UNIVERSITY OF CALIFORNIA
Los Angeles

Methodologies of Bicyclo[2.2.2]octane Compounds and Progress Toward the Total Synthesis of Parthenolide

A dissertation submitted in partial satisfaction of the requirements for the degree of Doctor of Philosophy in Chemistry

by

Courtney Arielle Roberts

2016

ABSTRACT OF THE DISSERTATION

Methodologies of Bicyclo[2.2.2]octane Compounds
and
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Doctor of Philosophy in Chemistry
University of California, Los Angeles, 2016
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In Chapter 1, rearrangements of 4-substituted bicyclo[2.2.2]oct-2-enyl-5-selenophenyl esters are explored. Reduction of the esters under radical-generating conditions initially generates a bicyclo[2.2.2]oct-5-en-2-yl radical which can rearrange to a bicyclo[3.2.1]oct-6-en-2-yl radical via a cyclopropylcarbinyl radical. Although the bicyclo[3.2.1]octene system exhibits greater strain than does the bicyclo[2.2.2]octene system, radical-stabilizing substituents can reverse this preference. The product ratios are influenced by the interplay of ring strain and radical stability. In addition, the rearranged products favored the equatorial over the axial isomers, which can be explained by torsional steering.

In Chapter 2, different approaches to the synthesis of the optically active bicyclo[2.2.2]octane-2,5-diones are presented. A stereoselective Diels-Alder cycloaddition was explored to construct the bicyclo[2.2.2]octane skeleton in an efficient manner. This approach was hindered by unexpected polymerization and lack of stereoselectivity. A different method of synthesizing the optically active bicyclo[2.2.2]octane-2,5-dione featuring a diastereoselective 1,4-addition is also presented.

In Chapter 3, progress toward the total synthesis of parthenolide is described. The synthetic route relies on ring-closing metathesis to close the 10-membered carbocycle of the natural product. The efforts leading up to and including the key ring-closing step are described. Specific attention is given to different methods for overcoming the difficulties associated with medium-sized ring formation.

The dissertation of Courtney Arielle Roberts is approved.

Kendall N. Houk

Caius Gabriel Radu

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University of California, Los Angeles

2016

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ACKNOWLEDGMENTS

I would first like to thank my advisor, Dr. Michael E. Jung, for his guidance and support over the past five years. He has always demonstrated incredible patience for even the most trivial questions. As for the more difficult problems, he has been an incredible resource. The hours he has spent examining NMR spectra, building models, and suggesting synthetic strategies have not gone unnoticed- and I am deeply grateful. I have learned an incredible amount from him and will surely miss his wisdom and knowledge.

I also thank my committee members, Dr. Ken Houk, Dr. Rob Clubb, Dr. Caius Radu, and Dr. Ken Bradley, for their time, attention, and academic guidance.

I have thoroughly enjoyed my time in the Jung lab, a sentiment only made possible by my incredible labmates. Everyone has been so kind, insightful, and supportive- I can't imagine spending the last five years with any other group of people.

I must also thank my friends and colleagues in other labs at UCLA. Whether it was a quick chat, a coffee break, or assistance with finding a chemical, I always had pleasant interactions with my peers and coworkers.

My deepest gratitude goes to my boyfriend, Noah Fine Nathel, for all of his kindness and support. He is one of the most levelheaded, compassionate, and intelligent people I have ever met, and I cannot thank him enough for everything he has done for me.

Finally, I don't know where I would be without the love and support of my family. They have always encouraged me to pursue whatever interests I have held, no matter how fleeting. Moreover, they have always enthusiastically supported my choices. For their unwavering love and support, I will be eternally grateful.

Chapter 1 is a version of Jung, M. E.; Roberts, C. A.; Perez, F.; Pham, H. V.; Zou, L.; Houk, K. N. *Org. Lett.* **2016**, *18*, 32-35.

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Michael E. Jung and Courtney A. Roberts, "Progress Toward the Total Synthesis of Parthenolide," *251st ACS National Meeting,* San Diego, CA, March 2016 (poster presentation).

Michael E. Jung, Courtney A. Roberts, Felix Perez, Hung V. Pham, Lufeng Zou, and K. N. Houk, "Thermodynamic Control of Isomerizations of Bicyclic Radicals: Interplay of Ring Strain and Radical Stabilization," *Org. Lett.* **2016**, *18*, 32.

Michael E. Jung, Courtney A. Roberts, Felix Perez, Lufeng Zou, and K. N. Houk, "Rearrangements of Bicyclo[2.2.2]oct-5-en-2-yl to Bicyclo[3.2.1]oct-6-en-2-yl Radicals: Surprising Trends in Radical Stabilities," *248th ACS National Meeting*, San Francisco, CA, August 2014 (poster presentation).

William L. Czaplyski, Grace E. Purnell, Courtney A. Roberts, Rebecca M. Allred, and Elizabeth J. Harbron, "Substituent Effects on the Turn-on Kinetics of Rhodamine-based Fluorescent pH Probes" *Org. Biomol. Chem.* **2014**, *12*, 526.

Elizabeth S. Childress, Courtney A. Roberts, Desmarie Y. Sherwood, Clare L.M. LeGuyader, and Elizabeth J. Harbron, "Ratiometric Fluorescence Detection of Mercury Ions in Water by Conjugated Polymer Nanoparticles" *Anal. Chem.* **2012**, *84*, 1235.

CHAPTER 1

Rearrangements of 4-Substituted Bicyclo[2.2.2]oct-2-enyl-5-selenophenyl Esters

Introduction

Previous studies in our laboratory, specifically led by former graduate student Felix Perez, resulted in the development of phenylseleno acrylate **1-1** as an ethylene equivalent in Diels-Alder reactions. The Diels-Alder cycloaddition between a diene and a dienophile represents a powerful method for building substituted cyclohexene products with a high degree of facial, regio-, and stereoselectivity. Generally, the reactions are most efficient when the dienophile contains an electron-withdrawing group. Occasionally in synthesis, an ethylene unit is required, but ethylene itself requires too forcing conditions for practical use. Accordingly, a number of ethylene equivalents have been developed, such as vinyl phenyl sulfone, acrolein, and nitroethylene, all of which require the subsequent removal of a functional group, e.g., sulfoxide, aldehyde, or a nitro group.[1] Our laboratory employed the known *Se*-phenyl prop-2-eneselenoate **1-1** as an ethylene equivalent in cycloadditions with various dienes **1-2**. The cycloadducts **1-3** were then reduced with tris(trimethylsilyl)silane **1-4**, the Chatgilialoglu reagent,[2] through a radical pathway to afford the desired formal cycloadducts of ethylene **1-5** (Figure 1-1).

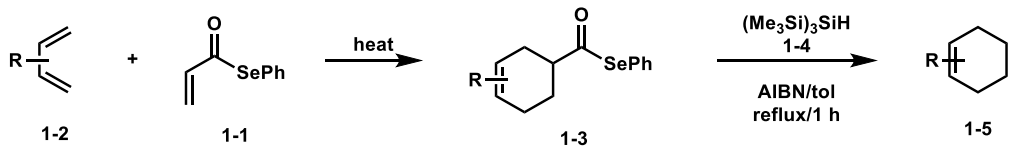
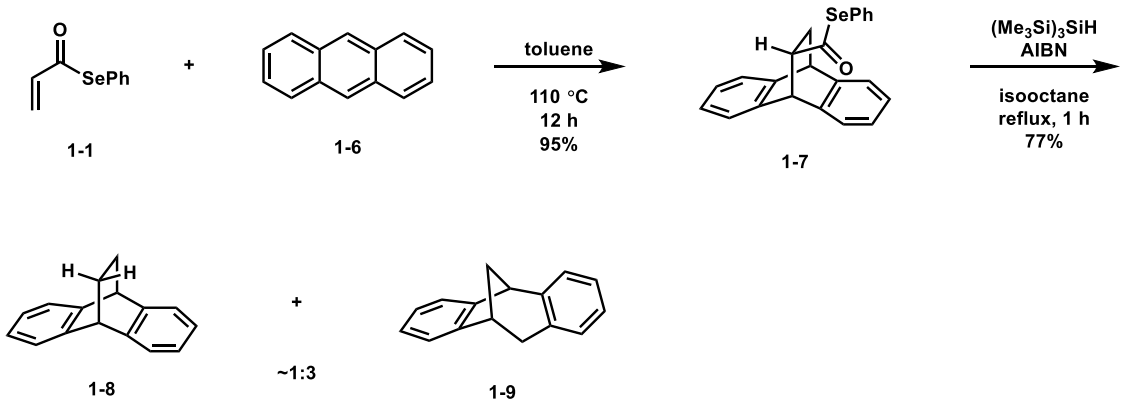


Figure 1-1. Use of **1-1** as an ethylene equivalent in Diels-Alder reactions.

During the course of these studies, it was discovered that certain cycloadducts can undergo rearrangement upon reduction.[3] The Diels-Alder cycloaddition of **1-1** and anthracene **1-6** produces the adduct **1-7**. Upon reduction under the standard conditions, **1-7** underwent rearrangement to a 1:3 mixture of the expected dibenzobicyclo[2.2.2]octane product **1-8** and the rearranged dibenzobicyclo[3.2.1]octane product **1-9** (Scheme 1-1).



Scheme 1-1. Rearrangement of the anthracene adduct **1-7**.

This rearrangement follows the well-known homoallyl-cyclopropyl carbinyl radical rearrangement pathway, driven by the formation of a more stable radical.[4] A general depiction of this process is shown in Figure 1-2. Homoallyl radicals **1-10** undergo a *3-exo-trig* cyclization to generate cyclopropylcarbinyl radicals **1-11**, which rearrange rapidly to the thermodynamically more stable homoallyl isomers **1-12**.[4c]

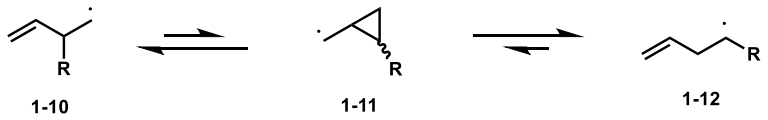
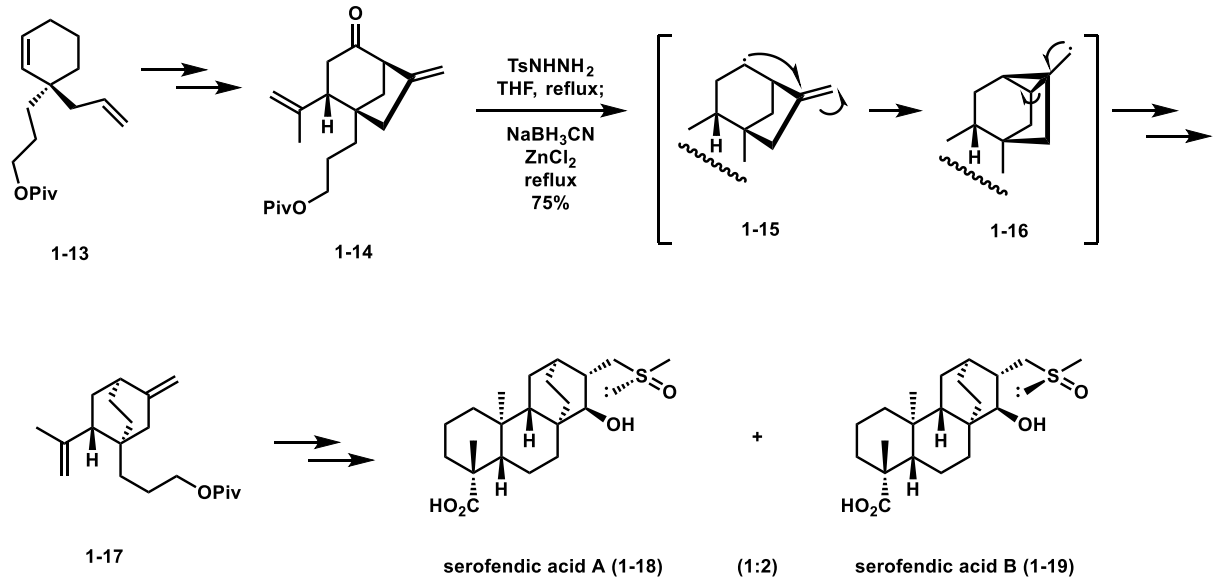


Figure 1-2. Homoallyl-cyclopropyl carbinyl-homoallyl radical rearrangement pathway.

A powerful tool for the construction of polycylic compounds, the homoallyl-homoallyl rearrangement has been successfully applied to the synthesis of natural products. Toyota and coworkers reported the total synthesis of serofendic acids A and B featuring a homoallyl-homoallyl radical rearrangement as a key step (Scheme 1-2). The bicyclo[3.2.1]octane **1-14** was constructed through various transformations beginning from the known cyclohexene **1-13**. The ketone **1-14** was then converted to its tosylhydrazone, which was treated with $NaBH_3CN$ in the presence of $ZnCl_2$ to generate the radical. Upon radical generation, the bicyclo[3.2.1]octane

compound rearranged via the mechanism shown to give the thermodynamically more stable bicyclo[2.2.2]octane product **1-17** in 75% yield. Further steps afforded serofendic acids A **1-18** and B **1-19**.[5]



Scheme 1-2. Homoallyl-homoallyl radical rearrangement as a key step in the total synthesis of serofendic acids A and B.

Results and Discussion

After our laboratory observed the rearrangement of anthracene adduct **1-7** primarily to the bicyclo[3.2.1]octane product **1-9**, we sought to explore the extent of this rearrangement with other radical-stabilizing groups. A variety of 1-substituted-1,3-cyclohexadienes **1-20** were chosen to represent various methods of radical stabilization (Figure 1-3).[6]

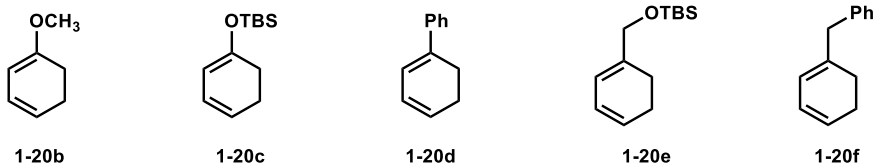
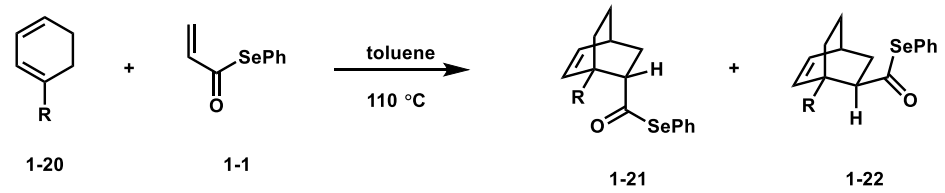


Figure 1-3. 1-Substituted 1,3-cyclohexadienes synthesized for this study.

Diels-Alder reactions of the freshly prepared dienes with the phenylseleno acrylate **1-1** were carried out in refluxing toluene for 14 h to generate mixtures of cycloadducts **1-21** and **1-22** as the endo and exo isomers, respectively (Table 1-1). In all cases, the endo products predominated as expected.[7] Cycloadditions proceeded in moderate to excellent yield, ranging from 66-97%.

Table 1-1. Diels-Alder cycloaddition of 1-substituted 1,3-cyclohexadienes **1-20** and phenylseleno acrylate **1-1**.



1-20 **1-1** **1-21** **1-22**

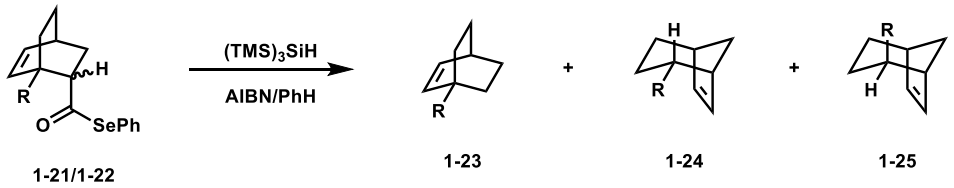
Entry	Compound	R	Yield (%)	Ratio **1-21**:**1-22**[a]
1	**a**	H	97	8:1
2	**b**	OCH_3	87	5.1:1
3	**c**	OTBS	76	3.4:1
4	**d**	Ph	66	4.4:1
5	**e**	CH_2OTBS	83	3.3:1
6	**f**	CH_2Ph	88	4.1:1

[a]The ratios of all products were determined by careful integration of the appropriate peaks in the ^1H NMR spectra.[7]

The Diels-Alder products obtained were then reduced under radical-generating conditions to afford the decarbonylated products. A mixture of the endo and exo esters was treated with tris(trimethylsilyl)silane and azobisisobutyronitrile (AIBN) and refluxed in benzene for several hours to generate a mixture of reduced products **1-23**, **1-24**, and **1-25** (Table 1-2). The parent unsubstituted cycloadduct **1-21a**/**1-22a** reduced cleanly to bicyclo[2.2.2]octene **1-**

23a as expected, with very little rearranged product observed (>20:1). Reduction of the substituted cycloadducts resulted in a more varied product distribution. Upon reduction, the 4-methoxy esters **1-21b/1-22b** generated a mixture of unrearranged to rearranged product in a ratio of 1:5.6.[8] Thus, the intermediate radical predominantly rearranges to afford the 2-methoxybicyclo[3.2.1]oct-6-enes **1-24b** and **1-25b** as the major isomers.

Table 1-2. Reduction of bicyclo[2.2.2]oct-2-enyl-5-selenophenyl esters **1-21** and **1-22**.

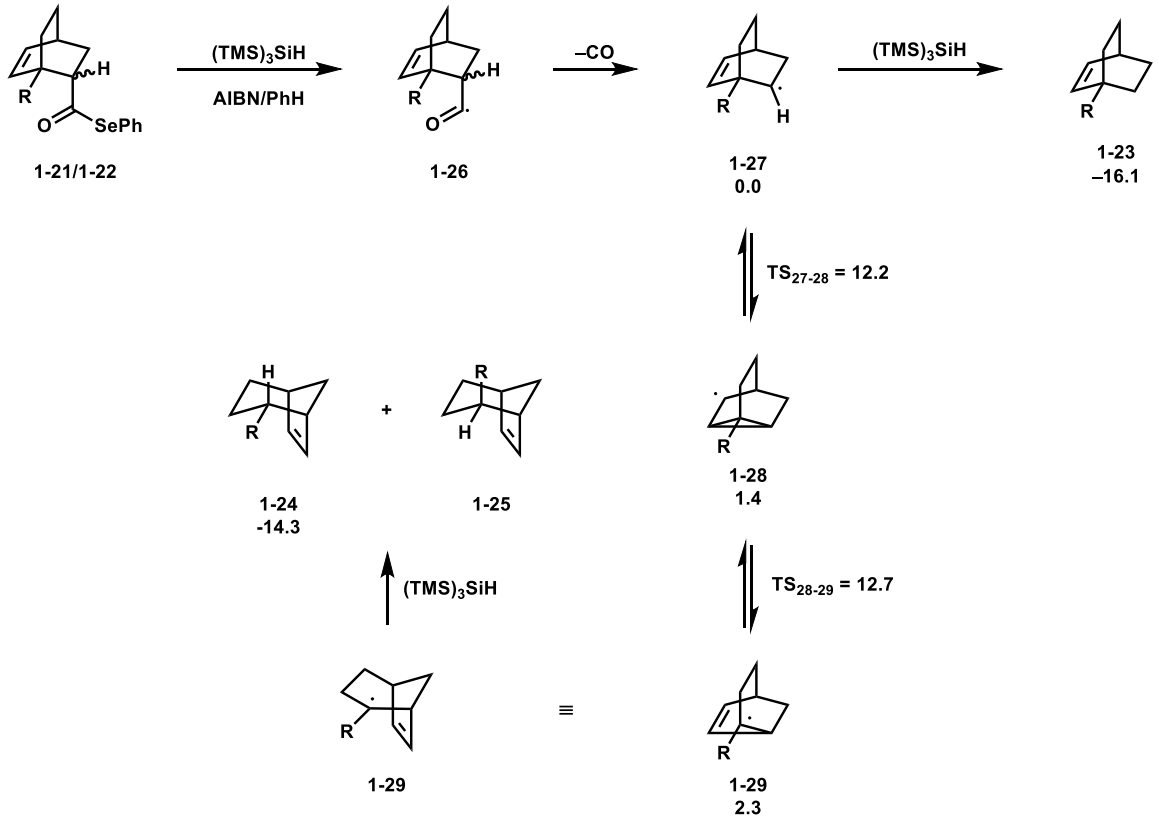


Entry	Compound	R	Ratio **1-23**:**1-24** + **1-25**	Ratio **1-24**:**1-25**[a]
1	**a**	H	>20:1	N/A
2	**b**	OCH_3	1:5.6	2.6:1
3	**c**	OTBS	1:2.5	2.5:1
4	**d**	Ph	1:10	2.4:1
5	**e**	CH_2OTBS	7:1	2.9:1
6	**f**	CH_2Ph	7:1	3.8:1

[a]The ratios of all products were determined by careful integration of the appropriate peaks in the ^1H NMR spectra.[8]

The proposed mechanism for the reduction and rearrangement pathways is shown in Scheme 1-3. The tris(trimethylsilyl)silane radical, generated in-situ with radical initiator AIBN, homolyzes the labile Se-C bond of the esters **1-21** and **1-22** to yield the acyl radical **1-26**.[9] Decarbonylation of **1-26** gives the secondary radical **1-27**, which can undergo simple reduction by the silane to afford the unrearranged bicyclo[2.2.2]octene product **1-23**. Alternatively, the

secondary radical **1-27** can rearrange, first forming the cyclopropylcarbinyl radical **1-28**, whose cyclopropyl ring then opens to afford the bicyclo[3.2.1]oct-6-en-2-yl radical **1-29**. Reduction of this radical by the silane produces a mixture of equatorial and axial isomers **1-24** and **1-25**.



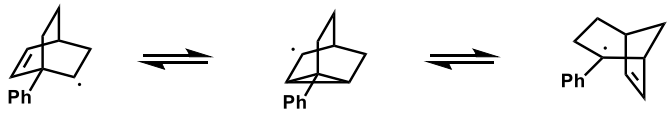
Scheme 1-3. Proposed mechanism of reduction of selenophenyl esters. Relative computed Gibbs free energies (kcal/mol) for parent compound (R = H) are given below compound numbers.

The reduction of the esters **1-21b**/**1-22b** initially generates the intermediate radical **1-27b** (Scheme 1-4). This secondary radical can undergo rearrangement through the cyclopropylcarbinyl radical **1-28b** to intermediate radical **1-29b**, in which the adjacent methoxy group provides stabilization to the radical. Comparing the methoxy-stabilized radical **1-29b** to the less stable secondary radical **1-27b**, the dominance of the rearranged products **1-24b**/**1-25b** is to be expected.

1-27b 1-28b 1-29b

Scheme 1-4. Homoallyl-cyclopropyl carbinyl-homoallyl radical rearrangement during reduction of the methoxy-substituted esters **1-21b** and **1-22b**.

The 4-silyloxy analogue **1-21c**/**1-22c**, upon exposure to the reduction conditions, follows an analogous pathway to afford predominantly the rearranged products **1-24c** and **1-25c** over the unrearranged bicyclo[2.2.2]octene product **1-23c** in a 2.5:1 ratio. As is the case for the reduction of **1-21b**/**1-22b**, the intermediate radical **1-29c** is more stable than the secondary radical **1-27c**, favoring formation of the bicyclo[3.2.1]octene products **1-24c**/**1-25c**. As expected, reduction of the phenyl-substituted esters **1-21d**/**1-22d** also predominantly affords the rearranged bicyclo[3.2.1]octene products **1-24d** and **1-25d** over the unrearranged product **1-23d** in a 10:1 ratio. Once again, this can be explained by the greater stabilization of radical **1-29d** versus **1-27d** (Scheme 1-5). In this case, the radical intermediate **1-29d** is tertiary and benzylic and therefore benefits from direct resonance stabilization by the adjacent phenyl group, leading to much greater stability than secondary radical **1-27d**.



1-27d 1-28d 1-29d

Scheme 1-5. Homoallyl-cyclopropyl carbinyl-homoallyl radical rearrangement during reduction of the phenyl-substituted esters **1-21d** and **1-22d**.

Considering the course of the reduction of the analogues **1-21b**/**1-22b**, **1-21c**/**1-22c**, and **1-21d**/**1-22d**, in which the more stable radical leads to the major product, the reduction of the esters **1-21e**/**1-22e** deviated from our expectations. The radical **1-27e**, a secondary radical with no additional stabilization, was presumed to be less stable than the tertiary radical **1-29e**, since radical stability is well-known to improve with increasing substitution on the radical center (Scheme 1-6). However, reduction of the esters **1-21e**/**1-22e** resulted in the unrearranged bicyclo[2.2.2]octene **1-23e** as the major product in a 7:1 ratio over the rearranged products **1-24e**/**1-25e**. These results indicate that **1-27e**, the bicyclo[2.2.2]octenyl intermediate containing a secondary radical, is more stable than bicyclo[3.2.1]octenyl intermediate **1-29e**, which contains a tertiary radical.

1-27e 1-28e 1-29e

Scheme 1-6. Homoallyl-cyclopropyl carbinyl-homoallyl radical rearrangement during reduction of the silyloxymethyl-substituted esters **1-21e** and **1-22e**.

Reduction of the 4-benzyl analogue **1-21f**/**1-22f** behaved in a like manner, producing the unrearranged bicyclo[2.2.2]octene compound **1-23f** predominantly over the rearranged isomers **1-24f** and **1-25f**, again in a ratio of 7:1.

To further investigate these results and develop an explanation for the unexpected product ratios, we initiated a collaboration with the computational laboratory of Dr. Kendall Houk, who performed density functional calculations at the M06-2X/6-311G(d,p)//B3LYP/6-31G(d) level of theory using the Gaussian09 program.[10] Activation free energies for the homoallyl-cyclopropyl

carbinyl-homoallyl radical rearrangement of **1-27a** to **1-28a** to **1-29a** were also computed (Scheme 1-3, R = H).

The relative energies of the radicals, the transition states for rearrangement, and the products for the parent system (R = H) are shown in Figure 1-4. The bicyclo[2.2.2]octene **1-23a** is calculated to be 1.8 kcal/mol more stable than the isomeric bicyclo[3.2.1]octene **1-24a**. Their radicals **1-27a** and **1-29a** differ in energy in the same direction by 2.3 kcal/mol. The higher energy of the bicyclo[3.2.1] compounds can be attributed to greater skeletal strain. The low activation barriers for $\mathbf{TS_{27\text{-}28}}$ and $\mathbf{TS_{28\text{-}29}}$, shown earlier in Scheme 1-3, are consistent with the proposed equilibrium between the radical species **1-27** and **1-29**.

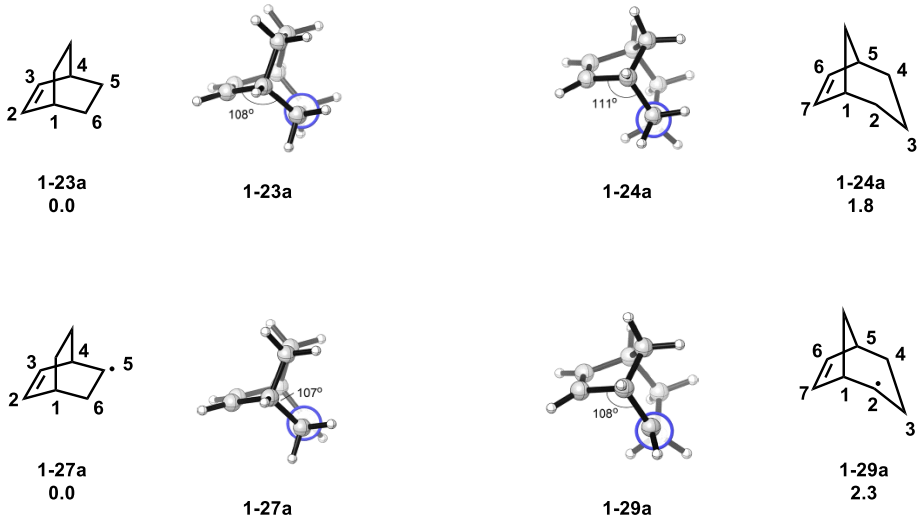


Figure 1-4. Structures of bicyclo[2.2.2]oct-2-ene **1-23a**, bicyclo[3.2.1]oct-6-ene **1-24a**, and their radicals **1-27a** and **1-29a**, with relative M06-2X/6-311G(d,p)//B3LYP/6-31G(d) Gibbs free energies in kcal/mol.

Figure 1-5 shows the effect of methyl substitution on the bicyclo[2.2.2]octenyl and bicyclo[3.2.1]octenyl radicals. The radical **1-30** is derived from **1-27a**, with an additional methyl at the bridgehead position adjacent to the secondary radical. The radical **1-31**, a derivative of **1-29a**, has an additional methyl at the radical center, forming a tertiary radical. Although tertiary

radicals are generally more stable than secondary radicals, the calculations show **1-30** to be more stable than **1-31** by 1.2 kcal/mol. However, converting the secondary radical center of **1-29a** to the tertiary radical center of **1-30** does stabilize the system by 1.1 kcal/mol. For comparison, simple acyclic analogues are shown in the right side of the figure. The substitution patterns are analogous to those of the bicyclic systems on the left side of the figure. Here, secondary radical **1-33** is less stable than tertiary radical **1-34** by 1.5 kcal/mol, as expected for the simple acyclic system.

