PART I: STEREOSELECTIVE SYNTHESES OF (+)-PEROVSKONE AND (+)-SALVADIONE-A

PART II: TOTAL SYNTHESIS OF (±)-KOMAROVIQUINONE AND STUDIES TOWARD THE SYNTHESIS OF (+)-KOMAROVIQUINONE

PART III: THE REGIOCHEMISTRY OF THE *ORTHO*-CLAISEN REARRANGEMENT OF *BIS*-(ALLYLOXY)-POLYCYCLIC AROMATICS

PART IV: THE USE OF *β*-BROMO DIMETHYLALKOXYSULFONIUM IONS FOR OLEFIN EPOXIDATION

by

YANG LI

(Under the Direction of George Majetich)

ABSTRACT

In Part I, the total syntheses of (+)-perovskone and (+)-salvadione-A were achieved using optically active *p*-benzoquinone as a common intermediate in the Diels-Alder reactions.

In Part II, the total synthesis of (±)-komaroviquinone has been achieved. An efficient Friedel-Crafts cycloalkylation method was developed in the study toward the stereoselective synthesis of (+)-komaroviquinone.

In Part III, the *ortho*-Claisen rearrangement of the *bis*-allyloxy ethers of naphthalene, anthracene, phenanthrene and heterocycle derivatives were studied. Every reaction gave only a single rearranged product, even where two or three isomers were possible.

In Part IV, a mild and efficient epoxidation of electron rich olefins was developed, applying *β*-bromo dimethylalkoxysulfonium ion as the common intermediate.

INDEX WORDS: Perovskone, Salvadione-A, *p*-Benzoquinone, Komaroviquinone, Cycloalkylation, Aren's reagent, *ortho*-Claisen rearrangement, Epoxidation, Dimethyl sulfoxide, *β*-Bromo dimethylalkoxysulfonium ion

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YANG LI

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YANG LI

Major Professor: George Majetich

Committee: Robert S. Phillips
Timothy M. Dore

Electronic Version Approved:

Maureen Grasso
Dean of the Graduate School
The University of Georgia
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TABLE OF ABBREVIATIONS

AIBN	*azo-bis*-isobutyronitrile
nBu$_3$SnH	*tris*-(*n*-butyl)-tinhydride
CAN	ceric ammonium nitrate
DABCO	1,4-diazobicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethylazodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	*N,N*′-dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
HMPA	hexamethylphosphoramide
IBX	*ortho*-iodoxybenzoic acid
LA	Lewis acid
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide

LHMDS	lithium hexamethyldisilazide
L-Selectride	lithium *tris*-(*sec*-butylborohydride)
mCPBA	*meta*-chloroperoxybenzoic acid
MOM	methoxymethyl
Ms	methanesulfonyl
MTBE	methyl *tert*-butyl ether
NBS	*N*-bromosuccinimide
NBSH	*ortho*-nitrobenzenesulfonylhydrazine
NCS	*N*-chlorosuccinimide
NMM	*N*-methylmorpholine
NMO	4-methylmorpholine *N*-oxide
PCC	pyridium chlorochromate
PMB	*para*-methoxybenzyl
TBDMS	*tert*-butyldimethylsilyl
TEA	triethylamine
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TPP	triphenylphosphine
p-TSA	*para*-toluenesulfonic acid

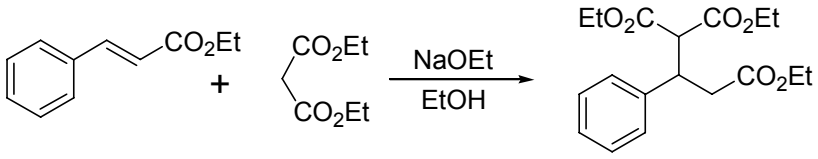
PART I:

STEREOSELECTIVE SYNTHESES OF

(+)-PEROVSKONE AND (+)-SALVADIONE-A

Introduction and Background

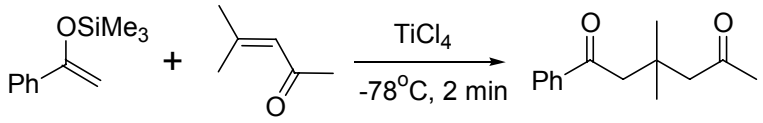
An *α,β*-unsaturated ketone (or enone) is electrophilic at both the carbonyl carbon and the *β*-carbon positions. Nucleophiles can attack to either of the two positions. In 1887, Michael systematically investigated the reaction of stabilized anions with *α,β*-unsaturated systems and reported that diethyl malonate added to the double bond of ethyl cinnamate in the presence of sodium ethoxide to afford a substituted pentanedioate (Scheme 1).[1]



Scheme 1

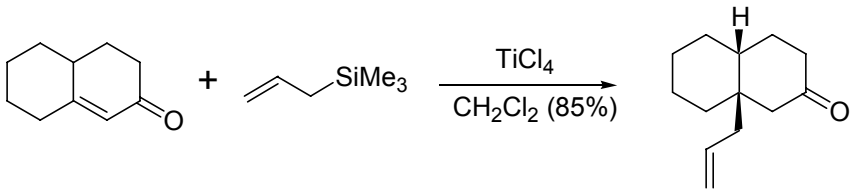
This method became exceedingly popular by the early 1900s, and currently, all reactions that involve a 1,4-addition of a nucleophile are referred to as the Michael reaction.[1,2] Michael reactions can take place under acidic,[3] basic or free radical conditions.[4] For example, in 1976,

Mukaiyama reported the addition of a silyl enol ether to a conjugated enone when catalyzed by $TiCl_4$ (Scheme 2).[5]



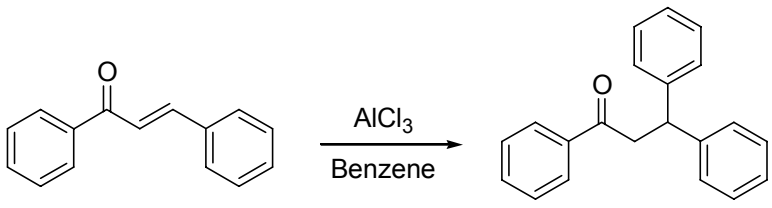
Scheme 2

Additional results were reported by Sakurai in 1976[6] when an allylsilane was reacted with a Michael acceptor in the presence of stoichiometric quantities of a Lewis acid such as $TiCl_4$, and the Michael adduct was collected in high yield (Scheme 3).[6c] Other Lewis acids, such as $AlCl_3$, $BF_3{\cdot}Et_2O$, $SnCl_4$, $EtAlCl_2$, can be used. This transformation is nowadays referred to as the Hosomi-Sakurai allylation.



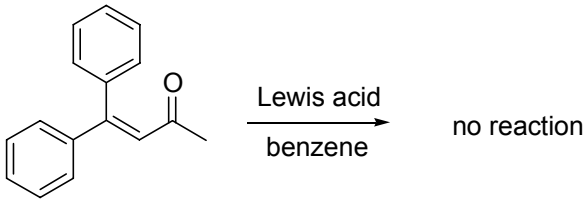
Scheme 3

The use of *α,β*-unsaturated ketones as electrophiles in Friedel-Crafts alkylations is nearly as old as the original method. In particular, the addition of benzene to benzalacetophenone was first reported by Vorlander and Friedberg in 1923 (Scheme 4).[7]



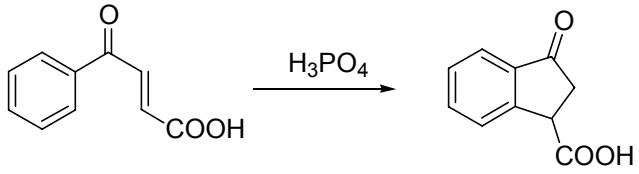
Scheme 4

Normally, groups on the β-carbon of the enone unit will not affect the addition except when high steric congestion exists. As shown in Scheme 5, there is no reaction with the β-biaryl enone.



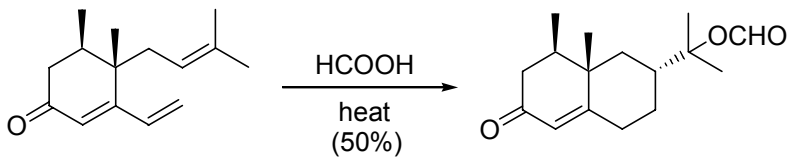
Scheme 5

Baddeley and co-workers reported the intramolecular Friedel-Crafts alkylation as shown in Scheme 6;[8] this reaction is catalyzed by strong mineral acids such as H_3PO_4.[9]



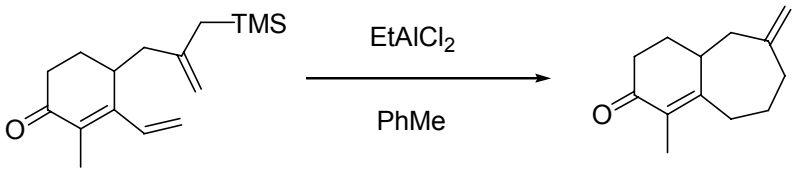
Scheme 6

In 1974, Dastur found that conjugated dienones work as excellent Michael acceptors when catalyzed by a protic acid (Scheme 7).[10] Although 1,4-addition could be a competing process, the only observed product was the one that involved 1,6-addition. This observation offered a new approach to carbocyclizations.



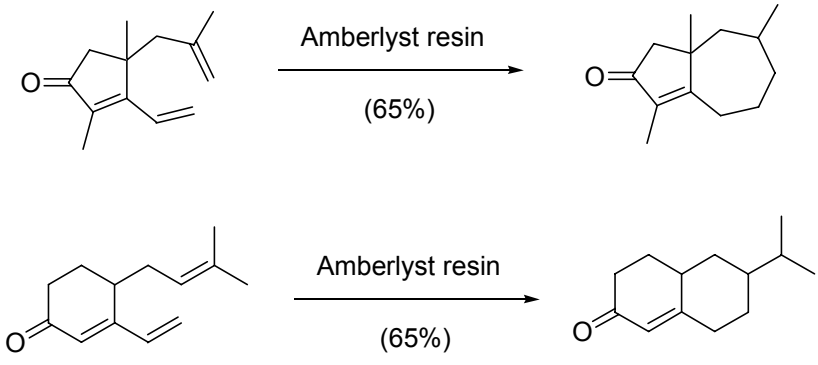
Scheme 7

In 1985, a new annulation strategy was reported by Majetich and co-workers using an allylsilane as an internal nucleophile and a conjugated dienone as the electrophilic species to form medium-sized rings (Scheme 8).[11] It can be interpreted as an intramolecular Sakurai reaction of a conjugated dienone.



Scheme 8

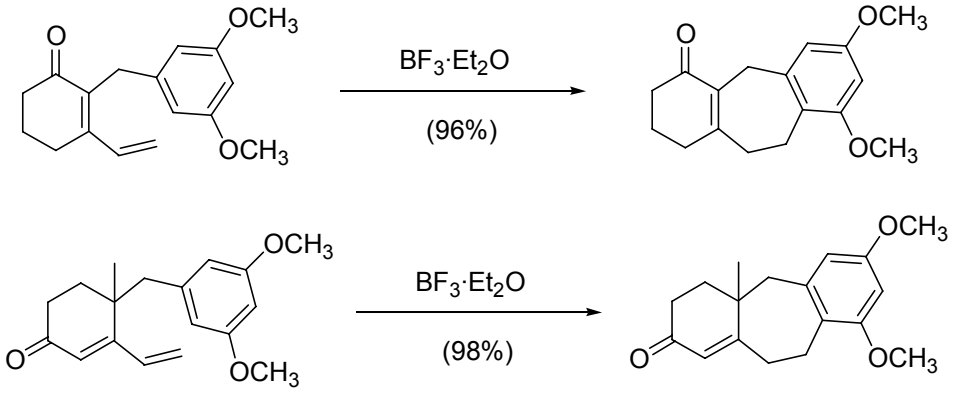
In 1990, Majetich and Khetani found that unactivated double bonds also add to conjugated dienones to form seven-membered rings when catalyzed by Lewis acids (Scheme 9).[12]



Scheme 9

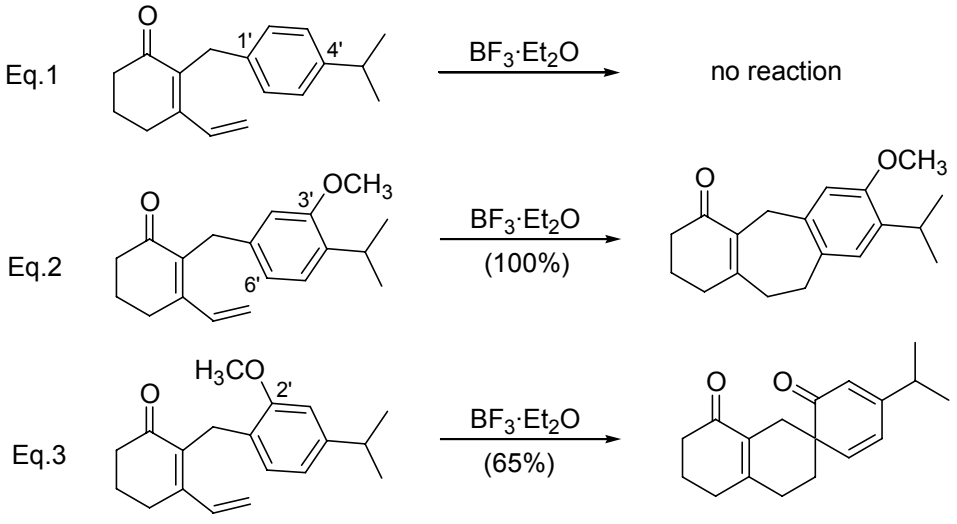
The demonstrated ability of conjugated dienones to react as Michael acceptors on the δ-position prompted the Majetich group to investigate intramolecular Friedel-Crafts allylations or

cycloalkylations. In 1993, Majetich and co-workers reported a preparation of 6,7,6-fused tricyclic systems via the Friedel-Crafts cycloalkylation shown in Scheme 10.[13] The cycloalkylation of two series of conjugated dienone systems gave 6,7,6-tricyclic systems, differing in whether the ring fusion contains one or both carbons of the double bond.[13]



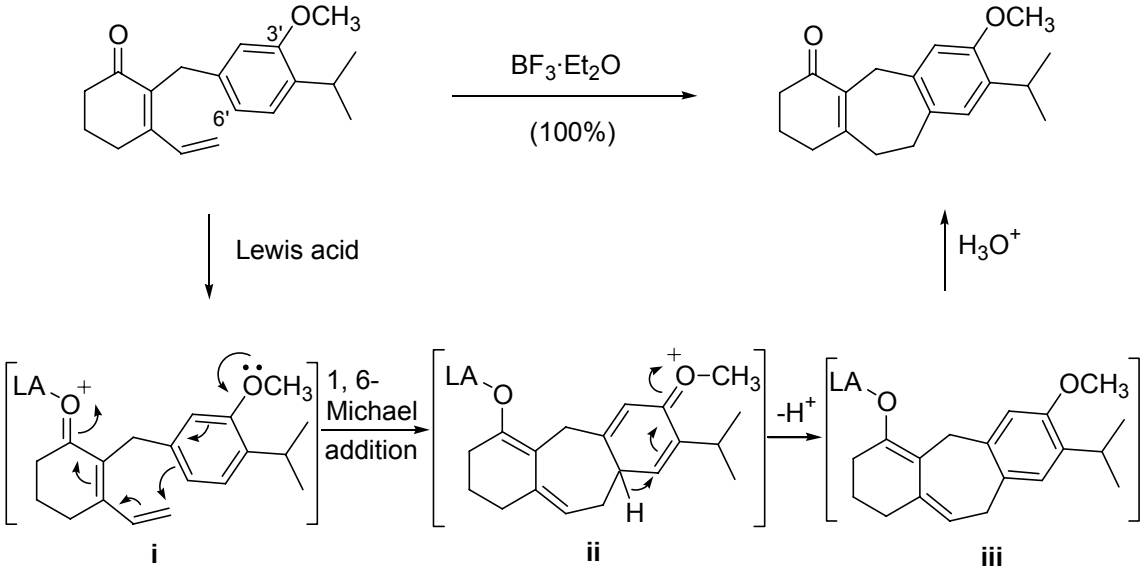
Scheme 10

In order to further understand these processes, additional precursors were prepared. As expected, the electronic nature of the substitutent dictated whether cyclization would or would



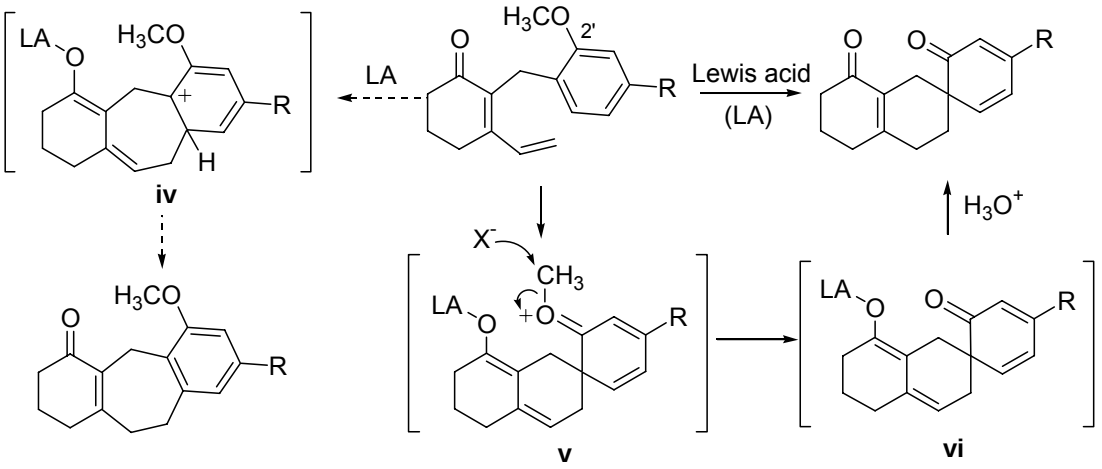
Scheme 11

not occur. For example, when an electron donating group is present in the 3′ position, the cycloalkylation proceeds smoothly on the 6′ position to give a single product (cf. eq. 1 and 2 in Scheme 11).[14] As shown in eq. 3 of Scheme 11, a spiro-fused dienone was obtained when the electron-donating group is on the 2′ position.[14]



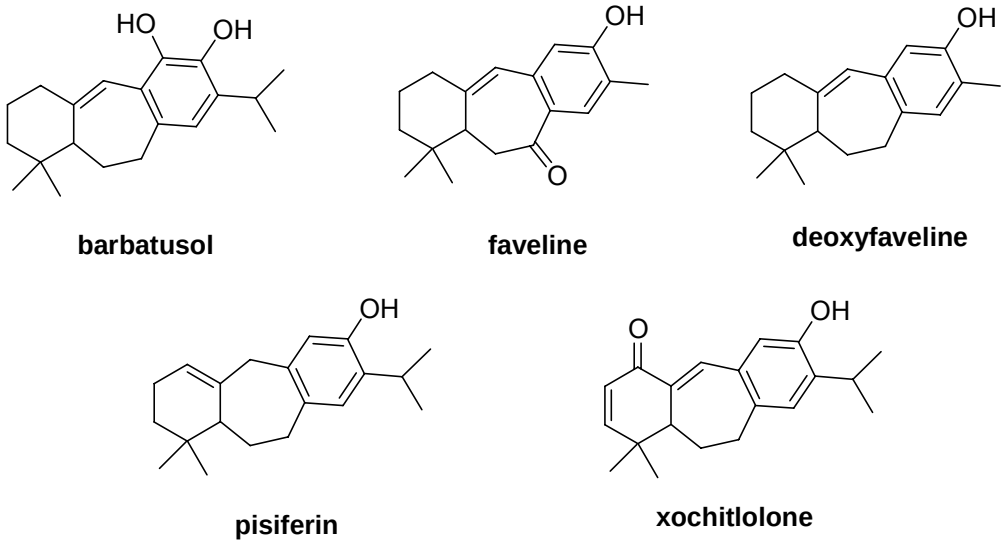
Scheme 12

Mechanistic studies have shown that electrophilic addition of the activated conjugated dienone **i** occurs *para* to the methoxy group to form a seven-membered ring and a resonance-stabilized carbocation intermediate **ii**, which loses a proton to re-establish aromaticity and form **iii** (Scheme 12). However, the electron-donating group on the 2′ position could only direct substitution toward the geometrically inaccessible 6′ position **iv**. Therefore, the formation of the cycloheptane ring is precluded. On the contrary, spiro intermediate **v** is preferred and undergoes demethylation through **vi** to give a spiro-fused enone (Scheme 13).



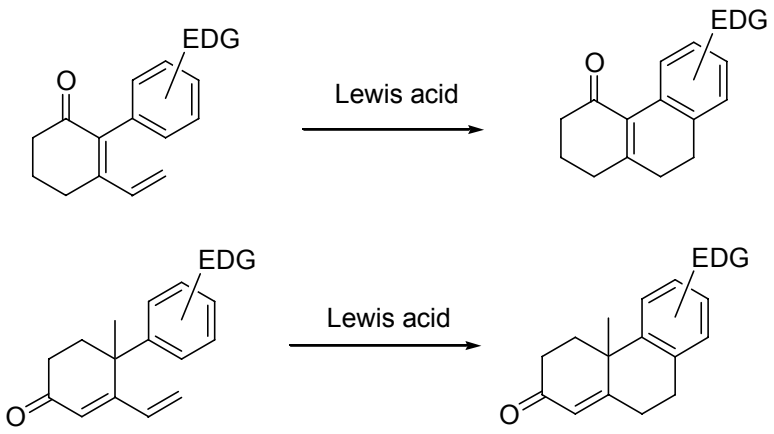
Scheme 13

This method was used to synthesize several bioactive natural terpenoids, five of which are shown in Scheme 14: barbatusol, faveline, deoxyfaveline, pisiferin and xochitlolone.[14]



Scheme 14

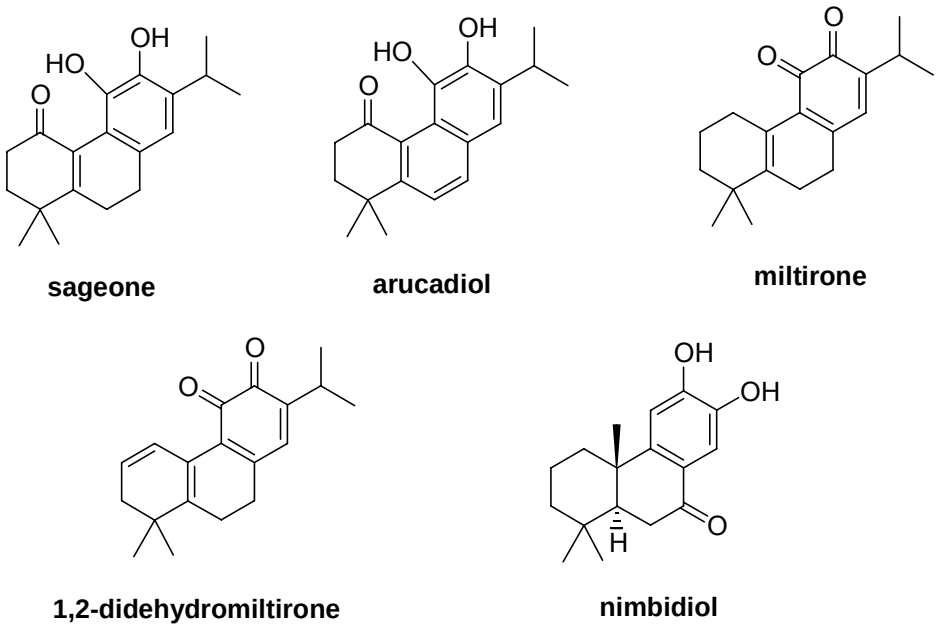
The formation of 6,6,6-fused tricyclic systems has also been studied.[15] As shown in Scheme 15, the framework can be built up from two series of conjugated dienone precursors



EDG = electron donating group

Scheme 15

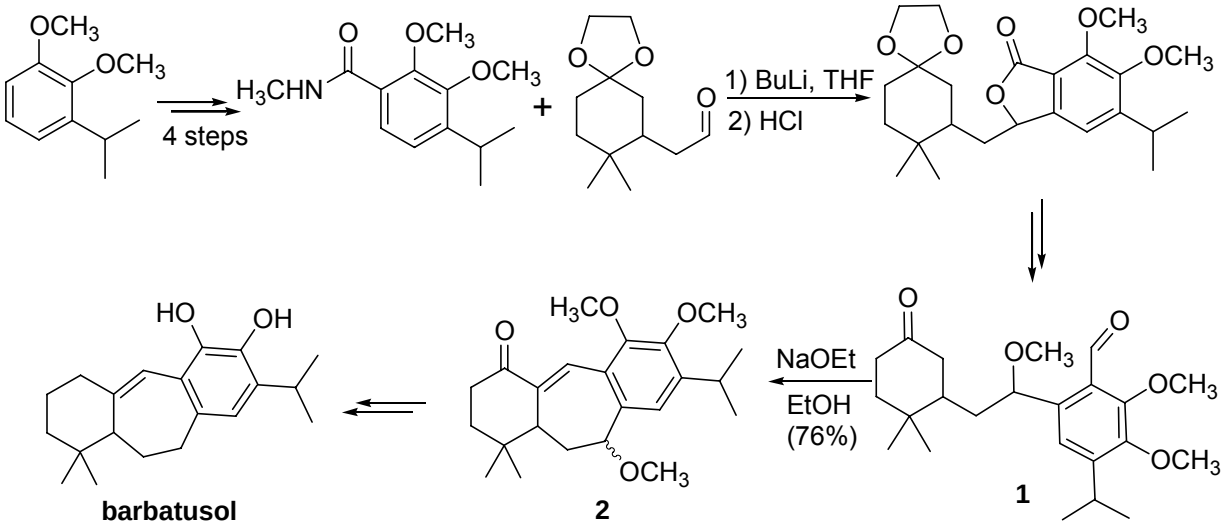
upon catalysis with Lewis acid. The synthetic application of this study led to the success in the syntheses of several natural products, including sageone, arucadiol, miltirone, 1,2-didehydromiltirone as well as nimbidiol (Scheme 16).[15]



Scheme 16

Syntheses of (±)-Barbatusol:

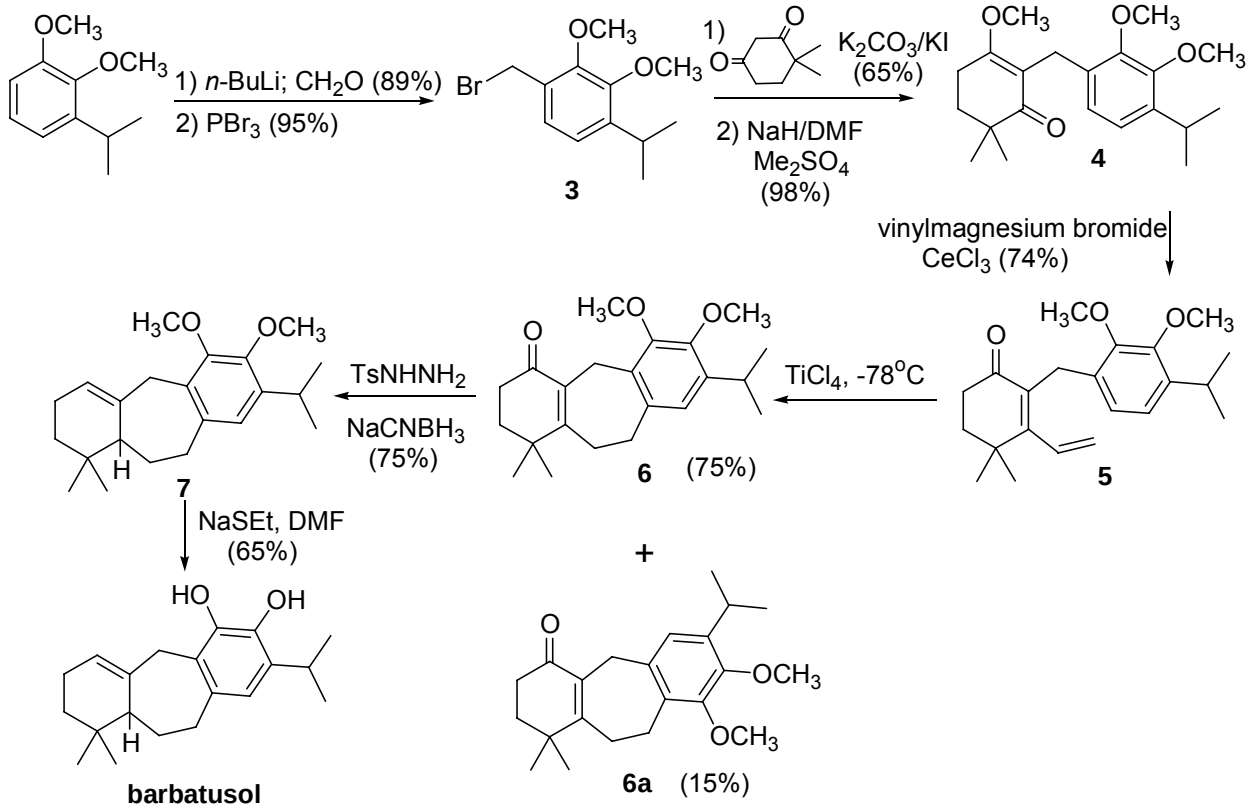
The ability to efficiently prepare 6,7,6-fused tricycles also permitted a synthesis of (±)-barbatusol. The first total synthesis of (±)-barbatusol was accomplished in 1987 by Koft and co-workers.[16] Their synthesis began with 3-isopropylcatechol and required fifteen steps in 4.5% overall yield. Scheme 17 briefly depicts the synthetic route. One of the key steps in this synthesis was to incorporate a seven-membered ring via an annulation reaction. As shown in Scheme 17, when dione **1** was treated with sodium ethoxide enone **2** was achieved in 76% yield and a 4.5% overall yield.



Scheme 17

Majetich and co-workers, based on their study on the intramolecular Friedel-Crafts alkylation of dienones, reported a more efficient synthesis of (±)-barbatusol.[14] In their synthesis, (±)-barbatusol was achieved in eight steps with a 15% overall yield.

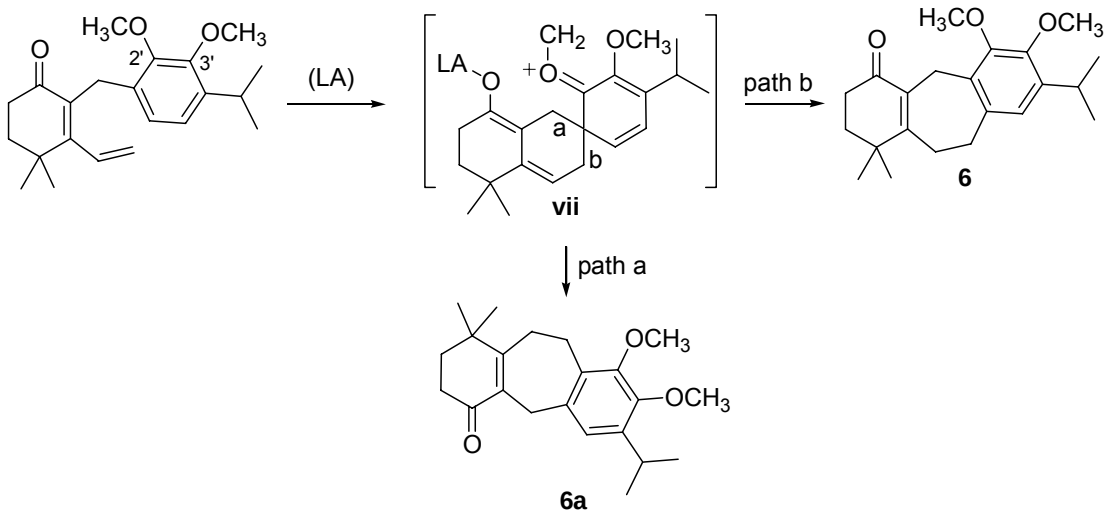
As shown in Scheme 18, 3-isopropylveratrole was transformed to benzyl bromide **3** in two steps. The coupling reaction of bromide **3** with 6,6-dimethyl-1,3-cyclohexadione, followed by methyl enol ether formation of the resulting intermediate, gave enone **4**. The following alkylation with vinylmagnesium bromide gave conjugated dienone **5** after acidic workup. Dienone **5** was then subjected to the Friedel-Crafts cycloalkylation and 75% of enone **6** was produced along with 15% of enone **6a**. A modified Wolff-Kishner reduction[17] gave alkene **7** in 75% yield. Finally, deprotection of methyl ethers of the alkene **7** completed the synthesis of (±)-barbatusol.



Scheme 18

In the synthesis, the Friedel-Crafts cycloalkylation incorporated a cycloheptane ring as a mixture of enone **6** and **6a**. As shown in Scheme 19, this outcome can be reasoned by the

generation of species **vii**, which was directed by the 2′ methoxyl group, followed by a skeletal rearrangement. Two rearrangement pathways can lead to enones **6a** and **6** through migration of the ‘a’ and ‘b’ bond, respectively.



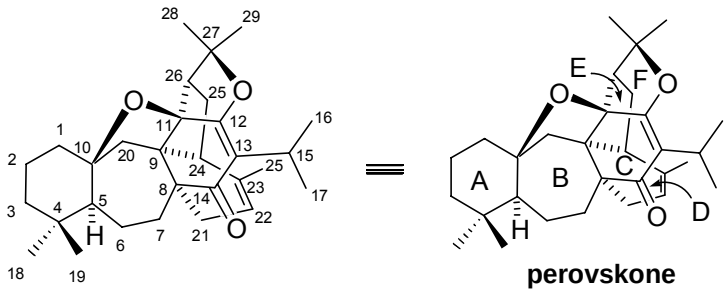
Scheme 19

A comparison of these two routes to the synthesis of (±)-barbatusol reveals that Majetich’s cycloheptane-annulation strategy produces the tricyclic system more efficiently. This method has found applications in the syntheses of more complex natural structural architectures. The next section of this dissertation will discuss the application of this method to synthesize (±)- and (+)-perovskone as well as (+)-salvadione-A.

First Total Synthesis of (±)-Perovskone.

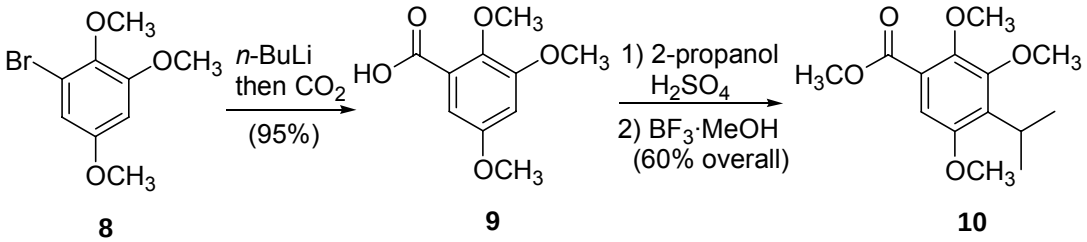
The genus *Salvia* is the largest genus of the Lamiaceae family,[18-21] comprising more than 800 species. Many of the *Salvia* species are used as medicines in the treatment of a variety of

disorders and diseases. *Salvia bucharica*, popularly known in Pakistan as "*sursaudah*", is found throughout Central Asia, and is used in popular medicines for liver disorders as well as for its cooling effects.[22,23] Several complex triterpene structures, *i.e.* salvadione-A and salvadiol, have been isolated from this family of natural sources. Another source of these triterpene structures is *Perovskia*. In 1992, perovskone was isolated by Ahmad and co-workers from *Perovskia abrotanoides, Karel syn. P. artemisioides* Boiss (Labiatae).[24,25] This first isolated novel triterpene structure contains a complex array of seven fused and bridged rings as well as asymmetric centers (Scheme 20).



Scheme 20

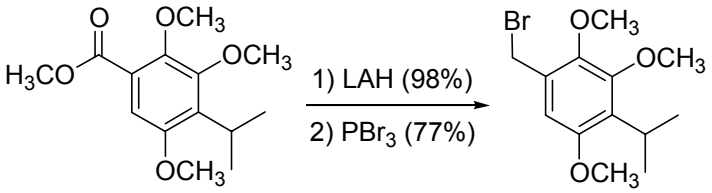
The first concise synthesis of (±)-perovskone was accomplished by Majetich and Zhang in 1994.[26] Starting from 1-bromo-2,3,5-trimethoxybenzene,[27] the tricyclic enone was obtained in nine steps.



8 **9** **10**

Scheme 21

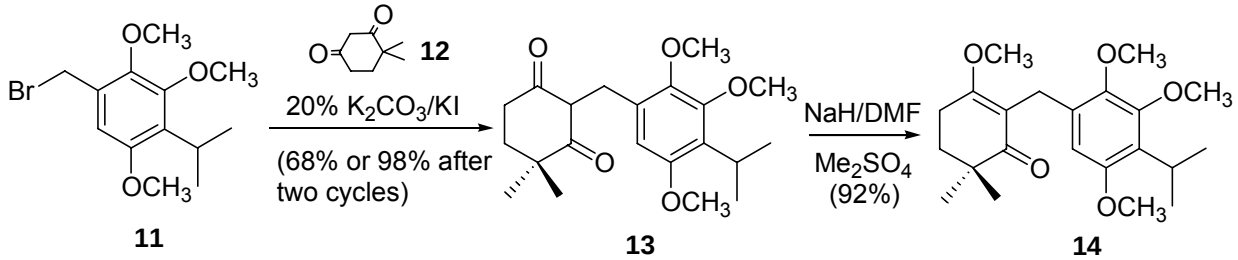
As shown in Scheme 21, treatment of **8** with *n*-butyllithium to undergo metal halogen exchange, followed by quenching of the intermediate aryl anion with carbon dioxide, gave acid **9** in 95% yield. An acid-catalyzed Friedel-Crafts alkylation introduced the isopropyl unit on the *para* position of the benzoic acid **9**. The crude alkylation mixture was then treated with methanolic boron trifluoride to esterify the benzoic acid group. Reduction of **10** followed by bromination of the resulting alcohol gave bromide **11** (Scheme 22).



10 **11**

Scheme 22

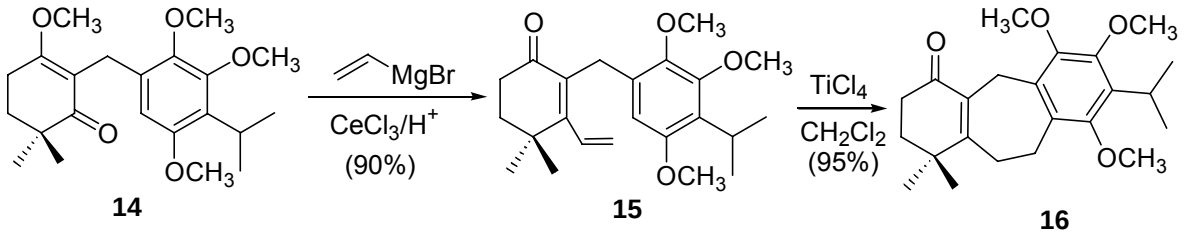
The alkylation of the enolate of 4,4-dimethyl-l,3-cyclohexanedione **12** with benzyl bromide **11**, using a concentrated solution of compounds **11** and **12** in 20% aqueous potassium carbonate, produced the monoalkylated dione **13** in 68% yield. Methyl enol ether formation of dione **13** with sodium hydride in dimethylformamide and dimethyl sulfate gave **14** in 92% yield (Scheme 23).



11 **13** **14**

Scheme 23

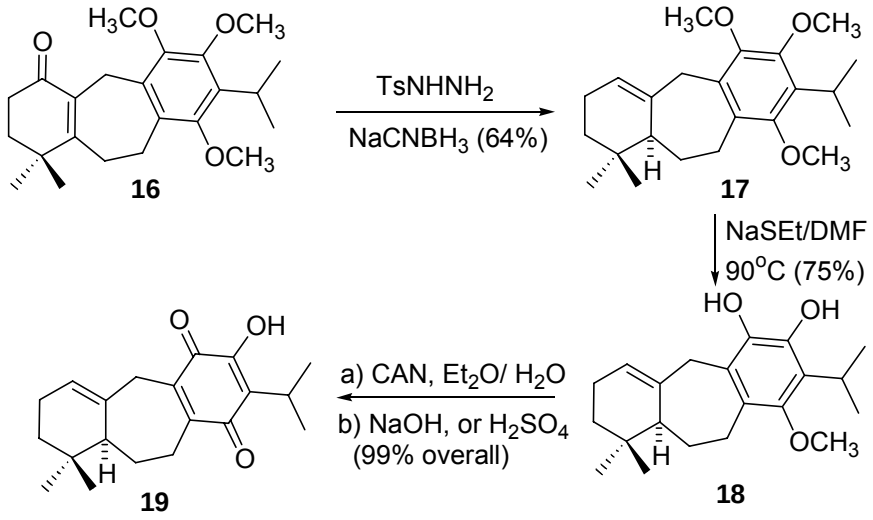
Cerium(III) chloride catalyzed 1,2-addition of vinylmagnesium bromide to **14,** followed by mild acid hydrolysis, made dienone **15**. Cycloalkylation of **15** achieved enone **16** in 95% yield using $TiC1_4$ (Scheme 24).



14 **15** **16**

Scheme 24

Tricyclic enone was then transformed to benzoquinone **19** in four steps. The route used to convert enone **16** into benzoquinone **19** is shown in Scheme 25. A modified Wolff-Kishner reaction[18] reduced the enone **16** with a double bond migration. Demethylation of two of the methyl ether moieties was achieved in 75% yield without isomerization of the trisubstituted double bond using the nucleophilic conditions developed by Feutrill and Mirrington.[28] The

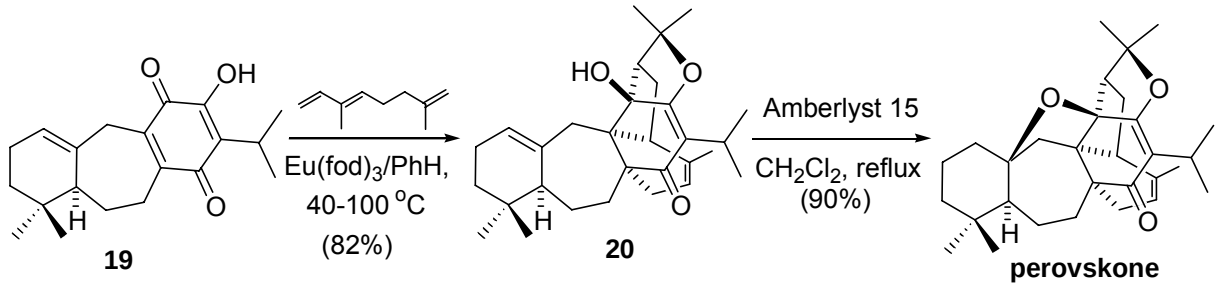


16 **17** **18** **19**

Scheme 25

resulting diol **18** resisted all attempts at further deprotection. *para*-Benzoquinone **19** was nevertheless furnished in nearly quantitative yield by treating **18** with cerium(IV) ammonium nitrate,[29] followed by the addition of either sodium hydroxide or sulfuric acid. In this reaction three transformations occur: (a) generation of *ortho*-benzoquinone**;** (b) hydrolysis of the vinylogous ester moiety; and (c) isomerization of *ortho*-benzoquinone to *para*-benzoquinone **19.**

The Diels-Alder reaction of *para*-benzoquinone **19** with *E*-*α*-ocimene gave the adduct **20** with 82% yield. Finally, perovskone was synthesized in 90% yield when heated with Amberlyst® 15 ion-exchange resin (Scheme 26).

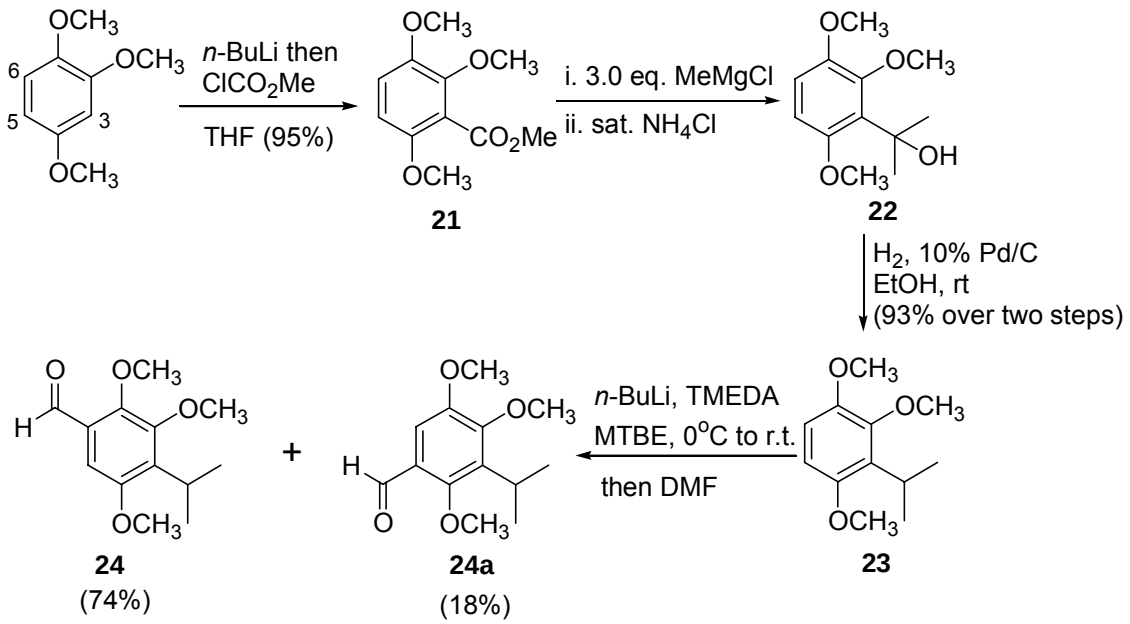


Scheme 26

A New Route toward the Synthesis of Enone 16

For his master's degree, John Briton achieved a shorter, more convergent route toward the synthesis of enone **16**.[30] In this new route the enone **16** was synthesized in nine steps starting from 1,2,4-trimethoxybenzene.

As shown in Scheme 27, commercially available 1, 2, 4-trimethoxybenzene was treated with 1.1 equivalents of *n*-butyllithium to deprotonate the 3 position of the aromatic ring, followed by quenching with ethyl chloroformate, giving the ethyl ester **21** in 95% yield. Excess

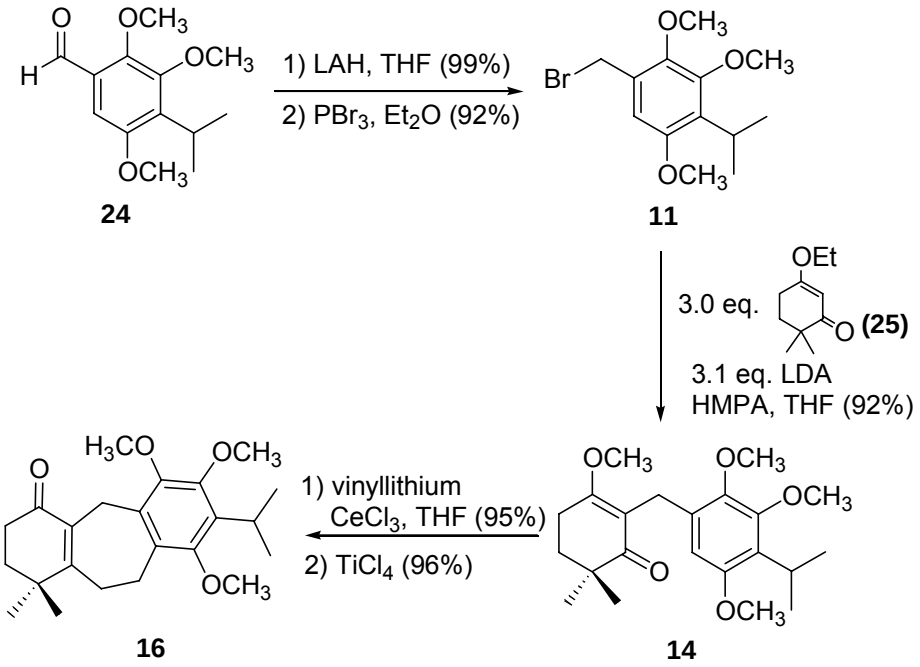


Scheme 27

methylmagnesium chloride was used to reduce the ester group to tertiary alcohol **22**. Acid catalyzed hydrogenation gave first *in situ* dehydration of tertiary alcohol **22** and then reduction to isopropyl trimethoxybenzene **23**. When this 3-(1-methylethyl)-1,2,4-trimethoxybenzene **23** was treated with 1.1 equivalent of *n*-butyllithium in MTBE and TMEDA and quenched with excess amount of DMF, a 4:1 ratio mixture of aldehydes were obtained. The desired aldehyde **24** could be isolated on silica gel column with 74% yield from 18% of unwanted aldehyde **24a** (Scheme 28).

Lithium aluminum hydride reduction and substitution of the resulting benzyl alcohol with phosphorous tribromide produced 4-(1-methylethyl)-2,3,5-trimethoxy benzyl bromide **11** in 95% overall yield (Scheme 28). The enolate of 3-ethoxy-6,6-dimethylcyclohex-2-en-1-one (**25**) was coupled with benzyl bromide **11** to afford product **14** in 92% yield. Addition of vinyllithium catalyzed by cerium(III) chloride, followed by isomerization of the resulting tertiary alcohol with

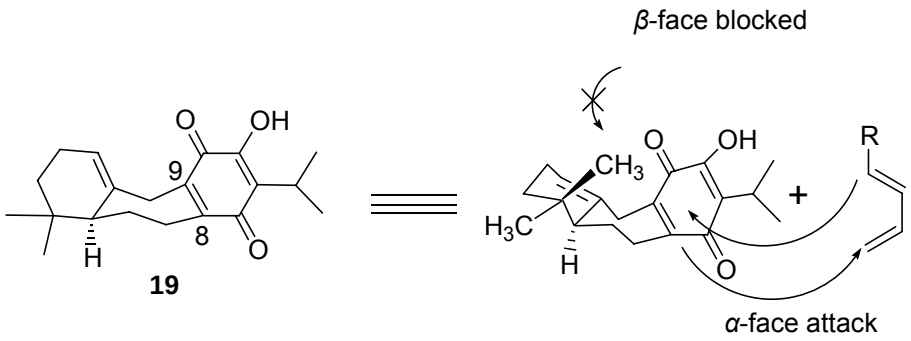
10% of hydrochloric acid, produced a high yield of dienone **15**. Finally, when the dienone **15** was treated with 2.0 equivalents of titanium tetrachloride in methylene chloride at -78 ℃, enone **16** was obtained in 96% yield. This new synthesis represents a more efficient way to prepare a large amount of enone **16**.



Scheme 28

Synthesis of Optically Active *p*-Benzoquinone

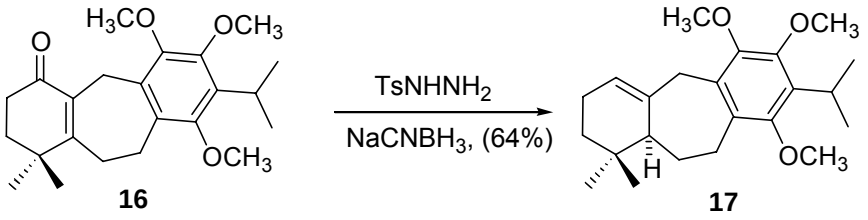
Based on NMR studies, St. Jacques and Vaziri[31] proposed that benzocycloheptanes favor a chair conformation; hence, *para*-benzoquinone **19** should prefer a cup-shaped conformation with its α-face readily accessible. More importantly, the β-face is blocked by the methyl group (Scheme 29). Thus, a diene would add from the α-face of this dienophile to create the desired relative configurations at C(8) and C(9) (Scheme 29).



Scheme 29

It follows that, as long as an optically active *para*-benzoquinone **19** is used, an enantioselective synthesis of (+)-perovskone would be accomplished. Thus, the preparation of chiral *para*-benzoquinone **19** became our initial goal.

As mentioned earlier, a modified Wolff-Kishner reduction[18] of enone **16** was used in the synthesis of (±)-perovskone.[27] As shown in Scheme 30, when the tosylhydrazone of enone **16** is reduced with sodium cyanoborohydride in the presence of an acid, alkene **17** was produced in 64% yield. Unlike the reduction of simple ketones, the Wolff-Kishner reduction of an enone not only removes the carbonyl oxygen but a migration of the double bond occurs.[27,28]

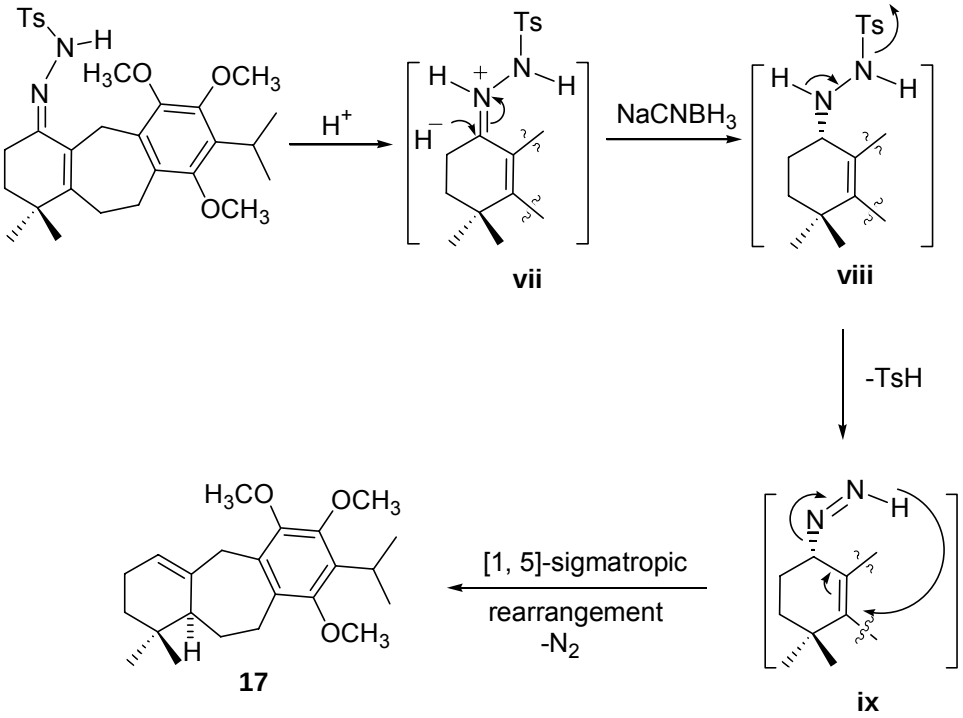


Scheme 30

The reaction mechanism is shown in Scheme 31. The first step is to form the tosylhydrazone of enone **16**. Protonation of this tosylhydrazone gives intermediate **vii**, which

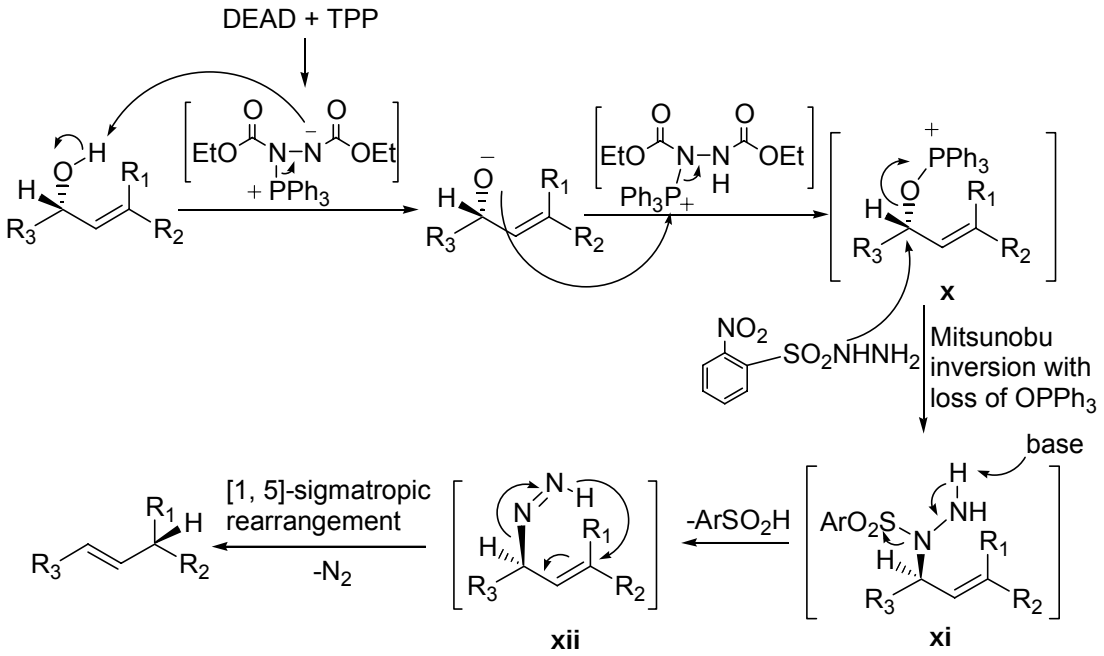
undergoes hydride addition to give **viii**. A monoalkyl diazene species (*i.e.*, **ix**) is generated after the elimination of *para*-toluene sulfinic acid. This diazene species is unstable and undergoes quick [1,5]-sigmatropic rearrangement with the loss of molecular nitrogen to generate alkene **17**.

While serving our purposes, the reduction with sodium cyanoborohydride is problematic. In order to activate the hydrazone for reduction, the pH of the reaction medium must be within a narrow range; a higher pH value does not activate the reaction. If the pH value is too low over-reduction occurs or elimination products are produced as an inseparable mixture with the desired alkene **17**. Indicators are normally used to control pH value in the required range. However, because of highly colored intermediates produced by our substrate, it is found that the color change is so weak that formation of the by-product could not be avoided.



Scheme 31

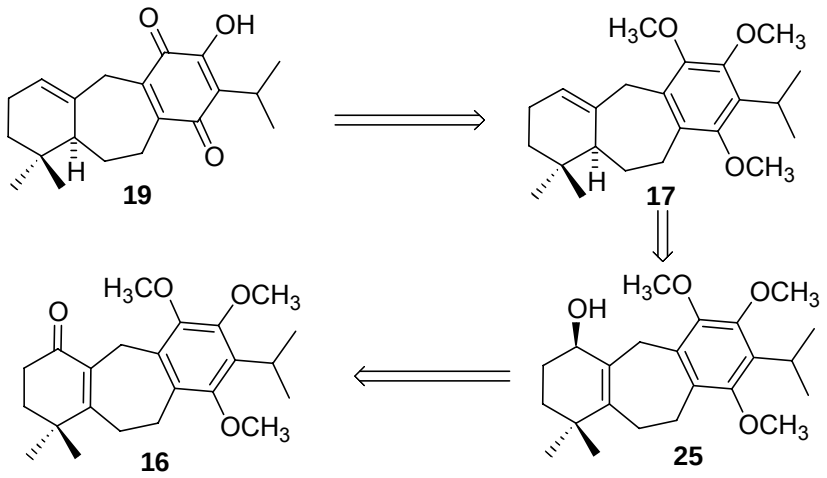
We believed that the single stereocenter present in *para*-benzoquinone **19** will control the Diels-Alder reaction and the subsequent transformations. A single-step asymmetric Wolff-Kishner reduction process is not known. However, Myers and Zheng reported a variation of this transformation to the hydride reduction of tosylhydrazones.[34,35] In his modification, an allyl alcohol is treated under Mitsunobu's condition [diethylazodicarboxylate (DEAD) and triphenylphosphine (TPP)] at low temperature to generate a leaving group on intermediate **x** (Scheme 32). The nucleophile, which is *ortho*-nitrobenzenesulfonylhydrazine (NBSH), is then added to **x** to displace the triphenylphosphine oxide. Elimination of *ortho*-nitrobenzenesulfinic acid of **xi** happens under slightly elevated temperature to generate a monoalkyl diazene **xii** *in situ*. The highly unstable diazene **xii** then undergoes an intramolecular [1,5]-sigmatropic rearrangement (Scheme 32).



Scheme 32

By comparing the mechanistic pathway in Myers's transformation with that in the hydride reduction of tosylhydrazone, we realized that Myers's protocol could be applied to an asymmetric synthesis of *para*-benzoquinone **19**. A four-step process was envisioned. First, optically active allylic alcohol **25** could be produced from enone **16**. The application of Myers's procedure[34] to alcohol **25** would transfer the stereochemistry of C(1) to the C(5) methine carbon of alkene **17** at the AB ring fusion (Scheme 33).

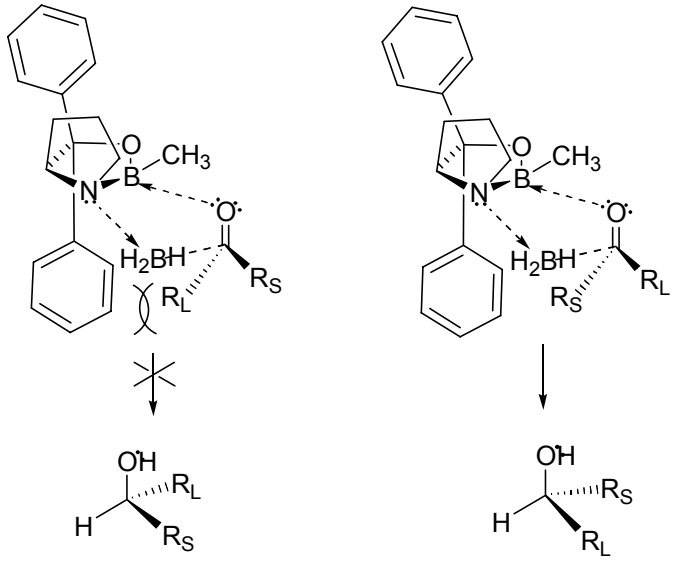
One of the most extensively used methods for the asymmetric reduction of ketones uses borane and chiral oxazaborolidine as the catalyst and source of chirality.[22] High to excellent enantioselectivities have been reported in the hydride reduction of α-substituted ketones by using these reagents.[23]



Scheme 33

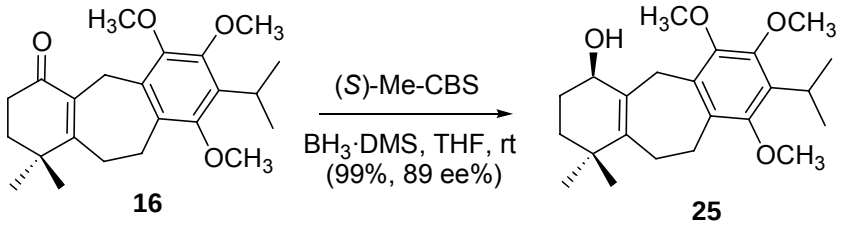
Mechanistically,[36-38] the oxazaborolidine catalyst first coordinates with the borane via its nitrogen site, rendering the hydride more nucleophilic (Scheme 34). This bulky asymmetric complex then selectively binds to one face of the carbonyl oxygen in order to minimize unfavorable steric interactions between the phenyl groups on oxazaborolidine and the large

group on the ketone. The next step in this reduction is for the borane addition to the carbonyl carbon with facial selectivity via a six-membered transition state to form the reduction product.



Scheme 34

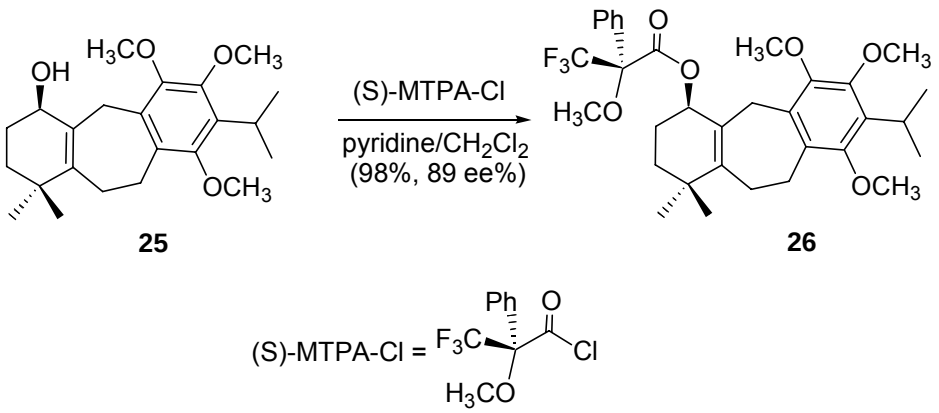
As shown in Scheme 35, when Corey's CBS reduction procedure was applied to our enone **16**, a 99% yield of allylic alcohol **25** was obtained.



16 **25**

Scheme 35

The ^{19}F NMR study of the Mosher's ester **26** of allylic alcohol **25** determined that its enantiomeric excess was 89% (Scheme 36). [30]



Scheme 36

O'Donnell[39h] and others[39a-g] have shown that often a partially enriched product can be recrystallized to yield only the optically pure enantiomer. Their observation is based on the fact that in the process of crystallization both enantiomers will have almost the same rate of crystallization. Thus whenever an enriched mixture is used, equal amounts of each enantiomer are removed from the mother liquor; hence, the mother liquor will be enriched in more of the excess enantiomer; after several recrystallizations, an optically pure compound will be obtained. In contrast, other experimental observations have shown that the crystallized molecule is often a single enantiomer leaving the racemate behind in the mother liquor. This presumably occurs because of the identical solubility of both enantiomers in limited amount of solvent system that will dissolve equal amounts of each enantiomer and further enriches the composition of the crystallized enantiomers. The drawback of this method, however, is that a crystalline compound is needed. Also, this method is not always applicable to any enriched crystal.[39h]

Fortunately, allylic alcohol **25** is crystalline. After three recrystallizations, using ethyl acetate and petroleum ether, optically pure allyl alcohol (+)-**25** was collected. The enantiomeric excess was determined by ^{19}F NMR of Mosher's ester of (+)-**25**, and the specific rotation in chloroform was determined to be +29.6º.

With optically pure allylic alcohol (+)-**25** in hand, we examined the Myers's transposition. Unfortunately, it turned out to be problematic. Although alkene **17** had been prepared using Myers's chemistry, standard workup and column chromatography could not collect pure olefin **x**, due to inherent native of triphenylphosphine. It is known in many reactions that triphenylphosphine often co-elutes on column chromatography with non-polar compounds. In our reaction, triphenylphosphine has the exact same R_f value with that of alkene **17**; therefore, the reaction yield or the specific rotation of alkene **17** could not be determined from this mixture.

Removal of the triphenylphosphine could be achieved using an extremely long column and using pentane as the eluant. However, often the triphenylphosphine could not be removed completely. This limited the preparation of large quantities of alkene **17**.

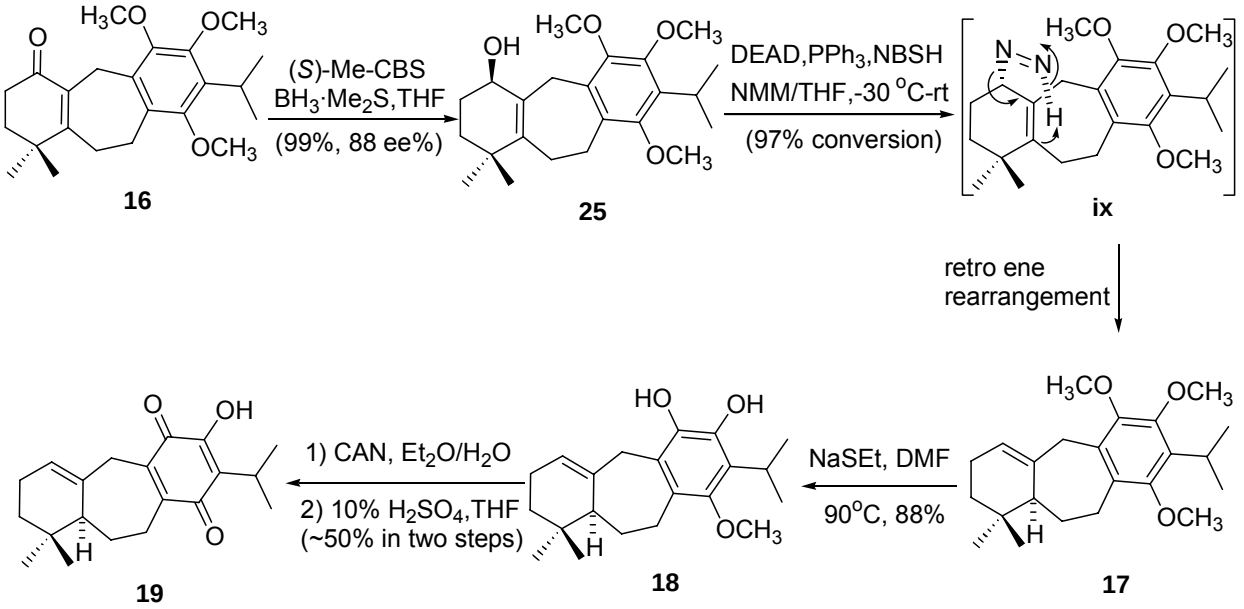
A convenient workup procedure solved this problem. In contrast to the low polarity of triphenylphosphine, triphenylphosphine oxide is very polar and much easier to deal with. Moreover, triphenylphosphine can be oxidized quickly to triphenylphosphine oxide using many mild oxidants, such as hydrogen peroxide or even air.[40] Consequently, we hoped to remove unreacted triphenylphosphine from our resulting alkene **17** by simply oxidizing it to triphenylphosphine oxide, which is easily separated from alkene **17**.

In order to test the feasibility of this idea, air was first used. When air was bubbled into a tetrahydrofuran solution of triphenylphosphine for one hour, only a small amount of the triphenylphosphine was oxidized. When 5% aqueous hydrogen peroxide[41] was added, the reaction was complete within ten minutes. This transformation can be monitored by ^{31}P NMR and by TLC analysis. Both allylic alcohol **25** and alkene **17** were inert to 5% aqueous hydrogen peroxide. Hence the 'PPh_3 problem' can be simplified as follows: In the workup, 5% aqueous hydrogen peroxide was added to the reaction mixture to oxidize excess triphenylphosphine. Most

of the triphenylphosphine oxide can be precipitated out of the diethyl ether solution using petroleum ether. If needed, a short column can be used to remove all triphenylphosphine oxide.

Finally, optically pure alkene **17** was obtained in roughly 50% yield and the specific rotation was determined to be -87.1º in chloroform. Unfortunately, the unreacted allylic alcohol **25** was determined by Mosher's ester **26** to be partially racemized. This pathway is superior to our earlier method of reducing the tosylhydrazone intermediate (cf. Scheme 31).

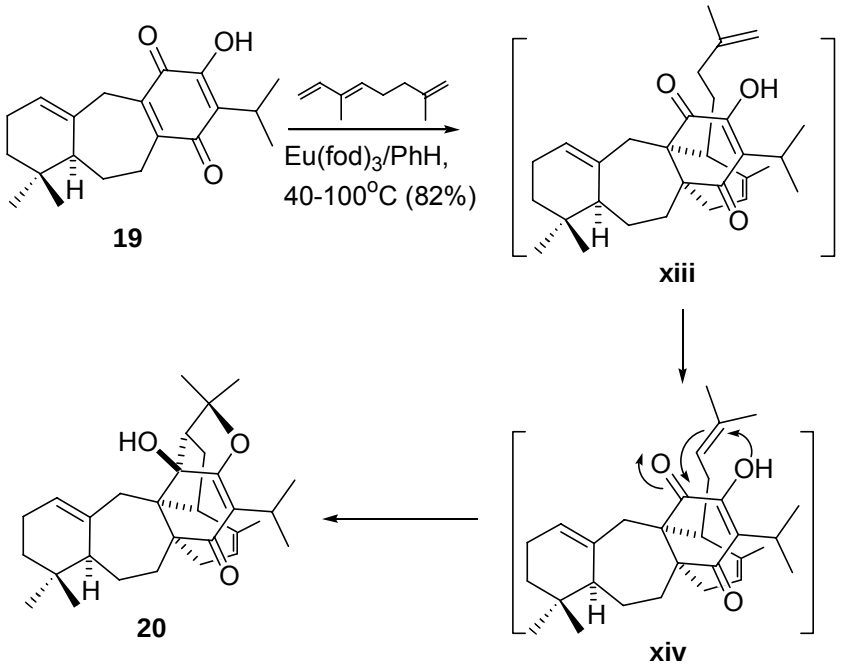
The selective NaSEt deprotection of the methoxy ethers gave diol **18** with 88% yield and the specific rotation was found to be -91.5° in benzene (Scheme 37). Strict temperature control (85~90 ℃) was required in this reaction to ensure the high yield, and the reaction time usually took longer than two or three days. Oxidation of **18** to the *ortho*-benzoquinone, followed by an acid-catalyzed isomerization, produced (+)-*para*-benzoquinone **19** in high yield. The specific rotation of (+)-*para*-benzoquinone **19** in chloroform was -155.2º.



Scheme 37

Stereoselective Synthesis of (+)-Perovskone

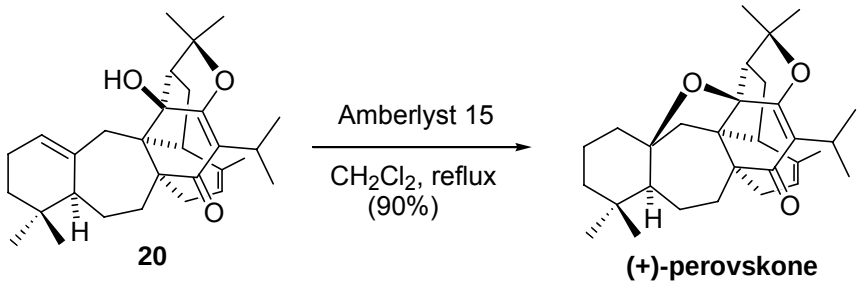
With optically pure (+)-*para*-benzoquinone **19** in hand, (+)-perovskone was synthesized using the same set of conditions used in our racemic synthesis. As analyzed earlier,[31] the Diels-Alder reaction of (+)-*para*-benzoquinone **19** with *trans*-*α*-ocimene added only from the *α*-face of the *para*-quinone and produced intermediate **xiii**, which underwent several other transformations to produce adduct **20** with specific rotation of +26.8° in benzene. Scheme 38 shows the



Scheme 38

mechanism of this series of transformations. *trans*-*α*-Ocimene first adds to (+)-*para*-benzoquinone **19** from the *α*-face to give **xiii**, catalyzed by Lewis acid. The terminal alkene in **xiii** then isomerizes to give trisubstituted alkene **xiv**. The following Lewis acid catalyzed

alkylation and etherification produces **20** in a cascade fashion. The final step needed to synthesize (+)-perovskone was accomplished when compound **20** was heated with Amberlyst® 15 ion exchange resin (Scheme 39). Our synthetic (+)-perovskone gave a specific rotation of +90.2° (in chloroform) which compares favorably with that of the isolated natural product (+94° in chloroform).



20 **(+)-perovskone**

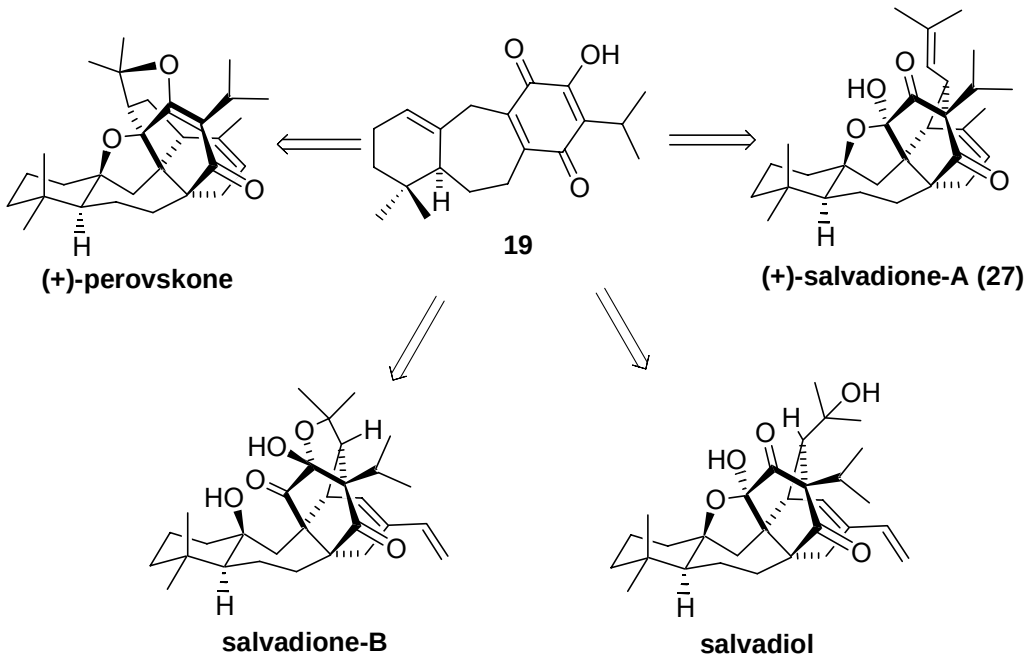
Scheme 39

First Total Synthesis of (+)-Salvadione-A

In 1999, a novel hexacyclic triterpene, salvadione-A **27**,[42] was isolated from *sursaudah* by Ahmad and co-workers, and its structure was rigorously established by means of 2D-NMR spectroscopy and X-ray diffraction analysis.[42] Structurally this new triterpene is among a family of triterpenes with perovskone,[25] salvadione-B[42] and salvadiol.[43] Since salvadione-A possesses many of the salient features of perovskone, we recognized that it could be synthesized from the same optically active *p*-benzoquinone **19**, the key intermediate in our (+)-perovskone synthesis (Scheme 40). [27]

By comparing the stereochemistry of the chiral methine in *para*-benzoquinone subunit of (+)-perovskone and that of (+)-salvadione-A, we realized that the same optically pure (+)-*para*-

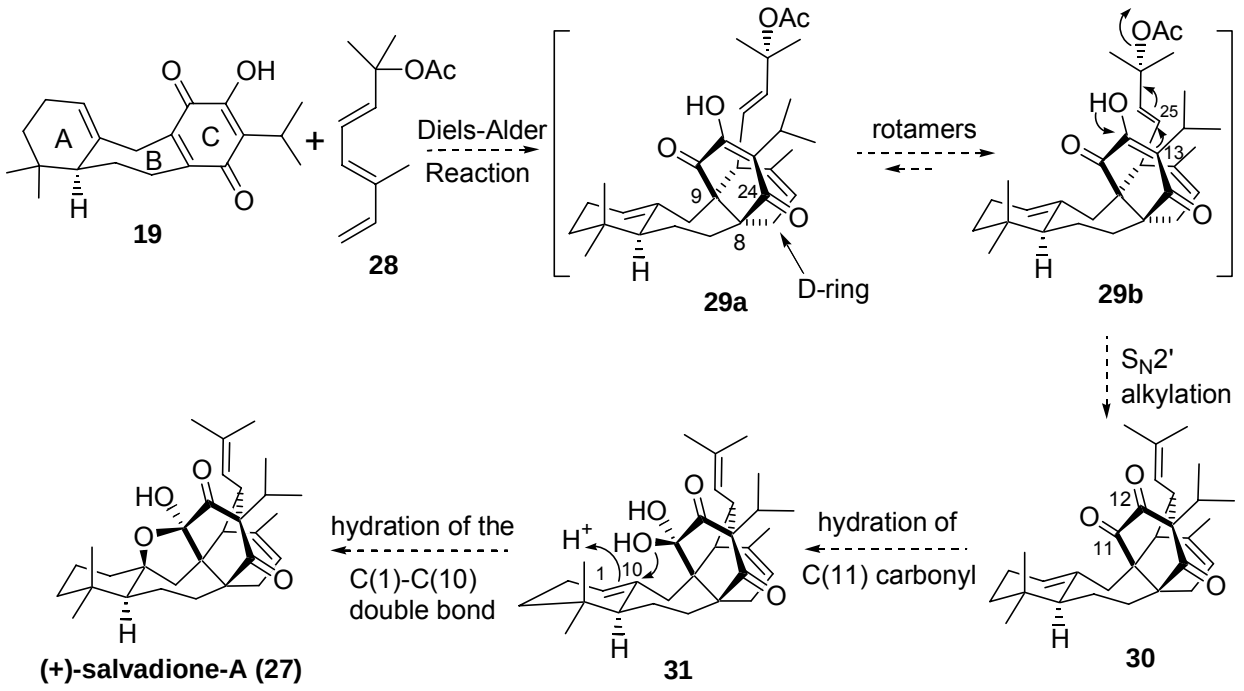
benzoquinone **19** could be used in our (+)-salvadione-A synthesis. In addition, natural salvadione-B and salvadiol have the same relative stereochemistry, which strongly suggests[25-27] that (+)-*para*-benzoquinone **19** is an important intermediate for the syntheses of this family of triterpenes.



