Sulfur Based Cyclizations by Intramolecular Carbometallation and Applications to Natural Product Syntheses

by

Kai Deng

BS, Peking University, 1996

MS, Peking University, 1999

Submitted to the Graduate Faculty of

University of Pittsburgh in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2004

UNIVERSITY OF PITTSBURGH

FACULTY OF ARTS AND SCIENCES

This dissertation was presented

by

Kai Deng

It was defended on

Oct. 15, 2004

and approved by

Dennis P. Curran

Paul E. Floreancig

Richard D. McCullough

Theodore Cohen

Dissertation Director

Advisor: Professor Theodore Cohen

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The versatility of intramolecular carbolithiation of simple unactivated alkenes to yield cyclopentylmethyllithiums by unconjugated organolithiums is greatly increased (1) by generating the organolithiums by reductive lithiation of phenyl thioethers with aromatic radical anions and (2) by using allylic alcohol groups on the receiving alkenes. This type of reductive lithiation allows virtually any kind of organolithium to be generated, usually in a connective manner. Furthermore, the allylic lithium oxyanionic groups on the alkenes greatly accelerate the reactions and lead, in most cases, to completely stereoselective cyclization at -78 °C. Most significantly, the *trans* stereoselectivity is the opposite from that observed when the organometallic is allylic. A four-membered ring has also been generated by this method.

Using allyl phenyl sulfones instead of using allyl acetates as precursors of Pd-catalyzed allylzinc formation greatly facilitates the efficiency of substrate preparation. The resulting allylzinc smoothly undergoes the Zn-ene cyclization onto a simple alkene or an alkyne. This methodology has been used for the most efficient of the published syntheses of the natural sesquiterpene (-)-erythrodiene in highly stereoselective fashion with an overall yield of 60% in 6 linear steps from commercially available (-)-perillyl alcohol. 15-Deoxy-$\Delta^{12,14}$-PGJ_2 (15d-PGJ_2) is a potent anti-inflammatory agent that represses the expression of a number of inflammatory

response genes in activated macrophages. The high-affinity binding of 15d-PGJ_2 to PPARγ (peroxisome proliferator activated receptor-gamma) is believed to be responsible for the repressive effect on gene expression. The total synthesis of this natural product by using the zinc-ene cyclization as the key step has been accomplished in 13 linear steps with good overall yield. Moreover, due to our strategy of installing the double bond on the cyclopentenone ring in the late stage of the synthesis, 9,10–dihydro-15-deoxy-$\Delta^{12,14}$-$PGJ_{2,}$ an analogue of PPARγ–binding prostaglandins, has been synthesized as the precursor of the natural product. The addition of a primary amine to 2-phenylsulfonyl-3-methyl-1,3-diene is a very efficient way to construct allyl phenyl sulfones capable of undergoing the Pd-catalyzed Zn-ene cyclization. A nitrogen-containing heterocycle has been synthesized in high stereoselectivity. The total synthesis of (-)–kainic acid by utilizing this methodology is being proposed and initial studies are reported in this thesis.

PREFACE

The five years that I have spent here have amounted to a fantastic experience; I have many people to thank for that. First and foremost, I want to thank my advisor Ted Cohen with my deepest gratitude. He guided me into the wonderful area of intramolecular carbometallation. He is always there to help when I have difficulties in experiments. Especially, he encouraged me to pursue my own ideas in the research. Besides his comprehensive knowledge in chemistry, his zeal for science and his healthy life style impress me too.

I would also like to thank Professors Dennis P. Curran, Paul E. Floreancig and Richard D. McCullough for serving on my thesis committee and Professors Kazunori Koide and Kay M. Brummond for being on the committee for proposal defense. Their willingness to share their expertise and provide valuable advice is greatly appreciated.

I am very grateful for the help provided by Dr. Fu-tyan Lin, Steven Gelb and Kasi Samayajula in NMR spectroscopy, X-ray crystallography and Mass spectrometry.

A large part of my graduate experience has been interacting with the great people in the Cohen's group, past or present. I want to thank them for their help and friendship. Especially, I want to thank Dr. Darren Harvey for his valuable help when I just started my lab work here. I had the privilege to talk with Dr. Ahlem Bensari on many chemistry problems. Ao Yang and Justin Chalker, Heather Butela, Joseph Whetstone worked with me on several experiments. I enjoyed working with them and want to thank them all. Especially I want to thank Justin Chalker, who read the first draft of this thesis and give me some valuable advice.

Last but not the least, I want to thank my wife Hanbin Liu, whose constant love and understanding supports me during the past five years. A special thank goes to my son David, who was born during this period, for being a good boy.

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Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	benzyloxycarbonyl
COSY	correlation spectroscopy
Cp	cyclopentadienyl
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
Dibal-H	diisobutylaluminum hydride
DMAP	4-N, N-dimethylaminopyridine
DMSO	dimethyl sulfoxide
GC	gas chromatography
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectroscopy
Im	imidazole
IR	infrared spectroscopy
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LDBB	lithium p,p'-di-*t*-butyldiphenylide
LDMAN	lithium 1-(dimethylamino)naphthalenide
LRMS	low resolution mass spectoscopy
L-Selectride	lithium tri(*sec*-butyl)boronhydride
*m*CPBA	3-chloroperoxybenzoic acid
m.p.	melting point
MS	molecular sieve
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
Nu	necleophile
ROESY	rotating-frame overhauser spectroscopy
PCC	pyridium chlorochromate
TBAF	tetra-*n*-butylammonium fluoride
TBACl	tetra-*n*-butylammonium chloride
TBS	*tert*-butyl-dimethyl-silyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TEMPO	Tetramethylpiperidinyl-1-oxy
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMS	Trimethylsilyl

1. Chapter 1

Cyclization by Intramolecular Carbolithiation of Alkyl- and Vinyllithiums Prepared by Reductive Lithiation

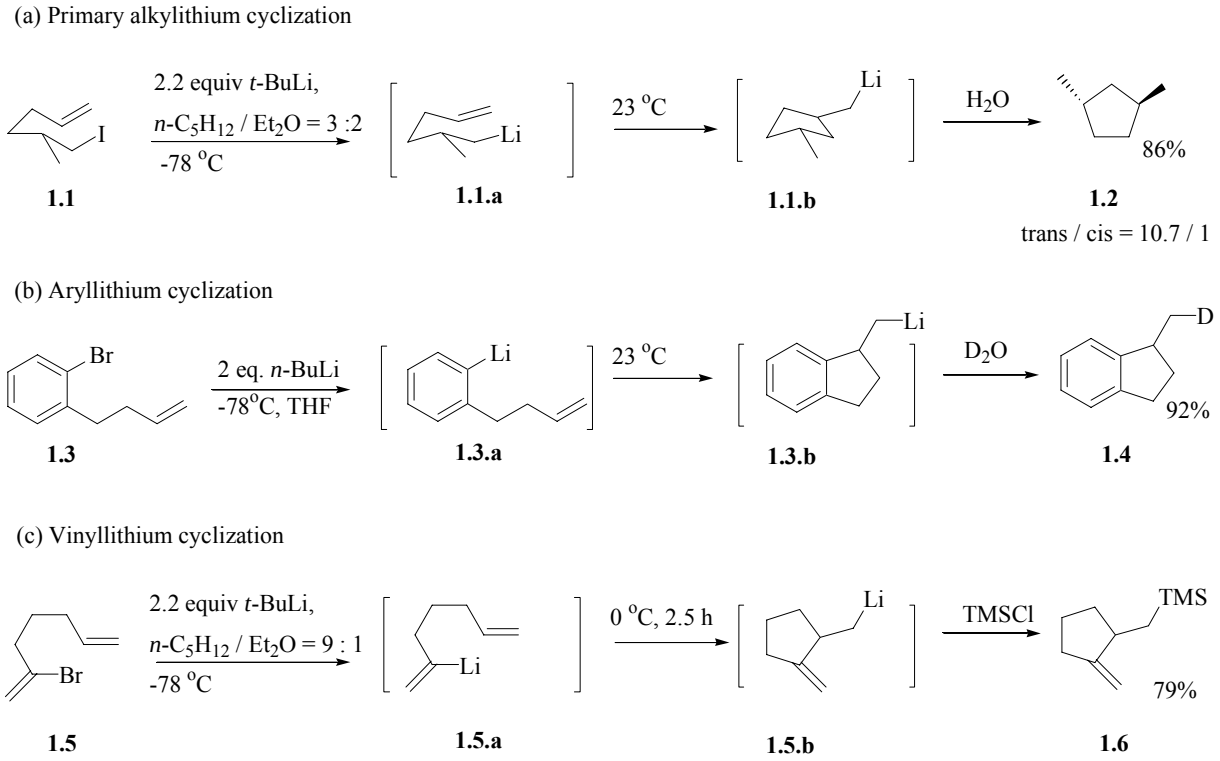
1.1. Introduction

1.1.1. Background for the Available Methods to Produce Organolithiums in Intramolecular Carbolithiation

The intramolecular addition of alkyl- and vinyllithiums to unactivated alkenes is rapidly growing in popularity as a preparative method for cyclopentylmethyllithiums, their heterocyclic analogues and, less effectively, the corresponding six-membered rings.[1] This cyclization method is exclusively regioselective; only 5-exo or 6-exo products are produced. Moreover, the resulting cyclized organolithiums can be trapped by various electrophiles to give functionalized products. However, despite the highly significant work of many chemists, the method has considerable limitations. A major one is the lack of general methods for preparing the organolithiums. In most cases, the organolithium is produced by halogen-lithium, tin-lithium or selenium-lithium exchanges, or by heteroatom-directed lithiation. These preparative methods can only be used for primary organolithiums, vinyllithiums, aryllithiums, or those with special stabilizing features such as adjacent heteroatom groups that direct lithiations.

As shown in Scheme 1.1, halogen-lithium exchange has been used for the generation of primary alkyllithiums (reaction **a**),[2] aryllithiums (reaction **b**)[3] and vinyllithiums (reaction **c**)[4] which are capable of undergoing intramolecular carbolithiation. Although these organolithiums can be produced at temperatures as low as –78 ˚C, higher temperatures (usually 0 ˚C or room temperature) are required for the carbolithiation reaction to occur. All three cyclizations in Scheme 1.1 proceeded smoothly to give cyclized products in good yield after quenching with electrophiles. The I-Li exchange described in reaction **a** by treating a primary iodide with 2.2 equivalent of *t*-BuLi in a solvent system of *n*-pentane-ether (3:2 by volume)[5,6] at –78 ˚C has

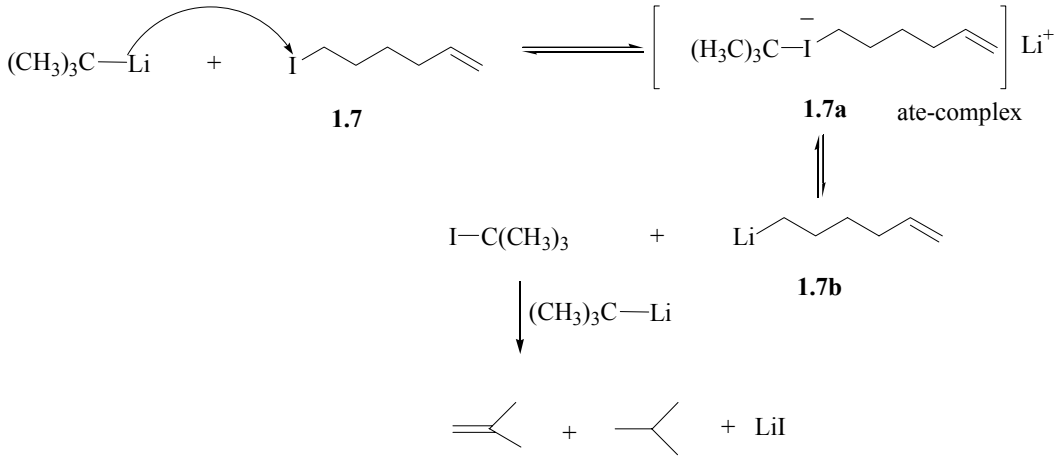
become a standard method to generate primary alkyllithiums and is widely used in organic synthesis.



Scheme 1.1 Halogen-lithium exchange in intramolecular carbolithiation

As illustrated in Scheme 1.2 (primary alkyl iodide **1.7** is a representative example), the mechanism of halogen-lithium exchange of primary alkyl iodides, aryl halides and vinyl halides with *t*-BuLi is generally believed to proceed through an ate-complex intermediate.[7] Usually, *t*-BuLi is used in iodide-lithium exchange in order to get favorable interchange equilibrium and to render the exchange operationally irreversible. Two equivalents of *t*-BuLi are required for the exchange reaction. The first equivalent of *t*-BuLi is used to form the ate-complex **1.7a** which is in equilibrium with the desired primary alkyllithium **1.7b** and byproduct *t*-BuI. The second

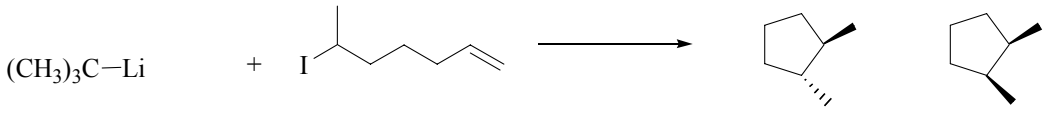
equivalent of *t*-BuLi consumes the *t*-BuI rapidly and drives the equilibrium to the product side. A similar mechanistic argument applies to the generation of aryllithium and vinyllithium by halogen-lithium exchange. However, unlike the reaction of primary alkyl iodide with *t*-BuLi, the reaction of alkyl bromide with *t*-BuLi is believed to involve radical intermediates. Radical cyclization products likely contaminate the cyclization products, when an alkyl bromide is used as a precursor.



Scheme 1.2 Mechanism of iodide-lithium exchange: formation of ate complex

The limitation of halogen-lithium exchange is that it is not appropriate for the generation of secondary and tertiary alkyllithiums due to severe Wurtz-type coupling and elimination reactions of secondary and tertiary alkyl halides. However, Bailey and coworkers have reported the lone example of cyclization of a secondary alkyllithium generated by iodide-lithium exchange (Scheme 1.3).[8] They found that the reaction was dependent on the order of addition of the two reactants. When *t*-BuLi was added to iodide **1.8**, two cyclized products, **1.9** and **1.9a**, were obtained with low yield (5.3% and 7.9% respectively) and poor selectivity (slightly

favoring the *cis* product). However, when iodide **1.8** was added to *t*-BuLi, almost pure *trans* product **1.9** was obtained. They suggested that two competing mechanisms exist for this reaction. One mechanism is the iodide-lithium exchange via an ate-complex. The secondary alkyllithium being produced then cyclizes to afford the *trans*-diastereomer. Another mechanism involves a single electron transfer. A radical intermediate is generated and it is known that radical cyclization of this type of substrate gives the *cis*-diastereomer as the major product.[9] When iodide **1.8** was added to the solution of *t*-BuLi, due to the high local concentration of *t*-BuLi, the reaction may proceed through the ate-complex to generate the secondary alkyllithium which cyclizes to give *trans* product **1.9**. The yield is low (44%) and Wurtz-type coupling products were found from the reaction. When *t*-BuLi is added to the solution of iodide **1.8**, due to the low local concentration of *t*-BuLi, a single electron transfer mechanism is operational and the radical intermediate cyclizes to afford products with more *cis* selectivity. Moreover, they observed that the secondary alkyllithium cyclization is very fast. Apparently the reaction is complete in 10 min at –78 ˚C with almost pure *trans* product being obtained.



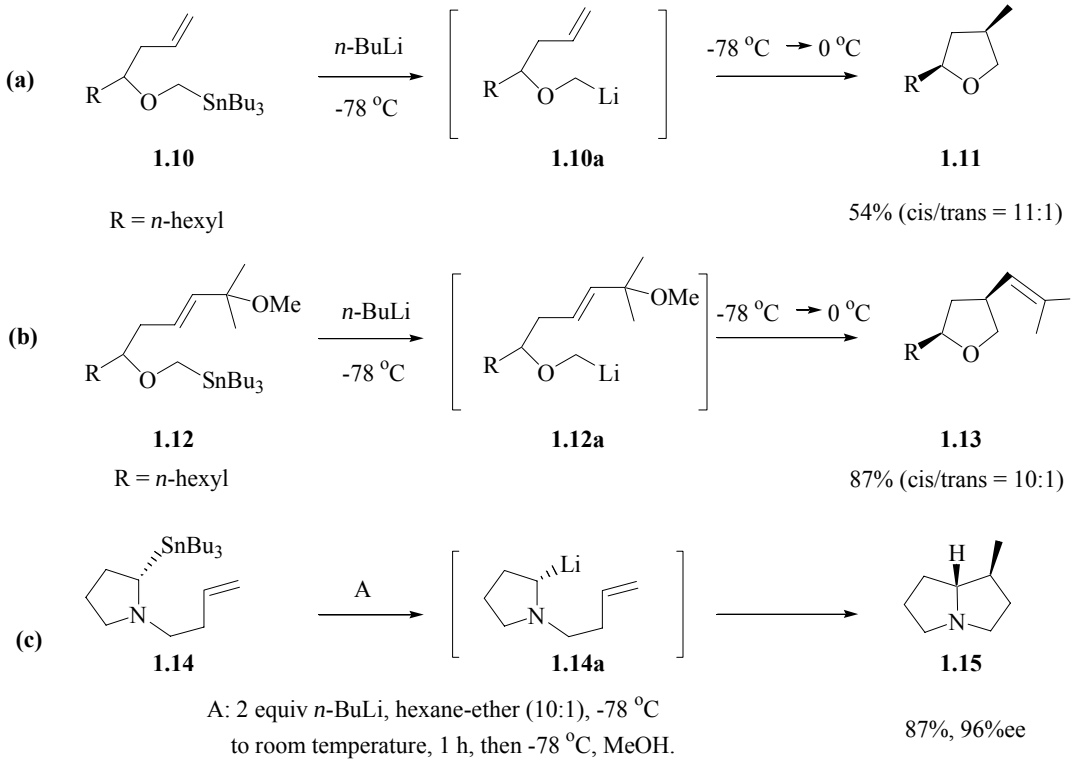
	1.8	**1.9**	**1.9a**
1. Addition of *t*-BuLi to iodide		5.3	7.9
2. Addition of iodide to *t*-BuLi		44.0	< 1

Scheme 1.3 Study of secondary alkyllithium cyclization by halogen-lithium exchange

Tin-lithium exchange has also been used to produce organolithiums in intramolecular carbolithiations (Scheme 1.4). Organolithiums react rapidly and reversibly with stannanes,

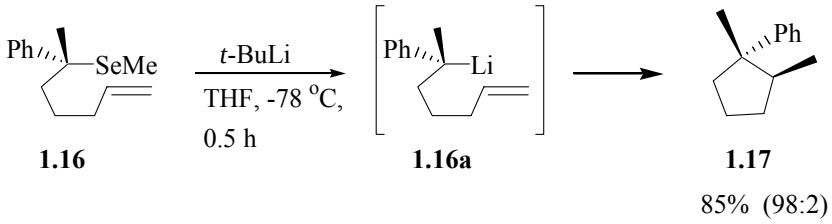
exchanging the alkyl group of the organolithium for an alkyl group of the stannane. The reaction is under thermodynamic control and produces the most stable organolithium. This method is good for the synthesis of aryllithiums, vinyllithiums and α-heterosubstituted organolithiums.[1c]

α-Alkoxylithium **1.10a**, prepared by treating **1.10** with *n*-BuLi in THF at –78 °C, undergoes anionic cyclization to afford *cis*-2, 4-disubstituted tetrahydrofuran **1.11** upon warming (Scheme 1.4, reaction **a**).[10] The use of allylic ether as cyclization terminator is also described (reaction **b**). Coldham and coworkers[11] used lithium-tin exchange to convert **1.14** to configurationally stable α-aminoorganolithium **1.14a** which undergoes stereoselective cyclization at – 78 ˚C in the efficient synthesis of (+)-pseudoheliotridane **1.15** (reaction **c**).



Scheme 1.4 Tin-lithium exchange in intramolecular carbolithiation

Selenium-lithium exchange is an alternative to tin-lithium and halogen-lithium exchange. This method can be useful only when there is a significant difference in stability between the starting organolithium and the resulting organolithium. Usually it is used to generate stabilized organolithiums, such as allyllithiums and benzyllithiums, which cannot be generated by halogen-lithium exchange because of coupling between the newly formed organolithium and the unreacted halide. Krief and co-workers[12] used selenium-lithium exchange to convert phenyl methyl selenide **1.16** to benzyllithium **1.16a**, which can undergo highly regio- and stereoselective cyclization to give **1.17** in good yield (Scheme 1.5).

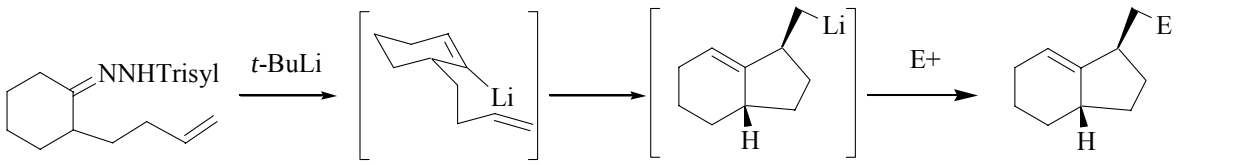


1.16 **1.16a** **1.17**

85% (98:2)

Scheme 1.5 Selenium-lithium exchange in intramolecular carbolithiation

The Shapiro reaction can only be used to generate vinyllithiums. Chamberlin's group[13] has explored the intramolecular addition of vinyllithium **1.18a**, derived from ketone 2,4,6-triisopropylbenzenesulfonyl hydrazone **1.18**, to unactivated alkenes (Scheme 1.6). Functionalized methylenecyclopentanes have been prepared by trapping of the product organolithiums with electrophiles.



1.18 **1.18a** **1.18b** **1.19**

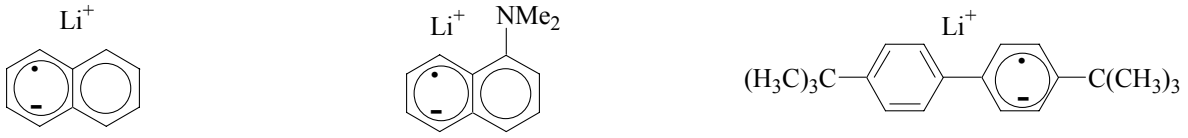
E = D (87%) **1.19a**
= Br (81%) **1.19b**
= CHO (61%) **1.19c**
= CO_2H (50%) **1.19d**

Scheme 1.6 Shapiro reaction in intramolecular carbolithiation

In summary, although several methods are available for the generation of organolithiums capable of undergoing intramolecular carbolithiation reactions, none of them is general. Each method is successful for certain substrates. However, the reductive lithiation method is different. Primary alkyllithiums, vinyllithiums, allyllithiums, but also secondary and tertiary alkyllithiums can be generated very efficiently. By using the reductive lithiation method to produce organolithiums, the versatility of intramolecular carbolithiation will be greatly expanded.

The reductive lithiation of phenylthioethers by lithium naphthalenide (LN), independently discovered by Cohen[14] and Screttas[15] in the late 70's, has proved to be a general method to produce organolithiums. Subsequent developments for alternative reducing agents resulted in the discovery of lithium 1-(dimethylamino)naphthalenide (LDMAN)[16] and lithium 4,4'-di-*tert*-butylbiphenylide (LDBB).[17] All three radical anion reducing agents (Figure 1.1) are generated in THF since other commonly used solvents have proved to be ineffective. One limitation of using THF as solvent is that the newly formed organolithium will self-destruct by removing a proton from THF at temperature higher than 0 ˚C. Recently the problem related to proton abstraction from THF was overcome by using LDMAN (lithium 1-

dimethylaminonaphthalenide) in dimethyl ether to generate the radical anion.[18] After the reductive lithiation of the phenylthioether at low temperature, usually at –78 °C, the desired solvent can be added and the volatile dimethyl ether can be removed at reduced pressure (the boiling point of Me_2O is -24 °C).



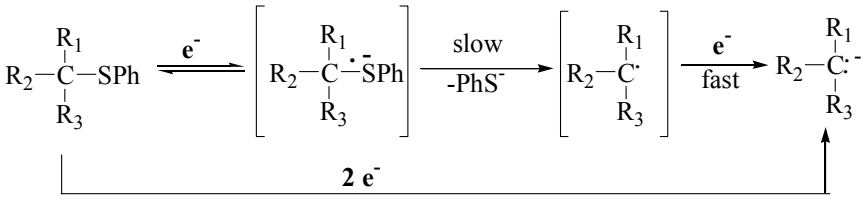
Lithium naphthalenide (LN)

Lithium 1-(dimethylamino)naphthalenide (LDMAN)

Lithium *p*,*p*'-di-*t*-butylbiphenylide (LDBB)

Figure 1.1 Aromatic radical anion reducing agents

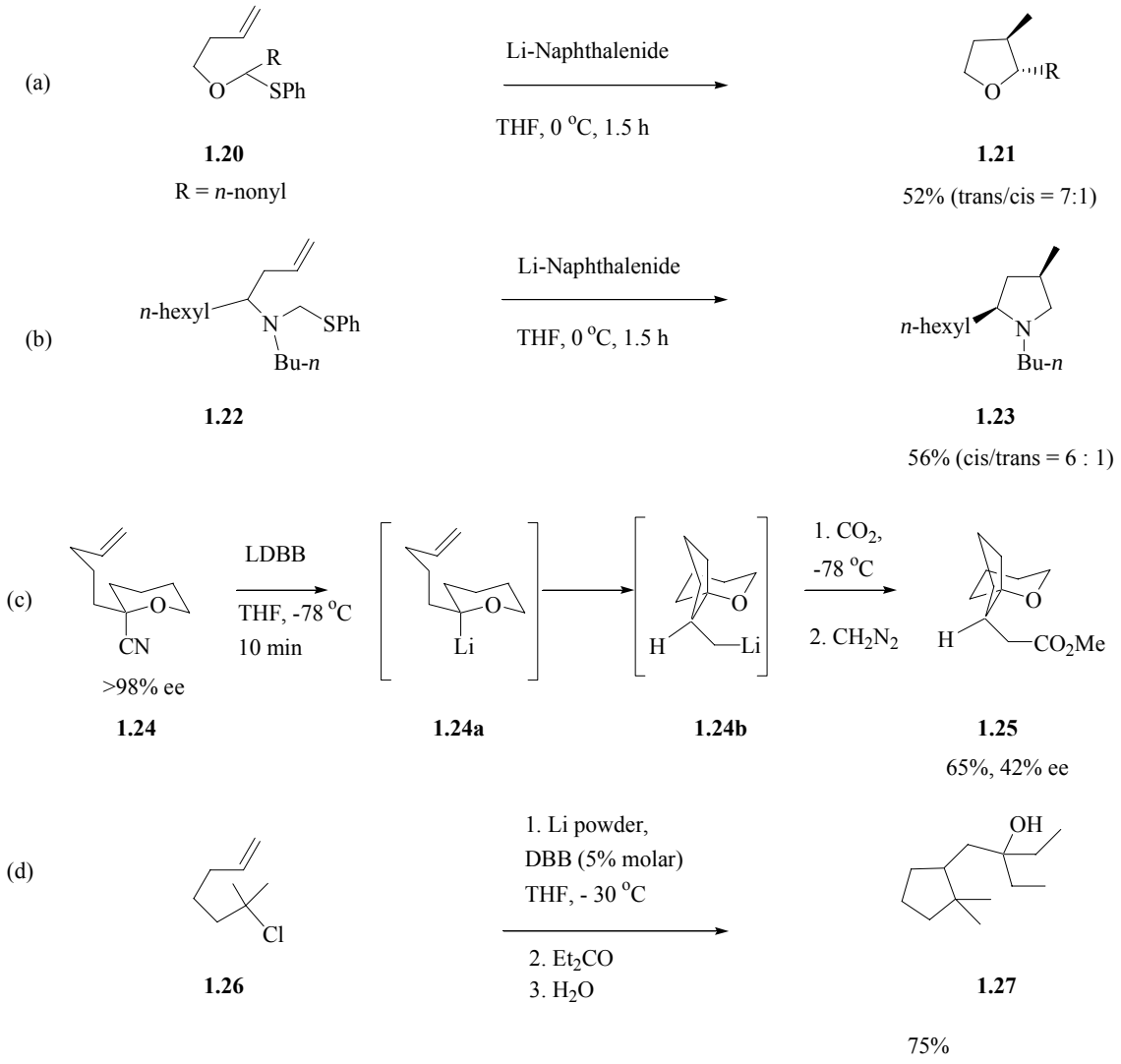
As shown in Scheme 1.7, the mechanism[19] of reductive lithiation of phenylthioethers is generally believed to involve the reversible transfer of an electron from the reducing agent (LN, LDMAN, LDBB) to the phenylthioether. The resulting radical anion intermediate liberates the thiophenoxide ion by homolytic cleavage of a C-S bond. A carbon radical, generated at the same time, can rapidly be reduced to the corresponding carbanion by another equivalent of radical anion reducing reagent. Thus, two molar equivalents of radical anion reducing agents are required for one molar equivalent of phenylthioether. The formation of the carbon radical is thought to be the rate-determining step; the rate is determined largely by the stability of the resulting radical. Thus, less stable carbanions are often produced more readily due to the stability order of the corresponding carbon radicals (tertiary radicals > secondary radicals > primary radicals and $sp^3 > sp^2$).



Scheme 1.7 Mechanism of reductive lithiation

Broka reported two examples of intramolecular carbolithiation of nonconjugated alkyllithiums prepared by reductive lithiation of **1.20** and **1.22** (Scheme 1.8, reaction **a** and **b**, respectively) to form substituted tetrahydrofuran **1.21** and pyrrolidine **1.23**, respectively, with good stereoselectivity and useful yield. However, no systematic studies of the use of reductive lithiation in intramolecular carbolithiation have been performed prior to the work reported here. Recently, while the work reported here was in progress, Rychnovsky's group reported[20] a tertiary carbanion cyclization during the study of a conformational radical clock for evaluating alkyllithium-mediated cyclization reactions (Scheme 1.8, reaction **c**). The tertiary carbanion **1.24a** was produced by reductive lithiation of a nitrile substrate **1.24**. The results show that the cyclization is very fast and is complete within 10 min at –78 °C. It was also demonstrated that although there is a radical intermediate during reductive lithiation, this method is suitable to generate alkyllithiums used in intramolecular carbolithiation without worrying about the conceived radical cyclization. While the present work was in press,[21] Yus reported another tertiary carbanion cyclization (reaction d).[22] The carbanion was generated by catalytic reductive lithiation of an alkyl chloride **1.26**. When the reaction was performed at -78 °C, no cyclization product was observed. Yus concluded that the tertiary carbanion is very unstable and it can abstract a proton from THF before it could cyclize. We think this explanation is not very likely due to the low temperature used. In my work, it is shown that the same tertiary carbanion,

produced by reductive lithiation of the corresponding phenylthioether, is stable at - 78 °C for at least 1 h and that the cyclization is very slow at - 78 °C. A likely explanation for Yus's result is that the tertiary carbanion, instead of attacking the ketone carbonyl group, removes an α-proton from 3-pentanone.

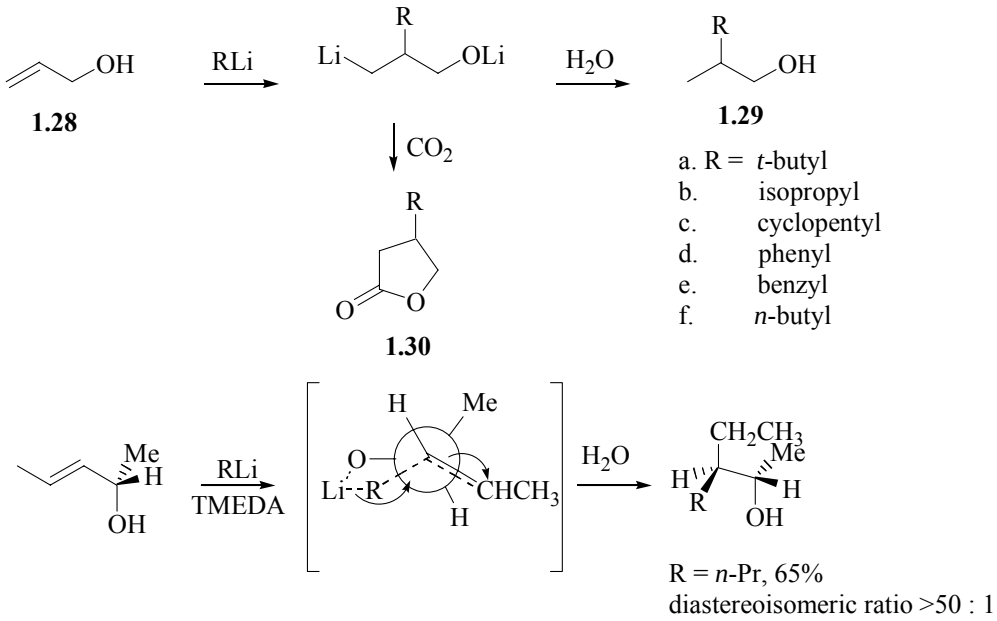


Scheme 1.8 Examples of using reductive lithiation in intramolecular carbolithiation

1.1.2. Background for Lithium Oxyanionic Effect in Accelerating Cyclization Rate and Exerting Stereocontrol over Intramolecular Carbolithiation Reactions

1.1.2.1. Intermolecular addition of organolithiums to allylic alcohols

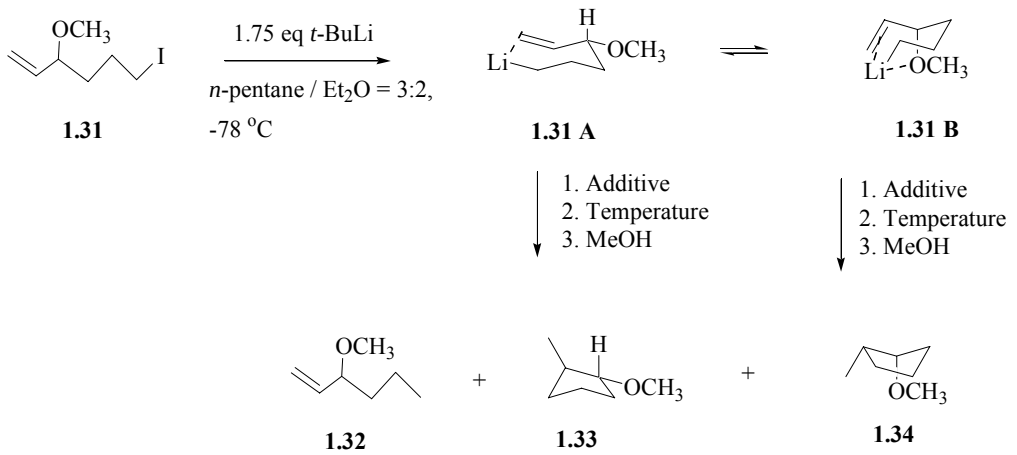
Intermolecular addition of simple organolithiums to nonconjugated olefins has proven to be difficult.[23] However, Crandall[24] and Felkin[25] discovered that organolithium compounds could add readily to allylic alcohol and some other substituted allylic alcohols (Scheme 1.9). The organolithium attacks regioselectively at the internal carbon atom of the double bond. It is believed that lithium-oxygen coordination plays an important role in the reaction. Felkin proposed a model in which lithium coordinates with the oxyanion to form a 5-membered ring transition state to account for the high diastereoselectivity of the reaction shown below.



Scheme 1.9 Intramolecular addition of organolithium to allylic alcohols

1.1.2.2. Intramolecular Addition of Organolithiums to Alkenes Bearing Allylic Lithium Oxyanionic Groups

Although intramolecular carbolithiation has been studied extensively, much less information is available on the cyclization of 5-hexenyllithiums bearing heteroatom substituents. In 1981, Smith and Wilson[26] published their studies on the influence of an allylic methoxy group on the cyclization of an alkenyllithium. They found that cyclization of 6-lithio-3-methoxy-1-hexene (prepared by treatment of 6-chloro-3-methoxy-1-hexene with a Li dispersion in Et_2O) followed by quenching with water provided a 34% yield of *cis*- and *trans*- cyclization products as a 1:1 mixture. It was further reported that the addition of 1 equivalent of *n*-BuLi changed the reaction completely and only *cis*-1-methoxy-2-methylcyclopentane was obtained. It is difficult to understand why *n*-BuLi has such a great effect in the cyclization. Bailey suspected that perhaps (4-methoxy-5-hexenyl)-1-radical was an intermediate in the reaction with *n*-BuLi as an additive and the cyclization is actually a radical-mediated process. In order to address this issue, Bailey and Jiang[27] studied the cyclization of 6-lithio-3-methoxy-1-hexene again by using low temperature lithium iodine exchange to generate the primary organolithium (Scheme 1.10).



1.31 **1.31 A** **1.31 B**

1.32 **1.33** **1.34**

product yields %

entry	additive	temp, °C	**1.32**	**1.33 + 1.34**	***trans/cis***
1	none	0	12.1	88.1	7.7
2	none	-30	73.9	22.0	21.9
3	THF (1.75 molar equiv.)	0	49.6	49.0	3.0
4	THF (72.5 molar equiv.)	0	9.7	77.1	0.66
5	TMEDA	0	22.2	74.5	0.25

Scheme 1.10 Intramolecular carbolithiation by the addition of an organolithium to an olefin bearing an allylic methoxy group

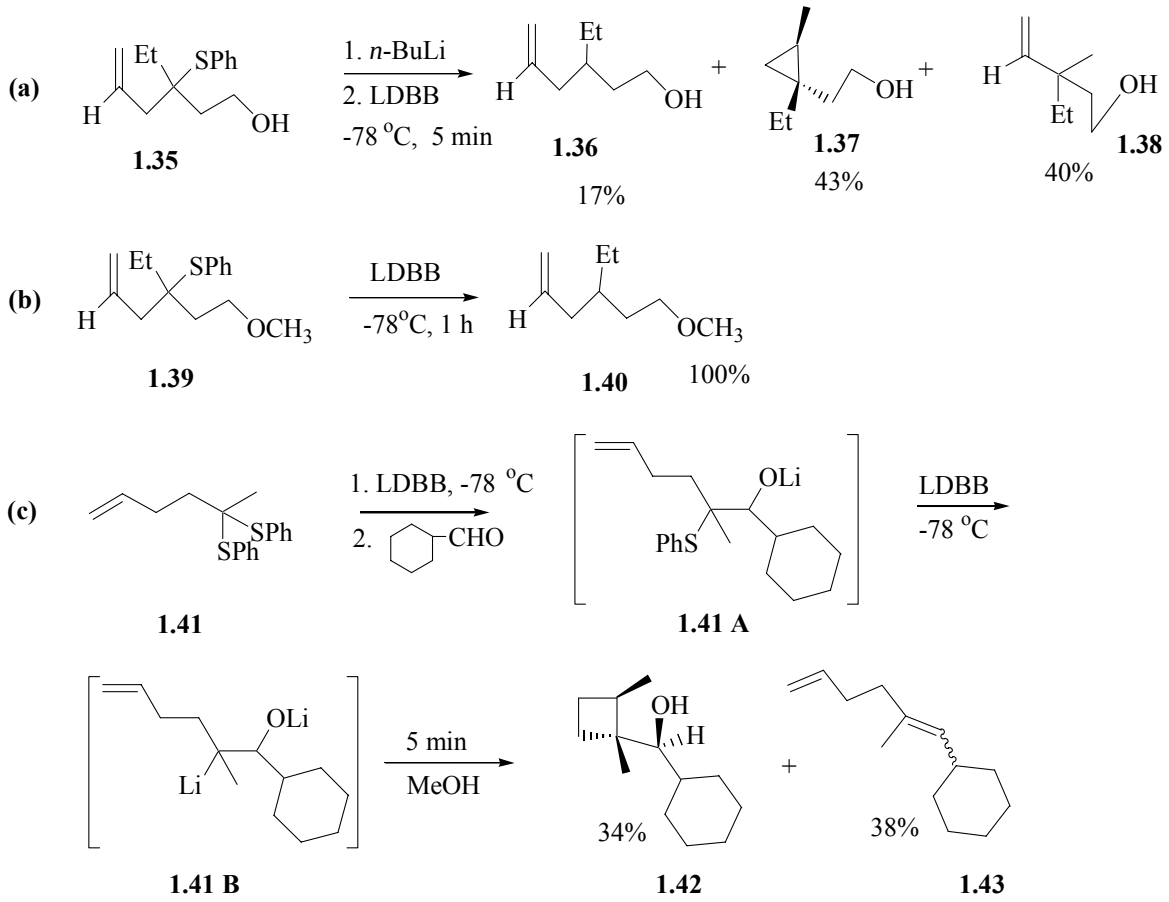
It was found that the isomeric composition of the *cis*- and *tran*-1-methoxy-2-methylcyclopentane, produced upon cyclization of 6-lithio-3-methoxy-1-hexene followed by quenching with MeOH, dramatically depended on the solvent system in which the cyclization is conducted. High *trans* product was obtained when the reaction was performed in a solvent system like pentane:Et_2O = 3:2 (by volume) at 0 ˚C (Scheme 1.12, entry 1). When the temperature is lowered to – 30 ˚C, the cyclization rate is decreased considerably but the *trans*-

selectivity increased to 21.9:1 (entry 2). Two transition states, **1.31 A** and **1.31 B,** have been proposed to explain the stereochemical outcome of the cyclization. In structure **1.31 A**, the methoxy group occupies a pseudoequatorial position in the chair-like transition state leading to *trans* product. The methoxy group just behaved like a normal alkyl substituent at this position. In structure **1.31 B**, the methoxy group occupies a pseudoaxial position so the primary alkyllithium can coordinate with the oxygen atom leading to *cis*-product. Obviously this transition state will develop a 1,3 diaxial interaction. In solvent systems like a mixture of pentane and ether, transition state **1.31 A** must be more favorable as shown by more *trans* product. However, it is difficult to understand why the addition of a polar solvent THF and TEMDA leads to more *cis* product (entry 3, 4, 5). The usual concept is that these lithiophilic solvents will break down the intramolecular coordination between the lithium and oxygen atoms in transition state **1.31 B** to give less *cis* product. We have done some experiments that bear on this issue and they will be discussed in detail in the discussion section.

1.1.2.3. Intramolecular Addition of Nonconjugated Organolithiums to Alkenes Bearing a Lithium Oxyanionic Group

During their studies on 1,2-vinyl rearrangements of secondary and tertiary homoallyllithiums to less substituted homoallyllithiums, Mudryk and Cohen[28] discovered a remarkable acceleration of a rearrangement by an oxyanionic group (Scheme 1.11, reaction **a**). This is the first observation of an oxyanionic acceleration of a carbanionic ring closure (in this case it is the formation of a cyclopropane ring). Moreover, the cyclization is completely stereoselective; compound **1.37** was obtained as a single diastereomer. Interaction between the

lithium oxyanion and the alkene together with the coordination of the oxyanion with the lithium attached to the tertiary carbanion is proposed to explain the *trans*-stereoselectivity. When the alcohol is masked as the corresponding methyl ether **1.39** (reaction **b**), no ring formation or rearrangement occurs after the corresponding tertiary anion was stirred at –78 ˚C for 1 h.



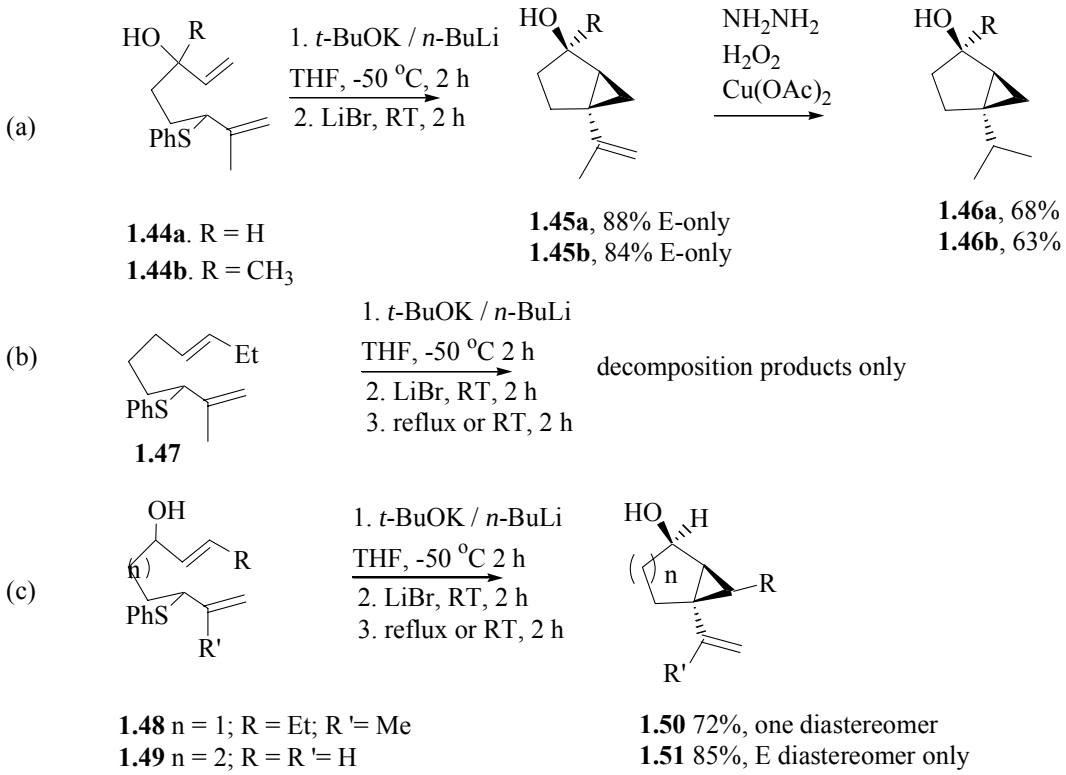
Scheme 1.11 Intramolecular additions of nonconjugated organolithium to olefins bearing lithium oxyanionic group

Later, Cohen and coworkers found another lithium oxyanion accelerated reaction.[29] A tertiary carbanion with an adjacent oxyanionic substituent cyclized very rapidly at –78 °C to

afford a 4-membered ring **1.42** as a single diastereomer together with olefin by-product **1.43** (reaction **c**). The X-ray crystal structure of compound **1.42** indicates that the CH_2Li group in the immediate precursor **1.41 B** of the cyclized product is oriented *trans* to the side chain bearing the oxyanion as in the similar homoallyllithium case shown in reaction **a**.

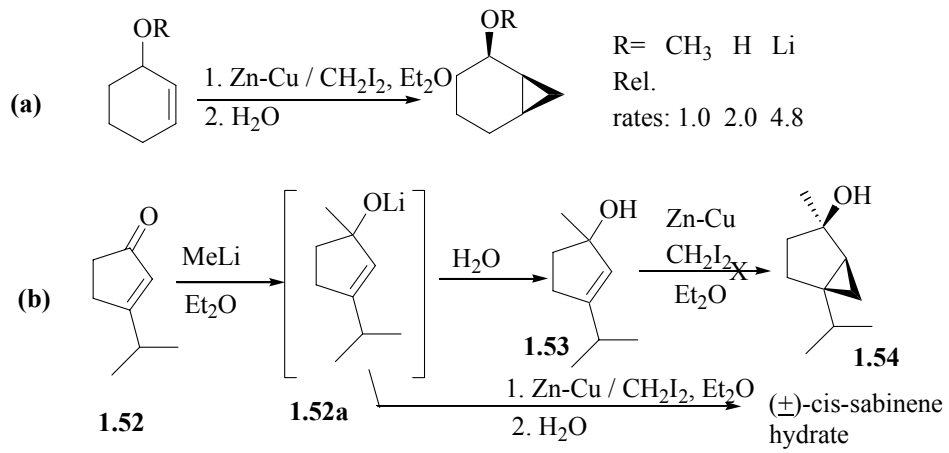
1.1.2.4. Intramolecular Addition of Conjugated Organolithiums to Olefins Bearing an Allylic Lithium Oxyanionic Group

Very recently, Cohen's lab published the first observation of allylic lithium oxyanion induced reactivity and stereoselectivity in a lithium-ene reaction.[30] The cyclization (Scheme 1.12 Reaction **a**) occurred at room temperature rather than the reflux temperature required in the absence of allylic lithium oxyanion. More importantly, the cyclization is completely stereoselective, single diastereomers **1.45a** and **1.45b** being obtained for each reaction as determined by chromatographic and NMR spectroscopic behavior. Utilizing this method, the most efficient synthesis of *cis*-sabinene hydrate **1.46b** has been achieved. The cyclization of 5-hexenyllithium has been confined to substrates in which the terminal alkene carbon is either unsubstituted, or bears a substituent that is able to stabilize the newly generated alkyllithium after cyclization. For example, in reaction **b**, substrate **1.47** has an ethyl group at the terminal carbon of the olefin and no cyclization occurs. The successful cyclization of **1.48**, which has a terminal substituted olefin to give compound 1.50, is an excellent demonstration of the facilitating effect of the allylic lithium oxyanionic group (reaction **c)**. Impressively, the cyclized product **1.50** was formed as a single diastereomer. Compound **1.51**, a 6-membered ring analogue of **1.50**, has also been obtained in good yield as a single diastereomer.



Scheme 1.12 Tandem lithium-ene cyclization and thiophenoxide expulsion to produce fused vinylcyclopropanes

An allylic lithium oxyanionic directed and facilitated Simmons-Smith cyclopropanation was studied by Cohen and coworkers recently (Scheme 1.15).[31] It was found that the cyclopropanations are faster for the lithium salts than for the allylic alcohols themselves (equation **a**). A more important discovery is that the lithium salts of acid-sensitive allyl alcohols such as **1.53**, which themselves decompose during Simmons-Smith cyclopropanation, undergo smooth cyclopropanation in the usual stereochemical fashion. This concept was applied to the most efficient synthesis of (±)-*cis*-sabinene hydrate **1.54**.



Scheme 1.13 The allylic lithium oxyanion directed and facilitated Simmons-Smith cyclopropanation

Although intermolecular addition of organolithiums to allylic alcohols, intramolecular addition of organolithiums with adjacent lithium oxyanion to alkenes to form 3- or 4-membered rings and intramolecular lithium-ene reactions mediated by allylic lithium oxyanion have been studied in depth, no studies have addressed the intramolecular addition of simple nonconjugated organolithiums to olefins bearing an allylic lithium oxyanionic group. We decided to work on this subject with the aim of increasing the versatility of intramolecular carbolithiation by introducing useful alcohol functionality into the cyclized product.

1.2. Results and Discussion

1.2.1. Intramolecular Carbolithiation Using Tertiary and Secondary Alkyllithiums Produced by Reductive Lithiation of Phenylthioethers

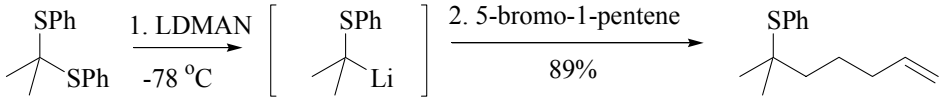
1.2.1.1. Preparation of 6-Methyl-6-phenylthio-1-heptene and 6-Phenylthio-1-heptene

Two phenylthio-substituted alkenes, **1.55** and **1.56**, were synthesized in high yield by taking the advantage of the unique properties of sulfur.

1.55 **1.56**

Figure 1.2 Precursors of tertiary and secondary carbanions capable of undergoing intramolecular carbolithiation

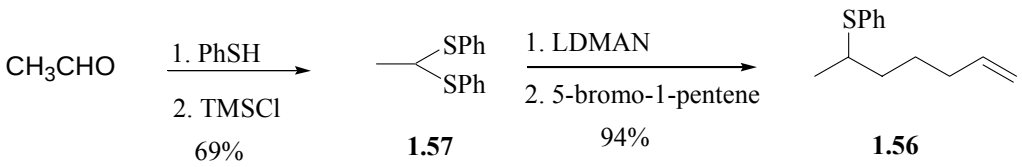
The synthesis of 6-methyl-6-phenylthio-1-heptene (**1.55**) was accomplished easily by using the strategy outlined in Scheme 1.14. Reductive lithiation of 2,2-bis(phenylthio)propane with LDMAN generated 2-phenylthio-2-lithopropane **1.55a,** which can be quenched directly by 5-bromo-1-pentene to afford the desired phenylthioether **1.55**. No formation of cuprate is needed. Although one equivalent of thiophenoxide anion is generated during the reductive lithiation, apparently the nucleophilicity of **1.55a** is much higher and no undesired attack of thiophenoxide on 5-bromo-1-pentene was observed when one equivalent of electrophile was used.



1.55a **1.55**

Scheme 1.14 Preparation of 6-methyl-6-phenylthio-1-heptene

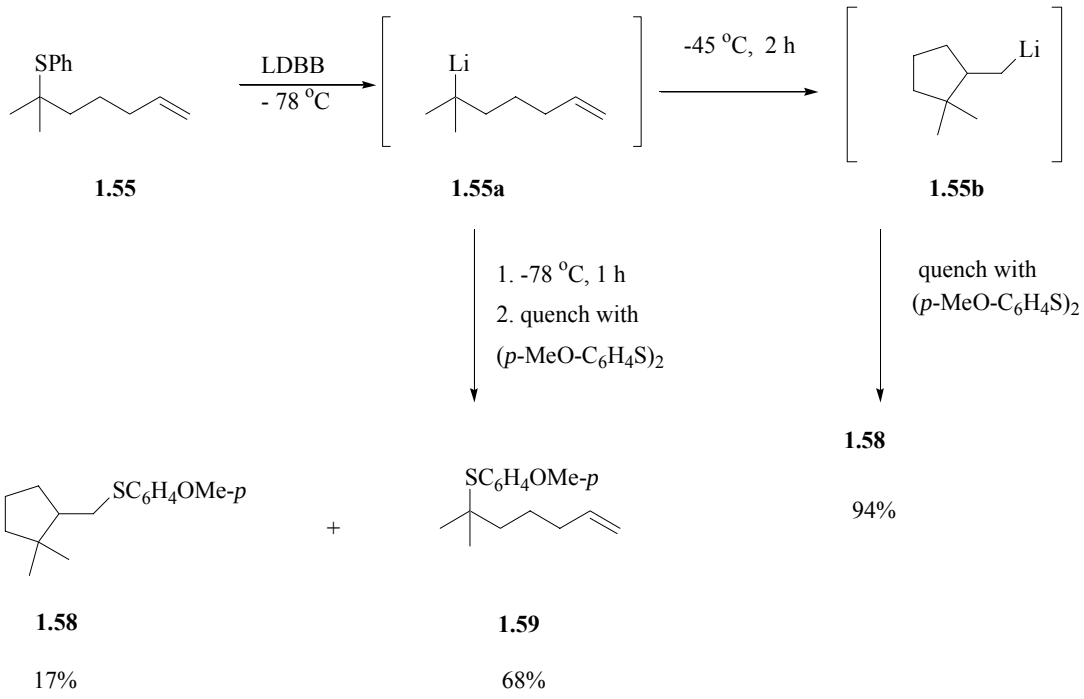
Similarly, 6-phenylthio-1-heptene **1.56** was synthesized as illustrated in Scheme 1.15. The phenylthioacetal **1.57** of acetaldehyde can be obtained very easily by trimethylsilyl chloride mediated thioacetalization of acetaldehyde.[32]



Scheme 1.15 Preparation of 6-phenylthio-1-heptene

1.2.1.2. Intramolecular Carbolithiation by a Tertiary Alkyllithium

Scheme 1.16 shows what was, when it was performed, the first example of a tertiary carbanionic cyclization. It occurs at a far lower temperature than that at which cyclizations of primary alkyllithiums are usually performed.



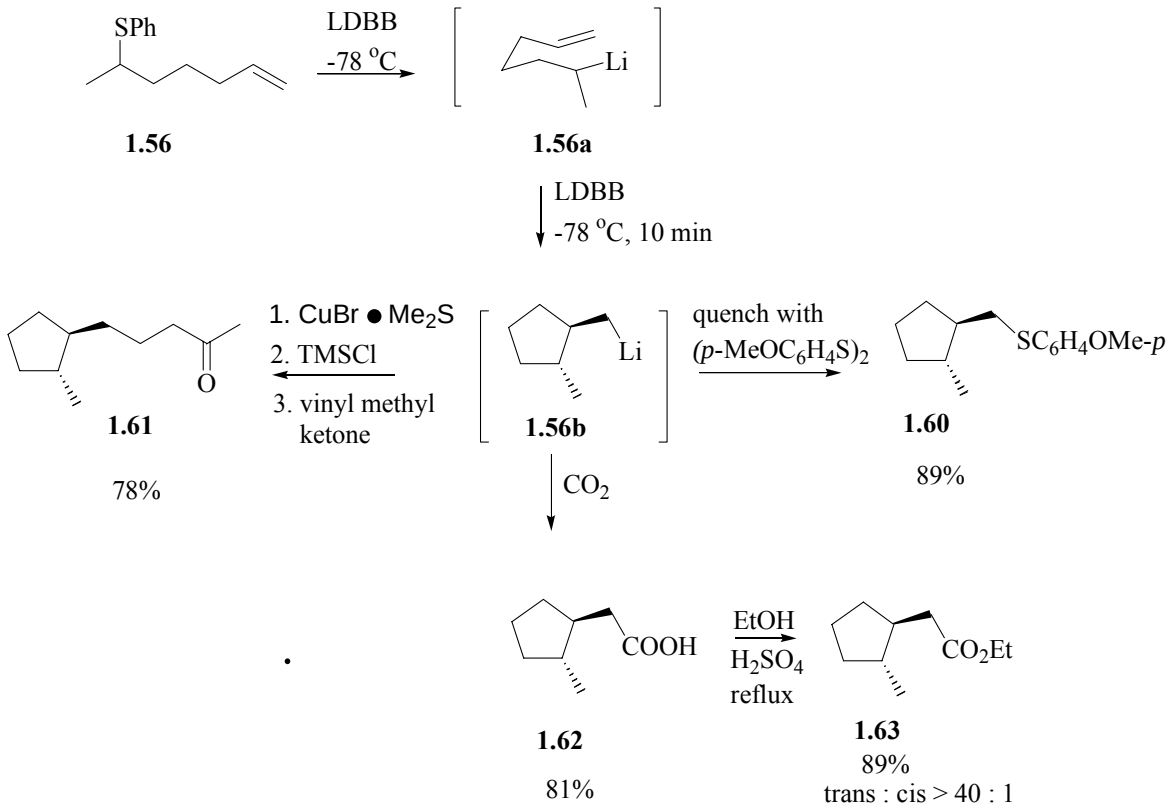
Scheme 1.16 Tertiary carbanion cyclization

Phenylthioether **1.55** was treated with LDBB to generate the corresponding tertiary carbanion **1.55a** which partially cyclized when the reaction was performed at –78 °C for 1 h. Cyclized product **1.58** was isolated in 17% yield in addition to 68% of uncyclized product **1.59**. Complete cyclization was achieved by performing the reaction at –45 °C for 2 h. For the cyclization of the primary alkyllithium to form a cyclopentane ring, room temperature is needed when a mixture of pentane and diethyl ether is used as the solvent.[33] When THF is used as the reaction medium in the primary case, no cyclization occurs at all at –78 °C and –30 °C is needed to realize the cyclization. Thus, the tertiary alkyllithium cyclization is far faster than that of a primary alkyllithium. This kinetic result is not surprising considering the fact that tertiary anions are more reactive than primary anions. Our result also shows that the tertiary carbanion is stable at –78 ˚C in THF, contrary to Yus's claim (Scheme 1.8, reaction **d**).

1.2.1.3. Intramolecular Carbolithiation of an Unconjugated Secondary Alkyllithium

The cyclization of a secondary organolithium has been studied by Bailey using I-Li exchange. This lone secondary example proceeded in less than quantitative yield (44%) and the reaction mixture contained hydrocarbons produced by Wurtz-type coupling and elimination. The authors concluded, "The secondary systems are not as well behaved as are the primary alkenyllithiums." However, when reductive lithiation of **1.56** is used to generate 1-lithio-1-heptene **1.56a**, the cyclization behaves as satisfactory as that of the primary one (Scheme 1.17). High yields of cyclized products are obtained when the reaction is quenched by various electrophiles. Three important points need to be addressed to fully understand such secondary alkyllithium cyclizations.

