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Kristen L. Stoltz Date

Chapter 1: The development of a model system for the B-ring of brevenal and methods for the formation of seven-membered rings.

Chapter 2: Iterative alkyne-epoxide cross-couplings toward the total synthesis of PM-toxin A.

Chapter 3: The development of synthons for 1,3-dimethylallylation of aldehydes.

By

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Doctor of Philosophy

Chemistry

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Date

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By

Kristen L. Stoltz
B.A., The College of Wooster, 2009

Advisor: Frank E. McDonald, Ph.D.

An abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
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Doctor of Philosophy
in Chemistry
2014

Abstract

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By Kristen L. Stoltz

The natural product brevenal is a non-toxic competitive inhibitor of red tide toxins including brevetoxin B_2, and shares a trans-syn-trans-fused polycyclic ether core with the brevetoxin family. Our research explores an *exo*-mode cascade cyclization pathway for the core structure of brevenal. Iodocyclizations of hydroxyalkenes provided the 8-membered ring regioisomer, and the approach was modified to develop stereoselective conjugate additions of oxygen nucleophiles onto unsaturated carbonyls to provide 7-membered rings. The enantioselective total synthesis of PM-toxin A via iterative alkyne-epoxide couplings was also explored. A new method of preparing functionalized homoallylic alcohols by employing stereospecific [3,3]-sigmatropic rearrangements of aldehydes with a family of synthons that contain three elements of stereochemistry was investigated.

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List of Illustrations

List of Schemes

List of Abbreviations

Ac	acyl group
app.	apparent
CSA	camphorsulfonic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DMAP	dimethylaminopyridine
DMF	dimethylformamide
dr	diastereomeric ratio
DVDS	1,3-divinyltetramethyldisiloxane
er	enantiomeric ratio
Et	ethyl
h.	hour(s)
^{i}Pr	isopropyl
LA	Lewis acid
LiHMDS	Lithium hexamethyldisilazide
m-CPBA	meta-chloroperbenzoic acid
Me	methyl
MS	mass spectra; Masters of Science
NBS	N-bromosuccinamide
*n*Bu	n-butyl
NMR	nuclear magnetic resonance
Pet. Ether	petroleum ether

py.	pyridine
TBAF	tetrabutylammonium fluoride
TBS	tert-butyldimethylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMDS	tetramethyldisilazide
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl

CHAPTER 1

The development of a model system for the B ring of brevenal and methods for the formation of seven-membered rings.

1.1 Introduction and Background

1.1.1 Red tide events

Harmful algae blooms, commonly called red tides, are large clusters of marine dinoflagellates that are responsible for widespread ecosystem dysfunction, public health risk, and economic losses. There are a number of different microorganisms that cause the red tide events, *Karenia brevis*. *K. brevis* blooms are typically found along the Gulf of Mexico and the mid-Atlantic coast of the United States.[1,2] The *K. brevis* blooms are responsible for the loss of millions of dollars to the commercial and recreational fisheries and tourist industries due to the harmful toxins released during red tide events.[3] The toxins are a class of marine natural products that contain *trans*-syn-*trans* fused polycyclic ethers.

1.1.2 Polycyclic ether marine natural products

Ciguatoxin (**1**) is one example of a fused polycyclic ether natural product and is produced by *Gambierdiscus toxicus* (Figure 1).[4] It is one of two main toxins indicated in seafood poisoning, and is regarded as the primary toxin for human illnesses in areas where *G. toxicus* is located. Another similar natural product is gambierol (**2**), also isolated from *G. toxicus*.[4] The polycyclic ether class of natural products is composed of a varying number of cyclic ethers ranging in size from 5- to 9-membered rings and contains *trans*-syn-*trans* fused ring junctures to create ladder-frame structures.

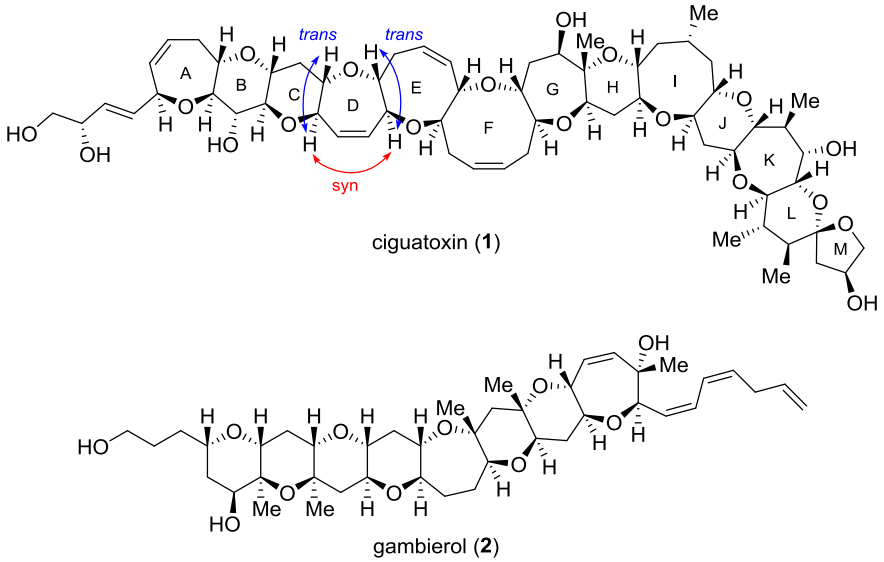


Figure 1: Fused polycyclic ether natural products.[1,4,5]

The proposed biosynthetic pathway for the formation of polycyclic ether natural products, such as brevetoxins A and B, was determined through ^{13}C labeling experiments carried out by two independent research laboratories. Both Nakanishi[6,7] and Shimizu[8] propose the carbon chain backbone is assembled through the combination of acetate metabolites, most likely involving the citric acid cycle. More recently, Satake and co-workers investigated the incorporation of oxygen the biosynthesis of yessotoxin (**3**), a polycyclic ether natural product originating from *Protoceratium reticulatum*.[9] They discovered that the oxygen atoms in the ether rings were derived from $^{18}O_2$ (shown in red), while the C32 oxygen was derived from an ^{18}O-labeled acetate molecule (shown in blue, Figure 2). Their findings suggest that a polyene precursor was oxidized by a monooxygenase after acetate condensation.

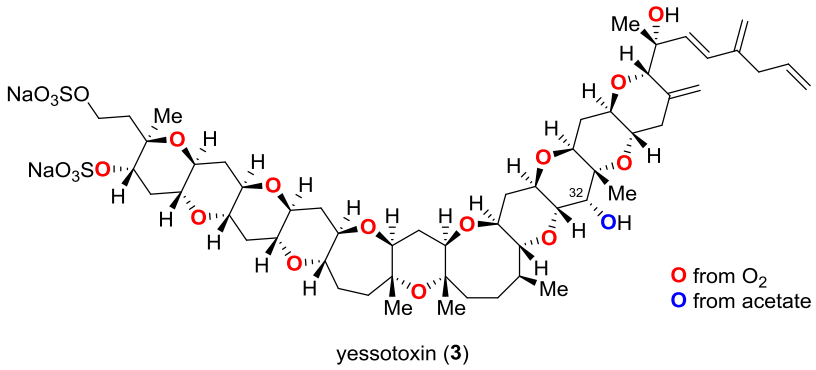
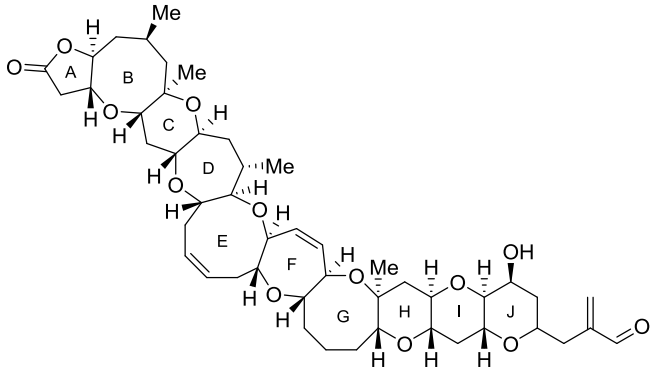


Figure 2: ^{18}O labeling studies in yessotoxin.

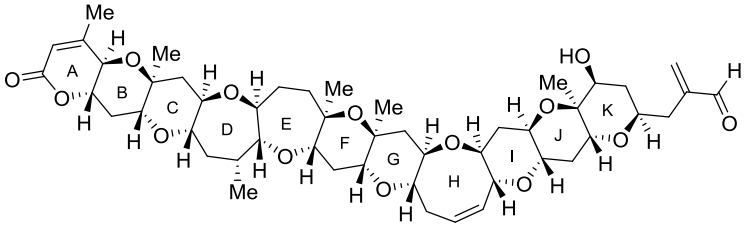
1.1.2.1 Brevetoxin family

The brevetoxin family of fused polycyclic ether marine natural products is produced by *K. brevis* during red tide events (Figure 3).[1] These toxins are responsible for widespread fish kills and the death of over 200 of Florida's endangered manatee population during the 1996 red tide.[1] Humans are also affected by the toxins resulting from *K. brevis* red tide events. Ingestion of shellfish that have been exposed to the brevetoxins leads to neurotoxic shellfish poisoning (NSP). NSP symptoms range from mild to severe gastroenteritis to neurological dizziness or tunnel vision.[1] Red tide mists found near the shores also contain brevetoxins and may be linked to respiratory effects, including shortness of breath from bronchoconstriction at pM concentrations.[1,10]

The brevetoxins bind to a voltage-sensitive sodium ion channel on neuronal membranes in the cerebellum, consistent with a higher concentration of voltage-gated sodium ion channels in that region.[10]



brevetoxin A (**4**)
neurotoxic natural product, sodium ion channel activator



brevetoxin B_2 (**5**)
neurotoxic natural product, sodium ion channel activator

Figure 3: Structure of brevetoxin B_2, a toxin produced during a red tide.

Brevenal (**6**) is a smaller polycyclic ether also produced by *K. brevis* during red tide events (Figure 4). Brevenal competitively displaces brevetoxin in a synaptosome receptor binding assay that evaluates sodium channel receptor site binding for natural brevetoxins.[10] Additionally, male mosquito fish exposed to equimolar concentrations of brevetoxin A or B with brevenal lived significantly longer than those exposed to the toxins alone, suggesting brevenal may have a neuroprotective effect. It may also be partly responsible for the variable potency of the red tides, as the concentration of brevenal relative to the other marine toxins varies over the course of the red tide.[10] This non-toxic natural product or structural analogs may therefore find use as a potential therapeutic for brevetoxin poisoning.

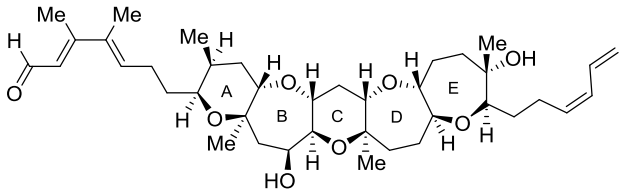


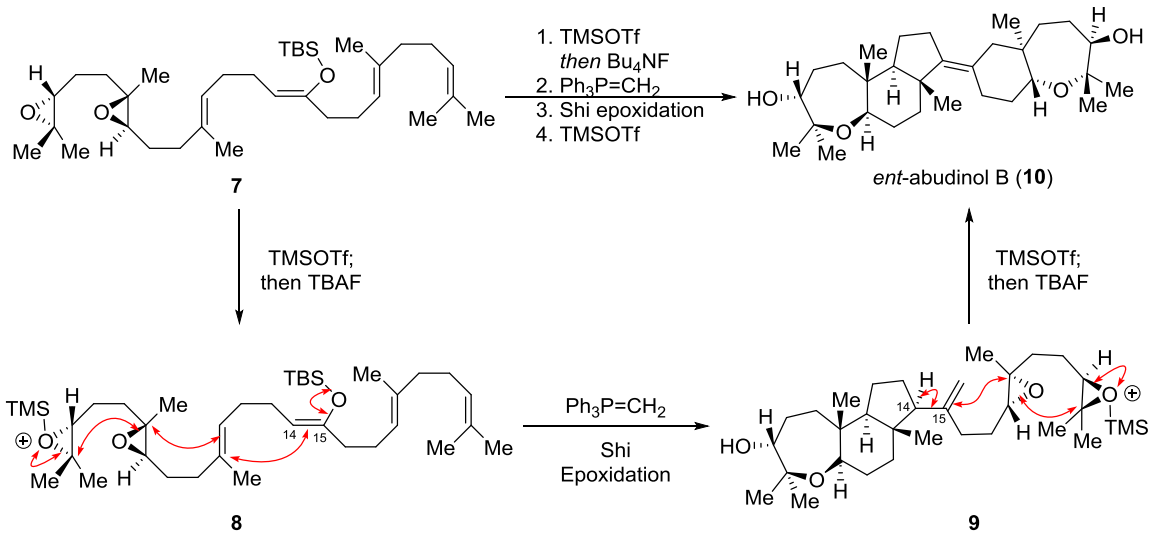
Figure 4: Structure of brevenal, a polycyclic ether natural product produced during red tide events.

1.1.3 Strategies for polycyclic ether synthesis

Many polycyclic ether syntheses use stepwise formation of each ring, followed by extension of the carbon skeleton. A number of strategies to make the ether rings have been employed, including hydroxy dithioketal cyclizations, Suzuki coupling/reductive etherification with Et_3SiH and $BF_3{\cdot}OEt_2$, hydroxyketone cyclization/reductive etherification, SmI_2-promoted cyclization of iodoesters and other radical-based cyclizations, and ring closing metathesis to make the larger 8- and 9-membered rings.[11]

A more efficient approach employed toward the synthesis of polycyclic ethers is the *endo*-mode polyepoxide cascade cyclizations developed by McDonald and Jamison. They have used this approach to form the fused 6- and 7-membered ether ring systems, although there are a number of limitations to this method. The McDonald laboratory was among the first to describe *endo*-mode polyepoxide cyclization cascades. The proposed biomimetic synthesis of *ent*-abudinol B (**10**) was accomplished through a cascade cyclization, Wittig homologation, and Shi epoxidation of diepoxy-enolsilane **7** to form

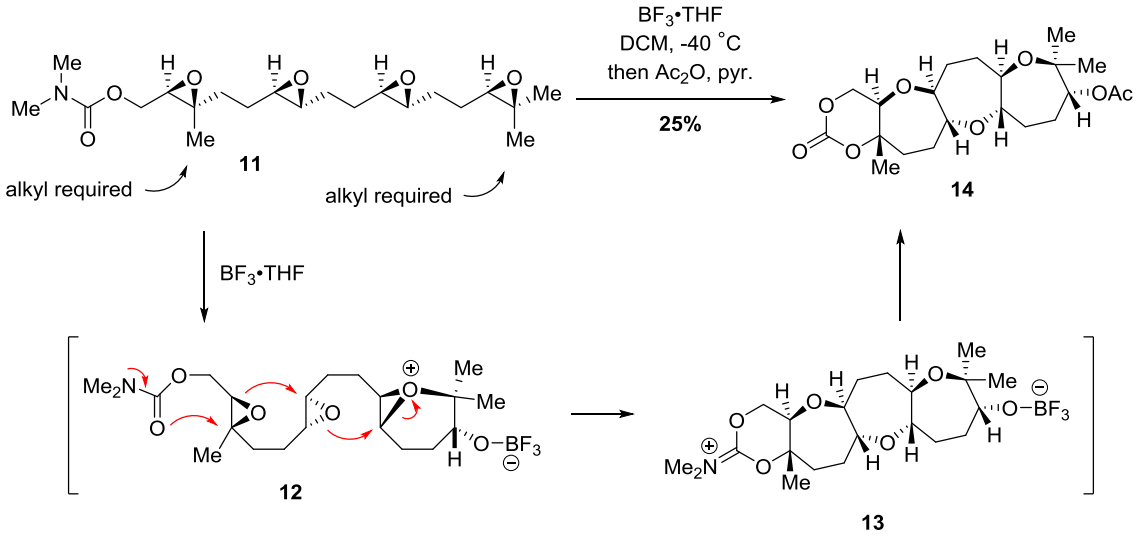
the tricyclic diepoxide **9**, which in turn was cyclized to form the target natural product (Scheme 1).[12,13]



Scheme 1: Biomimetic synthesis of abudinol B through polyepoxide cascade cyclizations.[12,13]

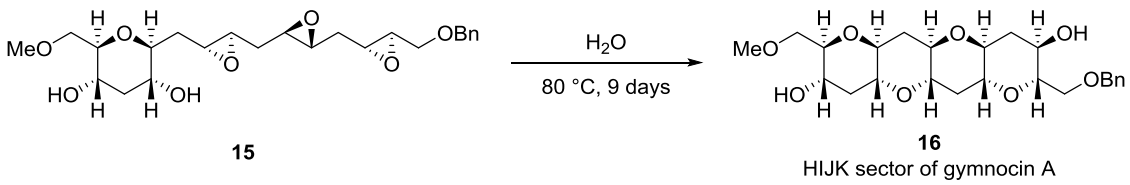
Our laboratory also reported the cascade cyclization of a tetraepoxide **11** to provide the trisoxepane **14** as the major isolable product (Scheme 2).[14] The proposed mechanism includes activation of the terminal epoxide with BF_3·THF to form the bicyclic epoxonim ion **12,** followed by sequential epoxide additions until termination with the carbamate nucleophile. Hydrolysis of the iminium ion **13** afforded the trisoxepane in 25% yield. The low yield is most likely due to poor regioselectivity in the initial activation of the tetraepoxide **11**, as a trisepoxide substrate afforded a bisoxepane in 50% yield and a pentaepoxide substrate gave only 10% yield of the desired tetraoxepane product.[14,15] With this fused oxepane synthesis, we discovered a terminating carbonyl group was required

for *endo*-mode pathways to succeed. Additionally, alkyl substituents at the terminal epoxide and the epoxide adjacent to the carbamate were critical to achieve *endo*-mode cyclization.



Scheme 2: *Endo*-mode cascade oxacyclization of tetraepoxide **11**.

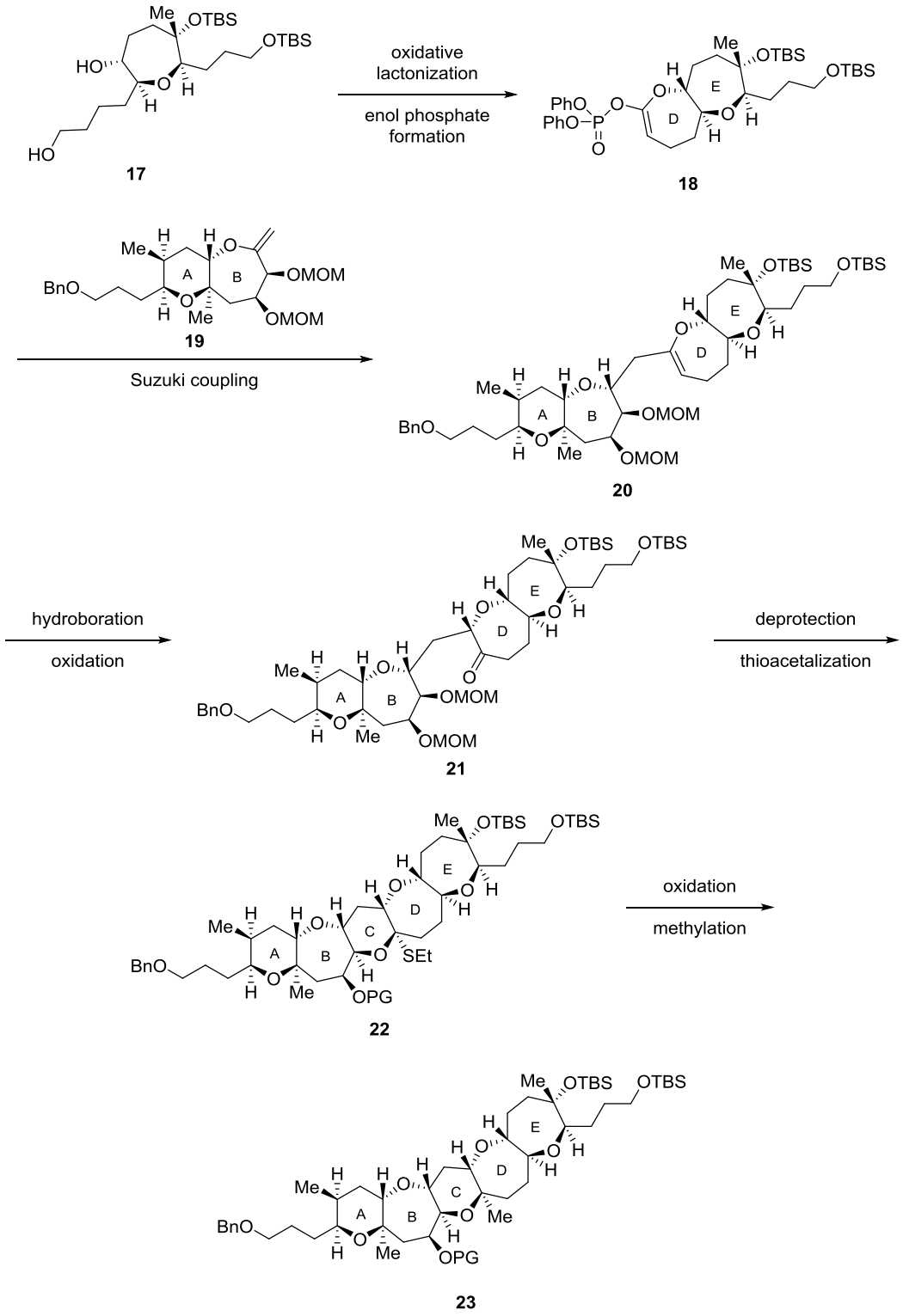
Jamison has developed a strategy in which a polyepoxide tethered to a pre-formed tetrahydropyran ring (**15**) was heated in water to provide up to four *trans*-syn-*trans* fused pyran rings (Scheme 3). However, this approach has not been extended to the synthesis of 7-membered rings, and thus restricts the structure of polycyclic ether natural products that can be assembled with this methodology.



Scheme 3: Jamison's *endo*-mode polyepoxide cyclization cascade.[16]

1.1.3.1 Previous syntheses of brevenal

Brevenal (**6**) has been synthesized previously by three laboratories with five reported syntheses. Sasaki *et* al. reported the first synthesis of **6** in 2006 and corrected the stereochemical assignment of the tertiary alcohol in the E ring.[17] Their second synthesis required 30 steps in the longest linear sequence, with 45 steps to the natural product.[18] The AB and DE rings were formed through successive monocyclizations and the two fragments were coupled to form the C ring and the pentacyclic core of brevenal (**6**) in a convergent synthesis. Their most recent synthesis in 2011 prepared gram quantities of **6** using oxidative lactonizations to form the A,B, D, and E rings and coupled the AB and DE fragments using the Suzuki cross coupling reaction (Scheme 4).[19] The C ring and pentacyclic core of **6** were completed using their thioacetylization methodology.



Scheme 4: Coupling of AB and DE rings in Sasaki's 2011 synthesis of brevenal.[19]

Kadota and Yamamoto also made the core of brevenal (**6**) in 40 steps in a linear synthesis by sequential formation of each ring and extension of the carbon skeleton using the Suzuki cross coupling reaction, followed by installation of the side chains for a total of 55 steps and 0.84% overall yield (Figure 5).

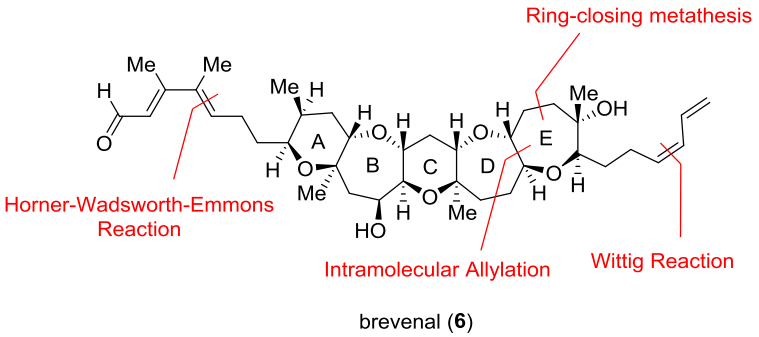
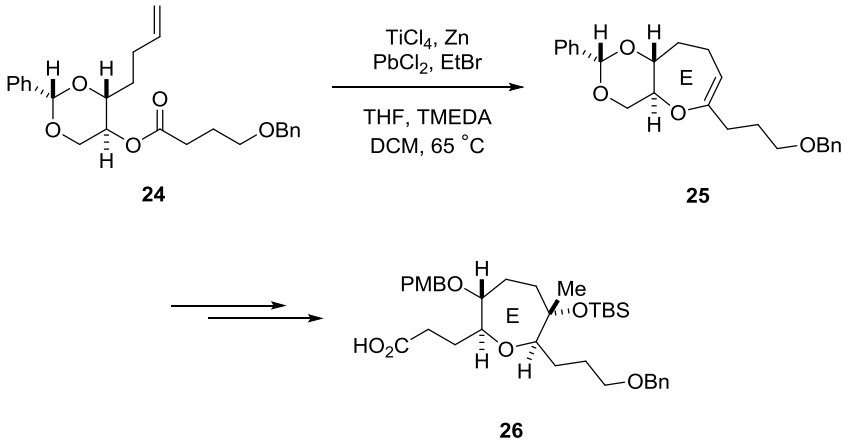


Figure 5: Kadota and Yamamoto synthetic route key steps to **6**.

In 2011, Rainier's group reported a convergent synthesis of brevenal (**6**) using titanium-promoted olefin-ester cyclizations to form the A, C, and E rings (Scheme 5).[20] They modified the synthetic sequence used by Kadota and Yamamoto to install the side chains for a synthesis totaling 38 steps (longest linear sequence).

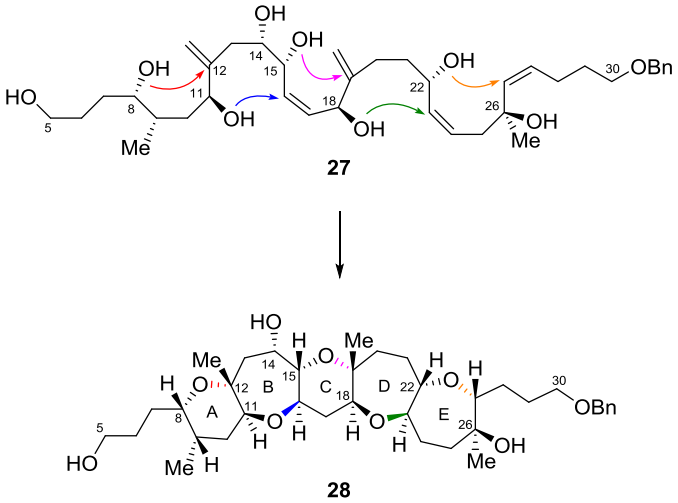
All of the previous syntheses form one ring at a time and then extend the carbon chain to prepare for the next cyclization. This stepwise approach is inefficient and contributes to the large number of steps required to synthesize fused polycyclic ether natural products.



Scheme 5: Titanium-mediated olefin-ester cyclization used in Rainier's synthesis of **6**.[20]

1.1.4 A new approach to polycyclic ether synthesis

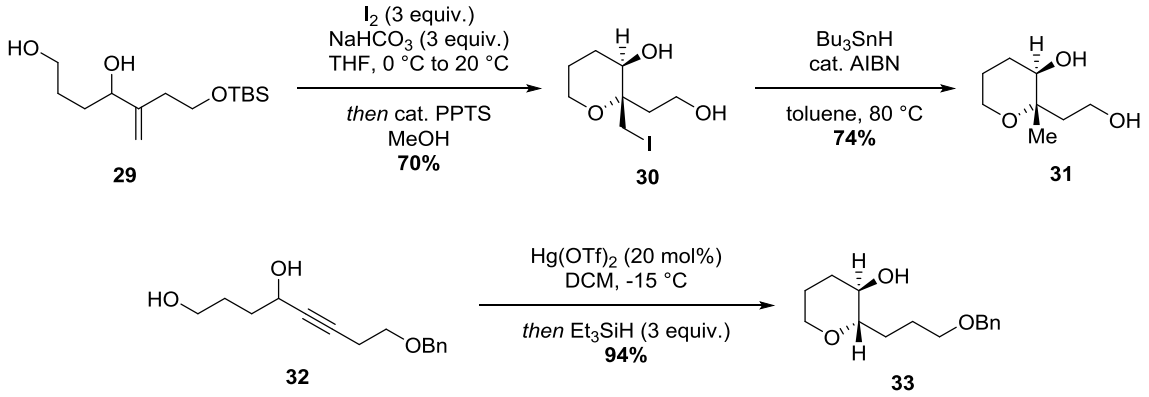
Our lab proposes address the issue of the large number of steps required to make the fused polycyclic ethers by using *exo*-mode cascade cyclizations of acyclic polyene precursors bearing allylic oxygen substituents as stereoinduction elements (Scheme 6). We are shifting the paradigm for cascade cyclization approaches from difficult *endo*-mode cyclizations to a novel synthetic strategy for fused polycyclic ethers using *exo*-mode pathways for ring formation.



Scheme 6: Proposed *exo*-mode cascade cyclization pathway to pentacyclic core of brevenal, first generation (2011).

1.1.4.3 Exo-mode cyclizations from the McDonald laboratory

Our laboratory recently reported the *exo*-mode cyclization of a variety of alkene and alkyne substrates to form tetrahydropyran rings with stereoinduction arising from an allylic alcohol (Scheme 7).[21] A variety of electrophiles successfully activated the alkenes with varying substitution patterns toward nucleophilic addition of the primary hydroxyl group. In the case of the 1,1-disubstituted alkenyl diol **29**, the *trans* diastereomer was the major product of the iodocyclization. Radical dehalogenation of **30** afforded the six-membered ring with the methyl group in the axial position, corresponding to the relative stereochemistry in the A ring of brevenal. Our laboratory also reported the diastereoselective mercury-promoted reductive oxacyclization of an alkynyl diol (**32**), which also provided the *trans* diastereomer of tetrahydropyran **33** as the major isomer (>95:5 dr).



Scheme 7: *Exo*-mode cyclizations of alkenyl and alkynyl diols to form tetrahydropyran rings.[21]

1.1.4.4 A model system for the B ring of brevenal

The B ring of brevenal contains a 1,2-diol system with a *trans* relationship between the protons on C15 and C16. We propose that the seven-membered ring can be formed by the 7-*exo* cyclization of an alcohol onto an activated alkene with stereoinduction derived from an allylic alcohol (Figure 6).

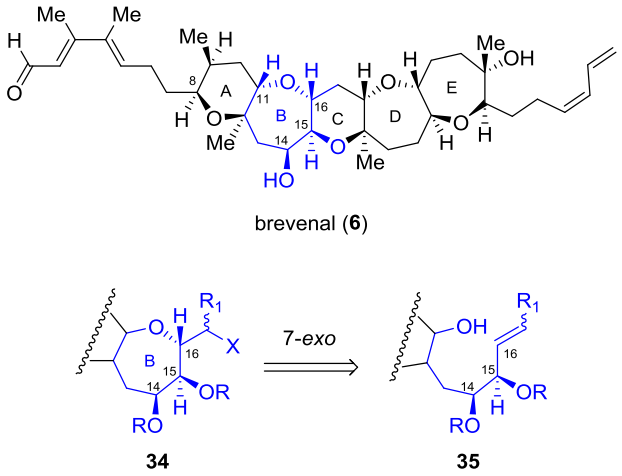


Figure 6: Structure of brevenal, and proposed cyclization strategy for the B ring.

The inclusion of an acetonide protecting group isolates the primary alcohol for subsequent transformations and serves as a conformational restraint to favor cyclization. The acetonide also mimics the substitution pattern in the polycyclic ether core of brevenal for future cascade cyclizations. To mimic the rigidity of a fused ring, a second site of unsaturation was installed in the model system (Figure 7).

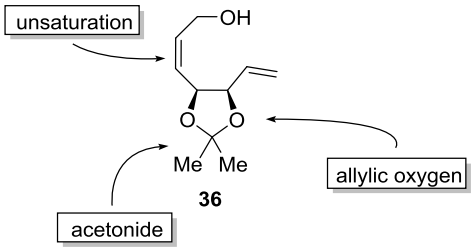
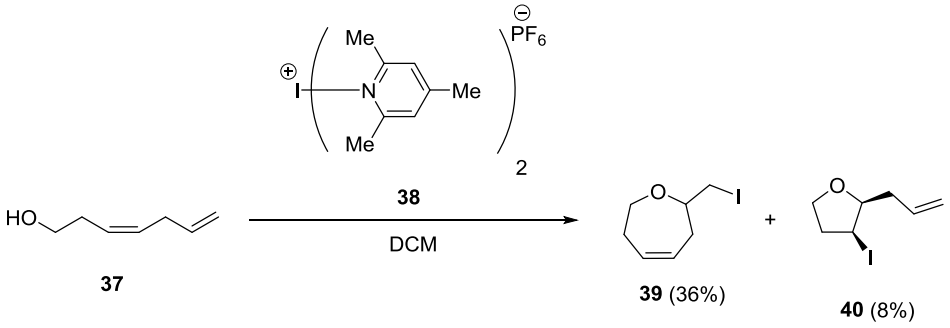


Figure 7: Structural considerations for cyclization substrates.

1.2 Results and Discussion

1.2.1 Electrophile-promoted oxacyclization of alkenyl alcohols

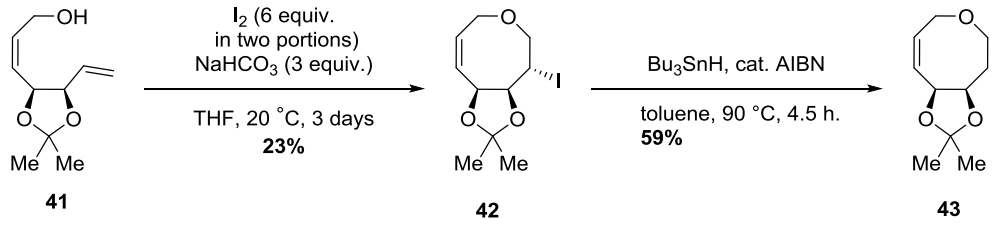
Iodine-promoted oxacyclizations have previously been used for tetrahydrofuran and tetrahydropyran formation.[21–24] There are only a few examples of selective 7-membered ring formation using iodocyclization methodology. Moreover, the effect of an allylic alcohol on the stereochemistry of the oxepane has not been explored (Scheme 8).[25,26]



Scheme 8: Iodocyclizations to form 7- and 5-membered ring iodoether products.[25]

1.2.1.1 Preliminary results from iodocyclizations

A visiting scholar, Dr. Roig Alba, synthesized hydroxy-diene substrate **41** according to a literature procedure[27,28] to test the effect of an allylic hydroxyl substituent on iodine-promoted cyclizations (Scheme 9). She discovered increasing the equivalents of I_2 (6 equiv.) was necessary to favor cyclization of the hydroxy-diene substrate. She isolated 23% of the cyclized product, which was confirmed as the iodooxocene **42** by X-ray crystallography (Figure 8).[29] The formation of the unexpected regioisomer as the major product led us to consider inclusion of an alkyl substituent on the accepting alkene as a way to sterically block the 8-*endo* pathway and favor 7-*exo* cyclization.



Scheme 9: Formation of 8-membered ring from iodocyclization of terminal alkene substrate **41**.[29]

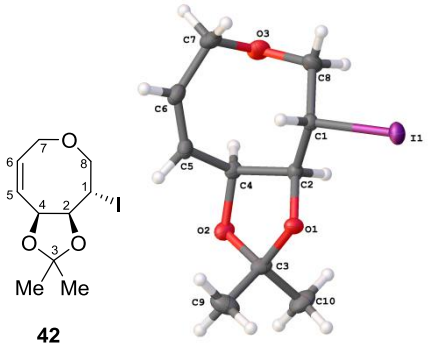
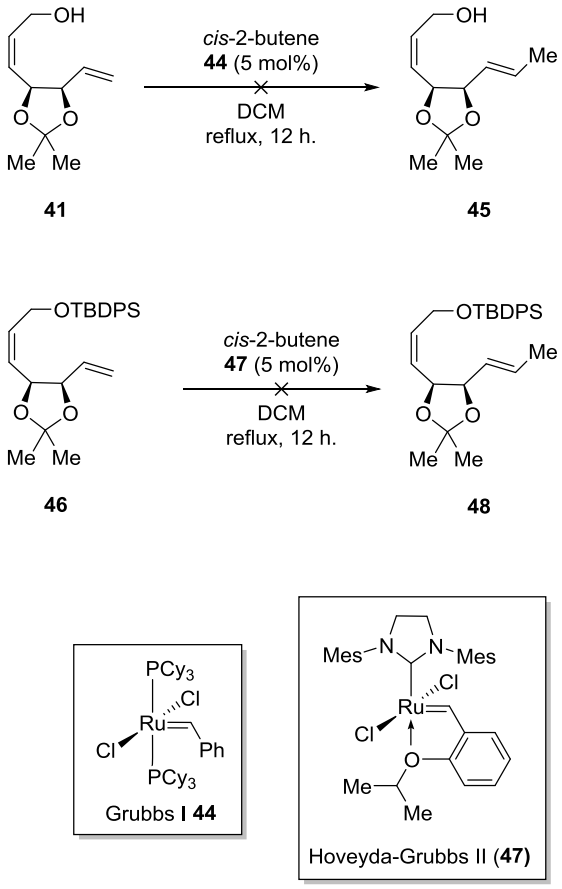


Figure 8: X-ray crystal structure of iodooxocene **42**.[29]

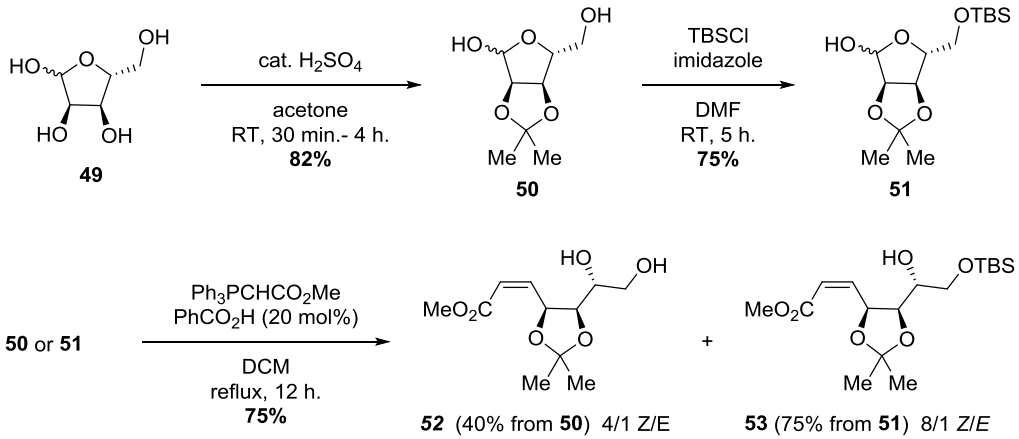
1.2.1.2.1 Synthesis of hydroxy-diene substrates

To make the *trans* methyl substitution (**45**), cross-metathesis was considered as a first attempt. Grubbs I was selected for a cross-metathesis of the terminal alkene substrate **41** with *cis*-2-butene (Scheme 10). We proposed that a less reactive catalyst would be more selective for the terminal alkene than the internal alkene; however, only starting material was recovered from the reaction. The TBDPS-protected derivative **46** was also subjected to cross metathesis conditions with a more reactive catalyst. The large silyl ether protecting group was proposed to sterically block the internal alkene from reacting with the catalyst and increase the selectivity for the terminal alkene. However, the crude ^{1}H NMR indicated a mixture of alkene isomers and an alternative route to the methyl substituted hydroxy-dienes was pursued.



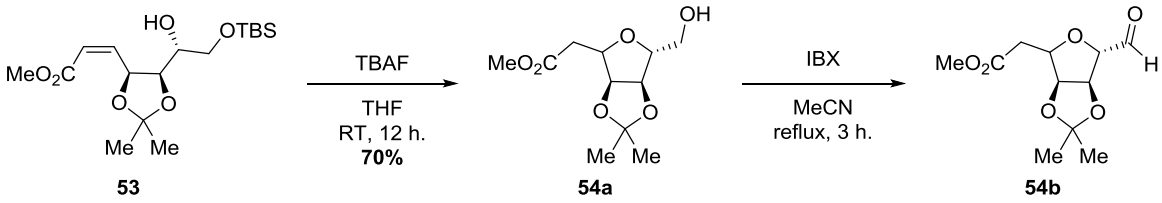
Scheme 10: Cross-metathesis to synthesize methyl-substituted hydroxy-diene substrates.

D-ribose was protected as the 2,3-isopropylidene acetal under acidic conditions and converted to α,β-unsaturated methyl ester **52** (4/1 *Z*/*E*) or **53** (8/1 *Z*/*E*) using the Wittig reaction (Scheme 11).[30,31] The inclusion of benzoic acid in the Wittig reaction decreases the formation of side products resulting from the addition of the secondary oxygen with the α,β-unsaturated ester in an oxa-Michael reaction.[31] The corresponding diol **51** was difficult to separate from the triphenylphosphine oxide by-product of the Wittig reaction, and the inclusion of a primary TBS protecting group[32] on ribofuranoside **50** made the separation from triphenylphosphine oxide easier.[33]



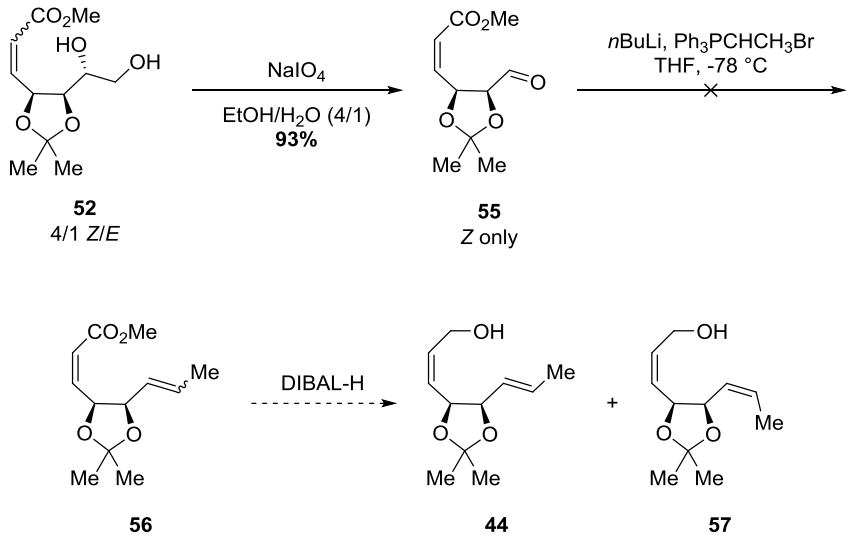
Scheme 11: Synthesis of unsaturated methyl esters from protected D-ribose.

The conversion to the aldehyde through oxidative cleavage required the removal of the primary TBS group. To prevent accidental deprotection of the acetonide, acidic conditions to remove the TBS group were avoided. However, deprotection of the TBS group using TBAF caused an intramolecular oxa-Michael cyclization to form a tetrahydrofuran (**54a**), which was confirmed by oxidation to the aldehyde **54b**, as the major product of the reaction (Scheme 12). As this formation of the cyclized product would inhibit this route, we devised a new synthetic sequence to the methyl-substituted substrates.



Scheme 12: Formation of tetrahydrofuran or tetrahydropyran product.

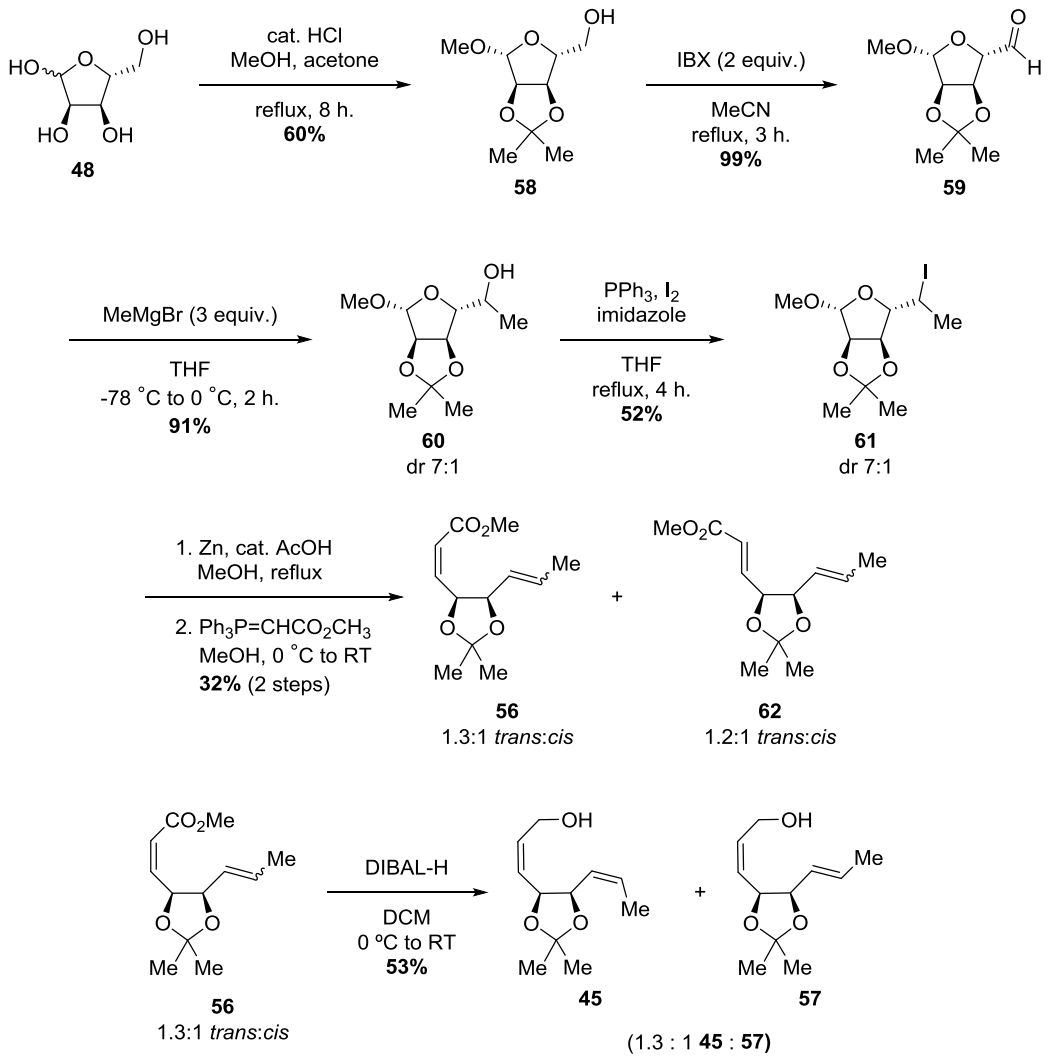
The diol **52** was carried forward, as the deprotection of the TBS group provided only the oxa-Michael addition product **54a/b**. Oxidative cleavage of diol **52** provided the aldehyde **55** as a single stereoisomer (Scheme 13).[34] Attempts to install the methyl alkene using the Wittig reaction were unsuccessful, resulting in the formation of unknown products lacking alkene peaks in the ^{1}H NMR. Therefore, we pursued a new route to the hydroxy-diene substrates.



Scheme 13: Synthetic route to hydroxy-diene substrates from **52**.

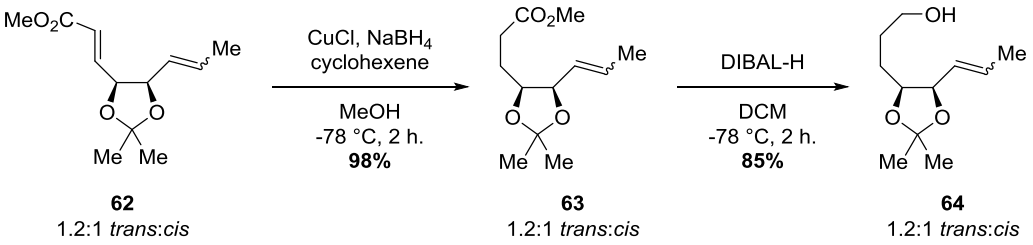
The hydroxy-diene substrates were prepared by modification of the literature procedure used to make compound **41**.[29] Protection of D-ribose proceeded smoothly to afford ribofuranose **58** as a single stereoisomer. Oxidation to the aldehyde, followed by the addition of methyl magnesium bromide, provided secondary alcohol **60** as an inseparable mixture of diastereomers (7:1 dr). Conversion to the secondary alkyl iodide **61** was accomplished using Appel conditions. The one-pot Zn-promoted elimination/ring opening and Wittig reaction sequence provided the unsaturated esters **56** and **62**, and the

Z-ester was reduced to the primary alcohol to synthesize hydroxy-diene substrates **44** and **57** as a mixture of alkene isomers.



Scheme 14: Synthetic route to hydroxy-diene substrates.[29]

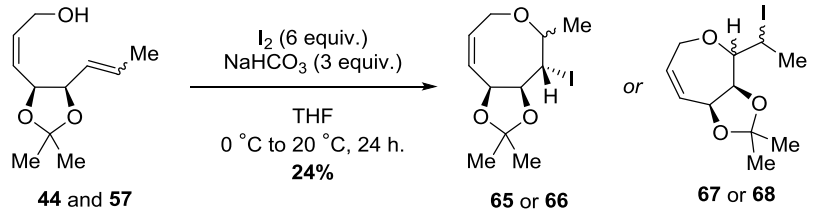
The saturated alkenyl alcohol was prepared by a 1,4-conjugate reduction of ester **61** and reduction to the primary alcohol (Scheme 15).



Scheme 15: Synthesis of the saturated substrate **64**.