Scheme 40

Scheme 41 summarizes our retrosynthetic analysis for salvadione-A. In our (+)-perovskone synthesis, we have found that dienes add to the α-face of (+)-*para*-benzoquinone **19**. In addition, the presence of a Lewis acid enables the Diels-Alder reaction to occur at temperatures as low as -20 ℃, and also controls the regioselectivity of the cycloaddition when an asymmetric diene, such as isoprene, is used.

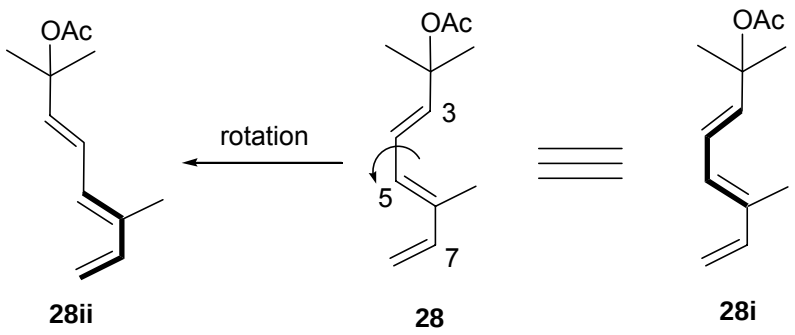
Our synthetic design required *para*-benzoquinone **19** to react with triene **28** to produce Diels-Alder adduct **29** with both regio- and stereoselectivity (Scheme 41). We also expected that mild Lewis acids may be used to promote this transformation.



Scheme 41

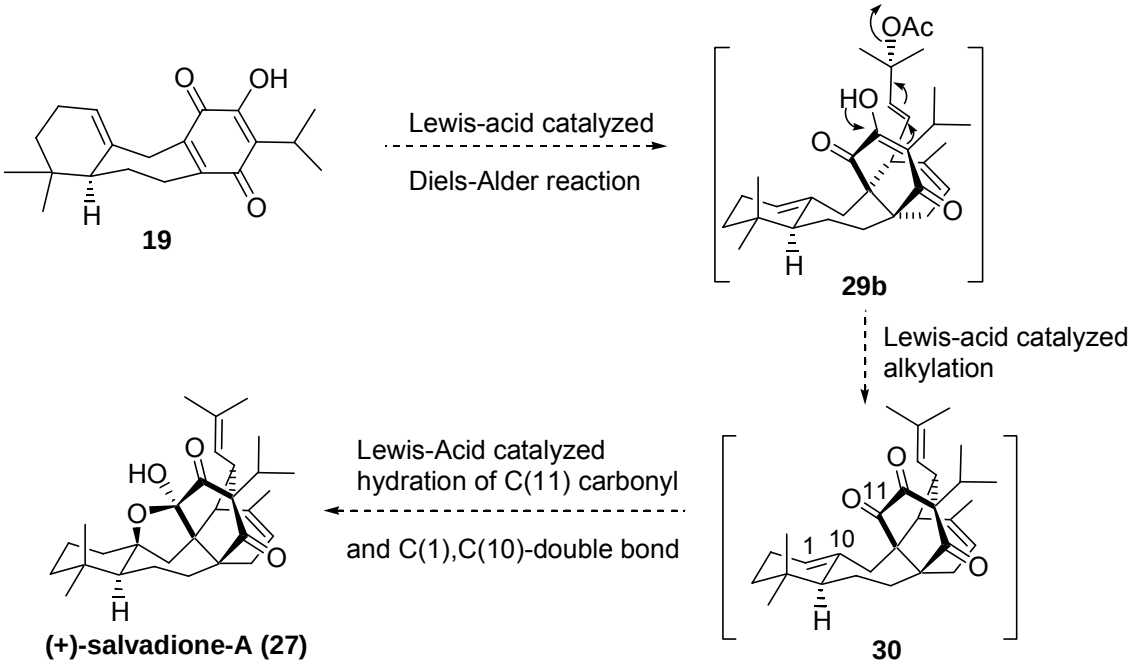
We expected that conformation **29b** would be preferred over conformer **29a** because of the non-steric interactions present in rotamer **29b** (Scheme 41). In light of this assumption, we expected only conformer **29b** would react to form a C(13)−C(25) bond through a S_N2' pathway upon exposure to Lewis Acid. Given the known tendency of 1,2-diketones to readily form hydrates, we predicted that the C(11) carbonyl would become hydrated and undergo fast reaction with the C(1)−C(10) double bond to produce a tetrahydrofuran ring.

There were several concerns to be addressed before we started our work. First, the use of triene **28** as the diene substrate raised the question of which conjugated diene moiety, the 3,5- or the 5,7-system, would preferentially take part in the Diels-Alder addition. Scrutiny of triene **28** indicates that the presence of a *Z*-methyl substitutent as part of the 3,5-butadiene moiety reduces its reactivity by hindering the likelihood of the *s-cis* form **28i**, (Scheme 42), whereas the 5,7-diene readily adopts an *s-cis* conformation **28ii**.



Scheme 42

Hence, the cycloaddition of **19** with triene **28** will produce only adduct **29**, which has the correct stereochemistry at C(8), C(9), and C(24). Protection of the C(2) hydroxyl of triene **28** as an acetate permits the subsequent formation of the C(13)–C(25) bond by means of an intramolecular S_N2'-alkylation of the latent 1,3-dione present in the C-ring. As discussed above, we predicted that simple conformational biasing, prior to the S_N2'-alkylation, would control the C(25) stereochemistry. In particular, non-bonded steric interactions between the C(24) side chain and the C(13) isopropyl unit would disfavor conformer **29a**, thus causing the less sterically congested conformation **29b** to predominate, leading to the formation of pentacycle **30**. Examination of a Dreiding molecular model of triketone **30** reveals that the C(11) carbonyl oxygen is situated almost directly above the C(10) carbon atom, which should facilitate hydration of the C(1)–C(10) trisubstituted double bond, thereby completing a synthesis of salvadione-A (*i.e.*, **30** → **31** → **27**). Since each of these transformations can in principle be carried out by using Lewis acid catalysis, the judicious choice of catalyst and reaction conditions should permit the Diels-Alder reaction, the intramolecular S_N2'-alkylation, and the sequential hydration of the C(11) carbonyl and tetrahydrofuran formation to proceed in a tandem cascade fashion (Scheme 43). While the synthesis of salvadione-A via this cascade-based process is our ultimate goal, we decided to first synthesize (+)-salvadione-A (**27**) in a stepwise fashion.



Scheme 43

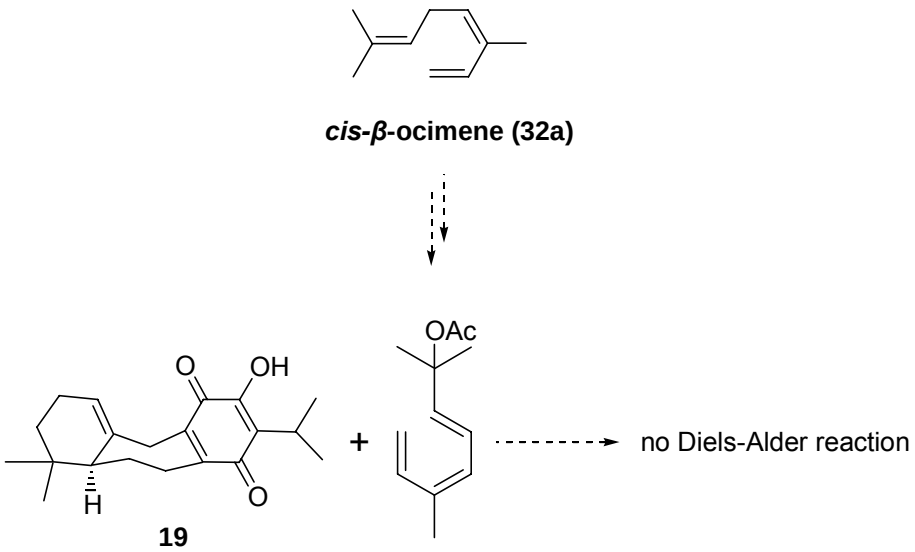
With optically active (+)-*para*-benzoquinone **19** in hand, our next goal focuses on the preparation of a suitable diene, such as triene **28**, precursor for the Diels-Alder reaction. We found that triene **28** could be synthesized from *trans*-*β*-ocimene (**32**) in three simple steps. Unfortunately, the commercially available *trans*-*β*-ocimene (**32**) was a 2:1 mixture of *trans*-*β*-ocimene (**32**) and *cis*-*β*-ocimene (**32a**) (Scheme 44).

***trans*-*β*-ocimene**
(**32**)

***cis*-*β*-ocimene**
(**32a**)

Scheme 44

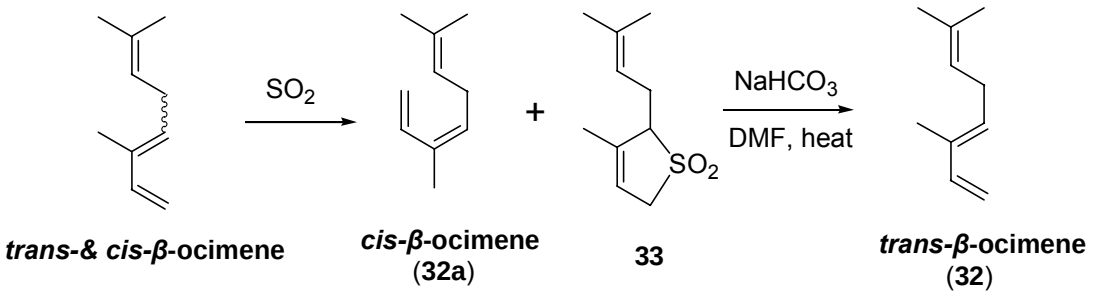
By comparing the structure of *cis*-*β*-ocimene (**32a**) and that of conformer **28i**, we believe that, due to the same steric consideration, the Diels-Alder reaction on a more advanced derivative of *cis*-*β*-ocimene (**32a**) would not take place with *para*-benzoquinone **19** at all (Scheme 45). Hence there should be no problem to use the mixture to start our study. However, in order to avoid problems, we decide to preclude this potential problem and only use pure triene **28** for the Diels-Alder reaction.



Scheme 45

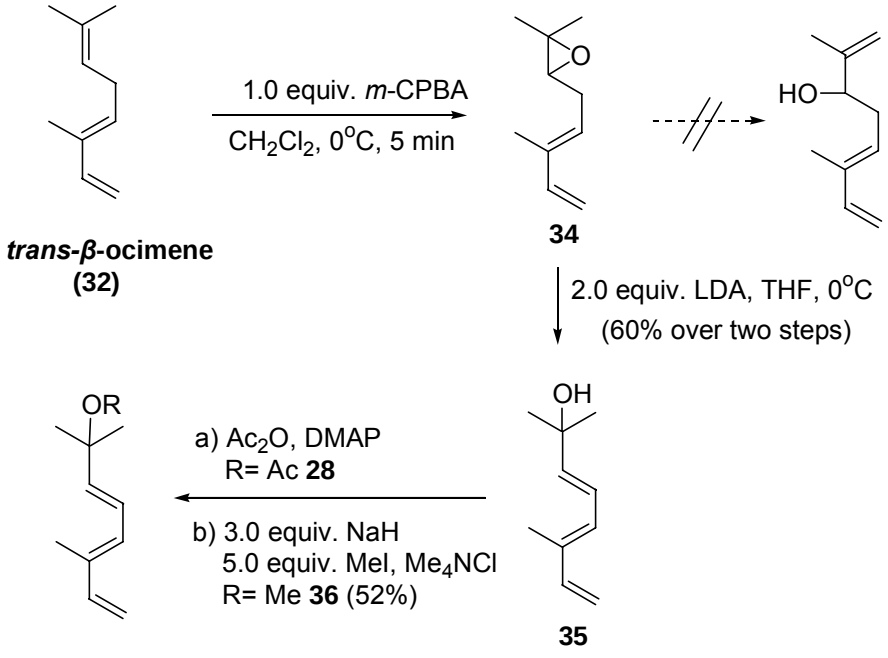
Sulfur dioxide undergoes facile cycloaddition with dienes.[44a-e] Simply heating the adduct in the presence of a weak base allows the regeneration of the diene moiety.[45a-c]

When the mixture of *trans*-*β*-ocimene (**32**) and *cis*-*β*-ocimene (**32a**) was treated with liquid SO_2 in a sealed tube at ambient temperature, the SO_2 only added to the *trans*-*β*-ocimene (**32**) to give adduct **33** (Scheme 46), and the unwanted *cis*-*β*-ocimene **32a** was left unreacted. Column chromatography on silica gel separated adduct **33** from *cis*-*β*-ocimene (**32a**). *trans*-*β*-Ocimene (**32**) was regenerated upon heating the adduct with sodium bicarbonate in DMF.[35a-c]



Scheme 46

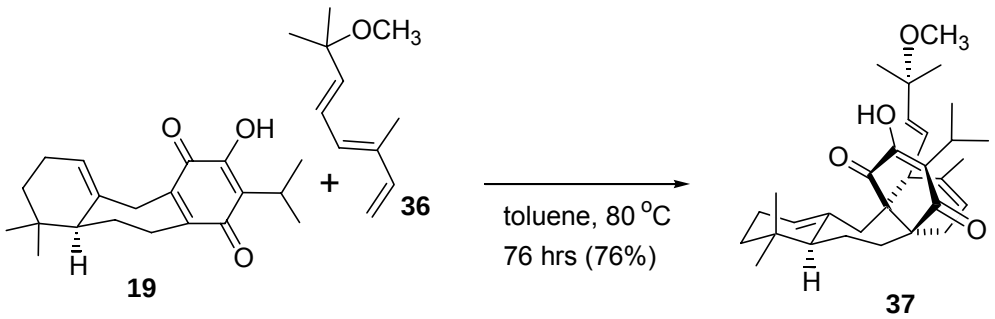
With *trans-β*-ocimene **(32)** in hand, a three-step process was envisioned to prepare potential triene derivatives for use in the Diels-Alder reaction. It has been studied by Hiyama[46] that isolated alkenes are usually more reactive upon epoxidation than conjugated dienes, since conjugation diminishes the reactivity of the alkene. Thus, isolated double bond in *trans-β*-



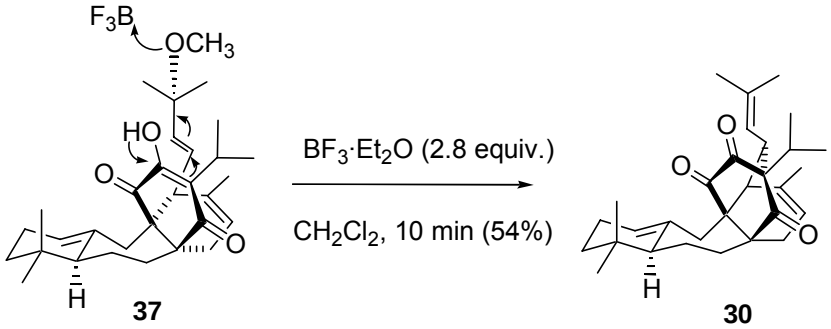
Scheme 47

ocimene (**32**) can be differentiated from the conjugated diene moiety. The regiospecific oxidation of *trans*-*β*-ocimene with 1.0 equiv of *m*-CPBA in cold methylene chloride gave a high yield of epoxide **34** (Scheme 47).[46] Octa-3(*E*),5(*E*)-trien-2-ol **35** was produced when treated with excess LDA at 0 °C. Although LDA could remove any of the protons on terminal *gem*-dimethyl groups, only triene **35** was collected, because the allylic protons were more acidic and hence easier to remove. In the beginning, acetate **28** was prepared when octa-3(*E*),5(*E*)-trien-2-ol **35** reacted with acetic anhydride catalyzed with 4-dimethylaminopyridine (DMAP).

Unfortunately, acetate **28**, derived from tertiary alcohol **35**, underwent rapid elimination at ambient temperature, or on attempted purification, or upon exposure to mild Lewis acid catalysts (even at low temperatures). Methyl ether **36** was prepared on the assumption that a methoxyl group would be less prone to eliminate and thus permit the Diels-Alder reaction to occur (Scheme 47). We were delighted to find that triene ether **36** was thermally stable and reacted over a 72-h period with *para*-benzoquinone **19** at 80 ℃ to afford adduct **37** in 76% yield (Scheme 48); an X-ray analysis of adduct **37** confirmed the predicted facial and regioselectivity of this cycloaddition.

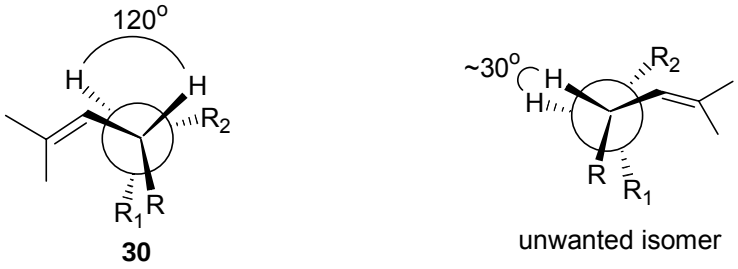


Scheme 48



Scheme 49

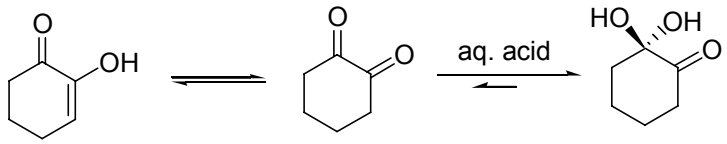
Treatment of adduct **37** with excess boron trifluoride etherate in CH_2Cl_2 at 0 ℃ rapidly gave the S_N2'-alkylation product **30** in 54% yield (Scheme 49). ^1H NMR data suggested that the 2.7 Hz coupling constant between the C(24) and C(25) methines was indicative of a dihedral angle of almost 120º, indicating that C(25) had the desired stereochemistry; molecular models indicated that the wrong stereochemistry at C(25) would produce a dihedral angle of about 30º and a coupling constant of >6 Hz (Scheme 50).



Scheme 50

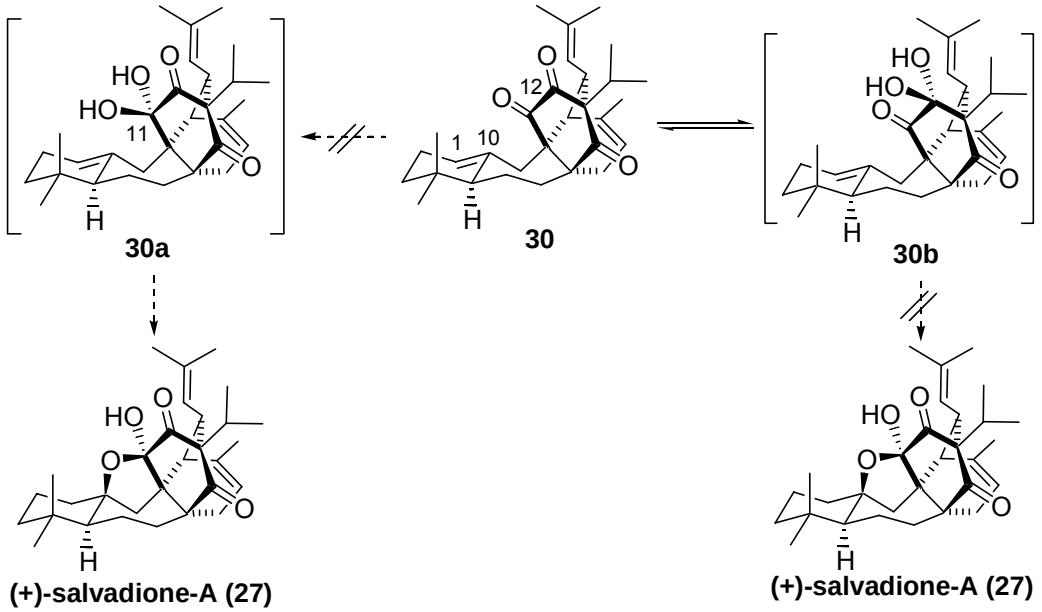
A fundamental belief in organic chemistry is that carbonyl groups with electron-withdrawing subsitutents are easily hydrated. Indeed, in 1963 Bakule and Long demonstrated

that 1,2-cyclohexandiones which cannot enolize, such as **30**, are completely and rapidly hydrated when exposed to dilute aqueous acid (Scheme 51).[47]



Scheme 51

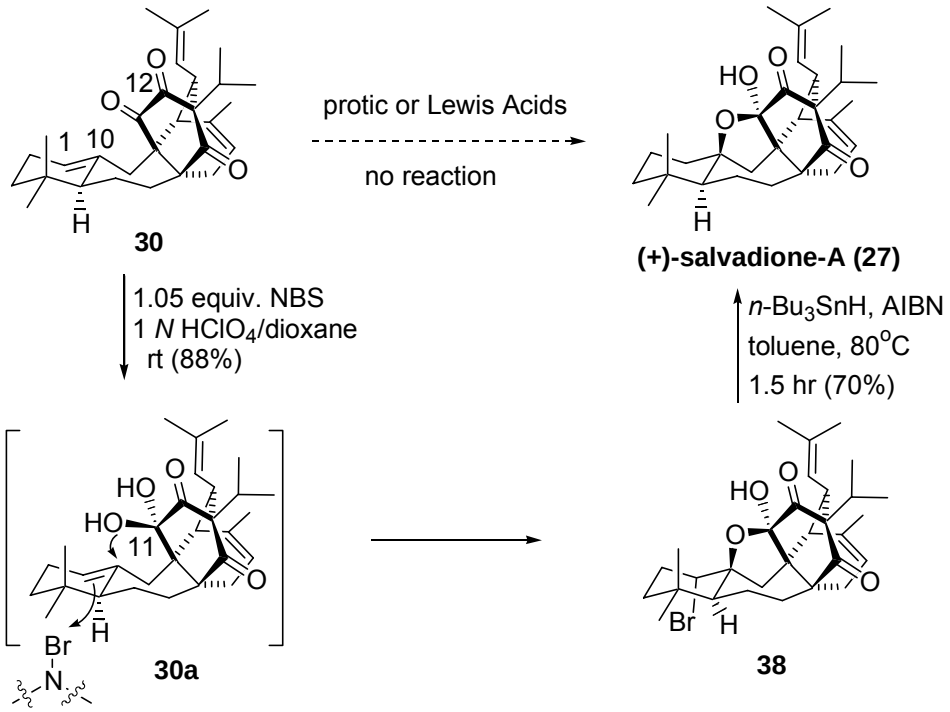
While the reaction of triketone **30** under various aqueous acidic conditions or with water-soluble Lewis acids produced a geminal diol, hydration of the C(1)−C(10) double bond was not observed. These observations suggested that instead of the expected hydrate **30a**, the C(12) carbonyl is preferentially hydrated to produce **30b**, geminal diol. This is significant since hydrate **30b** is geometrically unable to add to the C(1)−C(10) double bond (Scheme 52).



Scheme 52

In addition to the acid-promoted hydration of olefins, a time-tested means to activate an olefin is to generate a halonium ion from the double bond, which then reacts with many nucleophiles. Many activating reagents, such as I_2,[48] Br_2,[49] and NBS,[50] are useful for this transformation.

The observation that the C(11) carbonyl oxygen was spatially close to the C(10) carbon of the trisubstituted double bond of **30** offered an attractive solution to our hydration difficulties. We speculated that the bromonium ion intermediate generated from the C(1)−C(10) double bond would be preferentially opened by the oxygen atom of the C(11) carbonyl to form the desired tetrahydrofuran ring and ultimately a hemi-acetal as C(11). Treatment of **30** with NBS and 1 *N* perchloric acid gave bromide **38** in 88% yield (Scheme 53). Note that triketone **30** has two other trisubstituted double bonds that could form bromonium ions. The steric influence of the C-ring



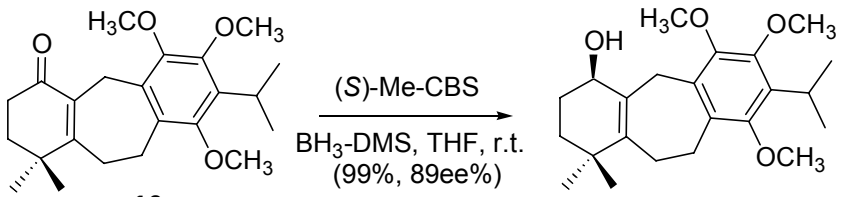
Scheme 53

of triketone **30**, however, prevents the bromonium ions derived from these alkenes from opening. Moreover, the use of 1 *N* perchloric acid facilitated the hydration of triketone **30**. Removal of the bromine atom via a free radical reduction completed our stepwise synthesis of (+)-salvadione-A (**27**). The use of optically active (+)-*para*-benzoquinone **19** produced (+)-salvadione-A with $[\alpha]^{24}_{D}$= +37.61º (*c* 0.36, $CHCl_3$) whereas the reported value for the natural molecule is +37.92º (*c* 0.37, $CHCl_3$).

In conclusion, (+)-salvadione-A, which has six rings and eight stereogenic centers, was synthesized from (+)-*para*-benzoquinone **19** in only four steps. The first two steps feature a stereo- and regiospecific Diels-Alder reaction and an intramolecular alkylation, respectively. The C(11) carbonyl was resistant to hydration, but a step-wise synthesis of (+)-salvadione-A was completed by means of a regioselective intramolecular bromohydrin reaction, followed by free radical reduction. Efforts to prepare (+)-salvadione-A from *para*-benzoquinone **19** via a cascade sequence are now underway.

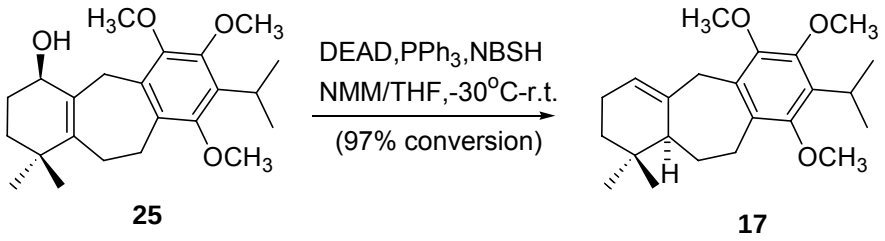
Experimental Section

General Procedures. All reactions were run under nitrogen atmosphere and monitored by TLC analysis. Unless otherwise indicated, all ethereal workups consisted of the following procedure: The reaction was quenched at room temperature with saturated aqueous ammonium chloride. The organic solvent was removed under reduced pressure on a rotary evaporator, and the residue was taken up in ether, washed with brine, and dried over anhydrous magnesium sulfate. Filtration, followed by concentration at reduced pressure on a rotary evaporator and at 1 torr to constant weight, afforded a crude residue which was purified by flash chromatography using silica gel 60 (230-400 mesh ASTM) and distilled reagent grade petroleum ether and diethyl ether. Proton NMR spectra were obtained in $CDCl_3$ and were calibrated using trace $CHCl_3$ present (δ 7.27) as an internal reference. The IR spectra were obtained using Avatar360FT-IR and high resolution MS were taken using LCT Premier from Waters.



(R)-11,12,14-Trimethoxy-9(10→20)-5αH-abeo-abieta-1(10),8,11,13-tetraen-1-ol 25: *(S)*-Methyl-CBS-oxazaborolidine (1.0 *M*, 1.35 mL, 1.35 mmol) and borane methyl sulfide complex (0.65 ml, 6.7 mmol) were dissolved in freshly distilled anhydrous THF (50 mL). Enone **16** (2.5 g, 6.7 mmol) in anhydrous THF (25 mL) was added through a syringe pump over a period of 2 h at

rt. The resulting mixture was stirred for 4 h at rt and then cooled to 0 ℃. Cold methanol (25 mL) was added dropwise to destroy any excess hydride. Standard ethereal workup and chromatography (elution with pet ether: ether, 4:1) afforded 2.27 g (99%) of allylic alcohol **25** as a white solid. The solid was recrystallized in EtOAc/pet ether (3 ×) to afford 1.99 g of optically pure enantiomer. The optical rotation was determined to be $[\alpha]^{24}_{D}$= +29.6º (*c* = 0.031 g. mL^{-1}, $CHCl_3$): ^1H (400 MHz) δ 0.99 (s, 3H), 1.03 (s, 3H), 1.33 (s, 3H), 1.35 (s, 3H), 1.57-1.64 (m, 1H), 1.68-1.74 (m, 1H), 1.82-1.91 (m, 1H), 2.03 (br s, 1H), 2.39-2.51 (m, 2H), 2.91-2.97 (m, 2H), 3.38 (heptet, *J* = 7.0 Hz, 1H), 3.58 (s, 1H), 3.60 (s, 1H), 3.65 (s, 3H), 3.79 (s, 3H), 3.86 (s, 3H), 4.05 (br t, 1H); ^{13}C NMR (100.6 MHz) 22.4 (q), 24.9 (t), 26.0 (d), 26.7 (q), 26.9 (t), 27.7 (t), 28.2 (q), 28.6 (t), 34.5 (t), 35.3 (s), 60.4 (q), 60.5 (q), 61.9 (q), 70.5 (d), 129.4 (s), 131.3 (s), 132.4 (s), 132.5 (s), 142.9 (s), 146.6 (s), 150.7 (s), 151.5 (s) ppm; HR-MS: $[M+H]^+$ = 375.2526; $[M+H]^+_{calculated}$ = 375.2535; IR (neat): 2936, 1453, 1414, 1341, 1244, 1121, 1039, 993, 956 cm^{-1}.



25 **17**

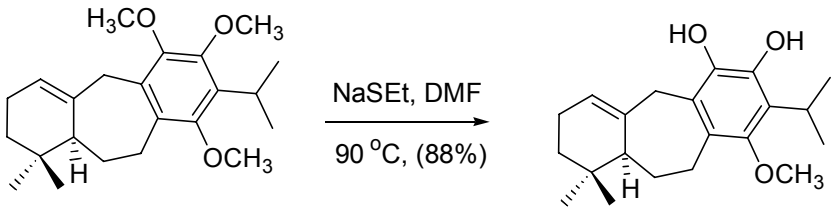
11,12,14-Trimethoxy-9(10→20)-5αH-abeo-abieta-1(10),8,11,13-tetraene[*(S)*-17]

Triphenylphosphine (2.20 g, 8.4 mmol) was dissolved in anhydrous *N*-methyl morpholine (NMM) (6 mL) at -30 ℃. Diethylazodicarboxalate (DEAD) (1.20 mL, 7.6 mmol) was added dropwise. The orange color of DEAD faded in seconds after each drop of addition to the solution. Finally after 10 minutes a viscous yellow solution was formed. Optically active allylic alcohol **25** (0.95 g, 2.54 mmol), dissolved in freshly distilled THF (6 mL), was added dropwise and the

reaction mixture was stirred at -30 ℃ for 30 minutes. The reaction mixture was allowed to warm to -15 ℃ over a period of 30 minutes. A lot of solid formed at -15 ℃. Finally, the whole reaction mixture solidified. This solid was vigorously shaked by hand every 5 minutes for 30 minutes. It was then cooled back to -30 ℃ and 2-nitrobenzenesulfonylhydrazine (NBSH) (1.55 g, 7.6 mmol) was added in one portion. The solid mixture "melted" quickly after the addition of NBSH, and a clear solution was formed within 10 minutes. The resulting solution was stirred at -30 ℃ for 1 h, and then the temperature was raised to -20 ℃ and stirred for 1 more hour. With stirring 1 more hour at -10 ℃, the orange mixture was allowed to slowly warm to rt and stirred overnight.

Ether (30 mL) was added to the resulting solution, followed by addition of 5% aqueous H_2O_2 (10 mL) and the resulting mixture was stirred for 15 minutes. The organic layer was separated, washed with water (15 mL) and brine (15 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and then concentrated using a rotary evaporator. The crude yellow solid was re-dissolved in 30 mL of diethyl ether. Petroleum ether (10 mL) was added to precipitate out most of the triphenylphosphine oxide. The ethereal layer was concentrated and purified on flash column chromatography to afford 900 mg (49%) of pure alkene **17** with recovery of allyl alcohol **25** (1.0 g, 50%). The conversion can reach up to 97%. The specific rotation was observed to be $[\alpha]^{24}_{D}$= -87.1º (*c* = 0.03 g.mL^{-1},$CHCl_3$): ^{1}H (400 MHz) δ 0.91 (s, 3H), 1.06-1.39 (m, 9H), 1.82-1.85 (m, 1H), 1.92-2.14 (m, 3H), 2.56-2.62 (m, 1H), 3.05-3.08 (br d, *J* = 14.4 Hz, 1H), 3.16-3.21 (m, 1H), 3.40-3.47 (heptet, *J* = 7.0 Hz, 1H), 3.67 (s, 3H), 3.80 (s, 3H), 3.89 (s, 3H), 5.52 (br s, 1H); ^{13}C NMR (100.6 MHz) 22.4 (q), 22.5 (q), 23.4 (t), 26.2 (d), 27.4 (q), 27.7 (q), 29.8 (t), 31.6 (t), 31.6 (t) [note: the preceding signals overlap], 32.2 (s), 35.5 (t), 51.7 (q), 60.5 (q), 62.5 (q), 121.6 (d), 130.4 (s), 132.2 (s), 134.0 (s), 138.4 (s), 146.8 (s), 151.0 (s),

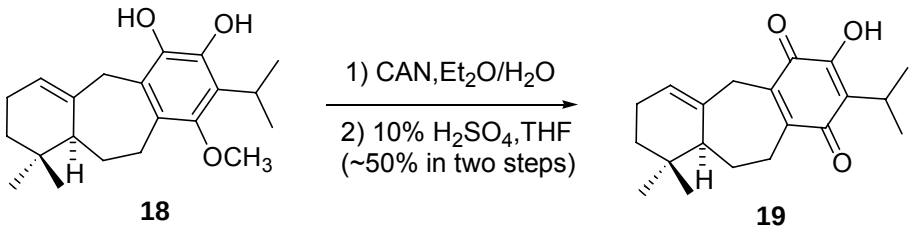
151.5 (s) ppm; HR-MS: $[M+H]^+$ = 359.2582; $[M+H]^+_{calculated}$ = 359.2586; IR (neat): 2928, 2855, 1453, 1413, 1341, 1266, 1247, 1121, 1041, 964, 738 cm^{-1}.



17 **18**

Diol 18 from alkene 17: To a solution of ethanethiol (7.5 mL, 0.101 mol, 20.0 equivalents) in dimethyl formamide (DMF) (80 mL) at 0 ℃ was added NaH (60% in mineral oil, 3.00 g, 0.075 mol, 15 equivalents) in 5 portions under N_2 atmosphere. The reaction mixture bubbles vigorously after each addition of NaH, and a viscous foam formed. The resulting mixture was stirred at 0 ℃ for 30 minutes until it became a clear brown solution. Alkene **17** (1.80 g, 0.0050 mol) was dissolved in DMF (20 mL) and was added to NaSEt solution slowly. The resulting mixture was heated for 4 days, during which time temperature was controlled exactly on a narrow range from 90 ℃ to 95 ℃. Distinct decreases in yield were observed whenever the temperature was higher than 95 ℃ due to decomposition of the product. TLC analysis revealed no starting material, and the resulting solution was cooled to 0 ℃. Aqueous HCl (a 5% solution) was added to acidify the reaction mixture. It was then extracted three times with EtOAc. The combined organic extracts were washed with water, brine and dried over anhydrous $MgSO_4$. Concentration using a rotary evaporator gave 1.89 g of a crude foam, which was purified via column chromatography (elution with pet ether: ether = 4:1) to afford 1.46 g (88%) of product **18** as a dark brown foam. The specific rotation was observed to be $[\alpha]^{24}_D$= -91.5º (*c* = 0.0064 g.mL^{-1}, benzene): ^1H (400 MHz)

δ 0.84-0.89 (m, 2H), 0.87 (s, 3H), 0.92 (s, 3H), 1.08-1.16 (m, 2H), 1.28-1.36 (m, 2H), 1.38 (d, J = 6.8 Hz, 3H), 1.39 (d, J = 6.8 Hz, 3H), 1.81 (dd, J_1 = 4.8 Hz, J_2 = 8.0 Hz, 1H), 1.92-2.11 (m, 3H), 2.56-2.63 (m, 1H), 3.06-3.13 (m, 2H), 3.40-3.50 (heptet, J = 6.8 Hz, 1H) 3.62 (d, J = 14.4 Hz, 1H), 3.63 (s, 3H), 4.71 (bs, 1H, OH), 5.22 (bs, 1H, OH), 5.49 (bt, J = 3.6 Hz, 1H); ^{13}C NMR (400 MHz) 21.27 (q), 21.27 (q), 23.18 (t), 25.37 (t), 25.63 (d), 27.26 (q), 27.28 (q), 30.05 (t), 31.49 (t), 32.08 (s), 35.53 (t), 50.68 (d), 62.59 (q), 121.35 (d), 124.70 (s), 126.04 (s), 126.33 (s), 136.85 (s), 137.84 (s), 142.02 (s), 148.86 (s) ppm; HR-MS: $[M+H]^+$ = 331.2285; $[M+H]^+_{calculated}$ = 331.2273; IR (neat): 3386, 2917, 1639, 1363, 1265 cm^{-1}.

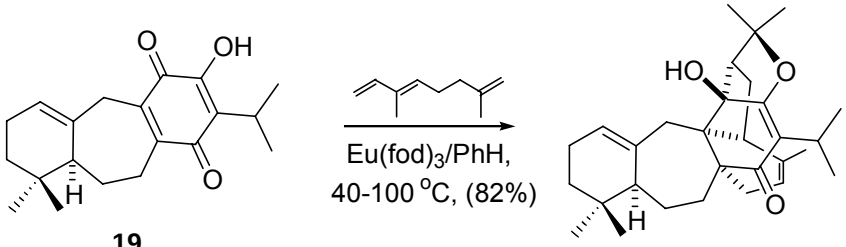


18 **19**

(+)-*para*-Benzoquinone 19: To a solution of diol **18** (1.46 g, 4.42 mmol) in diethyl ether/H_2O (40 mL/40 mL) at rt was added ceric(IV) ammonium nitrate (CAN) (4.85 g, 8.84 mmol, 2.0 equivalents). The resulting mixture was stirred for four hours at rt. The ether layer was separated and the aqueous layer was extracted three times with diethyl ether (20 mL). The combined ethereal extracts were dried over anhydrous $MgSO_4$, filtered and concentrated using a rotary evaporator to afford 1.50 g of a crude red solid.

This crude product was dissolved in THF (35 mL) and was treated with 10% aqueous H_2SO_4 (15 mL) for 1 h. Diethyl ether (50 mL) was added and organic phase was separated. The aqueous layer was extracted twice with ether (20 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated on rotary evaporator to give 1.50 g of a crude red

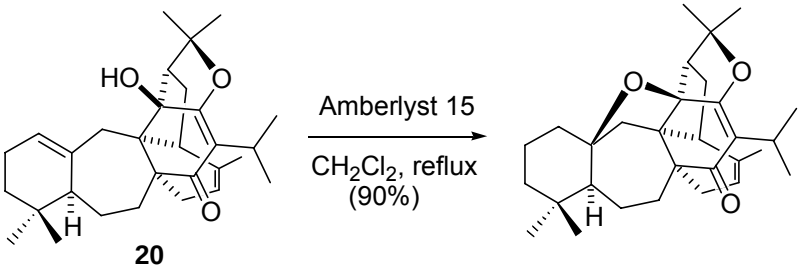
solid. Column chromatography (elution with pet ether: ether = 8:1) provided 1.32 g (95%) of *para*-benzoquinone **19**. The specific rotation was observed to be $[\alpha]^{24}_{D}$ = -155.2º (*c* = 0.0051 g.mL^{-1}, $CHCl_3$): ^{1}H (400 MHz) δ 0.87 (s, 3H), 0.91 (s, 3H), 1.11-1.21 (m, 2H), 1.22 (d, *J* = 6.8 Hz, 6H), 1.31-1.40 (m, 1H), 1.57 (d, *J* = 2.4 Hz, 1H), 1.82 (dd, J_1 = 4.0 Hz, J_2 = 11.2 Hz, 1H), 1.94-2.02 (m, 3H), 2.49 (ddd, J_1 = 2.8 Hz, J_2 = 9.6 Hz, J_3 = 14.8 Hz , 1H), 2.98 (d, *J* = 16.0 Hz, 1H), 3.06 (ddd, J_1 = 2.8 Hz, J_2 = 8.0 Hz, J_3 = 14.8 Hz , 1H), 3.21 (heptet, *J* = 6.8 Hz, 1H), 3.59 (d, *J* = 15.6 Hz, 1H), 5.49 (bt, *J* = 3.6 Hz, 1H), 7.06 (s, 1H, OH); ^{13}C NMR (400 MHz) 19.96 (q), 19.96 (q), 23.14 (t), 24.43 (d), 24.70 (t), 26.47 (q), 27.20 (t), 27.24 (q), 31.53 (t), 32.26 (s), 33.73 (t), 50.37 (d), 122.83 (d), 124.72 (s), 134.84 (s), 138.98 (s), 146.86 (s), 150.02 (s), 183.64 (s), 186 .71 (s) ppm; HR-MS: $[M+H]^+$ = 315.1956; $[M+H]^+_{calculated}$ = 315.1960; IR (neat): 3348, 2961, 2934, 2872, 1638, 1391, 1321, 1287, 1128, 1038, 758 cm^{-1}.



19 **20**

Diels-Alder adduct 20: A mixture of *para*-benzoquinone **19** (45 mg, 0.143 mmol), *β-E*-ocimene (170 mg, 1.25 mmol, 8.7 equivalents) and $Eu(fod)_3$ (5 mg), and anhydrous benzene (1.3 mL) was placed in a sealed tube. The resulting reaction mixture was stirred at rt under a nitrogen atmosphere for 64 h, then stirred at 40 ℃-45 ℃ for 69 h, and then stirred at 100 ℃-110 ℃ for an additional 48-hour. The reaction mixture was cooled back to rt and 3 mg of more $Eu(fod)_3$ was added. The mixture was sealed and heated at 100 ℃-110 ℃ for 72 more hours. Benzene was

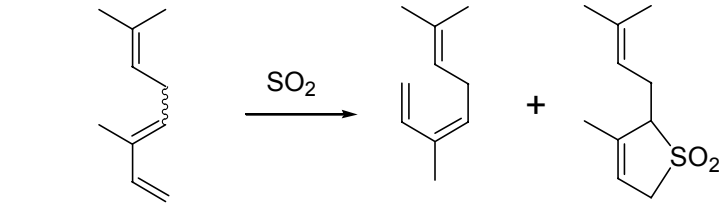
removed from the crude mixture and column chromatography (elution with pet ether: ether = 30:1, 20:1) afforded 51.6 mg (80%) of pure Diels-Alder adduct **20**. The specific rotation was observed to be $[\alpha]^{24}_{D}$= +26.8º (*c* = 0.0037 g.mL^{-1}, benzene): ^{1}H (400 MHz) δ 0.79 (s, 3H), 0.91 (s, 3H), 1.02 (d, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 7.2 Hz, 3H), 1.20-1.28 (m, 1H), 1.32-1.40 (m, 1H), 1.43 (s, 3H), 1.48-1.56 (m, 3H), 1.59 (s, 3H), 1.67 (s, 3H), 1.76-1.86 (m, 1H), 1.88-1.98 (m, 2H), 1.98-2.14 (m, 4H), 2.37-2.56 (4H), 2.70 (d, *J* = 14.4 Hz, 1H), 2.96 (heptet, *J* = 7.2 Hz, 1H), 3.95 (s, 1H), 5.07-5.08 (m, 1H), 5.85 (s, 1H); ^{13}C NMR (400 MHz) 19.90 (q), 20.31 (q), 20.92 (q), 23.51 (t), 23.60 (q), 24.18 (t), 24.62 (d), 25.58 (q), 27.47 (t), 27.99 (q), 28.70 (q), 32.64 (s), 33.08 (t), 33.82 (t), 34.98 (t), 49.73 (t), 50.09 (d), 50.25 (d), 50.71 (s), 51.88 (s), 53.69 (d), 89.71 (s), 89.73 (s), 120.91 (s), 121.90 (d), 127.06 (d), 137.10 (s), 142.26 (s), 171.00 (s), 202.32 (s) ppm; HR-MS: $[M+H]^{+}$ = 451.3226; $[M+H]^{+}_{calculated}$ = 451.3212; IR (neat): 3473, 2957, 2870, 1670, 1629, 1456, 1386, 1367, 1275, 1192, 1119, 1035, 838 cm^{-1}.



20 **(+)-perovskone**

(+)-Perovskone: To a solution of alkene **20** (51.6 mg, 0.115 mmol) in methylene chloride (10 mL) was added 100 mg of Amberlyst® 15 ion-exchange resin. The resulting mixture was refluxed under N_2 atmosphere for one hour. The Amberlyst® 15 ion-exchange resin was removed by filtration and the methylene chloride was removed under vacuum. Column chromatography (elution with pet ether: ether = 8:1) gave 46.4 mg (90%) of pure (+)-perovskone. The specific

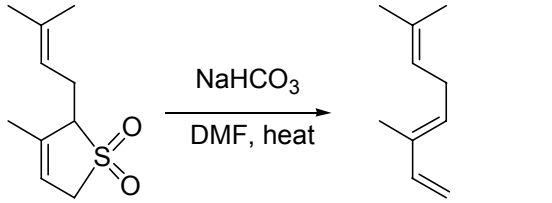
rotation was observed to be $[\alpha]^{24}_{D} = +90.2^{o}$ (c = 0.0108 g.mL^{-1}, $CHCl_3$): ^{1}H (400 MHz) δ 0.81 (s, 3H), 0.84 (s, 3H), 1.03 (d, J = 7.2 Hz, 3H), 1.12 (d, J = 7.2 Hz, 3H), 1.24-1.34 (m, 4H), 1.36 (s, 3H), 1.39-1.48 (m, 3H), 1.52 (s, 3H), 1.56-1.66 (m, 5H), 1.67 (s, 3H), 1.70-1.84 (m, 3H), 2.02 (dd, J_1 = 8.0 Hz, J_2 = 13.6 Hz, 1H), 2.13 (dt, J_1 = 7.2 Hz, J_2 = 15.2 Hz, 1H), 2.35 (dd, J_1 = 3.2 Hz, J_2 = 12.4 Hz, 1H), 2.42 (bt, J = 8.8 Hz, 1H), 2.56 (d, J = 13.6 Hz, 1H), 2.73 (dd, J_1 = 7.2 Hz, J_2 = 14.8 Hz, 1H), 3.11 (heptet, J = 7.2 Hz, 1H), 5.34 (d, J = 6.8 Hz, 1H); ^{13}C NMR (400 MHz) 18.60 (t), 18.71 (q), 19.13 (q), 19.53 (q), 20.58 (t), 20.84 (q), 23.18 (d), 23.35 (q), 26.08 (q), 31.04 (q), 32.47 (t), 32.62 (s) , 34.55 (t), 40.12 (t), 40.95 (t), 41.71 (t), 47.25 (s), 47.55 (d), 52.79 (d), 52.82 (d), 52.90 (s), 53.26 (t), 87.74 (s), 88.36 (s), 95.30 (s), 119.10 (d), 122.87 (s), 135.34 (s), 168.63 (s), 200.35 (s) ppm; MS: $[M+H]^+$ = 451.3230; $[M+H]^+_{Calculated}$ = 451.3212; IR (neat): 2922, 2852, 1628, 1460, 1368, 1265, 740, 703 cm^{-1}



***trans*-& *cis*-*β*-ocimene** **_cis_-*β*-ocimene 32a** **33**

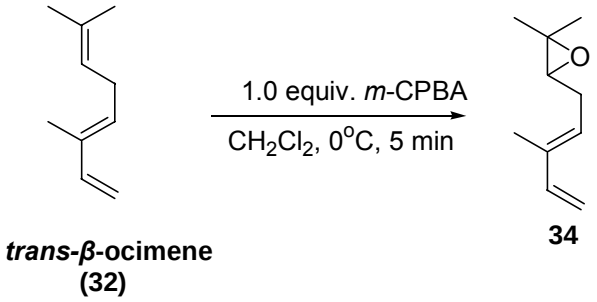
SO_2-Diels-Alder Adduct 33: A mixture of *β-Z-* and *β-E*-ocimene (11.0 g, 0.081 mmol) was placed in a long-neck thick-wall tube. SO_2 gas was collected into the tube as a liquid (~8 mL) at -78 ℃. The tip of the tube was then sealed and reaction vessel was allowed to warm to rt and stirred for 24 h. The resulting brown solution was cooled to -78 ℃ and the tube was opened carefully. The mixture was poured into a mixture of diethyl ether and dry ice. After warming to rt, the ethereal solution was washed with water and dried over anhydrous $MgSO_4$ and filtered.

After removal of the solvent, 14.5 g of crude brown liquid was obtained. Flash column chromatography gave 8.1 g (74% based on *β-Z*-ocimene) of sulfate **33** (TLC, hexane: EtOAc, 3:1, R_f **33** = 0.23) and 4.24 g (38.5%) of *β-Z*-ocimene (TLC, hexane: EtOAc, 3:1, R_f = 0.98): ^{1}H (400 MHz) δ 1.64 (s, 3H), 1.70 (s, 3H), 1.83 (s, 3H), 2.46-2.60 (m, 2H), 3.45-3.52 (bt, 1H), 3.55-3.74 (bq, 2H), 5.16-5.24 (bt, 1H), 5.64-5.70 (bs, 1H); ^{13}C NMR (400 MHz) 17.90 (q), 18.21 (q), 25.74 (t), 26.41 (q), 55.64 (t), 67.24 (d), 117.09 (d), 118.26 (d), 135.39 (s), 138.63 (s) ppm.



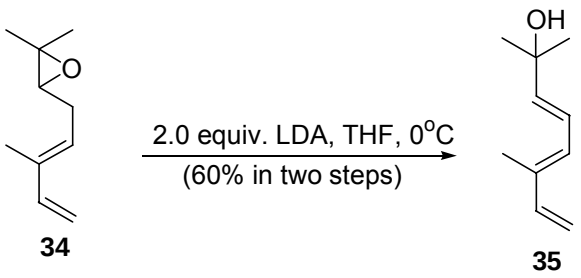
33 ***trans-β*-ocimene (32)**

***tans-β*-Ocimene (32)**: To a solution of the sulfate **33** (7.7 g, 38.5 mmol) in anhydrous dimethyl formamide (DMF) (90 mL) was added anhydrous sodium bicarbonate (3.5 g, 42.4 mmol, 1.1 equivalents). The resulting mixture was refluxed until TLC showed all the sulfate had been converted to product. It was then cooled to 0 ℃ and standard ethereal workup gave 5.9 g of crude product contaminated with trace amounts of DMF (TLC, hexane: EtOAc, 3:1, R_f **32** = 0.98): ^{1}H (400 MHz) δ 1.65 (s, 3H), 1.70 (s, 3H), 1.77 (s, 3H), 2.83 (t, J = 7.2 Hz, 2H), 4.93 (d, J = 10.4 Hz, 1H), 5.09 (d, J = 17.2 Hz, 1H), 5.11-5.16 (m, 1H), 5.46 (t, J = 7.2 Hz, 1H), 6.36 (dd, J_1 = 10.4 Hz, J_2 = 17.2 Hz, 1H); ^{13}C NMR (400 MHz) 11.86 (q), 17.95 (q), 25.90 (q), 27.54 (t), 110.79 (t), 122.40 (d), 131.98 (d), 132.36 (s), 133.92 (s), 141.73 (d) ppm.



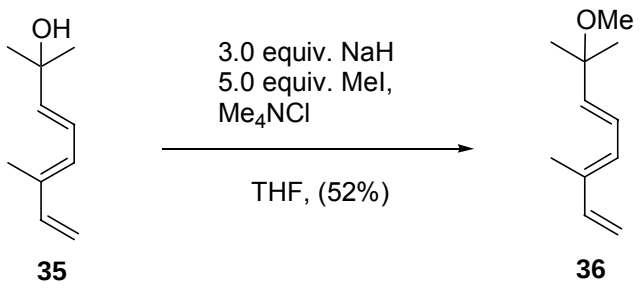
***trans*-β-ocimene (32)** **34**

Diene epoxide 34: A solution of *β*-*E*-ocimene (**32**) (3.0 g, 22.0 mmol) in anhydrous methylene chloride (120 mL) was cooled to 0 ℃ under N_2 atmosphere. *m*-CPBA (60% in weight, 6.34 g, 22.0 mmol, 1.0 equivalent) was added in a single portion. The reaction mixture was stirred at 0 ℃ for 5 minutes before 25 mL of 2 M NaOH was added to quench the reaction. The aqueous layer was separated. The organic layer was washed with water (10 mL) and brine (10 mL). The resulting organic layer was then dried over anhydrous $MgSO_4$. Removal of the solvent gave 5.9 g of crude **34** (TLC, hexane: EtOAc, 4:1, R_f **34** = 0.66). Because of the low boiling point and instability, this crude oil was used directly in the next step without further purification: ^{1}H (400 MHz) δ 1.32 (s, 3H), 1.33 (s, 3H), 1.78 (s, 3H), 2.26-2.36 (m, 1H), 2.44-2.54 (m, 1H), 2.79 (t, J = 6.8 Hz, 1H), 4.99 (d, J = 10.4 Hz, 1H), 5.15 (d, J = 17.2 Hz, 1H), 5.53 (t, J = 7.2 Hz, 1H), 6.40 (dd, J_1 = 10.4 Hz, J_2 = 17.2 Hz, 1H); ^{13}C NMR (400 MHz) 12.17 (q), 18.94 (q), 25.06 (q), 28.57 (t), 58.63 (s), 63.63 (d), 111.86 (t), 127.23 (d), 136.35 (s), 141.28 (d) ppm.



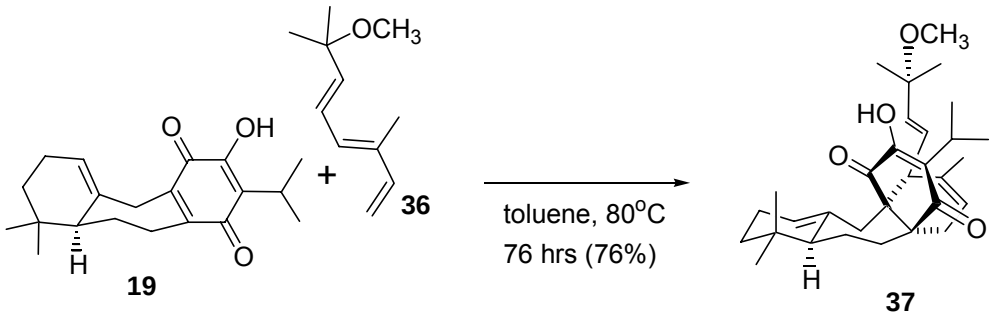
34 **35**

Triene alcohol 35: 1.0 *M* LDA was prepared by adding 1.6 *M* *n*-BuLi (35.6 mL, 57 mmol) to diisopropylamine (8.0 mL, 57 mmol) in anhydrous THF (13.0 mL) at 0 ℃. The crude diene epoxide (5.9 g, ~22.0 mmol) was dissolved in freshly distilled THF (30 mL) at 0 ℃ under nitrogen atmosphere and the 1.0 *M* LDA (55 mL, 55 mmol, 2.5 equivalents) was added slowly. The resulting mixture was stirred at 0 ℃ until TLC showed all the starting material was consumed (30 minutes). Diethyl ether (30 mL) was added, followed by addition of water (15 mL) to quench the reaction. The organic layer was separated and washed with brine (10 mL). The organic layer was then dried with anhydrous $MgSO_4$ and concentrated using a rotary evaporator. Column chromatography of the crude oil (elution with petroleum ether: ethyl ether = 8:1, 2:1) gave 1.36 g (60% yield) of triene alcohol **35** (TLC, hexane: EtOAc, 4:1, R_f **35** = 0.15): ^{1}H (400 MHz) δ 1.38 (s, 6H), 1.89 (s, 3H), 5.05 (d, J = 10.5 Hz, 1H), 5.23 (d, J = 16.5 Hz, 1H), 5.90 (d, J = 15.5 Hz, 1H), 6.07 (d, J = 10.5 Hz, 1H), 6.42 (dd, J_1 = 11.0 Hz, J_2 = 16.5 Hz, 1H), 5.59 (dd, J_1 = 11.0 Hz, J_2 = 16.5 Hz, 1H).

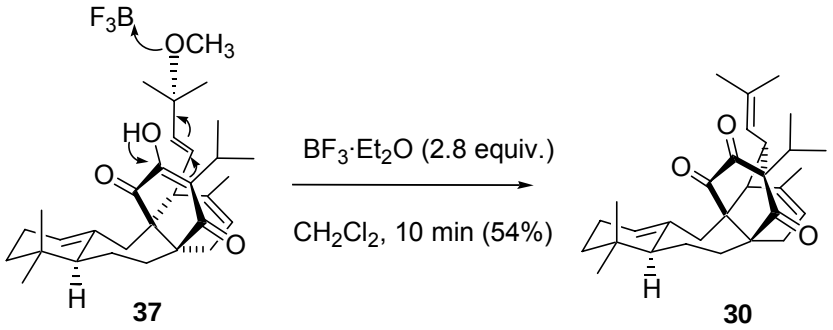


35 **36**

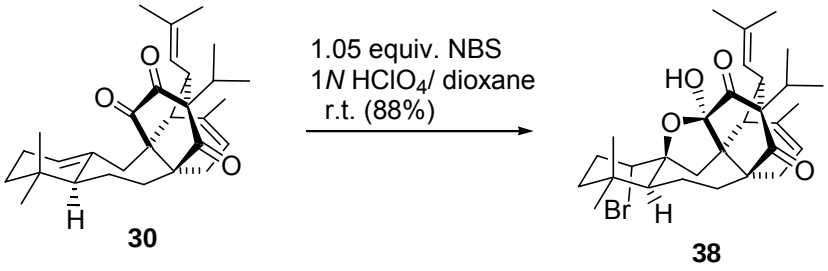
Triene methyl ether 36: Triene alcohol **35** (548 mg, 3.60 mmol) was dissolved in anhydrous THF (5.0 mL) at 0 ℃ under nitrogen atmosphere. NaH (260 mg, 10.82 mmol, 3.0 equivalents) was added and the resulting mixture was stirred at 0 ℃ for 5 minutes. The mixture was then cooled to -20 ℃ and iodomethane (1.12 mL, 18.03 mmol, 5.0 equivalents) was added. The resulting solution was stirred overnight under ambient temperature. Diethyl ether (20 mL) was added to dilute the solution, and then the resulting solution was washed with 5-mL portions of water and brine, respectively. The isolated organic layer was then dried over anhydrous $MgSO_4$. Removal of the solvent using a rotary evaporator afforded 548 mg of crude product. Column chromatography (elution with pet ether: ethyl ether = 8:1) on neutral alumina gave 313 mg (52% yield) triene methyl ether **36** as a colorless oil (TLC, hexane: EtOAc, 4:1, R_f **36** = 0.72): ^{1}H (400 MHz) δ 1.31 (s, 6H), 1.88 (s, 3H), 3.16 (s, 3H), 5.04 (d, J = 11.2 Hz, 1H), 5.22 (d, J = 17.2 Hz, 1H), 5.71 (d, J = 15.6 Hz, 1H), 6.07 (d, J = 11.2 Hz, 1H), 6.40 (dd, J_1 = 11.2 Hz, J_2 = 17.2 Hz, 1H), 6.47 (dd, J_1 = 11.2 Hz, J_2 = 15.6 Hz, 1H).



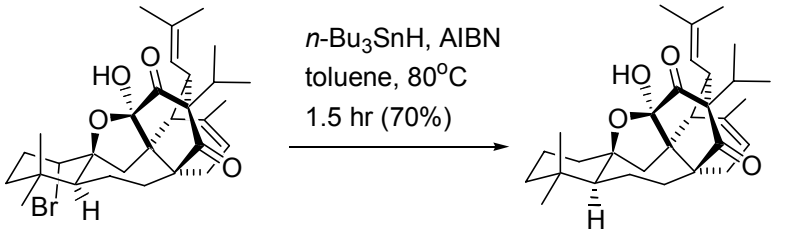
Diels-Alder adduct 37: *para*-Benzoquinone **19** (20.8 mg, 0.066 mmol) and triene ether (33 mg, 0.198 mmol, 3.0 equivalents) were dissolved in toluene (0.5 mL). The resulting solution was sealed in a tube with a stirring bar under the protection of a nitrogen atmosphere. The mixture was heated at 80 ℃ for 25 h. The toluene was removed directly under vacuum and flash column chromatography (elution with pet ether: ethyl ether = 8:1) gave 24.0 mg (76%) of Diels-Alder adduct **37** (TLC, hexane: EtOAc, 4:1, R_f **37** = 0.54). The specific rotation was observed to be $[\alpha]^{24}_D = +117.3^o$ (c = 0.021 g.mL^{-1}, $CHCl_3$): ^{1}H (500 MHz) δ 0.79 (s, 3H), 0.83 (s, 3H), 1.00-1.04 (m, 1H), 1.09 (d, J = 6.0 Hz, 6H), 1.17 (d, J = 7.0 Hz, 3H), 1.22 (d, J = 7.0 Hz, 3H), 1.24-1.36 (m, 3H), 1.50-1.54 (m, 1H), 1.54 (s, 3H), 1.62-1.68 (m, 2H), 1.78-1.84 (m, 1H), 1.86-2.00 (m, 2H), 2.06 (d, J = 14.5 Hz, 1H), 2.17 (dd, J_1 = 2.0 Hz, J_2 = 18.0 Hz, 1H), 2.37 (d, J = 10.0 Hz, 1H), 2.82 (dd, J_1 = 4.5 Hz, J_2 = 18.0 Hz, 1H), 3.03 (s, 3H), 3.04-3.12 (m, 1H), 3.19 (d, J = 14.0 Hz, 1H), 4.96 (dd, J_1 = 10.5 Hz, J_2 = 15.0 Hz, 1H), 5.25 (d, J = 15.5 Hz, 1H), 5.56 (m, 2H), 7.12 (s, 1H); ^{13}C NMR (400 MHz) 19.51 (q), 20.33 (q), 22.46 (q), 22.85 (s), 23.73 (t), 25.15 (q), 25.82 (d), 26.10 (t), 26.42 (q), 26.69 (t), 26.89 (q), 29.24 (t), 32.67 (s), 38.53 (t), 46.80 (t), 48.44 (d), 50.67 (q), 52.54 (s), 55.54 (d), 57.37 (s), 74.83 (s), 120.51 (d), 127.33 (d), 128.32 (d), 128.61 (s), 130.92 (s), 134.42 (s), 140.56 (d), 152.70 (s), 198.67 (s), 201.34 (s) ppm.



Triketone 30: To a solution of Diels-Alder adduct **37** (75 mg, 0.16 mmol) in CH_2Cl_2 (7 mL) was added $BF_3{\cdot}Et_2O$ (60 μL, 0.47 mmol, 3.0 equivalents) at 0 ℃. The reaction solution was stirred at 0 ℃ for 15 minutes. Saturated aqueous NH_4Cl was added to quench the reaction. Ethereal workup gave 76 mg of crude product. Column chromatography (elution with pet ether : ethyl ether = 8:1) afforded 38.0 mg (54%) of triketone **30** (TLC, hexane: EtOAc, 8:1, R_f **30** = 0.80) which was homogeneous based on TLC analysis: $[\alpha]^{24}_D$ = -90.6º (*c* = 0.0228 g. mL^{-1}, $CHCl_3$); ^1H (500 MHz) δ 0.81 (s, 3H), 0.83 (s, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.65 (dd, J_1 = 1.5 Hz, J_2 = 8.0 Hz, 6H), 1.69-1.72 (m, 1H), 1.74 (s, 3H), 1.75-1.84 (m, 2H) 1.89 (s, 1H), 1.93-2.06 (m, 4H), 2.47 (dd, J_1 = 2.0 Hz, J_2 = 16.5 Hz, 1H), 2.73 (dm, *J* = 18.5 Hz, 1H), 2.82 (d, *J* = 13.5 Hz, 1H), 2.88 (dd, J_1 = 2.0 Hz, J_2 = 12.0 Hz, 1H), 4.66 (dd, J_1 = 2.0 Hz, J_2 = 12.0 Hz, 1H), 5.42 (s, 1H), 5.93 (t, *J* = 3.5 Hz, 1H); ^{13}C NMR (400 MHz) 17.64 (q), 18.75 (q), 18.93 (q), 22.71 (q), 23.79 (t), 26.25 (q), 26.33 (d), 26.79 (q), 27.68 (q), 27.81 (t), 28.75 (t), 30.47 (t), 32.80 (s), 33.19 (t), 39.84 (t), 45.81 (d), 47.62 (d), 50.92 (d), 53.71 (s), 54.59 (s), 74.55 (s), 119.84 (d), 123.10 (d), 128.74 (d), 132.54 (s), 134.51 (s), 134.84 (s), 192.71 (s), 199.10 (s), 211.10 (s) ppm; HR-MS: $[M+H]^+$ = 449.3070; $[M+H]^+_{calculated}$ = 449.3055; IR (neat): 2931, 1735, 1709, 1457, 1384, 1123, 1044, 918, 848, 739 cm^{-1}.



Bromide 38: To a solution of triketone **30** (14.0 mg, 0.031 mmol) in dioxane (1 mL) was added 1.0 *N* $HClO_4$ (0.3 mL), followed by addition of NBS (6.0 mg, 0.033 mmol, 1.05 equiv.) at rt. The yellow solution turned to colorless within 5 minutes. Standard ethereal workup followed by column chromatography (elution with pet ether: ethyl ether = 4:1) gave 15.0 mg (88%) of bromide **38** (TLC, hexane: EtOAc, 8:1, R_f **38** = 0.64). The specific rotation was observed to be $[\alpha]^{24}_D$ = +66.3º (*c* = 0.0103 g.mL^{-1}, $CHCl_3$): ^{1}H (400 MHz) δ 0.90-0.93 (m, 7H), 0.99 (s, 3H), 1.09 (d, *J* = 7.2 Hz, 3H), 1.67 (d, *J* = 1.2 Hz, 3H), 1.71 (d, *J* = 1.2 Hz, 3 H), 1.74 (d, *J* = 2.0 Hz, 3H), 1.89-2.10 (m, 6H), 2.20 (d, *J* = 13.2 Hz, 1H), 2.35 (d, *J* = 2.8 Hz, 1H), 2.40-2.55 (m, 4H), 2.67 (dd, J_1 = 2.8 Hz, J_2 = 11.2 Hz, 1H), 3.16 (s, 1H), 4.59 (d, *J* = 1.2 Hz, 1H), 5.30 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (400 MHz) 17.21 (q), 19.02 (q), 19.15 (q), 20.25 (t), 22.59 (q), 22.83 (q), 26.11 (d), 26.46 (q), 27.83 (t), 29.63 (t), 31.85 (t), 32.61 (q), 35.13 (t), 35.74 (s), 40.51 (t), 42.71 (d), 46.23 (d), 50.60 (d), 50.96 (s), 51.11 (s), 62.59 (d), 71.84 (s), 92.55 (s), 100.28 (s), 119.54 (d), 124.63 (d), 132.58 (s), 136.87 (s), 203.07 (s), 210.72 (s) ppm; HR-MS: $[M+H]^+$ = 545.2277; $[M+H]^+_{calculated}$ = 545.2266; IR (neat): 2927, 2858, 1740, 1710, 1461, 1382, 1290, 1125, 1071, 1039, 1000, 953, 861 cm^{-1}.



(+)-Salvadione-A (27): A mixture of bromide **38** (35.0 mg, 0.064 mmol), AIBN (5.0 mg, 0.0032 mmol, 0.5 equivalent) and tributyltin hydride (nBu$_3$SnH) (17.3 μL, 0.64 mmol, 10.0 equivalents) in toluene (3.0 mL) was heated at 80 ℃ for 1.5 h under nitrogen atmosphere. The solvent was removed directly under vacuum and the resulting residue was chromatographed (elution with pet ether: ethyl ether = 4:1) to give 21.0 mg (70%) of (+)-salvadione-A (**27**) which was homogeneous to TLC analysis (TLC, hexane: EtOAc, 8:1, R_f (**27**) = 0.64). The specific rotation was observed to be $[\alpha]^{24}_D$ = +37.6º (c = 0.0036 g.mL^{-1}, $CHCl_3$): ^{1}H (400 MHz) δ 0.86 (s, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.95 (s, 3H), 1.07 (d, J = 6.8 Hz, 3H), 1.10-1.26 (m, 5H), 1.34-1.50 (m, 6H), 1.64 (d, J = 0.8 Hz, 3H), 1.68 (d, J = 0.8 Hz, 3H), 1.70 (d, J = 1.6 Hz, 3H), 1.74-2.02 (m, 10H), 2.30 (d, J = 2.4 Hz, 1H), 2.42 (d, J = 2.4 Hz, 1H), 2.63 (dd, J_1 = 2.4 Hz, J_2 = 11.6 Hz, 1H), 2.79 (s, 1H), 5.28 (s, 1H), 5.36 (d, J = 11.2 Hz, 1H); ^{13}C NMR (400 MHz) 17.28 (q), 19.00 (q), 19.18 (q), 19.73 (t), 20.89 (t), 22.10 (q), 22.85 (q), 26.11 (d), 26.47 (q), 29.51 (t), 32.03 (t), 32.83 (q), 36.12 (s), 40.61 (t), 41.49 (t), 42.54 (t), 46.34 (d), 50.04 (d), 50.19 (s), 50.91 (d), 51.26 (s), 71.71 (s), 91.21 (s), 100.07 (s), 119.56 (d), 125.02 (d), 132.14 (s), 137.10 (s), 203.31 (s), 211.41 (s) ppm; HR-MS: $[M+H]^+$ = 467.3173; $[M+H]^+_{calculated}$ = 467.3161; IR (neat): 2925, 2854, 1459, 1265, 739, 704 cm $^{-1}$.

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PART II:

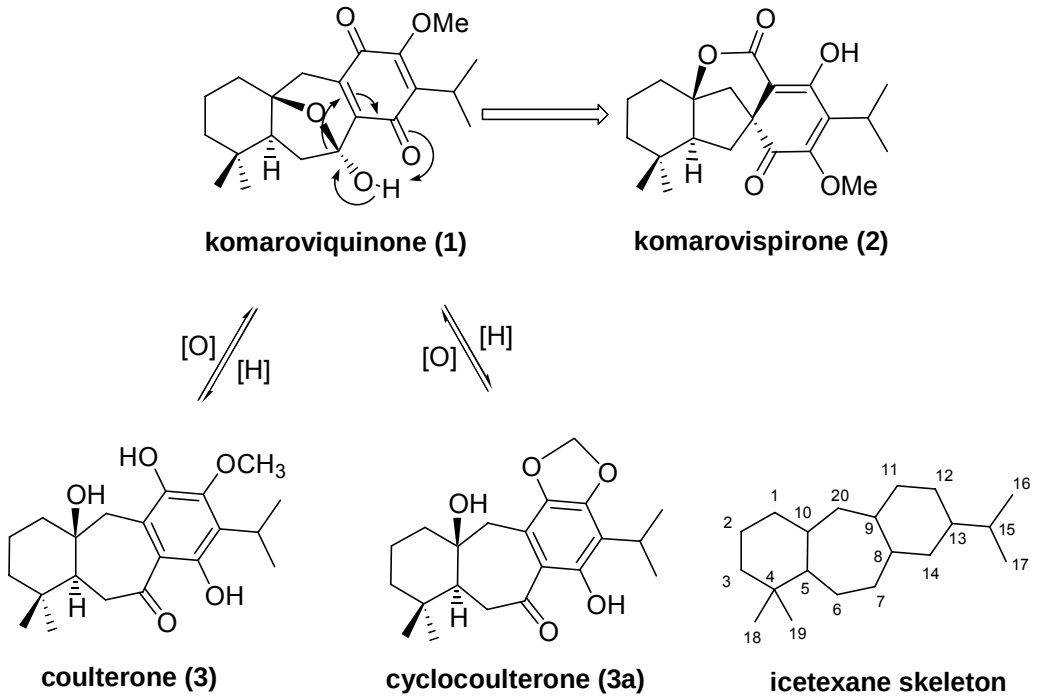
TOTAL SYNTHESIS OF (±)-KOMAROVIQUINONE AND STUDIES TOWARD THE SYNTHESIS OF (+)-KOMAROVIQUINONE

Introduction and Background

In 2003, komaroviquinone (**1**) (Scheme 1) was isolated from a perennial semishrub,[1] *Dracocephalum komarovi* Lipsky, which grows in the west Tian Shan Mountain system[2] at around 2300-3600 meters above sea level. This plant is known as "buzbosh" in Uzbekistan. The local people use the aerial parts to cure various disorders such as inflammatory diseases and hypertony. Komaroviquinone (**1**) showed strong trypanocidal activity against epimastigotes of *T. cruzi*, the causative agent of Chagas' disease in Central and South America,[3, 4] with a minimum lethal concentration (MLC) of 0.4 μM. The MLC of gentian violet, which is used to disinfect trypanosomes from transfusion blood in Latin America, was 6.3 μM under the same assay conditions. Several types of natural quinones have been reported to show trypanocidal activity, and their activities have been partly ascribed to the production of reactive oxygen species in the parasite.[5,6]

In addition, a new compound, which is called komarovispirone (**2**), was isolated from the same plant in 2004.[7] This diterpene possesses a novel spiro-octahydroindene skeleton and showed a moderate trypanocidal activity with a MLC of 23 μM. The authors also proposed that

komarovispirone (**2**) may be biogenetically derived from komaroviquinone (**1**) through a novel ring-contraction sequence (Scheme 1) [7]



Scheme 1

Another compound, cyclocoulterone (**3a**),[1] was isolated along with komaroviquinone (**1**) from the same plant. Moreover, the structure of coulterone (**3**) was also reported in 1994 by Frontana.[8] Structural analysis found that both cyclocoulterone (**3a**) and coulterone (**3**) have an icetexane skeleton (see above) and may interchange with komaroviquinone (**1**) through an oxidative/reductive process (Scheme 1).

Because of their significant biological activity and 6,7,6-fused tricyclic skeleta, we sought to synthesis komaroviquinone and coulterone using our cycloalkylation method. Given the syntheses of perovskone[9] and salvadione-A,[10] we recognized that komaroviquinone (**1**) could

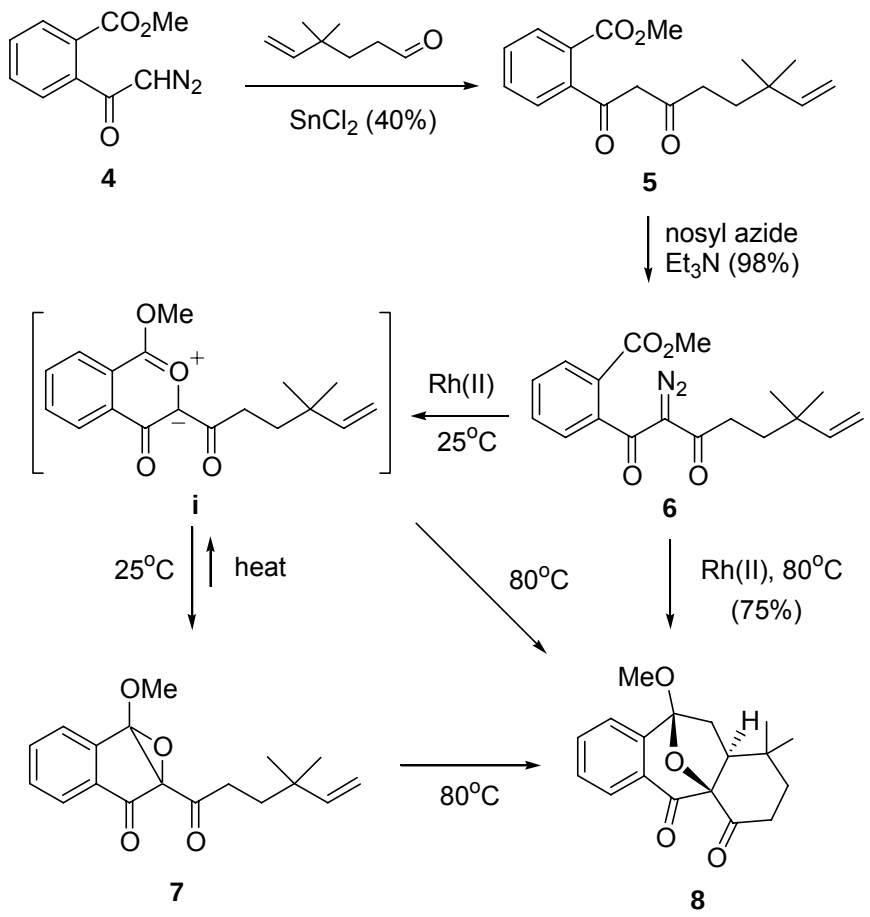
be synthesized from *para*-benzoquinone **19** from our previous work. A synthesis of (±)-komaroviquinone will be presented in this chapter, followed by a study toward the stereoselective synthesis of (+)-komaroviquinone (**1**). Our synthesis of (±)-komaroviquinone (**1**) was accomplished before both synthetic routes introduced in the following section were reported.

