University of Alberta

Generation and Trapping of Cyclic 2-Functionalized Allyl Cations

by

Nina Ngoc Vo 

A thesis submitted by the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of

Master of Science

Department of Chemistry

Edmonton, Alberta

Spring 2008

Your file Votre référence
ISBN: 978-0-494-45902-7
Our file Notre référence
ISBN: 978-0-494-45902-7

ABSTRACT

Allyl cations represent important intermediates in organic chemistry and are widely used in the synthesis of interesting organic compounds. It has been shown that allyl cations are relatively stable and can be generated under thermal or photochemical conditions, and many synthetic methods based on these processes have been developed. Because of this, the use of allyl cations in carbon-carbon bond formation has been widely explored and many groups have demonstrated the utility of allyl cations in the synthesis of natural products.

2-Oxyallyl cations are the most commonly applied 2-functionalized allyl cations in organic synthesis. There have been many methods developed for the generation of 2-oxyallyl cations. Among them is the generation of the cyclic oxyallyl cation intermediate resulting from a 4π electrocyclic ring closure of the Nazarov reaction. It has been demonstrated that this intermediate can be captured by nucleophilic addition of different functional groups such as alkenes, dienes, silanes, arenes or halides. However, there have been only few reports of this cyclic oxyallyl cation being intercepted by an oxygen functional group; therefore, trapping of the Nazarov reaction with an oxygen functional group was investigated.

2-Aminoallyl cations, although not as commonly utilized as 2-oxyallyl cations, have been demonstrated to undergo [4+3] cycloaddition reactions. This methodology was investigated in the [3+2] cycloaddition reaction of 2-aminoallyl cations with vinyl ethers, with the goal of applying this methodology to the synthesis of the natural product, asteriscanolide.

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Dr. F. G. West for his guidance, support and encouragement throughout my research.

I would also like to thank all the members of the West group for their help, advice and friendship. In particular, I would like to acknowledge my labmates, Chantel and Dr. Wan, for their help and all the fun times we shared in the lab. And many thanks to Tina for proofreading my thesis and for all her help and advice. I would also like to thank all spectral services staff for their work and patient help.

Last but not least, I would like to thank my parents, my brother and my husband for their understanding and love.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

ABSTRACT

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

CHAPTER 1 INTRODUCTION 1

1.1 Introduction to Allyl Cations 1

1.2 2-Oxyallyl Cations and 2-Aminoallyl Cations 5

1.3 2-Haloallyl Cations 22

1.4 Summary 27

1.5 Bibliography 29

CHAPTER 2 RESULTS AND DISCUSSION 32

2.1 Approach Towards the Synthesis of Asteriscanolide 32

2.1.1 Synthesis of the Enol Ether 33

2.1.2 [3+2] Schmid Cycloaddition 35

2.2 The Interrupted Nazarov Reaction 44

2.2.1 Synthesis of Bicylic Systems 45

2.2.2 Synthesis of Tricylic Systems 61

2.3 Summary and Future Directions 71

2.4 Bibliography 74

CHAPTER 3 EXPERIMENTAL 76

LIST OF TABLES

CHAPTER 1

Table 1.1 Yield of Diastereomers Furnished from [4+3] Cycloaddition Reaction 16

CHAPTER 2

Table 2.1 Vinyl Ethers Used in [3+2] Schmid Cycloaddition 39

Table 2.2 Conditions for Monoprotection of 1,3-Propanediol **87** 59

Table 2.3 Conditions for Deprotection of Dichlorocyclopropane **100** 65

LIST OF FIGURES

CHAPTER 1

Figure 1.1 Illustration of the Delocalization of the Positive Charge 1

Figure 1.2 The Molecular Orbitals of the Allyl Cation 3

Figure 1.3 The Three Types of Reactions of an Allyl Cation with a Diene 4

Figure 1.4 Natural Products Synthesized from Allyl Cation Intermediates 5

Figure 1.5 Isomerization of the Oxyallyl Cation 7

CHAPTER 2

Figure 2.1 Baeyer-Villiger Oxidation Reaction 37

Figure 2.2 Mechanism of [3+2] Cycloaddition of Enamine **18** with Enol Ethers 41

Figure 2.3 Mechanism of the Formation of Tetrahydropyran **64** 51

Figure 2.4 Mechanism of the Formation of Dienone **75** 56

Figure 2.5 Intramolecular Trapping of Dichlorocyclopropane **80** 58

Figure 2.6 Mechanism for the Formation of Enone **112** 69

LIST OF SCHEMES

CHAPTER 1

Scheme 1.1 [4+3] Cycloaddition of 2-Oxyallyl Cation Generated from α-Chloroketone 6

Scheme 1.2 [4+3] Cycloaddition of 2-Oxyallyl Cation Generated from α,α'-Dibromoketone and Zinc 7

Scheme 1.3 Synthesis of the Prelog-Djerassi Lactone 9

Scheme 1.4 [4+3] Cycloaddition of 2-Oxyallyl Cation Generated from α,α'-Dibromoketone and Iron Complex 10

Scheme 1.5 Synthesis of (±)-Campherenone and (±)-Epicampherenone 11

Scheme 1.6 Synthesis of Cycloadduct **36** 12

Scheme 1.7 Generation of 2-Alkoxyallyl Cation 13

Scheme 1.8 Generation of 2-Oxyallyl Cation Using Silver Salt 13

Scheme 1.9 Generation of 2-Oxyallyl Cation Using Triethylamine 14

Scheme 1.10 Synthesis of Lasidiol 16

Scheme 1.11 Synthesis of Sterpurene 17

Scheme 1.12 The Nazarov Reaction 18

Scheme 1.13 Intermolecular Trapping of the Nazarov Intermediate with Allylsilane 19

Scheme 1.14 Intermolecular Trapping of the Nazarov Intermediate with Vinylsulfide 20

Scheme 1.15 [4+3] Cycloaddition of 2-Aminoallyl Cations 21

Scheme 1.16 Application of the Schmid Cycloaddition 22

Scheme 1.17 Preparation of *gem*-Dichlorocyclopropane 23

Scheme 1.18 Generation of 2-Haloallyl Cations 23

Scheme 1.19 Synthesis of Indene Derivatives 24

Scheme 1.20 The Nazarov Reaction Using *gem*-Dichlorocyclopropane 25

Scheme 1.21 Arene Trapping of the Nazarov Reaction 26

CHAPTER 2

Scheme 2.1 Retrosynthesis of Asteriscanolide 33

Scheme 2.2 Synthesis of Enol Ether **9** 34

Scheme 2.3 Synthesis of Vinyl Sulfide **16** 35

Scheme 2.4 [3+2] Schmid Cycloaddition of Enamine **18**
with 2-Methoxypropene 36

Scheme 2.5 Baeyer-Villiger Oxidation of Ketone **19a** 38

Scheme 2.6 [3+2] Schmid Cycloaddition of Enamine **18** with Enol Ethers 39

Scheme 2.7 Synthesis of Enamine **5** 42

Scheme 2.8 [3+2] Schmid Cycloaddition of Enamine **5** with Alkenes 43

Scheme 2.9 Oxygen Trapping of the Nazarov Reaction 46

Scheme 2.10 Retrosynthesis of Dichlorocyclopropane **48** 47

Scheme 2.11 Synthesis of Silyl Enol Ether **61** 48

Scheme 2.12 One Pot Synthesis of Silyl Enol Ether **61** 49

Scheme 2.13 Synthesis of Dichlorocyclopropane **62** 49

Scheme 2.14 Synthesis of Tetrahydropyran Derivative **64** 50

Scheme 2.15 Retrosynthesis of Cyclic Ether **67** 51

Scheme 2.16 Synthesis of Tetrahydrofuran **72** 52

Scheme 2.17 Synthesis of Dichlorocyclopropane **68** 53

Scheme 2.18 Selective Deprotection of Dichlorocyclopropane **68** 55

Scheme 2.19 Synthesis of Tetrahydrofuran **79** 57

Scheme 2.20 Reduction of β-Propiolactone **84** 58

Scheme 2.21 Monoprotection of 1,3-Propanediol **87** 59

Scheme 2.22 Synthesis of Dichlorocyclopropane **80** 60

Scheme 2.23 Synthesis of Cyclic Ether **93** and Cyclopentenone **94** 61

Scheme 2.24 Interrupted Nazarov Reaction with Dichlorocyclopropane **95** 62

Scheme 2.25 Synthesis of Dichlorocyclopropane **100** 63

Scheme 2.26 Synthesis of Cyclopentenone **102** and **103** 64

Scheme 2.27 Deprotection of Dichlorocyclopropane **100** 65

Scheme 2.28 Synthesis of Enone **107** 66

Scheme 2.29 Synthesis of Dichlorocyclopropane **110** 67

Scheme 2.30 Deprotection of Dichlorocyclopropane **110** 68

Scheme 2.31 A New Approach to the Synthesis of Asteriscanolide 72

LIST OF ABBREVIATIONS

AcOH	Acetic acid
br s	Broad singlet
COSY	Homonuclear correlation spectroscopy
d	Doublet
dd	Doublet of doublets
dt	Doublet of triplets
ddd	Doublet of doublets of doublets
ddt	Doublet of doublets of triplets
dddd	Doublet of doublets of doublets of doublets
DIBALH	Diisobutylaluminum hydride
DIPEA	Diisopropylethylamine
DMAP	4-(*N,N*-Dimethylamino)pyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dtd	Doublet of triplets of doublets
EI	Electron impact
Et	Ethyl
g	Grams
h	Hours
HMBC	Heteronuclear multiple bond coherence
HMPA	Hexamethylphosphoramide

HOMO	Highest occupied molecular orbital
Hz	Hertz
IR	Infrared
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
Me	Methyl
MeCN	Acetonitrile
min	Minutes
mL	Milliliters
mm	Millimeters
mmol	Millimoles
MOM	Methoxymethyl
MS	Mass spectroscopy
NaOAc	Sodium acetate
NaOMe	Sodium methoxide
NaTFE	Sodium 2,2,2-trifluoroethoxide
NMR	Nuclear magnetic resonance
Nu	Nucleophile
OTf	Trifluoromethansulfonate
Ph	Phenyl
ppm	Parts per million
^{i}Pr	Isopropyl

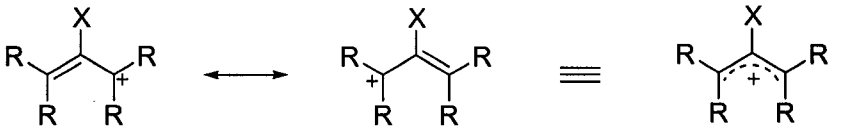
R	Generic alkyl group
R_f	Retention factor
r.t.	Room temperature
s	Singlet
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*t*-Butyldimethylsilyl
TEA	Triethylamine
TEBA	Triethylbenzylammonium chloride
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TIPSOTf	Triisopropylsilyl trifluoromethanesulfonate
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TsOH	p-Toluenesulfonic acid

CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION TO ALLYL CATIONS

Allyl cations represent important intermediates in the synthesis of a large number of compounds and are widely used due to their relative stability compared to other carbocations. The allyl cation is more stable than a simple carbocation as a result of delocalization. The empty p-orbital with the positive charge is in conjugation with the double bond and therefore the pair of electrons in the π system of the double bond are delocalized over the three carbons (Figure 1.1). This stabilizes the allyl cation because the positive charge is spread over the two terminal carbons instead of being concentrated on one. Accordingly, each of the two carbons has a charge of approximately ½ (the charge is exactly ½ if all the R groups are the same) and both carbons act as electrophilic sites where a nucleophilic attack can occur.



1 2 3

X = C, H, O, N, Br, Cl
R = H, alkyl

Figure 1.1 Illustration of the Delocalization of the Positive Charge

The delocalization can also be illustrated by the molecular orbital diagram of the allyl cation (Figure 1.2). The three 2p atomic orbitals of the three carbons combine to form three molecular orbitals. The bonding orbital, Ψ_1, has all the interactions of the atomic orbitals in phase and therefore is the orbital lowest in energy. The next orbital in energy, Ψ_2, has no interactions between adjacent atomic orbitals and is called the non-bonding orbital. The final molecular orbital, Ψ_3, is highest in energy because all of the interactions are out of phase and as a consequence, is an antibonding orbital. The two electrons in the π system of the allyl cation occupy the orbital lowest in energy, the bonding molecular orbital Ψ_1. Hence, this orbital is the highest occupied molecular orbital, HOMO, of the allyl cation and the electron density is spread over all three carbons, with the most electron density on the central carbon. The lowest unoccupied molecular orbital, LUMO, is the nonbonding molecular orbital Ψ_2. It is this orbital that will be involved in bonding in the event of a nucleophilic attack. From the coefficients of this orbital, it can be seen that the incoming electrons from the nucleophile will attack one of the terminal carbons and not the central carbon.

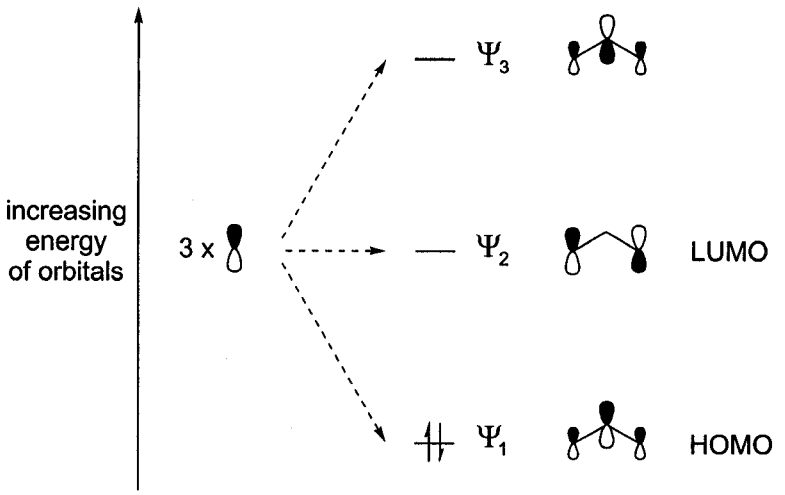


Figure 1.2 The Molecular Orbitals of the Allyl Cation

The use of allyl cations in carbon-carbon bond formation has been widely explored. In particular, cycloaddition reactions of allyl cations have been the subject of much investigation and are of growing interest. These cycloaddition reactions can be categorized into three different types based on mechanistic factors.[1,2] For example, the reaction of an allyl cation with a diene can be of Type A, B, or C (Figure 1.3). A concerted [4+3] cycloaddition reaction of the allyl cation and the diene is classified as Type A and the stereochemical outcome depends upon the conformation favored in the transition state. Cycloaddition reactions that go through a stepwise mechanism are considered as Type B and the stereochemistry of the cycloadduct produced is dependant upon the lifetime of intermediate **8**. Reactions of Type C do not result in cycloadducts but lead to products derived from nucleophilic addition. Distinction between Type B and C depends on the rate constant of the second step and therefore on the lifetime of intermediate **8**.

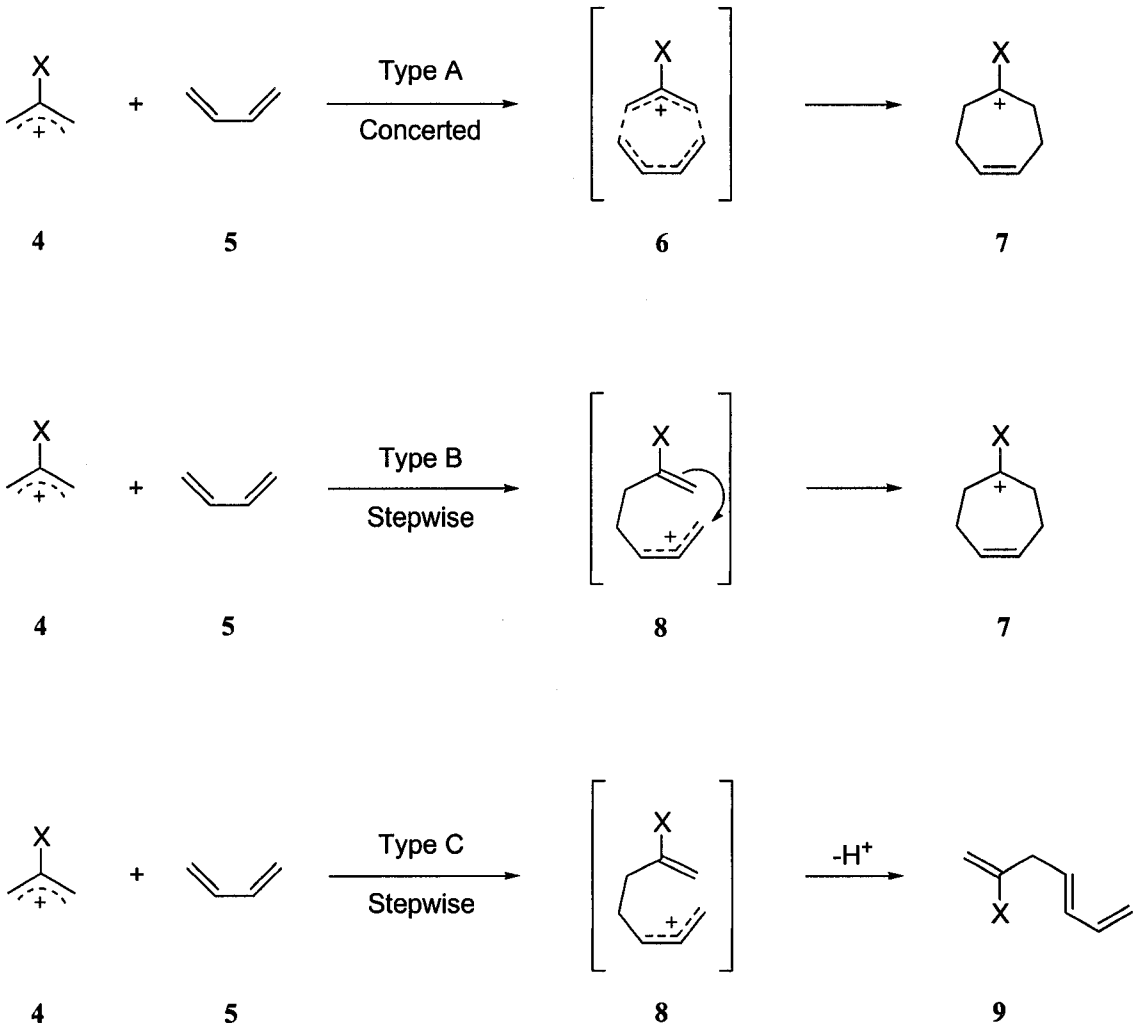
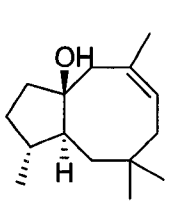
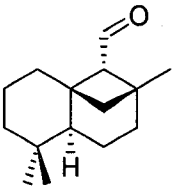


Figure 1.3 The Three Types of Reactions of an Allyl Cation with a Diene

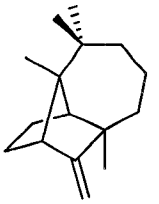
It has been shown that allyl cations can be generated thermally or photochemically[1] and their utility has been demonstrated by many groups in the synthesis of several natural products[3,4,5,6,7] (Figure 1.4).



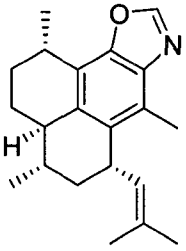
(+)-dactylol



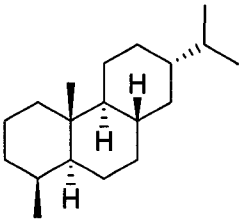
(+)-acanthodoral



longifoline



pseudopteroxazole

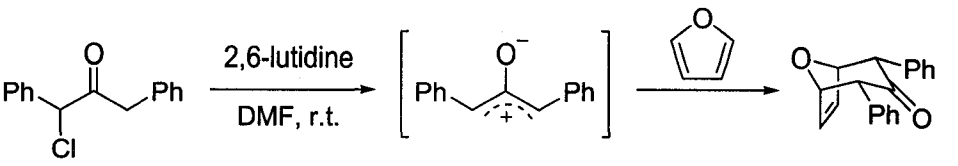


***dl*-fichtelite**

Figure 1.4 Natural Products Synthesized from Allyl Cation Intermediates

1.2 2-OXYALLYL CATIONS AND 2-AMINOALLYL CATIONS

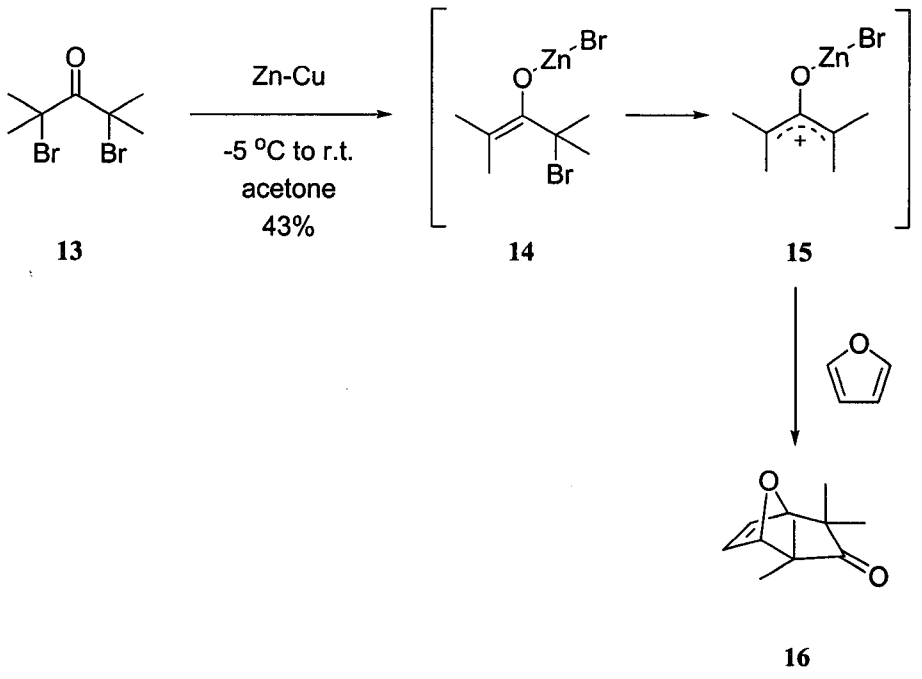
2-Oxyallyl cations are the most commonly applied 2-functionalized allyl cations in organic synthesis and were first generated by Fort.[1,8] He found that when α-chlorodibenzyl ketone **10** was treated with 2,6-lutidine, 2-oxyallyl cation **11** was generated. In the presence of furan, a [4+3] cycloaddition of this cation with the diene occurred to furnish cycloadduct **12** (Scheme 1.1).



10 **11** **12**

Scheme 1.1 [4+3] Cycloaddition of 2-Oxyallyl Cation Generated from α-Chloroketone

Since then there has been great focus and investigation into the preparation and utility of 2-oxyallyl cations. Hoffman and coworkers studied the feasibility of generating these cations from a variety of simple α,α'-dihaloketones and established the minimum structural requirements necessary for the formation of oxyallyl cation intermediates.[9] In one of the early examples, a two electron reduction of dihaloketone **13** was accomplished using zinc-copper couple resulting in zinc enolate **14** (Scheme 1.2). The metal enolate was converted to the oxyallyl cation **15** from loss of the allylic bromide. In the presence of furan, a [4+3] cycloaddition occurred to form the cycloadduct **16** in 43% yield.



Scheme 1.2 [4+3] Cycloaddition of 2-Oxyallyl Cation Generated from α,α'-Dibromoketone and Zinc

The oxyallyl species **17** is very labile when in a free dipolar form and is believed to isomerize immediately to **18** and **19** (Figure 1.5)[10,11] unless it is trapped by a suitable diene or nucleophile. However, it can be stabilized by electron-donating substituents (alkyl, aryl or halo groups) or by an increase in the covalent character of the oxygen-metal bond.

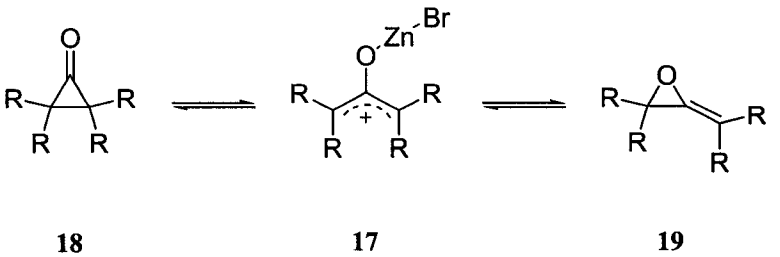
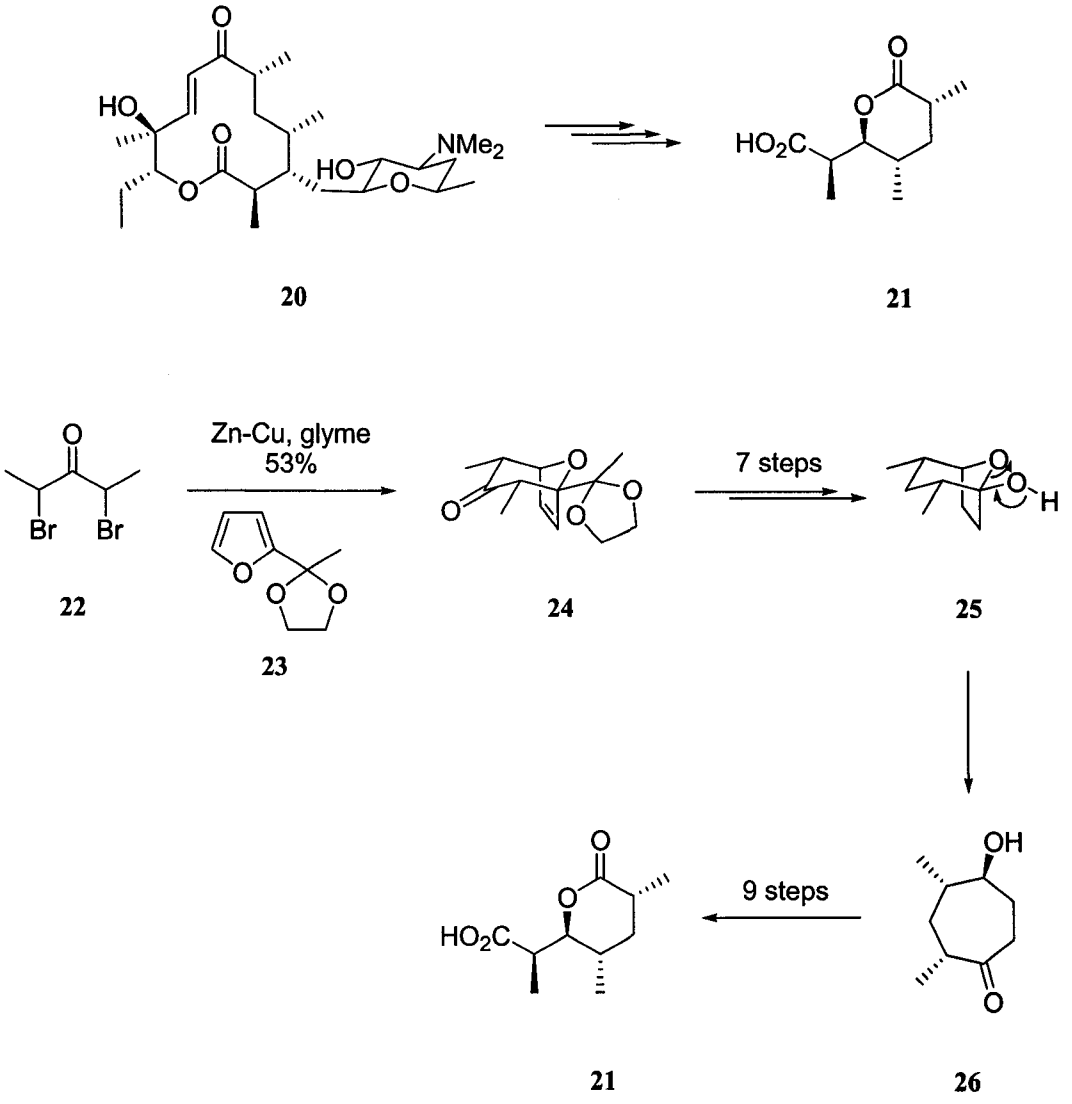


Figure 1.5 Isomerization of the Oxyallyl Cation

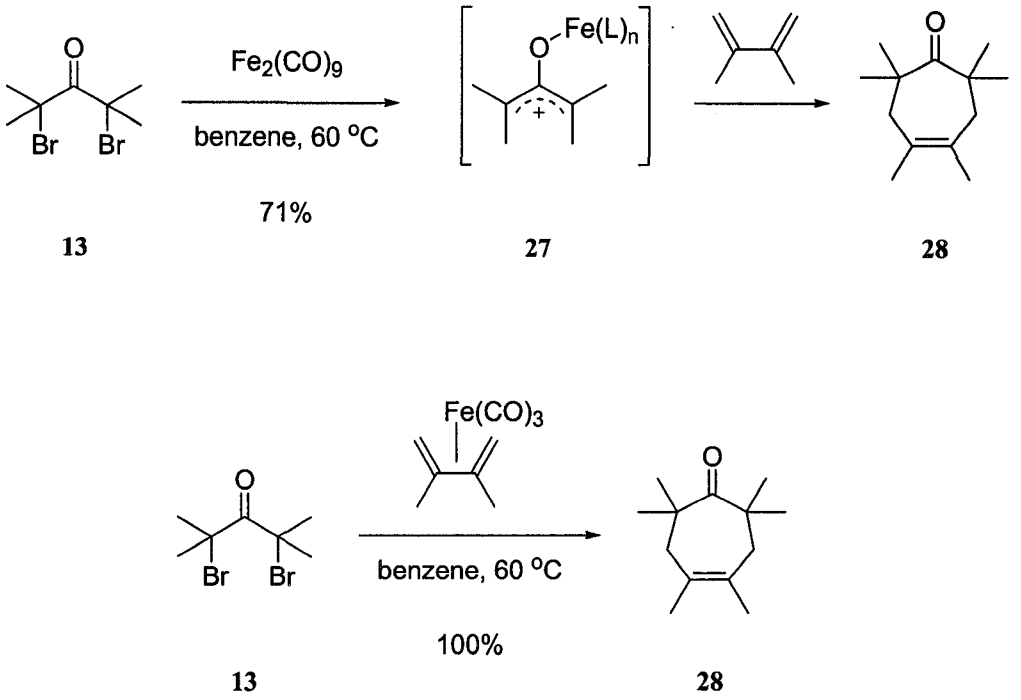
This method for generation and cycloaddition of 2-oxyallyl cations developed by Hoffman was utilized several years later by White and Fukuyama for the synthesis of the Prelog-Djerassi lactone **21**.[12] This lactone is a degradation product of the macrocyclic antibiotic methymycin **20** and has been used by Masamune and coworkers as a key intermediate in the synthesis of the antibiotic. White and Fukuyama's synthesis of the lactone commenced with a [4+3] cycloaddition reaction between the ethylene ketal of 2-acetylfuran **23** and the oxyallyl cation generated from 2,4-dibromopentan-3-one **22** to produce cycloadduct **24** (Scheme 1.3) in 53% yield. The resulting acetal **25** was formed after several steps and the bridgehead hydroxyl used to assist in ether cleavage to yield the functionalized cycloheptanone **26**. The subsequent steps involved routine functional group manipulation, converting the cycloheptanone to the desired lactone **21**.



