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Alice Long April 1, 2020

Development and Optimization of Monosubstituted and Disubstituted Alkene Synthesis for Future Intramolecular Alkene Hydroalkoxylation Reactions

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2020

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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

Development and Optimization of Monosubstituted and Disubstituted Alkene Synthesis for Future Intramolecular Alkene Hydroalkoxylation Reactions

By Alice Long

Chapter 1: Brevenal, Brevetoxin, and other marine ladder-frame polyether natural products

Brevenal, a fused polycyclic ether produced by the same dinoflagellate *Karenia brevis,* acts as an antagonist to brevetoxin reducing the effects of neurotoxic shellfish poisoning and making it a potential treatment option for organisms exposed to brevotoxin and other mucociliary diseases such as cystic fibrosis. Our research will explore the formation of six- and seven-membered ethers through an intramolecular alkenyldiol cyclization for future one-step cyclization cascade of the polycyclic ether structure in fused polycyclic ether natural products.

Chapter 2: Substrate synthesis for intramolecular cyclization reactions of alkenyldiols

This chapter focuses on the development of substrates (i.e monosubstituted alkenes and disubstituted alkenes) for intramolecular cyclization reactions. This chapter explores the synthetic route for substrates for future one-step cyclization reactions with various catalysts. Furthermore, this chapter explores future direction for cyclization reactions.

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Acknowledgements

First, I would like to express my deepest gratitude for my advisor Dr. Frank McDonald. He has served as a great mentor to me in helping strengthen my chemistry research and has given me the opportunity to develop myself as a scientist. Working in the McDonald laboratory has provided me a space that has allowed me to grow as a leader and work collaboratively in reaching a shared goal: our passion to do chemistry. This journey has inspired me to go into the organic chemistry industry with a goal of pursuing doctoral studies in chemistry.

I would like to show my appreciation for Dr. Brian Dyer and Dr. Keith Berland for their continuous presence in the classroom and beyond. Their guidance in physical chemistry and physics have taught me much appreciation for science.

I would like to recognize Dr. Lisa Rosen-Metsch, Dr. Ian Rosenstein, and Dr. Gary Molander. All of your influence, encouragement, and unwavering support has helped me get to where I am.

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Table 1. List of Catalyst and Conditions for Hydroalkoxylation Reactions

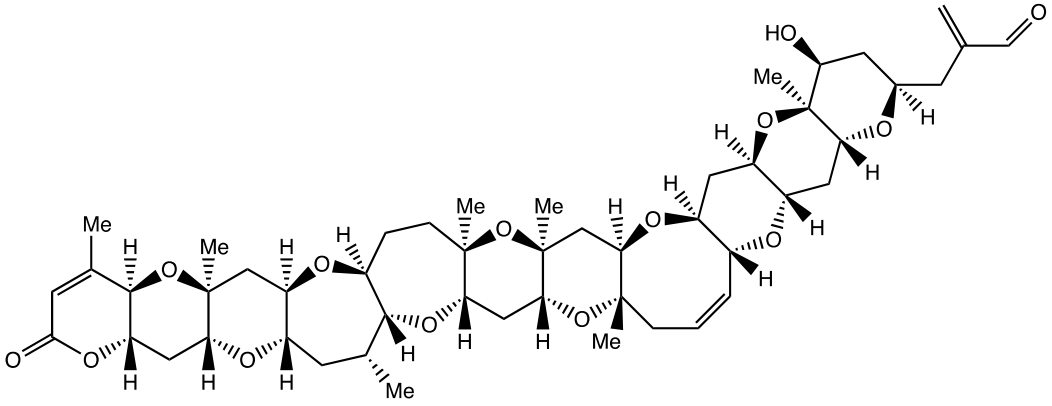
Chapter 1: Brevenal, Brevetoxin, and other marine ladder-frame polyether natural products

1.1 Background on Brevenal:

Along the coast of the Gulf of Mexico, high concentrations of algae build up in marine water systems. The accumulation of algae causes a red color change to coastal waters, commonly known as "red tide". The aggregation of microscopic, unicellular algae produces potent chemical toxin which affects many marine ecosystems and other organisms surrounding marine life. The algae produced by red tide events also consume molecular oxygen in water and release toxins, resulting in the death of marine organisms and subsequent ecological death of species. Death of marine organisms start when fish accumulate ichthyotoxic brevetoxin in their diet. Through the process of bioaccumulation, brevetoxin as well as other toxins can create a domino effect and move up in the food chain. Humans who consume contaminated shellfish can experience Paralytic Shellfish Poisoning (PSP), Diarrhetic Shellfish Poisoning (DSP), Amnesic Shellfish Poisoning (ASP), all of which, can be fatal.[1-2]

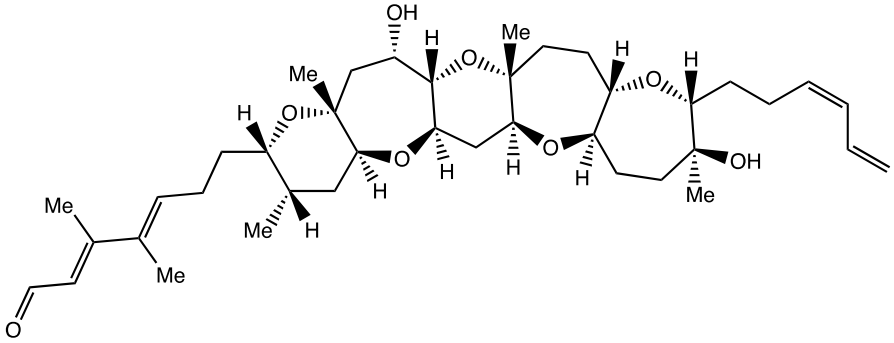
Brevetoxin BTX-B2 **1**, one of the potent chemical toxins secreted in algae blooms, is a naturally occurring compound produced by the dinoflagellate *Karenia brevis* (Figure 1). Virulent effects arise when brevetoxin binds to site 5 of voltage-sensitive sodium channels, which induces neurotoxic symptoms in humans. Brevenal **2**, an antagonist to Brevetoxin B2, has a high affinity to bind to the same sodium channel, thereby reducing the effects of neurotoxic shellfish poisoning in humans. Thus, brevenal is a potential treatment option for organisms exposed to brevetoxin.[3]

Figure 1. Chemical Structures of Brevetoxin BTX-B2 and Brevenal



1

Brevetoxin BTX-B2

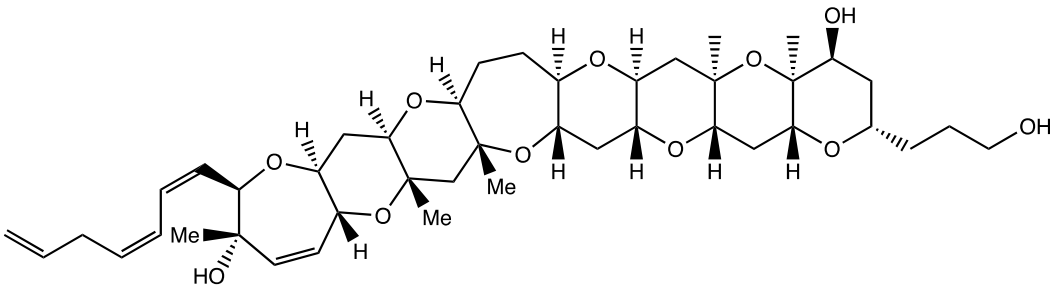


2

Brevenal

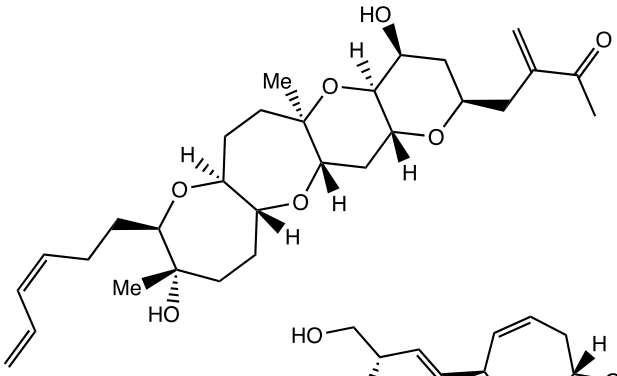
Due to strong biological activity, research on other marine polycyclic ether natural products have also been of great interest in the scientific community. For many marine polycyclic ether natural products, the mechanism of action is not known and therefore, treatment for toxic marine polycyclic ethers is not well defined. Marine polycyclic ether natural products are typically composed of a polycyclic ether core with fused five-to-nine membered rings, each containing varying oxygen-carbon-carbon stereochemistry. Examples of members of marine polycyclic ether natural products include gambierol **3**, hemibrevetoxin B **4**, and ciguatoxin CTX 1 **5** (Figure 2).[4]

