Intramolecular Radical Cyclization – Elimination Sequence: Studies toward the Synthesis of Phomoidride B

by
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This thesis entitled:

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Studies toward the Synthesis of Phomoidride B

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Prof. Randall Halcomb

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Prof. Tarek Sammakia

Date_____

The final copy of this thesis has been examined by the signators, and we find that both the content and the form meet the acceptable presentation standards of scholarly work in the above mentioned discipline.

Abstract

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Intramolecular Radical Cyclization – Elimination Sequence: Studies toward the Synthesis of Phomoidride B.

Thesis Directed by Professor Randall Halcomb

The phomoidrides are a family of natural products that are inhibitors of squalene synthase and Ras farnesyl transferase. Their tetracyclic ring system was an interesting target for synthesis. The objective of this research was to explore new strategies for synthesis of phomoidride ring system.

The plan was to develop an intramolecular radical cyclization – elimination sequence strategy to synthesize some model molecules of phomoidride ring system. Three different synthesis sequences have been developed. One model molecule with a bicyclo[4.3.1]-deca-1-ene core, has been synthesized. Model studies showed that this was a feasible strategy, but need more optimization.

The first approach failed in the 8-endo-iodocyclization reaction so that the intramolecular 5-exo-radical cyclization – elimination sequence could not be tested. The 7-exo-radical cyclization – elimination sequence was realized to synthesize a model molecule with a bicyclo[4.3.1]-deca-1-ene core. However, the reaction yield did not get good optimization.

The second approach to these structures got through the 8-endo-iodocyclization reaction to form the eight-membered ring, but failed in the intramolecular 5-exo-radical cyclization – elimination sequence to synthesize the model molecule. The 7-exo-radical cyclization – elimination sequence was also not realized. Leaving group was probably the reason for these results.

A radical-initialized cyclobutane ring expansion strategy was also developed. However, because of the cyclobutane ring orbital structure, the free radical did not open the cyclobutene ring to realize the original idea.

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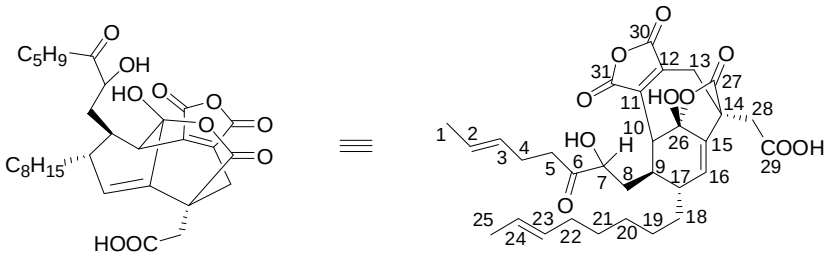
Chapter 3. Radical-Initialized Cyclobutane Ring Expansion Strategy toward the Synthesis of Model Molecule of Phomoidride B

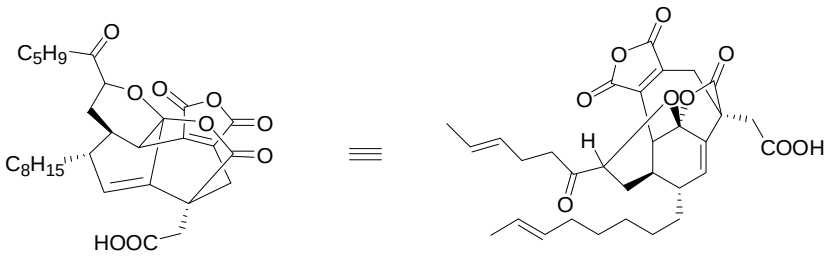
Chapter 1. Introduction

1.1 Isolation and Structure Determination

In 1997, workers from Pfizer isolated two fungal metabolites from Juniper twigs from Texas,[1,2] Phomoidride A (CP-225,917, **1**, Figure 1.1), and Phomoidride B (CP-263,114, **2**).[3] These compounds possess fantastic structures which are a significant challenge for synthesis.[4]



Phomoidride A (CP-225,916, 1): C7 = S
Phomoidride C (3): C7 = R



Phomoidride B (CP-263,114, 2): C7 = S
Phomoidride D (4): C7 = R

Figure 1.1 The phomoidrides.[4]

During the late synthetic studies towards **1** and **2**, Danishefsky group isolated the 7R isomer of Phomoidride B (**4**, Fig 1.1) and Sulikowski group isolated the 7R isomer of Phomoidride A (**3**) from fermentation broths of ATCC 74256, the producing organism of **1** and **2**.[5] Compounds **3** and **4** were named by Phomoidride C and D.[6]

Phomoidride A and B could be interconvert. Kaneko and colleagues observed the conversion of the γ-hydroxy lactone of **1** to the acetal **2**, by treating **1** with catalytic methanesulfonic acid,[2] and the Nicolaou group reported the reverse transformation under basic conditions.[7]

1.2 Biological Activity

Phomoidride A and B have shown the abilities to inhibit both the enzymes Squalene synthase and Ras farnesyl transferase.[1]

Squalene synthase (SQS) catalyzes the formation of squalene which represents a product of the first committed step in the formation of cholesterol and related sterols. Phomoidride A and B are modest inhibitors of SQS with IC_{50} values of 43 and 160 μM, respectively,[2] so that they are considered to be an effective intervention way to control cholesterol biosynthesis without affecting the level of non-sterol compounds derived from FPP such as dolichol, heam a, ubiquinone, and farnesylated proteins.[1]

Ras protein farnesyl transferases (FPTase) catalyze the covalent attachment of a farnesyl moiety to the cysteine thiol group of a variety of proteins.[1] Phomoidride A and B inhibited FPTase from rat brain with IC_{50} values of 6 and 20 μM, respectively.[2] Since that, they can be an effective compound to prevent the transformational effects of mutated Ras proteins.[1]

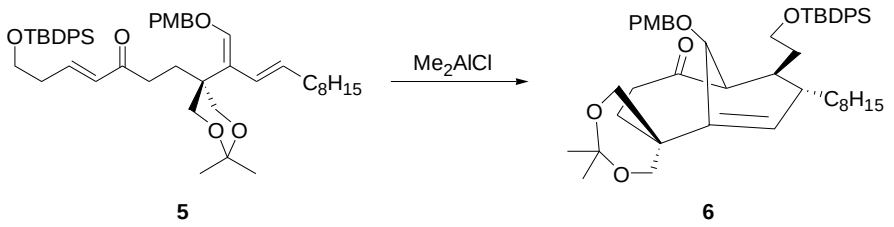
1.3 Approaches to the Synthesis of the Phomoidrides Core.

The Phomoidrides (CP molecules) are probably the most exciting target for organic synthetic chemists to achieve the total synthesis in the recent ten years. Until now, four groups have completed the total syntheses, at least eighteen groups have published papers about their approaches to the synthesis of the ring systems of the Phomoidrides.[4] Some reviews[3,4,8,9] and biomimetic studies were also published about the phomoidrides project.[10,11]

There were a lot of fantastic stories about the synthesis of incredible structural features of CP molecules: a bridgehead double bond contained in a bicyclo[4.3.1]deca-1,6-diene carbon framework, a quaternary center held in a caged spirolactone, a maleic anhydride moiety, and two pendant olefinic side chains.[4] In this thesis, the story will be focused on the ring system, bicyclo[4.3.1]deca-1,6-diene core.

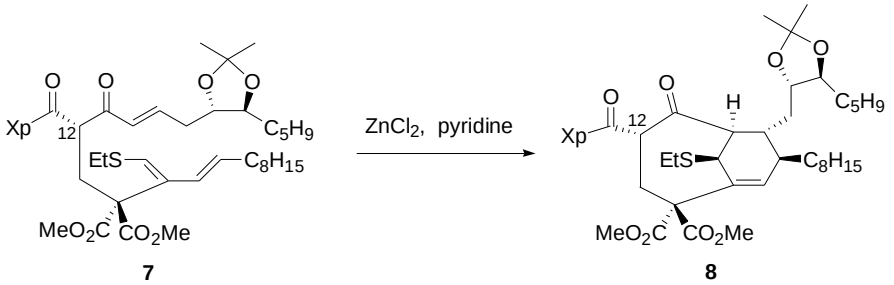
The first total synthesis was published by Nicolaou group.[7,12] Nicolaou chose the type II Intramolecular Diels-Alder reaction to construct the carbocyclic core

structure. (Scheme 1.1) One single transformation conveniently assembled the bridgehead double bond, four stereocenters and two ring systems.[13-16]



Scheme 1.1 Nicolaou's approach to the CP ring system.

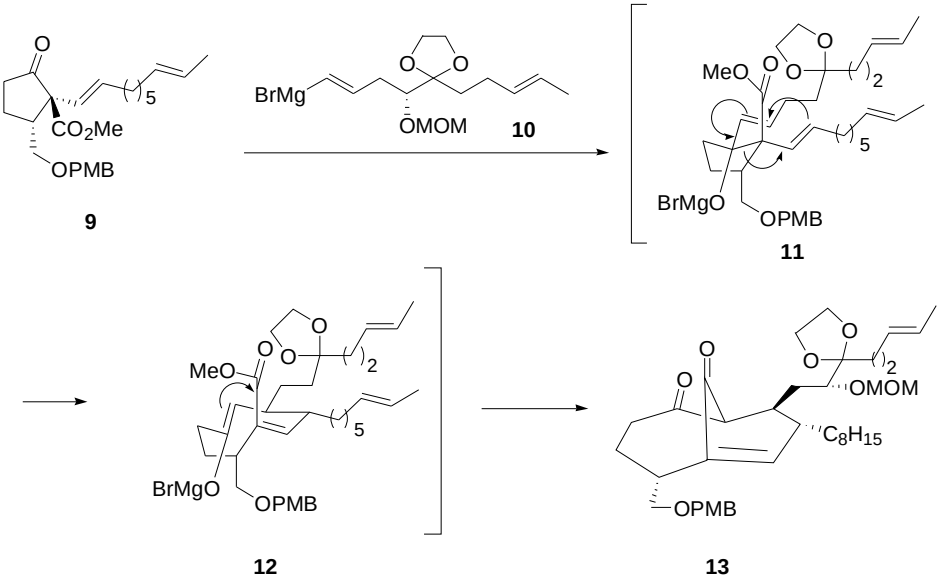
Fukuyama's group completed the second total synthesis.[17,18] He also applied the type II Intramolecular Diels-Alder reaction in his synthesis of the core structure. Comparing with Nicolaou's, the major difference and advantage in his strategy is the presence of a C12 carboxylate function, which controls the absolute stereochemical outcome of the IMDA reaction and can later be elaborated into the maleic anhydride moiety.[cited from ref.4] (Scheme 1.2)



Scheme 1.2 Fukuyama's approach to the CP ring system.

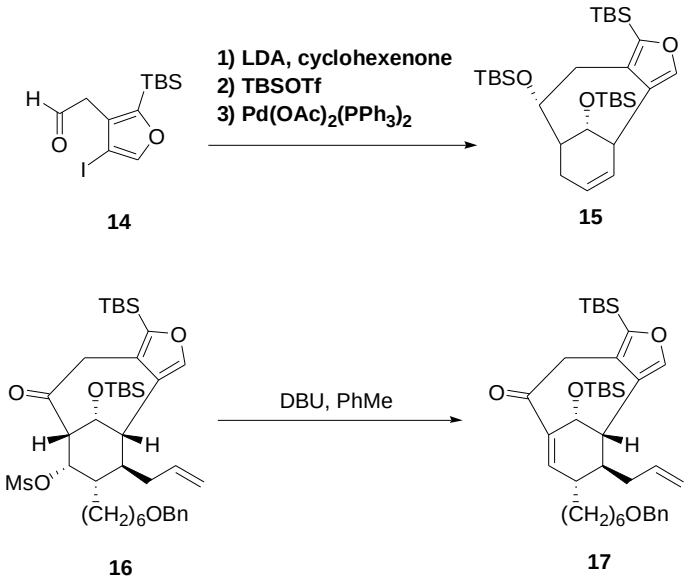
The third Phomoidride total synthesis was accomplished by Shair's group.[19,20] Shair's synthesis of the core system was definitely the most beautiful construction. As

shown in Scheme 1.3, Chelation-controlled vinyl Grignard addition (**9** - **11**), anion-accelerated oxy-Cope rearrangement (**11** - **12**), and transannular Dieckmann-like cyclization (**12** – **13**) proceed in a single convergent operation to provide a highly functionalized bicycle[4.3.1]decene core structure.



Scheme 1.4 Shair's approach to the CP ring system.

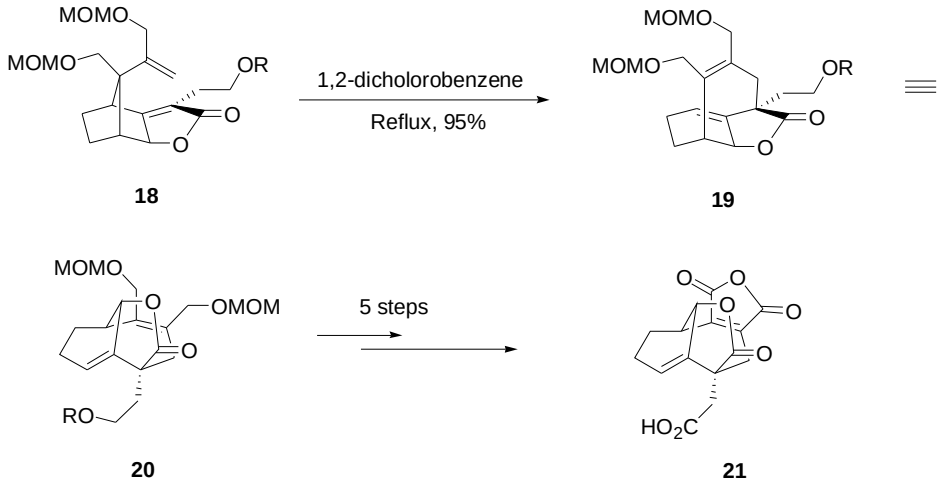
Danishefsky's group finished the last total synthesis.[21,22] His synthesis route is much more straightforward. He used a sequential aldol-Heck strategy to synthesize the ring system. (Scheme 1.4) However, the bridgehead olefin was not easy to install until the elimination strategy was employed to generate the corresponding conjugated enone **17** from the bicylco[4.3.1]-ketone **16**.



Scheme 1.4 Danishefsky's approach to the CP ring system.

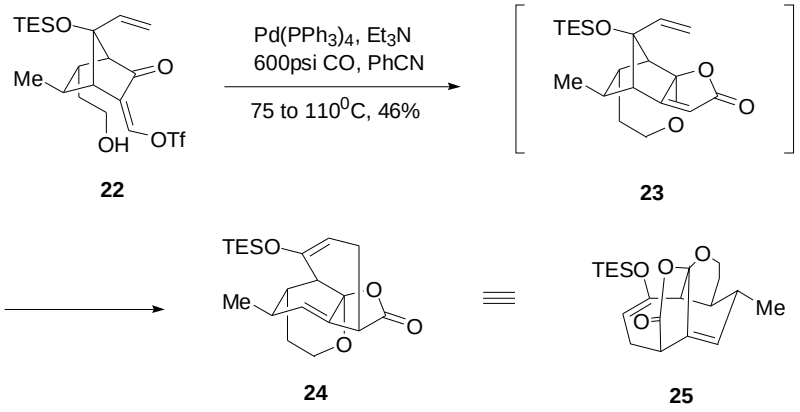
Cope rearrangement is the most popular method for constructing the phomoidrides ring systems. The groups of Clive, Leighton and Banwell all chose Cope rearrangement.[4]

The Clive's approach is shown in Scheme 1.5.[23-27] Heating **18** in 1,2-dichlorobenzene provided the Cope rearrangement product **20** in high yield.



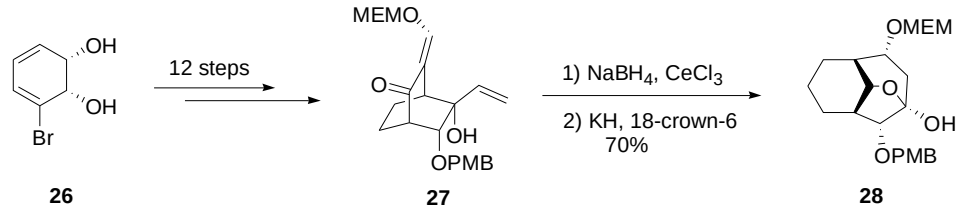
Scheme 1.5 Clive's approach to the CP ring system.

As shown in Scheme 1.6,[28,29] Leighton's group inserted palladium into the carbon-triflate bond of **22** giving a vinylpalladium species, which was followed by insertion of carbon monoxide, providing **23**. Without isolation, rearrangement of lactone **23** by [3, 3] Cope process gave **24**.



Scheme 1.6 Leighton's approach to the CP ring system.