Firstly, the secondary alkyllithium **1.56a**, generated by treating **1.56** with radical anion reducing agent LDBB, cyclized very fast and the reaction is complete in 10 min at –78 °C. The cyclization is far faster than the corresponding tertiary and primary alkyllithium cyclizations. It is known that tertiary carbanions are more reactive than secondary carbanions in nature. However, it is likely that the congestion of the transition state for the tertiary carbanion cyclization is responsible for the slower cyclization of tertiary alkyllithium than that of secondary alkyllithium.



Scheme 1.17 Secondary carbanion cyclization

Secondly, the resulting cyclized organolithium **1.56b**, and undoubtedly those from the cyclizations of primary and tertiary carbanions can be trapped by various electrophiles to give functionalized products. Scheme 1.17 shows three examples. **I:** Di-*p*-methoxyphenyl disulfide was added to the reaction mixture to afford **1.60** in excellent yield (89%). **II:** Due to the presence of lithium thiophenoxide in the solution, adding cuprous bromide-dimethyl sulfide complex formed a mixed cuprate bearing a thiophenoxide group. The derived mixed cuprate undergoes 1,4 addition to methyl vinyl ketone to give compound **1.61** in 78% yield and only the alkyl group is transferred during the conjugate addition. **III:** Passing CO_2 into the reaction mixture furnished carboxylic acid **1.62** which was transformed to **1.63** by Fisher esterification. The results here demonstrate that reductive lithiation of the phenylthioether is a much more

efficient method for the generation of a secondary carbanion than the low temperature lithium-iodine exchange.

Thirdly, and perhaps most interestingly, the stereochemistry of the cyclized products are almost purely *trans* (*trans*/*cis* > 40:1, determined by proton NMR spectra) as Bailey had observed previously in the one case that he studied. The spectroscopic data of **1.63** are identical in all respects to those of the known ethyl-*trans*-2-methylcyclopentylacetate.[34] The almost complete *trans* selectivity of the cyclization supports an anionic cyclization rather than a radical cyclization followed by reduction of the resulting cyclopentylmethyl radical because the corresponding 5-exo secondary radical cyclization gives a mixture of two diastereomers with a *cis*/*trans* ratio of 66/34. By examining a molecular model, it looks as if the *cis* product should be favored since it appears that as the new C-C bond is being formed, the methyl group can point away from the double bond, which would presumably reduce the steric interaction (Fig. 1.3).

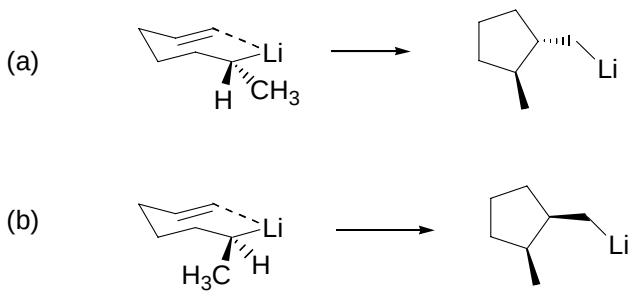


Figure 1.3 Models for the cyclization of 6-lithio-1-heptene

In order to address this issue, we are collaborating with Kenneth Jordan's group of this department to do the calculations. Preliminary results show that the solvent THF plays an important role in the stereoselectivity. In the gas phase, the calculated *trans* to *cis* ratio is poor.

However, when one THF molecule is used for the calculation, the activation energy for the *trans* product is lower than that for the *cis* one by about 2.4 kcal/mol which would result in about 91:9 stereoselectivity. When two THF molecules are used for the calculation, the activation energy for the *trans* product is lower than that for the *cis* one by about 6.87 kcal/mol which would result in about 99:1 stereoselectivity.

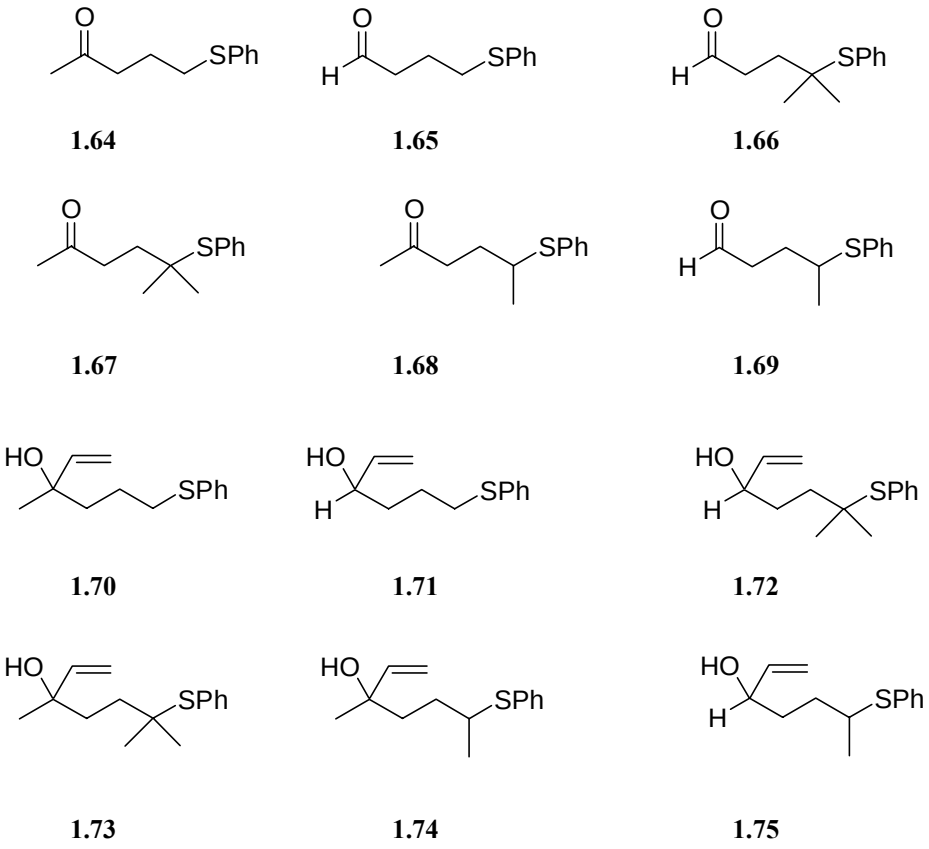
1.2.2. Stereoselective Intramolecular Carbolithiation of Alkenyllithiums Bearing an Allylic Lithium Oxyanionic Group

As noted in the background, an allylic lithium oxyanion on the receiving alkene greatly accelerates lithium-ene and magnesium-ene[35] cyclizations, as well as Simmons-Smith cyclopropanations. More importantly, in most cases studied, the allylic lithium anions exert almost complete stereocontrol over the reactions. Some other examples, like the formation of 3-membered and 4-member rings, the adjacent lithium oxyanionic groups accelerate the cyclization. Based on the previous work in our lab and the fact that almost any kind of organolithium can be generated by reductive lithiation, we studied the allylic lithium oxyanionic effect in alkyllithium and vinyllithium cyclizations.

1.2.2.1. Preparation of Phenylthio-substituted Allylic Alcohols

Six phenylthio-substituted allylic alcohols, **1.70-1.75** were constructed in high yield by vinyllithium addition to aldehydes and ketones **1.64-1.69** (Fig. 1.4). These ketones (except **1.69**)

were obtained by the conjugate addition of the corresponding cuprates to the appropriate α,β-unsaturated aldehydes or ketones.



1.64 **1.65** **1.66**

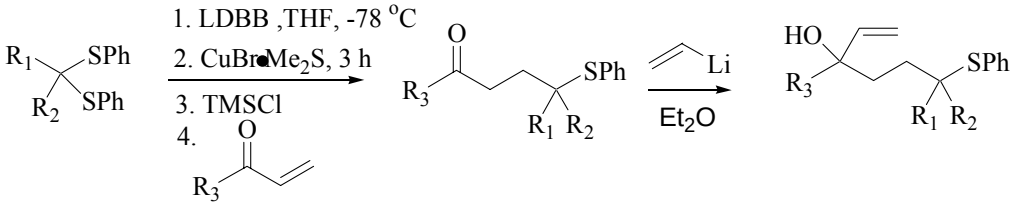
1.67 **1.68** **1.69**

1.70 **1.71** **1.72**

1.73 **1.74** **1.75**

Figure 1.4 Aldehydes, ketones and the corresponding allylic alcohols resulting from vinyllithium addition

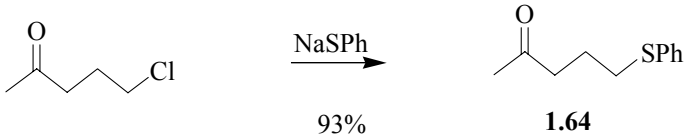
Table 1.1 shows the procedures for the preparation of these ketones and allylic alcohols. For example, the synthesis of ketone **1.64** commenced with reductive lithiation of 1,1-bis(phenylthio)methane followed by the addition of CuBr•Me_2S to form the mixed cuprate. The latter undergoes 1,4 addition to methyl vinyl ketone in the presence of TMSCl to give ketone **1.64** in 93% yield.



Entry	*Ketones or aldehydes*		*Alcohols*	
1	**1.64** $R_1 = R_2 = H, R_3 = CH_3$	93%	**1.70** $R_1 = R_2 = H, R_3 = CH_3$	87%
2	**1.65** $R_1 = R_2 = R_3 = H$	54%	**1.71** $R_1 = R_2 = R_3 = H$	90%
3	**1.66** $R_1 = R_2 = CH_3, R_3 = H$	64%	**1.72** $R_1 = R_2 = CH_3, R_3 = H$	96%
4	**1.67** $R_1 = R_2 = R_3 = CH_3$	75%	**1.73** $R_1 = R_2 = R_3 = CH_3$	96%
5	**1.68** $R_1 = H, R_2 = R_3 = CH_3$	77%	**1.74** $R_1 = H, R_2 = R_3 = CH_3$	96%

Table 1.1 Preparation of allylic alcohols

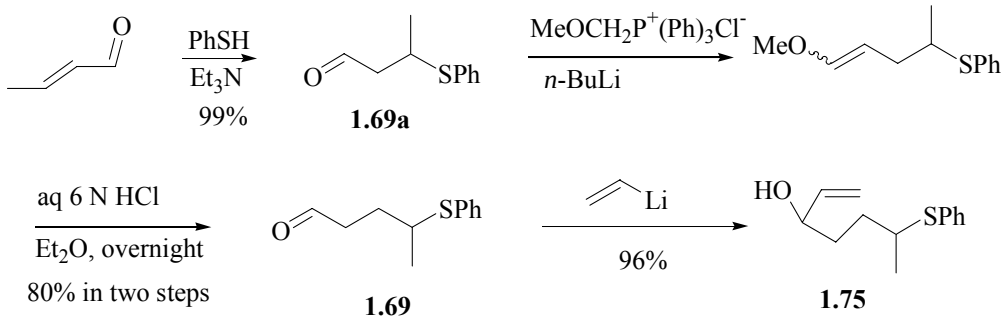
Ketone **1.64** can also be obtained by an alternative route shown in Scheme 1.18.[10] S_N2 Nucleophilic displacement of chloride in 5-chloro-2-pentanone (commercially available) by thiophenoxide ion afforded the desired ketone readily.



Scheme 1.18 An alternative way to synthesize 5-phenylthio-2-pentanone 1.64

Vinyllithium addition to the aldehydes or ketones in Et_2O afforded the corresponding allylic alcohols in excellent yields. Vinyllithium was prepared in situ by treating vinylbromide with 2 equivalent of *t*-BuLi.[36]

The synthesis of aldehyde **1.69** was accomplished as shown in Scheme 1.19. Conjugate addition of thiophenol to crotonaldehyde afforded **1.76** in almost quantitative yield.[28] The Wittig reaction followed by acid hydrolysis furnished aldehyde **1.69** in 80% over two steps.[37] Vinyl lithium addition to **1.69** afforded the desired allylic alcohol **1.75** as a 1:1 mixture of diastereomers.

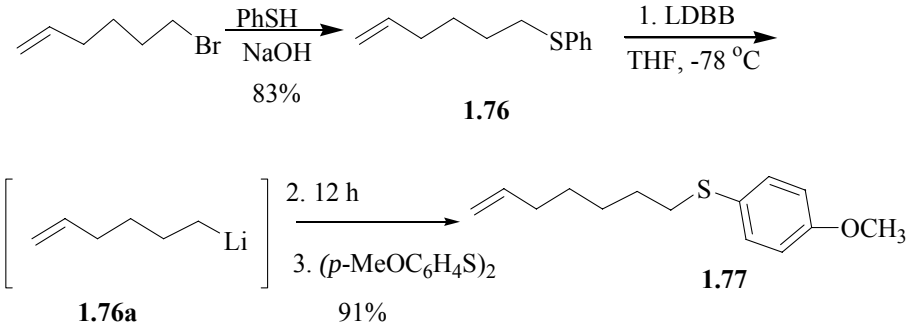


Scheme 1.19 Preparation of allylic alcohol 1.75

1.2.2.2. Intramolecular Carbolithiation of Primary Alkyllithiums Mediated by Allylic Lithium Oxyanionic Groups

Most intramolecular carbolithiations involving primary alkyllithiums are performed in hexane/ether mixtures at room temperature. THF is much more polar than pentane and diethyl

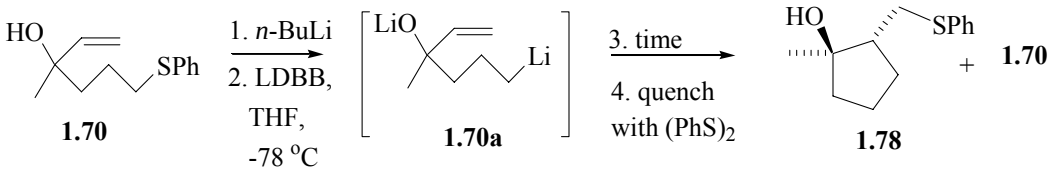
ether and it is known to be highly lithiophilic. Bailey and coworkers found that lithiophilic reagents such as TMEDA and THF greatly increase the cyclization rate.[1a] One of the strong advantages of using reductive lithiation is that it allows organolithium generation in THF. Thus, THF itself may increase the cyclization rate of primary alkyllithiums. The attempted cyclization of a primary alkyllithium in THF at –78 ˚C is shown in Scheme 1.20. The reaction of thiophenoxide anion with 6-bromo-1-hexene in an S_N2 fashion afforded **1.76**. Reductive lithiation of phenylthioether **1.76** afforded primary alkyllithium **1.76a**. However, no cyclization occurred during a 12 h reaction period at –78 °C followed by quenching with di-*p*-methoxyphenyl disulfide. Uncyclized quenched product **1.77** was obtained in 91% yield. Yus later reported that the cyclization of **1.76a** (generated by reductive lithiation of 1-chloro-5-hexene) in THF occurred at – 30 °C.



Scheme 1.20 Attempted primary alkyllithium cyclization at -78 °C

The first example of an allylic lithium oxyanion accelerated and directed alkyllithium cyclization is shown in Scheme 1.21. Alcohol **1.70** was treated with *n*-BuLi to remove the alcohol proton, followed by the addition of LDBB to generate the corresponding primary

alkyllithium. Surprisingly, the dianion **1.70a** cyclized at –78 °C. Thus, the presence of *the lithium oxyanionic group greatly accelerates the cyclization of primary alkyllithiums*.



Entry	time	yield of **1.78**	yield of **1.70**
1	**10 min**	**38%**	**52%**
2	**1 h**	**64%**	**30%**
3	**12 h**	**81%**	**8%**

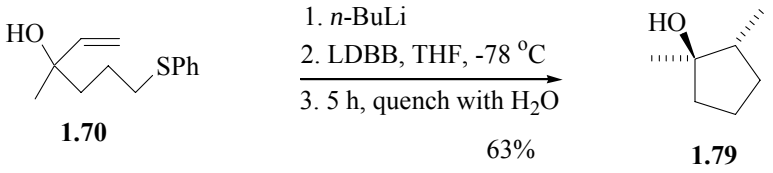
Scheme 1.21 The first alkyllithium cyclization mediated by allylic lithium oxyanionic group

However, the most surprising result in Scheme 1.21 is that the single diastereomer has the oxygen functionality and the functionality derived from the CH_2Li group on the opposite side of the cyclopentane ring. The spectroscopic data of **1.78** (H^1 NMR and C^{13} NMR) are identical with the literature values.[38] The directing effect of the lithium oxyanion is complete and *in the opposite sense to that in the case of intramolecular allylmetallic carbometalations.*[30, 35]

Another interesting finding about this reaction is that the cyclization proceeds very rapidly at the beginning, but slows with time. When the reaction was quenched immediately after the addition of LDBB (10 min), 38% of cyclized product **1.78** and 52% of uncyclized product were isolated. However, when the reaction was quenched after 1 h, 64% of cyclized product and 30% of uncyclized product were isolated respectively. Only 81% of cyclized product was isolated when the reaction was quenched after 12 h and still 8% of uncyclized

material was isolated. It appears that the reaction is not first order, which is unusual for cyclization. One possible explanation for this is that the freshly generated organolithium exists as a monomer, so the cyclization is very fast initially. However, the aggregation of the monomers reduces the reactivity of organolithium considerably. During their studies on the addition of organolithiums to chiral 1- and 2-substituted naphthalenes, Meyers and coworkers observed a similar phenomenon.[39] They found that as the organolithiums aged, they lost their ability to add to substituted naphthalenes even under prolonged contact. In order to obtain addition products, organolithiums have to be prepared as fresh as possible to produce monomeric organolithiums.

Instead of using phenyl disulfide, water was used as the eletrophile to quench the reaction. Alcohol **1.79** was obtained as a single diastereomer (Scheme 1.22). The spectroscopic data of **1.79** are identical to those reported.[40]



1.70 **1.79**

Scheme 1.22 Water quenched primary alkyllithium cyclization mediated by an allylic lithium oxyanion

Models to account for the *cis* stereoselectivity in metallo-ene cyclization (M = Li or Mg) and the *trans* stereoselectivity in alkyllithium cyclization (reactions shown in Scheme 1.21 and Scheme 1.22) are shown in Figure 1.5. For metallo-ene cyclization, the allylic oxyanion can participate as a nucleophile in coordination with the allylic metal (**A-1**). A half-chair 6-center transition state **A-2** leads to product **A-4** with all *cis* geometry, corresponding to the observed

stereochemical result.[30, 35] In the transition state **A-2**, the metal can coordinate both with the non-bonding electrons of the oxyanion and the π electrons of the alkene. However, in alkyllithium cyclizations, it is the lithium on the allylic oxyanion that coordinates with the double bond in an electrophilic fashion in the intermediate **B-1**. The allylic lithium oxyanion occupies the pseudo-equatorial position in the chair-like transition state **B-2** and product **B-4** with *trans* geometry is obtained. Since the reaction was performed in THF, surely the coordination of THF with lithium will make the lithium oxyanion a large substituent so as to occupy the pseudo-equatorial position in the chair-like transition state. Moreover, the lithium on the allylic oxyanion can also be viewed to act as a kind of intramolecular Lewis acid, which can polarize the double bond and make it more electrophilic for the attack of the internal alkyllithium. In the case of alkyllithium, a transition state such as that in **A-2** would be highly strained because the partially formed ring is so much smaller.

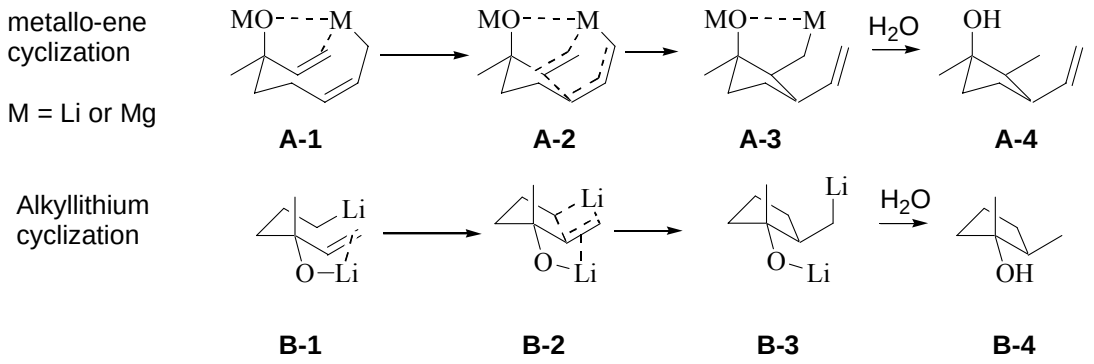
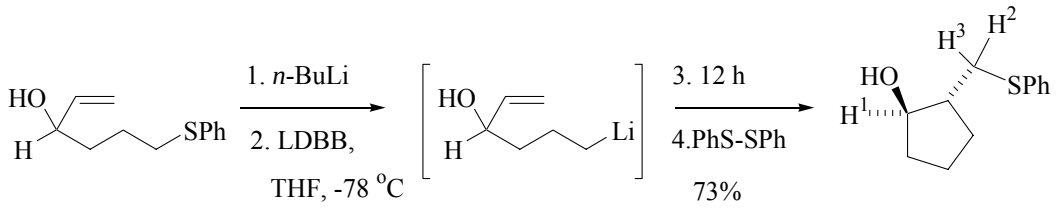


Figure 1.5 Models to rationalize the stereoselectivity in metallo-ene and alkyllithium cyclization

A study concerning whether the allylic methyl group plays a role in the exclusively stereoselective cyclization of **1.70a** is shown in Scheme 1.23. The allylic methyl group was replaced by a hydrogen atom. The dianion **1.71a** was generated by *n*-BuLi/LDBB. After the

reaction was performed at –78 ºC for 12 h, phenyl disulfide was added to quench the reaction. A single diastereomer **1.80** was obtained and the stereochemistry was again, pure *trans*. The stereochemistry of **1.80** was assigned by 2D-NMR spectroscopy (see Appendix A and B for COSY and ROESY spectra). The ROSEY spectrum clearly shows strong interaction between H^1 (on the carbinol carbon atom) and H^2, H^3 (on the carbon atom attached to the phenylthio group).

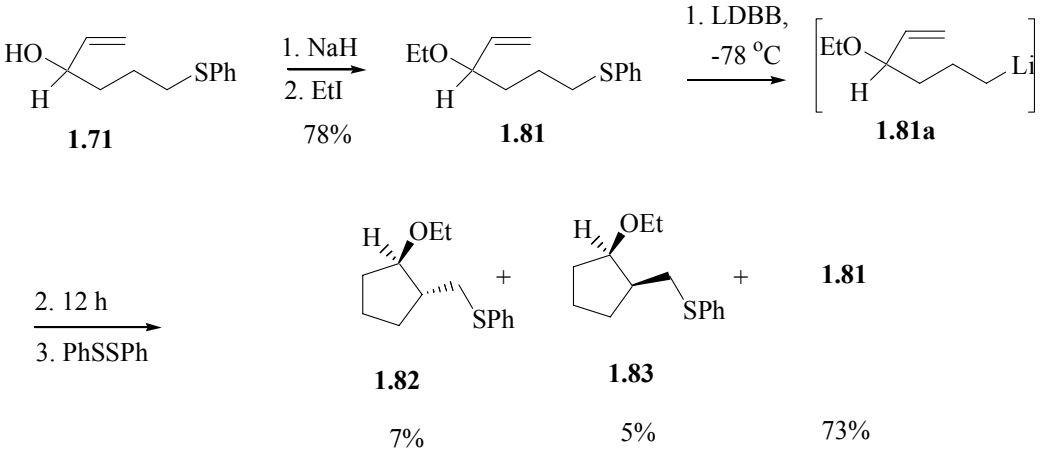


1.71 **1.71a** **1.80**

Scheme 1.23 Primary alkyllithium cyclization mediated by secondary allylic lithium oxyanion

The presence of a quaternary carbon atom (e. g. a gem-dimethyl group) in a chain has an accelerating effect on the cyclization rate, which is known as the Thorpe-Ingold effect.[41] There is a quaternary carbon center in **1.70** and a tertiary carbon center in **1.71**, it is possible that the greater rate for cyclizations of **1.70a** and **1.71a** than that of **1.76a** simply comes from the substituent effect on the allylic carbon atom. In order to address this question, the experiments in Scheme 1.24 were performed. The synthesis of **1.81** was accomplished easily by removing the alcohol proton of **1.71** with NaH followed by the addition of ethyl iodide. Treating 1.81 with LDBB generated primary alkyllithium 1.81a. After the reaction was performed at – 78 ˚C for 12 h, phenyl disulfide was added to quench the reaction. The major product, the open chain, uncyclized compound **1.81**, was obtained in 73% yield. The minor products are a mixture of two

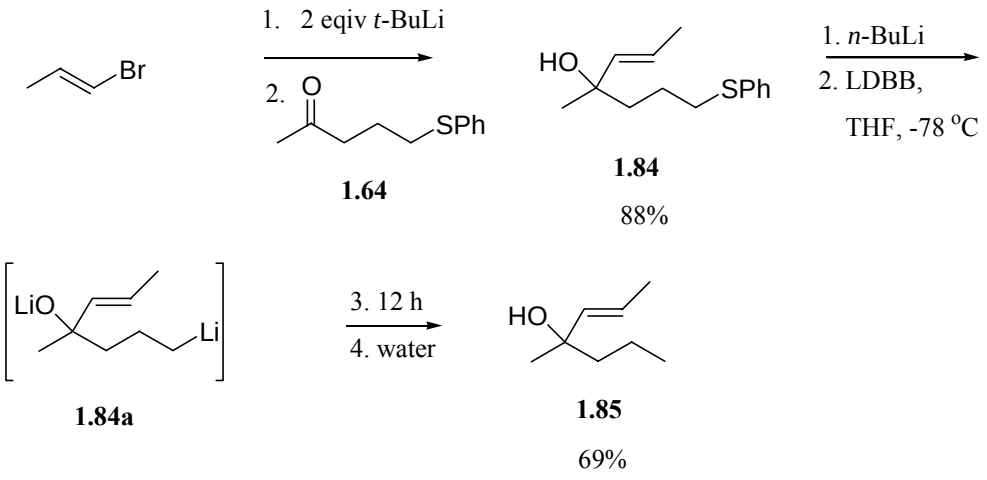
cyclized products, **1.82** and **1.83**, with *trans* to *cis* ratio of 1.5 to 1 (GC ratio; the *trans* product **1.82** was synthesized independently for comparative purposes). The results show that there exists a small substituent effect to accelerate the cyclization since 12% of cyclized products were obtained compared with no cyclization at all without the allylic ethoxy group (see Scheme 1.20). However, compared with the corresponding allylic lithium oxyanion substituent, the effect of an allylic ethoxy substituent on cyclization is limited. Moreover, the poor selectivity between the two cyclized products shows that allylic ethoxy group does not exert much stereocontrol over the cyclization.



Scheme 1.24 Cyclization of primary alkyllithium bearing an allylic ethoxy group

One major limitation for intramolecular carbolithiation is that ring closures are usually unsuccessful when an alkyl substituent is present at the terminus of the alkene. It is probably due to the fact that a less stable secondary anion would be generated from a primary alkyllithium cyclization. Thermodynamically, this may be an unfavorable process even although a σ bond is being formed at the expense of a π bond. To test whether the allylic oxyanionic effect could

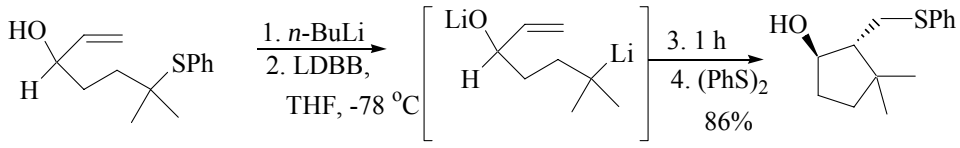
overcome this limitation, the experiments in Scheme 1.25 were performed. Allylic alcohol **1.84** was synthesized by the addition of *trans*-1-propenyllithium to ketone **1.64**. Dianion **1.84a** was generated by *n*-BuLi/LDBB. Unfortunately, only uncyclized product was found after the reaction was performed at –78 °C for 12 h and quenched with water. On the other hand, this result supports the carbanionic cyclization mechanism over the radical cyclization for our alkyllithium cyclization. Due to the radical intermediate in the reductive lithiation, it is conceivable that apparent cyclizations of organolithiums generated by this method are actually radical rather than anionic processes and the desired intramolecular C-C bond formation is a radical cyclization followed by further reduction of the resulting radical to the corresponding carbanion by LDBB. The radical cyclization of substrate **1.84** should be a very favorable process because of the primary radical cyclizing to give a more stable secondary radical. The failed cyclization here rules out the radical cyclization pathway. Furthermore, experiments performed by Joseph Whetstone in our lab show that no cyclization occurs for dianion **1.84a** at temperature –78 ˚C to 0 ˚C.



Scheme 1.25 Attempted cyclization of an alkyllithium with a terminally substituted olefin

1.2.2.3. Intramolecular Carbolithiation of Tertiary Alkyllithiums Mediated by an Allylic Lithium Oxyanionic Group

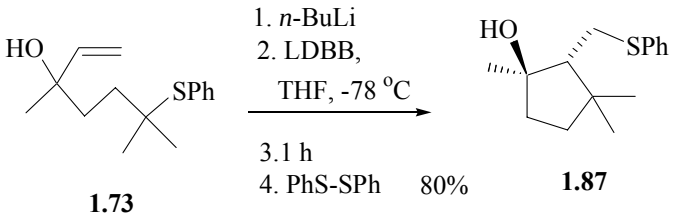
Reductive lithiation is an attractive method for the generation of tertiary carbanions that are very difficult to generate by other methods. After the discovery of allylic lithium oxyanion accelerated and directed primary alkyllithium cyclization, it became of interest to know if it is the case in tertiary carbanion cyclizations as well. Scheme 1.26 shows our study about this aspect. Dianion **1.72a** is generated by *n*-BuLi/LDBB from alcohol **1.72**. To our delight, **1.72a** cyclized very rapidly at –78 °C and a single diastereomer **1.86** was obtained after quenching the reaction with phenyl disulfide. Compared with the primary alkyllithium cyclization mediated by an allylic lithium oxyanion (12 h at –78 °C, 81% cyclized product, 8% uncyclized product) the cyclization of **1.72a** is much faster. Only 1 h was needed at –78 °C to obtain complete cyclization. Compared with the corresponding tertiary anionic cyclization without the allylic hydroxyl group (1 h at –78 °C, 17% cyclized product, 68% uncyclized product), the cyclization here is greatly accelerated by the allylic lithium oxyanion. Moreoever, the cyclization is completely stereoselective and only the *trans*-diastereomer is obtained.



1.72 **1.72a** **1.86**

Scheme 1.26 Tertiary carbanion cyclization mediated by a secondary allylic lithium oxyanion

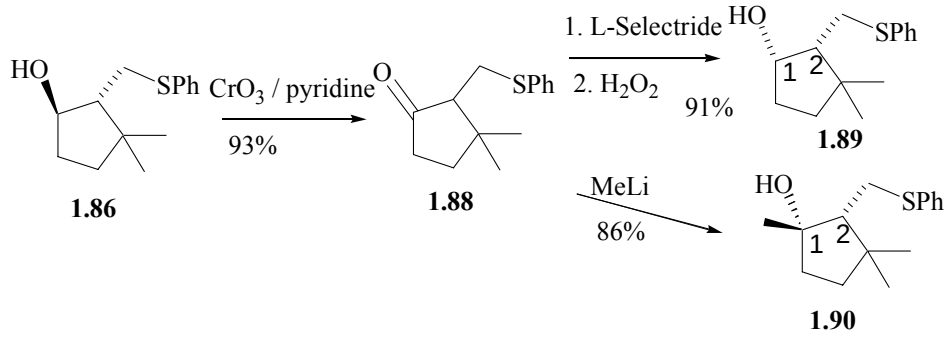
Similarly, Scheme 1.27 shows a tertiary alkyllithium cyclization in which an allylic methyl group is present. Compound **1.87** was isolated as a single diastereomer with *trans* stereochemistry. Thus, the presence of a methyl group at the allylic position has no effect on the stereoselectivity of tertiary alkyllithium cyclization mediated by an allylic lithium oxyanion group.



1.73 **1.87**

Scheme 1.27 Tertiary carbanion cyclization mediated by a tertiary allylic lithium oxyanion

Evidence for the *trans* stereochemistry of compounds **1.86** and **1.87** is shown in Scheme 1.28. Alcohol **1.86** was oxidized to the corresponding ketone **1.88** in 93% yield by CrO_3•pyridine.[42] Reduction of the ketone by L-Selectride gave a single diastereomer **1.89**. The addition of MeLi to the ketone **1.88** afforded a single diastereomer **1.90**. The stereochemistry of **1.89** and **1.90** were assigned on the assumption that hydride or MeLi addition to ketone **1.88** occurs from the less hindered face of the ketone, which is the opposite side from the face on which the $PhSCH_2$ group resides. Therefore, it is very likely that both **1.89** and **1.90** have *cis* stereochemistry between the hydroxy group attached to C-1 and $PhSCH_2$ group attached to C-2. Both compounds **1.89** and **1.90** are quite different in spectroscopic behavior compared with the corresponding cyclized compounds **1.86** and **1.87**. Therefore, the stereochemistry of **1.86** and **1.87** are assigned as *trans*.

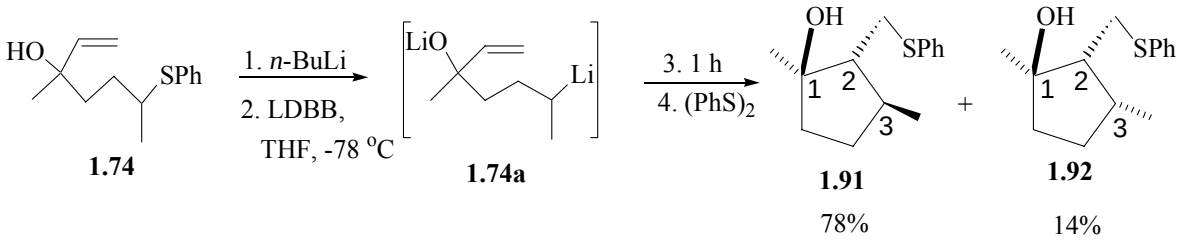


Scheme 1.28 Evidence for the stereochemistry of 1.86 and 1.87

1.2.2.4. Intramolecular Carbolithiation of Secondary Alkyllithiums Mediated by an Allylic Lithium Oxyanionic Group

Allylic lithium oxyanion mediated secondary alkyllithium cyclizations will afford products with three contiguous chiral centers. It is expected that the allylic lithium oxyanion can exert similar stereocontrol over the cyclization so as to obtain good diastereoselectivity. As illustrated in Scheme 1.29, the dianion **1.74a**, generated by *n*-BuLi/LDBB from alcohol **1.74**, cyclized efficiently at – 78 ˚C to afford two compounds **1.91** and **1.92** in a ratio of 6:1. Three contiguous chiral centers were established in one step with moderate stereoselectivity. The stereochemistry of the major product **1.91** has the hydroxy group and $PhSCH_2$ group on the opposite side of the cyclopentane ring, just as what had been observed in the primary and tertiary alkyllithium cyclizations mediated by an allylic lithium oxyanion. The CH_3 group attached to C-3 and the $PhSCH_2$ group attached to C-2 are *trans* to each other, just like what had been observed for simple secondary alkyllithium cyclizations without the allylic hydoxy and methyl groups.

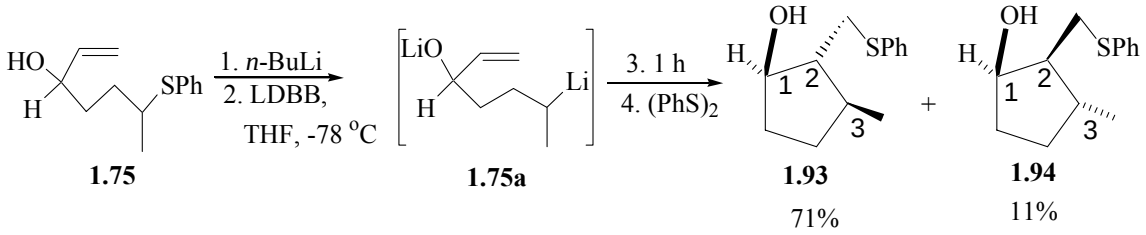
The minor product **1.92** is different from the major product **1.91** in that the CH_3 group attached to C-3 and the $PhSCH_2$ group are on the same side of the cyclopentane ring.



1.74 **1.74a** **1.91** 78% **1.92** 14%

Scheme 1.29 Secondary alkyllithium cyclization mediated by a tertiary allylic lithium oxyanion

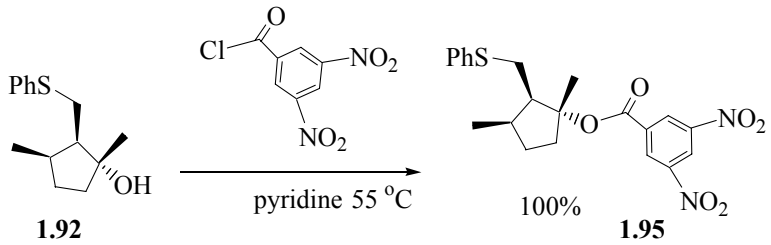
A secondary carbanionic cyclization in which an allylic methyl group is absent is shown in Scheme 1.30. The cyclization of the dianion **1.75a** afforded two diastereomers **1.93** and **1.94** in a ratio of 7:1. The stereochemistry of the major product **1.93** is similar to that of **1.91**. But the stereochemistry of the minor product **1.94** is different from **1.92**. For **1.94**, the hydroxy group and the $PhCH_2$ group are on the same side of the cyclopentane ring. The CH_3 group attached to C-3 is *trans* to the $PhSCH_2$ group attached to C-2. Thus, the allylic methyl group does play an important role in the transition state for the formation of the minor product **1.92**.



1.75 **1.75a** **1.93** 71% **1.94** 11%

Scheme 1.30 Secondary alkyllithium cyclization mediated by a secondary allylic lithium oxyanion

The stereochemistry of **1.92** and **1.93** were determined by x-ray crystal structure analysis of their derivatives. As shown in Scheme 1.31, alcohol **1.92** was converted to the corresponding dinitrobenzoate ester **1.95** by heating the alcohol and dinitrobenzoyl chloride in pyridine.[43] The ester **1.95** was being crystallized from CH_2Cl_2 and hexane as yellow needles. The X-ray crystal structure clearly shows the relative stereochemistry of the three contiguous chiral centers (Figure 1.6).



Scheme 1.31 Synthesis of 3,5-dinitrobenzoate ester 1.95

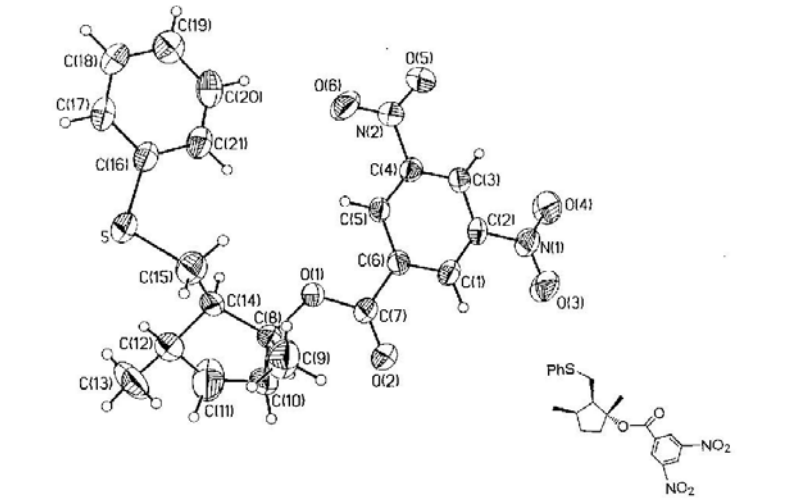
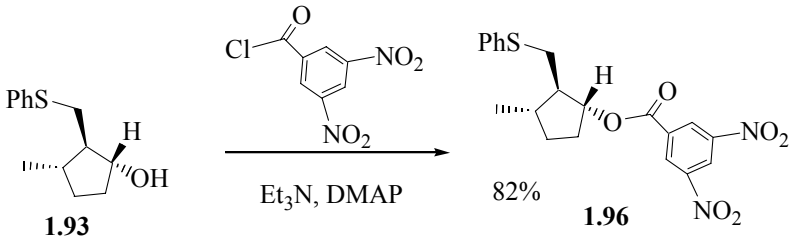


Figure 1.6 ORTEP drawing of 3,5-dinitrobenzoate ester 1.95

Similarly, alcohol **1.93** was converted to the corresponding dinitrobenzoate ester by mixing the alcohol, dinitrobenzoyl chloride, Et_3N and a catalytic amount of DMAP in CH_2Cl_2 at room temperature (Scheme 1.32).[44] The ester **1.96** was crystallized from CH_2Cl_2 and hexane as yellow needles. X-ray crystal structure analysis indicates the relative stereochemistry of the immediate precursor **1.93** (Figure 1.7).



Scheme 1.32 Synthesis of 3,5-dinitrobenzoate ester 1.96

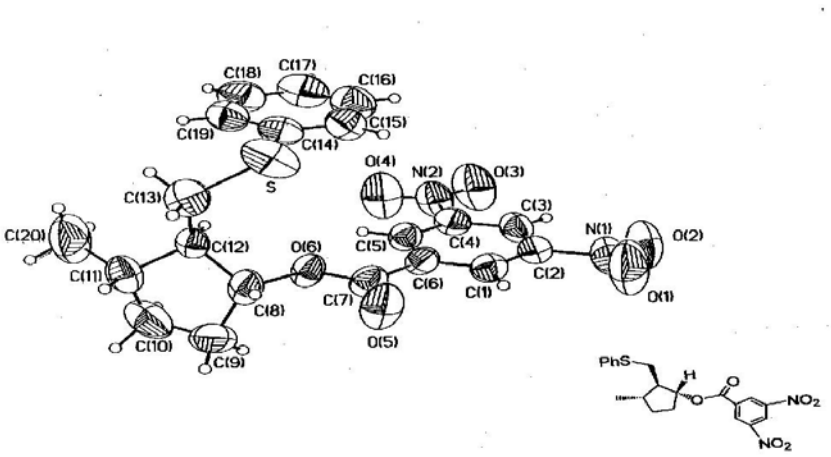
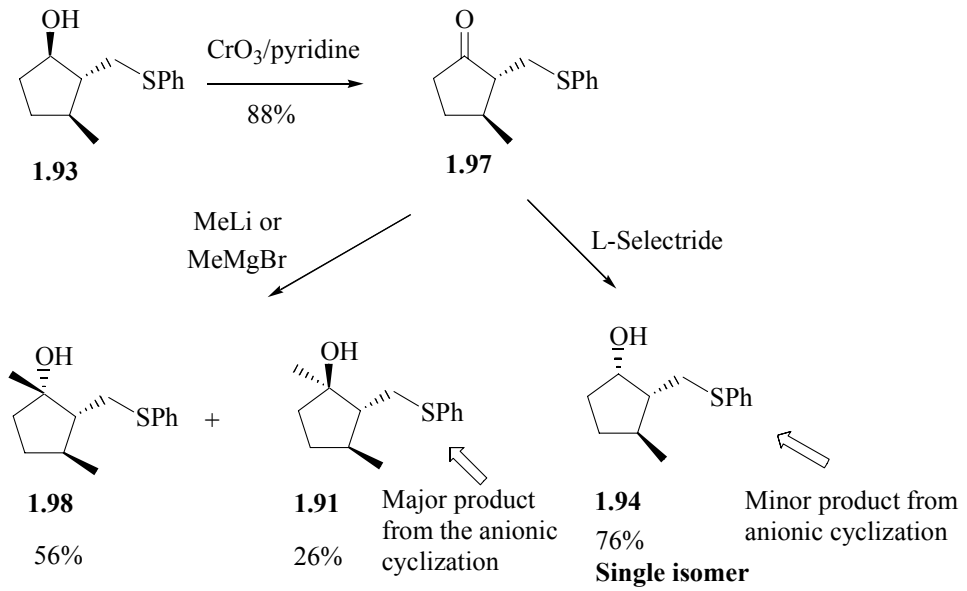


Figure 1.7 ORTEP drawing of 3,5-dinitrobenzoate ester 1.96

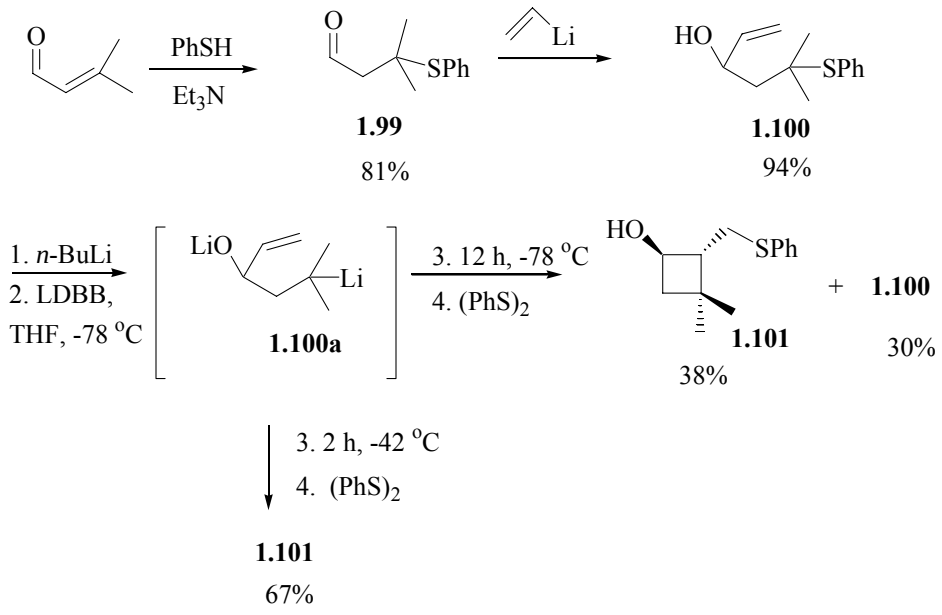
The stereochemical proof of **1.91** and **1.94** are shown in Scheme 1.33. Oxidation of alcohol **1.93**, the major product from the anionic cyclization, with Collins' reagent afforded the corresponding ketone **1.97**. Dess-Martin periodinane[45] can also be used to realize this transformation to furnish the same compound in a similar yield. Ketone **1.97** was reduced by bulky L-Selectride to give compound **1.94** as a single diastereomer. Presumably the hydride will attack from the less hindered face of the ketone **1.97**, which is the opposite side from the face on which the bulky $PhSCH_2$ group resides. Thus, alcohol **1.94** should have the hydroxy and $PhSCH_2$ group on the same side of the cyclopentane ring. **1.94** has identical spectroscopic data with the minor product from the anionic cyclization (Scheme 1.30). The addition of methyl lithium or methyl magnesium bromide[46] to ketone **1.97** gave compounds **1.98** and **1.91**, with 56% and 26% yield, respectively. It is also assumed that the major product **1.98** arises from the attack of the MeLi from the less hindered side of ketone **1.97**, which is the opposite side from the face on which the large $PhSCH_2$ group resides. The minor product **1.91** has completely identical spectroscopic behavior with the major product obtained from the cyclization (Scheme 1.29).



Scheme 1.33 Evidence for the stereochemistry of 1.91 and 1.94

1.2.2.5. A Cyclobutanol from a 4-exo-trig Cyclization, an Alkylidene-cyclopentanol from a Vinyl Anion Cyclization and Construction of a *tran*-Fused Diquinane Molecule

Even a cyclobutanol, **1.101**, can be generated by this method in a three-flask reaction from commercially available reactant 3-methyl-2-butenal (Scheme 1.34).



Scheme 1.34 Stereoselective formation of a cyclobutanol 1.101

Aldehyde **1.99** is prepared by conjugate addition of thiophenol to 3-methylbutanal.[47] Vinyllithium addition to **1.99** furnished **1.100** in excellent yield. Dianion **1.100a** was generated by treatment of **1.100** sequentially with *n*-BuLi and LDBB at –78 °C. Initially, the reaction was performed at –78 °C for 12 h and quenched with phenyl disulfide. To our delight, the cyclization of dianinon **1.100a** is completely stereoselective and **1.101** was obtained as a single diastereomer in 38% yield. Increasing the temperature from –78 °C to –42 °C did not affect the stereoselectivity but accelerated the cyclization rate considerably. Cyclized product **1.101** was obtained in 67% yield and no starting material could be detected after the reaction was performed at – 42 °C for 2 h. The stereochemistry of the cyclized product **1.01** is again exclusively *trans* as determined by 2D NMR spectroscopy shown in appendix C and D.

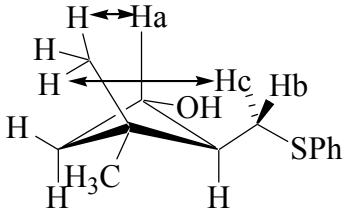
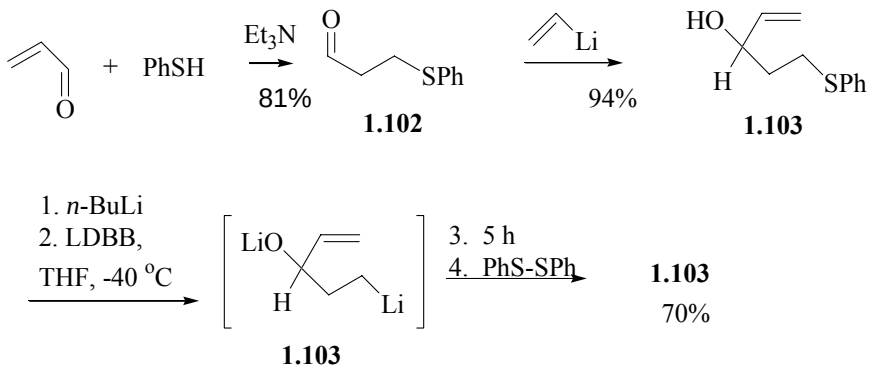


Figure 1.8 Interaction between hydrogen atoms of 1.101 shown by ROESY

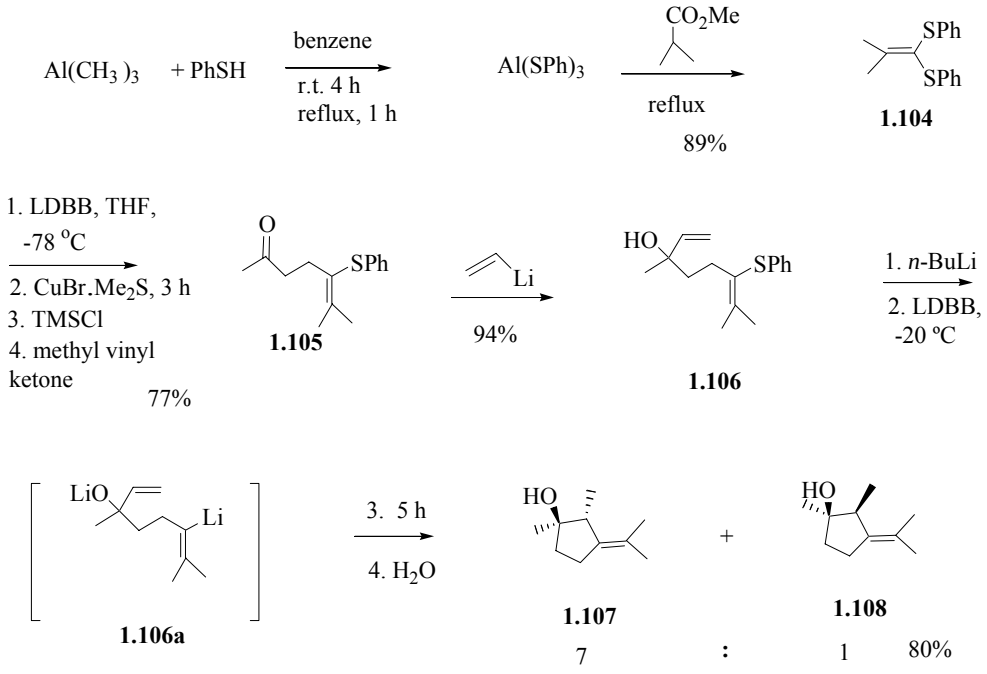
The COSY and ROSEY spectra clearly show interaction between H_a (attached to carbinol carbon atom) and protons of the methyl groups (Fig. 1.8). Interaction between the hydrogen on the same methyl group and H_b or H_c on the carbon attached to the PhS group is also observed. Therefore, compound **1.101** has *trans* configuration.

Attempted cyclization of a primary alkyllithium mediated by an allylic lithium oxyanion to form a 4-membered ring is shown in Scheme 1.35. Alcohol **1.103** was synthesized by vinyllithium addition to aldehyde **1.102,** which was prepared by base-catalyzed thiophenol addition to acrolein. Unfortunately, no cyclization product was detected after the dianion **1.103a** was stirred at –40 °C for 5 h. The cyclization in this case is likely thermodynamically unfavorable.



Scheme 1.35 Attempted cyclization of a primary alkyllithium to form a cyclobutanol

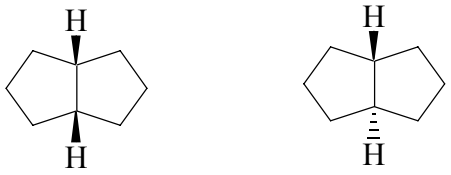
As shown in Scheme 1.36, an sp^2 organolithium **1.106a** is subject to the same type of stereochemical control by an allylic lithium oxyanionic group but with somewhat less stereoselectivity.



Scheme 1.36 Vinyllithium cyclization mediated by an allylic lithium oxyanion

Ketene bis(phenylthio)acetal **1.104** was synthesized by treating methyl isobutyrate with aluminum thiophenoxide, prepared *in situ* from trimethylaluminum.[48] Treating **1.104** with LDBB produced the corresponding vinyllithium which can undergo transmetallation with $CuBr{\cdot}Me_2S$, followed by 1,4 addition of the resulting cuprate to methyl vinyl ketone to afford **1.105**. Reaction of ketone **1.105** with vinyllithium furnished alcohol **1.106** in 94% yield. Studies of the cyclization of dianion **1.106a** showed that the cyclization is very sensitive to temperature. At a temperature lower than –40 °C, no cyclization was observed. When the reaction was performed at –20 °C for 5 h, two diastereomers (**1.107 and 1.108**) were formed in a ratio of 7:1 in favor to the *trans*-diastereomer. The two diastereomers are inseparable by flash-column chromatography so the ratio was determined by proton NMR spectroscopy. When the reaction was performed at -15 °C for 4.5 h, the diastereomeric ratio decreased to 3:1, still in favor to the *trans*-diastereomer. In both cases (-20 and -15 °C), product from protonation of vinyl anion **1.106a** was also isolated. A longer time is probably needed to obtain complete cyclization. Compound **1.107** is known[49] and the stereochemistry here was assigned by NMR comparison with values in the literature.

Cis-fused diquinane **1.109a** has a lower energy than *trans*-fused diquinane **1.109b** due to the strain at the fused ring junction. According to simple AM2 calculations, the *trans* one **1.109b** is about 4 kcal/mol higher in energy than the *cis* one **1.109a** (Fig. 1.9). However, owing to the favorable thermodynamics associated with anionic cyclization, a relatively inaccessible *trans*-bicylo[3.3.0]octane can be prepared albeit in reduced yield.

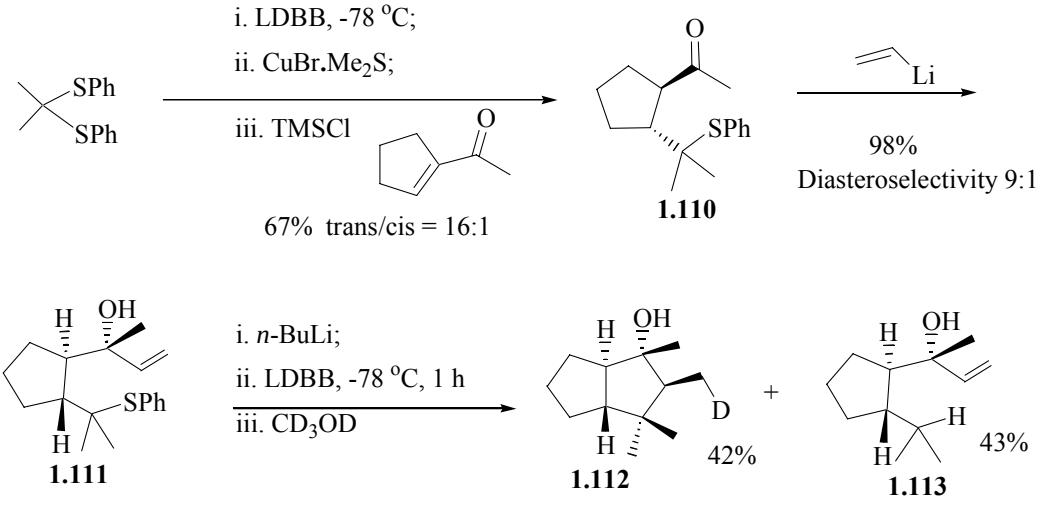


1.109a **1.109b**

Figure 1.9 *Cis* and *trans* diquinane

As illustrated in Scheme 1.37, for the first Michael addition step, two diastereomers were formed in yields of 63% and 4%, respectively. The *trans* product **1.110** was assumed to be the major product due to the quenching of the enolate intermediate from the opposite side of the large group. Later, an X-ray crystal structure of the diquinane **1.112** proved the *trans* configuration of compound **1.110**.

The reaction of vinyllithium with ketone **1.110** also occurs stereoselectively to give product **1.111** as the major product (The corresponding minor product was also formed and the major/minor ratio is 9/1). The stereochemistry of compound **1.111** was deduced from the X-ray crystal structure of the diquinane **1.112.** Alcohol **1.111** was treated with *n*-BuLi/LDBB to generate the corresponding dianion, followed by quenching with CD_3OD after the reaction had proceeded at -78 ºC for 1 h. Compound **1.112** was isolated as the major cyclized product in 42% yield together with uncyclized product **1.113** in 43% yield. MS and NMR spectroscopy show that compound **1.112** is deuterated but that there is no deuterium at all in **1.113**. Some of the generated tertiary carbanions were protonated somehow during the reaction before they could cyclize. It is not clear where the proton comes from at this stage. It is possible that coordination of the oxygen anion with the lithium cation associated with the tertiary carbanion makes the latter more basic than other tertiary alkyllithiums and that the proton is removed from THF.



Scheme 1.37 Synthesis of a *trans*-fused diquinane

The X-ray crystal structure of compound **1.112** is shown in figure 1.10. Clearly a *tran*-fused diquinane has been synthesized and the stereochemistry between OH- and CH_2D is *trans*, similar to the results obtained in the tertiary carbanion cyclization mediated by an allylic lithium oxyanion (see Scheme 1.26).

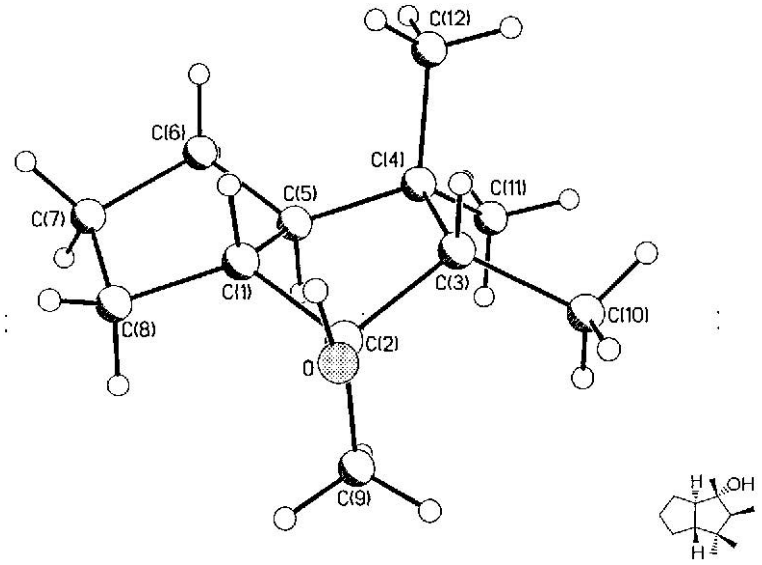
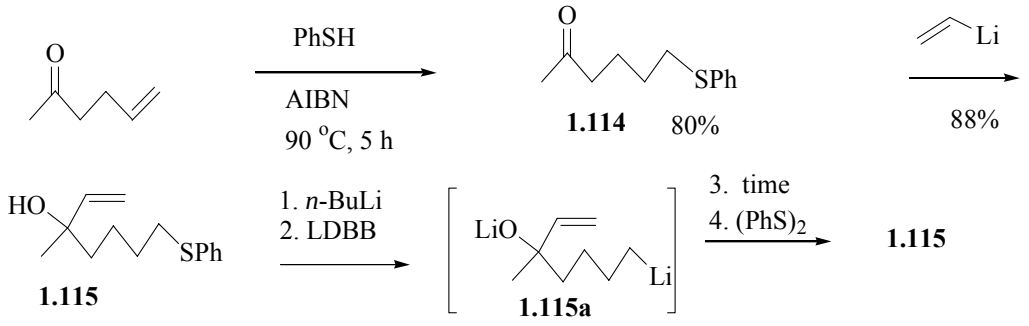


Figure 1.10 ORTEP drawing for *trans*-diquinane

1.2.3. Attempted Cyclization, Mediated by an Allylic Lithium Oxyanion, to Form a Six-Membered Ring

It is of interest to know whether allylic lithium oxyanion mediated cyclization could be extended to the construction of 6-membered rings. As shown in Scheme 1.38, **1.115** was subjected to *n*-BuLi/LDBB to generate the corresponding dianion **1.115a**. Unfortunately, all efforts to effect cyclization of **1.115a** at temperature between – 78 ˚C and –10 ˚C failed (Table 1.2). Room temperature and a TMEDA additive are the conditions Bailey used to effect cyclization of 7-lithio-1-heptene to form a 6-member ring. Thus, perhaps room temperature is needed in this case as well. It is well known that organolithiums can be protonated by THF at higher temperatures. As THF is usually used to generate the radical anion, it seems further experiments to study the formation of a 6-member ring will be difficult. However, using the

method developed recently in our laboratory to generate radical anions in dimethyl ether and then replacing the latter with a hydrocarbon or mixture of hydrocarbon and diethyl ether could enable us to study the cyclization to form a 6-membered ring at a higher temperature.