Figure 2. Chemical Structure of Gambierol, Hemibrevetoxin B, and Ciguatoxin



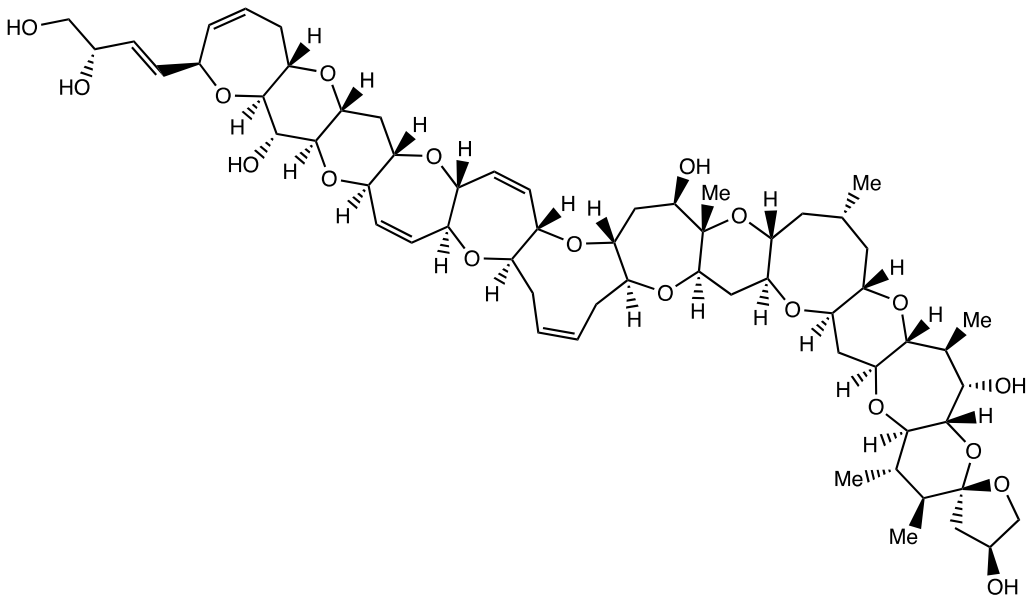
3

Gambierol



4

Hemibrevetoxin B



5

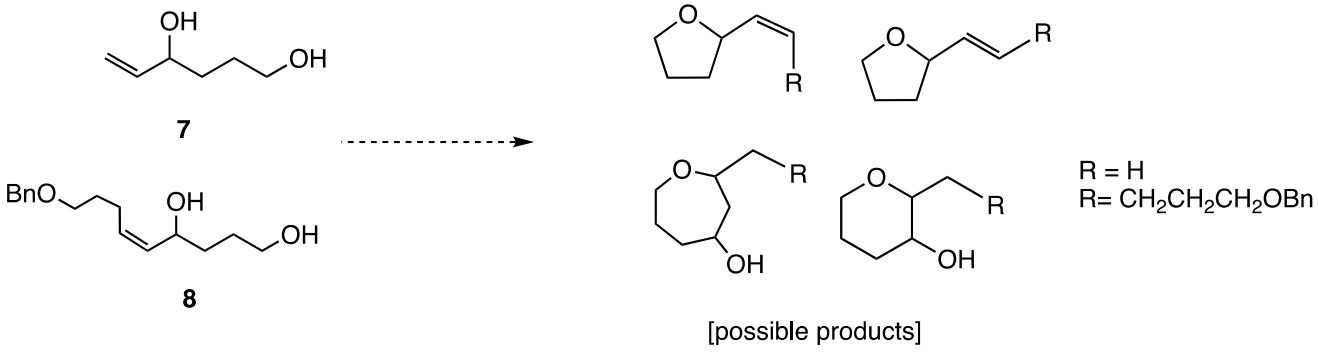
Ciguatoxin CTX 1

Although the total syntheses of brevenal and other marine ladder-frame polyether natural products have been performed, they involve ***more than 50+ steps***. Methods of efficiently synthesizing the fused polycyclic ether core of brevenal and potentially other marine natural products containing a polycyclic ether core have been an area of interest in the McDonald laboratory.[6-8]

1.2 Utility of Monosubstituted and Disubstituted Alkenes

The importance of synthesizing substrates **7** and **8** is ideally forming six and seven membered rings in one step (i.e the polycyclic ether core in brevenal is composed of six and seven membered rings). Upon controlling diastereoselectivity, regioselectivitiy and chemoselectivity, the formation of these rings could potentially and hopefully be translated to the formation of polycyclic ether cores in not only brevenal (main focus) but also other natural products (Scheme 1).

Scheme 1. Potential Ring Formations from Monosubstituted and Disubstituted Alkenes

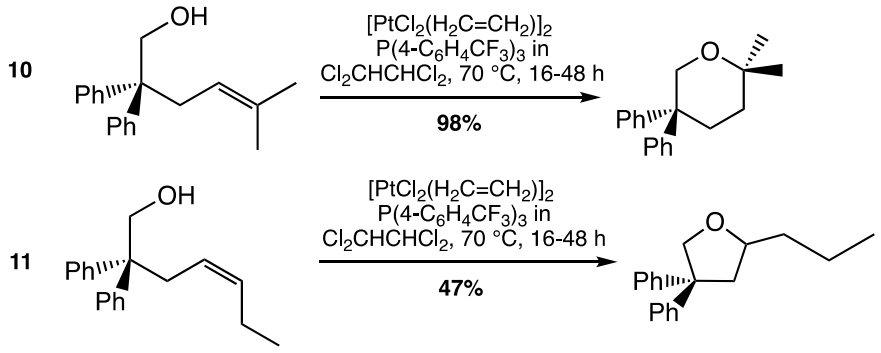


1.3 Background on Intramolecular Hydroalkoxylation

In 2004, Widenhoefer and coworkers used a platinum catalyst to perform an intramolecular hydroalkoxylation of hydroxyl olefins to form cyclic ethers (Scheme 2). In substrate **10**, the tether bearing the alcohol cyclized into a six-membered ring via *endo*-cyclization with a 98% yield. However, substrate **11** formed a five-membered ring via *exo*-cyclization. Widenhoefer and

coworkers suggested that hydroalkoxylation of alcohols are more selective to terminal olefinic substitution – resulting in a higher yield for substrate **10** than **11**. Although the scope of their work is limited to alkenyl alcohols, we drew inspiration by designing model substrates such as monosubstituted and disubstituted alkenyldiols to undergo intramolecular hydroalkoxylation reactions in one step.[9]

Scheme 2. Widenhoefer Group – Scope of Substrates



We were also inspired from Gagosz and coworkers who reported on Brønsted acid-catalyzed hydroalkoxylation reactions (Scheme 3). Their first attempt with hydroalkoxylation reactions used various catalysts such as Brønsted acid catalysts and gold catalysts. Interestingly enough, substrate **9** selectively formed compound **10**, a six-membered ring instead of **11** when $HNTf_2$ (Brønsted acid catalyst) was used (Table 1). Although their attempt at hydroalkoxylation reactions involve allenes, we may use acid catalysts in future work to promote intramolecular hydroalkylation reactions.[10]