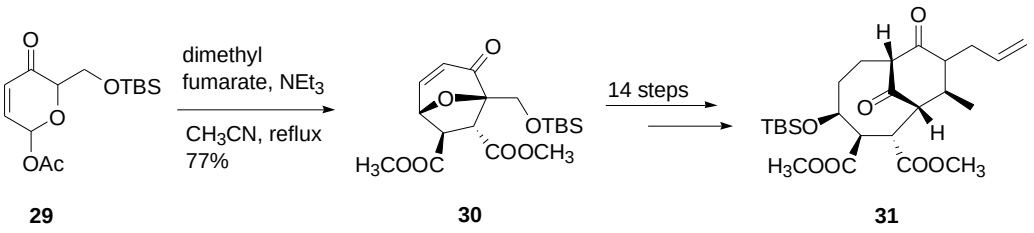
Banwell's synthesis started with commercial available compound **26**.[30] After 12 steps, **27** was synthesized for the Cope rearrangement reaction to get desired product **28**. (Scheme 1.7)



Scheme 1.7 Banwell's approach to the CP ring system.

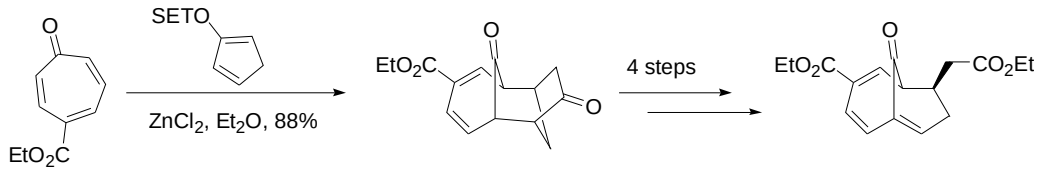
Cycloaddition routes to form the ring system were also widely studied. Nicolaou's and Fukuyama's type II IMDA were good examples. Besides, Ohmori's

[5+2] cycloaddition (Scheme 1.8),[31,32] Gleason's [6+4] cycloaddition (Scheme 1.9)[33] and Daives' [3+4] cycloaddition[34-36] all showed great potentials in synthesizing the real phomoidrides molecules.



29 **30** **31**

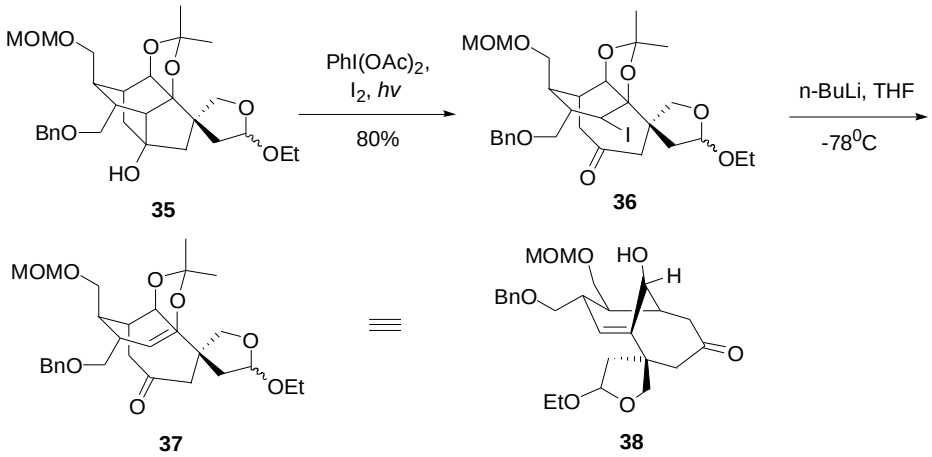
Scheme 1.8 Ohomori's approach to the CP ring system.



32 **33** **34**

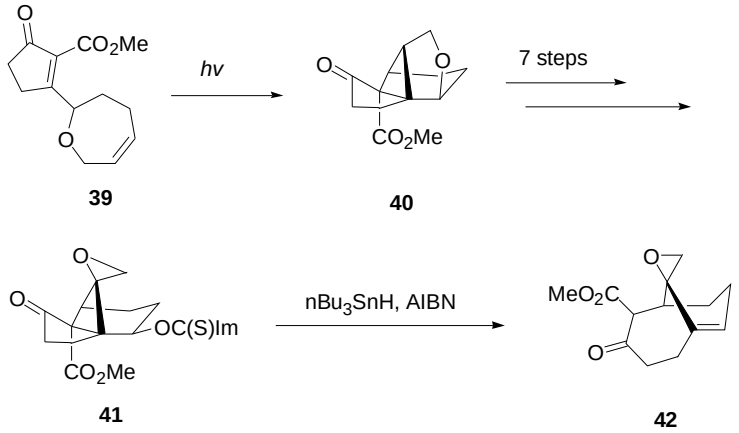
Scheme 1.9 Gleason's approach to the CP ring system.

Nagaoka,[37,38] Crimmin[39] and Wood[40,41] groups applied fragmentation strategies in the ring system synthesis. As shown in Scheme 1.10, Nagaoka group used a radical fragmentation-reductive olefination route to form the desired bridgehead olefin.[37,38]



Scheme 1.10 Nagaoka's approach to the CP ring system.

Another approach was described by Crimmins. (Scheme 1.11)[39] Photocycloaddition of **39** gave teracyclic intermediate **40**. After seven steps' synthesis, **41** reacted with tributyltin hydride and AIBN to selectively cleave the more substituted cyclobutene bond and form the bridgehead olefin **42**.

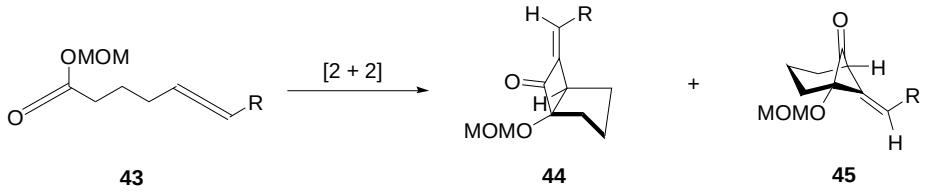


Scheme 1.11 Crimmins' approach to the CP ring system.

Armstrong,[42,43] Takemoto,[44] Mehta,[45] Paquette,[46] Baldwin[47] and Sulikowski[11,48] groups' efforts towards the ring system of the phomoidrides were also very appealing and interesting.

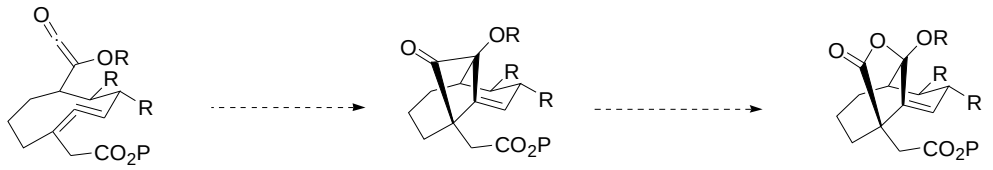
1.4 Halcomb's Intramolecular Ketene-Allene Cycloaddition Strategy toward the Synthesis of the Phomoidrides

Recently, Halcomb group have reported an intramolecular Ketene-Allene cycloaddition. (Scheme 1.12)[49]



Scheme 1.12 Intramolecular Ketene-Allene Cycloaddition.

This strategy could be applied in the synthesis of the phomoidrides ring system as shown in Scheme 1.13.[50] The advantage of this strategy is the convenience of constructing the ring system and also installing the quaternary center held in a caged spirolactone. The disadvantage is that the precursor **46** would be difficult to be synthesized.



46 **47** **48**

Scheme 1.13 Proposed Ketene-Allene Addition Route.

From all the above, the phomoidrides show great potentials for chemists to devise new methodologies and synthetic strategies. Eighteen groups could have eighteen different strategies. And even now, we still can design new synthetic routes toward the synthesis of the phomoidrides.

The following chapter discusses the results obtained in Halcomb's radical cyclization strategy toward the synthesis of the phomoidrides ring system.

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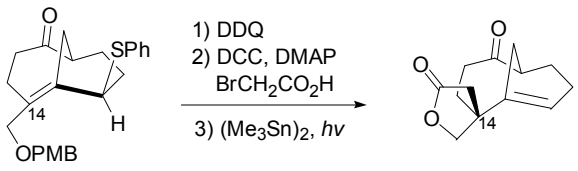
Chapter 2. Radical Cyclization toward the Synthesis of the Model Molecule of Phomoidride B

2.1 Introduction

The radical reaction is a very useful tool in natural product synthesis.[1] More and more organic synthetic chemists have used the radical cyclization to synthesize the ring systems of organic compounds.

In all the synthetic procedures towards the Phomoidrides, Nagaoka (Scheme 1.10)[2,3] and Crimmins (Scheme 1.11)[4] have used radical fragmentation methods to construct the core system of the phomoidrides. However, only Nicolaou applied radical cyclization in a model system (Scheme 2.1).[5] He employed a 5-exo-dig radical cyclization-elimination sequence to break the original bridgehead double bond and regenerate a bridgehead double bond on the other side by expelling out the thiophenol leaving group.

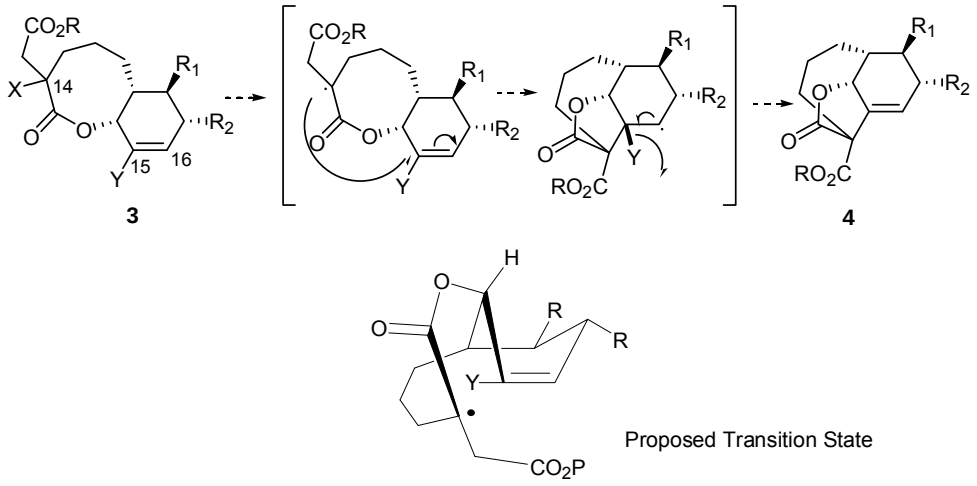


1 **2**

Scheme 2.1 Nicolaou's Radical Cyclization towards the Phomoidride Core Structure.

Nicolaou did not apply this method in the final total synthesis[6-8] because compound **2** possessed the incorrect relative stereochemistry at the C14 quaternary.[5]

Originally, the system chosen for our study was compound **3** (Scheme 2.2).[9] The first step is to synthesize the target molecule **3** with two leaving groups at C14 and C15. Under the radical reaction conditions, C14 will generate an electrophilic free radical. This radical will attack the nucleophilic center, the double bond, at C15 to generate another radical at C16. The radical at C16 will probably come back to take the elimination to form a bridgehead double bond with loss of Y group.



Scheme 2.2 Proposed Radical Cyclization-Elimination Route.

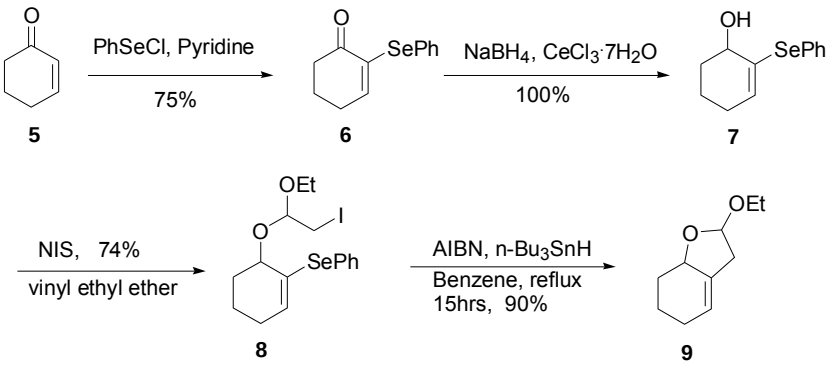
2.2 Specific Aims

The objective of this research was to investigate the intramolecular radical cyclization to synthesize the model system of Phomoidride B. Specific aims include:

1. Investigation of the plausibility of applying radical cyclization in a ring system containg a bridgehead double bond.
2. A study of the effects of leaving group-substituents on the reactivity patterns of the cyclization-elimination sequence.

2.3 Synthesis of a Model System without Bridgehead Double Bond

The 5-exo-dig radical cyclization-elimination sequence started from 2-cyclohexen-1-one **5** (Scheme 2.3). Compound **5** reacted with phenylselenenyl chloride and pyridine to provide **6** as the product. Luche Reduction of **6** in methanol solvent gave **7** in high yield. By using vinyl ethyl ether as the substrate, **7** was applied, as a nucleophile, in the iodolization reaction to give compound **8**. Appling **8** in Tin hydride initiated radical reaction, the final product **9** was isolated in high yield by the 5-exo-dig radical cyclization-elimination sequence.



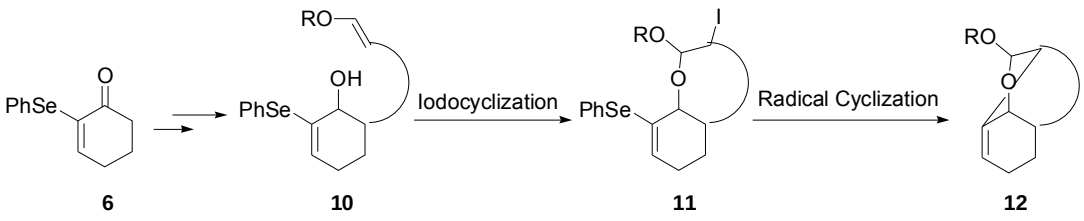
Scheme 2.3 Synthesis of a Model System without Bridgehead Double Bond.

Comparing with the designed model molecule **4**, compound **9** is a bicyclic core system without a bridgehead double bond. It has been expected that **9** would be synthesized efficiently.

The scientific sense of synthesizing the simple model system **9** is to investigate the plausibility of applying the 5-exo-dig radical cyclization-elimination sequence in a ring system to generate a non-bridgehead double bond. This work also provided us the basic idea about the Tin hydride radical reaction conditions.

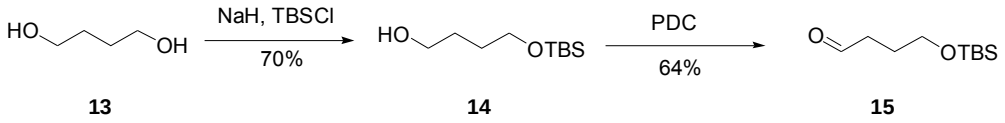
2.4 Synthesis of Bicyclo[4.3.1]-deca-1-ene Model System

After the feasibility of the proposed 5-exo-dig-radical cyclization-elimination sequence was demonstrated, the next goal of this project was the development and implementation of this strategy for a much more complicated model system. The strategy is shown in Scheme 2.4. Applying aldol reaction or alkylation reaction to put a long side chain on compound **6**, target molecule **10** can be synthesized with a vinyl ether group at the terminus, followed by two key reactions: Iodocyclization and Radical cyclization to synthesize the final model compound **12**.



Scheme 2.4 The strategy for the synthesis of the model molecule.

The first try was using the aldol reaction to put the long side chain. 4-tert-butyldimethylsilyloxybutaldehyde **15** was a good precursor (Scheme 2.5). 1, 4-butandiol **13** was mono-protected with TBS ether, followed by PDC oxidation. **15** can be synthesized smoothly.

