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Dian Ding March 28, 2019

The Control of Stereoselectivity and Regioselectivity both in Intramolecular and Intermolecular Carbon-Oxygen Bond-Forming Reactions

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2019

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An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
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Abstract

The Control of Stereoselectivity and Regioselectivity both in Intramolecular and Intermolecular Carbon-Oxygen Bond-Forming Reactions

By Dian Ding

The McDonald laboratory recently discovered epimerization of a chiral center in conversion of aldehyde to alkyne. We have now found that the Colvin rearrangement is a superior alternative for this conversion, proceeding without epimerization. Tungsten-catalyzed cycloisomerizations of the resultant *cis*- and *trans*-substituted benzylidene alkynes were performed to investigate the ring-size selectivity of tungsten cyclization. The results demonstrated that the regioselectivity of this cycloisomerization reaction was affected by the stereochemistry of the alkynyl diol substrate.

Stereoselective preparation of 1,2-cis-glycoside linkages are notoriously difficult. This type of structure is featured in many bioactive oligosaccharides such as the human tumor antigen Globo-H. Cyclization of alkenyl ether intermediate is a non-traditional way to prepare 1,2-cis-glycoside, but there lacks methodology for stereoselective synthesis of structurally complex alkenyl ethers. We aim to develop protocols for stereospecific intermolecular transalkenylations with alkenyl ester synthetic intermediate and carbohydrate alcohol to form the alkenyl ether. A model system starting from 1-hexyne has been developed to study the catalytic transalkenylation with an alcohol. Relay cross metathesis of a diene intermediate produced from a carbohydrate was also investigated as an alternative to stereoselectively synthesize the alkenyl ether.

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I would like to thank Mr. Andrew Ephron for mentoring my research. Your kindness and patience during the supervision has trained me into a careful chemist. I would like to thank every member in McDonald Lab for their concerns and supports. I would like to thank the Department of Chemistry and the Emory College for all the education, opportunities and resources.

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Introduction

Stereochemistry describes the specific spatial orientation of atoms that form the structure of a molecule. The major focuses of stereochemistry are stereoisomers which describe molecules differing only in the three-dimensional arrangement of bonds. Stereochemistry is very important in chemistry because a single difference in stereochemistry can cause a significant change in the chemical property and bioactivity of the compound. The most famous and well-cited example of the effect of stereochemistry is the case of thalidomide disaster. This compound was marketed as an over-the-counter sedative drug in 1957 and was popular among pregnant women to relieve morning sickness. Later, thalidomide was found to cause congenital malformations and has become the killer and disabler of about a million babies.[1] Studies have demonstrated that stereochemistry played a big role in this case. Thalidomide drug is a racemic mixture of the R and S enantiomer, (Figure 1) and it shows significant enantioselectivity in pharmacodynamics.[2] The sedation effect is related to the blood concentration of R-thalidomide,[3] while the S-thalidomide causes the teratogen which leads to congenital disabilities.[4]

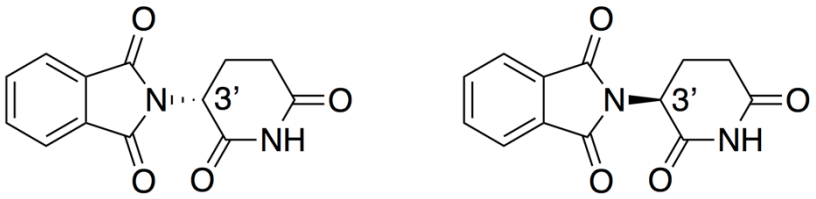


Figure 1. Structure of thalidomide enantiomers

Stereochemistry has always been an important topic in scientific research. This thesis primarily focused on stereochemical control in two different reaction system. Chapter 1 will focus on solving a problem of epimerization, which describes the process of changing one asymmetric center in a compound to forming a different stereoisomer. Chapter 2 will focus on developing a condition so that the formation of one stereoisomer is significantly favored.

Chapter 1: Alkynylation of Pentose Derivatives with Stereochemical Fidelity and Regioselective Cycloisomerization of the Alkynyldiol Products

1. Background

In 1978, Zamecnik and Stephenson demonstrated target silencing of a certain virus gene by a short synthetic oligonucleotide.[5] Nowadays, the usage of these type of non-natural biomolecules are common in laboratory and clinic as potential therapeutical agents.[6] Recently, the nucleoside monomer pool for therapeutic oligonucleotides is not limited to the furanose mimics of ribose and is expanded to pyranose and septanose derivatives. (Figure 2)[7] However, the stereoselective synthesis of septanose has not been well studied.

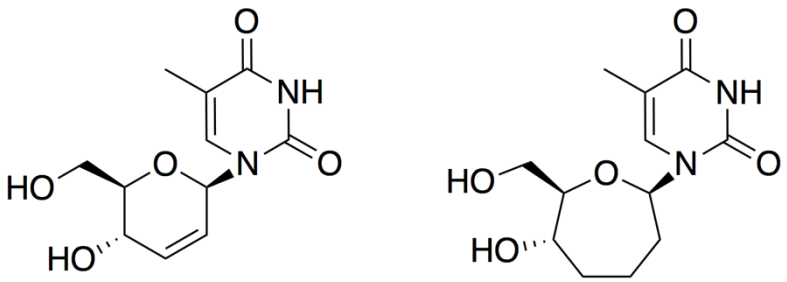


Figure 2. Examples of pyranose and septanose nucleosides

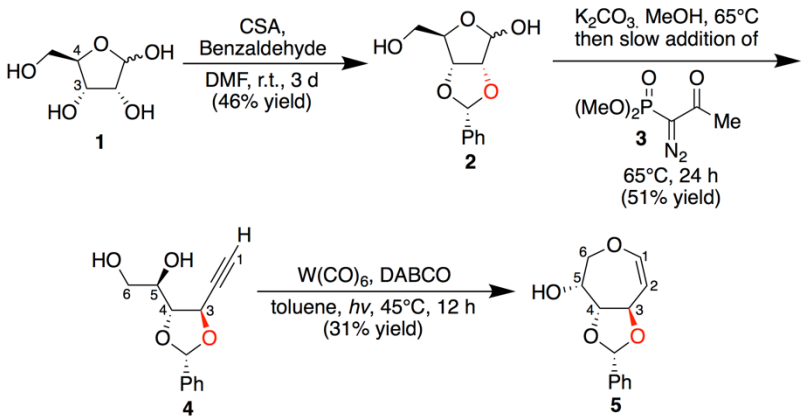
Previous work in the McDonald laboratory has developed a synthesis of seven-membered cyclic enol ethers.[8] This work converted protected furanose to the corresponding alkyne, followed by a tungsten-catalyzed cycloisomerization to produce the septanose. A recent re-investigation has been made into this work, trying to develop a septanose-based polymer. During this investigation, a previously undiscovered epimerization was found at an enolizable chiral center by Mr. Andrew Ephron in the McDonald laboratory. We determined that the epimerization happened during the Ohira-Bestmann homologation of the furanose. A similar epimerization problem has been reported in the literature but was not solved.[9]

In order to synthesize the correct epimer, this epimerization problem needs to be solved. Cycloisomerization reactions of unepimerized alkynes also require testing to see whether septanose or pyranose is formed. This work will describe an alternative route to the unepimerized alkyne and the cycloisomerization results of the alkynes.

2.1 Ohira-Bestmann Protocol which leads to epimerization

The sequence started with benzylidene acetal protection of the 2,3-diols of ribose **1** to produce the known benzylidene acetal **2**. (Scheme 1) The ribofuranose **2** was a 5:1 mixture of benzylidene acetals diastereomers which were separable through careful flash column chromatography. The more abundant diastereomer was used for further experiments. Ohira-Bestmann modified Seyferth-Gilbert homologations of compound **2** gave the alkynyl diol **4**. Since only one diastereomer was formed, the possibility of epimerization was previously undiscovered. The epimerized alkynyl diol **4** was then transformed into the septanose glycal **5** via tungsten-catalyzed cycloisomerization. Mr. Andrew Ephron and Dr. John Bacsa obtained a crystal structure of septanose **5** and discovered that the chiral center at C3 was opposite to what was originally in the D-ribofuranose starting materials **2**.

Scheme 1. Synthesis of septanose 5 with epimerization

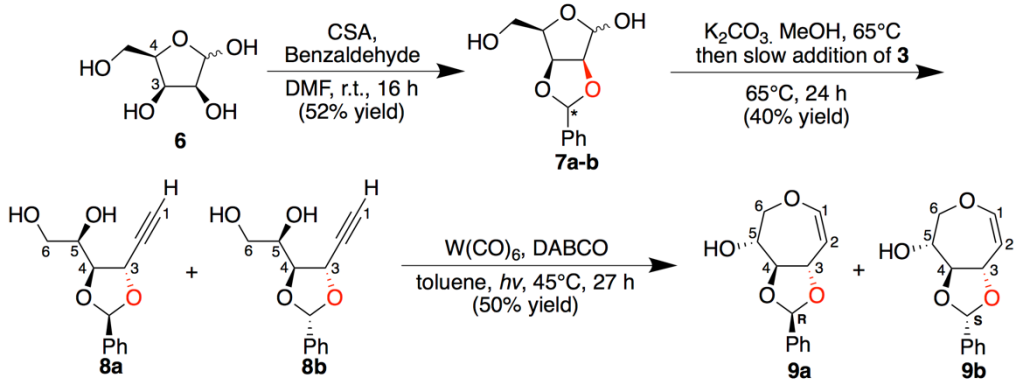


The same procedure was also tested on lyxose. (Scheme 2) Unlike the synthesis of **2** with mostly one separable diastereomer, a mixture of two inseparable benzylidene acetals

diastereomers of **7a-b** was formed. The cis and trans relationship between C3 and C4 of **1** and **6** can possibly affect the stereochemical selectivity of the protection reaction. Therefore, the benzylidene acetal protection of D-ribose gave mostly one diastereomer, while the protection of D-lyxose gave about 1:1 ratio of the two diastereomers **7a-b**. The Ohira-Bestmann alkynylation and tungsten-catalyzed cyclization produced glycal septanose **9** with epimerization at C3 as well, proved by the crystallographic analysis of **9a**.

Preliminary work in this section was done by Mr. Andrew Ephron. I have repeated all of the reactions and improved the yield for compound **2** and **7a-b**. My synthesis of the alkynyl diols and the septanoses were performed with primary focus on obtaining detailed data, as described in the experimental section.

Scheme 2. Synthesis of septanose 9a-b with epimerization



2.2 Alkynylation via Colvin rearrangement of benzylidene protected pentose

We proposed that the epimerization occurred under the Ohira-Bestmann condition. Due to the elevated temperature and the basic condition, the open-chain aldehyde-diol can be deprotonated to form an enolate, removing a chiral center. (Figure 3) As the enolate was protonated back to the aldehyde, the *trans*-dioxolanes were exclusively favored over the *cis*-dioxolanes. This mechanism likely happened faster than the alkynylation under the Ohira-

Bestmann condition. In order to synthesize the alkyne without epimerization, the enolization has to be inhibited or disfavored before the alkynylation.

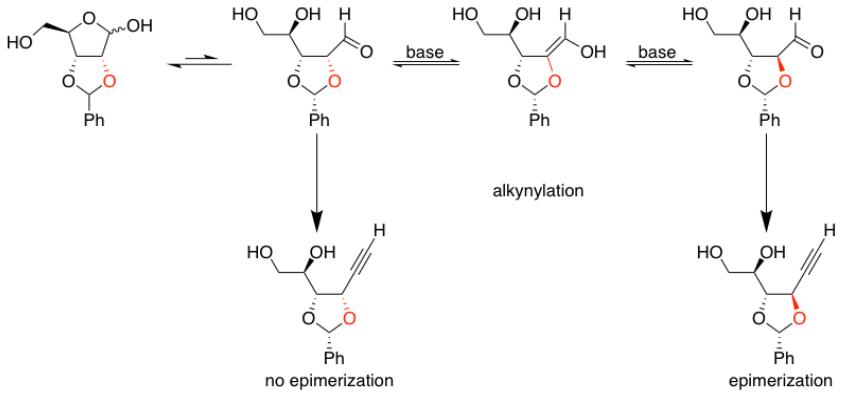
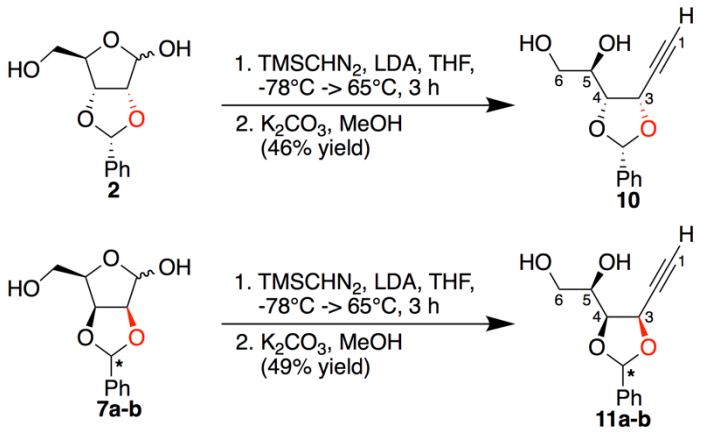


Figure 3. Proposed mechanism for epimerization

i. Alkynylation via Colvin rearrangement

To synthesize the desired alkynyl diol without epimerization, I tested some commonly used procedures that can convert carbonyl compounds to alkynes. After getting no desired alkyne with the Corey-Fuchs procedure, I explored the Colvin rearrangement as an alternative route.[10] This procedure has been used to convert an acetonide protected furanose to alkyne without epimerization.[11] In this procedure, the carbonyl compound was added to the lithium trimethylsilyl diazomethane at -78°C in THF. Under this aprotic and low-temperature condition, the epimerization is likely to be disfavored prior to the C-C bond formation. (Figure 2)

Scheme 3. Colvin rearrangement to synthesize alkynes without epimerization

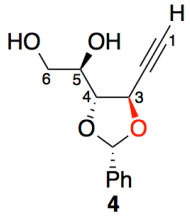


This protocol was tested on the ribose-derived furanose **2**. (Scheme 3) A mixture of terminal alkyne and alkynyltrimethylsilane was initially formed and the protiodesilylation of the crude product gave the alkynyl diol **10**. The spectroscopic data of **10** exhibits similar but distinguishable difference from the epimerized alkyne **4**. Similar results were obtained from the lyxofuranose **7**, producing two diastereomers **11a-b** with spectroscopic characteristics differing from the epimerized **8a-b**. The diastereomeric ratio of **11a-b** is similar to that of **7a-b**, indicating that the different stereochemistry was likely inherited from the benzylidene acetal of **7**.

ii. Spectroscopic data for all alkynyldiol diastereomers

The spectroscopic data of the alkynyl diol diastereomers are shown in Table 1.

