Synthesis of Alkynyl Ribofuranosides

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SYNTHESIS OF ALKYNYL RIBOFURANOSIDES

A Thesis Presented to
The Faculty of the Chemistry Program
The City College of New York

In (Partial) Fulfillment
of the Requirements for the Degree
Master of Arts

by
Christian Rodriguez
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Synthesis of Alkynyl Ribofuranosides
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Chapter 1: Carbohydrate Templates

1.1 Introduction

Over the years, carbohydrates have become important chiral starting materials that are commercially available and cost effective. Examples of carbohydrates range from simple molecules such as D-glucose, D-mannose, and D-ribose 1 to complex compounds such as disaccharides, oligosaccharides, and polysaccharides. These molecules are just a few of the many carbohydrates commonly found in living systems. Deoxy-D-ribose is a carbohydrate component which closely resembles D-ribose. It is commonly found in DNA nucleosides such as adenosine 2. D-ribose is the carbohydrate component found in the RNA nucleoside uridine 3.

![Figure 1. D-ribose and some derivatives](image)

D-ribose has been used as a chiral template for the preparation of various C-glycosides, such as the naturally occurring molecules pyrazomycin 4, formycin\(^2\) 5, and the synthetic enediyne compound oxabicycloenediyne\(^3\) 6 (Figure 2). D-ribofuranosyl derivatives like pyrazomycin 4 and formycin 5 are C-glycosides that are composed of a carbohydrate unit that is linked by a C-C bond at the C-1 position within the heterocyclic unit instead of the C-N bond found in DNA and RNA. The diverse biological activity of these C-nucleosides includes antibiotic, antitumor, antiviral, and carcinogenic activity.\(^2,4\)
Alkynyl-glycosides are key intermediates in the synthesis of a wide variety of C-glycoside derivatives. The alkynyl functional group can serve as a site for 1,3-dipolar cycloaddition reactions\(^2\), and coupling reactions.\(^4\) Many reports described the nucleophilic addition, and alkynylation of benzylated ribose,\(^2\), benzylated arabinose lactone,\(^6\), and isopropylidene ribonolactone\(^5\) derivatives with lithium acetylide, and other alkynyl Grignard reagents. The resulting alkynyl derivatives were reduced to yield the corresponding alkynyl C-glycosides. These alkynyl ribofuranosides (scheme 1) can be a suitable starting material for the synthesis of a novel enediyne class of compounds similar to 6 bearing the alkyne bond at the C-1 and C-5 position instead of the C-2 and C-5 position found in 6.

The aim of this project is the preparation of 1-ethynyl derivatives of ribose that may be suitable starting molecules for the synthesis of enediyne heterocyclic compounds that may have potential biological activity. For this purpose D-ribose 1 should be protected appropriately to
avoid interference of the hydroxyl groups during the reaction steps to prepare the enediyne moiety. This project is divided in three parts.

1) Preparation of Protected D-ribonolactone template.
2) Nucleophilic alkynylation followed by anomeric deoxygenation.
3) Intramolecular cyclization of prepared diols.

The first part of the project is the protection of the hydroxyl groups at the C-2, C-3 and C-5 positions. After the protected ribofuranoside is prepared, the anomeric center at the C-1 position will be oxidized to yield the corresponding protected ribonolactone (scheme 2). The second part will be the nucleophilic addition of the alkynyl group followed by the reduction of the anomeric hydroxyl group\(^6\) (Scheme 3). The third part includes the pursuit of a different synthetic route incorporating different intramolecular cyclization reactions.

**Scheme 2.** Preparation of the protected ribonolactone\(^7\)

1.2 Preparation of the protected ribonolactone template

Even though there are many D-ribose and D-ribonolactone derivatives which have different protecting groups, our preferred method was the transformation of D-ribose into 5-\(O\)-(tert-butyldimethylsilyl)-2,3-\(O\)-isopropylidene-D-ribonolactone \(9\). The silyl ether lactone derivative \(9\) was preferred because of the ease in preparation, isolation, and purification.\(^7\) It also provides an advantage for the selective removal of the \(tert\)-butyldimethylsilyl protecting group of the ribofuranose core using fluorinated reagents such as tetra-n-butyl ammonium fluoride (TBAF).
1.3 Synthesis of 5-O-(tert-butyldimethylsilyl)-2,3-O-isopropylidene-D-ribonolactone$^7$ (9)

The ribonolactone derivative 9 is prepared from D-ribose 1 in three steps (Scheme 3). D-ribose 1 is treated with a catalytic amount of concentrated sulfuric acid in acetone giving the 5-hydroxy-2,3-O-isopropylidene-D-ribofuranose 7 in 99% yield. The primary hydroxyl group at the fifth position is selectively protected as a silyl ether by treating the 5-hydroxy lactol 7 with imidazole and tert-butyldimethyl silyl chloride in dimethylformamide (DMF) yielding the lactol 5-O-(tert-butyldimethylsilyl)-2,3-O-isopropylidene-D-ribofuranose 8. This reaction is followed by the oxidation of the lactol 8 at the anomeric center yielding the protected ribonolactone 9. The oxidation was successful with potassium permanganate in acetone.

Oxidation of the lactol 8 with bromine, sodium bicarbonate, tertiary butanol, and water$^8$ was attempted giving a low yield and a product that was difficult to isolate. Therefore the potassium permanganate oxidation became the preferred oxidation method. The prepared protected ribonolactone 9 will be the substrate for the alkynylation reactions with organometallic reagents (Scheme 3).
Chapter 2: Preparation of Ethynyl Ribofuranosides

2.1 Proposed synthesis of ethynyl ribofuranosides

The protected ribonolactone 9 will be used as the electrophilic substrate for two different alkynylation reactions. In the first approach (Scheme 3 part A), the lactone 9 will be treated with ethynyl magnesium bromide. In the second approach, the lactone 9 will be treated with lithium trimethylsilyl acetylide prepared in situ from n-butyl lithium and trimethylsilyl acetylene. The resulting lactols 10 and 12 will be treated with the Lewis Acid boron trifluoride diethyl etherate (BF₃∙Et₂O) and triethylsilane to undergo hemiacetal deoxygenation in an attempt to yield the corresponding ethynyl glycosides 11 and 13 respectively.

Scheme 3. Proposed Alkynylation and Hemiacetal Reduction

Buchanan et al. and Wightman et al. employed these organometallic reactions in the preparation of ethynyl C-glycoside derivatives using the substrates 5-hydroxy isopropylidene ribonolactone 14 and 2,3,5-tri-O-benzyl-D-arabino-1,4-lactone 20 (Scheme 4A-B).
Scheme 4. Synthesis of protected alkynyl C-ribosyl glycoside derivatives\textsuperscript{5,6}

In Buchanan’s approach\textsuperscript{5} (scheme 4-A), isopropylidene ribonolactone 14 was treated with ethynylmagnesium bromide for 20 hours isolating the diyne triol 16 in 7\% yield, the cyclic alkynyl lactol 15, as well as unreacted ribonolactone 14 at 25\% yield. Reduction of the mixture with sodium borohydride yielded the alkynyl triol diastereomeric mixture 17. The primary hydroxyl groups of the purified triol was protected as a tri-phenyl methyl ether (trityl) yielding the corresponding alkynyl diol 18. Cyclization of the mixture of diols 18 occurred with p-toluenesulfonyl chloride (TsCl) and pyridine forming the $\alpha$ and $\beta$-D-ethyllyriboside 19. Even though this four step synthesis yielded the ethynylribosides, the reported overall yields were low.

In Wightman’s work\textsuperscript{6} (scheme 4-B), 2,3,5-tri-O-benzyl-D-arabino-1,4-lactone 20 was treated with lithium trimethylsilyl acetylide at low temperature yielding the hemiacetal product 21. The hemiacetal 21 was reduced with boron trifluoride diethyl etherate and triethylsilane giving both $\alpha$ and $\beta$ anomers of 22. The reported yield for the $\alpha$-anomer was 56\% and 15\% for the $\beta$-anomer.
The major product was a result of the hydride delivery occurring cis to the vicinal hydroxyl group.\(^6\)

The latter scheme is an attractive alternative method because it requires fewer reaction steps yielding the ethynyl arabinofuranoside 22 in modest yields. The boron trifluoride reaction conditions will be applied for the deoxygenation of both hemiacetals 10 and 12 (Scheme 3).

### 2.2 Reaction of ribonolactone with ethynylmagnesium bromide

In scheme 5 part A, the protected lactone 9 was treated with 2.0 equivalents of ethynyl magnesium bromide\(^2,5\) for 20 hours at room temperature yielding the ribofuranoside 5-\(O\)-tert-butyldimethylsilyl-2,3-\(O\)-isopropylidene-D-ribofuranosyl-1-ethyne 10 as the minor product and the major product being the diyne diol 23. In an attempt to suppress a second alkynylation, the reaction conditions were modified. The lactone 9 was treated with 1.5 equivalents of ethynylmagnesium bromide at -15 °C for 5 ½ hours. Spectroscopic and chromatographic analysis based on TLC, IR, and NMR showed that the reaction yielded the same compound.

Separation of the reaction mixture with column chromatography yielded the diyne diol 23 as the main product. Proton NMR analysis of the main product revealed two overlapping singlets at 2.623ppm, and 2.617ppm indicating the two diastereotopic alkynyl protons. In addition, carbon NMR analysis did not indicate the anomeric carbon signal around ≈101ppm that would be expected for compound 10.

The formation of the diyne diol 23 (Scheme 5) is the result of two successive alkynylation steps of the protected lactone 9. The magnesium bromide alkoxide 9a is formed when the electrophilic substrate 9 is added slowly to a nucleophilic solution of ethynylmagnesium bromide. The alkoxide 9a undergoes a ring opening to form the ketal intermediate 9b. With
excess ethynylmagnesium bromide present, a second alkynylation takes place producing diyn
dialkoxide 9c. Addition of ammonium chloride solution, converts the magnesium alkoxide 9a to
the hemiacetal 10 and the magnesium dialkoxide 9c to the diynyl diol 23.

**Scheme 5. Ethynylation of ribonolactone 9 and hemiketal 9b**

In order to increase the yield of the ethynyl hemiacetal 10, the alkynylation procedure was
modified a second time. In the previous conditions, the protected lactone 9 was added dropwise
to a stirring solution of ethynylmagnesium bromide (1.5 eq. at room temperature) which
produced the diyne diol 23 as the major product. In the modified procedure, 1.5 eq.
ethynylmagnesium bromide was added dropwise over a period of 1 hour to a stirred solution of
the protected ribonolactone 9 at -10°C. This inverse addition approach ensures that the lactone
is constantly in excess suppressing the second ethynyl attack. TLC analysis revealed two main
products Rf 0.24, 0.40, (8:2, hexane/ethyl acetate). ^1H NMR analysis of the fraction with the
higher \( R_f \) indicated a C-H absorption at (s, 1H) at 2.70 ppm which is indicative of an ethynyl proton. \(^{13}\)C NMR analysis indicated an absorption at 102 ppm which is indicative of a quaternary anomeric carbon supporting the proposed hemiacetal structure 10. The diyne diol side product 23 is an interesting compound that will be used as a substrate for an intramolecular cyclization reaction (Scheme 7).

### 2.3 Intramolecular cyclization of the diyne diol

In prior work, Wightman et al.\(^{10}\) reported the synthesis of C-glycosides and their derivatives starting with the protected ribonolactone 24 (Scheme 6). In the final synthetic steps, the compound 26 was treated with boiling pyridine and para-toluenesulfonyl chloride (tosylchloride, TsCl) yielding the \( \beta \)-cyclic diethyl acetal 27 in 50% yield.

![Scheme 6. Synthesis of C-nucleoside\(^{10}\)](image)

Cyclization of the diyne diol 23 (Scheme 7) was attempted using the same reaction conditions. The diol 23 was treated with pyridine and tosylchloride\(^{10}\) for 25 hours. The reaction yield of the crude product was 48%. Thin layer chromatography (TLC) analysis of the reaction mixture indicated the presence of three compounds with \( R_f \) values 0.67, 0.56, 0.31 (hexane/ethyl acetate 80:20). Analysis of the IR spectrum of the crude product revealed a sharp alkynyl C-H
peak at 3298 cm$^{-1}$ and a weak $\equiv C$ peak at 2115 cm$^{-1}$. Analysis of the $^1$H NMR spectra of an isolated fraction (R$_f$ 0.67) revealed two singlet at 2.48 and 2.46 ppm indicating the diastereotopic alkyne protons as well as some other impurities. Analysis of the $^1$H NMR spectrum of the last fraction R$_f$(0.31) indicated it was un-reacted diynyl diol 23. Further investigations for optimizing reaction conditions were not explored.

![Scheme 7](image.png)

**Scheme 7.** Reported diol cyclization

2.4 Reaction of ribonolactone with lithium acetylide

In the second alkynylation approach (Scheme 3 part B), the protected lactone 9 was treated with the lithium trimethylsilyl acetylide at low temperature (-78 °C) giving the hemiacetal 12. Increasing the reaction time from 30 minutes to 1 hour resulted in the partial desilylation of the trimethylsilyl (TMS) moiety confirmed by proton NMR analysis where a terminal alkyne signal at 2.70 ppm was identified.

2.5 Boron trifluoride hemiacetal deoxygenation

Both ethynyl lactols 10 and 12 were treated with boron trifluoride diethyl etherate and triethylsilane (Scheme 3 parts A and B) at low temperature yielding a complex mixture of products that were difficult to purify by column chromatography. Analysis of the $^1$H NMR spectra of some isolated fractions revealed a complex mixture of side products. The absorptions
corresponding to the isopropylidene germinal methyl protons, the tert-butyl dimethyl silyl protons, and the trimethylsilyl protons were identified as well as other impurities. Due to an overall low yield and complex mixture of products, alternative anomeric deoxygenation conditions were investigated in order to prevent side product formation and to improve the overall yield.

