THE TOTAL SYNTHESES OF SALVIA TERPENES: (+)-GRANDIONE, (–)-BRUSSONOL, (–)-SALVIASPERANOL AND (+)-SALVADIONE-B

by

GE ZOU

(Under the Direction of George Majetich)

ABSTRACT

By using an A + C → ABC cyclialkylation strategy we synthesized the icetexane-based diterpenes (–)-barbatusol, (+)-demethylsalvicanol, and (–)-brussonol. Synthetic (+)-demethylsalvicanol was dimerized to produce (+)-grandione using aqueous Diels–Alder conditions. A modification of our cyclialkylation strategy was used to construct the tricyclic skeleton of (–)-salviasperanol.

Our synthesis of (+)-salvadione-B featured a regio- and stereospecific Diels–Alder reaction as well as an efficient oxidative free radical cyclization.

INDEX WORDS: (+)-demethylsalvicanol, (–)-brussonol, (–)-barbatusol, (+)-grandione, (–)-salviasperanol, (+)-salvadione B, cyclialkylation, *p*-benzoquinone, Diels–Alder reaction, oxidative free radical cyclization

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Dean of the Graduate School
The University of Georgia
August 2009

DEDICATION

This dissertation is dedicated to my parents and grandparents. They have opened my eyes to the world and always encouraged me to move forward.

ACKNOWLEDGEMENTS

So many people have helped me during my graduate study. First and foremost I would like to thank Dr. George Majetich, my advisor and committee chair, for his guidance and kind support during these years, also for his patience and encouragement in my research. He has created an exhilarating environment of science. I feel fortunate and honored to study and pursue research under his supervision. The other members of my thesis committee, Professors Robert Phillips and Gregory Robinson, deserve my gratitude for their support and general comments over the years. I am also very grateful for Dr. Pingrong Wei, Dr. Greg Wylie and Dr. Dennis Phillips for their help regarding the X-ray crystallography, NMR and Mass Spectra, respectively.

My sincerest thank goes to Dr. Yang Li. He helped me at the early stage of my graduate research. I also thank my co-workers in the laboratory: Jianhua Yu, Dr. Shougang Hu, Joel Shimkus, Jeremy Grove and Eric Huddleston. I would like to thank my wife, Yunjie Peng, for her understanding, patience and support. Last but not least, I would like to thank all of my friends at UGA who have made my life at Athens a real pleasure.

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LIST OF ABBREVIATIONS

Abbreviation	**Full name**
AIBN	azo-*bis*-isobutyronitrile
CAN	ceric ammonium nitrate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
DEAD	diethylazodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*′-dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
HMPA	hexamethylphosphoramide
LA	Lewis acid
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
L-Selectride	lithium tris-(*sec*-butylborohydride)
m-CPBA	*meta*-chloroperoxybenzoic
Ms	methanesulfonyl

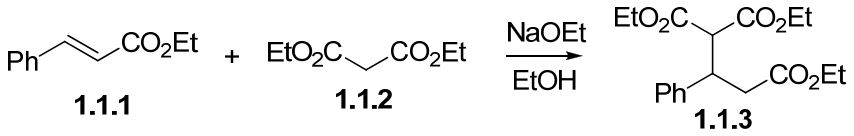
NBS	*N*-bromosuccinimide
NBSH	*ortho*-nitrobenzenesulfonylhydrazine
NMM	*N*-methylmorpholine
PCC	pyridium chlorochromate
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
p-TSA	*para*-toluenesulfonic acid

CHAPTER ONE

TOTAL SYNTHESES OF (+)-GRANDONE AND (–)-SALVIASPERANOL

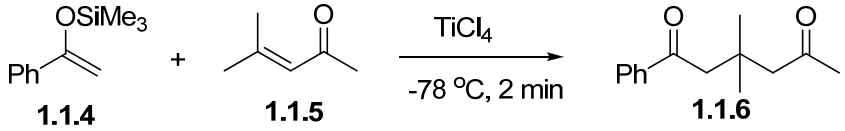
1.1 Introduction and Background

In 1887, Michael systematically investigated the 1,4-addition of stabilized anions with α,β-unsaturated systems.[1] Michael reactions can take place under acidic, basic and free radical conditions. Electrophiles in Michael reactions are activated olefin moieties, such as α,β-unsaturated ketones, esters and nitriles, which are also called "Michael acceptors." On the other hand, activated methylenes such as malonates and nitroalkanes are used as traditional nucleophiles in Michael reactions (Scheme 1.1.1).



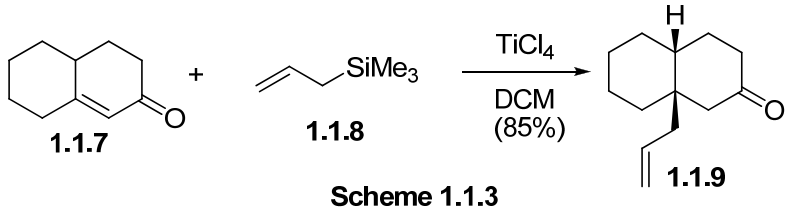
Scheme 1.1.1

Other nucleophiles also add to Michael acceptors. For example, in 1976, Mukaiyama and co-workers reported the addition of silyl enol ethers to conjugated enones when catalyzed by $TiCl_4$ (Scheme 1.1.2).[2]



Scheme 1.1.2

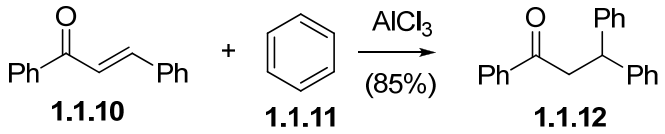
In the same year, Sakurai and co-workers found that allylsilane could react with Michael acceptors efficiently when being treated with stoichiometric quantities of Lewis acid (Scheme 1.1.3). This transformation is nowadays known as Hosomi–Sakurai allylation.[3]



1.1.7 1.1.8 1.1.9

Scheme 1.1.3

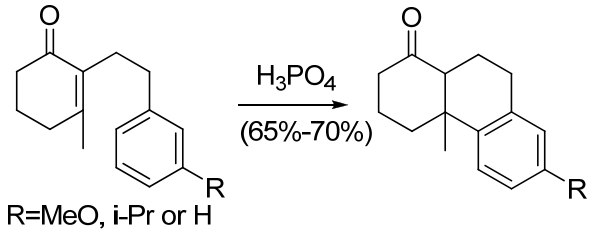
Michael acceptors react as electrophiles in Friedel–Crafts alkylations. In 1923, Vorlander and Friedberg reported the 1,4-addition of benzene to benzalacetophenone catalyzed by $AlCl_3$ (Scheme 1.1.4).[4]



1.1.10 1.1.11 1.1.12

Scheme 1.1.4

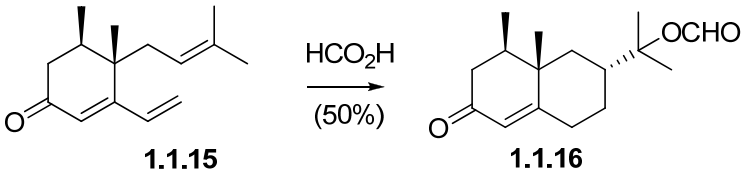
Intramolecular Friedel–Crafts reaction of α,β-unsaturated ketones can produce alkyl annulation products. In 1951, Stork and co-workers showed that a 6,6,6-tricyclic system can be constructed by heating enone **1.1.13** with phosphoric acid (Scheme 1.1.5).[5]



1.1.13 **1.1.14**

Scheme 1.1.5

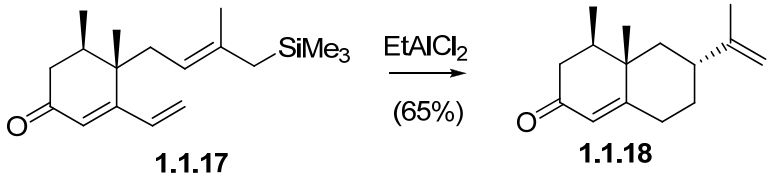
Conjugated dienones are also excellent Michael acceptors. In 1974, Dastur found that when dienone **1.1.15** was heated with a catalytic amount of formic acid, only the 1,6-addition product was founded (Scheme 1.1.6).[6] This observation represented a new approach to carbocyclization.



1.1.15 **1.1.16**

Scheme 1.1.6

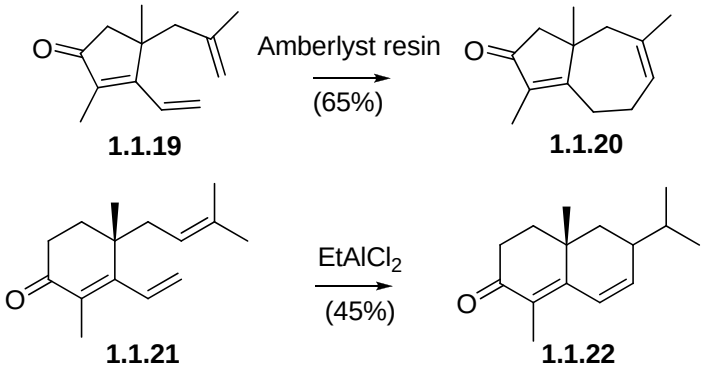
Majetich and co-workers have reported that intramolecular Sakurai addition to a conjugated dienone represents a new annulation strategy to produce medium-membered rings. Scheme 1.1.7 depicts the application of this strategy to synthesize nootkatone.[7]



1.1.17 **1.1.18**

Scheme 1.1.7

The Majetich group also found that unactivated double bonds can add to conjugated dienones intramolecularly to form six- and seven-membered rings (Scheme 1.1.8).[8]

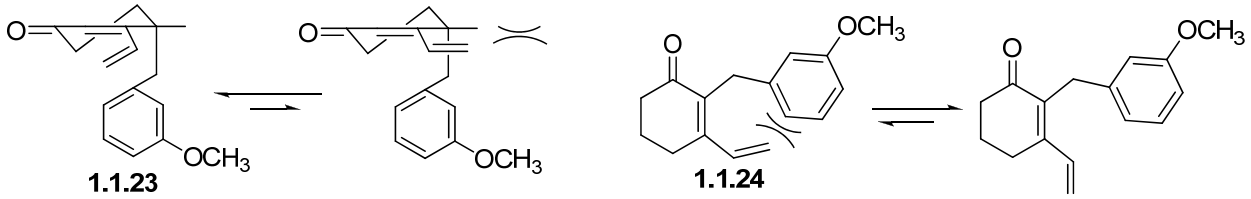


1.1.19 **1.1.20**

1.1.21 **1.1.22**

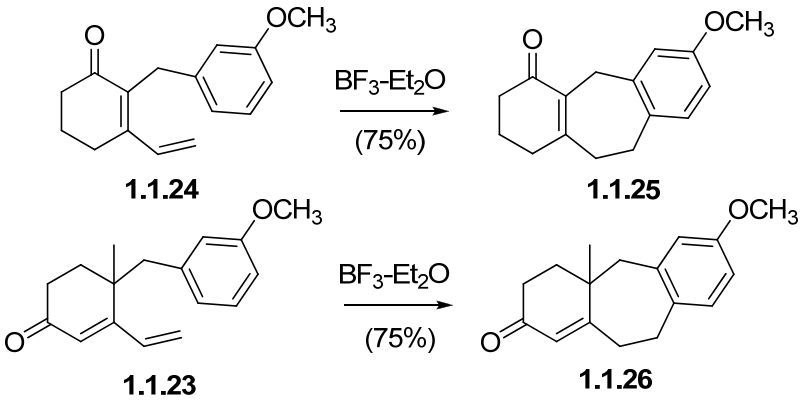
Scheme 1.1.8

The success of using conjugated dienones as Michael acceptors prompted our research group to investigate an intramolecular Friedel–Crafts reaction with conjugated dienones.[9] Two series of arene-dienones were tested. Although 4-arene-dienones were found to be more reactive than 2-arene-dienones because of conformational consideration, both can cyclize under Lewis acid catalyzation (Scheme 1.1.9, Scheme 1.1.10).

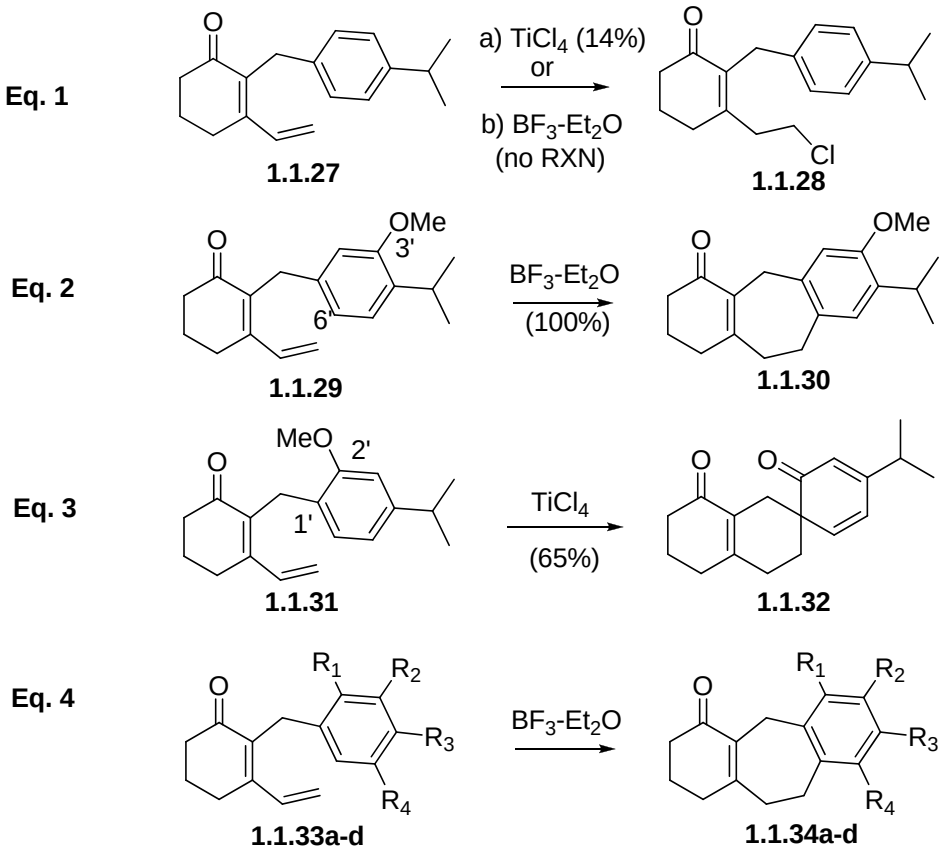


Scheme 1.1.9

It was also found that electron-donating groups dictate the outcome of regioselectivity. As shown in Scheme 1.1.11, cyclialkylation did not occur when the benzene ring is not sufficiently activated (Eq. 1). However with a single methoxy substitution on the 3′ postion, the cyclialkylation proceeds smoothly on 6′ (Eq. 2). When the methoxy substitution is on the 2′ position, a spiro-fused dienone was obtained (Eq. 3). In the case where the arene ring contains several strongly activating groups, all cyclialkylations are quite facile (Eq. 4).



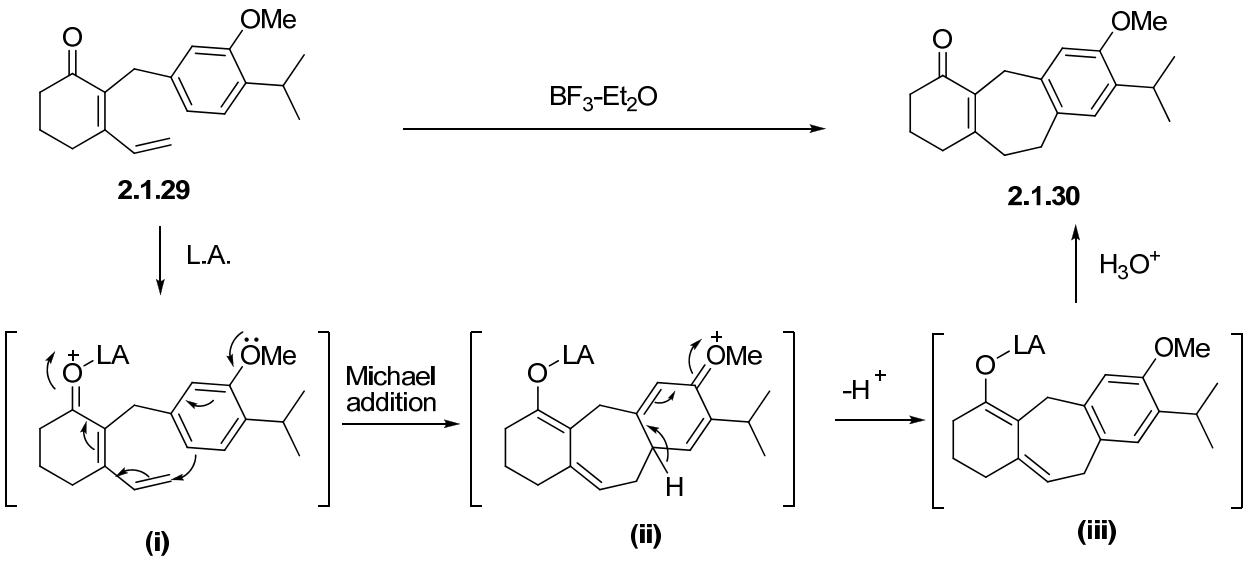
Scheme 1.1.10



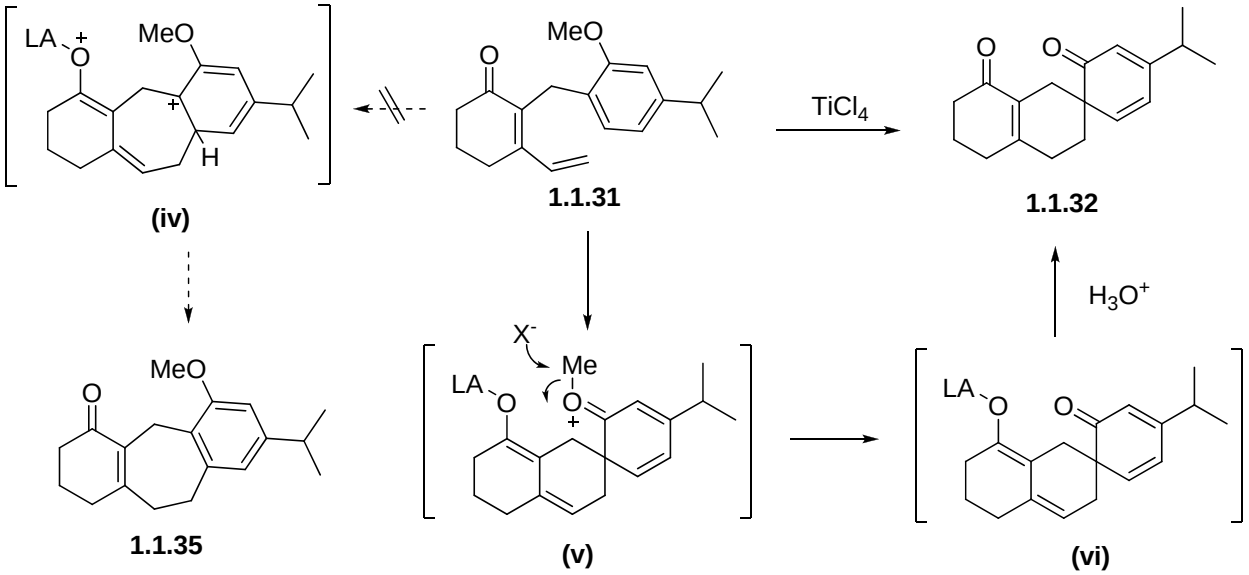
a: R_1=R_2=OMe, R_3=R_4=H, (82%)
b: R_2=R_3=OMe, R_1=R_4=H, (77%)
c: R_2=R_4=OMe, R_1=R_3=H, (97%)
d: R_1=R_4=OMe, R_2=R_3=H, (92%)

Scheme 1.1.11

Mechanistic studies reveal that in Eq. 2 of Scheme 1.1.12, 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 reestablish aromaticity (Scheme 1.1.12). However, when the electrodonating group is located at the 2′ position (Eq. 2 of Scheme 1.1.11); the cyclization to the geometrically inaccessible 5′ position is prohibited. On the contrary, *ipso*-attack leads to cyclohexane formation via carbocation (**v**) and its resonance contributors, whereas cycloheptane formation leads to a less stable carbocation (i.e., **iv**) and its various canonical forms. Lewis-acid-catalyzed demethylation of intermediate (**v**) generates ketone (**vi**), which provides the enone product on workup (Scheme 1.1.13).

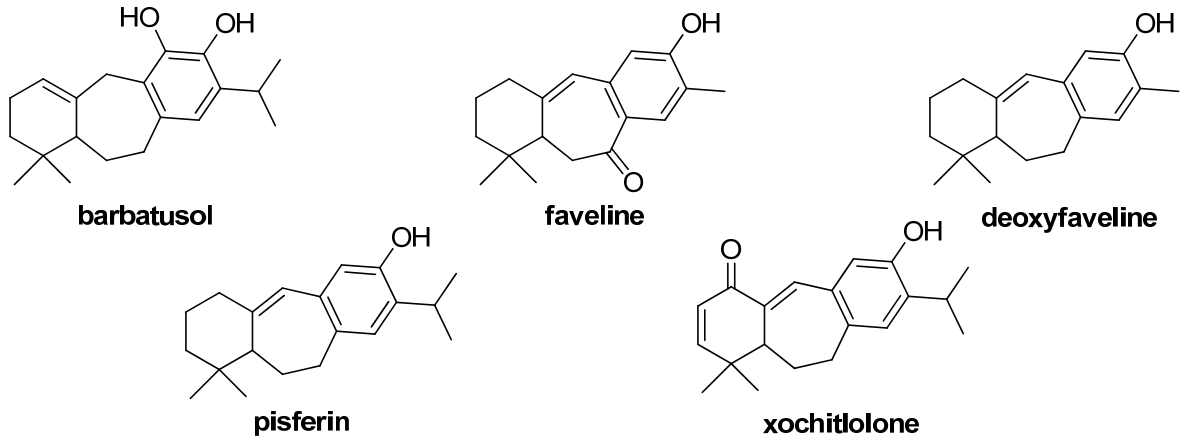


Scheme 1.1.12



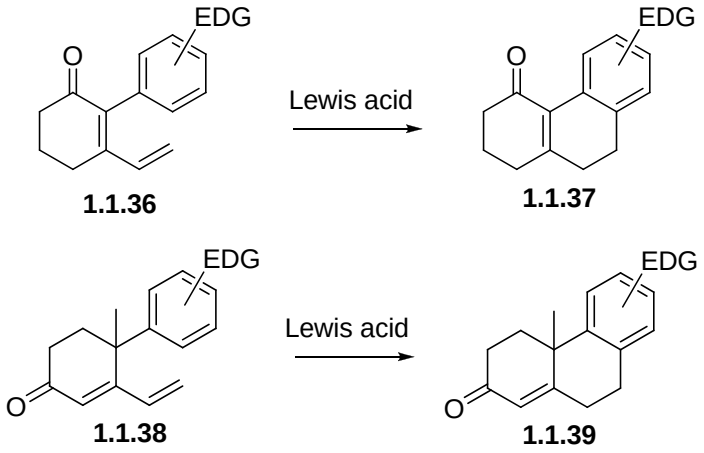
Scheme 1.1.13

This method permitted the total syntheses of (±)-barbatusol, (±)-pisiferin, (±)-deoxofaveline, (±)-xochitlolone, and (±)-faveline (Scheme 1.1.14).[10]

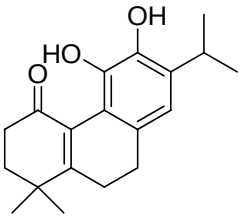


Scheme 1.1.14

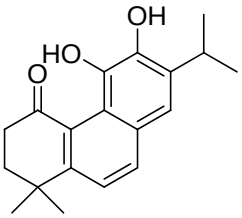
The Majetich group also formed 6,6,6-tricyclic carbon skeletons with this cyclialkylation strategy (Scheme 1.1.15) and reported the total syntheses of sageone, arucadiol, milreione, 1,2-didehydromilreione and nimbidiol in 1997 (Scheme 1.1.16).[11]



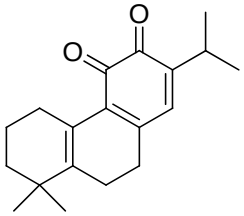
Scheme 1.1.15



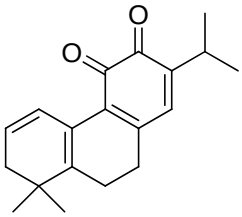
sageone



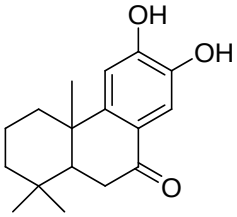
arucadiol



milreione



1,2-didehydromiltrione

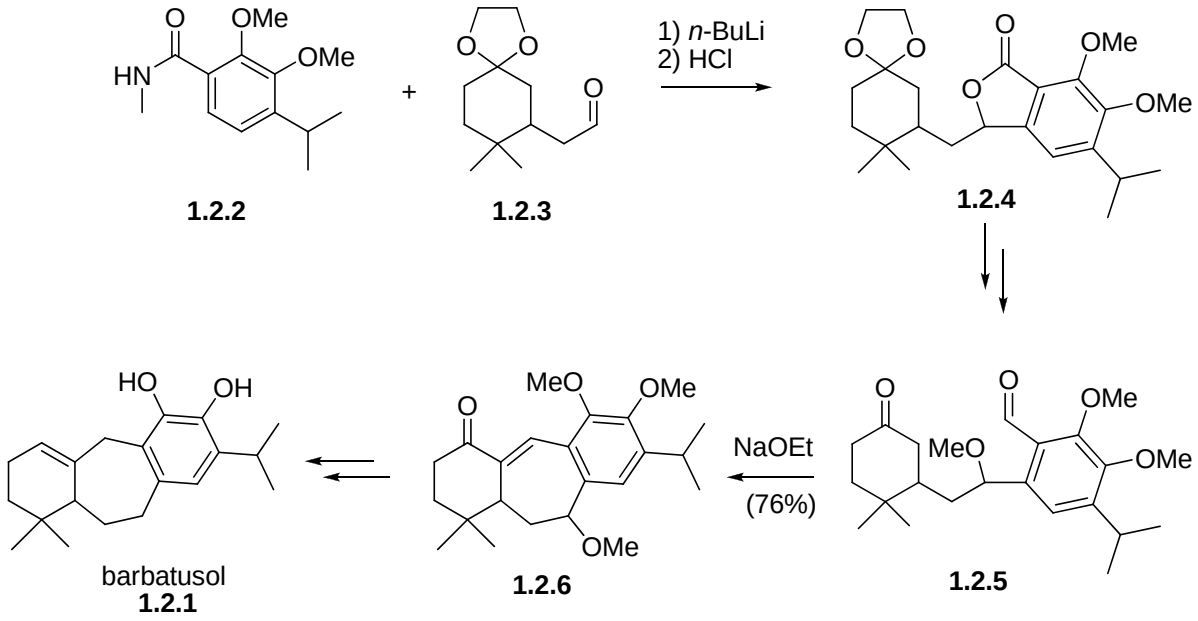


nimbidiol

Scheme 1.1.16

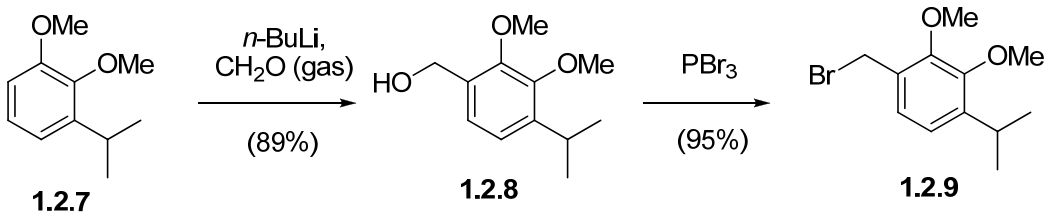
1.2 Synthesis of (±)-Barbatusol

Barbatusol (**1.2.1**) was isolated from the bark and heartwood of the Brazilian plant *Coleus barbatus* in 1983 and found to possess *in vivo* hypotensive activity in rats.[12] The first total synthesis of (±)-barbatusol was achieved by Emil Koft in 1987,[13] starting from commercially available 3-isopropylcatechol and requiring fifteen steps in 4.5% overall yield. One of the key steps in the synthesis was to annulate the central seven-membered ring with an Aldol reaction (Scheme 1.2.1).



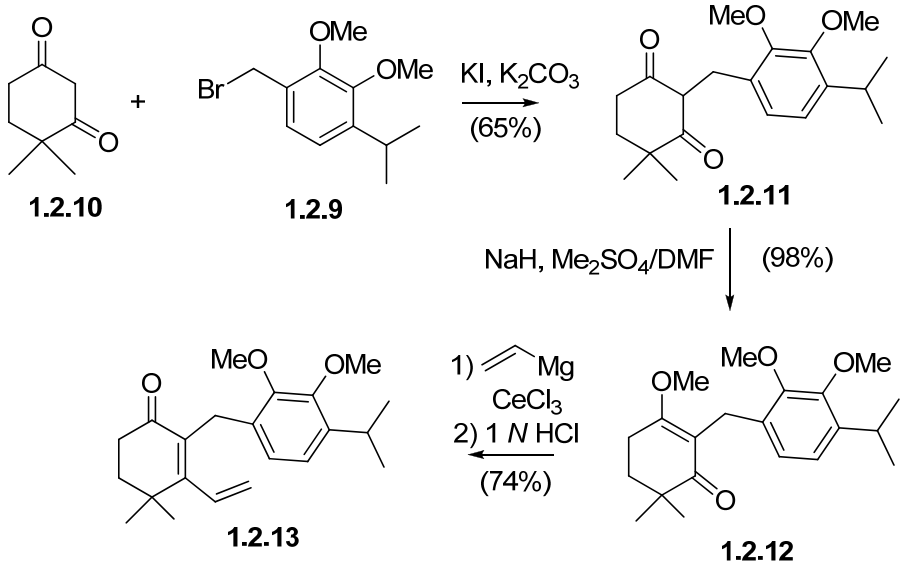
Scheme 1.2.1

In 1993, the Majetich group reported a nine-step synthesis of (±)-barbatusol, using their cyclialkylation strategy to construct the seven-membered B-ring.[14,11] This synthesis began with 2,3-dimethoxy-4-isopropyl benzyl bromide **1.2.9**, which is readily available from 3-isopropylveratole **1.2.7** through a two-step synthetic pathway (Scheme 1.2.2).



Scheme 1.2.2

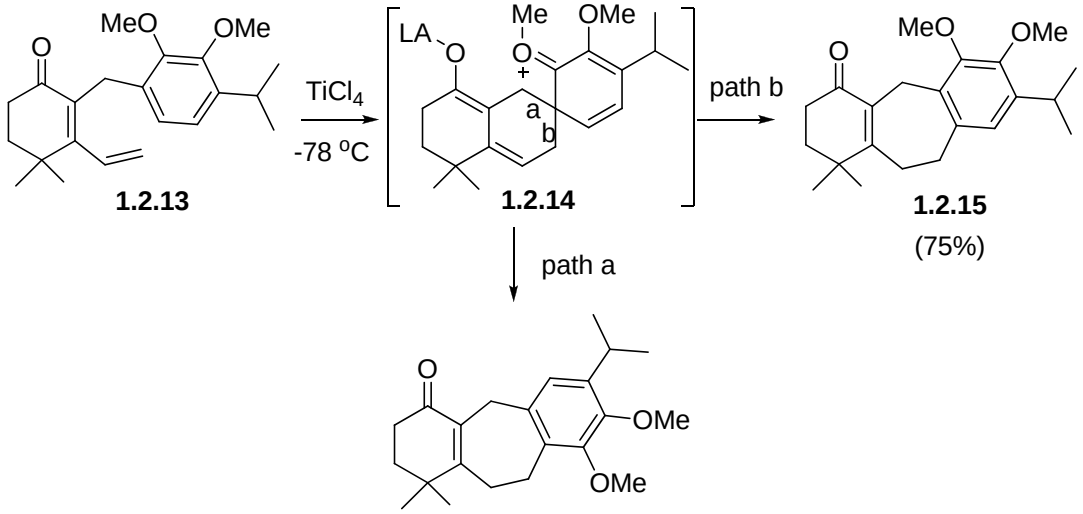
Benzyl bromide **1.2.9** was used to achieve *mono*-C-alkylation of 6,6-dimethyl-1,3-cyclohexadione **1.2.10** in 20% potassium carbonate solution. The resulting dione **1.2.11**, when treating with base and iodomethane, was selectively O-methylated at the less hindered carbonyl group to give enol ether **1.2.12**. 1,2-Addition of vinylmagnesium bromide to **1.1.12** under the help of $CeCl_3$ to activate the hindered carbonyl group, followed by mild acid hydrolysis, completed the cyclization precursor dienone **1.2.13** (Scheme 1.2.3).



Scheme 1.2.3

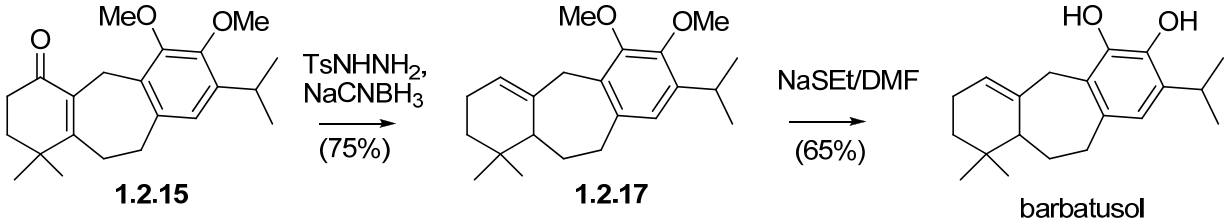
When dienone **1.2.13** was submitted to cyclization conditions, two different products **1.2.15** and **1.2.16** were produced. It was proposed that the cyclization initially took place at the *ipso*-position to give intermediate **1.2.14**. Two rearrangement pathways from **1.2.14** led to the

two isolated products. The desired product, conjugated ketone **1.2.15,** was produced in 75% yield (Scheme 1.2.4).



Scheme 1.2.4

Enone **1.2.15** underwent a modified Wolff–Kishner reduction, followed by basic demethylation, to furnish (±)-barbatusol (**1.2.1**) in 21% overall yield (Scheme 1.2.5).

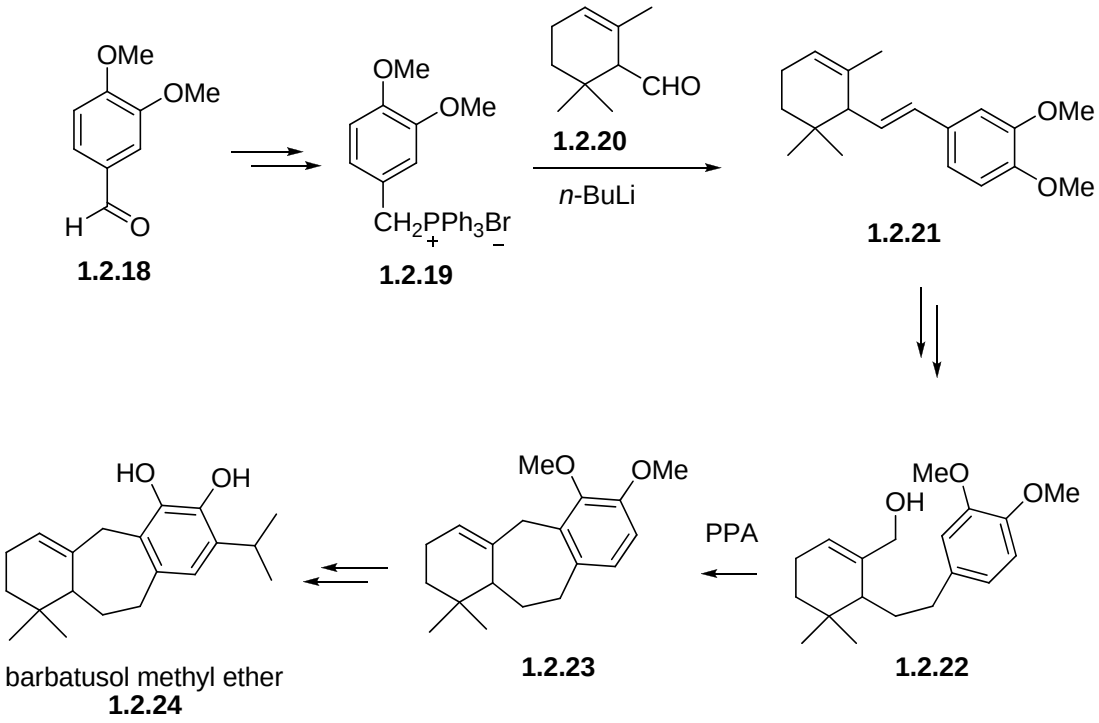


Scheme 1.2.5

Majetich's (±)-barbatusol synthesis was a more efficient way to construct the 6,7,6-tricyclo-skeleton of the rearranged abeitane diterpenes than Koft's approach. This cyclialkylation strategy has also constructed the core structure of many of the natural products synthesized in this dissertation.

Three years after Majetich's synthesis of barbatusol, Pan and co-workers reported their synthesis of (±)-barbatusol methyl ether (**1.2.24**) (Scheme 1.2.6).[15] Key reactions included the

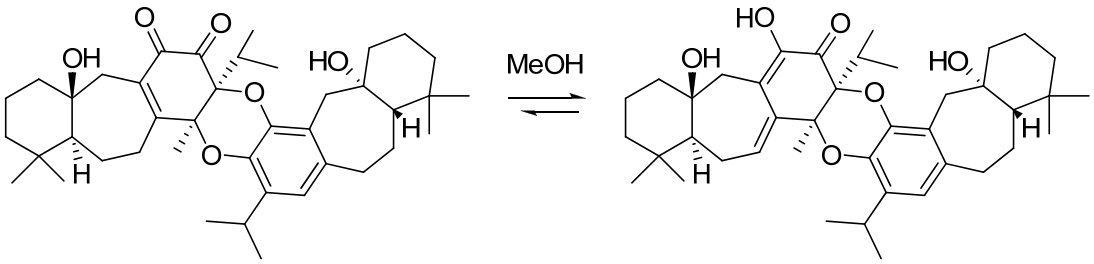
Wittig olefination between phosphonium salt **2.1.18** and racemic α-cyclocitral **1.2.20** resulting diene **1.2.20** and acid-assisted cyclization of intermediate **1.2.22**.



Scheme 1.2.6

1.3 Biomimetic Synthesis of (+)-Grandione from (+)-Demethylsalvicanol

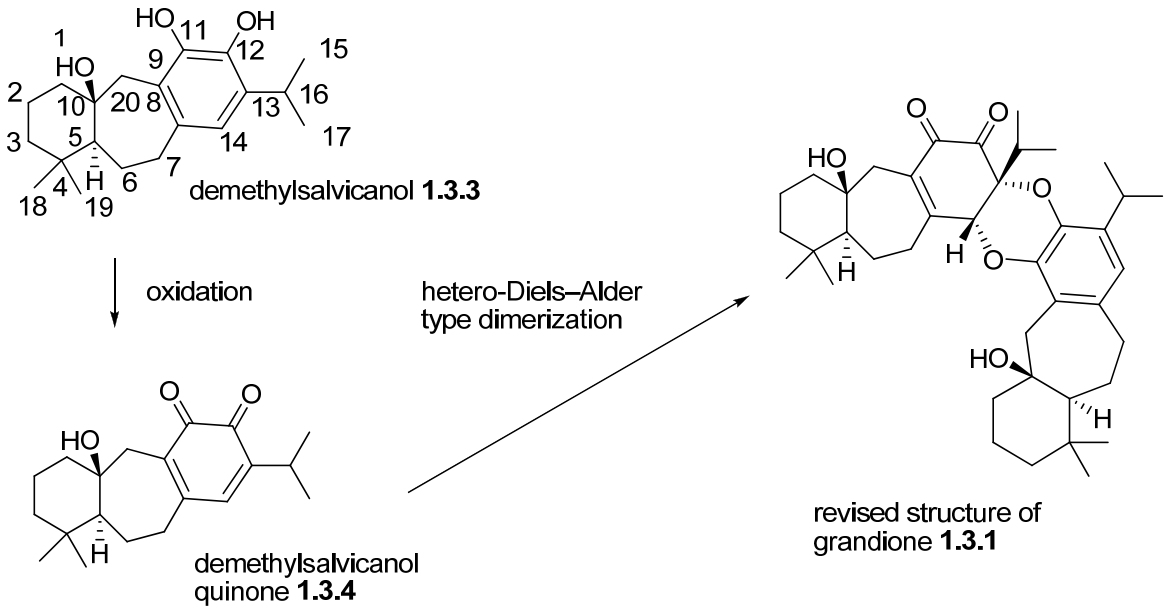
Dimeric diterpenes are rare in nature with many of them arising through a Diels–Alder cycloaddition of two monomeric moieties. Grandione **1.3.1** is particularly interesting because the two monomers are linked through two ether linkages, which is an unprecedented feature among the dimeric diterpenes. Originally isolated from the yellow wood of *Torreya grabdis* (Taxaceae) by Riccio and co-workers in 1999,[16] Grandione is a unique heptacyclic diterpene dimer, whose structure is based on two rearranged abietane-type monomeric units. It was also reported in the same paper that in a protic solvent grandione gives rise to a tautomeric equilibrium with **1.3.2**, the enol form of grandione (Scheme 1.3.1).



grandione 1.3.1 **1.3.2**

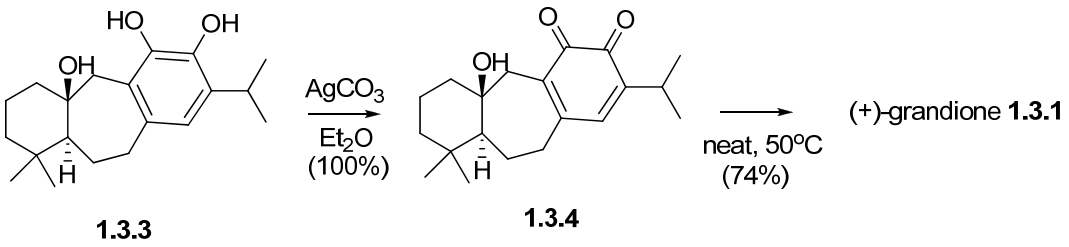
Scheme 1.3.1

In 2005, Takeshi group published a biomimetic synthesis of (+)-grandione from naturally occurred (+)-demethylsalvicanol **1.3.3** through an oxidation, hetero-Diels–Alder dimerization sequence and suggested a structural revision of grandione based on the X-ray crystallographic analysis on its epoxide derivative (Scheme 1.3.2).[17]



Scheme 1.3.2.

