SYNTHETIC METHODOLOGY FOR THE CONSTRUCTION OF
STRUCTURALLY DIVERSE CYCLOPROPANES

A Dissertation

Submitted to the Graduate School
of the University of Notre Dame
in Partial Fulfillment of the Requirements
for the Degree of

Doctor of Philosophy

by

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Notre Dame, Indiana

December 2004
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Abstract

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This Dissertation will cover cyclopropane methodology for the synthesis of 1,2,3-trisubstituted cyclopropanes. We envisioned building a cyclopropane precursor with two main features. The first feature was to use the known equilibrium between the homoallylic cation, the cyclobutane cation, and the cyclopropyl carbinyl cation. We incorporated this feature by having a homoallylic group (X) displaced with allylsilane forming the cyclopropyl carbinyl cation. This cation would then begin to equilibrate. However, the second feature was to include a silyl group beta to the olefin and in a position to stabilize the forming cyclopropyl carbinyl cation with the -silicon effect and therefore drive the equilibrium toward the cyclopropane. The silicon was necessary to make sure that ring fragmentation and subsequent 1,2-elimination did not occur. Also, the facile elimination of silicon allowed us to trap the cyclopropane, which resulted in a terminal olefin which can be elaborated further. The “state of the art” at the time of my arrival entailed building the cyclopropane precursor with a boron acetylide opening of mono-substituted epoxides. This methodology allowed us to prove our
concept, but was limited toward the synthesis of trisubstituted cyclopropanes. Therefore we proposed a method highlighted by the formation of the cyclopropane precursor using RCM chemistry. The goal was to investigate the closure of substituted cyclopropane precursors and determine the stereochemical course of the reaction. The new method allowed us to start from a substituted homoallylic alcohol and in three transformations yield the desired precursor. There are many methods known for the preparation of suitable homoallylic alcohols. However, for this summary I will only highlight the results obtained from homoallylic alcohols derived from an indium mediated crotylation of hydrocinnamaldehyde. The indium mediated crotylation resulted in a 3:1 mixture of anti:syn diastereomers. The predominance of anti is due to a closed six membered transition state where the crotyl indium species coordinates the aldehyde and delivers the crotyl group when the ethyl ester and the R group on the aldehyde are suedo equatorial in relationship. The diastereomers were separated by flash column chromatography. Then, each was taken on independently to yield a single 1,2,3-tribubstitued cyclopropane. The homoallylic alcohol was protected with allylchlorodimethylsilane followed by closure with Grubbs’ ruthenium catalyst to afford the silyloxyoctyloheptene. The seven-membered ring was opened with HF-pyridine to give the desired cyclopropane precursor bearing a fluorosilane to the olefin and a homoallylic alcohol ready for activation. Activation was accomplished with triflic anhydride and 2,6-lutidine in methylene chloride and afforded a single 1,2,3-trisubstituted cyclopropane from the displacement of triflate and subsequent elimination of the fluorosilane. After both diastereomers were taken through the sequence we postulated the transition state structure that would result in the formation of the 1,2,3-cyclopropane that resulted. We determined the relative cyclopropane stereochemistry after several 1H-NMR decoupling experiments. We concluded that the reaction was an SN2 displacement and that the steric environment controls the resulting stereochemistry. Once we limit the discussion to an SN2 reaction we find there are only two possible transition states that allow for the
Michael J. Schmitt

anti-bonding orbital of the carbon-triflate bond to overlap with the bond of the olefin. The allylsilane can be either on the same side as or oppose the ethyl ester. We found that a classic A-strain argument can be used to determine what transition state is preferred. Therefore the allylsilane and the ethylester will oppose each other, or the hydrogen to the carbonyl prefers to eclipse the olefin (A-strain). The transition states shown lead to the cyclopropane formed. The ethyl ester substituted case has also been further established using methyl substituted homoallylic alcohols showing that the argument was universal. Starting from the homoallylic alcohol we have established a four-step sequence to give a single diastereomeric cyclopropane. The method is highlighted by the RCM strategy and has shown to be quite robust. After finishing the trisubstituted cyclopropane work we looked back into the sequence at our silyloxy-cycloheptene intermediates and realized that within the molecule laid a latent homoallylic alcohol with a -silyl group. This is shown when we took the intermediate and reduced the ethyl ester to the corresponding primary alcohol. This reaction was carried out at low temperature to ensure that silicon-oxygen bond cleavage did not occur. With the silyloxy ring intact we activated the primary hydroxy and the cyclopropanation took place to afford a disubstituted cyclopropane with cis orientation of the two substituents. We then took the same intermediate and treated it with excess LAH which provided the corresponding diol from reduction of the ester followed by silicon-oxygen bond cleavage. This molecule was activated using standard conditions and cleanly yielded a disubstituted cyclopropane where the orientation of the two groups were trans to each other. This second case once again proved the A-strain argument. We have proposed that the reason for the diol to afford a cyclopropane of trans stereochemistry was because of the steric environment during the carbon-carbon forming step. We have postulated that the olefin and the -hydrogen are eclipsed or in other words, that the group containing the secondary hydroxyl and the olefin oppose each other. This theory is in concert with the transition states we have seen before in the trisubstituted case where the 1,3 interaction is the dominant force. All this
work was published in Organic Letters, Vol. 2, No. 5, 601-603. The paper summarizes the work that used the RCM strategy for the synthesis of trisubstituted cyclopropanes and disubstituted cyclopropanes of both cis and trans geometry. Our methodology had now developed from a limited three-step sequence from epoxides to a four-step sequence starting from a homoallylic alcohol that exploited the RCM reaction with Grubbs’ ruthenium catalyst. At this time Grubbs et. al. began publishing on a second generation catalyst that was quite promising for cross-metathesis reactions and exhibited a large range of functional group compatibility. We chose to exploit the new catalyst for our third generation synthesis of cyclopropanes. We envisioned using allyltrimethylsilane and a homoallylic alcohol as coupling partners in a cross metathesis reaction. We accomplished crossing both substituted and simple homoallylic alcohols with allyltrimethylsilane using the new Grubbs’ catalyst in yields ranging from 70% to 95%. This new procedure was then used to make all the cyclopropanes previously published. However, during the development of this two step method we found that when the cyclopropane precursor of substituted alcohols was activated we got a 50:50 mixture of desired cyclopropane and trimethylsilane protected starting material. Previously we did not encounter this problem when the fluorosilane was the stabilizer. Since the result ruined the efficacy of our route we explored other activation conditions. After attempting multiple conditions we found that thionyl chloride at rt in methylene chloride was a viable substitute. With these new activating conditions we then were able to synthesis a variety of cyclopropanes, both disubstituted and trisubstituted. We have now shown that cyclopropanes can be synthesized in two steps from a variety of homoallylic alcohols. We have demonstrated the viability of the Grubbs’ catalyst for the cross-metathesis of allyltrimethylsilane and varied homoallylic alcohols. We have also shown that thionyl chloride is an excellent reagent for the activation of the cyclopropane precursor. All this data was published as a full paper in The Journal of the American Chemical Society.
DEDICATION

This is for Stacie.
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ABBREVIATIONS

$^1$H NMR ............................................................. proton nuclear magnetic resonance

$^{13}$C NMR ............................................................. carbon nuclear magnetic resonance

Ac ................................................................. acetyl

Bn ................................................................. benzyl

calcd ............................................................. calculated

cat ................................................................. catalytic

CDCl$_3$ ............................................................. deuterated chloroform

(CD$_3$)$_2$CO ........................................................... deuterated acetone

CH$_2$Cl$_2$ ............................................................. dichloromethane

CM ................................................................. cross-metathesis

Cy ................................................................. cyclohexyl

$\delta$ ................................................................. chemical shift in parts per million

d ................................................................. doublet

de ................................................................. diastereomeric excess

DIPEA ............................................................. diisopropyl ethyl amine

DMF ................................................................. dimethylformamide

DMSO ............................................................. dimethylsulfoxide
dp .................................................. diastereomeric purity
dr .................................................. diastereomeric ratio
E ................................................... Entgegen
ee ................................................... enantiomeric excess
eq ................................................... equivalents
Eq ................................................... equation
er ................................................... enantiomeric ratio
Et ................................................... ethyl
EtOAc ............................................. ethyl acetate
EtOH .............................................. ethanol
Et₂O ................................................ diethyl ether
FT ................................................... Fourier transform
g ................................................... gram
h ................................................... hour
HF·pyr ........................................... 30% hydrofluoric acid in pyridine
HRMS ............................................. high-resolution mass spectrometry
Hz ................................................... hertz
IMes .............................................. 1,3-dimesityl-4,5-dihydroimidazol-2-ylidine ligand
IR ................................................... infrared spectroscopy
J ................................................... coupling constant in hertz
m ................................................... multiplet
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>m/z</td>
<td>mass-to-charge ratio</td>
</tr>
<tr>
<td>M</td>
<td>molar</td>
</tr>
<tr>
<td>M&lt;sup&gt;+&lt;/sup&gt;</td>
<td>molecular ion</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeLi</td>
<td>methyl lithium</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>Mes</td>
<td>mesityl or 2,4,6-trimethylphenyl</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>MgSO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>magnesium sulfate</td>
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<td>mL</td>
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</tr>
<tr>
<td>mmol</td>
<td>millimole</td>
</tr>
<tr>
<td>mol</td>
<td>mole</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-butyl lithium</td>
</tr>
<tr>
<td>NA</td>
<td>not available</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PhCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>toluene</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>pyr</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>quant</td>
<td>quantitative</td>
</tr>
</tbody>
</table>
RCM ................................................................. ring-closing metathesis
ROM ................................................................. ring-opening metathesis
ROMP ............................................................... ring-opening metathesis polymerization
rt ................................................................. retention time
RT ................................................................. room temperature
s ................................................................. singlet
s-BuLi ............................................................ sec-butyl lithium
sec ................................................................. seconds
SOCl₂ ............................................................. thionyl chloride
t ................................................................. triplet
t-Boc ............................................................. tert-butoxycarbonyl
t-BuLi ............................................................ tert-butyl lithium
TBAF ............................................................. tetrabutyl ammonium fluoride
TBS ............................................................. tert-butyldimethylsilyl
TBSCI ........................................................... tert-butyldimethylsilyl chloride
TBSOTf ......................................................... tert-butyldimethylsilyl triflate
TES ............................................................. triethyldimethylsilyl
TESCl .......................................................... triethyldimethylsilyl chloride
Tf ................................................................. triflate (trifluoromethylsulfonate)
Tf₂O ............................................................. trifluoromethanesulfonyl anhydride
THF ............................................................ tetrahydrofuran
TIPS ................................................................. triisopropylsilyle
TIPSCI ................................................................. triisopropylicl chloride
TLC ................................................................. thin layer chromatography
TMS ................................................................. trimethylsilyl
Z ................................................................. Zusamman
ACKNOWLEDGMENTS

I would like to acknowledge my committee, Prof. Miller, Prof. Wiest, and Prof. Brown, for all their help during my studies at Notre Dame. Without them this would have been impossible. I would like to acknowledge my advisor Prof. Taylor for his leadership and friendship. He taught me many things, not only how to be a good chemist but how to be successful.

All this would not be possible without my wife Stacie. She was there for me during all the trials and tribulations of graduate school. I’d like to thank my parents for getting me to grad school, without their guidance I wouldn’t have made it past first grade. I’d like to thank Brian Hearn, Jeffrey Ciavarri, Conrad Engelhardt, and Christina Rissati. They made graduate school in the Taylor Group more than just school.
CHAPTER 1

INTRODUCTION

1.1 Purpose

The purpose of this chapter is to introduce the cyclopropane unit and the chemistry used within this dissertation. Multiple reviews on the synthesis of cyclopropanes have been written\(^1\) and within these reviews there are numerous accounts of the synthetic methods used for the construction of this unique structural unit. To avoid major overlap with these reviews this chapter will detail a general introduction to the cyclopropane ring followed by a discussion of allylsilane nucleophilicity, the \(\beta\)-silicon effect, and lastly touch upon the use of ruthenium carbene catalysts for the synthesis substituted allylsilanes.
1.2 The Cyclopropane Ring

When considering the cyclopropane ring, a cursory analysis may suggest that they are rather unstable. One may even choose to avoid cyclopropanes in constructing molecules for orally available drug substances, since the molecule will have to encounter stomach acid and first pass metabolism. Amazingly, cyclopropanes are found in several active drug substances found on the market today, Figure 1.1, many of which have good oral bio-availability. Granted cyclopropanes are less stable than their acyclic counterparts, but they have unique properties, such as added rigidity and the ability to mimic an olefin sub-unit. These properties give cyclopropanes a valuable place in drug design and represent unique opportunities that should not be avoided due to assumed instability.

![Figure 1.1](image-url)

Singulair - L-706631 (MK-0476) (montelukast)
The inherent reactivity or instability of cyclopropane can be rationalized by comparison with acyclic hydrocarbons. Unlike acyclic hydrocarbons, cyclic hydrocarbons such as cyclopropane have strain energy that is inherent in their cyclic structures. This is called ring strain. Ring strain consists primarily of two different kinds of strain: (1) torsional strain and (2) angle strain. Torsional strain arises when bonds are not ideally staggered and in most ring systems it is impossible to perfectly stagger all bonds. Cyclohexane is the only example where ideal bond staggering occurs, but only in the chair conformation, Figure 1.2.

**Torsional Strain:**

![Torsional Strain Diagram](image)

**Figure 1.2**

Angle strain arises when the C-C-C bond angle of the ring deviate from the ideal tetrahedral angle preferred for sp³ carbon, 109.5°. In the chair conformation of cyclohexane, this angle is identical to the tetrahedral angle observed in the acyclic form of hexane or as in methane, Figure 1.3. Therefore the total ring
strain for the chair conformation of cyclohexane is zero compared to the open chain hexane. However, when considering cyclopropane all this changes.

**Angle Strain:**

<table>
<thead>
<tr>
<th>Cyclopropane</th>
<th>Cyclohexane and Methane</th>
</tr>
</thead>
<tbody>
<tr>
<td>strained 60° C-C-C bond angle</td>
<td>unstrained 109.5° C-C-C bond angle</td>
</tr>
</tbody>
</table>

*Figure 1.3*

Cyclopropane is highly strained. The estimated total ring strain (combined torsion and angle) in cyclopropane is 28 kcal/mol. When this value is compared with the strength of a typical C-C bond at 88 kcal/mol, one can infer that the ring strain substantially weakens the C-C bonds of the cyclopropane. This leads to cyclopropane being much more reactive than acyclic alkanes and other cycloalkanes that have less ring strain.

By definition of a plane (three points define a plane), the carbon framework of cyclopropane is planar. This means that there is only one possible conformation of any given cyclopropane structural unit, and this conformation is one in which all the substituents are eclipsed. Planar conformations are usually disfavored in ring systems, but for cyclopropane no other conformation is possible. The
restricted conformation of cyclopropane is responsible for only 9 kcal/mol of torsional strain, but since the total ring strain of cyclopropane is about 28 kcal/mol, it is evident that the major part of the ring strain arises from angle strain. Angle strain in cyclopropane arises from its geometry, as an equilateral triangle the C-C-C bond angle is 60°, this angle is 49.5° less than the desired angle for the typical C-C-C bond angle of a sp³ carbon.

Therefore, the C-C bonds of cyclopropane are "bent", Figure 1.4. This phenomenon of the cyclopropane is called "banana bonds". Since the bond angle is forced to be 60° and the desired interorbital angle is 109.5°, the orbital overlap is reduced by 20% relative to the orbital overlap in the C-C bond of propane. This accounts for 19 kcal/mol of strain. Amazingly even with the inherent ring strain of cyclopropane, it can be synthesized and is stable at room temperature. More importantly cyclopropane derivatives are found throughout nature and have been used by chemists both as a rigid structural unit and for mechanistic investigation of reactions.

"Banana Bonds"

Figure 1.4
1.3 Allysilanes as Anion Equivalents

In the chapters that follow, experiments will be described in which an allylsilane moiety is used as a trapping agent for cyclopropyl carbinyl cations. In order to appreciate the benefits of this system, allylsilane reactivity will be discussed here. Allylsilanes have been used extensively as allyl anion equivalents since the 1970’s.\textsuperscript{3} Competition experiments between allylsilane and propene have shown that the silyl version is five orders of magnitude more reactive towards diarylcarbenium ions.\textsuperscript{4} Their reaction with electrophiles forms an intermediate carbenium ion, 1.3, that is hyperconjugatively stabilized by the C-Si bond in the $\beta$ position, Scheme 1.1. This stabilization accounts for the increased reactivity of the moiety and also for the regiochemistry associated with the product formed during the reaction.\textsuperscript{5}

Interestingly the substitution pattern at silicon can have drastic effects on the reactivity toward diarylcarbenium ions. The allyltrimethylsilane group is an order of magnitude more reactive than isobutene and 5 orders of magnitude more reactive than propene, but amazingly a simple replacement of one of the methyl groups of the trimethylsilane with chlorine drastically alters this enhancement.
The allylchlorodimethylsilane unit is less reactive than isobutene by 2 orders of magnitude, and upon addition of more inductively withdrawing substituents, the rate of reaction is retarded further. This effect of withdrawing groups has been shown to be a cumulative effect. Isobutenyltrichlorosilane is 7 orders of magnitude less reactive that its trimethyl-counterpart. The reactivity sequence for the allyl group is \( \text{SiMe}_3 > \text{isobutene} > \text{SiPh}_3 > \text{SiClMe}_2 \gg \text{propene} > \text{SiCl}_3 \) as seen in Figure 1.5.

![Figure 1.5](image-url)
One important aspect of using the allylsilane group, is the facile β-elimination reaction associated with the β-silicon carbocation, 1.3 to 1.4. This process gives rise to olefin 1.4, Scheme 1.1, which allows for further elaboration through synthetic transformation, but most importantly it allows synthetic chemists to use highly reactive carbocations in synthesis and to predictably control their outcome.

![Scheme 1.1](image)

Evaluation of this β-elimination process would be extremely beneficial to organic chemists; however, since this β-elimination process is not rate limiting, the study of this process is difficult. Sugawara and Yoshida studied the relative ease of elimination. They compared group 14 elements in competition experiments where either β- or γ- elimination was possible. The system was setup by reacting α-acetoxybenzylstannane with a variety of allylmetals thereby creating a carbocation that is β to the metal and γ to tin, Scheme 1.2. This allowed for the comparison of rates of elimination.

![Scheme 1.2](image)
When comparing tributyltin with a variety of substituted allylsilanes their results illustrated that simple substitution of silicon can have a major effect on its participation in $\beta$-elimination. These experiments determined that the $\gamma$-elimination of tributyltin is faster than the $\beta$-elimination of trimethylsilane. Another interesting fact was highlighted during their investigation, they found that as the substituents on either tin or silicon get larger the $\beta$-elimination process can be slowed drastically, this allows for trapping of the carbocation with outside nucleophiles through an intermolecular process. These results help us understand the nature of the $\beta$-silicon effect.

1.4 The $\beta$-Silicon Effect

The increased nucleophilicity of the allylsilane unit relative to propene is due to the $\beta$-silicon effect; therefore, a discussion of the former without a mention of the latter would be incomplete. This stabilization occurs from hyperconjugation of the $\sigma$ bond between carbon and silicon. A common example of $\sigma$ bond stabilization is seen when comparing tertiary over primary carbocations, Scheme 1.3.
The valence bond representation of this stabilization is illustrated when a $\sigma$ bond donates electrons into an empty p orbital. This suggests a “double bond-no bond” resonance form that is commonly referred to as hyperconjugation or $\sigma\pi$ conjugation. This stabilization is similar to resonance seen by donation of $\pi$ electrons or by nonbonding electrons on heteroatoms, but in this case the $\sigma$ orbital is much higher in energy. Therefore its donation relative to $\pi$ or nb electrons is different, usually less stabilization in the case of a carbon-carbon bond. Since the empty p orbital is typically lower in energy than the $\sigma$ bond the interaction is weaker, but if the $\sigma$ bond is lower in energy, the hyperconjugation effect would be stronger, Scheme 1.4.
The ideal $\sigma$ donor bond is highly polarizable and has sufficiently low energy as to match that of the empty $p$ orbital. Therefore, as in the case of the carbon-silicon bond, it is polarized, and the electropositive silicon can receive the positive charge much better than a methyl group, making it a good partner for hyperconjugation. Other bonds also have these ideal characteristics described, for example the carbon-tin and carbon-germanium bonds have excellent cation stabilization properties.

Lambert and coworkers have investigated the stabilization of carbocations by $\sigma$ conjugation (hyperconjugation) of the carbon-silicon bond and have shown the mechanism of stabilization including the importance of dihedral angle and
induced demand.\textsuperscript{8} Studies have concluded that the mechanism of the $\beta$-silicon effect involves the open unbridged intermediate, this is in accord to the secondary deuterium isotope effect observed. After detailed examination of the stereochemical relationship between silicon and the nucleophage leaving group X (Si-C-C-X) the dihedral angle has been shown to be a critical factor for stabilization.\textsuperscript{9}

In order to determine the effect of dihedral angle on the kinetic enhancement of the $\beta$-silicon, experiments using tert-butyl substituted cyclohexanes were performed.\textsuperscript{10} When the dihedral angle between the silicon-carbon bond and the leaving group-carbon bond were locked at 180°, 1.15 (antiperiplaner) there was a rate enhancement of 2.4 x 10\textsuperscript{12} for $k_{\text{Si}}/k_{\text{H}}$. However, the rate enhancement was diminished to 4.0 x 10\textsuperscript{4} for the system that was held to 60°, 1.16 (gauche). This example clearly illustrates that $\beta$-silicon rate enhancement is sensitive to geometry. The norbornyl framework was used to determine enhancement in systems possessing dihedral angles of 0° and 120°. Both examples (1.17 and 1.18) resulted in enhancements of approximately 10\textsuperscript{5} $k_{\text{Si}}/k_{\text{H}}$.\textsuperscript{11} A bicyclo[2.2.2]octane system was used to differentiate hyperconjugation and inductive stabilization. This system allowed for the establishment of a 90° dihedral angle. At this angle stabilization can only occur by an inductive effect as overlap of the carbon-silicon bond with the empty p orbital of the cation is not possible. In this system only a weak enhancement of 1.2-1.3 was found.\textsuperscript{12}
The last question to answer pertaining to the β silicon effect was the structure associated with stabilization. Two possible structures can be envisioned, a vertical structure with minimal movement of the carbon-silicon bond or a bridged (nonvertical) structure where the silicon atom moves toward the β cation, Figure 1.6.

Scheme 1.5

The last question to answer pertaining to the β silicon effect was the structure associated with stabilization. Two possible structures can be envisioned, a vertical structure with minimal movement of the carbon-silicon bond or a bridged (nonvertical) structure where the silicon atom moves toward the β cation, Figure 1.6.

Figure 1.6
Jorgensen and coworkers published pioneering studies using \textit{ab initio} computer modeling. It was found that both modes, the vertical and nonvertical structures, provide considerable stabilization of the cation versus the hydrogen system.\textsuperscript{19} However rate enhancement studies with fixed geometry of interaction (described above) shed much light on the structural requirements of the stabilization. In the guache and synperiplanar geometry, 1.16 and 1.17, respectively, the bridged structure should not be possible, but as mentioned earlier a large rate enhancement was seen. Therefore the bridged structure seems unlikely. The counter to this argument involves the inductive effect that is responsible for the enhancement regardless of geometry. In the antiperiplanar geometry, the system is bridged and as the dihedral angle gets smaller the inductive effect takes over. Two experiments helped prove that vertical stabilization is most likely in the condensed phase. The bicyclo system with orthogonal geometry showed no rate enhancement and therefore ruled out a strong inductive effect. After ruling out the inductive effect, the second experiment was performed to address the mechanism associated with the antiperiplanar geometry. This question was addressed by using the $\alpha$ secondary kinetic isotope effect.\textsuperscript{14} The deuterated compound was compared to the hydrogen version and resulted in a $k_{\text{H}}/k_{\text{D}}$ of 1.17±0.01. This value indicated a transition state containing an $sp^2$ center rather than the $sp^3$ center associated with a bridged structure where silicon would participate in backside displacement. The value $k_{\text{H}}/k_{\text{D}}$ should be around 1.00-1.08 for the bridged mechanism of
stabilization when nucleophilic displacement is observed. The data supports the vertical structure with little movement of the silicon atom during stabilization.

