, 1 H, \(J = 3.5, 12.0\) Hz, H-5'), 4.42 (dd, 1 H, \(J = 4.0, 12.0\) Hz, H-5'), 4.25 (dd, 1 H, \(J = 5.5, 10.0\) Hz, H-5), 3.96 (dd, 1 H, \(J = 5.0, 10.0\) Hz, H-5), 3.82–3.76 (m, 2 H, H-3, H-4), 3.65 (d, 1 H, \(J = 3.5\) Hz, H-2), 3.48 (dd, 1 H, \(J = 1.5, 4.0\) Hz, H-2'), 3.41 (s, 3 H, OCH₃), 3.34 (d, 1 H, \(J = 4.0\) Hz, H-3'), 2.06 (s, 3 H, acetate CH₃); \(^{13}\)C NMR (125.7 MHz, CDCl₃, \(\delta_C\)) 180.6 (C=O), 166.1 (C=O), 133.4 (Ar-C), 129.4 (Ar-C), 128.5 (Ar-C), 102.7 (azi-C-1), 102.1 (epo-C-1), 74.9 (C-4'), 74.5 (C-4), 67.3 (C-5), 64.8 (C-5'), 56.3 (C-2), 55.5 (C-3), 42.5 (C-2'), 40.5 (C-2'), 24.0 (OCH₃); J_{C1-H1} = 169.1 Hz. HRMS (ESI) calcd for (M+Na) C_{20}H_{23}NO₇+Na: 428.1321, found 428.1316.
Methyl 5-\(O\)-(N-acetyl-2,3-aziridino-5-\(O\)-benzoyl-2,3-dideoxy-\(\beta\)-\(\alpha\)-D-ribofuranosyl)-2,3-anhydro-\(\alpha\)-D-lyxofuranoside (30\(\beta\)): The compound was isolated after chromatography (3:1, hexanes–EtOAc) as white solid: \(R_f\) 0.22 (3:2, hexanes–EtOAc); \(^1\)H NMR (500 MHz, CDCl\(_3\), \(\delta_H\)) 8.06–8.04 (m, 2 H, Ar), 7.66–7.63 (m, 1 H, Ar), 7.52–7.48 (m, 2 H, Ar), 5.24 (s, 1 H, H-1'), 4.97 (s, 1 H, H-1), 4.61 (dd, 1 H, \(J = 6.0, 7.0\) Hz, H-4'), 4.48 (dd, 2 H, \(J = 7.0, 7.0\) Hz, H-5'), 4.19 (dd, 1 H, \(J = 6.0, 10.0\) Hz, H-5), 3.96 (dd, 1 H, \(J = 5.5, 10.0\) Hz, H-5), 3.63–3.74 (m, 3 H, H-2', H-2, H-4), 3.43–3.47 (m, 2 H, H-3', H-3), 3.41 (s, 3 H, OCH\(_3\)), 2.15 (s, 3 H, acetate CH\(_3\)); \(^{13}\)C NMR (125.7 MHz, CDCl\(_3\), \(\delta_C\)) 179.2 (C=O), 166.1 (C=O), 133.3 (Ar-C), 129.7 (Ar-C), 128.4 (Ar-C), 102.4 (azi-C-1), 101.4 (epo-C-1), 75.1 (C-4'), 75.0 (C-4), 67.4 (C-5), 64.8 (C-5'), 56.0 (C-2), 55.6 (C-3), 42.7 (C-2'), 40.6 (C-3'), 23.7 (OCH\(_3\)); \(J_{\text{C1-H1}} = 177.2\) Hz. HRMS (ESI) calcd for (M+Na) C\(_{20}\)H\(_{23}\)NO\(_8\) + Na: 428.1321, found 428.1316.