Demethylsalvicanol, a natural product isolated by Gonzalez and co-workers in 1991,[18] was used as starting material and obtained from the aerial parts of *Perovskia abrotanoides* (Labiatae) in 0.37% yield.[19] In 1996 Pan and co-workers reported the first total synthesis of racemic demethylsalvicanol.[20] Oxidation of demethylsalvicanol was carried out under several conditions, and silver carbonate in diethyl ether at room temperature was found to be the best, producing demethylsalvicanol quinone in quantitative yield. Quinone **1.3.4** was then subjected to hetero-Diels–Alder reaction. It was found that the reaction did not proceed with heating when any solvent present. However, performing the reaction in the solid state improved the conversion ratio and it was found that heating the reaction at 50 ^{o}C to 70 ^{o}C gave the cycloadduct in good yields (Scheme 1.3.3).



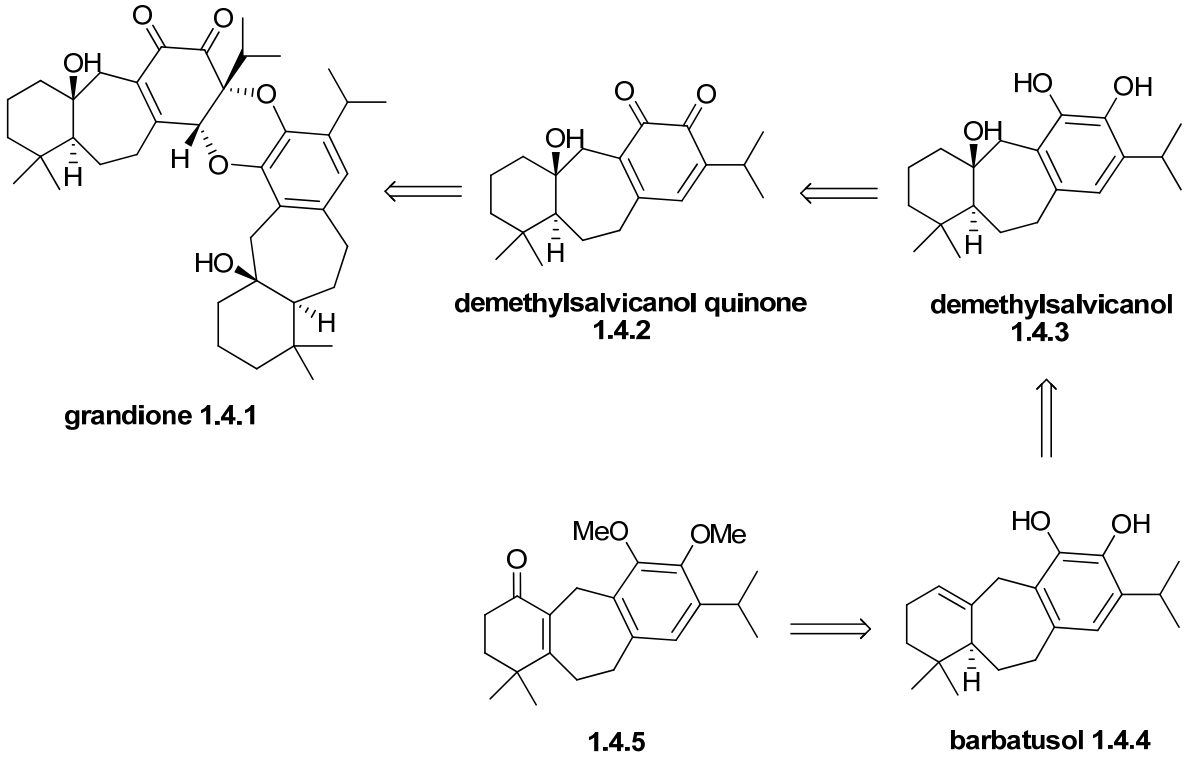
1.3.3 **1.3.4**

Scheme 1.3.3

Takeshi's research demonstrated that the nonenzymatic biomimetic hetero-Diels–Alder reaction of *o*-quinone **1.3.4** proceeded to produce a natural heptacyclic diterpene dimer, grandione **1.3.1**, efficiently and that the reaction gave primarily one of the four possible cycloadducts. Cytotoxity study of grandione and its analogues on P388 murine leukemia cells revealed that the C(11), C(12)-carbonyl or phenol groups, especially C(12)-oxygen functional group, may be essential for the cytotoxity.

1.4 Total Synthesis of (+)-Demethylsalvicanol and (+)-Grandione

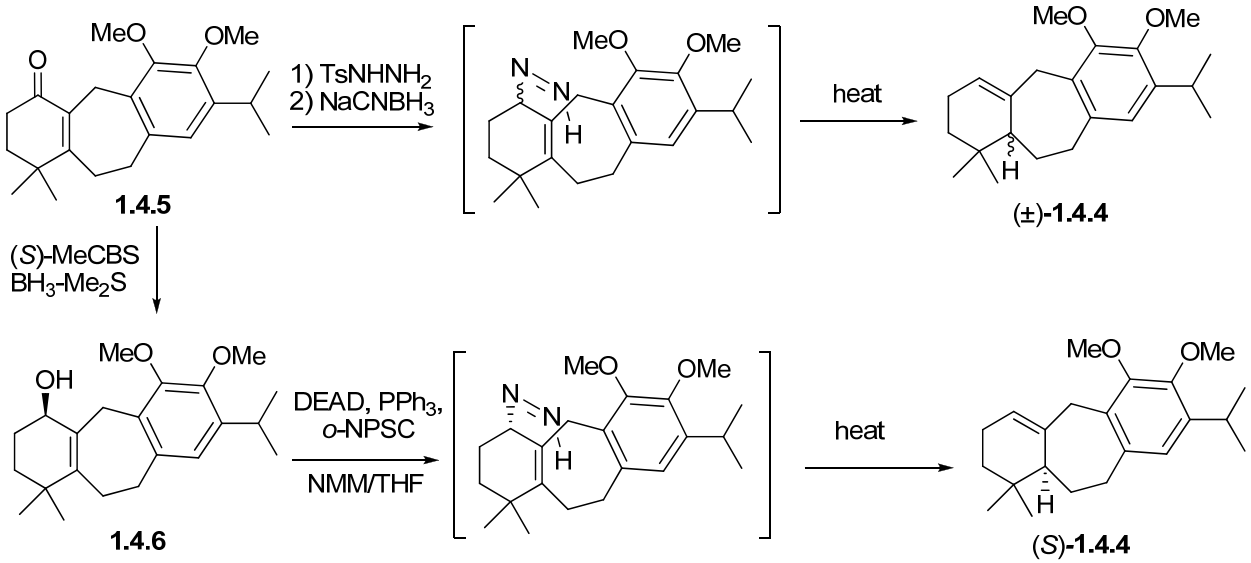
In the Takeshi group's biomimetic synthesis of (+)-grandione **1.4.1**,[17] the starting material, (+)-demethylsalvicanol **1.4.3** was obtained from the natural source. We recognized that (+)-demethylsalvicanol possesses many of the salient features of (–)-barbatusol **1.4.4**, and were confident that it could be synthesized from enone **1.4.5**, a key intermediate in our synthesis of (±)-barbatusol.[14] Thus, the initial goal of our project was to convert enone **1.4.5** into (+)-demethylsavicanol and to do further studies upon the reactivity of demethylsalvicanol quinone, including the hetero-Diels–Alder reaction to synthesize (+)-grandione (Scheme 1.4.1).[21]



Scheme 1.4.1

Enone **1.4.5,** was prepared by the same synthetic pathway as reported in our (±)-barbatusol synthesis (Scheme 1.2.2, 1.2.3, 1.2.4, 1.2.5).[14] We applied a two-step process, which was original developed in the course of our synthesis of (+)-perovskone,[22] to convert achiral

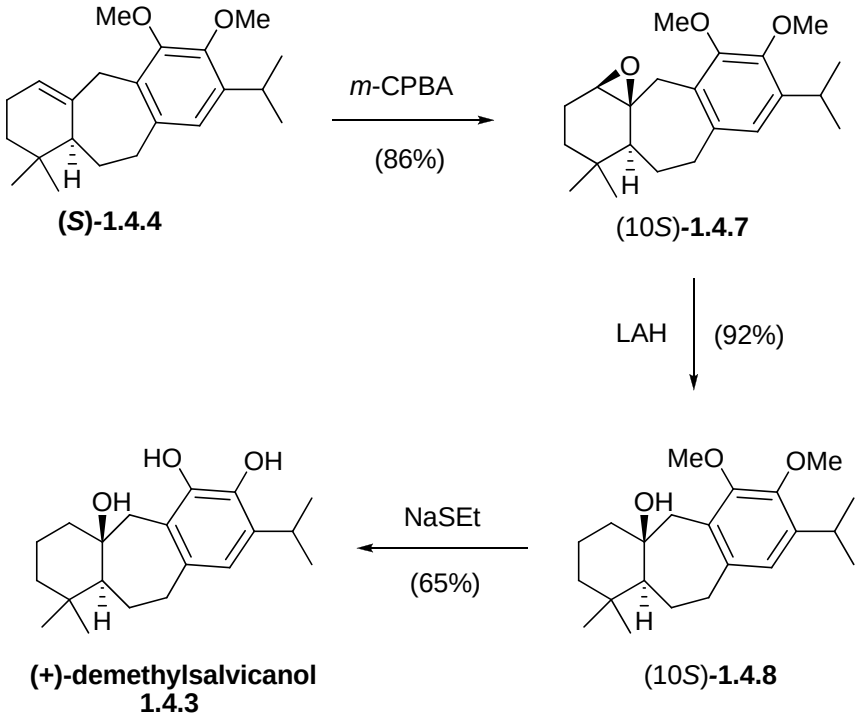
enone **1.4.5** into alkene (*S*)-**1.4.4**. In particular, instead of using a modified Wolff–Kishner reduction to produce racemic alkene **1.4.4**., enone **1.4.5** was reduced asymmetrically with Corey's CBS procedure[23] to produce allylic alcohol **1.4.6** in high chemical yield and excellent enantiomeric excess (>96% *ee*). The chirality at C(1) was then transferred to C(10) using Myers' Mitsunobu-based allylic transposition[24] (Scheme 1.4.2). The yield of the allylic transposition is moderate (50–70% based on the recovery of starting material). This is presumably due to the steric hindrance of the secondary alcohol and the poor solubility of the Mitsunobu intermediate.



Scheme 1.4.2

During the structure determination studies of demethylsalvicanol **1.4.3,** Kelecom and Medeiros[12,25] found that epoxidation of the C(1),C(10)-trisubstituted double bond occurs from the β-face of **1.4.4**, and that the opening of this epoxide with LAH introduces a β-oriented tertiary alcohol at C(10). We applied this strategy to convert barbatusol dimethyl ether (*S*)-**1.4.4** into alcohol **1.4.8** (Scheme **1.4.3**). Epoxidation of (*S*)-**1.4.4** with *m*-CPBA in cold methylene chloride gave epoxide **1.4.7** in 86% yield. Subsequent LAH opening of **1.4.7** in refluxing THF afforded alcohol (10*S*)-**1.4.8** in 92% yield. The relative stereochemistry of (10*S*)-**1.4.8** was

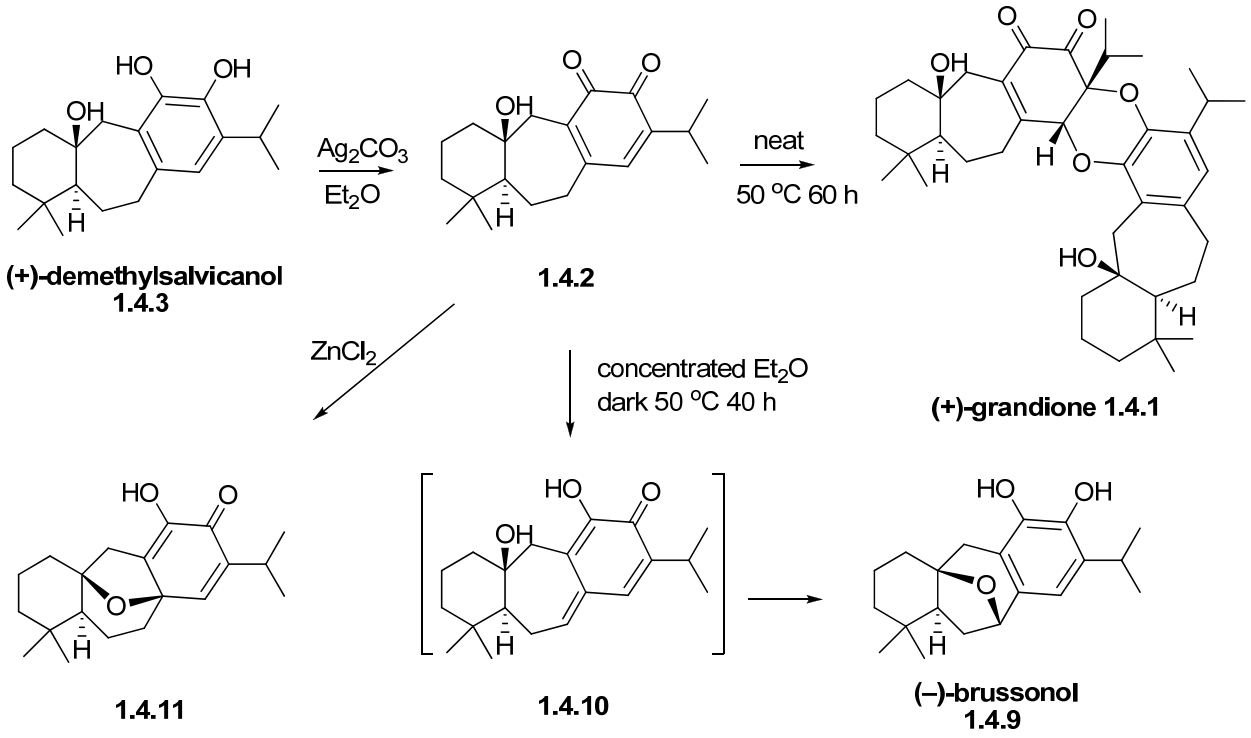
confirmed by X-ray crystal analysis. Treatment of (10*S*)-**1.4.8** with excess sodium ethanethiolate in hot DMF cleaved both of the C(11) and C(12) methyl ethers to furnish (+)-demethylsalvicanol (**1.4.3**) in 65% yield. The spectral data for synthetic **1.4.3** [^{1}H and ^{13}C NMR] were identical to those reported for the natural material.



Scheme 1.4.3

With synthetic demethylsalvicanol in hand, we repeated Takeya's oxidation condition to form *o*-quinone **1.4.2** by treating **1.4.3** with silver carbonate in diethyl ether. When neat **1.4.9** was heated at 50 ^{o}C for 60 hours, (+)-grandione **1.4.1** was generated through a hetero-Diels–Alder reaction in 72% yield together with small amount of (–)-brussonol **1.4.9**.[26,27] We speculated that the formation of **1.4.9** was cause by intramolecular Michael addition of the C(10) alcohol to quinone methide intermediate **1.4.10**. However, when zinc chloride, a mild Lewis acid, was used to facilitate the generation of **1.4.10**, dihydrofuran **1.4.11** was isolated as the only

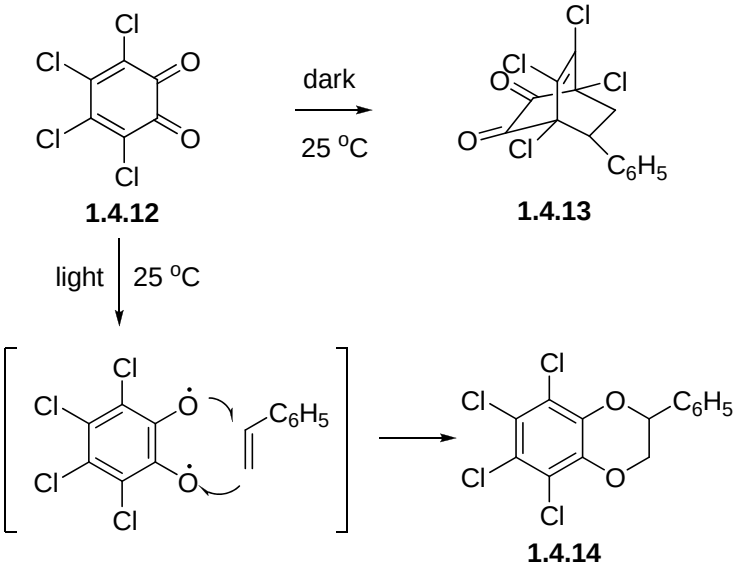
product resulting from the intramolecular Michael addition of the C(10) hydroxy group to the C(8) carbon. Treatment of quinone **1.4.2** with bases, such as DBU, triethylamine or sodium carbonate, only resulted in decomposition of the starting material. However, when a very concentrated ethereal solution of **1.4.2** was heated at 60 °C in the dark for 40 hours, (–)-brussonol was produced in 70% yield, together with about 10% (+)-grandione (Scheme 1.4.4).



Scheme 1.4.4

One of the goals of this study was to synthesize grandione without relying on Takeya's solid-state Diels–Alder reaction. Toward this end, two alternative strategies were investigated. Presumably, dioxane formation involves a triplet excited state of the quinone, which adds either in a concerted or in a stepwise fashion. The first strategy was based on the observation by Horner and Merz that styrene and tetrachloro-*o*-benzoquinone (**1.4.12**) undergo a Diels–Alder reaction in the dark at room temperature to give adduct **1.4.13**,[28] whereas in sunlight 1,4-dioxane **1.4.14**

is formed (Scheme 1.4.5).[29,28c,28d] Presumably, dioxane formation involves a triplet excited state of the quinone, which adds either in a concerted or in a stepwise fashion to the double bond of the alkene present. We were curious to see whether *o*-quinone **1.4.2**, which is sterically hindered and electron-rich, would undergo cyclodimerization to form (+)-grandione **1.4.1** upon photochemical excitation. Unfortunately, exposing **1.4.2** to sunlight in either THF or cyclohexane at room temperature gave no reaction.



Scheme 1.4.5

A common way to overcome the large negative activation entropy associated with the Diels–Alder reaction is to use water as solvent.[30] When nonpolar substrates are suspended in water, their relative insolubility causes them to associate together, which often results in increase of the reaction rate. We hoped that water's ability to bring the cycloaddition components together would facilitate the dimerization of quinone **1.4.2**. Adding a small amount of water to **1.4.2** and allowing the resulting mixture to stir at room temperature gave no reaction; however, warming the reaction medium to 50 °C overnight gave a 61% yield of (–)-brussonol (**1.4.9**) and

(+)-grandione (**1.4.1**) and in a 1:6 ratio. Further work established that the ratio of **1.4.9: 1.4.1** varied as a function of the reaction concentration. The above results suggest that π-stacking interactions in the crystalline state cause the *o*-quinone molecules to assume a fixed spatial orientation that controls the regiospecificity of the Diels–Alder reaction.[31] Although a preorganization of the Diels–Alder components does not exist in solution, the cycloaddition in water must benefit from the *o*-quinone molecules being forced closely together so as to mimic the situation in the solid state.

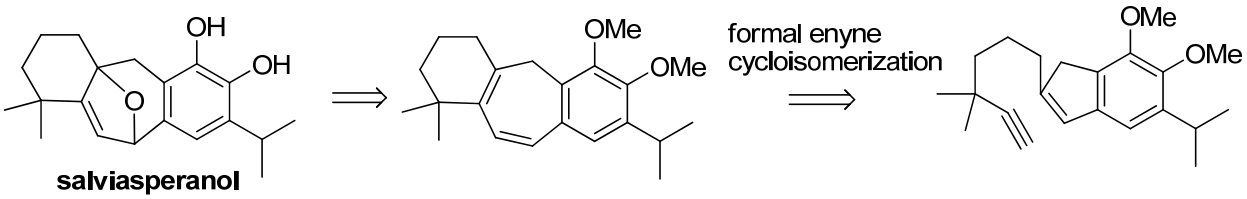
Brussonol can only be formed if **1.4.2** tautomerizes. Since intermolecular proton-transfer reactions are precluded in the solid state, the dimerization to form grandione is favored. Conducting the cycloaddition reaction in solution facilitates proton transfer and hence tautomerization. In enol-keto tautomerizations, keto formation usual benefits from solvents having high dielectric constants (water = 78.39 at 25 °C), whereas the enol form is favored by solvents with low dielectric constants, like diethyl ether (4.335 at 20 °C). Diethyl ether was the solvent used to prepare brussonol in good yield. In this case, the formation of quinone methide may benefit from an internal hydrogen bond.

In summary, (–)-barbatusol was converted into (+)-demethylsalvicanol, which enabled us to confirm its novel dimerization to produce (+)-grandione using thermal conditions. Although we were disappointed that we were not able to produce grandione photochemically, carrying out the cycloaddition in water gave grandione as the major product in good yield. In contrast, heating an ethereal solution of *o*-quinone **1.4.2** favored the production of (–)-brussonol.

1.5 Synthesis of (±)-Salviasperanol

Salviasperanol **1.5.1** was isolated from the roots of *Salvia aspera* by Esquivel and co-workers in 1995.[32] Although the biological activity of salviasperanol has not been studied in detail, a number of related compounds derived from this genus show significant activity against *Mycobacterium tuberculosis*, the causative agent of tuberculosis. Also, other icetexane diterpenoids brussonol **1.5.2** and demethylsalvicanol **1.5.3** show cytotoxic activity against P388 murine leukemia cells, with IC_{50} values of 1.9 and 0.71 μg/mL, respectively.[33]

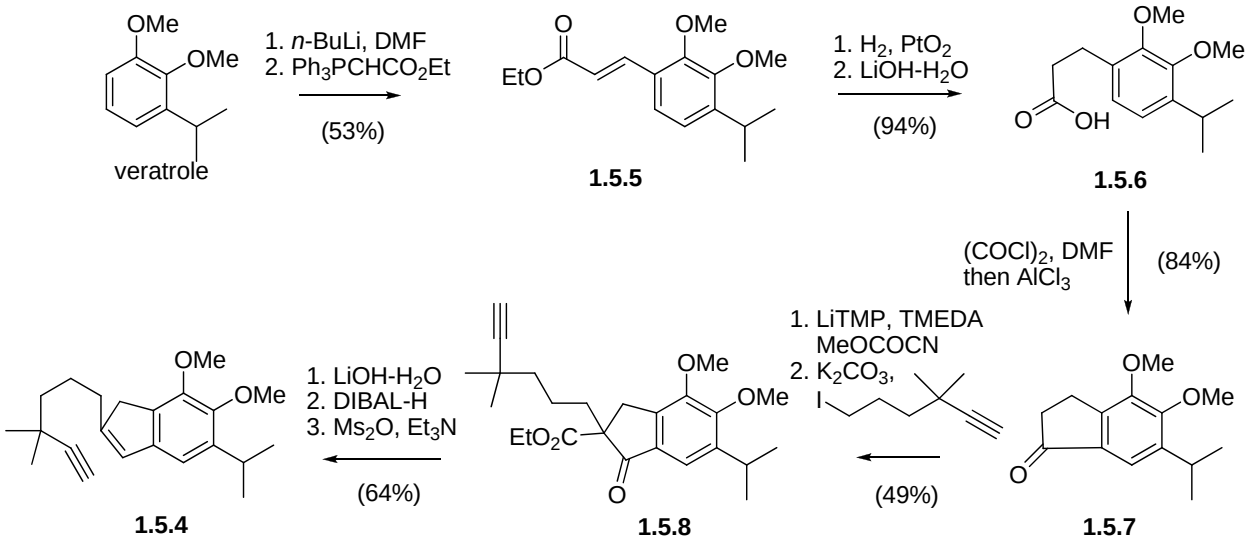
The intriguing structure of salviasperanol and its potential bioactivity prompted Richmond Sarpong at UC-Berkeley to investigate the total synthesis of this polycyclic diterpenoid.[34,35] In their work, the first total synthesis of salviasperanol, Sarpong and Simmons presented a general way to construct the tricyclic core of the icetexane natural products via the cycloisomerization of alkynyl indenes using $GaCl_3$ as a catalyst[36] (Scheme 1.5.1).



Scheme 1.5.1

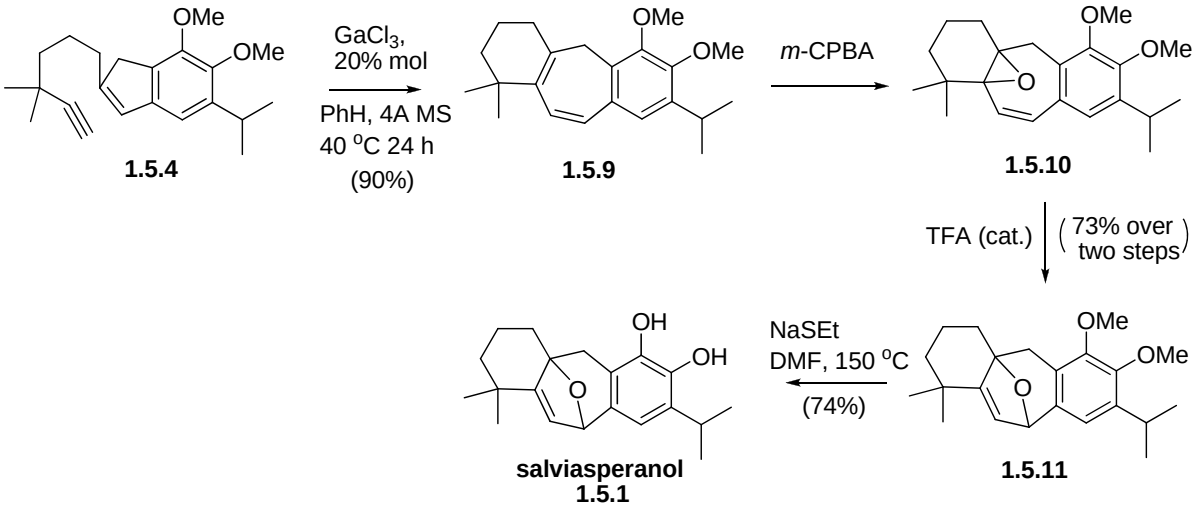
The first stage of their synthesis is to construct the indene precursor **1.5.4**. Starting from 3-isopropyl veratrole, a formylation with DMF followed by a Wittig reaction of the resulting aldehyde with the stabilized carbethoxymethylidene triphenylphosphorane ylide provided enoate **1.5.5**. After hydrogenation of the conjugated double bond and saponification of the ester moiety, a Fridel–Craft acylation of the corresponding acid chloride was used to provide indanone **1.5.6** in good yield.

To obviate the over-alkylation problem when direct alkylating **1.5.6** with iodide **1.5.7**, an initial Claisen reaction with Mander's reagent to install a carbomethoxy group followed by alkylation, affords β-ketoester **1.5.8**. After using a saponification followed by decarboxylation workup to cleave the ester moiety, a net dehydration yielded alkynyl indene **1.5.4** as a single alkene regioisomer (Scheme 1.5.2).



Scheme 1.5.2

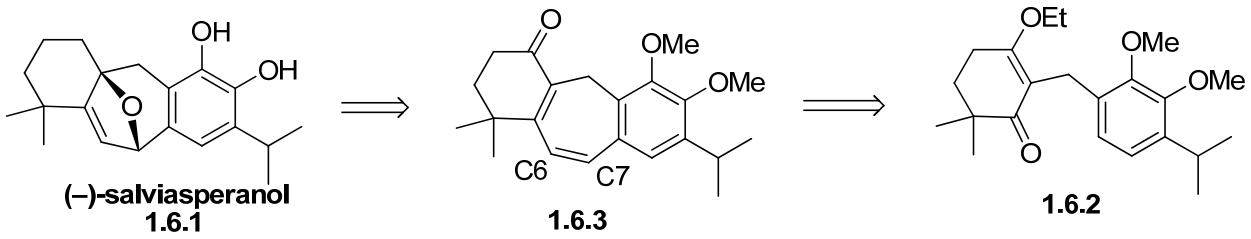
After a screen of various additives, an optimal set of conditions was identified that converted **1.5.4** to cycloheptadiene **1.5.9** in excellent yield. Selective epoxidation of C(10),C(5)-tetrasubstituted olefin followed by acid-catalyzed isomerization resulted in dihydrofuran **1.5.11** in good yield. Conversion of dimethylsalviasperanol **1.5.11** to salviasperanol **1.5.1** was achieved by *bis*-methyl ether cleavage using sodium ethanethiolate (Scheme 1.5.3). In summary, Sarpong's achiral total synthesis of the icetexane diterpenoid salviasperanol features a cycloisomerization of an alkynyl indene to access a key cycloheptadiene intermediate.


OMe
OMe
1.5.4
GaCl3,
20% mol
PhH, 4A MS
40 °C 24 h
(90%)
OMe
OMe
1.5.9
m-CPBA
OMe
OMe
O
1.5.10
TFA (cat.)
73% over
two steps
OH
OH
O
salviasperanol
1.5.1
NaSEt
DMF, 150 °C
(74%)
OMe
OMe
O
1.5.11

Scheme 1.5.3

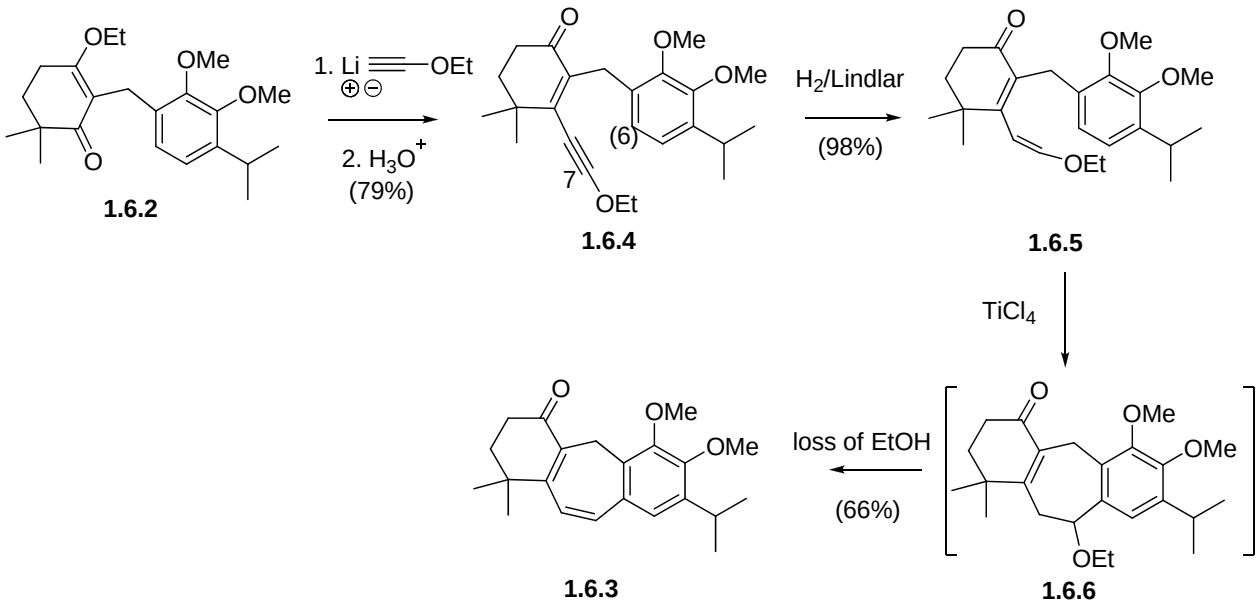
1.6 Total Synthesis of (–)-Salviasperanol

At the time Sarpong and Simmons published their asymmetric synthesis of salviasperanol, we had already completed the total synthesis of (+)-demethylsalvicanol and (+)-grandione. To accomplish our asymmetric synthesis of (–)-salviasperanol,[37] synthetic routes starting from the advanced intermediate acyclic ketone **1.6.2** were investigated to achieve the construction of the tricyclic core of salviasperanol with a C(6),C(7)-double bond (Scheme 1.6.1).



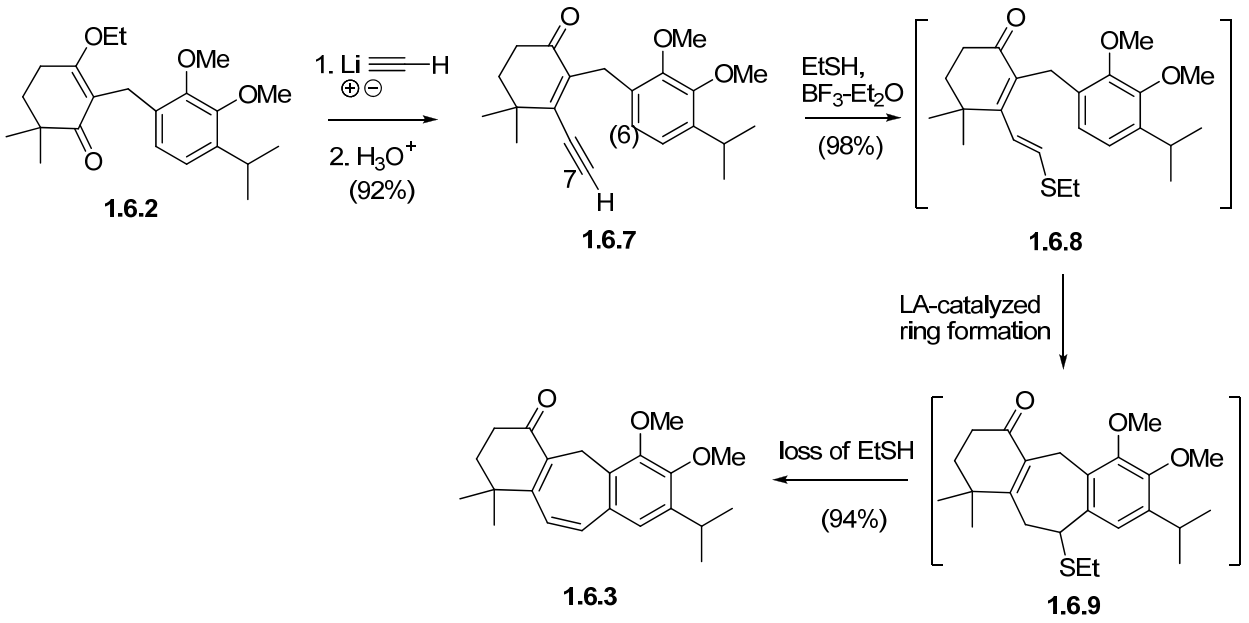
Scheme 1.6.1

In our synthesis of komaroviquinone[38] we found that treatment of enone **1.6.2** with Aren's reagent, the anion of ethoxyacetylene,[39] produced enynone **1.6.5**. While direct cyclization of enynone **1.6.5** to dienone **1.6.3** might be envisioned, analysis of Dreiding models of **1.6.4** indicated that the linear nature of the alkyne prevented the "6" carbon of the aryl ring and C(7) of the alkyne from ever becoming spatially close enough to react. Not surprisingly, the cyclialkylation of **1.6.4** was unsuccessful. In contrast, Lindlar hydrogenation[40] of the triple bond in **1.6.4** cleanly gave cyclialkylation precursor **1.6.5**, which upon treatment with excess $TiCl_4$ first formed intermediate **1.6.6**, which the presence of $TiCl_4$ caused the lost of ethanol to give dienone **1.6.3** in 66% isolated yield (Scheme 1.6.2).



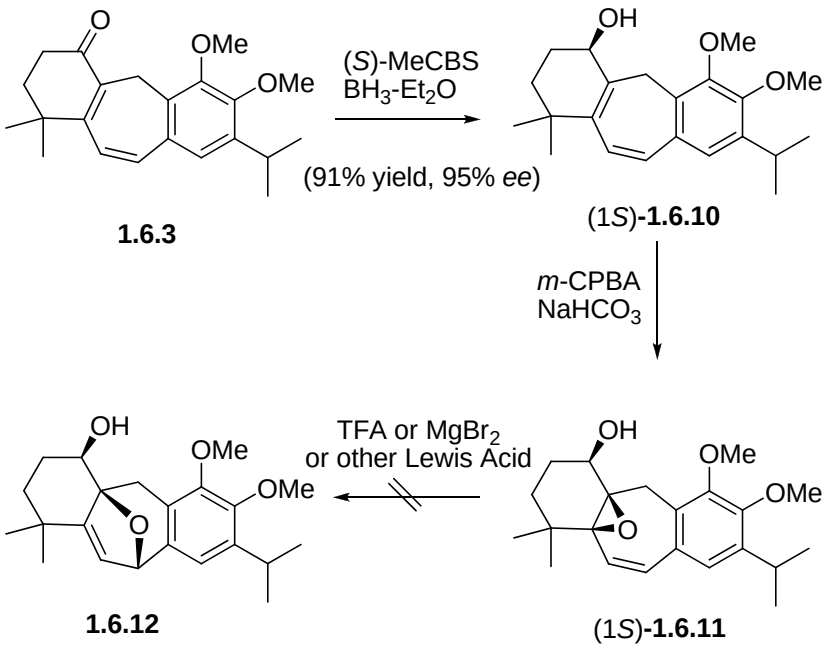
Scheme 1.6.2

Alternatively, 1,2-addition of lithium acetylide to ketone **1.6.2**, followed by mild acid hydrolysis, produced enynone **1.6.7** in 92% yield. Stirring **1.6.7** with excess BF_3-etherate and a 10% stoichiometric quantity of ethanethiol in CH_2Cl_2 at room temperature for 12 hours gave dienone **1.6.3** in 94% yield. Under these conditions, vinyl sulfide **1.6.8** was formed rapidly (<1 h). If an aliquot of the reaction mixture was worked up intermediate **1.6.8** could be isolated and characterized; however, longer reaction times permitted the cyclialkyation of **1.6.8** to give the seven-membered ring, and subsequent elimination of ethanethiol from intermediate **1.6.9**. This two-step sequence represents a more efficient way to functionalize the central carbocyclic ring in comparison with the Aren's reagent/reduction/and cyclialkylation route (Scheme 1.6.3).