Reported Study toward (±)-Komaroviquinone (1)

Within two years after the isolation of (±)-komaroviquinone (**1**) two groups reported their synthetic studies toward this natural structure. Padwa and co-workers achieved an efficient construction of the core structure of komaroviquinone[11] in their study of rhodium-catalyzed cyclization/cycloaddition cascade of a *ortho*-carbomethoxyaryl diazo dione.[12a-i]

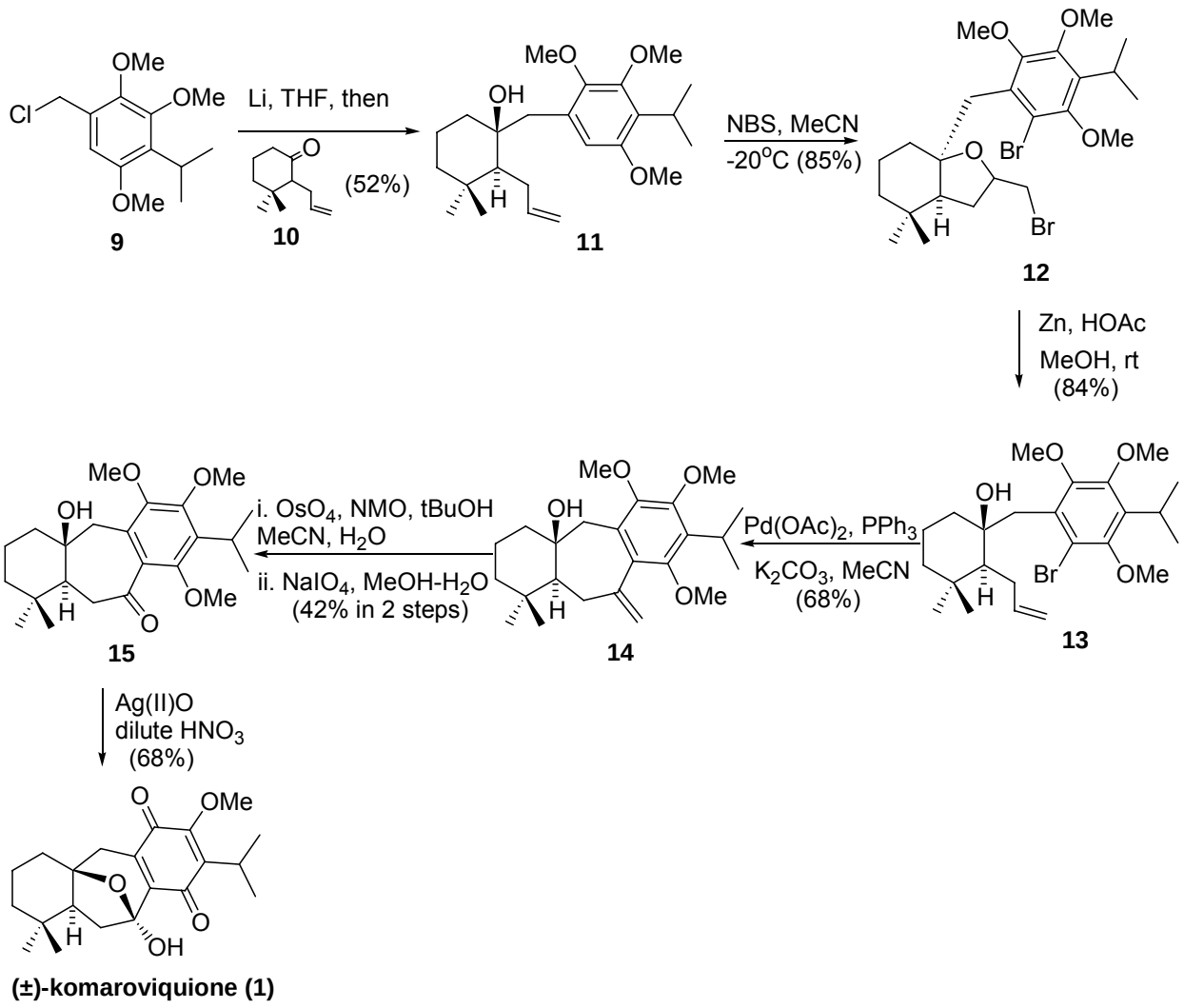
As shown in Scheme 2, in Padwa's study, a protocol developed by Holmquist and Roskamp,[13a,b] converts aldehydes into *β*-ketone esters by the addition of ethyl diazoacetate in the presence of tin(II) chloride, was used to make diketone **5** from **4** in moderate yield. Diazo dione **6** was obtained when diketone **5** was treated with nosyl azide and triethylamine under Regitz diazo transfer reaction conditions.[14a,b] When diazo dione **6** was heated with $Rh_2(OAc)_4$ in benzene at 80 ℃, cycloadduct **8** was produced in 75% yield. This reaction mechanism was believed to first produce carbonyl ylide dipole **i**, followed by an intramolecular [3+2]-cycloaddition. Epoxide **7** was isolated when the reaction underwent at room temperature, and it could also be transformed to **8** upon heating.

Almost at the same time, Banerjee and co-workers reported their synthesis of (±)-komaroviquinone (**1**) through an intramolecular Heck reaction.[15] Scheme 3 shows their synthetic route. Benzyl chloride **9** was prepared and converted into an organolithium reagent which



Scheme 2

added to ketone **10** to give alcohol **11** in 52% yield. Bromonium ion activation of the terminal alkene with intramolecular attack by alcohol, followed by aromatic bromination, gave dibromide **12** with 85% yield in a one-pot procedure. Zinc mediated debromination fragmentation of **12** produced **13** with high yield.[16] Then intramolecular Heck reaction[17] was applied on **13** and gave a moderate yield of tricyclic skeleton **14**. A standard two-step process to cleave the exocyclic alkene[18] furnished 42% of ketone alcohol **15**. The oxidation of hydroquinone **15** was achieved using Ag(II)O in dilute HNO_3,[19] thereby producing (±)-komaroviquinone (**1**) in 68% yield.

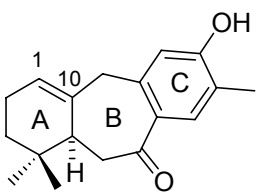


Scheme 3

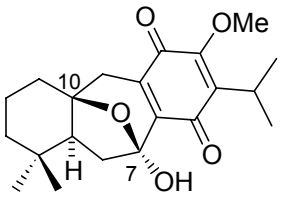
Early Study on the Synthesis of (±)-Faveline: A Similar Structure

Faveline, since its isolation by Nozoe,[20] has attracted much attention because of its promising anti-leukemia activity. Two synthetic routes, by the Ghatak[21a,b] and Majetich[22] research groups, were reported in the 1990's. The Majetich synthesis featured a Friedel-Crafts cycloalkylation and a benzylic oxidation as the key steps.[22] By comparing the structure of

faveline and that of komaroviquinone (**1**) (Scheme 4), we find that both natural products have a carbonyl group on C(7). The differences between these two structures are the hydrated C(1)−C(10) double bond in komaroviquinone (**1**) and different oxidation states on the C-ring. Given the structural similarities, it is not surprising that Majetich's earlier synthesis of faveline would greatly influence our synthesis of komaroviquinone (**1**). However, before detailing our exploration, I will review the syntheses of faveline by Ghatak and Majetich.



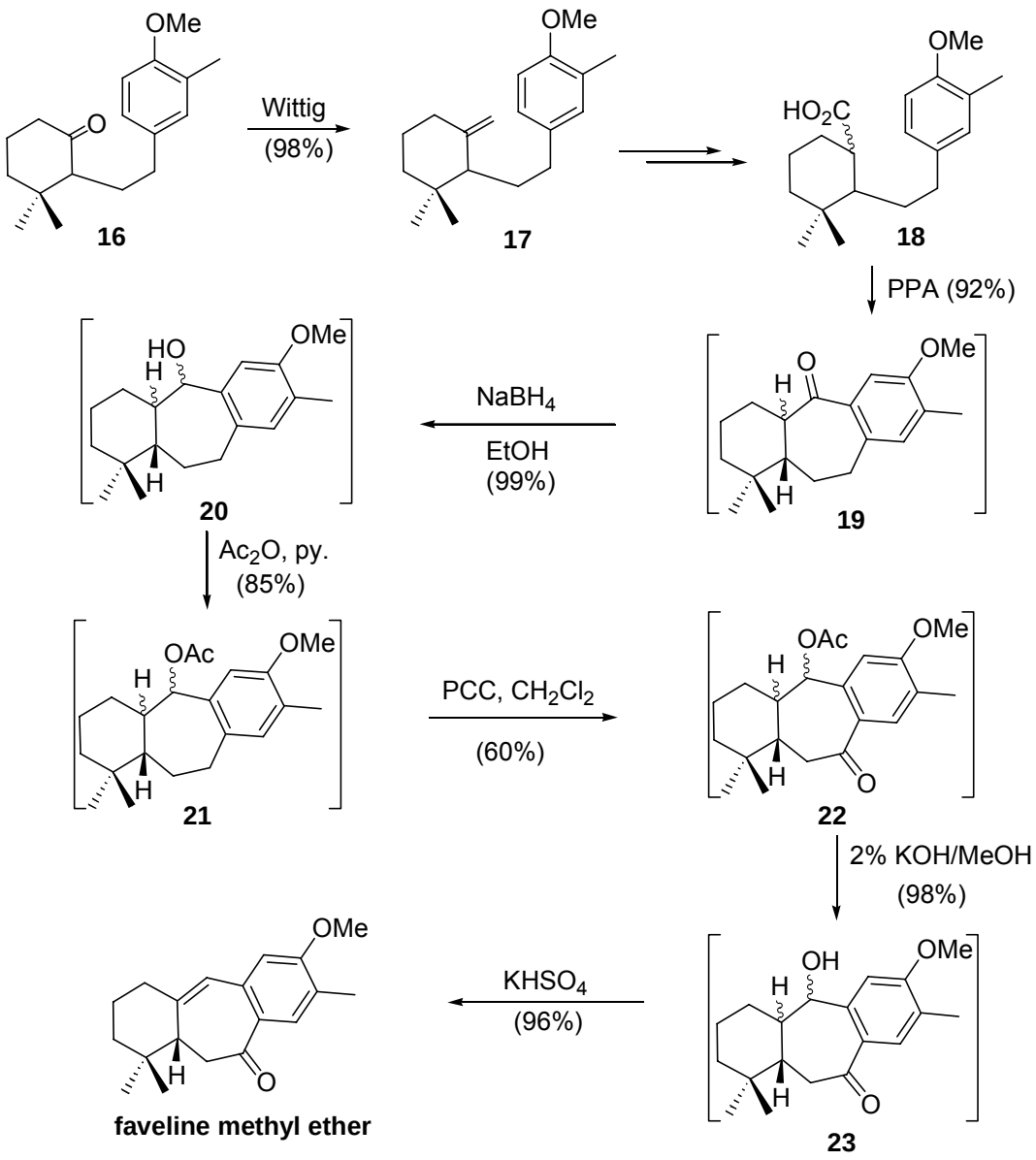
faveline



(±)-komaroviquione (1)

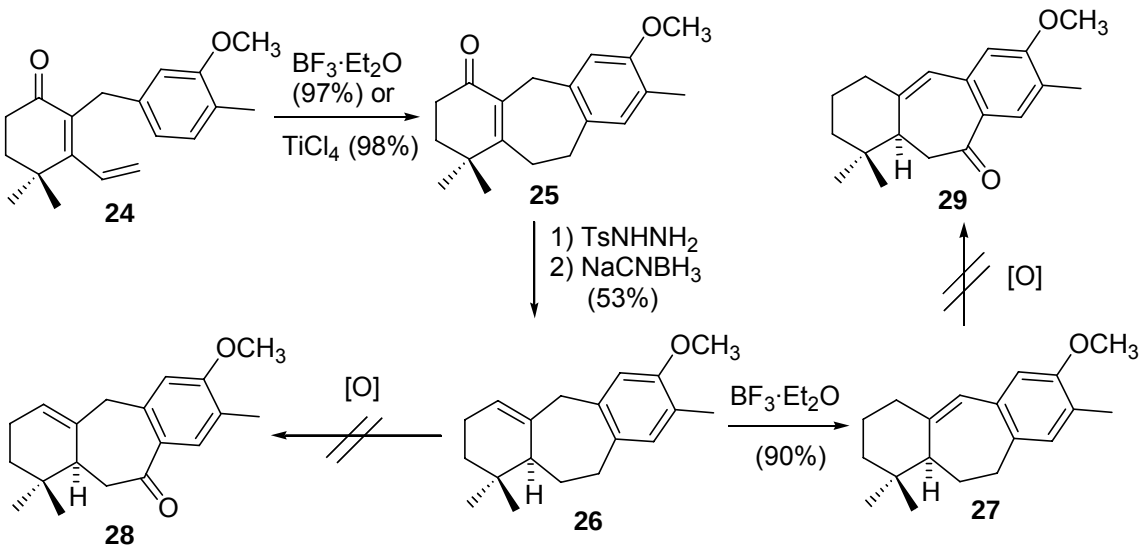
Scheme 4

The first synthesis of faveline methyl ether was accomplished by Ghatak and co-workers in 1992.[21a] As shown in Scheme 5, Wittig reaction of ketone **16** gave alkene **17** in 98% yield. After several transformations, acid **18** was obtained as key precursor for the formation of seven-membered B-ring. Friedel-Crafts acylation of acid **18** afforded tricyclic ketone **19** in excellent yield as a mixture of ketones with *cis* and *trans* stereochemistry on the A,B-ring junction. This mixture of ketone **19** was further reduced to alcohol **20**, followed by protection with acetic anhydride and pyridine, to afford acetate **21** in high yield. When acetate **21** was treated with PCC in DCM, a benzylic oxidation took place on the C(7) carbon to give ketone **22** in 60% yield. Deprotection of **22** to alcohol **23**, followed by dehydration, finally afforded faveline methyl ether in excellent yield.



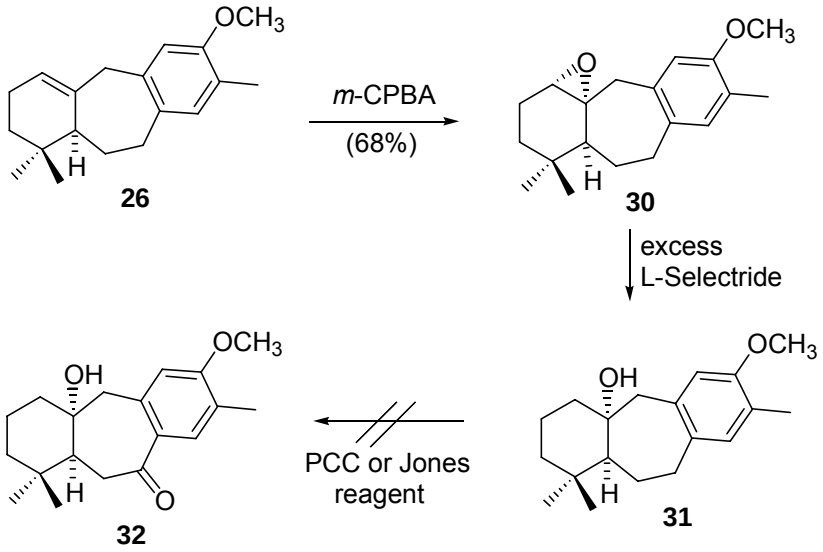
Scheme 5

In 1996, Majetich and co-workers finished a more efficient synthesis of faveline.[22] Dienone **24** was prepared and cyclized to give enone **25** with excellent yield (Scheme 6). A modified Wolff-Kishner reduction[23] gave alkene **26** in 53% yield. The double bond of alkene **26** readily isomerized to styrenyl alkene **27** using $BF_3 \cdot Et_2O$. Nevertheless, the oxidation of alkenes **26** or **27** to ketones **28** or **29**, respectively, with various oxidants failed.



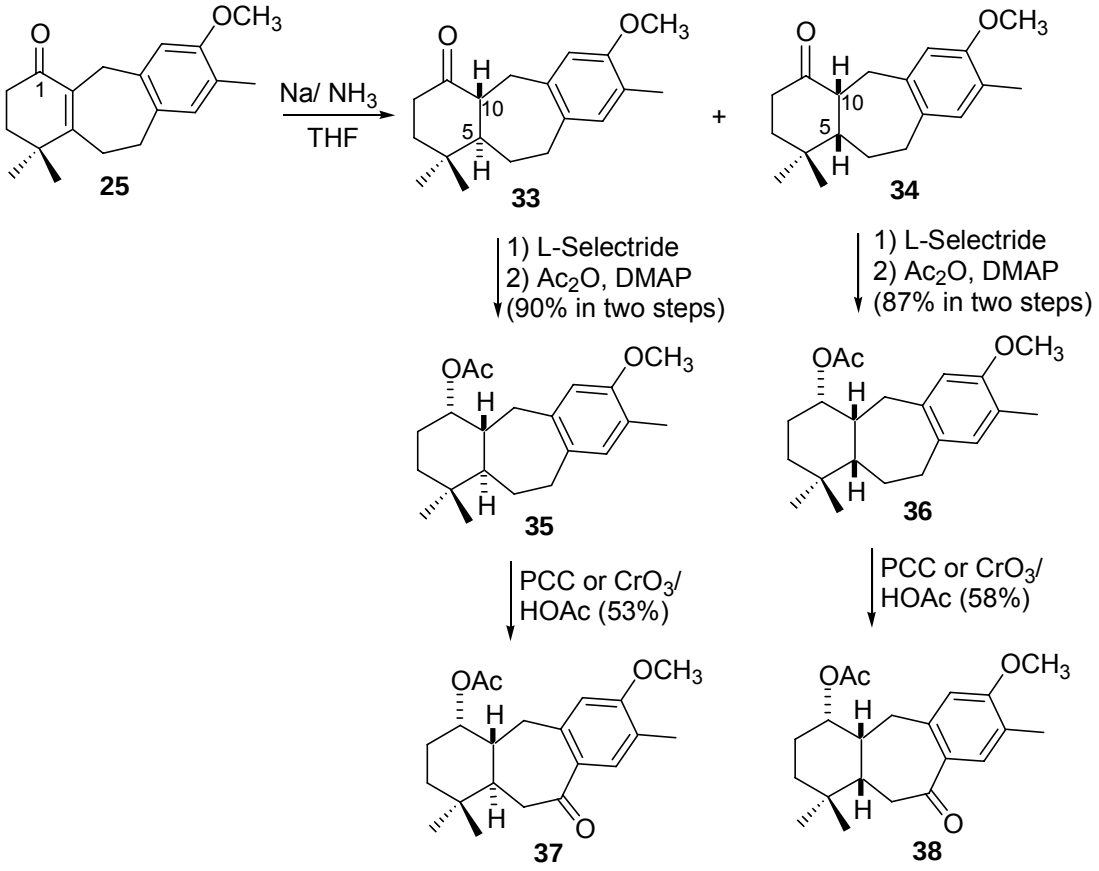
Scheme 6

Tertiary alcohol **31** was then prepared via epoxide **30** through epoxidation, followed by a reductive epoxide-opening process from alkene **26** (Scheme 7). Unfortunately, attempts to oxidize alcohol **31** to ketone **32** failed to afford unidentifiable products.



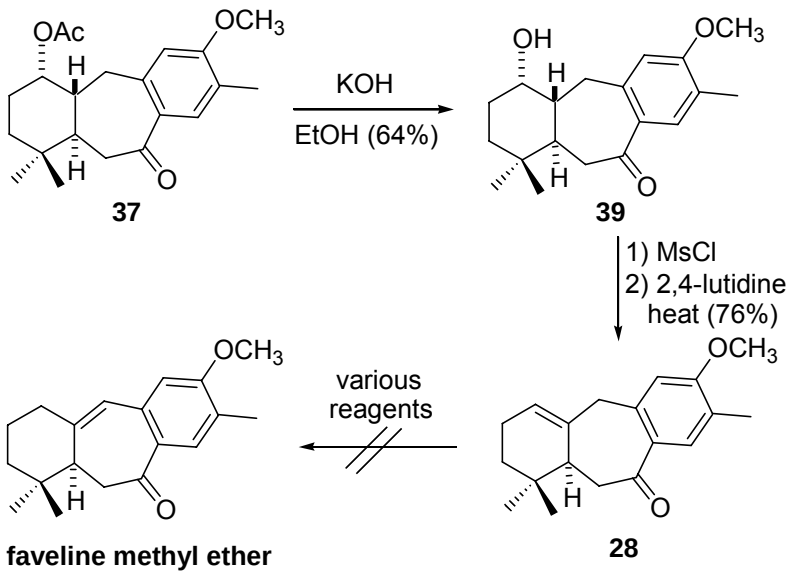
Scheme 7

An alternate promising approach was then developed (Scheme 8). Dissolving metal reduction of enone **25** gave a separable mixture of ketones **33** and **34**. L-Selectride reduction of the C(1) carbonyl followed by protection of the resulting alcohol with acetic anhydride gave acetates **35** and **36**. Both acetates were subjected under oxidation with PCC or CrO_3 in aqueous acetic acid and gave desired benzylic oxidized products **37** and **38**, respectively, in moderate



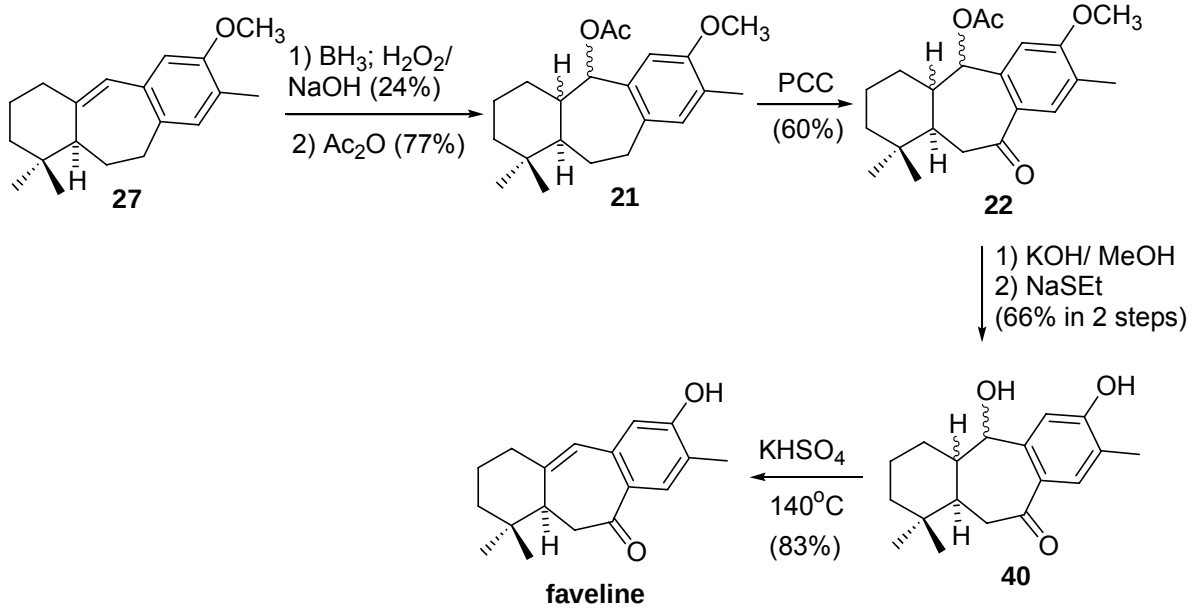
Scheme 8

yields. Saponification of ketone **37** produced alcohol **39** (Scheme 9). Mesylation of alcohol **39**, followed by elimination, gave ketone **28**. Surprisingly, the seemingly trivial isomerization of **28** to faveline methyl ether could not be achieved.



Scheme 9

Majetich and Hicks noted that Ghatak and co-workers could oxidize the C(7) position of acetate **21** to give ketone **22** in 60% yield using PCC (Scheme 5), which allowed them to complete a synthesis of faveline through acetate **21**. As shown in Scheme 10, acetate **21**



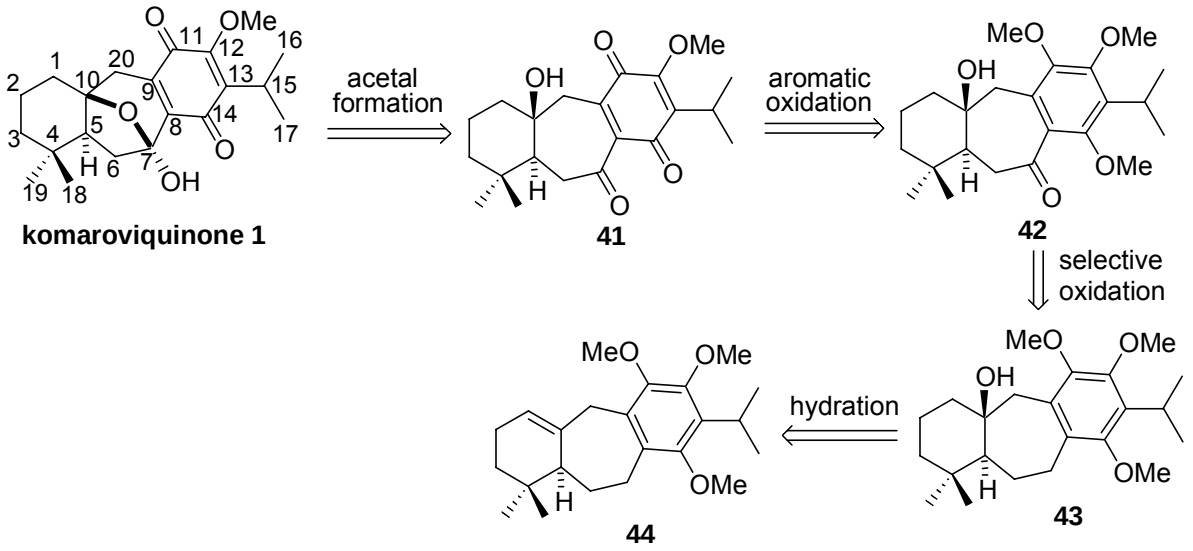
Scheme 10

could be prepared from alkene **27** in two steps, whereas oxidation of **21** with PCC gave ketone **22** in the same yield as observed by Ghatak and co-workers. Saponification of acetate as well as deprotection of aryl methyl ether produced phenol **40** which upon dehydration completed the synthesis of (±)-faveline.

Given the synthesis of (±)-faveline by Majetich and co-workers and considering the structural similarity, we were confident that the tactics used in this synthesis would permit a synthesis of komaroviquinone. The synthetic studies of (±)- and (+)-komaroviquinone (**1**) are detailed in the following section.

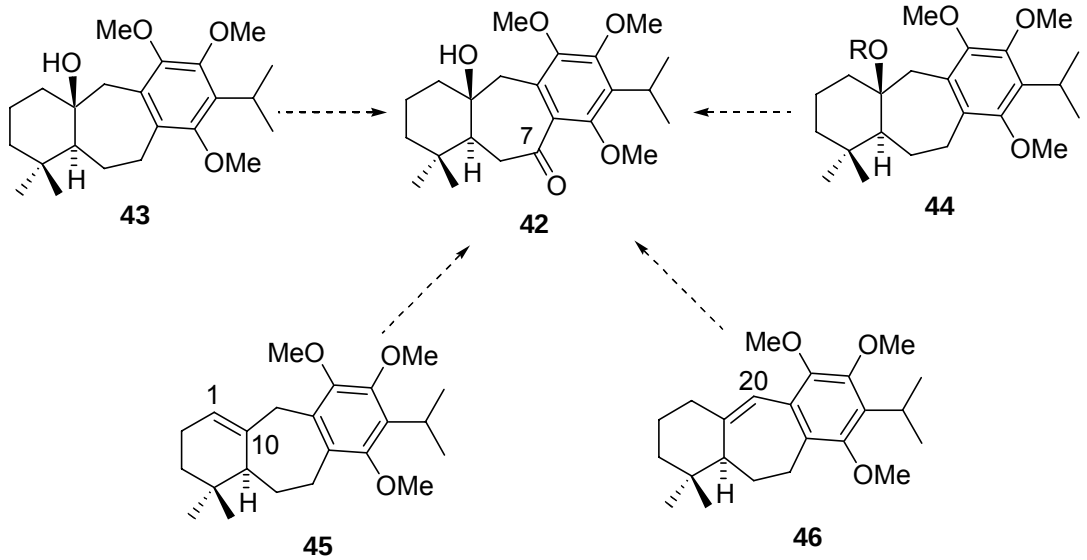
Total Synthesis of (±)–Komaroviquinone:
Our First Generation Synthesis

Soon after the structure of (±)–komaroviquinone (**1**) was reported in early 2003,[1] we undertook a synthesis of this interesting natural product. The first generation synthesis of (±)-komaroviquinone (**1**) was accomplished in early 2005, and is summarized in Scheme 11. The numbering system of carbon skeleton follows the assignment by Kuichi.[1] We believed that hydroxy ketone **42** would easily undergo oxidation to produce hydroxyl quinone **41**, as indicated by molecular models, which would readily undergo acetal formation to produce komaroviquinone (**1**). The direct oxidation of alcohol **43** not only would produce key intermediate **42** but would represent a new strategy for the functionalization of the icetexane skeleton. We expected alcohol **43** to be derived from alkene **44**, a key intermediate (and available in chiral form) from our perovskone work.[9,10]



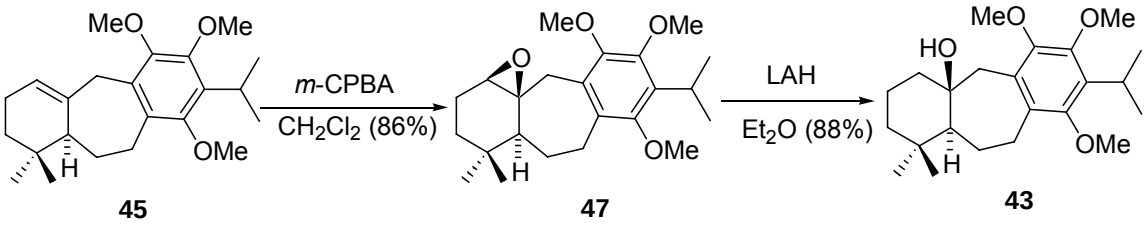
Scheme 11

Three possible pathways exist to make key intermediate **42**. As shown in Scheme 12, tertiary alcohol **43 (**or its derivative such as **44**) is the most straightforward precursor to achieve ketone alcohol **42** through a direct regiospecific benzylic oxidation of the C(7) position. Alternatively, oxidation of alkenes **45** or **46**, followed by hydration of the C(1)−C(10) or C(10)−C(20) double bond, would produce **42**.



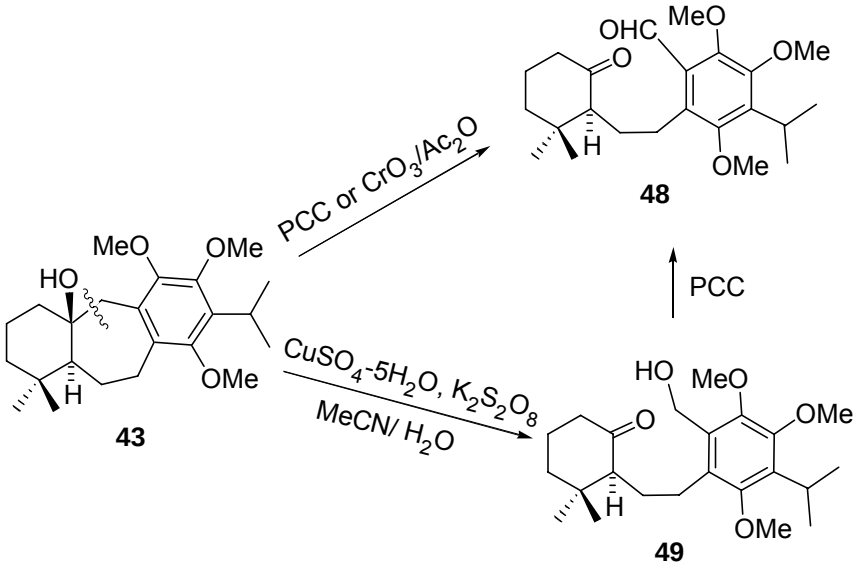
Scheme 12

Tertiary alcohol **43** was first prepared from alkene **45** in two steps. Epoxidation of alkene **45** with *m*-CPBA in methylene chloride gave epoxide **47** in 86% yield. The relative stereochemistry of epoxide **47** was confirmed by X-ray crystal structure (Appendix II). Subsequent lithium aluminumhydride (LAH) opening of epoxide **47** afforded tertiary alcohol **43** in 88% yield (Scheme 13).



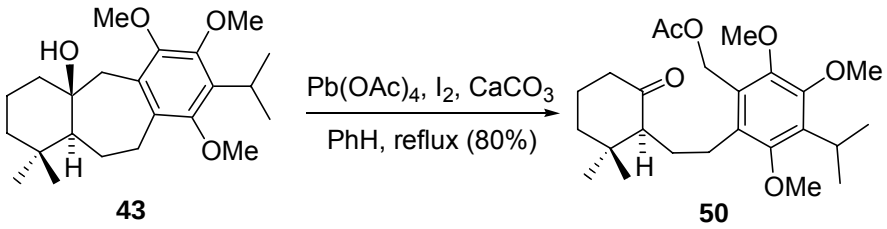
Scheme 13

With alcohol **43** in hand, various oxidation conditions were investigated. Since PCC and CrO_3 oxidants[24] were effective in the benzylic oxidation of intermediates in our synthesis of (±)-favoline,[22] we expected the desired oxidation of **43** would occur with either of these oxidants.



Scheme 14

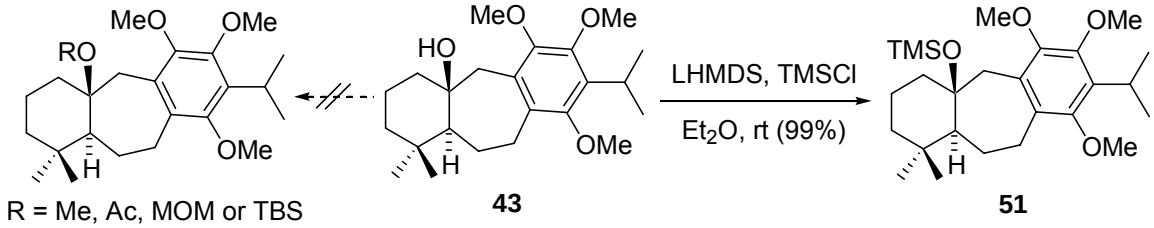
Instead, when PCC and CrO_3/Ac_2O were used, carbon−carbon bond cleavage took place quickly and only dione **48** was collected (Scheme 14). When $CuSO_4 \cdot 5H_2O/K_2S_2O_8$ was used,[25a-c] ketone alcohol **49** was formed. The structure of the ketone alcohol **49** was confirmed by oxidizing it to dione **48** with PCC. These results indicate that tertiary alcohol **43** is prone to fragment quickly under the oxidation conditions, presumably due to the stabilizing effect of resulting C(20) benzyl position by the aromatic ring. The free radical nature of this fragmentation was confirmed when **43** was subjected to Barton-like oxidation conditions and the only product was acetate **50** (Scheme 15).



43 **50**

Scheme 15

After finding that tertiary alcohol **43** would not tolerate oxidative or free radical conditions, we attempted to protect alcohol **43** in hopes of precluding carbon−carbon bond cleavage. Unexpectedly, tertiary alcohol **43** was inert as efforts to make an acetyl, a methyl ether,

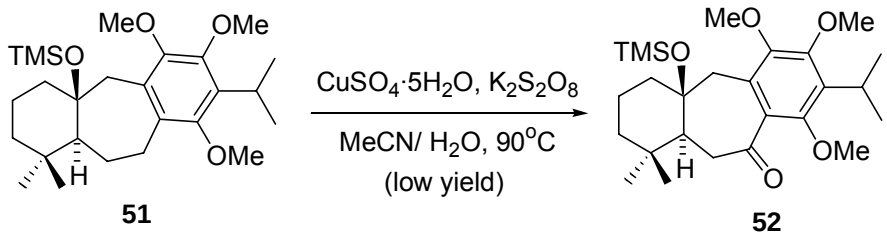


43 **51**

Scheme 16

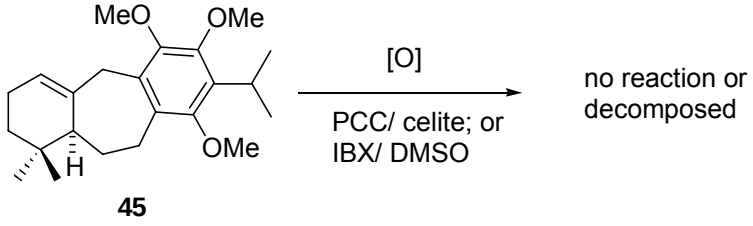
a methoxymethyl (MOM) ether or a *tert*-butyldimethylsilyl (TBS) ether were unsuccessful, presumably due to high steric hindrance. Fortunately, it was found that alcohol **43**, when treated with lithium hexamethyldisilazide (LHMDS) and trimethylsilyl chloride (TMSCl), gave **51** in 99% yield based on recovered starting material (Scheme 16).

TMS ether **51** was then treated with different oxidants. The oxidation of **51** with PCC or CrO_3/HOAc afforded only recovered starting material. When $K_2S_2O_8$ and $CuSO_4 \cdot 5H_2O$ were used, ketone **51** was produced in low yield (Scheme 17) presumably due to decomposition of TMS ether **51** or oxidation of the intermediates. Many different conditions were tried without improvement, including lower reaction temperature, lower amounts of oxidant and shorter reaction times.



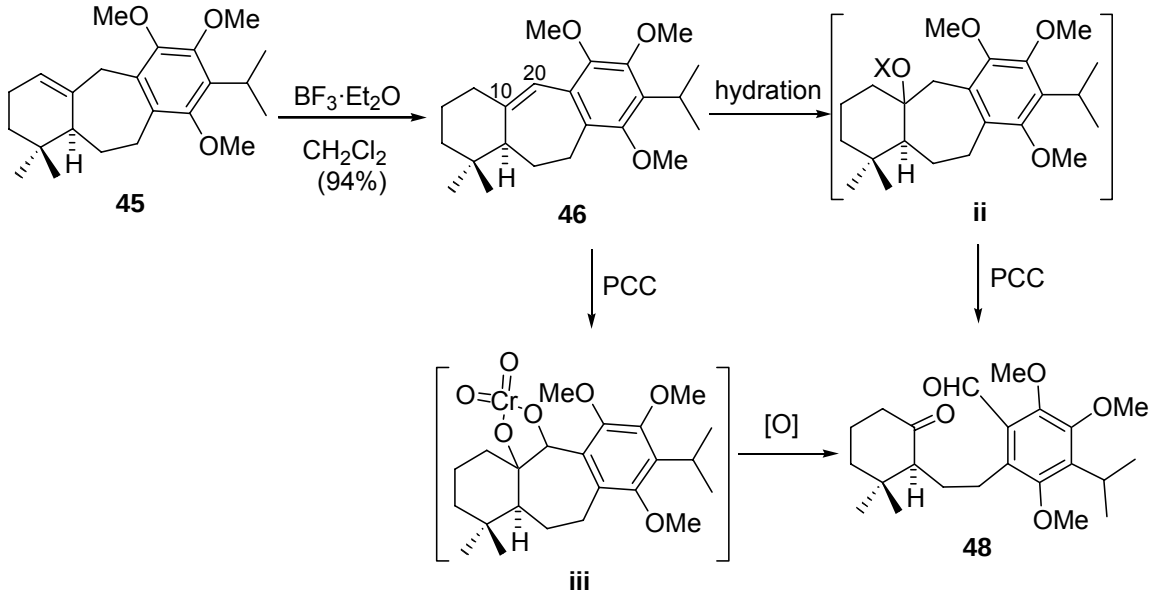
Scheme 17

We hoped to obtain better results by oxidizing other intermediates, such as alkene **45**. However, this intermediate also gave unsatisfactory results (Scheme 18).



Scheme 18

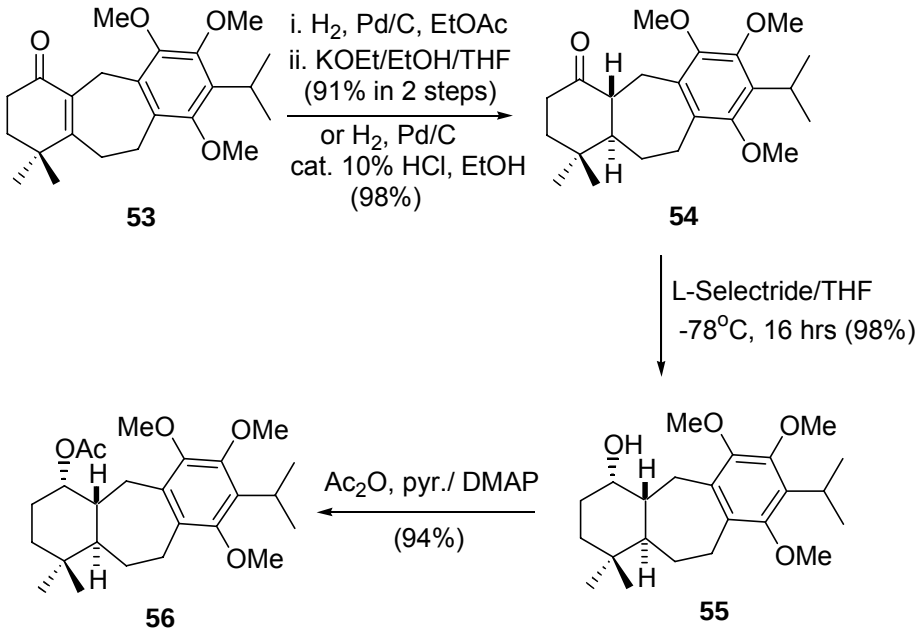
Concurrent with this work, alkene **45** was rearranged to styrenyl alkene **46** and treated with various oxidants. To our surprise, alkene **46** underwent double bond cleavage with PCC/ celite to generate dione **48**. By comparing different oxidation results of alkenes **45** and **46**, we reasoned that oxidative cleavage of the C(10)−C(20) double bond on alkene **46** involved the hydration of the double bond by trace amounts of moisture to give intermediate **ii**, or dihydroxylation of double bond to give intermediate **iii**. The following oxidation of intermediates resulted in dione **48** (Scheme 19).



Scheme 19

Since having a hydroxyl group at C(10) is not compatible with the oxidation of the C(7) position, this caused us to oxidize acetate **56** as shown in Scheme 20. Hydrogenation of enone **53**, followed by epimerization of the resulting crude ketone gave ketone **54** in 91% overall yield. The two adjacent methine hydrogens on the A,B-ring junction are *trans* to each other whose formation is controlled by thermodynamic isomerization. The direct transformation of enone **53**

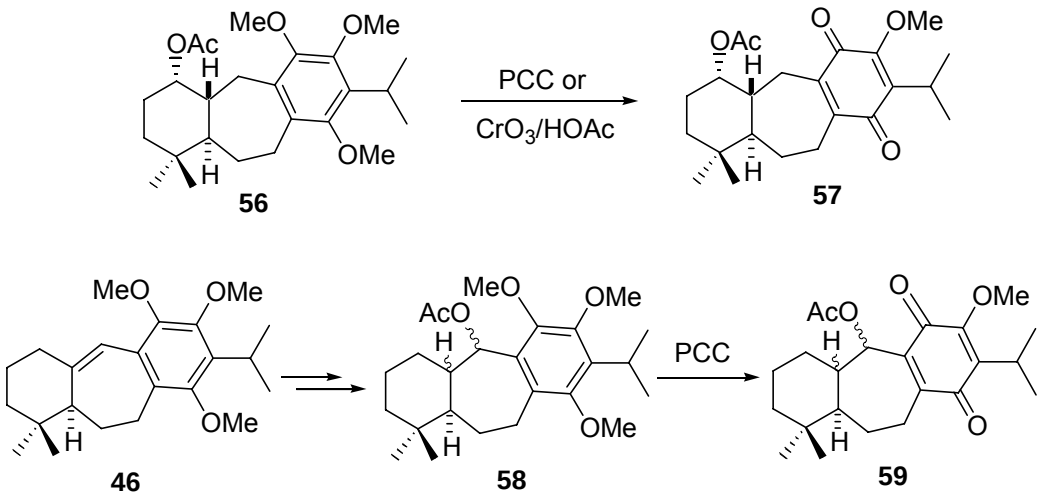
to ketone **54** was achieved in excellent yield by hydrogenation catalyzed by 10% HCl. LAH reduction of ketone **54** in diethyl ether at 0 ℃ was not facially selective as the "sterically small" hydride in LAH failed to differentiate between the two faces of the C(1) carbonyl group. We believed that increasing the steric congestion of the reducing agent would cause the hydride to add from the less hindered face of ketone **54**. Indeed, when ketone **54** reacted with L-Selectride in THF at -78 ℃ over a period of sixteen hours a high facial selectivity (>99:1) was obtained. Protection of alcohol **55** with acetic anhydride and pyridine in methylene chloride gave acetate **56** in 94% yield (Scheme 20).



Scheme 20

With acetate **56** in hand, we expected that the benzylic oxidation on C(7) would follow our faveline precedent. Instead of the desired benzylic oxidation, oxidation of the aromatic ring to give *para*-benzoquinone **57** occurred with PCC or CrO_3 (Scheme 21). Other oxidizing

conditions, including IBX/DMSO,[27] CAN/HOAc,[28] PFC,[29] *m*-CPBA/air/$NaHCO_3$,[30] *tert*-BuOOH/CuI/MeCN,[31] SeO_2/EtOH and DDQ/THF/H_2O were studied but gave either no reaction or decomposition. This observation was not limited to acetate **56**. Acetate **58** was prepared as a mixture of diastereoisomers from alkene **46** via hydroboration and acetylation of the resulting alcohol. Although the C(20) position was directly protected by acetate, oxidation of acetate **58** with PCC also resulted in quinone **59** formation (Scheme 21).

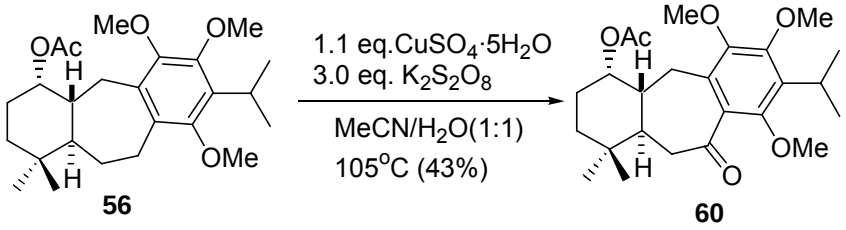


Scheme 21

Structurally, the difference between acetate **56** and acetates **35** and **36** (or acetate **58** and acetate **21**) from our faveline synthesis is the presence of two extra methoxyl groups on the aromatic ring. The increased electron density makes the hydroquinone ether vulnerable to moderate oxidation conditions. In fact, many common oxidants achieved this transformation, *i.e.*, PDC,[32] $Na_2Cr_2O_7/H_2SO_4$,[33] or CAN.[34] Presumably, the electron density difference between a trimethoxy arene and a monomethoxy arene, in addition with the *para*-dimethoxyl sub-structure in acetates **56** and **58**, made our substrates prone to oxidation instead of undergoing benzylic oxidation. Whereas, in faveline synthesis, the less electron-dense aromatic rings in acetates **35**

and **36** (or acetate **21**) make them robust enough to withstand the oxidation condition. Therefore, the oxidations of acetates **35** and **36** (or acetate **21**) only take place on the C(7) position.

This analysis gave us a new direction to explore for oxidation of the C(7) carbon without affecting the aromatic ring. When acetate **56** was treated with excess amount of $K_2S_2O_8$ and 1.0 equivalent of $CuSO_4 \cdot 5H_2O$ in acetonitrile and water at 110 ℃,[25a-c] a 43% yield of ketone **60** was obtained with complete consumption of acetate **56** (Scheme 22).

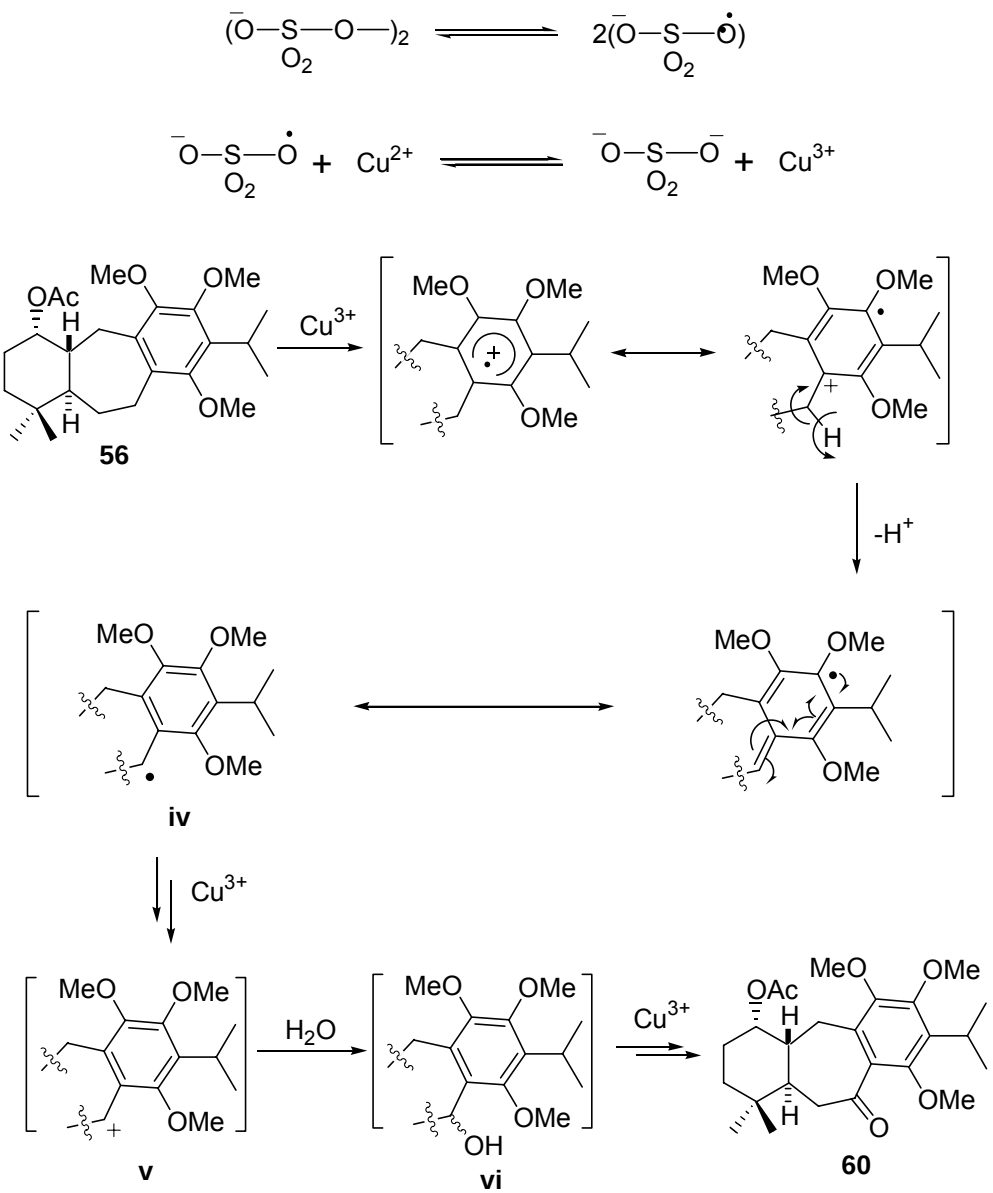


Scheme 22

Further study revealed that < 50% yield of ketone **60** was frustratingly reproducible. The mechanism using this condition was studied by Bhatt and Perumal[25a] in their original paper and a single electron oxidation pathway was proposed. As shown in Scheme 23, upon heating the reaction a Cu^{3+} species is generated, followed by the removal of one electron from the aromatic ring of acetate **56** by the Cu^{3+} species. This leads to the formation of benzylic radical **iv**. Upon further reaction with the Cu^{3+} ions, one more benzylic electron is removed to generate benzylic cation **v** which is reacted with water to produce benzylic alcohol **vi**. Further oxidation of alcohol **vi** gives ketone **60**.

By monitoring the reaction by TLC analysis, we noticed that the oxidation first generated a polar species on TLC plate; this intermediate corresponds to benzylic alcohol **vi**. Longer reaction times consumed the alcohol **vi** and generated a more non-polar spot, which, after workup and purification, proved to be ketone **60**. Before the complete consumption of acetate **56**

occurred, however, alcohol **vi** underwent rapid decomposition. Intermediate **vi** also decomposed on attempted silica gel column chromatography.

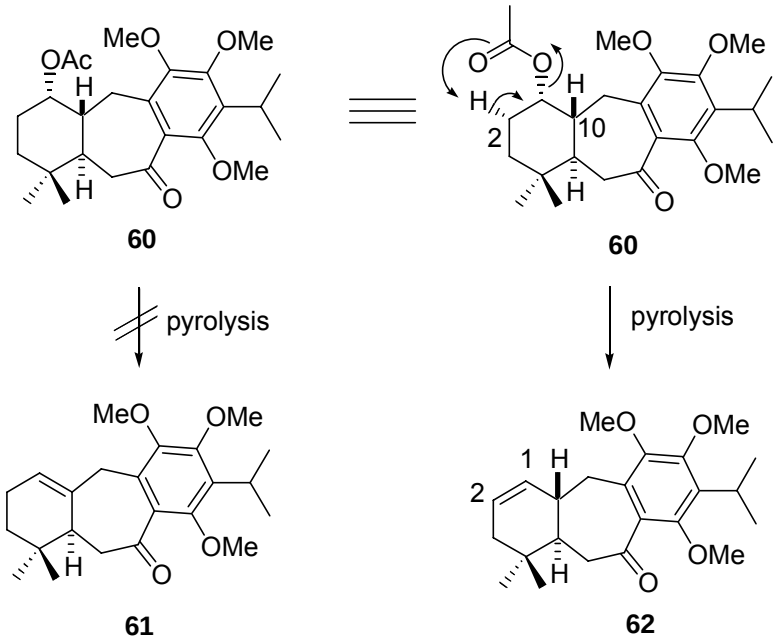


Scheme 23

Based on the above mechanistic analysis and our experimental observations, in order to avoid decomposition of intermediate **vi**, milder reaction conditions and a limited amount of

oxidant had to be used. The optimized procedure was to first oxidize acetate **56** to benzylic alcohol **vi** using 1.1 equivalent of $K_2S_2O_8$ and 0.5 equivalent of $CuSO_4 \cdot 5H_2O$ in $MeCN/H_2O$ (2:1) at 90 ℃ for only 1.5 hours, followed by rapid oxidation of the crude mixture with Jones reagent. Using this procedure, a 61% yield of ketone **60** was isolated along with 33% of unreacted acetate **56**.

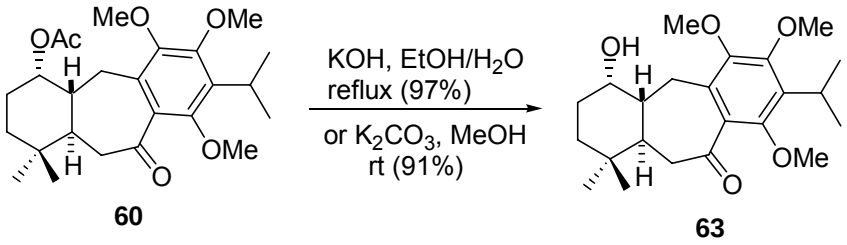
This oxidation was limited to a 300 mg scale, because the reaction rate of the benzylic oxidation is not fast enough to overcome the decomposition rate of intermediate **vi** whenever a comparatively large scale is used. Two grams of the ketone **60** was collected from many 300 mg-scale batches. The relative stereochemistry of ketone **60** was also confirmed by X-ray crystallographer structure (See Appendix I) to have a *cis* relationship of the C(1) and C(10) methines and a *trans* relationship of the C(5) and C(10) methines.



Scheme 24

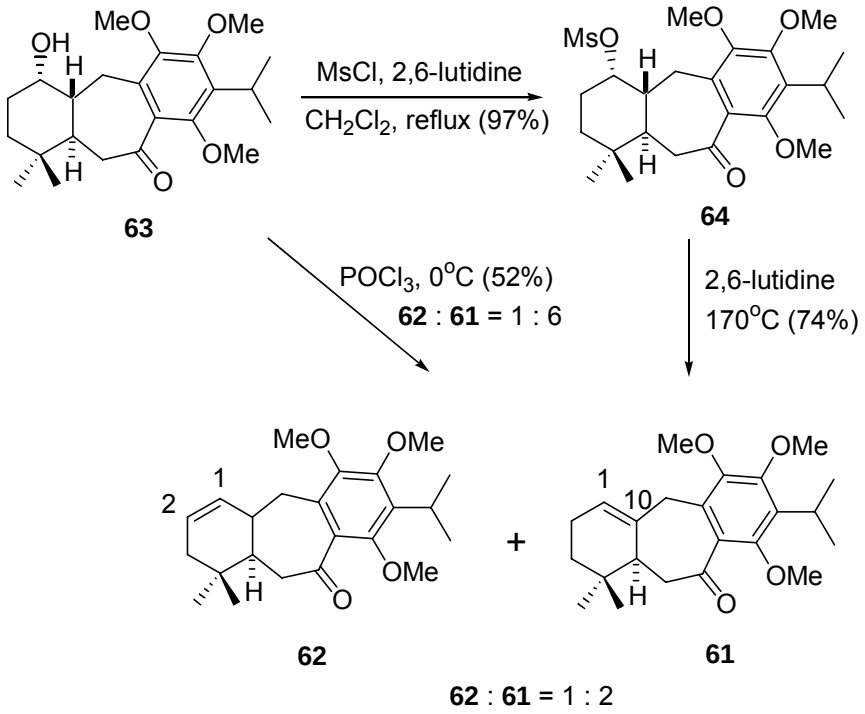
This result prompted us to further explore the preparation of alkene **61**. A direct and efficient method to form an alkene is to pyrolysize an acetate though a six-membered transition state and an Ei mechanism.[35a-c] However, pyrolytic elimination requires the presence of *cis* β-hydrogen due to a syn elimination mechanism.[38a,b] Since the acetate group in ketone **60** is *trans* to C(10) methine hydrogen, pyrolysis of ketone **60** has to pick up the only available *cis* C(2) hydrogen and only results in the C(1),C(2) disubstituted alkene **62** on the A-ring (Scheme 24).

A two-step procedure for the preparation of alkene **61** was then developed. Ketone **60** was saponified easily when treated with KOH/EtOH/H_2O or with K_2CO_3/MeOH to give secondary alcohol **63** in 97% and 91% yield, respectively (Scheme 25).



Scheme 25

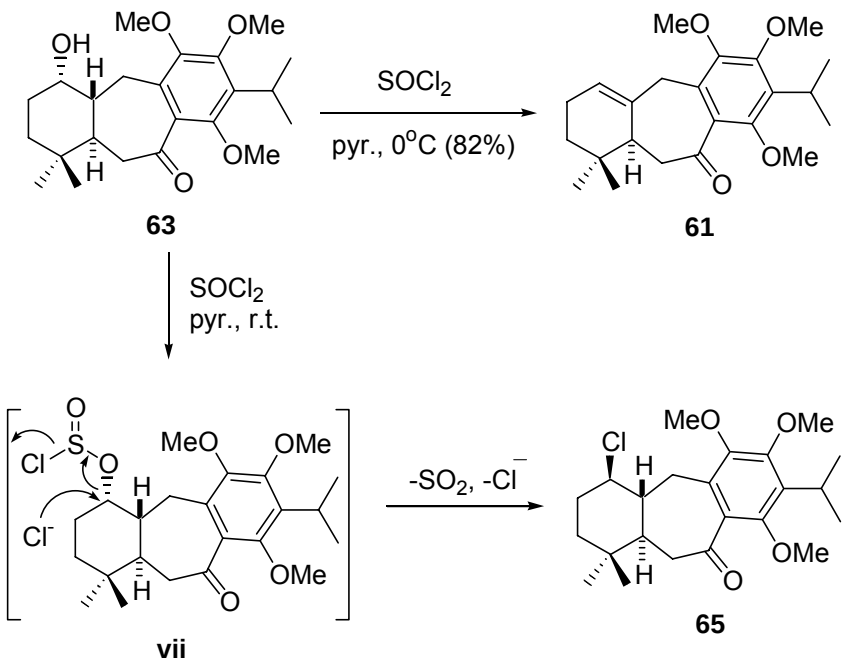
We then sought conditions for the selective elimination of alcohol **63** to form tri-substituted alkene **61**. As shown in Scheme 26, mesylate **64** was prepared in excellent isolated yield when alcohol **63** was heated with freshly distilled mesyl chloride (MsCl) and mild base in dichloromethane. Unlike pyrolysis reactions, the elimination of a mesylate occurs through an E1 mechanism and prefers more substituted alkene as product.[37a,b] The elimination of the mesylate **64** in refluxing 2,6-lutidine, however, gave a 2:1 inseparable mixture of alkene **61** and disubstituted alkene **62**. When mesylate **64** was formed in refluxing methylene chloride, removal of the methylene chloride followed by heating the crude product in 2,6-lutidine gave the same mixture of alkenes, but in lower yield.



Scheme 26

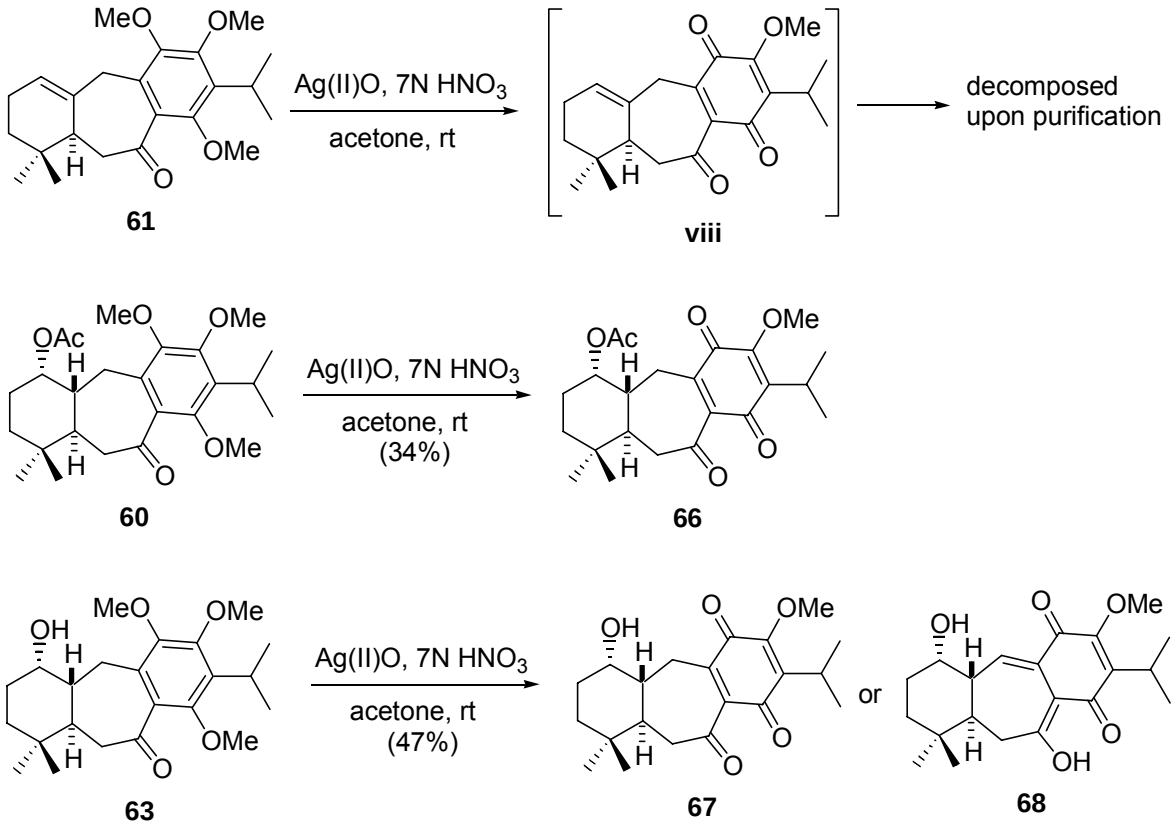
Exploration toward direct dehydration of alcohol **63** at 0 ℃ gave an improved **61** to **62** ratio of up to 6:1 when $POCl_3$ was used.[38] Moreover, careful treatment of alcohol **63** with excess thionyl chloride in pyridine[39a,b] at 0 ℃ gave alkene **61** as the only product in a yield of 82% (Scheme 27). It was also observed that when alcohol **63** was treated with thionyl chloride at room temperature, some chloride **65** was collected along with alkene **61**. Chloride **65** results from S_N2 displacement of intermediate **vii** with chloride ion.

With alkene **61** in hand, all that remained to complete a synthesis of komaroviquinone was the hydration of alkene **61** to form tertiary alcohol **42** followed by oxidation of the masked hydroquinone to generate the *para*-benzoquinone. Another option is to invert these two operations, but the oxidation of the aromatic ring turned out to be problematic. Many oxidation



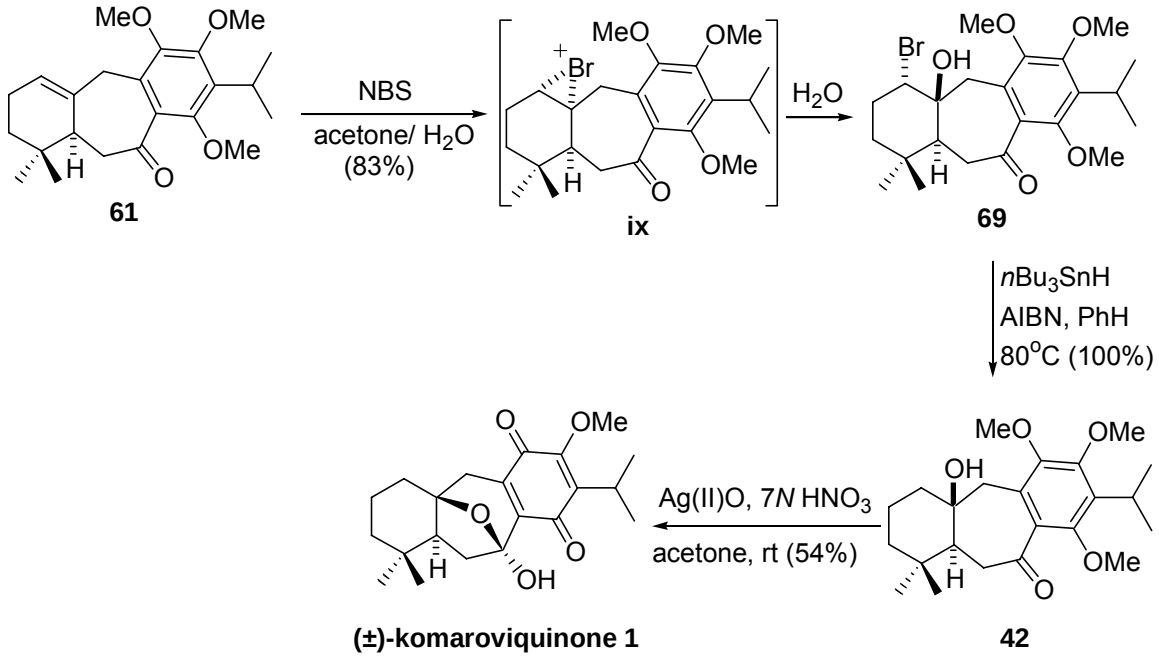
Scheme 27

conditions (CAN, PCC, HgO, etc.) were tried but gave no oxidation product. Presumably, the electron-withdrawing effect of the C(7) carbonyl group deactivates the reactivity of the aromatic ring toward mild oxidants. After extensive searching, it was observed that alkene **61** can be oxidized by Ag(II)O/7 *N* HNO_3 in acetone (Scheme 28).[19] However, when we tried to isolate *para*-benzoquinone species **viii**, it decomposed. Although there was no spectral proof for the formation of quinone **viii**, oxidation of ketone **60** and alcohol **63** gave the corresponding *para*-benzoquinones **66** and **67** (or **68**), respectively. These results support the formation of intermediate **viii**, and caused as to speculate that decomposition took place because of the C(1)−C(10) double bond. We therefore decided to hydrate the C(1)−C(10) double bond prior to the oxidation of the aromatic ring. However, in our hands, the C(1)−C(10) double bond was inert to common hydration conditions.



Scheme 28

After thorough investigation, it was found that bromohydrin formation of alkene **61** went smoothly to give bromide **69** with 83% yield via bromonium ion **ix** when treated with NBS in acetone/H_2O (Scheme 29).[40] Photochemical removal of the bromide yielded quantitative amount of tertiary alcohol **42**. The ^{1}H NMR data of both pure bromide **69** and alcohol **42** showed mixtures of several components, perhaps due to acetal formation or keto−enol tautomerization. Finally, oxidation of alcohol **42** with Ag(II)O/7 *N* HNO_3[19] in acetone accomplished the synthesis of (±)-komaroviquinone **1** as a single product in 54% yield.



Scheme 29

Table 1 compares the ^{1}H and ^{13}C data for both our synthesized (±)-komaroviquinone (**1**) and those of isolated (±)-komaroviquinone (**1**) by Kiuchi and co-workers.[1] The minor differences on ^{1}H NMR data as well as the identical ^{13}C NMR data confirms our success in the synthesis of (±)-komaroviquinone (**1**).

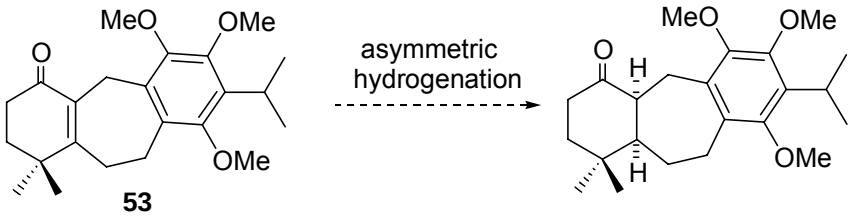
Table 1: NMR Data of Synthesized and Isolated (±)-Komaroviquinone (**1**)

	Our synthetic komaroviquinone (**1**)		Isolated komaroviquinone (**1**)[b]	
Carbon no.	^{1}H[a]	^{13}C	^{1}H[c]	^{13}C
1	1.56-1.64 (m)	15.67 (t)	1.60, overlap	15.6
2	1.68-1.76 (m)	29.80 (t)	*α*: 1.73, overlap	29.8
	1.98-2.08 (m)		*β*: 2.03, overlap	
3	1.12-1.18 (m)	31.20 (t)	*α*: 1.15, dd (5.8, 11.3)	31.2
	1.56-1.64 (m)		*β*: 1.59, overlap	
4		32.04 (s)		32.0
5	1.68-1.76 (m)	51.47 (d)	1.71, t (8.2)	51.4
6	2.30 (dd, 7.2, 13.6)	45.77 (t)	*α*: 2.30, dd (8.6, 12.8)	45.7
	1.98-2.08 (m)		*β*: 2.04, dd (7.8, 12.8)	
7		100.89 (s)		100.9
8		142.13 (s)		142.1
9		138.94 (s)		138.9
10		79.33 (s)		79.3
11		183.60 (s)		183.6
12		156.10 (s)		156.1
13		137.08 (s)		137.0
14		189.14 (s)		189.1
15	3.22 (heptet, 7.2)	24.34 (d)	3.22, sep (7.0)	24.3
16	1.21 (d, 7.2)	20.45 (q)	1.18, d (7.3)	20.4
17	1.21 (d, 7.2)	20.45 (q)	1.18, d (7.0)	20.4
18	0.95 (s)	30.34 (q)	0.95, s	30.3
19	0.87 (s)	27.10 (q)	0.86, s	27.0
20	2.25 (d, 20.0)	39.02 (t)	*α*: 2.26, d (19.6)	39.0
	2.55 (d, 20.0)		*β*: 2.55, d (19.6)	
OMe	3.99 (s)	61.19 (q)	3.98, s	61.1
OH	5.99 (s)		5.99, s	

[a] Recorded in $CDCl_3$ at 400 MHz for both ^{1}H and ^{13}C, data in δ ppm (*J* in Hz); b Kiuchi, F. *et. al. J. Nat. Prod.* **2003**, *66*, 128-131; [c] Recorded in $CDCl_3$ at 500 MHz (1H) and 125 MHz (13C), respectively.

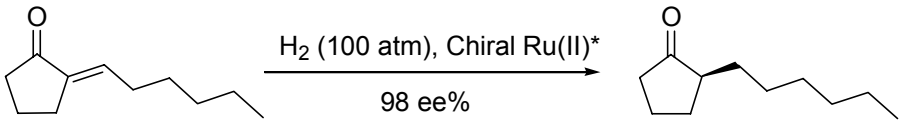
Toward a Stereoselective Synthesis of (+)-Komaroviquinone

Following our synthesis of (±)-komaroviquinone (**1**) we sought to synthesize (+)-komaroviquinone by controlling the chirality of the C(5) methine of alkene **61** prior to the final transformation. Thus, how to synthesize alkene **61** in optically active form became our next task.



Scheme 30

We were curious if the C(5) chiral center of alkene **61** could be introduced by an asymmetric hydrogenation of enone **53** (Scheme 30).[41] Transition metal complexes, such as Rh, Ru and Ir, with chiral dentates, can hydrogenate enones enantioselectively.[41,42] For example, as shown in Scheme 31, the asymmetric hydrogenation of an enone takes place under high pressure of hydrogen to give a chiral ketone.[42a]

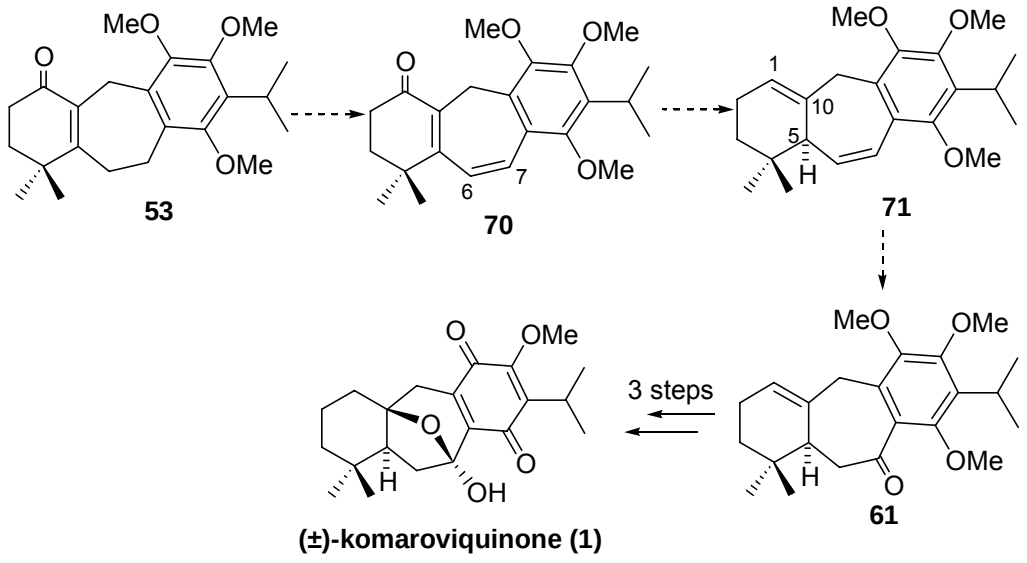


Scheme 31

Unfortunately, few examples of the asymmetric hydrogenation of hindered or tetrasubstituted enones are known or very high pressures are needed to achieve this transformation.[42] Since the high-pressure apparatus needed for high pressure hydrogenation was not available, we required an alternative method in order to produce the optically active alkene **61**.

In our syntheses of faveline and (±)-komaroviquinone (**1**), we were obsessed with the functionalization of the C(7) benzylic position of the 6,7,6-fused tricyclic systems. Since the establishment of the asymmetric C(5) methine had already been solved in our syntheses of (+)-perovskone and (+)-salvadione-A,[10] we realized that the functionalized enone **53** would lead to the desired asymmetric C(5) methine using the chemistry we had already worked out. Hence, we decided to combine these transformations together to develop a new, shorter route.

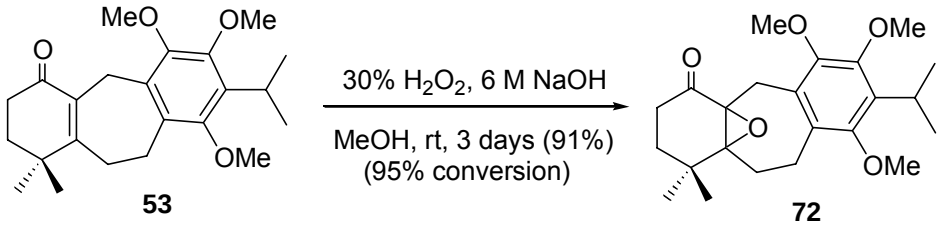
Given our desire to functionalize the C(7) position, we hoped to hydrate a double bond at C(6) and C(7). Thus, a synthetic analysis was proposed. As shown in Scheme 32, once a



Scheme 32

C(6)−C(7) double bond is introduced from enone **53**. The asymmetric transformations of the cyclohexenone portion of dienone **70** would produce diene **71** with an asymmetric C(5) methine. Differentiation of the trisubstituted C(1)−C(10) double bond from the disubstituted C(6)−C(7) double bond in the isolated diene **71** should produce alkene **61**, which is chiral and can be transformed to (+)-komaroviquinone (**1**) in the same three steps as used in our racemic synthesis. The attractive features of this design are the formation of conjugated dienone **70** and its transformation to alkene **61**.

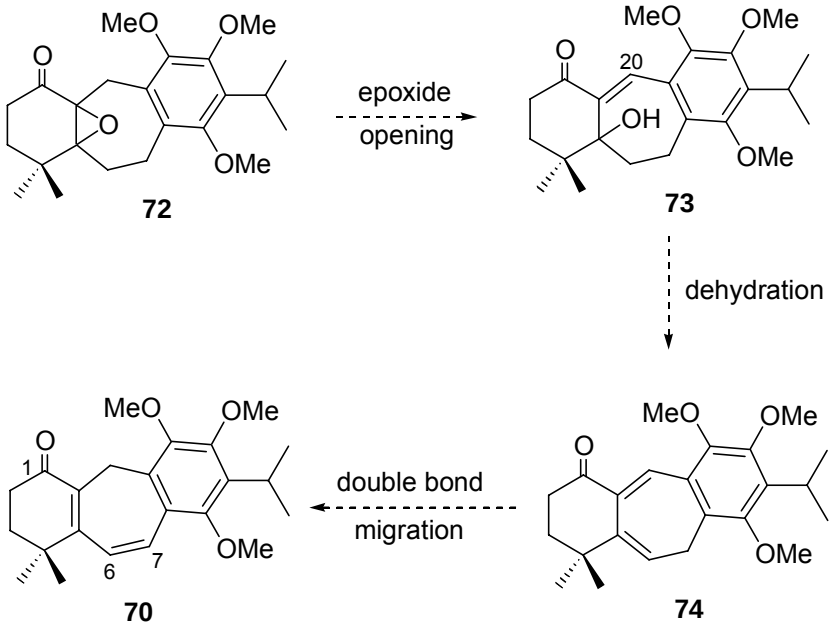
Several conditions were tried in hopes to extend the conjugation of enone **53** to the C(6) and C(7) positions to produce dienone **70**, *i.e.* SeO_2, Br_2/base, NBS/AIBN. Unfortunately, these reagents gave either no reaction or unwanted products. Instead of functionalizing the C(7) position, we found that by stirring enone **53** with 30% aqueous hydrogen peroxide and 6 *M* aqueous NaOH[43] epoxidation took place over three days and gave epoxide **72** as the only product in 91% yield (Scheme 33).



Scheme 33

We speculated that when epoxide **72** is treated with a strong base, deprotonation on the C(20) position would open the epoxide up to produce allyl alcohol **73** which would readily dehydrate under acidic or basic conditions to generate diene **74** (Scheme 34). Comparing the structures of diene **74** and dienone **70**, we felt that dienone **70** has a highly conjugated system,

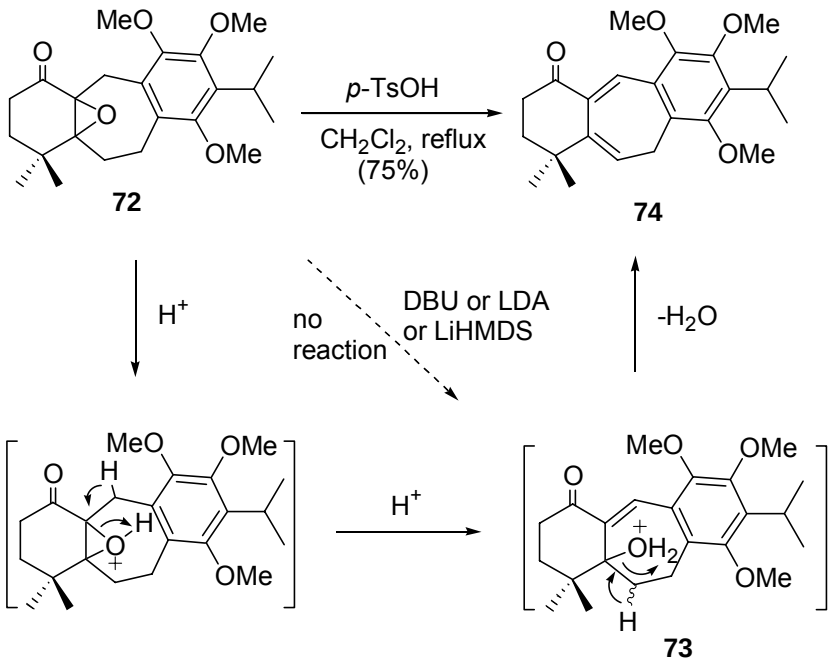
ranging from C(1) carbonyl to aromatic ring via C(6), C(7) alkene; whereas diene **74** bears less conjugation. Therefore, we believed that diene **74** would rearrange to the thermodynamically more stable conjugated dienone **70**.