The decomposition of the lactol 12 may be the result of the harsh acidic conditions when using boron trifluoride. It is suggested that the reaction conditions may promote partial desilylation of the tertiary butyl dimethyl silyl group (TBDMS) in the lactols 10 and 12 as well as the removal of the trimethylsilyl group of lactol 12. Also partial cleavage of the isopropylidene group may also be taking place thus giving a mixture of many side products. Alternative reduction conditions were investigated using an acetate derivative of the lactol 12 in order to prevent side product formation by using trimethylsilyl triflate (TMSOTf) and triethylsilane combination.

2.6 Alternative deacetylation

In prior work with C-nucleoside analogs of ribosyl nicotinamide (Scheme 8), Migaud et al.\textsuperscript{11} treated 5-O-(tert-butyldiphenylsilyl)-2,3-O-isopropylidene-D-ribonolactone 24 with lithiated derivatives of thiophenes trapping the alkoxide intermediate with the addition of acetic anhydride forming the acetylated hemiketal intermediate 1-O-acetyl-5-O-tert-butyldimethylsilyl-2,3-O,O-isopropylidene-1-(2-thiophene-3-carbonitrile)-ribofuranoside-29. The acetoxy derivative 29 was reduced with trifluoromethanesulfonic acid trimethylsilylester (TMSOTf) and triethylsilane (Et\textsubscript{3}SiH) in methylene chloride followed by the addition of tetra-n-butyl ammonium fluoride (TBAF). Under these conditions, the TBDPS group is removed yielding a mixture of the reduced
anomers 30 (α and β). It was reported that the major isomer of the acetate derivative 29, had the acetate group at the α position and the thiophene group at the β position.

Scheme 8. Synthesis of ribosyl nicotamide

The stereochemical assignments were based on a proton shift $\Delta \delta$ greater than 0.2 for the isopropylidene methyl groups in $^1$H NMR analysis. Nuclear Overhauser Effect (NOE) and crystallographic analysis were not conclusive in determining further the stereochemistry of 29.\textsuperscript{11}

It was also reported that reduction with boron trifluoride diethyl etherate and triethylsilane yielded a complex mixture of products. They have suggested that competitive desilylation and isopropylidene cleavage may be taking place justifying the preference to use the TMSOTf, triethylsilane reagents instead of the Lewis acid boron trifluoride triethylsilane combo.

This approach (Scheme 8) was adopted for the reduction of the alkynyl glycoside acetate derivative 32 (Scheme 9). The glycoside 32 was prepared by in situ acetylation of the lithium alkoxide 31 with acetic anhydride. The product was purified by column chromatography to remove the remaining acetic anhydride and acetic acid.

Scheme 9. Reduction and desilylation of the acetylated derivative 32
The successful acetylation was confirmed by IR, $^1$H NMR, and $^{13}$C NMR. $^1$H NMR analysis of the product revealed the acetate methyl protons peak at 2.05 ppm. The anomeric mixture of 32 was used for the reduction reaction without the determination of stereo chemistry.

Compound 32 was treated with trimethylsilyl triflate (TMSOTf) and triethylsilane followed by the addition of tetra-n-butylammonium fluoride (TBAF) to yield 33. Analysis of the IR spectrum indicated the C-H ethynyl signal at 3304 cm$^{-1}$. The reaction yielded a complex mixture of products that could not be isolated. The same reduction conditions were applied excluding the use of (TBAF) compound 13 was obtained but could not be isolated in purity. Both deacetylation reaction conditions in addition to the main product yielded a mixture of side products that make separation and isolation difficult and costly.
Chapter 3: Alternative Ribonolactone Substrate

3.1 Selecting alternative protecting group.

The mixture of side products from the reduction sequence rendered the protected ribonolactone 9 substrate unsuitable for the preparation of α/β-alkynyl ribofuranosides 11 and 13 (Schemes 3 and 9). The protected ribonolactone derivative 35 was then investigated as an alternate substrate in an attempt to improve the yield of the main product by minimizing the cleavage of the silyl ether protecting group at the C-5 position. The benzyl ether protecting group was selected because it is not cleaved by the Lewis acid boron trifluoride/ triethylsilane reagent combination during the deoxygenation step. The protected ribonolactone 35 will be the substrate for alkynylation followed by hemiacetal deoxygenation using boron trifluoride and triethylsilane (scheme 10).

Scheme 10. Preparation of protected lactone 35 and alkynyl ribofuranoside 38

3.2 Preparation of trimethylsilyl alkynyl 5-0-benzyl isopropylidene ribofuranoside

The starting material D-ribonolactone 34 was converted to isopropylidene ribonolactone 14 with acetone and a catalytic amount of sulfuric acid. The isopropylidene lactone 14 was treated
with sodium hydride and benzyl bromide or benzyl chloride\textsuperscript{12,13} yielding 5-\textit{O}-benzyl-2,3-\textit{O}-isopropylidene ribonolactone \textbf{35} in 78\% yield.

The protected lactone \textbf{35} was treated with lithium trimethylsilylacetylene to yield the hemiacetal \textbf{36} (51\% yield) and the desilylated product \textbf{37} (30\% yield). The hemiacetal \textbf{36} was treated with boron trifluoride (BF\textsubscript{3}) and triethylsilane (Et\textsubscript{3}SiH) giving the reduced product \textbf{38} in a quantitative yield. The main product formed was colorless crystals (Scheme 10). The structure was confirmed by NMR analysis. The \textsuperscript{1}H NMR absorptions of the trimethylsilyl group and the C-1 proton was evident at 0.19ppm and 4.89ppm respectively.

\textbf{3.3 Lewis acid promoted silane reduction mechanism}

The boron trifluoride triethylsilane reduction of the hemiacetals \textbf{10} and \textbf{12} was not practical because of the complex mixture of side products. However the Lewis acid promoted silane reduction of hemiacetals is still an attractive synthetic reaction for the stereo selective reduction of the anomeric center found in glycosides. During the Lewis acid promoted silane reduction, the hydride delivery occurs cis to the vicinal oxygen yielding the β-substituted product as reported by Wightman et al.\textsuperscript{14} in the synthesis of C-glycofuranosides. The reduction of the anomeric hemiacetal under these conditions is stereo selective. In Wightman’s later work (Scheme 4-B)\textsuperscript{6} in the synthesis of α substituted ethynyl arabino furanosides, the substrate \textbf{22} was reported as the major product in which the hydride is delivered cis to the vicinal oxygen group.

Larsen et al.’s studies on stereoselective C-glycolsylation reactions of ribose derivatives\textsuperscript{15} suggested that the stereo selectivity of the reaction proceeds via a 1,3 cis interaction between the C-3 alkoxy group and the nucleophile during the oxocarbenium transition state \textbf{39a} where the nucleophile approaches from the alpha face. It was also reported that the alkoxy group at the C-
2 position had little influence in the stereochemical outcome of the reaction (Scheme 11). In addition, the same study reported that substitution at the C-5 position has a negligible effect on the stereochemical outcome of the reaction. The conclusive evidence provided by Larsen was not applicable for substances with cyclic ketal protecting groups such as substrate 43.

**Scheme 11. Mechanism for C-glycosylation of ribose derivatives**

According to a study done by Matsuda et al. on the highly β-selective C-allylation of ribofuranosides such as 2,3-\(O\)-(3-pentylidene)-D-ribofuranosyl fluoride (Scheme 12), alkylation will occur on the less hindered β face giving the β product due to the increased steric hindrance on the alpha face by the exo pentylidene moiety in the oxocarbenium transition state 43a.
In this case the alkoxy moieties at C2 and C3 will not provide the same interaction towards the nucleophile as in scheme 1.\textsuperscript{16} Therefore for the preparation of alkynyl ribosides, the hydride nucleophile will be delivered on the less hindered \( \beta \)-face yielding the \( \alpha \)-alkynyl isomer. Since boron trifluoride was shown to be a harsh reagent for the isopropylidene and trimethylsilyl moieties, alternative reaction conditions were explored in order to optimize the yield of the ethynyltrimethylsilyl ribofuranosyl derivative. The lactols 10, 12, 36 were treated under various reaction conditions (Table 1). Decreasing the amount of boron trifluoride and using a 1:1 equivalent ratio of triethylsilane/Lewis acid combination have slightly improved the yield of the target compound 38. Reducing the amount of the reagents further resulted in the recovery of the starting material for a reaction time of 1 hour (Table 1).

**Table 1.** Hemiacetal reduction conditions

<table>
<thead>
<tr>
<th>Substrate</th>
<th>eq. BF(_3)</th>
<th>eq. Et(_3)SiH</th>
<th>Temp, Time</th>
<th>Product, %Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>36,12,10</td>
<td>14</td>
<td>7</td>
<td>-78 °C, 1h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>36</td>
<td>7</td>
<td>3.5</td>
<td>-78 °C, 1h</td>
<td>38, 21.6%</td>
</tr>
<tr>
<td>36</td>
<td>5.0</td>
<td>5.0</td>
<td>-78 °C, 1h</td>
<td>38, 30%</td>
</tr>
<tr>
<td>36,12</td>
<td>2.5</td>
<td>2.5</td>
<td>-78 °C, 1h</td>
<td>Starting materials recovered, products not isolated</td>
</tr>
</tbody>
</table>
Scheme 13. Proposed mechanism of the Lewis acid hemiacetal deoxygenation

The proposed reduction mechanism is shown in Scheme 13. Boron trifluoride complexes with the hydroxyl group of the hemiacetal 36 forming the stabilized oxocarbenium ion 36b. The oxocarbenium ion 36b undergoes nucleophilic attack by triethylsilane to form compound 38. Proton NMR analysis of the clear crystalline sample revealed a signal at 4.89 ppm. This chemical shift is similar to the 4.85 δ shift of the α-anomer 13α which will be discussed later in chapter 4. The reaction mechanism is in agreement with the mechanism proposed by Matsuda (Scheme 11) were the hydride delivery occurred anti to the vicinal oxygen giving the alpha isomer.

The stereochemistry of the alkynyl ribofuranoside 38 was determined by NOESY analysis where major coupling interactions between H₁, H₂, and H₅ab were observed. Coupling interaction between H₁ and H₄ were not observed which would usually be observed in some similar substrates with the beta configuration such as, the heterocyclic C-nucleoside Ex-1 reported by Guianvarc’h et al.¹⁷ giving conclusive evidence that the alpha product is the major isomer.
Figure 3. Major NOESY coupling interactions of proton H₁.
Chapter 4: Intramolecular Cyclization

4.1 Hemiacetal alkynylation

Since the yields of alkynyl ribofuranosides 11, 13, and 38 from the reduction of the precursor hemiacetals 10, 12 and 36 were low or negligible under the Lewis acid/triethylsilane promoted deoxygenating conditions, alternative synthetic methods were explored in order to improve yields. The alternative synthetic approaches will incorporate three different intramolecular cyclization of alkynyl diols.

The hemiacetal 5-O-(tert-butyldimethylsilyl)-2,3-O-isopropylidene-D-ribofuranose 8 is selected as a suitable substrate because it reacts as an aldehyde in the presence of a nucleophile (scheme 14).

**Scheme 14. Lactol hydroxy aldehyde equilibrium**

![Scheme 14](image)

The hemiacetal 8 was treated with lithiotrimethyl silyl acetylene forming the trimethylsilyl alkynyl diol 45R,S (Scheme 14, R,S designation is for the C-5position).¹⁸

**Scheme 15 Nucleophilic addition of hemiacetal 8**

![Scheme 15](image)
In order to increase product yield, different reaction conditions were explored. The results in Table 2 indicate that reducing the amount of the lithioacetylene nucleophile improved the overall yields (entry 3). However changes in the reaction time did not significantly change the product yield.

Table 2. reaction conditions for ring opening diol formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>eq. TMS acetylene</th>
<th>eq. n-BuLi</th>
<th>Reaction time (h)</th>
<th>Temperature</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.0</td>
<td>2.5</td>
<td>5</td>
<td>R.T.</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>2.0</td>
<td>5</td>
<td>R.T.</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>2.0</td>
<td>3</td>
<td>R.T.</td>
<td>59</td>
</tr>
<tr>
<td>4</td>
<td>2.5</td>
<td>2.0</td>
<td>2</td>
<td>R.T.</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>2.5</td>
<td>2.0</td>
<td>1</td>
<td>R.T.</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>2.5</td>
<td>2.0</td>
<td>3</td>
<td>0-10°C</td>
<td>47</td>
</tr>
</tbody>
</table>

The diols 45R and 45S (Scheme 15) were not separated. Proton NMR analysis of the purified product showed the TMS signal at 0.169ppm indicating a successful alkynylation. However the proton NMR spectra did not show the usual absorption signals that correspond to a mixture of diastereomers indicating that one of the isomers may be the major or the dominant product.