![Figure 1.7]

The complete picture for the β-silicon effect versus dihedral angle is shown in Figure 1.8. It is important to note that the β-silicon effect is strong at all angles except 90° where no overlay of the σ orbital is possible. This graph illustrates the combined effort of many scientists and the data excludes a strong inductive effect for stabilization.
Figure 1.8
1.5 Ruthenium Carbene Catalysts: Synthesis of Substituted Allylsilanes

The following chapters will discuss experiments where allylsilane moiety is used to trap cations, therefore a brief introduction to their synthesis using Grubbs’ ruthenium carbenes will be introduced. Allylsilanes are an important class of carbon nucleophiles that possess attractive characteristics, including their stability and ease of handling, and with the recent advances in ruthenium carbene catalysts, their synthesis has become quite efficient. Herein the use of the Grubbs’ first and second generation catalysts, Figure 1.9, for the synthesis of allylsilanes will be briefly introduced. Grubbs’ catalyst came into the lime light in the early 1990s and since has gained much attention from synthetic chemists for its ease in forming double bonds with either ring closing metathesis (RCM) or cross metathesis (CM) chemistry. Grubbs’ catalyst is quite remarkable as it can be used on the bench-top without need for Schlenk-ware or a glove-box, and it tolerates moisture and many solvent impurities. The catalyst’s remarkable selectivity for olefins, and broad functional group tolerance have resulted in extensive application of this groundbreaking chemical entity to synthetic targets.
Allylsilanes have been synthesized by a variety of methods,\(^{18}\) and in 1996 their synthesis was performed using cross-metathesis (CM) chemistry with Schrock’s molybdenum catalyst.\(^ {19}\) Schrock’s catalyst found some use for the synthesis of a limited series of allylsilanes, however after the discovery of Grubbs’ catalyst, a multitude of publications disclosed the synthesis of allylsilanes using this catalyst with RCM\(^ {20}\) and CM\(^ {21}\) chemistry. There is a great deal of precedent for the synthesis of allylsilanes using this transformation and in the following chapters it will be used to create cyclopropane precursors. Reviews can be found that highlight the utility and limitations of the Grubbs’ catalyst.

![Figure 1.9](image-url)

**Figure 1.9**

![Scheme 1.6](image-url)

**Scheme 1.6**
1.6 Conclusions

After reading this chapter one should have the adequate references to understand the usefulness of allylsilane nucleophiles in organic synthesis. The nucleophilicity of allylsilanes can be attributed, in large part to the β-silicon effect. The β-silicon effect relies on hyperconjugation of the carbon-silicon bond with the p orbital of the cation which it stabilizes. The geometry of the dihedral angle plays a major role in this stabilization, and the highest rate enhancement is seen when the carbon-silicon bond is antiperiplanar to the forming cation.

Substituents on silicon play a major role in nucleophilicity and hyperconjugation of allylsilanes. As more electron withdrawing substituents are placed on silicon, the ability of silicon to stabilize positive charge is diminished. Likewise the elimination of silicon to form a carbon-carbon double bond is extremely facile in the presence of almost all external nucleophiles. The rate of β-elimination is rapid, however γ-elimination of tin is faster. The β silicon effect coupled with β-elimination of silicon allows chemists to determine the fate of highly reactive carbocation intermedias. Given the usefulness of allylsilanes, there are also a variety of methods for their synthesis. This is highlighted with Grubbs’ ruthenium carbene catalysts.
SYNTHESIS OF 1,2,3-TRISUBSTITUTED CYCLOPROPANES

2.1 Purpose

Early work in our lab demonstrated a unique method for the synthesis of 1,2-disubstituted cyclopropanes.\textsuperscript{22} We began working in the area of cyclopropane construction, from the viewpoint of developing a method using cationic intermediates. As there are a variety of methods based on carbene chemistry\textsuperscript{23} and anionic displacements,\textsuperscript{24} we chose to explore a less tapped area of the cyclopropanation reaction based on the biosynthesis of oxylipins\textsuperscript{25} as described in Chapter 1.

Remarkably, few precedents\textsuperscript{26} for the cationic closure of cyclopropane rings leading to di- and trisubstituted cyclopropanes exist, and the literature explains several limitations to the described methodology. The lack of stereoselectivity, poor diversity, and generation of molecules that are unable to be functionalized
further offer this area to be exploited in more depth. In order to develop the technique as an approach to cyclopropanes we envisioned using silicon as a cation-stabilizing group. It has been shown that the cyclopropyl carbinyl cation is prone to rearrangement as shown in Figure 2.1, therefore to avoid rearranged product formation, stabilization of the cyclopropane intermediate is required.

By using an allylsilane moiety to displace a homoallylic leaving group, the desired cyclopropyl carbinyl cation is stabilized by two adjacent groups, the cyclopropane ring itself and the $\beta$-silicon, Figure 2.2. These groups prevent rearrangement by lowering the energy of this reactive intermediate relative to the fragmented homoallylic cation or cyclobutyl cation.$^{27}$

The energy diagram, Figure 2.3, shows how the successful use of the $\beta$-silicon effect was implemented. The key to success is the stabilization of the
desired cation using the β-silicon effect; thus, preventing ring fragmentation to occur. Essentially, by lowering the energy of the cyclopropyl carbinyl cation, the other two potential cations are energetically inaccessible. The silicon moiety is prone to facile elimination, which allows for an extremely efficient and fast capture of the cyclopropyl carbinyl cation to yield a terminal olefin. After elimination there is no chance of ring fragmentation and this sets the stereochemistry. Therefore, as long as the first step occurs with neighboring group participation of the allylsilane and without ionization there is no other pathway allowed except formation of the vinyl cyclopropane.

Figure 2.3
2.2 Proof of Concept: Boronacetylide Sequence

The seminal work using stabilized cyclopropyl carbinyl cations was illustrated through the three-step sequence starting from benzyl glycidyl ether and propargyl trimethylsilane, Scheme 2.1, to yield the trans-vinylcyclopropane 2.4. This work, accomplished in 1996, was the “proof of concept” for the Taylor laboratory.\(^1\) The epoxide was fragmented with the boronacetylide prepared from the deprotonation of propargyl trimethylsilane 2.1 at -78°C using conditions developed by Yamaguchi et al.\(^9\) At this point the homopropargylic alcohol 2.2 was reduced selectively with Lindlar’s catalyst under a hydrogen atmosphere to give the Z-olefin 2.3. The desired cyclopropane precursor 2.3 was then activated at the secondary alcohol using a slight excess of triflic anhydride and 2,6 lutidine in methylene chloride at -78°C. This resulted in clean formation of the trans-vinylcyclopropane 2.4 without detection of the cis isomer. The extremely high stereoselectivity made the sequence synthetically useful for the synthesis of 1,2-disubstituted cyclopropanes.
2.3 Stereochemistry of 1,2-Disubstituted Cyclopropane

The observed stereochemistry was rationalized using the model depicted in Figure 2.4. We proposed that, during displacement of the triflate leaving group, neighboring group participation (NGP) of the allyl silane required formation of either transition state A or transition state B. Therefore distribution of stereoisomers formed during this reaction was controlled by the difference in energy of the two transition states, kinetic control. Transition State A (TS-A) illustrates the more highly strained conformation compared with Transition State B (TS-B). In TS-A the allylsilane and benzyloxy substituents are cis in the forming ring structure which is sterically congested. Transition State B (TS-B) the allylsilane and benzyloxy substituents are trans about the forming ring structure.

Scheme 2.1

\[ \text{a) 1. nBuLi, 2. BF}_3\cdot\text{OEt}_2 \, 3. \text{benzyl glycidoxy ether, 60% } \]
\[ \text{b) Lindlar's catalyst, H}_2, \, 90\% \, \text{c) Tf}_2\text{O, 2,6-lutidine, -78}\degree\text{C, 78%}} \]
resulting in less steric congestion. Since formation of the cis isomer is not observed, the conclusion can be made that at -78°C the transition state leading to the formation of the cis isomer is inaccessible. Therefore the free energy difference between TS-A and TS-B is great enough that only the trans isomer is produced.

![Diagram of TS-A and TS-B](image)

**Figure 2.4**

To bolster the argument for kinetic control this sequence has been carried out on enantiomerically enriched material to prove that clean inversion at the homoallylic center is taking place. This study negated the potential equilibrium between the homoallylic cation and the cyclopropyl carbiny1 cation that could lead to thermodynamic control. Since there was no detectable loss of enantiomeric excess, the conclusion was made that NGP (and not ionization, S_N1-like process) and kinetics control the stereochemical outcome of this reaction.
2.4 Limitations to Sequence

The original sequence to trans-vinylcyclopropanes as depicted in Scheme 2.1 was efficient, however the route has limitations. There are several steps that require inert atmosphere and cryogenic conditions making this reaction less amenable to large-scale synthesis and industrial chemistry. Also the sequence does not allow access to a diverse range of cyclopropane products since a simple modification such as using an asymmetric 1,2-disubstituted epoxide leads to loss of regioselectivity during the fragmentation reaction. In Figure 2.5, Equation (2) it is shown that the regioselectivity is lost giving more than one product, whereas in Equation (1) ring fragmentation with the acetylide gives only one product. Therefore it is necessary to start from terminal epoxides which also leads to problems when using enantiomerically pure compounds. Terminal epoxides are not necessarily difficult to make, but their access with high enantiomeric purity has shown to be quite difficult. Several methods have been developed using kinetic resolutions of the racemate, but it would be advantageous to start with materials that are more readily available. In addition, propargyltrimethylsilane is an expensive reagent ($60/g), and its use is limited due to poor commercial availability. Furthermore this reagent is volatile and difficult to purify from the isomeric allene byproduct, which results in diminished yields for the oxirane fragmentation reaction. For these reasons, the sequence
was modified to accomplish several goals: (1) develop a method for the
construction of di- as well as trisubstituted cyclopropanes using cationic
intermediates, (2) develop a method that is stereoselective, and (3) develop a
method that is inexpensive.

![Figure 2.5](image)

2.5 A Route Based on Homoallylic Alcohols

In attempts to improve the overall generality of the sequence we envisioned a
route starting from homoallylic alcohols. This new route would resolve the issues
of expense and diversity associated with the original sequence. Since
homoallylic alcohols can be readily synthesized with a variety of methods and
can be substituted at several positions, they would provide access to highly functionalized cyclopropanes once taken through the desired sequence.

Retrosynthetically this is shown in Scheme 2.3. The cyclopropane precursor could be accessed in several steps from the homoallylic alcohol. In order to complete the precursor synthesis the allylsilane functionality would have to be incorporated into the starting homoallylic alcohol. We chose to investigate two approached: ring closing metathesis (RCM) as depicted in Scheme 2.4 and cross metathesis introduced in Scheme 2.13.

\[ \text{Scheme 2.3} \]

2.6 Synthesis of Disubstituted Vinylcyclopropane from a Homoallylic Alcohol

The incorporation of the allylsilane was made possible by using a RCM and a temporary silicon tether.\textsuperscript{31} Using the hydroxyl group of the homoallylic alcohol, the allylsilane moiety can be tethered internally by protecting with allylchlorodimethylsilane. The ring closing metathesis formed the essential carbon-carbon double bond and allowed for easy installation of the stabilizing

\[ \text{Schematic representation of the synthesis process} \]
silicon functionality. F. Conrad Engelhardt accomplished the first synthesis of a disubstituted cyclopropane using this the method starting from a homoallylic alcohol.\textsuperscript{32}

A representative example is shown in Scheme 2.4. The synthesis of 2.4 used the new RCM route and started from homoallylic alcohol 2.5. The homoallylic alcohol was protected with allylchlorodimethylsilane in the presence of imidazole in DMF to give diene 2.6. The diene was closed to the silyloxy-cycloheptene 2.7, forming the essential carbon-carbon double bond using Grubbs’ catalyst with complete selectivity for the Z-olefin. The cycloheptene 2.7 was unmasked with MeLi at 0°C to afford the free alcohol 2.3 with the allylsilane group in position to stabilize the cyclopropyl carbinyl cation. This substrate intercepts the boronacetylide sequence with the same precursor 2.3 shown previously. As before, activation with triflic anhydride resulted in the \textit{trans}-vinylcyclopropane 2.1 as the only isolated product.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme24}
\caption{Scheme 2.4}
\end{figure}

- a) allylchlorodimethylsilane, DMF, imidazole, 95% 
- b) Grubbs' 1st generation catalyst, 40°C, 90% 
- c) MeLi, 0°C, 90% 
- d) Tf\textsubscript{2}O, 2,6-lutidine, -78°C, 78%
2.7 Introduction to 1,2,3-Trisubstituted Cyclopropanes

The results for the synthesis of a disubstituted cyclopropane proved that starting from a homoallylic alcohol was a viable route. With the technology in place the exploration of the synthesis of more complex cyclopropanes was investigated. The first choice for diversification was to introduce an allylic substituent into the starting homoallylic alcohol, Scheme 2.5. By adding the allylic substituent \( \textit{R}_2 \) the RCM sequence would provide access to 1,2,3-trisubstituted cyclopropanes. The allylic substitution was ideal since the substrates could be accessed using a variety of methods found in the literature.\(^{33}\)

![Scheme 2.5]

2.8 Preparation of Homoallylic Alcohol for the Synthesis of 1,2,3-Trisubstituted Cyclopropane

In order to investigate our proposed synthesis of 1,2,3-trisubstituted cyclopropanes from cationic intermediates, it was necessary to prepare a
suitable homoallylic alcohol starting material. The homoallylic alcohol needed to have allylic substitution with a functional group that would be unreactive through the proposed four-step sequence. An ethyl ester was chosen as the candidate since it would be unreactive in the RCM cyclopropane synthesis and would allow for the further elaboration of the cyclopropane once synthesized.

The desired homoallylic alcohols 2.9 and 2.10 were synthesized using an indium metal mediated coupling of ethyl-4-bromocrotonate 2.8 and hydrocinnamaldehyde, Scheme 2.6. The ability to perform the reaction in aqueous media and at room temperature with no need for any special apparatus makes this reaction very attractive for the synthesis of homoallylic alcohols. This reaction allowed access to the desired material as a 3:1 mixture of the anti:syn diastereomers.

![Diagram](image)

a) 1. indium powder, H₂O, rt  2. hydrocinnamaldehyde

Scheme 2.6

The excess of the anti-diastereomer 2.9 can be attributed to the delivery of the allyl indium species through a closed transition state in which the ethyl ester and phenethyl groups are orientated in equatorial positions, Figure 2.6. The
diastereoselectivity of the reaction was unimportant, as both diastereomers were necessary to investigate the cyclopropane methodology.

![Figure 2.6]

The mixture of diastereomers 2.9 and 2.10 was separated by column chromatography with limited success. Typically two grams of the pre-purified mixture could be separated to yield ~900mg of anti-alcohol, ~200mg of syn-alcohol, and ~900mg of a 2:1 mixture of the two diastereomers. The 2:1 mixture could be put back on a column for further separation, but it was later found that separation of the diastereomers was much easier at a step later in the synthesis (vide infra). After the initial studies in which each diastereomer was taken on individually, later experiments were carried out where the mixture was taken on through the sequence. After the cyclopropanation, the two diastereomeric cyclopropanes in the resulting mixture were easily separable by column chromatography. Also when working on small-scale, chromatographic separation was performed using 5% acetonitrile in chloroform for the mobile phase. This greatly improved resolution, but on large scale this mobile phase was much too expensive and the large quantity of the mutagenic solvents was not advisable.
2.9 Synthesis of 1,2,3-Trisubstituted Cyclopropanes: RCM Study

With the pure *anti*-2.9 and *syn*-alcohol 2.10 in hand the allylsilane needed to be installed. The initial route used the RCM cyclization as in the synthesis of the disubstituted cyclopropanes. This route depended on the commercial availability of allylchlorodimethylsilane ($6.80/g) since its synthesis in the lab would have been expensive and inefficient.35

The *anti*-alcohol 2.9 was protected with allylchlorodimethylsilane in high yield using standard conditions, imidazole and DMF, Scheme 2.7. Later, it was found that triethylamine in methylene chloride made for an easier work-up and was used for the later synthetic sequences. Following the protection it was necessary to form the carbon-carbon double bond. This was accomplished using the 1st generation Grubbs’ ruthenium catalyst, Figure 2.7.36 The reaction was carried out at high dilution, 0.005M, in order to minimize the potentially competitive cross-metathesis pathways.

![Scheme 2.7](image)

a) allylchlorodimethylsilane, Et$_3$N, CH$_2$Cl$_2$, 90%  
b) Grubbs’ 1st generation catalyst, 40°C, 85%
The key RCM reaction was found to give the best yields in methylene chloride at reflux for a period of 12 hours with 20-mole % of Grubbs’ 1st generation catalyst. This was successful, but the overall cost of using 20-mole% of catalyst was too high. The yields were consistently between 70% and 90% with the 1st generation Grubbs’ catalyst. The cost was mitigated by synthesis of the 2nd generation catalyst\textsuperscript{37} and the use of the Grubbs-Hoveyda catalyst\textsuperscript{38} (Figure 2.7) for the RCM reaction. We found that the RCM reaction was near quantitative with the new catalysts, and several large-scale reactions were carried out with less than 1-mole % catalyst with yields in the >90% range. Table 2.1 gives a brief overview of the results of using the three catalysts. After finding suitable RCM conditions the next step was to unmask the latent cyclopropane precursor.

![Figure 2.7](image-url)
2.10 Unmasking the Precursor for 1,2,3-Trisubstituted Cyclopropanes

Care had to be taken with the silyloxycycloheptene intermediate 2.12 as the silicon-oxygen bond was labile and upon extended exposure to silica gel would fragment. In order to prevent silicon-oxygen bond cleavage all columns were run with 1% triethylamine added to the mobile phase. Also, the ester functionality limited the cleavage conditions to using HF•pyridine. Since the ester was not compatible with the use of MeLi we were left to the formation of the unstable...
silylfluoride precursor. The silyloxy ring was opened using HF•pyridine to cleave the silicon-oxygen bond and afford the unprotected alcohol 2.13 with the silane bearing a fluoride, Scheme 2.8. The material was unstable on silica gel and was therefore used crude for subsequent cyclopropanation.

2.11 Cyclopropanation of Silylfluorides with Triflic Anhydride

The molecule, 2.13, was now set up for activation. The desired features were in place, a homoallylic alcohol with an allylic substituent (ethyl ester) and a dimethylfluorosilane to stabilize the cyclopropyl carbinyl cation. The cyclopropane precursor 2.13 was dissolved in methylene chloride with several equivalents of 2,6-lutidine and cooled to -78°C. Then, two equivalents of triflic anhydride were added directly via syringe, Scheme 2.9. The reaction seemed to proceed instantaneously by TLC, but upon work-up this was found not to be the case. After several more attempts the cyclopropanation reaction yielded a single
cyclopropane, 2.14 in a modest 40% yield. A major undesired product was the protodesilylation compound 2.15, therefore it was postulated that the triflic anhydride was contaminated with triflic acid. However, even when freshly distilled triflic anhydride (from phosphorous pentoxide) was used, the yield could not be improved. Through different activation conditions and a slightly modified substrate the yield was improved to an acceptable level (vide infra).

![Scheme 2.9](image)

a) Tf$_2$O, 2,6-lutidine, -78°C, 40%

**Scheme 2.9**

**2.12 Sequence with syn-Diastereomer**

Even though the initial result was discouraging based on the yield of the anti-diastereomer, only one product did form as a single diastereomer 2.14. In order to investigate the synthetic pathway the syn-alcohol 2.10 was taken through the
RCM sequence, Scheme 2.10. The protection and RCM with the 1st generation catalyst generated 2.17 in 83% for the two steps. The subsequent silicon-oxygen bond cleavage with HF•pyridine proceeded in quantitative yield to afford the desired cyclopropane precursor 2.18. This compound was then exposed to the standard cyclopropanation conditions and after one hour at -78°C clean cyclization had occurred to afford cyclopropane 2.19. After purification, 70% yield was obtained from the syn-homoallylic alcohol 2.10. This was very interesting compared to the 40% from the anti-homoallylic alcohol 2.9. After running these two cyclizations several times it was found that this was not an experimental error but a reproducible result.

Scheme 2.10

a) allylchlorodimethylsilane, Et₃N, CH₂Cl₂, 90% b) Grubbs' 1st generation catalyst, 40°C, 92% c) HF•pyr, THF d) Tf₂O, 2,6-lutidine, -78°C, 70%
2.13 Question of Stereochemistry

As discussed in the introduction, the most important aspect of the method was in the development of a stereoselective synthesis of 1,2,3-trisubstituted cyclopropanes. The method’s usefulness would be gauged by the predictability of the diastereoselectivity based on the stereochemistry of the starting homoallylic alcohol. Therefore, it was essential to determine the stereochemical identity of the cyclopropane and develop a model for predicting its formation. The goal being that regardless of the starting homoallylic alcohol one started with, one could easily predict the end cyclopropane product.

Our original hypothesis was based on the stereoselectivity of the 1,2-disubstituted cyclopropanes. As seen in the two transition states for the disubstituted cyclopropane (Figure 2.4) it is clear that TS-B is favored relative to TS-A and therefore the stereochemistry of the cyclization is controlled by 1,3-steric interactions alone. However, now that a substituent was introduced at the allylic position the favored transition state became less clear. Experimental analysis of the cyclopropane product was necessary to determine the stereochemistry.
2.14 NMR Experiments to Determine Relative Stereochemistry

Determination of the cyclopropane stereochemistry was accomplished using simple $^1$H-$^1$H decoupling experiments on a 600MHz NMR. Vicinal coupling constants of cyclopropane protons can be used to determine their relative stereochemistry. The _trans_ protons have a dihedral angle of approximately 120° and this is seen as a 4-9Hz coupling constant, while the _cis_ protons have a dihedral angle of approximately 0° and a larger coupling constant 7-13Hz is usually observed, Figure 2.8.

The NMR data on the cyclopropane 2.14 derived from the _anti_-homoallylic alcohol 2.9 bearing the allylic ethyl ester made it clear that the geometry about the phenethyl and vinyl group was _trans_. The ester’s $\alpha$-proton (H$_a$, Figure 2.9) was the least complex, as it is only coupled to the two adjacent cyclopropane protons yielding a doublet of doublets (dd) at 1.75ppm. The coupling constants were, $J = 9.0$Hz, 4.5Hz allowing for the conclusion that ester was _cis_ in relationship to one proton and _trans_ to another. This immediately made it clear
that the phenethyl and vinyl group were \textit{trans} to each other. After decoupling the cyclopropane proton adjacent to the vinyl group (H\textsubscript{c}, Figure 2.9), the (dd) at 1.75ppm reduced to a doublet with a coupling constant of 9.0Hz. Therefore, the ester and phenethyl group are \textit{cis}. The NMR had illustrated that 2.14 is the diastereomer produced from the cyclopropanation reaction of 2.13, Figure 2.9.

![Figure 2.9](image)

\[ \begin{align*}
J_{ab} &= 9.0 \text{Hz} \\
J_{ac} &= 4.5 \text{Hz} \\
J_{bc} &= 4.5 \text{Hz}
\end{align*} \]

The NMR data on cyclopropane 2.18 derived from \textit{syn}-homoallylic alcohol gave a unique virtual triplet at 1.48ppm with a coupling constant of 4.5Hz. The signal was from the ethyl ester \(\alpha\)-proton (H\textsubscript{a}, Figure 2.10), and from this peak alone it was concluded that the vinyl functionality and the phenethyl substituent were both \textit{trans} to the ethyl ester. The structure was assigned as 2.18, Figure 2.10.

![Figure 2.10](image)

\[ \begin{align*}
J_{ab} &= 4.5 \text{Hz} \\
J_{ac} &= 4.5 \text{Hz} \\
J_{bc} &= 9.0 \text{Hz}
\end{align*} \]

Shown below are the four possible cyclopropane diastereomers that could be obtained from 2.13 and 2.18, Scheme 2.11. The top two structures are possible
from an inversion process on the anti-precursor 2.13, and the bottom two are the
other possible diastereomers that could arrive from an inversion of the syn-
precursor 2.18. The only cyclopropane formed during the activation of the anti-
alcohol is compound 2.14, while the only compound obtained from the activation
of the syn-precursor is compound 2.19. These results suggest that the product
formation was occurring with kinetic control and that there was no ring
fragmentation (thermodynamic equilibrium), but we had to be certain. The above
results did prove that we had accomplished a stereoselective synthesis, but it
was still not perfectly clear an enantiomerically pure synthesis of 1,2,3-
trisubstituted cyclopropane could be performed. This led to an investigation
using an Evans’ Aldol adduct.