Table 1. Chemical shifts and coupling constants for alkynyl diols 4, 8a-b, 10, and 11a-b.



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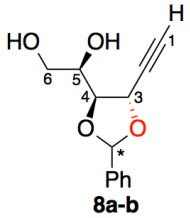
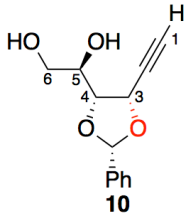


8a-b



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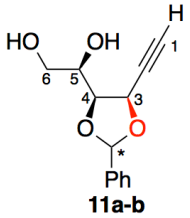


11a-b

	arabino	*xylo*		*ribo*	*lyxo*	
carbon	**4**	**8a**	**8b**	**10**	**11a**	**11b**
1	2.62, d (2.1 Hz)	2.63, d (2.1 Hz)	2.58, d (2.1 Hz)	2.71, d (2.2 Hz)	2.69, d (2.3 Hz)	2.68, d (2.2 Hz)
3	4.97, dd (*5.0*, 2.1 Hz)	4.88, dd (*5.9*, 2.1 Hz)	4.85, dd (*7.7*, 2.0 Hz)	5.02, dd (*6.3*, 2.2 Hz)	5.05, dd (*6.3*, 2.2 Hz)	4.95, dd (*6.6*, 2.2 Hz)
4	4.25, dd (**5.8**, *5.0* Hz)	4.30, dd (*6.0*, **3.7** Hz)	4.12, dd (*7.7*, **2.4** Hz)	4.22, dd (**8.7**, *6.3* Hz)	4.30, ddd (*7.0*, **6.1**, 1.0 Hz)	4.29, t (**6.6** Hz)
5	**3.91**, td (**5.8**, 3.6 Hz)	**3.82 – 3.80**, m	**3.82**, dd (8.6, **4.3** Hz)	**4.16**, ddd (**8.6**, 5.1, 3.0 Hz)	**4.14**, td (**6.1**, 3.8 Hz)	**4.18**, ddd (**6.5**, 5.3, 3.7 Hz)
6a	3.85, dd (11.4, 3.6 Hz)	3.75, d (2H) (4.8 Hz)	3.78, t (2H) (5.4 Hz)	3.92, dd (11.6, 3.0 Hz)	3.80, dd (11.6, 3.7 Hz)	3.85, dd (11.7, 3.8 Hz)
6b	3.76, td (11.4, 5.7 Hz)			3.81, dd (11.6, 5.1 Hz)	3.72, dd (11.7, 5.4 Hz)	3.77, dd (11.6, 5.3 Hz)
acetal	6.02, s	6.00, s	6.00, s	5.83, s	6.22, s	5.85, s
phenyl, 2H	7.52 – 7.45, m	7.51 – 7.47, m	7.53 – 7.47, m	7.54 – 7.49, m	7.50 – 7.42 m	7.59 – 7.55, m
phenyl, 3H	7.43 – 7.38, m	7.40 – 7.36, m	7.40 – 7.37, m	7.42 – 7.37, m	7.41 – 7.33 m	7.43 – 7.38, m

Unfortunately, the chemical shifts of C3 and C4 hydrogens were similar: chemical shift of C3 hydrogens showed up in 4.85 – 5.05 ppm, and those of C4 hydrogens showed up in 4.10 – 4.30 ppm. Their $^{3}J_{H3,\,H4}$ coupling constants were also close to each other, exhibiting between 5 – 8 Hz. This value is consistent with the gauche orientations of the C3 and C4 hydrogens on the benzylidene ring. However, regular differences were observed for C5 hydrogens. Those chemical shifts of the *arabino*-**4** and the *xylo*-**8a-b** diastereomers bearing a *trans*-relationship at C3 and C4 are upfield of 4.0 ppm. Differently, the C5 hydrogens of *ribo*-**10** and the *lyxo*-**11a-b** bearing a cis relationship at C3 and C4 exhibited chemical shifts downfield of 4.1 ppm. Moreover, the epimerized *arabino*-**4** has $^{3}J_{H4,\,H5}$ coupling constant about 3 Hz lower than that of *ribo*-**10**, and the $^{3}J_{H4,\,H5}$ coupling constants of *xylo*-**8a-b** are about 3 Hz lower than that of *lyxo*-**11a-b**.

2.3 Tungsten catalyzed cyclization of 3,4-cis and trans benzylidene alkyne

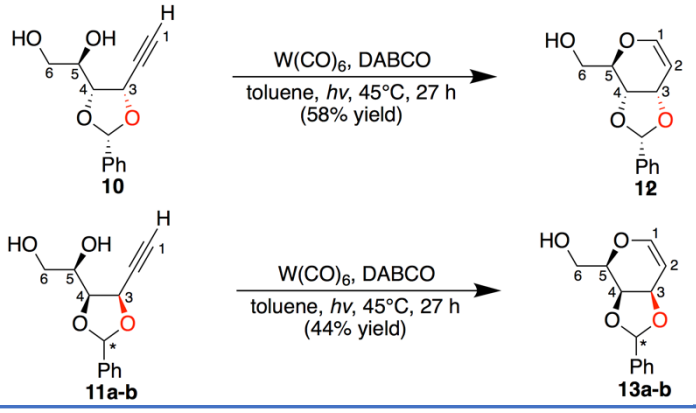
i. Cycloisomerization of alkynyldiol products[7]

These alkynyl diols were also used to investigate the regioselectivity of the tungsten-carbonyl-catalyzed cycloisomerization. The alkenyl diols have two vicinal hydroxyl groups: one oxygen is six-atom while the other oxygen is seven-atom away from the terminal carbon of the alkyne. These substrates have dioxolane space between the diol moieties and the alkyne. In previous work done in the McDonald lab, the cycloisomerization of the epimerized alkynes **4** and **8a-b** regioselectively gave the seven-membered septanose glycals **5** and **9a-b**. (Scheme 1, Scheme 2)

Contrarily, I demonstrated that the tungsten-catalyzed cycloisomerization of the *ribo*-alkynyl diol **10** gave exclusively the six-membered D-ribopyranose **12**. (Scheme 4) Similarly, the cycloisomerization of **11a-b** regioselectively produced D-lyxopyranose glycals **13a-b**, which were benzylidene acetal diastereomers and were chromatographically separable. No septanose

isomers were observed in either case.

Scheme 4. Cycloisomerization of *ribo*- and *lyxo*- alkynyl diols 10 and 11a-b.



During the cycloisomerization reaction, the terminal alkyne rearranged to the vinylidene carbene facilitated by the active catalyst (DABCO)$W(CO)_5$. (Figure 4) The electrophilic sp-hybridized carbon of the carbene intermediate can undergo nucleophilic addition of either the primary or the secondary alcohol. When the C3 and C4 of carbene bear a trans relationship, the **b** path is favored, leading to the septanose. This preference may result from the ring strain of *trans*-bicyclo[4.3.0] structure, which is therefore not formed. On the other hand, the *cis*-bicyclo[4.3.0] does not require this ring strain, causing the formation of pyranose via path **a** when the carbene processes a cis C3 and C4 relationship.

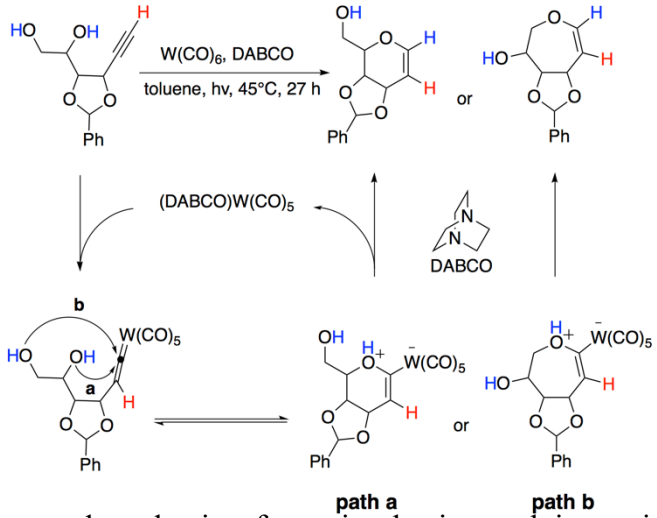
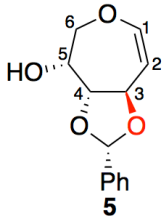


Figure 4. Proposed mechanism for regioselective cycloisomerization

ii. Stereochemistry, ring size, and spectroscopic data of cyclic enol ethers

In order to confirm whether a six- or a seven-membered ring was formed, the hydroxyl groups of the D-ribopyranose glycals **12** and the D-lyxopyranose glycals **13a-b** were acetylated. The proton chemical shifts of the C6 hydrogens were shifted downfield about 0.5 ppm, while the chemical shifts of the C5 hydrogens were shifted about 0.1 ppm. This is the evidence indicating that the cyclized products were the six-membered rings.

Table 2. Chemical shifts and coupling constants for the septanose 5, and 9a-b, and the pyranose 12, and 13a-b.



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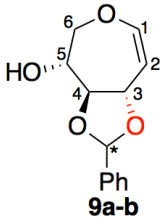
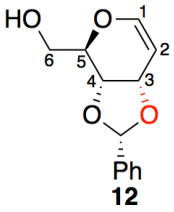


9a-b



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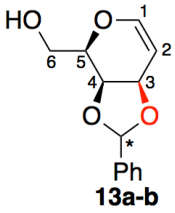


13a-b

	arabino	*xylo*		*ribo*	*lyxo*	
carbon	**5**	**9a**	**9b**	**12**	**13a**	**13b**
1	6.41, dd (6.3, 2.1 Hz)	6.42, dd (6.4, 2.0 Hz)	6.45, dd (6.5, 2.0 Hz)	6.71, d (6.0 Hz)	6.75, d (6.2 Hz)	6.50, d (6.2 Hz)
2	5.30, dd (6.3, 1.8 Hz)	5.19, dd (6.5, 1.6 Hz)	5.25, dd (6.4, 1.4 Hz)	5.26, dd (5.9, 4.7 Hz)	4.87, ddd (6.2, 3.1, 1.1 Hz)	4.95, ddd (6.3, 3.1, 1.4 Hz)
3	5.02, dt (**9.7**, 1.8 Hz)	4.66, dt (**9.7**, 1.8 Hz)	4.72, dt (**9.7**, 1.8 Hz)	4.50, ddd (**5.8**, 4.6, 1.1 Hz)	5.07, dd (**6.4**, 3.0 Hz)	4.80, dd (**6.8**, 3.1 Hz)
4	4.06, dd (**9.7**, **3.9** Hz)	4.16, dd (**9.2**, **7.5** Hz)	4.05, dd (**9.7**, **7.5** Hz)	4.15, dd (**10.0**, **6.0** Hz)	4.45, d (**6.3** Hz)	4.44, dt (**6.8**, **1.5** Hz)
5	4.54, dddd (7.8, 5.6, **3.9**, 1.9 Hz)	4.27, dt (**7.4**, 2.6 Hz)	4.18, dt (**7.1**, 3.0 Hz)	3.56, ddd (**10.0**, 5.3, 2.7 Hz)	4.01, dd (11.8, 8.1 Hz)	4.12, ddd (7.3, 4.0, **1.7** Hz)
6a	4.28, dd (12.5, 5.3 Hz)	4.17, dd (13.4, 2.1 Hz)	4.13, ddd (13.2, 2.4, 1.1 Hz)	4.06, dd (12.2, 4.0 Hz)	4.05, t (5.6 Hz)	4.07, dd (11.5, 7.3 Hz)
6b	3.79, dd (12.5, 8.0 Hz)	4.03, dd (13.3, 3.2 Hz)	4.08, dd (13.4, 3.1 Hz)	3.88, dd (12.1, 4.9 Hz)	3.90, ddd (11.6, 8.2, 3.6 Hz)	3.90, d (11.7 Hz)
acetal	**6.12, s**	**6.11, s**	**6.08, s**	**5.85, s**	**6.01, s**	**5.94, s**
phenyl, 2H	7.51 – 7.48 m	7.47 – 7.45 m	7.49 – 7.47 m	7.50 – 7.42 m	7.50 – 7.44 m	7.51 – 7.44, m
phenyl, 3H	7.44 – 7.39 m	7.40 – 7.36 m	7.40 – 7.38 m	7.42 – 7.35, m	7.42 – 7.33, m	7.41 – 7.36, m

The spectroscopic data of the pyranose and the septanose diastereomers was shown in Table 2. For the bicyclic glycals, the coupling constants were diagnostic of the stereochemistry

because of the rigid confirmation. The *arabino*-**5** and the *xylo*-**9a**-**b** bearing trans-relationship at C3 and C4 gave relatively larger $^{3}J_{H3,\,H4}$ coupling constants around 9.7 ppm, which are consistent with the anti-hydrogens. Differently, the $^{3}J_{H3,\,H4}$ coupling constants of the *ribo*-**12** and *lyxo*-**13a**-**b** with *cis*-relationship at C3 and C4 are much lower, which are between 5.8 and 6.8 Hz, as expected for *gauche* orientations. Moreover, the *ribo*-**12** has large $^{3}J_{H4,\,H5}$ of 10.0 Hz, which is consistent with *trans*-di-axial hydrogens, while the *lyxo*-**13a**-**b** gives very small to no coupling constants for $^{3}J_{H4,\,H5.}$

3. Conclusions

An epimerization was observed in previous work of the laboratory. This problem was solved by using the Colvin alkynylation protocol as an alternative. This approach inhibited epimerization with a milder condition during alkynylation, compared to the previously used Ohira-Bestmann approach. Regioselective cycloisomerization was also applied on the resultant alkynyl diols. *Cis*-substituted benzylidene favors the six-membered ring product. *Trans*-substituted benzylidene disfavors six-membered ring formation due to ring strain so that the seven-membered ring product forms. These results demonstrated that the ring size can thus be controlled by the stereochemistry of the alkynyl substrate.