Scheme 1.3 Synthesis of the Prelog-Djerassi Lactone

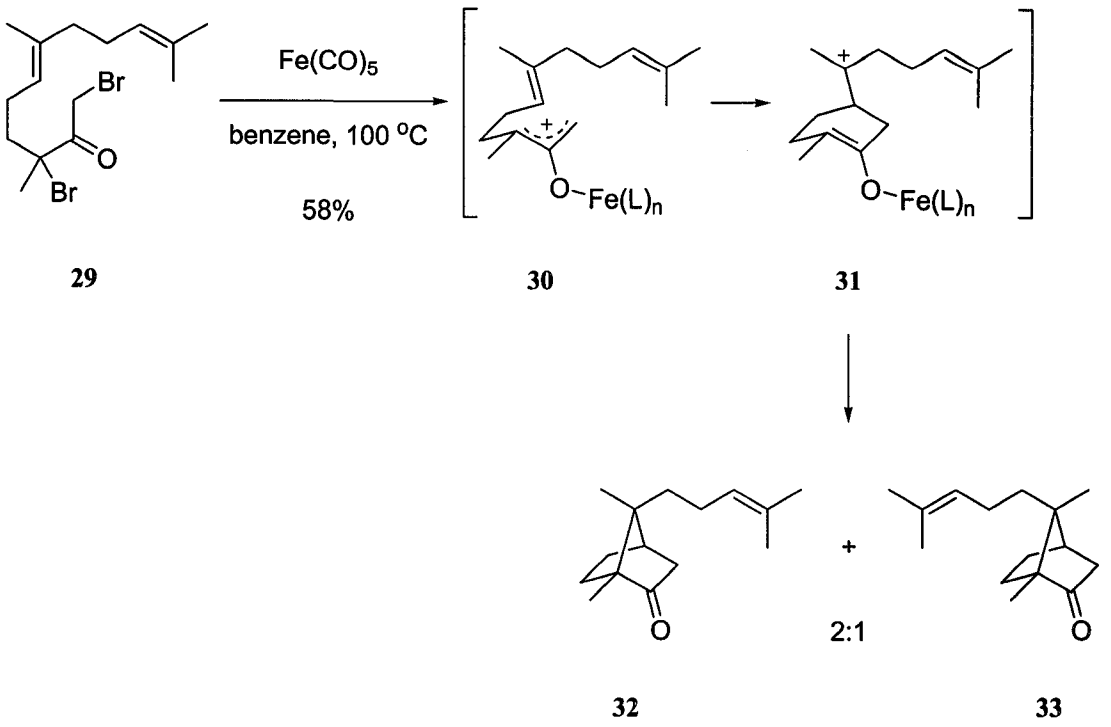
At approximately the same time that Hoffman developed the method of generating 2-oxyallyl cations from α,α'-dihaloketones using zinc-copper couple, Noyori and coworkers demonstrated the efficacy of a system involving $Fe_2(CO)_9$.[13,14] When $Fe_2(CO)_9$ was added to a solution of 2,4-dibromo-2,4-dimethylpentan-3-one **13** and 2,3-dimethylbutadiene in dry benzene and heated to 60 °C, oxyallyl cation **27** was generated in its iron enolate form and underwent a [4+3] cycloaddition with the diene to furnish

cycloheptenone **28** in 71% yield (Scheme 1.4). Interestingly, it was observed that there was a notable increase in yield when the diene tricarbonyl complexes were employed in place of the free diene.



Scheme 1.4 [4+3] Cycloaddition of 2-Oxyallyl Cation Generated from α,α'-Dibromoketone and Iron Complex

The same group then applied this methodology to the synthesis of the natural product campherenone.[15] Dibromoketone **29**, prepared from *trans*-farnesol in 5 steps, was treated with $Fe(CO)_5$ in benzene at 100 °C to generate allyl cation **30** (Scheme 1.5). The cation underwent an intramolecular stepwise [3+2] cycloaddition with the closer olefin to afford a 2:1 mixture of (±)-campherenone **32** and (±)-epicampherenone **33** in 58% yield.

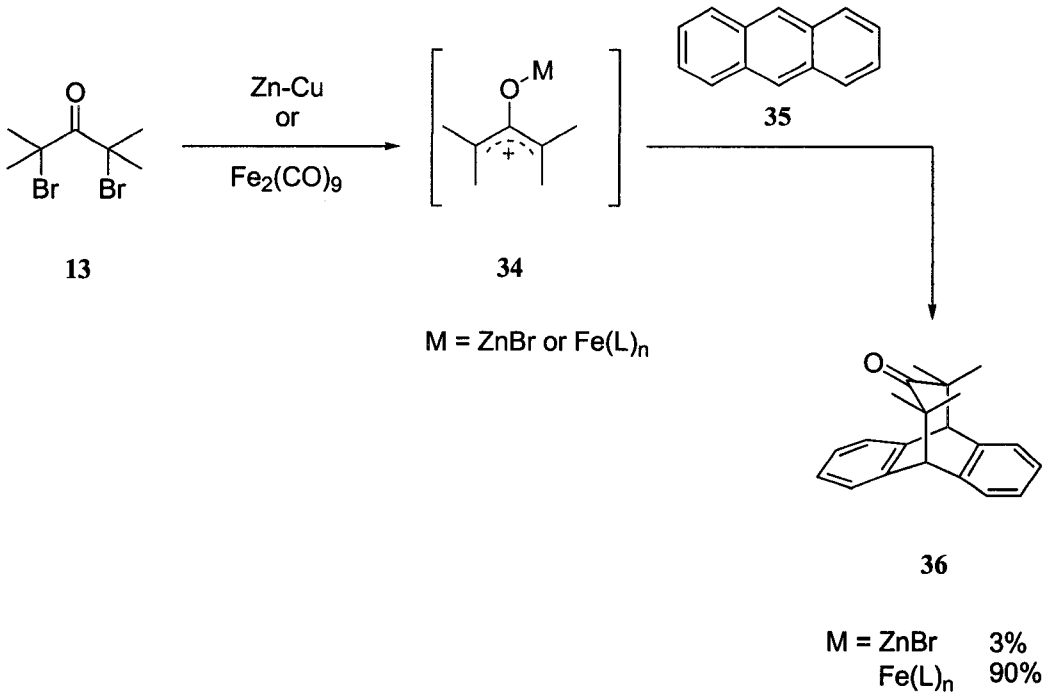


29 30 31

32 33

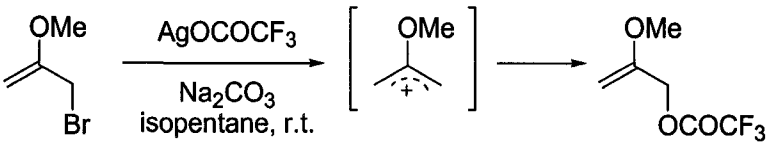
Scheme 1.5 Synthesis of (±)-Campherenone and (±)-Epicampherenone

The two reductive methods for generation of 2-oxyallyl cations, using zinc or iron, have been refined over the years and the majority of reports have employed species like **17** or **27**. However, it has been found that the zinc-bound cation is less electrophilic than the corresponding iron species due to greater covalency of the oxygen-metal bond in the latter species. As a consequence, cycloaddition reactions with poorly nucleophilic dienes proceed best with iron as the reductant. For example, Hoffman and coworkers have demonstrated that when 2,4-dibromo-2,4-dimethylpentan-3-one **13** was treated with either zinc-copper couple or $Fe_2(CO)_9$ to generate cation **34** followed by addition of anthracene **35**, the cycloadduct **36** was obtained in much higher yield when $Fe_2(CO)_9$ was used (Scheme 1.6).[16]



Scheme 1.6 Synthesis of Cycloadduct **36**

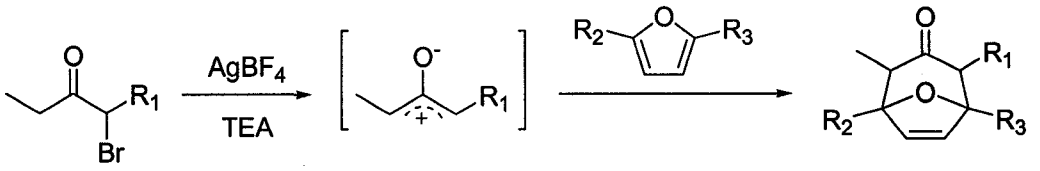
Many groups have demonstrated that 2-oxyallyl cations can also be prepared from α-haloketones. Early examples include experiments by Fort[8] involving the treatment of 2-chlorodibenzyl ketone **10** with 2,6-lutidine (Scheme 1.1) and the work of Mann and Usmani[17] as well as Föhlisch and coworkers[18,19] using silver (I) reagents. The method of utilizing silver (I) reagent to generate a 2-alkoxyallyl cation was first developed by Hoffman and coworkers.[20] It was discovered that when 2-methoxyallyl bromide **37** was treated with silver trifluoroacetate in isopentane at room temperature, 2-methoxyallyl cation **38** was generated (Scheme 1.7). This intermediate was then trapped by trifluoroacetate to furnish 2-methoxyallyl trifluoroacetate **39**.



37 38 39

Scheme 1.7 Generation of 2-Alkoxyallyl Cation

The silver salt route has also been applied to α-haloketones by research groups such as Mann and Föhlisch. Mann and Usmani[17] demonstrated that oxyallyl cations can be generated from α-bromoketones upon reaction with silver tetrafluoroborate and triethylamine, and can then react with a furan derivative to furnish cycloadduct **42** (Scheme 1.8). This reaction can be performed in acetonitrile or in neat furan, in which case the furan serves as both solvent and the trapping agent.

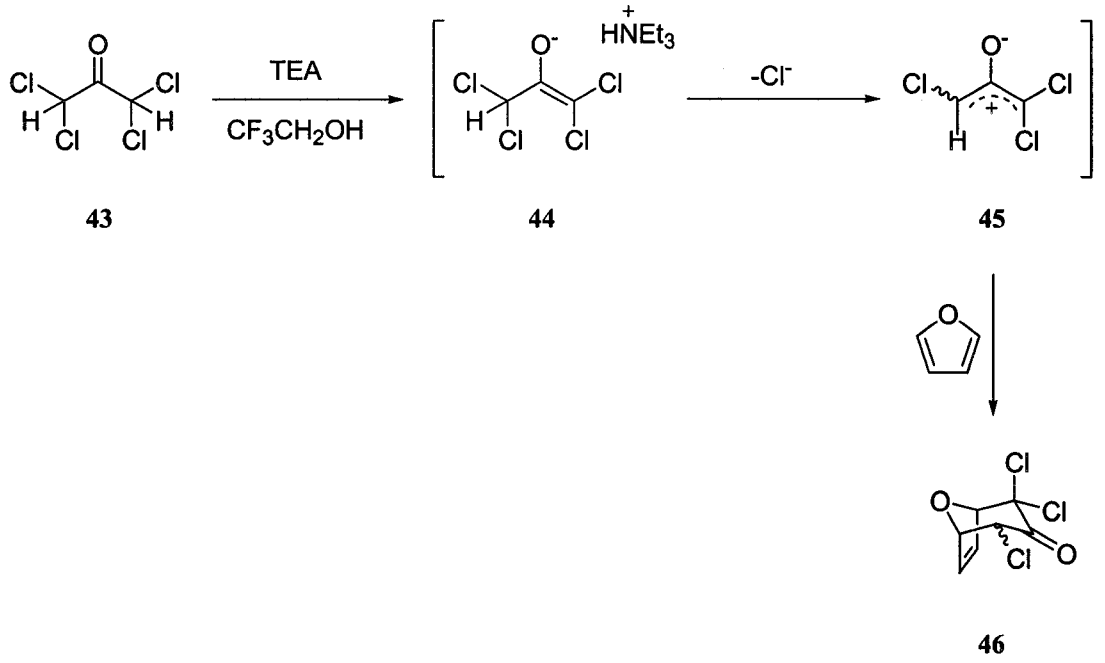


40 41 42

Scheme 1.8 Generation of 2-Oxyallyl Cation Using Silver Salt

Föhlisch and coworkers reported similar [4+3] cycloaddition reactions with furan acting as the solvent and trapping reagent, but employed the more acidic γ-bromo-β-oxonitriles in conjunction with silver oxide instead. However, Föhlisch's major contribution to 2-oxyallyl cation methodology was the demonstration that oxyallyl cations can be generated from α-chloro- and α-bromoketones under milder conditions,

using addition of triethylamine or sodium 2,2,2-trifluoroethoxide in methanol or 2,2,2-trifluoroethanol.[20] Triethylamine first deprotonates the ketone at the α position to form enolate **44**, which then loses a chloride to form the oxyallyl cation **45** (Scheme 1.9). This zwitterion reacts with furan in a [4+3] cycloaddition reaction to form the bicyclic system **46**. This method works particularly well with 1,1,3,3-tetrachloroacetone and provides good to excellent yields of the bridging ketone.



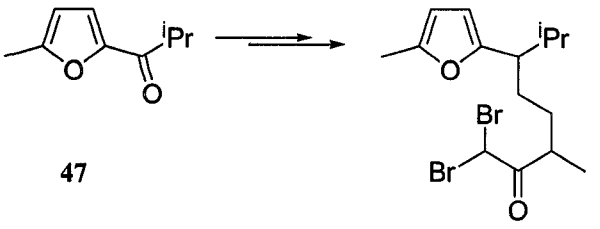
43 **44** **45**

46

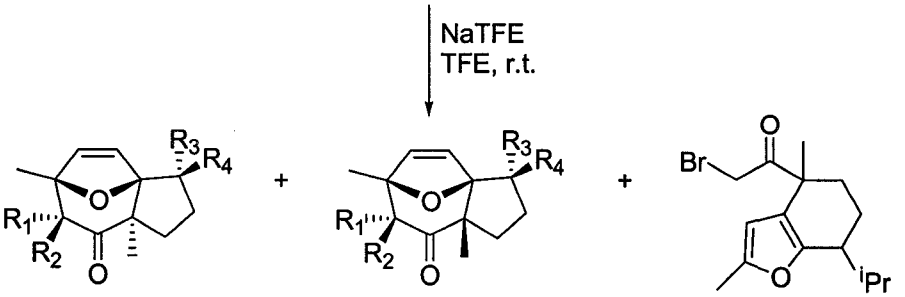
Scheme 1.9 Generation of 2-Oxyallyl Cation Using Triethylamine

The same group has also demonstrated the utility of the method in the synthesis of lasidiol **51** (Scheme 1.10).[21] Lasidiol is a sesquiterpenoid with a carotene skeleton and was of interest at the time because only a few strategies for the construction of the carotene framework have been reported. Also the placement of the oxygen moieties on the seven-membered ring could be established through an intramolecular [4+3]

cycloaddition reaction. α-Bromoketone **48** was prepared from ketone **47** in 7 steps and then treated with a solution of sodium 2,2,2-trifluoroethoxide in 2,2,2-trifluoroethanol at room temperature for the [4+3] cycloaddition to occur. Unfortunately the cycloaddition was not stereoselective and resulted in a separable mixture of six isomers **49a-f**, together with two diastereomeric furan derivatives **50** as byproducts (Scheme 1.10 and Table 1.1). Cycloadducts **49a** and **49d** were converted to lasidiol as a mixture of diastereomers by reduction, hydrogenation and then reductive elimination to open the bridging ether.



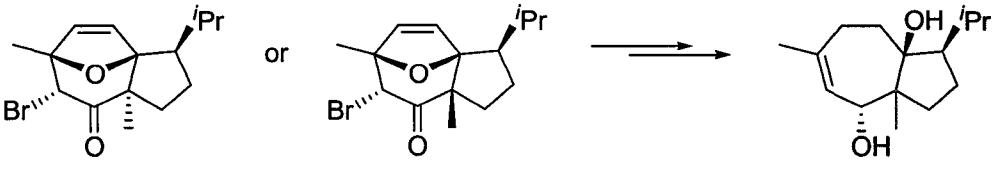
47 48



49a-c 49d-f 50

	R_1	R_2	R_3	R_4	YIELD
49a	Br	H	H	^{i}Pr	28
49b	H	Br	H	^{i}Pr	8
49c	Br	H	^{i}Pr	H	14
49d	Br	H	H	^{i}Pr	21
49e	H	Br	H	^{i}Pr	3
49f	Br	H	^{i}Pr	H	2
50					14

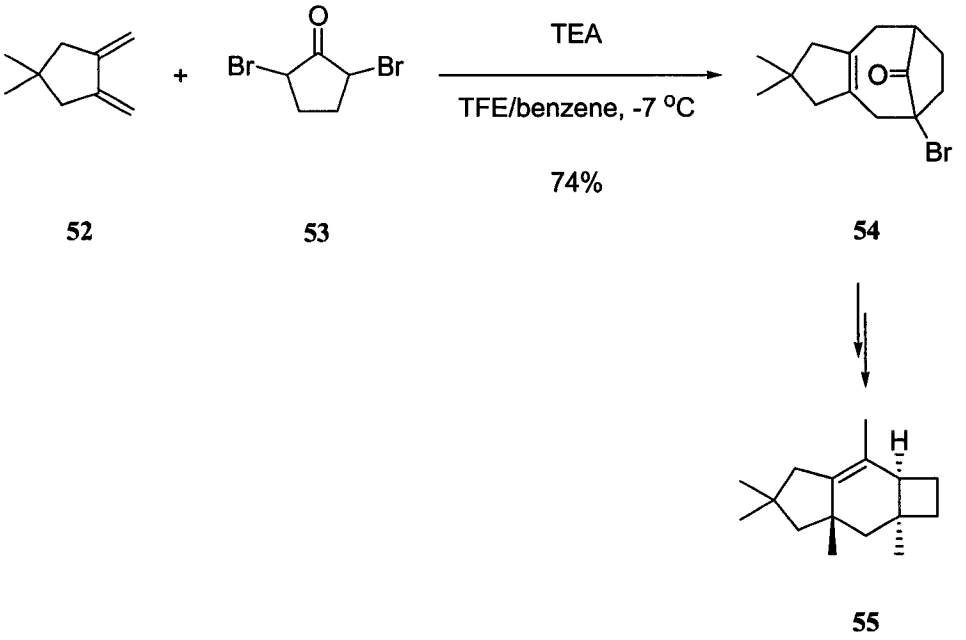
Table 1.1 Yield of Diastereomers Furnished From [4+3] Cycloaddition Reaction



49a 49d 51

Scheme 1.10 Synthesis of Lasidiol

Harmata and coworkers have applied this methodology to the synthesis of sterpurene **55**.[22] This natural product was first isolated in 1981 by Ayer and coworkers[23] as a metabolite of *Stereum purpuureum*, a fungus that is responsible for silver leaf disease. Due to its interesting structural features and biological activities, there has been much research invested into its synthesis. When treated with triethylamine in 2,2,2-trifluoroethanol and benzene, 2,5-dibromocyclopentane **53** was converted to the cyclic oxyallyl cation and underwent a [4+3] cycloaddition with diene **52**, prepared from dimedone, to furnish ketone **54** (Scheme 1.11). The tricyclic system was then carried on to synthesize sterpurene in 6 steps with an overall yield of 22%.

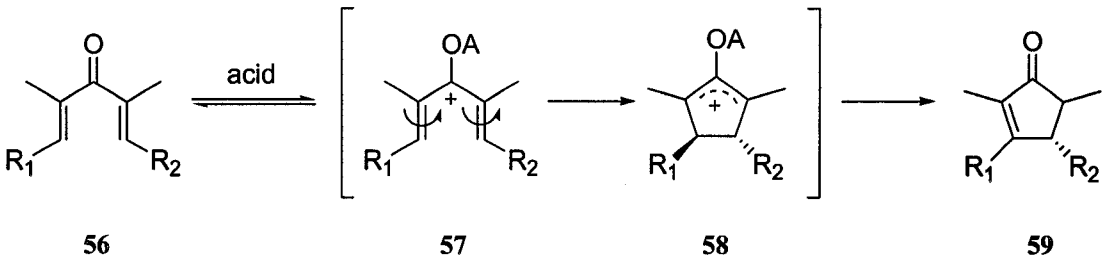


52 **53** **54** **55**

Scheme 1.11 Synthesis of Sterpurene

2-Oxyallyl cations are also generated as intermediates in the Nazarov cyclization reaction, in which a divinyl ketone **56** undergoes a 4π electrocyclic ring closure to form a

cyclopentenone **59** (Scheme 1.12).[24,25] In the presence of a Brønsted or Lewis acid, the divinyl ketone donates a pair of electrons to form a hydroxypentadienyl cation **57**. This cation undergoes a 4π conrotatory electrocyclization to generate the key intermediate, the cyclic 2-oxyallyl cation **58**, which upon elimination, results in the cyclopentenone **59**. However, if a nucleophile is present, the Nazarov reaction can be interrupted by trapping of the cyclic cation. There has been much investigation into the interrupted Nazarov reaction, and a variety of functional groups have been shown to trap the cyclic oxyallyl cation intermediate.



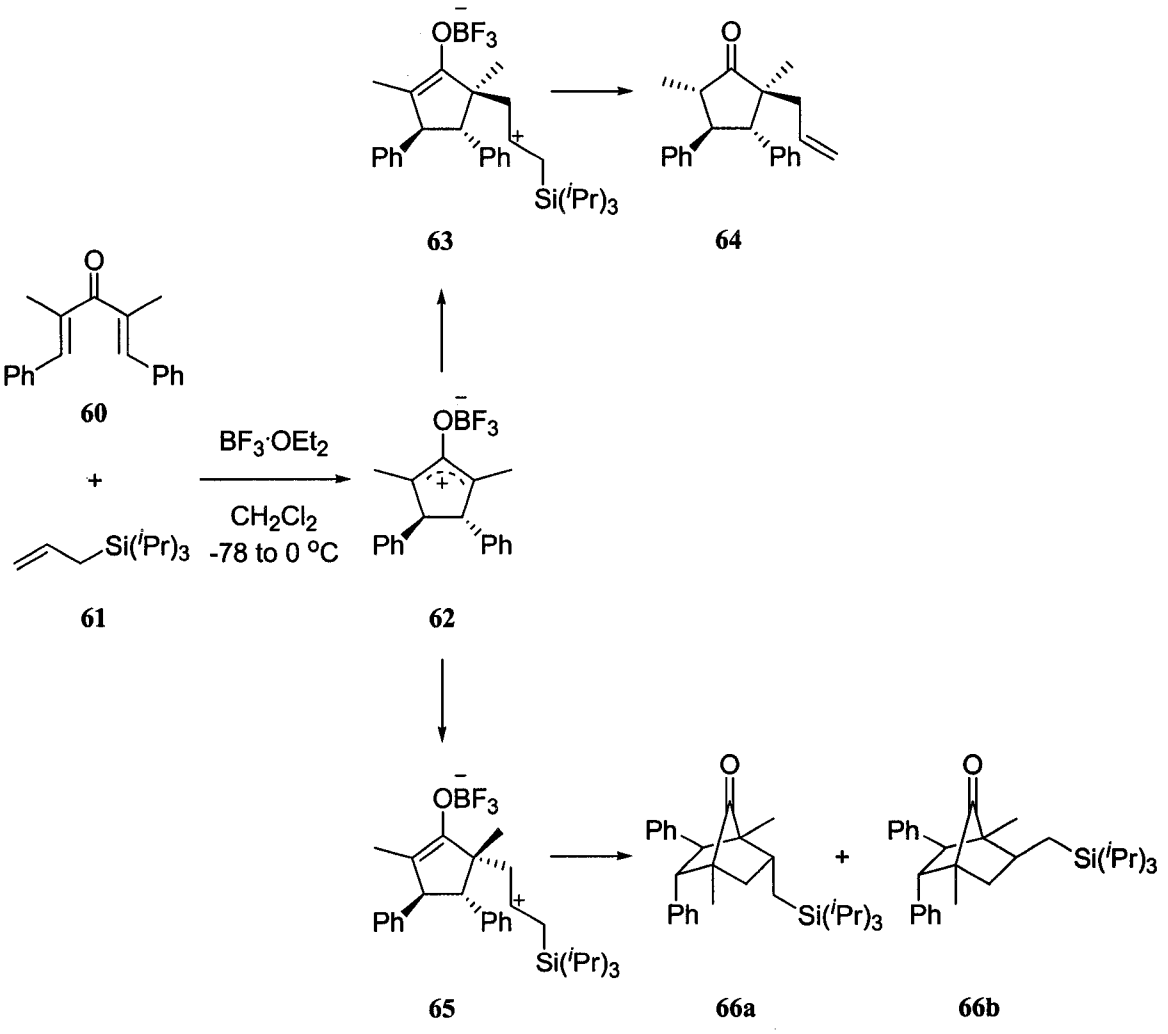
56 **57** **58** **59**

A = H or MX_n

Scheme 1.12 The Nazarov Reaction

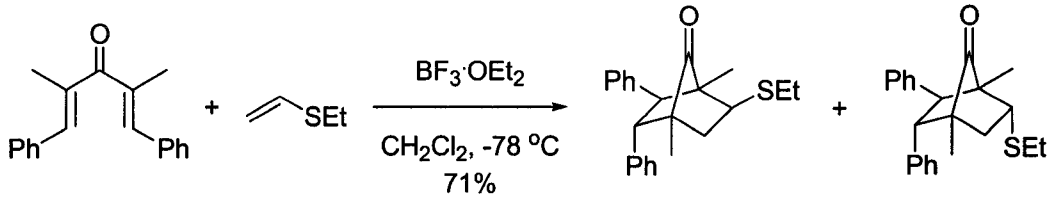
For example, West and coworkers have reported intermolecular trapping of the cation intermediate with olefins to form bicyclic systems.[26,27] Treatment of a mixture of dienone **60** and triisopropylallylsilane **61** with Lewis acid ($BF_3{\cdot}OEt_2$) at low temperature furnished allylated cyclopentanone **64** in 28% yield, along with a 1:1 diastereomeric mixture of compounds **66a** and **66b** in a combined yield of 50% (Scheme 1.13).[26] The cyclopentanone product **64** was formed as a result of a nucleophilic addition of the allylsilane to oxyallyl cation **62** followed by loss of a triisopropyl silyl group, whereas

bicyclo[2.2.0]heptanones **66a** and **66b** were formed from a stepwise [3+2] cycloaddition of the cyclic oxyallyl cation with the allylsilane. It is important to note that construction of **66a** and **66b** involves three successive carbon-carbon bond forming steps: 1) the electrocyclic ring closure of the hydroxypentadienyl cation, 2) the nucleophilic attack of the allylsilane to generate the carbocation **65** and 3) collapse of this carbocation to form the bridged bicyclic product.



Scheme 1.13 Intermolecular Trapping of the Nazarov Intermediate with Allylsilane

The same group has also demonstrated that similar trapping of the cyclic oxyallyl cationic intermediate can be accomplished using vinyl sulfides.[27] Treatment of the same divinyl ketone **60** with vinyl sulfide **67** in the presence of $BF_3{\cdot}OEt_2$ resulted in a 7:1 mixture of **68a** and **68b** in a combined yield of 71% (Scheme 1.14). The sulfide moiety could be modified further via reductive or oxidative pathways.



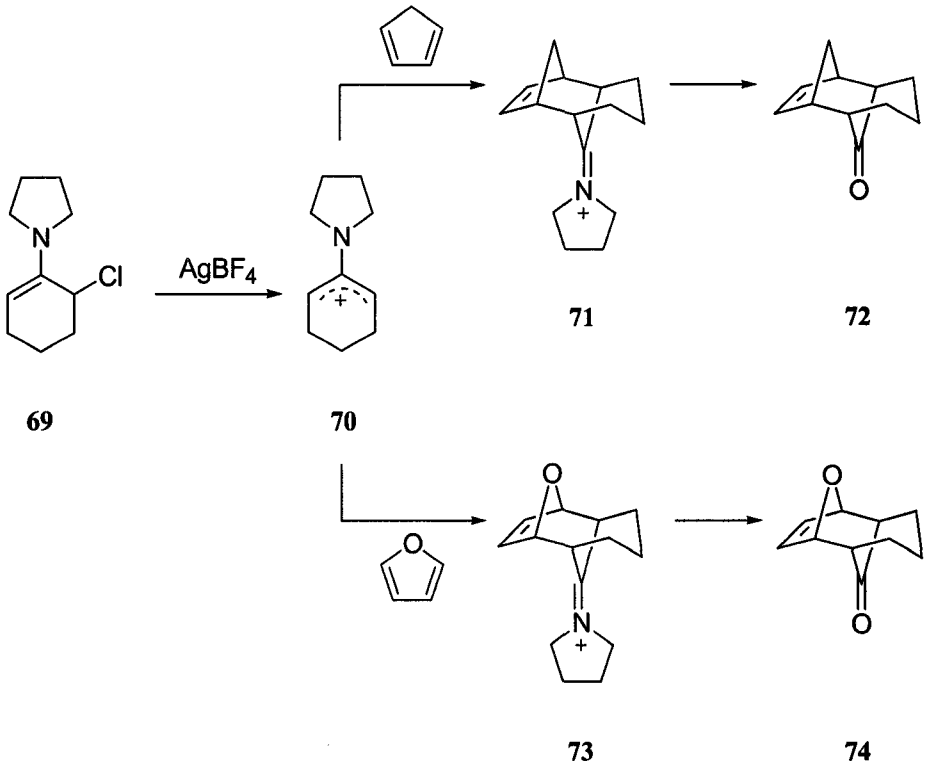
60 **67** **68a** **68b**

Scheme 1.14 Intermolecular Trapping of the Nazarov Intermediate with Vinylsulfide

West and coworkers have reported intermolecular trapping of the cyclic cation by other nucleophiles such as trialkyl silane[28] as a hydride source, or 2,3-dialkyl-1,3-butadiene[29] to undergo a [4+3] cycloaddition and form a keto-bridged cyclooctene. This group has also reported many examples of intramolecular trapping by alkenes, dienes and arenes.[30,31,32]

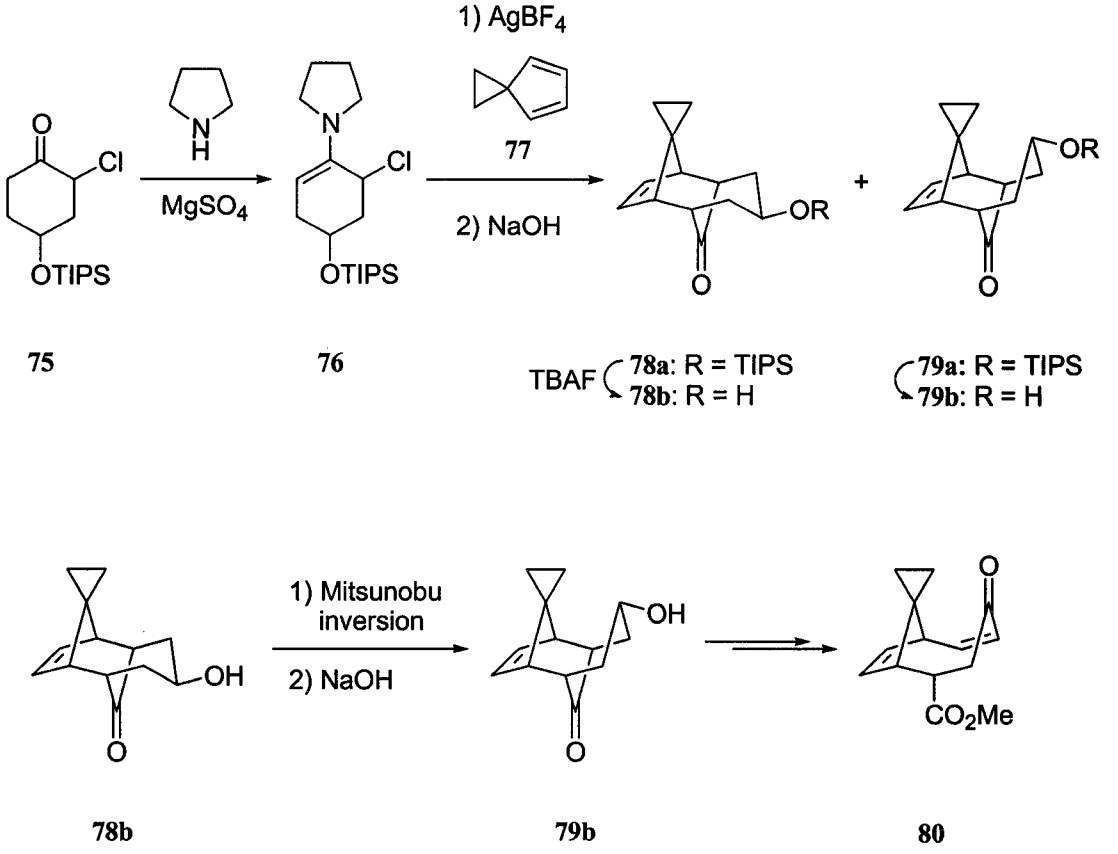
2-Aminoallyl cations, although not as commonly used as oxyallyl cations, have also been shown to undergo cycloadditions. 2-Aminoallyl cations are usually generated from enamines such as compound **69**. However, enamines are quite unstable and easily hydrolyzed to the corresponding ketone. As a result of this instability, 2-aminoallyl cations are not used as often as oxyallyl cations. Schmid and coworkers reported the first example of a cycloaddition involving a 2-aminoallyl cation,[33] in which enamine **69** was treated with silver tetrafluoroborate to generate the aminoallyl cation **70** (Scheme 1.15).