4.2 Hemiacetal nucleophilic addition mechanism

There are many published studies on the preparation of propargylic alcohols via the alkynylation of chiral aldehydes including the alkynylation of isopropylidene ribofuranosyl hemiacetal derivatives using lithioacetylene nucleophiles, ethynylmagnesium bromide derivatives, and other organometallic alkynyl reagents. It has been reported that product
formation depends on the nucleophile as well as the carbonyl substrate. In many cases it was often difficult to predict the stereochemistry of the major product.¹⁹

![Figure 4. Cram Chelate model for bidentate 1,2 and 1,3 chelation](image)

The stereo chemical outcome of the product can be predicted based on the size of the nucleophile, chelation properties of metal cation, and the steric hindrance from the moieties vicinal to the prochiral center of the electrophilic substrate. In some nucleophilic addition reactions, a 1,2 bi-dentate chelate is formed between the carbonyl oxygen and a vicinal functional group containing lone pair of electrons forming the 1,2-syn addition product as the major product. The 1,3-chelation yields the 1,3-anti addition product (figure 4). Organometallic nucleophiles as well as group II organometallic nucleophiles such as ethynyl magnesium bromide can form bi-dentate chelates. Organometallic nucleophiles such as lithioacetylene derivatives do not form bi-dentate chelates thus making it difficult to predict the stereo chemistry of the main product.¹⁹
Looking at the masked aldehyde structure 8a (Scheme 16), the bulky lithiotrimethyl silyl acetylene nucleophile approaches the prochiral center from the less hindered side following Felkin-Ahn’s model\textsuperscript{19} where the nucleophile approaches toward the small (S) and medium (M) moieties of 8a as opposed to an approach between the large (L) and small (S) or medium and large moieties forming the 1, 2-\textit{anti} addition product 45S. In an alternative conformation, the carbonyl oxygen is facing downward in the direction of the isopropylidene moiety 8a’. The nucleophile would have the same approach forming the diastereomer 45R. From the Newman projection of conformer 8b’ there may be an unfavorable interaction between the loan pairs of the carbonyl oxygen and the isopropylidene oxygen at the C-2 position thus making this the least favorable aldehyde conformation.
Table 3. Alkynylation of isopropylidene hemiacetals\textsuperscript{19}

<table>
<thead>
<tr>
<th>Hemiacetal</th>
<th>Alkynyl Nucleophile</th>
<th>Yield (%)</th>
<th>1,2 syn</th>
<th>1,2 anti</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Li\texttrademark{nBu}</td>
<td>67</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>BrMg\texttrademark{nBu}</td>
<td>74</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Li\texttrademark{H}</td>
<td>72</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Li\texttrademark{H}</td>
<td>100</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Li\texttrademark{nBu}</td>
<td>66</td>
<td>25</td>
<td>75</td>
</tr>
</tbody>
</table>

Prior studies on the alkynylation of isopropylidene ribofuranosyl derivatives have reported the 1, 2-\textit{anti} addition product as the major product and in some cases the only product\textsuperscript{19} supporting the claim for the formation of 45S as the major or only isomer. The results from the studies in table 3 supports the mechanism proposed in scheme 16.
4.3 Intramolecular cyclization of alkynyl diol

The alkynyl diol 45 was used as the substrate in three different cyclization approaches. The first approach follows the strategy outlined earlier (Scheme 6). The other two approaches are intramolecular cyclizations under different reaction conditions.

Scheme 17. Cyclization of alkynyl diol 45R,S

The alkynyl diol 45 was treated with tosylchloride in pyridine for 24 hours at 85-90 °C.10 The intramolecular cyclization yielded a mixture of products with a 72% yield for the crude product. The yield of the major product 13 was 31% yield after isolation and purification. Infrared spectrum analysis of the pure sample indicated a small sharp absorption peak at 2169 cm⁻¹ which is indicative of the alkynyl carbon-carbon triple bond. The absence of the absorption at 3500 cm⁻¹ corresponding to OH group confirmed the cyclization of the original diol. Proton NMR analysis of the colorless crystalline product indicated an absorption at 0.19ppm (singlet, 9H) indicating the presence of the trimethylsilylacetylene protons and a doublet at 4.85ppm indicating the presence of the proton at the C-1 position.

In order to improve yields and minimize the formation of side products, optimization studies were conducted and reported in table 4. Reducing the reaction temperature to room temperature, increasing the reaction time, and increasing equivalency of tosylchloride had a profound effect on the yield (Table 4).
Table 4. Tosylchloride pyridine cyclization reaction conditions

<table>
<thead>
<tr>
<th>eq. Tosylchloride</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>% Yield product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.6</td>
<td>24</td>
<td>85-90</td>
</tr>
<tr>
<td>2</td>
<td>3.6</td>
<td>24</td>
<td>RT</td>
</tr>
<tr>
<td>3</td>
<td>3.6</td>
<td>34.5</td>
<td>RT</td>
</tr>
<tr>
<td>4</td>
<td>4.0</td>
<td>48</td>
<td>RT</td>
</tr>
<tr>
<td>5</td>
<td>4.0</td>
<td>48</td>
<td>45-50</td>
</tr>
<tr>
<td>6</td>
<td>7.0</td>
<td>48</td>
<td>RT</td>
</tr>
</tbody>
</table>

*13β was not isolated

Comparisons of reported experimental data for the stereo chemical assignments of α/β ribofuranoside derivatives at the C-1 proton signal showed the absorption for the α-anomer to be at a lower field being slightly de-shielded than the β-anomer C-1 proton.\textsuperscript{20,21} Since different isomer were not isolated in quantitative yields for comparison studies, NOESY analysis was used as the experimental method for the stereo chemical determination of the ribofuranoside 13.

NOESY spectrum analysis of the isolated product indicated a strong nOe interaction between the geminal diastereotopic protons H\textsubscript{5ab} and the C-1 proton H\textsubscript{1} giving an indication that these protons are in the same spatial plane. There was also an increased interaction between the vicinal H\textsubscript{1} and H\textsubscript{2} protons, and H\textsubscript{1} with H\textsubscript{3}. Interactions between H\textsubscript{1} and H\textsubscript{4} were not observed (Figure 5) providing conclusive evidence that H\textsubscript{1} and H\textsubscript{4} are in different spatial planes thus giving 13α as the major isomer.
4.4 Proposed intramolecular cyclization mechanism

The thermodynamically stable α-anomer is probably formed via an S_N2 mechanism of the 1,2 anti isomer 45S which is suggested to be the major isomer from the alkynylation of the hemiacetals (Schemes 15, 26-1). The suggested mechanism for the formation of 13α is shown in scheme 18.

**Scheme 18.** Suggested mechanism for the tosylchloride pyridine cyclization
The less hindered propargylic hydroxyl group will react with tosylchloride forming the sulfonate ester 45a. Intra molecular nucleophilic attack by the C-2 hydroxyl group gives the cyclic intermediate 45b. De-protonation by the solvent pyridine produces the main anomer 13α, pyridinium chloride, and pyridinium toluene sulfonate salts. The proposed mechanism supports the formation of the alpha product as the favorable isomer under the given reaction conditions. The α-alkynyl ribofuranoside 13α produced in modest yields (61%) will be used as a model substrate for desilylation followed by oxidation at the C-5 hydroxyl group which will be discussed in chapter 6.

4.5 Intramolecular Nicholas reaction

In an attempt to improve overall yields and obtain the β-ribofuranoside anomer, the cyclization using the Nicholas reaction was explored. The mechanism for the Nicholas reaction appeared to be promising when applied to the mixture of diols 45R, 45S. In Nicholas’ prior work on the complexation of propargyl alcohols 46 with transition metal derivatives, dicobalt octacarbonyl Co₂(CO)₈ (Scheme 19) was used to protect the ethynyl moiety. In the presence of acids (including Lewis acids) this complex promotes the formation of a vicinal carbocation 47a. Reaction of 47a with nucleophiles creates a new bond yielding 47b. The organometallic complex is very effective in stabilizing a primary and secondary carbocation which would otherwise be unstable under different conditions.

Scheme 19. Acid promoted dehydration and nucleophilic addition of propargyl alcohols

\[
\begin{align*}
46 & \xrightarrow{1.\text{Co}_2\text{(CO)}_8} 47a & 47a & \xrightarrow{3.\text{Nu}} 47b \\
R^3 & \equiv \equiv \equiv \equiv R^1 & 2.\text{H}^+ \text{or Lewis acid} & 3.\text{Nu}
\end{align*}
\]

R^1 = R^3 = H, R^2 = Me or R^1 = H, R^2 = R^3 = Me
Takase et al.\textsuperscript{18} stereoselectively prepared an alkynyl C-2-deoxy-\(\beta\)-D-ribofuranosides 50 via an intramolecular Nicholas reaction using dicobalt octacarbonyl and a catalytic amount of triflic acid (Scheme 20).\textsuperscript{17} The Takase cyclization procedure was the most promising because of the mild one pot synthesis that gave the desired product 50\(\beta\) in high yields.

**Scheme 20. Synthesis \(\beta\)-D-ribofuranosides\textsuperscript{18}**

In scheme 20 the dicobalt octacarbonyl forms a complex with the alkynyl moiety promoting the formation of a stabilized carbocation intermediate. Cyclization occurs via an intramolecular nucleophilic attack by the C-4 hydroxyl group on the carbocation intermediate forming the anomer 50\(\beta\).

**Scheme 21. Synthesis of 13\(\alpha/\beta\) via intramolecular Nicholas reaction.\textsuperscript{18}**
In a similar fashion as in Scheme 20, the protected alkynyl diol 45 was treated under the same reaction in an attempt to promote an intramolecular cyclization (scheme 21). The diol mixture 45R,S was treated with dicobalt octacarbonyl and a catalytic amount (0.1 eq) of triflic acid (Scheme 21). When dicobalt octacarbonyl is added to the mixture of alkynyl diols 45R, and 45S, the organometallic complex 45a is formed (Scheme 22). A catalytic amount of triflic acid is added to promote the formation of the stabilized carbocation 45d. Intramolecular nucleophilic attack by the secondary hydroxyl group 45d yields the complex 45e. Decomplexation of the cobalt complex occurs via oxidation with iodine yielding the target compound 13α/β albeit in very low yields. The starting material was not recovered either. In order to promote the formation of the cationic species 45d, the amount of triflic acid was increased (0.4 eq). The modified conditions produced a low overall yield of the crude product as well as the formation of other unidentifiable side products. The highly acidic conditions may have caused the decomposition of the isopropylidene moiety leading to a complex mixture of unidentified products. Removal of excess iodine was also difficult.

**Scheme 22.** Proposed mechanism for intramolecular Nicholas reaction
4.6 Mitsunobu intramolecular cyclization

Since the acidic conditions from the prior method prevented a successful synthesis, another cyclization method was investigated that did not require acidic conditions.

In the synthesis of heterocyclic C-nucleosides Guianvarc’h et al. used Mitsunobu cyclization conditions with the diol 53 obtaining the protected C-nucleoside derivative 54.\(^{\text{17,23}}\) The beta anomer was reported to be the major product for the different derivatives. The overall yield of the major products ranged from 75%-90% for most of the reported substrates (Scheme 23).

\[
\text{Scheme 23. Synthesis of } \beta\text{-heterocyclic C-nucleosides}^{\text{17,23}}
\]

Therefore diol 45\(R,S\) was treated with triphenylphosphine ((Ph)\(_3\)P) and diethylazodicarboxylate (DEAD) in boiling tetrahydrofuran (THF) for 1 hour to give 13\(\alpha\). The 13\(\beta\) anomer was not isolated (Scheme 24). The yield of the reaction improved to 45% (crude) when DEAD was diluted in THF and added dropwise over a period of 20 minutes.
Scheme 24. Proposed synthesis of 13α/β via intramolecular Mitsunobu cyclization

Below is the proposed mechanism (Scheme 24) for the Mitsunobu reaction. When DEAD 55 is added to a boiling solution of triphenylphosphine 56 and the diol 45 in THF, it forms the reactive zwitterion adduct 57 triphenylphosphine. Adduct 57 then reacts with the alkynyl diol 45 \( R,S \). The alkoxide group at the C-2 position of the oxophosphonium salt intermediate \( 60a \) becomes the nucleophile and removes the oxophosphonium moiety via an intramolecular S_N2 mechanism forming product 13, phosphine oxide 62, and compound 55 is reduced to the hydrazine derivative 61.\(^{17}\)

Scheme 25. Proposed Mitsunobu cyclization mechanism on diol 45 \( R,S \)\(^{17}\)
In scheme 24 the reaction yielded unidentifiable side products and a low overall yield. The main isolated product was the alpha isomer 13a in 17% yield despite having non-acidic conditions found in scheme 24. A red colored side product co-eluted with the desired compound during the chromatographic process (9:1 hexane/ethyl acetate). The co-elution did not occur when the solvent composition was changed to hexane/ethyl acetate (16:1). Other reaction condition and dilution ratios of DEAD were explored in order to improve the overall yield of the reaction products but the overall yield of the desired product did not improve significantly.

4.7 Preparation of different diol substrates

**Scheme 26.** Attempted alkynylation and cyclization reactions

In scheme 26-1 the lactol 8 was treated with ethynyl magnesium bromide forming the diol 63. The diol 63 was treated with para-toluenesulfonyl chloride (TsCl) in pyridine to yield the α-ethynyl ribofuranoside 11α. Examination of the IR spectrum revealed a sharp absorption peak at 3299 cm\(^{-1}\) indicating the presence of the ethynyl C-H bond. Proton NMR analysis also confirmed the acetylene proton with a signal at 2.62δ and the proton signal at the C-1 position at 4.90 ppm.
Preliminary reactions with lithium trimethylsilyloxymethylacetylide with hemiacetal 64 (Scheme 26-2) were not successful in yielding the anticipated diol 65.

