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Nellie Ochs	Date

A menthol derived synthon for preparing homoallylic alcohols bearing three contiguous elements of stereochemistry

And

Progress towards a synthon with two centers of reactivity for the allylation of two different aldehydes

By

Nellie Ochs
Master of Science

Chemistry

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Dean of the James T. Laney School of Graduate Studies

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Date

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An abstract of
A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
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Abstract

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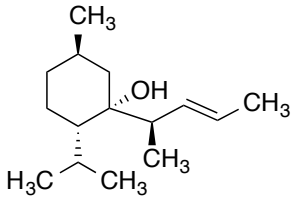
By Nellie Ochs

Homoallylic alcohols with α- and γ- functionality are prevalent in natural products and drug analogs and are valuable building blocks for the syntheses of these compounds. Allylic transfer reactions using organic allyl transfer agents have been developed to circumvent the complexity of synthesis and use of metal catalysis in allylboranes and carbonyl-ene reactions. These organic allyl transfer reactions with aldehydes undergo a 2-oxonia[3,3] sigmatropic rearrangement, proceeding through a pseudo-chair conformation transition state that dictates the stereochemistry of the product. We have synthesized two new synthons, the first for the formation of homoallylic alcohols bearing three contiguous elements of stereochemistry, and the second for the formation of 1,5-diols from two different aldehydes. The first synthon (**1**) has successfully reacted to produce a homoallylic alcohol moiety in >99:1 dr and 2.1:1 er. The er of this reaction suggests that the reaction of synthon **1** with aldehydes may go through an open transition state instead of the sigmatropic rearrangement. Conditions for the synthesis and rearrangement with the second synthon (**2**) are still being optimized. Future work will include the development of chiral aldehydes to react with these synthons and further work in complex synthon development.



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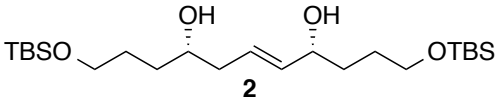

2

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I would also like to thank my committee members, Professor Simon Blakey and Professor Huw Davies for their contributions to my development as a scientist. Not only have they dedicated time to my thesis, but Professor Davies was a wonderful professor that reminded me how cool organic chemistry could be, and Professor Blakey has been a mentor and support system throughout my graduate school application process as well as a friendly face on the sixth floor.

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needed someone to confirm a theory (with a cheerful disposition and a willingness to help even on the worst days). Without them I wouldn't know how to format a ChemDraw image on word, let alone read complex spectra or do difficult reactions.

Finally a thank you to my friends at Emory and beyond, and my family who have all gotten me through stressful times in their own ways. Without them I probably would have dropped out and started filming sharks.

Table of Contents

List of Schemes

Abbreviations

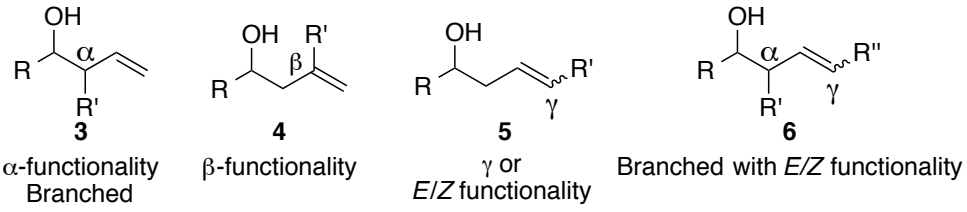
Ac	acetate
APCI	atmospheric pressure chemical ionization
aq	aqueous
BF_3•THF	boron trifluoride tetrahydrofuran complex
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
bpy	bypyridine
bs	broad singlet
$CDCl_3$	deuterated chloroform
CH_3CN	acetonitrile
d	doublet
DCE	dichloroethane
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublets of doublets
ddq	doublet of doublet of quartets
ddt	doublet of doublet of triplets
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
dq	doublet of quartets
dqd	doublet of quartet of doublets
dr	diastereomeric ratio
dtd	doublet of triplets of doublets
er	enantiomeric ratio
Et_2O	diethyl ether
EtOAc	ethyl acetate
FT-IR	Fourier transform infrared spectroscopy
h	hour
HRMS	high resolution mass spectrometry
Hz	hertz
IBX	2-iodoxybenzoic acid
*i*Pr	isopropyl
K_2CO_3	potassium carbonate
$LiAlH_4$	lithium aluminum hydride
M	molar
m	multiplet
*m*CPBA	meta-chloroperoxybenzoic acid
MeOH	methanol
mg	milligrams
$MgCl_2$	magnesium chloride
mL	milliliters
mmol	millimoles
MS	molecular sieves

n-BuLi	*n*- butyllithium
Na_2SO_4	sodium sulfate
$NaHCO_3$	sodium carbonate
NH_4Cl	ammonium chloride
NMR	nuclear magnetic resonance
OTf	trifluoromethanesulfonate
p	pentet
P-2 nickel	nickel boride
p-TSA	*p*-toluenesulfonic acid
Ph	phenyl
Pybox	pyridine bisoxazoline ligand
q	quartet
s	singlet
t	triplet
td	triplet of doublets
tt	triplet of triplets
TBS	tert-Butyldimethylsilyl
TBSCl	tert-Butyldimethylsilyl chloride
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
TIPS	triisopropylsilane
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl

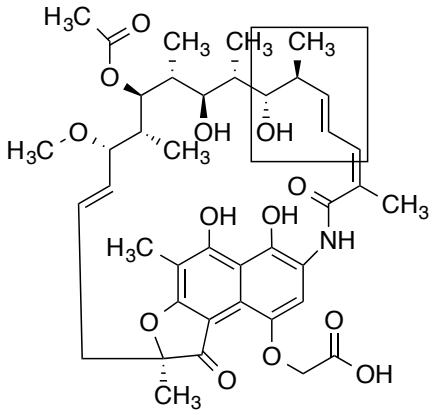
Introduction

Homoallylic alcohols are prevalent in natural products and drug analogs and thus are valuable building blocks for the synthesis of these compounds.[1] Synthesizing these stereochemically complex alcohols with high functionality is valuable for the total syntheses of natural products. Homoallylic alcohols can exhibit α-functionality (**3**), β- functionality (**4**), and γ- functionality (**5**) (Scheme 1). This nomenclature is derived from the position of the alcohol in the molecule. Developing methods to functionalize multiple positions is preferable for total synthesis due to the complexity of natural products and the use of these functional groups in further steps. The methodology discussed herein functionalizes both the α- and γ- positions of homoallylic alcohols (**6**). Rifamycin B (**7**) is one of many polyketide natural products that have homoallylic alcohols with the α- and γ- positions functionalized, showing the importance of these moieties in total synthesis (Scheme 2).

Scheme 1: Homoallylic alcohol functionality.



Scheme 2: Example of a homoallylic alcohol in natural products; Rifamycin B



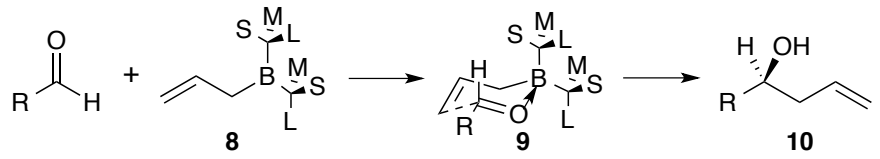
Rifamycin B

7

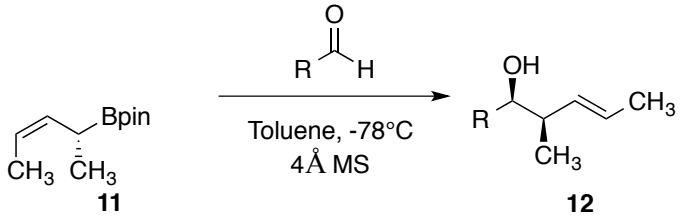
Classically, homoallylic alcohol moieties have been synthesized using carbonyl allylation and carbonyl-ene reactions. Stereochemically complex homoallylic alcohols were originally synthesized with allylborane reagents in 1983,[2] and further development of these reactions allowed access to α- and γ-functionality (Scheme 3).[3,4,5] These reactions are stereoselective due to the 6-member ring chair transition state (**9**). Furthermore, using a diboronate complex, the original transfer reactions can form diol or triols with complex aldehydes (Scheme 3).[6] This recent addition to the methodology for the formation of homoallylic alcohols inspired the second part of this work.

Scheme 3: Carbonyl allylation using allylborane reagents to form stereoselective homoallylic alcohols with γ,α-functionality[2,4] and diboronate for stereoselective formation of triol.[6]

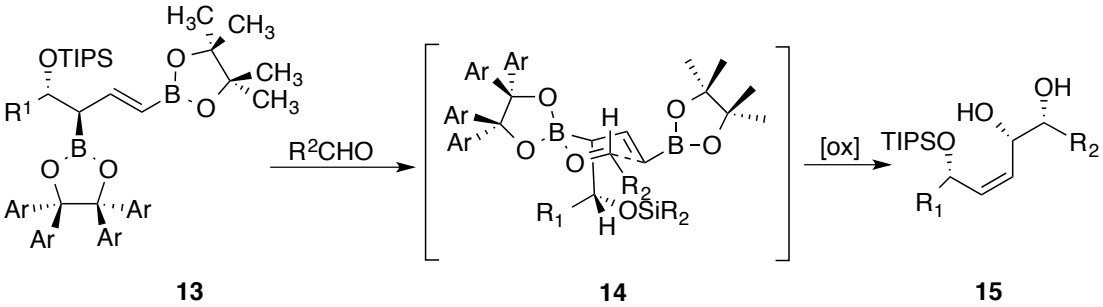
General allylborane reaction:

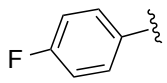


Examples:



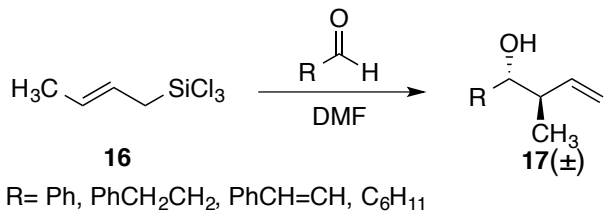
R= CH_3CH_2, $(CH_3)_2CH$, (*E*)-CH_3-CH=CH-CH_2, Ph



Ar= 

Due to the success of allylborane reagents, organosilicon compounds were developed as allyl transfer reagents in order to expand synthetic options (Scheme 4).[7] These techniques have been used successfully in synthesis,[8] however they require stoichiometric chiral allylboranes and allylsilanes which are difficult to synthesize. The byproducts of these reactions can also cause difficulty in purification.

Scheme 4: Carbonyl allylation using allylsilane reagents to form α-functionality.[7]

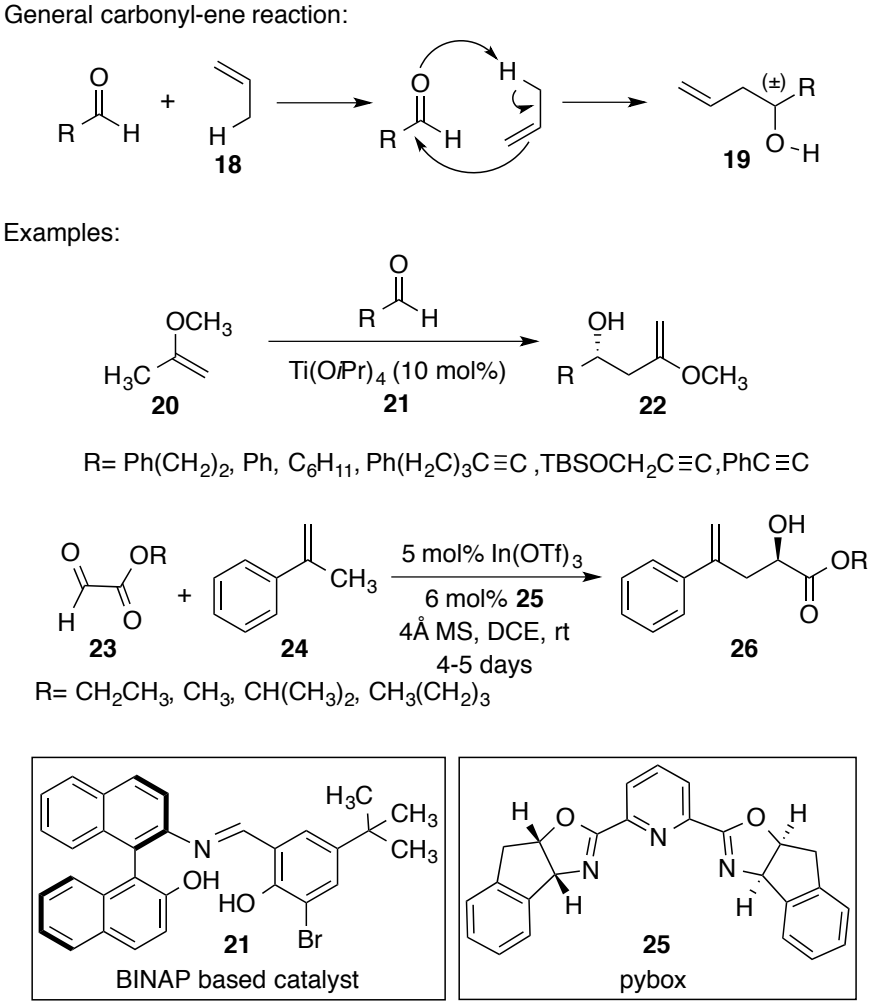


16 **17(±)**

R= Ph, $PhCH_2CH_2$, PhCH=CH, C_6H_{11}

Carbonyl-ene reactions are a widely used technique for synthesizing homoallylic alcohols. A number of metals have been used to catalyze these reactions including Ti[9] and In.[10,11] Loh et al. synthesized homoallylic alcohols with β-functionality using a carbonyl-ene reaction with a pybox catalyst (Scheme 5).[10]

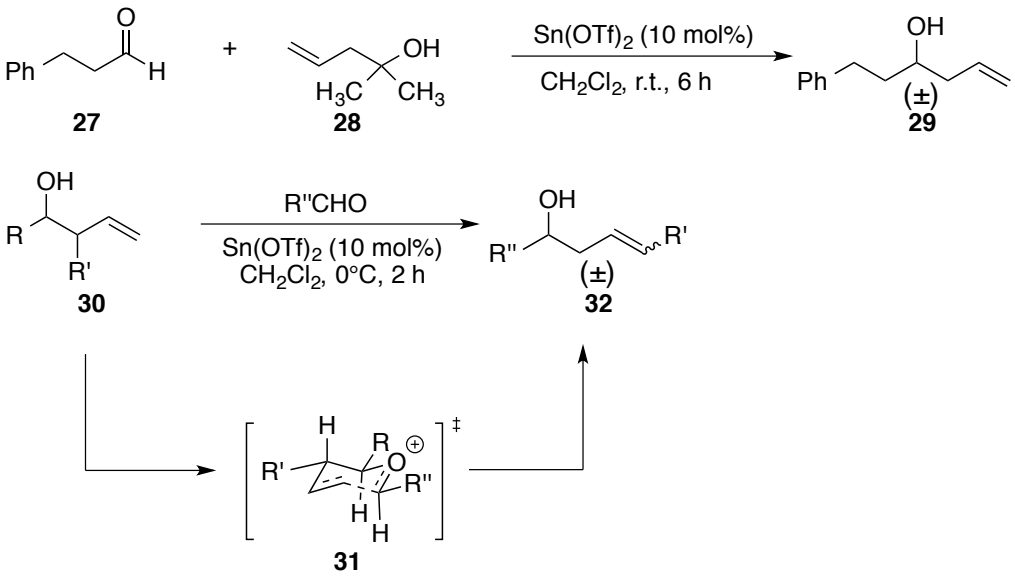
Scheme 5: General carbonyl-ene reaction and examples: carbonyl-ene reaction using a titanium and BINAP-based catalyst[12] and carbonyl-ene reaction using a pybox catalyst.[10]



However, the use of metal catalysts and enantiopure ligands makes these reaction conditions expensive. To avoid these concerns, non-metallic reagents were developed for the formation of these homoallylic alcohol functionalities. In 1998, Nokami developed an allyl transfer reaction for the allylation of aldehydes to form homoallylic alcohols using reagent **28** (Scheme 6).[13] The γ-position is difficult to functionalize using the boronate and carbonyl-ene reactions, and further studies by Nokami expanded the work in organic allyl transfer reagents to functionalize the γ-position (**32**) (Scheme 6).[14] Both

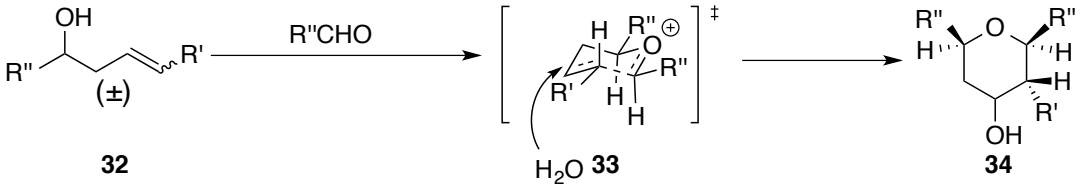
of Nokami's allylation reactions undergo a 2-oxonia[3,3] sigmatropic rearrangement, originally described by Overman,[15] proceeding through a pseudo-chair conformation transition state (**31**) that dictates the stereoselectivity of the reaction (Scheme 6). The 2-oxonia[3,3] sigmatropic rearrangement competes with the Prins cyclization (**33**) in these reactions (Scheme 6). Rychnovsky et al. demonstrated that in simple substrates, the sigmatropic rearrangement is faster than the Prins cyclization.[16] However, it is possible that the product of the oxonia-Cope rearrangement will undergo the Prins cyclization. These two reactions have even been used in tandem to form tetrahydropyranones with quaternary centers.[17] However, by using two equivalents of the allylation reagent and only one of aldehyde, the oxonia-Cope rearrangement is favored and the Prins cyclization is avoided. Most or all of the aldehyde reacts with the synthon before the product is formed. When the allyl reagent is synthesized to functionalize the β-position, the Prins cyclization becomes favored in the original reaction, so functionalizing at that position is the limitation of these allyl transfer reactions.