Scheme 3. Gagosz Group – $HNTf_2$ (Brønsted Acid Catalyst) and Gold catalyst

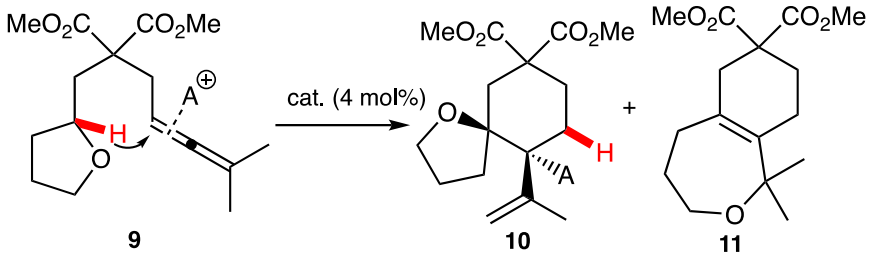
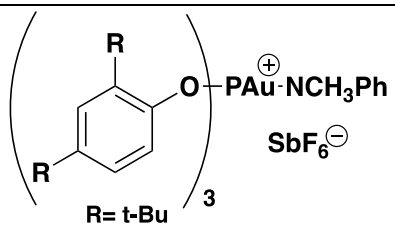


Table 1. List of Catalyst and Conditions for Hydroalkoxylation Reactions

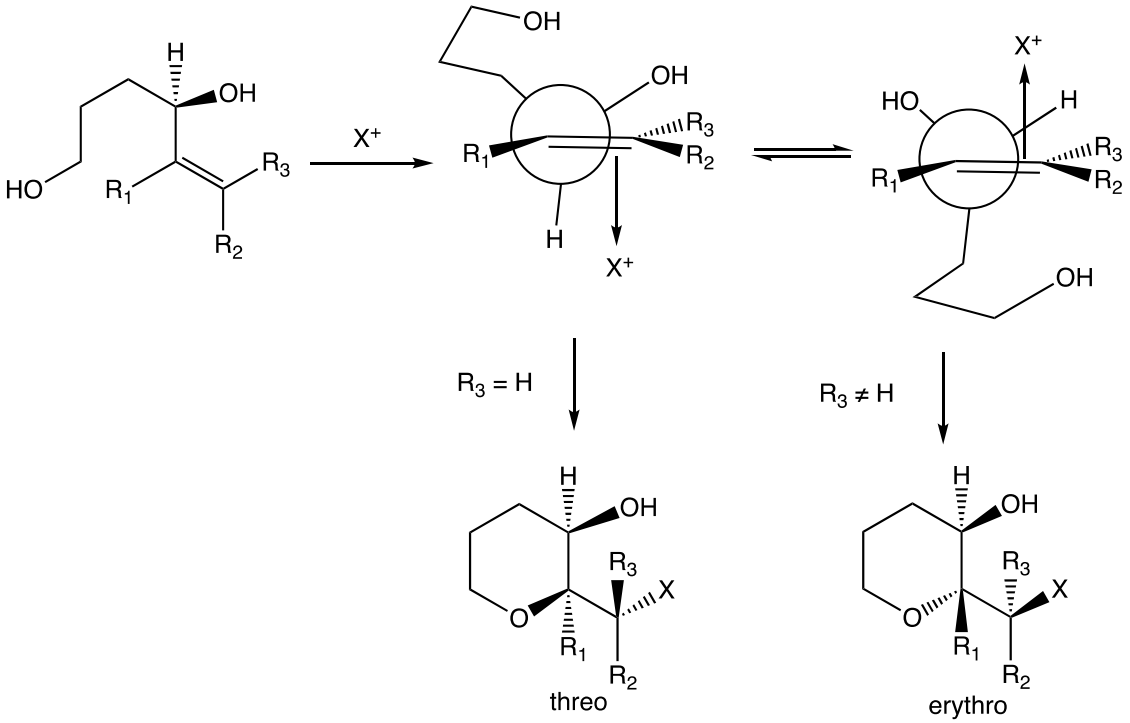
Catalyst	Solvent	Temp.	Time	Yield **10**	Yield **11**
	CH_2Cl_2	20 °C	0.5 h	**30%**	**61%**
$HNTf_2$	CH_2Cl_2	20 °C	22 h	**95%**	**0%**

1.4 Preparation of Oxacyclization Reactions of Alkenyl alcohols

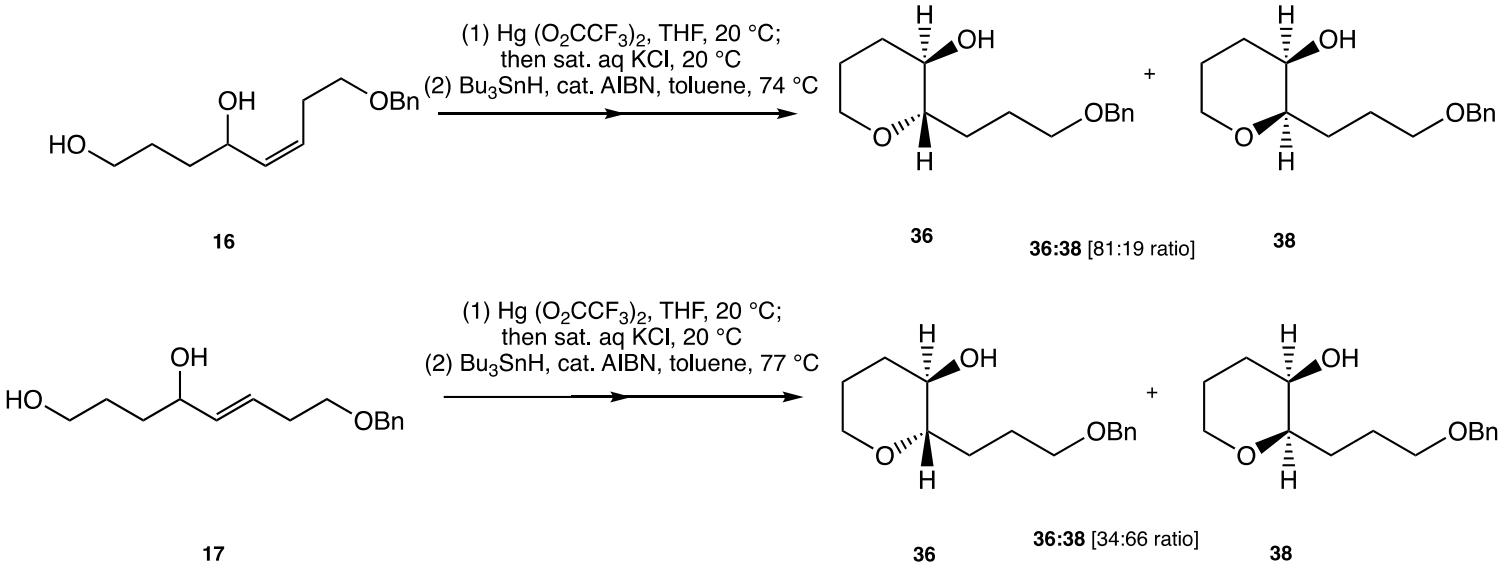
1.4.1. Mercury Cyclization

The McDonald Group has previously explored the stereoinduction of the allylic hydroxyl group of 1,4-dihydroxy-5-alkenes. Although these cyclization reactions were performed in two steps, they controlled diastereoselectivity using mercuric trifluoroacetate on *cis*- and (Z)-alkenyldiols. According to the Chamberlin-Hehre model, when the R_3 group is a hydrogen atom, the alcohol tether will attack from the top face of the alkene. However, when the R_3 group is bulky (i.e not a hydrogen atom), the alcohol tether is favored to attack from the bottom face of the alkene, which is the less sterically hindered side (Scheme 4). Following the Chamberlin-Hehre model, the McDonald Group found that mercuric trifluoroacetate-catalyzed cycloisomerization *trans*-1,2-disubstituted dihydroxyalkenes favored the *threo*-diastereomer and *cis*-1,2- disubstituted dihydroxyalkenes favored the *erythro*-diastereomer (Scheme 5).