The stereochemistry of the ethynyl ribofuranoside 11 was confirmed by its independent preparation from the alkynyl ribofuranoside 13α. Cleavage of the trimethylsilyl group of 13α yielded the ethynyl ribofuranoside 11α.
Chapter 5: Preparation of 1,2 syn Diol

5.1 Sodium borohydride reduction of the hemiacetal

Since the reported reactions with isopropylidene substrates yielded primarily the α products at the C1 position, a new approach was explored incorporating the formation of the 1,2-syn isomer 45R (Scheme 23). Guianvarc’h et al.17,23 reported the sodium borohydride reduction of the hemiketal group from various hemiacetals (Scheme 23). The 1,2 syn diol was reported as the major isomer.

The reported results are in agreement with the Felkin-Ahn model where the major product formation resulted from the nucleophile approaching from the less hindered position of the ketone. In addition, it was also reported that the S/R ratio depends on the different R group and heterocyclic moieties.17, 23 The proposed mechanism for the formation of 45R as the major product is shown in Scheme 28. A mixture of the R and S diastereomeric products are formed from the nucleophilic attack of the hydride on the pro-R and the pro S faces of the hemiacetal substrate.

Under these reaction conditions the diol 45 and ethynyl diol 63 were isolated as a result of the removal of the trimethylsilyl moiety. The diols 45 and 63 were cyclized with para-toluenesulfonyl chloride in pyridine. Separation of the reaction mixture yielded a small amount of product (10%) whose H¹ NMR spectrum analysis indicated a proton signal at (4.80δ).
Scheme 28. Proposed sodium borohydride reduction of hemiacetal 12

NOESY experiments for determining stereo chemistry were inconclusive because of the small product quantity.
Chapter 6: Oxidation of Ribofuranoside Templates

6.1 Selective deprotection of the silyl moieties of 13α

The protected alkynyl ribofuranoside 13α was used as the substrate template to employ in further synthesis. The silyl protecting groups were removed and the resulting alcohol was oxidized to aldehyde (Scheme 29).

![Scheme 29. Proposed deprotection and oxidation reaction](image)

The trimethylsilyl (TMS) group of the alkynyl ribofuranoside was selectively removed with potassium carbonate treatment in methanol yielding the ethynyl ribofuranoside 11α in 97% yield.6 Proton NMR analysis revealed identical chemical shifts of the ethynyl ribofuranoside 11 product formed via the intramolecular cyclization of the ethynyl diol 60 with tosyl chloride and pyridine thus confirming the formation of the α-anomer (Scheme 26-1). Upon treatment with tetra-n-butylammonium fluoride (TBAF), the tert-butylidemethylsilyl moiety was cleaved yielding the 5-hydroxy ethynyl ribofuranoside 33α in 78% yield.24 Doubling the equivalence of TBAF readily removed both silyl groups of 13α yielding the hydroxyl product 33 at 76% yield.
6.2 Oxidation of the 5-hydroxy-ethynylribofuranoside 33α

Two main oxidation methods were explored. These reactions required fewer reagents under mild atmospheric condition that would prevent over-oxidation of the corresponding aldehyde product. Both oxidations employed the use of TEMPO as a catalyst, which is a stable nitroxide radical and a co-oxidant such as TCCA or BAIB. The primary alcohol 33α was mildly oxidized using a TEMPO/trichloroisocyanuric acid (TCCA) reagent combination in an attempt to obtain corresponding aldehyde 67 (Scheme 30). The reaction yielded a complicated mixture of inseparable side products with column chromatography. Spectroscopic analysis of the mixture of products indicates the loss of the isopropylidene group, possibly a result of the reaction workup under acidic conditions.

Scheme 30. Proposed oxidation of primary hydroxyl group.²⁵,²⁶,²⁷,²⁸,²⁹

A second oxidation reaction was investigated using TEMPO/bisacetoxyiodobenzene (BAIB) (Scheme 30).²⁷,²⁸,²⁹ According to Windlanski et al., the TEMPO/BAIB system is compatible with alkenes, alkynes, acetals, silylethers, and various other protecting groups and functional groups thus making this a versatile oxidation method.²⁹ The reaction yielded side products that were difficult to separate as indicated by NMR analysis. The NMR spectrum also exhibited a
broad peak at 9.8ppm indicating a successful oxidation even though product separation was
difficult. Future plans may include a second alkynylation of the crude product in an attempt to
isolate a purified product as well as modifying chromatographic techniques.
Chapter 7: Conclusion

In summary, 5-O-(tert-butylidimethylsilyl)-2,3-O-isopropylidene-D-ribonolactone 9 was readily prepared in high yields. The nucleophilic addition of the ethynyl Grignard reagent to the protected ribonolactone 9 (Scheme 3-A)\(^3,4\) yielded the diyne diol 23 as the major product and the desired product 10 in low yield. However, the modified procedure\(^9\) in Scheme 3 where ethynyl magnesium bromide was added slowly to the protected lactone 9 yielded the desired product 11 as the major product. Unlike the approach using the lithium trimethylsilyl acetylide alkynylation, the use of ethynylmagnesium bromide can be advantageous because the reaction did not require temperatures below -10° C. Since ethynylmagnesium bromide is commercially available, the preparation of the Grignard reagent was not necessary.

The alkynylation procedure using lithium trimethylsilyl acetylide\(^6\) produced the alkynylated ribofuranosyl lactol 12 as the major product and the desilylated alkynyl lactol 10 as the minor product. The formation of the desilylated product 10 was minimized by reducing the reaction time from 1 hour to 30 minutes.

The two reduction schemes incorporated proved to be challenging with the hemiacetals 10 and 12. The Lewis acid promoted deoxygenation (Scheme 3, 9, and 10) were too harsh for the isopropylidene and TBDMS groups. Analysis of \(^1\)H NMR spectra indicated the isopropylidene and silicon moieties were preserved in the product. There is evidence that the reduction occurred but there were many side products. An alternative to the dehydroxylation scheme was explored (Scheme 9), the acetylated product 32 was produced successfully as indicated by IR, \(^1\)H NMR, and \(^13\)C NMR. Reduction of acetate derivative 32 with TMSOTf, Et\(_3\)SiH was expected to be milder on the isopropylidene group, but the reaction yielded many side products as indicated by thin layer chromatography.
Treatment of the benzyl ether lactol 36 with the Lewis acid BF$_3$ and triethylsilane (Scheme 10) generated a low overall yield of the $\alpha$–anomer.

Three different cyclization reactions were explored (Schemes 17, 21, and 24). Two of the three cyclization reactions gave low overall yields (Schemes 21 & 24). The cyclization incorporating tosyl chloride and pyridine (scheme 17) yielded the alpha ethynyl ribofuransides 11 and 13 in yields of 60%. The attempted oxidation of the alcohol 33 resulted in a mixture of side products that were not separated. Clearly optimization studies of the reaction conditions are needed to determine the appropriate conditions required in order to minimize side products and improve yields.

Future projects may include the use of different substrates in an attempt to synthesize $\beta$ alkynyl ribofuranoside derivatives in modest yields. Stefko et al.$^{31}$ successfully used the protected tertiarybutyl dimethylsilylether ribonolactone derivative 68 as a substrate for the synthesis of $\beta$ Pyridin-2-yl C-ribonucleosides (scheme 31)$^{31}$. Under the reported conditions, the boron trifluoride/triethylsilane reagent combination was successfully used during the deacetylation step using hexanes as the solvent yielding the $\beta$ isomer in 99% yield with a 91% overall yield. Under the reported conditions, the silyl ether protecting groups were not cleaved due the 10 min reaction time as well as the use of hexanes as the solvent which is nonpolar. This synthesis seems promising with the successful preparation of the protected ribonolactone 68 from D-ribonolactone 34.
Below is a proposed synthesis of protected β alkynyl ribofuranoside incorporating similar reaction conditions from scheme 31.

Scheme 32. Proposed future synthesis of alkynyl ribofuranoside 73
Scheme 32-1 is a proposed future plan where the ribonolactone substrate 68 will be alkynylated followed by the in situ acetylation similar to the reaction conditions found in scheme 10. The acetylated derivative will be subjected to triethylsilane/Lewis acid conditions in an attempt to obtain the alkynylated product 73. Scheme 32-2 can also be an alternative synthetic route if the protected ribose derivative 74 is successfully prepared. The ribose derivative 74 will be treated to ring opening conditions employed in scheme 15 followed by cyclization conditions found in scheme 17 in an attempt to quantify the formation of the major isomers. If the diol 75 is successfully prepared, it can be used as a suitable substrate for cyclization reactions incorporating Nicholas cyclization conditions scheme 21 and Mitsunobu cyclization conditions scheme 24, in an attempt to quantify and compare the major isomers and percent yields under the given reaction conditions.
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**Experimental**

Thin layer chromatography was performed on 250μm silica plates and column chromatography was performed on 220-440mesh silica gel. TLC plates were developed in an iodine chamber and phosphomolybdic acid charring solution. Reagents were obtained from commercial sources without further purification. Acetone was dried with anhydrous calcium chloride. Tetrahydrofuran was freshly distilled from sodium. Dichloromethane was freshly distilled from calcium hydride. Low temperature baths were prepared using dry ice and acetone -78°C, calcium chloride six hydrate and ice -20°C, sodium chloride and ice -10 to -15°C. 1H NMR spectra were recorded at 300MHz, and 13C NMR at 75MHz. Some 1H NMR spectra were recorded at 500MHz, and 13C NMR at 125MHz. Deuterated chloroform with TMS internal reference was used as the NMR solvent. The sugar carbons are labeled 1-5 beginning at the anomeric carbon and proceeding via the carbon chain to the carbinol carbon. The protons bonded to these carbons will have the same designated number 1-5. Chemical shifts are reported in parts per million (δ ppm). 1H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), multiplet (m), quartet (q), apparent (app) and broad (br). For those splitting patterns that could not be easily visualized or interpreted, a designation of multiplet (m) was used. Coupling constants are reported in Hertz (Hz) 1H NMR TMS internal reference signal is at 7.26δ ppm (1H), and 13C NMR CDCl3 signals are 76.79, 77.29, and 77.71δ. Certain experimental FID’s were processed offline using SpinWorks 3.1.7, NMR processing software Copyright © 2010, Kirk Marat, University of Manitoba.
Preparation of 2,3-\textit{O}-Isopropylidene-D-ribofuranose\textsuperscript{7} (7)

Concentrated sulfuric acid (0.125mL) was added to a 250mL round bottom flask charged with a stirring solution of 5.0g D-ribose 1 (33.3mmol) in 50mL of dry acetone. After 30 minutes of stirring, the slurry became clear and stirring continued for an additional 1hr. After 1.5 hours, 1.36g of calcium hydroxide was added in small portions until the pH of the solution increased to a range of 6-8. The mixture was filtered on a celite pad and evaporated in vacuo to give light yellow viscous oil. A yield of 6.27g (99\%) was obtained.

IR analysis indicated the two gem methyl isopropylidene peaks at 1452cm\textsuperscript{-1} (split peak), and 1369cm\textsuperscript{-1} (sharp peak) and a broad hydroxyl peak at 3391cm\textsuperscript{-1}.

IR (neat) \textit{\nu}max 1369 cm\textsuperscript{-1}s, 1452 cm\textsuperscript{-1}m, 3391 cm\textsuperscript{-1} br OH. \textsuperscript{1}H NMR (300MHz, CDCl\textsubscript{3}): \textit{\delta} 5.35 (1H, s, H-1), 4.76 (1H, d, \textit{\textit{J}}=5.7 Hz, H-2), 4.52 (1H, d, \textit{\textit{J}}=5.7 Hz, H-3), 4.33 (1H, br.s, H-4), 3.66 (2H, m, H-5\textsubscript{ab}), 2.14 (1H, s, OH), 1.44 (3H, s, O\textsubscript{2}C(CH\textsubscript{3})\textsubscript{2}), 1.27 (3H, s, O\textsubscript{2}C(CH\textsubscript{3})\textsubscript{2}). \textsuperscript{13}C NMR (125MHz, CDCl\textsubscript{3}): \textit{\textit{\delta}} 112.39(RO)\textsubscript{2}C(CH\textsubscript{3})\textsubscript{2}, 102.91 C-1, 87.81 C-4, 86.90 C-2, 82.01 C-3, 63.67 C-5, 26.57 O\textsubscript{2}C(CH\textsubscript{3})\textsubscript{2}, 24.93 O\textsubscript{2}C(CH\textsubscript{3})\textsubscript{2}. 

- 52 -
Preparation of 5-O-(tert-Butyldimethylsilyl)-2,3-O-Isopropylidene-D-ribofuranose\textsuperscript{7} (8)

Tert-butyldimethylsilyl chloride (5.502g, 36.7mmol) was added in one portion inside a 250mL round bottom flask charged with a solution of the crude 2,3-O-isopropylidene-D-ribofuranose \textsuperscript{7} (6.36g,33.4mmol) and imidazole (6.35g,93.3mmol) in 15mL of anhydrous N,N dimethylformamide (DMF). The solution was stirred at room temperature for two hours. After 2 hours the reaction was quenched with the addition of 50mL water. The mixture was extracted with ethyl acetate (50mL X 6). The combined extract was washed with water (50mL X 6). The organic phase was dried with anhydrous magnesium sulfate. The solvent was evaporated to a light yellow oil which crystallized upon refrigeration overnight. A yield of 94\% was obtained for the crude product. The crude sample was separated with column chromatography hexane/ethyl acetate (4:1). 4.58g (52\%) of the pure sample was obtained in the form of white needle like crystals.