Scheme 2.11
2.15 Closure of the Evans’ Aldol Product

In a final experiment to prove that the cyclopropanation was occurring with NGP and without operation of an $S_{N\ell}$ mechanism, the homoallylic alcohol with the Evans’ auxiliary was taken through the cyclopropane sequence, Scheme 2.12. This sequence was accomplished using similar conditions as shown before. Homoallylic alcohol 2.20 was protected with allylchlorodimethylsilane to afford the diene 2.21. This compound was subjected to Grubbs 2nd generation catalyst to afford the masked cyclopropane precursor, 2.22. The silicon-oxygen bond was cleaved with HF•pyridine to afford the desired cyclopropane precursor 2.23. Activation with triflic anhydride at -78°C afforded a single cyclopropane diastereomer, 2.24. The structure was assigned by NMR decoupling experiments as described in Section 2.14.
This result was instrumental in proving that the cyclopropanation reaction was proceeding with NGP and not through a direct ionization ($S_{N1}$-like). If ionization had occurred, the resulting cyclopropane that formed would have been two diastereomers since attack could occur at either face of the cation. But, since the reaction proceeded to give only one diastereomer we can conclude that the reaction mechanism is NGP (more discussed below).

Scheme 2.12

a) allylchlorodimethylsilane, Et$_3$N, CH$_2$Cl$_2$, 95%  b) Grubbs' 1st generation catalyst, 40$^\circ$C, 90% c) HF-pyr, THF d) Tf$_2$O, 2,6-lutidine, -78$^\circ$C, 40%
Now that it was clear the mechanism operating was NGP and the structure of all the 1,2,3-trisubstituted cyclopropanes had been determined by NMR we developed a model to predict future cyclopropane synthesis. In addition, the cyclopropane chemistry was also carried out on the \textit{anti}- and \textit{syn}-homoallylic alcohols with a methyl group at the allylic position (work accomplished by H. Yuan) with similar stereochemical results. Two factors were found to explain, or predict, the stereochemical outcome of the key cyclization step: (1) The alcohol stereocenter was being displaced by the allylsilane with inversion by NGP. (2) The system was under kinetic control and has only two transition state conformations available to close the cyclopropane. The allylsilane $\pi$ orbital must overlap with the anti-bonding orbital of the carbon-triflate bond, and in doing so the trimethylsilane group can either be on the same side as the phenethyl group or opposing it, Figure 2.11. After studying the stereochemistry of the 1,2,3-trisubstituted cyclopropanes, a model was developed for the prediction of the stereochemical outcome. It was determined that the most important interaction was A$_{1,3}$-strain between the substituent at the apex position and the olefin of the allylsilane group.

First, taking all the cases in which the allylic substituent is \textit{anti} to the alcohol, the allylic substituent and vinyl groups are \textit{trans} in all the cyclopropanes.
produced. Looking at Figure 2.11 it is evident that of the two possible transition states the one leading to the product, \textit{anti-TS-B}, has the allylic substituent opposing the allylsilane. Clearly \textit{anti-TS-A} is extremely strained, as all three substituents would be on the same side. However, this result did not allow us to conclude which factor was controlling the transition state geometry because the stereochemical outcome is identical to what was seen in the synthesis of 1,2-disubstituted cyclopropanes. Therefore from this result it was still unclear if the steric about the bond forming controls the stereochemistry or if the added substitution played a role.

Remarkably one phenomenon is consistent for the cyclizations on the \textit{syn}-precursors as well. The vinyl group and the allylic group are \textit{trans} in the final product. But, in these cases the substituents at the forming bond, the phenethyl
and vinyl groups are *cis*. The two possible conformations for closure with NGP for the *syn*-diastereomer are seen in Figure 2.12. *Syn-TS-A* is the transition state leading to product, it has two substituents *cis* and two substituents *trans*. *Anti-TS-B* also has the same number of substituents *cis* and *trans*, therefore it is unclear which TS should be favored. Amazingly, $A_{1,3}$-Strain of the substituent introduced at the allylic position was found to be the most important factor in the cyclization reaction. Since the bond forming is longer than an actual bonds in the TS, the closing bond should have less of an effect than the bonds already in place. Interestingly, the cyclopropane ring closes in a conformation that is not accessible to the 1,2-disubstituted cases.

![Figure 2.12](image)

Therefore, the outcome of the cyclization can be determined from the starting alcohol simply be applying a model that states the allylsilane moiety will adopt a
conformation that is away from the allylic substituent due to $A_{1,3}$-Strain, \textit{syn-TS-A}
and \textit{ant-TS-B}. This model is consistent with all the 1,2,3-trisubstituted
cyclopropanes produced using this sequence regardless of the electronics of the system, Table 2.2.
<table>
<thead>
<tr>
<th>homoallylic alcohol</th>
<th>silyloxy-cycloheptene</th>
<th>cyclopropane</th>
</tr>
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<td><img src="image10" alt="Structure" /></td>
<td><img src="image11" alt="Structure" /></td>
<td><img src="image12" alt="Structure" /></td>
</tr>
</tbody>
</table>

**TABLE 2.2**

- a) allylchlorodimethylsилane, imid.
- b) [(Cy)_3P]_2Cl_2Ru=CHPh
- c) HF•pyr, THF
- d) Tf_2O, 2,6-lutidine

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2.17 Advances in Synthesis of 1,2,3-Trisubstituted Cyclopropanes: Cross Metathesis

At this point a reliable method had been developed for the preparation of 1,2,3-trisubstituted cyclopropanes starting from allylic substituted homoallylic alcohols. The procedure entailed a four-step sequence with an overall yield ranging from 32% to 64%. However, modification of the sequence was desired due to the poor yield of cyclizations of substrates 2.13 and 2.23 and due to the limitations of cryogenic conditions. Also it would be beneficial to compete with the one step protocol of the Simmons-Smith reaction, so a shorter sequence was necessary. To this end, we began to explore the cross metathesis of homoallylic alcohols with allyltrimethylsilane. By installing the allylsilane in one step with a cross metathesis reaction between allyltrimethylsilane and the homoallylic alcohol, the need for protection and deprotection would be eliminated and the sequence would be reduced to two steps. However, at this time the 1st generation Grubbs catalyst was not able to complete such a task. We were limited to tethering the allylsilane to the alcohol providing the intramolecular reaction pathway. Therefore, the 2nd generation catalyst, Figure 2.7, was synthesized in our group and allowed for the exploration of the cross metathesis reaction with substituted homoallylic alcohols and allyltrimethylsilane.
The cross metathesis was performed with both anti and syn ethyl ester substituted homoallylic alcohols (2.9 and 2.10) and the Evans’ aldol product 2.18. It was found that, by using just two equivalents of the allylsilane and 5 mol % of the catalyst in methylene chloride at reflux, the reaction resulted in efficient formation of the key carbon-carbon double bond.

First the anti homoallylic alcohol 2.9 was subjected to the cross metathesis with two equivalents of allyltrimethylsilane in methylene chloride at a concentration of 0.1M with 5 mole % of the 2nd generation Grubbs catalyst, Scheme 2.13. The result was high conversion to the desired cyclopropane precursor 2.25 in a 9:1 E:Z ratio. With the trimethylsilane group in place rather than the fluorosilane, the product could be purified by column chromatography. This precursor was also able to be stored for long periods of time without decomposition unlike the precursor resulting from ring cleavage with HF•pyridine. At this time we began to explore the key cyclization from activation with triflic anhydride.

\[
\begin{align*}
\text{Ph} & \quad \text{EtO}_2\text{C} & \quad \text{OH} & \quad \text{a} & \quad \text{Ph} & \quad \text{EtO}_2\text{C} & \quad \text{OH} & \quad \text{Si(CH}_3\text{)}_3 \\
2.9 & & & & & 2.25 & & 9 : 1
\end{align*}
\]

\(a)\) Grubbs' 2nd generation catalyst, 40°C, 90%
2.18 Problem with Cross Metathesis

The trimethylsilane precursor was treated under standard activation conditions, and an unusual problem arose. Instead of clean cyclization the reaction resulted in about a 75% yield of a 1:1 mixture of 1,2,3-trisubstituted cyclopropane 2.14 and the trimethylsilane protected starting material 2.26, Scheme 2.14. This was a very interesting result since the main change was the single methyl group in place of fluoride on the silane.

\[
\begin{align*}
\text{Ph} & \quad \text{EtO}_2\text{C} \\
\text{OH} & \quad \text{Si(CH}_3)_3 \\
\text{Ph} & \quad \text{EtO}_2\text{C} \\
\text{H} & \quad \text{CO}_2\text{Et} \\
\text{Ph} & \quad \text{Ph} \\
\text{H} & \quad \text{H} \\
\text{Path A} & \quad 1:1 \\
\text{Path B} & \quad 1:1
\end{align*}
\]

\[\text{a) Tf}_2\text{O, 2,6-lutidine, -78°C, 78%}\]

Scheme 2.14

As shown in Scheme 2.15 the undesired silylation could have occurred by two very different pathways. Silylation from Path A occurred in the last step of vinylcyclopropane formation when the alcohol of the starting material acted as a nucleophile in the elimination of the silane. Path B shows that the by-production of TMS-triflate lead to silylation of the starting material in competition with its
activation. However, silylation was not always a problem. In experiments with other activators such as thionyl chloride (to be discussed), in which TMS-chloride is the main by-product, the result was only a trace amount of silylated starting material. Therefore, the problem of silylation has been overcome, but the pathway for its occurrence cannot be discerned. It is known that TMS-chloride is a less potent silylation agent than the triflate homologue, and this may be the reason for less silylation. However, chloride is also a much better nucleophile for the elimination of trimethylsilane compared to triflate or the starting hydroxyl. Therefore, since several variables had been changed at once, it is not known if the chloride more effectively promotes the elimination process, or if the rate of silylation by TMS-chloride was slower than activation of the secondary alcohol. Regardless of the mechanism, new conditions needed to be found.
In order to resolve the issue of undesired trimethylsilyl ether formation, we explored different activating conditions. Although triflic anhydride and 2,6-lutidine in methylene chloride have shown remarkable success for the activation of secondary and primary homoallylic alcohols for cyclopropanation, these conditions require low temperature, inert atmosphere, and the production of trimethylsilyl-triflate as the main by-product and can result in unfavorable silylation of the starting alcohol. It would be ideal to find activation conditions that
are less sensitive to air, can be carried out at room temperature, and do not produce a potent silylating reagent.

2.19 A Search for Alternative Activation Conditions

In the search for better activation conditions for cyclopropanation, the leaving group was first attenuated, Table 2.3. By lowering the energy of the intermediate, higher temperatures would be required for the cyclopropanation hopefully allowing the reaction to be run at room temperature. Mesyl anhydride was the first choice due to its similarity in structure with triflic anhydride and its difference in reactivity. The reaction was carried out at both $-78^\circ C$ to room temperature, and room temperature to reflux in methylene chloride. At room temperature the mesylate intermediate was isolable, having not enough energy to form the highly strained cyclopropane bond. Therefore, the isolated mesylate was put back in the flask and heated to reflux in methylene chloride, upon which cyclopropanation occurred, albeit in moderate yield. This procedure did produce the desired product, but required two steps. Any attempt to modify the procedure to a one step process was not successful. Therefore other conditions were explored in light of the poor yield produced with mesyl anhydride (all in Table 2.3).
In order to do a direct comparison for the activation conditions, all reactions were performed on the hydrocinnamaldehyde derivative cyclopropane precursor 2.27a, Table 2.3. First, thionyl chloride was attempted in the presence of three different bases and produced cyclopropane in similar yields, 73% - 82%. Even though extensive investigation of the base has not been explored, 2,6-lutidine consistently gave higher yields than pyridine or triethylamine.
Therefore, all cyclopropanations with thionyl chloride have since been carried out with 2,6-lutidine. \(^1\)H NMR analysis of the crude reaction revealed both protodesilylation 2.27d and chlorination products 2.27e and 2.27f, but only in trace amounts. The reaction required an excess of base, 3 to 6 equivalents, and
at least 1.5 equivalents of thionyl chloride. The reaction gave the best results when started at 0°C and brought to room temperature.

Even though thionyl chloride activation had made these reactions much more convenient, alternative methods for activation were also explored. Next, the secondary alcohol 2.27a was activated under Mitsunobu conditions. Triphenylphosphine and several azodicarbonyl-compounds were tried. The first attempt was made using standard conditions, Ph₃P and DEAD, with no success. Formation of the activated phosphine reagent was observed by precipitate formation prior to addition of the alcohol, but no cyclopropane was revealed by NMR analysis. DIAD and ADDP were also used to activate the phosphine. Regardless of azodicarbonyl used, no cyclopropane 2.27b was seen. After consideration of the mechanism, Scheme 2.16, it was thought that the intermediate nitrogen anion salt 2.27j might not get protonated under the initial conditions and therefore not allow the alcohol to attack the phosphorus resulting in poor activation. To circumvent this problem either one equivalent of benzoic acid or hydrochloric acid (in ether) was added to the preformed salt prior to addition of the alcohol. Unfortunately, this did not solve the problem, and no cyclopropane formation was observed. At this point, modified Mitsunobu conditions were explored. Activation with Ph₃P, triethylamine, and carbon tetrachloride was tried with no success. Therefore, Mitsunobu conditions were abandoned.
Our luck with sulfur reagents led us to explore conditions using $\text{SO}_3\cdot\text{pyridine}$ and DMSO with triethylamine. The idea was that the activated alcohol would be displaced, Path A, rather than oxidized, Path B, in the presence of the intramolecular allylsilane, Scheme 2.17. Unfortunately, these conditions did not give the desired cyclopropane, but rather resulted in ketone 2.27g and 2.27h, proto-desilylation 2.27d, and mostly recovery of starting material 2.27a. Similar conditions were tried using activated phenyl sulfoxide. Having no $\alpha$-protons it was thought that once the activation took place the only plausible outcome was displacement by the olefin. Activation of phenyl sulfoxide was accomplished with oxalyl chloride and acetic anhydride. However, this also resulted in
protodesilylation \(2.27d\) and recovery of starting material \(2.27a\), neither method gave the desired cyclopropane.

Scheme 2.17

After experimenting with multiple modes of hydroxyl activation, it was concluded that thionyl chloride, triflic anhydride, and mesyl anhydride are currently the best reagents capable of cyclopropanation of the homoallylic alcohol derived from hydrocinnamaldehyde. Thionyl chloride is superior to triflic anhydride being used at room temperature and minimizing silylation of the starting alcohol. Mesyl anhydride is a viable activator for cyclopropanation, but in the simple hydrocinnamaldehyde system is not as effective as thionyl chloride. Other results (not discussed) have shown that with more complex substrates mesyl anhydride is as effective as thionyl chloride; however, currently thionyl chloride is the method of choice. Table 2.3 shows the results from the activation
Regardless, the new conditions using thionyl chloride made it possible for the cyclization to be carried out at 0°C and greatly improved the sequence since this allowed us to get away from the cryogenic conditions necessary when using triflic anhydride.

2.20 Thionyl Chloride: Solving the Activation of TMS Precursor

With conditions for the cyclization worked out for the simple system, the next logical step was to optimize the thionyl chloride activation of the anti-precursor 2.25. Amazingly the reaction went with 80% yield when carried out from 0°C to room temperature over a 2 hr period, Scheme 2.18. The poor cyclization of substrate 2.13 was overcome by modifying the substrate to the more stable TMS derivative 2.25 and using thionyl chloride.

Scheme 2.18

\[
\begin{align*}
\text{a) SOCl}_2, & \quad 2,6\text{-lutidine, } 0^\circ\text{C, } 78\% \\
\end{align*}
\]
Next, the new synthetic strategy using the cross metathesis and activation with thionyl chloride was carried out on the syn-homoallylic alcohol 2.16 with the ethyl ester and the Evans’ product, Table 2.4. Starting with substrate 2.10 the cross metathesis was performed using the conditions outlined above and resulted in a 80% yield of a 7:1 ratio of E:Z isomers 2.28, Scheme 2.19. The mixture of isomers were then activated with thionyl chloride at 0°C in methylene chloride and resulted in the clean cyclization to give the desired trisubstituted product 2.19 in good yield.

![Scheme 2.19](image)

a) Grubbs' 2nd generation catalyst, 40°C, 90% b) SOCl₂, 2,6-lutidine, 0°C, 78%

Again, the last test was to synthesize the trisubstituted cyclopropane from the cyclization of the Evans’ product 2.20, Scheme 2.20. This would prove that changing the substrate’s olefin geometry and that going from dimethylfluorosilane to the trimethylsilane would have no affect on the mechanism of reaction. The Evans’ product 2.20 underwent CM with allyltrimethylsilane and afforded the cyclopropane precursor 2.29 as a 95:5 mixture of E:Z isomers. The mixture of
isomers was activated at 0°C with thionyl chloride using the standard conditions to afford a single diastereomer product 2.24. The stereochemistry of this product was as predicted using the model developed from earlier results. This result indicated that the changes did not affect the mechanism and that this was inversion by NGP.
### TABLE 2.4

<table>
<thead>
<tr>
<th>Homoallylic Alcohol</th>
<th>Selectivity</th>
<th>$E : Z$</th>
<th>Cyclopropane</th>
</tr>
</thead>
<tbody>
<tr>
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<td><img src="image2" alt="Selectivity 1" /></td>
<td>9 : 1</td>
<td><img src="image3" alt="Cyclopropane 1" /></td>
</tr>
<tr>
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<td><img src="image5" alt="Selectivity 2" /></td>
<td>7 : 3</td>
<td><img src="image6" alt="Cyclopropane 2" /></td>
</tr>
<tr>
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<td><img src="image8" alt="Selectivity 3" /></td>
<td>7 : 3</td>
<td><img src="image9" alt="Cyclopropane 3" /></td>
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<tr>
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<td><img src="image11" alt="Selectivity 4" /></td>
<td>9 : 1</td>
<td><img src="image12" alt="Cyclopropane 4" /></td>
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<td><img src="image14" alt="Selectivity 5" /></td>
<td>&gt; 9 : 1</td>
<td><img src="image15" alt="Cyclopropane 5" /></td>
</tr>
</tbody>
</table>

**Notes:**
- a) Grubbs' catalyst 2nd Gen., 40°C
- b) SOCl₂, 2,6-lutidine, 0°C - rt
2.21 Future Directions for Trisubstituted Cyclopropanes, Heteroatom Stabilization

We have developed a useful method for the construction of 1,2,3-trisubstituted cyclopropanes with a vinyl substituent “inherent” to the reaction pathway. The use of the $\beta$-silicon effect has allowed stereochemical control of the resulting product and has shown to be an efficient reaction. The overall synthetic achievement has been to develop a method for the stereoselective synthesis of trisubstituted cyclopropanes using cationic methodology that would be useful in the lab and be competitive with the Simmons-Smith methodology. To this end, we have shown that in two steps one can transform an allylic substituted homoallylic alcohol into a 1,2,3-trisubstituted cyclopropane using the cross metathesis route.

However, there are still advances that can be made, and we have begun to develop a new cyclization reaction based on heteroatom stabilization. Figure 2.13 shows how the lone pair of electrons on nitrogen can be used to stabilize the adjacent cation. The advantage of using a heteroatom such as nitrogen, in that following aqueous work-up, an aldehyde can be obtained from the hydrolysis of the intermediate iminium ion. This would add another degree of flexibility to the synthesis of cyclopropanes.
By exploiting the methodology of Beak and coworkers\textsuperscript{40} for the synthesis of homoaldol adducts, one has access to the desired cyclopropane precursor. The retrosynthesis shows the desired cyclopropane precursor, Scheme 2.21.

Investigation was begun on the activation of these substrates for cyclopropane formation.

The substrates necessary to test the cyclopropanation reaction with heteroatom stabilization were prepared using Beak’s method, Scheme 2.22. The initial substrate was prepared following Beak’s protocol on hydrocinnamaldehyde for the synthesis of allylic substituted homoallylic enamines. In this case the substrate with the methyl substituent at the central position was first prepared. This precursor 2.31 was then activated with triflic anhydride using the standard cyclopropanation conditions. The result was a 70\% yield of the desired
cyclopropane product 2.32 as one diastereomer. This work was also carried out with the phenyl substituted hydrocinnamaldehyde derivative and resulted in clean cyclization to afford compound 2.35.

Scheme 2.22

This work needs to be explored further as we have only proven the concept. At this time work needs to be done to ascertain the enantiomeric purity of the sequence and test the scope and limitations of this sequence. Remarkably, with this new trapping group, we still see formation of a single diastereomer. The diastereomer that forms can be predicted using the model developed earlier.
2.22 Summary

This chapter has described the early results on the synthesis of disubstituted vinyl cyclopropanes using both the boronacetylide fragmentation of oxiranes and the RCM reaction starting from homoallylic alcohols. Briefly stating the advantages of the two routes. After this, an introduction to the synthesis of 1,2,3-trisubstituted cyclopropanes was discussed using methodology that is highlighted by using Grubbs’ catalyst to form the key carbon-carbon double bond. Activation conditions were then modified and the use of less aggressive activation conditions was accomplished that allowed for cyclization of several precursors. This was followed by a discussion of the cross metathesis between homoallylic alcohols and allyltrimethylsilane to shorten the sequence to the desired cyclopropane precursors. Lastly, the next generation of cyclopropane methodology was introduced using heteroatom stabilization.

In conclusion, we have shown a robust route for the synthesis of 1,2,3-trisubstituted cyclopropanes. The route can be accomplished on a variety of substrates and has shown to be useful for the preparation of enantiomerically enriched material. Cyclopropanes can be prepared in two steps from simple substrates in high yield using the cross metathesis route. We have also proven that the relative stereochemistry around the cyclopropane can be predicted from
the starting homoallylic alcohol lending this route to the controlled synthesis of complex material.
CHAPTER 3

SYNTHESIS OF OXYGENATED CYCLOPROPANES

3.1 Purpose

During the synthesis of 1,2,3-trisubstituted cyclopropanes it was discovered that a common intermediate in the synthetic sequence could be exploited for the synthesis of $\alpha$-hydroxycyclopropanes. Figure 3.1 depicts the three intermediates that can be exploited, as all three molecules bear a functional group that can be reduced to a primary alcohol. The synthesis of $\alpha$-hydroxycyclopropanes is of synthetic interest because these molecules can be used in the direct synthesis of cyclopropane containing oxylipins$^{41}$ or they can be converted to divinyl cyclopropanes$^{42}$ through $\beta$-elimination of the alcohol, Figure 3.2.
This chapter will detail the synthesis of α-hydroxycyclopropanes from the common intermediates 2.12 and 2.17 and discuss the subsequent elimination of the α-hydroxyl group to form trans-divinylcyclopropanes. Also, the attempted synthesis of cis-divinylcyclopropanes will be discussed along with the reasons for failure to accomplish this goal. cis-Divinylcyclopropanes are of synthetic interest because they undergo the spontaneous Cope rearrangement to provide access to 1,4-cycloheptadienes, Figure 3.3. Lastly, this chapter will outline the future use of this method for the synthesis of Hormosirene, a divinyl cyclopropane containing natural product, Figure 3.4.
3.2 Analysis of Synthetic Sequence to $\alpha$-Hydroxycyclopropanes

Access to oxygenated cyclopropanes can be established using the common intermediates (2.12, 2.17, and 2.22) obtained during the synthesis the 1,2,3-tribubstituted cyclopropanes. The intermediate has two cyclopropane precursors latent within the molecule, Figure 3.5. Chapter 2 discussed the unmasking and activation of the secondary alcohol in the synthesis of 1,2,3-trisubstituted cyclopropanes, Path A. Now, this chapter will discuss the activation of the primary hydroxyl that was revealed by reduction of the carboxylate functionality, Path B. The system illustrated in Path B is unique since cyclization to form a cyclopropane can be done either with the silyloxy ring intact, as shown, or with
the straight chain precursor after cleavage of the silyl ether. With the ring intact the substituents are restricted by the seven membered ring, holding them cis during the cyclization step. This feature allows for the synthesis of cis-1,2-disubstituted cyclopropanes. Then, in the alternate sequence the tether is broken before cyclization allowing for access to the trans-isomer after activation of the same primary hydroxyl.