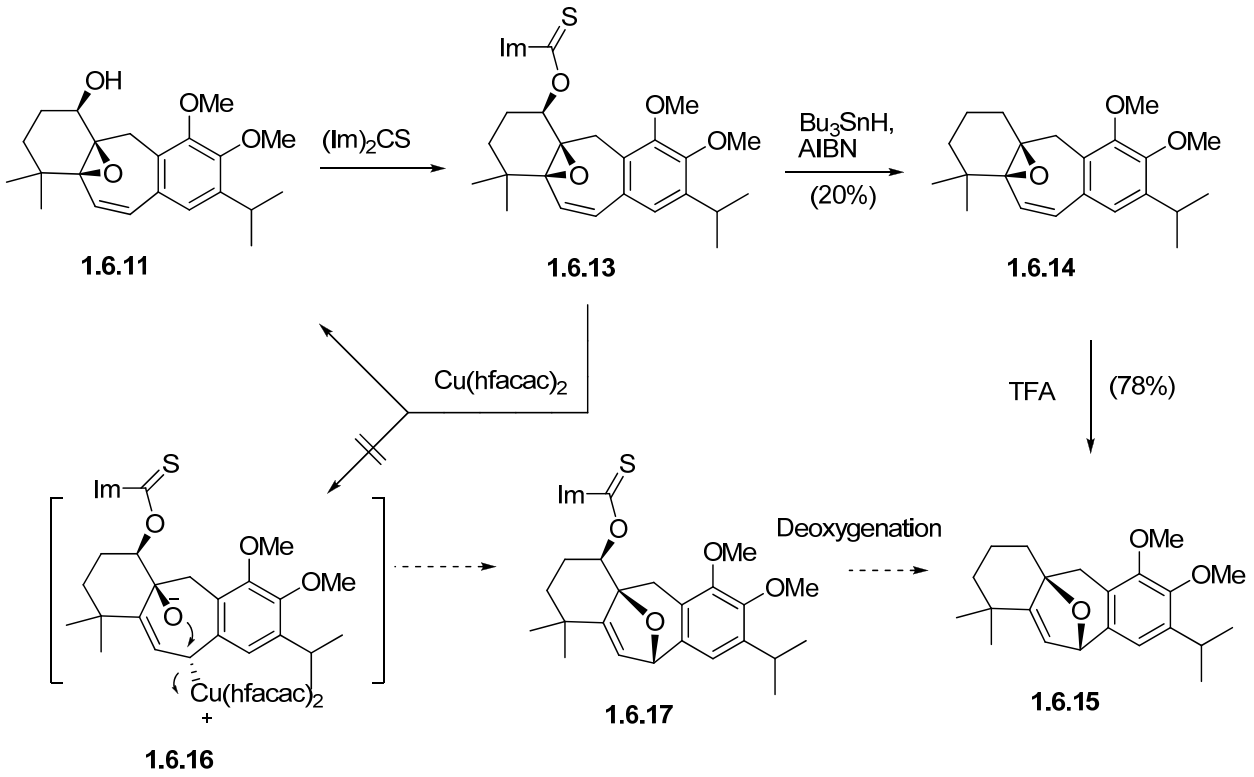
Scheme 1.6.3

Asymmetric reduction of the C(1) carbonyl would create enantiomerically enriched allylic alcohol **1.6.10**, which would permit the introduction of the C(10) and C(7) asymmetric centers (Scheme 1.6.4). 1,2-Reduction of **1.6.3** using Corey's CBS protocol[23] gave alcohol (1*R*)-**1.6.10** in 91% yield and excellent enantioselectivity (>95% *ee*). The final steps of our (–)-salviasperanol synthesis benefitted from Simmons and Sarpong's observation[34] that epoxide **1.6.11** isomerizes to dihydrofuran **1.6.12** under acidic conditions. We expected that the C(1) hydroxy group would direct the epoxidation to only the C(5),C(10)-double bond,[41] and that the subsequent rearrangement of epoxide **1.6.11** would produce dihydrofuran **1.6.12** with the desired configuration at C(7) and C(10). Indeed, treatment of dienol **1.6.10** with *m*-CPBA in CH_2Cl_2 at 0 °C in the presence of $NaHCO_3$ for 1 hour furnished only epoxy alcohol (1*R*)-**1.6.11** in good yield. Epoxy alcohol (1*R*)-**1.6.11**, however, was acid sensitive precluding its acid-promoted isomerization. This dictated that the C(1) hydroxy group must either be protected or removed before attempting to rearrange the C(5),C(10) epoxide.



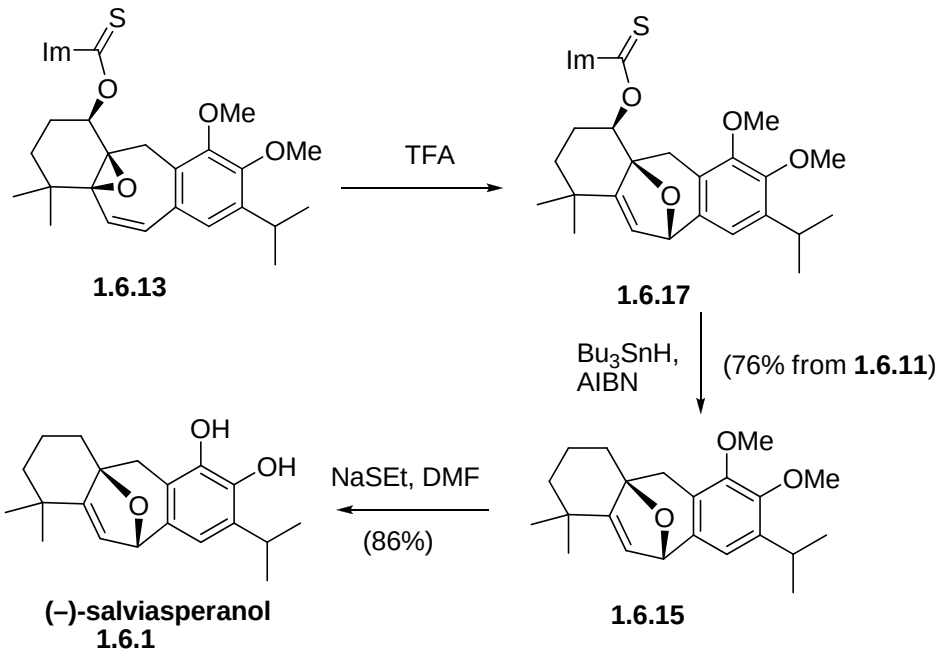
Scheme 1.6.4

Instead of using a common protecting group for the C(1) hydroxy group, crude **1.6.11** was treated with 1,1-thiocarbonyldiimidazole to give *O*-thiocarbamate **1.6.13** which could be chromatographed and characterized (Scheme 1.6.5).[42] Free radical deoxygenation of **1.6.13**, followed by isomerization of vinyl epoxide **1.6.14** using catalytic trifluoroacetic acid (TFA), produced salviasperanol dimethyl ether **1.6.15**, but in low overall yield. The isomerization of vinyl epoxides to dihydrofurans, via a π-allyl copper intermediate, such as **1.6.16**, is known even in the presence of ethers and esters.[43] However, treatment of vinyl epoxide **1.6.13** with copper *bis*-hexafluoroacetylacetonate [Cu(hfacac)2] only cleaved the *O*-thiocarbamate.



Scheme 1.6.5

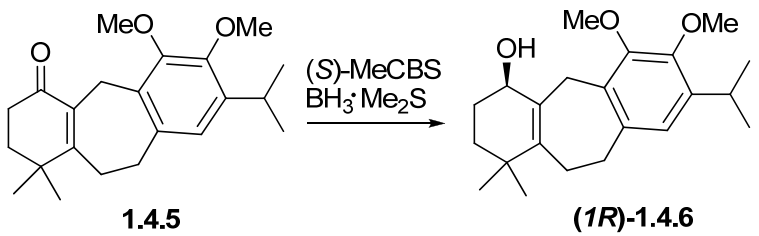
In contrast, *O*-thiocarbamate **1.6.13** could be rearranged to **1.6.17** using trifluoroacetic acid (Scheme 1.6.6). The removal of the thiocarbamate moiety was achieved by heating a toluene solution of (1*R*)-**1.6.17** with a catalytic amount of AIBN and excess tri-*n*-butyltin hydride at 110 °C for a 30-minute period. These conditions provided salviasperanol dimethyl ether **1.6.15** in 76% yield from epoxide **1.6.11**. Treatment of **1.6.15** with excess sodium ethanethiolate in hot DMF cleaved the C(11) and C(12) methyl ethers to furnish (–)-salviasperanol (**1.6.1**) in 86% yield. Our synthetic **1.6.1** displays ^{1}H and ^{13}C NMR, IR, and MS spectra identical to those reported for the natural sample.


Im
S
O
OMe
OMe
O
TFA
1.6.13
1.6.17
Bu3SnH,
AIBN
(76% from 1.6.11)
OH
OH
NaSEt, DMF
(86%)
(–)-salviasperanol
1.6.1
1.6.15

Scheme 1.6.6

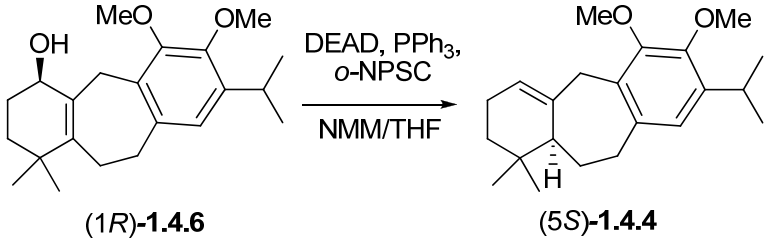
1.7 Experimental Section

General Procedures: All reactions were run under a nitrogen atmosphere and monitored by TLC analysis. Unless otherwise indicated, all extractive workups consisted of the following procedure: The organic solvent was removed under reduced pressure on a rotary evaporator, and the residue was taken up in diethyl 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 a 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. Melting points were recorded on a Laboratory Devices Mel-Temp 3.0. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVB-400 and DRX-500 MHz spectrometers with ^{13}C operating frequencies of 100 MHz and 125 MHz, respectively. Proton NMR spectra were obtained in $CDCl_3$ and were calibrated using trace $CHCl_3$ present (δ 7.27) as an internal reference. Carbon NMR spectra were obtained in $CDCl_3$ and were calibrated using trace $CHCl_3$ present (δ 77.23) as an internal reference. The IR spectra were obtained using an Avatar 360FT-IR and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. High resolution MS were taken using a LCT Premier from Waters.



1.4.5 **(*1R*)-1.4.6**

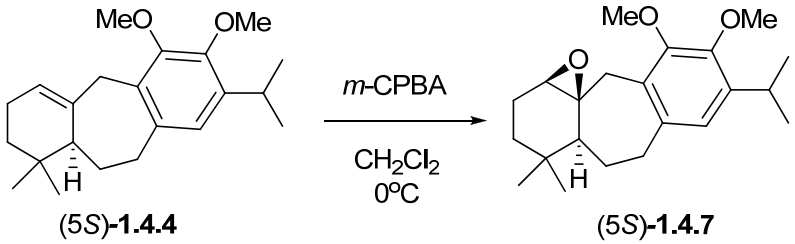
To a solution of **1.4.5** (2.26 g, 6.60 mmol) in 80 mL of anhydrous THF, BH_3-Me_2S (1.3 mL, 1 M, 1.32 mmol) was added. After the mixture was stirred for a 15 min-period at 40 °C, (*S*)-CBS (0.65 mL, 10~10.2 M) in 30 mL of THF was added using a syringe pump over an 8-hour period. The reaction mixture was cooled to 0 °C and methanol was added dropwise. The mixture was then concentrated and purified by silica gel column chromatography (elution with EtOAc/pet ether = 1:4) to give 2.05 g (90% yield, >96% *ee*) of allylic alcohol (1*R*)-**1.4.6** [R_f = 0.17, EtOAc/pet ether = 1:8]: $[\alpha]_D$ = +20.88^o ($CHCl_3$; c0.050); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (s, 1H), 4.06 (m, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 3.61(m, 1H), 3.27 (septet, *J* = 7.0 Hz, 1H), 3.01-2.84 (m, 2H), 2.51-2.39 (m, 2H), 1.91-1.84 (m, 1H), 1.74-1.69 (m, 2H), 1.64-1.58 (m, 1H), 1.38-1.33 (m, 1H), 1.22 (d, *J* = 2.0 Hz, 3H), 1.07 (d, *J* = 2.0 Hz, 3H), 1.04 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 148.4, 143.2, 140.0, 136.7, 132.0, 130.9, 121.8, 70.6, 60.9, 60.9, 35.4, 34.5, 32.0, 28.7, 28.3, 27.7, 27.1, 26.8, 26.8, 23.9, 23.8; IR (film) λ_{max} 3440, 2959, 1051, 732 cm-1; HRMS (EI) calcd for [M]+: m/z 344.2351, found 344.2344.



(1*R*)-**1.4.6** (5*S*)-**1.4.4**

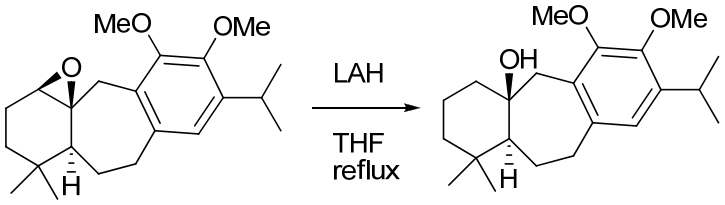
To a solution of tripheylphosphine (1.50 g, 5.72 mmol) in 7.0 mL of anhydrous *N*-methyl morpholine at 0 ^{o}C was added DEAD (1.1 mL, 6.95 mmol). The resulting mixture was stirred at

0 °C for 3-5 minutes and cooled to -30 °C. Allylic alcohol (1*R*)-**1.4.6** (700 mg, 2.04 mmol) in 7 mL of THF was added and the resulting mixture was stirred at -30 °C for another 30 minutes. *o*-Nitrobenzenesulfonylhydrazine (1.62 g, 7.50 mmol) was added to the reaction mixture before it solidified, followed by 5 mL of THF. The reaction mixture was vigorously shaken to dissolve any solid and then kept at -30 °C for 3 h. The temperature of the reaction was then raised to 30 °C. After stirring at 30 °C for 2 h, the reaction mixture was diluted by 30 mL of ethyl ether and cooled to 0 °C. A solution of 5% aqueous H_2O_2 (10 mL) was added to the mixture and stirred at 0 ^oC for an additional hour. The reaction mixture was then passed through a column containing a one-inch wad of silica gel prior to a standard extractive workup. The organic layer was then concentrated and the resulting light yellow oil was purified by silica gel chromatography (elution with pet ether/EtOAc = 20:1) to give 360 mg (54%) of (5*S*)-**1.4.4** as a white solid [R_f = 0.83, EtOAc/pet ether = 1:8]: mp = 63-65 °C; $[\alpha]_D = -73.10^o$ (MeOH; c0.013); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (s, 1H), 5.53 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.84 (d, *J* = 14.5 Hz, 1H), 3.31 (septet, *J* = 6.5 Hz, 1H), 3.07 (d, *J* = 14.5 Hz, 1H), 2.90-2.77 (m, 2H), 2.09-2.03 (m, 2H), 1.97-1.91 (m, 1H), 1.86-1.80 (m, 1H), 1.42-1.34 (m, 1H), 1.25 (d, *J* = 2.0 Hz, 3H), 1.24 (d, *J* = 2.0 Hz, 3H), 1.22-1.19 (m, 1H), 1.16-1.10 (m, 1H), 0.96 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 148.9, 139.4, 138.6, 138.1, 132.6, 121.8, 121.5, 60.9, 60.8, 51.7, 35.5, 35.3, 32.3, 31.6, 30.3, 27.8, 27.4, 26.9, 24.0, 23.8, 23.5; IR(film) λ_{max} 2957, 1447, 1410, 1047, 1000 cm^{-1}; HRMS (EI) calcd for $[M]^+$: m/z 328.2402, found 328.2392.



(5*S*)-**1.4.4** (5*S*)-**1.4.7**

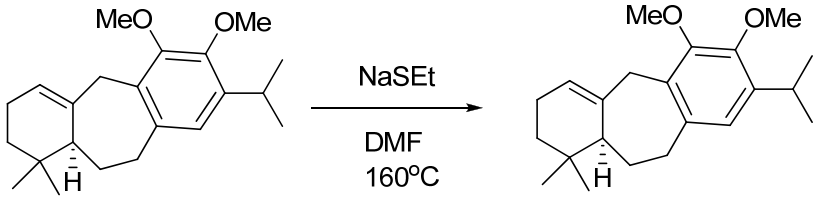
To a solution of (5*S*)-**1.4.4** (222 mg, 0.68 mmol) and in CH_2Cl_2 (10 mL) at 0 °C, was added *m*-CPBA (343 mg of a 77% mixture, 1.53 mmol). The resulting mixture was stirred for 2 h at 0 °C and quenched by 5% aqueous NaOH solution (3 mL). Standard extractive workup, followed by silica gel chromatography (elution with pet ether/Et_2O = 10:1), gave 221 mg of (5*S*)-**1.4.7** (95%) as colorless oil [R_f = 0.67, EtOAc/pet ether = 8:1]: $[\alpha]_D = -12.0^o$ (MeOH; c0.033); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (s, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.37 (d, *J* = 16.5 Hz, 1H), 3.29 (septet, *J* = 7.0 Hz, 1H), 3.23 (m, 1H), 3.16-3.08 (m, 1H), 2.70-2.62 (m, 2H), 2.98-2.90 (m, 2H), 1.87-1.80 (m, 1H), 1.69-1.54 (m, 2H), 1.42-1.36 (m, 1H), 1.26-1.20 (m, 6H), 1.06-1.00 (m, 1H), 0.90 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 151.2, 148.8, 140.2, 137.3, 128.5, 122.2, 61.7, 60.9, 60.4, 60.3, 45.4, 36.8, 33.9, 31.4, 31.2, 29.5, 26.9, 26.8, 24.7, 23.9, 23.7, 22.3; IR(film) λ_{max} 2958, 2931, 1448, 1411, 1299, 1046, 925 cm^{-1}; HRMS (EI) calcd for [M]+: m/z 344.2351, found 344.2348.



(5*S*)-**1.4.7** (10*S*)-**1.4.8**

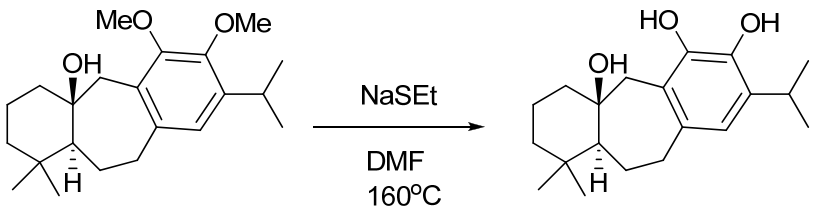
To a solution of (5*S*)-**1.4.7** (122 mg, 0.35 mmol) in THF (6.0 mL) at 0 °C, was added LAH (28 mg, 0.74 mmol). The resulting mixture was refluxed for 20 h and then quenched at 0 °C with brine. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/Et_2O = 10:1), gave 110 mg of (10*S*)-**1.4.8** (92%) as a white solid [R_f = 0.67, pet ether/EtOAc = 8:1]: mp = 130-133 °C; $[\alpha]_D$ = 8.50 ($CHCl_3$; c0.018); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (s, 1H), 3.83 (s, 6H), 3.32-3.22 (m, 2H), 2.82-2.64 (m, 2H), 2.51 (d, *J* = 14.0 Hz, 1H), 2.02-1.80 (m, 3H), 1.60-1.51 (m, 1H), 1.50-1.40 (m, 2H), 1.36-1.24 (m, 3H), 1.24-1.20 (m, 6H),

0.94 (s, 3H), 0.90 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 149.0, 140.9, 140.3, 127.6, 121.2, 70.9, 60.9, 58.5, 42.7, 42.4, 41.6, 36.6, 34.6, 32.7, 26.9, 24.2, 24.0, 23.7, 21.8, 19.0; IR(film) λ_{max} 3471, 2931, 1451, 1412, 1050 cm^{-1}; HRMS (EI) calcd for [M]+: m/z 346.2508, found 346.2501.



(S)-**1.4.4** (–)-barbatusol

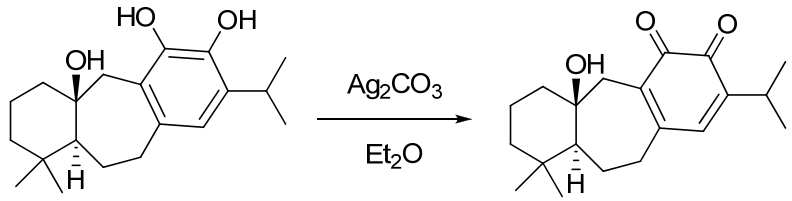
To a suspension of NaH (700 mg, 60%, 17.5 mmol) in DMF (10 mL) at 0 °C, ethanethiol (3.50 mL, 97%, 45.8 mmol) was added dropwise. The resulting solution was cannulated into a suspension of (5*S*)-**10** (318 mg, 0.97 mmol) in 2.0 mL of DMF. The reaction mixture was then stirred at 150 °C for 12 h. After cooling to rt, the reaction mixture was diluted by 15 mL of ethyl ether, quenched by 3 mL brine, and acidified by 3 mL 1 *N* HCl. The organic layer was washed with brine (5 x 5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Silica gel chromatography (elution with pet ether/Et_2O = 4:1) gave 189 mg (65%) of (–)-barbatusol as a gray amorphous solid, which can be easily oxidized by air [R_f = 0.51, pet ether/EtOAc = 2:1]: $[\alpha]^{24}_D$ = -90.4 ($CHCl_3$; c = 0.044 g/mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.53 (s, 1H), 5.52 (s, 1H), 5.14 (br s, 1H), 5.04 (br s, 1H), 3.69 (d, *J* = 15.0 Hz, 1H), 3.16-3.04 (m, 2H), 2.88 –2.70 (m, 2H), 2.08-1.98 (m, 2H), 1.98-1.90 (m, 1H), 1.85-1.78 (m, 1H), 1.40-1.32 (m, 1H), 1.30-1.24 (m, 6H), 1.26-1.16 (m, 1H), 1.12-1.08 (m, 1H), 0.94 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.6, 139.3, 138.3, 134.8, 131.4, 124.7, 121.4, 117.8, 50.9, 35.5, 34.7, 32.3, 31.4, 30.7, 27.7, 27.4, 27.3, 23.4, 23.0, 22.8.



(10*S*)-**1.4.8**

(+)-demethylsalvicanol
1.4.3

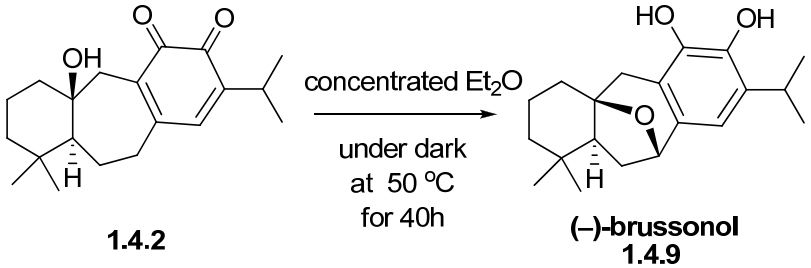
To a suspension of NaH (350 mg, 60%, 8.75 mmol) in DMF (6 mL) at 0 °C, ethanethiol (1.40 mL, 97%, 18.3 mmol) was added dropwise. The resulting solution was cannulated into a suspension of (10*S*)-**1.4.2** (250 mg, 0.72 mmol) in 2.0 mL of DMF. The reaction mixture was then stirred at 160 °C for 12 h. After cooling to rt, the reaction mixture was diluted by 15 mL of ethyl ether, quenched by 3 mL brine and acidified by 3 mL 1 *N* HCl. The organic layer was washed with brine (5 x 5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Silica gel chromatography (elution with pet ether/Et_2O = 4:1) gave 161 mg (70%) of (+)-demethylsalvicanol (**1.4.3**) as a white amorphous solid which can be easily oxidized by air [R_f = 0.42, pet ether/EtOAc = 4:1]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (br s, 1H), 6.58 (s, 1H), 5.90 (br s, 1H), 3.19 (septet, *J* = 7.0 Hz, 1H), 3.06 (d, *J* = 14.5 Hz, 1H), 2.80-2.60 (m, 2H), 2.56 (d, *J* = 14.5 Hz, 1H), 2.04-1.94 (m, 1H), 1.90-1.72 (m, 3H), 1.55-1.49 (m, 1H), 1.25 (d, *J* = 6.5 Hz, 3H), 1.22 (d, *J* = 6.5 Hz, 3H), 1.20-1.10 (m, 1H), 0.93 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (125M Hz, $CDCl_3$) δ 142.9, 141.4, 136.5, 133.2, 121.4, 118.1, 72.1, 58.3, 42.5, 41.8, 41.5, 36.3, 34.6, 32.4, 27.3, 24.3, 22.8, 21.8, 21.7, 18.8.



(+)-demethylsalvicanol
1.4.3

1.4.2

To a solution of (+)-demethylsalvicanol (**1.4.3**) (130 mg, 0.41 mmol) in ethyl ether (5 mL) was added Ag_2CO_3 (0.338 g, 1.22 mmol). The resulting mixture was stirred at rt for one hour before the reaction mixture was filtered through a column containing a one-inch wad of celite. The mixture was then concentrated to give 127 mg of quione 13 (98%) as a dark red amorphous solid [R_f = 0.61, pet ether/EtOAc = 4:1]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60 (s, 1H), 3.70 (m, 1H), 3.06 (d, *J* = 9.6 Hz, 1H), 2.93 (septet, *J* = 6.8 Hz, 1H), 2.67-2.42 (m, 2H), 2.18 (d, *J* = 6.8 Hz, 1H), 1.92-1.68 (m, 3H), 1.62-1.48 (m, 2H), 1.45-1.38 (m, 2H), 1.31-1.20 (m, 2H), 1.14-1.06 (m, 6H), 0.93 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.7, 180.5, 154.5, 147.0, 138.7, 134.6, 70.8, 62.2, 58.3, 42.7, 42.5, 40.2, 34.6, 33.9, 32.3, 29.4, 27.4, 21.8, 21.1, 18.5.

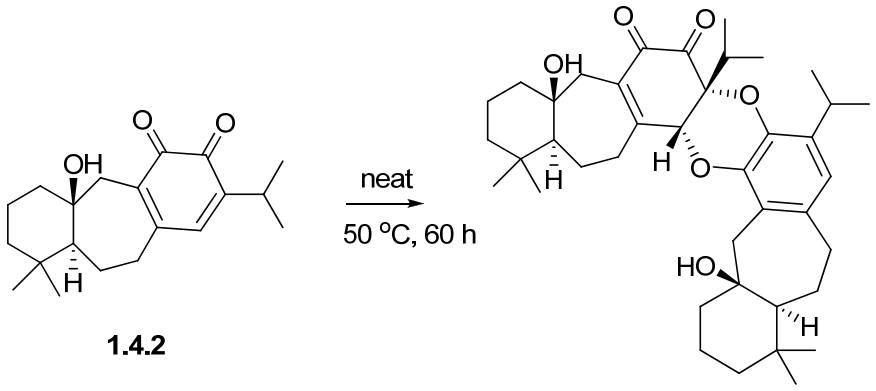


1.4.2

(–)-brussonol
1.4.9

A concentrated solution of crude **1.4.2** (113 mg, 0.36 mmol) in ethyl ether (10 μL) was heated in a sealed 1 mL round bottom flask at 50 °C for 40 h. Silica gel chromatography (elution with pet ether/Et_2O = 4:1) of the resulting mixture gave 77 mg (70%) of (–)-brussonol (**1.4.9**) as a dark brown gum [R_f = 0.46, pet ether/EtOAc = 2:1]: $[\alpha]_D$ = –33.4°($CHCl_3$; c0.024); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (s, 1H), 5.26 (br s, 1H), 5.17 (br s, 1H), 4.86 (d, *J* = 6.4 Hz, 1H), 2.73

(d, *J* = 16.4 Hz, 1H), 2.40 (d, *J* = 16.0 Hz, 1H), 2.16-2.08 (m, 1H), 2.03-1.94 (m, 1H), 1.93-1.86 (m, 1H), 1.83-1.76 (m, 3H), 1.64-1.47 (m, 2H), 1.24 (d, *J* = 3.2 Hz, 3H), 1.22 (d, *J* = 3.2 Hz, 3H), 1.20-1.08 (m, 1H), 0.96 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 139.7, 134.4, 132.2, 116.7, 112.9, 80.3, 79.4, 51.3, 39.9, 39.0, 32.4, 32.1, 30.9, 30.8, 27.3, 26.9, 23.0, 22.8, 16.4.

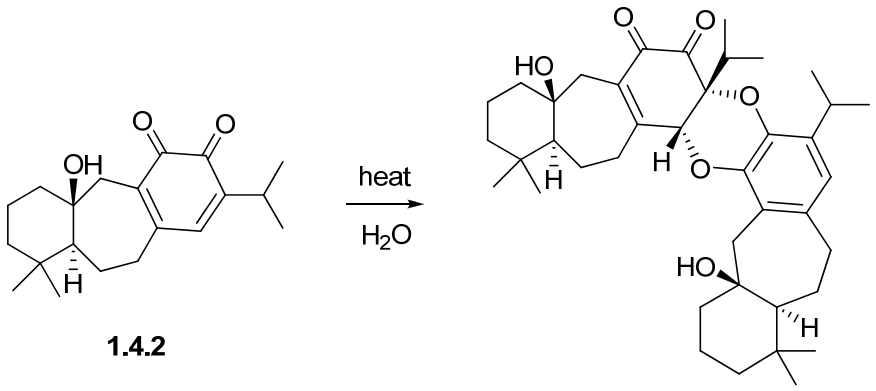


1.4.2

grandione 1.4.1

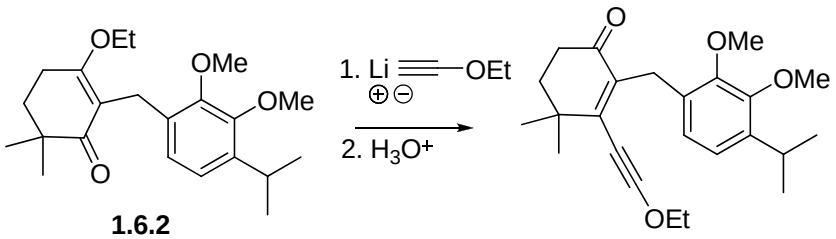
Crude quinone **1.4.2** (130 mg, 0.41mmol) was heated in a sealed 3 mL conical vial flask at 50 °C for 60 h. Silica gel chromatography (elution with pet ether/Et_2O = 6:1) of the resulting mixture gave 93.7 mg (72%) of (+)-grandione (**1.4.1**) as yellow needles [R_f = 0.55, pet ether/EtOAc = 4:1]: $[\alpha]_D$ = +66^o ($CHCl_3$; c0.033); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (s, 1H), 4.60 (s, 1H), 3.28 (septet, *J* = 6.5 Hz, 1H), 3.10 (d, *J* = 14.5 Hz, 1H), 2.86-2.70 (m, 3H), 2.67-2.58 (m, 2H), 2.36 (d, *J* = 14.0 Hz, 1H), 2.28 (d, *J* = 15.0 Hz, 1H), 2.00-1.84 (m, 2H), 1.86-1.68 (m, 4H), 1.68-1.60 (m, 2H), 1.60-1.52 (m, 4H), 1.52-1.39 (m, 5H), 1.36-1.31 (m, 1H), 1.30 (d, *J* = 1.5 Hz, 3H), 1.29 (d, *J* = 1.5 Hz, 3H), 1.28-1.20 (m, 5H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.94 (s, 3H), 0.92 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9, 186.5, 159.7, 141.4, 141.0, 137.9, 137.1, 134.9, 121.6, 119.5, 86.4, 78.2, 71.1, 71.0, 58.3, 58.2, 43.0,

42.7, 42.4, 40.4, 40.1, 36.1, 34.6, 34.5, 32.4, 32.3, 30.7, 27.8, 24.3, 22.7, 22.1, 21.8, 21.8, 20.4, 19.1, 18.4, 16.9, 16.3.



1.4.2 **grandione 1.4.1**

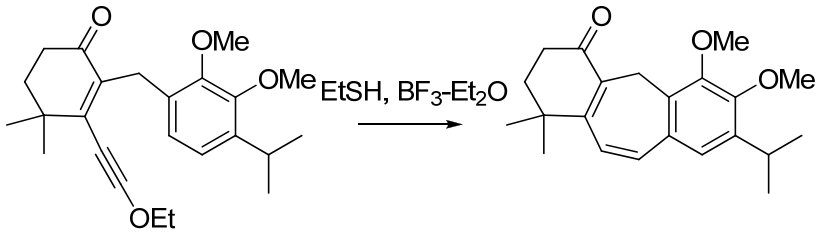
Crude quinone **1.4.2** (111 mg, 0.350 mmol) and 3 mL of water were heated in a sealed 5 mL mico-reaction vial at 50 °C for 60 h. After standard extractive workup, a ^{1}H NMR indicated that the crude reaction residue consisted of a 3:1 mixture of grandione (**1.4.1**) and brussonol (**1.4.9**), respectively. Silica gel chromatography (elution with pet ether/Et_2O = 6:1) gave recovered **1.4.2** and 58 mg (53%) of grandione (**1.4.1**) and 9 mg (8%) of brussonol (**1.4.9**) which were identical to that previously prepared. The yields cited are conversion yields.



1.6.2 **1.6.4**

To a solution of acetylene (3.5 mL, 94.2 mmol) in 25 mL THF at -78 °C, *n*-butyllithium (2.5 M, 20.0 mL, 50.0 mmol) in 25 mL THF was added over a 15-min period. After stirring 0.5 hour at –78 °C, enone **1.6.2** (6.8 g, 18.9 mmol) in 15 mL ether was added. The resulting mixture was warmed to 0 °C and then stirred for an additional 5 h. HCl solution (1.0 *M*, 10.0 mL) was

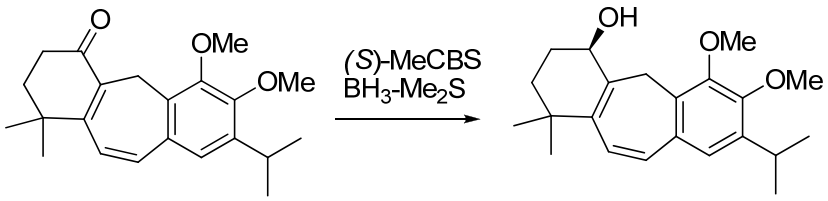
added dropwise at 0 °C and the resulting mixture was stirred for 30 minutes. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/Et_2O = 8:1), gave 5.88 g (92%) of enynone **1.6.4** as a colorless oil [R_f = 0.50, EtOAc/pet ether = 1:8]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, *J* = 8.4 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 3.83 (s, 2H), 3.68 (s, 1H), 3.27 (septet, *J* = 6.8 Hz, 1H), 2.51 (t, *J* = 6.8 Hz, 2H), 1.93 (t, *J* = 6.4 Hz, 2H), 1.23 (t, *J* = 6.8 Hz, 3H), 1.34 (s, 6H), 1.19 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 151.0, 150.6, 147.0, 141.8, 140.5, 130.7, 123.1, 120.9, 91.7, 80.6, 60.7, 60.1, 36.4, 35.7, 34.6, 27.9, 27.8, 26.8, 26.8, 23.8, 23.8; IR (film) λ_{max} 3264, 2960, 1672, 1022 cm^{-1}; HRMS (ESI) calcd for $[M+H]^+$: m/z 341.2117, found 341.2107.



1.6.4 **1.6.3**

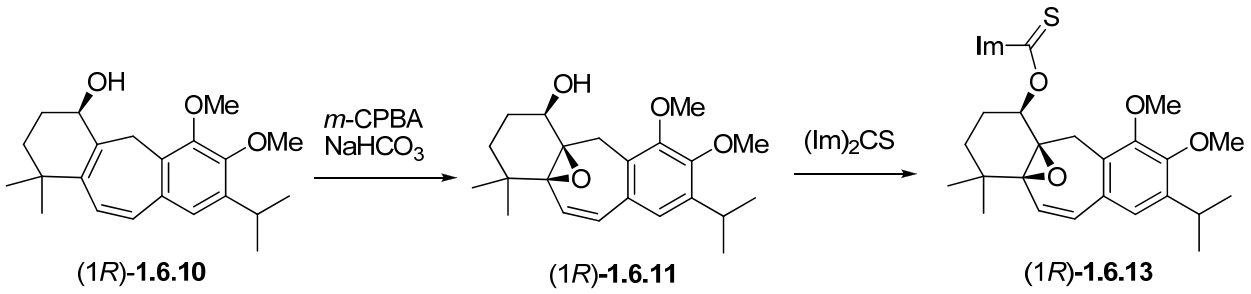
To a solution of **1.6.4** (1.10 g, 3.2 mmol) and ethanethiol (97%, 74 μL, 0.97 mmol) in 10 mL of CH_2Cl_2 at 0 °C, BF_3-Et_2O (1.0 mL, 8.0 mmol) was added dropwise. The resulting mixture was stirred for 1 h at 0 °C and 48 h at rt. Standard extractive workup, followed by silica gel chromatography (elution with pet ether/Et_2O = 8:1), gave 1.03 g (94%) of the dienone **1.6.3** as a white solid [R_f = 0.63, EtOAc/pet ether = 1:4]: mp = 152-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 12.0 Hz, 1H), 6.93 (s, 1H), 6.65 (d, *J* = 12.0 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.46 (br s, 2H), 3.30 (septet, *J* = 6.8 Hz, 1H), 2.49 (t, *J* = 6.8 Hz, 2H), 1.83 (t, *J* = 6.8 Hz, 2H), 1.23 (t, *J* = 6.8 Hz, 3H), 1.22 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 157.1, 152.3, 149.6, 140.2, 138.7, 132.5, 131.2, 127.5, 121.3, 61.6, 60.9, 37.3, 35.1, 34.8, 28.0, 27.0, 23.7, 22.5; IR (film)

λ_{max} 2974, 1665, 1381, 1120 cm^{-1}; HRMS (ESI) calcd for $[M+H]^+$: m/z 341.2117, found 341.2121.



1.6.3 (1*R*)-**1.6.10**

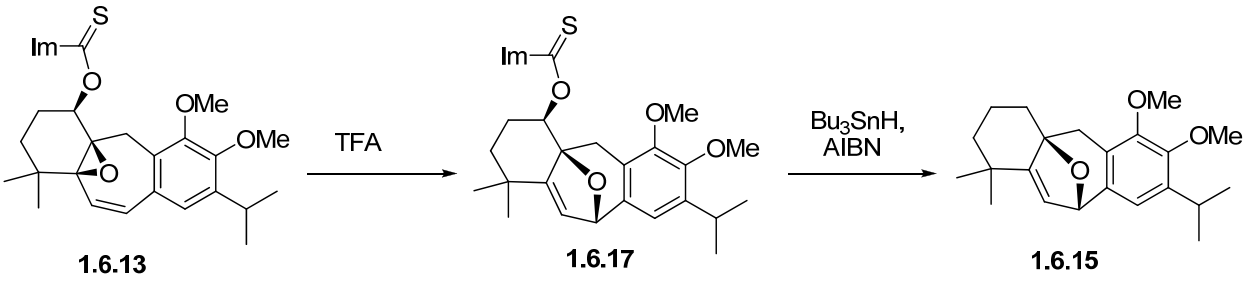
To a solution of **1.6.3** (1.47 g, 4.32 mmol) in 40 mL of anhydrous THF was added a solution of BH_3-Me_2S in THF (0.86 ml, 1 *M*). The resulting mixture was stirred for a 15 minutes at 40 °C. (*S*)-MeCBS (0.41mL, 10~10.2 *M*) in 30 mL of THF was added using a syringe pump over a 5-h period. The reaction mixture was cooled to 0 °C and methanol was added dropwise. The mixture was then concentrated and purified by silica gel column chromatography (elution with EtOAc/pet ether = 1:4) to give 1.34 g (91% yield, >95% *ee*) of allylic alcohol (1*R*)-**1.6.10** [R_f = 0.29, EtOAc/pet ether = 1:4]: $[\alpha]_D$ = -3.54° ($CHCl_3$; c0.081); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (d, *J* = 12.0 Hz, 1H), 6.91 (s, 1H), 6.55 (d, *J* = 11.6 Hz, 1H), 4.34 (m, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 3.23 (septet, *J* = 6.8 Hz, 1H), 3.08 (m, 2H), 2.41 (br s, 1H), 1.85-1.93 (m, 1H), 1.65-1.71 (m, 1H), 1.58-1.63 (m, 1H), 1.38-1.43 (m, 1H), 1.23 (m, 1H), 1.07(m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 147.9, 139.8, 139.5, 133.0, 132.7, 129.5, 128.5, 120.5, 69.5, 61.0, 60.8, 34.7, 34.2, 29.4, 29.3, 28.2, 28.1, 27.0, 23.9, 23.8; IR (film) λ_{max} 3419, 2958, 1399, 1049 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$: m/z 365.2093, found 365.2111.



(1*R*)-**1.6.10** (1*R*)-**1.6.11** (1*R*)-**1.6.13**

To a suspension of allylic alcohol (1*R*)-**1.6.10** (1.61 g, 4.67 mmol) and $NaHCO_3$ (0.78 g, 9.34 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added *m*-CPBA (1.26 g of a 77% mixture, 5.62 mmol). The resulting mixture was stirred at 0 °C for 1 h at which time TLC analysis showed that no (1*R*)-**1.6.10** remained. The reaction mixture was concentrated and filtered through only a one half-inch wad of silica gel because epoxy alcohol (1*R*)-**1.6.11** was unstable to silica gel. Crude (1*R*)-**1.6.10** was used in the next reaction without further purification [R_f = 0.44, elution with EtOAc/pet ether = 1:2].