Chapter 2: Stereoselective Synthesis of Alkenyl Ether

1. Background

There has been growing interest in the stereoselective synthesis of glycoside as a result of more and more attention into the therapeutic potential of oligosaccharides. 1,2-*cis*-glycoside linkage, featured in the human tumor antigen Globo-H[12] (Figure 5) and many other bioactive oligosaccharides, is difficult to prepare. Moreover, axial 2° alcohol structure seen in these compounds are also hindered. The synthesis of this kind of structure cannot take advantage of anchimeric assistance, which is commonly used in the stereospecific synthesis of glycoside linkage. A non-traditional approach using oxidative cyclization of an alkenyl ether joining two carbohydrate derivatives was performed to generate the chiral center of the glycoside linkage.[13,14] (Figure 6) However, there is a gap in the efficient and stereoselective synthesis of alkenyl ether between two complex structures.

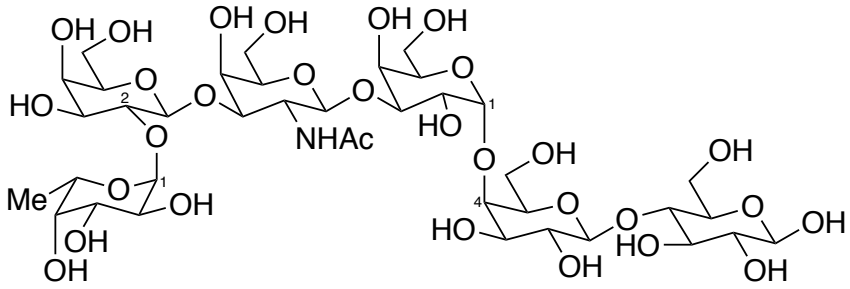


Figure 5. Structure for the human tumor antigen Globo-H

We would like to develop a one-pot catalytic alkenyl ether generation directly from alkyne. But since this strategy is particularly high risk, we decided to explore a more conservative approach first. Two routes have been proposed to generate the alkenyl ether through multi-step synthesis starting from the carbohydrate-derived alkyne derivatives made in chapter 1. The first route is the intermolecular transalkenylation of a carbohydrate alcohol with the alkenyl acetate generated from the alkyne. The second route uses relay metathesis to couple a

carbohydrate derived vinyl ether with a terminal diene generated from the alkyne. Both approaches will be described in this chapter.

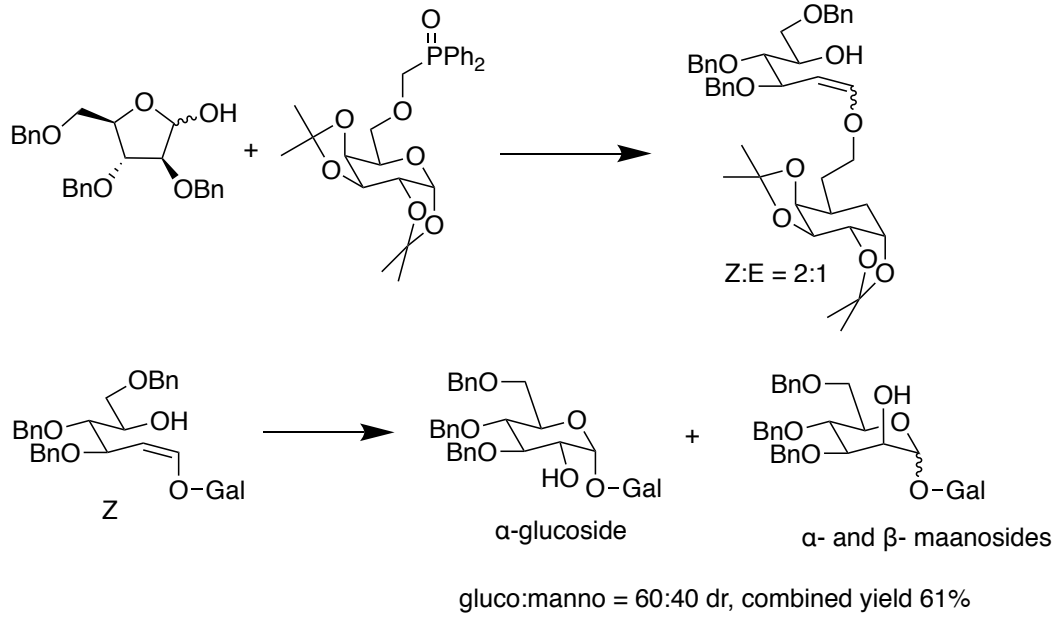


Figure 6. Non-traditional approach to synthesize the challenging glycoside linkage

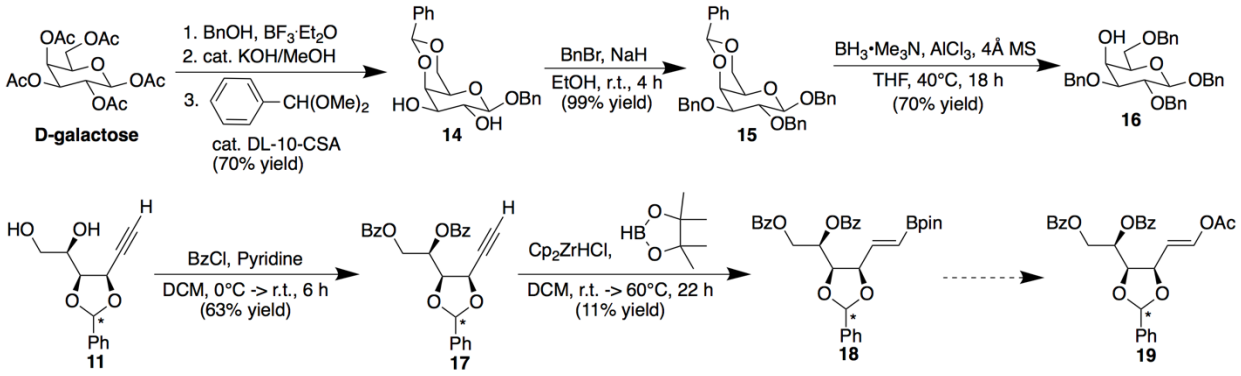
In summary, this work aims to develop a stereoselective synthesis of alkenyl ether between two complex carbohydrate derivatives. This alkenyl ether can then be applied to the generation of 1,2-cis glycoside linkage. As a long-term goal, we would like to develop an efficient and highly stereoselective synthesis of bioactive oligosaccharides, that can be applied in the design and synthesis of useful drugs.

2.1 Intermolecular Transalkenylation of alkenyl acetate and alcohol

First attempt was made on the synthesis of the alkenyl acetate and alcohol pieces from carbohydrates. (Scheme 5) The secondary alcohol **16** was produced according the literature procedure from the commercially available β-D-galactose pentaacetate with good overall yield.[15] At the same time, we proposed a synthesis of the alkenyl acetate **19** from the highly oxygenated alkyne **11a-b** which was made from the previous project. This sequence includes benzoyl protection of the diols, zirconocene-catalyzed cis-hydroboration[16], and stereospecific Cu-

catalyzed coupling with carboxylic acid[17] to provide the alkenyl ester **19**. However, the first few reactions of the zirconocene-mediated hydroboration of **17** with pinacolborane gave very low yield of the vinylboronate **18**. The first attempt to produce the vinylic ester failed. Therefore, I switched to a simpler model system to develop a synthesis of alkenyl ester and to investigate the Ir-catalyzed transalkenylation reaction.

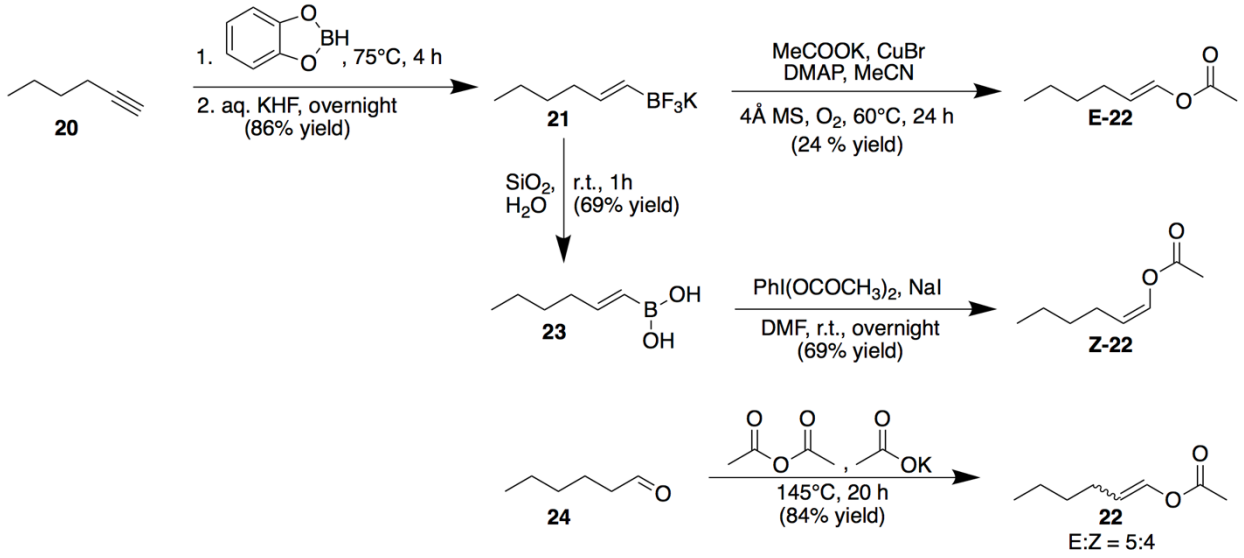
Scheme 5. Synthesis of carbohydrate-derived alcohol 16 and alkenyl ester 19



i. Substrate synthesis for model system

The simpler compound 1-hexenyl acetate **22** was synthesized as a model for the transalkenylation reaction. (Scheme 6) The sequence started with the hydroboration of alkyne, followed up with conversion to the corresponding trifluoroborate salt **21**. The Cu-catalyzed coupling[17] of **21** with potassium acetate afford the *trans*-alkenyl acetate **E-22** with a low yield. However, the reproductivity of this reaction is very poor, with only one success in four trials. At the same time, **21** was hydrolyzed to the corresponding boronic acid **23**,[18] followed up with a stereoselective conversion to the *cis*-alkenyl acetate **Z-22** by the treatment with (diacetoxyiodo)benzene and iodine.[19] This reaction has better yield and excellent reproducibility. Unfortunately, the synthesis of the *trans*-alkenyl boronic acid was much more complicated compared to that of **23**. Therefore, this reaction cannot be an improved alternative to synthesize **E-22**.

Scheme 6. Synthesis of hexenyl acetate 22

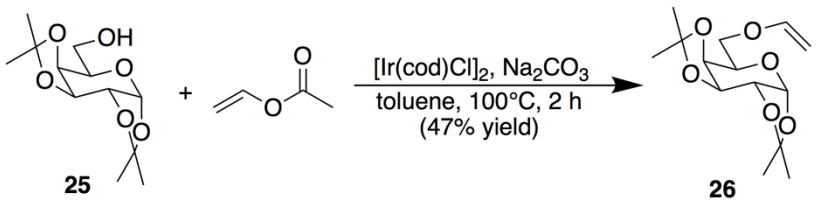


Since both the **E-22** and **Z-22** were valuable for investigating, a simpler synthesis of **22** was used. This convenient procedure converted the commercially available hexanal **24** into the alkenyl acetate **22** with an E:Z ratio of 5:4. This mixture was used primarily in the catalyst and ligands screening for the transalkenylation reaction.

ii. Catalysts and ligands screening for transalkenylation

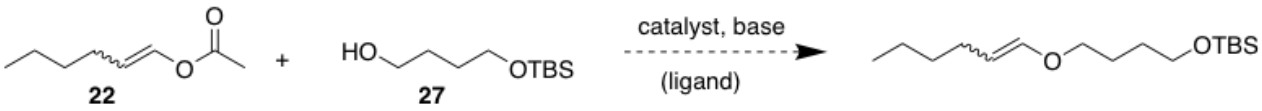
Ishii et al. have reported the $[IrCl(cod)]_2$-catalyzed transalkenylation reactions between vinyl acetate and alcohols to generate vinyl ethers.[20] This system has been applied with secondary and tertiary alcohols and was also tested with isopropenyl acetate. However, this Ir-catalyzed transalkenylation reaction was not explored on any 1,2- disubstituted alkenyl acetate. Part of the reason may be the lack of easy commercial availability of this type of compound.