Scheme 4. Chamberlin-Hehre Model on the Diastereoselectivity of Chiral Allylic Alcohol



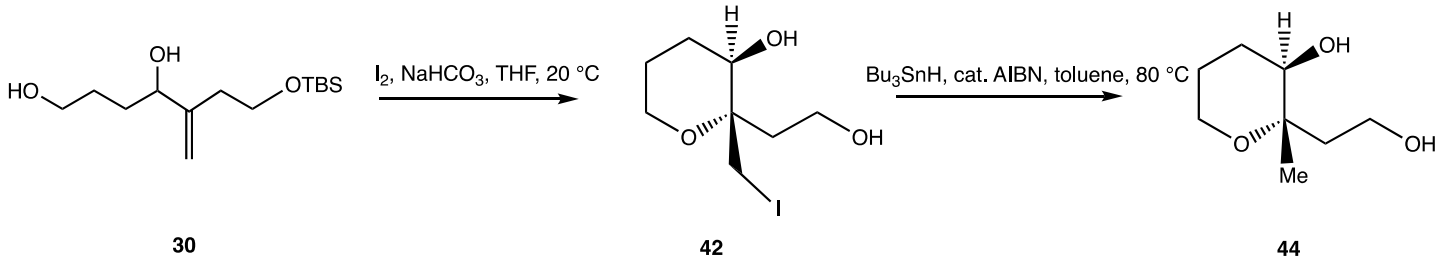
Scheme 5. Mercuric Trifluoroacetate Cycloisomerization of Disubstituted Alkenes



1.4.2. Iodocyclization

The McDonald Group has also previously explored the stereoselecitvity of 1,1-disubstituted 1,4-dihydroxy-5-alkene using iodine as a catalyst. Interestingly, Compound **30** was consistent with the Chamberlin-Hehre model, that is, it gave the *thero* product instead of the predicted *erythro* product. The McDonald group was able to form the *erythro*-diastereomer **44,** a six-membered ring, in two steps following the 6-*exo*-trig ring closure (Scheme 6).[11]

Scheme 6. Stereoselective Formation of Six-membered Ring with Disubstituted Alkene

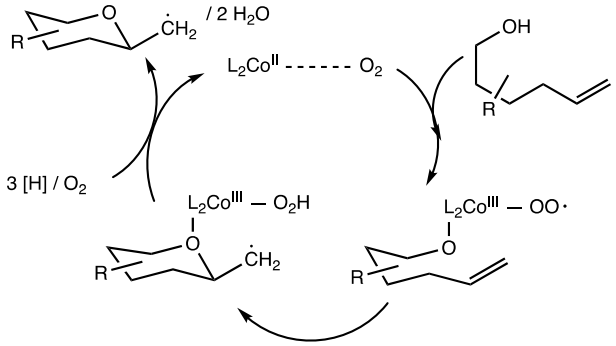


1.5 Focus on One Step Cyclization of Oxacyclization Reactions of Alkenyldiols

Our current focus in the McDonald laboratory is similar. Rather than having a mercuric-catalyzed cycloisomerization/ iodocylization and subsequent reductive demercuration/ deiodination, we aim to use a more environmentally friendly, nontoxic, and a more efficient method to synthesize six and seven membered rings using alkenyl diols in one single step.

Fries and Hartung have previously reported to control diastereoselectivity in forming six-membered rings through oxidative cyclization cascades of 5-hexen-1-ol. The cyclization reactions attempted by Fries and Hartung used fluoro-substituted cobalt(II) bis-(β-diketonate) complexes with 1,4 cyclohexadiene (CHD). The mechanism for this catalytic process begins with atmospheric oxygen complexing with cobalt, followed by an oxidative addition of 5-hexen-1-ol to cobalt. The cobalt complex rearranges to a six-membered ring and undergoes a reductive elimination to turnover a six-membered ring with a primary radical (Scheme 7). Then, the primary radical will interact with 1,4 cyclohexadiene (CHD) to form a benzene ring (not shown). [12-13] Interestingly enough, reactions with cobalt(II) bis-(β-diketonate) complexes and CHD reactions are reported to favor formations of **6-*exo***-rings – an ongoing focus in the McDonald laboratory.

Scheme 7. Proposed Mechanism for Aerobic 5-Hexenol Oxidation

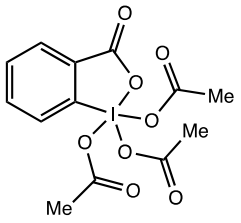


Chapter 2

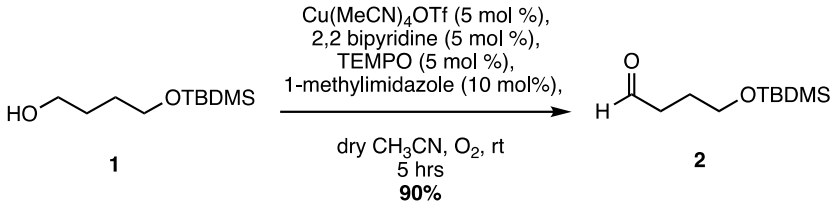
2.1 Design of Precursors for Cyclization Reactions:

2.1.1 Monosubstituted Alkenes

Figure 3. Structure of Dess-Martin Periodinane (DMP)



Scheme 8. Stahl's Oxidation of Primary Alcohol to Aldehyde



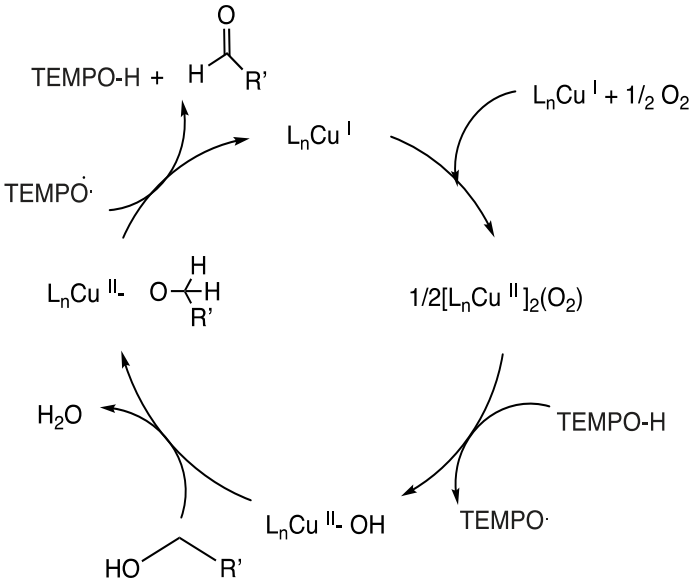
2.1.1.1 Early Oxidation Results

The synthesis begins with commercially available protected silyl alcohol **1.** The initial oxidation reaction was performed using a stock solution of $NaHCO_3$, Na_2CO_3, NaClO, KBr, and TEMPO in excess with respect to the alcohol. After monitoring the reaction via thin-layer chromatography, a further portion of the NaClO stock solution was added but it failed to convert the alcohol to the desired aldehyde **2**. After a series of failed reactions using NaClO, a mild oxidation using Dess-Martin periodinane (DMP) was performed (Figure 3). The oxidation reaction using DMP proved to be successful. However, the cost of DMP was not financially feasible on a large scale so other alternatives were sought.