![Chemical structures](image)

**Figure 3.5**

### 3.3 Synthesis of the Model cis-Vinylcyclopropane: Reduction of Ester

As detailed in Chapter 2, 2.12 was synthesized from 2.9 (Scheme 2.7) in excellent yield. With this compound in hand attempts to reveal the latent cyclopropane precursor with the silyloxy ring intact were made. Initially ester 2.12 was exposed to 5-10 equivalents of lithium aluminum hydride at -78°C,
Scheme 3.1. The conditions reduced the ethyl ester as desired but also cleaved the silicon-oxygen bond to afford 3.6 in excellent yield. The production of this compound was made apparent by the strong Si-H bond stretching frequency in the IR spectra at 2115 cm\(^{-1}\). To avoid the undesired fragmentation of the silyloxy ring, DIBAL was used in place of LiAlH\(_4\). The stoichiometery of the hydride source was controlled by using a 2 M DIBAL solution allowing for the precise addition of 2.2 equivalents of DIBAL. The reaction was carried out from -78°C to 0°C over a period of several hours, and a 68% yield of the desired compound 3.7 was obtained, Scheme 3.2. The low yield is attributed to the production of a 10-15% of the aldehyde 3.8 and a 10-15% of the ring fragmented diol 3.6.

Optimization of the reducing agent led to improvement of the synthetic sequence. By using LiBH\(_4\) in THF for the reduction, an 88% yield of the desired compound 3.7 was obtained. Attempts to improve this yield further only resulted in fragmentation of the silicon-oxygen bond.

\[
\begin{align*}
\text{Scheme 3.1} \\
\text{a) LiAlH}_4 \ 5-10\text{eq}, -78^\circ\text{C}, 86\%
\end{align*}
\]
3.4 Activation of the Primary Hydroxyl

With conditions for the reduction optimized, the cyclopropanation reaction involving activation of the primary hydroxyl of 3.7 was tested. Stability of the silyloxy ring was of concern since the bond was known to be labile and its cleavage was facilitated by long exposure to silica gel. The acidic cyclopropanation conditions could fragment the tether and if this were to occur before cyclization, the desired stereochemical control would be lost as the cyclization would take place without the conformational restriction of the substituents. This system is made more complex by the geometry of the allylsilane neighboring group. Since the silyloxy ring restricts the conformation of the allylsilane, complete overlap of the carbon-silicon $\sigma$-bond with the $\pi$-orbital of the olefin is not possible, Figure 3.6. With the ring in place the geometry of the
silicon carbon bond to the forming cation’s $\pi$-orbital is virtually orthogonal. Therefore the desired vertical alignment is not allowed and the rate enhancement by the $\beta$-silicon effect is negligible. This drastically alters the rate of ring closure compared to the previous examples in our lab in which there was no restriction of the allylsilane geometry. Furthermore, when the cyclopropane ring forms without full hyperconjugation of the silicon-carbon bond with the cyclopropyl carbinyl cation, the stability of the system is greatly diminished. This increase in energy could lead to potential rearrangement of the cation and capture of undesired rearranged products. Regardless of these concerns the reaction was attempted leaving all these questions to be answered following the reaction.

Figure 3.6
The primary hydroxyl of compound 3.7 was activated under standard conditions with 1.25 equivalents of triflic anhydride and 3 equivalents of 2,6-lutidine at -78°C to afford a 68% yield of cyclopropane 3.9 and a complex mixture of byproducts, Scheme 3.3. 1H NMR analysis of the crude reaction mixture revealed that there were multiple silylated cyclopropane products, 3.10. To resolve the problem with silylation, the crude mixture was treated with HF•pyridine in THF at room temperature for 10 minutes, at which point the complex mixture resolved. The result was isolation of cyclopropane 3.9 in an 88% yield over the two steps. Stereochemical determination of the α-hydroxyvinylcyclopropane 3.9 was made by NMR analysis (as described in Chapter 2, Section 2.9). The compound was determined to have cis-stereochemistry around the cyclopropane ring as desired. Remarkably no other cyclopropane isomers were observed.
3.5 Problems with Silylation

The reaction sequence detailed in Scheme 3.3 worked well, but unfortunately required two steps to give the desired cyclopropane 3.6. The need to use HF•pyridine to clean the reaction mixture was unacceptable, and a one-pot procedure needed to be developed to allow for clean cyclization without production of the silylated byproducts. This goal was accomplished by slightly altering the reaction conditions, Scheme 3.4. Simply by using an excess of freshly distilled triflic anhydride, 4-10 equivalents, and only 1.5 equivalents of 2,6-lutidine, the problem was averted. After the cyclization was complete the reaction was quenched with 25 equivalents of water and allowed to stir for an hour at room temperature, during this time the excess triflic anhydride was quenched thereby producing several equivalents of triflic acid. The acidic mixture was stirred until TLC analysis revealed that desilylation had taken place. After isolation, ¹H NMR revealed clean production of the desired cyclopropane 3.6 without contamination of the silylated byproducts. It is important to note that the triflic anhydride used was always freshly distilled. When triflic anhydride with any contamination of triflic acid was used, a mixture of products was obtained. Both the desired cis-1,2-disubstituted and the undesired trans-1,2-disubstituted cyclopropanes will result from exposure to triflic acid during the reaction.
3.6 *cis*-Vinylcyclopropane Stereochemistry

The cyclization of **3.7** proceeded in excellent yield and was the first example in our lab of using a ring to control the stereochemistry of the cyclopropanation reaction, Scheme 3.4. The next step was to take the *syn*-diastereomer **2.17** through the same sequence and determine if the reaction was stereoselective as well, Scheme 3.5. Compound **2.17** was reduced with LiBH₄ to afford **3.11** in 87% yield. The molecule was then activated using the optimized conditions, excess triflic anhydride, and after 1 hr the mixture was quenched with 25 equivalents of water and stirred. TLC of the reaction mixture showed clean desilylation. After column chromatography 91% yield of a single diastereomer **3.12** was observed. NMR analysis of the compound revealed the cyclopropane had *cis*-geometry as expected. With both the *syn* and *anti*-diastereomers taken through the sequence...
to give 1,2-cis-disubstituted cyclopropanes, a discussion of transition state that led to their production is possible. Figure 3.7 illustrates how the syn and anti diastereomers only differ about the stereochemistry of one center on the seven membered ring and how this center plays no role in the cyclization reaction. The figure depicts how the two substituents on the forming cyclopropane ring are held back in the seven membered silyloxy ring which results in formation of the cis-isomer. In this case, unlike earlier examples in Chapter 2, there is no inversion of the secondary alcohol center, therefore the relative stereochemistry in the starting material is retained in the cyclopropane 3.12.

\[ \text{Scheme 3.5} \]

\[ \text{a) LiBH}_4, \text{rt, 90\% b) Tf}_2\text{O, 2,6-lutidine, -78}^\circ\text{C, 91\%} \]
3.7 Synthesis of the Model \textit{trans}-Vinylcyclopropane

After the initial studies on the synthesis of \textit{cis}-vinylcyclopropanes, Schemes 3.4 and 3.5, our next goal was to synthesize their geometric isomers, the \textit{trans}-vinylcyclopropanes. The substrates necessary for the synthesis of the \textit{trans}-vinylcyclopropanes were also obtained from the common intermediate 2.12. The desired cyclopropane precursor is diol 3.6 that was initially generated when attempting to reduce the ethyl ester with Li\textsubscript{4}AH. Exposure to Li\textsubscript{4}AH cleaved the silicon-oxygen bond along with reduction of the ester to afford the desired diol 3.6, Scheme 3.1. Compound 3.6 could also be prepared by exposure to 6 equivalents of DIBAL to reveal the cyclopropane precursor containing...
allyldimethylsilane group (having a silicon-hydrogen bond). Interestingly this molecule has two hydroxyls that could be activated to form to very different cyclopropanes. Activation of the primary alcohol would lead to a 1,2-disubstituted vinylcyclopropane, but activation at the secondary alcohol would result in formation of the 1,2,3-trisubstituted cyclopropane. The goal was to activate the primary position selectively over the secondary hydroxyl, but we thought this would not be an issue since activation of the primary position is favored kinetically over the secondary center under the reaction conditions. The diol 3.6 was treated under the standard cyclopropanation conditions to afford cyclopropane 3.13 in good yield without detection of the 1,2,3-trisubstituted cyclopropane, Scheme 3.7.

![Scheme 3.7](image)

\[
\text{a) LiAlH}_4 \ 5\text{-}10\text{eq}, -78^\circ\text{C}, 86\% \quad \text{b) Tf}_2\text{O}, 2,6\text{-}\text{lutidine}, -78^\circ\text{C}, 73\%
\]

The stereochemistry of the cyclopropane was determined by $^1\text{H}$ NMR decoupling experiments, and the compound was found to be the trans-cyclopropane, as desired. Next the synthesis of the syn-cyclopropane 3.15 was carried out using the described sequence. This was performed to verify the utility
of the sequence, and as planned the synthesis proceeded in good yield, Scheme 3.8.

These two cyclizations illustrated that we could selectively activate a primary hydroxyl in the presence of the secondary alcohol and that the silane functionality was an effective cation stabilizing group. These cyclizations were nice additions to our repertoire, and these results are shown in Table 3.1 as are the results from the cis-cyclopropanes. The synthetic sequence is direct and is effective regardless of the stereochemistry of the starting homoallylic alcohol used.
TABLE 3.1

<table>
<thead>
<tr>
<th>Intermediate</th>
<th>cyclopropane</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Intermediate 1" /></td>
<td><img src="image2.png" alt="Cyclopropane 1" /></td>
</tr>
<tr>
<td><img src="image3.png" alt="Intermediate 2" /></td>
<td><img src="image4.png" alt="Cyclopropane 2" /></td>
</tr>
<tr>
<td><img src="image5.png" alt="Intermediate 3" /></td>
<td><img src="image6.png" alt="Cyclopropane 3" /></td>
</tr>
<tr>
<td><img src="image7.png" alt="Intermediate 4" /></td>
<td><img src="image8.png" alt="Cyclopropane 4" /></td>
</tr>
</tbody>
</table>

a) LiBH₄, rt  b) Tf₂O, 2,6-lutidine, -78°C c) LiAlH₄ 5-10eq, -78°C
3.8 *trans*-Vinylcyclopropane Stereochemistry

The stereochemical outcome of the cyclizations of both the *anti* and *syn* diastereomers 3.6 and 3.14 to afford the corresponding *trans*-vinylcyclopropanes 3.13 and 3.15 can be explained using a model similar to that seen in Chapter 2. The allylsilane group is unrestricted, and therefore the transition state with the least congested steric environment controls the outcome of the reaction. Assuming that the triflate is displaced with NGP there are two possible transition state structures, Figure 3.8. Transition state A (TS-A) illustrates the higher energy conformation where the two substituents are *cis* to each other. Whereas transition state B (TS-B) depicts the conformation that reduces steric interaction of the allylsilane moiety. This effect was observed previously in Chapter 2. Both of these conformations allow for the allylsilane to displace the triflate group, but TS-B is the favored pathway since there is less steric interaction.

![Figure 3.8](image-url)
3.9 Reactivity of Silanes

To date, our group has used several different silanes for the displacement of the homoallylic triflate, Figure 3.9. Remarkably all have shown great success regardless of the reactivity of the silane. Whether a flouro- or alkoxy-silane with diminished nucleophilicity or the trimethylsilane or hydro-silane with good nucleophilicity, cyclopropanation proceeded efficiently.

Studies have shown that by replacing one methyl group of trimethylsilane with an electronegative atom such as chloride, the nucleophilicity is diminished by 3 orders of magnitude, as discussed in the introduction (Chapter 1). More interesting is that this simple replacement lowers the nucleophilicity below that of isobutene, the nucleophile used by Suzuki\textsuperscript{45} for formation of disubstituted cyclopropanes. Therefore, even in our systems where nucleophilicity is greatly diminished, the reaction proceeds smoothly. This suggests that the formation of the cyclopropane is a rapid process and that the most important role of silicon is in the subsequent elimination step which traps the cation and does not allow for rearrangement.
Another interesting issue of reactivity was discovered when the silane (bearing a silicon-hydrogen bond) was activated. When compound \textbf{3.6} was activated with triflic anhydride, the reaction was less sensitive to the quality of the triflic anhydride reagent. This reaction was performed without freshly distilling the reagent and the yield was unaffected. It is probable that the reaction was less sensitive to presence of triflic acid because the silane precursor aided in cleaning the triflic anhydride reagent by scavenging the potentially harmful triflic acid that remained. This was not surprising, since it is known that triflic acid reacts with silanes to form the silyltriflate.\textsuperscript{46} To test this theory the trimethylsilyl analog \textbf{3.17} was synthesized independently using the Grubbs’ cross metathesis reaction, Scheme 3.9. This was accomplished by taking the mixture of starting homoallylic alcohols (\textbf{2.9} and \textbf{2.10}) and reducing them with LiAlH\textsubscript{4} to afford the \textit{syn} and \textit{anti} diols (\textbf{3.16}). The mixture of diols was dissolved in methylene chloride and refluxed with 2.5 equivalents of allyltrimethylsilane. Then the Grubbs 2nd generation catalyst was added. The precursor was then exposed to the standard cyclopropanation conditions to afford cyclopropanes \textbf{3.13} and \textbf{3.15}. However, when the cyclopropanation was performed on this precursor (\textbf{3.18} or \textbf{3.19}), the yield was very sensitive to the purity of the starting triflic anhydride. The yield was diminished by 10-20\% with undistilled triflic anhydride. This observation led to the conclusion that by adding a small amount of triethylsilane to the reaction, we were able to improve the yields of these reactions by a small, but substantial amount.
Scheme 3.9

a) LiAlH₄ 5-10eq, -78°C, 87% b) allyltrimethylsilane, Grubbs' 2nd generation catalyst, 40°C c) Tf₂O, 2,6-lutidine, -78°C
3.10 Elimination of the $\alpha$-Hydroxycyclopropane

At this point the strategy had developed to allow access to oxygenated cyclopropanes, but this would also allow access to divinylcyclopropanes if the $\alpha$-alcohol could be eliminated regiospecifically. The elimination at this position is not straightforward, since standard conditions tend to fragment the cyclopropane ring. Several literature precedents allude to the difficulty of the elimination, and in our system the literature was proven correct. Standard conditions for the elimination of the alcohol 3.13 proved fruitless. Ring fragmentation and decomposition were the common results. However, the transformation was found to be amenable to a two-step elimination with selenium. First the alcohol was converted to the corresponding selenide using conditions developed by Greco and coworkers then the selenide was oxidized with hydrogen peroxide at which point the syn-elimination occurred to give clean conversion to the desired divinylcyclopropane. Starting with the anti-trans-vinylcyclopropane 3.13 derived from an earlier sequence one could introduce the selenide with tri-$n$-butylphosphine and the cyanoselenate, Scheme 3.10. This reaction inverts the stereocenter and gave molecule 3.20 in good yield. Oxidation of the selenium with 30% hydrogen peroxide cleanly converted the molecule to the desired divinylcyclopropane 3.21 as a 9:1 mixture of $E$:Z isomers. The other regioisomer
3.23 was not observed. This reaction gave excellent yield of the desired product, however, it is very sensitive to both temperature and concentration. The optimized conditions required 0°C and low concentration of peroxide. If the temperature was raised or the peroxide was added too quickly, the reaction resulted in oxidative fragmentation of the cyclopropane ring to afford 3.22, Scheme 3.10. The syn-diastereomer 3.15 was also taken through the sequence with similar results Scheme 3.10. Thereby, using the selenide we were able to obtain the desired divinylcyclopropane 3.21 with either the anti or syn diastereomer (3.13 or 3.15) for the trans-cyclopropane. The question remained, however, if we could use this technology on the cis-α-hydroxyvinylcyclopropane 3.9 to gain access to cycloheptadienes from the Cope rearrangement.

\[ \text{Scheme 3.10} \]

\[\text{a)} \quad 2\text{-nitrophenyl selenocyanate, } \text{Bu}_3\text{P, THF b)} \quad 30\% \ H_2O_2, \ CH_2Cl_2, \ 0^\circ C \]
3.11 Cope Rearrangement of the Divinylcyclopropane

After discovering an effective method for the elimination of alcohols adjacent to
cyclopropanes, the next step was to exploit the method for the synthesis of
cycloheptadienes from the Cope rearrangement of cis-divinylcyclopropanes.
Several research groups have investigated the Cope rearrangement on these
systems,49 but we wanted to determine whether the selenide elimination
sequence would be a viable route to the desired cis-divinylcyclopropane system.

Cyclopropane 3.9 was dissolved in THF and the selanocyanate was added. Next, tri-n-butylphosphine was added dropwise over several minutes. However, upon TLC examination of the reaction mixture several compounds were revealed. 1H NMR analysis revealed a mixture of selenides. Both the desired
cyclopropyl selenide 3.25 and the ring fragmentation product 3.26 were observed
in a ratio of approximately 1:2. Furthermore the mixture could not be separated
by chromatography. This result was surprising since the trans-vinylcyclopropanes were carried through the sequence with no observed ring
fragmentation. We speculated that the increased ring strain of the cis geometry
and increased steric hindrance to backside attack at the activated hydroxyl have
led to the increase in competitive ring fragmentation. Regardless of the
activation conditions, the installation of the selenium was unsuccessful. The
mixture was taken on to the oxidation, but this proved fruitless. Observation of the desired compound 3.28 was possible, but only in trace amounts.

\[
\begin{align*}
\text{OH} & \quad \text{a) 2-nitrophenyl selenocyanate, Bu}_3\text{P, THF} \\
\text{Ph} & \quad \text{b) 30\% H}_2\text{O}_2, \text{CH}_2\text{Cl}_2, 0^\circ\text{C}
\end{align*}
\]

**Scheme 3.11**

Even though the elimination sequence was unable to afford the desired \textit{cis}-divinylcyclopropane, synthesis of Hormosirene might still be accomplished using the methodology developed. Preliminary studies have been accomplished to convert an enantiomerically pure substrate on to the synthesis of Hormosirene.
3.12 Synthesis of Cyclopropyl-Lactones, Activation of Iodide

This section will detail the synthesis of cyclopropyl lactones through the activation of a secondary iodide with silver salts. Previtera et al. developed the synthesis of a limited range of cyclopropyl carbinyl compounds from homoallylic iodides using silver acetate under anhydrous conditions. Starting from this lead example, the following will illustrate how a key modification improves the generality of this method. In the initial studies by Previtera et al., the synthesis was limited to the formation of monosubstituted cyclopropanes by the activation of primary iodides. Substituted olefins were used to trap the cationic position generated by activation with silver salts, Scheme 3.12. After ring closure, the cyclopropyl carbinyl cation was trapped with solvent or an external nucleophile. This route is limited by two factors: one, primary iodides were used and resulted in the formation of terminal cyclopropanes and two, the olefin had to be substituted with a phenyl, dimethyl, or an allyl group in order to facilitate ring closure rather than simple elimination. Our goal was to develop a method that used allylsilane to trap the activated iodide. Therefore the cyclopropane produced would have a terminal olefin and could be functionalized further. The second goal was to develop a synthesis where secondary iodides could be activated to afford disubstituted cyclopropanes, this would not only allow us to
produce synthetically useful cyclopropanes but it would allow us to determine if the ring closure is stereoselective through a NGP process.

Scheme 3.12
In order to improve upon the earlier results it was required to synthesize a molecule that contained a secondary homoallylic iodide with an allyltrimethylsilane group that could stabilize the cyclopropyl carbinyl cation. Molecule 3.45 was chosen for the synthesis. Installation of the allylsilane would be accomplished with a cross-metathesis reaction since this reaction would allow us to install the desired allylsilane functionality without protection of any of the functional groups in the molecule.

![Chemical structures](image)

**Scheme 3.13**

Late stage iodolactonization was envisioned that would allow for the installation of the iodide at the last step to avoid possible decomposition. Therefore, synthesis of skipped diene 3.46 would allow us to perform the iodolactonization as the last step giving the desired precursor 3.45. Molecule 3.46 would be obtained using the cross metathesis reaction of allyltrimethylsilane with the terminal olefin of the diene 3.47. This starting diene 3.47 can be
obtained from the Johnson-Claisen rearrangement of 1,5-hexadiene-3-ol (3.48) with triethyloxothoacetate.

Neat 1,5-hexadiene-3-ol (3.48) and 10 equivalents of triethyloxothoacetate with a catalytic amount of propionic acid was heated to 135°C thereby facilitating the Claisen rearrangement.

After 4 h TLC analysis revealed complete conversion of the starting alcohol to a single product. The resulting ethyl ester 3.49 was saponified with potassium hydroxide to afford the acid 3.47. The acid was then used as the cross metathesis partner with allyltrimethylsilane using 5-mole % of the Grubbs’ 2nd generation catalyst. The reaction was analyzed by TLC which revealed that multiple products had formed. Upon subsequent work-up and NMR analysis, a problem with the cross metathesis reaction was exposed. The catalyst was not selective for the terminal olefin and the reaction was leading to a mixture of cross metathesis products. Both the internal and terminal olefin sites were viable
substrates for Grubbs’ 2nd generation catalyst. This led to several problems. The lack of selectivity of this reaction is complicated on two fronts, the allyltrimethyl silane can couple at different centers of the starting diene, but also as the reaction proceeds homo-dimerization products began to form resulting in numerous products of similar polarity.

All in all this reaction was not selective and isolation of the desired material from the mixture was unsuccessful. This route was abandoned after several attempts to modify the synthetic scheme were attempted. Regardless of oxidation state of the molecule or if the allylsilane was tethered the reaction was unsuccessful for the installation of the allylsilane moiety, Scheme 3.14. Attempts using Grubbs 1st generation catalyst also failed due to poor yields of product. At this point we
rethought our initial synthetic sequence since all attempts to synthesize the material using the diene were unsuccessful.

The synthetic strategy was changed to accommodate the results of the first sequence, the internal olefin would have to be protected. This problem could be circumvented by performing the cross metathesis reaction last on substrate 5.26, with the iodolactone in place. This molecule could be made from the iodolactonization of diene 5.18. This route relies on a regioselective iodolactonization reaction to give the desired selectivity. The iodolactonization reaction with the internal olefin should be greatly favored since it is more electron rich and formation of the five membered ring is favored over the formation of the six, eight, or nine membered rings that could occur.

Molecule 3.48 was prepared as described above, then the iodolactonization reaction was accomplished using a two-phase system. The *anti* product was
formed stereospecifically and formation of the six, eight or nine membered iodolactones were not observed. The iodolactone 3.55 was isolated by column chromatography and then taken forward to the cross metathesis reaction. Two equivalents of allyltrimethylsilane were added and the mixture was refluxed with 5-mole % of Grubbs’ 2nd generation catalyst for 8 h. The result was an 84% yield of the desired cyclopropane precursor 3.45 as a 5:1 ratio of the $E:Z$ isomers. The isomers were separated by HPLC.

![Scheme 3.16](image)

With both the $E$ and $Z$ isomers in hand the next step was to activate the secondary iodide with a silver salt and see if cyclopropanation would occur. The $E$ isomer was dissolved in benzene and to this was added 2 equivalents of water. Then, silver nitrate was added directly and the reaction was stirred vigorously for several h at room temperature. The reaction was very clean and TLC analysis revealed complete conversion of the starting material to a single product. The reaction was extracted and purified to afford an 85% yield of the cyclopropane product as a 10:1 ratio of isomers. The major product was determined to be the
trans cyclopropane isomer, but the stereochemical identity of the minor isomer was unable to be determined.

\[
\begin{align*}
\text{Si} & \quad \text{I} \\
3.45E & \quad \xrightarrow{a} \quad 3.56 \\
\end{align*}
\]

a) AgNO₃, benzene, 2 eq. H₂O

**Scheme 3.17**

Separation of the minor product could not be accomplished by HPLC. The major product was believed to be derived through NGP and therefore the stereochemistry of the cyclopropane relative to the lactone hydroxyl should be *anti* for the major isomer. Comparison to several other known compounds supports this conclusion.