This intermediate was converted to the bridged iminium salts **71** or **73** via a [4+3] cycloaddition with a diene and then hydrolyzed to the bridging ketone **72** or **74**.



Scheme 1.15 [4+3] Cycloaddition of 2-Aminoallyl Cations

This methodology has been utilized by Cha and coworkers in the synthesis of functionalized medium-sized carbocycles.[34] 2-Chorocyclohexanone **75** was converted to the corresponding enamine **76** by treatment with pyrrolidine in the presence of magnesium sulfate (Scheme 1.16). Assisted by silver tetrafluoroborate, the enamine undergoes a [4+3] Schmid cycloaddition with diene **77** to furnish a 4:1 mixture of cycloadducts **78a** and **79a**. After deprotection of the silyl group, the major cycloadduct **78b** was easily converted to the minor cycloadduct **79b**. Further functional group manipulation furnished enone ester **80**.



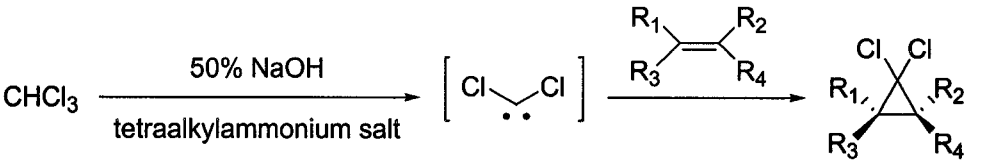
75 76 78b 79b 80

Scheme 1.16 Application of the Schmid Cycloaddition

1.3 2-HALOALLYL CATIONS

Generation and applications of 2-haloallyl cations have been investigated by many research groups. *gem*-Dihalocyclopropanes are precursors for the generation of 2-haloallyl cations and can be prepared through several methods.[35] Important methods for synthesizing *gem*-dihalocyclopropanes involve the addition of a dihalocarbene to the appropriate alkene. The most commonly used method involves α-elimination of a hydrogen halide from trihalomethane to generate the dihalocarbene. For example, in the phase-transfer catalysis method, dichlorocarbene is generated when concentrated aqueous sodium hydroxide is stirred with chloroform in the presence of a catalytic amount of

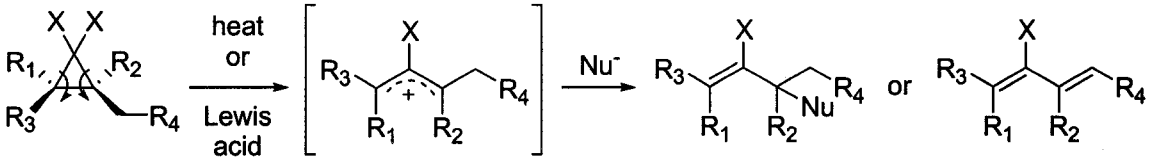
lipophilic tetraalkylammonium salt. In the presence of an alkene, the dichlorocarbene **82** undergoes a [2+1] addition to furnish the *gem*-dichlorocyclopropane derivatives **83** (Scheme 1.17).



81 **82** **83**

Scheme 1.17 Preparation of *gem*-Dichlorocyclopropane

2-Haloallyl cations can be generated from the dihalocyclopropane by exposure to heat or Lewis acid. Under these conditions, *gem*-dihalocyclopropanes undergo a concerted 2π disrotatory electrocyclic ring opening to form 2-haloallyl cations **85** (Scheme 1.18). The allyl cation can be trapped by a nucleophile or can undergo elimination to form a 1,3-diene such as **87**.

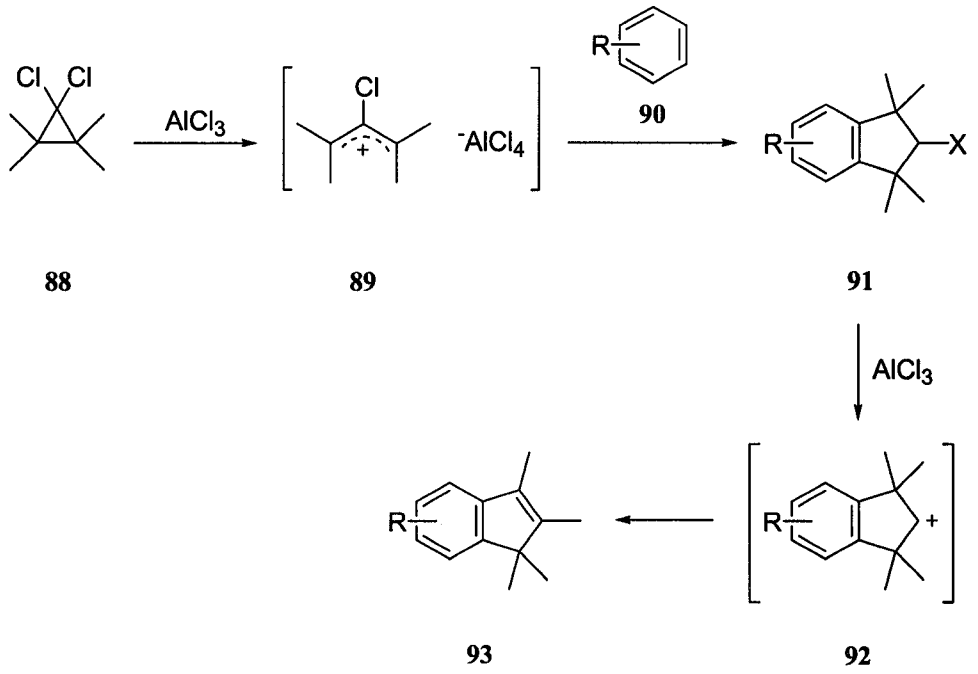


84 **85** **86** **87**

Scheme 1.18 Generation of 2-Haloallyl Cations

The classical Skattebøl synthesis of indene derivatives is an example of the utility of this process.[36] Dichlorocyclopropane **88** was converted to the chloroallyl cation **89** when

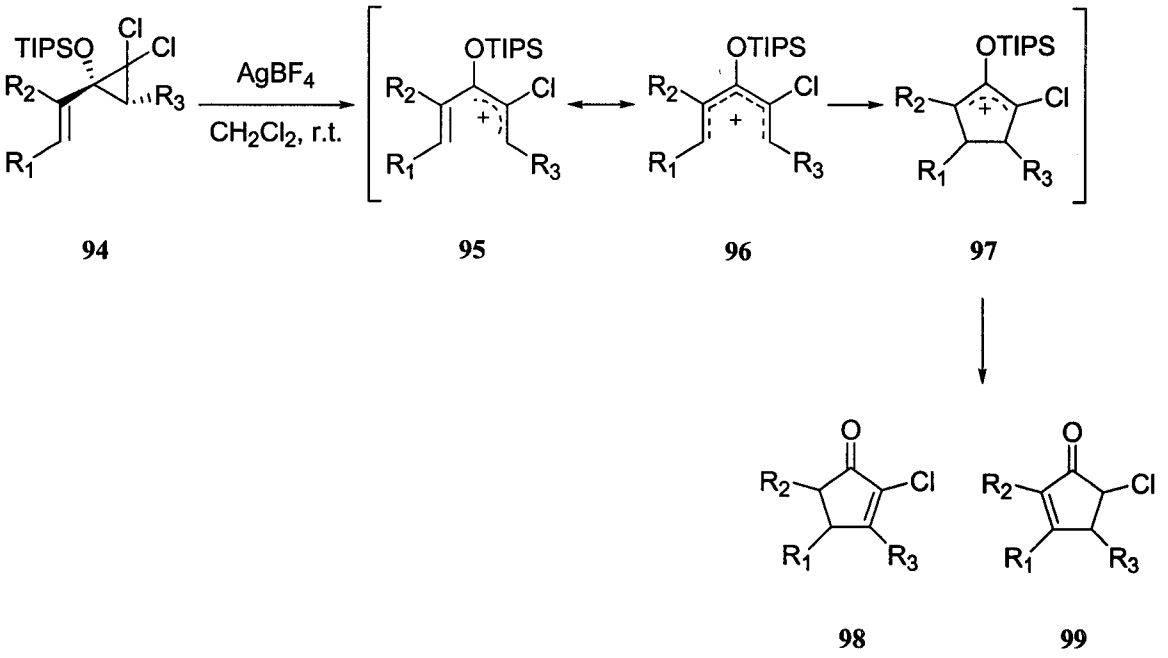
treated with the Lewis acid, aluminum chloride, at room temperature (Scheme 1.19). The chloroallyl cation generated was then trapped by the aromatic compound **90** through a Friedel-Crafts reaction to form the indane intermediate **91**. Further reaction with aluminum chloride generated carbocation **92**, which was converted to the indene derivative **93** via a 1,2-methide shift.



Scheme 1.19 Synthesis of Indene Derivatives

West and coworkers have recently reported a new approach to the Nazarov reaction involving a 2-chloroallyl cation intermediate.[37] In the presence of silver tetrafluoroborate, dichlorocyclopropane **94** underwent a disrotatory ring opening to form the expected 2-chloroallyl cation **95** (Scheme 1.20). This allyl cation is in conjugation with the neighboring double bond and as a result, the pentadienyl cation **96** was generated. The pentadienyl cation undergoes a 4π conrotatory electrocyclic ring closure,

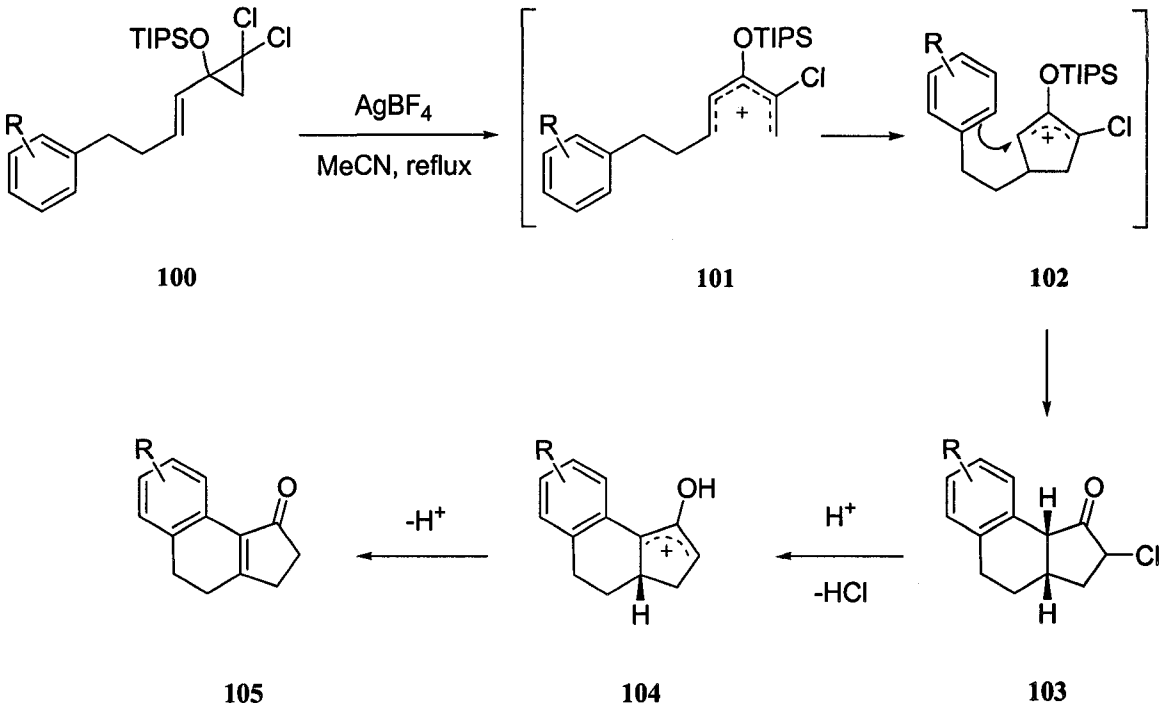
as in the simple Nazarov reaction, to form cyclopentenyl cation **97**, which was converted to cyclopentenones **98** and **99** upon elimination.



94 **95** **96** **97** **98** **99**

Scheme 1.20 The Nazarov Reaction Using *gem*-Dichlorocyclopropane

The same group has also demonstrated that the cyclopentenyl cation formed as a result of electrocyclization can be intramolecularly trapped like other oxyallyl cations to form a tricyclic system.[38] Similar to the previous example, dichlorocyclopropane **100** underwent a silver-assisted sequential electrocyclic ring opening and ring closure to generate the cyclopentenyl cation **102** (Scheme 1.21). The cyclic 2-oxyallyl cation was then trapped by the terminal aryl group to form intermediate **103**, which underwent another elimination via a second oxyallyl cation **104**.



Scheme 1.21 Arene Trapping of the Nazarov Reaction

1.4 SUMMARY

2-Functionalized allyl cations are important intermediates in organic synthesis and are highly utilized due to their stability and electrophilicity. As has been shown, 2-functionalized allyl cations can be generated by many methods and then further reacted with a nucleophilic species. These intermediates can be either trapped inter- or intramolecularly by a nucleophile or participate in a cycloaddition to furnish medium-sized rings.

The cyclic oxyallyl cation generated as an intermediate in the Nazarov reaction has been shown to undergo inter- or intramolecular trapping by many functional groups, such as alkenes, dienes, silanes, arenes, azides, and halides. Nevertheless, there have been limited examples reported of the Nazarov reaction being trapped by an oxygen functional group. The diversity of functional groups that may be used for the trapping of the Nazarov intermediate was investigated by examining whether the oxygen functional group was applicable. The results of this investigation will discussed in a later chapter.

As has been illustrated, there are many examples of cycloaddition reactions of 2-functionalized allyl cations. However, most of the examples reported have been of 2-oxyallyl cations, rather than 2-aminoallyl cations. There are very few examples of cycloaddition reactions of 2-aminoallyl cations, all of which are [4+3] cycloaddition reactions. There have been no reports of a [3+2] cycloaddition reaction involving a 2-aminoallyl cation. As such, this cycloaddition reaction was investigated and its application to the synthesis of natural products containing medium-sized rings examined.

A large number of examples have been discussed that validate the utility of 2-functionalized allyl cations. However, the chemistry of this intermediate is very diverse and there is still much investigation to be done in this field, some of which will be discussed in the following chapter.

1.5 BIBLIOGRAPHY

[1] Harmata, M. *Tetrahedron* **1997**, *53*, 6235-6280.

[2] Mann, J. *Tetrahedron* **1986**, *42*, 4611-4659.

[3] Harmata, H. M. R.; Rashatasakhon, P. *Org. Lett.* **2000**, *2*, 2913-2915.

[4] Zhang, L.; Koreeda, M. *Org. Lett.* **2004**, *6*, 537-540.

[5] Volkmann, R. A.; Andrews, G. C.; Johnson, W. S. *J. Am. Chem. Soc.* **1975**, *97*, 4777-4779.

[6] Davidson, J. P.; Corey, E. J. *J. Am. Soc.* **2003**, *125*, 13486-13489.

[7] Johnson, W. S.; Jensen, N. P.; Hooz, J.; Leopold, E. J. *J. Am. Soc.* **1968**, *90*, 5872-5881.

[8] Fort, A. W. *J. Am. Chem. Soc.* **1962**, *84*, 4979-4981.

[9] Hoffman, H.M.R.; Clemens, K. E.; Smithers, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 3940-3946.

[10] Hoffman, R. *J. Am. Chem. Soc.* **1968**, *90*, 1475-1485.

[11] Bingham, R. C.; Dewar, J. S.; Lo, D. H. *J. Am. Chem. Soc.* **1975**, *97*, 1302-1306.

[12] White, J. D.; Fukuyama, Y. *J. Am. Chem. Soc.* **1979**, *101*, 226-228.

[13] Noyori, R.; Makino, S.; Takaya, H. *J. Am. Chem. Soc.* **1971**, *93*, 1272-1273.

[14] Noyori, R.; Makino, S.; Okita, T.; Hayakawa, Y. *J. Org. Chem.* **1975**, *40*, 806-807.

[15] Noyori, R.; Nishizawa, M.; Shimizu, F.; Hayakawa, Y.; Maruoka, K.; Hashimoto, S.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1979**, *101*, 220-222.

[16] Giguere, R. J.; Rawson, D. I.; Hoffman, H. M. R. *Synthesis* **1978**, 902.

[17] Mann, J.; Usmani, A. A. *Chem. Commun.* **1980**, 1119.

[18] Föhlisch, B.; Flogaus, R.; Oexle, J; Schädel, A. *Tetrahedron Lett.* **1984**, *25*, 1773-1776.

[19] Föhlisch, B.; Gottstein, W.; Kaiser, R.; Wanner, I. *Tetrahedron Lett.* **1980**, *21*, 3005-3008.

[20] Hill, A. E.; Greenwood, G.; Hoffman, H. M. R. *J. Am. Chem. Soc.* **1973**, *95*, 1338-1340.

[21] Kreiselmeier, G.; Föhlisch, B. *Tetrahedron Lett.* **2000**, *41*, 1375-1379.

[22] Harmata, M.; Bohnert, G. J. *Org. Lett.* **2003**, *5*, 59-61.

[23] Ayer, W. A,; Saeedi-Ghomi, M. H. *Can. J. Chem.* **1981**, *59*, 2536.

[24] Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577-7606.

[25] Pellissier, H. *Tetrahedron* **2005**, *61*, 6479-6517.

[26] Giese, S.; Kastrup, L.; Stiens, D.; West, F. G. *Angew. Chem. Int. Ed.* **2000**, *39*, 1970-1973.

[27] Mahmoud, B.; West, F. G. *Tetrahedron Lett.* **2007**, *48*, 5091-5904.

[28] Giese, S.; West, F. G. *Tetrahedron* **2000**, *56*, 10221-10228.

[29] Yungai, A.; West, F. G. *Tetrahedron Lett.* **2004**, *45*, 5445-5448.

[30] Browder, C. C.; West, F. G. *Synlett.* **1999**, 1363-1366.

[31] Browder, C. C.; Marmsater, F. P.; West, F. G. *Org. Lett.* **2001**, *3*, 3033-3035.

[32] Wang, Y.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 876-877.

[33] Schmid, R.; Schmid, H. *Helv. Chim. Acta.* **1974**, *57*, 1883-1886.

[34] Lee, J.; Oh, J.; Jin, S.; Choi, J.; Atwood, J. L.; Cha, J. K. *J. Org. Chem.* **1994**, *59*, 6955-6955.

[35] Fedorynski, *M. Chem. Rev.* **2003**, *103*, 1099-1132.

[36] Skattebøl, L.; Boulette, B. *J. Org. Chem.* **1966**, *31*, 81-85.

[37] Grant, T. N.; West, F. G. *J. Am. Chem. Soc.* **2006**, *128*, 9348-9349.

[38] Grant, T. N.; West, F. G. *Org. Lett.* **2007**, *9*, 3789-3792.

CHAPTER 2

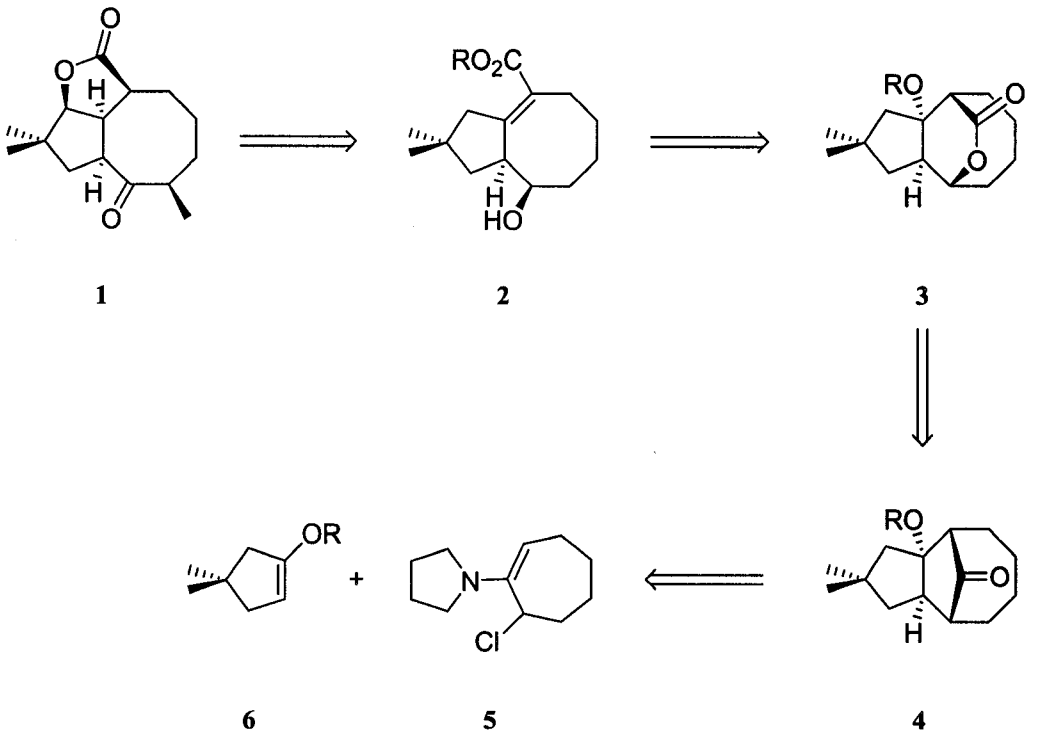
RESULTS AND DISCUSSION

2.1 APPROACH TOWARDS THE SYNTHESIS OF ASTERISCANOLIDE

Cycloaddition reactions of allyl cations play an important role in organic chemistry and have been utilized by many groups for the formation of small and medium-sized rings in natural products. In most cases, the cationic intermediates in the cycloaddition are 2-oxyallyl cations, mainly due to their stability and the broad number of methods developed for their formation. 2-Aminoallyl cations are not as commonly utilized because of the instability and easy hydrolysis of the imine or enamine precursors used to generate these cations. However, 2-aminoallyl cations, as has been shown, can also undergo cycloadditions and therefore can be applied to the synthesis of natural products containing medium-sized rings.

The cyclooctanoid sesquiterpene lactone, asteriscanolide **1,** has been the focus of a number of research groups[1,2,3,4,5] since it was first isolated from *Asteriscus aquaticus L* by Feliciano and coworkers.[6] The attraction offered by asteriscanolide is its uncommon bicyclo[6.3.0]undecane ring system bridged by a butyrolactone fragment and the five *cis* stereocenters. Due to these features, it was decided that the synthesis of asteriscanolide would be an interesting and challenging project. It was rationalized that asteriscanolide **1** could be formed from ester **2** (Scheme 2.1). The ester would be furnished from a ring opening of lactone **3**, which was to be synthesized from a regioselective Baeyer-Villiger

oxidation of bridging ketone **4**. The ketone would be the cycloadduct resulting from a [3+2] Schmid cycloaddition of enamine **5** and cyclic enol ether **6**.



1 **2** **3**

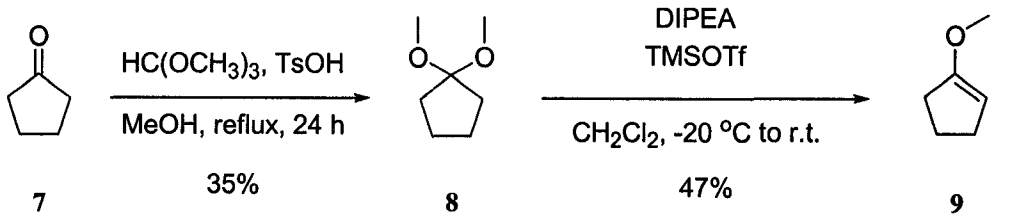
6 **5** **4**

Scheme 2.1 Retrosynthesis of Asteriscanolide

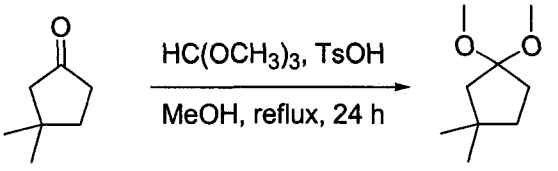
2.1.1 SYNTHESIS OF THE ENOL ETHER

The preparation of the enol ether **6** began with model studies in which cyclopentanone **7** was heated to reflux with trimethyl orthoformate and *p*-toluenesulfonic acid in methanol[7] to furnish dimethoxycyclopentane **8** in 35% yield (Scheme 2.2). Elimination of a methoxy group from the acetal was accomplished by treatment with DIPEA and TMSOTf. The resulting enol ether **9** was isolated in 47% yield. From these positive results of the model study, preparation of the actual enol ether substrate that

would be utilized in the synthesis of asteriscanolide was initiated. When 3,3-dimethylcyclopentanone **10** was treated under the same conditions as in the previous case, the expected acetal **11** was formed (Scheme 2). However, purification of acetal **11** appeared to be problematic. It was soon realized that during purification, acetal **11** was decomposing. As a result, this route to generate the alkene component of the [3+2] cycloaddition was not pursued further.



7 **8** **9**

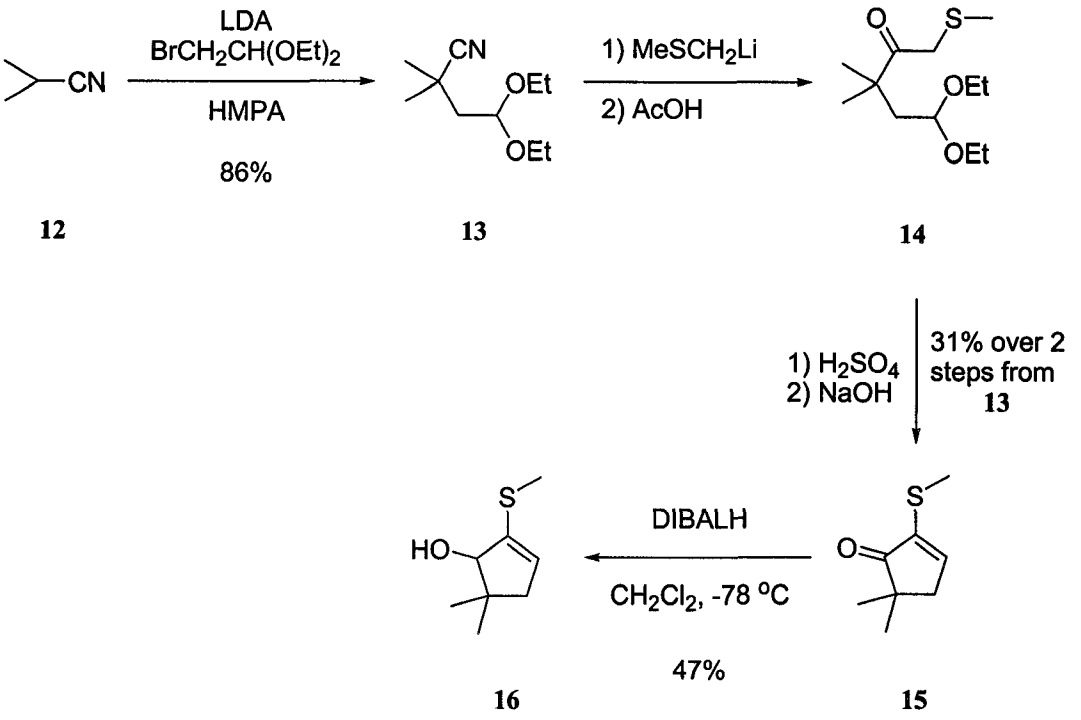


10 **11**

Scheme 2.2 Synthesis of Enol Ether **9**

It was decided that a vinyl sulfide could be used instead of an enol ether substrate for the [3+2] cycloaddition. Following a procedure reported by Kuwajima[8] and coworkers, vinyl sulfide **16** was easily prepared from isobutyronitrile **12** in 4 steps (Scheme 2.3). Nitrile **13** was prepared by alkylation of isobutyronitrile **12** and then allowed to react with (methylthio)methyl lithium followed by acetic acid to yield ketone **14**. Subsequent treatment of ketone **14** with sulfuric acid, followed by aqueous NaOH

produced cyclopentenone **15** via an intramolecular aldol condensation. Cyclopentenone **15** was obtained in 31% yield over 2 steps. Reduction of cyclopentenone **15** was accomplished by treatment with DIBALH in CH_2Cl_2 at -78 °C to form vinyl sulfide **16** in 47% yield.

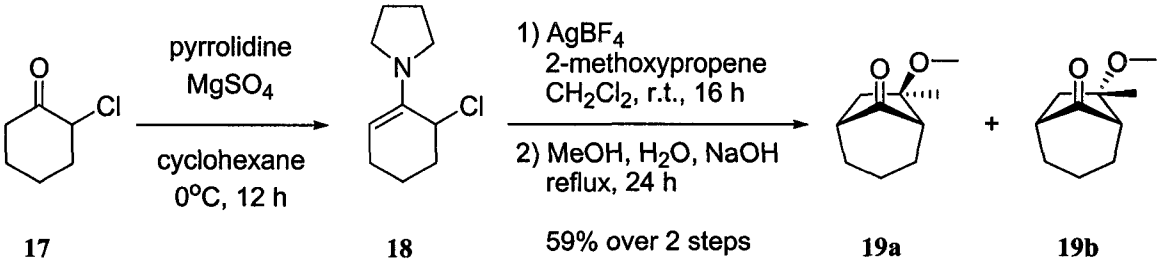


Scheme 2.3 Synthesis of Vinyl Sulfide **16**

2.1.2 [3+2] SCHMID CYCLOADDITION

With the vinyl sulfide in hand, the next step was to determine if it would undergo a [3+2] Schmid cycloaddition with the 2-aminoallyl cation generated from enamine **5**. Model studies were conducted using the commercially available 2-chlorocyclohexanone **17**. The ketone was first converted into the corresponding enamine **18** following a

procedure reported by Cha and coworkers.[9] 2-Chlorocyclohexanone **17** was treated with pyrrolidine in the presence of $MgSO_4$ (Scheme 2.4) to yield enamine **18**. It was found that enamine **18** was easily hydrolyzed back to the ketone when exposed to air or left at room temperature for too long. Therefore enamine **18** could not be purified and the crude material was used in the next reaction step. The Schmid cycloaddition reaction was carried out by adding the enamine to a mixture of 2-methoxypropene and silver tetrafluoroborate in CH_2Cl_2 followed by treatment with NaOH in methanol. The resulting cycloadduct was isolated as a separable 1:1 mixture of diastereomers **19a** and **19b** with a combined yield of 59% over 2 steps. The structures of cycloadducts **19a** and **19b** were determined by ^1H, COSY, HMBC, TROESY and ^{13}C NMR spectra.