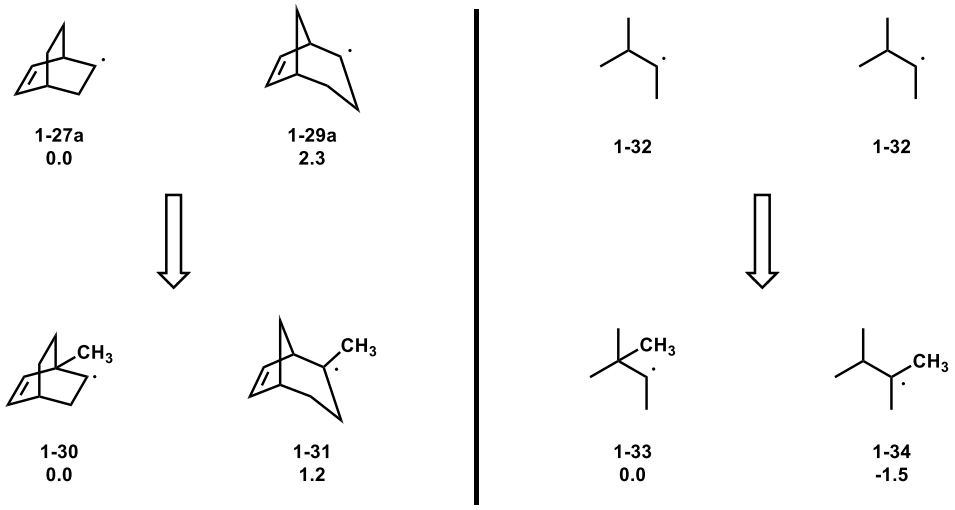


Figure 1-5. Comparison of radical stabilities with methyl substitution of **1-27a**/**1-29a** and model acyclic system. Gibbs free energies (kcal/mol) are shown below compound numbers.

Table 1-3 shows the computed energy differences between the radical species **1-27** and **1-29**, the theoretical ratios of **1-27**:**1-29**, and the experimental ratios of **1-23**:**1-24** + **1-25**. The theoretical and experimental ratios are generally in good accord.[11] Entry 3, which represents the analogue where R = Ph, shows a deviation between the predicted ration of **1-27**:**1-29**. During the reduction mechanism, once radical **1-27** is formed, reduction can occur before the radical reaches an equilibrium with radical species **1-29**, leading to a smaller amount of the major product compared to theoretical expectations. However, even though the magnitude of the ratios

does not align perfectly, the experimental observation matches the theoretical prediction in that the phenyl analogue undergoes the most rearrangement of all the substrates tested. Comparison of the computed and observed ratios supports our initial predictions that radical-stabilizing substituents favor rearrangement to generate the bicyclo[3.2.1]octene compounds as the predominant products, as seen in the methoxy and phenyl substituents. An alkyl substituent prefers to remain primarily unrearranged as the bicyclo[2.2.2] system, as the ring strain of the [3.2.1] system prevails over the stabilization of the tertiary radical.

Table 1-3. Computed radical stabilities and equilibrium ratios of bicyclic compounds with various substituents.

Entry	R	$\Delta\Delta G_{17\text{-}19}$ (kcal/mol)	Predicted ratio **1-27**:**1-29**	Experimental ratio **1-23**:**1-24** + **1:25**
1	H	2.3	48:1	>20:1
2	OCH_3	-1.0	1:5	1:5.6
3	Ph	-6.7	1:>8 x 10^4	1:10
4	CH_3	1.2	8:1	7:1[a]

[a]Experimental value for the CH_2OTBS and CH_2Ph substituents.

An additional observation made during the course of these studies relates to the ratio of the rearranged isomers **1-24**:**1-25**. Upon reduction of the radical **1-29**, hydrogen abstraction from the silane can occur from either face of the radical center, leading to a mixture of the equatorial product **1-24** and the axial product **1-25**. In each case, the equatorial product **1-24** is favored over the axial product **1-25** by a ratio of 2.3:1 to 3.8:1. As shown in Figure 1-6, the radical adopts a slightly nonplanar conformation to minimize eclipsing between the bonds to the radical center and the attached carbon, a preference that is reinforced in the transition states to

minimize eclipsing interactions with the newly forming bond. This is a well-known phenomenon in C-C bond-forming reactions that is also known as torsional steering.[12] As depicted in Figure 1-6, hydrogen abstraction from the silane occurs primarily from the top of the radical center of **1-29a** to avoid torsional strain from eclipsing bonds. This preference leads to formation of isomer **1-24** over **1-25**.

Figure 1-6. Newman projections for **1-29a**, viewing from (a) C2-C1 and (b) C2-C3

Conclusion

A recently developed ethylene equivalent for Diels-Alder cycloadditions was employed to generate a series of 4-substituted bicyclo[2.2.2]oct-2-enyl-5-selenophenyl esters. Reduction of these cycloadducts via a radical mechanism allows for the rearrangement of the initially formed bicyclo[2.2.2]oct-5-en-2-yl radical **1-27** to the bicyclo[3.2.1]oct-6-en-2-yl radical **1-29** via an intermediate cyclopropylcarbinyl radical **1-28**. The bicyclo[3.2.1]octene system exhibits greater ring strain than does the bicyclo[2.2.2]octene system, which leads to a mixture of products that favors the unrearranged bicyclo[2.2.2]octene products. However, radical-stabilizing substituents can reverse this preference, overriding the ring strain and pushing the product distribution to favor the rearranged bicyclo[3.2.1]octene systems. In addition, two bicyclo[3.2.1]octene isomers are possible, where the substituent is either in the equatorial (**1-24**) or the axial (**1-25**) position. Each rearranged reduction product favored the equatorial product, which can be explained by

torsional steering, i.e., hydrogen abstraction from the silane occurs from the face which avoids torsional strain from eclipsing bonds.

Experimental Section

General: All reactions were carried out in flame-dried glassware under an argon atmosphere using freshly distilled solvents unless otherwise noted. Reagents were purchased from Sigma-Aldrich, Acros, or Oakwood and used without further purification. Unless otherwise stated, reactions were conducted at room temperature (approximately 23 °C). Reactions were monitored by thin-layer chromatography (TLC) using SORBTECH Silica G TLC plates w/UV254 followed by UV visualization and iodine staining. Flash column chromatography was performed using SilicaFlash P60 (60 Å, 40-63 μM) from SiliCycle Inc. ^{1}H NMR spectra were recorded on Bruker spectrometers (400 and 500 MHz) and are reported in parts per million (ppm, δ). Splitting patterns are designated by: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad. ^{1}H NMR chemical shifts are referenced to the residual solvent peak at 7.26 ppm for $CDCl_3$ and at 7.15 ppm for C_6D_6. ^{13}C NMR spectra were acquired on Bruker spectrometers (100 and 125 MHz) and are reported in parts per million (ppm, δ). ^{13}C data are referenced to the residual solvent peak at 77.91 ppm for $CDCl_3$ and at 127.55 ppm for C_6D_6. The reported ratios of the isomeric products were determined by careful integration of the appropriate absorptions in the ^{1}H NMR spectra of the mixture. High-resolution mass spectrometry data was obtained using a Thermo Fisher Scientific Exactive Plus with IonSense ID-CUBE DART source.

1-((1,1-Dimethylethyl)dimethylsilyloxy)-1,3-cyclohexadiene (1-20c): To a solution of hexamethyldisilazane (3.0 mL, 14.2 mmol, 1.1 equiv.) in tetrahydrofuran (THF, 50 mL) was added *n*-butyllithium (5.7 mL, 14.2 mmol, 1.1 equiv.) at -78 °C, and the mixture was allowed to stir for 20 min. Hexamethylphosphoramide (HMPA, 4.5 mL, 25.9 mmol, 2 equiv.) was then added and the mixture continued to stir for 15 min. A solution of cyclohex-2-en-1-one (1.25 mL, 12.9 mmol,

1 equiv.) dissolved in THF (16 mL) was added dropwise over 45 min. The reaction was allowed to stir for 1 h before a solution of *tert*-butyldimethylsilyl triflate (TBSOTf, 3.6 mL, 15.5 mmol, 1.2 equiv.) in THF (30 mL) was added dropwise over 40 min. The solution was allowed to stir at -78 °C for 20 min, warmed to room temperature, and quenched by addition of a saturated aqueous NH_4Cl solution. The mixture was diluted with diethyl ether (70 mL), washed with water (5 x 40 mL) and brine (40 mL), and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. Short path vacuum distillation (1 mm Hg, 68 °C) yielded a 20:1 mixture of the diene **1-20c** and its regioisomer, the 2-silyloxydiene,[13] as a colorless liquid (1.75 g, 65%).

^1H NMR ($CDCl_3$, 500 MHz) δ:

5.81 (ddt, *J* = 9.5, 5.5, 1.5 Hz, 1H)

5.41 (dt, *J* = 9.5, 4.0 Hz, 1H)

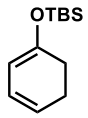
5.11 (d, *J* = 5.5 Hz, 1H)

2.30-2.24 (m, 2H)

2.23-2.17 (m, 2H)

0.93 (s, 9H)

0.17 (s, 6H).



1-20c

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 153.7, 124.4, 118.1, 102.2, 28.5, 25.6, 23.8, 18.0, -4.54.

1,3-Cyclohexadiene-1-methanol (SI-1): Ethyl 1,3-cyclohexadienecarboxylate was prepared according to a known literature procedure.[14] To a solution of this ester (1.44 g, 9.46 mmol, 1 equiv.) in toluene (50 mL) cooled to 0 °C was added dropwise diisobutylaluminum hydride (DIBAL,

1.5 M in toluene, 25 mL, 4 equiv.). The mixture was stirred for 1 h and then quenched by slow addition of ethanol (20 mL) and saturated aqueous potassium sodium tartrate (30 mL). The mixture was allowed to stir until the emulsion disappeared and the two phases separated. The mixture was diluted with diethyl ether (50 mL). The aqueous layer was extracted with diethyl ether (3 x 45 mL), and the organic layers were combined, washed with brine (45 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified via flash column chromatography on silica gel (20% ethyl acetate/hexanes) to afford alcohol **SI-1** (792 mg, 76%) as a light yellow liquid. The spectral data for alcohol **SI-1** are in accordance with those reported in the literature.[15]

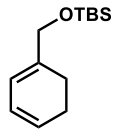
1-((1,1-Dimethylethyl)dimethylsilyloxy)methyl-1,3-cyclohexadiene (1-20e): To a solution of 1,3-cyclohexadiene-1-methanol (234 mg, 2.12 mmol, 1 equiv.) in dichloromethane (10 mL) at 0 °C was added triethylamine (0.89 mL, 6.37 mmol, 3 equiv.). The mixture was allowed to stir at 0 °C for 30 min, after which *tert*-butyldimethylsilyl chloride (482 mg, 3.19 mmol, 1.5 equiv.) was added. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with diethyl ether (2 x 5 mL) and the organic layers were combined, washed with brine (10 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified via flash column chromatography on silica gel (1-6% ethyl acetate/hexanes) to afford **1-20e** as a colorless liquid (417 mg, 88%); R_f 0.15 (100% hexanes).

^1H NMR ($CDCl_3$, 400 MHz) δ:

5.91 (m, 1H)

5.87 (m, 1H)

5.71 (dt, *J* = 8.8, 4.0 Hz, 1H)



1-20e

4.12 (s, 2H)

2.19 (m, 2H)

2.08 (bt, *J* = 9.0 Hz, 2H)

0.92 (s, 9H)

0.07 (s, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.2, 124.8, 124.2, 117.8, 66.0, 25.8, 23.2, 22.5, 18.3, -5.39.

1-(Phenylmethyl)cyclohexa-1,3-diene (1-20f): Following the procedure of Ishihara, et al.,[16] to a solution of 1-triflyloxy-1,3-cyclohexadiene[17] (913 mg, 4.00 mmol, 1 equiv.) in diethyl ether (20 mL) was added [1,3-bis(diphenylphosphino)propane]dichloronickel(II) ($NiCl_2$•dppp) (107 mg, 0.2 mmol, 0.05 equiv.). The mixture was cooled to -78 °C, and benzylmagnesium chloride (1.68 M in THF, 3.8 mL, 1.5 equiv.) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL). The aqueous layer was extracted with diethyl ether (2 x 10 mL) and the organic layers were combined, washed with brine (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The resulting residue was purified via flash column chromatography on silica gel (100% hexanes) to afford **1-20f** as a colorless liquid (543 mg, 80%); R_f 0.47 (100% hexanes). A minor, inseparable amount of the 2-benzyldiene, a known compound,[16] was also obtained.

^{1}H NMR ($CDCl_3$, 400 MHz) δ:

7.32-7.26 (m, 2H)

7.23-7.18 (m, 3H)

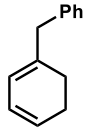
5.89 (m, 1H)

5.68 (m, 2H)

3.38 (s, 2H)

2.17-2.12 (m, 2H)

2.08-2.04 (m, 2H).



1-20f

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 139.6, 138.5, 128.9, 128.2, 126.0, 124.4, 123.9, 120.2, 43.7, 26.0, 22.9.

General Procedure for Diels-Alder Cycloadditions: A screw-cap vial was charged with the selenoacrylate **1-1** (1.0 mmol), the desired diene **1-20** (2.0 mmol), butylated hydroxytoluene (BHT, 0.03 mmol), toluene (3.3 mL), and a small stir bar. The mixture was purged with argon for 5 min. The vial was then sealed and the mixture was heated to 110 °C and allowed to stir for 14 h for **1-20c**, 20 h for **1-20d**, or 36 h for **1-20e** and **1-20f**. After completion, the reaction was cooled to room temperature, the solvent was removed under reduced pressure, and the mixture was purified by flash column chromatography on silica gel.

Compounds **1-21a**, **1-21b**, **1-22a**, and **1-22b** are all known compounds.[1]

(±) (1*S*, 2*R*, 4*R*) *Se*-Phenyl 1-((1,1-dimethylethyl)dimethylsilyloxy)bicyclo[2.2.2]oct-5-ene-2-carboselenoate (1-21c) and (±) (1*S*, 2*S*, 4*R*) *Se*-Phenyl 1-((1,1-dimethylethyl)dimethylsilyloxy)-bicyclo[2.2.2]oct-5-ene-2-carboselenoate (1-22c): Diene **1-20c** was subjected to the conditions outlined in the general Diels-Alder cycloaddition procedure. Flash column chromatography on silica gel (100% hexanes) afforded a 4:1 mixture of **1-21c** and **1-22c** as a yellow oil (320 mg, 76%); R_f of **1-21c** = 0.42, R_f of **1-22c** = 0.47 (5% ethyl acetate/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz) δ:

7.51-7.42 (m, 2H)

7.39-7.30 (m, 3H)

6.29-6.13 (m, 2H)

3.16 (dd, *J* = 10.0, 6.0 Hz, 0.8H)

3.00 (ddd, *J* = 11.2, 5.2, 1.6 Hz, 0.2H)

2.58 (m, 0.8H)

2.52 (m, 0.2H)

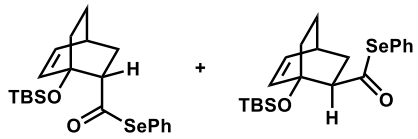
2.21 (m, 0.2H)

1.97 (ddd, *J* = 12.8, 10.0, 2.4 Hz, 0.8H)

1.79-1.55 (m, 3H)

1.50-1.22 (m, 2H)

0.97 (s, 1.8H)



1-21c **1-22c**

0.93 (s, 7.2H)

0.16 (s, 0.6H)

0.14 (s, 4.8H)

0.11 (s, 0.6H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 203.7, 202.0, 139.4, 136.6, 135.7, 135.5, 132.4, 131.8, 129.2, 129.1, 128.6, 128.5, 127.9, 127.6, 77.0, 76.5, 62.3, 60.7, 35.2, 33.8, 31.4, 30.3, 29.6, 29.3, 26.1, 25.8, 25.6, 25.2, 18.25, 18.16, -2.10, -2.13, -2.24, -2.36.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{31}O_2SeSi$ 423.12585; found, 423.12280.

(±) (1*S*, 2*R*, 4*R*) *Se*-Phenyl 1-((1,1-dimethylethyl)dimethylsilyloxy)bicyclo[2.2.2]oct-5-ene-2-carboselenoate (1-21c): The endo isomer was isolated as a more polar fraction after flash column chromatography on silica gel (100% hexanes) as a yellow oil; R_f 0.42 (5% ethyl acetate/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz) δ:

7.46-7.43 (m, 2H)

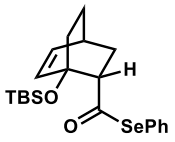
7.35-7.31 (m, 3H)

6.27 (d, *J* = 8.5 Hz, 1H)

6.21 (dd, *J* = 8.5, 6.5 Hz, 1H)

3.16 (dd, *J* = 9.5, 5.5 Hz, 1H)

2.58 (m, 1H)



1-21c

1.97 (ddd, *J* = 13.0, 10.0, 3.0 Hz, 1H)

1.68 (ddd, *J* = 10.0, 10.0, 3.0, 1H)

1.64-1.58 (m, 2H)

1.46 (td, *J* = 11.5, 4.0 Hz, 1H)

1.39 (m, 1H)

0.92 (s, 9H)

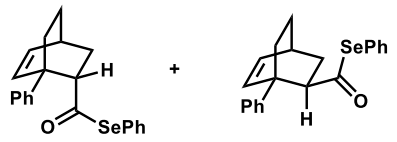
0.14 (s, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 201.7, 136.5, 135.6, 131.7, 129.3, 128.3, 127.5, 76.4, 62.2, 35.1, 33.7, 29.5, 25.7, 25.1, 18.1, -2.21, -2.46.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{31}O_2SeSi$ 423.12585; found, 423.12412.

(±) (1*S*, 2*R*, 4*R*) *Se*-Phenyl 1-phenylbicyclo[2.2.2]oct-5-ene-2-carboselenoate (1-21d) and (±) (1*S*, 2*S*, 4*R*) *Se*-Phenyl 1-phenylbicyclo[2.2.2]oct-5-ene-2-carboselenoate (1-22d): Diene **1-20d** was prepared according to the following literature sequence. Addition of phenyllithium to 1-cyclohex-2-enone[18] followed by regiospecific dehydration of the resultant allyl alcohol[19] afforded the diene **1-20d**. After cycloaddition following the general procedure, purification of the Diels-Alder cycloadduct by flash column chromatography on silica gel (0-1% ethyl acetate/hexanes) afforded a 7:3 mixture of **1-21d** and **1-22d** as a yellow oil (241 mg, 66%); R_f of **1-21d** = 0.10, R_f of **1-22d** = 0.13 (2% ethyl acetate/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz) δ:



1-21d 1-22d

7.48-7.34 (m, 5H)

7.33-7.17 (m, 5H)

6.70 (d, *J* = 8.4 Hz, 0.7H)

6.54-6.41 (m, 1.3H)

3.56 (dd, *J* = 10.4, 6.0 Hz, 0.7H)

3.03 (ddd, *J* = 11.2, 5.6, 2.0 Hz, 0.3H)

2.82-2.72 (m, 1H)

2.63 (ddd, *J* = 12.0, 9.2, 2.8 Hz, 0.3H)

2.18 (ddd, *J* = 12.8, 10.4, 2.4 Hz, 0.7H)

1.93 (m, 0.7H)

1.88-1.65 (m, 2H)

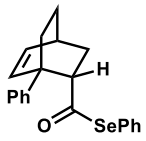
1.49-1.31 (m, 2.3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 203.5, 202.0, 145.0, 144.6, 138.8, 135.9, 135.6, 135.5, 135.1, 134.5, 134.2, 129.2, 129.0, 128.5, 128.43, 128.37, 128.35, 127.2, 126.8, 126.6, 126.5, 126.2, 62.6, 60.4, 44.6, 44.2, 35.9, 33.9, 31.1, 30.5, 30.2, 26.1, 25.5, 23.9.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{21}OSe$ 369.07576; found, 369.07435.

(±) (1*S*, 2*R*, 4*R*) *Se*-Phenyl 1-phenylbicyclo[2.2.2]oct-5-ene-2-carboselenoate (**1-21d**): The endo isomer was isolated as the more polar fraction after flash column chromatography on silica gel (0-1% ethyl acetate/hexanes) as a yellow oil; R_f = 0.10 (2% ethyl acetate/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ:



1-21d

7.50-7.47 (bd, *J* = 7.0 Hz, 2H)

7.42-7.38 (bt, *J* = 7.5 Hz, 2H)

7.32-7.29 (m, 5H)

7.29-7.25 (bt, *J* = 8.0 Hz, 1H)

6.73 (d, *J* = 8.5 Hz, 1H)

6.53 (dd, *J* = 8.5, 6.5 Hz, 1H)

3.58 (dd, *J* = 10.0, 5.5 Hz, 1H)

2.81 (m, 1H)

2.19 (ddd, *J* = 12.5, 10.5, 3.0 Hz, 1H)

1.95 (ddd, *J* = 11.5, 9.5, 3.0 Hz, 1H)

1.75-1.68 (m, 2H)

1.49-1.35 (m, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 202.1, 144.7, 135.8, 134.6, 134.3, 129.1, 128.6, 128.5, 126.9, 126.7, 126.4, 60.5, 44.3, 36.1, 34.0, 30.4, 25.7.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{21}H_{21}OSe$ 369.07576; found, 369.07458.

(±) (1*S*, 2*R*, 4*R*) *Se*-Phenyl 1-(((1,1-dimethylethyl)dimethylsilyloxy)methyl)-bicyclo[2.2.2]oct-5-ene-2-carboselenoate (1-21e) and (±) (1*R*, 2*R*, 4*S*) *Se*-Phenyl 4-((1,1-dimethylethyl)dimethylsilyloxy)methyl)-bicyclo[2.2.2]oct-5-ene-2-carboselenoate (SI-2): After Diels-Alder cycloaddition of **1-1** with the diene **1-20e** following the general procedure, flash column chromatography on silica gel (0-0.4% ethyl acetate/hexanes) afforded a mixture of **1-21e**, **1-22e**, and **SI-2** in a 3.3:1:1 ratio as a yellow oil (360 mg, 83%). An inseparable 3:2 mixture of **1-21e** and **SI-2** was isolated as the more polar fraction; R_f 0.11 (2% ethyl acetate/hexanes).

^{1}H NMR ($CDCl_3$, 400 MHz) δ:

7.48-7.42 (m, 2H)

7.36-7.30 (m, 3H)

6.32 (dd, *J* = 8.0, 6.8 Hz, 0.6H)

6.20 (dd, *J* = 8.0, 6.0 Hz, 0.4H)

6.16 (d, *J* = 8.0 Hz, 0.4H)

5.94 (d, *J* = 8.4 Hz, 0.6H)

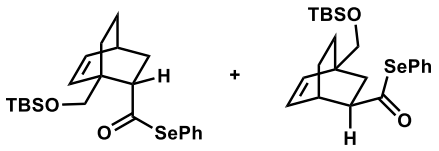
3.91 (d, *J* = 10.0 Hz, 0.6H)

3.66 (d, *J* = 9.6 Hz, 0.6H)

3.62 (d, *J* = 10.0 Hz, 0.4H)

3.58 (d, *J* = 10.0 Hz, 0.4H)

3.20 (dd, *J* = 10.4, 6.0 Hz, 0.6H)



1-21e SI-2

3.10-3.01 (m, 0.8H)

2.64 (m, 0.6H)

2.02 (ddd, *J* = 12.8, 10.4, 2.8 Hz, 0.6H)

1.76-1.63 (m, 2H)

1.57-1.49 (m, 1H)

1.40-1.30 (m, 1H)

1.23-1.16 (m, 0.6H)

1.14-1.06 (m, 0.8H)

0.94 (s, 5H)

0.91 (s, 4H)

0.080 (s, 1.5H)

0.076 (s, 1H)

0.07 (s, 1.5H)

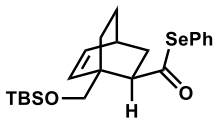
0.06 (s, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 202.9, 202.4, 136.3, 136.0, 135.8, 134.0, 132.7, 130.7, 129.2, 129.1, 128.6, 128.5, 127.2, 126.6, 68.4, 66.2, 56.6, 56.3, 42.3, 40.0, 34.2, 33.9, 33.0, 30.4, 29.5, 28.8, 27.1, 26.3, 26.0, 25.9, 25.0, 18.4, -5.37, -5.42, -5.55.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{33}O_2SeSi$ 437.14106; found, 437.13994.

(±) (1*S*, 2*S*, 4*R*) *Se*-Phenyl 1-(((1,1-dimethylethyl)dimethylsilyloxy)methyl)-bicyclo[2.2.2]oct-5-ene-2-carboselenoate (1-22e): The exo isomer was isolated as the less polar fraction after flash column chromatography on silica gel (0-0.4% ethyl acetate/hexanes) as a yellow oil; R_f 0.16 (2% ethyl acetate/hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ:



1-22e

7.50-7.46 (m, 2H)

7.39-7.35 (m, 3H)

6.28 (dd, *J* = 8.0, 6.0 Hz, 1H)

6.23 (d, *J* = 7.5 Hz, 1H)

3.76 (d, *J* = 10.0 Hz, 1H)

3.58 (d, *J* = 10.0 Hz, 1H)

2.99 (ddd, *J* = 10.5, 7.0, 2.0 Hz, 1H)

2.58 (m, 1H)

1.84 (ddd, *J* = 12.5, 10.0, 3.5 Hz, 1H)

1.74-1.70 (m, 2H)

1.69-1.62 (m, 1H)

1.32-1.28 (m, 2H)

0.95 (s, 9H)

0.12 (s, 3H)

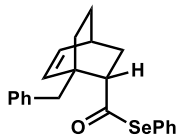
0.10 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 203.7, 136.4, 135.7, 134.1, 129.2, 128.7, 127.5, 66.1, 54.6, 43.3, 32.0, 26.1, 25.7, 23.2, 18.4, 14.1, -5.20, -5.51.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{33}O_2SeSi$ 437.14106; found, 437.14001.

(±) (1*S*, 2*R*, 4*R*) *Se*-Phenyl 1-(phenylmethyl)bicyclo[2.2.2]oct-5-ene-2-carboselenoate (1-21f): After Diels-Alder cycloaddition of **1-1** with the diene **1-20f** following the general procedure, flash column chromatography on silica gel (0-0.4% ethyl acetate/hexanes) afforded a 4.1:1 mixture of **1-21f** and **1-22f** as a yellow oil (334 mg, 88%). The endo isomer (**1-21f**) was isolated as the more polar fraction after flash column chromatography on silica gel; R_f 0.17 (2% ethyl acetate/hexanes).

^{1}H NMR (C_6D_6, 500 MHz) δ:



1-21f

7.55-7.52 (m, 2H)

7.16-7.09 (m, 3H)

7.08-6.98 (m, 5H)

6.27 (d, *J* = 8.5 Hz, 1H)

6.10 (dd, *J* = 8.5, 6.5 Hz, 1H)

3.02 (d, *J* = 13.5 Hz, 1H)

2.98 (d, *J* = 13.5 Hz, 1H)

2.68 (dd, *J* = 10.0, 5.5 Hz, 1H)

2.17 (m, 1H)

1.56 (ddd, *J* = 12.5, 10.5, 2.5 Hz, 1H)

1.51-1.46 (m, 1H)

1.06-1.01 (m, 2H)

0.98-0.86 (m, 2H).

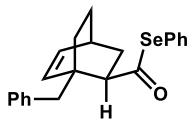
^{13}C NMR (C_6D_6, 125 MHz) δ: 200.9, 138.0, 136.0, 135.5, 133.3, 130.7, 129.2, 129.1, 128.4, 128.2, 126.2, 59.5, 42.2, 40.4, 34.0, 30.4, 30.1, 25.2.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{23}OSe$ 383.09097; found, 383.08983.

(±) (1*S*, 2*S*, 4*R*) *Se*-Phenyl 1-(phenylmethyl)bicyclo[2.2.2]oct-5-ene-2-carboselenoate (1-22f): The exo isomer was isolated as the less polar fraction after flash column chromatography on silica gel (0-0.4% ethyl acetate/hexanes); R_f = 0.10 (2% ethyl acetate/hexanes).

^{1}H NMR (C_6D_6, 500 MHz) δ:

7.54-7.51 (m, 2H)



1-22f

7.11-7.08 (m, 3H)

7.06-6.95 (m, 5H)

6.18 (d, *J* = 8.0 Hz, 1H)

5.93 (dd, *J* = 8.5, 6.5 Hz, 1H)

3.00 (d, *J* = 13.5 Hz, 1H)

2.88 (d, *J* = 13.5 Hz, 1H)

2.58 (ddd, *J* = 12.0, 6.0, 2.0 Hz, 1H)

2.28 (m, 1H)

2.17 (m, 1H)

1.62 (ddd, *J* = 12.5, 5.5, 2.0 Hz, 1H)

1.58-1.47 (m, 2H)

1.12-1.00 (m, 2H).

^{13}C NMR (C_6D_6, 125 MHz) δ: 202.1, 138.3, 135.9, 135.7, 133.8, 130.6, 129.1, 128.5, 128.2, 127.2, 126.2, 42.4, 41.6, 32.7, 29.9, 29.5, 26.5, 26.1.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{22}H_{23}OSe$ 383.09097; found, 383.08981.

General Procedure for Decarbonylation: A round-bottom flask was charged with 0.5 mmol of the cycloadduct and dissolved in benzene (5 mL) with stirring. Tris(trimethylsilyl)silane (TTMSS, 1.0 mmol) and azobisisobutyronitrile (AIBN, 0.10 mmol) were added and the mixture was purged with argon for 10 min. The flask was then lowered into a preheated (80 °C) oil bath and the solution was refluxed for 1 h, except for cycloadducts **1-21d** and **1-22d**, which required a reaction time of 5 h. The reaction was then cooled to room temperature and the solvent was removed under reduced pressure.

Compounds **1-23a** and **1-23b** are commercially available. Compound **1-24b**[20] is a known compound.

General Oxidation Procedure after Decarbonylation (Oxidation of 1,1,1,3,3,3-Hexamethyl-2-(phenylselanyl)-2-(trimethylsilyl)trisilane): The residue was dissolved in dichloromethane (3 mL), and H_2O_2 (30 wt. % in H_2O, 0.3 mL) was added. The mixture was then stirred vigorously for 30 min. During this time, the solution was observed to turn dark yellow before maintaining a final light yellow color. The mixture was diluted with water (2 mL), the layers were separated, and the aqueous layer was extracted with dichloromethane (2 x 2 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, and evaporated under reduced pressure.