Scheme 1.38 Studies about the allylic lithium oxyanion mediated cyclization to form 6-membered ring

entry	Temperature and time	Additive	results
1	-78 °C 5 h	none	no cyclization
2	-40 °C 4 h	none	no cyclization
3	-25 °C 8 h	TMEDA	no cyclization
4	-10 °C 4 h	none	no cyclization
5	-10 °C 40 min	TMEDA	no cyclization

Table 1.2 Attempted cyclization to form a 6-membered ring

1.3. Conclusions

In summary, reductive lithiation of phenyl thioethers is a very general method for generating organolithiums capable of intramolecular carbolithiation of alkenes to form 5-membered rings and in one case a 4-membered ring. The versatile properties of the thiophenyl

group makes it possible to readily construct alkenes bearing a phenylthioether substituent capable of reductive lithiation in high yield to a primary, secondary, or tertiary alkyllithium as well as a vinyllithium, all suitably juxtaposed for cyclization. This technology holds promise of greatly expanding the use of intramolecular carbolithiation as a method of ring formation.

Intramolecular carbolithiation of an alkene bearing an allylic lithium oxyanionic group is greatly accelerated compared to the same cyclization in which this substituent is absent. Furthermore, in all the cases studied so far, the stereoselectivity is high and often complete; the lithium oxyanion is *trans* to the CH_2Li in the cyclized product. The stereochemistry of these cyclizations, which is thought to proceed by a four-center transition state, is in the opposite sense to that observed for the lithium- and magnesium-ene cyclizations in the presence of an allylic oxyanion. In the latter cases, the organolithium or organomagnesium that adds to alkenes is an allyllithium or allylmagnesium and a six-center transition state is widely accepted. It is postulated that in the metallo-ene cyclizations, the flexible transition state allows the oxyanionic group to participate in a nucleophilic fashion whereas in the non-allylic cyclizations, the much more restricted transition state makes electrophilic acceleration, whereby the lithium counterion attached to the oxyanion activates the alkene by coordination, more favorable.

Besides the limitation of the lack of a general method for preparing organolithiums, another limitation of intramolecular carbolithiation is the paucity of functionality in the cyclized product in most cases due to the highly reactive nature of the organolithium intermediates. We introduced hydroxy groups at the allylic position in the starting alkene so the cyclized product can contain the useful alcohol function in addition to the CH_2Li group. Moreover, the lithium

oxyanion accelerates the cyclization and exerts complete stereocontrol in most cases. Therefore, the versatility of using this method to prepare functionalized products is greatly increased.

1.4. Experimental

General Experimental Procedures. All reactions were performed under an argon atmosphere in oven-dried (110 ºC) flasks and standard precautions against moisture were taken. A Dry Ice/acetone bath was used to obtain a temperature of –78 °C. An ice bath was used to obtain 0 °C. Silica gel 60 (40-60 μm, Sorbent Technologies) was used for flash column chromatography. Thin-layer chromatography was performed on glass supported 250-μm silica GF plates (Analtech). Visualization of TLC plates was accomplished with one or more of the following: 254 nm UV light; 7% phosphomolybdic acid in ethanol; 5% anisaldehyde in ethanol containing 5% sulfuric acid and a trace amount of acetic acid. Anhydrous magnesium sulfate was used as the drying reagent.

Instrumentation. Most ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX-300 spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C at 22 ºC unless otherwise noted. Some ^{1}H and ^{13}C NMR spectra and two-dimensional NMR spectra were recorded on a Bruker AM-500 spectrometer. Chemical shift data are reported in unit of δ (ppm) using $CHCl_3$ as internal standard: δ = 7.27 for ^{1}H NMR spectra and $CDCl_3$ as δ = 77.09 for ^{13}C NMR spectra unless indicated otherwise. Multiplicities are given as s (singlet), d (double), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants, *J*, are reported in Hz. Infrared spectra were recorded on an IR/32 FT-IR spectrometer and are reported in wave numbers (cm^{-1}). Low and high-resolution mass spectra were recorded on a VG-70SE mass spectrometer in EI

mode at 70 eV. Gas chromatographic mass spectra (GC-MS) analyses were performed on a Hewlett Packard 5890 Series II gas chromatograph equipped with a 5970 mass selective detector. Steven Gelb of this department determined X-ray crystal structure. Thomas Hoover capillary melting point apparatus was used to obtain the melting point.

Materials. Commercial solvents and reagents were used as received with the following exceptions. Tetrahydrofuran (THF) and diethyl ether were distilled over sodium benzophenone ketyl. Methylene chloride was distilled over CaH_2. Acrolein was distilled from anhydrous $CuSO_4$. A Dry Ice/acetone bath was used to obtain a temperature of –78 °C and Dry Ice/acetonitrile was used to obtain a temperature of –42 °C. An ice bath was used to obtain 0 °C.

Lithium 4, 4'di-*t*-butylbiphenylide (LDBB)

To a flame-dried three-neck round-bottom flask, equipped with a glass-coated stirring bar, argon inlet and rubber septum were added 4,4'-di-*tert*-butylbiphenyl (DBB) (4.00 g, 15.0 mmol). Lithium ribbon was prepared by scraping the dark oxide coating off the surface while it was immersed in mineral oil. The shiny metal was dipped in hexanes in order to remove the oil and then weighed (104 mg, 15.0 mmol) in a tared beaker containing mineral oil. The metal was sliced into small pieces while it was still immersed in mineral oil. The lithium pieces were dipped again in hexane prior to addition to the flask. THF (40 mL) was added to the DBB/lithium mixture via syringe. The reaction mixture was stirred at room temperature for about 5 min until a dark-blue color appeared on the lithium surface and it was then allowed to cool to 0 °C and stirred for 5 h. The resulting dark-blue solution of LDBB was ready for use in reductive lithiation (~ 7 mmol scale).

Lithium 1-(dimethylamino)naphthalenide (LDMAN)

To a flame-dried three-neck flask, equipped with a glass-coated stirring bar, rubber septum and argon inlet, was added 1-(dimethylamino)naphthalenide (DMAN) (3.8 mL, 23 mmol) and 45 mmol of THF. The solution was cooled to –55 °C. Lithium ribbon (161 mg, 23.0 mmol) was prepared and weighed by the method described for the preparation of LDBB. The lithium pieces were added while the flask was rapidly purged with argon. The reaction mixture was stirred at –55 °C for 5 h. The resulting dark-green solution of LDMAN was ready for use in reductive lithiation (~ 10 mmol scale).

Vinyllithium

The following is a representative procedure for the preparation of vinyl lithium.

To a solution of vinyl bromide (0.74 mL, 10.2 mmol) in anhydrous ether (6 mL) at –78 °C was added *t*-butyllithium (20.4 mmol, 12.0 mL). The resulting mixture was stirred at -78 °C for 2 h and then slowly warmed to 0 °C. After the mixture had been stirred at 0 °C for 20 min, the vinyllithium was ready to use.

Di-*p*-methoxyphenyl disulfide

A mixture of 6.00 g (42.8 mmol) of *p*-methoxybenzenethiol and 1.52 mL (21.4 mmol) of dimethyl sulfoxide was stirred at room temperature for 24 h. The reaction mixture was dissolved in diethyl ether and washed with 1 M NaOH solution. The aqueous phase was extracted with diethyl ether. The combined organic layer was dried over anhydrous $MgSO_4$ and filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to give 4.81 g (81% yield) of the title compound as a pale yellow solid. ^{1}H

NMR ($CDCl_3$) δ 7.36 (d, J = 8.1 Hz, 4 H, aromatic), 6.78 (d, J = 8.1 Hz, 4 H, aromatic), 3.71 (s, 6 H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 159.6, 132.3, 128.1, 114.4, 55.0.

6-Methyl-6-phenylthio-1-heptene (1.55)

A solution of LDMAN (23.0 mmol, prepared from 3.8 mL DMAN, and 161 mg of Li in 45 mL THF) was cooled to –78 °C and treated with 2,2-bis(phenylthio)propane (2.900 g, 11.15 mmol) 10 mL of THF. The dark green color of the solution turned into dark red. After 10 min of stirring, 1-bromo-4-pentene (1.39 mL, 11.2 mmol) was added. The resulting mixture was stirred at –78 °C for 2 h and then the temperature was raised to –20 °C. After the solution had been stirred at –20 °C for 30 min, saturated $NaHCO_3$ solution (30 mL) was added. The reaction mixture was extracted with ether (50 mL × 3). The combined organic layer, after being washed with 30 mL of 5% HCl (to remove DMAN) and 30 mL of brine, was dried over anhydrous $MgSO_4$, filtered through cotton and evaporated in vacuo. The resulting residue was purified by flash-column chromatography with pure hexane to give 2.19 g (89% yield) of **1.55** as a yellow oil. ^1H NMR ($CDCl_3$) δ 7.53-7.30 (m, 5 H, aromatic), 5.83 (m, 1 H), 5.06-4.95 (m, 2 H), 2.05 (m, 2 H), 1.58 (m, 2 H), 1.49 (m, 2 H), 1.24 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 138.7, 137.8 (2 C), 132.6, 128.8, 128.6 (2 C), 114.9, 49.3, 42.0, 34.3, 29.1, 24.3. IR ν_{max} (thin film) 3075, 2958, 2933, 2862, 1641, 1474, 1438, 1364, 911, 749, 694 cm^{-1}; MS (EI) m/z (relative intensity) 220 (M^+, 57), 179 (45), 151(65), 123 (45), 110(60), 95 (57), 81(75), 69(100), 55(75). HRMS: exact mass calcd for $C_{14}H_{20}S$ (M^+): 220.1286, found 220.1286.

6-Phenylthio-1-heptene (1.56)

A solution of LDMAN (54.5 mmol, prepared from 8.3 mL DMAN, and 378 mg Li in 60 mL THF) was cooled to –78 °C and treated with 1,1-bis(phenylthio)ethane (6.46 g, 26.3 mmol). The dark green color of LDMAN turned to dark red. After 10 min of stirring, 1-bromo-4-pentene (3.11 mL, 26.3 mmol) was added. The reaction mixture was stirred at –78 °C for 2 h and then the temperature was raised to –20 °C. After the solution had been stirred at –20 °C for 30 min, saturated $NaHCO_3$ solution (40 mL) was added. The reaction mixture was extracted with ether (70 mL × 3). The combined organic layer, after being washed with 5% HCl (to remove DMAN) and then brine, was dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by flash-column chromatography with pure hexane to give 5.04 g (93% yield) of **1.56** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.36-7.20 (m, 5 H, aromatic), 5.77 (m, 1 H), 4.98 (d, 1 H, J = 16.2 Hz), 4.93 (d, 1 H, J = 10.5 Hz), 3.19 (m, 1 H), 2.07-2.00 (m, 2 H), 1.70-1.46 (m, 4 H), 1.26 (d, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 138.6, 135.6, 132.0 (2 C), 128.9 (2 C), 126.7, 114.9, 43.3, 36.2, 33.7, 26.4, 21.3; IR ν_{max} (thin film) 3074, 2974, 2931, 2860, 1640, 1584, 1479, 1439, 912, 747, 692 cm^{-1}; MS (EI) m/z (relative intensity) 206 (M^+, 18), 137 (30), 110 (100), 96 (31), 81 (26), 55 (21); HRMS: exact mass calcd for $C_{13}H_{18}S$ (M^+): 206.1129, found 206.1137.

1-(2,2-Dimethylcyclopentylmethylthio)-4-methoxybenzene (1.58)

Freshly prepared LDBB (3.8 mmol in 10 mL of THF) at –78 °C was cannulated to a flask containing compound **1.55** (220 mg, 1.53 mmol) in 10 mL of THF at –78 °C under argon. The resulting mixture was stirred at –45 °C for 2 h before it was quenched with di-*p*-methoxyphenyl disulfide (650 mg, 2.3 mmol) in 5 mL of THF. The reaction mixture was extracted with ether

(20 mL × 3). The combined organic layer, after being washed with brine, was dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by flash-column chromatography with 1% ethyl acetate in hexane to give 360 mg (94% yield) of **1.58** as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.38 (d, 2 H, J = 9.4 Hz), 6.87 (d, 2 H, J = 9.4 Hz), 3.79 (s, 3 H), 3.06 (dd, 1 H, J = 12.0 Hz, 3.8 Hz), 2.61 (dd, 1 H, J = 12.0 Hz, 11.0 Hz), 2.10 (m, 1 H), 1.70-1.40 (m, 6 H), 1.05 (s, 3 H), 0.85(s, 3 H); ^{13}C NMR ($CDCl_3$) δ 158.7, 132.5 (2 C), 128.3, 114.7 (2 C), 55.3, 49.0, 42.2, 41.3, 37.6, 30.9, 28.2, 21.9, 21.4. IR ν_{max} (thin film): 2953, 2868, 1592, 1493, 1463, 1285, 1245, 1173, 1034, 825 cm^{-1}; MS (EI) m/z (relative intensity) 250 (M^+, 78), 153 (52), 140 (93), 125 (47), 111 (26), 96 (19), 77 (19), 69 (100), 55 (26). HRMS: exact mass calcd for $C_{15}H_{22}OS$ (M^+): 250.1381, found 250.1391.

1-((1R*, 2R*)[50]-2-Methylcyclopentylmethylthio)-4-methoxybenzene (1.60)

Freshly prepared LDBB (3.8 mmol in 10 mL of THF) at –78 °C was cannulated to a flask containing compound **1.56** (315 mg, 1.53 mmol) in 10 mL THF at –78 °C under argon. The reaction mixture was stirred at –78 °C for 10 min and then quenched with di-*p*-methoxyphenyl disulfide (640 mg, 2.30 mmol) in 5 mL of THF. The reaction mixture was extracted with ether (20 mL × 3). The combined organic layer, after being washed with brine, was dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by flash-column chromatography with 1% ethyl acetate in hexane to give 320 mg (89% yield) of **1.60** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.40 (d, 2 H, J = 9.6 Hz), 6.85 (d, 2 H, J = 9.6 Hz), 3.80 (s, 3 H), 3.05 (dd, 1 H, J = 12.3 Hz, 4.6 Hz), 2.68 (dd, 1 H, J = 12.3 Hz, 8.6 Hz), 1.93 (m, 1 H), 1.83 (m, 1 H), 1.60-1.20 (m, 6 H), 0.98 (d, 3 H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 158.6, 132.5 (2 C), 127.8, 114.6 (2 C), 55.3, 47.1, 41.1, 40.3, 34.9, 32.3, 23.7, 19.6. IR ν_{max} (thin film) 2951, 2867, 2835,

1593, 1494, 1462, 1284, 1244, 1180, 1034, 825 cm^{-1}; MS (EI) m/z (relative intensity) 236 (M^+, 74), 140 (100), 125 (20), 96 (9), 81 (8), 55 (17); HRMS: exact mass calcd for $C_{14}H_{20}OS$ (M^+): 236.1235, found 236.1234.

5-((1R*, 2S*)-2-Methylcyclopentyl)pentan-2-one (1.61)

Freshly prepared LDBB (3.4 mmol in 10 mL of THF) at –78 °C was cannulated to a flask containing compound **1.56** (278 mg, 1.35 mmol) in 10 mL THF at –78 °C under argon. The reaction mixture was stirred at –78 °C for 15 min and then CuBr•Me_2S (417 mg, 2.02 mmol) was added. After the resulting mixture had been stirred for 3 h at –78 °C, a solution of TMSCl (0.43 mL, 3.22 mmol) in 4 mL of THF was added followed by dropwise addition of a solution of methyl vinyl ketone (0.17 mL, 2.1 mmol) in 4 mL of THF. The resulting mixture was stirred at –78 °C for 12 h. After the addition of 20 mL of 5% NaOH and 1 mL of 40% aqueous *n*-Bu_4NOH, the reaction mixture was allowed to warm to 0 ºC. It was further stirred at room temperature for 1 h in order to hydrolyze all of the silyl enol ether to the corresponding ketone. Then the reaction mixture was filtered through Celite and extracted with ether (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (5% ethyl acetate) to give 176 mg (78% yield) of **1.61** as a yellow oil. IR ν_{max} (thin film): 2950, 2867, 1718, 1459, 1412, 1363, 1226, 1166 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.46-2.41 (m, 2 H), 2.15 (s, 3 H), 1.90-1.70 (m, 2 H), 1.70-1.40 (m, 6 H), 1.30-1.0 (m, 4 H), 0.96 (d, 3 H, J = 9.6 Hz); ^{13}C NMR ($CDCl_3$): δ 209.1, 47.5, 44.1, 40.6, 34.8, 34.3, 32.3, 29.8, 23.5, 23.4, 19.4; MS (EI) m/z (relative intensity) 168 (M^+, 4), 150 (4), 121 (6), 108 (36), 84 (50), 71 (34), 67 (24), 58 (100), 55 (43); HRMS: exact mass calcd for $C_{11}H_{20}O$ (M^+): 168.1514, found 168.1509.

2-((1R*, 2S*)-2- Methylcyclopentyl)acetic acid (1.62)

Freshly prepared LDBB (5.4 mmol in 15 mL of THF) at –78 °C was cannulated to a flask containing compound **1.56** (446 mg, 2.17 mmol) in 10 mL of THF at –78 °C under argon atmosphere. The reaction mixture was stirred at –78 °C for 15 min and CO_2 was bubbled in for about 1 h. After the addition of 5% HCl (15 mL), the temperature was allowed to warm to room temperature. The mixture was extracted with Et_2O (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to give 250 mg (81% yield) of **1.62** as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 11.5 (br, 1 H), 2.50 (dd, 1 H, J = 15.0, 4.9 Hz), 2.16 (dd, 1 H, J = 15.0, 9.4 Hz), 2.00-1.10 (m, 8 H), 0.99 (d, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 180.7, 43.8, 40.5, 39.1, 34.4, 32.4, 23.2, 18.9; IR ν_{max} (thin film) 3300-2400 (broad O-H stretch), 2954, 2870, 1708, 1410, 1289 cm^{-1}; MS (EI) m/z (relative intensity) 142 (M^+, 25), 127 (33), 124 (39), 113 (35), 109 (35), 99 (100), 88 (78); HRMS: exact mass calcd for $C_8H_{14}O_2$ (M^+): 142.0994, found 142.0991.

Ethyl 2-((1R*, 2S*)-2-methylcyclopentyl)acetate (1.63)

Carboxylate acid **1.62** (161 mg, 1.13 mmol) and a catalytic amount of concentrated H_2SO_4 (1 drop) were added to 20 mL of EtOH in a three-neck flask (50 mL) equipped with a reflux condenser. The resulting mixture was refluxed for 24 h. After the reaction mixture was cooled to room temperature, it was extracted with ether (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (5% ethyl acetate in hexane) to give

192 mg (89% yield) of **1.63** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 4.11 (q, 2 H, J = 7.1 Hz), 2.43 (dd, 1 H, J = 14.7, 5.1 Hz), 2.07 (dd, 1 H, J = 14.7, 9.2 Hz), 1.14-2.00 (m, 8 H), 1.23 (t, 3 H, J = 7.1 Hz), 0.95 (d, 3 H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 173.6, 60.1, 44.1, 40.5, 39.3, 34.5, 32.4, 23.2, 18.9, 14.3; IR ν_{max} (thin film) 2954, 2870, 1737, 1459, 1375, 1330, 1251, 1190, 1135, 1033, 734 cm^{-1}; MS (EI) m/z (relative intensity) 170 (M^+, 26), 155(7), 142(10), 125 (17), 97 (12), 88 (100), 84 (49), 67 (18), 61 (32), 55 (51); HRMS: exact mass calcd for $C_{10}H_{18}O_2$ (M^+): 170.1307, found 170.1307.

5-Phenylthiopentan-2-one (1.64)

5-Chloropentan-2-one (2.41 g, 20.0 mmol) was added to a solution containing 30 mL of water, 0.800 g NaOH (20.0 mmol) and 2.10 mL thiophenol (20.0 mmol). The resulting mixture was heated at 80 °C for 1 h. After the reaction mixture was cooled to room temperature, it was extracted with ether (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered through cotton and evaporated in vacuo to give 1.81 g of **1.64** (93% yield) as a yellow oil which did not need further purification. ^{1}H NMR ($CDCl_3$) δ 7.40-7.17 (m, 5 H, aromatic), 2.94 (t, 2 H, J = 7.0 Hz), 2.60 (t, 2 H, J = 7.0 Hz), 2.12 (s, 3 H), 1.90 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 208.1, 136.2, 129.2(2 C), 129.0(2 C), 126.1, 42.0, 32.9, 30.1, 23.0.

4-Phenylthiobutanal (1.65)

To a stirred solution of LDBB (40.0 mmol in 70 mL of THF) at -78°C was added bis(phenylthio)methane (4.64 g, 20.0 mmol) in 15 mL of THF. After the reaction mixture had been stirred at –78 °C for 10 min, CuBr•Me_2S (7.8 g, 30 mmol) was added quickly with increased argon flow. After the mixture had been stirred for 3 h at –78 °C, a solution of TMSCl

(3.4 mL, 23 mmol) in 4 mL of THF was added followed by dropwise addition of acrolein (1.20 mL, 18.0 mmol). The resulting mixture was stirred at –78 °C for 12 h. After the addition of 40 mL of aqueous 5% NaOH and 1 mL of 40% aqueous *n*-Bu_4NOH, the reaction mixture was allowed to warm to 0 ºC. It was stirred at room temperature for 1 h in order to hydrolyze all of the silyl enol ether to the corresponding aldehyde. The mixture was filtered through Celite and extracted with ether (60 mL ×3). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to give 1.75 g (54% yield) of **1.65** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 9.77 (s, 1 H), 7.47-7.16 (m, 5 H, aromatic), 2.98 (t, 2 H, J = 6.9 Hz), 2.83 (t, 2 H, J = 7.1 Hz), 1.95 (m, 2 H).

4-Methyl-4-(phenylthio)pentanal (1.66)[51]

To a solution of LDBB (40 mmol, in 70 mL of THF) at -78°C was added bis(phenylthio)propane (4.36 g, 16.7 mmol, in 10 mL of THF). After the reaction mixture had been stirred at –78 °C for 10 min, CuBr•Me_2S (5.16 g, 25.0 mmol) was added rapidly with increased argon flow. After the mixture had been stirred for 3 h at –78 °C, a solution of TMSCl (3.4 mL, 26.7 mmol) in 4 mL of THF was added followed by dropwise addition of a solution of acrolein (1.10 mL, 16.7 mmol) in 5 mL of THF. The resulting mixture was stirred at –78 °C for 12 h. After the addition of 40 mL of aqueous 5% NaOH and 1 mL of 40% aqueous *n*-Bu_4NOH, the reaction mixture was allowed to warm to 0 °C. Then it was stirred at room temperature for 1 h in order to hydrolyze all of the sily enol ether to the corresponding ketone. The mixture was filtered through Celite and extracted with ether (60 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered through cotton and evaporated in vacuo. The residue

was purified by flash-column chromatography to give 2.22 g (64% yiled) of **1.66** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 9.85 (t, 1 H, J = 1.3 Hz), 7.52-7.32 (m, 5 H, aromatic), 2.73 (td, 2 H, J = 7.9, 1.3 Hz), 1.79 (t, 2 H, J = 7.9 Hz), 1.26 (s, 6 H); ^{13}C NMR ($CDCl_3$) 201.4, 137.1 (2 C), 131.4, 128.7, 128.4 (2 C), 48.1, 39.7, 33.2, 28.5 (2 C).

5-Methyl-5-phenylthiohexan-2-one (1.67)

To a solution of LDBB (17.7 mmol, in 45 mL of THF) at -78°C was added 2,2-bis(phenylthio)propane (2.03 g, 7.80 mmol, in 10 mL of THF). After the reaction mixture had been stirred at –78 °C for 10 min, CuBr•Me_2S (2.41 g, 11.7 mmol) was added rapidly under increased argon flow. After the mixture had been stirred for 3 h at –78 °C to insure the formation of the cuprate, a solution of TMSCl (2.0 mL, 15.7 mmol) in 4 mL of THF was added, followed by dropwise addition of a solution of methyl vinyl ketone (0.79 mL, 9.5 mmol) in 5 mL of THF. The resulting mixture was stirred at –78 °C, under argon, for 12 h. After the addition of 40 mL of aqueous 5% NaOH and 1 mL of 40% aqueous *n*-Bu_4NOH (1 mL), the reaction mixture was allowed to warm to 0 °C. Then It was stirred at room temperature for about 1 h in order to hydrolyze all of the silyl enol ether to the the corresponding ketone. The mixture was filtered through Celite and extracted with ether (60 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to give 1.29 g (75% yield) of **1.67** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.41-7.24 (m, 5 H, aromatic), 2.65 (t, 2 H, J = 8.0 Hz), 2.11 (s, 3 H), 1.67 (t, 2 H, J = 8.0 Hz), 1.16 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 208.3, 137.4 (2 C), 131.9, 128.9, 128.7 (2 C), 48.7, 39.5, 35.2, 30.2, 29.0 (2 C).

5-phenylthiohexan-2-one (1.68)

To a solution of LDBB (25.6 mmol, in 64 mL of THF) at –78 °C was added 1,1-bis(phenylthio)ethane (2.78 g, 11.3 mmol, in 10 mL of THF). After the reaction mixture had been stirred at -78°C for 10 min, CuBr•Me_2S (3.26 g, 15.8 mmol) was added with increased argon flow. After the mixture had been stirred for 3 h at –78 °C to insure the formation of the cuprate, a solution of TMSCl (3.0 mL, 23.5 mmol) in 7.5 mL of THF was added followed by dropwise addition of a solution of methyl vinyl ketone (1.21 mL, 14.6 mmol). The resulting mixture was stirred for 12 h at –78 °C. Aqueous 5% NaOH (40 mL) and 40% aqueous *n*-Bu_4NOH (1 mL) were added and the reaction mixture was allowed to warm to 0 °C. It was stirred at room temperature for about 1 h in order to hydrolyze all of the sily enol ether to the ketone product. The mixture was filtered through Celite and extracted with ether (60 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (10% ethyl acetate in hexane) to give 1.79 g (77% yield) of **1.68** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.43-7.24 (m, 5 H, aromatic), 3.25 (m, 1 H), 2.68 (t, 2 H, J = 7.7 Hz), 2.15 (s, 3 H), 1.90-1.79 (m, 2 H), 1.30 (d, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 208.4, 134.9, 132.2(2 C), 129.0(2 C), 127.1, 42.98, 40.88, 30.33, 30.16, 21.57.

3-Phenylthiobutanal (1.69a)

To a mixture of thiophenol (11.0 g, 100 mmol) and triethylamine (0.5 mL) in 15 mL of THF at 0 °C, *trans*-crotonaldehyde (7.00 g, 100 mmol) was added dropwise. After being stirred at room temperature overnight, the reaction mixture was washed with 5% NaOH (40 mL × 3) and then 5% $NaHCO_3$ (40 mL). The organic phase was dried over $MgSO_4$ and concentrated in

vacuo to provide 14.2 g (80% yield) of **1.69a** as a yellow oil, which did not require further purification. ^{1}H NMR ($CDCl_3$) δ 9.71 (t, 1 H, J = 1.5 Hz), 7.27-7.40 (m, 5 H, aromatic), 3.68 (m, 1 H), 2.73 (ddd, 1 H, J = 17.2, 6.0, 1.5 Hz), 2.61 (ddd, 1 H, J = 17.2, 7.6, 1.5 Hz), 1.33 (d, 3 H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 200.3, 133.3, 132.7(2 C), 128.8(2 C), 127.5, 49.8, 37.3, 20.9.

4-(Phenylthio)pentanal (1.69)[52,53]

To a stirred solution of methoxymethyltriphenylphosphonium chloride (14.26 g, 41.6 mmol) in 100 mL of Et_2O at 0 °C was added *n*-BuLi (41.6 mmol, 26.0 mL of 1.60 M hexane solution) and stirred at that temperature for 1h. Then a solution of aldehyde **1.69a** (27.7 mmol, 5.00 g) in 10 mL of ether was slowly added at that temperature. The cooling bath was then removed and the solution was stirred at room temperature for an additional 1 h. After addition of 50 mL water, the resulting mixture was extracted with ether (50 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to give 1-methoxy-4-phenylthio-1-pentene. A solution of the latter in 30 mL of Et_2O was treated with aqueous 6 N HCl (10 mL). After stirring at room temperature for 12 h, the reaction mixture was diluted with water, basified with solid Na_2CO_3, and extracted with Et_2O (50 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to give 1.92 g (82 % yield) of **1.69** as a pale yellow oil over two steps. ^{1}H NMR ($CDCl_3$) δ 9.78 (s, 1 H), 7.42-7.15 (m, 5 H), 3.25 (m, 1 H), 2.67 (t, 2 H, J = 7.2 Hz), 1.98-1.80 (m, 2 H), 1.31 (d, 3 H, J = 6.7 Hz).

3-Methyl-6-phenylthiohex-1-en-3-ol (1.70)

To freshly prepared vinyl lithium (31.2 mmol) was added dropwise the ketone **1.64** (3.10 g, 16.0 mmol) in 5 mL of Et_2O via syringe. The reaction mixture was stirred for 2 h at –78 °C and then the temperature was raised to –20 °C and maintained at this temperature for 30 min before the addition of 40 mL of saturated aqueous $NaHCO_3$ solution (40 mL). The reaction mixture was extracted with ether (50 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to give 3.07 g (87% yield) of **1.70** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.36-7.18 (m, 5 H, aromatic), 5.90 (dd, 1 H, J = 17.3, 10.7 Hz), 5.21 (dd, 1 H, J = 17.3, 1.2 Hz), 5.07 (dd, 1 H, J = 10.7, 1.2 Hz), 2.98-2.93 (m, 2 H), 1.80-1.60 (m, 4 H), 1.39 (s, 1 H, -OH), 1.30 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.9, 136.9, 128.9 (4 C), 125.8, 112.1, 73.1, 41.3, 34.0, 27.9, 23.8; MS (EI) m/z (relative intensity): 222 (M^+, 24), 204 (19), 136 (51), 123(100), 110 (41), 95 (62), 84 (43), 79 (35), 71 (40), 55 (10); HRMS: exact mass calcd for $C_{13}H_{18}OS$ (M^+): 222.1078, found 222.1082.

6-Phenylthiohex-1-en-3-ol (1.71)

To freshly prepared vinyl lithium (36.7 mmol, prepared from 2.5 mL of vinyl bromide (36.7 mmol) and 43.2 mL of 1.7 M *t*-BuLi (73.4 mmol) in 20 mL anhydrous ether) at –78 °C, was added aldehyde **1.65** (3.55 g, 19.7 mmol) in 10 mL of diethyl ether via syringe. The reaction mixture was stirred for 2 h at –78 °C and then the temperature was raised to –20 °C and maintained there for 30 min before the addition of 20 mL of saturated aqueous $NaHCO_3$ solution. The reaction mixture was extracted with ether (50 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered through cotton and evaporated in vacuo. The residue

was purified by flash-column chromatography to give 3.66 g (89% yield) of **1.71** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.34-7.16 (m, 5 H, aromatic), 5.83 (ddd, 1 H, J = 16.6, 10.4, 6.2 Hz), 5.20 (dd, 1 H, J = 16.6, 2.6 Hz), 5.09 (dd, 1 H, J = 10.4, 2.6 Hz), 4.09 (m, 1 H), 2.94 (t, 2 H, J = 7.1 Hz), 1.98 (br, 1 H, -OH), 1.82-1.60 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 141.0, 136.8, 129.1 (4 C), 125.9, 115.0, 72.7, 36.0, 33.6, 25.2; MS (EI) m/z (relative intensity): 208 (M^+, 8), 190 (21), 149 (3), 136 (93), 110 (83), 98 (35), 77 (41), 70 (62), 65 (13), 57 (36); HRMS: exact mass calcd for $C_{12}H_{16}OS$ (M^+): 208.0922, found 208.0917.

6-Methyl-6-phenylthiohept-1-en-3-ol (1.72)

To freshly prepared vinyl lithium (10.4 mmol, prepared from 0.75 mL of vinyl bromide (10.4 mmol) and 12.3 mL of 1.7 M *t*-BuLi in 6 mL of anhydrous ether) at –78 °C, was added dropwise aldehyde **1.66** (1.39 g, 6.7 mmol) in 7 mL of Et_2O via syringe. The reaction mixture was stirred for 2 h at –78 °C and then the temperature was raised to –20 °C and maintained there for 30 min before the addition of 20 mL of saturated aqueous $NaHCO_3$ solution. The reaction mixture was extracted with ether (30 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (10% ethyl acetate in hexane) to give 1.52 g (96% yield) of **1.72** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.60-7.30 (m, 5 H, aromatic), 5.90 (m, 1 H), 5.25 (d, 1 H, J = 17.1 Hz), 5.13 (d, 1 H, J = 10.4 Hz), 4.10 (m, 1 H), 1.82-1.46 (m, 4 H), 1.26 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 141.3, 137.6 (2 C), 132.2, 128.8, 128.6 (2 C), 114.8, 73.3, 49.1, 37.9, 32.4, 29.1, 28.9; IR ν_{max} (neat) 3377(br), 3074, 2959, 2862, 1474, 1438, 1364, 1025, 993, 923, 750, 705, 695 cm^{-1}; MS (EI) m/z (relative intensity) 236 (M^+, 2), 218 (10), 149 (62), 126 (61),

109 (100), 93 (29), 81 (39), 67 (96), 55 (65); HRMS: exact mass calcd for $C_{14}H_{20}OS$ (M^+): 236.1235, found 236.1230.

3,6-Dimethyl-6-phenylthiohept-1-en-3-ol (1.73)

To freshly prepared vinyl lithium (8.1 mmol, prepared from 0.57 mL(8.1 mmol) of vinyl bromide and 9.5 mL (16.2 mmol) of 1.7 M *t*-BuLi in 6 mL of anhydrous ether) at –78 °C, was added dropwise 5 mL of a Et_2O solution of ketone **1.67** (856 mg, 3.86 mmol) via syringe. The reaction mixture was stirred for 2 h at –78 °C and then the temperature was raised to –20 °C and maintained there for 30 min before the addition of 20 mL of a saturated aqueous $NaHCO_3$ solution. The reaction mixture was extracted with ether (50 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (10% ethyl acetate in hexane) to give 941 mg (98% yield) of **1.73** as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.58-7.34 (m, 5 H, aromatic), 5.92 (dd, 1 H, J = 17.5, 10.8 Hz), 5.25 (d, 1 H, J = 17.5 Hz), 5.10 (d, 1 H, J = 10.8 Hz), 1.82 (m, 2 H), 1.58 (m, 2 H), 1.34 (s, 3 H), 1.26 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 145.1, 137.6 (2 C), 132.3, 128.8, 128.6 (2 C), 112.0, 73.2, 49.1, 37.2, 36.3, 29.14, 29.07, 28.1; MS m/z (relative intensity) 250 (M+, 20), 233(7), 141(96), 123(45), 110(65), 95(36), 86(65), 81(57), 71(100), 55(61); HRMS: exact mass calcd for $C_{15}H_{22}OS$ (M^+): 250.1391, found 250.1387.

3-Methyl-6-phenylthiohept-1-en-3-ol (1.74)

To freshly prepared vinyl lithium (3.2 mmol prepared from 0.23 mL (3.2 mmol) of vinyl bromide and 3.8 mL 1.7 M *t*-BuLi (6.5 mmol) in 4 mL of anhydrous ether) at –78 °C, was added dropwise 5 mL of a Et_2O solution of ketone **1.68** (417 mg, 2.0 mmol) via syringe. The reaction

mixture was stirred for 2 h at –78 °C and then the temperature was raised to –20 °C and maintained there for 30 min before the addition of 20 mL of saturated aqueous $NaHCO_3$ solution. The reaction mixture was extracted with ether (30 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (10% ethyl acetate in hexane) to give 456 mg (96% yield) of **1.74** (a colorless oil) as two diatereomers in an approximately 1:1 ratio. ^{1}H NMR ($CDCl_3$) δ 7.42-7.20 (m, 5 H, aromatic), 5.86 (dd, J = 17.6, 10.9 Hz), 5.22 (d, J = 17.6 Hz), 5.07 (d, 1 H, J = 10.9 Hz), 3.20 (m, 1 H), 1.78-1.58 (m, 4 H), 1.46 (s, 1 H, -OH), 1.29 (s, 3 H), 1.28 (d, 3 H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) diastereomer 1: δ 114.9, 135.3, 132.1 (2 C), 128.9 (2 C), 126.8, 112.1, 73.2, 43.85, 39.5, 30.91, 28.1, 21.5; diastereomer 2: δ 144.9, 135.3, 132.1 (2 C), 128.9 (2 C), 126.8, 112.1, 73.2, 43.78, 39.4, 30.85, 27.9, 21.4; MS m/z (relative intensity): 236 (M^+, 47), 219 (22), 150 (35), 137 (38), 127 (21), 110 (70), 109 (100), 81 (24), 71 (72), 67 (46), 55 (32); HRMS: exact mass calcd for $C_{14}H_{20}OS$ (M^+): 236.1235, found 236.1235.

6-Phenylthiohept-1-en-3-ol (1.75)

To freshly prepared vinyl lithium (3.2 mmol prepared from 0.23 mL (3.2 mmol) of vinyl bromide and 3.8 mL of 1.7 M *t*-BuLi (6.5 mmol) in 4 mL of anhydrous ether) at –78 °C, aldehyde **1.69** (417 mg, 2.0 mmol) in 5 mL of Et_2O was added dropwise via syringe. The reaction mixture was stirred for 2 h at –78 °C and then the temperature was raised to –20 °C and maintained there for 30 min before the addition of 20 mL of saturated aqueous $NaHCO_3$ solution. The reaction mixture was extracted with ether (30 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (10 % ethyl acetate in hexane) to give 456 mg

(96% yield) of **1.75** (a pale yellow oil) as two diastereomers with approximately 1:1 ratio. ^{1}H NMR ($CDCl_3$) δ 7.46-7.25 (m, 5 H, aromatic), 5.87 (m, 1 H), 5.26 (d, 1 H, J = 13.8 Hz), 5.15 (d, 1 H, J = 10.4 Hz), 4.13 (m, 1 H), 3.27 (m, 1 H), 2.01 (s, 1 H, -OH), 1.80-1.60 (m, 4 H), 1.26 (d, 3 H, J = 6.6 Hz); one diastereomer: ^{13}C NMR ($CDCl_3$) δ 141.0, 135.2, 132.1 (2 C), 129.0 (2 C), 126.8, 115.0, 73.1, 43.5, 34.4, 32.45, 21.42; another diastereomer: ^{13}C NMR ($CDCl_3$) δ 141.0, 135.2, 132.1 (2 C), 129.0 (2 C), 126.8, 115.0, 73.0, 43.4, 34.2, 32.3, 21.36; MS m/z (relative intensity) 222(M^+, 19), 150 (63), 137 (42), 123 (23), 110 (100), 95(35), 83 (24), 77 (28), 70 (54), 65 (30), 57 (51); HRMS: exact mass calcd for $C_{13}H_{18}OS$ (M^+): 222.1078, found 222.1081.

6-Phenylthio-1-hexene (1.76)

6-Bromo-1-hexene (0.80 ml, 6.00 mmol) was added to a solution containing 10 mL of water, 240 mg (6.00 mmol) NaOH and 0.61 mL (6.00 mmol) of PhSH at room temperature. The reaction mixture was heated at about 80 °C for 1 h. After the reaction mixture was cooled to room temperature, it was extracted with ether (20 mL × 3). The combined organic layer, after being washed with 5% NaOH (20 mL × 3), was dried over $MgSO_4$, filtered evaporated in vacuo. The residue was purified by flash-column chromatography with hexane to give 1.13 g (99% yield) of **1.76** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.48-7.28 (m, 5 H, aromatic), 5.91 (m, 1 H), 5.18-5.08 (m, 2 H), 3.05 (t, 2 H, J = 7.1 Hz), 2.18 (m, 2 H), 1.80 (m, 2 H), 1.67 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 138.6, 137.2, 129.1 (2 C), 129.0(2 C), 125.8, 115.0, 33.6, 33.4, 28.8, 28.2.

6-Lithio-1-hexene and its attempted cyclization in THF at –78 ° C

Freshly prepared LDBB (3.6 mmol in 10 mL of THF) at –78 °C was cannulated to a flask containing compound **1.76** (279 mg, 1.45 mmol) in 10 mL THF at –78 °C under argon. The

reaction mixture was stirred at –78 °C for 12 h before the addition of di-*p*-methoxyphenyl disulfide (650 mg, 2.3 mmol) in 5 mL of THF. After the mixture was stirred for 30 min further, saturated $NaHCO_3$ solution (20 mL) was added and the mixture was allowed to warm to room temperature. The reaction mixture was extracted with ether (20 mL × 3). The combined organic layer, after being washed with 5% NaOH (20 mL × 3), were dried, filtered and evaporated in vacuo. The resulting residue was purified with flash-column chromatography (1% ethyl acetate in hexane) to give 294 mg (91% yield) of **1.77** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.37 (d, 2 H, J = 8.7 Hz), 6.87 (d, 2 H, J = 8.7 Hz), 5.81 (m, 1 H), 5.05-4.95(m, 2 H), 3.82 (s, 3 H), 2.85 (t, 3 H, J = 6.9 Hz), 2.09 (m, 2 H), 1.61 (m, 2 H), 1.53 (m, 2 H); ^{13}C NMR ($CDCl_3$): δ 158.9, 138.6, 133.1 (2 C), 126.9, 114.8, 114.6 (2 C), 55.4, 35.8, 33.4, 28.9, 28.0.

(1R*, 2R*)-1-Methyl-2-(phenylthiomethyl)-cyclopetan-1-ol (1.78)

To a stirred solution of alcohol **1.70** (656 mg, 2.95 mmol) in 10 mL of THF at –78 °C under argon, was added *n*-BuLi (3.2 mmol, 2.0 mL) via syringe. Freshly prepared LDBB (7.4 mmol in 20 mL THF) at –78 °C was cannulated to the reaction flask. The reaction mixture was stirred at –78 °C for 12 h before the addition phenyl disulfide (966 mg, 4.40 mmol) in 5 mL of THF. After the mixture was stirred for 30 min further, saturated $NaHCO_3$ solution (20 mL) was added and the mixture was allowed to warm to room temperature. The resulting mixture was extracted with ether (20 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The resulting residue was purified by flash-column chromatography to give 531 mg (81% yield) of **1.78** as a yellow oil and 51 mg (8%) of **1.70**. ^{1}H NMR ($CDCl_3$) δ 7.36-7.10 (m, 5 H, aromatic), 3.05 (dd, 1 H, J = 12.4, 6.4 Hz), 2.79 (dd, J = 12.4, 8.0 Hz), 2.10-1.90 (m, 2 H), 1.80-1.40 (m, 4 H), 1.39 (m, 1 H), 1.22 (s, 3 H); ^{13}C NMR

($CDCl_3$) δ 136.7, 129.16 (2 C), 129.01 (2 C), 126.1, 80.5, 48.8, 41.2, 35.0, 29.8, 22.9, 20.2; IR ν_{max} (neat) 3387 (br), 3058, 2960, 2872, 1583, 1480, 1438, 1376, 1313, 1090, 1025, 738, 691 cm^{-1}; MS (EI) m/z (relative intensity) 222(M^+, 16), 204 (8), 123(12), 110 (58), 95 (44), 84 (100), 79 (14), 71 (5), 58 (7); HRMS: exact mass calcd for $C_{13}H_{18}OS$ (M^+): 222.1078, found 222.1085.

(*trans*)-1, 2-Dimethylcyclopentan-1-ol (1.79)

To a stirred solution of alcohol **1.70** (467 mg, 2.10 mmol) in 10 mL of THF at –78 °C under argon, was added *n*-BuLi (2.5 mmol, 1.6 mL of 1.6 M solution) via syringe. Freshly prepared LDBB (5.25 mmol in 15 mL THF) at –78 °C was cannulated to the reaction flask. The reaction mixture was stirred at –78 °C for 5 h. After the addition of saturated $NaHCO_3$ (20 mL), the resulting mixtue was extracted with ether (20 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to give 132 mg (63% yield) of **1.79** as a pale yellow oil. ^1H NMR ($CDCl_3$) δ 2.00 (m, 1 H), 1.83 (m, 1 H), 1.75-1.50 (m, 3 H), 1.50-1.20 (m, 2 H), 1.46 (br, 1 H, -OH), 1.17 (s, 3 H), 0.90 (d, 3 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 81.2, 45.0, 40.3, 32.0, 23.0, 20.7, 15.7.

(*trans*)-2-(Phenylthiomethyl)cyclopentan-1-ol (1.80)

To a stirred solution of alcohol **1.71** (600 mg, 2.88 mmol) in 10 mL of THF at –78 °C under argon, was added *n*-BuLi (3.0 mmol, 1.9 mL) via syringe. Freshly prepared LDBB (7.2 mmol in 20 mL THF) at –78 °C was cannulated to the reaction flask. The reaction mixture was stirred at –78 °C for 12 h. After the addition of phenyl disulfide (940 mg, 4.30 mmol) in 5 mL of THF, a saturated aqueous $NaHCO_3$ solution (20 mL) was added. The resulting mixture was

extracted with ether (20 mL × 3). The combined organic layer was dried over $MgSO_4$ and filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to give 434 mg (73% yield) of **1.80** as a yellow oil and 45 mg (8%) of **1.71**. ^{1}H NMR ($CDCl_3$) δ 7.42-7.19 (m, 5 H, aromatic), 4.02 (m, 1 H), 3.01 (m, 2 H), 2.60 (br, 1 H, -OH), 2.12-1.85 (m, 3 H), 1.90-1.50 (m, 3 H), 1.50-1.30 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 136.8, 129.2 (4 C), 126.1, 78.7, 47.3, 37.8, 34.5, 30.2, 21.9; MS (EI) m/z (relative intensity) 208 (M^+, 20), 190 (8), 123 (17), 110 (100), 98 (96); HRMS: exact mass calcd for $C_{12}H_{16}OS$ (M^+): 208.0922, found 208.0917.

1-Phenylthio-4-ethoxy-5-hexene (1.81)

To a stirred solution of NaH (290 mg, 7.25 mmol) in 4 mL DMF at 0 C was added alcohol **1.71** (333 mg, 1.6 mmol) in 4 mL of DMF. Then the ice bath was reomoved and the mixture was stirred at room temperature for 1 h before EtI (1.8 mL, 7.3 mmol) was added dropwise. After the mixture was stirred 20 min further, water was added carefully to quench the reaction. The reaction mixture was extracted with ether (15 mL × 3). The combined organic materials was dried $MgSO_4$ and the solvent was removed by rotary evaporation. The resulting residue was purified by column chromatography (3% ethyl acetate in hexane) to give 320 mg of product **1.81** in 86% yield as a colorless oil. IR (neat) 3075, 2974, 2928, 2864, 1585, 1481, 1439, 1091, 1026, 993, 925, 738, 691. ^{1}H NMR : 7.37-7.18 (m, 5 H), 5.68 (m, 1 H), 5.20 (m, 2 H), 3.65 (m, 1 H), 3.56 (m, 1 H), 3.33 (m, 1 H), 2.97 (m, 2 H), 1.83.25 (dd, J = 12.9, 5.1 Hz, 1 H), 3.01 (dd, J = 12.9, 8.0 Hz, 1 H), 2.18 – 1.80 (m, 5 H), 1.54-1.65 (m, 4 H), 1.21 (t, J = 7.0 Hz); ^{13}C NMR : 139.3, 137.0, 129.03, 128.95, 125.8, 116.7, 80.7, 63.9, 34.7, 33.6, 25.3, 15.5 ;

MS (EI) *m*/*z* (relative intensity) 236 (M^+, 9), 207 (6), 191 (6), 136 (100), 123 (23), 109 (21), 85 (26), 57 (50); HRMS (EI) calcd for $C_{14}H_{20}OS$ (M^+): 236.1235 found 236.1237.

Cis- and _trans_- 1-ethoxy-2-phenylthiomethylcyclopentane (1.82 and 1.83)

Freshly prepared LDBB (1 mmol in 3 mL THF) at –78 °C was cannulated to a stirred solution of compound **1.81** (101 mg, 0.43 mmol) in 3 mL of THF at –78 °C under argon. The reaction mixture was stirred at –78 °C for 12 h before phenyl disulfide (131 mg, 0.6 mmol) in 3 mL of THF was added. After the mixture was stirred for 30 min further, saturated $NaHCO_3$ solution (10 mL) was added and the mixture was allowed to warm to room temperature. The reaction mixture was extracted with ether (20 mL × 3). The combined organic layer was dried over $MgSO_4$ and filterd through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to give 85 mg (85%) a mixture of cyclized and uncyclized products. Proton NMR and GC-MS studies show that the product mixture consists of three species. The major one (73.5%) is the starting materials and the remaining two (11.5 %) are cyclized products in *trans* to *cis* ratio of 1.5 to 1.

(2*E*)- 4-Methyl-7-phenylthiohept-2-en-4-ol (1.84)

1-Propenyl lithium was prepared by a procedure similar to that for the preparation of vinyl lithium from vinyl bromide. To freshly prepared 1-Propenyl lithium (8.26 mmol, prepared from trans 1-bromopropene (1.00 g, 8.26 mmol) and *t*-BuLi (9.7 mL, 16.5 mmol) in 10 mL diethyl ether) at –78 °C, was added dropwisely ketone **1.64** (890 mg, 4.60 mmol) in 5 mL of Et_2O via syringe. The reaction mixture was stirred for 2 h at –78 °C and then temperature was raised to –20 °C and maintained there for 30 min before the addition of 20 mL of saturated

aqueous $NaHCO_3$ solution. The reaction mixture was extracted with ether (30 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (10% ethyl acetate in hexane) to give 954 mg (88% yield) of **1.84** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.40-7.15 (m, 5 H, aromatic), 5.64-5.37 (m, 2 H), 2.96-2.90 (m, 2 H, J = 5.4 Hz), 1.70-1.65 (m, 7 H), 1.24 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 137.9, 136.8, 129.1 (2 C), 129.0 (2 C), 125.9, 123.0, 72.7, 41.7, 34.2, 28.2, 23.9, 17.8.

(2*E*)-4-Methyl-4-OLi-7-lithiohept-2-ene and its attempted cyclization in THF at –78 °C

To a stirred solution of alcohol **1.84** (340 mg, 1.44 mmol) in 10 mL of THF at –78 °C under argon, was added *n*-BuLi (1.58 mmol, 1.0 mL of 1.6 M solution) via syringe. Freshly prepared LDBB (3.6 mmol in 10 mL THF) at –78 °C was cannulated to the reaction flask. The reaction mixture was stirred at –78 °C for 12 h before the addition of 15 mL of saturated aqueous $NaHCO_3$ solution. The reaction mixture was extracted with ether (20 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (10% ethyl acetate in hexane) to give 126 mg (69% yield) of **1.85** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 5.70-5.50 (m, 2 H), 1.70 (d, 3 H, J = 5.2 Hz), 1.50-1.46 (m, 2 H), 1.36-1.30 (m, 2 H), 1.26 (s, 3 H), 0.92 (t, 3 H, J = 7.0 Hz).

(1R*,2S*)-3,3-Dimethyl-2-(phenylthiomethyl)cyclopentan-1-ol (1.86)

To a stirred solution of alcohol **1.72** (237 mg, 1.00 mmol) in 10 mL of THF at –78 °C under argon, was added *n*-BuLi (1.1 mmol, 0.69 mL) via syringe. Then, freshly prepared LDBB (2.5 mmol in 7 mL THF) at –78 °C was cannulated to the reaction flask. The reaction mixture

was stirred at –78 °C for 1 h before the addition of phenyl disulfide (350 mg, 1.60 mmol) in 5 mL of THF. After the resulting mixture was stirred for 30 min further, 20 mL of saturated aqueous $NaHCO_3$ solution was added and the temperature was allowed to warm to room temperature. The reaction mixture was extracted with ether (3 × 20 mL). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (10% ethyl acetate in hexane) to give 205 mg (86% yield) of **1.86** as colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.40-7.20 (m, 5 H, aromatic), 4.17 (m, 1 H), 3.21 (dd, 1 H, J = 12.9, 3.93 Hz), 2.79 (dd, 1 H, J = 12.9, 11.1 Hz), 2.11 (m, 1 H), 1.70-1.20 (m, 4 H), 1.05 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 136.1, 129.2 (4 C), 126.4, 79.9, 56.2, 41.6, 39.3, 34.0, 31.5, 29.0, 23.1; IR ν_{max} (neat) 3401(br), 3058, 2953, 2867, 1584, 1480, 1463, 1439, 1366, 1090, 1061, 1026, 739, 691 cm^{-1}; MS(EI) m/z (relative intensity) 236 (M^+, 45), 218(7), 126 (40), 110(100), 97(18), 70 (99), 55 (39); HRMS: exact mass calcd for $C_{14}H_{20}OS$ (M^+): 236.1235, found 236.1236.

(1R*, 2S*)-1,3,3-Trimethyl-2-(phenylthiomethyl)cyclopentan-1-ol (1.87)

To a stirred solution of compound **1.73** (266 mg, 1.06 mmol) in 10 mL of THF at –78 °C under argon, was added *n*-BuLi (1.17 mmol, 0.74 mL of 1.6 M hexane solution) via syringe. Freshly prepared LDBB (2.65 mmol in 7 mL THF) at –78 °C was cannulated to the reaction flask. The reaction mixture was stirred at –78 °C for 1 h before the addition of phenyl disulfide (371 mg, 1.7 mmol) in 5 mL of THF. After the resulting mixture was stirred for 30 min further, 15 mL of saturated aqueous $NaHCO_3$ solution was added. The reaction mixture was extracted with ether (20 mL × 3). The combined organic layer was dried over $MgSO_4$, filttered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography

(10% ethyl acetate in hexane) to give 213 mg (80% yield) of **1.87** as a white solid. ^{1}H NMR ($CDCl_3$) δ7.42-7.13 (m, 5 H, aromatic), 3.06 (dd, 1 H, J = 12.6, 5.1 Hz), 2.91 (dd, 1 H, J = 12.6, 10.4 Hz), 2.2 (br, 1 H, -OH), 1.93-1.69 (m, 4 H), 1.46 (m, 1 H), 1.38 (s, 3 H), 1.11 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 136.3, 129.1 (4 C), 126.2, 81.3, 58.3, 41.0, 39.8, 39.0, 30.92, 30.86, 25.6, 23.4; MS m/z (relative intensity) 250(M^+, 30), 232(16), 123(100), 110(67), 81(58), 67(29), 55(40); HRMS: exact mass calc. for $C_{15}H_{22}OS$ (M^+): 250.1391, found 250.1405.

3,3-Dimethyl-2-(phenylthiomethyl)cyclopentanone (1.88)

Using a literature[54] procedure for the oxidation, the ketone **1.88** was isolated as an oil in 93% yield from **1.86** after column chromatography (5% ethyl acetate in hexanes). ^{1}H NMR ($CDCl_3$) δ 7.41-7.08 (m, 5 H), 3.28 (dd, 1 H, *J* = 13.3, 5.3 Hz), 2.69 (dd, 1 H, *J* = 13.3, 7.9 Hz), 2.24-2.08 (m, 3 H), 1.71-1.65 (m, 2 H), 1.23 (s, 3 H), 0.84 (s, 3 H). ^{13}C NMR ($CDCl_3$) δ 218.2, 136.75, 129.1 (2 C), 128.9 (2 C), 126.1, 59.3, 39.8, 35.9, 35.2, 29.3, 29.0, 21.6.

(1R*,2R*)-3,3-Dimethyl-2-(phenylthiomethyl)cyclopentan-1-ol (1.89)

L-Selectride (lithium tri-*sec*-butylborohydride, 1.0 M in THF, 0.60 mL, 0.60 mmol) was added dropwise via syringe to a solution of the ketone **1.88** (71 mg, 0.30 mmol), dissolved in dry THF (10 mL) at -78 °C. The mixture was stirred at -78 °C for 3 h before it was warmed to room temperature. A solution of NaOH (24 mg, 0.60 mmol) in 1 mL water was added followed by the addition of H_2O_2 (30% aqueous solution, 0.20 mL, 1.8 mmol). After the reaction mixture had been stirred at room temperature for 1 h, it was exacted with ether (20 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The resulting residue was purified by column chromatography to give 65 mg of **1.89** (91% yield) as

an oil. ^{1}H NMR ($CDCl_3$) 7.35-7.16 (m, 5 H), 4.41-4.39 (m, 1 H), 3.03-3.00 (m, 2 H), 1.96 (m, 2 H), 1.62 (m, 3 H), 1.36 (m, 1 H), 0.99 (s, 3 H), 0.96 (s, 3 H). ^{13}C NMR ($CDCl_3$) 136.6, 129.1 (4 C), 126.1, 74.0, 53.0, 40.7, 40.5, 32.6, 29.8, 29.3, 23.7.

(1R*, 2R*)-1,3,3-Trimethyl-2-(phenylthiomethyl)cyclopentan-1-ol (1.90)

MeLi (1.4 M in ether, 0.73 mL, 1.0 mmol) was added dropwise via syringe to a solution of the ketone **1.88** (48 mg, 0.21 mmol), dissolved in dry ether (5 mL) at -78 °C. The mixture was stirred at -78 °C for 1 h before it was warmed to 0 °C and quenched with water (10 mL). The reaction mixture was extracted with ether (15 mL × 3). The combined organic layer, after being washed with water (10 mL), was dried over $MgSO_4$, filtered and evaporated in vacuo. The resulting residue was purified by column chromatography (10% ethyl acetate in hexane) to give 44 mg of **1.90** (86% yield) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.33-7.02 (m, 5 H), 3.00 (m, 2 H), 2.14-1.45 (m, 5 H), 1.40 (s, 3 H), 1.03 (s, 3 H), 0.97 (s, 3 H). ^{13}C NMR ($CDCl_3$) δ 137.0, 129.0 (2 C), 128.7 (2 C), 125.9, 80.9, 56.2, 42.2, 40.7, 39.8, 31.6, 30.3, 30.2, 23.2.