Equation 1. Synthesis of vinyl ether from galactose derivative



As a control experiment, I tested this reaction on vinyl acetate and a commercially available primary alcohol **25**, following the procedure published by Ishii et al. (Equation 1) The corresponding vinyl ether **26** was produced in two hours with moderate yield. It has a very distinct dd peak at 6.47 ppm with ^{3}J coupling constants of 14.4 and 6.8 Hz, corresponding to the alkenyl hydrogen adjacent to oxygen. This success of this experiment indicated that this reaction worked well on more complicated carbohydrate system.

Equation 2. Proposed transalkenylation with 22 and 27



This reaction condition was then tested on the alkenyl acetate **22** and **27** at 100°C, which gave no reaction. (Equation 2) The complicated alcohol was changed to the simpler primary alcohol **25**, but no reaction had happened either. The solvent was changed to o-xylene and the reaction temperature was raised to 140°C. This time, even though peaks for starting materials can still be observed in the NMR spectrum of the crude reaction mixture, a lot of small peaks can be seen from the 4 – 7 ppm region. Most importantly, a tiny dd peak was observed at 6.41 ppm with ^{3}J coupling constants of 15.9 and 0.9 Hz and a tiny dd peak was observed at 5.86 ppm with ^{3}J coupling constants of 15.7 and 0.8 Hz.

Since the presence of these possible alkynyl ether component is so low, catalysts and ligands screening were tested on this reaction. (Table 3) For the four catalysts tried so far, only $[Ir(cod)Cl]_2$ gave a reaction, even though considerable amounts of starting material were still observed. (Table 3, Trial 1-4) The addition of electron-donating ligands gave reaction while the presence of electron-withdrawing ligand inhibited the reaction. (Table 3, Trial 5-7) After

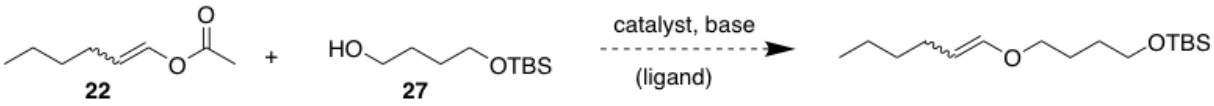
changing the base or the ligand, reaction still occured but different compounds containing alkene feature were formed. (Table 3, Trial 5-8)

Table 3. Select catalysts and ligand screen results for transalkenylation and new proton NMR peaks found in 5 – 7 ppm.[a]

Trial	Catalyst	Base	Ligand	NMR peaks in alkene region
1	$[Ir(cod)Cl]_2$	Na_2CO_3	N/A	6.41 (dd, J = 15.9, 0.9 Hz, 1H) 5.86 (dd, J = 15.7, 0.8 Hz, 1H)
2[b]	$[Ir(PCy_3)(Py)(cod)]PF_6$	Na_2CO_3	N/A	N/A
3[b]	$RhCl(PPh_3)_3$	Na_2CO_3	N/A	N/A
4[c]	$(PhCN)_2PdCl_2$	N/A	N/A	N/A
5[b]	$[Ir(cod)Cl]_2$	Na_2CO_3	PPh_3	6.27 (dq, J = 11.8, 1.7 Hz, 1H) 6.23 (dq, J = 5.8, 1.8 Hz, 0.5H) 5.86 (tt, J = 13.5, 6.7 Hz, 1H)
6[b]	$[Ir(cod)Cl]_2$	Na_2CO_3	$P(Cy)_3$	6.30 (dd, J = 11.8, 1.7 Hz, 1H) 6.26 (dt, J = 5.7, 1.7 Hz, 0.3H)
7[b]	$[Ir(cod)Cl]_2$	Na_2CO_3	$P(p\text{-}C_6H_4F)_3$	N/A
8[b]	$[Ir(cod)Cl]_2$	KOH	PPh_3	6.67 (t, J = 7.5 Hz, 0.5H) 6.34 (dd, J = 11.9, 1.6 Hz, 0.5H) 4.94 (td, J = 3.4, 2.0 Hz, 1H)
9	$[Ir(cod)Cl]_2$	Na_2CO_3	PPh_3	5.82 (ddt, J = 17.0, 10.3, 6.7 Hz, 1H) 5.00 (dq, J = 17.1, 1.7 Hz, 1H) 4.94 (dt, J = 10.2, 0.9 Hz, 1H)
10	$[Ir(cod)Cl]_2$	Na_2CO_3	PPh_3	5.99 (dq, J = 17.0, 8.5 Hz, 1H) 5.18 (ddd, J = 17.2, 3.9, 2.4 Hz, 1H) 5.12(ddt, J = 10.2, 2.2, 1.2 Hz, 1H)
11	$[Ir(cod)Cl]_2$	Na_2CO_3	N/A	5.77 (dt, J = 14.8, 6.7 Hz, 0.6 H) 5.56 (dtd, J = 17.2, 6.3, 5.6, 1.7 Hz, 1H) 5.45 – 5.28 (m, 1H) 4.62 (d, J= 6.8, 0.3 1H) 4.50 (d, J = 6.5, 1H)

[a] Reaction condition: 22 (1 equiv.), 27 (1 equiv.), $[Ir(cod)Cl]_2$ (1 mol%), base (0.6 equiv.), and ligand (0.1 equiv.) were dissolved in d^{10}-p-xylene and heated at 138°C overnight. [b] Reactions were conducted at the same time. [c] Reaction condition: 22 (1 equiv.) was dissolved in ethanol (10 equiv.) and stirred at -20°C for 4 h.[21]

Equation 2. Proposed transalkenylation with 22 and 27



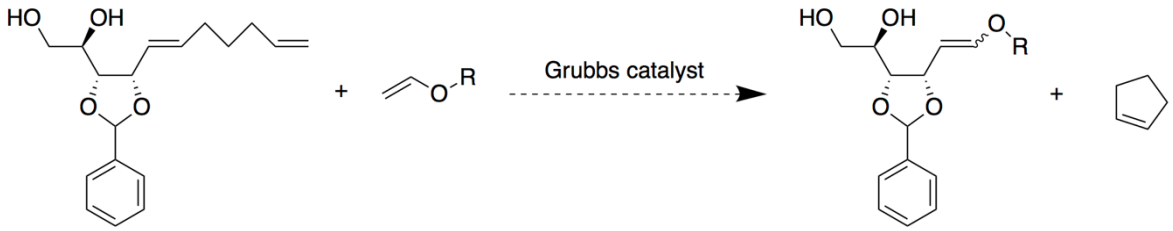
Most obvious is the poor reproducibility of this transformation. The reaction was repeated three times with PPh_3 ligands but giving different outcomes. (Table 3, Trial 5, 9, 10) One possible reason may have been the insufficient stirring for the small-scale reactions. The scale was increased at the second time and unfortunately flash column chromatography did not separate any compound with possible alkenyl ester proton peaks. (Table 3, Trial 9) Mass spectroscopic analysis was done for trial 10 and no desired product was found. (Table 3, Trial 10) Since the NMR spectrum of all the trials look different, it is hard to say no transalkenylation had happened in other trials even through trial 10 has failed. Trial 1 has also been repeated with excess vinylic acetate **22** (2 equiv.) in a better controlled condition. (Trial 11) Mass spectrometry showed a peak at 309.22236, corresponding to $C_{16}H_{34}O_2NaSi$ (M+23). Even though this formula is the same as the desired products, the proton NMR deviated from expectation. Silyl ether was a minor component, while the major component had doublets at 4.6 and 4.5 ppm with coupling constants around 6.8 Hz. These coupling constants are similar to the coupling constants of the peaks at the alkene region, COSY also indicated that those doublets were coupled to the alkene hydrogens. This compound may be a rearranged isomer of the desired product, with the alkene one carbon away from the ether oxygen. The desired alkenyl ether may still present but was buried under the rearranged isomer. Moreover, large amount of starting materials still presents in all of the reaction mixture. The current data indicate that it is difficult to find a condition which is harsh enough to push all the starting materials to react while keeping it mild to avoid rearrangement.

It will be beneficial to investigate the reason of the poor reproducibility. But at the same time, other catalysts can also be tested. Transfer vinylation of alcohols has also been reported with other catalytic systems such as (DPP)Pd(TFA)$_2$[22] and AuClPPh$_3$/AgOAc.[23] These systems will be tested for alkenylation in the future.

2.2 Relay Cross Metathesis

Giving the poor reproducibility of the transalkenylation approach, an alternative route was also examined to synthesize the alkenyl ether. We intend to use olefin metathesis to couple the alkene with the vinyl ether. Since the alkene site made from **2** is very hindered and the catalyst may meet with the vinyl ether first. If it occurs, the Fischer carbene complex will be generated, which is relatively unreactive. Indeed, ethyl vinyl ether has been adopted as a quenching reagent in olefin metathesis.[24] Therefore, relay metathesis was proposed to increase the reactivity of the coupling. (Equation 3) By generating a diene species with a more active terminal alkene and a following ring closing metathesis, the ruthenium catalyst can be more easily attached to the more hindered alkene site for coupling. If this approach works, the other carbohydrate-derived vinyl ether substrate can be generated using the Ir-catalyzed reaction discussed in section 2.1 from **17**. (Equation1)

Equation 3. Relay cross metathesis between diene and vinyl ether

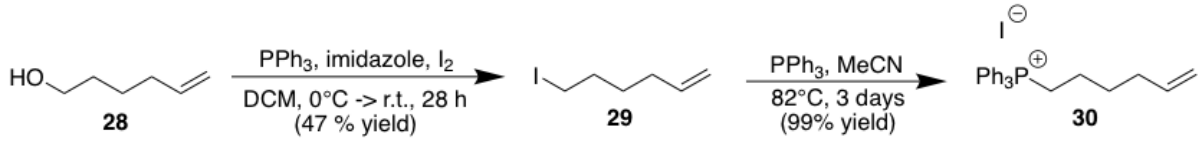


i. 1,6-Diene substrate synthesis

Wittig reaction was used to convert the ribofuranose **2** to the corresponding diene. The precursor for the Wittig reagent was synthesized from the commercially available hexenol **28** in

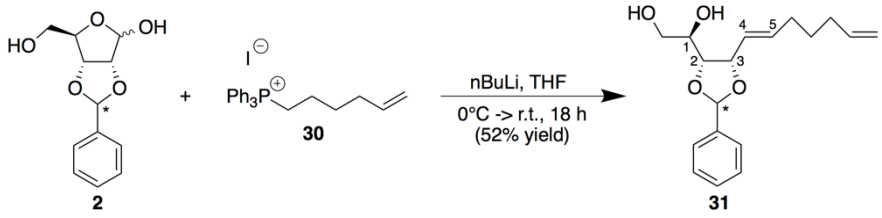
quantitative yield. This aliphatic alcohol was converted to iodide via Appel reaction, followed by quaternization with triphenylphosphine to produce the phosphonium salt. (Scheme 7)

Scheme 7. Preparation for precursor of Wittig reagent



The preparation of Wittig reagent has been tested using the two strong bases, nBuLi and NaHMDS. **2** was added directly to the reaction mixture after half an hour of Wittig reagent generation. The desired diene was observed for the reaction with nBuLi, but no reaction happened for the one with NaHMDS. Mass spectroscopy result strongly supports the presence of the product. Flash column chromatography separated two diastereomers from the mixture. In the proton NMR spectrum of the two, only the acetal hydrogen has a distinct chemical shift, while all the others are very similar. Knowing that the ribofuranose benzylidene acetal **2** used in this reaction was the 5:1 mixture of diastereomers, the diastereotopic center of the two are likely to be the acetal carbon center. (Equation 4)

Equation 4. Synthesis of diene 31



During this reaction, **2** was added to the Wittig reagent and the base at 0°C, which is a milder condition compared to that of the Ohira-Bestmann condition. Moreover, the $^{3}J_{H1,\,H2}$ coupling constants of **31** are around 8 Hz. As discussed in Chapter 1, Section 2.2ii, this value is close to the 8.5 Hz coupling constant ($^{3}J_{H4,\,H5}$) of *ribo*-alkynyl diol **10**, which is much larger than that of the epimerized for *arabino*-alkynyl diol **4**. These evidences support that **31** is not

epimerized. Meanwhile, the $^{3}J_{H4,\,H5}$ coupling constant of the vicinal hydrogen of **31** is around 15 Hz. Similar structure feature can be found in the literature. Coupling constants for trans vicinal hydrogens of an E-alkenyl dioxolanes are approximately 15 Hz,[25] while those of the cis vicinal hydrogens of a Z-alkynyl dioxolanes are about 11 Hz.[26] This evidence supports that the Wittig reaction of **2** generates exclusively the E alkynyl diol.

ii. Relay metathesis using Grubbs catalyst

Since there has been relay metathesis with trans alkene reported in the literature,[27] it is valuable to test metathesis with **31**. The relay metathesis of **31** was first conducted in the presence of the relatively more active Hoveyda-Grubbs catalyst 2nd generation at 50°C. Both the simple ethyl vinyl ether and the more hindered *t*-butyl vinyl ether were examined as the substrates, which were slowly added to the diene and catalyst solution. Mass spectrometry of the reaction mixture was conducted, and neither desired product nor starting material were obtained.