Cyclohexyl \(N\)-acetyl-2,3-aziridino-5-\(O\)-benzoyl-2,3-dideoxy-\(\alpha\)-D-ribofuranoside (31\(\alpha\)): The compound was isolated after silica gel chromatography (hexanes–EtOAc, 4:1) as a colorless oil. \(R_f\) 0.32 (hexanes–EtOAc, 3:1); \(^1\)H NMR (500 MHz, CDCl\(_3\), \(\delta_H\)) 8.12–8.03 (m, 2 H, Ar),
7.62–7.55 (m, 1 H, Ar), 7.51–7.46 (m, 2 H, Ar), 5.46 (d, 1 H, \( J = 1.0 \) Hz, H-1), 4.76 (dd, 1 H, \( J = 4.0, 4.5 \) Hz, H-4), 4.53 (dd, 1 H, \( J = 4.0, 12.0 \) Hz, H-5), 4.40 (dd, 1 H, \( J = 4.5, 12.0 \) Hz, H-5), 3.57–3.64 (m, 1 H, cyclohexyl CH), 3.38 (dd, 1 H, \( J = 1.0, 4.0 \) Hz, H-2), 3.26 (d, 1 H, \( J = 4.0 \) Hz, H-3), 2.18 (s, 3 H, acetate CH\(_3\)), 1.98–1.18 (m, 10 H cyclohexyl CH\(_2\)). 

\(^{13}\)C NMR (125.7 MHz, CDCl\(_3\), \( \delta_{c} \)) 180.8 (C=O), 166.1 (C=O), 133.4 (Ar-C), 129.6 (2 Ar-C), 128.6 (2 Ar-C), 100.7 (C-1), 78.2 (cyclohexyl-CH), 73.9 (C-4), 65.3 (C-5), 42.9 (C-2), 39.8 (C-3), 33.1 (cyclohexyl CH\(_2\)), 32.0 (cyclohexyl CH\(_2\)), 29.7 (cyclohexyl CH\(_2\)), 29.6 (cyclohexyl CH\(_2\)), 24.2 OCH\(_3\), 24.1 (cyclohexyl CH\(_2\)); \( J_{C1-H1} = 168.2 \) Hz. HRMS (ESI) calcd for (M+Na) \( C_{20}H_{25}NO_5 + Na \): 382.1629, found 382.1623.

**Cyclohexyl N-acetyl-2,3-aziridino-5-O-benzoyl-2,3-dideoxy-\( \beta \)-D-ribofuranoside (31\( \beta \))**: The compound was isolated after chromatography (hexanes–EtOAc, 4:1) as a colorless oil: R\(_f\) 0.37 (hexanes–EtOAc, 3:1); \(^1\)H NMR (500 MHz, CDCl\(_3\), \( \delta_{h} \)) 8.12–8.03 (m, 2 H), 7.62–7.55 (m, 1 H), 7.51–7.46 (m, 2 H), 5.33 (s, 1 H, H-1), 4.40–4.60 (m, 3 H, H-4, H-5), 3.70–3.64 (m, 1 H), 3.44 (d, 1 H, \( J = 3.5 \) Hz, H-2), 3.33 (d, 1 H, \( J = 4.0 \) Hz, H-3), 2.08 (s, 3 H, acetate CH\(_3\)), 1.98–1.17 (m, 10 H, cyclohexyl CH\(_2\)). 

\(^{13}\)C NMR (125.7 MHz, CDCl\(_3\), \( \delta_{c} \)) 179.3 (C=O), 166.1 (C=O), 133.2 (Ar-C), 129.7 (Ar-C), 129.6 (Ar-C), 128.4 (Ar-C), 99.1 (C-1), 78.2 (cyclohexyl-CH), 74.3 (C-4), 65.0 (C-5), 42.7 (C-2), 41.0 (C-3), 33.2 (cyclohexyl CH\(_2\)), 32.1 (cyclohexyl CH\(_2\)), 29.6 (cyclohexyl CH\(_2\)), 29.4 (cyclohexyl CH\(_2\)), 24.1 (acetate CH\(_3\)), 24.1(cyclohexyl CH\(_3\))
\( \text{CH}_2 \); \( J_{\text{C1-H1}} = 175.1 \text{ Hz} \). HRMS (ESI) calcd for (M+Na) \( \text{C}_{20}\text{H}_{25}\text{NO}_5\text{Na} \): 382.1629, found 382.1623.