1,3-Dimethyl-2-(phenylthiomethyl)cyclopentan-1-ol (1.91 and 1.92)

To a stirred solution of alcohol **1.74** (266 mg, 1.13 mmol) in 10 mL of THF at –78 °C under argon, was added *n*-BuLi (1.24 mmol, 0.80 mL of 1.60 M hexane solution) via syringe. Freshly prepared LDBB (2.8 mmol in 8 mL THF) at –78 °C was cannulated to the reaction flask. The reaction mixture was stirred at –78 °C for 1 h before the addition of phenyl disulfide (394 mg, 1.81 mmol) in 5 mL of THF. After the mixture was stirred for 30 min further, 10 mL of saturated aqueous $NaHCO_3$ solution was added. The resulting mixture was extracted with ether (20 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and

evaporated in vacuo. The resulting residue was purified by flash-column chromatography (10% ethyl acetate in hexane) to give two diastereomers in a ratio of 6:1. major: 208 mg (78% yield) and minor: 37 mg (14% yield). Major product **1.91**: ^{1}H NMR ($CDCl_3$) δ 7.43-7.23 (m, 5 H, aromatic), 3.10 (dd, 1 H, J = 12.6, 5.1 Hz), 2.99(dd, 1 H, J = 12.6, 8.5 Hz), 2.74 (br, 1 H), 1.93-1.66 (m, 5 H), 1.36 (m, 1 H), 1.33 (s, 3 H), 1.14 (d, 3 H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 136.7, 129.1 (2 C), 129.0 (2 C), 126.1, 81.1, 55.7, 40.1, 38.6, 33.9, 30.3, 24.1, 20.9; MS m/z (relative intensity): 236 (M^+, 26), 218 (19), 178 (8), 123 (10), 100 (100), 69 (17), 59 (23); HRMS: exact mass calcd $C_{14}H_{20}OS$ (M^+): 236.1235, found 236.1236.

Minor product **1.92**: 7.39-7.19 (m, 5 H, aromatic), 3.05-2.91 (m, 2 H), 2.42 (m, 1 H), 2.17 (m, 1 H), 1.97 (m, 1 H), 1.85-1.64 (m, 3 H), 1.30 (s, 3 H), 0.94 (d, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 136.8, 129.05 (2 C), 128.90 (2 C), 126.0, 73.95, 51.9, 37.2, 32.3, 31.5, 19.1. MS m/z (relative intensity): 236 (M^+, 22), 218 (25), 178 (6), 123 (14), 110 100), 69 (22), 55 (12); HRMS: exact mass calcd $C_{14}H_{20}OS$ (M^+): 236.1231, found 236.1235.

3-Methyl-2-(Phenylthiomethyl)cyclopentan-1-ol (1.93 and 1.94)

To a stirred solution of alcohol **1.75** (297 mg, 1.34 mmol) in 10 mL of THF at –78 °C under argon, was added *n*-BuLi (1.41 mmol, 0.88 mL, 1.6 M in hexane) via syringe. Freshly prepared LDBB (3.35 mmol in 10 mL of THF) at –78 °C was cannulated to the reaction flask. The reaction mixture was stirred at –78 °C for 1 h before the addition of phenyl disulfide (470 mg, 2.16 mmol) in 5 mL of THF. After the mixture was further stirred for 30 min, 10 mL of saturated $NaHCO_3$ solution was added. The resulting mixture was extracted with ether (20 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (10% ethyl acetate in

hexane) to give two diastereomers in a ratio of 7:1. major: 214 mg (72% yield) and minor: 33 mg (11% yield).

Major product **1.93**: ^{1}H NMR ($CDCl_3$) δ 7.51-7.30 (m, 5 H, aromatic), 4.19 (m, 1 H), 3.33 (dd, 1 H, J = 12.8, 4.7 Hz), 3.02 (dd, J = 12.8, 8.3 Hz), 2.92 (s, 1 H, -OH), 2.05-1.50 (m, 6 H), 1.19 (d, 3 H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 136.9, 129.1 (2 C), 128.9 (2 C), 126.0, 78.7, 54.6, 38.5, 36.5, 33.3, 31.5, 20.0; MS m/z (relative intensity): 222 (M^+, 59), 123 (19), 100 (100), 97 (53), 70 (64), 55 (18); HRMS: exact mass calcd $C_{13}H_{18}OS$ (M^+): 222.1078, found 222.1073.

Minor product **1.94**: ^{1}H NMR ($CDCl_3$) δ 7.39-7.17 (m, 5 H), 4.39 (m, 1 H), 3.18 (dd, 1 H, J = 12.2, 4.4 Hz), 3.01 (dd, 1 H, J = 12.2, 11.0 Hz), 2.02-1.10 (m, 6 H), 1.52 (s, 1 H, -OH), 1.04 (d, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 136.8, 129.05 (2 C), 128.90 (2 C), 126.0, 73.95, 51.9, 37.2, 32.29, 32.25, 31.5, 19.1. MS m/z (relative intensity): 222 (M+, 31), 123 (13), 100 (69), 95 (44), 84 (100), 70 (64); HRMS: exact mass calcd $C_{13}H_{18}OS$ (M^+): 222.1078, found 222.1077.

3,5-Dinitro-benzoic acid 1, 3-dimethyl-2-phenylsulfanylmethylcyclopentyl ester (1.95)

To a stirred solution of alcohol **1.93** (27 mg, 0.11 mmol) in 2 mL pyridine at room temperature was added 3,5 dinitrobenzoyl chloride (53 mg, 0.22 mmol, 2 equiv.), and the resulting mixture was heated at 55 °C for 12 h. After the reaction mixture was cooled to room temperature, it was diluted with water (3 mL) and extracted with ether (5 mL × 3). The combined organic layer was washed successively with 1 N H_2SO_4 (10 mL) and water (10 mL). After it was dried over $MgSO_4$ and filtered, the solvent was removed by rotary evaporation. The resulting residue was purified by column chromatography (10% ethyl acetate in hexane) to give 49 mg of **1.95** (yield 100%) as a yellow solid. The product was crystallized by the mixture solvents of CH_2Cl_2 and hexane. m.p. 129-131 °C; IR (neat) 3100, 2959, 2923, 2874, 1724, 1544,

1344, 1285, 1168, 730, 720, 691; ^{1}H NMR : 9.20 (t, J = 1.8 Hz, 1 H), 9.12 (d, J = 1.8 Hz, 2 H), 7.54-7.17 (m, 5 H), 3.38 (dd, J = 12.3, 6.0 Hz, 1 H), 2.96 (dd, J = 12.2, 8.9 Hz, 1 H), 2.64 (m, 1 H), 2.52 (m, 1 H), 2.28 (m, 2 H), 2.08 (m, 1 H), 1.70 (s, 3 H), 1.44 (m, 1 H), 1.03 (d, J = 7.2 Hz); ^{13}C NMR : 161.7, 148.7, 136.6, 135.5, 129.5, 129.2 (4 C), 126.3, 122.2, 93.6, 50.7, 38.3, 33.7, 31.1, 31.0, 21.9, 16.0; MS (EI) *m*/*z* (relative intensity) 430 (M^+, 42), 347 (11), 245 (17), 218 (43), 123 (38), 109 (100), 93 (64), 67 (49); HRMS (EI) calcd for $C_{21}H_{22}N_2O_6S$ (M^+) 430.1199, found 430.1197.

3,5-Dinitro-benzoic acid 3-methyl-2-phenylsulfanylmethyl-cyclopentyl ester (1.96)

To a solution of 3,5 dinitrobenzoyl chloride (208 mg, 0.90 mmol, 2 equiv.) in 4 mL of CH_2Cl_2, 4-dimethylaminopyridine (DMAP, 1.7 mg, 0.014 mmol, 0.03 equiv.) was added. The reaction mixture was stirred at rt for 5 min before the addition of the mixture of triethylamine (0.13 mL, 0.90 mmol, mw 101.10, d 0.726) and alcohol **1.93** (100mg, 0.45 mmol). After the resulting mixture was stirred at room temperature for 12 h, 10 mL of water was added. The reaction mixture was extracted with Et_2O (20 mL × 3). The combined organic layer, after being washed successively with 1 N H_2SO_4 (10 mL) and water (10 mL), was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The resulting residue was purified by column chromatography (10% ethyl acetate in hexane) to give 166 mg of **1.96** (82% yield) as a yellow solid. The product was crystallized by mixture solvents of CH_2Cl_2 and hexane. m.p. 116-118 °C; IR (neat) 3101, 2955, 2871, 1728, 1544, 1344, 1277, 1169, 730, 721, 691; ^{1}H NMR : 9.20 (m, 1 H), 9.08 (m, 2 H), 7.28-7.12 (m, 5 H), 5.34 (m, 1 H), 3.25 (dd, J = 12.9, 5.1 Hz, 1 H), 3.01 (dd, J = 12.9, 8.0 Hz, 1 H), 2.18 – 1.80 (m, 5 H), 1.53 (m, 1 H), 1.16 (d, J = 6.4 Hz); ^{13}C NMR : 162.3, 148.7, 136.6, 134.4, 129.5, 129.1, 128.9, 126.1, 122.3, 83.5, 52.1, 38.8, 35.9, 32.4, 31.5,

19.5; MS (EI) *m*/*z* (relative intensity) 416 (M^+, 31), 195 (30), 149 (23), 123 (26), 110 (100), 95 (70); HRMS (EI) calcd for $C_{20}H_{20}N_2O_6S$ (M^+) 416.1042 found 416.1047.

***Trans*-3-Methyl-2-phenylthiomethyl-cyclopentanone (1.97)**

Using a literature procedure for the oxidation of **1.93**, the ketone **1.97** was isolated as an oil in 88% yield after column chromatography. IR (neat) 3058, 2955, 2925, 2870, 1740, 1582, 1480, 1439, 1155, 740, 691. ^{1}H NMR : 7.37-6.97 (m, 5 H), 3.33 (dd, J = 12.9, 4.0 Hz, 1 H), 3.07 (dd, J = 12.9, 5.8 Hz, 1 H), 2.48-1.94 (m, 6 H), 1.45 (s, 3 H), 1.21 (d, J = 8.4 Hz); ^{13}C NMR : 218.7, 136.7, 129.5, 129.1, 126.3, 56.2, 38.2, 37.0, 32.4, 29.6, 19.8; MS (EI) *m*/*z* (relative intensity) HRMS (EI) calcd for $C_{13}H_{16}OS$ (M^+): 220.0922, found 220.0931.

(1S*, 2R*, 3R*) 1,3-Dimethyl-2-phenylsulfanylmethyl-cyclopentanol (1.98)

MeMgBr (3.0 M, 0.40 mL, 1.18 mmol) was added dropwise via syringe to a solution of ketone **1.97** (65 mg, 0.295 mmol) in THF (5 mL) at -78 °C. The mixture was stirred at -78 °C for 1 h before it was warmed to 0 °C and quenched with satuated $NaHCO_3$ solution (10 mL). The resulting mixture was extracted with ether (10 mL × 3). The combined organic layer. After being washed with water (10 mL), was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by column chromatography (10% ethyl acetate in hexanes) to give two products. The major product **1.98** (39 mg, 56%) has the following spectroscopic data: ^{1}H NMR ($CDCl_3$) δ7.35-7.04 (m, 5 H), 3.13 (dd, J = 12.3, 8.8 Hz, 1 H), 3.03 (dd, J = 12.4, 5.3 Hz, 1 H), 1.97-1.68 (m, 5 H), 1.37 (s, 3 H), 1.10 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 137.3, 129.0, 128.7, 125.9, 80.8, 55.2, 41.3, 39.9, 33.1, 31.6, 29.6, 20.3; The minor product (18 mg, 26%) has complete identical spectra with the alcohol **1.91**.

L-Selectride (lithium tri-*sec*-butylborohydride, 1.0 M in THF, 0.20 mL, 0.20 mmol) was added dropwise via syringe to a solution of the ketone **1.97** (22 mg, 0.10 mmol) dissolved in dry THF (10 mL) at -78 °C. The mixture was stirred at -78 °C for 3 h before it was warmed to room temperature. A solution of NaOH (8 mg, 0.20 mmol) in 1 mL water was added followed by the addition of H_2O_2 (30% aqueous solution, 0.07 mL, 0.6 mmol). After the reaction mixture had been stirred at room temperature for 1 h, it was exacted with ether (10 mL × 3). The conbined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by column chromatography (10% ethyl acetate in hexanes) to give an alcohol (17 mg, 76%) as a single diastereomer, which is completely identical in spectroscopy analysis with the minor product **1.94**.

3-Methyl-3-phenylthiobutanal (1.99)

To a mixture of thiophenol (11.0 g, 100 mmol) and triethylamine (0.5 mL) in 15 mL of THF at 0 °C, 3-methyl-2-butenal (8.40 g, 100 mmol) was added dropwise. After being stirred at room temperature overnight, 60 mL of Et_2O was added and the reaction mixture was washed with 5% NaOH (40mL × 3) and then 5% $NaHCO_3$ (40 mL). The organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo to provide 16.0 g (82%) of **1.99** as a pale yellow oil, which did not require further purification. ^{1}H NMR ($CDCl_3$) δ 9.92 (t, 1 H, J = 3.8 Hz), 7.60-7.36 (m, 5 H, aromatic), 2.48 (d, 2 H, J = 2.8 Hz), 1.42 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 202.0, 137.8 (2 C), 131.0, 129.4, 129.0 (2 C), 54.2, 46.2, 29.2 (2 C).

5-Methyl-5-phenylthiohex-1-en-3-ol (1.100)

To freshly prepared vinyl lithium solution (14.0 mmol prepared from 1.0 mL (14.0 mmol) of vinyl bromide and 16.5 mL of 1.7 M *t*-BuLi in 9 mL anhydrous ether) at –78 °C, was added dropwise aldehyde **1.99** (1.97 g, 10.1 mmol) in 20 mL of THF via syringe. The reaction mixture was stirred at –78 °C for 2 h and then the temperature was raised to –20 °C and maintained there for 30 min before the addition of 10 mL of saturated aqueous $NaHCO_3$. The resulting mixture was extracted with ether (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (10 % ethyl acetate in hexane) to afford 2.12 g (94% yield) of **1.100** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.60-7.30 (m, 5 H, aromatic), 5.90 (ddd, 1 H, J = 17.1, 10.3, 5.7 Hz), 5.31 (d, 1 H, J = 17.1 Hz), 5.10 (d, 1 H, J = 10.3 Hz), 4.56 (m, 1 H), 1.79 (dd, 1 H, J = 15.0, 9.3 Hz), 1.60 (dd, 1 H, J = 15.0, 2.7 Hz), 1.39 (s, 3 H), 1.30 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 141.9, 137.6 (2 C), 131.6, 129.1, 128.8 (2 C), 114.1, 70.6, 48.7, 47.8, 30.0, 29.1; IR ν_{max} (neat) 3412 (br), 3074, 2967, 2927, 1473, 1438, 1365, 1127, 1025, 992, 923, 751, 695 cm^{-1}; MS (EI) m/z (relative intensity) 222 (M^+, 3), 204 (2), 149 (60), 110 (100), 95 (20), 57 (6); HRMS: exact mass calcd for $C_{13}H_{18}OS$ (M^+): 222.1078, found 222.1073.

(2S*,1R*)-3,3-Dimethyl-2-(phenylthiomethyl)cyclobutan-1-ol (1.101)

To a stirred solution of alcohol **1.100** (300 mg, 1.35 mmol) in 10 mL of THF at –78 °C under argon, was added *n*-BuLi (1.5 mmol, 0.93 mL) via syringe. Freshly prepared LDBB (3.4 mmol in 10 mL of THF) at –78 °C was cannulated to the reaction flask. The reaction mixture was stirred at –42 °C for 2 h before the addition of phenyl disulfide (471 mg, 2.16 mmol) in 5 mL of THF. After the mixture was further stirred for 30 min, 10 mL of saturated $NaHCO_3$ solution was added. The resulting mixture was extracted with ether (20 mL × 3). The combined

organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (10% ethyl acetate in hexane) to afford 201 mg (67% yield) of **1.101** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.40-7.16 (m, 5 H, aromatic), 3.95 (m, 1 H), 3.04-3.00 (m, 2 H), 2.13-2.02 (m, 2 H), 1.76 (m, 1 H, -OH), 1.58 (m, 1 H), 1.16 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 136.7, 129.1 (4 C), 126.1, 69.1, 53.6, 43.4, 33.2, 31.2, 30.5, 23.2; IR ν_{max} (neat) 3332(br), 3058, 2954, 2930, 2863, 1585, 1481, 1439, 1066, 737, 690 cm^{-1}; MS (EI) m/z (relative intensity) 222(M^+, 35), 178 (17), 149(9), 123(15), 110(100), 95(26), 69(95), 57(43); HRMS: exact mass calcd $C_{13}H_{18}OS$ (M^+): 222.1078, found 222.1071.

5-Phenylthio-pent-1-en-3-ol (1.103)

To a mixture of thiophenol (11.0 g, 100 mmol) and triethylamine (0.5 mL) in 15 mL of THF at 0 °C, was added acrolein (5.60 g, 100 mmol). After being stirred at room temperature overnight, the reaction mixture was washed with 5% NaOH (40 mL × 3) and then 5% $NaHCO_3$ (40 mL). The organic layer, once dried over $MgSO_4$, filtered through cotton and was evaporated in vacuo to give 16.1 g of **1.102** which was immediately used in the next step without further purification.

To a freshly prepared vinyl lithium solution (21.6 mmol prepared from 1.54 mL of vinyl bromide and 25.5 mL of 1.7 M *t*-BuLi in 15 mL anhydrous ether) at –78 °C, was added dropwise 3-phenylthiopropanal **1.102** (2.53 g, 15.2 mmol) in 10 mL of Et_2O. The reaction mixture was stirred for 2 h at –78 °C and then the temperature was raised to –20 °C and maintained there for 30 min before the addition of 20 mL of saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with ether (40 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by

flash-column chromatography (10 % ethyl acetate in hexane) to afford 2.72 g (92% yield) of **1.103** as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.35-7.16 (m, 5 H, aromatic), 5.83 (ddd, 1 H, J = 17.2, 10.4, 6.0 Hz), 5.26-5.09 (m, 2 H), 4.26 (m, 1 H), 3.01 (m, 2 H), 2.33 (br, 1 H, -OH), 1.89-1.81 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 140.53, 136.42, 129.30 (2 C), 129.11 (2 C), 126.14, 115.40, 71.87, 36.18, 29.74.

1,1-bis(phenylthio)-2-methylpropene[55] (1.104)

To a three-neck flask equipped with a reflux condenser was charged sequentially 200 mL of anhydrous benzene, 20 mL of a 2.0 M solution of $Al(CH_3)_3$ in toluene and a solution of thiophenol (12.3 mL, 0.12 mol) in 50 mL of benzene. The resulting mixture was stirred for 4 h at ambient temperature and then heated at reflux for 1 h. After the reaction mixture was cooled to ambient temperature, methyl isobutyrate (2.1 mL, 0.018 mmol) was added. The resulting mixture was heated at reflux for 4 h. After the mixture was cooled to ambient temperature, 20% NaOH (30 mL) was added, and the resulting mixture was extracted with ether (50 mL × 3). The combined organic layer, after being washed with 10% NaOH (50 mL × 3), was dried over $MgSO_4$, filtered and evaporated in vacuo. The residue was purified by flash-column chromatography (hexane) to afford 4.19 g (86% yield) of **1.104** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.22-7.10 (m, 10 H, aromatic), 2.30 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 153.5, 136.1, 129.2 (2 C), 128.8 (2 C), 126.2, 120.9, 24.5 (2 C).

6-Methyl-5-(phenylthio)hept-5-en-2-one (1.105)

To a stirred solution of LDBB (16.9 mmol) in 40 mL THF at –78 °C was added a solution of 1,1-bis(phenylthio)-2-methylpropene (2.3 g, 8.5 mmol) in 6 mL of THF. The color of

the reaction mixture changed from deep green to red. After the reaction mixture was stirred for 30 min, CuBr•Me_2S (2.5 g, 12 mmol) was added and the resulting mixture was stirred for 3 h at –78 °C. Then a solution of TMSCl (1.87 mL, 14.7 mmol) in 4 mL of THF was added followed by dropwise addition of a solution of methyl vinyl ketone (0.73 mL, 8.8 mmol) in 4 mL of THF. The resulting mixture was stirred for 12 h at –78 °C before aqueous 5% NaOH (40 mL) and 40% aqueous *n*-Bu_4NOH (1 mL) were added. After the reaction mixture was allowed to warm to 0 °C, tt was stirred at room temperature for about 1 h in order to hydrolyze all of the silyl enol ether to the corresponding ketone. The mixture was filtered through Celite and extracted with ether (60 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The resulting residue was purified by flash-column chromatography to afford 1.71 g (86% yield) of **1.105** as pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.32-7.14 (m, 5 H, aromatic), 2.71-2.56 (m, 4 H), 2.11 (s, 3 H), 2.07 (s, 3 H), 1.99 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 208.4, 142.2, 136.9, 129.0 (2 C), 127.7 (2 C), 125.4, 124.4, 42.5, 30.0, 27.8, 23.7, 21.2.

3,7-Dimethyl-6-phenylthioocta-1,6-dien-3-ol (1.106)

To a freshly prepared vinyl lithium solution (6.8 mmol, prepared from 0.48 mL (6.8 mmol) of vinyl bromide and 8 mL of 1.7 M *t*-BuLi in 5 mL anhydrous ether) at –78 °C, was added ketone **1.105** (954 mg, 4.1 mmol) in 10 mL of THF via syringe. The reaction mixture was stirred for 2 h at –78 °C and then the temperature was raised to –20 °C and maintained there for 30 min before the addition of 20 mL of saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with ether (30 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (10% ethyl acetate in hexane) to give 1.05 g (94% yield) of **1.106**

as yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.30-7.10 (m, 5 H, aromatic), 5.83 (dd, 1 H, J = 17.4, 10.7 Hz), 5.15 (dd, 1 H, J = 17.4, 1.2 Hz), 5.99 (dd, 1 H, J = 10.7, 1.2 Hz), 2.33-2.25 (m, 2 H), 2.00 (s, 3 H), 1.90 (s, 3 H), 1.75-1.68 (m, 2 H), 1.34 (s, 1 H, -OH), 1.22 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.8, 140.4, 137.2, 129.0 (2 C), 128.0 (2 C), 125.8, 125.4, 112.0, 73.2, 41.0, 28.7, 27.8, 23.5, 21.1; MS m/z (relative intensity) 262 (M^+, 64), 245 (26), 206 (37), 191 (100), 135 (49), 119 (88), 110 (52), 91 (55), 81 (51), 71 (85), 55 (43); HRMS: exact mass calcd for $C_{16}H_{22}OS$ (M^+): 262.1391, found 262.1385.

(1R*,2R*)-1,2-dimethyl -3-(methylethylidene)cyclopentan-1-ol (1.107 and 1.108)

To a stirred solution of aochol **1.106** (266 mg, 1.06 mmol) in 10 mL of THF at –78 °C under argon, was added *n*-BuLi (1.17 mmol, 0.74 mL) via syringe. Freshly prepared LDBB (2.65 mmol in 7 mL of THF) at –78 °C was cannulated to the reaction flask. The temperature was then raised to –20 °C and the reaction mixture was stirred at that temperature for 5 h. After the addition of 20 mL of saturated $NaHCO_3$ solution, the resulting mixture was extracted with ether (20 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (10% ethyl acetate in hexane) to afford 135 mg (80 %) of a mixture of **1.107** and **1.108** in a major/minor ratio of 7:1. 31 mg (18%) of 3,7-dimethylocta-1,6-dien-3-ol was also isolated. Major diastereomer (1R*,2R*)-1,2-dimethyl-3-(methylethylidene)cyclopentan-1-ol **1.107**: ^{1}H NMR ($CDCl_3$) δ 2.42-2.25 (m, 3 H), 1.88-1.65 (m, 2 H), 1.66 (s, 3 H), 1.60 (s, 3 H), 1.26 (s, 3 H), 0.87(d, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 139.3, 124.0, 81.9, 48.8, 37.0, 27.1, 23.5, 21.0, 20.8, 17.2; Minor diastereomer (2S*,1R*)-1,2-dimethyl-3-(methylethylidene)cyclopentan-1-ol **1.108**: ^{1}H NMR ($CDCl_3$) δ 2.42-2.25 (m, 3 H), 1.88-1.65 (m, 3 H), 1.64 (s, 3 H), 1.55 (s, 3 H),

1.20 (s, 3 H), 0.96 (d, 3 H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 137.8, 123.5, 79.3, 46.6, 37.3, 27.9, 26.8, 20.8, 20.6, 14.5; MS m/z (relative intensity) 154 (M^+, 40), 136 (53), 121 (91), 111 (43), 107 (52), 96 (62), 81 (100), 69 (85), 55 (90); HRMS: exact mass calcd for $C_{10}H_{18}O$: 154.1358, found 154.1357.

3, 7-dimethylocta-1,6-dien-3-ol: ^{1}H NMR ($CDCl_3$) δ 5.91 (dd, 1 H, J = 17.3, 10.7 Hz), 5.21 (dd, 1 H, J = 17.3, 1.3 Hz), 5.12 (m, 1 H), 5.07 (dd, 1 H, J = 10.7, 1.3 Hz), 2.20-2.00 (m, 2 H), 1.69 (s, 3 H), 1.59 (s, 3 H), 1.60 – 1.28 (m, 2 H), 1.28 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 145.1, 132.1, 124.4, 111.8, 73.6, 42.1, 28.0, 25.8, 22.9, 17.8.

1-[(1R*,2R*)-2-(1-methyl-1-phenylthioethyl)cyclopentyl]-ethan-1-one (1.110)

To a solution of LDBB (15 mmol, in 40 mL of THF) at –78 °C was added 2,2-bis(phenylthio)propane (1.86 g, 7.14 mmol, in 8 mL of THF). After the mixture had been stirred at –78 °C for 10 min, CuBr•Me_2S (2.20 g, 10.7 mmol) was added with increased argon flow. After the mixture had been stirred for 3 h at –78 °C to insure the formation of the cuprate, a solution of TMSCl (1.48 mL, 11.6 mmol) in 4 mL of THF was added followed by dropwise addition of a solution of 1-acetylcyclopentene (0.74 mL, 6.43 mmol) in 3 mL of THF. The resulting mixture was stirred for 12 h at –78 °C. Aqueous 5% NaOH (40 mL) and 40% aqueous *n*-Bu_4NOH (1 mL) were added before the reaction mixture was allowed to warm to 0 °C. It was stirred at room temperature for about 1 h in order to hydrolyze all of the silyl enol ether to the ketone product. The mixture was filtered through Celite and extracted with ether (60 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The resulting residue was purified by flash-column chromatography (5% ethyl acetate) to afford 1.18 g (63% yield) of **1.110** as a pale yellow oil. The corresponding *Cis* product (78 mg,

4%) was also obtained. However, only the major *trans* product was fully characterized. ^{1}H NMR ($CDCl_3$) δ 7.54-7.20 (m, 5 H, aromatic), 3.14 (m, 1 H), 2.77 (m, 1 H), 2.27 (s, 3 H), 2.19 (s, 1 H, -OH), 2.00-1.50 (m, 6 H), 1.19 (s, 3 H), 1.13 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 211.4, 137.8 (2 C), 128.8, 128.6 (2 C), 53.9, 52.5, 50.8, 32.4, 29.6, 29.4, 28.2, 27.2, 26.5; IR ν_{max} (thin film) 3058, 2958, 2868, 1709, 1473, 1439, 1365, 1157, 751, 695 cm^{-1}; MS m/z (relative intensity) 262 (M^+, 13), 152 (100), 135 (20), 110 (95), 95 (52), 81 (26), 67 (79), 55 (39); HRMS: exact mass calcd $C_{16}H_{22}OS$ (M^+): 262.1391, found 262.1390.

2-(1-methyl-1-phenylthioethyl)cyclopentyl]but-3-en-2-ol (1.111)

To a freshly prepared vinyl lithium solution (5.7 mmol, prepared from 0.40 mL of vinyl bromide (5.7 mmol) and 8 mL of 1.7 M *tert*-BuLi in 5 mL anhydrous ether) at –78 °C, was added ketone **1.110** (0.87 g, 3.3 mmol) in 3 mL of Et_2O. The mixture was stirred for 2 h at –78 °C and then the temperature was raised to –20 °C and maintained at this temperature for 30 min before the addition of 20 mL of saturated aqueous $NaHCO_3$ solution. The reaction mixture was extracted with ether (30 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and filtered through cotton and evaporated in vacuo. The resulting residue was purified by flash-column chromatography (10% ethyl acetate in hexane) to give 844 mg (88% yield) of **2.111** as a colorless oil. Another diastereomer (78 mg, 8%) was also obtained, but only the major product was characterized. ^{1}H NMR ($CDCl_3$) δ 7.56-7.25 (m, 5 H, aromatic), 5.88 (dd, 1 H, J = 17.3, 10.7Hz), 5.28 (dd, 1 H, J = 17.3, 1.5 Hz), 5.05 (dd, 1 H, J = 10.6, 1.5 Hz), 2.38 (s, 1 H, -OH), 2.25-2.19 (m, 2 H), 1.95-1.58 (m, 6 H), 1.27 (s, 3 H), 1.18 (s, 3 H), 1.14 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 143.6, 137.8 (2 C), 132.2, 128.8, 128.5 (2 C), 112.8, 75.5, 54.1, 51.5, 50.1, 30.1, 30.0, 28.1, 27.9, 27.7, 26.7; IR ν_{max} (thin film) 3455 (br), 3050, 2964, 2875, 1473, 1367, 1266, 1112,

1002, 921, 748, 695 cm^{-1}; MS m/z (relative intensity) 290 (M^+, 2.4), 272 (0.9), 219 (12), 181 (30), 163 (57), 151 (54), 121 (36), 110 (100), 95 (93), 81 (89), 67 (88), 55 (72); HRMS: exact mass calcd $C_{18}H_{26}OS$ (M^+): 290.1704, found 290.1691.

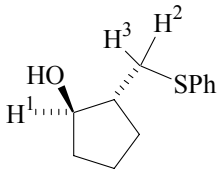
2,3,4,4-tetramethylbicyclo[3.3.0]octan-2-ol (1.112)

To a stirred solution of alcohol **1.111** (304 mg, 1.05 mmol) in 10 mL of THF at –78 °C under argon, was added *n*-BuLi (1.2 mmol, 0.74 mL) via syringe. Freshly prepared LDBB (2.63 mmol in 7 mL of THF) at –78 °C was cannulated to the reaction flask. The resulting mixture was stirred at –78 °C for 1 h before the addition of 20 mL of saturated $NaHCO_3$. The reaction mixture was extracted with ether (20 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (10% ethyl acetate in hexane) to give 80 mg cyclized product **1.112** (42%) as a white solid. Uncyclized product **1.113** (82 mg, 43%) was also isolated as a pale yellow oil.

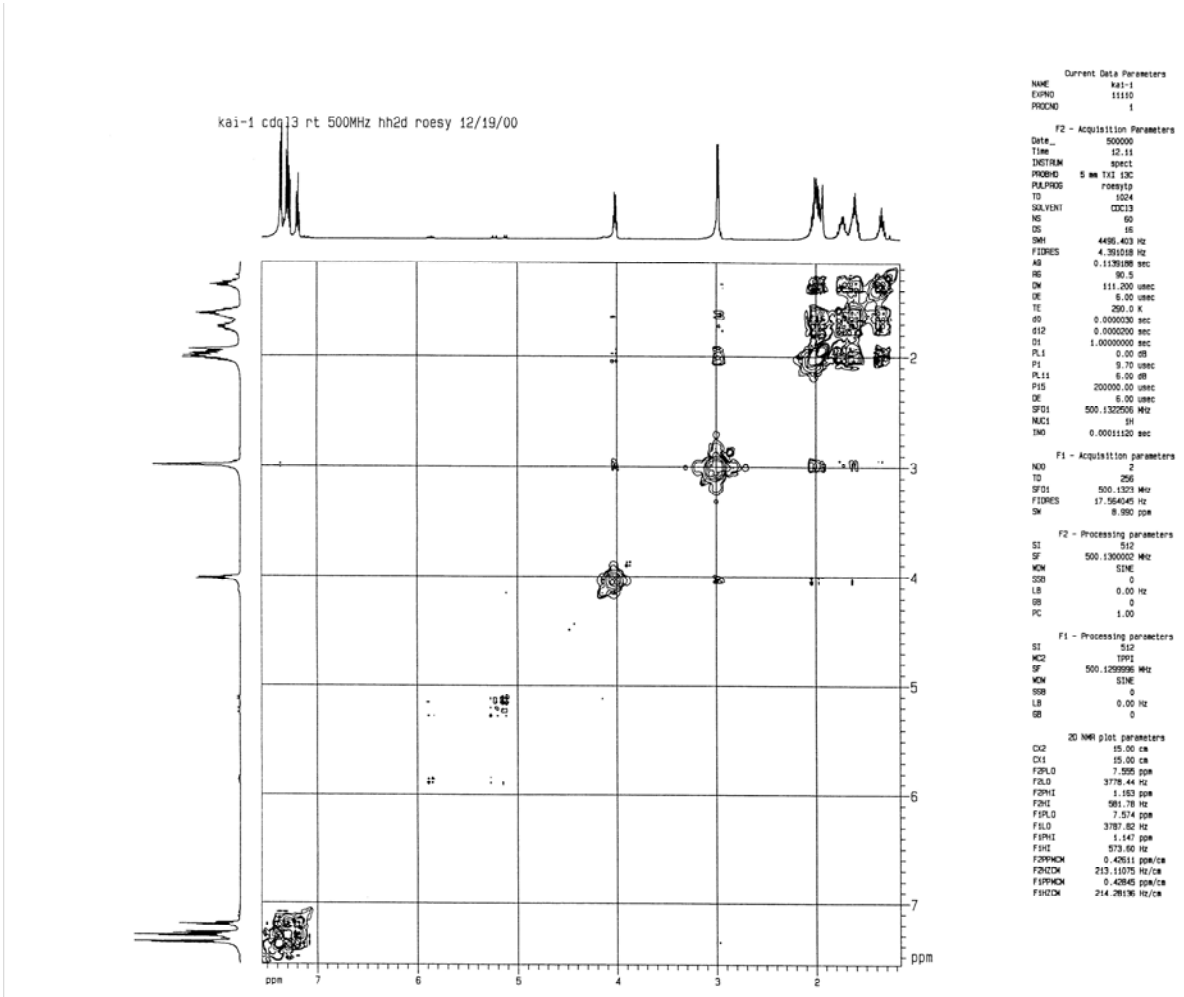
1.112: m.p. 67-68 °C; ^{1}H NMR ($CDCl_3$) δ 2.01-1.88 (m, 3 H), 1.60-1.42 (m, 3 H), 1.25-1.13 (m, 3 H), 1.03 (s, 3 H), 0.91(s, 3 H), 0.84 (d, 3 H, J = 7.6 Hz), 0.81 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 61.4, 59.1, 58.1, 34.5, 26.94, 26.89, 26.2, 21.8, 20.5, 17.3, 9.6; IR ν_{max} (thin film) 3334 (br), 2955, 2872, 1458, 1365, 1098, 978, 938 cm^{-1}; MS m/z (relative intensity) 167 (M^+-CH_3, 20), 149 (55), 113 (10), 97 (13), 83 (18), 71 (36), 57 (100); HRMS: exact mass calcd 167.1436 (M^+-CH_3), found 167.1433. Uncyclized product **1.113**: ^{1}H NMR ($CDCl_3$) δ 5.93 (dd, 1 H, J=17.3, 10.8 Hz), 5.20 (dd, 1 H, J = 17.3, 1.4 Hz), 5.05 (dd, 1 H, J = 10.8, 1.4 Hz), 1.87-1.42 (m, 9 H), 1.25 (s, 3 H), 0.90 (d, 3 H, J = 6.62 Hz), 0.81 (d, 3 H, J = 6.54 Hz); ^{13}C NMR ($CDCl_3$) δ 144.51, 111.89, 75.91, 52.06, 45.94, 31.69, 29.27, 27.65, 26.93, 26.31, 22.62, 17.46.

APPENDIX A

The COSY spetrum of compound 1.80

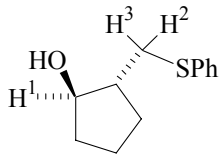


1.80

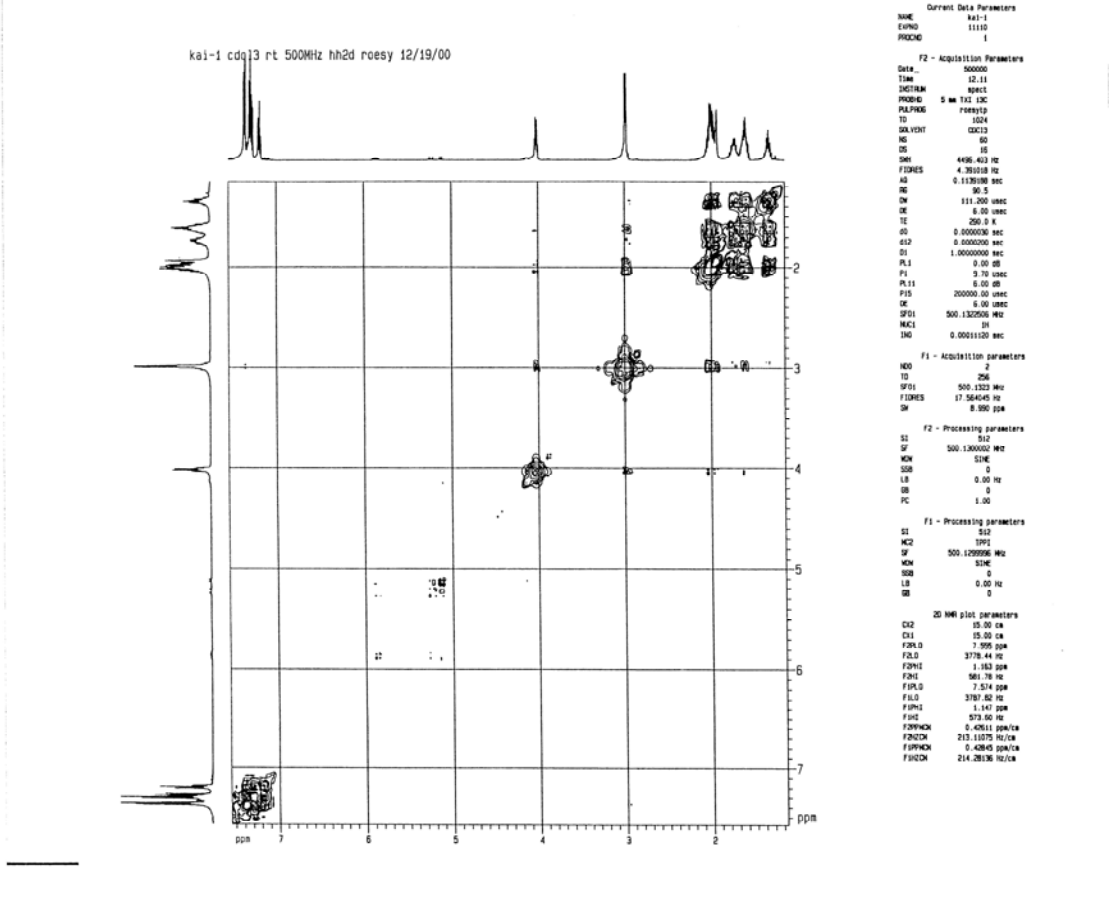


APPENDIX B

The ROSEY spetrum of compound 1.80

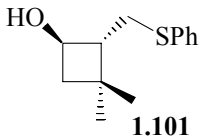


1.80

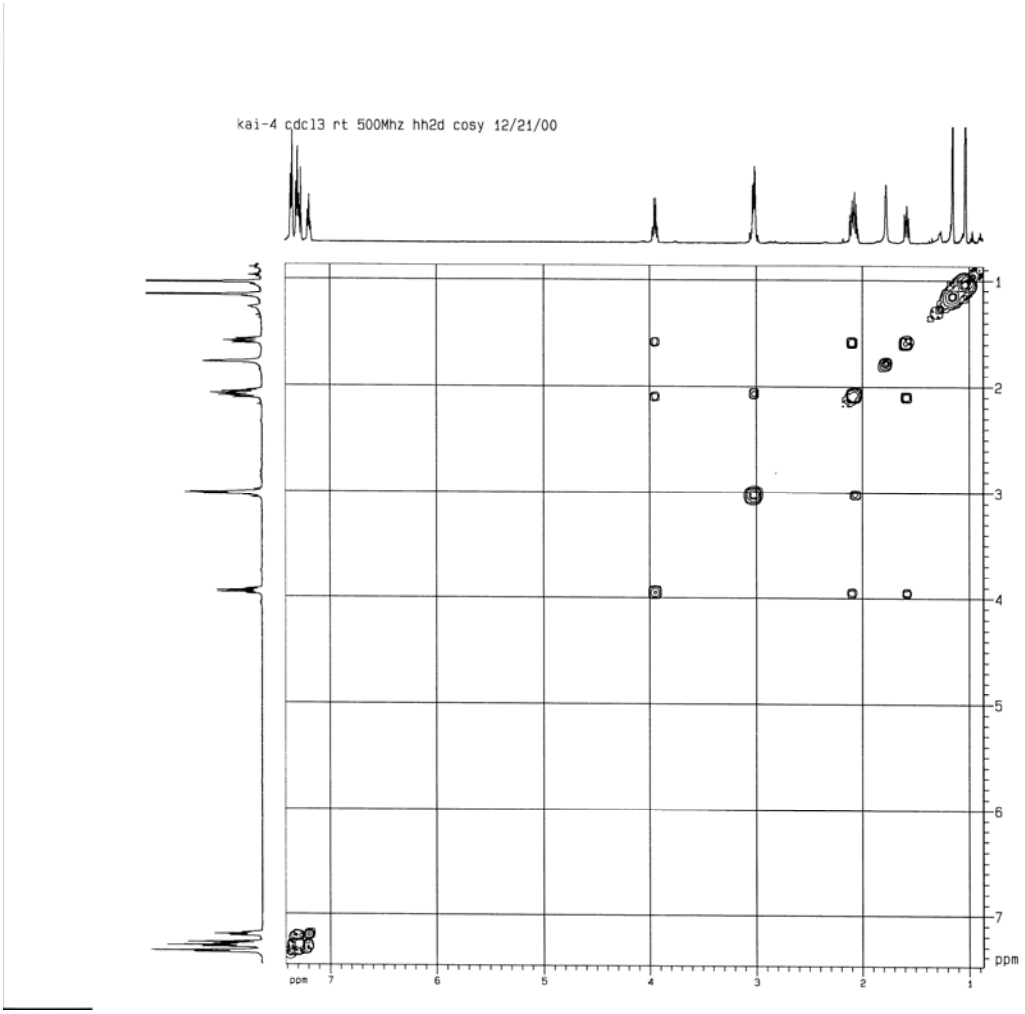


APPENDIX C

The COSY spetrum of compound 1.101



1.101



Current Data Parameters

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EXPNO	11
PROCNO	1

F2 - Acquisition Parameters

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TD	1024
SOLVENT	CDCl3
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DS	16
SWH	4496.403 Hz
FIDRES	4.391018 Hz
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RG	90.5
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DE	6.00 usec
TE	290.0 K
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DE	6.00 usec
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F1 - Acquisition parameters

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FIDRES	39.442066 Hz
SW	8.990 ppm

F2 - Processing parameters

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GB	0
PC	1.00

F1 - Processing parameters

SI	512
MC2	QF
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WDW	SINE
SSB	0
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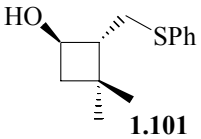
GB	0

2D NMR plot parameters

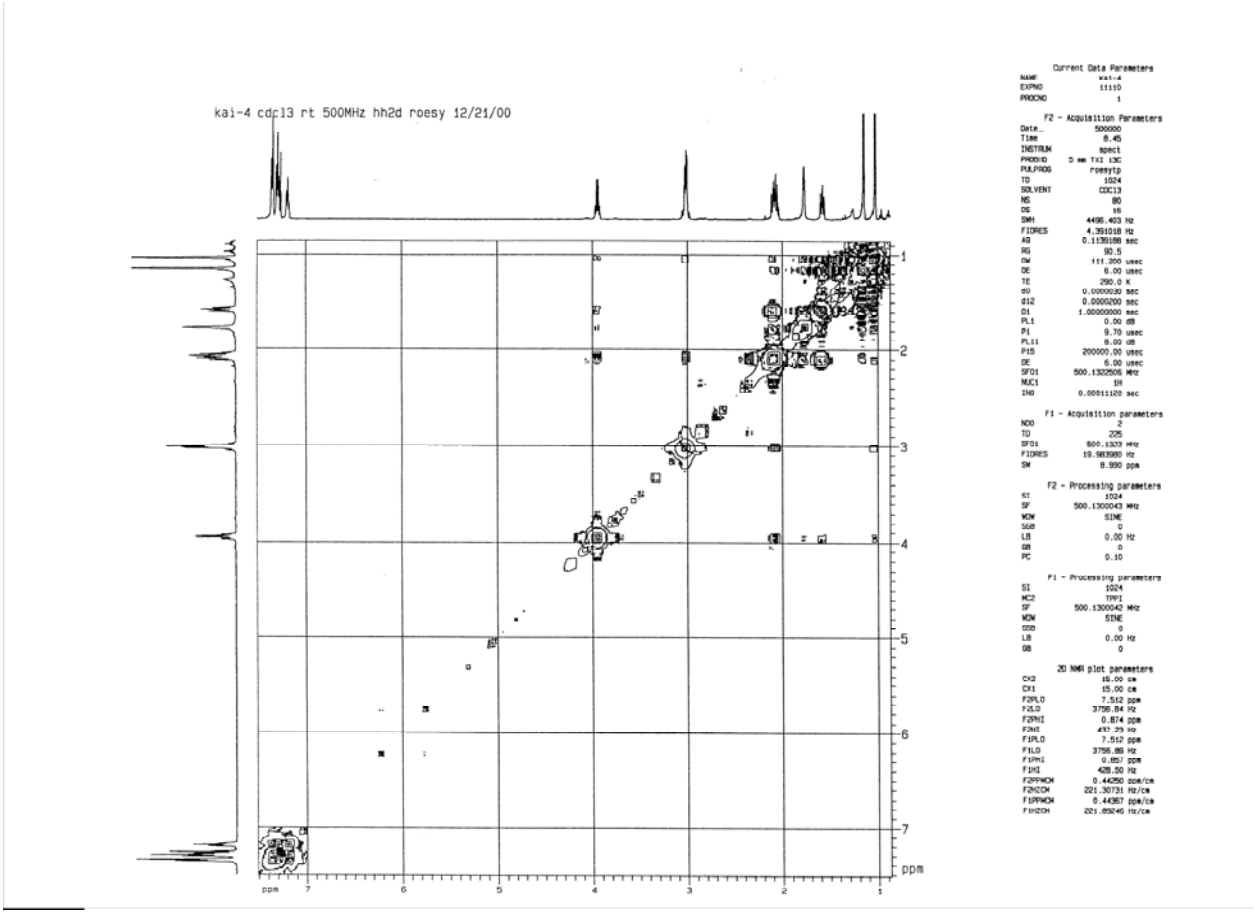
CX2	15.00 cm
CX1	15.00 cm
F2PLO	7.418 ppm
F2LO	3709.78 Hz
F2PHI	0.868 ppm
F2HI	434.08 Hz
F1PLO	7.488 ppm
F1LO	3745.14 Hz
F1PHI	0.868 ppm
F1HI	434.31 Hz
F2PPMCM	0.43665 ppm/cm
F2HZCM	218.37998 Hz/cm
F1PPMCM	0.44133 ppm/cm
F1HZCM	220.72151 Hz/cm

APPENDIX D

The ROSEY spetrum of compound 1.101



1.101



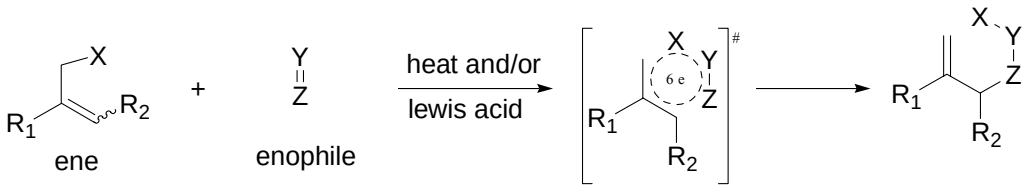
2. Chapter 2

The Use of Allyl Phenyl Sulfones as Precursors for Pd-catalyzed Zn-ene Cyclization and Its Applications to the Total Syntheses of (-)-Erythrodiene, 9,10-*2H*-15-Deoxy-$\Delta^{12,14}$-PGJ_2 and 15-Deoxy-$\Delta^{12,14}$-PGJ_2

2.1. Introduction

2.1.1. Background for the Metallo-ene Reaction

The ene reaction is the addition of a compound with a double bond having an allylic hydrogen (the "ene") to a compound with a multiple bond (the "enophile"). As illustrated in Figure 2.1, the formation of 1:1 adducts by ene and enophile usually involves a cyclic six-electron transition state.[56,57] When X = H, it is the normal ene reaction. A high temperature is usually needed for such a reaction without Lewis acid present, so it is often called the thermal ene reaction. When X = Li, Mg, Zn, B, Al, Pd, Pt or Ni, they are known as metallo-ene reactions. The advantage of metallo-ene reactions is that the reaction conditions are relatively less demanding than the corresponding thermal ene reactions. Moreover, more functionality can be introduced simply by trapping the cyclized organometallics with various electrophiles (for M = Li, Mg, Zn). Since the "ene" may have different substituent patterns and the enophiles can be carbon carbon multiple bonds or carbon heteroatom multiple bond, the various combinations will result in a vast variety of products from ene reactions.



X = H : ene reaction. X = M : metallo-ene reaction

enophile = carbonyl and thiocarbonyl compound, imines, alkenes, alkynes

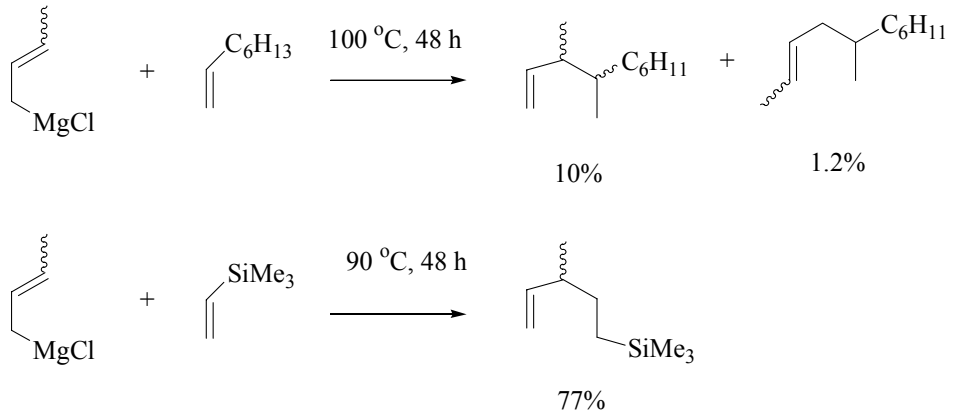
Lewis acid = BF_3•Et_2O , $SnCl_4$, $AlEtCl_2$, $AlMe_2Cl$

Figure 2.1 Ene reactions

2.1.2. Intermolecular Metallo-ene Reactions

2.1.2.1. Magnesium-ene Reactions

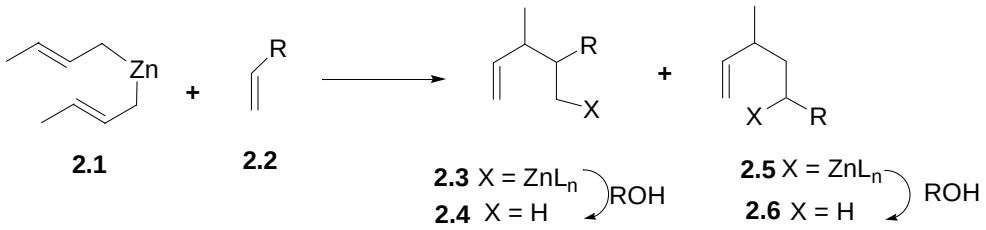
As illustrated in Scheme 2.1, the addition of allylmagnesium chloride to the non-strained alkene, 1-octene, is inefficient. The products are obtained with low yield and poor regio- and diastereoselectivity.[58] Only the addition of allylmagnesium chloride to a TMS substituted olefin gave synthetically useful regioselectivity and yield.



Scheme 2.1 Intermolecular addition of allylmagnesium chloride to olefins

2.1.2.2. Zn-ene Reactions

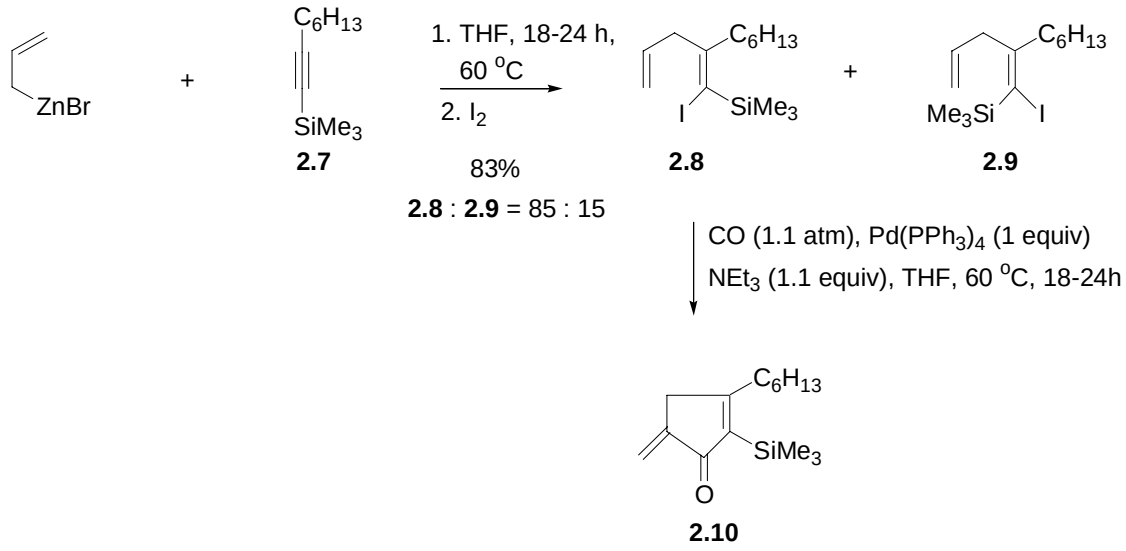
Preformed dicrotylzinc **2.1** underwent Zn-ene reactions with terminal alkenes under very mild conditions (20–50 °C) to give, after protonolysis, the alkene **2.4** (Scheme 2.2).[59] For simple unconjugated alkenes, the reactions are clean and almost pure regioisomers are obtained with good yields (entry 1 and 2). However, the reaction has poor regioselectivity for conjugated olefins like butadiene and styrene (entry 3 and 4). In general, the diastereoselectivity for **2.4** is low for all cases.



Entry	*R*	*temperature and time*	*yield* **2.4 + 2.6**	*ratio* **2.4/2.6**	*Diastereomer ratio of* **2.4**
1	H	20 °C, 20 h	100	99.9:0.1	
2	C_6H_{13}	50 °C, 20 h	85	100:0	35:65
3	Ph	20 °C, 66 h	42	33:67	75:25
4	$CH=CH_2$	20 °C, 43 h	81	42:58	52:48

Scheme 2.2 Intermolecular Zn-ene

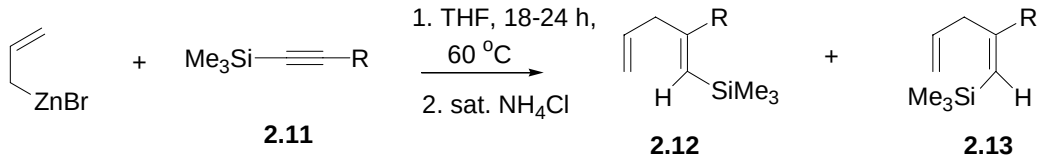
As shown in Scheme 2.3, the trimethylsilyl group completely controls the regioselectivity of the intermolecular addition of an allylzinc bromide to silylated alkyne **2.7** and the 1, 1-dimetalloalkene intermediate can be iodinated to afford compounds **2.8** and **2.9**, respectively, with a ratio of 85:15.[60] Vinyl iodide **2.8** can further undergo Pd-catalyzed carbon monoxide insertion to afford α,β-unsaturated cyclopentenone **2.10**.

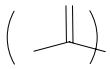
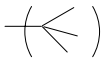


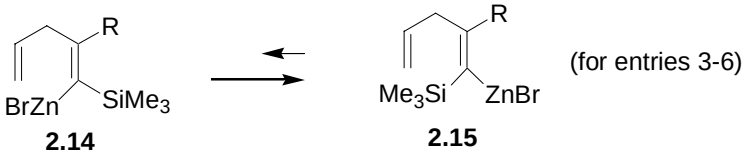
Scheme 2.3 Novel synthesis of α,β-unsaturated cyclopentenone via allylzincation of an alkyne

Molander also studied the allylzincation of 1-trimethylsilyl-1-alkynes (Scheme 2.4).[61] Again, the reactions were found to be completely regiospecific in all cases, placing the zinc on the carbon bearing the silicon. The most important observation about these reactions is that the stereochemistry of the products is highly dependent on the structure of the alkynes **2.11**. For simple alkyl substituted alkynes (entry 1 and 2), vinylsilane **2.12** is the major product obtained from *syn*-addition of allylzinc bromide to the alkyne followed by protonolysis. However, when phenyl substituted alkyne (entry 3), 3-benzyloxy and 3-trimethyloxy substituted alkynes (entries 4 and 5, respectively) and an enyne (entry 6) were used as the enophiles, almost complete *trans* carbometalations were observed. It was postulated by Molander that the initially formed *cis* alkenylzincs **2.14** isomerize to give the more stable *trans* ones **2.15** under the experimental conditions for entries 3-6. Considering the possible interaction after the isomerization between the zinc and the π electrons of phenyl group (entry 3), lone pairs of the oxygen in the BnO or TMSO group (entries 4 and 5, respectively), π electrons of alkene (entry 6), vinylsilanes **2.15**

could be more stable than **2.14**. Therefore, the reactions are most likely under thermodynamic control.

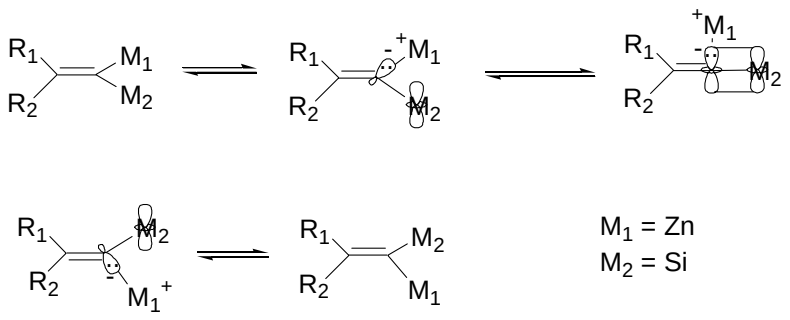


Entry	R	Yield (**2.12 + 2.13**)	Ratio of **2.12 / 2.13**
1	C_4H_9	85	85 : 15
2	$CH_2CH_2CH_2Cl$	88	81 : 19
3	Ph	78	5 : 95
4	$CH(OBn)CH_2CH_2CH_3$	74	5 : 95
5	$CH(OTMS)CH_2CH_2CH_3$	52	5 : 95
6		57	5 : 95
7		0	



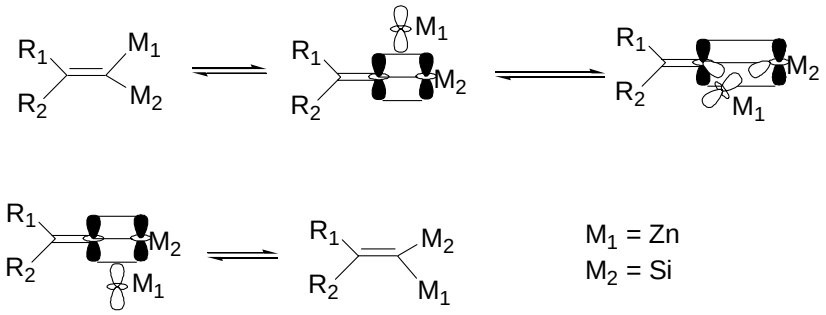
Scheme 2.4 Intermolecular addition of allylzinc bromide to 1-(trimethylsilyl)-1-alkynes 2.11

Negishi has discussed several mechanisms for the isomerization of 1-trimethylsilyl-1-alkenylzinc.[62] Of the seven mechanisms considered, the two most plausible mechanisms are shown below. The first one involves a synergistic or "push-pull" interaction between the Zn-C σ bond and an empty orbital of silicon (Scheme 2.5).



Scheme 2.5 "Push-pull" mechanism for the isomerization

The second mechanism (Scheme 2.6) does not involve the alkene π electrons, nor does it require the ionization of the C-Zn bond. Instead, the isomerization depends on the ability of an empty orbital of silicon to participate in three-center two-electron bonding.

