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INTRAMOLECULAR REACTIONS: USE OF ORGANOMETALLIC INTERMEDIATES IN THE SYNTHESIS OF CARBOCYCLES

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Ph. D. degree in Organic Chemistry

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# INTRAMOLECULAR REACTIONS: USE OF ORGANOMETALLIC INTERMEDIATES IN THE SYNTHESIS OF CARBOCYCLES

BY

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ABSTRACT

INTRAMOLECULAR REACTIONS:
USE OF ORGANOMETALLIC INTERMEDIATES
IN THE SYNTHESIS OF CARBOCYCLES

By

Arthur Eugene Harms

Organometallic reagents have been employed in the synthesis of various carbocycles. Ziegler-Natta conditions were the first studied that accomplished an intramolecular addition to yield four-, five-, and six-membered rings. Cyclization occurred through the treatment of an alkyltitanocene chloride with a Lewis acid ($EtAlCl_2$ or $Me_2AlCl$) to produce alkylidenecycloalkanes in good to excellent yields. The methodology included synthesis of the acyclic precursors. Stereochemistry of carbon-titanium insertion into a carbon-carbon triple bond was shown to result from a *syn* addition, and as a result, the cyclization produced only one isomer from an asymmetric substrate. Substitution on the alkyne was varied to study the effect of a trimethylsilyl group compared to the corresponding methyl substituted alkyne, and the results showed the steric bulk of the trimethylsilyl group impeded cyclization.

Another organometallic methodology to accomplish ring formation employed allylic ethers and an organometallic nucleophile. Organometallic nucleophile displaced the allylic ether in an $S_N'$ fashion to produce vinyl substituted five- and six-membered carbocycles. Substrates for the cyclization study were prepared that varied in tether length between the halide and the allylic functionality. Both *cis* and *trans* olefinic isomers were studied to investigate the effect of the olefin stereochemistry on the $S_N'$

cyclization. Metals that were successful for the promotion of $S_N'$ cyclization were magnesium, lithium, and magnesium with a catalytic amount of various copper(I) salts. The synthesis of *cis*-bicyclo[4.3.0]non-1-ene was accomplished through the exploitation of the preferred nucleophilic $S_N'$ displacement from the side *anti* to the leaving group. In a separate study, the competition of $S_N$ *versus* $S_N'$ cyclization showed that minor amounts of $S_N'$ cyclization occurred in the four- *versus* six-membered ring formation; however, in the five- *versus* seven-membered ring competition, significant amounts of $S_N$ cyclization (five-membered ring formation) took place.

Dedicated to my Mom, Dad, Aunt Wilma, Uncle Dee

Alan, Claire, and most importantly My Wife

## TABLE OF CONTENTS

## CHAPTER II. ORGANOMETALLIC $S_N'$ CYCLIZATIONS WITH ALLYLIC ETHERS

## LIST OF TABLES

### CHAPTER I. INTRAMOLECULAR REACTION WITH ALKYNES *VIA* ZIEGLER-NATTA CONDITIONS



### CHAPTER II. ORGANOMETALLIC $S_N'$ CYCLIZATIONS WITH ALLYLIC ETHERS

## LIST OF SCHEMES

### CHAPTER I. INTRAMOLECULAR REACTION WITH ALKYNES *VIA* ZIEGLER-NATTA CONDITIONS



### CHAPTER II. ORGANOMETALLIC $S_N$' CYCLIZATIONS WITH ALLYLIC ETHERS

## LIST OF FIGURES

### CHAPTER I. INTRAMOLECULAR REACTION WITH ALKYNES *VIA* ZIEGLER-NATTA CONDITIONS

## LIST OF ABBREVIATIONS

| | |
|---|---|
| AIBN | Azobisisobutyronitrile |
| Bu | Butyl |
| BuLi | Butyllithium |
| Cp | Cyclopentadienyl |
| DHP | Dihydropyran |
| DMF | *N*,*N*-Dimethylformamide |
| DMPU | 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone |
| DMSO | Dimethylsulfoxide |
| EDA | Ethylene Diamine |
| Et | Ethyl |
| HMPA | Hexamethylphosphoramide |
| LAH | Lithum Aluminum Hydride |
| Me | Methyl |
| NBS | *N*-Bromosuccinimide |
| Ph | Phenyl |
| PMDTA | *N*,*N*,*N'*,*N''*,*N''*-Pentamethyl diethylenetriamine |
| PPTs | Pyridinium *p*-Toluenesulfonate |
| RedAl® | Sodium Bis(2-methoxyethoxy)-aluminum Hydride |
| TBAF | Tetrabutylammonium Fluoride |
| TBDMS | *tert*-Butyldimethylsilyl |

| | |
|---|---|
| THF | Tetrahydrofuran |
| THP | Tetrahydropyranyl |
| TMEDA | *N,N,N',N'*Tetramethylethylene diamine |
| TMS | Trimethylsilyl |

# CHAPTER I

# INTRAMOLECULAR REACTION WITH ALKYNES *VIA* ZIEGLER-NATTA CONDITIONS

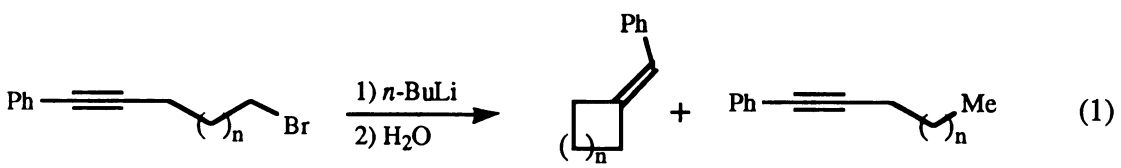
# I. INTRODUCTION

Alternate methods for carbon-carbon bond formation are constantly explored by organic chemists. When a new procedure can be applied in an intramolecular fashion with regio- and stereoselectivity, the methodology becomes an exceedingly powerful tool for synthesis. In the Stille labs, the Ziegler-Natta polymerization conditions were shown to facilitate intramolecular cyclization with regio- and diastereoselectivity.[1] Specifically, the *exo* insertion of an alkyne into a carbon-titanium bond proceeded to form five- and six-membered rings when the alkyltitanocene complex was treated with a Lewis acid.[2]

In the literature, intramolecular additions have been accomplished by several methods. This chapter reviews past methods of ring formation accomplished through insertion of activated $sp^3$ hybridized carbons into acetylenic bonds. In addition, the results of the intramolecular Ziegler-Natta reaction with alkynes are presented.

## A. Radical Cyclization

Radical cyclization was shown to be a very versatile means for natural product synthesis.[3] Generation of an alkyl radical can be accomplished by several methods, and successful techniques that are discussed utilize butyllithium,[4] chromium (II) salts,[5] zinc,[6] zinc/copper,[7] samarium (II) iodide,[8] and azoisobutyronitrile (AIBN) initiated stannane derivatives[9,10] for intramolecular reactions. One of the first examples of an intramolecular cyclization of a radical with an alkyne used *n*-butyllithium and bromide **1** (eq 1).[3] The major products of the reaction were **3** (60% yield), **4** (20% yield), and **5** (3% yield).




(1)

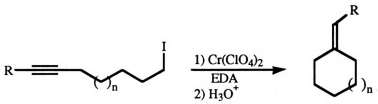
**1**: n=2

**3**: n=2 60%

**4**: n=2, 20%

**5**: n=6, 3%

Another reagent that was used for radical cyclization was chromium (II) perchlorate. Employment of a different radical generator, and use of the iodide increased the cyclization of **2** to yield **3** in 96% yield (eq 2).[5] In the model systems designed to give five-membered rings, the distinction in yields between the butyl and phenyl substituents was trivial, but in the case of the six-membered rings, substantial differences were observed (eq 2). These results suggested that the phenyl group may have stabilized the transient vinyl radical which in turn facilitated cyclization.[5]




(2)

**2**: n=0, R=Ph
**6**: n=0, R=$(CH_2)_3CH_3$
**8**: n=1, R=Ph
**10**: n=1, R=$(CH_2)_3CH_3$

**3**: n=0, R=Ph, 95%
**7**: n=0, R=$(CH_2)_3CH_3$, 85%
**9**: n=1, R=Ph, 86%
**11**: n=1, R=$(CH_2)_3CH_3$, 12%

Another metal used to generate the radical from the halide was zinc.[6] Knochel produced a radical intermediate by treatment of **2** with zinc in THF. As before, **3** was the major product (75% yield). This study only probed the formation of five-membered carbocycles. When this reaction was run in *N,N*-dimethylformamide (DMF), an atom transfer reaction took place to convert **6** to **13**.[7] The use of zinc in DMF was not as efficient for the promotion of cyclization as the conditions developed by Curran (*vide infra*).[10]

Radical cyclization with samarium(II) iodide was quite successful in the cyclization of **2** and **6**.[8] Conditions for the cyclization included DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, a less toxic alternative to HMPA) in THF at reflux. Yields for the formation of **3** and **7** were 80% and 81%, respectively.

Standard radical methodology using AIBN with tributyltin hydride did not work as well as the previously discussed radical methods.[9] The use of the same substrate

(compound **2**), resulted in only a 58:42 ratio of the cyclized product **3** to the reduced open chain alkyne **4** in a combined yield of 65%. An alternate method used a catalytic amount of bis(tributyltin) with **12** to produce **13** in 77% yield (eq 3).[10] Under the same conditions, **14** cyclized to produce **15** in 95% yield with 15:1 stereoselectivity (*E*:*Z*). However, **16** only gave **17** in a 3.3:1 (*E*:*Z*) ratio for an 87% yield.


(3)

**12**: $R^1$=$R^2$=H
**14**: $R^1$=$R^2$=$CH_3$
**16**: $R^1$=H, $R^2$=$CH_3$

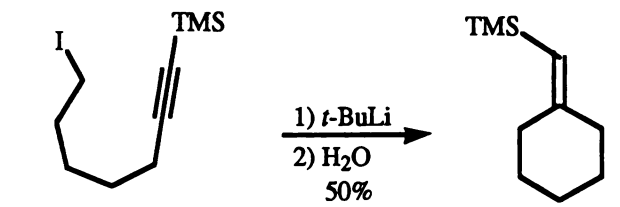
**13**: $R^1$=$R^2$ =H, 77%
**15**: $R^1$=$R^2$=$CH_3$, 15:1 (*E*:*Z*), 95%
**17**: $R^1$=H, $R^2$=$CH_3$, 3.3:1 (*E*:*Z*), 87%

Although the conditions for radical cyclization were generally mild and were tolerated by many functional groups, this process had several drawbacks. Unfortunately, intermolecular processess (*i.e.* hydrogen abstraction from the radical terminator prior to cyclization) forced the reaction to be run at high dilution (0.01-0.05M). Unlike alkenes, alkynes cyclized to form five- and six-membered rings selectively with good to excellent yields; however, most of the cyclizations required phenyl substitution on the alkyne. Another serious drawback was the limitation for further transformation of the cyclized product; but with use of a catalytic amount of the bis(tributyltin) radical initiator, a vinyl iodide was generated that could be employed for further functionalization.[10]

**B. Anionic Cyclization**

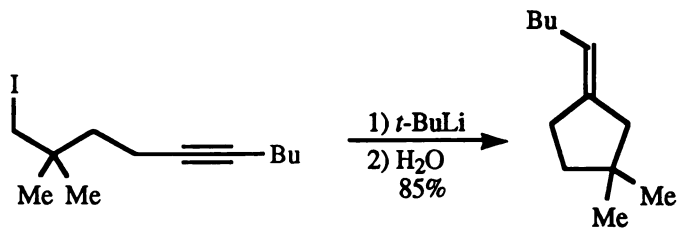
**1. Lithium Mediated Cyclization.** Anionic lithium cyclizations form five-membered rings quite easily. The anion was formed through lithium-iodide exchange.[11] Treatment of **2** with *t*-butyllithium (-78 to -25 °C) provided **3** in 94% yield.[11] Under similar conditions, six-membered rings have been formed with **18**, but the yield was only 50% (eq 4).[12] Excellent stereoselectivity was observed in the cyclization of **20** (eq 5)[12]

and **22** (eq 6).[11] Each cyclization produced only one olefinic isomer with 85% and 75% yields, respectively.



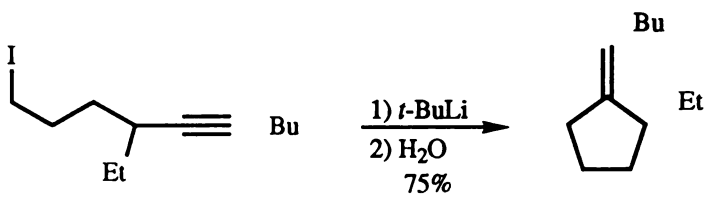

(4)

**18** **19**




(5)

**20** **21**



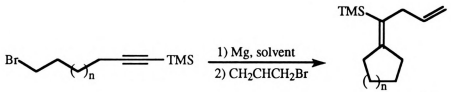

(6)

**22** **23**

Unlike radical cyclizations, lithium anionic cyclizations were not particularly tolerant of additional functional groups due to the basicity of the lithium reagent. However, five-membered ring formation was efficient and gave excellent stereoselectivity, and the resultant vinyllithium reagent could be easily functionalized with various electrophiles.[11]

**2. Magnesium Mediated Cyclization.** Alkyl Grignard reagents were easily generated from the corresponding alkyl halides (except fluoride), and the subsequent organomagnesium intermediate reacted with alkynes in an intramolecular fashion to generate exocyclic alkenes. Grignard cyclizations formed cyclopentanes in excellent yields. In 1968, Richey showed that 7-chloro-2-heptyne cyclized in the *exo* manner to

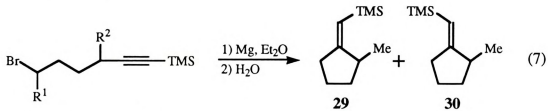
form ethylidenecyclopentane in 90% yield, but the cyclization required a temperature of 100 °C for six days.[13] This methodology was vastly improved through replacement of the methyl and the chloride with a trimethylsilyl group and a bromide, respectively. When **24** was treated with magnesium in diethyl ether at reflux, the organomagnesium intermediate cyclized after one hour and, when quenched with allyl bromide, provided **25** in 97% yield (eq 6).[14] Six-membered ring formation in dibutyl ether at reflux was successful and produced a nearly quantitative yield of **27**. Attempts to form the four-membered ring produced only 9% of the cyclized product. When a methyl group was placed α to the alkyne (compound **28**), the resultant stereoselectivity was 91:9 ratio of *Z* to *E* isomers (**29**:**30**) with an 87% yield (eq 7).[14] The stereoselectivity was reversed when compound **31** was subjected to similar conditions.




(6)

**24**: n=1
**26**: n=2

**25**: n=1, 97%
**27**: n=2, 99%




(7)

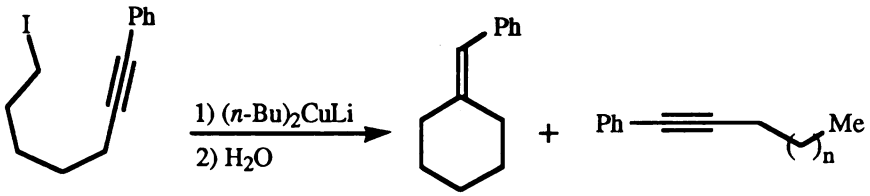
**28**: $R^1$=H, $R^2$=$CH_3$ — **29** 91 : **30** 9 — 87%

**31**: $R^1$=$CH_3$, $R^2$=H — 5 : 95 — 86%

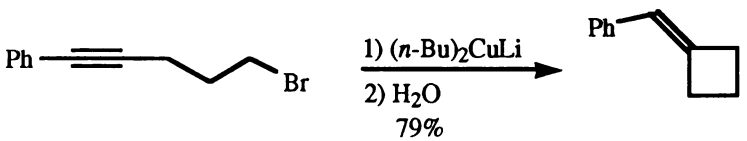
Although the strongly basic conditions used in the aforementioned method prohibited the use of most functional groups (especially acidic and carbonyl containing functional groups), the efficiency of cyclization surpassed most methods. The high

temperatures required for generation of the six-membered ring can easily be disregarded when one considered the yield of cyclization, and when the compound cyclized, the vinyl Grignard can react with many electrophiles for further functionalization.

3) **Copper Mediated Cyclization.** Through the employment of lithium di(*t*-butyl)cuprate, Crandall determined that **2** cyclized to give a 90% yield of **3**.[15] Under the same conditions, **9** was formed in only 58% yield along with several other products (**32**, **33**, eq 8). Attempts at seven-membered ring formation failed to give any cyclized product. Treatment of **34** with lithium di(*n*-butyl)cuprate followed by reflux (40 °C) for three hours successfully produced **35** in 79% yield (eq 9).[15]




**8** **9** 58% **32**: n=3, 12% **33**: n=7, 11% (8)



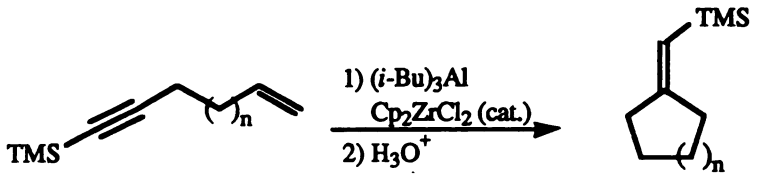

**34** **35** (9)

As was mentioned for the organomagnesium cyclization, the resultant vinyl cuprate reagent can also be functionalized in a variety of ways.[6b,15] Another advantage of the lithium dialkylcuprates is their well known tolerance of many functional groups. Although the success of six-membered ring formation was marginal, the ability to make four-membered rings was noteworthy.

### C. Transition Metal Mediated Cyclization

Early transition metals have also been shown to affect intramolecular cyclization. Studies conducted by Negishi proved that when **36** was treated with triisobutylaluminum

and a catalytic amount of zirconocene dichloride, **37** was formed in 85% yield (eq 10).[16] Likewise, **38** was treated with the same reagents to provide **39** in 72% yield. Unfortunately, attempts to produce four- and seven-membered rings were unsuccessful.

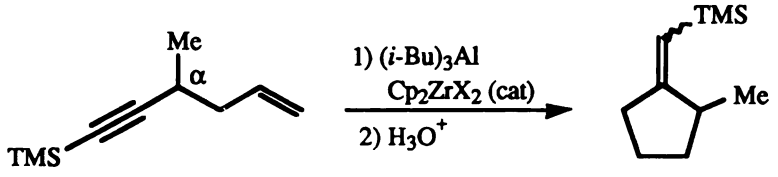



(10)

**36**: n=1
**38**: n=2

**37**: n=1, 85%
**39**: n=2, 72%

The stereoselectivity of the insertion was not affected when a methyl group was positioned on the α carbon. Through the use of triisobutylaluminum and a catalytic amount of zirconocene dichloride, compound **40** yielded **41** in a 50:50 mixture of *E* and *Z* isomers (79% yield, eq 11), but with zirconocene diiodide, the ratio was increased to 80:20 (*E*:*Z*).[16]




(11)

**40**

**41**

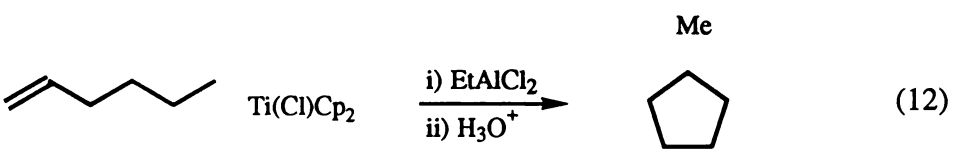
X=Cl, 50:50 (*E*:*Z*), 79%
X=I, 80:20 (*E*:*Z*), 80%

The methodology developed by Negishi was an effective way to make five- and six-membered rings. The extremely mild conditions far exceed the relatively harsh conditions of the magnesium cyclization, but yet, the yields and stereoselectivity with zirconocene could not compare to those of the magnesium cyclization.

### D. Ziegler-Natta Conditions for Intramolecular Addition of Alkenes

A study published by Grubbs gave an indication that intramolecular cyclization through the use of Ziegler-Natta conditions should be successful.[17] This study showed

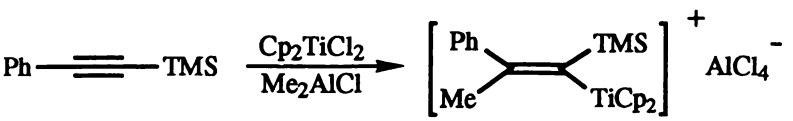
that olefins inserted into titanium-alkyl bonds to generate a carbocycle under Ziegler-type conditions gave excellent yields (eq 12). Our labs have now examined this reaction in detail.[1] Early investigations showed that ε-alken-1-yltitanocene chlorides, upon treatment with ethylaluminum dichloride, cyclized in the *exo* manner, and after protonolysis gave good yields of substituted cyclopentanes.[1a] Further studies proved that the cyclization proceeded with high diastereoselectivity (>96:4).[1b,c] Various 5-hexen-1-yl ligands with a methyl group on the tether were cyclized to give high yields of dimethylcyclopentanes. The selectivity was due to the equatorial preference of the bulky titanocene moiety, and the requirement that the alkene and the carbon-titanium bond must be coplanar for insertion (see Figure 1 for representation of the transition state for alkyne cyclization). Formation of six-membered rings has been very effective through the Ziegler-Natta method.[1c]



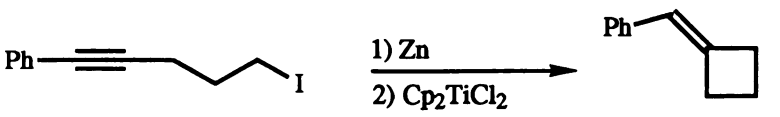

(12)

**E. Ziegler-Natta Conditions for Intermolecular Reactions of Alkynes**

An obvious extension of the Ziegler-Natta methodology was to investigate the cyclization of alkynes under similar conditions. Several observations have been made that encouraged the study of the intramolecular Ziegler-Natta chemistry with alkynes. The observations were as follows: 1) acetylene, like propylene, polymerized under Ziegler-Natta conditions,[18] 2) *syn* addition of the titanium-carbon bond into acetylene has been observed through the use of titanocene dichloride/methylaluminum dichloride polymerization catalyst (eq 13)[19] and 3) conditions that were similar to the Ziegler-Natta methodology accomplished four-membered ring formation *via* an organozinc intermediate and titanocene dichloride (eq 14).[6] When the organozinc intermediate was treated with titanocene dichloride, cyclization occurred to provide **35** in reportedly good yields.




(13)




(14)

**35**

## F. Goals For Ziegler-Natta Methodology

From the literature review on intramolecular cyclizations of acetylenic compounds, we realized that methods which had the ability to generate carbocycles with stereocontrol under mild conditions without the activation of the alkyne were rare. Improvements for the synthesis of alkylidenecycloalkanes would have to meet the following objectives:

1) Ability to make small to medium sized rings under mild conditions.

2) Cyclizations without the aid of phenyl or silyl groups on the alkyne.

3) Stereocontrol over olefin product formation.