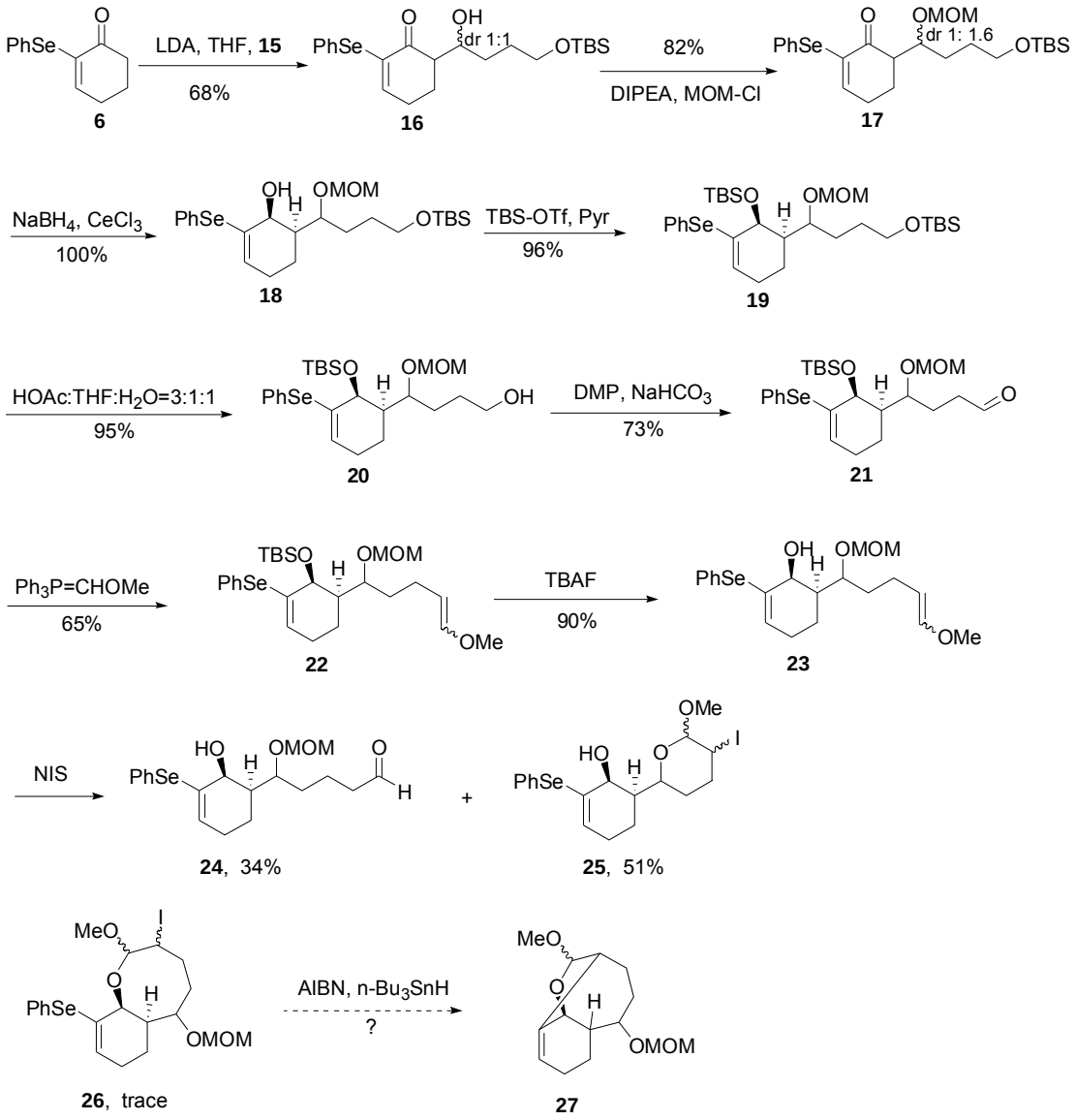


Scheme 2.5 Synthesis of 4-tert-butyldimethylsilyloxybutaldehyde.

Compound **26** was the target molecule for the radical reaction to form model molecule **27**. Using 4-tert-butyldimethylsilyloxybutaldehyde **15** in an aldol reaction with **6** formed **16** as a 1:1 mixture of diastereoisomers. After MOM-group protection of the hydroxyl in **17**, two diastereoisomers could be separated. The major one (the absolute stereochemistry was not determined) of them was carried through a series of high yield protection and deprotection reactions to form alcohol **20**. Dess-Martin oxidation, Wittig reaction, and deprotection provided compound **23**. However, the key reaction, Iodo-cyclization of **23** did not give the desired product **26**. Rather, the 6-exo-cyclization product **25** was the major product along with some hydrolysis compound **24**. (Scheme 2.6)

The hydrolysis compound **24** came out because there was a little bit of trace water in such a small scale reaction, which reacted as a nucleophile to attack the Iodo-activated vinyl ether group to hydrolyze it to the aldehyde.

From the crude NMR spectrum of the key Iodo-cyclization reaction, the desired compound **26** was probably made in a very trace amount so that it was difficult to be separated for the final radical cyclization reaction.

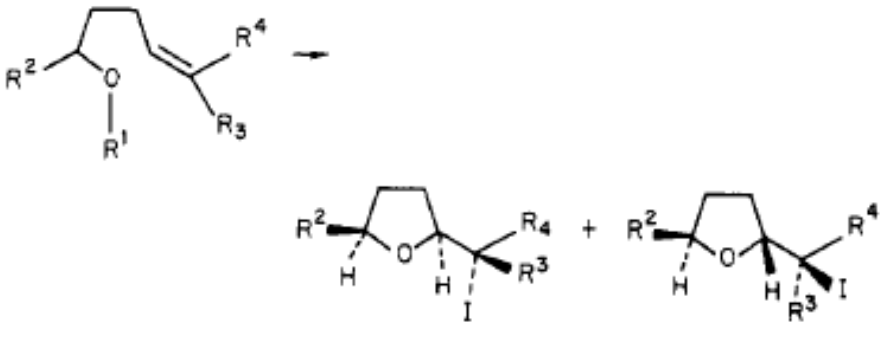


Scheme 2.6 Attempt to synthesize tricyclocore model **27** of Phomoidride B.

There is no doubt that 6-endo cyclization is faster than 8-endo cyclization if 6-alcohol and 8-alcohol is both non-protected. However, in the case of compound **23**, the protecting group of 6-alchol was the key point to determine the reaction speeds of 6-endo cyclization.

The Bartlett group has studied on this area and provided a series of results with different protecting groups. (Table 2.1) [10]

Table I. Iodocyclization of γ,δ-Unsaturated Ethers and Alcohols[a]



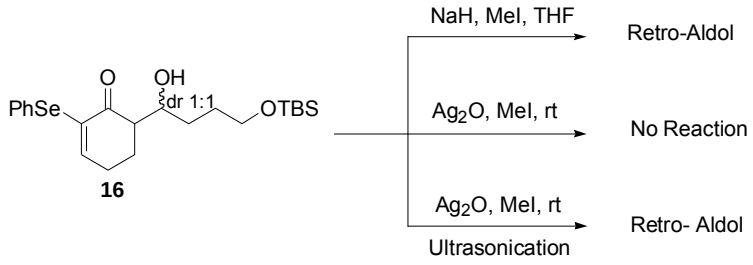
cis trans

example	R^1	R^2	R^3	R^4	cis/trans ratio[c]	yield,[d] %
1	H	CH_3	H	H	0.5	66
2	CH_3	CH_3	H	H	0.5	15
3	CH_2Ph	CH_3	H	H	2	60
4	$SiMe_2$-*t*-Bu	CH_3	H	H	3	43
5	Si-*t*-$BuPh_2$	CH_3	H	H	8	30
6	BB[b]	CH_3	H	H	3.7	74
7	DCB[b]	CH_3	H	H	21	63
8	H	$(CH_3)_2CH$	H	H	0.25	88
9	DCB	$(CH_3)_2CH$	H	H	20	95[e]
10	H	CH_3	CH_3	H	0.5	99
11	DCB	CH_3	CH_3	H	25	75
12	H	CH_3	H	CH_3	0.4	81
13	DCB	CH_3	H	CH_3	12	47
14	CH_2Ph	CH_3	CO_2CH_3	H	6	55
15	DCB	CH_3	CO_2CH_3	H	50	60
16	BB	CH_3	CO_2CH_3	CH_3	10	44

[a] Reaction conditions: I_2, CH_3CN, 0 °C; with the following exceptions: $NaHCO_3$ included for alcohol substrates (examples 1, 8, 10, and 12); cyclizations performed at 21 °C for ester substrates (examples 14–16). [b] BB = 4-bromobenzyl; DCB = 2,6-dichlorobenzyl. [c] Ratio determined by ^{13}C or ^1H NMR spectroscopy. [d] Isolated yield of purified product after chromatography or bulb-to-bulb distillation, unless otherwise indicated. [e] Yield based on ^1H NMR spectroscopy.

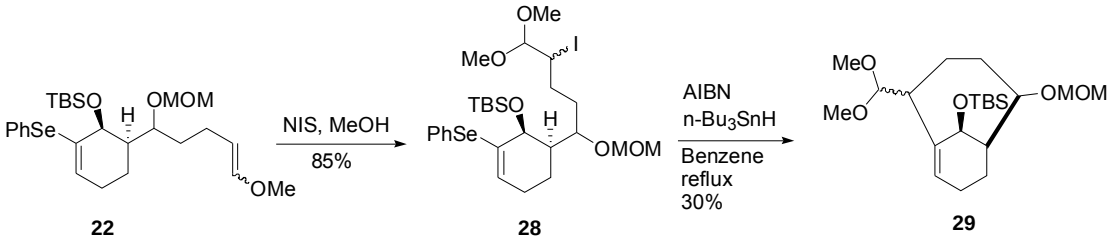
Table 2.1 Datas cited from ref 10.

From Table 2.1, methyl is the best protecting group to decrease the reaction speed. However, the effort to protect compound **16** with methyl group failed due to serious retro-aldol reaction. (Scheme 2.7)



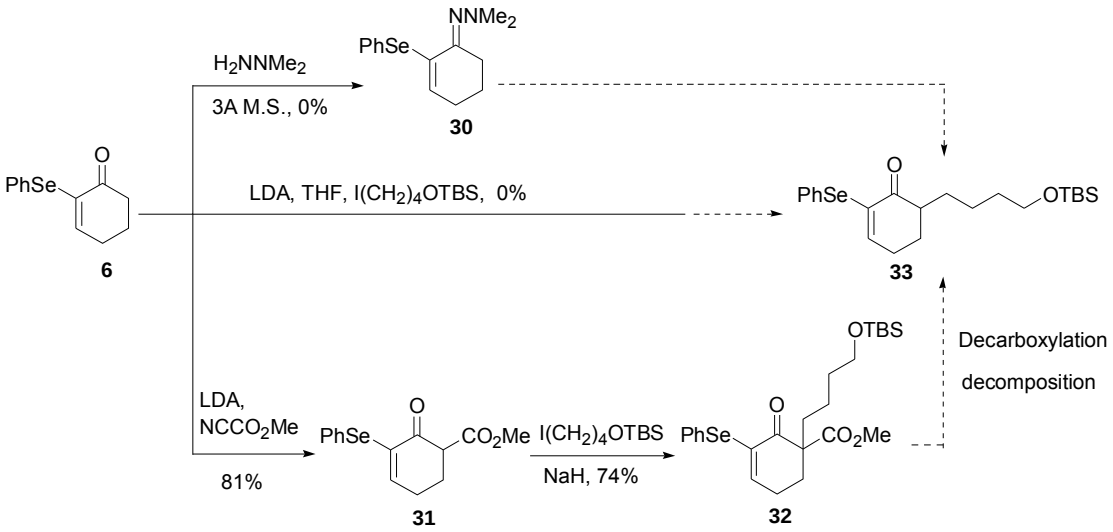
Scheme 2.7 Attempt to protect **16** with methyl group.

Since 8-endo iodocyclization could not be realized, intermolecular iodolization followed by 7-exo-dig radical cyclization sequence was worth to try. As shown in scheme 2.8, the desired compound **29** was formed as a bicyclo[4.3.1]-deca-1-ene model in two diastereoisomers. However, the yield was not good. The major product is the reduction compound of **28**. The compound **29** was the first model molecule synthesized by radical cyclization-elimination strategy.



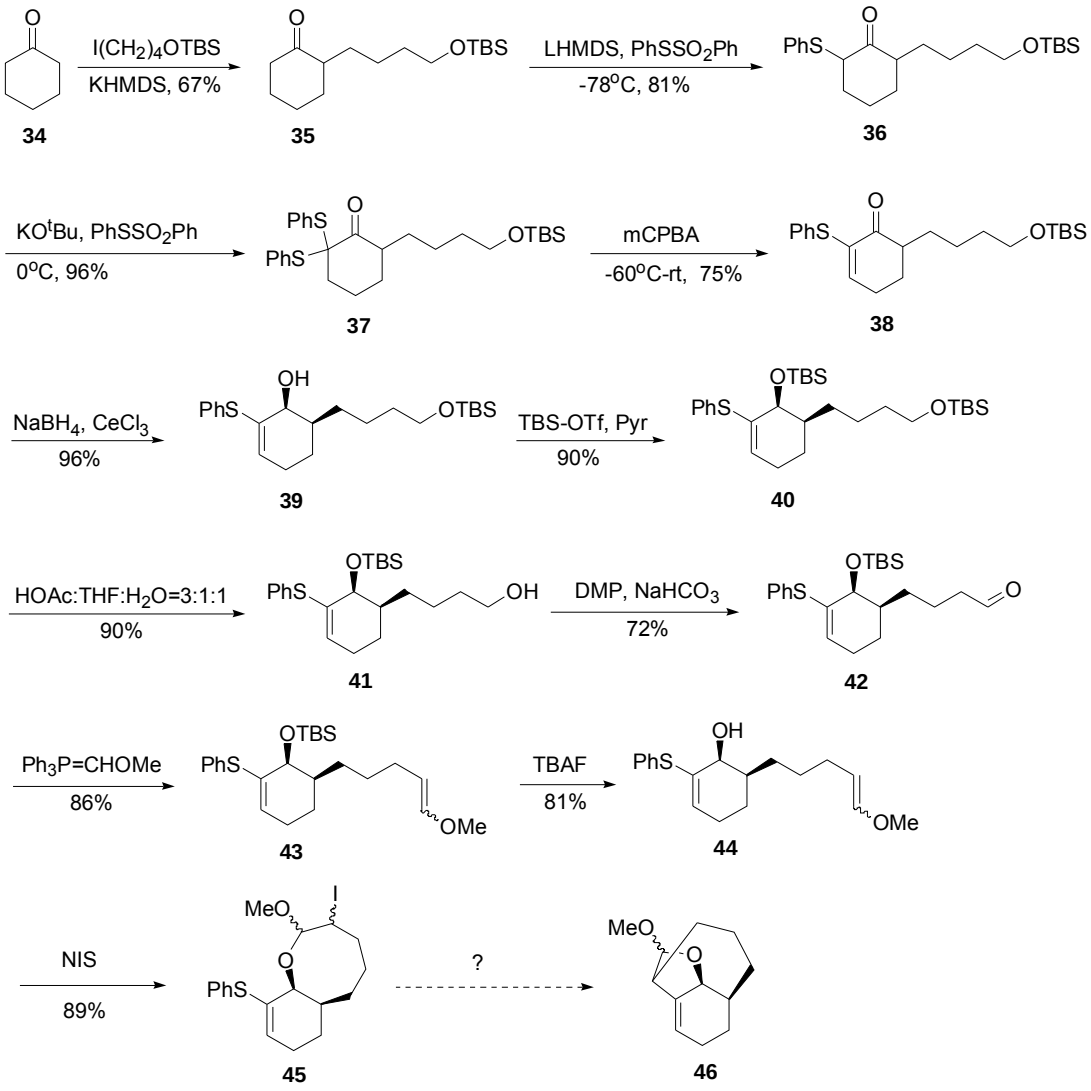
Scheme 2.8 Synthesis of bicyclo[4.3.1]-deca-1-ene core.

In order to realize the original idea (Scheme 2.4), the next effort was using sort of alkylation reactions to put a side chain on compound **6** to synthesize the ketone without β-alchol. However, alkylation, hydrazone alkylation, α-carboxylation-alkylation-decarboxylation did not give positive results (Scheme 2.9).



Scheme 2.9 Attempt to synthesize **33**.

The Kita group developed an efficient way to synthesize some compounds similar to the most important precursor **30** as shown in scheme 2.10.[11] Alkylation of cyclohexanone with *tert*-Butyl(4-iodobutoxy)dimethylsilane in the presence of KHMDS afforded the monoalkylated cyclohexanone **35** in 67% yield. Double phenylsulfenylation of **35** followed by oxidation with *m*-CPBA produced the desired product **38**. However, the leaving group designed here was thiophenyl but not phenylselenenyl group.

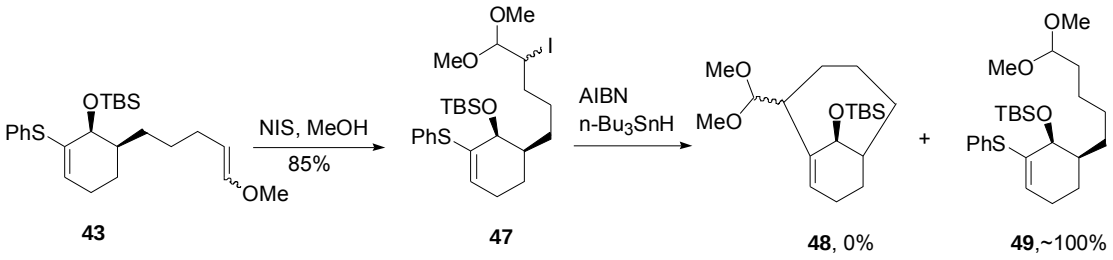


Scheme 2.10 Attempt to synthesize tricyclic core **46** of Phomoidride B.

The sequence started with compound **38** (Scheme 2.10). After a series of reactions similar to Scheme 2.6, pure compound **44** was made for the iodocyclization reaction and **46** was synthesized in four diastereoisomers. Three of them were isolated and applied separately in some radical reactions. However, we did not find out the suitable reaction conditions to get desired model target **46**. If there is a hydride source (n-Bu_3SnH) in the reaction, the reduction product of **46** is the major one; if

there is no hydride source (hexaalkyl ditin), only the starting material could be isolated.

We also tried the 7-exo radical cyclization of **47** to synthesize bicyclo[4.3.1]-deca-1-ene **48** (Scheme 2.11). However, to our surprise, we did not isolate even a trace of **48** but only the reduction product **49**. The major difference between **28** and **47** was the leaving group. The thiophenol group is not an enough good leaving group to be expelled in such a ring system comparing with the phenylselenenyl group. The leaving group problem is also probably the main reason of the failure of synthesizing tricyclic core **46**.