For the next step, milder conditions such as lower temperature can be tested. Other Grubbs catalyst such as slightly less reactive Grubbs catalyst 2nd generation can also be examined. Considering the hindered environment of the internal alkene, the ring-closing metathesis is likely inhibited mainly by steric hindrance. Such failure has been seen in the literature during ring-closing metathesis of a fused bicyclic substrate.[28] They solved the problem by the reductive opening of one lactone ring to reduce steric hindrance before ring-closing metathesis, followed by oxidation to restore the lactone ring. Therefore, it will also be valuable to test the relay metathesis with **31** unprotected.

3. Conclusions

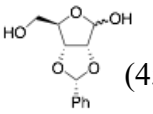
The transalkenylation reaction with a simpler model system was examined with different catalysts and ligands. Even though auspicious alkene peaks have been seen in the proton spectra, there is no further evidence indicating they are the desired product. The reproducibility of this

reaction is also very poor. In the further, different catalyst and reaction condition can be tested for this transformation.

The relay metathesis approach was also examined with the diene generated from the furanose. First two attempts using Hoveyda-Grubbs catalyst 2nd generation did not work. Further work can test different reaction conditions and Grubbs catalysts. Moreover, relay metathesis with **31** deprotected will also be tested in the future.

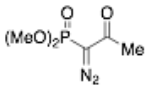
Chapter 3: Experimental Methods

(2*R*,3a*R*,6*R*,6a*R*)-6-(hydroxymethyl)-2-phenyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (2)



In a 500 mL round bottom flask, ribose **1** (10.0 g, 66.6 mmol) was dissolved in DMF (45 mL). Then, benzaldehyde (27.2 mL, 266 mmol) and camphorsulfonic acid (7.74 g, 33.3 mmol) were added. The reaction was stirred for three days under a balloon of argon, then quenched with triethylamine (30 mL), diluted with dichloromethane (70 mL), filtered through Celite, and concentrated by rotary evaporation. The solution was then filtered through silica gel, eluting with ethyl acetate, and reconcentrated. Then, the reaction mixture was diluted with large amount of dichloromethane and water. The organic layer was washed with water for three times and the three aqueous layers were also washed with dichloromethane for three times. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash column chromatography (3:2 EtOAc:Hexane → EtOAc) yielded 5:1 mixture of two diastereomers of **2** (7.25 g, 30.4 mmol, 46% yield) as a white solid. Careful column chromatography was able to separate the more abundant diastereomer, whose data were reported below. **^{1}H NMR** (400 MHz, $CDCl_3$) d 7.53 – 7.46 (m, 2H), 7.43 – 7.37 (m, 3H), 5.78 (s, 1H), 5.58 (d, J = 6.7 Hz, 1H), 4.94 (dq, J = 6.2, 0.6 Hz, 1H), 4.70 (d, J = 6.2 Hz, 1H), 4.65 – 4.58 (m, 1H), 4.30 (d, J = 6.7 Hz, 1H), 3.85 – 3.75 (m, 2H), 3.23 (dd, J = 7.3, 3.1 Hz, 1H), 1.64 (s, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.1, 130.0, 128.7, 126.9, 105.8, 102.5, 87.5, 82.6, 63.6 **FT-IR** ν_{max}/cm^{-1} 3391 (OH), 2939 (CH) **HRMS** Anal. Calcd. for $C_{12}H_{14}O_5Na$ (M +23) 261.07343; found: 261.07334 **Melting point** 102.6 – 104.3°C **Optical rotation** $[\alpha]_D^{20}$ -23.1 (c 0.31, $CHCl_3$)

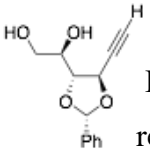
Ohira- Bestmann reagent (3)



To a 250 mL oven dried round bottom flask equipped with a stir bar, dimethyl acetylmethylphosphonate (5.11 g, 31 mmol) and THF (60 mL) were added. Next the solution was placed in an ice bath, and a 60% w/w suspension of NaH(1.33 g, 31mmol) in mineral oil was added over five portions. The solution was allowed to stir for 15 minutes, and 4-acetamidobenzenesulfonyl azide (*p*-ABSA) (6.74 g, 31 mmol) in THF (15 mL) was added via syringe pump over 30 minutes. The reaction was warmed to room temperature and allowed to react for 6 hours. Next the solution was filtered through a pad of Celite and washed with Et_2O. The filtrate was then concentrated in vacuo. To the concentrated solution chloroform (25 mL) was added and a precipitate formed. The solution was filtered through Celite again, washed with chloroform, and concentrated to yield a yellow oil **3** (4.65 g, 24.2 mmol, 78% yield) with no

further purification required. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.80 – 3.69 (s, 6H), 2.21 – 2.12 (s, 3H).

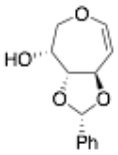
(*R*)-1-((2*S*,4*R*,5*R*)-5-ethynyl-2-phenyl-1,3-dioxolan-4-yl)ethane-1,2-diol (4)*



In a 1 L 3-neck flask, **2** (9 g, 41 mmol) was dissolved in MeOH (250 mL). Next K_2CO_3 (11 g, 82 mmol) was added and the mixture was stirred under argon. Then a reflux condenser was attached, and the solution was heated to 65 °C. The Bestmann-Ohira reagent **3** (15.75 g, 82 mmol) was dissolved in MeOH (120 mL) and added *via* syringe pump over 12 hours. After another 12 hours if stirring, the reaction was quenched with acetic acid (1 M, 82 mL). The solution was then concentrated by rotary evaporation. The concentrated solution was extracted with dichloromethane (3 x 100 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated. The resulting solid was purified by silica gel flash column chromatography (1:1→3:1 EtOAc:Hexane), yielding **4** (4.58 g, 20.6 mmol, 51% yield) as an oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.52 – 7.45 (m, 2H), 7.43 – 7.38 (m, 3H), 6.02 (s, 1H), 4.97 (dd, *J* = 5.0, 2.1 Hz, 1H), 4.25 (dd, *J* = 5.8, 5.0 Hz, 1H), 3.91 (dd, *J* = 5.8, 3.6 Hz, 1H), 3.85 (dd, *J* =11.4, 3.6 Hz, 1H), 3.76 (dd, *J* = 11.4, 5.7 Hz, 1H), 2.62 (d, *J* = 2.1 Hz, 1H), 1.57 (br, 1H). **^{13}C NMR** (151MHz, $CDCl_3$) δ 138.0, 130.0, 128.6, 126.8, 103.8, 83.3, 81.2, 75.5, 71.8, 67.5, 63.3**. FT-IR** ν_{max}/cm^{-1} 3279 (OH), 2926 (CH) **HRMS** Anal. Calcd. for $C_{13}H_{14}O_4Na$ (M+23) 257.07849; found: 235.07843 **Optical rotation** $[\alpha]_D^{20}$ -19.3 (c 0.33, $CHCl_3$)

*Experimental data of **4, 5** and **9a-b** were taken from Mr. Andrew Ephron's work. I have repeated the reactions in order to get pure products for analysis.

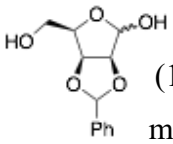
(2*S*,3a*R*,4*R*,8a*R*)-2-phenyl-3a,4,5,8a-tetrahydro-[1,3]dioxolo[4,5-*d*]oxepin-4-ol (5)*



In a 500 mL Schlenk flask, **4** (4.58 g, 20.6 mmol) was dissolved in toluene (200 mL). Then 1,4-diazabicyclo[2.2.2]octane (DABCO, 4.62 g, 41.2 mmol) and tungsten hexacarbonyl (1.81 g, 5.15 mmol) were added. Next the flask was transferred to a photoreactor, attached to a reflux condenser and stirred under a steady flow of argon. The reaction mixture was exposed to 350 nm light for 12 hours, without using the cooling fan, so that the reaction mixture was warmed to approximately 55°C. The solution was then transferred to a 500 mL round bottom flask and concentrated in vacuo. The resulting yellow oil was purified by silica gel flash column chromatography (1:3→1:1 EtOAc:Hexane), yielding **5** (1.43 g, 6.43 mmol, 31% yield) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 – 7.48 (m, 2H), 7.44 –

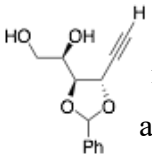
7.39 (m, 3H), 6.41 (dd, *J* = 6.3, 2.1 Hz, 1H), 6.15 (s, 1H), 5.30 (dd, *J* = 6.3, 1.8 Hz, 1H), 5.02 (dt, *J* = 9.7, 1.8 Hz, 1H), 4.54 (dddd, *J* = 7.8, 5.8, 3.9, 1.9 Hz, 1H), 4.28 (dd, *J* = 12.5, 5.3 Hz, 1H), 4.06 (dd, *J* = 9.7, 3.9 Hz, 1H), 3.79 (dd, *J* = 12.5, 8.0 Hz, 1H), 2.42 (d, *J* = 2.0 Hz). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.6, 138.7, 129.4, 128.6, 126.3, 109.3, 104.4, 82.0, 72.9, 71.7, 66.0 **FT-IR** ν_{max}/cm^{-1} 3444 (OH), 2884 (CH) **HRMS** Anal. Calcd. for $C_{13}H_{15}O_4$ (M +1) 235.09649; found: 235.09640 **Melting point** 87.5 – 88.6 °C **Optical rotation** $[\alpha]_D^{20}$ -46.0 (c 0.19, $CHCl_3$)

(3a*S*,6*R*,6a*S*)-6-(hydroxymethyl)-2-phenyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol (7a-b)



In a 250 mL round bottom flask, lyxose **6** (5.00 g, 33.3 mmol) and benzaldehyde (13.6 mL, 133 mmol) were dissolved in DMF (17.0 mL) before CSA (3.87 g, 16.7 mmol) was added. The reaction was allowed to proceed for 16 hours under a balloon of argon at which time the reaction was quenched with triethylamine (15 mL) and dichloromethane (35 mL), filtered through Celite, and concentrated in *vacuo*. The solution was then filtered through silica gel, eluting with ethyl acetate, and reconcentrated. Then, the reaction mixture was diluted with large amount of dichloromethane and water. The organic layer was washed with water for three times and the three aqueous layers were also washed with dichloromethane for three times. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The resulting solid was purified by silica gel flash column chromatography (1:1→3:1 EtOAc:Hexane), yielding white solid **7a-b** (4.07 g, 17.4 mmol, 52% yield) as an 1:1 inseparable mixture of diastereomers. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.47 – 7.36 (m, 5H), 6.52 (d, *J* = 4.3 Hz, 0.5H), 6.46 (d, *J* = 4.3 Hz, 0.5H), 5.79 (s, 0.5H), 5.72 (s, 0.5H), 5.32 (d, *J* = 4.4 Hz, 0.5H), 5.26 (d, *J* = 4.3 Hz, 0.5H), 4.85 (dd, *J* = 5.5, 3.7 Hz, 0.5H), 4.82 – 4.74 (m 1.5H), 4.59 (d, *J* = 5.5 Hz, 0.5H), 4.53 (d, *J* = 6.2 Hz, 0.5H), 4.11 (dddd, *J* = 12.3, 6.8, 5.7, 3.5 Hz, 0.5H), 3.72 (ddt, *J* = 29.0, 10.9, 5.4 Hz, 1H), 3.60 (dddd, *J* = 11.1, 8.9, 6.3, 3.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.2, 135.5, 130.1, 129.8, 128.5, 128.5, 127.0, 126.6, 106.33, 106.31, 105.65, 105.61, 101.2, 100.7, 86.2, 85.3, 81.0, 80.6, 80.0, 61.2. **FT-IR** ν_{max}/cm^{-1} 3334, 3198 (OH), 2924 (CH) **HRMS** Anal. Calcd. for $C_{12}H_{14}O_5Na$ (M +23) 261.07343; found: 261.07334 **Melting Point** 98.5 – 99.4°C **Optical rotation** $[\alpha]_D^{20}$ +25.2 (c 0.36, $CHCl_3$).

(1*R*)-1-((4*S*,5*S*)-5-ethynyl-2-phenyl-1,3-dioxolan-4-yl)ethane-1,2-diol (8a-b)



In a 50 mL 3-neck flask, **7a-b** (342 mg, 1.44 mmol) was dissolved in MeOH (6.80 mL). Then K_2CO_3 (447 mg, 3.23 mmol) was added and the mixture was stirred under argon. Next a reflux condenser was attached, and the solution was heated to 65 °C. The Bestmann-Ohira reagent **3** (552 mg, 2.87 mmol) was then dissolved in MeOH (3.40 mL) and added *via* syringe pump over 12 hours. The mixture was stirred for 12 more hours and was quenched with acetic acid (1M, 6.40 mL). The solution was then concentrated by rotary evaporation. The concentrated solution was then extracted with dichloromethane (3 x 30 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated. The resulting yellow oil was purified by silica gel flash column chromatography (7:5 EtOAc:Hexane), yielding a 1:1 mixture of diastereomers of **8a-b** (134 mg, 0.571 mmol, 40% yield) as a clear, colorless oil. Only some of the two diastereomers were successfully separated for NMR.