4) Further functionalization of the resultant vinyltitanocene complex.

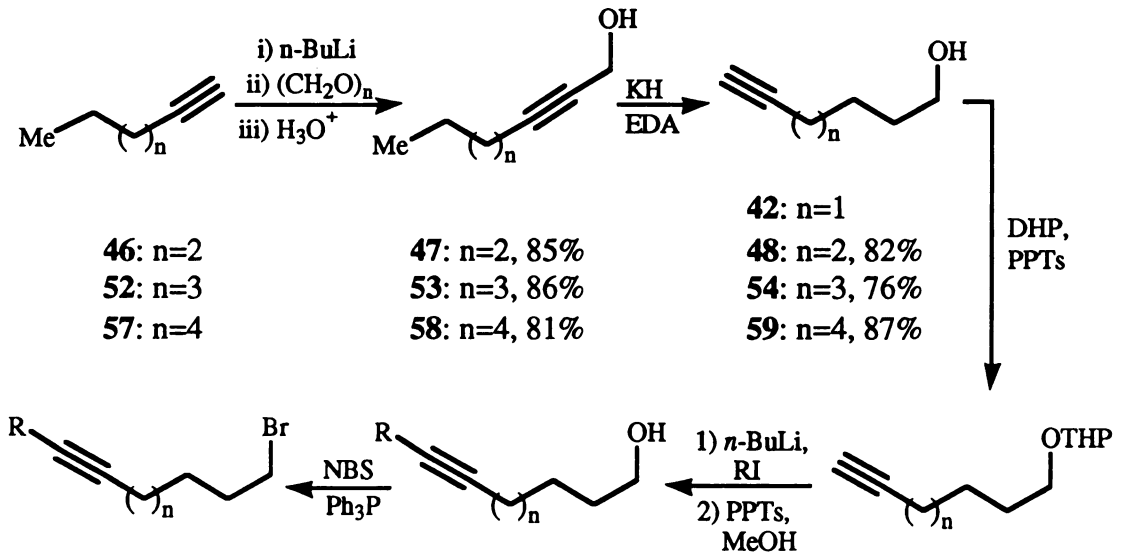
# II. RESULTS AND DISCUSSION

## A. Preparation of Acetylenic Substrates

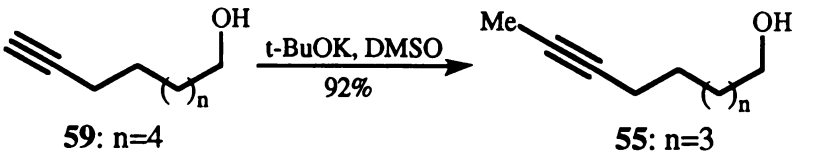
In order to test the feasability of Ziegler-Natta conditions for intramolecular cyclizations with alkynes, substrates were synthesized that differed in tether length between the bromide and the alkyne. The investigation began with the synthesis of the five-membered ring precursor **43.** First, commercially available 5-hexyn-1-ol (**40**) was protected as the tetrahydropyranyl ether (**41**, Scheme I).[20] Ethylation of the terminal alkyne with subsequent deprotection afforded 5-octyn-1-ol (**42**) in 80% yield. Conversion of the alcohol to the bromide using *N*-bromosuccinimide and triphenylphosphine provided 1-bromo-5-octyne (**43**) in 79% yield.

The synthesis of the six- and seven-membered ring precursors was approached from a slightly different angle. Terminal alkynes **46**, **52**, and **57** were deprotonated with butyllithium and quenched with paraformaldehyde to provide 2-alkyn-1-ols **47**, **53**, and **59** (Scheme I).[21] Using Brown's "acetylenic zipper",[22] the internal acetylene was "walked out" to the end of the chain opposite the alcohol to yield alkynols **48**, **54**, and **59**. Compound **48** was subjected to the same reaction sequence as 5-hexyn-1-ol (**42**) to yield bromide **51**.

**Scheme I.** Synthesis of Alkyl Substituted Acyclic Substrates.



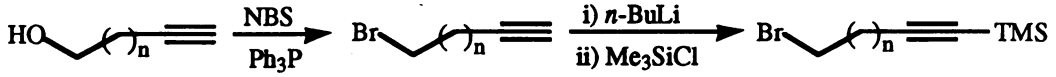

Synthesis of seven-membered ring precursor **56** utilized the increased thermodynamic stability of internal over terminal alkynes. Treatment of **59** with a catalytic amount of potassium *t*-butoxide in dimethylsulfoxide at 80 °C provided **55** (92% yield, eq 15),[21] which was easily converted to bromide **56** (Scheme I).




(15)

The synthesis of compounds **26** and **62** started with alkynols **48** and **54** (Scheme II). The method described previously was employed to convert the alcohol to the bromide. The resulting alkyne was deprotonated using *n*-butyllithium and quenched with trimethylsilyl chloride to give the desired products **26** and **62**.[21]

**Scheme II.** Synthesis of Trimethylsilyl Substituted Acyclic Substrates.

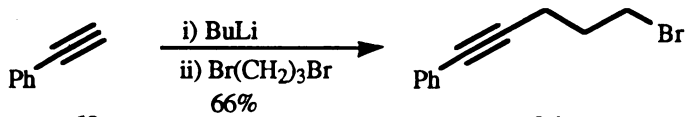



**48**: n=4
**54**: n=5

**60**: n=4, 84%
**61**: n=5, 82%

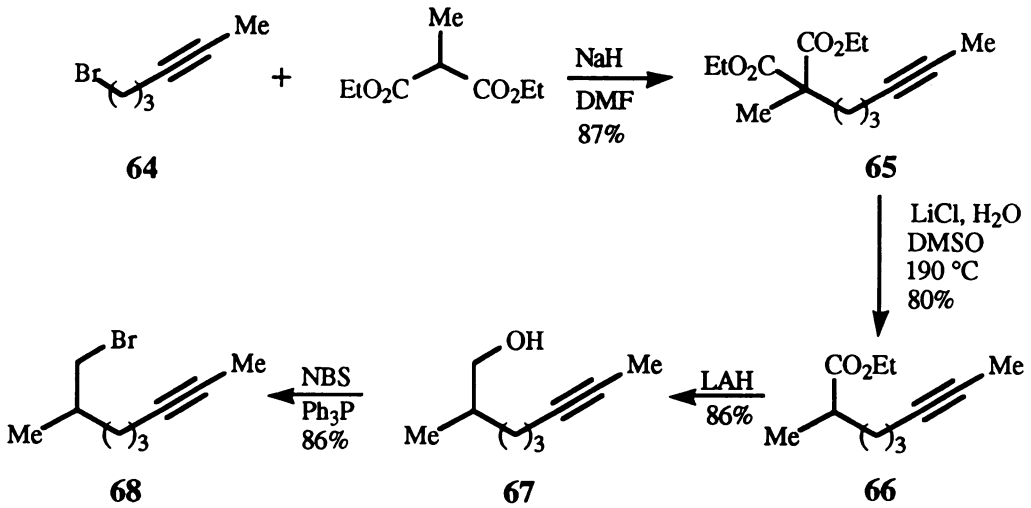
**26**: n=4, 76%
**62**: n=5, 93%

Since Crandall's methodology formed cyclobutane,[7] the same four-membered ring precursor was synthesized. The synthesis was simply accomplished by alkylation of the phenylacetylide anion with 1,3-dibromopropane to yield bromide **34** (eq. 16).




**63** **34** (16)

**Scheme III.** Synthesis of Precursor for Stereoselectivity Study.




**64** **65**

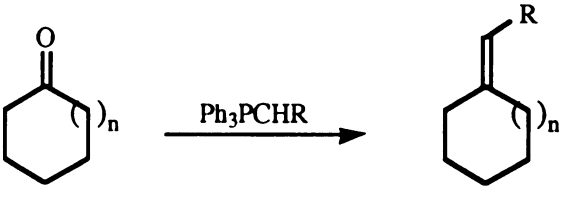
**68** **67** **66**

An asymmetric precursor was made through alkylation of the methylmalonate ester anion with **64** (Scheme III). Deethoxycarboxylation was required to convert the diester to ester **66**.[23] Using standard procedures, the ester was transformed to bromide **68** in two steps, with an overall yield of 74% from **66**. The stereochemistry of the carbon-titanium insertion was investigated through cyclization of compound **68**.

**B. Preparation of Standards**

In order to confirm the identity of the cyclized products from the intramolecular Ziegler-Natta cyclization, possible products of the cyclizations were made by alternate methods. Alkylidenecycloalkanes (**69**, **70**, and **71**) were synthesized using Corey's modification of the Wittig olefination (Scheme IV).[24] Standards for the cyclized vinylsilanes (Table 1, R=$SiMe_3$) were not commercially available, and the synthesis was not easily accessible, so the products of the cyclization were isolated by preparatory gas chromatography and fully characterized. Dehalogenated acyclic alkynes were synthesized either by protonolysis of the alkylmagnesium bromide or by methylation of the corresponding terminal alkyne (Scheme V).

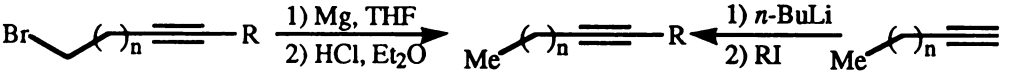
**Scheme IV.** Preparation of Standards of Cyclized Products.




n=0,1, or 2

**69**: n=0, R=Et, NYA%
**70**: n=1, R=Me, 70%
**71**: n=2, R=Me, 58%

**Scheme V.** Synthesis of Acyclic Standards.

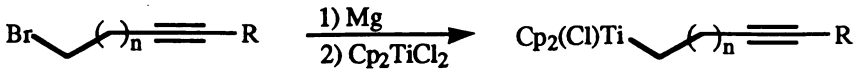



n= 2,3,4, or 5
R= Ph, Me, Et, or TMS

**C. Cyclization of Acetylenic Substrates**

With substrates in hand, our attention was turned toward synthesis of the alkyltitanocene and the corresponding cyclization. Preparation of the alkyltitanocene required the formation of the organomagnesium complex (Scheme VI). Since addition of Grignard reagents to alkynes was known,[13] care was taken to minimize cyclization during Grignard formation from **45**. Grignard formation was accomplished through a slow addition (3-6 hours) of bromide **45** to a stirred suspension of magnesium (4 equiv) in tetrahydrofuran (THF) at 0 °C followed by 1 hour at ambient temperature. Cannula transfer of the Grignard reagent to a solution of titanocene dichloride (1.2 equiv) in dichloromethane ($CH_2Cl_2$) at -40 °C was kept at -40 °C for 30 minutes and at room temperature for 4 hours. After a series of extractions and filtrations (see Experimental), the alkyltitanocene chloride **72** was isolated, and an aliquot was quenched with an HCl/ether solution at -78 °C, and the volatiles were analyzed by capillary gas chromatography. Results of the analysis showed 96% of 3-octyne and **69** (3%) in a combined yield of 67%. Compound assignments were based on retention times of known standards with confirmation of the compound through co-injection, and the yields were calculated relative to an internal standard with corrections for detector response. Upon treatment with ethylaluminum dichloride (0.5 equiv) at -78 °C for 20 minutes followed by an HCl quench, **72** yielded **69** (89% yield) and 3-octyne (4% yield, Table 1). In comparison, radical cyclization of **45** using AIBN and tributyltin hydride gave similar results. Products from *endo* cyclization (1-ethylcyclohexene) were not seen in either the radical or the titanocene cyclization.

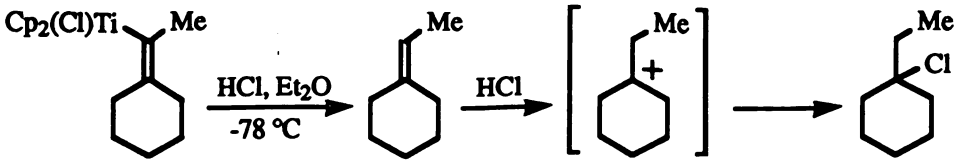
**Scheme VI.** Synthesis of Alkyltitanocene Compounds.




**45**: n=3, R=Et
**51**: n=4, R=Me
**26**: n=4, R=$SiMe_3$
**56**: n=5, R=Me
**62**: n=5, R=$SiMe_3$
**34**: n=2, R=Ph

**72**: n=4, R=Et, 67%
**73**: n=4, R=Me, 65%
**74**: n=4, R=$SiMe_3$, 55%
**75**: n=5, R=Me, 62%
**76**: n=5, R=$SiMe_3$, 79%
**77**: n=0, R=Ph, 50%

Results of six-membered ring formation were encouraging albeit perplexing. Formation of **73** occurred using the same conditions as before. Results of the alkyltitanocene protonolysis prior to addition of Lewis acid showed 2-octyne (>99%) and **70** (<1%) for a 65% yield from the bromide **51** (Scheme VI). A solution of **73** (0.07-0.10M in toluene) at -30 °C was treated with dimethylaluminum chloride (2 equiv). After 1.5 hrs, analysis of the quenched products showed the progression of cyclization, but the recovery of the uncyclized and cyclized products decreased significantly. At the same time, an unidentified peak of a higher retention time became more prominent. When **70** was subjected to the same protonolysis conditions, analysis also showed the same peak. Protonation of ethylidenecyclohexane resulted in a tertiary carbocation which was quenched by the chloride (eq 18). The glacial acetic acid/water (1/1 by volume) quench stopped the hydrochlorination of the alkene. The reaction was run again with the new protonolysis conditions. Analysis showed a 96:4 ratio of **70** to 2-octyne for a 75% yield (Table 1). The use of ethylaluminum dichloride (1 equiv) at -40 °C was also investigated, but these conditions only gave an 88:12 ratio of **70** to 2-octyne in only 42% yield. Comparison to standard radical cyclization conditions, 1-bromo-6-octyne yielded only a 78:22 ratio of 2-octyne to **70** for an 86% recovery. Again, no *endo* product (1-methylcycloheptene) was observed.




(18)

Another facet of the Ziegler-Natta methodology to be investigated was the effect of a trimethylsilyl group on the cyclization. In all of the previous cyclization methods discussed, the trimethylsilyl group significantly aided cyclization. Under the Lewis acidic conditions generated in the Ziegler-Natta cyclization, one may envision a transition state as shown in Figure 1. In the transition state (A), a partial positive charge develops on the β carbon. Silyl groups, which stablized vinyl β-carbocations, have not been observed to any great extent. However, Johnson and co-workers showed experimentally that silyl groups stabilized vinylic cations in their polyene biomimetic cyclizations.[25] This stabilization, we hoped, would facilitate our cyclization. On the other hand, the silyl group may also hinder cyclization, since trimethylsilyl groups are quite bulky, which may inhibit the approach of the titanocene. Expectations were that the stabilization effect would far outweigh the steric effect.

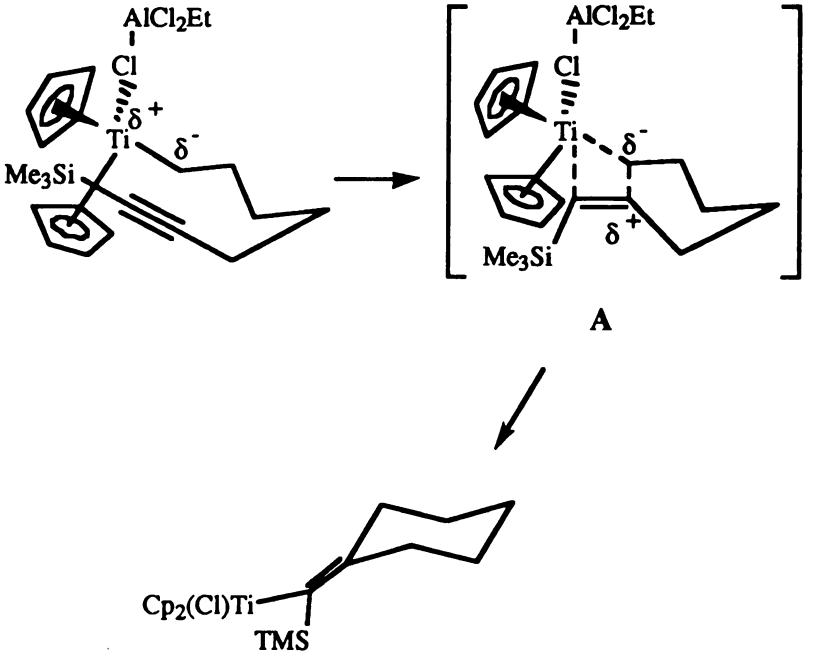
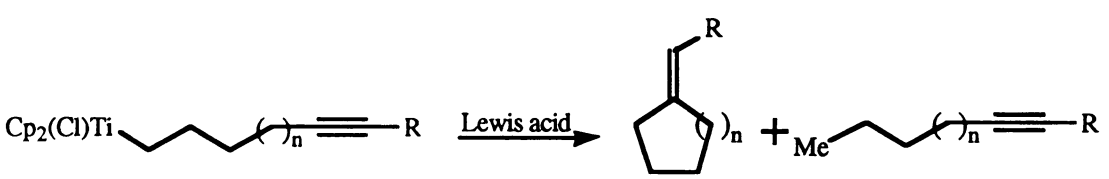



**Figure 1.** Proposed Transition State For Intramolecular Addition Under Ziegler-Natta Polymerization Conditions.

The cyclization of compound **26** was then investigated (Scheme VI and Table 1). Synthesis of **74** was accomplished using the standard conditions for a 62% yield from the bromide **26**. Initial cyclization utilized dimethylaluminum chloride (3.6 equiv) at -30 °C. After 6.5 hours, the mixture was quenched with acetic acid/$H_2O$ to yield **75** (97%) and 1-trimethylsilyl-2-heptyne (3%) in a 72% yield. This cyclization was repeated with ethylaluminum dichloride (2 equiv) as the catalyst at -78 °C. After 30 minutes, analysis of the quenched reaction products revealed **75** (84% conversion) and 1-trimethylsilyl-2-heptyne for 44% mass recovery.

Unfortunately, the seven-membered ring formation could not overcome the entropic energy needed for cyclization. The alkyltitanocenes of the methyl and silyl substituted alkynes were generated in good yields, but compounds **75** and **76** failed to cyclize (Scheme VI and Table 2). The use of dimethylaluminum chloride (2 to 4 equiv) at -30 and at 0 °C destroyed starting material with no evidence of cyclized product. The cyclizations were run at both 0.08 and at 0.02M. At higher dilution, the starting alkyltitanocene chloride lasted longer, but still no cyclization had taken place.

**Table 1.** Results of Alkyltitanocene Cyclization.



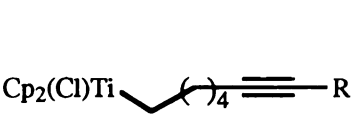

**A** **B**

| Compound | Lewis acid (equiv) | Temp (°C) | Time (hr) | A:B | Yield (A + B) | A |
|---|---|---|---|---|---|---|
| **72** n=1, R=Et | $EtAlCl_2$ (0.5) | -78 | 0.3 | 96:4 | 93 | **69** |
| **73** n=2, R=Me | $Me_2AlCl$ (1.5) | -30 | 4.0 | 96:4 | 75 | **70** |
| | $EtAlCl_2$ (1.0) | -40 | 0.5 | 88:12 | 42 | |
| **74** n=2, R=$SiMe_3$ | $Me_2AlCl$ (3.6) | -30 | 6.5 | 97:3 | 72 | **78** |
| | $EtAlCl_2$ (2.0) | -78 | 0.5 | 84:16 | 44 | |
| **75** n=3, R=Me | $Me_2AlCl$ (2.0) | 0 | 1.3 | 0:100 | 56 | **71** |
| **76** n=3, R=$SiMe_3$ | $Me_2AlCl$ (4.0) | 0 | 4.5 | 0:100 | 68 | **79** |
| **77** n=0, R=Ph | $EtAlCl_2$ (6.0) | -30→-10 | 8.0 | 96:4 | 84 | **80** |

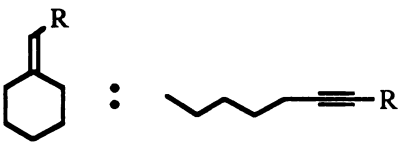
Alkyltitanocene complex **79** underwent intramolecular cyclization to generate **35** (Table 1). Ethylaluminum dichloride (6 equiv) catalyzed the reaction to give 96% cyclization. In an experiment similar to Crandall's,[6] the cyclization of alkyltitanocene **77** was catalyzed by zinc chloride at 60 °C; however, only 76% cyclization occurred.

In order to determine the effect of a silyl group on the rate of cyclization, an experiment was run in which equal amounts of the titanocene complexes **73** and **74** were generated in the same reaction flask. The vessel was cooled to -30 °C, and dimethylaluminum chloride (2 equiv) was added. After an allotted period of time, an aliquot was removed and quenched with acetic acid/water. The results showed that the methyl substituted alkyne cyclized more rapidly (Table 2). The experiment was repeated with 1.5 equivalents of dimethylaluminum chloride in order to validate the results of the previous competetive study. The second cyclization confirmed that the steric bulk of the silyl group inhibited the approach to the activated carbon which resulted in a slower rate of cyclization.

**Table 2.** Study of The Effects of Methyl *Versus* Silyl Substitution on Cyclization.




**73/74**

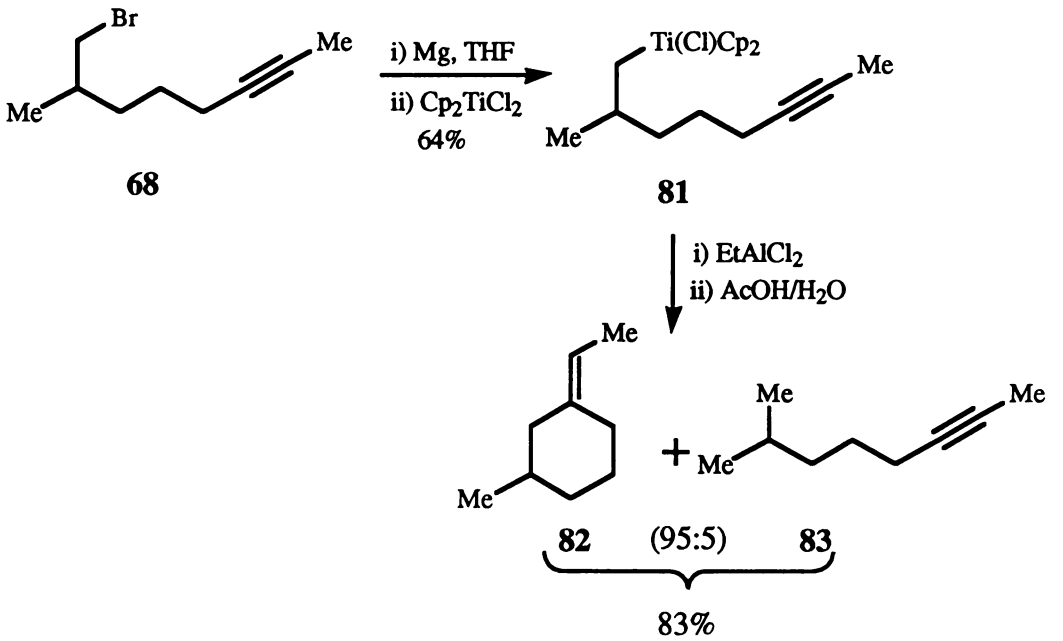



| Substrates | Lewis acid (equiv) | Time (hrs) | R=Me | (R=TMS) |
|---|---|---|---|---|
| **73** R=Me/ **74** R=TMS | $AlMe_2Cl$ (2.0) | 0.5 | 90:10 | (34:66) |
| | | 1.5 | 90:10 | (52:48) |
| | | 3.5 | 88:12 | (56:43) |
| **73** R=Me/ **74** R=TMS | $AlMe_2Cl$ (1.5 ) | 0.5 | 80:20 | (22:78) |
| | | 1.0 | 86:14 | (29:71) |
| | | 3.0 | 87:13 | (37:64) |

Placement of a methyl group on the alkyl tether provided the means to investigate stereoselectivity of the carbometallation of the alkyne. Standard preparation of the alkyltitanocene chloride was followed by treatment with ethylaluminum dichloride

(Scheme VII). A reaction took place to yield compound **80** along with a trace of the dehalogenated uncyclized substrate (**81**, 5%). The structure was confirmed by nuclear Overhauser enhancement NMR experiments. These results prove that carbometallation occurred through *syn* addition of the carbon and titanium across the alkyne, and no olefin isomerism takes place on the ligand. When compound **68** was submitted to radical conditions, only 28% cyclization took place with equal amounts of each olefin stereoisomer in the product mixture.