\( \text{t-Butyl N-acetyl-2, 3-aziridino-5-O-benzoyl-2, 3-dideoxy-}\alpha\text{-D-ribofuranoside} (34\alpha) \): The compound was isolated after chromatography (3:1, hexanes–EtOAc) as a colorless oil: \( R_f 0.26 (2:1, \text{hexanes–EtOAc}) \); \( ^1\text{H} \) NMR (500 MHz, CDCl\(_3\), \( \delta_H \)) 8.06–8.03 (m, 2 H, Ar), 7.61–7.58 (m, 1 H, Ar), 7.53–7.47 (m, 2 H, Ar), 5.52 (d, 1 H, \( J = 1.0 \text{ Hz}, \text{H-1} \)), 4.74 (dd, 1 H, \( J = 4.5, 4.5 \text{ Hz}, \text{H-4} \)), 4.55 (dd, 1 H, \( J = 4.5, 12.0 \text{ Hz}, \text{H-5} \)), 4.40 (dd, 1 H, \( J = 4.5, 12.0 \text{ Hz}, \text{H-5} \)), 3.29 (dd, 1 H, \( J = 1.5, 4.0 \text{ Hz}, \text{H-2} \)), 3.23 (d, 1 H, \( J = 4.0 \text{ Hz}, \text{H-3} \)), 2.24 (s, 3 H, acetate CH\(_3\)), 1.23 (s, 9 H, t-butyl CH\(_3\)); \( ^{13}\text{C} \) NMR (125.7 MHz, CDCl\(_3\), \( \delta_C \)) 181.0 (C=O), 166.1 (C=O), 133.4 (Ar-C), 129.6 (Ar-C), 129.6 (Ar-C), 128.5 (Ar-C), 96.8 (C-1), 75.8 (OCC(H\(_3\))\(_3\)), 73.8 (C-4), 65.1 (C-5), 43.3 (C-2), 39.3 (C-3), 29.7 (C(C(H\(_3\))\(_3\)), 28.4 (C(C(H\(_3\))\(_3\)), 24.2 (acetate CH\(_3\)); \( J_{\text{C1-H1}} = 168.6 \text{ Hz} \). HRMS (ESI) calcd for (M+Na) \( \text{C}_{18}\text{H}_{23}\text{NO}_5\text{Na} \): 356.1473, found 356.1468.

\( \text{t-Butyl N-acetyl-2,3-aziridino-5-O-benzoyl-2,3-dideoxy-}\beta\text{-D-ribofuranoside} (34\beta) \): The compound was isolated after chromatography (3:1, hexanes–EtOAc) as a colorless oil: \( R_f 0.31 (2:1, \text{hexanes–EtOAc}) \); \( ^1\text{H} \) NMR (500 MHz, CDCl\(_3\), \( \delta_H \)) 8.07–8.02 (m, 2 H, Ar), 7.60–7.58 (m, 1 H, Ar), 7.53–7.47 (m, 2 H, Ar), 5.47 (s, 1 H, H-1), 4.55–4.44 (m, 3 H, H-4, 2 H-5), 3.45 (d, 1 H, \( J = 4.0, \text{H-2} \)), 3.24 (d, 1 H, \( J = 4.0, \text{H-2} \)).
= 4.0, H-3), 2.15 (s, 3 H, acetate CH₃), 1.28
(s, 9 H, t-butyl CH₃); ¹³C NMR (125.7 MHz,
CDCl₃, δc) 181.0 (C=O), 166.1 (C=O), 133.2
(Ar-C), 129.8 (Ar-C), 129.7 (Ar-C), 128.4 (Ar-
C), 95.5 (C-1), 75.8 (OC(CH₃)₃), 74.3 (C-4),
65.1 (C-5), 43.1 (C-2), 41.4 (C-3), 29.7
(C(CH₃)₃), 28.8 (C(CH₃)₃), 23.7 (acetate
CH₃); J_C1-H1 = 174.5 Hz. HRMS (ESI) calcd for (M+Na) C₁₈H₂₃NO₅Na: 356.1473,
found 356.1468.