IR (neat) \textsuperscript{13}C NMR (125MHz, CDCl\textsubscript{3}): \textsuperscript{1}H NMR (500MHz, CDCl\textsubscript{3}): δ 5.29 (1H, d, \textit{J}=11.5 Hz, OH), 4.78 (1H, d, \textit{J}=11.5 Hz, H-1), 4.70 (1H, d, \textit{J}=5 Hz, H-2), 4.51 (1H, d, \textit{J}=5 Hz, H-3), 4.36 (1H, br.s, H-4), 3.77-3.73 (2H\textsubscript{ab}, m, H-5\textsubscript{ab}), 1.49 (3H,s, O\textsubscript{2}C(CH\textsubscript{3})\textsubscript{2}), 1.33 (3H, s, O\textsubscript{2}C(CH\textsubscript{3})\textsubscript{2}), 0.93 (9H, s, SiC(CH\textsubscript{3})\textsubscript{3}), 0.15 (6H,d, Si(CH\textsubscript{3})\textsubscript{2}, J=2.1 Hz).
Preparation of 5-O-(tert-Butyldimethylsilyl)-2,3-O-Isopropylidene-D-ribonolactone\(^7\) (9)

Crushed potassium permanganate 3.96g (25mmol) of was added slowly over a period of 1 hour into a 100mL round bottom flask charged with a stirring solution of the crude 5-O-(tert-butyldimethylsilyl)-2,3-O-isopropylidene-D-ribofuranose 8 (5.00g 16.4 mmol) in 50mL of acetone. The temperature was maintained between 35-45 °C during the addition of potassium permanganate. After the addition the reaction was stirred at room temperature for two additional hours. After two hours the mixture was filtered on a celite pad and the filtrate was evaporated and extracted with diethyl ether (90mL) and washed with water (20mL X 3). The ether layer was dried over anhydrous magnesium sulfate. After drying the mixture was filtered and evaporated to give white crystals. After purification with column chromatography (petroleum ether/ethyl acetate, 4:2), the yield was 3.43g (69%). Analysis of IR and NMR spectra of the lactone revealed a sharp singlet peak at 1791 cm\(^{-1}\) (C=O bond).

IR (neat) \(\nu\)max 1791 cm\(^{-1}\) S (C=O ). \(^1\)H NMR (500MHz, CDCl\(_3\) ): \(\delta\) 4.73 (2H, br s, H-2,H-3), 4.62(1H, s, H-4), 3.88 (2H\(_{ab}\), app q., \(J_{ab}=38\)Hz, \(J=11.5\)Hz, H-5\(_{ab}\)), 1.49 (3H, s, \(O_2C(CH_3)_2\)), 1.40 (3H, s, \(O_2C(CH_3)_2\)), 0.90δ (9H, s, \(SiC(CH_3)_3\)), 0.87 (6H, d, \(J=9\) Hz, \(Si(CH_3)_2\)). \(^13\)C NMR (125MHz, CDCl\(_3\) ): \(\delta\) 174.4 C-1, 113.2 \(O_2C(CH_3)_2\), 82.48 C-2, 78.68δ C-3, 75.98 C-4, 63.17 C-5, 27.00 \(O_2C(CH_3)_2\), 25.97 \(SiC(CH_3)_3\), 25.78 \(O_2C(CH_3)_2\), 18.4 \(SiC(CH_3)_3\), -5.42 \(Si(CH_3)_2\).
The statement of the reaction conditions yielded the diyne diol 23 as the major product. The hemiketal 10 was not isolated.

5-O-(tert-Butyldimethylsilyl)-2,3-O-isopropylidene-D-ribonolactone 9 (2.0g 6.6mmol) dissolved in 20mL dry THF inside an addition funnel was added dropwise over a period of 30 minutes inside a 100mL three neck round bottom flask charged with a stirring solution of 26.4mL (2.0eq) of ethynylmagnesium bromide (0.5M in THF). The reaction took place under nitrogen atmosphere at -15 °C. One and a half hours after the addition of the protected lactone, the intensity of the carbonyl peak at 1786cm⁻¹ was being monitored every hour with IR spectroscopy. After 5 ½ hours the intensity of the carbonyl peak was weak and the mixture was concentrated and extracted with 80mL ether and washed with 10% ammonium chloride solution (80mL X 3), washed with water (40mL X 3), dried in anhydrous MgSO₄, filtered and evaporated to a yellow liquid. The residue partially crystallized on standing over a few days under vacuum to yield yellow crystalline syrup in 73% yield.

The main product with an Rf of 0.23 (TLC 4:1 hexane/ethyl acetate) was isolated with column chromatography hexane/ethyl acetate (80:20) gave clear pale yellow crystals which was not the expected product 10 but the diyne diol 23 1.47g (63%) yield

IR (neat) omax 3400cm⁻¹ br (OH), 3287 cm⁻¹ s (C-H), 2116 cm⁻¹ w (C≡C). ¹H NMR (300MHz, CDCl₃): δ 4.55 (1H, br H-2), 4.38 (1H, d J=6.3 Hz, H-3), 4.21-4.26 (1H, m, H-4), 3.86 (1H, app
q \( J=9\text{Hz}, J=3\text{Hz}, H-5b \), 3.70 (1H, app q, \( J_{5,6}=9\text{Hz} \), \( J=6\text{Hz}, H-5a \)), 2.62 (1H, s, CCH), 2.61 (1H, s, CCH), 2.61 (1H, s, CCH), 1.37 (3H, s \( \text{O}_2\text{C(CH}_3)_2 \)), 0.903 (9H, s \( \text{SiC(CH}_3)_3 \)), 0.901 (6H, s, \( \text{Si(CH}_3)_2 \)). \(^{13}\text{C} \) NMR (75MHz, CDCl\(_3\)): \( \delta \) 110.2 \( \text{O}_2\text{C(CH}_3)_2 \), 82.33 C-1, 83.3 CCH weak signal, 82.5 CCH, 74.11 C-2, 71.93 C-3, 68.89 C-4, 64.38 C-5, 27.32 \( \text{O}_2\text{C(CH}_3)_2 \), 26.10 \( \text{SiC(CH}_3)_3 \), 25.19 \( \text{O}_2\text{C(CH}_3)_2 \), \( \approx 18.0\delta \) \( \text{C(CH}_3)_3 \), -5.12 \( \text{Si(CH}_3)_2 \).

**Synthesis of 5-O-(tert-butyldimethylsilyl-2,3-O-Isopropylidene-D-ribofuranosyl) ethyne**

![Chemical structure](image)

Ethynylmagnesium bromide (1.3 eq 13mL of 0.5M solution) was slowly added via an addition funnel over a period of 1 hour inside a 100mL 3 neck flask charged with a cooled (-10 °C) stirring solution of 5-O-(tert-Butyldimethylsilyl)-2,3-O-isopropylidene-D-ribonolactone 9 (1.5g 5.0mmol) dissolved in 10mL THF. After the addition of the Grignard reagent, the mixture was left stirring for 2 hours. After the 2 hours the reaction was quenched with the slow addition of saturated ammonium chloride solution (1.5mL) a light yellow precipitate was formed. The liquid layer was decanted into a separatory funnel and the yellow solid precipitate was washed with diethyl ether (20mL X 1 then 10mL X 2). The combined filtrates were washed with saturated sodium chloride solution (20mL X 2). The organic layer was dried over anhydrous sodium sulfate then concentrated giving a pale yellow syrup. The concentrate was diluted with 40mL hexane and filtered through a silica pad. The silica pad was washed with 50mL 20:80 ethyl acetate/Hexane mixture and concentrated and gave a pale yellow colored syrup. The crude product had two main products with an \( R_f \) of 0.23 and 0.41 (TLC 4:1 hexane/ethylacetate).
Purification of the yellow syrup yielded the two products the lactol 10 a pale yellow syrup 0.61g (38%) and the diyne diol 23 a yellow crystalline solid in 0.52g (30%) yield.

The proton NMR (CDCl3/TMS) analysis of the higher eluted fraction (Rf 0.23) revealed an alkynyl proton singlet at 2.70δ, and an anomeric proton signal at 5.47δ the. 13C NMR revealed a quaternary anomeric carbon signal at 101.5δ indicating a closed ring. 1H NMR (500MHz, CDCl3): δ 5.46 (1H, s, OH), 4.78 (1H, d J=6 Hz, H-2), 4.55 (1H, d, J=6 Hz, H-3), 4.37 (1H, br.s, H-4), 3.74, 3.78 (2H, app q, H-5ab), 2.69 (1H, s, CCH), 1.54 (3H, s, O2C(CH3)2), 1.36 (3H,s, O2C(CH3)2), 0.904 (9H,s, SiC(CH3)3), 0.124 (6H, d J= 1.8, Si(CH3)2). 13C NMR (75MHz, CDCl3): δ 113.6 O2C(CH3)2, 101.48 C-1, 88.86δ CCH, CCH unclear,87.00 C-3, 81.90 C-4, 74.23 C-2, 64.61 C-5, 26.88 O2C(CH3)2, 25.97 SiC(CH3)3, 25.68 O2C(CH3)2, 18.45 SiC(CH3)3, -5.48δ Si(CH3)2.

**Synthesis of 5-O-(tert-butyldimethylsilyl-2,3-O-Isopropylidene-D-ribofuranosyl)-1-hydroxy-1-trimethyl-silylethyne**

![Synthesis of 5-O-(tert-butyldimethylsilyl-2,3-O-Isopropylidene-D-ribofuranosyl)-1-hydroxy-1-trimethyl-silylethyne](image)

Under nitrogen atmosphere, n-Butyl lithium (6.00mL of 1.6M in hexanes, 15.07mmol) was added dropwise inside a 250mL round bottom flask charged with a stirring solution of 2.84mL of trimethylsilylacetylene (15.07mmol) diluted in 39.63mL dry THF (2.63mL/mmol) at -78 °C and allowed to stir for 15 minutes. After the 15 minutes, 3.0g (10.05mmol) of the protected ribonolactone 9 dissolved in 39mL dry THF was added drop-wise to the stirring solution. After the complete addition of the lactone, the reaction was stirred for 30 minutes. After 30 minutes,
the reaction was quenched with 30mL saturated ammonium chloride and extracted with diethyl ether (45mL x 3) the organic layer was washed with 5% sodium bicarbonate solution (45mL X 3), water (30mL X 2), saturated sodium chloride solution (20mL X 2), and dried under magnesium sulfate and evaporated under reduced pressure. The product was a light yellow colored oil that crystallized under vacuum. IR spectroscopy of the crude product revealed a small $\equiv\equiv\equiv$ singlet at 2169 cm$^{-1}$, a broad OH peak at 3321 cm$^{-1}$. TLC analysis (7:1) petroleum ether/ethyl acetate revealed two products ($R_f$ 0.26, 0.6) the major product 2.95g (74% yield, $R_f$ 0.6) is a clear syrup which crystalized under vacuum after isolation via column chromatography. $^1$H NMR and $^{13}$C NMR spectral analysis of the isolated fraction ($R_f$ 0.26) revealed absorption signals that are identical for the hemiacetal 10. The proton NMR (CDCl$_3$/TMS) spectra revealed an alkynyl proton singlet at 2.70δ and a signal at 5.43δ indicating anomeric hydroxyl proton. $^{13}$C NMR revealed a quaternary anomeric carbon signal at 101.5δ indicating a closed ring. $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 5.43 (1H, s, OH), 4.77 (1H, d, $J$=6 Hz, H-2), 4.54 (1H, d, $J$=6 Hz, H-3, 4.35(1H, s, H-4), 3.74-3.76 (2H, m, H-5), 2.6 (1H, s, CCH), 1.53 (3H, s, O$_2$C(CH$_3$)$_2$), 1.35 (3H, s, O$_2$C(CH$_3$)$_2$), 0.135 (6H, s, Si(CH$_3$)$_2$), 0.89 (9H, s, SiC(CH$_3$)$_3$). $^{13}$C NMR (75MHz CDCl$_3$): $\delta$ 113.6 O$_2$C(CH$_3$)$_2$, 101.48 C-1, 88.86δ CCH, CCH unclear, 87.00 C-3, 81.90 C-4, 74.23 C-2, 64.61 C-5, 26.88 O$_2$C(CH$_3$)$_2$, 25.97 SiC(CH$_3$)$_3$, 25.68 O$_2$C(CH$_3$)$_2$, 18.45 SiC(CH$_3$)$_3$, -5.48δ Si(CH$_3$)$_2$.

The major fraction has an absorption at 0.20δ indicating the trimethylsilyl protons are present in giving the hemiacetal 12. $^{13}$C NMR revealed a quaternary anomeric carbon signal at 102 δ. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.30 (1H, s, OH), 4.76 (1H, d, $J$=6Hz, H-2), 4.53(1H, d, $J$=5.5 Hz, H-3), 4.39(1H, br, H-4), 3.79 (1H, app q, $J_{5b,4}$= 11.5 $J_{5b,4}$=2.5, H-5b), 3.74 (1H, app q, $J_{5a,b}$=11.0, $J_{5a,4}$=2.0, H-5a), 1.54 (3H, s, O$_2$C(CH$_3$)$_2$), 1.36 (3H, s, O$_2$C(CH$_3$)$_2$), 0.92 (9H, s SiC(CH$_3$)$_3$),
0.20 (9H, s, Si(CH$_3$)$_3$), 0.13 (6H, d, Si(CH$_3$)$_2$). $^{13}$C NMR (125MHz, CDCl$_3$): δ 113.3 O$_2$C(CH$_3$)$_2$, 101.9 C-1, C$_{CCTMS}$100.02, 91.42 C$_{CCTMS}$, 89.05 C-3, 86.44 C-4, 82.32 C-2, 64.72 C-5, 26.86 O$_2$C(CH$_3$)$_2$, 25.93 SiC(CH$_3$)$_3$, 25.85 O$_2$C(CH$_3$)$_2$, 18.40 SiC(CH$_3$)$_3$, -0.13 Si(CH$_3$)$_3$, -5.53 Si(CH$_3$)$_2$.