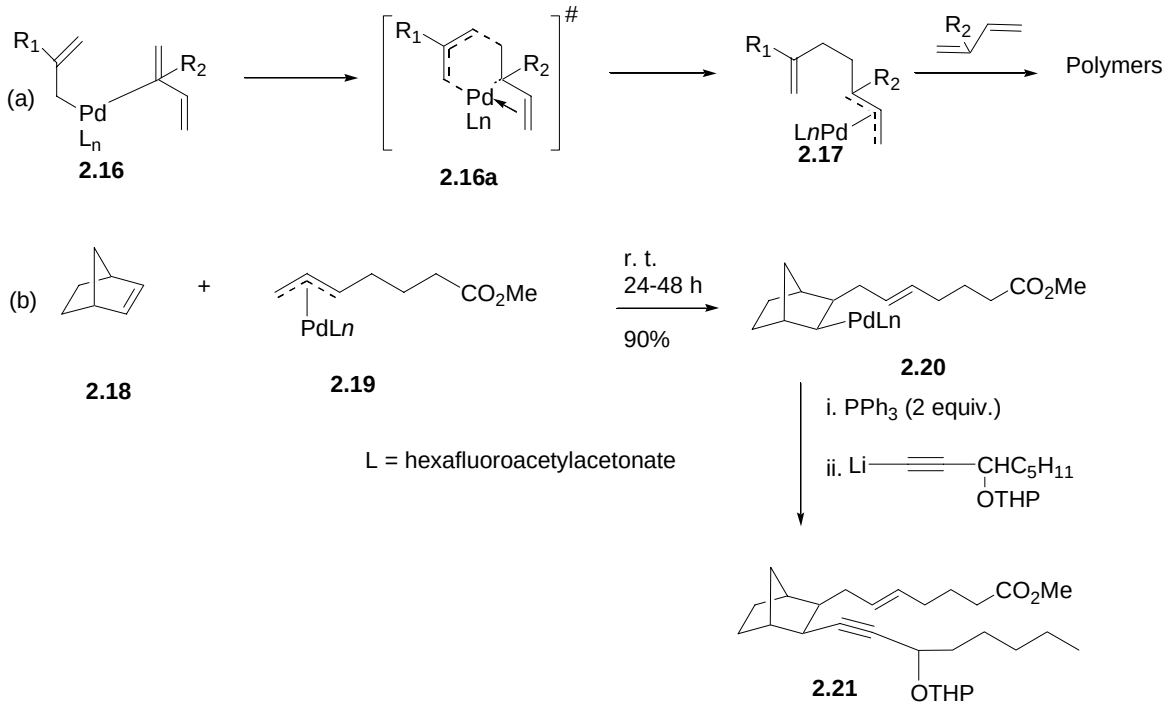


Scheme 2.6 Three-center two-electron bonding for the isomerization

2.1.2.3. Pd-ene Reactions

A well known Pd-ene reaction is the polymerization of butadiene (Scheme 2.7, reaction **a**). Allylic complexes **2.16** undergo the palladium-ene reactions via transition states **2.16a** to afford allylpalladium products **2.17**.[63] Further diene insertions result in polymer formation.

When nonconjugated alkenes are used as the enophiles, synthetically useful reactions can be developed. For example, the prostaglandin endoperoxide analogue **2.21** was synthesized efficiently by coupling σ-Pd product **2.20** with lithium acetylide (reaction **b**).[64] **2.20** itself was produced by a regio- and stereo-selective addition of allylpalladium **2.19** to bicyclo [2.2.1] hept-2-ene **2.18**.



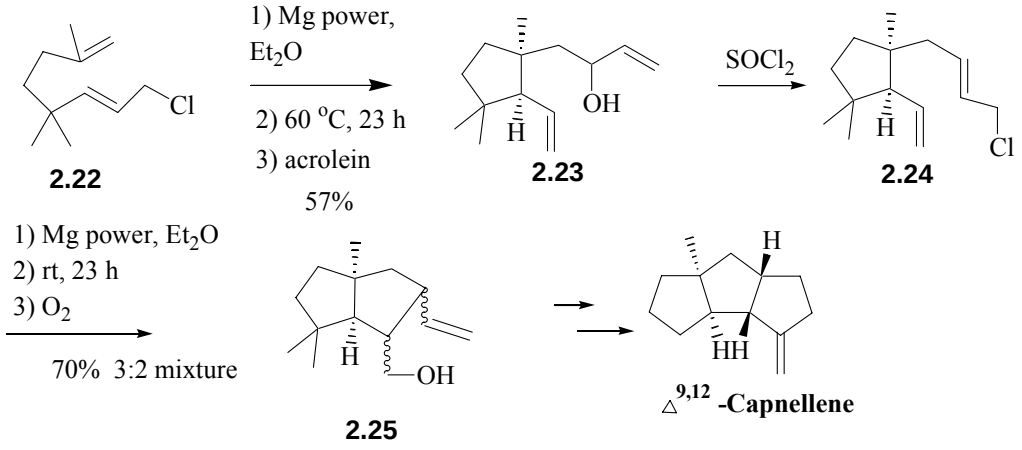
Scheme 2.7 Pd-ene reactions

2.1.3. Intramolecular Metallo-ene Reactions

In contrast to intermolecular metallo-ene reactions, the intramolecular versions are entropically favored and should be more regio- and stereo-selective due to the rigid transition state for the ring formation.

2.1.3.1. Intramolecular Mg-ene Reactions

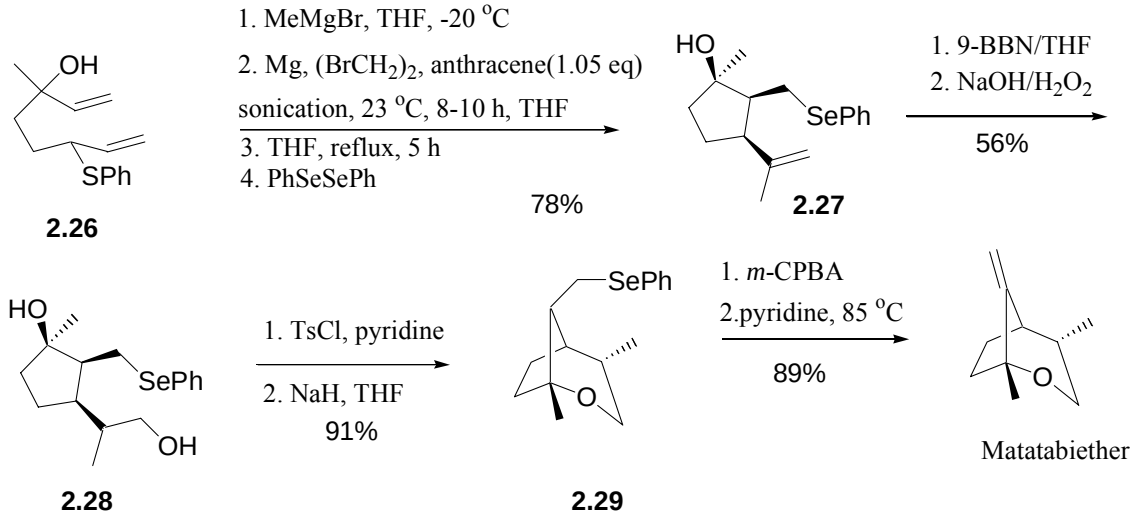
Intramolecular Mg-ene reactions are well known for the syntheses of 5-membered rings in a stereoselective fashion due to the work of many chemists, especially Oppolzer.[56,57] Scheme 2.8 shows the total synthesis of $\Delta^{9,12}$-capnellene[65] by using two Mg-ene cyclizations as the key steps to construct two cyclopentane rings stereoselectively. Treatment of allylic chloride **2.22** with Mg powder afforded the corresponding allylmagnesium chloride which underwent intramolecular Mg-ene cyclization to provide a cyclopentane ring with high stereoselectivity. After the resulting primary alkylmagnesium was quenched with acrolein, compound **2.23,** was obtained. Treating allylic alcohol **2.23** with $SOCl_2$ provided the corresponding allylic chloride **2.24**. The second Mg-ene cyclization gave, after trapping the cyclized organomagnesium by O_2, alcohol **2.25** which was further elaborated to synthesize $\Delta^{9,12}$-capnellene.



Scheme 2.8 Total synthesis of $\Delta^{9,12}$-capnellene

Many other superb total syntheses of natural products have been achieved by using this methodology. For examples, the syntheses of (±)-6-protoilludene,[66] sinularene,[67] 12-acetoxysinularene,[68] (+)-α-skytanthine,[69] all involve highly diastereoselective Mg-ene cyclizations as key steps.

Recently, Cohen and co-workers developed a novel method to perform the Mg-ene cyclization by using allyl phenyl sulfides as precursors of the allylmagnesium species. As illustrated in Scheme 2.9, compound **2.26** was first treated with MeMgBr to remove the proton on the allylic alcohol followed by the reductive allyl magnesiation using the magnesium-anthracene complex. The Mg-ene cyclization proceeded smoothly. After quenching the reaction with PhSeSePh, compound **2.27** was obtained with high stereoselectivity. Further elaboration completed the most efficient synthesis of matatabiether to date.



Scheme 2.9 Synthesis of metatabiether using the Mg-ene cyclization as the key step

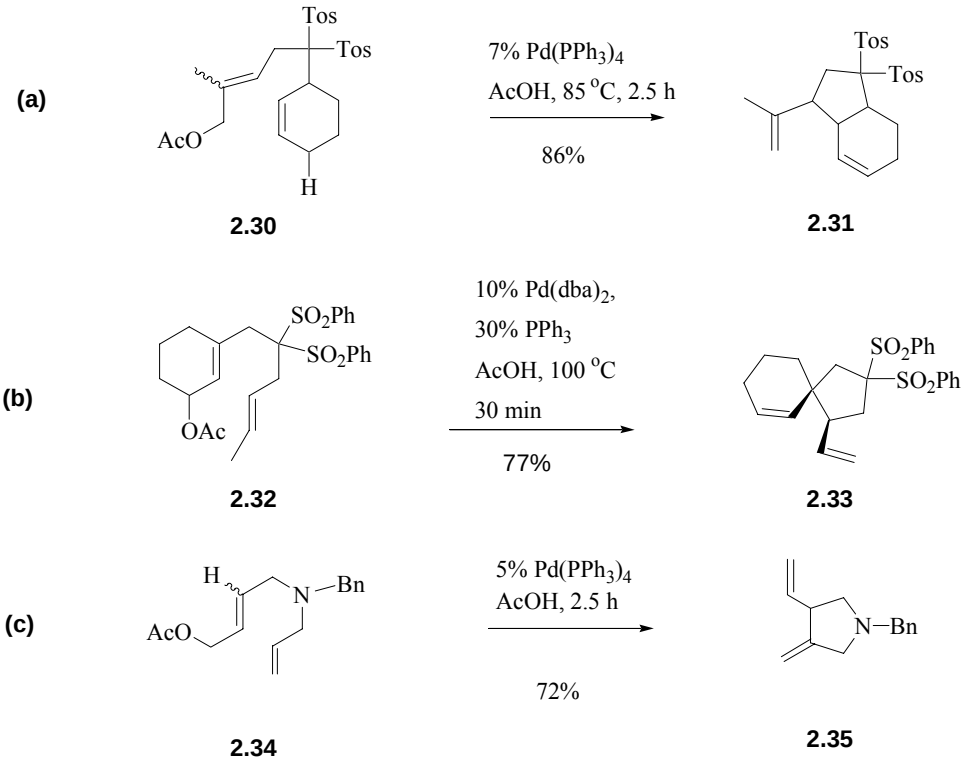
Allyl phenylsulfides will probably prove to be superior to allyl halides as precursors of allylmagnesium species due to their ease of assembly, particularly in a connective fashion and also because allyl phenyl sulfides, unlike allyl halides, give no coupling product upon treatment with magnesium.

One major limitation of the intramolecular Mg-ene reaction is that olefinic enophiles can only be terminally unsubstituted or strained olefins. Another limitation is that attempts to apply these cyclizations to the preparation of pyrrolidines have so far failed.

2.1.3.2. Intramolecular Pd-ene Reaction

Some of the limitations of the Mg-ene cyclization can be overcome by the Pd-ene cyclization. Intramolecular Pd-ene reactions have been proven to constitute an excellent method for the construction of ring systems. As shown in Scheme 2.10, allyl acetates **2.30**, **2.32**, **2.34** were treated with Pd (0) species in AcOH. The required temperature is usually high (close to the boiling point of AcOH, 116 °C). Under these conditions, Pd (0) can insert into the allylic acetates to generate π-allylpalladium complexes which can undergo ene reactions efficiently to provide useful ring systems. For example, a bicyclo[4.3.0] molecule **2.31**[70] and a spirobicyclo[4.4.0] compound **2.33**[71] were synthesized in good yield in reactions **a** and **b**, respectively. Even pyrrolidine derivative **2.35**, which couldn't be obtained from Mg-ene cyclization, can be synthesized successfully by this methodology (reaction **c**).[72] Another advantage of the Pd-ene reaction is that the mild conditions allow better functional group tolerance than the corresponding Mg-ene cyclization. Moreover, since only a catalytic amount of Pd (0) is used, it is a very efficient transformation. However, the drawback of this method is

that no organometallic intermediates are generated. Thus, the reaction cannot be quenched by electrophiles to add more functionality to the cyclization products.

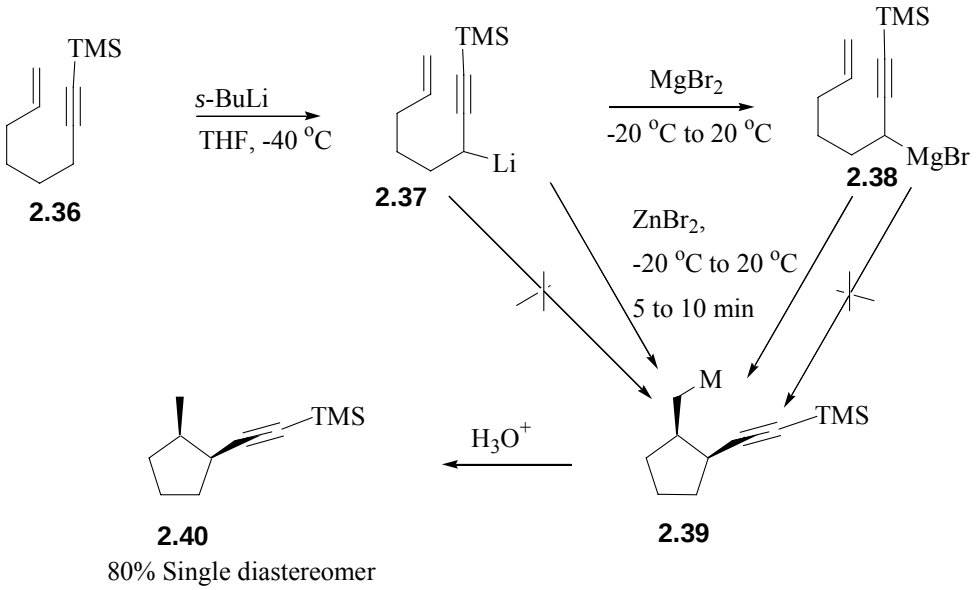


Scheme 2.10 Intramolecular Pd-ene reactions

2.1.3.3. Intramolecular Zn-ene Reactions

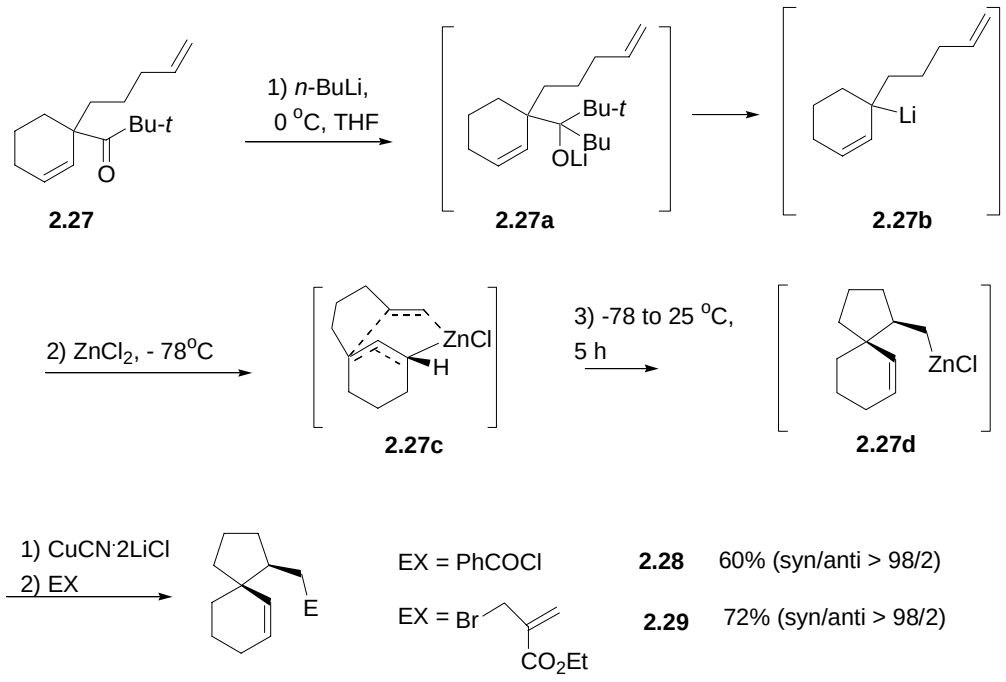
Due to the mild nature of organozinc species, intramolecular Zn-ene cyclizations have the potential to embrace both the features of intramolecular Mg-ene cyclizations (high stereochemical control over the cyclization and the possibility of trapping the cyclized intermediates with various electrophiles) and those of intramolecular Pd-ene cyclization (compatibility with various functionalities), but without the elimination of metal hydride.

However, the intramolecular Zn-ene reaction has not been widely used in organic synthesis probably due to the tedious preparation method needed for the generation of allylzincs. Traditionally, allylzincs are obtained by the transmetallation method by treating allyllithium or allylmagnesium reagents with $ZnCl_2$ or $ZnBr_2$. As illustrated in Scheme 2.11,[73] a propargyllithium **2.37**, produced by treating alkyne **2.36** with *s*-BuLi, does not undergo the lithium-ene cyclization under the reaction conditions. The corresponding propargyl magnesium reagent **2.38**, prepared by transmetallation from **2.37**, does not undergo the Mg-ene cyclization either. However, after the generation of the propargylzinc by treating either **2.37** or **2.38** with $ZnBr_2$ at – 20 °C, the Zn-ene cyclization proceeded smoothly to afford the cyclized intermediate **2.39,** which delivered compound **2.40** with excellent stereoselectivity after protonolysis.



Scheme 2.11 Zn-ene cyclizations by transmetallation from a propargyllithium and a propagylmagnesium

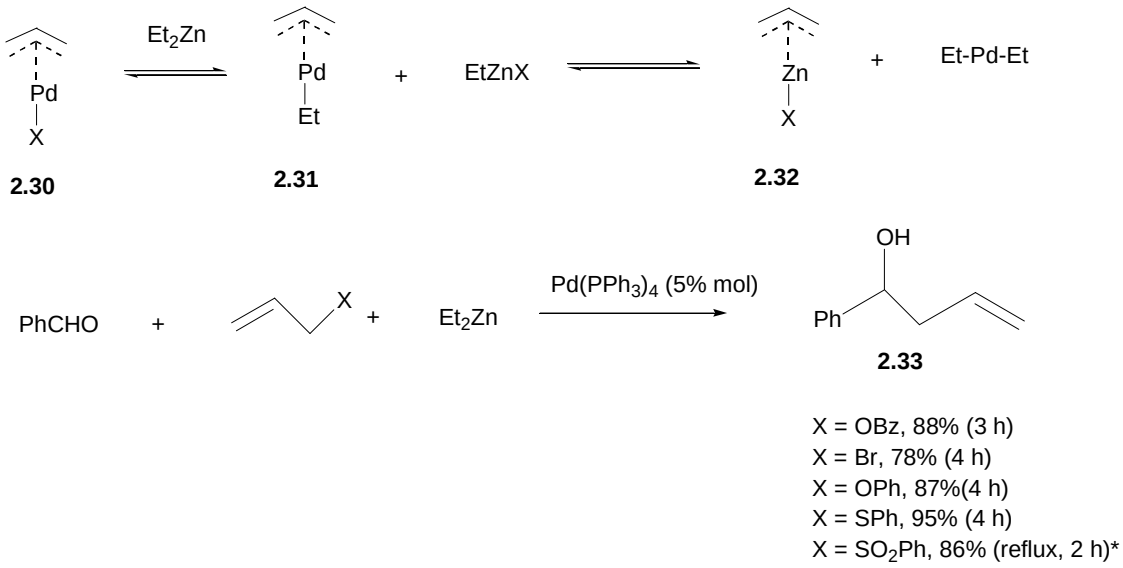
Knochel's group has reported an interesting Zn-ene cyclization to construct spirobicyclic molecules (Scheme 2.12).[74] A tertiary homoallylic alcohol **2.27a**, generated by treating ketone **2.27** with *n*-BuLi, fragments immediately to afford the corresponding allyllithium **2.27b**. An allylzinc **2.27c**, produced by the addition of $ZnCl_2$ to the corresponding allyllithium precursor, cyclized efficiently at room temperature to furnish a spirobicyclic intermediate **2.27d** in a highly stereoselective fashion. The alkylzinc **2.27d** undergoes transmetallation with CuCN•2LiCl to afford the corresponding cuprate which could be quenched either by benzoyl chloride to afford **2.28** or by 2-bromomethyl-acrylic acid ethyl ester to afford **2.29**.



Scheme 2.12 Zn-ene cyclization by the generation of an allylzinc from an allyllithium

Due to the highly reactive nature of allyllithium and allylmagnesium intermediates, it is not surprising to see that this transmetallation method has poor functional group tolerance. In

1994, Oppolzer developed an excellent Pd-catalyzed Zn-ene method to overcome this limitation.[75] Palladium-catalyzed intermolecular allylation of carbonyl compounds via umpolung of π-allylpalladium by diethylzinc is known.[76] The nature of π-allylpalladium species is electrophilic. As illustrated in Scheme 2.13, by treating π-allylpalladium **2.30** with diethylzinc, a transmetallation reaction occurs which affords a nucleophilic allylzinc species **2.32**. A wide variety of leaving groups (OBz, Br, OPh, SPh, SO_2Ph[77]) can be used to undergo this kind of umpolung reaction to afford allylzincs that can attack an aldehyde efficiently to give a homoallylic alcohol under mild reaction conditions with excellent yield.

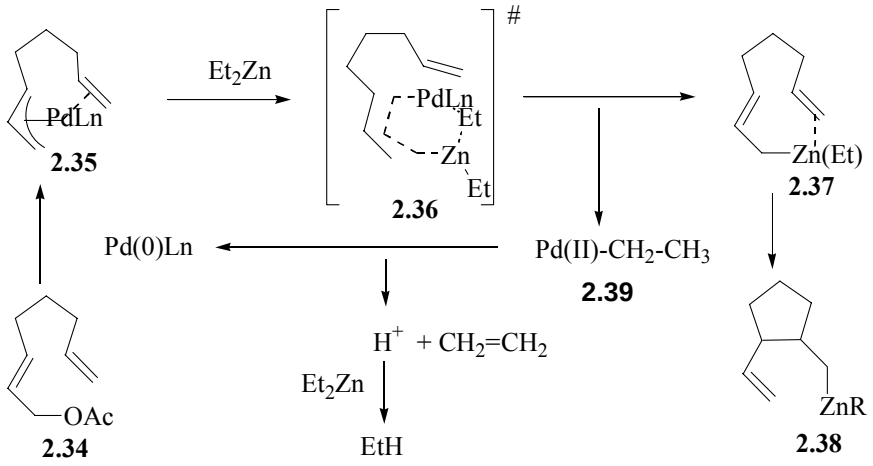


* When the leaving group is phenyl sulfone, the work was done by Julia. [77]

Scheme 2.13 Mechanism of the umpolung reaction to produce allylzincs and allylations of benzylaldehyde by using various allylic substrates

Oppolzer used this umpolung method to generate allylzincs from allyl acetates as the substrates and intramolecular Zn-ene reactions were studied. As shown in Scheme 2.14, the

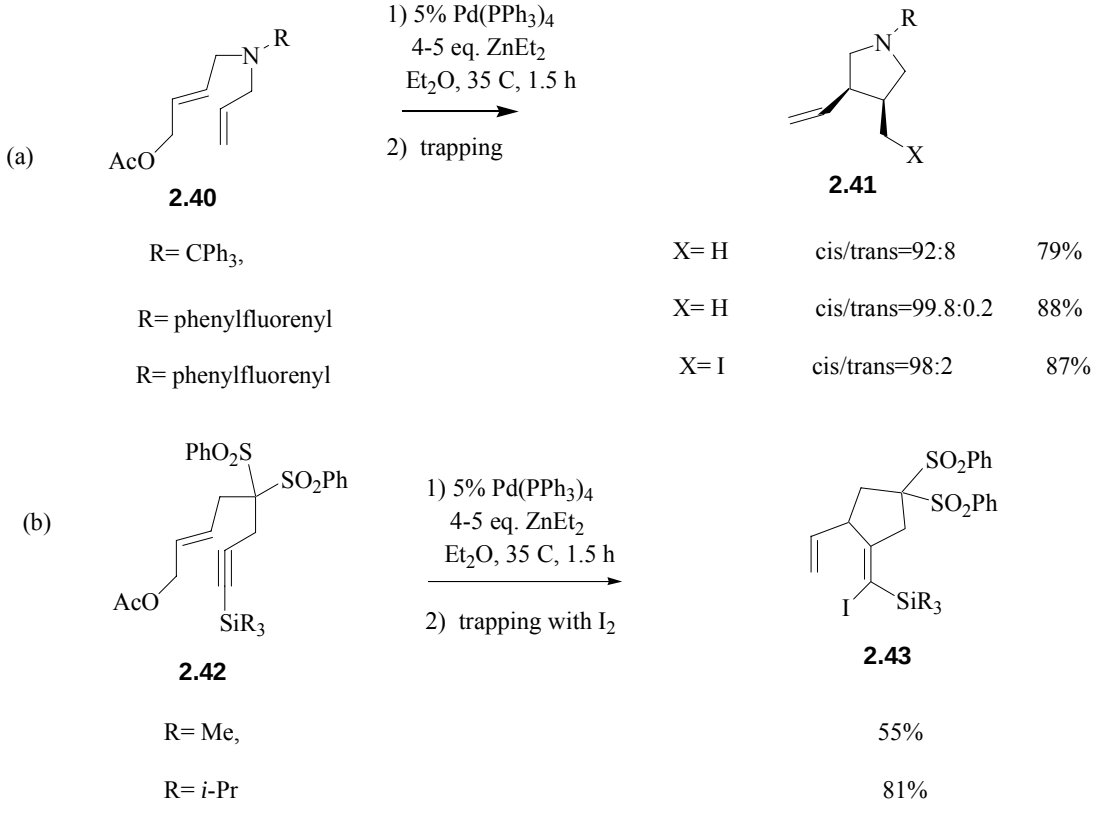
mechanism of this reaction is thought to involve Pd(0) insersion into allyl acetate **2.34** to generate π-allylpalladium intermediate **2.35** that can undergo transmetallation with diethylzinc through transition state **2.36** to give the corresponding allylzinc intermediate **2.37** together with ethylpalladium species **2.39**. The allylzinc **2.37** can attack the carbon carbon multiple bond efficiently to give cyclized organozinc **2.38** which can be trapped by electrophiles to give functionalized products. Ethylpalladium **2.39** can undergo β-hydride elimination to release ethylene and to regenerate Pd(0) which can participate in the catalytic cycle again. Since the release of ethylene is the key to drive the reaction in the forward direction, the use of Me_2Zn instead of Et_2Zn causes no reaction because the methyl group has no β-hydride available to eliminate.



Scheme 2.14 Mechanism of palladium-catalyzed intramolecular zinc-ene reactions

By utilizing this method, 2,3-di-substituted pyrrolidine derivatives, which could not be prepared by the Mg-ene cyclization (probably due to the facile elimination of allyl amines from

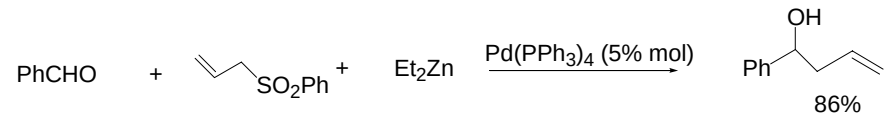
the allyl magnesium intermediate before the cyclization), have been synthesized with excellent diastereoselectivity by intramolecular addition of an allylzinc to an olefin (Scheme 2.15, reaction **a**). Intramolecular addition of an allylzinc to an alkyne in a *cis* fashion is shown in reaction **b** and compound **2.43** is obtained as a single diastereomer.



Scheme 2.15 Synthesis of pyrrolidine derivatives from intramolecular addition of allylzincs to alkens and alkynes

We envisioned that instead of using allyl acetates as the precursors for Pd-catalyzed Zn-ene cyclization, using allyl phenyl sulfones could greatly increase the efficiency of substrates preparation. Allyl phenyl sulfones are readily available. Due to the α-acidity of allyl phenyl

sulfones, many precursors for Pd-catalyzed Zn-ene reactions can be constructed in a connective manner, leading to enormous versatility. Allyl phenyl sulfones can also be prepared by simple oxidation of allyl phenyl sulfides, which are known to be readily available. Julia has used allyl phenyl sulfones as precursors of allylzincs which are capable of undergoing intermolecular addition to aldehydes (Table 2.1). By heating a mixture of an allyl phenyl sulfone, 5% Pd (0), 2 equivalents of Et_2Zn and PhCHO at reflux in THF, the allylzinc was produced *in situ* and attacked benzylaldehyde to afford the corresponding homoallylic alcohol in good yield. As shown in Table 2.1, in most cases, allyl phenylsulfones work well. Unsymmetrical allylic phenylsulfones (entry 3 and 4) react with complete regioselectivity at their more-substituted terminus in accordance with the expected behavior of allylzinc species. The reactions become slow when allyl phenylsulfones have γ substitution (entry 4) and the reaction is completely shut down when γ, γ-disubstituted allyl phenylsulfone is being used (entry 5). However, it should be noted that the products expected in the latter case was the same as those formed from the allylically isomeric analogue in entry 3.



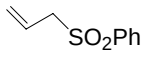
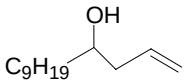
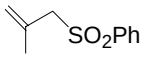
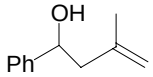
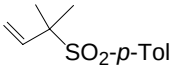
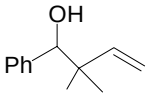
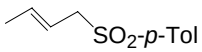
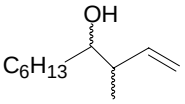
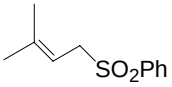
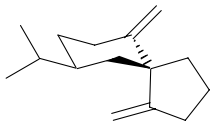
Entry	sulfone	aldehyde or ketone	product	yield
1		*n*-$C_9H_{19}CHO$		97%
2		PhCHO		88%
3		PhCHO		86%
4		*n*-$C_6H_{13}CHO$		76%
5		PhCHO	no reaction	

Table 2.1 Allyl phenyl sulfones as precursors for Pd-catalyzed allylzincation

Even though the use of allyl phenyl sulfones as precursors for Pd-catalyzed allylzinc formation and studies about the intermolecular addition of the resulting allylzinc to aldehydes have been performed, no studies of intramolecular addition of such allylzincs to carbon carbon multiple bonds have been reported. We envisioned that the use of allyl phenyl sulfones as precursors for Pd-catalyzed Zn-ene cyclization could provide an excellent alternative to traditional allyl acetates due to the ease of preparing allyl phenylsulfones, particularly in a connective fashion. The efficiency of substrate preparation will be demonstrated by the syntheses of some natural products.

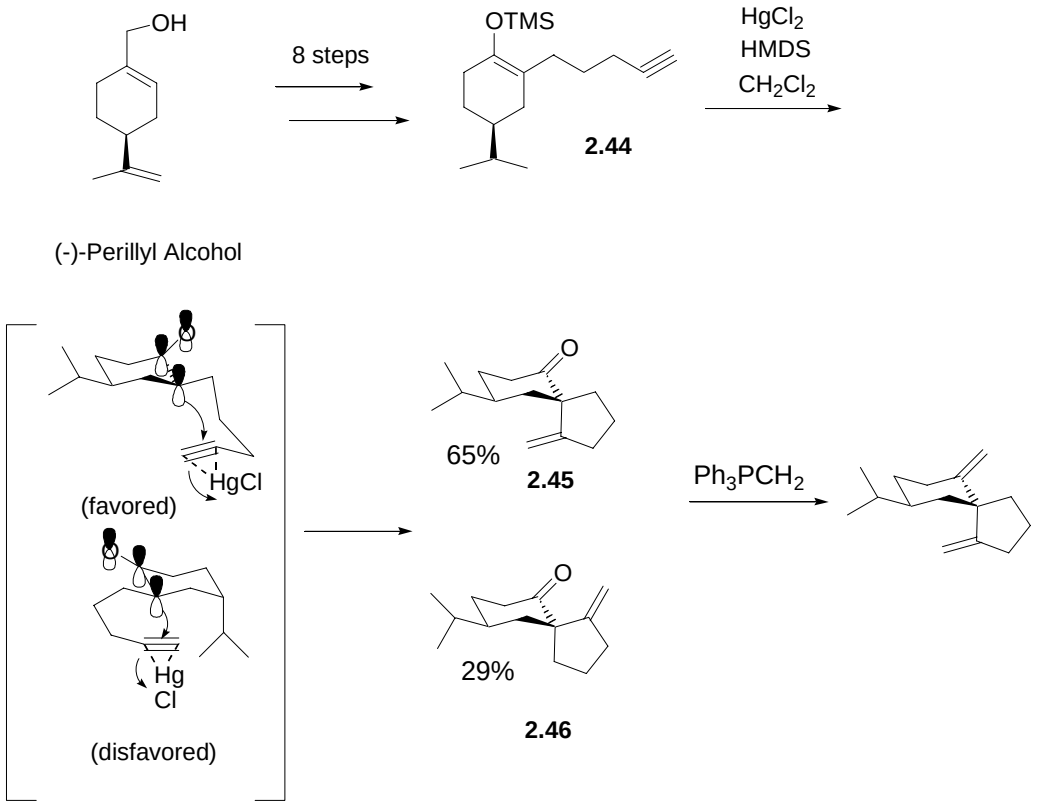
2.1.4. Background for the Total Synthesis of (-)-Erythrodiene



(-) - Erythrodiene

(-)-Erythrodiene is a sesquiterpene isolated from the Caribbean gorgonian coral erythropodium caribaeorum.[78] The rare spirobicylo[4.5]decane skeleton of erythrodiene has attracted considerable synthetic effort over the past decade and two total syntheses of this molecule have been reported to date.

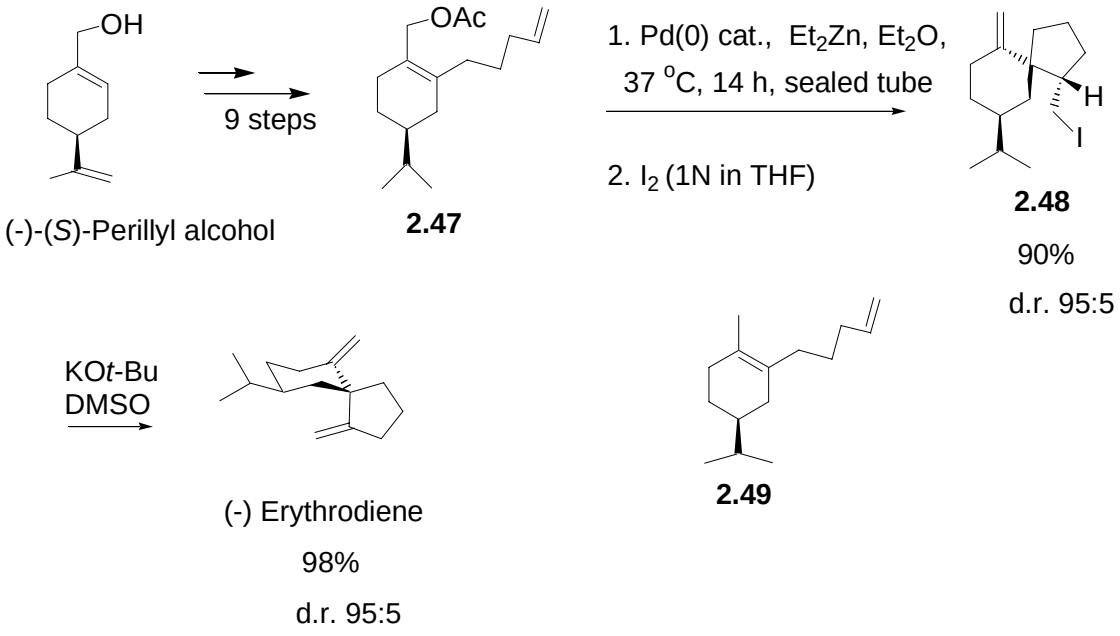
The first synthesis came from Forsyth's group.[79] As illustrated in Scheme 2.16, an intramolecular alkyne carbomercuration reaction was used as the key step to construct the spiro carbon center of the natural product. Silyl enol ether **2.44**, the key substrate for the cyclization study, was prepared from commercially available (*s*)-perillyl alcohol in 8 steps. Treating trimethylsilyl enol ether **2.44** with mercuric chloride afforded a transient α-keto mercurial intermediate, which added to the tethered alkyne in an *anti* fashion. The *anti* addition of the carbon-mercury bond to a triple bond was proven by deuteration studies. After demercuration, two cyclized compounds, **2.45** and **2.46**, were isolated with moderate selectivity of 7:3. The major product **2.45** undergoes Wittig olefination to afford the desired natural product. In total, ten steps were used with an overall yield of 35%. Therefore, it is a reasonably efficient synthesis.



Scheme 2.16 Forsyth's synthesis of (-)-erythrodiene

A highly diastereoselective synthesis of (-)-erythrodiene was accomplished by Oppolzer's group[80] via an intramolecular Pd-catalyzed Zn-ene reaction as the key step (Scheme 2.17). Allyl acetate **2.47** was obtained in 9 steps from (*s*)-perillyl alcohol. After **2.47** had been treated with 5% of Pd $(PPh_3)_4$ and 10 equiv. of Et_2Zn in Et_2O at 37 °C for 14 h, the desired cyclized product **2.48** was obtained in 51% yield (entry 1, table 2.2). About 10-15% of starting material **2.47** was recovered, together with 15% of reduced by-product **2.49**. A better yield of 72% was obtained by using $Pd(OAc)_2$ and 1 equiv. of $P(Bu)_3$ as the *in situ* Pd(0) source[81] together with the use of 10 equiv of Et_2Zn (entry 3). Increasing the amount of Et_2Zn to 20 equiv. successfully suppressed the undesired reduction pathway and compound **2.48** was obtained in

90% yield with excellent diastereoselectivity of 95:5. Dehydroiodination with KO*t*-Bu afforded the natural product in quantitative yield and unchanged diastereoselectivity of 95:5. Thus, the stereochemistry of the two diastereomers of **2.48** only differs in the spiro carbon center. A large excess of Et_2Zn (20 equiv) is necessary to accomplish a high yield reaction. Therefore, although it paved the way for our synthesis, it is not a very economical transformation.



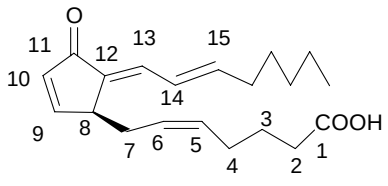
Scheme 2.17 Oppolzer's synthesis of (-)-erythrodiene using Pd-catalyzed Zn-ene cyclization as the key step

Entry	Catalyst	Et_2Zn (equiv.)	2.47 (%)	2.49 (%)	2.48(%)
1	5% $Pd(PPh_3)_4$	10	10 - 15	15	51
2	5% $Pd_2(dba)_2$, 4 equiv. $P(fur)_3$	10	0	(61)	(26)
3	5% $Pd(OAc)_2$, 4 equiv. $P(fur)_3$	10	0	(3)	72
4	5% $Pd(OAc)_2$, 1 equiv. $P(Bu)_3$	20	0	0	90

(yield in parentheses are GC yields)

Table 2.2 Cyclization studies of allyl acetate 2.47: conditions and yields

2.1.5. Background for the Total Synthesis of 15-Deoxy-$\Delta^{12,14}$-PGJ_2



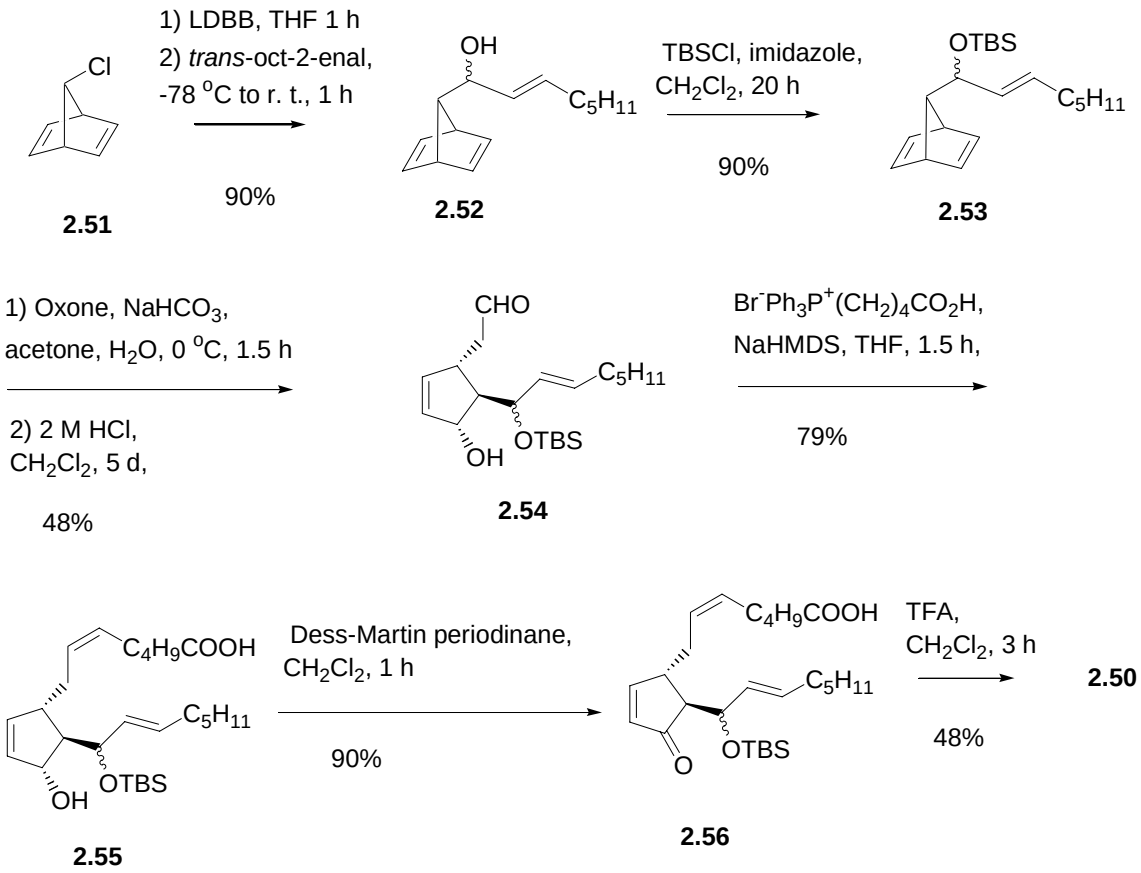
2.50

15-deoxy- $\triangle^{12,14}$-PGJ_2

15-Deoxy-$\Delta^{12,14}$-PGJ_2 (15-d-PGJ_2) is one of the ultimate dehydration products of PGD_2.[82] PGD_2 is formed from PGH_2 which itself is synthesized from arachidonic acid by the enzyme prostaglandin synthetase. In aqueous solution, PGD_2 forms PGJ_2. It has been shown that 15d-PGJ_2 is the agonist of the peroxisome proliferator activated receptor (PPAR)-gamma. The high-affinity binding of 15d-PGJ_2 to PPARγ is believed to be responsible for the repressive effect on gene expression.[83] Moreover, 15-d-PGJ_2 is a potent anti-inflammatory agent that prevents cytokine- and endotoxin-stimulated activation of peripheral and resident tissue macrophages and cytokine-induced *i*NOS expression by β-cells by the inhibition of transcriptional activation and

induction of the heat shock response.[84] There is also evidence that 15-d-PGJ_2 may have anti-tumorigenic effects due to its inhibitory effects on tumor cell proliferation and angiogenesis.[85] This compound is commercially available for biological studies.[86]

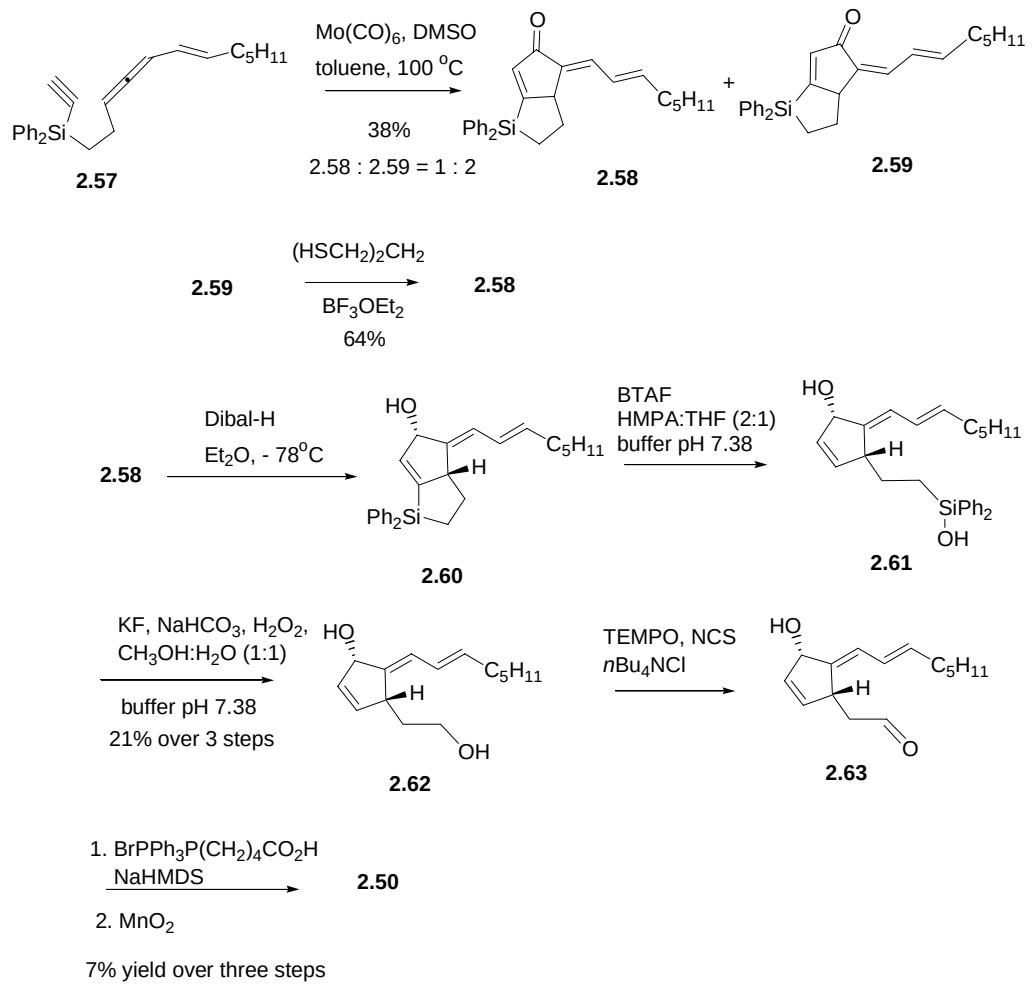
Despite this obvious biological activity, no total synthesis of this compound had been reported when the present study was undertaken. The first total synthesis came from Sutton's group (Scheme 2.18).[87] Treating 7-chloronorbornadiene **2.51** with LDBB afforded the corresponding secondary alkyllithium which adds to *trans*-oct-2-enal to provide alcohol **2.52** in excellent yield. After the protection of the secondary alcohol, the key transformation is the oxidative rearrangement by treating **2.53** with oxone. The subsequent acid hydrolysis gave hydroxyaldehyde **2.54**. After Wittig olefination to install the desired *cis* double bond, Dess-Martin oxidation provided enone **2.56**. Acid induced desilylation/dehydration furnished the natural product **2.50**. This is a rather efficient racemic synthesis even though it suffers two low yield transformations. Enantioselective syntheses of (+)-**2.50** and (-)-**2.50** have also been reported in the same paper via enzyme resolution of intermediates **2.54** and **2.52**, respectively. However, the yields for several steps are quite low. Biological tests show that the mirror image of the natural prostaglandin (-)-**2.50** is almost equi-active to its enatiomer as an *anti*-viral agent against Sendai virus and as an effective inhibitor of NF-κB.



Scheme 2.18 Total synthesis of 15-deoxy-$\Delta^{12,14}$-PGJ_2 by Sutton

The second synthesis of 15-deoxy-$\Delta^{12,14}$-PGJ_2 came from Brummond's group[88] by using an allenic [2+2+1] Pauson-Khand-type reaction in which the alkyne and allene functions were silicon-tethered. As illustrated in Scheme 2.19, compound **2.57**, prepared in 5 steps in 40% of overall yield, was subjected to Pauson-Khand reaction conditions to afford **2.58** and **2.59** in 38% yield (**2.58**:**2.59** = 1:2). The undesired enone **2.59** can be completely transformed to the desired **2.58** by using boron trifluoride and propanedithiol. Dibal-H reduction of **2.58** furnished bisallylic alcohol **2.60** which underwent a ring-opening reaction followed by oxidative desilylation to afford diol **2.62**. Selectively oxidation of the primary alcohol followed by Wittig olefination and MnO_2 oxidation furnished 15-deoxy-$\Delta^{12,14}$-PGJ_2 **2.50**. However, by a careful

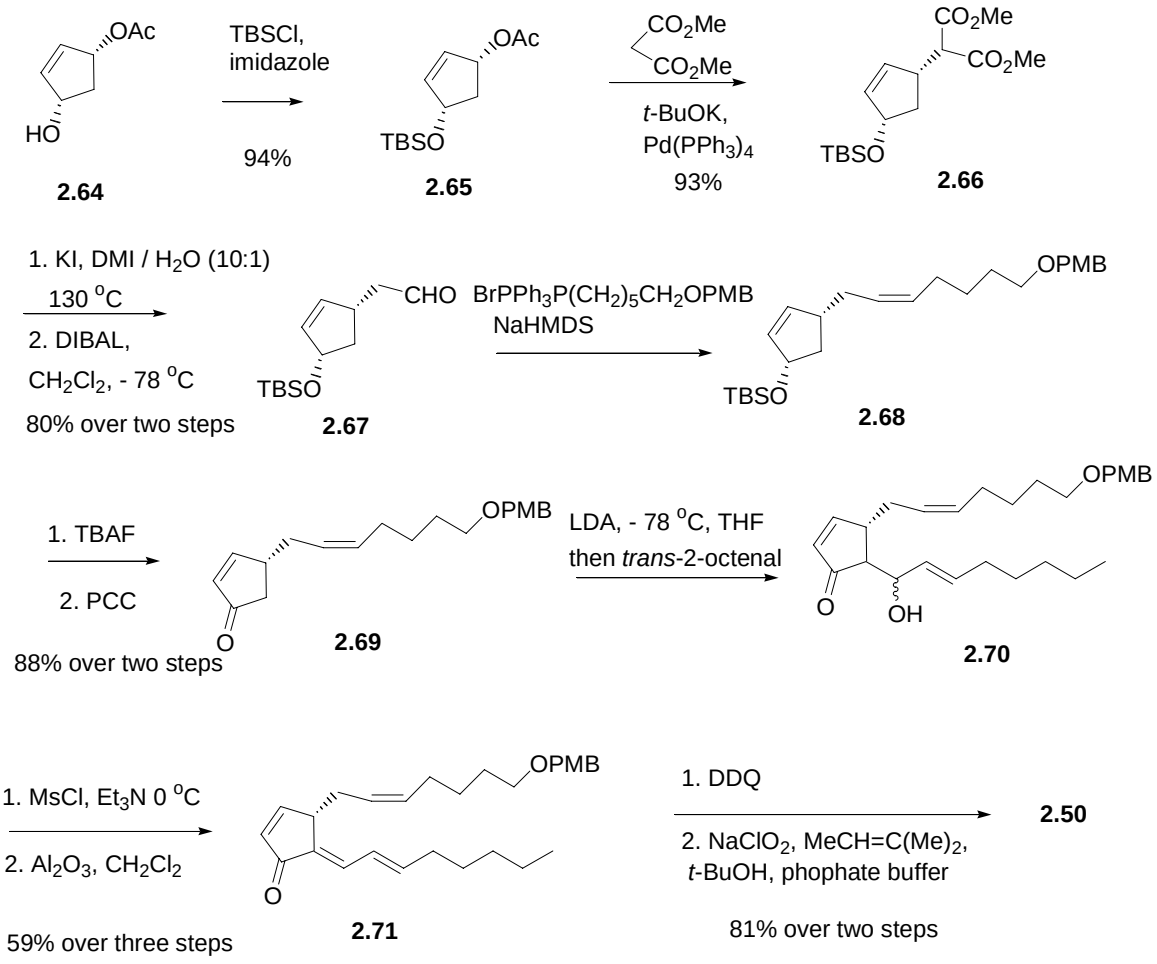
study of the 2D NMR spectra of the synthetic compound and the natural product, the stereochemistry at C-14 (prostaglandin carbon number) was unambiguously assigned as the E configuration.



Scheme 2.19 Total synthesis of (±)-15-deoxy-$\Delta^{12,14}$-PGJ$_2$ by Brummond

The third total synthesis came from Kobayashi's group (Scheme 2.20).[89] The scheme for the synthesis of this natural product was not illustrated in the paper. The authors only mentioned that the synthesis of 15-d-PGJ$_2$ is similar to that of $\Delta^{12,14}$-PGJ$_2$ which is shown in the paper.

Therefore, Scheme 2.20 is an analogue deduced from similar reactions for the synthesis of $\Delta^{12,14}$-PGJ_2. The first key step in the synthesis is palladium-catalyzed alkylation of allyl acetate **2.65** to afford **2.66**. The second key transformation is the aldol reaction between **2.69** and *trans*-2-octenal to furnish **2.70**. Further transformations afforded the optical active natural product **2.50**.

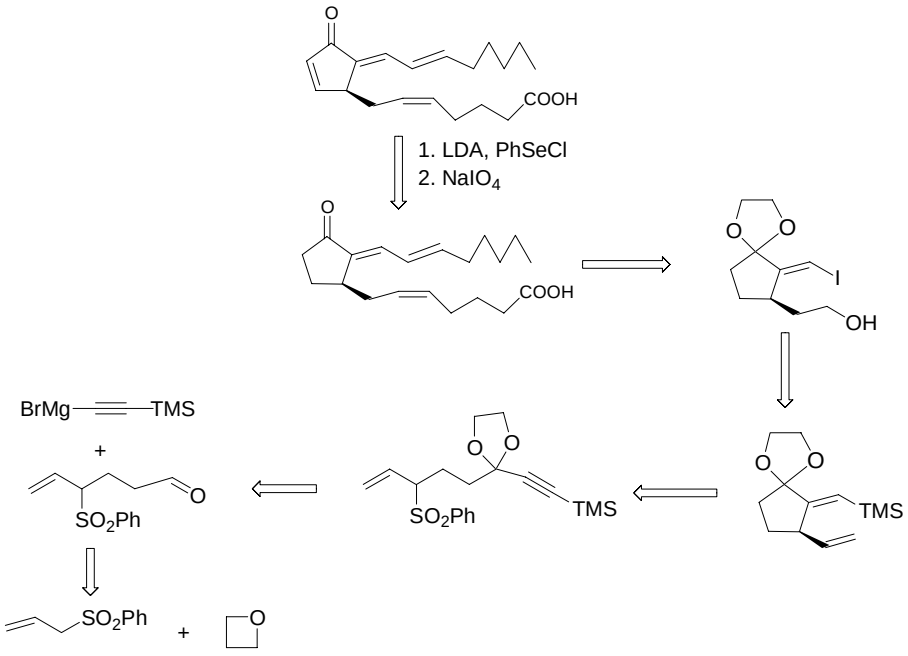


Scheme 2.20 Total synthesis of (+)-15-deoxy-$\Delta^{12,14}$-PGJ_2 by Kobayashi

The three reported syntheses of 15-deoxy-$\Delta^{12,14}$-PGJ_2 share a common synthetic feature, the introduction of the double bond on the cyclopentanone ring at a very early stage of their

syntheses. It is an advantage for the synthesis of 15-deoxy-$\Delta^{12,14}$-PGJ_2, but their methods are not suitable for synthesizing 9,10-*2H*-15-deoxy-$\Delta^{12,14}$-PGJ_2,[90] an important prostaglandin analogue of 15-d-PGJ_2 with structural modifications intended to give it PPARγ ligand activity and resistance to metabolism.[91]

Our retrosynthetic analysis is shown in Scheme 2.21, which features the Pd-catalyzed Zn-ene cyclization to construct the cyclopentane ring and the late stage installation of the double bond on the cyclopentanone ring. Thus, the syntheses of both 15-deoxy-$\Delta^{12,14}$-PGJ_2 and 9,10-*2H*-15d-$\Delta^{12,14}$-PGJ_2 can be achieved. Moreover, analogues of the natural product can be easily synthesized due to the connective nature of this synthesis.



Scheme 2.21 Retrosynthetic analysis using a Zn-ene cyclization as the key step

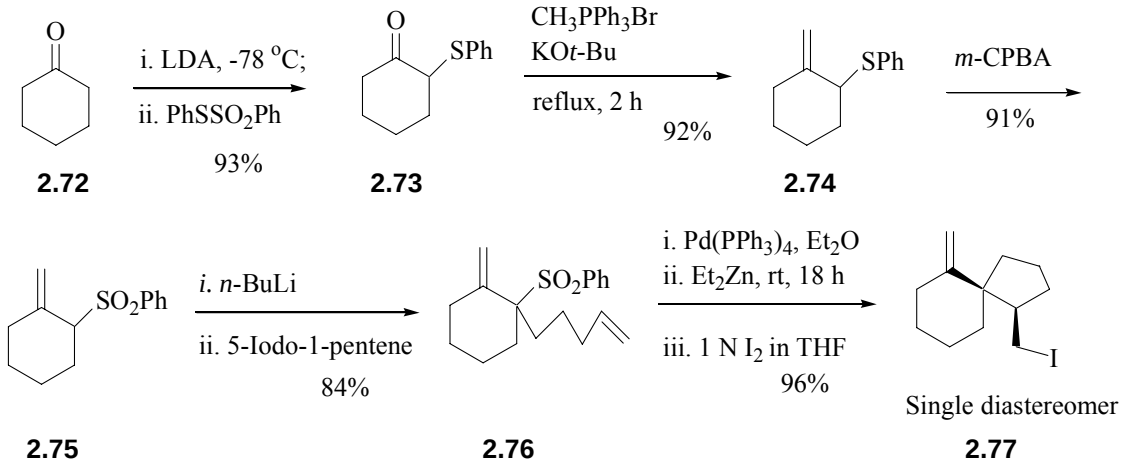
2.2. Results and Discussion

2.2.1. Pd-catalyzed Zn-ene Cyclization to Construct Spirobicyclic Molecules Using Allyl Phenyl Sulfones as Precursors of Allylzincs

Many natural products have spirobicylic structures, so new methodologies to construct such molecules with high stereoselectivity are always welcome. The Zn-ene cyclization has been shown to be an excellent method for synthesizing spirobicyclic molecules with high stereoselectivity by Oppolzer and Knochel. Traditionally, allyl acetates are used as the substrates to study Pd-catalyzed Zn-ene cyclizations. However, the use of allyl phenyl sulfones provides an excellent alternative due to the ease of assembly of such compounds by taking advantage of the unique properties of sulfur. Moreover, the difference in the nature of the two leaving groups, the phenylsulfinate and acetate, causes different reactivity in some cases. This difference will be discussed in detail later.