1-((1,1-Dimethylethyl)dimethylsilyloxy)bicyclo[2.2.2]oct-2-ene (1-23c) and (±) (1*R*, 2*S*, 4*S*) 2-((1,1-Dimethylethyl)dimethylsilyloxy)bicyclo[3.2.1]oct-6-ene (1-25c): The mixture of cycloadducts **1-21c** and **1-22c** was decarbonylated following the general decarbonylation procedure. The residue was subjected to the oxidation conditions outlined in the general oxidation procedure. After oxidation, the residue was subjected to flash chromatography on silica gel (100% hexanes) to give an inseparable mixture of **1-23c** and **1-25c** in a 9:1 ratio as a colorless oil (18 mg, 15%); R_f 0.72 (100% hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ:

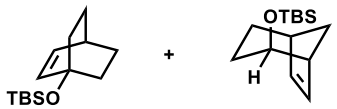
6.17 (d, *J* = 8.5 Hz, 0.9H)

6.08 (dd, *J* = 8.5, 6.5 Hz, 0.9H)

5.96 (dd, *J* = 5.5, 2.7 Hz, 0.1H)

5.86 (dd, *J* = 5.5, 2.5 Hz, 0.1H)

3.74 (m, 0.1H)



1-23c 1-25c

2.57-2.50 (m, 0.2H)

2.42 (m, 0.9H)

1.65-1.28 (m, 7.8H)

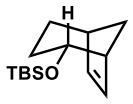
0.88 (bs, 9H)

0.09 (bs, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 139.3, 135.3, 133.7, 131.1, 74.8, 66.5, 47.2, 38.9, 37.6, 34.6, 34.4, 29.5, 28.1, 26.5, 26.1, 25.9, 25.8, 25.7, 21.9, 18.0, -2.09, -2.21, -4.75, -4.87.

(±) (1*R*, 2*R*, 4*S*) 2-((1,1-Dimethylethyl)dimethylsilyloxy)bicyclo[3.2.1]oct-6-ene (1-24c): Compound **1-24c** was obtained from the above chromatography as a colorless oil (12 mg, 10%); R_f 0.43 (100% hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ:



1-24c

5.91 (dd, *J* = 6.0, 2.5 Hz, 1H)

5.88 (dd, *J* = 6.0, 2.7 Hz, 1H)

3.62 (ddd, *J* = 9.0, 6.0, 3.0 Hz, 1H)

2.52 (dddd, *J* = 2.7, 2.7, 2.7, 2.7 Hz, 1H)

2.45 (ddddd, *J* = 2.5, 2.5, 2.5, 2.5, 2.5 Hz, 1H)

1.95 (dddd, *J* = 10.8, 5.4, 5.4, 2.0 Hz, 1H)

1.65 (m, 1H)

1.48 (m, 1H)

1.32-1.26 (m, 3H)

0.87 (s, 9H)

0.04 (s, 3H)

0.02 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 133.7, 131.2, 69.3, 47.4, 42.3, 38.5, 29.1, 25.9, 23.7, 18.1, -4.60, -4.64.

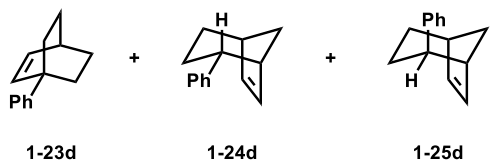
1-Phenylbicyclo[2.2.2]oct-2-ene (1-23d), (±) (1*R*, 2*R*, 4*S*) 2-Phenylbicyclo[3.2.1]oct-6-ene (1-24d), and (±) (1*R*, 2*S*, 4*S*) 2-Phenylbicyclo[3.2.1]oct-6-ene (1-25d): The mixture of cycloadducts **1-21d** and **1-22d** was decarbonylated following the general decarbonylation procedure. The residue was purified by flash column chromatography on silica gel (100% hexanes). The fractions corresponding to R_f 0.64 were combined, evaporated under reduced pressure, and subjected to the oxidation conditions outlined in the general oxidation procedure. After oxidation, the residue was purified by flash column chromatography on silica gel (100% hexanes). An inseparable mixture of **1-23d**, **1-24d**, and **1-25d** was obtained as a colorless oil in a 1:3:6 ratio (24 mg, 26%); R_f 0.64.

^{1}H NMR ($CDCl_3$, 400 MHz) δ:

7.44-7.27 (m, 2.8H)

7.23-7.15 (m, 2.2H)

6.41 (dd, *J* = 8.4, 6.4 Hz, 0.1H)



1-23d **1-24d** **1-25d**

6.35 (d, *J* = 8.4 Hz, 0.1H)

6.13 (dd, *J* = 5.6, 2.8 Hz, 0.3H)

6.00 (dd, *J* = 5.6, 2.8 Hz, 0.3H)

5.98 (dd, *J* = 6.0, 2.8 Hz, 0.6H)

5.92 (dd, *J* = 6.0, 2.8 Hz, 0.6H)

2.87 (dd, *J* = 7.2, 2.4 Hz, 0.3H)

2.74 (ddd, *J* = 12.0, 4.8, 2.0 Hz, 0.6H)

2.69-2.58 (m, 1.9H)

2.20-2.07 (m, 1H)

1.94-1.76 (m, 1.5H)

1.75-1.66 (m, 0.9H)

1.61-1.46 (m, 1.8H)

1.46-1.37 (m, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 147.1, 146.8, 137.8, 135.7, 134.6, 134.5, 134.4, 134.0, 130.6, 128.21, 128.16, 128.1, 128.0, 127.2, 126.5, 125.8, 125.7, 125.3, 46.7, 46.1, 43.1, 39.5, 39.1, 38.0, 37.4, 34.0, 33.2, 32.2, 30.5, 30.4, 30.3, 26.8, 26.1, 25.9, 24.22, 24.21.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{14}H_{17}$ 185.13248; found, 185.12803.

1-(((1,1-Dimethylethyl)dimethylsilyloxy)methyl)bicyclo[2.2.2]oct-2-ene (1-23e): The mixture of cycloadducts **1-21e** and **1-22e** was decarbonylated following the general decarbonylation procedure. The residue was purified by flash chromatography on silica gel (100% hexanes). The fractions corresponding to R_f 0.56 were combined, evaporated under reduced pressure, and subjected to the oxidation conditions outlined in the general oxidation procedure. After oxidation, the residue was subjected to flash chromatography on silica gel (100% hexanes) to give **1-23e** as a colorless oil (56 mg, 44%); R_f 0.56 (100% hexanes).

^{1}H NMR ($CDCl_3$, 500 MHz) δ:

1-23e

6.25 (dd, *J* = 8.0, 6.5 Hz, 1H)

6.11 (d, *J* = 8.5 Hz, 1H)

3.52 (s, 2H)

2.49 (m, 1H)

1.58-1.52 (m, 2H)

1.36-1.24 (m, 5H)

1.17-1.10 (m, 1H)

0.89 (s, 9H)

0.09 (s, 3H)

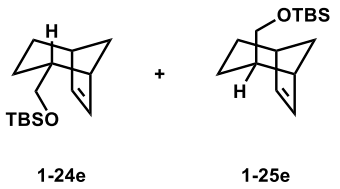
0.09 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 135.2, 133.8, 69.2, 39.3, 31.6, 30.4, 28.4, 26.5, 26.0, 22.7, 18.4, -2.20.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{15}H_{29}OSi$ 253.19822; found, 253.18043.

(±) (1*R*, 2*R*, 4*S*) 2-(((1,1-Dimethylethyl)dimethylsilyloxy)methyl)bicyclo[3.2.1]oct-6-ene (1-24e) and (±) (1*R*, 2*S*, 4*S*) 2-(((1,1-Dimethylethyl)dimethylsilyloxy)-methyl)bicyclo[3.2.1]oct-6-ene (1-25e): Following decarbonylation of cycloadducts **1-21e** and **1-22e**, initial purification by flash column chromatography on silica gel (100% hexanes) yielded an inseparable mixture of **1-24e** and **1-25e** as a colorless oil in a 3:1 ratio (12 mg, 9%); R_f 0.38 (100% hexanes).

^1H NMR ($CDCl_3$, 400 MHz) δ:



1-24e 1-25e

5.97 (dd, *J* = 5.6, 2.8 Hz, 0.25H)

5.89 (dd, *J* = 5.6, 2.4 Hz, 0.25H)

5.86 (dd, *J* = 6.0, 2.8 Hz, 0.75H)

5.81 (dd, *J* = 6.0, 2.4 Hz, 0.75H)

3.65 (d, *J* = 7.6 Hz, 0.5H)

3.23 (d, *J* = 7.2 Hz, 1.5H)

2.62-2.58 (m, 0.75H)

2.58-2.54 (m, 0.25H)

2.54-2.48 (m, 1H)

2.00 (dtd, *J* = 10.0, 5.6, 2.0 Hz, 0.75H)

1.79 (m, 0.25H)

1.72-1.57 (m, 2H)

1.48-1.34 (m, 3H)

1.19-1.04 (m, 1H)

0.89 (s, 9H)

0.06 (s, 0.75H)

0.04 (s, 4.5H)

0.02 (s, 0.75H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 134.5, 133.8, 133.3, 130.7, 67.5, 65.5, 44.8, 40.8, 40.6, 39.33, 39.30, 39.1, 37.8, 35.0, 31.4, 26.01, 26.00, 24.0, 22.9, 21.8, 20.0, 18.4, -5.32, -5.34.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{15}H_{29}OSi$ 253.19822; found, 253.17932.

1-(Phenylmethyl)bicyclo[2.2.2]oct-2-ene (1-23f), (±) (1*R*, 2*R*, 4*S*) 2-(Phenylmethyl)bicyclo[3.2.1]oct-6-ene (1-24f), (±) (1*R*, 2*S*, 4*S*) 2-(Phenylmethyl)bicyclo[3.2.1]oct-6-ene (1-25f), and 2-(Phenylmethyl)-bicyclo[2.2.2]oct-2-ene (SI-3): The mixture of cycloadducts **1-21f** and **1-22f** was decarbonylated following the general decarbonylation procedure. The residue was purified by flash column chromatography on silica gel (100% hexanes). The fractions corresponding to R_f 0.65 were combined, evaporated under reduced pressure, and subjected to the oxidation conditions outlined in the general oxidation procedure. After oxidation, the residue was purified by flash column chromatography on silica gel (100% hexanes). An inseparable mixture of **1-23f** and **1-24f** was obtained as a colorless oil in a 4:1 ratio (28 mg, 28%); R_f 0.65.

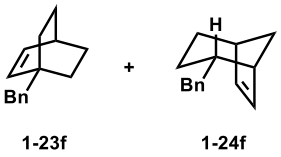
^{1}H NMR ($CDCl_3$, 500 MHz) δ:

7.30-7.25 (m, 2H)

7.22-7.13 (m, 3H)

6.23 (dd, *J* = 8.5, 6.5 Hz, 0.8H)

6.18 (d, *J* = 8.5 Hz, 0.8H)



1-23f **1-24f**

5.95-5.90 (m, 0.4H)

2.77 (s, 1.6H)

2.50 (m, 0.2H)

2.47 (m, 0.8H)

2.37 (dd, *J* = 13.5, 8.0 Hz, 0.2H)

2.31 (dd, *J* = 13.5, 7.2 Hz, 0.2H)

1.95 (dddd, *J* = 10.5, 5.2, 5.2, 1.7 Hz, 0.2H)

1.69 (m, 0.2H)

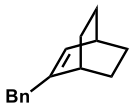
1.57-1.49 (m, 1H)

1.41-1.09 (m, 6.6H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 139.1, 136.4, 134.3, 134.1, 130.5, 130.3, 129.1, 129.0, 128.1, 127.8, 125.9, 125.6, 45.6, 45.0, 43.0, 42.7, 39.3, 38.6, 37.6, 31.5, 30.5, 26.9, 26.7, 26.1, 26.0, 24.9.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{15}H_{19}$ 199.14813; found, 199.17990.

1-25f and **SI-3** were also present in minor amounts, inseparable from the mixture. Major peaks for **SI-3** in ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 5.89 (dd, *J* = 6.8, 1.6 Hz, 1H), 3.40 (s, 2H).



SI-3

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6. Most of the 1-substituted 1,3-cyclohexadienes **1-20** were known. The new 1-silyloxymethyl diene **1-20e** was prepared by reduction of the known methyl 1,3-cyclohexadiene-1-carboxylate with DIBAL followed by silylation. Harding, K. E.; Strickland, J. B.; Pommerville, J. *J. Org. Chem.* **1988**, *53*, 4877. The new benzyl analogue **1-20f** was prepared by cross-coupling of benzyl Grignard reagent with the known 1-(triflyloxy)-1,3-cyclohexadiene in the presence of $NiCl_2$(dppp) catalyst. Corey, E. J.; Kigoshi, H. *Tetrahedron Lett.* **1991**, *32*, 5025. For full details on the preparation of these dienes, see experimental section.

7. In general, the mixture of isomers could not be fully separated, but the assignment of the stereochemistry of the two diastereomeric cycloadducts was made by NMR measurements. All exo isomers **1-22** display an additional small coupling (J = 1.6-2.0 Hz) for the proton α to the carbonyl group as a result of W coupling, which does not exist in the endo isomers **1-21**.

8. Although the mixture of diastereomers could not be separated, their stereochemistry could be assigned by analysis of the crude NMR spectra. The proton α to the R substituent in **1-24** consistently exhibited a very large coupling constant (J = 9.0-12.0 Hz), attributable to the axial-axial coupling, which was absent from the isomeric compounds **1-25**.

9. Occasionally, small amounts of aldehydes are isolated due to reduction of acyl radical **1-26** before decarbonylation.

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CHAPTER 2

Approaches to the Synthesis of Optically Active Bicyclo[2.2.2]octane-2,5-diones

Introduction

The synthesis of enantiomerically pure compounds is of central importance to organic chemistry. Enantioselective reactions influence the synthesis of optically active natural products, medicinal compounds, and other important organic molecules. Asymmetric catalysis provides an efficient route towards the preparation of enantiomerically pure compounds and generally features chiral ligands as the source of chirality. In particular, C_2-symmetric bicyclo[2.2.2]octadienes have emerged as useful chiral ligands for a number of rhodium-catalyzed asymmetric transformations.[1] Hayashi and coworkers established the chiral diene ligands (1*R*,4*R*)-2,5-diphenylbicyclo[2.2.2]octa-2,5-diene [(*R*,*R*)-Ph-bod*, **2-1**] and (1*R*,4*R*)-2,5-dibenzylbicyclo[2.2.2]octa-2,5-diene [(*R*,*R*)-Bn-bod*, **2-2**], as well as the opposite enantiomers (*S*,*S*)-Ph-bod* **2-3** and (*S*,*S*)-Bn-bod* **2-4** (Figure 2-1).

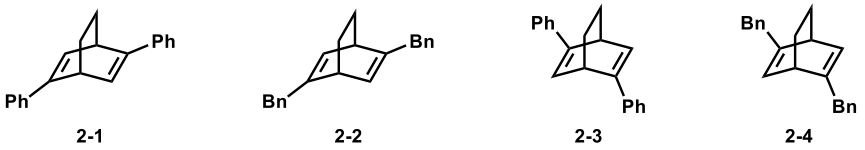


Figure 2-1. Chiral diene ligands (*R*,*R*)-Ph-bod* **2-1**, (*R*,*R*)-Bn-bod* **2-2**, (*S*,*S*)-Ph-bod* **2-3**, and (*S*,*S*)-Bn-bod* **2-4**.

Rhodium is a popular choice in transition metal catalysis for carbon-carbon bond formation due to both its utility in asymmetric catalysis and its potential for the development of more environmentally friendly conditions for transition metal catalysis.[2] Shown in Figure 2-2 are three types of rhodium-catalyzed asymmetric reactions that employ the previously described chiral diene ligands: 1,4-addition of an arylboronic acid to an α,β-unsaturated ketone,[1] arylative cyclization of alkynals,[3] and the addition of sodium tetraarylborates to alkyne-tethered 2-cycloalken-1-ones for the synthesis of spriocarbocycles.[4] The aforementioned carbon-carbon bond forming reactions are particularly significant, as they display exceptionally high catalytic

activity and enantioselectivity. Clearly, the synthetic utility of these rhodium-catalyzed reactions creates a marked need for an easy access to the chiral diene ligands **2-1**, **2-2**, **2-3**, and **2-4**.

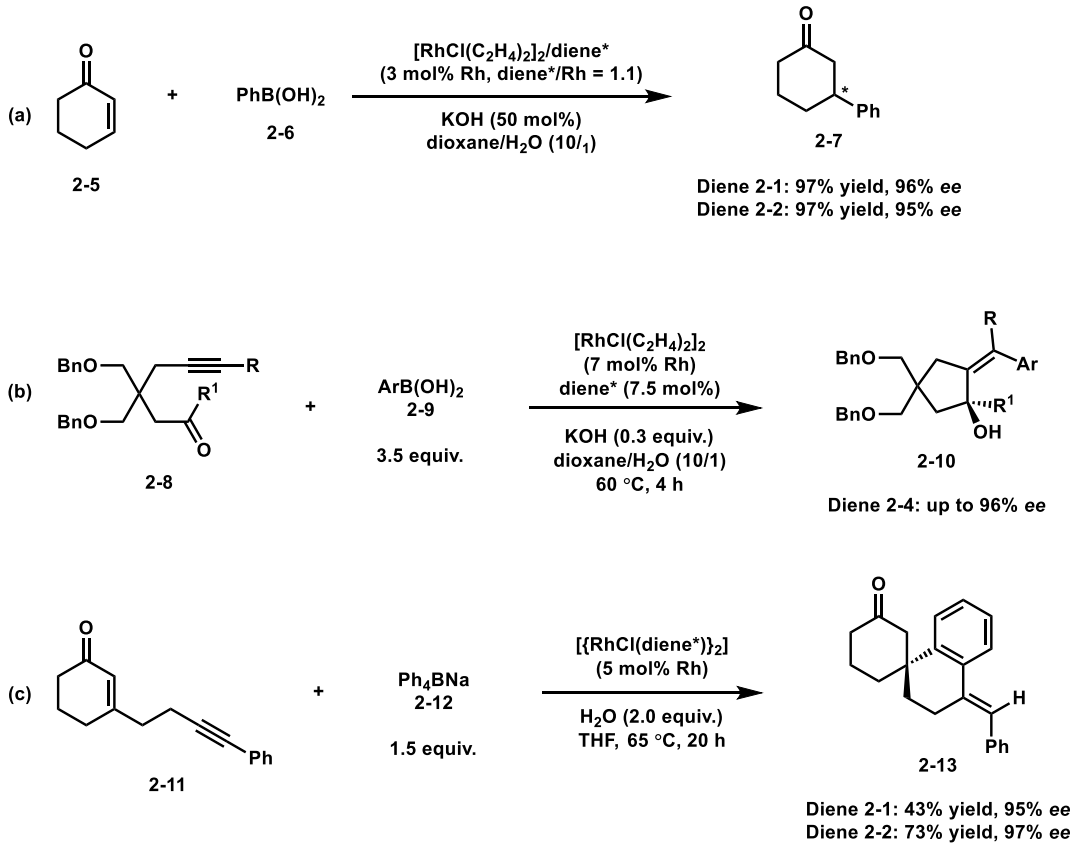
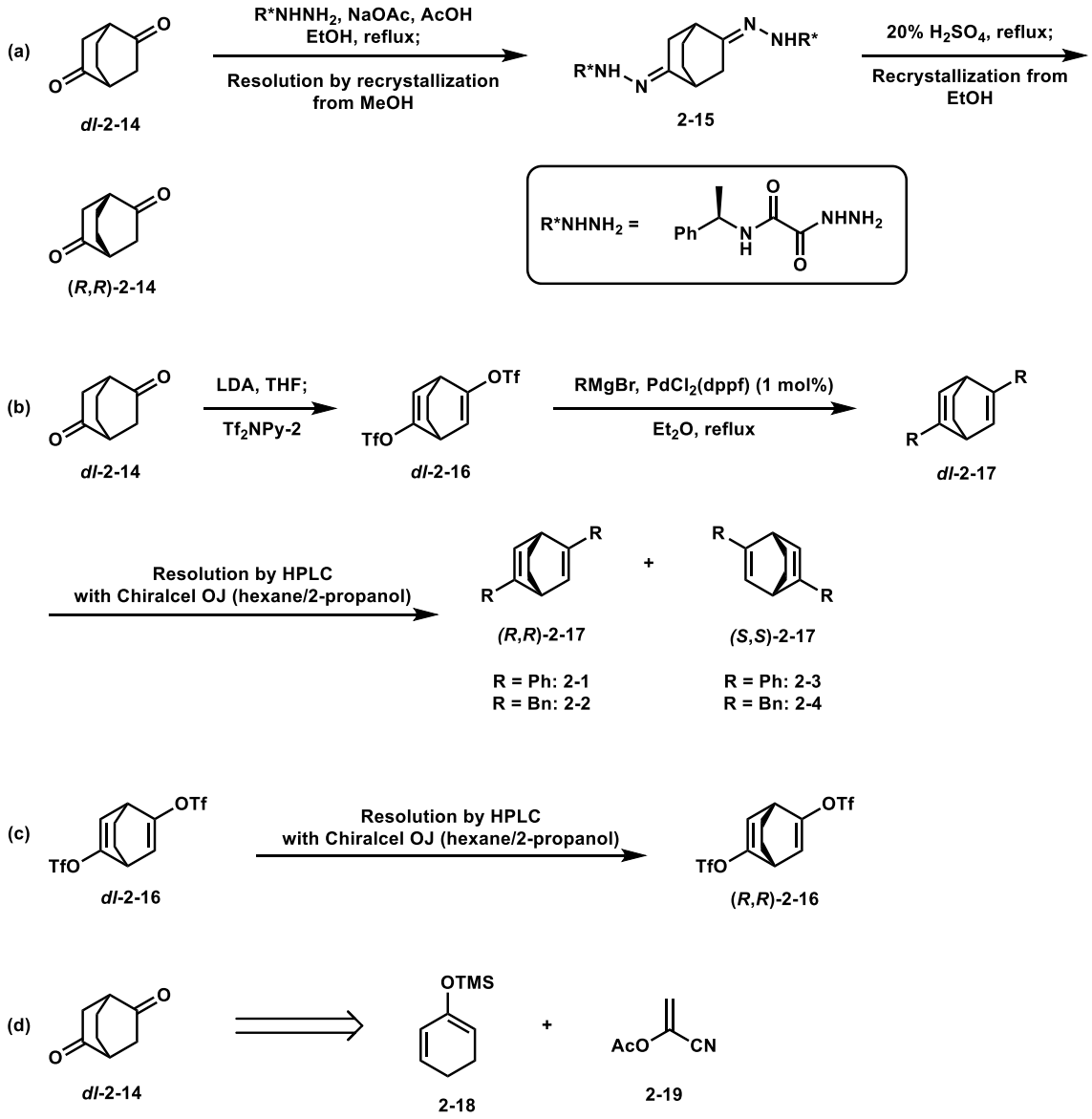


Figure 2-2. Examples of rhodium-catalyzed asymmetric reactions that use the chiral diene ligands estabalished by Hayashi and coworkers.

Hayashi and coworkers originally presented three routes for the synthesis of the (*R*,*R*) chiral dienes. Shown in Scheme 2-1 are the steps involved in the separation of enantiomers for each synthetic route. The first route (entry a) requires fractional recrystallization of a diastereomeric mixture of chiral dihydrazones, while the second (entry b) and third (entry c) routes rely on high-performance liquid chromatography to separate the respective pairs of enantiomers.[1] In each synthesis, a key compound is the racemic bicyclo[2.2.2]octane-2,5-dione **2-14**, which is readily obtained by Diels-Alder cycloaddition of the silyl enol ether **2-18** with 2-

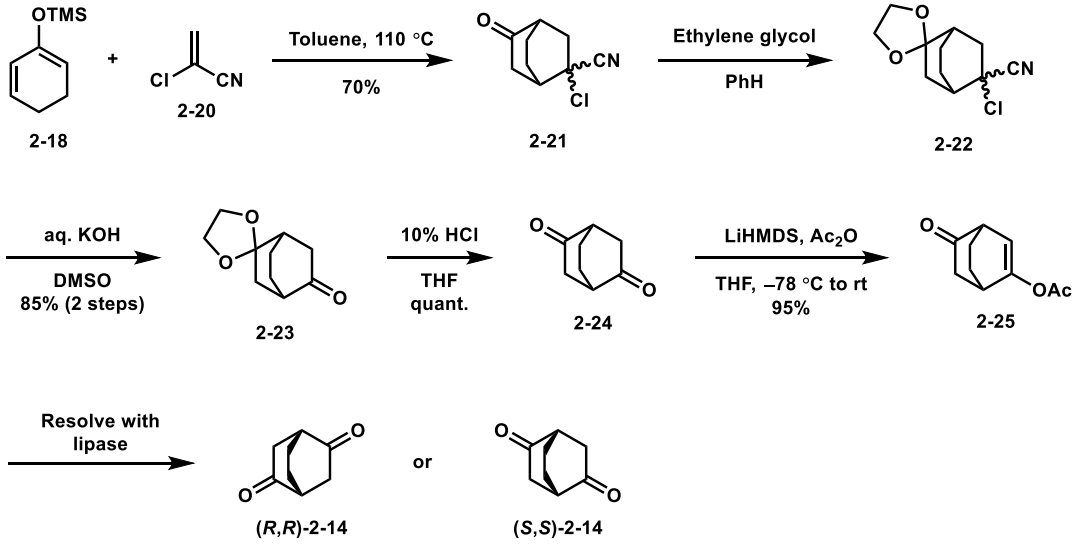
acetoxypropenenitrile **2-19** (entry d). These complicated synthetic strategies contribute to the limited commercial availability and high costs of these chiral diene ligands.



Scheme 2-1. Original routes for the synthesis of the (*R,R*) chiral dienes.

In 2010, Carnell and coworkers presented a chemoenzymatic route for the preparation of the optically active bicyclo[2.2.2]octane-2,5-dione (Scheme 2-2). An initial Diels-Alder cycloaddition between the silyl enol ether **2-18** and 2-chloroacrylonitrile **2-20** afforded the

bicyclo[2.2.2]octane **2-21**. Protection of the ketone **2-21** gave the ketal **2-22**, basic hydrolysis of which afforded the ketone **2-23**. Acidic hydrolysis of the ketal produced the racemic diketone **2-24**. The key compound for the lipase-catalyzed resolution, the racemic enol acetate **2-25**, was formed from the racemic diketone. Immobilized *Humicola* sp. lipase catalyzed the resolution to give the (*S*,*S*)-diketone **2-14**, while Cal-B lipase gave the (*R*,*R*)-diketone **2-14**.[5]



Scheme 2-2. Chemoenzymatic route for the preparation of the optically active bicyclo[2.2.2]-octane-2,5-dione.

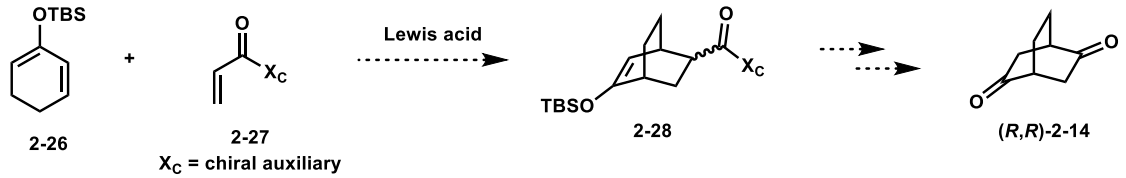
The Diels-Alder cycloaddition features prominently in the construction of racemic bicyclo[2.2.2]octane-2,5-diones. We envisioned that an enantio- or diastereoselective Diels-Alder cycloaddition could lead to optically active bicyclo[2.2.2]octane-2,5-dione without the need for intricate separation techniques or enzymatic resolution. Methods of inducing stereoselectivity in cycloadditions include chiral catalysts and chiral auxiliaries. Many chiral catalysts have been established for use in [4+2] cycloadditions, notably from the groups of Corey, Evans, and Yamamoto.[6] These catalysts display remarkable enantioselectivity and many are readily available from commercial sources. Chiral auxiliaries, temporary chiral components of either the dienophile or diene, have also proven effective in stereoselective cycloadditions. Common chiral auxiliaries

include oxazolidinones, phenylmenthol derivatives, and camphor derivatives.[7] Advantages of the use of chiral auxiliaries include excellent diastereomeric ratios, ease of auxiliary cleavage, and readily accessible starting materials.

Our goal for this study was to efficiently construct the bicyclo[2.2.2]octane skeleton with a stereoselective Diels-Alder cycloaddition. Subsequent functional group manipulations would then allow rapid access to the optically active bicyclo[2.2.2]octane-2,5-diones. A highly selective cycloaddition would presumably avoid the need for resolution or separation of enantiomers, presenting a highly improved route to the chiral diene ligands of interest.

Results and Discussion

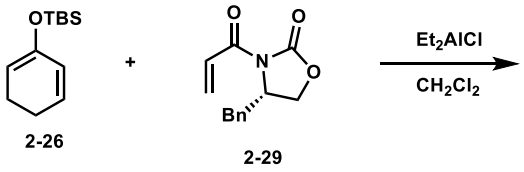
Our initial synthetic plan is summarized in Scheme 2-3. A diastereoselective Diels-Alder cycloaddition between the silyloxy diene **2-26** and the acrylate **2-27**, bearing a chiral auxiliary, could afford the cycloadduct **2-28**. The silyl enol ether **2-26** is an ideal choice for the diene, as simple hydrolysis of the silyl enol ether could efficiently provide one of the ketone moieties of the target diketone **2-14**. This type of diene is known to be quite reactive in Diels-Alder cycloadditions.[8] Simple functional group transformations could transform the group at the C2 position to the ketone and generate the optically active **(*R*,*R*)-2-14**. A similar sequence could be used to access **(*S*,*S*)-2-14**, here using a chiral auxiliary that induces the opposite facial selectivity.