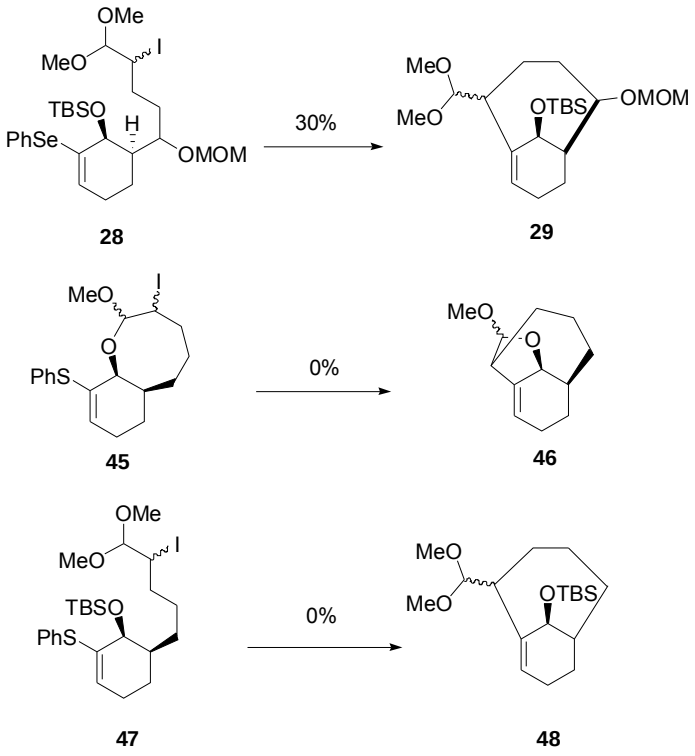
43 **47** **48**, 0% **49**,~100%

Scheme 2.11 Attempt to synthesize bicyclo[4.3.1]-deca-1-ene core **48**.

2.5 Summary and Future Work

In this chapter, three different radical cyclization-elimination reactions have been studied. (Scheme 2.12) The structures of **28** and **47** are very similar. The reaction conditions for all of them were constant. But the results were totally different. As to **28**, every reaction could give the desired product **29** (determined by crude NMR and TLC) and the only difference was the yield. But as to **47**, none of the

reaction conditions could give even trace of the cyclization product **48**. Another point is that the reaction speed of 5-exo-dig radical cylization (such like **45**) should be faster than 7-exo-dig radical cyclization (such like **27**). However, the results did not prove it. What are the reasons behind the experimental results?



Scheme 2.12 Comparison of Three Radical Cyclization-Elimination Reactions.

First, Steric hindrance would be the problem of 5-exo-dig cyclization of **45**. The radical generated by expelling out the iodo- group could get closed to the double bond if the transition state of the six-membered ring took boat-conformation as shown in Scheme 2.2. The energy of the transition state rised up but was not too high to go through.

Secondly, since the structures of **28** and **47** are almost same, the reaction speed rates of the reduction of **28** and **47** could be supposed to be almost same.

Base on all the facts above, the two leaving groups, thiophenol and phenylselenenyl group determined all the results.

There are two possibilities. The first one is that **27**, **45** and **47** all cyclized but only **27** could go on to the elimination step while **45** and **47** could not, but rebroke the bond which was lately trapped by the Tin hydride to make the reduction products. This supposition is consistent with the fact that the dissociation energy of C-SePh is around 10Kcal/mol lower than C-SPh so that phenylselenenyl group is easier to be eliminated. However, the supposition did not obey the basic rule. Professor Curran has said:" Radical additions to C=C bonds are usually exothermic and irreversible, with early, reactnt-like transition states." [1]

The second supposition is that **45** and **47** could not cyclize at all. Houk group has studied on the theoretical transition structures for radical additions to alkenes.[12] As shown in Figure 2.1, when a radical attacks the double bond, there are three angles determined by different substitutes. Different geometries of these three angles would give out totally different transition state energies. This fact probably raised up the transition state energy of **45** and **47** so that they could not cyclize.

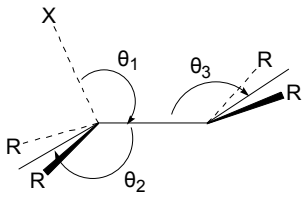


Fig 2.1 Transition Structure for Radical Addition to Alkene.[12]

The future work will focus on synthesizing some precursors like **45** and **47** with phenylselenenyl group but not thiophenol as leaving groups for radical cyclization. In one word, only if a method which greatly increase the lifetime of the radical of the model system to make a cyclization but not reduction can be found, the original strategy can make the synthesis of the ring system of the phomoidrides work in high yields.

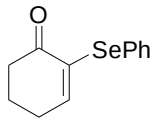
2.6 Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded on either a Varian Unity INOVA-500 or on a Bruker AM-400 spectrometer . ^{1}H NMR spectra are reported in parts per million (δ) relative to residual solvent peaks (7.24 for $CDCl_3$). ^{1}H assignments were made on the basis of ^{1}H-^{1}H coupling constants, homonuclear decoupling experiments, and ^{1}H-^{1}H correlated spectroscopy (COSY). ^{13}C NMR spectra are reported in parts per million (δ) relative to residual solvent peaks (77.0 for $CDCl_3$). Infrared spectra were obtained using a Perkin Elmer 1600 series FTIR. Electron ionization (EI) mass spectra were obtained at 70 eV. Chemical ionization (CI) mass spectra were performed with *iso*-butane, methane, or ammonia. Optical rotations were measured on a Jasco model DIP-370 polarimeter at 25 °C ± 2 °C.

Commercially available reagents were used as purchased without further purification unless noted. THF was purified by distillation from sodium/benzophenone ketyl prior to use under an N_2 atmosphere. Dichloromethane was distilled from CaH_2 prior to use under an N_2 atmosphere. Benzene and toluene were purified by distillation from CaH_2 under an N_2 atmosphere, and stored over 3Å molecular sieves. Pyridine was purified by distillation from CaH_2 under aspirator vacuum and stored over KOH. All reactions were performed under an atmosphere of dry N_2 unless otherwise noted. . All aqueous solutions used for reaction work up were saturated unless explicitly mentioned otherwise. All flash chromatography was

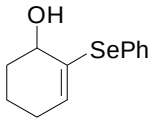
performed with silica gel (32-63 microns, 250-450 mesh) which was purchased from Scientific Adsorbents Inc.

Analytical thin-layer chromatography (TLC) was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm). Compounds were visualized with UV or by staining with cerium ammonium molybdate, *p*-anisaldehyde, or $KMnO_4$ and heating.



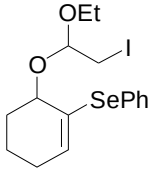
6

2-Phenylselanyl-cyclohex-2-enone (6). PhSeCl (1.025g, 5.35 mmol) was dissolved in 25 mL anhydrous CH_2Cl_2 at rt. Distilled pyridine (0.46 mL, 5.62 mmol) was added and stirred for 10 min. 2-cyclohexen-1-one (0.49 mL, 5.08 mmol) was then added. The reaction mixture was stirred at rt for 5 h. The mixture was diluted by 100 mL CH_2Cl_2 washed by 3M HCL solution, brine and dried over $MgSO_4$. Flash chromatography on silica gel (10:1 hexanes:EtOAc) gave **6** (956 mg, 75%) as a yellow crystal. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (m, 2H, Ar-*H*), 7.34 (m, 3H, Ar-*H*), 6.43 (t, *J* = 4.40 Hz, 1H, C=C-*H*), 2.55 (t, *J* = 6.60 Hz, 2H), 2.29 (m, 2H), 1.99 (m, 2H).



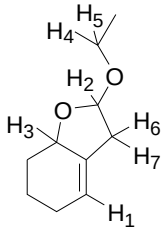
7

2-Phenylselanyl-cyclohex-2-enol (7). Ketone **6** (375 mg, 1.50 mmol) was dissolved in 15 mL MeOH. $CeCl_3 \cdot 7H_2O$ (837 mg, 2.25 mmol) was added at 0 °C. $NaBH_4$ (85 mg, 2.25 mmol) was added into the mixture very slowly. Let the reaction worm to rt and stirred for 1 h. The solution was then quenched by saturated NH_4Cl solution, concentrated under vacuum, re-dissolved in Et_2O (100 mL). The Et_2O layer was concentrated under vacuum to provide product **7** as a yellow oil (379 mg, 100%); ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (m, 2H, Ar-*H*), 7.25 (m, 3H, Ar-*H*), 6.30 (t, *J* = 3.95 Hz, 1H, C=C-*H*), 4.05 (t, *J* = 4.84 Hz, 1H, O-C-*H*), 2.16 (m, 2H), 1.85 (m, 2H), 1.75 (m, 1H), 1.62 (m, 1H).



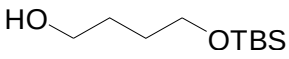
8

[6-(1-Ethoxy-2-iodo-ethoxy)-cyclohex-1-enylselanyl]-benzene (8). **7** (375 mg, 1.50 mmol) was dissolved in 15 mL anhydrous CH_2Cl_2 and protected by N_2. At 0 $^{\circ}$C, vinyl ethyl ether (0.287 mL, 3.00 mmol) and NIS (404 mg, 1.80 mmol) were added. The reaction mixture was stirred at 0 $^{\circ}$C for 1 h and was then kept in fridge overnight. The mixture was concentrated without work-up. Flash chromatography on silica gel (1:1 hexanes:CH_2Cl_2) gave **8** (500 mg , 74%, pale yellow oil) as two diastereoisomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2H, Ar-*H*), 7.25 (m, 3H, Ar-*H*), 6.23 (t, *J* = 3.75 Hz, 0.50H, C=C-*H*), 6.20 (t, *J* = 3.94 Hz, 0.50H, C=C-*H*), 4.75 (t, *J* = 5.58 Hz, 0.50H, O-C*H*-O), 4.63 (dd, *J* = 7.05, 3.66 Hz, 0.50H, O-C*H*-O), 4.14 (m, 0.5H, O-C*H*), 3.97 (m, 0.5H, O-C*H*), 3.81 (m, 2H), 3.19 (m, 2H), 2.14 (m, 2H), 1.94 (m, 2H), 1.76 (m, 1.5H), 1.60 (m, 1.5H), 1.17 (t, *J* = 7.05 Hz, 1.50H), 1.14 (t, *J* = 6.96 Hz, 1.50H).



9

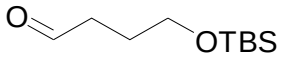
2-Ethoxy-2,3,5,6,7,7a-hexahydro-benzofuran (9). Compound **8** (49 mg, 0.109 mmol) and AIBN (1.8 mg, 0.011 mmol) were dissolved in anhydrous benzene (10 mL) and stirred under N_2 at rt. The n-Bu_3SnH (0.065 mL, 0.240 mmol) was added dropwise. The mixture was then refluxed for 20 h. The reaction mixture was concentrated under vacuum and extracted in 2.5 mL ether and 2.5 mL saturated KF solution. The solution was stirred for another 1 h and concentrated. Flash chromatography (SiO_2, gradient, 15:1 hexanes:EtOAc) gave **9** (16 mg, 90%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54 (t, unresloved, 1H, H_1), 5.09 (d, J = 5.49 Hz, 1H, H_2), 4.21 (m, H_3), 3.72 (m, 1H, H_4), 3.44 (m, 1H, H_5), 2.66 (m, 1H, H_6), 2.40 (m, 1H, H_7), 2.14 (m, 2H), 2.07 (m, 2H), 1.82 (m, 2H), 1.16 (t, J = 7.03 Hz, 3H).



14

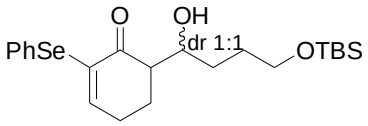
4-(*tert*-Butyl-dimethyl-silanyloxy)-butan-1-ol (14). Diol **13** (5.03 g, 55.8 mmol) was added in 125 mL anhydrous THF which already contained NaH (1.34 g, 55.8 mmol). This solution was stirred for 45 min at rt. TBS-Cl (8.42 g, 55.8 mmol) was then added and stirred for another 45 min. The reaction mixture was washed by 10% K_2CO_3 solution, brine and dried over $MgSO_4$. Flash chromatography on silica

gel (10:1 hexanes:EtOAc) gave alcohol **14** (8.124 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70 (m, 4H), 2.50 (br s, 1H), 1.60 (m, 4H), 0.81 (s, 9H, Si-C(C*H*$_3$)$_3$), 0.04 (s, 6H, Si-C*H*$_3$).



15

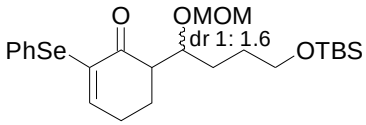
4-(*tert*-Butyl-dimethyl-silanyloxy)-butyraldehyde (15). **14** (4.85 g, 23.5 mmol) was dissolved in anhydrous CH_2Cl_2 (125 mL). PDC (10.8 g, 28.2 mmol) was then added. The reaction mixture was stirred for 12 h at rt. The mixture was then poured through a plug of celite and concentrated. Flash chromatography on silica gel (20:1 hexanes:EtOAc) gave **15** (3.1 g, 64%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.76 Hz, 1H, O=C-*H*), 3.63 (t, *J* = 5.94 Hz, 2H), 2.48 (dt, *J* = 1.75, 7.25 Hz, 2H), 1.84 (m, 2H), 0.86 (s, 9H, Si-C(C*H*$_3$)$_3$), 0.02 (s, 6H, Si-C*H*$_3$).



16

6-[4-(*tert*-Butyl-dimethyl-silanyloxy)-1-hydroxy-butyl]-2-phenylselanyl-cyclohex-2-enone (16). Diisopropylamine (1.91 mL, 13.65 mmol) was dissolved in anhydrous THF (70 mL) and stirred under N_2 at 0 °C for 10 min. *n*-BuLi (9.39 mL, 1.35 M, 12.68 mmol) was added and the reaction was stirred at 0 °C for 3 min. The 0 °C bath was changed by the dry ice – acetone bath. **6** (2.447 g, 9.75 mmol) was dissolved in anhydrous THF (20 mL) and added dropwise to the organolithium solution via cannular over a period of 1 h. After another 30 min stirring, **15** (2.219 mL, 10.78 mmol) was added fast into the reaction mixture by syringe at -78 °C. The reaction was stirred for 1.5 h at -78 °C. The reaction mixture was poured into saturated $NaHCO_3$ solution and extracted by ethyl acetate. The mixture was washed by brine and dried over $MgSO_4$, filtered, and concentrated under vacuum to give a yellow oil. The crude material was purified by flash chromatography (SiO_2, gradient, 10:1 $\rightarrow$ 5:1 hexanes:EtOAc) to give **16** (1.268 g, 72%) as two diastereoisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (m, 2H, Ar-*H*), 7.33 (m, 3H, Ar-*H*), 6.43 (m, 1H, C=C-*H*), 4.03 (m, 1H), 3.65 (m, 2H), 2.52 (m, 1H), 2.36 (m, 2H), 1.70 (m, 3H), 1.46 (m, 1H), 1.26 (m, 2H), 0.88 (s, 9H, Si-C(C*H*$_3$)$_3$), 0.04 (s, 6H, Si-C*H*$_3$); ^{13}C NMR (400 MHz, $CDCl_3$) δ 199.7, 198.4, 146.6, 146.5, 136.8, 136.7, 135.3, 135.2, 129.9, 129.8,

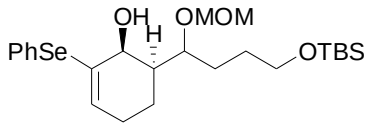
129.0, 128.9, 127.1, 126.9, 71.4, 69.6, 63.4, 63.3, 52.7, 52.6, 30.5, 29.7, 28.8, 28.0, 27.8, 26.2, 24.9, 22.8, 18.5, -5.1.



17

6-[4-(*tert*-Butyl-dimethyl-silanyloxy)-1-methoxymethoxy-butyl]-2-phenylselanyl-cyclohex-2-enone (17). **16** (1.165 g, 2.57 mmol) was dissolved in anhydrous CH_2Cl_2 (25 mL) and stirred at 0 °C under N_2. Hunig's base (4.48 mL, 25.70 mmol) and MOM-Cl (1.32 mL, 15.42 mmol) were added and the solution was stirred for 2 h at 0 °C and 7.5 h at rt. The reaction mixture was then quenched by saturated NH_4Cl solution, extracted with CH_2Cl_2 (3 × 50 mL). The organic fractions were combined and washed with saturated H_2O (2 × 40 mL), and saturated NaCl (1 × 40 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. Flash chromatography on silica gel (9:1 hexanes:EtOAc) gave **17** (2 diastereoisomers, 1.6:1 ratio of major:minor, 1.047 g, 82%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) Diastereoisomer **I**: δ 7.54 (m, 2H, Ar-*H*), 7.33 (m, 3H, Ar-*H*), 6.36 (dd, *J* = 5.72, 3.08 Hz, 1H, C=C-*H*), 4.63 (s, 2H, O-C*H*$_2$-O), 4.20 (m, 1H), 3.59 (m, 2H), 3.34 (s, 3H, O-C*H*$_3$), 2.84 (dt, *J* = 12.96, 4.18 Hz, 1H), 2.32 (m, 2H), 2.13

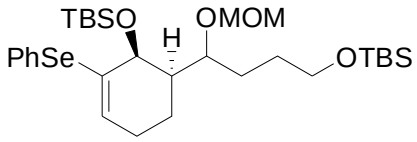
(m, 1H), 1.84 (m, 1H), 1.68 (m, 1H), 1.54 (m, 1H), 1.45 (m, 1H), 0.86 (s, 9H, -C(C*H*$_3$)$_3$), 0.02 (s, 6H, -C*H*$_3$); Diastereoisomer **II**: δ 7.60 (m, 2H, Ar-*H*), 7.38 (m, 3H, Ar-*H*), 6.46 (dd, *J* = 5.94, 3.08 Hz, 1H, C=C-*H*), 4.72-4.37 (dd, *J* = 53.83, 6.37 Hz, 2H, O-C*H*$_2$-O), 4.38 (dt, *J* = 2.64, 6.81 Hz, 1H, -C*H*-O), 3.65 (m, 2H), 3.36 (s, 3H, O-C*H*$_3$), 2.47 (m, 2H), 2.32 (m, 1H), 2.08 (m, 2H), 1.73 (m, 1H), 1.57 (m, 2H), 1.51 (m, 1H), 0.91 (s, 9H, Si-C(C*H*$_3$)$_3$), 0.07 (s, 6H, Si-C*H*$_3$).