Scheme 2.4 [3+2] Schmid Cycloaddition of Enamine **18** with 2-Methoxypropene

Diastereomer **19a** was then converted into the corresponding lactone via a Baeyer-Villiger oxidation. The Baeyer-Villiger oxidation involves treatment of a ketone **20** with a peroxy-acid **21** to produce an ester **25** (Figure 2.1). The first step involves addition of the peroxy-acid to the carbonyl carbon to form intermediate **22**. Migration of the alkyl group occurs in concert with the loss of a carboxylate to form the resulting ester **25**. When the two substituents (R_1 and R_2) on the ketone are inequivalent, there is

competition for migration between the two substituents. It has been found that this reaction can be very regioselective and the group that migrates is the one which can better stabilize a positive charge. This can be illustrated in the transition state **26** of this reaction, in which the positive charge is delocalized over the molecule as the carboxylate leaves as an anion. If the migrating group can stabilize the positive charge, the transition state will be lower in energy and hence the activation energy of the reaction is lowered.

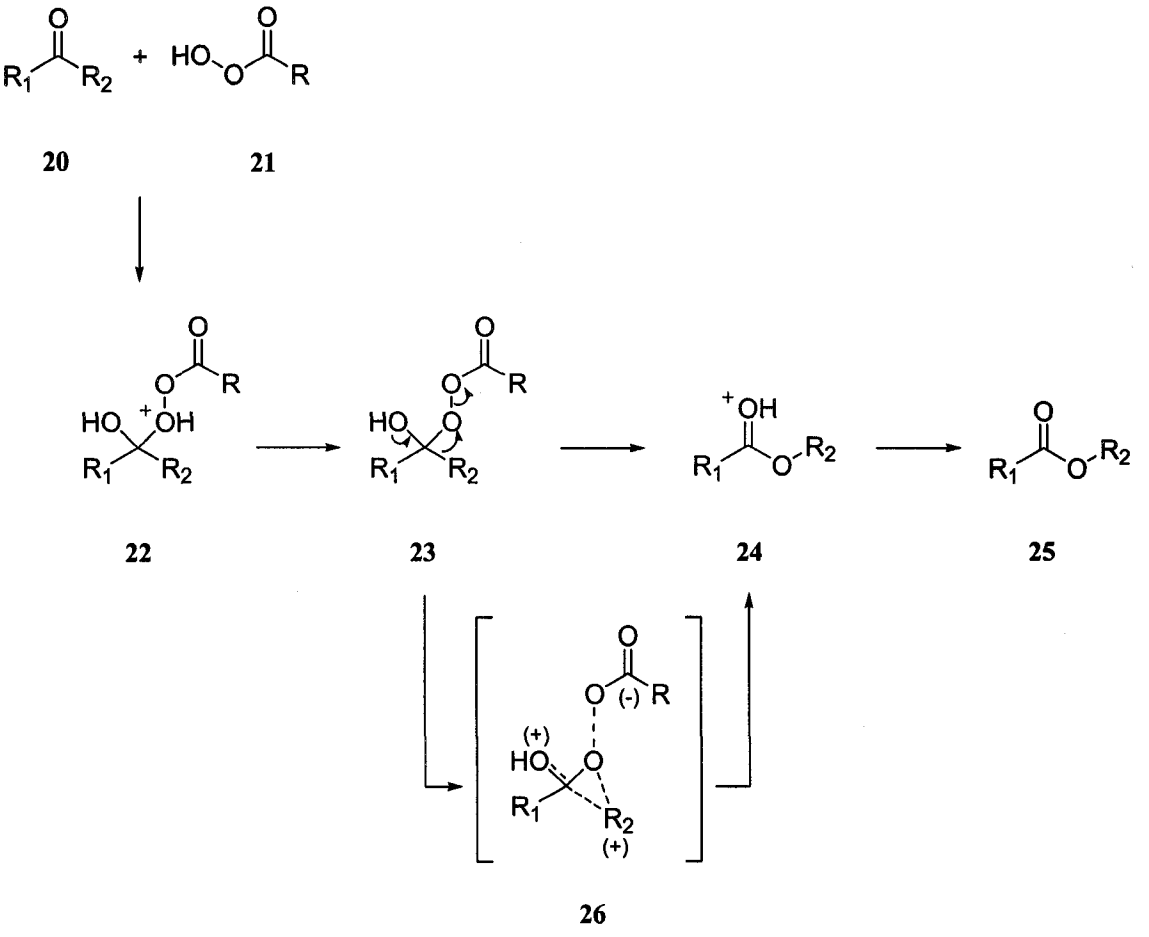
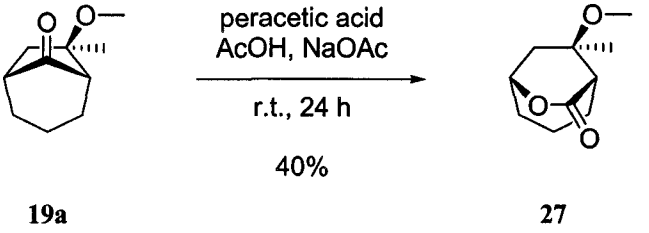


Figure 2.1 Baeyer-Villiger Oxidation Reaction

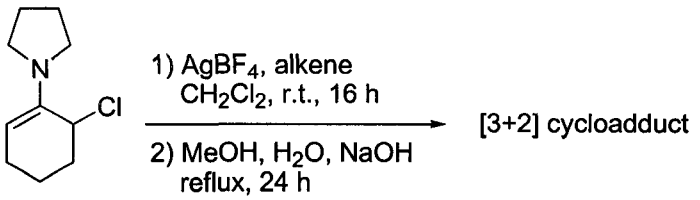
Baeyer-Villiger oxidation of diastereomer **19a** was accomplished via reaction with peracetic acid in acetic acid and sodium acetate (Scheme 2.5). Lactone **27** was furnished in 40% yield with the expected regioselectivity, in which the simple methine group has migrated instead of the methine group adjacent to the inductively destabilizing methoxy group. The regioselectivity was determined by the ^{1}H, COSY, HMBC and ^{13}C NMR spectra of compound **27**.



19a **27**

Scheme 2.5 Baeyer-Villiger Oxidation of Ketone **19a**

The [3+2] cycloaddition of the enamine was then attempted with other enol ethers. Enamine **18** was treated under the same conditions as in the previous case with 2,3-dihydrofuran **28**, 3,4-dihydro-2H-pyran **29**, and ethyl vinyl ether **30** (Scheme 2.6). In all three cases, the starting material was consumed but the reaction resulted in a complicated mixture (Table 1.1). TLC of the reaction mixtures indicated that there were many new compounds formed and ^{1}H NMR spectra of the crude reaction mixtures implied that there might be a trace amount of the cycloadduct formed, but not as one of the major products.



18

Scheme 2.6 [3+2] Schmid Cycloaddition of Enamine **18** with Enol Ethers

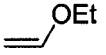
ALKENE	RESULTS
 **28**	complicated reaction mixture
 **29**	complicated reaction mixture
 **30**	complicated reaction mixture

Table 2.1 Vinyl Ethers Used in [3+2] Schmid Cycloaddition

Although the structures of the compounds formed were not determined, a mechanistic view of the reaction can help illustrate the possible products. 2-Aminoallyl cation **31** is generated when enamine **18** reacts with silver tetrafluoroborate (Figure 2.2). It then undergoes a nucleophilic attack from the enol ether to form oxocarbenium ion intermediate **32**. Formation of the desired cycloadduct **34** would result from an intramolecular nucleophilic addition to form imine intermediate **33**, followed by hydrolysis. As illustrated, the cycloadduct is formed through a non-concerted [3+2]

cycloaddition. However, oxocarbenium ion **32** may participate in other chemical transformations rather than the desired intramolecular nucleophilic attack. After addition of NaOH and MeOH, the oxocarbenium ion is liable to undergo deprotonation under the basic conditions to form an isomeric mixture of enamine **35** and then hydrolyze to the corresponding ketones **36**. Oxocarbenium ion **32** may also undergo an intermolecular nucleophilic attack, instead of intramolecular to form ketone **38** from MeOH attack, or oxocarbenium ion **39** from attack by another molecule of enol ether. This intermediate can undergo an inter- or intramolecular nucleophilic attack or deprotonation, as in the case of oxocarbenium ion **32** to form different products. Another possibility is that the enol ether does not even attack the 2-aminoallyl cation **31**. MeOH can act as the nucleophile instead of the enol ether and form intermediate **40** which could be converted to ketone **41** by hydrolysis. With the many possible side reactions that may occur, it is easily understood why the reaction was messy and there was indication of only a trace of the desired product.

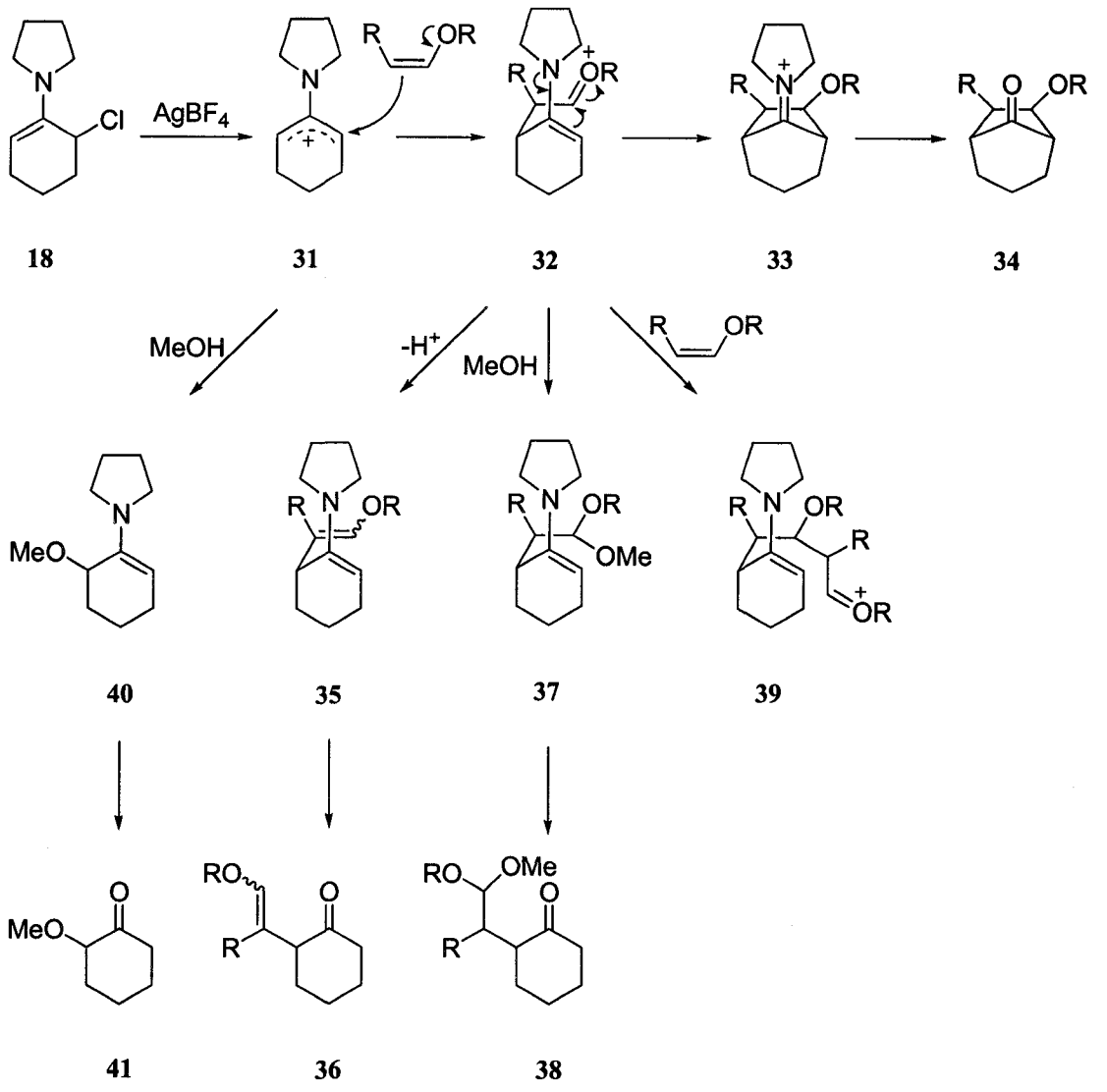
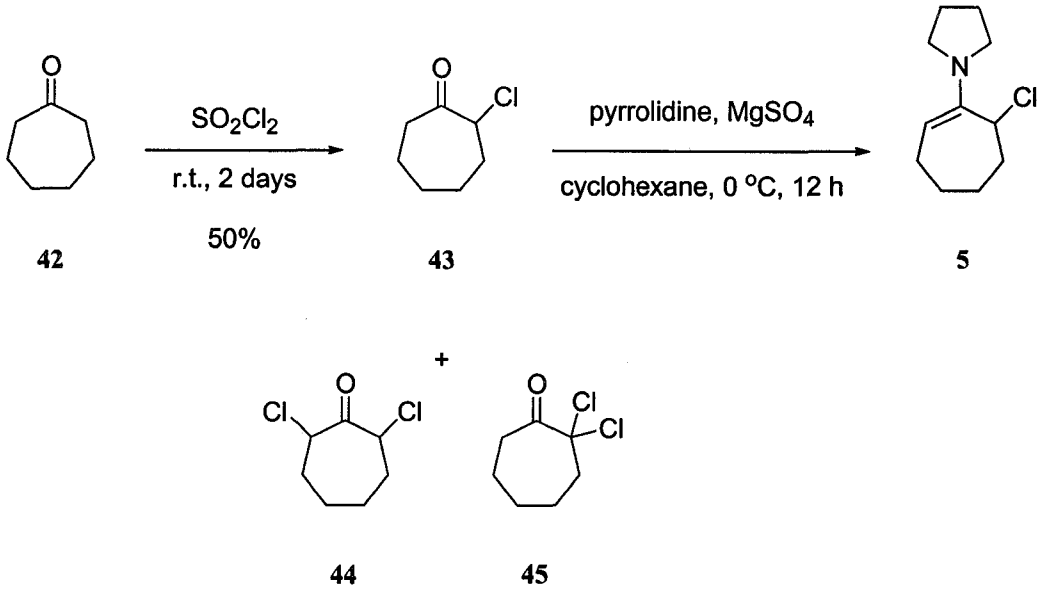


Figure 2.2 Mechanism of [3+2] Cycloaddition of Enamine **18** with Enol Ethers

Despite these unsuccessful results, attempts to synthesize asteriscanolide were nonetheless pursued. Enamine **5**, which is the actual substrate that would be used in the synthesis (Scheme 2.1), was prepared from commercially available cycloheptanone using conditions reported by Wyman and Kaufman.[10] When treated with neat sulfuryl chloride, cycloheptanone **42** was converted to 2-chlorocycloheptanone **43** in 50% yield (Scheme 2.7). It was implied that the low yield was a result of incomplete consumption of the

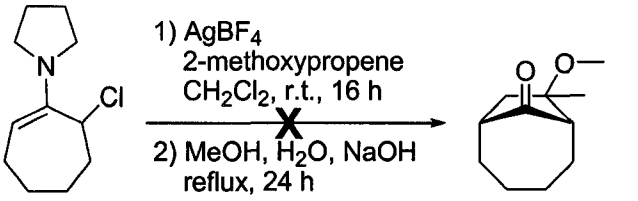
starting material and the formation of dichlorinated ketones **44** and **45** as byproducts. 2-Chlorocycloheptanone **43** was carried on to the next step and allowed to react with pyrrolidine in the presence of $MgSO_4$ to form enamine **5**. Enamine **5** was not subjected to purification due to its instability and susceptibility to hydrolysis and was used directly in the next step.



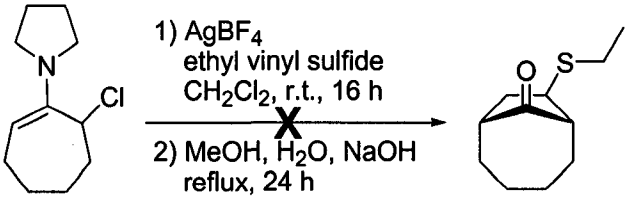
Scheme 2.7 Synthesis of Enamine **5**

Enamine **5** was then used in the [3+2] Schmid cycloaddition. Prior to using cyclic vinyl sulfide **16** prepared for the synthesis of asteriscanolide, other vinyl ethers were examined as model substrates for the [3+2] cycloaddition reaction. Utilizing the same conditions as in the previous successful case, enamine **5** was treated with silver tetrafluoroborate and 2-methoxypropene followed by NaOH and MeOH (Scheme 2.8). In this case, however, unlike the [3+2] cycloaddition reaction of the 6-membered enamine ring **18**, the desired cycloadduct was not produced. TLC analysis of the reaction

mixture showed that the starting material was consumed but many products were observed. The ^{1}H NMR spectrum of the crude reaction mixture showed the presence of many compounds and no indication of the desired [3+2] cycloaddition product. The reaction was further investigated, using different alkene traps to determine if the [3+2] cycloaddition would occur. Using the same conditions as before, the reaction was repeated, using ethyl vinyl sulfide instead of 2-methoxypropene (Scheme 2.8). Ethyl vinyl sulfide was used because of its commercial availability and its similarity to cyclic vinyl sulfide **16** which would be used in the actual synthesis. The results of the reaction were similar to the case of using 2-methoxypropene, in which the reaction yielded a number of different products but the desired cycloadduct was not observed.



5 **46**



5 **47**

Scheme 2.8 [3+2] Schmid Cycloaddition of Enamine **5** with Alkenes

The results of these reactions, in which many undesired products were formed, can be explained by the mechanism. Similar to the previous case involving enamine **18** (Figure 2.2), the oxocarbenium ion generated after addition of the vinyl ether may undergo reactions other than the desired intramolecular addition. Furthermore, the strain energy of cyclooctanes is higher than that of cycloheptanes by 4.3 kcal per mole, making closure of the ring more difficult. As a result, studies on the synthesis of asteriscanolide using this methodology were not pursued further.

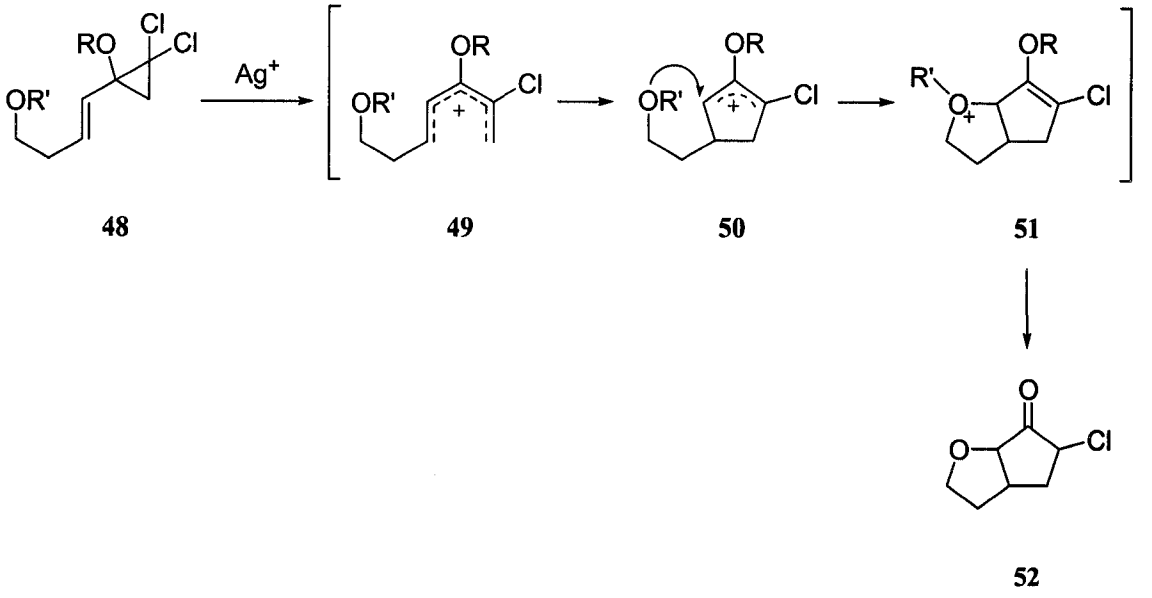
2.2 THE INTERRUPTED NAZAROV REACTION

The Nazarov reaction plays an important role in organic synthesis and has been utilized by many research groups in the synthesis of natural products.[11,12,13,14] As discussed earlier, in the presence of a nucleophile, interruption of the Nazarov reaction may occur, in which the cyclic oxyallyl cation generated from the 4π conrotatory electrocyclic ring closure undergoes a nucleophilic addition. There have been many examples of the interrupted Nazarov reaction reported by research groups. West and coworkers have demonstrated that trapping of the oxyallyl cation can occur by using alkenes,[15,16,17,18] dienes,[19,20] silanes,[21] arenes,[22,23] azides,[24] or halides[25] as the nucleophilic source. Although there have been reports of the trapped Nazarov reaction utilizing oxygen functional groups, the examples were not of the cyclic 2-oxyallyl cation generated in the traditional Nazarov reaction.

2.2.1 SYNTHESIS OF BICYCLIC SYSTEMS

Recently, a new approach to the Nazarov reaction has been reported, in which the pentadienyl cation **49** involved in the 4π electrocyclic ring closure is generated from a dichlorocyclopropane precursor **48**.[26] There has been only one example of trapping with this new type of Nazarov reaction, involving an intramolecular nucleophilic addition of an arene group.[23] It was recognized that there was still much of this reaction to be investigated and the scope of suitable substrates for this reaction needed to be determined. Intramolecular trapping of the Nazarov intermediate with an oxygen functional group has not been achieved with the traditional Nazarov reaction. In the traditional Nazarov reaction a Lewis acid is used to activate the carbonyl group and generate the pentadienyl cation which would undergo the 4π electrocyclization. In cases where trapping by an oxygen nucleophile is desired, the Lewis acid might also deactivate the oxygen functional group, making it less nucleophilic and therefore less likely to trap the cyclic oxyallyl cation intermediate. Alternatively, silver (I), rather than Lewis Acid, is used in the new approach to the Nazarov reaction. Silver (I) does not deactivate the oxygen functional group, making it more likely to trap the cyclic oxyallyl cation intermediate than when a Lewis acid is used. In addition, under the silver conditions, the cyclic oxyallyl cation generated from the 4π electrocyclic ring closure is a simple cation whereas under Lewis acid conditions, a zwitterion in generated instead. As a result, the cyclic cation intermediate in the new Nazarov reaction is more electrophilic and hence more likely to be trapped by an oxygen functional group. It was rationalized that if the cyclic oxyallyl cation **50** generated from the 4π electrocyclization was to undergo an

intramolecular nucleophilic attack from an oxygen functional group then a cyclic ether would be produced (Scheme 2.9). This bicyclic system would be useful in organic synthesis and be could further manipulated to form other compounds.



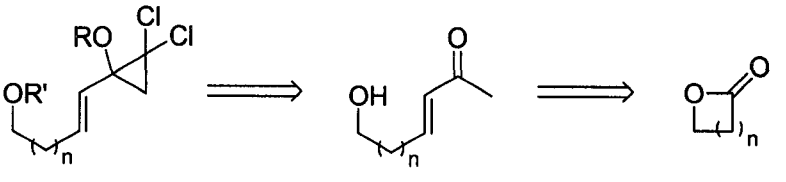
48 **49** **50** **51**

52

Scheme 2.9 Oxygen Trapping of the Nazarov Reaction

The precursor **48** for the Nazarov reaction can be prepared from enone **53** through several steps (Scheme 2.10). Enone **53** was to be prepared from the corresponding lactone **54**. It was rationalized that the primary alcohol should be protected in order to avoid intramolecular addition prior to the Nazarov reaction and that the protecting group should be one in which the oxygen is still nucleophilic enough to trap the Nazarov intermediate. In addition, the protecting group should be one that can be removed under conditions that will not affect the rest of precursor **48** to furnish the free primary alcohol in case the protected alcohol is not nucleophilic enough to trap the cyclic oxyallyl cation

intermediate. Due to these requirements, a silyl group was chosen as the protecting group.

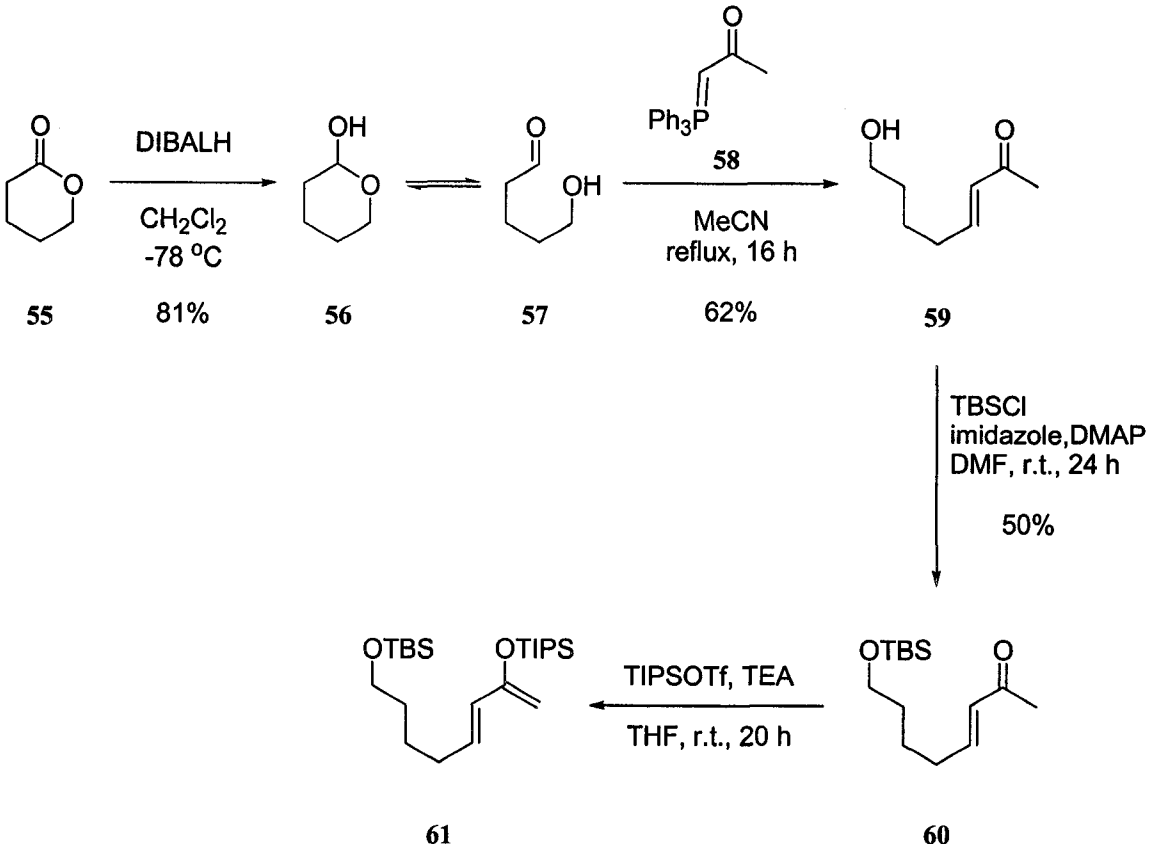


48 **53** **54**

n = 1, 2, 3

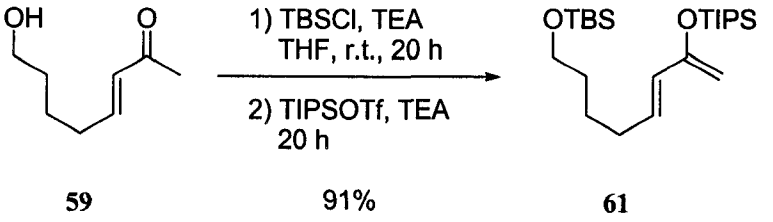
Scheme 2.10 Retrosynthesis of Dichlorocyclopropane **48**

Preparation of the dichlorocyclopropane precursor in which n = 2 began with reduction of commercially available δ-valerolactone **55** (Scheme 2.11). When treated with DIBALH in dichloromethane at -78 °C, lactone **55** was reduced to lactol **56** in 81% yield. ^{1}H NMR spectra indicated that the lactol was in equilibrium with aldehyde **57**. Heating aldehyde **57** with Wittig reagent **58** at reflux furnished enone **59** in 62% yield. Protection of the primary alcohol was accomplished by treating enone **59** with TBSCl, imidazole, and DMAP. The silyl ether **60** was isolated in 50% yield and there was no indication of competing formation of the silyl enol ether. The chemoselectivity of this reaction is due to the fact that the primary alcohol reacts faster with the TBSCl than the ketone, furnishing the observed silyl ether. The low yield probably results from partial deprotection of the silyl group during purification. The protected alcohol was carried through to the next step. Following the procedure reported by West and coworkers,[26] silyl ether **60** was treated with TIPSOTf and triethylamine to yield the desired silyl enol ether **61**.



Scheme 2.11 Synthesis of Silyl Enol Ether **61**

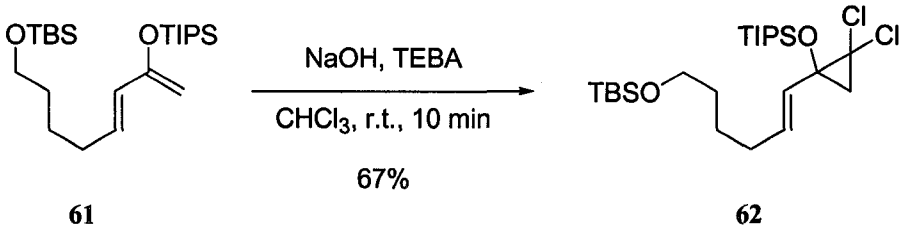
Upon optimization of the last two steps, it was discovered that formation of silyl enol ether **61** from enone **59** can be accomplished via a one pot procedure. Enone **59** was treated with TBSCl and triethylamine in THF at room temperature (Scheme 2.12). After 20 hours, additional triethylamine was added followed by TIPSOTf and the reaction was stirred for an additional 20 hours. Silyl enol ether **61** was furnished in 91% yield through the one pot procedure.