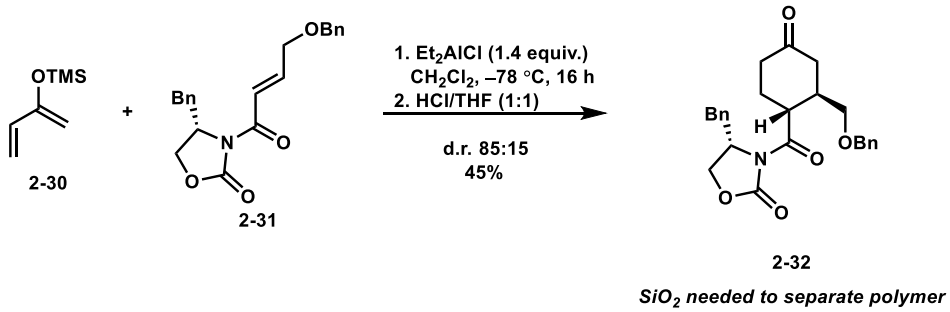
Scheme 2-3. Our initial synthetic plan for the synthesis of the optically active bicyclo[2.2.2]-octane-2,5-dione.

We first employed the L-phenylalanine-derived chiral α,β-unsaturated *N*-acyloxazolidinone **2-29** for Diels-Alder cycloadditions with the diene **2-26** (Table 2-1).[7a] In most cases we obtained products of polymerization, as evidenced by broad peaks in the ^{1}H NMR spectra (characteristic of polymeric compounds) and a plastic-like product. An example from the literature of a cycloaddition between a similar system, the silyloxy diene **2-30** and the α,β-unsaturated *N*-acyloxazolidinone **2-31**, also noted polymer formation, supporting our results (Scheme 2-4).[9] While this reaction yielded 45% of the desired cycloadduct **2-32**, filtration through a pad of silica gel was necessary to remove the polymeric material. We concluded that the silyl enol ether/acrylate system tends to promote polymerization under Lewis acidic conditions. We then proposed that these types of dienes would be better suited to thermal Diels-Alder reactions.

Table 2-1. Attempted Diels-Alder cycloadditions between the diene **2-26** and the acrylate **2-29**.

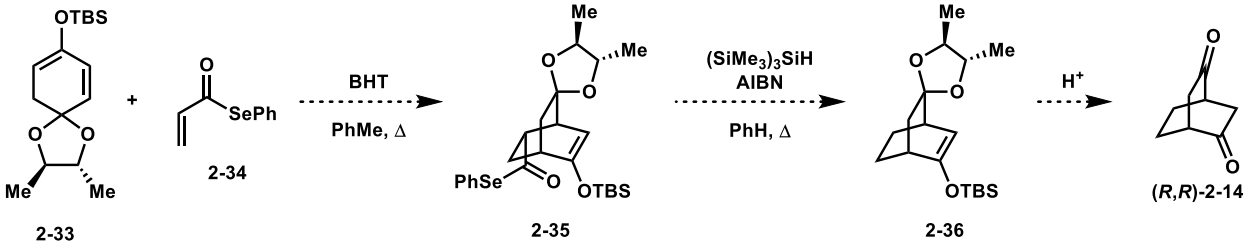


Entry	Time (h)	Temp (°C)	Workup	Result
1	7	−78	HCl	N.R.
2	2	−78 to 23	$NaHCO_3$	Polymer
3	2.5	−78 to 0	$NaHCO_3$	Polymer
4	2.5	0	$NaHCO_3$	Polymer
5	2.5	0	HCl	Polymer



Scheme 2-4. Diels-Alder cycloaddition between the silylated diene **2-30** and the oxazolidinone **2-31** resulting partially in polymer formation.

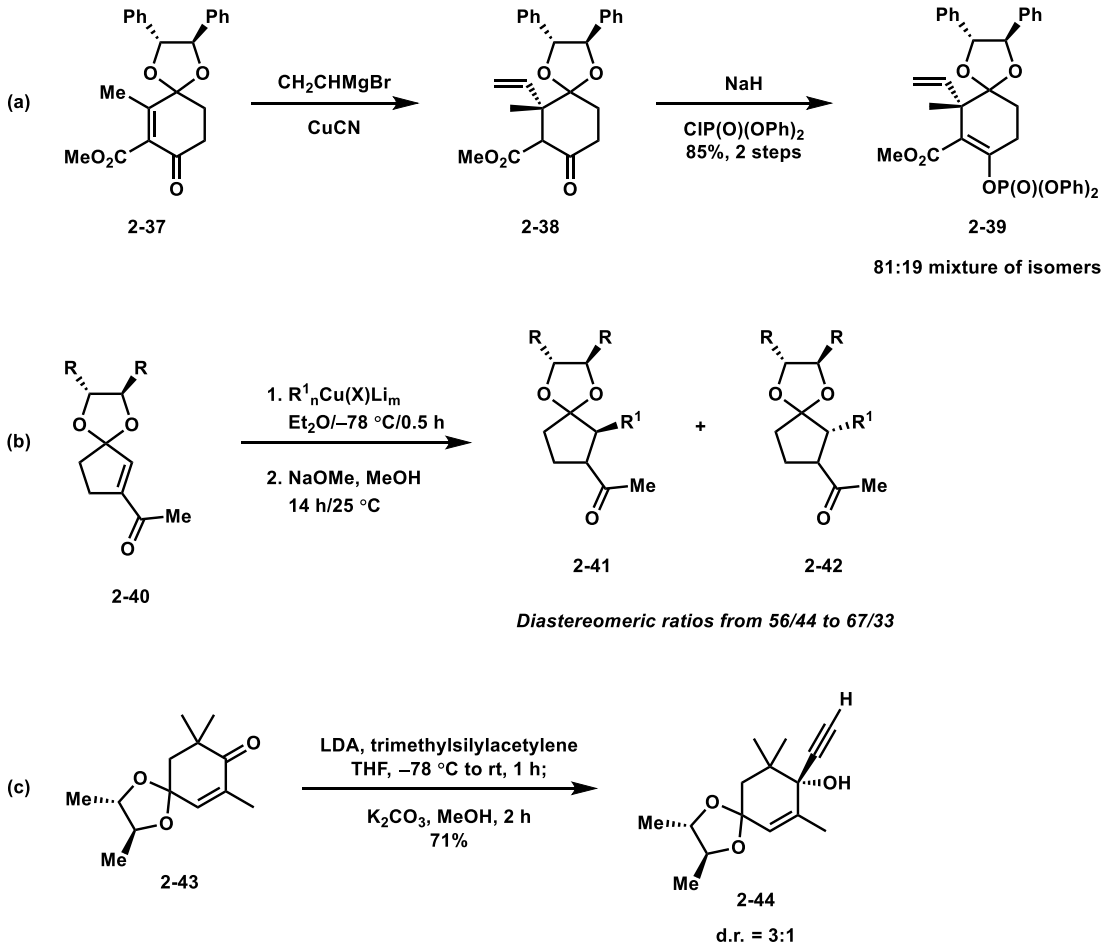
We then considered a different approach (Scheme 2-5). We envisioned a diene such as **2-33**, bearing a chiral ketal, could be the source of the two requisite ketone units for the desired bicyclic diketone products and could potentially induce stereoselectivity in the cycloaddition. Reaction of this diene with an ethylene equivalent, such as *Se*-phenyl prop-2-eneselenoate **2-34**, could afford the cycloadduct **2-35** that would then be subjected to reductive decarbonylation followed by hydrolysis to generate the desired optically active dione **(*R*,*R*)-2-14**. Our group has shown the acrylate **2-34** to be a useful ethylene equivalent for Diels-Alder reactions.[10]



Scheme 2-5. Proposed Diels-Alder cycloaddition between the diene **2-33** and the acrylate **2-34** and subsequent steps leading to the optically active bicyclo[2.2.2]octane-2,5-dione.

Several groups have shown that enantiomerically pure ketals can serve as excellent directing groups for reactions at adjacent and even distal centers (Scheme 2-6). In an effort toward the synthesis of *N*-methylwelwitindolinone C isothiocyanate, Konopelski and coworkers performed a diastereoselective conjugate addition of a vinyl nucleophile to the cyclohexenone **2-**

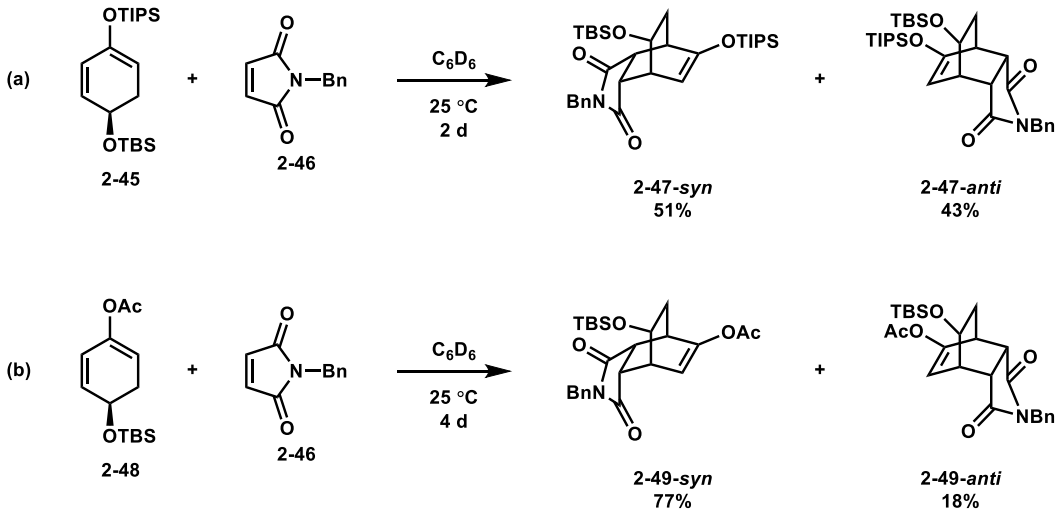
37 that gave an 81:19 mixture of facial isomers (entry a).[11] Research in our own group has shown diastereoselectivity ranging from 12-34% in additions of organocuprates to homochiral ketals of 3-acetylcyclopentenone **2-40** (entry b).[12] Smith, *et al.*, achieved a diastereoselective 1,2-alkynylation of the ketone **2-43** to give the alcohol **2-44** in a diastereomeric ratio of 3:1 (entry c).[13]



Scheme 2-6. Examples from the groups of Konopelski, Jung, and Smith of facially selective nucleophilic additions directed by chiral ketals.

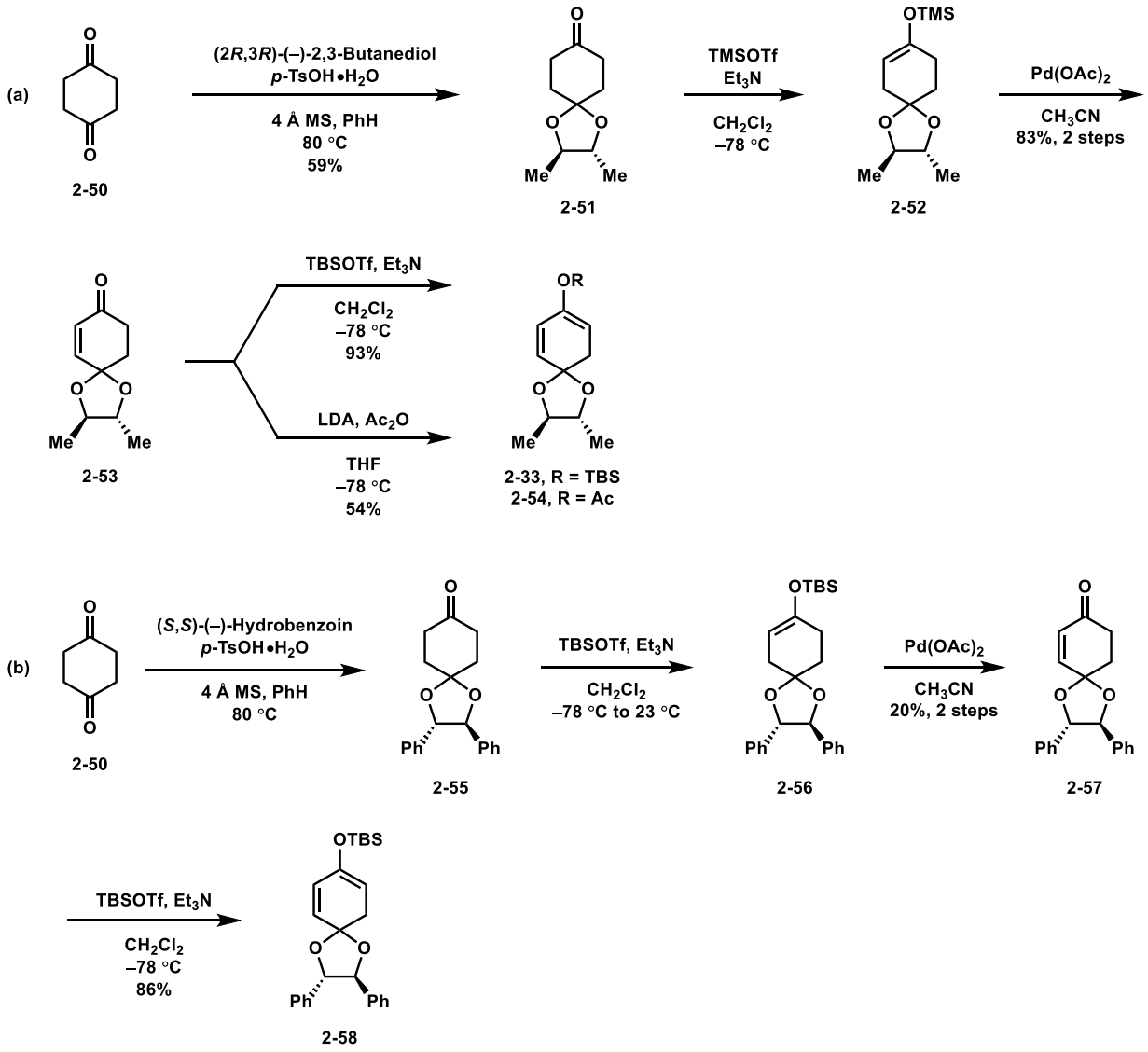
Hua and coworkers demonstrated the viability of a stereoselective [4+2] cycloaddition directed by a chiral moiety at the allylic center (Scheme 2-7). The [4+2] cycloaddition between the 1,3-diene **2-45** and *N*-benzyl maleimide **2-46** afforded the compounds **2-47-*syn*** (51%) and

2-47-*anti* (43%). This cycloaddition proceeded with exclusive *endo* selectivity but poor facial selectivity. Cycloaddition between the diene **2-48**, bearing an acetoxy rather than a triisopropylsilyloxy group, and **2-46** provided improved facial selectivity, giving **2-49-*syn*** and **2-49-*anti*** in a 4.3:1 ratio. This reaction was also exclusively *endo*-selective.[14]



Scheme 2-7. Facially selective [4+2] cycloadditions directed by a chiral moiety at the allylic center.

The syntheses of our proposed dienes are shown in Scheme 2-8. The synthesis of the dienes **2-33** and **2-54** commenced with mono-ketalization of commercially available 1,4-cyclohexanedione **2-50** with (2*R*,3*R*)-(−)-butanediol to afford the ketone **2-51** in 59% yield (entry a). Conversion of the ketone **2-51** to the silyl enol ether **2-52**, followed by Saegusa-Ito oxidation with palladium (II) acetate [$Pd(OAc)_2$], afforded the α,β-unsaturated ketone **2-53** in 83% yield over 2 steps. Treatment of the ketone **2-53** with *tert*-butyldimethylsilyl trifluoromethanesulfonate and triethylamine provided the diene **2-33** in 93% yield. The acetyloxy diene **2-54** could be synthesized in 54% yield from the ketone **2-53** by treatment with lithium diisopropylamide (LDA) and acetic anhydride. The diphenyl diene **2-58** could be accessed in 4 steps in a similar manner to **2-33** and **2-54** (entry b).



Scheme 2-8. Syntheses of the dienes **2-33**, **2-54**, and **2-58**.

The projected approaches of a dienophile to each of our proposed dienes are shown in Figure 2-3. The dienes **2-33** and **2-54** should direct the dienophile to the bottom face as drawn, as the dienophile would encounter steric hindrance from the top face (entry a). The diene **2-58** should provide the opposite facial selectivity, with the dienophile projected to approach from the top face as drawn (entry b), since the diketal has the two large groups on the enantiomeric faces.

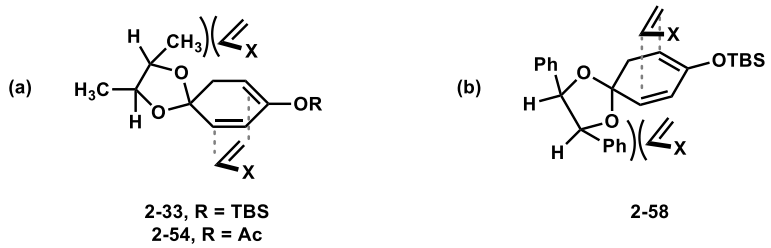
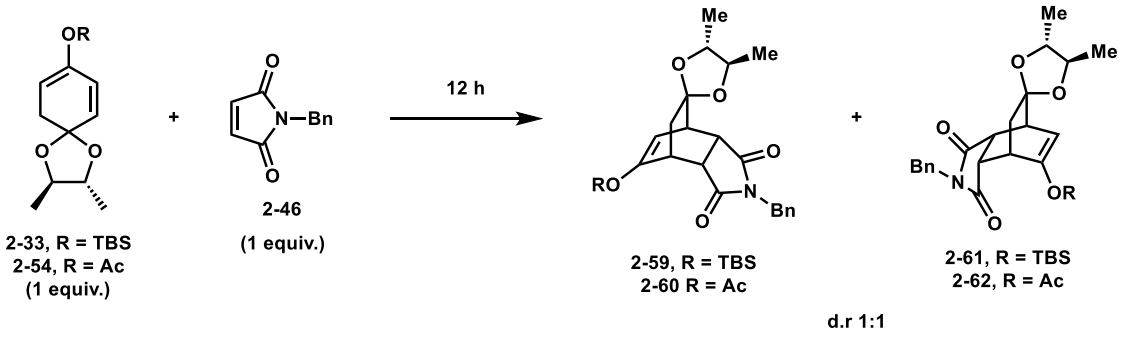


Figure 2-3. Projected approaches of a dienophile to the dienes **2-33**, **2-54**, and **2-58**.

We first reacted the dienes **2-33** and **2-54** with *N*-benzyl maleimide **2-46**, a reactive dienophile, to test the viability of our substrates and determine if they would provide enough steric bias for the cycloaddition (Table 2-2). Unfortunately, we did not observe facial selectivity in any case; only a 1:1 inseparable mixture of diastereomers was produced. We believe that the reactions proceeded with exclusive *endo* selectivity, as seen in the work of Hua and coworkers.[14] Lower temperatures may have improved stereoselectivity, but the cycloadditions did not proceed in those cases. The addition of a Lewis acid, $ZnCl_2$, resulted in aromatization of the diene and only trace cycloaddition products. The acetoxy-substituted diene **2-54** did not improve facial selectivity, as the acetoxy-substituted diene **2-48** had in the cycloadditions studied by Hua and coworkers.[14]

Table 2-2. Cycloadditions between *N*-benzyl maleimide **2-46** and the dienes **2-33** and **2-54**.

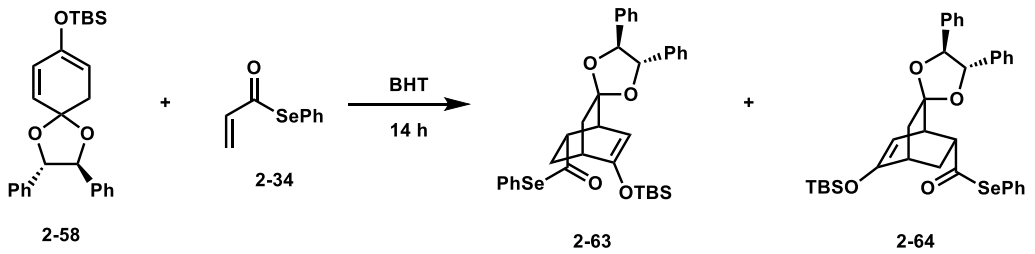


Entry	Diene	Solvent	Temp (°C)	Lewis Acid	Yield (%)
1	**2-33**	PhH	23	---	81
2	**2-33**	PhMe	−18	---	(low conversion)
3	**2-33**	PhMe	−78 to −18	$ZnCl_2$	(low conversion)[a]
4	**2-54**	PhH	23	---	49
5	**2-54**	PhMe	−78 to −18	$ZnCl_2$	Trace

[a]Most of the diene reacted with the Lewis acid to give an aromatic side product.

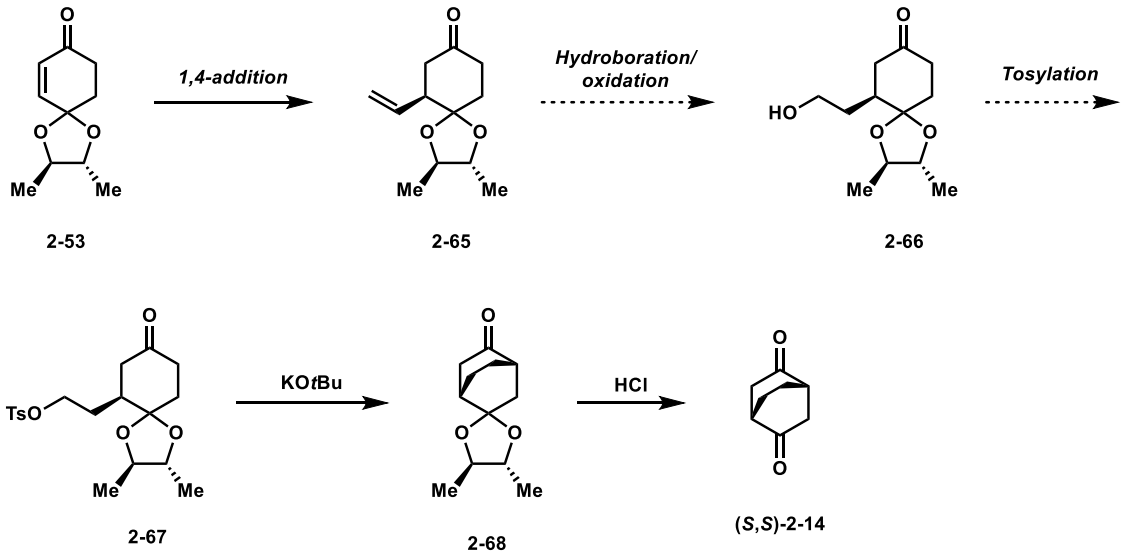
We then reacted the diene **2-58** with the phenyl selenoacrylate **2-34** with the hopes that the diastereomers could at least be separated by silica gel chromatography. Surprisingly, even after heating at 110 °C, we did observe some facial selectivity (Table 2-3). The facial selectivity improved slightly by lowering the temperature, but only poor diastereomeric ratios were obtained. Unfortunately, at lower temperatures the cycloadditions did not proceed to full conversion, and the isomers were inseparable on silica gel.

Table 2-3. Cycloadditions between the acrylate **2-34** and the diene **2-58**.



Entry	Solvent	Temp (°C)	Ratio **2-63**:**2-64**
1	PhMe	110	1.8:1
2	PhH	80	2:1
3	PhH	23	2.3:1

Since the chiral ketal moieties on the dienes had not provided the amount of facial selectivity we had hoped for, we turned our attention to a diastereoselective 1,4-addition. We thought that a diastereoselective conjugate addition of a vinyl nucleophile to **2-53** could generate the ketone **2-65** (Scheme 2-9). Regioselective hydroboration/oxidation to give alcohol **2-66** followed by tosylation could afford the ketone **2-67**. The ketone **2-67** could cyclize in the presence of potassium *tert*-butoxide to give the bicyclic ketone **2-68**. Cyclization of this type of compound has been reported in the literature.[15] Hydrolysis of the ketal **2-68** would then afford the dione **(*S*,*S*)-2-14**.

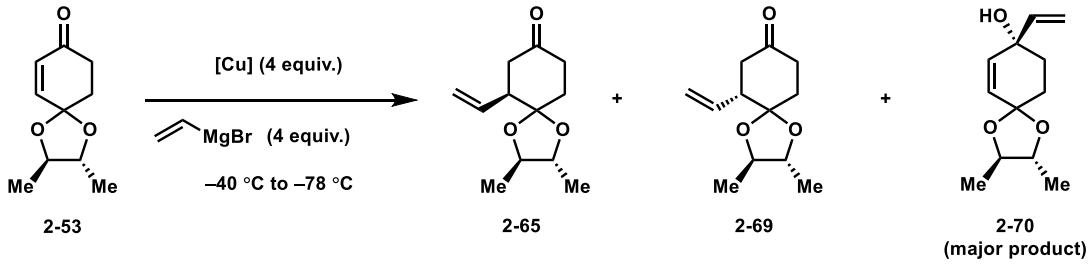


Scheme 2-9. Proposed route to the optically active bicyclo[2.2.2]octane-2,5-dione starting with a diastereoselective conjugate addition.

The results of our attempts at conjugate addition of vinylmagnesium bromide to the enone **2-53** are shown in Table 2-4. Various copper salts were tested. No reaction occurred with copper (I) bromide dimethyl sulfide ($CuBr•SMe_2$) complex, except in the presence of trimethylsilyl chloride (TMSCl), where we obtained the 1,4-addition product diastereomers **2-65** and **2-69** in 11% yield. Reactions with copper (I) iodide (CuI) and copper (I) chloride (CuCl) gave complex mixtures of starting material, the 1,4-addition products **2-65** and **2-69**, and the 1,2-addition product **2-70**. The best results were obtained with copper (I) cyanide (CuCN), except in the presence of a large excess of the copper salt, where no reaction occurred. The conjugate addition products **2-65** and **2-69** were obtained in a 4:1 diastereomeric ratio. Unfortunately, the highest yield obtained was only 17%. We noted greater formation of the 1,2-addition product **2-70** than 1,4-addition products **2-65** and **2-69** in all cases. It is possible that the β-position is too sterically hindered, leaving the carbonyl more accessible to attack by the nucleophile. Examples in the literature of stereoselective conjugate additions directed by a proximal chiral ketal are all doubly activated alkenes, namely ones bearing two electron-withdrawing groups at the α-position. The

steric strain in these cases may be overcome because of the highly electrophilic nature of the β-carbon. Our system is only singly activated and thus may not be able to overcome the steric congestion at the β-carbon.

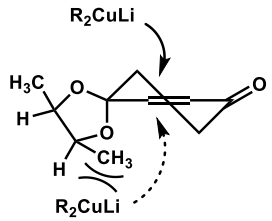
Table 2-4. Conjugate additions of vinylmagnesium bromide to the enone **2-53**.



Entry	[Cu]	Solvent	Yield of **2-65** + **2-69**	Ratio **2-65**:**2-69**	Lewis acid
1[a]	CuCN	Et_2O	Trace	---	---
2[b]	CuCN	Et_2O	N.R.	---	---
3[a]	CuCN	Et_2O	17%	4:1	TMSCl
4	CuCN	Et_2O	12%	4:1	TMSCl
5	CuI	THF	Complex mixture	---	---
6	CuCl	Et_2O	Complex mixture	---	---
7	CuBr•SMe_2	Et_2O	N.R.	---	---
8[a]	CuBr•SMe_2	Et_2O	N.R.	---	---
9	CuBr•SMe_2	Et_2O/HMPA	N.R.	---	---
10	CuBr•SMe_2	Et_2O	11%	4:1	TMSCl

[a]Reaction was warmed to 23 °C after stirring at −78 °C.
[b]20 equivalents of CuCN was used.

We propose the nucleophile approaches from the top face of enone **2-53** as shown in Figure 2-4. Steric congestion on the bottom face from the proximal chiral ketal functionality should direct the nucleophile to the top face.



2-53

Figure 2-4. Approach of a nucleophile to the enone **2-53**.

Conclusion and Future Work

The diastereoselective conjugate addition is the most promising methodology we have investigated thus far. We observed a diastereomeric ratio of 4:1 for the conjugate addition, but these reactions suffered from poor yields. Addition of a second electron-withdrawing group may lead to increased conjugate addition; however this group would later need to be removed to give the alkane. We did see an increase in 1,4-addition product when trimethylsilyl chloride was added, so experimenting with different Lewis acids may help activate the system.

Experimental Section

General: All reactions were carried out in flame-dried glassware under an argon atmosphere using freshly distilled solvents unless otherwise noted. Reagents were purchased from Sigma-Aldrich, Acros, Alfa Aesar or Oakwood and used without further purification. Unless otherwise stated, reactions were conducted at room temperature (approximately 23 °C). Reactions were monitored by thin-layer chromatography (TLC) using SORBTECH Silica G TLC plates w/UV254 followed by UV visualization and iodine staining. Flash column chromatography was performed using SilicaFlash P60 (60 Å, 40-63 μM) from SiliCycle Inc unless otherwise noted. ^{1}H NMR spectra were recorded on Bruker spectrometers (400 and 500 MHz) and are reported in parts per million (ppm, δ). Splitting patterns are designated by: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad. ^{1}H NMR chemical shifts are referenced to the residual solvent peak at 7.26 ppm for $CDCl_3$. ^{13}C NMR spectra were acquired on Bruker spectrometers (100 and 125 MHz) and are reported in parts per million (ppm, δ). ^{13}C data are referenced to the residual solvent peak at 77.91 ppm for $CDCl_3$. The reported ratios of the isomeric products were determined by careful integration of the appropriate absorptions in the ^{1}H NMR spectra of the mixture. High-resolution mass spectrometry data was obtained using a Thermo Fisher Scientific Exactive Plus with IonSense ID-CUBE DART source.