The third experiment that was tested was an oxidation reaction using Cu/TEMPO to oxidize **1** to **2** (Scheme 8). The catalytic process begins with tetrakis(acetonitrile)copper(I) triflate

undergoing an oxidative addition with atmospheric oxygen to turn copper(I) into copper (II). Then, TEMPO was used to form the hydroxyl group on the copper complex. Lastly, the primary alcohol binds to the copper and undergoes a reductive elimination (turnover-limiting step) to give the aldehyde (Scheme 9).

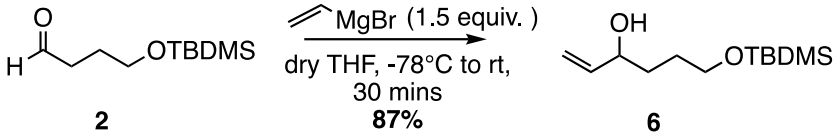
Scheme 9. Catalytic Cycle of the Oxidation of Primary Alcohols



This reaction proved to be successful in converting the alcohol to the aldehyde. Furthermore, this reaction was cost effective and the product was easily purified. [14]

2.1.1.2 Discovery with Vinylmagnesium Bromide

Scheme 10. Grignard Addition of Vinylmagnesium Bromide to Aldehyde

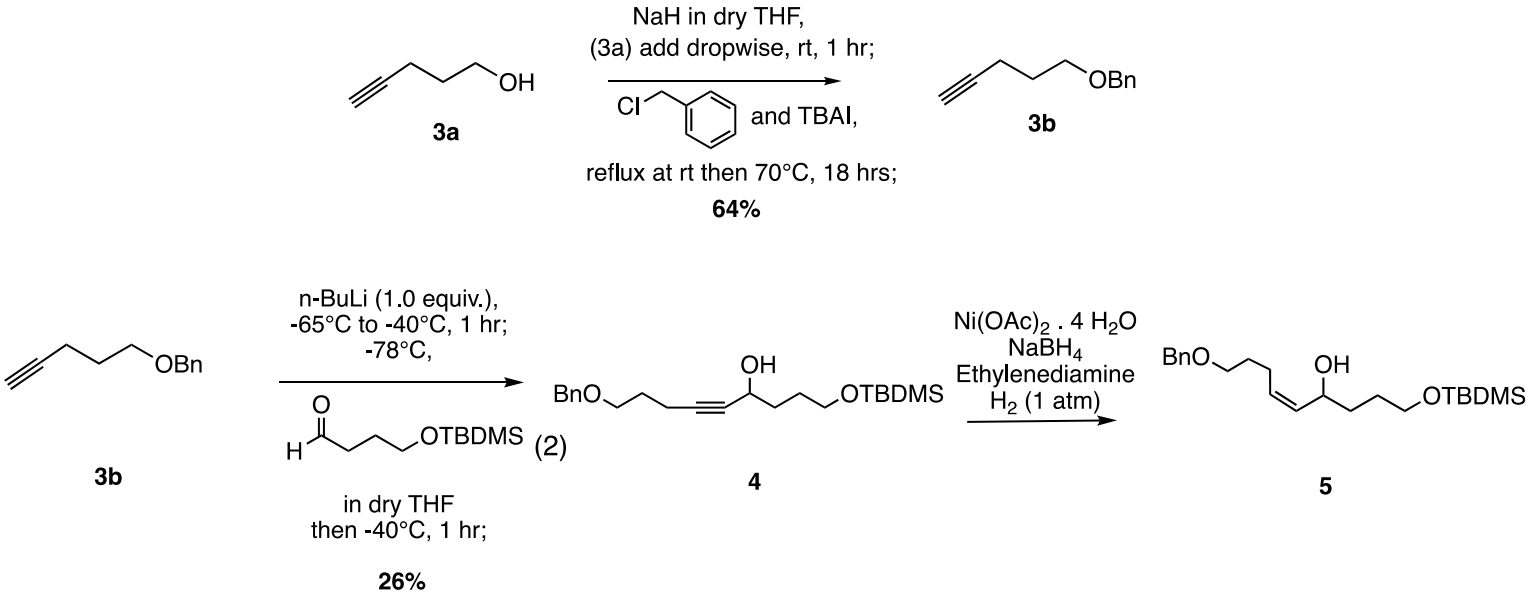


2 **6**

Through a series of failed reactions, it was later discovered that vinylmagnesium bromide was subject to degredation. Over time, the formation of divinyl magnesium as well as magnesium dibromide could possibly form – both compounds will not give desired compound **6**. Furthermore, a bottle of vinylmagnesium bromide that was sitting on the shelf for an unknown amount of time is subject to react with THF and produce peroxides which could be hazardous to work with. After purchasing a new bottle of vinylmagnesium bromide, vinyl addition to Substrate **2** was easily achieved with vinylmagnesium bromide to give Compund **6** (Scheme 10).

2.1.2 Disubstituted Alkene

Scheme 11. Synthetic Pathway for Disubstituted *Cis*-Alkene



2.2 Synthetic Pathway for Disubstituted Cis-Alkene

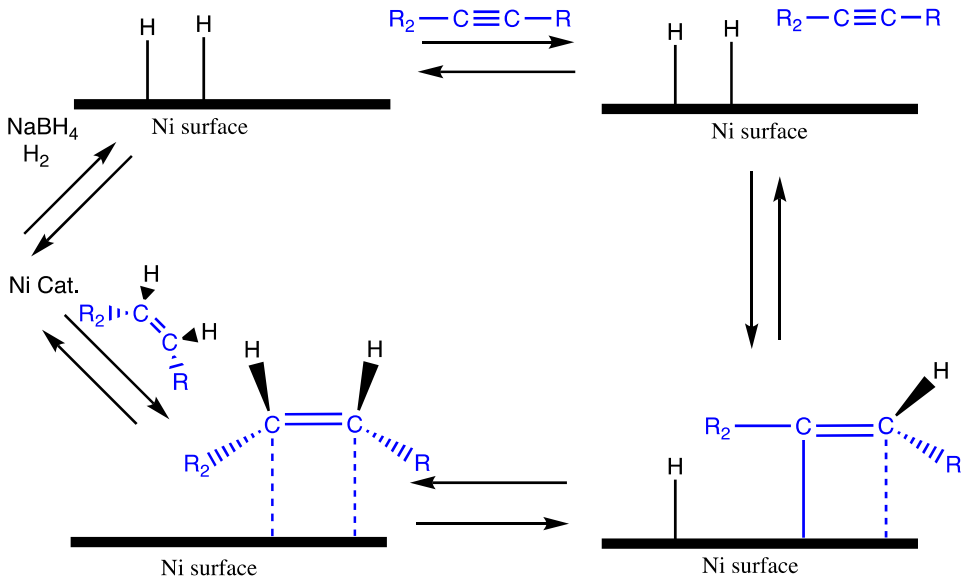
The synthesis begins with a 4-pentyn-1-ol, a terminal alkyne with an alcohol tether **3a**. Substrate **3a** undergoes subsequent nucleophilic substitution with benzyl chloride to afford Compound **3b**.

Using n-butyl lithium as a strong base to deprotonate the terminal hydrogen on the alkyne, the terminal alkyne will undergo nucleophilic addition to the aldehyde to afford Substrate **4**. After formation of Compound **4**, $Ni(OAc)_2$ and $NaBH_4$ are used to undergo a partial stereoselective reduction of an alkyne to afford disubstituted *cis*-alkene **5** (Scheme 11).