To a solution of crude (1*R*)-**1.6.11** in CH_2Cl_2 (50 mL) at rt was added 1,1-thiocarbonyldiimidazole (1.56 g, 8.75 mmol). The resulting mixture was stirred at rt for 24 h. The solution was then concentrated and the resulting light yellow oil was purified by silica gel chromatography (elution with pet ether/EtOAc = 3:1) to give 1.16 g (2.47 mmol, 53% over two steps) of (1*R*)-**1.6.13** as a colorless oil [R_f = 0.44, EtOAc/pet ether = 1:2]: $[\alpha]_D$ = -14.33° ($CHCl_3$; c0.043); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.78 (s, 1H), 7.09 (s, 1H), 6.83 (s, 1H), 6.61 (d, *J* = 11.6 Hz, 1H), 6.17 (d, *J* = 11.6 Hz, 1H), 5.75 (m, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 3.64 (d, *J* = 13.6 Hz, 1H), 3.30 (septet, *J* = 6.4 Hz, 1H), 2.42 (d, *J* = 13.2 Hz, 1H), 1.70-1.89 (m, 2H), 1.54-1.60 (m, 1H), 1.22 (m, 6H), 1.15 (s, 3H), 1.03-1.09 (m, 1H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.1, 150.5, 149.8, 141.5, 132.8, 132.2, 131.0, 127.1, 126.6, 122.4, 81.5, 77.6, 69.9, 67.7, 60.8, 60.7, 33.5, 32.9, 31.4, 27.0, 25.8, 25.1, 23.7, 23.1; IR (film) λ_{max} 2960, 1387, 1282, 1229, 968 cm^{-1}; HRMS (ESI) calcd for $[M+H]^+$: m/z 469.2161, found 469.2138.



1.6.13 **1.6.17** **1.6.15**

To a solution of (1*R*)-**1.6.13** (521 mg, 1.10 mmol) and 4 Å molecular sieves (1.12 g) in 35 mL of CH_2Cl_2 at 0 °C, trifluoroacetic acid (390 μL) was added dropwise. The resulting mixture was stirred for 1 h at 0 °C and then stirred for 24 h at rt. Standard extractive workup gave 496 mg of crude (1*R*)-**1.6.17** as colorless oil. The crude (1*R*)-**1.6.17** was directly used in the next step without further purification or characterization [R_f = 0.44, EtOAc/pet ether = 2:1].

To a solution of crude (1*R*)-**1.6.17** (496 mg, 1.05 mmol) and AIBN (17.3 mg, 0.1 mmol) in 15 mL toluene at 110 °C, tri-*n*-butyltin hydride (0.56 mL, 2.12 mmol) dissolved in 5 mL of toluene was added dropwise. The resulting mixture was refluxed for 30 minutes. The mixture was then concentrated and purified by silica gel chromatography (elution with pet ether/Et_2O = 20:1) to give 290 mg of (10*S*,7*S*)-**1.6.15** (76% yield over 2 steps) as white crystals [R_f = 0.66, pet ether/EtOAc = 8:1]: $[\alpha]_D$ = -23.7° ($CHCl_3$; c0.018); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 (s, 1H), 6.04 (d, *J* = 1.4 Hz, 1H), 5.10 (d, *J* = 1.9 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.27 (septet, *J* = 6.9 Hz, 1H), 2.97 (d, *J* = 17.2 Hz, 1H), 2.69 (d, *J* =17.2 Hz, 1H), 2.16-2.09 (m, 1H), 1.82-1.71 (m, 3H), 1.57-1.49 (m, 1H), 1.42-1.34 (m, 1H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.13 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 150.1, 149.4, 139.4, 135.6, 128.5, 124.9, 116.2, 83.8, 79.9, 60.9, 60.0, 40.3, 38.9, 34.1, 30.9, 30.1, 27.7, 26.8, 24.1, 23.6, 19.3.

1.6.15 **salviasperanol 1.6.1**

To a suspension of NaH (7.4 mg, 60%, 0.185 mmol) in 3.0 mL of DMF at 0 °C was added dropwise 62 μL of ethanethiol (0.37 mmol). The resulting solution was cannulated into a solution of salviasperanol dimethyl ether (10*S*,7*S*)-**1.6.15** (12.5 mg, 0.036 mmol) dissolved in 2.0 mL of DMF. The reaction mixture was then stirred at 140 °C for 12 h. After cooling to rt, the reaction mixture was diluted by 15 mL of ethyl ether, quenched by 3 mL brine and acidified by 3 mL of 1 *N* HCl. The organic layer was washed with brine (5 x 5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Silica gel chromatography (elution with pet ether/Et_2O = 4:1) gave 10.0 mg (86%) of (–)-salviasperanol (**1.6.1**) as a white solid, which can be easily oxidized by air [R_f = 0.51, pet ether/EtOAc = 2:1]: $[\alpha]_D$ = -27.40^o ($CHCl_3$; c0.018); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.44 (s, 1H), 6.05 (s, 1H), 5.11 (s, 1H), 5.04 (br, 2H), 3.09 (septet, *J* = 6.5 Hz, 1H), 2.88 (d, *J* = 17.0 Hz, 1H), 2.66 (d, *J* = 16.5 Hz, 1H), 2.13 (m, 1H), 1.87-1.65 (m, 3H), 1.53 (m, 1H), 1.41-1.35 (m, 1H), 1.26 (d, *J* = 7.0 Hz, 3H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.13 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 142.6, 139.9, 132.0, 130.9, 128.8, 117.3, 112.5, 83.7, 80.1, 40.3, 38.9, 34.0, 30.4, 30.2, 27.9, 27.3, 23.1, 22.7, 19.3; HRMS (ESI) calcd for $[M+H]^+$: m/z 315.1960, found 315.1960.

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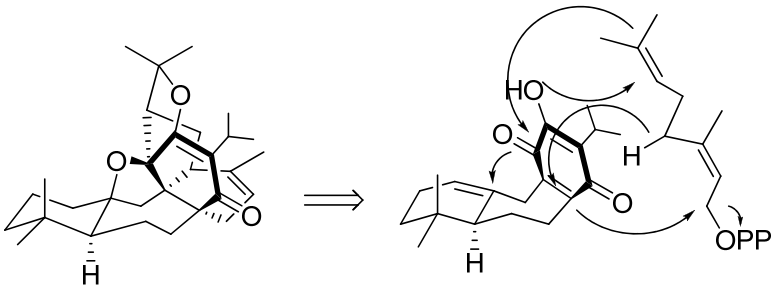
CHAPTER TWO

TOTAL SYNTHESES OF (+)-SALVADIONE-B AND STUDIES TOWARD (+)-SALVADIOL

2.1 First Total Synthesis of (±)-Perovskone

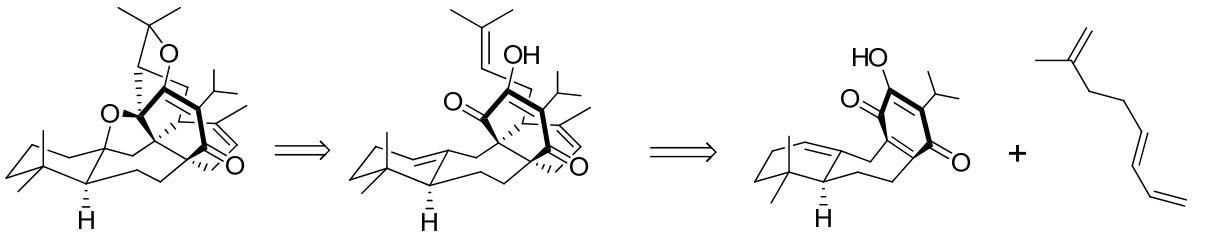
The genus *Salvia*, comprising more than 900 species, is the largest genus of the *Lamiaceae* family.[1] The name *Salvia* comes from the Latin word "*salvare*", which means "to heal". *Salvia* species have been used since ancient times for more than sixty different ailments ranging from aches to epilepsy, and mainly to treat colds, bronchitis, tuberculosis, hemorrhage, and menstrual disorders.[2] *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.[3] Several complex triterpene structures, *i.e.*, salvadione-A, salvadione-B and salvadiol have been isolated from this family of natural sources. *Perovskia* is another source of these triterpene structures. Perovskone was isolated from *Perovskia abrotanoides*, Karel syn. *P. artemisioides Boiss* (Labiatae) which was collected from the Baluchistan and North West Frontier provinces of Pakistan by Ahmad and co-workers in 1992.[4] Perovskone contains a complex array of seven fused and bridged rings as well as seven asymmetric centers, therefore posing a formidable challenge to total synthesis (Scheme 2.1.1).



perovskone

Scheme 2.1.1

In 1994, Majetich and Zhang reported a concise synthesis of (±)-perovskone in which three of the rings and five of the stereocenters were established in a single operation.[5] Inspired by the biosynthesis proposal (Scheme 2.1.1), which suggested that the skeleton may be constructed by the addition of geranyl pyrophosphate to an icetexone precursor, a diastereoselective Diels–Alder reaction of cup-shaped *p*-benzoquinone (**2.1.2**) and ocimene (**2.1.3**) was used to construct the carbocyclic skeleton of perovskone (Scheme 2.1.2).

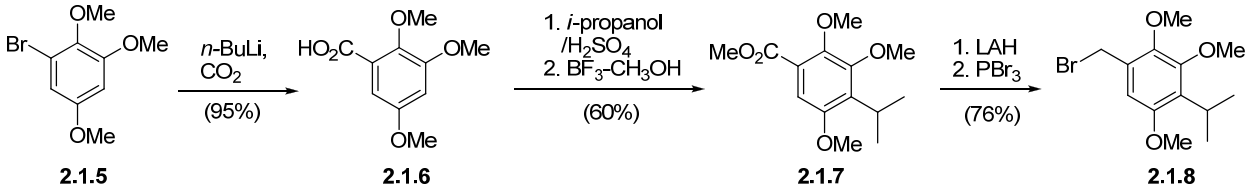


perovskone (**2.1.1**) Diels–Alder adduct *p*-benzoquione **2.1.2** ocimene (**2.1.3**)

Scheme 2.1.2

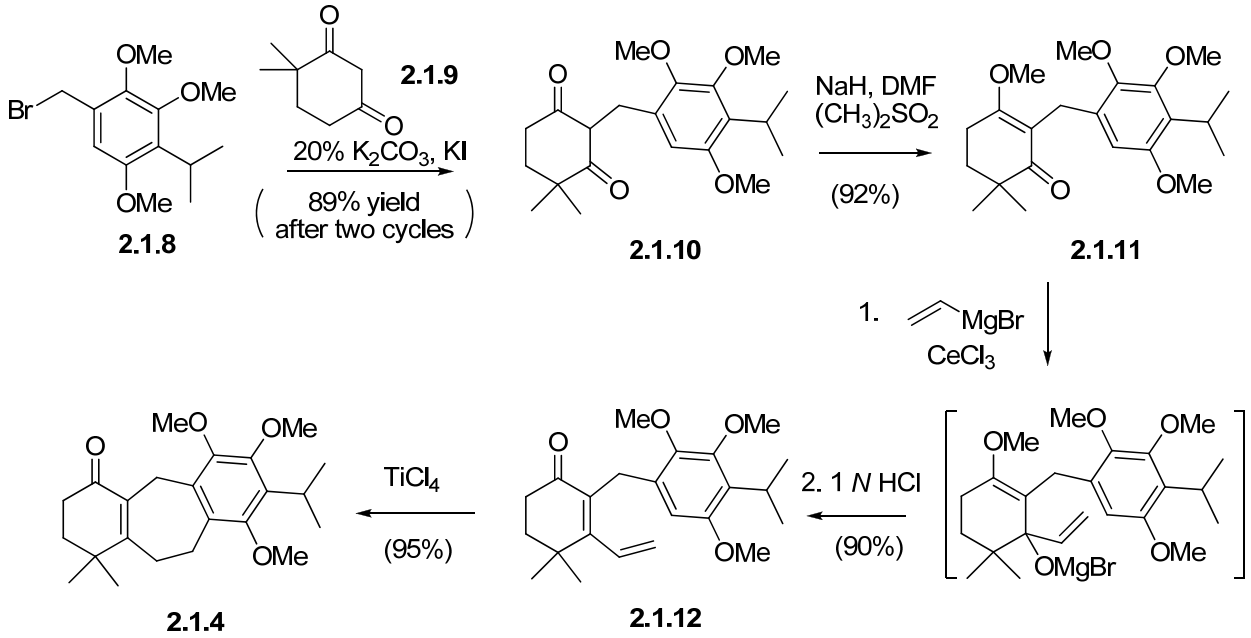
The synthesis involved the construction of tricyclic enone **2.1.4**, which is available from 1-bromo-2,3,5-trimethoxybenzene **2.1.5**[6] in nine steps. As shown in Scheme 2.1.3, treatment of **2.1.5** with *n*-butyllithium, followed by quenching of the anion with gaseous carbon dioxide, gave acid **2.1.6** in 95% yield. An acid-catalyzed Friedel–Crafts alkylation with 2-propanol was then used to introduced the required isopropyl unit at C(13). The crude alkylation mixture was treated

with methanolic boron trifluoride etherate, which esterified the carboxylic acid group and remethylated any unmasked phenol. A two step reduction and bromination sequence converted ester **2.1.7** to bromide **2.1.8.**



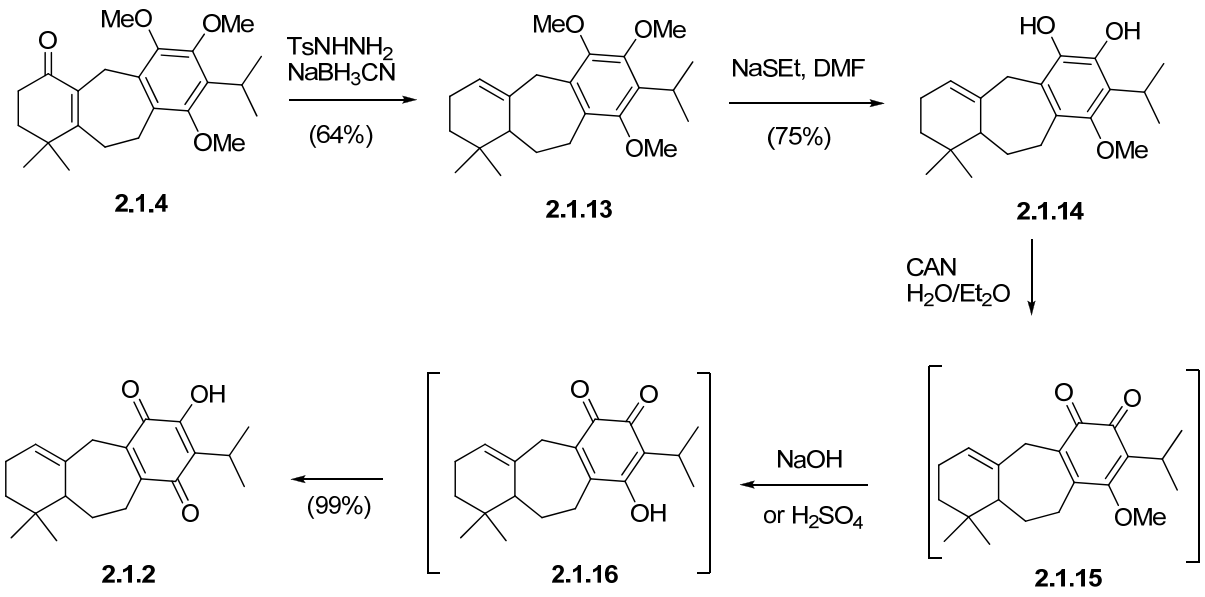
Scheme 2.1.3

Monoalkylation of the enolate of 4,4-dimethyl-l,3-cyclohexanedione (**2.1.9**) with bromide **2.1.8** was achieved by stirring the two starting materials with 20% aqueous potassium carbonate. The resulting dione **2.1.10** afforded enol ether **2.1.11** in 92% yield upon the treatment with sodium hydride and dimethyl sulfate in DMF. 1,2-Addition of vinylmagnesium bromide to **2.1.11**, followed by mild acid hydrolysis, completed the preparation of the key cyclization precursor **2.1.12**. This Grignard reaction required activation of the C(5) carbonyl by cerium chloride undoubtedly due to steric hindrance imparted by the C(4) *gem*-dimethyl substituent. Cyclialkylation of **2.1.12** was accomplished in 95% yield using $TiC1_4$ as catalyst (Scheme 2.1.4).



Scheme 2.1.4

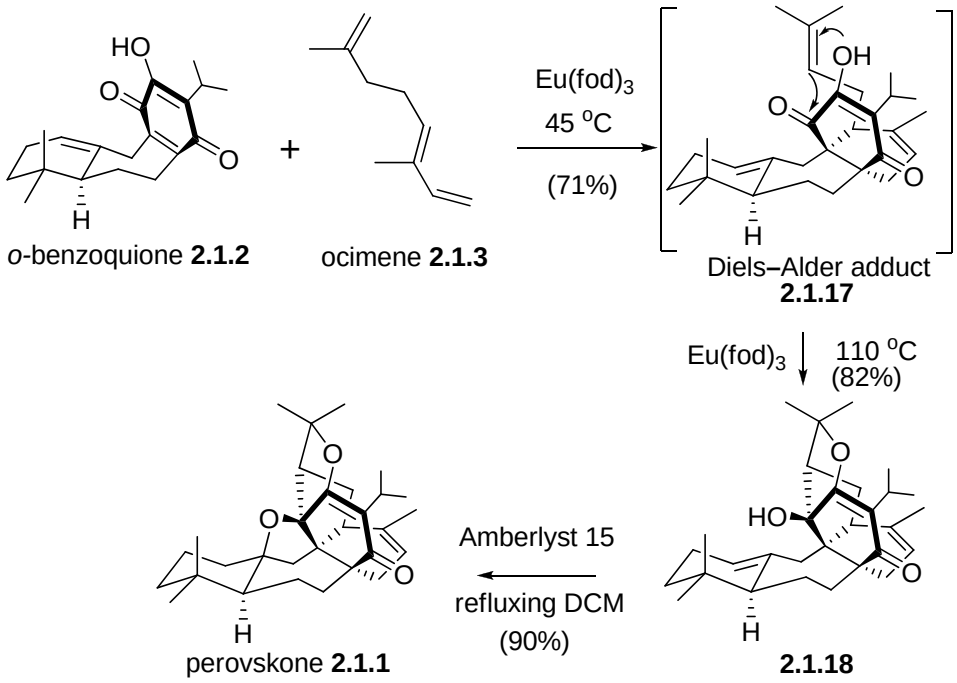
The route used to convert enone **2.1.4** into benzoquinone **2.1.2** is shown in Scheme 2.1.5. A modified Wolff–Kishner reaction reduced the enone **2.1.4** along with double bond migration.[7] Demethylation of two of the three methyl ether moieties was achieved in 75% yield without isomerization of the trisubstituted double bond using the nucleophilic conditions developed by Feutrill and Mirrington.[8] The resulting diol **2.1.13** resisted all attempts at further deprotection. *p*-Benzoquinone **2.1.2** was nevertheless furnished in nearly quantitative yield by treating **2.1.13** with cerium(IV) ammonium nitrate,[9] followed by the addition of either sodium hydroxide or sulfuric acid. In this reaction three transformations occur: (a) generation of an *o*-benzoquinone; (b) hydrolysis of the vinylogous ester moiety using base or acid; and (c) isomerization of the *o*-benzoquinone to a *p*-benzoquinone **2.1.2**



2.1.4 **2.1.13** **2.1.14** **2.1.15** **2.1.16** **2.1.2**

Scheme 2.1.5

The Diels–Alder reaction between *p*-benzoquinone **2.1.2** and trans-α-ocimene in the presence of *tris*-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium[$Eu(fod)_3$], a mild Lewis acid gives the desired cycloadduct **2.1.17** in 71% yield (Scheme 2.1.6). After the Diels–Alder reaction was completed (45 ^{o}C for 24 hours), the reaction mixture was then heated at 110 ^{o}C for an additional 48 hours to facilitate the intramolecular ene reaction giving alcohol **2.1.18** in 82% yield. Reaction of **2.1.18** with Amberlyst resin in CH_2Cl_2 under reflux for 30 minutes promoted the final ring closure in 90% yield without migration of the C(22),C(23)-trisubstituted double bond.



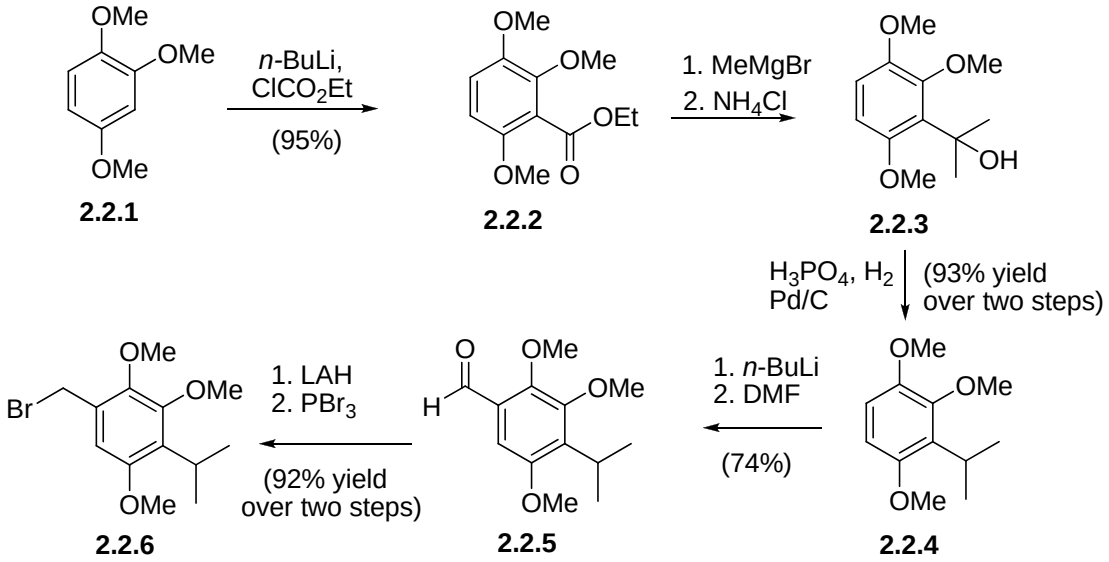
Scheme 2.1.6

In summary, (±)-perovskone was prepared in thirteen steps in greater than a 5% overall yield starting from l-bromo-2,3,5- trimethoxybenzene (**2.1.5**). Remarkably, a single chiral center, i.e., C(10) was used to establish all of the stereocenters present and a cascade of transformations established four bonds, three rings, and five stereocenters in a single step.

2.2 Stereoselective Synthesis of (+)-Perovskone

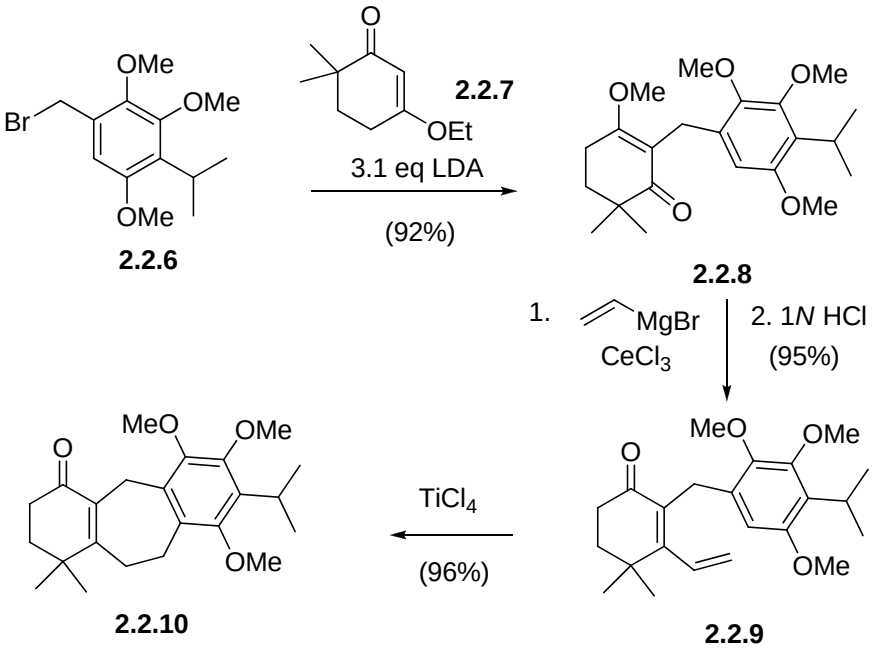
In 2002, John Britton, a M.S. candidate in our group, achieved a shorter, more convergent route toward the synthesis of enone **2.2.10**.[10] In this improved route[11] enone **2.2.10** was synthesized in nine steps starting from 1,2,4-trimethoxybenzene.

As shown in Scheme 2.2.1, commercially available 1, 2, 4-trimethoxybenzene (**2.1.1**) was deprotonated at the 3-position of the aromatic ring by *n*-butyllithium. The resulting anion was quenched with ethyl chloroformate to give the ethyl ester **2.2.2** in 95% yield. Excess methylmagnesium chloride was used to react with the ester group to form tertiary alcohol **2.2.3**. Acid-catalyzed hydrogenation gave *in situ* dehydration of tertiary alcohol and then reduction to (3)-isopropyl-(1,2,4)-trimethoxybenzene (**2.2.4)**. When **2.2.4** was treated with 1.1 equivalents of *n*-butyllithium in MTBE and TMEDA and quenched with excess amount of DMF, the desired aldehyde **2.2.5** could be isolated via silica gel chromatography in 74% yield. LAH reduction and substitution of the resulting benzyl alcohol with phosphorous tribromide produced benzyl bromide **2.2.6** in 95% yield for the two steps.



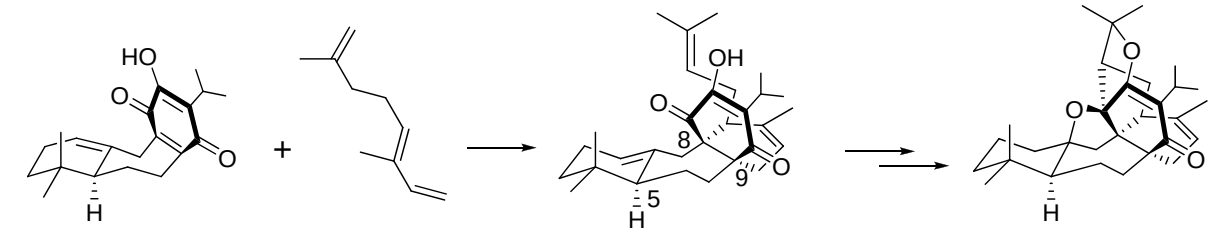
Scheme 2.2.1

As shown in Scheme 2.2.2, the enolate of 3-ethoxy-6,6-dimethylcyclohex-2-en-1-one (**2.2.7**) was alkylated with benzyl bromide **2.2.6** to afford product **2.2.8** in 92% yield. Addition of vinyllithium catalyzed by cerium(III) chloride, followed by isomerization of the resulting tertiary alcohol with 10% aqueous hydrochloric acid, produced a high yield of dienone **2.2.9**. When dienone **2.2.9** was treated with 2.0 equivalents of titanium tetrachloride in methylene chloride at -78 ^{o}C, tricyclic enone **2.2.10** was obtained in 96% yield. This "second generation" synthesis represents a more efficient way to prepare a large amount of enone **2.2.10** and proceeds in 60% overall yield.



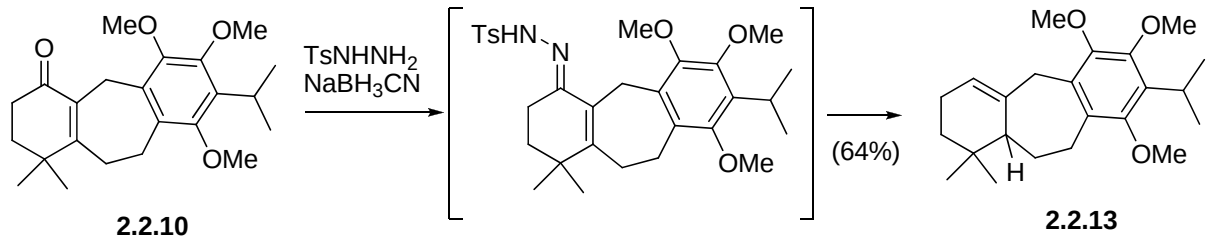
Scheme 2.2.2

Our efforts to synthesize (+)-perovskone necessitated the large-scale preparation of optically active *p*-benzoquinone **2.2.11**. Based on NMR studies, St. Jacques and Vaziri[12] proposed that benzocycloheptanes favor a chair conformation; hence, *p*-benzoquinone **2.2.11** should prefer a cup-shaped conformation with its α-face readily accessible because the β-face is blocked by the methyl group (Scheme 2.2.3). Thus, diene **2.2.12** will add only from the α-face of this dienophile to create the requisite relative configurations at C(8) and C(9). We believed that the single stereocenter at C(5) in *p*-benzoquinone **2.2.11** will control the Diels–Alder reaction and the subsequent transformations.



Scheme 2.2.3

As mentioned earlier, a modified Wolff–Kishner reduction[7] of enone **2.2.10** was used in the synthesis of (±)-perovskone.[5] Unlike the reduction of simple ketones, the Wolff–Kishner reduction of an enone not only removes the carbonyl oxygen but also migrates the double bond. As shown in Scheme 2.2.4, when the tosylhydrazone of enone **2.2.10** is reduced with sodium cyanoborohydride in the presence of an acid, racemic alkene **2.2.13** was produced in 64% yield.

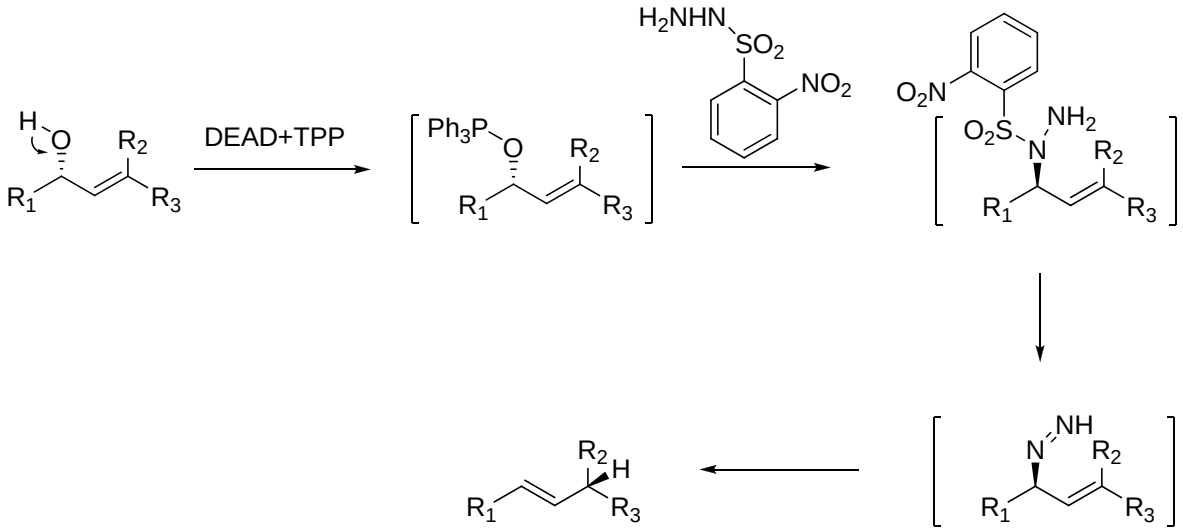


2.2.10 **2.2.13**

Scheme 2.2.4

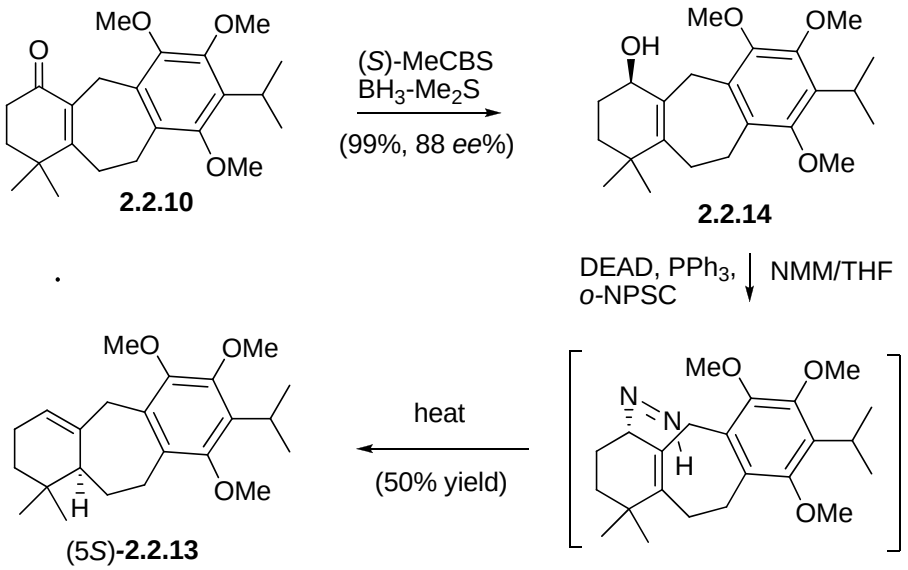
Although a one-pot asymmetric Wolff–Kishner reaction is unknown, Myers and Zheng reported a two-step modification of this transformation.[13] In Myers' variation, an allyl alcohol is treated under Mitsunobu's condition at low temperature to generate a Mitsunobu intermediate with an allylic leaving group (Scheme 2.2.5). The nucleophile, which is *o*-nitrobenzenesulfonylhydrazine (NBSH), is then added to displace the triphenylphosphine oxide. At slightly elevated temperatures, the elimination of *o*-nitrobenzenesulfinic acid occurs to generate a monoalkyl diazene *in situ*; the highly reactive diazene then undergoes an

intramolecular [1,5]-sigmatropic rearrangement to complete the stereoselective allylic transposition.



Sheme 2.2.5

By combining Myers's allylic alcohol transposition with Corey's CBS-chiral reduction,[14] a two-step sequence was developed to control the stereochemistry at C(5) position (Scheme 2.2.6). Firstly, chirality was introduced to C(1) position by using Corey's CBS-protocol to reduce enone **2.2.10** to produce optically active allylic alcohol **2.2.14**. Myer's allylic transposition protocol was then used to transfer the C(1) chirality of **2.2.14** to C(5) and form (5*S*)-**2.2.13**.

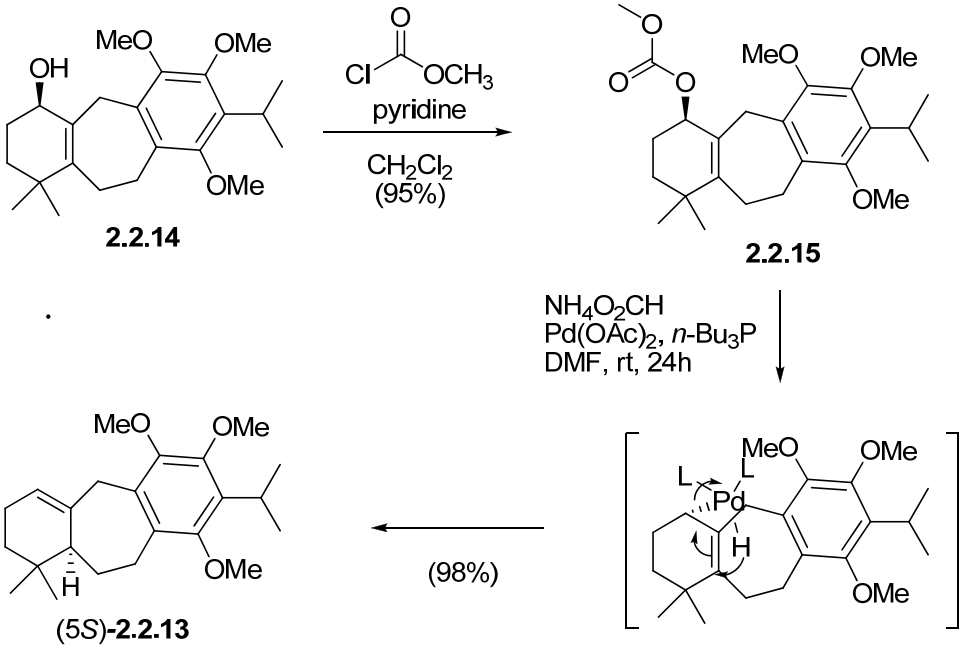


Scheme 2.2.6

The asymmetric reduction of enone **2.2.10** produces optically active **2.2.14** in high yield and good enantioselectivity, which could be improved further by recrystalizatio[15]. Unfortunately, the Myers' transposition averaged at best 50% conversion and could only be carried out on less than 500 mg scale. In our opinion, the steric hinderance of the secondary alcohol was responsible for the low conversion rate of the initial Mitsunobu reaction in this tranposition.

In 2008 Dr. Ryan Phillips, a postdoctoral fellow in our research group, developed a two-step sequence using Pd-π-allyl chemistry which optimized this allylic transposition.[16] As shown in Scheme 2.2.7, optically active alcohol **2.2.14** was first reacted with methyl chloroformate and pyridine to form asymmetric carbonate **2.2.15**. It is known that hydride delivery to a Pd-π-allyl system via ammonium formate is a metal centered process as opposed to a ligand center attack. This means that the hydride is delivered to the π-allyl complex by the Pd instead of coming from the opposite side of the Pd-π-allyl complex and essentially displacing the Pd. Therefore, establishing the carbonate on the β face of the molecule allowed the formation of

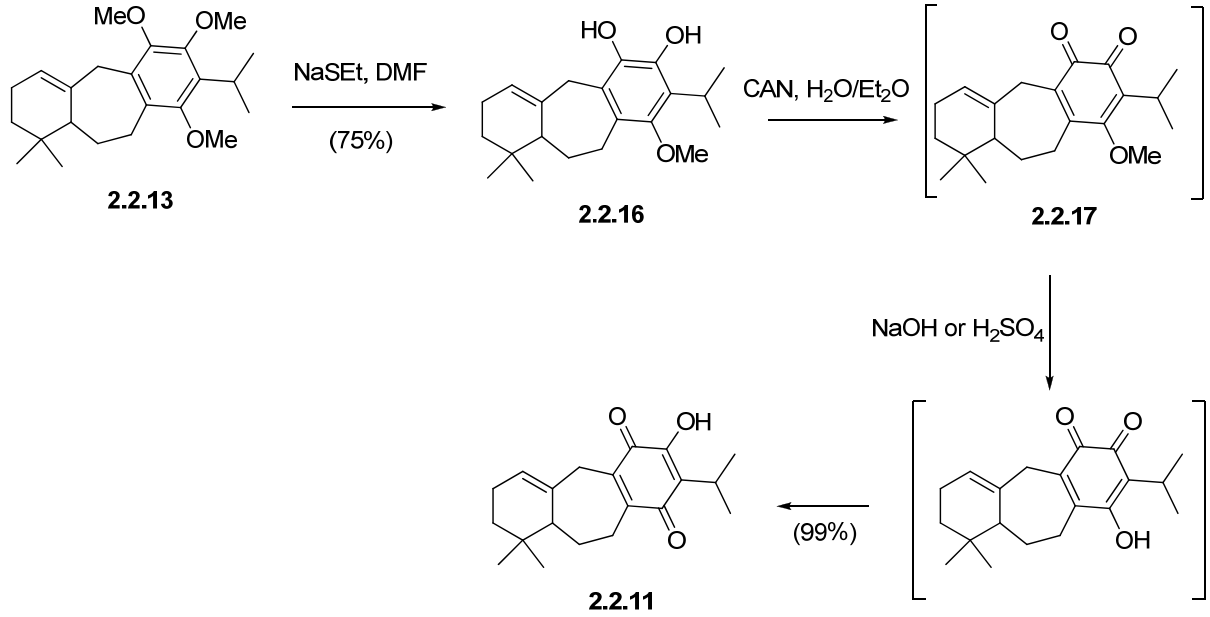
the Pd-π-allyl complex from the α face of the molecule which consequently caused hydride addition to occur from the α face of C(5). A 1:1 ratio of ligand to metal is important in that it allows the reaction to proceed at a reasonable rate and temperature (higher ratios of ligand to metal afforded slower or no reaction). Also it was found that the larger ligand enforced the regiochemistry associated with the metal centered attack of Pd-π-allyl systems. Metal centered attack delivers the nucleophile to the more hindered carbon since the nucleophile is always smaller than the Pd atom with its associated ligand. After extensive optimization, the reaction of carbonate **2.2.15** with 6 equivalents of ammonium formate, 0.2 equivalents of $Pd(OAc)_2$ and 0.2 equivalent of PBu_3 gives optical pure (5*S*)-**2.2.13** in quantitative yield.