(2*R*,3*R*)-2,3-Dimethyl-1,4-dioxaspiro[4.5]decan-8-one (2-51): To a round-bottom flask fitted with a reflux condenser was added 4 Å molecular sieves (150 mg), 1,4-cyclohexanedione **2-50** (500 mg, 4.46 mmol, 2.0 equiv.), *p*-toluenesulfonic acid monohydrate (*p*-TsOH•H_2O, 42 mg, 0.223 mmol, 0.1 equiv.), (2*R*,3*R*)-(−)-2,3-butanediol (0.20 mL, 2.23 mmol, 1.0 equiv.) and benzene (11 mL). The solution was heated to 80 °C and allowed to reflux for 2 h. The reaction

was then cooled to room temperature and the solvent was evaporated under reduced pressure. The resulting residue was purified via flash column chromatography over silica gel (7-17% ethyl acetate/hexanes) to afford the ketone ketal **2-51** as a colorless oil (244 mg, 59%); R_f 0.64 (50% ethyl acetate/hexanes).

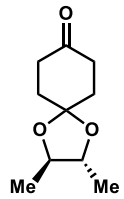
^{1}H NMR (400 MHz, $CDCl_3$, δ):

3.71 (m, 2H)

2.51 (dd, *J* = 6.8, 6.8 Hz, 4H)

2.01 (dd, *J* = 6.8, 6.8 Hz, 4H)

1.28 (m, 6H).



2-51

^{13}C NMR (100 MHz, $CDCl_3$, δ): 210.8, 106.1, 78.5, 38.2, 35.4, 16.8.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{10}H_{17}O_3$ 185.11722; found, 185.11711.

(((2*R*,3*R*)-2,3-Dimethyl-1,4-dioxaspiro[4.5]dec-7-en-8-yl)oxy)trimethylsilane (2-52): To a solution of the ketone **2-51** (218 mg, 1.18 mmol, 1.0 equiv.) in dichloromethane (12 mL) at −78 °C was added triethylamine (0.66 mL, 4.73 mmol, 4.0 equiv.) and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 0.49 mL, 2.72 mmol, 2.3 equiv.). The reaction was allowed to stir at −78 °C for 1 h and quenched with saturated aqueous sodium bicarbonate ($NaHCO_3$, 10 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL), dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to afford the crude silyl enol ether **2-52** as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$, δ):

4.70 (ddd, *J* = 3.0, 3.0, 1.0 Hz, 1H)

3.64 (m, 2H)

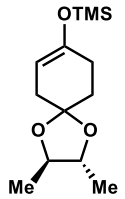
2.33-2.12 (m, 4H)

1.80 (dd, *J* = 6.0, 6.0 Hz, 2H)

1.25 (d, *J* = 6.0 Hz, 3H)

1.23 (d, *J* = 6.0 Hz, 3H)

0.18 (s, 9H).



2-52

^{13}C NMR (125 MHz, $CDCl_3$, δ): 149.8, 106.7, 100.8, 78.2, 78.1, 35.4, 32.8, 28.5, 17.1, 16.9, 0.36.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{25}O_3Si$ 257.15675; found, 257.15605.

(2*R*,3*R*)-2,3-Dimethyl-1,4-dioxaspiro[4.5]dec-6-en-8-one (2-53): To a solution of crude silyl ether **2-52** in acetonitrile (12 mL) was added palladium (II) acetate [$Pd(OAc)_2$, 837 mg, 1.24 mmol, 1.05 equiv.]. The solution was allowed to stir for 12 h and the solvent was removed under reduced pressure. Purification of the crude residue via flash column chromatography over silica gel (9-17% ethyl acetate/hexanes) afforded the enone **2-53** as a colorless oil (178 mg, 83% over 2 steps); R_f 0.67 (50% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

6.62 (d, *J* = 10.0 Hz, 1H)

5.97 (d, *J* = 10.0 Hz, 1H)

3.73 (m, 1H)

3.67 (m, 1H)

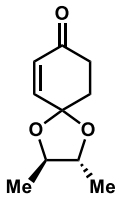
2.68 (ddd, *J* = 17.0, 10.5, 5.5 Hz, 1H)

2.57 (ddd, *J* = 17.0, 5.5, 5.5 Hz, 1H)

2.26-2.14 (m, 2H)

1.30 (d, *J* = 6.0 Hz, 3H)

1.29 (d, *J* = 6.0 Hz, 3H).



2-53

^{13}C NMR (125 MHz, $CDCl_3$, δ): 199.0, 147.6, 130.1, 102.9, 79.1, 78.6, 35.3, 34.1, 16.6, 16.5.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{10}H_{15}O_3$ 183.10157; found, 183.10152.

***tert*-Butyl(((2*R*,3*R*)-2,3-dimethyl-1,4-dioxaspiro[4.5]deca-6,8-dien-8-yl)oxy)dimethylsilane (2-33):** To a solution of the enone **2-53** (82 mg, 0.450 mmol, 1.0 equiv.) in dichloromethane (4.4 mL) at −78 °C was added triethylamine (0.18 mL, 1.32 mmol, 2.9 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 0.18 mL, 0.784 mmol, 1.7 equiv.). After the reaction was allowed to stir for 1 h, saturated aqueous $NaHCO_3$ (5 mL) was added. The aqueous layer was extracted with dichloromethane (3 x 3 mL) and the combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, and the solvent was removed

under reduced pressure. The crude residue was purified via flash column chromatography over silica gel (2-4% ethyl acetate/hexanes) to afford the silyloxy diene **2-33** as a colorless oil (124 mg, 93%); R_f 0.34 (6% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

5.87 (dd, *J* = 10.0, 2.5 Hz, 1H)

5.70 (d, *J* = 10.5 Hz, 1H)

4.93 (m, 1H)

3.67 (m, 1H)

3.63 (m, 1H)

2.66 (dd, *J* = 19.0, 4.0 Hz, 1H)

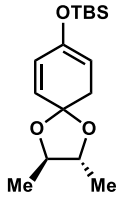
2.58 (dd, *J* = 19.0, 4.5 Hz, 1H)

1.26 (d, *J* = 5.5 Hz, 3H)

1.24 (d, *J* = 5.5 Hz, 3H)

0.91 (s, 9H)

0.13 (s, 6H).



2-33

^{13}C NMR (125 MHz, $CDCl_3$, δ): 146.4, 129.3, 129.2, 104.8, 101.4, 78.4, 77.9, 35.6, 25.6, 18.0, 17.0, 16.7, -4.53, -4.55.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{16}H_{29}O_3Si$ 297.18805; found, 297.18730.

(2*R*,3*R*)-2,3-Dimethyl-1,4-dioxaspiro[4.5]deca-6,8-dien-8-yl acetate (2-54): To a cooled (−78 °C) solution of diisopropylamine (95 µL, 0.675 mmol, 1.5 equiv.) in tetrahydrofuran (2.3 mL) was added *n*-butyllithium (2.47 M in hexanes, 0.24 mL, 0.585 mmol, 1.3 equiv.) dropwise. The mixture was allowed to stir at −78 °C for 45 min to allow lithium diisopropylamide to form. A solution of the enone **2-53** (82 mg, 0.450 mmol, 1.0 equiv.) in tetrahydrofuran (1.0 mL) was then added dropwise and the solution stirred for an additional 30 min. A solution of acetic anhydride (0.11 mL, 1.13 mmol, 2.5 equiv.) in tetrahydrofuran (2.3 mL) was slowly added to the reaction mixture. The solution was allowed to gradually warm to 23 °C and stirred for 2 h. Saturated aqueous ammonium chloride (NH_4Cl, 3 mL) was added and the mixture was diluted with diethyl ether (10 mL). The aqueous layer was extracted with diethyl ether (3 x 2 mL), and the combined organic layers were washed with water (3 x 5 mL) and brine (5 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The resulting residue was purified via flash column chromatography over silica gel (9-17% ethyl acetate/hexanes) to give the acetyloxy diene **2-54** as a colorless oil (54 mg, 54%); R_f 0.68 (50% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

5.91 (dd, *J* = 10.0, 2.5 Hz, 1H)

5.77 (d, *J* = 10.0 Hz, 1H)

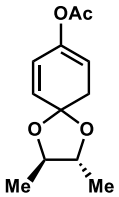
5.55 (m, 1H)

3.70-3.63 (m, 2H)

2.78 (dd, *J* = 19.0, 4.5 Hz, 1H)

2.70 (dd, *J* = 19.0, 5.0 Hz, 1H)

2.14 (s, 3H)



2-54

1.26 (d, J = 6.0 Hz, 3H)

1.25 (d, J = 6.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 169.2, 143.8, 129.7, 125.6, 111.2, 104.3, 78.6, 78.1, 35.6, 21.0, 16.9, 16.6.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{12}H_{17}O_4$ 225.11214; found, 225.11201.

***tert*-Butyl(((2*S*,3*S*)-2,3-diphenyl-1,4-dioxaspiro[4.5]dec-7-en-8-yl)oxy)dimethyl-silane (2-56):** To a cooled (−78 °C) solution of the ketone **2-55**[16] (393 mg, 1.27 mmol, 1.0 equiv.) in dichloromethane (13 mL) was added triethylamine (0.71 mL, 5.10 mmol, 4.0 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.38 mL, 1.66 mmol, 1.3 equiv.). The solution was gradually allowed to warm to 23 °C and stirred for 1.5 h. Saturated aqueous $NaHCO_3$ (15 mL) was added and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and the solvent was removed under reduced pressure. Purification via flash column chromatography over silica gel (5% ethyl acetate/hexanes) afforded the silyl enol ether **2-56** as a colorless oil (537 mg, 100%); R_f 0.43 (6% ethyl acetate/hexanes).

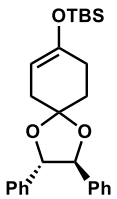
^{1}H NMR (400 MHz, $CDCl_3$, δ):

7.33-7.29 (m, 6H)

7.24-7.20 (m, 4H)

4.81 (dd, J = 4.0, 4.0 Hz, 1H)

4.79 (d, J = 8.8 Hz, 1H)



2-56

4.75 (d, *J* = 8.8 Hz, 1H)

2.72-2.40 (m, 3H)

2.30 (ddd, *J* = 16.8, 5.6, 5.6 Hz, 1H)

2.17-2.05 (m, 2H)

0.92 (s, 9H)

0.15 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, δ): 150.1, 137.1, 136.9, 128.4 (2), 128.3, 128.2, 126.8, 126.7, 108.6, 100.7, 85.3, 85.2, 35.4, 32.7, 28.6, 25.7, 18.0, -4.39, -4.42.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{26}H_{35}O_3Si$ 423.23500; found, 423.23418.

(2*S*,3*S*)-2,3-Diphenyl-1,4-dioxaspiro[4.5]dec-6-en-8-one (2-57): A solution of **2-56** (537 mg, 1.27 mmmol, 1.0 equiv.) and palladium (II) acetate (901 mg, 1.34 mmol, 1.05 equiv.) in acetonitrile (13 mL) was allowed to stir for 12 h at 23 °C. Following removal of the solvent under reduced pressure, the crude mixture was subjected to flash column chromatography over silica gel (9-13% ethyl acetate/hexanes) to afford the enone **2-57** as a light yellow solid (78 mg, 20% over 2 steps); R_f 0.82 (50% ethyl acetate/hexanes). The spectral data for **2-57** are in accordance with those reported in the literature for its enantiomer, (2*R*,3*R*)-2,3-diphenyl-1,4-dioxaspiro[4.5]dec-6-en-8-one.[17]

***tert*-Butyl(((2*S*,3*S*)-2,3-diphenyl-1,4-dioxaspiro[4.5]deca-6,8-dien-8-yl)oxy)di-methyllsilane (2-58):** To a solution of the enone **2-57** (17 mg, 0.0555 mmol, 1.0 equiv.) in

dichloromethane (0.6 mL) at −78 °C was added triethylamine (25 µL, 0.179 mmol, 3.2 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (20 µL, 0.0871 mmol, 1.6 equiv.). The reaction was allowed to stir at −78 °C for 2 h and quenched with saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was extracted with dichloromethane (3 x 2 mL), and the combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, and the solvent was removed under reduced pressure. The resulting residue was purified via flash column chromatography over silica gel (5% ethyl acetate/hexanes) to afford the silyloxy diene **2-58** as a yellow oil (20 mg, 86%); R_f 0.27 (6% ethyl acetate/hexanes).

^1H NMR (500 MHz, $CDCl_3$, δ):

7.33-7.29 (m, 6H)

7.24-7.20 (m, 4H)

6.03-5.98 (m, 2H)

5.05 (m, 1H)

4.78 (d, *J* = 8.5 Hz, 1H)

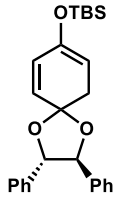
4.76 (d, *J* = 8.5 Hz, 1H)

3.00 (dd, *J* = 18.5, 4.5 Hz, 1H)

2.87 (dd, *J* = 18.5, 5.0 Hz, 1H)

0.93 (s, 9H)

0.16 (s, 6H).



2-58

^{13}C NMR (125 MHz, $CDCl_3$, δ): 146.6, 136.7, 136.4, 130.0, 128.4 (4), 128.3, 126.8, 126.7, 106.6, 101.6, 85.3, 84.8, 35.6, 25.7, 18.0, -4.49, -4.52.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{26}H_{33}O_3Si$ 421.21935; found, 421.21775.

(4*R*,4'*R*,5*R*,7'*R*,7a'*S*)-2'-(Phenylmethyl)-5'-((*tert*-butyldimethylsilyl)oxy)-4,5-dimethyl-3a',4',7',7a'-tetrahydro-1'*H*-spiro[[1,3]dioxolane-2,8'-[4,7]ethanoisoindole]-1',3'-(2'*H*)-dione (2-59) and (3a'*S*,4*R*,4'*S*,5*R*,7'*S*,7a'*R*)-2'-(phenylmethyl)-5'-((*tert*-butyldimethyl-silyl)oxy)-4,5-dimethyl-3a',4',7',7a'-tetrahydro-1'*H*-spiro[[1,3]dioxolane-2,8'-[4,7]ethanoisoindole]-1',3'(2'*H*)-dione (2-61): To a small dram vial was added the diene **2-33** (22 mg, 0.0742 mmol, 1.0 equiv.), *N*-benzylmaleimide **2-46** (14 mg, 0.0748 mmol, 1.0 equiv.), and benzene (0.2 mL). The reaction was allowed to stir for 12 h and the solvent was removed under reduced pressure. The crude residue was purified via flash column chromatography over silica gel (9-17% ethyl acetate/hexanes) to give an inseparable 1:1 mixture of the cycloadducts **2-59** and **2-61** (29 mg, 81%); R_f 0.28 (20% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

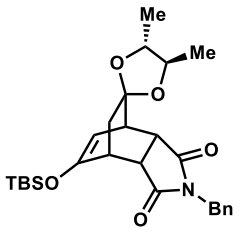
7.32-7.21 (m, 5H)

4.77 (dd, *J* = 7.5, 2.0 Hz, 0.5H)

4.76 (dd, *J* = 7.5, 2.5 Hz, 0.5H)

4.59 (d, *J* = 14.5 Hz, 1H)

4.54 (d, *J* = 14.0, 0.5H)



2-59

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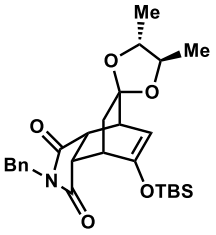


2-61

4.53 (d, *J* = 14.5, 0.5H)

3.70-3.51 (m, 2H)

3.34 (dd, *J* = 8.0, 3.5 Hz, 0.5H)

3.28 (dd, *J* = 8.0, 3.5 Hz, 0.5H)

3.02 (dd, *J* = 7.0, 3.0 Hz, 0.5H)

3.00 (dd, *J* = 7.0, 3.0 Hz, 0.5H)

2.96-2.89 (m, 2H)

1.96 (dd, *J* = 11.5, 3.0 Hz, 0.5H)

1.93 (dd, *J* = 11.5, 3.0 Hz, 0.5H)

1.79 (dd, *J* = 8.0, 2.0 Hz, 0.5H)

1.76 (dd, *J* = 8.0, 2.0 Hz, 0.5H)

1.22 (d, *J* = 6.0 Hz, 3H)

1.20 (d, *J* = 6.0 Hz, 3H)

0.88 (s, 4.5H)

0.87 (s, 4.5H)

0.10 (s, 3H)

0.02 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 178.7 (2), 177.5, 177.4, 155.6, 155.5, 135.8 (2), 128.5 (4), 127.7 (2), 110.9, 110.6, 98.5 (2), 78.9, 78.8, 78.4 (2), 43.7, 43.3, 42.4, 42.3 (3), 41.6, 41.5, 41.3, 41.1, 39.6, 39.4, 25.5 (2), 17.9 (2), 17.4, 17.1, 16.7 (2), -4.52, -4.85.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{27}H_{38}NO_5Si$ 484.25138; found, 484.25105.

(4*R*,4'*R*,5*R*,7'*R*,7a'*S*)-2'-(Phenylmethyl)-4,5-dimethyl-1',3'-dioxo-2',3',3a',4',7',7a'-hexa-hydro-1'*H*-spiro[[1,3]dioxolane-2,8'-[4,7]ethanoisoindol]-5'-yl acetate (2-60) and (3a'*S*,4*R*,4'*S*,5*R*,7'*S*,7a'*R*)-2'-(phenylmethyl)-4,5-dimethyl-1',3'-dioxo-2',3',3a',4',7',7a'-hexahydro-1'*H*-spiro[[1,3]dioxolane-2,8'-[4,7]ethanoisoindol]-5'-yl acetate (2-62): To a small dram vial was added the diene **2-54** (11 mg, 0.0491 mmol, 1.0 equiv.), *N*-benzylmaleimide **2-46** (9 mg, 0.0481 mmol, 1.0 equiv.) and benzene (0.12 mL). The reaction was allowed to stir for 12 h and the solvent was then evaporated under reduced pressure. Purification via flash column chromatography (17% ethyl acetate/hexanes) afforded an inseparable 1:1 mixture of the cycloadducts **2-60** and **2-62** (10 mg, 51%); R_f 0.06 (20% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

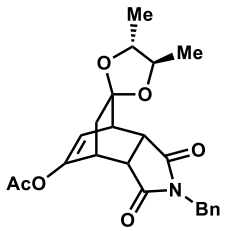
7.30-7.22 (m, 5H)

5.62 (dd, *J* = 7.5, 2.0 Hz, 0.5H)

5.60 (dd, *J* = 7.5, 2.5 Hz, 0.5H)

4.58 (s, 2H)

3.72-3.54 (m, 2H)



2-60

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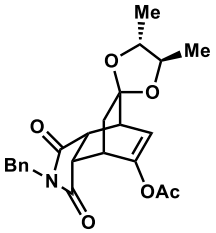


2-62

3.42 (dd, *J* = 8.0, 3.0 Hz, 0.5H)

3.36 (dd, *J* = 8.0, 3.5 Hz, 0.5H)

3.18 (dd, *J* = 6.5, 3.5 Hz, 0.5H)

3.17 (dd, *J* = 7.0, 3.5 Hz, 0.5H)

3.14 (dd, *J* = 6.5, 3.5 Hz, 0.5H)

3.13 (dd, *J* = 6.5, 3.5 Hz, 0.5H)

2.97 (dd, *J* = 7.5, 3.0 Hz, 0.5H)

2.96 (dd, *J* = 7.5, 3.0 Hz, 0.5H)

2.22 (m, 1H)

2.03 (s, 1.5H)

2.02 (s, 1.5H)

1.84 (dd, *J* = 7.0, 2.0 Hz, 0.5H)

1.81 (dd, *J* = 7.0, 2.0 Hz, 0.5H)

1.26-1.20 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 178.0, 177.9, 177.3, 177.2, 168.5 (2), 151.9, 151.8, 135.7 (2), 128.5 (2), 128.4 (2), 127.7 (2), 111.0, 110.8, 110.5, 110.1, 79.0, 78.9, 78.6 (2), 43.6, 43.3, 42.5, 42.4 (3), 41.3, 41.2 (2), 41.0, 37.8, 37.6, 20.8 (2), 17.3, 17.0, 16.5 (2).

***Se*-Phenyl (1S,4R,4'S,5'S,7S)-5-((*tert*-butyldimethylsilyl)oxy)-4',5'-diphenylspiro-[bicyclo[2.2.2]octane-2,2'-[1,3]dioxolan]-5-ene-7-carboselenoate (2-35) and *Se*-phenyl (1R,4S,4'S,5'S,7R)-5-((*tert*-butyldimethylsilyl)oxy)-4',5'-diphenylspiro-[bicyclo[2.2.2]octane-2,2'-[1,3]dioxolan]-5-ene-7-carboselenoate (2-63):** To a small dram vial was added *Se*-phenyl prop-2-eneselenoate **2-34** (1.3 mg, 0.00616 mmol, 1.0 equiv.), the diene **2-58** (6.0 mg, 0.0143 mmol, 2.3 equiv.), a single crystal of butylated hydroxytoluene (BHT), and toluene (50 µL). The vial was sealed with Teflon tape, heated to 110 °C, and allowed to stir for 14 h. The resulting residue was purified via flash column chromatography over silica gel (3-9% ethyl acetate/hexanes) to give an inseparable 1.8:1 mixture of the cycloadducts **2-35** and **2-63**. The title compounds are inseparable from *Se*-phenyl prop-2-eneselenoate **2-34**.

^{1}H NMR (500 MHz, $CDCl_3$, δ):

7.53-7.17 (m, 15H)

5.11 (dd, *J* = 7.0, 2.0 Hz, 0.4H)

4.99 (dd, *J* = 7.0, 2.5 Hz, 0.6H)

4.80-4.68 (m, 2H)

3.73 (ddd, *J* = 9.5, 4.5, 2.5 Hz, 0.6H)

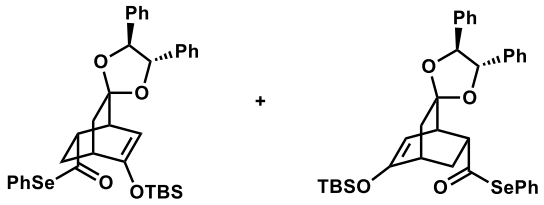
3.57 (ddd, *J* = 9.5, 5.5, 2.0 Hz, 0.4H)

3.39 (dd, *J* = 7.0, 2.0 Hz, 0.6H)

3.33 (dd, *J* = 7.0, 2.0 Hz, 0.4H)

2.58 (m, 1H)

2.25-1.95 (m, 3.4H)



2-35 **2-63**

1.92 (ddd, *J* = 12.5, 9.5, 2.5 Hz, 0.6H)

0.92 (s, 3.6H)

0.91 (s, 5.4 H)

0.17 (s, 1.2H)

0.16 (s, 1.2H)

0.15 (s, 1.8H)

0.14 (s, 1.8H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 202.3, 202.0, 158.9, 158.8, 137.4, 136.6, 136.4, 136.2, 136.1 (2), 136.0, 129.4, 129.3, 129.2, 128.7 (2), 128.6 (2), 128.5, 128.4 (3), 128.1, 127.1, 126.9, 126.7, 126.5, 126.2, 113.5, 112.9, 99.1, 99.0, 86.0, 85.4 (2), 85.3, 52.4, 52.3, 44.9, 44.1, 42.4, 41.9, 37.7, 37.6, 30.3, 29.7, 29.4, 28.4, 25.7, 18.0, -4.22, -4.24, -4.55, -4.57.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{35}H_{41}O_4SeSi$ 633.19338; found, 633.19254.

(2*R*,3*R*,6*R*)-2,3-Dimethyl-6-vinyl-1,4-dioxaspiro[4.5]decan-8-one (2-64), (2R,3R, 6S)-2,3-dimethyl-6-vinyl-1,4-dioxaspiro[4.5]decan-8-one (2-69), and (2*R*,3*R*,8*S*)-2,3-dimethyl-8-vinyl-1,4-dioxaspiro[4.5]dec-6-en-8-ol (2-68): To a cooled (−40 °C) solution of copper (I) cyanide (51 mg, 0.569 mmol, 4.0 equiv.) in diethyl ether (2.9 mL) was slowly added vinylmagnesium bromide (1.0 M in tetrahydrofuran, 0.57 mL, 0.570 mmol, 4.0 equiv.). The solution was allowed to stir at −40 °C for 40 min and was then cooled to −78 °C. Trimethylsilyl chloride (55 µL, 0.435 mmol, 3.0 equiv.) was added and the solution was allowed to stir for 30 min. A solution of the enone **2-53** (26 mg, 0.143 mmol, 1.0 equiv.) in

tetrahydrofuran (0.25 mL) was added and the solution was allowed to stir at −78 °C for 1 h. The solution was warmed to 23 °C and quenched with the addition of saturated aqueous ammonium chloride (5 mL). The aqueous layer was extracted with diethyl ether (3 x 3 mL) and the combined organic layers were washed with saturated aqueous ammonium chloride (5 mL) and brine (5 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude mixture was purified via flash column chromatography over silica gel (9-17% ethyl acetate/hexanes) to afford an inseparable mixture of the diastereomeric adducts **2-64** and **2-69** as a colorless oil (5.0 mg, 17%); R_f 0.41 (20% ethyl acetate/hexanes), in a 4:1 ratio.

^{1}H NMR (500 MHz, $CDCl_3$, δ):

5.90 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 0.8H)

5.89 (ddd, *J* = 17.0, 10.5, 6.5 Hz, 0.2H)

5.15 (ddd, *J* = 10.5, 1.5, 1.5 Hz, 0.8H)

5.14 (ddd, *J* = 10.5, 1.5, 1.5 Hz, 0.2H)

5.11 (ddd, *J* = 17.0, 1.5, 1.5 Hz, 0.2H)

5.09 (ddd, *J* = 17.0, 1.5, 1.5 Hz, 0.8H)

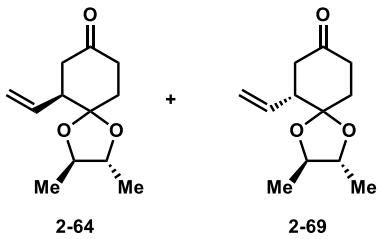
3.73 (dq, *J* = 8.5, 6.0 Hz, 0.8H)

3.71-3.65 (m, 1.2H)

2.77-2.70 (m, 1H)

2.65-2.52 (m, 3H)

2.50-2.39 (m, 1H)



2-64 2-69

2.06 (ddd, *J* = 13.0, 6.0, 6.0 Hz, 0.8H)

2.04 (ddd, *J* = 13.0, 6.0, 6.0 Hz, 0.2H)

1.95-1.85 (m, 1H)

1.28 (d, *J* = 5.5 Hz, 0.6H)

1.27 (d, *J* = 5.5 Hz, 2.4H)

1.26 (d, *J* = 6.0 Hz, 2.4H)

1.24 (d, *J* = 6.0 Hz, 0.6H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 210.2, 210.0, 136.2, 136.1, 117.4, 117.2, 107.4 (2), 79.7, 79.1, 78.5 (2), 49.0, 48.2, 43.3, 42.8, 38.4, 38.2, 34.5, 34.4, 17.2, 17.0, 16.2, 16.1.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{12}H_{19}O_3$ 211.13287; found, 211.13268.

The separation also afforded the alcohol **2-68** as a colorless oil (4.0 mg , 13%); R_f 0.13 (20% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

5.89 (dd, *J* = 17.0, 10.5 Hz, 1H)

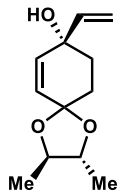
5.68 (s, 2H)

5.22 (dd, *J* = 17.0, 1.5 Hz, 1H)

5.13 (dd, *J* = 10.5, 1.0 Hz, 1H)

3.66 (dq, *J* = 8.0, 6.0 Hz, 1H)

3.58 (dq, *J* = 8.5, 6.0 Hz, 1H)



2-68

2.07-1.78 (m, 4H)

1.76 (bs, 1H)

1.26 (d, J = 6.0 Hz, 3H)

1.24 (d, J = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 141.1, 135.3, 130.4, 114.6, 104.0, 78.6, 78.1, 71.7, 35.1, 32.1, 29.7, 16.6.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{12}H_{19}O_3$ 211.13287; found, 211.13231.

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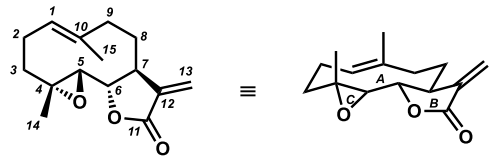
CHAPTER 3

Progress Toward the Total Synthesis of Parthenolide

Introduction

Parthenolide (**3-1**, Figure 3-1), first isolated in 1959, is the predominant sesquiterpene lactone present in the Feverfew herb, *Tanacetum parthenium*. Feverfew has been recognized since ancient times for its medicinal properties against such ailments as toothaches, insect bites, and asthma. It was first isolated from *T. parthenium* in 1959 by Sorm and colleagues, who incorrectly assigned the structure.[1] Later, isolation from the roots of *Michelia champaca* allowed for correct structural analysis. Subsequent studies confirmed the conformation to exist as shown in Figure 3-1 (right side). Parthenolide, a germacranolide, features a 10-membered carbocyclic core, four contiguous stereocenters (4*R*, 5*R*, 6*S*, 7*R*), a strained epoxide, a tri-substituted (*E*)-alkene, and a *trans*-fused γ-lactone.[2] Germacranolides draw attention from the synthetic community for their unique structural and conformational features, general occurrence in nature, and critical role in the biosynthesis of other sesquiterpenes. Characteristic germacrane structures, as well as select examples of germacrane natural products, are shown in Figure 3-2.[3]



Parthenolide (3-1)

Figure 3-1. Ring and numbering assignments of parthenolide **3-1** (left side) and its preferred conformation (right side).