Scheme 34

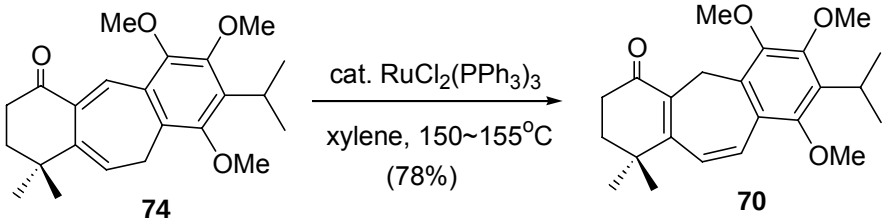
Epoxide **72** did not open with DBU, LDA or LHMDS. Interestingly, when **72** was treated with *para*-toluenesulfonic acid in refluxing dichloromethane, a polar species was generated first. Before complete consumption of epoxide **72**, this polar species was transformed into a new non-polar intermediate. After longer reaction times, only a single non-polar species was collected in 75% yield; the structure of this non-polar species was determined to be diene **74** (Scheme 35).

Since it's plausible to rearrange diene **74** to dienone **70** under acidic condition, we tried to include this step into the acid-catalyzed cascade process. Extended reaction times, more acid and/or harsher reaction conditions were tried on epoxide **72**, but only diene **74** was



Scheme 35

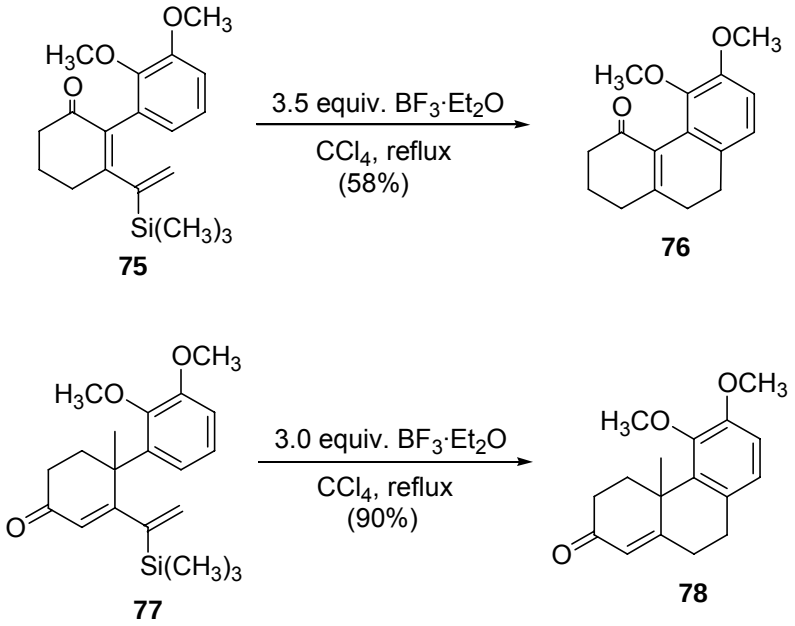
collected as the thermodynamic product. The addition of strong bases to diene **74** failed to achieve the isomerization. Thus, diene **74** is quite inert under both acidic and basic conditions. Nevertheless, isolated olefins can rearrange to styrenyl alkenes when treated with transition metals.[44a-c] Indeed, when diene **72** was heated with $Ru(PPh_3)_3Cl_2$ in refluxing xylene, it isomerized smoothly to conjugated dienone **70** in high yield (Scheme 36).



Scheme 36

Novel Cycloalkylation Methods to Functionalize the C(7) Position

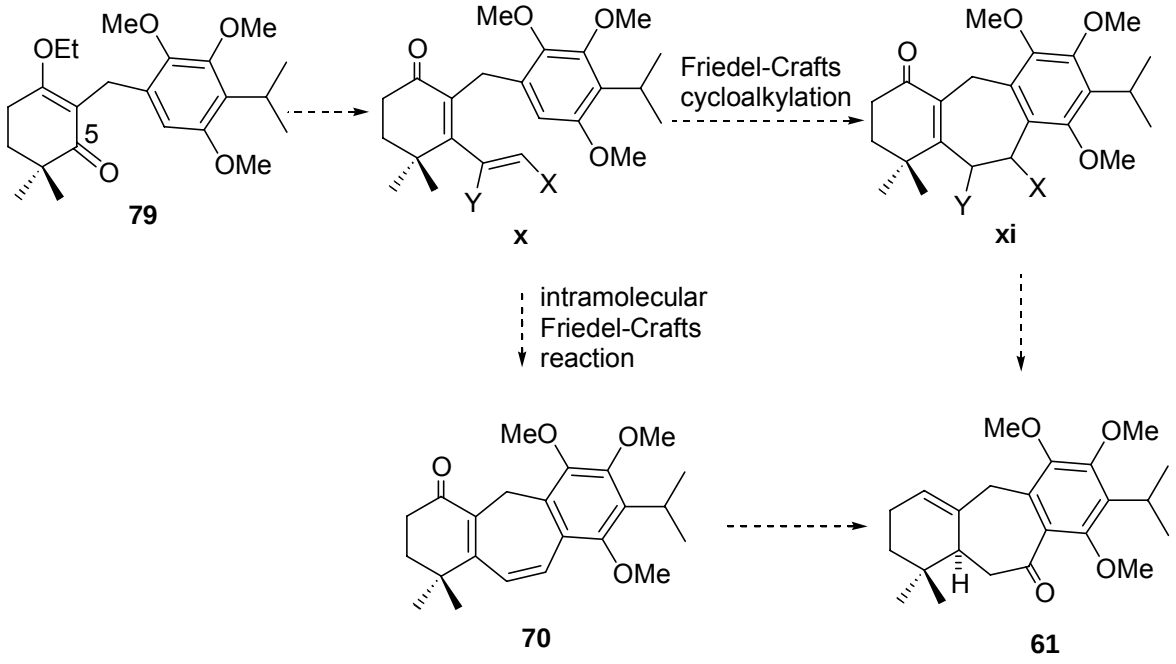
We were confident that conjugated dienone **70** would allow us to functionalize C(7) benzylic position as a styrenyl alkene. Thus our goal was to synthesize intermediate **70** or a derivative thereof via a shorter synthetic route using Friedel-Crafts ring closure. Even though the Friedel-Crafts cycloalkylation of conjugated dienones has been extensively studied, few examples with functional groups on the γ- or δ-positions of the conjugated dienone have been investigated. In the only published examples of a functionalized conjugated dienone precursor, dienones **75** and **77**, bearing γ-trimethylsilyl group cyclized to incorporate 6,6,6-fused tricycles **76** and **78** with subsequent loss of the TMS group (Scheme 37).[45]



Scheme 37

We decided to investigate the cycloalkylation of γ- or δ-functionalized conjugated dienones in hopes of synthesizing dienone **70** more efficiently. As proposed in Scheme 38, we

sought to synthesize variants of **x** representing masked C(7) carbonyl moiety or other functional groups positioned at C(7) which could be transformed to a carbonyl later on. Once we could obtain functionalized cyclization product **xi**, the optically active alkene **61** would be synthesized using simple functional group interconversions.



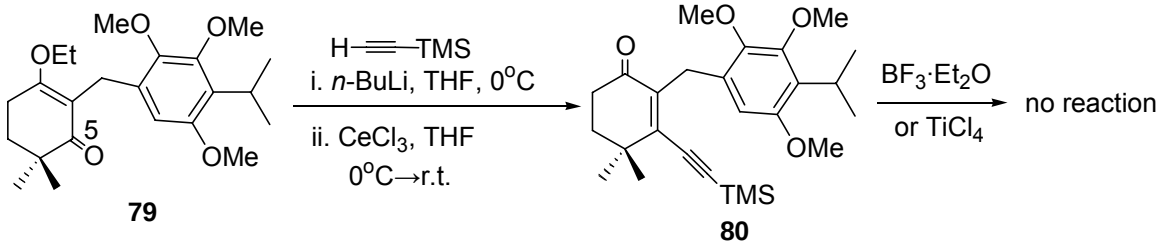
Scheme 38

Since conjugated dienone **70** had already been prepared, we wanted to make it in fewer steps. It is conceivable that the cyclization of an enynone **x**, where X and Y are π electrons, such as an alkyne, would give dienone **70** directly (Scheme 38). Hence, we sought to prepare a functionalized enynone.

It is important to note that the C(5) carbonyl in cyclohexenone **79** is hindered. Weak and mild alkylating reagents do not add to it. Ordinarily, when we use strongly nucleophilic reagents such as vinyllithium, a catalytic amount of cerium(III) chloride must be added to activate the

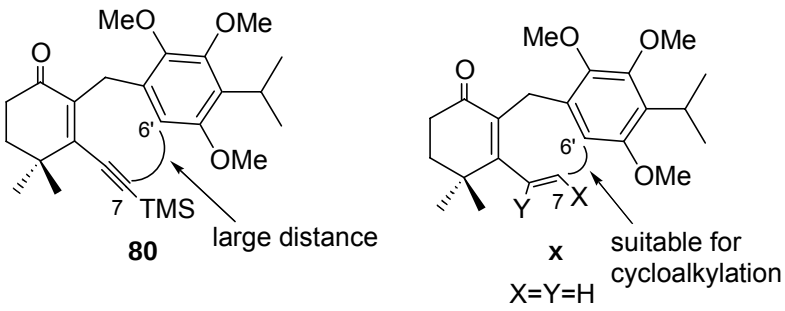
carbonyl to addition. Hence, the selection of suitable nucleophilic reagents becomes an important decision.

The next nucleophile we investigated was trimetylsilyl acetylene (Scheme 39). The lithium reagent, generated from trimethylsilyl acetylene and *n*-BuLi at 0 ℃, added smoothly to ketone **79** and gave enynone **80**. However, as we expected this product did not cyclize under even harsh Lewis acid conditions.



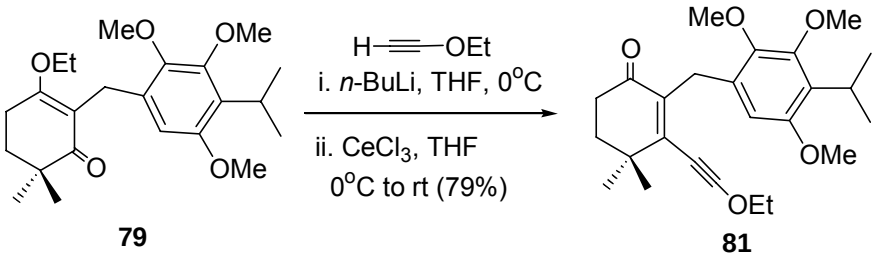
Scheme 39

Analysis of Drieding models of enynone **80** showed that the distance between terminal C(7) alkyne carbon and 6′ carbon on aromatic ring is larger than that of a standard carbon-carbon single bond; whereas this distance in **x** is much shorter (Scheme 40). Therefore, the cycloalkylation of not only enynone **80** but all enynone derivatives will not take place. On the other hand, when X and Y are hydrogens, the distance between the terminal carbon of alkene **x** and the C(6) position of aromatic ring permits the cycloalkylation.



Scheme 40

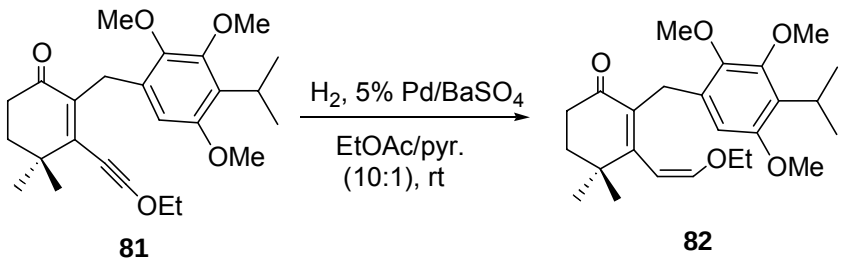
Among terminal alkyne reagents, ethoxy acetylene or Aren's reagent was once a widely used alkylating reagent.[46] Since it bears an ethoxy group on alkyne, it is traditionally viewed as an ester equivalent. When Aren's reagent was added to ketone **79**, compound **81** was obtained in 79% yield (Scheme 41).[46]



79 **81**

Scheme 41

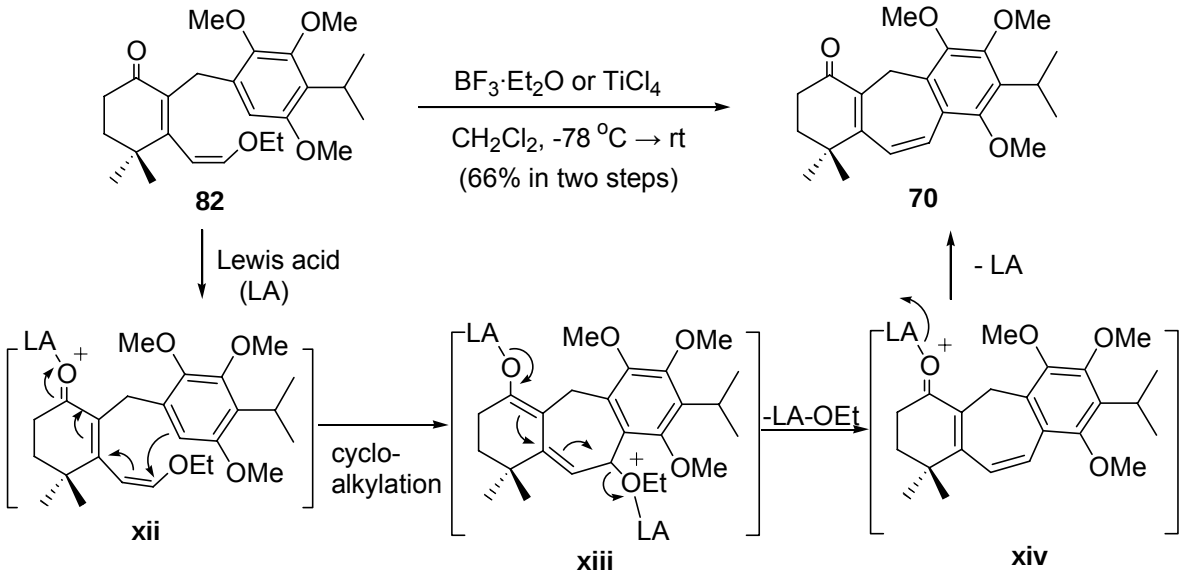
As expected, compound **81** does not undergo cycloalkylation. Hydrogenation of alkyne to alkene, however, should reduce the distance between the C(7) and the terminal carbon of the conjugated system so that it is comparable to that of a conjugated dienone; thus, cycloalkylation should occur. The hydrogenation of **81** using Lindlar's catalyst (5% $Pd/BaSO_4$),[47] and pyridine as solvent cleanly provided enol ether **82** (Scheme 42). Decomposition of **82** was observed when acid was used in the workup or when it was purified by silica gel chromatography. It was also noticed that the *Z*-alkene will isomerize to *E*-alkene when it was exposed to water over a period of extended time. These observations are consistent with the instability of enol ether **82**. In order to avoid acid-promoted decomposition of enol ether **82** during workup, a small amount of pyridine was added to act as a proton sponge. It was found that a 10:1 mixture of ethyl acetate and pyridine worked well, and that the pyridine could be removed by washing with saturated copper sulfate ($CuSO_4$) without affecting enol ether **82**. For convenience, ethyl enol ether **82** was isolated as a crude product and was subjected to cycloalkylation without further purification.



81 **82**

Scheme 42

When ethyl enol ether **82** was treated with excess $BF_3{\cdot}Et_2O$ or $TiCl_4$, cycloalkylation took place and a new compound was obtained in 66% overall yield from enynone **81** (Scheme 43). More importantly, the cyclization product no longer contains an ethoxy group as the product of this ring closure was realized to be dienone **70**.

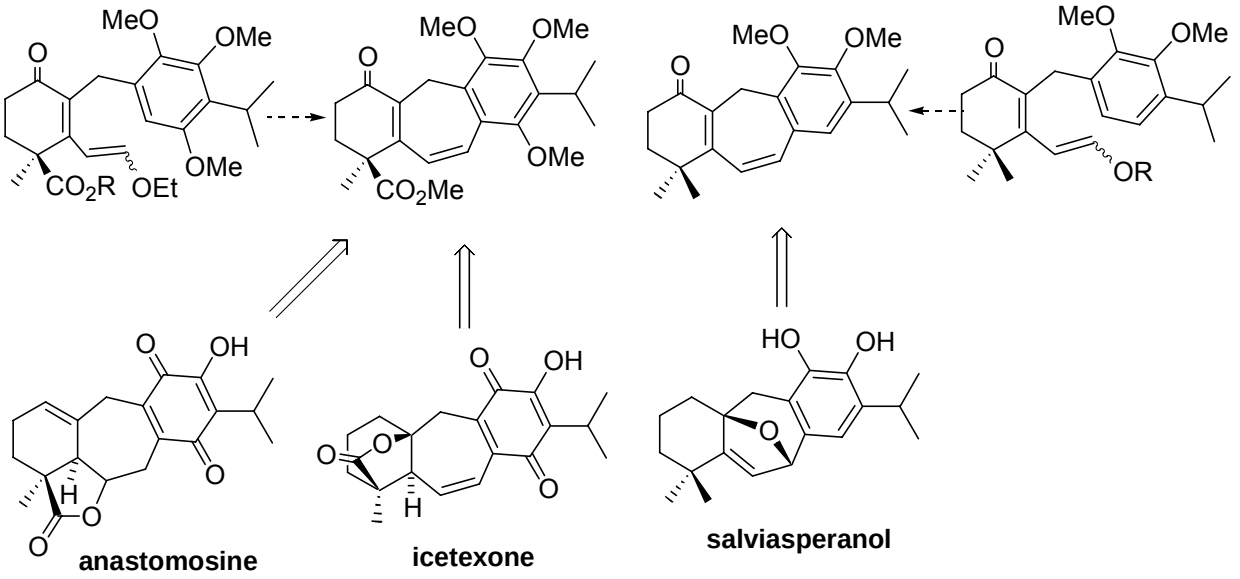


Scheme 43

A possible mechanism for this transformation follows: a) Lewis acid coordination of the carbonyl oxygen on conjugated diene **82** gives intermediate **xii** which, through resonance, makes

the δ-carbon of the conjugated enone system electrophilic; the ethoxy group also contributes to the stabilization of the cationic character of the δ-carbon; b) Friedel-Crafts cycloalkylation forms intermediate **xiii**; c) excess Lewis acid activates the C(7) ethoxy group of **xiii** and makes it into an excellent leaving group; d) the lone pair electrons on the C(1) oxygen generates the highly conjugated dienone **xiv** via the loss of the Lewis acid-activated C(7) ethoxy group. Finally, dienone **70** was obtained in 66% overall yield after aqueous workup.

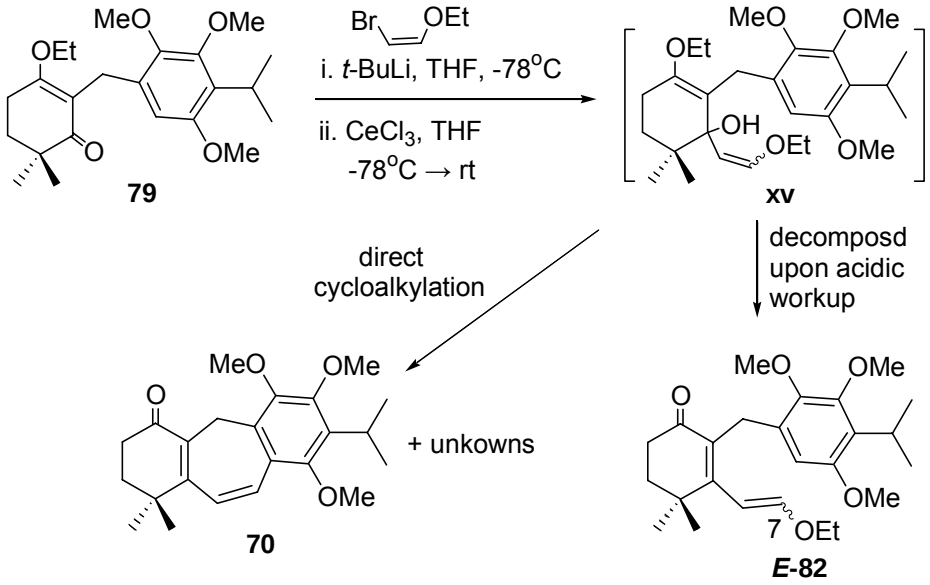
We were excited that dienone **70** could be efficiently made via this cycloalkylation strategy and confident that the C(6)−C(7) double bond would permit the synthesis of several other natural products, such as anastomosine, icetexone and salviasperanol.[48a-g] Scheme 44 presents our tentative retrosynthetic analysis for these syntheses, which are being investigated by others within the Majetich research group.



Scheme 44

The formation of enol ether **82** required the addition of Aren's reagent, followed by hydrogenation. We proposed that a functionalized vinyllithium reagent, if stable, would produce

enol ether **82** in a single operation. After searching for suitable reagents, (*Z*)-2-ethoxyvinyl bromide was prepared using Pericas and Valenti's method.[49] Starting from ethyl vinyl ether, bromination followed by dehydrobromination with triethylamine at -78 ℃ was able to achieve 2-ethoxyvinyl bromide with *Z*:*E* ratio more than 50:1. (*Z*)-2-ethoxyvinyl bromide was then subjected to cycloalkylation condition (Scheme 45).



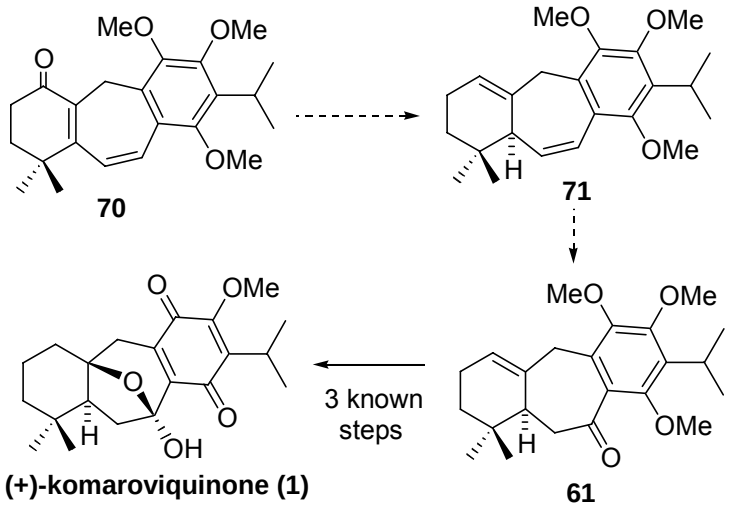
Scheme 45

While cycloalkylation occurred rapidly at low temperature, the dilute aqueous acid, used to quench the reaction and transform tertiary alcohol **xv** to *E* enol ether **82**, caused its rapid decomposition. Moreover, by comparing the crude ^{1}H NMR with that from Aren's reagent pathway, we found that, in addition to dominating decomposition, more *E* isomer was presented than *Z* enol ether **82**, which suggests that the *Z* enol ether **82** is far less stable. A mild work up was carried out then. The reaction was quenched by water and stirred for less than 5 minutes, and then the crude product was subjected directly to cyclization with excess Lewis acid to provide

30-40% of dienone **70** and several unknowns. Although this alternate route produced dienone **70**, the use of the three-step process though the addition of Aren's reagent, followed by hydrogenation and cycloalkylation, was a cleaner and easier process to execute.

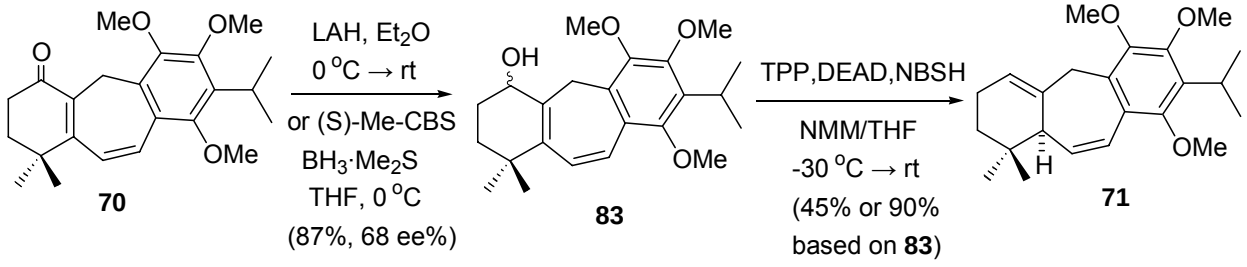
Study toward the Synthesis of (+)-Komaroviquinone

The preparation of dienone **70** allowed us to study the synthesis of optically active (+)-komaroviquinone (**1**). As presented in Scheme 46, application of the Corey CBS asymmetric reduction, followed by the Myers based Mitsunobu-type dehydration, would produce diene **71**. We fully expect to be able to differentiate the two double bonds presented in the molecule and selectively transform the styrenyl alkene to C(7) benzylic ketone **61**. Once we prepare ketone **61**, (+)-komaroviquinone (**1**) will be obtained in three known steps. Before we embarked on an asymmetric synthesis, we decided to first achieve a racemic synthesis.



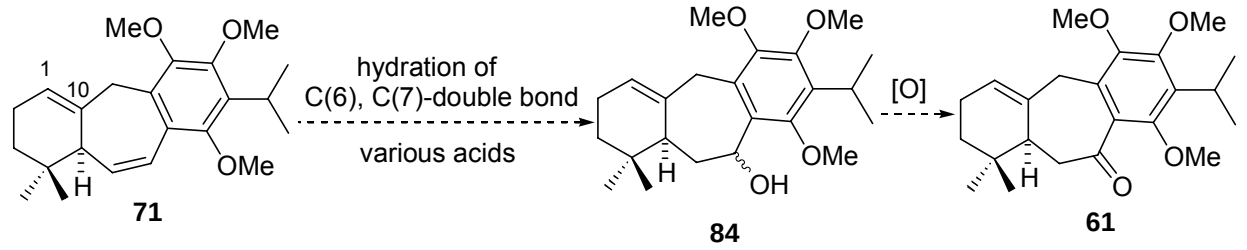
Scheme 46

Reduction of dienone **70** with LAH produced allylic alcohol **83** in excellent yield. Corey CBS reduction of dienone **70** gave alcohol **83** in 87% yield with 68 ee%, which is determined from the ^{19}F NMR of its Mosher's ester. After three recrystallizations in EtOAc/pet ether, optically pure alcohol **83** was achieved. The specific rotation of alcohol **83** was observed to be $[\alpha]^{24}_{D}$= -11.5º (*c* = 0.0412 g·mL^{-1}, $CHCl_3$). The resulting alcohol **83** was then subjected to the allylic transposition of Myers,[50] and diene **71** was obtained in 45% yield (Scheme 47). The specific rotation of diene **71** was determined to be $[\alpha]^{24}_{D}$= +24.5º (*c* = 0.034 g·mL^{-1}, $CHCl_3$).



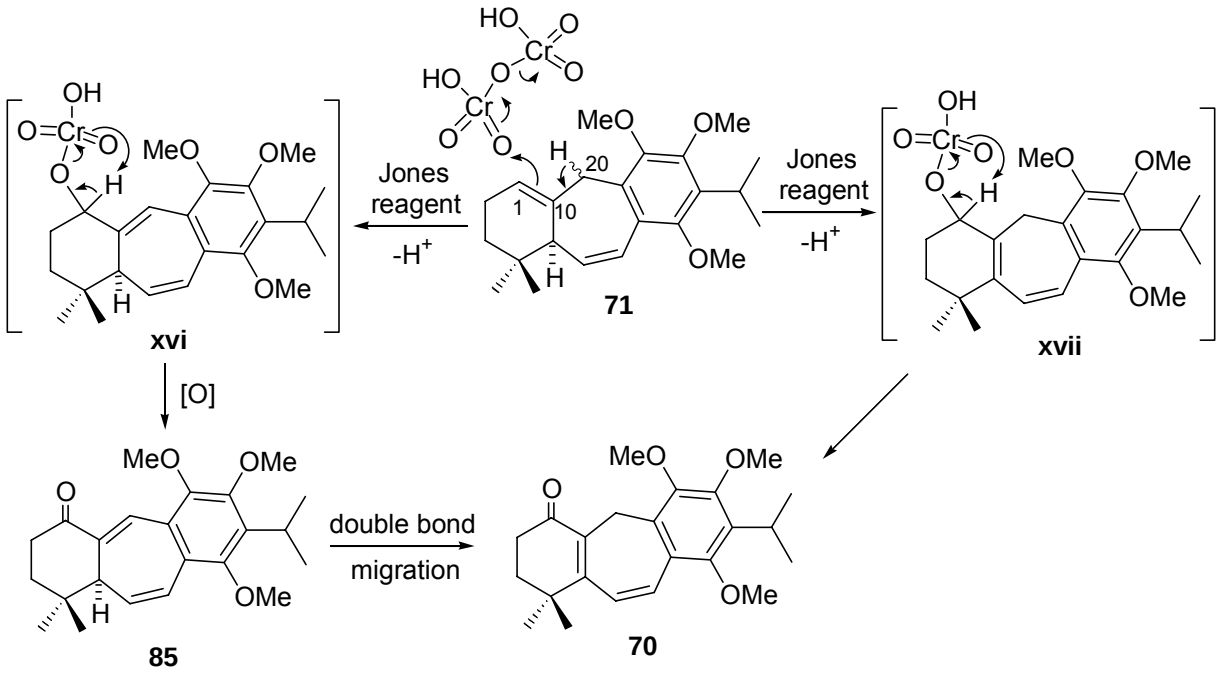
Scheme 47

We expected that the styrenyl double bond would be hydrolyzed preferentially to afford benzylic alcohol **84**; oxidation of alcohol **84** would give ketone **61** (Scheme 48). However, diene **71** did not hydrolyze under various acidic conditions and oxymercuration, hydroboration and Wacker reactions[51] were also studied without success. Diene **71** was treated with Jones reagent



Scheme 48

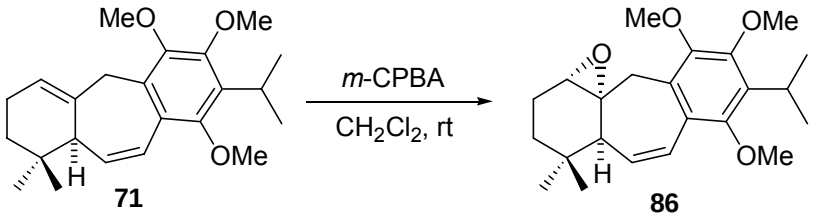
in hopes of first hydrating the C(6)−C(7) double bond, followed by the in situ oxidation of the benzylic alcohol. Instead, dienone **70** was obtained in quantitative yield. A mechanism that accounts for the formation of dienone **70** is generalized in Scheme 49. In the first step, the oxidant adds to the C(1) carbon with migration of double bond to the conjugated C(20) benzylic position and forms intermediate **xvi** due to the stabilizing effect of the conjugated C(10)−C(20) double bond; next, intramolecular hydrogen abstraction at C(1) by another oxygen on Cr(IV) oxidizes chromate ester **xvi** to enone **85**. In the last step enone **85** undergoes double bond rearrangement to generate conjugated dienone **70**. Another plausible pathway is the generation of intermediate **xvii**, which can be oxidized to dienone **70** directly.



Scheme 49

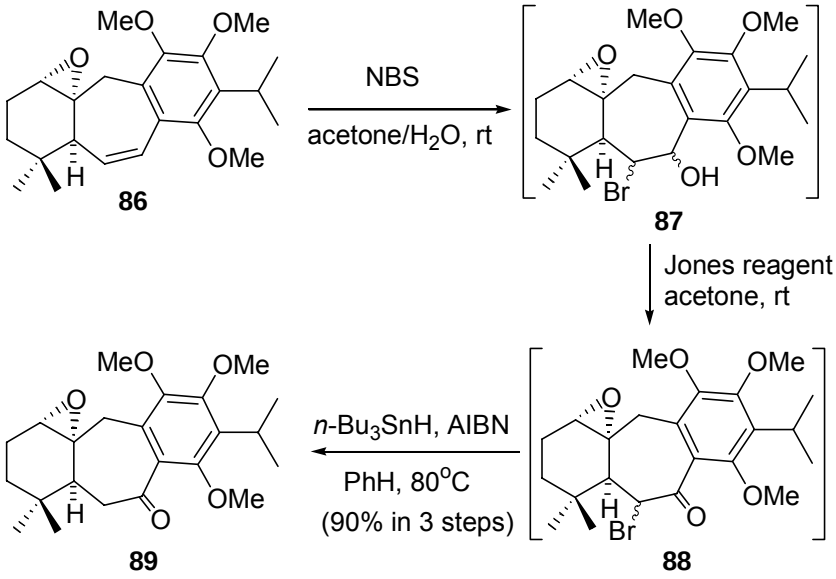
When diene **71** was reacted with NBS/H_2O, a mixture of unknowns was rapidly produced; however, a trisubstituted alkene was not present (Scheme 50). Selective epoxidation of the

trisubstituted alkene took place when diene **71** was treated with one equivalent of *m*-CPBA. Epoxide **86** was obtained with almost no influence on the C(6)−C(7) double bond. Epoxidation occurred from the α-face of the C(1)−C(10) double bond; the specificity of this facial selectivity will be discussed later in this chapter.



Scheme 50

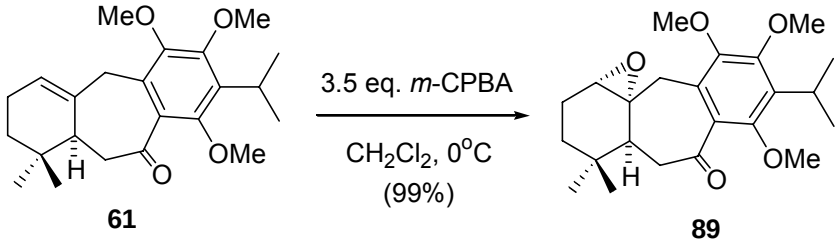
Molecular models of diene **71** suggested that the C(6)−C(7) double bond is not conjugated to the aromatic ring due to ring strain within the seven-membered ring. Thus, the electron density as well as the reactivity of this double bond is less than those of an ordinary styrenyl alkene. This analysis explains why the more electron-dense trisubstituted double bond reacts exclusively to form epoxide **86**.



Scheme 51

Since the only encouraging result obtained was the selective formation of epoxide **86**, we decided to postpone opening it up to generate a C(10) tertiary alcohol until later on. With the tri-substituted double bond "protected" as an epoxide, we were curious to learn if the styrenyl double bond would react under harsher conditions.

When this epoxide **86** was treated with NBS/H_2O, the C(6)−C(7) double bond was rapidly consumed to give a mixture of diastereoisomeric bromohydrins (Scheme 51). The oxidation of this mixture of bromohydrins (cf. **87**) produces bromoketone **88**, which presumably consists of two isomers due to the stereochemistry at C(6). Removal of the C(6) bromide from ketone **88** using *n*-Bu_3SnH/AIBN gave epoxy ketone **89** as single product in 90% overall yield from epoxide **86**. This structure was also confirmed when alkene **61**, obtained from our first generation synthesis, was epoxidized using *m*-CPBA (Scheme 52).

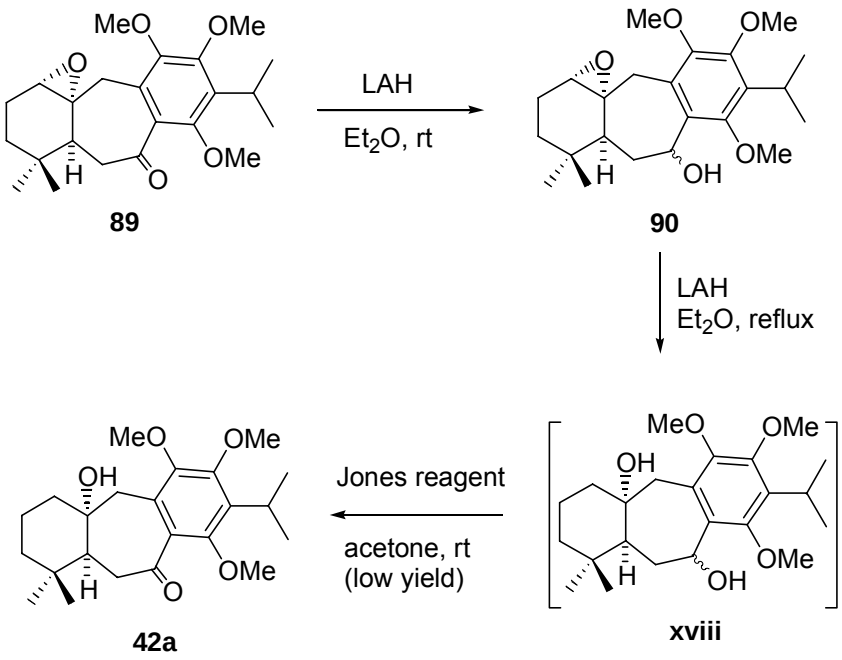


61 **89**

Scheme 52

We expected to transform ketone epoxide **89** into alcohol **42a** by a reductive epoxide opening of **89**. However, LAH only reduced the C(7) carbonyl to give benzylic alcohol **90**; reduction of the epoxide present in **90** did not occur even with large excess of LAH (Scheme 53). Other hydride sources such as Superhydride[52] or *n*Bu_3SnH-NaI[53] were also ineffective on **89**. Epoxide **89** did open to give diol **xviii** under refluxing ethereal solutions of LAH but only after

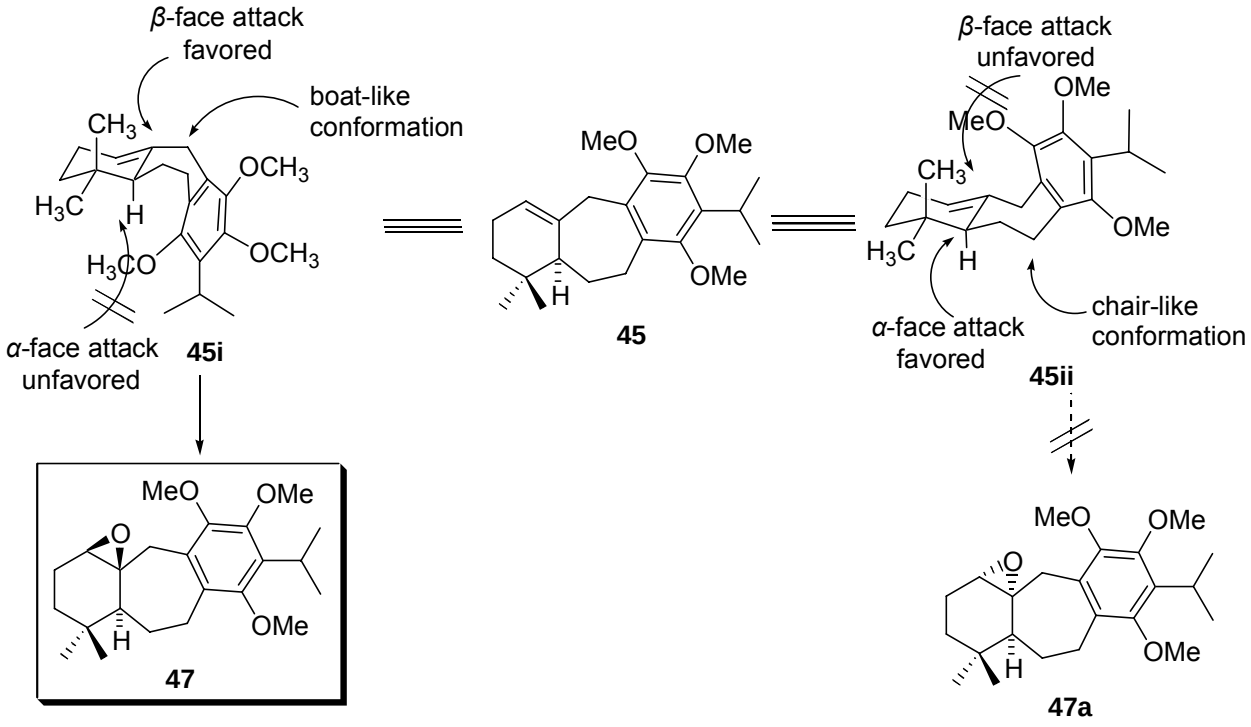
several days. Diol **xviii** was oxidized by Jones reagent to produce ketone alcohol **42a**, but in low yield.



Scheme 53

When ketone alcohol **42a** was reacted with Ag(II)O/7 *N* HNO_3 in acetone, a quinone was formed. However, this quinone is not komaroviquinone based on its R_f value and its ^1H NMR data. These observations dictated that the stereochemistry on C(10) alcohol was wrong. Therefore, a systematic investigation of the facial selective epoxidation of several precursors was conducted.

As shown in Scheme 54, when a chair-like seven-membered ring is predicted to be the most stable conformation of alkene **45**, epoxidation of the C(1)−C(10) double bond takes place from the α-face and produces epoxide **47a** with a *cis* relative stereochemistry of the C(10) epoxide oxygen and the C(5) methine.

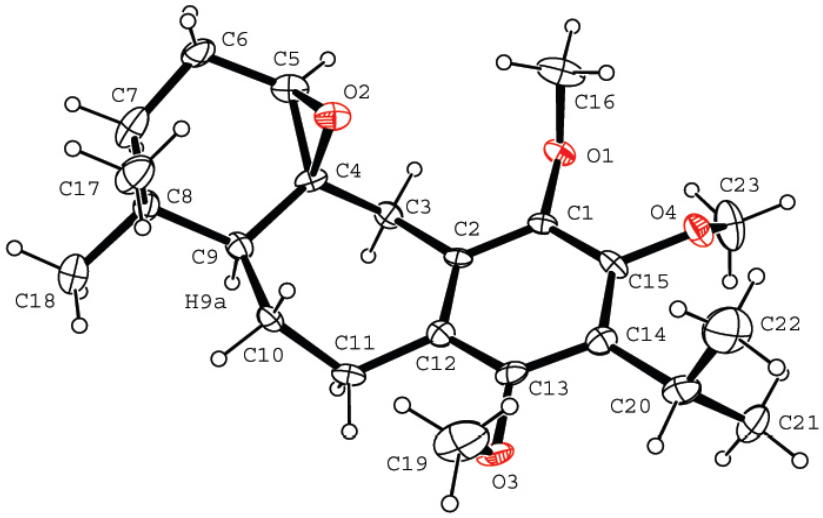


Scheme 54

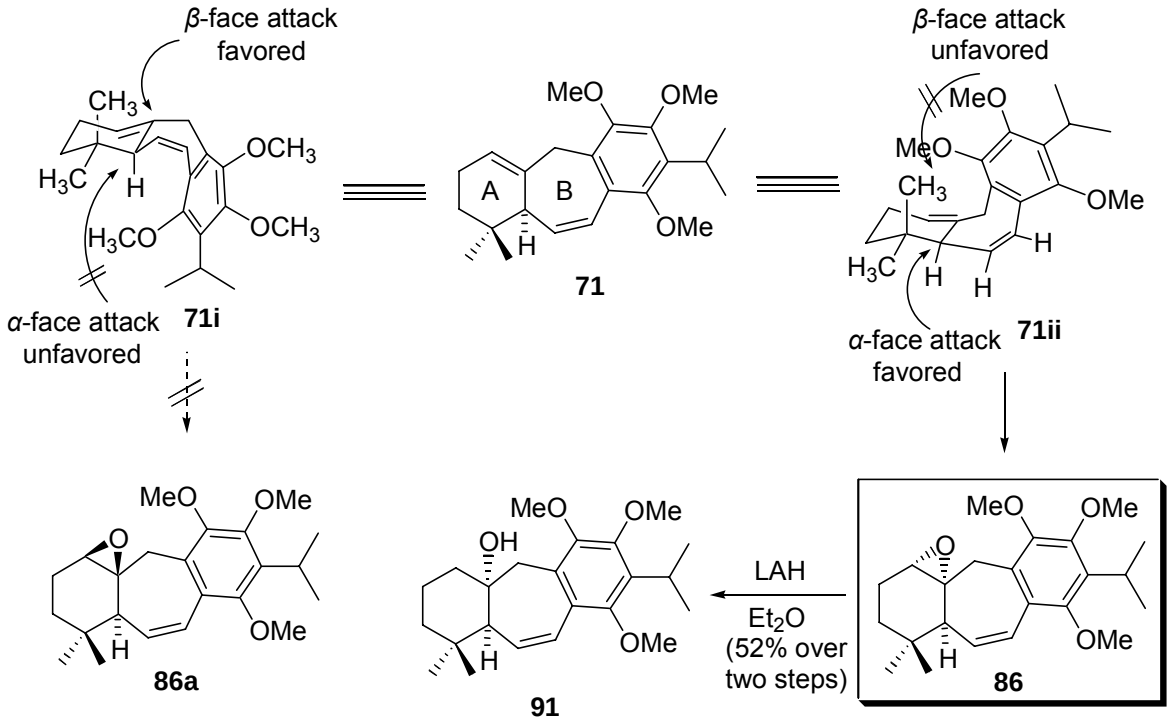
An X-ray crystal structure of epoxide **47a** was obtained (Figure 1 and Appendix II) and, to our surprise, the absolute stereochemistry was determined to be **47** which has a trans relationship between the C(10) epoxide oxygen and the C(5) methine. In light of this, we concluded that alkene **45** must prefer a boat-like conformation, so that epoxidation occurs from the *β*-face of the alkene and produces epoxide **47**.

Based on this observation, we expected that the same facial- and regioselectivity would be obtained if diene **71** were epoxidized, cf. **86a**. Nevertheless, tertiary alcohol **42a**, obtained from epoxide **86**, could not be oxidized to komaroviquinone; whereas, komaroviquinone has already been synthesized from alcohol **42**. We concluded that alcohol **42a** has a *cis* relationship between the C(10) epoxide oxygen and the C(5) methine (Scheme 53).

Figure 1: X-ray structure of epoxide **47**



As shown in Scheme 55, conformational analysis of diene **71** shows that the endocyclic C(6)−C(7) double bond, plus an exocyclic alkene at C(10), makes conformer **71ii** favored over

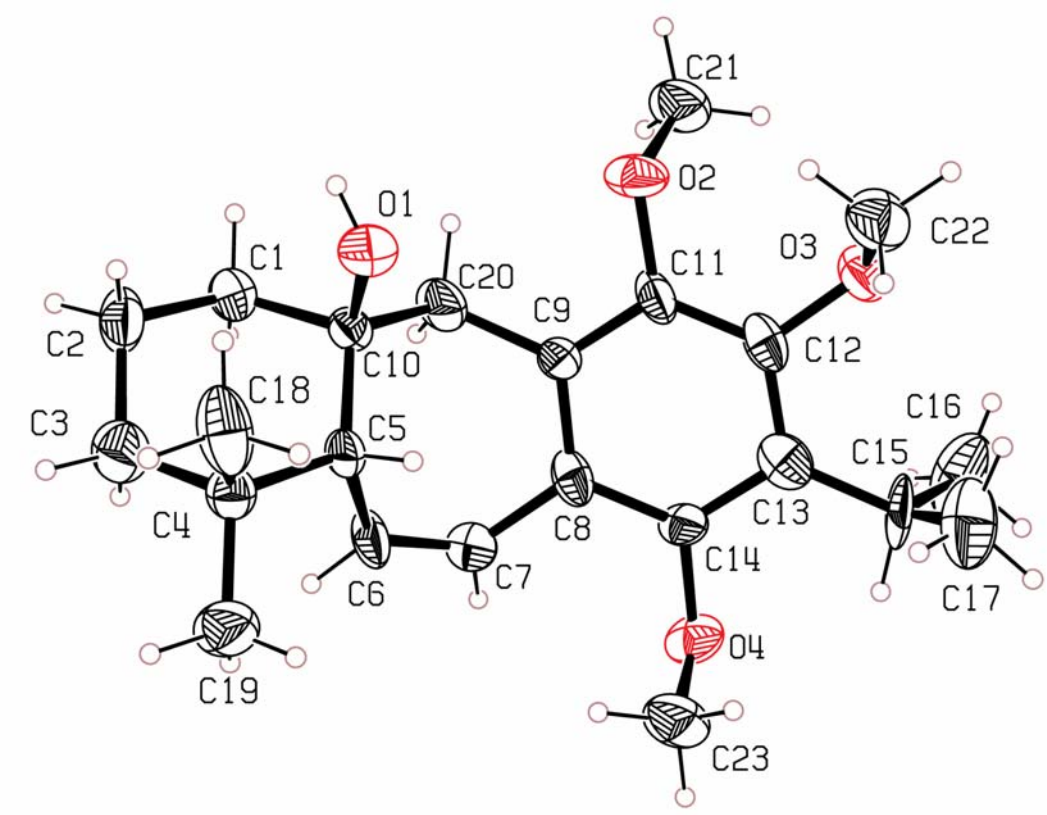


Scheme 55

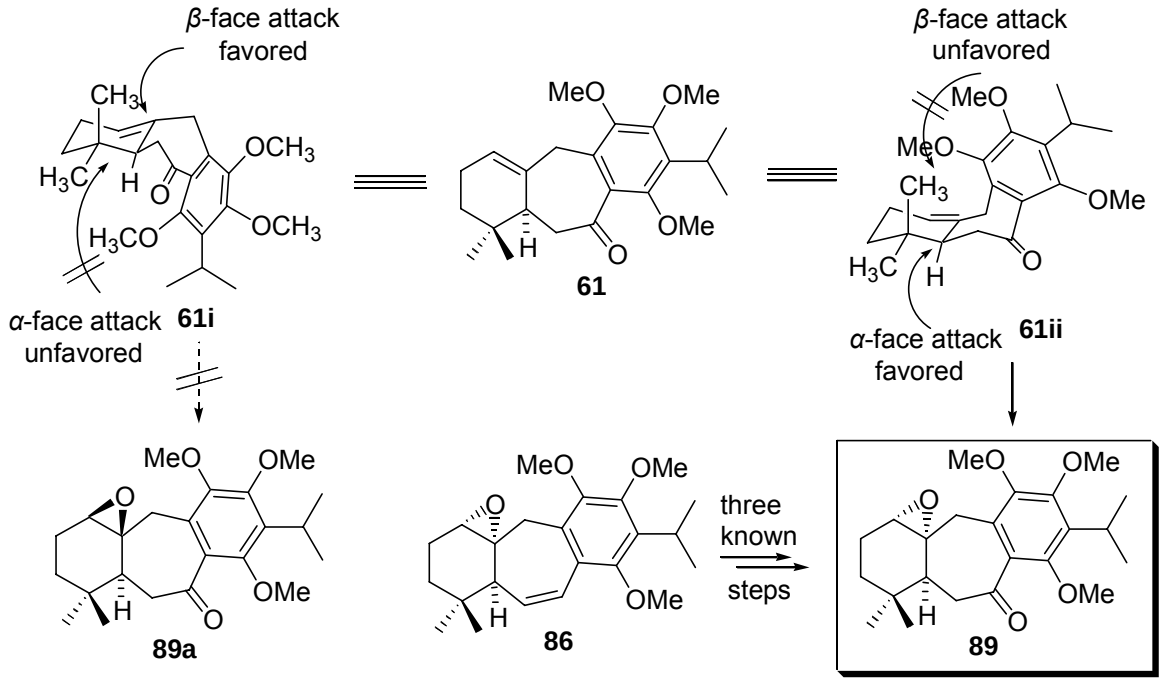
conformer **71i**. Hence, the oxidant accesses the α-face of conformer **71ii** and gives epoxide **86** exclusively. The "cis" stereochemistry also explains why epoxide **86** was so sluggish to LAH opening since the β–face of the epoxide **86** is so sterically hindered. On the other hand, if conformer **71i** dominates, the resulting *trans* epoxide **86a** will lead to the formation of **42** which can be smoothly oxidized to komaroviquinone.

When epoxide **86** was treated with excess LAH, alcohol **91** was obtained in 52% overall yield from diene **71** (Scheme 55). The X-ray structure of alcohol **91** shows a "cis" stereochemistry of the C(10) hydroxyl group and C(5) methine, which supports our conformational analysis (Figure 2 and Appendix III).

Figure 2: X-ray structure of epoxide **91**



Since ketone epoxide **89** can be prepared from ketone **61** using *m*CPBA, and it has the identical NMR data as those obtained from epoxide **86** (Scheme 51), we conclude that the favored conformation in ketone **61** must be **61ii** and the stereochemistry of epoxide **89** is "cis" between the epoxy oxygen and the C(5) methine (Scheme 56).



Scheme 56

In order to further understand our proposed rational, the lowest zero point energies (H) of both *cis* and *trans* conformers of alkene **45**, diene **71** and ketone **61** were calculated using the B3LYP/6-31G* method.[54] The definition of *cis* or *trans* conformation is based on the relative stereochemistry of C(5) methine and the axial hydrogen of C(20) in the structure. As shown in table 2, the equilibrium constant (K) in the interconversion of both conformers of each compound was calculated based on the assumption that there was no entropy change (ΔS). As we can see, all those three compounds favor *cis* conformations (**45ii**, **71ii** and **61ii**) (See Appendix

IV for calculated structures). The percentages of *cis* conformers in diene **71** and ketone **61**, 99.6% and 98.2% respectively, are very high. These results predict that the epoxidation on both diene **71** and ketone **61** can only take place from the *α*-face of the double bonds by kinetic control, hence support our early analysis (cf. Scheme 55 and 56).

Table 2: Calculation of the conformations of alkene **45**, diene **71** and ketone **61**

	H_{cis}[a]	H_{trans}	ΔH ($\sim\Delta G$)[b]	$K_{[cis]/[trans]}$[c]	cis %[d]
Alkene **45**	-1122.017960	-1122.016313	-4.32	5.7	85.1%
Diene **71**	-1120.818714	-1120.813613	-13.39	221.4	99.6%
Ketone **61**	-1196.045933	-1196.042178	-9.86	53.5	98.2%

[a] Calculated using B3LYP/6-31G* method, H = lowest zero point energy (Hartree); [b] ΔG ($kJ.mol^{-1}$) = $\Delta H - \Delta ST$, where $\Delta ST \approx 0$; [c] Equilibrium constant $\ln K = -\Delta G/RT$, $R = 8.314 \times 10^{-3}$ $kJ.mol^{-1}.K^{-1}$, $T = 298K$; u[d] percentage of cis conformer in the mixture.

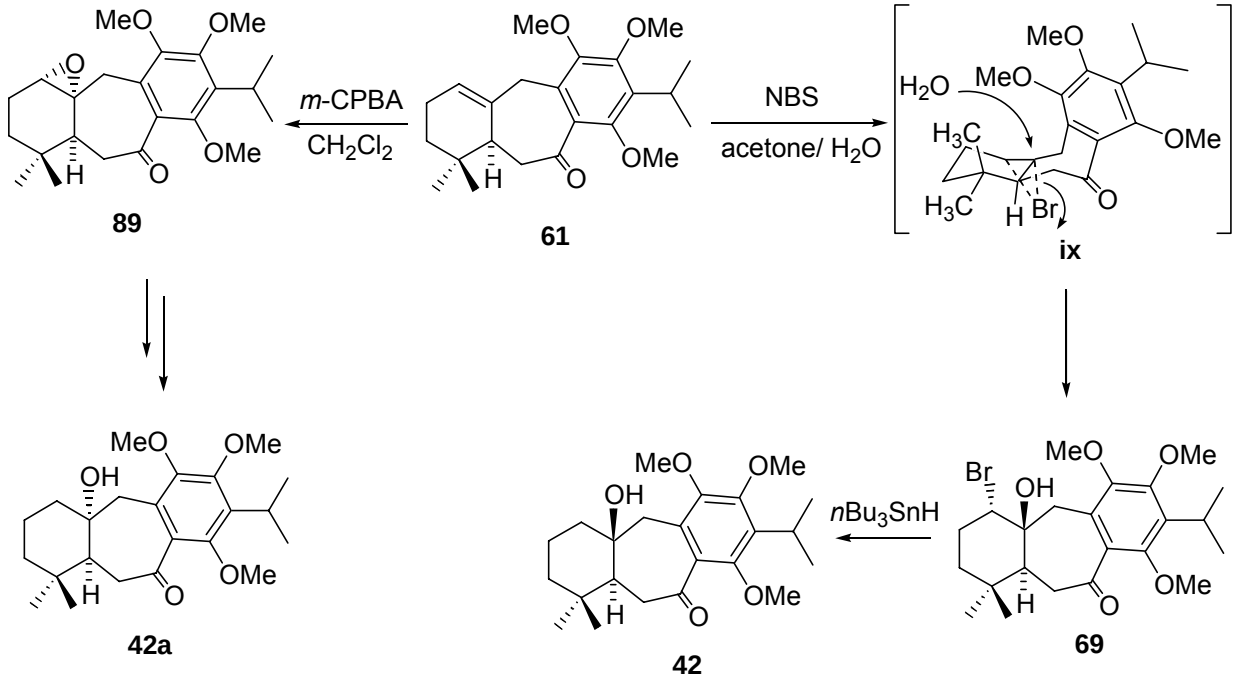
However, this calculation shows that the *cis* conformer of alkene **45ii** is the most stable conformer and exists in 85.1% in the mixture of conformers. Consequently, the epoxidation would have undergone from the *α*-face of alkene **45** to give epoxide **47a**. This result is opposite to the X-ray structure of epoxide **47**.

It can be reasoned that the ~15% of *trans* conformer reacts quickly to give a thermodynamically stable epoxide, such as **47**; whereas, although there is more *cis* conformer, epoxide **47a** is less stable than epoxide **47**. Hence, thermodynamic control results in the consumption of the *trans* conformer of alkene **45** and leaves the *cis* conformer unchanged. It can be easily understood that since the seven-membered B-ring in alkene **45** is flexible in the interconversion of conformations, the remaining *cis* conformer in the epoxidation would convert

to *trans* conformer quickly before it can be oxidized. Therefore, the only observed product has to be epoxide **47**.

The structure of epoxide **47** has a perfect chair-like conformation on its B-ring; whereas, the B-ring in epoxide **47a** deviates from a chair-like conformation, which indicates higher energy than epoxide **47**.

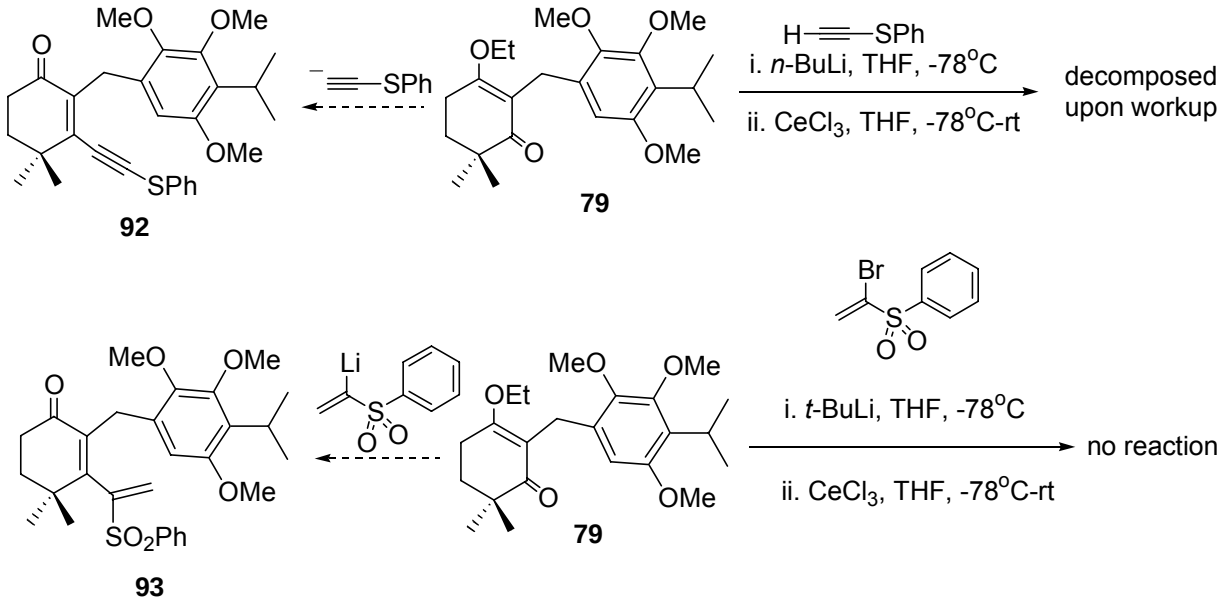
Tertiary alcohol **42** was formed with the correct stereochemistry for komaroviquinone, because bromonium ion formation occurs from the α–face of the C(1)−C(10) double bond causing the C(10) hydroxyl group to be on the β–face of the molecule (Scheme 57).



Scheme 57

More Efforts on Functionalized Cycloalkylation

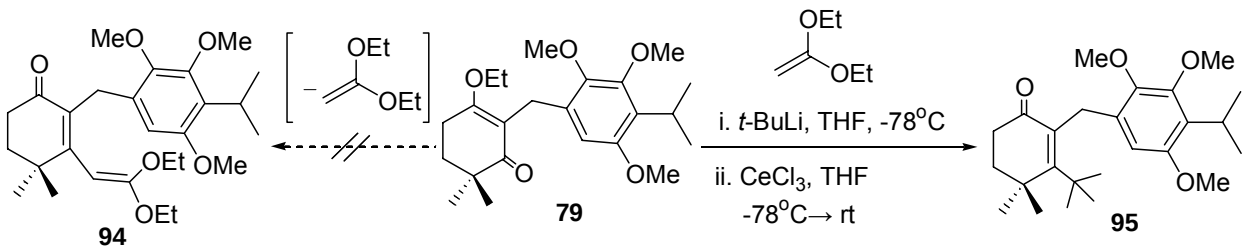
Other functionalized conjugated dienones were prepared for cycloalkylation. As shown in Scheme 58, phenylmercapto ethyne was made and added to ketone **79** to prepare cycloalkylation precursor **92**. Alkylation of the acetylide anion consumed the starting material; however, the resulting intermediate decomposed even upon mild work up.



Scheme 58

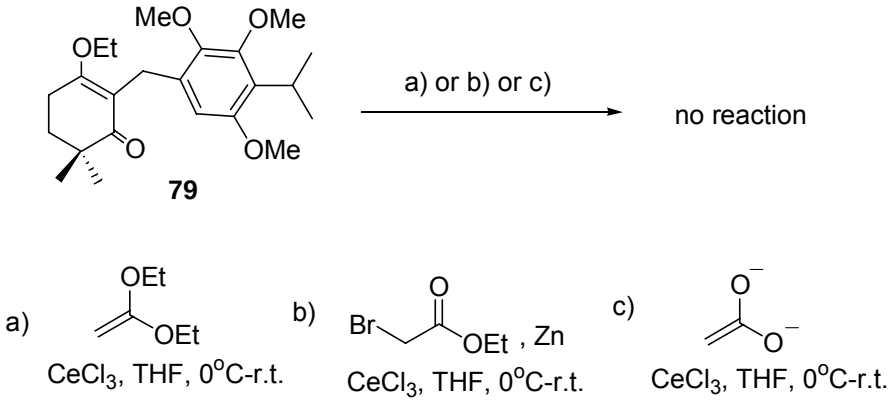
1-(Bromovinyl)-phenylsulfoxide[55] was then prepared from phenyl vinylsulfoxide through bromination, followed by dehydrobromination with triethylamine, in expectation to make **93** after alkylation (Scheme 58). However, the 1,2-addition of this nucleophile failed, presumably due to the steric hindrance.

We then attempted to deprotonate one of the olefinic hydrogens of 1,1-diethyoxy ethylene using *tert*-butyllithium and then allow this anion add to **79** to make **94**. Indeed the *tert*-butyl group from the *tert*-butyllithium added despite how bulky the *t*-butyl group is (Scheme 59).



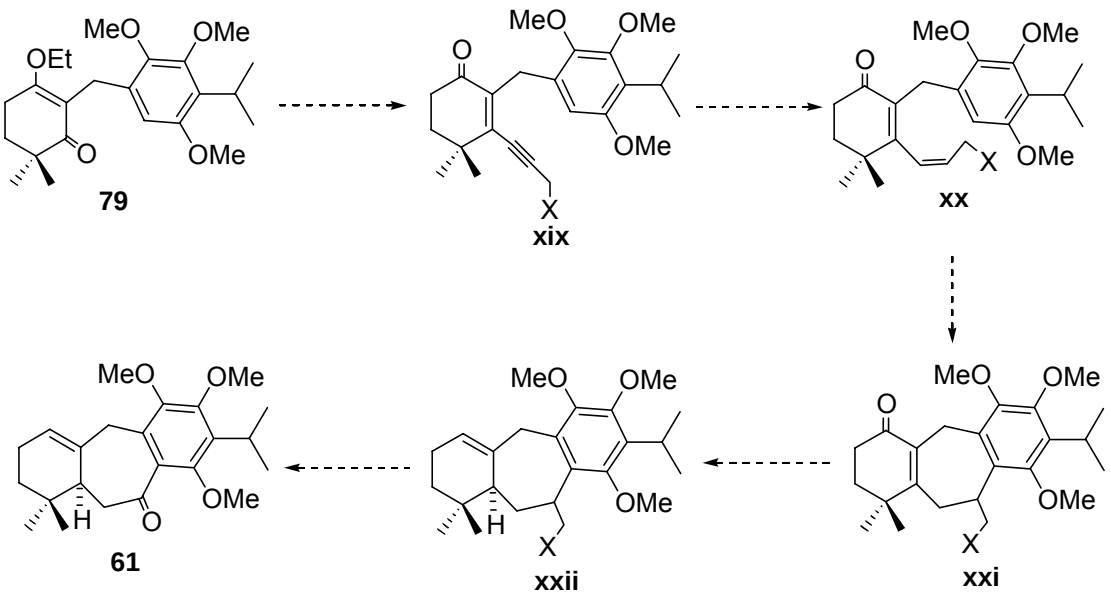
Scheme 59

Weak nucleophiles do not add in 1,2-fashion to sterically hindered ketone **79** (Scheme 60). We therefore considered adding a carbon chain to our substrate.



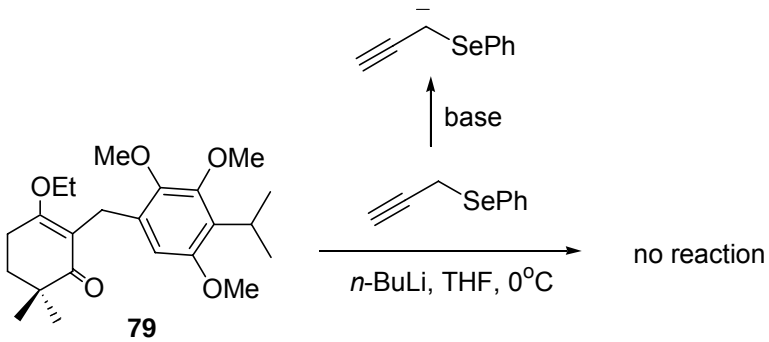
Scheme 60

We have observed that acetylide anions add to hindered carbonyls, independent of steric hindrance, and the reaction adducts are stable to acidic workup (cf. Scheme 39 and 41). An interesting extension of this involves using the anions derived from propynes, or 1-butynes as the nucleophiles. 1,2-Addition of these acetylide anions would produce alkenynes, such as **xix** (Scheme 61), which could be reduced to permit the desired intramolecular Friedel-Crafts reaction (**xx** → **xxi**). If "X" is an easy group to eliminate, selective oxidation of the resulting exocyclic double bond would give us ketone **61** which can then be transformed to komaroviquinone (**1**).



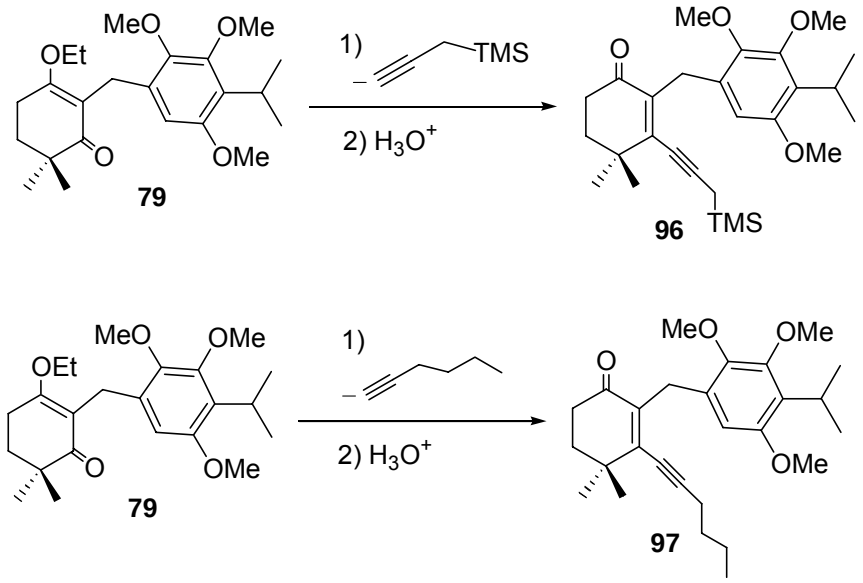
Scheme 61

An ideal alkyne derivative, we speculated, was where "X" was a selenium derivative, since after cycloalkylation the exocyclic double bond could be formed very easily by eliminating a selenooxide. Unfortunately, 2-(propenyl)-selenobenzene, which could be prepared from phenyl selenium anion and propargyl bromide, failed to add to ketone **79** (Scheme 62). Analysis of the literature, we found that the base will first deprotonate the α- position of the selenium and not form the requisite acetylide anion.



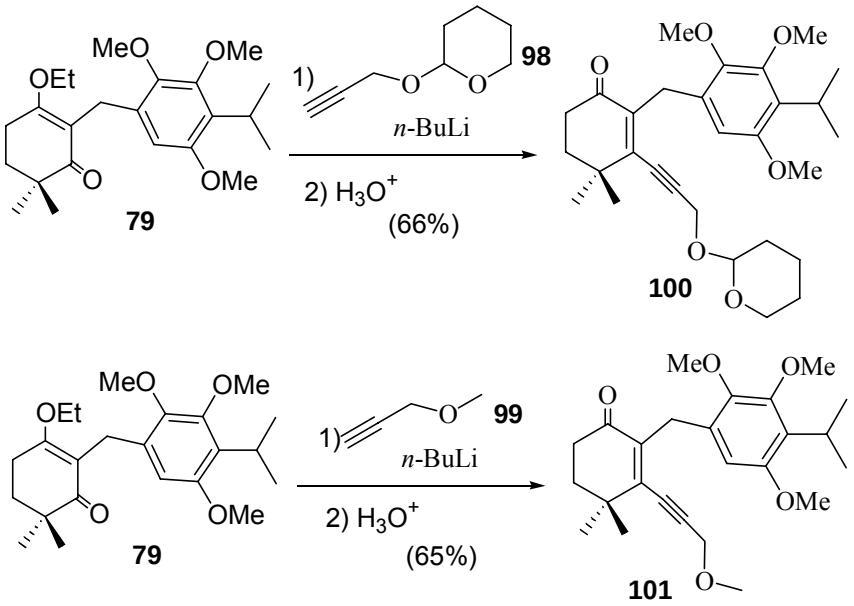
Scheme 62

Protected propargyl alcohols became our next reagents, since dehydration would generate the exocyclic double bond on C(7). A *para*-methoxybenzylic (PMB) group was chosen to be the protecting group since it can be removed by DDQ, a mild reagent, which would avoid functional group change at other sites of the molecule. Unfortunately, all attempts to add the anion derived from PMB propargyl ether failed. Next, the anion derived from trimethyl propargylsilane was used. It added to enone **79** smoothly and gave us a high yield of product **96** (Scheme 63). Similarly, the anion produced from 1-hexyne rapidly added to enone **79** to produce **97**.



Scheme 63

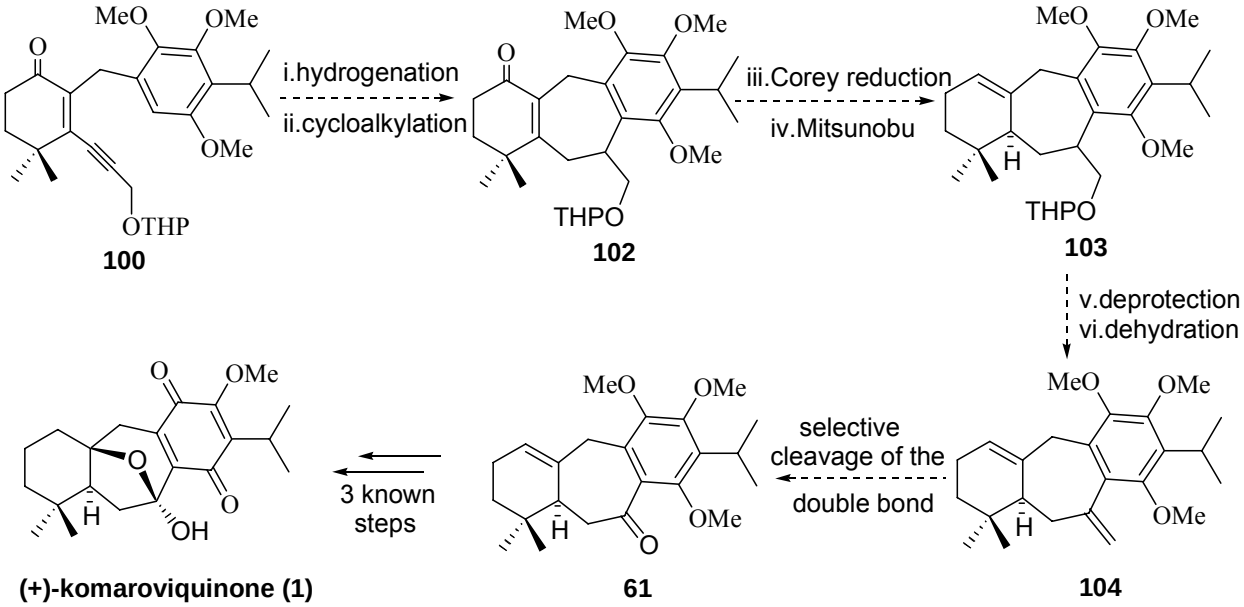
These results encouraged us to prepare PBA and methyl protected propargyl alcohols **98** and **99**, respectively (Scheme 64). Interestingly, the anions of these alkynes added to enone **79** smoothly to give **100** and **101**, even though we were afraid that alkyne **98** contains no less steric hindrance than that in PMB group.



Scheme 64

Future Work to Complete the Synthesis of (+)-Komaroviquinone (1)

Based on our obtained enynone **100** and **101** (or other enynones which could be easily prepared using this alkylation method), our future work will target an asymmetric synthesis of (+)-komaroviquinone (**1**). As shown in Scheme 65, for example, enynone **100** could be transformed to enone **102** via hydrogenation and Friedel-Crafts cycloalkylation. The application of Corey reduction and Myers's Mitsunobu chemistry would produce optically pure alkene **103**. Deprotection of the THP group, followed by dehydration of the resulting primary alcohol, would give diene **104**. At this stage, we expect to see the differentiation of the two double bonds, which can preferentially cleave the exocyclic double bond to generate ketone **61**. Since the C(5) methine should stay unchanged in the transformations from alkene **103**, ketone **61** must be a single enantiomer. Finally, after three known transformations (+)-komaroviquinone (**1**) should be synthesized.

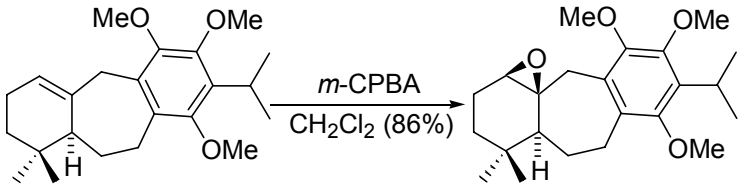


Scheme 65

In summary, a first generation synthesis of (±)-komaroviquinone (**1**) was accomplished via a benzylic oxidation and aromatic oxidation pathway. However, to date our efforts to make the optically active (+)-komaroviquinone (**1**) have failed and instead produced alcohol **42a** with the wrong stereochemistry at C(10), because of conformational biasing of the two faces of a double bond. In the course of our work toward a synthesis of (+)-komaroviquinone (**1**), a novel Friedel-Crafts cycloalkylation method has been developed to incorporate a C(6)−C(7) styrenyl double bond. Further investigation showed the potential application of longer chain alkynes to achieve the synthesis of (+)-komaroviquinone (**1**).

Experimental Section

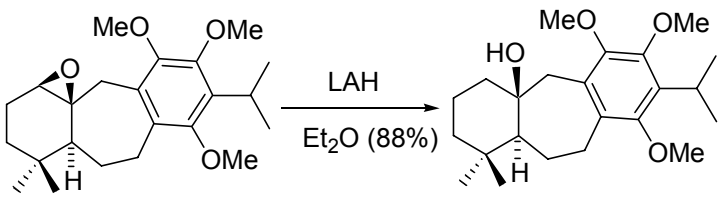
General Procedures. All reactions were run under a nitrogen atmosphere and monitored by TLC analysis. Unless otherwise indicated, all ethereal workups consisted of the following procedure: the reaction was quenched at room temperature with saturated aqueous ammonium chloride. The organic solvent was removed under reduced pressure on a rotary evaporator, and the residue was taken up in ether, washed with brine, and dried over anhydrous magnesium sulfate. Filtration, followed by concentration at reduced pressure on a rotary evaporator and at 1 torr to constant weight, afforded a crude residue which was purified by flash chromatography using silica gel 60 (230-400 mesh ASTM) and elution with distilled reagent grade petroleum ether and diethyl ether. Proton NMR spectra were obtained in $CDCl_3$ and were calibrated using trace $CHCl_3$ present (δ 7.27) as an internal reference. The IR spectra were obtained using Avatar360FT-IR and high resolution MS were taken using LCT Premier from Waters.



45 **47**

Epoxide 47 from alkene 45: To a solution of alkene **45** (164 mg, 0.46 mmol) in anhydrous DCM (7 mL) at 0 ℃ was added *m*-CPBA (77%, 205 mg, 0.92 mmol, 2.0 equivalents). The resulting reaction mixture was stirred at 0 ℃ for 2 h during which time 50 mg of more 77% of *m*-CPBA was added and the mixture was stirred for an additional 15 minutes. Aqueous NaOH (1

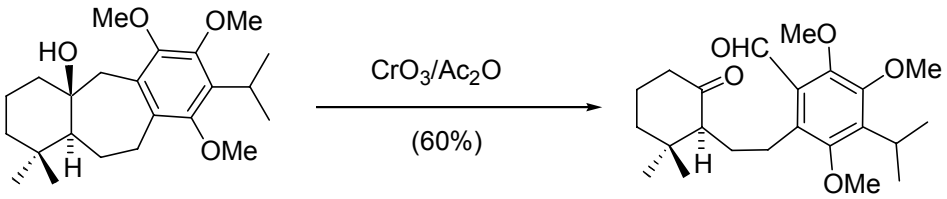
mL, 0.5 *M*) was added to quench the reaction. Ethereal workup followed by silica gel chromatographic purification (elution with pet ether: ether, 8:1) afforded 148.5 mg (86%) of epoxide **47** (TLC, hexane: EtOAc, 4:1, R_f **47** = 0.75): ^{1}H (400 MHz) δ 0.77 (s, 3H), 0.90 (s, 3H), 0.4-0.98 (m, 1H), 1.03-1.11 (m, 1H), 1.34 (d, *J* = 7.2 Hz, 6H), 1.50-1.60 (m, 1H), 1.64-1.70 (m, 1H), 1.86-1.94 (m, 1H), 2.65-2.80 (m, 2H), 3.07-3.18 (m, 1H), 3.20-3.24 (m, 1H), 3.25-3.34 (m, 1H), 3.42 (heptet, *J* = 7.2 Hz, 1H), 3.68 (s, 3H), 3.70 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (400 MHz) 22.10 (t), 22.21 (q), 22.27 (q), 24.05 (q), 25.14 (t), 26.08 (d), 26.24 (t), 29.69 (q), 31.20 (s), 32.20 (t), 36.44 (t), 46.42 (d), 59.97 (q), 60.29 (s), 60.39 (q), 62.15 (d), 62.51 (q), 129.82 (s), 129.93 (s), 132.87 (s), 148.07 (s), 150.72 (s), 151.42 (s) ppm; HR-MS: $[M+H]^+$ = 375.2523; $[M+H]^+_{calculated}$ = 375.2535; IR (neat): 2924, 2854, 1458, 1265, 740 cm^{-1}.