**Synthesis of 5-O-(tert-butyldimethylsilyl-2,3-O-Isopropylidene-D-ribofuranosyl)-1 trimethylsilylethyne**

Boron trifluoride diethyl etherate 9.62mL (14eq) was added slowly to 250mL round bottom flask charged with a cooled -78 °C stirring solution of 2.2g(5.5mmol) of the hemiacetal 12 in 137.5mL dichloromethane (25mL/mmol) followed by the slow addition of 6.05mL(6.5eq) of triethylsilane the reaction took place under nitrogen atmosphere. After the addition of triethylsilane the reaction was stirred for an additional 1 hour. After 1 hour, the solution was slowly warmed to 4-7 °C by being placed in the refrigerator for 20 minutes. After 20 minutes 100mL sodium bicarbonate was added to neutralize the reaction.

The mixture was extracted with dichloromethane (50mL X 3) and evaporated under vacuum. The dark green colored oil was filtered with column chromatography 80:20 hexane/ethyl acetate. A complex mixture of products were formed which were difficult to separate with column chromatography. Proton NMR spectra of one of the collected fractions revealed the anomeric hydrogen peak H$_1$ (1H, 5.29δ) indicating the presence of the starting material. Pure analytical sample could not be obtained.
Synthesis of 5-O-(tert-butyldimethylsilyl-2,3-O-Isopropylidene-D-ribofuranosyl)-1-trimethyl-silylethyne-1-acetate\textsuperscript{6,11} 33

Under nitrogen atmosphere, n-butyl lithium was added dropwise via syringe (1.5eq 9.9mmol 4.00ml of 1.6M) in a 100mL two neck round bottom flask charged with a solution of trimethylsilylacetylene (1.5eq 1.42mL, 9.9mmol) diluted in 26.00ml dry THF (2.63mL/mmol) at -78 °C and allowed to stir for 15minutes under nitrogen atmosphere. After the 15 minutes, the protected ribonolactone \textbf{9} (2.0g, 6.6mmol) dissolved in 26mL dry THF was added drop-wise via an addition funnel to the stirring solution. After the complete addition of the protected ribonolactone, the mixture was stirred for 30minutes. After the 30minutes, 3.11mL acetic anhydride (5eq) was added and the mixture was allowed to stir for an additional 30minutes. After 30 minutes, 20mL diethyl ether was added and the reaction was quenched with 20mL saturated ammonium chloride and extracted with diethyl ether (20mL X 3) the organic layer was washed with sodium bicarbonate (15mL X 3), water (15mL X 2), then saturated sodium chloride solution (15mL X 2). The organic layer was evaporated under reduced pressure giving a pale yellow colored oil. The reaction was purified (5:1 hexane/ethyl acetate R\textsubscript{f} 0.56) giving the acetate 2.14g (73\%) yield. IR analysis of the crude product revealed a small C≡C singlet at 2175cm\textsuperscript{-1}, and an intense acetate peak (C=O) at 1758.90 cm\textsuperscript{-1}. \textsuperscript{1}H NMR revealed acetate protons 2.05ppm, CNMR revealed a weak carbonyl carbon peak at 168.09ppm and quaternary carbon signal at C\textsubscript{1} 98.77ppm.
IR (neat) umax 1758.90. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 4.81 (1H, d, \(J=3.6\)Hz, H-2), 4.79 (1H, m, H-3), 4.22 (1H, m, H-4), 3.73-3.72 (2H\(_{ab}\), br, H-5\(_{ab}\)), 2.05 (s, 3H, O\(_2\)C(CH\(_3\))\(_2\)), 1.31 (3H, s, O\(_2\)C(CH\(_3\))\(_2\)), 0.85 (9H, s), 0.089 (9H, s, Si(CH\(_3\))\(_3\)), 0.026 (6H, s, Si(CH\(_3\))\(_2\)). \(^1\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 167.8 O\(_2\)CCH\(_3\), 115.2 O\(_2\)C(CH\(_3\))\(_2\), 100.2 CCTMS, 98.52 CCTMS, 91.56 C-1, 87.86 C-2, 84.40 C-3, 81.08 C-4, 62.76 C-5, 26.30 SiC(CH\(_3\))\(_3\), 26.15 O\(_2\)C(CH\(_3\))\(_2\), 21.96 SiC(CH\(_3\))\(_3\), 18.47 O\(_2\)CCH\(_3\), -0.12 Si(CH\(_3\))\(_3\), -5.34 Si(CH\(_3\))\(_2\).

**Ring closing procedure of the diyne diol 23 to form the di-alkynyl furan\(^\text{10}\) 28**

The diyne diol 23 (1.0 g of 2.8mmol) was added inside a 100mL round bottom flask charged with a hot solution 85-90 °C of tosyl chloride (1.95g 3.6eq) in 50mL dry pyridine. The reaction was allowed to stir for 25 hours. After 25 hours the reaction mixture was allowed to cool to room temperature then 0.7mL water was added. The mixture was concentrated and 2% copper-sulfate (50mL) solution was added. The mixture was washed with ether (30mL X 3). The organic phase was washed with 2% copper sulfate solution (40mL X 3), then water (15mLX 3). The organic layer was dried over anhydrous magnesium sulfate and evaporated to give a dark crimson colored syrup 48.5% yield. The sample was purified with column chromatography 80:20 Hexane/ethyl acetate. \(^1\)H NMR analysis revealed a large split singlet peak at 2.40, and 2.38ppm. The isopropylidene and TBDMS protons were also present.
Synthesis of 5-hydroxy-(tert-butyldimethylsilyl-2,3-O-Isopropylidene-D-ribofuranosyl)-1-ethyne

The acetylated derivative 32 (1.54 grams 3.5mmol) was added inside a 100mL round bottom flask charged with 29.4mL dichloromethane and molecular sieves. The solution was cooled to 0 °C under nitrogen atmosphere. 2.8mL (17.5mmol 5eq.) triethylsilane was added then 1.55mL (8.5mmol, 2.5eq.) of trimethylsilyl trifluoromethanesulfonate was added slowly to the stirring solution. After the addition, the reaction was warmed up to room temperature and stirred for 30 minutes. After 30 minutes, triethylamine 5.88mL (1.68mL/mmol) was added drop wise following the slow addition of 7.05mL of TBAF (7mmol 2.0eq.). The reaction was allowed to stir for 4 hours. After 4 hours, the reaction was quenched with saturated ammonium chloride (40mL) and extracted with dichloromethane (30mL X 3) then dried in anhydrous magnesium sulfate. Percent yield of the crude product could not be calculated because it was over the calculated theoretical yield of 1.45grams.

The product was chromatographed with flash chromatography. The mobile phase was petroleum ether and ethyl acetate (3:1) with the gradual increase of diethyl ether to elute the rest of the fractions. IR analysis revealed C-H alkyn peak at 3305cm⁻¹ and very small C,C alkynyl peak at 2110cm⁻¹ and the broad hydroxyl group peak is not present. Proton NMR analysis of the sample revealed unknown signals which can indicate an impure sample which made the product unidentifiable. However the isopropylidene, and silicon moieties were present. Pure analytical sample could not be obtained.
Synthesis of D-Ribonolactone\(^8\) \((35)\)

![Chemical Reaction Diagram]

A 100mL round bottom flask was charged with D-ribose (5g, 33.34mmol) dissolved in 30mL H\(_2\)O. Sodium bicarbonate (2.0 eq, 5.567g) was added to the mixture and allowed to stir for 15 minutes. After 15 minutes, bromine (1.04 eq, 1.79ml) was added dropwise to the mixture via syringe. The reaction was stirred for 50 minutes. After 50 minutes, sodium thiosulfate (Na\(_2\)S\(_2\)O\(_3\), 0.323g) was added until the orange color turned cleared. The clear aqueous solution was evaporated under reduced pressure until a wet slurry remained. Absolute ethanol (20mL) and toluene (5mL) mixture was added to the slurry. The solution was evaporated again. Ethanol (20mL) was added to the suspension and the mixture was heated under a steam bath for 30 minutes. The hot ethanolic suspension was filtered with a celite pad under vacuum and the filtrate was washed with hot ethanol. The filtrate was cooled to room temperature then refrigerated for 16 hours. After the 16 hours, filtration was attempted but was unsuccessful. The crude sample was evaporated to give 4.45 grams of the crude product that will be carried out in the next step without purification. IR analysis of the product reveals a C=O peak at 1780 cm\(^{-1}\). Pure analytical sample could not be obtained.
Preparation of 5-hydroxy-2,3-O-isopropyldene-D-ribonolactone$^{7,8}$ 14

Dry acetone (46mL) was added to the crude product 34 from the previous reaction. A catalytic amount of concentrated sulfuric acid (0.111mL) was added to the stirring solution at room temperature. The reaction was allowed to stir for 1.5 hours. After 1.5 hours, calcium hydroxide was added (0.500g) following the addition in small portions until the pH of the solution became neutral. After neutralization, the solution was filtered with a celite pad and evaporated to give light yellow crystals 2.62g 46% yield. $R_f$ 0.633 hexane/ethyl acetate/isopropanol (3/1.5/0.5). IR analysis indicated the acetonide gem methyl groups at 1452 cm$^{-1}$, and 1369 cm$^{-1}$ (sharp peak) and a broad hydroxyl peak at 3500 cm$^{-1}$, and broad sharp C=O peak at 1780 cm$^{-1}$. 2,3 isopropyldene-D-ribonolactone was also prepared from commercial ribonolactone to give white crystals with a 98% yield.

Alternate procedure using commercially prepared ribonolactone 34. A catalytic amount of concentrated sulfuric acid (100μL) was added to a 100mL round bottom flask charged with a stirring solution of ribonolactone (34) 4.0g in dry acetone (43mL) the reaction was stirred for 1.5 hours at room temperature. After 1.5 hours, calcium was added slowly until the pH of the solution became neutral to slightly basic. The mixture was filtered through a celite pad and evaporated to give white crystals 4.98g (98%) yield. $^1$H NMR (500MHz, CDCl$_3$): $\delta$ 4.85 (1H, d, $J$=5.5, H-2), 4.80 (1H, d, $J$=5.5, H-3), 4.65 (1H, s, H-4), 3.91 (2H, app q, $J_{5a/b}$=12.5Hz, $J_{5,4}$ =4Hz,
H-5_{ab}), 2.95 (1H, br, OH), 1.48 (3H, s, O_{2}C(CH_{3})_{2}), 1.39 (3H, s, O_{2}C(CH_{3})_{2}). 13C NMR (125MHz, CDCl_{3}): δ 175.52 C-1, 113.38 O_{2}C(CH_{3})_{2}, 83.20 C-2, 78.66 C-3, 62.10 C-5, 76.05 C-4, 27.00 O_{2}C(CH_{3})_{2} 25.70 O_{2}C(CH_{3})_{2}.

**Synthesis of 5-O-Benzyl-2,3-O-isopropylidene-D-ribo-1,4-lactone^{12,13} (35)**

![Chemical Structure](image)

60% sodium hydride dispersion in mineral oil (1.2eq, 1.018g) was added in one portion to a 100mL round bottom flask charged with a stirring solution containing the dissolved lactone 14 (3.99g, 21.2mmol) in DMF (16.0mL) and benzyl chloride (1.2eq, 3.02mL) under 0 °C ice water bath under nitrogen atmosphere. The mixture was stirred for 30 minutes and the reaction was stirred overnight for 16 hours under room temperature. The next day, the reaction was diluted with ethyl acetate (45mL) and washed with 0.1N HCl (25mL X 3). The organic layer was washed with saturated sodium bicarbonate (20mL X 3) then washed with brine (20mL X 2). The organic layer was dried over anhydrous magnesium sulfate and concentrated to give an oily mixture to give a yield of 95%. The mixture was chromatographed using hexane: ethyl acetate (3:2) to give a clear syrup and a yield of 4.62g (78%).

IR (neat) v_{max} 1781cm^{-1} (C=O). 1H NMR (500MHz, CDCl_{3}): δ 7.27-7.15 (5H, m, C_{6}H_{5}), 4.69 (1H, d, J_{2,3}=5.0Hz, H-2), 4.62 (1H, d, J_{3,2} 5.0Hz, H-3), 4.55 (1H, m, H-4), 4.47 (2H, app q, AB-q, J=12 Hz, CH_{2}C_{6}H_{5}) 3.60 (2H, app q, J_{5_{ab}}=10.8 Hz, J_{3,4}=2.0 Hz, H-5_{ab}), 1.73 (3H, s, O_{2}C(CH_{3})_{2}), 1.27 (3H, s, O_{2}C(CH_{3})_{2}). 13C NMR (125 MHz, CDCl_{3}): δ 174.7 C-1, Phenyl carbons 137.2, 128.9, 127.9, 128.3, 128.0, 127.8, 113.4 O_{2}C(CH_{3})_{2} 81.37 C-2, 78.73 C-4, 76.06 C-3, 74.09 CH_{2}C_{6}H_{5}, 69.26 C-5, 27.1 O_{2}C(CH_{3})_{2}, 25.89 O_{2}C(CH_{3})_{2}.
The lithioacetylene was prepared by adding 7.27mL of 1.6M n-butyl lithium in hexane (1.5 eq., 11.63mmol) drop wise via syringe to a 250mL two neck round bottom flask charged with 1.65mL trimethylsilylacetylene (1.5 eq., 11.675 mmol) diluted in THF (31mL) under nitrogen atmosphere at a temperature of -78 °C. The reaction was stirred for 30 minutes followed by the drop wise addition of benzylated ribonolactone 35 (2.16g, 7.77 mmol) diluted in freshly distilled THF (31mL) via an addition funnel to the stirring solution of the lithium trimethylsilylacetylene at the constant temperature. After the lactone was added, the reaction mixture was stirred for 30 minutes then quenched with 35mL of saturated ammonium chloride. The mixture was extracted with diethyl ether (35mL X 3), and the organic layer was washed with saturated sodium bicarbonate solution (20mL X 3) followed by washing with saturated sodium chloride solution (20mL X 3). The organic layer was dried with anhydrous magnesium sulfate followed by rotary evaporation to give a yield of 81.1%. The crude product was purified with column chromatography hexane: ethyl acetate (4:1) to give two main products. The products that were isolated are the alkynylated lactol 36 1.49g (51%) yield, and the desilylated product 37 0.74g (30%) yield. The desilylation can be minimized by having a shorter reaction time. The complete addition of the lactone to the stirring solution of the lithioacetylene took approximately 20 minutes thus extending the overall reaction time. A faster addition of the lactone can reduce the overall reaction time and possibly prevent desilylation forming the product 37. 