Scheme 2.2.7

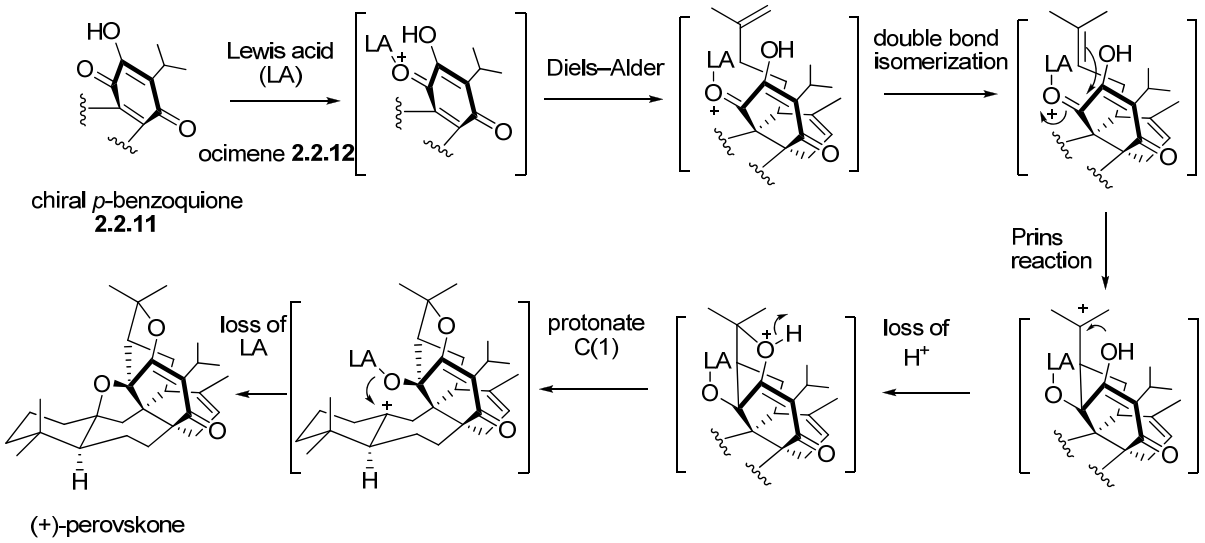
The conversion of (5*S*)-**2.2.13** into optically active quinone **2.2.11** benefits from our racemic synthesis of perovskone[5] and occurs in high yield. Heating **2.2.13** with ethanethiol in DMF deprotected the C(11) and C(12) methyl ether and generates catechol **2.2.16**. Ceric

ammonium nitrate was used to oxidize **2.2.16** to *o*-quinone **2.2.17**, which isomerizes *in situ* into *p*-quinone **2.2.11** upon stirring with acid (Scheme 2.2.8).



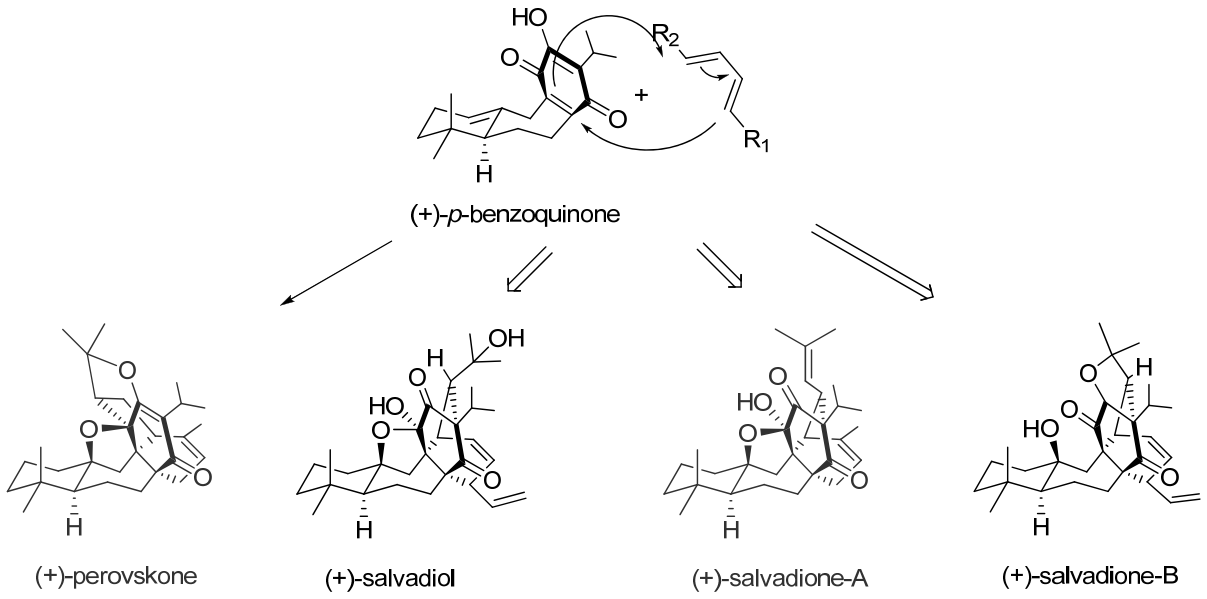
Scheme 2.2.8

Treatment of quinone (*S*)-**2.2.11** with (*E*)-α-ocimene (**2.2.12**) and BF_3-Et_2O at 0 ^oC, followed by warming to 50 ^oC, gives (+)-perovskone in 50% yield. BF_3-Et_2O not only promotes the regio- and stereoselective Diels–Alder reaction, but also causes the isomerization of the terminal double bound of the side chain to a more stable trisubstituted double bond. Thus, an intramolecular Prins reaction forms one of the two tetrahydrofuran rings present in the product. Proton transfer and protonation of the C(1), C(10)-double bond facilitates the final tetrahydrofuran ring closure and produces (+)-perovskone (Scheme 2.2.9).



Scheme 2.2.9

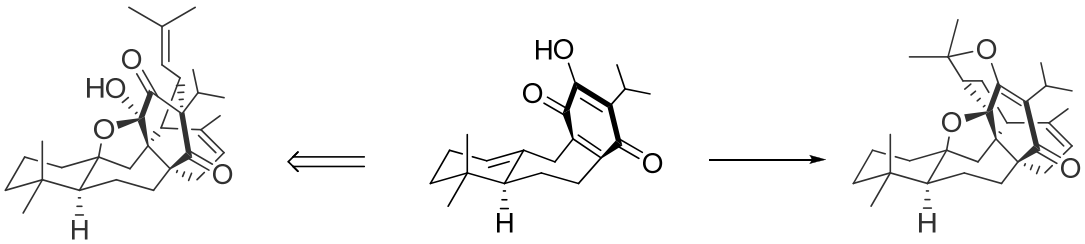
Our synthesis of (+)-perovskone[11] demonstrated an efficient cascade pathway starting from chiral benzoquinone **2.2.11** (with one chiral center) to create four rings, five bonds, and six stereocenters in 50% yield. We believe that chiral quinone **2.2.11** can also serve as a common intermediate for the syntheses of (+)-salvadiol, (+)-salvadione-A and (+)-salvadione-B (Scheme 2.2.10).



Scheme 2.2.10

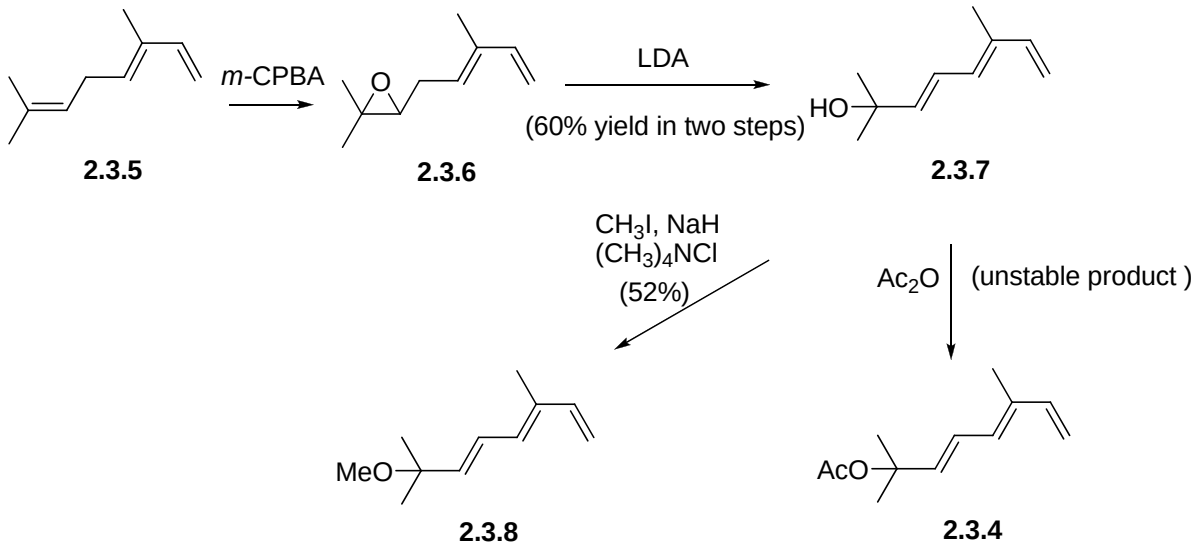
2.3 Concise Synthesis of (+)-Salvadione-A[17]

In 1999, salvadione-A (**2.3.1**) was isolated from *sursaudah* by Ahmad and co-workers, and its structure was established by means of 2D-NMR spectroscopy and X-ray diffraction analysis.[18] Since salvadione-A possesses many of the salient features of perovskone[4,5] (**2.3.2**), we recognized that it could be synthesized from quinone **2.3.3**, a key intermediate in our (+)-perovskone synthesis[11] (Scheme 2.3.1).



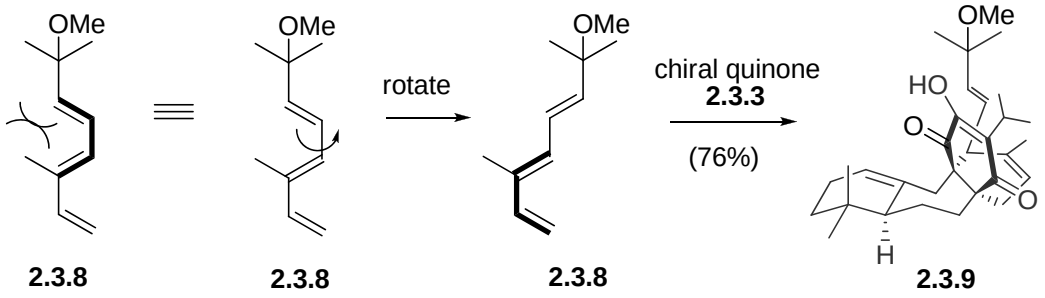
Scheme 2.3.1

Triene **2.3.4** was designed to react with chiral benzoquinone **2.3.3** and was synthesized from *trans*-β-ocimene[19] (**2.3.5**) in three simple steps (Scheme 2.3.2). The reaction of **2.3.5** with one equivalent of *m*-CPBA in cold methylene chloride gave a high yield of epoxide **2.3.6**,[20] which produced octa-3(*E*),5(*E*)-trien-2-ol (**2.3.7**) when treated with excess LDA at 0 °C. Protection of the tertiary alcohol moiety with acidic anhydride gave acetate **2.3.4**. Unfortunately, upon exposure to mild Lewis acid catalysts (even at low temperatures), acetate **2.3.4** underwent rapid decomposition. Alcohol **2.3.7** was heated with sodium hydride and methyl iodide when produced tertiary methyl ether **2.3.8**.



Scheme 2.3.2

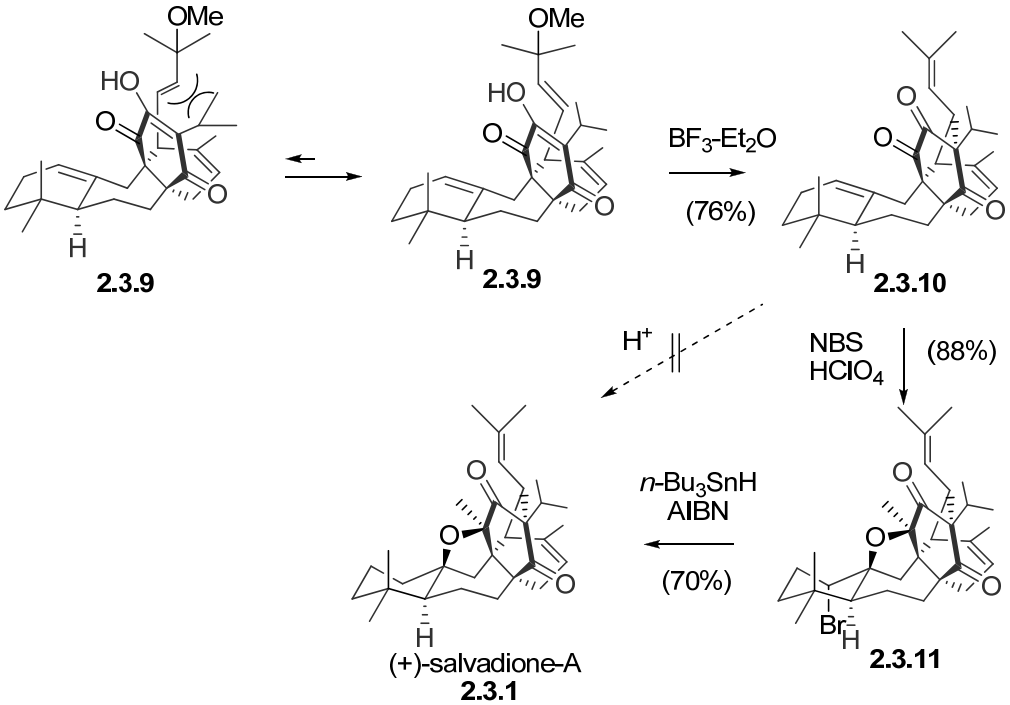
We found that methyl ether **2.3.8** is less prone to elimination and its increased stability allows **2.3.8** to react over a 72-h period with quinone **2.3.3** at 80 °C. Since the presence of a *Z*-methyl substitutent as part of the 3,5-butadiene moiety reduces its reactivity by hindering the likelihood of the s-*cis* form (Scheme 2.3.3), whereas the 5,7-diene readily adopts an s-*cis* conformation, the cycloaddition of **2.3.8** with **2.3.3** produces only adduct **2.3.9** in 76% yield, which has the correct stereochemistry at C(8), C(9), and C(24) as confirmed by X-ray analysis.



Scheme 2.3.3

When adduct **2.3.9** was exposed to BF_3-Et_2O, an S_N2' reaction took place and formed the key C(13),C(25) carbon-carbon bond.[21] The stereochemistry of the newly formed C(25)

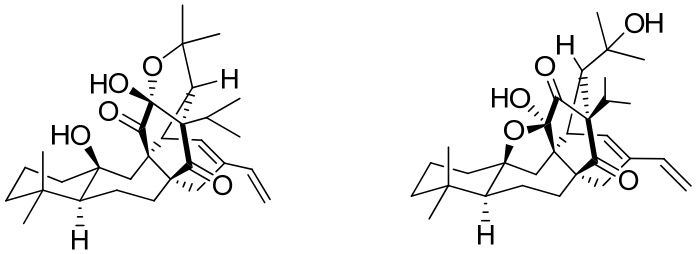
methide is controlled by the conformation of **2.3.9**, in which the non-bonding steric interactions between the C(24) sidechain and the C(13) isopropyl unit causes the less sterically congested conformation to predominate (Scheme 2.3.4). Acidic hydration of the C(1),C(10)-double bond in **2.3.10** was problematic. To overcome this obstacle, **2.3.10** was submitted to acidic NBS[22] conditions, in which the bromonium ion was opened intramolecularly[23] to form intermediate **2.3.11**. Free radical debromination using tri-*n*-butyltinhydride completed a synthesis of (+)-salvadione-A. In summary, (+)-salvadione-A **2.3.1** was synthesized from chiral quinone **2.3.3** in four steps which produced six new chiral centers thanks to the pre-existing C(5) asymmetric center. The regio- and stereospecific Diels–Alder reaction was carried out using thermal conditions without the aid of Lewis acid catalyst. Hydration of the A-ring double bond was accomplished by a bromohydrin formation-debromonation sequence.



Scheme 2.3.4

2.4 Our Efforts to Synthesize (+)-Salvadione-B and (+)-Salvadiol

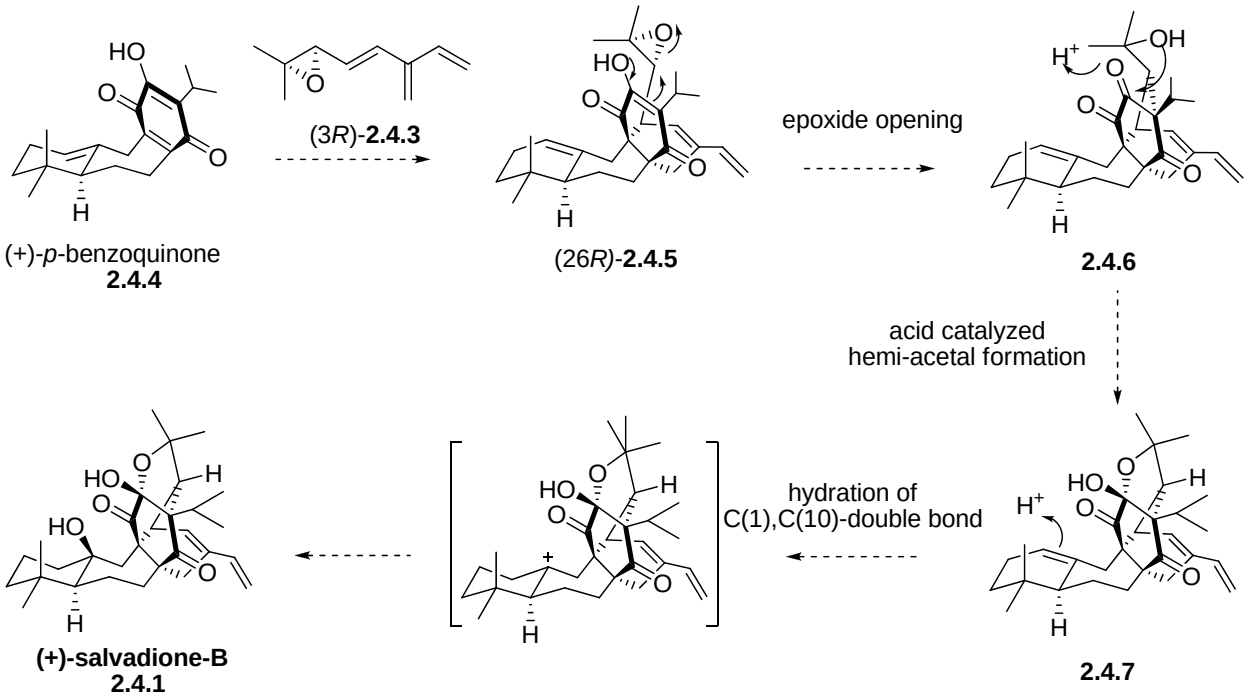
In 1999, salvadione-B (**2.4.1**) was isolated along with salvadione-A from the hexane-soluble extract of *sursaudah* by Ahmad and co-workers.[17] In the same year, salvadiol (**2.4.2**) was isolated from the hexane soluble part of *Salvia bucharica* by the same group and characterized by single-crystal X-ray diffraction (Scheme 2.4.1).[24] Both of these novel triterpenes contain complex arrays of six fused and/or bridged rings and eight asymmetric centers. Moreover, these natural products are isomeric, differing only at a single asymmetric center, which suggest that they can be synthesized from a common intermediate.



Scheme 2.4.1

We envisioned four transformations to achieve a synthesis of salvadione-B, beginning with the Diels–Alder reaction between triene epoxide (3*R*)-**2.4.3** and chiral benzoquinone **2.4.4**[10] (Scheme 2.4.2). As we learned from our (+)-perovskone synthesis,[10] a geminal-dimethyl group on the A-ring caused the quinone **2.4.4** to be cup-shaped which blocks the β-face of the molecule, leaving the α-face available to react with the diene component; thus, three chiral centers, at C(6), C(9) and C(25) are formed with control because of the existing chiral center at C(5). The second transformation proposed is the intramolecular opening of the C(26),C(27) epoxide unit present in Diels–Alder adduct (26*R*)-**2.4.5** by the latent 1,3-diketone moiety[21] hidden within the D-ring.

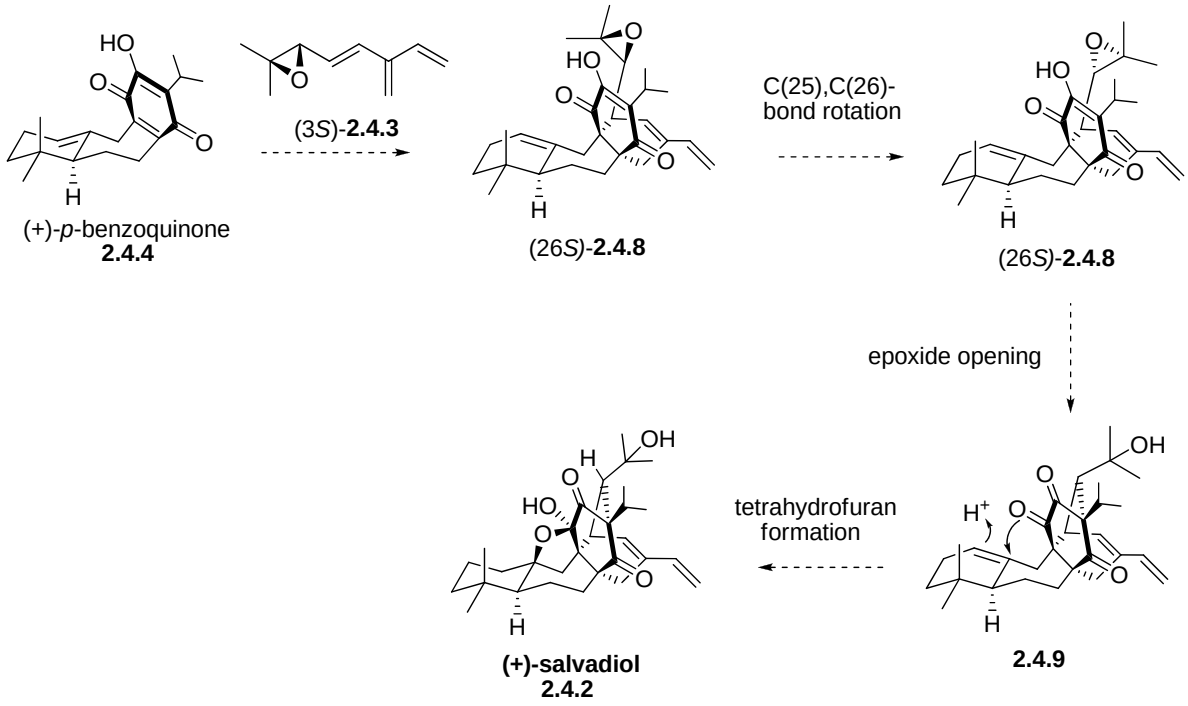
Since epoxides open in an *anti*-fashion, the preset stereochemistry at C(26) will be able to control the outcome of the chirality of the newly formed C(26) methide. When (26*R*)-**2.4.5** is used as the starting material for the epoxide opening reaction, alcohol **2.4.6** should be formed. Moreover, since tertiary alcohol moiety at C(27) in **2.4.6** is close enough to the C(12) carbonyl, cyclic hemi-acetal **2.4.7** is expected to be produced upon weak acid treatment. The last transformation, which would benefit from our previous conditions in perovskone and salvadione-A synthesis, is expected to hydrate the C(1),C(10)-double bond and yield salvadione-B.



Scheme 2.4.2

We also expected to synthesize salvadiol (**2.4.2**) by reacting (*S*)-**2.4.3** with quinone **2.4.4** to produce epoxide (26*S*)-**2.4.8**. Intramolecular epoxide opening of (26*S*)-**2.4.8** should produce **2.4.9**, which has the epimerized C(26) methide comparing with **2.4.6.** While the configuration of C(26) methide precludes the C(27) tertiary alcohol from reacting with C(12) carbonyl group,

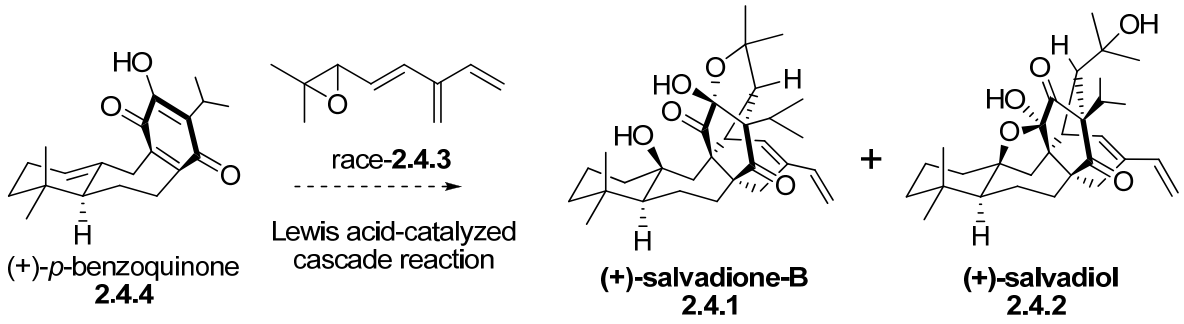
hydration of the C(11) carbonyl will place a hydroxy group right above the C(1),C(10)-double bond. A tetrahydrofuran ring would form easily thereby completing the synthesis of salvadiol (Scheme 2.4.3).



Scheme 2.4.3

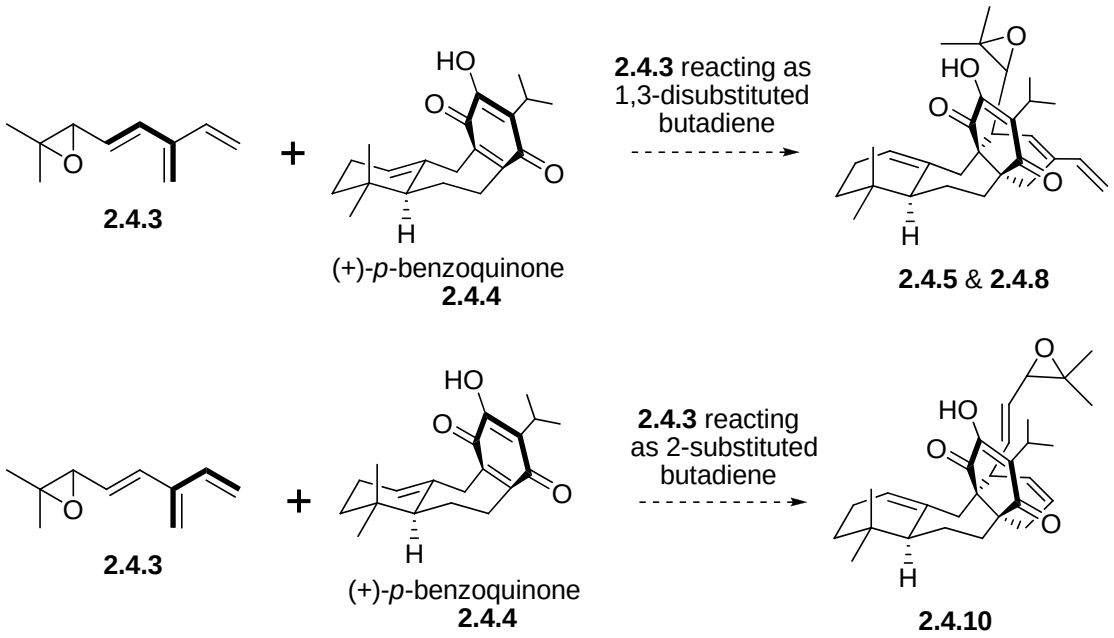
Prior work in our labs suggests that the Diels–Alder reaction, the opening of the epoxide moiety by the latent 1,3-dione[17] and the requisite carbonyl, and double bond hydrations could be achieved under Lewis acid-catalyzed conditions. Suitable conditions would therefore enable us to achieve the above transformations in tandem using a Lewis acid catalyst. If that is the case, the reaction of racemic triene **2.4.3** with quinone **2.4.4** under such optimized conditions would directly produce salvadione-B and salvadiol in a one-pot operation. While this cascade process presented in Scheme 2.4.4 represents a long-term goal, we decided to first gain valuable insight

by synthesizing these complex triterpenoids in a step-wise fashion before advancing a cascade-based strategy.



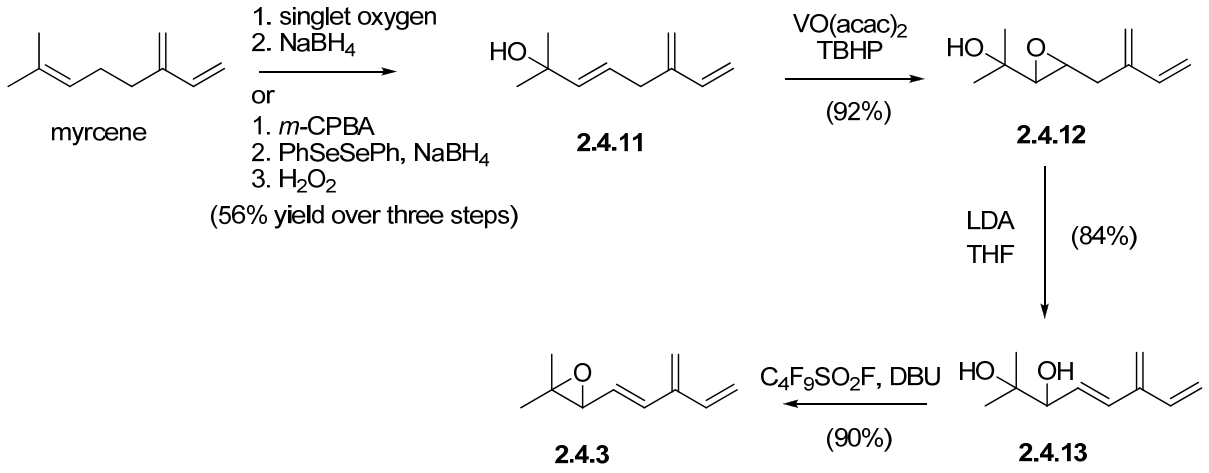
Scheme 2.4.4

The use of conjugated triene **2.4.3** as the diene component raises an interesting, albeit serious, question about the regioselectivity of the Diels–Alder reaction: Will triene **2.4.3** react as a 2-substituted butadiene or will it react as a 1,3-substituted butadiene? Further analysis reveals that both dienes can adopt an s-cisoid conformation, where steric configurations neither rules out, nor favors, either possibility. Based on electronic effects, the more substituted butadiene is assumed to be more reactive. However, an epoxide is an electron-withdrawing substitute which could have a negative effect on the reactivity of the 1,3-disubstituted butadiene (Scheme 2.4.5). These questions make this Diels–Alder reaction difficult to predict and therefore can only be answered experimentally.



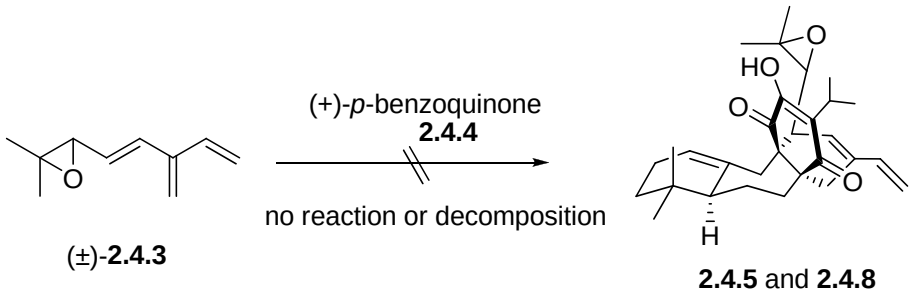
Scheme 2.4.5

An attractive starting material for synthesizing epoxide **2.4.3** is β-myrcene which has the complete carbon skeleton of **2.4.3** and one of the conjugated diene moieties. The reaction of β-myrcene with singlet oxygen followed by *in situ* reduction of the hydroperoxide intermediate with sodium borohydride, provided allylic alcohol **2.4.11** (Scheme 2.4.6). We found that allylic alcohol **2.4.11** could also be prepared on a 5-gram scale by selectively epoxidizing myrcene with *m*-CPBA, followed by opening of the trisubstituted epoxide with sodium phenyl selenide and then eliminating the selenoxide intermediate.[25] Sharpless directed-epoxidation[26] of **2.4.11** produced both enantiomers of epoxide **2.4.12**, which upon treatment with LDA at 0 ^{o}C, gave diol **2.4.13** in 70% yield over two steps. It is noteworthy that the stereochemistry of C(3) secondary alcohol can be controlled by enantioselective Sharpless epoxidation. Although traditional means of converting the diol **2.4.13** into triene epoxide **2.4.3** was failed [i.e., Ms-, Ts-, or Mitsunobu reactions], the perfluorosulfonyl fluoride reagent[27] gave triene epoxide **2.4.3** in 90% yield.

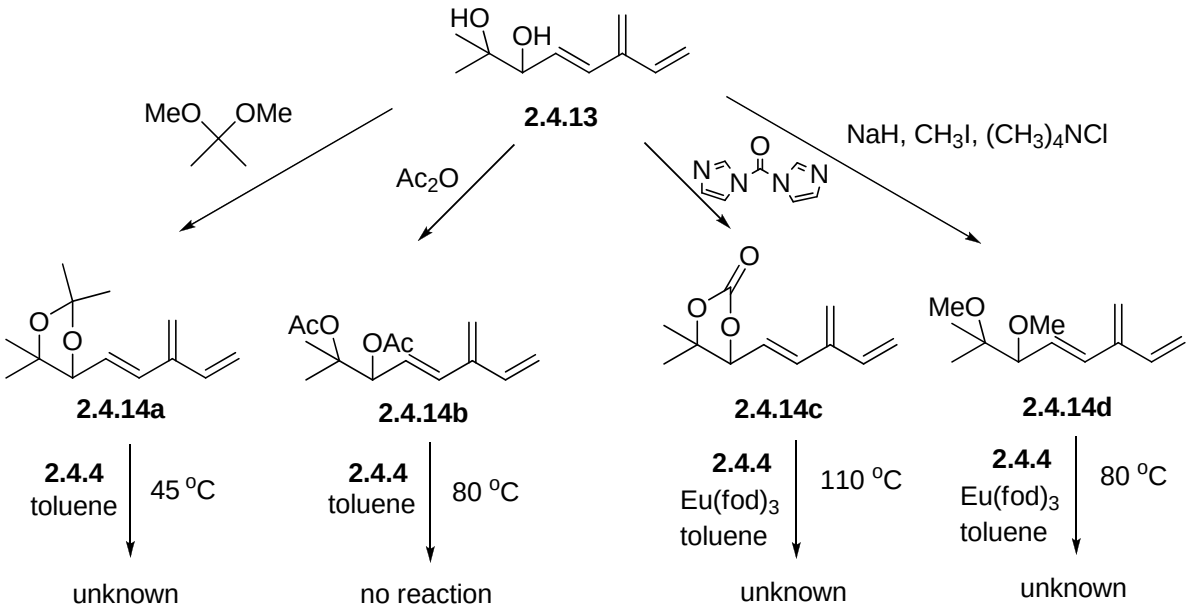


Scheme 2.4.6

Unfortunately, triene epoxide **2.4.3** failed to undergo thermal or Lewis acid-catalyzed Diels–Alder reaction with quinone **2.4.4** (Scheme 2.4.7). Several derivatives of diol **2.4.13** were prepared but none of these substances reacted with quinone **2.4.4** (Scheme 2.4.8).

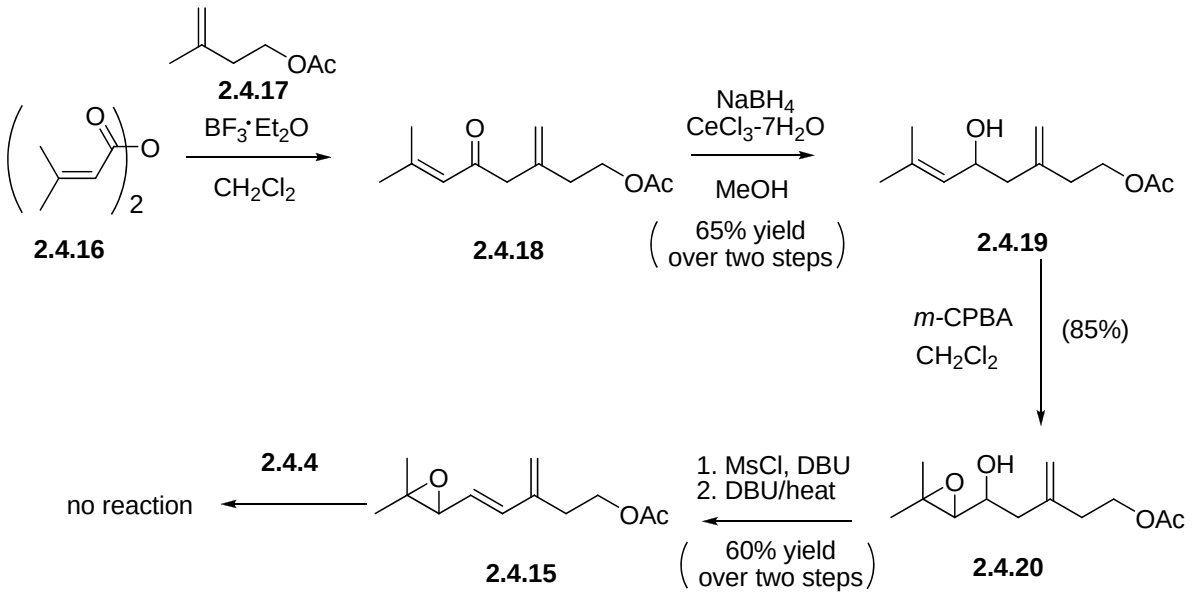


Scheme 2.4.7



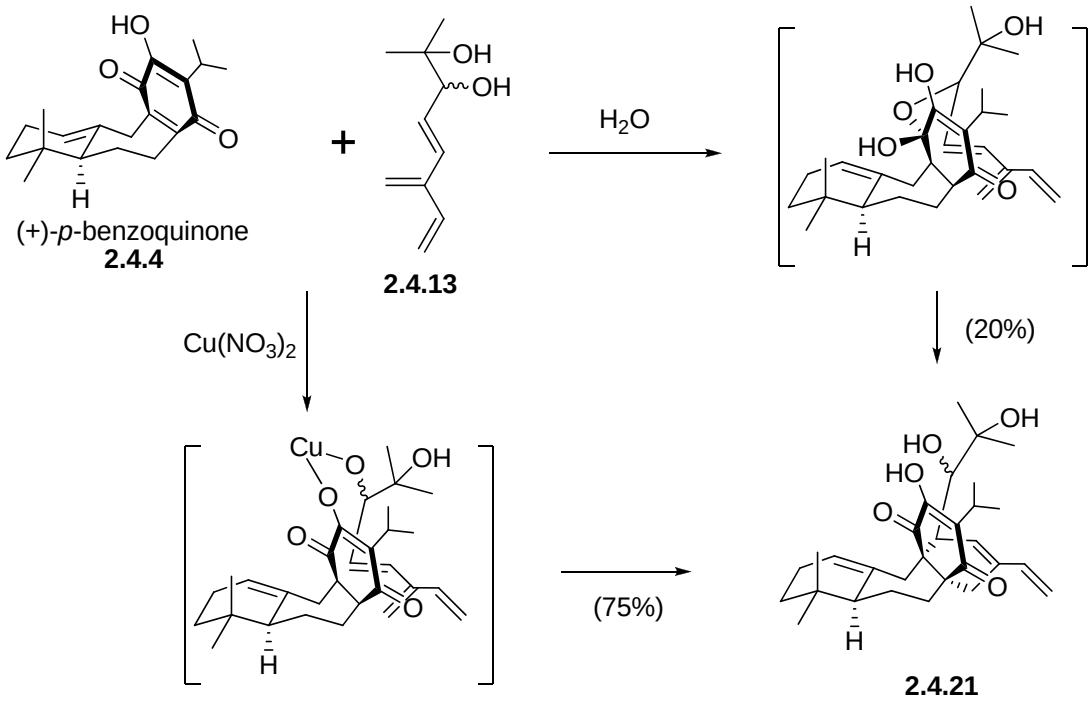
Scheme 2.4.8

Instead of using a triene in the Diels–Alder reaction with quinone **2.4.4**, we decided to use an appropriately substituted butadiene thereby simplifying this transformation. In particular, diene epoxide **2.4.15** was designed to have the terminal double bond masked as acetate, which can be eliminated later in the synthesis. As shown in Scheme 2.4.9, diene epoxide **2.4.15** was prepared in five steps starting from senecioic anhydride **2.4.16**. Condensing anhydride **2.4.16** with 3-methylbut-3-en-l-y1 acetate (**2.4.17**) produced ketone **2.4.18** as the major product.[28] Luche reduction of **2.4.18**, followed by directed epoxidation, generated epoxide **2.4.20**. Dehydration of the secondary alcohol moiety on **2.4.20** was achieved by a mesylation/elimination sequence, to produce diene epoxide **2.4.15**. Unfortunately, **2.4.15** failed to undergo thermal or Lewis acid-catalyzed Diels–Alder reaction with quinone **2.4.4**.