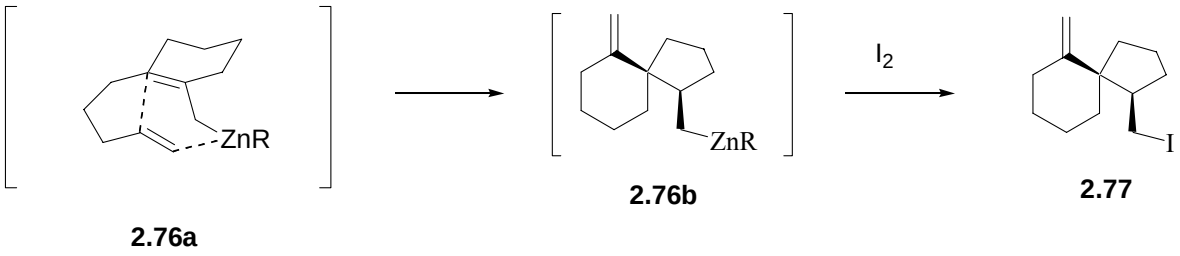
As illustrated in Scheme 2.22, allyl phenyl sulfone **2.76**, the substrate for a Zn-ene cyclization, was prepared in a connective manner. After treating cyclohexanone **2.72** with LDA to generate a lithium enolate, phenylsulfenylation with $PhSSO_2Ph$ afforded the known ketone **2.73**.[92] Subsequent Wittig reaction by heating ketone **2.73** with $CH_2=PPh_3$, generated by treating CH_3PPh_3Br with KO*t*-Bu, provided allyl phenylsulfide **2.74** in excellent yield.[93] Oxidation of allyl phenyl sulfide **2.74** with *m*-CPBA in Et_2O at -20 °C gave the corresponding allyl phenyl sulfone **2.75** in 91% yield. Due to the α acidity of allyl phenyl sulfone, the corresponding allyl anion was produced easily by treating **2.75** with *n*-BuLi. The formation of the allylanion is indicated by the red color of the THF solution. The attack of the resulting allyl anion on 1-iodo-4-pentene[94] occurred after the temperature of the reaction mixture was raised from -78 °C to -30 °C and the reaction mixture was stirred at -30 °C for 30 min. The desired product **2.76** was

obtained in 84% yield. The use of 1-bromo-4-pentene as an alternative electrophile provided no desired product under the same reaction conditions. It is likely due to the fact that iodide ion is a better leaving group than bromide ion. Treating **2.76** with 5 mol% $Pd(PPh_3)_4$ in diethyl ether, followed by the addition of Et_2Zn (1.0 M solution in hexane) led to the smooth generation of the allylzinc which attacked the tethered olefin successfully. After the reaction was performed for 18 h at room temperature, 1 N I_2 in THF was added to quench the reaction. Spirobicylic molecule **2.77** was obtained in 96% yield as a single diastereomer as verified by GC and NMR spectra.



Scheme 2.22 Synthesis of a spiro-bicyclic molecule 2.77

The stereochemistry of compound **2.77** is deduced from the half-chair transition state shown in Figure 2. Moreover, it is known that metallo-ene cyclizations usually afford intermediates with a *cis* relationship between the olefin and the resulting alkylmetal species.

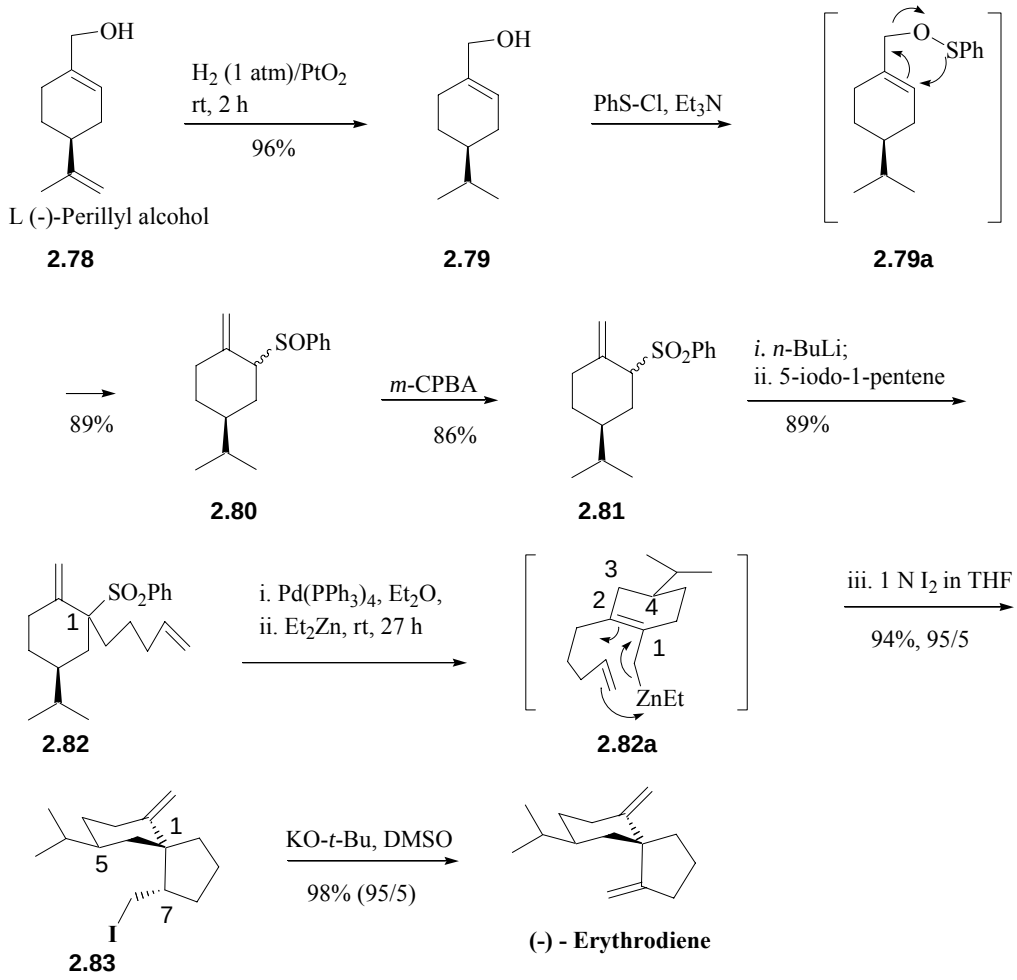


2.76a **2.76b** **2.77**

Figure 2.2 Transition state for the Zn-ene cyclization to form spirobicyclic structure

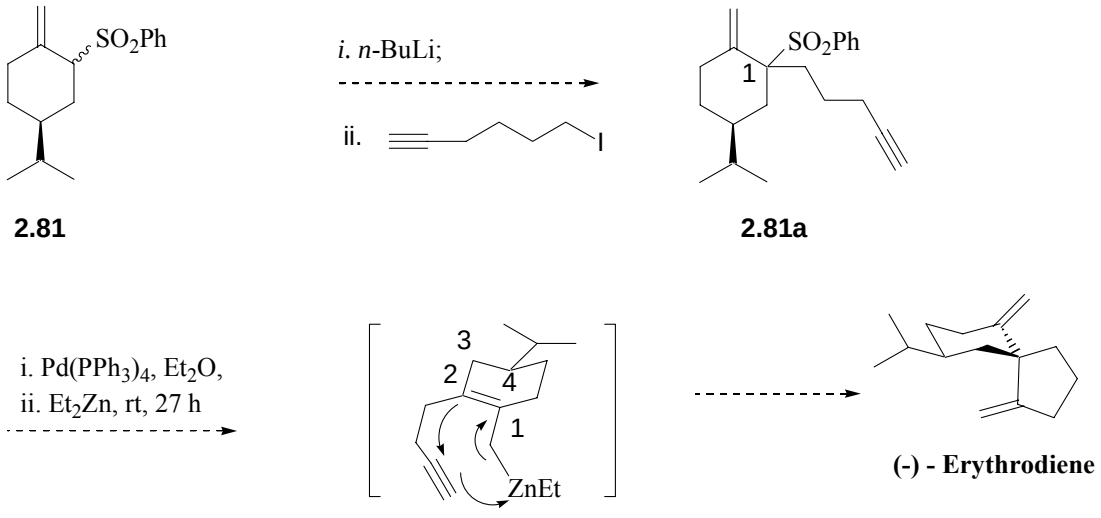
Encouraged by the easy assembly of spirobicyclic molecule **2.77**, we turned our attention to the synthesis of (-)-erythrodiene, a natural sesquiterpene, which has a similar spiro carbon center as **2.77**. As illustrated in Scheme **2.23**, (-)-perillyl alcohol **2.78** is converted into allylic alcohol **2.79** easily by selective hydrogenation of the more accessible double bond of **2.78** using a catalytic amount of PtO_2 under 1 atm of H_2.[79,80] Treating allylic alcohol **2.79** with PhSCl[95] (generated by mixing PhSH with NCS in benzene) in the presence of an excess of Et_3N produced intermediate **2.79a** which underwent a facile [2,3]-sigmatropic rearrangement to afford allyl phenyl sulfoxide **2.80** in 89% yield.[96] Oxidation of **2.80** with *m*-CPBA in Et_2O at -20 °C afforded the corresponding allyl phenyl sulfone **2.81** in 86% yield. Treating **2.81** with *n*-BuLi afforded the corresponding allyl anion, which was quenched with 1-iodo-4-pentene to provide the desired allyl phenyl sulfone **2.82** in 89% yield as two diastereomers in a ratio of 4:1 (determined by proton NMR spectra).[97] The stereochemical divergence at C-1 of **2.82** is not important since the stereochemistry at this carbon atom is destroyed by the subsequent allylzinc formation. It is known that allylmetal species undergo relative rapid 1,3 metal ion migration, especially when the metal is Li, Mg or Zn. Usually this 1,3-metal shift precedes the metallo-ene reaction. Treating allyl phenyl sulfone **2.82** with $Pd(PPh_3)_4/Et_2Zn$ generates allylzinc intermediate **2.82a**. In the half-chair transition state structure **2.82a**, the isopropyl group at C-4 tends to occupy the pseudoequatorial position. This isopropyl group will direct the tethered

olefin enophile coming from the other side of the 6-membered ring. The Zn-ene reaction proceeded smoothly to afford **2.83** in excellent yield and good diastereoselectivity of 95:5 over the two newly formed stereogenic centers. Oppolzer observed similar selectivity in his Zn-ene cyclization using an allyl acetate as the precursor of the allylzinc species. However, the use of the most common Pd(0) source, $Pd(PPh_3)_4$, in his reaction gave a poor yield. A special combination of $Pd(OAc)_2/PBu_3$ was required as the Pd (0) source in his case and a very large excess of Et_2Zn (20 equiv) was crucial in obtaining a high yield of the cyclization product. In our case, using allyl phenylsulfones 2**.82** as the substrates for the Zn-ene cyclization, $Pd(PPh_3)_4$ together with 6 equiv of Et_2Zn works extremely well. No effort was made to optimize the amount of Et_2Zn used. The last step in the synthesis is the base-induced dehydroiodination by treating iodide **2.83** with KO-*t*Bu in DMSO. (-)-Erythrodiene was obtained in almost quantitative yield as two diastereomers with excellent diastereoselectivity of 95:5. The same diastereoselectivity between iodide **2.83** and (-)-erythrodiene shows that the chiral center at C-7 must have been generated in a completely diastereoselective manner during cyclization and the stereochemical divergence comes from the spiro carbon center. In total, 6 linear steps were used to obtain (-)-erythrodiene starting from commercially available (-)-perillyl alcohol with an overall yield of 60%. This is the most efficient of the published syntheses of this natural product so far. Oppolzer required 11 steps starting with the same alcohol and the overall yield was 24%.



Scheme 2.23 Total synthesis of (-)-erythrodiene

In our synthesis of (-)-erythrodiene, the key reaction is the intramolecular addition of an allylzinc to the tethered alkene enophile. Since an alkene is the desired functionality in the natural product, the use of a tethered alkyne enophile should make it possible to synthesize the desired olefin directly without going through the iodide **2.83**. The proposed synthesis, utilizing this idea, is illustrated in Scheme 2.24. Substrate **2.81a** with a tethered alkyne should be produced very easily by the same protocol described above. The Zn-ene cyclization should provide the desired natural product directly.

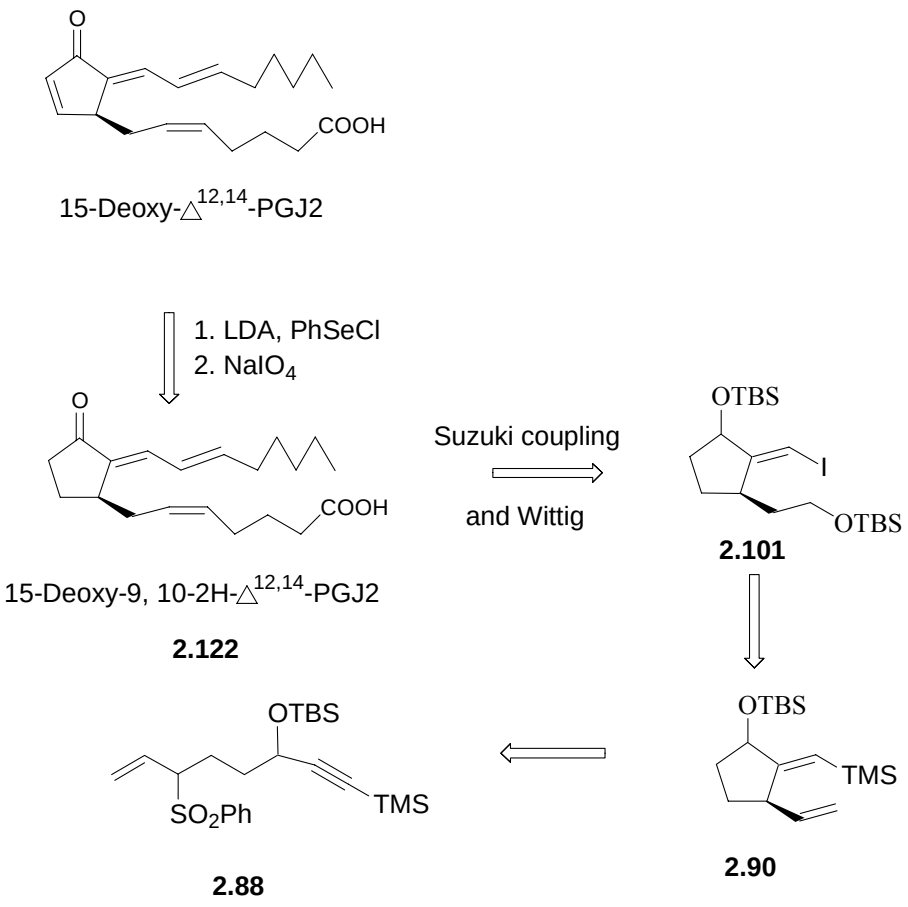


Scheme 2.24 Proposed synthesis of (-)-erythrodiene using a tethered alkyne as the enophile

2.2.2. Total Synthesis of (±)-15-Deoxy-$\Delta^{12,14}$-PGJ_2, (±)-9,10-*2H*-15-deoxy-$\Delta^{12,14}$-PGJ_2

2.2.2.1. Approach I to the Synthesis of (±)-15-Deoxy-$\Delta^{12,14}$-PGJ_2

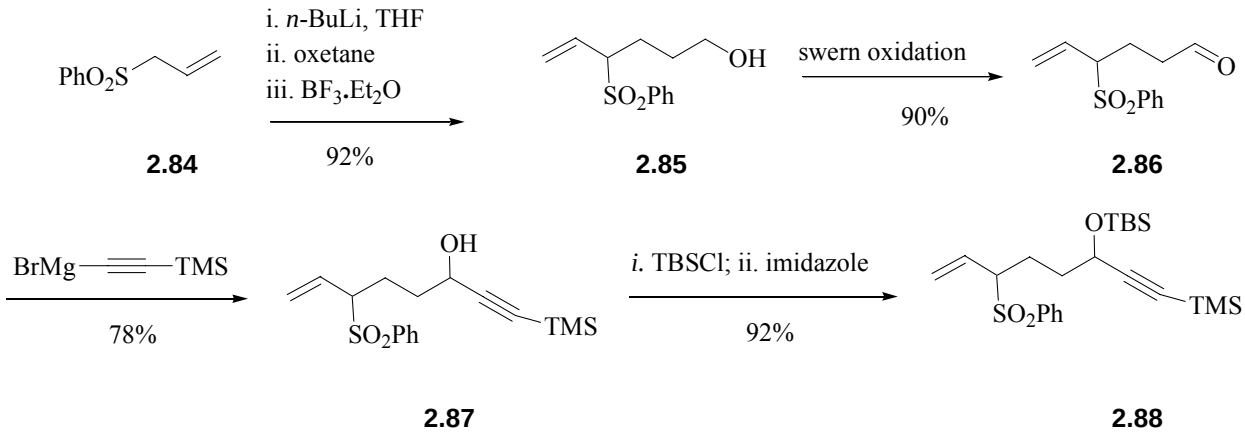
Our retrosynthetic approach to the total synthesis of (±)-15-deoxy-$\Delta^{12,14}$-PGJ_2 is shown in Scheme 2.25. The key reaction in the retrosynthetic analysis is the Zn-ene cyclization of substrate **2.88** to afford **2.90**. Vinylsilane **2.90** is elaborated to synthesize vinyl idodide **2.10**, which can undergo a Suzuki coupling reaction to install the desired diene side chain. A Wittig reaction can set the Z-double bond in another side chain. This approach also features a late stage introduction of a double bond on the cyclopentane ring. Therefore, both 15-deoxy-9,10-*2H*-$\Delta^{12,14}$-PGJ_2 and 15-deoxy-$\Delta^{12,14}$-PGJ_2 could be available by this route.



Scheme 2.25 Retrosynthetic analysis for (±)-15-deoxy-$\Delta^{12,14}$-PGJ$_2$ (approach I)

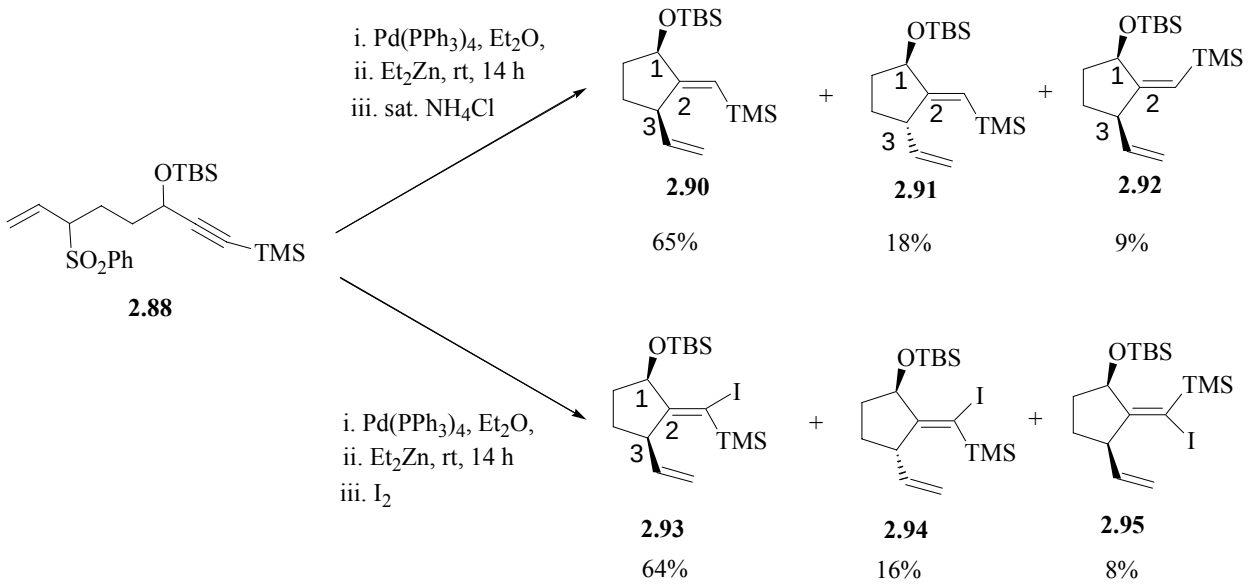
The synthesis of substrate **2.88**, capable of Zn-ene cyclization, was straightforward (Scheme 2.26). Treating allyl phenyl sulfone **2.84** with *n*-BuLi afforded the corresponding allyl carbanion which attacked oxetane highly selectively at the α position in the presence of the Lewis acid BF_3•Et_2O, even though THF is used as solvent. No product resulting from attack of the allyl carbanion on THF was observed. A 92% yield of alcohol **2.85** was produced. Swern oxidation[98] converted alcohol **2.85** to aldehyde **2.86** in 90% yield. Trimethylsilylethyne magnesium bromide (generated by treating trimethylsilylacetylene with EtMgBr) added to aldehyde **2.86** to give propargylic alcohol **2.87** in 78% yield. Protection of the alcohol as the

corresponding TBS ether by treating **2.87** with TBSCl and imidazole afforded precursor **2.88** in 92% yield.



Scheme 2.26 Synthesis of allyl phenyl sulfone 2.88

When allyl phenyl sulfone **2.88** was treated with $Pd(PPh_3)_4/Et_2Zn$ in diethyl ether, the resulting allylzinc added to the internal alkyne enophile smoothly. After the reaction was performed at room temperature for 14 h, saturated NH_4Cl aqueous solution was added to quench the reaction. Three products **2.90**, **2.91**, **2.92** were isolated with 65%, 18%, and 9% yields, respectively, after purification by flash-column chromatography. When the reaction was quenched with I_2, products **2.93**, **2.94**, **2.95** were isolated with 64%, 16% and 8% yields, respectively. Therefore, the cyclization is not very stereoselective.



Scheme 2.27 Cyclization studies of allyl phenyl sulfone 2.88

The stereochemistry of **2.90** was assigned based on the 2D NMR spectra of its derivative **2.96** (Figure 2.3). The ROESY spectrum clearly shows the cross peaks between H^1 and H^2, H^1 and H^3 (see appendix E and F for COSY and ROSEY spectra for **2.96**). The cross peak between H^1 and H^3 indicates that the hydroxy group at C-1 and the vinyl group at C-3 are on the same side of the ring. The cross peak between H^1 and H^2 supports the *trans* geometry of the vinylsilane.

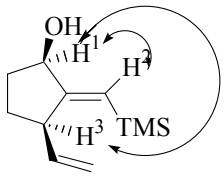
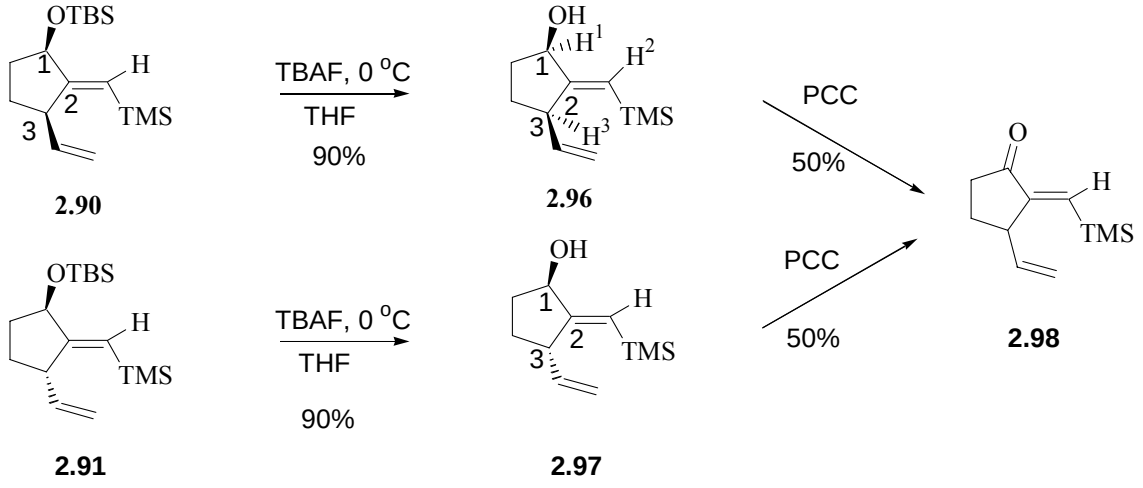


Figure 2.3 ROESY cross peaks for 2.96

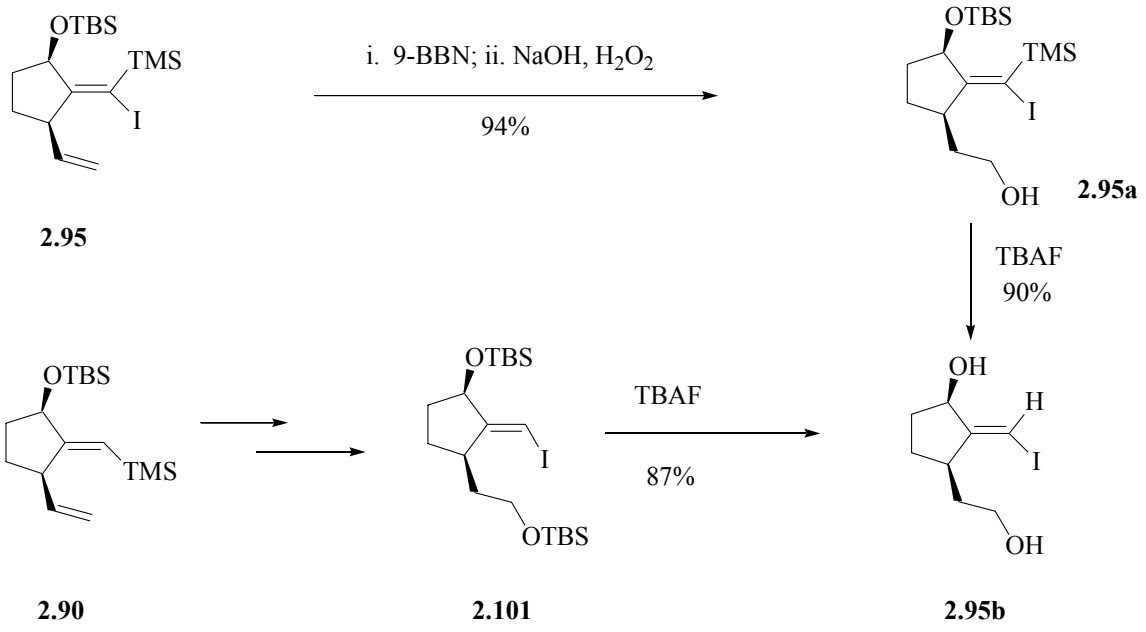
As illustrated in Scheme 2.28, alcohols **2.96** and **2.97** were obtained by TBAF treatment of **2.90** and **2.91** respectively. Oxidation of alcohol **2.96** and **2.97** provided the same enone **2.98**. Therefore, alcohol **2.96** and **2.97** must have the same *trans* vinylsilane geometry and the difference between these two compounds can only be the different orientation of the two substituents at the C-1 and C-3 positions. Since the stereochemistry of alcohol **2.96** has been determined to have a 1,3-*cis* relationship between the two substituents, alcohol **2.97** must have the two substituents at C-1 and C-3 *trans* to each other. Because the desilylation reactions from **2.90** to **2.96** and **2.91** to **2.97** do not involve a change in stereochemistry, compounds **2.90** and **2.91** should have the same stereochemistry as **2.96** and **2.97**, respectively.



Scheme 2.28 Stereochemical proof for vinylsilanes

The remaining task is to determine the stereochemistry of compound **2.92**. As shown in Scheme 2.29, the I_2 quenched minor product **2.95** undergoes hydroboration with 9-BBN, followed by oxidation, to provide primary alcohol **2.95a**. Desilylation with TBAF furnished diol **2.95b,** which is identical to the compound obtained by desilylation of vinyl iodide **2.101**. Vinyl iodide **2.101** was obtained from **2.90** by the transformations shown in Scheme 2.30. These

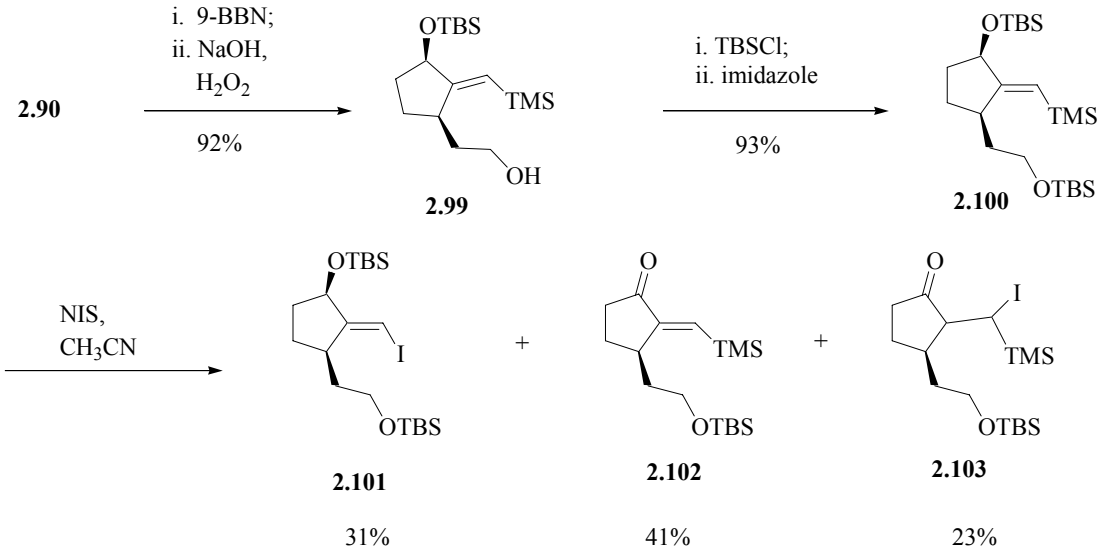
transformations do not change the initial stereochemistry of **2.90**. These results confirmed the 1,3-*cis* relationship between the two substituents at C-1 and C-3 positions for compounds **2.90** and **2.95**. Since compound **2.92** should have exactly the same stereochemistry as **2.95**, **2.92** must have two substituents at C-1 and C-3 *cis* to each other. The double bond geometry in **2.90** is known to be *trans*. Thus, the vinylsilane geometry in **2.92** must be *cis*.



Scheme 2.29 Evidence for 1,3 *cis* relationship in major cyclized product 2.90 and minor cyclized products 2.95

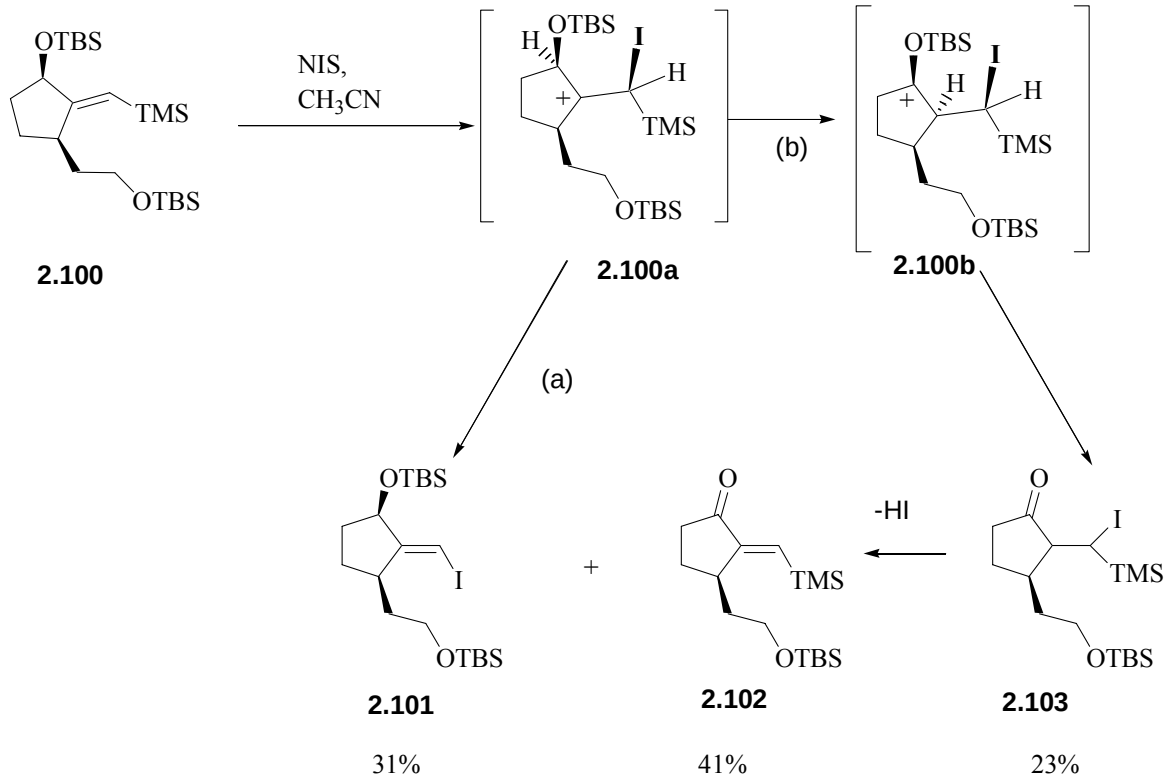
As shown in Scheme 2.30, primary alcohol **2.99** was obtained very easily by hydroboration of **2.90** with 9-BBN at 0 °C followed by oxidation of the resulting alkylboron with H_2O_2. Protection of the primary alcohol as its TBS ether afforded vinylsilane **2.100** in excellent yield. The desired vinyl iodide **2.101** was produced by treating vinylsilane **2.100** with NIS in CH_3CN at 0 °C.[99] The solvent seems to play an important role in this reaction. When THF or DMF was used instead of CH_3CN, no reaction occured after the mixture of vinylsilane **2.100** and

NIS was stirred at room temperature for 24 h. Only starting materials were recovered. However, the reaction proceeded when CH_3CN was used as the solvent. Unfortunately, the desired product is obtained in only 31% yield. Two by-products, enone **2.102** (41%) and ketone **2.103** (23%) were produced.



Scheme 2.30 Synthesis of vinyl iodide 2.101

The mechanism of this reaction is shown in Scheme 2.31. After the addition of I^+ across the double bond of the vinylsilane, an intermediate **2.100a** is formed. There are two pathways that **2.100a** can take. The first pathway (a) is the elimination of TMS group to afford the desired vinyl iodide **2.101**. Another pathway (b) involves a 1,2 hydride shift to afford cation **2.100b**, which is stabilized by an adjacent oxygen atom. Cation **2.100b** can eliminate the TBS group, after attack on Si by a nucleophile such as the succinimidyl anion, to provide ketone **2.103**. Further elimination of HI from ketone **2.103** affords **1.102**.



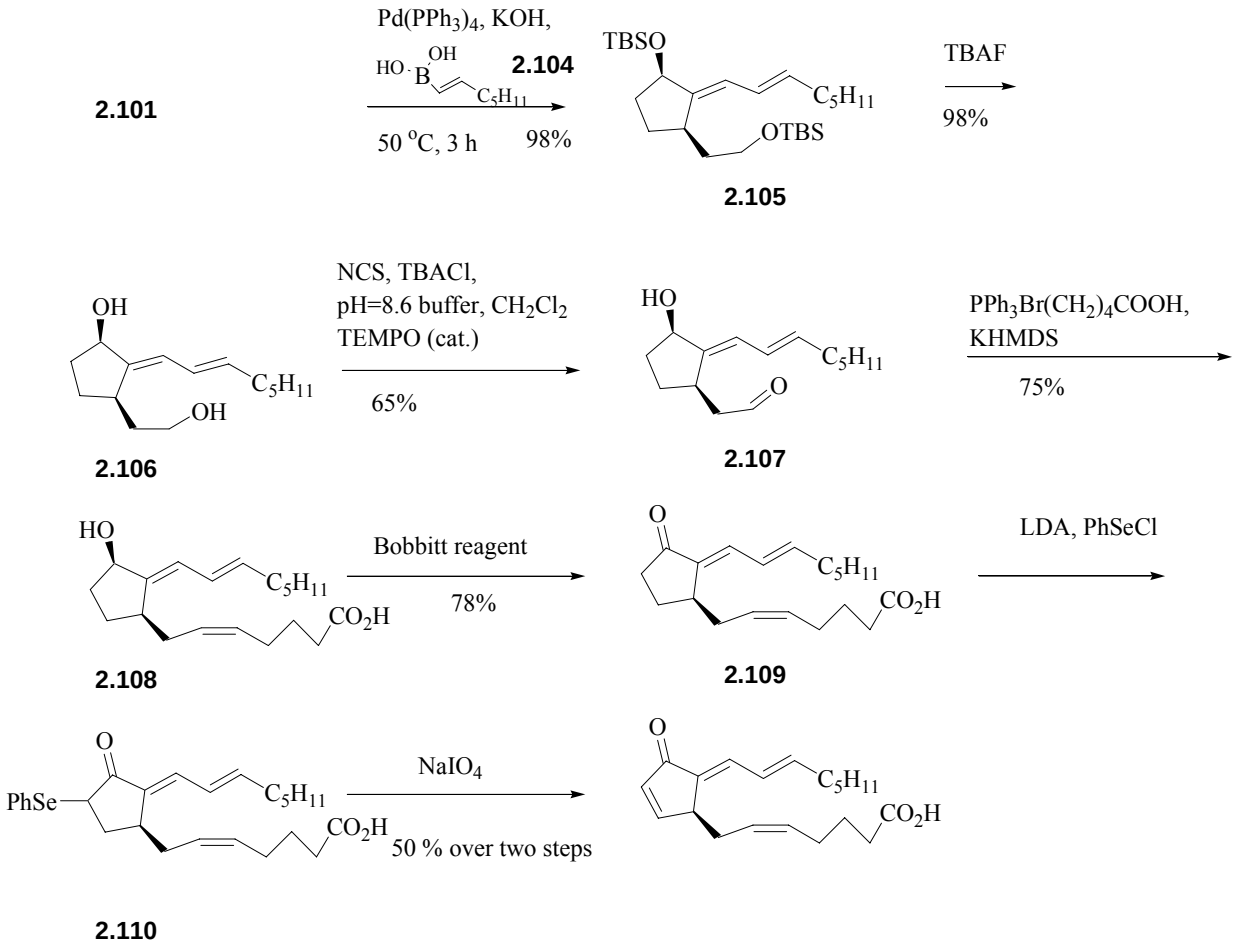
Scheme 2.31 Mechanism for the formation of vinyl iodide 2.101 and by-products

With vinyl iodide **2.101** in hand, we set out to synthesis 9,10-*2H*-15-deoxy-$\Delta^{12,14}$-PGJ_2 and 15-d-$\Delta^{12,14}$-PGJ_2. As shown in Scheme 2.32, Suzuki coupling[100] between vinyl iodide **2.101** and vinylboronic acid **2.104**[101] afforded the desired diene **2.105** in almost quantitative yield. Desilylation with TBAF gave diol **2.106**. Selectively oxidation of the primary alcohol in the presence of a secondary alcohol was realized by the TEMPO based methodology developed by Einhorn.[102] A Wittig reaction[103] installed the desired *Z*-double bond to afford **2.108**. Oxidation of allylic alcohol **2.108** with Bobbitt reagent[104] furnished 9,10-*2H*-15-deoxy-$\Delta^{12,14}$-PGJ_2 **2.109**. Installation of the double bond on the cyclopentanone ring was accomplished by organoselenium chemistry which converts ketones to enones by selenoxide *syn* elimination.[105] Stork had used this methodology to introduce a double bond into a cyclopentanone ring to form an enone in his

synthesis of (+)-15-(*s*)-prostaglandin-A_2.[106] In our experiment, treating **2.109** with 2.3 equivalent of LDA at -78 °C generated the corresponding dianion, which was quenched by PhSeCl to provide α-phenylselenyl substituted ketoacid **2.110.** The dehydroselenylation involved oxidation followed by *syn*-elimination. The oxidation of phenylselenide to phenylselenoxide is a facile transformation for which many reagents have been employed in the literature. These include H_2O_2, *m*-CPBA, O_3, $NaIO_4$. Here, $NaIO_4$ was used to oxidized α-phenylselenyl substituted ketoacid **2.110** in aqueous methanol and subsequent elimination of the resulting α-phenylselenoxide occurred readily at room temperature to provide the desired natural product in 50% overall yield in two steps from **2.109**.

Unfortunately, although the 300 MHz proton NMR and 75 MHz C^{13} NMR spectra of 15-d-$\Delta^{12,14}$-PGJ_2 show the matching of all peaks with reported values, the 600 MHz proton NMR spectrum reveals the presence of 15% of another isomer, which was not observed by the 300 MHz proton NMR spectrum. By examining the adopted reaction procedures carefully it was found that very likely the Wittig reaction caused this problem. Room temperature has been used to perform the Wittig reaction as described by Snapper. A mixture of Z and E isomers was apprently obtained but 300 MHz NMR spectroscopy could not distinguish them. Kobayashi et al found a similar problem in their Wittig reaction to install the Z double bond in the synthesis of Δ^{12}-PGJ_2. In their case, when the Wittig reaction was performed initially at 0 °C, followed by raising the temperature to room temperature, 5% of E isomer was found contaminating the product. Kobayashi found that the problem could be solved by starting the Wittig reaction at a much lower temperature (e.g. -78 °C) followed by raising the temperature slowly to room temperature. Therefore, it is not very surprising to find 15% of E isomer in my product since room temperature is the initial temperature in my Wittig reaction. Further efforts are needed to

obtain pure 15-deoxy-$\Delta^{12,14}$-PGJ_2 by performing the Wittig reaction at a more appropriate temperature.



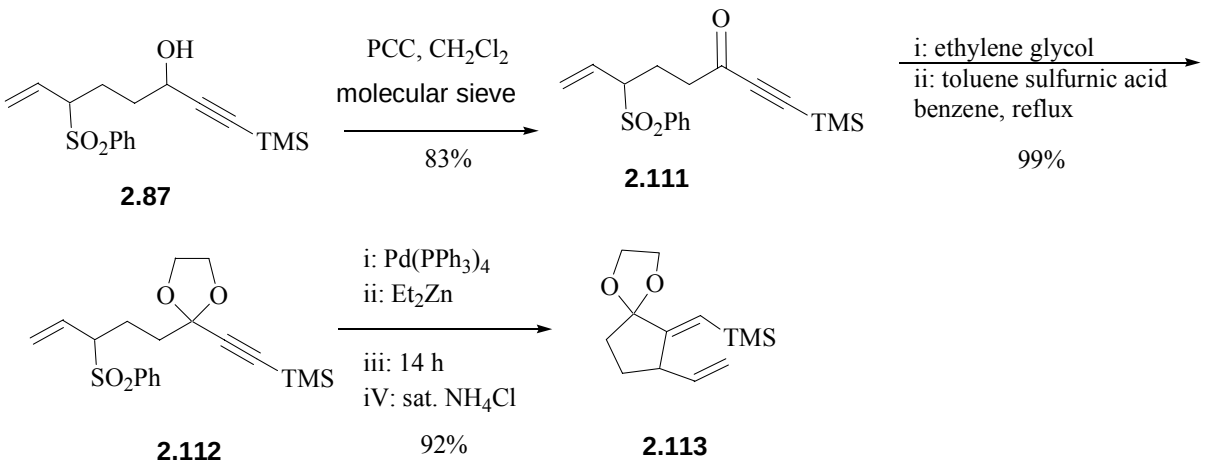
Scheme 2.32 Total synthesis of 9, 10-*2H*-15-deoxy-$\Delta^{12,14}$-PGJ_2 and 15-deoxy-$\Delta^{12,14}$-PGJ_2

2.2.2.2. Approach II to the Synthesis of 9,10-*2H*-15-Deoxy-$\Delta^{12,14}$-PGJ_2

Since there was substantial trouble in the transformation from vinylsilane **2.100** to vinyl iodide **2.101** and since the stereoselectivity in the Zn-ene cyclization was low in our first generation approach to the natural product, we set about to develop a more efficient approach II.

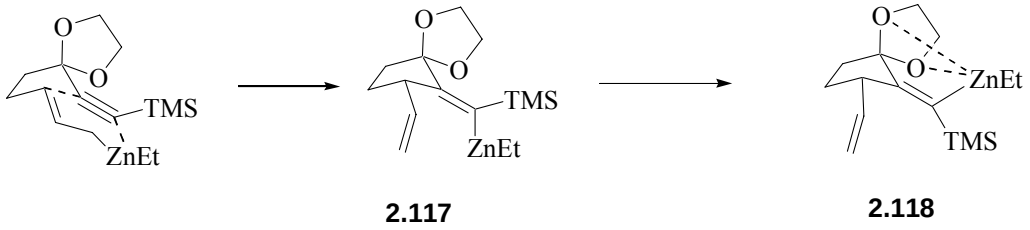
The main feature of this approach is to introduce a ketal group at an early stage of the synthesis (Scheme 2.33). The use of a ketal has the following advantages. Firstly, due to the symmetry, the formation of a ketal destroys a chiral carbon center and this should provide a far cleaner Zn-ene cyclization since only two stereoisomers can be obtained. Secondly, the quarternary carbon center that bears the ketal group has no hydrogen atom available that could lead to by-products such as **2.102** and **2.103** which were observed in the transformation from **2.100** to **2.101** in approach I (Scheme 2.30 and 2.31). Thirdly, the ketal can be removed easily by simple acid work-up to reveal the ketone functionality. No additional deprotection step is needed.

As illustrated in Scheme 2.33, propargylic alcohol **2.87** was oxidized to the corresponding ketone **2.111** easily by PCC in CH_2Cl_2 at room temperature.[107] The desired ketal **2.112** was produced in quantitative yield by treating a ketone **2.111** with ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid in benzene.[108] A Dean-Stark trap was used in this reaction to remove the by-product water in order to shift the equilibrium toward the product. When **2.112** was subjected to $Pd(PPh_3)_4/Et_2Zn$ in Et_2O, the Zn-ene cyclization proceeded smoothly to afford **2.113** in 92% yield as a single diastereomer. Compared with the poor stereoselectivity obtained in the Zn-ene cyclization in our first generation approach, the use of the ketal protecting group greatly increased the efficiency of the Zn-ene cyclization.



Scheme 2.33 a Zn-ene cyclization with a ketal at the propargylic position

The mechanism of the formation of the precursor **2.118** of vinylsilane **2.113** is shown in Scheme 2.34. Initially, vinylzinc intermediate **2.117**, resulting from *syn* addition of allylzinc to the internal alkyne, is obtained. The ketal group apparently caused isomerization of vinylzinc intermediate **2.117** into **2.118** completely. Both oxygen atoms in the ketal can probably coordinate with the zinc in **2.118** so the latter is more stable than **2.117**. Aqueous work-up provided vinylsilane **2.113** as the only product.



Scheme 2.34 Isomerization of vinylzinc

An alternative mechanistic pathway for cyclization that would also rationalize the stereochemistry of **2.113** is shown in Figure 2.4. The Et_2Zn coordinates with the ketal oxygen atoms as well as the alkyne (**2.117a**). The triple bond is polarized by the zinc and made more electrophilic. The allylzinc adds to the polarized triple bond to afford intermediate **2.118**, which can provide **2.113** after aqueous work-up.

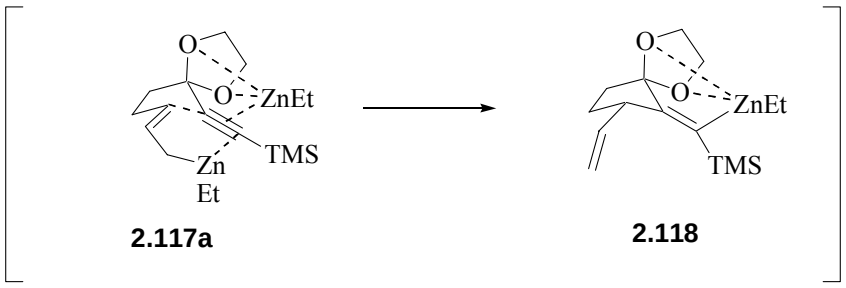
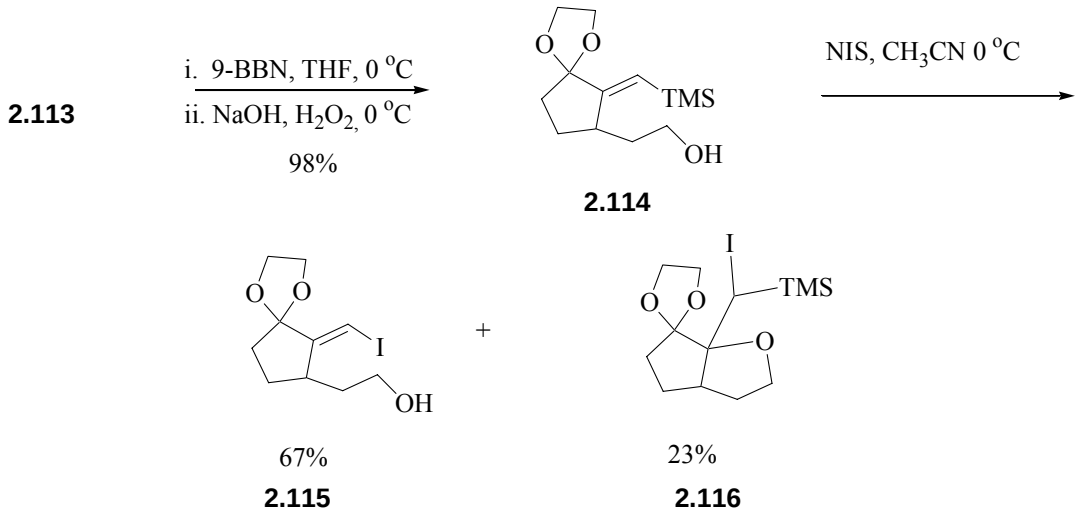


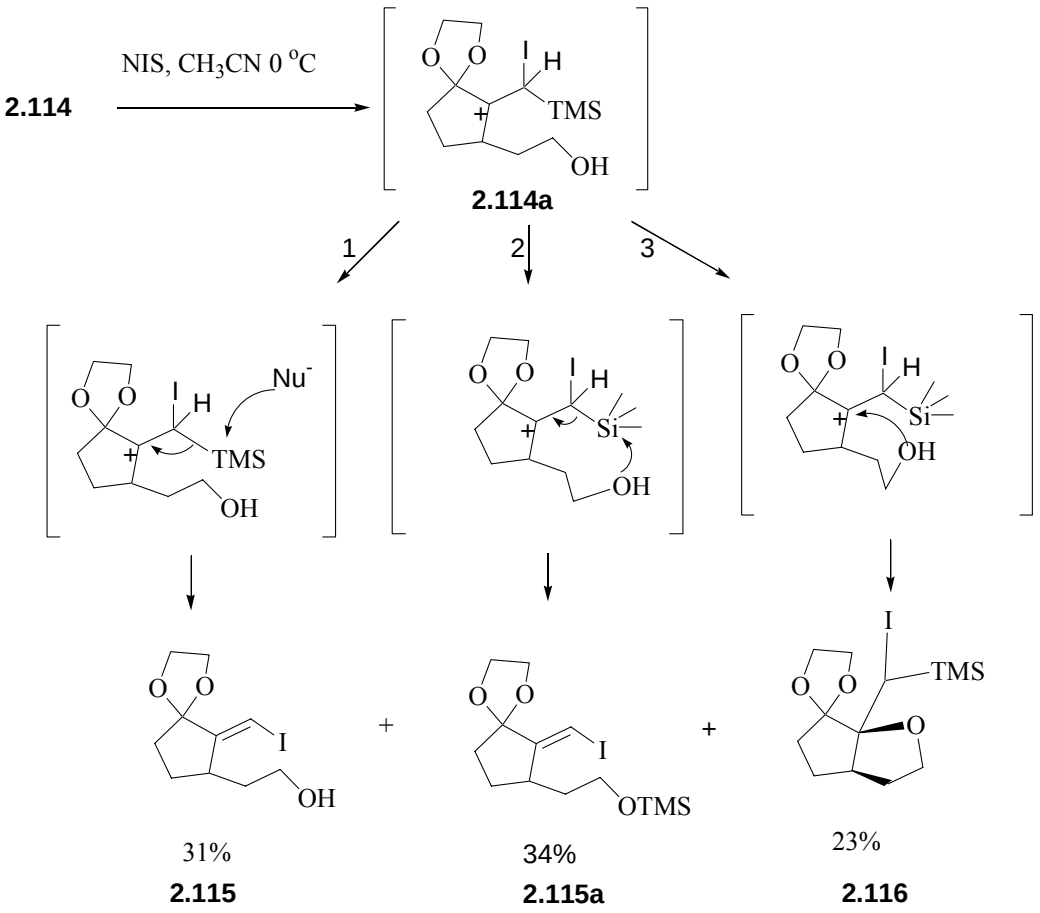
Figure 2.4 Mechanism of the Zn-ene cyclization

As shown in Scheme 2.35, hydroboration of the mono-substituted alkene of **2.113** with 9-BBN at 0 ˚C for 12 h, followed by oxidation with $NaOH/H_2O_2$ at 0 ˚C for 1 h provided primary alcohol **2.114** in almost quantitative yield. Si-I exchange was performed by treating alcohol **2.114** with N-iodosuccinimide in acetonitrile. The desired vinyl iodide **2.115** was generated in 67% yield together with 23% of by-product **2.116**.



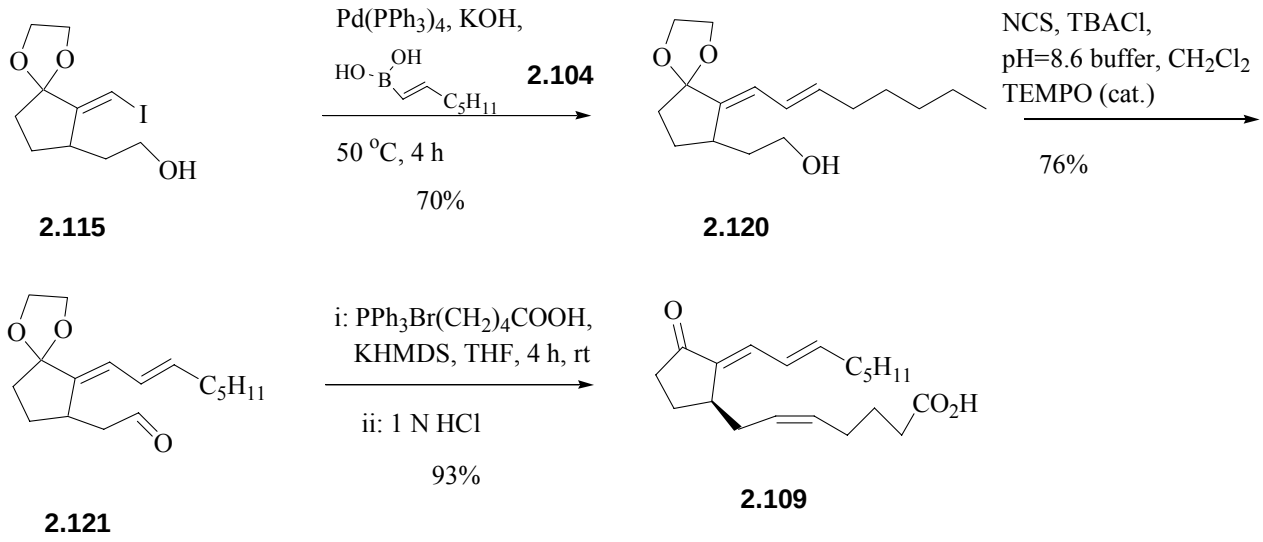
Scheme 2.35 Hydroboration and Si-I exchange reactions

0.1 N HCl was needed to wash the ether extracts of the reaction mixture in order to obtain products **2.115** and **2.116**. As illustrated in Scheme 2.36, without acid wash, three compounds, **2.115**, **2.115a** and **2.116** were obtained in 31%, 34% and 23% yields, respectively, after flash-column chromatography purification. The mechanism of the reaction is proposed as follows. Cationic intermediate **2.114a**, produced by the addition of I^+ across the vinylsilane, has three reaction pathways. The first pathway involves the elimination of TMS group by attack of an external nucleophile to afford the desired vinyl iodide **2.115**. The second pathway involves the internal neucleophilic attack of the primary alcohol on the TMS group to generate the vinyl iodide **2.115a**, which can be converted into the desired **2.115** by washing the ether extracts of the reaction mixture with 0.1 N HCl. The third pathway is the internal attack of the alcohol oxygen atom onto the cation itself to form a bicyclic compound **2.116** as a single diastereomer. It is also possible that only pathway 2 and pathway 3 are operational. Since the TMS group on the primary alcohol is lost very easily, compound **2.115** could possibly come from **2.115a** during work-up even though no acid wash was applied.



Scheme 2.36 Mechanism of the reaction of vinylsilane 2.114 with NIS

As shown in Scheme 2.37, Suzuki coupling of vinyl iodide **2.119** with vinyl boronic acid **2.104** afforded diene **2.120** in 70% yield. Oxidation of **2.120** to the corresponding aldehyde **2.121** was performed by the TEMPO based methodology described before. A Wittig reaction installed the Z-olefin side chain and the subsequent acid work-up removed the ketal protecting group to reveal the desired ketone functionality. 9,10-*2H*-15-deoxy-$\Delta^{12,14}$-PGJ_2 **2.109** was obtained in 93% yield in this step. Compared with the first generation approach, this approach is far more efficient.



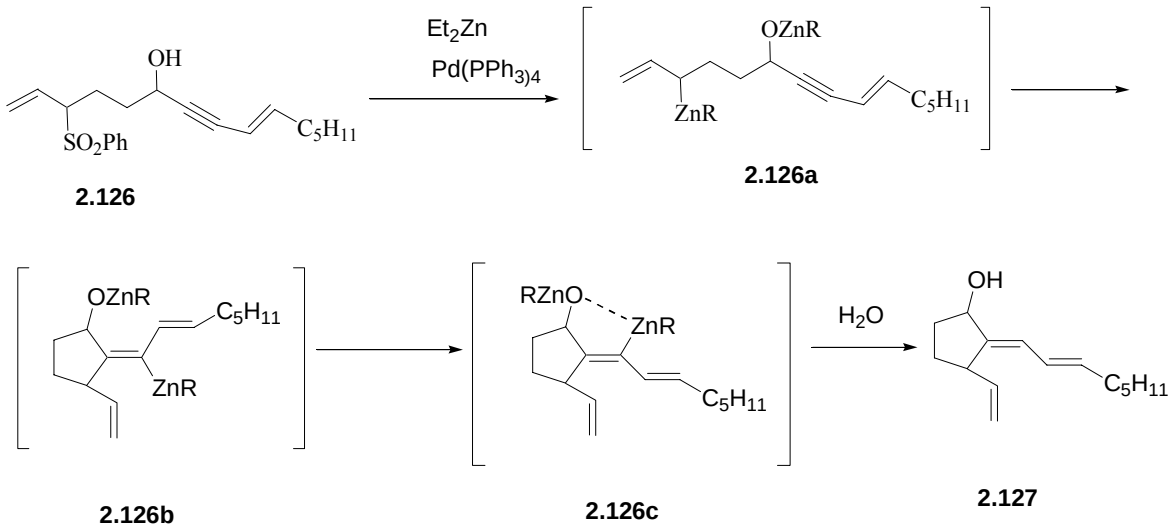
Scheme 2.37 Synthesis of 9,10-*2H*-15-deoxy-$\Delta^{12,14}$-PGJ_2

2.2.2.3. Approach III to the Synthesis of 9,10-*2H*-15-Deoxy-$\Delta^{12,14}$-PGJ_2

In approaches I and II for the total synthesis of 15-deoxy-$\Delta^{12, 14}$-PGJ_2, the isomerization of the vinylzinc intermediate makes the subsequent Si-I exchange necessary to produce the vinyl iodide with the desired double bond geometry. In approach III, we wanted to take advantage of the vinylzinc isomerization during the Zn-ene cyclization so the desired natural product can be synthesized more efficiently.