Scheme 6: Preliminary allyl transfer reactions used for formation of stereoselective homoallylic alcohols with chair transition state,[13,14] and Prins cyclization byproduct.



R=Aryl, alkyl, allyl

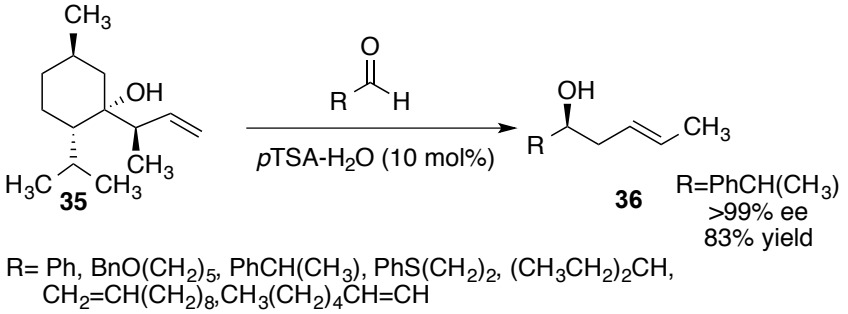
Prins cyclization byproduct:

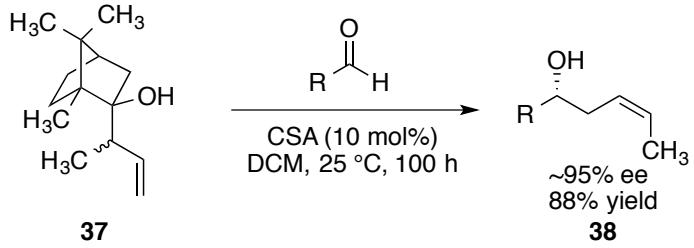


The transformations with the γ-functionalization still required the use of a Lewis acid so further work was done to expand upon these rearrangements to use Brønsted acids and milder conditions. Nokami and Loh developed a family of synthons that uses milder conditions (such as *p*-TSA) for the acid catalysis.[18,19,20] Both (+)-isomenthone and (-)-menthone were used as foundations for synthon development with high stereoselectivity for the rearrangement products with γ-functionality.[18,19] A camphor-based synthon (**37**) was developed which also formed γ-functionality in these products (Scheme 7).[21] In this reaction only the *E* isomer was produced, and the majority of the recovered starting material had the *anti* homoallylic alcohol. It was hypothesized that only the *syn*

homoallylic alcohol was allowed to transfer using the camphor based chiral auxiliary, making it unnecessary to purify synthon **37**. Both the camphor (**37**) and the menthone-based synthons (**35**) used a Grignard reaction to form the synthon for the rearrangement. The camphor reaction was also performed in a one pot synthesis with a cross metathesis to show efficiency and the ease of further functionalizing these products.[22] Loh additionally discovered that linear allyl transfer reagents also work for the 2-oxonia [3,3]sigmatropic rearrangements.[20]

Scheme 7: Allylic transfer reactions with rigid (-)-menthone[18] and camphor[21] based synthons.

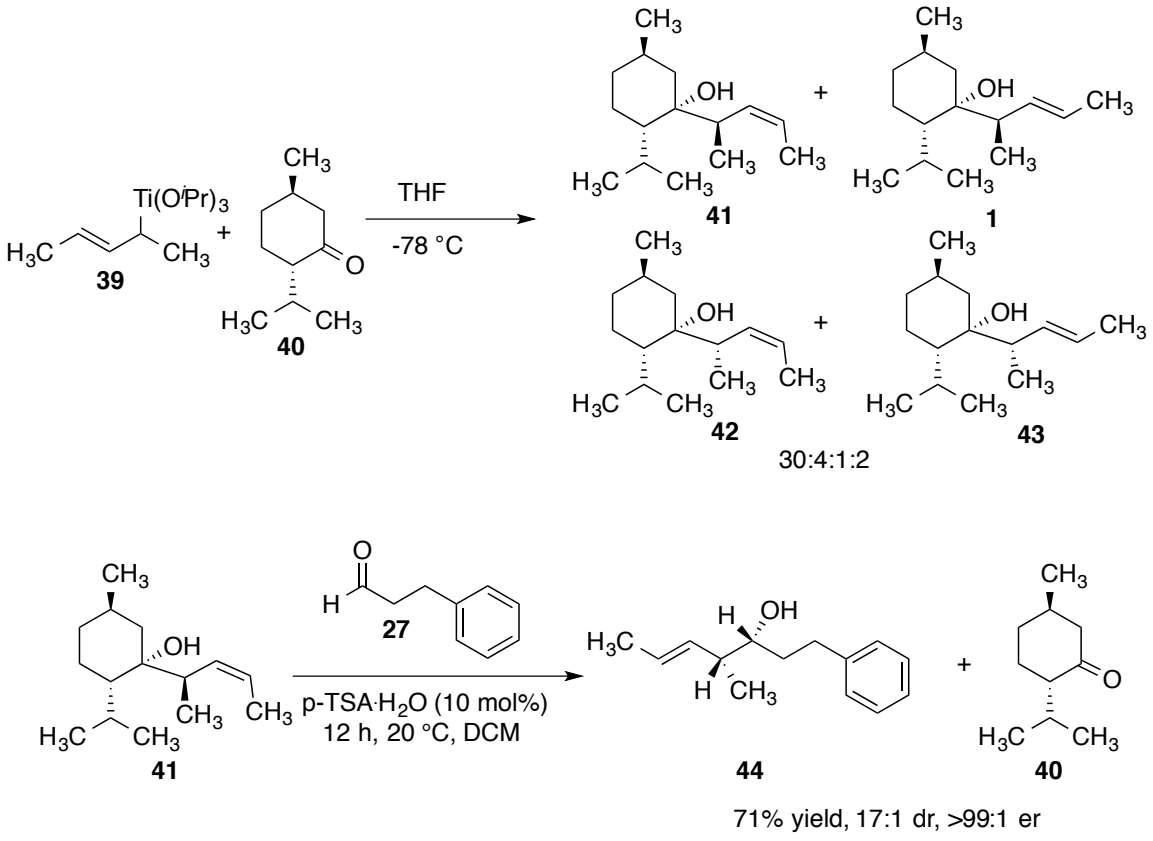




Lee then showed that it was possible to transfer both γ–functionality and α-functionality to form a homoallylic alcohol moiety using a Brønsted acid with the menthone-based synthon (Scheme 8).[23] Functionalizing synthon **41** in the γ-position translated to the α-functionality in the product due to the oxonia -Cope rearrangement

(Scheme 8). Lee used this approach with a menthone-based synthon **41** to perform these rearrangements selectively on a variety of aldehydes (Scheme 8). One of the limitations of this technique is the poor diastereoselectivity of the Grignard reaction in the formation of the synthon. The diastereomers formed must be separated before the synthesis can continue selectively.

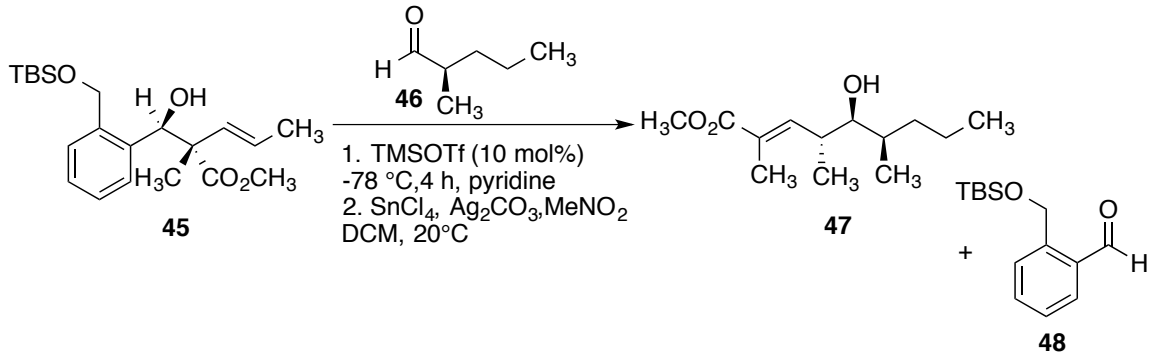
Scheme 8: A (-)-menthone-based synthon for 1,3 dimethylallylation of aldehydes.[23]



The McDonald lab has also done a significant amount of work in this field. Our group showed that it is possible to use a chiral synthon (**45**) for the 2-oxonia[3,3] sigmatropic transformations. Aldehydes with chiral functional groups are reactive and

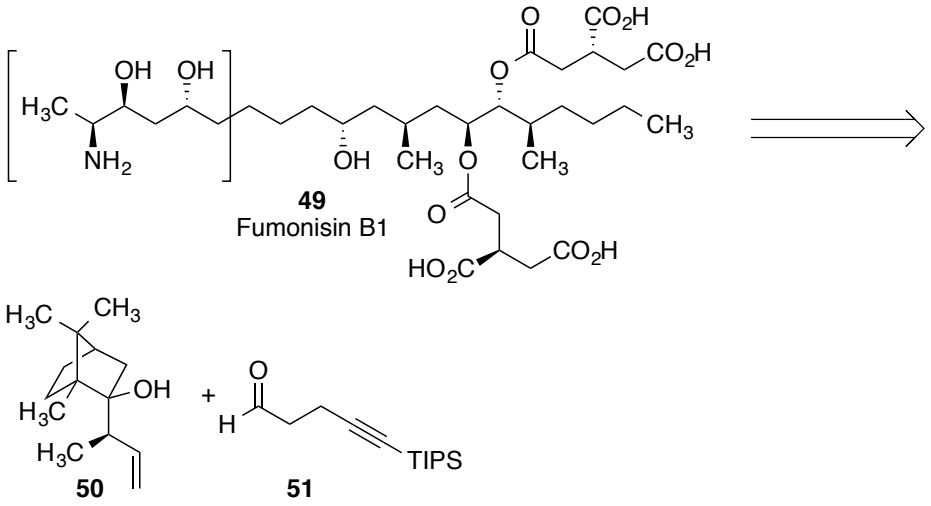
retain their stereochemistry while undergoing these stereoselective rearrangements, which is important for larger natural product syntheses (Scheme 9).[24]

Scheme 9: 2-oxonia [3,3]sigmatropic rearrangement using complex synthon and aldehydes with stereocenters at the α- position.[24]



These allyl transfer reactions have been used successfully in natural product syntheses, as demonstrated by the total synthesis of Fumonisin B_1. The bracketed section of Fumonisin B_1 (**49**) was originally synthesized using the allyl transfer methodology with the camphor synthon developed by the Lee group (Scheme 10).[21, 25]

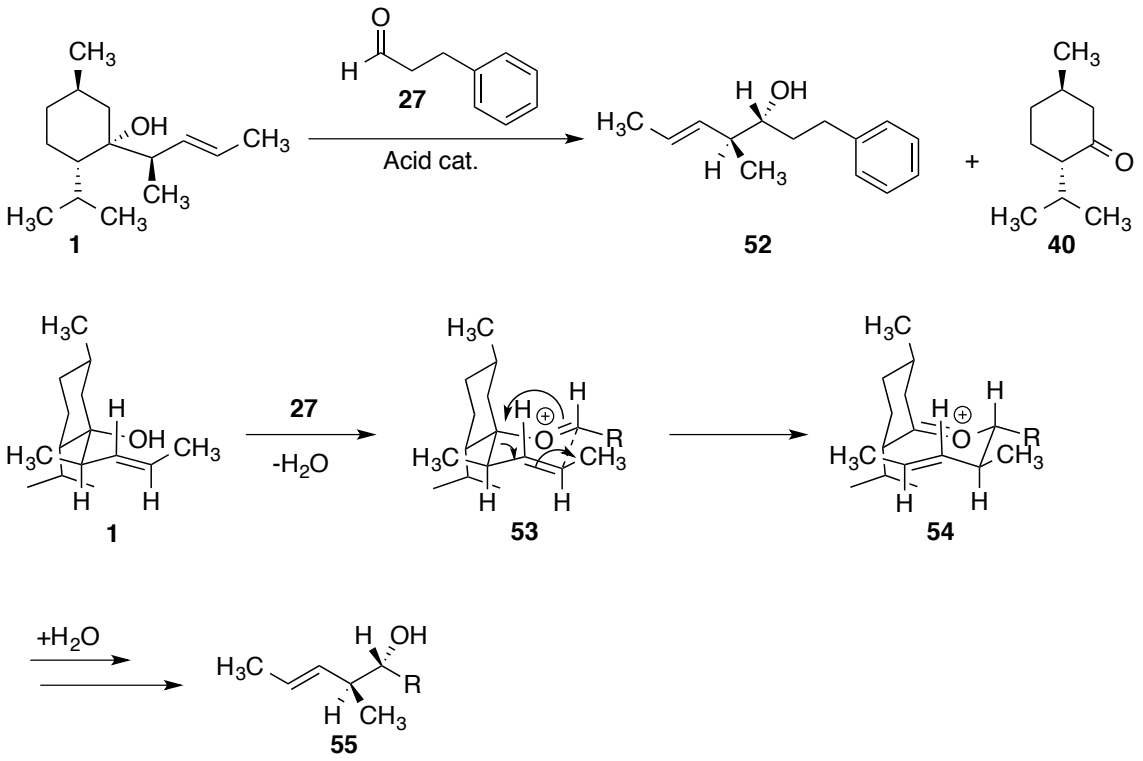
Scheme 10: Application of this work towards total synthesis of natural products and medicinal products.[25]



Extension of current methods for allyl-transfer reactions

The McDonald group proposes extending the current methodology of the allyl transfer reactions to include the *trans*-alkene menthone based synthon **1,** which upon condensation with an aldehyde forms the *anti-trans*-homoallylic alcohol **52** (Scheme 12). The predicted pathway of this reaction is the 2-oxonia[3,3] sigmatropic rearrangement originally suggested by Nokami (Scheme 11).[19] With acid catalysis, the alcohol on synthon **1** adds to the aldehyde and loses water to form compound **53**. This compound sits in a pseudo-chair transition state with the large groups pseudo-equatorial to minimize steric interactions. The oxonia Cope rearrangement occurs to produce compound **54**. Water then adds back into this rearrangement to form the product (**55**) (Scheme 11). This synthon for the dimethylallylation of aldehydes will test the generality of the methodology and extent of the functionality and stereochemistry possible with the allyl-transfer reactions.