1-Adamantyl N-acetyl-2,3-aziridino-5-o-benzoyl-2,3-dideoxy-α-D-
ribofuranoside (35α): The compound was isolated after silica gel column
chromatography (hexanes–EtOAc, 3:1) as a colorless oil: Rf 0.22 (hexanes–
EtOAc, 2:1); ¹H NMR (500 MHz, CDCl₃,
δh) 8.12–8.03 (m, 2 H, Ar), 7.62–7.52 (m,
1 H, Ar), 7.51–7.40 (m, 2 H, Ar), 5.64 (d,
1 H, J = 1.5 Hz, H-1), 4.74 (dd, 1 H, J =
4.5, 4.5 Hz, H-4), 4.55 (dd, 1 H, J = 4.5,
12.0 Hz, H-5), 4.39 (dd, 1 H, J = 4.5, 12.0
Hz, H-5), 3.28 (dd, 1 H, J = 1.5, 4.0 Hz, H-2), 3.22 (d, 1 H, J = 4.0 Hz, H-3), 2.18
(br, s, 3 H), 1.90–1.75 (m, 6 H, adamantyl CH₂), 1.55–1.65 (m, 6 H, adamantyl
CH₂); ¹³C NMR (125.7 MHz, CDCl₃, δc) 181.0 (C=O), 166.1 (C=O), 133.3 (Ar-C),
129.7 (Ar-C), 129.6 (Ar-C), 128.5 (Ar-C), 95.2 (C-1), 75.0 (C-4), 73.7
(adamantylCO), 65.1 (C-5), 43.4 (C-2), 42.2 (adamantylCH), 39.4 (C-3), 36.2
(adamantyl\(\text{CH}\)), 30.6 (adamantyl\(\text{CH}\)), 24.3 (\(\text{CH}_3\)); \(J_{\text{C1-H1}} = 167.4\) Hz. HRMS (ESI) calcd for (M+Na) \(\text{C}_{24}\text{H}_{29}\text{NO}_{5}\text{Na}\): 434.1942, found 434.1936.

1-Adamantyl \(N\)-acetyl-2,3-aziridino-5-\(O\)-benzoyl-2,3-dideoxy-\(\beta\)-\(D\)-ribofuranoside (35\(\beta\)): The compound was isolated after chromatography (hexanes–EtOAc, 3:1) as a colorless oil: \(R_f\) 0.24 (hexanes–EtOAc, 2:1); \(^1\)H NMR (500 MHz, CDCl\(_3\), \(\delta_H\)) 8.12–8.03 (m, 2 H, Ar), 7.62–7.52 (m, 1 H, Ar), 7.51–7.40(m, 2 H, Ar), 5.6 (s, 1 H, H-1), 4.56–4.45 (m, 3 H, H-4, H-5), 3.45 (d, 1 H, \(J = 3.5\) Hz, H-2), 3.25 (d, 1 H, \(J = 3.5\) Hz, H-3), 2.14 (br, s, 3 H);1.90–1.76(m, 6 H, adamantyl CH\(_2\)), 1.58–1.68 (m, 6 H, adamantyl CH\(_2\)); \(^{13}\)C NMR (125.7 MHz, CDCl\(_3\), \(\delta_C\)) 179.4 (C=O), 166.1 (C=O), 133.2 (Ar-C), 129.9 (Ar-C), 129.7 (2 Ar-C), 128.4 (2 Ar-C), 94.0 (C-1), 75.2 (C-4), 74.2 (adamantyl\(\text{CO}\)), 65.1 (C-5), 43.0 (C-2), 42.8 (adamantyl \(\text{CH}\)), 41.4 (C-3), 36.1 (adamantyl\(\text{CH}\)), 30.6 (adamantyl\(\text{CH}\)), 23.7 (acetate \(\text{CH}_3\)); \(J_{\text{C1-H1}} = 176.9\) Hz. HRMS (ESI) calcd for (M+Na) \(\text{C}_{24}\text{H}_{29}\text{NO}_{5}\text{Na}\): 434.1942, found 434.1936.
4.2. Bibliography