After the initial success using silver nitrate in benzene with water to facilitate the elimination reaction, the next goal was to optimize and refine the reaction. Benzene worked well but a more practical solvent was desired. Running the reaction in THF, ether, or methylene chloride all gave similar results using silver nitrate and 5 equivalents of water. The substrate 3.45E was reacted with a 5% solution of silver nitrate in water and after 2 h the reaction was complete. Work-up and purification resulted in an isolated yield of 79% of 3.56. This result was surprising since an earlier attempt to close the ring with silver triflate in methanol did not work. Silver acetate and silver triflate were effective in benzene, but their use was limited in range compared to silver nitrate.
This section has introduced a new leaving group for the allylsilane trapping of cyclopropyl carbinyl cations to give disubstituted cyclopropanes. By using silver salts and a variety of solvents, including water, the activation of a secondary iodide followed by NGP of the allylsilane unit has afforded cyclopropyl lactones in excellent yield. This sequence has been optimized and has shown success for this substrate. Farther analysis of this sequence on the generality of the substrate still needs to be carried out. Lastly closure of an intermediate with allyl substitution should be accomplished to determine if 1,2,3-trisubstituted cyclopropanes could be accessed using these conditions.

3.13 Conclusion and Future Directions

This chapter has detailed the synthesis of oxygenated cyclopropanes, structures that are commonly observed in cyclopropane containing natural products. The method detailed herein allowed for the synthesis of four isomers of oxygenated cyclopropanes. Synthesis of the cis-isomers was performed using a silyloxy tether to restrict the two substituents on one face of the closing cyclopropane ring. While in the synthesis of the trans-isomers, the tether was broken and the activation of a primary alcohol was accomplished in the presence of a secondary hydroxyl to afford the desired cyclopropane product. Lastly, these studies have shown that the cationic method has a range of potential
allylsilane participants. Overall the method as proven to be very general and has a wide range of compatibility for substrates.
CHAPTER 4

SYNTHESIS OF BIS-CYCLOPROPANES

4.1 Purpose

During the 1990’s two natural products were isolated with several contiguous cyclopropane units,\textsuperscript{52} Figure 4.1. These molecules have gained much interest due to their pharmacological properties, but they are also unique because of their structural and conformational properties.

U-106305

FR-900848

Figure 4.1
Several groups have investigated the synthesis of the contiguous cyclopropane motif, but to date most have used modified Simmons-Smith methodology. Our goal was to apply our methodology using cyclopropyl carbinyl cationic intermediates to the synthesis of these interesting molecules. The purpose of this chapter is to discuss the synthesis of bis-cyclopropanes from skipped dienes with a single activation step. The synthesis of skipped dienes will be detailed and examples involving several different routes will be discussed. Lastly an interesting substituent effect will be examined.

As described in Chapter 2, a cationic method has been developed to access vinyl cyclopropanes in three steps from an aldehyde. However, the question remained if we could reiterate this sequence to produce contiguous cyclopropanes units as seen in the isolated natural products. The terminal olefin of initial vinyl cyclopropane 4.4 could be transformed to an aldehyde 4.5 then the sequence to synthesize this initial cyclopropane could be reiterated to afford a bis-cyclopropane 4.6, Scheme 4.1. After the bis-cyclopropane was synthesized we envisioned that one could continue on to access the tris- or tetra-cyclopropane. Work on this reiterative sequence has been accomplished in our lab, and during the synthesis of the bis-cyclopropane unit some very interesting results were discovered upon closure of the second cyclopropane ring.
A distal substituent effect was observed when the cyclopropane precursor 4.9 was activated with triflic anhydride. Table 4.1 illustrates the unusual distal substituent effect that was observed. This effect was unfortunate, as it resulted in loss of stereochemistry during the second ring closure, but it did allude to the potential for synthesis of bis-cyclopropanes in one step from skipped dienes. In the case with the benzyloxy substituent the closure of the second cyclopropane occurs through an ionization ($K_C$) pathway, Scheme 4.2.
### TABLE 4.1

<table>
<thead>
<tr>
<th>Precursor</th>
<th>syn : anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>R = -CN</td>
<td>35 : 1</td>
</tr>
<tr>
<td>R = -OAc</td>
<td>9 : 1</td>
</tr>
<tr>
<td>R = -OPh</td>
<td>3 : 1</td>
</tr>
<tr>
<td>R = -OBn</td>
<td>1 : 1</td>
</tr>
</tbody>
</table>

a) Tf$_2$O, 2,6-lutidine, -78°C
Therefore, the triflate group leaves to form the cyclopropyl carbinyl cation 4.12 which is subsequently trapped by the allylsilane moiety from either face of the cation to give both anti and syn products. This reaction proceeded in high yield and led us to conclude that the reactive cyclopropyl carbinyl cation favors being trapped by the allylsilane moiety without rearrangement of the initial cyclopropane ring. After studying this reaction pathway, we envisioned that the same bis-cyclopropane products could be synthesized in a similar manner from a skipped diene by taking the iterative route back one step further to the ring fragmented homoallylic alcohol 4.14, Scheme 4.3. The activation of the skipped diene with triflic anhydride should close initially to give the cyclopropyl carbinyl cation intermediate 4.12, and since this cation is the same intermediate seen in the iterative route the formation of the bis-cyclopropane would have to occur as shown through the earlier work.
However, it was essential that the NGP of the propene unit occur faster than NGP of the allylsilane unit to form the cyclohexene ring, 4.17, Figure 4.2. Kinetically this seems likely as formation of the six-membered ring should be slower than closure of the three membered ring, also the internal olefin restricts the allylsilane moiety from interaction with the activated center and slows down formation of the cyclohexene product even more. A-strain forces the allylsilane group away from the reactive center and therefore six membered ring formation should not occur. To avoid this problem completely the skipped diene with the $E$ internal olefin geometry could be synthesized, since formation of cyclohexene with a trans olefin is highly strained and extremely unlikely. The closure of the propene unit to form the initial cyclopropane has precedent. White has shown that activated centers can be trapped with propene to give cyclopropyl carbinylications. Therefore, the next step was to synthesize the desired skipped diene and test to see if activation would give the desired bis-cyclopropane unit.

Scheme 4.3

a) $\text{Tf}_2\text{O}$, 2,6-lutidine, $-78^\circ\text{C}$
4.2 Synthesis and Activation of the (Z,Z) Skipped Diene with the Benzyloxy Group

The original synthesis of the skipped diene was riddled with experimental challenges. Several steps are not amenable to large-scale synthesis and decomposition of two separate intermediates was problematic. However, the first route developed did allow us to test the hypothesis. Later the route was shortened and optimized for much better results. The initial strategy involved the
synthesis of the skipped di-yne 4.18 as the precursor to the skipped diene 4.14, Scheme 4.4. This would allow for the direct conversion to the \((Z,Z)\)diene 4.14 after hydrogenation using Lindlar’s catalyst. The skipped di-yne can be obtained by coupling propargyl trimethylsilane and propargyl bromide 4.19 using copper. Lastly, the bromide can be obtained in three steps starting from benzyl glycidyl ether 4.20. This route took advantage of the boronacetylide chemistry previously accomplished, but relied on the expensive propargyl trimethylsilane reagent.
Benzyl glycidyl ether was fragmented with the boron acetylide of O-THP-propargyl alcohol 4.21 to give compound 4.22 from the regioselective opening at the terminal position of the epoxide. The THP group was immediately hydrolyzed with catalytic tosic acid in methanol to afford the diol. The diol was then transformed to the primary bromide 4.19 without protection of the secondary hydroxyl center. The reaction was very selective with almost no production of the secondary bromide or dibromide side products. Next it was necessary to couple propargyl trimethylsilane with the bromide. This introduced the second latent olefin and result in the skipped di-yne, 4.18. The coupling reaction was extremely sluggish and low yielding. After 36 h the isolated yield was approximately 65%. More problematic was that the material decomposed upon isolation and turned bright yellow after 10 minutes of standing. Once the material had turned yellow the subsequent hydrogenation to afford the cyclopropane
precursor was impossible. It was necessary to extract the mixture, run a column, then immediately run the hydrogenation. The hydrogenation was performed with Lindlar’s catalyst in ethyl acetate and pyridine and the reaction had to be monitored every couple of minutes. It was best to work-up the reaction at the point where almost all of the starting material was consumed, but not completely since over reduction was a real problem and resulted in a mixture of inseparable saturated and unsaturated hydrocarbons. With the skipped diene in hand the molecule was then exposed to the standard cyclopropanation conditions.

\[
\begin{align*}
  &\text{4.21} \xrightarrow{a} \text{4.22} \xrightarrow{b} \text{4.19} \\
  &\text{c} \quad \text{4.18} \xrightarrow{d} \text{4.14} \xrightarrow{e} \text{4.23}
\end{align*}
\]

a) 1. nBuLi 2. BF₃·OEt₂ 3. benzylglycidyl ether b) 1. TsOH 2. PPh₃, CBr₄ c) DMF, Cul, propargylTMS, K₂CO₃ d) Lindlar’s cat., H₂ e) Tf₂O, 2,6-lutidine, -78°C

Scheme 4.5
The skipped diene 4.14 was dissolved in methylene chloride and 2-3 equivalents of 2,6-lutidine were added. Then, the mixture was cooled to -78°C and triflic anhydride was added drop-wise. The reaction was monitored by TLC, and, after 1 h at -78°C, all of the starting diene had been consumed. ¹H NMR analysis revealed clean formation of the desired bis-cyclopropane 4.23 as a 1:1 mixture of syn:anti diastereomers with both of the cyclopropanes having trans geometry. After isolation a 72% yield was recorded. The cyclohexene byproduct derived from intermediate 4.17 was not observed, and tentative assignment for the other 28% of the mixture was attributed to protodesilylation product and β-elimination product. Since the sequence was clean and the cyclopropanation worked so efficiently we were interested in exploring the scope of the synthetic sequence. The next step was to attenuate the benzyloxy substituent and determine the generality of the sequence.
4.3 Synthesis and Activation of \((Z,Z)\) Skipped Diene with the Phenethyl Group

Since the activation of the benzyloxy substituted precursor 4.14 proceeded in good yield, we began to explore the generality of the sequence. 4-Phenylbuteneoxide was taken through the same synthetic sequence to afford the desired skipped diene 4.27 with the \(Z:Z\) olefin geometry, Scheme 4.6. This sequence was also problematic. The synthesis of the di-yne and the subsequent reduction were difficult and led to significant loss of material in the later synthetic steps. However, the skipped diene 4.27 was prepared, and with the material in hand the cyclopropanation reaction was attempted. The substrate was dissolved in methylene chloride and treated with triflic anhydride. However, upon TLC examination of the reaction after 10 minutes, two new compounds were observed. More importantly they did not have the expected Rf on TLC of the desired all hydrocarbon bis-cyclopropane product, 4.28. This was different from the earlier case with the benzyloxy substituent. In the benzyloxy system a single spot was observed at a higher Rf value compared to the stating alcohol, but in the phenethyl system the spots were not recognized and the reaction was allowed to proceed for 1 h, at which point the TLC looked as expected; all the starting material was consumed and the compounds produced had a high Rf value. However, interpretation of the NMR data on the crude mixture was
extremely difficult. Multiple peaks were found in both the cyclopropane and olefin region, and even after extensive purification this issue did not resolve. The products were inseparable, and a mixture of hydrocarbons was obtained in 85% yield. Attempts to resolve the mixture with both normal and reverse phase HPLC were unsuccessful. To complicate matters, the synthetic sequence was too cumbersome for the preparation of more material, and the mixture looked to be at least 4 compounds by GC analysis. Since isolation and characterization of the compounds was desired, we sought a better synthetic sequence that would allow for the synthesis of larger amounts of the mixture in hopes that with more material separation could be accomplished. At this point identification of the resulting mixture of hydrocarbons was impossible. However, it was speculated that cyclopropanation did occur since peaks located at 0.1 to 0.7ppm were observed, but even in this region multiple cyclopropane peaks were seen. Therefore it would be required to get more material and more data to resolve this issue.
With the successful synthesis of two unique skipped dienes we were able to accomplish the synthesis of bis-cyclopropanes in one step, but issues during the synthesis of the bis-cyclopropane precursor were limiting the exploration of the generality of the key reaction. To this end, we set out to optimize the synthesis of these important precursors. The biggest problem in the synthesis was the low yield and long reaction time for the coupling of propargyl trimethylsilane with the

Scheme 4.6

4.4 Optimization of the Synthesis of Skipped Dienes

With the successful synthesis of two unique skipped dienes we were able to accomplish the synthesis of bis-cyclopropanes in one step, but issues during the synthesis of the bis-cyclopropane precursor were limiting the exploration of the generality of the key reaction. To this end, we set out to optimize the synthesis of these important precursors. The biggest problem in the synthesis was the low yield and long reaction time for the coupling of propargyl trimethylsilane with the
primary propargyl bromide. This step was not only slow, but once complete the isolated compound underwent rapid decomposition. Other problems included the hydrogenation of the di-yne, which was extremely sensitive to over-reduction and the purity of the starting material. Lastly, the initial ring fragmentation reaction with the anion of O-THP-propargyl alcohol was low yielding and took an entire day to set up and execute. Our goal was to fix these problems and find a sequence that was amenable to large-scale synthesis.

At this time we also began to question the problem associated with the cyclopropanation of the phenethyl system. It was speculated that one of the possible byproducts in the cyclopropanation reaction was competitive formation of the cyclohexene byproduct. Therefore, in the development of a new synthesis it would be desirable to prepare a skipped diene with an \( E \) internal olefin to avoid the possibility of any six membered ring formation. To this end, a sequence was developed that prepared the desired phenethyl substituted bis-cyclopropane precursor with the \( E \) internal olefin, 4.29. With the development of the cross metathesis reaction in our lab and in others,\(^ {56} \) we chose to exploit this reaction for the synthesis of allylbromide 4.31. From molecule 4.30 the carbon-carbon bond between the allyl and propargyl group can be retrosynthetically cleaved to afford the allylic bromide 4.31. The allylic bromide can be cleaved at the olefin to afford the homoallylic alcohol, 4.32. This is the double bond that will be formed by the cross metathesis reaction between allylbromide and the homoallylic alcohol. Therefore, the compound needed to start the synthesis was homoallylic alcohol.
4.32, which was easily synthesized from the allylmagnesium bromide addition to hydrocinnamaldehyde.

More than twenty-five grams of the homoallylic alcohol 4.32 were prepared from the Grignard addition to hydrocinnamaldehyde. Next, this material was coupled with allylbromide using 5 mole % of Grubbs’ 2nd generation catalyst in methylene chloride at reflux, Scheme 4.8. The result was an 85% yield of a mixture of $E:Z$ isomers in a $>10:1$ ratio. The next step was to couple propargyl trimethylsilane with the bromide. Using the same conditions as before, the reaction gave a 65% yield of the desired ene-yne 4.30 in 36 h. Nicely, the resultant product was more stable to standing and did not decompose as quickly as the corresponding di-yne, but the yield was low and the reaction was still extremely sluggish. Several variations of the coupling reaction were attempted to improve the yield, and the best conditions were found when using Cul with DBU as the base run in acetone at room temperature. This change greatly improved
the reaction. Commonly the reaction would take <10 minutes and give >85% yield. The allylbromide was dissolved in acetone then 1.1 equivalent of Cul was added followed by addition of 3 equivalents of propargyl trimethylsilane. The reaction was stirred vigorously and DBU was titrated into the reaction mixture until the mixture became a clear dark brown. Typically this would take a little less than one equivalent of base. After the reaction went clear from heterogeneous, TLC analysis revealed complete consumption of starting material and the reaction mixture was put directly on silica and loaded onto a column for purification. These conditions for the coupling worked well in this system and for the earlier coupling to prepare the di-yne, making this step quite trivial. With the ene-yne 4.30 in hand the next step was to reduce the alkyn. This was accomplished using modified conditions from the earlier sequence. By changing the solvent from ethyl acetate and pyridine to a 9.0 : 1.0 : 0.1 mixture of hexane : 1-octene : quinoline the hydrogenation with Lindlar’s catalyst proceeded nicely with less over reduction. The reaction afforded a 90% yield of 4.29, the cyclopropane precursor with the $E,Z$ olefin geometry. This four-step sequence allowed access to the precursor in good yield and quantity.
With the preparation of 4.29 accomplished, the activation was attempted. Unfortunately, under the standard cyclopropanation conditions and allowing the reaction to proceed for one h, the result was an identical mixture of hydrocarbon products as seen earlier from the activation of the Z,Z isomer. The mixture was verified by GC analysis, and regardless of the internal olefin geometry, the product ratio was identical. Several attempts to separate the compounds were made using silver impregnated TLC and HPLC, but isolation of a single pure compound was never achieved. As a result of the inability to separate the mixture, a second experiment to determine what was happening was run. The precursor was dissolved in methylene chloride with 3 equivalents of lutidine and

Scheme 4.8

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Scheme 4.8

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cooled to -78°C. Then triflic anhydride was added drop-wise. However, instead of allowing the reaction to proceed for 1 h, the reaction was quenched with water at 10 minutes. The TLC of the quenched mixture revealed two compounds of similar polarity. The compounds were also similar in polarity to the starting secondary alcohol precursor. Preparative HPLC of the mixture was used to separate the two compounds and NMR analysis revealed the identity of the compounds as 4.33 and 4.34, the syn and anti isomers of the trans-cyclopropane. After ten minutes a 1:1 ratio of the cyclopropyl carbinols was isolated in 78% yield. The only other isolated material was that of the starting alcohol. This result was surprising. It seems that when the first cyclopropane forms the resulting cyclopropyl carbinyl cation is relatively low in energy and the allylsilane moiety does not attack to form the second cyclopropane. The cation is present in solution until water is added and the mixture begins to warm up, then capture occurs in an intermolecular process. Why the second cyclopropane does not close in this case but it does in the benzyloxy case is speculated to be a long-range inductive effect. The phenethyl system is able to donate more electron density to the first cyclopropane ring and in turn allows the cyclopropane to stabilize the cation more so than in the benzyloxy precursor. To prove that this was not an artifact of the new precursor, the Z:Z precursor was also trapped with water to afford the same mixture of compounds.
4.5 Synthesis and Activation of the \((E, Z)\) Skipped Diene with the Benzyloxy Group

To make sure the olefin geometry played no role in the result of the bis-cyclopropanation reaction, the benzyloxy substituted precursor with \((E, Z)\) geometry was synthesized using the new metathesis method. The synthesis went with similar results as the phenethyl substituted case, Scheme 4.10. The main difference was starting with benzyl glycidyl ether and performing a copper catalyzed vinyl addition to fragment the oxirane regioselectively at the terminal position to give the desired homoallylic alcohol 4.35. The homoallylic alcohol 4.35 was then coupled with allylbromide using Grubbs’ 2nd generation catalyst.
This afforded the allylbromide 4.36 in 83% yield as a >10:1 mixture of $E$:$Z$ olefin isomers. The mixture was then coupled with propargyl trimethylsilane using the modified conditions. The ene-yne was hydrogenated with Lindlar’s catalyst to afford 4.38 in 89% yield. The precursor was activated at -78°C with 1.5 equivalents of triflic anhydride and after 1 h the mixture was purified to afforded 73% yield of a 1:1 mixture of bis-cylopropanes 4.23. From this result we could conclude that olefin geometry had little to no effect on the cyclopropanation reaction. More importantly this sequence also verified the utility of the new method for the synthesis of the desired bis-cyclopropane precursor.
4.6 Conclusion and Future Directions

The above results have shown that skipped dienes can be activated to afford bis-cyclopropanes in one activation step. A synthesis of the precursor has been outlined that has used the coupling of propargyl trimethylsilane with allylic or propargylic bromides. This reaction has been optimized, and the sequence has been adapted to incorporate the use of the cross metathesis reaction to form the initial carbon-carbon double bond. This has allowed a four-step sequence to the bis-cyclopropane precursor that is amenable to large-scale synthesis. This
sequence should allow for further testing of the cyclopropanation reaction in these systems.

With this sequence in place the next step would be the synthesis of an enantiomerically enriched bis-cyclopropane precursor. This would allow us to test if the first cyclopropane is formed through inversion by NGP of the propene unit. Synthesis of enantiomerically enriched material should be straightforward starting from commercially available (R) or (S)-benzyl glycidyl ether. The resulting enantiomerically enriched substrate could then be activated, and determination of the enantiomeric excess of the resulting mixture could tell what pathway, $K_C$ or NGP, is taking place.
CHAPTER 5

EXPERIMENTAL

5.1 General Conditions

Unless otherwise noted, all materials were used as received from a commercial supplier without further purification. All anhydrous reactions were performed using oven-dried or flame-dried glassware under nitrogen or argon. Tetrahydrofuran (THF), diethyl ether (Et₂O), dichloromethane (CH₂Cl₂), and toluene (PhCH₃) were filtered through activated alumina under nitrogen. Anhydrous dichloromethane was also obtained by distillation over calcium hydride in some cases, as was anhydrous toluene sometimes distilled over sodium metal.
All reactions were monitored by either E. Merck analytical thin layer chromatography (TLC) plates (silica gel 60 GF, glass back) or Whatman UV active aluminum backed TLC plates (silica gel 250 µm) and analyzed with 254 nm UV light and/or anisaldehyde/sulfuric acid treatment. Silica gel for column chromatography was purchased from E. Merck (Silica Gel 60, 230-400 mesh). Preparative thin layer chromatography (PTLC) plates were purchased from Whatman (LK6F Silica Gel 60 Å). Biotage chromatography was performed using Flash 12+M, 25+S, and 25+M KP-Sil™ Silica (32-63 mm, 60 Å, nominally 500 m²/g silica) Cartridges.

All \(^1\)H and \(^{13}\)C NMR spectra were obtained either on a Varian Unity Plus 300 spectrometer (operating at 299.701 MHz for \(^1\)H and 75.367 MHz for \(^{13}\)C) or on a Varian Unity Plus 500 spectrometer. Chemical shifts were reported as δ-values in parts per million (ppm) relative to either residual CHCl₃ as internal reference (\(^1\)H: δ7.26, \(^{13}\)C: δ77.00) or to TMS (\(^1\)H: δ0.00, \(^{13}\)C: δ0.00) and coupling constants (\(J\)) were reported in Hertz (Hz). Peak multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), b (broad), and v (virtual). (FTIR spectra were obtained on Perkin-Elmer Paragon 1000 spectrometer and absorption frequencies were reported in reciprocal centimeters (cm⁻¹). Mass spectra (CI/FAB/EI) were obtained at the Department of Chemistry and Biochemistry, University of Notre Dame using either a JEOL AX505HA or JEOL JMS-GCmate mass spectrometer.
5.2 Chapter 2 Experimental

\[ \text{anti-2-(1-Hydroxy-3-phenyl-propyl)-but-3-enoic acid ethyl ester (2.9) and syn-2-(1-Hydroxy-3-phenyl-propyl)-but-3-enoic acid ethyl ester (2.10).} \]

To a solution of ethyl-4-bromocrotonate (1.54 mL, 11.20 mmol) in a 1:1 mixture of THF and water (40 mL) was added indium powder (1.70 g, 14.92 mmol). The mixture was stirred at room temperature for 30 minutes, at which point hydrocinnamaldehyde (1.00 mL, 7.46 mmol) was added via syringe. The reaction was stirred vigorously for 18 h. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 \times 100 mL). The combined organic layers were washed with water and brine, dried with MgSO4, filtered, and concentrated \textit{in vacuo}. The crude extract was purified and the diastereomers separated by flash column chromatography (silica gel, 10% ether in hexanes), to afford pure anti-2-(1-hydroxy-3-phenyl-propyl)-but-3-enoic acid ethyl ester 2.9 (1.05 g, 56%) as a clear oil and pure syn-2-(1-hydroxy-3-phenyl-propyl)-but-3-enoic acid ethyl ester 2.10 (350 mg, 19%) as a clear oil. Spectra for 2.9: \textsuperscript{1}H NMR (300MHz, CDCl\textsubscript{3}) \( \delta \) (ppm) 7.31-7.26 (m, 2H), 7.21-7.16 (m, 3H), 5.94 (ddd, \( J = 17.2, 10.3, 9.2 \), 1H),
5.30 (dd, J = 10.3, 1.3, 1H), 5.24 (d, J = 17.2, 1H), 4.16 (q, 7.1, 2H), 3.94 (ddd, J = 4.6, 4.2, 4.0, 1H), 3.06 (dd, J = 9.2, 4.2, 1H), 2.85 (m, 1H), 2.67 (m, 1H), 1.82 (m, 1H), 1.69 (m, 1H), 1.26 (t, 7.1, 3H). $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 173.3, 141.8, 131.6, 128.4, 128.3, 125.8, 120.4, 70.5, 61.0, 55.8, 35.8, 31.9, 14.0. FTIR (cm$^{-1}$) 3482, 3084, 3063, 1639, 1604, 1730. HRMS calculated for C$_{15}$H$_{20}$O$_3$ (M+H)$^+$ m/z 249.1491, found 249.1487. Spectra for 2.10: $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.32-7.19 (m, 5H), 5.87-5.75 (m, 1H), 5.24 (d, J = 15.9, 1H), 5.23 (d, J = 11.7, 1H), 4.19 (q, J = 7.2, 2H), 3.93-3.82 (m, 1H), 3.13 (dd, J = 8.4, 7.8, 1H), 2.93-2.84 (m, 1H), 2.74-2.64 (m, 1H), 1.94-1.82 (m, 1H), 1.76-1.63 (m, 1H), 1.27 (t, J = 7.2, 3H). $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 173.1, 141.8, 132.7, 128.4, 128.4, 125.8, 119.5, 71.6, 60.9, 56.8, 36.3, 31.7, 14.1. FTIR (cm$^{-1}$) 3458, 3085, 3069, 3027, 1732, 1639, 1604, 1496, 1455. HRMS calculated for C$_{15}$H$_{20}$O$_3$ (M+H)$^+$ m/z 249.1491, found 249.1527.