1.2.1.2.2 Iodocyclization results and discussion

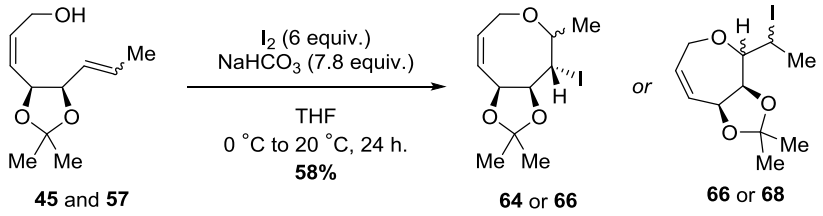
The mixture of alkene isomers was subjected to the reaction conditions Dr. Roig Alba discovered using the terminal alkene system (Scheme 16). However, spectroscopic analysis of the products could not determine if the 8-membered ring (**65** or **66**) or 7-membered ring (**67** or **68**) were formed during the cyclization reaction. Both compounds contained a methyl doublet ($^3J_{HH}$ = 5.8 Hz, $^3J_{HH}$ = 6.5 Hz), consistent with the structures for both possible regioisomers.



Scheme 16: Iodocyclization of hydroxy-diene as a mixture of alkene isomers.

The low yield of the iodocyclization reaction could possibly be due to halohydrin formation from the addition of iodine and water to the substrate. Alternatively, any HI formed during the course of the reaction due to the excess of iodine used to cyclize the hydroxy-diene substrate could be responsible for the low yield of cyclized materials. The

acid could promote side reactions, including loss of the acetonide protecting group under acidic conditions. To test this theory, the equivalents of $NaHCO_3$ were increased in the reaction mixture. Equimolar amounts of $NaHCO_3$ and I_2 did not alter the outcome of the reaction, but an excess of $NaHCO_3$ (7.8 equiv.) relative to I_2 (6 equiv.) more than doubled the yield of the reaction (Scheme 17).



Scheme 17: Increase in yield with excess $NaHCO_3$ in the iodocyclization of hydroxy-dienes **45** and **57**.

With the increased yield of the reaction, the partial separation of the two cyclized compounds was achieved using column chromatography. One compound was confirmed by X-ray crystallography to be the iodooxocene **65**, arising from 8-*endo* cyclization of the *cis*-alkene isomer **45** (Figure 9). Since the identity of the other cyclized product was unconfirmed at this time, the separation of **45** and **57** was undertaken. Although the methyl *E* and *Z* alkene isomers of the dienyl ester compounds **56** and **62** were inseparable, the pure dienyl alcohols could be isolated by chromatography on silver nitrate-impregnated silica gel.[35]

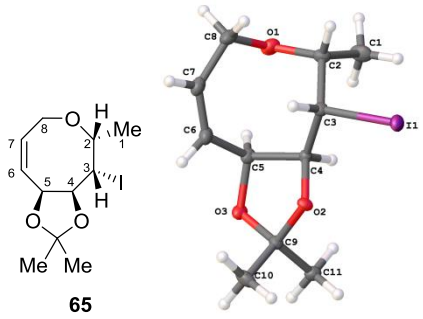
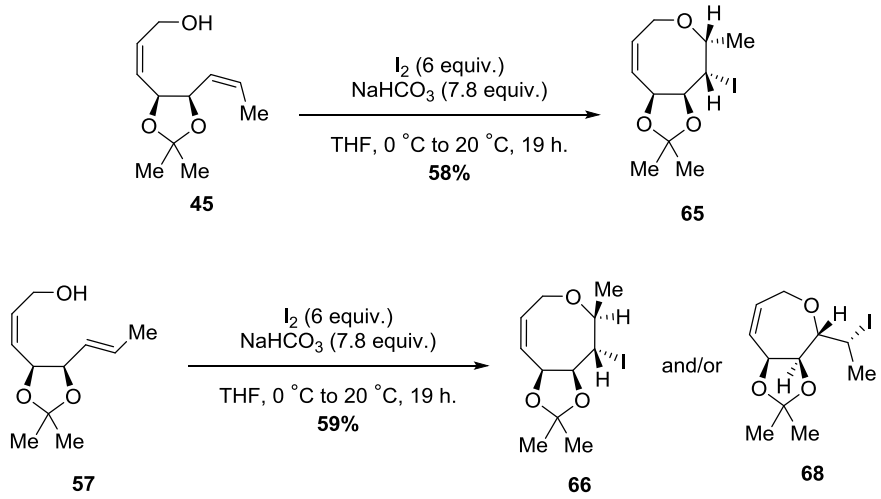


Figure 9: X-ray crystal structure of iodooxocene **65** from iodocyclization of cis hydroxy-diene **45**.

Iodine-promoted cyclization of the pure *cis* hydroxy-diene **45** provided the expected 8-*endo* regioisomer **65**. However, the iodocyclization of *trans* hydroxy-diene **57** afforded a different product than the *cis* counterpart when subjected to the optimized conditions.



Scheme 17: Iodocyclizations of hydroxy-dienes **45** and **57**.

Spectroscopic analysis using ^{1}H NMR data was unable to differentiate between the two possible regioisomers. In compound **65**, a small coupling ($^{3}J_{HH}$ = 4.5 Hz) was

observed and attributed to the *cis* relationship between the protons on C1 and C2 (Figure 10). A larger coupling ($^3J_{HH}$ = 11.1 Hz) was assigned to the coupling of protons on C2 and C3, which have a *trans* relationship. The NOE effect observed between the C3 hydrogen and the C1 methyl group provided additional evidence of the 8-membered ring regioisomer (**65**) and stereochemistry at C1.

The analysis of the product from iodocyclization of *trans* hydroxy-diene **57** was unable to confirm either the 7-*exo* or 8-*endo* products. A large coupling constant in the ^{1}H NMR ($^3J_{HH}$ = 10.2 Hz) could be attributed to a *trans* relationship between the protons on C1 and C2 in the 8-membered ring (**66**). However, this could also easily be explained as a large coupling constant between the protons on C2 and C3 in the 7-membered ring (**68**). The NOE effect observed between the C1 methyl group and the proton on C3 did not provide any additional information that could differentiate the two possibilities (Figure 10).

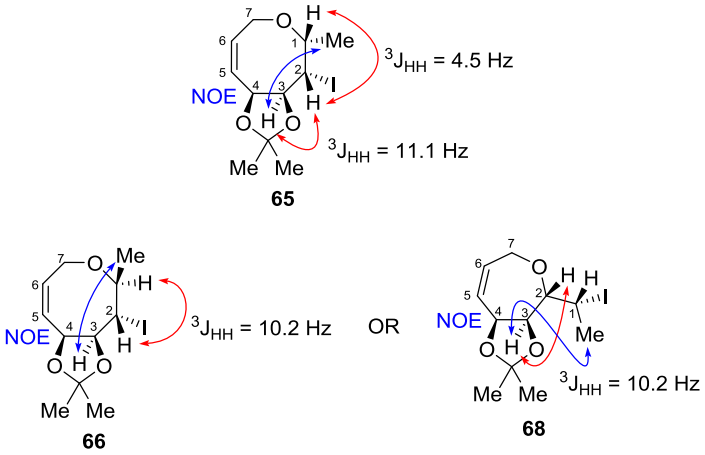


Figure 10: Spectroscopic data of possible regioisomers from iodocyclization of **45** and **57**.

The deiodination of iodooxocene **65** provided additional confirmation of the structure with the appearance of a methyl doublet (δ 1.30 ppm, $^{3}J_{HH}$ = 6.6 Hz, Figure 11). The ring size of the unknown cyclization product can be determined by deiodination. If the 8-membered ring regioisomer (**68**) was formed, a methyl doublet would be expected in the ^{1}H NMR of the deiodinated product **70**. However, a methyl triplet would be expected in the ^{1}H NMR if the deiodinated product was a 7-membered ring (**71**). After deiodination, a methyl doublet was observed (δ 1.28 ppm, $^{3}J_{HH}$ = 6.7 Hz), indicating the formation of the 8-membered ring **70**.[29]

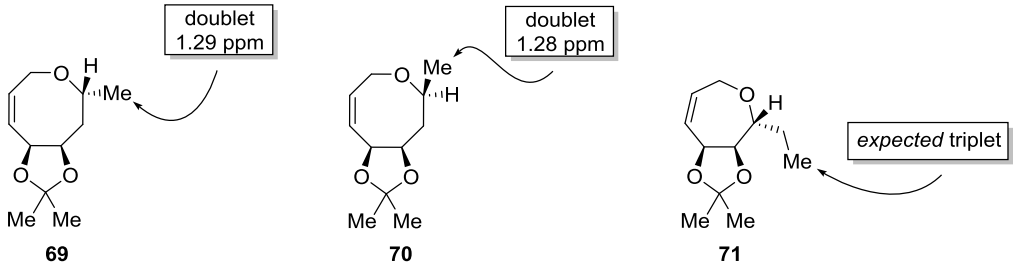
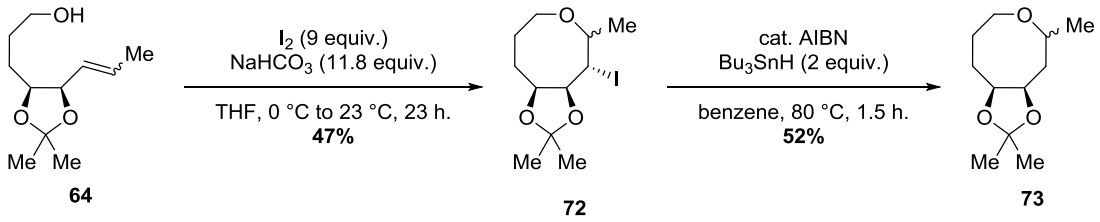


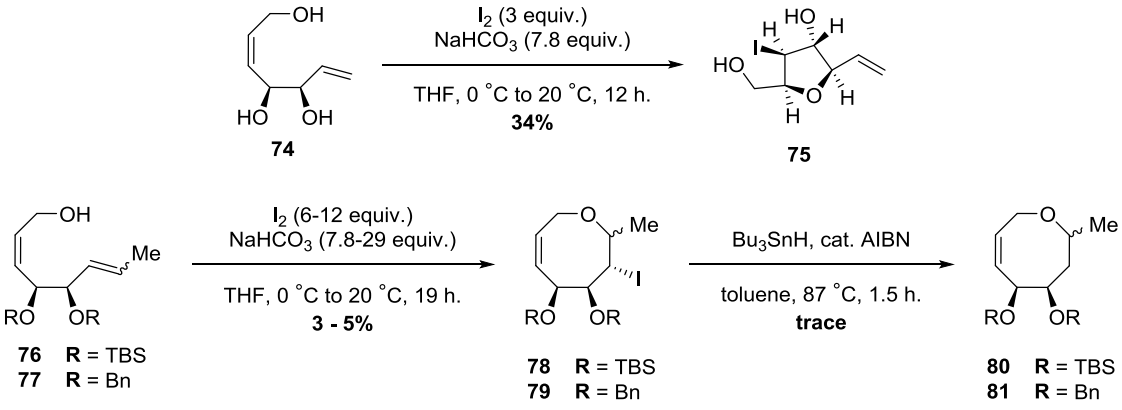
Figure 11: Deiodination products and confirmation of regioselectivity.

With both alkene isomers forming the 8-membered ring regioisomer, we turned our attention to the conformational restrictions placed on the model system for the B ring. The saturated substrate **64** was subjected to iodocyclization conditions, requiring additional I_2 and $NaHCO_3$ to push the reaction to complete conversion (Scheme 19).[29] After deiodination and observation of two methyl doublets in the ^{1}H NMR, we concluded the saturated system was also selective for 8-membered ring formation.



Scheme 19: Iodine-promoted 8-*endo* cyclization of saturated alkenyl alcohol **63** and deiodination of cyclized intermediate **72**.[29]

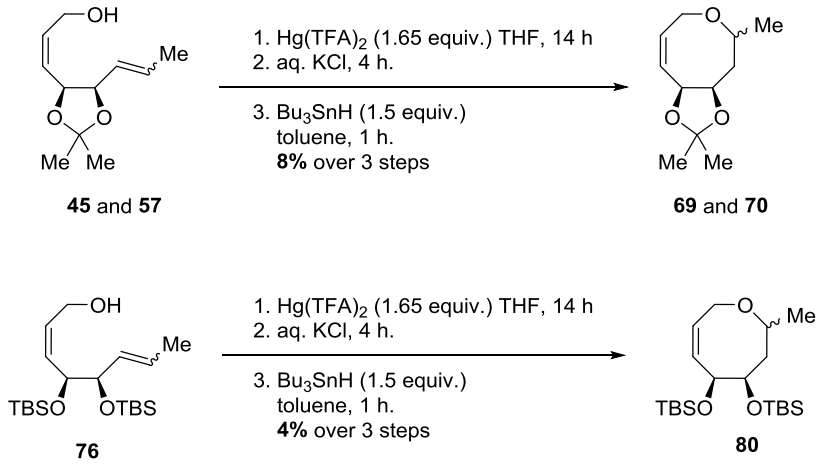
The effect of the rigid cyclic protecting group was evaluated by removal of the acetonide and subjecting the diol, TBS, or Bn derivatives to the iodocyclization conditions (Scheme 20). In the case of the diol **74**, the tetrahydrofuran **75** was the major product as expected. No evidence of the 7- or 8-membered rings was observed. However, both the bis-TBS (**76**) and bis-Bn (**77**) protected compounds favored formation of the 8-membered ring. At this point, we decided a cursory investigation of other electrophiles may determine if the choice of electrophile affects the regioselectivity of the reaction.



Scheme 20: Protecting group choice has no effect on regioselectivity of the iodocyclization.

Mercury trifluoroacetate-promoted oxacyclization of a mixture of hydroxy-dienes **45** and **57** provided the 8-membered ring regioisomers **69** and **70** in low yield (Scheme 21). Some starting material is recovered from the reactions (~15%); however the majority of the material is unaccounted for. TLC analysis of the reaction mixture shows complete consumption of the starting material. Upon addition of Bu_3SnH to the organomercury intermediate, the reduced mercury immediately precipitates from the solution and suggests that a mercury adduct is forming without cyclization of the substrate.

The TBS-protected hydroxy-diene **76** also preferentially forms the 8-membered ring **80** under these conditions. We concluded that these hydroxy-diene systems result in exclusive formation of 8-membered rings.



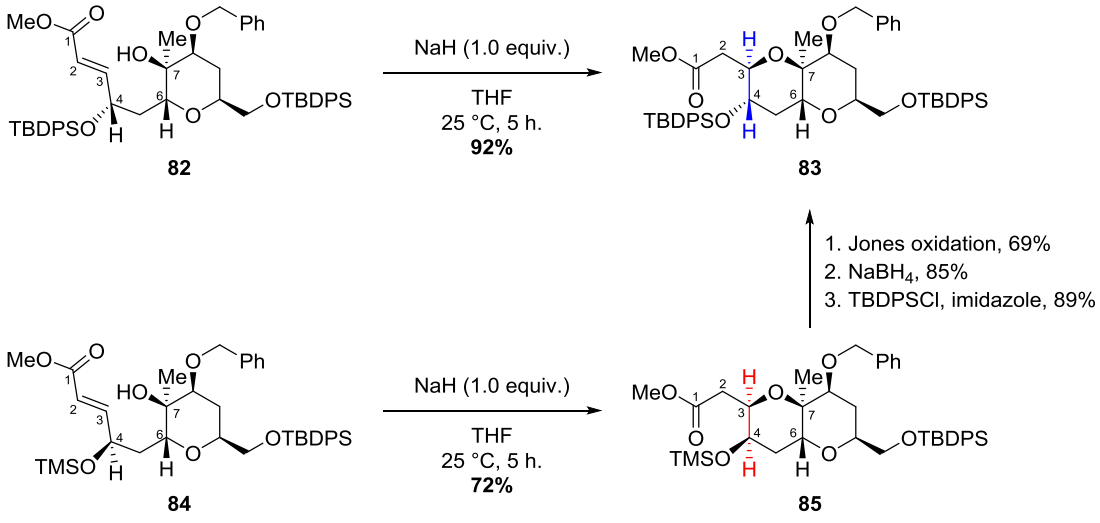
Scheme 21: Hg^{2+} -promoted oxacyclization of hydroxy-dienes **45/57** and **76**.

During the course of substrate synthesis, I noticed a side product forming from an oxa-Michael addition of an oxygen nucleophile onto an α,β-unsaturated ester (for an

example, see Scheme 12). I proposed the oxa-Michael reaction may be a solution to forming the 7-*exo* product in the model for the B ring of brevenal.

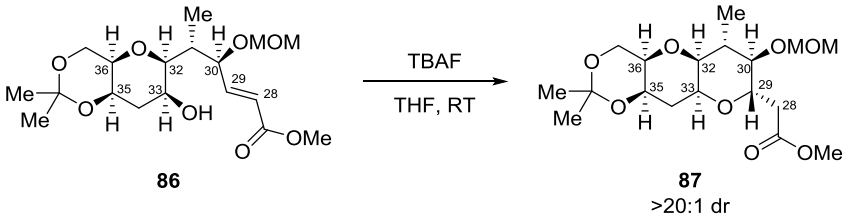
1.2.2 Conjugate additions for 7-membered ring formation

Conjugate additions have successfully been implemented in the synthesis of polycyclic ethers in the past. In the synthesis of the IJK ring system of brevetoxin, Nicolaou's laboratory used an oxa-Michael addition to form the J-ring (Scheme 22).[36] The conjugate addition step resulted in the formation of only one stereoisomer, most likely due to the preset stereochemistry of the oxygen nucleophile and the rigidity of the K-ring system. The formation of the *trans* (blue) or *cis* (red) relationship between the C3 and C4 protons is independent of the stereochemistry of the allylic hydroxyl at C4. The stereochemistry was confirmed by the 10.5 Hz for the C3 and C4 protons in **83**, and a coupling constant of <1 Hz for the same protons in **85**. However, a three-step procedure converted compound **85** to the desired *trans* stereoisomer **83**.



Scheme 22: Conjugate additions in the synthesis of the IJK ring system of brevetoxin B.[36]

While investigating the C27-C38 segment of the halichondrin B series, Kishi and coworkers reported the use of an oxa-Michael addition to form the O-C29 bond (Scheme 23).[37] In this system, the *trans* stereoisomer is formed with >20:1 diastereoselectivity from the oxa-Michael reaction. However, they note that the corresponding triol (deprotected at C33, C35, and C37) initially yielded the desired *trans* diastereomer, but rapidly isomerized to form the undesired *cis* diastereomer as the major product.



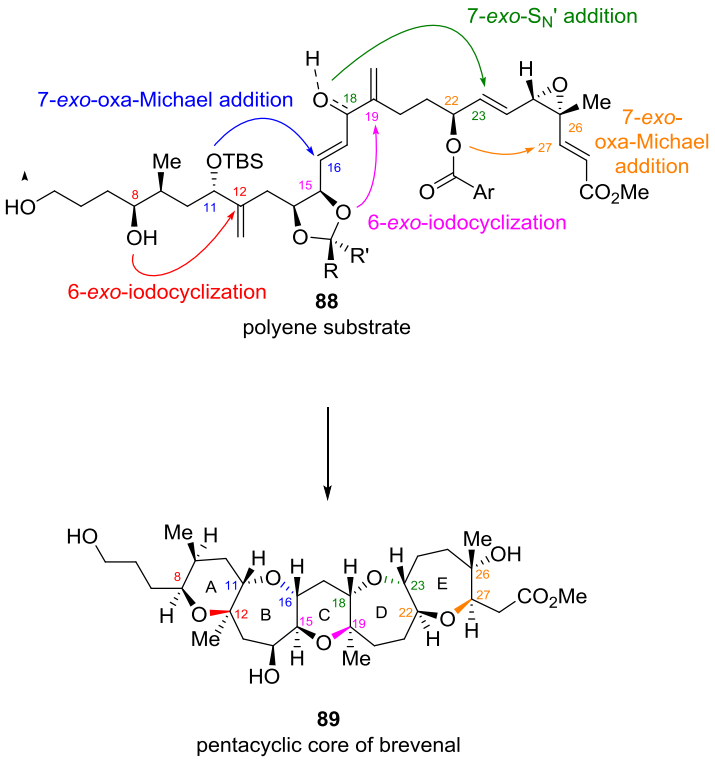
Scheme 23: Use of oxa-Michael reaction in the synthesis of halichondrin B.[37]

In both the halichondrin syntheses and JIK ring system of brevetoxin B, the stereochemistry of the oxygen nucleophile was set in a previous step and appears to be the controlling factor in the stereochemistry of the oxa-Michael addition. The polyene substrate for the pentacyclic core of brevenal would also have an oxygen nucleophile with preset stereochemistry, but the model system for the B ring of brevenal contains a primary oxygen nucleophile. Therefore, we were interested to determine the effect of an allylic oxygen diastereoselectivity of the oxa-Michael addition.

1.2.2.1 Re-evaluation of synthetic plan for brevenal

Based on previous results from our lab, we propose that sequential formation of each ring through an *exo*-mode cyclization of a modified polyene substrate could access

the pentacyclic core of brevenal by careful application of cyclization conditions (Scheme 24). We imagined the A ring can be formed through a 6-*exo*-iodocyclization onto a 1,1-disubstituted alkene, followed by B ring formation through an intramolecular 7-*exo* conjugate addition pathway. The C ring can be formed through and iodine promoted 6-exo-cyclization from the acetal-protected diol. D ring formation can occur through a Pd- or acid-mediated 7-exo addition to a vinyloxirane, and the E ring can be accessed by 7-*exo*-intramolecular conjugate addition.



Scheme 24: Proposed pentacyclization pathway to the core structure of brevenal, second generation (2013).

1.2.2.1 Synthesis of conjugate addition substrates

The substrates were imagined to come from a partial reduction of a propargyl ester to the *cis* α,β-unsaturated methyl ester (Figure 12). The propargyl ester can be prepared in four steps from an alkynyl alcohol **92** derived from D-ribose.

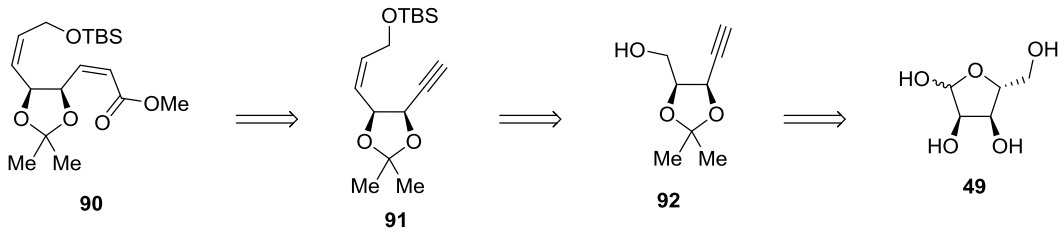
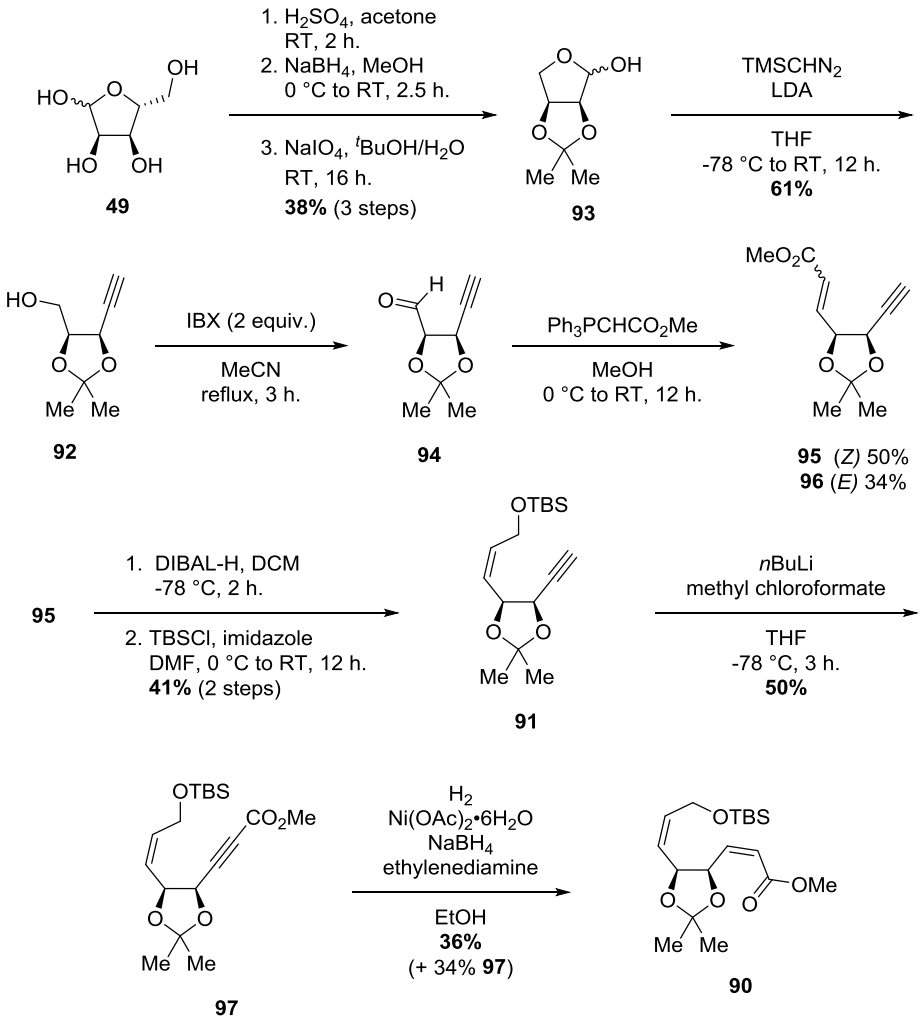


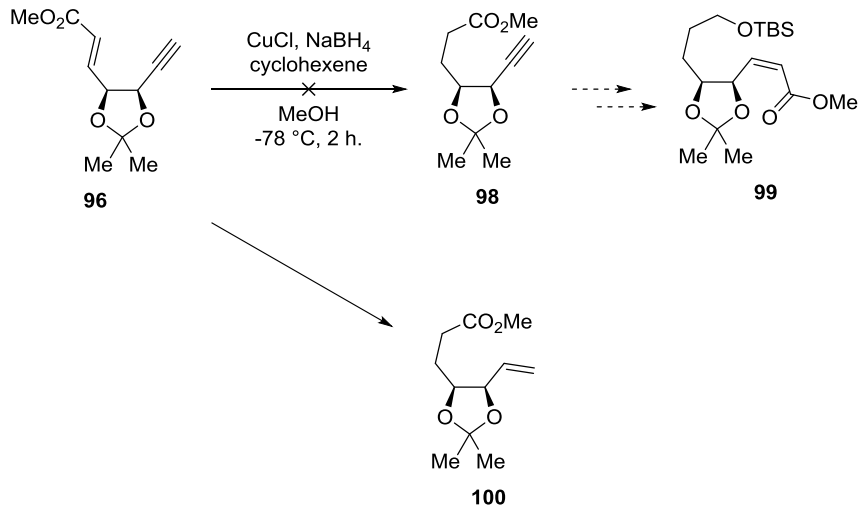
Figure 12: Retrosynthetic analysis of conjugate addition substrates from intermediate propargyl esters.

D-ribose was protected as the 2,3-isopropylidene acetal and was converted to the hemiacetal **93** in a two-step procedure (Scheme 25).[30] Alkynylation of the hemiacetal was accomplished with TMS-diazomethane to afford the alkynyl alcohol **92** in moderate yield.[38] Oxidation of the primary alcohol to the aldehyde and subsequent Wittig reaction provided the α,β-unsaturated esters **95** and **96**. Z-ester **95** was reduced to the primary alcohol and protected as the TBS-ether. Addition to methyl chloroformate produced the propargyl ester **97** in variable yields, with the highest yields corresponding with distillation of methyl chloroformate prior to use in the reaction. Partial reductions of alkyne **97** using both P-2 nickel and Lindlar's catalyst afforded an inseparable mixture of the desired α,β-unsaturated methyl ester **90** and the propargyl methyl ester (**97**) starting material. Although the mixture of products was used for an oxa-Michael cyclization, a new route was pursued in order to obtain the substrates with higher purity.



Scheme 25: First successful route to conjugate addition substrates.

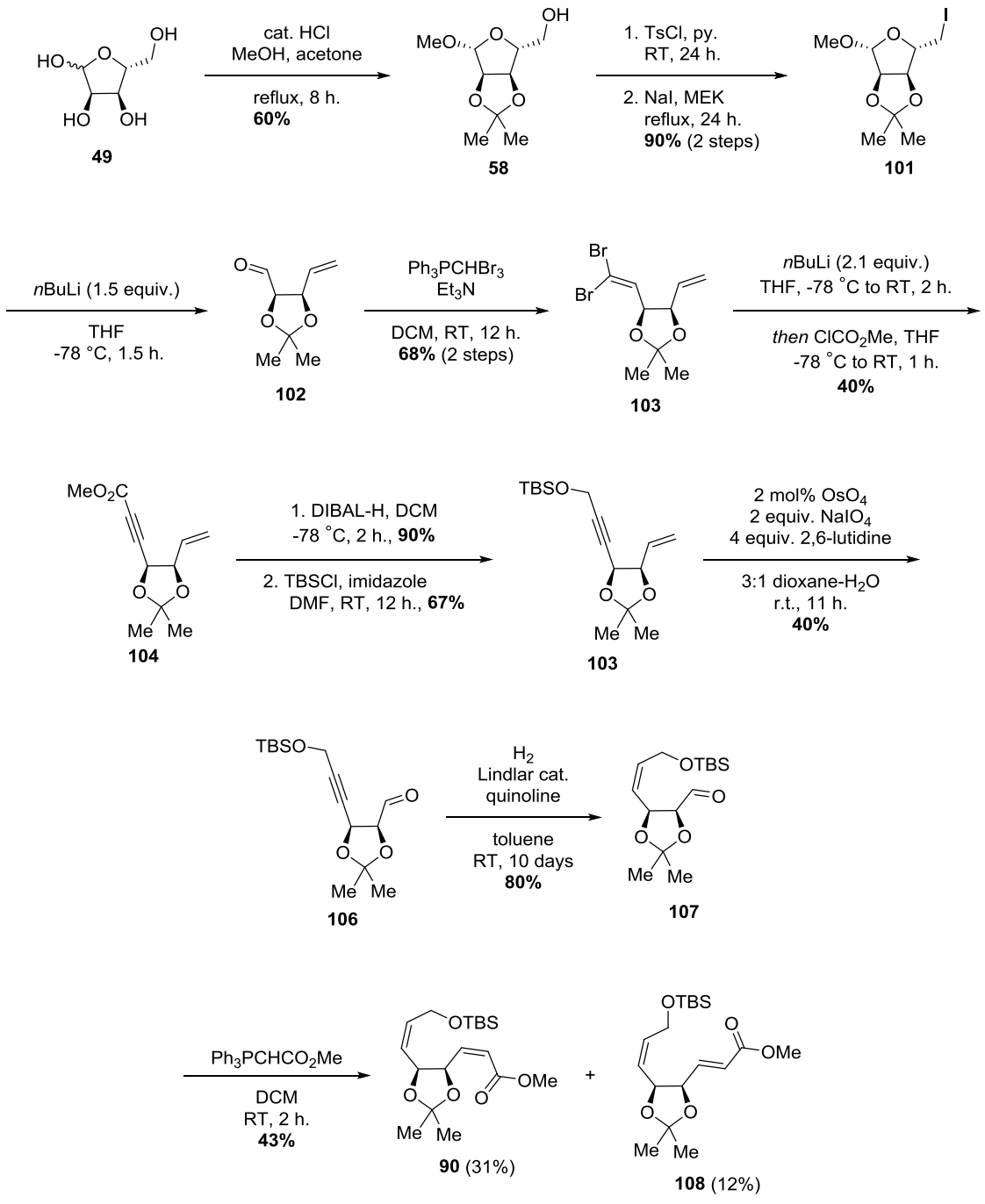
The E-ester **96** was subjected to conditions for 1,4-conjugate reduction to synthesize the saturated substrate **99** (Scheme 26). However, the terminal alkyne was also reduced under these conditions to afford the terminal alkene **100** as an inseparable contaminant in the product.



Scheme 26: Attempted synthesis of saturated conjugate substrate.

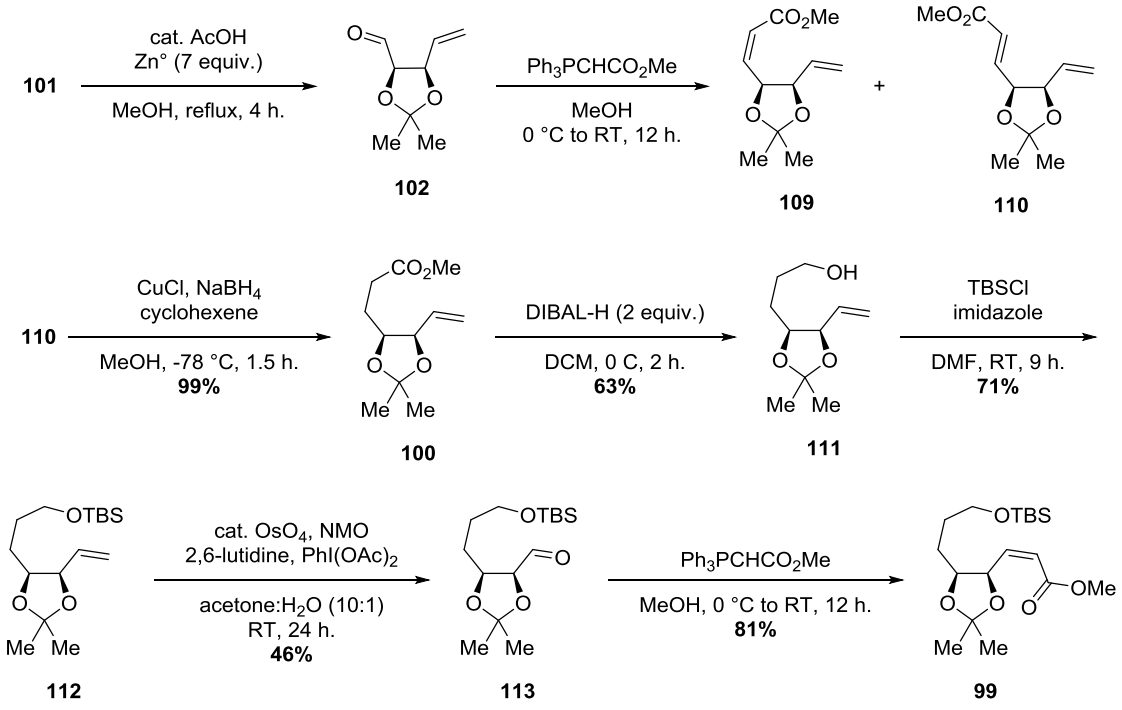
The conjugate addition substrates were synthesized through a modification of the route for the hydroxy-diene substrates (Scheme 27). D-ribose was converted in three steps to the alkyl iodide **101**. Lithium-halogen exchange resulted in elimination and ring opening of the ribofuranoside to provide aldehyde **102**. The aldehyde was subjected to the Corey-Fuchs procedure to form the dibromoalkene **103**, followed by elimination and quench with methyl chloroformate to synthesize propargyl ester **104**. Yields did not seem to be improved by the distillation of the methyl chloroformate prior to use in the reaction. Reduction of the ester and protection of the resulting primary alcohol as the silyl ether proceeded smoothly. Alkene **110** was converted to the aldehyde using Johnson-Lemieux conditions, and the alkyne was partially reduced to the alkene **107** using Lindlar's catalyst. The extended reaction time for the partial reduction of the alkyne may be due to poisoning of the Pd catalyst by residual OsO_4 from the Johnson-Lemieux procedure, in addition to the quinolone and $BaSO_4$ normally used to poison the catalyst. The aldehyde was transformed into the α,β-unsaturated methyl esters **90** and **108**, which were separated

by column chromatography. The order of the final two steps was important to avoid unwanted reduction of the alkene in the α,β-unsaturated ester during the Lindlar reduction of the alkyne.



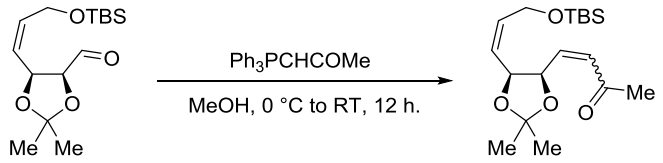
Scheme 27: Synthesis of unsaturated conjugate addition substrates **90** and **108**.

The saturated substrate **99** was synthesized in a similar manner to the hydroxy-diene substrates used earlier. Zinc-promoted ring opening/elimination of iodide **101** provided aldehyde **102**, which was immediately used in the following step as a crude solution in MeOH to avoid epimerization of the α-stereocenter. The α,β-unsaturation in the *E* methyl ester **110** from the Wittig reaction was reduced to provide the saturated ester **100**. Reduction of the ester to the primary alcohol followed by TBS protection produced the terminal alkene **112**. The alkene was dihydroxylated and oxidatively cleaved to provide aldehyde **113**, which was used as a crude material in the Wittig reaction to afford the *Z*-methyl ester **99**.



Scheme 28: Synthesis of saturated conjugate addition substrate **99**.

The ketones were also of interest and were synthesized from the unsaturated aldehyde **107** *via* a Wittig reaction to provide both the *Z* (**114**) and *E* (**115**) methyl ketones (Scheme 29).



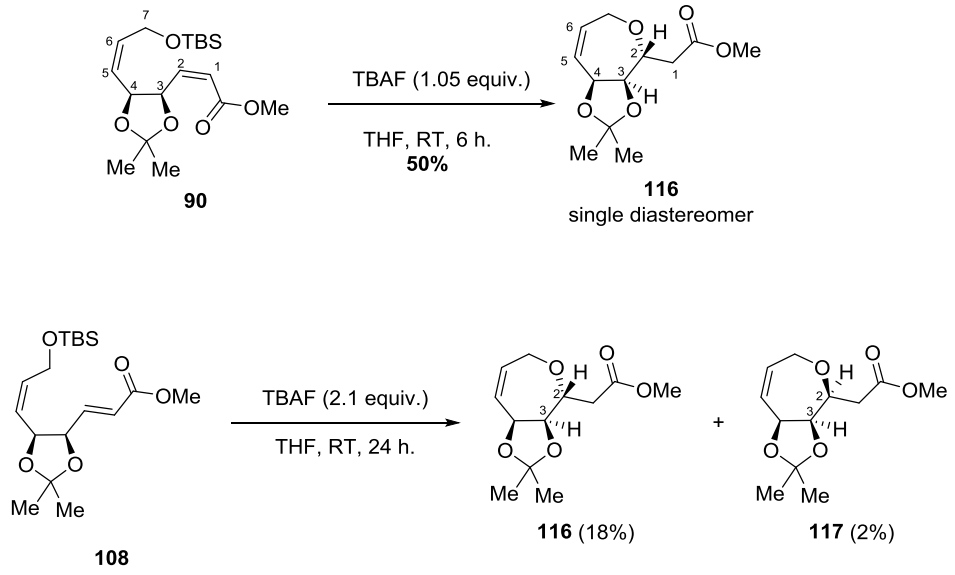
107

114 *Z* 6%
115 *E* 43%

Scheme 29: Synthesis of ketone cyclization substrates.

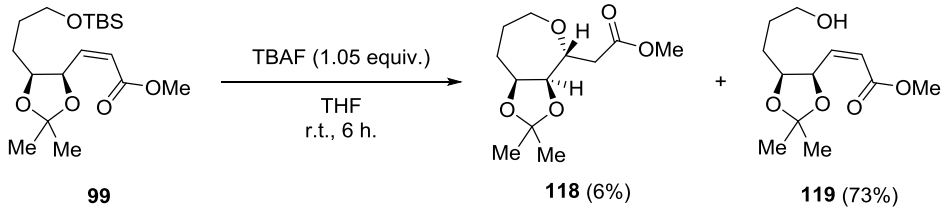
1.2.2.2 Conjugate addition results and discussion

TBAF was selected to deprotect the primary silyl ether on the *Z,Z*-methyl ester **90** and to our delight, the major product of the reaction was the cyclized ether **116** (Scheme 30). The compound was determined to be the *trans* diastereomer, due to a large coupling constant between the two protons on C2 and C3 ($^3J_{HH}$ = 10.0 Hz). The *cis* diastereomer was not observed, however small amounts of the deprotected starting material (~13%) were recovered along with other unidentifiable products. When the *E,Z*-methyl ester **108** was used as the substrate for conjugate addition using TBAF, both the *trans* (**116**, $^3J_{HH}$ = 9.9 Hz for protons on C2 and C3) and the *cis* (**117**, $^3J_{HH}$ = 1.7 Hz for protons on C2 and C3) diastereomers were isolated. The remainder of the material was unable to be identified, although it is possible that it contains some form of cyclized material as evidenced by a pair of ddd (δ 2.14, J = 14.2, 9.2, 6.5 Hz and δ 1.97, J = 14.2, 8.9, 6.8 Hz) with a chemical shift in the appropriate region for protons located alpha to an ester.



Scheme 30: Conjugate addition during deprotection of primary silyl ethers.

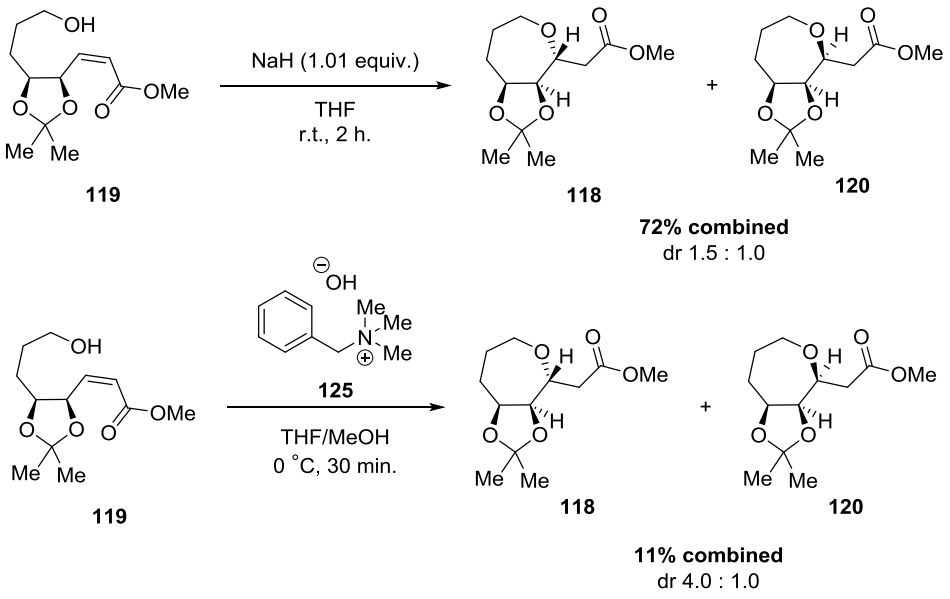
Based on the preliminary results, the saturated substrate was also investigated for conjugate addition as a viable route to 7-membered ring ether systems (Scheme 31). However, only a small amount of *trans* cyclized product **118** was observed when the saturated substrate **99** was exposed to TBAF. The majority of the isolated material was the deprotected primary alcohol (**119**).



Scheme 31: TBS-deprotection of saturated substrate.

The primary alcohol was subjected to basic conditions to explore cyclization options for the free hydroxyl group (Scheme 32). The reaction proceeded to the highest

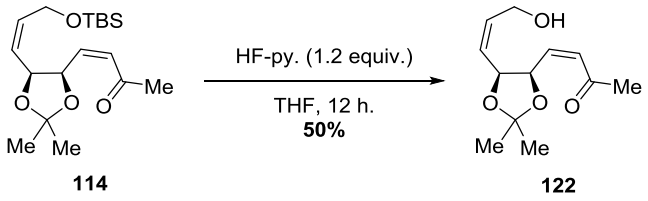
conversion (72% isolated yield) when sodium hydride was used, as compared to other basic conditions or silyl deprotection conditions. However, the low diastereoselectivity (1.5:1.0 dr) observed with this reagent prompted our search for additional bases to perform the cyclization. Triton B (**121**), a quaternary ammonium hydroxide base, was used to induce cyclization of the saturated substrate. There have been reports of Triton B catalyzing oxa-Michael reactions, however catalytic amounts of the reagent did not produce any cyclized materials. When one equivalent was used at low conversion, small amounts of the desired cyclized products were formed and isolated as mixture of diastereomers (4:1 dr). A significant amount of starting material was also recovered from this reaction (~36% recovery). However, the TBS deprotection of the unsaturated substrate seemed more promising in terms of selectivity, and our focus switched to investigating the conjugate addition of a primary silyl ether to an α,β-unsaturated ketone to better model the brevenal carbon skeleton.



Scheme 32: Conjugate addition of primary alcohol **119** under basic conditions.

It was unclear if the *trans*/*cis* relationship was a result of kinetic formation of the products or an equilibrium process through a retro-oxa-Michael pathway. However, when the *trans* diastereomer **120** was resubjected to the cyclization conditions for an extended period of time (1 equiv. TBAF, 24 h.) the *cis* diastereomer **121** was not observed. The same held true for **121** when resubjected to reaction conditions (1 equiv. TBAF, 24 h.), in that none of the *trans* diastereomer was observed. This suggests the ratio of *trans* to *cis* diastereomers that are formed during the cyclization are most likely a result of a kinetic process.

We also investigated the ability of the *Z* substrate **114** to undergo an oxa-Michael addition using HF·py to deprotect the primary TBS group (Scheme 33). It is also possible the slightly acidic conditions could also activate the ketone for conjugate addition. However, only deprotected starting material was isolated without evidence of any cyclization products.

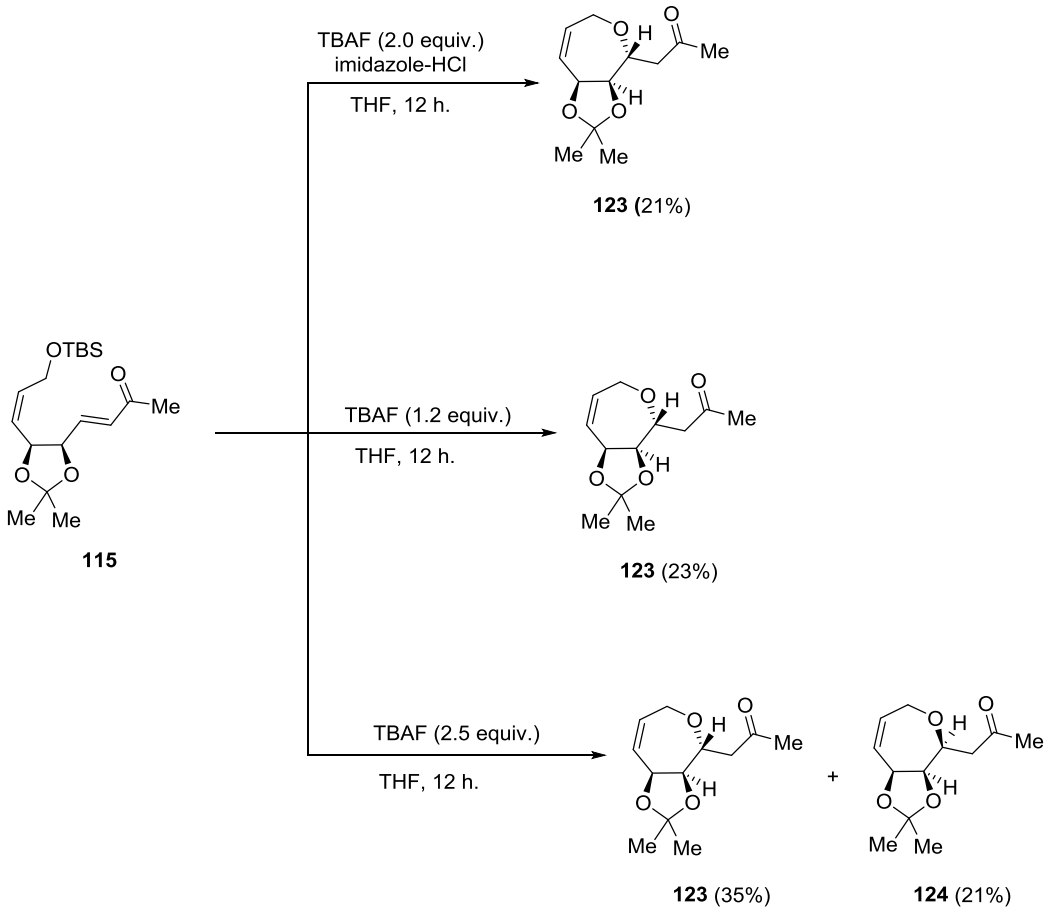


114 **122**

Scheme 33: Deprotection of primary TBS group with HF·py.

Due to the low yield of **114**, the other conjugate addition reactions were performed using the *E* substrate **116** (Scheme 34). When TBAF was buffered with imidazole-HCl, only the desired *trans* product **123** was isolated in 21% yield. Unbuffered

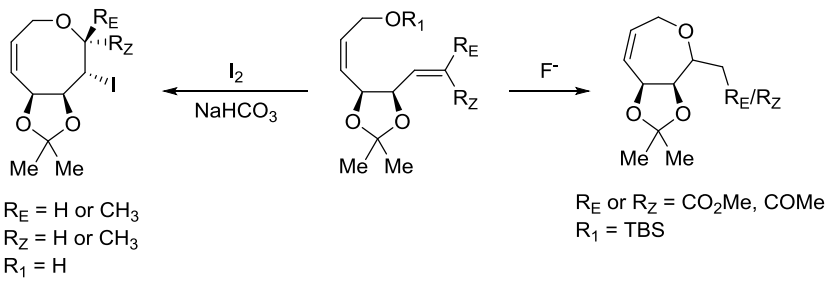
TBAF produced a similar result to the buffered solution, with isolation of the *trans* diastereomer **123** in 23% yield. However, with higher equivalents of TBAF on a slightly larger scale, the *cis* diastereomer **124** was isolated in addition to the desired product. The remainder of the material was very polar products that were unable to be identified due to large quantities of TBAF salts contaminating the samples.



Scheme 34: Intramolecular conjugate additions to α,β-unsaturated ketones.

A method has been described for the exclusive formation of 8-membered rings using iodine-promoted cyclizations of hydroxy-dienes through an 8-*endo* pathway.

However, when the alkene is substituted with an ester or ketone, the 7-*exo* pathway dominates through an oxa-Michael addition (Scheme 35).