Scheme 11: Proposed alternative to Nokami and Lee's (-)-menthone synthons.[23]

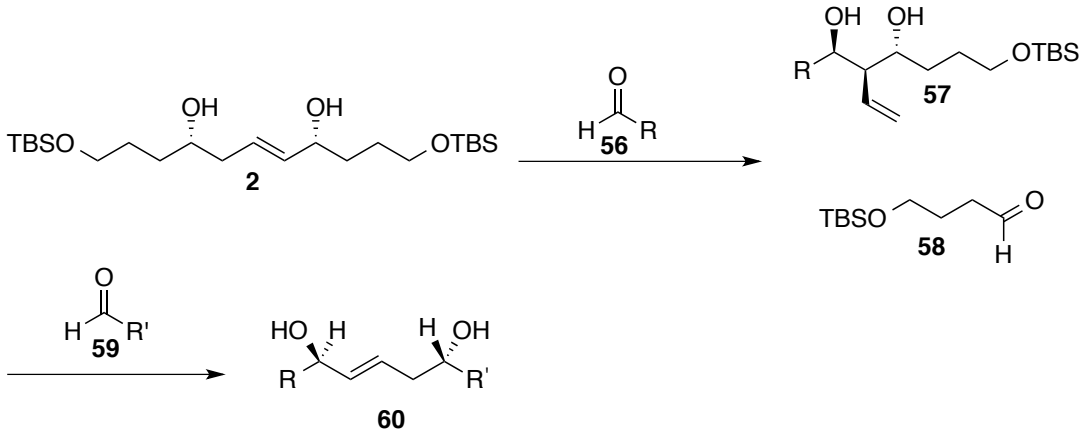


Novel synthon with two centers of reactivity for allyl transfer

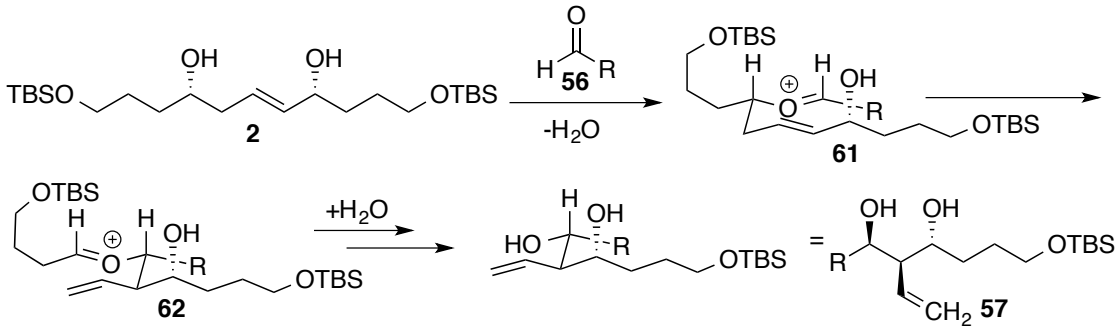
This diboronate complex and linear allyl transfer have inspired the McDonald lab to propose a new synthon (**2**) for the allylation of two aldehydes, resulting in a selective 1,5- diol (Scheme 12). Synthon **2** would undergo two rearrangements, the first with aldehyde **56** and synthon **2**, and the second with aldehyde **59** and the 1,3-diol product of the first rearrangement (**57**). Both rearrangements are shown in Scheme 12. Preliminarily, the homoallylic alcohol on compound **2** adds to aldehyde **56** and water is lost to form compound **61**. This then does a 2-oxonia [3,3] sigmatropic rearrangement and gains water to form product **57**, with the stereochemistry controlled by the chair transition state of the reaction. The homoallylic alcohols on 1,3-diol **57** can then add to

aldehyde **59**. The preferred product is formed when the homoallylic alcohol with the closest proximity to the R group on **57** adds to aldehyde **59**, forming compound **63**. This compound can then undergo the 2-oxonia [3,3] sigmatropic rearrangement to form stereoselective product **60**. The homoallylic alcohol on C1 (with respect to the R group) is more likely to add to the aldehyde due to the acid-catalyzed deprotection of the primary alcohol on the molecule followed by the formation of a 7-member ring acetal on the C3 alcohol. The homoallylic alcohol involved in the acetal (the one farthest from the R group) cannot then add to the aldehyde, favoring product **60**. If aldehydes **56** and **59** are different, it may be possible to put two different R groups on the allylic diol (**60**) through careful timing and use of equivalents, significantly extending this methodology and complexity of desired homoallylic alcohols. For example this approach could be used to tether two larger compounds as one of the final steps in a total synthesis. This will not only add functionality and versatility to this method for use in total synthesis, but a new approach to the techniques described herein.

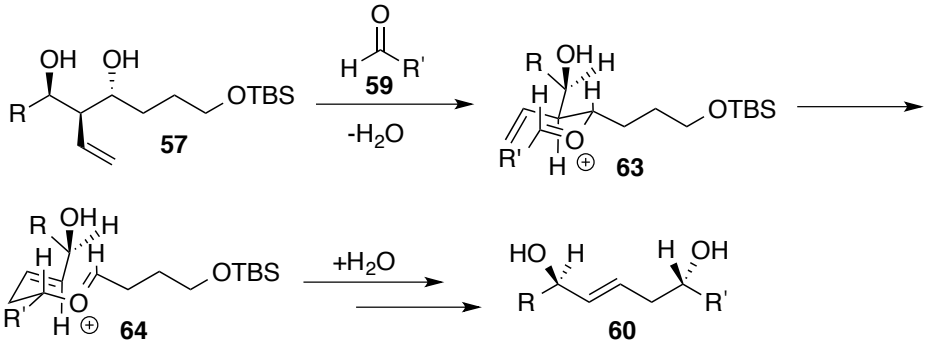
Scheme 12: Proposed organic allyl-transfer reagent for the formation of functionalized 1,5-diols.



First rearrangement between synthon and aldehyde **56**



Second rearrangement between product **57** and aldehyde **59**



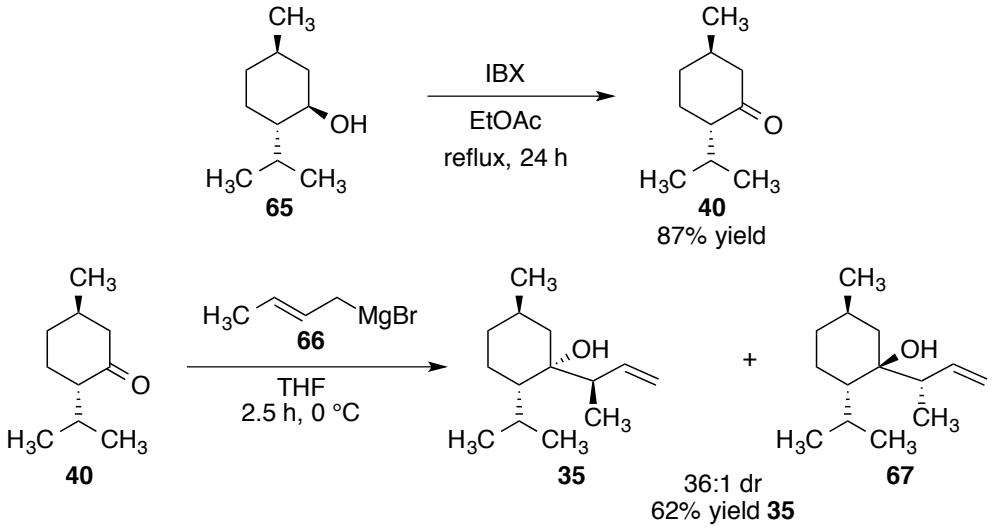
Results and Discussion

Menthol based synthon and rearrangements

This project extends the current methodology of the allyl transfer reactions to include the *trans*-alkene methone based synthon **1,** which upon reaction with an aldehyde forms an *anti*-*trans*-homoallylic alcohol **52**. Preliminary results by Kristen Carroll, an undergraduate in our lab, indicated that these reactions were effective, but they were not optimized for yield, purity or enantioselectivity.

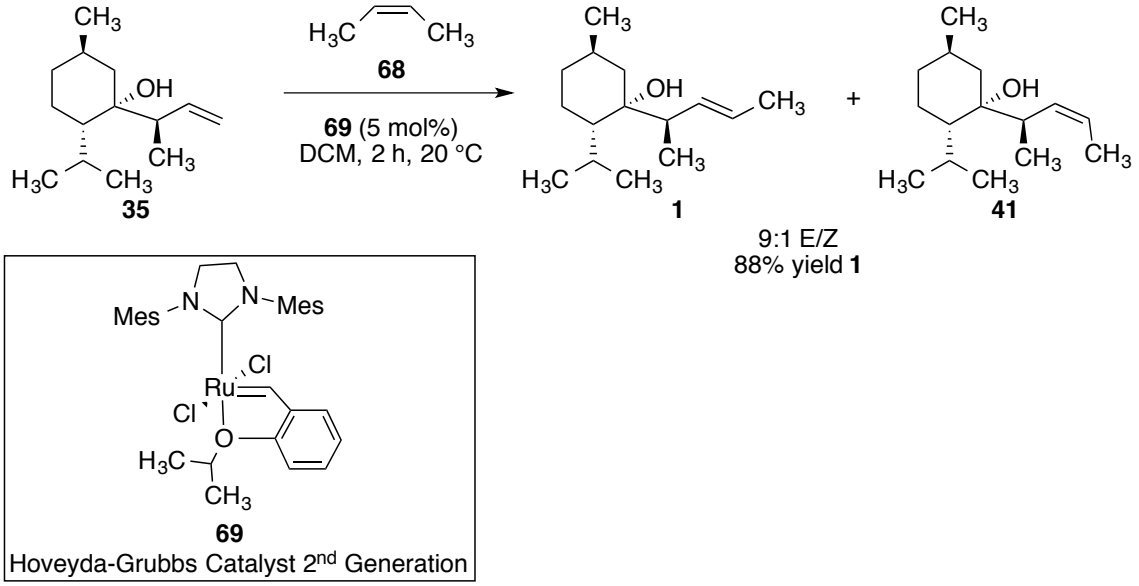
Menthol based synthon **1** was synthesized in 3 steps from (1*R*, 2*S*, 5*R*)-(-)-menthol **65** by oxidation, Grignard reaction, and Hoveyda-Grubbs catalyzed cross metathesis with *cis*-2-butene. Oxidation of **65** with IBX provided (-)-menthone **40**. The reaction of Grignard reagent **66** with compound **40** resulted in formation of alkenes **35** and **67** with a mix of diastereomers (36:1 dr).[23] Compound **35** was isolated by column chromatography, but the other diastereomer **67** was not separable from byproducts and was not carried forward (Scheme 13).

Scheme 13: Oxidation of menthol and synthesis of Nokami synthon (**35**).



Cross metathesis of alkene **35** and excess *cis*-2-butene (**68**) catalyzed by Hoveyda-Grubbs (II) (**69**) afforded a 9:1 ratio of **1**:**41** in 88% yield (Scheme 14).[26] The *trans*- and *cis*- alkenes were not separable using standard purification techniques, so column chromatography with $AgNO_3$ doped silica was used to isolate the pure alkene isomers. To obtain adequate purity, chromatography had to be performed multiple times. If the catalytic loading of this reaction was too high, a byproduct was formed from a cross metathesis between the synthon and part of the catalyst. After extensive experimentation, this loading was optimized to 5 mol % of catalyst.

Scheme 14: Hoveyda-Grubbs cross-metathesis with *cis*-2-butene.

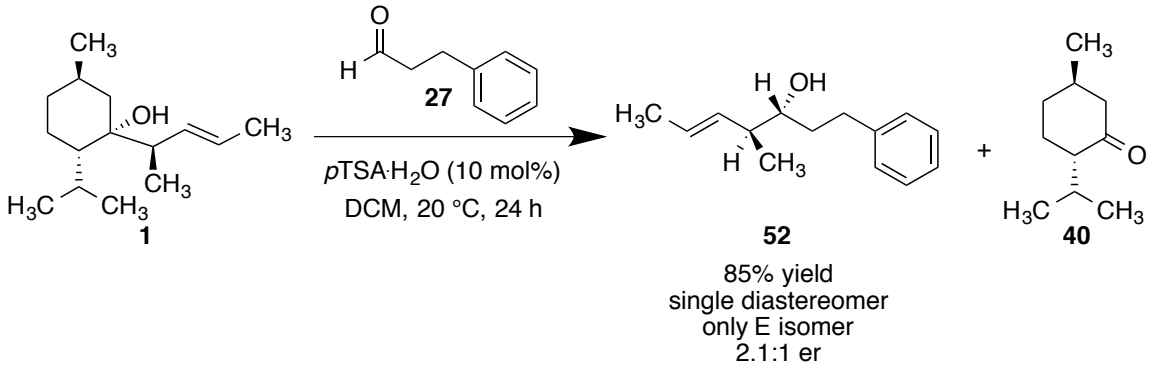


Rearrangement of synthon **1** with 3-phenylpropanal (**27**) and catalytic *p*-TSA afforded one diastereomer of **52** in 58% yield, with no *cis*-alkene present. Unexpectedly the product was in 2.1:1 er as determined by Mosher ester analysis of the secondary alcohol (Scheme 15).[27] The actual diastereomer formed has not been determined due to the difficulty of studying the relationship between the freely rotating alcohol and methyl groups by NMR, so the predicted diastereomer **52** is shown. The er and thus the stereochemical assignment of the alcohol was determined by the Mosher ester analysis (Scheme 16). The rearrangement was performed a number of times and afforded different results due to issues of purity in the synthon.

Initially, this series of reactions was performed without careful diastereomeric separation of the synthon after the Grignard and cross metathesis reactions and afforded the rearrangement product in 3:1 dr, with the major product **52** in a 2.3:1 er. Additional chromatography during the synthesis of compound **1** afforded product **52** with a >99:1 dr,

with 2.1:1 er upon rearrangement. However, the commercial starting material (-)-menthone had an optical rotation of -19.5°, which was significantly lower than the literature value of -31.0°.[19] The reduced enantiopurity of the commercially available menthone resulted in the need to use another starting material. It was replaced by commercial (1*R*, 2*S*, 5*R*)-(-)-menthol, which was oxidized with IBX to the ketone. Careful chromatographic separation of diastereomers was used throughout the synthon development process. However, >99:1 dr and 2.1:1 er was maintained. The optical rotation of the (-)-menthone produced from this method was –26.2°, which indicated that the synthesized menthone was less enantiopure than the (-)-menthone used by Nokami.[19] The er of the product did not improve with the optical rotation of the (-)-menthone used, so the hypothesis is that improving the er to match the value of Nokami's would not change the enantioselectivity of this rearrangement.

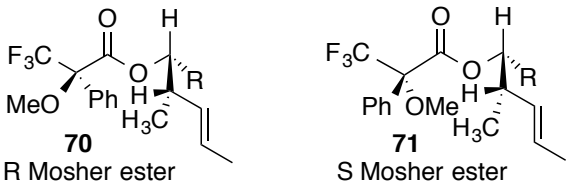
Scheme 15: Rearrangement conditions and results with the (-)-menthone-based synthon.