59 91% **61**

Scheme 2.12 One Pot Synthesis of Silyl Enol Ether **61**

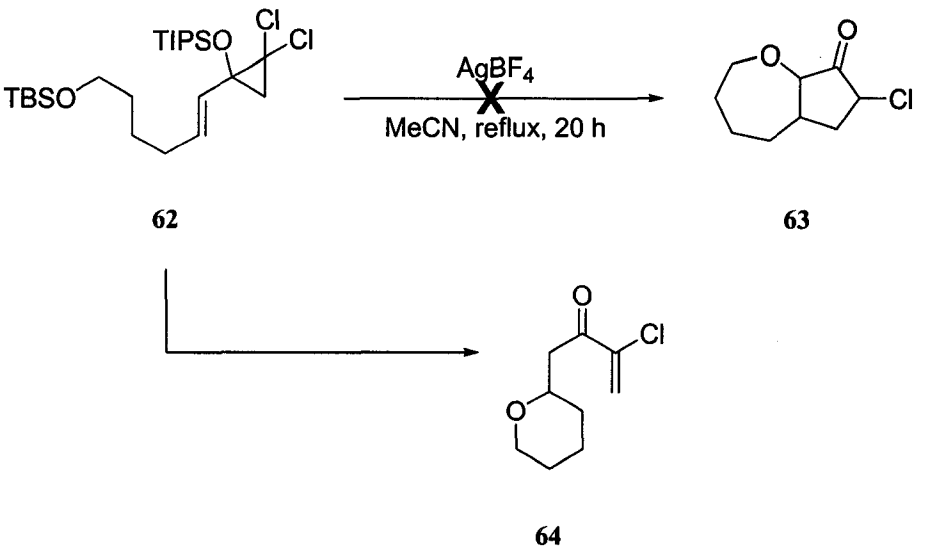
Synthesis of dichlorocyclopropane **62** was accomplished by reacting silyl enol ether **61** with concentrated NaOH and triethylbenzylammonium chloride (TEBA) in $CHCl_3$ (Scheme 2.13). Dichlorocyclopropane **62** was formed through a phase transfer mechanism, which has been discussed in the previous chapter, and the precursor for the Nazarov reaction was obtained in 67% yield.



61 **62**

Scheme 2.13 Synthesis of Dichlorocyclopropane **62**

Dichlorocyclopropane **62** was treated with silver tetrafluoroborate in MeCN at reflux to perform the expected trapping of the Nazarov reaction (Scheme 2.14). However, the desired bicyclic compound **63** was not produced and tetrahydropyran derivative **64** was isolated instead. Although the reaction was examined using different conditions, by varying the solvent, temperature, time and purification method, the tetrahydropyran was still produced in most cases.



Scheme 2.14 Synthesis of Tetrahydropyran Derivative **64**

A plausible mechanism for the formation tetrahydropyran **64** begins with ring opening of the dichloropropane ring in the presence of silver (I) to generate pentadienyl cation **65** (Path A, Figure 2.3). It should be realized that the pentadienyl cation can undergo two different reactions. There is competition between the desired 4π electrocyclic ring closure and direct trapping of the conjugated carbocation (Path A). Tetrahydropyran **64** could be obtained if the pentadienyl cation **65** undergoes an intramolecular trapping rather than the Nazarov reaction to form intermediate **66**. Intermediate **66** is then converted into the observed tetrahydropyran derivative **64** upon work-up. An alternative mechanism for the generation of the observed product would involve an intramolecular addition to dichlorocyclopropane **62** (Path B), involving simultaneous ring opening of the cyclopropane and ether formation to give intermediate **66** as in the mechanism shown in Path A.

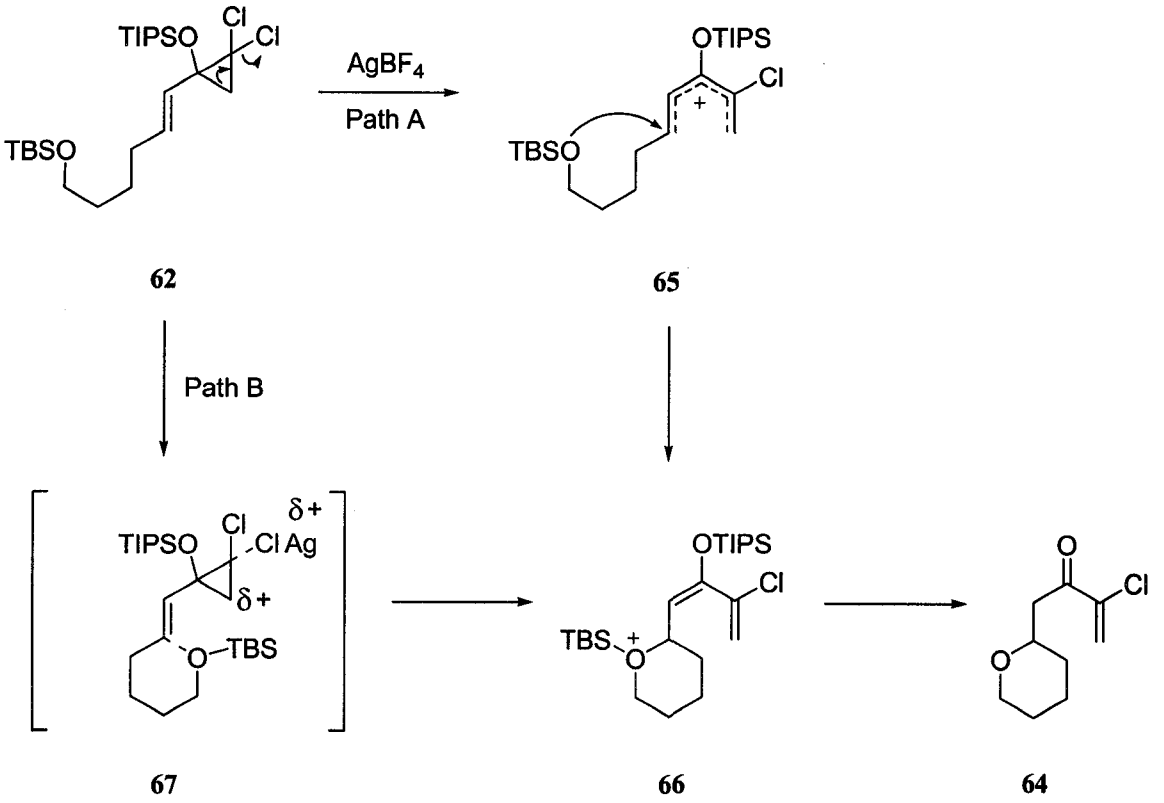
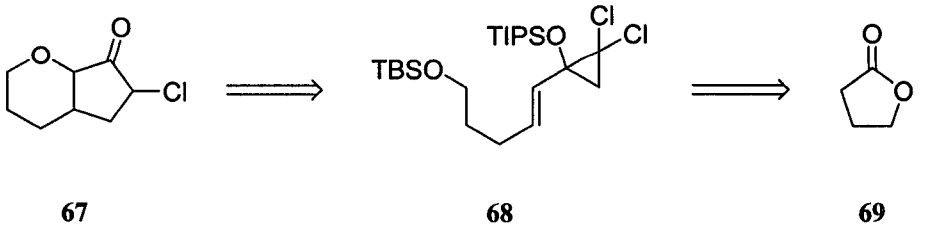


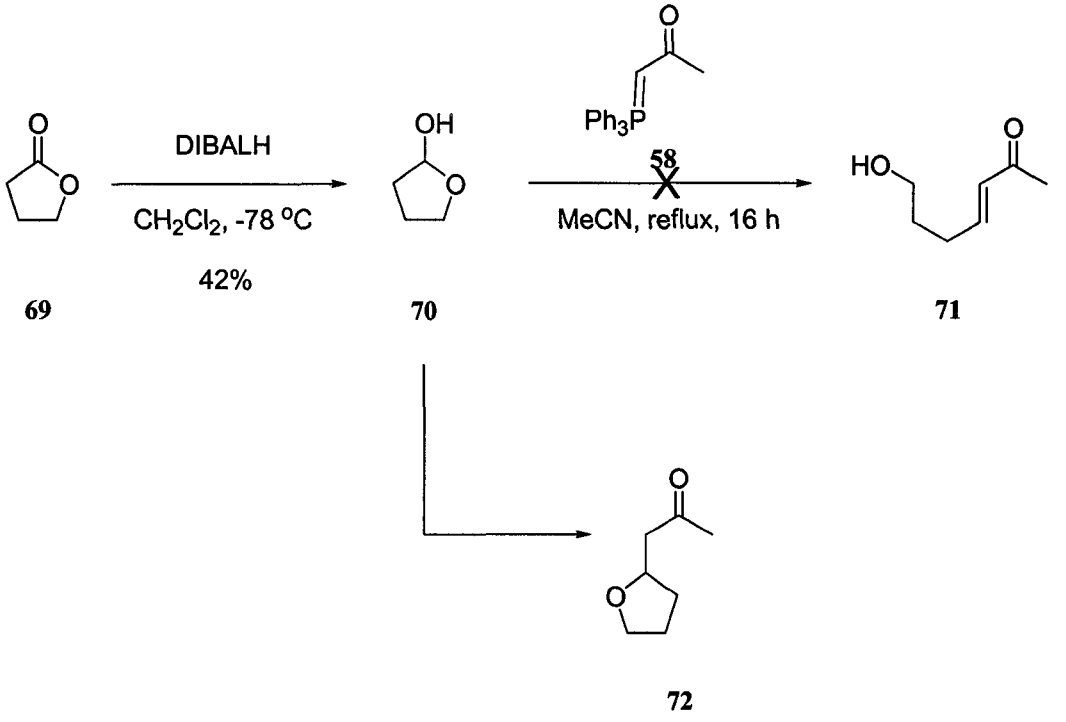
Figure 2.3 Mechanism of the Formation of Tetrahydropyran **64**

At the same time, dichlorocyclopropane **68** was being prepared from γ-butyrolactone **69** (Scheme 2.15). It was rationalized that dichlorocyclopropane **68** was more likely to undergo an intramolecular nucleophilic attack than dichlorocyclopropane **62** to produce bicyclic compounds because six-membered rings are more easily formed than seven-membered rings.



Scheme 2.15 Retrosynthesis of Cyclic Ether **67**

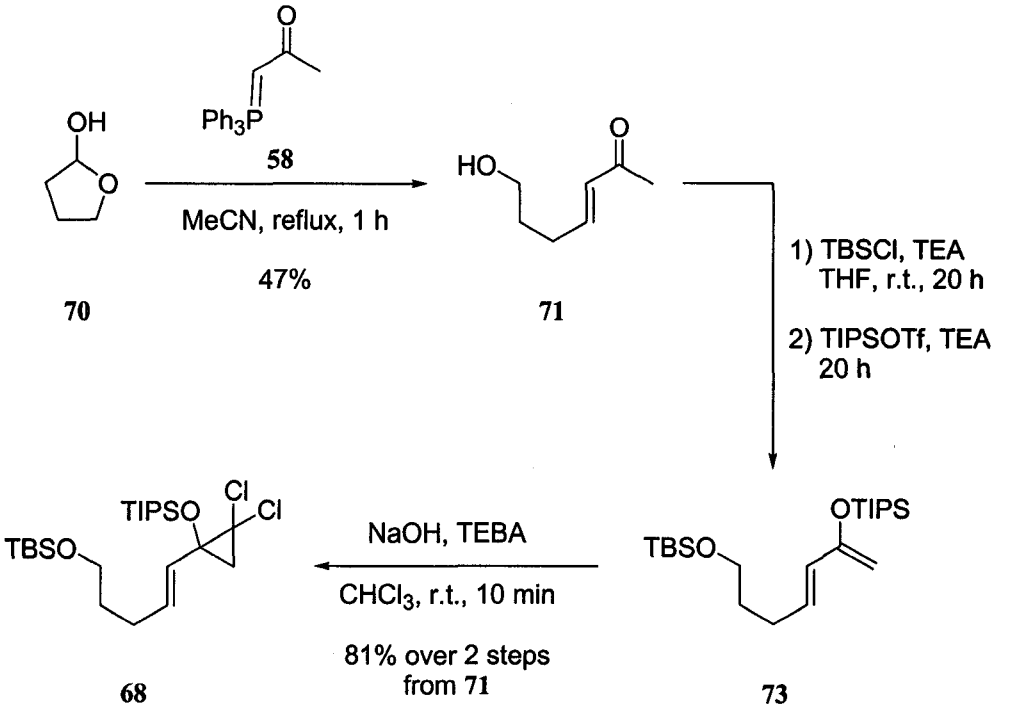
Reduction of γ-butyrolactone **69** was accomplished by treatment with DIBALH in CH_2Cl_2 at -78 °C (Scheme 2.16). Lactol **70** was isolated in 42 % yield. Following the same procedure as in the previous example, conversion of the lactol into enone **71** was attempted by reaction with the Wittig reagent **58** at reflux for 16 hours. However, unlike the previous example, enone **71** could not be isolated. Rather, tetrahydrofuran **72** had been formed and is believed to be a result of an intramolecular conjugate addition of enone **71** from increased heating at reflux for too long a time.



Scheme 2.16 Synthesis of Tetrahydrofuran **72**

The Wittig reaction with lactol **70** was repeated and monitored more carefully. By TLC, it was found that the reaction was complete after only 1 hour of heating at reflux and enone **71** was isolated in 47% yield (Scheme 2.17). Enone **71** was then treated with

TBSCl and triethylamine in THF at room temperature. After 20 hours, TIPSOTf and additional triethylamine were added to yield silyl enol ether **73**. The silyl enol ether was not subjected to purification and was directly carried on to the next step. Treating silyl enol ether **73** with concentrated NaOH and TEBA in $CHCl_3$ produced dichlorocyclopropane **68** in 81% yield over 2 steps.

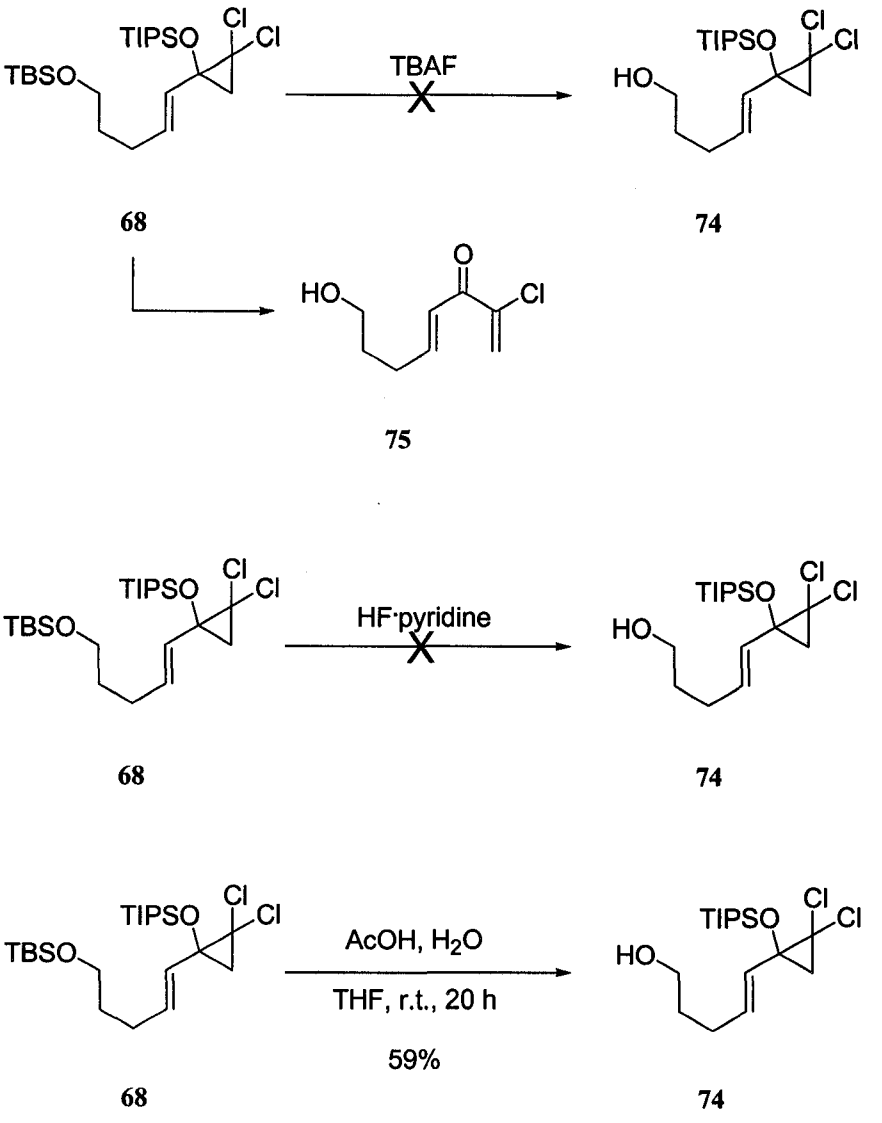


Scheme 2.17 Synthesis of Dichlorocyclopropane **68**

Selective deprotection of the dichlorocyclopropane **68** was then pursued. The TIPS group is more bulky than the TBS group and therefore should be more difficult to deprotect due to steric hinderance. In addition, the OTBS group is located on a primary carbon, whereas the OTIPS group is located on a tertiary carbon making the TBS group less sterically hindered and therefore more approachable. As a result, the TBS group was

expected to be selectively deprotected in the presence of the TIPS group. The reason for the deprotection step is that the free hydroxyl group resulting from selective deprotection would be more nucleophilic than the silyl protected hydroxyl group and therefore the trapping of the Nazarov reaction would occur more rapidly.

Dichlorocyclopropane **68** was treated with TBAF in THF at 0 °C to effect selective deprotection of the TBS group. However, the ^{1}H NMR spectrum of the crude reaction mixture indicated that primary alcohol **74** was not obtained and dienone **75** was produced instead (Scheme 2.18). Treatment of dichlorocyclopropane **68** with HF·pyridine, also resulted in dienone **75** instead of the desired primary alcohol **74**. Other conditions for the selective deprotection were examined and it was found that the desired product could be obtained by treating dichlorocyclopropane **68** with acetic acid and water. Under these conditions, primary alcohol **74** was furnished in 59% yield.



Scheme 2.18 Selective Deprotection of Dichlorocyclopropane **68**

The formation of dienone **75** was a result of deprotection of the TIPS group to generate anion **76** (Figure 2.4). The pair of electrons on the oxygen assisted in ring opening of the dichlorocyclopropane to form the observed dienone.

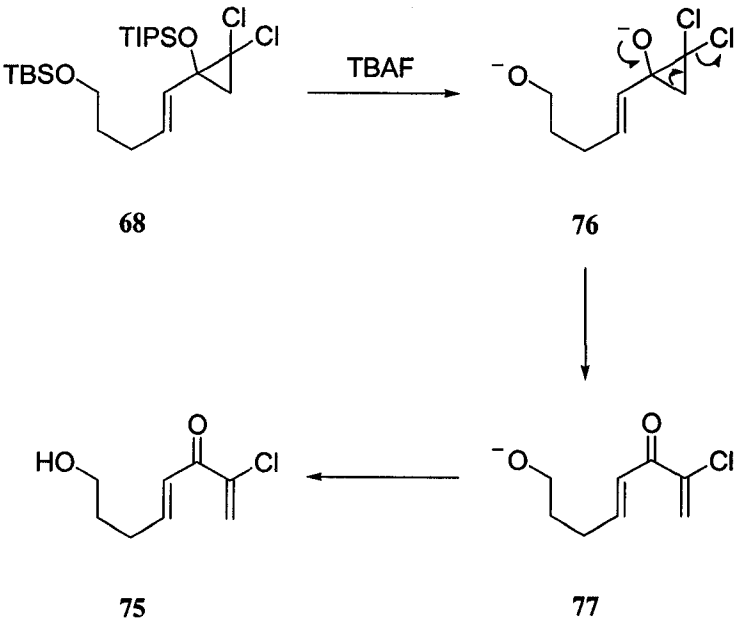
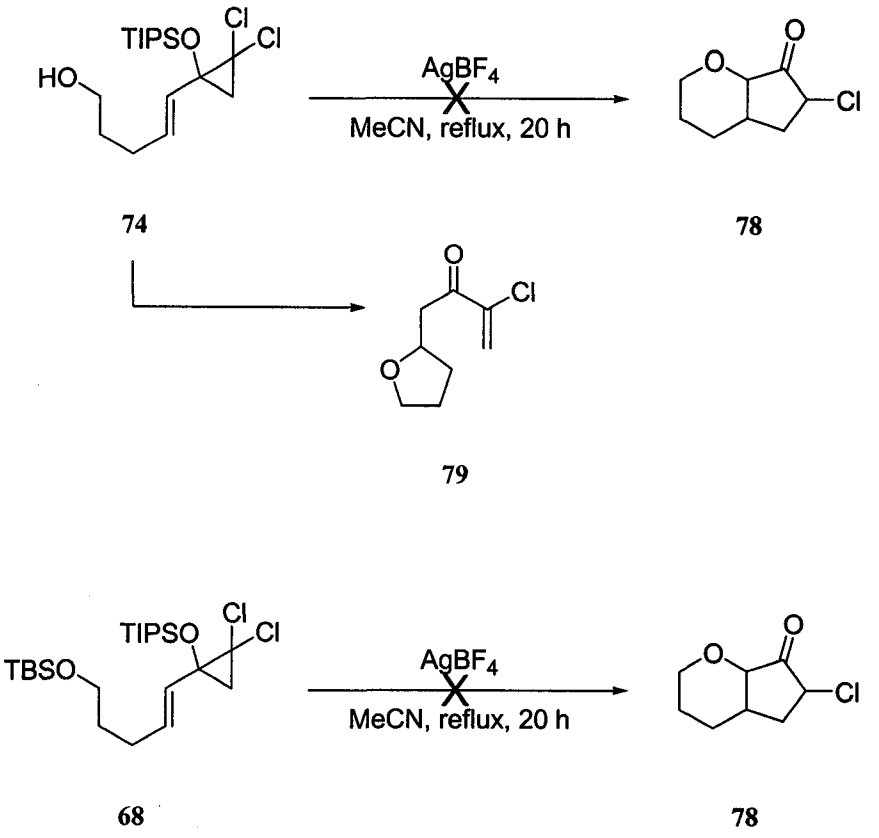


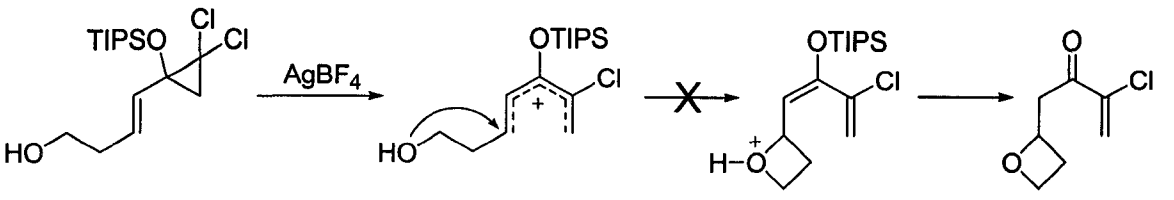
Figure 2.4 Mechanism of the Formation of Dienone **75**

Alcohol **74** was carried through to the key step and treated with silver tetrafluoroborate in MeCN (Scheme 2.19). The desired bicyclic system **78**, which would result from trapping of the Nazarov reaction, was not formed and there was evidence of the formation tetrahydrofuran **79** from the ^{1}H NMR spectrum. It was rationalized that trapping of the pentadienyl cation took place preferentially over electrocyclization, due to the high reactivity of the hydroxyl group. As a result, tetrahydrofuran **79** was produced rather then cyclic ether **78**. If the hydroxyl group were to be protected, it would be less nucleophilic and premature trapping of the pentadienyl cation might be slow enough to permit electrocyclization. To test this theory, the protected alcohol **68** was allowed to react with silver tetrafluoroborate at reflux to undergo the Nazarov reaction. However, as in the case of the free alcohol, trapping of the pentadienyl cation occurred to produce tetrahydrofuran **79**. When the reaction was repeated by varying the conditions, such as the solvent, temperature and reaction time, the results were similar.



Scheme 2.19 Synthesis of Tetrahydrofuran **79**

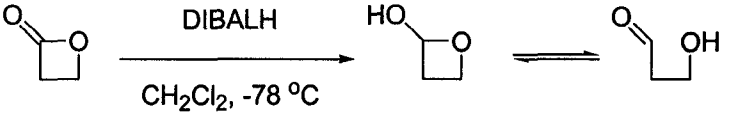
From the unexpected generation of tetrahydropyran **64** and tetrahydrofuran **79**, it was rationalized that if the dichlorocyclopropane precursor for the Nazarov reaction had one methylene group less, as in compound **80**, then the intramolecular trapping of the conjugated carbocation would be less likely to occur because it would require closure of a strained four membered ring (Figure 2.5). However, the desired trapping process would proceed through a more favorable 5-membered transition state.



80 **81** **82** **83**

Figure 2.5 Intramolecular Trapping of Dichlorocyclopropane **80**

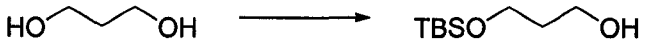
Preparation of dichlorocyclopropane **80** began with reduction of β-propiolactone **84** by treatment with DIBALH in CH_2Cl_2 at -78 °C (Scheme 2.20). TLC analysis of the reaction mixture and the ^1H NMR spectrum of the crude reaction showed a complicated product mixture with some starting material and only a trace of the desired aldehyde **86**.



84 **85** **86**

Scheme 2.20 Reduction of β-Propiolactone **84**

Due to these results, an alternative route was used for the synthesis of dichlorocyclopropane **80**. Preparation of the dichlorocyclopropane began with monoprotection of commercially available 1,3-propanediol **87** (Scheme 2.21). The reaction was examined with different conditions (Table 2.2) and it was found that monoprotected glycol **88** was obtained in a highest yield of 66% when treated with TBSCl and triethylamine.



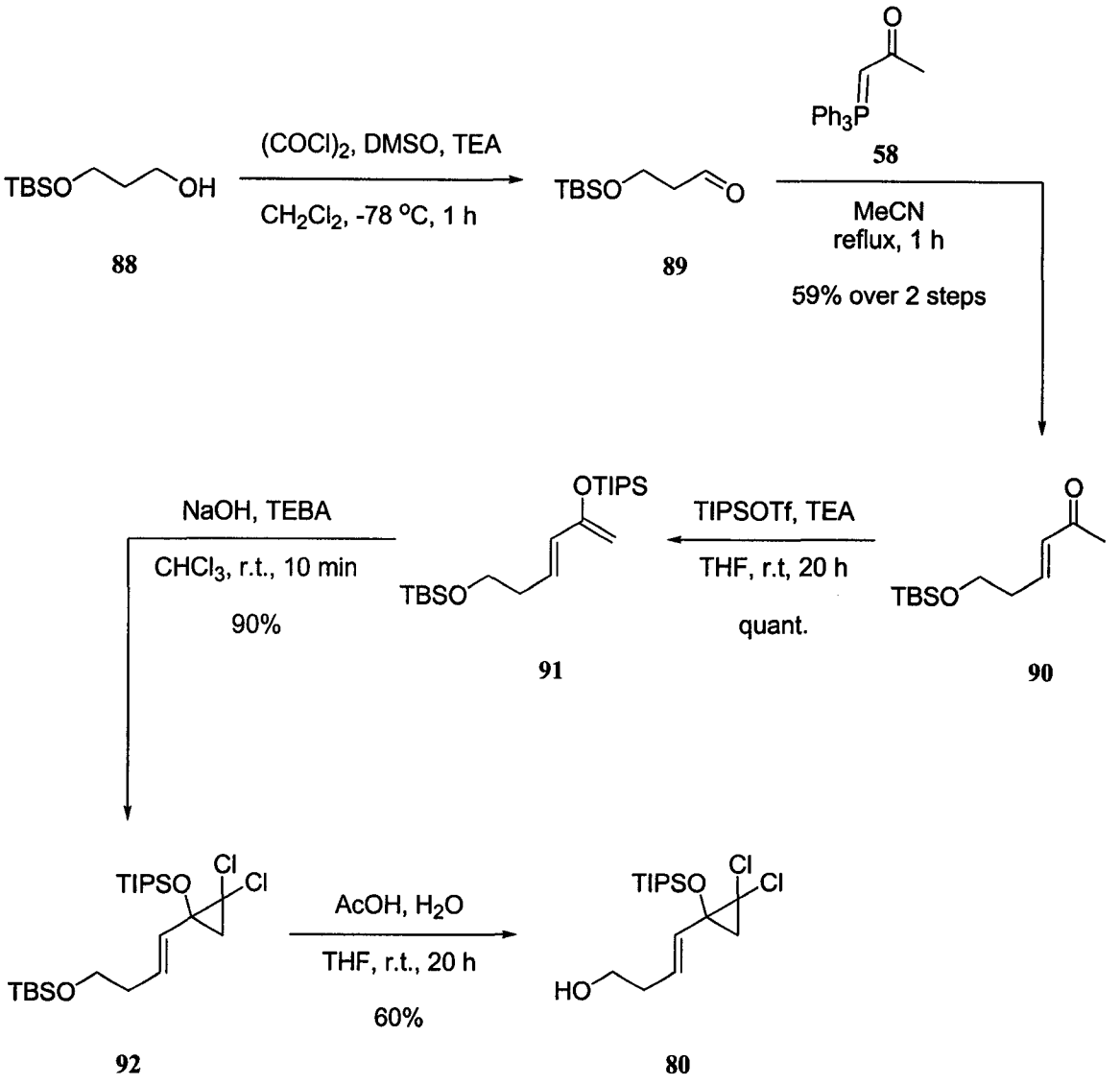
87 88

Scheme 2.21 Monoprotection of 1,3-Propanediol **87**

CONDITIONS	YIELD (%)
TBSCl, TEA CH_2Cl_2, r.t.	66
TBSCl, imidazole CH_2Cl_2, r.t.	25
TBSCl, NaH CH_2Cl_2, r.t.	61

Table 2.2 Conditions for Monoprotection of 1,3-Propanediol **87**

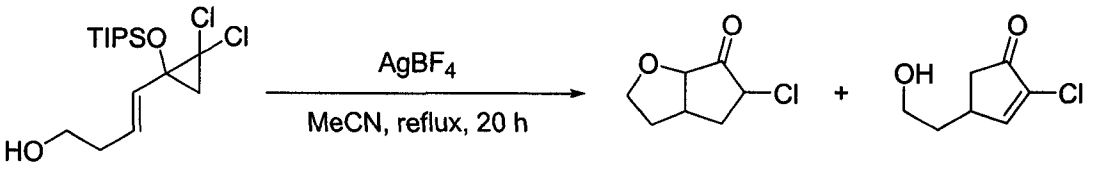
Monoprotected glycol **88** was then oxidized to aldehyde **89** via the Swern oxidation by treatment with oxalyl chloride, DMSO and triethylamine (Scheme 2.22). Due to its instability, aldehyde **89** was carried on to the next step without purification. Aldehyde **89** was converted into enone **90** via the Wittig reaction with compound **58**. Enone **90** was obtained in 59% yield over 2 steps. Silyl enol ether **91** was furnished by treatment of enone **90** with TIPSOTf and triethylamine and was produced in quantitative yield. Using the same conditions for cyclopropanation as in previous cases, silyl enol ether **91** was treated with concentrated NaOH, TEBA and $CHCl_3$ to generate dichlorocyclopropane **92** in 90% yield. Selective deprotection of silyl ether **92** was accomplished by reaction with acetic acid and water. Primary alcohol **80** was isolated in 60% yield.



Scheme 2.22 Synthesis of Dichlorocyclopropane **80**

With dichlorocyclopropane **80** in hand, the next step was to attempt the interrupted Nazarov reaction. Precursor **80** was treated with silver tetrafluoroborate at reflux to effect the Nazarov reaction followed by an intramolecular nucleophilic addition (Scheme 2.23). TLC analysis of the reaction mixture and the ^{1}H NMR spectrum of the crude material indicated a complex mixture of products. After purification, trace amounts of desired cyclic ether **93** were isolated as an impure mixture of diastereomers.

There was also indication of a small amount of cyclopentenone **94** present, which could be a result of the simple Nazarov reaction.