18

6-[4-(*tert*-Butyl-dimethyl-silanyloxy)-1-methoxymethoxy-butyl]-2-phenylselanyl-cyclohex-2-enol (18). The major diastereoisomers **I** of **17** (582 mg, 1.17 mmol) was dissolved in 12 mL MeOH. $CeCl_3 \cdot 7H_2O$ (654 mg, 1.76 mmol) was added at 0 °C. $NaBH_4$ (67 mg, 1.76 mmol) was added into the mixture very slowly. Let the reaction worm to rt and stirred for 1 h. The solution was then quenched by saturated NH_4Cl solution, concentrated under vacuum, re-dissolved in Et_2O (100 mL). The Et_2O layer was concentrated under vacuum to provide product **18** as a yellow oil (582 mg, 100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (m, 2H, Ar-*H*), 7.21 (m, 3H, Ar-*H*), 6.24 (dd, *J* = 5.05, 2.42 Hz, 1H, C=C-*H*), 4.63-4.56 (dd, *J* = 30.98, 6.81 Hz, 2H,

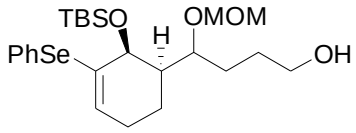
O-CH_2-O), 4.24 (br s, 1H, -C*H*-O), 3.63 (m, 1H), 3.58 (m, 2H), 3.49(d, *J* = 4.40 Hz, 1H), 3.19 (s, 3H, O-CH_3), 2.22 (m, 2H), 1.67 (m, 2H), 1.60 (m, 2H), 1.52 (m, 3H), 1.44 (m, 1H), 0.86 (s, 9H, Si-C(CH_3)$_3$), 0.02 (s, 6H, Si-CH_3).



19

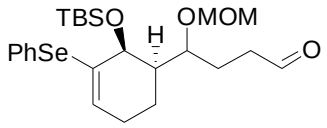
{6-(*tert*-Butyl-dimethyl-silanyloxy)-5-[4-(*tert*-butyl-dimethyl-silanyloxy)-1-methoxymethoxy-butyl]-cyclohex-1-enylselanyl}-benzene (19). Alcohol **18** (550 mg, 1.10 mmol) was dissolved in 11 mL anhydrous CH_2Cl_2 and stirred at 0 °C under N_2 for 5 min. Distilled pyridine (0.54 mL, 6.60 mmol) and TBS-OTf (0.78 mL, 3.30 mmol) were added and the solution was stirred 1 h at 0 °C and 5 h at rt. The reaction mixture was then quenched by water, extracted by CH_2Cl_2, washed by $NaHCO_3$ solution, brine, dried over $MgSO_4$ and concentrated under vacuum. Flash chromatography on silica gel (50:1 hexanes:EtOAc) gave **19** (647 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (m, 2H, Ar-*H*), 7.21 (m, 3H, Ar-*H*), 6.11 (t, *J* = 3.74 Hz, 1H, C=C-*H*), 4.58-4.50 (dd, *J* = 31.42, 6.59 Hz, 2H, O-CH_2-O), 4.30 (br s, 1H, -C*H*-O), 3.64 (m, 1H), 3.57 (m, 2H), 3.15 (s, 3H, O-CH_3), 2.23 (m, 2H), 1.68 (m, 3H),

1.55 (m, 3H), 1.46 (m, 2H), 0.87 (s, 9H, Si-C(CH_3)$_3$), 0.86 (s, 9H, Si-C(CH_3)$_3$), 0.14 (d, J = 23.28 Hz, 6H, Si-CH_3), 0.02 (s, 6H, Si-CH_3).



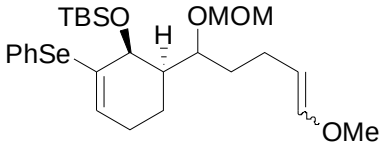
20

4-[2-(*tert*-Butyl-dimethyl-silanyloxy)-3-phenylselanyl-cyclohex-3-enyl]-4-methoxymethoxy-butan-1-ol (20). **19** (647 mg, 1.06 mmol) was dissolved in THF (4 mL) and stirred at rt. An AcOH (15 mL)/ H_2O (5 mL) mixture was added dropwise. The reaction mixture was stirred overnight and then concentrated. Flash chromatography on silica gel (5:1 hexanes:EtOAc) gave **19** (502 mg, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (m, 2H, Ar-*H*), 7.23 (m, 3H, Ar-*H*), 6.11 (t, J = 3.52 Hz, 1H, C=C-*H*), 4.60-4.51 (dd, J = 35.82, 6.59 Hz, 2H, O-CH_2-O), 4.28 (br s, 1H, -C*H*-O), 3.68 (m, 1H), 3.63 (m, 2H), 3.18 (s, 3H, O-CH_3), 2.26 (m, 2H), 1.73 (m, 3H), 1.64 (m, 4H), 1.45 (m, 1H), 0.86 (s, 9H, Si-C(CH_3)$_3$), 0.14 (d, J = 27.93 Hz, 6H, Si-CH_3).



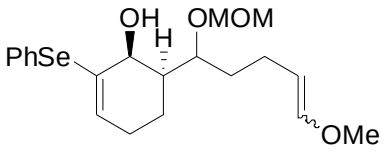
21

4-[2-(*tert*-Butyl-dimethyl-silanyloxy)-3-phenylselanyl-cyclohex-3-enyl]-4-methoxymethoxy-butyraldehyde (21). Alcohol **20** (500 mg, 1.00 mmol) was dissolved in wet CH_2Cl_2 (10 mL). $NaHCO_3$ (370 mg, 4mmol) and DMP (932 mg, 2mmol) were added and stirred for 0.5 h at rt. The reaction mixture was then diluted with CH_2Cl_2 (50 mL), and washed with saturated $Na_2S_2O_3$ (2 × 10 mL), saturated $NaHCO_3$ (1 × 10 mL), and saturated NaCl (1 × 10 mL). The organic layer was then dried with $MgSO_4$, filtered, and concentrated under vacuum to provide the crude product. Flash chromatography on neutral silica gel (9:1 hexanes:EtOAc) gave **21** (363 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (t, *J* = 9.76 Hz, 1H, O=C-*H*), 7.37 (m, 2H, Ar-*H*), 7.22 (m, 3H, Ar-*H*), 6.09 (t, *J* = 3.52 Hz, 1H, C=C-*H*), 4.55-4.47 (dd, *J* = 32.52, 6.81 Hz, 2H, O-CH_2-O), 4.28 (br s, 1H, -C*H*-O), 3.66 (m, 1H), 3.16 (s, 3H, O-CH_3), 2.50 (m, 2H), 2.27 (m, 2H), 2.06 (m, 1H), 1.73 (m, 2H), 1.65 (m, 1H), 1.44 (m, 1H), 0.86 (s, 9H, Si-C(CH_3)$_3$), 0.14 (d, *J* = 26.37 Hz, 6H, Si-CH_3).



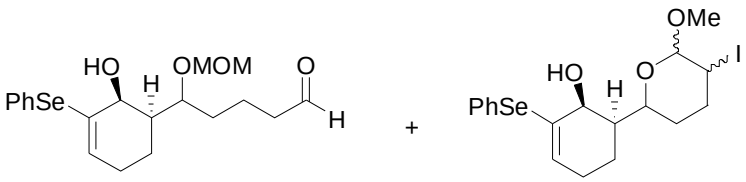
22

***tert*-Butyl-[6-(5-methoxy-1-methoxymethoxy-pent-4-enyl)-2-phenylselanyl-cyclohex-2-enyloxy]-dimethyl-silane (22).** Methoxymethyl triphenylphosphonate chloride (92.6 mg, 0.262 mmol) was dissolved in anhydrous THF (2 mL) and protected by N_2. KO^tBu (0.25 mL, 1M in THF, 0.25 mmol) was added dropwise at 0 °C and stirred for 30 min. Aldehyde **21** (62 mg, 0.125 mmol) in 1 mL THF was transferred into the mixture by cannular at 0 °C. The reaction was stirred for 20 min at 0 °C and 10 min at rt. The reaction was then quenched by water. The mixture was concentrated under vacuum. Flash chromatography on neutral silical gel (15:1 hexanes:EtOAc) gave **22** (43.3 mg, 65%) as E : Z = 62: 38 diastereoisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (m, 2H, Ar-*H*), 7.21 (m, 3H, Ar-*H*), 6.28 (br d, *J* = 12.52 Hz, 0.62H, C=C(OMe)-*H*), 6.12 (m, 1H, C=C-*H*), 5.84 (dt, *J* = 6.14, 1.32 Hz, 0.38H, C=C(OMe)-*H*), 4.69 (dt, *J* = 12.52, 7.25 Hz, 0.62H, (OMe)HC=C-*H*) 4.54 (m, 2H, O-CH_2-O), 4.30 (m, 1.38H), 3.62 (m, 1H), 3.55 (s, 1.26H, O-CH_3), 3.47 (s, 2.01H, O-CH_3), 3.16 (s, 1.87H, O-CH_3), 3.14 (s, 1.23H, O-CH_3), 2.25 (m, 2H), 2.10 (m, 1H), 1.97 (m, 1H), 1.68 (m, 3H), 1.48 (m, 2H), 0.86 (s, 9H, Si-C(CH_3)$_3$), 0.14 (d, *J* = 21.75 Hz, 6H, Si-CH_3).



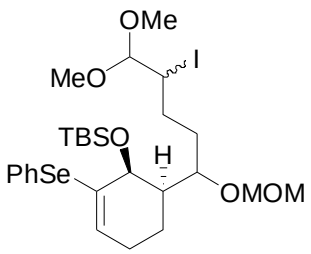
23

6-(5-Methoxy-1-methoxymethoxy-pent-4-enyl)-2-phenylselanyl-cyclohex-2-enol (23). **22** (52 mg, 0.1 mmol) was dissolved into 1 mL THF. TBAF/THF (0.3 mL, 0.3 mmol) was added, and the mixture was stirred for 6 h under N_2. The reaction was then quenched with water, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (1 × 20 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. Flash chromatography on neutral silical gel (20:1 hexanes:EtOAc) gave **23** (37 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (m, 2H, Ar-*H*), 7.22 (m, 3H, Ar-*H*), 6.28 (br s, 0.58H, C=C(OMe)-*H*), 6.25 (m, 1H, C=C-*H*), 5.86 (dt, *J* = 6.15, 1.54 Hz, 0.42H, C=C(OMe)-*H*), 4.69-4.29 (m, 2.5H), 4.26 (m, 1.5H), 3.66 (d, *J* = 4.40 Hz, 0.46H), 3.59 (m, 1H), 3.55 (s, 1.45H, O-CH_3), 3.52 (d, *J* = 4.39 Hz, 0.57H), 3.48 (s, 1.71H, O-CH_3), 3.20 (s, 1.66H, O-CH_3), 3.18 (s, 1.44H, O-CH_3), 2.21 (m, 2H), 2.10 (m, 1H), 2.09 (m, 1H), 1.68 (m, 3H), 1.57 (m, 1H), 1.43 (m, 1H).



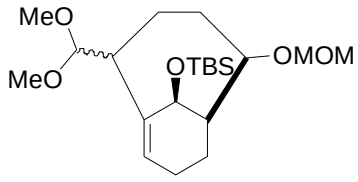
24 + **25**

5-(2-Hydroxy-3-phenylselanyl-cyclohex-3-enyl)-5-methoxymethoxy-pentanal (24), 6-(5-Iodo-6-methoxy-tetrahydro-pyran-2-yl)-2-phenylselanyl-cyclohex-2-enol (25). **23** (10 mg, 0.024 mmol) was dissolved in 0.5 mL anhydrous CH_2Cl_2 and protected by N_2. At 0 $^{\circ}$C, NIS (7 mg, 0.029 mmol) was added. The reaction mixture was stirred at 0 $^{\circ}$C for 2 h and was then concentrated without work-up. Flash chromatography on silica gel (20:1 hexanes: EtOAc) gave **24** (3 mg , 34%,) and **25** (6.5 mg, 51%). **24** ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (dd, *J* = 5.27, 2.41 Hz, 1H), 7.47 (m, 2H, Ar-*H*), 7.24 (m, 3H, Ar-*H*), 6.25 (m, 1H, C=C-*H*), 4.59 (s, 2H, O-C*H*-O), 4.48 (m, 1H, O-C*H*), 4.20 (m, 1H, O-C*H*), 3.40 (m, 2H), 3.21 (s, 3H, O-C*H*$_3$), 2.24 (m, 2H), 1.99 (m, 2H), 1.70 (m, 2H), 1.53 (m, 2H), 1.42 (m, 1H). **25** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (m, 2H, Ar-*H*), 7.24 (m, 3H, Ar-*H*), 6.14 (dd, *J* = 4.84, 2.90 Hz, 1H, C=C-*H*), 4.83 (br s, 1H, O-C*H*-O), 4.39 (t, *J* = 3.48 Hz, 1H), 4.25 (m, 1H), 3.98 (m, 1H, I-C-*H*), 3.35 (s, 3H, O-C*H*$_3$), 2.37 (d, *J* = 3.74 Hz, 1H), 2.19 (m, 3H), 1.83 (m, 3H), 1.62 (m, 3H).



28

***tert*-Butyl-[6-(4-iodo-5,5-dimethoxy-1-methoxymethoxy-pentyl)-2-phenylselanyl-cyclohex-2-enyloxy]-dimethyl-silane (28)**. Compound **22** (18 mg, 0.034 mmol) was dissolved in 1 mL anhydrous CH_2Cl_2 and protected by N_2. At 0 °C, anhydrous methanol (0.015 mL, 0.34 mmol) and NIS (9 mg, 0.04 mmol) were added. The reaction mixture was stirred at 0 °C for 1.5 h and was then concentrated without work-up. Flash chromatography on silica gel (5:1 hexanes: EtOAc) gave **28** (19.7 mg , 85%, pale yellow oil) as two diastereoisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (m, 2H, Ar-*H*), 7.22 (m, 3H, Ar-*H*), 6.09 (m, 1H, C=C-*H*), 4.58 (m, 2H, O-C*H*$_2$-O), 4.29 (br s, 1H), 4.24 (m, 1H), 4.05 (m, 1H, I-C-*H*), 3.42 (m, 4H, O-C*H*$_3$), 3.18 (s, 2H, O-C*H*$_3$), 2.25 (m, 2H), 1.90 (m, 2H), 1.78 (m, 2H), 1.65 (m, 2H), 1.47 (m, 1H) 0.87 (s, 9H, Si-C(C*H*$_3$)$_3$), 0.12 (2s, 6H, Si-C*H*$_3$).



29

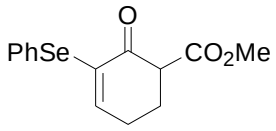
10-(*tert*-Butyl-dimethyl-silanyl)-2-dimethoxymethyl-5-methoxymethoxy-bicyclo[4.3.1]dec-1(9)-en-10-ol (29). **Method A**: Compound **22** (18 mg, 0.034

mmol) and AIBN (1 mg, 0.0056 mmol) were dissolved in anhydrous benzene or toluene (3 mL) and stirred under N_2 at rt. The n-Bu_3SnH (0.018 mL, 0.06 mmol) was added dropwise. The mixture was then refluxed for 15 h. The reaction mixture was concentrated under vacuum and extracted in 2.5 mL ether and 2.5 mL saturated KF solution. The solution was stirred for another 1 h and concentrated. Flash chromatography (SiO_2, gradient, 100:1 → 50:1 → 20:1 hexanes:EtOAc) gave **29** (3.4 mg, 30%) as two diastereoisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (m, 1H, C=C-*H*), 4.67 (dd, *J* = 33.50, 6.82 Hz, 1.38H, O-C*H*$_2$-O), 4.62 (dd, *J* = 22.83, 6.67 Hz, 0.62H, O-C*H*$_2$-O), 4.36 (m, 1H), 4.23 (br s, 1H), 3.98 (m, 0.36H), 3.62 (m, 0.64H), 3.36 (2 s, 3H, O-C*H*$_3$), 3.29 (m s, 6H, O-C*H*$_3$), 2.11 (m, 1H), 1.96 (m, 2H), 1.76 (m, 2H), 1.59 (m, 2H), 1.43(m, 2H), 0.86 (2 s, 9H, -C(C*H*$_3$)$_3$), 0.07 (2 s, 6H, -C*H*$_3$).