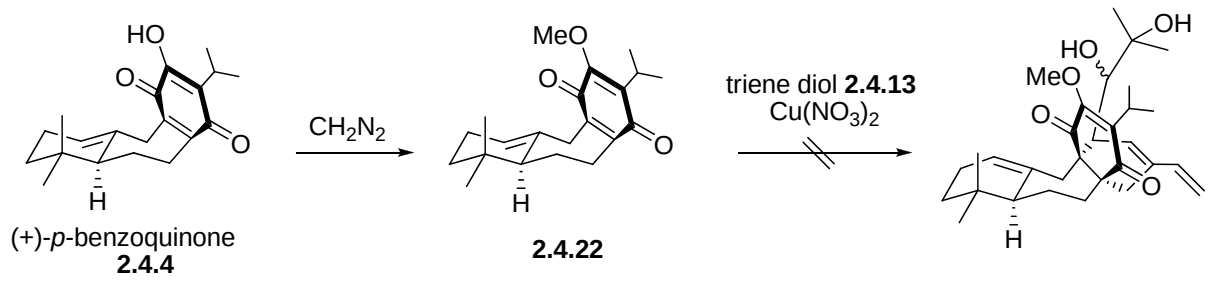
Scheme 2.4.9

Because both triene epoxide **2.4.3** and diene acetate **2.4.15** failed to react with quinone **2.4.4**, we concluded that the electron withdrawing effect of the epoxide moiety must be preventing the Diels–Alder reaction from taking place. This conclusion prompted us to re-evaluate the Diels–Alder reaction between the unprotected triene diol **2.4.13** and quinone **2.4.4**. As shown in Scheme 2.4.10, when water was used as the reaction medium, a 20% yield of the desired Diels–Alder adduct **2.4.21** was isolated, presumably through the *in situ* generation of hemi-acetal intermediate followed by intramolecular cycloaddition. This aqueous Diels–Alder reaction could not be optimized further primarily because of the poor solubility of quinone **2.4.4**. Surprisingly, the use of weak bases, such as sodium bicarbonate or sodium hydroxide to solubilize the quinone[29] did not improve the yield of the cycloaddition. Finally, using copper(II) nitrate in trifluorothanol[30] to tether the dienophile and the triene diol together produced **2.4.21** rapidly in 85% yield.



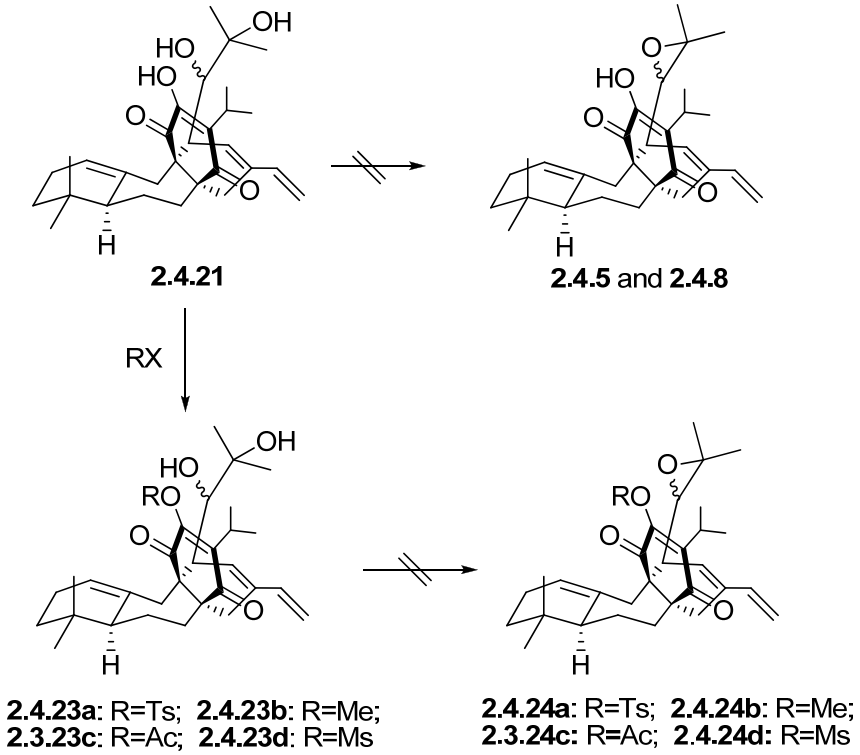
Scheme 2.4.10

We recognized that the C(12) hydroxy group on quinone **2.4.4** is essential for the Diels–Alder reaction to take place regioselectively. Protecting this hydroxy group as a methyl ether resulted in quinone **2.4.22**, which did not react in Diels–Alder fashion with triene epoxide **2.4.13** and copper(II) nitrate in trifluoroethanol (Scheme 2.4.11). This observation further confirmed that the chelation of the C(12) hydroxy group on quinone **2.4.4** and a hydroxy group on the triene changes an intermolecular Diels–Alder reaction into an intramolecular process, which occurs in good yield.



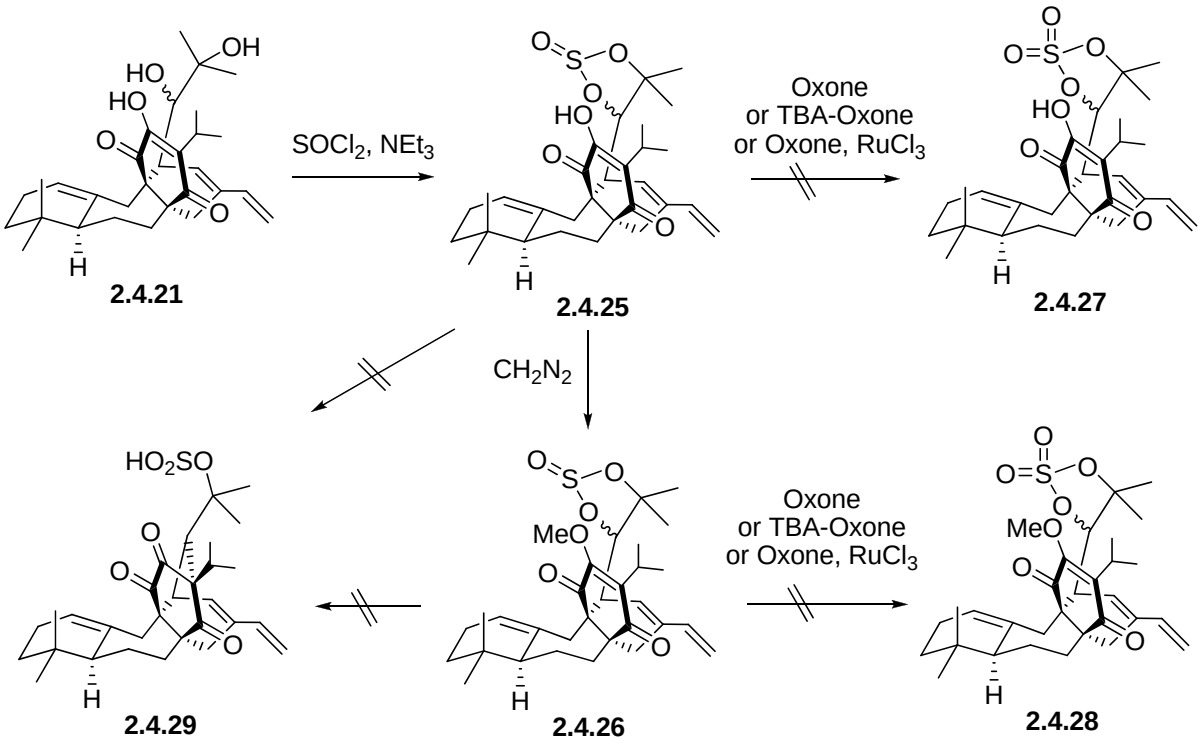
Scheme 2.4.11

With Diels–Alder adduct **2.4.21** in hand, extensive efforts were made to synthesize epoxide **2.4.5** and **2.4.8**. To our disappointment, diol **2.4.21** did not behave as expected because the hydroxy group at C(12) is the most acidic one. Various intermediates having the C(12)-hydroxy group protected were synthesized (**2.4.23a-d**); however, these substances did not permit the formation of epoxides **2.4.24a-d** (Scheme 2.4.12).



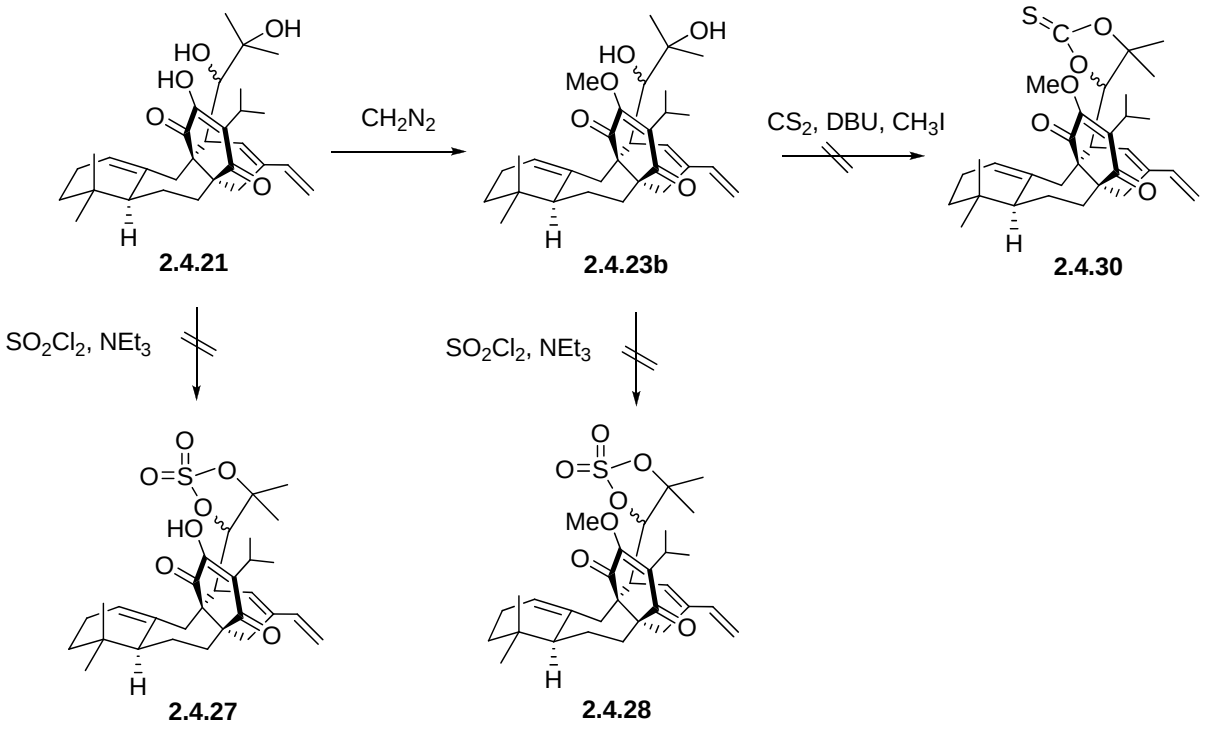
Scheme 2.4.12

Treating Diels–Alder adduct **2.4.21** with thionyl chloride and base produced sulfite **2.4.25**. However, neither **2.4.25** nor the C(12)-protected sulfite **2.4.26** could be oxidized to give sulfate **2.4.27** or **2.4.28** (Scheme 2.4.13). Attempts to intramolecularly open the sulfite *in situ* to generate epoxide **2.4.29** failed.



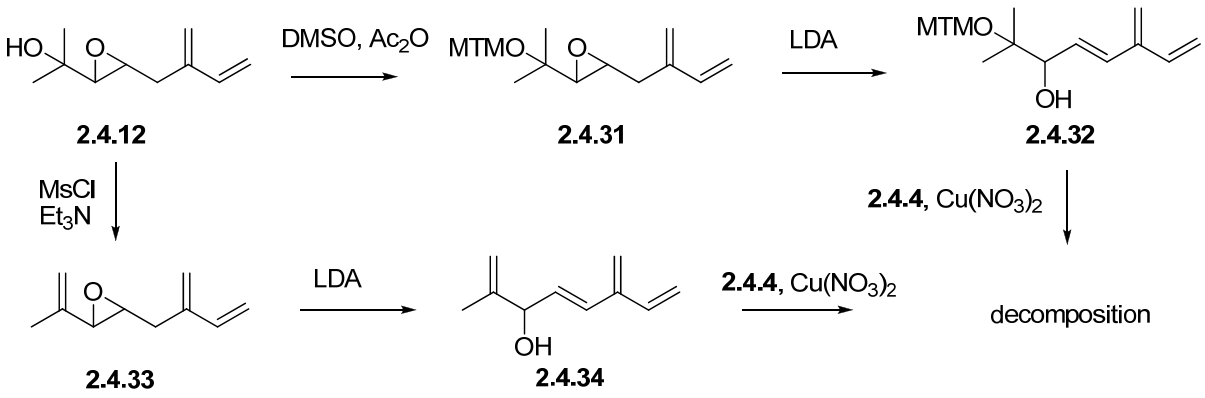
Scheme 2.4.13

Treating adduct **2.4.21** or its C(12)-protected derivative **2.4.23b** to sulfuryl dichloride in the presence of triethylamine resulted in decomposition (Scheme 2.4.14). We tried to convert the diol moiety in **2.4.23b** to a double bond using a Corey–Winter olefination,[31] however thiocarbonate **2.4.30**, the initial intermediate, did not form.



Scheme 2.4.14

As shown in Scheme 2.4.15, other Diels–Alder dienes, such as **2.4.31** and **2.4.32**, were synthesized starting from intermediate **2.4.12** to differentiate the C(26) secondary hydroxy moiety from the C(27) tertiary hydroxy moiety. Unfortunately, these substances failed to react with quinone **2.4.4**.

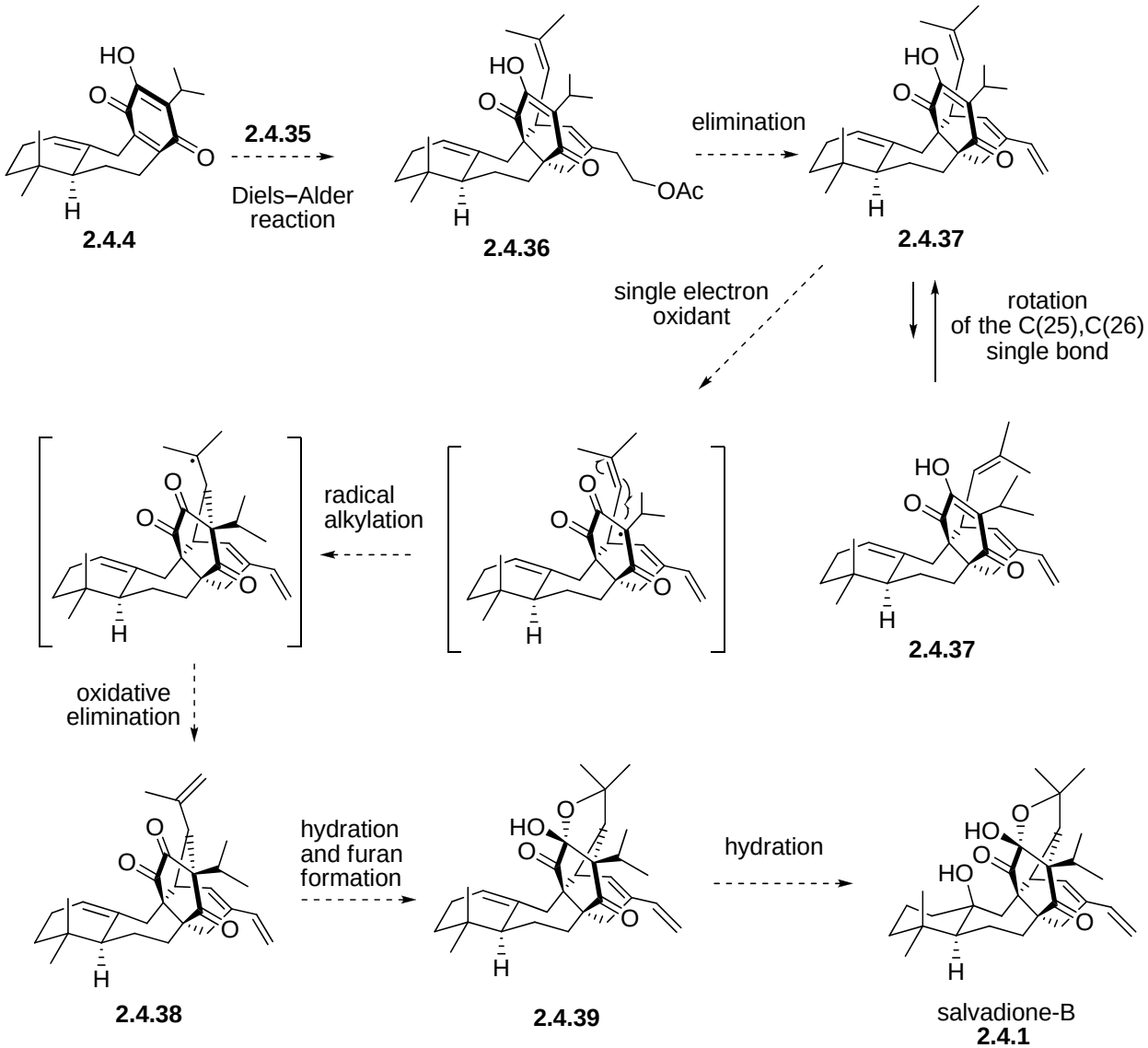


Scheme 2.4.15

As a short summary, in our original synthetic plan to salvadione-B and salvadiol, we proposed that the intramolecular S_N2 opening of the C(26),C(27) epoxide unit (or its equivalent, *i.e.*, a cyclic sulfite, a cyclic sulfate, or a cyclic thiocarbonate) present in the Diels–Alder adduct by the latent C(12),C(14)–diketone moiety present within the C-ring would form the key C(13),C(26) carbon-carbon bond and control the stereochemistry of the newly formed chiral centers. Experimentally, however, the electron withdrawing nature of the epoxide moiety reduced the reactivity of the diene side chain. Diels–Alder adduct **2.4.21** was regioselectively generated from the triene diol **2.4.13** and quinone **2.4.4** in high yield. Unfortunately, efforts to convert the C(26) hydroxy group into a good leaving group and displace it with the 1,3-diketone moiety in C-ring were not successful. Reluctantly, we concluded that a new way was needed to form the C(13),C(26)-bond.

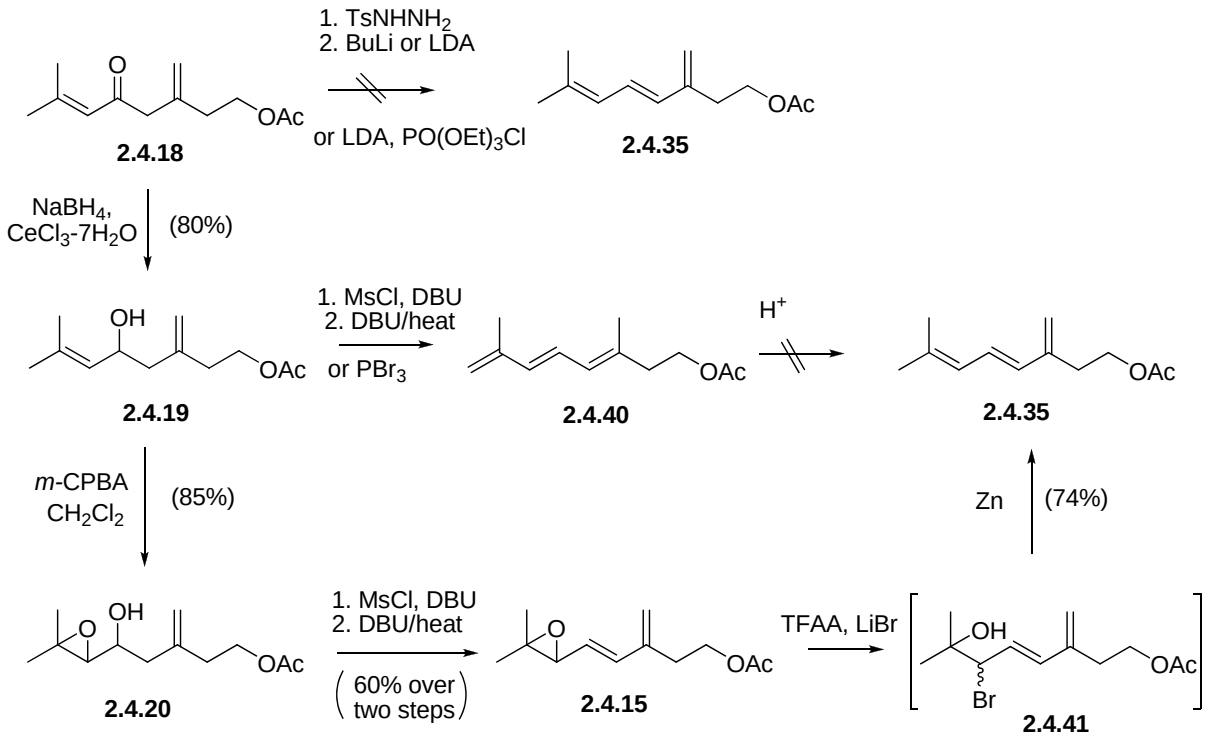
Oxidative radical alkylations have been well-known for constructing polycyclic skeletons.[32] Our revised synthetic plan towards salvadione-B and salvadiol features an oxidative radical alkylation to form the key C(13),C(26)-bond. As shown in Scheme 2.4.16, triene **2.4.35** was designed to react with quinone **2.4.4** to give Diels–Alder adduct **2.4.36**. After converting the primary acetate to a terminal double bond, oxidative radical formation was expected to take place at C(13) position by treating enol **2.4.37** with single electron oxidants. With the knowledge gained from our salvadione-A synthesis, this radical should undergo an intramolecular alkylation with the C(26),C(27)-olefin moiety to form the desired C(13),C(26)-bond. The stereochemistry of the newly formed C(26) methine is controlled by the conformation of **2.4.37**, in which the non-bonding steric interactions between the C(24) side chain and the C(13) isopropyl unit causes

the less sterically congested conformation to predominate. Quenching the resulting radical at C(27) by oxidative elimination should give trione **2.4.38**, which has all of the carbon skeleton and the requisite stereochemistry at C(26) for salvadione-B. Hydration of C(12) ketone moiety on **2.4.38** should promote tetrahydrofuran formation with the C(27),C(28)-double bond to give **2.4.39**, which would finish a synthesis of salvadione-B upon hydration of the C(1),C(10)-double bond.



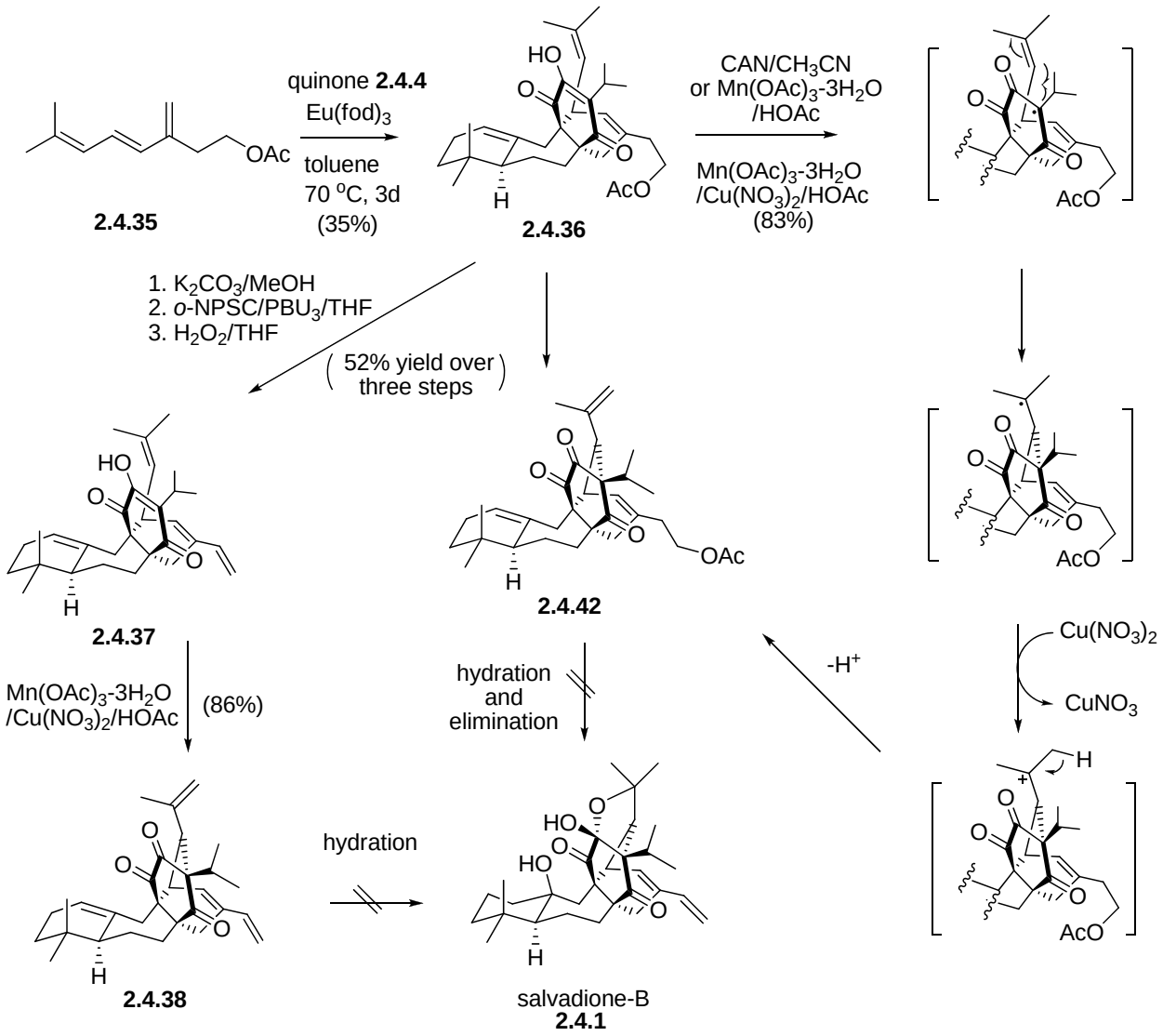
Scheme 2.4.16

Several synthetic routes were explored to synthesize triene **2.4.35** (Scheme 2.4.17). Surprisingly, a Bamford–Stevens reaction of enone **2.4.18** failed to directly produce **2.4.35**. Allylic alcohol **2.4.19**, which was generated by the Luche reduction of **2.4.18**, resulted in kinetic product **2.4.40** under several elimination conditions. Stirring **2.4.40** with mineral acid failed to isomerize the conjugated double bonds and produce the desired triene **2.4.35**. Dehydration of secondary alcohol moiety on **2.4.20** was achieved by directed epoxidation followed by mesylation-elemination sequence, resulting diene epoxide **2.4.15**. Finally, opening the epoxide moiety on **2.4.15** upon treatment of triflic anhydride and lithium bromide in DMF resulted in bromohydrin **2.4.41**, which could be reduced by zinc powder without purification to give triene **2.4.35**.



Scheme 2.4.17

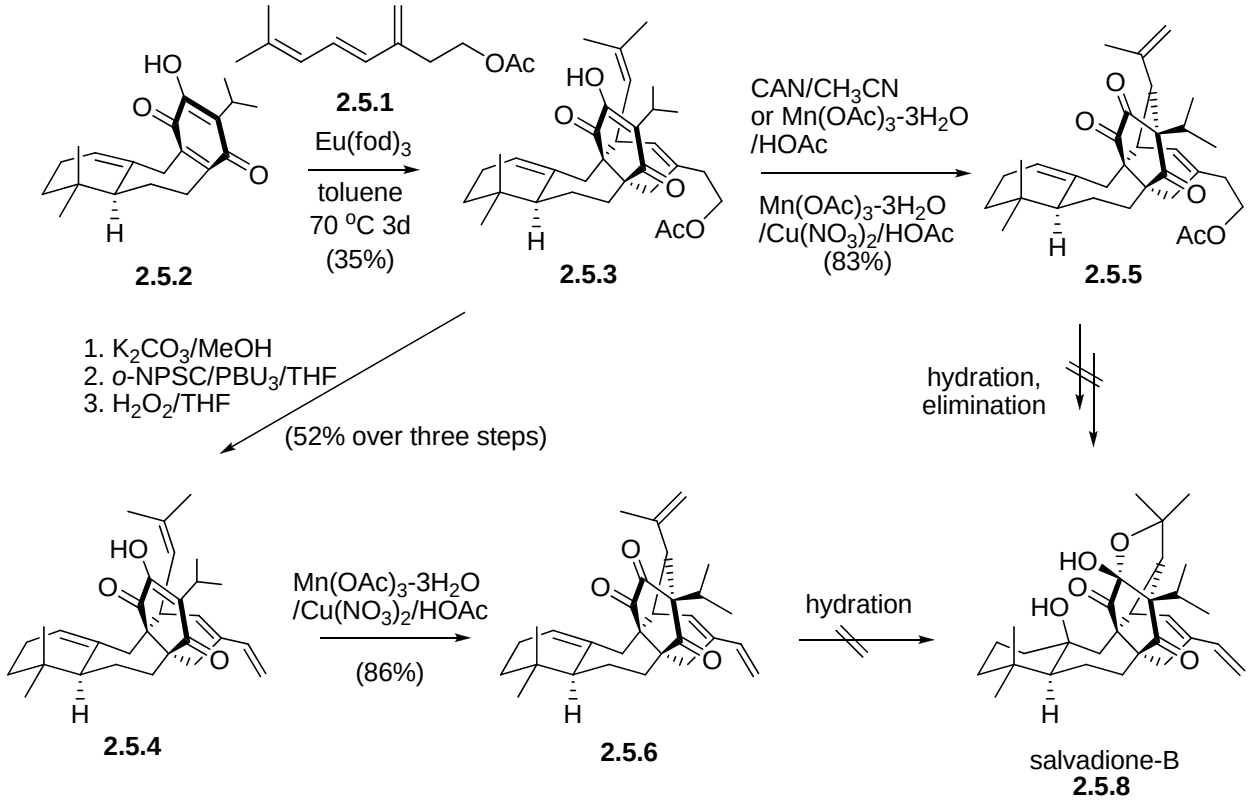
Several conditions for the Diels–Alder reaction of **2.4.35** with quinone **2.4.4** were explored. Heating with catalytic amounts of $Eu(fod)_3$ at 80 ^oC for 3 days produced the desired adduct **2.4.36** as the major product in 35% yield (Scheme 2.4.18). Submitting **2.4.36** to single electron oxidants generated trione **2.4.42**. Among the three oxidative radical alkylation conditions tested, the combination of manganese(III) acetate and copper(II) nitrate in acetic acid gave the highest yield of **2.4.42** because the copper(II) nitrate can promote the oxidative elimination of tertiary radical at C(27) to form *in situ* a tertiary carbocation which loses an α-proton to generate C(27),C(28)-double bond (Scheme 2.4.18).[33] Excited about this result, a three-step sequence was carried out to eliminate the primary acetate in **2.4.36** and generate **2.4.37**. Although deprotection of the acetate was almost quantitative, the subsequent Grieco olefination only gave moderate yield, possibly caused by the acidity of the C(12) vinylogous acid moiety. Repeating the radical alkylation conditions on **2.4.37** generated trione **2.4.38** in high yield. Several double bond hydration reactions were investigated to selectively hydrate the C(1),C(10)- and C(26),C(27)-double bonds. Unfortunately, neither **2.4.42** nor **2.4.38** underwent hydration dictating that a new strategy was needed to achieve hydration.


quinone 2.4.4
Eu(fod)3
toluene
70 °C, 3d
(35%)
2.4.35
2.4.36
CAN/CH3CN
or Mn(OAc)3-3H2O
/HOAc
Mn(OAc)3-3H2O
/Cu(NO3)2/HOAc
(83%)
1. K2CO3/MeOH
2. o-NPSC/PBU3/THF
3. H2O2/THF
52% yield over
three steps
2.4.37
2.4.42
Mn(OAc)3-3H2O
/Cu(NO3)2/HOAc
(86%)
hydration
and
elimination
-H+
Cu(NO3)2
CuNO3
hydration
2.4.38
salvadione-B
2.4.1

Scheme 2.4.18

2.5 Concise Synthesis of (+)-Salvadione-B

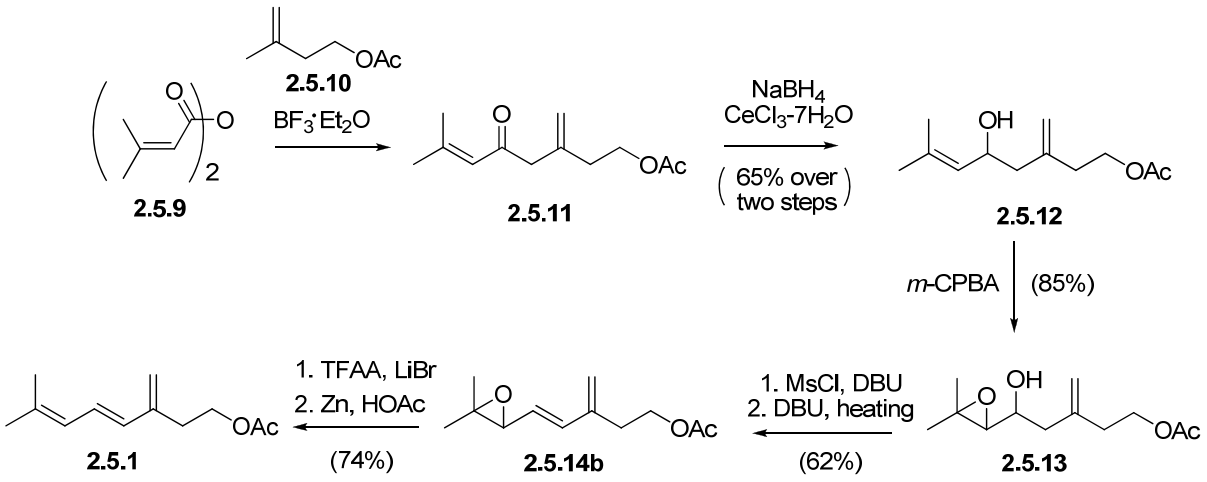
As discussed in the last section, in our second generation synthetic route toward salvadione-B, we learned that: (1) triene **2.5.1** is able to react with *p*-benzoquinone **2.5.2** to produce Diels–Alder adduct **2.5.3** in moderate yield; (2) the primary acetate in **2.5.3** can be transformed into a terminal olefin through a three-step deprotection-displacement-oxidative elimination sequence to yield **2.5.4**; (3) both **2.5.4** and **2.5.3** undergo oxidative radical cyclization to form the key C(13),C(26)-bond; (4) the cyclization products **2.5.5** and **2.5.6** have the requisite stereochemistry at C(26) in salvadione-B; and (5) problems arose when we tried to selectively hydrate the C(1),C(10)- and the C(26),C(27)-double bonds (Scheme 2.5.1).



Scheme 2.5.1

In order to improve our synthetic route for salvadione-B, we needed to optimize the synthesis of triene **2.5.1**, its reaction with quinone **2.5.2** and determine conditions to selectively hydrate the C(1),C(10)-double bond to form the furan ring between C(12) ketone and C(26) carbon. After we achieved a stepwise synthesis of (+)-salvadione-B, we also wanted to develop a cascade-based synthesis of (+)-salvadione-B.

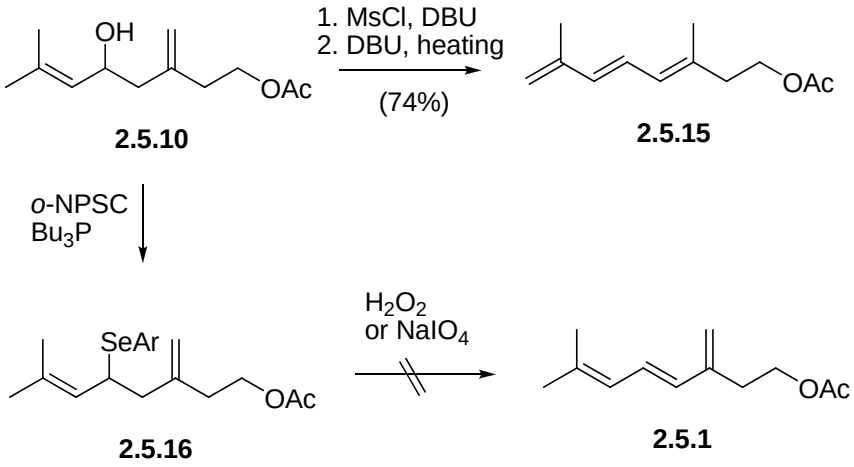
As shown in Scheme 2.5.2, triene **2.5.1** can be synthesized from senecioic anhydride (**2.5.7**) in seven steps; incredibly, six of these steps are involved to introduce the C(4),C(5)-double bond. Among these six steps, protecting the C(6),C(7)-double bond as an epoxide and then deoxygenating the epoxide to regenerate the olefin moiety requires three steps because the direct elimination of allylic alcohol **2.5.12** gives undesired elimination product **2.5.15**.



Scheme 2.5.2

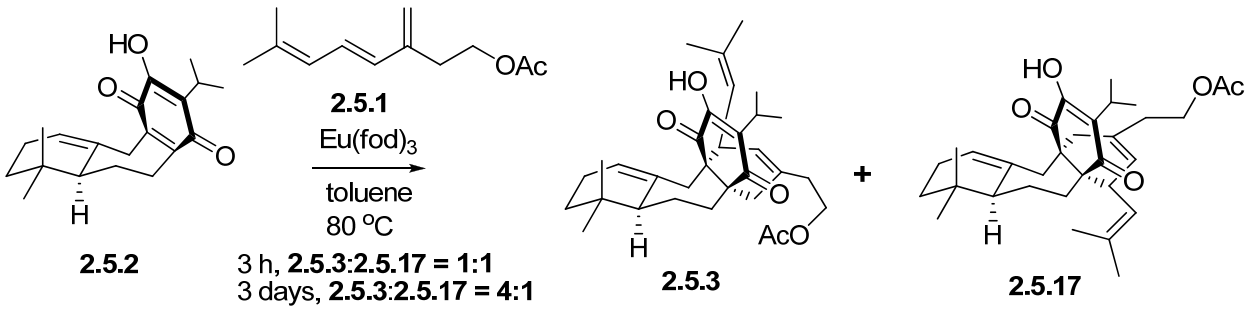
Since selenoxides are known to give *syn*-elimination products, we converted allylic alcohol **2.5.12** into selenide **2.5.16** by treating it with *n*-tributylphosphine and *o*-nitrophenyl

selenocyanate (Scheme 2.5.3). Unfortunately, treating **2.5.16** with oxidants resulted in decomposition or failed to react.



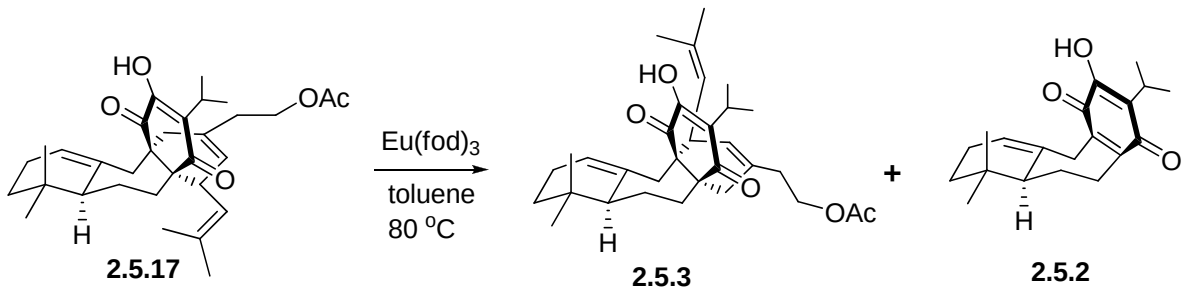
Scheme 2.5.3

The Diels–Alder reaction between triene **2.5.1** and benzoquinone **2.5.2** has been thoroughly studied. When the reaction was carried out in toluene at 80 ^{o}C for 3 hours with a catalytic amount of $Eu(fod)_3$, two major products were produced along with unreacted quinone and triene; the two products were separated and characterized by proton and carbon NMR. The less polar product was identified as the desired Diels–Alder adduct **2.5.3** while the more polar product, which was found to have similar spectra and same molecular weight to the desired adduct, was identified as the regioisomer **2.5.17**. The rate of the Diels-Alder reaction slowed down after the mixture was heated over six hours and took up to 3 days to consume all of triene **2.5.1**. The ratio of **2.5.3** to **2.5.17** increased from 1:1 to about 4:1 as the reaction went on. Triene **2.5.1** was found to react at a faster rate than quinone **2.5.2**, which caused about 20% of **2.5.2** to remain unreacted at the end of the reaction when four equivalents of **2.5.1** was used (Scheme 2.5.4) We believe that under thermal conditions employed, triene **2.5.1** polymerizes.