As illustrated in Scheme 2.38, a tethered enyne (compound **2.126**) is to be used as the enophile for the allylzinc addition during the Zn-ene cyclization. We envisioned that after the generation of allylzinc **2.126a** by treating **2.126** with $Pd(PPh_3)_4/Et_2Zn$, the allylzinc would add to the enyne moiety in a *syn*-fashion initially to afford **2.126b**, which may isomerize to the corresponding more stable vinylzinc **2.126c** due to coordination between the Zn and oxygen

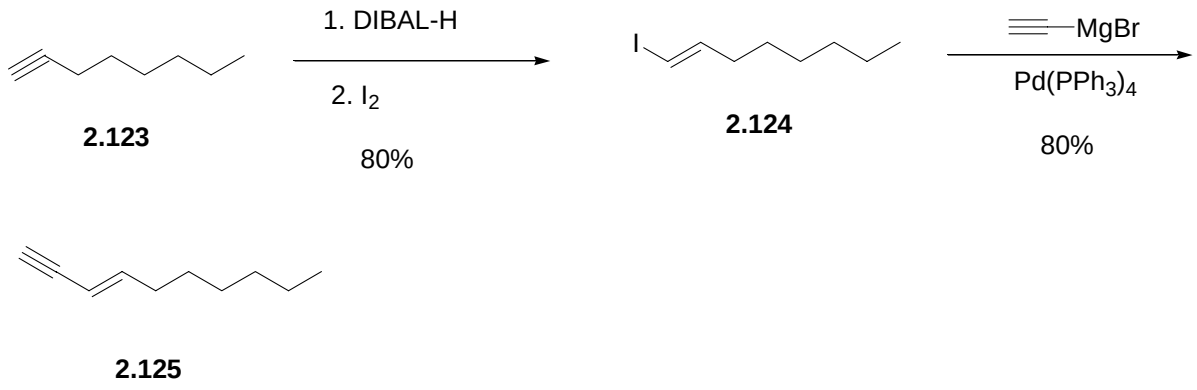
atom. Intermediate **2.126c** has the desired double bond geometry so the desired diene **2.127** would be obtained after aqueous quenching.



2.126 **2.126a** **2.126b** **2.126c** **2.127**

Scheme 2.38 Synthetic plan to prepare diene 2.127 taking advantage of vinylzinc isomerization

As shown in Scheme 2.39, enyne **2.125** was prepared in 80% yield by Pd-catalyzed coupling between the vinyl iodide **2.124**[109] and ethynemagnesium bromide according to Negishi's protocol.[110]



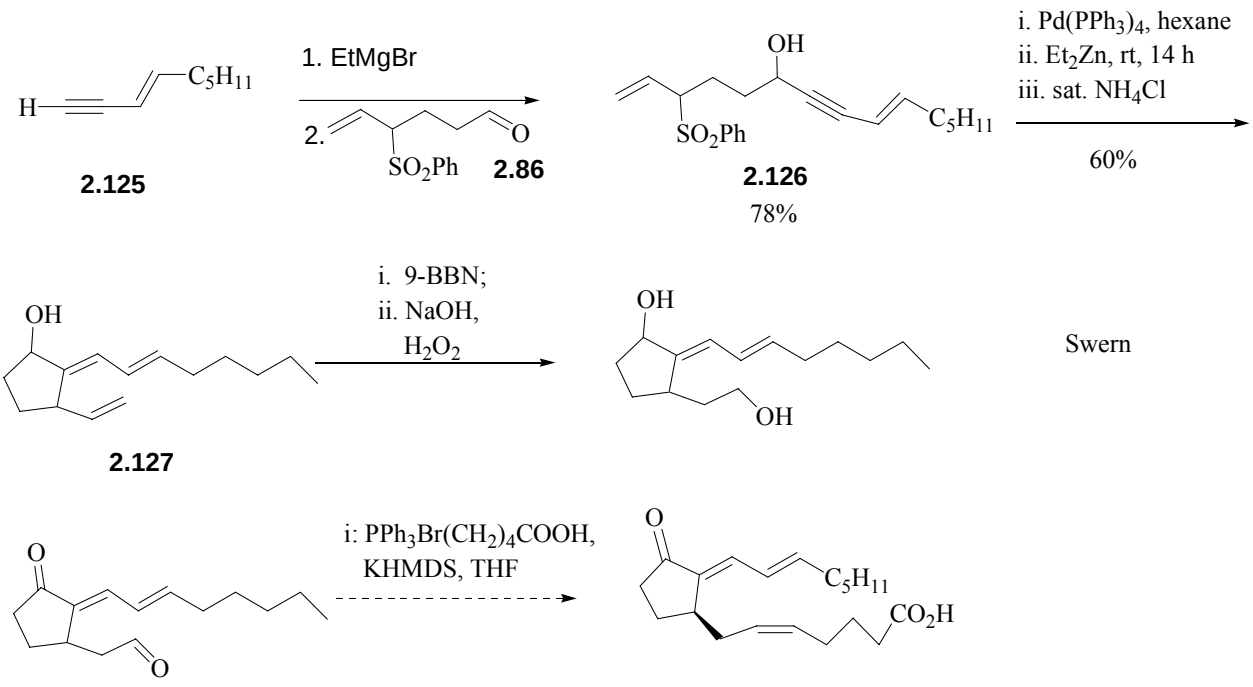
2.123 **2.124** **2.125**

Scheme 2.39 Synthesis of enyne 2.125

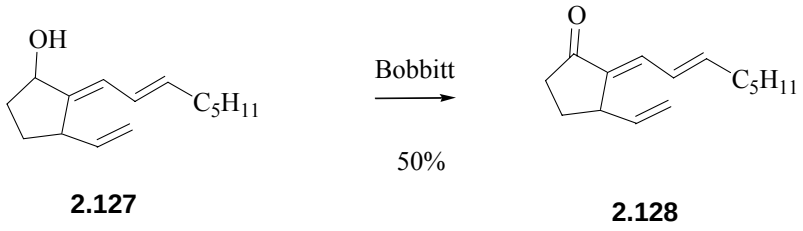
As illustrated in Scheme 2.40, the addition of the enynemagnesium bromide, produced by treatment of enyne **2.125** with ethylmagnesium bromide, to the aldehyde **2.86** afforded **2.126** in 80% yield. Upon treating **2.126** with $Pd(PPh_3)_4/Et_2Zn$ using hexane as solvent, the cyclization proceeded smoothly to provide the desired compound **2.127** in 60% yield as a mixture of two diastereomers in a ratio of 4:1 (^{1}H NMR spectrum). As expected, the diene has the desired double bond geometry as verified (Scheme 2.41) by oxidation of **2.127** (mixture of two) to the corresponding enone **2.128** (a single diastereomer). The solvent was found to have a dramatic effect on the cyclization. When the reaction was performed in Et_2O, only 36% of desired compound **2.127** was obtained. The by-products from the reaction, appear pure by TLC, but have a complicated proton NMR spectrum, especially in the olefin region. It is not clear what the reaction pathway for the formation of by-products is.

Unfortunately, hydroboration on the mono-substituted double bond of **2.127** by using 9-BBN at room temperature was unsuccessful. Starting material was recovered back. Other hydroboration conditions, such as using 9-BBN in refluxing THF or

catecholborane/$Rh(PPh_3)_3Cl$, were also unsuccessful. Studies are underway to try other hydroboration conditions in this laboratory.



Scheme 2.40 Approach III to 9, 10-*2H*-15-deoxy-$\Delta^{12,14}$-PGJ_2

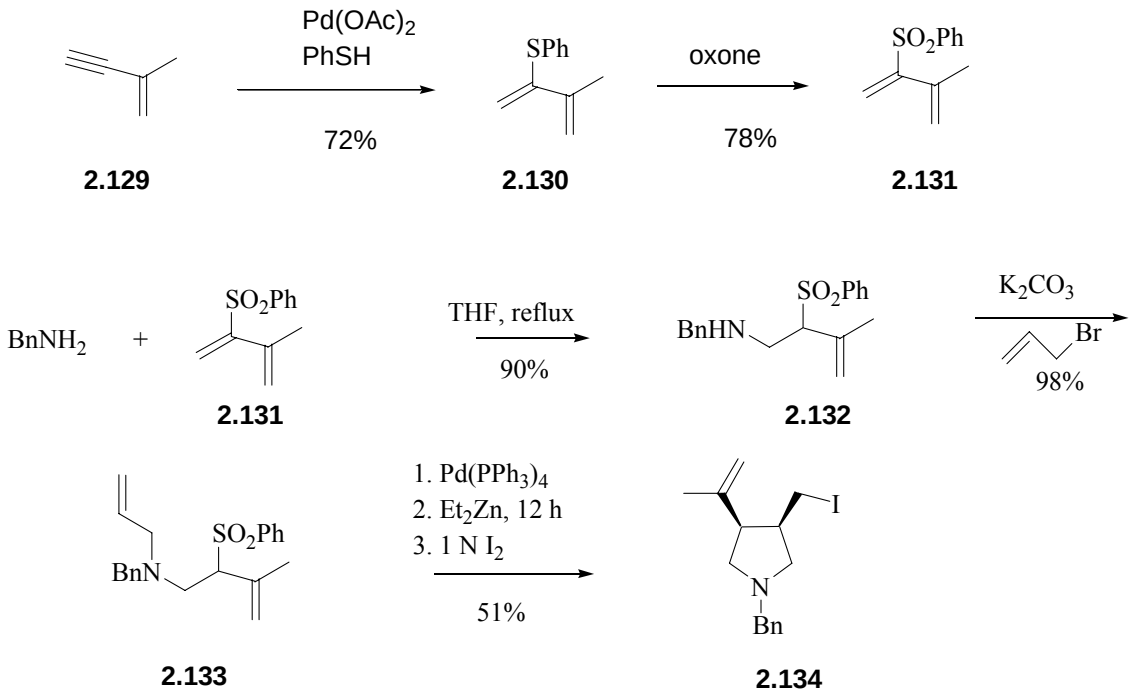


Scheme 2.41 Oxidation to verify the diene geometry

2.2.3. The Use of the Zn-ene Cyclization to Synthesize N-Containing Heterocycles

2.2.3.1. Synthesis of 3,4-di-Substituted Pyrrolidine Derivative

It is known that primary amines add readily to vinyl phenyl sulfones.[111] We envisioned that the addition of primary amine to 2-phenylsulfonyl-3-methyl-1,3-butadiene would be especially valuable because the resulting product is an allyl phenyl sulfone which can be further elaborated to synthesize a precursor for the Zn-ene cyclization. As illustrated in Scheme 2.42, 2-phenylsulfonyl-3-methyl-1,3-butadiene was prepared in two steps by following Bäckvall's protocol.[112] Mixing benzylamine with 2-phenylsulfonyl-3-methyl-1,3-butadiene in THF under reflux condition afforded the desired allyl phenyl sulfone **2.132** in 90% yield. N-alkylation proceeded smoothly by treating **2.132** with allyl bromide in the presence of potassium carbonate to provide **2.133** in 98% yield.[113] When **2.133** was treated with $Pd(PPh_3)_4/Et_2Zn$, the Zn-ene cyclization proceeded smoothly to afford cyclization product **2.134** with high stereoselectivity, (> 40 : 1) as verified by GC in 51% yield.



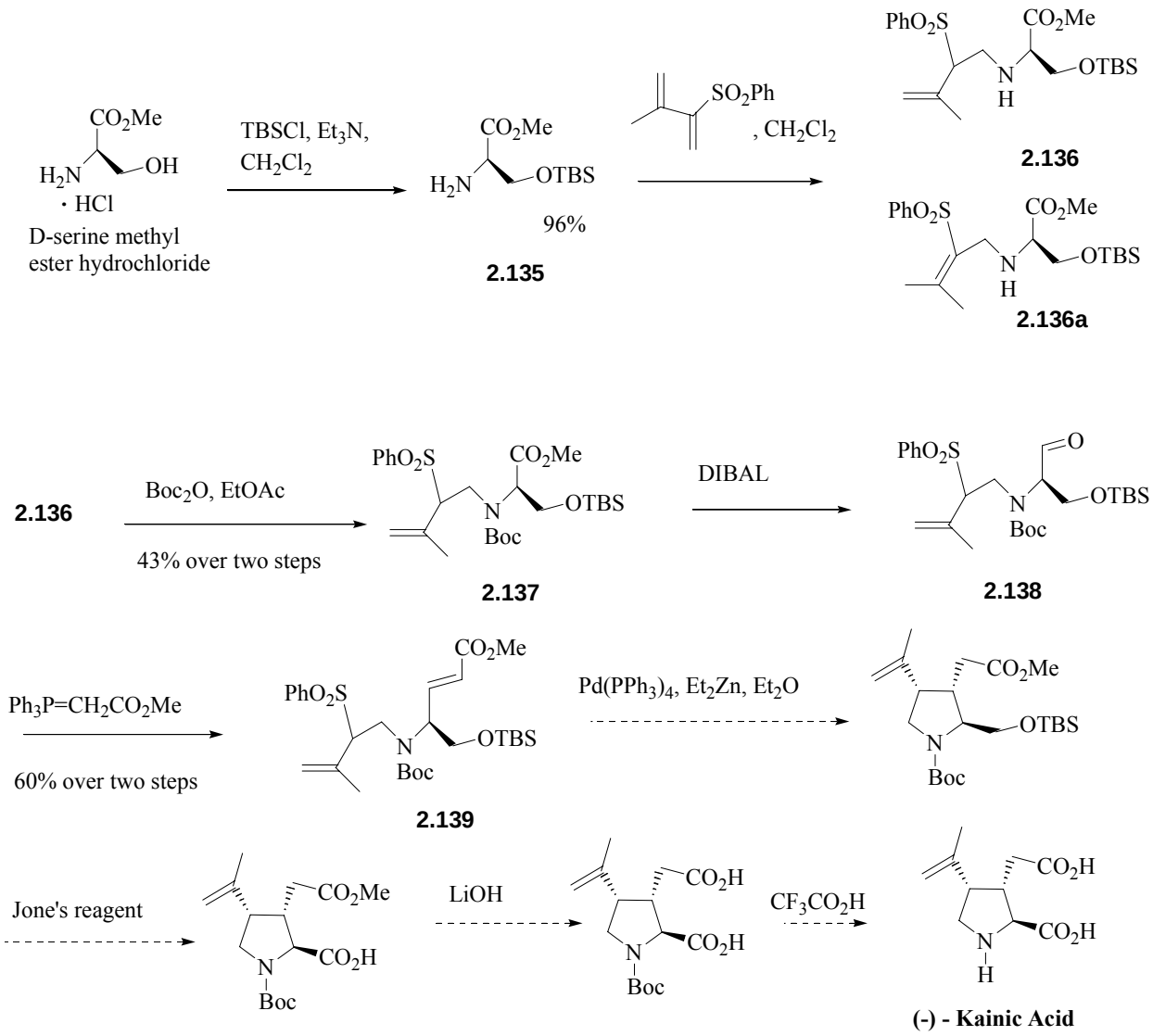
Scheme 2.42 Synthesis of a 3,4-di-substituted pyrrolidine derivative

2.2.3.2. Approach to the total synthesis of (-)-kainic acid

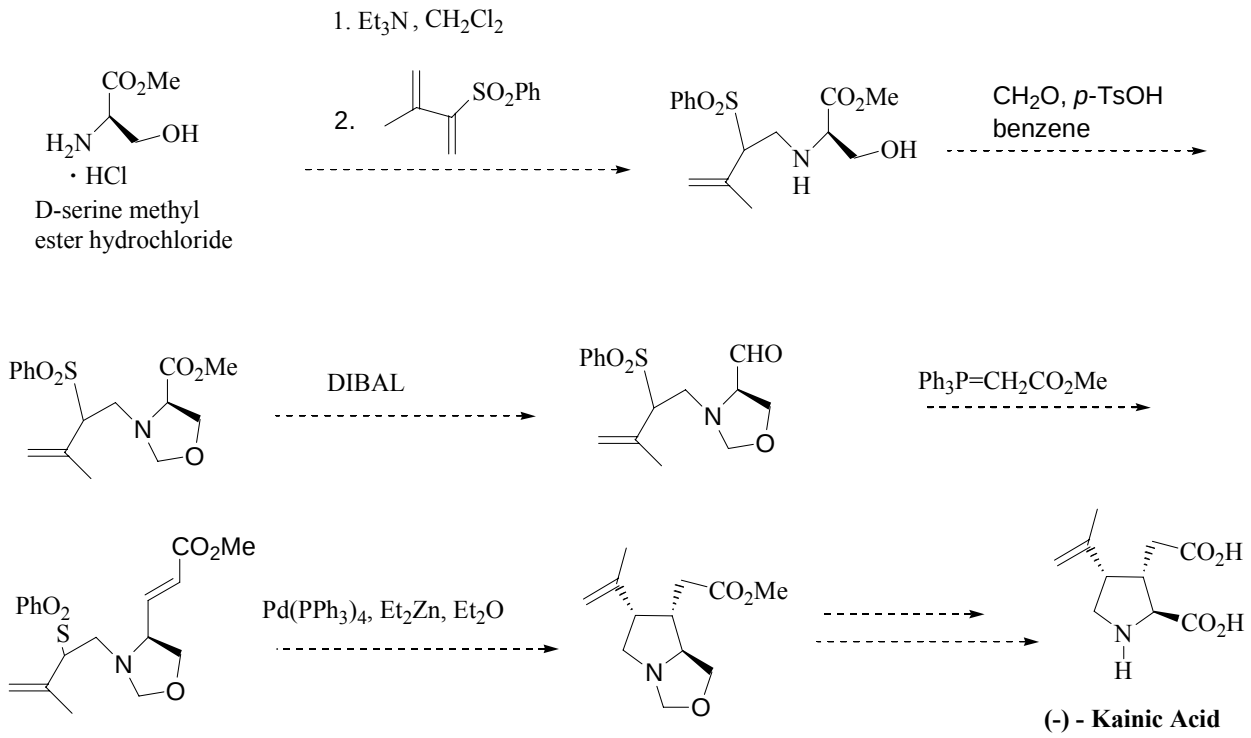
With this result in hand, an approach to the total synthesis of (-)-kainic acid was attempted. (-)-Kainic acid has attracted considerable interest due to its neuroexcitatory activity.[114] Since the supplies of this compound were interrupted in 1999, many total syntheses of this compound have been reported.[115]

Scheme 2.43 shows our approach to the total synthesis of (-)-kainic acid. D-Serine methyl ester hydrochloride was chosen as the starting material because it has the desired stereochemistry at the chiral carbon center. Protection of the free hydroxyl group as the corresponding TBS ether afforded compound **2.135**.[116] Addition of the primary amine to 2-phenylsulfonyl-3-methyl-1,3-butadiene was performed in CH_2Cl_2 at room temperature. Refluxing THF provides no reaction. A mixture of two compounds, **2.136** and **2.136a**, was

obtained. The undesired prototropic isomer **2.136a** could not be separated from the desired compound **2.136** by flash-column chromatography. When the mixture of **2.136** and **2.136a** was treated with $(Boc)_2O$ in EtOAc at room temperature,[117] compound **2.137** was obtained in pure form with an overall yield of 43% over two steps. **2.136a** does not react with $(Boc)_2O$, presumably due to the fact that the resulting Boc protected **2.136a** would be too crowded. DIBAL-H reduction of the methyl ester **2.137** afforded the corresponding aldehyde **2.138** which undergoes Horner reaction to establish the α,β-unsaturated ester **2.139** in 60% yield over two steps.[118] Unfortunately, when **2.139** was treated with $Pd(PPh_3)_4/Et_2Zn$, no cyclization occurs after the mixture was stirred for 12 h at room temperature. Starting material **2.139** (90%) was recovered. Perhaps the Pd(0) can not insert into allyl phenylsulfone **2.139** to form the π-allylpalladium intermediate due to the crowded environment exerted by the adjacent Boc protecting group. Further effort can be focused on screening the Pd(0) source or using a protecting group smaller than Boc. As illustrated in Scheme 2.44, a new approach is proposed which features the formation of an oxazolidine ring to protect the primary hydroxy and the nitrogen at the same time. This protecting group is much smaller than the Boc and hopefully it can lead to the completion of the synthesis of (-)-kainic acid.



Scheme 2.43 Approach to the total synthesis of (-)-kainic acid



Scheme 2.44 An alternative approach to (-)-kainic acid

2.3. Conclusions

Allyl phenyl sulfones have been used as an alternative to traditionally used allyl acetates for Pd-catalyzed Zn-ene cyclizations. Due to the ease of assembly of allyl phenyl sulfones, particularly in a connective fashion, the efficiency of substrates preparation is greatly increased. The total synthesis of sesquiterpene (-)-erythrodiene was achieved in 6 linear steps with an overall yield of 60% using a Zn-ene cyclization as the key step. The synthesis also features the introduction of sulfur into a molecule by a [2,3]-sigmatropic rearrangement of an allyl sulfenate.

The total synthesis of 15-d-$\Delta^{12,14}$-PGJ_2 has been achieved using the same type of cyclization. The late stage installation of conjugated double bond on the cyclopentanone ring

allows as well the total synthesis of 15d-9,10-*2H*-$\Delta^{12,14}$-PGJ_2, an important analogue of 15d-PGJ_2 and a key precursor of 15d-PGJ_2. Two different approaches have been adopted to synthesize 15d-9,10-*2H*-$\Delta^{12,14}$-PGJ_2. The first approach involved the addition of an allylzinc to an internal TMS-substituted alkyne bearing a propargylic TBSO group. Si-I exchange was used to obtain the vinyl iodide with the desired double bond geometry and rearrangement of the intermediate cation was observed thus decreasing the yield. The second approach features the use of a ketal group at the propargylic position during the Zn-ene cyclization. A single diastereomer was obtained probably due to complete isomerization of the vinylzinc intermediate mediated by the ketal group. The ketal group completely shuts down the cation rearrangement pathway that caused by-product formation during the Si-I exchange step in the previous synthesis. Moreover, the ketal protecting group was removed readily by an acid wash after the Wittig reaction without the need of an additional deprotection step. The third approach to 15d-9,10-*2H*-$\Delta^{12,14}$-PGJ_2 is under investigation now and it takes advantage of the vinylzinc isomerization which was a disadvantage in approaches I and II. Preliminary results show that the addition of allylic zinc to the internal enyne does afford the desired diene side chain successfully. The solvent was found to have a dramatic effect on the cyclization and hexane has been the best choice so far. If the recalcitrant hydroboration step is successful, this approach holds promise as a very efficient synthesis of the natural product.

A disubstituted pyrrolidine has been produced with high stereoselectivity and moderate yield. The synthesis features the addition of a primary amine to 2-phenylsulfonyl-3-methyl-1,3-butadiene followed by N-allyllation to afford the substrate for Pd-catalyzed Zn-ene cyclization. The total synthesis of (-)-kainic acid is proposed and initial studies have been performed. However, the Boc protected amine may prevent the Pd(0) insertion so the key Zn-ene reaction

could not proceed. Investigations are under way in this laboratory to develop suitable conditions for the Zn-ene cyclization in these cases.

2.4. Experimental

General Experimental Procedures. All reactions were performed under an argon atmosphere in oven-dried (110 ºC) flasks and standard precautions against moisture were taken. A Dry Ice/acetone bath was used to obtain a temperature of –78 °C. An ice bath was used to obtain 0 °C. Silica gel 60 (40-60 μm, Sorbent Technologies) was used for flash column chromatography. Thin-layer chromatography was performed on glass supported 250-μm silica GF plates (Analtech). Visualization of TLC plates was accomplished with one or more of the following: 254 nm UV light; 7% phosphomolybdic acid in ethanol; 5% anisaldehyde in ethanol containing 5% sulfuric acid and a trace amount of acetic acid. Anhydrous magnesium sulfate was used as the drying reagent.

Instrumentation. Most ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX-300 spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C at 22 ºC unless otherwise noted. Some ^{1}H and ^{13}C NMR spectra and two-dimensional NMR spectra were recorded on a Bruker AM-500 spectrometer. Chemical shift data are reported in units of δ (ppm) using $CHCl_3$ as the internal standard: δ = 7.27 for ^{1}H NMR spectra and δ = 77.09 for ^{13}C NMR spectra unless indicated otherwise. Multiplicities are given as s (singlet), d (double), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants, *J*, are reported in Hz. Infrared spectra were recorded on an IR/32 FT-IR spectrometer and are reported in wave numbers (cm^{-1}). Low and

high-resolution mass spectra were recorded on a VG-70SE mass spectrometer in EI mode at 70 eV. Gas chromatographic mass spectra (GC-MS) analyses were performed on a Hewlett Packard 5890 Series II gas chromatograph equipped with a 5970 mass selective detector.

Materials. Commercial solvents and reagents were used as received with the following exceptions. Tetrahydrofuran (THF) and diethyl ether were distilled over sodium benzophenone ketyl. Methylene chloride and CH_3CN were distilled over CaH_2. Benzene was dried over melting sodium.

2-Phenylthiocyclohexanone (2.73)

To a stirred solution of THF (5 mL) at –78 ˚C was added LDA (1.1 mL, 2.2 mmol, 2 M solution in THF) followed by the addition of cyclohexanone (196 mg, 2.00 mmol) in 2 mL of THF. The resulting mixture was stirred at –78 ˚C for half an hour before the reaction mixture was raised to 0 ˚C. After the mixture had been stirred at 0 ˚C for 10 min, the temperature was cooled to –78 ˚C. $PhSSO_2Ph$ (600 mg, 2.40 mmol) in 5 mL of THF was added dropwise into the reaction mixture. The mixture was stirred for 2 h further at this temperature before 10 mL of saturated $NaHCO_3$ was added. The resulting mixture was extracted with Et_2O (15 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford 380 mg of **2.73** (92% yield). ^{1}H NMR ($CDCl_3$) δ 7.43-7.27 (m, 5 H), 3.85 (t, 1 H, J = 5.2 Hz), 2.90 (m, 1 H), 2.32-2.21 (m, 2 H), 2.15-2.00 (m, 1 H), 2.00-1.75 (m, 3 H), 1.72-1.60 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 207.7, 134.0, 132.0, 129.1, 127.5, 56.6, 39.2, 34.1, 27.5, 22.8.

1-(Phenylthio)-2-(methylene)cyclohexane (2.74)

A mixture of methyltriphenylphosphonium bromide (2.68 g, 7.50 mmol) and potassium *t*-butoxide (842 mg, 7.50 mmol) was placed in a three-neck flask (100 mL) which was equipped with a stirring bar, a reflux condenser. THF (40 mL) was added and the resulting mixture was stirred at r.t. for 1 h before the dropwise addition of 2-(phenylthio)-cyclohexanone (1.0 g, 5.0 mmol) in 5 mL of THF via syringe. The reaction mixture was heated to reflux for 2 h. After the reaction mixture was cooled to room temperature (22 ºC), the solution was concentrated in vacuo. Hexane was used to take the residue in the flask onto a silica gel column which was then eluted with hexane to give 949 mg of **2.74** (93% yield). ^{1}H NMR ($CDCl_3$) δ 7.40-7.00 (m, 5 H), 4.67 (s, 2 H), 3.87 (t, 1 H, J = 4.6 Hz), 2.52 (m, 1 H), 2.10 (m, 1 H), 2.00-1.40 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 147.8, 132.1, 128.8, 126.9, 109.7, 53.1, 33.6, 32.1, 28.1, 22.9.

1-(Benzenesulfonyl)-2-(methelene)cyclohexane (2.75)

To a stirred solution of **2.74** (204 mg, 1.00 mmol) in 5 mL of CH_2Cl_2 at 0 ˚C was added *m*-CPBA (542 mg, 2.20 mmol) in 5 mL of CH_2Cl_2 in dropwise fashion via dropping pipet. The resulting mixture was stirred at 0 ˚C for 1 h before the addition of 10 mL of saturated $NaHCO_3$. The reaction mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The resulting residue was purified by flash-column chromatography to afford 214 mg of **2.75** (91% yield). IR (neat) 3127 (br), 2951, 2925, 2859, 1401, 922. ^{1}H NMR ($CDCl_3$) δ 7.83-7.47 (m, 5 H), 4.88 (s, 1 H), 4.37 (s, 1 H), 3.65 (m, 1 H), 2.70-2.57 (m, 2 H), 2.22 (m, 1 H), 2.04-1.98 (m, 1 H), 1.87 (m 1 H), 1.80-1.58 (m, 2 H), 1.35-1.27(m, 1 H); ^{13}C NMR ($CDCl_3$) δ 140.4, 137.9, 133.5, 129.0, 128.8, 117.8,

68.2, 31.8, 26.8, 26.1, 21.4; MS (EI) *m*/*z* (relative intensity) 236 (M^+, 1.6), 143 (11), 95 (100), 77 (40), 67 (45), 55 (26). HRMS (EI) calcd for $C_{13}H_{16}O_2S$ (M^+): 236.0871, found 236.0870.

(2-Methylene-1-pent-4-enyl-cyclohexanesulfonyl)-benzene (2.76)

To a stirred solution of **2.75** (930 mg, 3.94 mmol) in THF (30 mL) at -78 ˚C was added *n*-BuLi (2.7 mL, 4.3 mmol, 1.6 M solution in hexane). The resulting mixture was stirred at – 78 ˚C for 1 h before neat 1-iodo-4-pentene (3.0 mL, 23.6 mmol) was added. After the resulting mixture was stirred at -78 ˚C for 3 h, the temperature was slowly warmed to -30 ˚C during a 0.5 h period and stirring at -30 ˚C was continued for an additional 0.5 h. Saturated $NaHCO_3$ (20 mL) was added to quench the reaction. The resulting mixture was extracted with Et_2O (40 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford **2.76** (1.011 g) in 84% yield. IR (neat) 3071, 2938, 2857, 1639, 1629, 1446, 1297, 1136, 1075, 912, 718, 691. ^{1}H NMR ($CDCl_3$) δ 7.74-7.39 (m, 5 H), 5.62 (m, 1 H), 5.11 (s, 1 H), 4.92-4.83 (m, 2 H), 4.48 (s, 1 H), 2.78 (m, 1 H), 2.37-2.23 (m, 2 H), 2.16-1.74 (m, 5 H), 1.68-1.55 (m, 4 H), 1.40-1.17 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 141.1, 137.9, 135.2, 133.5, 130.8, 128.2, 118.3, 115.3, 70.5, 34.2, 33.8, 33.7, 29.3, 25.7, 22.8, 22.2; MS (EI) *m*/*z* (relative intensity) 304 (M^+, 1), 266 (1), 163 (57), 121 (50), 109 (47), 95 (72), 81 (100), 67 (79), 55 (46). HRMS (EI) calcd for $C_{18}H_{24}O_2S$ (M^+): 304.1497, found 304.1503.

1-(Iodomethyl)-6-(methylene)spiro[4.5]decane (2.77)

To a stirred solution of **2.76** (113 mg, 0.37 mmol) in Et_2O (10 mL) at room temperature were added $Pd(PPh_3)_4$ (21 mg, 0.018 mmol). The resulting solution was stirred for 5 min before

Et_2Zn (2.2 mL, 2.2 mmol, 1.0 M solution in hexane) was added. The resulting mixture was stirred for 18 h at room temperature before it was cooled to 0 ºC and the reaction was quenched with I_2 (1.2 g, 4.7 mmol) in 5 mL of THF. After the resulting mixture was stirred at room temperature for 30 min, it was extracted with Et_2O (15 mL × 3). The combined organic layer, after being washed with 20% $Na_2S_2O_3$ (10 mL) and brine (10 mL), was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford 103 mg of **2.77** (96% yield). IR (neat) 3081, 2931, 2855, 1638, 1445, 1183, 895. ^{1}H NMR ($CDCl_3$) δ 4.79 (s, 1 H), 4.63 (s, 1 H), 3.16 (ddd, 1 H, J = 9.6, 2.8, 1.6 Hz), 2.70 (dd, 1 H, J = 12.5, 9.6 Hz), 2.52 (m, 1 H), 2.28 (m, 1 H), 2.30-1.90 (m, 2 H), 1.90-1.48 (m, 5 H), 1.39-1.20 (m, 3 H), 1.12-1.02 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 152.2, 108.2, 53.9, 45.6, 38.2, 35.5, 33.8, 29.6, 28.8, 22.7, 19.7, 14.2; MS (EI) *m*/*z* (relative intensity) 290 (M^+, 18), 163 (100), 121 (71), 109 (63), 95 (85), 81 (87), 67 (62), 55 (37). HRMS (EI) calcd for $C_{12}H_{19}I$ (M^+): 290.0532, found 290.0533.

(5*S*)-5-isopropyl-2-methylene-1-phenylsulfonylcyclohexane (2.81)

To a solution of allylic alcohol **2.79** (371 mg, 2.41 mmol) in Et_3N (1.34 mL, 9.6 mmol) was added a solution of benzenesulfenyl chloride (12 mL, 3.13 mmol, 0.26 M solution in benzne). The resulting solution was stirred at room temperature for 15 min, then diluted with water, and extracted with ether (30 mL × 3). The combined organic layer, after being washed with saturated NH_4Cl and brine, was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford 560 mg of allylic phenylsulfoxide **2.80** (89% yield).

To the above phenylsulfoxide **2.80** (560 mg, 2.1 mmol) in 10 mL of Et_2O at -20 ˚C was added *m*-CPBA (580 mg, 2.3 mmol). After the resulting mixture was stirred at -20 ˚C for 1 h, Sat. $NaHCO_3$ (10 mL) was added to quench the reaction. The resulting mixture was extracted with Et_2O (20 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford **2.81** (501 mg) in 86% yield as two diastereomers with a ratio of 12.5:1. Spectra of major diasteomer: IR (neat) 3067, 2956, 2871, 1446, 1305, 1142, 1084. ^{1}H NMR ($CDCl_3$) δ 7.91-7.31 (m, 5 H), 4.97 (s, 1 H), 4.44 (s, 1 H), 2.78 (m, 1 H), 3.77 (m, 1 H), 2.82-2.70 (m, 1 H), 2.63-2.57 (m, 1 H), 2.10-1.90 (m, 2 H), 1.54-1.42 (m, 2 H), 0.96 (d, 3 H, J = 3.5 Hz), 0.93 (d, 3 H, J = 3.5 Hz); ^{13}C NMR ($CDCl_3$) δ 140.4, 137.9, 133.0, 129.0, 128.8, 117.8, 68.8, 37.8, 32.6, 31.8, 29.8, 29.4, 19.8, 19.5; MS (EI) *m*/*z* (relative intensity) 278 (M^+, 4), 137 (83), 95 (72), 81 (100), 67 (36), 55 (32). HRMS (EI) calcd for $C_{16}H_{22}O_2S$ (M^+): 278.1341, found 278.1342.

(5*S*)-5-isopropyl-2-methylene-1-(4-pentyl)-1-phenylsulfonylcyclohexane (2.82)

To a stirred solution of **2.81** (454 mg, 1.63 mmol) in THF (20 mL) at -78 ˚C was added *n*-BuLi (1.1 mL, 1.8 mmol, 1.6 M solution in hexane). The resulting mixture was stirred at – 78 ˚C for 1 h before neat 1-iodo-4-pentene (1.2 mL, 9.8 mmol) was added. After the resulting mixture was stirred at -78 ˚C for 3 h, the temperature was slowly raised to -30 ˚C during a 0.5 h period and stirring at -30 ˚C was continued for an additional 0.5 h. Sat. $NaHCO_3$ (20 mL) was added to quench the reaction. The reaction mixture was extracted with Et_2O (30 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford 501 mg of **2.82** (89% yield) as two diatereomers in a ratio of 4:1. Spectra of major diatereomer: IR (neat) 3071, 2955, 2871,

1639, 1446, 1298, 1140, 1082, 910, 721, 691. ^{1}H NMR ($CDCl_3$) δ 7.83-7.49 (m, 5 H), 5.75 (m, 1 H), 5.18 (s, 1 H), 5.02-4.96 (m, 2 H), 2.22 (m, 1 H), 2.10-1.95 (m, 5 H), 1.82-1.73 (m, 2 H), 1.64-1.57 (m, 3 H), 1.45 (m, 1 H), 1.31-1.25 (m, 2 H), 0.86 (d, 3 H, J = 2.5 Hz), 0.84 (d, 3 H, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 142.6, 138.1, 135.7, 133.5, 131.2, 128.3, 116.8, 115.3, 70.9, 37.3, 34.3, 34.0, 32.9, 31.7, 26.7, 23.6, 19.8, 19.4; MS (EI) *m*/*z* (relative intensity) 346 (M^+, 0.1), 278 (0.2), 221 (0.5), 205 (51), 163 (17), 149 (83), 135 (62), 123 (73), 109 (97), 95 (99), 81 (100), 67 (85), 55 (46). HRMS (EI) calcd for $C_{21}H_{30}O_2S$ (M^+): 346.1967, found 346.1956.

(1*S*), (9*S*)-1-Iodomethyl-9-isopropyl-6-methylene-spiro[4.5]decane (2.83)

To a stirred solution of **2.82** (101 mg, 0.29 mmol) in Et_2O (10 mL) at room temperature were added $Pd(PPh_3)_4$ (17 mg, 0.015 mmol). The resulting solution was stirred for 5 min before Et_2Zn (1.7 mL, 1.7 mmol, 1.0 M solution in hexane) was added. The mixture was stirred for 27 h at room temperature before it was cooled to 0 ºC and quenched with I_2 (900 mg, 3.5 mmol) in 5 mL of THF. After the resulting mixture was stirred at room temperature for 30 min, it was extracted with Et_2O (15 mL × 3). The combined organic layer, after being washed with 20% $Na_2S_2O_3$ (15 mL) and brine (15 mL), was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford 89 mg of **2.83** (92% yield) as two diastereomers in a ratio of 95 : 5. Major diastereomer: IR (neat) 3080, 2955, 2872, 1640, 1443, 1184, 894. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80(s, 1 H), 4.65 (s, 1 H), 3.16 (ddd, 1 H, J = 9.7, 2.7, 1.7 Hz), 2.70 (dd, 1 H, J = 12.5, 9.7 Hz), 2.51 (m, 1 H), 2.33 (dt, 1 H, J = 13.0, 3.8 Hz), 2.03-1.90 (m, 3 H), 1.88-1.71 (m, 4 H), 1.43-1.35 (m, 3 H), 1.28-1.20 (m, 1 H), 1.04 (m, 1 H), 0.88 (d, 3 H, J = 6.1 Hz), 0.87 (d, 3 H, J = 6.0 Hz), 0.82 (t, 1 H, J = 12.4 Hz); ^{13}C NMR ($CDCl_3$) δ 152.2, 107.9, 53.8, 46.1, 41.8, 39.8, 35.3, 33.6, 32.6, 31.6, 29.5, 20.2,

19.8, 19.7, 14.3; MS (EI) *m*/*z* (relative intensity) 332 (M^+, 7), 205 (75), 149 (88), 135 (65), 123 (73), 109 (97), 95 (98), 81 (100), 67 (82), 55 (64). HRMS (EI) calcd for $C_{15}H_{25}I$ (M^+): 332.1001, found 332.1004.

(-)-Erythrodiene

To a stirred solution of iodide **2.83** (57 mg, 0.17 mmol) in dry DMSO (2 mL) was added KO-*t*Bu (116 mg, 1.0 mmol). Anhydrous Et_2O (1 mL) was added to generate a homogeneous solution. After the reaction mixture was stirred at room temperature for 30 min, saturated NH_4Cl (5 mL) was added to quench the reaction. The resulting mixture was extracted with pentane (10 mL × 3). The combined pentane layer was dried over $MgSO_4$, filtered through cotton and evaporated in cold to give (-)-erythrodiene (33 mg) in 95% yield as a 95:5 diastereomeric mixture. IR (neat) 2956, 2931, 2871, 1637, 1443, 891. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.98(s, 1 H), 4.87 (s, 1 H), 4.77 (s, 1 H), 4.75 (s, 1 H), 2.50-2.33 (m, 3 H), 2.28 (dt, 1 H, J = 13.6, 4.0 Hz), 2.10 (dt, 1 H, J = 12.3, 7.1 Hz), 1.84-1.76 (m, 2 H), 1.70 (quint, 2 H, J = 7.4 Hz), 1.61-1.38 (m, 4 H), 0.88 (d, 3 H, J = 6.7 Hz), 0.86 (d, 3 H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 158.0, 152.8, 106.7, 105.9, 51.2, 41.1, 39.65, 39.60, 33.8, 33.0, 32.5, 31.0, 20.7, 20.0, 19.6; MS (EI) *m*/*z* (relative intensity) 332 (M^+, 7), 205 (75), 149 (88), 135 (65), 123 (73), 109 (97), 95 (98), 81 (100), 67 (82), 55 (64). HRMS (EI) calcd for $C_{15}H_{24}$ (M^+): 204.1878, found 204.1868.

4-(Benzenesulfonyl)hex-5-en-1-ol (2.85)

To a stirred solution of allyl phenyl sulfone **2.84** (2.574 g, 14.14 mmol) in 60 mL of THF at –78 ºC was added *s*-BuLi (11.1 mL, 15.5 mmol, 1.4 M solution in cyclohexane). The resulting red solution was stirred at –78 ºC for 1 h followed by the addition of oxetane (21.2 mmol, 1.38

mL). Then $BF_3.Et_2O$ (21.2 mmol, 2.70 mL) was added in a dropwise fashion via a syringe. The resulting mixture was stirred at -78 ºC for 30 min before the addition of 60 mL of saturated aqueous NH_4Cl. The reaction mixture was exacted with Et_2O (50 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by column chromatography to give 3.17 g of alcohol **2.85** (93% yield) as a pale yellow oil. IR (neat) 3516, 2937, 2874, 1447, 1304, 1289, 1146, 1085, 727, 690, 634. ^{1}H NMR ($CDCl_3$) δ7.83-7.27 (m, 5 H), 5.58 (m, 1 H), 5.28 (d, J = 10.2 Hz), 5.03 (d, J = 17.0 Hz), 3.70-3.50 (m, 3 H), 2.25-2.05 (m, 2 H, including the OH hydrogen), 1.75-1.35 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 137.2, 133.8, 130.3, 129.3, 128.9, 124.0, 69.8, 62.0, 29.5, 23.7; MS (EI) *m*/*z* (relative intensity) 241 (M^++1, 8), 223 (4), 210 (9), 169 (49), 143 (18), 125 (9), 99 (50), 81 (100), 77 (31), 67 (17). HRMS (EI) calcd for $C_{12}H_{17}O_3S$ (M^++1): 241.0898, found 241.0908.

4-Benzenesulfonyl-hex-5-enal (2.86)

To a solution of oxalyl chloride (1.4 mL, 15.4 mmol) at –60 ºC in dichloromethane (60 mL) was added dimethylsulfoxide (2.20 mL, 30.8 mmol) and the temperature was carefully maintained below -50 ºC. After the reaction mixture was stirred for 5 min, a solution of alcohol **2.85** (2.84 g, 11.8 mmol) in CH_2Cl_2 (10 mL) was added. After the reaction temperature was raised from -50 ºC to -30 ºC during a 15 min period, Et_3N (8.4 mL, 60 mmol) was added and the reaction mixture was stirred for another 5 min at -30 ºC before it was warmed to room temperature. After the addition of 50 mL of water, the aqueous phase was extracted with dichloromethane (30 mL × 3). The combined organic layer, after being washed sequentially with 1% HCl (20 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by column

chromatography (25% ethyl acetate in hexane) to give 2.55 g aldehyde **2.86** (90% yield) as a yellow oil. IR (neat) 3066, 2936, 2832, 2730, 1723, 1447, 1305, 1147, 1085, 940, 722, 690, 634. ^{1}H NMR ($CDCl_3$) δ 9.67 (s, 1 H), 7.79-7.46 (m, 5 H), 5.54 (m, 1 H), 5.26 (d, J = 10.2 Hz), 5.00 (dd, J = 17.0 Hz), 3.55 (m, 1 H), 2.59-2.49 (m, 2 H), 2.39-2.32 (m, 1 H), 1.95-1.88 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 200.5, 137.1, 134.0, 129.6, 129.2, 129.0, 124.5, 68.6, 40.4, 20.0; MS (EI) *m*/*z* (relative intensity) 239 (M^++1, 17), 210 (14), 195 (21), 143 (15), 125 (15), 97 (100), 79 (57), 69 (53). HRMS (EI) calcd for $C_{12}H_{15}O_3S$ (M^++1): 239.0742, found 239.0743.

6-Benzenesulfonyl-1-trimethylsilanyl-oct-7-en-1-yn-3-ol (2.87)

Trimethylsilylacetylene (22.8 mmol, 2.23 g) in THF (30 ml) at – 78 ºC was treated with EtMgBr (21 mmol, 21 mL, 1.0 M solution THF). The cooling bath was removed and the solution was allowed to warm to room temperature. After the reaction mixture was heated at reflux for 2 h, it was cooled to room temperature. In a separate flask, a solution of aldehyde **2.86** (2.50 g, 10.5 mmol) in THF (40 mL) at – 78 ºC under argon with magnetic stirring was treated with $Me_3SiC{\equiv}CMgBr$ (40 mL of the solution prepared above). The solution was stirred at – 78 ºC for 30 min and was then allowed to warm to – 20 ºC during a 1 h period before the addition of 100 mL of saturated aqueous NH_4Cl. The reaction mixture was extracted with Et_2O (150 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by column chromatography to give 2.76 g of **2.87** (78% yield) as two diastereomers with a ratio of 1: 1 according to C^{13} NMR. IR (neat) 3491, 3067, 2960, 1447, 1305, 1250, 1146, 1084, 844. ^{1}H NMR ($CDCl_3$) δ 7.82-7.46 (m, 5 H), 5.58 (m, 1 H), 5.29 (d, J = 10.1 Hz), 5.06 (d, J = 17.0 Hz), 4.34 (m, 1 H), 3.59 (m, 1 H), 2.41 (b, 1 H), 2.25 (m, 1 H), 1.90-1.60 (m, 3 H), 0.12 (s, 9 H); ^{13}C NMR ($CDCl_3$) some of the peaks of another

isomer was shown in brackets. δ 137.2, 133.8, 130.0, 129.3, 128.9, 124.2, 106.05 (105.96), 90.12 (90.05), 69.4, 62.15 (61.98), 34.3, 23.12 (22.92), -0.059; MS (EI) *m*/*z* (relative intensity) 321 (M^+-CH_3, 9), 281 (7), 253 (11), 239 (8), 135 (13), 97 (20), 84 (100), 73 (34), 58 (37). HRMS (EI) calcd for $C_{16}H_{21}O_3SiS$ (M^+-CH_3): 321.0981, found 321.0980.

6-Benzenesulfonyl-3-(*t*-Butyl-dimethyl-silanyloxy)-1-trimethylsilanyl-oct-7-en-1-yne (2.88)

To a solution of **2.87** (3.73 g, 11.1 mmol) in DMF (50 mL) was added TBSCl (2.5 g, 16.5 mmol) followed by imidazole (1.51 g, 22.2 mmol). The mixture was stirred for 12 h and then diluted with brine (30 mL). The resulting mixture was extracted with diethyl ether (70 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography on silica gel (15% ethyl acetate in hexane) to give 4.90 g (98%) of **2.88** as a yellow oil. IR (neat) 3067, 2957, 2929, 2897, 2857, 2172, 1447, 1307, 1251, 1149, 1080, 842, 779, 723. ^{1}H NMR ($CDCl_3$) δ 7.84-7.50 (m, 5 H), 5.61 (m, 1 H), 5.33 (m, 1 H), 5.10 (m, 1 H), 4.31 (m, 1 H), 3.57 (m, 1 H), 2.20 (m, 1 H), 1.90-1.50 (m, 3 H), 0.86 (s, 9 H), 0.13 (s, 9 H), 0.07 (S, 3 H), 0.009 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 137.4, 133.7, 130.1, 129.4, 128.9, 124.1, 106.9, 89.4, 69.5, 62.8, 35.2, 25.9, 23.2, 18.3, - 0.10, - 4.3, - 4.8; MS (EI) *m*/*z* (relative intensity) 393 (M^+-C_4H_9, 39), 309 (30), 289 (11), 199 (10), 135 (100), 73 (67), 59 (96). HRMS (EI) calcd for $C_{19}H_{29}O_3Si_2S$ (M^+-C_4H_9): 393.1376, found 393.1377.

Cyclization reactions

(I) Saturated aqueous NH_4Cl quenched reaction: compounds 2.90, 2.91, 2.92.

To a solution of **2.88** (2.26 g, 5.01 mmol) in Et_2O (50 mL) at room temperature was added $Pd(PPh_3)_4$ (290 mg, 0.250 mmol). The resulting solution was stirred for 5 min before Et_2Zn (23 mL, 25 mmol, 1.1 M solution in toluene) was added. The mixture was stirred for 12 h at room temperature before it was cooled to 0 ºC and the reaction mixture was quenched with 25 mL of saturated NH_4Cl solution. The resulting mixture was extracted with ether (50 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (3% ethyl acetate in hexane) to afford **2.90**, **2.91** and **2.92**, respectively, as colorless liquids.

(1R*,3R*)-1-(*tert*-Butyl-dimethyl-silanyloxy)-2-*trans*-trimethylsilanylmethylene-3-vinyl-cyclopentane (2.90)

1.006 g, 64.4% yield.

IR (neat) 2956, 2929, 2895, 2857, 1247, 1066, 835, 774. ^{1}H NMR ($CDCl_3$) δ 5.88 (m, 1 H), 5.63 (s, 1 H), 4.98 (m, 2 H), 4.26 (m, 1 H), 3.21 (m, 1 H), 1.90 – 1.50 (m, 4 H), 0.91 (s, 9 H), 0.09 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 163.9, 143.0, 123.5, 114.0, 78.7, 44.6, 33.0, 29.7, 26.0, 18.3, -0.03, -4.3, -4.4; MS (EI) *m*/*z* (relative intensity) 310 (M^+, 7), 253 (42), 237 (45), 195 (21), 165 (41), 147 (85), 133 (56), 73 (100), 59 (39). HRMS (EI) calcd for $C_{17}H_{34}OSi_2$ (M^+): 310.2148, found 310.2147.

(1R*,3S*)-1-(*tert*-Butyl-dimethyl-silanyloxy)-2-*trans*-trimethylsilanylmethylene-3-vinyl-cyclopentane (2.91)

287 mg, 18.5% yield.

IR (neat) 2956, 2930, 2896, 2858, 1632, 1248, 1149, 836, 775. ^{1}H NMR ($CDCl_3$) δ 5.77 (m, 1 H), 5.65 (s, 1 H), 4.97 (m, 2 H), 4.34 (m, 1 H), 3.30 (m, 1 H), 1.90 – 1.70 (m, 3 H), 1.55 (m, 1 H), 0.90 (s, 9 H), 0.14 (s, 9 H), 0.133 (s, 3 H), 0.126 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 163.3, 142.7, 120.4, 113.3, 76.1, 44.1, 33.4, 27.9, 26.1, 18.5, 0.10, -4.5, -4.6; MS (EI) *m*/*z* (relative intensity) 310 (M^+, 10), 253 (50), 237 (53), 195 (34), 147 (55), 133 (59), 73 (100), 59 (38). HRMS (EI) calcd for $C_{17}H_{34}OSi_2$ (M^+): 310.2148, found 310.2155.

(1R*,3R*)-1-(*tert*-Butyl-dimethyl-silanyloxy)-2-*cis*-trimethylsilanylmethylene-3-vinyl-cyclopentane (2.92)

149 mg, 9.6%

IR (neat) 2956, 2930, 2896, 2858, 1630, 1248, 1072, 860, 773. ^{1}H NMR ($CDCl_3$) δ 5.78 (m, 1 H), 5.44 (s, 1 H), 4.96 (m, 2 H), 4.61 (m, 1 H), 2.93 (m, 1 H), 1.90 – 1.70 (m, 3 H), 1.55 (m, 1 H), 0.90 (s, 9 H), 0.14 (s, 9 H), 0.133 (s, 3 H), 0.126 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.5, 143.5, 125.0, 113.5, 74.0, 51.3, 35.5, 29.3, 26.1, 18.2, 0.37, -3.3, -3.8; MS (EI) *m*/*z* (relative intensity) 310 (M^+, 3.7), 253 (40), 195 (36), 147 (80), 133 (83), 73 (100), 59 (34). HRMS (EI) calcd for $C_{17}H_{34}OSi_2$ (M^+): 310.2148, found 310.2138.

(II) I_2 quenched reaction: compounds 2.93, 2.94, 2.95.

To a solution of **2.88** (2.83 g, 6.28 mmol) in Et_2O (60 mL) at room temperature was added $Pd(PPh_3)_4$ (363 mg, 0.314 mmol). The resulting solution was stirred for 5 min before Et_2Zn (28.5 mL, 31.4 mmol, 1.10 M solution in toluene) was added. The mixture was stirred for

12 h and then I_2 (16 g, 63.0 mmol) in 30 mL of THF was added. The resulting purple mixture was stirred for 30 min before the addition of 25 mL of saturated $Na_2S_2O_3$ solution. The aqueous phase was extracted with ether (50 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (3% ethyl acetate in hexane) to give **2.93**, **2.94** and **2.95**, respectively, as pale yellow oils.

(1R*,3R*)-1-(*tert*-Butyl-dimethyl-silanyloxy)-2-*cis*-(ido-trimethylsilanyl-methylene)-3-vinyl-cycopentane (2.93)

The medium polar product among the three products, 1.733 g, 63.3%

IR (neat) 2955, 2929, 2896, 2856, 1250, 1076, 838, 775. ^{1}H NMR ($CDCl_3$) δ 5.85 (ddd, 1 H, J = 17.1, 10.3, 5.7 Hz), 5.04 (m, 2 H), 4.63 (m, 1 H), 3.40 (m, 1 H), 2.00-1.40 (m, 4 H), 0.90 (s, 9 H), 0.26 (s, 9 H), 0.23 (s, 3 H), 0.12 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 163.4, 141.5, 115.0, 108.2, 83.4, 47.1, 33.8, 31.6, 26.1, 18.1, 1.1, -3.6; MS (EI) *m*/*z* (relative intensity) 421 (M^+-CH_3, 1.1), 379 (52), 309 (13), 259 (21), 179 (46), 147 (20), 105 (25), 73 (100), 59 (24). HRMS (EI) calcd for $C_{16}H_{30}OSi_2I$ (M^+-CH_3): 421.0880, found 421.0888.

(1R*,3S*)-1-(*tert*-Butyl-dimethyl-silanyloxy)-2-*cis*-(ido-trimethylsilanyl-methylene)-3-vinyl-cycopentane (2.94)

The most polar product among the three products, 431 mg, 15.7%

IR (neat) 2955, 2928, 2896, 2856, 1249, 836. ^{1}H NMR ($CDCl_3$) δ 5.79 (ddd, 1 H, J = 17.2, 10.3, 4.8 Hz), 5.06 (dt, 1 H, J = 10.3, 1.7 Hz), 5.10 (dt, 1 H, J = 17.2, 1.7 Hz), 4.69 (m, 1 H), 3.54 (m, 1 H), 2.31 (m, 1 H), 1.80 - 1.60 (m, 3 H), 0.93 (s, 9 H), 0.26 (s, 9 H), 0.25 (s, 3 H), 0.17 (s, 3 H);

^{13}C NMR ($CDCl_3$) δ 163.4, 141.9, 114.9, 110.2, 83.3, 46.7, 32.6, 26.4, 18.5, 0.71, -3.3, -3.6; MS (EI) *m*/*z* (relative intensity) 421 (M^+-CH_3, 1.2), 379 (85), 310 (29), 259 (24), 241 (27), 179 (63), 147 (17), 105 (20), 73 (100), 59 (24). HRMS (EI) calcd for $C_{16}H_{30}OSi_2I$ (M^+-CH_3): 421.0880, found 421.0879.

(1R*,3R*)-1-(*tert*-Butyl-dimethyl-silanyloxy)-2-*trans*-(ido-trimethylsilanyl-methylene)-3-vinyl-cycopentane (2.95)

The least polar product among the three products, 216 mg, 7.9%.

IR (neat) 2956, 2929, 2897, 2857, 1250, 1070, 836. ^{1}H NMR ($CDCl_3$) δ 5.79 (ddd, 1 H, J = 17.7, 9.9, 7.7 Hz), 5.17 (dd, 1 H, J = 17.7, 0.8 Hz), 5.10 (dd, 1 H, J = 10.0, 0.7 Hz), 4.75 (m, 1 H), 3.30 (m, 1 H), 2.03 (m, 1 H), 1.87 (m, 1 H), 1.61 (m, 1 H), 0.88 (s, 9 H), 0.31 (s, 9 H), 0.12 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.6, 140.3, 115.5, 112.2, 74.7, 56.1, 35.5, 29.1, 25.9, 18.1, 1.7, -3.3, -4.3; MS (EI) *m*/*z* (relative intensity) 421 (M^+-CH_3, 0.6), 379 (40), 309 (48), 259 (44), 185 (35), 147 (70), 73 (100), 59 (25). HRMS (EI) calcd for $C_{16}H_{30}OSi_2I$ (M^+-CH_3): 421.0880, found 421.0892.

(1R*, 3R*)-2-(*trans*)-Trimethylsilanylmethylene-3-vinyl-cyclopentanol (2.96)

To a stirred solution of **2.90** (89 mg, 0.287 mmol) in 4 mL of THF at 0 ºC was added TBAF (1.44 mL, 1.44 mmol, 1 M solution in THF). After the resulting mixture was stirred at 0 ºC for 3 h, saturated aqueous NH_4Cl (5 mL) was added. The reaction mixture was extracted with ether (10 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford 55 mg of **2.96** (90% yield). IR (neat) 3334 (br), 2955, 2899, 2871, 1626, 1246, 856, 837. ^{1}H NMR

($CDCl_3$) δ 5.90 (m, 1 H), 5.81 (t, 1 H, J = 1.7 Hz), 5.06 (m, 1 H), 5.00 (m, 1 H), 4.31 (td, 1 H, J = 6.0, 1.6 Hz), 3.27 (m, 1 H), 1.99-1.59 (m, 4 H), 0.10 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 164.2, 142.5, 125.3, 114.6, 78.3, 45.5, 32.5, 29.8, -0.064; MS (EI) *m*/*z* (relative intensity) 196 (M^+, 9), 181 (11), 163 (15), 135 (16), 105 (17), 91 (49), 75 (100), 73 (92), 59 (26). HRMS (EI) calcd for $C_{11}H_{20}OSi$ (M^+): 196.1283, found 196.1278.

(1R*, 3S*)-2-(*trans*)-Trimethylsilanylmethylene-3-vinyl-cyclopentanol (2.97)

To a stirred solution of compound **2.91** (70 mg, 0.22 mmol) in 4 mL of THF at 0 ºC was added TBAF (1.1 mL, 1.1 mmol, 1 M solution in THF). After the resulting mixture was stirred 0 ºC for 3 h, 5 mL saturated NH_4Cl was added. The reaction mixture was extracted with ether (10 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford 35 mg of **2.97** in 81% yield. IR (neat) 3325 (br), 2955, 2871, 1631, 1246, 864, 836. ^1H NMR ($CDCl_3$, 500 MHz) δ 5.80 (m, 1 H), 5.73 (s, 1 H), 5.01-4.97 (m, 2 H), 4.35 (m, 1 H), 3.35 (m, 1 H), 2.05 (m, 2 H), 1.50 (m, 2 H), 0.12 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.8, 141.9, 122.2, 113.9, 76.0, 45.2, 33.3, 28.7, -0.011; MS (EI) *m*/*z* (relative intensity) 196 (M^+, 2), 178 (9), 163 (16), 135 (24), 106 (49), 91 (92), 75 (100), 73 (62), 57 (35). HRMS (EI) calcd for $C_{11}H_{20}OSi$ (M^+): 196.1283, found 196.1279.

2-(*trans*)-Trimethylsilanylmethylene-3-vinyl-cyclopentanone (2.98)

To a stirred solution of allylic alcohol **2.96** (10.4 mg, 0.053 mmol) in CH_2Cl_2 (1.5 mL) was added silica gel (3 mg) followed by Bobbitt's reagent (17.4 mg, 0.056 mmol). The resulting mixture was stirred for 30 min. After evaporation of the solvent, the residue was purified by

flash-column chromatography. Ketone **2.98** (5.2 mg) was isolated in 50% yield. The oxidation of **2.97** by the same procedure gave the same ketone **2.98** with a similar yield. IR (neat) 2956, 1720, 1248, 1170, 860, 839. ^{1}H NMR ($CDCl_3$) δ 6.83 (d, 1 H, J = 1.6 Hz), 5.91 (ddd, 1 H, J = 17.1, 10.3, 5.5 Hz), 5.10 (dt, 1 H, J = 10.3, 1.4 Hz), 4.97 (dt, 1 H, J = 17.2, 1.4 Hz), 2.35-2.27 (m, 2 H), 2.9-1.92 (m, 2 H), 0.16 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 206.1, 152.1, 140.2, 136.3, 115.4, 43.9, 34.7, 26.1, -0.71; MS (EI) *m*/*z* (relative intensity) 194 (M^+, 15), 179 (75), 151 (26), 105 (21), 84 (100), 73 (76), 59 (16). HRMS (EI) calcd for $C_{11}H_{18}OSi$ (M^+): 194.1127, found 194.1119.