**Scheme VII.** Synthesis and Cyclization of Substrate for Stereoselectivity Study.




## III. CONCLUSIONS

The results of these studies show that the alkyltitanocene chlorides can be accessed through the corresponding organomagnesium intermediate in moderate yields (50-79%). Our Ziegler-Natta methodology does not require the use of stabilizing groups (*i.e.* phenyl and silyl groups) for cyclization to take place. *Exo* cyclization to form four, five, and six-membered rings occurred with the use of Lewis acids such as dimethylaluminum chloride and ethylaluminum chloride which produced high conversion

in moderate to excellent yields of the alkylidenecycloalkanes. Unfortunately, attempts to form seven-membered rings failed to provide any cyclized substrates. Competitive rate studies between the trimethylsilyl and methyl substituted alkynes showed that the steric bulk of the trimethylsilyl group dominated over the trimethylsilyl electronic effect which resulted in inhibited cyclization. The intramolecular alkyne insertion was observed to be stereospecific from *syn* addition of the organotitanium species to the alkyne, and no olefin isomerization occurred at the metal. Overall, the Ziegler-Natta methodology provided a reasonable alternative for the synthesis of alkylidenecycloalkanes which could be functionalized,[26] and further proved that alkyne insertion occurred through *syn* addition.

## IV. EXPERIMENTAL

**General methods.** All reactions were carried out under a positive pressure of dry nitrogen or dry argon and employed freshly distilled solvents under anhydrous conditions unless otherwise stated. Diethyl ether, hexane, toluene, and THF were distilled from benzophenone-sodium ketyl; triethylamine and dichloromethane from calcium hydride; and ethylene diamine from sodium metal. All glassware was oven-dried and, when necessary, evacuated through theuse of a Schlenk line. Reagents and solvents were handled with standard syringe and cannula techniques. Paraformaldehyde was dried under vacuum over anhydrous phosphorus pentoxide. Other reagents were used as received from the manufacturer. Distillation of compounds through Kugelrohr apparatus was reported as the oven temperature at which the compound distilled.

Analytical TLC was carried out on 0.25 mm E. Merck precoated silica gel plates (60F-254) with detection by 5% phosphomolybdic acid in ethanol and potassium permanganate solutions. Mass spectra were recorded on a Finnigan 9610 instrument. Infrared spectra were recorded on a Nicolet IR/42 Spectrometer. Gas chromatographs were carried out on a Perkin-Elmer 8500 equipped with RSL200 column (methyl 5%

phenylsilicone equivalent to SE54 or DB-5) and Hewlett Packard 5880A series equipped with RTX-1 column (Restek Corp.). Preparatory gas chromatography was carried out on a Varian Aerograph 90-P equipped with a 20% SE-30 column. $^{1}H$ and $^{13}C$ NMR were recorded on Varian VXR-300. $^{13}C$ spectra were completely decoupled. NMR chemical shifts are reported in ppm downfield from TMS. The following abbreviations were used to describe peak patterns when appropriate: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, and m = multiplet.

**Typical Procedure for Protection of Alcohol as the THP Ether.** A solution of 5-hexynol (**42**, 2.0 g, 20.4 mmol), dihydropyran (3.4 g, 40.8 mmol), pyridinium *p*-toluenesulfonate (0.5 g, 2.0 mmol) and dichloromethane (20 mL) was stirred at ambient temperature for 2 hours. The reaction was diluted with diethyl ether (16 mL) and washed with half-saturated sodium chloride (3 x 8 mL). Organic layers were dried ($MgSO_4$), filtered, and concentrated (rotary evaporator). Bulb-to-bulb distillation produced 3.5 g (95% yield) of the THP protected alcohol (**43**). bp 99-100 °C (7 mmHg); $^{1}H$ NMR (300 MHz, $CDCl_3$) δ 1.43-1.87 (m, 10H), 1.87 (t, 1H), 2.16 (m, 2H), 3.30-3.50 (m, 2H), 3.67-3.86 (m, 2H), 4.53 (t, 1H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 18.0, 19.5, 25.2, 25.4, 28.7, 30.9, 62.2, 66.8, 68.3, 84.5, 98.7. IR (film) 3298, 2943, 2870, 2180, 1033 $cm^{-1}$.

**Preparation of 5-Octyn-1-ol (44).** Step 1. To tetrahydrofuran (72 mL) at -78 °C, *n*-butyllithium (2.4 mL, 2.3 M in hexane, 5.5 mmol) was added. 5-Hexyn-1-yl THP ether (9.0 g, 42.8 mmol) was added over a 10 minute period and stirred at -78 °C for 1.5 hours. The cold bath was removed for 5 minutes and then returned. Ethyl iodide (26.7 g, 171.2 mmol) was added, and the reaction was allowed to warm to ambient temperature. The was stirred for 24 hours and partitioned between half-saturated brine (120 mL) and diethyl ether (120 mL). The aqueous layer was extracted with diethyl ether (2 x 30 mL). The combined organic layers were washed with water (1 x 45 mL), dried (sodium

sulfate), filtered and concentrated (rotary evaporator). Distillation of the residue through a short path equipped with an insulated vigreaux column resulted in 8.3 g. (81% yield) of product ($R_f$= 0.53 in 30% diethyl ether in petroleum ether, stained with phosphomolybdic acid and potassium permanganate). bp 87-92 °C (<3 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, *J* = 7.4 Hz, 3H), 1.43-1.87 (m, 10H), 2.05-2.17 (m, 4H), 3.36 (m, 1H), 3.45 (m, 1H), 3.70 (m, 1H), 3.81 (m, 1H), 4.53 (t, *J* = 3.4 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 12.5, 14.3, 18.8, 19.7, 25.6, 26.0, 29.0, 31.0, 62.2, 67.1, 79.0, 81.7, 98.8; IR (film) 2943, 2870, 1035 cm$^{-1}$. Step 2. A solution of the above THP ether (8.0 g, 33.6 mmol), and PPTs (0.84 g., 3.4 mmol) in ethanol (264 mL) was heated at 55 °C for 10 hours. The reaction was cooled to room temperature, and the solvent was removed *in vacuo*. Flash chromatography of the residual oil yielded 4.0 g (94% yield, 76% yield from **42**) of the desired product ($R_f$= 0.18 in 30% diethyl ether in petroleum ether, stained with phosphomolybdic acid and potassium permanganate). $^1$H NMR (300 MHz, $CDCl_3$) δ 1.07 (t, *J*= 7.3 Hz, 3H), 1.45-1.67 (m, 4H), 1.77 (bs, 1H), 2.07-2.19 (m, 4H), 3.62 (t, *J*= 6.3 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 12.2, 14.2, 18.4, 25.2, 31.6, 62.3, 78.9, 81.9. IR (film) 3358, 2974, 2939, 2874, 1062 cm$^{-1}$; HRMS calcd for $C_8H_{14}O$ *m/z* 126.1045, obsd *m/z* 126.1053.

**Typical Procedure for Synthesis of Propargylic Alcohol from the Corresponding Alkynes.** To a stirred solution of *n*-butyllithium (10.8 mL, 27 mmol, 2.5M in hexanes) in THF (54 mL) at -78 °C was introduced 1-hexyne (2.4 g, 30 mmol) followed by 30 minutes at -78 °C. The cold bath was taken away for 5 minutes and replaced with an ice-water bath. After the addition of paraformaldehyde (2.2 g), the reaction was stirred at rt for 1 hr and at 45-50 °C for an additional 1.5 hr. The reaction was poured into a $NH_4Cl$ solution (7 mL of sat. $NH_4Cl$ diluted to 70 mL with water) followed by extractions with diethyl ether (5 x 20 mL). The organic layers were dried ($MgSO_4$), filtered and concentrated (rotary evaporator). Distillation of the residue provided 2-heptyn-1-ol (**47**).

**Physical data of 2-heptyn-1-ol (47).** 2.9 g, 85% yield, bp 67-68 °C (5 mmHg, lit. 94[12]); $^1$H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.1 Hz, 3H), 1.31-1.52 (m, 4H), 1.82 (bs, 1H), 2.28 (tt, *J*=7.0, 2.0 Hz, 2H), 4.21 (t, *J*=2.0 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 12.4, 18.3, 21.9, 30.7, 51.3, 78.2, 86.5; IR (neat) 3600-3100, 2960, 2950, 2870, 2270, 2200, 1000 $cm^{-1}$.

**Physical data of 2-octyn-1-ol (53).** 11.3 g, 86% yield, bp 79-80 °C (5 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, *J*=6.8 Hz, 3H), 1.30 (m, 2H), 1.49 (quint, *J*=7.0 Hz, 2H), 1.82 (s, 1H), 2.15 (tt, *J*=2.5, 6.0 Hz, 2H), 4.19 (t, *J*=2.5 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 13.9, 18.6, 22.0, 28.0, 31.0, 51.2, 78.2, 86.3; IR (neat) 3400-3200, 2960, 2930, 2850, 2270, 2200, 1020 $cm^{-1}$.

**Physical data of 2-nonyn-1-ol (58).** 10.3 g, 81% yield, bp 73-74 °C (1 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, *J*=6.8 Hz, 3H), 1.19-1.40 (m, 6H), 1.46 (quint, *J*=7.5 Hz, 2H), 1.86 (bs, 1H), 2.17 (tt, *J*=2.2, 7.0 Hz, 2H), 4.22 (t, *J*=2.2 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.1, 18.6, 22.5, 28.4, 28.5, 31.3, 51.3, 78.2, 86.4. IR (neat) 3400-3100, 2960, 2930, 2870, 2320, 2260, 1000 $cm^{-1}$.

**Separation of Potassium Hydride From its Protective Oil.** In a glove bag filled with nitrogen, potassium hydride (6.9 g of a 35% oil dispersion, 60 mmol of KH) was weighed out into a 100 mL round bottom flask equipped with a magnetic stir bar. The round bottom flask was removed from the glove bag, and the solids were treated with light petroleum ether (70 mL). The suspension was stirred briefly and allowed to settle with occasional tapping. The solvent was removed by cannula transfer to an erlenmeyer flask which contained *t*-butanol in order to quench any residual potassium hydride. This procedure was repeated two more times. Nitrogen was gently blown through the flask to remove the last traces of solvent.

**Typical Procedure for Isomerization of Propargylic Alcohol to the Terminal Alkynol .** A solution of KAPA was prepared by slowly adding 1,3-diaminopropane (45 mL) to KH (2.4 g, 60 mmol) and stirred for 1 hr at rt. Hept-2-yn-1-ol (**47**, 2.2 g, 20 mmol) was introduced, and the mixture was stirred overnight. The reaction was very carefully poured into ice/water (150 mL). [Beware! Potassium metal is present in KH]. The mixture was extracted with diethyl ether (6 x 100 mL). The organic layers were washed with an acidic NaCl solution (100 mL, half sat'd brine/conc. HCl, 9:1), dried ($MgSO_4$), filtered and concentrated (rotary evaporator). Bulb-to-bulb distillation of the yellow residue yielded 6-heptyn-1-ol (**48**).

**Physical data for 6-heptyn-1-ol (48).** 2.1 g, 82% yield, bp oven=80-90 °C (8 mmHg, lit. 105[20]); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.40-1.60 (m, 6H), 1.72 (bs, 1H), 1.91 (t, *J*=2.6 Hz, 1H), 2.16 (td, *J*=6.7, 2.6 Hz, 2H), 3.61 (t, *J*=6.4 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 18.1, 24.7, 28.2, 32.1, 62.4, 69.1, 84.2; IR (neat) 3400-3100, 2940, 2870, 2190, 1050 $cm^{-1}$.

**Physical data for 7-octyn-1-ol (54).** 6.8 g, 76% yield, bp 85-87 °C (5 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.26-1.57 (m, 8H), 1.70 (bs, 1H), 1.90 (t, *J*=2.6 Hz, 1H), 2.27 (dt, *J*=2.6, 6.8 Hz, 2H), 3.60 (t, *J*=6.6 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 19.0, 25.1, 28.4, 28.5, 32.5, 62.6, 68.1, 84.5; IR (neat) 3400-3100, 2930, 2870, 2110, 1060 $cm^{-1}$.

**Physical data for 8-nonyn-1-ol (59).** 5.3 g, 87% yield, bp 68-69 °C (1 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.22-1.55 (m, 10H), 1.86 (t, *J*=2.6 Hz, 1H), 1.92 (bs, 1H), 2.14 (dt, *J*=2.6, 7.0 Hz, 2H), 3.56 (t, *J*=6.6 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 18.3, 25.5, 28.3, 28.5, 28.7, 32.6, 62.7, 68.1, 84.6; IR (neat) 3400-3100, 2940, 2860, 2130, 1450, 1050 $cm^{-1}$.

**Preparation of 6-Octyn-1-ol (50).** To tetrahydrofuran (65 mL) at -78 °C, *n* -butyllithium (17.2 mL, 2.5 M in hexane, 42.8 mmol) was added. 6-Heptyn-1-yl THP ether (**49**, 7.0 g, 35.6 mmol) was added over a 10 minute period and stirred at -78 °C for

1.5 hours. The cold bath was removed for 5 minutes and then returned. Methyl iodide (10.1 g, 71.3 mmol) was added, and the reaction was allowed to warm to ambient temperature. The reaction was stirred for 24 hours and then partitioned between half-saturated brine (40 mL) and diethyl ether (40 mL). The aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic layers were washed with brine (1 x 10 mL), dried ($MgSO_4$), filtered and concentrated. The residue was taken up in methanol (200 mL), treated with PPTs (1.0 g) and refluxed for three hours. Methanol was removed by atmospheric pressure distillation until 15 mL of residue remained. The residue was partitioned between half-saturated brine (40 mL) and diethyl ether (40 mL). The aqueous layer was washed with diethyl ether (3 x 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated (rotary evaporator). The yellow oil was distilled to yield 3.5 g. (80% yield) of 6-octyn-1-ol (**50**). bp 55-57 °C (<1 mmHg); $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.38-1.61 (m, 7H), 1.74 (t, *J* =2.6 Hz, 3H), 1.80 (bs, 1H), 2.11 (tq, *J* =6.7, 2.6 Hz, 2H), 3.61 (t, *J* =6.4 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 3.4, 18.4, 24.9, 28.6, 32.1, 62.5, 75.5, 78.9; IR (neat) 3600-3200, 2940, 2860, 1420, 1050 $cm^{-1}$. HRMS calcd for $C_8H_{14}O$ *m/z* 126.1045, obsd *m/z* 126.1074.

**Isomerization of a Terminal Alkynol to a Methyl Substituted Alkynol (55).** To a solution of potassium *t*-butoxide (0.08 g, 0.7 mmol) in DMSO (7 mL), 8-nonyn-1-ol (**59**, 0.5 g, 3.6 mmol) was introduced. The mixture was stirred at rt for 2 minutes, at which point, the reaction was heated to 80 °C and kept there for 2 to 3 minutes. The reaction was cooled to rt and diluted with water (80 mL). The mixture was extracted with a diethyl ether/pentane mixture (6 x 90 mL, 1:1 by volume). The organic phases were dried ($MgSO_4$) and concentrated (rotary evaporator). Distillation yielded 0.5 g of 6-octyn-1-ol (**53**, 92% yield). bp oven=85-100 °C (5 mmHg); $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.21-1.52 (m, 8H), 1.68 (t, *J*=2.5 Hz, 3H), 2.02 (m, 2H), 3.53 (t, *J*=6.7 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 3.2, 18.3, 25.1, 28.6, 28.8, 32.7, 62.6, 75.4, 79.1; IR (neat)

3400-3200, 2940, 2860, 1055 $cm^{-1}$; HRMS calcd for $C_9H_{16}O$ *m/z* 140.1201, obsd *m/z* 140.1262.

**Typical Procedure for Silylation of Terminal Alkynyl Bromides.** A solution of 1-bromo-6-heptyne (**60**, 1.8 g, 10.6 mmol) in THF (8 mL) was cooled to -78 °C. *n*-Butyllithium (4.4 mL, 11.1 mmol, 2.5M in hexanes) was introduced over a 15 minute period. Once the addition was complete, the reaction was stirred for two minutes, and TMSCl (1.5 g, 13.8 mmol) was added. The reaction was warmed to -10 °C and stirred for 20 minutes at this temperature. Ice water (20 mL) was added, and the mixture was vigorously stirred. The aqueous phase was extracted with diethyl ether (3 x 15 mL). The organic phase was dried ($MgSO_4$), concentrated (rotary evaporator) and distilled to provide 7-bromo-1-trimethylsilyl-1-heptyne (**26**).

**Physical data for 7-bromo-1-trimethylsilyl-1-heptyne (26).** 2.0 g, 76% yield, bp 71-73 °C (<1 mmHg); $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 9H), 1.52 (m, 4H), 1.85 (m, 2H), 2.21 (m, 2H), 3.39 (t, *J*=6.8 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 0.2, 19.6, 27.2, 27.5, 32.2, 33.3, 84.6, 106.8; IR (neat) 2960, 2930, 2870, 2850, 2170, 1260 $cm^{-1}$.

**Physical data for 8-bromo-1-trimethylsilyl-1-octyne (62).** 2.6 g, 93% yield, bp oven=70-80 °C (<1 mmHg); $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 9H), 1.37-1.56 (m, 6H), 1.84 (quint, *J*=7.0 Hz, 2H), 2.20 (t, *J*=6.8 Hz, 2H), 3.38 (t, *J*=6.8 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 0.3, 19.6, 27.5, 27.7, 28.1, 32.6, 33.5, 84.4, 107.1; IR (neat) 2950, 2910, 2850, 2170, 1240 $cm^{-1}$; HRMS calcd for $C_8H_{13}Br$ *m/z* 188.0200, obsd *m/z* 188.0195.

**Preparation of 1-Bromo-5-phenyl-2-pentyne (34).** To a precooled solution of phenylacetylene (2.0 g, 20.0 mmol) in tetrahydrofuran (40 mL) at -78 °C, *n* -butyllithium (9.2 mL, 2.4 M in hexane, 22.2 mmol) was added. The reaction was stirred at -78°C for 30 minutes and without the dry ice-acetone bath for 5 minutes. 1,3-Dibromopropane

(12.1 g, 60.0 mmol) was added, and the reaction was allowed to warm to ambient temperature. The reaction was stirred for 48 hours and quenched by the addition of water (20 mL). The aqueous layer was extracted with light petroleum ether (3 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated (rotary evaporator). Distillation of the residue resulted in 2.9 g (66% yield) of product. bp 107-110 °C (1 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 2.16 (quint, *J*= 6.6 Hz, 2H), 2.60 (t, *J*=6.7 Hz, 2H) 3.56 (t, *J*=6.7 Hz, 2H), 7.23-7.42 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 18.1, 31.3, 32.4, 81.6, 87.9, 123.5, 127.7, 128.2, 131.7; IR (neat) 3220, 3200, 2950, 2800, 2250, 1610, 1490, 1250 cm$^{-1}$; HRMS calcd for $C_{11}H_{11}Br$ *m/z* 222.0044, obsd *m/z* 222.0037.

**Synthesis of Diethyl 2-(5'-heptyn-1'-yl)-2-methyl-1,3-propanedioate (65).** A 50 mL round bottom flask equipped with a pressure equalizing dropping funnel was charged with sodium hydride (0.7 g, 30.0 mmol) followed by the addition of dry *N,N*-dimethylformamide (28 mL). Diethyl methylmalonate (4.8 g, 27.3 mmol) was added *via* the addition funnel over a 15 minute period to the sodium hydride suspension. After 2 hours at ambient temperature, 1-bromo-4-hexyne (**64**, 4.4 g, 27.3 mmol) was slowly added. Upon completion of the addition, the reaction was stirred at rt for 30 minutes and at 65 °C for several hours. The reaction was cooled to rt and diluted with diethyl ether (45 mL). The mixture was washed with water (2 x 20 mL). The water layer was extracted with diethyl ether (2 x 10 mL), and the combined organic layers were dried ($MgSO_4$). After concentration (rotary evaporation), the colorless residue was distilled (124-127 °C, <1mmHg) to yield 6.0 g (87% yield) of the title compound. $^1$H NMR (300 MHz, $CDCl_3$) δ 1.20 (t, *J*=7.1 Hz, 6H), 1.71 (t, *J*=2.5 Hz, 3H), 1.90 (m, 2H), 1.92 (t, *J*=2.5 Hz, 3H), 2.09 (qt, *J*=2.4, 7.1 Hz, 2H), 4.14 (q, *J*=7.1 Hz, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 3.2, 13.8, 18.8, 19.6, 23.8, 34.5, 53.2, 61.0, 75.7, 78.4, 172.2; IR (neat) 2970, 2850, 2810, 1690, 1720 cm$^{-1}$.

**Deethoxy Carboxylation of Diethyl 2-(4'-Hexyn-1'-yl)-2-methyl-1,3-propanedioate (63).** A 100 mL round bottom flask was loaded with lithium chloride (1.8 g, 41.8 mmol), water (0.8 g, 44.0 mmol), DMSO (45 mL) and the diester (**67**, 5.6 g, 22.0 mmol). The mixture was heated at 200 °C until completion. The reaction was cooled to rt, and water (50 mL) was added. The mixture was extracted with diethyl ether (6 x 60 mL). The organic layers were washed with water (2 x 12 mL), dried ($MgSO_4$), and concentrated (rotary evaporator). Distillation of the yellow residue provided 3.2 g (80% yield) of ethyl 2-methyl-7-nonynoate (**66**). bp 82-85 °C (<1mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, *J*=7.0 Hz, 3H), 1.22 (t, *J*=7.1 Hz, 3H), 1.40-1.70 (m, 4H), 1.73 (t, *J*=2.5 Hz, 3H), 2.08 (tq, *J*=2.5, 6.7 Hz, 2H), 2.38 (sext, *J*=7.0 Hz, 1H), 4.08 (q, *J*=7.0 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 3.3, 14.0, 16.9, 18.2, 26.7, 32.8, 39.0, 59.8, 75.4, 78.5, 176.2. IR (neat) 2970, 2930, 2850, 1730, 1400 $cm^{-1}$.