47 **43**

Tertiary alcohol 43 from epoxide 47: To a solution of epoxide **47** (147mg, 0.393 mmol) in freshly distilled diethyl ether (6 mL) under nitrogen atmosphere at 0 ℃ was added LAH (22.4 mg, 0.59 mmol, 1.5 equivalents). The reaction mixture was stirred at rt overnight. More LAH (22.4 mg, 0.59 mmol, 1.5 equivalents) was added and the mixture was stirred for additional 24 h. (Since the product has identical R_f value with that of epoxide **47**, the reaction process was monitored on ^{1}H NMR.) Water was added dropwise to quench the reaction. Ethereal workup followed by silica gel chromatographic purification (elution with pet ether: ether, 4:1) afforded 130 mg (88%) of pure alcohol **43** (TLC, hexane: EtOAc, 4:1, R_f **43** = 0.75): ^{1}H (400 MHz) δ

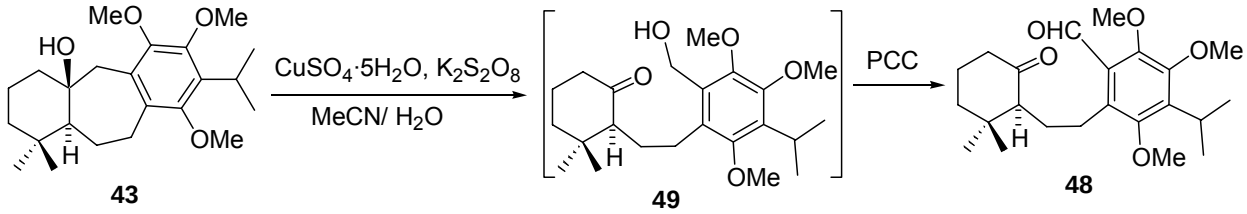
0.90 (s, 3H), 0.94 (s, 3H), 1.18-1.30 (m, 3H), 1.34 (d, J = 7.2 Hz, 3H), 1.36 (d, J = 7.2 Hz, 3H), 1.40-1.50 (m, 2H), 1.51-1.61 (m, 1H), 1.80-1.90 (m, 2H), 2.02-2.10 (m, 1H), 2.27 (dd, J_1 = 11.2 Hz, J_2 = 14.0 Hz, 1H), 2.51 (d, J = 14.0 Hz, 1H), 3.25 (d, J = 14.0 Hz, 1H), 3.30-3.37 (m, 1H), 3.43 (heptet, J = 7.2 Hz, 1H), 3.66 (s, 3H), 3.77 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (400 MHz) 18.81 (t), 21.62 (q), 22.11 (q), 22.32 (q), 23.69 (t), 26.06 (d), 27.23 (t), 32.23 (q), 34.34 (s), 41.53 (t), 42.13 (t), 42.46 (t), 58.38 (d), 60.35 (q), 60.42 (q), 62.30 (q), 70.66 (s), 128.91 (s), 132.49 (s), 133.43 (s), 149.33 (s), 150.76 (s), 150.88 (s) ppm; HR-MS: $[M+H]^+$ = 377.2686; $[M+H]^+_{calculated}$ = 377.2692; IR (neat): 2825, 2854, 1458, 1264, 739, cm^{-1}.



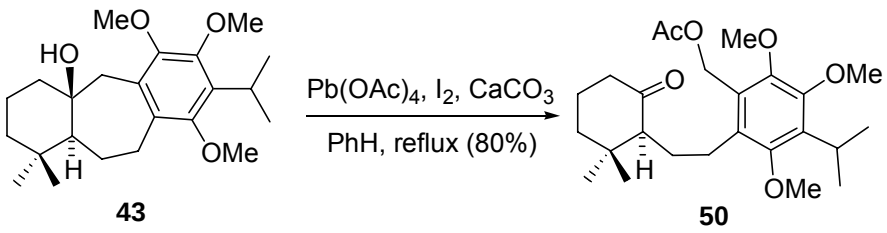
43 **48**

Dione 48 by the oxidation of alcohol 43: To a solution of alcohol **43** (12.8 mg, 0.034 mmol) in freshly distilled acetic anhydride (0.5 mL) under nitrogen atmosphere at rt was added chromium trioxide (5.1 mg, 0.051 mmol, 1.5 equivalents). The reaction mixture was stirred overnight. Unreacted acetic anhydride was then removed via vacuum and the crude product was purified on silica gel chromatography (elution with pet ether: ether, 8:1) without aqueous workup to afford 8.0 mg (60%) of dione **48** (TLC, hexane: EtOAc, 4:1, R_f **48** = 0.60): ^{1}H (400 MHz) δ 0.77 (s, 3H), 1.00 (s, 3H), 1.35 (d, J = 6.8 Hz, 3H), 1.37 (d, J = 6.8 Hz, 3H), 1.46-1.55 (m, 1H), 1.56-1.62 (m, 2H), 1.82-1.92 (m, 3H), 2.23 (dd, J_1 = 2.0 Hz, J_2 = 10.8 Hz, 1H), 2.27-2.38 (m, 1H), 2.48-2.56 (dt, J_1 = 5.6 Hz, J_2 = 12.8 Hz, 1H), 2.67-2.76 (dt, J_1 = 5.2 Hz, J_2 = 10.8 Hz, 1H), 2.82-2.91 (dt, J_1 = 5.2 Hz, J_2 = 12.8 Hz, 1H), 3.45 (hetptet, J = 6.8 Hz, 1H), 3.71 (s, 3H), 3.89 (s, 3H),

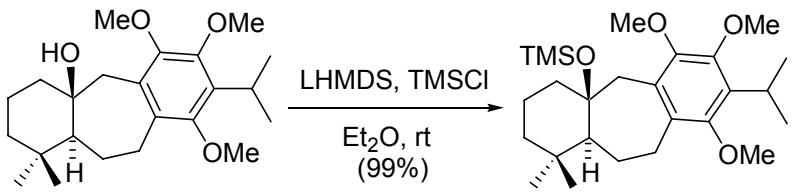
3.91 (s, 3H); ^{13}C NMR (400 MHz) 21.88 (q), 21.96 (q), 23.31 (q), 23.35 (t), 25.38 (t), 26.46 (t), 26.97 (d), 29.29 (q), 38.52 (t), 39.66 (s), 40.85 (t), 60.69 (q), 61.50 (d), 61.89 (q), 62.55 (q), 126.80 (s), 133.40 (s), 142.88 (s), 151.43 (s), 153.04 (s), 154.60 (s), 192.13 (d), 214.30 (s) ppm.



Oxidation of alcohol 43 with $K_2S_2O_8$/$CuSO_4$: To a solution of alcohol **43** (9.5 mg, 0.025 mmol) and $CuSO_4·5H_2O$ (7.5 mg, 0.030 mmol, 1.2 equivalents) in MeCN/H_2O (5 mL/3 mL) under nitrogen atmosphere was added $K_2S_2O_8$ (11 mg, 0.041 mmol, 1.6 equivalents). The reaction mixture was heated at 90 ℃ for 15 minutes during which time TLC showed complete consumption of alcohol **43** and produced a polar spot. The reaction mixture was cooled to rt and ethereal workup afforded 10 mg of crude product. This crude compound was oxidized directly with PCC (16.2 mg, 0.075 mmol, 3.0 equivalents) to give 5 mg (66% over two steps) dione **48** which could prove the structure of **49**: ^{1}H (400 MHz) δ 0.73 (s, 3H), 1.06 (s, 3H), 1.34 (d, J = 7.2 Hz, 6H), 1.55-1.70 (m, 3H), 1.75-1.96 (m, 3H), 2.22 (d, J = 10.8 Hz, 1H), 2.30-2.50 (m, 3H), 2.52-2.62 (dt, J_1 = 4.4 Hz, J_2 = 12.0 Hz, 1H), 3.38 (heptet, J = 7.2 Hz, 1H), 3.68 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 4.67 (d, J = 12.0 Hz, 1H), 4.81 (d, J = 12.0 Hz, 1H).

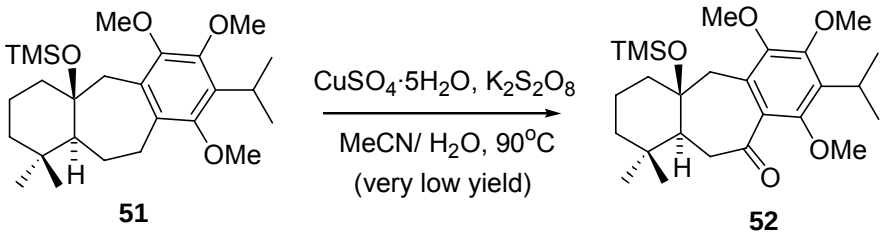


Acetate 50 from the oxidation of 43 with $Pb(OAc)_4/I_2/CaCO_3$: A mixture of $Pb(OAc)_4$ (35 mg, 0.079 mmol, 1.5 equivalents), I_2 (13.5 mg, 0.053 mmol, 1.0 equivalent) and $CaCO_3$ (5.3 mg, 0.053 mmol, 1.0 equivalent) in anhydrous benzene (2 mL) was refluxed under nitrogen atmosphere for 10 minutes. A solution of alcohol **43** in anhydrous benzene (1 mL) was added to the refluxing mixture, and the resulting solution was refluxed for additional three hours. The reaction mixture was cooled to rt and was diluted with diethyl ether (15 mL). Sodium thiosulfate (2 mL of a 10% aqueous solution) was used to wash the ethereal layer, followed by washing with brine (2 mL). The organic layer was dried over anhydrous $MgSO_4$ and was concentrated under vacuum to give 22 mg of the crude oil. Column chromatographic purification (elution with pet ether: ether, 8:1) afforded 17 mg (80%) of acetate **50** as a colorless oil (TLC, hexane: EtOAc, 4:1, R_f **50** = 0.30): ^{1}H (400 MHz) δ 0.76 (s, 3H), 1.00 (s, 3H), 1.35 (d, J = 7.2 Hz, 6H), 1.46-1.53 (m, 1H), 1.57-1.63 (m, 2H), 1.80-1.94 (m, 3H), 2.09 (s, 3H), 2.17 (d, J = 8.8 Hz, 1H), 2.30-2.46 (m, 3H), 2.61 (dt, J_1 = 4.8 Hz, J_2 = 11.6 Hz, 1H), 3.41 (hetpet, J = 7.2 Hz, 1H), 3.69 (s, 3H), 3.80 (s, 3H), 3.88 (s, 3H), 5.20 (d, J = 3.2 Hz, 2H); ^{13}C NMR (400 MHz) 21.42 (q), 22.16 (q), 22.24 (q), 22.67 (q), 23.35 (t), 26.41 (t), 26.52 (d), 29.52 (q), 29.97 (t), 39.08 (t), 39.78 (s), 41.16 (t), 58.97 (t), 60.36 (q), 60.90 (q), 61.32 (d), 62.29 (q), 126.15 (s), 131.70 (s), 136.62 (s), 149.83 (s), 151.43 (s), 152.60 (s), 171.26 (s), 213.63 (s) ppm.

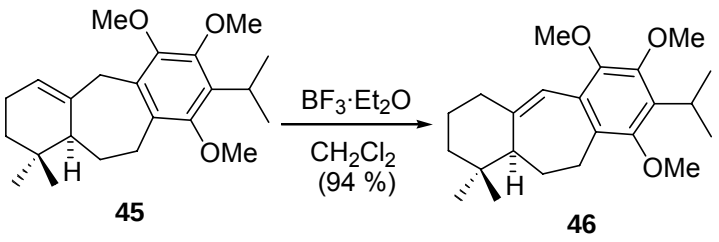


43 **51**

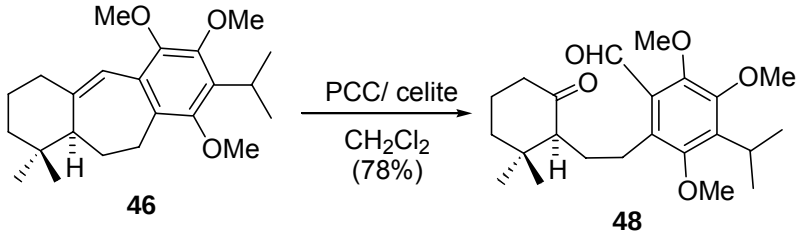
TMS ether 51 from the protection of alcohol 43: LHMDS (1 M, 7.79 mL, 7.79 mmol, 10.0 equivalents) was added to a solution of alcohol **43** (295 mg, 0.779 mmol) in freshly distilled diethyl ether (50 mL) under nitrogen atmosphere. The reaction mixture was stirred at rt for 30 minutes. Freshly distilled trimethylsilyl chloride (2.0 mL, 15.6 mmol, 20.0 equivalents) was added and the resulting solution was stirred for five days during which time a lot of white precipitate was generated along with a yellow solution (yet TLC analysis still showed an incomplete transformation). Water (10 mL) was added to quench the reaction. Ethereal workup followed by silica gel chromatographic purification afforded 246 mg (68%) of pure TMS ether **51** along with 92 mg (31%) of recovered alcohol **43** (the conversion was 99%) (TLC, hexane: EtOAc, 4:1, R_f **51** = 0.98): ^{1}H (400 MHz) δ 0.01 (s, 9H), 0.84 (s, 3H), 0.87 (s, 3H), 0.94 (d, *J* = 11.2 Hz, 1H), 1.15 (t, *J* = 13.2 Hz, 1H), 1.23-1.30 (m, 1H), 1.33 (d, *J* = 7.2 Hz, 3H), 1.35 (d, *J* = 7.2 Hz, 3H), 1.38-1.48 (m, 2H), 1.62-1.72 (m, 1H), 1.72-1.88 (m, 3H), 2.53-2.66 (bs, 1H), 2.73-2.82 (bd, *J* = 12.8 Hz, 1H), 2.96-3.08 (m, 2H), 3.44 (heptet, *J* = 7.2 Hz, 1H), 3.64, (s, 3H), 3.73 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (400 MHz) 0.00 (q), 16.75 (t), 18.80 (t), 19.43 (q), 19.92 (q), 20.13 (q), 23.68 (d), 24.17 (t), 30.33 (q), 31.69 (s), 39.44 (t), 39.47 (t), 39.98 (t), 57.85 (q), 58.08 (q), 60.11 (q), 74.13 (q), 128.38 (s), 128.55 (s), 130.31 (s), 145.61 (s), 147.96 (s), 149.11 (s) ppm; HR-MS: $[M+H]^+$ = 449.3069; $[M+H]^+_{calculated}$ = 449.3087; IR (neat): 2945, 1453, 1413, 1339, 1250, 1122, 1089, 1030, 837 cm^{-1}.



Ketone 52 from the oxidation of TMS ether 51: TMS ether **51** (32 mg, 0.071mmol) and $CuSO_4 \cdot 5H_2O$ (8.7 mg, 0.035 mmol, 0.5 equivalent) were dissolved in MeCN (8 mL) and H_2O (4 mL) under nitrogen atmosphere. $K_2S_2O_8$ (21 mg, 0.078mmol, 1.1 equivalents) was added and the reaction mixture was heated at 75 ℃ for 1.5 h. The reaction was cooled to rt and was subjected to standard ethereal workup. The crude produce was dissolved in acetone (5 mL) and Jones reagent (2 drops) was added. After 5 minutes, 2-propanol (5 drops) and water (2 mL) was added to quench the reaction. Acetone and excess 2-propanol were removed under vacuum using a rotary evaporator and the aqueous solution was subjected to ethereal workup. Column chromatographic purification of the crude product gave 5.0 mg of ketone **52** (^{1}H NMR shows some inseparable mess) (TLC, hexane: EtOAc, 8:1, R_f **52** = 0.65): ^{1}H (400 MHz) δ 0.17 (s, 9H), 0.81 (s, 3H), 0.93 (s, 3H), 1.32 (d, J = 6.8 Hz, 3H), 1.34 (d, J = 6.8 Hz, 3H), 1.76-1.84 (m, 3H), 2.46-2.58 (m, 3H), 2.74-2.84 (dd, J_1 = 12.0 Hz, J_2 = 19.6 Hz, 2H), 3.18 (d, J = 13.2 Hz, 1H), 3.43 (heptet, J = 6.8 Hz, 1H), 3.65 (s, 3H), 3.78 (s, 3H), 3.89 (s, 3H); HR-MS: ^{13}C NMR (400 MHz) 0.24, 16.47, 19.09, 19.15, 19.42, 19.52, 23.21, 27.31, 37.58, 38.56, 57.93, 60.68, 65.75, 75.22, 123.13, 125.23, 126.40, 128.50, 130.04, 132.28, 144.02, 149.89, 152.00, 205.30; HR-MS: $[M+H]^+$ = 463.2875; $[M+H]^+_{calculated}$ = 467.2880; IR (neat): 2932, 1692, 1456, 1412, 1321, 1283, 1261, 1118, 1091, 1059, 1033, 842 cm^{-1}.

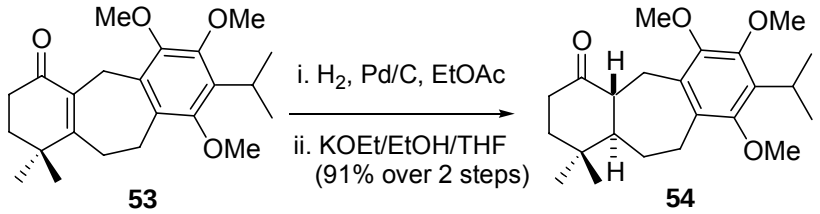


Alkene 46 from the rearrangement of 45: To a solution of alkene **45** (110.9 mg, 0.310 mmol) in freshly distilled DCM (5 mL) under nitrogen atmosphere was added $BF_3{\cdot}Et_2O$ (47.1 μL, 0.372 mmol, 1.2 equivalents). The resulting solution was stirred at rt for three days. Standard ethereal workup followed by chromatographic purification afforded 104.5 mg (94%) of alkene **46** (TLC, hexane: EtOAc, 4:1, R_f **46** = 0.85): ^{1}H (400 MHz) δ 0.73 (s, 3H), 0.84-0.90 (m, 2H), 0.99 (s, 3H), 1.33 (d, J = 7.2 Hz, 3H), 1.35 (d, J = 7.2 Hz, 3H), 1.38-1.47 (m, 2H), 1.60-1.70 (m, 3H), 2.16-2.25 (m, 2H), 2.30-2.36 (m, 1 H), 2.43-2.50 (m, 1H), 3.20 (dd, J_1 = 8.0 Hz, J_2 = 14.0 Hz, 1H), 3.42 (heptet, J = 7.2 Hz, 1H), 3.63 (s, 3H), 3.79 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (400 MHz) 20.57, 22.42, 22.53, 24.75, 24.91, 26.30, 30.38, 30.44, 36.93, 41.42, 42.32, 55.56, 60.61, 60.86, 62.30, 118.87, 129.28, 132.00, 132.77, 145.80, 148.23, 150.19, 150.39 ppm.



Dione 48 from the oxidation of alkene 46: To a solution of alkene **46** (10.0 mg, 0.028 mmol) in anhydrous DCM (2 mL) under nitrogen atmosphere was added PCC (60.2 mg, 0.28 mmol, 10.0 equivalents) and celite (60 mg). The resulting mixture was stirred at rt for 48 h. The solution was

filtrated through a short pad of silica gel and washed the filtrate with ether. The combined organic layer was concentrated under vacuum and was subjected with column chromatography to afford 8.5 mg (78%) of dione **48**. (cf. exp. **43→48** for spectral data)



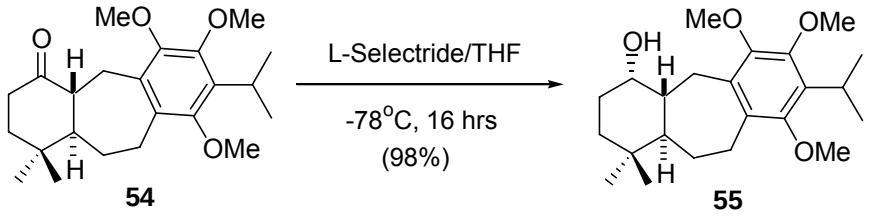
53 **54**

Ketone 54 from enone 53: A solution of enone **53** (1.18 g, 3.17 mmol) in ethyl acetate (35 mL) was added to a 500-mL hydrogenation vessel and the vessel was protected with nitrogen atmosphere. 10% Pd/C (120 mg, 10% in weight) was added and the vessel was placed in a shaker. H_2 was flushed in to remove N_2. The hydrogenation vessel was then shaked under 35 psi of H_2 for 72 h. Excess hydrogen gas was removed under vacuum and the palladium catalyst was removed by filtration through a short pad of celite. After concentration it was afforded 1.2 g of crude solid. (^{1}H NMR analysis of this crude solid showed a mixture of two diastereoisomers with a ratio of 2:3) This crude mixture was used directly in the next step without purification or characterization.

The crude product (1.2 g) from the hydrogenation was dissolved in THF (10 mL). A solution of KOEt in EtOH (25 mL, made from 750 mg of K in 50 mL of EtOH) was added. The resulting solution was stirred at rt for 42 h. The mixture was quenched by saturated NH_4Cl (15 mL), direct concentration of the resulting solution under vacuum removed all volatiles. Standard ethereal workup followed by column chromatographic purification (elution with pet ether: ether, 6:1) gave 1.08 g (91% in two steps) of ketone **54** (TLC, hexane: EtOAc, 4:1, R_f **54** = 0.51): ^{1}H

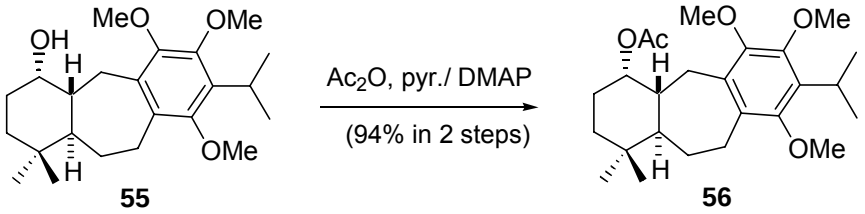
(500 MHz) δ 1.00 (s, 3H), 1.03 (s, 3H), 1.32 (d, J = 7.5 Hz, 3H), 1.34 (d, J = 7.5 Hz, 3H), 1.60-1.80 (m, 3H), 2.10-2.20 (m, 3H), 2.30-2.40 (m, 2H), 2.50-2.60 (dt, J_1 = 6.0 Hz, J_2 = 13.5 Hz, 1H) 3.20-3.30 (dd, J_1 = 8.0 Hz, J_2 = 15.0 Hz, 1H), 3.40 (heptet, J = 7.5 Hz, 1H), 3.63 (s, 3H), 3.72 (s, 3H), 3.85 (s, 3H), 3.98 (d, J = 13.5 Hz, 1H); ^{13}C NMR (400 MHz) 20.07 (q), 22.21 (q), 22.26 (q), 24.64 (t), 25.58 (t), 26.00 (d), 29.18 (t), 29.46 (q) , 34.23 (s), 38.67 (t), 42.41 (t), 50.81 (d), 57.96 (d), 60.40 (q), 60.58 (q), 62.26 (q), 132.46 (s), 132.53 (s), 132.93 (s), 147.58 (s), 150.59 (s), 150.72 (s), 212.06 (s) ppm; HR-MS: $[M+H]^+$ = 375.2520; $[M+H]^+_{calculated}$ = 375.2535; IR (neat): 2937, 2869, 1710, 1453, 1414, 1340, 1122, 1042, 1022, 960, 737 cm^{-1}.

Hydrogenation of enone 53 catalyzed by 10% HCl to give ketone 54: A solution of enone **53** (500 mg, 1.34 mmol) in ethanol (20 mL) was added to a 500-mL hydrogenation vessel and the vessel was protected with nitrogen atmosphere. 10% Pd/C (50 mg, 10% in weight) and two drops of aqueous HCl (10% solution) were added and the vessel was placed in a shaker. H_2 was flushed in to remove N_2. The hydrogenation vessel was then shaked under 35 psi of H_2 for 18 h. Excess hydrogen gas was removed under vacuum and the palladium catalyst was removed by filtration through a short pad of celite. After concentration it was afforded 550 mg of crude solid. ^{1}H NMR analysis of this crude solid showed only ketone **54** with no *cis*-isomer present. Column chromatographic purification (elution with pet ether: ether, 6:1) gave 490 mg (98%) of ketone **54** (TLC, hexane: EtOAc, 4:1, R_f **54** = 0.51).



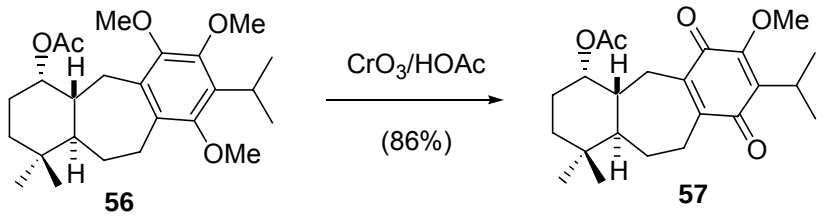
54 **55**

Alcohol 55 by L-Selectride reduction of ketone 54: To a solution of ketone **54** (2.0 g, 5.35 mmol) in freshly distilled THF (100 mL) was added L-Selectride (8.0 mL of 1 *M* solution in THF, 8.0 mmol, 1.5 equivalents) slowly through a syringe. The resulting yellow solution was stirred at -78 ℃ for 16 h, and then the temperature was allowed to increase to rt over a period of 5 h. The resulting solution was cooled to 0 ℃, quenched with 30% H_2O_2 (4 mL). Standard ethereal workup afforded 2.38 g of a crude yellow oil. Column chromatographic purification gave 1.99 g (99%) of alcohol **55** (TLC, hexane: EtOAc, 4:1, R_f **55** = 0.35): ^{1}H (400 MHz) δ 0.74 (s, 3H), 0.97 (s, 3H), 1.12 (d, *J* = 6.4 Hz, 1H), 1.33 (d, *J* = 7.2 Hz, 3H), 1.35 (d, *J* = 7.2 Hz, 3H), 1.60-1.76 (m, 5H), 2.10-2.20 (m, 1H), 2.38-2.46 (m, 1H), 2.58 (dd, J_1 = 5.6 Hz, J_2 = 14.0 Hz, 1H), 3.09 (d, *J* = 14.0 Hz, 1H), 3.12-3.18 (m, 1H), 3.42 (heptet, *J* = 7.2 Hz, 1H), 3.64 (s, 3H), 3.76 (s, 3H), 3.87 (s, 3H), 4.00 (s, 1H); ^{13}C NMR (400 MHz) 20.06 (q), 22.46 (q), 22.54 (q), 25.77 (t), 26.17 (d), 26.17 (d), 27.56 (t), 29.78 (t), 30.70 (q), 31.25 (t), 33.99 (s), 35.42 (t), 42.02 (d), 60.71 (q), 60.88 (q), 62.49 (q), 73.64 (d), 132.41 (s), 132.41 (s), 134.12 (s), 147.28 (s), 150.66 (s), 150.93 (s) ppm; HR-MS: $[M+H]^+$ = 377.2689; $[M+H]^+_{calculated}$ = 377.2692; IR (neat): 2926, 2854, 1458, 1265, 739, 705 cm^{-1}.



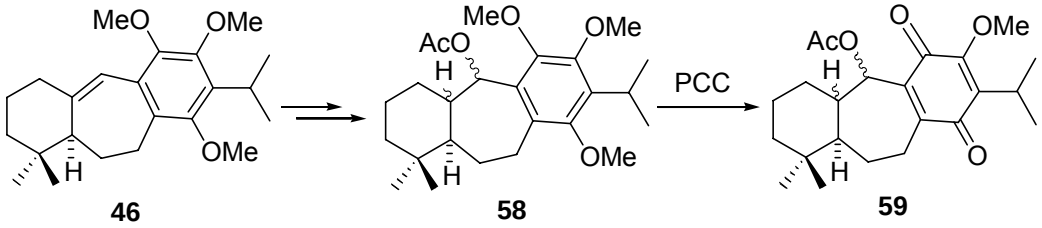
Acetate 56 from the protection of alcohol 55: To a solution of alcohol **55** (1.99 g, 5.29 mmol) in freshly distilled DCM (50 mL) and anhydrous pyridine (10 mL) was added acetic anhydride

(10 mL), followed by addition of DMAP (200 mg, 10% in weight). The resulting reaction mixture was stirred at rt for 36 h. TLC analysis indicated that no starting material remained. The resulting mixture was washed with 10-mL portions of saturated $CuSO_4$ until the organic layer was no longer blue. The $CuSO_4$ wash was extracted three times with 10-mL portions of ether. The combined organic extracts were then washed with brine (10 mL) and dried over anhydrous $MgSO_4$, followed by concentrated using a rotary evaporator. Column chromatographic purification (elution with pet ether: ether, 8:1) gave 2.08 g (94%) of acetate **56** (TLC, hexane: EtOAc, 4:1, R_f **56** = 0.85): ^{1}H (400 MHz) δ 0.75 (s, 3H), 1.00 (s, 3H), 1.14 (d, J = 9.6 Hz, 1H), 1.32 (d, J = 6.8 Hz, 3H), 1.34 (d, J = 6.8 Hz, 3H), 1.41(t, J = 10.0 Hz, 1H), 1.54-1.84 (m, 4H), 2.12 (s, 3H), 2.14-2.23 (m, 1H), 2.30-2.46 (m, 2H), 2.97 (d, J = 14.8 Hz, 1H), 3.18-3.24 (dd, J_1 = 8.0 Hz, J_2 = 14.8 Hz, 1H), 3.40 (heptet, J = 6.8 Hz, 1H), 3.63 (s, 3H), 3.73 (s, 3H), 3.85 (s, 3H), 5.09 (s, 1H); ^{13}C NMR (400 MHz) 20.09 (q), 21.59 (q), 22.42 (q), 22.54 (q), 26.00 (t), 26.18 (d), 26.69 (t), 28.12 (t), 30.67 (q), 30.87 (t), 33.91 (s), 36.02 (t), 40.78 (d), 50.32 (d), 60.67 (q), 60.91 (q), 62.48 (q), 76.53 (d), 132.49 (s), 132.63 (s), 133.92 (s), 147.50 (s), 150.73 (s), 150.78 (s), 171.18 (s) ppm; HR-MS: $[M+H]^+$ = 419.2783; $[M+H]^+_{calculated}$ = 419.2797; $[M+Na]^+$ = 441.8478; $[M+K]^+$ = 457.8446; IR (neat): 2925, 2854, 1734, 1456, 1264, 1247, 1122, 1042, 739, 704 cm^{-1}.



***p*-Benzoquinone 57 from the oxidation of acetate 56**: To a solution of acetate **56** (20.0 mg, 0.048 mmol) in glacial acetic acid (2 mL) at rt was added ceric(IV) ammonium nitrate (CAN)

(26.2 mg, 0.048 mmol, 1.0 equivalent). The reaction mixture was stirred at rt for two days and a yellow solution formed (TLC analysis showed incomplete transformation). More CAN (26.2 mg, 0.048 mmol, 1.0 equivalent) was added and the mixture was stirred for two more days. Standard ethereal workup followed by column chromatographic purification (elution with pet ether: ether, 10:1) afforded 16 mg (86%) of *para*-benzoquinone **57** (TLC, hexane: EtOAc, 4:1, R_f **57** = 0.85): ^{1}H (400 MHz) δ 0.77 (s, 3H), 0.98 (s, 3H), 1.11-1.17 (bd, 1H), 1.21 (d, J = 6.8 Hz, 6H), 1.37-1.43 (m, 1H), 1.52-1.62 (m, 2H), 1.62-1.72 (m, 2H), 1.77-1.83 (m, 1H), 1.98-2.06 (m, 1H), 2.09 (s, 3H), 2.13-2.28 (m, 2H), 2.87 (dd, J_1 = 1.6 Hz, J_2 = 14.8 Hz, 1H), 3.14 (dd, J_1 = 7.2 Hz, J_2 = 14.8 Hz, 1H), 3.25 (heptet, J = 6.8 Hz, 1H), 3.94 (s, 3H), 5.02 (s, 1H); ^{13}C NMR (400 MHz) 19.74, 20.59, 20.63, 21.27, 24.03, 24.84, 24.99, 26.28, 28.83, 30.31, 33.85, 35.65, 38.05, 49.42, 61.00, 75.53, 137.09, 142.58, 147.13, 155.42, 170.60, 183.41, 187.08 ppm.



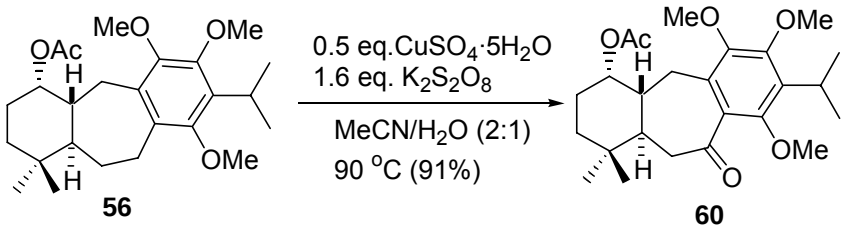
Benzylic Acetate 58 from alkene 46: To a solution of alkene **46** (149 mg, 0.416 mmol) in freshly distilled THF (6 mL) was added boron (4.2 mL of 1 *M* solution in THF, 4.2 mmol, 10.0 equivalents) under nitrogen atmosphere at 0 ℃. The resulting reaction mixture was stirred for 74 h at rt. Aqueous NaOH (6 mL of a 2 *M* solution) and H_2O_2 (3 mL of a 30% aqueous solution) were added and stirred for 4.5 h. The resulting solution was diluted with saturated NH_4Cl (5 mL) and ethereal workup gave 209 mg of a crude oil. Column chromatography (elution with pet ether: ether = 8:1) afforded 95 mg (61%) of a colorless oil, which, ^{1}H NMR analysis indicated,

consisted of a mixture of diastereoisomers with a ratio of ~6:1. This mixture of alcohol was converted to an acetate without purification or characterization.

A mixture of benzylic alcohol (86.6 mg, 0.23 mmol), anhydrous acetic anhydride (0.5 mL) and DMAP (10 mg) in anhydrous pyridine (2 mL) and freshly distilled DCM (8 mL) was stirred at rt for 48 h. The resulting solution was diluted with 20 mL of DCM and washed with 5-mL portions of saturated aqueous $CuSO_4$ until the organic layer was no longer blue. The aqueous wash was extracted once with DCM (10 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated using a rotary evaporator. Column chromatographic purification (elution with pet ether: ether = 8:1) afforded 88 mg (91.4%) of acetate **58** as a colorless oil (TLC, hexane: EtOAc, 4:1, R_f **58** = 0.82) (^{1}H NMR showed a mixture with a ratio of ~6:1). The NMR of the major isomer is as following: ^{1}H (400 MHz) δ 0.90 (s, 3H), 1.01 (s, 3H), 1.04-1.17 (m, 2H), 1.22-1.28 (m, 3H), 1.31 (d, J = 7.2 Hz, 3H), 1.34 (d, J = 7.2 Hz, 3H), 1.43-1.52 (m, 2H), 1.74-1.82 (m, 1H), 1.90-1.98 (m, 1H), 2.08 (s, 3H), 2.56-2.65 (m, 1H), 2.77 (t, J = 12.8 Hz, 1H), 3.11 (dd, J_1 = 7.2 Hz, J_2 = 15.2 Hz, 1H), 3.41 (heptet, J = 7.2 Hz, 1H), 3.62 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 6.49 (s, J = 6.4 Hz, 1H); ^{13}C NMR (400 MHz) 20.35 (q), 21.04 (t), 21.11 (q), 21.13 (q), 22.28 (t), 22.53 (t), 23.36 (t), 25.14 (d), 26.43 (q), 29.46 (q), 33.05 (t), 33.10 (s), 34.96 (d), 45.11 (d), 59.09 (q), 59.37 (q), 61.23 (q), 71.20 (d), 127.49 (s), 131.11 (s), 134.10 (s), 147.54 (s), 149.33 (s), 149.96 (s), 169.13 (s) ppm.

Quinone 59 from the oxidation of 58: To a solution of acetate **58** (7.0 mg, 0.017 mmol) in glacial acetic acid (0.5 mL) was added 10% of CrO_3 in acetic acid (33.6 μL, 0.035 mmol, 2.1 equivalents). The resulting solution was stirred at rt for 3 h. Water (1 mL) and diethyl ether (10 mL) were added and the isolated ether layer was washed with saturated $NaHCO_3$ (3 mL). The

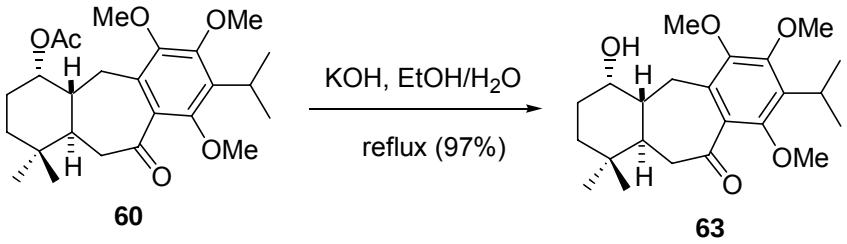
organic layer was dried over anhydrous $MgSO_4$, followed by concentration using a rotary evaporator. Column chromatographic purification (elution with pet ether: ether = 8:1) afforded 3 mg (46%) of quinone **59** (TLC, hexane: EtOAc, 4:1, R_f **59** = 0.63): ^1H (400 MHz) δ 0.90 (s, 3H), 1.04 (s, 3H), 1.10-1.40 (m, 7H), 1.20 (d, *J* = 5.6 Hz, 7H), 1.83-1.92 (m, 2H), 2.07 (s, 3H), 2.34-2.40 (m, 1H), 2.51-2.58 (m, 1H), 3.10-3.17 (m, 1H), 3.24 (heptet, *J* = 5.6 Hz, 1H), 3.97 (s, 3H), 5.90 (d, *J* = 5.2 Hz, 1H).



Ketone 60 from the benzylic oxidation of acetate 56: The acetate **56** (300 mg, 0.72 mmol) was dissolved in MeCN (80 mL) and H_2O (40 mL). $CuSO_4·5H_2O$ (90 mg, 0.36 mmol, 0.5 equivalent) was added. The mixture was heated at 90 ℃ under nitrogen atmosphere for 5 minutes during which time $K_2S_2O_8$ (213 mg, 0.79 mmol, 1.1 equivalents) was added in one portion, and the resulting mixture was heated at 90 ℃ for 2 h. More $K_2S_2O_8$ (105 mg, 0.36 mmol, 0.5 equivalent) was then added and the solution was heated for 50 more minutes. The resulting mixture was cooled to rt, followed by standard ethereal workup, to give 350 mg of a crude oil which was used in the next step without further purification or characterization.

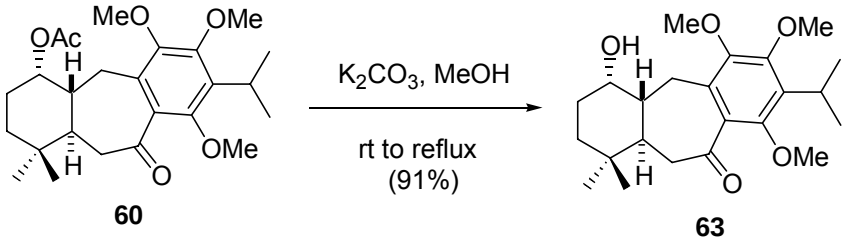
To the crude oil from the first step in acetone (50 mL) was added Jones reagent (5 drops each time in every 5 minutes) until TLC analysis showed a complete consumption of the intermediate alcohol. The mixture was quenched with 2-propanol (0.5 mL) and water (5 mL).

Acetone and excess of 2-propanol were removed under vacuum using a rotary evaporator. Standard ethereal workup of the aqueous layer gave 370 mg of crude product. Column chromatographic purification (elution with pet ether: ether, 8:1) afforded 235 mg of ketone **60** (TLC, hexane: EtOAc, 4:1, R_f **60** = 0.45) with recovery of 50 mg of acetate **56** (91% based on recovered starting material): ^{1}H (400 MHz) δ 0.84 (s, 3H), 0.99 (s, 3H), 1.16-1.24 (m, 1H), 1.31 (d, J = 7.2 Hz, 6H), 1.48-1.57 (m, 1H), 1.62-1.72 (m, 1H), 1.76-1.90 (m, 2H), 1.94-2.00 (m, 1H), 1.98 (s, 3H), 2.44 (dd, J_1 = 12.0 Hz, J_2 = 14.8 Hz, 1H), 2.64-2.70 (dd, J_1 = 5.2 Hz, J_2 = 14.8 Hz, 1H), 2.75- 2.84 (m, 2H), 3.38 (heptet, J = 7.2 Hz, 1H), 3.69 (s, 3H), 3.70 (s, 3H), 3.89 (s, 3H), 5.10 (s, 1H); ^{13}C NMR (400 MHz) 19.80 (q), 21.69 (q), 22.06 (q), 22.06 (q), 25.86 (d), 26.78 (t), 29.30 (t), 30.38 (q), 33.72 (s), 35.32 (t), 40.24 (d), 44.26 (d), 44.60 (t), 60.61 (q), 60.74 (q), 63.68 (q), 75.21 (d), 128.86 (s), 131.42 (s), 134.23 (s), 147.02 (s), 150.74 (s), 154.38 (s), 171.05 (s), 207.61 (s) ppm; HR-MS: $[M+H]^+$ = 433.2610; $[M+H]^+_{calculated}$ = 433.2590; IR (neat): 2936, 1735, 1692, 1454, 1411, 1371, 1324, 1244, 1030, 737, 703 cm^{-1}.



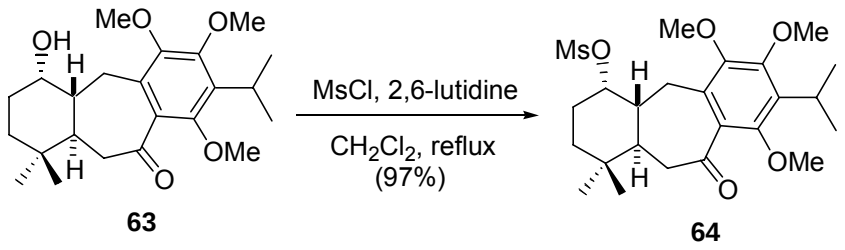
Alcohol 63 from saponification of acetate 60 with KOH/EtOH: To a solution of acetate **60** (150 mg, 0.35 mmol) in THF/EtOH/H_2O (50 mL/16 mL/16 mL) was added KOH (583 mg, 10.5 mmol, 3.0 equivalents). The resulting mixture was refluxed for 4 h and more KOH (583 mg, 10.5 mmol, 3.0 equivalents) was added. The solution was refluxed for additional 1.5 h and then

cooled to rt. Sufficient 5% aqueous HCl was added dropwise to neutralize the basic solution. Standard ethereal workup follow by column chromatography (elution with pet ether: ether, 6:1) afforded 132.3 mg (98%) of alcohol **63** (TLC, hexane: EtOAc, 4:1, R_f **63** = 0.28): ^{1}H (400 MHz) δ 0.83 (s, 3H), 0.90 (s, 3H), 1.08- 1.24 (m, 1H), 1.29 (d, J = 7.2 Hz, 3H), 1.30 (d, J = 7.2 Hz, 3H), 1.55- 1.64 (m, 1H), 1.66- 1.72 (m, 2H), 1.78- 1.84 (m, 2H), 2.27 (dd, J_1 = 11.6 Hz, J_2 = 18.4 Hz, 1H), 2.61 (dd, J_1 = 6.8 Hz, J_2 = 14.8 Hz, 1H), 2.74 (d, J = 18.4 Hz, 1H), 2.92 (d, J = 14.8 Hz, 1H), 3.40 (d, J = 7.2 Hz, 1H), 3.65 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 4.02 (s, 1H); ^{13}C NMR (400 MHz) 19.42 (q), 21.89 (q), 21.89 (q), 25.60 (d), 28.41 (t), 28.94 (t), 30.11 (q), 32.98 (s), 34.73 (t), 39.10 (d), 41.34 (d), 43.14 (t), 60.67 (q), 60.76 (q), 63.30 (q), 72.36 (d), 128.99 (s), 129.17 (s), 134.57 (s), 145.27 (s), 152.02 (s), 154.65 (s), 206.70 (s) ppm; HR-MS: $[M+H]^+$ = 391.2489; $[M+H]^+_{calculated}$ = 391.2484; IR (neat): 2960, 1690, 1454, 1412, 1324, 1118, 1031 cm^{-1}.



Alcohol 63 from soponification of acetate 60 with K_2CO_3/MeOH: To a solution of acetate **60** (303 mg, 0.70 mmol) in anhydrous methanol (20 mL) was added anhydrous K_2CO_3 (966 mg, 7.0 mmol, 10.0 equivalents). The resulting mixture was stirred at rt for 24 h and was then refluxed for 1 h. Water (10 mL) was added to dilute the reaction, and methanol was removed under vacuum using a rotary evaporator. Ethereal workup of the crude residue followed by column

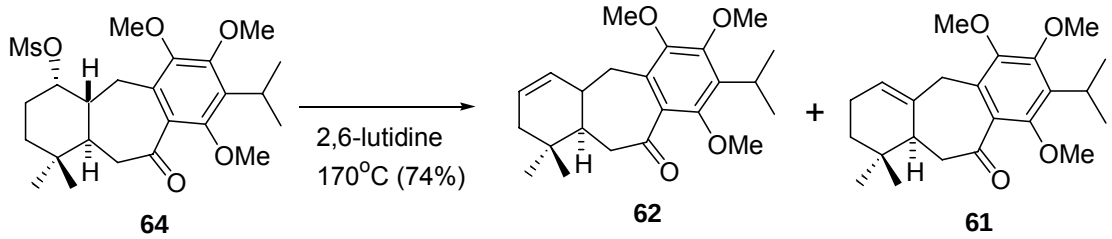
chromatographic purification (elution with pet ether: ether, 4:1) afforded 250 mg (91%) of alcohol **63**, see above for spectral data.



63 **64**

Mesylate 64 from alcohol 63: To a solution of alcohol **63** (40 mg, 0.106 mmol) in freshly distilled DCM (10 mL) was added anhydrous 2,4-lutidine (1.0 mL), followed by addition of mesyl chloride (100 μL) under nitrogen atmosphere. The resulting mixture was refluxed for 4 h and cooled to rt. The reaction was quenched by water (2 mL) and the mixture was extracted with three 5-mL portions of diethyl ether. The combined ethereal layer was washed three times with HCl (1 mL of 5% aqueous solution). The organic layer was dried over anhydrous $MgSO_4$, filtered, and then concentrated under vacuum using a rotary evaporator to give 50 mg of a crude yellow oil. Column chromatographic purification (elution with pet ether: ether, 2:1) afforded 46.2 mg (96%) of mesylate **64** (TLC, hexane: EtOAc, 4:1, R_f **64** = 0.12): ^{1}H (400 MHz) δ 0.84 (s, 3H), 1.03 (s, 3H), 1.18-1.24 (m, 1H), 1.31 (d, J = 7.2 Hz, 6H), 1.73-1.78 (m, 2H), 1.83-1.91 (m, 1H), 2.00 (dt, J_1 = 3.2 Hz, J_2 = 12.0 Hz, 1H), 1.32-1.38 (m, 1H), 2.52 (t, J = 12.0 Hz, 1H), 2.60 (dd, J_1 = 8.0 Hz, J_2 = 14.8 Hz, 1H), 2.79 (dd, J_1 = 3.2 Hz, J_2 = 12.8 Hz, 1H), 3.04-3.11 (dd, J_1 = 3.2 Hz, J_2 = 14.8 Hz, 1H), 3.06 (s, 3H), 3.36 (heptet, J = 7.2 Hz, 1H), 3.69 (s, 3H), 3.73 (s, 3H), 3.88 (s, 3H), 4.99 (s, 1H); ^{13}C NMR (400 MHz) 19.77 (q), 21.82 (q), 21.82 (q), 25.64 (d), 27.68 (t), 30.01 (q), 30.08 (t), 33.76 (s), 34.44 (t), 38.62 (q), 40.93 (d), 44.80 (t), 45.82 (d), 60.56 (q),

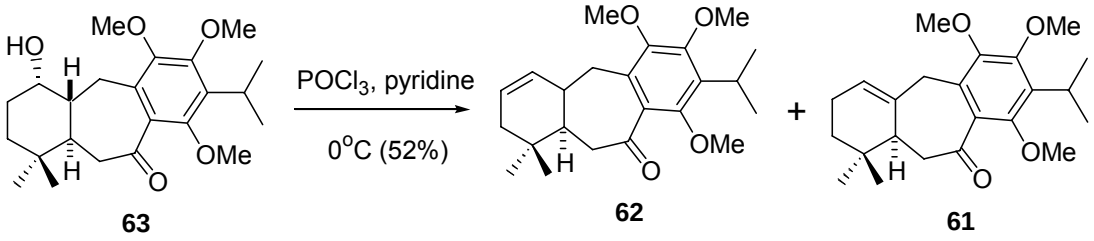
60.62 (q), 63.62 (q), 84.43 (d), 127.76 (s), 132.10 (s), 134.38 (s), 146.84 (s), 150.02 (s), 154.18 (s), 206.97 (s) ppm; HR-MS: $[M+H]^+ = 469.2281$; $[M+H]^+_{calculated} = 469.2260$; IR (neat): 2939, 1454, 1415, 1340, 1173, 1122, 1042, 969, 899 cm^{-1}.



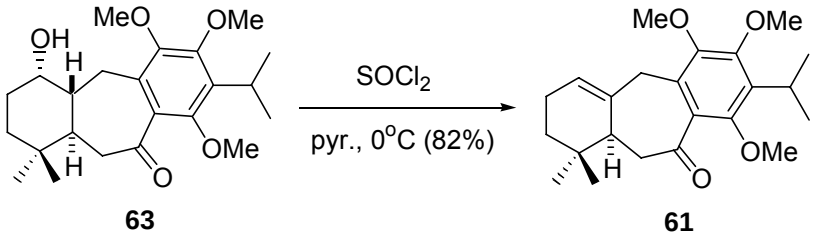
64 **62** **61**

62 : **61** = 1 : 2

Alkenes 61 and 62 from the elimination of mesylate 64: A solution of mesylate **64** (36.0 mg, 0.08 mmol) in 2,4-lutidine (1 mL) was heated at 170 ℃ for 2.5 h under nitrogen atmosphere. The mixture was then cooled to rt. Diethyl ether (20 mL) and water (5 mL) were added to quench the reaction. The organic layer was washed three times with 8-mL of a 5% HCl and once with brine (5 mL). The resulting organic layer was dried over anhydrous $MgSO_4$ and concentrated under vacuum using a rotary evaporator to give 37 mg of a crude colorless oil. Column chromatographic purification (elution with pet ether: ether, 10:1) gave 23.5 mg (82%) of an inseparable mixture of alkene **61** and alkene **62**. ^{1}H NMR showed a 2:1 ratio of alkenes **61**:**62**.

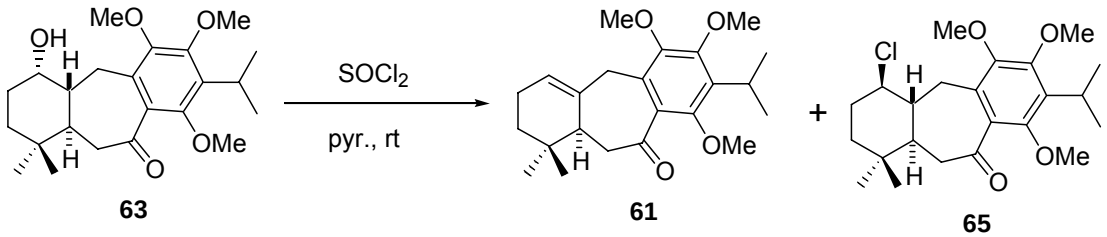


Alkenes 61 and 62 from the dehydration of alcohol 63 with $POCl_3$: Alcohol **63** (15.0 mg, 0.04 mmol) was dissolved in anhydrous pyridine (0.5 mL) and the light yellow solution was cooled in an ice bath under nitrogen atmosphere. $POCl_3$ (30 μL) was added and the reaction mixture was stirred at 0 ℃ for 1 h during which time a white precipitate formed. Ethyl acetate (10 mL) and water (1 mL) were added to the resulting mixture. The pyridine was removed by washing the organic layer three times with 2-mL of saturated $CuSO_4$. The organic layer was dried over anhydrous $MgSO_4$ and then concentrated under vacuum using a rotary evaporator to afford 14 mg of a crude colorless oil. ^{1}H NMR of the crude product showed a 6:1 ratio of alkenes **61**:**62**.



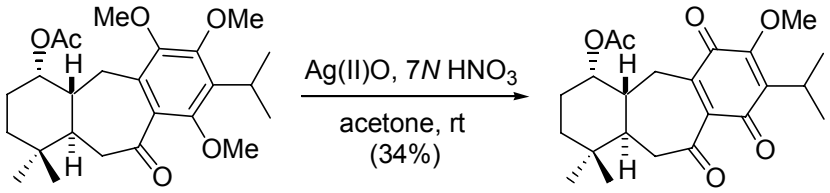
Alkene 61 from the dehydration of alcohol 63 with $SOCl_2$: To a solution of alcohol **63** (17.0 mg, 0.045 mmol) in anhydrous pyridine (0.5 ml) at 0 ℃ was added thionyl chloride (150 μL,

0.45 mmol, 10.0 equivalents) slowly under nitrogen atmosphere. The resulting mixture was stirred at 0 ℃ for 1.5 h. Wet diethyl ether (15 mL) was added to quench the reaction. The ether layer was washed with 2-mL portions of saturated $CuSO_4$ until the organic layer was no longer blue. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under vacuum using a rotary evaporator. Column chromatographic purification (elution with pet ether: ether, 10:1) afforded 16.0 mg (99%) of alkene **61** (TLC, hexane: EtOAc, 4:1, R_f **61** = 0.74): ^{1}H (400 MHz) δ 0.82 (s, 3H), 0.96 (s, 3H), 1.32 (d, J = 7.2 Hz, 6H), 1.35-1.40 (m, 2H), 1.98-2.05 (m, 2H), 2.19 (d, J = 13.2 Hz, 1H), 2.40 (dd, J_1 = 13.2 Hz, J_2 = 18.8 Hz, 1H), 2.84 (dd, J_1 = 2.4 Hz, J_2 = 18.8 Hz, 1H), 3.11 (d, J = 14.4Hz, 1H), 3.41 (d, J = 7.2 Hz, 1H), 3.69 (d, J = 14.4 Hz, 1H), 3.70 (s, 3H), 3.75 (s, 3H), 3.90 (s, 3H), 5.70 (s, 1H); ^{13}C NMR (400 MHz) 20.70 (q), 21.79 (q), 21.89 (q), 22.95 (t), 25.58 (d), 29.12 (q), 31.74 (s), 33.50 (t), 36.46 (t), 42.65 (d), 43.17 (t), 60.55 (q), 60.84 (q), 63.31 (q), 122.48 (d), 128.27 (s), 129.59 (s), 134.06 (s), 134.96 (s), 146.10 (s), 152.57 (s), 155.26 (s), 206.53 (s) ppm; HR-MS: $[M+H]^+$ = 373.2384; $[M+H]^+_{calculated}$ = 373.2379; IR (neat): 2958, 1701, 1458, 1412, 1331, 1287, 1201, 1121, 1032 cm^{-1}.



Chloride 65 was generated along with alkene **61** when the reaction occurred at rt (TLC, hexane: EtOAc, 4:1, R_f **65** = 0.78): ^{1}H (400 MHz) δ 0.90 (s, 3H), 0.91 (s, 3H), 1.33 (d, J = 6.8 Hz, 3H),

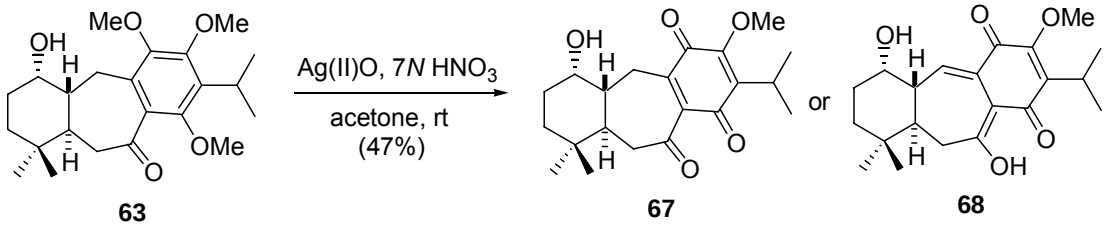
1.34 (d, J = 6.8 Hz, 3H), 1.88-2.00 (m, 2H), 2.10-2.17 (m, 1H), 2.36 (dd, J_1 = 12.0 Hz, J_2 = 18.4 Hz, 1H), 2.54 (dd, J_1 = 6.0 Hz, J_2 = 14.4 Hz, 1H), 2.73 (d, J = 18.4 Hz, 1H), 3.43 (heptet, J = 6.8 Hz, 1H), 3.54-3.62 (m, 2H), 3.68 (s, 3H), 3.83 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (400 MHz) 20.05 (q), 22.03 (q), 22.13 (q), 25.83 (d), 26.14 (t), 30.22 (q), 33.21 (s), 33.96 (t), 40.82 (t), 43.40 (t), 45.39 (d), 47.18 (d), 60.59 (q), 60.66 (q), 63.57 (q), 64.03 (d), 127.59 (s), 129.62 (s), 134.94 (s), 147.76 (s), 151.82 (s), 155.13 (s), 206.01 (s) ppm; HR-MS: $[M+H]^+$ = 409.2146; $[M+H]^+_{calculated}$ = 409.2145; IR (neat): 2924, 2854, 1459, 1265, 1030, 742 cm^{-1}.



60 **66**

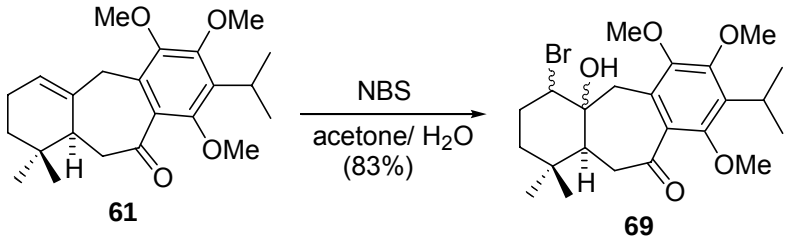
Quinone 66 from the oxidation of acetate 60: To a mixture of acetate **60** (31.0 mg, 0.072 mmol) and Ag(II)O (35.6 mg, 0.287 mmol, 4.0 equivalents) in acetone (6 mL) under nitrogen atmosphere was added 7 N HNO_3 (3 drops). The resulting mixture was stirred at rt for 5 minutes and more 7 N HNO_3 (three drops) was added. This operation was repeated and monitored by TLC analysis until acetate **60** was completely consumed. The resulting dark green solution was directly concentrated under vacuum using a rotary evaporator to remove acetone, followed by standard ethereal workup. Column chromatographic purification (elution with pet ether: ether, 8:1) afforded 10.0 mg (34%) of quinone **66** as a yellow oil along with isolation of another yellow oil (10.5 mg) which may be the enol form of quinone **66** (TLC, hexane: EtOAc, 4:1, R_f **66** = 0.47). The NMR data of quinone **66** is as follows: ^{1}H (400 MHz) δ 0.87 (s, 3H), 1.00 (s, 3H), 1.24 (d, J = 7.2 Hz, 6H), 1.49 (dt, J_1 = 4.0 Hz, J_2 = 13.6 Hz, 1H), 1.60-1.63 (m, 3H), 1.80-1.87

(m, 1H), 1.88 (s, 3H), 1.96-2.02 (m, 2H), 2.22-2.32 (dd, J_1 = 11.6 Hz, J_2 = 17.6 Hz, 1H), 2.46 (dd, J_1 = 6.4 Hz, J_2 = 14.8 Hz, 1H), 2.74-2.82 (m, 2H), 3.25 (heptet, J = 7.2 Hz, 1H), 3.96 (s, 3H), 4.99 (s, 1H); ^{13}C NMR (400 MHz) 19.33 (q), 20.37 (q), 20.56 (q), 21.07 (q), 24.68 (d), 26.45 (t), 26.52 (t), 30.18 (q), 33.60 (s), 35.10 (t), 38.61 (d), 41.36 (d), 42.22 (t), 61.20 (q), 74.84 (d), 138.16 (s), 138.89 (s), 139.87 (s), 155.65 (s), 170.19 (s), 183.33 (s), 184.56 (s), 202.93 (s) ppm.

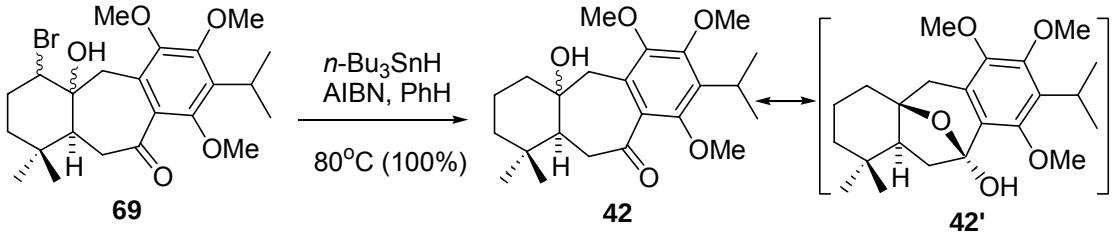


Quinone 67 or 68 from the oxidation of alcohol 63: To a mixture of alcohol **63** (46.0 mg, 0.118 mmol) and Ag(II)O (58.4 mg, 0.472 mmol, 4.0 equivalents) in acetone (8 mL) under nitrogen atmosphere was added 7 *N* HNO_3 (3 drops). The resulting mixture was stirred at rt for 5 minutes and additional 7 *N* HNO_3 (three drops) was added. This operation was repeated and monitored by TLC analysis until alcohol **63** was completely consumed. The resulting dark yellow solution was directly concentrated under vacuum using a rotary evaporator to remove the acetone, followed by standard ethereal workup. Column chromatographic purification (elution with pet ether: ether, 8:1) afforded 20.0 mg (47%) of quinone **67** (or **68**) as a yellow oil (TLC, hexane: EtOAc, 4:1, R_f = 0.55): ^{1}H (400 MHz) δ 0.86 (s, 3H), 0.98 (s, 3H), 1.22 (d, J = 6.8 Hz, 6H), 1.60-1.82 (m, 4H), 2.00-2.16 (m, 2H), 2.42 (dd, J_1 = 12.4 Hz, J_2 = 19.6 Hz, 1H), 2.70 (dd, J_1 = 2.0 Hz, J_2 = 19.6 Hz, 1H), 3.23 (heptet, J = 6.8 Hz, 1H), 3.97 (s, 3H), 4.26 (s, 1H), 6.13 (s, 1H); ^{13}C NMR (400 MHz) 19.22 (q), 20.25 (q), 20.50 (q), 24.93 (d), 29.86 (t), 29.92 (q), 33.26

(s), 34.37 (t), 37.49 (d), 40.03 (t), 44.95 (d), 61.18 (q), 69.99 (d), 79.10 (d), 137.05 (s), 137.18 (s), 138.57 (s), 155.71 (s), 182.07 (s), 184.05 (s), 200.21 (s) ppm.

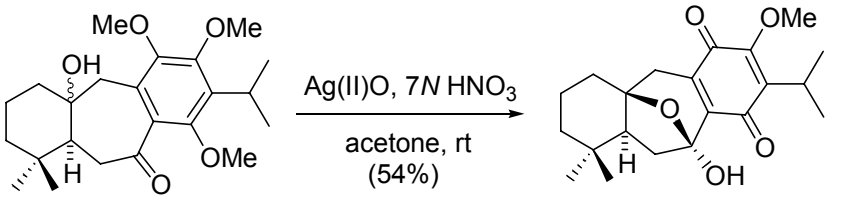


Bromohydrine 69 from alkene 61: To a solution of alkene **61** (57.4 mg, 0.155 mmol) in acetone (10 mL) and H_2O (3 mL) was added *N*-bromosuccinimide (NBS) (35.8 mg, 0.201 mmol, 1.3 equivalents) in one portion. The resulting mixture was stirred at rt for 1.5 h and was quenched with water (5 mL). Acetone was directly removed under vacuum using a rotary evaporator, followed by standard ethereal workup, to give 100 mg of a crude oil. Column chromatographic purification (elution with pet ether: ether, 8:1) afforded 60 mg (83%) of bromide **69** (TLC, hexane: EtOAc, 4:1, R_f **69** = 0.56). ^{1}H NMR showed a mixture of several compounds, and it was used in next steps without attempts to further purify it or characterize it.



Alcohol 42 from the photochemical reduction of bromide 69: To a solution of bromide **69** (55.0 mg, 0.117 mmol) in anhydrous benzene (10 mL) under nitrogen atmosphere were added

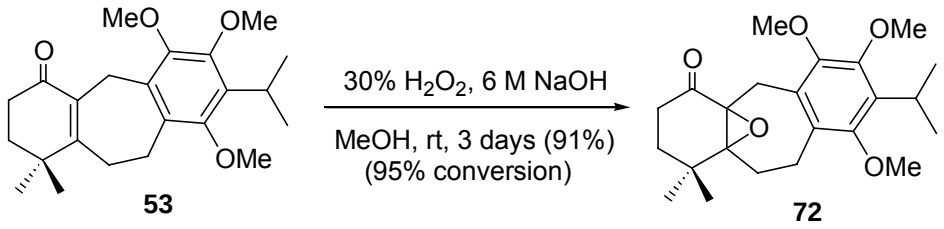
tributyltin hydride (nBu$_3$SnH) (315 μL, 1.17 mmol, 10.0 equivalents) and *azo-bis*-isobutyronitrile (AIBN) (9.6 mg, 0.058 mmol, 0.5 equivalent). The resulting mixture was refluxed for two hours. The resulting dark yellow solution was concentrated directly under vacuum using a rotary evaporator. Column chromatographic purification (elution with pet ether: ether, 8:1) afforded 46.0 mg (100%) of a mixture which contained alcohol **42** and hemiacetal **42′** (TLC, hexane: EtOAc, 4:1, R_f = 0.52). The ^{1}H NMR showed a mixture of three compounds: ^{1}H (400 MHz) δ 0.91 (s), 0.96 (s), 0.97 (s), 1.26-1.40 (m), 1.55 (s), 3.28-3.35 (m, 1H), 3.36-3.46 (m, 2.7H), 3.68 (s, 4H), 3.69 (s, 3H), 3.75 (s, 7H), 3.79 (s, 3H), 3.81 (s, 2.7H), 3.86 (s, 2.7H), 3.88 (s, 4H), 3.92 (s, 3H).



42 **(±)-komaroviquinone 1**

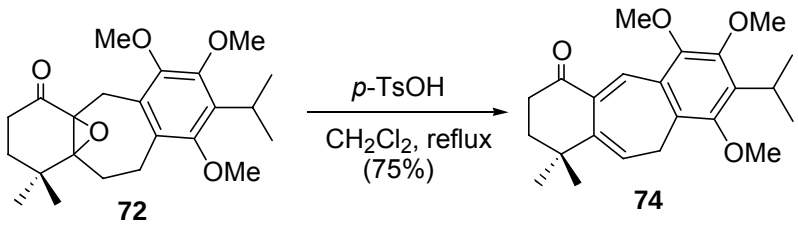
(±)-Komaroviquinone 1 from the oxidation of alcohol 42: To a mixture of alcohol **42** (46.0 mg, 0.117 mmol) and Ag(II)O (36.8 mg, 0.468 mmol, 4.0 equivalents) in acetone (8 mL) under nitrogen atmosphere was added 7 N HNO_3 (3 drops). The resulting mixture was stirred at rt for 5 minutes and more 7 N HNO_3 (three drops) was added. This operation was repeated and monitored by TLC analysis until alcohol **42** was completely consumed. The resulting dark yellow solution was directly concentrated under vacuum using a rotary evaporator to remove the acetone, followed by standard ethereal workup. Column chromatographic purification (elution with pet ether: ether, 8:1) afforded 23 mg (54%) of (±)-komaroviquinone **1** as a light orange oil

(TLC, hexane: EtOAc, 4:1, R_f **1** = 0.85): ^{1}H (400 MHz) δ 0.87 (s, 3H), 0.95 (s, 3H), 1.12-1.18 (m, 1H), 1.21 (d, *J* = 7.2 Hz, 6H), 1.56-1.64 (m, 3H), 1.68-1.76 (m, 2H), 1.83-1.92 (m, 1H), 1.98-2.08 (m, 2H), 2.25 (d, *J* = 20.0 Hz, 1H), 2.30 (dd, J_1 = 7.2 Hz, J_2 = 13.6 Hz, 1H), 2.55 (d, *J* = 20 Hz, 1H), 3.22 (heptet, *J* = 7.2 Hz, 1H), 3.99 (s, 3H), 5.99 (s, 1H); ^{13}C NMR (400 MHz) 15.67 (t), 20.45 (q), 20.45 (q), 24.34 (d), 27.10 (q), 29.80 (t), 30.34 (q), 31.20 (t), 32.04 (s), 39.02 (t), 45.77 (t), 51.47 (d), 61.19 (q), 79.33 (s), 100.89 (s), 137.08 (s), 138.94 (s), 142.13 (s), 156.10 (s), 183.60 (s), 189.14 (s) ppm; HR-MS: $[M+H]^+$ = 361.2008; $[M+H]^+_{calculated}$ = 361.2015; IR (neat): 3410, 2949, 1649, 1560, 1438, 1323, 1261, 1232, 1178, 1134, 1061, 957 cm^{-1}. A comparison between the spectral data of our synthesize komaroviquinone and that of isolated natural product has been shown in table 1. The identical ^{13}C data and only minor differences on the ^{1}H NMR support our success in the total synthesis.



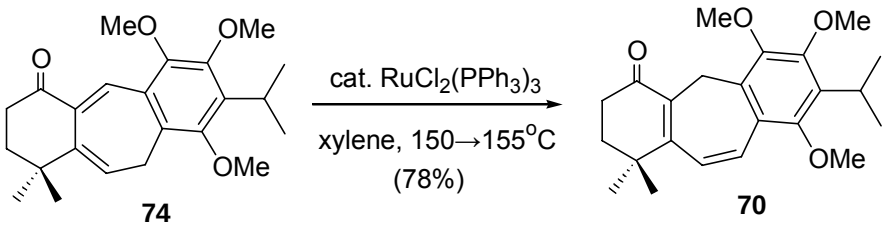
Epoxide 72 from enone 53: To a solution of enone **53** (1.0 g, 2.69 mmol) in methanol (40 mL) was added 6 *M* aqueous NaOH (5 mL), followed by addition of 30% aqueous H_2O_2 (2 mL). The resulting mixture was stirred at rt for two days. More 30% H_2O_2 (1 mL) and 6 *M* NaOH (2 mL) were added and the mixture was stirred for additional 36 h. Water (15 mL) was added to the resulting solution and methanol was removed under vacuum using a rotary evaporator. The aqueous solution was extracted three times with 20-mL portions of EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum

using a rotary evaporator to afford 1.3 g of a crude oil. Column chromatographic purification (elution with pet ether: ether, 8:1, 4:1) gave 945 mg (91%) of epoxide **72** (TLC, hexane: EtOAc, 4:1, R_f **72** = 0.58) as a pure colorless oil with recovery of enone **53** (47 mg) (95% conversion based on recovered enone **53**): ^{1}H (400 MHz) δ 0.93 (s, 3H), 1.07 (s, 3H), 1.22 (dd, J_1 = 8.4 Hz, J_2 = 13.2 Hz, 1H), 1.32 (d, J = 7.2 Hz, 3H), 1.33 (d, J = 7.2 Hz, 3H), 2.04-2.26 (m, 3H), 2.29-2.40 (m, 1H), 2.50 (dd, J_1 = 8.4 Hz, J_2 = 18.0 Hz, 1H), 2.61-2.69 (m, 1H), 2.73-2.82 (m, 1H), 3.23 (d, J = 15.6 Hz, 1H), 3.38 (heptet, J = 7.2 Hz, 1H), 3.66 (s, 3H), 3.77 (s, 3H), 3.86 (s, 3H), 3.98 (d, J = 15.6 Hz, 1H); ^{13}C NMR (400 MHz) 22.06 (t), 22.35 (q), 22.41 (q), 23.43 (t), 23.58 (q), 25.65 (q), 26.24 (d), 27.34 (t), 31.96 (t), 34.19 (t), 36.02 (s), 60.56 (q), 60.93 (q), 62.74 (s), 66.80 (q), 73.42 (s), 128.49 (s), 129.72 (s), 133.48 (s), 148.20 (s), 150.79 (s), 151.46 (s), 207.93 (s) ppm; HR-MS: $[M+H]^+$ = 389.2325; $[M+H]^+_{calculated}$ = 389.2328; IR (neat): 2924, 2854, 1706, 1459, 1416, 1370, 1341, 1265, 1121, 1042, 740, 703 cm^{-1}.



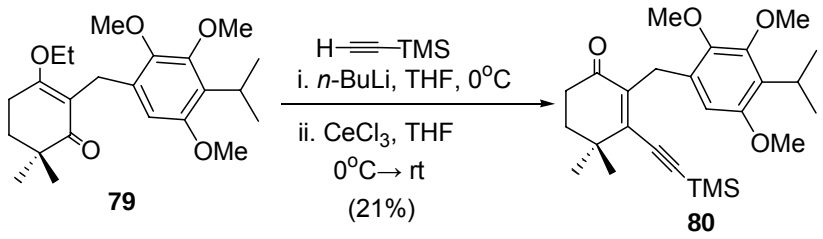
Diene 74 from epoxide 72: A solution of epoxide **72** (89.0 mg, 0.22 mmol) and *p*TSA·H_2O (21.8 mg, 0.11 mmol, 0.5 equivalent) in anhydrous benzene (15 mL) was refluxed for 24 h under nitrogen atmosphere. The resulting reaction mixture was then equipped with a Dean-Stark trap to remove the water and 15 mL of benzene was added. Refluxing was continued for 48 h until TLC analysis showed only one non-polar species. The benzene was removed directly under vacuum using a rotary evaporator. Column chromatographic purification (elution with pet ether: ether,

8:1) afforded 64.0 mg (75%) of diene **74** (TLC, hexane: EtOAc, 4:1, R_f **74** = 0.63): ^{1}H (400 MHz) δ1.13 (bs, 6H), 1.35 (d, *J* = 6.8 Hz, 6H), 1.81 (t, *J* = 7.2 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 3.47 (heptet, *J* = 6.8 Hz, 1H), 3.75 (s, 3H), 3.79 (s, 3H), 3.87 (s, 3H), 5.70 (t, *J* = 7.2 Hz, 1H), 8.23 (s, 1H); ^{13}C NMR (400 MHz) 21.94 (q), 21.94 (q), 25.72 (t), 26.36 (d), 28.56 (q), 28.56 (q), 35.01 (s), 36.03 (t), 36.16 (t), 60.54 (q), 60.69 (q), 62.50 (q), 120.73 (d), 127.64 (s), 128.99 (s), 133.71 (d), 137.20 (s), 138.16 (s), 143.90 (s), 148.73 (s), 149.52 (s), 149.95 (s), 201.36 (s) ppm; HR-MS: $[M+H]^+$ = 371.2224; $[M+H]^+_{Calculated}$ = 371.2222; IR (neat): 2924, 2852, 1456, 1342, 1121, 1043, 910, 734 cm^{-1}.

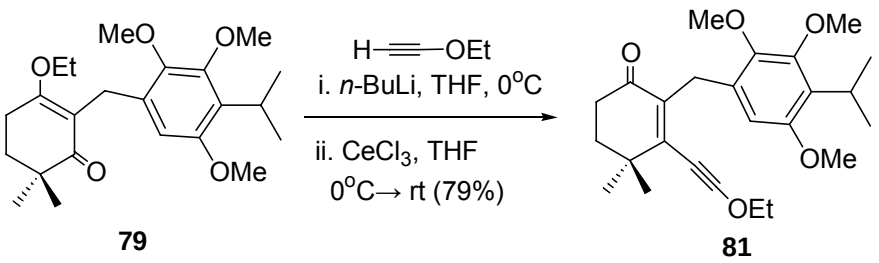


Dienone 74 from the rearrangement of diene 70: To a solution of diene **70** (23.0 mg, 0.062 mmol) in anhydrous *ortho*-xylene was added $RuCl_2(PPh_3)_3$ (3 mg). The resulting mixture was heated at 150→155 ℃ under nitrogen atmosphere overnight. Although TLC showed no change on R_f values, the product conjugate dienone gave a golden stain whereas the starting diene showed a blue color. Xylene was then removed directly under vacuum, and the crude ^{1}H NMR showed complete consumption of diene **74**. Column chromatographic purification afforded 18.0 mg (78%) of conjugated dienone **70** as a light yellow oil (TLC, hexane: EtOAc, 4:1, R_f **70** = 0.65): ^{1}H (400 MHz) δ 1.23 (bs, 6H), 1.33 (d, *J* = 7.2 Hz, 6H), 1.84 (t, *J* = 7.2 Hz, 2H), 2.49 (t, *J* = 7.2 Hz, 2H), 3.44 (heptet, *J* = 7.2 Hz, 1H), 3.67 (s, 3H), 3.76 (d, *J* = 23.2 Hz, 1H), 3.83 (s, 3H), 3.86 (d, *J* = 23.2 Hz, 1H), 3.91 (s, 3H), 6.75 (d, *J* = 12.4 Hz, 1H), 7.46 (d, *J* = 12.4 Hz, 1H); ^{13}C

NMR (400 MHz) 22.06 (q), 22.06 (q), 22.34 (t), 25.66 (d), 27.69 (q), 27.69 (q), 34.58(t), 34.81 (s), 37.06 (t), 60.47 (q), 61.17 (q), 62.11 (q), 124.93 (s), 127.66 (d), 130.38 (s), 132.33 (s), 133.55 (s), 133.90 (d), 146.23 (s), 151.86 (s), 154.21 (s), 157.32 (s), 196.61 (s) ppm; HR-MS: $[M+H]^+ = 371.2231$; $[M+H]^+_{Calculated} = 371.2222$; IR (neat): 2957, 2926, 2869, 1664, 1455, 1342, 1122, 1043, 910, 734 cm^{-1}.

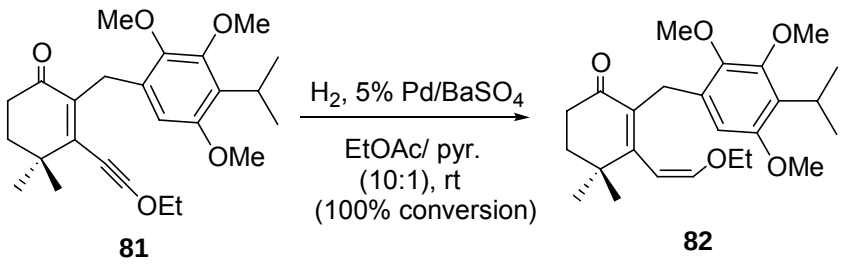


Enynone 80 from ketone 79: To a solution of *n*-BuLi (2.5 M in hexanes, 1.54 mL, 3.85 mmol, 3.0 equivalents) in freshly distilled THF (10 mL) under nitrogen atmosphere at 0 ℃ was added trimethylsilyl acetylene (543 μL, 3.85 mmol, 3.0 equivalents). The resulting reaction mixture was stirred at 0 ℃ for 20 minutes and was then cannulated to a cold (0 ℃) mixture of ketone **79** (500 mg, 1.28 mmol) and anhydrous $CeCl_3$ (16 mg) in anhydrous THF (15 mL). The solution was stirred overnight. Removal of all volatiles, followed by standard ethereal workup, and column chromatography (elution with pet ether: ether, 8:1) afforded 120 mg (21%) of enynone **80** (TLC, hexane: EtOAc, 4:1, R_f **80** = 0.83): ^{1}H (400 MHz) δ 0.17 (s, 9H), 1.27 (d, *J* = 7.2 Hz, 6H), 1.33 (s, 6H), 1.92 (t, *J* = 6.8 Hz, 2H), 2.50 (t, *J* = 6.8 Hz, 2H), 3.44 (heptet, *J* = 7.2 Hz, 6H), 3.68 (s, 3H), 3.81 (s, 2H), 3.82 (s, 3H), 3.87 (s, 3H), 6.29 (s, 1H); ^{13}C NMR (400 MHz) 0.00 (q), 0.00 (q), 0.00 (q), 21.35 (q), 21.35 (q), 25.03 (d), 27.82 (q), 27.82 (q), 27.93 (t), 34.46 (t), 35.60 (s), 36.29 (t), 55.48 (q), 60.23 (q), 60.72 (q), 101.81 (s), 106.48 (d), 111.01 (s), 127.91 (s), 130.15 (s), 140.79 (s), 145.28 (s), 147.78 (s), 151.60 (s), 154.05 (s), 197.36 (s) ppm.