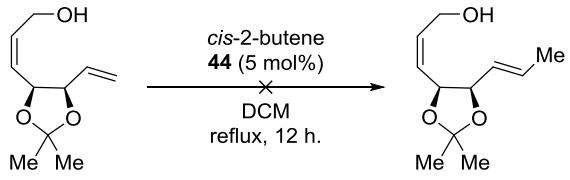
Scheme 35: Pathways for 8-*endo* and 7-*exo* cyclizations of hydroxy-alkenes.

1.3 Conclusions and Future Work

Iodocyclizations of hydroxy-alkenes exclusively provided the 8-membered ring cyclized product. Variations in both the conformational restrictions of the substrate and choice of electrophile to promote cyclization were unsuccessful in producing the desired 7-membered ring regioisomer. However, oxa-Michael additions are a potentially viable route to the 7-*exo* product. Further investigation on the necessity of the hydroxyl protecting group and alkene geometry may improve the yield and diastereoselectivity of the reaction. Additionally, an A/B ring model system would help determine if the conjugate addition diastereoselectivity can be improved when the stereochemistry of the secondary oxygen nucleophile is set in a previous step, and other students in our laboratory are working toward an AB and an ABC model system.

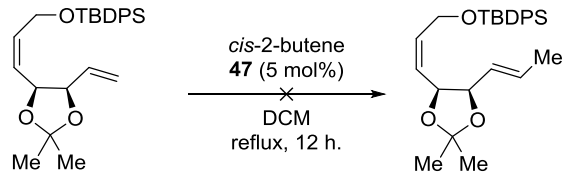
1.4 Experimental Detail

General information: Proton and carbon NMR spectra were recorded on an INOVA-400 (400 MHz), VNMRS 400 (400 MHz), INOVA-600 (600 MHz), or Unity-600 (600 MHz). NMR spectra were recorded in solutions of deuterated chloroform ($CDCl_3$) with the residual chloroform (7.27 ppm for ^1H NMR and 77.23 ppm for ^{13}C NMR) taken as the internal standard, deuterated methanol (CD_3OD) with residual methanol (3.31 ppm for ^1H NMR and 49.3 ppm for ^{13}C NMR) taken as the internal standard, or deuterated benzene with residual benzene (7.16 ppm for ^1H NMR and 128.23 ppm for ^{13}C NMR) taken as the internal standard, and were reported in parts per million (ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; ddd, doublet of doublet of doublet; dt, doublet of triplet; m, multiplet. IR spectra were collected on a Nicolet Avatar 370 DTGS. Mass spectra (high resolution ESI and APCI) were recorded on a Finnigan LTQ FTMS Mass spectrometer. Optical rotations were measured using a Perkin-Elmer 341 polarimeter (concentration in g/100mL). Thin layer chromatography (TLC) was performed on precoated glass backed plates purchased from Whatman (silica gel 60F254; 0.25mm thickness). Flash column chromatography was carried out with silica gel 60 (230-400 mesh ASTM) from Silicycle. All reactions were carried out with anhydrous solvents in oven dried or flame dried and argon-charged glassware unless otherwise specified. All anhydrous solvents were dried with 4Å molecular sieves purchased from Sigma-Aldrich and tested for trace water content with Coulometric KF titrator from Denver instruments. All solvents used in extraction procedures and chromatography were used as received from commercial suppliers without prior purification.



41 45

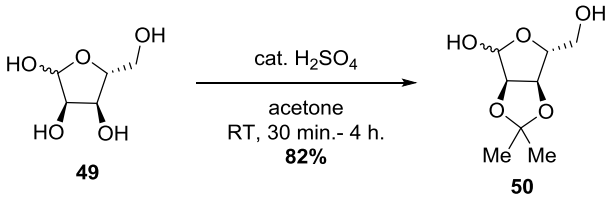
(Z)-3-((4S,5R)-2,2-dimethyl-5-((E)-prop-1-en-1-yl)-1,3-dioxolan-4-yl)prop-2-en-1-ol (45): A solution of alkene **41** (50 mg, 0.27 mmol) and **44** (11 mg, 0.01 mmol) dissolved in DCM (1 mL) was cooled to -78 ˚C in a thick-walled tube. *Cis*-2-butene (0.25 mL, 2.7 mmol) was condensed into a measuring cuvette at -78 ˚C and transferred to a thick-walled tube *via* cuvette. The tube was sealed and warmed to 40 ˚C for 24 h. The tube was cooled to -78 ˚C, opened, and slowly warmed to RT. The solvent was removed under reduced pressure. Recovered only unreacted starting material. Spectral data matched those in the literature.[27,29] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.84 (dt, J = 12.4, 6.4 Hz, 1H), 5.77 (ddd, J = 17.4, 10.3, 7.5 Hz, 1H), 5.57 – 5.50 (m, 1H), 5.32 (dd, J = 17.1, 1.6 Hz, 1H), 5.24 (dd, J = 10.1, 1.4 Hz, 1H), 4.99 (t, J = 7.5 Hz, 1H), 4.60 (t, J = 7.0 Hz, 1H), 4.28 (dd, J = 13.3, 7.0 Hz, 1H), 4.15 (dd, J = 13.5, 6.0 Hz, 1H), 1.87 – 1.79 (bs, 1H), 1.53 (s, 3H), 1.41 (s, 3H).



46 48

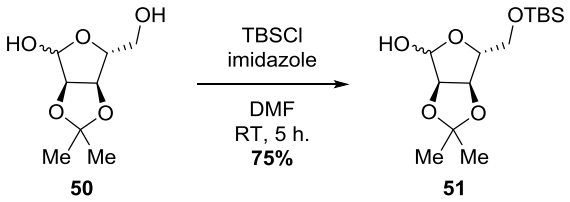
tert-butyl(((Z)-3-((4S,5R)-2,2-dimethyl-5-((E)-prop-1-en-1-yl)-1,3-dioxolan-4-yl)allyl)oxy)diphenylsilane (48): A solution of alkene **46** (114 mg, 0.27 mmol) and **47** (9 mg, 0.01 mmol) dissolved in DCM (2.7 mL) was cooled to -78 ˚C in a thick-walled

tube. *Cis*-2-butene (1 mL, 10.8 mmol) was condensed into a measuring cuvette at -78 ˚C and transferred to a thick-walled tube *via* cuvette. The tube was sealed and warmed to 40 ˚C for 24 h. The tube was cooled to -78 ˚C, opened, and slowly warmed to RT. The solvent was removed under reduced pressure. The crude ^{1}H NMR indicates the starting material was consumed, but there are three vinylic methyls. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.76 (ddd, J = 11.7, 8.0, 1.7 Hz, 6H), 7.53 – 7.37 (m, 10H), 5.86 (dp, J = 12.3, 6.3, 5.6 Hz, 1H), 5.81 – 5.65 (m, 2H), 5.64 (m, 1H), 5.50 (dddt, J = 12.2, 8.2, 6.5, 1.7 Hz, 1H), 5.46 – 5.40 (m, 2H), 4.80 – 4.72 (m, 1H), 4.60 – 4.52 (m, 1H), 4.43 (dd, J = 8.4, 6.6 Hz, 1H), 4.36 – 4.30 (m, 1H), 4.29 – 4.18 (m, 2H), 4.21 (d, J = 1.3 Hz, 2H), 1.77 (dd, J = 6.6, 1.7 Hz, 3H), 1.74 (dd, J = 6.4, 1.6 Hz, 3H), 1.71 (dd, J = 6.6, 1.7 Hz, 3H), 1.56 (s, 3H), 1.52 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H), 1.13 (s, 9H).

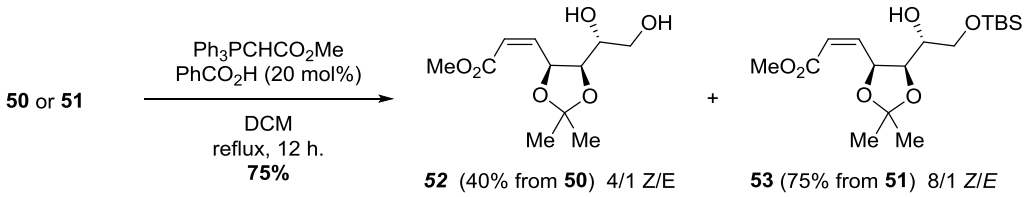


(3aR,6R,6aR)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (50): D-(-)-ribose **49** (10.0 g, 100 mmol) was suspended in Acetone (145 mL) and H_2SO_4 (0.3 mL, 5.63 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 30 min. The solvents were removed under reduced pressure and the oil was diluted with H_2O (75 mL). The crude material was purified by flash column chromatography (1/1 hexanes/EtOAc) to obtain **50** as a clear, colorless oil (10.35 g, 82% yield). Spectral data matched those in the literature.[30] **^{1}H NMR** (400 MHz, $CDCl_3$) δ

5.42 (d, J = 5.6 Hz, 1H), 4.99 (d, J = 6.4 Hz, 1H), 4.83 (d, J = 5.9 Hz, 1H), 4.58 (d, J = 5.9 Hz, 1H), 4.41 (t, J = 2.4 Hz, 1H), 3.84 – 3.64 (m, 3H), 1.49 (s, 3H), 1.32 (s, 3H).



(3aR,6R,6aR)-6-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyltetrahydrofuro-[3,4-d][1,3]dioxol-4-ol (51): To a solution of **50** (4.78 g, 25.1 mmol) and imidazole (4.79 g, 70.4 mmol) in DMF (10 mL) was added TBSCl (4.16 g, 27.6 mmol). The reaction stirred at room temperature for 5 h. and was quenched with 100 mL H_2O. The aqueous layer was extracted with Et_2O (5 x 25 mL) and the combined organic fractions were washed with H_2O (5 x 25 mL), brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The crude material was purified (2/1 hexanes/EtOAc) to obtain **51** as a clear, colorless oil (5.70 g, 75% yield). Spectral data matched those in the literature.[32] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.29 (d, J = 11.9 Hz, 1H), 4.78 (d, J = 11.9 Hz, 1H), 4.71 (d, J = 5.9 Hz, 1H), 4.51 (d, J = 5.9 Hz, 1H), 4.37 (d, J = 2.16 Hz, 1H), 3.77 (qd, J = 11.1, 2.2 Hz, 2H), 1.49 (s, 3H), 1.33 (s, 3H), 0.94 (s, 9H), 0.15 (s, 3H), 0.15 (s, 3H).



methyl 3-((4S,5R)-5-((R)-1,2-dihydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl) acrylate (52): To a solution of ribofuranoside **50** (3.00 g, 15.8 mmol) and benzoic acid

(96 mg, 0.8 mmol) in DCM (53 mL) was added methyl (triphenylphosphoranylidene) acetate (9.50 g, 28.4 mmol). The solution was heated to reflux for 18 h. and cooled to RT. The solvents were removed under reduced pressure and the crude material was purified (1/1 hexanes/EtOAc) to obtain **52** as a mixture of *Z* and *E* alkene isomers (4:1 *Z*:*E*, 1.59 g, 40% yield).

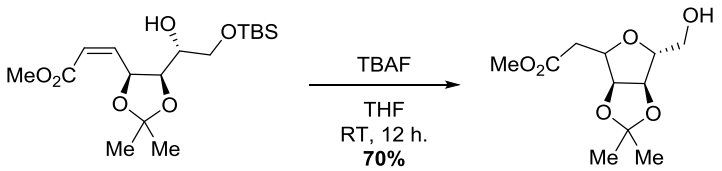
Z isomer: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.30 (dd, J = 11.9, 8.5 Hz, 1H), 6.07 – 6.00 (m, 1H), 5.55 (ddd, J = 8.6, 6.8, 2.5 Hz, 1H), 4.35 (ddd, J = 8.4, 6.3, 2.1 Hz, 1H), 3.84 – 3.62 (m, 6H), 1.51 (s, 3H), 1.39 (s, 3H).

E isomer: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.13 (dd, J = 15.5, 4.4 Hz, 1H), 6.17 (ddd, J = 15.6, 3.3, 1.7 Hz, 1H), 4.86 (dtd, J = 6.6, 4.7, 1.8 Hz, 1H), 4.22 – 4.16 (m, 1H), 3.85 – 3.58 (m, 6H), 1.49 (s, 3H), 1.37 (s, 3H).

methyl (Z)-3-((4S,5R)-5-((R)-2-((tert-butyldimethylsilyl)oxy)-1-hydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (53): TBS-protected ribose **51** (5.70 g, 15.44 mmol) was dissolved in DCM (51 mL). Benzoic acid (380 mg, 3.09 mmol) was added, followed by methyl (triphenylphosphoranylidene)acetate (5.67 g, 16.98 mmol). The reaction was refluxed for 24 h. and additional methyl (triphenylphosphoranylidene) acetate (5.67 g, 16.98 mmol) was added. After refluxing an additional 24 h., the reaction was cooled to room temperature and concentrated. The residue was diluted with Et_2O and the precipitate was removed by filtration through a pad of Celite (2 x). The crude material was purified (5/1 hexanes/EtOAc) to obtain **53** as a mixture of E and Z isomers as a clear, colorless oil. (4.15 g, 75%, 8/1 *Z*/*E*).

Z-isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.32 (dd, J = 11.6, 8.6 Hz, 1H), 6.00 (dd, J = 11.7, 1.3 Hz, 1H), 5.78 (ddd, J = 8.6, 6.2, 1.3 Hz, 1H), 4.26 (dd, J = 8.6, 6.3 Hz, 1H), 3.80 – 3.66 (m, 6H), 2.68 (d, J = 4.7 Hz, 1H), 1.48 (s, 3H), 1.37 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 145.0, 122.0, 109.4, 78.2, 74.0, 70.1, 64.5, 51.8, 28.2, 26.1, 25.6 (3C), 18.6, -5.1, -5.2.

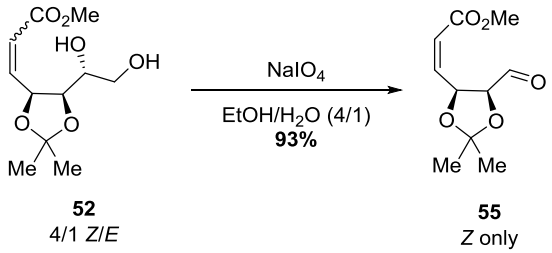
E-isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 (dd, J = 15.6, 4.8 Hz, 1H), 6.17 (dd, J = 15.7, 1.7 Hz, 1H), 4.86 (ddd, J = 6.6, 4.8, 1.8 Hz, 1H), 4.68 (dd, J = 6.4, 3.1 Hz, 1H), 4.43 (dd, J = 6.4, 4.5 Hz, 1H), 4.17 – 4.02 (m, 2H), 3.71 (s, 3H), 2.56 (d, J = 5.7 Hz, 1H), 1.49 (s, 3H), 1.37 (s, 3H), 0.91 (s, 9H), 0.10 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 144.5, 122.0, 109.7, 77.6, 77.0, 69.8, 64.0, 51.9, 27.8, 27.6, 25.6 (3C), 18.5, -5.3, -5.4.



53 **54a**

methyl 2-((3aS,6R,6aR)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]-dioxol-4-yl)acetate (54a) or methyl 2-((3aS,7S,7aR)-7-hydroxy-2,2-dimethyl-tetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-4-yl)acetate (54b): To a solution of **53** (4.15 g, 11.51 mmol) in THF was added TBAF(17.3 mL, 17.3 mmol). The reaction stirred at room temperature for 15 h. and the solvent was removed under reduced pressure. The crude material was purified (1/1 hexanes/EtOAc) to obtain **54a** as a clear, colorless oil (2.00 g, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (dd, J = 6.2, 4.1 Hz, 1H), 4.67 (dd, J = 6.3, 1.4 Hz, 1H), 4.40 (td, J = 6.8, 4.1 Hz, 1H), 4.15 (t, J = 5.8 Hz, 1H), 3.72 (s, 3H), 3.66 – 3.58 (m, 2H), 2.77 (dd, J = 6.8, 4.7 Hz, 2H), 1.50 (s, 3H), 1.34 (s, 3H). **^{13}C**

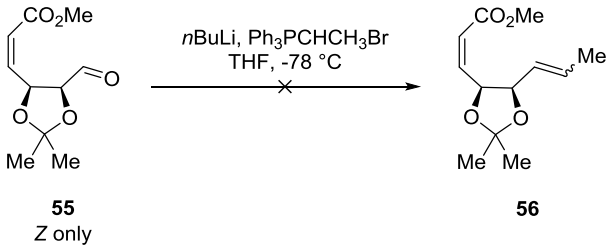
NMR (100 MHz, $CDCl_3$) δ 204.6, 113.0, 84.9, 84.4, 82.7, 81.6, 62.1, 52.1, 34.5, 26.4, 25.2.



52
4/1 *Z*/*E*

55
Z only

methyl (Z)-3-((4S,5S)-5-formyl-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (55): The diol **52** (1.59 g, 6.46 mmol) was dissolved in EtOH (16 mL) and water (4 mL) and $NaIO_4$ (1.79 g, 8.39 mmol) was added in one portion at RT. The reaction was stirred for 19 h. and diluted with Et_2O. The solids were removed by filtration and the solvents were removed under reduced pressure. The crude material was purified (3/1 hexanes/EtOAc) to obtain only the *Z* isomer **55** as a clear, colorless oil (1.29 g, 93% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.49 (d, J = 2.8 Hz, 1H), 6.25 (dd, J = 11.6, 6.8 Hz, 1H), 6.00 (dd, J = 11.6, 1.9 Hz, 1H), 5.87 – 5.69 (m, 1H), 4.81 (dd, J = 7.8, 2.9 Hz, 1H), 3.76 (s, 3H), 1.62 (s, 3H), 1.45 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 199.5, 166.0, 122.8, 111.6, 82.1, 52.0, 27.4, 25.3.

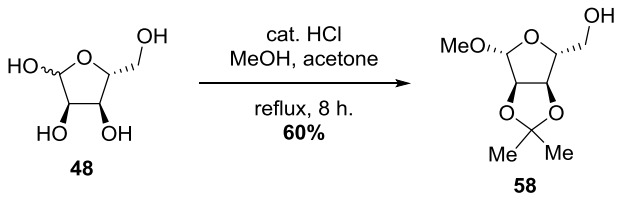


55
Z only

56

methyl (2Z)-3-((4S,5R)-2,2-dimethyl-5-(prop-1-en-1-yl)-1,3-dioxolan-4-yl)acrylate (56): Ethyltriphenylphosphonium bromide (2.13 g, 5.74 mmol) was suspended in THF

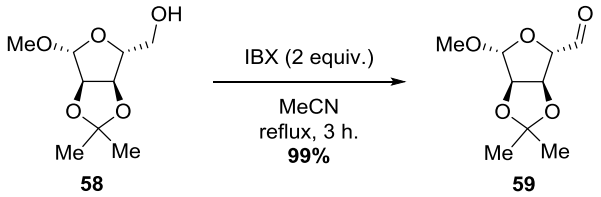
(57 mL) and cooled to -78 ˚C. *n*BuLi (2.6 mL, 6.63 mmol) was added dropwise and the bright orange reaction mixture was stirred at 0 ˚C for 30 min. The reaction was cooled to -78 ˚C and a solution of the aldehyde **55** (945 mg, 4.42 mmol) in THF (2.2 mL) was added dropwise and the reaction slowly warmed to room temperature over 3 h. The reaction was quenched with the addition of aq. NH_4Cl (100 mL). The organic and aqueous phases were separated, and the aqueous phase was extracted with Et_2O (2 x 70 mL). The combined organic phases were washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated. The crude material was purified (4/1 hexanes/EtOAc) to obtain 14 mg of an unknown product. No alkene peaks were visible in the ^1H NMR, and mass spectral data did not provide any insight.



48 58

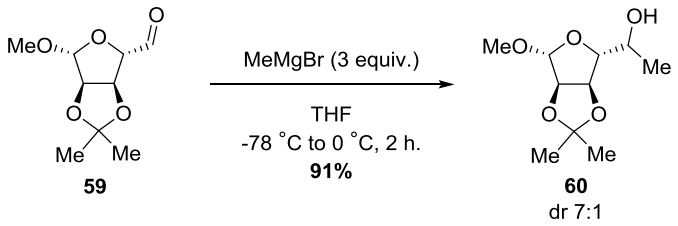
2,3-O-isopropylidene-1-O-methyl-D-ribofuranose (58): D-ribose **49** (30.28 g, 202 mmol) was dissolved in MeOH (115 mL) and acetone (115 mL). Concentrated HCl (1.8 mL) was added at room temperature and the solution was heated to reflux for 6 h. The reaction mixture was poured into H_2O (200 mL) and the organic solvents were removed under reduced pressure. The aqueous phase was extracted with Et_2O (3 x 100 mL) and the combined organic layers were washed with H_2O (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to obtain **58** as a clear, colorless oil (16.66 g, 55% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.97 (s, 1H), 4.83 (d, *J* = 5.8 Hz, 1H), 4.59 (d, *J* = 6.1 Hz, 1H), 4.43 (t, *J* = 2.9 Hz, 1H), 3.69 (dd, *J* = 12.7, 2.3 Hz, 2H),

3.62 (ddd, *J* = 12.5, 6.5, 2.8 Hz, 2H), δ 3.28 (dd, *J* = 10.7, 2.6 Hz, 1H), 1.48 (s, 3H), 1.32 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 112.29, 110.17, 88.56, 86.02, 81.66, 64.21, 55.76, 26.54, 24.88. **FT-IR** (neat, cm^{-1}): 869, 1090, 1107, 1160, 1210, 1379, 1456, 2836, 2940, 2989, 3402. **HRMS** (NSI): *m/z* calcd. $C_9H_{17}O_5$ ($M+H^+$) 205.10705, found 205.10690. **$[\alpha]_D^{25}$** = -73.2, (c=1.00, $CHCl_3$).

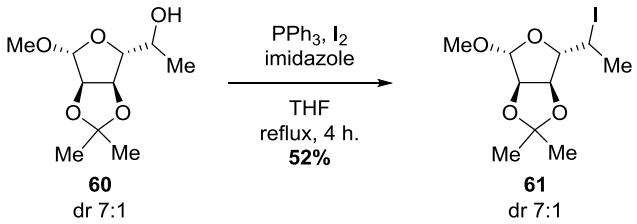


58 **59**

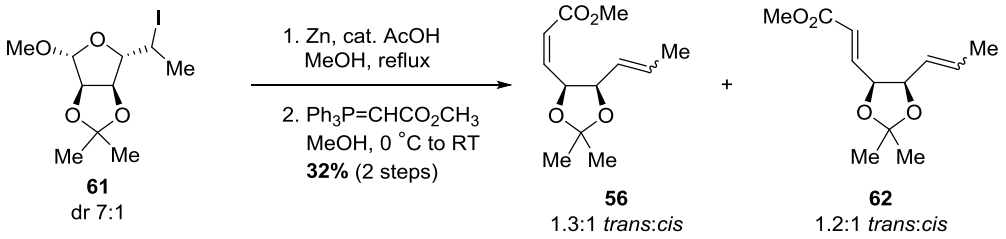
(3a*R*,4*S*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxole-4-carbaldehyde (59): The primary alcohol **58** (22.73 g, 111 mmol) was dissolved in MeCN (330 mL), and IBX (51.77 g, 202 mmol) was added in one portion at room temperature. The suspension was refluxed for 3 h and stirred at room temperature overnight. The cloudy white reaction mixture was filtered, rinsed with EtOAc, and concentrated under reduced pressure to obtain aldehyde **59** as a white crystalline solid that melted at room temperature (22.74 g, 99% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 5.08 (s, 1H), 5.04 (d, *J* = 5.9 Hz, 1H), 4.49 (d, *J* = 5.9 Hz, 1H), 4.47 (s, 1H), 3.44 (s, 3H), 1.48 (s, 3H), 1.32 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.9, 112.8, 109.3, 89.6, 84.1, 80.9, 55.9, 26.3, 25.0. **HRMS** (APCI): *m/z* calcd. $C_9H_{15}O_5$ ($M+H^+$) 203.09140, found 203.09143. **FT-IR** (neat, cm^{-1}): 2857, 1730, 1376, 1274, 1200, 1162, 1090, 1038, 941, 868. **$[\alpha]_D^{25}$** = -151 (c = 1.00, $CHCl_3$).



(*S*)-1-((3a*R*,4*R*,6*R*,6a*R*)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)ethanol (60): Aldehyde **59** (22.73 g, 111 mmol) was dissolved in THF (448 mL), the solution was cooled to -50 ˚C, and MeMgBr (70 mL, 191 mmol) was added dropwise at -50 ˚C, maintaining the temperature with the addition of dry ice as needed. The reaction was stirred at -40 ˚C for 2 h before slowly warming to 0 ˚C. The reaction was quenched by the slow addition of sat. aq. NH_4Cl (250 mL). The aqueous phase was extracted with EtOAc (3 x 100 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to obtain secondary alcohol **60** as a 7:1 mixture of diastereomers as a clear, yellow oil (22.35 g, 91% yield). We have not independently confirmed the stereochemical assignment of reference 2 for the secondary alcohol, as this was inconsequential for the preparation of compounds **44** and **57**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.97 (s, 1H), 4.86 (d, *J* = 6.0 Hz, 1H), 4.58 (d, *J* = 6.1 Hz, 1H), 4.19 (d, *J* = 1.8 Hz, 1H), 3.89 (q, *J* = 6.7 Hz, 1H), 3.66 (s, 1H), 3.44 (s, 3H), 1.49 (s, 3H), 1.33 (s, 3H), 1.23 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 112.1, 110.1, 110.0, 92.6, 92.6, 85.9, 79.6, 68.3, 55.7, 55.6, 26.4, 24.7, 18.7. **HRMS** (NSI): *m/z* calcd. $C_{10}H_{18}O_5Na$ ($M+Na^+$) 241.10464, found 241.10479. **FT-IR** (neat, cm^{-1}): 3458, 2973, 1374, 1209, 1087, 1056, 1025, 864, 754. **$[\alpha]_D^{25}$** = -56.6 (c = 1.00, $CHCl_3$).



(3a*S*,4*S*,6*R*,6a*R*)-4-((*R*)-1-iodoethyl)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole (61): The secondary alcohol **60** (22.35 g, 102 mmol) was dissolved in THF (500 mL), and PPh_3 (53.51 g, 204 mmol), imidazole (20.83 g, 306 mmol) and I_2 (38.83 g, 153 mmol) were added to form a dark brown suspension that turned to a clear, yellow solution after 1 min at room temperature. The reaction mixture was refluxed for 4 h. After cooling to room temperature, the yellow solution was diluted with sat. aq. $Na_2S_2O_3$ (300 mL) and EtOAc (200 mL). The aqueous and organic layers were separated, and the organic layer was washed with $Na_2S_2O_3$ (200 mL), H_2O (2 x 125 mL) and brine (125 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (3-5% EtOAc in hexanes) to obtain the iodide **61** as a clear, colorless oil (17.50 g, 52% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.97 (s, 1H), 4.62 – 4.58 (m, 2H), 4.23 – 4.10 (m, 2H), 3.45 (s, 3H), 1.91 (d, *J* = 6.5 Hz, 3H), 1.46 (s, 3H), 1.29 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 113.0, 109.4, 93.0, 85.9, 80.0, 56.6, 29.4, 26.7, 25.4, 24.5. **HRMS** (NSI): *m/z* calcd. 329.02443 ($M+H^+$), found 329.02425. **FT-IR** (neat, cm^{-1}): 2985, 2933, 1374, 1271, 1209, 1158, 1090, 1056, 1037, 864. **$[\alpha]_D^{25}$** = 1.5 (c = 1.00, $CHCl_3$).

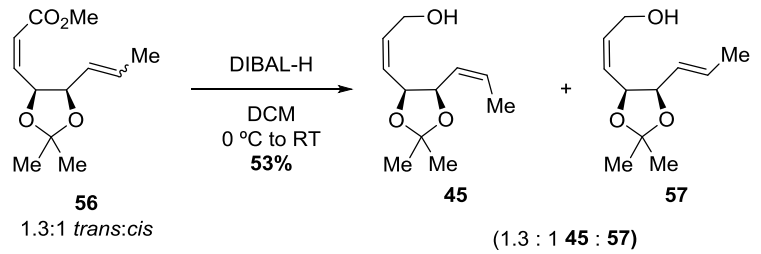


(2*Z*)-methyl 3-((4*S*,5*R*)-2,2-dimethyl-5-(prop-1-en-1-yl)-1,3-dioxolan-4-yl)acrylate (56): The secondary iodide **61** (14.83 g, 45.20 mmol) was diluted with MeOH (450 mL), and activated zinc dust (<10 μm, 20.67 g, 316.4 mmol) was added in one portion, followed by AcOH (1.45 mL). The reaction mixture was refluxed for 4 h. The reaction mixture was cooled to room temperature, and filtered through a pad of silica gel to remove excess Zn˚ and Zn salts, collecting the filtrate directly into a 250 mL round-bottom flask, containing a solution of (4*R*,5*R*)-2,2-dimethyl-5-(prop-1-en-1-yl)-1,3-dioxolane-4-carbaldehyde (mixture of *E* and *Z*-alkene isomers), which was not further purified. This aldehyde solution in methanol was cooled to 0˚ C, and methyl(triphenylphosphoranylidene) acetate (18.14 g, 54.20 mmol) was added in one portion. The reaction mixture was stirred overnight at room temperature and the solvent was removed under reduced pressure. The residue was partitioned between sat. aq. NH_4Cl and EtOAc. The aqueous layer was extracted with EtOAc (2x), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was diluted with Et_2O and the solids were removed by gravity filtration (2x). The crude was purified by flash column chromatography (93:7 to 9:1 hexanes: EtOAc). Although the alkene isomers of **56**(1 : 1.3 ratio, arising from the elimination stage) could not be separated from each other, the *Z*-unsaturated ester (from the Wittig olefination stage) was obtained as a clear, colorless oil (5.47 g, 54% yield). A

small quantity of the *E*-unsaturated ester **62** was isolated from more polar chromatography fractions, as a clear, colorless oil (734 mg, 14% yield).

Data for **56**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.22 (ddd, *J* = 11.7, 7.8, 3.9 Hz, 1H), 6.21 (ddd, *J* = 11.4, 7.6, 3.6 Hz, 1H), 5.89 (m, 2H), 5.81 – 5.54 (m, 4H), 5.39 – 5.21 (m, 3H), 4.80 (t, *J* = 7.6 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 1.67 (dd, *J* = 6.9, 1.9 Hz, 3H), 1.63 (dd, *J* = 6.4, 1.6 Hz, 3H), 1.54 (s, 3H), 1.53, (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.1, 166.1, 146.8, 146.7, 130.7, 129.4, 126.7, 126.3, 121.1, 120.9, 109.15, 109.0, 79.9, 75.6, 74.5, 51.6, 51.6, 28.3, 28.1, 25.5, 25.4, 17.9, 13.3. **HRMS** (APCI): *m/z* calcd. $C_{12}H_{19}O_4$ ($M+H^+$) 227.12779, found 227.12762. **FT-IR** (neat, cm^{-1}): 3415, 2986, 2935, 1374, 1214, 1163, 1029, 965, 872. **$[\alpha]_D^{25}$** = +120.2 (c = 1.00, $CHCl_3$).

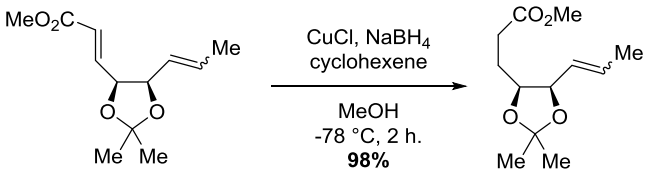
Data for **(2*E*)-methyl 3-((4*S*,5*R*)-2,2-dimethyl-5-(prop-1-en-1-yl)-1,3-dioxolan-4-yl)acrylate (62)**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.81 (ddd, *J* = 16.2, 11.1, 5.7 Hz, 1H), 6.12 – 6.02 (m, 1H), 5.83 (dq, *J* = 15.0, 6.5 Hz, 1H), 5.78 – 5.71 (m, 1H), 5.35 (ddt, *J* = 13.1, 9.4, 1.9 Hz, 1H), 5.10 (dd, *J* = 8.8, 6.9 Hz, 1H), 4.78 – 4.70 (m, 1H), 4.69 – 4.65 (m, 1H), 3.75 (s, 3H), 1.72 (td, *J* = 7.2, 1.7 Hz, 3H), 1.54 (s, 3H), 1.41 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.68, 166.63, 144.63, 144.54, 132.40, 129.96, 126.15, 125.75, 122.25, 109.46, 109.35, 79.92, 77.66, 77.42, 77.30, 74.12, 51.88, 28.05, 27.99, 25.61, 25.57, 18.06, 13.77. **HRMS** (NSI) *m/z* calcd. 227.12779 ($M+H^+$), found 227.1770. **FT-IR** (neat, cm^{-1}): 2989, 2949, 1723, 1662, 1436, 1373, 1307, 1253, 1214, 1161, 1041, 968, 873, 755. **$[\alpha]_D^{25}$** = -88.3 (c = 1.00, $CHCl_3$).



(2*Z*)-3-((4*S*,5*R*)-2,2-dimethyl-5-(prop-1-en-1-yl)-1,3-dioxolan-4-yl)prop-2-en-1-ol (mixture of 44 and 57): The dienyl ester **56** (5.20 g, 22.98 mmol; 1 : 1.3 *cis* : *trans*) was dissolved in DCM (130 mL), cooled to 0 ^{o}C, and DIBAL-H (72 mL, 72 mmol) was added along the sides of the flask. The reaction mixture warmed to room temperature over 3 hours. Solid NH_4Cl (2.0 g) and MeOH (2 mL) were added. After bubbling ceased, the cloudy reaction mixture was filtered through a short pad of silica gel. The filter cake was rinsed with 5 % MeOH in EtOAc, and the solvents were removed under reduced pressure. The crude material was purified by flash column chromatography (2:1 to 3:2 hexanes:EtOAc) to obtain the mixture of dienyl alcohols **44** and **57** as a clear, colorless oil (1.68 g, 53% yield). A portion of the product was subjected to flash column chromatography on 25% $AgNO_3$ silica gel (2:1 hexanes:EtOAc) to obtain the *cis,trans*-dienyl alcohol **56** (197 mg) as a clear, colorless oil, followed by elution of the *cis,cis*-isomer **44** as a clear, colorless oil (154 mg).

Data for **44: ^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.85 – 5.77 (m, 1H), 5.72 (dq, *J* = 11.1, 6.9 Hz, 1H), 5.60 – 5.52 (m, 1H), 5.42 (ddq, *J* = 10.8, 8.8, 1.9 Hz, 1H), 5.04 – 4.87 (m, 2H), 4.26 (dd, *J* = 13.3, 7.2 Hz, 1H), 4.12 (ddd, *J* = 13.3, 6.0, 1.6 Hz, 1H), 1.91 (bs, 1H), 1.68 (dd, *J* = 7.0, 1.8 Hz, 3H), 1.51 (s, 3H), 1.40 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 132.6, 129.4, 128.6, 126.4, 108.9, 74.4, 74.2, 58.9, 28.4, 25.8, 13.5. **HRMS** (NSI): *m/z* calcd. $C_{11}H_{18}O_3Na$ ($M+Na^+$) 221.11482, found 221.11467. **FT-IR** (neat, cm^{-1}): 3127, 3039, 2923, 2852, 1644, 1401, 1185, 1049, 879, 716. $[\alpha]_D^{25}$ = -12.7 (c = 1.00, $CHCl_3$).

Data for **57:** **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.89 – 5.68 (m, 2H), 5.56 (ddt, *J* = 11.2, 8.5, 1.4 Hz, 1H), 5.43 (ddq, *J* = 15.3, 8.6, 1.7 Hz, 1H), 4.92 (ddd, *J* = 8.1, 6.4, 1.3 Hz, 1H), 4.56 (dd, *J* = 8.5, 6.4 Hz, 1H), 4.33 – 4.20 (m, 1H), 4.20 – 4.08 (m, 1H), 1.72 (dd, *J* = 6.6, 1.7 Hz, 3H), 1.7 (bs, 1H), 1.51 (s, 3H), 1.39 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 132.60, 131.42, 128.55, 126.94, 108.82, 80.05, 77.42, 76.98, 74.48, 58.90, 28.33, 25.75, 18.06. **HRMS** (NSI): *m/z* calcd. $C_{11}H_{18}O_3Na$ ($M+Na^+$) 221.11482, found 221.11471. **FT-IR** (neat, cm^{-1}): 3415, 2986, 2935, 1451, 1374, 1214, 1163, 1029, 965, 872, 766. **$[\alpha]_D^{25}$** = +34.2 (c = 1.00, $CHCl_3$).

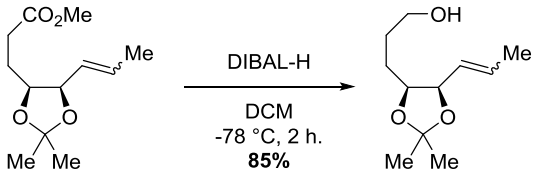


62
1.2:1 *trans*:*cis*

63
1.2:1 *trans*:*cis*

methyl 3-((4S,5R)-2,2-dimethyl-5-(prop-1-en-1-yl)-1,3-dioxolan-4-yl)propanoate (63), mixture of alkene isomers at C7: The unsaturated ester **62** (813 mg, 3.6 mmol, recovered from multiple batches) was dissolved in MeOH (60 mL) and cooled to -78 °C. Copper (I) chloride (274 mg, 2.8 mmol) and cyclohexene (1.4 mL, 13.8 mmol) were added, followed by $NaBH_4$ (652 mg, 17.3 mmol). The reaction mixture turned dark brown over the course of 1.5 h. at -78 °C. The mixture was then concentrated while the solvent was still cold. The residue was partitioned between aq. NH_4Cl and Et_2O, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to provide the saturated ester (802 mg, 98% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.88 – 5.66 (m, 2H), 5.56 – 5.40 (m, 2H), 4.95 (ddd, *J* = 9.0, 6.1, 1.2 Hz, 1H), 4.51 (dd, *J* = 8.5, 6.2 Hz, 1H), 4.11 (dddd, *J*

= 17.1, 9.1, 6.1, 4.5 Hz, 2H), 3.68 (s, 3H), 3.68 (s, 3H), 2.49 (ddt, *J* = 16.4, 8.8, 5.7 Hz, 2H), 2.44 – 2.30 (m, 2H), 1.76 – 1.72 (m, 3H), 1.70 (dd, *J* = 7.0, 1.8 Hz, 3H), 1.47 (s, 3H), 1.46 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.05, 131.38, 129.26, 126.63, 126.24, 108.29, 108.24, 79.63, 77.31, 73.80, 51.81, 30.84, 28.50, 26.39, 26.22, 25.84, 18.11, 13.59. **HRMS** (ESI): *m/z* calcd. $C_{12}H_{20}O_4Na$ ($M+Na^+$) 251.12538, found 251.12522. **FT-IR** (neat, cm^{-1}) 3691, 3619, 3189, 2986, 2930, 1738. **$[\alpha]_D^{25}$** = -38.6 (c = 0.67, $CHCl_3$).

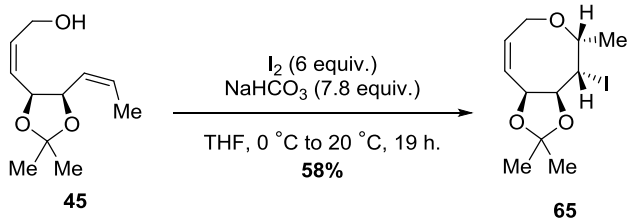


63
1.2:1 *trans*:*cis*

64
1.2:1 *trans*:*cis*

3-((4S,5R)-2,2-dimethyl-5-(prop-1-en-1-yl)-1,3-dioxolan-4-yl)propan-1-ol (64), mixture of alkene isomers at C7**:** The ester **63** (398 mg, 1.74 mmol) was dissolved in DCM (11.6 mL) at 0 °C. DIBAL-H (3.7 mL, 3.66 mmol) was added dropwise to the solution. The reaction slowly warmed to room temperature over 2 h., was diluted with Et_2O, and was quenched by the sequential addition of H_2O (0.1 mL), 15% aqueous NaOH (0.1 mL), and H_2O (0.22 mL). The cloudy reaction mixture stirred at room temperature for 15 min, and $MgSO_4$ was added. After 15 min, the solids were removed by filtration and the solvents removed by rotary evaporation. The crude material was purified by flash column chromatography (2:1 hexanes:EtOAc) to obtain compound **63** as a clear, colorless oil (185 mg, 53% yield). No additional attempt was made to separate the alkene isomers. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.78 – 5.68 (m, 2H), 5.51 – 5.41 (m, 2H), 4.94 (ddd, *J* = 8.4, 6.2, 1.6 Hz, 1H), 4.48 (ddd, *J* = 8.2, 6.1, 1.8 Hz, 1H), 4.18 – 4.09 (m, 2H),

3.71 – 3.63 (bs, 4H), 2.06 (bs, 1H), 2.03 (bs, 1H), 1.73 (dt, *J* = 6.5, 1.8 Hz, 3H), 1.70 (dt, *J* = 6.9, 2.0 Hz, 3H), 1.72 – 1.61 (m, 4H), 1.57 – 1.51 (m, 4H), 1.48 (s, 6H), 1.38 (s, 3H), 1.36 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 130.99, 128.91, 127.17, 126.60, 108.20, 108.11, 80.02, 78.50, 78.35, 73.93, 62.92 (2), 29.99, 29.94, 28.54, 28.46, 27.68, 27.46, 25.92, 25.82, 18.08, 13.46. **HRMS** (NSI): *m/z* calcd. $C_{11}H_{20}O_3Na$ ($M+Na^+$) 223.13047, found 223.13059. **FT-IR** (neat, cm^{-1}): 3414, 2986, 2936, 2870, 1450, 1370, 1242, 1215, 1164, 1059, 1022, 969, 877, 753. **$[\alpha]_D^{25}$** = -20.4 (c = 1.00, $CHCl_3$).



(3aS,4S,5R,9aS,Z)-4-iodo-2,2,5-trimethyl-4,5,7,9a-tetrahydro-3aH-[1,3]dioxolo[4,5-d]oxocine (65): The dienyl alcohol **45** (82 mg, 0.41 mmol) was dissolved in THF (4.1 mL), the solution was cooled to 0 ˚C, and solid $NaHCO_3$ (265 mg, 3.2 mmol) was added, followed by I_2 (624 mg, 2.5 mmol). The reaction mixture slowly warmed to room temperature over 19 h and was quenched with saturated aqueous $Na_2S_2O_3$ (30 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude yellow material was purified by flash column chromatography (9:1 hexanes:EtOAc) to obtain iodooxocene **65** as a clear, colorless oil that solidified over time (77 mg, 58% yield). mp 82 - 84 ^oC; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.54 (ddd, *J* = 12.0, 5.4, 4.2 Hz, 1H), 5.36 (ddd, *J* = 12.0, 6.0 Hz, 1H), 5.28 (ddd, *J* = 6.0, 5.4 Hz, 1H), 4.55 (dd, *J* = 11.1, 4.5 Hz, 1H), 4.46 (dt, *J* = 18.6, 4.8, 4.2 Hz, 1H), 4.29 (dd, *J* = 11.1, 5.2 Hz, 1H), 3.91 –

3.85 (m, 2H), 1.53 (d, *J* = 6.5 Hz, 3H), 1.48 (s, 3H), 1.39 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 129.9 (2 carbons), 107.1, 80.5, 77.9, 76.1, 71.2, 29.3, 28.3, 26.6, 18.5. **HRMS** (APCI): *m/z* calcd. $C_{11}H_{18}O_3I$ ($M+H^+$) 325.02951, found 325.02930. **FT-IR** (neat, cm^{-1}): 2990, 2932, 2889, 1454, 1434, 1368, 1268, 1246, 1222, 1158, 1101, 1077, 1059, 1028, 935, 879, 711, 652. **$[\alpha]_D^{25}$** = +24.0 (c = 1.00, $CHCl_3$). Deposition number CCDC-946586 for compound **65**.

Table 1 Crystal data and structure refinement for compound 65

Identification code	KLS-2-120
Empirical formula	$C_{11}H_{17}IO_3$
Formula weight	324.14
Temperature/K	109.1
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	7.4901(6)
b/Å	10.2210(8)
c/Å	15.9521(12)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1221.23(16)
Z	4
ρ_{calc}mg/mm^3	1.763

m/mm^{-1}	2.609
F(000)	640.0
Crystal size/mm^3	0.593 × 0.253 × 0.1
2Θ range for data collection	4.734 to 61.012°
Index ranges	$-10 \leq h \leq 10$, $-14 \leq k \leq 14$, $-22 \leq l \leq 22$
Reflections collected	14797
Independent reflections	3719[R(int) = 0.0319]
Data/restraints/parameters	3719/0/139
Goodness-of-fit on F^2	1.066
Final R indexes [I>=2σ (I)]	R_1 = 0.0283, wR_2 = 0.0671
Final R indexes [all data]	R_1 = 0.0293, wR_2 = 0.0681
Largest diff. peak/hole / e Å^{-3}	1.72/-0.45
Flack parameter	-0.01(3)

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for compound 65. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
I1	3338.5(3)	6933.0(2)	8081.9(2)	18.65(8)
C3	1309(4)	7147(3)	7123(2)	14.1(6)
O3	1157(3)	5299(3)	5140.9(17)	18.9(5)
O2	2314(3)	5151(2)	6467.1(16)	13.9(4)
O1	-552(4)	8714(3)	6400.6(18)	20.8(5)

C4	1906(4)	6498(3)	6316(2)	12.7(6)
C2	837(5)	8604(3)	7016(2)	16.6(6)
C10	1671(6)	3153(3)	5750(2)	24.1(7)
C9	2350(5)	4546(3)	5657(2)	14.4(6)
C11	4194(5)	4597(3)	5278(2)	17.4(6)
C6	-1390(5)	6050(4)	5935(2)	19.9(7)
C7	-2512(5)	6804(4)	6361(2)	21.2(7)
C8	-2232(5)	8185(4)	6640(3)	22.4(7)
C5	464(4)	6376(3)	5627(2)	16.0(6)
C1	2348(6)	9470(4)	6702(3)	25.6(8)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for compound 65.

The Anisotropic displacement factor exponent takes the form:

$-2\pi^2[h^2a^{*2}U_{11}+...+2hka\times b\times U_{12}]$

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
I1	16.89(11)	24.80(11)	14.26(11)	-4.32(8)	-3.29(8)	0.98(9)
C3	14.5(15)	15.0(14)	12.8(15)	-0.3(10)	1.1(11)	0.3(10)
O3	18.4(12)	25.5(12)	12.8(12)	-5.5(10)	-2.6(9)	5.5(9)
O2	19.7(11)	12.9(10)	8.9(11)	-1.4(8)	0.0(9)	1.0(8)
O1	22.0(13)	21.5(12)	18.8(13)	4.1(10)	0.2(10)	5.6(10)
C4	12.4(15)	13.0(12)	12.7(14)	0.7(10)	-0.1(12)	-0.5(10)
C2	20.7(15)	14.1(13)	14.8(17)	0.2(12)	2.7(14)	1.6(12)

C10	34.2(18)	17.4(14)	20.7(17)	-5.0(13)	5.2(17)	-7.3(19)
C9	16.8(14)	14.7(12)	11.6(15)	-1.8(11)	-0.4(12)	-0.2(11)
C11	18.6(16)	17.8(14)	15.9(17)	-0.3(12)	1.0(13)	2.7(12)
C6	14.5(16)	27.4(16)	17.8(17)	-2.9(13)	-2.3(13)	-0.7(12)
C7	14.0(15)	31.2(18)	18.2(17)	1.2(15)	-1.4(13)	1.1(14)
C8	19.1(15)	27.5(17)	20.5(17)	-1.9(15)	-0.5(13)	8.7(14)
C5	15.4(14)	20.9(14)	11.6(16)	-0.1(12)	0.3(11)	1.4(12)
C1	30.3(19)	16.0(15)	31(2)	0.8(14)	8.6(16)	-3.6(14)

Table 4 Bond Lengths for compound 65.

Atom	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**
I1	C3	2.168(3)	O1	C8	1.422(5)
C3	C4	1.515(5)	C4	C5	1.546(5)
C3	C2	1.541(5)	C2	C1	1.521(5)
O3	C9	1.439(4)	C10	C9	1.519(4)
O3	C5	1.443(4)	C9	C11	1.508(5)
O2	C4	1.430(4)	C6	C7	1.327(5)
O2	C9	1.433(4)	C6	C5	1.511(5)
O1	C2	1.434(5)	C7	C8	1.494(6)

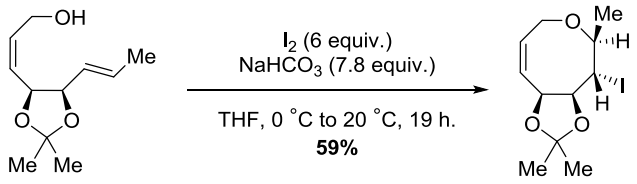
Table 5 Bond angles for compound 65.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C4	C3	I1	110.4(2)	O3	C9	C10	110.4(3)
C4	C3	C2	113.4(3)	O3	C9	C11	108.7(3)
C2	C3	I1	109.7(2)	O2	C9	O3	105.9(3)
C9	O3	C5	108.9(3)	O2	C9	C10	108.1(3)
C4	O2	C9	105.5(2)	O2	C9	C11	111.3(3)
C8	O1	C2	115.4(3)	C11	C9	C10	112.2(3)
C3	C4	C5	115.6(3)	C7	C6	C5	128.3(4)
O2	C4	C3	110.0(3)	C6	C7	C8	127.8(4)
O2	C4	C5	101.0(3)	O1	C8	C7	113.8(3)
O1	C2	C3	108.5(3)	O3	C5	C4	101.1(3)
O1	C2	C1	105.6(3)	O3	C5	C6	109.7(3)
C1	C2	C3	115.3(3)	C6	C5	C4	115.4(3)

Table 6 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for compound 65.