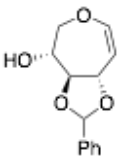
8a (less polar): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.51 – 7.47 (m, 2H), 7.40 – 7.36 (m, 3H), 6.00 (s, 1H), 4.88 (dd, *J* = 5.9, 2.1 Hz, 1H), 4.30 (dd, *J* = 6.0 , 3.7 Hz, 1H), 3.82 – 3.80 (m, 1H), 3.75 (d, *J* = 4.8 Hz, 1H), 2.63 (d, *J* = 2.1 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 135.7, 129.9, 128.5, 126.7, 104.0, 83.8, 80.6, 75.6, 70.4, 67.3, 64.0

8b (more polar): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.53 – 7.47 (m,2H), 7.40 – 7.37 (m, 3H), 6.00 (s, 1H), 4.85 (dd, *J* = 7.7, 2.0 Hz, 1H), 4.12 (dd, *J* = 7.7, 2.4 Hz, 1H), 3.82 (dd, *J* = 8.6, 4.3 Hz, 1H), 3.78 (t, *J* = 5.4 Hz, 1H), 2.58 (d, *J* = 2.1 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 136.7, 129.7, 128.4, 128.4, 126.7, 105.3, 82.4, 75.8, 69.7, 68.2, 64.5

Mixture:

FT-IR ν_{max}/cm^{-1} 3450 (OH), 3284 (CH alkyne), 2889 (CH alkane) **HRMS** Anal. Calcd. for $C_{13}H_{15}O_4$ (M +1) 235.09628; found: 235.09649, **Optical rotation** $[\alpha]_D^{20}$ +5.5 (c 0.86, $CHCl_3$).

(3a*S*,4*R*,8a*S*)-2-phenyl-3a,4,5,8a-tetrahydro-[1,3]dioxolo[4,5-*d*]oxepin-4-ol (9a-b)*



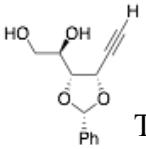
In a 50 mL Schlenk flask, **8a-b** (558 mg, 2.37 mmol) was dissolved in toluene (20 mL). Then DABCO (570 mg, 4.7 mmol) and tungsten hexacarbonyl (230 mg, 0.5925 mmol) were added and stirred. Next the flask was transferred to a photoreactor, attached to a reflux condenser and stirred under a steady flow of argon. The reaction mixture was exposed to 350 nm light for 12 hours, without using the cooling fan, so that the reaction mixture was warmed to approximately 55°C. The solution was then transferred to a 50 mL round bottom flask and concentrated by rotary evaporation. The resulting yellow oil was purified by silica gel

flash column chromatography (1:5→1:1 EtOAc:Hexane), yielding 1:1 mixture of separable diastereomers **9a-b** (0.278 g, 1.19 mmol, 50% combined yield) as a white solid. Some of the **9a** (53.9 mg, 0.23 mmol) and **9b** (59.4 mg, 0.25 mmol) were successfully separated from the mixture during the flash column chromatography for analysis.

9a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 2H), 7.40 – 7.36 (m, 3H), 6.42 (dd, *J* = 6.4, 2.0 Hz, 1H), 6.11 (s, 1H), 5.19 (dd, *J* = 6.5, 1.6 Hz, 1H), 4.66 (dt, *J* = 9.7, 1.8 Hz, 1H), 4.27 (dt, *J* = 7.4, 2.6 Hz, 1H), 4.17 (dd, *J* = 13.4, 2.1 Hz 1H), 4.16 (dd, *J* = 9.2, 7.5 Hz 1H), 4.03 (dd, *J* = 13.3, 3.2 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.2, 138.3, 129.4, 128.5, 126.3, 107.1, 104.6, 86.0, 75.4, 73.5, 72.7 **FT-IR** ν_{max}/cm^{-1} 3456 (OH), 2919, 2852 (CH) **HRMS** Anal. Calcd. for $C_{13}H_{15}O_4$ (M +1) 235.09649; found: 235.09643 **Melting Point** 84.6 **–** 85.4°C **Optical rotation** $[\alpha]_D^{20}$ -10.0 (c 0.21, $CHCl_3$).

9b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.47 (m, 2H), 7.40-7.38 (m, 3H), 6.45 (dd, *J* = 6.5, 2.0 Hz, 1H), 6.08 (s, 1H), 5.25 (dd *J* = 6.4, 1.4 Hz, 1H), 4.72 (dt, *J* = 9.7, 1.8 Hz, 1H), 4.18 (td, *J* = 10.4, 3.0 Hz, 1H), 4.13 (ddd, *J* = 13.2, 2.4, 1.1 Hz, 1H), 4.08 (dd, *J* = 13.4, 3.1 Hz, 1H), 4.05 (dd, *J* = 9.7, 7.5 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.3, 149.7, 129.4, 128.4, 126.5, 106.1, 104.4, 84.0, 75.6, 74.9, 73.3 **FT-IR** ν_{max}/cm^{-1} 3537 (OH), 2912 (CH) **HRMS** Anal. Calcd. for $C_{13}H_{15}O_4$ (M +1) 235.09649; found: 235.09654 **melting point** 80.8 – 81.3 °C **optical rotation** **[**$\alpha]_D^{20}$ +30.0 (c 0.16, $CHCl_3$)

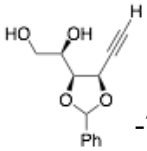
(*R*)-1-((2*S*,4*R*,5*S*)-5-ethynyl-2-phenyl-1,3-dioxolan-4-yl)ethane-1,2-diol (10)



In a 50 mL round bottom flask, nBuLi (1.58 M in hexanes, 4.3 mL, 6.76 mmol) was slowly added to a solution of *i*Pr$_2$NH (0.95 ml, 6.76 mmol) in THF (6 mL) at -78 °C. The resulting mixture was stirred for 20 min before a solution of $TMSCHN_2$ (2.0 M in hexanes, 1.27 mL, 2.54 mmol) was added dropwise at -78 °C. After stirring for another 20 min, a solution of benzaldehyde acetal protected ribose **2** (0.4 g, 1.69 mmol) in THF (2 mL) was added. The resulting mixture was stirred at -78 °C for 1 hour and then heated at 65°C for 2h. The reaction mixture was quenched with crude ice and *sat. aq.* NH_4Cl. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude product was a red residue containing a mixture of terminal alkynyl diol and trimethylsilyl-substituted alkyne, which was dissolved in MeOH (0.65 mL) and *aq.* K_2CO_3 (10% w/w, 0.65 mL) and stirred for 2 h. The reaction was carefully neutralized with *aq.* HCl (1 M). The aqueous layer was extracted with EtOAc and the combined

organic extracts were dried over Na_2SO_4 and concentrated by rotary evaporation. Purification by flash column chromatography (2:1 Ether/Hexane → 1:1 EtOAc/Hexane) afforded **10** (0.182 g, 0.78 mmol, 46% yield) as a yellow oil. **^{1}H NMR** (400 MHz, CDCl3) δ 7.54 – 7.49 (m, 2H), 7.42 – 7.37 (m, 3H), 5.83 (s, 1H), 5.02 (dd, J = 6.3, 2.2 Hz, 1H), 4.22 (dd, J = 8.7, 6.3 Hz, 1H), 4.16 (ddd, J = 8.6, 5.1, 3.0 Hz, 1H), 3.92 (dd, J = 11.6, 3.0 Hz, 1H), 3.81 (dd, J = 11.6, 5.1 Hz, 1H), 2.71 (d, J = 2.2 Hz, 1H), 2.44 (br. 1H). **^{13}C NMR** (151Hz, $CDCl_3$) δ 136.3, 129.9, 128.6, 127.2, 105.3, 79.4, 78.9, 77.0, 71.2, 68.6, 64.0. **FT-IR** ν_{max}/cm^{-1} 3394 (OH), 3285 (CH alkyne), 2926 (CH alkane). **HRMS** Anal. Calcd. for $C_{13}H_{14}O_4Na$ (M +23) 257.07843; found: 257.07813. **Optical rotation** $[\alpha]_D^{20}$ +0.9 (c 0.60, $CHCl_3$).

(1*R*)-1-((4*S*,5*R*)-5-ethynyl-2-phenyl-1,3-dioxolan-4-yl)ethane-1,2-diol (11a-b)

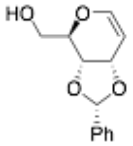


In a 100 mL round bottom flask, nBuLi (1.45 M in hexane, 12.17 mL, 17.64 mmol) was slowly added to a solution of *i*Pr_2NH (2.47 ml, 17.64 mmol) in THF (14.8 mL) at -78 °C. The resulting mixture was stirred for 20 min before a solution of $TMSCHN_2$ (2.0 M in hexanes, 3.78 mL, 7.56 mmol) was added dropwise at -78°C. After stirring for another 20 min, a solution of benzaldehyde acetal protected lyxose **7a-b** (1.15 g, 4.85 mmol) in THF (5.8 mL) was added. The resulting mixture was stirred at -78 °C for 1 hour and then heated at 65 °C for 3h. The reaction mixture was quenched with crude ice and *sat. aq.* NH_4Cl. The aqueous layer was extracted with EtOAc and the combined organic extracts were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude product was a red residue containing a mixture of terminal alkynyl diol and trimethylsilyl-substituted alkyne, which was dissolved in MeOH (1.68 mL) and *aq.* K_2CO_3 (10% w/w, 1.68 mL) and stirred for 2 h. The reaction was carefully neutralized with *aq.* HCl (1 M). The aqueous layer was extracted with EtOAc and the combined organic extracts were dried over Na_2SO_4 and concentrated by rotary evaporation. Purification by flash column chromatography (5:3 Hexane/EtOAc) afforded a 1:1 mixture of diastereomers of **11a-b** (0.555 g, 2.37 mmol, 49% yield) as a brown oil. A second silica gel flash column chromatography (2:1 Pentane/Hexane) separated some of the two diastereomers, which were only sufficient for proton NMR.

7a (less polar): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.50 – 7.42 (m, 2H), 7.41 – 7.33 (m, 3H), 6.22 (s, 1H), 5.05 (dd, J = 6.3, 2.2 Hz, 1H), 4.30 (ddd, J = 7.0, 6.1, 1.0 Hz, 1H), 4.14 (td, J = 6.1, 3.8 Hz, 1H), 3.80 (dd, J = 11.6, 3.7 Hz, 1H), 3.72 (dd, J = 11.7, 5.4 Hz, 1H), 2.69 (d, J = 2.3, 1H), 2.69 (d, J = 2.3 Hz, 1H).

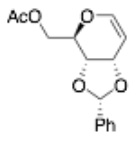
7b (more polar): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 – 7.55 (m, 2H), 7.43 – 7.38 (m, 3H), 5.85 (s, 1H), 4.95 (dd, *J* = 6.6, 2.2 Hz, 1H), 4.29 (t, *J* = 6.6 Hz, 1H), 4.18 (ddd, *J* = 6.5, 5.3, 3.7 Hz, 1H), 3.85 (dd, *J* = 11.7, 3.8 Hz, 1H), 3.77 (dd, *J* = 11.6, 5.3 Hz, 1H), 2.68 (d, *J* = 2.2 Hz, 1H).
Mixture:
^{13}C NMR (151 MHz, $CDCl_3$) δ 137.1, 136.1, 130.1, 129.8, 128.68, 128.66, 127.4, 126.6, 104. 9, 103.8, 79.1, 78.7, 78.4, 78.3, 77.7, 77.3, 71.9, 71.6, 67.9, 67.6, 63.49, 63.48. **FT-IR** ν_{max}/cm^{-1} 3386 (OH), 3286 (CH alkyne), 2930 (CH alkane) **HRMS** Anal. Calcd. for $C_{13}H_{15}O_4Na$ (M +23) 257.07843; found: 257.07813 **Optical rotation** $[\alpha]_D^{20}$ -8.3 (c 0.42, $CHCl_3$).

((2*S*,3a*S*,4*R*,7a*S*)-2-phenyl-3a,7a-dihydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-4-yl)methanol (12)



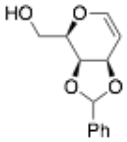
In a 25 mL Schlenk flask, **10** (0.1026 g, 0.438 mmol) was dissolved in toluene (3.5 mL). Then, DABCO (0.098g, 0.876mmol) and $W(CO)_6$ (0.0385 g, 0.1095 mmol) were added and stirred. Next the flask was transferred to a photoreactor, attached to a reflux condenser and stirred under a steady flow of argon. The reaction mixture was exposed to 350 nm light for 12 hours, without using the cooling fan, so that the reaction mixture was warmed to approximately 55°C. The resulting mixture was then transferred to a round bottom flask and concentrated by rotary evaporation. Purification by flash column chromatography (hexane/EtOAc 1:1) afforded **12** (0.0622 g, 0.263 mmol, 58% yield) as a brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 7.50 – 7.42 (m, 2H), 7.42 – 7.35 (m, 3H), 6.71 (d, *J* = 6.0 Hz, 1H), 5.85 (s, 1H), 5.26 (dd, *J* = 5.9, 4.7, 1H), 4.50 (ddd, *J* = 5.8, 4.6, 1.1 Hz, 1H), 4.15 (dd, *J* = 10.0, 6.0 Hz, 1H), 4.06 (dd, *J* = 12.2, 4.0 Hz, 1H), 3.88 (dd, *J* = 12.1, 4.9 Hz, 1H), 3.56 (ddd, *J* = 10.0, 5.3, 2.7 Hz, 1H). **^{13}C NMR** (151Hz, $CDCl_3$) *δ* 148.6, 136.6, 129.7, 128.6, 127.0, 103.3, 98.8, 76.2, 70.1, 69.9, 61.9. **FT-IR** ν_{max}/cm^{-1} 3423 (OH), 2924, 2883 (CH). **HRMS** Anal. Calcd. for $C_{13}H_{14}O_4Na$ (M +23) 257.07843; found: 257.07814. **Optical rotation** $[\alpha]_D^{20}$ +195.1 (c 1.15, $CHCl_3$).