79 **81**

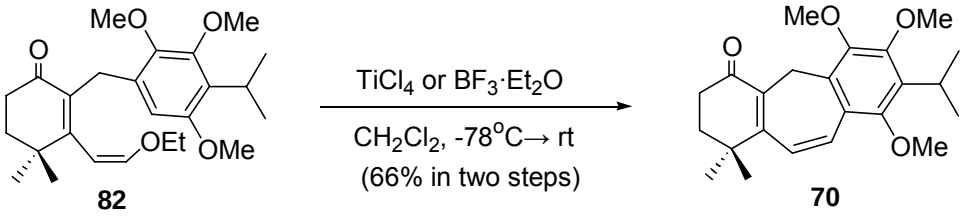
Enynone 81 from the alkylation of ketone 79 with Aren's reagent: To a solution of ethoxyacetylene (Aren's reagent) (162 mg, 2.31 mmol, 3.0 equivalents) in freshly distilled THF (15 mL) was added *n*-BuLi (2.5 M in hexanes, 923 µl, 2.31 mmol, 3.0 equivalents) under nitrogen atmosphere at 0 ℃. The resulting solution was stirred at 0 ℃ for 20 minutes, and then stirred at rt for 20 minutes. This mixture was cooled back to 0 ℃ and was then cannulated to a cold (0 ℃) mixture of ketone **79** (300 mg, 0.769 mmol) and anhydrous $CeCl_3$ (15 mg, 5% in weight) in anhydrous THF (10 mL). The resulting yellow solution was stirred overnight (0 ℃→rt) and then quenched with saturated aqueous NH_4Cl (5 mL). Aqueous HCl (5 mL of a 10% aqueous solution) was added and stirred for 10 minutes. Standard ethereal workup gave 400 mg of crude oil. Column chromatographic purification (elution with pet ether: ether, 8:1) afforded 250 mg (79%) of enynone **81** (TLC, hexane: EtOAc, 4:1, R_f **81** = 0.55): ^{1}H (400 MHz) δ 1.26 (d, *J* = 7.2 Hz, 6H), 1.29 (s, 6H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.91 (t, *J* = 7.2 Hz, 2H), 2.51 (t, *J* = 7.2 Hz, 2H), 3.43 (heptet, *J* = 7.2 Hz, 1H), 3.67 (s, 3H), 3.75 (s, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 6.25 (s, 1H); ^{13}C NMR (400 MHz) 14.43 (q), 21.36 (q), 21.36 (q), 25.03 (d), 27.47 (t), 28.02 (q), 28.02 (q), 34.36 (t), 36.13, 36.40 (t), 39.76 (s), 55.48 (q), 60.26 (q), 60.74 (q), 76.07 (t), 106.14 (d), 106.19 (s), 114.60 (s), 127.61 (s), 130.81 (s), 137.07 (s), 145.24 (s), 150.91 (s), 151.52 (s), 154.12 (s), 197.10 (s) ppm; HR-MS: $[M+H]^+$ = 415.2499; $[M+H]^+_{Calculated}$ = 415.2484; IR (neat): 2927, 1265, 896, 736, 705 cm^{-1}.



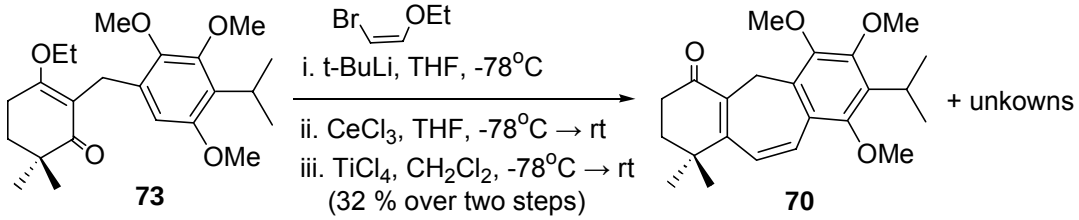
81 **82**

Dienone 82 from the hydrogenation of enynone 81: To a dry 100-mL round-bottomed flask was added enynone **81** (1.0 g, 2.42 mmol) under nitrogen atmosphere, followed by addition of anhydrous EtOAc (10 mL), anhydrous pyridine (1.0 mL), and 5% of $Pd/BaSO_4$ (100 mg, 10% in weight). Nitrogen in the round-bottomed flask was removed by bubbling H_2 under the reaction medium until the whole flask was filled with H_2. A balloon filled with H_2 was connected to the round-bottomed flask and the whole system was sealed with Teflon tape. The resulting mixture was stirred under H_2 for 40 h. At which time the H_2 balloon was disconnected and the residue H_2 gas was removed by N_2. EtOAc (30 mL) was added and the mixture was filtrated through a short pad of silica gel to remove the catalyst. The filtrate was washed with EtOAc and the organic phases were combined. The EtOAc solution was then washed with portions of saturated $CuSO_4$ (5 mL each) until the organic layer was no longer blue. The organic solution was dried over anhydrous $MgSO_4$, filtered, concentrated under vacuum using a rotary evaporator to afford 1.1 g of crude dienone **82** (TLC, hexane: EtOAc, 4:1, R_f **82** = 0.55) as a yellow oil (^{1}H NMR was recorded neat): ^{1}H (400 MHz) δ 1.17 (t, *J* = 7.2 Hz, 3H), 1.22 (s, 6H), 1.26 (d, *J* = 7.2 Hz, 6H), 1.91 (t, *J* = 7.2 Hz, 2H), 2.52 (t, *J* = 7.2 Hz, 2H), 3.42 (heptet, *J* = 7.2 Hz, 1H), 3.61 (s, 2H), 3.67 (s, 3H), 3.79 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 3.83 (s, 3H), 4.90 (d, *J* = 7.2 Hz, 1H), 6.09 (d, *J* = 7.2 Hz, 1H), 6.20 (s, 1H); ^{13}C NMR (400 MHz) 15.31 (q), 21.38 (q), 21.38 (q), 25.01 (d), 26.78 (t), 27.13 (q), 27.13 (q), 34.60 (t), 36.17 (s), 37.22 (t), 55.49 (q), 60.12 (q), 60.81 (q), 68.50 (t), 101.48 (d), 106.50 (d), 127.27 (s), 131.91 (s), 133.93 (s), 145.17 (s), 146.39 (d), 151.43 (s),

154.01 (s), 160.35 (s), 198.39 (s) ppm. This compound was used immediately in the next reaction without further purification or characterization.



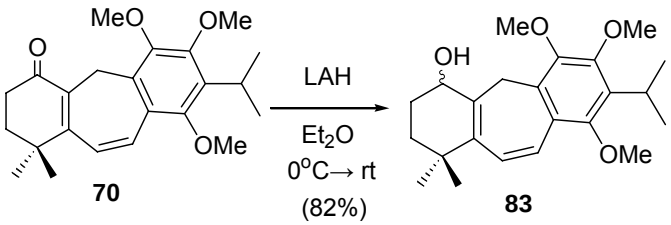
Dienone 70 via cycloalkylation of dienone 82 with $TiCl_4$: To a solution of dienone **82** (1.0 g, 2.40 mmol, crude from above) in freshly distilled DCM (40 mL) under a nitrogen atmosphere at -78 ℃ was added $TiCl_4$ (0.66 mL, 6.01 mmol, 2.5 equivalents) slowly by means of a microliter syringe. The resulting dark brown solution was stirred at -78 ℃ for at least 6 h, and then it was stirred for 20 more hours during which time the temperature was raised slowly to rt. The resulting reaction mixture was cooled to 0 ℃ and water (15 mL) was added slowly to quench the reaction. Standard ethereal workup followed by column chromatographic purification (elution with pet ether: ether, 8:1, 4:1, 2:1) afforded 520 mg of cyclic dienone **70** as a light yellow foam (66% yield over two steps). NMR data are identical with the spectra obtained earlier (cf. exp. **74→70**).



Dienone 70 from the alkylation of 79 with the anion derived from (*cis*-2-bromovinyl) ethyl ether: To a solution of *cis*-(2-bromovinyl) ethyl ether (233 mg, 1.54 mmol, 3.0 equivalents) in

freshly distilled THF (10 mL) under nitrogen atmosphere at -78 ℃ was added *t*-BuLi (1.7 M in pentane, 1.81 mL, 3.08 mmol, 6.0 equivalents). The resulting solution was stirred for 20 minutes at which time the temperature raised to -40 ℃. This solution was then cannulated to a cold (-78 ℃) mixture of ketone **79** (200 mg, 0.51 mmol) and anhydrous $CeCl_3$ (20 mg, 10 % in weight) in anhydrous THF (10 mL). The resulting mixture was then stirred for 24 h at rt. Water (5 mL) was added to quench the reaction. Ethereal workup gave 220 mg of crude oil which was used directly in next step without purification or characterization.

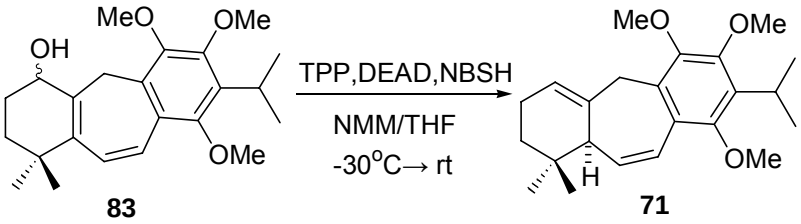
To a solution of the crude product (220 mg) from last step in anhydrous DCM (15 mL) under nitrogen atmosphere at -78 ℃ was added $TiCl_4$ (0.51 mL, 4.62 mmol, 3.0 equivalents). The resulting solution was stirred 36 h from -78 ℃ to rt. Ethereal workup followed by column chromatographic purification afforded 61.0 mg (32% over two steps) of dienone **70**, which was identical to that previously characterized.



Alcohol 83 from the LAH reduction of dienone 70: To a solution of dienone **70** (521mg, 1.40 mmol) in freshly distilled THF (80 mL) at 0 ℃ under nitrogen atmosphere was added LAH (53.5mg, 1.40 mmol, 1.0 equivalent). The resulting reaction mixture was stirred for five hours (0 ℃→ rt) and then was cooled back to 0 ℃. Water was slowly added to quench the reaction, followed by standard ethereal workup. Column chromatographic purification (elution with pet ether: ether, 4:1) afforded 430 mg (82%) of alcohol **83** (TLC, hexane: EtOAc, 4:1, R_f **83** = 0.42):

^{1}H (400 MHz) δ 1.06 (bs, 6H), 1.33 (d, *J* = 7.2 Hz, 3H), 1.34 (d, *J* = 7.2 Hz, 3H), 1.37-1.44 (m, 1H), 1.56-1.73 (m, 2H), 1.84-1.95 (m, 1H), 3.46 (heptet, *J* = 7.2 Hz, 1H), 3.66 (s, 3H), 3.89 (s, 6H), 4.32 (bt, 1H), 6.64 (d, *J* = 12.4 Hz, 1H), 7.21 (d, *J* = 12.4 Hz, 1H); HR-MS: $[M+H]^+$ = 373.2366; $[M+H]^+_{calculated}$ = 373.2379; IR (neat): 2930, 2868, 1453, 1400, 1342, 1316, 1120, 1045, 995, 966, 911, 733 cm^{-1}.

(S)-CBS catalyzed reduction of dienone 70: To a solution of (S)-Methyl-CBS-oxazaborolidine (220 μL of 1 *M* solution in $CHCl_3$, 0.22 mmol, 0.2 equivalent) and $BH_3 \cdot Me_2S$ (105 μL, 1.11 mmol, 1.0 equivalent) in freshly distilled THF (30mL) was added through a syringe pump a solution of dienone **70** (410 mg, 1.11 mmol) in anhydrous THF (15mL) over six hours at rt The resulting solution was stirred overnight and was cooled to 0 ℃. MeOH (10 mL) was added to quench the reaction. Standard ethereal workup followed by column chromatography (elution with pet ether: ether, 4:1) gave 360 mg (87%) of alcohol **83** (TLC, hexane: EtOAc, 4:1, R_f **83** = 0.42). The ee% was observed to be 68 ee% by formation of Mosher's ester. The solid was recrystallized in EtOAc/pet ether (3 x) to afford 210 mg of optically pure enantiomer. The specific rotation was determined to be $[\alpha]^{24}_D$= -11.5º (*c* = 0.0412 g. mL^{-1}, $CHCl_3$).



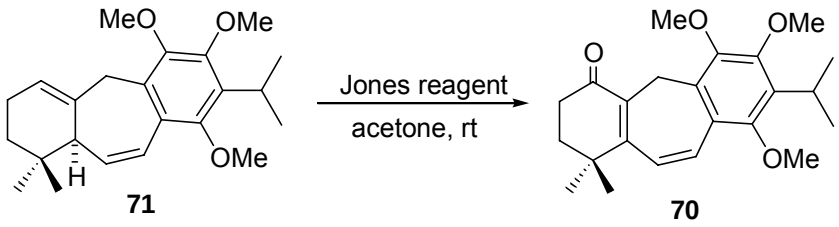
83 **71**

Diene 71 from allylic alcohol 83: Triphenylphosphine (TPP) (2.33 g, 8.90 mmol, 3.3 equivalents) was dissolved in anhydrous *N*-methylmorpholine (NMM) (6.4 mL) at -30 ℃. Diethylazodicarboxalate (DEAD) (1.2 mL, 8.06 mmol, 3.0 equivalents) was added dropwise

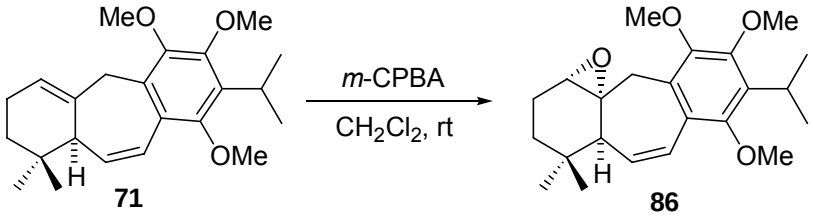
through a syringe. The orange color of DEAD faded in seconds after each drop to the reaction mixture. After 10 minutes a viscous yellow solution was formed. Allylic alcohol **83** (1.0 g, 2.69 mmol), dissolved in freshly distilled THF (6.4 mL), was added and the reaction mixture was stirred at -30 ℃ for 30 minutes. Then the temperature was slowly raised to -15 ℃ over a period of 30 minutes. It was then cooled back to -30 ℃ and 2-nitrobenzenesulfonylhydrazine (NBSH) (1.64 g, 8.06 mmol, 3.0 equivalents) was added in one portion. This solution was stirred at -30 ℃ for one hour, then at -20 ℃ and -10℃ for one hour each. The resulting orange solution was allowed to slowly warm to rt and stirred overnight.

Ether (30 ml) was added to dilute the resulting solution, followed by addition of 5% aqueous H_2O_2 (10 mL) and stirred for 15 minutes. The ethereal solution was separated, washed with water (15 mL) and brine (15 mL). The organic layer was dried over anhydrous $MgSO_4$ and was concentrated under vacuum using a rotary evaporator to afford a crude yellow solid which was re-dissolved in ether (30 mL). Petroleum ether was added to precipitate out the triphenylphosphine oxide. After decant the organic solution, it was concentrated and purified on flash column chromatography to afford 300 mg (31%) of diene **71** (TLC, hexane: EtOAc, 4:1, R_f **71** = 0.93) with recovery of allylic alcohol **83** (560 mg). The conversion was 71% based on recovered alcohol **83**. The specific rotation was determined to be $[\alpha]^{24}_D$= +24.5º (*c* = 0.034 g. mL^{-1}, $CHCl_3$): ^1H (400 MHz) δ 0.84 (s, 3H), 1.05 (s, 3H), 1.33 (d, *J* = 7.2 Hz, 3H), 1.34 (d, *J* = 7.2 Hz, 3H), 1.94-2.10 (m, 3H), 2.83-2.88 (bs, 1H), 3.21 (d, *J* = 13.2 Hz, 1H), 3.42-3.50 (m, 2H), 3.69 (s, 3H), 3.80 (s, 3H), 3.89 (s, 3H), 5.48 (s, 1H), 6.08 (dd, J_1 = 5.6 Hz, J_2 = 12.0 Hz, 1H), 6.69 (dd, J_1 = 1.6 Hz, J_2 = 12.0 Hz, 1H); ^{13}C NMR (400 MHz) 20.62 (q), 22.20 (q), 22.20 (q), 22.79 (t), 25.63 (d), 29.93 (q), 32.67 (s), 34.09 (t), 37.61 (t), 51.27 (d), 60.60 (q), 60.85 (q), 61.83 (q), 120.44 (d), 125.62 (s), 126.13 (d), 131.83 (s), 131.97 (s), 132.19 (d), 142.50 (s), 146.36 (s),

151.58 (s), 152.21 (s) ppm; HR-MS: $[M+H]^+ = 357.2419$; $[M+H]^+_{Calculated} = 357.2429$; IR (neat): 2924, 2853, 1457, 1265, 1121, 1042, 740, 703 cm^{-1}.

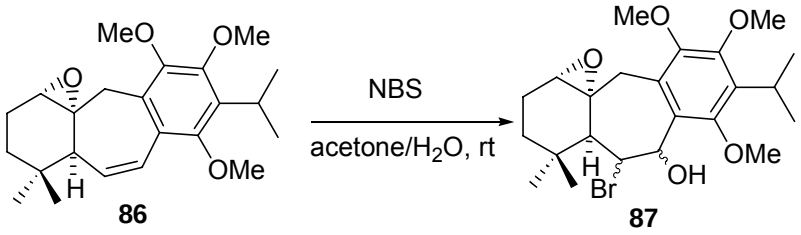


Dienone 70 from the oxidation of diene 71 with Jones reagent: To a solution of diene **71** (6.0 mg, 0.017 mmol) in acetone (3 mL) under nitrogen atmosphere at r.t. was added Jones reagent (1 drop). The resulting brown solution turned to green color with a precipitate and TLC analysis showed a complete consumption of diene **71**. 2-Propanol (3 drops) and water (0.5 mL) were added to quench the reaction. Acetone and excess 2-propanol were removed from the resulting mixture under vacuum using a rotary evaporator. Ethereal workup afforded 7.0 mg of crude dienone **70**. The crude NMR data were identical with that previously characterized.

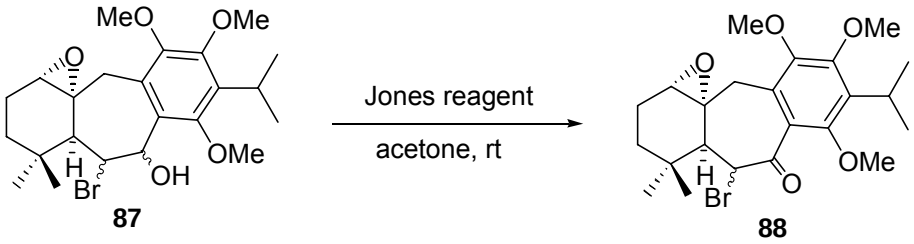


Epoxide 86 from diene 71: To a solution of diene **71** (26.0 mg, 0.073 mmol) in freshly distilled DCM (4 mL) under nitrogen atmosphere was added *m*-CPBA (77%, 19.7 mg, 0.088 mmol, 1.2 equivalents). The resulting mixture was stirred at rt for 1 h. More DCM (15 mL) was added. The solution was washed with 10% Na_2CO_3 (2 × 3 mL) and brine (3 mL), and dried over anhydrous

$MgSO_4$. Concentration of the filtered organic phase afforded 35 mg of crude epoxide **86** as an oil (TLC, hexane: EtOAc, 4:1, R_f **86** = 0.75). Because crude epoxide **86** underwent decomposition upon exposure to silica gel, it was used directly in next reaction without purification or characterization.

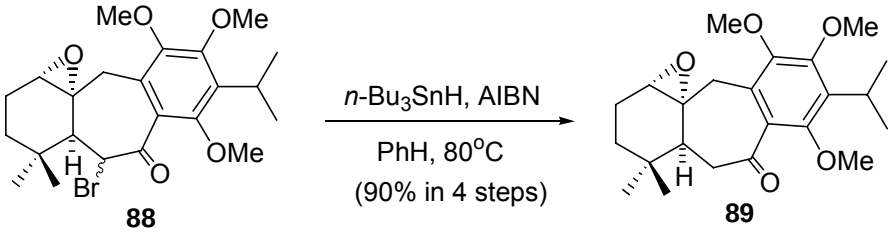


Bromohydrin 87 from epoxide 86: To a solution of crude epoxide **86** (35 mg, 0.073 mmol) in a mixture of acetone (5 mL) and water (1mL) was added NBS (12.6 mg, 0.073 mmol, 1.0 equivalent). The resulting solution was stirred at rt for 20 minutes. Acetone was directly removed under vacuum using a rotary evaporator, and the aqueous layer was extracted with ether (3 × 5 mL). The combined ethereal extracts were washed with brine (3 mL) and dried over anhydrous Na_2SO_4. Concentration of the ethereal solution afforded 40 mg of crude bromohydrin **87** (TLC, hexane: EtOAc, 4:1, R_f **87** = 0.48). The ^{1}H NMR of crude **87** showed a mixture with at least three compounds. To avoid decomposition, the crude bromohydrin **87** was used in next step without further purification.



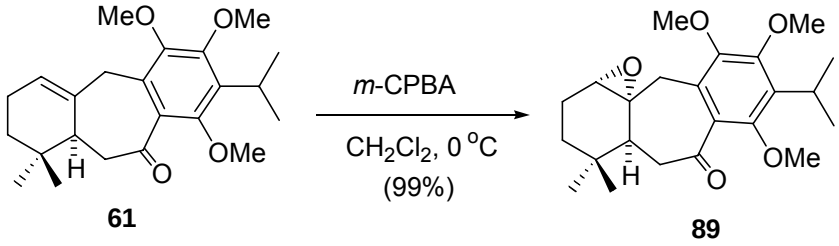
***α*-Bromoketone 88 from the oxidation of bromohydrin 87 with Jones reagent**: To a solution of crude bromohydrin **87** (40 mg) in acetone (4 mL) was added Jones reagent (one drop). After 5

minutes two more drop of Jones reagent were added and the resulting mixture was stirred for 5 more minutes. 2-Propanol (5 drops) and water (1 mL) were added to quench the reaction. Acetone and excess 2-propanol were removed directly under vacuum using a rotary evaporator. The aqueous solution was extracted with diethyl ether (3 × 5 mL). The combined ethereal extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford 40 mg of crude α-bromoketone **88** as an oil (TLC, hexane: EtOAc, 4:1, R_f **88** = 0.80). Although the crude ^{1}H NMR showed a single compound, it underwent tautomerizaiton in $CDCl_3$ to give two compounds which were assumed to be the α- and β-substituted bromide isomers. For convenience, the crude α-bromoketone **88** was used directly in next step.

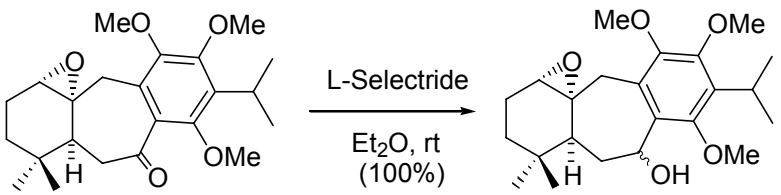


Epoxy ketone 89 by removal of the bromide from α-bromoketone 88: To a solution of crude α-bromoketone **88** (40 mg) in anhydrous benzene (2 mL) under nitrogen atmosphere was added nBu$_3$SnH (2 drops), followed by the addition of AIBN (5 mg). The resulting reaction mixture was heated at 80 ℃ for 40 minutes. Benzene was removed directly under vacuum and the resulting crude mixture was subjected on column chromatography (elution with pet ether: ether, 8:1) to afford 28.0 mg (90% over four steps) of epoxy ketone **89** as a colorless oil (TLC, hexane: EtOAc, 4:1, R_f **89** = 0.46): ^{1}H (400 MHz) δ 0.82 (s, 3H), 0.92 (s, 3H), 1.04-1.10 (m, 1H), 1.32 (d, J = 6.8 Hz, 3H), 1.33 (d, J = 6.8 Hz, 3H), 1.39-1.48 (m, 1H), 1.90-2.04 (m, 3H), 2.58 (dd, J_1 = 13.6 Hz, J_2 = 19.6 Hz, 1H), 2.82-2.96 (m, 3H), 3.33 (s, 1H), 3.47 (heptet, J = 6.8 Hz, 1H), 3.70 (s,

3H), 3.79 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (400 MHz) 20.42 (q), 20.67 (q), 20.70 (t), 20.78 (q), 24.50 (d), 28.57 (q), 29.46 (t), 31.44 (t), 31.57 (t), 40.05 (d), 42.94 (t), 59.35 (q), 59.46 (s), 59.65 (q), 60.40 (d), 62.19 (q), 125.88 (s), 127.43 (s), 133.86 (s), 145.91 (s), 154.92 (s), 202.92 (s) ppm; HR-MS: $[M+H]^+$ = 389.2311; $[M+H]^+_{Calculated}$ = 389.2328; IR (neat): 2932, 1676, 1455, 1321, 1265, 1136, 1031, 735, 704 cm^{-1}.

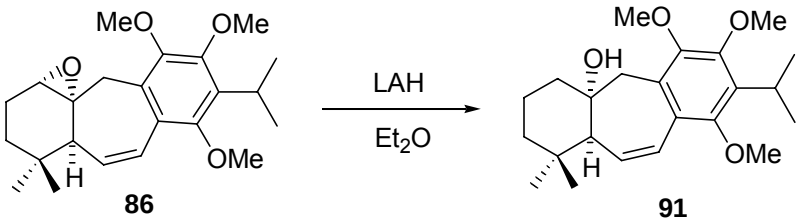


Epoxy ketone 89 from the epoxidation of alkene 61: To a solution of alkene **61** (30.0 mg, 0.081 mmol) in freshly distilled DCM (4 mL) under nitrogen atmosphere was added *m*-CPBA (77%, 36.1 mg, 0.162 mmol, 2.0 equivalents). The resulting mixture was stirred at 0 ℃ for 2 h. More *m*-CPBA (77%, 27.1 mg, 0.122 mmol, 1.5 equivalents) was added and the solution was stirred for two more hours. Water (3 mL) and DCM (20 mL) was added to quench the reaction. The separated organic layer was washed with brine (3 mL) and dried over anhydrous Na_2SO_4, followed by concentration using a rotary evaporator. Column chromatographic purification (elution with pet ether: ether, 4:1) afforded 31.0 mg (99%) of epoxy ketone **89**, which was identical to the material prepared in the preceding experimental.

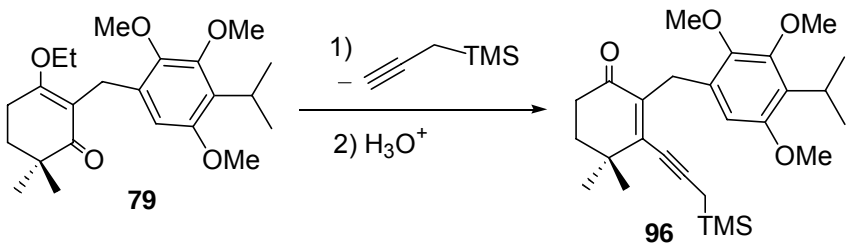


89 **90**

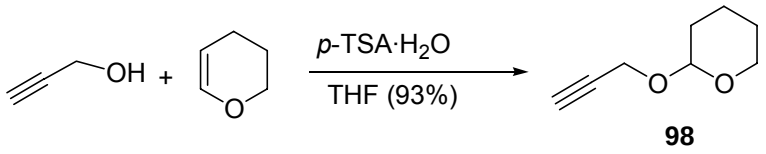
Alcohol 90 from the reduction of epoxy ketone 89 by L-Selectride: To a solution of epoxy ketone **89** (13.4 mg, 0.035 mmol) in freshly distilled diethyl ether (1.5 mL) under nitrogen atmosphere at 0 ℃ was added L-Selectride (1 M in THF, 82.8 μL, 0.083 mmol, 2.4 equivalents). The resulting mixture was stirred overnight under ambient temperature. Water (0.5 mL) and ether (10 mL) were added. The separated ethereal layer was washed with brine (1 mL) and dried over anhydrous $MgSO_4$. After concentration using a rotary evaporator, the crude product was subjected to column chromatography to afford 13.7 mg (100%) of alcohol **90** (TLC, hexane: EtOAc, 4:1, R_f **90** = 0.40): ^{1}H (400 MHz) δ 0.83 (s, 3H), 0.98 (s, 3H), 1.29 (d, *J* = 7.2 Hz, 3H), 1.31-1.35 (m, 1H), 1.38 (d, *J* = 7.2 Hz, 3H), 1.84-1.94 (m, 1H), 1.95-2.03 (m, 1H), 2.10-2.14 (m, 2H), 2.16-2.23 (m, 1H), 2.83 (d, *J* = 15.2 Hz, 1H), 3.12 (d, *J* = 15.2 Hz, 1H), 3.16 (s, 1H), 3.34 (heptet, *J* = 7.2 Hz, 1H), 3.71 (s, 3H), 3.79 (s, 3H), 3.88 (s, 3H), 4.35 (s, 1H), 5.33 (t, *J* = 3.2 Hz, 1H); ^{13}C NMR (400 MHz) 20.25 (q), 21.81 (q), 21.92 (t), 21.98 (q), 25.97 (d), 29.32 (q), 30.79 (s), 32.08 (t), 32.12 (t), 33.15 (t), 40.34 (d), 60.33 (q), 60.51 (q), 60.92 (d), 61.64 (q), 62.59 (s), 69.04 (d), 128.01 (s), 129.78 (s), 133.74 (s), 148.38 (s), 152.83 (s), 153.02 (s) ppm; HR-MS: $[M+H]^+$ = 391.5214; $[M+H]^+_{Calculated}$ = 391.5210.



Alcohol 91 from the reduction of epoxide 86 by LAH: To a solution of epoxide **86** (50 mg, ~0.11 mmol, crude product from the epoxidation of 40 mg of diene **71**) in freshly distilled diethyl ether (15 mL) at 0 ℃ was added LAH (8.5 mg, 0.22 mmol, 2.0 equivalents). The resulting mixture was then stirred at rt under a nitrogen atmosphere for four days during which time TLC analysis showed complete transformation. Water (5 drops) was added slowly to quench the reaction. The ethereal layer was separated and dried over anhydrous $MgSO_4$, followed by filtration and concentration using a rotary evaporator. Column chromatographic purification (elution with pet ether: ether, 4:1) afforded 22 mg (52% over two steps from diene **71**) of alcohol **91** (TLC, hexane: EtOAc, 4:1, R_f **91** = 0.65): ^{1}H (400 MHz) δ 0.86 (s, 3H), 1.13 (s, 3H), 1.34 (d, J = 7.2 Hz, 3H), 1.37 (d, J = 7.2 Hz, 3H), 1.42-1.64 (m, 7H), 1.70-1.85 (m, 3H), 2.25 (d, J = 14.0 Hz, 1H), 2.99 (d, J = 14.0 Hz, 1H), 3.46 (heptet, J = 7.2 Hz, 1H), 3.67 (s, 3H), 3.81 (s, 3H), 3.90 (s, 3H), 6.11 (dd, J_1 = 6.8 Hz, J_2 = 10.4 Hz, 1H), 6.58 (d, J = 10.4 Hz, 1H); ^{13}C NMR (400 MHz) 18.57 (t), 22.38 (q), 22.38 (q), 25.86 (d), 29.49 (q), 30.98 (q), 32.49 (s), 36.00 (t), 36.62 (t), 42.48 (t), 53.45 (d), 60.66 (q), 60.66 (q), 61.86 (q), 85.53 (s), 126.32 (d), 127.84 (s), 129.92 (s), 133.09 (s), 134.37 (d), 148.20 (s), 151.50 (s), 152.04 (s) ppm; HR-MS: $[M+H]^+$ = 375.2528; $[M+H]^+_{Calculated}$ = 375.2535; IR (neat): 2948, 1453, 1415, 1340, 1122, 1072, 1034, 995, 966 cm^{-1}.

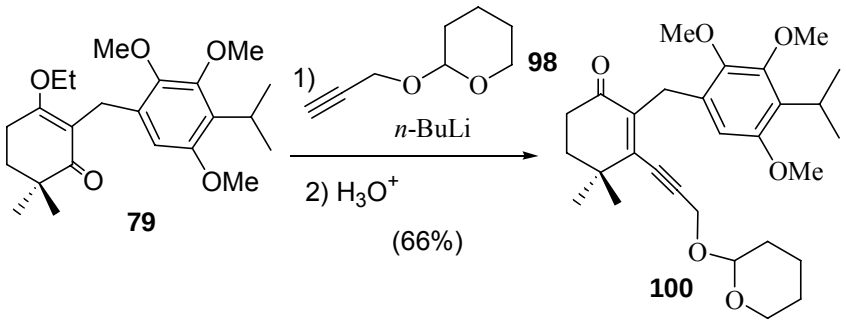


Enynone 96 from ketone 79: To a solution of propargyl trimethylsilane (301 mg, 2.69 mmol, 3.5 equivalents) in freshly distilled THF (20 mL) was added slowly *n*-BuLi (2.5 *M* in hexanes, 0.93 mL, 2.33 mmol, 3.0 equivalents) at 0 ℃ under nitrogen atmosphere. The resulting solution was stirred at 0 ℃ for 20 minutes, during which time it was cannulated to a cold (0 ℃) mixture of ketone **79** (300 mg, 0.77 mmol) and anhydrous $CeCl_3$ (30 mg, 10% in weight) in anhydrous THF (20 mL). The resulting cloudy mixture was stirred at rt for 6 h. Aqueous HCl (15 mL of a 5% solution) was added and stirred for ten minutes. Extraction with ether, washed with brine, dried over anhydrous $MgSO_4$ and concentration using a rotary evaporator gave 410 mg of crude oil. Column chromatography (elution with pet ether: ether, 8:1) afforded 315 mg (90%) of enynone **96** (TLC, hexane: EtOAc, 4:1, R_f **96** = 0.77): ^{1}H (400 MHz) δ 0.03 (s, 9H), 1.26 (d, *J* = 6.8 Hz, 6H), 1.31 (s, 6H), 1.74 (s, 2H), 1.91 (t, *J* = 6.8 Hz, 2H), 1.50 (t, *J* = 6.8 Hz, 2H), 3.44 (Heptet, *J* = 6.8 Hz, 1H), 3.66 (s, 3H), 3.78 (s, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 6.22 (s, 1H); ^{13}C NMR (400 MHz) 0.00 (q), 0.00 (q), 0.00 (q), 11.29 (t), 23.31 (q), 23.31 (q), 26.97 (d), 29.51 (t), 29.97 (q), 29.97 (q), 36.37 (t), 37.99 (t), 38.37 (s), 57.34 (q), 62.15 (q), 62.71 (q), 79.57 (s), 107.89 (d), 108.22 (s), 129.56 (s), 132.55 (s), 140.29 (s), 147.21 (s), 152.43 (s), 153.54 (s), 156.08 (s), 199.28 (s) ppm; HR-MS: $[M+H]^+$ = 457.2768; $[M+H]^+_{Calculated}$ = 457.2774; IR (neat): 2957, 2195, 1666, 1577, 1454, 1408, 1354, 1337, 1249, 1125, 1062, 1030, 846, 733 cm^{-1}.

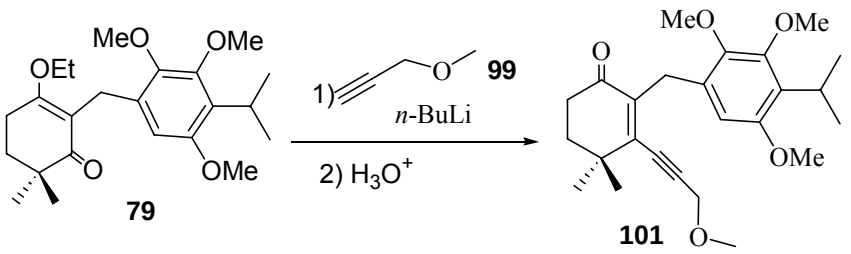


98

THP protected propargyl alcohol 98 (Registry number: 6089-04-9): To a mixture of 3,4-dihydro-2H-pyran (5.87 mL, 64.3 mmol, 1.2 equivalents) and propargyl alcohol (3.0 g, 53.5 mmol, 1.0 equivalent) in anhydrous THF (30 mL) was added *p*-tolulenesulfonic acid monohydrate (250 mg, 1.31 mmol, 0.025 equivalent). The resulting solution was stirred at rt for 16 h. Water (10 mL) was added to quench the reaction. Diethyl ether (100 mL) was added, and the organic layer was washed with water (10 mL) and brine (10 mL). The organic layer was then dried over anhydrous $MgSO_4$, and filtered. Concentration gave 7.5 g of a crude oil. Flash column chromatography (elution with pet ether: ether, 10:1) afforded 7.1 g (93%) of **98** as a colorless oil: ^{1}H (400 MHz) δ 1.50-1.66 (m, 4H), 1.69-1.84 (m, 2H), 2.41 (t, J = 2.4 Hz, 1H), 3.48-3.56 (m, 1H), 3.82 (dt, J_1 = 3.2 Hz, J_2 = 12.0 Hz, 1H), 4.24 (dq, J_1 = 2.4 Hz, J_2 = 16.0 Hz, 2H), 4.80 (t, J = 3.2 Hz, 1H); ^{13}C NMR (400 MHz) 19.19 (t), 25.53 (t), 30.40 (t), 54.18 (d), 62.16 (t), 74.22 (t), 79.97 (s), 97.01 (d) ppm.



Enynone 100 from the alkylation of ketone 79 with THP ether 98: To a solution of THP ether **98** (1.08 g, 7.7 mmol, 6.0 equivalents) in freshly distilled THF (30 mL) at 0 ℃ was added *n*-BuLi (2.5 *M* in hexanes, 2.56 mL, 6.4 mmol, 5.0 equivalents) slowly. The resulting solution was stirred for 20 minutes at 0 ℃, during which time it was cannulated to a cold (0 ℃) mixture of ketone **79** (500 mg, 1.28 mmol, 1.0 equivalent) and anhydrous $CeCl_3$ (50 mg, 10% in weight) in anhydrous THF (30 mL). The resulting cloudy mixture was stirred at r.t. overnight. Aqueous HCl (20 mL of a 5% solution) was added and stirred for 10 minutes. The mixture was extracted with three portions of ether (20 mL each) and the combined organic extracts were washed with brine (10 mL). It was then dried over anhydrous $MgSO_4$, and filtered. Concentration using a rotary evaporator gave 550 mg of crude oil. Column chromatography (elution with pet ether: ether, 10: 1) afforded 410 mg (66%) of enynone **100** (TLC, hexane: EtOAc, 4:1, R_f **100** = 0.65) with recovery of 60 mg of ketone **79**. The yield was 75% based on recovered ketone **79**: ^{1}H (400 MHz) δ 1.26 (d, J = 7.2 Hz, 6H), 1.33 (s, 6H), 1.40-1.76 (m, 6H), 1.93 (t, J = 7.2 Hz, 2H), 2.51 (t, J = 7.2 Hz, 2H), 3.49-3.54 (m, 2H), 3.68 (s, 3H), 3.79 (s, 2H), 3.82 (s, 3H), 3.86 (s, 3H), 4.78 (dd, J_1 = 16.4 Hz, J_2 = 22.0 Hz, 2H), 4.74 (bt, J = 3.6 Hz, 1H), 6.28 (s, 1H); ^{13}C NMR (400 MHz) 19.40 (t), 21.53 (q), 21.53 (q), 25.23 (d), 25.51 (t), 27.97 (t), 28.04 (q), 28.07 (q), 30.44 (t), 34.65 (t), 35.98 (s), 36.52 (t), 54.77 (t), 55.64 (q), 60.50 (q), 60.99 (q), 62.53 (t), 83.26 (s), 96.96 (d), 100.67 (s), 106.36 (d), 128.14 (s), 130.25 (s), 140.73 (s), 145.43 (s), 147.92 (s), 151.92 (s), 154.31 (s), 197.38 (s) ppm; MS: $[M+H]^+$ = 485.2909; $[M+H]^+_{Calculated}$ = 485.2903; IR (neat): 2937, 2869, 1672, 1454, 1408, 1338, 1122, 1062, 1026, 902, 733 cm^{-1}.



Enynone 101 from the alkylation of ketone 79 with methyl ether 99: To a solution of propargyl methyl ether **99** (270 mg, 3.85 mmol, 6.0 equivalents) in freshly distilled THF (15 mL) at 0 ℃ was slowly added *n*-BuLi (2.5 *M* in hexanes, 1.28 mL, 3.2 mmol, 5.0 equivalents). The resulting solution was stirred for 20 minutes at 0 ℃, during which time it was cannulated to a cold (0 ℃) mixture of ketone **79** (250 mg, 0.64 mmol) and anhydrous $CeCl_3$ (25 mg, 10% in weight) in anhydrous THF (15 mL). The resulting cloudy mixture was stirred at rt overnight. Aqueous HCl (10 mL of a 5% solution) was added and stirred for 10 minutes. The mixture was extracted with three 15-mL portions of ether and the combined organic extracts were washed with brine (5 mL). It was then dried over anhydrous $MgSO_4$, and filtered. Concentration using a rotary evaporator gave 310 mg of crude oil. Column chromatography (elution with pet ether: ether, 10:1) afforded 172 mg (65%) of enynone **101** (TLC, hexane: EtOAc, 4:1, R_f **101** = 0.58): ^{1}H (400 MHz) δ 1.27 (d, *J* = 7.2 Hz, 6H), 1.34 (s, 6H), 1.94 (t, *J* = 7.2 Hz, 2H), 2.53 (t, *J* = 7.2 Hz, 2H), 3.33 (s, 3H), 3.44 (heptet, *J* = 7.2 Hz, 2H), 3.68 (s, 3H), 3.80 (s, 2H), 3.82 (s, 3H), 3.86 (s, 3H), 4.31 (s, 2H), 6.27 (s, 1H); ^{13}C NMR (400 MHz) 21.53 (q), 21.53 (q), 25.24 (d), 28.05 (q), 28.05 (q), 28.05 (t), 34.63 (t), 35.98 (s), 36.52 (t), 55.70 (q), 57.88 (q), 60.46 (q), 60.63 (t), 60.96 (q), 83.73 (s), 100.47 (s), 106.50 (d), 128.22 (s), 130.36 (s), 140.78 (s), 145.47 (s), 147.65 (s), 151.89 (s), 154.33 (s), 197.41 (s) ppm; HR-MS: $[M+H]^+$ = 415.2476; $[M+H]^+_{calculated}$ = 415.2484; IR (neat): 2958, 2870, 2831, 1673, 1454, 1408, 1352, 1127, 1101, 1029 cm^{-1}.

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Appendix I (Ketone 60)

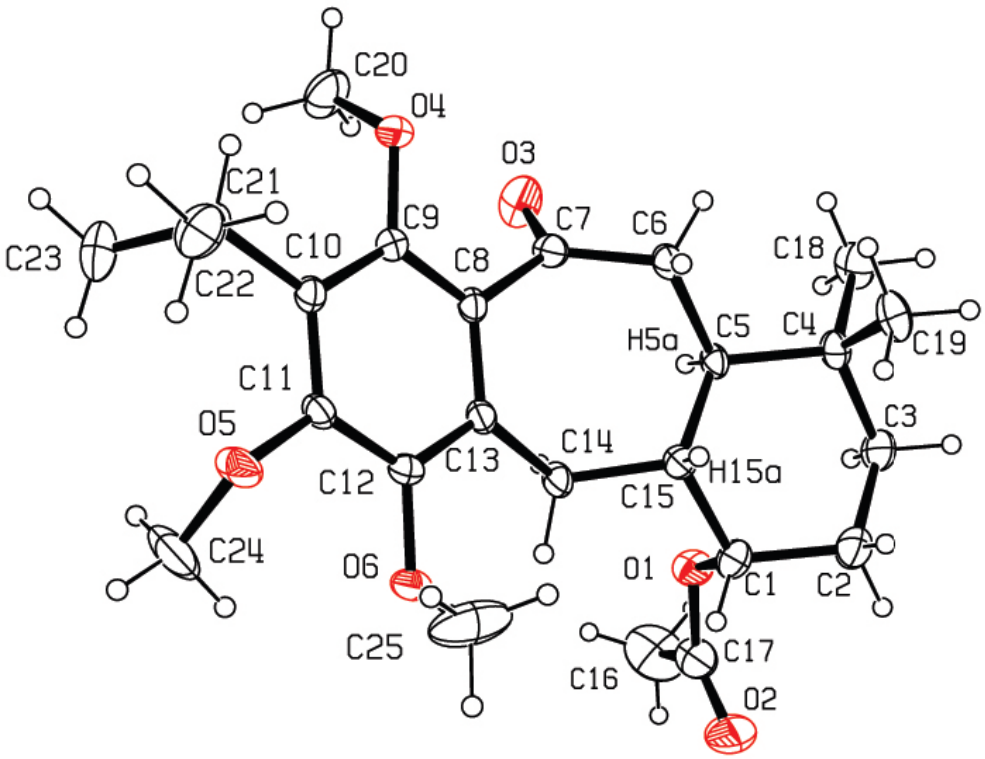


Table 1. Crystal data and structure refinement for Majetich1.

Identification code	Majetich1
Empirical formula	C25 H36 O6
Formula weight	432.54
Temperature	273(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, C2/c
Unit cell dimensions	a = 50.488(5) A alpha = 90 deg.

	b = 5.9426(5) A beta = 106.877(3) deg.
	c = 16.8889(16) A gamma = 90 deg.
Volume	4848.9(8) Aˆ3
Z, Calculated density	8, 1.185 Mg/mˆ3
Absorption coefficient	0.083 mmˆ-1
F(000)	1872
Crystal size	0.40 x 0.35 x 0.20 mm
Theta range for data collection	2.41 to 25.00 deg.
Limiting indices	-60<=h<=56, -6<=k<=7, -19<=l<=20
Reflections collected / unique	11886 / 4188 [R(int) = 0.0288]
Completeness to theta = 25.00	98.3 %
Refinement method	Full-matrix least-squares on Fˆ2
Data / restraints / parameters	4188 / 0 / 280
Goodness-of-fit on Fˆ2	1.033
Final R indices [I>2sigma(I)]	R1 = 0.0447, wR2 = 0.1157
R indices (all data)	R1 = 0.0658, wR2 = 0.1323
Largest diff. peak and hole	0.212 and -0.189 e.Aˆ-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for j.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	2022(1)	139(2)	3730(1)	44(1)
O(2)	2298(1)	-2032(3)	3229(1)	75(1)
O(3)	1152(1)	4675(2)	4133(1)	58(1)
O(4)	574(1)	3229(2)	3330(1)	41(1)
O(5)	562(1)	-890(3)	887(1)	53(1)
O(6)	1123(1)	-1763(2)	1535(1)	41(1)
C(1)	1870(1)	-1843(3)	3878(1)	39(1)
C(2)	2026(1)	-2926(4)	4689(1)	50(1)
C(3)	2048(1)	-1313(4)	5404(1)	50(1)
C(4)	1769(1)	-515(3)	5479(1)	37(1)
C(5)	1594(1)	474(3)	4632(1)	31(1)
C(6)	1297(1)	1031(3)	4653(1)	37(1)
C(7)	1148(1)	2664(3)	3998(1)	34(1)
C(8)	992(1)	1727(3)	3168(1)	30(1)
C(9)	710(1)	2106(3)	2842(1)	31(1)
C(10)	559(1)	1275(3)	2067(1)	32(1)
C(11)	707(1)	4(3)	1642(1)	34(1)
C(12)	988(1)	-459(3)	1978(1)	32(1)
C(13)	1139(1)	428(3)	2741(1)	31(1)
C(14)	1450(1)	199(3)	3043(1)	36(1)
C(15)	1585(1)	-1003(3)	3874(1)	32(1)
C(16)	2364(1)	1952(6)	3288(2)	95(1)
C(17)	2232(1)	-208(5)	3404(1)	54(1)
C(18)	1826(1)	1338(4)	6140(1)	50(1)
C(19)	1618(1)	-2443(3)	5770(1)	52(1)
C(20)	542(1)	5608(4)	3185(2)	65(1)
C(21)	251(1)	1782(3)	1713(1)	39(1)
C(22)	70(1)	-310(4)	1499(1)	55(1)
C(23)	192(1)	3372(4)	968(1)	63(1)
C(24)	657(1)	-253(7)	196(1)	100(1)
C(25)	1094(1)	-4108(4)	1631(2)	91(1)

Appendix II (Epoxide 47)

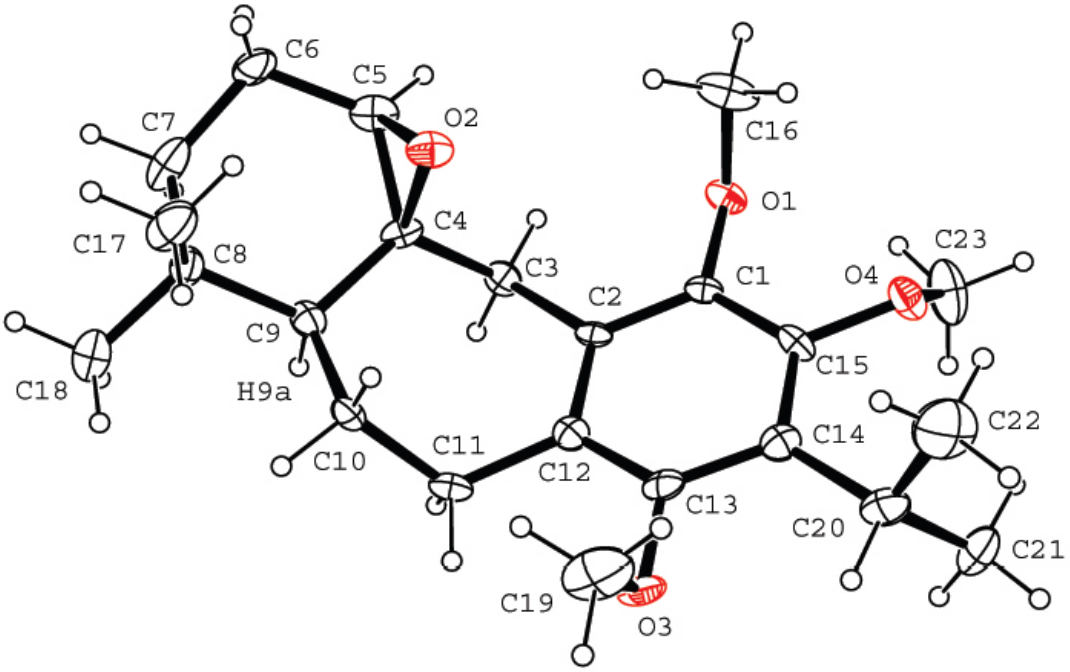


Table 1. Crystal data and structure refinement for Majetich2.

Identification code	Majetich2
Empirical formula	C23 H34 O4
Formula weight	374.50
Temperature	273(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, Pbca
Unit cell dimensions	a = 20.550(5) A alpha = 90 deg.
	b = 8.198(2) A beta = 90 deg.

	c = 25.071(7) A gamma = 90 deg.
Volume	4223.7(19) Aˆ3
Z, Calculated density	8, 1.178 Mg/mˆ3
Absorption coefficient	0.079 mmˆ-1
F(000)	1632
Crystal size	0.40 x 0.30 x 0.25 mm
Theta range for data collection	1.62 to 25.00 deg.
Limiting indices	-24<=h<=24, -9<=k<=9, -29<=l<=29
Reflections collected / unique	17257 / 3177 [R(int) = 0.1316]
Completeness to theta = 25.00	85.5 %
Refinement method	Full-matrix least-squares on Fˆ2
Data / restraints / parameters	3177 / 0 / 248
Goodness-of-fit on Fˆ2	1.016
Final R indices [I>2sigma(I)]	R1 = 0.0842, wR2 = 0.1814
R indices (all data)	R1 = 0.1663, wR2 = 0.2281
Largest diff. peak and hole	0.260 and -0.247 e.Aˆ-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for sad.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	416(1)	1719(4)	859(1)	40(1)
O(2)	1449(1)	1248(4)	-439(1)	41(1)
O(3)	1721(2)	7463(4)	496(1)	46(1)
O(4)	946(2)	3426(4)	1697(1)	45(1)
C(1)	741(2)	3142(5)	760(2)	26(1)
C(2)	781(2)	3752(5)	247(2)	26(1)
C(3)	455(2)	2818(5)	-210(2)	31(1)
C(4)	919(2)	2240(5)	-632(2)	28(1)
C(5)	946(2)	486(5)	-751(2)	41(1)
C(6)	1129(3)	-166(6)	-1282(2)	53(2)
C(7)	1072(3)	1154(7)	-1704(2)	57(2)
C(8)	1408(2)	2761(6)	-1568(2)	39(1)
C(9)	1093(2)	3483(6)	-1057(2)	32(1)
C(10)	1470(2)	4915(5)	-824(2)	38(1)
C(11)	1132(2)	5932(5)	-403(2)	38(1)
C(12)	1106(2)	5209(5)	147(2)	30(1)
C(13)	1401(2)	6026(5)	583(2)	31(1)
C(14)	1345(2)	5476(6)	1109(2)	35(1)
C(15)	1001(2)	4017(5)	1185(2)	33(1)
C(16)	845(3)	316(6)	892(3)	70(2)
C(17)	2152(2)	2429(7)	-1501(3)	64(2)
C(18)	1329(3)	3960(8)	-2026(2)	65(2)
C(19)	2400(3)	7267(7)	349(3)	78(2)
C(20)	1640(3)	6421(6)	1561(2)	56(2)
C(21)	1151(3)	6984(7)	1974(3)	79(2)
C(22)	2190(3)	5465(9)	1826(3)	88(2)
C(23)	300(3)	3183(9)	1890(2)	71(2)

Appendix III (Epoxide 91)

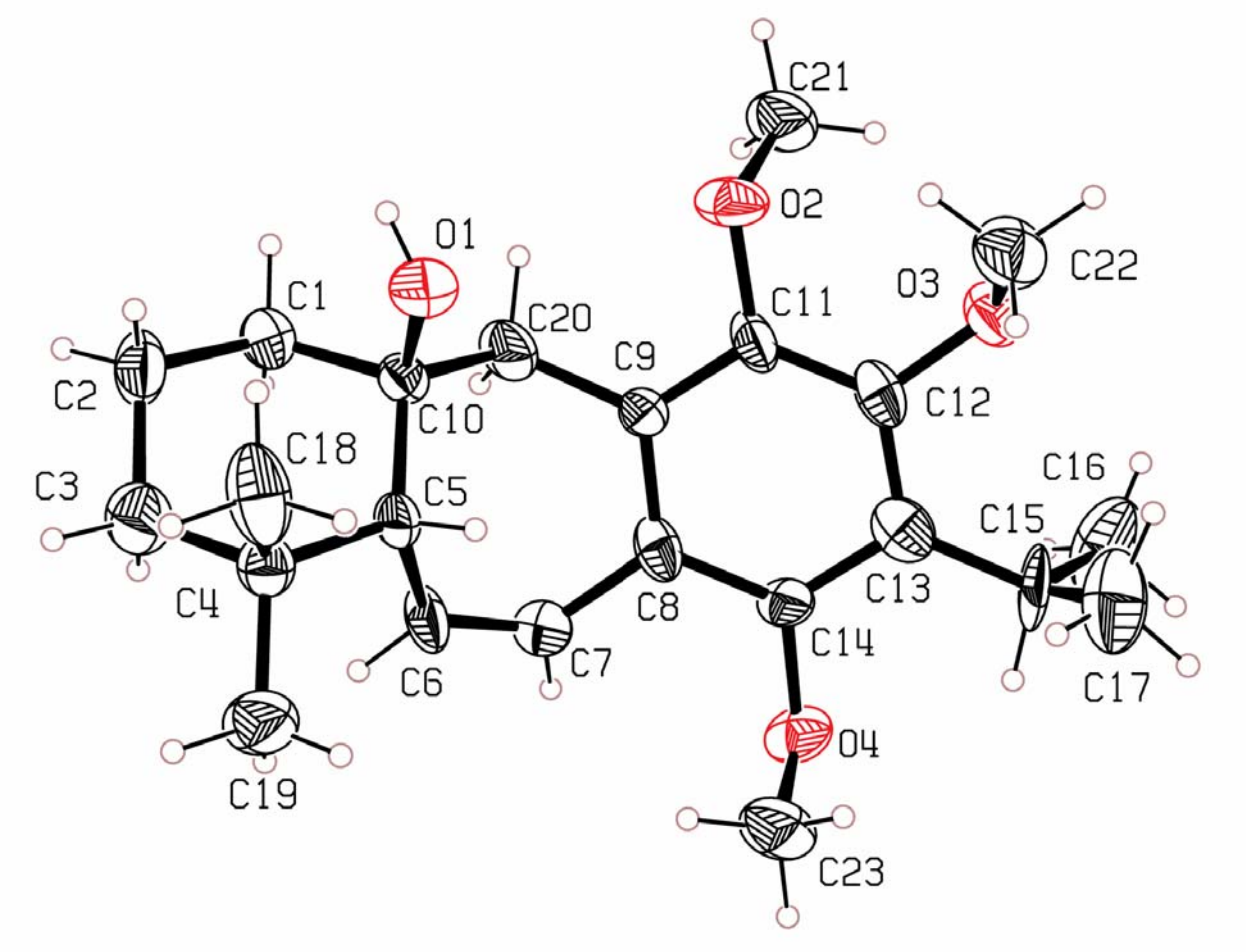


Table 1. Crystal data and structure refinement for uga519.

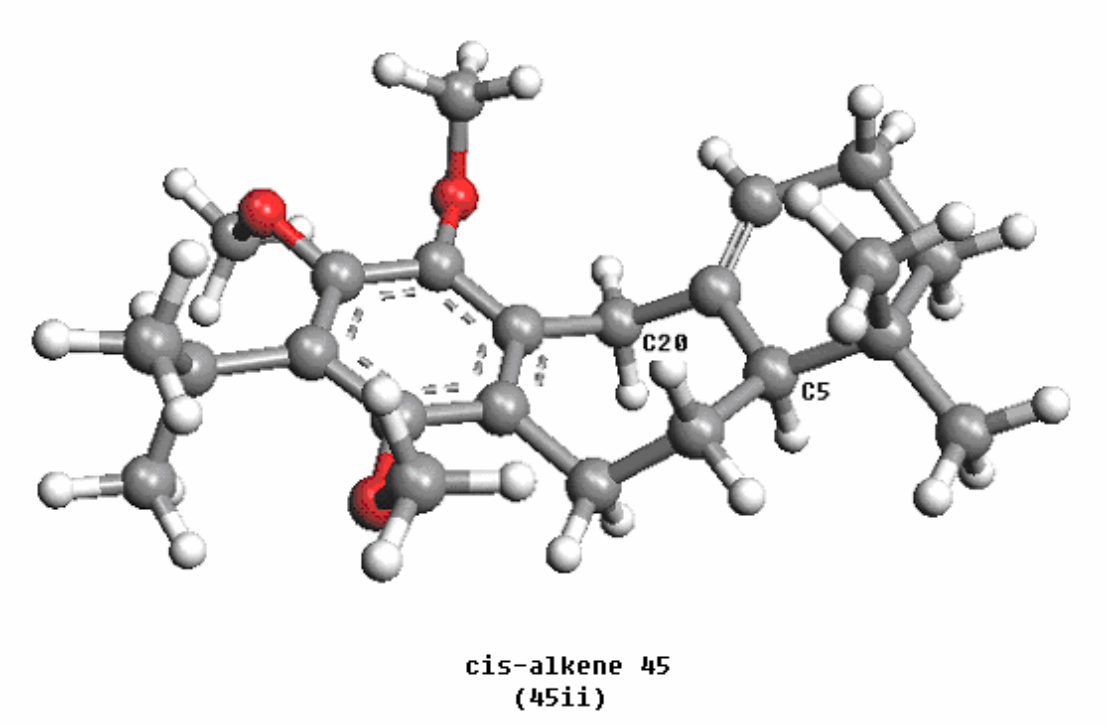
Identification code	uga519
Empirical formula	C46 H68 O8
Formula weight	749.00
Temperature	273(2) K

Wavelength	0.71073 A
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 11.242(12) A alpha = 89.054(14) deg.
	b = 13.548(14) A beta = 79.511(14) deg.
	c = 14.696(15) A gamma = 83.547(14) deg.
Volume	2187(4) A^3
Z, Calculated density	2, 1.137 Mg/m^3
Absorption coefficient	0.076 mm^-1
F(000)	816
Crystal size	0.18 x 0.12 x 0.06 mm
Theta range for data collection	2.06 to 28.91 deg.
Limiting indices	-15<=h<=15, -18<=k<=18, -19<=l<=19
Reflections collected / unique	23385 / 11265 [R(int) = 0.3577]
Completeness to theta = 28.91	97.6 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9955 and 0.9864
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11265 / 0 / 488
Goodness-of-fit on F^2	0.897
Final R indices [I>2sigma(I)]	R1 = 0.1911, wR2 = 0.3640
R indices (all data)	R1 = 0.5174, wR2 = 0.5368
Extinction coefficient	0.38(3)
Largest diff. peak and hole	0.523 and -0.285 e.A^-3

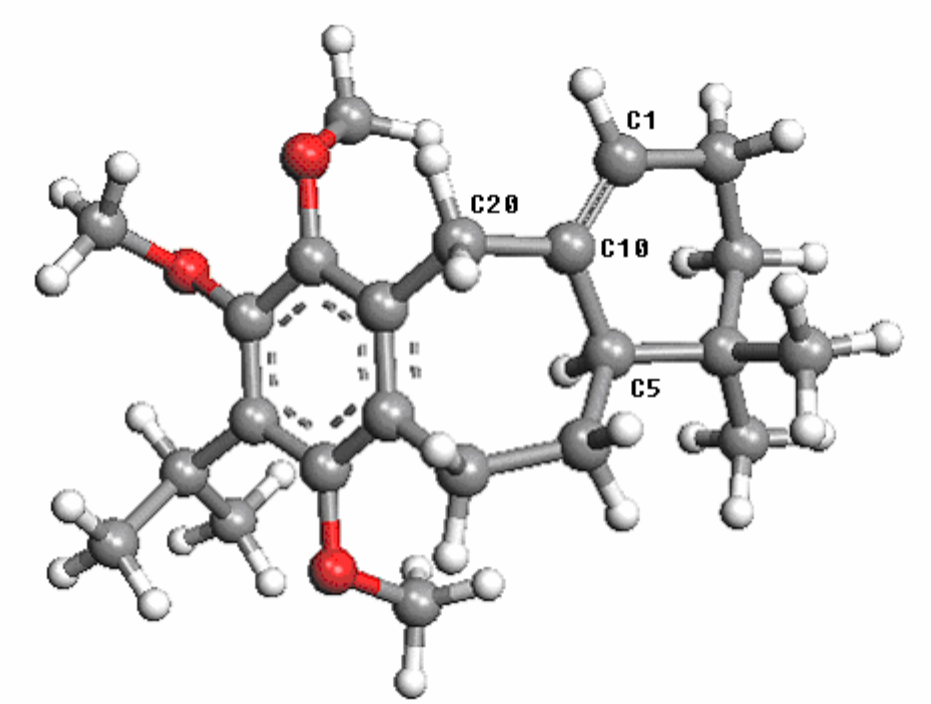
Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for uga519.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	-9913(8)	-5241(6)	4058(5)	92(3)
O(2)	-9878(8)	-7760(6)	4409(5)	85(3)
O(3)	-10536(8)	-9338(6)	3421(6)	83(3)
O(4)	-8347(8)	-8080(6)	623(6)	81(3)
C(1)	-7867(13)	-4734(9)	3866(8)	84(4)
C(2)	-8195(14)	-3629(9)	3763(10)	97(5)
C(3)	-8247(14)	-3392(10)	2750(10)	101(5)
C(4)	-9168(12)	-3953(9)	2349(8)	66(3)
C(5)	-8897(11)	-5075(7)	2520(7)	60(3)
C(6)	-7821(12)	-5540(9)	1783(8)	81(4)
C(7)	-7650(12)	-6495(10)	1588(8)	76(4)
C(8)	-8395(11)	-7247(8)	2057(9)	66(3)
C(9)	-8754(11)	-7203(8)	3033(8)	61(3)
C(10)	-8710(10)	-5405(8)	3476(7)	53(3)
C(11)	-9500(12)	-7876(9)	3435(9)	73(4)
C(12)	-9830(12)	-8635(9)	2964(10)	74(4)
C(13)	-9474(12)	-8757(10)	1994(10)	78(4)
C(14)	-8730(11)	-8031(9)	1574(7)	63(3)
C(15)	-9817(17)	-9551(9)	1481(11)	105(5)
C(16)	-9125(18)	-10595(12)	1642(13)	162(8)
C(17)	-11080(16)	-9506(13)	1392(13)	145(7)
C(18)	-10457(13)	-3575(10)	2849(11)	111(5)
C(19)	-9062(14)	-3731(10)	1338(9)	106(5)
C(20)	-8200(13)	-6459(8)	3582(9)	82(4)
C(21)	-9357(14)	-8549(10)	4960(9)	108(5)
C(22)	-11771(13)	-8923(11)	3814(9)	104(5)
C(23)	-9004(14)	-7463(10)	75(9)	108(5)

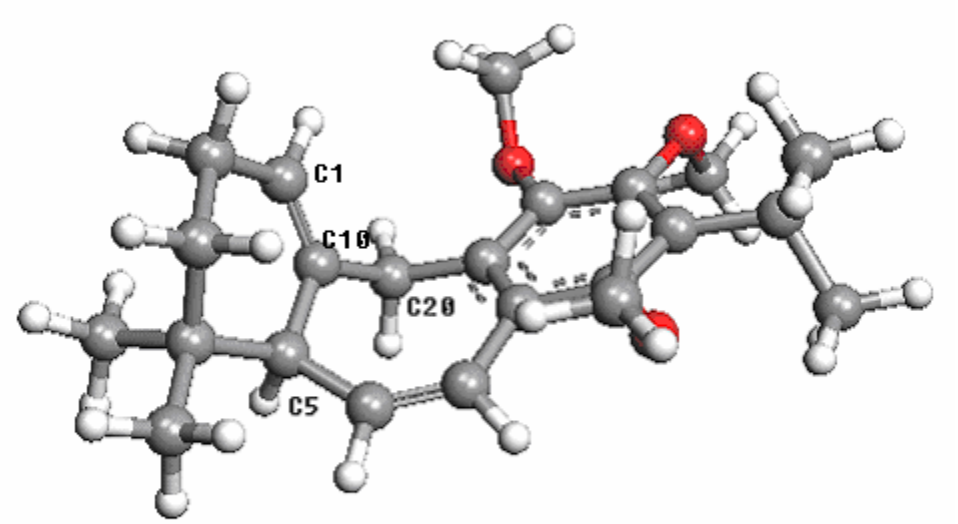
Appendix IV: Calculation of Olefins



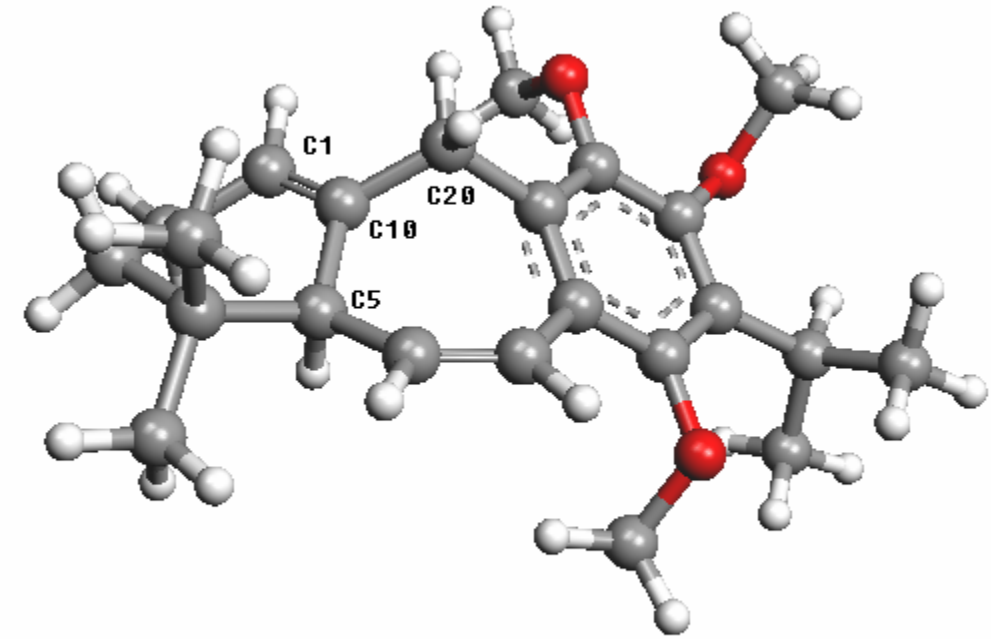
cis-alkene 45
(45ii)



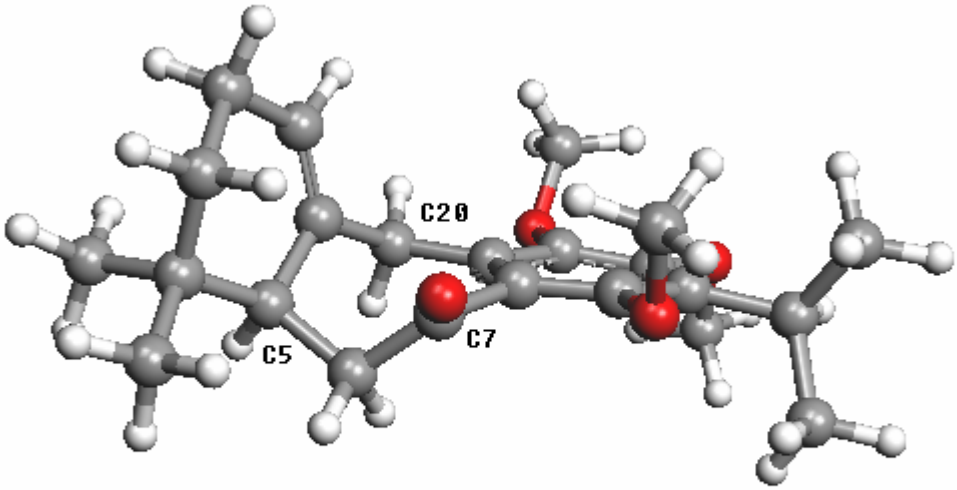
trans-alkene 45
(45i)



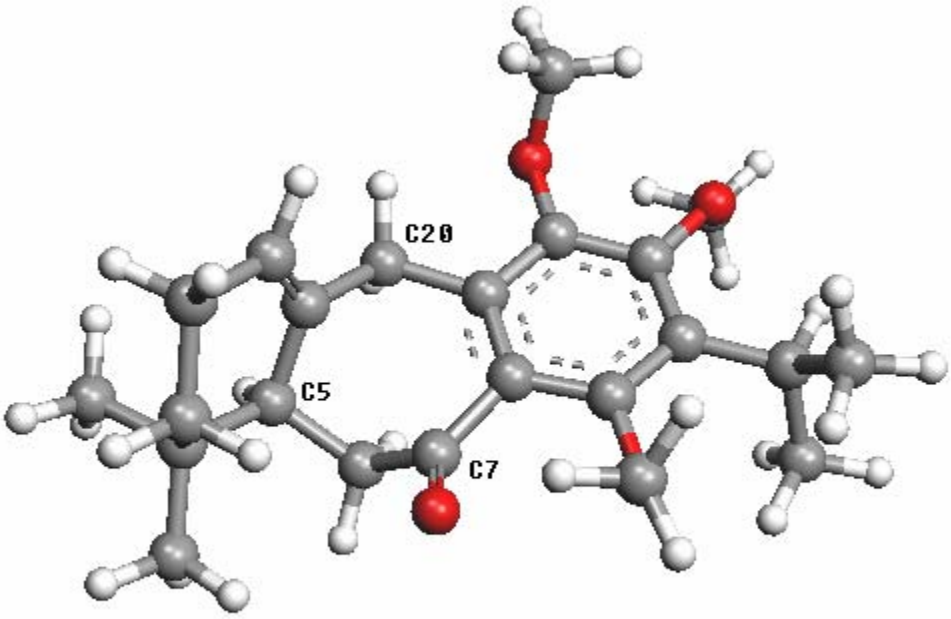
cis-diene 71
(71ii)



trans-diene 71
(71i)



cis-ketone 61
(61ii)



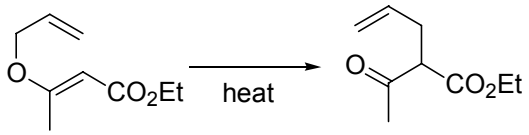
cis-ketone 61
(61ii)

PART III:

THE REGIOCHEMISTRY OF THE *ORTHO*-CLAISEN REARRANGEMENT OF *BIS*-(ALLYLOXY)-POLYCYCLIC AROMATICS

Introduction and Background

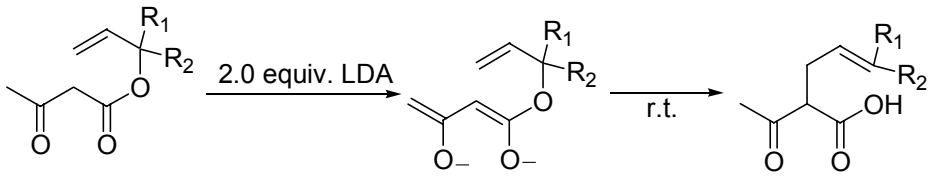
The first Claisen rearrangement was reported by Ludwig Claisen in 1912,[1] when *ortho*-allylated ethyl acetoacetate was distilled in the presence of NH_4Cl and a C-allyl isomer was collected (Scheme 1).



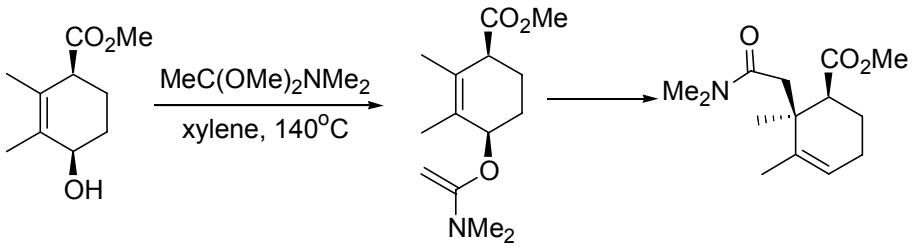
Scheme 1

The utility of the Claisen rearrangement has resulted in the development of a considerable number of related [3,3]-sigmatropic rearrangements,[2a-h] such as the Carroll rearrangement,[3] the Eschenmoser rearrangement,[4] the Johnson rearrangement,[5] the Ireland-Claisen rearrangement,[6] the Reformatsky−Claisen rearrangement,[7] the thio-Claisen rearrangement,[8] and the aza-Claisen rearrangement[9] (Scheme 2).

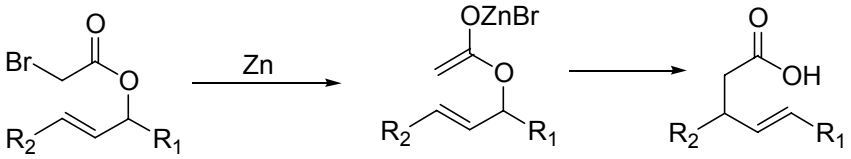
Carroll rearrangement:



Eschenmoser rearrangement:

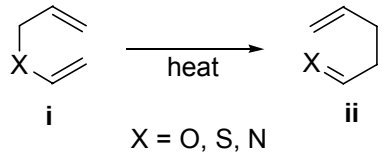


Reformatsky-Claisen rearrangement:



Scheme 2

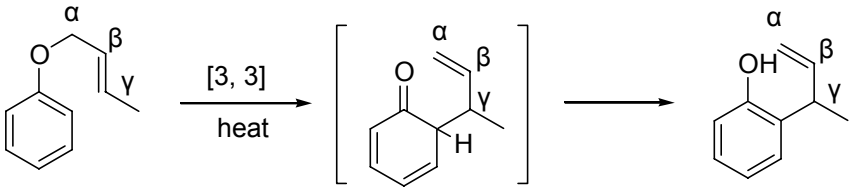
As originally described,[1] this type of process is defined as "the thermal isomerization of an allyl vinyl ether **i** or of its nitrogen or sulfur containing analogue derivatives to afford a bifunctionalized molecule **ii**" in a [π2s +π2s +π2s] process (Scheme 3). A Claisen rearrangement can be formally considered the intramolecular S_N2' addition of a carbonyl enol to an allylic alcohol, forming a carbon−carbon σ bond (a [3,3]-sigmatropic rearrangement) with simultaneous double bond migration.



Scheme 3

When the X is sulfur it is called a thio-Claisen rearrangement,[8] whereas it is called an aza-Claisen rearrangement[9] when X is nitrogen (Scheme 3).

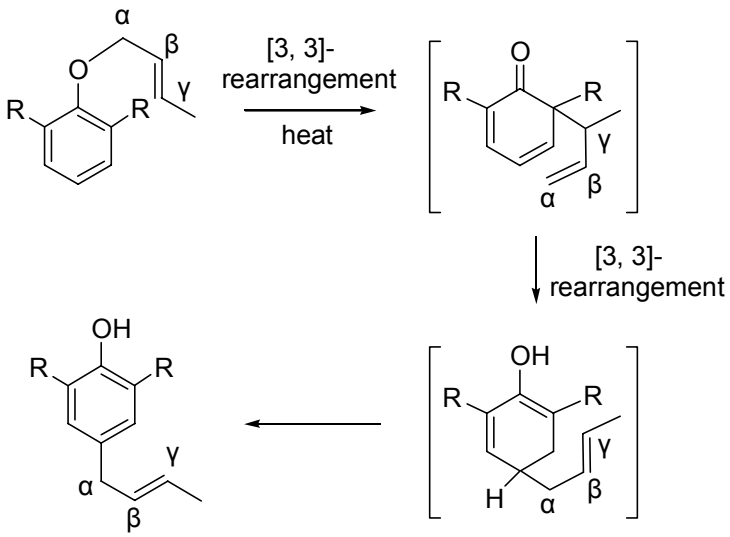
The first paper published by Ludwig Claisen[1] also described the transformation of allyl phenyl ether into C-allyl phenol. In the Claisen rearrangement of an allyl aryl ether, the first [3,3]-sigmatropic rearrangement step affords an *ortho*-allylphenol after enolization. This process is known as the *ortho*-Claisen rearrangement.[10] Note that in the product the γ-position of the allyl ether is the point of attachment of the aromatic ring and the β,γ-double bond of the substrate migrates to the α,β-position (Scheme 4).[11]



Scheme 4

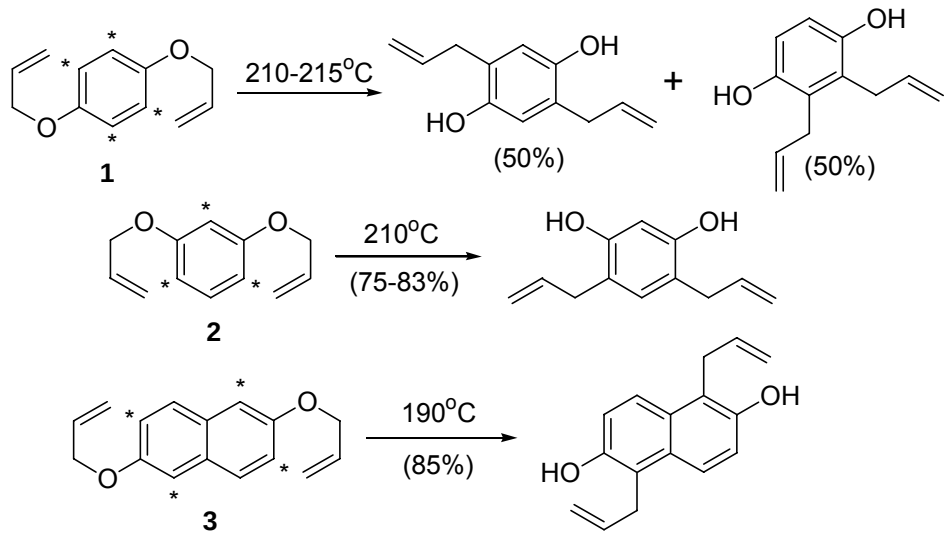
When both of the *ortho* positions of the allyl ether are occupied, the rearrangement takes place first to the *ortho* position, followed by a second [3,3]-sigmatropic rearrangement (Cope rearrangement) and enolization, to give a *para*-allyl phenol. This reaction is called the *para*-Claisen rearrangement.[12] In contrast to the inversion of the allyl group in an *ortho*-Claisen rearrangement, the migration proceeds without inversion of the allyl group in a *para*-Claisen rearrangement (Scheme 5).