Atom	*x*	*y*	*z*	U(eq)
H3	212	6683	7321	17
H4	2981	6957	6088	15
H2	392	8955	7562	20
H10A	471	3166	5995	36

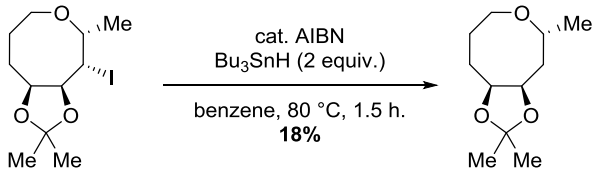
H10B	2476	2661	6118	36
H10C	1628	2734	5198	36
H11A	4160	4233	4710	26
H11B	5019	4084	5624	26
H11C	4601	5508	5254	26
H6	-1807	5194	5808	24
H7	-3626	6421	6505	25
H8A	-3191	8737	6401	27
H8B	-2337	8223	7258	27
H5	434	7190	5279	19
H1A	3336	9448	7104	38
H1B	1918	10370	6642	38
H1C	2764	9149	6157	38



57 **66**

(3aS,4S,5S,9aS,Z)-4-iodo-2,2,5-trimethyl-4,5,7,9a-tetrahydro-3aH-[1,3]dioxolo[4,5-d]oxocine (66): Dienyl alcohol **57** (113 mg, 0.57 mmol) was dissolved in THF (5.7 mL), the solution was cooled to 0 ˚C, and solid $NaHCO_3$ (369 mg, 4.4 mmol) was added, followed by I_2 (868 mg, 3.4 mmol). The reaction slowly warmed to room temperature

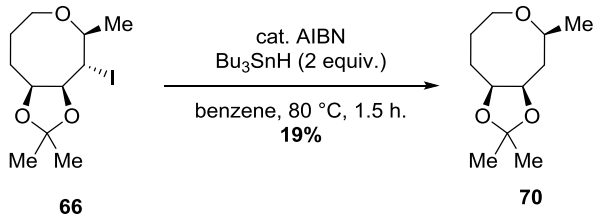
over 19 h. and was quenched with saturated aqueous $Na_2S_2O_3$ (40 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude yellow material was purified by flash column chromatography (9:1 hexanes:EtOAc) to obtain iodooxocene **66** as a clear, colorless oil (108 mg, 59% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.61 (dq, *J* = 11.8, 2.7 Hz, 1H), 5.41 (dq, *J* = 11.8, 2.6, 1.6 Hz, 1H), 5.33 (dq, *J* = 6.3, 2.4 Hz, 1H), 4.44 – 4.32 (m, 1H), 4.25 – 4.20 (m, 2H), 4.18 (ddd, *J* = 18.0, 3.4, 1.9 Hz, 1H), 4.12 (ddd, *J* = 18.1, 2.6 Hz, 1H), 1.59 (d, *J* = 4.9 Hz, 3H), 1.48 (s, 3H), 1.40 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 131.4, 130.0, 107.3, 83.2, 77.5, 76.7, 62.0, 35.4, 28.3, 26.2, 17.7. **FT-IR** (neat, cm^{-1}): 2984, 283, 1376, 1247, 1218, 1165, 1080, 1048, 910, 866, 732, 694, 650. **$[\alpha]_D^{25}$ =** +14.8 (c = 1.94, $CHCl_3$).



65 69

(3a*R*,5*R*,9a*S*,*Z*)-2,2,5-trimethyl-4,5,7,9a-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*d*]oxocine (69): Iodooxocene **65** (73 mg, 0.23 mmol) was dissolved in toluene (3.8 mL) and AIBN (8 mg, 0.05 mmol) was added to the flask, immediately followed by Bu_3SnH (0.12 mL, 0.46 mmol). The reaction mixture was heated to 87 ˚C for 1.5 h, then was cooled to room temperature. The reaction was diluted with Et_2O (5 mL) and saturated aqueous KF (5 mL). The aqueous layer was washed with Et_2O (2 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude material was purified by flash column chromatography (5-10% Et_2O in pentane as

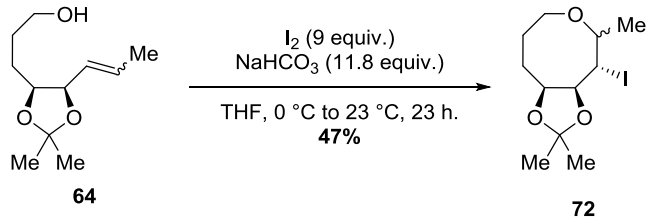
eluent) to afford oxocene **69** as a clear colorless oil (7.4 mg, 15% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.55 – 5.49 (ddd, *J* = 12, 2.4, 2.4 Hz, 1H), 5.36 (ddd, *J* = 12.2, 2.8, 2.8 Hz, 1H), 5.27 (m, 1H), 4.48 (ddd, *J* = 18.3, 2.5, 2.5 Hz, 1H), 4.42 (ddd, *J* = 11.7, 5.8, 3.7 Hz, 1H), 3.87 (ddd, *J* = 18.2, 3.0, 2.5 Hz, 1H), 3.75 (app. p, *J* = 6.4 Hz, 1H), 2.31 (ddd, *J* = 13.6, 11.9, 5.7 Hz, 1H), 1.90 (dd, *J* = 13.8, 3.6 Hz, 1H), 1.47 (s, 3H), 1.40 (s, 3H), 1.30 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 129.75, 129.71, 107.38, 77.68, 75.66, 74.01, 71.30, 34.12, 28.38, 26.50, 21.27. **HRMS** (APCI): *m/z* calcd. $C_{11}H_{19}O_3$ ($M+H^+$) 199.13287, found 199.13291. **FT-IR** (neat, cm^{-1}): 3023, 2978, 2889, 2845, 1456, 1366, 1246, 1212, 1063, 1030, 880, 860, 659, 644. **$[\alpha]_D^{25}$** = -18.5 (c = 0.61, $CHCl_3$).



66 **70**

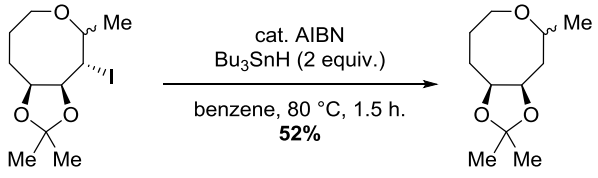
(3a*R*,5*S*,9a*S*,*Z*)-2,2,5-trimethyl-4,5,7,9a-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*d*]oxocine (70): Iodooxocene **66** (146 mg, 0.45 mmol) was dissolved in toluene (7.7 mL) and AIBN (15 mg, 0.09 mmol) was added to the flask, immediately followed by Bu_3SnH (0.25 mL, 0.93 mmol). The reaction mixture was heated to 87 ˚C for 1.5 h, and then was cooled to room temperature. The reaction was diluted with Et_2O (5 mL) and saturated aqueous KF (5 mL). The aqueous layer was washed with Et_2O (2 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude material was purified by flash column chromatography (5-10% Et_2O in pentane as eluent) to afford oxocene **70** as a clear colorless oil (17 mg, 19% yield). **^{1}H NMR** (600

MHz, $CDCl_3$) δ 5.53 (ddd, *J* = 12.2, 3.0, 2.8 Hz, 1H), 5.39 (ddd, *J* = 12.4, 2.9, 1.8 Hz, 1H), 5.27 (m, 1H), 4.33 (ddd, *J* = 10.6, 5.9, 3.6 Hz, 1H), 4.16 (ddd, *J* = 18.6, 2.7, 2.7 Hz, 1H), 4.12 – 4.03 (m, 2H), 2.04 (app. dd, *J* = 13.7, 11.7 Hz, 1H), 1.91 (dt, *J* = 13.9, 3.3 Hz, 1H), 1.47 (s, 3H), 1.37 (s, 3H), 1.28 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 130.27 130.14 78.56 77.68 71.63 61.70 35.73 28.24 26.38, 18.57. **HRMS** (APCI): *m/z* calcd. $C_{11}H_{19}O_3$ ($M+H^+$) 199.13287, found 199.13298. **FT-IR** (neat, cm^{-1}): 2982, 2934, 1459, 1377, 1215, 1173, 1130, 1043, 879, 861, 644. **$[\alpha]_D^{25}$** = -26.3 (c = 1.00, $CHCl_3$).



(3aS,4S,9aS)-4-iodo-2,2,5-trimethylhexahydro-5H-[1,3]dioxolo[4,5-d]oxocine (72), mixture of diastereomers at C5: Alkenyl alcohol **64** (174 mg, 0.87 mmol) was dissolved in THF (8.6 mL). $NaHCO_3$ (569 mg, 6.8 mmol) was added, followed by I_2 (1.32 g, 5.2 mmol). The reaction was stirred for 14 h, at which time additional $NaHCO_3$ (292 mg) and I_2 (662 mg) were added. After 9 h, the reaction mixture was diluted with saturated aqueous sodium thiosulfate (10 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash column chromatography (92:8 hexanes:EtOAc) to obtain iodooxocine **72** as an inseparable mixture of diastereomers (1:1.3), as a clear, colorless oil (134 mg, 47% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.61 (dd, J = 11.4, 4.8 Hz, 1H), 4.35 – 4.22 (m, 6H), 4.04 (ddd, J = 13.8, 7.2, 6.6 Hz, 1H), 3.93

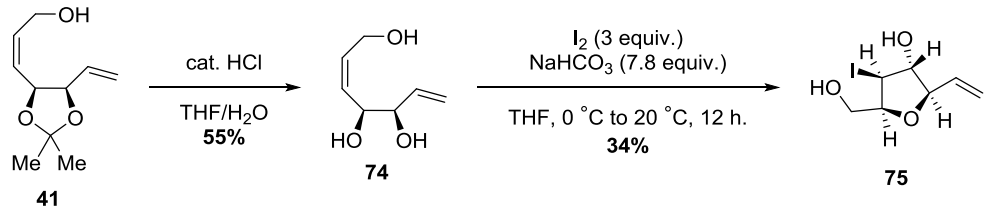
– 3.84 (m, 2H), 3.56 (ddd, J = 11.4, 4.5, 2.7 Hz, 1H), 3.32 (td, J = 11.6, 2.4 Hz, 1H), 3.26 (t, J = 12.2 Hz, 1H), 1.93 – 1.82 (m, 1H), 1.80 – 1.69 (m, 3H), 1.69 – 1.61 (m, 4H), 1.60 (d, J = 6.5 Hz, 3H), 1.52 (d, J = 6.2 Hz, 3H), 1.43 (s, 6H), 1.36 (s, 3H), 1.36 (s, 3H). **^{13}C NMR** (150 MHz, C_6D_6) δ 105.83, 105.71, 83.02, 80.18, 79.67, 77.71, 77.45, 76.01, 68.48, 62.14, 34.85, 31.57, 30.58, 29.43, 29.17, 28.74, 26.52, 26.26 (2), 19.27, 18.63. **HRMS** (NSI): m/z calcd. $C_{11}H_{20}IO_3$ (M-H+) 325.02951, found 325.02928. **IR** (neat, cm-1): 2984, 2932, 2877, 1451, 1369, 1220, 1168, 1080, 1037, 961, 939, 866, 826, 753, 706. **$[\alpha]_D^{25}$** = +10.8 (c = 0.80, $CHCl_3$).



72 **73**

(3a*R*,9a*S*)-2,2,5-trimethylhexahydro-3a*H*-[1,3]dioxolo[4,5-*d*]oxocine (73), mixture of diastereomers at C7: Iodooxocane **72** (125 mg, 0.38 mmol) was dissolved in benzene (6.4 mL), and AIBN (1 crystal) and tributyltin hydride (0.16 mL, 0.58 mmol) were added at room temperature. The reaction mixture was heated to reflux for 1 h. and cooled to room temperature. The solvent was removed by rotary evaporation and the residue diluted with Et_2O and saturated aqueous KF. The aqueous layer was extracted with Et_2O (3 x 8 mL) and the combined organic layers were washed with saturated aqueous KF (2 x 5 mL), brine (5 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude material was purified by flash column chromatography (8-10% Et_2O in pentane), which allowed separation and independent characterization of diastereomers. Data for the diastereomer eluting first (16 mg, 21% yield): **^{1}H NMR** (600 MHz, $CDCl_3$)

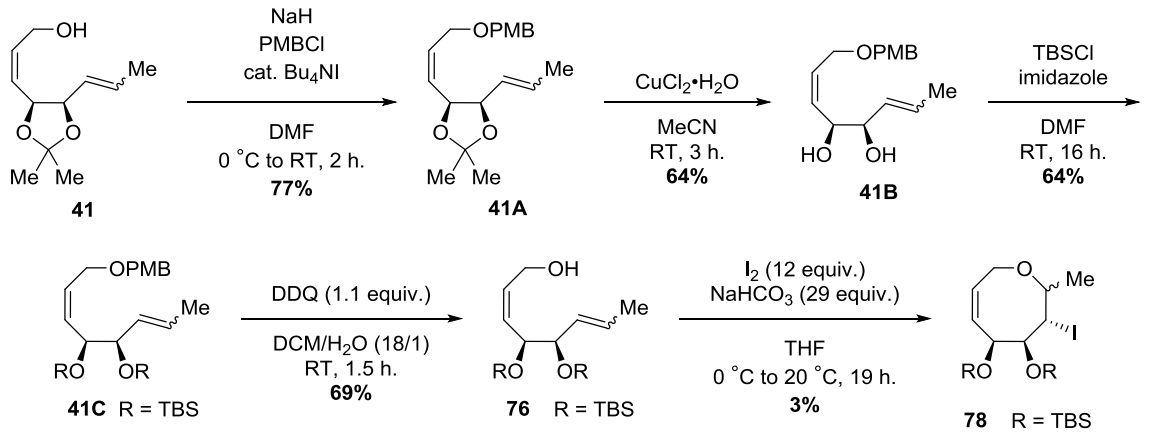
δ 4.38 (ddd, *J* = 11.8, 5.7, 3.2 Hz, 1H), 4.27 (dd, *J* = 10.7, 5.8 Hz, 1H), 3.93 (ddd, *J* = 13.2, 5.1, 4.2 Hz, 1H), 3.73 (app. p, *J* = 6.4 Hz, 1H), 3.20 (td, *J* = 12.3, 2.1 Hz, 1H), 2.31 (ddd, *J* = 14.4, 11.8, 5.4 Hz, 1H), 1.90 – 1.81 (m, 1H), 1.78 (dd, *J* = 14.5, 3.2 Hz, 1H), 1.75 – 1.60 (m, 3H), 1.41 (s, 3H), 1.34 (s, 3H), 1.27 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 105.79, 80.37, 72.77, 72.74, 69.29, 32.89, 30.76, 29.33, 28.50, 25.75, 20.51. **HRMS** (NSI): *m/z* calcd. $C_{11}H_{21}O_3$ ($M+H^+$) 201.14852, found 201.14849. **FT-IR** (neat, cm^{-1}): 2980, 2931, 2872, 1456, 1376, 1243, 1217, 1172, 1092, 1044, 1024, 892, 870, 754. **$[\alpha]_D^{25}$** = -23 (c = 0.26, $CHCl_3$). Data for the diastereomer eluting subsequently (24 mg, 31%): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.30 (ddd, *J* = 11.3, 5.9, 2.6 Hz, 1H), 4.22 (ddd, *J* = 11.1, 5.9, 1.8 Hz, 1H), 3.80 (dqd, *J* = 13.1, 6.5, 2.2 Hz, 1H), 3.62 (ddd, *J* = 12.1, 8.4, 3.6 Hz, 1H), 3.32 (ddd, *J* = 12.4, 6.4, 3.9 Hz, 1H), 2.00 (dt, *J* = 14.6, 11.4 Hz, 1H), 1.89 (tdd, *J* = 13.6, 11.0, 3.0 Hz, 1H), 1.78 – 1.67 (m, 3H), 1.59 – 1.51 (m, 1H), 1.41 (s, 3H), 1.33 (s, 3H), 1.21 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 105.94, 79.44, 77.73, 72.97, 63.72, 37.11, 28.52, 28.32, 28.13, 25.46, 20.78. **HRMS** (NSI): *m/z* calcd. $C_{11}H_{21}O_3$ ($M+H^+$) 201.14852, found 201.14859. **FT-IR** (neat, cm^{-1}): 2931, 2874, 1454, 1375, 1242, 1216, 1175, 1108, 1069, 1036, 896, 755. **$[\alpha]_D^{25}$** = -11.9 (c = 0.54, $CHCl_3$).



(2R,3R,4S,5S)-5-(hydroxymethyl)-4-iodo-2-vinyltetrahydrofuran-3-ol (75):

To a solution of **41** (0.160 g, 0.868 mmol) in THF (2.3 mL)/water (0.58 mL) was added 1 drop of HCl. The reaction mixture stirred 12 h. and additional HCl (1 drop) was added. After 24 h., the reaction mixture was quenched by the addition of solid $NaHCO_3$. The solvents were removed under reduced pressure and the crude residue was purified (95/5 to 93/7 DCM/MeOH) to obtain **74** as a clear, colorless oil (0.069 g, 0.479 mmol, 55 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.02 – 5.81 (m, 2H), 5.74 – 5.58 (m, 1H), 5.40 (dt, J = 17.3, 1.4 Hz, 1H), 5.34 – 5.30 (m, 1H), 4.49 (ddd, J = 7.9, 4.9, 1.4 Hz, 1H), 4.31 – 4.18 (m, 2H), 4.16 (ddd, J = 6.4, 3.9, 2.5 Hz, 1H), 2.26 (bs, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.2, 132.4, 130.6, 118.2, 75.5, 70.5, 58.7.

Triol **74** (0.069 g, 0.479 mmol) was dissolved in THF (4.8 mL) and $NaHCO_3$ (0.314 g, 3.7 mmol) was added, followed by I_2 (0.364 g, 1.436 mmol). The reaction stirred for 12 h. and was quenched with $Na_2S_2O_3$ (4 mL). The aq. layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with $Na_2S_2O_3$ (3 x 5 mL, until solution turns clear), dried over $MgSO_4$, filtered, and concentrated. The crude material was purified (2/1 hexanes/EtOAc) to obtain the tetrahydrofuran **75** as a clear, colorless oil (44 mg, 34% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.00 (ddd, J = 17.3, 10.3, 7.2 Hz, 1H), 5.41 (dt, J = 17.2, 1.4 Hz, 1H), 5.26 (dq, J = 10.4, 1.4 Hz, 1H), 4.43 (t, J = 4.8 Hz, 1H), 4.31 – 4.20 (m, 1H), 4.13 (ddt, J = 7.3, 5.1, 1.1 Hz, 1H), 3.90 – 3.68 (m, 3H).



(((3S,4S,5S,Z)-3-iodo-2-methyl-3,4,5,8-tetrahydro-2H-oxocine-4,5-diyl)bis(oxy))bis(tert-butyldimethylsilane) (78): Hydroxy-diene **41** (500 mg, 2.52 mmol) was dissolved in DMF (2.5 mL) and NaH (202 mg, 5.04 mmol) was added at 0 °C. The reaction was stirred for 10 min, and PMBCl (0.376 mL, 2.77 mmol) and Bu_4NI (93 mg, 0.252 mmol) were added at room temperature. The reaction mixture stirred for 2 h. and was quenched with water. The aq. layer was extracted with Et_2O (5 x 8 mL) and the combined organic layers were washed with water (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated. Crude purified (9/1 hex/EtOAc) to obtain the intermediate PMB-ether **41A** as a clear, colorless oil (619 mg, 1.944 mmol, 77 % yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.26 (d, J = 7.9 Hz, 4H), 6.89 (d, J = 8.7 Hz, 4H), 5.83 – 5.75 (m, 2H), 5.75 – 5.65 (m, 2H), 5.60 (ddt, J = 11.0, 8.9, 2.0 Hz, 2H), 5.46 – 5.37 (m, 2H), 4.97 – 4.92 (m, 1H), 4.91 – 4.81 (m, 2H), 4.50 (ddd, J = 8.1, 6.4, 1.6 Hz, 1H), 4.11 – 4.05 (m, 2H), 4.03 (dddd, J = 12.3, 5.8, 3.8, 1.8 Hz, 2H), 3.82 (s, 4H), 1.70 (dd, J = 6.5, 1.8 Hz, 3H), 1.65 (dd, J = 7.0, 1.8 Hz, 3H), 1.51 (s, 6H), 1.40 (s, 3H), 1.37 (s, 3H).

The intermediate PMB-ether **41A** (586 mg, 1.84 mmol) was dissolved in MeCN and copper(II) chloride dihydrate (627 mg, 3.68 mmol) was added at room temperature. The

reaction stirred for 3 h. and the solvent was removed under reduced pressure. The green residue was diluted with EtOAc and aq. NH_4Cl / NH_4OH (pH 9). The dark blue aq. layer was extracted with EtOAc (3 x 25 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified by flash column chromatography (1/1 to 1/2 hexanes/EtOAc) to obtain the diol **41B** as a pale yellow oil (325 mg, 64% yield). Starting material **41A** was also recovered (86 mg, 8.6%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (d, J = 9.4 Hz, 4H), 6.89 (d, J = 8.6 Hz, 4H), 5.91 – 5.80 (m, 2H), 5.80 – 5.73 (m, 2H), 5.51 (dq, J = 7.4, 1.6 Hz, 2H), 5.49 – 5.39 (m, 2H), 4.47 (d, J = 2.6 Hz, 4H), 4.36 (ddd, J = 10.2, 6.4, 2.8 Hz, 2H), 4.17 – 4.08 (m, 3H), 4.04 (ddd, J = 12.5, 6.0, 1.5 Hz, 3H), 3.81 (s, 6H), 2.27 (s, 4H), 1.73 (dd, J = 6.5, 1.6 Hz, 3H), 1.70 (dd, J = 7.0, 1.8 Hz, 3H).

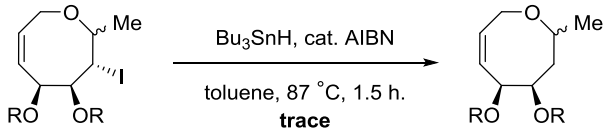
The diol **41B** (193 mg, 0.693 mmol) was dissolved in DMF (2 mL) and TBSCl (418 mg, 2.77 mmol) and imidazole (425 mg, 6.24 mmol) were added. The reaction stirred at room temperature for 16 h. The reaction was quenched with water and the aqueous layer was extracted with Et_2O (5 x 10 mL). The combined organic layers were washed with water (5 x), brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified (95:5 hexanes:EtOAc) to obtain the bis-TBS compound **41C** as a clear, colorless oil (224 mg, 0.44 mmol, 64% yield). **^{1}H NMR** (600 MHz, cdcl3) δ 5.66 (ddt, J = 11.7, 8.1, 4.2 Hz, 2H), 5.61 – 5.43 (m, 5H), 5.44 – 5.35 (m, 1H), 5.30 (ddq, J = 10.6, 9.0, 1.7 Hz, 1H), 4.50 – 4.40 (m, 4H), 4.26 (dd, J = 8.9, 5.6 Hz, 1H), 4.20 – 4.09 (m, 5H), 4.00 (dddd, J = 12.7, 7.4, 4.9, 1.9 Hz, 3H), 3.85 (t, J = 6.5 Hz, 1H), 3.82 (s, 6H), 1.68 (dd, J =

6.6, 1.6 Hz, 3H), 1.63 (dd, J = 6.9, 1.8 Hz, 3H), 0.86 (app. t, J = 2.8 Hz, 36H), 0.02 (s, 3H), 0.01 (s, 9H), 0.00 (s, 9H), -0.01 (s, 3H).

The bis-TBS ether **41C** (208 mg, 0.410 mmol) was dissolved in a 18/1 mixture of DCM (3.9 mL) and water (0.22 mL), and DDQ (102 mg, 0.45 mmol) was added slowly in one portion. The reaction mixture immediately turned dark green with the addition of DDQ, and was stirred at room temperature for 1.5 h., during which the reaction started bubbling and brown solids began to form. The reaction was quenched with $NaHCO_3$ (10 mL) and the aqueous layer was extracted with DCM (3 x 8 mL). The combined organic layers were washed with $NaHCO_3$ (3 x 10 mL), brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. The crude material was purified (9:1 pentane:Et_2O) to obtain the desired compound **76** as a clear, colorless oil (109 mg, 0.28 mmol, 69 % yield). **^{1}H NMR** (600 MHz, cdcl3) δ 5.80 (dq, J = 11.7, 6.0 Hz, 2H), 5.65 – 5.55 (m, 2H), 5.55 – 5.45 (m, 2H), 5.41 (ddq, J = 15.3, 7.4, 1.8 Hz, 1H), 5.36 – 5.25 (m, 1H), 4.34 (dt, J = 18.5, 8.0 Hz, 2H), 4.27 – 4.22 (m, 1H), 4.22 – 4.09 (m, 5H), 3.83 (t, J = 7.4 Hz, 1H), 2.48 (dt, J = 11.1, 5.7 Hz, 2H), 1.70 (dd, J = 6.6, 1.6 Hz, 3H), 1.67 (dd, J = 7.0, 1.8 Hz, 3H), 0.87 (app. d, J = 1.9 Hz, 18H), 0.86 (app. d, J = 3.1 Hz, 18H), 0.04 (t, J = 6.5 Hz, 9H), 0.01 (d, J = 2.1 Hz, 9H).

Alcohol **76** (50 mg, 0.13 mmol) was dissolved in THF (1.3 mL) and sodium bicarbonate (33 mg, 0.39 mmol) was added. Iodine (98 mg, 0.39 mmol) was added at room temperature and the reaction mixture stirred at room temperature for 14 h. Additional $NaHCO_3$ was added (15 mg, 1.5 equiv.) After 4 h., additional I_2 (98 mg) and $NaHCO_3$

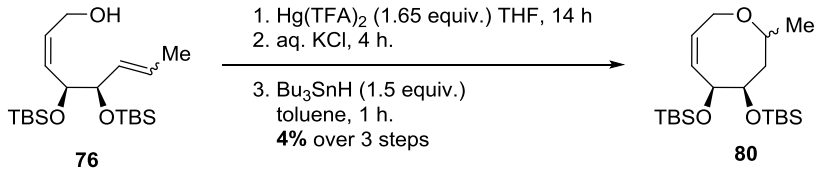
(277 mg) were added. The reaction mixture stirred 12 h. and was quenched by the addition of $Na_2S_2O_3$. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude material was purified (5-20% Et_2O/pentane) to obtain the compound **78** as a pale yellow oil (1.8 mg, 3.51 µmol, 3 % yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.49 (d, J = 4.6 Hz, 1H), 5.40 – 5.26 (m, 2H), 4.35 (dt, J = 17.0, 2.0 Hz, 1H), 4.22 (d, J = 3.3 Hz, 1H), 4.10 – 3.96 (m, 1H), 3.92 (d, J = 3.6 Hz, 2H), 0.97 – 0.85 (m, 21H), 0.15 – 0.03 (m, 12H).



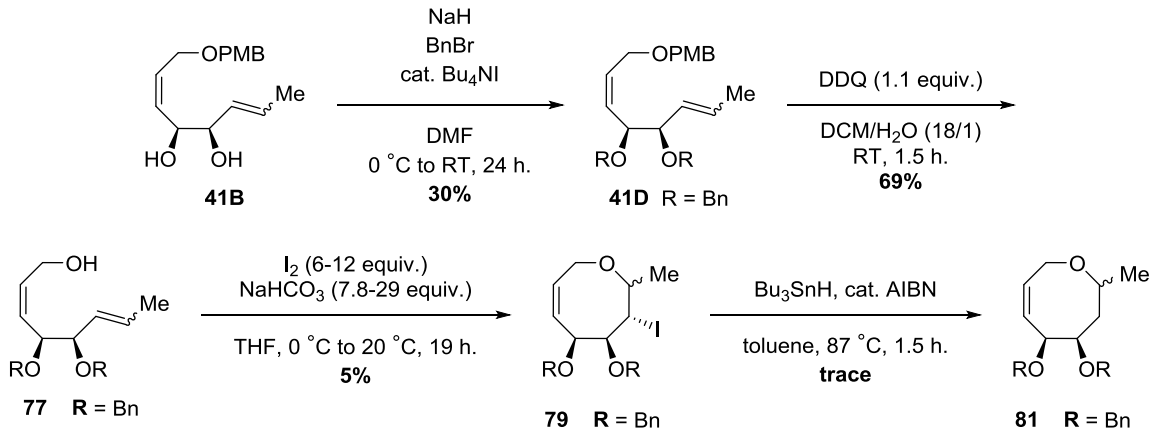
78 **R** = TBS **80** **R** = TBS

(((4R,5S,Z)-2-methyl-3,4,5,8-tetrahydro-2H-oxocine-4,5-diyl)bis(oxy))bis(tert-butyldimethylsilane) (80):

Route 1 (Scheme 19): To a solution of **78** (1.8 mg, 3.5 µmol) in benzene (0.5 mL) in a 8 mL vial was added 1 crystal of AIBN, followed by Bu_3SnH (1.4 µL in 0.5 mL of benzene, 5.27 µmol). The vial was sealed and heated to 80 ˚C for 1.5 h. The reaction mixture was concentrated and purified (9/1 pentane/Et_2O) to obtain trace amounts of the oxepene **80**. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.88 (ddd, J = 17.6, 11.0, 4.6 Hz, 1H), 5.42 – 5.29 (m, 3H), 5.27 (dt, J = 9.3, 1.8 Hz, 1H), 5.24 (d, J = 2.1 Hz, 1H), 5.13 (d, J = 5.2 Hz, 2H), 4.36 (dd, J = 4.9, 2.4 Hz, 1H), 4.31 (dt, J = 17.3, 2.0 Hz, 2H), 3.99 – 3.97 (m, 2H), 3.99 – 3.92 (m, 2H), 3.88 – 3.79 (m, 3H), 1.22 (d, J = 6.3 Hz, 3H), 1.15 (d, J = 6.4 Hz, 3H), 0.92 (s, 9H), 0.90 (s, 18H), 0.87 (s, 9H), 0.09 (s, 6H), 0.06 (s, 3H), 0.06 (s, 3H), 0.04 (s, 6H), 0.04 (s, 6H).



Route 2 (Scheme 20): Alcohol **76** (50 mg, 0.13 mmol) was dissolved in THF (1.3 mL) and mercury trifluoroacetate (91 mg, 0.21 mmol) was added in one portion at RT. The reaction mixture stirred 14 h. Aqueous KCl (0.096 mL, 1.3 mmol) was added and the reaction mixture stirred 4 h. The reaction mixture was diluted with EtOAc and H_2O, and the aq. layer was extracted with EtOAc (3 x 3 mL). Combined organic fractions were dried over $MgSO_4$. The solvent was removed by rotary evaporation, and the residue was diluted with toluene (2.6 mL). Tributyltin hydride (0.052 mL, 0.19 mmol) was added at room temperature, and the reaction immediately turned cloudy gray. The reaction stirred at room temperature for 1 h., and was diluted with Et_2O. The org. layer was washed with sat. aq. KF (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated. The crude was purified by flash column chromatography doped with 10% KF (95:5 to 9:1 pentane/Et_2O) to obtain **80** as a clear, colorless oil (2 mg, 5.17 µmol, 4% yield). The ^1H NMR spectra matched those from the deiodination of compound **80**.

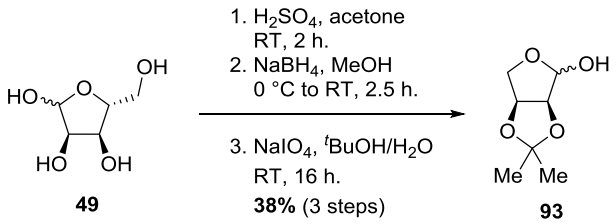


(4R,5S,Z)-4,5-bis(benzyloxy)-2-methyl-3,4,5,8-tetrahydro-2H-oxocine (81): The diol **41B** (0.325 g, 1.17 mmol) was dissolved in DMF (1.2 mL) and NaH (0.117 g, 2.9 mmol) was added at room temperature. After 20 min., benzyl bromide (0.29 mL, 2.39 mmol) was added, followed by Bu_4NI (0.086 g, 0.23 mmol). The reaction stirred at room temperature for 24 h. The reaction was quenched with water, and the aq. layer was extracted with Et_2O (5 x 10 mL). The organic layer was washed with water (5 x 5 mL), dried over $MgSO_4$, filtered, and concentrated. The crude was purified (4:1 hexanes:EtOAc) to obtain **41D** as a clear, yellow oil (160 mg, 30% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 20H), 7.23 (d, J = 8.5 Hz, 4H), 6.86 (d, J = 8.4 Hz, 4H), 5.89 (dt, J = 12.4, 6.5 Hz, 2H), 5.79 (dq, J = 10.9, 6.8 Hz, 1H), 5.69 (dq, J = 15.5, 6.5 Hz, 1H), 5.65 – 5.57 (m, 2H), 5.50 – 5.40 (m, 2H), 4.68 – 4.54 (m, 4H), 4.48 – 4.32 (m, 8H), 4.24 (dd, J = 9.2, 4.3 Hz, 1H), 4.15 (ddd, J = 14.3, 9.4, 4.7 Hz, 2H), 4.01 (ddd, J = 12.3, 7.2, 1.4 Hz, 2H), 3.95 – 3.85 (m, 2H), 3.80 (s, 6H), 3.78 (dd, J = 8.3, 4.7 Hz, 1H), 1.76 (dd, J = 6.4, 1.7 Hz, 3H), 1.59 (dd, J = 6.9, 1.9 Hz, 3H).

To a solution of **41D** (0.150 g, 0.33 mmol) in DCM (3.1 mL)/water (0.17 mL) at room temperature was added DDQ (0.082 g, 0.36 mmol). The reaction mixture stirred at room

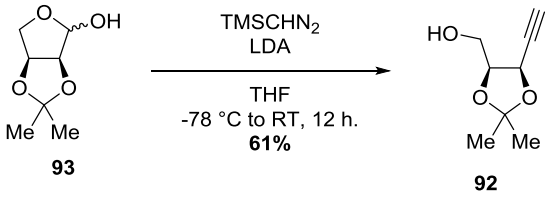
temperature for 1 h. and was quenched with sat. aq. $NaHCO_3$. The aq. layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with water (2 x 10 mL), dried over $MgSO_4$, filtered, and concentrated. The crude material was purified (2/1 hex/EtOAc) to obtain **77** as a clear, light brown oil (0.069 g, 0.20 mmol, 62 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 20H), 6.08 – 5.97 (m, 2H), 5.93 – 5.83 (m, 1H), 5.83 – 5.69 (m, 1H), 5.66 – 5.50 (m, 2H), 5.50 – 5.34 (m, 2H), 4.67 – 4.59 (m, 5H), 4.44 (d, J = 4.8 Hz, 1H), 4.42 – 4.38 (m, 1H), 4.38 – 4.30 (m, 1H), 4.24 – 4.15 (m, 3H), 4.00 (d, J = 13.8 Hz, 4H), 3.72 (dd, J = 8.2, 6.9 Hz, 1H), 2.11 (bs, 2H), 1.81 (dd, J = 6.5, 1.7 Hz, 3H), 1.64 (dd, J = 7.0, 1.8 Hz, 3H).

Alcohol **77** (0.037 g, 0.11 mmol) was dissolved in THF (2.19 mL) and sodium bicarbonate (0.072 g, 0.85 mmol) was added, followed by I_2 (0.166 g, 0.66 mmol). The reaction mixture stirred at room temperature for 48 h., and was quenched by addition of sat. aq. $Na_2S_2O_3$. The aq. layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude material was purified (9/1 to 2/1 hex/EtOAc) to obtain **79** as a clear, colorless oil (2.5 mg, 5.38 µmol, 5% yield). The iodooxocine intermediate (2.5 mg, 5.38 µmol) was dissolved in benzene (0.5 mL) and 1 crystal of AIBN was added, followed by Bu_3SnH (1.448 µl in 0.5 mL of benzene, 5.38 µmol). The reaction mixture was heated to reflux for 1 h. The reaction mixture was diluted with Et_2O and sat. aq. KF. The organic layer was washed with KF (3x), dried over $MgSO_4$, filtered, and concentrated.

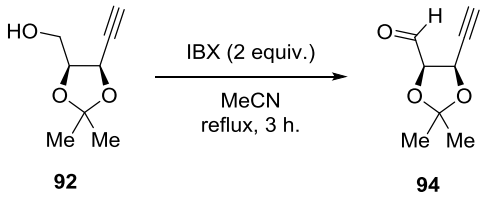


49 **93**

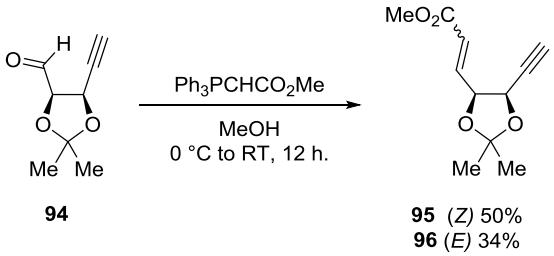
(3aS,6aS)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-ol (93): D-ribose **49** (10.0 g, 66.6 mmol) was suspended in acetone (145 mL) and H_2SO_4 (0.28 mL, 5.3 mmol) was added dropwise. The reaction was stirred at room temperature for 2 h. and was neutralized with $NaHCO_3$. The inorganic solids were removed by filtration and the solvent removed by rotary evaporation. The crude material was dissolved in MeOH (83 mL) and $NaBH_4$ (3.78 g, 100 mmol) was added in small portions at 0 °C. The reaction was stirred at 0 °C and slowly warmed to RT. After 15 h., the solvent was removed by rotary evaporation and the residue was dissolved in a mixture of water (66 mL) and ^{t}BuOH (100 mL). $NaIO_4$ (57.0 g, 266 mmol) was added slowly (CAUTION: EXOTHERM), and the reaction mixture stirred 16 h. at RT. The reaction mixture was diluted with DCM (200 mL). Solid $NaHCO_3$ was added to neutralize the mixture, and the inorganic solids were removed by filtration. The aqueous layer was extracted with DCM (2 x 100 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude material was purified by flash column chromatography (3:1 hexanes:EtOAc + 10% MeOH) to obtain the compound as a clear, colorless oil (4.10 g, 38% over 3 steps). Spectral data matched those in the literature.[30] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.85 (dd, J = 5.9, 3.7 Hz, 1H), 4.59 (d, J = 6.0 Hz, 1H), 4.09 (dd, J = 10.4, 3.6 Hz, 1H), 4.04 (d, J = 10.4 Hz, 1H), 2.60 (bs, 1H), 1.48 (s, 3H), 1.33 (s, 3H).



((4S,5R)-5-ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (92): Diisopropylamine (2.7 mL, 18.7 mmol) was dissolved in THF (104 mL) and *n*BuLi (9.5 mL, 18.7 mmol) was added dropwise at -78 °C. TMS-diazomethane (9.4 mL, 18.7 mmol) was added dropwise, and the solution was stirred for 30 min. at -78 °C. A solution of **93** (2.50 g, 15.6 mmol) in THF (30 mL) was added dropwise, and the reaction stirred 2.5 h. at this temperature. After warming to room temperature for 1 h., the reaction was quenched with water and the aqueous layer was extracted with Et_2O (3 x 75 mL). The combined org. layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified (3/1 hexanes/EtOAc to 2/1 hexanes/EtOAc + 10% MeOH) to obtain **92** as a clear, yellow oil (1.50 g, 61% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.86 (dd, J = 6.2, 2.3 Hz, 1H), 4.29 (q, J = 6.1 Hz, 1H), 3.86 (dd, J = 5.9, 2.1 Hz, 2H), 2.58 (d, J = 2.3 Hz, 1H), 2.10 (s, 1H), 1.55 (s, 3H), 1.37 (s, 3H).



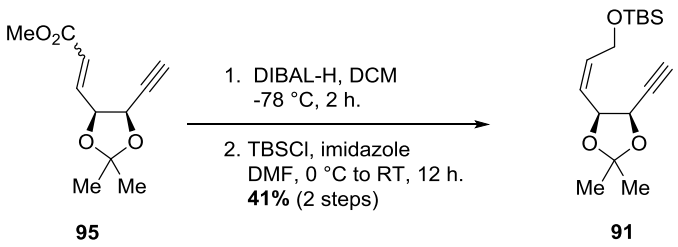
(4R,5R)-5-ethynyl-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (94): To a solution of **92** (1.18 g, 7.56 mmol) in MeCN (25 mL) was added IBX (4.23 g, 30.2 mmol). The reaction mixture refluxed for 3 h., cooled to RT, and filtered. The crude aldehyde (**94**) was used directly for the next reaction as a solution in MeCN.



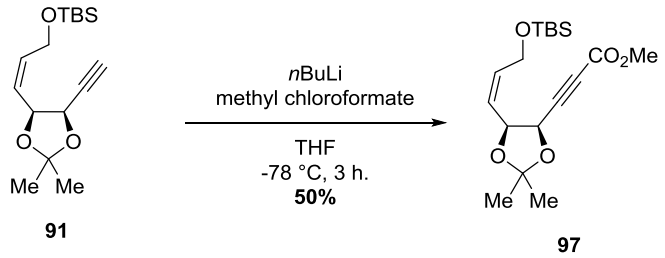
methyl 3-((4S,5R)-5-ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (95 and 96): To a solution of **94** (1.17 g, 7.59 mmol) in MeCN (25.3 mL) was added methyl (triphenylphosphoranylidene)acetate (2.79 g, 8.35 mmol) and the reaction stirred at room temperature for 18 h. The solvent was removed by rotary evaporation and the residue was diluted with Et_2O. The precipitate was removed by filtration and the solvent was evaporated (2 x). The crude material was purified (9/1 hexanes/EtOAc to 85/15 hexanes/EtOAc) to obtain **95** (0.808 g, 3.84 mmol, 50% yield) as a clear, colorless oil, followed by the elution of **96** (0.555 g, 2.64 mmol, 34% yield).

Data for **95**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.41 (dd, J = 11.6, 6.8 Hz, 1H), 6.02 (dd, J = 11.7, 1.5 Hz, 1H), 5.60 (td, J = 6.5, 1.5 Hz, 1H), 5.11 (dd, J = 6.1, 2.1 Hz, 1H), 3.74 (s, 3H), 2.46, (d, J = 2.3 Hz, 1H), 1.60 (s, 3H), 1.40 (s, 3H).

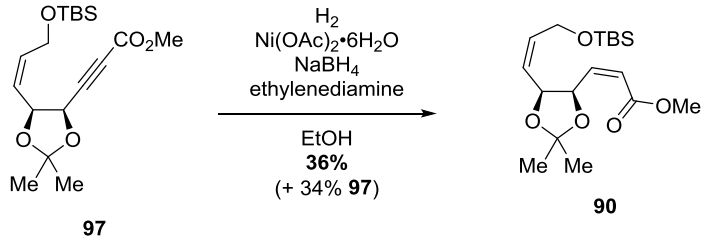
Data for **96**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.99 (dd, J = 15.6, 5.8 Hz, 1H), 6.17 (dd, J = 15.8, 1.2 Hz, 1H), 4.91 (dd, J = 6.1, 2.3 Hz, 1H), 4.74 (td, J = 6.1, 1.4 Hz, 1H), 3.77 (s, 3H), 2.57 (d, J = 2.4 Hz, 1H), 1.59 (s, 3H), 1.40 (s, 3H).



tert-butyl(((Z)-3-((4S,5R)-5-ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)oxy)-dimethylsilane (91): To a solution of **95** (0.808 g, 3.84 mmol) in DCM (25 mL) at 0 °C was added DIBAL-H (9.6 mL, 9.6 mmol) dropwise and the reaction stirred at 0 °C for 2 h. The reaction was quenched with H_2O (0.38 mL), 15% aq. NaOH (0.38 mL) and H_2O (0.96 mL). The reaction stirred at 0 °C for 15 min. and $MgSO_4$ was added. After 15 min. the solids were removed by filtration and the solvent was evaporated. The crude material (0.700 g, 3.84 mmol) was dissolved in DMF (1.5 mL) and imidazole (0.732 g, 10.8 mmol) was added, followed by TBSCl (0.608 g, 4.03 mmol). The reaction mixture stirred 20 h. and was quenched with water. The aq. layer was extracted Et_2O (5 x 3 mL) and the combined organic layers were washed with water (5 x 3 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude material was purified (95/5 pentane/Et_2O) to obtain **91** (525 mg, 46% over 2 steps) as a clear, colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.86 (dt, J = 11.5, 5.8 Hz, 1H), 5.72 (ddt, J = 10.7, 8.5, 1.8 Hz, 1H), 4.96 (dd, J = 8.3, 5.8 Hz, 1H), 4.76 (dd, J = 5.6, 2.2 Hz, 1H), 4.40 – 4.21 (m, 2H), 2.52 (d, J = 2.2 Hz, 1H), 1.58 (s, 3H), 1.39 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 135.2, 125.4, 110.6, 80.2, 76.0, 74.0, 69.5, 60.1, 28.0, 26.4, 26.1 (3C), 18.5, -4.9, -5.0.

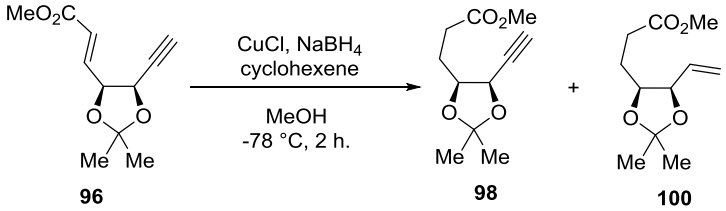


Methyl 3-((4R,5S)-5-((Z)-3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-ylpropiolate (97): To a solution of **91** (0.423 g, 1.43 mmol) dissolved in THF (2 mL) was added *n*BuLi (1.3 mL, 2.14 mmol) at -78 °C. After 30 min., a solution of methyl chloroformate (0.22 mL, 2.85 mmol) in THF (2.8 mL) was added. After 2.5 h, the reaction was warmed to room temperature and quenched with NH_4Cl. The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude material was purified (95/5 hex/EtOAc) to obtain **97** as a clear, colorless oil, followed by the elution of starting material (65 mg, 34% recovery). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.96 – 5.83 (m, 1H), 5.67 (ddt, J = 11.5, 8.2, 1.7 Hz, 1H), 5.13 – 4.99 (m, 1H), 4.84 (d, J = 5.6 Hz, 1H), 4.30 (ddd, J = 5.3, 3.4, 1.7 Hz, 2H), 3.78 (s, 3H), 1.57 (s, 3H), 1.39 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H).



methyl (Z)-3-((4R,5S)-5-((Z)-3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (90): Diacetoxynickel tetrahydrate (8.4 mg, 0.034 mmol) was dissolved in EtOH (3 mL) $NaBH_4$ (1.3 mg, 0.034 mmol) was added as a

solution in EtOH (1.5 mL) under argon. The green solution immediately turned black and the argon was replaced with a hydrogen balloon. Ethylenediamine (4.76 µl, 0.071 mmol) was added and hydrogen was bubbled through the suspension for 30 min. A solution of **97** (0.100 g, 0.282 mmol) in EtOH (2.5 mL) was added dropwise and the reaction stirred at room temperature for 6 h. The suspension was filtered through a pad of Celite and the filter cake was rinsed with DCM. The filtrate was washed with brine (2 x) and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified (95/5 pentane/Et_2O) to obtain **90** (12 mg, 12% yield) as a ~1:2 mixture with starting material **97** (24 mg, 24% recovery). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.91 – 5.77 (m, 1H), 5.73 – 5.56 (m, 1H), 5.29 (ddt, J = 11.2, 9.2, 1.9 Hz, 1H), 5.14 (dd, J = 9.1, 6.9 Hz, 1H), 4.35 – 4.31 (m, 1H), 4.11 (ddd, J = 13.9, 5.1, 1.9 Hz, 1H), 3.70 (s, 3H), 1.53 (s, 3H), 1.40 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H).



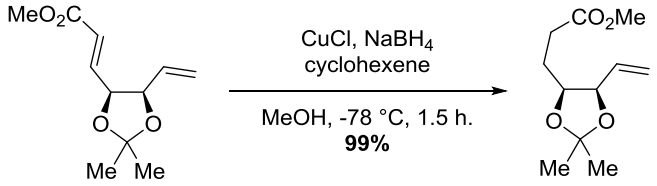
methyl 3-((4S,5R)-5-ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate (98): *E*-methyl ester **96** (0.555 g, 2.64 mmol) was dissolved in MeOH (44.0 mL) and cooled to -78 °C. Copper (I) chloride (0.201 g, 2.033 mmol) and cyclohexene (1.070 mL, 10.56 mmol) were added, followed by $NaBH_4$ (0.479 g, 12.67 mmol). The reaction mixture turned dark brown over the course of 1.5 h. at -78 °C, then concentrated while the solvent was still cold. The residue was partitioned between aq. NH_4Cl and Et_2O, and the aq. layer (adjusted to pH 9) was extracted with Et_2O (2 x). The combined organic layers were

dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified (9/1 hexanes/EtOAc) to obtain **98** contaminated with **100** (approximately 6.8/1 **98** : **100**, 280 mg, combined 50% yield).

Data for **98**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.74 (dd, J = 5.5, 2.2 Hz, 1H), 4.11 (dt, J = 8.6, 5.3 Hz, 1H), 3.67 (s, 3H), 2.51 (d, J = 2.1 Hz, 1H), 2.50 – 2.41 (m, 2H), 2.11 – 1.97 (m, 2H), 1.50 (s, 3H), 1.31 (s, 3H).

methyl 3-((4S,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)propanoate (100):

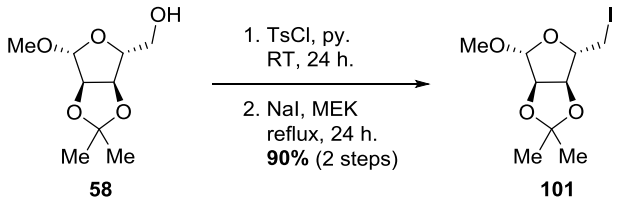
Spectral data matched those in the literature.[27] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.82 (ddd, J = 17.2, 10.3, 7.6 Hz, 1H), 5.35 (dt, J = 17.2, 1.3 Hz, 1H), 5.27 (dd, J = 10.4, 1.4 Hz, 1H), 4.55 (dd, J = 7.6, 6.3 Hz, 1H), 4.16 (ddd, J = 9.0, 6.2, 4.9 Hz, 1H), 3.68 (s, 3H), 2.50 (ddd, J = 16.5, 8.5, 6.2 Hz, 1H), 2.44 – 2.36 (m, 1H), 1.79 – 1.69 (m, 2H), 1.48 (s, 3H), 1.36 (s, 3H).