Acetylation of 12



In a 10 mL round bottom flask, **12** (47 mg, 0.20 mmol) was dissolved in DCM (4 mL). Acetic anhydride (0.76 mL, 8.0 mmol) and pyridine (0.32 mL, 4.0 mmol) were added. The mixture was stirred overnight to give the **acetylated 12**. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 7.40 – 7.28 (m, 5H), 6.67 (d, *J* = 6.0 Hz, 1H), 5.83 (s, 1H), 5.24 (dd, *J* = 6.0, 4.6 Hz, 1H), 4.52 (dd, *J* = 12.3, 2.3 Hz, 1H), 4.48 (ddd, *J* = 5.9, 4.6, 1.2 Hz, 1H), 4.31 (dd, *J* = 12.3, 5.8 Hz, 1H), 4.09 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.65 (ddd, *J* = 10.1, 5.8, 2.3 Hz, 1H), 2.06 (s, 3H).

((3a*R*,4*R*,7a*R*)-2-phenyl-3a,7a-dihydro-4*H*-[1,3]dioxolo[4,5-*c*]pyran-4-yl)methanol (13a-b)

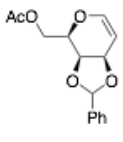


In a 25 mL Schlenk flask**, 11a-b** (0.0819 g, 0.346 mmol) was dissolved in toluene (2.6 mL). Then DABCO (0.0776g, 0.692 mmol) and $W(CO)_6$ (0.049 g, 0.138 mmol) were added and stirred. Next the flask was transferred to a photoreactor, attached to a reflux condenser and stirred under a steady flow of argon. The reaction mixture was exposed to 350 nm light for 27 hours, without using the cooling fan, so that the reaction mixture was warmed to approximately 55°C. The resulting mixture was the transferred to a round bottom flask and concentrated by rotary evaporation. Purification by flash column chromatography (4:1 Hexane/EtOAc) afforded thick white oil **13a-b** (0.036 g, 0.154 mmol, 44% yield) as 1:1 ratio of two separable diastereomers. Some of the **13a** (13 mg, 0.055 mmol) and **13b** (20 mg, 0.085 mmol) were successfully separated during the flash column chromatography for analysis.

13a (less polar)**: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 2H), 7.41 – 7.36 (m, 3H), 6.75 (d, *J* = 6.2 Hz, 1H), 6.01 (s, 1H), 5.07 (dd, *J* = 6.4, 3.0 Hz, 1H), 4.87 (ddd, *J* = 6.2, 3.1, 1.1 Hz, 1H), 4.45 (d, *J* = 6.3 Hz, 1H), 4.05 (t, *J* = 5.6 Hz, 1H), 4.01 (dd, *J* = 11.8, 8.1 Hz, 1H), 3.90 (ddd, *J* = 11.6, 8.2, 3.6 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.7, 137.2, 129.7, 128.6, 126.9, 102.5, 99.7, 76.0, 73.8, 70.1, 63.6. **FT-IR** ν_{max}/cm^{-1} 3422 (OH), 2923, 2854 (CH) **HRMS** Anal. Calcd. for $C_{13}H_{14}O_4Na$ (M +23) 257.07843; found: 257.07814 **Optical rotation** $[\alpha]_D^{20}$ -2.6 (c 0.34, $CHCl_3$).

13b (more polar)**: ^{1}H NMR** (600 MHz, $CDCl_3$) *δ* 7.51 – 7.44 (m, 2H), 7.42 – 7.33 (m, 3H), 6.50 (d, *J* = 6.2 Hz, 1H), 5.94 (s, 1H), 4.95 (ddd, *J* = 6.3, 3.1, 1.4 Hz, 1H), 4.80 (dd, *J* = 6.8, 3.1 Hz, 1H), 4.44 (dt, *J* = 6.8, 1.5 Hz, 1H), 4.12 (ddd, *J* = 7.3, 4.0, 1.7 Hz, 1H), 4.07 (dd, *J* = 11.5, 7.3 Hz, 1H), 3.90 (d, *J* = 11.7 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) *δ* 145.2, 137.4, 129.7, 128.5, 127.3, 105.6, 102.3, 75.0, 74.9, 68.6, 63.1. **FT-IR** ν_{max}/cm^{-1} 3404 (OH), 2923, 2853 (CH). **HRMS** Anal. Calcd. for $C_{13}H_{14}O_4Na$ (M +23) 257.07843; found: 257.07814 **Optical rotation** $[\alpha]_D^{20}$ -43.6 (c 0.41, $CHCl_3$).

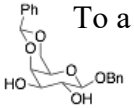
Acetylation of 13b



In a 5 mL round bottom flask, **13b** (4.1 mg, 0.018 mmol) was dissolved in DCM (0.4 mL). Acetic anhydride (0.07 mL, 0.70 mmol) and pyridine (0.03 mL, 0.35 mmol) were added. The mixture was stirred overnight to give the **acetylated 13b**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.35 – 7.32 (m, 5H), 6.43 (d, *J* = 6.3 Hz, 1H), 5.91 (s, 1H), 4.91 (ddd, *J* =

6.3, 3.1, 1.3 Hz, 1H), 4.74 (dd, *J* = 6.8, 3.1 Hz, 1H), 4.45 – 4.35 (m, 3H), 4.19 (ddd, *J* = 8.1, 4.4, 1.7 Hz, 1H), 2.07 (s, 3H).

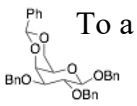
(2*S*,4a*R*,6*R*,7*R*,8*R*,8a*R*)-6-(benzyloxy)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxine-7,8-diol (15)[15]



To a solution of **14** (3.0 g, 7.7 mmol) in dichloromethane (60 mL) were added BnOH (4.0 mL) and BF_3•Et_2O (9.5 mL, 77 mmol) at 0°C under an atmosphere of argon. After the reaction mixture was stirred at 0°C for 3.5 h, it was diluted with dichloromethane and washed with *sat. aq.* $NaHCO_3$. The aqueous layer was extracted with dichloromethane for three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in *vacuo*. Purification by flash column chromatography (2:1 Hexane/EtOAc) afforded colorless syrup (1.6 g, 3.65 mmol). The syrup was dissolved in MeOH (40 mL) and KOH (19.9 mg, 0.3 mmol) was added at room temperature. The mixture was stirred for 2.5 hours before concentrated in *vacuo* to give the tetrol.

To a solution of the crude tetrol in DMF (48 mL) were added benzaldehyde dimethyl acetal (2.74 mL, 18.25 mmol) and DL-10-CSA (424 mg, 1.825 mmol) at room temperature. The mixture was then heated at 80°C for 16 h. After completion of the reaction, the mixture was diluted with EtOAc and washed with *sat. aq.* $NaHCO_3$. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in *vacuo*. Purification by flash column chromatography (EtOAc) afforded **15** (3.65 mmol, 70% yield) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.35 (m, 10H), 5.58 (s, 1H), 5.01 (d, *J* = 11.7 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.45 – 4.32 (m, 2H), 4.23 (d, *J* = 3.8 Hz, 1H), 4.16 – 4.06 (m, 1H), 3.83 (t, *J* = 8.7 Hz, 1H), 3.70 (td, *J*= 9.4, 3.8 Hz, 1H), 3.55 – 3.46 (m, 2H), 2.53 – 2.34 (m, 2H).

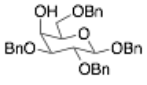
(2*S*,4a*R*,6*R*,7*R*,8*S*,8a*S*)-6,7,8-tris(benzyloxy)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxine (16)[15]



To a solution of **15** (0.19 g, 0.53 mmol) in DMF (2.5 mL) was added 60% NaH (0.08 g, 1.86 mmol) at 0°C and the mixture was stirred at room temperature for 30 min. Then BnBr (0.3 mL, 1.86 mmol) was added at 0°C and the reaction mixture was stirred at room temperature for 1 h. After completion of the reaction, EtOH (1.3 mL) was added at 0°C and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was washed

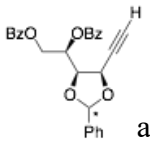
twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in *vacuo*. Purification by flash column chromatography (3:1 Hexane: EtOAc) afforded **16** (0.284 g, 0.538 mmol, 99% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 – 7.27 (m, 20H), 5.51 (s, 1H), 5.01 (d, *J* = 12.1 Hz, 1H), 4.95 (d, *J* = 10.7 Hz, 1H), 4.82 – 4.78 (m, 1H), 4.76 (d, *J* = 10.6 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 7.5 Hz, 1H), 4.35 (dd, *J* = 12.3, 1.6 Hz, 1H), 4.13 – 4.10 (m, 1H), 4.04 (dd, *J* = 12.2, 1.8 Hz, 1H), 3.93 (dd, *J* = 9.7, 7.8 Hz, 1H), 3.56 (dd, *J* = 9.7, 3.7 Hz, 1H), 3.33 (d, *J* = 1.4 Hz, 1H).

(2*R*,3*S*,4*S*,5*R*,6*R*)-4,5,6-tris(benzyloxy)-2-((benzyloxy)methyl)tetrahydro-2*H*-pyran-3-ol (17)[15]



To a mixture of **16** (0.324 g, 0.602 mmol) in THF (17 mL) were added BH_3•NME_3 (0.285 g, 3.91 mmol), $AlCl_3$ (0.52 g, 3.91 mmol), and activated 4Å MS (0.95 g) at 0°C under an atmosphere of argon. The mixture was stirred at room temperature for 18 hours before diluted with EtOAc and saturated *aq.* $NaHCO_3$. The aqueous layer was washed twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in *vacuo*. Purification by flash column chromatography (8:1:2 Toluene: Ether: Hexane -> 1:1 Ether: Hexane) afforded **17** (0.229 g, 0.423 mmol, 70% yield) as colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 20H), 4.99 (d, *J* = 12.0 Hz, 1H), 4.93 (d, *J* = 10.9 Hz, 1H), 4.76 (d, *J* = 11.5 Hz, 1H), 4.69 (d, *J* = 11.9 Hz, 1H), 4.73 (s, 2H), 4.63 (s, 2H), 4.48 (d, *J* = 7.7 Hz, 1H), 4.12 – 3.98 (m, 1H), 3.86 – 3.71 (m, 3H), 3.58 (t, *J* = 5.9 Hz, 1H), 3.51 (dd, *J* = 9.4, 3.4 Hz, 1H), 2.54 (dd, *J* = 2.3, 1.1 Hz, 1H).

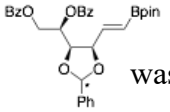
(1*R*)-1-((4*R*,5*R*)-5-ethynyl-2-phenyl-1,3-dioxolan-4-yl)ethane-1,2-diyl dibenzoate (18)



In a solution of **11** (0.36 g, 1.537 mmol) in dichloromethane (3.6 mL), pyridine (0.62 mL, 7.7 mmol) was added and the mixture was cooled to 0°C under an atmosphere of argon. Then, BzCl (0.54 mL, 4.65 mmol) was added over 30 min and the reaction mixture was allowed to reach room temperature After 5.5 hours over stirring, the reaction was quenched by ice-cold saturated *aq.* $NaHCO_3$ (4 mL). The phases were separated, and the organic layer was washed with saturated *aq.* $NaHCO_3$ twice and brine once. The organic layer was dried over Na_2SO_4, filtered, and concentrated in *vacuo*. Purification by flash column chromatography (10:1 Hexane: EtOAc) afforded **18** (0.425 g, 0.96 mmol, 63% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 – 8.00 (m, 5H), 7.61 – 7.54 (m, 2H), 7.51 – 7.37 (m, 8H), 6.38 (s, 1H),

5.90 (q, *J* = 5.2 Hz, 1H), 5.20 (dd, *J* = 6.4, 2.3 Hz, 1H), 4.79 – 4.68 (m, 3H), 2.63 (d, *J* = 2.3, 1H).

(1*R*)-1-((4*R*,5*R*)-2-phenyl-5-((*E*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-1,3-dioxolan-4-yl)ethane-1,2-diyl dibenzoate (19)

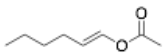


In a 5 mL round bottom flask under an atmosphere of argon, **18** (0.18 g, 0.4 mmol) was dissolved in dichloromethane (0.4 mL) and cooled to 0°C. H-Bpin (0.09 mL, 0.6 mmol) was then added dropwise to the reaction mixture. After stirring for 1 min, the reaction mixture was transferred via syringe to another 5 mL round bottom flask, which was immersed in an ice bath, containing Cp_2ZrHCl (20 mg, 0.08 mmol). The mixture was slowly heated to 60°C, and the stirring was continued for 22 h. Next, the reaction mixture was quenched with H_2O (0.4 mL) and extracted with ether twice. The combined organic layers were washed with water for three times, dried over Na_2SO_4, filtered, and concentrated in *vacuo*. Purification by flash column chromatography (5:1 Hexane: EtOAc) afforded **19** (0.238 g, 0.042 mmol, 11% yield) and recover the starting material **18** (0.036 g, 0.081 mmol, 20%). 1H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.95 (m, 5H), 7.52 – 7.35 (m, 10H), 6.65 (dd, *J* = 18.1, 5.9 Hz, 1H), 6.41 (s, 1H), 5.81 (dd, *J* = 18.0, 1.5 Hz, 1H), 5.61 (ddd, *J* = 6.7, 4.9, 3.4 Hz, 1H), 4.92 (ddd, *J* = 7.1, 5.8, 1.5 Hz, 1H), 4.71 (dd, *J* = 6.9, 3.5 Hz, 1H), 4.66 (dd, *J* = 11.6, 5.0 Hz, 1H), 4.59 (dd, *J* = 11.5, 6.6 Hz, 1H).