**Reduction of Ethyl 2-Methyl-6-octynoate (66).** Ethyl 2-methyl-6-octynoate (**66**, 2.8 g, 15.3 mmol) in diethyl ether (47 mL) was added dropwise to a solution of lithium aluminum hydride (0.37 g, 9.9 mmol) in diethyl ether (30 mL) at 0 °C. The reaction was allowed to warm to rt and then stirred for 3 hr. The reaction was cooled to 0 °C, and water (0.4 mL) was carefully added. Addition of 15% aqueous sodium hydroxide (0.4 mL) and water (1.2 mL) completed the quench. The reaction was warmed to rt and stirred for 30 minutes. *Via* cannula filtration, the solvent was transferred to another flask, and the solvent was removed *in vacuo*. Distillation of the residue provided 1.8 g (86% yield) of 2-methyl-6-octyn-1-ol (**65**). bp 85-87 °C (1 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, *J*=6.7 Hz, 3H), 1.39-1.67 (m, 6H), 2.08 (m, 2H), 3.33-3.51 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 3.4, 12.3, 19.0, 26.3, 32.4, 35.2, 68.0, 75.5, 79.0; IR (neat) 3600-3100, 2910, 2870, 1050 $cm^{-1}$; HRMS calcd for $C_9H_{16}O$ *m/z* 140.1202, obsd *m/z* 140.1176.

**Typical Procedure for Conversion of an Alcohol to a Bromide.** A solution of 6-heptyn-1-ol (**48**, 2.7 g, 23.8 mmol) and triphenylphosphine (7.4 g, 28.5 mmol) in dichloromethane (25 mL) was cooled to 0 °C. *N*-Bromosuccinimide (5.0 g, 28.5 mmol) was added over a 15 minute period. The reaction was stirred at 0 °C for 1 hour and at ambient temperature for 1 hr was followed by removal of dichloromethane *in vacuo*. Dichloromethane (11 mL) was added to the dark orange sludge, and the mixture was stirred for five minutes. Light petroleum ether (47 mL) was added, and the reaction was stirred vigorously followed by solvent removal *via* cannula filtration. The remainder of the solids were washed with light petroleum ether (2 x 25 mL). The filtration procedure was repeated. The solvent was removed *in vacuo* until 3-4 mL remained, at which point, the residue was filtered through 1" of basic alumina in a pipette and rinsed through with petroleum ether (10 mL). The solvent again was removed with a rotary evaporator. Distillation yielded 1-bromo-6-heptyne (**60**).

**Physical data for 1-bromo-5-octyne (45).** 1.0 g, 79% yield, bp oven=50-60 °C (1 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, *J*=7.4 Hz, 3H), 1.56 (quint, *J*=7.3 Hz, 2H), 1.95 (quint, *J*=7.1 Hz, 2H), 2.09-2.20 (m, 4H), 3.41 (t, *J*=6.7 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 12.6, 14.3, 18.0, 27.5, 31.8, 34.0, 78.5, 81.5; IR (film) 2974, 2937, 2876, 2845, 1452, 1435, 1251 cm$^{-1}$. HRMS calcd for $C_8H_{13}Br$ *m/z* 188.0200, obsd *m/z* 188.0201.

**Physical data for 1-bromo-6-octyne (51).** 1.8 g, 90% yield, bp 40-45 °C (<1 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.42-1.56 (m, 4H), 1.75 (t, *J*=2.6 Hz, 3H), 1.83 (m, 2H), 2.12 (m, 2H), 3.39 (t, *J*=6.8 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 3.5, 18.4, 27.3, 28.1, 32.3, 33.6, 75.7, 78.6; IR (neat) 2970, 2930, 2870, 1410 cm$^{-1}$; HRMS calcd for $C_8H_{13}Br$ *m/z* 188.0194, obsd *m/z* 188.0194.

**Physical data for 1-bromo-7-nonyne (56).** 2.7 g, 90% yield, bp oven=110-120 °C (8 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.32-1.50 (m, 6H), 1.74 (t, *J*=2.6 Hz, 3H), 1.82 (quint, *J*=7.0 Hz, 2H), 2.09 (tq, *J*=2.6, 7.0 Hz), 3.38 (t, *J*=6.8 Hz, 2H); $^{13}$C NMR (75

MHz, $CDCl_3$) δ 3.3, 18.4, 27.6, 27.8, 28.6, 32.6, 33.8, 75.2, 79.0; IR (neat) 2940, 2860, 1190 $cm^{-1}$; HRMS calcd for $C_9H_{15}Br$ *m/z* 202.0358, obsd *m/z* 202.0348.

**Physical data for 1-bromo-6-heptyne (60).** 3.3 g, 84% yield, bp 31-33 °C (<1 mmHg); $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.45-1.60 (m, 4H), 1.74 (t, *J*=2.6 Hz, 3H), 1.85 (m, 2H), 1.91 (t, *J*=2.6 Hz, 1H), 2.18 (m, 2H), 3.38 (t, *J*=6.7 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 18.2, 27.2, 27.5, 32.1, 33.5, 68.5, 84.0; IR (neat) 3300, 2930, 2860, 2090 $cm^{-1}$; HRMS calcd for $C_7H_{11}Br$ *m/z* 174.0044, obsdd *m/z* 174.0051.

**Physical data for 1-bromo-7-octyne (61).** 3.7 g, 82% yield, bp 79-80 °C (5 mmHg); $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.39-1.60 (m, 6H), 1.85 (m, 2H), 1.91 (t, *J*=2.6 Hz, 1H), 2.17 (dt, *J*=2.6, 7.0 Hz, 2H), 3.38 (t, *J*=6.7 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 18.3, 27.5, 27.7, 28.1, 32.6, 33.5, 68.1, 84.3; IR (neat) 3300, 2930, 2870, 2120, 1470, 1410, $cm^{-1}$; HRMS calcd for $C_8H_{13}Br$ *m/z* 188.0200, obsd *m/z* 188.0195.

**Physical data for 1-bromo-2-methyl-6-octyne (68).** 1.9 g, 86% yield, bp oven= 51-62 °C (1 mmHg); $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.98 (d, *J*=6.7 Hz, 3H), 1.20-1.56 (m, 2H), 1.62-1.81 (m, 2H), 1.72 (t, *J*=2.6 Hz, 3H), 2.40 (m, 1H), 3.28 (dd, *J*=5.9, 9.8 Hz, 1H), 3.36 (dd, 5.0, 9.8 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 3.4, 18.5, 18.7, 26.0, 34.0, 34.7, 41.1, 75.6, 78.7; IR (neat) 2940, 2920, 2860, 1420, 1210 $cm^{-1}$.

**Synthesis of Propylidenecyclopentane (69).** Sodium hydride (0.17 g., 7.1 mmol) was weighed out into a 25 mL round bottom flask followed by addition of anhydrous dimethyl sulfoxide (3.0 mL). The mixture was heated at 75-80 °C for 45 minutes or until evolution of hydrogen ceased. The dark green solution was cooled in an ice-water bath. A solution of n-propyltriphenylphosphonium bromide (2.75 g, 7.1 mmol) in warm dimethyl sulfoxide (7.1 mL) was added. The resultant dark red solution was stirred at ambient temperature for 10 minutes. At which time, cyclopentanone (0.5 g., 5.9 mmol) was added and allowed to react at room temperature for 2 hours. Water (15 mL) was used to quench the reaction. The reaction mixture was extracted with pentane (3 x 10

mL), and the combined organic layers were washed with water (2 x 10 mL), dried ($NaSO_4$) filtered, and concentrated. Preparatory gas chromatography was used to purify the product. $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.92 (t, *J*=7.5 Hz, 3H), 1.50-1.68 (m, 4H), 1.95 (m, 2H), 2.10-2.23 (m, 4H), 5.21 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 14.0, 23.7, 26.2, 26.4, 28.3, 33.2, 123.0, 127.2; IR (neat) 3040, 2960, 2890, 2870, 2840, 1450, 1430 $cm^{-1}$; MS *m/z* (rel. intensity) 110 (31), 95 (26), 81 (32), 67 (100), 41 (28).

**Physical data for ethylidenecyclohexane (70).** 2.3 g, 70% yield, bp 128-130 °C (760 mmHg); $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.30-1.52 (m, 6H), 1.60 (d, *J*=6.7 Hz, 3H), 2.04 (t, *J*=4.4 Hz, 2H), 2.11 (t, *J*=5.4 Hz, 2H), 5.11 (qt, *J*=1.1, 6.7 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 12.5, 26.9, 27.6, 28.2, 28.6, 37.1, 115.0, 140.1; IR (neat) 3050, 2920, 2860, 1440 $cm^{-1}$.

**Physical data for ethylidenecycloheptane (71).** 1.9 g, 58% yield, bp 69-70 °C (30 mmHg); $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.30-1.52 (m, 11H), 2.04-2.13 (m, 4H), 5.09 (qt, *J*=1.1, 6.7 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 12.9, 23.4, 24.5, 24.6, 24.8, 25.1, 29.9, 119.3, 142.0; IR (neat) 3010, 2950, 1440 $cm^{-1}$.

**General Procedure for Grignard Formation.** A Schlenk flask equipped with a magnetic stirring bar and activated magnesium (4.0 mmol) was placed under vacuum and heated with a flame for 10 minutes to drive off any advantageous water. The flask was cooled, and the flask was purged with argon for 30 minutes after the glass stopper was replaced with a rubber septum. At the desired temperature, two to three drops of the bromide were used to initiate the Grignard formation. Tetrahydrofuran (1 mL) was added followed by the remainder of the bromide (1.0 mmol, total) at a rate of 1 drop every 5 minutes. After addition, the reaction was followed by gas chromatography. The aliquots were quenched at -78 °C with 1:1 methanol/HCl solution.

**General Method for Transmetallation to Titanocene Dichloride.** The Grignard mixture from above was transferred *via* cannula into a previously evacuated Schlenk flask charged with titanocene dichloride (1.2 mmol) in dichloromethane (4.0 mL) at -40 °C. Additional tetrahydrofuran (0.5 mL) was used to transfer any residual organomagnesium bromide. The dark red solution was stirred at -40 °C for 30 minutes and at room temperature for 5-6 hours. After the solvent was removed *in vacuo*, the residue was taken up in toluene (2.5 mL) and hexane (2.5 mL). Removal of the excess titanocene dichloride and Grignard salts was accomplished by filtration at 0 °C *via* cannula filter into another deoxygenated Schlenk flask. Additional toluene (2 mL) was used to wash the solids, and the solids were dissolved in dichloromethane (2 mL). Toluene (2.5 mL) and hexane (2.5 mL) was then introduced into the flask. The slurry was filtered and washed as before. Evaporation of the solvents resulted in a dark red oil that was taken up in toluene (10 mL), and *n*-octane (internal standard, 1.0 mmol) was added. With methanol/HCl as the method of protonolysis, analysis of the 5-octyn-1-yltitanocene chloride revealed 80% yield (72% of 5-octyne, 8% of propylidenecyclopentane) based on the bromide.

**Procedure for 5-Octynyltitanocene Cyclization.** Ethylaluminum dichloride (0.01 mL, 0.02 mmol, 1.8M in toluene) was added to a 0.5M 5-octyn-1-yltitanocene chloride (**72** 2.0 mL, 0.1 mmol) in toluene at -78 °C. After 15 minutes, the reaction was quenched in the usual manner. With *n*-octane as an internal standard, the g.c. analysis revealed 96% cyclization with 4% of 3-octyne for a 93% combined yield. [Note: substrates that were sensitive to the methanolic HCl were quenched with a water/acetic acid mixture (1:1)].

**Cyclization of 74 and Isolation of Vinylsilane 78.** Dimethylaluminum dichloride (2 mL, 3.6 mmol, 1.8M in toluene) was added to 7-trimethylsilyl-6-heptyn-1-yltitanocene chloride (**74**, 2.0 mL, 0.1 mmol, 0.07M) in toluene at -30 °C. After 6.5h, the reaction was

quenched with a water/acetic acid mixture (1:1 by volume) at -50 °C. Analysis of the volatiles by g.c. showed 97% cyclization (72% combined yield). The organic layer was washed with sat. $NaHCO_3$ (2 x 10 mL), water (10 mL), and dried ($MgSO_4$). Vinylsilane (**78**) was isolated by preparatory gas chromatography. $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 9H), 1.51 (m, 6H), 2.10-2.21 (m, 4H), 5.17 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 0.03, 26.2, 28.5, 28.9, 34.5, 40.3, 120.1, 160.0; MS *m/z* (rel. intensity) 168 (16), 153 (100), 125 (32), 73 (44), 59 (40).

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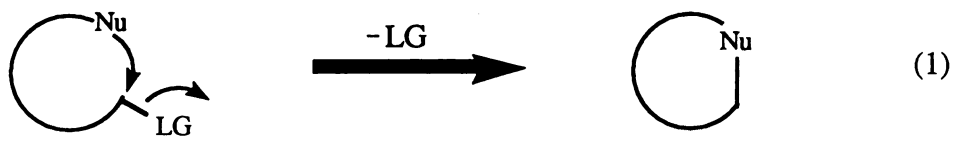
# CHAPTER II

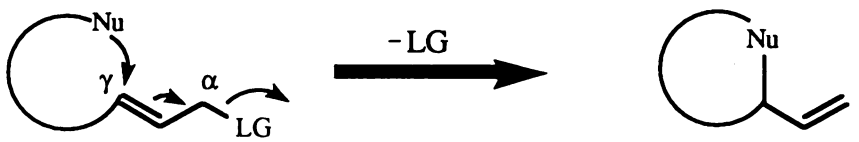
# ORGANOMETALLIC $S_N'$ CYCLIZATIONS WITH ALLYLIC ETHERS

## I. INTRODUCTION

Many natural products contain a variety of elaborate as well as relatively simple ring skeletons. The synthesis of such compounds depends heavily on the functionalization and stereochemistry desired in the molecule. Complex natural products could not have been synthesized without methods of cyclization which generated stereocontrolled ring systems in the presence of various functional groups. One simple method of cyclization utilized an attack of a nucleophilic carbon on a carbon bearing a leaving group ($S_N$ reaction). Unfortunately, this method was unable to maintain functionality for further transformations. A variation of this cyclization involved a nucleophilic attack upon an allylic system bearing a leaving group which resulted in an olefin in the final product ($S_N'$ reaction). Intramolecular $S_N'$ reactions have occurred one of three ways (eqs 2-4).[1]




(1)

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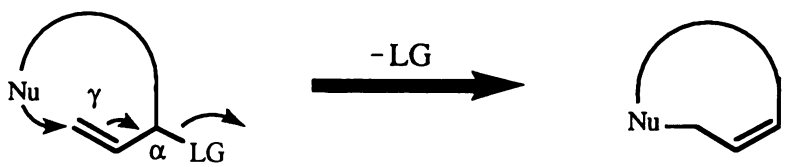


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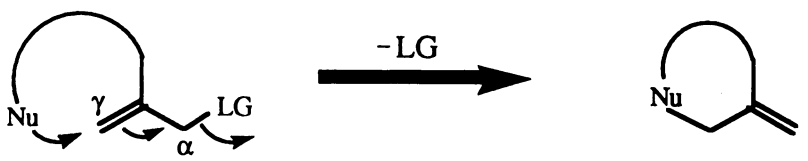
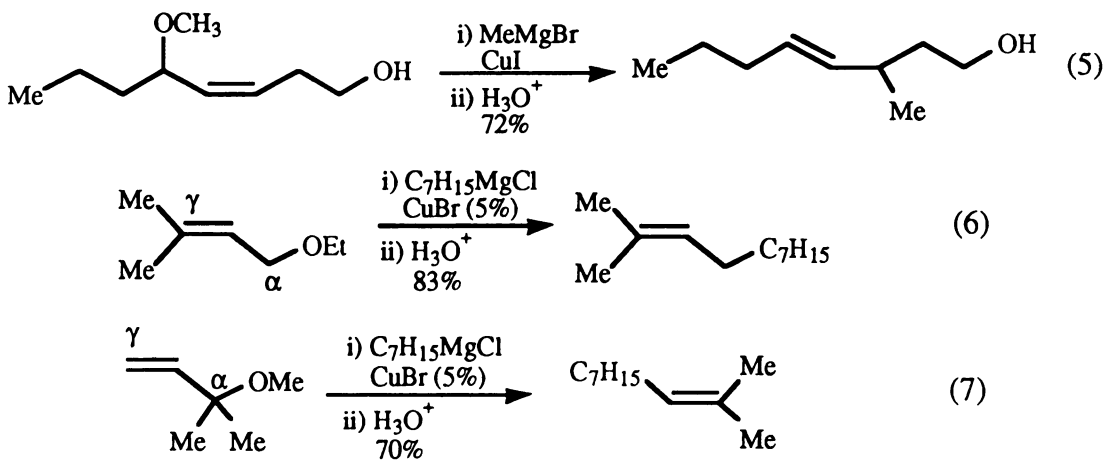



(4)

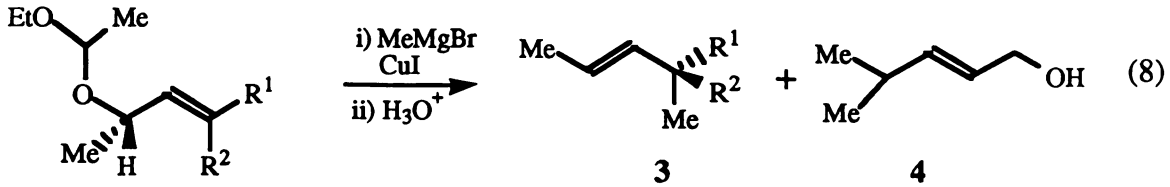
In the discussion that follows, past methods for $S_N'$ reaction that employed various organometallic nucleophiles to displace an allylic alkoxy group will be presented. In addition, advancements with our proposed methodology will be discussed. This methodology has addressed the synthesis of various carbocycles, and the olefin stereochemistry was varied to further investigate the $S_N'$ reaction.[1,2]

## A. Intermolecular $S_N2'$ Reactions

**1. Organocuprate Nucleophiles.**[2b,3] Although stable toward lower order cuprates ($R_2CuLi$), allylic ethers reacted with Grignard reagents in the presence of Cu(I) halides (eq 5).[4] In cases where the δ carbon was more substituted than the α carbon, the nucleophiles added in an $S_N2$ fashion (eq 6).[5] The opposite regiochemistry was observed when the α carbon was more substituted than the δ carbon (eq 7).[5] As demonstrated in the previous examples (eq 6 and 7), intermolecular $S_N2'$ additions were sensitive to the steric bulk of the electrophilic carbon.




The stereochemistry of the nucleophilic addition was probed through **1** and **2** (eq 8).[6] As seen in both examples, the nucleophile preferred the addition *anti* to the leaving group. An important observation was that both **1** and **2** resulted in the same $S_N2$ product (**4**). The intermediate copper complex must have some bond rotation, since the $S_N2$ product has exclusively the *E* stereochemistry regardless of the starting olefin.

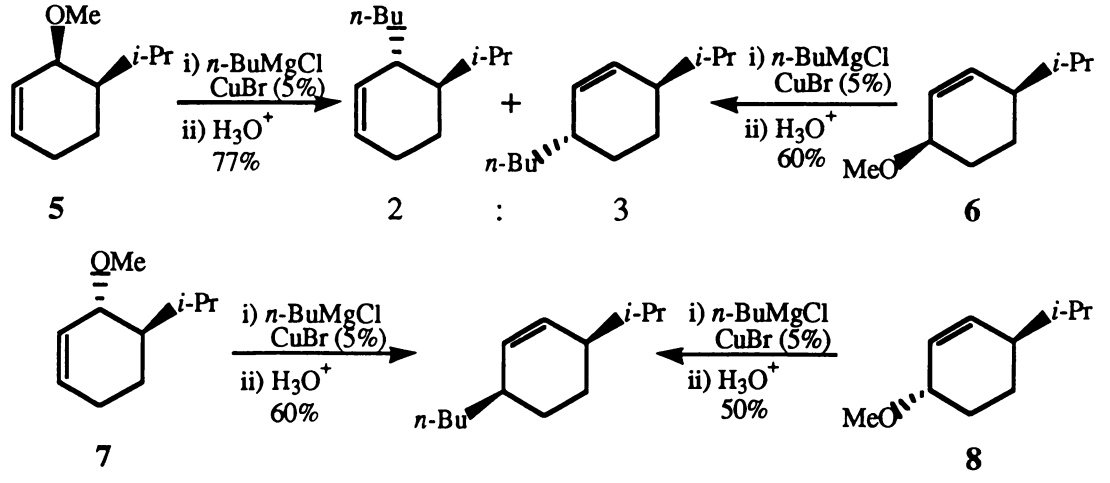



(8)

| | | | |
|---|---|---|---|
| **1** $R^1$=$CH_2OH$, $R^2$=H | 1 | : | 2 |
| **2** $R^1$=H, $R^2$=$CH_2OH$ | 4 | : | 1 |

Intermolecular addition onto a cyclic allyl ether also exhibited poor regioselectivity. When **5** was treated with butylmagnesium chloride in the presence of 5% CuBr, both regioisomers were generated in nearly equal amounts (Scheme I).[7] The 1,4-isomer (**6**) also gave the same products in the same ratios, while the corresponding *trans* isomers (**7** and **8**) only yielded one regio- and stereochemical isomer under similar conditions (Scheme I).[7] The reason for this selectivity was based on the *anti*-preference of the incoming nucleophile. In both cases, the isopropyl group impeded one nucleophilic pathway. In **6**, the isopropyl group blocked the olefin from $S_N2'$ attack, and in **7**, the isopropyl group blocked the top face from $S_N2$ attack.