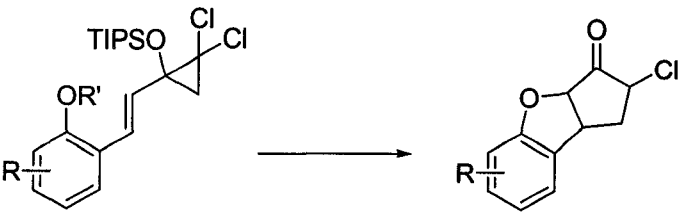
80 **93** **94**

Scheme 2.23 Synthesis of Cyclic Ether **93** and Cyclopentenone **94**

Up to this point, it was clear that intramolecular trapping of the Nazarov reaction with an oxygen functional group was more problematic than expected. Due to these unsuccessful results, there was consideration that these precursors might not be ideal substrates and other cases would have to be examined.

2.2.2 SYNTHESIS OF TRICYLIC SYSTEMS

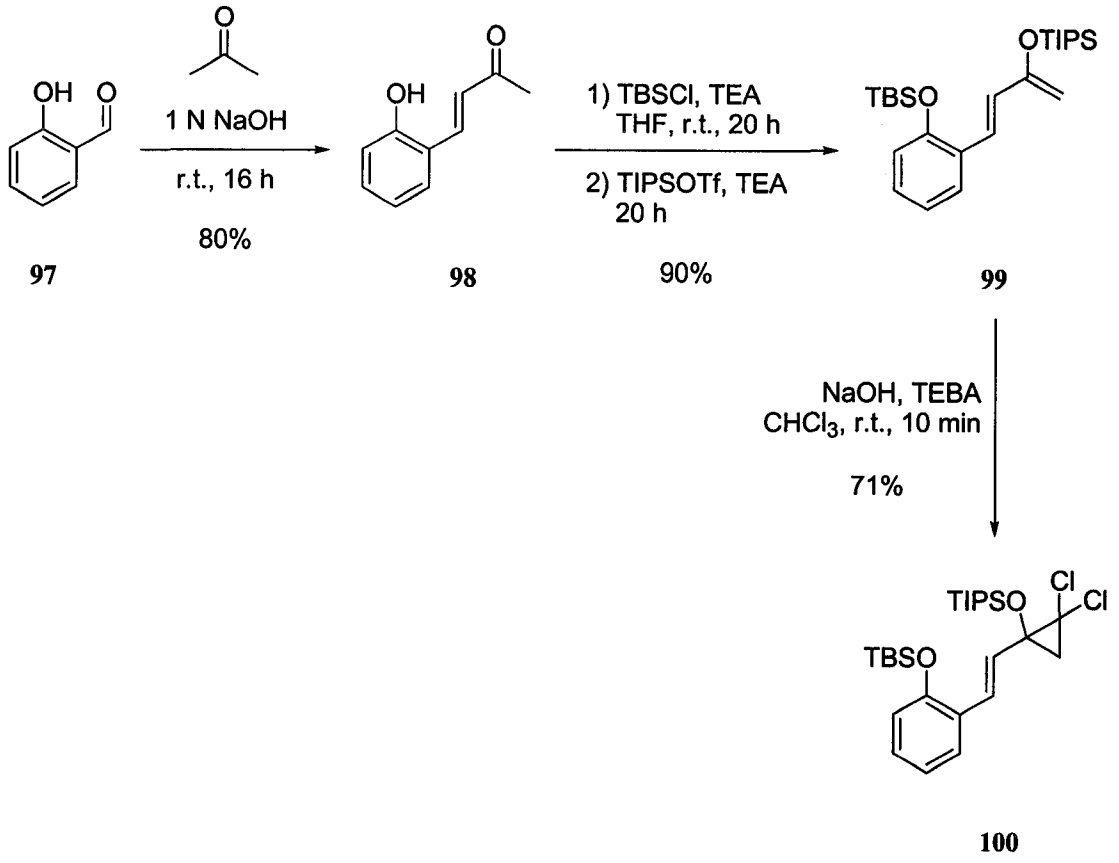
Trapping of the Nazarov reaction with precursors analogous to those discussed previously were studied. It was rationalized that precursor **95** could be converted to the tricyclic system **96** via trapping of the Nazarov intermediate (Scheme 2.24).



95 **96**

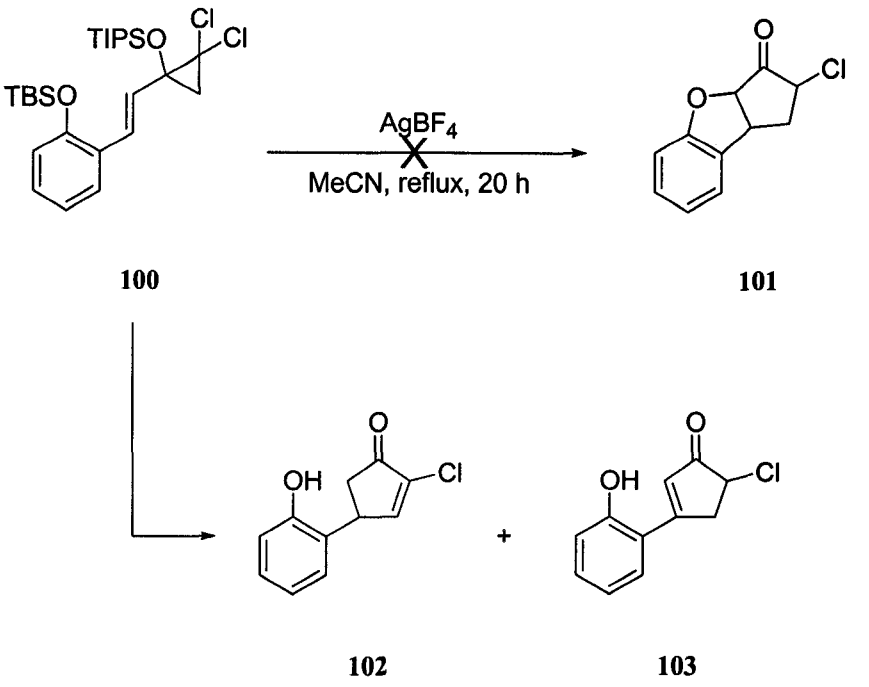
Scheme 2.24 Interrupted Nazarov Reaction with Dichlorocyclopropane **95**

Synthesis of dichlorocyclopropane **100** began with an aldol condensation of salicylaldehyde **97** with acetone. Following a procedure reported by Lee and coworkers,[27] salicylaldehyde was treated with NaOH and acetone to furnish phenol derivative **98** in 80% yield (Scheme 2.25). Protection of the phenol and conversion of the ketone into a silyl enol ether were accomplished through a one pot procedure. Treatment of phenol derivative **98** with TBSCl and triethylamine followed by addition of TIPSCl and excess triethylamine produced silyl enol ether **99** in 90% yield. Silyl enol ether **99** was converted into dichlorocyclopropane **100** in 71% yield by reaction with NaOH, TEBA and $CHCl_3$.



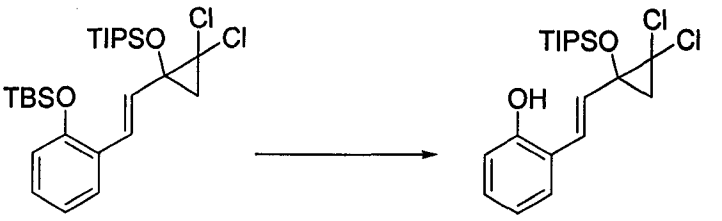
Scheme 2.25 Synthesis of Dichlorocyclopropane **100**

The interrupted Nazarov reaction was first attempted with dichlorocyclopropane **100** without deprotection of the TBS group. Dichlorocyclopropane **100** was treated with silver tetrafluoroborate at reflux (Scheme 2.26). Unfortunately, the desired tricyclic compound **101** was not produced and cyclopentenones **102** and **103** were obtained instead, as a result of the simple Nazarov reaction. It was believed that the intramolecular trapping did not occur because the TBS group makes the phenolic oxygen less nucleophilic. Therefore the next goal was to selectively deprotect the TBS group in the presence of the TIPS group to form the phenol derivative **104**.



Scheme 2.26 Synthesis of Cyclopentenone **102** and **103**

Deprotection of the TBS group was attempted by treatment of the dichlorocyclopropane **100** with many different conditions (Scheme 2.27 and Table 2.3). In most cases, no reaction occurred and only the starting material was recovered. Deprotection of the TBS group on the oxygen of the phenol was discovered to be more difficult than in the case of the primary alcohol. To avoid this problem, a different protecting group was considered, one that would be more easily deprotected than the TBS group.



100 **104**

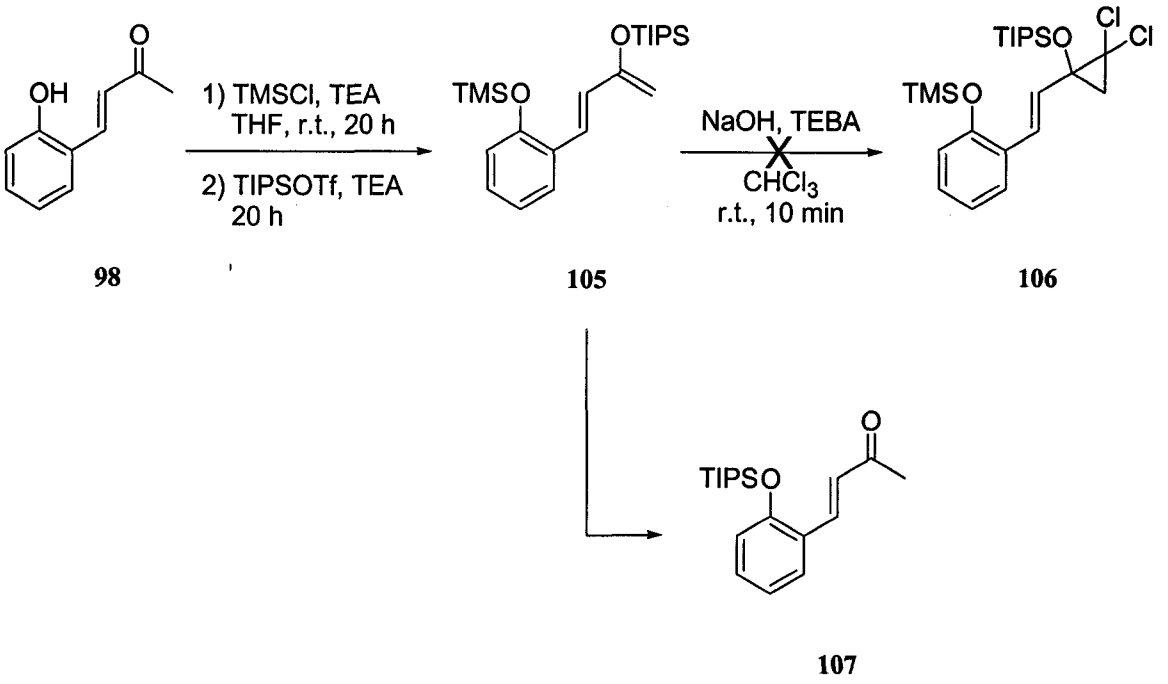
Scheme 2.27 Deprotection of Dichlorocyclopropane **100**

CONDITIONS	RESULTS
AcOH, water	no reaction
0.1 M HCl, MeOH	no reaction
1.0 M HCl, MeOH	no reaction
Conc. HCl, MeOH	no reaction
Conc. HCl, 1,4-dioxane	no reaction
Conc. HCl, EtOH	no reaction
1.0 M NaOH, MeOH	no reaction
NaOMe, MeOH, ether	starting material consumed but no desired product
Copper (II) bromide, MeCN	no reaction

Table 2.3 Conditions for Deprotection of Dichlorocyclopropane **100**

It was rationalized that a TMS group would be a good choice due to its smaller size, and consequently, its greater hydrolytic reactivity. Following the one pot process as described before, silyl enol ether **105** was obtained by treatment of enone **98** with TMSCl and triethylamine followed by addition of TIPSOTf and additional triethylamine (Scheme 2.28). Due to the instability, silyl enol ether **105** was carried on to the next step without purification and treated with concentrated NaOH, TEBA and $CHCl_3$ to perform the cyclopropanation. It was anticipated that under basic conditions, the TMS group would

be lost and the deprotection step would not be necessary. Unfortunately, cyclopropanation did not occur and the TIPS protected phenol **107** was isolated rather then the expected dichlorocyclopropane **106**.

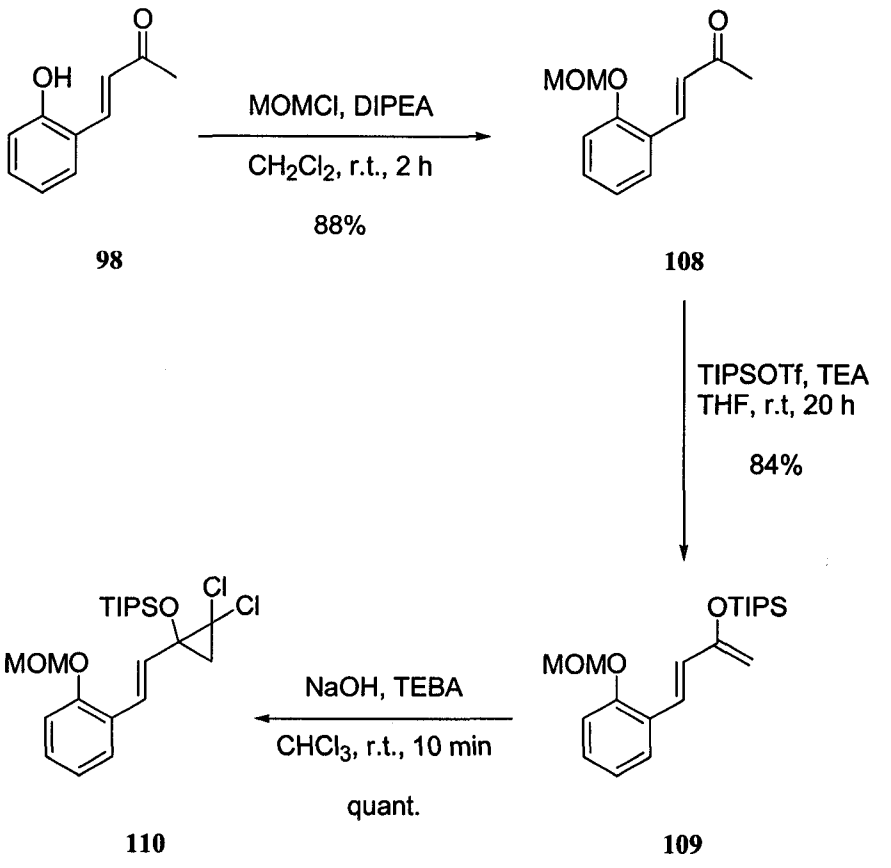


98 **105** **106** **107**

Scheme 2.28 Synthesis of Enone **107**

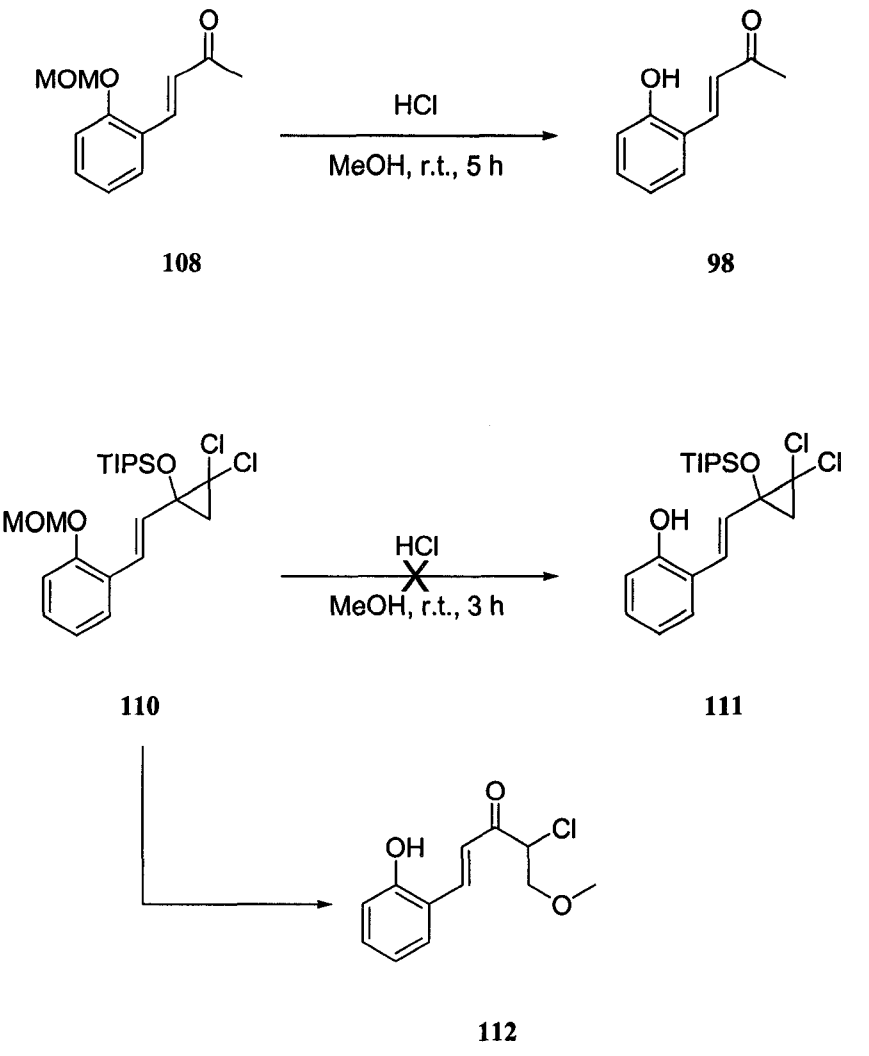
From these results, it was rationalized that a different protecting group should be used. The ideal protecting group would be one that is stable under the strong basic conditions used in the cyclopropanation step and yet can be easily removed later to generate the free hydroxyl group. It was determined that the methoxymethyl (MOM) group should be used rather than another silyl group. Phenol derivative **98** was then protected by treatment with MOMCl and DIPEA in CH_2Cl_2 (Scheme 2.29). MOM protected phenol **108** was obtained in 88% yield and then reacted with TIPSOTf and triethylamine to produce silyl enol ether **109** in 84% yield. Dichlorocyclopropane **110**

was furnished after treatment of silyl enol ether **109** with NaOH, TEBA, and $CHCl_3$ and isolated in quantitative yield.



Scheme 2.29 Synthesis of Dichlorocyclopropane **110**

Prior to attempting the deprotection of dichlorocyclopropane **110**, model studies were first conducted. Treatment of enone **108** with concentrated HCl, MeOH and H_2O resulted in the desired deprotected phenol **98** (Scheme 2.30). The same conditions were then applied to dichlorocyclopropane **110**. However, the deprotected dichlorocyclopropane was not formed and enone **112** was isolated instead.



Scheme 2.30 Deprotection of Dichlorocyclopropane **110**

A plausible mechanism for the unexpected formation of enone **112** begins with protonation of the oxygen to generate oxocarbenium ion **113** (Figure 2.6). This is followed by loss of methanol to form intermediate **114**, which then reacts with water to generate intermediate **116**. Loss of the methanol derivative results in the formation of the desired phenol derivative **111**. However, this product reacts further. Due to conjugation, the pair of electrons from the oxygen on the phenol can be pushed all the way to the cyclopropane and cause ring opening to generate intermediate **117**. Methanol would then

act as a nucleophile and attack the least sterically hindered electrophilic carbon to form methoxy intermediate **118**. The silyl enol ether is then converted to the ketone **112** in the presence of acid.

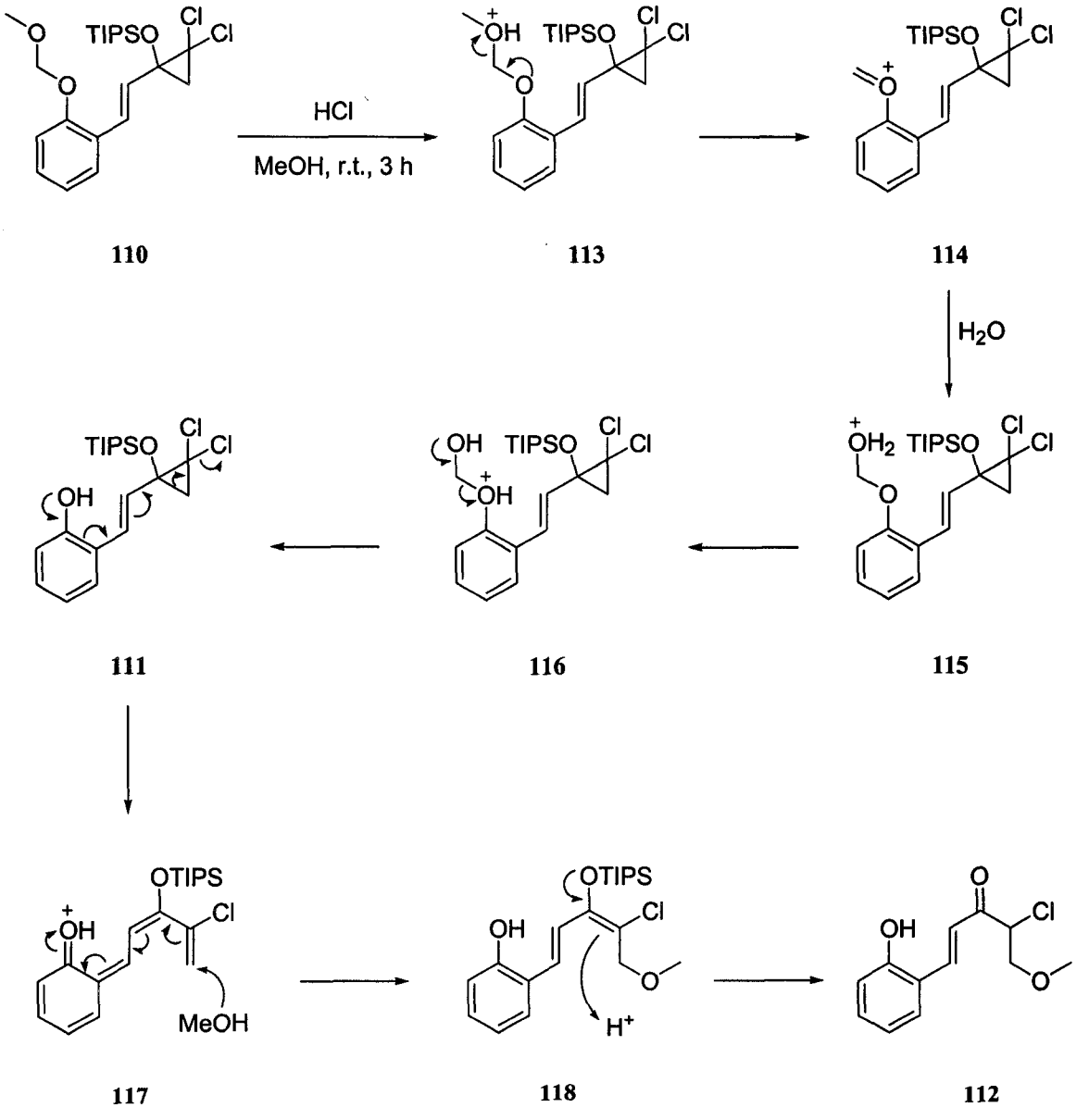


Figure 2.6 Mechanism for the Formation of Enone **112**

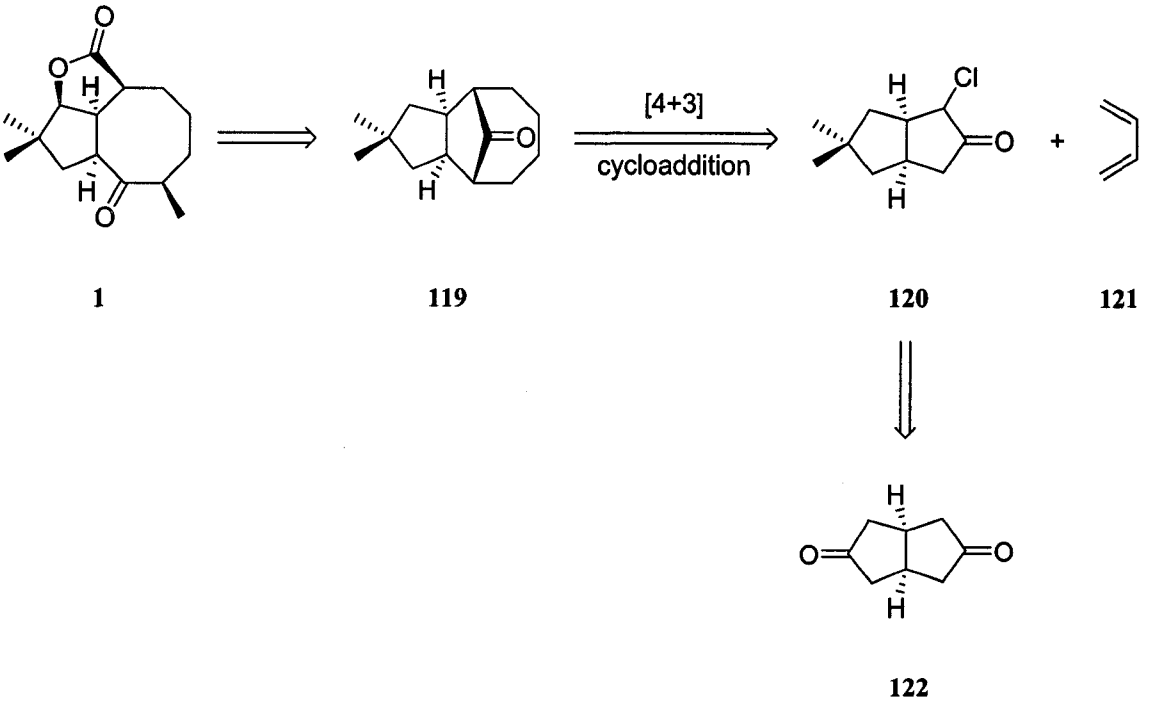
This mechanism illustrates the instability of the cyclopropane ring in the presence of the deprotected phenol. As a result, the interrupted Nazarov reaction using this precursor was not pursued further.

2.3 SUMMARY AND FUTURE DIRECTIONS

Asteriscanolide has received much attention since it was first isolated and its structure makes it both appealing and challenging to synthesize. The key step in our synthetic route to this natural product is a [3+2] Schmid cycloaddition of a cyclic 2-aminoallyl cation with a cyclic alkene to form the bicyclo[6.3.0]undecane ring skeleton containing an eight-membered ring.

Model studies were conducted using a 2-aminoallyl cation, similar to the one that would be used in the actual synthesis, to furnish the desired seven-membered ring. Despite these results and reported examples of the related [4+3] Schmid cycloaddition reaction, the [3+2] cycloaddition reaction of the 2-aminoallyl cation forming the eight-membered ring proved to be unsuccessful. There are many factors that may cause difficulty in this [3+2] cycloaddition reaction. One example is the strain energy of cyclooctanes compared to cycloheptanes. The results provide evidence that formation of the eight-membered ring is more difficult than that of the seven-membered ring and that addition of one methylene group can have a considerable effect. Also, as mentioned previously, the non-concerted mechanism of this reaction may cause formation of many undesired products. This results in a complicated reaction mixture wherein only a small amount of the desired product was formed. Another important factor that causes difficulty in this reaction is the instability of the enamine precursor used to generate the 2-aminoallyl cation. The enamine is easily hydrolyzed and once converted to the ketone, the 2-aminoallyl cation can not be generated to participate in the desired [3+2] Schmid cycloaddition reaction.

Due to these factors, future research would involve a different approach to the synthesis of asteriscanolide. The bicyclo[6.3.0]undecane ring skeleton may be formed from the more commonly demonstrated [4+3] cycloaddition of the stable ketone **120** with diene **121** (Scheme 2.31). Ketone **120** may be produced through several steps starting with commercially available diketone **122**.



1 **119** **120** **121**

122

Scheme 2.31 A New Approach to the Synthesis of Asteriscanolide

Similarly to the [3+2] Schmid cycloaddition reactions, it has been demonstrated that there are limitations to the interrupted Nazarov reaction and the types of substrates that will undergo this reaction. Even though there are reports of the traditional Nazarov reaction being trapped by many different functional groups, there are only limited examples utilizing an oxygen functional group. It was rationalized that the Lewis acid used in the traditional Nazarov reaction causes deactivation of the oxygen functional

group, making it less nucleophilic and therefore less likely to trap the Nazarov intermediate. However, the new approach to the Nazarov reaction uses complimentary conditions without the usual oxaphilic Lewis acids, and for that reason trapping with an oxygen functional group was investigated for this new Nazarov reaction. Unfortunately, attempts to trap the Nazarov intermediate with an oxygen functional group were proven to be more challenging than expected. It was found that the oxygen functional group was highly reactive and would, in many examples, carry out a nucleophile attack before the 4π electrocyclization occurred, causing ring opening of the unstable dichlorocyclopropane ring.

Regardless of the outcome, there is still much research to be invested into the interrupted Nazarov reaction. Despite the many examples of the traditional interrupted Nazarov reaction, utilizing many different functional groups, there has only been one example for the new Nazarov reaction. Further investigation into the trapping of the new approach to the Nazarov reaction should be conducted, using different nucleophiles such as alkenes, dienes, silanes, or halides.

Although numerous experiments have been conducted for both projects, there appears to be many challenges and limitations. Nevertheless, there are still many other routes and substrates that can be examined. Therefore both projects still need further research invested.

2.4 BIBLIOGRAPHY

[1] Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904-5906.

[2] Limanto, J.; Snapper, M. L. *J. Am. Chem. Soc.* **2000**, *122*, 8071-8072.

[3] Paquette, L. A.; Jinsung, T.; Arrington, M. P.; Sadoun, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2742-2748.

[4] Krafft, M. E.; Cheung, Y. Y.; Abboud, K. A. *J. Org. Chem.* **2001**, *66*, 7443-7338.

[5] Booker-Milburn, K. I.; Cowell, J. K. *Tetrahedron Lett.* **1996**, *37*, 2177-2180.

[6] San Feliciano, A; Barrero, A. F.; Medarde, M.; Miguel del Correl, J. M.; Aramburu, A.; Perales, A.; Fayos, J. *Tetrahedron Lett.* **1985**, *26*, 2369-2372.

[7] Gassman, P. G.; Burns, S. J.; Pfister, K. B. *J. Org. Chem.* **1993**, *58*, 1449 – 1457.

[8] Mizuno, H.; Domon, K.; Masuya, K.; Tanino, K.; Kuwajima, I. *J. Org. Chem.* **1999**, *64*, 2648-2656.

[9] Lee, J.; Oh, J.; Jin, S.; Choi, J.; Atwood, J.; Cha, J. K. *J. Org. Chem.* **1994**, *59*, 6955-6964.

[10] Wyman, D. P.; R. Kaufman, P. R. *J. Org. Chem.* **1964**, *29*, 1956 – 1960.

[11] Motoyoshiya, J.; Mizuno, K.; Tsuda, T.; Hayashi, S. *Synlett.* **1993**, 237-238.

[12] Fernandez Mateos, A.; Mateos Buron, L.; Martin de la Nava, E. M.; Rubio Gonzalez, R. *J. Org. Chem.* **2003**, *68*, 3585-3592.

[13] Harding, K. E.; Clement, K. S.; Tseng, C. Y. *J. Org. Chem.* **1990**, *55*, 4403-4410.

[14] Tius, M. A.; Hu, H.; Kawakami, J. K.; Busch-Petersen, J. *J. Org. Chem.* **1996**, *52*, 5971-5976.