The conformation used for the Mosher Ester analysis is shown in Scheme 16.[27] The methoxy group is deshielding in NMR, and the phenyl group is shielding. The protons close to the methoxy move downfield when compared to those close to the phenyl group, which can be seen when the R and S Mosher esters are compared. The

integral ratio of these shifted peaks provides the er. The protons used in this analysis were the protons on the stereoselective methyl on carbon 4 (Scheme 16). The 2.1:1 er is derived from the ratio of peaks in the proton NMR.

Scheme 16: Mosher Ester analysis of rearrangement product **51** from synthon **1**.[27]

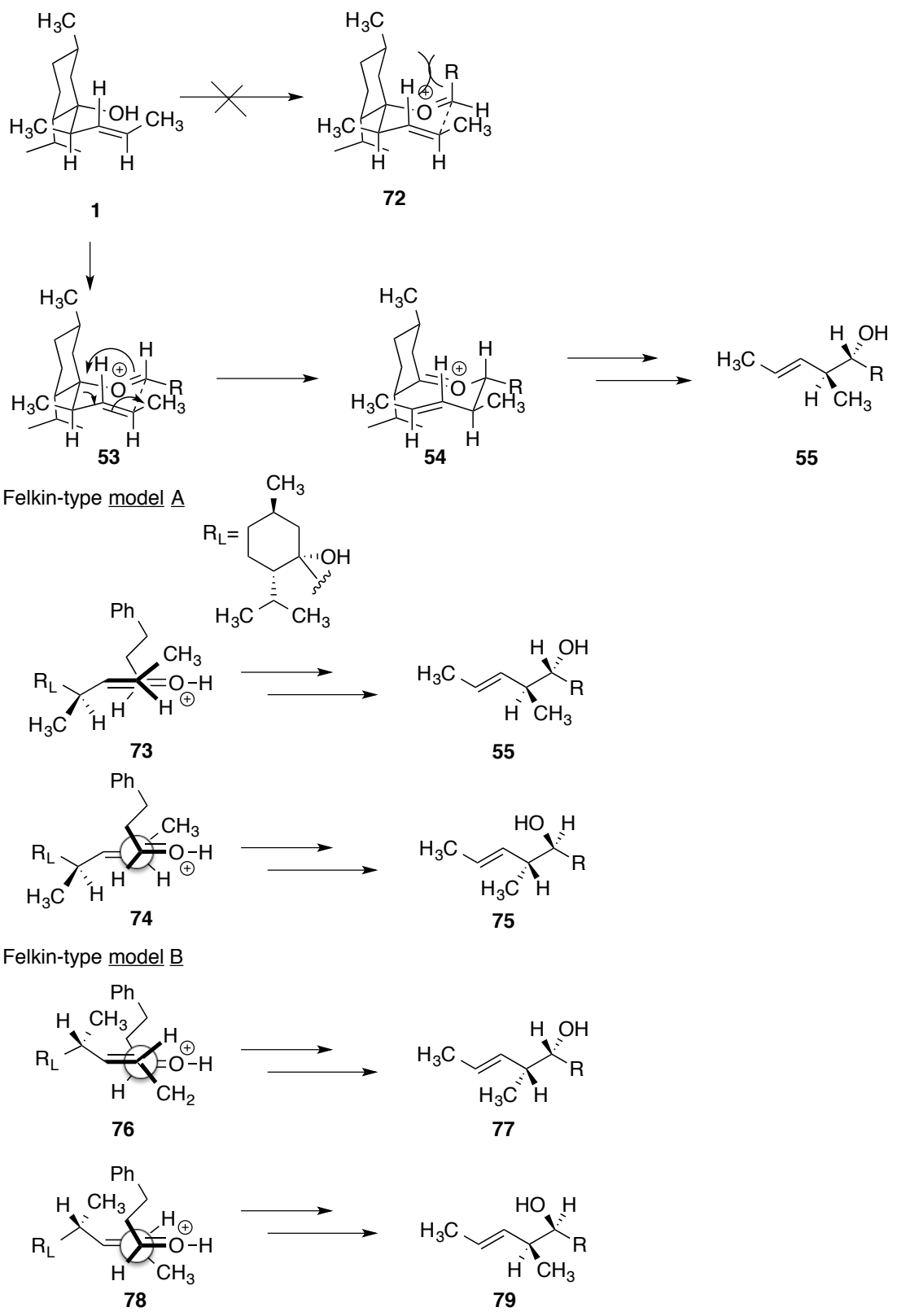


Nokami has proposed a model for the allyl transfer with a pseudo-chair tethered to the synthon backbone.[19] The original model proposed for the rearrangement with synthon **1** was based on the same 6-member ring chair conformation (Scheme 17). The large groups favor pseudo-equatorial positions to minimize steric interactions during the rearrangement, which dictate the stereochemistry in the product. However, based on the low er of the rearrangement, another mechanism may be operating in this reaction.

The second model goes through an open transition state, a proposed alternative mechanism that would account for the lower er. This acyclic Felkin-type model may show the cause of the high diastereoselectivity and lack of enantiocontrol of the reaction (Scheme 17). Depending on the orientation of the synthon, and the face upon which the aldehyde reacts, any of the diastereomers (**55**, **75**, **77** and **79**) can be formed. However, because there is only one diastereomer present, the orientation of the synthon must remain the same, so either model A (**55** and **75**) or model B (**77** and **79**) are the transition states present. In model A, **73** would be preferred over **74** due to the larger aldehyde avoiding steric interactions with the forward facing methyl group on the synthon (Scheme

17). On compound **74** the aldehyde is attacking from the same face as the methyl group, which would lead to the steric interactions mentioned above. In this case product **55** is favored over product **75**, which could explain the 2.1:1 er found in the product. In model B, **77** would be preferred over **76** due to the aldehyde avoiding steric interactions with the backward facing methyl group on the synthon (Scheme 17). On compound **78** the aldehyde is attacking from the same face as the methyl group, which would lead to the same steric interactions mentioned in model A. This model however, would not explain the 2.1:1 er because the favored product has the alcohol in the wrong conformation. The prediction is that model A is the correct Felkin-type model for this open transition-state because it explains the 2.1:1 er of the product (Scheme 17). Alternatively, **55** and **75** could come from equally preferred orientations, in which part of the reaction proceeds through the cyclic transition state, and part of the reaction proceeds through the acyclic transition state, which could also result in the 2.1:1 er observed**.** Identifying the major diastereomer is essential for the determination of the reaction pathway.

Scheme 17: Original proposed model for 2-oxonia [3,3] sigmatropic rearrangement and redesigned Felkin-type model.



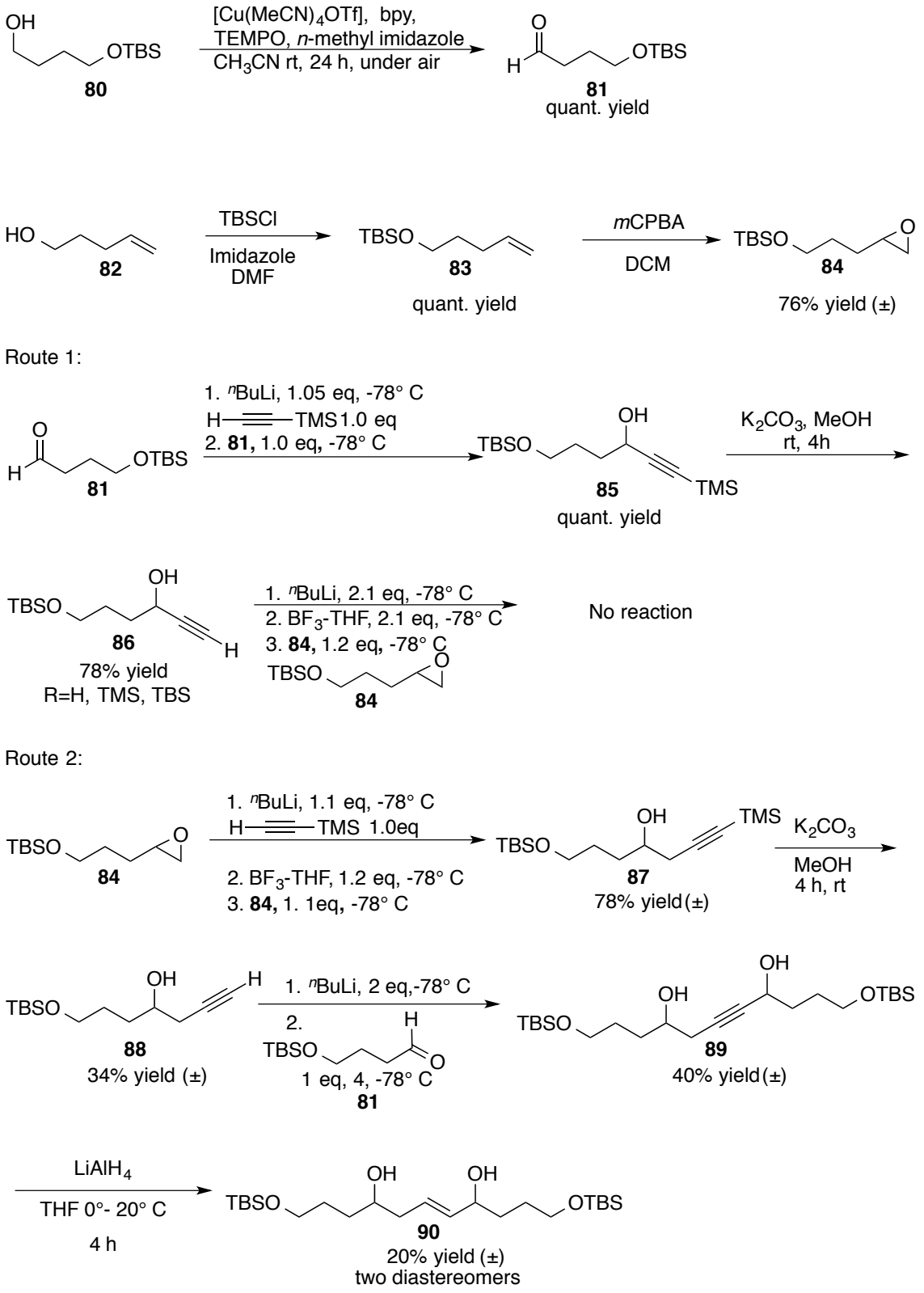
Work was also performed to find a new selective route to the *cis*-synthon in order to compare the Mosher ester spectra. Primarily we attempted to synthesize new *Z*-selective ruthenium based catalysts developed by Grubbs with which to perform the cross metathesis.[28] Due to the expense of the catalysts, and after failing to produce the catalyst after multiple attempts, a new route was attempted. By tethering an allyl group to a silicon reagent and forming an oxy-silyl bond with the alcohol on the menthol-based synthon, it could be possible to do a ring closing metathesis and then break off the silyl group. This would favor the *Z*-conformation due to the tethering of the ring. However, the menthol was too sterically hindered to add a large silyl group, and the addition could not be performed. After attempting the addition with a number of silyl groups, the route was abandoned. While a more selective route to the *Z*-synthon would be an effective tool, the published route with a Grignard reaction is well precedented and the synthon is being developed through that route.

Studies of a synthon with two centers of reactivity

The McDonald lab proposes a new synthon for the allylation of aldehydes, resulting in a selective 1,5- diol. This synthon will undergo sequential rearrangements, for the allylation of two aldehydes. Initially, the synthon for the allylation of two aldehydes was synthesized as a racemate to probe reactivity (Scheme 18). Monoprotected diol **80** was oxidized to aldehyde **81** in quantitative yield using an aerobic copper-based procedure developed by Stahl.[29] Penten-5-ol **82** was TBS-protected in quantitative yield to afford compound **83** and subsequently epoxidized using *m*CPBA to obtain racemic epoxide **84** (Scheme 18).[30] Initially aldehyde **81** was coupled to TMS-acetylene using *n*-BuLi.[31] The larger alkyne **85** was then deprotected to yield compound

86 and coupled to epoxide **84** through the lithium acetylide (Scheme 18).[32] The coupling reaction did not proceed under the conditions shown and starting material was recovered. The alcohol on alkyne **86** was protected with TBS and TMS to improve the reaction conditions, and significant work was done optimizing the equivalents of each reagent in this reaction. Due to the free alcohol, more than two equivalents of *n*-BuLi and BF_3•THF were required for the reaction, however many different equivalencies were explored. Despite this, the alkyne never successfully added to the epoxide. The deprotonation was occurring, but addition of the epoxide did not occur and starting material was recovered. This may be attributed to the complexity of the alkyne. Epoxide-alkyne couplings are significantly less reactive than aldehyde alkyne couplings, so coupling a complex alkyne with a free alcohol present would be significantly more difficult with the epoxide than the aldehyde. To circumvent this problem, the order of reactions was altered. Epoxide **84** was coupled to TMS-acetylene to produce compound **87**, which was then deprotected to obtain alkyn-ol **88** (Scheme 18).[32]

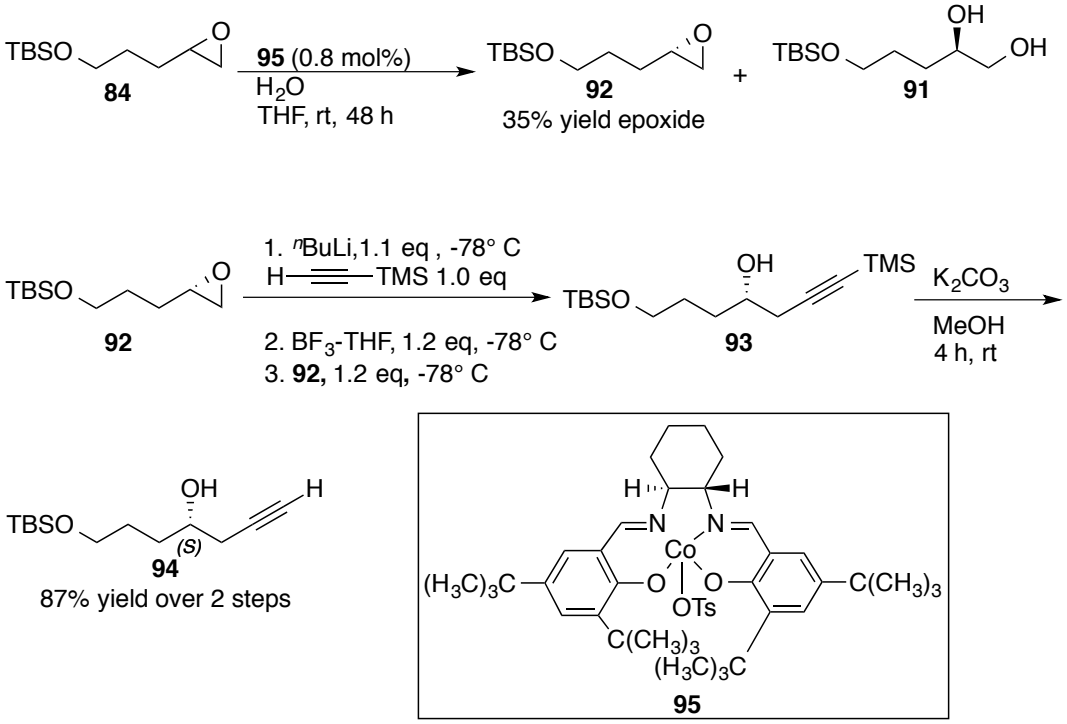
Scheme 18: Synthesis of racemic synthon for proof of concept.



Alkynol **88** was successfully coupled to aldehyde **81** using *n*-BuLi to obtain the racemic diol **89**.[31] When the aldehyde was added quickly to the reaction it formed primarily an aldol product, so a slow addition of **81** to the alkyne was extremely important to optimize yield of **89**. Alkyne **89** was reduced to alkene **90** using lithium aluminum hydride,[33] which also partially deprotected the TBS groups forming the triol and tetraol byproducts, which lowered the yield of compound **90** (Scheme 18).