Scheme 2.5.4

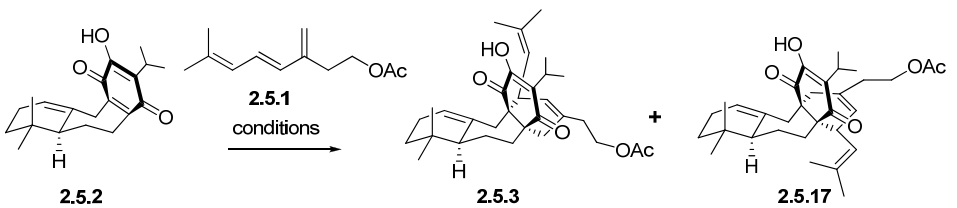
The decrease in reaction rates and the ratio change of the products could also be explained by a retro-Diels–Alder reaction of the cycloadducts. The more cycloaddition adduct formed, the faster its retro-Diels–Alder reaction would be; and thus, the overall reaction rate would slow down. Moreover, the increase of the ratio of the desired cycloadduct to its regioisomer is possibly because the desired Diels–Alder adduct undergoes the retro-Diels–Alder reaction more slowly than its regioisomer. To confirm this hypothesis, pure regioisomer **2.5.17** was submitted to the same conditions of the Diels–Alder reaction (Scheme 2.5.5). After six hours of heating, the desired isomer **2.4.3**, triene **2.4.1** and quinone **2.4.2** were identified from the reaction mixture by TLC analysis. Prolonged heating of the mixture gave similar result as starting with pure diene **2.4.1** and benzoquinone **2.4.2**.



Scheme 2.5.5

It was observed that concentrated diene **2.5.1** decomposed at room temperature after three days but required two weeks to decompose at -30 ^{o}C. Under prolonged heating, decomposition of diene **2.5.1** necessitated that more than one equivalent of diene was needed to drive the reaction to completion.

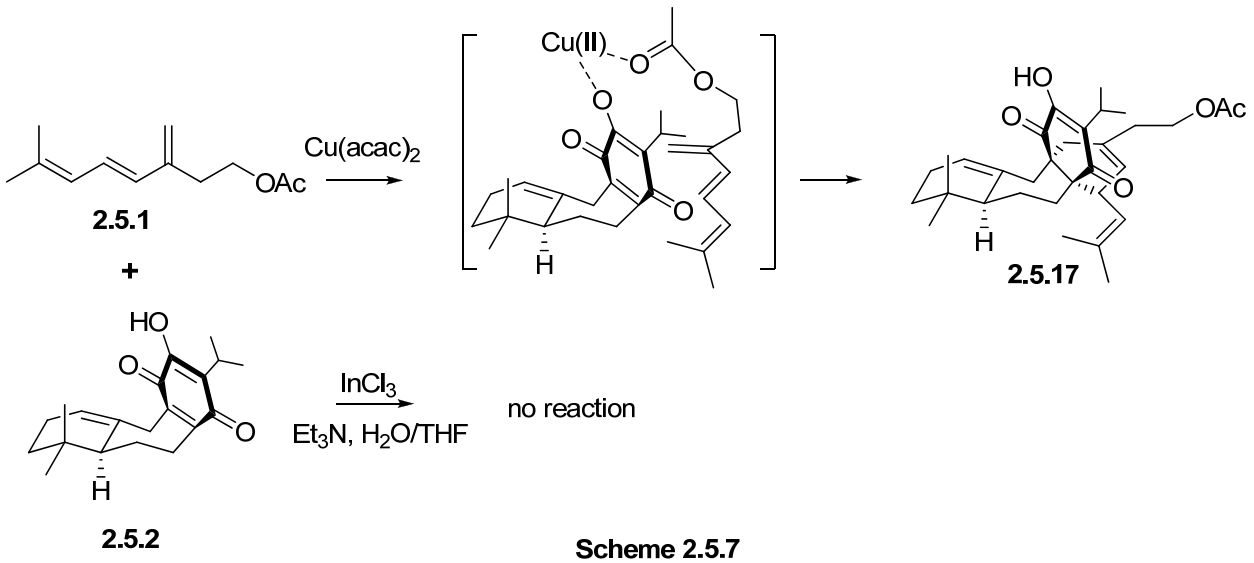
Lowering the reaction temperature and using stronger Lewis acids were investigated to optimize the Diels–Alder reaction between **2.5.1** and **2.5.2**. We found that strong Lewis acids ($AlCl_3$ or BF_3-Et_2O) in dichloromethane caused decomposition of diene **2.5.1** (Scheme 2.6.6), whereas milder Lewis acids ($MgBr_2$, $ZnBr_2$ or $FeCl_3$) in dichloromethane resulted in decomposition at 0 ^{o}C. When $Cu(acac)_2$ was used as a catalyst in dichloromethane at 0 ^{o}C, diene **2.5.1** reacted rapidly with quinone **2.5.2**, but only produced undesired regioisomer **2.5.17**. Water has been known for its ability to promote Diels–Alder reactions. Several water soluble Lewis acids were used to catalyze the desired Diels–Alder reaction in water. For example, $InCl_3$ in water at 50 ^{o}C slowed down the decomposition rate of diene **2.5.1** and only 2 equivalents of **2.5.1** were needed to drive the reaction to completion. This reaction took two weeks to complete due to the poor solubility of quinone **2.5.2** in water. A mixture of THF/H_2O (25%) increased the quinone's solubility and shortened the reaction time to 3 days. Unfortunately, the retro-Diels–Alder reaction of the undesired adduct **2.5.17** was also slowed down so that both **2.5.17** and **2.5.3** were produced in the equal amounts. Other water compatible Lewis acids, such as $Eu(fod)_3$, $GaCl_3$, $SmBr_2$, $Yb(OTf)_3$ and $Sc(OTf)_3$, were tried and found to have slower reaction rates than $InCl_3$. Heating the starting materials in a THF/H_2O (20%) mixture with $Eu(fod)_3$ as catalyst produces a 2:1 mixture of **2.5.3** to **2.5.17** after being heated for seven days at 50 ^{o}C.



Lewis acid	solvent	reaction temperature	reaction time	**2.5.3** : **2.5.17**
BF_3-Et_2O or $AlCl_3$	CH_2Cl_2	-78 °C - 0 °C	0.5 h	**2.5.1** decomposed
$FeCl_3$ or $ZnBr_2$ or $MgBr_2$	CH_2Cl_2	0 °C	0.5 h	**2.5.1** decomposed
$Cu(acac)_2$	CH_2Cl_2	0 °C	0.5 h	0 : 1
$InCl_3$	H_2O/THF	50 °C	3 days	1 : 1
$GaCl_3$ or $SmBr_2$	H_2O/THF	50 °C	7 days	1 : 1
$Yb(OTf)_3$ or $Sc(OTf)_3$	H_2O/THF	50 °C	13 days	1 : 1
$Eu(fod)_3$	H_2O/THF	50 °C	7 days	2 : 1

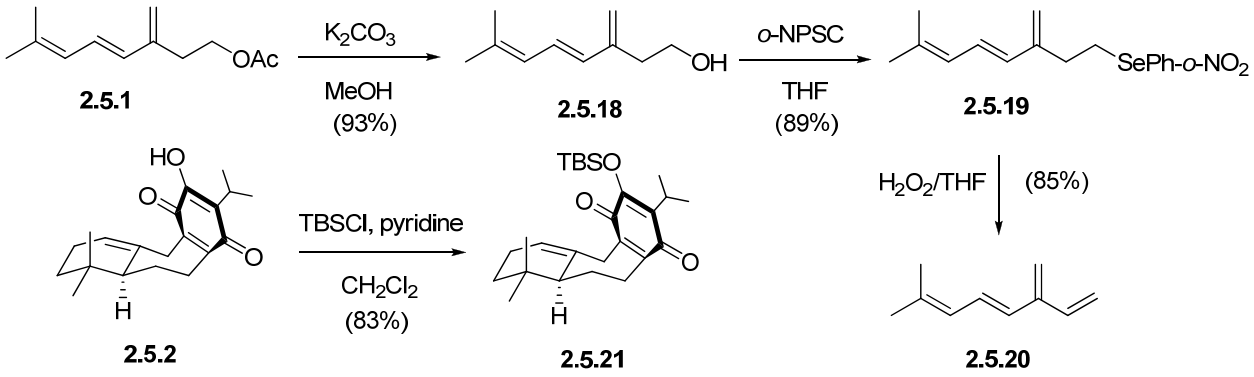
Scheme 2.5.6

When we compared the regioselectivity between the Diels–Alder reaction catalyzed by $Cu(acac)_2$ and that catalyzed by $InCl_3$, it was noticed that by having strong chelation with both the C(12) hydroxy group on quinone **2.5.2** and the acetate moiety of triene **2.5.1**, the Cu(II) salt was able to speed up the reaction by bringing the two reactants together, but this chelation resulted in the unwanted Diels–Alder isomeric adduct **2.5.17** (Scheme 2.5.7). Because In(III) has weaker chelation effects with oxygen atoms, it resulted in both regioisomers. Taking the chelation ability away from indium(III) chloride was expected to improve the selectivity of the reaction but adding triethylamine to the reaction mixture caused indium(III) chloride to be inactive and caused **2.5.1** and **2.5.2** not to react.



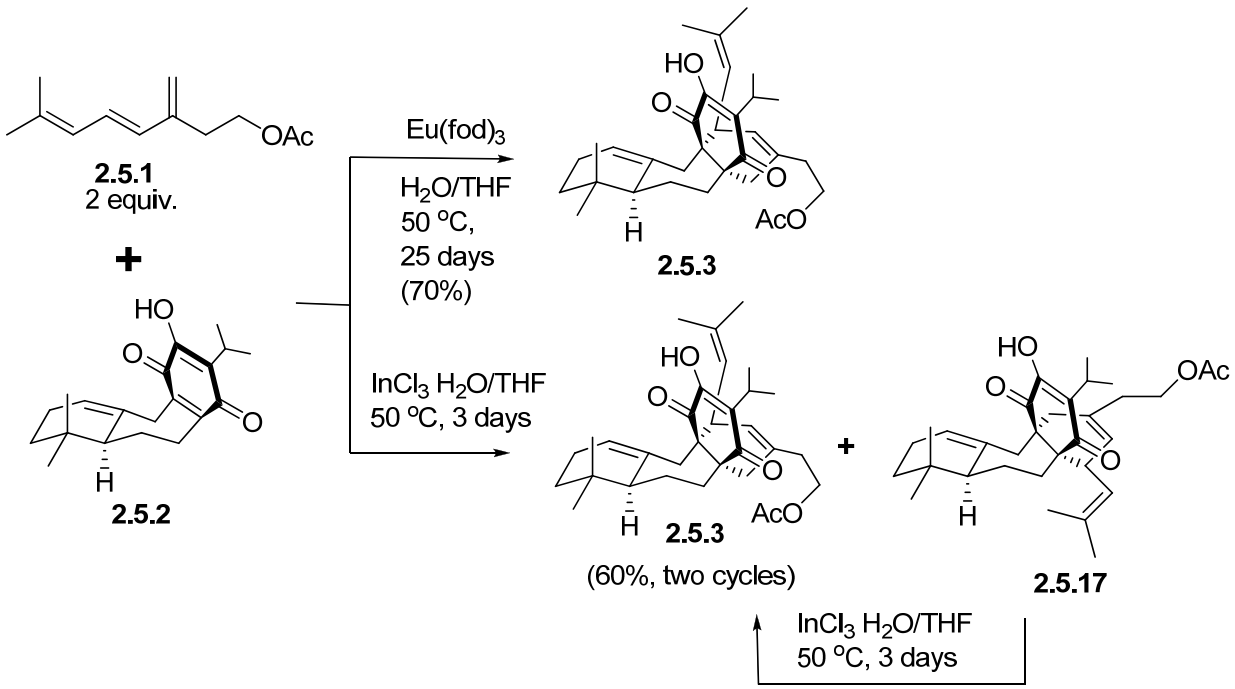
Scheme 2.5.7

Three derivatives of **2.5.1** were synthesized in hopes of optimizing the Diels–Alder reaction (Scheme 2.5.8): (1) alcohol **2.5.18** resulted from the deprotection of **2.5.1** under basic condition; (2) tetraene **2.5.20** was made from **2.5.18** through a replacement-oxidation-elimination sequence; and (3) a TBS-silyl ether was used to protect the C(12) hydroxy group of **2.5.2** to generate **2.5.21.** When these derivatives were submitted to Diels–Alder conditions, **2.5.18** and **2.5.18** were found to have reactivity comparable to triene **2.5.1** whereas tetraene **2.5.20** was less reactive. C(12)-Protected quinone **2.5.21** produced a selectivity increase (from 0:1 to 1:1) when reacted with triene **2.5.1** or **2.5.16** under the influence of a Cu(II) salt. This result further confirmed that the chelation effect between the C(12) hydroxy group of the quinone and the C(1) acetate or hydroxy moiety on the triene with a Lewis acid favors the production of the undesired regioisomer, but taking away this chelation effect does not preclude the generation of the undesired regioisomer.



Scheme 2.5.8

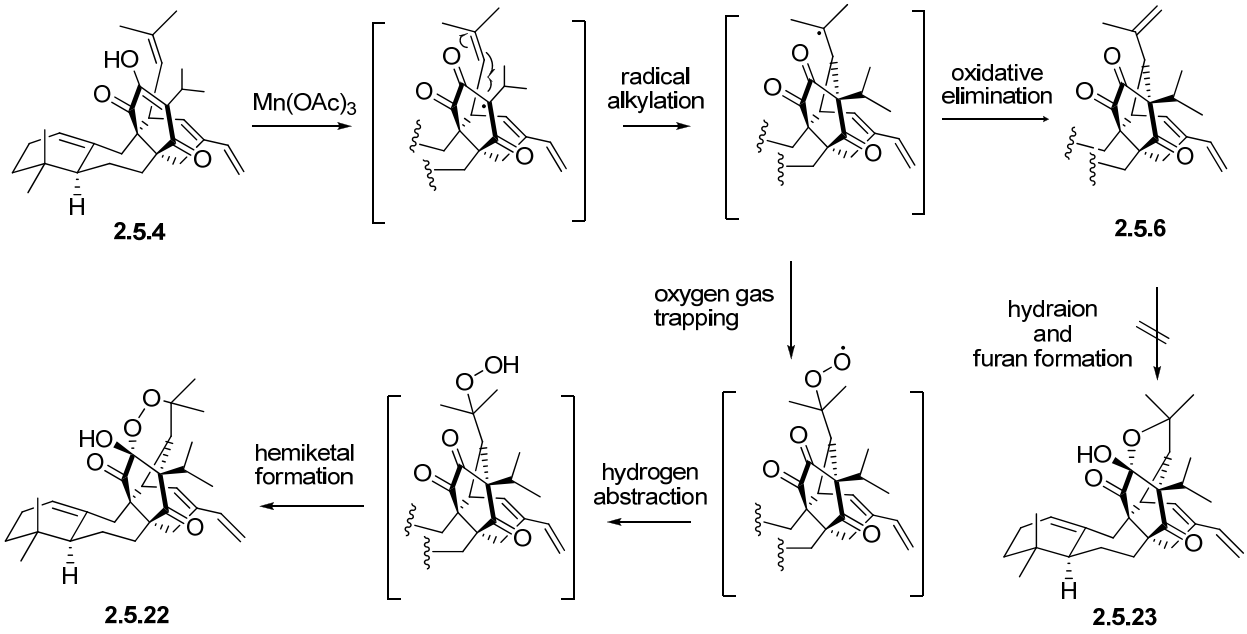
In hindsight, exploiting the different retro-Diels–Alder reaction rates between the desired regioisomer **2.5.3** and the undesired one **2.5.17** became our best option for obtaining the desired adduct in better than 50% yield. Thus, the best Diels–Alder conditions involve prolonged heating (for up to 25 days) two equivalents of **2.5.1** and one equivalent of **2.5.2** at 50 ^{o}C in a 1:4 mixture of THF/H_2O with $Eu(fod)_3$ as catalyst which generated Diels–Alder adduct **2.5.3** regio- and stereoselectively in 70% yield. Heating the same mixture with $InCl_3$ as the catalyst for three days followed by isolating the desired adduct and resubmitting the undesired isomer to retro-Diels–Alder conditions produced the desired adduct in 60% yield after two cycles (Scheme 2.5.9).



Scheme 2.5.9

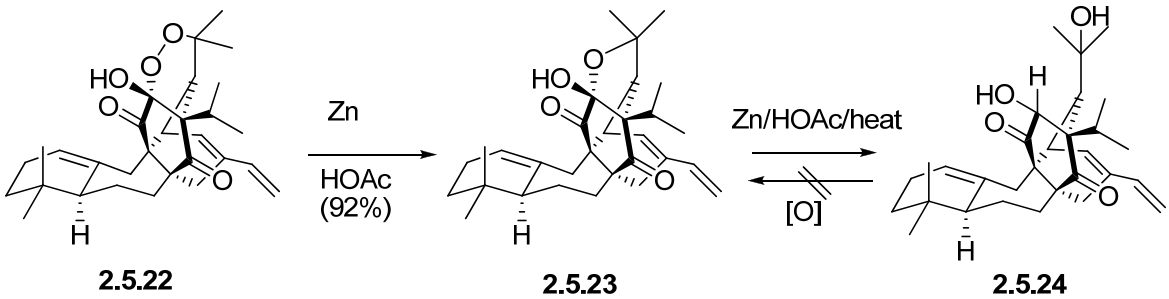
Having optimized the Diels–Alder reaction of **2.5.1** with **2.5.2**, we explored other methods to selectively hydrate the C(1),C(10)-double bond and to form a furan moiety between the C(12) ketone and C(26) carbon. Manganese(III) acetate mediated radical cyclization has been proven to form the C(13),C(26)-bond efficiently, whereas the use of cupper(II) nitrate produces the disubstituted olefin at C(27). Re-examination of the synthetic plan revealed that oxidative elimination followed by the addition of water should install the tertiary alcohol at C(27) position. Alternatively, oxygen gas can be used to trap radicals and the resulting peroxides can be then reduced to alcohols. Thus, conducting the radical cyclization in an oxygen atmosphere, followed by reduction, should introduce the C(27) tertiary alcohol. This conjecture was confirmed by a literature search, which revealed that similar transformations have been studied by Kurosawa and co-workers.[34] Carrying out the radical cyclization of **2.5.4** with oxygen gas bubbled into the

reaction mixture produced peroxide hemi-ketal **2.5.22** in 91% yield. X-ray analysis of a single crystal of **2.5.22** confirmed that the hemi-ketal moiety involved the C(12) carbonyl, which is due to the stability of a six-membered ring over a seven-membered ring [i.e., attack at C(11)].



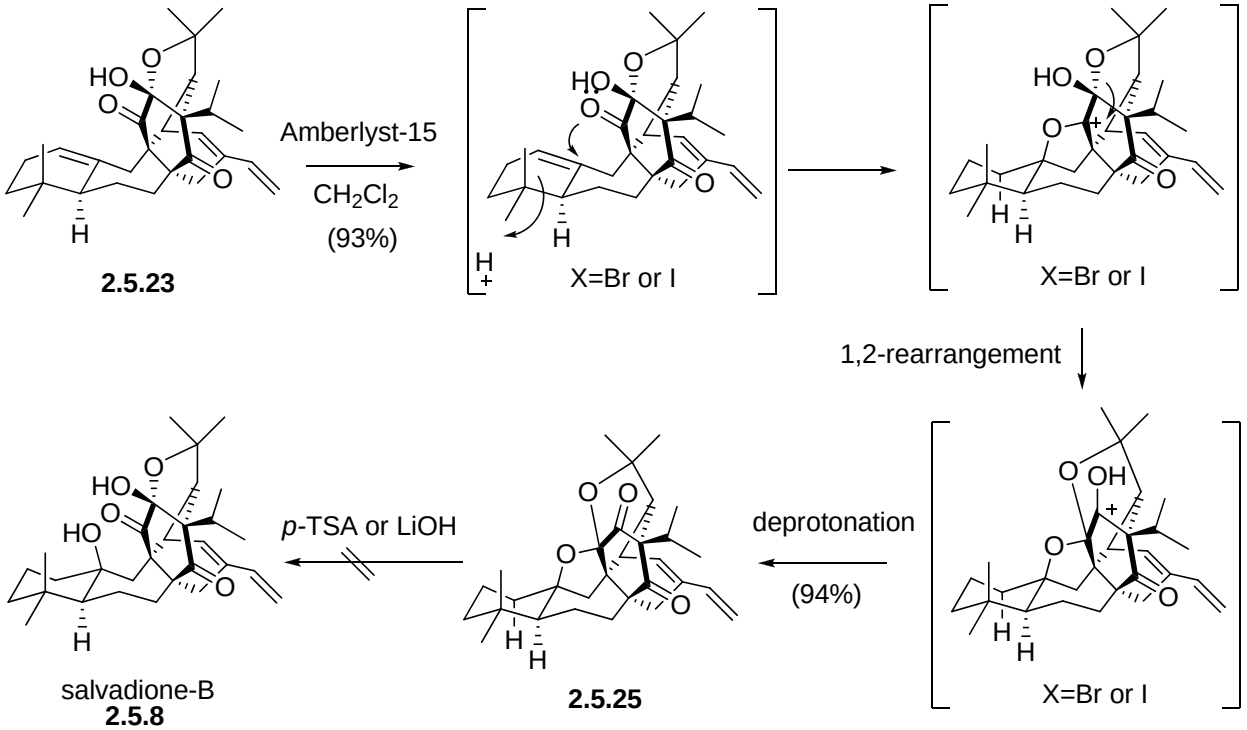
Scheme2.5.10

Zinc powder in acetic acid was chosen to reduce peroxide **2.5.22** to **2.5.23**. While zinc powder can also reduce 1,2-diketones,[35] byproduct **2.5.24** was generated as a pair of diastereoisomers if the reaction temperature was greater than 30 ^{o}C. Efforts to oxidize **2.5.24** back to **2.5.23** were unsuccessful (Scheme 2.5.11).



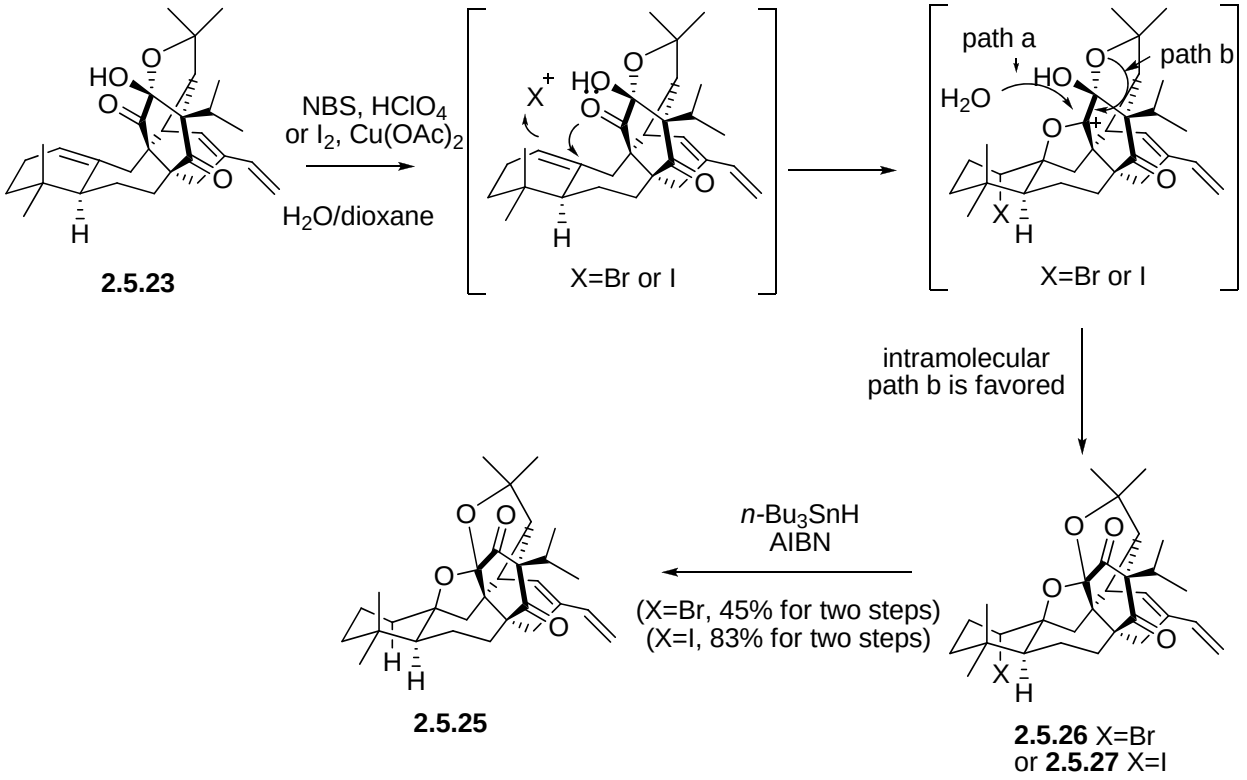
Scheme 2.5.11

In order to complete a step-wise synthesis of salvadione-B (**2.5.8**), we need to selectively hydrate the C(1),C(10)-double bond of **2.5.23**. Treating **2.5.23** with mild aqueous acid (1 *N* HCl) resulted in either no reaction or decomposition (refluxing with *p*-TSA). In our previous synthesis of perovskone, Amberlyst-15® resin was used to hydrate the C(1),C(10)-double bond. Applying these conditions to **2.5.23** afforded furan ketal **2.5.26** in high yield. Mechanistic study on this transformation revealed that while the C(1),C(10)-double bond was activated by Amberlyst-15® resin, the C(11) ketone oxygen acted as a intramolecular nucleophile to add to C(10). The resulting carbocation at C(11) position promoted a 1,2-rearrangement to generate the more stable furan ketal **2.5.26**. Unfortunately, all of our efforts to isomerize **2.5.26** to salvadione-B by reacting it with acid were unsuccessful (Scheme 2.5.12).



Scheme 2.5.12

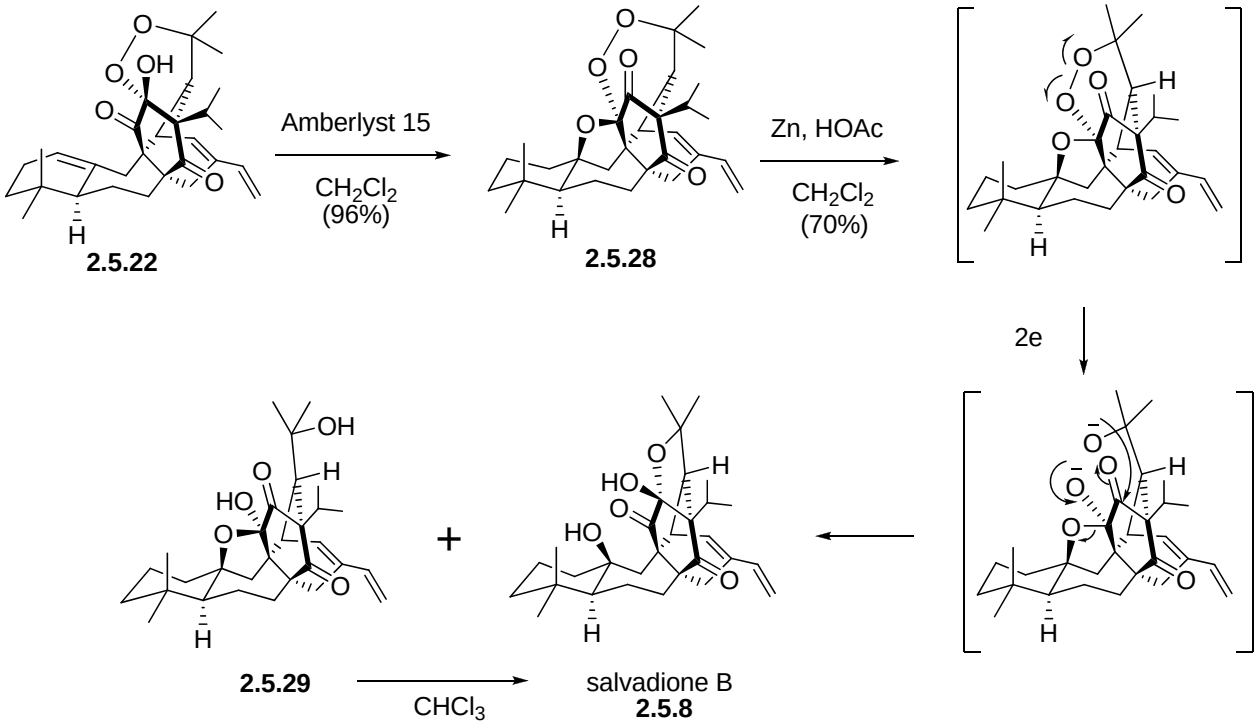
We then tried to add trap the activated C(11) carbonyl by reacting **2.5.23** with NBS in water. Unfortunately, bromide **2.5.26** was formed, and its structure was confirmed by treating with typical radical dehalogenation conditions, generating furan **2.5.25**. Replacing NBS with milder $Cu(OAc)_2$ and iodine in 25% water in 1,4-dioxane only improved the yield of **2.5.25**. This observation can be explained by the fact that oxygen atom of C(27)-hydroxy group is a better intramolecular nucleophile than water as an intermolecular nucleophile (Scheme 2.5.13).



Scheme 2.5.13

An intriguing and atom economic solution to hydrate the C(1),C(10)-double bond was to direct treat peroxide **2.5.22** with Amberlyst-15® resin to afford isomerized peroxide ketal **2.5.28**, which is at the same oxidation state as the target molecule salvadione-B (**2.5.8**). Reductive cleavage of the peroxide bond in **2.5.28** under acidic condition would complete the synthesis. We were excited to find that **2.5.28** was produced in high yield as predicted when we submitted

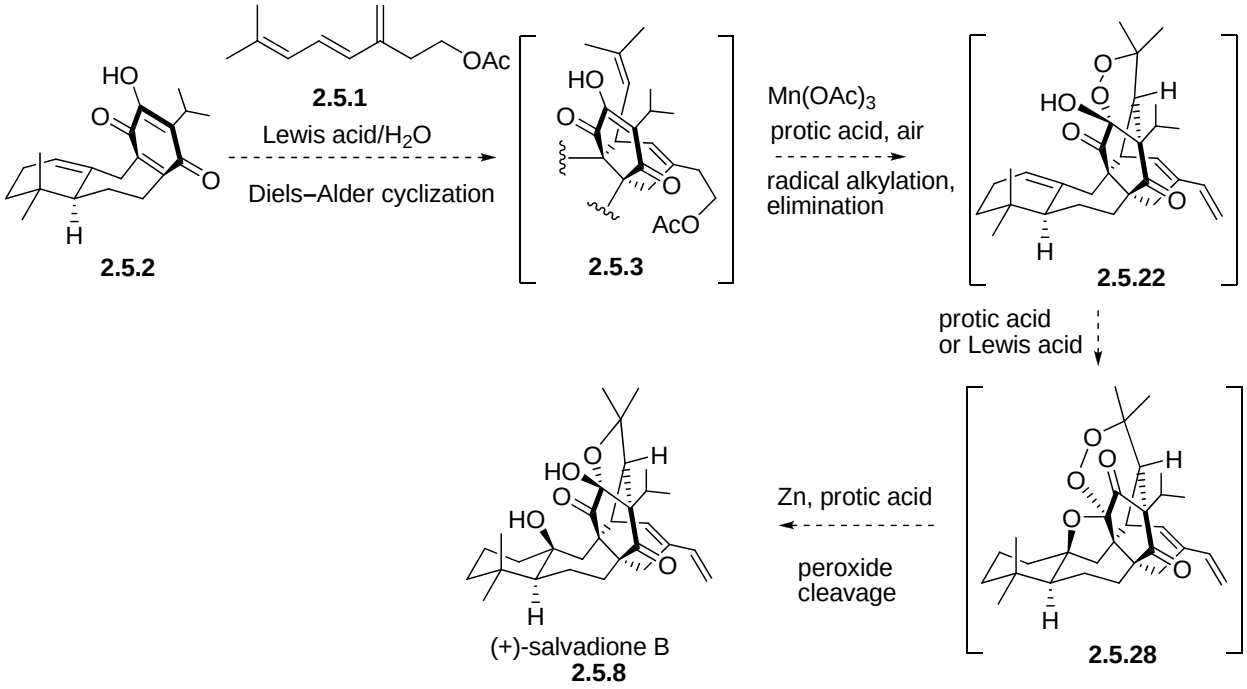
2.5.22 and Amberlyst-15® resin in refluxing dichloromethane for one hour. However, **2.5.28** was unstable in polar solvents like DMF or ethanol. Several typical reduction conditions for peroxides were tested on **2.5.28**. While dimethylsulfide was unreactive, triphenylphosphine in THF or magnesium powder in methanol led to decomposition, whereas treating **2.5.28** carefully with six equivalents of acetic acid and ten equivalents of zinc powder in dichloromethane produced salvadione-B (**2.5.8**) together with trace amount of hemiacetal **2.5.29** which can be isomerized back to salvadione-B in chloroform at room temperature (Scheme 2.5.14).



Scheme 2.5.14

We were fully aware that each transformation in our stepwise synthesis of (+)-salvadione-B, other than the three transformations needed to prepare the terminal vinyl moiety, was acid-catalyzed. Our next effort was to develop a one-pot reaction sequence whereby

a Lewis acid-promoted Diels–Alder reaction of quinone **2.5.2** and triene **2.5.1** takes place, followed by the addition of manganese(III) acetate to the reaction mixture to generate the cyclic peroxide ketal **2.5.22** *in situ*; the Lewis acid present should also permit the hemiacetal isomerization and hydration of the A-ring double bond. We have already established that addition of zinc and acetic acid to the reaction mixture cleaves the peroxide linkage and produces salvadione-B. In this one-pot procedure, the compatibility of the acid source and the choice of solvent system were two major considerations (Scheme 2.5.15).

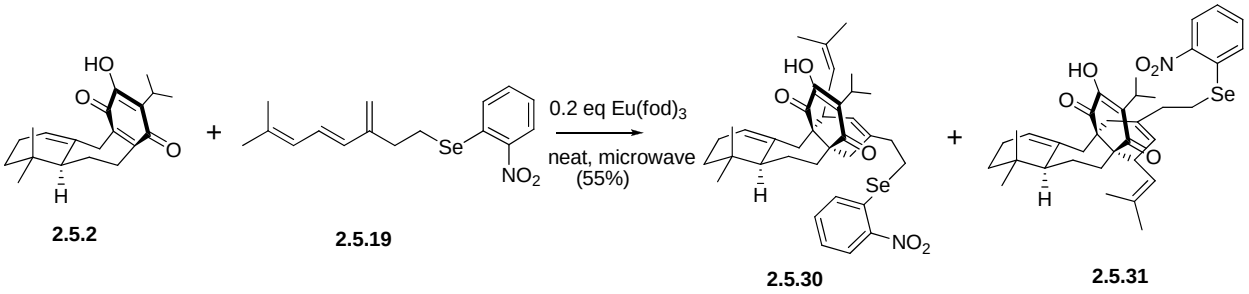


Scheme 2.5.15

In our stepwise synthesis of salvadione-B, a primary acetate was used as a precursor for the terminal C(21),C(22)-double bond, but this required three functional group manipulations to convert the acetate into a vinyl group, which precluded the possibility to perform a one-pot synthesis of salvadione-B. To overcome this hurdle, selenide **2.5.19** was prepared. First of all, being a yellow solid and stable at room temperature for up to seven days, **2.5.19** is easier to

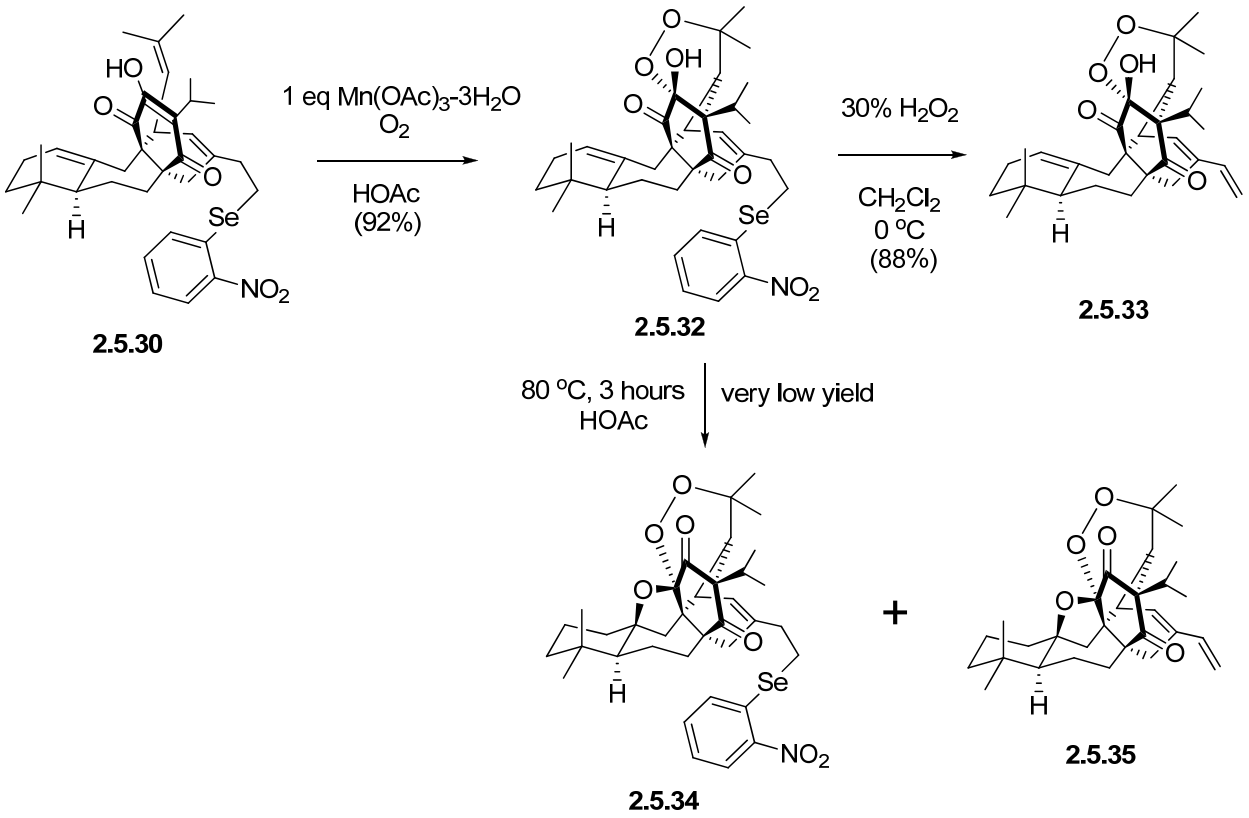
handle when compared to the more volatile tetraene **2.5.20**. Secondly, the yellowish color from all of the selenide intermediates made them easy to be identified by TLC analysis and separated by column chromatography. Finally, and most importantly, only one oxidation-elimination transformation was required to generate the terminal double bond from any of the selenide intermediates, which made it possible to develop a one-pot procedure to synthesize salvadione-B.

We were delighted to find that **2.5.19** reacted with quinone **2.5.2** in hot toluene to give the desired cycloadduct **2.5.30** in moderate yield. Optimizing the reaction by carrying out the Diels–Alder reaction neat makes it faster so that it is completed within 48 hours. The choice of reaction temperature was found to be very important to the yield and regioselectivity. Carrying out the reaction below 70 ^{o}C would generate the desired adduct **2.5.30** and its regioisomer **2.5.31** in 1:1 ratio. However, if the reaction temperature is higher than 90 ^{o}C, the decomposition rate of triene **2.5.19** was found to be much faster than the rate of retro-Diels–Alder reaction of **2.5.31**. Therefore, 80 ^{o}C for 48 hours was regarded as the best conditions to generate **2.5.30** stereoselectively from one equivalent of quinone **2.5.2** and two equivalents of **2.5.19**. We also used a Milestone microwave reactor to accelerate the Diels–Alder reaction[36] and found that irradiating the mixture at 65 ^{o}C for 30 hours produced the desired cycloadduct **2.5.30** in 55% yield (Scheme 2.5.16).