Method B: Almost same with Method A. The n-Bu_3SnH and a half AIBN mixture was added via syringe pump in a period of 4 h.

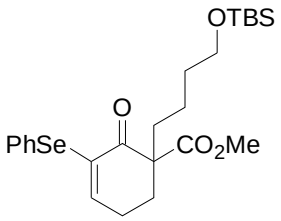
Method C: The mixture of **22** and AIBN was added with 1.5 equiv. $Bu_3SnSnBu_3$ or $Me_3SnSnMe_3$ and irradiated by sun lamp or mercury lamp.

(All the radical reactions followed the three methods above.)



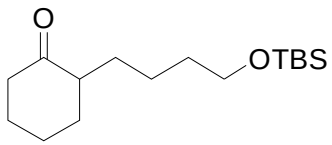
31

2-Oxo-3-phenylselanyl-cyclohex-3-enecarboxylic acid methyl ester (31). Diisopropylamine (0.119 mL, 0.852 mmol) was dissolved in anhydrous ether (6.5 mL) and stirred under N_2 at 0 °C for 10 min. *n*-BuLi (0.57 mL, 1.35 M, 0.767 mmol) was added and the reaction was stirred at 0 °C for 30 min. The 0 °C bath was changed by the dry ice – acetone bath. **6** (107 mg, 0.426 mmol) was dissolved in anhydrous ether (2.5 mL) at at 0 °C and added dropwise to the organolithium solution via cannular over a period of 30 min. After another 40 min stirring, Mander's reagent (0.169 mL, 2.13 mmol) dissolved in 1 mL ether was added fast into the reaction mixture by cannular. Let the reaction warm to rt in a period of 2 h. The reaction was stirred for 1 h at rt. The reaction was quenched by $NaHCO_3$ solution and extracted with EtOAc (4 × 100 mL). The organic layer was washed by brine and dried over $MgSO_4$, filtered, and concentrated under vacuum to give a yellow oil. The crude material was purified by flash chromatography (SiO_2, gradient, 5:1 hexanes:EtOAc) to give **31** (107 mg, 81%) as a pale yellow crystal. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (m, 2H, Ar-*H*), 7.34 (m, 3H, Ar-*H*), 6.48 (t, *J* = 4.50 Hz, 1H, C=C-*H*), 3.74 (s, 1H, O-C*H*$_3$), 3.52 (dd, *J* = 9.89, 5.05 Hz, 1H), 2.40 (m, 3H), 2.20 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 190.9 (C=O), 170.2, 146.6, 136.8, 134.3, 129.9, 129.0, 126.9, 53.8, 52.7, 26.6, 26.0.



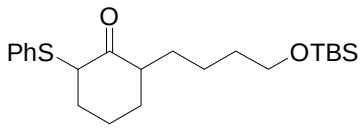
32

1-[4-(*tert*-Butyl-dimethyl-silanyloxy)-butyl]-2-oxo-3-phenylselanyl-cyclohex-3-enecarboxylic acid methyl ester (32). NaH (3 mg, 0.125 mmol) was dissolved in anhydrous DMF (1 mL) and stirred at 0 °C under N_2. **31** (31 mg, 0.10 mmol) dissolved in 1 mL anhydrous DMF was added via cannular. The reaction was tirred for 10 min at 0 °C and 30 min at rt. It was then recooled to 0 °C and *tert*-Butyl-(4-iodo-butoxy)-dimethyl-silane (0.125 mL, 0.40 mmol) was added. Let the reaction warm to rt and stir overnight. The reaction mixture was then quenched by saturated NH_4Cl solution, extracted with CH_2Cl_2 (3 × 50 mL). The organic fractions were combined and washed with saturated H_2O (2 × 40 mL), and saturated NaCl (1 × 40 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. Flash chromatography on silica gel (25:1 hexanes:EtOAc) gave **32** (36.7 mg, 74%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (m, 2H, Ar-*H*), 7.32 (m, 3H, Ar-*H*), 6.42 (t, *J* = 4.62 Hz, 1H, C=C-*H*), 3.66 (s, 3H, O-C*H*$_3$), 3.57 (t, *J* = 6.37 Hz, 2H, O-C*H*$_2$-), 2.44 (m, 2H), 2.27 (m, 1H), 1.95 (m, 2H), 1.76 (m, 1H), 1.49 (m, 2H), 1.32 (m, 2H), 0.86 (s, 9H, Si-C(C*H*$_3$)$_3$), 0.01 (s, 6H, Si-C*H*$_3$); ^{13}C NMR (400 MHz, $CDCl_3$) δ 193.2 (C=O), 171.8, 145.8, 136.6, 134.3, 129.7, 128.8, 127.5, 63.0, 58.0, 52.6, 34.0, 33.3, 30.2, 26.2, 25.8, 21.2, 18.5, -5.0.



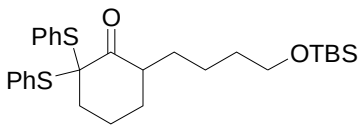
35

2-[4-(*tert*-Butyl-dimethyl-silanyloxy)-butyl]-cyclohexanone (35). KHMDS (0.9 M in THF, 6 mL, 5.5 mmol) was dissolved in anhydrous THF (50 mL). **34** (0.46 mL, 4.44 mmol) was added dropwise at -78 °C by syringe. The reaction was stirred for 1.5 h at -78 °C and *tert*-Butyl-(4-iodo-butoxy)-dimethyl-silane (1.16 mL, 4.44 mmol) was added. The reaction mixture was warmed to rt naturally and stirred for 5.5 h. The reaction was quenched by $NaHCO_3$ solution and extracted with EtOAc (4 × 100 mL). The organic layer was washed by brine and dried over $MgSO_4$, filtered, and concentrated under vacuum to give a colorless oil. The crude material was purified by flash chromatography (SiO_2, gradient, 25:1 hexanes:EtOAc) to give **35** (841 mg, 67%) as a pale yellow crystal. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.57 (t, J = 6.53 Hz, 2H), 2.30 (m, 3H), 2.08 (m, 2H), 1.83 (m, 2H), 1.64 (m, 2H), 1.50 (m, 2H), 1.21 (m, 4H), 0.86 (s, 9H, Si-C(CH_3)$_3$), 0.01 (s, 6H, Si-CH_3).



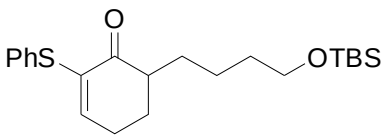
36

2-[4-(*tert*-Butyl-dimethyl-silanyloxy)-butyl]-6-phenylsulfanyl-cyclohexanone (36). Under a nitrogen atmosphere, to a solution of **35** (2.0 g, 7.06 mmol) in THF (20 mL) was added LHMDS (1.0 M in the THF, 8.1 mL, 8.12 mmol) at -78 °C. After being stirred for 1 h, a solution of $PhSSO_2Ph$ (1.875 g, 7.42 mmol) in the THF (10 mL) was added. The reaction mixture was allowed to warm to rt over a period of 2 h, then quenched with aqueous NH_4Cl solution and extracted with AcOEt. The reaction mixture was washed by brine, dried over $MgSO_4$ and concentrated under vacuum. Flash chromatography on silica gel (50:1 hexanes:EtOAc) gave **36** (2.235 g, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (m, 2H, Ar-*H*), 7.26 (m, 3H, Ar-*H*), 3.97 (m, 1H), 3.86 (t, *J* = 3.96 Hz, 1H), 3.60 (m, 4H), 3.11 (m, 1H), 2.39 (m, 1H), 2.27 (m, 1H), 1.90 (m, 1H), 1.75 (m, 2H), 1.53 (m, 2H), 1.38 (m, 2H), 0.91 (s, 9H, Si-C(CH_3)$_3$), 0.06 (s, 6H, Si-CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 210.5, 208.1, 134.3, 134.2, 132.8, 131.5, 129.3, 129.2, 127.5, 127.4, 63.3, 59.2, 55.8, 51.5, 45.8, 36.8, 34.8, 34.4, 34.1, 33.2, 33.1, 29.3, 29.2, 26.2, 25.7, 23.7, 23.5, 21.5, 18.6, -5.0.



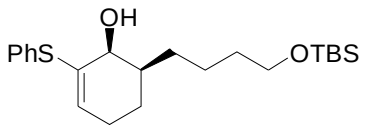
37

6-[4-(*tert*-Butyl-dimethyl-silanyloxy)-butyl]-2,2-bis-phenylsulfanyl-cyclohexanone (37). A solution of **36** (2.29 g, 5.86 mmol) in THF (12 mL) was added dropwise to a slurry of ^{t}BuOK (757 mg, 6.74 mmol) in THF (20 mL) at 0 °C via cannular, under a nitrogen atmosphere. The reaction mixture was stirred for 30 min, and a solution of $PhSSO_2Ph$ (1.556 g, 6.15 mmol) in THF (10 mL) was added. The reaction mixture was stirred for 2 h, then quenched with aqueous NH_4Cl solution and extracted with AcOEt. The reaction mixture was washed by brine, dried over $MgSO_4$ and concentrated under vacuum. Flash chromatography on silica gel (1:1 hexanes:CH_2Cl_2) gave **37** (2.810 g, 96%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (m, 4H, Ar-*H*), 7.33 (m, 6H, Ar-*H*), 3.50 (t, *J* = 6.59 Hz, 2H), 3.19 (m, 1H), 2.09 (m, 4H), 1.66 (m, 2H), 1.36 (m, 3H), 1.09 (m, 3H), 0.88 (s, 9H, Si-C(CH_3)$_3$), 0.02 (s, 6H, Si-CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 205.6, 137.5, 134.2, 131.4, 131.3, 129.3, 129.2, 129.1, 128.7, 74.2, 63.3, 46.7, 42.3, 34.1, 33.1, 29.5, 26.2, 23.5, 22.6, 18.6, -5.0.



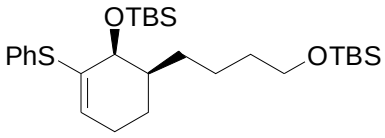
38

6-[4-(*tert*-Butyl-dimethyl-silanyloxy)-butyl]-2-phenylsulfanyl-cyclohex-2-enone (38). To a solution of **37** (2.8 g, 5.6 mmol) in CH_2Cl_2 (50 mL) was added recystalized *m*-CPBA (100% purity, 966 mg, 5.6 mmol) at -61 °C ($CHCl_3/CO_2$ bath). After being stirred for 2.5 h, the reaction was warmed to rt and stirred for 30 min. The reaction was then quenched by saturated $Na_2S_2O_3$ solution and extracted by CH_2Cl_2. The reaction mixture was washed by $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated under vacuum. Flash chromatography on silica gel (25:1 hexanes: EtOAc) gave **38** (1.634 g, 75%) as a colorless oil and the alcohol without TBS- group as the byproduct. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (m, 2H, Ar-*H*), 7.31 (m, 3H, Ar-*H*), 6.38 (t, *J* = 4.39 Hz, 1H, C=C-*H*), 3.58 (t, *J* = 6.38 Hz, 2H, O-C*H*$_2$), 2.36 (m, 3H), 2.08 (m, 1H), 1.86 (m, 1H), 1.75 (m, 1H), 1.52 (m, 2H), 1.40 (m, 2H), 1.32 (m, 1H), 0.86 (s, 9H, Si-C(C*H*$_3$)$_3$), 0.02 (s, 6H, Si-C*H*$_3$); ^{13}C NMR (400 MHz, $CDCl_3$) δ 197.7, 144.0, 137.4, 134.1, 132.5, 129.6, 128.4, 63.2, 47.4, 33.1, 29.9, 29.2, 27.8, 26.3, 26.2, 23.4, 18.6, -5.0.



39

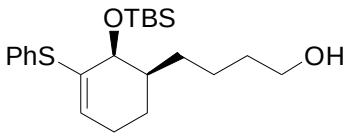
6-[4-(tert-Butyl-dimethyl-silanyloxy)-butyl]-2-phenylsulfanyl-cyclohex-2-enol (39). Compound **38** (1.309 g, 3.365 mmol) was dissolved in 30 mL MeOH. $CeCl_3 \cdot 7H_2O$ (1.87 g, 5.05 mmol) was added at 0 °C. $NaBH_4$ (192 mg, 5.05 mmol) was added into the mixture very slowly. Let the reaction worm to rt and stirred for 1 h. The solution was then quenched by saturated NH_4Cl solution, concentrated under vacuum, re-dissolved in Et_2O (100 mL). The Et_2O layer was concentrated under vacuum to provide product **39** as a colorless oil (1.263 g, 96%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (m, 4H, Ar-*H*), 7.20 (m, 1H, Ar-*H*), 6.20 (dd, *J* = 4.83, 3.07 Hz, 1H, C=C-*H*), 3.88 (t, *J* = 3.30 Hz, 1H, O-C*H*), 3.56 (t, *J* = 6.60 Hz, 2H, -CH_2-O), 2.21 (m, 2H), 1.83 (m, 1H), 1.49(m, 6H), 1.33 (m, 3H), 0.85 (s, 9H, Si-C(CH_3)$_3$), 0.00 (s, 6H, Si-CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 137.2, 135.0, 134.3, 130.3, 129.3, 126.9, 77.6, 68.1, 63.4, 40.4, 33.2, 31.6, 27.8, 26.2, 23.5, 21.8, 18.6, -5.0.



40

{6-(*tert*-Butyl-dimethyl-silanyloxy)-5-[4-(tert-butyl-dimethyl-silanyloxy)-butyl]-cyclohex-1-enylsulfanyl}-benzene (40). Alcohol **39** (1.156 g, 2.96 mmol) was dissolved in 30 mL anhydrous CH_2Cl_2 and stirred at 0 °C under N_2 for 5 min.

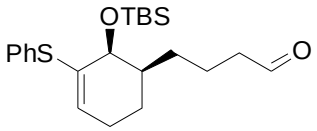
Distilled pyridine (1.2 mL, 14.8 mmol) and TBS-OTf (1.8 mL, 7.4 mmol) were added and the solution was stirred 1 h at 0 °C and 5 h at rt. The reaction mixture was then quenched by water, extracted by CH_2Cl_2, washed by $NaHCO_3$ solution, brine, dried over $MgSO_4$ and concentrated under vacuum. Flash chromatography on silica gel (10:1 hexanes:EtOAc) gave **40** (1.345 g, 90%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (m, 4H, Ar-*H*), 7.15 (m, 1H, Ar-*H*), 6.02 (t, *J* = 3.52 Hz, 1H, C=C-*H*), 3.94 (d, *J* = 2.64 Hz, 1H, C*H*-O), 3.55 (t, *J* = 6.59 Hz, 2H, -CH_2-O), 2.19 (m, 2H), 1.66 (m, 1H), 1.46 (m, 5H), 1.27 (m, 3H), 0.86 (s, 9H, Si-C(CH_3)$_3$), 0.84 (s, 9H, Si-C(CH_3)$_3$), 0.01 (s, 6H, Si-CH_3), 0.00 (s, 6H, Si-CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 137.2, 136.7, 134.3, 129.4, 129.1, 126.1, 70.1, 63.5, 41.8, 33.3, 31.5, 27.4, 26.3, 26.2, 25.9, 23.6, 21.6, 18.8, -2.7, -3.3, -4.3, -5.0.



41

4-[2-(*tert*-Butyl-dimethyl-silanyloxy)-3-phenylsulfanyl-cyclohex-3-enyl]-butan-1-ol (41). **40** (1.345 g, 2.66 mmol) was dissolved in THF (9 mL) and stirred at rt. An AcOH (30 mL)/ H_2O (15 mL) mixture was added dropwise. The reaction mixture was stirred overnight and then concentrated. Flash chromatography on silica gel (5:1

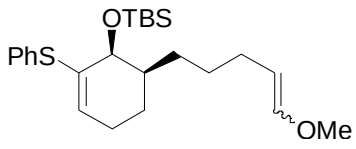
hexanes:EtOAc) gave **40** (937 mg, 90%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (m, 4H, Ar-*H*), 7.16 (m, 1H, Ar-*H*), 6.02 (t, *J* = 3.51 Hz, 1H, C=C-*H*), 3.95 (d, *J* = 2.64 Hz, 1H, C*H*-O), 3.59 (t, *J* = 6.58 Hz, 2H, -CH_2-O), 2.18 (m, 2H), 1.68 (m, 1H), 1.52 (m, 5H), 1.32 (m, 3H), 0.86 (s, 9H, Si-C(CH_3)$_3$), 0.12 (s, 3H, Si-CH_3), 0.00 (s, 3H, Si-CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 137.1, 136.6, 134.3, 129.5, 129.2, 126.2, 70.1, 63.2, 41.7, 33.2, 31.4, 27.3, 26.3, 23.5, 21.6, 18.8, 14.4, -3.3, -4.3.