The total synthesis of germacranes has historically presented a challenging problem due to their thermal instability and the ease with which these compounds undergo transannular cyclizations. However, many reports in the literature have detailed successful syntheses of germacrane natural products. Perhaps the most crucial aspect of total synthesis of a germacrane

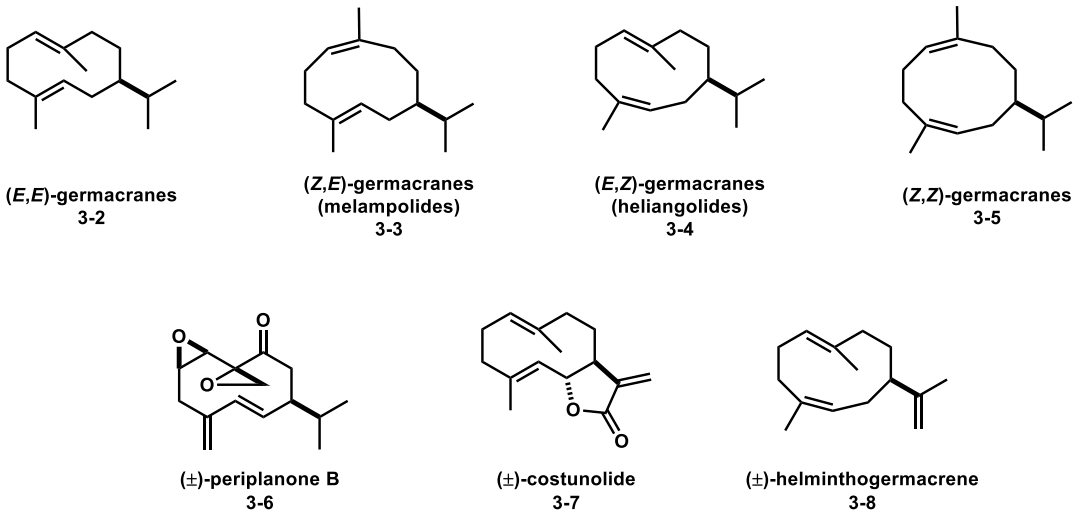


Figure 3-2. Characteristic germacrane skeletons **3-2** to **3-5** and select germacrane natural products **3-6**, **3-7**, and **3-8**.

compound is the formation of the 10-membered carbocyclic core, as medium-sized rings are traditionally difficult to form. Successful approaches taken toward forming the 10-membered carbocyclic core of germacrane sesquiterpenes include: intramolecular C-C bond formation, ring cleavage reactions, and ring expansion reactions.[3]

Parthenolide has attracted significant attention due to its extensive biological activites. Studies have shown that it exhibits potent anti-inflammatory and anti-cancer properties. For example, parthenolide induces cell death in prostate, pancreatic, colorectal, and breast cancer cells. Significantly, parthenolide has shown cytotoxicity toward cancer stem cells. As cancer stem cells are postulated to be the cause of metastasis and relapse, parthenolide has quickly become a popular therapeutic target.[4]

Despite its exceptionally promising biological activities, parthenolide itself exhibits poor water-solubility, limiting its oral bioavailability and ultimate utility as a drug. Several research groups, including ours, have synthesized analogues of parthenolide with the hopes of achieving a more water-soluble compound that retains the biological activity of the natural product. One

such analogue, dimethylamino parthenolide (DMAPT, **3-9**, Figure 3-3), was prepared as one of several parthenolide analogues by Guzman, Crooks, and coworkers. Formulated as the fumarate salt, DMAPT demonstrates more than 1000-fold greater aqueous solubility relative to parthenolide. These studies also showed that DMAPT, like parthenolide, successfully eradicates human acute myelogenous leukemia (AML) stem and progenitor cells in vitro while sparing normal hematopoietic stem and progenitor cells. Specifically, these compounds induce oxidative stress and inhibit NF-κB, which are factors known to facilitate leukemia stem cell (LSC) selective cell death.[5] Also shown in Figure 3-3 are several promising analogues (**3-10**, **3-11**, **3-12**, and **3-13**) prepared by Gang Deng, a former postdoctoral associate in our laboratory. These analogues were prepared by reaction of parthenolide with various amines and demonstrate increased water-solubility and enhanced antitumor properties over parthenolide. [6]

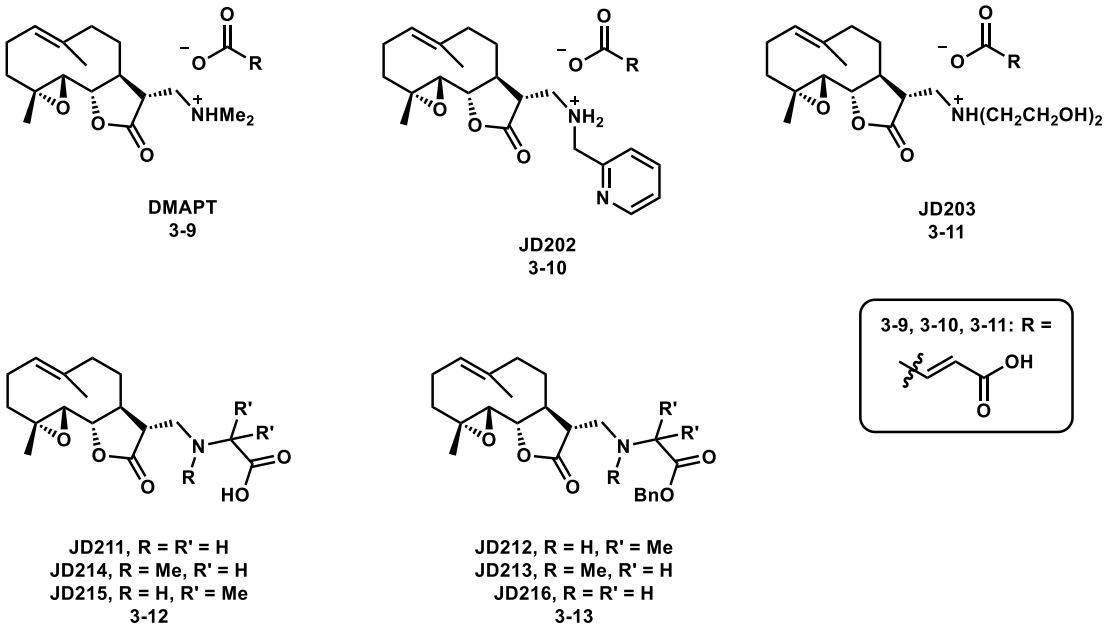
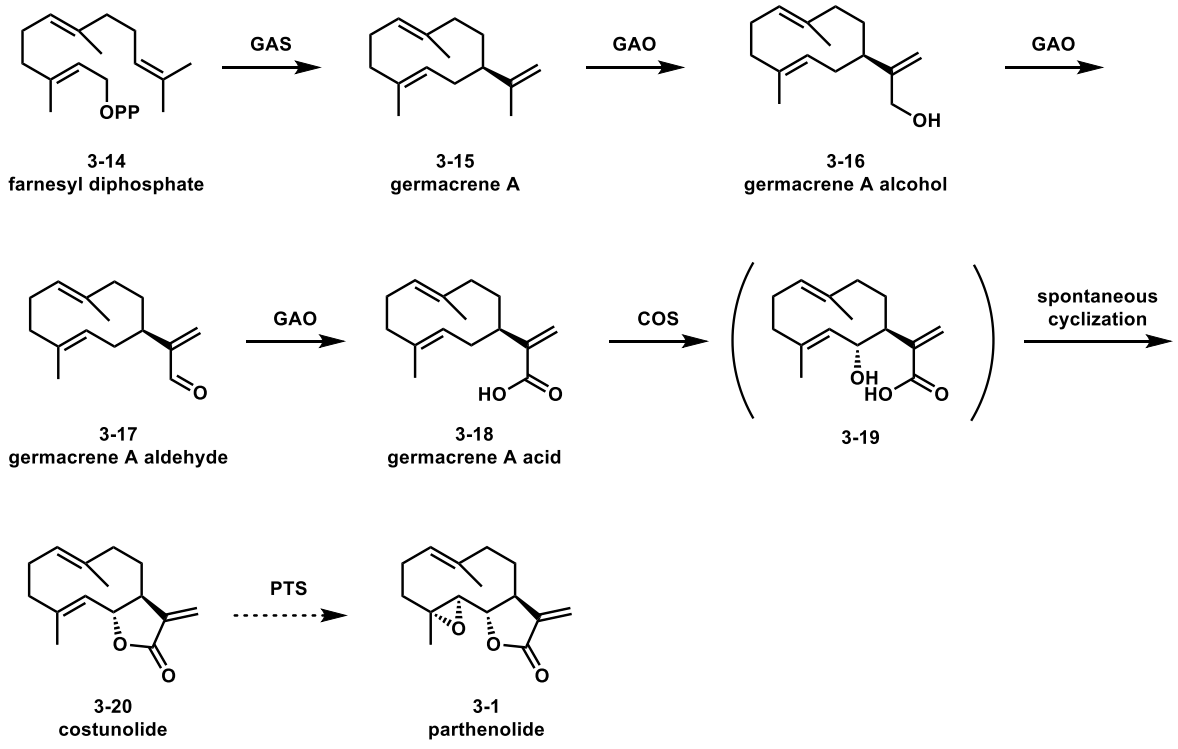


Figure 3-3. Water-soluble parthenolide analogues.

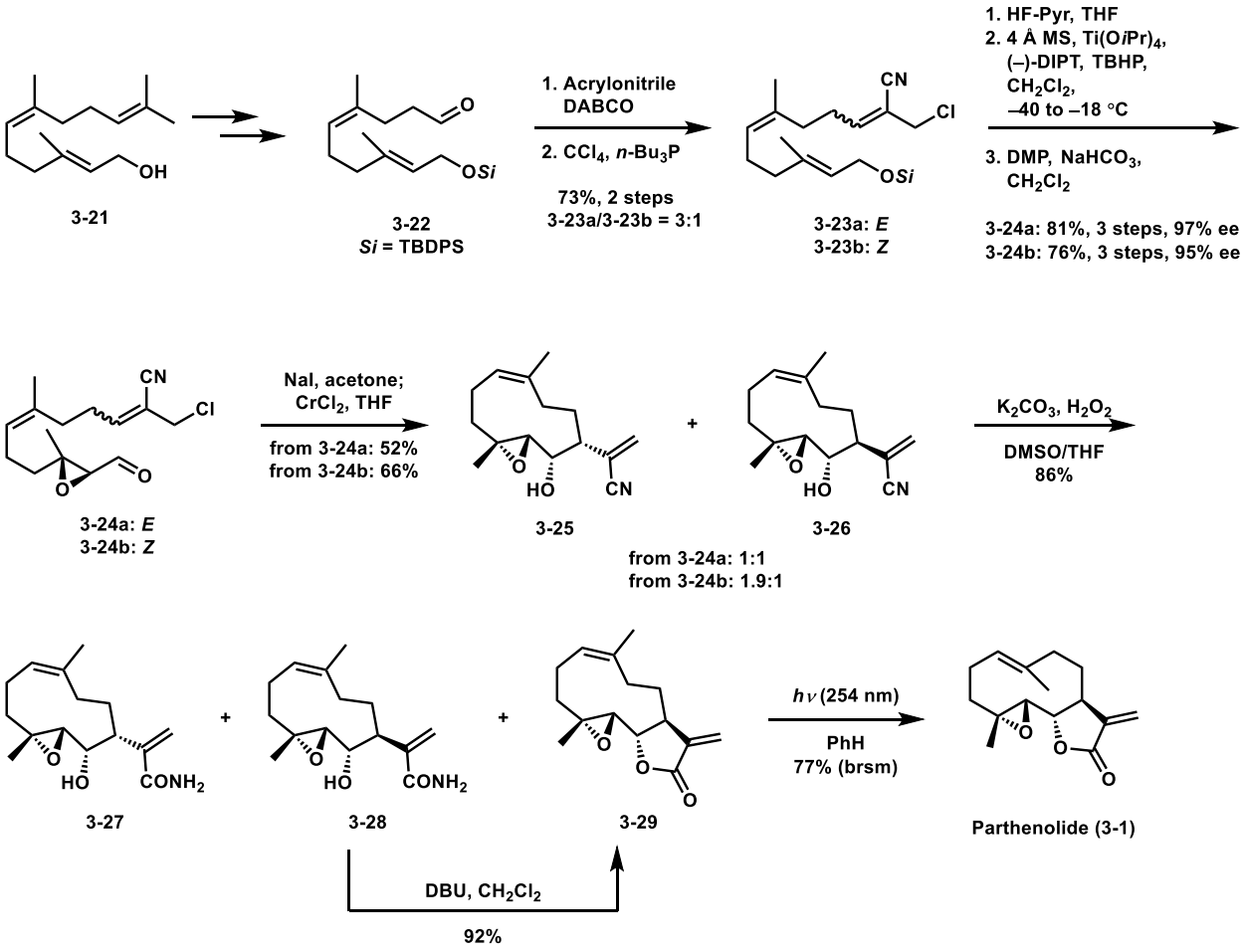
Liu, *et al.*, elucidated the biosynthetic pathway of parthenolide and identified all of the genes from feverfew that are required for its biosynthesis. This biosynthetic sequence is shown in Scheme 3-1 and begins with farnesyl diphosphate **3-14**. The enzyme (+)-germacrene A synthase (GAS) catalyzes the formation of germacrene A **3-15** from **3-14**. A number of subsequent oxidation steps catalyzed by germacrene A oxidase (GAO), a cytochrome P450 enzyme, result in the oxidation of **3-15** all the way to germacra-1(10),4,11(13)-trien-12-oic acid (germacrene A acid) **3-18**. An additional oxidation by costunolide synthase (COS) produces 6α-hydroxy-germacra-1(10),4,11(13)-trien-12-oic acid **3-19**, which then experiences a spontaneous lactone ring formation to generate costunolide **3-20**, the putative precursor to parthenolide. The last step, epoxidation of the C4-C5 double bond of costunolide to afford parthenolide **3-1**, is presumed to be catalyzed by a P450 monooxygenase. However, the gene encoding the enzyme responsible for this epoxidation, *parthenolide synthase* (*PTS*), has not yet been reported.[7]



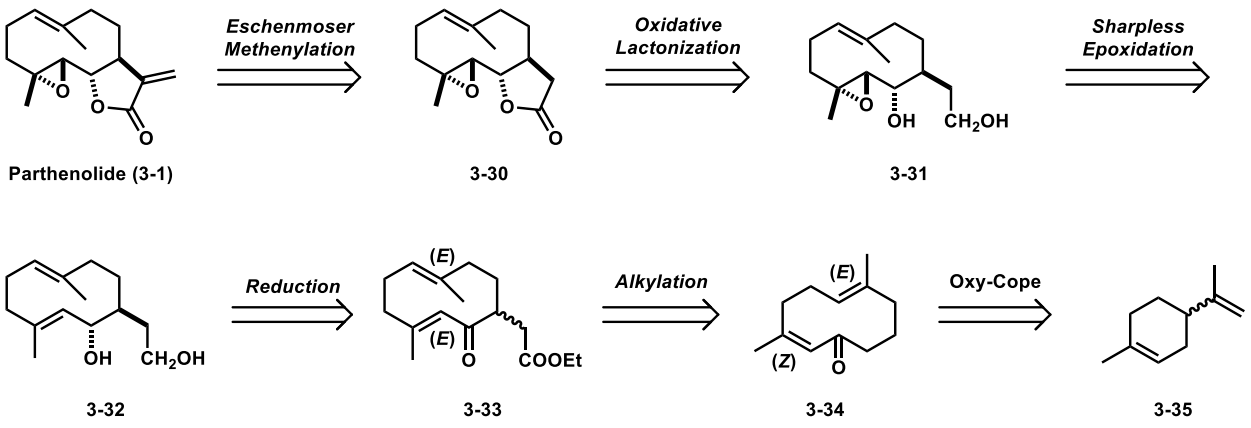
Scheme 3-1. Proposed biosynthesis of parthenolide **3-1**.

Several total syntheses of parthenolide and various analogues have been published in the recent literature. The first known synthesis was completed in an asymmetric fashion by Long and coworkers (Scheme 3-2).[8] The known alcohol **3-21** was taken through a series of transformations to generate the aldehyde **3-22**. This aldehyde underwent a key Baylis-Hillman reaction followed by chlorination to produce a 3:1 mixture of alkene isomers **3-23a** (*E*) and **3-23b** (*Z*). Then, the cyclization precursors **3-24a** and **3-24b** were formed in a three-step sequence in 81% and 76% yields, respectively. The desired macrocyclic stereocontrolled Barbier cyclization was achieved by first converting the allylic chloride to an allylic iodide, followed by treatment with $CrCl_2$ to give a mixture of isomers **3-25** and **3-26**. Cyclization of **3-24a** gave **3-25** and **3-26** in a 1:1 ratio in 52% yield, whereas starting from **3-24b** gave 66% yield of a 1.9:1 mixture of **3-25** and **3-26**. The mixture of **3-25** and **3-26** was hydrolyzed with basic hydrogen peroxide to produce a mixture of amides **3-27** and **3-28**, the latter of which partially cyclized to **3-29** during purification with silica gel chromatography. Complete conversion of **3-28** to **3-29** occurred by stirring with DBU in dichloromethane. Finally, conversion of the 1(10)-*Z*-double bond of **3-29** to the desired *E* configuration was achieved by irradiation of **3-29** with UV light (254 nm) to afford parthenolide **3-1** in 77% yield based on recovered starting material.

A stereoselective total synthesis of (±)-parthenolide was recently accomplished by Li and coworkers.[9] The retrosynthetic analysis, showing the key transformations of this approach, is shown in Scheme 3-3. The *exo* double bond of (±)-parthenolide **3-1** was installed via Eschenmoser methenylation of lactone **3-30**. Cyclization of **3-31** was achieved under oxidative conditions to generate lactone **3-30**. Sharpless asymmetric epoxidation of diol **3-32** installed the *trans*-epoxide moiety of **3-31**. Diol **3-32** was formed by reduction of ester **3-33**, which was formed by alkylation and double bond isomerization of **3-34**. Oxy-Cope rearrangement generated the 10-membered carbocyclic core of **3-34** starting from readily available limonene **3-35**.

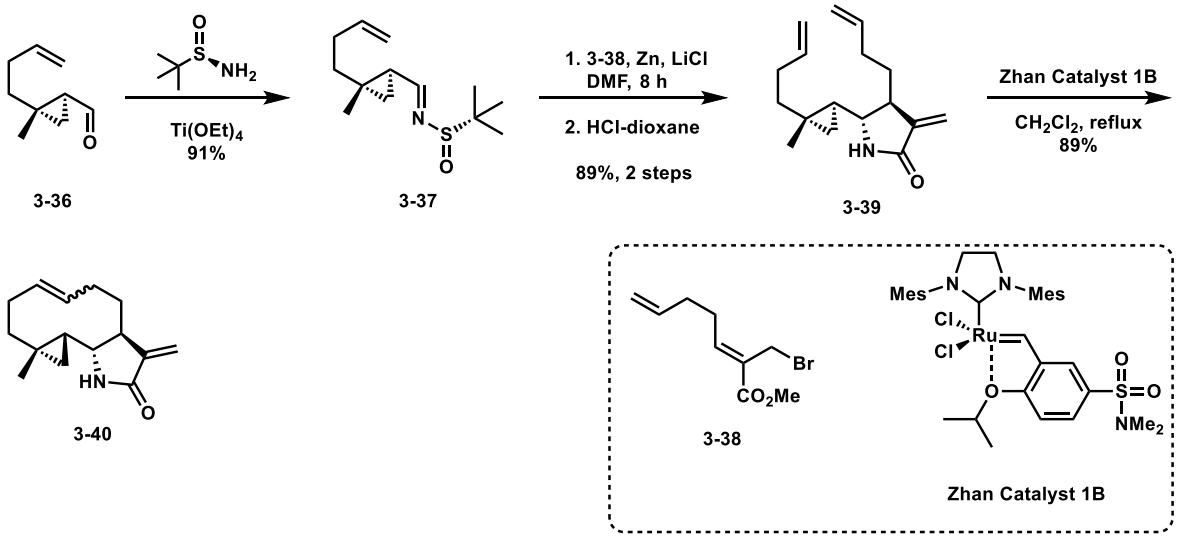


Scheme 3-2. First published total synthesis of parthenolide **3-1**.



Scheme 3-3. Retrosynthetic analysis of Li's route to parthenolide **3-1**.

Another study by Long and coworkers resulted in the total syntheses of two parthenolide analogues, one of which was obtained using ring-closing metathesis (RCM) as a key step.[10] The steps leading up to this key ring closure are shown in Scheme 3-4. The aldehyde **3-36** was condensed with (*S*)-*N*-*tert*-butanesulfinylimine, catalyzed by $Ti(OEt)_4$, to afford the imine **3-37** in 91% yield. Coupling of **3-37** with the allylic anion formed from the bromide **3-38** followed by treatment with HCl-dioxane afforded the lactam **3-39** in 89% yield over 2 steps. Finally, ring-closing metathesis of **3-39** with Zhan catalyst 1B provided the parthenolide analogue **3-40** in 89% yield, with a 7:3 ratio of geometric isomers.

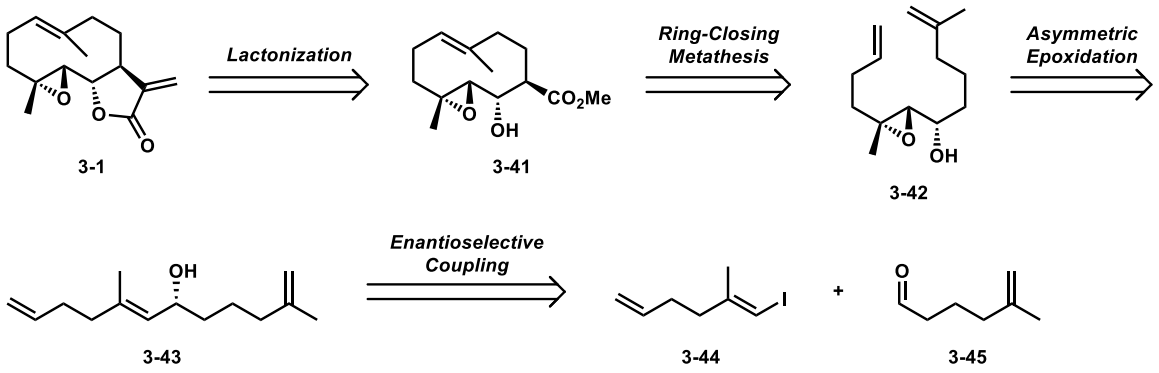


Scheme 3-4. Application of ring-closing metathesis to the synthesis of the parthenolide analogue **3-40**.

In light of the synthetically intriguing features and promising biological activity of parthenolide, we wanted to carry out a total synthesis of parthenolide. Although there are published reports of total syntheses of parthenolide and its analogues, we hoped to accomplish an efficient and scalable synthesis for the purpose of accessing large quantities of parthenolide and various analogues. We designed our approach to feature ring-closing metathesis as a key step to form the 10-membered carbocycle.

Results and Discussion

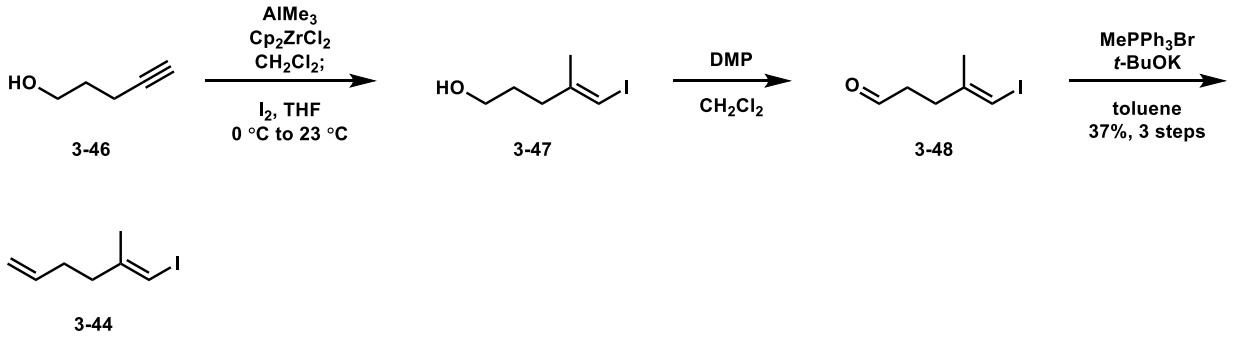
Our retrosynthetic scheme, shown in Scheme 3-5, depicts the key transformations of our approach toward parthenolide. Late-stage lactonization and olefination of **3-41** could afford parthenolide **3-1**. We envisioned that ring-closing metathesis (RCM) of **3-42** could simultaneously form the 10-membered carbocyclic core and establish the (*E*)-alkene of intermediate **3-41**. A hydroxyl-directed epoxidation of the allylic alcohol **3-43** could generate the epoxy alcohol **3-42** with diastereoselectivity. The allylic alcohol **3-43** might be enantioselectively prepared by coupling the vinyl iodide **3-44** with the aldehyde **3-45** in the presence of a chiral ligand.



Scheme 3-5. Retrosynthetic analysis showing the key steps of our approach toward the total synthesis of parthenolide **3-1**.

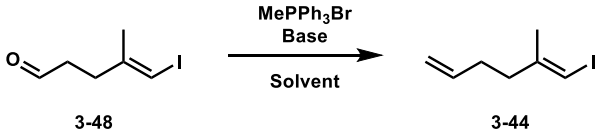
Our effort toward parthenolide started with the syntheses of the vinyl iodide **3-44** and the aldehyde **3-45**, the key intermediates needed for the enantioselective coupling. The vinyl iodide **3-44** can be accessed in 3 steps, shown in Scheme 3-6, starting from 4-pentyn-1-ol **3-46**. Carboalumination of 4-pentyn-1-ol followed by quenching with iodine affords the alcohol **3-47**.[11] Oxidation with Dess-Martin periodinane (DMP) generated the aldehyde **3-48**. Finally, Wittig olefination of **3-48** installed the alkene to afford the vinyl iodide **3-44** in 37% overall yield over 3 steps. The vinyl iodide tended to decompose in the presence of light, but the compound

remained stable when stored in the refrigerator in the absence of light. The compound also seemed to be sensitive to various methods of purification, but passing the crude mixture over alumina gratifyingly gave the pure product in good yield over 3 steps (Table 3-1). The use of potassium *tert*-butoxide (*t*-BuOK) as base and toluene as solvent led to the cleanest conversion of starting material to product, with no undesired byproducts.



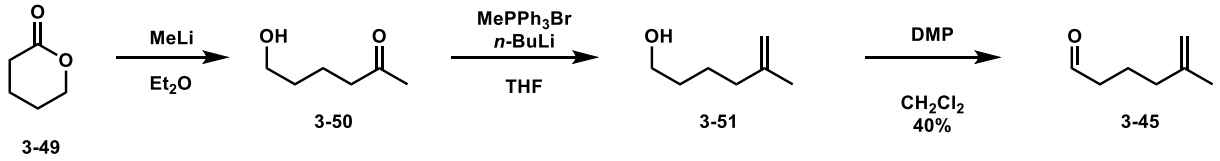
Scheme 3-6. Synthesis of the vinyl iodide **3-44**.

Table 3-1. Optimization of Wittig olefination to afford the vinyl iodide **3-44**.



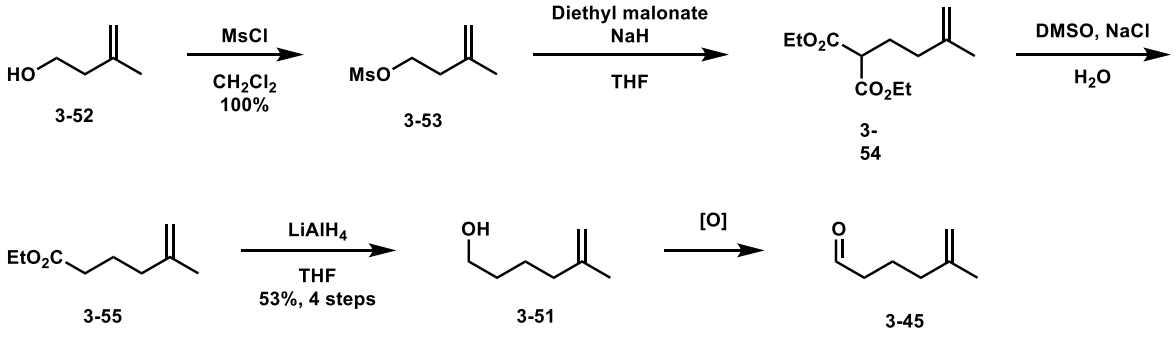
Entry	Base	Solvent	Purification	Yield (%)
1	*n*-BuLi	THF	---	0
2	*t*-BuOK	THF	SiO_2	4
3	*t*-BuOK	THF	Rinse with hexanes	10
4	*t*-BuOK	THF	Distillation	Impure
5	*t*-BuOK	PhMe	Al_2O_3	37 (3 steps)

The synthesis of the aldehyde intermediate **3-45** is shown in Scheme 3-7 and began with methyllithium addition to δ-valerolactone **3-49** to provide the keto alcohol **3-50**. Wittig olefination of the ketone **3-50** gave the alcohol **3-51**.[12] Finally, oxidation of the alcohol with DMP provided the aldehyde **3-45** in 40% yield. Unfortunately, the aldehyde decomposed even at room temperature, so high yields could not be achieved upon distillation.