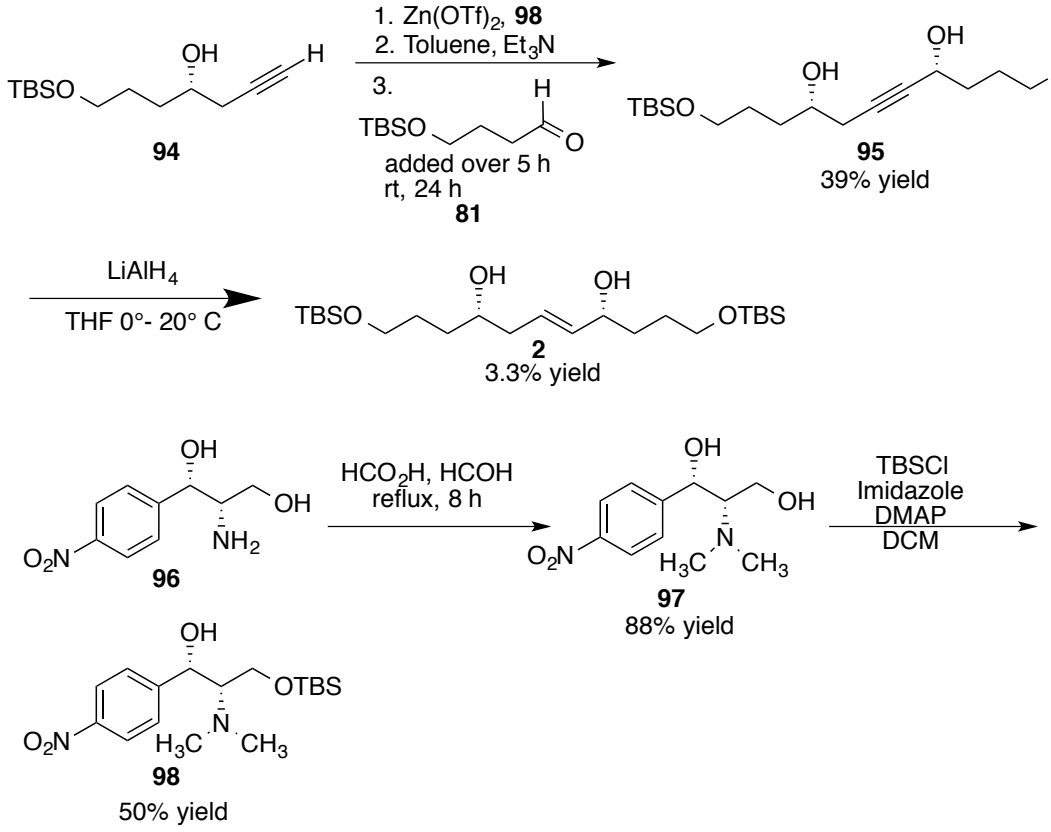
After forming compound **90** as a racemate and showing proof of concept, synthon **2** was synthesized stereoselectively. Epoxide **84** was resolved using the Jacobsen cobalt catalyst **95** to *S*-epoxide **92** in a 35% yield. [34] Epoxide **92** was subsequently coupled to TMS-acetylene using *n*-BuLi and BF_3-THF to produce alkyne **93**.[32] Alkyne **93** was deprotected to obtain compound **94** in 87% yield over two steps (Scheme 19).

Scheme 19: Synthesis of the first chiral center in synthon **2**.



Compound **94** was coupled to aldehyde **81** using an enantioselective carbon-carbon bond forming addition procedure developed by Carreira et al. with a ligand (**98**) developed by Jiang et al. to produce alkyne diol **95** (Scheme 20).[35,35b] This was reduced to alkene **2** in 3.3% yield using lithium aluminum hydride.[33] The allylic and homoallylic alcohol er will be determined using further Mosher ester analysis. The lithium aluminum hydride reaction caused the TBS groups to hydrolyze, and the triols and tetraol were formed, lowering the yield of the reaction significantly. Despite altering reaction conditions and attempting the reaction with RED-AL, this alkene could not be formed in high yield.

Scheme 20: Synthesis of the second chiral center in synthon **2**.



The synthon could not be produced in large enough quantities to perform an acid catalyzed rearrangement. Thus, due to the low yield in the reduction step of this synthesis, the synthesis has been modified to produce the *cis*-alkene using a P-2 nickel reduction while exploring other routes to the *trans*-alkene. This work is still in progress.

The proposed rearrangement models for the *trans*-synthon is also based upon Nokami's work.[13] As was stated, the homoallylic alcohol on **2** adds to the aldehyde, forming intermediate **61**, and the [3,3]-sigmatropic rearrangement then proceeds in the pseudo-chair conformation as shown. The *trans*-alkene model shows the formation of diol **57.** If the allylic alcohol in compound **2** adds to the aldehyde, the rearrangement cannot be performed due to lack of possible electron movement between bonds, so **57** is the favored product. The second part of this rearrangement is a reaction between a second aldehyde **59** and **57** (Scheme 13).

If successful, this reaction would allylate two separate aldehydes and tether them together, making it a synthetically useful methodology. Preliminarily this reaction will be performed with a single aldehyde to test the reactivity of both rearrangements in one pot. Testing different equivalents of synthon and aldehyde will be necessary both to optimize production of **60**, and to determine the time needed to form and isolate intermediate **57**. If isolated this intermediate will give important information on the selectivity and mechanism of this reaction, and may confirm the predicted model shown. The rearrangement will then be done with two separate aldehydes to determine whether or not they can be tethered together. This reaction will afford a synthetically useful moiety and expands upon the previous methodology developed for these rearrangements.

Conclusion and future directions

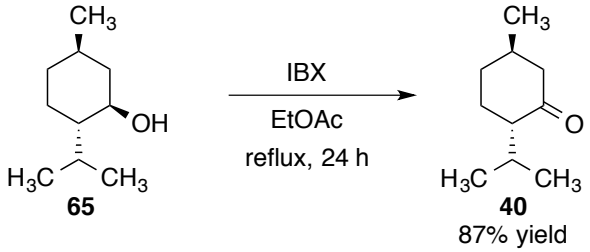
The high diastereoselectivity of synthon **1** as a reagent for the dimethylallylation of aldehydes demonstrates the versatility of this methodology for the formation of stereoselective homoallylic alcohols with α- and γ- functionality. However, the 2.1:1 er was inconsistent with expectations from the results with similar synthons, and suggests that the 2-oxonia[3,3] sigmatropic rearrangement may not be the dominant mechanism for the *trans*- synthon. The low er may be a result of an acyclic transition state proceeding through the Felkin-type model. This model and competitive reaction show a limitation of this methodology for high enantioselectivity. The synthon will be compared more closely to the successful rearrangement of similar compounds with high er in order to determine the direct cause of the lack of enantiomeric control.[23] It is clear that manipulating the methodology of these rearrangements to form multiple homoallylic alcohol derivatives is difficult. This information will help with the design of future synthons for the dimethylallylation of aldehydes.

Synthon **2** will demonstrate the breadth of this methodology in that it functionalizes the two aldehydes with an alkene, 1,5 diol and two protected primary alcohols for further reactivity in larger syntheses. Due to the low yield of the reduction step in the formation of this synthon, it will be produced with a *cis*-alkene functionality while determining a new route to the *trans*-alkene functionality (**2**). Both of these moieties may give interesting rearrangement results, which would be valuable for total syntheses. If this rearrangement is successful and can be optimized, it will be valuable to test this methodology with more complex aldehydes to ensure and expand upon the versatility of these methods in larger syntheses. It would also be worthwhile to test

different protecting groups on the primary alcohols on synthon **2,** as well as performing the rearrangement without protecting groups. This will ensure the versatility of the methodology for complex natural product synthesis.

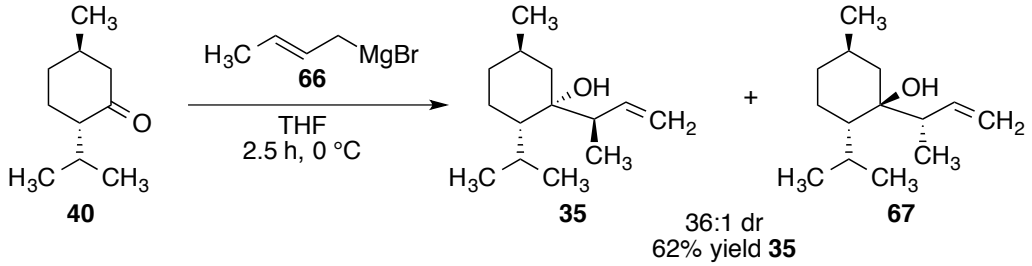
Experimental details

All experiments were carried out under Argon in oven-dried round bottom flasks unless otherwise specified. All reagents were purchased from Sigma-Aldrich unless synthesized during these experiments or otherwise specified. All solvents used in reaction were anhydrous and dried with 3 Å MS (10-12 Mesh) purchased from Sigma-Aldrich. Solvents used in workups, extractions and column chromatography were received from Aldrich and not purified or dried before use. Analytical thin layer chromatography (TLC) on precoated glass backed 0.25mm silica gel 60 plates was used to measure reaction progress and determine reaction time. Column chromatography was performed solely on P60 silica gel (40-63 μm, 60 Å) unless otherwise stated. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR were recorded at 400 MHz, 100 MHz and 400 MHz respectively on a VNMR 500, a Varian Inova 400 or a Mercury 300 spectrometer at room temperature in $CDCl_3$ with internal $CHCl_3$ as the standard reference at 7.26 ppm (unless otherwise stated). Mass spectra were recorded on a Finnigan LTQ FTMS Mass spectrometer at Emory University.



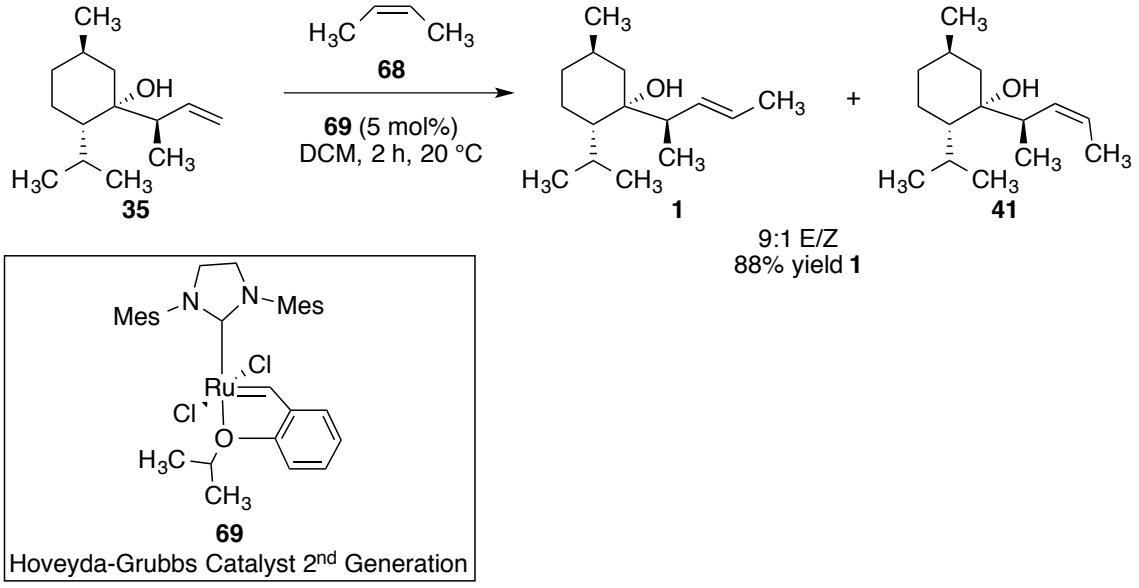
(-)-menthone[36]: To a solution of (1*R*, 2*S*, 5*R*)-(-)-menthol **65** (6.00 g, 38.4 mmol) in EtOAc (274 mL) was added IBX (32.3 g, 115.2 mmol) at room temperature. The IBX was prepared using methodology developed by Finney.[36] Temperature was slowly raised

to 80 °C and reaction was refluxed for 3 h. The reaction was cooled to room temperature, and filtered through a coarse glass frit. The filter was washed with 3 x 80 mL EtOAc and combined filtrates were concentrated *in vacuo*. Crude material was purified by column chromatography (5% EtOAc in hexanes) to afford the desired product **40** as a clear colorless oil (5.17 g, 87% yield). Spectra matched that of known compound.[36] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.36 (m,1H), 1.86- 2.13 (m, 6H), 1.35 (m, 2H), 1.00 (dd, J = 6.2, 0.6 Hz, 3H), 0.87 (ddd, J = 24.2, 6.8, 0.6 Hz, 6H); **$[\alpha]_D^{25}$** = -26.2° (c = 1.00, $CHCl_3$), literature value **$[\alpha]_D^{25}$** = -31.0° (c = 1.00, $CHCl_3$).



(1*R*,2*S*,5*R*)-1-((*R*))-but-3-en-2-yl)-2-isopropyl-5-methylcyclohexan-1-ol[23]: To solution of (-)-menthone **40** (5.18 g, 33.6 mmol, 5.79 mL) at 0 °C in THF (33.6 mL) was added but-2-enylmagnesiumchloride **66** in THF (50.4 mmol, 0.248 M, 100 mL). Reaction mixture was stirred for 2 hours and quenched with EtOAc (40 mL). Aqueous layer was extracted with EtOAc (3 x 30 mL), and the combined organic fractions were washed with brine (30 mL). The organic fraction was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Crude was purified by column chromatography (1% EtOAc in hexanes) to afford a clear oil **35** (4.29 g, 62%). Crude NMR indicated diastereomeric ratio, but diastereomers were separated by column chromatography. Spectra matched that of known compound.[19] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.87 (ddd, J = 16.7, 10.6, 8.3 Hz,

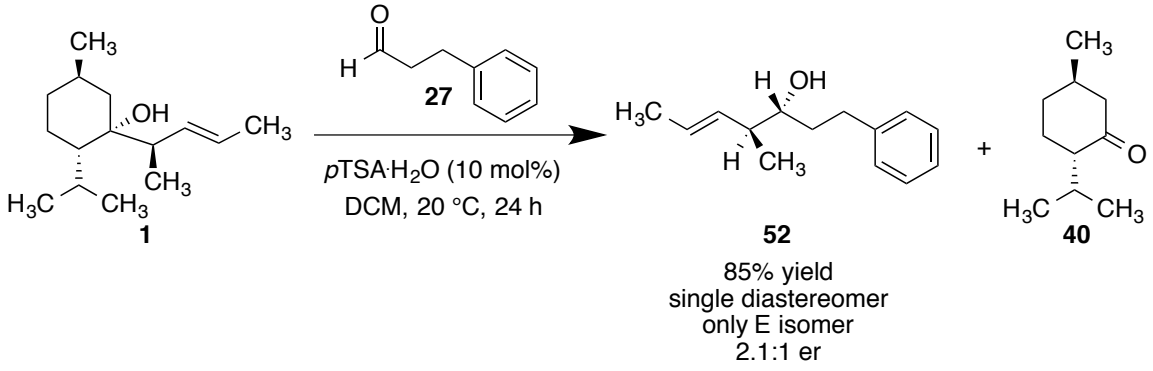
1H), 5.12 (m, 1H), 5.11 (ddd, *J* = 9.8, 2.1, 0.9 Hz, 1H), 2.59 (p, *J* =7.2 Hz, 1H), 2.08 (ddd, *J* = 13.7, 6.8, 1.8 Hz, 1H), 1.74 (m, 2H), 1.50 (m, 2H), 1.37 (m, 1H), 1.33 (dd, *J* = 3.7, 2.2 Hz, 1H), 1.26 (m, 1H), 0.96 (d, *J* =7.0 Hz, 3H), 0.91 (dd, *J* = 6.9, 2.1 Hz, 6H), 0.85 (d, *J* =6.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.8, 116.6, 77.0, 45.9, 45.2, 41.4, 35.2, 27.5, 25.0, 23.4, 22.6, 20.5, 18.0, 14.7; **HRMS (APCI):** *m/z* calcd. for $C_{14}H_{26}ONa$ ($M+H^+$) 233.1876, found 233.1881; **$[\alpha]_D^{25}$** = 21.0° (c = 1.00, $CHCl_3$), literature value **$[\alpha]_D^{25}$** = 27.4° (c = 1.00, $CHCl_3$).[19]