¹H NMR for 37
(500MHz, CDCl₃): δ 7.29-7.37 (5H, m, C₆H₅), 5.01 (1H, s, OH), 4.80 (1H, d, J₂,₃=5.6 Hz H-2), 4.54, 4.62 (2H, q, J = 11.6Hz, CH₂C₆H₅), 4.52 (1H, d, J₃,₂=5.7 Hz H-3), 4.43 (1H, m, H-4), 3.65 (1H, app q J₅b,a = 10.5 Hz, J₅,a = 2.5Hz, H-5ₐ), 3.60 (1H, app q J₅a,b = 10.5 Hz, J₅,a = 2.5Hz, H-5ₐ), 1.54 (3H, s, O₂C(CH₃)₂), 1.34 (3H, s, O₂C(CH₃)₂), 0.194 (9H, s, Si(CH₃)₃). ¹³C NMR (125MHz, CDCl₃): δ aromatic carbons 136.3, 129.1, 128.7, 128.5, 128.4, 113.4 O₂C(CH₃)₂, 102.24 C-1, 100.09 C-CTMS, 91.54 C-CTMS, 88.84 C-2, 84.84 C-4, 82.72 C-3, 74.38 CH₂C₆H₅, 71.13 C-5, 26.92 O₂C(CH₃)₂, 25.86 O₂C(CH₃)₂, -0.07 Si(CH₃)₃.

5-O-(benzyl-2,3-O-Isopropylidene-D-ribofuranosyl)-1-trimethylsilylethyne⁶ 38

Boron trifluoride (32.8mmol, 4.05mL) was added drop-wise under nitrogen atmosphere at -78 °C to a 250mL round bottom flask charged with the alkynyl lactol 36 (2.47g, 6.56mmol) dissolved in distilled methylene chloride (155mL). After the addition of the Lewis acid, triethylsilane was added (32.8mmol, 5.24mL) and the mixture was stirred for 1 hour. After 1 hour, the reaction was immediately quenched with saturated sodium bicarbonate (70mL). The reaction mixture was transferred to a 500mL separatory funnel. An additional 60mL of saturated sodium bicarbonate was added. The organic layer was separated then washed with saturated sodium chloride (75mL X 4). The organic layer was dried under anhydrous magnesium sulfate then evaporated to yield a crude mixture of products exceeding the theoretical yield. The compound was isolated with column chromatography (petroleum ether: ethyl acetate 6:1) to give clear crystals 0.71g (30%). [α]D⁻²⁴⁻¹⁴.45 (c, 1.1, CH₂Cl₂). ¹H NMR (500MHz, CDCl₃): δ 7.28-7.35(5H, m, C₆H₅), 4.89 (1H, d, J=5.0 Hz, H-1), 4.80 (1H, d, J=5.0Hz H-2), 4.75(1H, t, J=5.5,
Nucleophilic alkynylation of lactol to Alkynyl diol

The lithioacetylene was prepared by adding dropwise 16.44mL of n-butyl lithium (1.6M in hexanes, 2.0 eq) in a 250mL round bottom flask charged with a stirring solution containing 4.68mL of trimethylsilylacetylene (32.88 mmol, 2.5 eq.) in 40mL dry THF at 0 °C. The mixture was stirred for 15 minutes at 0 °C. The lactol 8 (4.00g, 13.15 mmol) was dissolved in 40mL dry THF and was added drop wise to the stirring solution of the lithioacetylene at 0 °C. After the addition of the lactol 8, the reaction mixture was stirred in the ice water bath for 1 hour then stirred at room temp for 2 hours. After 2 hours, the reaction was quenched with the addition of saturated ammonium chloride solution (50mL). The mixture was transferred to a separatory funnel 40mL diethyl ether was added and the mixture washed with saturated ammonium chloride solution (25 X 2) then washed with saturated sodium chloride solution (3 X 40mL). The organic phase was dried under anhydrous magnesium sulfate then evaporated under reduced pressure to
give a yellow syrup in 86% yield. The crude product was purified with column chromatography hexane: ethyl acetate (4:1) giving a pale yellow syrup in 3.12 g (59%) yield.

$^1$H NMR (300MHz, CDCl$_3$): $\delta$ 4.64 (1H, dd, $J_{5,4} = 4.2$ Hz, $J_{5,OH} = 9.3$ Hz, H-5), 4.33 (1H, dd, $J_{4,3} = 6.3$ Hz $J_{4,5} = 4.2$ Hz, H-4), 4.16 (1H, dd, $J_{3,4} = 6.3$ Hz $J_{3,2} = 9.0$ Hz, H-3), 3.98 (1H, d, $J = 9.3$ OH, OH), 3.84 (1H, app q $J_{Jab} = 10.2$ Hz, $J_{1,2} = 3.0$ Hz, H-1b), 3.66 (1H, app q $J_{Jab} = 10.2$ Hz, $J_{1,2} = 5.7$ Hz, H-1a), 3.12 (1H, d, $J = 7.2$ Hz, OH), 1.49 (3H, s, O$_2$C(CH$_3$)$_2$), 1.34 (3H, s, O$_2$C(CH$_3$)$_2$), 0.90 (9H, s, SiC(CH$_3$)$_3$), 0.16(9H, s, Si(CH$_3$)$_3$), 0.083 (6H, s, Si(CH$_3$)$_2$). $^{13}$C NMR (75MHz, CDCl$_3$): $\delta$ 109.4 O$_2$C(CH$_3$)$_2$, 104.4 CCTMS, 90.70 CCTMS, 80.25 C-2, 76.49 C-3, 69.30 C-4, 64.44 C-5, 62.08 C-1, 27.83 O$_2$C(CH$_3$)$_2$, 26.06 SiC(CH$_3$)$_3$, 18.51SiC(CH$_3$)$_3$, 25.64 O$_2$C(CH$_3$)$_2$, 0.001 Si(CH$_3$)$_3$, -5.22 Si(CH$_3$)$_2$.

Cyclization of Alkynyl diol with tosyl chloride and pyridine $^{15}$

Synthesis of 5-0-(tert-butyldimethylsilyl-2,3-O-Isopropylidene-D-ribofuranosyl)-trimethylsilyl ethyne 13

A round bottom flask was charged with a mixture of the alkynyl diols 43 (0.69g, 1.72mmol) diluted in dry pyridine (37 mL). The stirring solution was maintained at room temperature. Tosyl chloride was added in one portion (2.30g, 12.07mmol) and the mixture was stirred for 48 hours with a drying tube. After 48hr, the mixture was diluted with water (5mL) and evaporated. The residue was triturated with hot ether and evaporated to give oily syrup which was chromatographed with petroleum ether /ethyl acetate (16:1). The isolated product (R$_f$ 0.51) was clear crystals 0.404g (61.4%). $[^{[\alpha]}]_D^{24}$ 23.72 (c 0.51, CH$_2$Cl$_2$)
^1^H NMR (500 MHz CDCl\textsubscript{3}): δ 4.85 (1H, d, J\textsubscript{1,2}=5.0 H-1), 4.78 (1H, d, J\textsubscript{3,2}=5.5, H-3), 4.72 (1H, t, J\textsubscript{2,1}=5.0, J\textsubscript{2,3}=5.5, H-2), 4.17 (1H, m, H-4), 3.75 (1H, app q, J\textsubscript{5b,5a}= 10.5, J\textsubscript{5b,4}= 2.0, H-5\textsubscript{b}), 3.67 (1H, app q, J\textsubscript{5a,5b}=10.5, J\textsubscript{5a,4}=2.0, H-5\textsubscript{a}), 1.543 (3H, s, O\textsubscript{2}C(CH\textsubscript{3})\textsubscript{2}), 1.36 (3H, s, O\textsubscript{2}C(CH\textsubscript{3})\textsubscript{2}), 0.86 (9H, s, SiC(CH\textsubscript{3})\textsubscript{3}), 0.17δ (9H, s Si(CH\textsubscript{3})\textsubscript{3}), 0.03 (6H, s, Si(CH\textsubscript{3})\textsubscript{2}).

^13^CNMR (125MHz CDCl\textsubscript{3}/TMS): δ 113.2 O\textsubscript{2}C(CH\textsubscript{3})\textsubscript{2}, C\textsubscript{1}-C\textsubscript{TMS} 100.2, C\textsubscript{1}-C\textsubscript{TMS} 93.39, 84.20 C-4, 83.43 C-3, 82.44 C-2, 74.75 C-1, 65.62 C-5, 26.66 O\textsubscript{2}C(CH\textsubscript{3})\textsubscript{2}, 26.05 SiC(CH\textsubscript{3})\textsubscript{3}, 25.75 O\textsubscript{2}C(CH\textsubscript{3})\textsubscript{2}, 18.29 SiC(CH\textsubscript{3})\textsubscript{3}, 0.05 Si(CH\textsubscript{3})\textsubscript{3}, -5.51 Si(CH\textsubscript{3})\textsubscript{2}.

Cyclization of Alkynyl diol under Mitsunobu condition\textsuperscript{16,17}

Synthesis of 5-O-(tert-butyldimethylsilyl)-2,3-O-Isopropylidene-D-ribofuranosyl)-1-trimethylsilylethyne (13)

Under refluxing conditions a solution of 40% diethylazodicarboxylate (DEAD) in toluene (2.51mL, 1.5eq) was added dropwise via syringe to 100ml round bottom flask charged with a mixture of the alkynyl diols 45 R,S (1.48g, 3.68 mmol) and triphenylphosphine (1.44g, 1.5eq) dissolved in freshly distilled tetrahydrofuran (30mL). After the addition of DEAD, the reaction was refluxed for 1hour. After 1 hour the solvent was evaporated and giving a thick dark brown oil (4.00g) which was chromatographed with column chromatography using hexane: ethyl acetate (12:1) as the solvent system.

(Alternative procedures) Under the same refluxing conditions 1.7mL DEAD in toluene was further diluted in 15mL freshly distilled tetrahydrofuran and added dropwise via an addition funnel over a period of 15 minutes to a 100mL round bottom flask charged with a mixture of the
alkynyl diols 45 R,S (1.0g, 2.48mmol) and triphenylphosphine (0.975g, 3.72mmol) dissolved in 20mL THF. After the addition of DEAD, the mixture was allowed to stir for 1-1.5 hours then evaporated, concentrated, then purified by column chromatography hexane: ethyl acetate 12:1 to give a clear crystalline product which is the alpha anomer in 0.233g (17%) yield.