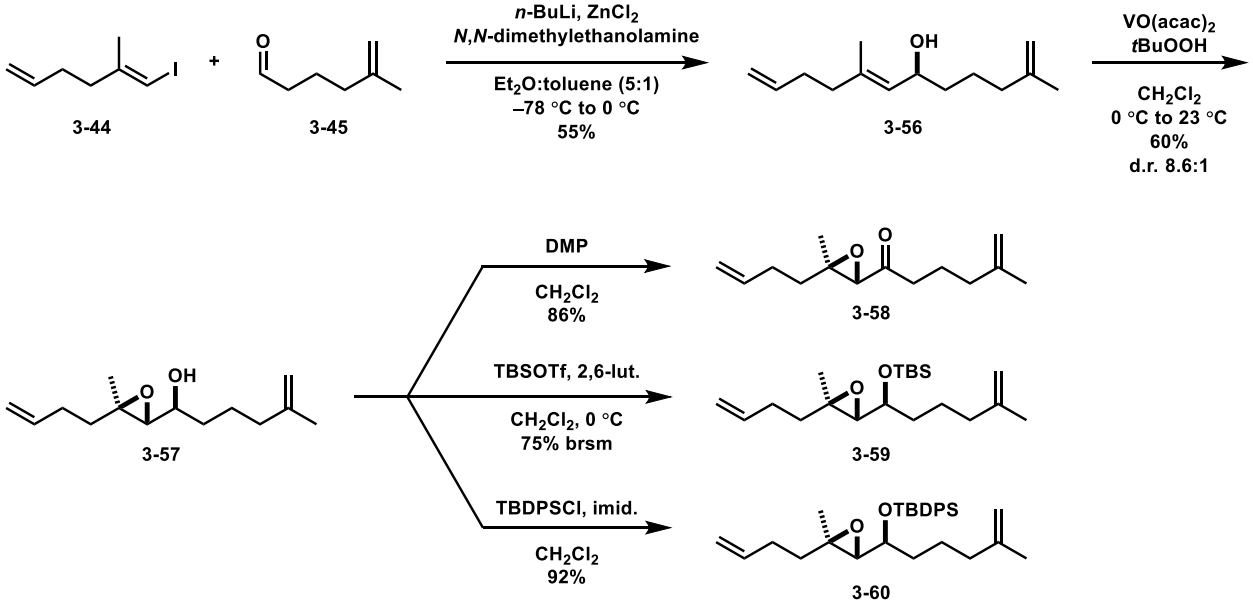
Scheme 3-7. Synthesis of the aldehyde **3-45**.

Alternatively, the aldehyde **3-45** could be accessed by a different sequence, shown in Scheme 3-8. Mesylation of 3-methyl-3-buten-1-ol **3-52** gave the mesylate **3-53**, which was subsequently displaced by the anion of diethyl malonate to generate the diester **3-54**. Decarboalkoxylation of **3-54** at 180 °C in dimethyl sulfoxide (DMSO) afforded the mono ester **3-55**.[13] Reduction of the ester **3-55** with lithium aluminum hydride afforded the alcohol **3-51**, which could then be oxidized as previously described to afford the aldehyde **3-45**.



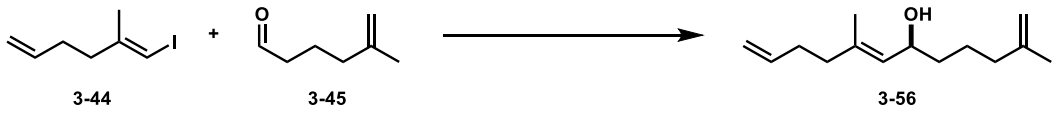
Scheme 3-8. Alternate synthetic route to access the aldehyde **3-45**.

With the coupling partners **3-44** and **3-45** in hand, several ring-closing metathesis (RCM) precursors **3-58**, **3-59**, and **3-60** could be accessed (Scheme 3-9). Lithium-halogen exchange of the vinyl iodide **3-44** with *n*-butyllithium, followed by transmetallation with zinc (II) chloride ($ZnCl_2$), afforded the vinylzinc intermediate which was then added to the electrophilic aldehyde **3-45** in the presence of the hydroxylamine ligand, *N,N*-dimethylethanolamine, to afford the allylic alcohol **3-56** in 55% yield. The aminoalcohol ligand was found to be necessary for full conversion to the allylic alcohol with no undesired side reactions (Table 3-2). Hydroxyl-directed epoxidation of the allylic alcohol **3-56** in the presence of vanadyl acetylacetonate [$VO(acac)_2$)] afforded the epoxy alcohol **3-57** in 60% yield with a diastereomeric ratio (d.r.) of 8.6:1.[14]



Scheme 3-9. Synthesis of the RCM precursors **3-58**, **3-59**, and **3-60**.

Table 3-2. Optimization of coupling between the vinyl iodide **3-44** and the aldehyde **3-45**.



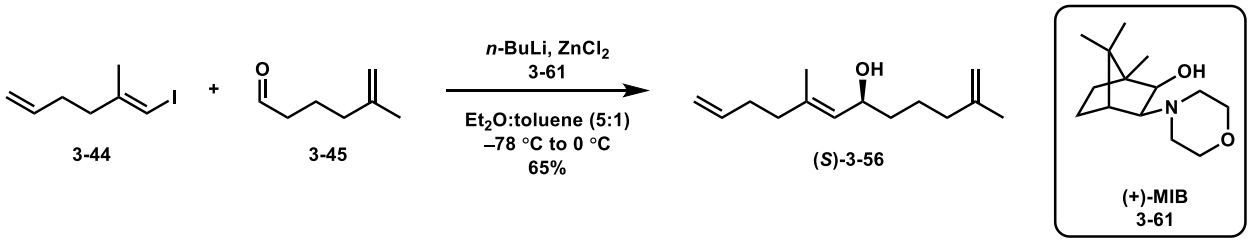
3-44 3-45 3-56

Entry	Reagents	Solvent	Temp. (°C)	Yield of **3-56** (%)
1	*n*-BuLi	THF	−78 to 23	44% + major side product
2	*n*-BuLi, $ZnCl_2$	Et_2O:PhMe	−78 to 23	11%
3	*n*-BuLi, $ZnCl_2$, ligand	Et_2O:PhMe	−78 to 0	65%
4	Mg	Et_2O	35	N.R.
5	$CrCl_2$, $NiCl_2$(dppp), Cp_2ZrCl_2, Mn, LiCl	MeCN	23	Unidentifiable mixture

A number of chiral ligands, mainly β-aminoalcohols, have been shown to enantioselectively catalyze the addition of organozinc reagents to aldehydes. 3-*exo*-*N*-Morpholinoisoborneol (MIB) has emerged as a useful chiral ligand for this purpose, promoting yields up to 98% and *ee*'s as high as 99%. The advantages of MIB over other known chiral liagnds include ease of synthesis, stability to air, and success with aliphatic aldehydes. Admittedly, enantioselectivity begins to erode in the case of straight-chain aliphatic aldehydes, but *ee*'s up to 91% in these cases could still be achieved.[15]

For the enantioselective addition of the organozinc intermediate derived from **3-44** to the aldehyde **3-45**, (2*R*)-(+)-3-*exo*-*N*-morpholinoisoborneol [(+)-MIB] **3-61** was employed as a chiral ligand to generate the allylic alcohol **(*S*)-3-56** in 65% yield (Scheme 3-10). Various

attempts were made to resolve the mixture of enantiomers using chiral high-performance liquid chromatography (HPLC). No separation of the racemic mixture of the allylic alcohol **3-56** was achieved, even though several different chiral columns were used. The allylic alcohol **3-56** as well as the enantioenriched compound, **(*S*)-3-56**, were converted to the corresponding benzoates. Unfortunately, no separation of the enantiomers of the benzoate derivatives was achieved either. Difficulty in scaling up the allylic alcohol **3-56** has made it impractical to find suitable conditions for resolution with chiral chromatography at this stage.[16]

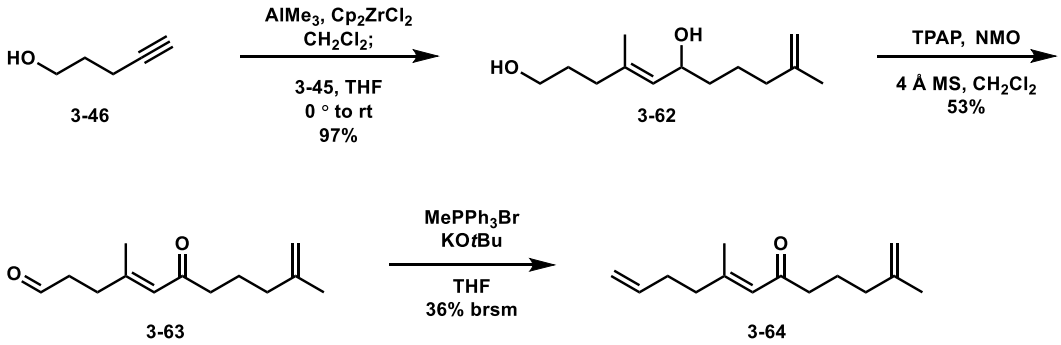


Scheme 3-10. Coupling of the vinyl iodide **3-44** and the aldehyde **3-45** in the presence of (+)-MIB **3-61** to afford **(*S*)-3-56** with undeteremined *ee*.

Oxidation of the alcohol **3-57** with DMP provided the epoxy ketone **3-58** (Scheme 3-9). Alternatively, treatment of the epoxy alcohol **3-57** with *tert*-butyldimethylsilyl trifluoromethanesulfonate and 2,6-lutidine or *tert*-butyldiphenylsilyl chloride and imidazole provided the silyl ethers **3-59** and **3-60** respectively.

One additional precursor for the RCM reaction, the enone **3-64**, was explored (Scheme 3-11). Carboalumination of 4-pentyn-1-ol **3-46**, followed by quenching with the aldehyde **3-45**, afforded the diol **3-62** in 97% yield. Double oxidation of the diol with tetrapropylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO) gave the keto aldehyde **3-63** in 53% yield. Selective Wittig olefination of the aldehyde moiety over the ketone moiety of **3-63** with

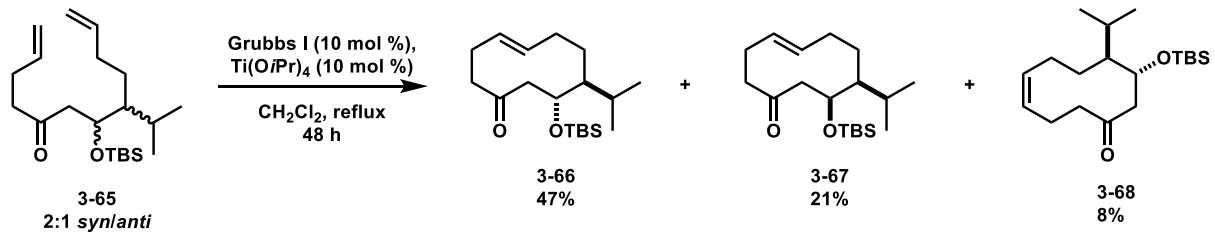
methyltriphenylphosphonium bromide and potassium *tert*-butoxide afforded the enone **3-64** in 36% yield based on recovered starting material.



Scheme 3-11. Synthesis of the enone **3-64**.

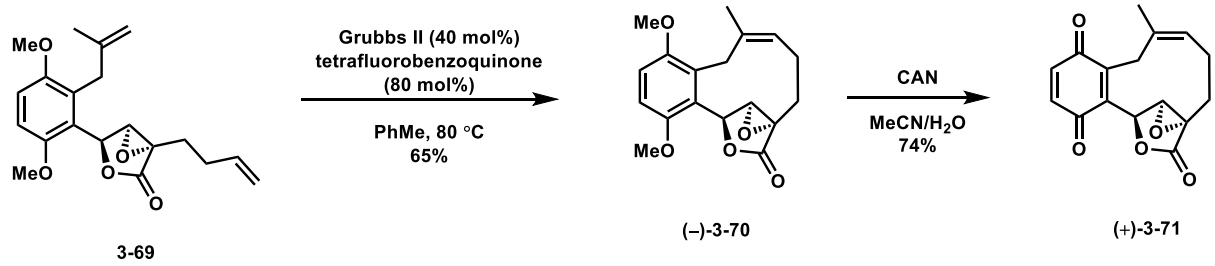
Many methods of ring construction exist in organic synthesis. Cycloadditions, cyclizations, and ring transformations are common methods and have shown great versatility in organic synthesis, especially total synthesis. Ring-closing metathesis, in which a metal carbene complex catalyzes the conversion of a nonconjugated diene to a cyclic alkene, has also established itself as a popular method. Regardless of the approach to ring-closure, medium-sized rings, especially carbocycles, have historically been the most difficult to prepare due to enthalpic and entropic arguments. Successful examples of medium-sized ring formation with ring-closing metathesis feature substrates that contain some sort of conformational constraint.[17] Nevalainen and coworkers reported the first successful use of RCM to target a 10-membered carbocycle, (±)-9-(*tert*-butyldimethylsilyloxy)-8-isopropylcyclodec-4-enone (Scheme 3-12). During their optimization studies, they noted that they initially observed only oligomers and unreacted starting material. Eventually, they installed a bulky *tert*-butyldimethylsilyl (TBS) group as a conformational control element to facilitate ring closure. Shown in Scheme 3-12 is their key RCM step. They employed a binary Grubbs first generation catalyst/Ti(O*i*Pr)$_4$ system, which allowed the Lewis acid

catalyst to coordinate to the carbonyl group of the intermediate **3-65** and confer maximal conformational constraint on the bis-olefin. The total yield of cyclization was 76% with an 11:1 ratio of *E*:*Z* alkene isomers being formed. They obtained a mixture of *syn*/*anti* and *E*/*Z* isomers **3-66**, **3-67**, **3-68**.[18]



Scheme 3-12. First reported use of ring-closing metathesis to form a 10-membered carbocycle by Nevalainen and coworkers.

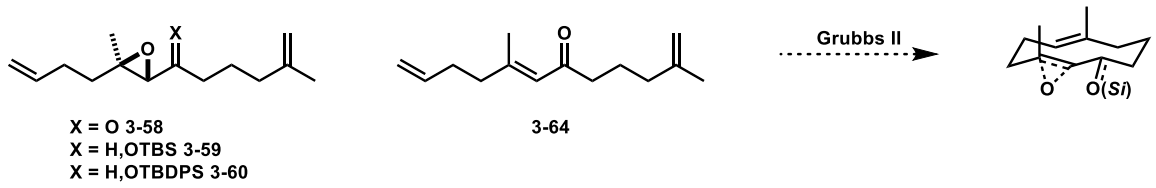
One additional example of a successful application of RCM to the formation of a 10-membered carbocycle is shown in Scheme 3-13. In an effort to synthesize *ent*-clavilactone B (+)-**3-71**, RCM was used to close the 10-membered carbocycle. Possibly the most challenging aspect of this ring-closure was the presence of a trisubstituted alkene in the intermediate diene, which is known to impede RCM. Slow addition of Grubbs second generation catalyst and tetrafluorobenzoquinone to a 0.03 M solution of diene **3-69** in toluene at 80 °C afforded the clavilactone A dimethyl ether (−)-**3-70** in 65% yield. Oxidation then provided the desired target, *ent*-clavilactone B (+)-**3-71**.[19]



Scheme 3-13. Ring-closing metathesis as a key step in the total synthesis of *ent*-clavilactone B **(+)-3-71**.

Results of our initial attempts at ring-closing metathesis with the four proposed substrates are shown in Table 3-3. We performed the initial screenings with Grubbs second generation catalyst. We varied solvent and temperature, and all reactions were run under extremely dilute conditions. Titanium isopropoxide was added to the diene **3-64** in an effort to chelate the ketone and draw the substrate into a favorable conformation for ring-closure.[18] Unfortunately, this did not prove beneficial in our system. Benzoquinone is commonly added to metathesis reactions to suppress double bond isomerization caused by the ruthenium hydride byproduct of catalyst decomposition.[20] The biggest impediment we faced while trying to optimize ring-closing metathesis was competing cross-metathesis, leading to the homo-dimer of the RCM precursor. Given the difficulty of ring-closing metathesis on medium-sized rings, this was not unexpected. As in the work of Nevalainen, *et al.*, we envisioned that a bulky silyl group at C6 would impose a conformational constraint upon the molecule to promote ring-closing metathesis.[18] MM2 calculations show the lowest energy conformation for each substrate (Figure 3-4). The lowest energy conformations for the silyl ethers **3-59** and **3-60**, containing the bulky *tert*-butyldimethylsilyl and *tert*-butyldiphenylsilyl groups, respectively, show the two alkene units in closer proximity to each other than in any other substrates. Indeed, the diene **3-60** was the only substrate for which we observed ring-closing metathesis. Slow addition of dilute solutions of the catalyst and benzoquinone to a dilute solution of the diene **3-60**, followed by refluxing for 20 h, led to a small amount (6% isolated yield) of the ring-closed product **3-76**. The homo-dimer **3-74** (Figure 3-5) was still the major product, and an additional amount of the carbocycle **3-76** was inseparable from the reaction products.

Table 3-3. Initial attempts at ring-closing metathesis on the dienes **3-58**, **3-59**, **3-60**, and **3-64**.



Entry	Diene	Solvent	T (°C)	Time (h)	Conc.[d]	Additive	Result
1[a]	**3-58**	CH_2Cl_2	23	48	30	---	Homodimer and starting material
2[a]	**3-58**	PhMe	80	24	1	---	Homodimer and starting material
3[a]	**3-64**	CH_2Cl_2	35	16	2	---	Homodimer and starting material
4[b]	**3-64**	PhMe	110	16	5	$Ti(O\textit{i}Pr)_4$	Homodimer and starting material
5[a]	**3-59**	CH_2Cl_2	35	72	2	1,4-benzoquinone	Homodimer and starting material
6[b]	**3-60**	PhMe	110	48	2	---	Homodimer and starting material
7[b]	**3-60**	PhH	80	72	2	---	Homodimer and starting material
8[c]	**3-60**	PhMe	80	20	3	1,4-benzoquinone	6% **3-76**

[a]Method 1: Everything added all at once under dilute conditions
[b]Method 2: Solution of substrate added to dilute (1 mM) solution of Grubbs catalyst
[c]Method 3: Dilute (1 mM) solution of Grubbs catalyst and dilute (2 mM) solution of benzoquinone added simultaneously to a solution of substrate
[d]Concentration of substrate (mM)

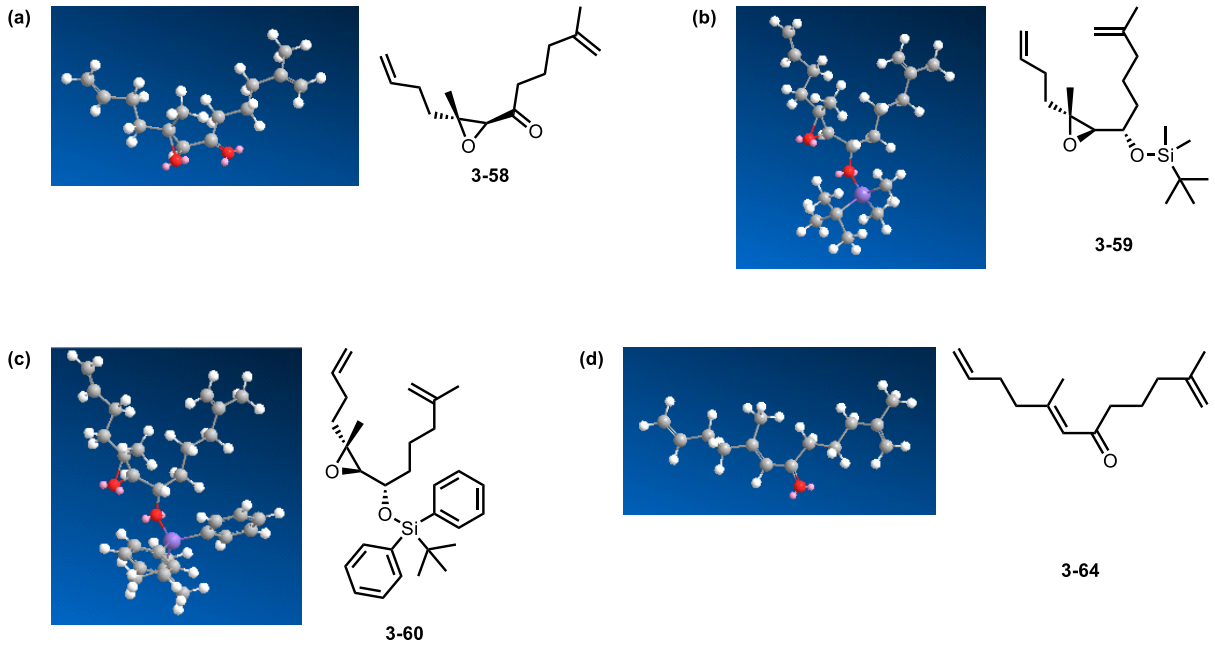


Figure 3-4. Structures of the dienes **3-58** (a), **3-59** (b), **3-60** (c), and **3-64** (d) in their lowest energy conformations as computed by MM2 energy minimizations. Shown next to the three-dimensional figures are the corresponding skeletal formulas. Energy minimizations performed with Chem3D Pro.

The cross-metathesis (CM) products generated from each diene, **3-72**, **3-73**, **3-74**, and **3-75**, are shown in Figure 3-5. In each case, the mono-substituted, rather than the di-substituted, alkenes participate in metathesis. Careful analysis of ^{1}H NMR integration and chemical shifts confirms this assessment. Specifically, the characteristic *exo*-methylene vinyl peaks are still present in the ^{1}H NMR spectrum and integrate to four protons. The terminal vinyl peaks present in the starting material are no longer present, and instead the spectrum shows a single vinyl shift that integrates to two protons, corresponding to the central alkene in the cross-metathesis products.[21] We assume that the *E*-isomer of the homodimers are the major products formed but we have not shown this conclusively.

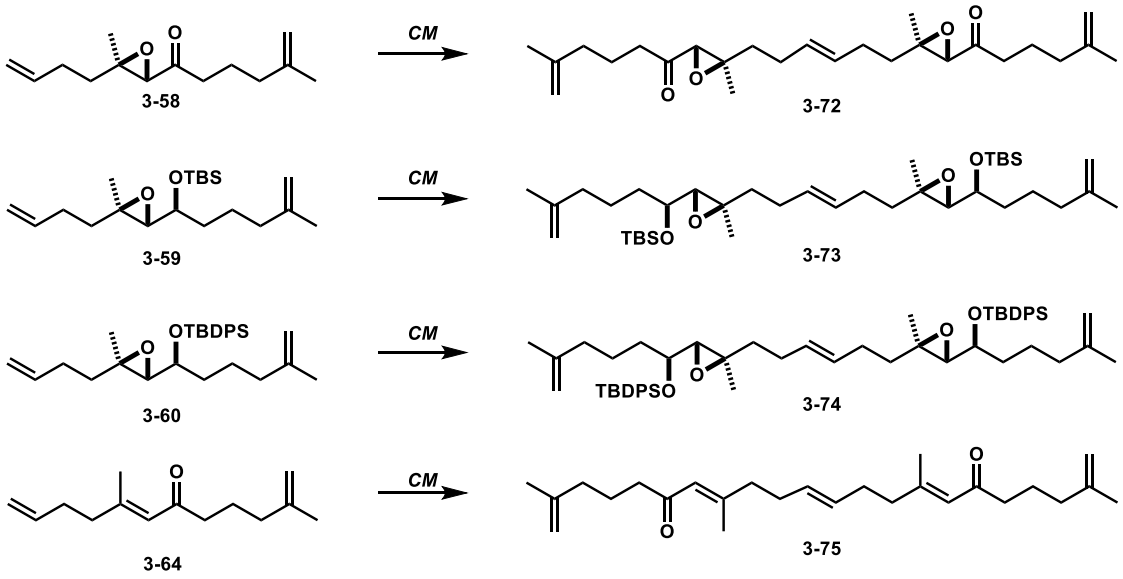
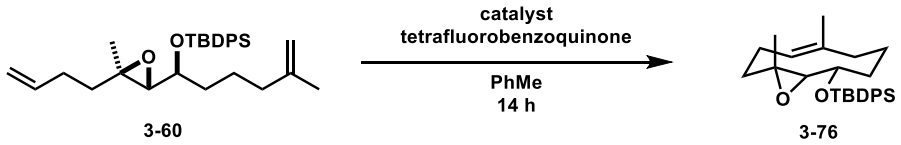


Figure 3-5. Cross-metathesis products **3-72**, **3-73**, **3-74**, and **3-75**.

We chose to carry the diene **3-60** forward for further optimization. We tested different metathesis catalysts, e.g., the Grubbs first generation catalyst (Grubbs I), the Grubbs third generation catalyst (Grubbs III), and the Grubbs-Hoveyda second generation catalyst (Grubbs-Hoveyda II). As shown in Table 3-4, the best results were obtained under conditions catalyzed by the Grubbs-Hoveyda second generation catalyst, where we obtained the ring-closed product **3-76** and observed no remaining starting material or significant side products (entry 4). The homo-dimer was still produced as a major product, although the ratio of **3-76** to **3-74** was greater than that of reactions with any other catalyst. Metathesis with the Grubbs I catalyst resulted in the homo-dimer **3-74** as the only product. Incomplete addition of the solution of the Grubbs II catalyst also resulted in the homo-dimer **3-74** as the sole product (entry 2). Higher temperature and reaction with the Grubbs III catalyst led to complex mixtures of many products. Interestingly, the method of addition proved crucial in attempts to optimize the RCM reaction. When the substrate was slowly added to the metathesis catalyst, no RCM product was observed and the major products were starting material and homo-dimer. However, as in the synthesis of

ent-clavilactone B by Larrosa and coworkers, when the catalyst and benzoquinone were simultaneously added dropwise to the substrate, the RCM product was observed.[19] Significantly in our study, only one double bond isomer was isolated. We could not determine the double bond geometry of compound **3-76**, as no two-dimensional NMR technique was determined to be appropriate and the compound was not crystalline.

Table 3-4. Further optimization of ring-closing metathesis on the diene **3-60**.



3-60 **3-76**

Method of addition: Dilute solutions of catalyst (1 mM) and benzoquinone (2 mM) were added very slowly simultaneously via syringe pumps to a dilute (3 mM) solution of **3-60**.

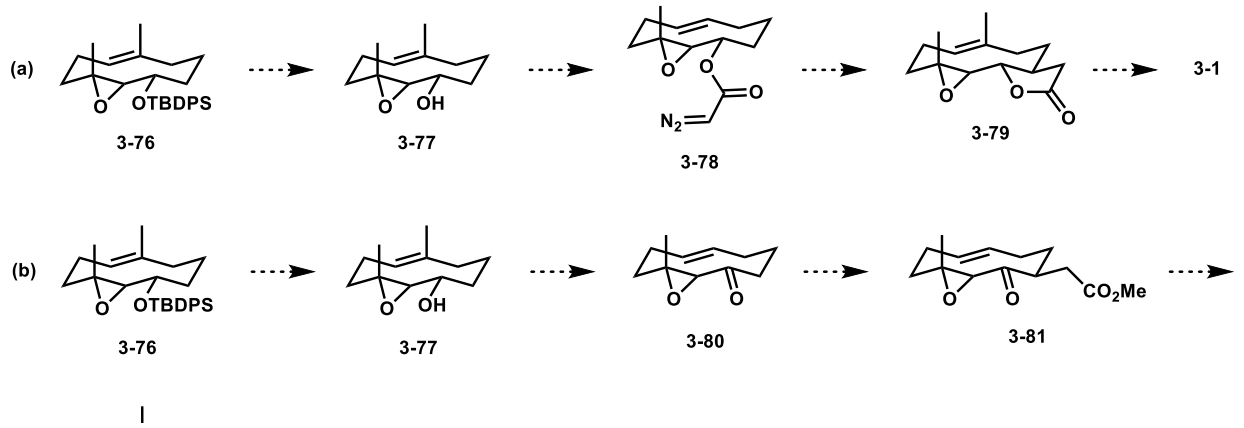
1	Grubbs II	80	6% **3-76**
2[a]	Grubbs II	80	**3-60** + **3-74**
3	Grubbs I	80	**3-60** + **3-74**
4	Grubbs-Hoveyda II	80	**3-76** + **3-74**
5	Grubbs-Hoveyda II	110	Complex mixture
6	Grubbs III	80	Complex mixture

[a]Addition was stopped after 1/6 completion to identify sole product shown on thin-layer chromatography (TLC).

Conclusion and Future Work

Shown in Scheme 3-14 are two proposed routes to the completion of the total synthesis of parthenolide **3-1**. In the first route (a), desilylation of **3-76** could afford the alcohol **3-77**. After installation of a diazoacyl unit to generate **3-78**, rhodium-catalyzed carbene insertion could

afford the lactone **3-79**. Finally, Eschenmoser methenylation could install the *exo*-methylene unit and complete the total synthesis of parthenolide **3-1**. Alternatively, a second route (b) could be explored. The alcohol **3-77** could be oxidized to the ketone **3-80**. Alkylation of the kinetic enolate of the ketone **3-80** could provide the ester **3-81**, which could then be cyclized to the lactone **3-79**. Once again, methenylation could afford parthenolide **3-1**.



Scheme 3-14. Two possible routes toward the completion of the total synthesis of parthenolide **3-1**.

Further optimization of the key ring-closing metathesis step as well as the enantioselective coupling of the vinyl iodide **3-44** and the aldehyde **3-45** should be done. The *ee* of the coupling step may be determined by converting the allylic alcohol **3-56** to a more polar derivative than the benzoate, which may afford better separation. The double bond geometry must be determined at a later step, possibly by X-ray crystallography or by conversion to a known material such as parthenolide **3-1**. Finally, if the double bond geometry is found to be *Z* rather than *E*, it may still be possible to target other similar germacrane natural products that contain a *Z* alkene.

Experimental Section

General: All reactions were carried out in flame-dried glassware under an argon atmosphere using freshly distilled solvents unless otherwise noted. Reagents were purchased from Sigma-Aldrich, Acros, Alfa Aesar or Oakwood and used without further purification. Unless otherwise stated, reactions were conducted at room temperature (approximately 23 °C). Reactions were monitored by thin-layer chromatography (TLC) using SORBTECH Silica G TLC plates w/UV254 followed by UV visualization and iodine staining. Flash column chromatography was performed using SilicaFlash P60 (60 Å, 40-63 μM) from SiliCycle Inc unless otherwise noted. ^{1}H NMR spectra were recorded on Bruker spectrometers (400 and 500 MHz) and are reported in parts per million (ppm, δ). Splitting patterns are designated by: s, singlet; d, doublet; t, triplet; m, multiplet; b, broad. ^{1}H NMR chemical shifts are referenced to the residual solvent peak at 7.26 ppm for $CDCl_3$. ^{13}C NMR spectra were acquired on Bruker spectrometers (100 and 125 MHz) and are reported in parts per million (ppm, δ). ^{13}C data are referenced to the residual solvent peak at 77.91 ppm for $CDCl_3$. The reported ratios of the isomeric products were determined by careful integration of the appropriate absorptions in the ^{1}H NMR spectra of the mixture. High-resolution mass spectrometry data was obtained using a Thermo Fisher Scientific Exactive Plus with IonSense ID-CUBE DART source.