While the *ortho*-Claisen rearrangement of allyl phenyl ethers has been rigorously studied,[13] the rearrangement of *bis*-allyl aryl ethers has been limited to the ethers of hydroquinone (**1**),[14] resorcinol (**2**),[15] and 2,6-dihydroxynaphthalene (**3**).[16] As shown in scheme 6, the rearrangement of *bis*-1,4-(allyloxy)benzene (**1**)[14] gives two isomeric *ortho*-Claisen



Scheme 5

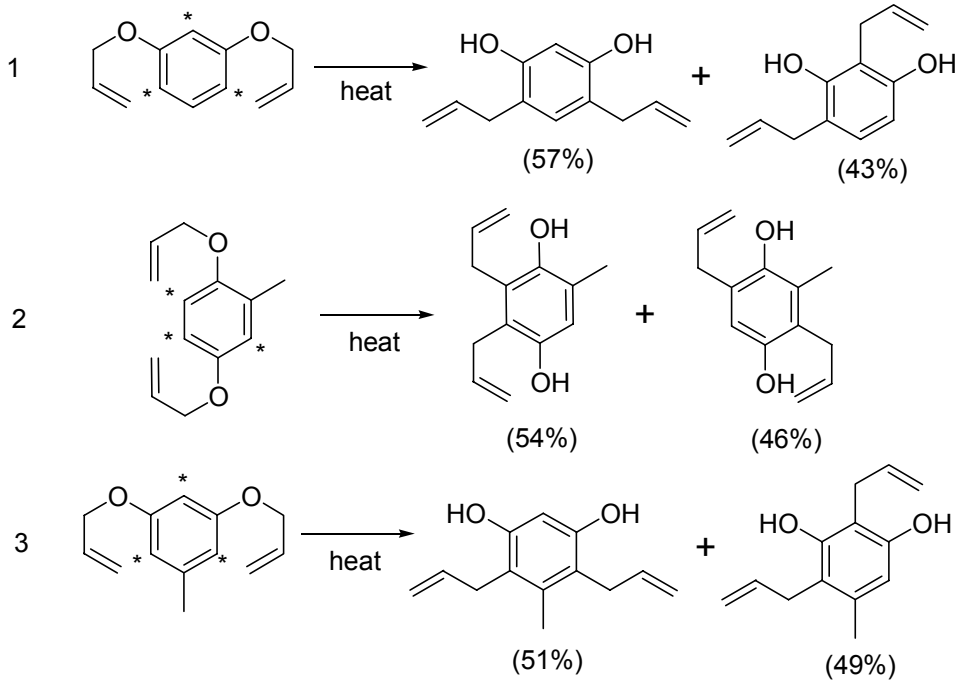
rearrangement products, whereas the rearrangements of *bis*-1,3-(allyloxy)benzene (**2**)[15] and *bis*-2,6-(allyloxy)naphthalene (**3**)[16] give single products (an asterisk indicates an available *ortho* position).



Scheme 6

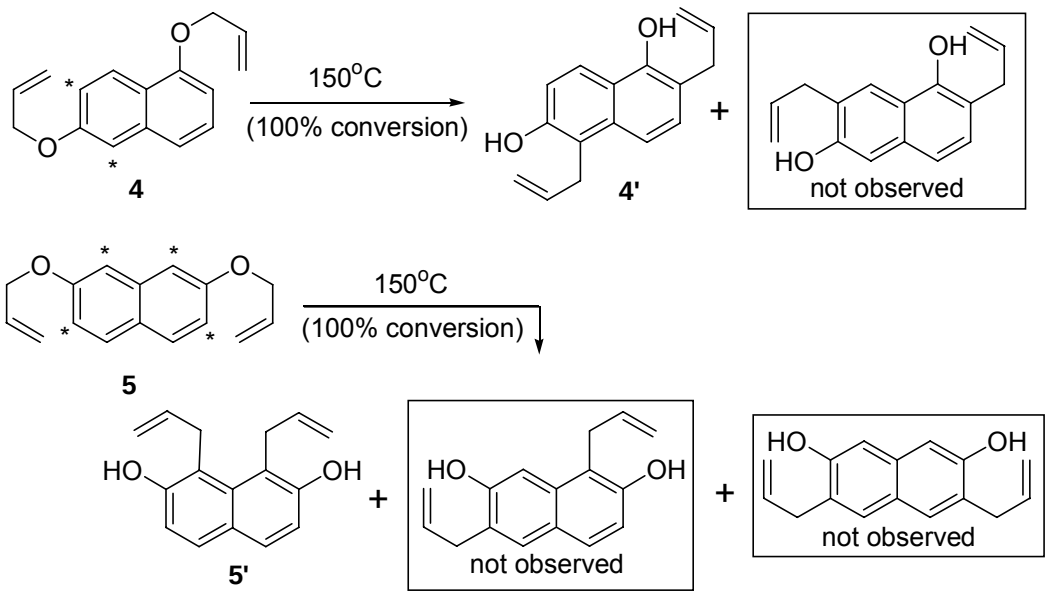
Early Study in the Rearrangement of Simple *bis*-Allyl Ethers

The rearrangement of three resorcinol derivatives has been studied (Scheme 7).[17] The rearrangement of these substrates obeys the statistical distribution where there is no preference for migration to either of the two unoccupied *ortho* positions. In contrast to the result reported by Hurd and Greengard in the rearrangement of resorcinol derivative **2**[15] we observed an equal amount of two possible products.



Scheme 7

While the Claisen rearrangement of benzene derivatives is not selective, a distinct pattern in the rearrangement of the *bis*-(allyloxy)naphthalenes has been revealed.[17] As shown in Scheme 8, rearrangement of two *bis*-(allyloxy)naphthalene derivatives **4** and **5** gave a single product although **4** could generate two possible products, and **5** would give three different products.



Scheme 8

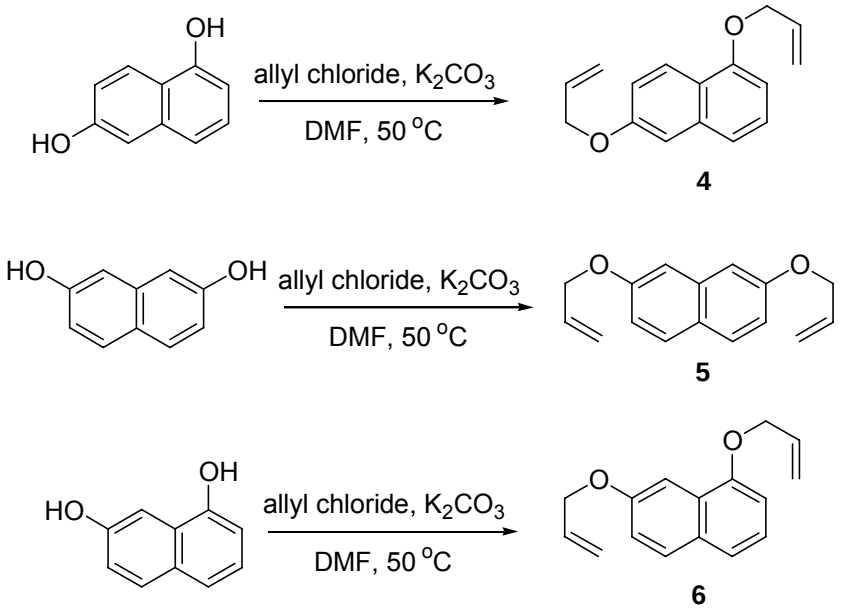
Based on these early observations, we decided to study the *ortho*-Claisen rearrangement of related *bis*-(allyloxy)polycyclic aromatics. Our hope was to observe the same selectivity of rearrangement on larger aromatic systems. Because we required various allyl substituted anthracenes and phenanthrenes for other projects, the rearrangement of the *bis*-allyl ethers of eight polycyclic aromatic compounds was investigated.

Results and Discussion

The dihydroxy naphthalene derivatives are available in a single step synthesis from commercially available starting materials. The *bis*-allyl ethers can be formed by heating the requisite diol with 2.5 equivalents of freshly distilled allyl chloride and 4.0 equivalents of K_2CO_3 in anhydrous DMF at 50 ℃ overnight. However, the preparation of anthracene and phenanthrene

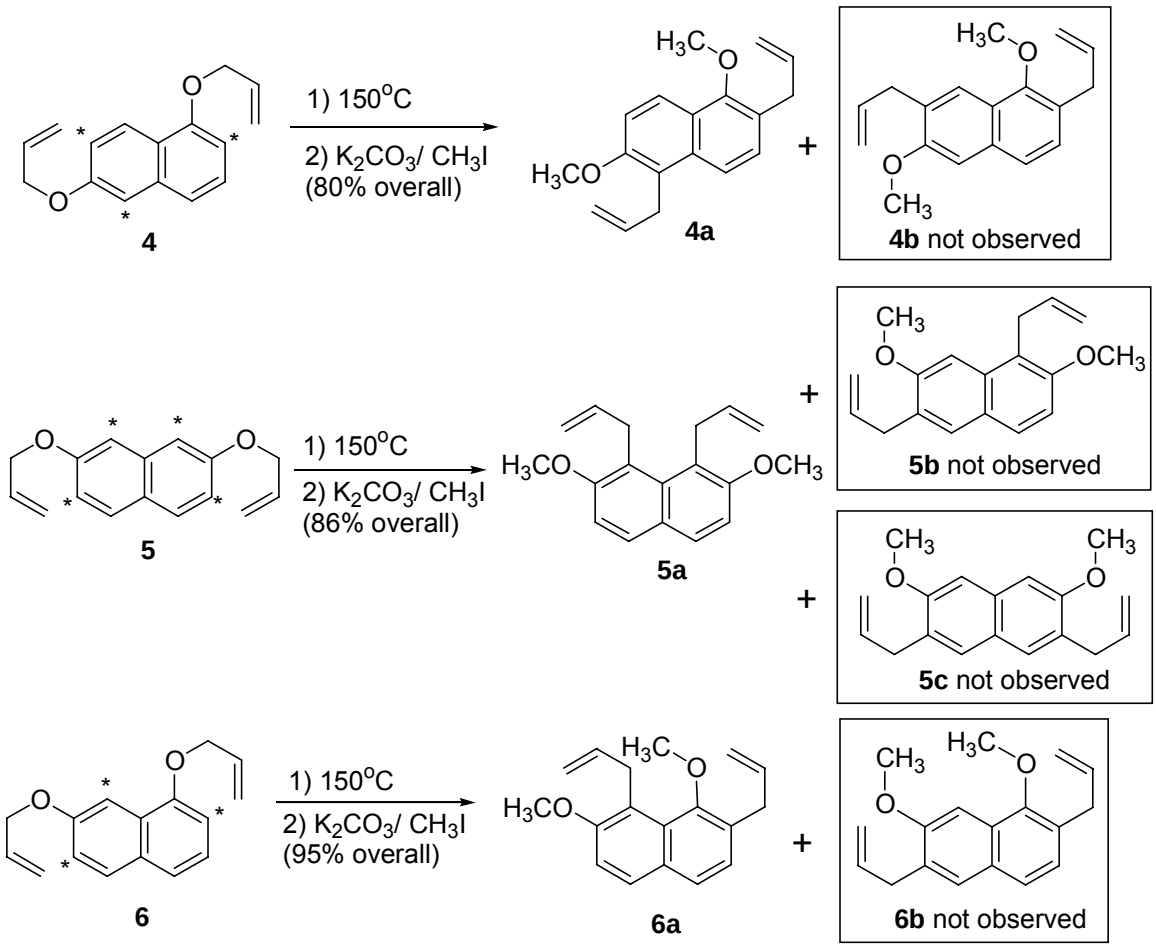
derivatives turned out to be problematic. Many of the known preparation methods required harsh conditions and gave low yields of the desired *bis*-allyl ethers, or the isolation of the desired product was difficult.

Scheme 9 gives the preparation of *bis*-1,6-(allyloxy)naphthalene (**4**), *bis*-2,7-(allyloxy)naphthalene (**5**) and *bis*-1,7-(allyloxy)naphthalene (**6**), using commercially available starting materials. Gram scales of these *bis*-allyl ethers were prepared.



Sceme 9

The [3,3]-sigmatropic rearrangements were achieved by dissolving the *bis*-allyl ether in an equal amount of diethylaniline,[18] and the resulting mixture was placed in a sealed tube, heated for 12 h, cooled, and then subjected to standard ethereal workup. Without further purification, the crude phenolic product was then methylated using a standard procedure.[19] Moderate to high yields were obtained through this two-step process (Scheme 10).

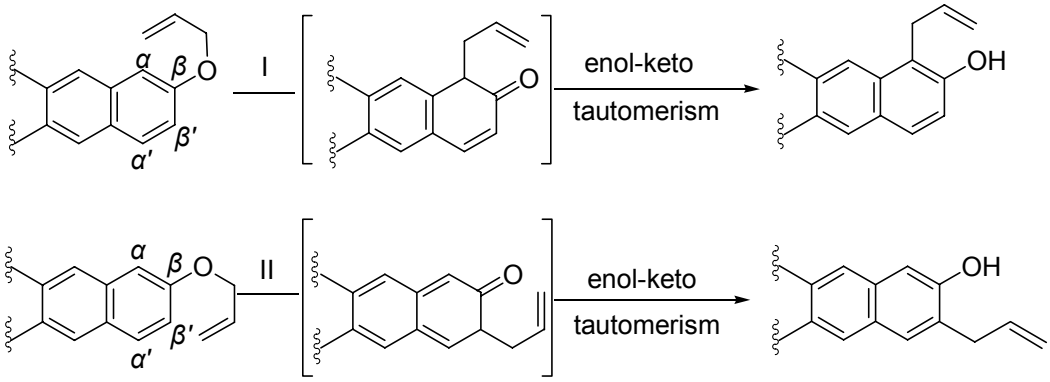


Scheme 10

The resulting methylated products were analyzed by their ^{1}H NMR spectra. ^{1}H NMR analysis of compounds **4a** and **5a** supported our proposed structures. In the rearrangement of **5**, the highly symmetric product **5a** showed only two aromatic signals with a *J* value of 9.0 Hz. In the rearrangement of **4**, all four aromatic hydrogen atoms had the identical coupling constants of 9.0 Hz. There are four aromatic peaks in **6a** with two pairs of coupling constants. The *J* values are 8.4 Hz and 8.8 Hz, respectively. These two high values of the coupling constants indicated that the rearranged product **6a** had two pairs of adjacent aromatic hydrogens; if rearrangement had occurred isomer **6b** had been produced and this compound would have shown two singlets in

the aromatic range on ^{1}H NMR, due to two isolated aromatic hydrogens in the left ring after the reaction. Analysis of the coupling constants revealed that, even though there are other sites for the *ortho* rearrangement, *bis*-allyl ethers **4**, **5** and **6** gave only the proposed structures of **4a**, **5a** and **6a** without any observation of compounds **4b**, **5b**, **5c** or **6b**.

These results indicate that when there is a choice between two unsubstituted *ortho* positions, the rearrangement always occurs at the *α*-position (Scheme 11). This regioselectivity can be explained by considering the aromaticity of the initial ketone product that is generated. For example, rearrangement toward the *β′*-position generates a non-aromatic initial ketone (cf. II), making this a higher energy intermediate and therefore a less likely reaction pathway. Alternatively, molecular orbital calculations show bond orders of 1.724 and 1.603 for the *α*,*β*- and *β*,*β′*-bonds of naphthalene, respectively,[20] indicating that the *α*,*β*-bond (cf. I) has more double bond character than does the *β*,*β′*-bond (cf. II) (Scheme 11).

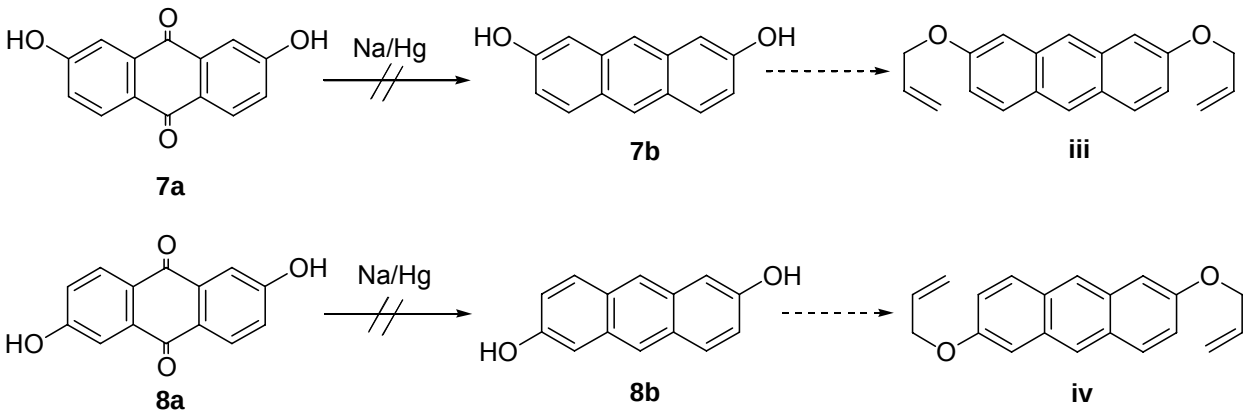


Scheme 11

Given these results on naphthalene derivatives, we wanted to extend this chemistry to larger aromatic systems, such as anthracene derivatives. Anthracene has an extra six-membered

aromatic ring compared to naphthalene derivatives. Therefore, it should present similar chemical behavior as the naphthalene derivatives.

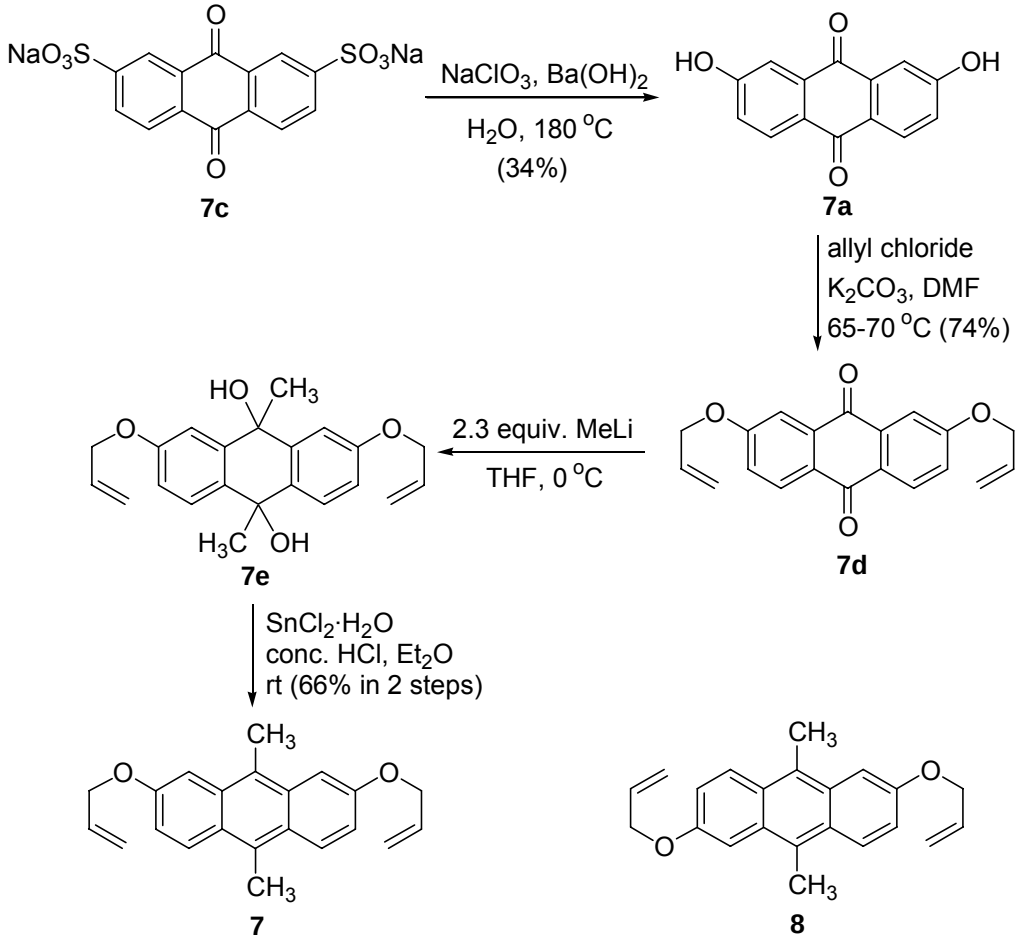
Since the requisite dihydroxyanthracenes are not commercially available, the preparation of *bis*-(allyloxy)-anthracene derivatives was required. In the beginning, we expected to have allyl ethers on two of the 2, 3, 6 and 7 positions of the anthrathene system. Our original design was to prepare **iii** or **iv**. It was expected that **iii** and **iv** could be synthesized from 2,7-dihydroxyanthraquinone (**7a**) and commercially available anthraflavic acid **8a**, respectively, by reductive aromatization to **7b** and **8b** and then alkylation (cf. Scheme 12).



Scheme 12

The reductive aromatization of anthraflavic acid **8a** to **8b** was reported by using aluminium amalgam.[21] Unfortunately, our efforts to reduce the C(9)−C(10) carbonyls did not give the desired products, presumably due to the instability of the product. Moreover, the extreme low solubility of the diol caused difficulty in identification and purification. It turned out to be a better choice to protect the OH groups before the reduction of C(9)−C(10) carbonyl groups. We were aware that the free 9 and 10 positions of the anthracene system would not be

robust enough to withstand the further reaction conditions. Therefore, a variation on the original synthetic route was explored.

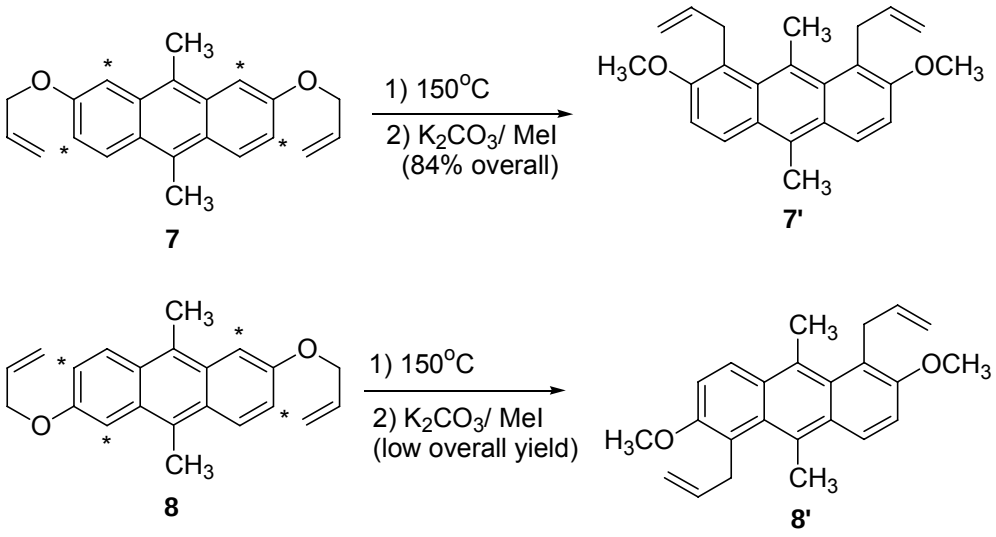


Scheme 13

The synthesis of **7** is summarized in Scheme 13. Starting from commercially available anthraquinone-2,7-disulfonic acid disodium salt (**7c**), 2,7-dihydroxyanthraquinone (**7a**) was achieved in 34% yield in an autoclave with $NaClO_3$, $Ba(OH)_2$ and water.[22] Although the yield was low, a sufficient amount of 2,7-dihydroxyanthraquinone was collected to permit further study. In view of the solubility issue, it was decided to protect the hydroxyl groups at an early stage. Alkylation of 2,7-dihydroxyanthraquinone (**7a**) with allyl chloride and anhydrous K_2CO_3

in DMF gave *bis*-allyl ether **7d** in moderate yield. Although direct reduction of *bis*-allyl ether **7d** by using aluminum amalgam should give the anthracene system, this process did not work well on our hands.

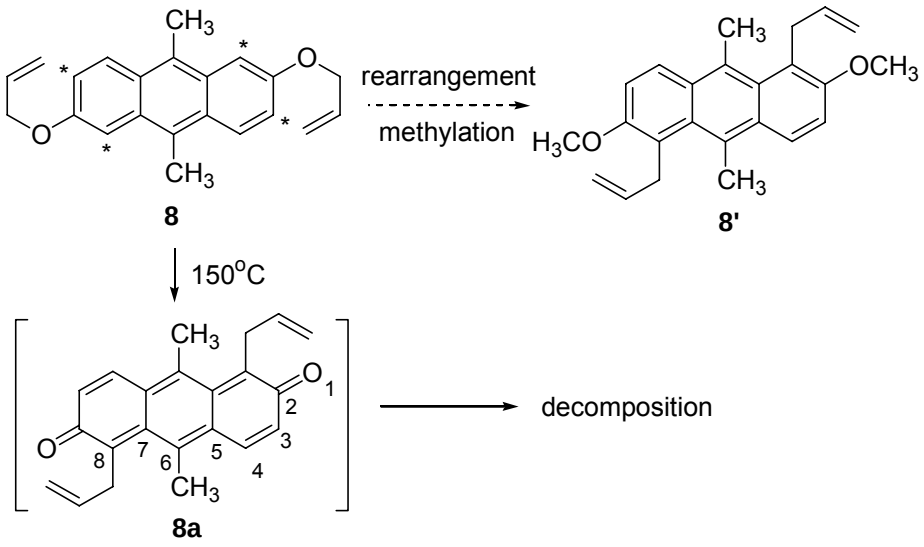
Study by Dufraisse in 1942,[23a-e] showed that the C(9) and C(10) carbonyls of anthraquinone behave like normal carbonyls, and react with Grignard[23a-e] or organolithium reagents.[24a-d] Reductive aromatization of the resulting *bis*-alcohol using a variety of reagents gave the anthracene framework.[23,24] Hence, when intermediate **7d** was subjected to 2.3 equivalents of methyl lithium, addition to the 9 and 10 carbonyls produced crude *bis*-alcohol **7e**.[24] On the assumption that **7e** would not be stable to silica gel, the crude diol was used directly in the next step. The reductive aromatization was achieved with $SnCl_2 \cdot H_2O$ and concentrated HCl in diethyl ether[25] at room temperature to give 2,7-diallyloxy-9,10-dimethylanthracene (**7**) in 66% yield. The presence of methyl groups at C(9) and C(10) reduces the tendency toward oxidation on those sites. This strategy was also applied to the synthesis of 2,6-diallyloxy-9,10-dimethylanthracene **8**.



Scheme 14

bis-Allyl ethers **7** and **8** were then subjected to *ortho*-Claisen rearrangement and methylation. *bis*-Allyl ether **7** gave a single product with 83% overall yield (Scheme 14). ^{1}H NMR of the product showed two doublets at 6.85 and 7.58 with identical coupling constant of 8.4 Hz. This supported the highly symmetric structure of **7′**.

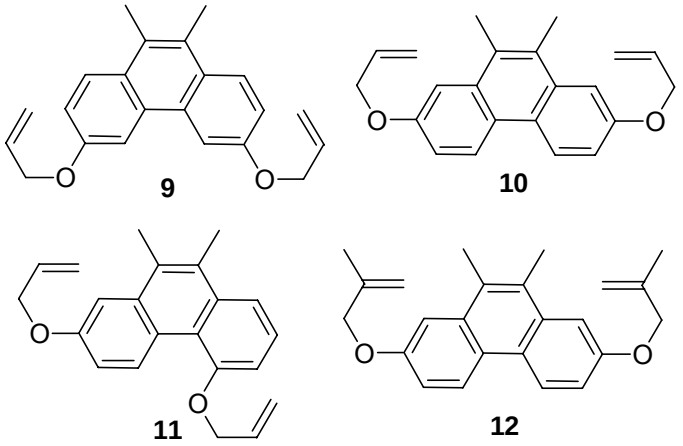
In contrast to the high yield of the single rearranged product **7′**, the rearrangement and methylation of *bis*-allyl ether **8** did not give any desired product, presumably because the intermediate **8a** undergoes rapid decomposition under the reaction conditions (Scheme 15). Any nucleophile present in the reaction medium could attack **8a** via 1,2-, 1,4-, 1,6- or even 1,8-fashions.



Scheme 15

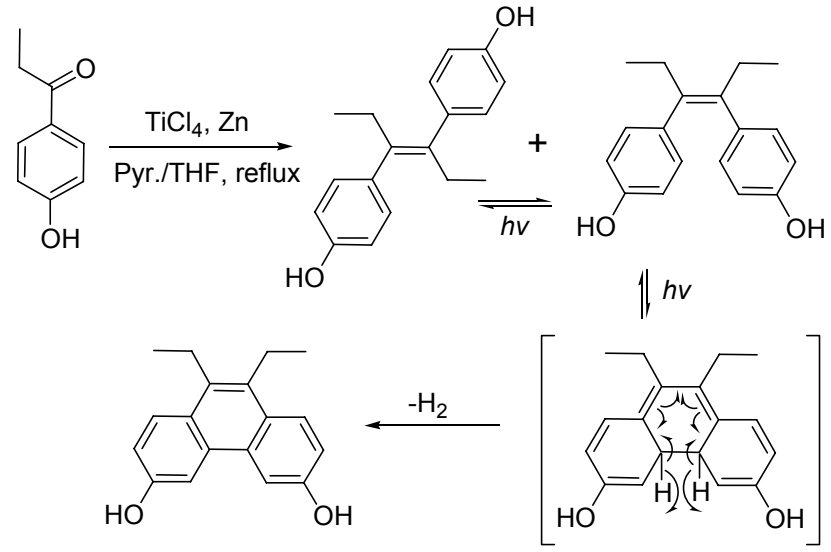
Rearrangement of Phenanathrene Derivatives

We then explored the application of *ortho*-Claisen rearrangement of *bis*-allyl ethers on the phenanthrene system. Although there are many possible phenanthrene derivatives, *bis*-allyl ethers **9**-**12** were the focus of our study (Scheme 16).



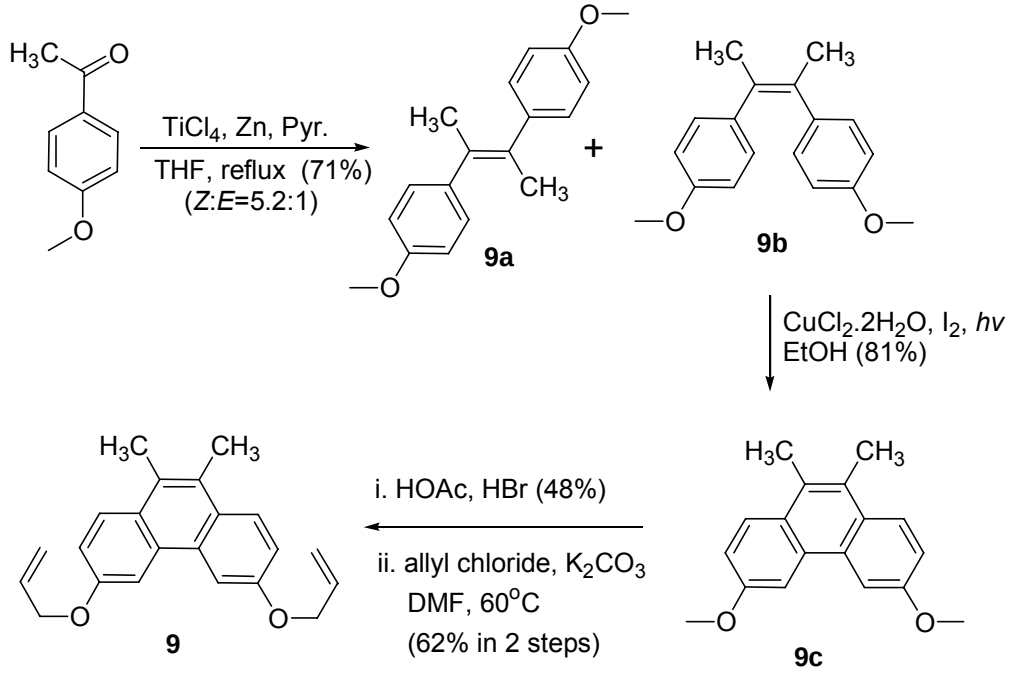
Scheme 16

Once again, these phenanthrene derivatives are not commercially available, and there are few methods to make or isolate the desired substituted frameworks. Fortunately, Leimner[26] *et al.* have reported a dimerization of 4′-hydroxypropiophenone to give a mixture of *E*- and *Z*-alkenes under McMurry conditions. Based on Doyle's study,[27] this stilbene derivative will undergo photochemical oxidative cyclization to give a phenanthrene (Scheme 17).



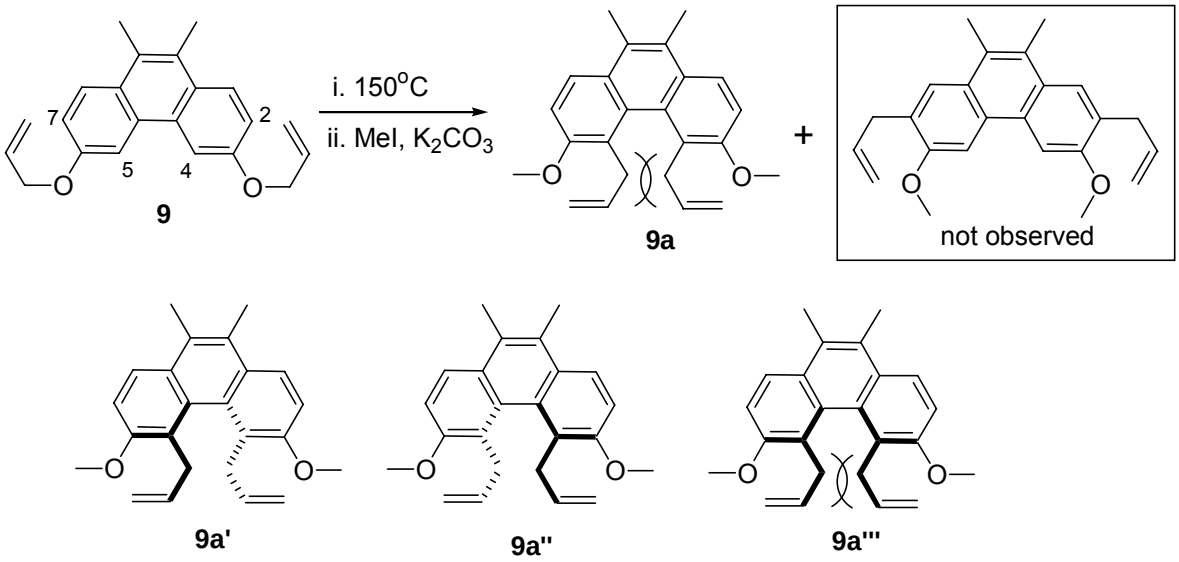
Scheme 17

The protected hydroxyl group improved the yield in both the dimerization and photochemical oxidative cyclization reactions. *para*-Methoxyacetophenone was first used. As shown in Scheme 18, symmetric *bis*-allyl ether **9** was prepared using Collins's route.[28] *para*-Methoxyacetophenone was dimerized under McMurry coupling conditions in 71% yield by using Zn/$TiCl_4$. The reaction gave a mixture of *E*- and *Z*-stilbenes **9a** and **9b** with a ratio of 1:5.2. When this mixture was subjected to irradiation and catalyzed by I_2 and $CuCl_2$, phenantherene **9c** was isolated in 81% yield. In theory, only the *E*-stilbene **9b** can cyclize to give **9c**, this indicated that all of the *Z*-stilbene **9a** had been photoisomerized to **9b** under the reaction conditions. Deprotection of the methoxy groups of **9c** using concentrated HBr in refluxing HOAc gave a polar diol. After protection of the resulting crude diol with allyl chloride, *bis*-allyl ether **9** was obtained in 62% overall yield.



Scheme 18

The *ortho*-Claisen rearrangement of *bis*-allyl ether **9** gave a product having an unsymmetric ^{1}H NMR spectrum. If the allyl groups rearrange to the 4 and 5 positions, steric congestion would distort the aromatic system to produce a helical molecule. As shown in Scheme 19, **9a** is no longer a planar molecule; instead, two pairs of enantiomers will be present as a mixture. We can see, **9a′** and **9a′′** are enantiomers, and **9a′′′** is a less stable structure and most likely will not be formed. This explains the complex ^{1}H NMR spectrum which shows a major product along with minor amounts of a more complicated species. The major product should be the enantiomers of **9a′** and **9a′′**, whereas the minor component would be **9a′′′**. On the other hand, if the *ortho*-Claisen rearrangement takes place at either the 2- or 7-positions, the NMR spectrum would be symmetric and thus easy to interpret (cf. rearrangements of *bis*-allyl ethers **10** and **11**).

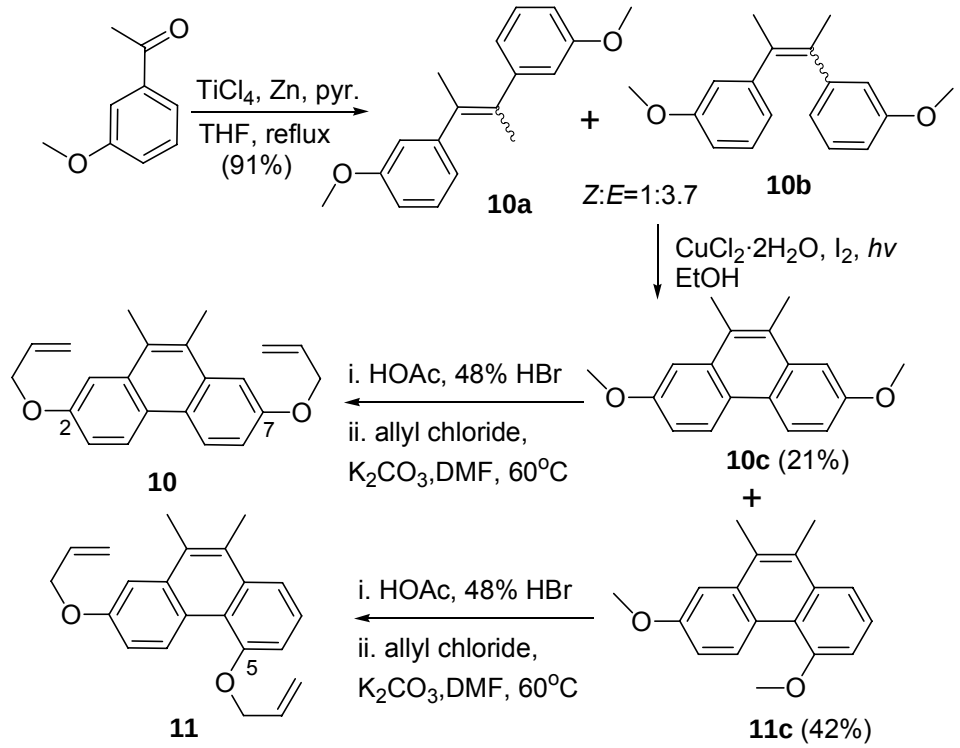


Scheme 19

In view of the steric congestion of alkyl groups on the 4- and 5-positions and the difficulty in characterizing the structures of the products, we decided to modify our original

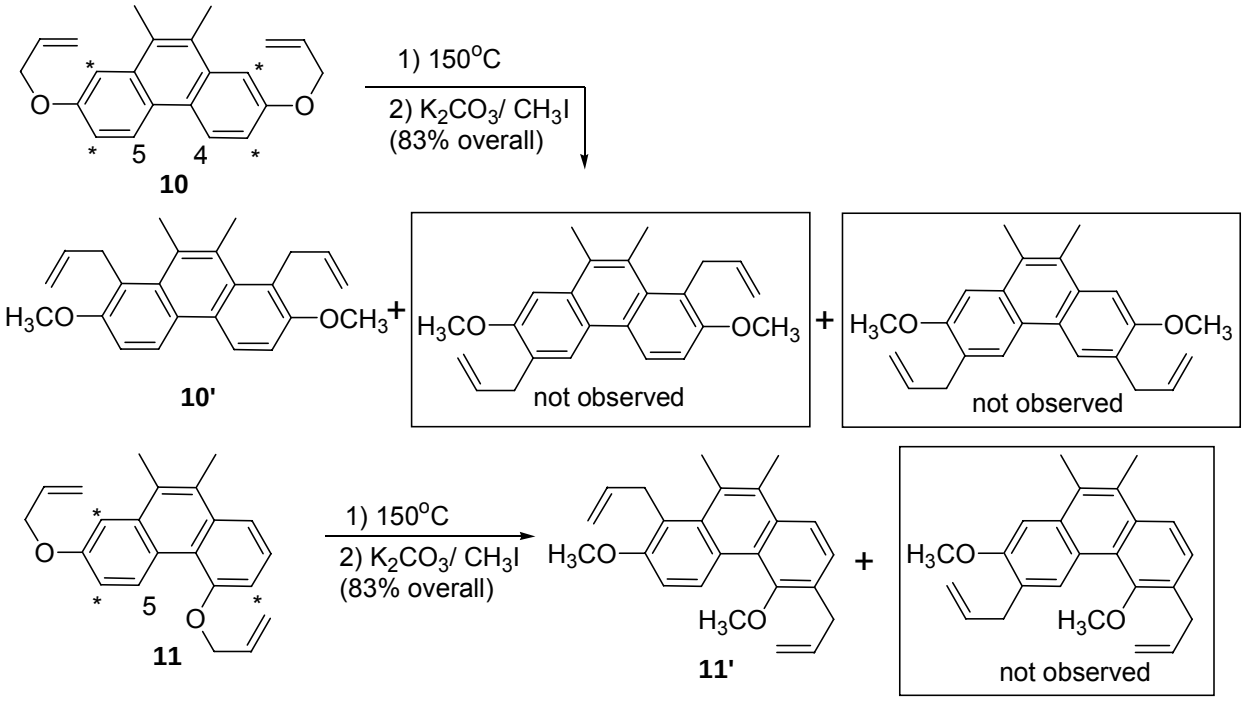
design to make some easily identifiable isomers, and to have as many unsubstituted benzylic positions as possible. Therefore, the hydroxyl groups at the 2,7-positions (cf. **10**), or at least one on either 2 or 7 position (cf. **11**), would be preferred.

The above synthetic strategy was used to prepare *bis*-allyl ethers **10** and **11** (Scheme 20). In the synthesis of *bis*-allyl ether **9**, *para*-methoxyacetophenone was used in the McMurry coupling reaction, which resulted in a single product after aromatization. The use of unsymmetrical acetophenones, however, produces mixtures of phenanthrene derivatives having different substitution patterns. For example, by starting with *meta*-methoxyacetophenone, the McMurry coupling, followed by irradiation, resulted in the formation of two separable methyl ethers **10c** and **11c**. Methyl ethers **10c** and **11c** were then subjected to deprotection and readily converted into the requisite *bis*-allyl ethers **10** and **11**.



Scheme 20

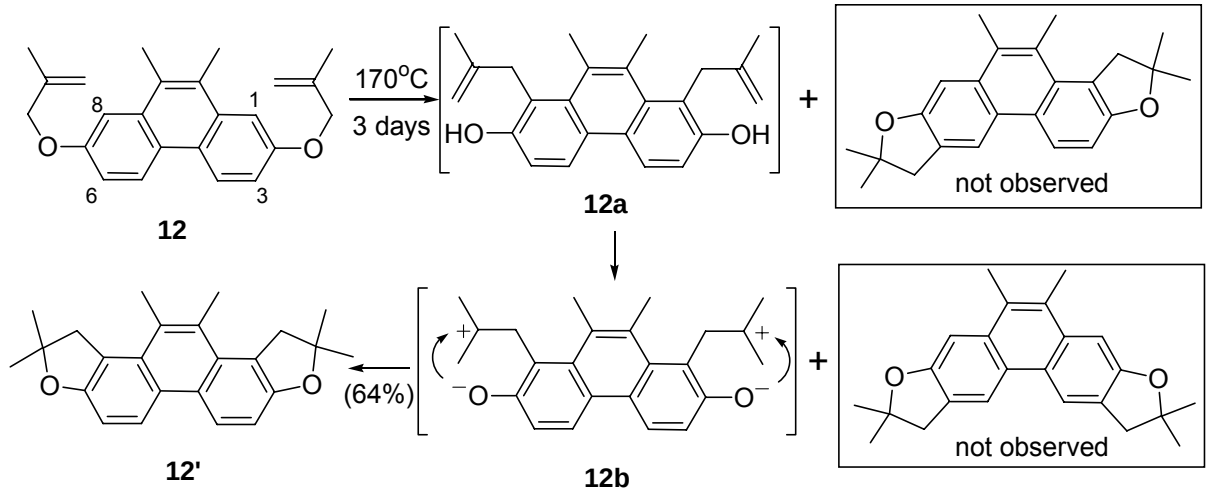
Because an allyl group can not rearrange to the more hindered 4- or 5-position in both *bis*-allyl ethers **10** and **11**, after methylation only one product was isolated in each case, and the spectra can be easily assigned. A single *J* value of 8.8 Hz in **10′** and two *J* values of 8.4 Hz and 9.2 Hz in **11′** on aromatic range supported our proposed structures (Scheme 21).



Scheme 21

In order to expand the scope of these *ortho*-Claisen rearrangements, a more substituted allyl ether, *bis*-allyl ether **12**, was synthesized from methyl ether **10c** via deprotection and allylation using 3-bromo-2-methylpropene and anhydrous K_2CO_3. However, the rearrangement reaction did not produce any diol. Instead, a non-polar spot was isolated without requiring methylation. ^{1}H NMR analysis of this unknown showed that this highly symmetric compound was ether **12′** which was cyclized after the *ortho*-Claisen rearrangement of *bis*-allyl ether **12**

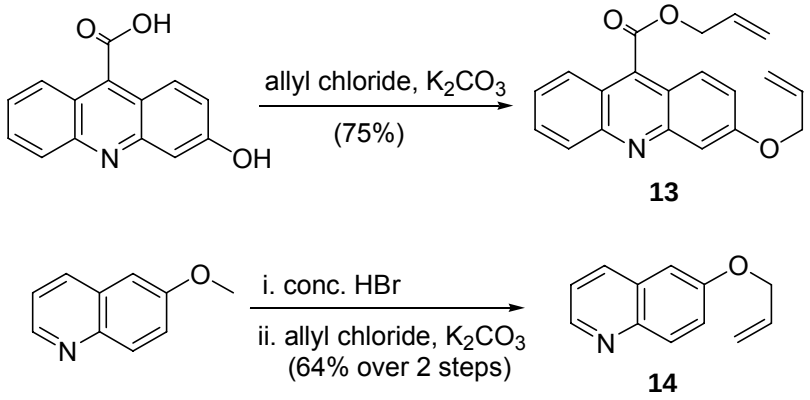
(Scheme 22). The other two possible compounds, resulted from rearrangement to 1,6- and 3,6-positions, were not observed in this reaction.



Scheme 22

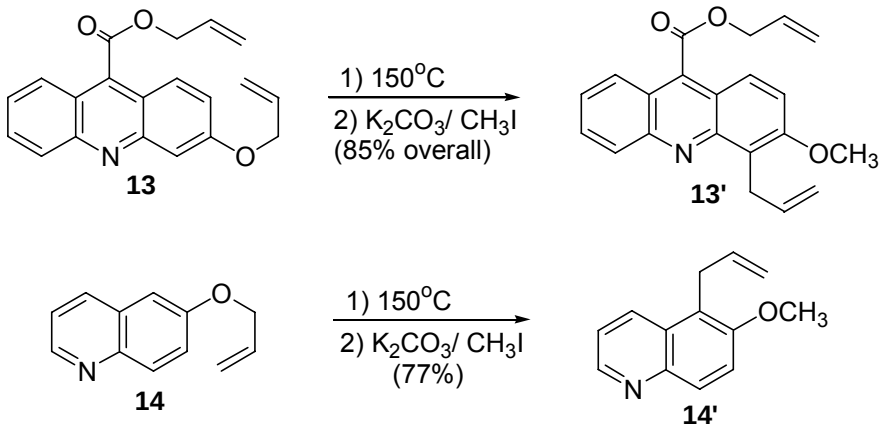
Rearrangement on Heterocyles

With these results in hand, we wanted to explore our study on the regioselectivity of the *ortho*-Claisen rearrangement of allyl ethers of heterocyclic polycyclic aromatics. As shown in Scheme 23, allyl ethers **13** and **14** were prepared.



Scheme 23

The rearrangement followed by methylation gave **13′** and **14′**, respectively, which is consistent with the trend seen with our polycyclic aromatic systems (Scheme 24).



Scheme 24

In summary, seven examples of the *ortho*-Claisen rearrangement of the *bis*-allyloxy ethers of naphthalene, anthracene, and phenanthrene derivatives were studied. Every reaction gave only a single rearranged product, even where two or three isomers were possible. The rearrangement of a substituted *bis*-allyloxy ether gave the same result.

Experimental Section

All reactions were run in anhydrous solvents under an atmosphere of nitrogen.

General Procedure A: Synthesis of *bis*-allyl ethers

The diol (1.0 equivalent) is dissolved in freshly distilled *N, N*-dimethyl formamide (DMF) under nitrogen. Freshly distilled allyl chloride (2.5 molar equivalents relative to the diol) is added. Anhydrous K_2CO_3 (4.0 molar equivalents relative to the diol) is added. A reflux condenser is installed and the reaction mixture is stirred at 50 ℃ overnight. The resulting mixture is cooled to rt and ether and saturated aqueous NH_4Cl are added. The mixture is transferred to a separatory funnel, where the layers are shaken and aqueous layer drained. The aqueous layer is extracted with ether and combined ethereal extracts are washed with water (2 ×) and brine (2 ×). The ethereal layer is dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product is purified using flash chromatography on silica gel.

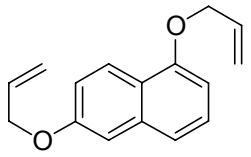
General procedure B: Rearrangement of allyl ethers

A *bis*-allyl ether is dissolved in ether and the solution is transferred to a 10-mL thick-walled glass reaction vessel with a Teflon screw top. The ether is removed by gently heating the vessel and bubbling nitrogen. An equal amount (by mass) of *N, N*-diethylaniline is added. The reaction vessel is purged with nitrogen and sealed. The mixture is heated for 12 h and then cooled to rt. Ether is added and the mixture is transferred to a separatory funnel. The organic phase is washed with 5% aqueous HCl solution (3 ×) and brine (2 ×). The organic phase is dried over anhydrous

$MgSO_4$, filtered, and concentrated. The crude product is used directly in next step without further purification or characterization.

General procedure C: Methylation of phenolic products

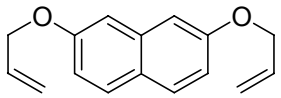
The crude phenolic product (1.0 equivalent from *bis*-allyl ether) in the rearrangement reaction is dissolved in anhydrous acetone under an atmosphere of nitrogen. MeI (4.0 molar equivalents relative to the *bis*-allyl ether) is added. Anhydrous K_2CO_3 (4.0 molar equivalents relative to the *bis*-allyl ether) is added. The reaction vessel is equipped with a reflux condenser and the mixture is heated at 60 ℃ for 48 h. The resulting mixture is concentrated under vacuum to remove all the acetone and excess MeI. The product is purified using flash chromatography on silica gel.



(4)

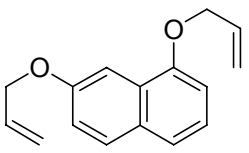
1,6-Dihydroxynaphthalene *bis*-Allyl ether (4): The reaction (1.5 g scale) was prepared as described in general procedure "A". After standard workup, the crude residue was chromatographed on silica gel (elution with pet ether: ethyl acetate, 8:1) to isolate 2.2 g (98%) of *bis*-allyl ether (**4**): ^{1}H NMR (400 MHz) δ 4.72-4.77 (m, 4H), 5.32-5.37 (m, 2H), 5.46-5.56 (m, 2H), 6.10-6.22 (m, 2H), 6.70 (dd, J_1 = 2.0 Hz, J_2 = 4.8 Hz, 1H), 7.12 (d, J = 2.0 Hz, 1H), 7.17 (dd, J_1 = 2.0 Hz, J_2 = 7.2 Hz, 1H), 7.30-7.35 (m, 2H), 8.23 (d, J = 7.2 Hz, 1H); ^{13}C NMR (400 MHz) 68.82 (t), 68.90 (t), 103.40 (d), 107.01 (d), 117.40 (d), 117.83 (t), 117.98 (t), 119.58 (d), 121.14 (s), 124.05 (d), 126.78 (d), 133.36 (d), 133.52 (d), 136.08 (s), 154.66 (s), 157.22 (s) ppm;

HR-MS: $[M+H]^+$ = 241.1236; $[M+H]^+_{calculated}$ = 241.1229; IR (neat): 3080, 2862, 1628, 1598, 1584, 1439, 1269, 1220, 1177, 1021, 1000, 925 cm^{-1}.



(5)

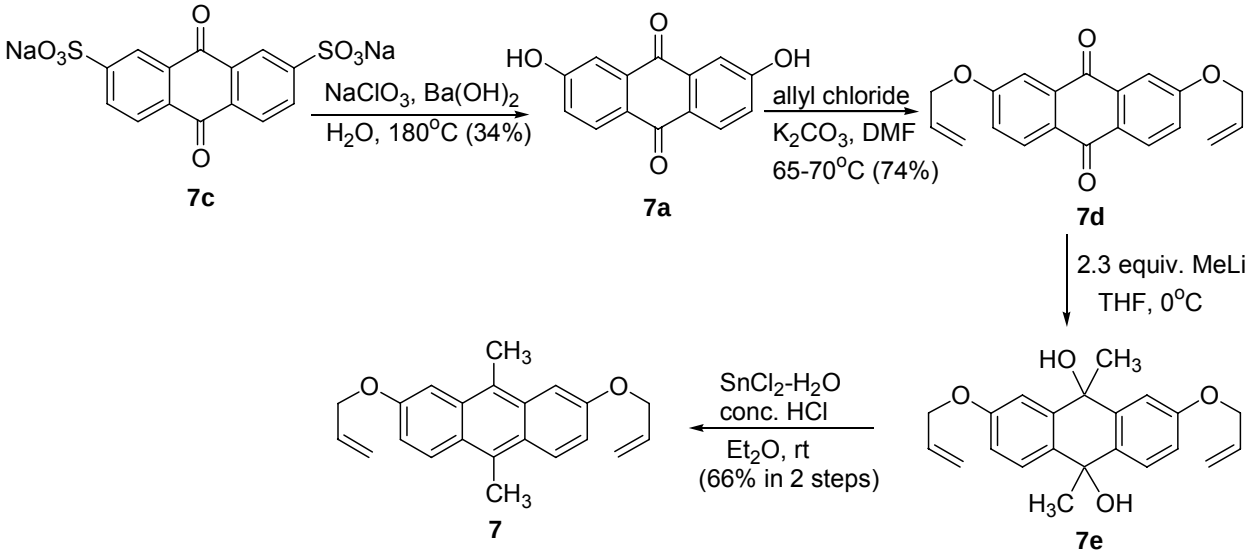
2,7-Dihydroxynaphthalene *bis*-Allyl ether (5): The reaction (0.8 g scale) was prepared as described in general procedure "A". After standard workup, the crude residue was chromatographed on silica gel (elution with pet ether: ethyl acetate, 8:1) to isolate 1.08 g (90%) of *bis*-allyl ether (**5**): ^{1}H NMR (400 MHz) δ 4.64-4.67 (m, 4H), 5.31-5.36 (m, 2H), 5.45-5.52 (m, 2H), 6.05-6.20 (m, 2H), 7.04 (dd, J_1 = 2.8 Hz, J_2 = 8.4 Hz, 2H), 7.06 (d, J = 2.8 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H); ^{13}C NMR (400 MHz) 68.82 (t), 106.51 (d), 116.47 (d), 117.82 (t), 124.49 (s), 129.24 (d), 133.32 (d), 135.85 (s), 157.20 (s) ppm; HR-MS: $[M+H]^+$ = 241.1233; $[M+H]^+_{calculated}$ = 241.1229; IR (neat): 3083, 2866, 1883, 1628, 1513, 1423, 1387, 1250, 1207, 1173, 1014, 933, 825, 737, 632 cm^{-1}.



(6)

1,7-Dihydroxynaphthalene *bis*-Allyl ether (6): The reaction (1.5 g scale) was prepared as described in general procedure "A". After standard workup, the crude residue was chromatographed on silica gel (elution with pet ether: ethyl acetate, 8:1) to isolate 2.08 g (92%)

of *bis*-allyl ether (**6**): ^{1}H NMR (400 MHz) δ 4.66-4.76 (m, 4H), 5.32-5.37 (m, 2H), 5.48-5.56 (m, 2H), 6.10-6.24 (m, 2H), 6.82 (d, J = 6.0 Hz, 1H), 7.20 (dd, J_1 = 2.0 Hz, J_2 = 7.2 Hz, 1H), 7.24 (t, J = 6.8 Hz, 1H), 7.38 (d, J = 6.8 Hz, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.72 (d, J = 7.2 Hz, 1H); ^{13}C NMR (400 MHz) 68.94 (t), 69.02 (t), 101.73 (d), 105.78 (d), 117.36 (t), 117.90 (t), 119.36 (d), 120.32 (d), 123.54 (d), 126.68 (s), 129.24 (d), 130.12 (s), 133.42 (d), 133.60 (d), 153.50 (s), 156.43 (s) ppm; HR-MS: $[M+H]^+$ = 241.1229; $[M+H]^+_{calculated}$ = 241.1229; IR (neat): 3077, 2867, 1628, 1598, 1583, 1509, 1439, 1422, 1374, 1268, 1220, 1177, 1143, 1021, 100, 925, 827, 778, 742 cm^{-1}.



2,7-*bis*-(Allyloxy)-9,10-dimethylanthracene 7: A mixture of commercially available anthraquinone-2,7-disulfonic acid disodium salt **7c** (12.5 g, 30.0 mmol), $Ba(OH)_2$ (10.38 g, 60.0 mmol, 2.0 equivalents), $NaClO_3$ (6.5 g, 60.0 mmol, 2.0 equivalents) and H_2O (50.0 mL) was sealed in an autoclave and heated at 175 ℃ for 44 h. The autoclave was cooled to 0 ℃. The resulting purple mixture was acidified using 10% H_2SO_4 and was extracted with ether (3 × 50 mL). The ethereal extracts were dried over anhydrous $MgSO_4$ and filtered. Concentration using a

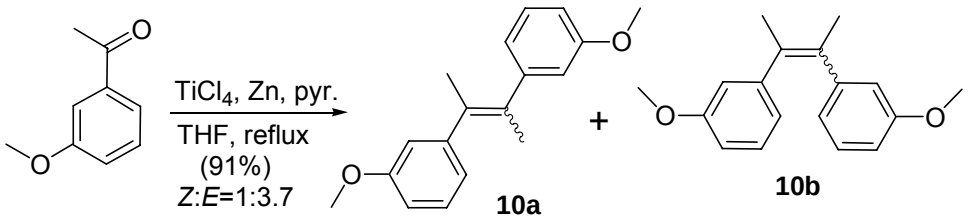
rotary evaporator afforded 2.5 g (34%) of 2,7-dihydroxyanthraquinone **7a** as a crude orange solid which was used in next step without further purification.

A mixture of 2,7-dihydroxyanthraquinone **7a** (300 mg, 1.25 mmol), allylic chloride (407 μL, 6.0 mmol, 4.0 equivalents) and K_2CO_3 (690 mg, 6.0 mmol, 4.0 equivalents) in anhydrous DMF (15 mL) was heated at 60~70 ℃ under a nitrogen atmosphere for three days. The resulting mixture was poured to ice cold saturated NH_4Cl (10 mL) and this mixture was extracted with ether (3 × 15 mL). The combined ethereal extracts were washed with water (2 × 3 mL), saturated $CuSO_4$ (2 × 2 mL) and brine (2 × 3 mL), and was dried over anhydrous $MgSO_4$. Concentration using a rotary evaporator gave 273 mg of crude solid. Column chromatography (elution with pet ether : ether, 4:1) afforded 266 mg (74%) of **7d**: ^{1}H NMR (400 MHz) δ 4.72 (d, J = 4.8 Hz, 2H), 5.37 (d, J = 9.2 Hz, 2H), 5.48 (d, J = 9.2 Hz, 2H), 6.04-6.16 (m, 2H), 7.28 (dd, J_1 = 3.2 Hz, J_2 = 8.4 Hz, 2H), 7.71 (d, J = 3.2 Hz, 2H), 8.24 (d, J = 8.4 Hz, 2H).

To a solution of **7d** (260 mg, 0.90 mmol) in freshly distilled THF (50 mL) at 0 ℃ was added MeLi (1.3 *M*, 1.5 mL, 2.06 mmol, 2.3 equivalents). The resulting mixture was stirred at 0 ℃ for two hours and then was poured to brine (30 mL). The mixture was extracted with ether (3 × 20 mL). The combined ethereal extracts were dried over anhydrous $MgSO_4$ and filtered. Concentration using a rotary evaporator gave 300 mg of crude **7e** which was used directly in next step.

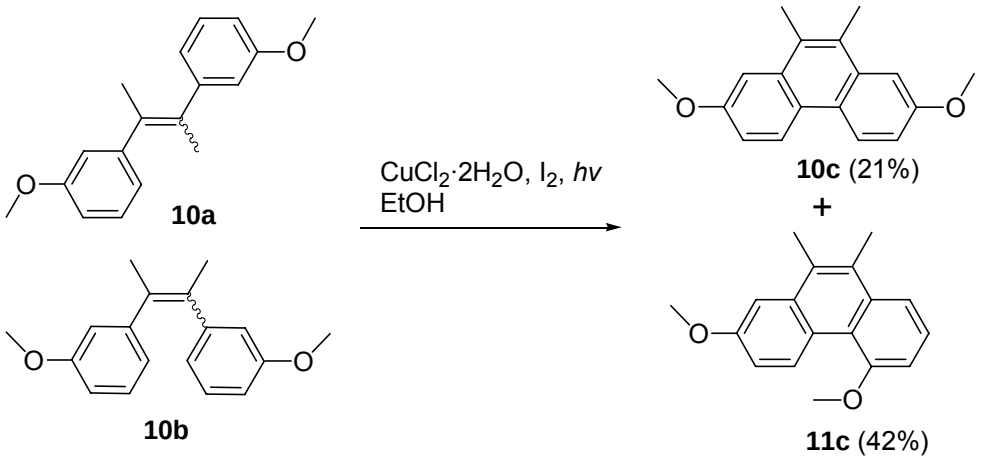
A solution of crude **7e** (~300 mg) in ether (5 mL) was added slowly to a mixture of $SnCl_2{\cdot}2H_2O$ (350 mg, 9.0 mmol, 10.0 equivalents) and concentrated HCl (1.7 mL) in ether (10 mL) and the resulting reaction mixture was stirred at rt for one hour. Water (10 mL) was added to dilute the reaction. Saturated $NaHCO_3$ was used to neutralize the mixture. The separated aqueous layer was extracted with ether (3 × 15 mL) and the combined ethereal extracts were

dried over anhydrous $MgSO_4$ and filtered. Concentration using a rotary evaporator followed by column chromatography (elution with pet ether: ether, 4:1) afforded 170 mg (66% over two steps) of *bis*-allyl ether **7**: ^{1}H NMR (400 MHz) δ 2.91 (s, 3H), 3.02 (s, 3H), 4.75 (d, J = 5.2 Hz, 4H), 5.40 (dd, J_1 = 1.2 Hz, J_2 = 10.4 Hz, 2H), 5.57 (dd, J_1 = 1.2 Hz, J_2 = 17.2 Hz, 2H), 6.16-6.30 (m, 2H), 7.21 (dd, J_1 = 2.0 Hz, J_2 = 9.2 Hz, 2H), 7.41 (d, J = 2.0 Hz, 2H), 8.21 (d, J = 9.2 Hz, 2H); ^{13}C NMR (400 MHz) 14.26 (q), 14.45 (q), 68.78 (t), 102.63 (d), 117.95 (t), 118.34 (d), 123.81 (s), 125.14 (s), 127.30 (d), 128.77 (s), 131.46 (s), 133.38 (d), 155.74 (s) ppm; HR-MS: $[M+H]^+$ = 319.1699; $[M+H]^+_{calculated}$ = 319.1698; IR (neat): 3081, 2926, 2859, 1612, 1454, 1421, 1282, 1203, 998, 932, 813, 777, 729, 647 cm^{-1}.



McMurry Coupling of 3-Methoxyacetophenone: To a solution of $TiCl_4$ (12.1 mL, 0.11 mol, 1.1 equivalents) in freshly distilled THF (250 mL) at 0 ℃ under a nitrogen atmosphere was added Zn powder (13.8 g, 0.2 mol, 2.0 equivalents) in portions, followed by addition of anhydrous pyridine (8 mL). The resulting reaction mixture was stirred at 0 ℃ for ten minutes. 3'-Methoxyacetophenone (15.0 g, 0.1 mol) in anhydrous THF (30 mL) was added dropwise and the resulting mixture was refluxed for 22 h. The cooled reaction mixture was poured to 5% Na_2CO_3 (400 mL) and filtrated. The filtrate cake was washed with ether (100 mL). The mother liquor was extracted with ether (3 × 100 mL). The combined ethereal extracts were dried over anhydrous $MgSO_4$ and filtrated. Concentration using a rotary evaporator followed by column

chromatography (elution with heptane: ether, 10:1, 6:1) afforded 9.5 g (71%) of **10a** and **10b** as an isolable mixture with a ratio of 1:5.2. This mixture was used directly in next step.

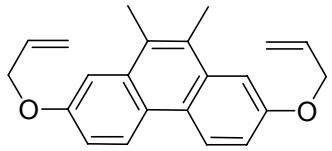


2,7-Dimethoxy-9,10-dimethylphenanthrene 10c and 2,5-Dimethoxy-9,10-dimethylphen anthrene 11c from the Photochemical Aromatization of 10a and 10b: A mixture of **10a** and **10b** (1.60 g, 6.0 mmol), $CuCl_2 \cdot 2H_2O$ (1.03 g, 6.0 mmol, 1.0 equivalent), I_2 (76 mg, 0.3 mmol, 0.05 equivalent) in anhydrous EtOH (60 mL) was irradiated under UV light (254 nm) for three days. EtOH was removed under vacuum and the resulting reaction mixture was directly purified on silica gel column chromatography (elution with heptane: ether, 20:1) to afford 338 mg (21%) of **10c** and 650 mg (42%) of **11c**.

10c: ^{1}H NMR (400 MHz) δ 2.70 (s, 6H), 3.99 (s, 6H), 7.23 (dd, J_1 = 2.4 Hz, J_2 = 9.2 Hz, 2H), 7.45 (d, J = 2.4 Hz, 2H), 8.52 (d, J = 9.2 Hz, 2H); ^{13}C NMR (400 MHz) 15.17 (q), 54.33 (q), 104.97 (d), 114.02 (d), 122.78 (s), 122.82 (d), 128.33 (s), 131.37 (s), 156.52 (s); HR-MS: $[M+H]^+$ = 267.1383; $[M+H]^+_{calculated}$ = 267.1385; IR (neat): 2924, 2852, 1610, 1490, 1462, 1279, 1230, 1042, 814 cm^{-1}.

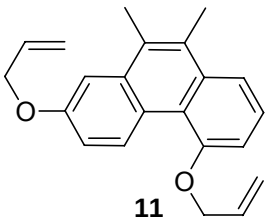
11c: ^{1}H NMR (400 MHz) δ 2.70 (s, 3H), 2.73 (s, 3H), 4.00 (s, 3H), 4.11 (s, 3H), 7.13 (d, J = 8.0 Hz, 1H), 7.27 (dd, J_1 = 2.4 Hz, J_2 = 9.6 Hz, 1H), 7.48-7.54 (m, 2H), 7.78 (d, J = 9.2 Hz, 1H),

9.70 (d, J = 9.2 Hz, 1H); ^{13}C NMR (400 MHz) 16.80 (q), 17.29 (q), 55.48 (q), 56.02 (q), 106.06 (d), 107.95 (d), 114.12 (d), 117.65 (d), 120.44 (s), 123.83 (s), 125.59 (d), 129.77 (s), 130.07 (s), 130.64 (d), 133.92 (s), 134.69 (s), 157.56 (s), 158.38 (s); HR-MS: $[M+H]^+$ = 267.1389; $[M+H]^+_{calculated}$ = 267.1385; IR (neat): 2995, 2935, 2837, 1612, 1531, 1457, 1248, 1227, 1048, 828, 758 cm^{-1}.



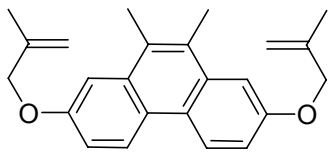
10

2,7-*bis*-(Allyloxy)-9,10-dimethylphenanthrene 10: The reaction (100 mg scale) was prepared as described in general procedure "A". After standard workup, the crude residue was chromatographed on silica gel (elution with pet ether: ethyl acetate, 8:1) to isolate 70.5 mg (55%) of *bis*-allyl ether **10**: ^{1}H NMR (400 MHz) δ 2.65 (s, 6H), 4.70-4.74 (m, 4H), 5.38 (dd, J_1 = 1.6 Hz, J_2 = 10.4 Hz, 2H), 5.54 (dd, J_1 = 1.6 Hz, J_2 = 17.6 Hz, 2H), 6.14-6.24 (m, 2H), 7.24 (dd, J_1 = 2.0 Hz, J_2 = 9.2 Hz, 2H), 7.46 (d, J = 2.0 Hz, 2H), 8.49 (d, J = 9.2 Hz, 2H); ^{13}C NMR (400 MHz) 16.21 (q), 69.02 (t), 107.34 (d), 115.46 (d), 117.87 (d), 123.87 (d), 123.94 (s), 129.38 (s), 132.46 (s), 133.51 (d), 156.61 (s) ppm; HR-MS: $[M+H]^+$ = 319.1696; $[M+H]^+_{calculated}$ = 319.1698; IR (neat): 2924, 1612, 1226, 1034, 926, 828 cm^{-1}.



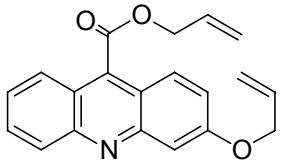
11

2,5-*bis*-(Allyloxy)-9,10-dimethylphenanthrene 11: The reaction (100 mg scale) was prepared as described in general procedure "A". After standard workup, the crude residue was chromatographed on silica gel (elution with pet ether: ethyl acetate, 8:1) to isolate 73.0 mg (57%) of *bis*-allyl ether **11**: ^{1}H NMR (400 MHz) δ 2.73 (s, 3H), 2.76 (s, 3H), 4.78-4.82 (m, 2H), 4.85-4.88 (m, 2H), 5.42-5.48 (m, 2H), 5.56-5.66 (m, 2H), 6.20-6.40 (m, 2H), 7.16 (d, J = 7.2 Hz, 1H), 7.32 (dd, J_1 = 2.8 Hz, J_2 = 9.6 Hz, 1H), 7.52 (t, J = 8.4 Hz, 1H), 7.59 (d, J = 2.8 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 9.81 (d, J = 9.6 Hz, 1H); ^{13}C NMR (400 MHz) 16.59 (q), 17.06 (q), 68.90 (t), 70.28 (t), 107.17 (d), 109.49 (d), 114.23 (d), 117.74 (d), 117.83 (t), 117.91 (t), 120.49 (s), 123.69 (s), 125.37 (d), 129.54 (s), 129.84 (s), 133.62 (d), 133.83 (s), 134.51 (s), 156.45 (s), 157.08 (s) ppm; HR-MS: $[M+H]^+$ = 319.1699; $[M+H]^+_{calculated}$ = 319.1698; IR (neat): 2921, 2854, 1611, 1445, 1225, 1032, 754, 717 cm^{-1}.



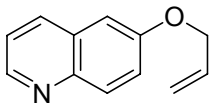
12

9,10-Dimethyl-2,7-*bis*-(2-methyl-allyloxy)phenanthrene 12: The reaction (100 mg scale) was prepared as described in general procedure "A". After standard workup, the crude residue was chromatographed on silica gel (elution with pet ether: ethyl acetate, 8:1) to isolate 87.0 mg (60%) of *bis*-allyl ether **12**: ^{1}H NMR (400 MHz) δ 1.91 (s, 6H), 2.67 (s, 6H), 4.61(s, 4H), 5.06 (s, 2H), 5.21(s, 2H), 7.24 (dd, J_1= 2.4 Hz, J_2 = 9.2 Hz, 2H), 7.47 (d, J = 2.4 Hz, 2H), 8.50 (d, J = 9.2 Hz, 2H); ^{13}C NMR (400 MHz) 16.42, 19.80, 72.18, 107.63, 113.15, 115.76, 124.03, 124.14, 129.58, 132.67, 141.40, 156.99 ppm; HR-MS: $[M+H]^+$ = 347.2017; $[M+H]^+_{calculated}$ = 347.2011; IR (neat): 2984, 1739, 1373, 1241, 1176, 1046 cm^{-1}.



13

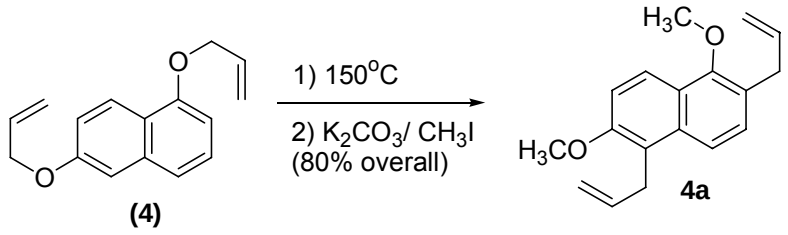
3-Allyloxy-9,10-dihydro-acridine-9-carboxylic acid allyl ester 13: The reaction (2.0 g scale) was prepared as described in general procedure "A". After standard workup, the crude residue was chromatographed on silica gel (elution with pet ether: ethyl acetate, 8:1) to isolate 2.0 g (75%) of *bis*-allyl ether **13**: ^{1}H NMR (500 MHz) δ 4.70 (d, J = 6.0 Hz, 2H), 5.09 (d, J = 6.0 Hz, 2H), 5.34 (dd, J_1 = 11.0 Hz, J_2 = 19.0 Hz, 2H), 5.48 (dd, J_1 = 6.0 Hz, J_2 = 17.0 Hz, 2H), 6.05-6.16 (m, 2H), 7.28 (dd, J_1 = 2.5 Hz, J_2 = 9.0 Hz, 1H), 7.44 (d, J = 2.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.74 (t, J = 7.5 Hz, 1H), 7.91 (d, J = 10.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 8.16 (d, J = 9.0 Hz, 1H); ^{13}C NMR (400 MHz) 66.79 (t), 69.00 (t), 106.41 (d), 118.42 (t), 118.68 (s), 120.10 (t), 121.25 (s), 122.91 (d), 125.19 (d), 126.08 (d), 126.32 (d), 129.21 (d), 130.37 (d), 131.27 (d), 132.30 (d), 136.55 (s), 148.82 (s), 150.42 (s), 160.08 (s), 167.18 (s) ppm; HR-MS: $[M+H]^+$ = 320.1281; $[M+H]^+_{calculated}$ = 320.1287; IR (neat): 3082, 2926, 1727, 1632, 1611, 1446, 1288, 1270, 1199, 1156, 994, 929, 821, 761, 637 cm^{-1}



14

6-Allyloxyquinoline 14: The reaction (610 mg scale) was prepared as described in general procedure "A". After standard workup, the crude residue was chromatographed on silica gel (elution with pet ether: ethyl acetate, 8:1) to isolate 500 mg (64%) of allyl ether **14**: ^{1}H NMR

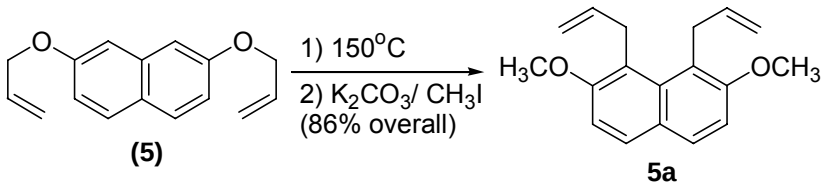
(400 MHz) δ 4.63 (dt, J_1 = 1.6 Hz, J_2 = 5.2 Hz, 2H), 5.33 (dq, J_1 = 1.6 Hz, J_2 = 10.4 Hz, 1H), 5.47 (dq, J_1 = 1.6 Hz, J_2 = 17.2 Hz, 1H), 6.04-6.16 (m, 1H), 7.05 (d, J = 2.8 Hz, 1H), 7.32 (dd, J_1 = 4.0 Hz, J_2 = 8.0 Hz, 1H), 7.39 (dd, J_1 = 2.8 Hz, J_2 = 9.2 Hz, 1H), 8.00 (d, J = 8.0 Hz, 2H), 8.75 (dd, J_1 = 1.6 Hz, J_2 = 4.0 Hz, 1H); ^{13}C NMR (400 MHz) 68.91 (t), 106.22 (d), 117.94 (t), 121.30 (d), 122.46 (d), 129.18 (s), 130.81 (d), 132.75 (d), 134.75 (d), 144.35 (s), 147.93 (d), 156.55 (s) ppm; HR-MS: $[M+H]^+$ = 186.0921; $[M+H]^+_{calculated}$ = 186.0919; IR (neat): 3026, 2873, 1621, 1501, 1224, 1015, 999, 923, 834, 617 cm^{-1}.



(4) **4a**

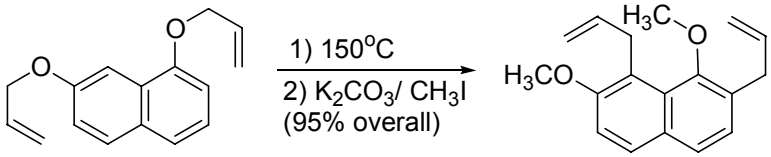
Rearrangement and Methylation of 1,6-Dihydroxynaphthalene *bis*-Allyl ether 4: The reaction was prepared as in general procedure "B" using **4** (400 mg, 1.67 mmol) and *N,N*-diethylaniline (400 mg). The reaction was heated at 150 ℃ for 5 h. After standard workup, the solvent was removed at reduced pressure to yield a crude residue. This crude residue was methylated directly as in general procedure "C". Chromotographic separation (elution with pet ether: ethyl acetate, 8:1) afforded 2,5-diallyl-1,6-dimethoxynaphthalene **4a** (356 mg, 80% in two steps): ^{1}H NMR (500 MHz) δ 3.70 (d, J = 6.5 Hz, 2H), 3.97 (d, J = 6.0 Hz, 2H), 4.02 (s, 6H), 5.10-5.16 (m, 2H), 5.20-5.26 (m, 2H), 6.12-6.22 (m, 2H), 7.39 (d, J = 9.0 Hz, 1H), 7.43 (d, J = 9.0 Hz, 1H), 7.80 (d, J = 9.0 Hz, 1H), 8.17 (d, J = 9.0 Hz, 1H); ^{13}C NMR (400 MHz) 29.49 (t), 33.83 (t), 56.73 (q), 62.32 (q), 113.47 (d), 115.10 (t), 115.87 (t), 119.91 (d), 121.34 (s), 122.27 (d), 124.00 (s), 125.26 (s), 129.10 (d), 133.93 (s), 136.94 (d), 137.52 (d), 153.99 (s), 154.53 (s)

ppm; HR-MS: $[M+H]^+$= 269.1540; $[M+H]^+_{calculated}$= 269.1542; IR (neat): 3077, 2937, 2839, 1637, 1599, 1378, 1257, 1072, 1021, 910, 812, 798 cm^{-1}.