**Scheme I.** Nucleophilic Additions of Cyclic Allyl Ethers.

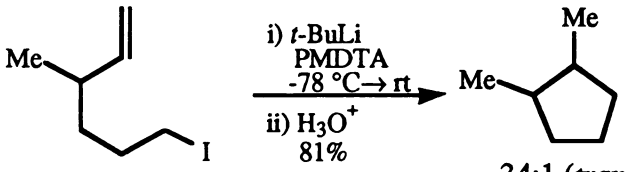



Another family of compounds that $S_N2'$ additions have occurred in are vinyloxiranes. Vinyloxiranes behave in the same manner as the methoxy groups, but due

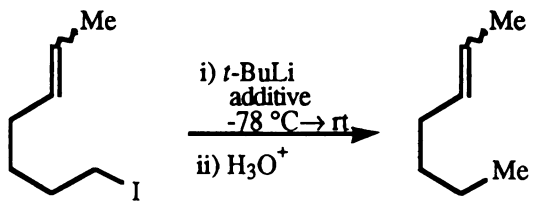
to the increased reactivity as a result of the ring strain, the vinyloxiranes will not be discussed here.[8]

**B. Intramolecular $S_N'$ Reaction**

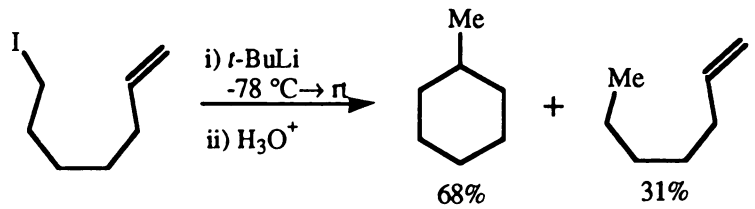
**1. Anionic Cyclization.** In order to appreciate the $S_N'$ cyclizations, ring formation through the intramolecular insertion of an unactivated alkene into a carbon-lithium bond will be discussed. Lithium mediated cyclization is a powerful tool for the formation of five-membered carbocycles with reasonably good diastereoselectivity (eq 9).[9] However, compounds with an alkyl group on the terminal olefinic carbon failed to cyclize under anionic conditions (eq 10).[9] In the case of six-membered ring formation, only a moderate conversion to the cyclized product was detected (eq 11).[9a]




34:1 (*trans*:*cis*) (9)

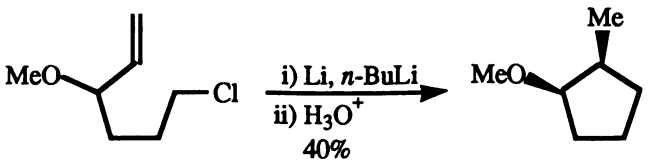



(10)




(11)

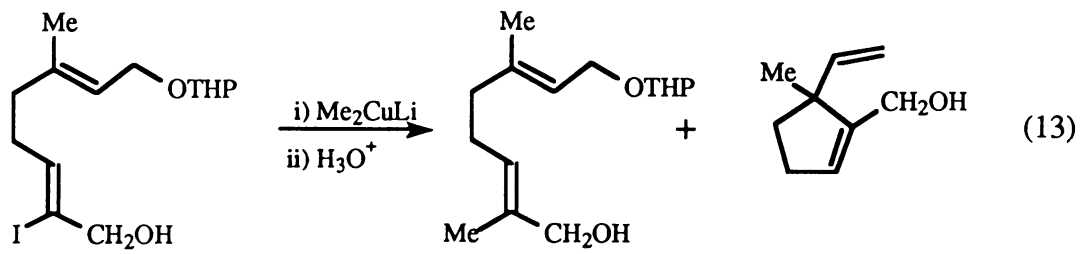
Lithium anionic cyclization has taken place in the presence of an allylic methoxy group (eq 12),[10] and with this substrate, the trajectory for the nucleophile to initiate an $S_N'$ attack cannot be accommodated due to geometrical constraints. The trajectory needed for an $S_N'$ attack follows the same pathway as if the nucleophile attacked a carbonyl carbon. As a result, the typical anionic *exo* cyclization was observed.




(12)

Although lithium mediated cyclizations were efficient for the formation of five-membered rings, the methodology for six-membered ring formation suffered from low conversion. While limited to the cyclization of monosubstituted alkenes, the methodology was strengthened by the ability to functionalize the molecule once cyclization was complete.

**2. $S_N'$ Reactions with Organocuprate Reagents.** A rare $S_N'$ cyclization with a cuprate reagent was seen when attempts were made to methylate **9**. The cyclization was observed when **9** was treated with lithium dimethylcuprate to yield not only the methylated product but also the $S_N'$ cyclized product **11** (eq 13).[11] The formation of **11** was quite remarkable since tetrahydropyranyl ethers (THP), which were commonly used for protection in organometallic reactions, functioned as the leaving group. The reason for this unexpected reactivity can be partially attributed to the allylic nature of the THP ether.

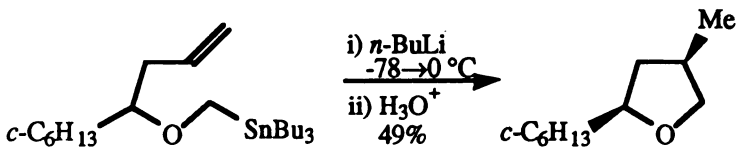



**9** **10** 30% **11** 30%

(13)

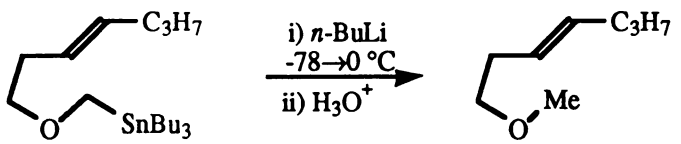
**3. $S_N'$ Reactions with Organolithium Reagents.** $S_N'$ reactions have been used to generate tetrahydrofuran derivatives. The α-alkoxylithium reagent that has succeeded in tetrahyrofuran formation was produced by the treatment of **12** with *t*-butyllithium (eq 14).[12] After transmetallation, the anion underwent cyclization to produce **13** in poor

yields, and when a disubstituted olefin was used, no cyclization occurred (eq 15).[12] The efficiency of cyclization was greatly improved with the employment of an allylic methoxy substituent as in **14** (eq 16). Such cyclizations provided higher yields and higher *cis* to *trans* ratios, and the resultant vinyl group was easily handled and was suitable for further transformations.




(14)

**12** **13** 11:1 (*cis*:*trans*)

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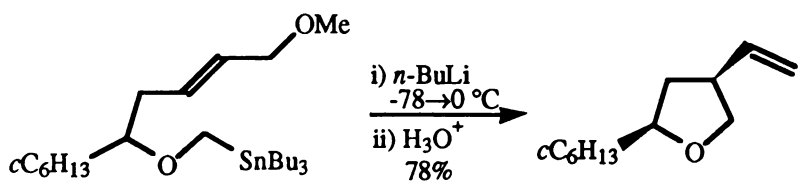
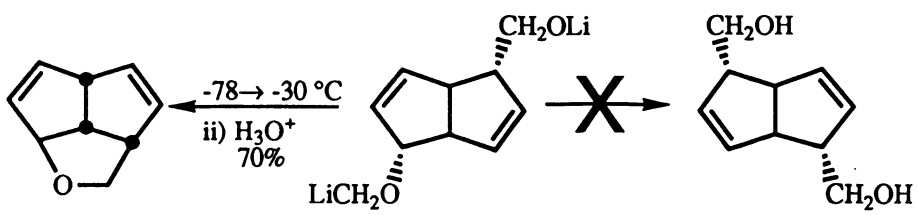



(16)

**14** **15** >15:1 (*cis*:*trans*)

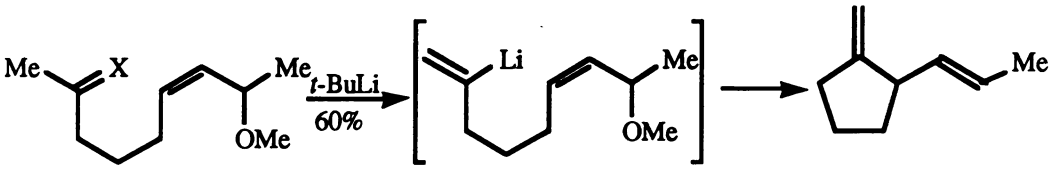
A similar cyclization was seen in the formation of an intermediate for the synthesis of dodecahedrane.[13] The intermediate was to be generated by a bis [2,3] sigmatropic rearrangement (Scheme II), but instead of rearrangement, the compound underwent an $S_N'$ cyclization to yield **18**.

**Scheme II.** $S_N'$ Cyclization in Dodecahedrane Intermediate.




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

Vinyllithium intermediates have also undergone $S_N'$ cyclization.[14] Preparation of the vinyllithium was accomplished by the treatment of [(triisopropylphenyl)sulfonyl]-hydrazone (NNHTris) with *t*-butyllithium (eq 20). The resultant vinyllithium displaced the allylic methoxy group in an $S_N'$ fashion to yield the cyclic compound **21** in 60% yield. Unfortunately, the formation of six-membered rings was not investigated in this study.

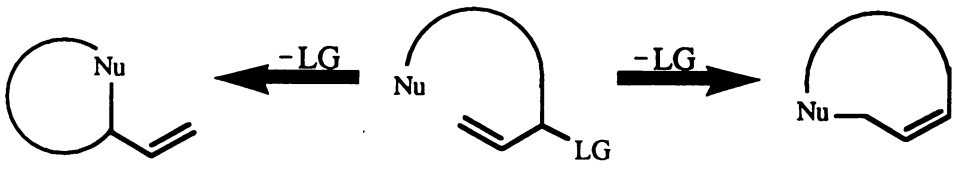



(17)

**19** X=NNHTris **20** **21**

**4. Goals for $S_N'$ Methodology.** In past methods for $S_N'$ cyclization, success in six-membered ring formation was rare. In the methodology proposed, these six points were addressed:

1) Efficient synthesis of $S_N'$ precursors.
2) High conversions and yields for the formation of small to medium size carbocycles.
3) Use of stable methoxy and *t*-butyldimethylsilyloxy substituents as leaving groups.
4) Investigation into the effect of the olefin stereochemistry on the cyclization.
5) Exploitation of the *anti*-addition preference to generate stereoselective products.
6) Investigation of competition between $S_N'$ and $S_N$ modes of cyclization (eq 18).




(18)

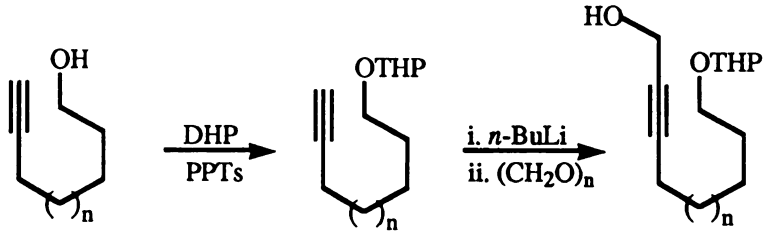
These points are invaluable to establish a methodology that could be incorporated into a natural product synthetic scheme and would surpass the previously discussed $S_N'$ cyclizations.

## II. RESULTS AND DISCUSSION

### A. Preparation of Substrates For $S_N'$ Cyclizations

The study of $S_N'$ cyclization required substrates that varied in tether length between the activated $sp^3$ carbon and the olefinic carbon of the allylic methoxy group (eq 2). After careful consideration, a substrate was designed that would be used for the synthesis of both *cis* and *trans* olefinic isomers. Synthesis of these key substrates was similar to the preparation of the alkyne substrates in the Ziegler-Natta study with alkynes.[15] Compounds **22a-c** were protected as the THP ether **23**, and with subsequent deprotonation and paraformaldehyde quench quickly provided the key intermediate **24** (Scheme III).[16]

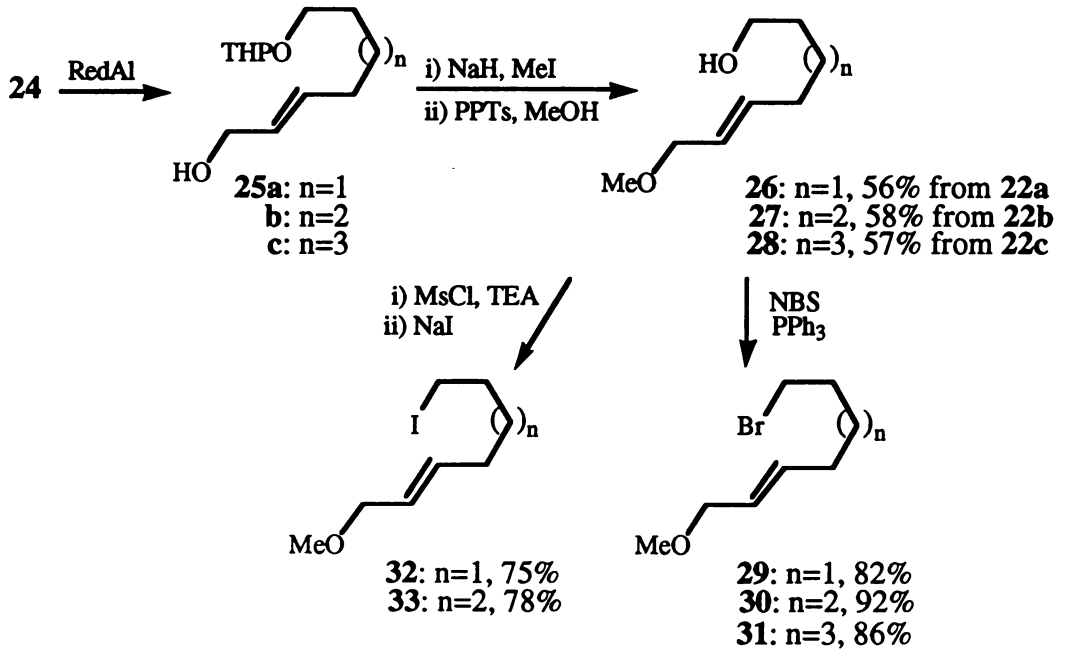
**Scheme III.** Synthesis of Precursor to *Cis* and *Trans* Olefins.



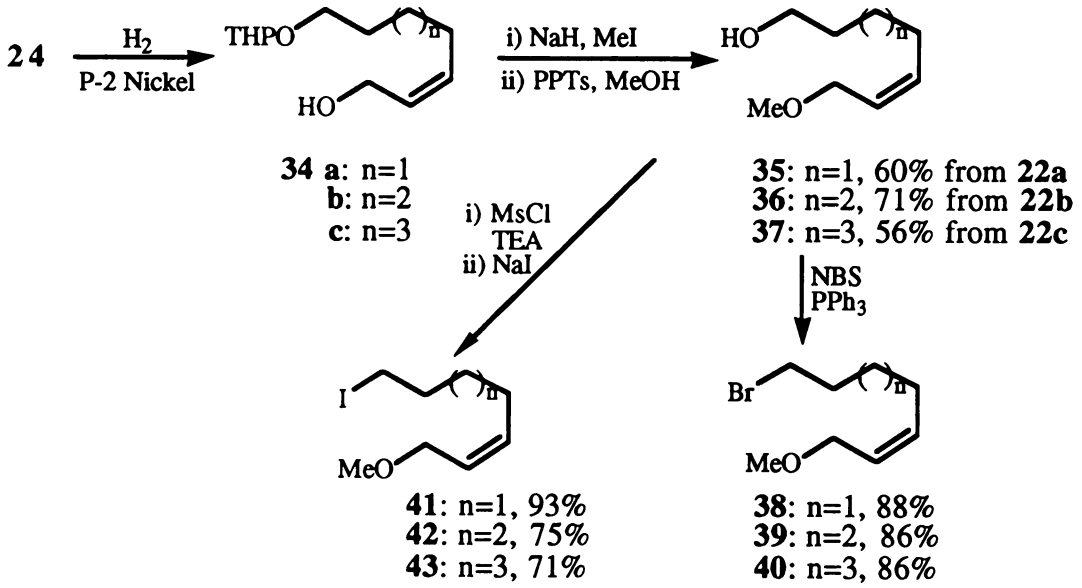

The synthetic pathway to the *trans* isomer employed a procedure developed by Denmark.[17] RedAl® [$NaAlH_2(OCH_2CH_2OCH_3)_2$] efficiently reduced the alkynol **24** stereoselectively to give only one isomer (Scheme IV). The resultant alcohol was methylated, and the THP ether was removed to provide **26**, **27**, and **28**, respectively.[18] The sequence of reactions to synthesize **26**, **27**, and **28** was performed without purification of the intermediate products. The resultant alcohols were then converted to the corresponding bromides with triphenylphosphine and *N*-bromosuccinimide and to the

iodides by conversion of the alcohol to the mesylate which was displaced by the iodide of sodium iodide.

**Scheme IV.** Preparation of *Trans* Olefins for $S_N'$ Cyclization.



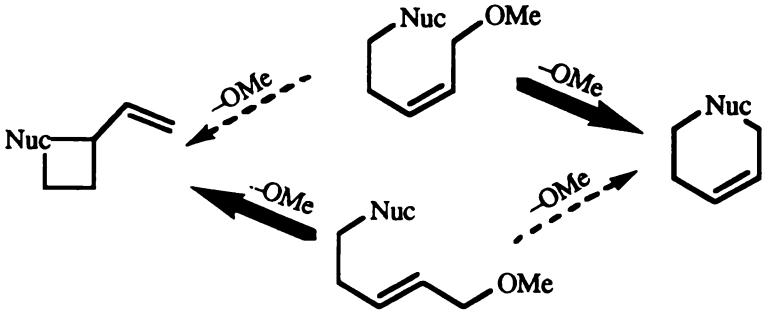

**Scheme V.** Preparation of *Cis* Olefins for $S_N'$ Cyclization.



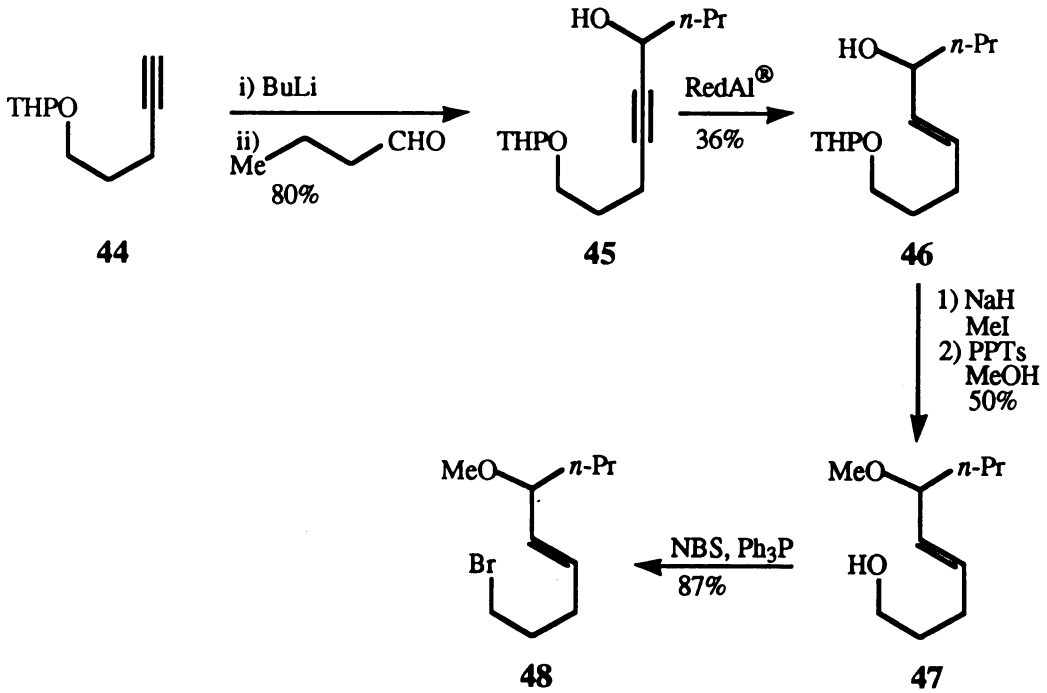
In order to examine the stereochemical effects of the *cis* olefin on the $S_N'$ cyclization, the *cis* olefin substrates were prepared in the same fashion as the *trans* isomer with the exception of the establishment of the *cis* stereochemistry with a hydrogen/nickel boride reduction (Scheme V).[19]

In order to address the feasability of four-membered ring formation, the *trans* isomer (**44**) was synthesized. The decision to pursue the *trans* isomer was based on the assumption that the *cis* isomer would most likely undergo $S_N$ cyclization to generate the more stable six-membered carbocycle (Scheme VI). The *trans* olefin cannot undergo an $S_N$ cyclization because the nucleophile cannot reach the distal allylic carbon.

**Scheme VI.** Potential Reaction Pathways For *Cis* And *Trans* Olefins.

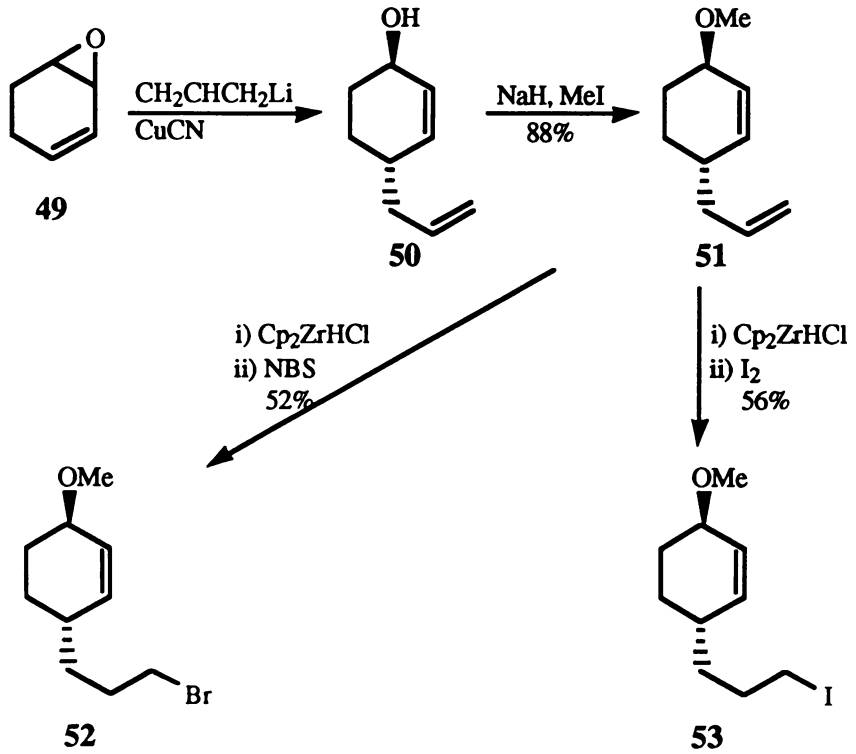



**Scheme VII.** Synthesis of Four-Membered Ring Precursor (*Trans* Olefin).



Synthesis of the four-membered ring precursor began with the deprotonation of THP protected alcohol **44** followed by the addition of butanal to produce **45** (Scheme VII). The use of butanal instead of paraformaldehyde was required to increase the molecular weight, so g.c. analysis could be easily performed on the cyclization products. RedAl® reduction yielded the *trans* isomer which was methylated and deprotected to provide **47** in poor yields. Under the normal bromination conditions, **47** was converted to **48** in 87% yield.