(anti)-2-[1-(Allyl-dimethyl-silanyloxy)-3-phenyl-propyl]-but-3-enoic acid ethyl ester (2.11) – To a solution of 2.9 (1.57 g, 6.35 mmol) and triethylamine (1.5 mL, 12.70 mmol) at 0°C in methylene chloride was added allylchlorodimethylsilane (1.18 mL, 7.93 mmol) over 0.5 h. The solution was allowed to come to rt. After 5
h of stirring, the reaction was quenched with sat. sodium bicarbonate and extracted with methylene chloride. The organic layer was dried with magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 10% EtOAc in hexanes) to afford (anti)-2-[1-(allyl-dimethyl-silanyloxy)-3-phenyl-propyl]-but-3-enoic acid ethyl ester 2.11 (2.20 g, 6.35 mmol, quantitative) as a colorless oil. 

$^1$H NMR (300MHz, CDCl$_3$) δ (ppm) 7.31-7.26 (m, 2H), 7.21-7.16 (m, 3H), 5.94 (ddd, $J = 17.2, 10.3, 9.3, 1H$), 5.78 (ddt, 20.8, 11.3, 9.1, 1H), 5.25 (d, $J = 10.3, 1H$), 5.15 (d, 17.2, 1H), 4.89 (d, $J = 11.3, 1H$), 4.87 (d, $J = 20.8, 1H$), 4.20-4.12 (m, 3H), 3.12 (dd, $J = 9.3, 5.3, 1H$), 2.76-2.52 (m, 2H), 1.83-1.75 (m, 2H), 1.61 (d, $J = 9.1, 2H$), 1.27 (t, $J = 7.1, 3H$), 0.12 (s, 3H), 0.11 (s, 3H).

$^{13}$C NMR (75MHz, CDCl$_3$) δ (ppm) 172.43, 141.89, 134.06, 133.09, 128.38, 125.84, 119.05, 113.74, 73.30, 60.67, 56.45, 37.20, 31.77, 25.19, 14.16, -1.71 (2C). FTIR (cm$^{-1}$) 3078.7, 3027.7, 1731.8, 1630.9, 1604.0, 1496.2, 1454.7. HRMS calculated for C$_{26}$H$_{30}$O$_3$Si (M+H)$^+$ m/z 347.2042, found 347.2059.
anti-2,2-Dimethyl-7-phenethyl-2,3,6,7-tetrahydro-[1,2]oxasilepine-6-carboxylic acid ethyl ester (2.12). In an inert atmosphere, to a solution of 2.11 (1.50 g, 4.34 mmol) in methylene chloride was added bis-(tricyclohexylphosphine) benzylidene ruthenium(IV) dichloride (10 mol%, 350 mg, 0.430 mmol) at reflux. The reaction was refluxed for 8 h. After which the reaction was exposed to atmosphere then blown dry with house air. The residue was purified by flash chromatography (silica gel, 10% EtOAc in hexanes) to afford anti-2,2-dimethyl-7-phenethyl-2,3,6,7-tetrahydro-[1,2]oxasilepine-6-carboxylic acid ethyl ester 2.12 (1.34g) as a pale brown oil. \(^1\)H NMR (300MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.31-7.25 (m, 2H), 7.20-7.15 (m, 3H), 5.95-5.86 (m, 1H), 5.54-5.49 (m, 1H), 4.23-4.09 (m, 3H), 3.44-3.38 (m, 1H), 2.93-2.83 (m, 1H), 2.66-2.56 (m, 1H), 1.76-1.64 (m, 4H), 1.24 (t, \(J = 7.1\), 3H), 0.20 (s, 3H), 0.17 (s, 3H). \(^13\)C NMR (75MHz, CDCl\(_3\)) d (ppm) 172.4, 142.1, 128.8, 128.4, 128.3, 125.7, 125.0, 72.5, 60.7, 54.6, 38.3, 32.0, 17.6, 14.1, -0.5, -1.5. FTIR (cm\(^{-1}\)) 2956, 1732. HRMS calculated for C\(_{18}\)H\(_{20}\)O\(_3\)Si (M+H)\(^+\) m/z 319.1729, found 319.1711.
anti-5-(Fluoro-dimethyl-silanyl)-2-(1-hydroxy-3-phenyl-propyl)-pent-3-enoic acid ethyl ester (2.13). A plastic vial was charged with a solution of the 7-membered siloxycycloheptene 2.12 (1.25 g, 3.93 mmol) in THF (15 mL). Then 2 eq. of HF•pyr was added. The reaction was complete after several minutes and quenched with water. The reaction mixture was then diluted with ether and the organic layer was washed once with 10 mL of a saturated sodium bicarbonate solution. The organic was concentrated to yield 1.32 g of anti-5-(fluoro-dimethyl-silanyl)-2-(1-hydroxy-3-phenyl-propyl)-pent-3-enoic acid ethyl ester 2.13. $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.24-7.32 (m, 3H), 7.16-7.24 (m, 2H), 5.76 (dd, $J =$ 10.7, 10.7, 1H), 4.15 (q, $J =$ 7.2, 2H), 3.88-3.98 (m, 1H), 3.35 (dd, $J =$ 10.0, 4.7, 1H), 2.81-2.94 (m, 1H), 2.79 (bs, 1H) 2.62-2.74 (m, 1H) 1.60-1.90 (m, 4H), 1.25 (t, $J =$ 7.1, 3H), 0.26 (d, $J =$ 2.0, 3H), 0.24 (d, $J =$ 2.0, 3H), $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 173.51, 141.88, 128.70, 128.48, 128.34, 125.80, 122.25, 70.99, 60.90, 49.42, 35.78, 31.93, 19.00 (d, $J =$ 14.5) 14.10, -1.06 (d, $J =$ 14.5), -1.21 (d, $J =$ 14.5), HRMS calculated for C$_{16}$H$_{20}$O$_2$ (M+H)$^+$ $m$/z 339.1792, found .339.1789.
2-Phenethyl-3-vinyl-cyclopropanecarboxylic acid ethyl ester (2.14). Using crude 2.13 (1.32 g, 3.93 mmol) in a 50 mL round bottom flask was dissolved in CH₂Cl₂ (20 mL). The reaction flask was then cooled to –78 °C and flushed with nitrogen. Then 2,6-lutidine (0.93 mL, 8.0 mmol) was added to the reaction via syringe, directly followed by triflic anhydride (0.67 mL, 4.0 mmol). After 1 h the mixture was quenched with triethylamine (3 eq. excess). The reaction mixture was allowed to warm to room temperature. The product was extracted with ether and washed with sat. sodium bicarbonate. The organic layer was evaporated and the residue was purified by flash chromatography (silica gel, 20% EtOAc in hexanes) to give the 2-phenethyl-3-vinyl-cyclopropanecarboxylic acid ethyl ester 2.14 (575 mg, 2.35 mmol) as a clear oil.¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.31-7.26 (m, 2H) 7.21-7.17 (m, 3H), 5.41 (ddd, J = 17.1, 10.5, 8.1, 1H), 5.10 (d, J = 17.1, 1H), 4.96 (d, J = 10.5, 1H), 4.15 (q, J = 7.1, 2H), 2.65 (t, J = 7.5, 2H), 2.08-1.84 (m, 3H), 1.75 (dd, J = 9.0, 4.5, 1H), 1.38-1.28 (m, 1H), 1.28 (t, J = 7.1, 3H).¹³C NMR (75 MHz, CDCl₃) δ (ppm) 171.7, 141.7, 138.3, 128.5, 128.3, 125.8, 114.2, 60.4, 35.6, 30.9, 29.1, 28.2, 26.7, 14.3. FTIR (cm⁻¹) 3027, 2981, 1723, 1638, 1454, 1378. HRMS calculated for C₁₆H₂₀O₂ (M+H)⁺ m/z 245.1542, found 245.1541.
(syn)-2-[1-(Allyl-dimethyl-silanyloxy)-3-phenyl-propyl]-but-3-enoic acid ethyl ester (2.16) – See procedure for synthesis of 2.11. $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.32-7.27 (m, 2H), 7.22-7.15 (m, 3H), 5.88-5.73 (m, 2H), 5.26 (dd, $J = 15.9, 1.5, 1$H), 5.21 (dd, $J = 9.0, 1.5, 1$H), 4.95-4.86 (m, 2H), 4.22-4.13 (m, 3H), 3.24 (dd, $J = 9.0, 9.0, 1$H), 2.78-2.59 (m, 2H), 1.91-1.70 (m, 2H), 1.66 (d, $J = 8.1, 2$H), 1.29 (t, $J = 6.9, 3$H), 0.17 (s, 3H), 0.15 (s, 3H). $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 172.53, 142.12, 134.02, 132.87, 128.37, 128.27, 125.78, 119.27, 113.78, 73.01, 60.61, 57.63, 36.16, 30.45, 25.10, 14.12, -1.86. FTIR (cm$^{-1}$) 3080.0, 3027.3, 1733.2, 1630.8, 1454.9, 1369.5. HRMS calculated for C$_{20}$H$_{30}$O$_3$Si (M+H)$^+$ $m/z$ 347.2042, found 347.2014.
**syn-2,2-Dimethyl-7-phenethyl-2,3,6,7-tetrahydro-[1,2]oxasilepine-6-carboxylic acid ethyl ester (2.17).** See procedure for synthesis of 2.12. $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.29-7.24 (m, 2H), 7.19-7.14 (m, 3H), 6.04-5.95 (m, 1H), 5.81-5.75 (m, 1H), 4.29 (ddd, $J = 10.5, 2.7, 2.7$, 1H), 4.19-4.04 (m, 2H), 3.99-3.93 (m, 1H), 2.87-2.77 (m, 1H), 2.64-2.53 (m, 1H), 2.01-1.88 (m, 2H), 1.70-1.61 (m, 1H), 1.40-1.33 (m, 1H), 1.20 (t, $J = 6.9$, 3H), 0.23 (s, 3H), 0.16 (s, 3H).

$^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 171.7, 142.1, 129.4, 128.4, 128.3, 125.7, 124.4, 74.8, 60.7, 50.6, 35.0, 32.5, 18.5, 14.1, 0.4, 0.1. FTIR (cm$^{-1}$) 3028, 2953, 1735, 1640, 1604, 1497, 1454. HRMS calculated for C$_{18}$H$_{26}$O$_3$Si (M+H)$^+$ m/z 319.1729, found 319.1711.
2-Phenethyl-3-vinyl-cyclopropanecarboxylic acid ethyl ester (2.19). See procedure for synthesis of 2.14. $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.30-7.24 (m, 2H), 7.21-7.14 (m, 3H), 5.55 (ddd, $J = 17.1$, 10.2, 8.6, 1H), 5.23 (dd, $J = 17.1$, 1.8, 1H), 5.10 (dd, $J = 10.2$, 1.8, 1H), 4.11 (q, 7.2, 2H), 2.73-2.63 (m, 2H), 2.14 (ddd, $J = 8.6$, 8.6, 4.5, 1H), 1.83-1.56 (m, 3H), 1.46 (dd, $J = 4.5$, 4.5, 1H), 1.26 (t, $J = 7.2$, 3H). $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 173.3, 141.6, 134.0, 128.4, 128.3, 125.9, 117.0, 60.5, 35.4, 30.5, 29.8, 28.0, 27.7, 14.3. FTIR (cm$^{-1}$) 3027, 1723, 1636, 1454. HRMS calculated for C$_{16}$H$_{20}$O$_2$ (M+H)$^+$ m/z 245.1542, found 245.1540.

anti-3-[2-(1-Hydroxy-3-phenyl-propyl)-but-3-enoyl]-4-isopropyl-oxazolidin-2-one (2.20). Prepared as described in the literature. $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.30-7.14 (m, 5H), 5.97 (ddd, $J = 17.4$, 10.2, 9.0, 1H), 5.40 (dd, $J = 17.4$, 4.5, 1H).
1.2, 1H), 5.36 (dd, J = 10.2, 1.2, 1H), 4.58 (dd, J = 9.3, 3.3, 1H), 4.48-4.42 (m, 1H), 4.29-4.16 (m, 2H), 4.10-3.94 (m, 1H), 3.27 (-OH, bs, 1H), 2.88-2.78 (m, 1H), 2.73-2.62 (m, 1H), 2.37-2.25 (m, 1H), 1.93-1.78 (m, 1H), 1.76-1.64 (m, 1H), 0.90 (d, J = 6.9, 3H), 0.83 (d, J = 6.9, 3H). \(^{13}\)C NMR (75MHz, CDCl\(_3\)) \(\delta\) (ppm) 174.5, 153.4, 141.8, 131.1, 128.5, 128.3, 125.8, 121.6, 70.5, 63.1, 58.2, 51.8, 35.7, 31.8, 28.2, 17.8, 14.5. FTIR (cm\(^{-1}\)) 3514, 3064, 3027, 1780, 1693, 1634, 1604, 1496, 1454. HRMS calculated for C\(_{19}\)H\(_{25}\)NO\(_4\) (M+H)\(^+\) m/z 322.1862, found 332.1862.

\[\text{anti-3-(2,2-Dimethyl-7-phenethyl-2,3,6,7-tetrahydro-[1,2]oxasilepine-6-carbonyl)-4-isopropyl-oxazolidin-2-one (2.22).} \]

See a Representative Allylsilane Protection/Ring Closing Metathesis Procedure above. \(^1\)H NMR (300MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.29-7.15 (m, 5H), 5.99-5.88 (m, 1H), 5.48 (dd, J = 11.0, 6.9, 1H), 4.83-4.76 (m, 1H), 4.51-4.39 (m, 2H), 4.26-4.14 (m, 2H), 2.95-2.85 (m, 1H), 2.62-2.52 (m, 1H), 2.40-2.24 (m, 1H), 1.89-1.56 (m, 4H), 0.89 (d, J = 6.9, 3H), 0.84 (d, J = 6.9, 3H), 0.21 (s, 3H), 0.18 (s, 3H). \(^{13}\)C NMR (75MHz, CDCl\(_3\)) \(\delta\) (ppm) 172.2, 153.3, 142.2, 129.8, 128.4, 128.3, 125.7, 123.5, 71.9,
63.1, 58.3, 52.0, 38.8, 32.5, 28.3, 17.9, 17.3, 14.7, -0.7, -1.1. FTIR (cm\(^{-1}\)) 3062, 3026, 1781, 1696, 1636, 1603, 1466, 1455. HRMS calculated for C\(_{22}\)H\(_{31}\)NO\(_4\)Si (M+H)\(^+\) m/z 402.2101, found 402.2083.

4-Isopropyl-3-(2-phenethyl-3-vinyl-cyclopropanecarbonyl)-oxazolidin-2-one (2.24). See a Representative Cyclopropane Formation Procedure. \(^1\)H NMR (300MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.28-7.14 (m, 5H), 5.46 (ddd, \(J = 17.1, 10.2, 8.4, 1\)H), 5.13 (dd, \(J = 17.1, 1.5, 1\)H), 4.96 (dd, \(J = 10.2, 1.5, 1\)H), 4.33-4.27 (m, 1H), 4.23-4.11 (m, 2H), 3.21 (dd, \(J = 9.1, 4.9, 1\)H), 2.73-2.54 (m, 2H), 2.40-2.24 (m, 1H), 2.17-2.10 (m, 1H), 1.99-1.75 (m, 2H), 1.61-1.42 (m, 1H) 0.89 (d, \(J = 7.2, 3\)H), 0.86 (d, \(J = 7.2, 3\)H). \(^{13}\)C NMR (75MHz, CDCl\(_3\)) \(\delta\) (ppm) 170.6, 154.4, 141.7, 138.4, 129.0, 128.4, 125.9, 114.7, 63.1, 58.7, 35.9, 31.8, 31.6, 28.4, 28.0, 27.2, 18.2, 14.8. FTIR (cm\(^{-1}\)) 3086, 1778, 1688, 1639, 1487, 1454. HRMS calculated for C\(_{20}\)H\(_{25}\)NO\(_3\) (M+H)\(^+\) m/z 328.1913, found 328,1910.
(E) and (Z)-anti-2-(1-Hydroxy-3-phenyl-propyl)-5-(trimethyl-silanyl)-pent-3-enoic acid ethyl ester (2.25). A solution of anti-2-(1-hydroxy-3-phenyl-propyl)-but-3-enoic acid ethyl ester 2.9 (113 mg, 0.46 mmol) in 5 mL of CH$_2$Cl$_2$ was heated to reflux under an atmosphere of nitrogen. The solution was allowed to reflux for 30 minutes, then allyltrimethylsilane (0.29 mL, 1.82 mmol) was added via syringe to the reaction vessel, followed by the solid addition of Grubbs’ 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ruthenium carbene (20 mg, 5 mol%). The solution immediately took on a transparent rose color and was stirred under reflux for 6 h. The reaction vessel was removed from heat and stirred open to the air for several h. The reaction volume was reduced to 1 mL by evaporation and the residue was flushed through a plug of silica gel using CH$_2$Cl$_2$ (5 mL) followed by 25% EtOAc in hexanes (10 mL). The resulting light brown solution was concentrated in vacuo and purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to give an inseparable mixture of E and Z isomers (92:8) 2.25 (93.2 mg, 67%) as a colorless oil. $^1$H NMR (300MHz, CDCl$_3$) δ (ppm) - CH(OH)CH(CO$_2$Et)CH: E-isomer 3.01-2.96 (dd, J = 4.6, 4.6, 1H), Z-isomer 3.39-3.33 (dd, J = 4.6, 4.6, 1H); Si(CH$_3$)$_3$: (E) -0.01 (s, 9H), (Z) 0.02 (s, 9H). All Peaks: $^{13}$C NMR (75MHz, CDCl$_3$) δ (ppm) 174.1, 142.0, 133.7, 132.0, 128.5,
128.3, 125.7, 120.9, 71.2, 70.7, 64.1, 60.8, 55.0, 49.4, 35.84, 35.78, 32.0, 31.9,
30.1, 23.3, 19.2, 14.1, -1.8, -2.0. HRMS calculated for $\text{C}_{19}\text{H}_{30}\text{O}_3\text{Si} (\text{M+H})^+$ $m/z$
335.2044, found 335.2007.

\[
\text{Ph} \quad \text{OH} \quad \text{Si}(\text{CH}_3)_3 \quad 9 : 1
\]

\(2.28\)

\((E)\) and \((Z)\)-syn-2-(1-Hydroxy-3-phenyl-propyl)-5-(trimethyl-silanyl)-pent-3-
enoic acid ethyl ester (2.28). See a Representative Cross-Metathesis
Procedure. An inseparable mixture of \(E\) and \(Z\) isomers (80:20) 2.28 (25 mg,
81%) as a colorless oil was obtained. \(^1\)H NMR (300MHz, CDCl$_3$) d (ppm) -

CH(OH)CH(C$_2$Et)CH-: \(E\)-isomer 3.06-3.00 (dd, \(J = 8.4\), 1H), \(Z\)-isomer 3.39-
3.33 (dd, \(J = 8.1\), 1H); Si(CH$_3$)$_3$: \((E)\) -0.02 (s, 9H), \((Z)\) 0.00 (s, 9H). All Peaks:
\(^{13}\)C
NMR (75MHz, CDCl$_3$) d (ppm) 174.0, 142.0, 132.5, 130.9, 128.5, 128.3, 125.8,
122.3, 121.3, 72.4, 71.9, 60.7, 56.1, 50.5, 36.31, 36.25, 32.0, 31.9, 23.2, 19.2,
14.2, -1.3, -1.5. HRMS calculated for $\text{C}_{19}\text{H}_{30}\text{O}_3\text{Si} (\text{M+H})^+$ $m/z$
335.2044, found 335.2051.
(E) and (Z)-anti-3-[2-(1-Hydroxy-3-phenyl-propyl)-5-(trimethyl-silanyl)-pent-3-enoyl]-4-isopropyl-oxazolidin-2-one (2.29). See a Representative Cross-Metathesis Procedure. An inseparable mixture of E and Z isomers (>95:<5) 2.29 (37 mg, 69%) as a colorless oil was obtained. Data for E-isomer only: $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.29-7.14 (m, 5H), 5.86 (dt, $J = 15.2$, 8.2, 1H), 5.35 (dd, $J = 15.2$, 9.3, 1H), 4.51-4.41 (m, 2H), 4.28-4.15 (m, 2H), 3.96-3.88 (m, 1H), 3.22 (-OH, bs, 1H), 2.88-2.77 (m, 1H), 2.72-2.61 (m, 1H), 2.36-2.24 (m, 1H), 1.88-1.77 (m, 1H), 1.74-1.60 (m, 1H), 1.52 (d, $J = 8.2$, 2H), 0.90 (d, $J = 6.9$, 3H), 0.83 (d, $J = 6.9$, 3H), -0.02 (s, 9H). $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 174.6, 153.6, 142.3, 135.6, 128.8, 128.5, 126.0, 120.5, 71.0, 63.3, 58.4, 51.5, 35.9, 32.1, 28.5, 23.8, 18.2, 14.2, -1.7. HRMS calculated for C$_{23}$H$_{35}$NO$_4$Si (M+H)$^+$ m/z 418.2414, found 418.2415.
(4-Hydroxy-3-methyl-6-phenyl-hex-1-enyl)-(4-methoxy-phenyl)-carbamic acid tert-butyl ester (2.31) To a pre-cooled (−78 °C) solution of (-)-sparteine (0.29mL, 1.23mmol) and n-BuLi (2.2M) (1.23 mmol) in toluene (15 mL) under argon was added crotylamine (294 mg, 1.06 mmol) in toluene (2 mL) and the reaction turned bright yellow. After stirring for 2 h at −78 °C then chlorotriisopropoxidetitanium (1.23 mmol) was added and stirred for 2 hr. Finally hydrocinnamaldehyde (0.12 mL, 0.88 mmol) in toluene (1 mL) was added dropwise. The mixture was stirred at −78 °C for 2 h and then quenched with MeOH (1 mL). The reaction was diluted with diethyl ether and 2M HCl was added. The aqueous layer was extracted with Et₂O, the ethereal extracts were combined and then washed with NaHCO₃ to neutralize residual acid. Then the organic layer was dried over MgSO₄, filtered, and concentrated by rotary evaporation. Flash column chromatography with (EtOAc:hexanes) as eluent provided (4-hydroxy-3-methyl-6-phenyl-hex-1-enyl)-(4-methoxy-phenyl)-carbamic acid tert-butyl ester 2.31 (159 mg, 45%). ¹H NMR (300MHz, (CD₃)₂CO) δ (ppm) 7.15-7.30 (m, 7H), 6.85-6.93 (m, 2H), 6.53 (d, J = 8.8, 1H), 4.96 (dd, J = 8.8, 10.3, 1H) 3.78 (s, 3H), 3.47 (d, J = 5.4, 1H), 3.21-3.31 (m, 1H), 2.60-2.72 (m,
1H), 2.46-2.59 (m, 1H), 2.00-2.12 (m, 1H), 1.45-1.65 (m, 2H), 1.39 (s, 9H), 0.71 (d, 6.8, 3H). 13C NMR (75MHz, (CD3)2CO) δ (ppm) 158.56, 154.16, 143.62, 136.30, 129.19, 129.11, 129.03, 128.81, 126.32, 114.50, 80.93, 74.34, 55.67, 38.07, 36.94, 32.81, 30.70, 28.33, 17.07. FTIR (cm⁻¹) 3448.7, 2974.4, 2931.8, 1706.1, 1654.5, 1511.5, 1247.3, 1155.6. HRMS calculated for C26H34NO4 (M+H)+ m/z 412.2488, found 412.2486.