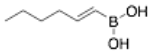
(*E*)-trifluoro(hex-1-en-1-yl)- λ^4-borane, potassium salt (21)

To a 50 mL round bottom flask with neat catecholborane (2.13 mL, 20 mmol) was slowly added **20** (2.25 mL, 20 mmol) at 0°C with vigorous stirring. The solution was heated at 75°C for 4 hours. The reaction mixture was then cooled to room temperature and opened to air. KHF_2 (6.25 g, 80 mmol) was dissolved in H_2O (17 mL) and the aqueous solution was added to the reaction mixture. The mixture was stirred for 5 hours before the resulting precipitate was vacuum filtered and washed with cold methanol. The white solid was dissolved in hot acetone (100 mL) and recrystallized. The precipitate was vacuum filtered, washed with EtO_2, and dried under high vacuum overnight to afford white crystal **21** (1.74 g, 9.16 mmol, 46% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.41 (dt, *J* = 17.4, 6.4 Hz, 1H), 5.20 (dqd, *J* = 17.5, 3.6, 1.9 Hz, 1H), 1.83 (d, *J* = 6.7 Hz, 2H), 1.25 – 1.18 (m, 4H), 0.85 – 0.78 (m, 3H).

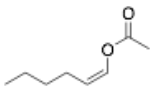
(*E*)-hex-1-en-1-yl acetate (E-22)

 In a round bottom flask under an atmosphere of O_2, **21** (0.21 g, 1.11 mmol), MeCOOK (0.055 g, 0.555 mmol), CuBr (8 mg, 0.0555 mmol), DMAP (0.014 g, 0.111 mmol), and activated 4 Å MS (0.43 g) were added to MeCN (4.5 mL). The mixture was then stirred at 60°C for 24 h. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite and washed with dichloromethane. The filtrate was concentrated. Purification by flash column chromatography (Hexane -> 50:1 Hexane: EtOAc) afforded **E-22** (0.037 g, 0.26 mmol, 24% yield). 1H NMR (400 MHz, $CDCl_3$) δ 7.05 (ddt, *J* = 12.4, 6.6, 1.5 Hz, 1H), 5.43 – 5.31 (m, 1H), 2.09 (s, 3H), 1.98 (qd, *J* = 7.3, 1.5 Hz, 2H), 1.38 – 1.18 (m, 4H), 0.98 – 0.83 (m, 3H).

(*E*)-hex-1-en-1-ylboronic acid (23)

 To a 250 mL round bottom flask containing a mixture of 21 (4.44 g, 23.36 mmol) and SiO_2 (1.4 g, 23.36 mmol) under an atmosphere of argon, H_2O (70 mL) was added in one portion. The reaction was stirred at room temperature for 1 h. Then, the reaction mixture was filtered to remove the silica gel, and the filter cake was rinsed with EtOAc. The mixture was separated, and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The solid was furthered dried overnight under high vacuo to afford the product **23** (2.08 g, 16.0 mmol, 69% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (dt, *J* = 17.6, 6.5 Hz, 1H), 5.53 (dt, *J* = 17.6, 1.5 Hz, 1H), 2.29 – 2.14 (m, 2H), 1.44 (dtd, *J* = 8.1, 6.8, 5.3 Hz, 2H), 1.34 (h, *J* = 7.3 Hz, 2H), 0.91 (t, *J* = 7.2 Hz, 3H)

(*Z*)-hex-1-en-1-yl acetate (Z-22)

 Under an atmosphere of argon, **23** (0.1773 g, 1.385 mmol), $PhI(OCOCH_3)_2$ (0.491 g, 1.524 mmol), and NaI (0.228 g, 1.524 mmol) were dissolved in DMF (8.3 mL). The reaction mixture was stirred at room temperature. for 21 h. Next, the mixture was extracted with EtO_2, and the extract was washed with water and dried over Na_2SO_4, filtered, and concentrated in *vacuo*. Purification by flash column chromatography (50:1 Hexane: EtOAc) afforded **Z-22** (0.136 g, 0.96 mmol, 69% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (dt, *J* = 6.4, 1.5 Hz, 1H), 4.84 (td, *J* = 7.4, 6.4 Hz, 1H), 2.12 (s, 3H), 1.38 – 1.28 (m, 4H), 0.95 – 0.82 (m, 3H).

hex-1-en-1-yl acetate (22)

A mixture of hexanal (14.4 mL, 120 mmol), acetic anhydride (27.2 mL, 288 mmol), and potassium acetate (2.35 g, 24 mmol) was dissolved in EtOAc (50 mL) under an atmosphere of argon. The solution was heated to 145°C and stirred for 20 hours. The reaction mixture was diluted with EtOAc and allowed to cool to room temperature. The yellow cloudy mixture was washed with H_2O (3×20 mL) and *aq.* $NaHCO_3$ (3×20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The resulting yellow liquid was distilled under vacuum while heated by a heat gun. The reflux ring was too low for successful distillation and only some clear liquid of **22** (E: Z=5: 4, 2.87 g, 20.2 mmol, 17% yield) was distilled, leaving the undistilled yellow liquid of **22** (11.5 g, 80.8 mmol, 67% yield). The NMR spectra of the two look very similar. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (dt, *J* = 12.4, 1.5 Hz, 1H), 6.96 (dt, *J* = 6.4, 1.6 Hz, 0.8H), 5.38 (dt, *J* = 12.4, 7.5 Hz, 1H), 4.83 (td, *J* = 7.5, 6.4 Hz, 0.8H), 2.11 (s, 2.4H), 2.08 (s, 3H), 1.38 – 1.23 (m, 7.2H), 0.93 – 0.81 (m, 5.4H).

(3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-2,2,7,7-tetramethyl-5-((vinyloxy)methyl)tetrahydro-5*H*-bis([1,3]dioxolo)[4,5-*b*:4',5'-*d*]pyran (26)

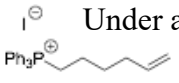
In a 5ml round bottom flask under an atmosphere of argon, $[Ir(cod)Cl]_2$ catalyst (7.0 mg, 0.01 mmol) and Na2CO3 (64 mg, 0.6 mmol) were dissolved in toluene (1 mL). vinyl acetate (0.19 mL, 2.0 mmol) and 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose (0.26 g, 1.0 mmol) was added to the mixture. It was then stirred at 100°C for 2 hours, before quenched with ether and concentrated in *vacuo*. Purification by flash column chromatography (5:1 Hexane: EtOAc) afforded **24** (0.135 g, 0.47 mmol, 47% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (dd, *J* = 14.3, 6.8 Hz, 1H), 5.54 (d, *J* = 5.0 Hz, 1H), 4.62 (dd, *J* = 7.9, 2.5 Hz, 1H), 4.32 (dd, *J* = 5.0, 2.4 Hz, 1H), 4.26 (dd, *J* = 7.9, 1.9 Hz, 1H), 4.22 (dd, *J* = 14.3, 2.2 Hz, 1H), 4.05 (td, *J* = 5.4, 2.8 Hz, 1H), 4.01 (dd, *J* = 6.9, 2.2 Hz, 2H), 3.90 – 3.80 (m, 3H), 1.53 (s, 4H), 1.45 (s, 4H), 1.34 (s, 4H), 1.32 (s, 4H).

6-iodohex-1-ene (29)[29]

In a 500 mL round bottom flask, **28** (6 mL, 50 mmol) was added to a mixture of PPh3 (19.0 g, 72 mmol), imidazole (5.0 g, 73 mmol), and iodine (18.0 g, 71 mmol) in dichloromethane (200 mL) at 0°C. The reaction mixture was stirred for an hour at 0°C under an atmosphere of argon. The mixture was then slowly warmed to room temperature and continue

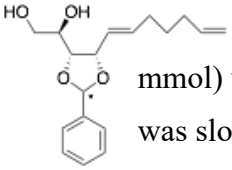
stirred for 27 hours. The resultant mixture was filtered, and the filtrate was concentrated. The residue was taken up in petroleum ether and again filtered. The filtrate was concentrated in *vacuo.* Purification by flash column chromatography (Pentane) afforded **29** (4.9 g, 23.33 mmol, 47% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.02 (ddt, *J* = 17.1, 2.0, 1.4 Hz, 1H), 4.97 (ddt,*J* = 10.2, 2.2, 1.2 Hz, 1H), 3.19 (t, *J* = 7.0 Hz, 2H), 2.13 – 2.02 (m, 2H), 1.92 – 1.77 (m, 2H), 1.58 – 1.44 (m, 2H).

hex-5-en-1-yltriphenylphosphonium iodide (30)



Under an atmosphere of argon, **29** (4.9 g, 23.33 mmol) and PPh_3 (9.18 g, 35.0 mmol) were dissolved in MeCN (110 mL) in a 250 mL round bottom flask. The flask was attached to water condenser and the mixture was heated to 82°C. The reaction mixture was continue stirred at this temperature for three days. All the MeCN was evaporated over the weekend and left with yellow solid. The solid was washed with EtO_2 and vacuum filtered to afford **30** (11 g, 23.3 mmol, 99% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.62 (m, 15H), 5.61 (ddt, *J* = 16.8, 10.1, 6.7 Hz, 1H), 4.92 – 4.80 (m, 2H), 3.62 – 3.49 (m, 2H), 2.02 (q, 2H), 1.79 – 1.67 (m, 2H), 1.62 – 1.55 (m, 2H).

(*R*)-1-((2*S*,4*R*,5*S*)-5-((*E*)-hepta-1,6-dien-1-yl)-2-phenyl-1,3-dioxolan-4-yl)ethane-1,2-diol (31)



In a 50 mL round bottom flask under an atmosphere of argon, **30** (2.78 g, 5.9 mmol) was dissolved in THF (19 mL) at 0°C. nBuLi (2.07 M, 2.7 mL, 5.58 mmol) was slowly added to reaction mixture at 0°C. Next, the ice bath was removed, and the mixture was stirred at room temperature for 30 minutes. After re-cooling to 0°C, a solution of **2** (400 mg, 1.69 mmol, dr = 5:1) in THF (1 mL) was slowly added to the red reaction mixture. The ice bath was removed, and the mixture was stirred for 20 hours. Next, the reaction was quenched with sat. *aq.* NH_4Cl and diluted with Et_2O. The aqueous layer was washed with Et_2O three times and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in *vacuo*. Purification by flash column chromatography (2:1 -> 3:2 Hexane: EtOAc) afforded two diastereomers of **31a-b** (265 mg, 0.871 mmol, 52% yield) as colorless oil. Some of the diastereomers **31a** (78.0 mg, 0.256 mmol, 15%) and **26b** (58.0 mg, 0.191 mmol, 11%) were successfully separated for NMR analysis, showing that the diastereocenter is at the acetal carbon, inherited from the starting material **2**.

31a (less polar): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (dt, *J* = 7.7, 2.1 Hz, 2H), 7.40 – 7.33 (m, 4H), 6.14 (d, *J* = 1.6 Hz, 1H), 5.91 (dtd, *J* = 15.3, 7.2, 6.8, 2.3 Hz, 1H), 5.79 (dtd, *J* = 17.3, 6.8, 3.1 Hz, 1H), 5.71 (ddq, *J* = 15.1, 7.5, 1.7 Hz, 1H), 5.02 (dd, *J* = 17.1, 1.8 Hz, 0H), 4.96 (dt, *J* = 12.3, 2.2 Hz, 1H), 4.81 – 4.76 (m, 1H), 4.10 (ddd, *J* = 8.5, 6.0, 2.3 Hz, 1H), 3.84 (dt, *J* = 11.2, 3.2 Hz, 1H), 3.80 (td, *J* = 5.8, 3.0 Hz, 1H), 3.71 (ddd, *J* = 11.3, 5.8, 3.8 Hz, 2H), 2.17 – 2.08 (m, 2H), 2.07 (t, *J* = 7.0 Hz, 2H), 1.51 (dq, *J* = 14.0, 7.2 Hz, 3H).

31b (more polar): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 – 7.44 (m, 2H), 7.39 – 7.35 (m, 3H), 5.91 (ddd, *J* = 15.1, 7.4, 6.1 Hz, 1H), 5.78 (s, 1H), 5.82 – 5.72 (m, 1H), 5.67 (ddt, *J* = 15.4, 7.8, 1.5 Hz, 1H), 4.99 (dt, *J* = 17.2, 1.9 Hz, 1H), 4.94 (dt, *J* = 10.2, 1.6 Hz, 1H), 4.72 (t, *J* = 7.4 Hz, 1H), 4.12 (dd, *J* = 8.1, 6.9 Hz, 1H), 3.80 (dd, *J* = 6.7, 2.3 Hz, 2H), 3.78 (d, *J* = 3.3 Hz, 1H), 3.70 (ddd, *J* = 12.2, 6.5, 1.2 Hz, 1H), 2.11 (q, *J* = 7.3 Hz, 2H), 2.05 (q, J = 6.8 Hz, 2H), 1.49 (p, J = 7.5 Hz, 2H).

Mixture: HRMS Anal. Calcd. for $C_{18}H_{24}O_4Na$ (M +23) 327.15668; found: 327.15671.

Chapter 4: Reference

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