42

4-[2-(*tert*-Butyl-dimethyl-silanyloxy)-3-phenylsulfanyl-cyclohex-3-enyl]-butyraldehyde (42). Alcohol **41** (730 mg, 1.87 mmol) was dissolved in wet CH_2Cl_2 (20 mL). $NaHCO_3$ (785 mg, 9.35mmol) and DMP (2.38 g, 5.61mmol) were added and stirred for 0.5 h at rt. The reaction mixture was then diluted with CH_2Cl_2 (100 mL), and washed with saturated $Na_2S_2O_3$ (2 × 10 mL), saturated $NaHCO_3$ (1 × 10 mL), and saturated NaCl (1 × 20 mL). The organic layer was then dried with $MgSO_4$, filtered, and concentrated under vacuum to provide the crude product. Flash chromatography on neutral silica gel (15:1 hexanes:EtOAc) gave **42** (525 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (t, *J* = 1.76 Hz, 1H, O=C*H*), 7.24 (m, 4H, Ar-*H*),

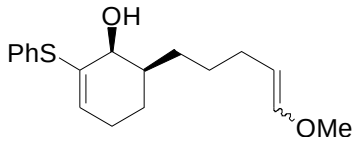
7.16 (m, 1H, Ar-*H*), 6.00 (t, *J* = 3.41 Hz, 1H, C=C-*H*), 3.96 (d, *J* = 2.85 Hz, 1H, C*H*-O), 2.38 (m, 2H), 2.20 (m, 2H), 1.55 (m, 6H), 1.28 (m, 1H), 0.85 (s, 9H, Si-C(CH_3)$_3$), 0.13 (s, 3H, Si-CH_3), 0.00 (s, 3H, Si-CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 202.8, 136.7, 136.4, 134.3, 129.6, 129.2, 126.3, 70.1, 44.3, 41.5, 31.0, 27.1, 26.3, 21.5, 20.0, 18.8, -3.3, -4.3.



43

***tert*-Butyl-[6-(5-methoxy-pent-4-enyl)-2-phenylsulfanyl-cyclohex-2-enyloxy]-dimethyl-silane (43).** Methoxymethyl triphenylphosphonate chloride (1.0 g, 2.84 mmol) was dissolved in anhydrous THF (10 mL) and protected by N_2. KO^{t}Bu (2.7 mL, 1M in THF, 2.7 mmol) was added dropwise at 0 °C and stirred for 30 min. Aldehyde **42** (525 mg, 13.5 mmol) in 5 mL THF was transferred into the mixture by cannular at 0 °C. The reaction was stirred for 20 min at 0 °C and 10 min at rt. The reaction was then quenched by water. The mixture was concentrated under vacuum. Flash chromatography on neutral silical gel (20:1 hexanes:EtOAc) gave **43** (484 mg, 86%) as E : Z = 59 : 41 diastereoisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 4H, Ar-*H*), 7.17 (m, 1H, Ar-*H*), 6.24 (br d, *J* = 12.52 Hz, 0.59H, C=C(OMe)-*H*), 6.05 (m,

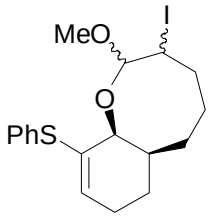
1H, C=C-*H*), 5.85 (dt, *J* = 6.38, 1.31 Hz, 0.41H, C=C(OMe)-*H*), 4.69 (dt, *J* = 7.47, 7.25 Hz, 0.60H, (OMe)HC=C-*H*), 4.31 (m, 0.35H, (OMe)HC=C-*H*), 3.96 (br s, 1H, C*H*-O), 3.55 (s, 1.22H, O-CH_3), 3.48 (s, 1.65H, O-CH_3), 2.19 (m, 2H), 2.03 (m, 1H), 1.88 (m, 1H), 1.68 (m, 1H), 1.52 (m, 2H), 1.28 (m, 4H), 0.88 (s, 9H, Si-C(CH_3)$_3$), 0.15 (s, 3H, Si-CH_3), 0.02 (s, 3H, Si-CH_3); ^{13}C NMR (400 MHz, $CDCl_3$) δ 147.3, 146.3, 137.5, 137.3, 136.8, 136.7, 134.3, 129.4, 129.3, 129.2, 126.1, 126.0, 107.0, 103.1, 70.3, 70.1, 59.7, 56.1, 41.7, 31.4, 31.1, 28.7, 28.2, 27.7, 27.5, 27.4, 26.4, 26.3, 24.2, 21.6, 21.5, 18.8, -3.2, -4.2.



44

6-(5-Methoxy-pent-4-enyl)-2-phenylsulfanyl-cyclohex-2-enol (44). **43** (87 mg, 0.21 mmol) was dissolved into 2 mL THF. TBAF/THF (0.63 mL, 0.3 mmol) was added, and the mixture was stirred for 6 h under N_2. The reaction was then quenched with water, and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (1 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum. Flash chromatography on neutral silical gel (10:1 hexanes:EtOAc) gave **44** (51.5 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (m, 4H,

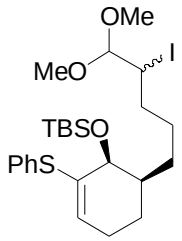
Ar-*H*), 7.19 (m, 1H, Ar-*H*), 6.23 (d, *J* = 12.52 Hz, 0.64H, C=C(OMe)-*H*), 6.20 (m, 1H, C=C-*H*), 5.83 (dt, *J* = 4.84, 1.53 Hz, 0.42H, C=C(OMe)-*H*), 4.68 (dt, *J* = 12.53, 7.47 Hz, 0.63H, *H*-C=CH(OMe)), 4.29 (m, 0.34H, *H*-C=CH(OMe)), 3.87 (m, 1H), 3.53 (s, 1.12H, O-C*H*$_3$), 3.46 (s, 2.03H, O-C*H*$_3$), 2.20 (m, 2H), 2.02 (m, 1H), 1.87 (m, 2H), 1.50 (m, 4H), 1.34 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 147.3, 146.4, 137.4, 137.3, 135.0, 134.3, 134.3, 130.3, 130.2, 129.3, 129.3, 126.9, 126.8, 107.0, 103.1, 68.2, 68.1, 59.7, 56.1, 40.3, 40.2, 31.4, 31.3, 28.5, 28.1, 27.8, 27.8, 27.5, 24.1, 21.9, 21.8.



45

3-Iodo-2-methoxy-10-phenylsulfanyl-3,4,5,6,6a,7,8,10a-octahydro-2H-benzo[b]oxocine (45). **44** (40 mg, 0.132 mmol) was dissolved in 2 mL anhydrous CH_2Cl_2 and protected by N_2. At 0 °C, NIS (35 mg, 0.158 mmol) was added. The reaction mixture was stirred at 0 °C for 2 h and was then concentrated without work-up. Flash chromatography on silica gel (100:1 hexanes: EtOAc) gave **45** (50.5 mg , 89%) as four diastereoisomers. **The major diastereoisomers:** ^{1}H NMR (500 MHz,

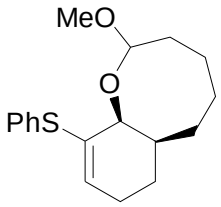
$CDCl_3$) δ 7.27 (m, 4H, Ar-*H*), 7.17 (m, 1H, Ar-*H*), 6.11 (br s, 1H, C=C-*H*), 4.93 (br s, 1H, O-C*H*-O), 4.66 (br s, 1H), 4.31 (m, 1H), 3.61 (br s, 3H, O-CH_3), 2.38 (br s, 1H), 2.18 (m, 3H), 1.70 (m, 1H), 1.55 (m, 4H), 1.38 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 138.2, 136.4, 134.2, 133.0, 132.0, 129.7, 129.3, 129.2, 127.2, 126.4, 107.1, 104.0, 61.1, 40.0, 31.4, 31.3, 28.5, 28.1, 27.8, 27.5, 24.3, 21.9, 13.9.



47

***tert*-Butyl-[6-(4-iodo-5,5-dimethoxy-pentyl)-2-phenylsulfanyl-cyclohex-2-enyloxy]-dimethyl-silane (47)**. Compound 4**3** (31 mg, 0.074 mmol) was dissolved in 1 mL anhydrous CH_2Cl_2 and protected by N_2. At 0 °C, anhydrous methanol (0.03 mL, 0.74 mmol) and NIS (20 mg, 0.089 mmol) were added. The reaction mixture was stirred at 0 °C for 1.5 h and was then concentrated without work-up. Flash chromatography on neutral silica gel (100:1 hexanes: EtOAc) gave **47** (36.1 mg , 85%, clolorless oil) as two diastereoisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (m, 5H, Ar-*H*), 6.00 (m, 1H, C=C-*H*), 4.22 (m, 1H, O-CH_2-O), 4.03 (m, 1H), 3.96 (br s, 1H), 3.40 (m, 3H, O-CH_3), 3.38 (s, 3H, O-CH_3), 2.20 (m, 2H), 1.71 (m, 3H), 1.51 (m, 4H), 1.30 (m, 2H), 0.86 (s, 9H, Si-C(CH_3)$_3$), 0.13 (s, 3H, Si-CH_3), 0.00 (s, 3H, Si-CH_3);

^{13}C NMR (400 MHz, $CDCl_3$) δ 144.9, 136.7, 135.9, 133.8, 129.8, 129.7, 129.4, 128.8, 128.7, 127.6, 127.2, 47.9, 29.5, 26.1, 31.4, 31.3, 28.5, 28.1, 27.8, 27.5, 24.3, 21.9.



2-Methoxy-10-phenylsulfanyl-3,4,5,6,6a,7,8,10a-octahydro-2H-benzo[b]oxocine.

Exactly as the methods of compound **29**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (m, 4H, Ar-*H*), 7.19 (m, 1H, Ar-*H*), 5.99 (dd, *J* = 4.40, 3.08 Hz, 1H, C=C-*H*), 4.51 (m, 1H, O-C*H*-O), 4.17 (d, *J* = 2.42 Hz, 1H), 3.47 (s, 3H, O-C*H*$_3$), 2.18 (m, 2H), 1.80 (m, 1H), 1.64 (m, 6H), 1.44 (m, 1H), 1.35 (m, 2H), 1.16 (m, 1H).

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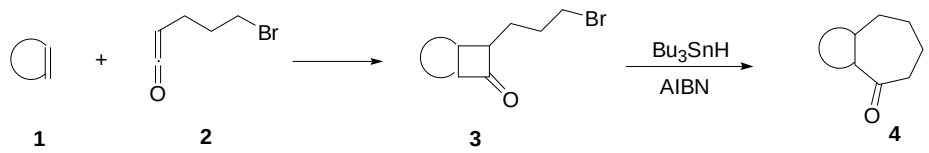
Chapter 3. Radical-Initialized Cyclobutane Ring Expansion Strategy toward the Synthesis of the Model Molecule of Phomoidride B

3.1 Introduction

Free radical-mediated ring expansion and related annulations have been widely studied and used in the synthesis of natural and unnatural products.[1]

Cyclobutane ring is the most popular project for the radical-mediated ring expansion and related annulations strategy. For example, free radical reaction of the cyclobutanone adduct yields the ring-expanded annulation product. (Scheme 3.1)[2,3]

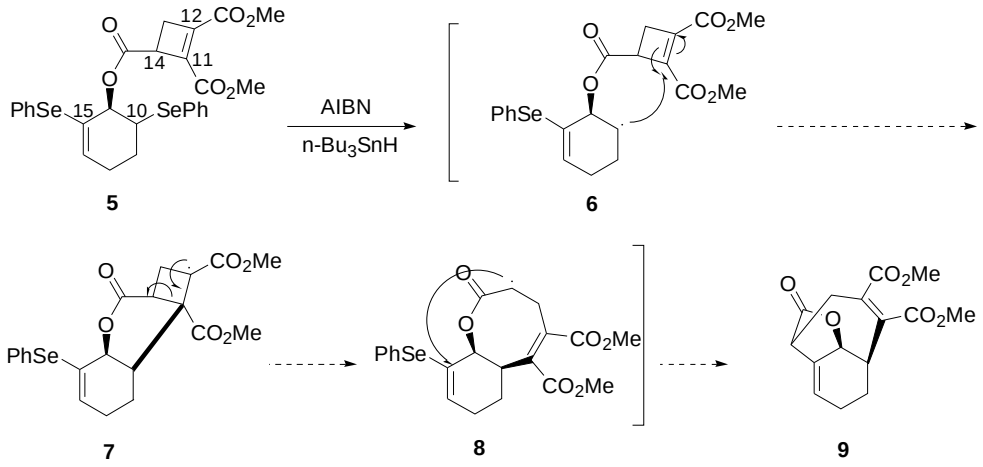


Scheme 3.1 Cyclobutane Ring Expansion.[2,3]

This radical-initiated ring expansion strategy was also designed to synthesize a Phomoidride model. (Scheme 3.2) When compound **5** is treated under regular radical generation conditions, it should generate a radical at C10. This radical will attack the C11-C12 double bond to generate a new radical at C12. Because of the

cyclobutane ring strain, the C12 radical will break the C11-C14 bond to form an 8-membered ring and a radical at C14. The C14 radical will cyclize into the selenenyl ether of **8**, expelling the phenylselenenyl group to provide **9**.

This strategy would be much more convenient than any route that has been applied in Phomoidrides synthesis if it really worked, since it simply avoids the trouble brought by the maleic anhydride group. As shown in scheme 3.2, the double bond at C11-C12 is a Z-olefin which can not be easily made by some alkylation or aldol type reactions described in Chapter 2.



Scheme 3.2 Radical-Initialized Cyclobutane Ring Expansion Strategy..

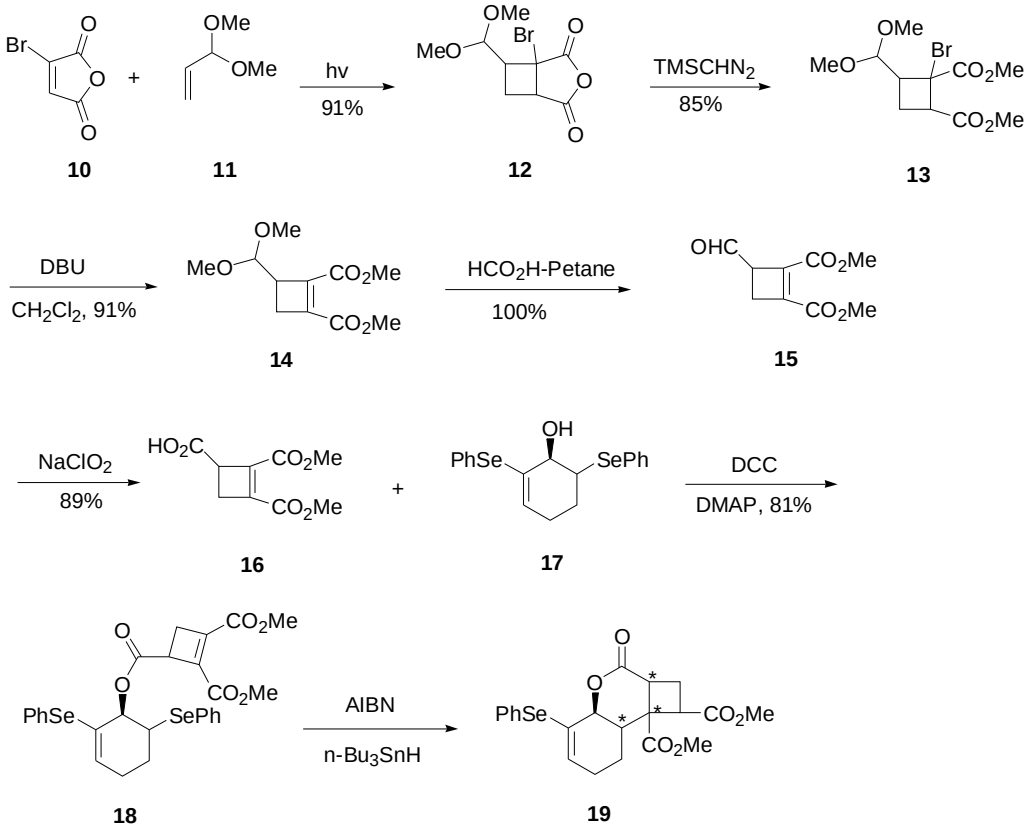
3.2 Specific Aims

The objective of this research was to investigate the radical-initialized cyclobutane ring expansion strategy to synthesize the model system of Phomoidride B. Specific aims include:

1. Investigation of the plausibility of applying radical-initialized cyclobutane ring expansion followed by radical cyclization-elimination strategy in the synthesis of the model system of Phomoidride B.
2. A study of the preparation of some molecule which contains cyclobutene ring generated by photolysis reactions.

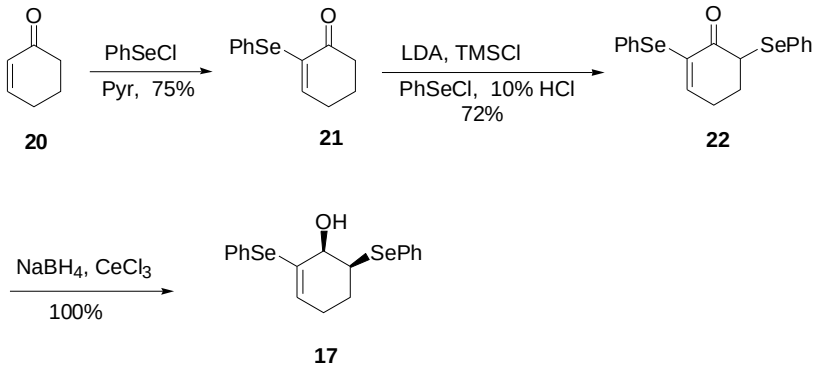
3.3 Attempt to Synthesize a Model Molecule of Phomoidride B

The story started from the photolysis reaction (Scheme 3.3).