**Scheme VIII.** Synthesis of Precursor For Bicyclic System.



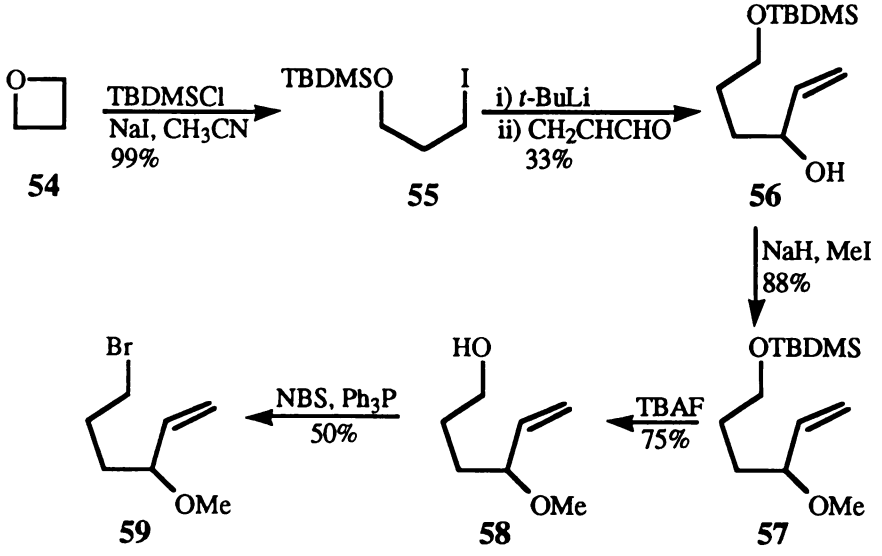

For the previous substrates, the exact nucleophilic approach was arbitrary since the *anti* or *syn* displacement resulted in the same cyclic product. One method to investigate the *anti* or *syn* approach was through a cyclization onto a preexisting ring. Through the examination of molecular models, the *cis* 1,4 isomer had the best orbital overlap for nucleophilic $S_N'$ displacement of the alkoxy group. Establishment of the *cis* stereochemistry was accomplished through the allylation of 3,4-epoxycyclohexene with

an allyl cuprate reagent (Scheme VIII).[20] Alcohol **50** was protected as a methyl ether followed by hydrozirconation[21] and with subsequent treatment of NBS gave **52** or with treatment with iodine yielded **53**.

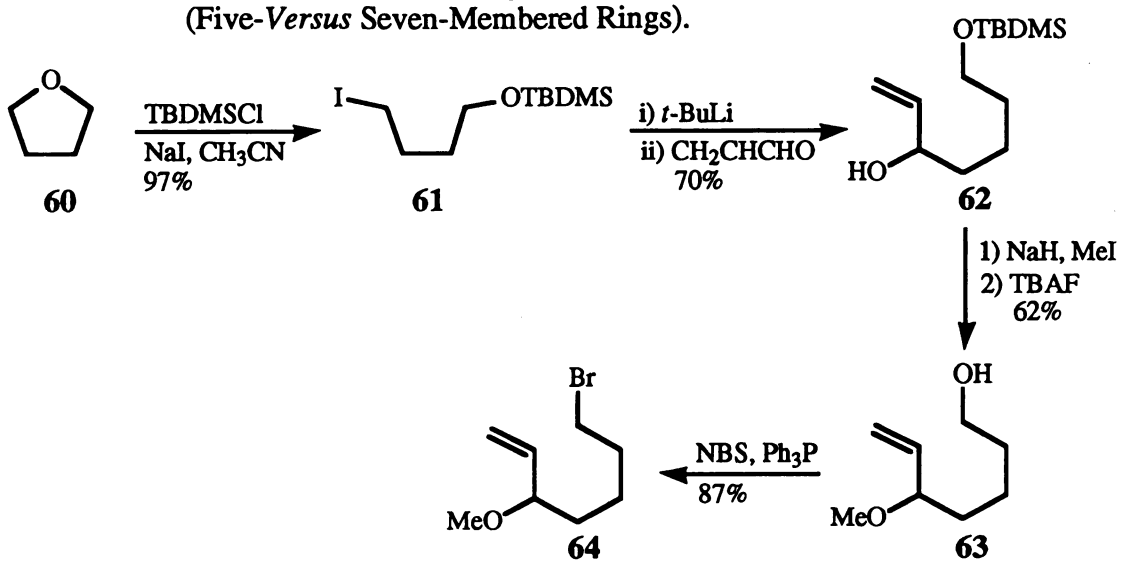
### A. Preparation of Substrates For $S_N$ *Versus* $S_N'$ Investigation

For the study of $S_N$ *versus* $S_N'$ cyclizations, substrates were prepared that positioned the methoxy group on the internal allylic carbon. Preparation of the substrates for the competitive study between $S_N$ and $S_N'$ was accomplished with the three or four carbon unit generated from trimethylene oxetane (**54**) or tetrahydrofuran (**60**), respectively (Schemes IX and X).[22] Lithium-iodide exchange with *t*-butyllithium followed by addition of acrolein yielded the properly substituted carbon chains **56** and **62**. Further transformations of methylation and deprotection with tetrabutylammonium fluoride[23] provided alcohols **58** and **63**, which were routinely converted to **59** and **64**, respectively.

**Scheme IX.** Synthesis of $S_N$ *Versus* $S_N'$ Substrate (Four-*Versus* Six-Membered Rings).



**Scheme X.** Synthesis of $S_N$ *Versus* $S_N'$ Substrate (Five-*Versus* Seven-Membered Rings).

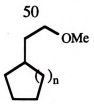



Standards of cyclized products **66** and **67** were commercially available from Aldrich or Wiley Organics. The uncyclized standards were obtained through protonolysis of the corresponding organomagnesium intermediate prior to cyclization.

## B. Cyclization of Substrates

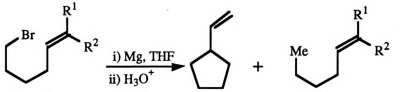
### 1. $S_N'$ Cyclization.

**a. Five-Membered Ring Formation.** Anionic cyclization was first observed when the Grignard intermediate of **38** was stirred at rt for 5 hrs (Table 1). The amount of cyclization was increased dramatically when the Grignard intermediate was generated in THF at reflux. Vinylcyclopentane (**65**) was formed in 94% conversion. Cyclization of the *transs* isomer **29** was not as successful and only gave 87% conversion to **65**. Some cyclization for both the five- and six-membered ring studies occurred through a radical intermediate, which resulted in 1-methoxy-2-cyclopentylethane or 1-methoxy-2-cyclohexylethane, respectively. These compounds accounted for the balance of recovered material for the five and six-membered ring cyclizations.




n=1 or 2

**Table 1.** Results of Five-Membered Ring Formation *Via* Grignard $S_N'$ Cyclization.

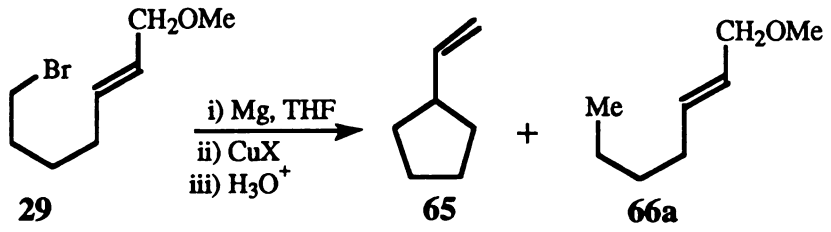



**29/38** **65** **66**

| Substrate | Temp (°C) | Time (hr) | Ratio (65:66) | % Yield (65+66) |
|---|---|---|---|---|
| **29** $R^1$=$CH_2OMe$, $R^2$=H | 66 | 15 | 87:12 | 85 |
| **38** $R^1$=H, $R^2$=$CH_2OMe$ | 0→25 | 5 | 13:85 | 68 |
| | 66 | 15 | 94:6 | 87 |

In order to make this methodology more synthetically useful, alternate conditions were investigated for the promotion of cyclization at lower temperatures. The above cyclizations were repeated with the following changes: (1) Grignard formation maintained at 0 °C to minimize cyclization, and (2) addition of copper(I) salt to reaction mixture at -78 °C. Compounds **29** and **38** were subjected to these new conditions (Tables 2 and 3). The effects of the copper(I) salt were that the cyclizations occurred at lower temperatures with slightly better conversions and yields. The addition of more copper(I) salt (0.5 equiv) did not improve the efficiency of the cyclization (Table 2). All copper(I) salts catalyzed the cyclization of **38** admirably.

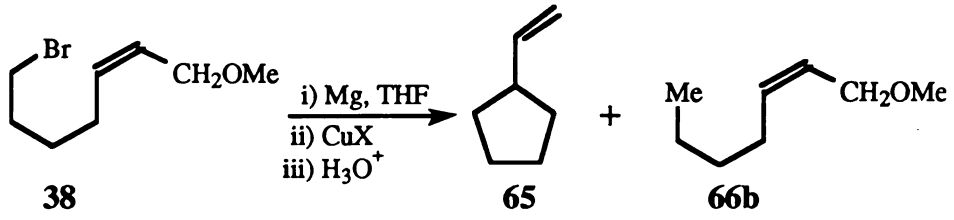
**Table 2.** Results of Five-Membered Ring Formation*Via* Copper(I) Catalyzed $S_N'$ Cyclization With *Trans* Olefins.




**29** **65** **66a**

| Copper(I) salt (equiv) | Temp (°C) | Time (hr) | Ratio (65:66a) | % Yield (65+66a) |
|---|---|---|---|---|
| CuI (0.05) | -78→rt | 0.5 | 68:30 | 74 |
| CuI (0.50) | -78→rt | 0.5 | 66:33 | 68 |
| CuBr (0.05) | -78→rt | 0.5 | 69:30 | 64 |
| CuBr•$SMe_2$ (0.05) | -78→rt | 0.5 | 67:31 | 67 |

**Table 3.** Results of Five-Membered Ring Formation*Via* Copper(I) Catalyzed $S_N'$ Cyclization With *Cis* Olefins.

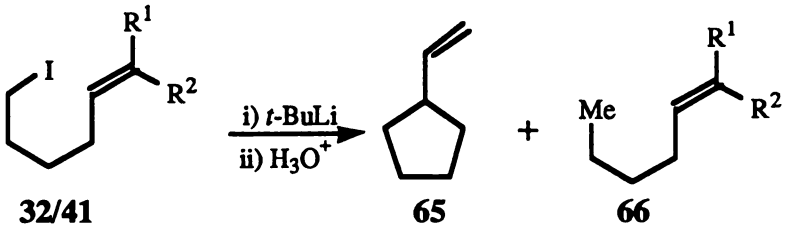



**38** **65** **66b**

| Copper(I) salt (equiv) | Temp (°C) | Time (hr) | Ratio (65:66b) | % Yield (65+66b) |
|---|---|---|---|---|
| CuI (0.05) | -78→rt | 0.5 | 92:8 | 76 |
| CuBr (0.05) | -78→rt | 0.5 | 93:7 | 81 |
| CuBr•$SMe_2$ (0.05) | -78→rt | 0.5 | 91:9 | 74 |

Since the vinyllithium underwent an $S_N'$ displacement of the methoxy group in Chamberlin's studies (eq 20), the decision was made to see if the alkyllithium from iodides **32** and **41** would undergo $S_N'$ cyclization. Lithium-halogen exchange with *t*-butyllithium at -78 °C for 20 minutes generated the alkyllithium which, when warmed, cyclized to provide **65** in high yields (Table 4). This procedure was as successful as the copper catalyzed cyclizations. The lithium cyclization was repeated with a catalytic amount CuI, but this resulted in decreased conversions to and yields of **65**.

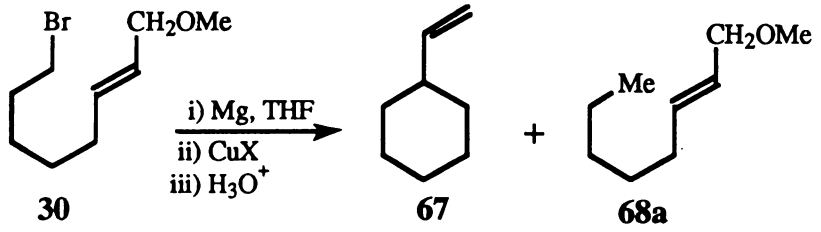
**Table 4.** Results of Five-Membered Ring Formation *Via* Organolithium $S_N'$ Cyclization




**32/41** **65** **66**

| Substrate | Temp (°C) | Time (hr) | Ratio (65:66) | % Yield (65+66) |
|---|---|---|---|---|
| **32** $R^1$=$CH_2OMe$, $R^2$=H | -78→rt | 2 | 94:6 | 88 |
| **41** $R^1$=H, $R^2$=$CH_2OMe$ | -78→rt | 2 | 90:10 | 76 |
| **41** + CuI (0.05 equiv) | -78→rt | 2 | 87:13 | 73 |

**Table 5.** Results of Six-Membered Ring Formation *Via* Copper(I) Catalyzed $S_N'$ Cyclization With *Trans* Olefins.

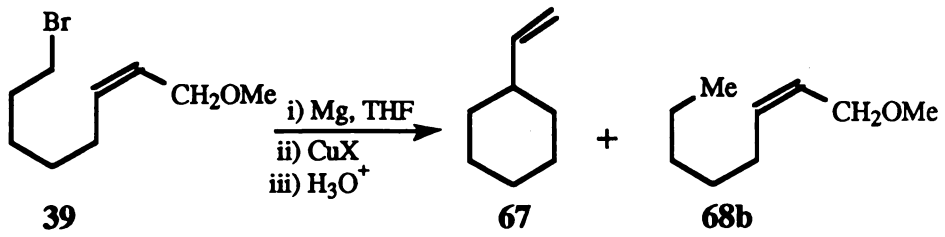



**30** **67** **68a**

| Copper(I) salt (equiv) | Temp (°C) | Time (hr) | Ratio (67:68a) | % Yield (67+68a) |
|---|---|---|---|---|
| CuI (0.05) | -78→rt | 1.0 | 83:17 | 66 |
| CuBr (0.05) | -78→rt | 1.0 | 88:12 | 66 |
| $CuBr•SMe_2$ (0.05) | -78→rt | 1.0 | 85:15 | 68 |
| | -78→rt | 1.0 | 84:16 | 63 |

**b. Six-Membered Ring Formation.** Six-membered ring formation was the major goal for the $S_N'$ methodology. When the organomagnesium intermediates of **30** and **39** were generated in THF at reflux, no cyclization occurred. However, when the organomagnesium intermediate was treated with a catalytic amount of copper(I) salt at lower temperatures, cyclization proceeded to provide vinylcyclohexane (**67**) in relatively good yields (Tables 5 and 6).

**Table 6.** Results of Six-Membered Ring Formation*Via* Copper(I) Catalyzed $S_N'$ Cyclization With *Cis* Olefins.

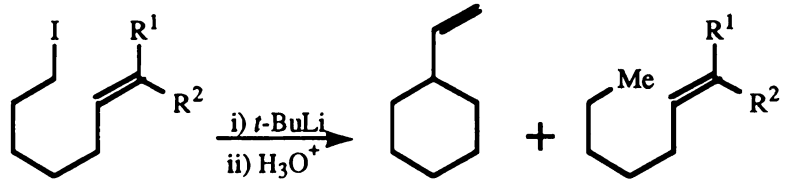



**39** **67** **68b**

| Copper(I) salt (equiv) | Temp (°C) | Time (hr) | Ratio (67:68b) | % Yield (67+68b) |
|---|---|---|---|---|
| CuI (0.05) | -78→rt | 1.0 | 84:12 | 74 |
| CuBr (0.05) | -78→rt | 1.0 | 67:30 | 66 |
| CuBr•$SMe_2$ (0.05) | -78→rt | 1.0 | 70:30 | 67 |

The lithium cyclizations to form six-membered carbocycles performed slightly better than the copper catalyzed cyclizations, and vinylcyclohexane (**67**) was the observed cyclized product. *N,N,N',N'*-Tetramethylethylenediamine (TMEDA) was added to chelate the lithium cation to increase the reactivity of the carbanion, but unfortunately, no significant improvement in either conversion or recovery was observed.

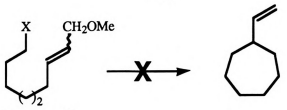
**Table 7.** Results of Six-Membered Ring Formation*Via* Organolithium $S_N'$ Cyclization.




**33/42** **67** **68**

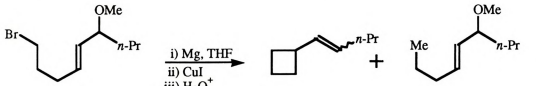
| Substrate | Temp (°C) | Time (hr) | Ratio (67:68) | % Yield (67+68) |
|---|---|---|---|---|
| **33** $R^1$=$CH_2OMe$, $R^2$=H | -78→rt | 2 | 85:9 | 82 |
| **42** $R^1$=H, $R^2$=$CH_2OMe$ | -78→rt | 2 | 78:6 | 76 |

**c. Seven-Membered Ring Formation.** With the unprecedented results of six-membered ring formation, attempts were made to synthesize vinylcycloheptane. Conditions that were successful in earlier cyclizations could not cyclize bromides **31** or **40** or iodide **43** (eq 23).




**31**, **40** or **43** (23)

**d. Four-Membered Ring Formation.** Under the same conditions as the copper catalyzed cyclizations of the previous bromides, **48** cyclized to yield cyclobutane **69** with only 26% conversion (eq 24). This result was not unexpected since intramolecular cyclizations to yield four-membered rings were rare.

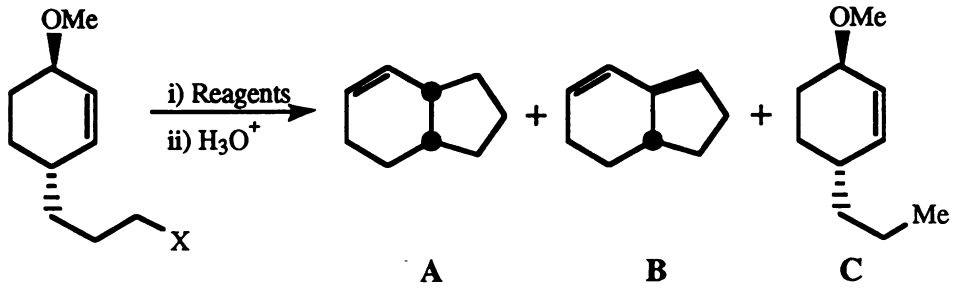



**48** **69** : **70** (24)

26 : 74

**e. Bicyclo[4.3.0]nonene Formation.** Based on previous studies, the cyclization of **52** and **53** was expected to generate the *cis* ring fusion from the nucleophilic attack from the face opposite to that occupied by the methyl ether. When the organomagnesium intermediate was generated in THF at reflux, 73% cyclization was observed. Cyclizations with the copper catalyst had comparable conversions (Table 8). When the methyl group was replaced by the*t*-butyldimethylsilyl group, only 11% conversion to cyclized product was obtained. After workup, the reaction mixture was reduced with $PtO_4$ and $H_2$. The ratios were determined by coinjection with known standards of *cis* and *trans* bicyclo[4.3.0]nonane.

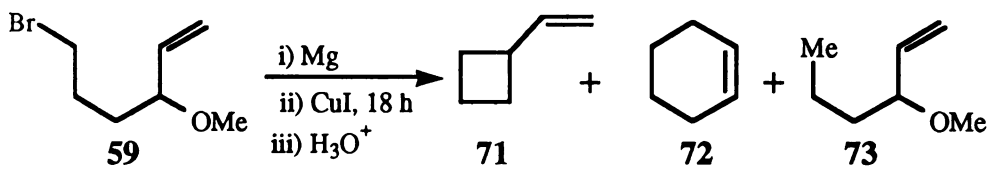
**Table 8.** Results of Bicyclo[4.3.0]nonene Formation.




| Substrate | Reagents | Temp (°C) | Time (h) | Ratio (A:B:C) | % Yield |
|---|---|---|---|---|---|
| **53** X=I | *t*-BuLi | -78→rt | 3 | 75:<3:22 | 77 |
| **54** X=Br | Mg, THF | 66 | 10 | 73:<3:24 | 59 |
| **54** X=Br | i) Mg<br>ii) CuBr•$SMe_2$<br>(0.05 equiv) | -78→rt | 10 | 77:<3:20 | 52 |
| **54** X=Br | i) Mg<br>ii) CuI<br>(0.05 equiv) | -78→rt | 10 | 72:<3:25 | 58 |

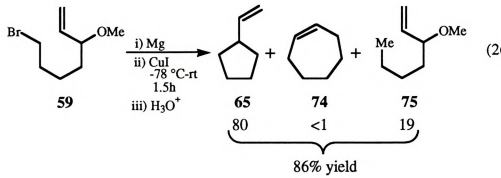
## 2. $S_N$ *Versus* $S_N'$ Cyclizations.

**a. Four-*Versus* Six-Membered Ring Formation.** As was mentioned briefly in the introduction, the $S_N'$ reaction depicted in eq 3 has rarely been observed. Lithium cyclizations do not undergo this type of $S_N'$ cyclization (eq 14), but the possibility remained that softer copper nucleophiles would have a better propensity for ring formation. In substrate **59**, $S_N'$ cyclization occurred to a greater extent than the $S_N$ cyclization. Unfortunately, only 5% conversion to the cyclohexene (**72**) was detected (eq 25).




**59** → **71** – : **72** 5 : **73** 95 (25)

**b. Five- *Versus* Seven-Membered Ring Formation.** Cyclizations in the five- *versus* seven-membered ring formation met with greater success than the four *versus*. six competitive cyclization. The $S_N$ cyclization proceeded to yield **65** with only a trace of the $S_N'$ product (**74**). The Grignard intermediate heated at 66 °C only had 11% conversion to **65** with only a 40% combined yield. In comparison to the copper catalyzed $S_N'$ cyclization (Tables 2 and 3), the $S_N'$ cyclization was the favored process to synthesize **60**.




(26)

**59** **65** **74** **75**

80 <1 19

86% yield

## III. CONCLUSIONS

At the onset of the $S_N'$ cyclization study, several goals were established. Synthesis of the precursors for four, five, and six-membered carbocycles was easily accomplished with employment of the common alkyne intermediate. The cyclization to form vinylcyclopentane from both the *cis* and *trans* isomers went well for the Grignard intermediate at 66 °C, copper(I) catalyzed Grignard cyclization, and for the lithium mediated cyclization. Although the yields of the six-membered rings cyclization were moderate, the high conversion to cyclized product in an area where six-membered ring formation was rare made this a powerful method for intramolecular cyclization. The *cis* isomer gave slightly better cyclization results than the corresponding *trans* isomer for six-membered ring generation. Formation of vinylcycloheptane was not accomplished by the $S_N$ methodology for either the bromide or the iodide. Generation of the cis bicyclo[4.3.0]non-1-ene was moderately successful. Even with the aid of copper(I) catalysts, the cyclization only proceeded 78% conversion. The competition between the

$S_N$ and $S_N'$ modes of cyclization in the copper(I) catalyzed case proved that four-membered ring formation ($S_N$) was not as efficient as six-membered formation ($S_N'$) although the amount of cyclization for the $S_N'$ was trivial. In the competition between five- and seven-membered rings, vinylcyclopentane which was formed by $S_N$ cyclization had formed with trace evidence of the cycloheptene. In comparison to the $S_N'$ cyclization, the $S_N$ mode of cyclization was not as effective. Overall, a new method for generation of vinylcyclopentanes and vinylcyclohexanes was developed which surpassed the methods currently available.