[15] Bender, J. A.; Blize, A. E.; Browder, C. C.; Giese, S.; West, F. G. *J. Org. Chem.* **1998**, *63*, 2430-2431.

[16] Giese, S.; Kastrup, L.; Stiens, D.; West, F. G. *Angew. Chem. Int. Ed.* **2000**, *39*, 1970-1973.

[17] Mahmoud, B.; West, F. G. *Tetrahedron Lett.* **2007**, *48*, 5091-5904.

[18] Browder, C. C.; West, F. G. *Synlett.* **1999**, 1363-1366.

[19] Wang, Y.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 876-877.

[20] Yungai, A.; West, F. G. *Tetrahedron Lett.* **2004**, *45*, 5445-5448.

[21] Giese, S.; West, F. G. *Tetrahedron* **2000**, *56*, 10221-10228.

[22] Browder, C. C.; Marmsater, F. P.; West, F. G. *Org. Lett.* **2001**, *3*, 3033-3035.

[23] Grant, T. N.; West, F. G. *Org. Lett.* **2007**, *9*, 3789-3792.

[24] Rostami, A.; Wang, Y.; Arif, A. M.; McDonald. R.; West, F. G. *Org. Lett.* **2007**, *9*, 703-706.

[25] White, T. D.; West, F. G. *Tetrahedron Lett.* **2005**, *46*, 5629-5632.

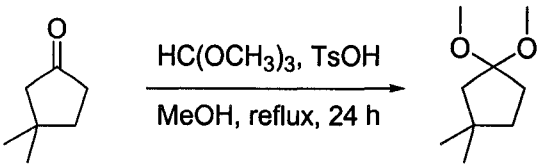
[26] Grant, T. N.; West, F. G. *J. Am. Chem. Soc.* **2006**, *128*, 9348-9349.

[27] Tatsuzaki, J.; Bastow, K. F.; Nakagawa-Goto, K.; Nakamura, S.; Itokawa, H.; Lee, K. H. *J. Nat. Prod.* **2006**, *69*, 1445-1449.

CHAPTER 3

EXPERIMENTAL

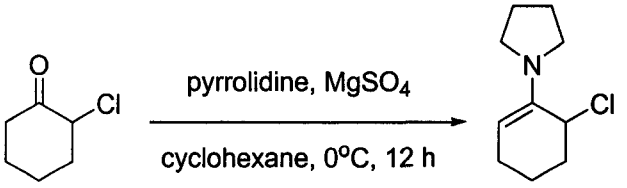
General Methods: Reactions were carried out in flame-dried glassware under a positive nitrogen atmosphere unless otherwise stated. Transfer of anhydrous solvents and reagents was accomplished with oven-dried syringes or cannulae. Solvents were distilled before use: methylene chloride from calcium hydride, tetrahydrofuran and diethyl ether from sodium/benzophenone ketyl. Thin layer chromatography was performed on glass plates precoated with 0.25 mm Kieselgel 60 F254 (Merck). Flash chromatography column were packed with 230-400 mesh silica gel (Silicycle). Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 300 MHz, 400 MHz or 500 MHz and coupling constants (*J*) are reported in Hertz (Hz). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 100 MHz or 125 MHz and are reported (ppm) relative to the center line of the triplet from chloroform-d (77.23 ppm). Infrared (IR) spectra were measured with a Mattson Galaxy Series FT-IR 3000 spectrophotometer. Mass spectra were determined on a PerSeptive Biosystems Mariner high-resolution electrospray positive ion mode spectrometer.



10 **11**

1,1-Dimethoxy-3,3-dimethylcyclopentane (11)

To a solution of 3,3-dimethylcyclopentanone (0.335 mL, 2.98 mmol) in MeOH (0.30 mL), trimethylorthoformate (0.49 mL, 4.5 mmol) was added, followed by TsOH (0.029 g, 0.15 mmol). The mixture was heated at reflux for 24 h and then distilled leaving TsOH in the remainder flask. The solvent was removed at reduced pressure. The remaining residue was found to contain impurities and was not pursued further. R_f 0.57 (hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.18 (s, 6H), 1.89 (t, J = 7.5 Hz, 2H), 1.66 (s, 2H), 1.50 (t, J = 7.5 Hz, 2H), 1.05 (s, 6H).

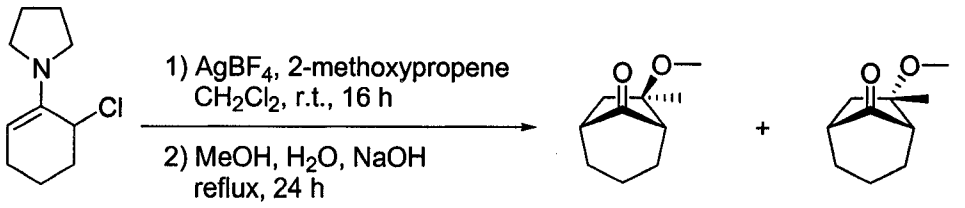


17 **18**

1-(6-Chloro-cyclohex-1-enyl)-pyrrolidine (18)

To a solution of 2-chlorocyclohexanone (0.530 g, 4.00 mmol) in cyclohexane (10.0 mL), $MgSO_4$ (3.94 g, 32.8 mmol) was added. The mixture was cooled to 0 °C and pyrrolidine (1.7 mL, 21 mmol) was added dropwise. After 12 h, the reaction mixture was filtered

through celite to remove $MgSO_4$ and the residue was rinsed with hexane (3 x 5 mL). The solvent was removed at reduced pressure and the resulting crude yellow oil was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (dd, J = 2.6, 2.6 Hz, 1H), 4.41 (dd, J = 5.2, 2.8 Hz, 1H), 2.97-3.23 (m, 4H), 2.13-2.29 (m, 2H), 2.00 (dddd, J = 13.7, 13.7, 3.3, 3.3 Hz, 2H), 1.84-1.91 (m, 4H), 1.61-1.66 (m, 2H).



18 **19a** **19b**

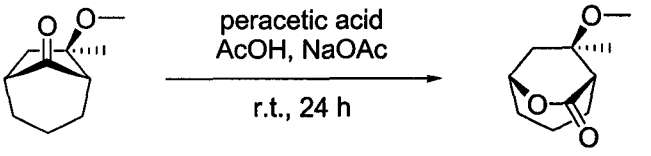
6-Methoxy-6-methyl-bicyclo[3.2.1]octan-8-one (19)

A solution of $AgBF_4$ (0.673 g, 3.46 mmol) in CH_2Cl_2 (13 mL) was prepared in the dark. The solution was cooled to -78 °C and 2-methoxypropene (2.7 mL, 28 mmol) was added dropwise. In a separate flask, a solution of enamine **18** (0.522 g, 2.81 mmol) in CH_2Cl_2 (3.0 mL) was prepared and transferred by cannula into the $AgBF_4$ solution. After stirring at -78 °C for 4 h, the reaction mixture was warmed to room temperature and stirred for an additional 16 h. The mixture was then filtered through celite and the residue was washed with CH_2Cl_2 (3 x 10 mL). The solvent was removed at reduced pressure and the residue was dissolved in a mixture of MeOH (5.6 mL) and H_2O (11.2 mL). NaOH (1.12 g, 28.1 mmol) was added to the solution and heated at reflux for 24 h. MeOH was removed at reduced pressure and the remaining solution was extracted with ether (3 x 10 mL). The

organic extracts were combined, washed with 1 N HCl (10 mL), followed by saturated NaCl solution (10 mL) and then dried with $MgSO_4$. $MgSO_4$ was removed by filtration. Solvent was removed at reduced pressure and the residue was purified by flash chromatography (silica gel, hexane/ether/CH_2Cl_2 12:2:1) to furnish ketones **19a** and **19b** (280 mg, 59%) as a yellow oil; 1:1 ratio of diastereomers.

Diastereomer 19a: R_f 0.76 (hexane/EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.30 (s, 3H), 2.39-2.43 (m, 1H), 2.19-2.20 (m, 1H), 2.17-2.22 (m, 1H), 2.10 (dddd, J = 17.2, 11.9, 11.9, 4.7 Hz, 1H), 2.01-2.03 (m, 2H), 1.99-2.01 (m, 1H), 1.94 (dd, J = 13.7, 7.4 Hz, 1H), 1.86 (m, 1H), 1.47-1.53 (m, 1H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.0, 77.0, 56.6, 51.0, 47.0, 39.0, 37.2, 32.7, 26.2, 17.8; HRMS (EI) [M^+] for $C_{10}H_{16}O_2$ calculated 168.1150, found: m/z 168.1146.

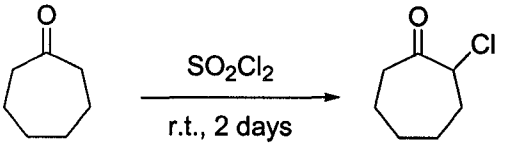
Diastereomer 19b: R_f 0.68 (hexane/EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.14 (s, 3H), 2.39-2.44 (m, 1H), 2.26-2.29 (m, 1H), 2.24 (dd, J = 7.3, 7.3 Hz, 1H), 1.92-2.05 (m, 4H), 1.74 (d, J = 14.1 Hz, 1H), 1.69 (dddd, J = 12.8, 12.8, 6.4, 6.4 Hz, 1H), 1.50-1.57 (m, 1H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.5, 79.1, 54.5, 49.3, 45.3, 37.9, 36.5, 31.9, 17.7, 17.0; HRMS (EI) [M^+] for $C_{10}H_{16}O_2$ calculated 168.1150, found: m/z 168.1148.



19a **27**

9-Methoxy-9-methyl-6-oxa-bicyclo[3.2.2]nonan-7-one (27)

To a solution of bicyclooctanone **19a** (0.119 g, 0.707 mmol) and AcOH (0.70 mL), peracetic acid (0.55 mL, 2.3 mmol) and NaOAc (0.071 g, 0.87 mmol) were added. After stirring at room temperature for 24 h, CH_2Cl_2 (2 mL) was added. The mixture was then washed with saturated Na_2CO_3 (2 x 2 mL), followed by saturated $NaHCO_3$ (2 mL). It was then washed with saturated NaCl (2 mL) and dried with $MgSO_4$. $MgSO_4$ was removed by filtration. Solvent was removed at reduced pressure and the residue was purified by gradient flash chromatography (silica gel, hexane/EtOAc 4:1 to 1.5:1) to obtain lactone **27** (52 mg, 40%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 (ddd, J = 7.5, 5.0, 2.6 Hz, 1H), 3.25 (s, 3H), 2.86 (dd, J = 5.6, 2.9 Hz, 1H), 2.20 (dd, J = 14.6, 7.5 Hz, 1H), 1.95–2.10 (m, 4H), 1.85 (ddt, J = 13.7, 5.0, 5.0 Hz, 1H), 1.60-1.73 (m, 2H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 75.1, 74.6, 49.9, 49.5, 38.1, 32.6, 27.7, 23.6, 19.8; HRMS (EI) [M^+] for $C_{10}H_{16}O_3$ calculated 184.1099, found: m/z 184.1096.

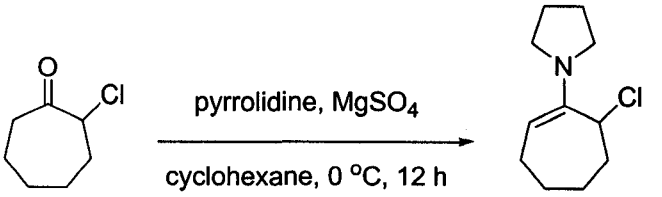


42 **43**

2-Chlorocycloheptanone (43)

SO_2Cl_2 (6.9 mL, 0.86 mol) was added dropwise over a period of 30 minutes to cycloheptanone (12 mL, 0.10 mol) and stirred at room temperature. After 2 days the mixture was purified by flash chromatogaphy (silica gel, hexane: EtOAc 9:1) to furnish

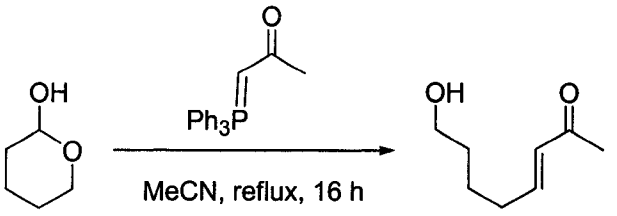
43 (6.32 g, 50%) as a colorless oil. R_f 0.52 (hexane/EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.43 (dd, J = 8.7, 4.2 Hz, 1H), 2.77 (ddd, J = 13.5, 8.2, 4.2 Hz, 1H), 2.53 (ddd, J = 14.6, 8.1, 3.9 Hz, 1H), 2.20-2.27 (m, 1H), 1.87-2.01 (m, 3H), 1.50-1.72 (m, 4H).



43 **5**

1-(7-Chloro-cyclohept-1-enyl)-pyrrolidine (5)

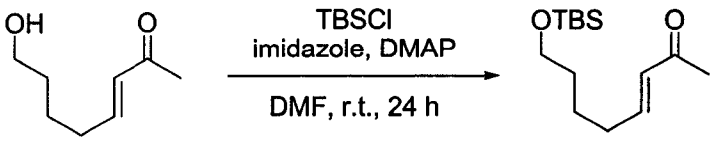
To a solution of 2-chlorocycloheptanone **43** (1.01 g, 6.86 mmol) and cyclohexane (19 mL), $MgSO_4$ (9.07 g, 75.3 mmol) was added. The mixture was cooled to 0 °C and pyrrolidine (6.2 mL, 75 mmol) was added dropwise. After 12 hours, the reaction mixture was filtered through celite to remove $MgSO_4$ and the residue was rinsed with hexane (3 x 5 mL). The solvent was removed at reduced pressure and the resulting crude yellow oil was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.89 (dt, J = 6.0, 1.6 Hz, 1H), 4.65 (ddd, J = 7.4, 5.5, 1.3 Hz, 1H), 2.96-3.05 (m, 4H), 2.90-2.94 (m, 2H), 2.36 (dddd, J = 16.5, 13.1, 5.5, 2.1 Hz, 2H), 2.07-2.18 (m, 2H), 1.85-1.88 (m, 4H), 1.71-1.74 (m, 2H).



56 59

8-Hydroxy-oct-3-en-2-one (59)

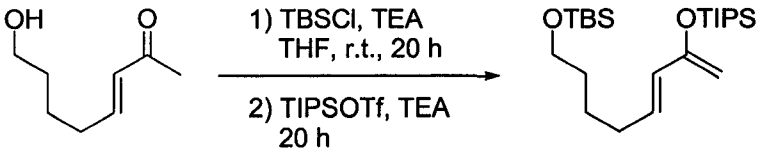
1-(Triphenylphosphoranylide)-2-propanone (1.71 g, 5.38 mmol) was added to a solution of tetrahydro-pyran-2-ol **56** (0.183 g, 1.79 mmol) in MeCN (30 mL) and the mixture was heated to reflux. After stirring overnight, the mixture was cooled to room temperature and the solvent was removed at reduced pressure. The residue was purified by flash chromatography (silica gel, hexane/EtOAc 1:1) to obtain enone **59** (158 mg, 62%) as a colorless oil. R_f 0.43 (EtOAc); IR (neat) 3420.6, 2936.3, 2864.1, 1672.6, 1626.0 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.80 (dt, J = 16.0, 6.9 Hz, 1H), 6.09 (d, J = 16.0 Hz, 1H), 3.68 (dt, J = 5.5, 5.5 Hz, 2H), 2.28 (dt, J = 6.9, 6.1 Hz, 2H), 2.25 (s, 3H), 1.54-1.65 (m, 4H), 1.27 (t, J = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, CDCl3) δ 198.9, 148.2, 131.4, 62.3, 32.1, 32.0, 26.8, 24.3; HRMS (EI) [M^+] for $C_8H_{14}O_2$ calculated 142.0994, found: m/z 142.0998.



59 60

8-(tert-Butyl-dimethyl-silanyloxy)-oct-3-en-2-one (60)

To a solution of enone **59** (0.030 g, 0.21 mmol) in DMF (0.53 mL), imidazole (0.023 g, 0.33 mmol) was added. DMAP (0.0023 g, 0.019 mmol) was added to the mixture followed by TBSCl (0.038 g, 0.25 mmol). After stirring for 24 h, the mixture was quenched with TEA (0.5 mL), saturated $NaHCO_3$ (0.5 mL), and hexane (1 mL). The aqueous layer was extracted with ether (3 x 2 mL) and the combined organic extracts were dried with $MgSO_4$. $MgSO_4$ was removed by filtration. The solvent was removed by reduced pressure and flash chromatography (silica gel, hexane/EtOAc/TEA 10:2:1) was used to purify the residue to furnish **60** (28 mg, 50%) as a pale yellow oil. R_f 0.45 (hexane/EtOAc 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 (dt, J = 15.9, 7.0 Hz, 1H), 6.07 (d, J = 15.9 Hz, 1H), 3.60-3.64 (m, 2H), 2.23-2.26 (m, 2H), 2.24 (s, 3H), 1.52-1.57 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6, 148.2, 131.4, 62.7, 32.3, 32.2, 26.8, 25.9, 24.4, 18.3, -5.3

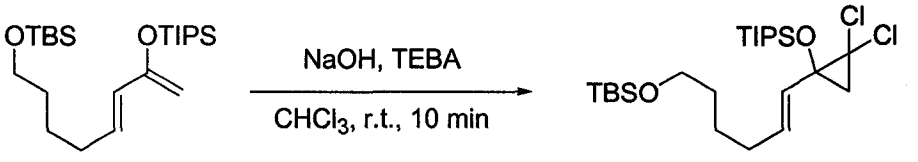


59 **61**

8-(tert-Butyl-dimethyl-silanyloxy)-2-triisopropylsilanyloxy-octa-1,3-diene (61)

To a solution of enone **59** (0.100 g, 0.704 mmol) in THF (1.8 mL), TEA (0.195 mL, 1.40 mmol) was added, followed by TBSCl (0.159 g, 1.05 mmol). After 20 h, additional TEA (0.195 mL, 1.40 mmol) was added, followed by TIPSOTf (0.375 mL, 1.40 mmol). After

20 h, the mixture was quenched with saturated $NaHCO_3$ (2 mL) and hexane (2 mL). The aqueous layer was extracted with ether (3 x 3 mL) and the combined organic extracts were dried with $MgSO_4$. $MgSO_4$ was removed by filtration. The solvent was removed at reduced pressure and the residue was purified by flash chromatography (neutral aluminum oxide, hexane/TEA 50:1) to obtain silyl enol ether **61** (270 mg, 91%) as a pale yellow oil. R_f 0.79 (hexane/EtOAc 10:1); IR (neat) 2945.3, 2893.9, 2867.0, 1589.5, 1463.5 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.07 (dt, J = 15.2, 7.1 Hz, 1H), 5.87 (d, J = 15.2 Hz, 1H), 4.21 (s, 1H), 4.17 (s, 1H), 3.62 (t, J = 6.4 Hz, 2H), 2.12 (dt, J = 7.1, 7.1 Hz, 2H), 1.51-1.57 (m, 2H), 1.42-1.48 (m, 2H), 1.24 (m, 3H), 1.11 (d, J = 7.0 Hz, 18H), 1.06 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 131.4, 128.0, 92.9, 63.1, 32.4, 31.8, 26.0, 25.5, 18.4, 18.1, 12.8, -5.3; HRMS (EI) [M^+] for $C_{23}H_{48}O_2Si_2$ calculated 412.3193, found: m/z 412.3195.

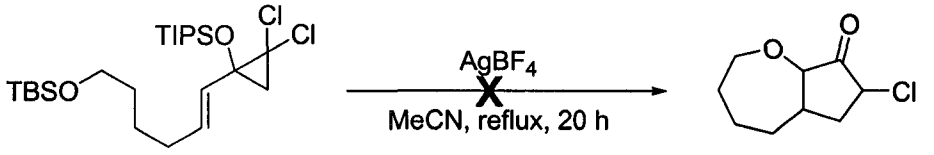


61 **62**

1-[6-(tert-Butyl-dimethyl-silanyloxy)-hex-1-enyl]-2,2-dichloro-1-triisopropylsilanyloxy-cyclopropane (62)

50% NaOH aqueous solution (3.6 g, 45 mmol) was added to a solution of silyl enol ether **61** (0.105 g, 0.249 mmol) and TEBA (0.017 g, 0.075 mmol) in $CHCl_3$ (2.1 mL). After 10 minutes, the mixture was slowly quenched with water (5 mL) and the aqueous layer was

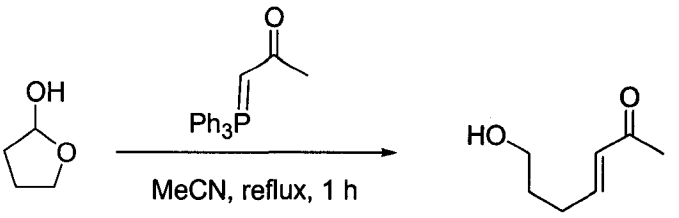
extracted with CH_2Cl_2 (3 x 3 mL). The combined organic extracts were dried with $MgSO_4$. $MgSO_4$ was removed by filtration and the solvent was removed at reduced preesure. The residue was purified by flash chromatography (neutral aluminum oxide, hexane/EtOAc 50:1) to obtain **62** (84 mg, 67%) as a yellow oil. R_f 0.61 (hexane/EtOAc 1:1); IR (neat) 2946.4, 2894.5, 2867.3, 1463.5 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.69-5.79 (m, 2H), 3.61 (t, J = 6.2 Hz, 2H), 2.10-2.16 (m, 2H), 1.83 (d, J = 8.3 Hz, 1H), 1.62 (d, J = 8.3 Hz, 1H), 1.50-1.57 (m, 2H), 1.40-1.49 (m, 2H), 1.07 (d, J = 7.5 Hz, 18H), 1.05-1.12 (m, 3H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.1, 127.4, 66.3, 64.1, 62.9, 32.3, 32.2, 31.8, 26.0, 25.1, 18.0, 17.7, 12.8, -5.3; HRMS (EI) $[M\text{-}HCl]^+$ for $C_{24}H_{47}O_2{}^{35}ClSi_2$ calculated 458.2803, found: m/z 258.2803.



62 **63**

7-Chloro-octahydro-cyclopenta[b]oxepin-8-one (63)

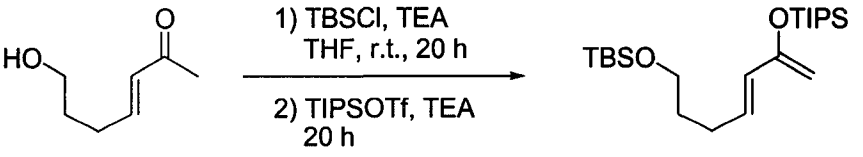
To a solution of dichlorocyclopropane **62** (0.050 g, 0.10 mmol) in MeCN (2.0 mL), $AgBF_4$ (0.028 g, 0.14 mmol) was added and heated to reflux. After 20 h, the mixture was cooled to room temperature, filtered through celite and rinsed with ether (5 x 3 mL). Reduced pressure was used to remove the solvent. The reaction did not yield the desired compound by ^1H NMR of the crude material and the reaction was abandoned.



70 71

7-Hydroxy-hept-3-en-2-one (71)

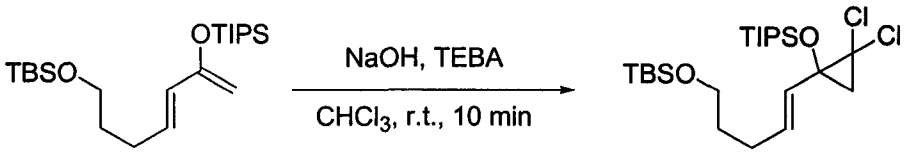
To a solution of tetrahydro-furan-2-ol **70** (0.250 g, 2.84 mmol) in MeCN (50 mL), 1-(triphenylphosphoranylide)-2-propanone (1.85 g, 5.81 mmol) was added and heated to reflux for 1 h. The mixture was cooled to room temperature and the solvent was removed at reduced pressure. The residue was purified by flash chromatography (silica gel, hexane/EtOAc 1:1) to obtain enone **71** (170 mg, 47%) as a colorless oil. R_f 0.37 (EtOAc); IR (neat) 3420.8, 2938.8, 2875.9, 1670.9, 1626.4 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.83 (dt, J = 15.9 Hz, 1H), 6.11 (d, J = 15.9 Hz, 1H), 3.69 (t, J = 6.3 Hz, 2H), 2.34 (dt, J = 7.5, 6.3 Hz, 2H), 2.25 (s, 3H), 1.75 (tt, J = 6.3, 6.3 Hz, 2H), 1.34 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 147.4, 131.6, 62.0, 31.0, 28.8, 26.9; HRMS (EI) [M^+] for $C_7H_{12}O_2$ calculated 128.0837, found: m/z 128.0840.



71 73

7-(tert-Butyl-dimethyl-silanyloxy)-2-triisopropylsilanyloxy-hepta-1,3-diene (73)

To a solution of enone **71** (0.274 g, 2.14 mmol) and THF (5.4 mL), TEA (0.60 mL, 4.3 mmol) was added, followed by TBSCl (0.485 g, 3.22 mmol). After 20 h, additional TEA (0.60 mL, 4.30 mmol) was added, followed by TIPSOTf (1.10 mL, 4.09 mmol). After 20 h, the mixture was quenched by the addition of saturated aqueous $NaHCO_3$ (6 mL) and hexane (6 mL) and the aqueous layer was extracted with ether (3 x 10 mL). The organic extracts were combined and dried with $MgSO_4$. $MgSO_4$ was removed by filtration. The solvent was removed at reduced pressure and the resulting crude yellow oil was used in the next step without further purification. R_f 0.68 (hexane/EtOAc 10:1); ^1H NMR (500 MHz, $CDCl_3$) δ 6.06 (dt, J = 15.2, 7.4 Hz, 1H), 5.88 (dt, J = 15.2, 1.2 Hz, 1H), 4.21 (s, 1H), 4.16 (s, 1H), 3.62 (t, J = 6.5 Hz, 2H), 2.16 (dt, J = 7.4, 7.4 Hz, 2H), 1.60-1.67 (m, 2H), 1.24 (m, 3H), 1.11 (d, J = 7.3 Hz, 18H), 1.06 (s, 9H), 0.05 (s, 6H).

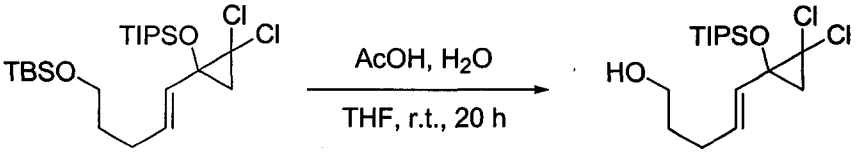


73 **68**

1-[5-(tert-Butyl-dimethyl-silanyloxy)-pent-1-enyl]-2,2-dichloro-1-triisopropylsilanyloxy-cyclopropane (68)

50% NaOH aqueous solution (30.8 g, 0.385 mol) was added to a solution of crude silyl enol ether **73** (2.14 mmol) and TEBA (0.146 g, 0.639 mmol) in $CHCl_3$ (18 mL). After 10 minutes, the mixture was slowly quenched with water (30 mL) and the aqueous layer was

extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried with $MgSO_4$. $MgSO_4$ was removed by filtration and the solvent was removed at reduced pressure. The residue was purified by flash chromatography (neutral aluminum oxide, hexane/EtOAc 50:1) to furnish **68** (854 mg, 81%, 2 steps) as a yellow oil. R_f 0.64 (hexane/EtOAc 1:1); IR (neat) 2947.2, 2893.7, 2867.6 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.70-5.80 (m, 2H), 3.62 (t, J = 6.5 Hz, 2H), 2.17 (dt, J = 7.6, 5.7 Hz, 2H), 1.83 (d, J = 8.4 Hz, 1H), 1.62 (d, J = 8.4 Hz, 1H), 1.58-1.55 (m, 2H), 1.07 (d, J = 7.3 Hz, 18H), 1.04-1.13 (m, 3H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.7, 127.6, 66.3, 64.1, 62.4, 32.2, 31.9, 28.4, 25.9, 18.0, 17.9, 12.8, -5.3; HRMS (ESI) $[M+Na]^+$ for $C_{23}H_{46}O_2Si_2Cl_2Na$ calculated 503.2306, found: m/z 503.2307.

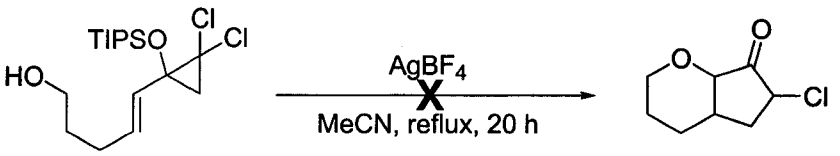


68 **74**

5-(2,2-Dichloro-1-triisopropylsilanyloxy-cyclopropyl)-pent-4-en-1-ol (74)

To a solution of dichlorocyclopropane **68** (0.300 g, 0.611 mmol) in THF (4.0 mL), AcOH (12 mL) and water (4.0 mL) were added and stirred at room temperature for 20 h. The mixture was quenched with saturated $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (5 x 5 mL). The combined organic extracts were washed with water (5 x 5 mL) and dried with $MgSO_4$. $MgSO_4$ was removed by filtration. The solvent was removed at reduced pressure and the residue was purified by

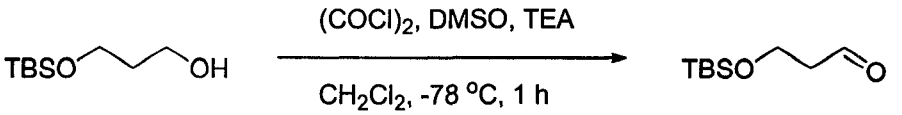
flash chromatography (neutral aluminum oxide, hexane/EtOAc 1:1) to furnish **74** (131 mg, 59%) as a pale yellow oil. IR (neat) 3340.3, 2945.3, 2892..8, 2868.0, 1464.2 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.70-5.83 (m, 2H), 3.66 (t, J = 6.5 Hz, 2H), 2.22 (dt, J = 6.1, 6.1 Hz, 2H), 1.84 (d, J = 8.5 Hz, 1H), 1.63-1.74 (m, 2H), 1.63 (d, J = 8.5 Hz, 1H), 1.09-1.17 (m, 3H), 1.07 (d, J = 4.7 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.3, 128.0, 65.5, .64.0, 62.3, 32.6, 31.7, 28.4, 18.0, 17.9, 12.8; HRMS (ESI) $[M+Na]^+$ for $C_{17}H_{32}O_2SiCl_2Na$ calculated 389.1441, found: m/z 189.1440.



74 **78**

6-Chloro-hexahydro-cyclopenta[b]pyran-7-one (78)

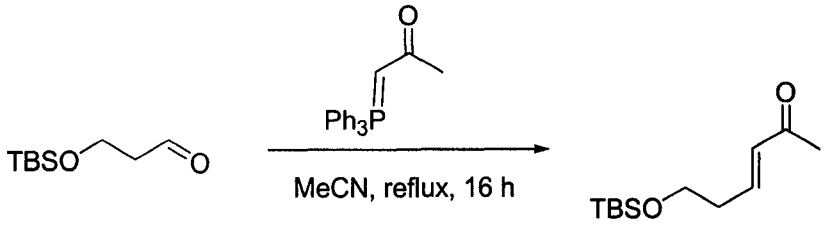
To a solution of dichlorocyclopropane **74** (9.6 mg, 0.020 mmol) in MeCN (0.4 mL), $AgBF_4$ (7.3 mg, 0.037 mmol) was added and heated to reflux. After 20 h, the mixture was cooled to room temperature, filtered through celite and rinsed with ether (5 x 1 mL). The solvent was removed at reduced pressure. The reaction did not yield the desired compound by ^1H NMR of the crude and the reaction was abandoned.