110 **100**

Route 2 (Scheme 28): *E*-methyl ester **110** (1.72 g, 8.10 mmol) was dissolved in MeOH (135 ml)and cooled to -78 °C. CuCl (0.618 g, 6.24 mmol) and cyclohexene (3.16 ml, 31.2 mmol) were added, followed by $NaBH_4$ (1.472 g, 38.9 mmol). The reaction mixture turned dark brown over the course of 1.5 h. at -78 °C, then concentrated while the solvent was still cold. The residue was partitioned between aq. NH_4Cl and Et_2O, and the aqueous layer (adjusted to pH 9) was extracted with Et_2O (2 x). The combined organic layers

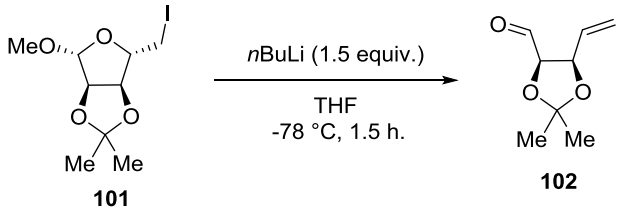
were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to obtain **100** (1.74 g, 99% yield) as a clear, colorless oil. The spectral data matched those above.



58 **101**

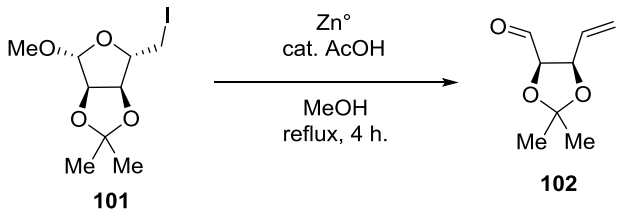
(3aS,4S,6R,6aR)-4-(iodomethyl)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole (101): To a solution of **58** (12.20 g, 59.7 mmol) in pyridine (25 mL) was added TsCl (20.50 g, 108 mmol). The reaction stirred for 17 h. at room temperature and was quenched by the addition of water (100 mL). The aqueous layer was extracted with Et_2O (4 x 100 mL). The combined organic layers were washed with 5% aq. H_2SO_4 (2 x 75 mL), 0.2 M KOH (3 x 100 mL), dried over $MgSO_4$, filtered, and concentrated. Pyridine was still present, and the off-white solid was dissolved in Et_2O/EtOAc and washed with sat. aq. $CuSO_4$ (3 x 25 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The crude tosylate was used without further purification. Spectral data matched those reported in the literature.[27] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.81 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 4.94 (s, 1H), 4.61 (d, J = 5.4 Hz, 1H), 4.54 (d, J = 5.9 Hz, 1H), 4.32 (t, J = 7.3 Hz, 1H), 4.02 (ddd, J = 5.2, 3.7, 1.6 Hz, 2H), 3.24 (s, 3H), 2.47 (s, 3H), 1.46 (s, 3H), 1.29 (s, 3H). To a solution of the tosylate (21.41 g, 59.7 mmol) in MEK (199 mL) was added sodium iodide (17.91 g, 119 mmol), and the reaction was heated to reflux for 20 h. The reaction was cooled to room temperature and the solvent removed. The residue was partitioned between Et_2O and water (100 mL). The aq. layer was extracted with Et_2O (3 x 100 mL)

and the combined organic layers were washed with $Na_2S_2O_3$ (2 x 100 mL), dried over $MgSO_4$, filtered, and concentrated. The crude material was purified (85/15 hexanes/EtOAc) to obtain **101** (37.44 g, 90% over 2 steps) as a clear, pale yellow oil. Spectral data matched those reported in the literature.[27] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.07 (s, 1H), 4.78 (dd, J = 5.7, 0.9 Hz, 1H), 4.64 (d, J = 5.9 Hz, 1H), 4.45 (ddd, J = 10.1, 6.0, 1.0 Hz, 1H), 3.38 (s, 3H), 3.30 (dd, J = 9.9, 6.0 Hz, 1H), 3.17 (dd, J = 10.3, 9.9 Hz, 1H), 1.49 (s, 3H), 1.34 (s, 3H).



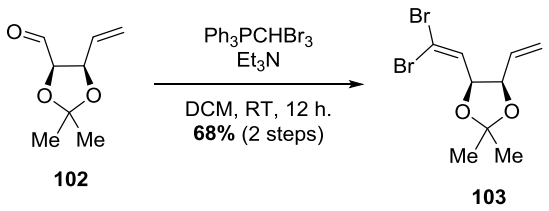
(4R,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolane-4-carbaldehyde (102):

Route 1 (Scheme 27):[39] To a solution of **101** (4.00 g, 12.73 mmol) in THF (64 mL) at -78 °C was added *n*BuLi (9.7 mL, 19.10 mmol) dropwise over 12 min. The reaction mixture stirred at -78 °C for 2 h. and was quenched with solid NH_4Cl (1.2 g). The flask was removed from the dry ice bath and water (30 mL) was added. The biphasic reaction mixture stirred at room temperature until the ice melted. The cold aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude **102** was used to make **103** without further purification.



101 **102**

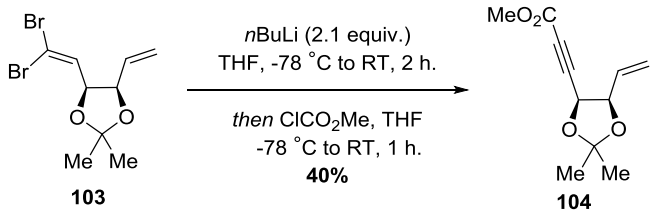
Route 2 (Scheme 28):[27] To a solution of **101** (37.44 g, 119 mmol) in MeOH (397 ml) was added activated Zn^0 (44.4 g, 679 mmol) and AcOH (3.75 ml, 65.6 mmol). The mixture was refluxed or 4 h. then cooled to RT. The solids were removed by filtration through a short plug of silica gel, and the crude aldehyde **102** was used as a solution in MeOH for the preparation of compounds **109** and **110**.



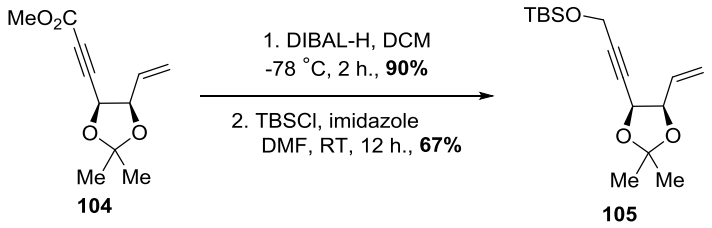
102 **103**

(4S,5R)-4-(2,2-dibromovinyl)-2,2-dimethyl-5-vinyl-1,3-dioxolane (103): To a solution of **102** from Route 1 (1.989 g, 12.74 mmol) in DCM (43 mL) at 0 °C was added TEA (3.73 mL, 26.7 mmol), followed by (dibromomethyl)triphenylphosphonium bromide[39] (13.12 g, 25.5 mmol). The reaction mixture warmed to room temperature over 17 h. The reaction was diluted with pentane (120 mL) and the solids were removed by filtration. The solvent was removed and the filtration process was repeated. The solvent was removed and the crude material was purified (9/1 hexanes/EtOAc) to obtain **103** (2.70 g, 68% yield) as a clear, pale yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.45 (d, J = 8.0 Hz, 1H), 5.76 (ddd, J = 17.2, 10.5, 7.0 Hz, 1H), 5.49 – 5.36 (m, 1H), 5.31 (dd, J = 10.4, 1.5 Hz, 1H), 4.83 (dd, J = 8.3, 6.4 Hz, 1H), 4.71 (t, J = 6.7 Hz, 1H), 1.52 (s, 3H), 1.40 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 135.5, 135.5, 132.6, 119.3, 109.8, 92.8, 79.0, 76.9,

28.1, 25.7. HRMS (APCI): *m/z* calcd. For $C_9H_{12}Br_2O_2$ ($M+H^+$) 310.92768, found 310.92783.



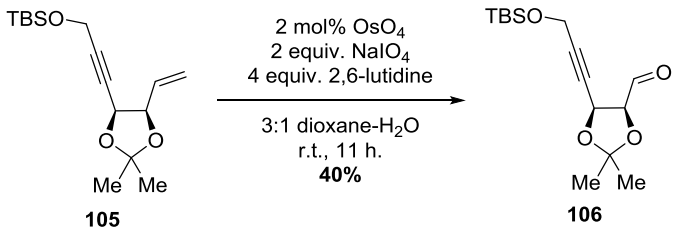
methyl 3-((4S,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)propiolate (104): To a solution of **103** (1.04 g, 3.33 mmol) in THF (16.67 mL) at -78 °C was added *n*BuLi (3.41 mL, 7.00 mmol) dropwise. The reaction stirred at -78 °C for 1 h, then at room temperature for 1 h. The reaction was cooled to -78 °C and freshly distilled methyl chloroformate (0.52 mL, 6.67 mmol) was added as a solution in THF (5 mL). The reaction stirred at -78 °C for 30 min., then was warmed to room temperature for 1 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (10 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (10 mL), dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash column chromatography (4/1 hexanes/EtOAc) to obtain **104** as a clear, colorless oil (0.315 g, 45% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.99 (ddd, J = 17.5, 10.3, 7.6 Hz, 1H), 5.48 (dt, J = 17.1, 1.2 Hz, 1H), 5.46 – 5.33 (m, 1H), 4.89 (d, J = 5.8 Hz, 1H), 4.61 (dd, J = 7.6, 5.9 Hz, 1H), 3.79 (s, 4H), 1.58 (s, 4H), 1.40 (s, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.5, 132.2, 121.0, 111.2, 83.2, 79.5, 78.8, 69.1, 52.8, 27.6, 26.0. **HRMS** (NSI): *m/z* calcd. for $C_{11}H_{15}O_4$ [$M+H^+$] 211.09649, found 211.09621. **FT-IR** (neat, cm^{-1}): 2988, 2956, 2935, 2239, 1717, 1435, 1374, 1343, 1246, 1157, 1055, 1025, 988, 937, 864, 779, 750. **$[\alpha]_D^{25}$** = -68.5 (c = 1.4, $CHCl_3$).



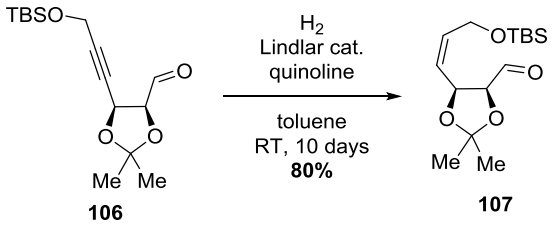
tert-butyl((3-((4S,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)prop-2-yn-1-yl)oxy)dimethylsilane (105): DIBAL-H (2.67 ml, 2.67 mmol) was added dropwise to a solution of **104** (0.255 g, 1.21 mmol) in DCM (4.0 ml) at 0 °C. The reaction stirred at 0 °C for 2.5 h. The reaction was diluted with Et_2O and 0.11 mL of water was added, followed by 0.11 mL 15% aq. NaOH and 0.3 mL of water. After 15 min., $MgSO_4$ was added and the reaction stirred for 15 min. The solids were removed by filtration through a coarse frit and the solvent removed under reduced pressure. The crude material (207 mg, 94% yield) was used without further purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.00 (ddd, J = 17.6, 10.3, 7.6 Hz, 1H), 5.43 (dt, J = 17.2, 1.2 Hz, 1H), 5.36 (dd, J = 10.3, 1.1 Hz, 1H), 4.86 (dt, J = 6.0, 1.8 Hz, 1H), 4.55 (dd, J = 7.6, 5.9 Hz, 1H), 4.32 (dd, J = 6.2, 1.7 Hz, 2H), 3.42 (d, J = 6.8 Hz, 1H), 1.57 (s, 3H), 1.39 (s, 3H).

To a solution of the crude material (0.206 g, 1.13 mmol) in DMF (0.57 ml) was added imidazole (0.354 g, 5.20 mmol) and TBSCl (0.341 g, 2.261 mmol). The reaction stirred at room temperature for 12 h. and was quenched by the addition of water (5 mL). The aqueous layer was extracted with Et_2O (5 x 5 mL) and the combined organic layers were washed with water (5 x 5 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude material was purified (95/5 hexanes/EtOAc) to obtain **105** as a clear, colorless oil (0.324 g, 97% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.01 (ddd, J = 17.1, 10.3, 7.7 Hz, 1H), 5.41 (dd, J = 17.2, 1.2 Hz, 1H), 5.33 (dd, J = 10.4, 1.2 Hz, 1H),

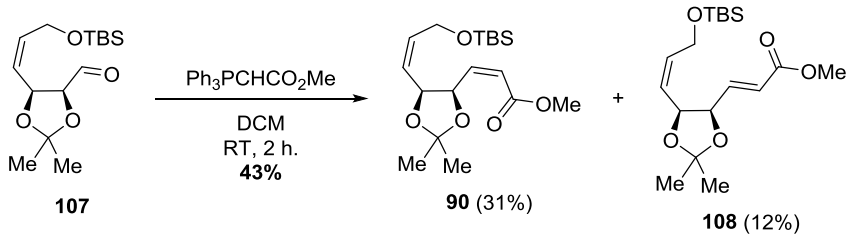
4.85 (dt, J = 6.0, 1.7 Hz, 1H), 4.53 (ddt, J = 7.8, 5.9, 0.9 Hz, 1H), 4.36 (d, J = 1.6 Hz, 2H), 1.57 (s, 3H), 1.38 (s, 3H), 0.91 (s, 9H), 0.12 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 133.9, 120.0, 110.4, 86.9, 80.6, 79.8, 69.6, 51.9, 28.0, 26.3, 26.0 (3C), 18.5, -5.0 (2C). **HRMS** (NSI): *m/z* calcd. for $C_{16}H_{28}O_3NaSi$ [M+Na^+] 319.16999, found 319.16992.



(4S,5S)-5-(3-((tert-butyldimethylsilyl)oxy)prop-1-yn-1-yl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (106): To a solution of **105** (0.324 g, 1.09 mmol) in dioxane (7.95 ml)/water (2.98 ml) was added 2,6-lutidine (0.51 ml, 4.37 mmol), OsO_4 (0.274 ml, 0.022 mmol), and $NaIO_4$ (0.467 g, 2.186 mmol). The cloudy white reaction mixture was stirred at room temperature for 11 h, turning bright yellow over time. The reaction mixture was diluted with Et_2O and the insoluble material was removed by gravity filtration. The organic phase was washed with water (3 x 10 mL), $Na_2S_2O_3$ (10 mL) and $CuSO_4$ (4 x 10 mL). The pale brown organic phase was dried over $MgSO_4$, filtered and concentrated. The crude material was used w/o further purification.



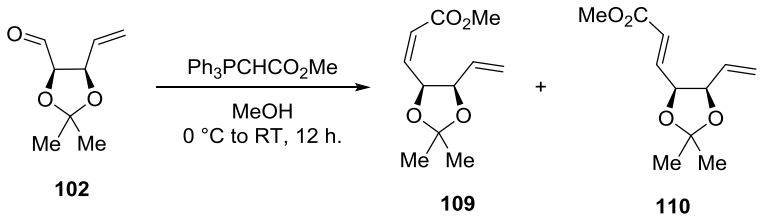
(4S,5S)-5-((Z)-3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (107): To a solution of **106** (136 mg, 0.456 mmol) in toluene (2.3 ml) was added quinoline (26 µl, 0.219 mmol) and Lindlar catalyst (485 mg, 0.228 mmol). H_2 was bubbled through the solution for 30 min. and the reaction was stirred under an atmosphere of H_2 for 12 h. Additional Lindlar catalyst (485 mg, 0.228 mmol) was added and the reaction stirred under hydrogen for an additional 24 h., changing the H_2 balloon every 8-12 h. as needed. Another portion of the Lindlar catalyst (485 mg, 0.228 mmol) was added and the reaction stirred under hydrogen for an additional 24 h., changing the H_2 balloon every 8-12 h. as needed. Additional Lindlar catalyst was added (485 mg, 0.228 mmol) was added and the reaction stirred for 7.5 days (total of 10 days from the start of the reaction, balloon of hydrogen changed every 8-12 h. as needed). Aliquots were taken every 12 h. to monitor the reaction by ^{1}H NMR. Once the starting material was consumed, the solids were removed by filtration through a short pad of Celite and the solvent was removed by rotary evaporation. The crude material was used without further purification for the next reaction. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.56 (d, J = 3.1 Hz, 1H), 5.86 – 5.68 (m, 1H), 5.49 – 5.39 (m, 1H), 5.36 – 5.28 (m, 1H), 4.42 – 4.38 (m, 1H), 4.29 (dd, J = 6.1, 1.7 Hz, 1H), 4.26 (dd, J = 4.7, 2.1 Hz, 1H), 1.62 (s, 3H), 1.44 (s, 3H), 0.92 (s, 9H), 0.10 (s, 6H).



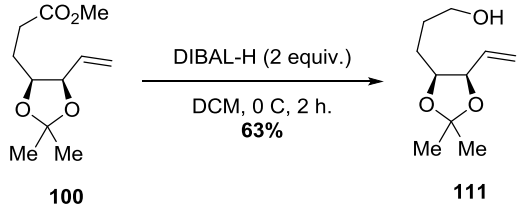
methyl (Z)-3-((4R,5S)-5-((Z)-3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (90) and methyl (E)-3-((4R,5S)-5-((Z)-3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (108): To a solution of **107** (0.326 g, 1.092 mmol, combined from multiple batches) in DCM (3.64 ml) was added methyl (triphenylphosphoranylidene)acetate (0.483 g, 1.445 mmol) and the reaction stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the material was purified by flash column chromatography (9/1 to 85/15 hexanes/EtOAc) to obtain **90** (0.119 g, 0.336 mmol, 31 % yield), followed by the elution of **108** (0.048 g, 0.135 mmol, 12 % yield).

Z isomer: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.20 (dd, J = 11.6, 7.6 Hz, 1H), 5.88 (dd, J = 11.7, 1.5 Hz, 1H), 5.68 – 5.63 (m, 2H), 5.29 (ddt, J = 11.0, 9.0, 1.8 Hz, 1H), 5.21 – 5.12 (m, 1H), 4.33 (ddd, J = 14.0, 6.9, 1.8 Hz, 1H), 4.12 (ddd, J = 14.0, 5.1, 1.9 Hz, 1H), 3.71 (s, 3H), 1.54 (s, 3H), 1.41 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H).

E isomer: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.81 (dd, J = 15.6, 5.5 Hz, 1H), 6.06 (dd, J = 15.7, 1.6 Hz, 1H), 5.75 (dt, J = 11.5, 5.7 Hz, 1H), 5.38 (ddt, J = 10.8, 8.7, 1.8 Hz, 1H), 5.16 (dd, J = 8.6, 7.0 Hz, 1H), 4.73 (td, J = 6.9, 6.3, 1.5 Hz, 1H), 4.32 – 4.22 (m, 2H), 3.75 (s, 3H), 1.54 (s, 3H), 1.41 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 204.6, 144.1, 133.3, 127.7, 122.6, 109.9, 77.7, 74.5, 59.0, 52.0, 28.0, 25.8 (3C), 25.6, 18.2, -3.4 (2C).

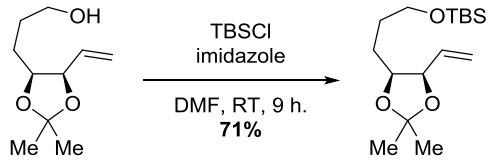


methyl (Z)-3-((4S,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)acrylate (109) and **methyl (E)-3-((4S,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)acrylate (110):** To a solution of **102** (18.62 g, 119 mmol) in MeOH (426 ml) was added methyl (triphenylphosphoranylidene)acetate (43.8 g, 131 mmol) and the reaction stirred 12 h. at RT. The solvent was removed under reduced pressure and the residue diluted with Et_2O and filtered through a pad of silica gel. The solvent was evaporated and the crude material was purified (9/1 to 85/15 hexanes/EtOAc) to obtain **109** (10.20 g, 40% yield) as a clear, colorless oil, followed by the elution of **110** (1.74 g, 7% yield). The spectral data for **109** and **110** matched those in the literature.[27,29]

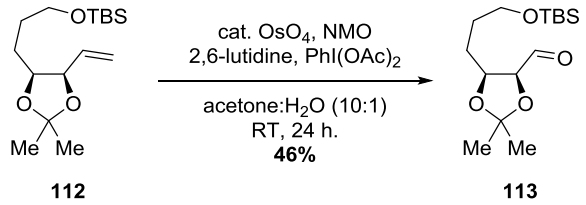


3-((4S,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)propan-1-ol (111): Methyl ester **100** (1.74 g, 8.12 mmol) was dissolved in DCM (27 ml) at -15 °C and DIBAL-H (17.1 ml, 17.1 mmol) was added dropwise. The reaction slowly warmed to room temperature over 2 h and 20 min. The reaction was diluted with Et_2O and 0.69 mL water, 0.69 mL 15% aq. NaOH, and 1.7 mL water was added. After 15 min. $MgSO_4$ was added, and the

mixture stirred an additional 15 min. The solids were removed by gravity filtration and the solvent removed by rotary evaporation. The crude material was purified (97/3 DCM/MeOH) to obtain **111** (945 mg, 63% yield) as a clear, pale yellow oil. Spectral data matched those in the literature.[27,29] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.81 (ddd, J = 17.2, 10.3, 7.8 Hz, 1H), 5.31 (dd, J = 16.8, 1.4 Hz, 2H), 5.24 (dd, J = 10.5, 1.5 Hz, 1H), 4.51 (t, J = 7.1 Hz, 1H), 4.21 – 4.14 (m, 1H), 3.75 – 3.65 (m, 2H), 1.70 (dddd, J = 32.9, 12.4, 8.2, 5.9 Hz, 4H), 1.49 (s, 3H), 1.37 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 134.5, 118.6, 108.5, 80.1, 78.4, 77.4, 77.0, 62.9, 30.0, 25.8.

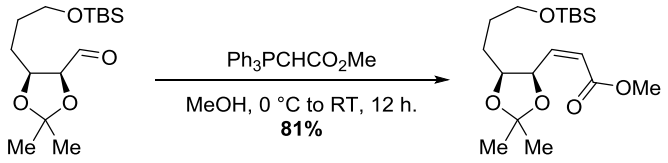


tert-butyl(3-((4S,5R)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)propoxy)dimethylsilane (112): Alcohol **111** (0.935 g, 5.02 mmol) was dissolved in DMF (1.9 ml) and TBSCl (0.908 g, 6.02 mmol) was added, followed by imidazole (0.957 g, 14.06 mmol). The reaction stirred at room temperature for 15 h. and was quenched by the addition of water. The aqueous layer was extracted with Et_2O (5 x 25 mL). The combined organic layers were washed with water (5 x 15 mL), brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. The crude material was purified (95/5 pentane/Et_2O) to obtain **112** (1.07 g, 71% yield) as a clear, colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.83 (ddd, J = 17.6, 10.3, 7.8 Hz, 1H), 5.31 (dt, J = 17.1, 1.3 Hz, 1H), 5.27 – 5.13 (m, 1H), 4.50 (dd, J = 7.8, 6.2 Hz, 1H), 4.17 (dt, J = 7.9, 5.6 Hz, 1H), 3.76 – 3.55 (m, 2H), 1.68 (m, 1H), 1.56 – 1.50 (m, 3H), 1.49 (s, 3H), 1.37 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H).



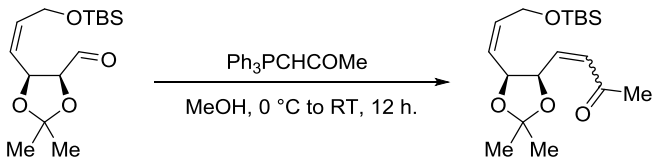
112 **113**

(4S,5S)-5-(3-((tert-butyldimethylsilyl)oxy)propyl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (113): To a solution of **112** (0.500 g, 1.664 mmol) in acetone (15 ml)/water (1.5 ml) was added 2,6-lutidine (0.388 ml, 3.33 mmol), NMO (0.292 g, 2.49 mmol), and OsO_4 (1.26 ml, 0.100 mmol). The reaction was stirred at room temperature for 5 days, and additional OsO_4 (1.26 ml, 0.100 mmol) was added. After 3 h., additional NMO (0.292 g, 2.49 mmol) was added and the reaction stirred 18 h. The reaction was quenched with aqueous $Na_2S_2O_3$. The organic solvent was removed by rotary evaporation and the residue was partitioned between $Na_2S_2O_3$ and EtOAc. The aqueous layer was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with $CuSO_4$, water, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. the crude material was purified (9/1 pentane/Et_2O) to obtain **113** (229 mg, 46 % yield) as a clear, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.65 (d, J = 3.4 Hz, 1H), 4.38 (td, J = 7.2, 3.8 Hz, 1H), 4.27 (dd, J = 7.0, 3.5 Hz, 1H), 3.63 (td, J = 5.4, 3.7 Hz, 2H), 1.76 – 1.50 (m, 7H), 1.42 (s, 3H), 0.89 (s, 9H), 0.05 (s, 6H).



113 **99**

methyl (Z)-3-((4R,5S)-5-(3-((tert-butyldimethylsilyl)oxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (99): To a solution of **113** (0.222 g, 0.73 mmol) in MeOH (7.3 ml) was added methyl (triphenylphosphoranylidene)acetate (0.270 g, 0.807 mmol). The reaction stirred 12 h. at room temperature and the solvent was removed under reduced pressure. The residue was diluted with Et_2O, filtered, and the solvent evaporated (2 x.) The crude material was purified (95/5 hexanes/EtOAc) to obtain **99** (0.213 g, 81 % yield) as a clear, pale yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.25 (dd, J = 11.6, 8.1 Hz, 1H), 5.93 (dd, J = 11.6, 1.4 Hz, 1H), 5.62 (ddd, J = 8.2, 6.5, 1.5 Hz, 1H), 4.38 (ddd, J = 9.4, 6.5, 4.1 Hz, 1H), 3.68 – 3.52 (m, 2H), 1.69 (ddq, J = 12.9, 11.2, 5.8 Hz, 1H), 1.57 – 1.51 (m, 1H), 1.50 (s, 3H), 1.49 – 1.39 (m, 2H), 1.38 (s, 3H), 0.88 (s, 9H), 0.03 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.0, 146.8, 121.2, 108.7, 78.4, 75.2, 75.0, 62.6, 51.5, 29.8, 28.1, 27.3, 25.9, 25.6 (2C), 25.4, -3.6, -5.4.



107

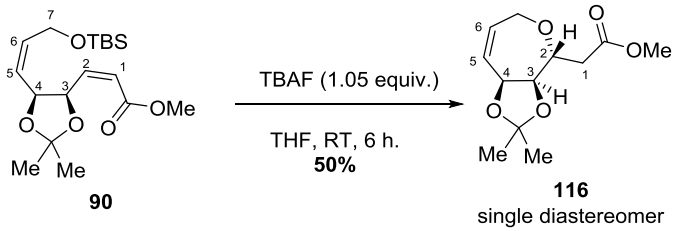
114 *Z* 6%
115 *E* 43%

4-((4R,5S)-5-((Z)-3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-2-one (114 and 115): To a solution of **107** (0.110 g, 0.366 mmol) in DCM (1.2 ml) at room temperature was added 1-(triphenyl-l5-phosphanylidene)propan-2-one (0.140 g, 0.439 mmol). The reaction stirred for 12 h., and additional 1-(triphenyl-l5-phosphanylidene)propan-2-one (0.140 g, 0.439 mmol) was added. The reaction stirred another 12 h. and was diluted with pentane. The solids were

removed by filtration and the crude material was purified to obtain **114** (8 mg, 6% yield), followed by the elution of **115** (53 mg, 0.156 mmol, 43% yield).

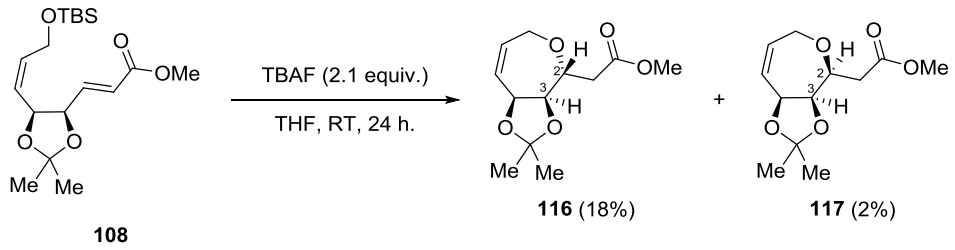
Data for **114**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.26 (d, J = 11.4 Hz, 1H), 6.05 (dd, J = 11.6, 7.4 Hz, 1H), 5.61 (dt, J = 11.7, 5.8 Hz, 1H), 5.52 – 5.44 (m, 1H), 5.25 (ddt, J = 11.2, 9.4, 1.8 Hz, 1H), 5.17 (dd, J = 9.3, 6.6 Hz, 1H), 4.35 – 4.30 (m, 1H), 4.15 – 4.00 (m, 1H), 2.22 (s, 3H), 1.53 (s, 3H), 1.39 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H).

Data for **115**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.61 (dd, J = 16.0, 5.7 Hz, 1H), 6.26 (dd, J = 15.9, 1.4 Hz, 1H), 5.74 (dtd, J = 11.5, 5.7, 1.3 Hz, 1H), 5.38 (ddt, J = 11.8, 8.6, 1.8 Hz, 1H), 5.17 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 4.75 (ddd, J = 7.1, 5.7, 1.5 Hz, 1H), 4.35 – 4.10 (m, 2H), 2.26 (s, 3H), 1.55 (s, 3H), 1.41 (s, 3H), 0.90 (d, J = 0.9 Hz, 9H), 0.08 (s, 3H), 0.08 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 198.1, 142.8, 133.9, 131.6, 126.1, 109.7, 77.9, 74.8, 60.0, 29.9, 28.0, 27.6, 26.1 (2C), 25.5, 18.5, -5.0, -5.1.



methyl 2-((3aR,4R,8aS)-2,2-dimethyl-3a,4,6,8a-tetrahydro-[1,3]dioxolo[4,5-c]oxepin-4-yl)acetate (116): To a solution of **90** (0.012 g, 0.034 mmol) in THF (0.317 ml) was added TBAF (0.10 ml, 0.100 mmol) and the reaction stirred at room temperature for 6 h. The reaction was quenched with water (0.7 mL) and the aqueous layer was extracted with Et_2O (3 x 2.5 mL). The organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude material was purified (95/5 to 7/3 hexanes/EtOAc) to obtain the desired compound **120** (4.1 mg, 0.017 mmol, 50% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.67

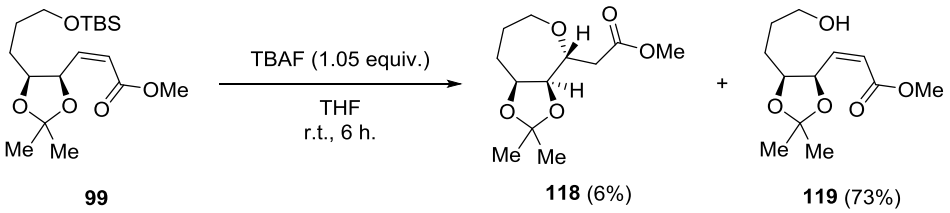
(app. dq, J = 12.4, 2.6 Hz, 1H), 5.55 (app. dq, J = 12.9, 2.7 Hz, 1H), 4.99 (app. dp, J = 5.5, 2.9 Hz, 1H), 4.31 (app. dq, J = 5.4, 2.9 Hz, 2H), 4.11 (dd, J = 9.9, 6.6 Hz, 1H), 4.03 (td, J = 9.9, 2.6 Hz, 1H), 3.72 (s, 3H), 2.80 (dd, J = 16.4, 2.7 Hz, 1H), 2.50 (dd, J = 16.4, 10.0 Hz, 1H), 1.44 (s, 3H), 1.37 (s, 3H).



methyl 2-((3aR,4S,8aS)-2,2-dimethyl-3a,4,6,8a-tetrahydro-[1,3]dioxolo[4,5-c]oxepin-4-yl)acetate (117): To a solution of **108** (63 mg, 0.177 mmol) dissolved in THF (0.71 ml) was added TBAF (0.19 ml, 0.19 mmol) at RT. After 4.5 h., additional TBAF (0.19 ml, 0.19 mmol) was added and the reaction mixture stirred for 21 h. The reaction was quenched with water and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified (5/1 to 3/1 to 2/1 hex/EtOAc) to obtain **116** (8 mg, 0.033 mmol, 18% yield), followed by the elution of **117** (1 mg, 4.13 µmol, 2% yield).

^{1}H NMR data for **116** matches that above.

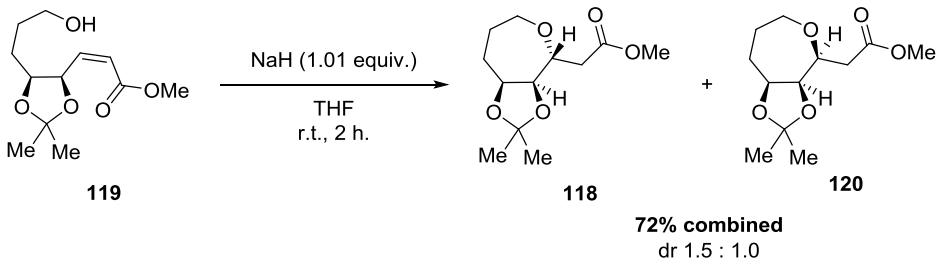
Data for **117**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.88 – 5.77 (m, 2H), 4.67 (t, J = 6.7 Hz, 1H), 4.48 (dt, J = 18.3, 2.3 Hz, 1H), 4.30 (dt, J = 18.3, 2.3 Hz, 1H), 4.21 (dd, J = 6.6, 1.6 Hz, 1H), 3.99 (ddd, J = 9.7, 3.4, 1.4 Hz, 1H), 3.71 (s, 3H), 2.80 (dd, J = 16.7, 9.7 Hz, 1H), 2.50 (dd, J = 16.7, 3.7 Hz, 1H), 1.55 (s, 3H), 1.37 (s, 3H).



methyl 2-((3aR,4R,8aS)-2,2-dimethylhexahydro-[1,3]dioxolo[4,5-c]oxepin-4-yl) acetate (118): To a solution of **99** (0.072 g, 0.2 mmol) in THF (0.67 ml) was added TBAF (0.21 ml, 0.210 mmol) and the reaction stirred at room temperature for 6 h. and quenched with water. The aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash column chromatography (9/1 to 3/1 hexanes/EtOAc) to obtain **118** (0.003 g, 6% yield) as a clear, colorless oil, followed by the elution of **119** (0.036 g, 73% yield).

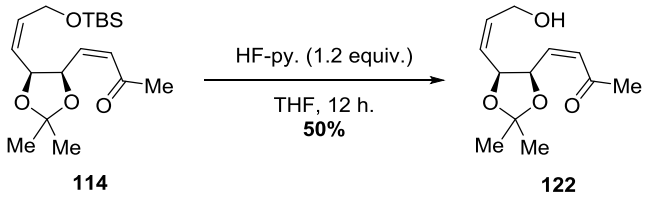
Data for **118**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.38 (ddd, J = 10.4, 6.6, 4.2 Hz, 1H), 4.09 – 3.83 (m, 3H), 3.71 (s, 3H), 3.58 (ddd, J = 12.7, 10.4, 3.1 Hz, 1H), 2.75 (dd, J = 15.9, 2.7 Hz, 1H), 2.43 (dd, J = 16.1, 9.8 Hz, 1H), 2.10 – 1.97 (m, 1H), 1.96 – 1.83 (m, 1H), 1.82 – 1.68 (m, 1H), 1.68 – 1.51 (m, 1H), 1.43 (s, 3H), 1.34 (s, 3H).

Data for **(119)**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.25 (ddd, J = 11.6, 8.1, 1.1 Hz, 1H), 5.95 (dt, J = 11.6, 1.3 Hz, 1H), 5.62 (ddt, J = 7.9, 6.6, 1.3 Hz, 1H), 4.41 (ddd, J = 9.9, 6.7, 3.3 Hz, 1H), 3.73 (s, 3H), 3.70 – 3.57 (m, 2H), 1.89 (bs, 1H), 1.78 – 1.61 (m, 1H), 1.58 – 1.51 (m, 5H), 1.49 – 1.40 (m, 1H), 1.39 (s, 3H).



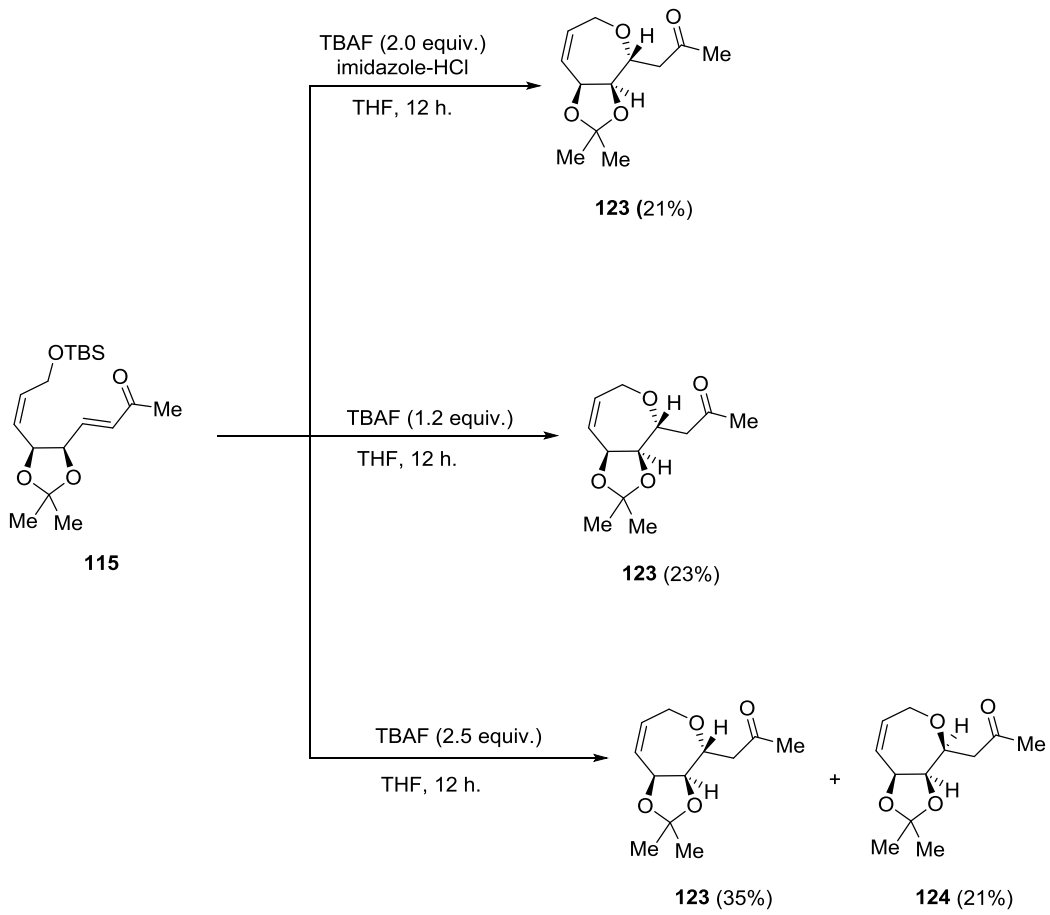
methyl 2-((3aR,4S,8aS)-2,2-dimethylhexahydro-[1,3]dioxolo[4,5-c]oxepin-4-yl)acetate (120): NaH (1.819 mg, 0.045 mmol) was added to a solution of **119** (0.011 g, 0.045 mmol) in THF (0.45 ml) at room temperature. The reaction stirred for 2 h. and was quenched with sat. aq. NH_4Cl. The aqueous layer was extracted with Et_2O (3 x 7 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude material was purified (95/5 hexanes/EtOAc) to obtain and inseparable mixture of **118** and **120** (8 mg, combined 72% yield).

Spectral data for **118** matches above.



(Z)-4-((4R,5S)-5-((Z)-3-hydroxyprop-1-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-2-one (122): To a solution of **114** (10 mg, 0.029 mmol) in THF (0.59 ml) was added HF-pyridine (4.38 µl, 0.035 mmol) and the cloudy reaction was stirred at room temperature for 12 h. The reaction was quenched with $NaHCO_3$ and extracted with Et_2O (3 x 3 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to obtain **122** (3 mg, 50% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.62 (dd, J = 16.0, 5.7 Hz, 1H), 6.27 (dd, J = 15.9, 1.5 Hz, 1H), 5.75 (dtd, J = 11.3, 5.7, 1.3 Hz, 1H),

5.44 – 5.32 (m, 1H), 5.17 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H), 4.75 (ddd, J = 7.0, 5.6, 1.5 Hz, 1H), 4.40 – 4.31 (m, 1H), 4.26 (td, J = 5.5, 1.8 Hz, 2H), 2.27 (s, 3H), 1.55 (s, 3H), 1.42 (s, 3H).



1-((3aR,4R,8aS)-2,2-dimethyl-3a,4,6,8a-tetrahydro-[1,3]dioxolo[4,5-c]oxepin-4-yl)propan-2-one (123): To a solution of **115** (33 mg, 0.097 mmol) in THF (3.5 ml) was added TBAF (0.24 mL, 0.24 mmol). The reaction stirred at room temperature overnight 12 h. and solvents were removed under reduced pressure. The crude material was purified (3/1 hexanes/EtOAc) to obtain **127** (7.6 mg, 35 % yield), followed by **124** (4.6 mg, 21 % yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.65 (app. dq, J = 12.7, 2.5 Hz, 1H), 5.55 (app. dq, J = 12.6, 2.4 Hz, 1H), 4.98 (app. dq, J = 5.4, 2.7 Hz, 1H), 4.34 (app. dq, J = 17.8, 2.6 Hz,

1H), 4.27 (app. dq, J = 17.7, 2.6 Hz, 1H), 4.06 (td, J = 9.5, 2.2 Hz, 1H), 2.81 (dd, J = 17.3, 2.1 Hz, 1H), 2.69 (dd, J = 17.2, 9.4 Hz, 1H), 2.20 (s, 3H), 1.42 (s, 3H), 1.36 (s, 3H).

Data for **1-((3aR,4S,8aS)-2,2-dimethyl-3a,4,6,8a-tetrahydro-[1,3]dioxolo[4,5-c]oxepin-4-yl)propan-2-one (128): ^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.98 – 5.62 (m, 2H), 4.66 (t, J = 6.6 Hz, 1H), 4.43 (dt, J = 18.0, 2.2 Hz, 1H), 4.31 (dt, J = 18.1, 2.2 Hz, 1H), 4.17 (dd, J = 7.1, 1.6 Hz, 1H), 4.10 – 3.93 (m, 1H), 2.98 (dd, J = 17.6, 9.1 Hz, 1H), 2.56 (dd, J = 17.6, 3.6 Hz, 1H), 2.20 (s, 3H), 1.56 (s, 3H), 1.37 (s, 3H).

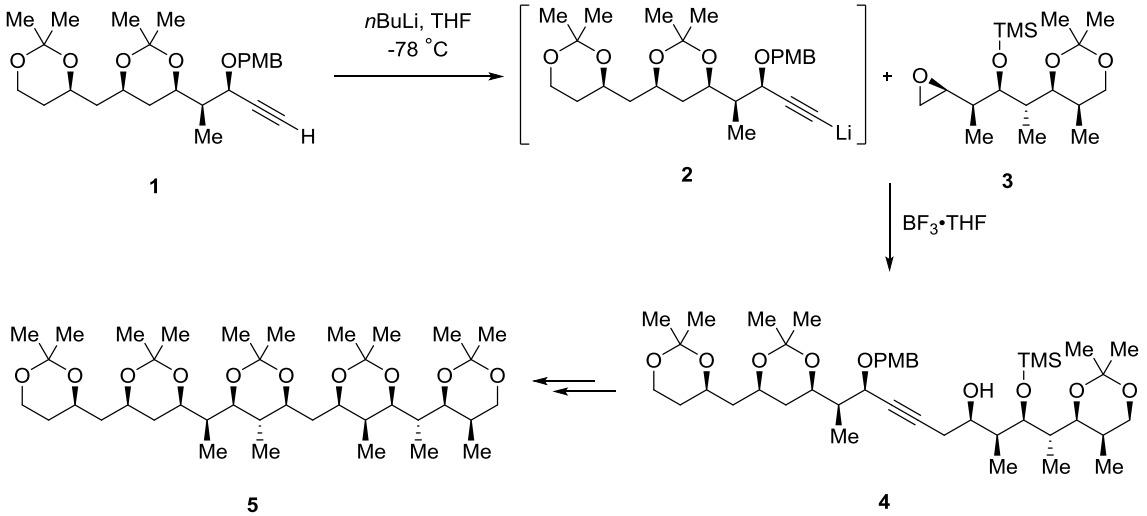
CHAPTER 2

Iterative alkyne-epoxide couplings toward the total synthesis of PM-toxin A.

2.1 Introduction and Background

2.1.1 Classical alkyne-epoxide couplings

The construction of carbon-carbon bond forming reactions between two structurally complex partners remains a central problem in synthetic organic chemistry. One such example is the alkyne-epoxide cross coupling reaction, in which a strong base (nBuLi) is used to deprotonate a terminal alkyne. The lithium acetylide adds to an epoxide that is activated by a strong Lewis acid, such as $BF_3{\cdot}OEt_2$ or $BF_3{\cdot}THF$.[40,41] These reactions are usually performed at cryogenic temperatures and require the strict exclusion of air and moisture. A number of natural product syntheses use alkyne-epoxide couplings as a key step in the route to the target molecule.[42–44] Our laboratory has successfully used this approach in the synthesis of an aflastatin A degradation product (Scheme 1).[45] Two structurally complex partners were coupled together using the classical conditions and subsequent functionalization of the internal alkyne afforded the C9-C27 substructure of aflastatin A.



Scheme 1: Application of classical procedure for alkyne-epoxide coupling in synthesis.[45]

The antimicrobial and anticancer agent RK-397 was also completed using a synthetic strategy of alkyne-epoxide couplings to connect building blocks of six or more carbons in a modular synthesis of the natural product (Figure 1). The 1,3-diols were established using hydroxyl-directed hydrosilylation, C-Si bond oxidation, and stereoselective reduction of ketones with induction from the β-hydroxyl group.[44]

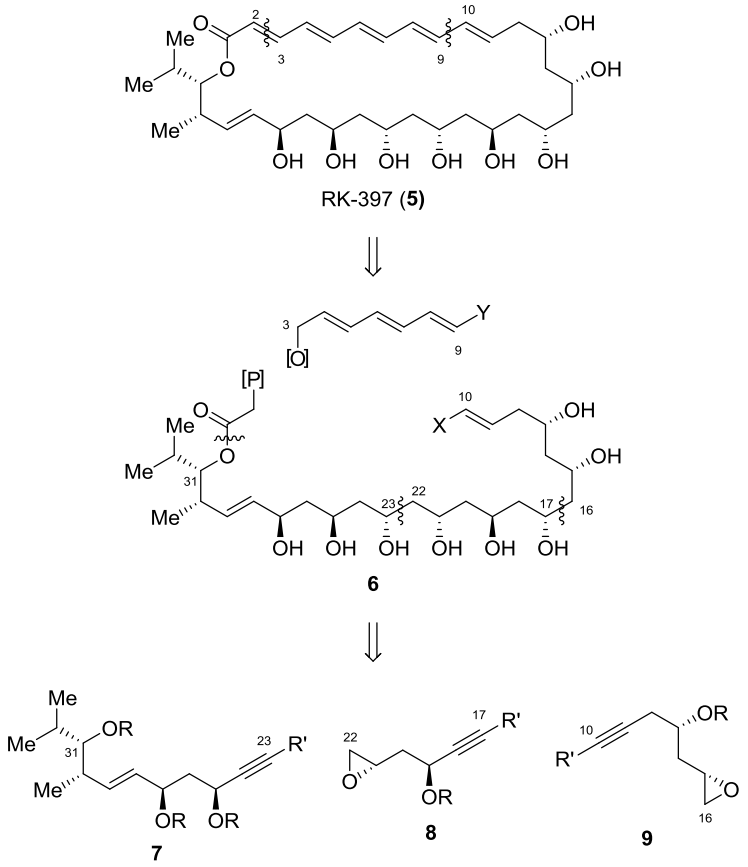
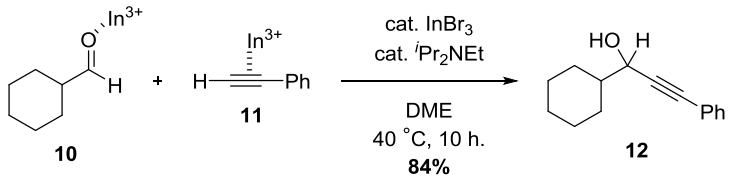


Figure 1: Retrosynthetic analysis of RK-397 featuring alkyne-epoxide couplings as key building blocks.[44]

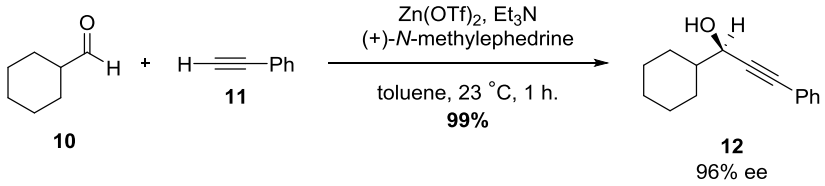
2.1.2 Mild activations of alkyne nucleophiles and various electrophiles

Related methods of alkyne addition to an aldehyde can be performed under less harsh conditions by activation of the alkyne and aldehyde with Lewis acids in the presence of bases, as in the work of Shibasaki and Carreira. These approaches are notable for the milder alkyne activation and deprotonation step as compared to conditions requiring organolithium reagents. Shibasaki's work in 2005 employed a "dual-activation" method of both the soft nucleophile (terminal alkyne) and hard electrophile (aldehyde or ketone) using an In^{3+}-based catalyst (Scheme 2).[46]



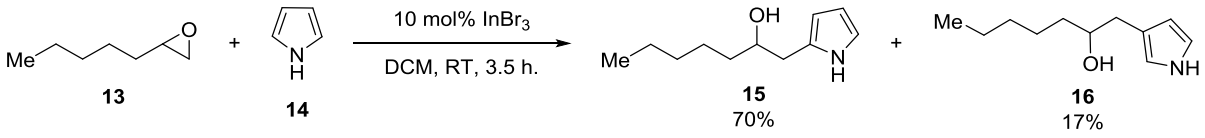
Scheme 2: Shibasaki's alkynylation of carbonyl compounds *via* dual activation with In^{3+}-based catalysts.[46]

Carreira's laboratory developed an asymmetric alkynylation of aldehydes in which addition of a zinc acetylide to an aldehyde occurs with stereoinduction from an *N*-methylephedrine ligand.[47,48] The zinc acetylide is formed by activation of the alkyne with Zn^{2+} and deprotonation of the terminal alkyne with an amine base (Scheme 3).