Scheme 3.3 Attempt to synthesize model molecule **9**.

[2 + 2] cycloadditon of compound **10** and **11** via photolysis initiation gave **12** in a high yield.[4] Without purification, **12** was methylesterificated by using TMS-diazomethane providing **13** as the major product.[5] Elimination, acidification and oxidation gave compound **16**. DCC coupling reaction with **17** (preparation shown in scheme 3.4) gave the precursor **18**. However, when the reaction was attempted in the radical reaction conditions, compound **19** was the only product isolated.



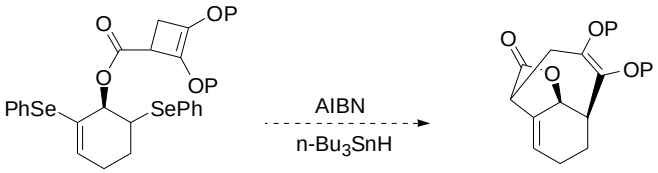
Scheme 3.4 Preparation of **17**.

The potential reason is that there are no or very few overlaps between the radical orbital of intermediate **7** and C11-C14 bond because the cyclobutane ring is very planar. So, the reaction will stop at **19**.

3.4 Summary and Future Work

This strategy did not work at the first try. However, a lot of promising revision works can be tried in the future.

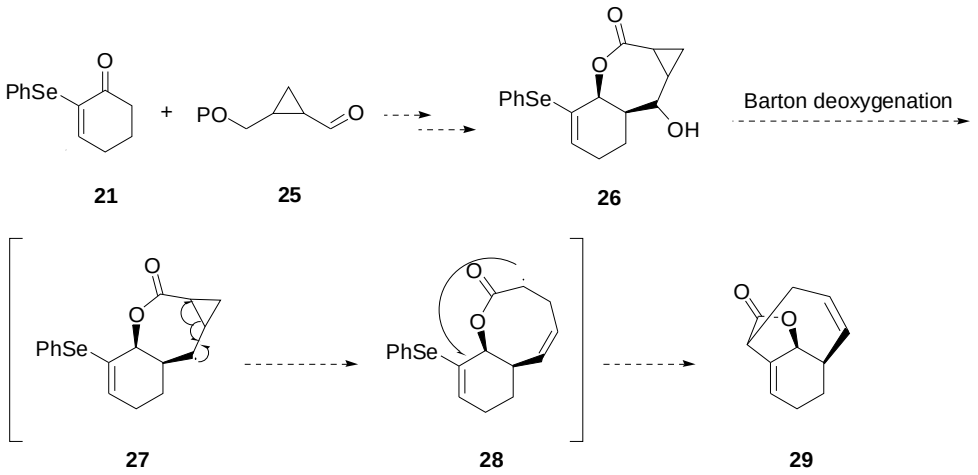
First of all, synthesize compound **23** (scheme 3.5) having two protected hydroxy groups instead of two carbonyl groups which could stabilize the radical to maintain the original ring system. In this way, it is supposed to make the radical more active to achieve the ring expansion idea.



23 **24**

Scheme 3.5 Future Work I.

Secondly, the original system can be optimized to synthesize a target molecule **29** including a cyclopropyl ring. (scheme 3.6) Generate a radical by Barton deoxygenation to open the cyclopropyl ring and to convert the 7-membered ring into an 8-membered ring, followed by a 5-exo radical cyclization to synthesize the real bicyclo[4.3.1]-deca-1,6-diene model molecule **29**.

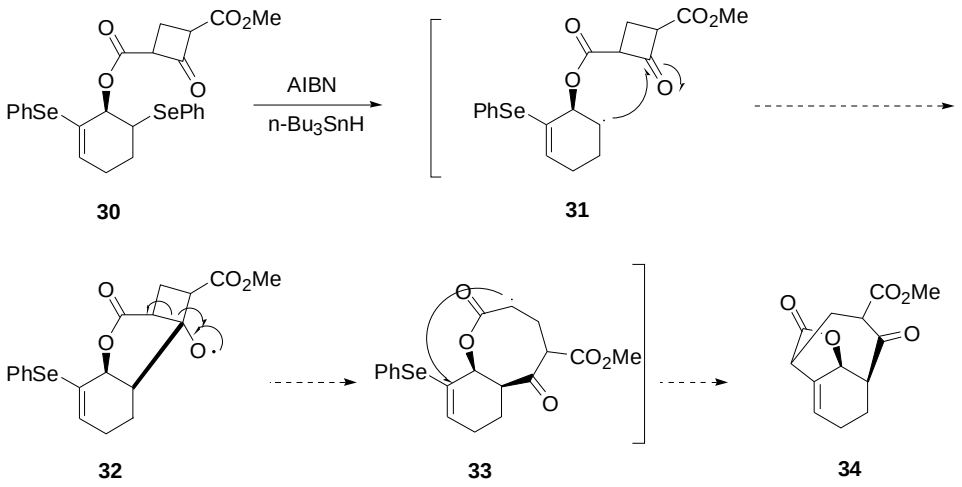


21 **25** **26**

27 **28** **29**

Scheme 3.6 Future Work II.

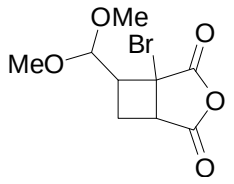
Another possible way is shown in scheme 3.7. This strategy is very similar to the original one (scheme 3.2), but could avoid the cyclobutane ring planar problem.



Scheme 3.7 Future Work III.

3.5 Experimental Section

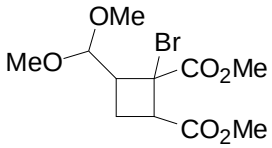
General Methods. See chapter 2.6 for a complete description of all of the relevant general methods. Carbon and proton numbering (in both structures and assignments), when given, generally refers to the Phomoidride B numbering system, not to the IUPAC numbering used in naming these compounds.



12

1-Bromo-7-dimethoxymethyl-3-oxa-bicyclo[3.2.0]heptane-2,4-dione (12). A 25 mL round bottom flask was charged with dry acetonitrile (8.5 mL), bromomaleic anhydride (0.150 mL, 1.57 mmol), acrolein dimethyl acetal (0.58 mL, 6.28 mmol), and benzophenone (72 mg, 0.39 mmol). The solution was purged with argon for 1 h at 0 °C. The mixture was irradiated with a 450-W Hanovia mercury lamp, using a Pyrex filter, for 4 h at 0 °C. The solvent was evaporated under reduced pressure and the residue (91% determined by NMR) was kept for next step reaction

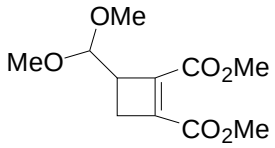
without purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.55 (d, *J* = 3.74 Hz, 1H, O-C*H*-O), 3.42 (m, 6H, C*H*$_3$-O), 2.98 (m, 1H, CH_2-C*H*-CO), 2.60 (m, 1H), 2.31 (m, 2H).



13

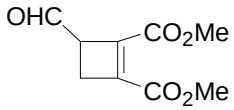
1-Bromo-4-dimethoxymethyl-cyclobutane-1,2-dicarboxylic acid dimethyl ester (13). The reaction to give **12** was repeated three times. The residues **12** were combined into a 100 mL round bottom flask. Anhydrous THF (20 mL) and anhydrous MeOH (20 mL) were added. (Trimethylsilyl)diazomethane (2.0 *M* in hexanes, 6.86 mL, 13.72 mmol) was added dropwise by syringe. The reaction was stirred overnight at rt. The reaction was then quenched by adding several drops of acetic acid, and stirring for 5 min. Saturated NaCl (20 mL) was added and the mixture was extracted with Et_2O (3 × 50 mL). The organic extracts were dried with $MgSO_4$, filtered, and concentrated to provide black oil. Flash chromatography (SiO_2, 9:1 hexanes:EtOAc) gave **13** (1.89 g, 85%, an inseparable, 2:1:1 mixture of diastereoisomers) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.55, 4.41, 4.32 (d, *J* = 5.15, 7.69, 4.62

Hz, 1H, O-C*H*-O), 3.72 (s, 3H, C*H*$_3$-OCO), 3.67 (s, 3H, C*H*$_3$-OCO), 3.33 (s, 3H, C*H*$_3$-O), 3.28 (s, 3H, C*H*$_3$-O), 3.56 (m, 1H, CH$_2$-C*H*-CO), 2.90 (m, 2H), 2.37 (m, 1H).



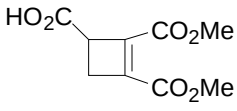
14

3-Dimethoxymethyl-cyclobut-1-ene-1,2-dicarboxylic acid dimethyl ester (14). **13** (993 mg, 3.06 mmol) was added to an oven dried flask which had been previously purged with N_2. Anhydrous chloroform (30 mL) was added. Under N_2 atmosphere, distilled DBU (1.06 mL, 7.65 mmol) was added dropwise via syringe. The pale yellow solvent was refluxed for 2 h. The solution was then concentrated under vacuum. Without work-up, flash chromatography gave **14** (680 mg, 91%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.52 (d, *J* = 5.05 Hz, 1H, O-C*H*-O), 3.78 (s, 3H, C*H*$_3$-OCO), 3.75 (s, 3H, C*H*$_3$-OCO), 3.35 (s, 3H, C*H*$_3$-O), 3.34 (s, 3H, C*H*$_3$-O), 3.26 (m, 1H), 2.66 (dd, *J* = 14.94, 4.40 Hz, 1H), 2.61 (dd, *J* = 15.05, 2.20 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 161.9, 161.7, 142.5, 104.3, 55.7, 53.9, 52.2, 42.7, 29.3.



15

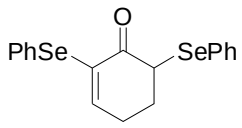
3-Formyl-cyclobut-1-ene-1,2-dicarboxylic acid dimethyl ester (15). **14** (630 mg, 2.58 mmol) was dissolved in formic acid (88%, 9 mL) and pentane (12.5 mL). The mixture was stirred at rt for 1.5 h concentrated under vacuum to provide **15** (510 mg, 100%). This was usually used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (d, *J* = 2.86 Hz, 1H, O=C-*H*), 3.82 (s, 3H, C*H*$_3$-OCO), 3.80 (s, 3H, C*H*$_3$-OCO), 3.78 (m, 1H), 2.86 (m, 2H).



16

Cyclobut-1-ene-1,2,3-tricarboxylic acid 1,2-dimethyl ester (16). Aldehyde **15** (510 mg, 2.58 mmol) was dissolved in *tert*-butanol (13 mL), and the solution was stirred at rt. $NaH_2PO_4{\cdot}H_2O$ (427 mg, 3.10 mmol) and 2-methyl-2-butene (2.6 mL, 2 M in THF, 5.2 mmol) were added and the reaction was stirred for 5 min. $NaClO_2$ (700 mg, 7.74 mmol) was added and the reaction was stirred for an additional 3.5 h. The reaction was quenched with H_2O (2 mL), and 7 drops of 1 M HCl were added (to

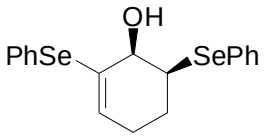
adjust the pH to ca. 1.5). The aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL), dried over $MgSO_4$, filtered, and concentrated to provide 491 mg of acid **16** which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H, C*H*$_3$-OCO), 3.83 (s, 3H, C*H*$_3$-OCO), 3.79 (dd, *J* = 4.95, 2.02 Hz, 1H, O=C-*H*), 3.00 (dd, *J* = 15.20, 4.95 Hz, 1H), 2.88 (dd, *J* = 15.20, 2.01 Hz, 1H).



22

2,6-Bis-phenylselanyl-cyclohex-2-enone (22). Diisopropylamine (0.85 mL, 6.08 mmol) was dissolved in anhydrous THF (25 mL) and stirred under N_2 at 0 °C for 10 min. *n*-BuLi (4 mL, 1.41 M, 5.64 mmol) was added and the reaction was stirred at 0 °C for 3 min. The 0 °C bath was changed by the dry ice – acetone bath. **21** (1.089 g, 4.34 mmol) was dissolved in anhydrous THF (10 mL) and added dropwise to the organolithium solution via cannular over a period of 30 min. After another 40 min stirring, fresh distilled TMSCl (0.83 mL, 6.51 mmol) was added fast into the reaction mixture by syringe. Let the reaction warm to rt and stir for 1 h. PhSeBr (1.15 g, 4.77 mmol) in 10 mL anhydrous THF was added into the mixture slowly via syringe. The reaction was stirred for 1 h at rt. The reaction was quenched by 6.5 mL 10% HCl and

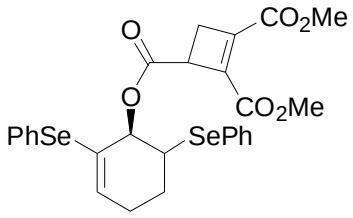
stirred for 2 h. The mixture was extracted with EtOAc (4 × 100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum to give a yellow oil. The crude material was purified by flash chromatography (SiO_2, gradient, 20:1 → 10:1 hexanes:EtOAc) to give **22** (1.268 g, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (m, 4H, Ar-*H*), 7.30 (m, 6H, Ar-*H*), 6.39 (m, 1H, C=C-*H*), 4.11 (t, *J* = 4.40 Hz, 1H), 2.50 (m, 1H), 2.37 (m, 1H), 2.22 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 191.9 (C=O), 144.9, 136.7, 135.9, 133.8, 129.8, 127.6, 127.2, 77.6, 77.3, 77.0, 48.0, 29.5, 26.1.



17

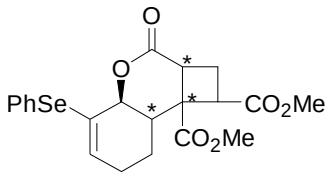
2,6-Bis-phenylselanyl-cyclohex-2-enol (17). Ketone **22** (468 mg, 1.15 mmol) was dissolved in 12 mL MeOH. $CeCl_3 \cdot 7H_2O$ (642 mg, 1.72 mmol) was added at 0 °C. $NaBH_4$ (66 mg, 1.72 mmol) was added into the mixture very slowly. Let the reaction worm to rt and stirred for 1 h. The solution was then quenched by saturated NH_4Cl solution, concentrated under vacuum, re-dissolved in Et_2O (100 mL). The Et_2O layer was concentrated under vacuum to provide product **17** as a yellow oil (469 mg, 100%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (m, 4H, Ar-*H*), 7.25 (m, 6H, Ar-*H*), 6.17

(dd, *J* = 4.61, 2.85 Hz, 1H, C=C-*H*), 4.15 (t, *J* = 3.96 Hz, 1H, O-C-*H*), 3.47 (ddd, 1H, Se-C-*H*), 2.59 (d, *J* = 4.40 Hz, 1H, O –*H*), 2.60 (m, 2H), 2.07 (m, 1H), 1.97(m, 1H).



18

Cyclobut-1-ene-1,2,3-tricarboxylic acid 3-(2,6-bis-phenylselanyl-cyclohex-2-enyl) ester 1,2-dimethyl ester (18). **16** (45 mg, 0.21 mmol) and **17** (43 mg, 0.11 mmol) were dissolved in anhydrous CH_2Cl_2 (2 mL). DCC (0.312 mL, 1M in CH_2Cl_2, 0.63 mmol) 26.8 μL, 0.46 mmol) was added via cannular. The reaction was stirred for 30 min at 0 °C and 12 h at rt. The reaction mixture was then quenched by several drops of acetic acid and concentrated under vacuum. Flash chromatography (SiO_2, gradient, 10:1 hexanes:EtOAc) gave **18** (51.6 mg, 81%) as two diastereoisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (m, 6H, Ar-*H*), 7.22 (m, 4H, Ar-*H*), 6.30 (m, 1H, C=C-*H*), 5.73 (m, 1H, O-C*H*), 3.81 (s, 3H, O-CH_3), 3.78 (s, 3H, O-CH_3), 3.68 (m, 1H, O_2C-C*H*), 3.43 (m, 1H, Se-C*H*), 2.81 (m, 2H), 2.35 (m, 2H), 2.23 (m, 2H).



19

3-Oxo-5-phenylselanyl-1,2,2a,3,4a,7,8,8a-octahydro-4-oxa-cyclobuta[a]naphthalene-1,8b-dicarboxylic acid dimethyl ester (19). Compound **18** (50 mg, 0.083 mmol) and AIBN (2.7 mg, 0.0016 mmol) were dissolved in anhydrous benzene (3 mL) and stirred under N_2 at rt. The n-Bu_3SnH (0.049 mL, 0.183 mmol) was added dropwise. The mixture was then refluxed for 20 h. The reaction mixture was concentrated under vacuum and extracted in 2.5 mL ether and 2.5 mL saturated KF solution. The solution was stirred for another 1 h and concentrated. Flash chromatography (SiO_2, gradient, 15:1 hexanes:EtOAc) gave **19** (31 mg, 84%) as eight diastereoisomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 3H, Ar-*H*), 7.24 (m, 2H, Ar-*H*), 6.32 (m, 1H, C=C-*H*), 5.45 (m, 1H, O-C*H*), 3.67 (s, 3H, O-CH_3), 3.63 (s, 3H, O-CH_3), 3.43 (m, 2H, O_2C-C*H*), 2.33 – 1.82 (m, 7H).

3.6 References

(1) See review and references therein: Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091.

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