2-Methyl-3-phenethyl-cyclopropanecarbaldehyde (2.32) A flame dried flask was charged with ene carbamate 2.31 (96mg, 0.23mmol) and CH2Cl2 (3 mL). The flask was flushed with argon and 2,6-lutidine (0.11 mL, 0.93 mmol) was added via syringe. The resulting mixture was cooled to -78°C and then triflic anhydride (0.12 mL, 0.70 mmol) was added. The mixture was allowed to warm to -20 °C and stirred for 4 h. The solution was quenched with sat. bicarbonate and MeOH then diluted with 55 mL of CH2Cl2 and washed with NaHCO3 and then dried over MgSO4, filtered, and concentrated. The concentrated material was purified by HPLC, normal phase (ether:hexanes) to provide 2-methyl-3-phenethyl-cyclopropanecarbaldehyde 2.32 (30 mg, 70%) as a colorless oil. ¹H NMR (300MHz, CDCl3) δ (ppm) 9.05 (d, J = 5.3, 1H), 7.15-7.28 (m, 5H), 2.72 (t, J = 7.7, 2H), 1.50-1.90 (m, 4H), 1.32 (dd, J = 4.4, 9.5, 1H), 1.12 (d, J = 6.0, 3H).
\[ ^{13}\text{C NMR (75MHz, CDCl}_3 \] \( \delta \) (ppm) 201.0, 141.44, 128.45, 128.42, 126.02, 38.51, 35.65, 28.84, 27.80, 22.05, 11.77. FTIR (cm\(^{-1}\)) 2928.8, 1704.5, 1496.0, 1454.0, 1171.0, 1058.4. HRMS calculated for C\(_{13}\)H\(_{16}\)O (M+H)\(^+\) m/z 189.1279, found 189.1290.

(4-Hydroxy-3,6-diphenyl-hex-1-enyl)-(4-methoxy-phenyl)-carbamic acid tert-butyl ester (2.34) See above procedure for synthesis. \(^1\)H NMR (300MHz, (CD\(_3\))\(_2\)CO) \( \delta \) (ppm) 7.03-7.30 (m, 9H), 6.90-6.96 (m, 2H), 6.78-6.86 (m, 2H) 6.72 (d, J = 9.0, 1H), 5.46 (dd, J = 9.0, 10.5, 1H), 3.81 (s, 3H), 3.60 (td, J = 5.4, 12.0, 1H), 3.15 (dd, J = 10.5, 5.4, 1H), 2.64-2.78 (m, 1H), 2.48-2.63 (m, 1H), 1.50-1.64 (m, 2H), 1.42 (s, 9H). \(^{13}\text{C NMR (75MHz, (CD}_3\text{)}\(_2\)CO) \( \delta \) (ppm) 158.11, 153.48, 142.83, 142.71, 135.05, 129.34, 128.54, 128.44, 128.40, 128.04, 126.12, 125.76, 113.93, 80.52, 74.21, 55.10, 48.28, 37.51, 32.01, 27.67. FTIR (cm\(^{-1}\)) 3411.7, 2931.2, 1694.2, 1512.3, 1454.4, 1157.4, 1136.5, 699.7 HRMS calculated for C\(_{30}\)H\(_{35}\)NO\(_4\) (M+H)\(^+\) m/z 474.2566, found 474.2569.
2-Phenethyl-3-phenyl-cyclopropanecarbaldehyde (2.35) See above procedure for synthesis. $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 9.33 (d, $J = 4.6$, 1H) 7.15-7.35 (m, 8H), 6.99-7.02 (m, 2H), 2.93 (dd, $J = 4.9$, 9.7, 1H), 2.60 (t, $J = 7.7$, 2H), 2.18 (dt, $J = 4.6$, 4.6, 1H), 1.87 (m, 1H), 1.58-1.72 (m, 1H), 1.34-1.50 (m, 1H) $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 200.46, 141.49, 135.48, 129.04, 128.59, 127.12, 126.21, 35.57, 35.31, 31.66, 29.51, 29.21. FTIR (cm$^{-1}$) 3026.7, 2925.5, 1708.5, 1496.6, 1453.7. HRMS calculated for C$_{19}$H$_{19}$O (M+H)$^+$ m/z 250.1358, found 250.1364.
Preparation of \textit{anti}-2-[3-(Dimethyl-silanyl)-propenyl]-5-phenyl-pentane-1,3-diol (3.6). A nitrogen-flushed solution of ethyl ester 2.12 (100 mg, 0.31 mmol) in methylene chloride (2.5 mL) was cooled to -78 °C, to which was added dropwise a 1 M solution of DIBAL (1.55 mL) via syringe. The reaction was allowed to come to room temperature over 5 h. The reaction was quenched with a saturated solution of Rochelle salt. The resultant salts were filtered and washed with ethyl acetate. The organic layer was dried with MgSO$_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 25% ether in hexanes) to afford 3.6 (77 mg, 88%) as a clear oil. Crystallization to a white solid occurred upon long periods of standing. Spectra for 3.6: 1H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) 7.32-7.15 (m, 5H), 5.73 (td, $J$) 8.7, 11.1, 1H), 5.32 (dd, $J$) 11.1, 11.0, 1H), 3.90-3.63 (m, 4H), 2.89-2.78 (m, 1H), 2.71-2.61 (m, 1H), 1.89-1.52 (m, 5H), 0.102 (d, $J$) 3.6, 6H). 13C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) 142.0, 130.4, 128.4, 128.4, 125.8, 123.1, 72.8, 65.0, 44.3, 36.4, 32.3, -4.5. FTIR (cm$^{-1}$) 3305, 3013, 2114, 1604, 1497, 1454. HRMS calculated for C$_{16}$H$_{26}$O$_2$Si (M + H)$^+$ $m/z$ 279.1780, found 279.1770.
Preparation of anti-(2,2-Dimethyl-7-phenethyl-2,3,6,7-tetrahydro-[1,2]oxasilepin-6-yl)-methanol (3.7). A nitrogen flushed solution of ethyl ester 2.12 (75 mg, 0.24 mmol) in methylene chloride (5 mL) was cooled to –78°C, to which was added dropwise a 1 M solution of DIBAL (0.53 mL) via syringe. The reaction was closely monitored for disappearance of starting ester. After 2 h at -78 °C, the reaction was quenched with a saturated solution of Rochelle salt, and the resultant salts were filtered and washed with ethyl acetate. The organic layer was dried with MgSO$_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, 25% ether in hexanes) to afford 3.7 as a clear oil. Spectra for 3.7: 1H NMR (300 MHz, CDCl$_3$) δ (ppm) 7.31-7.14 (m, 5H), 5.99-5.90 (m, 1H), 5.41 (ddd, $J = 11.2, 6.3, 1.2, 1$H), 4.03 (td, $J = 9.6, 2.4, 1$H), 3.66 (d, $J = 3.9, 2$H), 2.97-2.86 (m, 1H), 2.64-2.46 (m, 2H), 1.99-1.87 (m, 1H), 1.80-1.65 (m, 2H), 1.54-1.44 (m, 2H), 0.20 (s, 3H), 0.16 (s, 3H). 13C NMR (75 MHz, CDCl$_3$) δ (ppm) 142.5, 128.6, 128.5, 128.3, 128.2, 125.7, 71.9, 63.2, 50.3, 38.1, 32.4, 17.7, -0.8, -1.1. FTIR (cm$^{-1}$) 3392, 3025, 1639, 1604, 1496,1454. HRMS calculated for C$_{16}$H$_{26}$O$_2$Si (M + H)$^+$ m/z 276.1546, found 276.1526.
3-Phenyl-1-[(cis)-2-vinyl-cyclopropyl]-propan-1-ol (cis-3.9). See a Representative Cyclopropane Formation. 

$^1$H NMR (300MHz, CDCl$_3$) δ (ppm) 7.32-7.15 (m, 5H), 5.65 (ddd, $J = 17.1$, 10.2, 9.0, 1H), 5.24 (ddd, $J = 17.1$, 1.8, 0.6, 1H), 5.09 (ddd, $J = 10.2$, 1.8, 0.6, 1H), 3.32-3.24 (m, 1H), 2.88-2.67 (m, 2H), 2.0-1.91 (m, 2H), 1.69-1.56 (m, 1H), 1.26-1.15 (m, 1H), 1.04-0.96 (m, 1H), 0.51-0.45 (m, 1H). 

$^{13}$C NMR (75MHz, CDCl$_3$) δ (ppm) 141.2, 137.2, 128.3 (2C), 125.7, 115.9, 72.5, 38.7, 32.0, 25.9, 19.1, 11.6. FTIR (cm$^{-1}$) 3436, 3065, 3026, 1634, 1603, 1496, 1454. HRMS calculated for C$_{14}$H$_{18}$O (M+H)$^+$ -H$_2$O m/z 185.1330, found 185.1329.
syn-(2,2-Dimethyl-7-phenethyl-2,3,6,7-tetrahydro-[1,2]oxasilepin-6-yl)-methanol (3.11). See a Representative Ethyl Ester Reduction with DIBAL. \(^1\)H NMR (300MHz, CDCl\(_3\)) \(\delta\) (ppm) 7.32-7.15 (m, 5H), 5.97-5.87 (m, 1H), 5.38-5.31 (m, 1H), 4.22 (dt, \(J = 10.2, 2.7\), 1H), 3.83 (dd, \(J = 10.5, 6.0\), 1H), 3.70-3.60 (m, 1H), 2.93-2.78 (m, 2H), 2.63-2.53 (m, 1H), 2.05-1.89 (m, 3H), 1.70-1.59 (m, 1H), 1.44-1.31 (m, 1H), 0.22 (s, 3H), 0.17 (s, 3H). \(^{13}\)C NMR (75MHz, CDCl\(_3\)) \(\delta\) (ppm) 142.2, 128.9, 128.4, 128.2, 125.8, 74.3, 63.8, 47.8, 35.8, 33.0, 17.9, -0.2, -0.4. FTIR (cm\(^{-1}\)) 3384, 3086, 3062, 3026, 1637, 1496, 1455. HRMS calculated for C\(_{16}\)H\(_{24}\)O\(_2\)Si (M+H)\(^+\) \(m/z\) 277.1624, found 277.1604.
3-Phenyl-1-[(cis)-2-vinyl-cyclopropyl]-propan-1-ol (cis-3.12). See a Representative Cyclopropane Formation. $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.32-7.14 (m, 5H), 5.42 (ddd, $J = 17.1, 10.2, 9.0, 1$H), 5.12 (ddd, $J = 17.1, 1.8, 0.6, 1$H), 4.97 (ddd, $J = 10.2, 1.8, 0.6, 1$H), 3.23 (ddd, $J = 9.3, 7.7, 4.6, 1$H), 2.87-2.77 (m, 1H), 2.73-2.62 (m, 1H), 1.95-1.82 (m, 2H), 1.70-1.55 (m, 1H), 1.24-1.10 (m, 1H), 0.97 (ddd, $J = 8.1, 8.1, 4.8, 1$H), 0.54 (ddd, $J = 5.7, 5.7, 4.8, 1$H). $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 142.1, 137.1, 128.4, 128.3, 125.7, 115.2, 72.0, 38.6, 31.8, 25.4, 20.1, 10.9. FTIR (cm$^{-1}$) 3369, 3066, 3026, 1634, 1604, 1496, 1496, 1455. HRMS calculated for C$_{14}$H$_{18}$O (M+H)$^+$ $m/z$ 203.1436, found 203.1447.
3-Phenyl-1-[(trans)-2-vinyl-cyclopropyl]-propan-1-ol (trans-3.13). See a Representative Cyclopropane Formation. $^1$H NMR (300MHz, CDCl$_3$) δ (ppm) 7.32-7.15 (m, 5H), 5.41 (ddd, $J = 17.1$, 10.2, 8.7, 1H), 5.08 (ddd, $J = 17.1$, 1.8, 0.6, 1H), 4.88 (dd, $J = 10.2$, 1.8, 1H), 3.06 (dt, $J = 7.8$, 6.3, 1H), 2.87-2.66 (m, 2H), 1.90 (td, $J = 8.1$, 6.3, 2H), 1.47-1.38 (m, 1H), 1.07-0.98 (m, 1H), 0.69-0.64 (m, 2H). $^{13}$C NMR (75MHz, CDCl$_3$) δ (ppm) 142.1, 140.7, 128.38, 128.36, 125.8, 112.2, 74.8, 38.5, 31.9, 27.4, 20.3, 11.5. FTIR (cm$^{-1}$) 3401, 3064, 3026, 1636, 1460, 1454. HRMS calculated for C$_{14}$H$_{18}$O (M+H)$^+$ -H$_2$O m/z 185.1330, found 185.1342.
syn-2-[3-(Dimethyl-silanyl)-propenyl]-5-phenyl-pentane-1,3-diol (3.14). See a Representative Ethyl Ester Reduction and Silyloxy Ring Cleavage with DIBAL.

$^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.33-7.15 (m, 5H), 5.56-5.55 (m, 1H), 5.05-4.97 (m, 1H), 3.88-3.82 (m, 1H), 3.75-3.64 (m, 3H), 2.89-2.79 (m, 1H), 2.72-2.50 (m, 2H), 1.98-1.86 (m, 1H), 1.76-1.51 (m, 4H), 0.10 (d, $J = 0.6$, 3H), 0.09 (d, $J = 0.6$, 3H). $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 142.0, 129.2, 128.4, 128.4, 125.8, 124.4, 75.4, 66.2, 45.0, 37.2, 31.8, 16.5, -4.5. FTIR (cm$^{-1}$) 3351, 3063, 3027, 3004, 2117, 1645, 1604, 1496, 1454. HRMS calculated for C$_{16}$H$_{26}$O$_2$Si (M+H)$^+$ $m/z$ 279.1780, found 279.1787.
3-Phenyl-1-[(\textit{trans})-2-vinyl-cyclopropyl]-propan-1-ol (\textit{trans}-3.15). See a Representative Cyclopropane Formation. $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.32-7.16 (m, 5H), 5.40 (ddd, $J = 17.1, 10.2, 8.4, 1H$), 5.06 (dd, $J = 17.1, 1.8, 1H$), 4.88 (dd, $J = 10.2, 1.8, 1H$), 3.09-3.02 (m, 1H), 2.85-2.66 (m, 2H), 2.00-1.89 (m, 2H), 1.37-1.25 (m, 1H), 1.05-0.96 (m, 1H), 0.78-0.72 (m, 1H), 0.68-0.62 (m, 1H). $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 142.3, 140.6, 128.6 (2C), 126.1, 112.7, 75.0, 39.0, 32.1, 27.5, 20.2, 11.6. FTIR (cm$^{-1}$) 3370, 3083, 3000, 1638, 1496, 1454. HRMS calculated for C$_{14}$H$_{18}$O (M+H)$^+$ -H$_2$O $m/z$ 185.1330, found 185.1322.

5-Phenyl-2-vinyl-pentane-1,3-diol (3.16) See Ethyl Ester Reduction with DIBAL. \textit{syn}-diastereomer $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.25-7.33 (m, 2H), 7.16-7.24 (m, 3H), 5.63 (ddd, $J = 9.6, 10.0, 14.1, 1H$), 5.18 (dd, $J = 14.1, 1.31, 1H$), 5.17(dd, $J = 10.0, 1.3, 1H$), 3.71-3.84 (m, 3H), 2.61-2.92 (m, 4H), 2.30-2.40 (m, 1H), 1.85-1.98 (m, 1H), 1.68-1.82 (m, 1H) $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm)
141.95, 135.86, 128.40, 128.39, 125.84, 118.26, 73.95, 65.30, 51.55, 37.21, 31.61. *anti*-diastereomer $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.25-7.33 (m, 2H), 7.15-7.24 (m, 3H), 5.86 (ddd, $J = 9.0, 10.5, 17.4$, 1H), 5.27 (dd, $J = 10.5, 1.5$, 1H), 5.19(dd, $J = 17.4, 1.5$, 1H), 3.71-3.89 (m, 3H), 2.74-2.88 (m, 1H), 2.60-2.73 (m, 1H), 2.28-2.40 (m, 1H), 1.70-1.90 (m, 2H). $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 141.86, 134.59, 128.41, 128.31, 125.87, 119.23, 72.21, 64.73, 50.91, 36.66, 32.18. FTIR (cm$^{-1}$) 3368.5, 2931.6, 1639.5, 1603.4, 1495.3, 1454.3 HRMS calculated for C$_{13}$H$_{19}$O$_2$ (M+H)$^+$ -H$_2$O $m/z$ 207.1385, found 207.1368.

5-Phenyl-2-[3-(trimethyl-silanyl)-propenyl]-pentane-1,3-diol (3.18) See a Representative Cross-metathesis with Grubbs’ catalyst. *Z*-isomer $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.25-7.38 (m, 2H), 7.15-7.24 (m, 3H), 5.60 (dt, $J = 10.8, 8.6$, 1H), 5.00 (dd, $J = 10.8, 9.9$, 1H), 3.62-3.80 (m, 3H), 2.86-2.92 (m, 1H), 2.62-2.80 (m, 1H), 1.89-2.00 (m, 1H), 1.40-1.86 (m, 4H), 0.01 (s, 9H). *E*-isomer $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.25-7.38 (m, 2H), 7.18-7.22 (m, 3H), 5.57 (dt, $J = 15.3, 7.8$, 1H), 5.00 (dd, $J = 15.3, 9.0$, 1H), 3.61-3.82 (m, 3H), 2.78-2.96 (m, 1H), 2.61-2.78 (m, 1H), 2.21-2.50 (m, 1H), 1.85-2.00 (m, 1H), 1.61-1.80 (m, 1H), 1.40-1.51 (m, 2H) 0.01 (s, 9H). *Z*-isomer $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 142.54, 131.36, 128.74, 128.51, 126.28, 119.32, 72.53, 68.25, 50.98, 35.98,
32.91, 23.80, -1.49. *E-isomer* $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 142.54, 132.53, 128.74, 128.51, 126.28, 125.23, 72.64, 65.82, 50.98, 36.42, 33.05, 23.80, -1.69.

5-Phenyl-2-[3-(trimethyl-silanyl)-propenyl]-pentane-1,3-diol (3.19) as an 4:1, $E:Z$ mixture. See Representative Cross-metathesis with Grubbs' catalyst. $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.16-7.38 (m, 5H) $_{(E,Z)}$, 5.49-5.70 (m, 1H) $_{(E,Z)}$, 4.90-5.10 (m, 1H) $_{(E,Z)}$, 3.62-3.81 (m, 3H) $_{(E,Z)}$, 2.58-2.92 (m, 2H) $_{(E,Z)}$, 2.22-2.36 (m, 1H) $_{(E,Z)}$, 1.81-2.01 (m,1H) $_{(E,Z)}$, 1.40-1.78 (m, 3H) $_{(E,Z)}$, 0.03 (s, 9H) $_{(E)}$, 0.02 (s, 9H) $_{(Z)}$.

$^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 142.81$_{(E,Z)}$, 131.84$_{(E)}$, 129.94$_{(Z)}$, 128.81$_{(E,Z)}$, 128.60$_{(E,Z)}$, 126.40$_{(E,Z)}$, 125.01$_{(E)}$, 123.98$_{(Z)}$, 75.73$_{(Z)}$, 74.82$_{(E)}$, 66.45$_{(E)}$, 66.38$_{(Z)}$, 51.20$_{(E)}$, 45.07$_{(Z)}$, 37.60$_{(E)}$, 37.41$_{(Z)}$, 32.08$_{(Z)}$, 31.89$_{(E)}$, 23.43$_{(E)}$, 19.41$_{(Z)}$, -1.50$_{(Z)}$, -1.73$_{(E)}$.
[3-(2-Vinyl-cyclopropyl)-allyl]-benzene (3.21) See a Representative Cyclopropane Formation. Spectral data for the major isomer, the E-isomer. $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.16-7.35 (m, 5H), 5.62 (dt, $J = 15.1$, 6.9, 1H), 5.40 (ddd, $J = 8.4$, 10.2, 16.9, 1H), 5.04-5.18 (m, 1H), 5.05 (dd, $J = 1.9$, 16.9, 1H), 4.86 (dd, $J = 1.9$, 10.2, 1H), 3.32 (d, $J = 6.9$, 2H), 1.36-1.46 (m, 2H), 0.81 (vt, $J = 6.95$, 2H). $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 141.06, 140.91, 133.54, 128.78, 128.64, 127.71, 126.17, 112.35, 39.14, 24.63, 23.80, 15.10. FTIR (cm$^{-1}$) 3083, 3000, 1638, 1496, 1454. HRMS calculated for C$_{14}$H$_{16}$ (M+H)$^+$ -H$_2$O $m/z$ 185.1252, found 185.1249.
5-[1-iodo-5-(trimethyl-silanyl)-pent-3-enyl]-dihydro-furan-2-one (3.45). The iodolactone (115mg, 0.43mmol) was dissolved in methylene chloride and heated to reflux. Then allyltrimethylsilane (0.14mL, 0.86mmol) was added followed by Grubbs’ second generation catalyst (18mg, 0.02mmol) and the mixture was refluxed for 4 h. The mixture was then cooled and blown dry with compressed air. The residue was then purified by flash chromatography (silica, 25% ether:Hex) to afford 5-[1-iodo-5-(trimethyl-silanyl)-pent-3-enyl]-dihydro-furan-2-one 3.45 (85%, 128mg) as a yellow oil. 

**E-isomer**

$^1$H NMR (300MHz, CDCl$_3$) δ (ppm) 5.50-5.64 (m, 1H), 5.18-5.30 (m, 1H), 4.34-4.42 (m, 1H), 4.10-4.18 (m, 1H), 2.40-2.70 (m, 5H), 1.95-2.10 (m, 1H), 1.26 (d, $J$ = 8.0, 2H), 0.08 (s, 9H).

**Z-isomer**

$^1$H NMR (300MHz, CDCl$_3$) δ (ppm) 5.47-5.70 (m, 1H), 5.21-5.38 (m, 1H), 4.36-4.42 (m, 1H), 4.06-4.18 (m, 1H), 2.40-2.80 (m, 5H), 1.97-2.15 (m, 1H), 1.42-1.50 (m, 2H), 0.09 (s, 9H).