Scheme 3: Asymmetric alkynylation of aldehydes developed by Carreira *et al*.[49]

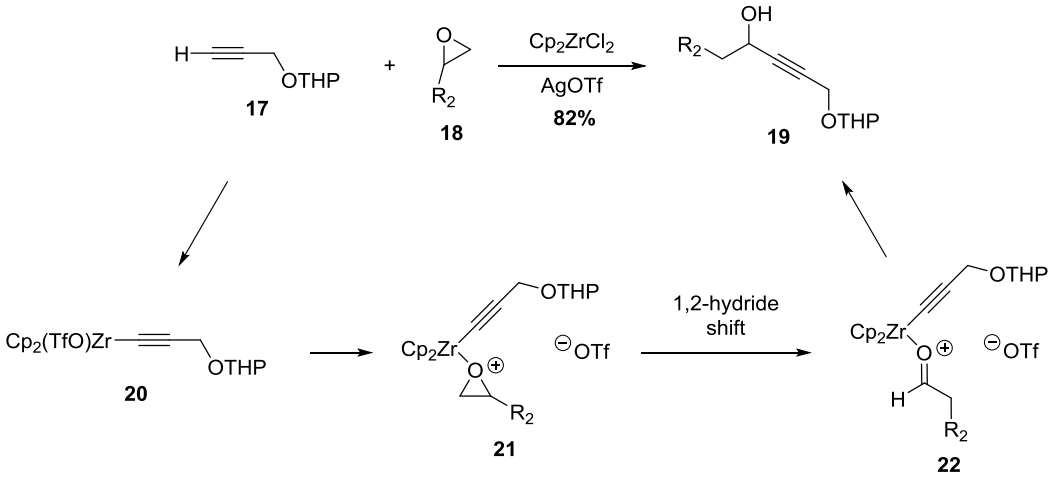
Epoxides can also be activated under mild conditions to afford 1,2-difunctionalized systems with *trans* stereochemistry after the addition of a nucleophile. A number of Lewis acids have been reported to do this, including Al_2O_3, $Bi(OTf)_3$, $Zn(ClO_4)_2$, $ZnBr_2$, and $InBr_3$.[50–54] For example, Yadav *et al*. reported the regioselective addition of pyrrole to In^{3+}-activated epoxides, with nucleophilic attack occurring at the sterically less hindered position of aliphatic epoxides (Scheme 4).[54] Attack on aryl epoxides preferentially occurred at the benzyl position of the epoxides.



Scheme 4: In^{3+}-catalyzed regioselective epoxide-opening with pyrrole.[54]

One potential complication is the Meinwald rearrangement of the epoxide under Lewis acidic conditions to form the corresponding aldehyde *in situ*.[53,55,56] This rearrangement has been used to form propargyl alcohols from epoxides through rearrangement to the aldehyde *in situ*, followed by addition of a zirconium acetylide to the newly-formed aldehyde (Scheme 5).[56] This phenomenon has also been observed in the addition of zinc-acetylides to aryl and alkyl epoxides.[53] The zinc acetylide

preferentially reacts at the benzylic position of aryl epoxides to form homopropargyl alcohols. However, the alkyl epoxides rearrange under the reaction conditions to form the corresponding aldehyde and result in formation of propargyl alcohols. Aldehyde formation may be circumvented by balancing the ability of the Lewis acid to mediate epoxide opening upon nucleophilic addition versus promoting the rearrangement of the epoxide.



Scheme 5: Zr-promoted rearrangement of epoxides to aldehydes.[56]

2.1.3 Mild conditions for alkyne-epoxide couplings.

If the alkynylation of aldehydes can occur under mild Lewis acidic conditions, and epoxides can be opened by a range of nucleophiles under mild Lewis acidic conditions, then perhaps epoxides can be opened by terminal alkynes under similar conditions (Figure 2). A milder method of alkyne-epoxide coupling is attractive because this approach could potentially tolerate a wider range of functional groups. Additionally, milder methods would be amenable to industrial large scale processes due to reduced

corrosive waste streams from side products from the hydrolysis of BF_3·etherate complexes and avoidance of strongly basic alkyllithium reagents.

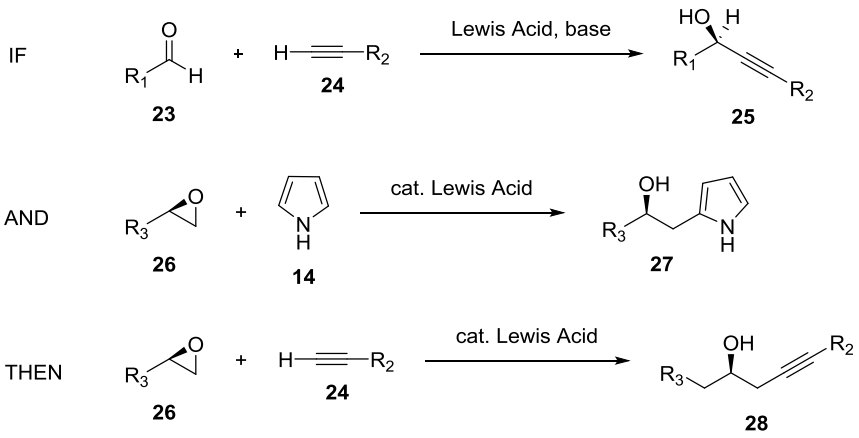
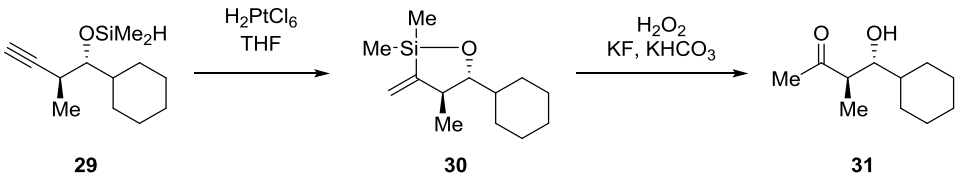


Figure 1: Rationale for discovery of mild conditions for alkyne-epoxide coupling.

The homopropargylic alcohols products of the coupling reactions provide two functional groups (alcohol and alkyne) that can be further manipulated to generate compounds of similar or increasing structural complexity. For example, homopropargylic alcohols can be converted to β-hydroxy ketones using through intramolecular hydrosilylation and oxidation (Scheme 6). β-hydroxy ketones are a common motif in polyketide natural products. PM-toxin A is a natural product that contains four β-hydroxy ketone units, which could come from the hydrosilylation and oxidation of four homopropargyl alcohols. The homopropargyl alcohols could in turn be prepared using mild Lewis acid-based alkyne-epoxide couplings. However, the simultaneous hydrosilylation and oxidation of four homopropargylic alcohols is unprecedented. To investigate if simultaneous hydrosilylation and oxidation of more than one homopropargylic alcohol was a feasible approach to prepare multiple β-hydroxy ketones

at once, we began the synthesis of PM-toxin A using classical alkyne-epoxide coupling methods.



Scheme 6: Intramolecular hydrosilylation and oxidation of homopropargylic alcohols to form β-hydroxy ketones.

2.1.4 Biological significance and structures of PM-toxins

PM-toxin is a corn host-specific fungal pathotoxin produced by *Phyllosticta maydis*.[57,58] Of the 10-15 components of PM-toxins, the four major components (PM-toxins A-D) have been isolated so far (Figure 3). PM-toxins A-D are linear C-33 and C-35 compounds containing at least three β-hydroxyketone functional groups.

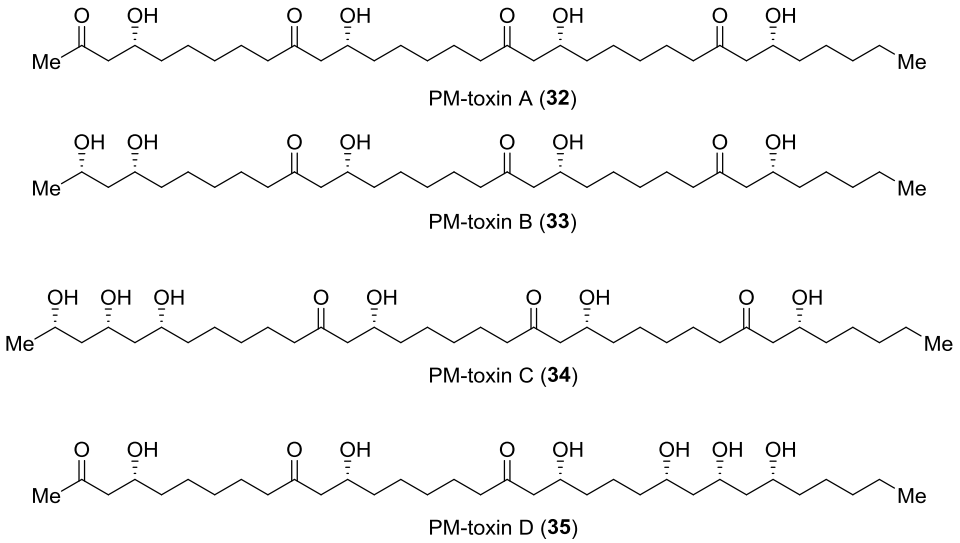
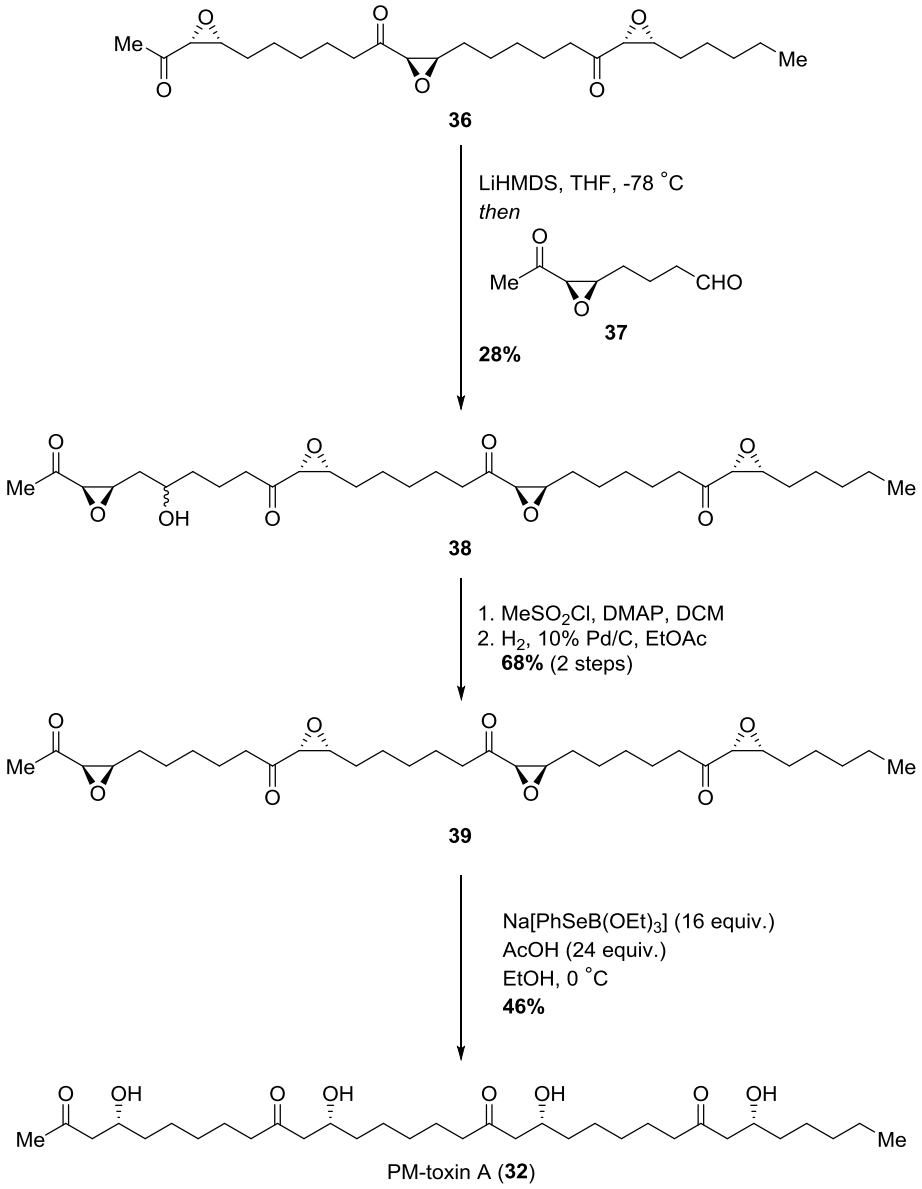


Figure 3: Structures of PM-toxins isolated to date.

The toxins are the cause of Northern T-corn leaf blight, characterized by a long cigar-shaped lesion on the leaves of the corn plant.[59] Northern T-corn leaf blight can severely affect the crop yields, reducing the yields up to 50% in some cases.[59] Due to their specific toxicities and structural components, the PM-toxins have become of interest to both biologists and synthetic chemists.[60] An efficient asymmetric synthesis of these types of compounds would allow larger quantities to be synthesized, which can be used to help understand plant disease resistance through determination of the mode of action of these host-specific toxins.

2.1.1 Previous Syntheses of PM-toxin A

In 1997, Miyashita and coworkers reported the first total synthesis of PM-toxin A (**32**) using tandem aldol reactions and the regiospecific organoselenium-mediated reduction of α,β-epoxy ketone units as the key steps in the 23-step route (Scheme 7).[57] Their lengthy synthesis is further hindered by the need to remove extraneous functional groups during the synthesis. Their tandem aldol approach results in the formation of a secondary alcohol as a mixture of diastereomers. This alcohol is then eliminated to form an α,β-unsaturated ketone, followed by hydrogenation of the alkene to produce the appropriate alkyl chain oxidation state. The elimination and hydrogenation steps between each aldol coupling reaction are required to prevent unwanted side reactions at either the alcohol or α,β-unsaturated ketone intermediates. Additionally, the yield of the aldol coupling reactions decrease as the length of the carbon chain increases, further decreasing the efficiency of their synthetic route.



Scheme 7: Miyashita's synthesis of PM-toxin A (**32**).

2.2 New Approach toward the synthesis PM-toxin A

2.2.1 Retrosynthetic Analysis

To address the issues of the current route, a new approach to the total synthesis of PM-toxin A (**32**) is warranted. The β-hydroxy ketone motif can be installed by the one-step oxidation and deprotection of four siloxanes (**40**).[61,62] The siloxanes can be accessed

by simultaneous hydrosilylation of four homopropargylic alcohols (**41**), which can in turn be synthesized by iterative alkyne-epoxide couplings (Figure 4). The TIPS-acetylene **42** is commercially available, and the enantiomerically pure epoxides **43** and **44** can be made from the hydrolytic kinetic resolution of the racemic epoxides, which in turn be synthesized by epoxidation of the known alkenes. This approach would reduce the total number of steps and eliminate the need to remove unnecessary functional groups as compared with the route employed by Miyashita and coworkers.[57] Additionally, multiple analogs of **32** could be rapidly synthesized by varying the structure of the epoxide for each alkyne-epoxide cross coupling sequence.

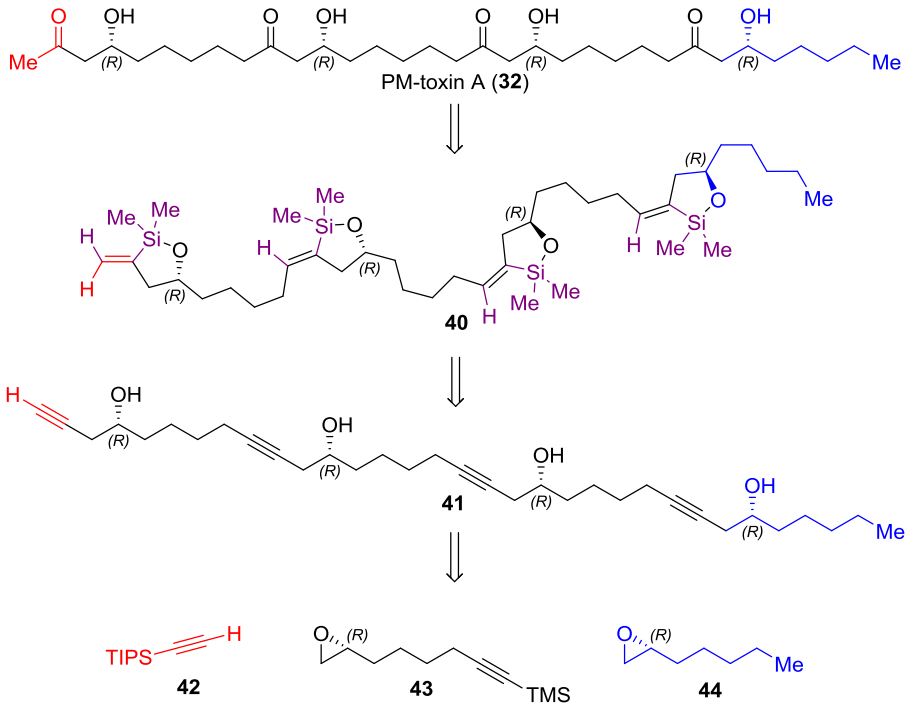
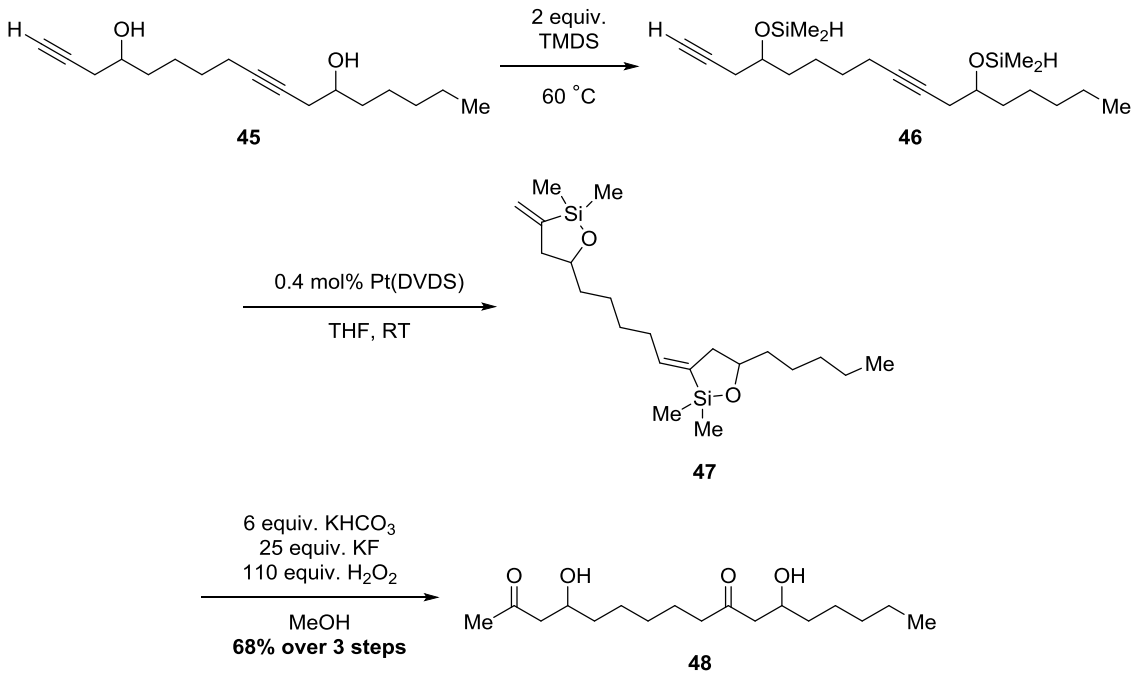


Figure 4: Retrosynthetic analysis of PM-toxin A (**32**).

2.3 Results and Discussion

2.3.1 Preliminary results for hydrosilylation and oxidation of multiple homopropargylic alcohols

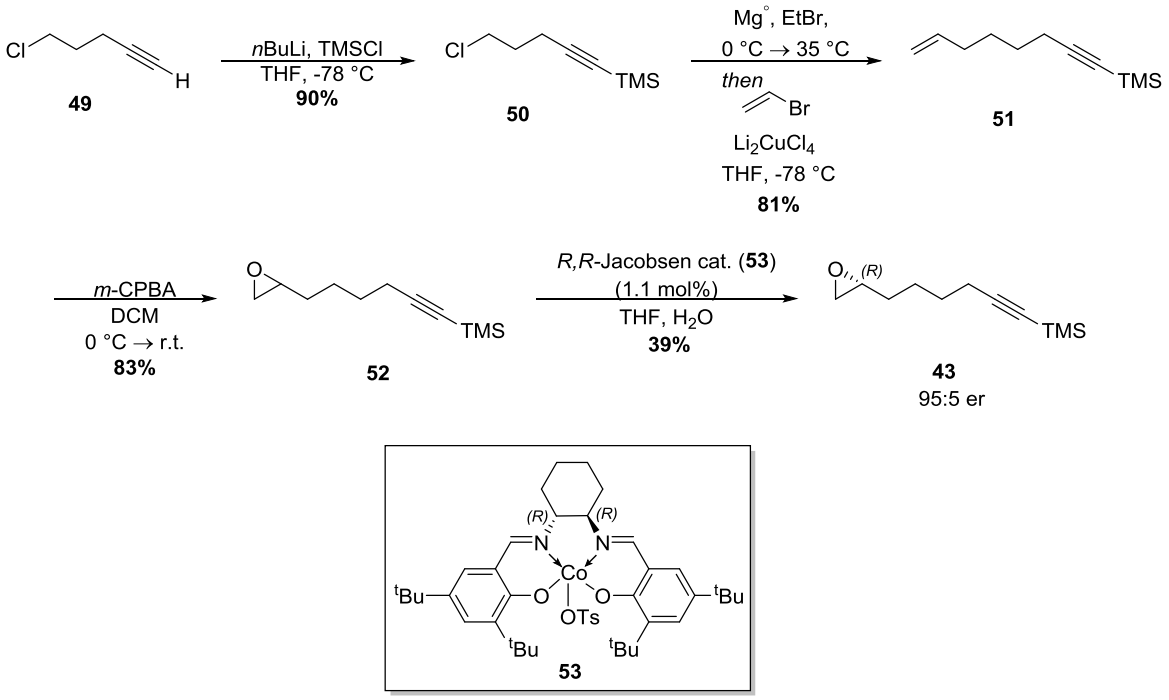
A model system for PM-toxin A was developed by another student in the McDonald lab. Chandra Potter synthesized a racemic system containing two homopropargylic alcohols for testing a double hydrosilylation and oxidation (Scheme 8).[63] She discovered that the intramolecular hydrosilylation and oxidation was successful, resulting in the formation of a short alkyl chain containing two β-hydroxy ketone subunits. This initial result encouraged us to pursue the longer carbon chain which would ultimately contain four β-hydroxy ketone moieties.



Scheme 8: Hydrosilylation and oxidation of model system for PM-toxin A.

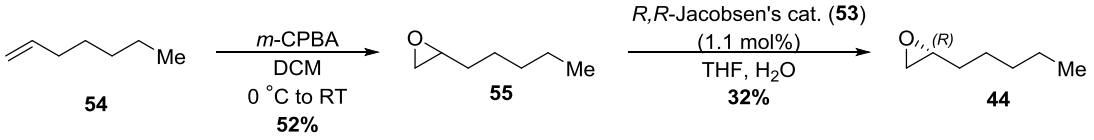
2.3.2 Synthesis of the Carbon Skeleton

One of the three components for the iterative alkyne-epoxide coupling sequences is commercially available. The two enantiopure epoxides, however, are readily synthesized by epoxidation of known alkenes and resolution of the epoxides using Jacobsen's catalyst (Scheme 9). The TMS-protection of chloroalkyne **49** proceeded smoothly. The best yields of **50** were obtained when the crude reaction mixture was quenched with NH_4Cl for an extended period of time, extracted with DCM instead of Et_2O, and then purified by distillation instead of flash column chromatography.[64] The Grignard coupling[65] of allyl bromide and the chloroalkyne **50** produced the desired alkene **51** in good yield. Epoxidation of the terminal alkene was accomplished with *m*-CPBA, followed by resolution of epoxide **52** with the *R,R*-Jacobsen catalyst.[66] The enantiopurity of epoxide **43** was determined by addition of TIPS-protected acetylene **42** to the epoxide and Mosher ester analysis of the resulting chiral secondary alcohol.[67]



Scheme 9: Synthesis of enantiopure epoxide coupling partner **43**.

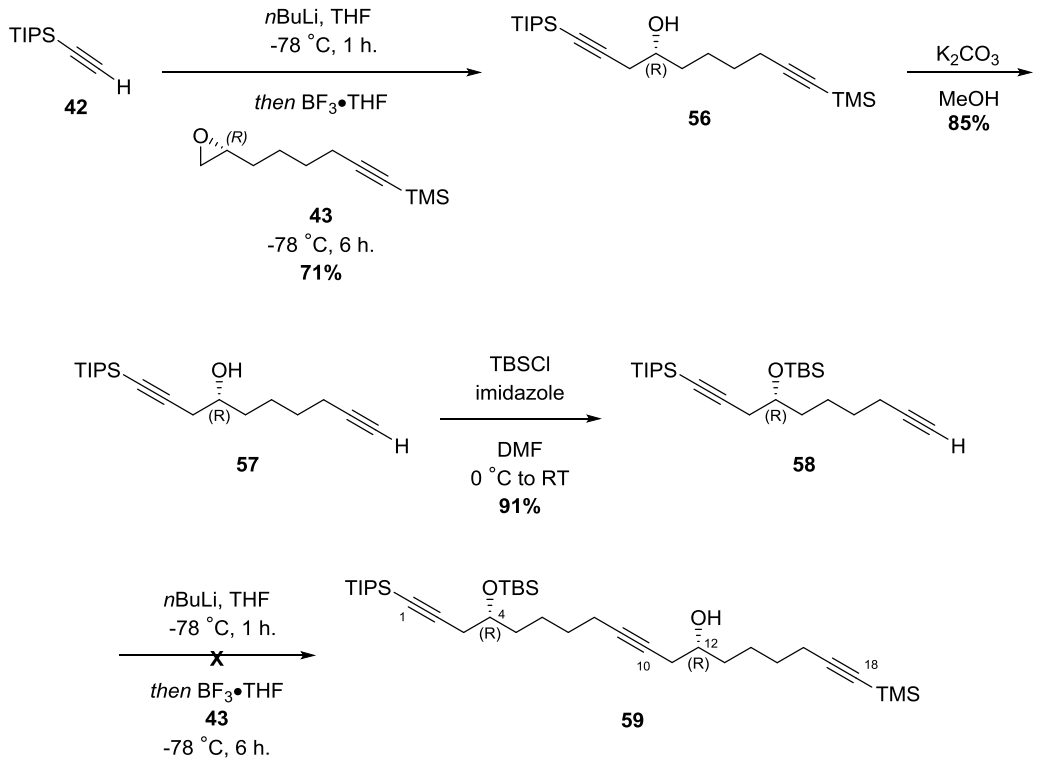
The terminal coupling partner **44** was synthesized in the same manner from commercially available 1-heptene (Scheme 10). The yields of the epoxidation and resolution were lower compared to **43** most likely due to the volatility of the product.



Scheme 10: Synthesis of enantiopure epoxide coupling partner **44**.

TIPS-protected alkyne **42**was added to epoxide **43** using classical alkyne-epoxide coupling conditions (Scheme 11).[40,41] The alkyne protecting group was removed,

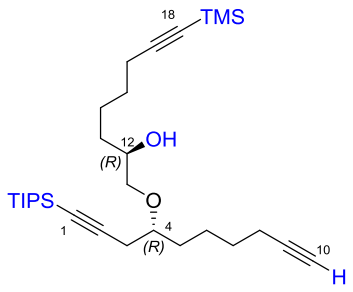
followed by the protection of homopropargylic alcohol **56** with a TBS group. The same reaction conditions employed in the first coupling sequence were used for the addition of epoxide **43** to the alkyne **58**. However, the desired coupling product **59** was not isolated when using these reaction conditions.



Scheme 11: First and second alkyne-epoxide couplings.

The product that was isolated from the second epoxide coupling attempts was determined to be an ether side product (**60**), resulting from the addition of an alkoxy-anion to the epoxide coupling partner. The ^{1}H NMR data suggested the presence of a TIPS group, TMS group, a terminal alkyne proton, and an unprotected secondary alcohol (highlighted in blue). When combined with the mass spectral data, it is apparent that the

TBS group on C4 was removed during the course of the reaction which ultimately led to the formation of the ether side product (Table 1).



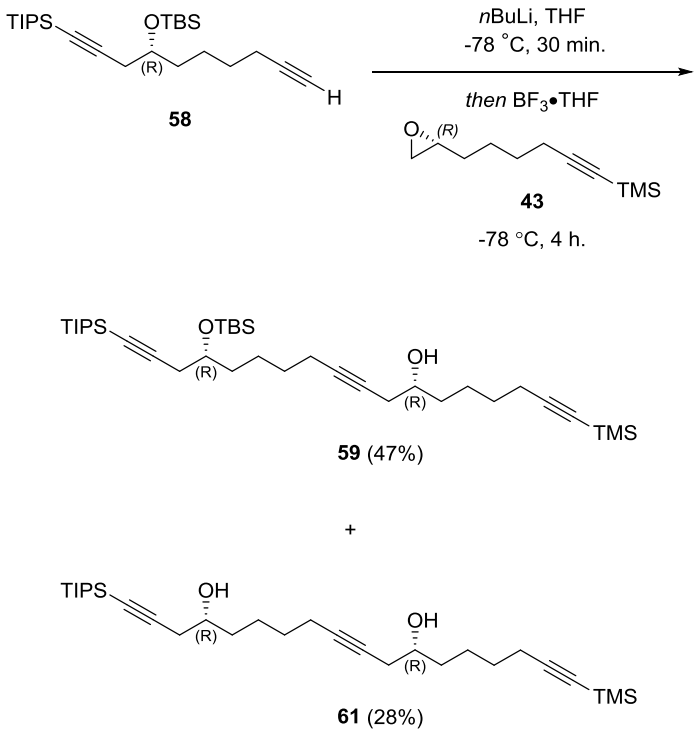
60
Exact Mass: 502.37

Chemical shift (ppm)	Multiplicity	$^{3}J_{H}$ (Hz)	Integration	Assignment
1.97	d	5.2	1	C12 –OH
1.95	t	2.6	1	C10 –H
1.08	m	--	21	C1 –TIPS
0.15	s	--	9	C18 –TMS

Table 1: Proposed ether side product **60** and ^{1}H NMR data.

There are two possible explanations for the loss of the TBS group under these conditions: 1) trace amounts of HF can be found in BF_3·THF that has been stored for long periods of time, which can remove the silyl group and allow the oxygen to react with the epoxide, or 2) a C-H on the TBS group may have been deprotonated during the reaction, leading to removal of the silyl group and subsequent reaction of the oxygen atom with the epoxide. This deprotonation of a silyl group hydrogen has been observed in carbohydrate synthesis, organolithium additions to epoxides unactivated by BF_3·THF, and used intentionally as a transfer agent in anion relay chemistry.[68–71]

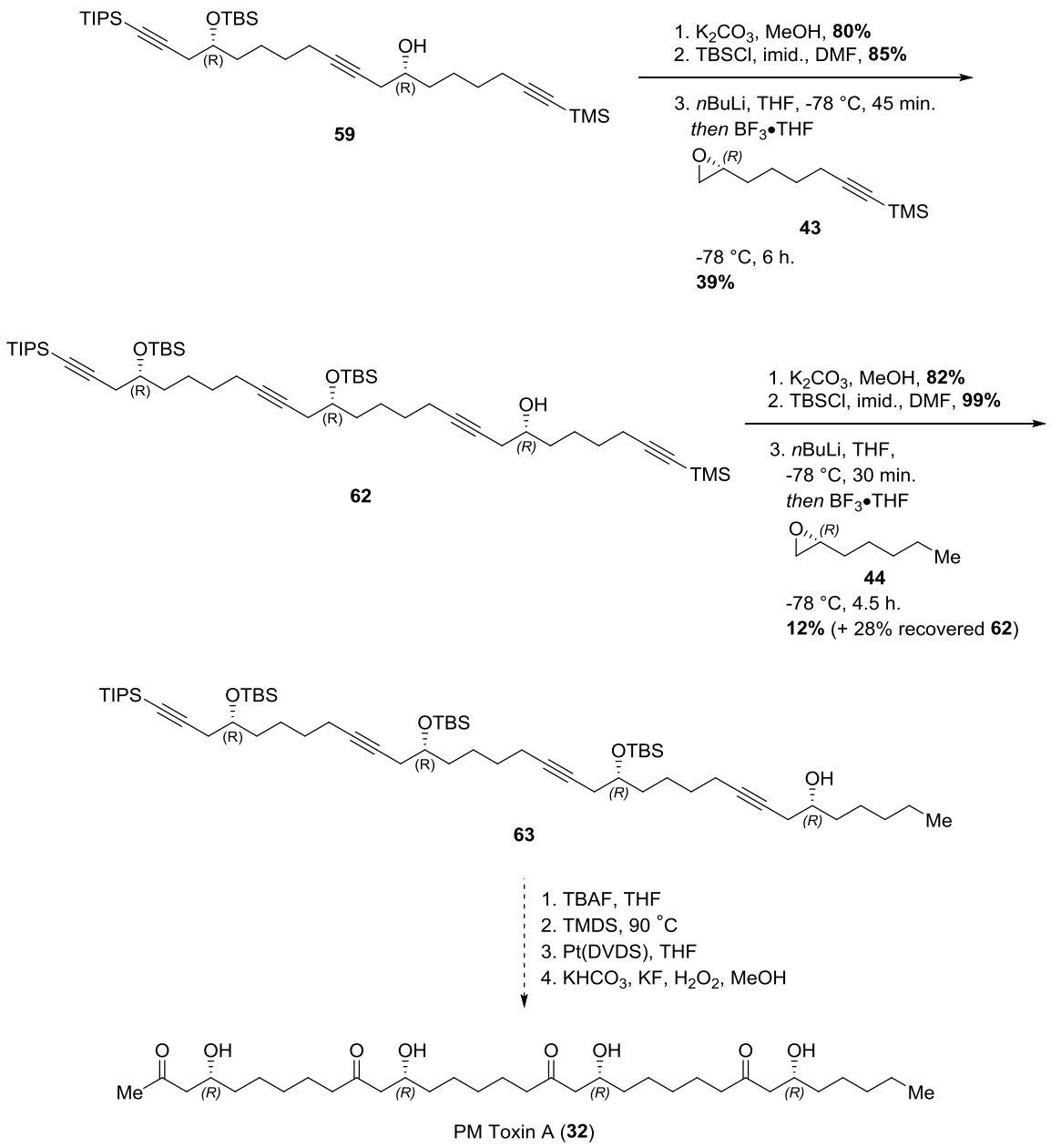
Freshly distilled BF_3·THF was used for every reaction to prevent trace amounts of HF from entering the reaction flask. Additionally, when the reaction time was shortened from 1 h. to 30 min. for the alkyne deprotonation step, the major product formed in the reaction was the desired homopropargylic alcohol **59** and the ether side product was not observed after this change was made (Scheme 12). However, the corresponding diol, resulting from loss of the TBS group, was also isolated (26%) in this instance.



Scheme 12: Successful second alkyne-epoxide coupling.

After optimization of reaction time and temperature, the carbon skeleton was extended following iterative sequence of alkyne-epoxide coupling, alkyne deprotection, and protection of the homopropargylic alcohol to provide compounds **62** and the complete carbon skeleton (**63**) as single enantiomers (Scheme 13).

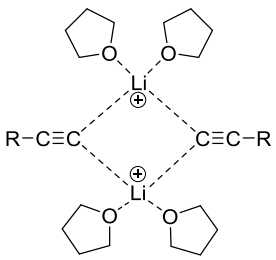
The four remaining steps to synthesize PM-toxin A (**32**) start with a global deprotection of the silyl ethers using TBAF to make a tetraol (**41**). The tetraol will then be converted to the hydrodimethylsilyl ethers using neat TMDS at elevated temperatures, followed by hydroxyl-directed intramolecular hydrosilylation catalyzed by Pt(DVDS). Finally, the siloxanes (**41**) will be oxidized using a combination of KF, $KHCO_3$, and H_2O_2 to afford the natural product (**32**) as a single enantiomer. However, the global deprotection of the silyl groups, hydrosilylation of the tetraol, and oxidation of the tetrakis-siloxane intermediate were not completed due to insufficient quantities of **63**.



Scheme 13: Synthesis of the complete carbon skeleton (**63**) of PM-toxin A as a single enantiomer.

The biggest challenge in this approach was the coupling reactions in the later stages of the synthesis. Using classical coupling methods, the simpler alkynes (**42**) add to the epoxide readily, providing the desired intermediates in good yield. However, as the

chain length and complexity increase in the alkyne substrate (**62**), the coupling reactions steadily decrease in efficiency from 88% to 12% yield for each coupling step (Schemes 12 and 13). Although the data obtained is inconclusive, it is likely that the formation of alkyne and Li+ ion aggregates is responsible for the decreased yield. Lithium salts can exist as dimeric or tetrameric complexes in solution, with two THF molecules per lithium ion (Figure 5).[72] It is possible that the long carbon chains containing multiple internal alkynes are coordinating to Li^+ ions in such a way as to inhibit the alkyne addition to the epoxide electrophile. Inclusion of TMEDA or other additives could be used to complex the Li+ ions, thereby allowing the alkyne to successfully react with the epoxide, however this was not explored.[73,74]



64

Figure 6: Lithium-acetylene coordination in solution.

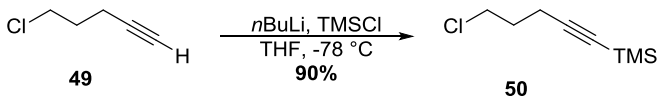
2.4 Conclusions

The asymmetric total synthesis of PM-toxin A may be completed, in principle, in fewer steps than previously accomplished by using an iterative alkyne-epoxide coupling strategy. However, we have discovered the yield of the coupling step decreases with extended carbon chains, which is a limiting factor for this synthetic approach. These later coupling steps may benefit from the inclusion of a chelating additive may be able to help

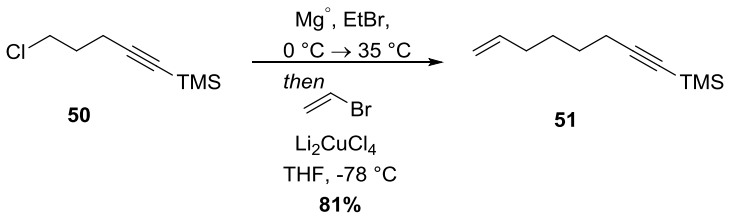
by preventing the possible formation of aggregates during the reaction. In the future, this hypothesis may be tested by adding TMEDA or other similar agents. If the yields of the alkyne-epoxide coupling reaction can be increased and the four remaining steps can be completed, the iterative coupling approach may be a viable route to natural products similar to PM-toxin A. Additionally, the synthesis of PM-toxin A demonstrates a need for milder alkyne-epoxide coupling conditions, especially for more complex substrates.

2.4 Experimental Details

General information: Proton and carbon NMR spectra were recorded on an INOVA-400 (400 MHz), VNMRS 400 (400 MHz), INOVA-600 (600 MHz), or Unity-600 (600 MHz). NMR spectra were recorded in solutions of deuterated chloroform ($CDCl_3$) with the residual chloroform (7.27 ppm for ^1H NMR and 77.23 ppm for ^{13}C NMR) taken as the internal standard, deuterated methanol (CD_3OD) with residual methanol (δ 3.31 ppm for ^1H NMR and 49.3 ppm for ^{13}C NMR) taken as the internal standard, or deuterated benzene with residual benzene (δ 7.16 ppm for ^1H NMR and 128.23 ppm for ^{13}C NMR) taken as the internal standard, and were reported in parts per million (ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; ddd, doublet of doublet of doublet; dt, doublet of triplet; m, multiplet. IR spectra were collected on a Nicolet Avatar 370 DTGS. Mass spectra (high resolution ESI and APCI) were recorded on a Finnigan LTQ FTMS Mass spectrometer. Optical rotations were measured using a Perkin-Elmer 341 polarimeter (concentration in g/100mL). Thin layer chromatography (TLC) was performed on precoated glass backed plates purchased from Whatman (silica gel 60F254; 0.25mm thickness). Flash column chromatography was carried out with silica gel 60 (230-400 mesh ASTM) from Silicycle. All reactions were carried out with anhydrous solvents in oven dried or flame dried and argon-charged glassware unless otherwise specified. All anhydrous solvents were dried with 4Å molecular sieves purchased from Sigma-Aldrich and tested for trace water content with Coulometric KF titrator from Denver instruments. All solvents used in extraction procedures and chromatography were used as received from commercial suppliers without prior purification.

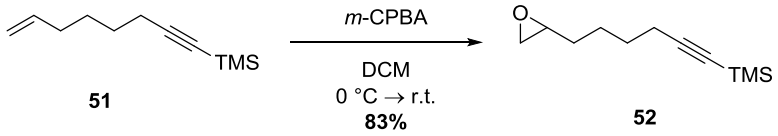


(5-chloropent-1-yn-1-yl)trimethylsilane (50)[64]: To a cooled (-78˚C) solution of 1-chloro-5-pentyne **49** (25.00 g, 244 mmol, 25.8 mL) in THF (203 mL) was added *n*BuLi (97.6 mL, 244 mmol, 2.5 M in hexanes) in three portions. The reaction mixture was stirred for 1 h at -78˚C, followed by the addition TMSCl (34.43g, 317 mmol, 40.2 mL). The reaction mixture was warmed to room temperature overnight, then quenched by pouring the mixture into aq. NH_4Cl (200 mL) and stirring for 1 h. The aqueous and organic layers were separated and the aqueous layer was extracted with DCM (3 x 150 mL). The combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude was distilled under reduced pressure to obtain **51** as a clear colorless oil (38.40 g, 90% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.65 (t, *J* = 6.4 Hz, 2H), 2.42 (t, *J* = 6.8 Hz, 2H), 1.97 (p, *J* = 6.6 Hz, 2H), 0.15 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 105.4, 85.9, 43.8, 31.5, 17.5, 0.3. **FT-IR** (neat, cm^{-1}): 2960, 2900, 2175, 1442, 1431, 1290, 1249, 1041, 848, 760. **HRMS** (APCI): *m/z* calcd. For $C_8H_{16}ClSi$ ($M+H^+$) 175.07043, found 175. 07033.



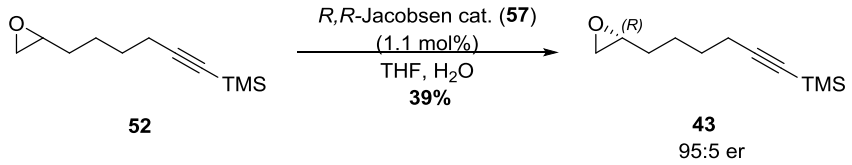
Trimethyl(oct-7-en-1-yn-1-yl)silane (51)[65]: To a cooled (0˚C) mixture of Mg˚ (58.83 g, 242 mmol) and EtBr (1.68g, 15.4 mmol, 1.1 mL) in THF (65 mL) was added a solution of **50** in 65 mL of THF. The reaction mixture was warmed to 35˚C (exotherm-warm

slowly) and stirred for 4.5 h. The stirring was stopped and the gray/green liquid was transferred via cannula to a -78˚C stirring solution of Li_2CuCl_4 and allyl bromide in THF (65 mL). The reaction mixture turned dark green with the addition of the Grignard reagent and slowly turned into a cloudy tan mixture. The reaction mixture warmed to room temperature over 12 h. while stirring and was slowly quenched with NH_4Cl (400 mL). The organic and aqueous phases were separated and the aqueous was extracted with pentane (3 x 300 mL). The combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under vacuum to obtain **51** as a clear yellow oil (39.68 g, 81% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.02 (dq, *J* = 17.1, 1.6 Hz, 1H), 4.96 (ddt, *J* = 10.3, 2.3, 1.3 Hz, 1H), 2.23 (t, *J* = 6.8 Hz, 2H), 2.07 (tdd, *J* = 6.9, 5.5, 1.4 Hz, 2H), 1.52 (dddt, *J* = 8.7, 7.0, 4.1, 2.4 Hz, 4H), 0.15 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.8, 114.7, 107.6, 84.6, 33.4, 28.24, 28.2, 19.9, 0.4. **FT-IR** (neat, cm^{-1}): 3078, 2959, 2901, 2861, 2175, 1641, 1430, 1325, 1249, 1046, 922, 912, 843, 759.



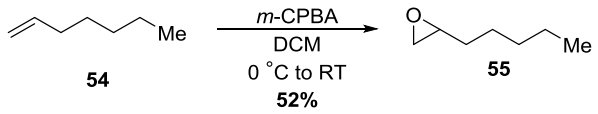
Trimethyl(6-(oxiran-2-yl)hex-1-yn-1-yl)silane (52)[75]: A solution of *m*-CPBA (77%, 51.69 g, 230 mmol) in DCM (250 mL) was added to **51** (32.00 g, 177 mmol) in DCM (250 mL) at 0˚C and the reaction mixture warmed to room temperature overnight. The cloudy, pink solution was diluted with aqueous Na_2SO_4 at 0˚C and stirred until the peroxide was no longer observed when tested with starch paper. The reaction was neutralized with $NaHCO_3$ until it was slightly basic (pH ~8). The aqueous and organic

layers were separated and the aqueous was extracted twice with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum to obtain the compound as a clear colorless oil (28.24 g, 83% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.91 (q, *J* = 3.6, 3.1 Hz, 1H), 2.75 (t, *J* = 4.5 Hz, 1H), 2.47 (dd, *J* = 5.1, 2.7 Hz, 1H), 2.24 (t, *J* = 6.2 Hz, 2H), 1.56 (dp, *J* = 15.2, 6.0, 4.9 Hz, 6H), 0.14 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 107.3, 84.8, 52.4, 47.2, 32.1, 28.5, 25.4, 19.9, 0.3. **HRMS** (APCI): *m/z* calcd. For $C_{11}H_{21}OSi$ ($M+H^+$) 197.13562, found 197.13547. **FT-IR** (neat, cm^{-1}): 3044, 2957, 2939, 2861, 2173, 1460, 1429, 1409, 1327, 1249, 1032, 914, 842.

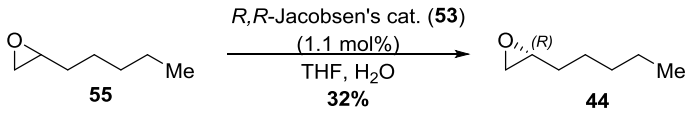


(*R*)-trimethyl(6-(oxiran-2-yl)hex-1-yn-1-yl)silane (43)[66]: The racemic epoxide **52** (28.84 g, 146 mmol) and the Jacobsen cobalt catalyst **53** (1.25 g, 1.62 mmol, 1.1 mol%) were dissolved in THF (65 mL) and H_2O (2.84 mL, 158 mmol) was added to the flask. The dark green reaction mixture stirred at room temperature overnight, then concentrated under reduced pressure. The crude was purified by flash column chromatography (2-5% Et_2O in pentane as eluent) to obtain **44** as a yellow oil (7.54 g, 26% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.92 (dt, *J* = 4.3, 2.7 Hz, 1H), 2.76 (dd, *J* = 5.2, 3.9 Hz, 1H), 2.48 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.25 (t, *J* = 6.5 Hz, 2H), 1.58 (dddd, *J* = 15.5, 9.7, 5.4, 2.1 Hz, 6H), 0.15 (s, 9H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 107.28, 84.87, 52.39, 47.24, 32.16, 28.52, 25.38, 0.36. **HRMS** (APCI): *m/z* calcd. for $C_{11}H_{19}OSi$ [M^+], 195.11997, found

195.11984. **FT-IR** (neat, cm^{-1}): 3044, 2858, 2940, 2862, 2173, 1728, 1249, 84. **$[\alpha]_D^{25}$** = +2.5(c = 1.25, $CHCl_3$).

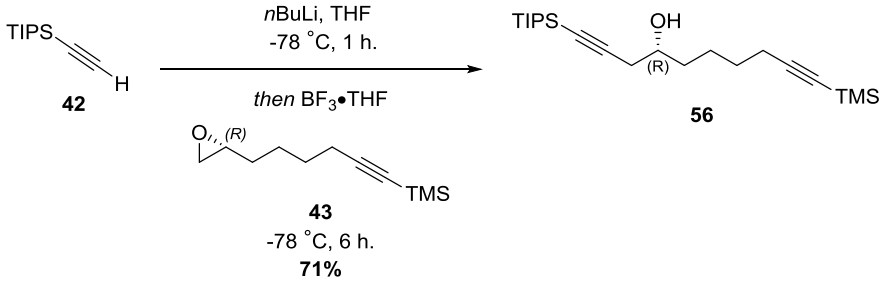


2-pentyloxirane (55): To a solution of 1-heptene (3.00 g, 30.6 mmol) in DCM (100 mL) was added *m*-CPBA (10.27 g, 45.8 mmol). The reaction mixture stirred overnight 12 h. at RT. The cloudy white reaction mixture was diluted with Na_2SO_3 and the pH raised to 8 with $NaHCO_3$. The aqueous and organic layers were separated and the aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was used without further purification (1.81 g, 50% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 2.91 (tt, J = 5.7, 2.8 Hz, 1H), 2.75 (dd, J = 5.1, 4.0 Hz, 1H), 2.47 (dd, J = 5.0, 2.8 Hz, 1H), 1.56 – 1.50 (m, 3H), 1.51 – 1.39 (m, 4H), 1.36 – 1.32 (m, 3H), 0.90 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 52.6, 47.3, 32.7, 32.7, 25.9, 22.8, 15.5.