5-Methylhex-5-enal (3-45): To a solution of the Dess-Martin Periodinane (DMP, 5.97 g, 14.1 mmol, 1.2 equiv.) in dichloromethane (50 mL) was slowly added a solution of the alcohol **3-51** (1.34 g, 11.7 mmol, 1.0 equiv.) in dichloromethane (50 mL). The solution was allowed to stir overnight and then quenched with saturated aqueous sodium thiosulfate ($Na_2S_2O_3$, 75 mL) and saturated aqueous sodium bicarbonate ($NaHCO_3$, 20 mL). The solution was allowed to stir until

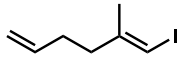
the bubbling ceased and the layers cleared. The aqueous layer was extracted with diethyl ether (3 x 30 mL), and the organic layers were combined, washed with saturated aqueous $Na_2S_2O_3$ (45 mL), saturated aqueous $NaHCO_3$ (45 mL), and brine (45 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude residue was purified via vacuum distillation as described in the literature to give the aldehyde **3-45** (522 mg, 40%). The spectral data are in accordance with those reported in the literature.[22]

(4*E*)-5-Iodo-4-methyl-4-pentenal (3-48): To a solution of the Dess-Martin Periodinane (10.9 g, 25.8 mmol, 1.2 equiv.) in 90 mL dichloromethane was added the alcohol **3-47** (4.86 g, 21.5 mmol, 1.0 equiv.) in toluene (90 mL) dropwise via an addition funnel. The reaction was stirred for 12 h and then quenched with sodium hydroxide (NaOH, 1.4 M, 75 mL) and allowed to stir until the two phases cleared. The aqueous layer was extracted with diethyl ether (3 x 30 mL), and the organic layers were combined, washed with NaOH (1.4 M, 30 mL), saturated aqueous sodium thiosulfate (3 x 25 mL), water (30 mL), and brine (30 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to give the aldehyde **3-48**. The spectral data for **3-48** are in accordance with those reported in the literature.[23]

(5*E*)-1-Iodo-2-methylhexa-1,5-diene (3-44): To a solution of freshly dried methyltriphenylphosphonium bromide (15.7 g, 43.9 mmol, 3.0 equiv.) in toluene (50 mL) was added potassium *tert*-butoxide (4.44 g, 39.5 mmol, 2.7 equiv.). This solution was allowed to stir for 1 h 15 min. During this time the solution became bright yellow, indicating formation of the ylide. The solution was then cooled to 0 °C, and the aldehyde **3-48** (3.28 g, 14.6 mmol, 1.0 equiv.) in toluene (50 mL) was added dropwise via an addition funnel. Upon addition of the

aldehyde, the solution turned orange. The mixture was allowed to stir for 2 h and was then quenched with saturated aqueous ammonium chloride (30 mL). The aqueous layer was extracted with diethyl ether (3 x 15 mL), and the organic layers were combined, washed with water (20 mL), saturated aqueous sodium thiosulfate (2 x 20 mL), and brine (20 mL), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The resulting residue was purified via flash column chromatography using aluminum oxide (100% hexanes, Brockman activity I, neutral, activated, 150 mesh, 58 Å from Sigma Aldrich) to afford the iodide **3-44** as a colorless liquid (1.74 g, 37% over 3 steps); R_f 0.82 (10% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$, δ):



3-44

5.90 (q, *J* = 1.0 Hz, 1H)

5.76 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H)

5.02 (ddt, *J* = 17.0, 1.5, 1.5 Hz, 1H)

4.98 (ddt, *J* = 10.0, 1.5, 1.5 Hz, 1H)

2.29 (t, *J* = 7.0 Hz, 2H)

2.20 (t, *J* = 6.5 Hz, 2H)

1.84 (d, *J* = 1.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 147.4, 137.4, 114.6, 75.0, 38.9, 31.9, 23.9.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_7H_{12}I$ 222.99782; found, 223.06299.

(*S*)-2,8-Dimethyldodeca-1,7,11-trien-6-ol [(*S*)-3-56]: To a cooled (−78 °C) solution of the vinyl iodide **3-44** (340 mg, 1.53 mmol, 4.0 equiv.) in diethyl ether (5 mL) was added *n*-butyllithium (0.60 mL, 1.53 mmol, 4.0 equiv.) dropwise. The mixture was allowed to stir at that temperature for 40 min to allow the lithium-halogen exchange to occur. $ZnCl_2$ (0.77 mL, 0.767 mmol, 2.0 equiv.) was then added dropwise and the solution allowed to warm to 23 °C. (2*R*)-(+)-3-*exo*-(*N*-morpholino)isoborneol [(+)-MIB, 6.0 mg, 0.0230 mmol, 0.06 equiv.] was added and the solution was cooled to 0 °C and allowed to stir for 30 min. A solution of the aldehyde **3-45** (43 mg, 0.383 mmol, 1.0 equiv.) in toluene (1 mL) was cannulated into the reaction flask dropwise. The mixture was allowed to stir at 0 °C for 50 min, at which point TLC indicated that the reaction was complete. Saturated ammonium chloride (5 mL) was added to quench the reaction and the organic layer was extracted with diethyl ether (3 x 3 mL). The combined organic layers were then washed with brine (5 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude residue was purified via flash column chromatography (4-7% ethyl acetate/hexanes) on silica gel to afford the alcohol **(*S*)-3-56** as a colorless oil (52 mg, 65%); R_f 0.08 (6% ethyl acetate/hexanes).

^1H NMR (500 MHz, $CDCl_3$, δ):

5.78 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H)

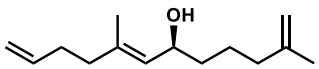
5.18 (dd, *J* = 9.0, 1.0 Hz, 1H)

5.01 (dd, *J* = 17.0, 1.5 Hz, 1H)

4.95 (bd, *J* = 10.5 Hz, 1H)

4.70 (s, 1H)

4.67 (s, 1H)



(*S*)-3-56

4.37 (ddd, *J* = 8.5, 8.5, 6.5 Hz, 1H)

2.21-2.14 (m, 2H)

2.09 (t, *J* = 7.5 Hz, 2H)

2.02 (t, *J* = 7.5 Hz, 2H)

1.70 (s, 3H)

1.68 (d, *J* = 1.0 Hz, 3H)

1.62-1.40 (m, 4H)

1.27 (bs, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 145.8, 138.2, 138.0, 128.3, 114.7, 110.0, 68.5, 38.9, 37.7, 37.3, 32.0, 23.4, 22.3, 16.6.

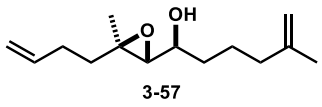
HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{14}H_{25}O$ 209.18999; found, 209.19038.

2,8-Dimethyldodeca-1,7,11-trien-6-ol (3-56): The procedure outlined for the synthesis of **(*S*)-2,8-dimethyldodeca-1,7,11-trien-6-ol [(*S*)-3-56]** was followed, with *N,N,*-dimethylethanolamine substituted for (+)-MIB, to afford **3-56** (65 mg, 55%). The spectral data match that of **3-56** given above.

(±)-1*S*-((2*R*,3*R*)-3-(But-3-en-1-yl)-3-methyloxiran-2-yl)-5-methylhex-5-en-1-ol (3-57) and (±)-1*S*-((2*S*,3*S*)-3-(But-3-en-1-yl)-3-methyloxiran-2-yl)-5-methylhex-5-en-1-ol (SI-3-1): To a solution of the allylic alcohol **3-56** (44 mg, 0.211 mmol, 1.0 equiv.) in

dichloromethane (2.1 mL) at 0 °C was added vanadyl acetylacetonate (9.0 mg, 0.0317 mmol, 0.15 equiv.). The solution was allowed to stir at 0 °C for 15 min before *tert*-butyl hydroperoxide (70 µL, 0.385 mmol, 1.8 equiv.) was added and the solution was allowed to warm to 23 °C and stir overnight. Water (5 mL) was added and the aqueous layer was extracted with dichloromethane (3 x 3 mL). The combined organic layers were washed with water (2 x 5 mL) and brine (5 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude ^1H NMR spectrum showed a diastereomeric ratio of 8.5:1. The crude mixture was subjected to flash column chromatography on silica gel (10% ethyl acetate/hexanes). The major diastereomer **3-57** eluted as the more polar fraction (25 mg, 53%); R_f 0.26 (20% ethyl acetate/hexanes).

^1H NMR (500 MHz, $CDCl_3$, δ):



3-57

5.79 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H)

5.04 (ddt, *J* = 17.0, 1.5, 1.5 Hz, 1H)

4.98 (ddt, *J* = 10.0, 1.5, 1.5 Hz, 1H)

4.72 (bs, 1H)

4.67 (bs, 1H)

3.50 (ddd, *J* = 8.0, 8.0, 5.5 Hz, 1H)

2.70 (d, *J* = 8.0 Hz, 1H)

2.22-2.08 (m, 2H)

2.05 (t, *J* = 6.5 Hz, 2H)

1.75 (ddd, *J* = 14.0, 9.5, 6.0 Hz, 1H)

1.72 (s, 3H)

1.66-1.44 (m, 6H)

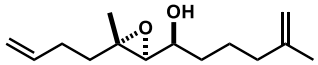
1.30 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 145.4, 137.7, 115.1, 110.3, 70.2, 66.9, 61.9, 37.9, 37.6, 33.3, 29.4, 22.9, 22.3, 17.3.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{14}H_{25}O_2$ 225.18491; found, 225.18430.

The minor diastereomer **SI-3-1** eluted as a less polar fraction (4.0 mg, 8.5%); R_f 0.32 (20% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$, δ):



SI-3-1

5.82 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H)

5.04 (ddt, *J* = 17.0, 1.5, 1.5 Hz, 1H)

4.98 (ddt, *J* = 10.5, 1.5, 1.5 Hz, 1H)

4.71 (bs, 1H)

4.68 (bs, 1H)

3.54 (ddd, *J* = 7.5, 7.5, 4.5 Hz, 1H)

2.65 (d, *J* = 7.5 Hz, 1H)

2.24-2.12 (m, 2H)

2.05 (t, *J* = 7.0 Hz, 2H)

1.74 (ddd, *J* = 13.5, 9.0, 6.0 Hz, 1H)

1.71 (s, 3H)

1.58-1.51 (m, 5H)

1.37 (s, 3H)

1.25 (bs, 1H).

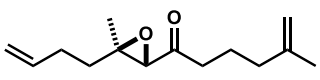
^{13}C NMR (125 MHz, $CDCl_3$, δ): 145.5, 138.0, 115.0, 110.2, 70.0, 65.4, 60.8, 37.7 (2), 34.8, 29.6, 23.0, 22.3, 16.6.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{14}H_{25}O_2$ 225.18491; found, 225.18444.

(±)-1-((2*S*,3*R*)-3-(But-3-en-1-yl)-3-methyloxiran-2-yl)-5-methylhex-5-en-1-one (3-58): To a solution of epoxy-alcohol **3-57** (7.0 mg, 0.0312 mmol, 1.0 equiv.) in 0.4 mL dichloromethane was added Dess-Martin Periodinane (49 mg, 0.116 mmol, 3.7 equiv.). The solution was allowed to stir overnight, and then diluted with ethyl acetate (3 mL), washed with saturated aqueous sodium thiosulfate (3 mL), saturated aqueous sodium bicarbonate (3 mL), and brine (3 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The resulting residue was purified over a silica gel plug (20% ethyl acetate/hexanes) to afford **3-58** as a colorless oil (6.0 mg, 86%); R_f 0.60 (20% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

5.81 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H)



3-58

5.06 (ddt, *J* = 17.0, 1.5, 1.5 Hz, 1H)

5.01 (ddt, *J* = 10.0, 1.5, 1.5 Hz, 1H)

4.73 (m, 1H)

4.67 (m, 1H)

3.40 (s, 1H)

2.52 (ddd, *J* = 17.0, 8.0, 6.5 Hz, 1H)

2.46 (ddd, *J* = 17.0, 8.0, 6.5 Hz, 1H)

2.26-2.14 (m, 2H)

2.03 (t, *J* = 7.5 Hz, 2H)

1.82 (ddd, *J* = 14.0, 9.0, 6.5 Hz, 1H)

1.76 (m, 2H)

1.70 (s, 3H)

1.65 (ddd, *J* = 14.0, 9.0, 6.5 Hz, 1H)

1.57 (s, 3H).

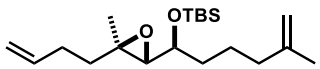
^{13}C NMR (125 MHz, $CDCl_3$, δ): 206.2, 144.7, 137.3, 115.5, 110.8, 64.5, 63.2, 40.1, 37.4, 37.0, 29.3, 22.1, 20.9, 16.2.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{14}H_{23}O_2$ 223.16926; found, 223.16837.

(±)-((1*S*-((2*R*,3*R*)-3-(But-3-en-1-yl)-3-methyloxiran-2-yl)-5-methylhex-5-en-1-yl)-oxy)(*tert*-butyl)dimethylsilane (3-59): To a solution of the epoxy alcohol **3-57** (80 mg,

0.357 mmol, 1.0 equiv.) in dichloromethane (0.9 mL) at 0 °C was added 2,6-lutidine (90 µL, 0.773 mmol, 2.2 equiv.) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (125 µL, 0.544 mmol, 1.5 equiv.). The solution was stirred for 3 h, water (5 mL) was added, and the aqueous layer was extracted with dichloromethane (3 x 3 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The resulting residue was purified via flash column chromatography over silica gel (0-20% ethyl acetate/hexanes) to afford the silyl ether **3-59** as a colorless oil (45 mg, 37%, 75% brsm); R_f 0.83 (20% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$, δ):



3-59

5.78 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H)

5.02 (ddt, *J* = 17.0, 1.5, 1.5 Hz, 1H)

4.96 (ddt, *J* = 10.5, 1.5, 1.5 Hz, 1H)

4.71 (s, 1H)

4.66 (s, 1H)

3.43 (ddd, *J* = 8.5, 8.5, 4.0 Hz, 1H)

2.67 (d, *J* = 8.0 Hz, 1H)

2.20-1.95 (m, 4H)

1.75 (m, 1H)

1.71 (s, 3H)

1.65-1.33 (m, 5H)

1.25 (s, 3H)

0.90 (s, 9H)

0.12 (s, 3H)

0.07 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 145.6, 137.8, 115.0, 110.1, 72.1, 67.2, 60.4, 38.1, 37.6, 34.1, 29.5, 25.9, 22.9, 22.3, 18.2, 17.6, -4.17, -5.01.

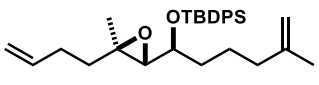
(±)-((1*S*-((2*R*,3*R*)-3-(But-3-en-1-yl)-3-methyloxiran-2-yl)-5-methylhex-5-en-1-yl)oxy)(*tert*-butyl)diphenylsilane (3-60): To a solution of the alcohol **3-57** (50 mg, 0.223 mmol, 1.0 equiv.) in dichloromethane (2.2 mL) was added imidazole (96 mg, 1.41 mmol, 6.3 equiv.) followed by *tert*-butyldiphenylsilyl chloride (0.17 mL, 0.654 mmol, 3.0 equiv.). The solution was allowed to stir for 14 h. Water (2 mL) was added and the mixture was diluted with diethyl ether. The aqueous layer was extracted with diethyl ether (3 x 2 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude residue was purified via flash column chromatography over silica gel (4% ethyl acetate/hexanes) to give the silyl ether **3-60** as a colorless oil (95 mg, 92%); R_f 0.52 (6% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

7.74-7.68 (m, 4H)

7.42-7.32 (m, 6H)

5.77 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H)



3-60

5.00 (ddt, *J* = 17.0, 1.5, 1.5 Hz, 1H)

4.95 (ddt, *J* = 10.5, 1.5, 1.5 Hz, 1H)

4.63 (bs, 1H)

4.51 (bs, 1H)

3.47 (m, 1H)

2.86 (d, *J* = 8.0 Hz, 1H)

2.16-2.01 (m, 2H)

1.79 (bt, *J* = 7.5 Hz, 2H)

1.72 (ddd, *J* = 13.5, 9.5, 5.5 Hz, 1H)

1.60 (s, 3H)

1.50-1.30 (m, 5H)

1.08 (s, 9H)

1.01 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 145.4, 137.9, 136.2, 136.0, 134.4, 133.7, 129.5, 129.4, 127.4, 127.3, 114.9, 110.0, 72.7, 66.7, 60.4, 38.0, 37.6, 34.5, 29.4, 27.0, 22.4, 22.2, 19.5, 17.5.

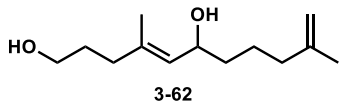
HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{30}H_{43}O_2Si$ 463.30268; found, 463.30379.

(6*R*,*S*)-(*E*)-4,10-Dimethylundeca-4,10-diene-1,6-diol (3-62): Zirconocene dichloride (188 mg, 0.643 mmol, 0.33 equiv.) was dissolved in dichloromethane (15 mL) and the solution

was cooled to 0 °C. Trimethylaluminum (2.8 mL, 5.61 mmol, 2.9 equiv.) was added dropwise and the solution was stirred at 0 °C for 25 min. 4-Pentyn-1-ol **3-46** (0.20 mL, 2.15 mmol, 1.1 equiv.) was added and the solution was allowed to gradually warm to 23 °C and stir for 14 h. The solution was then cooled to 0 °C, and a solution of the aldehyde **3-45** (216 mg, 1.93 mmol, 1.0 equiv.) in tetrahydrofuran (3.0 mL) was cannulated into the reaction mixture dropwise. This mixture was allowed to stir at °C for 3.5 h. The reaction was quenched with the slow addition of saturated aqueous sodium bicarbonate (15 mL) and Rochelle's salt (15 mL). The mixture was stirred overnight to allow the layers to separate. The aqueous layer was extracted with ethyl acetate (5 x 10 mL), and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude residue was purified via flash column chromatography over silica gel (50% ethyl acetate/hexanes) to afford the diol **3-62** as a colorless oil (398 mg, 97%); R_f 0.24 (50% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

5.20 (d, *J* = 8.5 Hz, 1H)



3-62

4.69 (s, 1H)

4.66 (s, 1H)

4.37 (ddd, *J* = 8.5, 8.5, 6.0 Hz, 1H)

3.63 (t, *J* = 6.5 Hz, 2H)

2.08 (t, *J* = 7.5 Hz, 2H)

2.02 (t, *J* = 7.5 Hz, 2H)

1.70 (s, 3H)

1.69 (s, 3H)

1.61-1.37 (m, 6H).

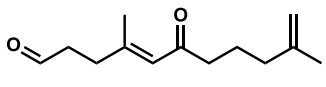
^{13}C NMR (125 MHz, $CDCl_3$, δ): 145.7, 138.1, 128.3, 110.0, 68.5, 62.6, 37.7, 37.2, 35.8, 30.6, 23.4, 22.3, 16.6.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{25}O_2$ 213.18491; found, 213.18410.

(*E*)-4,10-Dimethyl-6-oxoundeca-4,10-dienal (3-63): To a round-bottom flask containing 500 mg of 4 Å molecular sieves was added dichloromethane (20 mL), the diol **3-62** (213 mg, 1.00 mmol, 1.0 equiv.), and *N*-methylmorpholine *N*-oxide (353 mg, 3.01 mmol, 3.0 equiv.). The solution was allowed to stir at 23 °C for 40 min, at which point tetrapropylammonium perruthenate (TPAP, 34 mg, 0.0967 mmol, 0.10 equiv.) was added and the solution was allowed to stir for 2.75 h. Saturated aqueous sodium thiosulfate (10 mL) was added and after 1 h of stirring the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with saturated aqueous sodium thiosulfate (5 mL) and brine (5 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The resulting residue was purified through a pad of silica gel (50% ethyl acetate/hexanes) to afford the keto aldehyde **3-63** as a colorless oil (110 mg, 53%); R_f 0.08 (10% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$, δ):

9.79 (t, *J* = 1.0 Hz, 1H)



3-63

6.04 (q, *J* = 1.0 Hz, 1H)

4.71 (m, 1H)

4.67 (m, 1H)

2.64 (td, *J* = 7.5, 1.0 Hz, 2H)

2.45 (t, *J* = 7.5 Hz, 2H)

2.41 (t, *J* = 7.5 Hz, 2H)

2.13 (d, *J* = 1.0 Hz, 3H)

2.01 (t, *J* = 7.5 Hz, 2H)

1.76-1.71 (m, 2H)

1.70 (s, 3H).

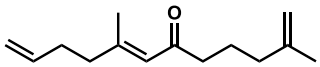
^{13}C NMR (125 MHz, $CDCl_3$, δ): 201.0, 200.7, 155.3, 145.2, 123.8, 110.4, 43.7, 41.5, 37.1, 32.9, 22.2, 21.8, 19.2.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{13}H_{21}O_2$ 209.15361; found, 209.15293.

(*E*)-2,8-Dimethyldodeca-1,7,11-trien-6-one (3-64): To a solution of freshly dried methyltriphenylphosphonium bromide (357 mg, 0.999 mmol, 1.9 equiv.) in tetrahydrofuran (2.3 mL) was added potassium *tert*-butoxide (110 mg, 0.980 mmol, 1.9 equiv.), and the solution was stirred for 50 min. A solution of the keto aldehyde **3-63** (108 mg, 0.518 mmol, 1.0 equiv.) in tetrahydrofuran (2.6 mL) was cannulated dropwise into the solution containing the newly formed ylide. The mixture was allowed to stir at 23 °C for 14 h and was quenched with saturated aqueous ammonium chloride (10 mL) and diluted with diethyl ether (15 mL). The aqueous layer was extracted with diethyl ether (3 x 5 mL), and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude

residue was purified via flash column chromatography over silica gel (4-6% ethyl acetate/hexanes) to afford the enone **3-64** as a colorless oil (25 mg, 23%, 36% brsm); R_f 0.56 (10% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$, δ):



3-64

6.05 (q, *J* = 1.0 Hz, 1H)

5.78 (ddt, *J* = 16.5, 10.5, 6.5 Hz, 1H)

5.04 (ddt, *J* = 17.0, 1.5, 1.5 Hz, 1H)

4.98 (ddt, *J* = 10.5, 1.5, 1.5 Hz, 1H)

4.71 (m, 1H)

4.67 (m, 1H)

2.41 (t, *J* = 7.5 Hz, 2H)

2.27-2.18 (m, 4H)

2.13 (d, *J* =1.5 Hz, 3H)

2.02 (t, *J* = 7.5 Hz, 2H)

1.77-1.71 (m, 2H)

1.71 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 201.2, 157.4, 145.3, 137.3, 123.5, 115.3, 110.4, 43.7, 40.4, 37.2, 31.6, 22.2, 22.0, 19.3.

General Procedure for Metathesis Method 1: To a round-bottom flask was added solvent, diene, catalyst (20-40 mol%), and additive (if applicable). The solution was allowed to stir for the indicated time and temperature. The flask was allowed to cool to 23 °C and the solvent was evaporated under reduced pressure.

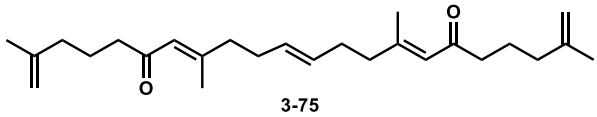
General Procedure for Metathesis Method 2: To a round-bottom flask was added solvent, catalyst (20-40 mol%), and additive (if applicable). The mixture was heated to the indicated temperature. The solution of the diene was added slowly to the reaction mixture via syringe pump or addition funnel. The reaction was allowed to stir for the indicated time, allowed to cool to 23 °C, and the solvent was removed under reduced pressure.

General Procedure for Metathesis Method 3: The diene and solvent were added to a round-bottom flask, and the solution was heated to the indicated temperature. Separate solutions of the catalyst (40 mol%) and the benzoquinone (0.8 equiv.) were simultaneously added slowly (via syringe pumps) to the diene. The solution was allowed to stir for the indicated time and cooled to 23 °C. The solvent was evaporated under reduced pressure.

(*7E*,11*E*,15*E*)-2,8,15,21-Tetramethyldocosa-1,7,11,15,21-pentaene-6,17-dione (3-75): Following the general procedure for metathesis method 1, to a round-bottom flask was added the diene **3-64** (4.0 mg, 0.0194 mmol, 1.0 equiv.), Grubbs second generation catalyst (Grubbs II, 4.0 mg, 0.00485 mmol, 0.25 equiv.), and dichloromethane (10 mL). The mixture was allowed to reflux for 16 h and then cooled to 23 °C. The solvent was removed under reduced

pressure. The crude residue was purified by preparatory thin layer chromatography (10% ethyl acetate/hexanes). The cross-metathesis product **3-75** was isolated as the most polar fraction in trace amounts.

^{1}H NMR (500 MHz, $CDCl_3$, δ):



3-75

6.03 (s, 2H)

5.40 (m, 2H)

4.71 (s, 2H)

4.67 (s, 2H)

2.40 (m, 4H)

2.18-2.08 (m, 8H)

2.15 (s, 6H)

2.02 (t, *J* = 7.5 Hz, 4H)

1.76-1.71 (pentet, *J* = 7.5 Hz, 4H)

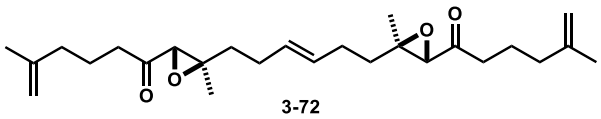
1.71 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 201.2, 157.6, 145.3, 129.8, 123.4, 110.4, 43.7, 41.1, 37.2, 30.5, 22.2, 22.0, 19.3.

(±)-1,1'-((2*S*,2'*S*,3*R*,3'*R*)-((*E*)-Hex-3-ene-1,6-diyl)bis(3-methyloxirane-3,2-diyl))bis(5-methylhex-5-en-1-one) (3-72): Following the general procedure for metathesis method 1, the diene **3-58** (6.0 mg, 0.0270 mmol, 1.0 equiv.), Grubbs second generation catalyst

(4.6 mg, 0.00540 mmol, 0.2 equiv.), and dichloromethane (1.0 mL) were added to a round-bottom flask and allowed to stir at 23 °C for 48 h. The solvent was evaporated under reduced pressure. The crude residue was purified via flash column chromatography over silica gel (6% ethyl acetate/hexanes) to afford the dimer **3-72** as a colorless oil (2.0 mg, 18%); R_f 0.35 (6% ethyl acetate/hexanes).

^{1}H NMR (500 MHz, $CDCl_3$, δ):



3-72

5.45 (m, 2H)

4.74 (s, 2H)

4.67 (s, 2H)

3.38 (s, 2H)

2.55-2.42 (m, 4H)

2.20-2.10 (m, 4H)

2.03 (t, *J* = 6.5 Hz, 4H)

1.80-1.59 (m, 8H)

1.70 (s, 6H)

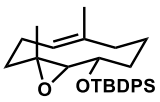
1.23 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 206.3, 144.7, 129.7, 110.8, 64.5, 63.2, 40.1, 38.0, 37.0, 31.6, 22.1, 20.8, 16.3.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{26}H_{41}O_4$ 417.29994; found, 417.29830.

(*E*)-tert-butyl((6,10-dimethyl-11-oxabicyclo[8.1.0]undec-6-en-2-yl)oxy)diphenyl-silane (3-76): A solution of the silyl ether **3-60** (58 mg, 0.125 mmol, 1.0 equiv.) in toluene (45 mL) was heated to 80 °C. A solution of 1,4-benzoquinone (11 mg, 0.102 mmol, 0.8 equiv.) in toluene (50 mL) and a solution of Grubbs second generation catalyst (43 mg, 0.0506 mmol, 0.4 equiv.) were simultaneously added to the solution of **3-60** via syringe pumps over 12 h. The solution was then allowed to stir at 80 °C for an additional 8 h and was then cooled to 23 °C and the solvent was removed under reduced pressure. The crude residue was purified via flash column chromatography over silica gel (0-2% ethyl acetate/hexanes) to afford the carbocycle **3-76** as a colorless oil (3.0 mg, 6%); R_f 0.50 (6% ethyl acetate/hexanes), inseparable from minor impurities. An additional amount of the carbocycle **3-76** was also inseparable from the diene **3-76** and other reaction side products.

^{1}H NMR (500 MHz, $CDCl_3$, δ):



3-76

7.73-7.67 (m, 4H)

7.42-7.34 (m, 6H)

5.24 (dd, *J* = 7.5, 7.5 Hz, 1H)

3.57 (m, 1H)

2.76 (d, *J* = 7.5 Hz, 1H)

2.34 (m, 1H)

2.14 (m, 1H)

1.99 (m, 1H)

1.88 (m, 1H)

1.77-1.60 (m, 3H)

1.65 (s, 3H)

1.34-1.26 (m, 3H)

1.25 (s, 3H)

1.07 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 136.1, 136.0, 135.8 (2), 134.9, 133.7, 129.5 (2), 127.4 (2), 72.6, 68.1, 60.0, 37.1, 31.9, 31.4, 30.2, 29.7, 27.0, 22.7, 19.5, 16.6.

HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{28}H_{39}O_2Si$ 435.27138; found, 435.27080.

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14. The diastereomeric ratios were determined by careful integration of the appropriate peaks in the ^{1}H NMR spectra. Specifically, the peak at 2.70 ppm of the major diastereomer **3-57** was integrated against the peak at 2.65 ppm of minor diastereomer **SI-3-1**.

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16. HPLC columns used: Regis (*R*,*R*)-DACH DNB, CHIRALCEL OJ-H, CHIRALCEL OD-H, and CHIRALPAK AD-H

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21. Cross-metathesis products **3-72** and **3-75** were isolated and characterized (see experimental section). We were unable to separate products **3-73** and **3-74** from the other reaction products, but the ^{1}H NMR spectra of these compounds displayed similar peaks to **3-72** and **3-75**.

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