2.2.1 Mechanism of *$Ni(OAc)_2$ and $NaBH_4$ Hydrogenation*

The catalytic process begins with the cleavage of H_2 gas and each hydrogen attaching to the nickel surface, forming Ni-H bonds. Furthermore, sodium borohydride ($NaBH_4$) also provides a catalytically active hydrogen that interacts with the nickel surface. Upon activation, alkyne association to the nickel catalyst is the next step to this hydrogenation reaction. In the following step, migratory insertion of a hydrogen atom to the carbon and another hydrogen from the nickel surface inserts to the same face of the other carbon (*syn* addition) produces *cis*-alkene (Scheme 12).

Scheme 12. Proposed Mechanism of Stereoselective Hydrogenation of Alkyne to Cis-Alkene

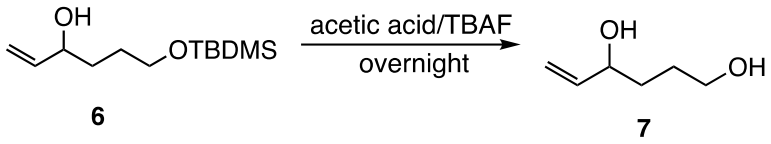


2.2.2 Challenges with $Ni(OAc)_2$, $NaBH_4$, and H_2 Gas for Stereoselective Hydrogenation

After multiple trials of this experiment, I discovered that it was best to use a flask that exposed the greatest surface area of this reaction mixture. As you can see from the mechanism above, this reaction works best if hydrogen gas can readily interact with the reaction mixture containing the nickel catalyst in ethanol. Furthermore, there was also a color change (black to light purple), possibly indicating that the reaction was complete. Due to the sudden closure of campus during COVID-19, quantification of yield was not determined for this reaction. However, the crude $_1$H-NMR of this reaction showed formation of **5**. [15]

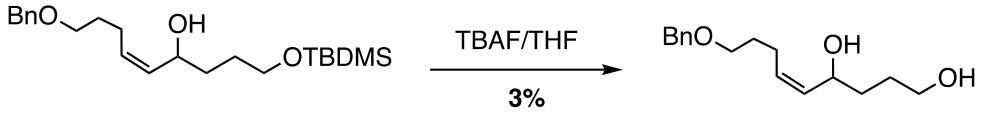
2.3 Problems with Deprotection of TBDMS

Scheme 13. Monosubstituted Alkene Deprotection Reaction with Acetic Acid/TBAF



6 **7**

Scheme 14. Disubstituted Alkene Deprotection Reaction with TBAF



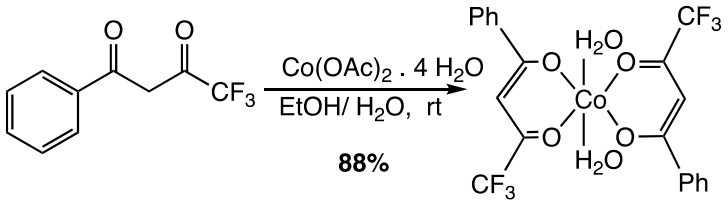
5 **8**

Initially, only TBAF was used to remove the silyl group however, purification via column chromatography and Biotage proved to be more difficult than originally anticipated. After a series of literature reviews and trial and error, the silyl protecting group on Compound **7** was easily removed with acetic acid/TBAF (Scheme 13). Examination of the crude NMR of this reaction showed no hint of the silyl protecting group. However, quantification of the yield cannot be determined. Attempts of deprotection of disubstituted alkene **8** were only done with TBAF (Scheme 14). Since attempts of deprotection of disubstituted alkenes were only done with TBAF, future experiments using acetic acid/TBAF can be tested to remove the silyl protecting group on **8**. Subsequent column chromatography of this reaction can also be optimized.

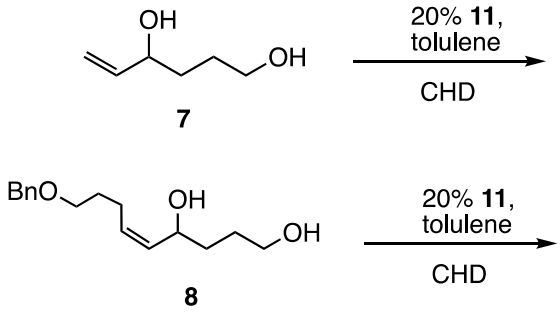
2.4 Future Direction

Attempts in cyclization reactions using catalyst **11** were performed (Scheme 15). Examination of the crude NMR of these reactions showed formation of new peaks and a significant difference when compared to the starting material used. However, the product was unable to be determined. In the future, optimization of structure determination can be done for this reaction

Scheme 15. Synthesis of Cobalt Catalyst



Scheme 16. Synthesis of Attempted Cyclization Reactions

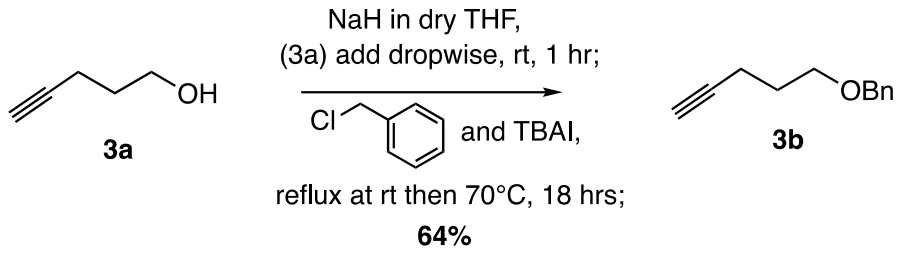


In the future, synthesizing various substrates such as disubstituted and trisubstituted alkenyldiols can be done. Furthermore, synthesizing the stereoselective trans-alkenyl diol of **8** can be tested by using Red Al® sodium bis(2-methoxyethoxy)aluminum hydride solution on alkyne **4** (Scheme 17).

Scheme 17. Proposed Synthesis of *trans*-alkenyl diol using Red Al®

2.5 Experimental Results

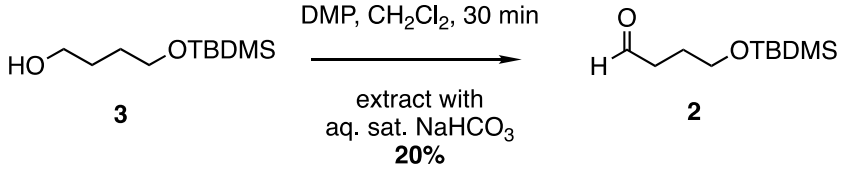
4-pentynyl-benzylether (**3b**) [1]



Sodium hydride (1.55g, 64 mmol) and THF (90 mL) were added to an oven-dried, 500 mL three neck round-bottom flask with an oven-dried oval stir bar, fitted with a reflux condenser. Neat 4-pentyn-1-ol (**3a**, 2.5 mL, 27 mmol) was added dropwise by syringe to this reaction mixture. The reaction mixture was stirred at room temperature for 1 hour. Benzyl chloride (3.1 mL, 27 mmol) was added and tetrabutylammonium iodide (0.45 g, 1.2 mmol) was subsequently added. After heating the flask 70 °C for 19 hours, the reaction mixture was cooled to 23°C and then quenched with EtOAc (100mL). The combined organic layer was washed with water (2x100) and brine (100 mL) and dried with Na_2SO4. The mixture was then concentrated *in vacuo*. The crude yellow oil was then dissolved in 5% EtOAc/hexanes with a small addition of silica gel. After the mixture was concentrated through rotary evaporation *in vacuo*, the silica gel containing the product was then dry packed and placed in chromatography column to afford pure ((pent-4 ynyoxy)methyl)benzene (**3b**, 3.05 g, 64%), a yellow oil.