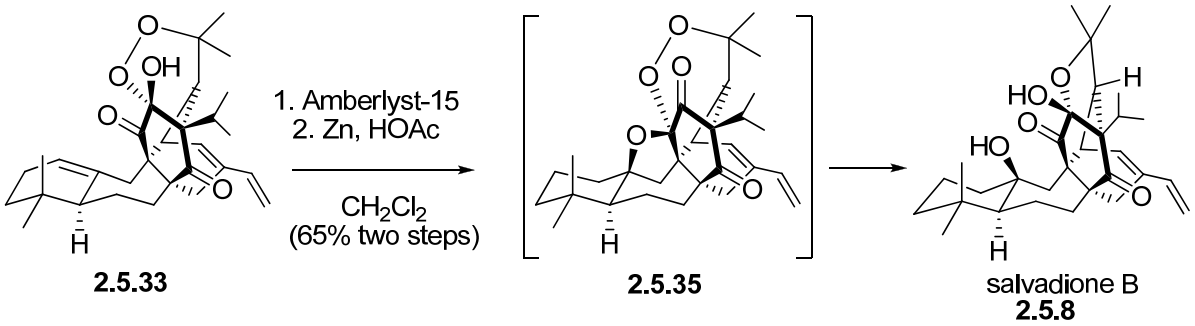
Scheme 2.5.16

The mixture resulting from the Diels–Alder reaction was then submitted to the oxidative radical cyclization condition. When one equivalent of manganese(III) acetate was used as oxidant and oxygen gas was bubbled into the reaction flask, the cyclization was complete in three hours at room temperature to afford hemiketal **2.5.32** with trace amount of oxidative elimination product **2.5.33**. Three equivalents of hydrogen peroxide were added to the reaction mixture to convert **2.5.32** to **2.5.33**. Neither isomerization product **2.5.34** nor **2.5.35** was found (Scheme 2.5.17). Increasing the reaction temperature to 50 ^{o}C or adding two equivalent of trifluoroacetic acid failed to produce any isomerization product **2.5.34** or **2.5.35**, only causing partial decomposition of **2.5.32**. Increasing the reaction temperature to 80 ^{o}C afforded a complex mixture including traces of **2.5.34** and **2.5.35**.



Scheme 2.5.17

Although we did not identify conditions to complete a one-pot synthesis of salvadione-B (**2.5.8**) from quinone **2.5.2**, we nevertheless showed that the Diels–Alder reaction, oxidative radical cyclization, and oxidative elimination could be achieved by a one-pot reaction sequence to annulate two rings and create four chiral centers. The remaining two transformations required to afford salvadione-B were found to be compatible with each other. Thus, submitting purified **2.5.33** to Amberlyst-15® resin in refluxing dichloromethane for 1 hour followed by the additions of zinc to the peroxide at room temperature furnished salvadione-B (**2.5.8**) in high yield (Scheme 2.5.18).



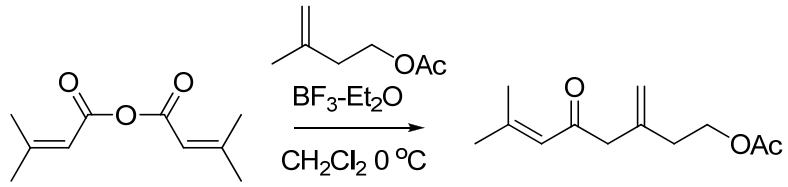
2.5.33 **2.5.35** salvadione B **2.5.8**

Scheme 2.5.18

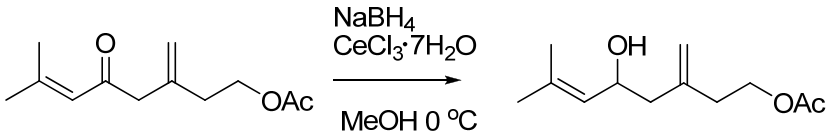
In summary, two synthetic routes toward salvadione-B were achieved. The first step-wise route paved the way for the second "cascade" synthetic route, which featured two one-pot reactions to complete the salvadione-B synthesis starting from chiral quinone **2.5.2** and triene **2.5.19**.

2.6 Experimental Section

General Procedures: All reactions unless otherwise indicated were run under a nitrogen atmosphere and monitored by TLC analysis. Unless otherwise indicated, all extractive workups consisted of the following procedure: The organic solvent was removed under reduced pressure on a rotary evaporator, and the residue was taken up in diethyl ether, washed with brine, and dried over anhydrous sodium sulfate or anhydrous magnesium sulfate. Filtration, followed by concentration at reduced pressure on a rotary evaporator and at 1 torr to a 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. Melting points were recorded on a Laboratory Devices Mel-Temp 3.0. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVB-400 and DRX-500 MHz spectrometers with ^{13}C operating frequencies of 100 MHz and 125 MHz, respectively. Proton NMR spectra were obtained in $CDCl_3$ and were calibrated using trace $CHCl_3$ present (δ 7.27) as an internal reference. Carbon NMR spectra were obtained in $CDCl_3$ and were calibrated using trace $CHCl_3$ present (δ 77.23) as an internal reference. The IR spectra were obtained using an Nicolet 6700FT-IR and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. High resolution MS were taken using a LCT Premier from Waters.

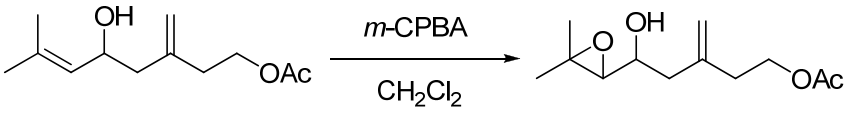


7-Methyl-3-methylene-5-oxo-oct-6-enyl acetate (2.5.11): Senecioic anhydride **2.5.9** (5.00 g, 27.44 mmol) and 3-methylbut-3-enyl acetate (**2.5.10**) (4.10 g, 31.99 mmol) were dissolved in CH_2Cl_2 (15.0 mL) and cooled to 0 °C. BF_3-Et_2O (7.90 mL, 64.00 mmol) was added to the reaction mixture and stirred at 0 °C for 30 min. After monitoring the reaction by TLC showed that the reaction was complete, water (20 mL) was added at 0 °C. The organic layer was washed with brine (2 x 25 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated. Because the crude product was acid sensitive, it was reduced without purification or characterization.



5-Hydroxy-7-methyl-3-methylene-oct-6-enyl acetate (2.5.12): To a solution of crude enone **2.5.11** dissolved in MeOH (300 mL), $CeCl_3$-$7H_2O$ (10.06 g, 27.00 mmol) was added at rt. Once all of the solids were dissolved, the reaction mixture was cooled to 0 °C and $NaBH_4$ (4.08 g, 0.11 mmol) was added in small portions over a 30-min period. After stirring at 0 °C for 1 h, the ice bath was removed and the reaction was stirred at rt until TLC analysis showed that the reaction was complete (in ~2 h). The reaction mixture was cooled to 0 °C and 1 *M* HCl (100 mL) was added followed by extractive workup. The crude residue was purified by silica gel

chromatography (elution with EtOAc/pet ether = 1:3) to give allylic alcohol **2.5.12** (3.78 g, 17.81 mmol, 65% from anhydride **2.5.9**), which was homogeneous by TLC analysis [R_f = 0.48, EtOAc/pet ether = 1:2]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.15 (d, *J* = 9.0 Hz, 1H), 4.91 (d, *J* = 10.5 Hz, 2H), 5.15 (d, *J* = 9.0 Hz, 3H), 4.44-4.48 (m, 1H), 4.17 (t, *J* = 7.0 Hz, 2H), 2.36 (t, *J* = 7.0 Hz, 2H), 2.22-2.26 (m, 1H), 2.16-2.20 (m, 1H), 2.02 (s, 3H), 1.70 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2(q), 142.2(q), 135.4(q), 127.5(s), 114.6(d), 66.6(s), 62.9(d), 44.7(d), 35.1(d), 25.9(t), 21.1(t), 18.4(t); IR(neat) λ_{max} 3432, 2970, 2931, 1739, 1237, 1037 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$: m/z 235.1302, found 235.1310.



6,7-Epoxy-5-hydroxy-7-methyl-3-methylene-octyl acetate (2.5.13): To a solution of allylic alcohol **2.5.12** (1.55 g, 7.30 mmol) in CH_2Cl_2 (30 mL) at 0 °C, *m*-CPBA (1.89 g, 70%, 7.67 mmol) was added and the resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched with 20 mL of 1 *M* NaOH. The crude residue obtained from extractive workup was purified by silica gel chromatography (elution with EtOAc/pet ether = 1:2) to give allylic epoxide **2.5.13** (1.42 g, 85% yield), which was homogeneous by TLC analysis [R_f = 0.25, EtOAc/pet ether = 1:2]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.93 (d, *J* = 8.0 Hz, 2H), 4.19 (t, *J* = 7.0 Hz, 2H), 3.58-3.62 (m, 1H), 2.72 (d, *J* = 8.0 Hz, 1H), 2.53 (d, *J* = 2.5 Hz, 1H), 2.38 (t, *J* = 7.0 Hz, 2H), 2.33-2.38 (m, 1H), 2.24-2.28 (m, 1H), 2.02 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2(q), 141.4(q), 114.9(d), 69.2(s), 67.6(s), 62.7(d), 59.6(q), 41.0(d),

35.2(d), 25.0(t), 21.1(t), 19.6(t); IR(neat) λ_{max} 3458, 2970, 2931, 1739, 1241, 1037 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$: m/z 251.1259, found 251.1253

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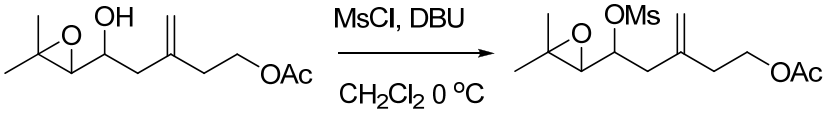
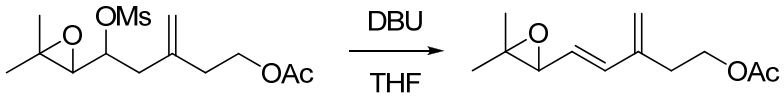


6,7-Epoxy-7-methyl-5-methylsulfonyl-3-methylene-octyl acetate (2.5.14a): To a solution of allylic epoxide **2.5.13** (1.50 g, 6.57 mmol) in CH_2Cl_2 (25 mL), DBU (3.93 mL, 26.28 mmol) was added at 0 °C followed by MsCl (1.53 mL, 19.77 mmol). The reaction mixture was then stirred at rt for 3 h. Brine (30 mL) was added slowly at 0 °C to quench the reaction. After extractive workup, the crude mesylate was purified by silica gel chromatography (elution with EtOAc/pet ether = 1:2) to give mesylate **2.5.14a** (1.80 g, 83% yield) which was homogeneous by TLC analysis [R_f = 0.35, EtOAc/pet ether = 1:2]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (d, *J* = 6.5 Hz, 2H), 4.49-4.52 (m, 1H), 4.16-4.24 (m, 2H), 3.13 (s, 3H), 2.91 (d, *J* = 8.5 Hz, 1H), 2.55-2.60 (m, 1H), 2.38-2.46 (m, 3H), 2.04 (s, 3H), 1.34 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2(q), 139.1(q), 116.8(d), 82.0(s), 64.3(s), 62.4(d), 59.8(q), 39.8(d), 39.1(t), 35.0(d), 24.7(t), 21.1(t), 19.7(t); IR(neat) λ_{max} 2971, 2737, 1357, 1234, 1173, 922 cm^{-1}; HRMS (ESI) calcd for $[M+K]^+$: m/z 345.0774, found 345.0771.

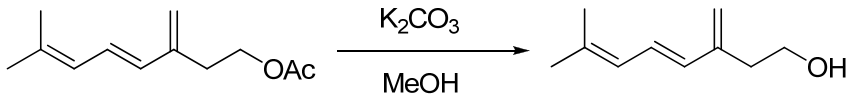


6,7-Epoxy-7-methyl-3-methylene-octa-4(*E*)-enyl acetate (2.5.14b): The solution of mesylate **2.5.14a** (1.50 g, 4.90 mmol) and DBU (2.20 mL, 14.71 mmol) in THF (25 mL) was

refluxed for 12 h. The reaction mixture was cooled to rt and diluted with Et_2O (30 mL). The crude diene isolated by extractive workup was purified by column chromatography (elution with EtOAc/pet ether = 1:8) to give diene epoxide **2.5.14b** (0.80 g, 76% yield) which was homogeneous by TLC analysis [R_f = 0.40, EtOAc/pet ether = 1:8]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.43 (d, *J* = 15.5 Hz, 1H), 5.60-5.64 (m, 1H), 5.15 (s, 1H), 5.07 (s, 1H), 4.49-4.52 (m, 1H), 4.16-4.25 (m, 2H), 3.27 (d, *J* = 7.5 Hz, 1H), 2.55 (t, *J* = 7.5 Hz, 2H), 2.05 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2(q), 141.3(q), 137.7(s), 125.1(s), 118.3(d), 64.5(s), 63.2(d), 61.0(q), 31.4(d), 24.9(t), 21.2(t), 19.2(t); IR(neat) λ_{max} 2964, 1741, 1379, 1239, 1035 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$: m/z 233.1154, found 233.1146.

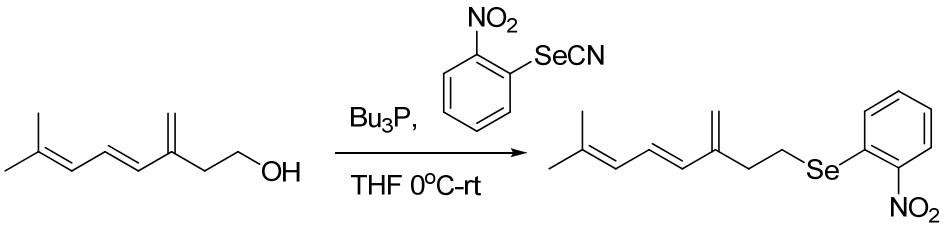
7-Methyl-3-methylene-octa-4(*E*),6-dienyl acetate (2.5.1): To a mixture of LiBr (0.54 g, 6.22 mmol) in DMF (6.4 mL) was added TFAA (0.8 mL, 5.71 mmol). The resulting solution was stirred at 0 °C for 30 min. A solution of diene epoxide **2.5.14b** (1.00 g, 4.76 mmol) dissolved in DMF (11.0 mL) was cannulated into the reaction mixture at 0 °C and stirred for 4 h at 0 °C. TLC analysis indicated that the starting material had been consumed. Brine (20 mL) was slowly added at 0 °C to the reaction mixture to quench the reaction. The resulting mixture was diluted by ether. The ethereal phase was washed with ice cold brine (20 mL), dried over anhydrous Na_2SO_4 at 0 °C, filtered and concentrated to generate a mixture of two bromohydrins.

The crude bromohydrins were dissolved in DMF (20 mL) and the resulting mixture was cooled to 0 ^{o}C. Acidic acid (2.0 mL) and zinc powder (1.24 g, 19 mmol) were added to the reaction mixture and stirred for 2 h. The reaction mixture was filtered through a small pad of Celite® to remove inorganic salts and unreacted zinc powder. The resulting solution was diluted with diethyl ether and the ethereal phase was washed by brine (5 x 20 mL). After drying over anhydrous Na_2SO_4, followed by filtration, the ethereal phase was concentrated using a rotary evaporator. The crude residue was purified with a neutral Al_2O_3 column to give triene acetate **2.5.1** (0.68 g, 74 % yield) as colorless oil which was homogeneous by TLC analysis [R_f = 0.82, EtOAc/pet ether = 1:8]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48-6.56 (m, 1H), 6.14 (d, *J* = 15.2 Hz, 1H), 5.87 (d, *J* = 13.5 Hz, 1H), 5.05 (s, 1H), 4.96 (s, 1H), 4.22 (t, *J* = 7.2 Hz, 2H), 2.59 (t, *J* = 7.2 Hz, 2H), 2.05 (s, 3H), 1.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2(q), 142.6(q), 137.0(q), 131.5(s), 125.9(s), 125.5(s), 116.2(d), 63.6(d), 31.6(d), 26.4(t), 21.2(t), 18.7(t); HRMS (ESI) calcd for $[M+Na]^+$: m/z 217.1204, found 217.1202.



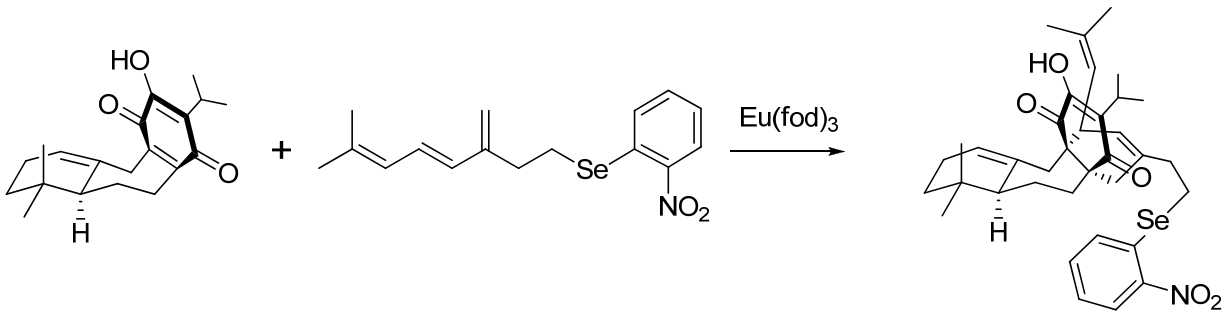
7-Methyl-3-methylene-octa-4(*E*),6-dien-1-ol (2.5.18): To a solution of triene acetate **2.5.1** (0.50 g, 2.57 mmol) in MeOH (10 mL) at 0 ^{o}C, K_2CO_3 (1.07 g, 7.80 mmol) was added. After being stirred at 0 ^{o}C for 1 h, the reaction mixture was quenched by 1 *M* HCl (10 mL). After extractive workup, the crude product was purified using a neutral Al_2O_3 column to give triene alcohol **2.5.18** (0.36 g, 93% yield) as colorless oil which was homogeneous by TLC analysis [R_f

= 0.15, EtOAc/pet ether = 1:8]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45-6.51 (m, 1H), 6.15 (d, *J* = 15.2 Hz, 1H), 5.88 (d, *J* = 13.5 Hz, 1H), 5.09 (s, 1H), 4.99 (s, 1H), 3.77 (t, *J* = 6.4 Hz, 2H), 2.55 (t, *J* = 6.4 Hz, 2H), 1.81 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0(q), 137.1(q), 131.5(s), 126.0(s), 125.5(s), 116.4(d), 61.4(d), 35.7(d), 26.4(t), 18.7(t); IR(neat) λ_{max}3355, 2925, 1441, 1044, 739 cm^{-1}; HRMS (ESI) calcd for $[M]^+$: m/z 152.1201, found 152.1202.



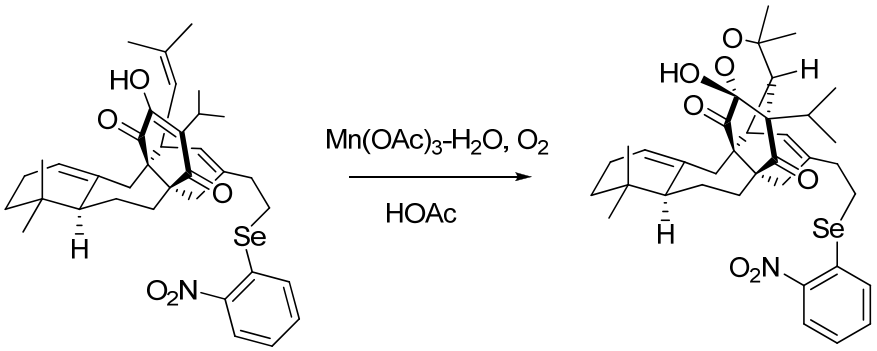
7-Methyl-3-methylene-octa-4(*E*),6-dienyl-2-nitrophenyl selenide (2.5.19): To a solution of triene alcohol **2.5.18** (300 g, 1.97 mmol) and *o*-nitrophenylselenocyanate (1.03 g, 4.53 mmol) in THF (20 mL) at 0 °C, Bu_3P (1.22 mL, 4.88 mmol) was added dropwise. The ice bath was removed and the reaction mixture was stirred for 4 h at rt. The solution was then concentrated using a rotary evaporator and purified by silica gel chromatography (elution first with EtOAc/pet ether = 1:50, followed by EtOAc/pet ether = 1:20) to give triene **2.5.19** (0.59 g, 89% yield) as a yellow powder, which was homogeneous by TLC analysis [R_f = 0.56, EtOAc/pet ether = 1:8]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.8 Hz, 1H), 7.25-7.27 (m, 2H), 7.05-7.07 (m, 1H), 6.21 (dd, J_1 =11.2 Hz, J_2 =15.6 Hz, 1H), 5.89 (d, *J* = 15.6 Hz, 1H), 5.62 (d, *J* = 10.4 Hz, 1H), 4.80 (d, *J* = 12.8 Hz, 2H), 2.83 (t, *J* = 8.0 Hz, 2H), 2.45 (t, *J* = 8.0 Hz, 2H), 1.55 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8(q), 145.1(q), 137.0(q), 133.7(s), 131.1(s), 129.1(s), 126.5(s), 125.6(s), 125.5(s), 125.3 (s), 115.5(d), 31.2(d), 26.3(t), 24.8(d), 18.7(t);

IR(neat) λ_{max} 2926, 1736, 1590, 1514, 1332, 731 cm^{-1}; HRMS (ESI) calcd for $[M+H]^+$: m/z 338.0659, found 338.0657; mp = 58.0-60.0 ^oC.



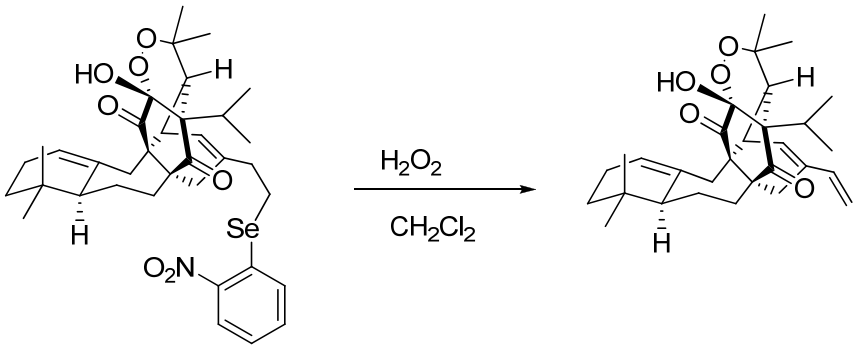
Diels–Alder Adduct (2.5.30): A mixture of chiral benzoquinone **2.5.2** (50.0 mg, 0.16 mmol), triene **2.5.1** (160.6 mg, 0.48 mmol) and $Eu(fod)_3$ (32.67 mg, 0.032 mmol) was dissolved in Et_2O and concentrated using a rotary evaporator. The resulting residue was further concentrated using a vacuum pump. The resulting mixture was heated using a Milestone microwave reactor (200 W, 65 ^oC for 30 h). The reaction mixture was purified with column chromatography (elution with EtOAc/pet ether = 1:15) to give **2.5.30** (57.1 mg, 55% yield) as yellow oil which was homogeneous by TLC analysis [R_f = 0.51, EtOAc/pet ether = 1:8]: $[\alpha]^{24}_D$ = +64.7^o ($CHCl_3$; c = 0.012 g/mL); ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 (dd, J_1 = 1.0 Hz, J_2 = 8.5 Hz, 1H), 7.62-7.63 (m, 1H), 7.56 (dt, J_1 = 1.5 Hz, J_2 = 7.5 Hz, 1H), 7.33 (dt, J_1 = 1.0 Hz, J_2 = 7.5 Hz, 1H), 7.05 (s, 1H), 5.65 (m, 1H), 5.19 (m, 1H), 4.56, (d, J = 11.0 Hz, 1H), 3.32 (d, J = 13.5 Hz, 1H), 3.20-3.26 (m, 1H), 3.06-3.11(m, 2H), 2.95 (dd, J_1 = 3.5 Hz, J_2 = 11.5 Hz, 1H), 2.75 (d, J = 17.5 Hz, 1H), 2.50-2.62 (m, 2H), 2.20 (d, J = 17.5 Hz, 1H), 2.10 (d, J = 14.0 Hz, 1H), 1.88-2.06 (m, 2H), 1.82 (t, J = 8.3 Hz, 1H), 1.62-1.71 (m, 2H), 1.55 (s, 3H), 1.46 (s, 3H), 1.44 (s, 1H), 1.24-1.36 (m, 1H), 1.22 (d, J = 7.0 Hz, 3H), 1.19 (d, J = 7.0 Hz, 3H), 1.02 (dd, J_1 = 8.5 Hz, J_2 =

14.0 Hz, 1H), 0.84-0.92 (m, 1H), 0.82 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.0(q), 198.7(q), 153.7(q), 147.2(q), 134.4(q), 134.0(q), 133.8(q), 133.8(s), 133.4(q), 129.5(s), 127.8(q), 127.3(s), 126.7(s), 125.5(s), 125.0(s), 122.5(s), 56.4(q), 53.2(q), 48.5(s), 46.5(d), 45.7(s), 38.6(d), 36.0(d), 32.6(q), 29.0(t), 28.6(q), 27.2(d), 26.7(t), 26.7(d), 26.0(t), 25.4(s), 24.4(d), 23.7(d), 20.0(t), 19.1(t), 17.7(t); IR(neat) λ_{max} 3360, 2922, 2852, 1662, 1567 cm^{-1}; HRMS (ESI) calcd for $[M+H]^+$: m/z 652.2541, found 652.2537.



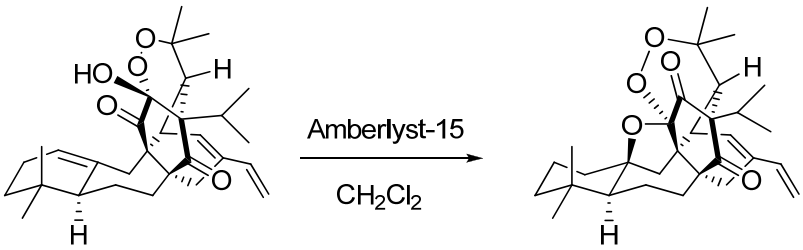
Peroxide hemiacetal (2.5.32): To a solution of Diels–Alder adduct **2.5.30** (50.0 mg, 0.077 mmol) in HOAc (5 mL) was bubbled dry nitrogen gas for 15 min. $Mn(OAc)_3$-H_2O (21.1 mg, 0.085 mmol) was added to the solution and dry oxygen gas was bubbled into the reaction mixture. After stirring at rt for 3 h, TLC analysis indicated that the reaction was completed. The reaction mixture was filtered through a small pad of Celite® and the filtering cake was washed with Et_2O (15 mL). The fltrate was concentrated using a rotary evaporator. Once most of the solvent was removed, the reaction flask was connected to vacuum pump for 30 min and the resulting residue was purified via silica gel column chromatography (elution with EtOAc/pet ether = 1:4) to give **2.5.32** (48.2 mg, 92% yield) as a yellow oil which was homogeneous by TLC

analysis [R_f = 0.50, EtOAc/pet ether = 1:4]: $[\alpha]^{24}_D$ = -13.2° ($CHCl_3$; c = 0.011 g/mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.5 Hz, 1H), 7.48-7.62 (m, 2H), 7.34 (dt, J_1 = 2.5 Hz, J_2 = 7.3 Hz, 1H), 6.01 (m, 1H), 5.44 (d, *J* = 6.0 Hz, 1H), 3.93 (s, 1H), 3.07-3.12 (m, 1H), 2.93-3.00 (m, 2H), 2.66-2.75 (m, 3H), 2.43-2.51 (m, 4H), 2.11 (s, 1H), 2.02-2.08 (m, 1H), 1.98 (d, *J* = 13.5 Hz, 1H), 1.74 (s, 6H), 1.67-1.82 (m, 1H), 1.32-1.44 (m, 2H), 1.30 (s, 3H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.22 (t, *J* = 4.0 Hz, 1H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.03 (dd, J_1 = 5.5 Hz, J_2 = 12.5 Hz, 1H), 0.84-0.90 (m, 2H), 0.81 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.1, 210.8, 147.2, 134.2, 133.9, 133.4, 133.0, 129.5, 128.4, 126.7, 125.8, 124.7, 97.3, 81.8, 57.2, 53.1, 52.2, 50.7, 47.9, 41.0, 38.3, 34.9, 33.3, 32.9, 32.4, 29.1, 27.8, 27.7, 27.5, 27.3, 27.0, 26.9, 24.3, 23.9, 20.6, 20.2; IR(neat) λ_{max} 3385, 2924, 1743, 1719, 1512, 1258 cm^{-1}; HRMS (ESI) calcd for $[M+H]^+$: m/z 684.2439, found 684.2450.



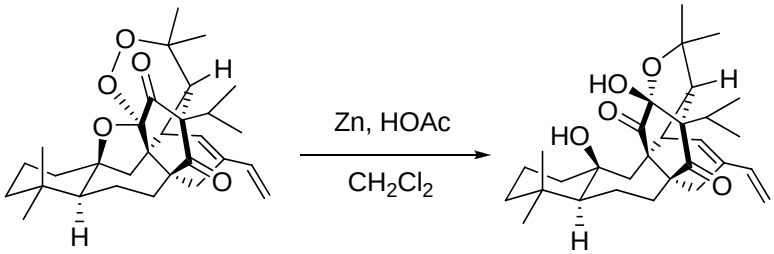
Peroxide hemiacetal (2.5.33): To a solution of **2.5.32** (34.0 mg, 0.050 mmol) in CH_2Cl_2 (5 mL) at 0 °C, 30% H_2O_2 (22.5 μL) was added. The ice bath was removed and the reaction mixture was stirred at rt until the TLC analysis showed no starting material remained. Et_2O (10 mL) was used to dilute the reaction mixture. The organic phase was washed with brine (5.0 mL), saturated Na_2SO_3 (5.0 mL) and brine (5.0 mL). After being dried over anhydrous Na_2SO_4,

filtered, and concentrated, the resulting residue was chromatographed on silica gel (elution with EtOAc/pet ether = 1:8) to give **2.5.33** (21.1 mg, 88% yield) as a white solid which was homogeneous by TLC analysis [R_f = 0.33, EtOAc/pet ether = 1:8]: $[\alpha]^{24}_D$ = -23.2° ($CHCl_3$; c = 6.1 mg/mL); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.5 Hz, 1H), 7.48-7.62 (m, 2H), 7.34 (dt, J_1 = 2.5 Hz, J_2 = 7.3 Hz, 1H), 6.01 (m, 1H), 5.44 (d, *J* = 6.0 Hz, 1H), 3.93 (s, 1H), 3.07-3.12 (m, 1H), 2.93-3.00 (m, 2H), 2.66-2.75 (m, 3H), 2.43-2.51 (m, 4H), 2.11 (s, 1H), 2.02-2.08 (m, 1H), 1.98 (d, *J* = 13.5 Hz, 1H), 1.74 (s, 6H), 1.67-1.82 (m, 1H), 1.32-1.44 (m, 2H), 1.30 (s, 3H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.22 (t, *J* = 4.0 Hz, 1H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.03 (dd, J_1 = 5.5 Hz, J_2 = 12.5 Hz, 1H), 0.84-0.90 (m, 2H), 0.81 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.5, 210.8, 137.9, 133.7, 133.1, 128.5, 128.3, 113.4, 97.3, 81.7, 57.3, 52.7, 52.5, 50.7, 47.7, 41.1, 38.7, 32.9, 32.6, 29.8, 29.2, 27.7, 27.7, 27.4, 27.3, 27.0, 26.9, 23.9, 20.6, 20.1; IR(neat) λ_{max} 3400, 2929, 1745, 1720, 1386 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$: m/z 503.2773, found 503.2781.



Peroxide acetal (2.5.35): To a solution of **2.5.33** (30.0 mg, 0.062 mmol) in CH_2Cl_2 (5 mL), Amberlyst-15® (70.0 mg) was added. The resulting mixture refluxed for 1 h. After filtration through a small pad of Celite®, the organic phase was concentrated to give **2.5.35** (28.9 mg, 96%) as a white solid which was homogeneous by TLC analysis [R_f = 0.80, EtOAc/pet ether = 1:4]: $[\alpha]^{24}_D$ = +62.0° ($CHCl_3$; c = 0.0023 g/mL); ^{1}H NMR (500MHz, $CDCl_3$) δ 6.31 (dd, J_1 = 11.0 Hz,

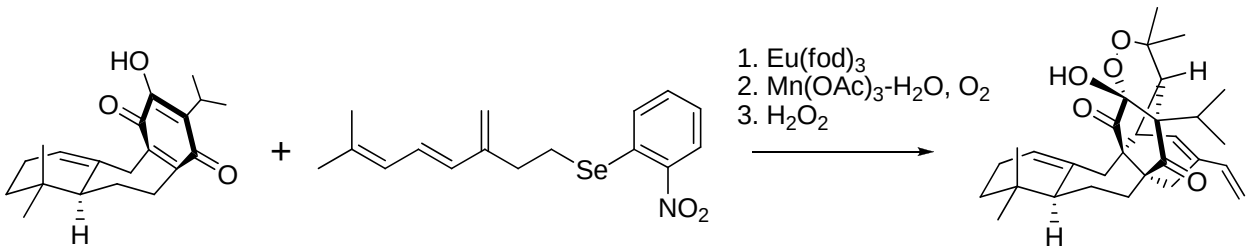
J_2 = 17.5 Hz, 1H), 5.59 (d, *J* = 5.5 Hz, 1H), 5.24 (d, *J* = 17.5 Hz, 1H), 5.07 (d, *J* = 11.0 Hz, 1H), 3.34 (d, *J* = 7.0 Hz, 1H), 2.62 (d, *J* = 17.0 Hz, 1H), 2.48 (heptet, *J* = 7.0 Hz, 1H), 2.42 (d, *J* = 17.0 Hz, 1H), 2.00-2.11 (m, 1H), 2.02 (d, *J* = 18.0 Hz, 1H), 1.82-1.93 (m, 3H), 1.71-1.76 (m, 1H), 1.69 (d, *J* = 18.0 Hz, 1H), 1.63 (s, 3H), 1.41-1.52 (m, 3H), 1.35 (s, 3H), 1.25-1.31 (m, 1H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.20-1.25 (m, 1H), 1.12-1.20 (m, 1H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.06 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.7, 197.2, 137.9, 136.6, 129.5, 113.6, 113.4, 92.7, 87.2, 70.1, 55.4, 53.0, 50.9, 50.0, 42.8, 42.4, 41.5, 40.6, 36.3, 32.9, 30.7, 28.1, 28.0, 27.0, 25.8, 21.9, 20.8, 20.4, 19.8, 19.0; IR(neat) λ_{max} 2936, 1758, 1720, 1258, 1122, 1088, 736 cm^{-1}; HRMS (ESI) calcd for $[M+H]^+$: m/z 481.2654, found 481.2654.



salvadione B

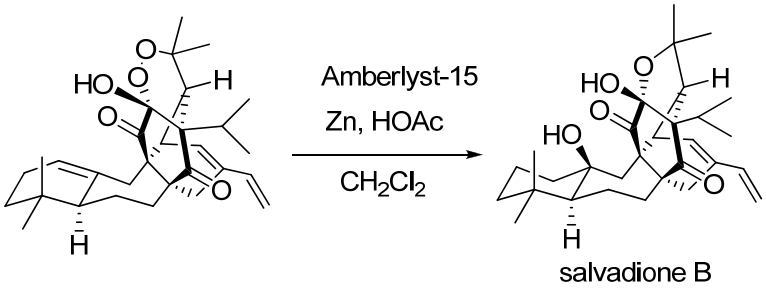
(+)-Salvadione B (2.5.8): To a solution of peroxide acetal **2.5.35** (14.4 mg, 0.03 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C, HOAc (3.68 μL, 0.060 mmol) in CH_2Cl_2 (0.2 mL) and actived Zn powder (7.8 mg, 0.12 mmol) was added. The resulting mixture was stirred at 0 °C for 15 min and rt for 1 h. After being concentrated using a rotary evaporator, the crude residue was purified by column chromatography (elution with EtOAc/pet ether = 1:8) to give pure (+)-salvadione-B (**2.5.8**) as a white solid (10.2 mg, 70%) which was homogeneous by TLC analysis [R_f = 0.35, EtOAc/pet ether = 1:8]: $[\alpha]^{24}_D$ = -26.2° ($CHCl_3$; c = 0.007 g/mL); ^{1}H NMR (500 MHz, $CDCl_3$)

δ 6.26 (dd, J_1= 10.5 Hz, J_2 = 17.5 Hz, 1H), 5.58 (s, 1H), 5.49 (d, *J* = 5.5 Hz, 1H), 5.28 (d, *J* = 15.5 Hz, 1H), 5.12 (d, *J* = 10.5 Hz, 1H), 4.00 (s, 1H), 2.87 (d, *J* = 17.5 Hz,1H),2.52-2.63 (m, 1H), 2.53 (d, *J* = 5.5 Hz,1H), 2.40-2.46 (m, 2H), 2.27 (d, *J* = 15.5 Hz,1H), 1.94-2.08 (m, 2H), 1.74-1.86 (m, 2H), 1.44 (s, 3H), 1.34 (d, *J* = 7.0 Hz,3H), 1.15 (s, 3H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.1, 209.4, 137.1, 136.3, 126.7, 113.5, 100.1, 78.6, 72.7, 61.3, 55.3, 53.7, 51.7, 49.1, 46.1, 43.4, 42.1, 40.5, 35.0, 34.0, 32.0, 29.8, 28.6, 26.2, 21.2, 20.2, 18.9, 18.5, 18.7; IR(neat) λ_{max} 3400, 2929, 1745, 1720, 1386 cm^{-1}; HRMS (ESI) calcd for $[M+Na]^+$: m/z 505.2930, found 505.2922.



One-pot procedure to synthesize peroxide hemiacetal 2.5.33 from chiral benzoquinone (2.5.33): Chiral benzoquinone **2.5.2** (100.0 mg, 0.32 mmol), selenide **2.5.19** (321.2 mg, 0.96 mmol) and $Eu(fod)_3$ (65.34 mg, 0.064 mmol) were dissolved in Et_2O and placed on a rotary evaporator. Once most of the solvent was removed, the reaction flask was connected to a vacuum pump for 30 min. The resulting mixture was heated in a Milestone microwave reactor (200 W, 65 ^{o}C for 30 h). The resulting Diels–Alder adduct was dissolved in HOAc (10.0 mL) and nitrogen gas was bubbled through the solution for 30 min. $Mn(OAc)_3$-H_2O (80.0 mg, 0.32 mmol) was added and dry oxygen gas was bubbled into the reaction mixture. After stirring

at rt for 3 h, TLC analysis indicated that the reaction was completed. The reaction mixture was cooled to 0 ^{o}C and 30% aqueous H_2O_2 (120.0 μL) was added. The resulting mixture was stirred at 0 ^{o}C for 15 min, and then filtered through a small pad of Celite®. The filting cake was washed with Et_2O (30.0 mL). The combined organic phases were washed with brine (5 mL), saturated Na_2SO_3 (5 mL) and brine (5 mL). The resulting organic phase was dried over anhydrous Na_2SO_4, filtrated and concentrated using a rotary evaporator, following by further concentration using a vacuum pump for 30 min. The crude peroxide was submitted to the next reaction without purification and characterization.



One-pot procedure to synthesize (+)-salvadione B (2.5.8) from peroxide hemiacetal (2.5.33): To a solution of the above crude peroxide hemiacetal **2.5.33** in CH_2Cl_2 (10.0 mL) was added Amberlyst-15® (140.0 mg). The resulting mixture was refluxed until TLC analysis indicated that all of the starting materials had reacted (~1 h). The reaction mixture was cooled to 0 ^{o}C whereupon HOAc (14.8 μL, 0.24 mmol) in CH_2Cl_2 (200 μL) was added followed by actived Zn powder (31.2 mg, 0.48 mmol). The resulting mixture was stirred at 0 ^{o}C for 15 min and rt for 1 h. After being concentrated by using a rotary evaporator, the crude product was purified by silica gel chromatography (elution with EtOAc /pet ether = 1:8) to give pure (+)-salvadione B

(**2.5.8**) (24.8 mg, 33% yield from benzoquinone **2.5.2**) which is identical to that previously prepared.

2.7 References and Notes

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