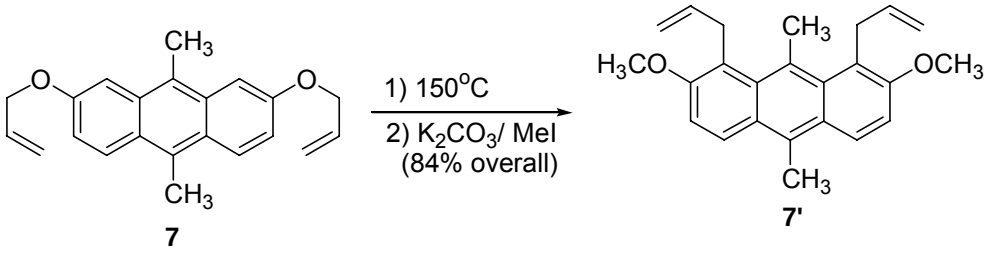
(5) **5a**

Rearrangement and Methylation of 2,7-Dihydroxynaphthalene *bis*-Allyl ether 5: The reaction was prepared as in general procedure "B" using **5** (400 mg, 1.67 mmol) and *N,N*-diethylaniline (400 mg). The reaction was heated at 150 ℃ for 5 h. After standard workup, the solvent was removed at reduced pressure to yield a crude residue. This crude residue was directly methylated as in general procedure "C". Chromotographic separation (elution with pet ether: ethyl acetate, 8:1) afforded 1,8-diallyl-2,7-dimethoxynaphthalene **5a** (383 mg, 86% in two steps): ^{1}H NMR (500 MHz) δ 3.98 (s, 6H), 4.00-4.02 (m, 4H), 4.90-4.97 (dd, J_1 = 2.0 Hz, J_2 = 17.5 Hz, 2H), 5.17-5.20 (dd, J_1 = 2.0 Hz, J_2 = 10.0 Hz, 2H), 6.27-6.36 (m, 2H), 7.23 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H); ^{13}C NMR (400 MHz) 31.03 (t), 56.85 (q), 111.06 (d), 114.65 (t), 120.48 (s), 126.38 (s), 129.54 (d), 135.04 (s), 139.15 (d), 156.80 (s) ppm; HR-MS: $[M+H]^+$ = 269.1537; $[M+H]^+_{calculated}$ = 269.1542; IR (neat): 3076, 2998, 2936, 2836, 1613, 1515, 1253, 1131, 1048, 906, 818 cm^{-1}.



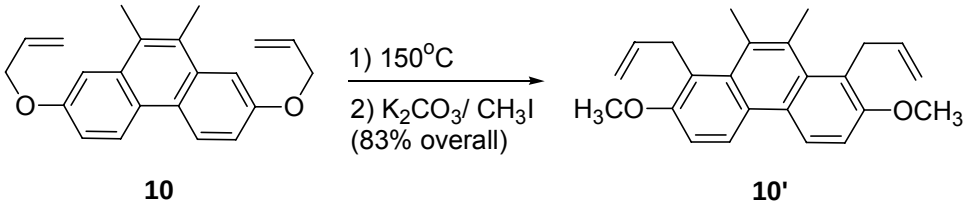
(6) **6a**

Rearrangement and Methylation of 1,7-Dihydroxynaphthalene *bis*-Allyl ether 6: The reaction was prepared as in general procedure "B" using **6** (400 mg, 1.67 mmol) and *N,N*-diethylaniline (400 mg). The reaction was heated at 150 ℃ for 5 h. After standard workup, the solvent was removed at reduced pressure to yield a crude residue. This crude residue was methylated directly as in general procedure "C". Chromotographic separation (elution with pet ether: ethyl acetate, 8:1) afforded 2,8-diallyl-1,7-dimethoxynaphthalene **6a** (424 mg, 95% in two steps): ^{1}H NMR (400 MHz) δ 3.63-3.66 (m, 2H), 3.75 (s, 3H), 3.96 (s, 3H), 4.16-4.20 (m, 2H), 4.88-4.98 (m, 2H), 5.12-5.20 (m, 2H), 6.03-6.22 (m, 2H), 7.21 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H); ^{13}C NMR (400 MHz) 30.62 (t), 34.24 (t), 56.96 (q), 62.65 (q), 113.42 (d), 113.74 (t), 116.12 (t), 121.00 (s), 125.24 (d), 126.12 (d), 127.78 (s), 128.53 (d), 130.12 (s), 130.96 (s), 137.68 (d), 138.95 (d), 154.50 (s), 156.02 (s) ppm; HR-MS: $[M+H]^+$ = 269.1531; $[M+H]^+_{calculated}$ = 269.1542; IR (neat): 3076, 2936, 2835, 1636, 1602, 1512, 1453, 1336, 1252, 1136, 1070, 1034, 995, 910, 832 cm^{-1}.



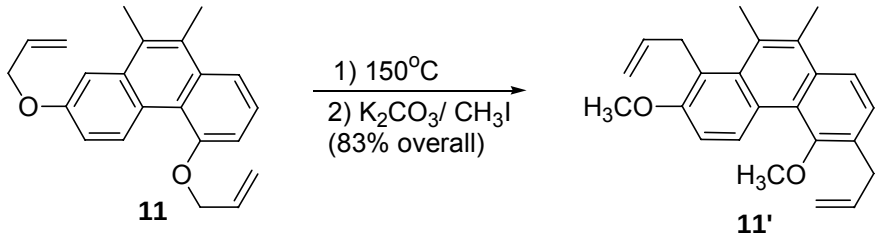
7 **7'**

Rearrangement and Methylation of 2,7-*bis*-(Allyloxy)-9,10-dimethylanthracene 7: The reaction was prepared as in general procedure "B" using **7** (60 mg, 0.208 mmol) and *N, N*-diethylaniline (100 mg). The reaction was heated at 150 ℃ for 9 h. After standard workup, the solvent was removed at reduced pressure to yield a crude residue. This crude residue was methylated directly as in general procedure "C". Chromotographic separation (elution with pet ether: ethyl acetate, 8:1) afforded 1,8-diallyl-2,7-dimethoxy-9,10-dimethylanthrathene **7′** (55.0 mg, 84% in two steps): ^{1}H NMR (400 MHz) δ 3.52 (dd, J_1 = 5.6 Hz, J_2 = 15.6 Hz, 2H), 3.73 (dd, J_1 = 5.6 Hz, J_2 = 15.6 Hz, 2H), 3.87 (s, 6H), 4.58 (q, J = 7.2 Hz, 1H), 5.01 (dd, J_1 = 1.6 Hz, J_2 = 7.2 Hz, 2H), 5.05 (s, 2H), 5.51 (s, 2H), 5.98-6.08 (m, 2H), 6.85 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H); ^{13}C NMR (400 MHz) 23.90 (q), 29.76 (t), 33.03 (q), 55.79 (q), 106.22 (t), 108,84 (d), 114.92 (s), 123.74 (d), 124.00 (s), 129.03 (s), 136.95 (d), 140.78 (s), 142.74 (s), 157.25 (s) ppm; HR-MS: $[M+H]^+$ = 347.2001; $[M+H]^+_{calculated}$ = 347.2011; IR (neat): 3077, 2971, 2838, 1651, 1590, 1481, 1462, 1343, 1264, 1122, 1044, 910 cm^{-1}.



10 **10'**

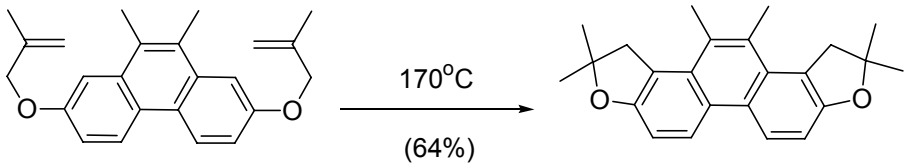
Rearrangement and Methylation of 2,7-*bis*-(Allyloxy)-9,10-dimethylphenanthrene 10: The reaction was prepared as in general procedure "B" using **10** (70 mg, 0.220 mmol) and *N, N*-diethylaniline (100 mg). The reaction was heated at 150 ℃ for 24 h. After standard workup, the solvent was removed at reduced pressure to yield a crude residue. This crude residue was methylated directly as in general procedure "C". Chromotographic separation (elution with pet ether: ethyl acetate, 8:1) afforded 1,8-diallyl-2,7-dimethoxy-9,10-dimethylphenanthrene **10′** (63.2 mg, 83% in two steps): ^{1}H NMR (400 MHz) δ 2.46 (s, 6H), 3.62-3.66 (m, 4H), 3.81 (s, 6H), 4.95-5.04 (m, 4H), 6.08-6.18 (m, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 8.24 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (400 MHz) 21.27 (q), 34.33 (t), 56.22 (q), 110.62 (d), 114.87 (t), 121.28 (d), 122.79 (s), 125.48 (s), 131.21 (s), 134.38 (s), 138.37 (d), 156.91 (s) ppm; HR-MS: $[M+H]^{+}$ = 347.2000; $[M+H]^{+}_{calculated}$ = 347.2011; IR (neat): 3076, 2938, 2836, 1591, 1465, 1438, 1252, 1220, 1141, 1053, 1036, 908, 788 cm^{-1}.



11 **11'**

Rearrangement and Methylation of 2,5-*bis*-(Allyloxy)-9,10-dimethylphenanthrene 11: The reaction was prepared as in general procedure "B" using **11** (73.0 mg, 0.230 mmol) and *N, N*-

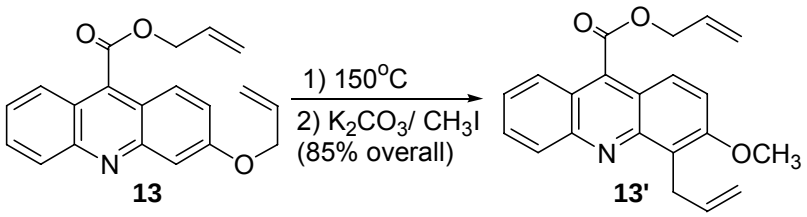
diethylaniline (100 mg). The reaction was heated at 150 ℃ for 24 h. After standard workup, the solvent was removed at reduced pressure to yield a crude residue. This crude residue was methylated directly as in general procedure "C". Chromotographic separation (elution with pet ether: ethyl acetate, 8:1) afforded 1,6-diallyl-2,5-dimethoxy-9,10-dimethylphenanthrene **11′** (66.0 mg, 83% in two steps): ^{1}H NMR (400 MHz) δ 2.66 (s, 3H), 2.76 (s, 3H), 3.72-3.76 (m, 2H), 3.77 (s, 3H), 3.88-3.92 (m, 2H), 4.03 (s, 3H), 5.10-5.24 (m, 4H), 6.14-6.24 (m, 1H), 6.28-6.38 (m, 1H), 7.28 (d, *J* = 9.2 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 9.63 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (400 MHz) 16.71 (q), 22.56 (q), 33.77 (t), 34.42 (t), 56.09 (q), 60.17 (q), 109.97 (d), 114.71 (t), 115.64 (t), 119.87 (d), 121.83 (s), 123.36 (s), 124.08 (s), 126.80 (d), 127.65 (d), 129.62 (s), 130.54 (s), 132.03 (s), 132.45 (s), 136.02 (s), 137.86 (d), 138.62 (d), 155.53 (s), 157.22 (s) ppm; HR-MS: $[M+H]^{+}$ = 347.2016; $[M+H]^{+}_{calculated}$ = 347.2011; IR (neat): 2916, 1462, 1252, 1215, 1120, 1051, 899, 794 cm^{-1}.



12 **12'**

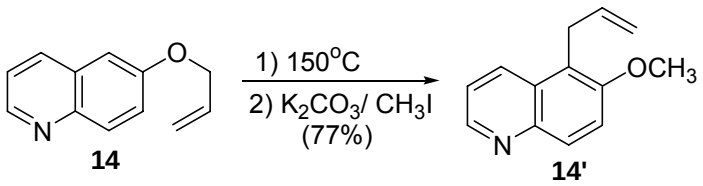
Rearrangement of 9,10-Dimethyl-2,7-*bis*-(2-methylallyloxy)phenanthrene 12: The reaction was using **12** (78.6 mg, 0.227 mmol) and *N, N*-diethylaniline (100 mg). The reaction was heated at 170 ℃ for 48 h. This solvent was removed directly under vacuum and the crude residue was purified by column chromatography (elution with pet ether: ethyl acetate, 8:1) afforded *bis*-ether **12′** (50.3 mg, 64%): ^{1}H NMR (400 MHz) δ 1.54(s, 12H), 2.69(s, 6H), 3.69(s, 4H), 7.05(d, *J* = 8.8 Hz, 2H), 8.41(d, *J* = 8.8 Hz, 2H); ^{13}C NMR (400 MHz) 19.52 (q), 28.57 (q), 48.10 (t), 85.81

(s), 110.81 (d), 119.53 (s), 124.00 (d), 125.56 (s), 130.63 (s), 130.98 (s), 157.62 (s) ppm; HR-MS: $[M+H]^+$ = 347.2015; $[M+H]^+_{calculated}$ = 347.2011; IR (neat): 2973, 2934, 1598, 1454, 1386, 1369, 1243, 1173, 1122, 1001, 803, 738 cm^{-1}.



13 **13'**

Rearrangement and Methylation of 3-Hydroxyacridine-9-carboxylic Acid *bis*-Allyl ether 13: The reaction was prepared as in general procedure "B" using **13** (370 mg, 1.16 mmol) and *N, N*-diethylaniline (400 mg). The reaction was heated at 150 ℃ for 7 h. After standard workup, the solvent was removed at reduced pressure to yield a crude residue. This crude residue was methylated directly as in general procedure "C". Chromotographic separation (elution with pet ether: ethyl acetate, 8:1) afforded *bis*-allyl ether **13′** (330 mg, 85% in two steps): ^{1}H NMR (400 MHz) δ 4.05 (s, 3H), 4.22 (md, 2H), 4.97 (md, 1H), 5.07-5.15 (m, 3H), 4.01 (md, 1H), 5.53 (md, 1H), 6.10-6.24 (m, 2H), 7.51 (d, J = 9.6 Hz, 1H), 7.54 (dd, J_1 = 1.2 Hz, J_2 = 8.8 Hz, 1H), 7.50 (ddd, J_1 = 1.2 Hz, J_2 = 6.8 Hz, J_3 = 9.2 Hz, 1H), 7.96 (d, J = 9.6 Hz, 1H), 7.97 (md, 1H), 8.24 (d, J = 8.8 Hz, 1H); ^{13}C NMR (400 MHz) 28.61 (t), 56.67 (q), 66.75 (t), 114.59 (t), 116.62 (d), 118.49 (s), 120.03 (t), 120.92 (s), 122.73 (s), 124.54 (d), 124.98 (d), 126.16 (d), 129.94 (d), 130.37 (d), 131.46 (d), 136.67 (s), 137.51 (d), 148.04 (s), 148.79 (s), 157.17 (s), 167.63 (s) ppm; HR-MS: $[M+H]^+$ = 334.1434; $[M+H]^+_{calculated}$ = 334.1443; IR (neat): 3075, 2938, 2840, 1728, 1607, 1461, 1426, 1273, 1209, 1143, 1125, 1053, 986, 911, 760, 738 cm^{-1}.



14 14'

Rearrangement and Methylation of 6-Allyloxyquinoline 14: The reaction was prepared as in general procedure "B" using **14** (80 mg, 0.432 mmol) and *N, N*-diethylaniline (100 mg). The reaction was heated at 150 ℃ for 6 h. After standard workup, the solvent was removed at reduced pressure to yield a crude residue. This crude residue was methylated directly as in general procedure "C". Chromotographic separation (elution with pet ether: ethyl acetate, 8:1) afforded allyl ether **14′** (66 mg, 77% in two steps): ^{1}H NMR (400 MHz) δ 3.83 (d, J = 5.2 Hz, 2H), 3.98 (s, 3H), 4.91 (dd, J_1 = 1.6 Hz, J_2 = 17.2 Hz, 1H), 5.01 (dd, J_1 = 1.6 Hz, J_2 = 10.4 Hz, 1H), 5.95-6.08 (m, 1H), 7.38 (dd, J_1 = 3.6 Hz, J_2 = 8.4 Hz, 1H), 7.53 (d, J = 9.6 Hz, 1H), 8.07 (d, J = 9.6 Hz, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.78 (d, J = 3.6 Hz, 1H); ^{13}C NMR (400 MHz) 28.77 (t), 56.70 (q), 115.33 (t), 116.82 (d), 120.70 (s), 121.07 (d) 128.18 (s), 129.06 (d), 132.34 (d), 136.29 (d), 143.73 (s), 147.54 (d), 154.59 (s) ppm; HR-MS: $[M+H]^+$ = 200.1073; $[M+H]^+_{calculated}$ = 200.1075; IR (neat): 2935, 1503, 1256, 1077, 912, 827, 810 cm^{-1}.

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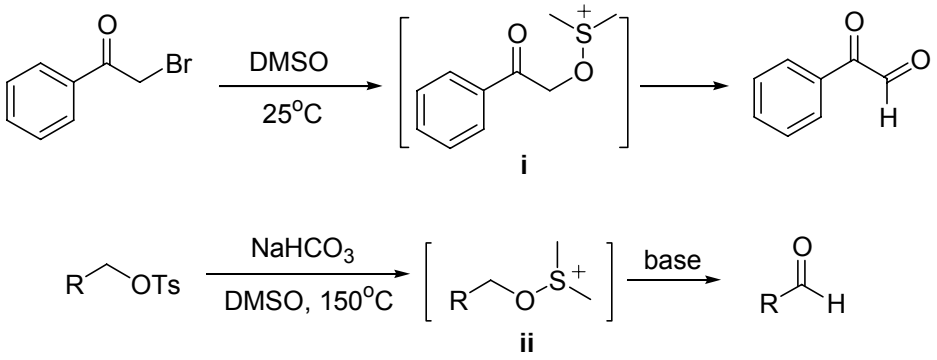
PART IV:

THE USE OF *β*-BROMO DIMETHYLALKOXYSULFONIUM IONS FOR OLEFIN EPOXIDATION

Introduction and Background

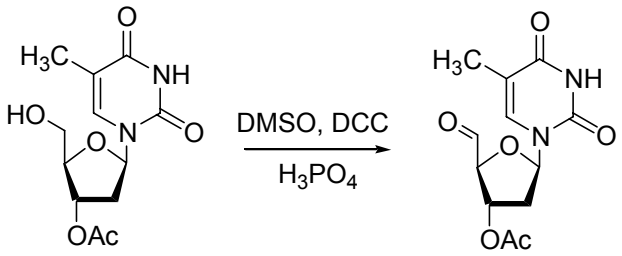
Dimethyl sulfoxide (DMSO), first prepared in 1866,[1] was used solely as a solvent until 1957, when Kornblum and co-workers discovered that *α*-bromo ketones were converted into glyoxals by treatment with DMSO and sodium bicarbonate[2,3] (Scheme 1). The initial step of these transformations involves a displacement by DMSO to give alkoxysulfonium ions **i** and **ii**. The following base-assisted 1,2-elimination generates the carbonyl species.[4]



Scheme 1

The oxidizing capacity of DMSO is dependent on its ability to act as a nucleophile; the basicity of DMSO is slightly greater than that of water,[5] and its nucleophilicity was estimated to exceed that of ethanol toward alkyl sulfonate esters.[4]

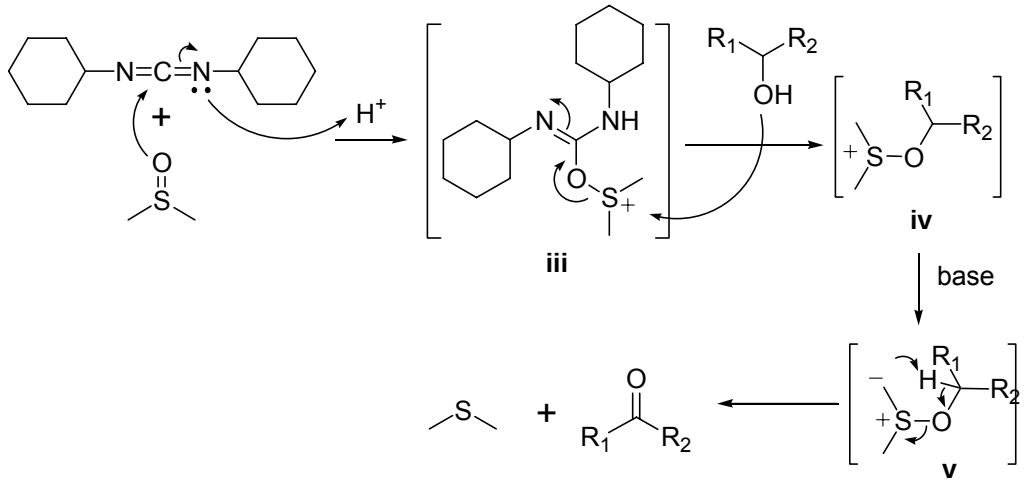
In the early 1960s, Moffatt and Pfitzner[6] observed that alcohols were oxidized to carbonyl compounds when treated with DMSO, dicyclohexylcarbodiimide (DCC) and phosphoric acid (Scheme 2). This method, which involved mild conditions, uncomplicated workups and high yields, was immediately recognized as an efficient procedure for the oxidation of sensitive substrates, and has been extensively reviewed.[7]



Scheme 2

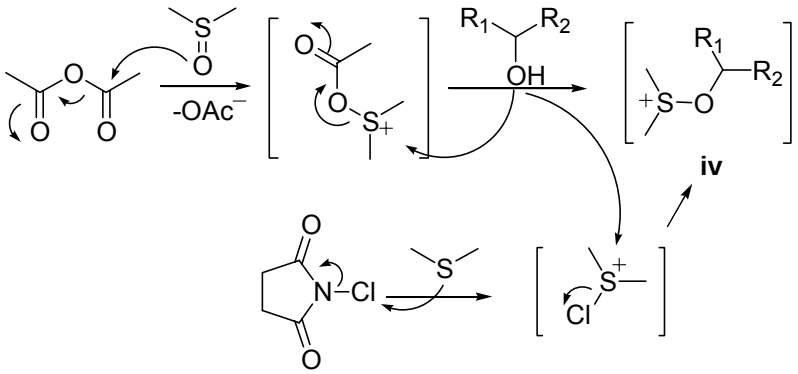
The mechanism of the Moffatt oxidation is illustrated in Scheme 3. The first step involves the acid-catalyzed addition of DMSO to DCC to give intermediate **iii**. Addition of the alcohol to **iii** produces dimethylalkoxysulfonium ion **iv** and *N*,*N*′-dicyclohexylurea. Deprotonation of **iv** affords oxysulfonium ylide **v** which undergoes intramolecular hydrogen transfer to give the carbonyl product along with dimethyl sulfide.[7a,8] This mechanism has been confirmed by several deuterium-labeling experiments: 1) the formation of intermediate **iii** is supported by oxygen transfer from ^{18}O-labeled DMSO but not from ^{18}O-labeled alcohol to the product dicyclohexylurea;[9] 2) the generation of CH_3SCH_2D is supported from the reaction with *n*-$C_3H_7CD_2OH$ and the production of monodeuterodicyclohexylurea; 3) the generation of CD_3SCD_2H from the reaction using DMSO-d_6 confirms the intramolecular hydrogen transfer pathway via oxysulfonium ylide **v**; and 4) the reaction of tritium-labeled alcohol substrate R_1CTOHR_2 gives CH_3SCH_2T along with less that 5% of tritium-substituted *N*,*N*′-

dicyclohexylurea[10] which can only result from the direct abstraction of a proton from ylide **v** after deprotonation by base.



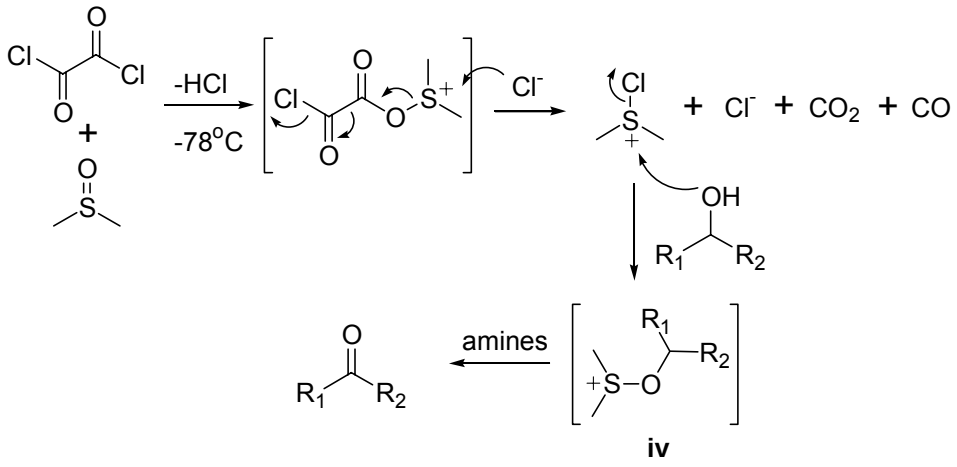
Scheme 3

Other variations of this procedure have been developed utilizing DMSO activated by acetic anhydride,[11] phosphorus pentoxide,[12] sulfur trioxide/pyridine complex[13] and chlorine.[14] All variants form dimethylalkoxysulfonium ion **iv** as a common intermediate, which undergoes oxidation of the alcohol upon treatment with base. The complexes of dimethyl sulfide (DMS) with chlorine or *N*-chlorosuccinimide (NCS) afford the same intermediate with alcohols. Scheme 4 shows examples for the formation of dimethylalkoxysulfonium ion **iv** using DMSO/acetic anhydride and DMS/NCS.



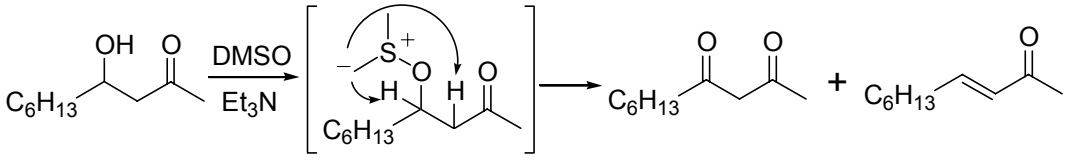
Scheme 4

The activation of DMSO by oxalyl chloride, which is known as the Swern oxidation,[15] is a popular oxidation procedure and is shown in Scheme 5. The reaction is carried out at -78 ℃ with rapid formation of dimethylalkoxysulfonium ion **iv**, and the subsequent oxidation can take place only after a base (preferably an amine) is added. These mild reaction conditions result in high yields and minimize side reactions often observed during DMSO-effected oxidation. For



Scheme 5

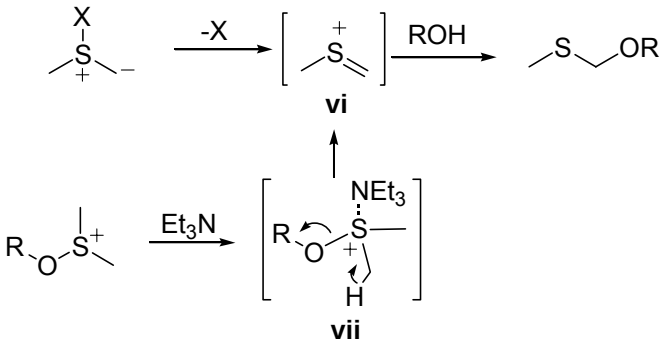
example, when *β*-keto alcohols were reacted with trifluoroacetic anhydride activated DMSO, 1,2-elimination occurred via a six-membered transition state to give enone in 33% yield. This was not observed with oxalyl chloride activation, which demonstrates a reagent dependent effect (Scheme 6).[16]



$(COCl)_2$ activation	(69%)	(0%)
$(CF_3CO)_2O$ activation	(50%)	(33%)

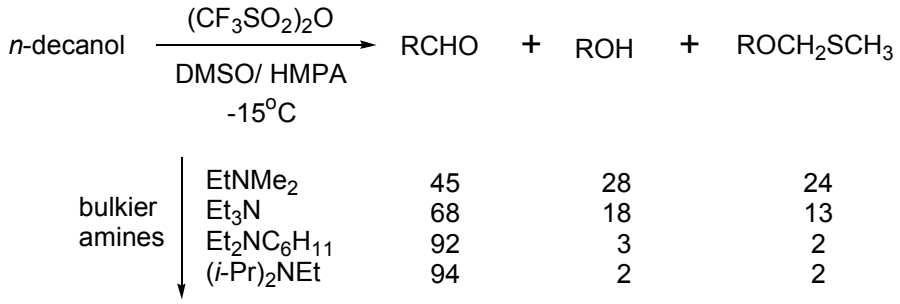
Scheme 6

Methylthiomethyl ethers are common byproducts of the Moffatt oxidation.[17] This unwanted side reaction is found to be most serious with DMSO/acetic anhydride at 25 ℃ but can be avoided by using Swern conditions at -60 ℃, DMSO/SO_3·pyridine at 25 ℃ or DMS/NCS at -25 ℃. The formation of methylthiomethyl ethers involves the formation of the electrophilic species $CH_3S^+{=}CH_2$ **vi**, which then alkylates the alcohol (Scheme 7). The preferred pathway is through dissociation of activated ylides where X^- is derived from either the activator or the alcohol.



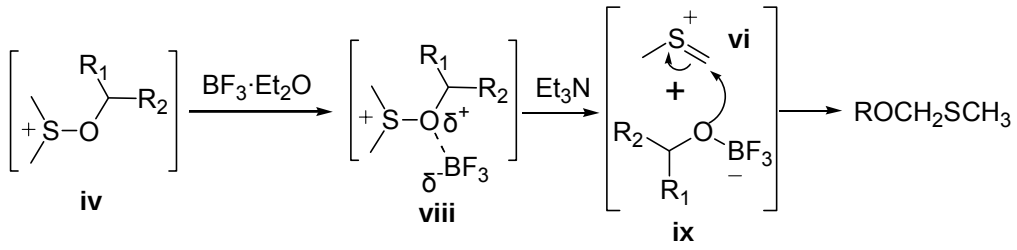
Scheme 7

As shown in Scheme 8,[17] decreased yields of alcohol and methylthiomethyl ether follow increased sizes of amines. This trend suggests that competition exists between deprotonation to promote oxidation and nucleophilic attack to form intermediate **vii**, which is disfavored by bulky alcohols or bulky amines. Amines that are more sterically hindered than TEA give the best results.



Scheme 8

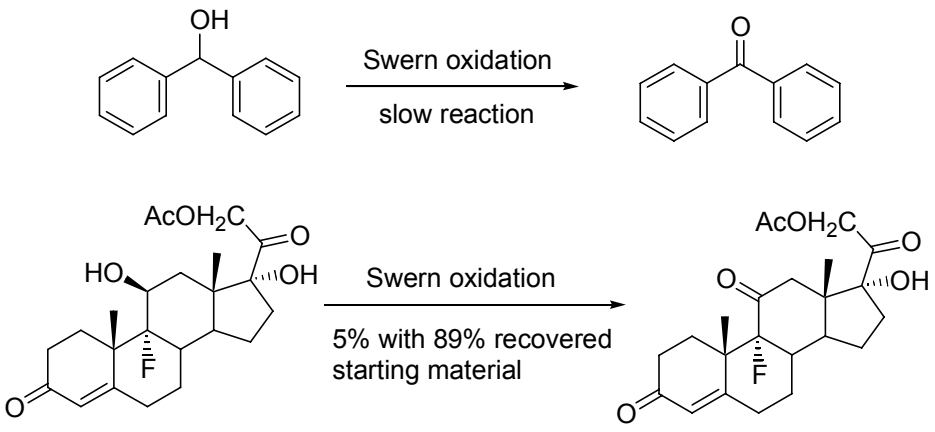
Addition of either a Lewis acid or a protic acid enhances the formation of methylthiomethyl ethers.[17] For example, when boron trifluoride etherate was added to alkoxysulfonium ion **iv**, followed by addition of triethylamine, a high yield of methylthiomethyl ether was collected (Scheme 9). Coordination of the boron trifluoride to the oxygen in **iv** results in **viii**, which facilitates dissociation to the alkoxy residues **ix** and **vi** and enhances ether formation.



Scheme 9

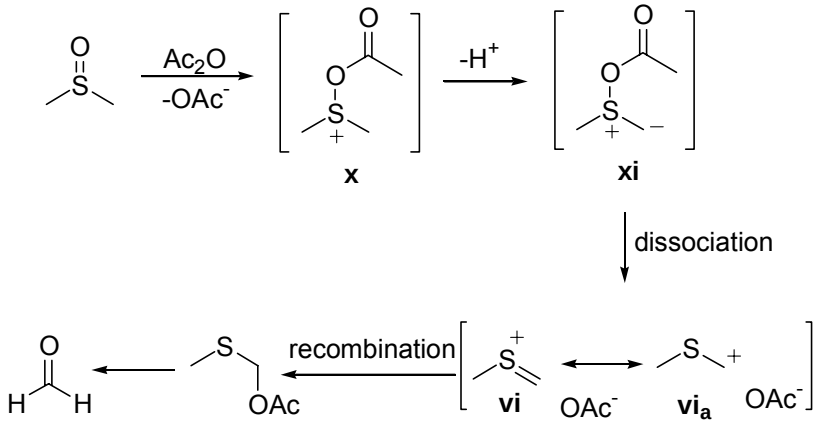
Marx and Tidwell[18] systematically studied the nature of the R groups in the oxidation of dimethylalkoxysulfonium ion **iv**. Competitive oxidation of mixtures of alcohols shows that intermediate **iv** is disfavored by R groups that are bulky or electron-withdrawing. The rapid dissociation of **iv** gives **vi** and an oxygen anion of the starting alcohol. For example, the low reactivity of benzhydrol was attributed to steric factors as well as the electron withdrawing effect of the two aryl rings. The deactivating influence of the 9*α*-fluoro substituent in 9*α*-fluorohydrocortisone acetate was so strong that oxidation was inefficient at -60 ℃ and gave only 5% of the ketone (Scheme 10).[18]

The Pummerer rearrangement,[19,20] a useful method for the preparation of *α*-substituted sulfides, also involves the intermediate **vi** in its mechanism. Commonly, a sulfoxide bearing an



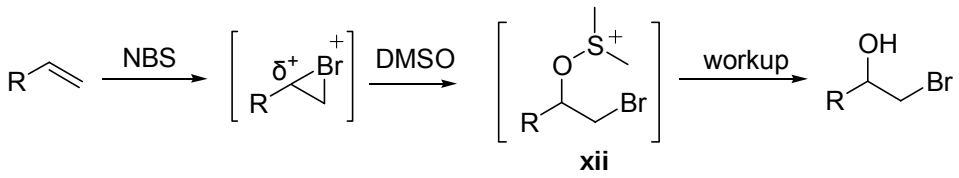
Scheme 10

α-hydrogen, when treated with acetic anhydride, generates an α-acetoxy sulfide that is hydrolyzed to a carbonyl compound. As shown in Scheme 11, intermediate **x** is generated from DMSO and acetic anhydride,[21] and undergoes dissociation to give intermediate **vi** through **xi**. Recombination of the dissociated intermediates gives methylthiomethyl acetate, which can be hydrolyzed to formaldehyde. ^{18}O isotopic labeling studies have shown that this process is intermolecular.[22]



Scheme 11

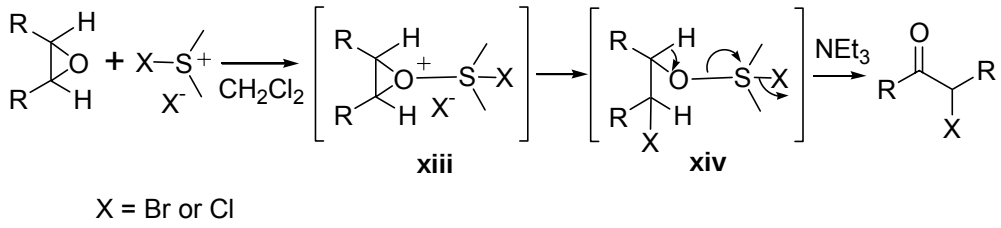
In 1968, Dalton and co-workers[23] studied bromohydrin formation in moist DMSO in order to overcome the poor solubility of olefins in water. After the addition of NBS, bromohydrins were obtained after workup. Interestingly, the formation of *β*-bromo dimethylalkoxysulfonium ion **xii** was supported by ^{18}O-labeling experiments, where at least 95% of the bromohydrin arose from ^{18}O-labeled DMSO oxygen (Scheme 12). The crystalline structures of various *β*-hydroxy dimethylalkoxysulfonium salts isolated by Swern and co-workers[24] imply the high stability of structurally similar *β*-bromo dimethylalkoxysulfonium ion **xii** under anhydrous conditions. (cf. Scheme 12)



^{18}O-labeling:	DMSO-^{16}O/ $H_2{}^{18}O$	$H_2{}^{16}O$ workup	no ^{18}O observed
	DMSO-^{16}O/ $H_2{}^{16}O$	$H_2{}^{18}O$ workup	no ^{18}O observed
	DMSO-^{18}O/ $H_2{}^{16}O$	$H_2{}^{16}O$ workup	^{18}O only

Scheme 12

Another example for the formation of *β*-halo dimethylalkoxysulfonium ions was reported by Olah and co-workers[25] in the conversion of epoxides to *α*-haloketones using bromodimethylsulfonium bromide (BDMS) or chlorodimethylsulfonium chloride (CDMS). They proposed the mechanism shown in Scheme 13. The activation of the epoxide with BDMS or CDMS results in the formation of complex **xiii**; the activated epoxide is opened by X^- to give *β*-halo dimethylalkoxysulfonium ion **xiv**, which results in high yields of *α*-haloketone upon treatment with a mild base.



Scheme 13

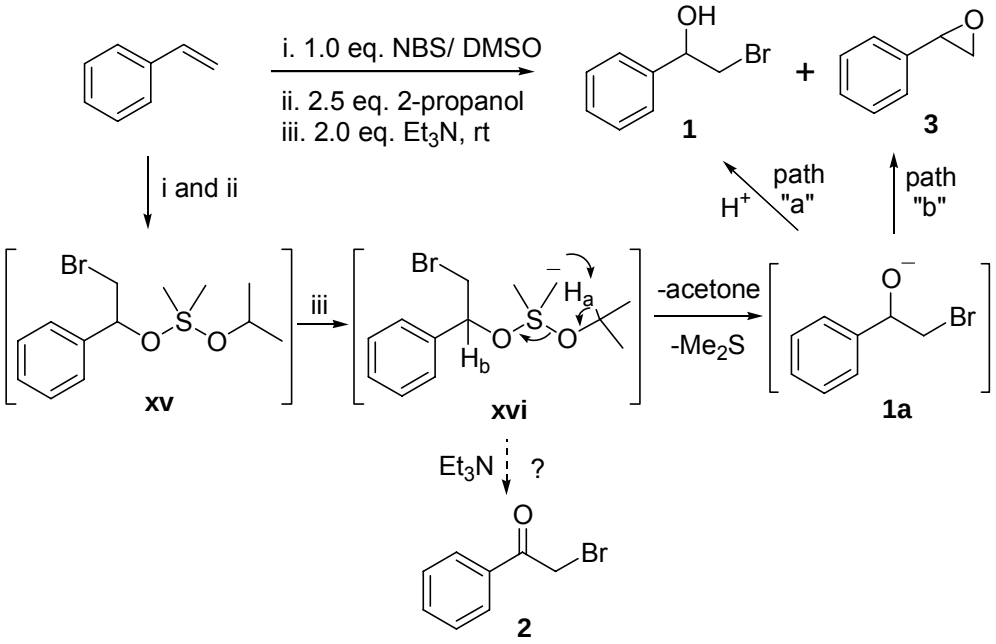
Results and Discussion

Although dimethylalkoxysulfonium ions (**iv**) have been extensively investigated for almost a century, the study of *β*-bromo dimethylalkoxysulfonium ions (**xii**) has been limited during the past half century. The existence of this intermediate was reported by Olah and co-workers[25] by reacting epoxides with bromodimethylsulfonium bromide (BDMS). The ^{18}O-labeling experiments of Dalton and co-workers[23] supported the existence of *β*-bromo dimethylalkoxysulfonium ions (**xii**), generated from olefins and NBS in moist DMSO.

In the beginning of our study on *β*-bromo dimethylalkoxysulfonium ions (**xii**), we expected to develop a convenient process to directly transform olefins into epoxides. The idea was to combine Dalton's observation[23] with traditional oxidation conditions of dimethylalkoxysulfonium ions, *i.e.*, Moffatt or Swern oxidation. It was postulated that the addition of an easily oxidized alcohol to *β*-bromo dimethylalkoxysulfonium ion **xii** could (in the case of styrene) produce intermediate **xvi**, which would enable two pathways of deprotonation (*i.e.*, H_a vs. H_b) (Scheme 14). While removal of H_b to form *α*-bromoacetophenone **2** would be traditionally expected, we were hopeful that removal of less hindered H_a to produce alkoxide **1a**

would predominate. This anion could either be protonated to form bromohydrin **1** or collapse to produce epoxide **3** through an intramolecular S_N2 reaction. When 2-propanol was added with subsequent addition of TEA, a mixture of two compounds was given. Careful ^1H NMR analysis showed that the product was a 4:1 mixture of bromohydrin **1** and epoxide **3**. Therefore, oxidation on the less sterically hindered isopropoxide took place preferentially, as no trace of **2** was observed.

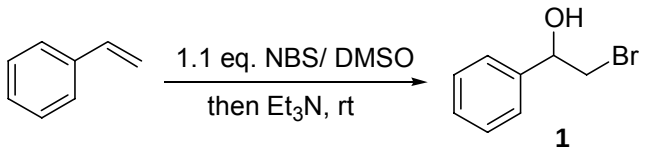
Decreasing the amount of 2-propanol (1.5 equivalents) resulted in decreased yields of epoxide **3** in the crude mixture. This observation supports the formation of intermediate **xv**, since the extra percentage of bromohydrin **1** could be explained by hydrolysis of the unreacted *β*-bromo dimethylalkoxysulfonium ion during aqueous workup.



Scheme 14

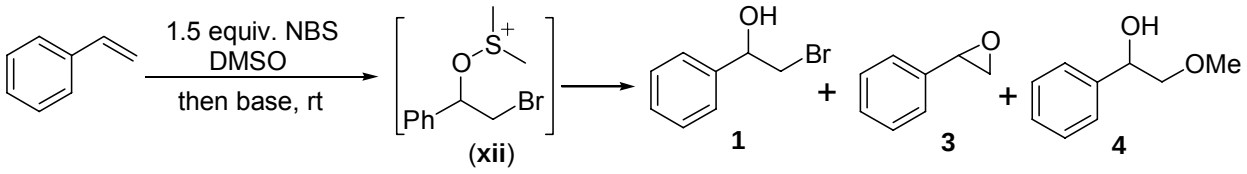
When styrene was treated with NBS/DMSO at room temperature, followed by addition of excess triethylamine (TEA), only bromohydrin **1** was collected after workup (Scheme 15). Although it has been extensively used for similar oxidations, we believe that under these

conditions TEA is not basic enough to deprotonate the dimethylalkoxysulfonium ion leading to oxidation.



Scheme 15

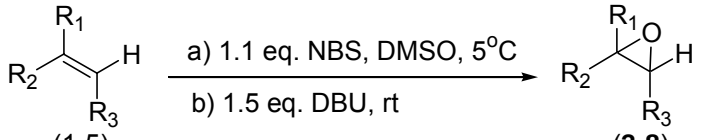
Other traditional bases were then studied. To our surprise, weak bases gave only bromohydrin **1**, whereas strong bases produced only epoxide **3** without addition of 2-propanol (Scheme 16). This simplified procedure became our primary method of study. The bases which gave epoxide formation were DBU, sodium dimsyl ($CH_3SOCH_2^-Na^+$), potassium *tert*-butoxide (*t*-BuOK) and sodium methoxide. Note that sodium methoxide also produced ether **4** by an S_N2 displacement. Because of its non-nucleophilicity, and its ease of handling, DBU became our choice of base for this study.



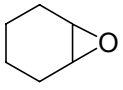
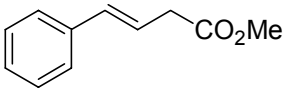
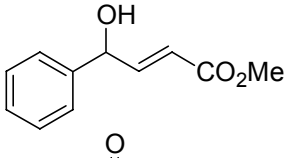
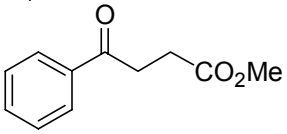
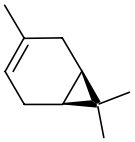
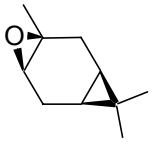
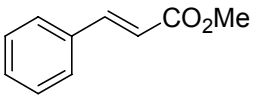
Bases:	Et_3N	1	:	0	
	i-Pr_2NEt	1	:	0	
	DABCO	1	:	0	
	DBU	**0**	**:**	**1**	
	NaOMe	0	:	1	+ (4)
	$NaCH_2SOCH_3$	0	:	1	
	KO*t*-Bu	0	:	1	
	K_2CO_3	1	:	0	
	KOH	decomposed			

Scheme 16

Scheme 17[26] shows the epoxidation of a partial series of olefins with modest to high yields. The full series has revealed that this transformation is a general method to transform olefins into epoxides. Optimized reaction conditions are as follows: NBS (1.5 equivalents) is added to a solution of olefin in anhydrous DMSO at 10 ℃. After consumption of the olefin, DBU (1.5 equivalents) is added. Each part of the reaction usually goes to completion within 30 minutes. The reaction is worked up by extraction of the product into diethyl ether, followed by column chromatography. These conditions represent a mild procedure for the epoxidation of olefins and a convenient workup.

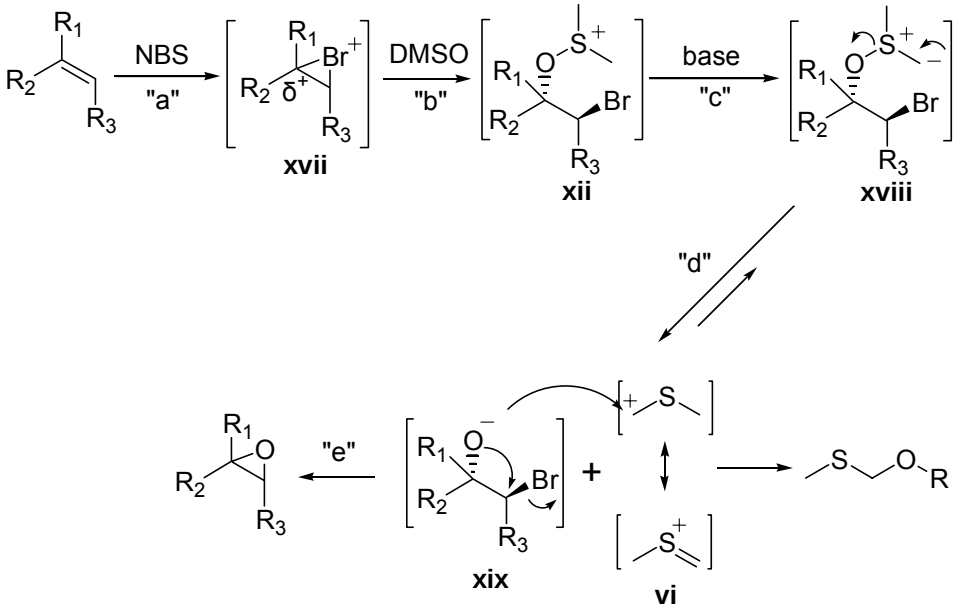


(1-5) (**3**-**8**)

entry	R_1	R_2	R_3	product	yield (%)
(1)	Ph	H	H	**3**	77
(2)	Ph	H	Ph	**5**	76
(3)	Ph	H	Me	**6**	70
(4)	Ph	Me	H	**7**	50
(5)	$C_{10}H_{21}$	H	H	**8**	50
(6)				**9** 	60-71
(7)				**10a** 	53
				10b 	31
(8)				**11** 	73
(9)					0

Scheme 17

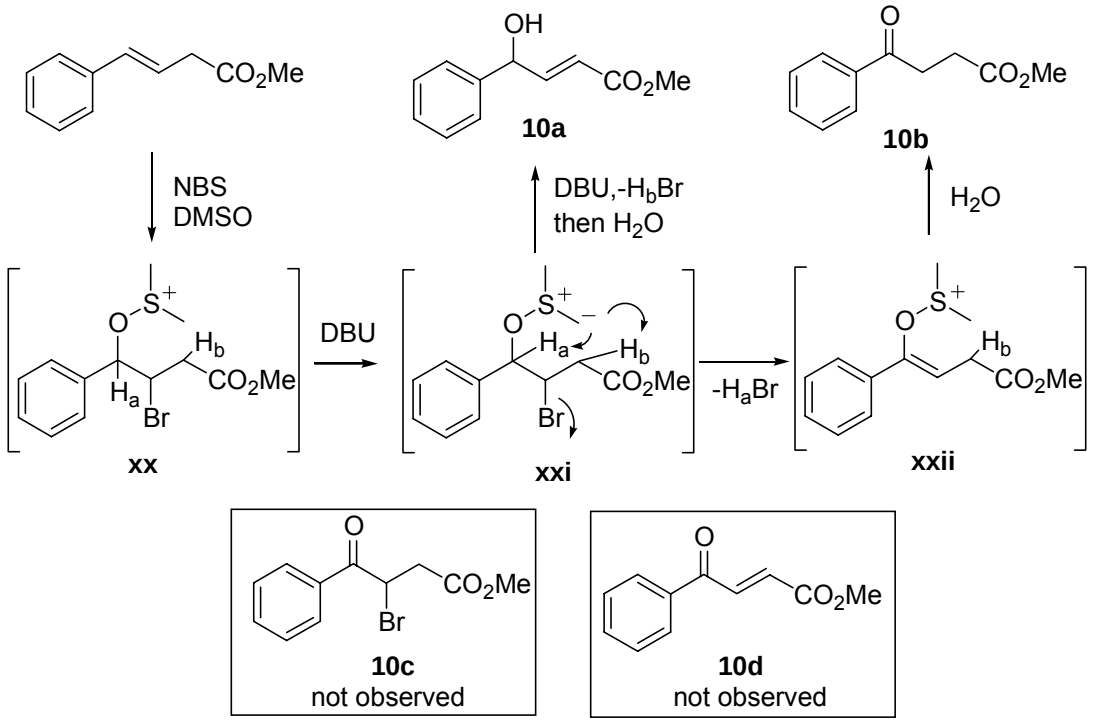
The possible pathway is summarized in Scheme 18: a) initial activation of the olefin by NBS generates bromonium ion **xvii**; b) the oxygen atom of DMSO attacks the most electrophilic carbon of the bromonium ion and generates *β*-bromo dimethylalkoxysulfonium ion **xii**; c) deprotonation of one of the sulfur methyl groups produces *β*-bromo oxysulfonium ylide **xviii**; d) the ylide undergoes dissociation to give intermediate **vi** and oxygen anion **xix**. Anion **xix** may either recombine to give ylide **xviii** or produce a methylthiomethyl ether as a byproduct; e) the intramolecular displacement of bromide in anion **xix** results in the formation of an epoxide.



Scheme 18

Instead of an epoxide, entry 7 gave a mixture of alcohol **10a** and ketone ester **10b**. As shown in Scheme 19, *β*-bromo dimethylalkoxysulfonium ion **xx** is the first intermediate generated. Once DBU is added, oxysulfonium ylide **xxi** will be formed. Hydrogen abstraction of either H_a or H_b can take place (cf. Scheme 6). Because hydrogen H_b is acidic ($pK_a < 24$) due to the electron-withdrawing effect of the neighboring carbonyl group and bromide, preferential

abstraction of H_b produces alcohol **10a**. Abstraction of hydrogen H_a should have resulted in ketone **10c** or enone **10d** after subsequent dehydrobromonation. However, the only observed ketone species is **10b**, which suggests that elimination of bromide to give intermediate **xxii** is preferred over the loss of DMS. Hydrolysis of **xxii** produces ketone **10b**.

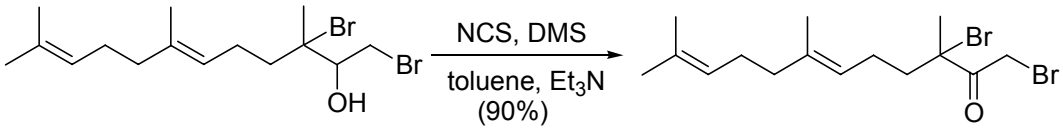


Scheme 19

Although the above mechanism accounts for most of our observations, a few concerns remain. For example, we wanted to show that the epoxide is formed from *β*-bromo dimethylalkoxysulfonium ion **xii** but not from the cyclization of a bromohydrin by adventitious hydrolysis during the reaction. Fortunately, the steps "a" and "b" have been well established by Dalton and co-workers[22] in their ^{18}O-labeling experiments. Precautions, such as the use of fresh distillation of DBU and DMSO, were taken during the reaction in order to ensure strictly

anhydrous conditions. TLC analysis could detect no bromohydrin during any step of the reaction. Moreover, the formation of **10b** as in Scheme 19 also encourages the existence of *β*-bromo dimethylalkoxysulfonium ion **xii**. Thus, the cyclization of a bromohydrin could be reasonably ruled out from our proposed mechanism.

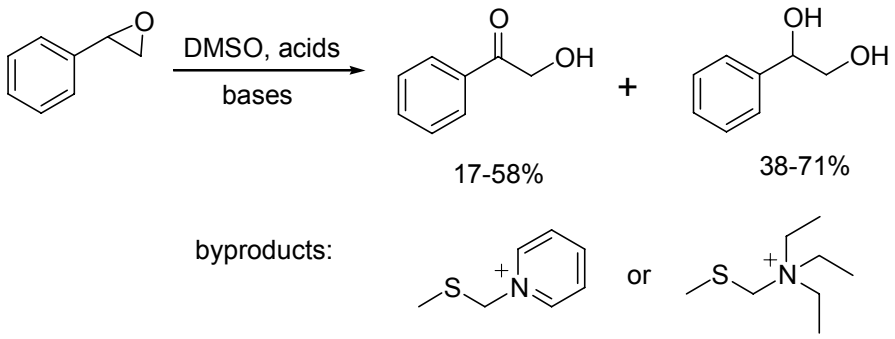
Given that the DMSO-promoted oxidations have been so widely studied, we were curious that if there were other oxidations of bromohydrins involving intermediate **xii**. However, it was found that chromium (VI) oxidants have been used in the oxidation of bromohydrins, but there is only a single example for the oxidation of a *β*-bromo dimethylalkoxysulfonium ion (**xii**) intermediate. In 1979, Noyori and co-workers[27] oxidized a bromohydrin *in situ* to an *α*-bromoketone using NCS/DMS complex and TEA (Scheme 20). Despite the presence of both a primary *β*-bromide and a tertiary *β*-bromide, an excellent yield of the ketone was obtained. This is closely paralleled by the previously related work by Olah and co-workers where intermediate **xiv** was suggested for the oxidation to *α*-haloketones (Scheme 13).



Scheme 20

In 1975, Swern and co-workers, in their study of acid-catalyzed epoxide opening with DMSO, reported that ketols (*α*-hydroxy ketones) could be obtained when the intermediate *β*-hydroxyl dimethylalkoxysulfonium ions were treated with base.[24,28] However, only a low yield of phenylacyl alcohol was observed in the study of styrene oxide, and a significant percentage of phenyl ethylene glycol was collected (Scheme 21). It was rationalized that, after exclusion of a

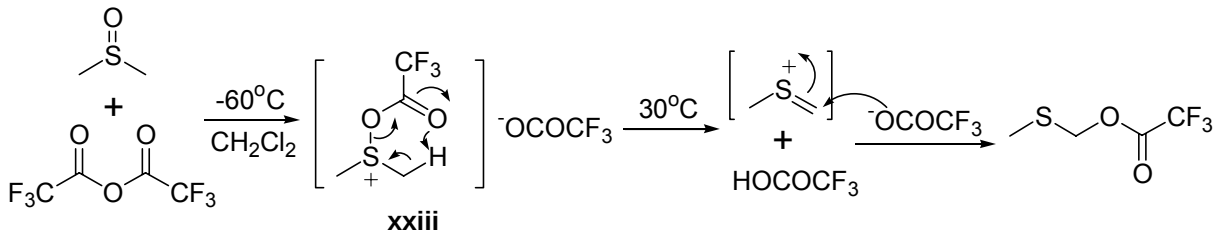
hydration pathway, the dissociation of the alkoxysulfonium ylide to intermediate **xiii** and oxygen anion was preferred over hydrogen abstraction of this ylide to afford ketol. The observance of (methylthio)methylpyridium ion when pyridine was used as a base and that of (methylthio)methyltriethylammonium ion when TEA was applied were thought to facilitate this process. A systematic study of the R groups[18] in the oxidation of alkoxysulfonium ions found that bulky R groups or electron-withdrawing functional groups (such as fluoride and aryl) on the alcohols destabilize the alkoxysulfonium ions, which make dissociation more feasible. Before the dissociated intermediates recombine to give a methylthiomethyl ether, base or another nucleophile attacks intermediate **vi** (as in Scheme 18) and the alcohol is recovered after protonation. Thus, the electron-withdrawing effect of both phenyl and *β*-hydroxyl groups can contribute to the inertness of the intermediate ylide upon hydrogen abstraction (Scheme 21).



Scheme 21

The choice of the leaving group greatly influences the mechanistic pathway. For example, Swern also studied Pummerer reactions where trifluoroacetic anhydride was used to activate DMSO.[29] As shown in Scheme 22, intermediate **xxiii** could only be obtained at low temperature; at higher temperatures the Pummerer rearrangement resulted in the formation of methylthiomethyl trifluoroacetate. It was proposed that the ability of trifluoroacetate to serve as a

leaving group allows intermediate **xxiii** to readily dissociate without addition of base; whereas the traditional acetate intermediate **xi** requires harsher conditions for the transformation.

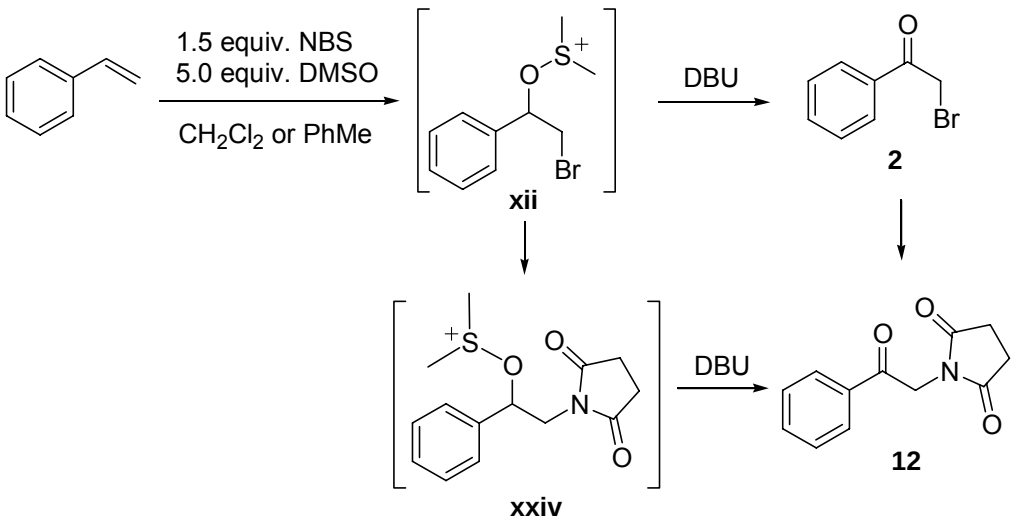


xxiii

Scheme 22

The above analysis indicates that the better the leaving group the easier it is to dissociate the alkoxysulfonium ion intermediate. Indeed, we consider the neutral epoxide and bromide anion as excellent "leaving groups" which therefore promote the dissociation of oxysulfonium ylide **xxi** along our proposed mechanistic pathway.

DMSO is a polar aprotic solvent which stabilizes polar intermediates, such as **xix** and **vi**. We noticed that the solvents used in Olah's (Scheme 13), Noyori's (Scheme 20) and Swern's (Scheme 22) studies are dichloromethane or toluene. We observed that when dichloromethane or toluene was used as solvent with 5.0 equivalents of DMSO, a normal Swern-type oxidation took place to give ketone **12** (with little unreacted styrene when toluene was used) (Scheme 23). Although it is not clear whether α-bromoketone **2** or intermediate **xxiv** is first generated, the formation of **12** implies that non-polar solvents do not stabilize the dissociated intermediates which prevent the potential formation of epoxides when *β*-bromo dimethylalkoxysulfonium ions (**xii)** are generated. By using DMSO as solvent, the equilibrium is driven toward the dissociation by the stabilizing effect of the solvent. Therefore, subsequent epoxide formation was observed to be the only product.



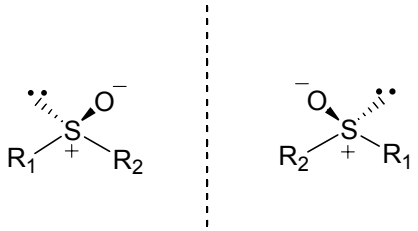
Scheme 23

In conclusion, the factors that play an important role in this epoxidation are the basicity of the base, the bulkiness of the R groups and bromide, the electron-withdrawing effect of the *β*-bromide, the nature of the leaving groups and the solvent effect.

Toward the Asymmetric Epoxidation of Alkoxysulfonium Ions

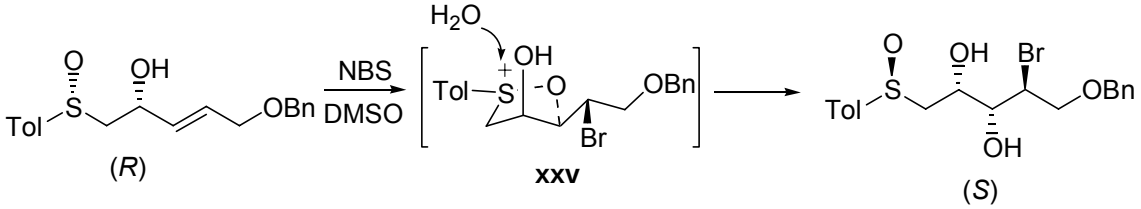
We are confident that an asymmetric version of this epoxidation process could be developed via chiral *β*-bromo dimethylalkoxysulfonium ions. Unsymmetrical sulfoxides are chiral because of the lone pair of electrons (Scheme 24)[30] and have been used as chiral auxiliaries since the 1980s.[31] Since then, other synthetic applications of chiral sulfoxides have been developed, such as Michael additions[32] and Diels-Alder reactions.[33] There are three basic advantages in using chiral sulfoxides:[30] a) the thermal stereomutation of sulfoxides only becomes significant near 200 ℃; b) the large stereoelectronic differences between the oxygen atom, the

two alkyl or aryl substituents and the lone pair of electrons make a well-defined asymmetric environment around the sulfur atom; c) since the 1990s, many methods have been developed to prepare both enantiomeric forms of the chiral sulfoxides.



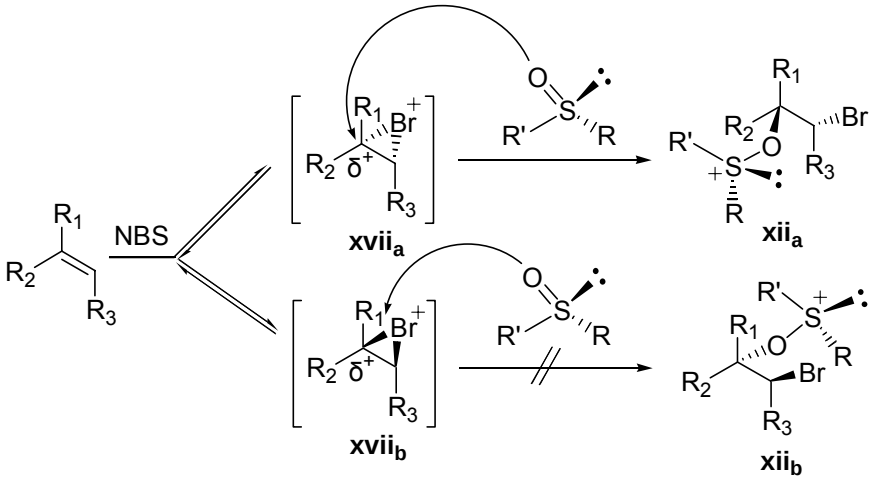
Scheme 24

In 2003, Raghaven and co-workers reported an asymmetric bromohydrin synthesis via an intramolecular chiral sulfoxide reaction with a bromonium ion.[34] As shown in Scheme 25, NBS activates the olefin from its less hindered face, followed by nucleophilic attack of the sulfoxide oxygen to generate intermediate **xxv**; water then attacks the sulfur atom of intermediate **xxv** to give the bromohydrin as single product. It was observed that an inversion of chirality on sulfoxide sulfur atom took place along with this transformation, which supported the formation of intermediate **xxv**.



Scheme 25

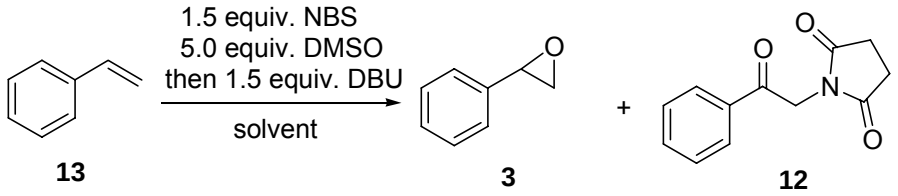
In our procedure, a chiral sulfoxide would produce an asymmetric *β*-bromo dimethylalkoxysulfonium ion (**xii$_a$**) which retains its chirality on the sulfur atom. As shown in Scheme 26, the bromonium ion formation will give two intermediates **xvii$_a$** and **xvii$_b$**. A chiral sulfoxide will selectively attack **xvii$_a$** to give the sterically less hindered intermediate **xii$_a$**, which culminates in the formation of a chiral epoxide after treatment with DBU.



Scheme 26

Since having the chiral reagent also serve as the solvent is undesirable, we investigated the use of non-nucleophilic co-solvents. As shown in Scheme 27, four other solvents have been studied using only 5.0 equivalents of DMSO. We observed that DMSO no longer reacted rapidly in low concentrations. Instead, S_N2 displacement of the bromide in intermediate **xii** occurred by the *in situ* generated succinimide anion, presumably due to the decreased nucleophilicity of DMSO in less polar solvents. Interestingly, the displaced product underwent the normal Swern oxidation to give ketone C.

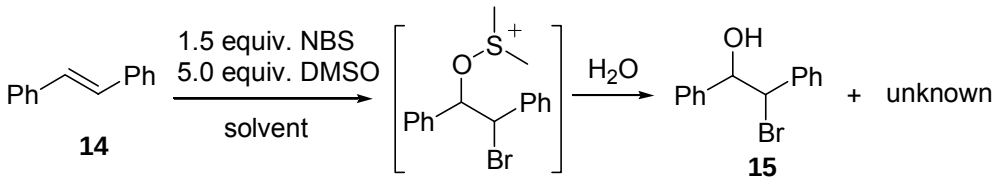
Stilbene was then employed to minimize S_N2 displacement products (base was not added as only the rate of the reaction was studied). As shown in Scheme 28, although the rate of



solvent	Products
CH_2Cl_2	**12** + **13** only
MeCN	**12** + trace **13**
dioxane	**13**: **3**: **12** = 1: 1.5: 1.5
PhMe	**12** only

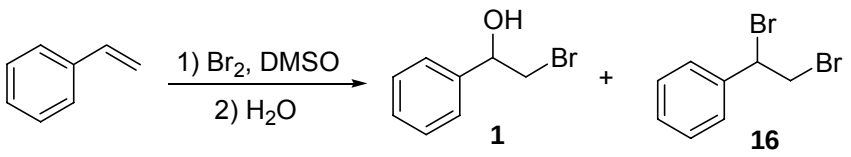
Scheme 27

side reactions was reduced, the reaction rate for the formation of **xii** was also slowed, and significant amounts of stilbene were recovered despite long reaction times. When bromine was used instead of NBS, a significant amount of dibromide was always collected along with bromohydrin (Scheme 29).



solvent	reaction time	products
CH_2Cl_2	24 hours	**14**: **15** = 1: 0.24
MeCN	22 hours	**14**: **15** = 1: 0.42
Dioxane	48 hours	**14**: **15** = 1: 1.6
PhMe	22 hours	**14**: **15** = 1: 0.45

Scheme 28

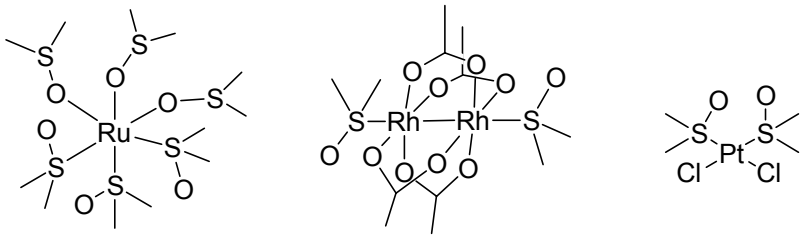


1: **16** = 2: 1 (add Br_2 to styrene/DMSO)
1: **16** = 1: 0.8 (add Br_2/DMSO to styren/DMSO)

Scheme 29

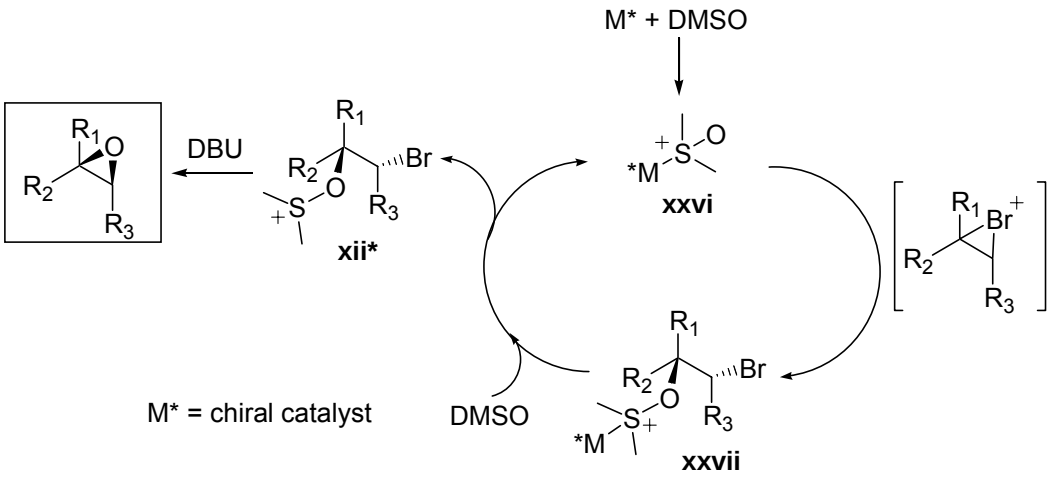
Methyl phenyl sulfoxide was used as part of our asymmetric study. However, it was found to be much less reactive than DMSO, and even extended reaction times did not lead to completion. These results, combined with the fact that use of at least one equivalent of chiral sulfoxide is an expensive process, led us to abandon this approach to stereoselectivity.

As shown in Scheme 30, structures with Ru, Rh, or Pt as cores have been found to be able to coordinate with DMSO on its sulfur atom.[35] Encouraged by these structures, we proposed that the selective coordination of a chiral metal catalyst with the sulfur atom on simple sulfoxide, such as DMSO, would fulfill the role of a chiral sulfoxide nucleophile.



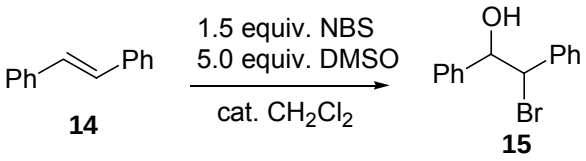
Scheme 30

A possible mechanistic cycle of the catalytic asymmetric epoxidation of olefins is proposed in Scheme 31. The selective coordination of a transition metal catalyst bearing a chiral dentate with DMSO sulfur will generate intermediate **xxvi**. The following reaction with a bromonium ion will produce intermediate **xxvii** with facial selectivity. Simple dissociation of the



Scheme 31

metal sulfur bond or displacement by another molecule of DMSO would give *β*-bromo dimethylalkoxysulfonium ion **xii*** and regenerate the chiral complex **xxvi**. Thus, a new reaction cycle can start from intermediate **xxvi**.



14 **15**

catlyst	reaction time	products
$RuCl_2(PPh)_3$	**6 hours**	**mostly 15**
$RhCl(PPh_3)_3$	18 hours	**14**: **15** > 1
$PdCl_2$	**19 hours**	**15 only**
$RbOAc\text{-}xH_2O$	19 hours	no reaction
$Pd_2dba_3\text{-}CHCl_3$	40 hours	**14**: **15** = ~1: 1
$RhCl(CO)(PPh_3)_3$	40 hours	no reaction
$PdCl_2(MeCN)_2$	**15 hours**	**15 only**
$Pd(OAc)_2$	**15 hours**	**mostly 15**
$Re(CO)_5Br$	44 hours	**14**: **15** > 1
$PtCl_2$	44 hours	**14**: **15** < 0.25
$IrCl_3\text{-}xH_2O$	**45 hours**	**15 only**
$RhCl_3\text{-}xH_2O$	**6.5 hours**	**mostly 15**

Scheme 32

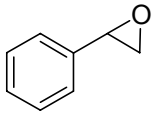
The ideal catalyst in our proposed mechanism will accelerate the nucleophilic addition of coordinated DMSO, and dissociate from intermediate **xxvii** easily. As shown in Scheme 32, numerous transition metal catalysts have been investigated and several of them have demonstrated promising results.

In summary, a mild and efficient epoxidation of electron rich olefins in moderate to excellent yields has been developed. A detailed mechanistic discussion excluded Moffatt or Swern type oxidation and supported a preferred dissociation of intermediate **xii** which could conduct the intramolecular displacement of bromide to give epoxide. A catalytic asymmetric epoxidation mechanism was proposed and the study on the accelerating effect of transition metal catalysts showed potential for facilitating catalytic asymmetric epoxidation.

Experimental Section

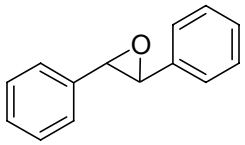
All reactions were run under an inert atmosphere of nitrogen and monitored by TLC analysis until the starting material was completely consumed. Anhydrous DMSO was distilled over KOH under high vacuum. The crude products were purified by flash chromatography using silica gel 60 (230-400 mesh ASTM) and distilled reagent grade petroleum ether and diethyl ether. Proton NMR spectra were obtained in $CDCl_3$ and were calibrated using trace $CHCl_3$ present (δ 7.27) as an internal reference.

General Procedure: To a solution of styrene (208 mg, 2 mmol) in anhydrous DMSO (5 mL) at 10 ℃ was added *N*-bromosuccinimide (NBS) (535 mg, 3 mmol, 1.5 equivalents). The resulting reaction mixture was stirred for 10 minutes at which time the yellow color faded. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (447 μL, 3 mmol, 1.5 equivalents) was added and the resulting mixture was stirred for 30 minutes. Diethyl ether (15 mL) was used to extract the DMSO solution. The ethereal extract was concentrated directly, followed by column chromatographic purification, to afford 178 mg (77%) of styrene oxide (**3**).



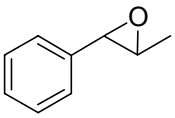
(3)

Registry Number: 96-09-3; ^{1}H NMR (400 MHz) δ 2.80 (d, J = 5.6 Hz, 1H), 3.14 (t, J = 5.6 Hz, 1H), 3.85 (m, 1H), 7.21-7.40 (m, 5H).



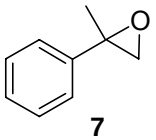
5

Registry Number: 1439-07-2; ^{1}H NMR (400 MHz) δ 3.88 (s, 2H), 7.30-7.45 (m, 10H).



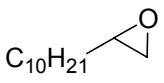
6

Registry Number: 4518-66-5; ^{1}H NMR (400 MHz) δ 1.49 (d, J = 4.8 Hz, 3H), 3.05-3.10 (m, 1H), 3.61 (d, J = 2.4 Hz, 1H), 7.25-7.40 (m, 5H).



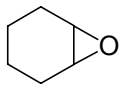
7

Registry Number: 2085-88-3; ^{1}H NMR (400 MHz) δ 1.77 (s, 3H), 2.85 (d, J = 5.6 Hz, 1H), 3.03 (d, J = 5.6 Hz, 1H), 7.30-7.45 (m, 5H); ^{13}C NMR (400 MHz) 21.76 (q), 56.62 (s), 56.89 (t), 125.30 (d), 127.41 (d), 128.30 (d), 141.25 (s) ppm.



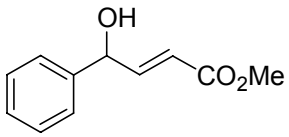
8

Registry Number: 2855-19-8; ^{1}H NMR (400 MHz) δ 0.85-0.91 (m, 4H), 1.22-1.36 (m, 20H), 1.40-1.56 (m, 5H), 2.47 (dd, J_1 = 2.8 Hz, J_2 = 4.8 Hz, 1H), 2.75 (dd, J_1 = 4.0 Hz, J_2 = 4.8 Hz, 1H), 2.88-2.95 (m, 1H).



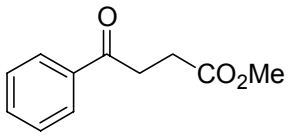
9

Registry Number: 286-20-4; ^{1}H NMR (400 MHz) δ 1.23 (m, 2H), 1.42 (m, 2H), 1.82 (m, 2H), 1.94 (m, 2H), 3.11 (s, 2H); ^{13}C NMR (400 MHz) 19.53 (t), 24.54 (t), 52.07 (d) ppm.



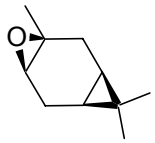
10a

Registry Number: 55980-63-7; ^{1}H NMR (400 MHz) δ 3.74 (s, 3H), 5.34 (bs, 1H), 6.18 (dd, J_1 = 2.0 Hz, J_2 = 15.6 Hz, 1H), 7.06 (dd, J_1 = 5.2 Hz, J_2 = 15.6 Hz, 1H), 7.30-7.40 (m, 5H); ^{13}C NMR (400 MHz) 51.73 (q), 73.45 (d), 119.65 (d), 126.63 (d), 128.37 (d), 128.86 (d), 140.89 (s), 149.09 (d), 167.09 (s) ppm.



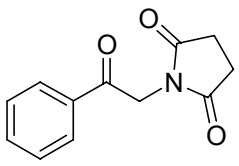
10b

Registry Number: 25333-24-8; ^{1}H NMR (400 MHz) δ 2.77 (t, *J* = 6.8 Hz, 2H), 3.33 (t, *J* = 6.8 Hz, 2H), 3.71 (s, 3H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (400 MHz) 28.02 (t), 33.41 (t), 51.91 (q), 128.07 (d), 128.65 (d), 133.30 (d), 136.49 (s), 173.43 (s), 198.11 (s) ppm.



11

Registry Number: 35671-18-2; ^{1}H NMR (400 MHz) δ 0.53-0.58 (m, 2H), 0.93 (s, 3H), 0.97 (s, 3H), 1.31 (s, 3H), 1.78 (d, *J* = 14.0 Hz, 2H), 2.00-2.10 (dd, J_1 = 8.8 Hz, 1H), 2.23-2.32 (m, 1H), 2.88 (d, *J* = 5.6 Hz, 1H).



Registry Number: 24246-87-5; ^{1}H NMR (400 MHz) δ 2.86 (s, 4H), 4.95 (s, 2H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (400 MHz) 28.39 (t), 44.77 (t), 128.14 (d), 128.93 (d), 134.14 (d), 134.32 (s), 176.78 (s), 190.27 (s) ppm.

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