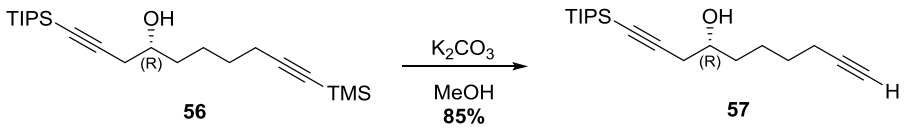
(R)-2-pentyloxirane (48): To a solution of epoxide **55** (1.70 g, 14.9 mmol) in THF (6.4 mL) was added H_2O (0.18 mL) and Jacobsen catalyst **53** (850 mg). The reaction mixture stirred at room temperature for 12 h. and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (98/2 to 95/5 pentane/Et_2O) to obtain the compound as a pale yellow oil (550 mg, 32% yield). **^{1}H**

NMR (400 MHz, $CDCl_3$) δ 2.90 (ddt, *J* = 8.0, 5.7, 2.8 Hz, 1H), 2.80 – 2.64 (m, 1H), 2.46 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.58 – 1.47 (m, 3H), 1.44 (ddt, *J* = 12.4, 9.0, 4.8 Hz, 1H), 1.32 (h, *J* = 4.9, 4.4 Hz, 4H), 0.92 – 0.86 (m, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 52.6, 47.4, 32.7, 31.9, 25.9, 22.8, 14.2.

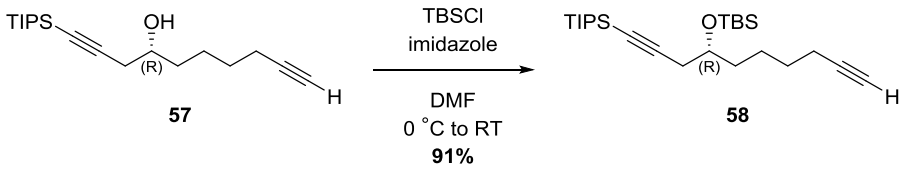


(*R*)-1-(triisopropylsilyl)-10-(trimethylsilyl)deca-1,9-diyn-4-ol (56): To a cooled (-78˚C) solution of triisopropylacetylene (1.95 g, 10.7 mmol, 2.4 mL) in THF (8 mL) was added nBuLi (5.0 mL, 10.7 mmol, 2.12 M in hexanes). The reaction mixture was stirred at -78˚C for 1 h, then BF_3·THF (1.2 mL, 11.2 mmol) was added, stirred for 10 min. at -78˚C, followed by epoxide **43** (2.00 g, 10.2 mmol) dissolved in THF (35 mL). The reaction stirred at -78˚C for 6 hours and was quenched with brine. The organic and aqueous phases were separated and the aqueous was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum to obtain the compound as a clear, pale yellow oil (3.41 g, 88% yield, >95:5 er as determined by Mosher ester analysis). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.80 – 3.66 (m, 1H), 2.50 (dd, *J* = 16.8, 4.9 Hz, 1H), 2.39 (dd, *J* = 16.7, 6.6 Hz, 1H), 2.23 (t, *J* = 6.7 Hz, 2H), 1.97 (d, *J* = 5.1 Hz, 1H), 1.59 – 1.48 (m, 5H), 1.49 – 1.40 (m, 1H), 1.09 – 1.00 (m, 21H), 0.14 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 107.5, 104.8, 84.7, 83.9, 70.0, 35.8, 29.1, 28.8 25.1, 20.0, 18.8, 11.4, 0.4. **HRMS** (APCI): *m/z* calcd. for$C_{19}H_{35}OSi$ [$M+H^+$,

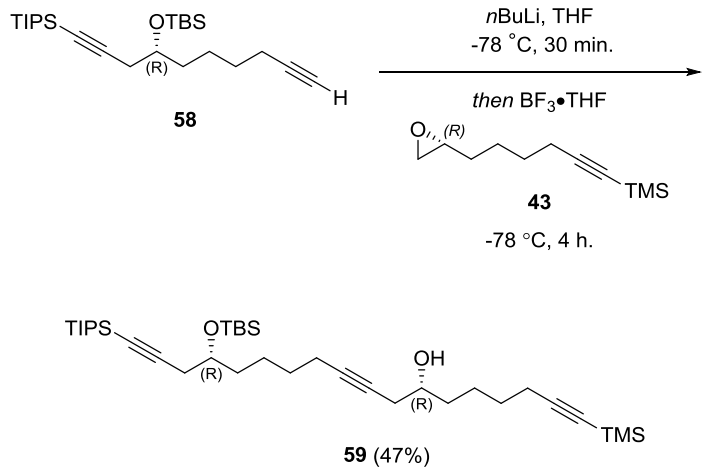
without -TMS], 307.24517, found 307.24531. **FT-IR** (neat, cm^{1}): 3389, 3293, 2941, 2865, 2173, 1462, 1333, 1249, 1071, 1028, 882, 842, 759. $\mathbf{[\alpha]_D^{25}}$ = -2.5 (c = 1.00, $CHCl_3$).



(*R*)-1-(triisopropylsilyl)deca-1,9-diyn-4-ol (57): The TMS-protected alkyne **56** (3.40 g, 8.98 mmol) was dissolved in MeOH (60 mL) and K_2CO_3 (3.47 g, 25.1 mmol) was added in one portion directly to the flask. The suspension was stirred overnight at room temperature for 12 h, and the organic solvent was removed under reduced pressure. The residue was diluted with H_2O and the aqueous solution was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum to obtain the compound as a clear, colorless oil (2.59 g, 94% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.84 – 3.71 (m, 1H), 2.52 (dd, *J* = 16.7, 4.9 Hz, 1H), 2.41 (dd, *J* = 16.8, 6.7 Hz, 1H), 2.21 (td, *J* = 6.7, 2.7 Hz, 2H), 1.98 (d, *J* = 5.1 Hz, 1H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.64 – 1.52 (m, 6H), 1.13 – 1.02 (m, 21H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.8, 114.7, 107.6, 84.6, 33.4, 28.2, 28.2, 19.9, 0.4. **HRMS** (APCI): *m/z* calcd. for$C_{19}H_{35}OSi$ [$M+H^+$], 307.24517, found 307.24531. **FT-IR** (neat, cm^{-1}): 3566 3389, 3312, 2941, 2171, 1462, 1383, 1365, 1243, 1086, 996, 883. $\mathbf{[\alpha]_D^{25}}$ = -3.0 (c = 1.00, $CHCl_3$).

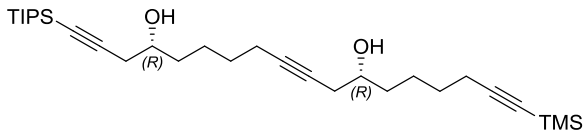


(*R*)-tert-butyldimethyl((1-(triisopropylsilyl)deca-1,9-diyn-4-yl)oxy)silane (58): To a solution of alcohol **57** (2.59 g, 8.44 mmol) in DMF (28 mL) at 0˚C was added TBSCl (2.67 g, 17.7 mmol) and imidazole (3.22 g, 47.3 mmol). The solution was stirred at room temperature overnight and was quenched with H_2O (30 mL). The reaction was diluted with Et_2O and the organic and aqueous phases were separated. The aqueous layer was extracted with Et_2O (5 x 20 mL) and the combined organic layers were washed with H_2O (5 x 15 mL). The organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum to obtain **58** as a clear, colorless oil (2.68 g, 75% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.79 (tt, *J* = 6.9, 4.5 Hz, 1H), 2.47 – 2.34 (m, 2H), 2.20 (td, *J* = 6.8, 2.8 Hz, 2H), 1.94 (t, *J* = 2.7 Hz, 1H), 1.70 (ddt, *J* = 14.1, 9.9, 5.4 Hz, 1H), 1.55 (dddd, *J* = 14.5, 10.9, 9.0, 5.6 Hz, 4H), 1.46 – 1.36 (m, 1H), 1.11 – 1.03 (m, 21H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 105.8, 84.7, 82.3, 71.1, 36.0, 31.8, 29.0, 28.8, 26.0, 24.5, 22.9, 18.8, 18.6, 18.2, 14.4, 11.5, 11.2, -4.3, -4.5. **HRMS** (APCI): *m/z* calcd. for $C_{25}H_{49}OSi_2$ [M+H$^+$], 421.33165, found 421.33208. **FT-IR** (neat, cm^{-1}): 3314, 2941, 2893, 2864, 2173, 1462, 1361, 1254, 1098, 1029, 835.



(7*R*,15*R*)-15-((tert-butyldimethylsilyl)oxy)-18-(triisopropylsilyl)-1-(trimethylsilyl)octadeca-1,9,17-triyn-7-ol (59): *n*BuLi (3.3 mL, 6.7 mmol, 2.04 M in hexanes) was added dropwise to a cooled (-78˚C) solution of alkyne **58** (2.68 g, 6.4 mmol) in THF (5 mL) and stirred for 30 min. BF_3·THF (1.54 mL, 14.0 mmol) was added and stirred for 10 min, followed by the addition of epoxide **43** (1.26g, 6.4 mmol) in THF (21 mL). The reaction was stirred at -78˚C for 2 h, warmed to room temperature for 30 min., and quenched with brine. The organic and aqueous phases were separated and the aqueous was extracted with Et_2O (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude was purified by flash column chromatography (silica gel, 230-400 mesh, 1-5% EtOAc in hexane as eluent) to obtain **63** as a pale yellow oil (1.87g, 47% yield, with 26% recovery of the corresponding diol **65**). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.78 (ddt, *J* = 9.2, 7.0, 3.5 Hz, 1H), 3.69 (q, *J* = 5.8 Hz, 1H), 2.47 – 2.33 (m, 3H), 2.29 (dt, *J* = 7.1, 2.4 Hz, 1H), 2.28 – 2.20 (m, 2H), 2.18 (d, *J* = 3.4 Hz, 2H), 1.95 (d, *J* = 4.7 Hz, 1H), 1.77 – 1.35 (m, 10H), 1.07 (d, *J* = 4.7 Hz, 21H), 0.89 (s, 9H), 0.15 (s, 9H), 0.07 (s,3H), 0.06 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 107.5, 105.8, 94.6, 84.7, 82.3, 71.1, 70.2, 36.0, 35.9, 29.4, 29.0, 28.7, 28.0, 26.0, 25.1,

24.6, 20.0, 19.0, 18.8, 18.2, 11.5, 04, -4.3, -4.5. **HRMS** (APCI): *m/z* calcd. for $C_{11}H_{19}OSi$ [M^+], 195.11997, found 195.11984.



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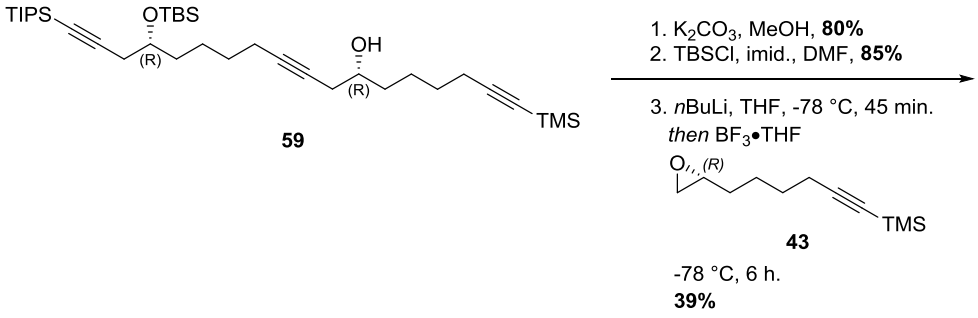
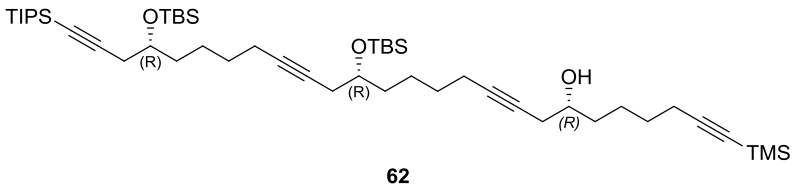
(4*R*,12*R*)-1-(triisopropylsilyl)-18-(trimethylsilyl)octadeca-1,9,17-triyne-4,12-diol (61): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.76 (tt, *J* = 9.7, 4.8 Hz, 1H), 3.70 (tt, *J* = 6.8, 3.1 Hz, 1H), 2.50 (dd, *J* = 16.7, 4.8 Hz, 1H), 2.44 – 2.37 (m, 2H), 2.30 – 2.26 (m, 1H), 2.24 (t, *J* = 6.9 Hz, 2H), 2.20 (tt, *J* = 6.8, 2.5 Hz, 2H), 1.55 (ddddt, *J* = 21.9, 12.0, 8.7, 5.5, 2.6 Hz, 9H), 1.45 (dddd, *J* = 15.6, 9.1, 5.0, 2.0 Hz, 1H), 1.11 – 1.01 (m, 21H), 0.15 (s, 9H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 107.5, 104.8, 84.7, 70.2, 70.0, 60.6, 35.9, 35.8, 29.17, 29.0, 28.7, 28.0, 25.1, 25.0, 20.0, 18.8, 14.4, 11.4, 0.4.





62

(7*R*,15*R*,23*R*)-15,23-bis((tert-butyldimethylsilyl)oxy)-26-(triisopropylsilyl)-1-(trimethylsilyl)hexacosa-1,9,17,25-tetrayn-7-ol (62): The TMS-protected alkyne **59**

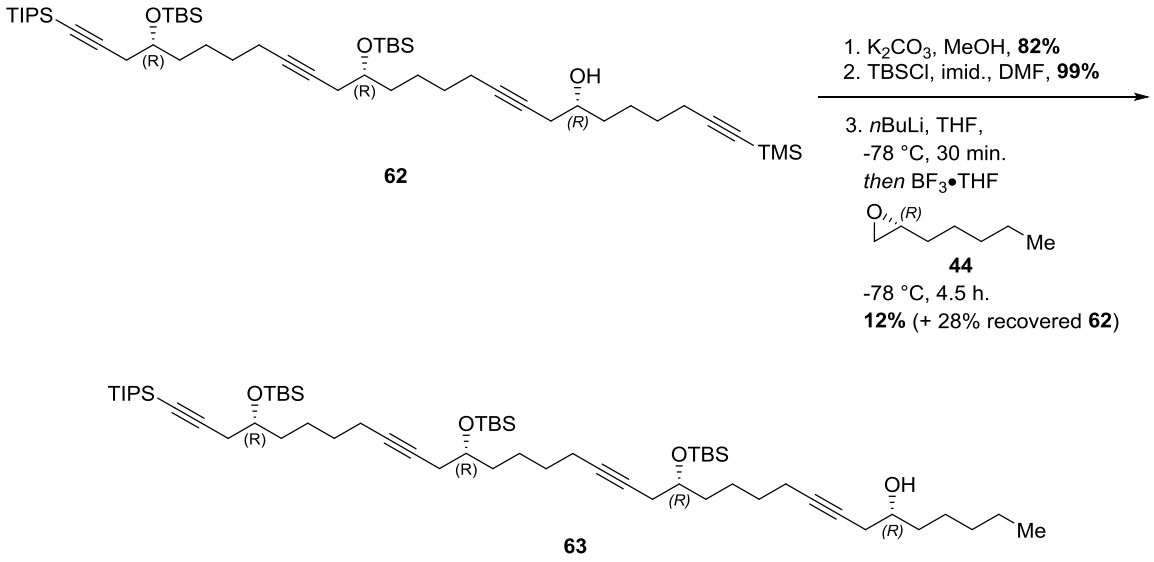
(1.52 g, 2.79 mmol) was dissolved in MeOH (19 mL) and K_2CO_3 (1.08 g, 7.8 mmol) was added in one portion directly to the flask. The suspension was stirred overnight at room temperature for 12 h, and the organic solvent was removed under reduced pressure. The residue was diluted with H_2O and the aqueous solution was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum to obtain the compound as a clear, colorless oil (1.21 g, 80% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.79 (tt, *J* = 7.5, 4.5 Hz, 1H), 3.70 (q, *J* = 5.1, 4.7 Hz, 1H), 2.52 (dd, *J* = 16.7, 4.8 Hz, 1H), 2.46 – 2.33 (m, 2H), 2.27 (ddt, *J* = 16.3, 7.1, 2.4 Hz, 1H), 2.21 (td, *J* = 6.7, 2.7 Hz, 2H), 2.18 (ddt, *J* = 6.7, 4.7, 2.3 Hz, 2H), 1.97 (d, *J* = 5.0 Hz, 1H), 1.95 (t, *J* = 2.7 Hz, 1H), 1.68 (ddt, *J* = 13.7, 9.2, 4.8 Hz, 1H), 1.63 – 1.43 (m, 7H), 1.40 (dtd, *J* = 8.5, 6.7, 3.4 Hz, 1H), 1.13 – 0.99 (m, 21H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 105.8, 84.6, 83.4, 82.3, 76.2, 71.1, 70.2, 68.5, 36.0, 35.9, 29.3, 29.0, 28.6, 28.0, 26.0, 25.0, 24.6, 19.0, 18.8, 18.6, 18.2, 11.5, -4.3, -4.5. **HRMS (**APCI): *m/z* calcd. for $C_{33}H_{61}OSi_2$ $[M+H^+]$, 545.42046, found 545.42102.

To a solution of the corresponding alcohol (1.41 g, 2.15 mmol) in DMF (7 mL) at 0˚C was added TBSCl (0.68 g, 4.5 mmol) and imidazole (0.82 g, 12.0 mmol). The solution was stirred at room temperature overnight and was quenched with H_2O (10 mL). The reaction was diluted with Et_2O and the organic and aqueous phases were separated. The aqueous layer was extracted with Et_2O (5 x 10 mL) and the combined organic layers were washed with H_2O (5 x 10 mL). The organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum to obtain the compound as a clear,

colorless oil (1.20 g, 85% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.79 (dtt, *J* = 10.1, 5.1, 2.6 Hz, 1H), 3.77 – 3.72 (m, 1H), 2.46 – 2.34 (m, 2H), 2.28 (tddd, *J* = 16.3, 9.1, 4.1, 2.0 Hz, 2H), 2.20 (dtt, *J* = 6.5, 4.1, 2.2 Hz, 2H), 2.15 (tq, *J* = 6.8, 2.2 Hz, 1H), 1.94 (q, *J* = 2.3 Hz, 1H), 1.68 (ddq, *J* = 13.8, 9.2, 4.7 Hz, 1H), 1.65 – 1.59 (m, 1H), 1.58 – 1.45 (m, 5H), 1.41 (dtd, *J* = 23.1, 11.3, 9.3, 4.9 Hz, 1H), 1.14 – 0.98 (m, 21H), 0.89 (d, *J* = 1.2 Hz, 9H), 0.89 (d, *J* = 1.4 Hz, 9H), 0.08 (t, *J* = 1.8 Hz, 6H), 0.07 (t, *J* = 1.9 Hz, 6H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 109.6, 105.9, 84.7, 82.3, 81.9, 71.6, 71.1, 71.1, 68.4, 36.3, 36.1, 36.0, 29.4, 29.0, 28.8, 28.0, 26.0, 24.7, 24.5, 19.0, 18.6, 18.6, 18.2, 11.5. **HRMS** (APCI): *m/z* calcd. for $C_{11}H_{19}OSi$ [M^+], 195.11997, found 195.11984.

*n*BuLi (0.92 mL, 1.75 mmol, 1.91 M in hexanes) was added dropwise to a cooled (-78˚C) solution of the corresponding terminal alkyne (1.10 g, 1.67 mmol) in THF (1.3 mL) and stirred for 30 min. BF_3·THF (0.40 mL, 3.68 mmol) was added and stirred for 10 min, followed by the addition of epoxide **43** (0.37 g, 1.67mmol) in THF (5.6 mL). The reaction was stirred at -78˚C for 2 h., warmed to room temperature for 30 min., and quenched with brine. The organic and aqueous phases were separated and the aqueous was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude was purified by flash column chromatography (1-5% EtOAc in hexane as eluent) to obtain **62** as a pale yellow oil (0.56 g, 39% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.78 (tt, *J* = 7.7, 4.8 Hz, 1H), 3.74 (ddt, *J* = 9.7, 6.6, 3.4 Hz, 1H), 3.72 – 3.66 (m, 1H), 2.47 – 2.34 (m, 3H), 2.34 – 2.21 (m, 5H), 2.18 (ddt, *J* = 6.8, 4.6, 2.3 Hz, 2H), 2.15 (tt, *J* = 6.7, 2.4 Hz, 2H), 1.95 (dd, *J* = 4.8, 2.3 Hz, 1H), 1.68 (ddt, *J* = 13.8, 9.5, 4.9 Hz, 1H), 1.59 – 1.43 (m, 11H), 1.39 (ddd, *J*

= 11.0, 6.6, 3.0 Hz, 1H), 1.33 – 1.22 (m, 1H), 1.12 – 1.00 (m, 21H), 0.89 (s, 9H), 0.89 (s, 9H), 0.15 (s, 9H), 0.08 (d, *J* = 2.9 Hz, 6H), 0.06 (d, *J* = 2.3 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 107.5, 105.8, 84.7, 83.4, 82.3, 81.9, 76.2, 71.6 71.1, 70.2, 36.4, 36.1, 35.9, 31.8, 29.4, 29.3, 29., 28.7, 28.0, 28.0, 26.1, 26.0, 25.1, 24.7, 24.7, 22.9, 20.0, 19.0, 19.0, 18.8, 18.3, 18.2, 14.3, 11.5, 0.4, -4.2, -4.3, -4.4, -4.5. **HRMS** (APCI): *m/z* calcd. for $C_{50}H_{95}O_3Si_4$ [M+H$^+$], 855.63529, found 855.63592.



(6R,14R,22R,30R)-14,22,30-tris((tert-butyldimethylsilyl)oxy)-33-(triisopropylsilyl)-tritriaconta-8,16,24,32-tetrayn-6-ol (63): To a solution of **62** (230 mg, 0.27 mmol) dissolved in MeOH (1.8 mL) was added K_2CO_3 (104 mg, 0.75 mmol) and the resulting suspension was stirred 12 h. The MeOH was removed under reduced pressure and the remaining residue was diluted with H_2O. The aqueous phase was extracted with EtOAc (3 x 10 mL), and the combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to obtain the compound as a clear, pale yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.78 (tt, *J* = 7.9, 4.8 Hz, 1H),

3.74 (q, *J* = 5.8 Hz, 1H), 3.69 (p, *J* = 5.7 Hz, 1H), 2.45 – 2.34 (m, 3H), 2.34 – 2.23 (m, 3H), 2.20 (dddd, *J* = 17.9, 7.4, 5.0, 2.3 Hz, 4H), 2.15 (q, *J* = 5.0, 3.4 Hz, 2H), 1.95 (td, *J* = 5.1, 4.5, 2.2 Hz, 1H), 1.67 (qt, *J* = 11.8, 5.9 Hz, 1H), 1.64 – 1.42 (m, 15H), 1.38 (dt, *J* = 10.4, 7.0 Hz, 2H), 1.11 – 0.99 (m, 21H), 0.89 (s, 9H), 0.89 (s, 9H), 0.081 (s, 3H), 0.076 (s, 3H), 0.066 (s, 3H), 0.064 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 83.4, 81.9, 71.6, 71.1, 70.2, 68.5, 36.4, 36.1, 35.9, 29.4, 29.0, 28.6, 28.1, 28.0, 26.0, 25.1, 24.7, 19.1, 19.0, 18.9, 18.6, 18.2. **HRMS** (APCI): *m/z* calcd. for $C_{47}H_{87}O_3Si_3$ [$M+H^+$], 783.59576, found 783.59653.

The corresponding alcohol (179 mg, 0.23 mmol) was dissolved in DMF (0.75 mL) and cooled to 0 ˚C. TBSCl (72 mg, 0.48 mmol) was added, followed by imidazole (88 mg, 1.29 mmol) and the reaction mixture was stirred overnight 12 h. The reaction was quenched with H_2O and the aqueous layer was extracted with EtOAc (5 x 15 mL). The combined organic layers were washed with H_2O (5 x 20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum to obtain the compound as a pale yellow oil (315 mg, 99% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.78 (app. ddd, J = 8.7, 7.1, 4.4 Hz, 1H), 3.74 (app. qd, J = 7.8, 7.3, 3.6 Hz, 2H), 2.46 – 2.35 (m, 2H), 2.32 – 2.28 (m, 2H), 2.27 – 2.22 (m, 2H), 2.20 (td, J = 6.9, 2.7 Hz, 2H), 2.15 (m, 4H), 1.94 (t, J = 2.6 Hz, 1H), 1.71 – 1.34 (m, 18H), 1.07 (s, 7H), 1.06 (s, 14H), 0.89 (s, 18H), 0.89 (s, 9H), 0.08 (app. d, J = 2.8 Hz, 9H), 0.07 (app. d, J = 2.6 Hz, 9H).

To a solution of the corresponding terminal alkyne (224 mg, 0.25 mmol) in THF (0.2 mL) at -78 ˚C was added dropwise *n*BuLi (0.15 mL, 0.26 mmol) and the reaction mixture

stirred for 30 min. A solution of **44** in THF (0.8 mL) was added, and the reaction mixture stirred at -78 ˚C for 4.5 h. The reaction was quenched with aqueous NH_4Cl (1 mL) and the aqueous layer was extracted with EtOAc (3 x 2 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash column chromatography (95/5 hexanes/EtOAc) to obtain unreacted **57** (62 mg, 28% recovery), followed by the elution of **63** as a clear, colorless oil (32 mg, 12% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.78 (tt, J = 7.4, 4.6 Hz, 1H), 3.73 (dtt, J = 6.5, 4.5, 2.0 Hz, 2H), 3.71 – 3.63 (m, 1H), 2.44 – 2.34 (m, 4H), 2.28 (ddtt, J = 19.6, 16.3, 6.2, 3.0 Hz, 6H), 2.21 – 2.17 (m, 2H), 2.14 (tt, J = 5.5, 3.0 Hz, 4H), 1.93 (d, J = 5.0 Hz, 1H), 1.72 – 1.21 (m, 24H), 1.07 (s, 7H), 1.06 (bs, 14H), 0.89 (bs, 21H), 0.89 (s, 9H), 0.08 (app. d, J = 3.1 Hz, 9H), 0.06 (app. d, J = 2.5 Hz, 9H). **HRMS** (ESI): *m/z* calcd. for $C_{60}H_{114}O_{43}Si_4$ [$M+H^+$], 1011.78670, found 1011.78821.

CHAPTER 3

The development of synthons for the stereoselective 1,3-dimethylallylation of aldehydes.

3.1 Introduction and Background

3.1.1 Homoallylic alcohols in natural products and current methods for preparation.

Homoallylic alcohols are important building blocks for natural products and other organic molecules.[76–78] There are a number of ways to synthesize these structurally important moieties, but the most widely used methods are carbonyl allylation and carbonyl-ene reactions.[79–81] Homoallylic alcohols formed in these reactions contain at least one chiral center and double bond, which can be used to further functionalize the molecule.

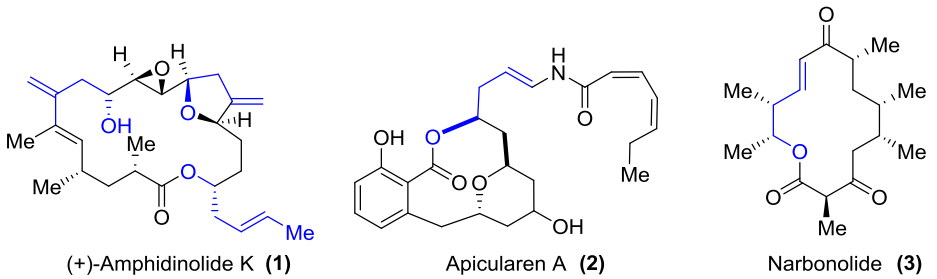


Figure 1: Natural products containing homoallylic alcohols (highlighted in blue).

These approaches can generate both branched (γ-functionality) and linear (no γ-functionality) homoallylic alcohols, but are unable to produce substitution patterns with α-functionality (Figure 2). Therefore, a new approach to linear or branched homoallylic alcohols with α-functionality is desired.

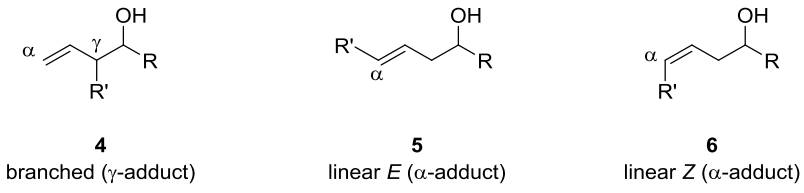
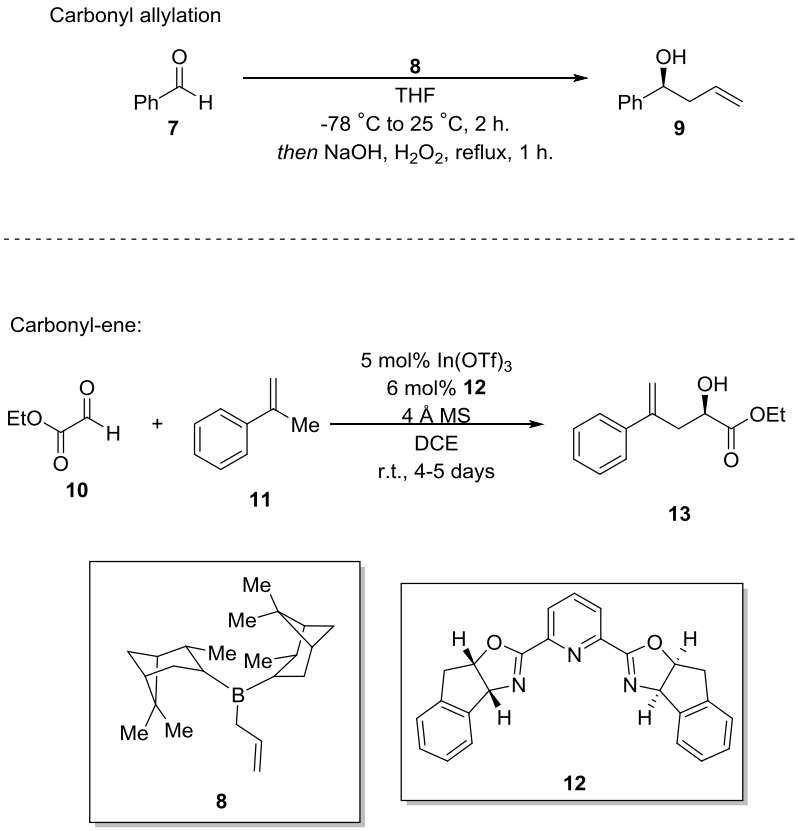


Figure 2: Branched and linear homoallylic alcohol adducts.[82]

Both approaches have limitations: stoichiometric amounts of chiral allylborane are environmentally unfriendly and create unnecessary waste, and the organometallic transformations require carefully controlled reaction conditions and extended reaction times up to several days.[81]

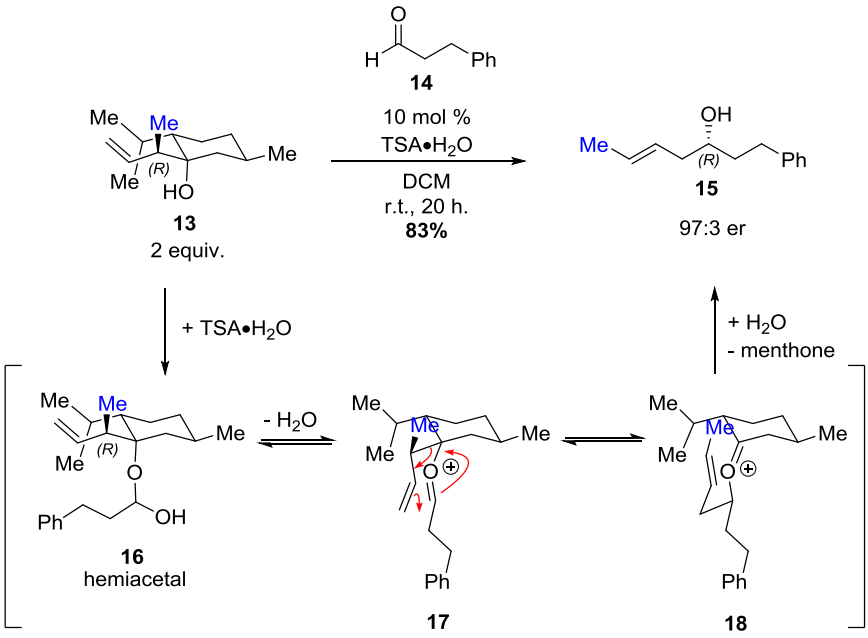


Scheme 1: Carbonyl allylation using allylborane reagent **8** and carbonyl-ene reaction using $In(OTf)_3$ and a chiral pybox ligand **12**.

3.1.2 Allyl transfer via the oxonia-Cope rearrangement to form linear homoallylic alcohols.

Nokami *et al.* discovered the first allyl transfer reaction using an organic molecule as the allyl transfer agent in 1998, referring to the addition of an allylic functionality from

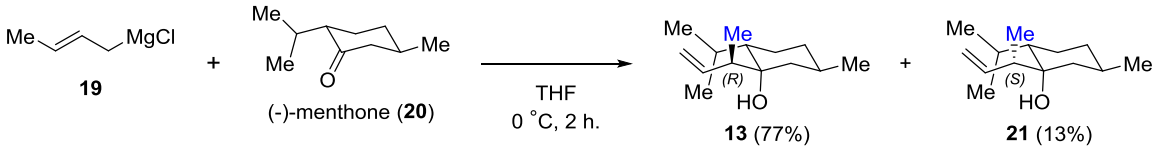
a donor molecule (not a metallic reagent) to an acceptor (aldehyde) to form a linear homoallylic alcohol.[83,84] The group later reported the first Brønsted acid-catalyzed enantioselective allyl transfer reaction in which a linear, *trans*-homoallylic alcohol (**15**) was obtained from a rearrangement of 3-phenylpropanal **14** with an optically pure branched allyl donor **13** (Scheme 2).[84] Nokami described the six-membered transition state as a 2-oxonia-[3,3]-sigmatropic rearrangement, based on Overman's earlier use of the term.[85] The linear homoallylic alcohol **15** was obtained in high enantiopurity (97:3 er) with complete *E*-selectivity.



Scheme 2: Nokami's enantioselective allyl transfer reaction.[84]

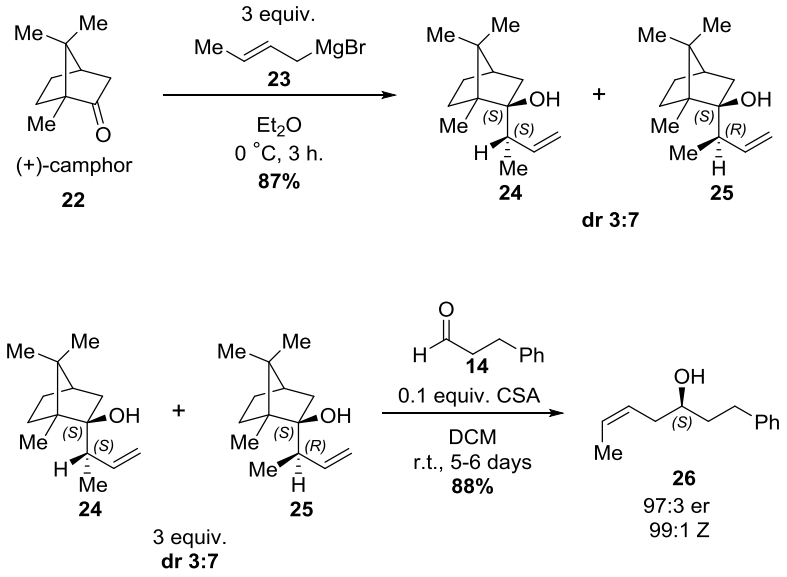
This approach has limitations, including the method of preparing the allyl donor. The crotyl Grignard reagent **19** adds to the optically pure (-)-menthone (**20**) to yield *R* (**13**) and *S* (**21**) diastereomers in a Mg°-mediated allyl group transfer, which must be

separated prior to condensation with the aldehyde in the allyl transfer reaction (Scheme 3). Additionally, two equivalents of the chiral allyl transfer reagent **13** are required to give a high yield (83%) of the desired homoallylic alcohol (Scheme 2). Although 55% of **13** is recoverable, the use of excess reagent increases the amount of waste generated from the reaction and required purification steps.



Scheme 3: Preparation of Nokami's allyl transfer reagent.[84]

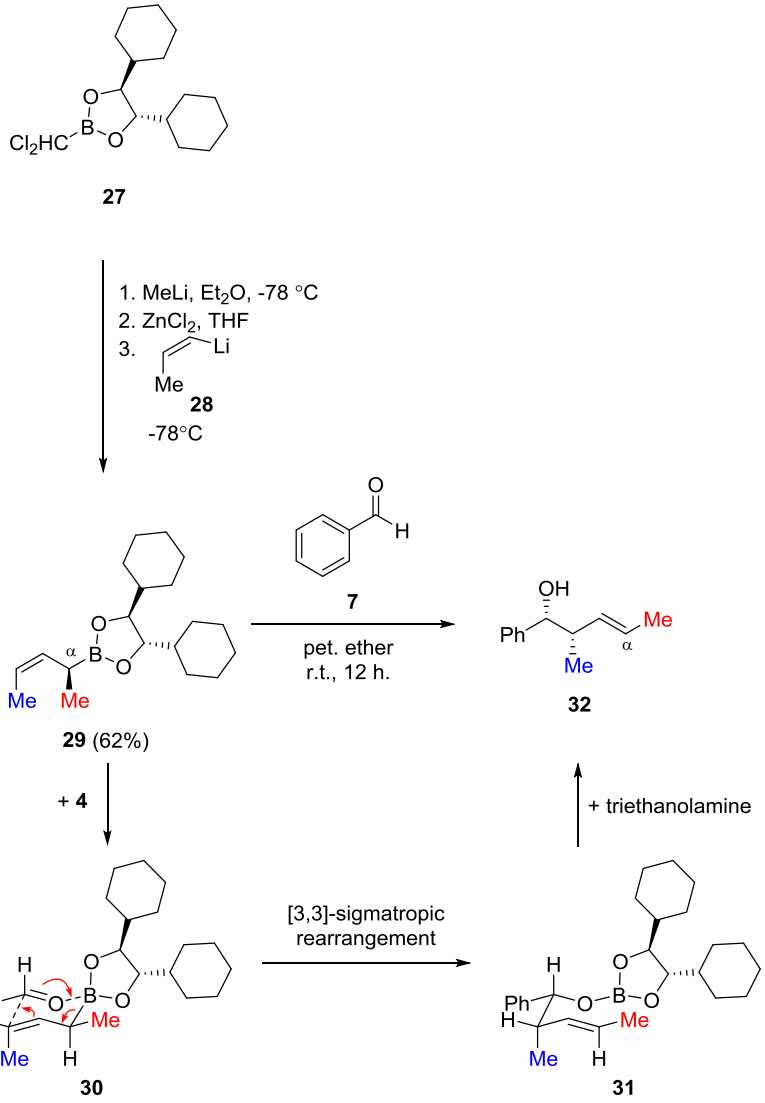
Loh *et al.* proposed another chiral allyl transfer reagent using (*R*)-(+)-camphor and a crotyl Grignard reagent **23**. The camphor-based transfer agent **24/25** was obtained as a 3:7 mixture of diastereomers, however only one of the isomers (**24**) reacted under optimized conditions with camphorsulfonic acid (CSA) to yield *Z*-homoallylic alcohol **26** in 88% yield and 97:3 er (Scheme 3). The camphor-based system has a few drawbacks, requiring excess quantities of the allyl transfer agent **24/25** (3 equiv.) and an extended reaction time of several days.



Scheme 3: Formation of linear homoallylic alcohol using camphor-based transfer reagent.

3.1.3 1,3-dimethylallylation of aldehydes to synthesize branched homoallylic alcohols.

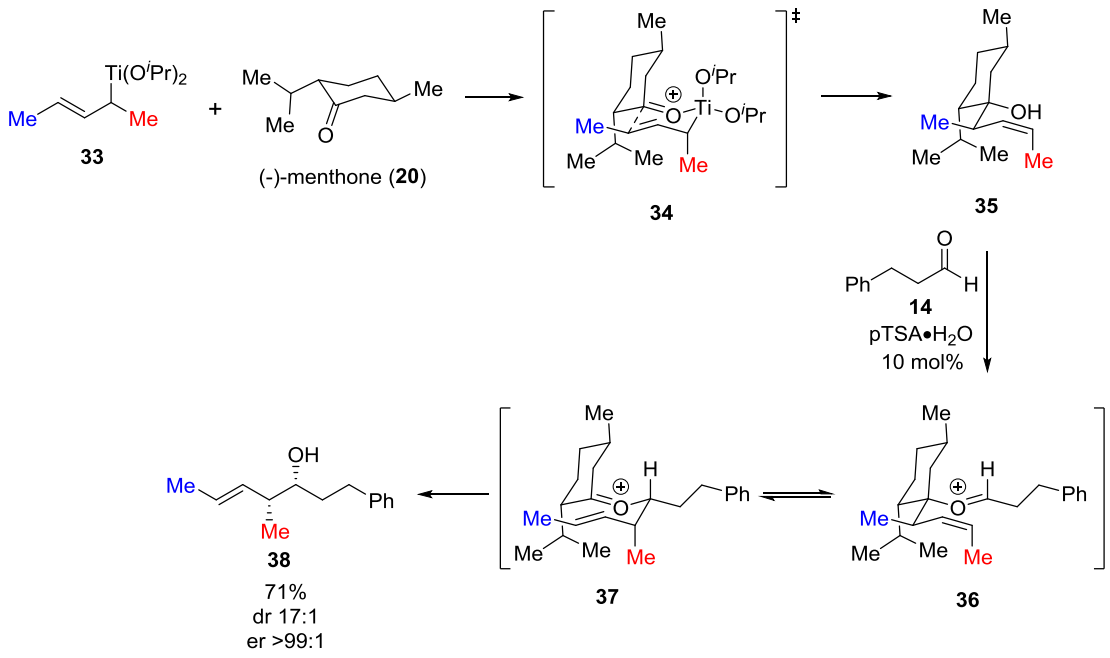
Hoffmann and Lee have both proposed methods for introducing the 1,3-dimethylallyl group to homoallylic alcohols. Hoffmann utilized pentenylboranes in the allylic transfer reaction (Scheme 5).[86] Addition of methyllithium, zinc chloride, and *Z*-propenyllithium to (α-chloroethyl)boronate **27** formed pentenyl transfer agent **29** in high diastereomeric purity, and allyl transfer with benzaldehyde resulted in formation of the branched homoallylic alcohol **32** with a *syn* relationship between the hydroxyl and methyl groups in the chain (Scheme 5). However, the *Z*-pentenylboronates require the methyl group in the α-position to boron to create non-racemic homoallylic alcohols, as exclusion of this group results in racemic mixtures of homoallylic alcohols without α-functionality.



Scheme 5: Hoffmann's *Z*-pentenylboronates act as 1,3-dimethylallyl transfer reagents.[86]

Lee *et al.* have proposed a (-)-menthone pentenyl transfer agent similar to Nokami's reagent (**13**).[82,87] Addition of the titanium reagent **33** to (-)-menthone (**20**) produced the pentenyl transfer agent **35** containing *Z* double bond geometry as a single stereoisomer (Scheme 6).[87] A 2-oxonia-Cope rearrangement of **35** with aldehyde **14** yielded the *E*-homoallylic alcohol **38** with *syn* stereochemistry (dr = 17:1, er = >99:1,

Scheme 6). Rearrangements with Lee's allylic transfer agent required excess transfer reagent **35** (2 equiv.), due to the competing Prins reaction of the product and **14**.

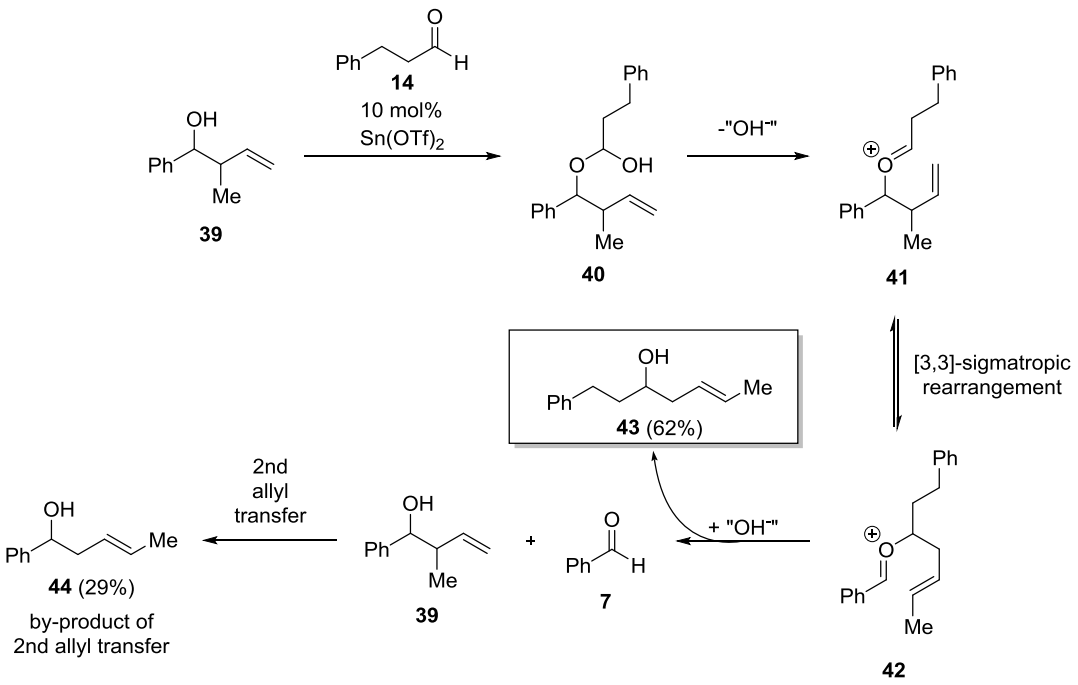


Scheme 6: Lee's pentenylation reaction to introduce the 1,3-dimethylallyl group.

The driving force for the allyl transfer reaction through a 2-oxonia-Cope rearrangement is the formation of a sterically less hindered and thermodynamically more stable homoallylic alcohol.[83] Although the allyl transfer reaction is a useful transformation, there are a number of issues that need to be addressed:

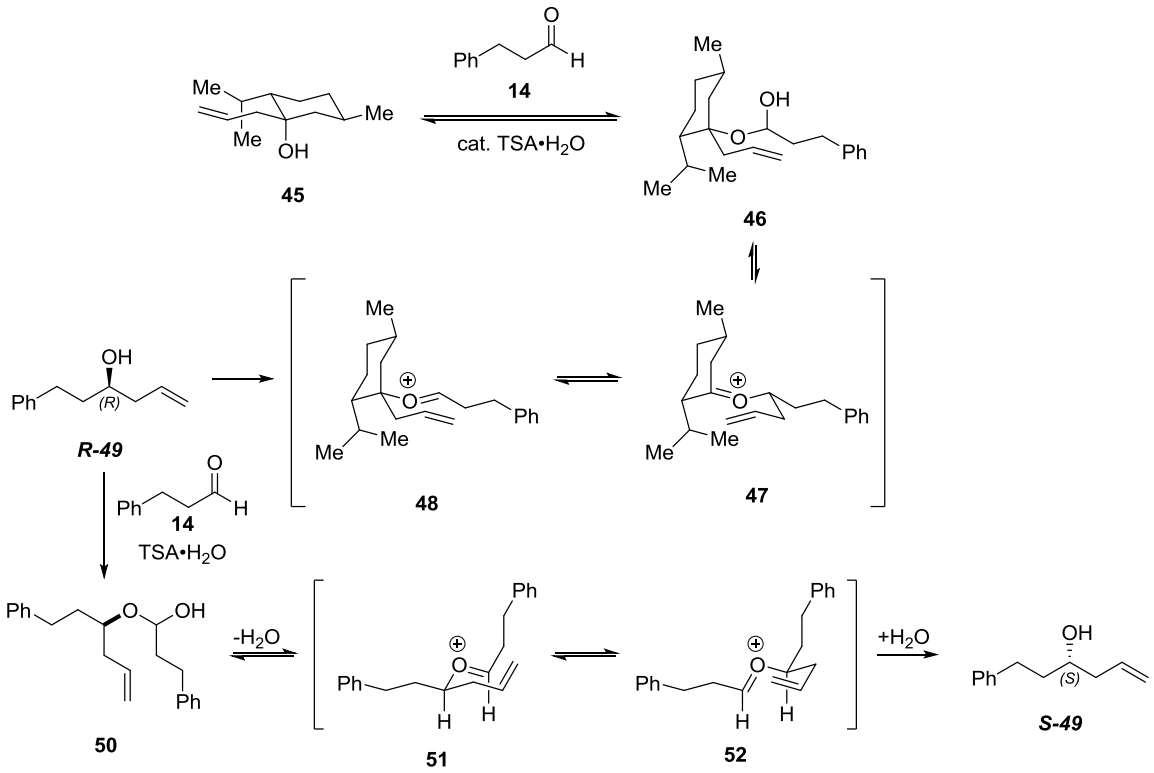
1) formation of by-products from the aldehyde that is released during the first round of allyl transfer (Scheme 7). Homoallylic alcohol **39** is condensed onto aldehyde **14**, forming a hemiacetal, which will dehydrate to generate the oxonium ion **41**. After the [3,3]-sigmatropic rearrangement, oxonium ion **42** will be hydrated to form the desired

product **43** in 62% yield. The benzaldehyde **7** that is also released during the hydration step may enter a second cycle of allyl transfer with the starting material **39** to afford the benzylic alcohol **44** as a major by-product of the allyl transfer step.