$_1$H-NMR (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 4H), 7.29-7.23 (m, 1H), 4.51 (s, 2H), 3.55 (t, *J* = 8.0 Hz, 2H), 2.30 (td, *J* = 8.0, 4.0 Hz, 2H), 1.92 (t, *J* = 4.0 Hz, 1 H), 1.82 (tt, *J* = 8.0 Hz, 4.0 Hz, 2H)

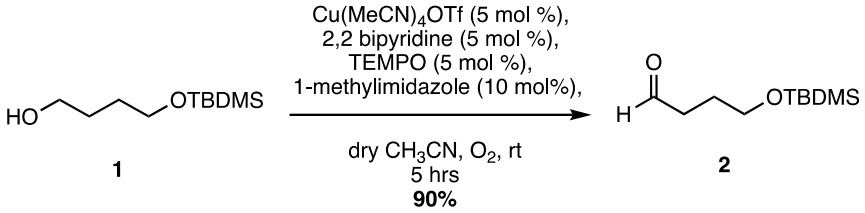
4-tertbutyldimethylsilyl)oxy)butanal (TBOB) (**2**) *2*



In a 20.0 mL flask, the alcohol (**3**, 0.5g, 2.4 mmol) was dissolved in CH_2Cl_2 (50 mL) and treated with Dess-Martin periodinane (1.55 g, 3.7 mmol) at room temperature. The reaction mixture was stirred for 30 minutes. Then, Et_2O (50 mL) and aqueous saturated $NaHCO_3$ solution were added to quench the reaction. In a 250 mL separatory funnel, addition of aq. saturated $NaHCO_3$ solution and deionized H_2O were added to the organic layer and gave clear separation. The mixture was dried with Na_2SO_4. The concentrated crude product was given through rotary evaporation *in vacuo*. The crude aldehyde was then dissolved in 20% EtOAc/hexanes and a small amount of silica gel. The solution was then loaded on to packed chromatography column to afford 4-tertbutyldimethylsilyl)oxy)butanal *(***2**, 0.1g, 20%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.76 (m, 1 H) 3.61 (m, 2H), 2.47 (m, 2H), 1.82 (m, 2H), 0.85 (d, *J* = 4.0 Hz, 9H), 0.01 (d, J= 4.0 Hz, 6H).

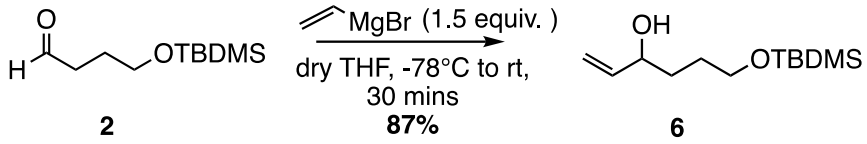
4-tertbutyldimethylsilyl)oxy)butanal (Stahl's Oxidation of Primary Alcohols) **(2)** [3]



In a 250-mL flame-dried flask with stir bar, a solution of 4-((*tert*-butyldimethylsilyl)oxy)butan-1-ol **(5,** 2.04 g, 10.0 mmol) was dissolved in dry CH_3CN (10.0 mL). The following solutions were added to the alcohol: (1) $[Cu(MeCN)_4]X$ (X = **OTf-**, 0.50 mmol in 10.0 mL CH_3CN) (2) 2,2'-dipyridyl (0.50 mmol in 10.0 mL CH_3CN) (3) TEMPO (0.50 mmol in 10.0 mL CH_3CN) (4) *N*-methyl imidazole (1.0 mmol in 10.0 mL CH_3CN). The dark brown reaction mixture was stirred rapidly open to air and monitored by TLC until no starting material was present. The dark brown reaction mixture changed to teal after 5 hours of stirring. After TLC showed no presence of starting material, the reaction mixture was filtered through a plug of silica (Cu complex and TEMPO remain on the bed of silica upon filtration). The concentrated crude product was given through rotary evaporation *in vacuo* to afford aldehyde, 4-((*tert*-butyldimethylsilyl)oxy)butanal (**2**, 1.82g, 90%)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.73 (s,1 H) 3.59 (t, *J* = 4.0 Hz, 2H), 2.45 (t, *J* = 4.0, 2H), 1.81 (m, 2H), 0.82 (m, 9H), 0.01 (m, 6H).

6-((tert-butyldimethylsilyl)oxy)hex-1-en-3-ol (**6**) [4]

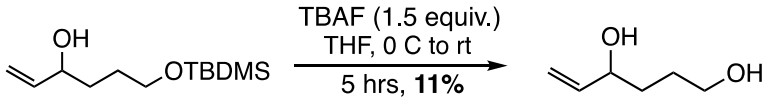


2 **6**

In a 100-mL flame-dried flask with stir bar, a solution of 4-((tert-butyldimethylsilyl)oxy)butanal (**7**, 4.02 mL, 18.2 mmol) in dry THF was added to 1.0 M vinylmagnesium bromide solution in THF (20.5 mL, 20.5 mmol) dropwise at -78 °C under argon atmosphere. Upon addition of aldehyde, the reaction was slowly brought to room temperature. Conversion of the starting aldehyde was complete as indicated by TLC, quenched with 2-propanol (1.5 mL) and aqueous sat. NH_4Cl (30 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL) and the combined organic layer was washed with brine (1 × 100 mL), H_2O (1 x 20), and dried over $MgSO_4$. The concentrated crude product was given through rotary evaporation *in vacuo* to afford 6-((*tert*-butyldimethylsilyl)oxy)hex-1-en-3-ol, (**6**, 3.01g, 72%).

$_1$H-NMR (400 MHz, $CDCl_3$) δ 5.90 (m, 1H), 5.26 (dd, *J*=18 Hz, *J*= 16 Hz, 2H), 4.15 (s, 1H), 3.69 (s, 2H) 2.72 (s, 1H), 0.93 (s, 9H), 0.08 (s, 6H)

hex-5-ene-1,4-diol (**7**) [5]



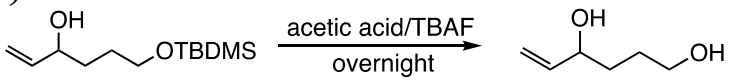
6 **7**

In a 250-mL flame-dried flask with stir bar, a solution of 6-((tert-butyldimethylsilyl)oxy)hex-1-en-3-ol (**6**, 3.01 g, 13.1mmol) in THF (20 mL) was cooled to 0 °C. Tetra-n-butylammonium fluoride (1 M in THF, 19.6 mL, 19.6mmol) was added dropwise and the solution was warmed to room temperature. After 5 hours, the concentrated crude product was given through rotary

evaporation in vacuo. The crude was purified by column chromatography to afford a light orange oil, hex-5-ene-1,4-diol (**7**, 0.176g, 11%).

$_1$H-NMR (400 MHz, $CDCl_3$) δ 5.89 (m, 1H), 5.26 (dd, *J*=16 Hz, *J*= 16 Hz, 2H), 4.16 (m, 1H), 3.67 (m, 2H) 2.43 (s, 1H), 1.69 (m, 4H)

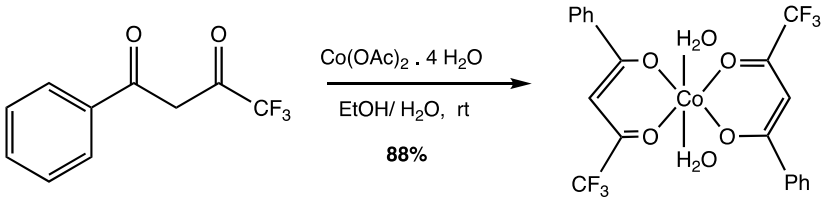
*hex-5-ene-1,4-diol (**7**)*[5]



6 **7**

To a 25-mL flame-dried round bottom flask, the protected silyl ether (**6,** 0.5 g, 2.17 mmol) was dissolved in THF and cooled to 0 °C before addition of acetic acid (0.26 g, 0.24 mL,4.34 mmol) and TBAF in 1 M of THF. The solution was gradually warmed to room temperature and stirred overnight to afford **7.**