(1*R*, 2*S*, 5*R*)-2-isopropyl-5-methyl-1-((*R,E*)-pent-3-en-2-yl)cyclohexan-1-ol:

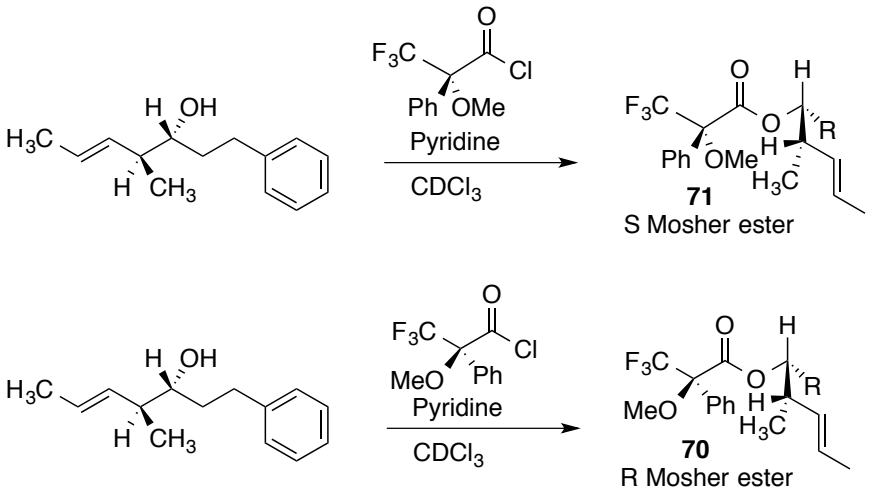
Following the procedure developed by Grubbs and Hoveyda[26], to a solution of (1*R*,2*S*,5*R*)-1-((*R*))-but-3-en-2-yl)-2-isopropyl-5-methylcyclohexan-1-ol **35** (0.895 g, 4.26 mmol) in DCM (4.0 mL) at -78 °C was added the Hoveyda Grubbs (II) catalyst **69** (0.18 g, 2.13 mmol) followed by cis-2-butene **68** (7.06 g, 12.6 mmol, 11.69 mL). Reaction mixture was warmed to room temperature and stirred for 20 h. Reaction mixture was then cooled to -78°C, opened and allowed to warm to room temperature. Product was

purified by column chromatography with silica impregnated with 25% silver nitrate in 10% EtOAc in hexanes to afford clear oil **1** (.95 g, 88% yield).[37] **^{1}H NMR** (400MHz, $CDCl_3$) δ 5.58 (dq, J=15.2, 6.2 Hz, 1H), 5.43 (ddq, J= 15.2, 8.8, 1.5 Hz, 1H), 2.52 (m, 1H), 2.07 (dq, J=7.0, 1.9 Hz, 1H), 1.70 (m, 5H), 1.50 (m, 2H), 1.38 (d, J= 1.2 Hz, 1H), 1.35 (d, J=1.4 Hz, 1H), 1.23 (m, 2H), 0.96 (m, 1H), 0.93 (s, 1H), 0.90 (m, 7H), 0.85 (d, J=6.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 133.2, 128.0, 76.2, 46.1, 44.5, 41.8, 35.5, 27.7, 25.2, 23.6, 22.9, 20.8, 18.3, 15.6; **HRMS (APCI):** *m/z* calcd. for $C_{15}H_{28}ONa$ ($M+H^+$) 247.203, found 247.203; $[\alpha]_D^{25} = 13.2°$ (c = 1.00, $CHCl_3$).



(3*R*, 4*S*, *E*)-4-methyl-1-phenylhept-5-en-3-ol: Following the procedure developed by Nokami[18], to a solution of (1*R*, 2*S*, 5*R*)-2-isopropyl-5-methyl-1-((*R,E*)-pent-3-en-2-yl)cyclohexan-1-ol **1** (0.132 g, 0.59 mmol) and 3-phenylpropanal **27** (0.04 g, .0.29 mmol, 0.038 mL) in DCM (2 mL) was added *p*-TSA (0.011 g, 0.06 mmol) at room temperature. Reaction mixture quenched with Na_2CO_3 (5 mL) after 20 h. Aqueous layer was washed with EtOAc and combined organic fractions were washed with sodium carbonate, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Crude was purified by column chromatography (2% EtOAc in hexanes) to afford **52** as a light yellow oil (0.050 g, 85% yield). Proton NMR spectra showed single diastereomer and only *trans*-alkene. **^{1}H**

NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.24 (m, 3H), 5.58 (dqd, *J* = 15.5, 6.4, 0.9 Hz, 1H), 5.36 (ddq, *J* =15.4, 8.5, 1.6 Hz, 1H), 3.38 (ddd, *J*=9.3, 6.3, 3.2 Hz, 1H), 2.88 (ddd, *J* = 13.7, 10.3, 5.2 Hz, 1H), 2.70 (ddd, *J* = 13.7, 10.0, 6.5 Hz, 1H), 2.19 (m, 1H), 1.87 (dddd, *J* = 13.6, 10.0, 6.5, 3.2 Hz, 1H), 1.72 (m, 3H), 1.65 (m, 1H), 1.40 (s, 1H), 1.03 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.7, 133.0, 128.7, 128.6, 127.7, 125.92, 74.4, 43.6, 36.4, 32.4, 18.3, 17.0; $[\alpha]_D^{25}$ = 1.0° (c = 1.00, $CHCl_3$). **HRMS (APCI):** *m/z* calcd. for $C_{12}H_{20}ONa$ ($M+H^+$) 227.141, found 227.141; $[\alpha]_D^{25}$ = 1.0° (c = 1.00, $CHCl_3$).



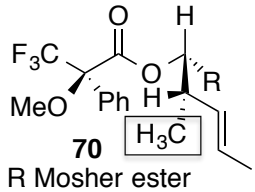
Mosher esters: Following the procedure developed by Shao,[27] to two NMR tubes with $CDCl_3$ and 5 mg of compound **51** were added 3 drops of deuterated pyridine. 2-3 drops of R acid chloride were added to one tube to form the S-ester and 2-3 drops of S acid chloride were added to the other to form the R-ester. These reactions proceeded at room temperature for 24 h.

To two NMR tubes with $CDCl_3$ and 5 mg of compound **51** were added 3 drops of deuterated pyridine. 2-3 drops of R acid chloride were added to one tube to form the S-

ester and 2-3 drops of S acid chloride were added to the other to form the R-ester. These reactions proceeded at room temperature for 24 h.

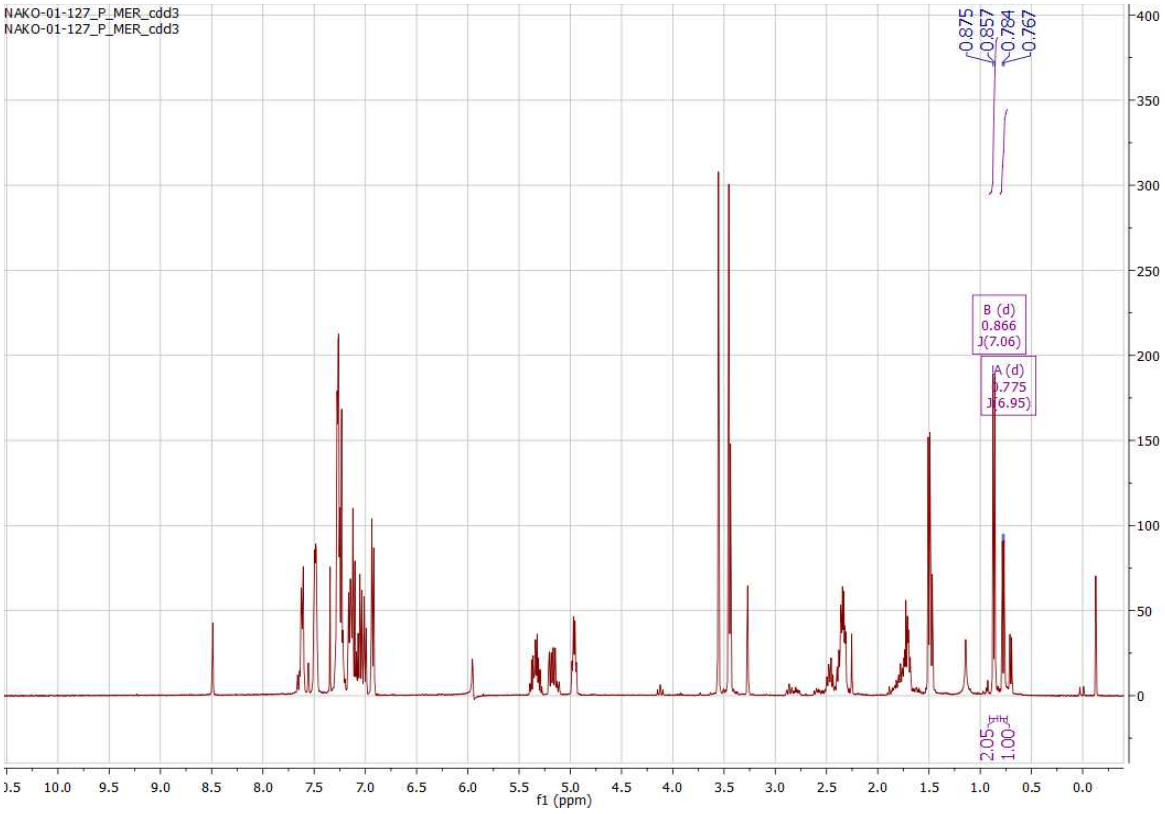
^{1}H NMR (400 MHz, $CDCl_3$)

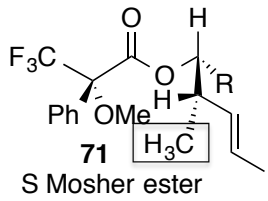
Protons analyzed were the methyl protons circled below, with 2.05:1 and 2.13:1 ratios respectively as shown in NMR spectra.



70

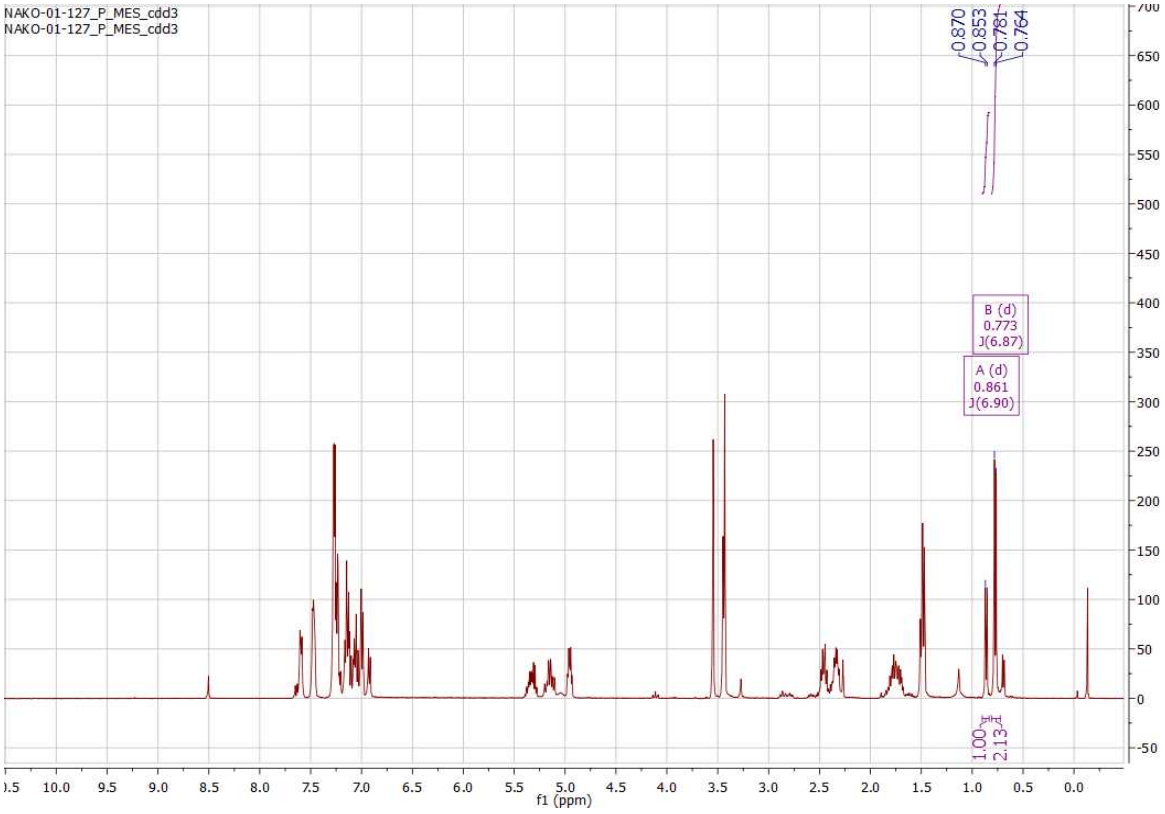
R Mosher ester



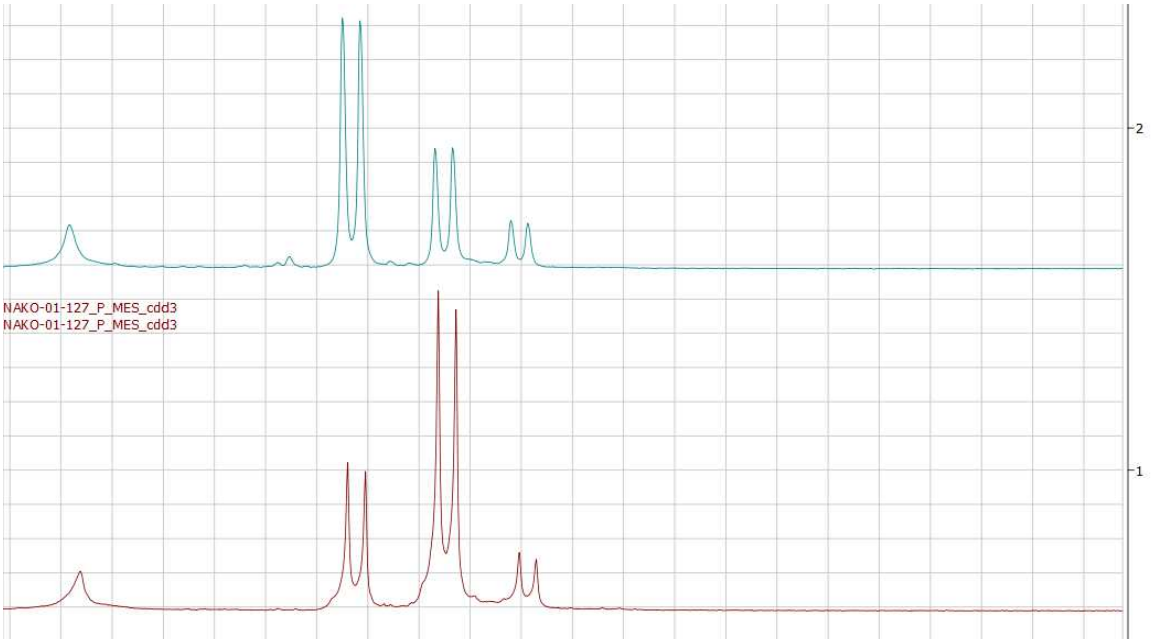


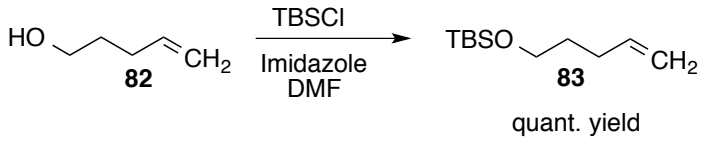
71

S Mosher ester



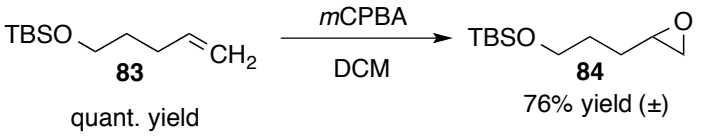
Peaks compared directly:



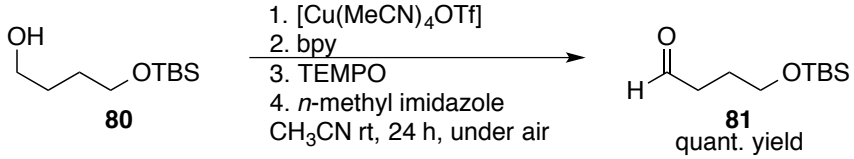


***tert*-butyldimethyl(pent-4-en-1-yloxy)silane:** To a solution of 4-penten-1-ol **82** (10 g, 116 mmol, 11.99 mL) at 0 °C in DMF (58 mL) was added TBSCl (36.6 g, 243 mmol) and Imidazole (44 g, 650.16 mmol). The reaction mixture was warmed to room temperature gradually. The reaction was quenched with H_2O and the aqueous and organic fractions were separated after 20 minutes. The aqueous layer was extracted with Et_2O (5 x 50 mL) and the combined organic fractions were washed with H_2O (5 x 150 mL) and brine (50 mL). The organic fraction was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting compound **83** was a clear oil in quantitative yield. Spectra matched that of the known compound.[38] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.82 (m, 1H), 5.01 (dq, J = 17.2, 1.8 Hz, 1H), 4.95 (ddd, J = 10.2, 2.2, 1.1 Hz, 1H), 3.62 (td, J =

6.5, 1.2 Hz, 2H), 2.10 (m, 2H), 1.61 (dtd, *J* = 8.4, 7.5, 7.0, 5.9 Hz, 2H), 0.90 (s, 9H), 0.07, (s, 6H).

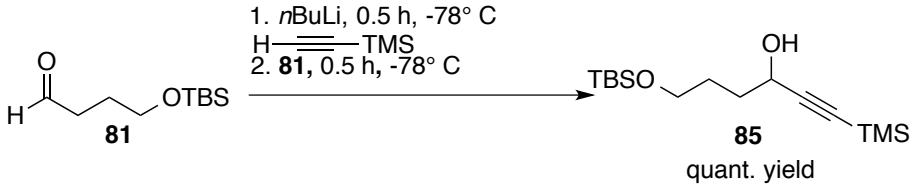


***tert*-butyldimethyl(3-(oxiran-2-yl)propoxy)silane[30]:** *m*CPBA (26.02 g, 150.8 mmol) was dissolved in CH_2Cl_2 (195 mL). This solution was slowly added to a solution of *tert*-butyldimethyl(pent-4-en-1-yloxy)silane **83** (23.3 g, 116.1 mmol) in DCM (195 mL) at 0 °C. The reaction mixture was warmed to room temperature gradually and stirred for 20 h. The reaction was diluted with Na_2SO_3. $NaHCO_3$ was added until the pH was greater than 8. Aqueous and organic layers were separated and the aqueous layer was extracted with Et_2O (2 x 250 mL). The combined organic fractions were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Crude was purified by column chromatography 5% EtOAc in hexanes to produce an orange oil **84** (19.13 g, 76% yield). Spectra matched that of the known compound.[30] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.65 (m, 2H), 2.94 (dddd, *J* = 6.0, 4.9, 3.9, 2.6 Hz, 1H), 2.75 (m, 1H), 2.48 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.6 (m, 4H), 0.91 (s, 9H), 0.08 (s, 6H).

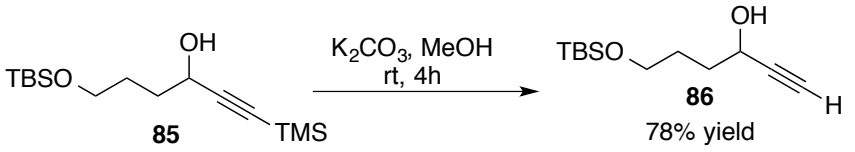


4-((*tert*-butyldimethylsilyl)oxy)butanal[29]: 4-(tert-butyldimethylsilyl)oxy-1-butanol **80** (25 g, 122 mmol) was dissolved in acetonitrile (120 mL) with round bottom flask open to air. Tetrakisacetonitrile copper(I) triflate (2.29 g, 6.1 mmol) in 120 mL acetonitrile was

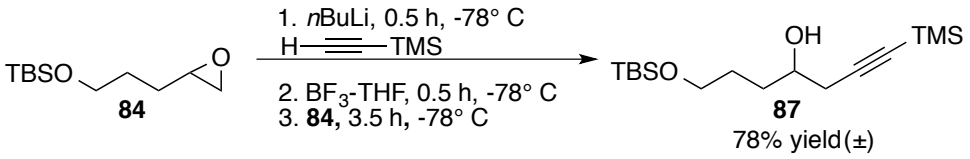
added to the solution. The color changed from clear to yellow. Then bipyridine (0.95 g, 6.1 mmol) in 120 mL of acetonitrile was added to the reaction mixture with an accompanying color change of yellow to dark brown. TEMPO (0.95 g, 6.1 mmol) was dissolved in 120 mL acetonitrile and added to the reaction mixture, followed by the addition of N-methyl imidazole (1.002 g, 12.2 mmol) in 120 mL acetonitrile. Reaction mixture was stirred for 20 h under air. Once the mixture became a green-blue color it was quenched by concentrating *in vacuo*. The result was filtered through silica with 10% EtOAc in hexanes. Mixture was concentrated *in vacuo* and afforded quantitative yield of **81**. Spectra matched that of the known compound.[39] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.7, 1H), 3.65 (t, *J* = 6.0 Hz, 2H), 2.50 (td, *J* = 7.0, 1.8 Hz, 2H), 1.86 (tt, *J* = 7.0, 6.0 Hz, 2H), 0.88 (s, 9H), 0.04 (s, 6H).



6-((*tert*-butyldimethylsilyl)oxy)-1-(trimethylsilyl)hex-1-yn-3-ol[31]: *n*-BuLi (24 mL, 45.6 mmol) was added to a solution of ethynyltrimethylsilane (4.23 g, 43.43 mmol) in THF (120 mL) at -78 °C. A solution of 4-((*tert*-butyldimethylsilyl)oxy)butanal **81** (8.78 g, 43.43 mmol) in 25 mL THF was added to the reaction mixture after 30 min at -78 °C. Reaction mixture was stirred for 30 min. Reaction was quenched with 100 mL saturated NH_4Cl. Crude was purified using column chromatography with 5% EtOAc in hexanes to afford a quantitative yield of **85**. Spectra matched that of known compound.[31] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.42 (q, J= 5.2 Hz, 1H), 3.69 (m, 2H), 3.27 (s, 1H), 1.82 (m, 4H), 1.66 (ddt, J= 12.1, 7.2, 4.5 Hz, 2H), 0.89 (s, 9H), 0.16 (d, J= 0.9 Hz, 9H), 0.07 (s, 6H).



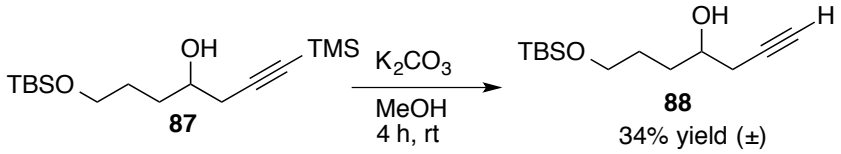
6-((*tert*-butyldimethylsilyl)oxy)hex-1-yn-3-ol[40]: 6-((*tert*-butyldimethylsilyl)oxy)-1-(trimethylsilyl)hex-1-yn-3-ol **85** (5 g, 16.63 mmol) was added to MeOH (55 mL) under argon. K_2CO_3 (0.46 g, 3.32 mmol) was added and the reaction mixture was stirred at room temperature for 4 h. Reaction was diluted with 20 mL H_2O and extracted with Et_2O. Organic extracts were combined, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Reaction afforded **86**, an orange oil in 78% yield with no purification. Spectra matched that of known compound.[41] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.41 (d, *J* = 6.1 Hz, 1H), 3.66 (m, 2H), 3.46 (m, 1H), 2.41 (d, *J* = 1.8 Hz, 1H), 1.79 (m, 3H), 1.68 (td, *J* = 6.8, 4.7 Hz, 1H), 1.19 (m, 1H), 0.88 (m, 9H), 0.05 (q, *J* = 1.19 Hz, 6H).



7-((*tert*-butyldimethylsilyl)oxy)-1-(trimethylsilyl)hept-1-yn-4-ol[32]:

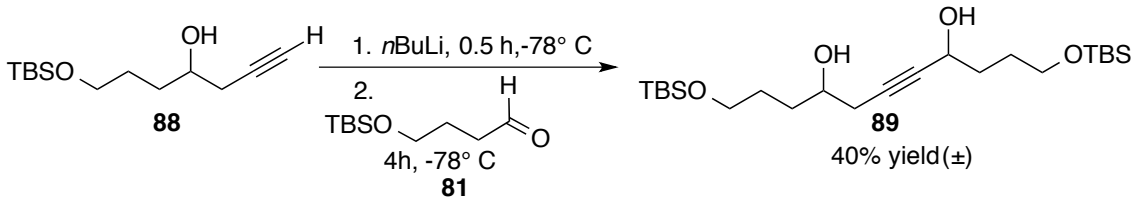
TMS acetylene (0.37 g, 0.702 mmol, 0.53 mL) was added to 20 mL THF in a round bottom flask under argon at -78 °C. *n*-Butyl Lithium (1.9 M, 4.22 mmol, 2.22 mL) was added dropwise to the solution and reaction mixture was stirred for 1 h at -78°C. BF_3•THF (0.64 g, 4.6 mmol, 0.51 mL) was added dropwise to the reaction mixture and stirred for 15 minutes. *tert*-butyldimethyl(3-(oxiran-2-yl)propoxy)silane **84** (1 g, 4.6 mmol) was added dropwise to the flask and reaction was stirred for 3.5 h at -78 °C. Reaction was quenched with saturated NH_4Cl (15 mL) and the organic layer was

separated. Aqueous layer was back extracted with Et_2O (3 x 15 mL) and crude product **87** (0.94 g, 78% yield) was taken forward. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.75 (m, 2H), 3.67 (td, *J* = 5.8, 3.2 Hz, 1H), 2.42 (d, *J* = 6.1 Hz, 1H), 1.88 (m, 2H), 1.66 (m, 1H), 1.56 (m, 1H), 0.90 (m, 9H), 0.15 (s, 6H).



7-((*tert*-butyldimethylsilyl)oxy)hept-1-yn-4-ol:

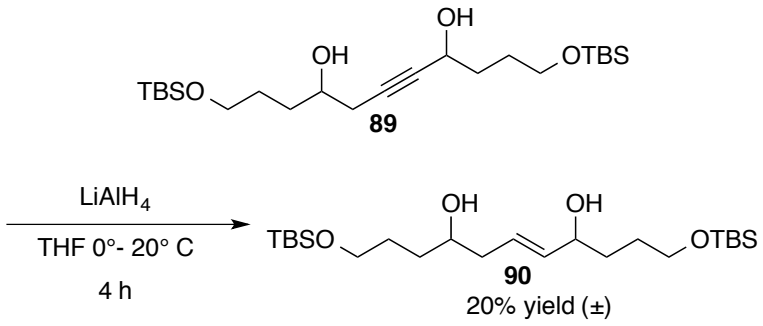
7-((*tert*-butyldimethylsilyl)oxy)-1-(trimethylsilyl)hept-1-yn-4-ol **87** (0.94 g, 2.98 mmol) was added to MeOH (14.9 mL) under argon. K_2CO_3 (0.041 g, 0.298 mmol) was added and the reaction mixture was stirred at room temperature for 4 h. Reaction was diluted with 20 mL H_2O and extracted with Et_2O. Organic extracts were combined, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification was unnecessary and crude product afforded **88** (0.25 g, 34% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.74 (bs, 1H), 3.64 (m, 2H), 3.22 (d, *J* =3.6 Hz, 1H), 2.34 (dd, *J* =6.0, 2.7 Hz, 2H), 1.99 (t, *J* = 2.6 Hz, 1H), 1.73 (m, 1H), 1.62 (tt, *J* = 7.5, 5.9 Hz, 2H), 1.53 (m, 1H), 0.86 (d, *J* = 2.9 Hz, 9H), 0.03 (s, 6H).



2,2,3,3,17,17,18,18-octamethyl-4,16-dioxa-3,17-disilanonadec-9-yne-8,12-diol:

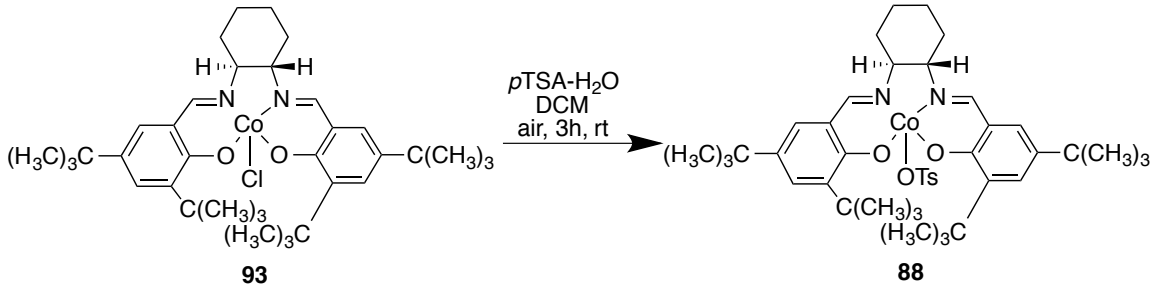
Following a procedure developed by Evans[31], *n*-BuLi (1.21 mmol, 2.04 M, 0.59 mL)

added dropwise to a solution of 7-((*tert*-butyldimethylsilyl)oxy)hept-1-yn-4-ol **88** (0.14 g, 0.58 mmol) in THF (1.93 mL) at -78°C. Reaction mixture stirred for 3 h at -78°C before the dropwise addition of 4-((*tert*-butyldimethylsilyl)oxy)butanal **81** (0.12 g, 0.58 mmol). Reaction mixture stirred for 2.5 h at -78°C, warmed to room temperature for 15 min, cooled to -78°C and quenched with saturated aqueous NH_4Cl. Organic layers separated and aqueous layer extracted with Et_2O (3x 5 mL). Column chromatography performed with 10% EtOAc in hexanes followed by 100% EtOAc to obtain product **89** (40% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.42 (m, 1H), 3.74 (ddt, J = 6.2, 4.4, 2.6 Hz, 2H), 3.69 (m, 1H), 2.40 (dd, J= 6.1, 2.0 Hz, 2H), 1.77 (m, 4H), 1.66 (m, 4H), 1.55 (m, 2H), 0.89 (m, 18H), 0.06 (m, 12H).