**Cyclization of Alkynyl diol via intramolecular Nicholas reaction**

**Synthesis of 5-O-(tert-butyldimethylsilyl-2,3-O-Isopropylidene-D-ribofuranosyl) trimethylsilyylethyne**\(^{17}\) (13)

Dicobalt octacarbonyl was adding in one portion (0.66g, 1.908mmol) to a 50mL round bottom flask charged in the alkynyl diol 45 (0.64g, 1.59mmol) dissolved in methylene chloride (16mL). After 1.5 hours stirring under an argon atmosphere, triflic acid was added via 100µL syringe (12.75 µL, 0.465mmol) and the reaction mixture was stirred for an additional 5 hours. After 5 hours, the reaction was quenched with triethylamine (0.636mL) followed by the slow addition of iodine (4.035g) at room temperature and the reaction was stirred for an additional 1 hour. After 1 hour the reaction mixture was concentrated in vacuo the diluted with 50mL methylene chloride. The organic phase was washed with saturated sodium sulfite (5 X 20mL) followed by washing with saturated sodium chloride (3 X 30mL). The organic layer collected and dried in anhydrous sodium sulfate then concentrated to give dark red syrup (0.59g). The crude mixture contained many side products and did not separate well via TLC analysis and column chromatography using hexane/ ethyl acetate eluent (12:1). Pure analytical sample could not be obtained.
Desilylation of trimethylsilyl moiety

5-O-(tert-butyldimethylsilyl-2,3-O-Isopropylidene-α-D-ribofuranosyl)-1-ethyne 11

A catalytic amount of potassium carbonate (31.8mg) was added in one portion to a 125mL round bottom flask charged with the trimethylsilylalkynyl-ribofuranoside 13α (1.115g) dissolved in anhydrous methanol (25mL). The reaction was monitored with TLC (hexane/ethyl acetate 9:1). After 5 hours the spot for the starting material disappeared (Rf 0.47) and the product was formed (Rf 0.31) afterwards, the reaction was evaporated to dryness then quenched with 15mL saturated sodium bicarbonate. The aqueous phase was washed with methylene chloride (25mL X 3) followed by drying under anhydrous magnesium sulfate then evaporated to give a pale yellow liquid which gave white crystals upon purification (hexane/ethyl acetate, 9:1) in 0.89g (97%) yield. 1H NMR (300 MHz, CDCl₃): δ 4.90 (1H, dd, J=2.1 Hz, 4.5 Hz, H-1), 4.84 (1H, d, J=6.0 Hz, H-3), 4.76 (1H, t, J₂,₁= 5.5 Hz J₂,₂=5.0 Hz H-2), 4.17 (1H, m, H-4), 3.75 (2H, app q, Jₐₜ₆=11.1, J₅,₄=2.7, H-5ₐₖ₆), 2.62 (1H, d, J = 2.1 Hz, CCH₂), 1.57 (3H, s, O₂C(CH₃)₂), 1.39δ (3H, s O₂C(CH₃)₂), 0.88 (9H, s, SiC(CH₃)₃), 0.05 (6H, s, Si(CH₃)₂).
Ethynylation of hemiacetal 8 1-\textit{O-tert}-butyldimethylsilyl-3,4-\textit{O,O}-isopropylidene-6,7-ethyne-2,5 diol 63

Method A)

Ethynyl magnesium bromide (20.55mmol, 41.1 mL, 0.5M solution in THF) was added dropwise via syringe in a 125mL round bottom flask charged with a stirring solution of the protected hemiacetal 8 (2.5 grams 8.21mmol) dissolved in THF (25mL) under nitrogen atmosphere at 0 °C. After the addition, the solution was stirred at the same temperature for thirty minutes then stirred at room temperature for four and a half hours. After four and half hours, the reaction was quenched with saturated ammonium chloride solution (50mL) followed by the addition of diethyl ether (50mL). The aqueous layer was decanted and the organic phase was washed with saturated ammonium chloride solution (3 X 40mL) followed by washing with saturated sodium chloride solution (3 X 40mL). The organic layer was dried under anhydrous magnesium sulfate and evaporated to give a yellow syrup 89%. The crude product was purified via column chromatography (hexane/ethyl acetate, 4:1, \(R_f\) 0.39) giving a light yellow syrup in 1.70g (63%). The yellow syrup crystallized over a couple of days under refrigeration.

Method B:

The reaction conditions were modified using the unpurified hemiacetal 8. Ethynylmagnesium bromide (40mL of 0.5M in THF) was added dropwise to 250mL round bottom flask charged with a stirring solution of the crude hemiacetal 8 dissolved in THF (3.06 grams, 33mL) under nitrogen atmosphere in an ice water bath. The reaction was stirred in an ice water bath for 30
minutes then allowed to stir for four and a half hour. The workup and chromatography was the same as the latter method. After purification the product yield was 1.43g (43%). $^1$H NMR (500MHZ, CDCl$_3$): δ 4.76 (1H, dt, $J_{5,OH}$= 10Hz, $J_{5,a}$=5.0Hz, $J_{5,CH}$=5.0Hz, H-5), 4.36 (1H, dd, H-4), 4.29 (1H, br, H-2), 4.17 (1H, m, $J$= 10Hz, $J$=5.0Hz, H-3), 3.84 (1H, app q, $J_{1b,a}$= 10Hz, $J_{1b,2}$=5.0Hz. H-1b), 3.69 (1H, app q, $J_{1a,b}$= 10Hz, $J_{1a,2}$=5.0Hz, H-1a), 3.60 (1H, d, $J_{OH,5}$=10Hz, OH), 2.95 (1H, d, $J_{2,OH}$=10Hz, OH), 2.52 (1H, d $J_{CH,5}$= 5.0 Hz, CCH), 1.51 (3H, s, O$_2$C(CH$_3$)$_2$), 1.36 (3H, s, O$_2$C(CH$_3$)$_2$), 0.91 (9H, s, SiC(CH$_3$)$_3$), 0.091 (6H, s, Si(CH$_3$)$_2$). $^{13}$C NMR (125MHz, CDCl$_3$): δ 109.5 O$_2$C(CH$_3$)$_2$, 82.69 CCH, 80.13 C-2, 76.66 CCH, 73.77 C-3, 69.32 C-4, 64.31 C-1, 61.45 C-5, 27.98 O$_2$C(CH$_3$)$_2$, 26.04 SiC(CH$_3$)$_3$, 25.58 O$_2$C(CH$_3$)$_2$, 18.50 SiC(CH$_3$)$_3$, -5.15 Si(CH$_3$)$_2$.

**Preparation of 5-O-(tert-butyldimethylsilyl-2,3-O-Isopropylidene-α-D-ribofuranosyl)-1-ethyne (11)**

Tosyl chloride (4.0 eq 7.831g) was added to 500mL round bottom flask charged with a stirring solution of the diol 63 (2.60g, 7.87mmol) dissolved in anhydrous pyridine (168.65mL). Within a couple hours the solution turned from a light yellow color to a dark brown color. The solution was stirred for 48hours. After 48 hours, the reaction was quenched with 20mL water then evaporated under reduced pressure. The slurry mixture was titurated with hot diethyl ether then evaporated yielding a light yellow syrup. The yellow syrup was purified via column chromatography with hexane/ethyl acetate (10:1). The product (R$_f$ 0.28) was concentrated to give white crystals upon refrigeration giving a yield of 1.53g (62.1%). $^1$H NMR (500 MHz,CDCl$_3$): δ
4.90δ (1H, dd, J = 2.1Hz, J = 4.5Hz, H-1), 4.84 (1H, d, J=6.0, H-3), 4.76 ( 1H, t, J= 5Hz, J=5.5Hz, H-2), 4.17(1H, m, H-4), 3.80 (2H, app q, J_{5b,a}=11.0, J_{5b,4}=3.0, H-5_b), 3.69 (1H, app q, J_{5a,b}=11Hz, J_{5a,4}=3Hz, H-5_a), 2.62 (1H, d, J=2.1, CCH), 1.57 (3H, s O_2C(CH_3)_2), 1.39 (3H, s, O_2C(CH_3)_2), 0.878δ (9H, s, SiC(CH_3)_3), 0.051(6H, s, Si(CH_3)_2). 1^3CNMR (125MHz CDCl_3): δ 113.28 O_2C(CH_3)_2, 84.61 C-4, 83.24 C-3, 82.54 C-2, 78.64 CCH, 76.06 CCH, 73.87 C-1, 65.62 C-5, 26.60 O_2C(CH_3)_2, 25.98 SiC(CH_3)_3, 25.46 O_2C(CH_3)_2, 18.23 SiC(CH_3)_3, -5.48 Si(CH_3)_2.

The reaction was done without purification of the crude product 63 giving a product yield of 40.64%.

**Synthesis of 5-O-Triphenylmethyl-2,3-O-Isopropylidene-D-ribofuranose 66**

![Synthesis process](image)

Triphenylmethyl chloride (12.905g, 46.29mmol) was added in one portion to a 250mL round bottom flask charged with a stirring solution of 2,3 isopropylidene-D-ribofuranose 7 (8.0g, 42.8mmol) in 40mL anhydrous pyridine. The reaction vessel was equipped with a drying tube and the reaction mixture was stirred for 24 hours. After six hours, a white precipitate was observed. After 24 hours, the reaction mixture was diluted with 200mL water, the aqueous supernatant was decanted and the oily residue was diluted in methylene chloride (120mL) and washed with 10% copper sulfate solution (5 X 60mL) then washed with water (4 X 50mL). The organic layer was dried under anhydrous magnesium sulfate then evaporated to give thick yellow syrup with a yield of 94%. The mixture was purified via column chromatography using heptane/ethyl acetate (3:1) as the solvent system. After purification the reaction yield was
10.82g (60%) giving a yellow syrup that turned milk white upon refrigeration. The reaction product was used for the ring opening nucleophilic addition procedure.

**Nucleophilic addition of hemiacetal 64**

The lithium propyloxyacetylene was prepared by adding 2.0 eq n-butyl lithium (8.68mL, of 1.6M in hexane) dropwise via syringe to a two neck 250 mL round bottom flask charged with a stirring solution of 2.5 eq (2.67mL) of 3-trimethylsiloxyl-1-propyne diluted in 22mL THF at 0 °C under nitrogen atmosphere. The reaction was stirred for 15 minutes followed by the dropwise addition of the protected lactol 64 (3.0g, 6.94mmol) dissolved in 22 mL THF via an addition funnel. After the addition of the lactol 64, the reaction was stirred under the same temperature for 30 minutes then stirred at room temperature for 3 hours. After 3 hours, the reaction was quenched with the addition of 40mL saturated ammonium chloride diethyl ether was added to the mixture and transferred to a 250mL separatory funnel. The aqueous layer was removed and the organic layer was washed further with saturated ammonium chloride (3 X 40mL) then saturated sodium chloride (3 X 30mL). The organic layer was dried under magnesium sulfate and evaporated to give a yellow syrup with a yield of 85%. The crude product was purified via column chromatography using heptane/ethyl acetate (3:1) as the solvent system to give a yield of the major fraction as a white syrup 44%. NMR analysis did not indicate the formation of the product. TLC analysis showed the same R<sub>f</sub> as the starting material. Pure analytical sample could not be obtained.
Desilylation of 11α

Synthesis of 5-hydorxy-2,3-O-Isopropylidene-D-ribofuranosyl-1-ethyne 33

A 1M solution of tetra-n-butylammonium fluoride in tetrahydrofuran (1.5 eq 4.56mL) was added dropwise to a 100mL round bottom flask charged with the ethynyl ribofuranoside 11α (0.96g 3.08mmol) dissolved in 23mL dry tetrahydrofuran. After the addition, the reaction was stirred for 1 hour then evaporated via rotary evaporator the crude syrup was purified via column chromatography using methylene chloride: methanol (95:5) as the mobile phase to give a yellow syrup 0.48g (79%). Proton NMR analysis indicated the removal of the TBDMS group giving the corresponding alcohol. 

$$^1$$H NMR (300 MHz, CDCl₃): δ 4.81 (1H, br, H-1), 4.79-4.73δ, (2H, m, H-2, H-3), 4.22 (1H, br, H-4), 3.75 (1H, app q, Jₜₐ₄ =11.7, Jₕₐ₄ =3.3, H-5ₕ), 3.66 (1H, app q, Jₜₐ₄ =11.7, Jₕₐ₄ =5.4, H-5ₕ), 2.16 (1H, br, OH) 2.64(1H, s, CCH), 1.58δ (3H, s, O₂C(CH₃)₂), 1.373 (3H, s, O₂C(CH₃)₂).
Desilylation of 13α Synthesis of 5-hydroxy-2,3-O-Isopropylidene-D-ribofuranosyl-1-ethyne (34)

A 1M solution of tetra-n-butylammonium fluoride in tetrahydrofuran (3.0 eq 4.63mL) was added dropwise to a 100mL round bottom flask charged with the ethynyl ribofuranoside 13β (0.60g 1.56mmol) dissolved in 12mL dry tetrahydrofuran. After the addition, the reaction was stirred for 1 hour then evaporated via rotary evaporator the crude syrup was purified via column chromatography using methylene chloride: methanol (95:5) as the mobile phase to give a yellow syrup in 0.25g (76%).

Oxidation of 5-hydroxy-2,3-O-Isopropylidene-D-ribofuranosyl-1-ethyne (35)

Method (A)

A catalytic amount of tempo (5mg, 0.01eq) was added in one portion to a 25mL round bottom flask charged with a stirring solution of the 5-hydroxy ethynyl furanoside 33 (0.5g, 2.66mmol) and trichloroisocyanuric acid (TCCA) (0.240g, 1.0eq) previously added in one portion in methylene chloride (6mL). The reaction was stirred for 3 hours at room temperature under dry atmospheric conditions. After the three hours, the reaction was diluted with 30mL methylene chloride. The mixture was transferred to a separatory funnel and the organic layer was washed with saturated sodium bicarbonate solution (3 X 30mL) followed by saturated sodium chloride.
solution (3X 20mL). The organic layer was dried under anhydrous sodium sulfate then evaporated yielding a dark syrup. Isolation of the pure aldehyde was not successful via column chromatography due to many side products observed by TLC (methylene chloride: methanol 8:1). Proton NMR analysis of the crude product indicated a weak broad signal at around 9.8 ppm indicating the possibility of aldehyde proton. Pure analytical sample could not be obtained.

Method (B)

A catalytic amount of tempo (23mg, 0.1eq) was added in one portion to a 25mL round bottom flask charged with a stirring solution of the 5-hydroxy ethynyl ribofuranoside 33 (0.28g, 1.41mmol) bis-acetoxy iodobenzene (BAIB) (0.51g, 1.1eq) previously added in one portion in methylene chloride (5mL). The reaction was stirred for two and a half hours then monitored with TLC until the starting material was gone. After 24 hours, the solution was diluted with 5mL methylene chloride and transferred to a separatory funnel where the organic phase was washed with saturated sodium sulfite (3X 8mL) then the aqueous layer was washed with methylene chloride (3X8mL) the combined organic layer was washed with saturated sodium bicarbonate (3 X 5mL), then saturated sodium chloride (3 X 5mL) then dried under anhydrous sodium sulfate and concentrated. After concentration via rotary evaporation cold diethyl ether was added and a white precipitate formed. The precipitate was filtered and the organic layer was concentrated to give a light yellow syrup. IR analysis of the crude product indicated a carbonyl signal at 1724 cm\(^{-1}\). Pure analytical sample could not be obtained.
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