Bis-[1,1,1-trifluoro-4-phenyl-2-(oxo-κO)-but-3-en-4-(olato-κO)]cobalt(II) dehydrate (**11**) [6]



10 **11**

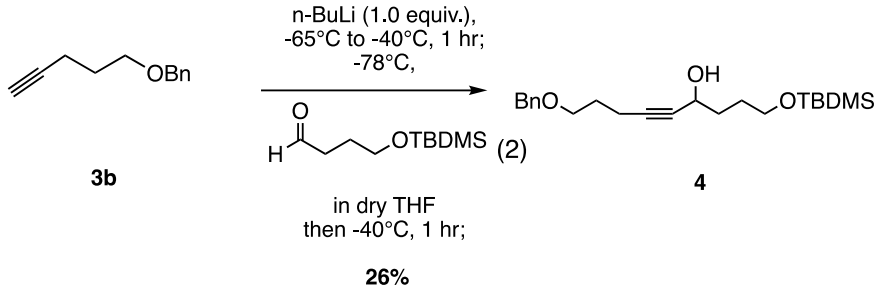
To a 100-mL round bottom flask, benzoyltrifluoroacetone (**10**, 2.01 g, 9.27 mmol) in EtOH was added to a solution of cobalt(II) acetate tetrahydrate (1.11 g, 4.46 mmol in 20 mL H_2O). Upon addition of benzoyltrifluoroacetone, yellow precipitate crashed out. The reaction was stirred at room temperature for 1 hour. The precipitate was filtered through a frit filter and a vacuum line. Hexanes was used to wash the remaining catalyst from the flask. Upon collection of catalyst, the

catalyst was placed in a vacuum desiccator overnight to afford Bis-[1,1,1-trifluoro-4-phenyl-2-(oxo-κO)-but-3-en-4-(olato-κO)]cobalt(II) dehydrate, a yellow precipitate (**11**, 2.11g, 88%)

Note: Avoid using EtOH and EtOAc to rinse out the catalyst, the catalyst will dissolve.

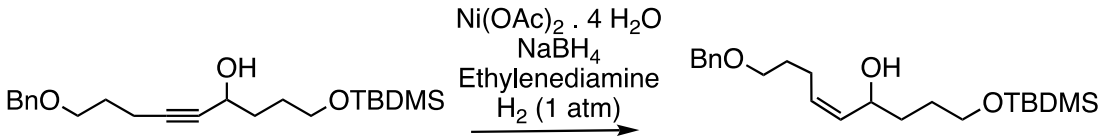
$_1$H-NMR (600 MHz, Acetone-d_6) δ 8.24 (d, *J*= 6 Hz 2H), 7.82 (d, *J*= 6 Hz, 1H), 7.70 (d, *J*= 6 Hz, 2H), 7.06 (s, 1H)

*9-(benzyloxy)-1-((tert-butyldimethylsilyl)oxy)non-5-yn-4-ol (***4***)* [7]



To a 25-mL flame-dried round bottom flask, the terminal alkyne (**3b**, 0.5 g, 5.94 mmol) was dissolved in dry THF (15 mL) and cooled to -65 °C. *N*-butyllithium (2.5 M in hexane, 2.37 mL, 5.94 mmol) was added slowly. The reaction was slowly warmed to -40 °C and stirred for one hour and returned to -78 °C. Aldehyde 2 (0.53g, 2.65 mmol) dissolved in 10 mL of dry THF was then added to the reaction mixture and the temperature was raised to -40 °C within 1 hour. The reaction was quenched with NH_4Cl and extracted with ether (3 x 30 mL). The combined organic layers were dried with $MgSO_4$. The concentrated crude product was given through rotary evaporation *in vacuo.* The crude was purified by column chromatography (1:9 ethyl acetate- hexanes) to afford (**4**, 0.54 g, 26%).

*(Z)-9-(benzyloxy)-1-((tert-butyldimethylsilyl)oxy)non-5-en-4-ol (**5**)*[8]



4 **5**

In a 5-mL flame-dried round bottom flask, $Ni(OAc)_2$ $4H_2O$ in ethanol, followed by $NaBH_4$ was added to give a black suspension. After purging the flask with hydrogen gas, ethylenediamine was added followed by addition of disubstituted alkyne **4** in ethanol. The reaction mixture was vigorously stirred under H_2 overnight. The reaction turned from black to a purple solution and the reaction mixture was filtered through filter paper and washed with dichloromethane. The organic layer was washed with brine and dried with magnesium sulfate. The concentrated crude product **5** was given through rotary evaporation *in vacuo*.

References

1. Bourdelais, A. J.; Campbell, S.; Jacocks, H.; Wright, J. L.; Carsi, J.; Baden, D.G. *Cell Mol. Neurobiol*. **2004,** 24, 553–563.
2. Keeler, D. M.; Grandal, M. K.; McCall, J.R. *Mar. Drugs*. **2019**, *17*, 184.
3. Baden, D. G.; Bourdelais, A. J.; Jacocks, H.; Michelliza, S.; Naar, J. *Environ Health Perspect*. **2005**, *113*, 621–625.
4. Cuypers, E.; Abdel-Mottaleb, Y.; Kopljar, I.; Rainier, J. D.; Raes, A. L.; Snyders, D.J.; Tytgat, J. *Toxicon*. **2008**, *51*, 974–983.
5. Sasaki, M. *Topics in Heterocyclic Chemistry Marine Natural Products*. **2006**, *5*, 149-178
6. Nakata, T. *Chem. Rev.* **2005**, *105*, 4314-4347.
7. Fuwa, H.; Ebine, M.; Bourdelais, A. J.; Baden, D. G.; Sasaki, M. *J. Am. Chem. Soc*. **2006**, *128*, 16989–16999.
8. Zhang, Y.; Rohanna, J.; Zhou, J.; Iyer, K.; Rainier, J. D. *J. Am. Chem. Soc*. **2011**, *133*, 3208–3216.
9. Qian, H.; Han, X.; Widenhoefer R. A. *J. Am. Chem. Soc.* **2004**, *126*, 9536-9537.
10. Bolte, B.; Gagosz, F. G. *J Am Chem Soc.* **2011**, *133*, 7696-7699.
11. Hurtak, J.; McDonald, F. E. *Synlett*. **2017**, *28*, 2951-2955.
12. Fries, P.; Halter, D.; Kleinschek, A.; Hartung, J. *J. Am. Chem. Soc*. **2011**, *133*, 3906–3912.
13. Fries, P; Muller, M. K.; Hartung, J. *Tetrahedron*. **2014**, 70, 1336-1347.
14. Hoover, J. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 16901.
15. Brown, C. *J. Org. Chem.* **1970**, 35, 6, 1900-1904

Experimental References

1. Tenenbaum, J. M.; Morris, W. J.; Custar, D. W.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2011**, 50, 5892 –5895.
2. Zhang, W.; Lin, S.; Du, C.; Feng, S.; Liu, Z.; Zhang, J.; Xie, X.; Wang, X.; Li, H.; She, X. *J. Org. Chem.* **2019,** *84*, 1111-1116.
3. Hoover, J. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 16901.
4. Kwan, E. E.; Scheerer, J. R.; Evans, D. A.; *J. Org. Chem*. **2013**, *78*, 175-203.

5. Jessica Hurtak. *Exo-mode oxacyclization strategies for synthesis of trans-fused polycyclic ethers: the ABC ring sector of brevenal*. PhD dissertation, Emory University, **2017**.
6. Fries, P.; Halter, D.; Kleinschek, A.; Hartung, J. *J. Am. Chem. Soc.* **2011**, *133*, 3906–3912.
7. Pichlmair, S.; de Lera Ruiz, M.; Basu, K.; Paquette, L. A. *Tetrahedron* **2006**, *62*, 5178-5194.
8. McDonald, F. E.; Ishida, K.; Hurtak, J. A. *Tetrahedron* **2013**, *69*, 7746-7758.