**E-isomer**

$^{13}$C NMR (75MHz, CDCl$_3$) δ (ppm) 176.28, 131.44, 124.11, 81.29, 39.20, 39.11, 28.91, 28.38, 22.93, -1.87, 

**Z-isomer**

176.48, 129.76, 123.64, 81.77, 38.24, 33.75, 29.21, 28.78, 19.35, -1.51. FTIR (cm$^{-1}$) 2952.8, 1785.1, 1419.8, 1168.1, 854.4. HRMS calculated for C$_{12}$H$_{21}$O$_2$Si (M+H)$^+$ m/z 353.0434, found 353.0443.
9-(Trimethyl-silanyl)-nona-4,7-dienoic acid (3.46) The iodolactone 3.45 (36 mg, 0.10 mmol) was dissolved in 95% ethanol and zinc powder (20 mg, 0.30 mmol) was added and the mixture was stirred vigorously for 2 hours. The mixture was diluted with ether and filtered through a plug of celite. The organic was concentrated under reduced pressure to afford 9-(trimethyl-silanyl)-nona-4,7-dienoic acid 3.46, (99%, 22mg) as a colorless oil. \(^1\)H NMR (300MHz, CDCl\(_3\)) \(\delta\) (ppm) 5.64-5.81 (m, 1H), 5.40-5.56 (m, 2H), 5.15-5.24 (m, 1H), 2.77 (t, \(J = 5.3\), 2H), 2.29-2.47 (m, 4H) 1.42-1.50 (m, 2H), 0.09 (s, 9H). \(^13\)C NMR (75MHz, CDCl\(_3\)) \(\delta\) (ppm) 180.20, 137.12, 129.68, 129.21, 115.33, 36.82, 29.21, 28.78, 19.35, -1.51. FTIR (cm\(^{-1}\)) 2978.5, 2673.4, 1712.1, 1431.6, 913.8. HRMS calculated for \(\text{C}_{12}\text{H}_{22}\text{O}_{2}\text{Si} (\text{M+H})^+\ m/z\) 227.1389, found 227.1398.
Octa-4,7-dienoic acid (3.47) 1,5-Hexadiene-3-ol (3 mL, 26.8 mmol), triethylorthoacetate (50mL, 268.4mmol), and propionic acid (0.2 mL, 2.68 mmol) were combined and heated to reflux for 4 hours. After the mixture was diluted with ether and washed with 2N HCl, the organic was dried with MgSO₄, filtered, then concentrated under reduced pressure. The crude material was dissolved in THF:MeOH then 2N LiOH (20 mL) was added and stirred for 4 hours. The material was then concentrated under reduced pressure. The residue was dissolved in water then acidified with 1N HCl. The oil was extracted with ether, the organic was dried with MgSO₄, filtered, and concentrated to give 3.47, (90% yield, 3.38g), as a clear yellow oil. ¹H NMR (300MHz, CDCl₃) δ (ppm) 5.81 (ddt, J = 16.5, 10.0, 6.2, 1H), 5.40-5.56 (m, 2H), 4.95-5.10 (m, 2H), 2.74 (t, J = 5.3, 2H), 2.29-2.47 (m, 4H). ¹³C NMR (75MHz, CDCl₃) δ (ppm) 180.20, 137.14, 129.58, 129.21, 115.35, 36.82, 34.27, 27.75. FTIR (cm⁻¹) 2979.5, 2673.2, 1711.7, 1431.6, 913.8. HRMS calculated for C₉H₁₂O₂ (M+H)⁺ m/z 141.0916, found 141.0921.
5-(1-iodo-but-3-enyl)-dihydro-furan-2-one (3.55). The acid 3.47 (180 mg, 1.34 mmol) was dissolved in ether (1.5 mL) then a layer of sat. sodium bicarbonate (1.5 mL) was added. The layers were stirred vigorously while iodine (1.01 g, 4.02 mmol) was added in 5 mL THF. The mixture was stirred for 3 hours then quenched with sat. sodium thiosulfate. The product was extracted with ether and dried with MgSO₄, filtered, then the organic was concentrated under reduced pressure to afford 5-(1-iodo-but-3-enyl)-dihydro-furan-2-one 3.55 (99%, 356 mg) as a yellow oil. ¹H NMR (300MHz, CDCl₃) δ (ppm) 5.91 (ddt, J = 16.9, 10.0, 6.5, 1H), 5.15-5.23 (m, 2H), 4.38-4.42 (m, 1H), 4.05-4.19 (m, 1H), 2.41-2.87 (m, 5H), 1.97-2.17 (m, 1H). ¹³C NMR (75MHz, CDCl₃) δ (ppm) 176.57, 134.99, 119.16, 81.64, 40.35, 37.03, 29.25, 28.79. FTIR (cm⁻¹) 3534.9, 3078.3, 1779.5, 1170.8, 927.4. HRMS calculated for C₉H₁₁IO₂ (M+H)⁺ m/z 266.9882, found 266.9898.
5-(2-Vinyl-cyclopropyl)-dihydro-furan-2-one (3.56). Iodolactone 3.45 (114 mg, 0.43 mmol) was dissolved in methylene chloride then a 2M solution of silver nitrate (0.65 mL) was added. The mixture was stirred for 2 hours then diluted with methylene chloride and washed with water. The organic was dried with MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20% ether:hexane) to afford 5-(2-vinyl-cyclopropyl)-dihydro-furan-2-one 3.56 (87%, 59 mg) as a clear oil. $^1$H NMR (300MHz, CDCl$_3$) δ (ppm) 5.38(ddd, $J = 9.0, 12.1, 17.8, 1H$), 5.05 (dd, $J = 17.8, 1.1, 1H$), 4.86 (dd, $J = 12.1, 1.1, 1H$), 4.02 (dt, $J = 7.8, 8.0, 1H$), 2.21-2.61 (m, 3H), 1.90-2.15 (m, 1H), 1.50 (ddddd, $J = 9.0, 8.2, 4.5, 4.5, 1H$), 1.09 (dddd, $J = 8.9, 7.8, 4.5, 4.5, 1H$), 1.62-1.78 (m, 2H). $^{13}$C NMR (75MHz, CDCl$_3$) δ (ppm) 177.33, 139.58, 113.47, 83.78, 29.09, 28.03, 24.34, 20.72, 10.39. FTIR (cm$^{-1}$) 3003.4, 1773.0, 1636.2, 1180.8. HRMS calculated for C$_9$H$_{12}$O$_2$ (M+H)$^+$ m/z 153.0837, found 158.0845.
1-Benzyloxy-6-bromo-hex-4-yn-2-ol (4.19). Starting with THP protected propargyl alcohol (1.5 mL, 10.5 mmol) in THF (15ml) at -78°C n-butyllithium (5.1 mL, 2.5M in hexane) was added slowly. After 30 minutes, BF$_3$•OEt$_2$ (1.6 mL, 12.6 mmol) was added dropwise. The mixture was stirred for 30 minutes and benzyl glycidal ether (1.9 g, 11.5 mmol) was added in 5 mL of THF. After 4 h the reaction was quenched with sat. ammonium chloride and extracted with ether. The ether was dried with MgSO$_4$, filtered, and concentrated. The crude material was then dissolved in methanol and a catalytic amount of tosic acid monohydrate was added. The mixture was stirred for 4 hours then concentrated. The crude alcohol was purified by flash column chromatography with 50% EtOAc:Hex to afford 1.06 g (4.8 mmol) of pure alcohol. The alcohol was dissolved in methylene chloride then carbon tetrachloride (2.4 g, 7.2 mmol) and triphenylphosphine (2 g, 7.2 mmol) were added and the reaction was stirred for 5 h. The mixture was concentrated and purified by column chromatography with 25% EtOAc:Hex to afford 1.99 g of 1-benzyloxy-6-bromo-hex-4-yn-2-ol 4.19. $^1$H NMR (300MHz, CDCl$_3$) δ (ppm) 7.25-7.44 (m, 5H), 3.91-3.99 (m, 1H), 3.89 (vt, $J$ = 2.7, 2H), 3.59 (dd, $J$ = 3.9, 9.9, 1H), 3.48 (dd, $J$ = 6.6, 9.9, 1H), 2.51 (dt, $J$ = 6.3, 2.4, 2H), 2.44
(bs, 1H). $^{13}$C NMR (75MHz, CDCl$_3$) δ (ppm) 137.70, 128.42, 127.80, 127.73, 83.60, 77.43, 73.39, 72.73, 68.74, 23.93, 15.07. FTIR (cm$^{-1}$) 3429.4, 2911.9, 2234.6, 1453.8. HRMS calculated for C$_{13}$H$_{15}$BrO$_2$ (M+H)$^+$ m/z 283.0334, found 283.0369.

![4.18]

1-Benzyloxy-9-(trimethyl-silanyl)-nona-4,7-diyn-2-ol (4.18)

The primary bromide 4.19 (520 mg, 1.84 mmol) was dissolved in acetone and then copper (I) iodide (513 mg, 2.7 mmol) was added. The mixture was stirred vigorously while DBU (1.1 eq) was added dropwise. As the full equivalent was added the heterogeneous mixture became a clear homogeneous solution. The reaction was stirred for 30 minutes then the concentrated. The material was flashed through a plug of silica to afford 1-benzyloxy-9-(trimethyl-silanyl)-nona-4,7-diyn-2-ol 4.18 as a clear oil, 515mg (1.63 mmol). $^1$H NMR (300MHz, CDCl$_3$) δ (ppm) 7.24-7.40 (m, 5H), 4.57 (s, 2H), 3.89-4.00 (m, 1H), 3.60 (dd, J = 3.9, 9.4, 1H), 3.49 (dd, J = 6.6, 9.4, 1H), 3.07-3.13 (m, 2H), 2.40-2.48 (m, 2H), 1.43 (t, J = 2.7, 2H), 0.09 (s, 9H). $^{13}$C NMR (75MHz, CDCl$_3$) δ (ppm) 137.88, 128.40, 127.73, 127.69, 78.24, 77.67, 75.52, 73.36, 72.95, 72.62, 68.98, 23.80, 9.85, 6.86, -2.07. FTIR (cm$^{-1}$) 3429, 2955.0, 2197.5, 1723.3, 1453.9, 1250.1. HRMS calculated for C$_{19}$H$_{26}$O$_2$Si (M+H)$^+$ m/z 315.1780, found 315.1759.
1-Benzyloxy-9-(trimethyl-silanyl)-nona-4,7-dien-2-ol (4.14). Di-yne 4.18 (515 mg, 1.63 mmol) was dissolved in 10:1, EtOAc:Pyridine then the flask was flushed with nitrogen. 10 mole % of palladium on carbon (5%) was added. A balloon filled with hydrogen was then attached. The mixture was stirred for 4hr and then filtered through silica and concentrated under reduced pressure to afford 1-benzyloxy-9-(trimethyl-silanyl)-nona-4,7-dien-2-ol 4.14 in 98% yield (507mg). 

$^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.25-7.40 (m, 5H), 5.14-5.56 (m, 4H), 4.57 (s, 2H), 3.81-3.92 (m, 1H), 3.48-3.57 (m, 1H), 3.30-3.43 (m, 1H), 2.70-2.79 (m, 2H), 2.20-2.36 (m, 2H), 1.35-1.51 (m, 2H), 0.01 (s, 9H).

$^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 138.23, 131.58, 128.69, 127.98, 126.48, 125.73, 125.33, 124.88, 74.20, 73.65, 70.52, 33.32, 30.05, 18.66, -1.53. FTIR (cm$^{-1}$) 3446.1, 2953.1, 1453.9, 1247.8, 854.8. HRMS calculated for C$_{19}$H$_{30}$O$_2$Si (M+H)$^+$ m/z 319.2015, found 319.2002.
2'-Benzyloxyethyl-2-vinyl-bicyclopropyl (4.23). The diene (4.14) (250 mg, 0.78 mmol) was dissolved in CH$_2$Cl$_2$ and 2,6-lutidine (0.14mL, 1.18mmol) was added. The mixture was cooled to –78 °C and triflic anhydride (0.16mL, 0.94mmol) was added to the reaction mixture. The reaction was stirred at –78 °C for 1 h. then quenched with sat. sodium bicarbonate and warmed to room temperature. The material was extracted with ether and washed with sat. sodium bicarbonate. The product was isolated as a crude residue by removing the solvent under reduced pressure and purified by column chromatography (silica gel, 10% EtOAc in hexanes) to give a 1:1 mixture of the anti and syn bis-cyclopropanes (128mg, 72 %) as a clear oil. $^1$H NMR (300MHz, CDCl$_3$) δ (ppm) 7.34-7.26 (m, 5H), 5.43-5.30 (m, 1H), 5.00 (dd, $J = 17.1$, 1.8, 1H), 4.82 (dd, $J = 10.2$, 1.2, 1H), 4.51 (d, $J = 1.8$, 2H), 3.38-3.22 (m, 2H), 1.25-1.15 (m, 1H), 0.97-0.82 (m, 2H), 0.80-0.72 (m, 1H), 0.54-0.44 (m, 2H), 0.42-0.26 (m, 2H). All Peaks: $^{13}$C NMR (75MHz, CDCl$_3$) δ (ppm) 141.7, 128.4, 127.6, 127.5, 111.40, 111.36, 73.91, 73.89, 72.40, 72.36, 72.36, 22.0, 21.8, 21.4, 21.0, 18.3, 18.2, 17.1, 16.4, 11.6, 8.9, 8.0. FTIR (cm$^{-1}$) 2999, 2854, 1636, 1454, 1096, 1028, 893, 734, 697. HRMS (Cl) calcd for C$_{16}$H$_{20}$O (M+H)$^+$ m/z 229.1592, found 229.1603.
7-Bromo-1-phenyl-hept-5-yn-3-ol (4.25). See a representative procedure for the synthesis of the primary bromide 4.19. $^1$H NMR (300MHz, CDCl$_3$) δ (ppm) 7.17-7.35 (m, 5H), 3.93 (t, $J = 2.4$, 2H), 3.74-3.83 (m, 1H), 2.65-2.87 (m, 2H), 2.37-2.56 (m, 2H), 1.83-1.91 (m, 2H). $^{13}$C NMR (75MHz, CDCl$_3$) δ (ppm) 141.51, 128.40, 128.38, 125.91, 84.00, 77.91, 69.13, 37.78, 31.79, 27.95, 15.02. FTIR (cm$^{-1}$): 3391.9, 2931.2, 2233.9, 1495.5, 1454.0, 1212.6, 1050.1. HRMS calculated for C$_{13}$H$_{15}$BrO (M+H)$^+$ m/z 267.0385, found 267.0374.

1-Phenyl-10-(trimethyl-silanyl)-deca-5,8-diyn-3-ol (4.26) See a representative procedure for the synthesis of the di-yne 4.18. $^1$H NMR (300MHz, CDCl$_3$) δ (ppm) 7.25-7.31 (m, 2H), 7.13-7.23 (m, 3H), 3.68-3.76 (m, 1H), 3.10-3.15 (m, 2H), 2.64-2.84 (m, 2H), 2.26-2.48 (m, 2H), 1.79-1.87 (m, 2H). $^{13}$C NMR (75MHz, CDCl$_3$) δ (ppm) 141.77, 128.42, 128.37, 125.83, 78.37, 78.29, 75.96, 72.61, 69.27, 37.77,
31.77, 27.81, 9.89, 6.87, -2.07. FTIR (cm⁻¹) 3401.1, 2953.7, 1495.5, 1249.99, 851.5. HRMS calculated for C₁₉H₂₆OSi (M+H)⁺ m/z 298.1753, found 298.1773

1-Phenyl-10-(trimethyl-silanyl)-deca-5,8-dien-3-ol (4.27) See a representative procedure for the synthesis of the di-ene 4.14. ¹H NMR (300MHz, CDCl₃) δ (ppm) 7.15-7.32 (m, 5H), 5.51-5.62 (m, 1H), 5.36-5.48 (m, 2H), 5.15-5.27 (m, 1H), 3.62-3.71 (m, 1H), 2.64-2.87 (m, 4H), 2.25-2.31 (m, 2H), 1.76-1.85 (m, 2H), 1.43-1.51 (m, 2H), 0.01 (s, 9H). ¹³C NMR (75MHz, CDCl₃) δ (ppm) 142.06, 132.00, 128.41, 128.36, 126.33, 126.32, 125.77, 125.03, 125.00, 70.66, 38.43, 35.48, 32.08, 25.51, 18.54, -1.79. FTIR (cm⁻¹) 3369.4, 2953.1, 1454.2, 1248.0. HRMS calculated for C₁₉H₃₀OSi (M+H)⁺ m/z 303.2144, found 303.2167.
7-Bromo-1-phenyl-hept-5-en-3-ol (4.31) Hydrocinnamaldehyde (1.4 g, 10.45 mmol) was dissolved in THF then cooled to -78°C. 10.6 mL of a 1 M allyl magnesium bromide solution was then added over 15 minutes. The reaction was stirred for 2 h then quenched with sat. ammonium chloride. The product was extracted with ether and the organic was dried with MgSO₄, filtered, then the organic layer was concentrated to a residue then purified by flash chromatography (silica, 25% ether:Hex) to afford 1.74 g of allylalcohol 4.32. The alcohol was then dissolved in methylene chloride and heated to reflux. Allylbromide (1.7 mL, 19.77 mmol) was added followed by addition of Grubbs’ second generation cat. (420 mg, 5 mol %). The reaction was stirred at reflux for 6 h then blown dry with compressed air. The material was purified by flash chromatography with 15% ether in hexanes to afford 4.31, (72% yield, 1.89 g). ¹H NMR (300MHz, CDCl₃) δ (ppm) 7.17-7.35 (m, 5H), 3.93 (t, J = 2.4, 2H), 3.74-3.83 (m, 1H), 2.65-2.87 (m, 2H), 2.37-2.56 (m, 2H), 1.83-1.91 (m, 2H). ¹³C NMR (75MHz, CDCl₃) δ (ppm) 141.51, 128.40, 128.38, 125.91, 84.00, 77.91, 69.13, 37.78, 31.79, 27.95, 15.02. FTIR (cm⁻¹). 3391.9, 2931.2, 2233.9, 1495.5, 1454.0, 1212.6, 1050.1. HRMS calculated for C₁₃H₁₇BrO (M+H)⁺ m/z 267.0385, found 267.0374.
1-Phenyl-10-(trimethyl-silanyl)-dec-5-en-8-yn-3-ol (4.30). See a representative procedure for the synthesis of the di-yne 4.18. $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.14-7.40 (m, 5H), 5.62-5.79 (m, 2H), 5.50-5.62 (m, 2H), 3.60-3.72 (m, 1H), 2.62-3.04 (m, 4H), 2.10-2.38 (m, 2H), 1.68-1.90 (m, 2H), 1.38-1.55 (m, 2H), 0.09 (s, 9H). $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 142.09, 129.53, 128.42, 128.33, 126.76, 125.74, 79.85, 75.59, 70.14, 40.49, 38.35, 32.26, 22.26, 6.97, -2.06. HRMS calculated for C$_{19}$H$_{28}$OSi (M+H)$^+$ m/z 301.1988, found 301.1968.

1-Phenyl-10-(trimethyl-silanyl)-deca-5,8-dien-3-ol (4.29) See a representative procedure for the synthesis of the di-ene 4.14. $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.14-7.35 (m, 5H), 5.38-5.63 (m, 3H), 5.21-5.34 (m, 1H), 3.58-3.70 (m, 1H), 2.61-2.90 (m, 4H), 2.22-2.34 (m, 1H), 2.08-2.20 (m, 1H), 1.72-1.88 (m, 2H), 1.44-1.54 (m, 2H), 0.10 (s, 9H). $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 142.43, 133.34, 128.67, 128.59, 126.72, 126.06, 126.00, 125.01, 70.41, 41.06, 38.62, 32.30, 30.54,
18.69, -1.53. FTIR (cm$^{-1}$) 3429.4, 2911.9, 2234.6, 1453.8. HRMS calculated for C$_{19}$H$_{30}$OSi (M+H)$^+$ m/z 303.2144, found 303.2137.

$\text{PhCH}_2\text{OH}$

1-(2-Phenethyl-cyclopropyl)-5-(trimethyl-silanyl)-pent-3-en-1-ol (4.33) and (4.34). The compound 4.29 (167 mg, 0.55 mmol) was dissolved in methylene chloride and 2,6-lutidine (0.13 mL, 1.10 mmol) was added. The mixture was cooled to $-78 \, ^\circ\text{C}$ and triflic anhydride (0.10 mL, 0.60 mmol) was added to the reaction mixture. The reaction was stirred at $-78 \, ^\circ\text{C}$ for 5 minutes then quenched with sat. sodium bicarbonate and warmed to room temperature. The mixture was extracted with methylene chloride and dried with Na$_2$SO$_4$, filtered, then the organic was concentrated under reduced pressure and purified on HPLC (silica, gradient from 5% ether to 50% ether in hexane) to afford 4.33 (61 mg) and 4.34 (59 mg) as clear colorless oils. Spectral data for less polar compound, $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.14-7.34 (m, 5H), 5.50-5.62 (m, 1H), 5.28-5.41 (m, 1H), 2.90 (vq, $J$ = 7.8, 1H), 2.72 (vt, $J$ = 7.7, 2H), 2.25-2.32 (m, 2H), 1.40-1.70 (m, 4H), 0.64-0.78 (m, 2H), 0.28-0.44 (m, 2H), 0.01 (m, 9H). $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 142.23, 128.45, 128.33, 125.77, 122.82, 77.26, 75.92, 35.86, 35.39, 34.64, 25.29, 18.64, 16.64, 9.82, -1.77. FTIR (cm$^{-1}$) 3400.7, 2953.2, 1247.7, 852.3. HRMS calculated for C$_{19}$H$_{30}$OSi (M-OH)$^+$ m/z 285.2038, found
285.2022. $^1$H NMR (300MHz, CDCl$_3$) δ (ppm) 7.15-7.31 (m, 5H), 5.54-5.64 (m, 1H), 5.31-5.40 (m, 1H), 2.94 (vq, J = 6.9, 1H), 2.71 (vt, J = 7.6, 2H), 2.22-2.38 (m, 2H), 1.44-1.64 (m, 4H), 0.61-0.79 (m, 2H), 0.47-0.56 (m, 1H), 0.31-0.39 (m, 1H), 0.02 (m, 9H). $^{13}$C NMR (75MHz, CDCl$_3$) δ (ppm) 142.25, 128.60, 128.33, 128.25, 125.68, 122.74, 75.57, 35.72, 35.50, 34.94, 25.33, 18.69, 16.55, 9.91, -1.78. FTIR (cm$^{-1}$) 3369.2, 2953.1, 1247.7, 852.5. HRMS calculated for C$_{19}$H$_{30}$OSi (M-OH)$^+$ m/z 285.2038, found 285.2037.

![4.36](image)

**1-Benzzyloxy-6-bromo-hex-4-en-2-ol (4.36)** See a representative procedure for the synthesis of the allylbromide 4.31. $^1$H NMR (300MHz, CDCl$_3$) δ (ppm) 7.24-7.43 (m, 5H), 5.74-5.84 (m, 2H), 4.56 (s, 2H), 3.91-3.96 (m, 2H0, 3.83-3.91 (m, 1H), 3.51 (dd J = 3.3, 9.3, 1H), 3.36 (dd, J = 7.4, 9.3, 1H), 2.27 (t, J = 6.0, 2H).

$^{13}$C NMR (75MHz, CDCl$_3$) δ (ppm) 137.84, 131.59, 129.20, 128.46, 127.83, 127.74, 73.68, 73.40, 69.72, 36.05, 32.75. HRMS calculated for C$_{13}$H$_{17}$BrO$_2$ (M+H)$^+$ m/z 285.0490, found 285.0478.
1-Benzylxyloxy-9-(trimethyl-silanyl)-non-4-en-7-yn-2-ol (4.37). See a representative procedure for the synthesis of the di-yne 4.18. $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.25-7.40 (m, 5H), 5.63-5.76 (m, 1H), 5.45-5.60 (m, 1H), 4.55 (s, 2H), 3.80-3.91 (m, 1H), 3.51 (dd, $J = 3.3$, 9.5, 1H), 3.37 (dd, $J = 7.4$, 9.5, 1H), 2.86-2.95 (m, 2H), 2.21-2.33 (m, 2H), 1.45 (t, $J = 2.6$, 2H), 0.09 (s, 9H). $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 138.02, 128.89, 128.43, 127.74, 127.70, 126.41, 79.69, 75.67, 73.88, 73.37, 69.98, 36.39, 22.23, 6.99, -2.05. HRMS calculated for C$_{19}$H$_{28}$OSi (M+H)$^+$ m/z 317.1937, found 317.1920.

1-Benzylxyloxy-9-(trimethyl-silanyl)-nona-4,7-dien-2-ol (4.38) See a representative procedure for the synthesis of the di-ene 4.14. $^1$H NMR (300MHz, CDCl$_3$) $\delta$ (ppm) 7.24-7.42 (m, 5H), 5.38-5.60 (m, 3H), 5.20-5.37 (m, 1H), 4.56 (s, 2H), 3.79-3.90 (m, 1H), 3.51 (dd, $J = 3.4$, 9.5, 1H), 3.38 (dd, $J = 7.2$, 9.5, 1H), 2.72 (vt, $J = 6.2$, 2H), 2.21 (vt, $J = 6.2$, 2H), 1.48 (vd, $J = 8.4$, 2H), 0.14 (s, 9H). $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ (ppm) 138.30, 132.56, 128.66, 127.96, 127.95, 126.59, 125.73, 125.11, 74.13, 73.58, 70.31, 36.97, 30.51, 18.66, -1.53. FTIR
(cm$^{-1}$) 3448.5, 2965.1, 1453.9, 1254.8, 854.8. HRMS calculated for $\text{C}_{19}\text{H}_{30}\text{O}_2\text{Si}$ (M+H)$^+$ m/z 319.2015, found 319.2002.
LIST OF REFERENCES


See the ref. 7.


For recent reviews of olefin metathesis see: (a) Grubbs, R. H.; Chang, S. “Recent Advances in Olefin Metathesis and Its Application in Organic


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