## IV. EXPERIMENTAL

**General methods.** See Chapter I for General Methods.

**Typical Procedure for Protection of Alkynols as the THP ether (23).** A solution of 6-hexynol (**22a**, 2.0 g, 20.4 mmol), dihydropyran (3.4 g, 40.8 mmol), pyridinium p-toluenesulfonate (0.5 g, 2.0 mmol) and dichloromethane (20 mL) was stirred at rt for 2 hours. The reaction was concentrated, and the oil partitioned between half-saturated sodium chloride (24 mL) and diethyl ether (24 mL). The aqueous layer was extracted with diethyl ether (3 x 24 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated (rotary evaporator). The crude product was carried on without purification. The yield was assumed to be quantitative.

**Typical Procedure for Conversion of Compound 23 to Compound 24- Preparation of 24b.** To a solution of *n*-butyllithium (32.7 mL, 65.4 mmol, 2.0M in hexanes) in THF (100 mL) at -78 °C was introduced 6-heptyn-1-yl THP ether (**23b**, 11.6 g, 59.4 mmol) and the reaction was stirred for 30 minutes at -78 °C. The cold bath was removed for 5 minutes and replaced with an ice-water bath. Paraformaldehyde (4.0 g) was added, and the reaction was stirred at rt for 1 hr and at 45-50 °C for an additional 1.5 hr. The

reaction was poured into a 10% $NH_4Cl$ solution (140 mL). The aqueous layer was extracted with diethyl ether (4 x 75 mL), and the organic layers were dried ($MgSO_4$), filtered, and concentrated (rotary evaporator). The crude product was carried on without purification. The yield was assumed to be quantitative.

**Typical Procedure for Trans Reduction of Propargylic Alcohol 24- Preparation of 25b** A solution of RedAl® (27 mL, 95.1 mmol, 3.4M in toluene) and diethyl ether (24 mL) was cooled to 0 °C and a solution of 1-hydroxy-2-octyn-1-yl THP ether (**24b**, 13.4 g, 59.4 mmol) in diethyl ether (24 mL) was added dropwise. Ten minutes after the addition of the alkynol, the cold bath was removed, and the reaction was stirred at rt until reaction was complete (approx. 1-2 hrs). Diethyl ether (50 mL) and 2N $H_2SO_4$ (43 mL) were carefully added to the reaction flask, and the solids were subsequently filtered off. Diethyl ether (2 x 20 mL) was used to wash the solids. The aqueous phase was washed with diethyl ether (2 x 25 mL). The organic phase was washed with water (25 mL) and brine (25 mL). Organic layers were dried ($MgSO_4$), concentrated (rotary evaporator) and carried on to the procedure for methylation and deprotection.

**Typical Procedure for Cis Reduction of Propargylic Alcohol 24 - Preparation of 34b.** The reaction flask was charged with nickel acetate tetrahydrate (1.4 g, 6.0 mmol) and denatured ethanol (80 mL). Sodium borohydride (0.68 g, 17.6 mmol) was slowly added ($H_2$ evolution), and the reaction was stirred at rt for 1 hr. After the addition of ethylene diamine (0.75 mL, 12 mmol) and 1-hydroxy-2-octyn-8-yl THP ether (**24b**, 9.0 g, 39.8 mmol), the flask was placed under an atmosphere of hydrogen, and the hydrogen uptake was monitored by a gas buret. Once the reaction was complete, the ethanol was removed *in vacuo,* and the greyish-blue slush was diluted with diethyl ether (50 mL). The solution was filtered through a pad of silica gel, and the silica pad was washed with diethyl ether (3 x 50 mL). The organic layers were dried ($MgSO_4$) and concentrated (rotary

evaporator). The crude product was carried on to the procedure for methylation and deprotection without further purification.

**Typical Procedure for Methylation and Deprotection of Compounds 25 and 34-Preparation of 27.** A suspension of sodium hydride (1.6 g, 65.3 mmol) in diethyl ether (50 mL) at 0 °C was treated with *E*-1-hydroxy-2-octen-8-yl THP ether (**25b**, 13.6 g, 59.4 mmol) in diethyl ether (10 mL). The reaction was stirred at rt for 1 hr with subsequent addition of methyl iodide (16.8 g, 118.8 mmol). The reaction was stirred at rt overnight. A minimal amount of water was used to dissolve the inorganic salts, and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The organic layers were dried ($MgSO_4$) and concentrated (rotary evaporator). The residue was taken up in methanol (90 mL) and treated with PPTs (1.7 g, 6.7 mmol). The reaction was heated at reflux for 2 hrs. Upon completion of the reaction, methanol was removed *in vacuo*, and the residue was partitioned between half-saturated brine (50 mL) and diethyl ether (50 mL). The aqueous layer was extracted with diethyl ether (2 x 50 mL), and the organic layers were dried ($MgSO_4$) and concentrated (rotary evaporator). Distillation of the residue provided *E*-1-methoxy-2-octen-8-ol (**27**).

**Physical data for *E*-1-methoxy-2-hepten-7-ol (26).** 1.2 g, 56% yield from 5-hexyn-1-ol **22a**, bp 85-90 °C (1 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.35-1.55 (m, 4H), 2.01 (q, *J*=6.7 Hz, 2H), 2.30 (bs, 1H), 3.24 (s, 3H), 3.55 (t, *J*=6.4 Hz, 2H), 3.80 (dd, *J*=0.8, 6.1 Hz, 2H), 5.42-5.70 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 25.0, 32.0, 32.1, 57.3, 62.2, 73.0, 126.0, 134.2; IR (neat) 3600-3100, 2940, 2870, 1660 $cm^{-1}$; HRMS calcd for $C_8H_{16}O_2$ *m/e* 144.1150, obsd (M-1) *m/e* 143.1011.

**Physical data of *E*-1-methoxy-2-octen-8-ol (27).** 5.5 g, 58% yield from 6-heptyn-1-ol **24b**, bp 105-109 °C (1 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.25-1.40 (m, 4H), 1.49 (quint, *J*=6.8 Hz, 2H), 2.00 (q, *J*=6.6 Hz, 2H), 2.24 (bs, 1H), 3.23 (s, 3H), 3.54 (t, *J*=6.6 Hz, 2H), 3.79 (d, *J*=6.1 Hz, 2H), 5.50 (m, 1H), 5.61 (m, 1H); $^{13}$C NMR (75 MHz,

$CDCl_3$) δ 25.0, 28.7, 31.9, 32.3, 57.3, 62.2, 73.0, 125.9, 134.2; IR (neat) 3600-3100, 3010, 2920, 2870, 1670, 1080 $cm^{-1}$. HRMS calcd for $C_9H_{18}O_2$ *m/e* 158.1307, obsd (M-1) *m/e* 158.1311.

**Physical data for *E*-1-methoxy-2-nonen-9-ol (28).** 1.9 g, 57% yield from 7-octyn-1-ol **22c**, bp 113-115 °C (<1 mmHg); $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.23-1.40 (m, 6H), 1.44 (quint, *J*=6.6 Hz, 2H), 1.99 (q, *J*=6.7 Hz, 2H), 2.22 (bs, 1H), 3.25 (s, 3H), 3.55(t, *J*=6.6 Hz, 2H), 3.80 (d, *J*=6.1 Hz, 2H), 5.49 (m, 1H), 5.63 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 25.3, 28.7, 28.8, 32.0, 32.3, 57.3, 62.2, 73.2, 126.0, 134.6; IR (neat) 3600-3100, 3010, 2920, 2870, 1610 $cm^{-1}$.

**Physical data for *Z*-1-methoxy-2-hepten-7-ol (35).** 1.2 g, 60% yield from 5-hexyn-1-ol, **22a**, bp 75-80 °C (1 mmHg); $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.37-1.47 (m, 2H), 1.50 (m, 1H), 1.53-1.67 (m, 2H), 2.08 (q, *J*=6.7 Hz, 2H), 3.29 (s, 3H), 3.61 (t, *J*=6.4 Hz, 2H), 3.95 (d, *J*=5.0 Hz, 2H), 5.47-5.61 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 25.6, 27.2, 32.2, 57.9, 62.6, 68.0, 126.2, 133.3; IR (neat) 3600-3200, 3020, 2940, 2860, 2820, 1620, 1200 $cm^{-1}$; HRMS calcd for $C_8H_{16}O_2$ *m/e* 144.1150, obsd *m/e* 144.1183.

**Physical data for *Z*-1-methoxy-2-octen-8-ol (36).** 4.4 g, 71% yield from 6-heptyn-1-ol **22b**, bp 100-103 °C (1 mmHg); $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.32 (m, 4H), 1.49 (quint, *J*=6.7 Hz, 2H), 2.02 (q, *J*=6.7 Hz, 2H), 2.28 (bs, 1H), 3.25 (s, 3H), 3.54 (t, *J*=6.6 Hz, 2H), 3.91 (d, *J*=5.8 Hz, 2H), 5.40-5.56 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 25.0, 27.1, 29.0, 32.2, 57.7, 62.2, 68.0, 125.8, 133.3; IR (neat) 3020, 2920, 2860, 2810, 1650, 1110 $cm^{-1}$. HRMS calcd for $C_9H_{18}O_2$ *m/e* 158.1307, obsd *m/e* 158.1324.

**Physical data for *Z*-1-methoxy-2-nonen-9-ol (37).** 2.9 g, 56% yield from 7-octyn-1-ol **22c**, bp 110-115 °C (<1 mmHg); $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.20-1.40 (m, 6H), 1.50 (quint, *J*=6.6 Hz, 2H), 2.06 (q, *J*=6.7Hz, 2H), 2.20 (bs, 1H), 3.26 (s, 3H), 3.55 (t, *J*=6.6 Hz, 2H), 3.91 (d, *J*=5.6 Hz, 2H), 5.40-5.59 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 25.3, 27.1, 28.7, 29.0, 32.3, 57.6, 62.4, 68.0, 125.7, 131.8; IR (neat) 3600-3200, 3070, 2930, 2870, 1610, 1200 $cm^{-1}$.

**Physical data for *E*-6-methoxy-4-nonen-1-ol (47).** 0.9 g, 50% yield, bp 77-79 °C (<1 mmHg); $^1$H NMR δ 0.82 (t, *J*=7.2 Hz, 3H), 1.19-1.42 (m, 4H), 1.50 (m, 1H), 1.60 (quint, *J*=7.0 Hz, 2H), 2.01 (bs, 1H), 2.09 (q, *J*=7.2 Hz, 2H), 3.18 (s, 3H), 3.42 (q, *J*=7.4 Hz, 1H), 3.58 (t, *J*=6.5 Hz, 2H), 5.24 (dd, *J*=15.3, 8.0 Hz, 1H), 5.55 (dt *J*=15.3, 6.7 Hz, 1H); $^{13}$C NMR δ 13.9, 18.5, 28.4, 32.1, 37.6, 55.6, 62.1, 82.2, 131.1, 133.1; IR 3100-3600, 2960, 2940, 2870, 2820, 1670, 1097, 970 cm$^{-1}$.

**Typical Procedure for Conversion of an Alcohol to the Corresponding Bromide-Preparation of 29.** A solution of *E*-1-methoxy-2-nonen-9-ol (**28**, 1.1 g, 6.3 mmol) and triphenylphosphine (1.8 g, 7.0 mmol) in dichloromethane (6 mL) was cooled to 0 °C. *N*-Bromosuccinimide (1.2 g, 7.0 mmol) was added over a 15 minute period. The reaction was stirred at 0 °C for 1 hour and at ambient temperature for 2 hours and concentrated *in vacuo*. Dichloromethane (2 mL) was added to the dark orange sludge, and the mixture was stirred for 5 minutes. Light petroleum ether (12 mL) was added, and the reaction was stirred vigorously followed by solvent removal *via* cannula filtration. The solids were washed with light petroleum ether (2 x 7 mL). The filtration procedure was repeated, and the solvent was removed *in vacuo* until 3-4 mL remained, at which point, the residue was filtered through 1" of basic alumina in a pipette and rinsed through with petroleum ether (10 mL). The solvent again was removed with a rotary evaporator. Bulb-to-bulb distillation yielded *E*-1-methoxy-9-bromo-2-nonene (**31**).

**Physical data for *E*-1-methoxy-7-bromo-2-heptene (29).** 1.0 g, 82% yield, bp oven=80-90 °C (1 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.51 (quint, *J*=7.5 Hz, 2H), 1.82 (quint, *J*=7.2 Hz, 2H), 2.03 (q, *J*=7.1 Hz, 2H), 3.24 (s, 3H), 3.38 (t, *J*=6.8 Hz, 2H), 3.81 (dd, *J*=1.1, 5.8 Hz, 2H), 5.47 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 27.5, 31.3, 32.0, 33.6, 57.7, 126.7, 133.7; IR (neat) 2920, 2850, 1720, 1680, 1110 cm$^{-1}$; HRMS calcd for $C_8H_{15}BrO$ *m/e* 206.0306, obsd *m/e* 206.0267.

**Physical data for *E*-1-methoxy-8-bromo-2-octene (30).** 1.3 g, 92% yield, bp oven=84-95 °C (1 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.40 (m, 4H), 1.80 (quint, *J*=6.8 Hz, 2 H), 2.03 (q, *J*=6.5 HZ, 2H), 3.27 (s, 3H), 3.36 (t, *J*=6.8 Hz, 2H), 3.82 (dd, *J*=1.0, 6.0 Hz, 2H), 5.53 (m, 1H), 5.62 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 27.6, 28.1, 31.9, 32.6, 33.6, 57.6, 73.1, 126.5, 134.1; IR (neat) 3010, 2930, 2860, 1620, 1110 $cm^{-1}$; HRMS calcd for $C_9H_{17}BrO$ *m/z* 220.0463, obsd *m/z* 220.0451.

**Physical data for *E*-1-methoxy-9-bromo-2-nonene (31).** 1.2 g, 86% yield, bp oven=72-80 °C (1 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.25-1.45 (m, 6H), 2.10 (q, *J*=6.6 Hz, 2H), 3.28 (s, 3H), 3.36 (t, *J*=6.7 Hz, 2H), 3.81 (dd, *J*=1.0, 5.0 Hz, 2H), 5.45-5.55 (m, 1H), 5.60-5.71 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 28.0, 28.2, 28.8, 32.1, 32.6, 33.9, 57.6, 73.2, 126.2, 134.5; IR (neat) 3020, 2934, 2856, 1670, 1116, 972 $cm^{-1}$; HRMS calcd for $C_{10}H19BrO$ *m/e* 234.0620, obsd *m/e* 234.0621.

**Physical data for *Z*-1-methoxy-7-bromo-2-heptene (38).** 2.3 g, 88% yield, bp 50-53 °C (1 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.50 (quint, *J*=7.2 Hz, 2H), 1.83 (quint, *J*=7.2, 2H), 2.08 (q, *J*=6.7 Hz, 2H), 3.32 (s, 3H), 3.40 (t, *J*=6.7 Hz, 2H), 3.94 (d, *J*=4.5 Hz, 2H), 5.53 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 26.6, 27.9, 32.1, 33.4, 57.9, 68.0, 126.6, 132.6; IR (neat) 3020, 2930, 2890, 2860, 2820, 1110, 1450 $cm^{-1}$; HRMS calcd for $C_8H_{15}BrO$ *m/e* 208.0286, obsd *m/e* 208.0198.

**Physical data for *Z*-1-methoxy-8-bromo-2-octene (39).** 1.2 g, 86% yield, bp 75-90 °C (1 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.32-1.60 (m, 4H), 1.83 (quint, *J*=7.0 Hz, 2H), 2.00 (q, *J*=6.3 Hz, 2H), 3.30 (s, 3H), 3.37 (t, *J*=6.8 Hz, 2H), 3.94 (d, *J*=5.3 Hz, 2H), 5.53 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 27.2, 27.6, 28.6, 32.5, 33.6, 57.8, 68.0, 126.2, 133.1; IR (neat) 3020, 2920, 2860, 2810, 1650, 1095 731 $cm^{-1}$; HRMS calcd for $C_9H_{17}BrO$ *m/z* 220.0463, obsd *m/z* 220.0307.

**Physical data for *Z*-1-methoxy-9-bromo-2-nonene (40).** 1.2 g, 86% yield, bp oven=75-90 °C (1 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.22-1.47 (m, 6H), 1.82 (quint, *J*=7.0, 2H), 2.05 (q, *J*=6.4 Hz, 2H), 3.31 (s, 3H), 3.38 (t, *J*=6.8 Hz, 2H), 3.94 (d, *J*=5.0 Hz, 2H),

5.46-5.60 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 27.4, 27.9, 28.2, 29.2, 32.7, 33.9, 58.0, 68.0, 126.1, 143.4; IR (neat) 3010, 2930, 2850, 1650, 1100 727 $cm^{-1}$; HRMS calcd for $C_{10}H_{19}BrO$ *m/z* 234.0620, obsd *m/z* 234.0631.

**Physical data for *E*-1-bromo-6-methoxy-4-nonene (48).** 0.9 g, 87% yield, bp oven=60-75 °C (1 mmHg); $^1H$ NMR 0.87 δ (t, *J*=7.1 Hz, 3H), 1.20-1.80 (m, 4H), 1.92 (quint, *J*=7.0, 2H), 2.20 (q, *J*=7.1 Hz, 2H), 3.21 (s, 3H), 3.38 (t, *J*=6.8 Hz, 3H), 3.41 (m, 1H); $^{13}C$ NMR δ 12.1, 18.8, 30.7, 32.0, 33.0, 37.5, 56.0, 82.1, 131.7, 132.3; IR (neat) 2960, 2930, 1650, 1500, 1190, 990 $cm^{-1}$.

**Typical Procedure for Conversion of an Alcohol to the Corresponding Iodide-Preparation of 29.** At -10 °C, a solution of *E*-1-methoxy-2-hepten-7-ol (**26**, 0.7 g, 4.8 mmol), triethylamine (1 mL, 7.2 mmol) in $CH_2Cl_2$ (20 mL) was treated dropwise with methanesulfonyl chloride (0.6 g, 5.3 mmol). After 15 minutes at -10 °C, the reaction was diluted with $CH_2Cl_2$ (18 mL), and the mixture was washed with 10% aqueous HCl (1 mL), saturated $NaHCO_3$ (9 mL) and brine (1 mL). The organic layer was dried ($MgSO_4$) and concentrated (rotary evaporator). The residue was added to a solution of sodium iodide (1.4 g, 9.7 mmol) in THF (12 mL) at 0 °C. The reaction was warmed to rt and stirred until complete. The reaction was diluted with diethyl ether (35 mL) and washed with saturated $NaHCO_3$ (2 x 65 mL) and brine (6 mL). The organic layer was dried ($MgSO_4$) and concentrated (rotary evaporator). Bulb-to-bulb distillation provided *E*-7-iodo-1-methoxy-2-heptene (**32**).

**Physical data for *E*-7-iodo-1-methoxy-2-heptene (32).** 0.9 g, 75% yield, bp oven=54-70 °C (1 mmHg); $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.46 (quint, *J*=7.5 Hz, 2H), 1.80 (quint, *J*=7.2 Hz, 2H), 2.05 (q, *J*=6.8 Hz, 2H), 3.16 (t, *J*=7.0 Hz, 2H), 3.29 (s, 3H), 3.83 (dd, *J*=0.8, 5.8 Hz, 2H), 5.43-5.71 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 6.6, 29.7, 31.0, 33.0, 57.8, 73.0, 126.8, 133.8; IR (neat) 3010, 2930, 2850, 1670, 1110 $cm^{-1}$.

**Physical data for *E*-8-iodo-1-methoxy-2-octene (33).** 2.2 g, 78% yield, bp oven=70-90 °C (1 mmHg); $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.34-1.47 (m, 4H), 1.76-1.87 (m, 2H),

2.30 (dq, *J*=0.84, 6.1 Hz, 2H), 3.17 (t, *J*=7.0 Hz, 2H), 3.30 (s, 3H), 3.83 (dd,*J*=0.84, 5.8 Hz, 2H), 5.57 (m, 1H), 5.65 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 6.6, 28.0, 30.0, 32.0, 33.4, 57.8, 72.6, 126.3, 134.2; IR (neat) 3010, 2920, 2860, 1600, 1110 $cm^{-1}$.

**Physical data for *Z*-7-iodo-1-methoxy-2-heptene (41).** 1.8 g, 93% yield, bp oven=64-70 °C (1 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.45 (quint, *J*=7.4 Hz, 2H), 1.80 (quint, *J*=7.3 Hz, 2H), 2.07 (q, *J*=6.7 Hz, 2H), 3.17 (t, *J*=6.8 Hz, 2H), 3.29 (s, 3H), 3.93 (d,*J*=4.5 Hz, 2H), 5.50-5.56 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 6.4, 26.4, 30.2, 32.9, 57.9, 68.0, 126.7, 132.6 $cm^{-1}$; HRMS calcd for $C_8H_{15}IO$ *m/z* 254.0168, obsd *m/z* 254.0170.

**Physical data for *Z*-8-iodo-1-methoxy-2-octene (42).** 0.9 g, 75% yield, bp oven=70-85 °C (1 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.32-1.40 (m, 2H), 1.72-1.84 (m, 2H), 2.00-2.10 (m, 2H), 3.15 (t, *J*=7.0 Hz, 2H), 3.29 (s, 3H), 3.93 (d,*J*=5.3 Hz, 2H), 5.44-5.56 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 6.8, 27.2, 28.3, 30.0, 33.3, 57.8, 68.0, 126.2, 133.1; IR (neat) 2990, 2930, 2850, 1650, 1480, 1200 $cm^{-1}$; HRMS calcd for $C_9H_{17}IO$ *m/z* 268.0325, obsd *m/z* 268.0377.

**Physical data for *Z*-9-iodo-1-methoxy-2-nonene (43).** 1.5 g, 71% yield, bp oven=80-95 °C (1 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.22-1.41 (m, 6H), 1.79 (quint, *J*=7.3 Hz, 2H), 2.02 (q, *J*=6.4 Hz, 2H), 3.28 (s, 3H), 3.57 (t, *J*=7.0 Hz, 2H), 3.82 (dd,*J*=0.98, 6.1 Hz, 2H), 5.43-5.60 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 7.0, 27.3, 27.9, 29.2, 30.2, 33.3, 57.8, 68.0, 126.0, 133.3; IR (neat) 3010, 2930, 2850, 1670, 1500, 1100 $cm^{-1}$.