2-[(1R*,3R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-(*trans*)-iodo-trimethylsilanylmethylene-cyclopentyl]-ethanol (2.95a)

To a stirred solution of vinyl silane **2.95** (106 mg, 0.243 mmol) in THF (2 mL) at 0 ºC were added 9-BBN (1.1 mL, 0.55 mmol, 0.50 M solution in THF). The resulting solution was allowed to warm to room temperature and was stirred for 12 h before it was cooled to 0 ºC. A mixture of NaOH (64 mg, 1.6 mmol) in 2 mL of H_2O was added followed by the addition of H_2O_2 (0.55 mL, 4.8 mmol). The resulting mixture was stirred at room temperature for 1 h before it was extracted with ether (10 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford 104 mg of **2.95a** (94% yield). IR (neat) 3354 (br), 2954, 2895, 2857, 1250, 1045, 838, 773. ^{1}H NMR ($CDCl_3$) δ 4.73 (m, 1 H), 3.72 (m, 2 H), 2.78 (m, 1 H), 2.11 (m, 1 H), 2.00 – 1.80 (m, 5 H), 0.90 (s, 9 H), 0.32 (s, 9 H), 0.14 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.5, 111.7, 75.2, 61.6, 48.9, 38.4, 36.0, 28.2, 26.2, 18.3, 1.90, -3.2, -4.2; MS (EI) *m*/*z* (relative intensity) 397 (M^+- C_4H_9, 3), 381 (42), 327 (32), 233 (11), 185 (20), 147 (30), 105

(35), 73 (100), 59 (21). HRMS (EI) calcd for $C_{13}H_{26}O_2Si_2I$ (M^+-C_4H_9): 397.0516, found 397.0526.

(1R*,3S*)-3(2-hydroxy-ethyl)-2-(*trans*)-iodomethylene-cyclopentanol (2.95b)

To a stirred solution of alcohol **2.95a** (32 mg, 0.07 mmol) in THF (3 mL) at – 20 ºC was added TBAF (0.15 mL, 0.15 mmol, 1.0 M solution in THF). The resulting solution was allowed to warm to room temperature and stirred for 12 h before the addition of 4 mL of saturated aqueous NH_4Cl. The resulting mixture was extracted with Et_2O (10 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford 17 mg of **2.95b** (91% yield). IR (neat) 3331 (br), 2928, 2870, 1623, 1243, 1054, 1016, 774. ^{1}H NMR ($CDCl_3$) δ 6.46 (d, 1 H, J = 1.9 Hz), 4.49 (m, 1H), 3.77 (m, 2 H), 2.70 (m, 1 H), 2.10 – 1.80 (m, 6 H); ^{13}C NMR (d_6 acetone) δ 161.8, 76.4, 74.4, 60.2, 42.0, 36.5, 34.2, 27.8; MS (EI) *m*/*z* (relative intensity) 250 (M^+- H_2O, 9), 196 (20), 181 (11), 141 (43), 123 (98), 105 (39), 95 (56), 79 (100), 67 (69). HRMS (EI) calcd for $C_8H_{11}OI$ (M^+- H_2O): 249.9855, found 249.9848.

2-[(1S*,3R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-2-(*trans*)-trimethylsilanylmethylene-cyclopentyl]-ethanol (2.99)

To a stirred solution of vinyl silane **2.90** (973 mg, 3.14 mmol) in THF (20 mL) at 0 ºC was added 9-BBN (14.0 mL, 7.0 mmol). The resulting solution was allowed to warm to room temperature and was stirred for 12 h before it was cooled to 0 ºC. A mixture of NaOH (840 mg, 21.0 mmol) in 15 mL of H_2O was added followed by the addition of H_2O_2 (7.2 mL, 63.0 mmol). The resulting mixture was stirred at room temperature for 1 h before it was extracted with ether

(40 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford 948 mg of **2.99** (92% yield). IR (neat) 3353 (br), 2954, 2895, 2857, 1248, 835, 774. ^{1}H NMR ($CDCl_3$) δ 5.55 (t, 1 H, J = 1.6 Hz), 4.25 (m, 1 H), 3.72 (m, 2 H), 2.66 (m, 1 H), 1.90 – 1.60 (m, 6 H), 0.90 (s, 9 H), 0.14 (s, 9 H), 0.092 (s, 3 H), 0.085 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.4, 122.7, 79.8, 61.4, 39.8, 37.5, 33.6, 28.2, 26.0, 18.3, 0.06, -4.2, -4.4; MS (EI) *m*/*z* (relative intensity) 328 (M^+, 0.9), 313 (0.5), 283 (5.1), 255 (43), 183 (24), 147 (52), 107 (55), 73 (100), 59 (23). HRMS (EI) calcd for $C_{17}H_{36}O_2Si_2$ (M^+): 328.2254, found 328.2254.

(1R*,3S*)-1-(*tert*-Butyl-dimethyl-silanyloxy)-3-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-2-trimethylsilanylmethylene-cyclopentane (2.100)

To a stirred solution of vinyl silane **2.99** (313 mg, 0.95 mmol) in CH_2Cl_2 (6 mL) at room temperature were added TBSCl (216 mg, 1.43 mmol) followed by the addition of imidazole (130 mg, 1.91 mmol). The resulting solution was stirred for 12 h before the addition of 10 mL of brine. The reaction mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography (3% ethyl acetate in hexane) to afford 410 mg of **2.100** (97% yield). IR (neat) 2955, 2895, 2857, 1629, 1472, 1463, 1250, 1128, 836, 774. ^{1}H NMR ($CDCl_3$) δ 5.49 (t, 1H, J = 1.7 Hz), 4.22 (m, 1 H), 3.66 (m, 2 H), 2.64 (m, 1 H), 1.90 – 1.50 (m, 6 H), 0.91 (s, 9 H), 0.90 (s, 9 H), 0.13 (s, 9 H), 0.083 (s, 3 H), 0.076 (s, 3 H), 0.06 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 167.5, 121.4, 79.5, 62.0, 40.9, 37.4, 33.5, 27.7, 26.3, 26.2, 18.6, 18.5, 0.34, -4.0, -4.3, -5.0, -5.1; MS (EI) *m*/*z* (relative intensity) 442 (M^+, 5.4), 369 (30), 327 (17), 237 (42), 147

(100), 133 (38), 107 (23), 73 (79), 59 (17). HRMS (EI) calcd for $C_{23}H_{50}O_2Si_3$ (M^+): 442.3119, found 442.3127.

Si-I exchange reaction:

To a stirred solution of vinyl silane **2.100** (54 mg, 0.122 mmol) in CH_3CN (4 mL) at 0 ºC was added *N*-iodosuccinimide (55 mg, 0.244 mmol). The resulting solution was stirred at room temperature for 1 h before the addition of 15 mL of Et_2O. After the separation, the aqueous phase was extracted with Et_2O (10 mL × 2). The combined organic layer, after being washed with 20% $Na_2S_2O_3$ (10 mL) and brine (10 mL), was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford **2.101** (19 mg, 31%), **2.102** (17 mg, 41%) and **2.103** (13 mg, 23%).

(1R*,3S*)-1-(*tert*-Butyl-dimethyl-silanyloxy)-3-[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-2-iodomethylene-cyclopentane (2.101)

IR (neat) 2955, 2929, 2894, 2857, 1471, 1253, 1100, 1053, 835, 775. ^{1}H NMR ($CDCl_3$) δ 6.19 (t, 1 H, J = 1.0 Hz), 4.40 (m, 1 H), 3.70 (m, 2 H), 2.52 (m, 1 H), 2.15 (m, 1 H), 1.88 – 1.70 (m, 6 H), 0.92 (s, 9 H), 0.88 (s, 9 H), 0.083 (s, 3 H), 0.078 (s, 3 H), 0.07 (s, 3 H), 0.05 (3 H); ^{13}C NMR ($CDCl_3$) δ 160.8, 77.3, 74.6, 61.9, 41.7, 37.3, 35.4, 29.9, 28.2, 26.2, 25.9, 18.5, 18.2, 0.34, -4.4, -4.6, -5.04, -5.10; MS (EI) *m*/*z* (relative intensity) 481 (M^+- CH_3, 0.6), 453 (0.5), 439 (50), 307 (12), 233 (65), 147 (32), 106 (69), 73 (100), 59 (26). HRMS (EI) calcd for $C_{19}H_{38}O_2Si_2I$ (M^+-CH_3): 481.1455, found 481.1443.

3-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-2-trimethylsilanylmethylene-cyclopentanone (2.102)

IR (neat) 2955, 2930, 2897, 2856, 1721, 1472, 1251, 1167, 1103, 856, 837, 776. ^{1}H NMR ($CDCl_3$) δ 6.62 (d, 1H, J = 1.5 Hz), 3.73 (m, 2 H), 3.19 (m, 1 H), 2.40 – 2.30 (m, 2 H), 1.96 – 1.90 (m, 2 H), 1.75 – 1.65 (m, 1 H), 1.57 (m, 1 H), 0.91 (s, 9 H), 0.21 (s, 9 H), 0.07 (S, 6 H); ^{13}C NMR ($CDCl_3$) δ 206.9, 156.2, 133.8, 60.9, 38.2, 37.0, 34.5, 26.0, 23.2, 18.4, -0.5, -5.25, -5.32; MS (EI) *m*/*z* (relative intensity) 311 (M^+- CH_3, 12), 269 (83), 225 (18), 195 (15), 179 (17), 147 (47), 73 (100), 59 (22). HRMS (EI) calcd for $C_{16}H_{31}O_2Si_2$ (M^+- CH_3): 311.1863, found 311.1872.

3-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-2-(iodo-trimethylsilanyl-methyl)-cyclopentanone (2.103)

IR (neat) 2954, 2929, 2897, 2857, 1742, 1249, 837. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.73 (m, 2 H), 3.03 (d, 1 H, J = 1.4 Hz), 2.74 (d, 1 H, J = 8 Hz), 2.63 (m, 1 H), 2.40 (m, 1 H), 2.39 (m, 1 H), 2.23 (m, 1 H), 2.14 (m, 1 H), 1.96 (m, 2 H), 1.83 (m, 1 H), 0.92 (s, 9 H), 0.23 (s, 9 H), 0.086 (S, 6 H); ^{13}C NMR ($CDCl_3$, 125.75 MHz) δ 219.0, 61.5, 50.5, 38.1, 37.3, 32.0, 25.98, 25.92, 18.3, 12.6, -1.0, -5.4; MS (EI) *m*/*z* (relative intensity) 454 (M^+, 0.6), 439 (1.5), 397 (22), 269 (12), 195 (58), 147 (22), 105 (18), 73 (100), 59 (14). HRMS (EI) calcd for $C_{17}H_{35}O_2Si_2I$ (M^+): 454.1220, found 454.1220.

(1R*,3S*)-1-(*tert*-Butyldimethylsilanyloxy)-3-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-2*E*-oct-2*E*-enylidenecyclopentane (2.105)

To a stirred solution of vinyl iodide **2.101** (35 mg, 0.07 mmol) in THF (2 mL) was added $Pd(PPh_3)_4$ (8.2 mg, 0.0070 mmol), and the resulting solution was stirred at room temperature for 5 min before the addition of a solution of heptenyldihydroxyborane (40 mg, 0.28 mmol) in 2 M KOH (0.42 mL, 0.85 mmol). The resulting mixture was heated at 50 ºC for 4 h under an argon atmosphere. After the mixture was cooled to room temperature, 10 mL of brine was added. The resulting mixture was extracted with Et_2O (10 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford 32 mg of **2.105** (97% yield). IR (neat) 2955, 2928, 2856, 1471, 1253, 1099, 1046, 835, 774. ^{1}H NMR ($CDCl_3$) δ 6.21 (dd, 1 H, J = 14.8, 11.0 Hz), 5.97 (d, 1 H, J = 11.0 Hz), 5.63 (dt, 1 H, J = 14.8, 7.0 Hz), 4.36 (m, 1 H), 3.68 (m, 2 H), 2.83 (m, 1 H), 2.10 (m, 2 H), 1.89 (m, 1 H), 1.80 – 1.50 (m, 5 H), 1.44 – 1.24 (m, 6 H), 0.92 (s, 9 H), 0.92 – 0.88 (m, 3 H), 0.89 (s, 3 H), 0.11 – 0.07 (m, 12 H); ^{13}C NMR (d_6 acetone) δ 149.1, 134.6, 127.3, 123.3, 77.2, 61.8, 40.1, 35.6, 34.4, 33.0, 31.6, 29.3, 28.4, 26.1, 26.0, 22.6, 18.4, 18.2, 14.2; MS (EI) *m*/*z* (relative intensity) 466 (M^+, 15), 334 (6), 307 (34), 277 (17), 147 (12), 133 (28), 105 (29), 91 (32), 73 (100). HRMS (EI) calcd for $C_{27}H_{54}O_2Si_2$ (M^+): 466.3662, found 466.3678.

(1R*,3S*)-3-(2-hydroxyethyl)-2*E*-oct-2*E*-enylidenecyclopentanol (2.106)

To a stirred solution of diene **2.105** (266 mg, 0.57 mmol) in THF (10 mL) at – 20 ºC was added TBAF (1.4 mL, 1.4 mmol, 1.0 M solution in THF). The resulting solution was allowed to warm to room temperature and stirred for 12 h before the addition of 10 mL of saturated NH_4Cl aqueous solution. The resulting mixture was extracted with Et_2O (15 mL × 3). The combined

organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford 133 mg of diol **2.106** (98% yield). IR (neat) 3334 (br), 2960, 2926, 2855, 1462, 1054, 968. ^{1}H NMR ($CDCl_3$) δ 6.15 (m, 2 H), 5.70 (m, 1 H), 4.44 (m, 1 H), 3.74 (m, 2 H), 2.90 (m, 1 H), 2.14 – 1.70 (m, 6 H), 1.50 – 1.20 (m, 6 H), 0.89 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (d_6 acetone) δ 148.1, 136.5, 126.6, 125.5, 77.4, 61.3, 38.5, 36.3, 33.8, 33.1, 31.5, 29.21, 29.16, 22.6, 14.2; MS (EI) *m*/*z* (relative intensity) 238 (M^+, 11), 220 (35), 193 (28), 165 (51), 149 (100), 121 (42), 105 (36), 91 (66), 79 (48), 67 (36), 55 (44). HRMS (EI) calcd for $C_{15}H_{26}O_2$ (M^+): 238.1933, found 238.1931.

(1R*,3R*)-(3-Hydroxy-2*E*-oct-2*E*-enylidenecyclopentyl)acetaldehyde (2.107)

To a solution of diol **2.106** (62 mg, 0.26 mmol) and TBACl (15 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) and H_2O at pH 8.6 (carbonate buffer, 2 mL) was added NCS (121 mg, 0.91 mmol) followed by TEMPO (8.0 mg, 0.052 mmol). The resulting mixture was stirred at r.t. for 40 min and TLC showed the complete consumption of the starting materials. CH_2Cl_2(5 mL) was added and the organic layer was washed with brine. The aqueous phase was extracted with CH_2Cl_2 (5 mL × 2). The combined organic layer wasd dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford aldehyde **2.107** (41 mg), a 67% yield. IR (neat) 3311 (br), 2956, 2927, 2871, 2856, 1722, 1460, 971. ^{1}H NMR ($CDCl_3$) δ 9.81 (s, 1 H), 6.17 (d, 1 H, J = 11.2 Hz), 6.06 (dd, 1 H, J = 14.5, 11.2 Hz), 5.74 (dt, 1 H, J = 14.5. 7.0 Hz), 4.45 (m, 1 H), 3.20 (m, 1 H), 2.85 – 2.65 (m, 2 H), 2.20 – 2.00 (m, 3 H), 1.87 – 1.60 (m, 3 H), 1.44 – 1.24 (m, 6 H), 0.90 (t, 3 H, J = 7.0 Hz); ^{13}C NMR (d_6 acetone) δ 202.1, 146.7, 137.3, 125.9, 125.4, 76.9, 50.3, 33.8, 33.66, 33.0, 31.5, 29.6, 29.1, 22.6,

14.1; MS (EI) *m*/*z* (relative intensity) 218 (M^+-H_2O, 17), 174 (27), 129 (64), 117 (100), 91 (64), 79 (31), 55 (27). HRMS (EI) calcd for $C_{15}H_{22}O$ (M^+-H_2O): 218.1671, found 218.1663.

(1R*,3R*)-7-(3-hydroxy-2*E*-oct-2*E*-enylidene-cyclopentyl)hept-5*Z*-enoic acid (2.108)

To a three-neck flask was added KHMDS (200 mg, 0.442 mmol) and 4-carboxybutyl triphenylphosphonium bromide (186 mg, 0.884 mmol). THF (5 mL) was introduced and the resulting red solution was stirred at room temperature for 30 min. A solution of aldehyde **2.107** (21 mg, 0.089 mmol) in THF (3 mL) was added to the above ylide solution and the resulting mixture was stirred for 4 h before 10 mL of Et_2O was introduced. The reaction mixture was washed sequentially with HCl (1 M, 10 mL) and brine (10 mL). The ether solution was dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation. The resulting residue was purified by flash-column chromatography to afford **2.108** (20 mg) in 70% yield. IR (neat) 3396 (br), 2956, 2927, 2856, 1709, 1453, 1238, 968. ^{1}H NMR ($CDCl_3$, 500 MHz) δ, 6.20 – 6.10 (m, 2 H), 5.69 (m, 1 H), 5.45 (m, 2 H), 4.44 (m, 1 H), 2.77 (m, 1 H), 2.35 (t, 3 H, J = 7.0 Hz), 2.21 (m, 1 H), 2.18 – 2.05 (m, 4 H), 1.90 – 1.69 (m, 6 H), 1.44 – 1.36 (m, 2 H), 1.44 – 1.23 (m, 4 H), 0.90 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (*125 MHz*) δ 178.5, 148.1, 135.8, 129.7, 129.3, 126.7, 125.0, 76.9, 39.7, 33.6, 33.25, 33.16, 32.8, 31.3, 28.9, 28.1, 26.6, 24.5, 22.4, 13.9; MS (EI) *m*/*z* (relative intensity) 302 (M^+-H_2O, 20), 175 (100), 131 (18), 119 (47), 105 (75), 91 (54), 79 (34), 67 (36), 55 (21). HRMS (EI) calcd for $C_{20}H_{28}O_2$ (M^+-H_2O): 218.1671, found 218.1663.

(±)-9,10-*2H*-15-Deoxy-$\Delta^{12,14}$-PGJ_2 (2.109)

To a stirred solution of hydroxy acid **2.108** (7 mg, 0.022 mmol) in CH_2Cl_2 (2 mL) was added silica gel (2.5 mg) followed by Bobbitt's reagent (7.2 mg, 0.023 mmol). The resulting

mixture was stirred for 20 min and it was loaded directly on the top of silica gel for purification by flash-column chromatography. The title compound **2.109** (5.1 mg) was obtained in 73% yield. IR (neat) 3500 - 2500 (br), 2956, 2929, 2857, 1708, 1628, 1604, 1459, 1411, 1203, 974. ^{1}H NMR ($CDCl_3$) δ, 6.94 (m, 1 H), 6.27 – 6.17 (m, 2 H), 5.50 – 5.40 (m, 2 H), 3.10 (m, 1 H), 2.44 – 2.30 (m, 4 H), 2.28 – 2.18 (m, 3 H), 2.13 – 2.06 (m, 2 H), 1.96 – 1.81 (m, 2 H), 1.76 – 1.65 (m, 2 H), 1.50 – 1.40 (m, 2 H), 1.33 – 1.18 (m, 5 H), 0.88 (t, 3 H, J = 6.5 Hz); ^{13}C NMR δ 208.6, 179.3, 147.2, 138.6, 133.2, 130.8, 128.3, 126.5, 39.0, 36.3, 33.55, 33.48, 32.5, 31.5, 28.5, 26.7, 24.7, 24.6, 22.6, 14.1; MS (EI) *m*/*z* (relative intensity) 318 (M^+, 32), 247 (6), 191 (100), 173 (38), 121 (48), 109 (32), 105 (21), 97 (50), 91 (47), 79 (71), 67 (39), 55 (31). HRMS (EI) calcd for $C_{20}H_{30}O_3$ (M^+): 318.2195, found 318.2184.

(±)-15-Deoxy-$\Delta^{12,14}$-PGJ$_2$

To a stirred solution of THF (1.5 mL) at – 78 ºC was added (*i*-Pr)$_2$NH (0.025 mL, 0.17 mmol) followed by dropwise addition of *n*-BuLi (0.09 mL, 0.144 mmol). After being stirred at – 78 ºC for 30 min, the mixture was allowed to warm to 0 ºC and stirring at this temperature was continued for 10 min before the solution was cooled to –78 ºC. The keto-acid **2.109** (20 mg, 0.063 mmol) in 2 mL THF was added in dropwise fashion and the resulting mixture was stirred at – 78 ºC for 1 h before PhSeCl (36 mg, 0.19 mmol) in THF (2 mL) was added. The resulting reaction mixture was stirred for 2 h and then 5 mL of 1 N HCl was introduced to quench the reaction. The resulting mixture was extracted with Et_2O (10 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to give 21 mg of α-phenylselenium ketoacid **2.110** (71% yield). Compound **2.110** (18 mg, 0.038 mmol) was dissolved in a mixture of methanol (2

mL) and H_2O (0.6 mL). To the above mixture was added $NaIO_4$ (16 mg, 0.076 mmol). After the mixture was stirred for 20 min, TLC showed the complete consumption of the starting materials. The reaction mixture was loaded directly onto the top of silica gel in the column for purification to give 8.3 mg of 15-deoxy-$\Delta^{12,14}$-PGJ_2 (69% yield). IR (neat) 3500 - 2500 (br), 2955, 2925, 2854, 1709, 1693, 1629, 1207, 978. ^{1}H NMR ($CDCl_3$, 600 MHz) δ, 7.48 (ddd, 1 H, J = 6.0, 2.6, 0.95 Hz), 6.96 (d, 1 H, J = 11.4 Hz), 6.37 (dd, 1 H, J = 6.0, 1.8 Hz), 6.33 (ddt, 1 H, J = 14.9, 11.4, 1.4 Hz), 6.25 (dt, 1 H, J = 14.9, 7.8 Hz), 5.46 (m, 1 H), 5.38 (m, 1 H), 3.59 (m, 1 H), 2.60 (m, 1 H), 2.34 (t, 2 H, J = 7.5 Hz), 2.36-2.29 (m, 1 H), 2.23 (q, 2 H, J = 6.8 Hz), 2.06 (q, 2 H, J = 7.1 Hz), 1.69 (p, 2 H, J = 7.4 Hz), 1.46 (p, 2 H, J = 7.1 Hz), 1.34-1.26 (m, 4 H), 0.90 (t, 3 H, J = 6.7 Hz); ^{13}C NMR δ 197.6, 178.5, 160.8, 147.1, 135.5, 135.1, 131.9, 131.4, 126.2, 125.7, 43.5, 33.6, 33.3, 31.5, 30.8, 28.6, 26.6, 24.5, 22.6, 14.1; MS (EI) *m*/*z* (relative intensity) 316 (M^+, 40), 245 (58), 190 (90), 133 (93), 119 (96), 91 (85), 81 (48), 67 (53), 55 (100). HRMS (EI) calcd for $C_{20}H_{28}O_3$ (M^+): 316.2038, found 316.2034.

6-Benzenesulfonyl-1-trimethylsilanyl-oct-7-en-1-yn-3-one (2.111)

To alcohol **2.87** (10.14 g, 30.18 mmol) in CH_2Cl_2 (250 mL) was added PCC (13.02 g, 60.4 mmol), celite (11 g), and molecular sieves (4 Å, 11 g). After being stirred at room temperature for 7 h, the solution was filtered through celite and the solvent was removed by rotary evaporation. The residue was purified by flash-column chromatography to give ketone **2.111** (8.36 g, 83% yield). IR (neat) 3067, 2961, 2897, 1737, 1447, 1306, 1251, 1148, 1086, 1044, 846. ^{1}H NMR ($CDCl_3$) δ 7.83-7.50 (m, 5 H), 5.59 (m, 1 H), 5.31(d, J = 10.3 Hz), 5.06 (d, J = 17.0, Hz), 4.34 (m, 1 H), 3.61 (m, 1 H), 2.71-2.58 (m, 2 H), 2.44-2.38 (m, 1 H), 2.02-1.95 (m, 1 H), 0.21 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 185.6, 137.1, 133.9, 129.5, 129.3, 129.0, 124.6, 101.6,

98.9, 68.5, 41.7, 21.6, -0.73; MS (EI) *m*/*z* (relative intensity) 319 (M^+-CH_3, 2), 193 (87), 125 (75), 97 (43), 73 (100), 67 (17). HRMS (EI) calcd for $C_{16}H_{19}O_3SiS$ (M^+-CH_3): 319.0824, found 319.0811.

[2-(3-Benzenesulfonylpent-4-enyl)-[1,3]dioxolan-2-ylethynyl]trimethylsilane (2.112)

To a three-neck flask equipped with Dean-Stark trap was added ketone **2.111** (7.75 g, 23.2 mmol) and 170 mL of dry benzene. After the addition of ethylene glycol (12.9 mL, 232 mmol), *p*-toluene sulfonic acid monohydrate (250 mg, 1.3 mmol) was charged as the catalyst. The resulting mixture was heated at reflux for 12 h with water removal. After the mixture was cooled to room temperature, saturated $NaHCO_3$ (100 mL) was added to quench the reaction. The resulting mixture was extracted with Et_2O (100 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to give ketal **2.112** (8.580 g, 99% yield). IR (neat) 3067, 2959, 2897, 1447, 1306, 1251, 1147, 1085, 844. ^{1}H NMR ($CDCl_3$) δ 7.84-7.49 (m, 5 H), 5.61 (m, 1 H), 5.32 (d, J = 10.4 Hz), 5.09 (d, J = 17.0, Hz), 4.06-4.01 (m, 2 H), 3.96-3.88 (m, 2 H), 3.63 (m, 1 H), 2.36 (m, 1 H), 1.99-1.81 (m, 3 H), 0.14 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 137.4, 133.7, 130.0, 129.3, 128.9, 124.2, 102.3, 102.1, 89.2, 69.3, 64.9, 64.8, 35.7, 21.7, -0.15; MS (EI) *m*/*z* (relative intensity) 363 (M^+-CH_3, 3), 295 (3), 237 (95), 169 (96), 99 (100), 73 (82). HRMS (EI) calcd for $C_{18}H_{23}O_4SiS$ (M^+-CH_3): 363.1086, found 363.1099.

Trimethyl-(7-vinyl-1,4-dioxa-spiro[4.4]non-6-ylidenemethyl)-silane (2.113)

To a stirred solution of **2.112** (8.33 g, 22.0 mmol) in Et_2O (150 mL) at room temperature were added $Pd(PPh_3)_4$ (1.27 g, 1.1 mmol). The resulting solution was stirred for 5 min before

Et_2Zn (88 mL, 88 mmol, 1.0 M solution in hexane) was added. The mixture was stirred for 20 h at room temperature before it was cooled to 0 ºC and quenched with 80 mL of saturated NH_4Cl solution. The reaction mixture was extracted with ether (150 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford **2.113** (4.70 g, 90% yield). IR (neat) 2955, 2880, 1247, 1040, 847. ^{1}H NMR ($CDCl_3$) δ 5.89 (d, 1 H, J = 2.1 Hz), 5.90 (ddd, 1 H, J = 17.1, 10.2, 6.9 Hz), 5.07-5.00 (m, 2 H), 4.11-3.91 (m, 4 H), 3.35 (m, 1 H), 2.04-1.57 (m, 4 H), 0.11 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 159.6, 141.9, 125.2, 114.4, 113.9, 65.0, 64.6, 44.6, 33.9, 28.5, -0.10; MS (EI) *m*/*z* (relative intensity) 238 (M^+, 31), 207 (17), 195 (51), 169 (61), 141 (68), 125(50), 99 (61), 73 (100). HRMS (EI) calcd for $C_{13}H_{22}O_2Si$ (M^+): 238.1389, found 238.1391.

2-(6-Trimethylsilanylmethylene-1,4-dioxa-spiro[4.4]non-7-yl)-ethanol (2.114)

To a stirred solution of vinyl silane **2.113** (4.46 g, 18.74 mmol) in THF (150 mL) at 0 ºC was added 9-BBN (83.0 mL, 41.5 mmol). The resulting solution was stirred at 0 ºC for 14 h. NaOH (5.0 g, 0.12 mol) in 20 mL of H_2O was added followed by the addition of H_2O_2 (42.3 mL, 373.5 mmol). After the resulting mixture was stirred at 0 ºC for 1 h, the reaction mixture was extracted with ether (150 mL × 3). The combined ether solution was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford alcohol **2.114** (4.66 g, 98% yield). IR (neat) 3439 (br), 2952, 2881, 1248, 1040, 844. ^{1}H NMR ($CDCl_3$) δ 5.72 (d, 1 H, J = 1.9 Hz), 4.11-3.90 (m, 4 H), 3.74-3.65 (m, 2 H), 2.76 (m, 1 H), 1.85-1.50 (m, 6 H), 0.11 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 161.7, 122.1, 113.7, 65.2, 64.0, 60.7, 39.2, 36.8, 34.1, 25.9, -0.10; MS (EI) *m*/*z* (relative intensity) 256 (M^+, 4),

211 (24), 183 (72), 99 (100), 73 (47), 55 (22). HRMS (EI) calcd for $C_{13}H_{24}O_3Si$ (M^+) 256.1495, found 256.1500.

Si-I exchange reaction:

A stirred solution of vinyl silane **2.114** (712 mg, 2.78 mmol) in CH_3CN (25 mL) at 0 ºC was treated with *N*-iodosuccinimide (0.94 mg, 4.2 mmol). The resulting solution was stirred at this temperature for 1 h before the addition of 30 mL of Et_2O. The organic solution, after being washed by 20% $Na_2S_2O_3$ (25 mL) and 0.1 N HCl (30 mL), brine (25 mL), was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The crude product was purified by flash-column chromatography (35% ethyl acetate in hexane) to afford **2.115** (580 mg, 67%) and **2.116** (245 mg, 23%).

Vinyl iodide **2.115**:

IR (neat) 3406 (br), 2945, 2880, 1630, 1320, 1245, 1037. ^{1}H NMR ($CDCl_3$) δ 6.46 (d, 1 H, J = 2.1 Hz), 4.11-3.90 (m, 4 H), 3.74-3.65 (m, 2 H), 2.76 (m, 1 H), 1.85-1.50 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 155.9, 114.1, 77.3, 65.6, 64.0, 60.6, 40.5, 36.2, 35.4, 26.0; MS (EI) *m*/*z* (relative intensity) 310 (M^+, 0.4), 251 (17), 183 (100), 155 (24), 139(27), 109 (25), 99 (48), 73 (18). HRMS (EI) calcd for $C_{10}H_{15}O_3I$ (M^+): 310.0066, found 310.0055.

Cyclic ether **2.116**:

IR (neat) 2957, 2882, 1246, 1069, 1039, 839. ^{1}H NMR ($CDCl_3$) δ 4.14-3.85 (m, 6 H), 3.66 (s, 1 H), 2.91 (m, 1 H), 2.24 (m, 1 H), 2.00-1.75 (m, 3 H), 1.65-1.55 (m, 1 H), 1.35-1.20 (m, 1 H), 0.18 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 116.7, 94.0, 69.1, 64.75, 64.65, 49.5, 35.1, 34.8, 26.8, 25.8,

1.2; MS (EI) *m*/*z* (relative intensity) 382 (M^+, 0.5), 223 (15), 255 (80), 211 (100), 139 (21), 117 (12), 99 (34), 73 (25), 55 (10). HRMS (EI) calcd for $C_{13}H_{23}O_3SiI$ (M^+): 382.0461, found 382.0479.

2-(6*E*-Oct-2*E*-enylidene-1,4-dioxa-spiro[4.4]non-7-yl)-ethanol (2.120)

To a stirred solution of vinyl iodide **2.119** (573 mg, 1.89 mmol) in THF (40 mL) was added $Pd(PPh_3)_4$ (218 mg, 0.19 mmol), and the resulting solution was stirred at room temperature for 5 min before the addition of a solution of 1-heptenyldihydroxyborane (0.54 mg, 3.8 mmol) in 2 M KOH (7.60 mL, 15.2 mmol). The resulting mixture was heated at 50 ºC for 4 h under an argon atmosphere. After the reaction mixture was cooled to room temperature, 20 mL of brine was added. The resulting mixture was extracted with Et_2O (50 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford diene **2.120** (362 mg, 70% yield). IR (neat) 3430 (br), 2955, 2927, 2872, 1660, 1467, 1318, 1036, 971. ^{1}H NMR ($CDCl_3$) δ 6.21-6.10 (m, 2 H), 5.80-5.70 (m, 1 H), 4.11-3.89 (m, 4 H), 3.70-3.60 (m, 2 H), 2.99 (m, 1 H), 2.14-2.03 (m, 2 H), 1.96-1.50 (m, 6 H), 1.45-1.18 (m, 6 H), 0.88 (t, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 143.2, 137.8, 126.4, 124.6, 114.9, 65.5, 64.3, 61.1, 38.4, 35.5, 35.3, 33.2, 31.7, 29.3, 27.2, 22.8, 14.3; MS (EI) *m*/*z* (relative intensity) 280 (M^+, 60), 235 (65), 219 (53), 191 (34), 165(100), 137 (55), 105 (80), 99 (75), 91 (82), 79 (63), 67 (33), 55 (41). HRMS (EI) calcd for $C_{17}H_{28}O_3$ (M^+) 280.2038, found 280.2046.

(6*E*-Oct-2*E*-enylidene-1,4-dioxa-spiro[4.4]non-7-yl)-acetaldehyde (2.121)

To a solution of alcohol **2.120** (81 mg, 0.29 mmol) and TBACl (16 mg, 0.058 mmol) in CH_2Cl_2 (4 mL) and H_2O (pH 8.6, carbonate buffer, 4 mL) was added NCS (116 mg, 0.87 mmol) followed by TEMPO (9 mg, 0.058 mmol). The resulting mixture was stirred at r.t. for 1.5 h and TLC showed the complete consumption of the starting materials. 10 mL of CH_2Cl_2 was added and the organic layer was washed with brine. The aqueous phase was extracted with CH_2Cl_2 (15 mL × 2). The combined organic layer was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford **2.121** (61 mg, 76% yield). IR (neat) 3430 (br), 2957, 2928, 2874, 2717, 1723, 1661, 1459, 1318, 1140, 1036, 970. ^{1}H NMR ($CDCl_3$) δ 9.81 (s, 1 H), 6.19 (dd, 1 H, J = 11.3, 2.0 Hz), 6.06 (dd, 1 H, J = 14.6, 11.3 Hz), 5.80 (dt, 1 H, J = 14.6, 7.1 Hz), 4.14-3.90 (m, 4 H), 3.34 (m, 1 H), 2.72 (ddd, 1 H, J = 17.4, 5.0, 0.8), 2.59 (ddd, 1 H, J = 17.4, 9.9, 1.9 Hz), 2.18-2.02 (m, 3 H), 1.93-1.76 (m, 2 H), 1.52-1.20 (m, 7 H), 0.89 (t, 3 H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 202.1, 141.9, 138.6, 125.6, 124.5, 114.3, 65.2, 64.2, 50.0, 34.9, 33.1, 32.6, 31.4, 29.0, 27.7, 22.6, 14.1; MS (EI) *m*/*z* (relative intensity) 278 (M^+, 89), 249 (18), 235 (100), 221 (32), 207 (54), 195 (42), 179 (37), 163(26), 137 (27), 99 (32), 79 (30), 67 (12), 55 (16). HRMS (EI) calcd for $C_{17}H_{26}O_3$ (M^+): 278.1882, found 278.1879.

9,10-*2H*-15-Deoxy-$\Delta^{12,14}$-PGJ_2 (2.109)

To a three-neck flask was added KHMDS (400 mg, 0.884 mmol) and 4-carboxybutyl triphenylphosphonium bromide (372 mg, 1.77 mmol). THF (5 mL) was introduced and the resulting red solution was stirred at room temperature for 30 min. A solution of aldehyde **2.121** (50 mg, 0.18 mmol) in THF (5 mL) was added to the above ylide solution and the resulting

mixture was stirred for 4 h before 20 mL of Et_2O was introduced. The organic solution, after being washed sequentially with HCl (1 M, 30 mL) and brine (30 mL), was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by flash-column chromatography to afford **2.109** (53 mg) in 93% yield.

(*E*)-3-nonen-1-yne (2.125)

To a three-neck flask under an Ar atmosphere were sequentially added THF (10 mL), (*E*)-1-iodo-1-heptene (1.12 g, 5.00 mmol), $Pd(PPh_3)_4$ (285 mg, 0.25 mmol), and ethynylmagnesium bromide (15 mL, 7.5 mmol, 0.5 M solution in THF). The resulting mixture was stirred at room temperature for 1 h and then quenched with 10 mL of saturated NH_4Cl. The resulting mixture was extracted with pentane (20 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered through cotton and concentrated in vacuo. Flash-column chromatography with pentane gave the 490 mg of **2.125** (80% yield). ^{1}H NMR ($CDCl_3$) δ 6.19 (dt, 1 H, J = 15.9, 7.0 Hz), 5.40 (dq, 1 H, J = 15.9, 1.7 Hz), 2.70 (d, 1 H, J = 2.1 Hz), 2.10-2.01 (m, 2 H), 1.39-1.18 (m, 6 H), 0.85 (t, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 146.8, 108.7, 82.6, 75.7, 33.1, 31.4, 28.4, 22.6, 14.1.

9Z-3-Benzenesulfonyl-pentadeca-1,9-dien-7-yn-6-ol (2.126)

(E)-3-nonen-1-yne **2.125** (129 mg, 1.06 mmol) in THF (2 ml) was cooled to – 78 ºC and treated with EtMgBr (1.06 mL, 1.06 mmol, 1.0 M solution in THF). The cooling bath was then removed and the solution was allowed to warm to room temperature. After the reaction mixture was heated at reflux for 2 h, it was cooled to room temperature. In a separate flask, aldehyde **2.86** (144 mg, 0.6 mmol) in THF (10 mL) was cooled to – 78 ºC under argon with magnetic

stirring and treated with the alkynylmagnesium bromide solution prepared above. The solution was stirred at – 78 ºC for 30 min and was then allowed to warm to – 20 ºC during a 1 h period before the addition of 10 mL of saturated aqueous NH_4Cl. The reaction mixture was extracted with Et_2O (20 mL × 3) and the combined ether solution was dried over $MgSO_4$, filtered through cotton and evaporated in vacuo. The residue was purified by column flash-column chromatography to give 173 mg of **2.126** (80% yield). Instead of using alkynylmagsenium bromide to add to aldehyde **2.86**, the use of the alkynyllithium, generated by treating enyne 2.125 with *n*-BuLi, gave a lower yield (64%) for **2.126**. IR (neat) 3492 (br), 3065, 2957, 2928, 2857, 1447, 1305, 1290, 1146, 1085. ^{1}H NMR ($CDCl_3$) δ 7.87-7.52 (m, 5 H), 6.14 (dt, 1 H, J = 15.9, 7.0 Hz), 5.65 (m, 1 H), 5.46 (m, 1 H), 5.32 (d, 1 H, J = 10.2 Hz), 5.07 (d, 1 H, J = 17.1 Hz), 4.50 (m, 1 H), 3.59 (m, 1 H), 2.31 (m, 1 H), 2.10-2.02 (m, 2 H), 1.90-1.60 (m, 4 H), 1.50-1.28 (m, 5 H), 0.88 (t, 3 H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 145.6, 137.3, 133.7, 130.1, 129.3, 128.9, 124.0, 108.8, 87.9, 83.9, 69.5, 61.9, 34.5, 33.0, 31.3, 28.4, 23.0, 22.5, 14.0; MS (EI) *m*/*z* (relative intensity) 360 (M^+, 4), 342 (8), 289 (6), 263 (8), 235 (26), 219 (100), 164 (44), 117 (46), 91 (97), 77 (100), 67 (91), 55 (69). HRMS (EI) calcd for $C_{21}H_{28}O_3S$ (M^+): 360.1759, found 360.1759.

2*E*-Oct-2*E*-enylidene-3-vinyl-cyclopentanol (2.127)

To a stirred solution of **2.126** (91.7 mg, 0.255 mmol) in hexane (5 mL) at room temperature was added $Pd(PPh_3)_4$ (15 mg, 0.013 mmol). The resulting solution was stirred for 5 min before Et_2Zn (1.3 mL, 1.28 mmol, 1.0 M solution in hexane) was added. The resulting mixture was stirred for 20 h at room temperature before it was cooled to 0 ºC and the reaction was quenched with 5 mL of saturated NH_4Cl solution. The reaction mixture was extracted with Et_2O (15 mL × 3) and the combined extract was dried over $MgSO_4$, filtered, and evaporated in

vacuo. The residue was purified by flash-column chromatography to afford 34 mg of **2.127** (60% yield) as two diatereomers in a ratio of 4 : 1. IR (neat) 3386 (br), 2957, 2927, 2858, 1632, 1459, 1090, 969. ^{1}H NMR ($CDCl_3$) δ 6.24-6.18 (m, 2 H), 5.75-5.67 (m, 2 H), 5.04-4.96 (m, 2 H), 4.50-4.45 (m, 1 H), 3.48 (m, 1 H, major diastereomer), 3.35 (m, 1 H, minor diastereomer), 2.12 – 1.94 (m, 4 H), 1.64 – 1.20 (m, 8 H), 0.89 (t, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) (major diastereomer) δ 146.5, 141.1, 136.0, 127.1, 125.4, 113.8, 75.6, 44.3, 34.4, 33.1, 31.6, 29.6, 29.2, 22.8, 14.2; (minor diastereomer) δ 146.2, 142.2, 136.4, 126.8, 125.4, 114.0, 77.5, 44.7, 33.9, 33.3, 30.6, 30.0, 28.6, 21.3, 14.5; MS (EI) *m*/*z* (relative intensity) 202 (M^+-H_2O, 34), 167 (13), 149 (31), 131 (60), 117 (60), 105 (37), 91 (100), 74 (52), 59 (92). HRMS (EI) calcd for $C_{15}H_{22}$ (M^+-H_2O): 202.1722, found 202.1717.

2-Oct-2-enylidene-3-vinyl-cyclopentanone (2.128)

To a stirred solution of the allylic alcohol **2.127** (14 mg, 0.064 mmol) in CH_2Cl_2 (2 mL) was added silica gel (4 mg) followed by Bobbitt's reagent (21 mg, 0.067 mmol). The resulting mixture was stirred for 30 min and it was loaded directly on the top of silica gel in a column for purification to give 8.0 mg of **2.128** (50% yield). IR (neat) 2958, 2928, 2858, 1714, 1630, 1607, 1201, 973. ^{1}H NMR ($CDCl_3$) δ 7.03 (d, 1 H, J = 8.9 Hz), 6.24-6.18 (m, 2 H), 5.88 (m, 1 H), 5.08-5.00 (m, 2 H), 3.68 (m, 1 H), 2.38 – 2.29 (m, 2 H), 2.30-2.09 (m, 3 H), 1.87 (m, 1 H), 1.45-1.25 (m, 6 H), 0.89 (t, 3 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 207.5, 147.5, 139.8, 135.7, 134.4, 126.4, 114.8, 43.0, 36.6, 33.5, 31.4, 28.5, 26.9, 22.5, 14.1; MS (EI) *m*/*z* (relative intensity) 218 (M^+, 7), 169 (35), 149 (100), 105 (12), 91 (18), 71 (25), 57 (39). HRMS (EI) calcd for $C_{15}H_{22}O$ (M^+): 218.1671, found 218.1675.

N-(2-Benzenesulfonyl-3-methyl-but-3-enyl)-benzylamine (2.132)

To a three-neck flask equipped with a reflux condenser was added sequentially THF (9 mL), 2-benzenesulfonyl-3-methyl-1,3-butandiene (170 mg, 0.817 mmol) and benzylamine (0.11 mL, 1 mmol). The resulting mixture was heated at reflux for 12 h. After the reaction mixture had cooled to room temperature, the solvent was evaporated and the residue was subjected to flash-column chromatography to give 232 mg of **2.132** (90% yield). IR (neat) 3334 (br), 3062, 3028, 2922, 2849, 1447, 1305, 1145, 1084. ^{1}H NMR ($CDCl_3$) δ 7.82-7.49 (m, 5 H), 7.31-7.20 (m, 5 H), 5.05 (s, 1 H), 4.73 (s, 1 H), 3.83 (dd, 1 H, J = 13.7, 7.1 Hz), 3.70 (d, 2 H, J = 5.3 Hz), 3.30 (dd, 1 H, J = 12.5, 5.5 Hz), 3.07 (dd, 1 H, J = 12.5, 8.4 Hz), 1.77 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 139.6, 137.7, 136.6, 133.8, 129.1, 128.9, 128.6, 128.2, 127.3, 120.5, 71.7, 53.7, 46.1, 21.0; MS (EI) *m*/*z* (relative intensity) 315 (M^+, 2), 174 (16), 120 (82), 91 (100), 77 (18), 65 (17). HRMS (EI) calcd for $C_{18}H_{21}NO_2S$ (M^+): 315.1293, found 315.1297.

N-Allyl-(2-benzenesulfonyl-3-methyl-but-3-enyl)-benzyl-amine (2.133)

To a stirred solution of phenyl sulfone **2.132** (228 mg, 0.723 mmol) in CH_3CN (5 mL) at 0 ºC was added allyl bromide (0.125 mL, 1.45 mmol) followed by K_2CO_3 (300 mg, 2.17 mmol). The resulting mixture was stirred at room temperature for 14 h. The solvent was evaporated and the residue was subjected to flash-column chromatography to give the title compound **2.133** (253 mg) in 98% yield. IR (neat) 3063, 3028, 2976, 2924, 2806, 1447, 1306, 1146, 1085. ^{1}H NMR ($CDCl_3$) δ 7.84-7.49 (m, 5 H), 7.30-7.20 (m, 5 H), 5.76 (m, 1 H), 5.14-5.09 (m, 2 H), 5.06 (s, 1 H), 4.72 (s, 1 H), 3.78 (dd, 1 H, J = 9.1, 5.2 Hz), 3.64 (d, 1 H, J = 13.5 Hz), 3.42 (d, 1 H, J = 13.5 Hz), 3.18-3.05 (m, 3 H), 2.93 (dd, 1 H, J = 14.1, 7.3 Hz), 1.78 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.7, 138.4, 137.0, 135.0, 133.7, 129.1, 129.0, 128.4, 127.3, 120.7, 118.4, 70.8, 58.5, 57.3, 50.3,

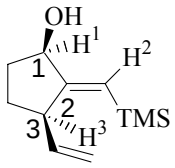
20.5; MS (EI) *m*/*z* (relative intensity) 355 (M^+, 2), 328 (1), 214 (9), 160 (100), 91 (81), 77 (15), 65 (11). HRMS (EI) calcd for $C_{21}H_{25}NIO_2S$ (M^+): 355.1606, found 355.1593.

1-Benzyl-3-iodomethyl-4-isopropenyl-pyrrolidene (2.134)

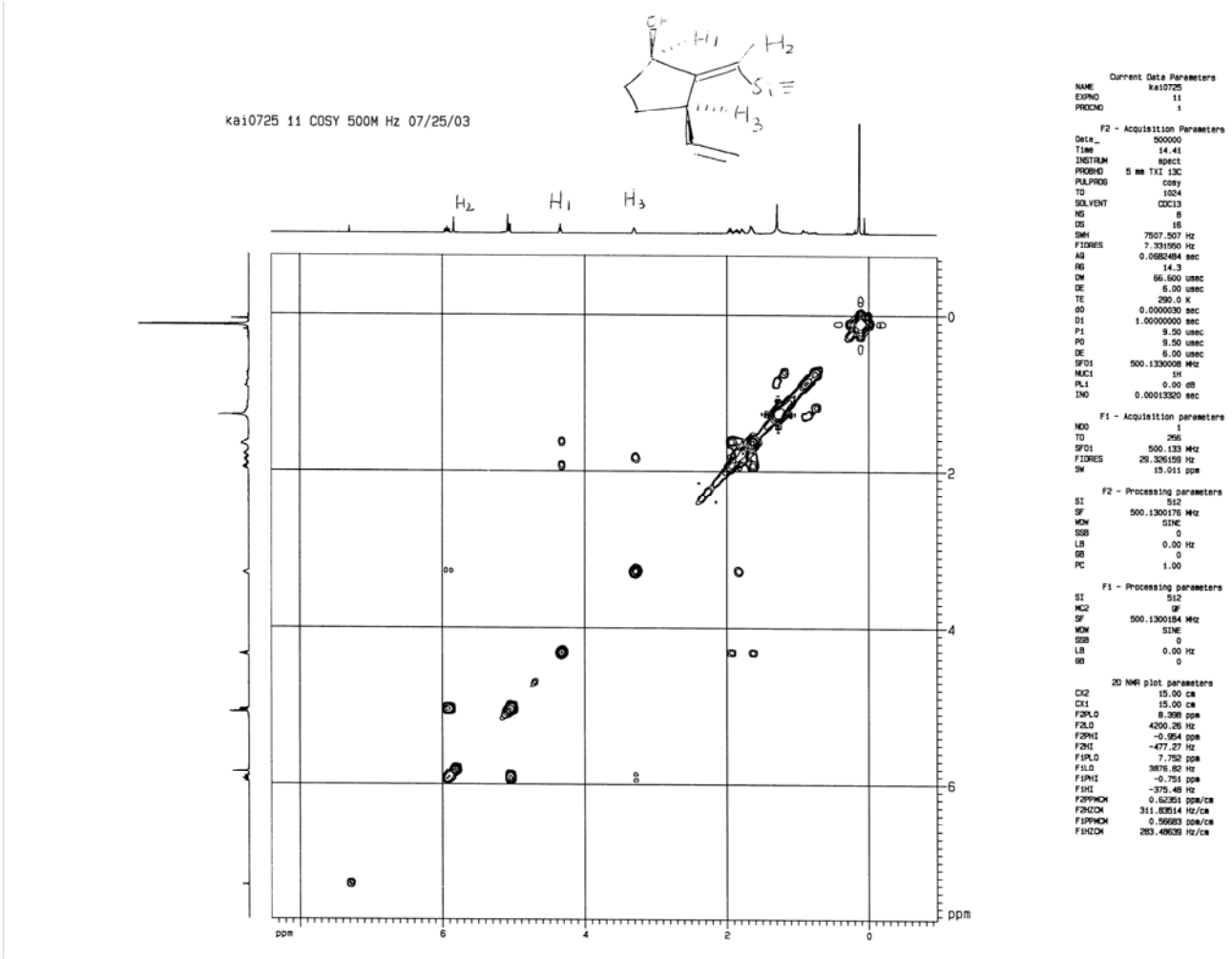
To a stirred solution of **2.133** (108 mg, 0.304 mmol) in Et_2O (8 mL) at room temperature was added $Pd(PPh_3)_4$ (18 mg, 0.015 mmol). The resulting solution was stirred for 5 min before Et_2Zn (1.7 mL, 1.82 mmol, 1.1 M solution in toluene) was added. The mixture was stirred for 20 h at room temperature before it was cooled to 0 ºC and quenched with 5 mL of brine. The reaction mixture was extracted with ether (15 mL × 3) and the combined organic layer was washed with 20% $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash-column chromatography to afford **2.134** (53 mg) in 51% yield. IR (neat) 3062, 3026, 2960, 2924, 2791, 1452, 1147, 894, 749, 699. ^{1}H NMR ($CDCl_3$) δ 7.36-7.25 (m, 5 H), 4.92 (s, 1 H), 4.76 (s, 1 H), 3.67 (s, 2 H), 3.16 (dd, 1 H, 7.6, 3.9 Hz), 3.20-3.15 (m, 1 H), 2.98 (dd, 1 H, J = 11.5, 9.6 Hz), 2.87-2.70 (m, 3 H), 2.63 (dd, 1 H, J = 11.5, 11.5 Hz), 2.44 (dd, 1 H, J = 9.6, 5.3 Hz), 1.77 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 142.52, 139.2, 128.7, 128.4, 127.1, 112.7, 61.9, 60.5, 56.5, 49.0, 43.2, 23.8, 9.9; MS (EI) *m*/*z* (relative intensity) 341 (M^+, 10), 250 (8), 214 (86), 125 (10), 91 (100), 65 (17), 55 (12). HRMS (EI) calcd for $C_{15}H_{20}NI$ (M^+): 341.0641, found 341.0655.

APPENDIX E

The COSY spetrum of compound 2.96

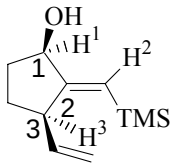


2.96

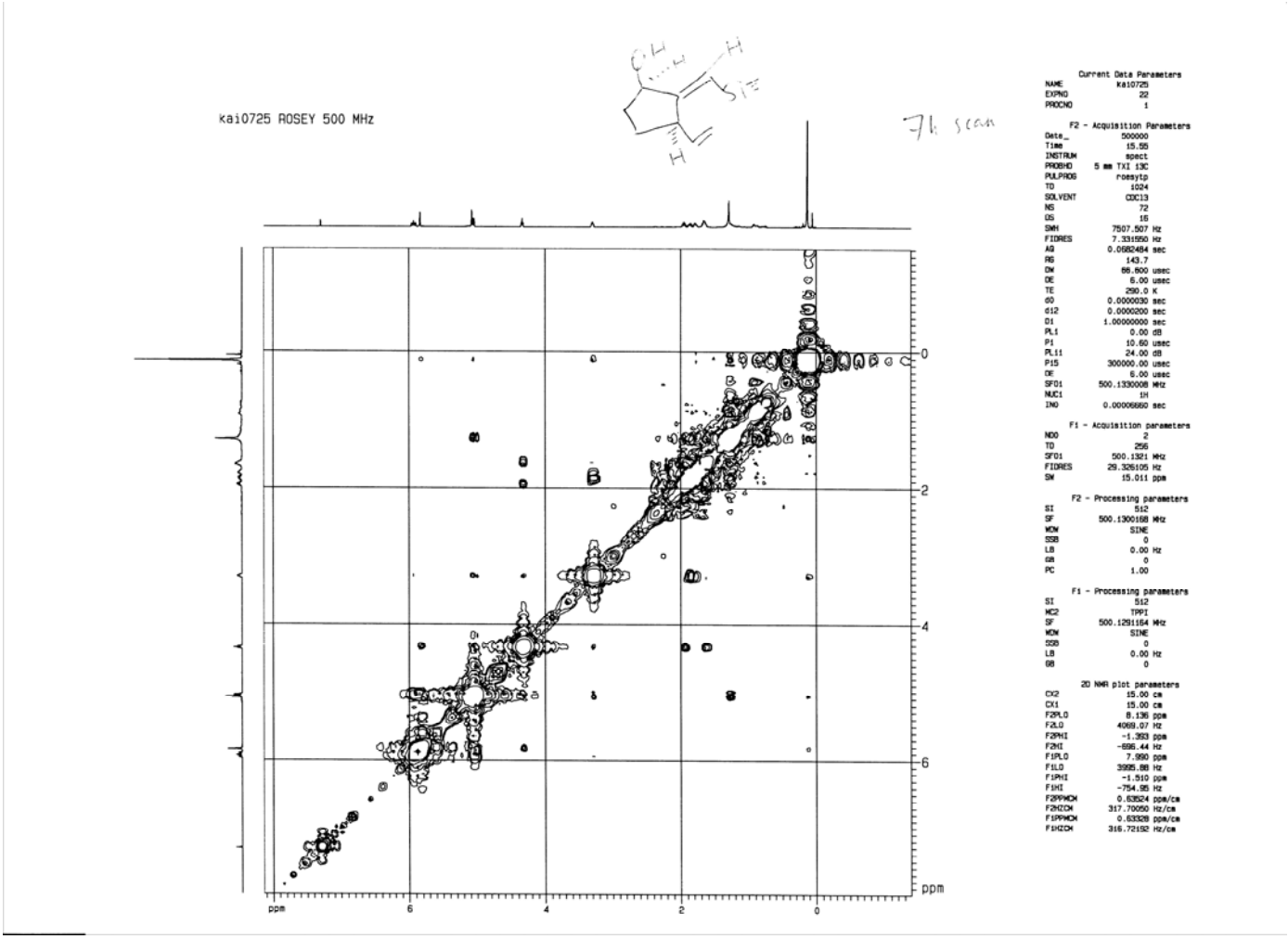


APPENDIX F

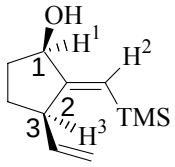
The ROSEY spetrum of compound 2.96



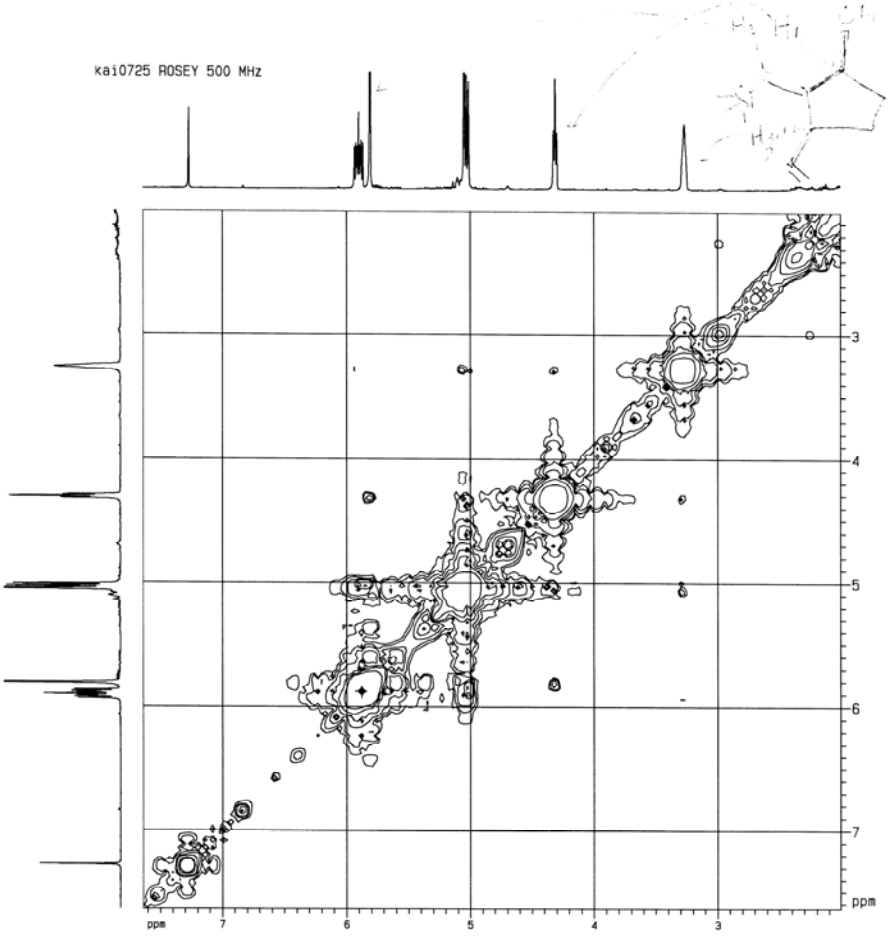
2.96



Continued from previous ROSEY spectrum for 2.96



2.96



Current Data Parameters

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EXPNO	22
PROCNO	1

F2 - Acquisition Parameters

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DS	16
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FIDRES	7.331550 Hz
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RG	143.7
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DE	6.00 usec
TE	290.0 K
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d12	0.0000200 sec
D1	1.00000000 sec
PL1	0.00 dB
P1	10.60 usec
PL11	24.00 dB
P15	300000.00 usec
DE	6.00 usec
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NUC1	1H
IN0	0.00006660 sec

F1 - Acquisition parameters

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SW	15.011 ppm

F2 - Processing parameters

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WDW	SINE
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LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

SI	512
MC2	TPPI
SF	500.1291164 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	7.636 ppm
F2LO	3819.80 Hz
F2PHI	2.008 ppm
F2HI	1004.48 Hz
F1PLO	7.636 ppm
F1LO	3819.92 Hz
F1PHI	2.009 ppm
F1HI	1004.62 Hz
F2PPMCM	0.37526 ppm/cm
F2HZCM	187.68758 Hz/cm
F1PPMCM	0.37526 ppm/cm
F1HZCM	187.68707 Hz/cm

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