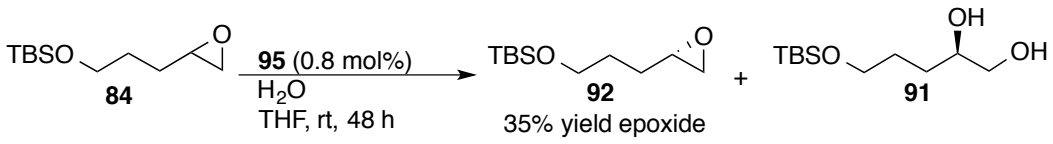


(*E*)-2,2,3,3,17,17,18,18-octamethyl-4,16-dioxa-3,17-disilanonadec-9-ene-8,12-diol: Following a procedure developed by Reddy,[33] To a stirred solution of lithium aluminum hydride (0.09 g, 2.25 mmol, 1.125 mL) in dry THF (5.304 mL) at 0 °C was added a solution of 2,2,3,3,17,17,18,18-octamethyl-4,16-dioxa-3,17-disilanonadec-9-yne-8,12-diol **89** (0.20 g, 0.45 mmol) in 1.29 mL dry THF dropwise. Mixture was allowed to warm to room temperature and stirred for 4 h. Reaction mixture cooled to 0°C and 1 mL of H_2O added, followed by 1 mL 15% NaOH and 3 mL H_2O. Reaction warmed to room temperature and stirred for 15 min. Anhydrous $MgSO_4$ added and reaction mixture

stirred for an addition 15 min. Slurry filtered and evaporated *in vacuo* to afford **90** (0.04 g, 20% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.68 (dt, *J* = 14.2, 6.9 Hz, 1H), 5.56 (dd, *J* = 15.4, 6.2 Hz, 1H), 4.10 (t, *J* = 6.2 Hz, 1H), 3.66 (m, 5H), 2.20 (m, 3H), 2.17 (s, 1H), 1.62 (m, 6H), 1.48 (m, 1H), 1.25 (m, 1H), 0.89 (d, *J* = 0.58, 18H), 0.06 (s, 12H).

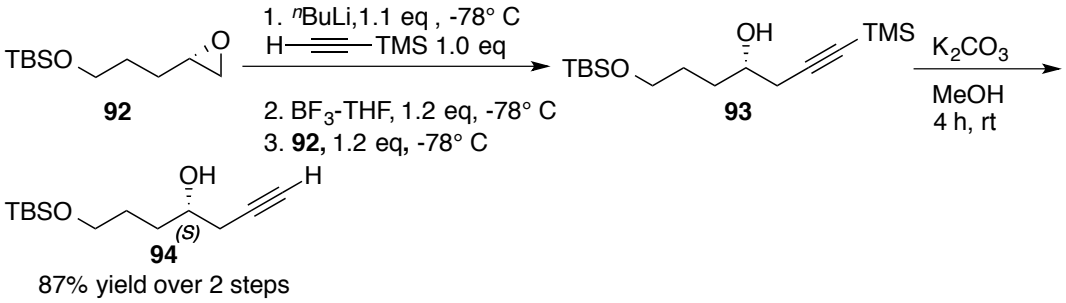


Jacobsen's catalyst[34]: Red (S,S)-(+)-N,N'-BIS(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminocobalt(III) Chloride (5 g, 8.3 mmol) was added to DCM (83 mL) in a round bottom flask open to atmosphere. *p*-TSA was added at room temperature and the reaction mixture was stirred vigorously for 3 h. Dark green reaction mixture was concentrated *in vacuo*, dried under reduced pressure, and suspended in pentanes. Suspension was filtered and the solid was dried on filter. Color and texture matched that of known compound and was used as crude material.[34]



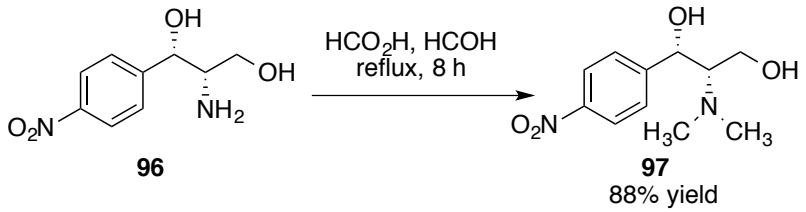
***(S)-tert*-butyldimethyl(3-(oxiran-2-yl)propoxy)silane[34]:** To a solution of *tert*-butyldimethyl(3-(oxiran-2-yl)propoxy)silane **84** (5.00 g, 23.1 mmol) in THF (10.04 mL) was added the Jacobsen cobalt catalyst **95**. Deionized H_2O was added and the reaction mixture was stirred for 24 h at room temperature. Crude was purified by column

chromatography to afford epoxide **92 (**1.79 g, 36% yield). Spectra matched that of known compound.[42] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.65 (m, 2H), 2.94 (m, 1H), 2.75 (m, 1H), 2.48 (dd, J= 5.0, 2.7 Hz, 1H), 1.64 (m, 4H), 0.91 (s, 9H), 0.08 (s, 6H).



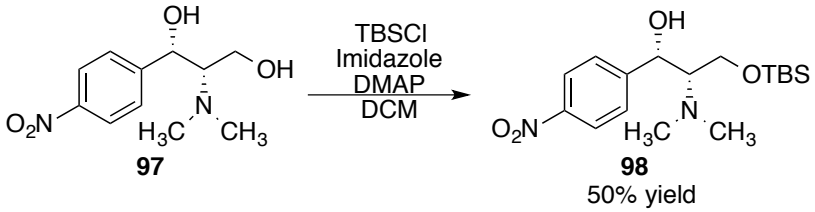
(*S*)-7-((*tert*-butyldimethylsilyl)oxy)-1-(trimethylsilyl)hept-1-yn-4-ol[32]: *n*BuLi (7.6 mmol, 3.6 mL) was added dropwise to a stirred solution of ethynyltrimethylsilane (6.9 mmol, 0.68 g, 0.97 mL) in 40 mL dry THF (35 mL) under argon at -78 °C. The solution was stirred for 30 minutes at -78 °C and then BF_3-THF (8.3 mmol, 1.16 g, 0.91 mL) was added dropwise. The reaction mixture was stirred for another 15 min and then *(S)-tert*-butyldimethyl(3-(oxiran-2-yl)propoxy)silane **92** (8.3 mmol, 1.79 g) in 5 mL THF was added dropwise. Reaction mixture was stirred for 4 h at -78 °C and then quenched with saturated NH_4Cl (10 mL). Organic layer was separated and aqueous layer extracted with Et_2O (3 x 20 mL). The combined organic fractions were washed in brine, dried over $MgSO_4$, and concentrated *in vacuo*. Resulting oil was taken onto next step without purification. An aliquot was taken to confirm production of intermediate **93** before carrying forwards. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.75 (m, 1H), 3.67 (m, 2H), 2.92 (d, *J* = 4.4 Hz, 1H), 2.42 (d, *J* = 6.07 Hz, 2H), 1.74 (m, 1H), 1. 66 (m, 2H), 1.56 (m, 1H), 0.90 (s, 9H), 0.15 (s, 6H), 0.07 (s, 9H).

(*S*)-7-((*tert*-butyldimethylsilyl)oxy)hept-1-yn-4-ol: (*S*)-7-((*tert*-butyldimethylsilyl)oxy)-1-(trimethylsilyl)hept-1-yn-4-ol **93** (6.83 mmol, 2.15 g) added to MeOH (34 mL) under argon at room temperature. K_2CO_3 (1.37 mmol, 0.188 g) added and reaction stirred for 4 h at room temperature. Reaction diluted with deionized H_2O (34 mL) and aqueous layer extracted with Et_2O (3 x 15 mL). Organic extracts combined, washed with brined, dried over $MgSO_4$ and concentrated *in vacuo* to afford 87% yield of **94** over two steps. Mosher ester analysis of this compound afforded a 92:8 er. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.78 (dtd, *J* = 7.9, 4.0, 1.9 Hz, 1H), 3.67 (m, 2H), 3.10 (d, *J* = 4.3 Hz, 1H), 2.39 (ddd, *J* = 6.0, 2.7, 0.6 Hz, 2H), 2.03 (t, *J* = 2.7 Hz, 1H), 1.77 (m, 1H), 1.67 (m, 3H), 0.89 (m, 9H), 0.07 (m, 6H).

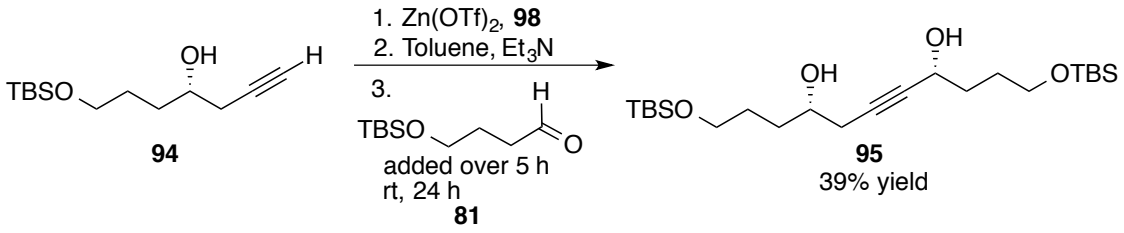


96 **97** 88% yield

(1*S*,2*S*)-2-(dimethylamino)-1-(4-nitrophenyl)propane-1,3-diol[35a]: (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)propane-1,3-diol **96** (21.22 g) added to Formic acid (90% in H_2O, 40 mL) and Formaldehyde (37% in H_2O, 30 mL) at room temperature. Reagents were refluxed for 24 h. Solvent was removed using distillation, residue was neutralized in 130 mL 1M NaOH and extracted with DCM (3 x 50 mL). Combined organic phase was dried over Na_2SO_4 and filtered. After subsequent removal of solvent *in vacuo*, residue was passed through basic alumina using 10:1 DCM:MeOH as eluent. Result was concentrated *in vacuo* to form yellow powder. Crude powder **97** was taken onto next reaction without purification. Spectra matched that of the known compound. [35a]

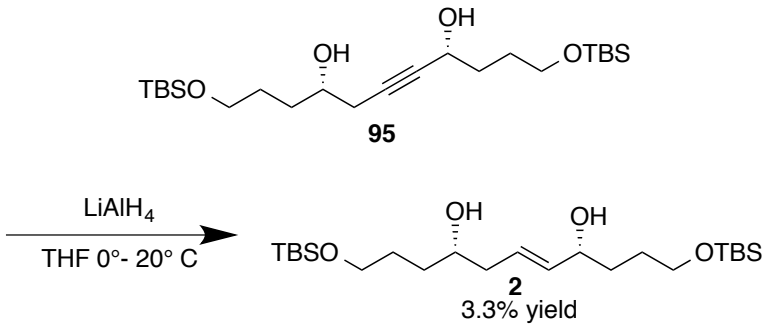


(1*S*,2*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2-(dimethylamino)-1-(4-nitrophenyl)propan-1-ol (Jiang's Ligand): TBSCl, imidazole and DMAP were added to a solution of (1*S*,2*S*)-2-(dimethylamino)-1-(4-nitrophenyl)propane-1,3-diol **97** in DCM at 0 °C. Reaction mixture was warmed to room temperature and stirred overnight. Reaction mixture poured into 370 mL H_2O and neutralized with cold aqueous HCl (0.5 M) to pH=8. Aqueous phase extracted with DCM (3x 125 mL) and combined organic layer washed with saturated Na_2CO_3 solution, then brine, dried over Na_2SO_4 and filtered. Result concentrated *in vacuo* to residue **98**. Spectra matched that of the known compound.[35a] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (m, 2H), 7.50 (m, 2H), 4.62 (d, J= 9.7 Hz, 1H), 3.63 (dd, J= 11.3, 2.6 Hz, 1H), 3.46 (dd, J= 11.3, 5.9 Hz, 1H), 2.48 (d, J= 0.9 Hz, 7H), 0.86 (d, J= 0.73 Hz, 9H), -0.04 (d, J =2.2 Hz, 6H).



(8*R*,12*S*)-2,2,3,3,17,17,18,18-octamethyl-4,16-dioxa-3,17-disilanonadec-9-yne-8,12-diol: Following a procedure developed by Carreira and Jiang[43,35a]**,** Round bottom flask was charged with zinc trifluoromethanesulfonate (1.5 g, 4.12 mmol) and the Jiang Ligand **98** (1.46 g, 4.12 mmol) and stirred for 15 min at room temperature. Toluene (10.3 mL)

and Et_3N (0.38 g, 3.78 mmol, 0.53 mL) were added and reaction mixture stirred for 2 h. (*S*)-7-((*tert*-butyldimethylsilyl)oxy)hept-1-yn-4-ol **94** (1.0 g, 4.12 mmol) added and stirred for an additional 15 min. 4-((*tert*-butyldimethylsilyl)oxy)butanal **81** (0.69 g, 3.43 mmol) in 4.8 mL toluene added over a period of 5 h at room temperature and reaction mixture stirred overnight. After approximately 20 h, saturated aqueous NH_4Cl was added to quench. Organic layer extracted with Et_2O (3x 20 mL), filtered and evaporated *in vacuo*. Resulting oil was chromatographed in 30% EtOAc in hexanes to afford **95** as a yellow oil (0.60 g, 39% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.38 (td, *J* = 4.7, 4.2, 2.7, 1H), 3.72 (m, 1H), 3.65 (m, 4H), 3.15 (bs, 1H), 3.06 (bs, 1H), 2.38 (dd, *J* =5.9, 2.0 Hz, 2H), 2.15 (s, 1H), 1.70 (m, 7H), 0.90 (d, J= 1.9 Hz, 18H), 0.07 (s, J=12 Hz, 12 Hz) **^{13}C NMR** (100 MHz, $CDCl_3$) δ 83.7, 81.8, 70.2, 63.49, 63.47, 62.4, 35.6, 33.7, 29.3, 28.8, 27.7, 26.1, 18.5, -5.2 **HRMS (APCI):** *m/z* calcd. for $C_{23}H_{48}O_4NaSi_2$ ($M+H^+$) 467.298, found 467.298; **$[\alpha]_D^{25}$** = 0.3° (c = 1.00, $CHCl_3$).



(8*R*,12*S*,*E*)-2,2,3,3,17,17,18,18-octamethyl-4,16-dioxa-3,17-disilanonadec-9-ene-8,12-diol: To a stirred solution of lithium aluminum hydride (0.26 g, 6.74 mmol, 3.37 mL) in dry THF (20 mL) at 0°C was added a solution of (8*R*,12*S*)-2,2,3,3,17,17,18,18-octamethyl-4,16-dioxa-3,17-disilanonadec-9-yne-8,12-diol **95** (0.20 g, 0.45 mmol) in 1.29 mL dry THF dropwise. Mixture was allowed to warm to room temperature and

stirred for 4 h. Reaction mixture cooled to 0 °C and 1 mL of H_2O added, followed by 1 mL 15% NaOH and 3 mL H_2O. Reaction warmed to room temperature and stirred for 15 min. Anhydrous $MgSO_4$ added and reaction mixture stirred for an addition 15 min. Slurry filtered and evaporated *in vacuo*. Crude product purified with 30% EtOAc in hexanes followed by 10% MeOH in DCM to obtain **2** as a light yellow oil (0.02 g, 3.3% yield) and recovered starting material (0.13 g, 22%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.68 (dt, J= 14.2, 6.9 Hz, 1H), 5.56 (dd, J=15.4, 6.2 Hz, 1H), 4.10 (q, J=6.0 5.4 Hz, 1H), 3.66 (m, 5H), 2.80 (bs, 2H), 2.21 (m, 2H), 1.62 (m, 8H), 1.25 (m, 1H), 0.89 (d, J= 0.58 Hz, 21H), 0.06 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.4, 127.6, 71.1, 63.7, 63.6, 40.6, 32.2, 29.3, 29.4, 26.1, -5.2, **HRMS (APCI):** *m/z* calcd. for $C_{23}H_{50}O_4NaSi_2$ ($M+H^+$) 469.314, found 469.313. $[\alpha]_D^{25} = 0.8°$ (c = 1.00, $CHCl_3$).

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