**Preparation of 45.** A solution of **44** in THF (60 mL) was cooled to -78 °C, and *n*-butyllithium (5.3 mL, 13.2 mmol, 2.5M in hexanes) was added. The mixture was stirred at -78 °C for 30 minutes, at which point, the cold bath was removed for 5 minutes, and the cold bath was returned. Butyraldehyde (0.9 g, 13.2 mmol) was introduced into the reaction dropwise. Upon completion of the addition, the reaction was stirred at -78 °C for 10 minutes and slowly warmed to rt. The mixture was stirred at rt overnight. The reaction was quenched with 10% $NH_4Cl$ (40 mL). The layers were separated, and the

aqueous layer was extracted with diethyl ether (3 x 40 mL). The organic layers were dried ($MgSO_4$), filered, and concentrated. Flash chromatography yielded 2.2 g (82% yield) of the desired product. $R_f$=0.4 (50% diethyl ether/petroleum ether, stained with phosphomolybdic acid); $^1H$ NMR (300 MHz) δ 0.92 (t, *J*=7.1 Hz, 3H), 1.36-1.82 (m, 12H), 1.97 (bs, 1H), 2.30 (dt, *J*=1.7, 6.8 Hz, 2H), 3.40-3.53 (m, 2H), 3.74-3.87 (m, 2H), 4.31 (m, 1H), 4.57 (t, *J*=7.1 Hz, 1H); $^{13}C$ NMR (75 MHz) δ 13.7, 15.6, 18.4, 19.5, 25.4, 28.8, 30.6, 40.2, 62.2, 62.4, 65.8, 81.8, 84.6, 98.7; IR 3600-3100, 2955, 2872, 2212 $cm^{-1}$.

**Preparation of 3,4-epoxycyclohex-1-ene (49).**[23] A mixture of glacial acetic acid (24 g), 90% hydrogen peroxide (22 g) and $H_2SO_4$ (0.3 mL) was stirred for 3h at rt. This solution with sodium acetate (0.3 g) was added dropwise to a solution of sodium carbonate (60 g), 1,3-cyclohexadiene (18 g, 224.6 mmol) in dichloromethane (150 mL), and the mixture was stirred overnight. The solids were filtered off, and the dichloromethane was removed by distillation at atmospheric pressure. Vacuum distillation yielded 14.1 g (65% yield) of desired product. bp 64-65 °C (65 mmHg), $^1H$ NMR (300 MHz) δ 1.53 (m, 1H), 1.81-2.05 (m, 2H), 3.13 (dt, *J*=2.0, 4.0 Hz, 1H), 3.40 (ddd, *J*=1.4, 2.6, 5.4 Hz, 1H), 5.75-5.90 (m, 2H); $^{13}C$ NMR (75 MHz) δ 20.5, 20.8, 47.0, 55.1, 123.0, 133.0; IR 3040, 3017, 2934, 2847, 1639, 1024
$cm^{-1}$.

**Preparation of 50.** To a 500 mL round bottom flask equipped with a pressure equalizing addition funnel were added Li (4.2 g, 0.6 mol) anf THF (50 mL). The flask was cooled to -15 °C, and allyl phenyl ether (6.7 g, 50.0 mmol) in diethyl ether (25 mL) was added dropwise. The reaction was stirred at -15 °C for 45 minutes and at rt for 20 minutes. The dark red solution was cannula transferred to copper(I) cyanide in diethyl ether (10 mL) at -40 °C and stirred at this temperature for 30 minutes. 3,4-Epoxycyclohex-1-ene (2.4 g, 25.0 mmol) was introduced, and the reaction was allowed to warm to rt. Water (75 mL)

and diethyl ether (75 mL) were added, and the aqueous layer was extracted with diethyl ether (3 x 75 mL). The combined organic layers were washed with 10% NaOH (50 mL), brine (75 mL), dried ($MgSO_4$) and concentrated (rotary evaporator) to yield an oil that was distilled to yield 2.3 g of crude product. bp 75-80 °C (1 mmHg), $R_f$=0.6 (40% ethyl acetate/petroleum ether, stained with phosphomolybdic acid); $^1H$ NMR (300 MHz) δ 1.23 (m, 1H), 1.45 (m, 1H), 1.80 (m, 1H), 1.90-2.28 (m, 1H), 2.30 (bs, 1H), 4.18 (m, 1H), 4.95-5.05 (m, 2H), 5.60-5.57 (m, 2H); $^{13}C$ NMR (75 MHz) δ 26.6, 31.7, 35.0, 40.0, 66.8, 116.2, 130.6, 133.5, 136.4; IR 3100-3600, 3076, 3020, 2932, 2858, 1641, 1448, 1060, 736 $cm^{-1}$.

**Preparation of TBDMS Protected 50.** The crude **50** (2.6 g) in DMF (18 mL) at 0 °C was treated with TBDMSCl (3.1 g, 20.7 mmol) and imidazole (2.8 g, 41.4 mmol). The reaction was stirred at rt for 4h. Water (30 ml) was added, and the mixture was extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated (rotary evaporator). Flash chromatography yielded 3.0 g (48% yield from **49**) of pure desired product. $R_f$=0.10 (100% light petroleum ether, stained with phosphomolybdic acid); $^1H$ NMR (300 MHz) δ 0.059 (s, 3H), 0.060 (s, 3H), 0.89 (s, 9H), 1..18 (m, 1H), 1.50 (m, 1H), 1.81 (m, 1H), 1.87-2.08 (m, 4H), 2.16 (m, 1H), 4.22 (m, 1H), 4.99 (dd, *J*=15.3, 1.8 Hz, 1H), 5.00 (dd, *J*=11.7, 1.8 Hz, 1 H), 5.57 (m, 1H), 5.58 (s, 1H); $^{13}C$ NMR (75 MHz) δ -4.6, -4.5, 18.2, 25.9, 27.2, 32.4, 35.2, 40.4, 67.9, 116.0, 131.5, 132.4, 136.5; IR (neat) 3078, 3024, 2932, 2858, 1641, 1471, 1093 $cm^{-1}$.

**Preparation of 3-Methoxy-6-allylcyclohex-1-ene (51).** At 0 °C, a suspension of NaH (0.3 g, 12.5 mmol) in THF (9 mL) was treated with **50** (1.6 g, 11.4 mmol) in THF (1 mL). The mixture was stirred for 2h at rt. The reaction was cooled to 0 °C, and methyl iodide (3.2 g, 22.8 mmol) was added dropwise. The reaction was allowed to warm to rt and stirred overnight. Upon completion of reaction, a minimal amount of water was added to

dissolve the inorganic salts. The layers were separated, and the aqueous layer was extracted with diethyl ether (1 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated (rotary evaporator). The residue was distilled to yield 1.5 g (88% yield) of the methyl ether. bp 33-35 °C (1 mmHg); $^1H$ NMR δ 1.18 (m, 1H), 1.44 (m, 1H), 1.82 (m, 1H), 1.93-2.10 (m, 3H), 2.16 (m, 1H), 3.33 (s, 3H), 3.75 (m, 1H), 4.98 (d, *J*=11.7 Hz, 1H), 4.99 (dd, *J*=17.0, 5.3 Hz, 1H) 5.64-5.82 (m, 3H); $^{13}C$ NMR δ 26.6, 27.7, 35.3, 40.2, 55.6, 75.4, 116.1, 128.0, 134.0, 136.5; IR (neat) 3076, 3024, 2978, 2930, 2862, 2818, 1641, 1103 $cm^{-1}$.

**Preparation of 52.** Diene **51** (3.2 g, 12.9 mmol) was added to a slurry of $Cp_2ZrHCl$ (3.6 g, 13.8 mmol) in 1,2-dichloroethane (20 mL) at 0 °C. The reaction was stirred at 0 °C for 2h and at rt until the reaction was complete. The reaction was cooled to 0 °C, NBS (2.4 g, 13.8 mmol) was introduced, and the reaction was stirred at rt 5h. Light petroleum ether (60 mL) was added, and the suspension was filtered through silica gel. The silica gel was eluted with petroleum ether. The organic layers were concentrated and chromatographed to yield 1.2 g (56% yield) of the desired product. $R_f$=0.3 (10% diethyl ether/petroleum ether, stained with phosphomolybdic acid); $^1H$ NMR (300 MHz) δ 1.16 (m, 1H), 1.26-1.50 (m, 4H), 1.85 (quint, *J*=7.4 Hz, 2H), 1.98-2.16 (m, 2H), 3.32 (s, 3H), 3.36 (t, *J*=6.8 Hz, 2H), 3.74 (m, 1H), 5.60-5.75 (m, 2H); $^{13}C$ NMR δ (75 MHz) 26.6, 27.6, 30.0, 33.8, 34.3, 34.8, 55.5, 75.3, 128.2, 133.9; IR (neat) 3022, 2932, 2858, 2818, 1651, 1450, 1103 $cm^{-1}$.

**TBDMS Protected 52.** Diene **51** (3.2 g, 12.9 mmol) was added to a slurry of $Cp_2ZrHCl$ (3.3 g, 12.9 mmol) in 1,2-dichloroethane (25 mL) at 0 °C. The reaction was stirred at 0 °C for 2h and at rt until the reaction was complete. Addition of 10% HCl (20 mL) was followed by extraction with pentane (3 x 30 mL). The organic layers were dried ($MgSO_4$), filtered, and concentrated (rotary evaporator). The residue was distilled to

yield 3.0 g (70% yield) of desired product. bp 92-95 °C (1 mmHg), $^1$H NMR (300 MHz) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 1.08-1.53 (m, 4H), 1.76-1.98 (m, 4H), 2.09 (m, 1H), 3.38 (t, *J*-=6.8, 2H), 4.21 (m, 1H), 5.56 (s, 2H); $^{13}$C NMR (75 MHz) δ -4.6, -4.4, 18.3, 25.9, 27.3, 30.1, 32.3, 33.8, 34.7, 34.8, 67.9, 132.1, 132.5; IR 3022, 2932, 2857, 1647, 1252, 1089 cm$^{-1}$.

**Preparation of 53.** Diene **51** (1.0 g, 6.5 mmol) was added to a slurry of $Cp_2ZrHCl$ (2.4 g, 9.2 mmol) in benzene (20 mL) at 0 °C. The reaction was stirred at 0 °C for 2h and at rt until the reaction was complete. The reaction was cooled to 0 °C, iodine (2.3 g, 9.2 mmol) was introduced, and the reaction was stirred for 3h. The reaction was filtered through silica gel and concentrated. The residue was chromatographed chromatographed to yield 1.0 g (56% yield) of the desired product. $R_f$=0.3 (10% diethyl ether/petroleum ether, stained with phosphomolybdic acid); $^1$H NMR (300 MHz) δ 1.10-1.50 (m, 6H), 1.85 (quint, *J*=7.4 Hz, 2H), 2.05 (m, 1H), 3.13 (t, *J*=6.8 Hz, 2H), 3.32 (s, 3H), 3.74 (m, 1H), 5.60-5.75 (m
, 2H); $^{13}$C NMR δ (75 MHz) 6.8, 26.6, 27.6, 30.8, 33.8, 34.3, 34.8, 55.5, 75.3, 128.2, 133.9; IR (neat) 3022, 2932, 2858, 2818, 1649, 1450, 1103 cm$^{-1}$.

**Preparation of TBDMS Protected 53.** Corresponding bromide **52** (0.26 g, 0.8 mmol), potassium iodide (1.3 g, 8.0 mmol) in DMF (4 mL) was heated to 55 °C for 18h. The reaction was diluted with water (10 mL) with subsequent extractions with pentane (3 x 10 mL). The combined organic layers were washed with water (10 mL), dried ($MgSO_4$), and concentrated (rotary evaporator). The residual oil was filtered through basic alumina. $R_f$=0.3 (10% diethyl ether in petroleum ether, stains with phosphomolybdic acid); $^1$H NMR (300 MHz) δ 0.48 (s, 3H), 0.55 (s, 3H), 0.87 (s, 9H), 1.07-1.56 (m, 4H), 1.82 (q, *J*=7.4 Hz, 3H), 1.92 (m, 1H), 2.08 (m, 1H), 3.15 (t, *J*=7.1 Hz, 2H), 4.2 (m, 1H), 5.56 (s,

2H); $^{13}C$ NMR (75 MHz) δ -4.7, -4.5, 7.0, 18.2, 25.9, 27.3, 30.8, 32.3, 34..6, 36.9, 67.8, 132.0, 132.5; IR (neat) 3022, 2932, 2858, 1643, 1471, 1253, 1091 $cm^{-1}$.

**Preparation of 1-*t*-butyldimethylsilyloxy-4-iodopropane (55).** Trimethylene oxetane (**54**, 2.6 g, 44.2 mmol), *t*-butyldimethylchlorosilane (4.4 g, 29.4 mmol) and sodium iodide (8.8 g, 58.8 mmol) in acetonitrile (25 mL) were stirred for 3h at ambient temperature. Water (75 mL) was added followed by extractions with petroleum ether/diethyl ether (3 x 28 mL, 9:1 by volume). The organic layers were washed with saturated sodium bicarbonate (12 mL) and dried ($MgSO_4$). Solvent was removed *in vacuo*, and the colorless oil (7.9 g, 99% yield) was used without further purification. $^1H$ NMR (300 MHz) δ 0.06 (s, 6H), 0.87 (s, 9H), 2.16 (quint, *J*= 6.2 Hz, 2H), 3.25 (t, *J*= 6.6 Hz, 2H), 3.64 (t, *J*= 5.6 Hz, 2H). $^{13}C$ NMR (75.5 MHz, $CDCl_3$) δ -5.3, 3.6, 18.2, 25.9, 30.0, 62.3. IR (neat) 2957, 2860, 1471, 1099 $cm^{-1}$.

**Synthesis of 6-*t*-butyldimethylsilyloxy-1-hexen-3-ol (56).** A solution 1-*t*-butyldimethylsilyloxy-4-iodopropane (7.9 g, 26.3 mmol) in hexane/diethyl ether (132 mL/ 88 mL) at -78 °C was treated with *t*-butyllithium (34 mL, 1.7 M in pentane). The reaction was stirred at -78 °C for 20 minutes and allowed to warm to -10 °C. The reaction was cooled again to -78 °C, and acrolein (1.6 g, 28.9 mmol) was added. The reaction was stirred for 2h at -78 °C and allowed to warm to room temperature. Work up of the reaction was accomplished by the addition of half-saturated ammonium chloride (200 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 100 mL). Distillation provided the desired product (2.0 g, 33% yield). bp 72-74 °C, (<1 mmHg); $^1H$ NMR (300 MHz) δ 0.06 (s, 6H), 0.86 (s, 9H), 1.50-1.71 (m, 4H), 2.87 (bs, 1H), 3.63 (m, 2H), 4.11 (m, 1H), 5.23-5.27 (m, 2H), 5.77-5.92 (m, 1H). $^{13}C$ NMR (75.5 MHz, $CDCl_3$) δ -5.4, 18.4, 25.9, 28.7, 34.3, 63.3, 72.6, 114.2, 141.2. IR (neat) 3600-3200, 3080, 2859, 1645, 1105, 835 $cm^{-1}$.

**Methylation of 6 -*t*-butyldimethylsilyloxy-1-hexen-3-ol (57).** A solution of 6-*t*-butyldimethylsilyloxy-1-hexen-3-ol (1.7 g, 7.4 mmol) in THF (0.6 mL) was added dropwise to sodium hydride (0.2 g, 8.8 mmol) in THF (5 mL). The reaction was stirred for 1 h and cooled to 0 °C. At this time, iodomethane (2.1 g, 14.8 mmol) was introduced, and the reaction was stirred for another 3 h. Standard workup provided the methylated product in 88% yield.

**Deprotection of 6-*t*-butyldimethylsilyloxy-3-methoxy-1-hexene (58).** A solution of tetrabutylammonium fluoride (TBAF) in THF (9.8 mL, 1.0M) was cooled to 0 °C, and 6-*t*-butyldimethylsilyloxy-3-methoxy-1-hexene (**56**, 1.6 g, 6.5 mmol) was introduced. The mixture was stirred at room temperature for 3 h. The reaction was worked up by addition of half-saturated brine (20 mL) and subsequent extractions with diethyl ether (5 x 20 mL). The concentrated sample was chromatographed to yield 6-hydroxy-3-methoxy-1-hexene (**53**, 0.6 g, 75% yield). $R_f$=0.17 (30% diethyl ether/petroleum ether), stained with phosphomolybdic acid; $^1$H NMR (300 MHZ) δ 1.58-1.65 (m, 2H), 2.35 (bs, 1H), 3.26 (s, 3H), 3.47-3.62 (m, 3H), 5.12-5.20 (m, 2H), 5.63 (m, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ 28.7, 32.1, 56.1, 62.7, 82.8, 117.2, 138.3; IR (neat) 3600-3300, 3078, 2936, 1643, 1068, 927 $cm^{-1}$.

**Synthesis of 7-butyldimethylsilyloxy-1-hepten-3-ol (62).** A solution 1-*t*-butyldimethylsilyloxy-4-iodobutane (9.2 g, 29.0 mmol, preparation similar to **55** except reaction was heated to 55 °C overnight) in hexane/diethyl ether (130 mL/ 87 mL) at -78 °C was treated with *t*-butyllithium (37.5 mL, 1.7 M in pentane). The reaction was stirred at -78 °C for 20 minutes and allowed to warm to -10 °C. The reaction was cooled again to -78 °C, and acrolein (1.8 g, 32.0 mmol) was added. The reaction was stirred for 2h at -78 °C and allowed to warm to room temperature. Work up of the reaction was accomplished by the

addition of half-saturated ammonium chloride (200 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 100 mL). Chromatography provided the desired product (5.0 g, 70% yield), or the crude product was carried on without purification. $R_f$=0.5 (40% diethyl ether/petroleum ether), stained with phosphomolybdic acid; $^1$H NMR (300 MHz) δ 0.02 (s, 6H), 0.84 (s, 9H), 1.30-1.53 (m, 6H), 1.83 (bs, 1H), 3.57 (t, *J*=6.4 Hz, 2H), 4.06 (bq, *J*=6.2 Hz, 1H), 5.05 (dt, *J*=10.6, 1.26, Hz, 2H), 5.17 (dt, *J*=17.3, 1.4 Hz, 1H), 5.82 (ddd, *J*=17.6, 10.5, 6.3 Hz, 1H). $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ -5.3, 18.3, 21.6, 25.9, 32.6, 36.7, 63.0, 73.1, 114.5, 141.2. IR (neat) 3600-3200, 3080, 2934, 2860, 1645, 920 cm$^{-1}$.

**Synthesis of 7-hydroxy-3-methoxy-1-heptene (63).** A solution of 7-butyldimethylsilyloxy-1-hepten-3-ol (1.7 g, 32.5 mmol, crude) in THF (4.0 mL) was added dropwise to sodium hydride (0.8 g, 35.8 mmol) in THF (32 mL). The reaction was stirred for 1 h and cooled to 0 °C. At this time, iodomethane (9.2 g, 65.0 mmol) was introduced, and the reaction was stirred for another 3h. After workup, the residue was added to a solution of TBAF (23 mL, 1.0M in THF) at 0 °C. The reaction was worked up by addition of half-saturated brine (20 mL) and subsequent extractions with diethyl ether (5 x 20 mL). The concentrated sample was chromatographed to yield 0.8 g (62% yield) of 6-hydroxy-3-methoxy-1-hexene. $R_f$=0.17 (30% diethyl ether/petroleum ether), stained with phosphomolybdic acid; $^1$H NMR (300 MHz) δ 1.30-1.62 (m, 6H), 2.00 (bs, 1H), 3.20 (s, 3H), 3.46 (m, 1H), 3.57 (t, *J*=6.4 Hz, 2H), 5.15 (ddd,*J*=0.84, 1.9, 18.4 Hz, 1H), 5.17 (dd, *J*-=1.0, 10.8 Hz, 1H), 5.60 (ddd,*J*=7.8, 10.9, 16.6 Hz, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ 21.4, 32.5, 34.9, 56.1, 62.6, 83.0, 117.1, 138.6; IR (neat) 3600-3100, 3080, 2934, 2858, 1643, 1080, 925 cm$^{-1}$.

**Synthesis of 7-bromo-3-methoxy-1-heptene (64).** The preparation of **64** was accomplished through use of the NBS/triphenylphosphine method. 0.7 g, 87% yield, bp

32-35 °C (4 mmHg); $^1$H NMR (300 MHz) δ 1.40-1.62 (m, 4H), 1.75-1.90 (m,, 2H), 3.22 (s, 3H), 3.36 (t, *J*=6.8 Hz, 2H), 3.46 (m, 1H), 5.15 (ddd, *J*=0.84, 1.6, 18.2 Hz, 1H), 5.17 (dd, *J*=0.86, 10.6 Hz, 1H), 5.60 (ddd, *J*=7.8, 10.6, 16.6 Hz, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ 24.0, 32.7, 33.6, 34.4, 56.1, 82.6, 117.3, 138.5; IR (neat) 3078, 2980, 2938, 2820, 1643, 1101, 927 cm$^{-1}$.

**General Procedure for Grignard Formation.** A Schlenk flask equipped with a magnetic stirring bar and activated magnesium (10.0 mmol) was placed under vacuum, and flame-dried for 5 minutes to drive off advantageous water. The flask was purged with argon for 10 minutes after the glass stopper was replaced with a rubber septum. At the desired temperature, two drops of the bromide were used to initiate the Grignard formation. Tetrahydrofuran (10 mL) was added followed by the slow addition of the bromide (1.0 mmol). The reaction was stirred at the desired temperature until Grignard formation was complete as shown by g.c. analysis.

**Typical Procedure for Copper Mediated Cyclization.** A solution of the organomagnesium bromide prepared as stated above was treated with a copper (I) salt (0.05 equivalent) at the appropriate temperature by direct addition of the copper salt to the Grignard solution. The cold bath was removed, and the mixture was stirred at room temperature until reaction was complete. An aliquot was quenched by addition to a cooled saturated $NH_4Cl$ solution and analyzed by gas chromatography. Yields were determined with the use of an internal standard (*n*-heptane for five-membered ring study, and *n*-octane for the six-membered ring study), and confirmation of peaks was accomplished by co-injection with a known standard.

**Typical Procedure for Lithium Mediated Cyclization.** A solution of the iodide (1.05 mmol) in diethyl ether/hexane (10 mL, 2:3 by volume) was cooled to -78 °C. Addition of

*t*-butyllithium (1.3 mL of 1.7M in pentane, 2.2 mmol) was dropwise. After addition, the reaction was stirred at -78 °C for 15 minutes. The dry ice-acetone bath was removed, and the reaction was stirred until completion. An aliquot was quenched by addition to a cooled saturated $NH_4Cl$ solution and analyzed by gas chromatography. Yields were determined with the use of an internal standard (see copper mediated cyclization).

**Bicyclization Hydrogenation.** The cyclization was run on a 1 mmol scale. Upon completion of cyclization, the reaction mixture was cannula transferred to an erlenmeyer which contained sat $NH_4Cl$ (5 mL). The mixture was extracted with diethyl ether (3 x 5mL). the organic layers were dried and concentrated by distillation at atmospheric pressure. Once all the solvent was removed, the residue was taken up in methanol (5 mL), and $PtO_4$ was added. The reaction was placed under 1 atm of $H_2$, and the reaction was stirred for 3h. Identification of the cyclized products was determined through a coinjection with standards of *c* and *t* bicyclo[4.3.0]nonane which were available from Wiley Organics.

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