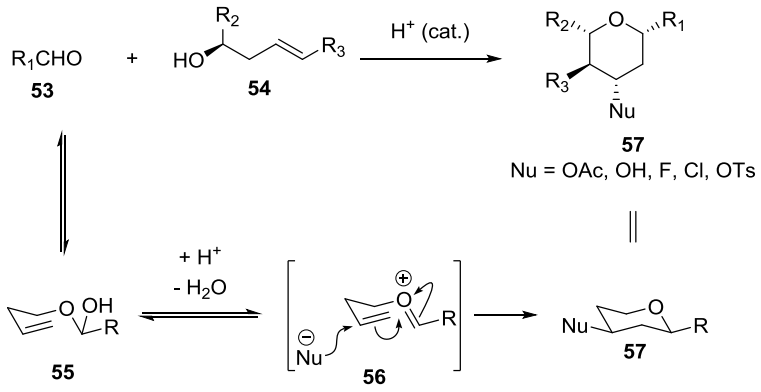
Scheme 7: By-product formed during allyl transfer reaction.

2) epimerization that arises from a second cycle of allyl transfer of the product with the aldehyde partner (Scheme 8).[88,89]



Scheme 8: Racemization of ***R*-49** to ***S*-49** due to second cycle of allyl transfer.[89]

3) formation of the Prins cyclization product in the presence of an external nucleophile to produce the tetrahydropyran (Scheme 9).[90–94]

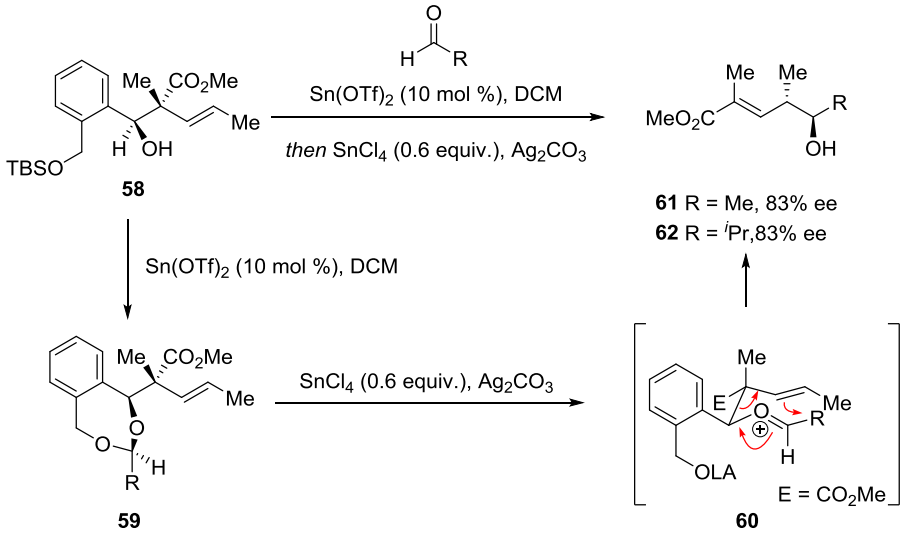


Scheme 9: Prins cyclization to form tetrahydropyrans.[94]

3.2 New concepts and design for allyl transfer

3.2.1 Previous results in the McDonald lab.

The McDonald lab is interested in the development of a new reagent to transfer allylic moieties to aldehydes in the formation of homoallylic alcohols. Chen and McDonald proposed synthon **58** for the transfer of bispropionates to form highly functionalized polypropionate products (Scheme 10).[95]



Scheme 10: Chiral synthons for efficient introduction of bispropionates via stereospecific oxonia-cope rearrangements.[95]

A variation on this methodology was applied in the synthesis of the sphinoglipid biosynthesis inhibitor Fumonisin B_1 to construct the C10-C20 core (Figure 3).[96] The McDonald allyl transfer reagent successfully provided the core of Fumonisin B_1 with the stereochemistry of the C14 alcohol and stereochemistry of the *trans* alkene expected from a 2-oxonia-Cope rearrangement (Scheme 11). Another allylic transfer was also used to construct the C1-C9 section of Fumonisin B_1 using a camphor-based allyl transfer agent.

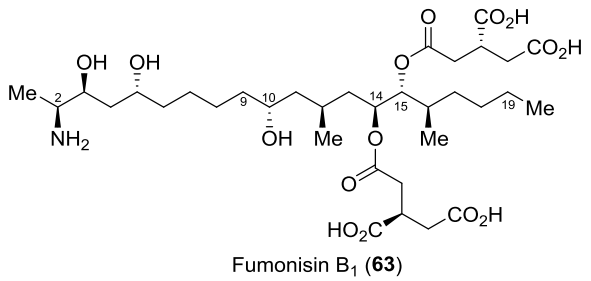
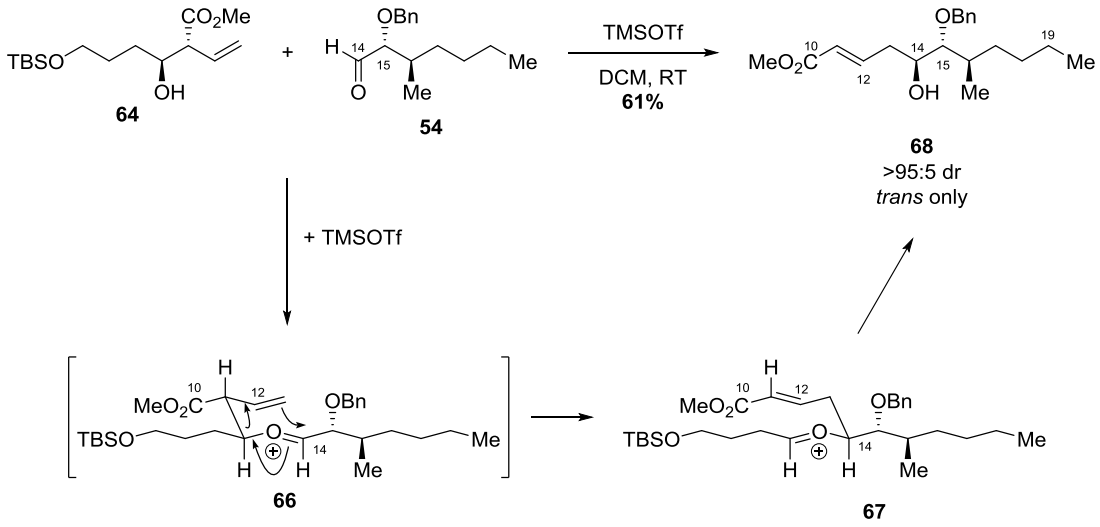
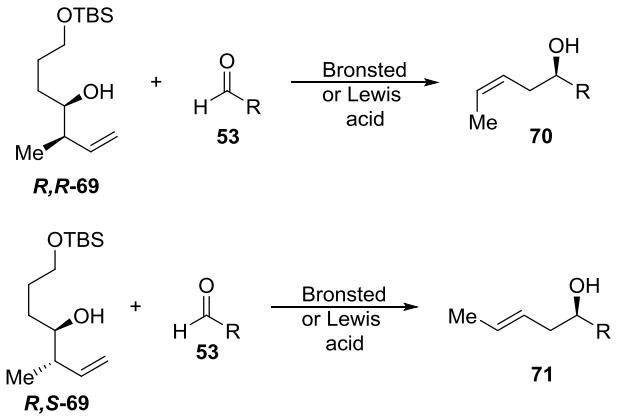


Figure 3: Structure of Fumonisin B_1.



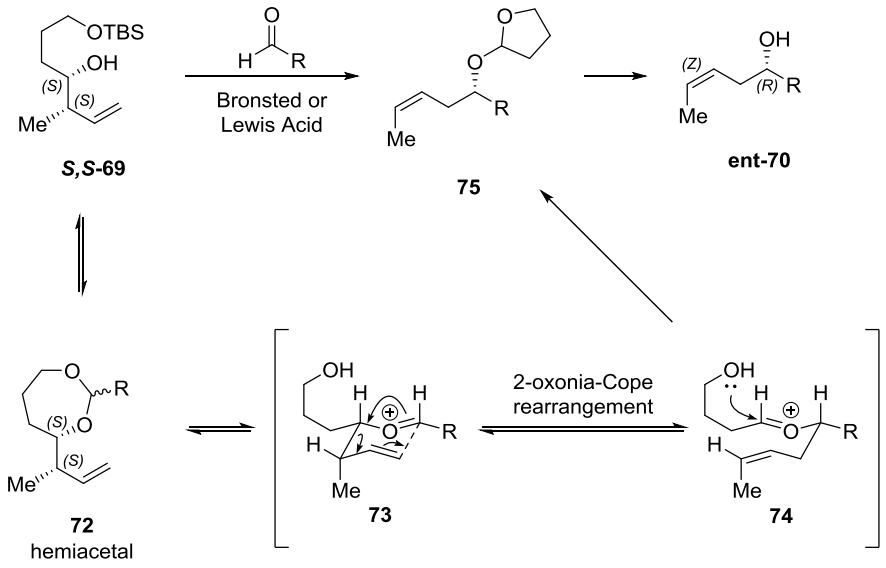
Scheme 11: Preparation of the C10-C20 core of Fumonisin B_1 using the McDonald allyl transfer reagent.[96]

Extension of this concept to linear homoallylic alcohols was investigated by a previous lab member, Dr. Claney Pereira, using a pair of synthons without an α,β-conjugated system (Scheme 12).[97] The *syn*-synthon **69** provides the *Z*-homoallylic alcohol and the anti-synthon provides the *E*-homoallylic alcohol, both without γ-functionality.



Scheme 12: McDonald allyl transfer reagents provide *Z* and *E* linear homoallylic alcohols.[97]

An acid-catalyzed 2-oxonia-Cope rearrangement of ***S,S*-69** with an aldehyde will afford the branched homoallylic alcohol **ent-70**, with translation of the *syn*-stereochemistry in the synthon to the *Z*-alkene product. Translation of the *E*-stereochemistry in ***S,S*-69** will produce an *anti*-relationship between the alcohol and methyl group in **ent-70**. The pendant silyloxy group drives the reaction toward the product and forms a protecting group for the newly-formed alcohol. This protecting group suppresses epimerization of the alcohol stereocenter as in Scheme 7 and formation of other side products by preventing the products of the rearrangement from entering a second cycle of allyl transfer (Scheme 13).[98]



Scheme 13: Mechanism for allyl transfer reagents developed in the McDonald laboratory.

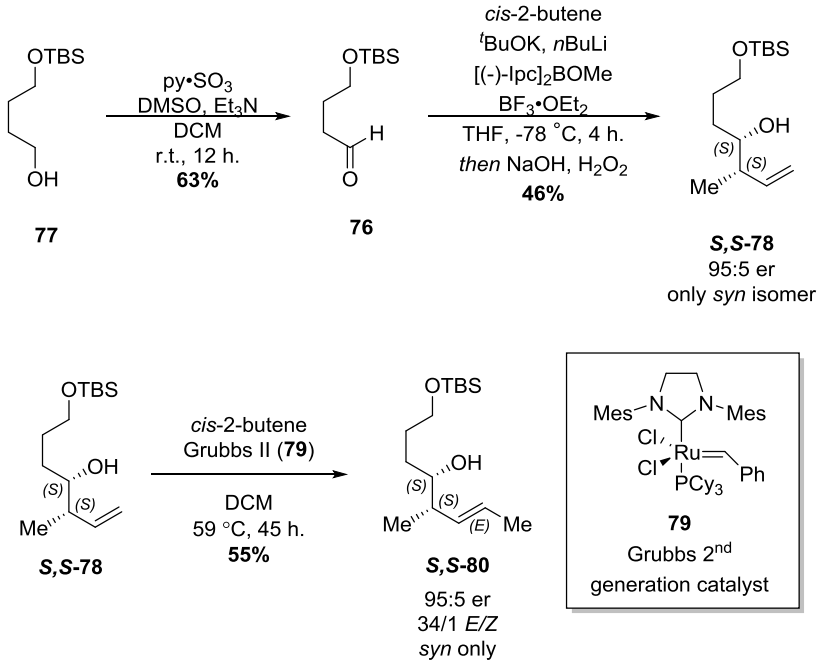
A new reagent is proposed for introducing a 1,3-dimethyallyl group during an allyl transfer reaction with control of enantio- and diastereoselectivity to synthesize branched homoallylic alcohols with α-functionality (***S,S*-80**, Scheme 14).

3.3 Results and Discussion

3.3.1 Synthon Preparation.

Dimethyl synthon ***S,S*-80** was synthesized through the crotylation of TBS-protected butanal **77** and Ru-mediated cross metathesis with *cis*-2-butene. Oxidation of alcohol **76** using the Parikh-Doering method produced aldehyde **77** in good yield, followed by the Brown crotylation using (-)-B-methoxy diisopinocampheylboraneborane to obtain *syn*-synthon ***S,S*-78** in 95:5 er as determined by Mosher ester analysis (Scheme 14). The diastereoselectivity of the Brown crotylation varied between batches, forming the homoallylic alcohol with ratios as low as 2.5:1 *syn*:*anti* to >50:1 *syn*:*anti*. Cross

metathesis of ***S,S*-78** with *cis*-2-butene using Grubbs second generation catalyst afforded the dimethyl-synthon ***S,S*-80** in 61% yield. The Grubbs cross metathesis also provided variable results, with E/Z ratios as low as 6/1 and as high as 50/1 after purification. Longer reaction times increased the ratio of E/Z alkenes, but did not affect the yield of the product.

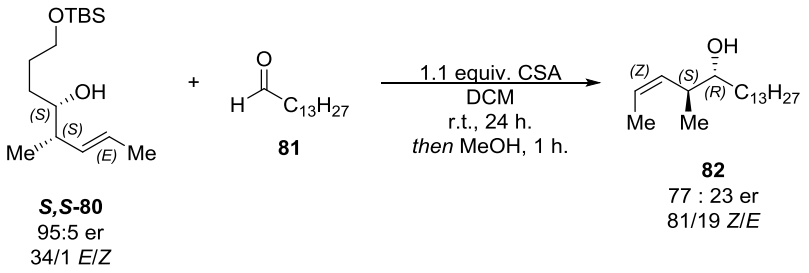


Scheme 14: Synthetic route to *syn*-synthon ***S,S*-80**. The ratio of *E*/*Z*-alkene was determined by the analysis of ^{1}H NMR data.

3.3.2 Initial results from 2-oxonia-Cope rearrangement.

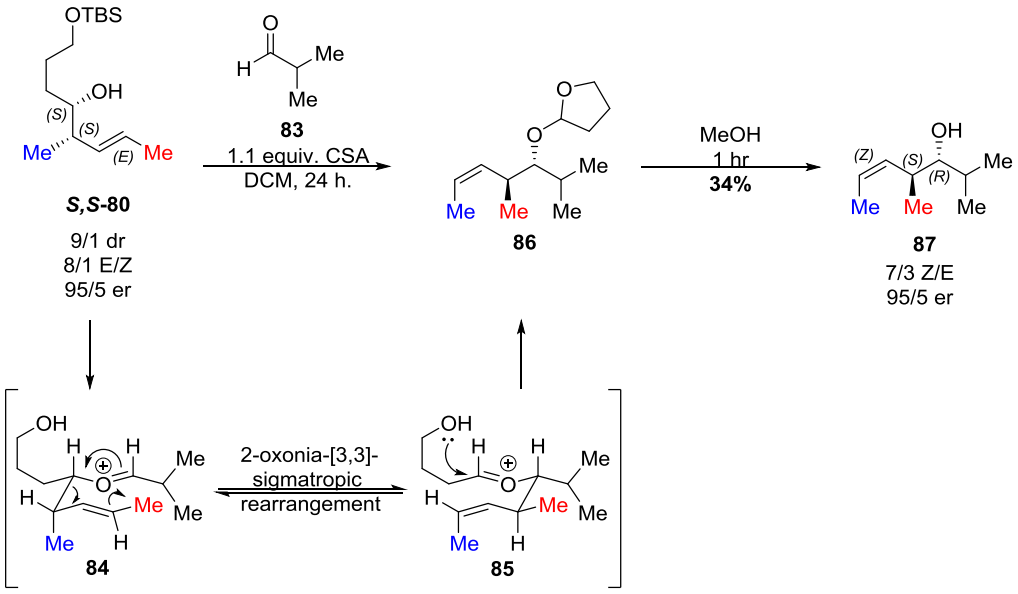
Allylic transfer reactions of ***S,S*-80** and tetradecanal (**81**), a linear aldehyde, formed *Z*-homoallylic alcohol **82** with *anti*-stereochemistry in 20% yield as the (*S*,*R*)-enantiomer (77:23 er, 81/19 *Z*/*E*, Scheme 13). In the mechanism proposed, dimethyl synthon ***S,S*-80** reacts with tetradecanal under acidic conditions to form a 7-membered

ring hemiacetal before continuing through the 2-oxonia-Cope rearrangement to produce the branched, *Z*-homoallylic alcohol **82**. Support for this mechanism is found in the ^{1}H NMR spectrum, which indicates the formation of the 7-membered ring acetal as two sets of multiplets at δ 4.60-4.74 ppm after the addition of catalytic CSA (0.1 equiv.). Since the enantiomeric purity is reflected in the alkene selectivity, it is expected that the synthon with lower enantiomeric excess would result in a homoallylic alcohol product with lower *Z*/*E* selectivity. In addition, the cross metathesis reaction produces both *Z*- and *E*-alkene products. The alkene geometries affect the dr of the product by changing the relative configuration of the methyl group in the homoallylic alcohol product of the 2-oxonia-Cope rearrangement.



Scheme 15: 1,3-dimethyallylation of a linear aldehyde. The ratio of *Z*/*E* alkene was determined by analysis of the ^{1}H NMR spectrum.

The allylic transfer reaction of ***S,S*-80** with isobutyraldehyde produced *Z*-homoallylic alcohol **87** (34% yield, 7/3 *Z*/*E* selectivity) with *anti*-stereochemistry provided by the *E*-alkene present in ***S,S*-80** (Scheme 16).



Scheme 16: Allyl transfer to isobutyraldehyde.

The low yield of the rearrangement product is most likely due to the large number of side products (~5-9 different spots by TLC) formed during the course of the reaction. Although not all side products were isolated and characterized, some of the side products suggest the reaction does not go to completion and instead stops at a 7-membered ring hemiacetal (such as **72**). The starting materials are consumed after approximately 30 min. to form the hemiacetal intermediate. However, the hemiacetal is not fully converted into the rearrangement product.

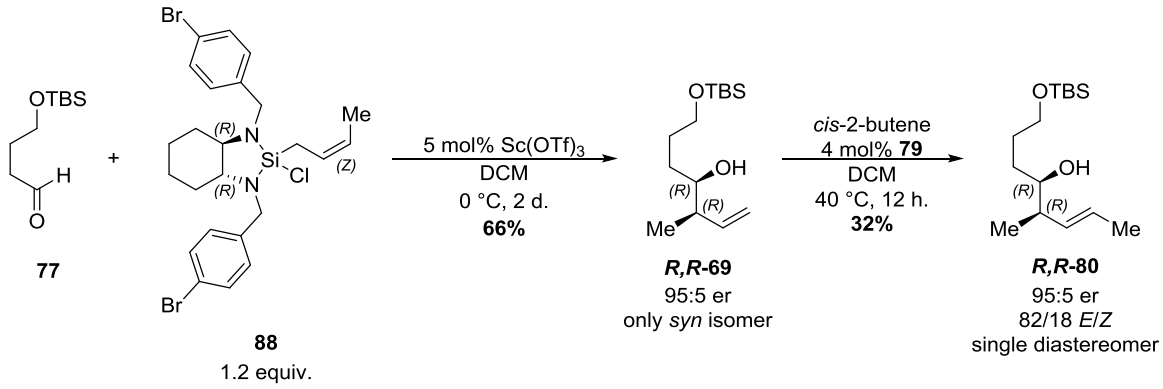
A related system explored by another student, Nellie Ochs, seems to have a higher conversion to rearrangement products.[99] Using a menthone-based synthon, 3-phenylpropanal was able to undergo the rearrangement to provide the desired homoallylic alcohol in 85% yield. In addition to using a different synthon, TsOH-H_2O was used as the acid catalyst. This acid is much stronger than CSA (pK_a = -2.8 for TsOH, 1.2 for CSA),

and the acid strength may be important in the conversion of the starting material to the product through catalyzing the decomposition of the hemiacetal intermediate.

Additionally, the unreliability of the diastereoselectivity in the crotylation reaction and low selectivity in the cross metathesis reaction further complicated the analysis of the rearrangement products. This limited our ability to determine the stereospecificity of the reaction, and other routes were explored for the preparation of the synthons.

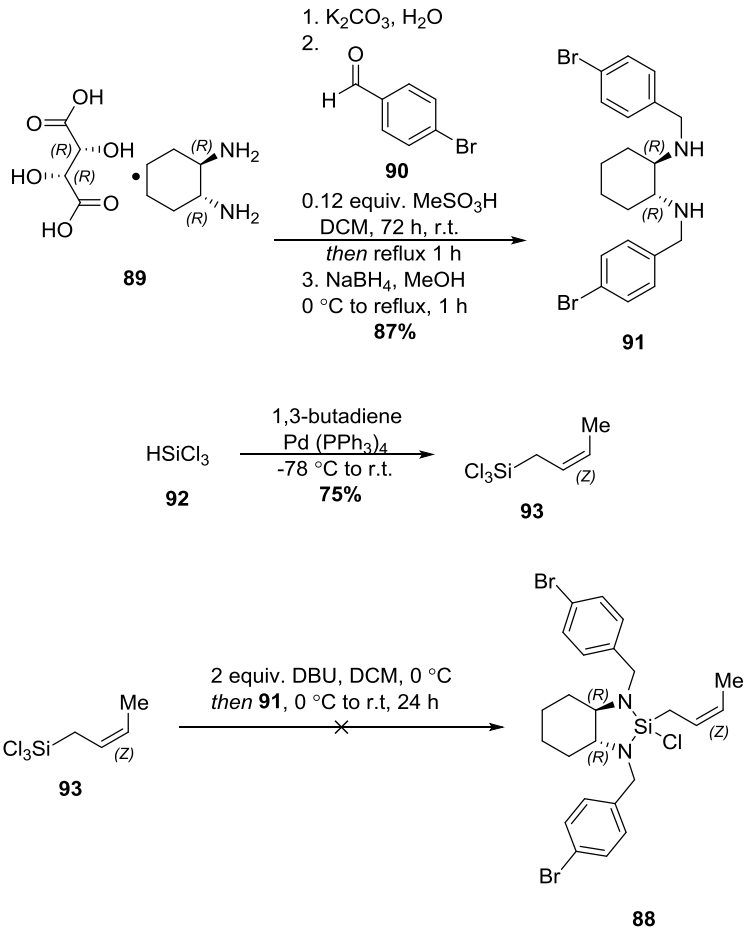
3.3.3 Revised synthetic route toward syn-*synthon.*

Syn-synthon ***S,S*-80** was prepared as a single diastereomer in excellent enantiopurity by crotylation of **77** using the commercially available Leighton reagent **88**, followed by cross metathesis (Scheme 17).[100,101] The improved reliability of the Leighton crotylation reaction compared to the Brown method was promising, however the reagent is used in excess and is expensive. As it is used in the first step of synthon preparation, large quantities of the reagent would be needed. Therefore, the synthesis of the Leighton reagent was explored (Scheme 18).



Scheme 17: Commercially available *R,R*-Leighton reagent used in synthesis of ***R,R*-80**.

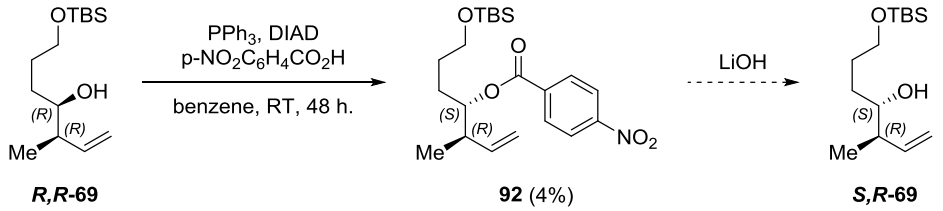
The diamine **83** was readily synthesized in 87% over three steps (Scheme 18). The *Z*-crotyltrichlorosilane **85** was obtained by hydrosilylation of 1,3-butadiene with trichlorosilane. Coupling of the diamine with the *Z*-crotyltrichlorosilane proved to be a challenge, and pure samples of the desired crotylsilane reagent **88** were unable to be obtained. The compound is moisture sensitive, and numerous attempts to exclude moisture by using a Schlenk filter or performing the workup in a glove box during the isolation and recrystallization processes were ineffective, resulting in decomposition of the product.[102] This route was ultimately abandoned, as the Leighton reagent was used in excess and the synthesis of the reagent proved difficult on a larger scale.



Scheme 18: Synthesis of *R,R*-Leighton reagent **88**.

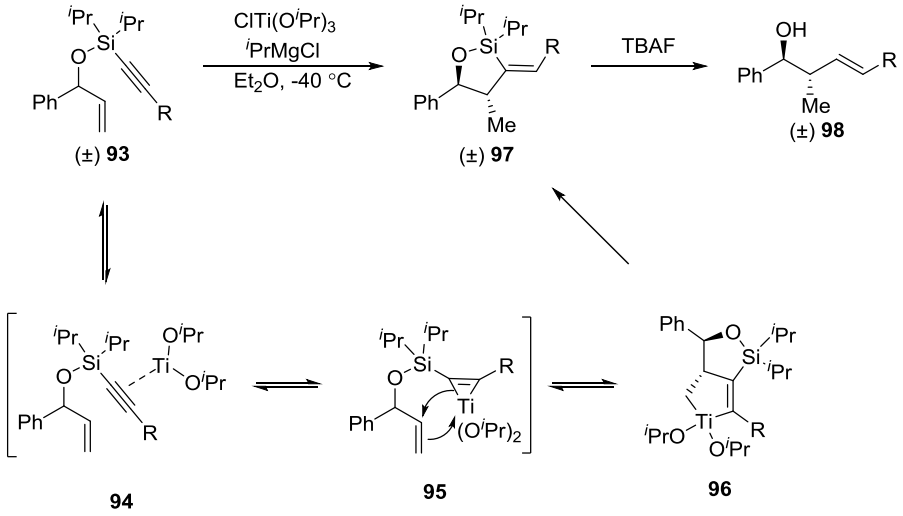
3.3.4 Revised synthetic route toward anti-*synthon.*

The *anti*-synthon ***S,R*-80** was also of interest for the 2-oxonia-Cope rearrangement. The terminal alkene precursor to ***S,R*-69** was synthesized as a 4:1 mixture of diastereomers using the Brown crotylation. However, the dr of the products resulting from the synthesis of ***R,R*-69** was generally higher, and we decided to prepare the *anti* synthon from the *syn* synthon by inversion of the alcohol stereocenter. Mitsunobu conditions were employed to perform this transformation, however the reaction was low yielding and provided only trace amounts of the desired product (Scheme 19).



Scheme 19: Inversion of alcohol stereocenter using Mitsunobu conditions to synthesize ***S,R*-69.**

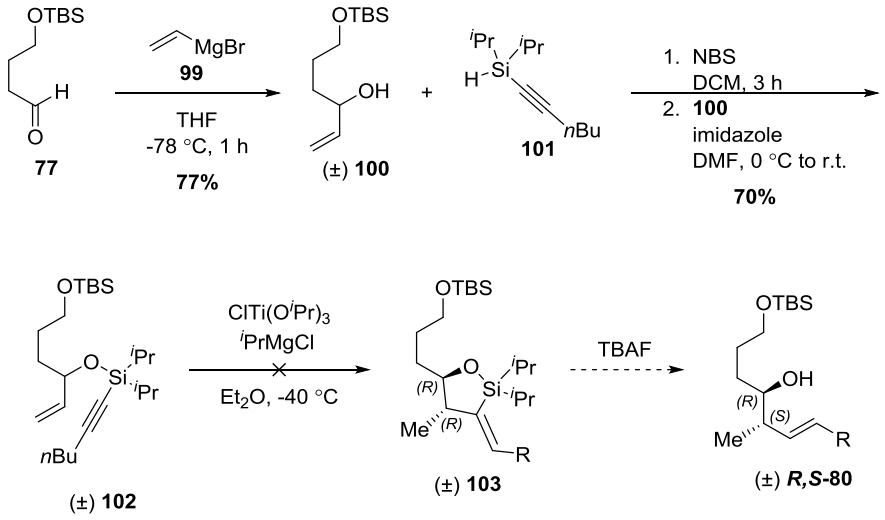
An alternative route using Phillips' titanium-promoted enyne cyclization was then explored (Scheme 20).[103] The method forms a five-membered ring titanacycle, which is then hydrolyzed to the siloxane. Desilylation of the siloxane results in the exclusive formation of the *anti* diastereomer of the branched homoallylic alcohol.



Scheme 20: Phillips' titanium-mediated enyne cyclization.

The synthesis of enyne **102** progressed smoothly, starting with the addition of vinylmagnesium bromide to TBS-butanal **77** (Scheme 21).[104] The alkynyl silane **101**,

easily obtained by addition the lithium acetylide of 1-hexyne to chlorodiisopropyl silane, was treated with NBS to generate the silyl bromide *in situ*, and silylation of **100** occurred in good yield.[105,106] However, all (silyloxy)enyne cyclization efforts were unsuccessful, **102** was recovered from the reaction mixtures. The characteristic color change with the addition of Grignard was observed, indicating formation of the active Ti-complex,[107] but evidence of the cyclization product was never found. Further investigation discovered the cyclization conditions to be very sensitive to substrate, scale and temperature.[103,105]



Scheme 21: Application of titanium-mediated enyne cyclization.

Although the Brown crotylation, Leighton crotylation, and Phillis' titanium enyne cyclization methods were unable to successfully provide either ***S,S*-80** or ***R,S*-80**, it may still be possible to access this homoallylic alcohol through Hall's method using chiral allylboronates and $Sc(OTf)_3$-catalyzed allylboration of aldehydes.[108]

3.4 Conclusions

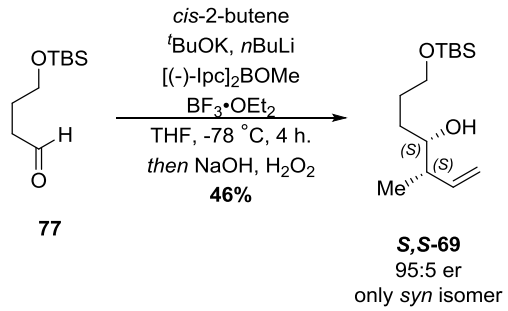
High stereochemical purity of the family of synthons for the 1,3-dimethylallylation of aldehydes is required to aid in determination of the results from the 2-oxonia-Cope rearrangement, as it is not immediately apparent if the reaction is completely stereoselective. The best approach to synthon preparation is the Leighton crotylsilane reagent, due to its reliability. However, the reagent is expensive and difficult to synthesize on a larger scale due to complications with atmospheric moisture. The classical approach, using the Brown crotylation methodology, can provide the synthon with high stereochemical purity and may function as an alternative route if the Leighton reagent is unavailable due to cost. The Phillips' titanium-mediated (silyloxy)enyne cyclization is extremely sensitive to reaction conditions, and was unsuccessful in this case. Additionally, the choice of acid catalyst may be important to ensure conversion of starting material to the rearrangement product.

3.5 Chemistry Experimental Details

General information: Proton and carbon NMR spectra were recorded on an INOVA-400 (400 MHz), VNMRS 400 (400 MHz), INOVA-600 (600 MHz), or Unity-600 (600 MHz). NMR spectra were recorded in solutions of deuterated chloroform ($CDCl_3$) with the residual chloroform (7.27 ppm for ^1H NMR and 77.23 ppm for ^{13}C NMR) taken as the internal standard, deuterated methanol (CD_3OD) with residual methanol (3.31 ppm for ^1H NMR and 49.3 ppm for ^{13}C NMR) taken as the internal standard, or deuterated benzene with residual benzene (7.16 ppm for ^1H NMR and 128.23 ppm for ^{13}C NMR) taken as the internal standard, and were reported in parts per million (ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; ddd, doublet of doublet of doublet; dt, doublet of triplet; m, multiplet. IR spectra were collected on a Nicolet Avatar 370 DTGS. Mass spectra (high resolution ESI and APCI) were recorded on a Finnigan LTQ FTMS Mass spectrometer. Optical rotations were measured using a Perkin-Elmer 341 polarimeter (concentration in g/100mL). Thin layer chromatography (TLC) was performed on precoated glass backed plates purchased from Whatman (silica gel 60F254; 0.25mm thickness). Flash column chromatography was carried out with silica gel 60 (230-400 mesh ASTM) from Silicycle. All reactions were carried out with anhydrous solvents in oven dried or flame dried and argon-charged glassware unless otherwise specified. All anhydrous solvents were dried with 4Å molecular sieves purchased from Sigma-Aldrich and tested for trace water content with Coulometric KF titrator from Denver instruments. All solvents used in extraction procedures and chromatography were used as received from commercial suppliers without further purification.

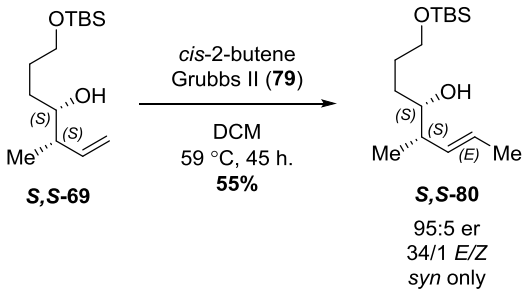
76 **77**

4-((tert-butyldimethylsilyl)oxy)butanal (77): To a solution of 4-(*tert*-Butyldimethylsilyl)oxy-1-butanol **70** (5.23 g, 25.6 mmol, 5.9 mL) at 0 ˚C in DCM (37 mL) was added Et_3N (7.13 mL, 51.2 mmol) and DMSO (3.6 mL, 51.2 mmol). SO_3-py. (8.15 g, 51.2 mmol) was added and the reaction mixture was warmed to room temperature. The reaction was quenched with H_2O and the aqueous and organic phases were separated. The aqueous was extracted with DCM, and the combined organic layers were washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude material was purified by flash column chromatography (9/1 hexanes/Et_2O as eluent) to obtain the compound as a pale yellow oil (3.09 g, 60% yield). The spectral data matched those in the literature.[109] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.72 (t, *J* = 1.8 Hz, 1H), 3.57 (dt, *J* = 8.9, 6.1 Hz, 2H), 2.44 (td, *J* = 7.1, 1.8 Hz, 1H), 1.79 (tt, *J* = 5.9, 7.2 Hz, 2H), 0.82 (s, 9H), -0.02 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.9, 62.3, 41.0, 31.1, 26.1, 18.5, -5.2. **HRMS** (APCI): Calculated for $C_{10}H_{23}O_2Si$ [M+H], 203.14616; found 203.14619.

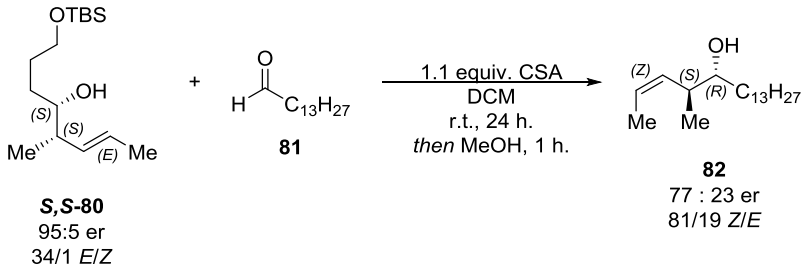


(3*S*,4*S*)-7-((tert-butyldimethylsilyl)oxy)-3-methylhept-1-en-4-ol (*S*,*S*-78):[110] *t*BuOK (0.33 g, 2.96 mmol) was dried overnight under vacuum at 90-95 ˚C. THF (6.2 mL) was added at room temperature and the suspension was cooled to -78 ˚C. C*is*-2-butene (0.69 g, 12 mmol, 1.14 mL) was collected in a measuring cuvette at -78 ˚C and transferred *via* cannula to the reaction flask. *n*BuLi (1.18 mL, 2.96 mmol) was added along the sides of the flask and the bright yellow reaction mixture was stirred for 10 min. at -45 ˚C then cooled to -78 ˚C. To the yellow-green mixture was added a solution of $[(-)\text{-Ipc}]_2\text{BOMe}$ (0.93 g, 2.96 mmol) in THF (5.2 mL) and the colorless reaction mixture was stirred at -78 ˚C for 30 min. $BF_3{\cdot}OEt_2$ (0.37 mL, 2.96 mmol) was added along the sides of the flask, immediately followed by aldehyde **77** (0.505 g, 2.47 mmol). The resulting solution was stirred at -78 ˚C for 2.5 h., quenched with 3 M NaOH (2.5 mL) and H_2O_2 (1.88 mL), and stirred at room temperature for 24 hours. The organic and aqueous layers were separated and the aqueous was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The crude material was purified by flash column chromatography (92/8 hexanes/EtOAc as eluent) to obtain the compound as a pale yellow oil (294 mg, 46% yield, 95:5 er by Mosher ester analysis). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.88 – 5.74 (m, 1H), 5.12 – 5.01 (m, 2H), 3.71 – 3.59 (m, 2H), 2.48 (bs, 1H), 2.35 – 2.21 (m, 1H), 1.66 (m,4H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.07 (s,

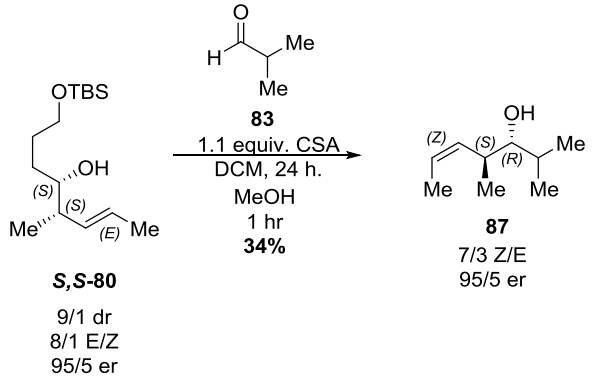
6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141. 5, 115.0, 74.8, 63.7, 43.9, 31.5, 29.6, 26.1, 15.0, -5.2. **HRMS** (APCI): Calculated [M+H] 259.20879; found 259.20874.



(4*S*,5*S*,*E*)-1-((tert-butyldimethylsilyl)oxy)-5-methyloct-6-en-4-ol (*S*,*S*-80) : Into a flame dried sealed tube was placed DCM (1 mL) and ***S*,*S*-69** (88 mg, 0.33 mmol). The tube was cooled to -78 ˚C and *cis*-2-butene (0.94 mL, 10.2 mmol) was condensed into a measuring cuvette, then transferred to the tube via cannula. Grubbs II catalyst **79** (14 mg, 0.01 mmol) was added to the tube, and the mixture was heated to 59 ˚C for 48 h. The reaction was cooled to -78 ˚C, opened, and slowly warmed to room temperature. The mixture was concentrated under reduced pressure and purified on silica gel (97/3 hexanes/EtOAc as eluent) to obtain **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.60 – 5.43 (m, 1H), 5.43 – 5.32 (m, 1H), 3.73 – 3.60 (m, 2H), 3.47 – 3.33 (m, 1H), 2.21 (h, *J* = 7.1 Hz, 1H), 1.78 – 1.52 (m, 7H), 1.01 (dt, *J* = 6.9, 1.6 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H).

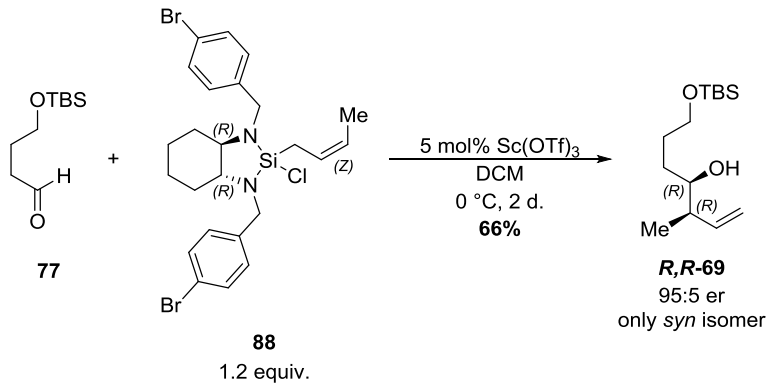


(4*S*,5*R*,*Z*)-4-methyloctadec-2-en-5-ol (82): To a glass vial at room temperature was added tetradecanal **81** (21 mg, 97 μmol), synthon ***S,S*-80** (29 mg, 0.11 mmol), and CSA (25 mg, 0.11 mmol) in DCM (0.6 mL). The mixture was stirred at room temperature for 24 h. MeOH (0.1 mL) was added and the solution was stirred for 1 h. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (98/2 hexanes/EtOAc as eluent) to obtain the compound as a pale yellow oil (5 mg, 19% yield, 4:1 Z:E). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (dq, *J* = 13.6, 6.7 Hz, 1H), 5.45 (dt, *J* = 9.1, 6.7 Hz, 1H), 3.75 – 3.55 (m, 1H), 3.35 (m, 1H), 2.23 (t, *J* = 6.9 Hz, 2H), 1.66 (d, *J* = 6.8 Hz, 3H), 1.24 (m, 24H).

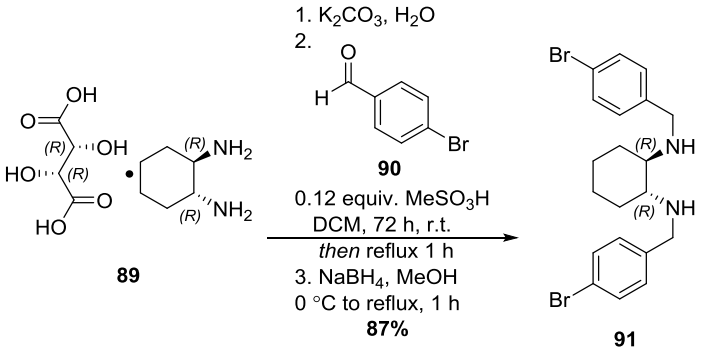


(3R,4S,Z)-2,4-dimethylhept-5-en-3-ol (87): To a glass vial at room temperature was added isobutryaldehyde **83** (7 mg, 97 μmol), synthon ***S,S*-80** (29 mg, 0.11 mmol), and CSA (25 mg, 0.11 mmol) in DCM (0.6 mL). The mixture was stirred at room temperature for 24 h. MeOH (0.1 mL) was added and the solution was stirred for 1 h.

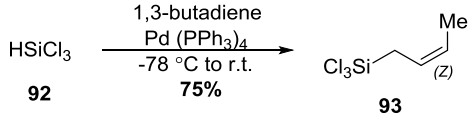
The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (98/2 hexanes/EtOAc as eluent) to obtain the compound as a pale yellow oil (5 mg, 33% yield).



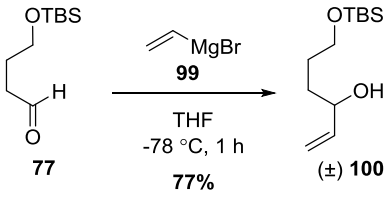
(3*R*,4*R*)-7-((tert-butyldimethylsilyl)oxy)-3-methylhept-1-en-4-ol (*R*,*R*-69): To a solution of (*R*,*R*)-Leighton reagent **88** (312 mg, 0.29 mmol) in DCM (6 mL) at 0˚C was added dropwise TBS aldehyde **77** (100 mg, 0.49 mmol). The reaction mixture slowly warmed to r.t. and stirred for 48 h. The reaction was concentrated under rotary evaporation, and purified by flash column chromatography (97/3 hexanes/EtOAc as eluent) to obtain the compound as a pale yellow oil (84 mg, 66% yield). Spectral data matched those in the literature.[97] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 17.6, 10.4, 7.5 Hz, 1H), 5.14 – 5.03 (m, 2H), 3.67 (t, *J* = 5.4 Hz, 2H), 2.54 (bs, 1H), 2.28 (dt, *J* = 15.7, 7.9 Hz, 1H), 1.78 – 1.55 (m, 4H), 1.46 – 1.35 (m, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H).



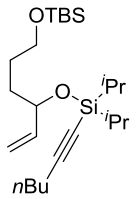
(1*R*,2*R*)-*N*1,*N*2-bis(4-bromobenzyl)cyclohexane-1,2-diamine (91):[100–102] 87% yield. The spectral data matched those in the literature.[101] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 4H), 7.20 – 7.16 (m, 4H), 3.84 (d, *J* = 13.4 Hz, 2H), 3.61 (d, *J* = 13.4 Hz, 2H), 2.27 – 2.16 (m, 2H), 2.14 (dt, *J* = 12.8, 2.5 Hz, 2H), 1.81 (s, 2H), 1.73 (dq, *J* = 9.0, 3.2 Hz, 2H), 1.22 (tt, *J* = 8.7, 2.4 Hz, 2H), 1.02 (dtt, *J* = 15.2, 9.9, 2.8 Hz, 2H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 140.29, 131.59, 129.90, 120.69, 77.01, 61.17, 50.44, 31.81, 25.19. **FT-IR** (neat, cm^{-1}): 3297, 3022, 2922, 2853, 1896, 1591, 1483, 1453, 1340, 1115, 1070, 797. **HRMS** (APCI): Calculated for $C_{20}H_{25}N_2Br_2$ [M+H], 451.30790; found 451.03704.



(Z)-but-2-en-1-yltrichlorosilane (93):[111] 75% yield. Spectral data matched those in the literature.[111] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.81 – 5.65 (m, 1H), 5.48 – 5.34 (m, 2H), 2.36 (d, *J* = 8.1 Hz, 3H), 1.67 (dd, *J* = 6.9, 1.8 Hz, 4H). **FT-IR** (neat, cm^{-1}): 3028, 2977, 2939, 2921, 2897, 1450, 1404, 1394, 1170, 1064, 902, 738, 677, 547.



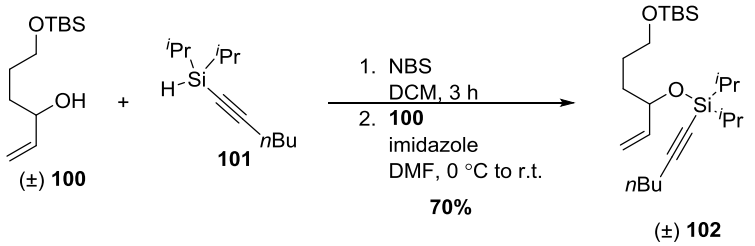
6-((tert-butyldimethylsilyl)oxy)hex-1-en-3-ol (100):[112] Aldehyde **77** (200 mg, 0.98 mmol) was dissolved in THF (3.3 mL) and cooled to -78˚C. Vinylmagnesium bromide (2.8 mL, 1.98 mmol) was added, and the reaction was stirred for 1 h. The reaction was quenched with NH_4Cl and the aqueous and organic phases were separated. The aqueous was extracted with EtOAc, and the combined organic fractions were washed with H_2O (2x) and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude material was purified by flash column chromatography (97/3 hexanes/EtOAc) to obtain the compound as a yellow oil (173 mg, 77% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.88 (ddd, *J* = 16.7, 10.4, 6.0 Hz, 1H), 5.25 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.17 – 5.03 (m, 1H), 4.14 (ddd, *J* = 10.1, 5.0, 3.1 Hz, 1H), 3.67 (qd, *J* = 5.2, 4.7, 1.9 Hz, 2H), 2.68 (d, *J* = 4.0 Hz, 1H), 1.74 – 1.55 (m, 5H), 0.91 (s, 9H), 0.08 (s, 6H).



(±) **102**

Hex-1-yn-1-yldiisopropylsilane (102):[106] To a -78˚C solution of 1-hexyne (86 µL, 0.75 mmol) in THF (0.75 mL) was added *n*BuLi (320 µL) and the reaction was stirred for 15 min. Chlorodiisopropylsilane (136 mg, 150 µL) was added dropwise, and the reaction mixture was warmed to room temperature. At room temperature, the solution was diluted

with Et_2O and washed with sat. aq. NH_4Cl and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to obtain **101** as a clear colorless oil (131 mg, 89% yield). Spectral data matched those in the literature.[106] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.67 (d, *J* = 2.7 Hz, 1H), 2.27 (t, *J* = 7.1 Hz, 2H), 1.57 – 1.49 (m, 2H), 1.49 – 1.38 (m, 2H), 1.06 (dd, *J* = 9.7, 7.0 Hz, 14H, 0.93 (t, *J* = 7.3 Hz, 3H).



10,10-diisopropyl-2,2,3,3-tetramethyl-8-vinyl-4,9-dioxa-3,10-disilahexadec-11-yne (102):[103,105] To a solution of silane **101** (585 mg, 2.38 mmol) in DCM (12 mL) was added NBS (562 mg, 2.38 mmol) in one portion. The reaction mixture was stirred at room temperature for 3 h, and transferred *via* cannula to a solution of alcohol **100** (510 mg, 2.21 mmol) and imidazole (376 mg, 5.53 mmol) in DMF (7.4 mL) at 0˚C. The reaction was stirred 16 h at room temperature, and quenched with 10 mL of H_2O. The mixture was diluted with Et_2O and the organic and aqueous layers were separated. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (98/2 hexanes/EtOAc as the eluent) to obtain the compound as a clear colorless oil (661 mg, 70% yield.) **^{1}H NMR** (400 MHz,$CDCl_3$) δ 5.82 (ddd, *J* = 17.0, 10.4, 6.1 Hz, 1H), 5.18 (dt, *J* = 17.1, 1.6 Hz, 1H), 5.05 (dt, *J* = 10.4, 1.5 Hz, 1H), 4.34 (td, *J* = 5.9, 5.0, 3.2 Hz, 1H), 3.62 (td, *J* = 5.3, 4.5, 2.2 Hz, 2H), 2.33 – 2.19 (m, 2H), 1.66 – 1.37 (m, 11H), 1.04 (ddd, *J* = 13.0, 7.4, 2.5 Hz, 14H), 0.90 (s, 9H), 0.05 (s, 6H).

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