88 89

3-(tert-Butyl-dimethyl-silanyloxy)-propionaldehyde (89)

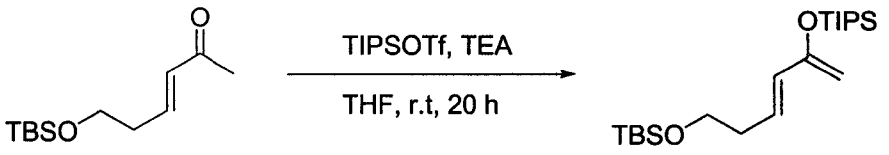
A solution of dimethyl sulfoxide (5.0 mL, 70 mmol) in CH_2Cl_2 (12 mL) was transferred dropwise by cannula to a solution of oxalyl chloride (3.4 mL, 40 mmol) in CH_2Cl_2 (60 mL) at -78 °C. After 30 minutes, a solution of 3-(tert-butyl-dimethyl-silanyloxy)-propan-1-ol **88** (6.44 g, 33.8 mmol) in CH_2Cl_2 (12.0 mL) was transferred dropwise by cannula to the mixture and stirred for 1 h. TEA (21 mL, 0.15 mol) was then added and after 1 h, the mixture was quenched with water (30 mL). The organic layer was washed with 1 N HCl (30 mL) followed by saturated $NaHCO_3$ (30 mL) and dried with $MgSO_4$. The solvent was removed at reduced pressure and resulting crude colorless oil was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (t, J = 2.1 Hz, 1H), 3.99 (t, J = 6.0 Hz, 2H), 2.60 (dt, J = 6.0, 2.1 Hz, 2H), 0.89 (s, 9H), 0.07 (s, 6H).



89 90

6-(tert-Butyl-dimethyl-silanyloxy)-hex-3-en-2-one (90)

To a solution of crude aldehyde **89** (33.8 mmol) in MeCN (560 mL), 1-(triphenylphosphoranylide)-2-propanone (21.54 g, 67.65 mmol) was added and heated to reflux. After stirring overnight, the mixture was cooled to room temperature and the solvent was removed by reduced pressure. The residue was purified by flash chromatography (silica gel, hexane/EtOAc 10:2) to obtain enone **90** (4.56 g, 59%, 2 steps) as a pale yellow oil. R_f 0.43 (hexane/EtOAc 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (dt, J = 16.0, 7.0 Hz, 1H), 6.12 (dt, J = 16.0, 1.5 Hz, 1H), 3.75 (t, J = 6.6 Hz, 2H), 2.44 (dtd, J = 7.0, 6.6, 1.5 Hz, 2H), 2.25 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.9, 144.9, 132.6, 61.4, 35.7, 26.4, 25.7, 18.1, -5.5; HRMS (EI) $[M\text{-}^t\text{Bu}]^+$ for $C_8H_{15}O_2Si$ calculated 171.0841, found: m/z 171.0842.

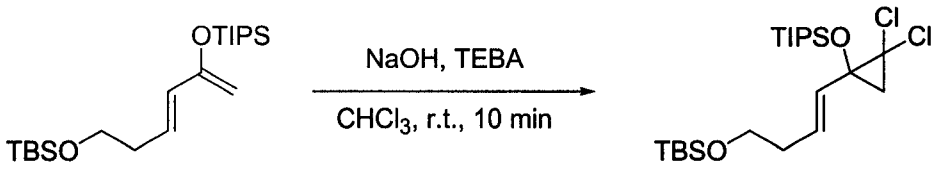


90 **91**

6-(tert-Butyl-dimethyl-silanyloxy)-2-triisopropylsilanyloxy-hexa-1,3-diene (91)

A solution of enone **90** (1.69 g, 7.41 mmol) and THF (18 mL) was prepared at room temperature. TEA (2.6 mL, 19 mmol) was added followed by TIPSOTf (4.0 mL, 15 mmol) and the mixture was stirred for 20 h. The reaction was quenched by saturated $NaHCO_3$ (20 mL) and the aqueous layer was extracted with ether (3 x 20 mL). The organic extracts were combined and dried with $MgSO_4$. $MgSO_4$ was removed by

filtration. The solvent was removed at reduced pressure and purification of the residue was accomplished by flash chromatography (neutral aluminum oxide, hexane/TEA 50:1). Silyl enol ether **91** (2.85 g, quant.) was obtained as a pale yellow oil. R_f 0.71 (hexane/EtOAc 10:1); IR (neat) 2946.4, 2894.2, 2867.4, 1589.1, 1463.7 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.08 (dt, J = 15.2, 6.7 Hz, 1H), 5.91 (d, J = 15.2 Hz, 1H), 4.22 (s, 1H), 4.17 (s, 1H), 3.67 (t, J = 6.7 Hz, 2H), 2.33 (dt, J = 6.7, 6.7 Hz, 2H), 1.24 (m, 3H), 1.11 (d, J = 7.1 Hz, 18H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 129.7, 127.8, 93.1, 62.8, 35.8, 25.9, 18.3, 18.1, 12.8, -5.3; HRMS (ESI) $[M+H]^+$ for $C_{21}H_{45}O_2Si_2$ calculated 385.2953, found: m/z 385.2953.

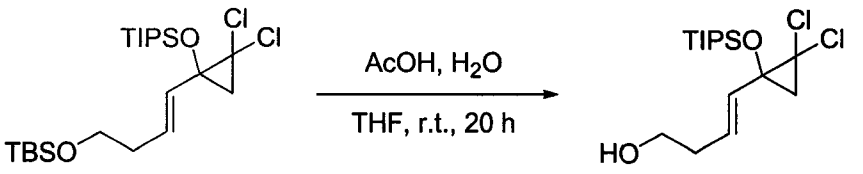


91 **92**

1-[4-(tert-Butyl-dimethyl-silanyloxy)-but-1-enyl]-2,2-dichloro-1-triisopropylsilanyloxy-cyclopropane (92)

50% NaOH aqueous solution (106 g, 1.33 mol) was added to a solution of silyl enol ether **91** (2.85 g, 7.41 mmol) and TEBA (0.509 g, 2.24 mmol) in $CHCl_3$ (62 mL). After 10 minutes, the mixture was slowly quenched by the addition of water (100 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried with $MgSO_4$. $MgSO_4$ was removed by filtration and the solvent was removed at reduced pressure. The residue was purified by flash chromatography (silica gel,

hexane/EtOAc 50:1) to furnish dichlorocyclopropane **92** (3.12 g, 90%) as a yellow oil. R_f 0.86 (hexane/EtOAc 1:1); IR (neat) 2927.3, 2857.1, 1463.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.71-5.86 (m, 2H), 3.66 (t, J = 6.8 Hz, 2H), 2.34 (dt, J = 6.8, 5.6 Hz, 2H), 1.83 (d, J = 8.4 Hz, 1H), 1.63 (d, J = 8.4 Hz, 1H), 1.07 (d, J = 7.2 Hz, 18H), 1.02-1.12 (m, 3H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.6, 129.0, 64.0, 62.4, 35.7, 32.3, 30.3, 25.9, 18.1, 18.0, 12.8, -5.3; HRMS (ESI) $[M+Na]^+$ for $C_{22}H_{44}O_2Si_2Cl_2Na$ calculated 489.2149, found: m/z 489.2148.

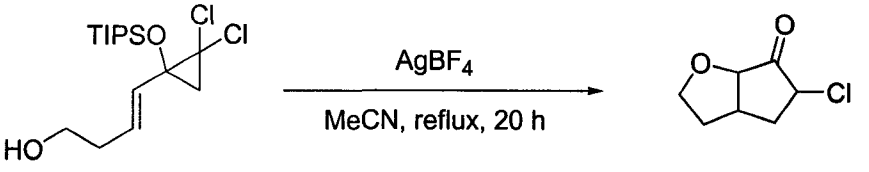


92 **80**

4-(2,2-Dichloro-1-triisopropylsilanyloxy-cyclopropyl)-but-3-en-1-ol (80)

To a solution of dichlorocyclopropane **92** (1.99 g, 4.26 mmol) in THF (29 mL), AcOH (86 mL) and water (29 mL) were added and stirred at room temperature for 20 h. The mixture was quenched with saturated $NaHCO_3$ (30 mL) and CH_2Cl_2 (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (5 x 20 mL). The combined organic extracts were washed with water (5 x 20 mL) and dried with $MgSO_4$. $MgSO_4$ was removed by filtration. The solvent was removed at reduced pressure and the residue was purified by flash chromatography (silica gel, hexane/EtOAc 4:1) to obtain dichlorocyclopropane 77 (0.900 g, 60%) as a pale yellow oil. R_f 0.73 (EtOAc); IR (neat) 3379.2, 2945.5, 2892.8, 2868.0, 1464.3 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.88 (dt, J =

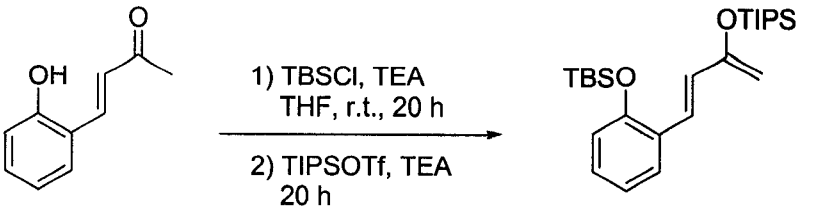
15.5, 7.1 Hz, 1H), 5.73 (dd, J = 15.5, 1.1 Hz, 1H), 3.71 (dt, J = 10.7, 6.7 Hz, 1H), 3.65 (dt, J = 10.7, 6.7 Hz, 1H), 2.39 (dtd, J = 7.1, 6.7, 1.1 Hz, 2H), 1.87 (d, J = 8.5 Hz, 1H), 1.67 (d, J = 8.5 Hz, 1H), 1.47 (br s, 1H), 1.09-1.17 (m 3H), 1.08 (d, J = 4.8 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.7, 130.6, 65.4, 63.9, 61.5, 35.4, 32.2, 18.0, 17.9, 12.8; HRMS (ESI) $[M+Na]^+$ for $C_{16}H_{30}O_2SiCl_2Na$ calculated 375.1284, found: m/z 375.1287; Anal. Calcd. for $C_{16}H_{30}O_2Cl_2Si$: C, 54.38; H, 8.56. Found: C, 54.49; H, 8.54.



80 **93**

5-Chloro-hexahydro-cyclopenta[b]furan-6-one (93)

To a solution of dichlorocyclopropane **80** (0.100 g, 0.282 mmol) in MeCN (5.8 mL), $AgBF_4$ (0.082 g, 0.42 mmol) was added and heated to reflux. After 20 h, the mixture was cooled to room temperature, filtered through celite and rinsed with ether (5 x 3 mL). The solvent was removed by reduced pressure and the residue was purified by flash chromatography (silica gel, hexane/EtOAc, 2:1) to obtain **93** as a yellow oil containing an impure mixture of diastereomers. R_f 0.82 (hexane/EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40 (d, J = 7.5 Hz, 1H), 4.29 (dd, J = 6.2, 6.2 Hz, 1H), 3.98 (ddd, J = 12.2, 8.3, 4.5 Hz, 1H), 3.79 (ddd, J = 8.3, 8.3, 4.5 Hz, 1H), 3.20 (m, 1H), 2.36 (ddd, J = 14.2, 8.4, 6.2 Hz, 1H), 2.24 (dddd, J = 12.2, 8.3, 8.3, 8.3 Hz, 1H), 2.16 (m, 1H), 1.80 (dddd, J = 14.3, 8.3, 4.5, 4.5 Hz, 1H).

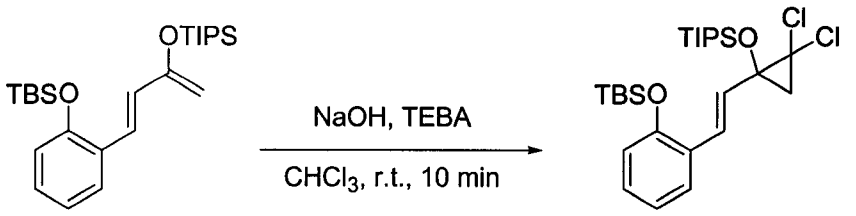


98 **99**

1-(tert-Butyl-dimethyl-silanyloxy)-2-(3-triisopropylsilanyloxy-buta-1,3-dienyl)-benzene (99)

4-(2-Hydroxy-phenyl)-but-3-en-2-one **98** was prepared from salicylaldehyde following a procedure reported by Lee and coworkers.[1] To a solution of 4-(2-hydroxy-phenyl)-but-3-en-2-one **98** (0.100 g, 0.617 mmol) in THF (1.5 mL), TEA (0.175 mL, 1.26 mmol) was added, followed by TBSCl (0.102 g, 0.678 mmol). After 20 h, additional TEA (0.175 mL, 1.26 mmol) was added, followed by TIPSOTf (0.330 mL, 1.23 mmol) and stirred an additional 20 h. The mixture was quenched with saturated $NaHCO_3$ (2 mL) and hexane (2 mL). The aqueous layer was extracted with ether (3 x 3 mL) and the combined organic extracts were dried with $MgSO_4$. $MgSO_4$ was removed by filtration. The solvent was removed at reduced pressure and the residue was purified by flash chromatography (neutral aluminum oxide, hexane/TEA 50:1) to furnish silyl enol ether **99** (0.240 g, 90%) as a pale yellow oil. R_f 0.89 (hexane/EtOAc 1:1); IR (neat) 2946.6, 2893.0, 2866.7, 1597.3, 1585.0, 1570.4, 1484.5, 1452.6 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, J = 7.8, 1.7 Hz, 1H), 7.21 (d, J = 15.8 Hz, 1H), 7.12 (ddd, J = 7.8, 7.8, 1.7 Hz, 1H), δ 6.93 (dd, J = 7.8, 7.8 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 6.57 (d, J = 15.8 Hz, 1H), 4.39 (s, 2H), 1.27-1.38 (m, 3H), 1.16 (d, J = 7.2 Hz, 18H), 1.02 (s, 9H), 0.27 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 153.4, 128.6, 128.2, 127.4, 127.2, 124.6, 121.3, 119.6, 94.9, 25.9,

18.4, 18.2, 13.0, -4.0; HRMS (ESI) $[M+H]^+$ for $C_{25}H_{45}O_2Si_2$ calculated 433.2953, found: m/z 433.2955.

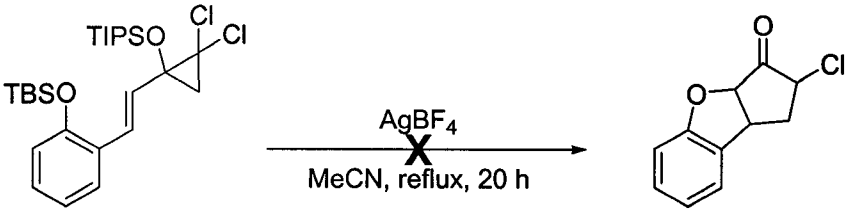


99 **100**

1-(tert-Butyl-dimethyl-silanyloxy)-2-[2-(2,2-dichloro-1-triisopropylsilanyloxy-cyclopropyl)-vinyl]-benzene (100)

50% NaOH aqueous solution (8.8 g, 0.11 mol) was added to a solution of silyl enol ether **99** (0.266 g, 0.615 mmol) and TEBA (0.042 g, 0.19 mmol) in $CHCl_3$ (5.1 mL). After 10 minutes, the mixture was slowly quenched with water (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic extracts were dried with $MgSO_4$. $MgSO_4$ was removed by filtration and the solvent was removed at reduced pressure. The residue was purified by flash chromatography (silica gel, hexane) to furnish dichlorocyclopropane **100** (0.226 g, 71%) was a yellow oil. R_f 0.70 (hexane/EtOAc 10:1); IR (neat) 2929.7, 2865.8, 1599.0, 1484.4, 1471.7, 1454.7, 1409.2 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (dd, J = 7.5, 1.7 Hz, 1H), 7.17 (ddd, J = 8.7, 7.5, 1.7 Hz, 1H), 6.96 (ddd, J = 7.5, 7.5. 0.8 Hz, 1H), 6.94 (d, J = 16.4 Hz, 1H), 6.82 (dd, J = 8.7, 1.0 Hz, 1H), 6.44 (dd, J = 16.4, 1.0 Hz, 1H), 2.01 (d, J = 8.4 Hz, 1H), 1.74 (dd, J = 8.4, 1.1 Hz, 1H), 1.05-1.15 (m, 3H), 1.09 (d, J = 12.1 Hz, 18H), 1.02 (s, 9H), 0.23 (s,

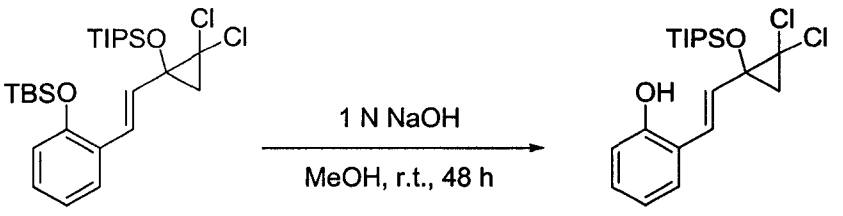
3H), 0.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 129.1, 128.3, 127.2, 126.2, 125.8, 121.5, 119.5, 65.7, 64.7, 32.2, 25.8, 18.1, 17.7, 12.8, -4.1; Anal. Calcd. for $C_{26}H_{44}O_2Cl_2Si_2$: C, 60.55; H, 8.60. Found: C, 60.26; H, 8.61.



100 **101**

2-Chloro-2,3,3a,8a-tetrahydro-8-oxa-cyclopenta[a]inden-1-one (101)

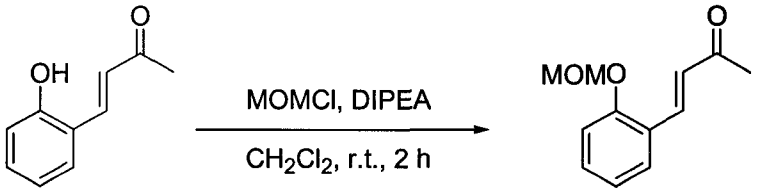
To a solution of dichlorocyclopropane **100** (0.021 g, 0.040 mmol) in MeCN (0.78 mL), $AgBF_4$ (0.011 g, 0.055 mmol) was added and heated to reflux. After 20 h, the mixture was cooled to room temperature, filtered through celite and rinsed with ether (5 x 2 mL). The solvent was removed at reduced pressure. ^1H NMR spectrum of the crude material indicated that the reaction did not yield the desired compound and the reaction was abandoned.



100 **104**

2-[2-(2,2-Dichloro-1-triisopropylsilanyloxy-cyclopropyl)-vinyl]-phenol (104)

1 N NaOH (1.0 mL) was added to a solution of dichlorocyclopropane **100** (0.049 g, 0.10 mmol) and MeOH (1.0 mL). After 2 days, the mixture was quenched with 1 N HCl (2.0 mL) and majority of solvent was removed under reduced pressure. CH_2Cl_2 (2.0 mL) was added to the mixture and the aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were dried with $MgSO_4$ and the solvent was removed at reduced pressure. The residue contained mainly starting material by ^1H NMR analysis and the reaction was not pursued further.

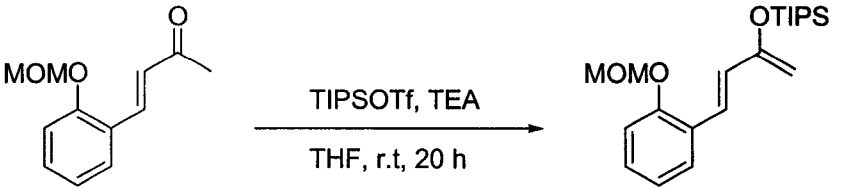


98 **108**

4-(2-Methoxymethoxy-phenyl)-but-3-en-2-one (108)

To a solution of 4-(2-hydroxy-phenyl)-but-3-en-2-one **98** (0.500 g, 3.08 mmol) in CH_2Cl_2 (30 mL), DIPEA (1.1 mL, 6.3 mmol) was added followed by MOMCl (0.350 mL, 4.61 mmol). After 2 h, the mixture was quenched with saturated $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The organic extracts were combined and dried with $MgSO_4$. $MgSO_4$ was removed by filtration. The solvent was removed at reduced pressure. Flash chromatography (silica gel, hexane/EtOAc 1:1) was used for purification of the residue and enone **108** (0.556 g, 88%) was obtained as a pale yellow

oil. R_f 0.38 (hexane/EtOAc 2:1); IR (neat) 2956.7, 2827.8, 1689.7, 1668.3, 1599.1, 1574.7, 1485.6, 1458.5 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 16.5 Hz, 1H), 7.57 (dd, J = 7.8, 1.7 Hz, 1H), 7.35 (ddd, J = 7.8, 7.8, 1.7 Hz, 1H), 7.17 (d, J = 7.8 Hz, 1H), 7.03 (dd, J = 7.8, 7.8 Hz, 1H), 6.76 (d, J = 16.5 Hz, 1H), 5.28 (s, 2H), 3.52 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 156.1, 138.4, 131.8, 128.0, 127.8, 124.1, 122.0, 114.9, 94.7, 56.3, 27.4; HRMS (EI) [M^+] for $C_{12}H_{14}O_3$ calculated 206.0943, found: m/z 206.0941; Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.82; H, 6.81.

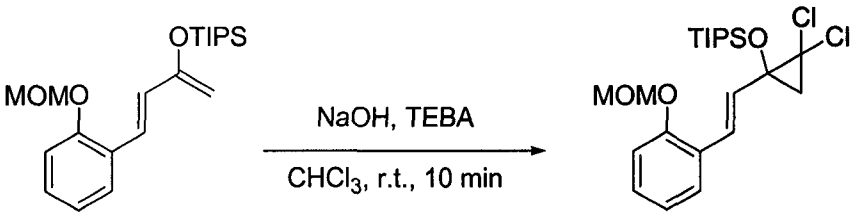


108 **109**

Triisopropyl-[3-(2-methoxymethoxy-phenyl)-1-methylene-allyloxy]-silane (109)

A solution of enone **108** (0.050 g, 0.20 mmol) in THF (0.5 mL) was prepared at room temperature. TEA (0.069 mL, 0.50 mmol) was added followed by TIPSOTf (0.110 mL, 0.409 mmol) and the mixture was stirred for 20 h. The reaction was quenched by saturated $NaHCO_3$ (1 mL) and the aqueous layer was extracted with ether (3 x 1 mL). The organic extracts were combined and dried with $MgSO_4$. $MgSO_4$ was removed by filtration. The solvent was removed at reduced pressure and purification of the residue was accomplished by flash chromatography (neutral aluminum oxide, hexane/TEA 50:1).

Silyl enol ether **109** (0.060 g, 84%) was obtained as a pale yellow oil. R_f 0.62 (hexane/EtOAc 2:1); IR (neat) 2945.2, 2893.3, 2867.1, 1631.9, 1599.2, 1587.5, 1575.2, 1485.2, 1457.1, 1402.5 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J = 7.8, 1.6 Hz, 1H), 7.42 (d, J = 15.9 hz, 1H), 7.21 (ddd, J = 7.8, 7.8, 1.6 Hz, 1H), 7.10 (dd, J = 7.8, 1.0 Hz, 1H), 7.00 (dd, J = 7.8, 7.8 Hz, 1H), 6.65 (d, J = 15.9 Hz, 1H), 5.23 (s, 2H), 4.45 (s, 1H), 4.44 (s, 1H), 3.50 (s, 3H), 1.28-1.38 (m, 3H), 1.19 (d, J = 7.0 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 154.6, 128.6, 126.8, 126.7, 126.4, 123.9, 121.8, 114.6, 95.5, 94.5, 56.0, 18.1, 12.8; HRMS (EI) [M^+] for $C_{21}H_{34}O_3Si$ calculated 362.2277, found: m/z 362.2284.

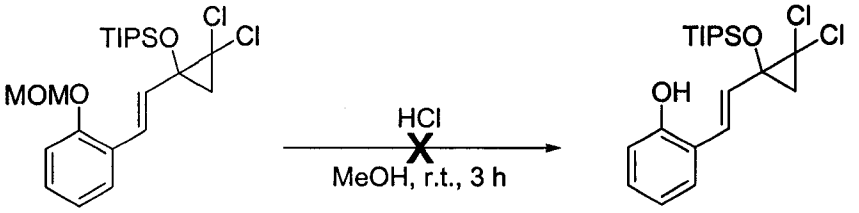


109 **110**

2,2-Dichloro-1-[2-(2-methoxymethoxy-phenyl)-vinyl]-cyclopropoxy-triisopropyl-silane (110)

50% NaOH aqueous solution (22.8 g, 0.285 mol) was added to a solution of silyl enol ether **109** (0.573 g, 1.58 mmol) and TEBA (0.108 g, 0.475 mmol) in $CHCl_3$ (13.2 mL). After 10 minutes, the mixture was slowly quenched with water (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried with $MgSO_4$. $MgSO_4$ was removed by filtration and the solvent was removed by reduced

pressure. The residue was purified by flash chromatography (silica gel, hexane/EtOAc 30:1) to furnish dichlorocyclopropane **110** (0.705, quant.) as a pale yellow oil. R_f 0.79 (hexane/EtOAc 2:1); IR (neat) 2946.7, 2894.0, 2868.0, 1599.3, 1487.1, 1458.7, 1405.7 cm^{-1}; ^1H NMR (500 MHz, CDCl3) δ 7.45 (dd, J = 7.7, 1.7 Hz, 1H), 7.23 (ddd, J = 8.7, 7.7, 1.7 Hz, 1H), 7.12 (dd, J = 7.7, 1.1 Hz, 1H), 7.02 (d, J = 16.1 Hz, 1H), 7.00 (ddd, J = 7.7, 7.7, 1.1 Hz, 1H), 6.43 (dd, J = 16.1, 0.7 Hz, 1H), 5.22 (d, J = 6.8 Hz, 1H), 5.20 (d, J = 6.8 Hz, 1H), 3.48 (s, 3H), 2.03 (d, J = 8.5 Hz, 1H), 1.80 (d, J = 8.5 Hz, 1H), 1.13-1.20 (m, 3H), 1.11 (d, J = 10.9 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 129.1, 128.1, 127.7, 127.0, 125.8, 122.0, 114.6, 94.5, 65.8, 64.5, 56.1, 33.3, 18.1, 12.8; HRMS (EI) $[M\text{-}HCl]^+$ for $C_{22}H_{33}O_3{}^{35}ClSi$ calculated 408.1888, found m/z 408.1886.



110 **111**

2-[2-(2,2-Dichloro-1-triisopropylsilanyloxy-cyclopropyl)-vinyl]-phenol (111)

Concentrated HCl (0.22 mL) was added to a solution of dichlorocyclopropane **110** (0.021 g, 0.046 mmol) and MeOH (1.1 mL). After 3 h, CH_2Cl_2 (3 mL) was added to the mixture and the aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were dried with $MgSO_4$. $MgSO_4$ was removed by filtration and the solvent was removed at reduced pressure. The residue was purified by flash chromatography (silica

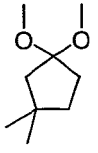
gel, hexane/EtOAc 5:1). The reaction did not yield the desired compound and the reaction was abandoned.

BIBLIOGRAPHY

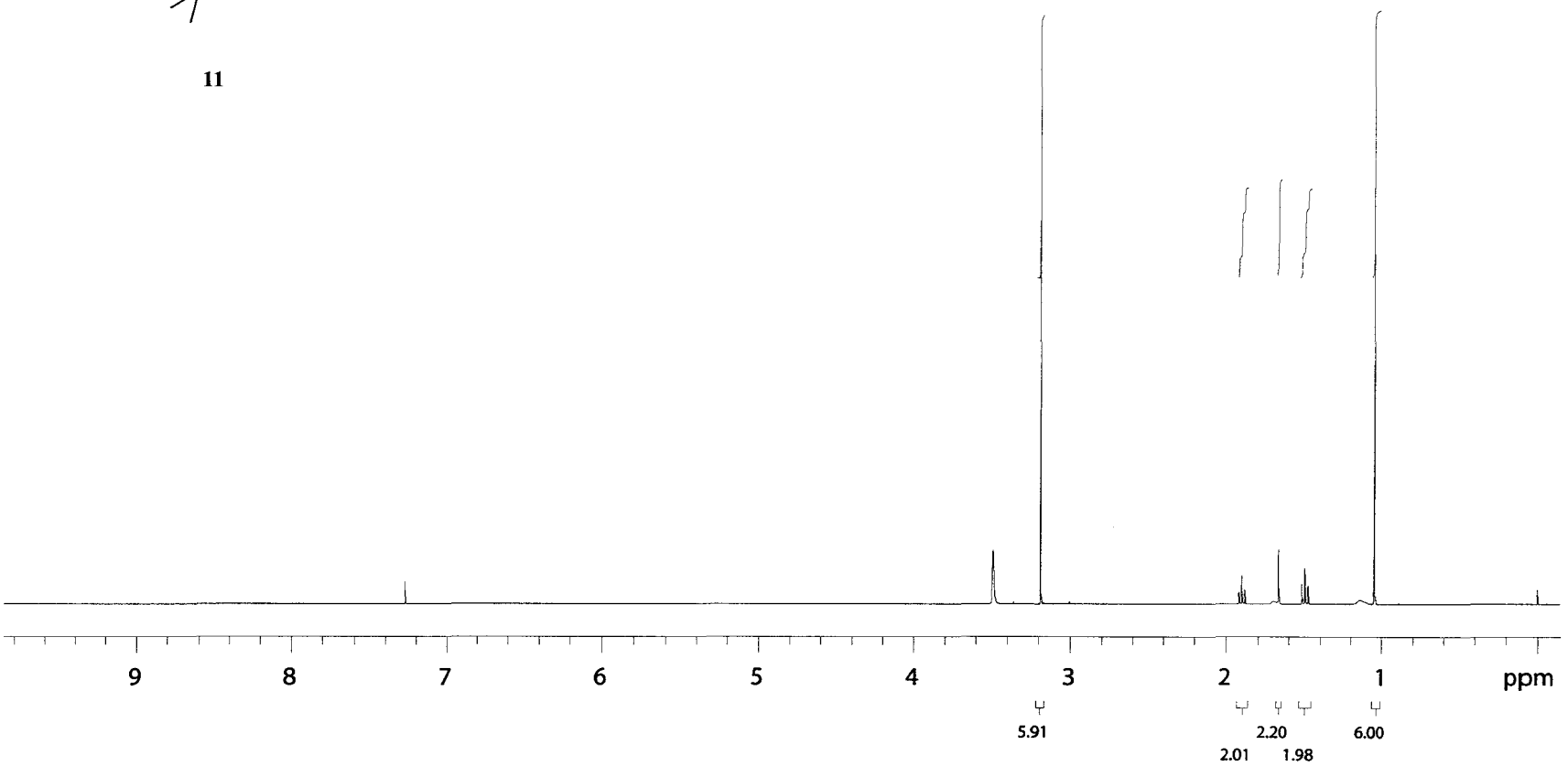
[1] Tatsuzaki, J.; Bastow, K. F.; Nakagawa-Goto, K.; Nakamura, S.; Itokawa, H.; Lee, K. H. *J. Nat. Prod.* **2006**, *69*, 1445-1449.

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe
1,1-dimethoxy-3,3-dimethylcyclopentane

Pulse Sequence: s2pul

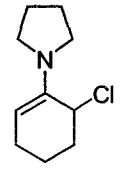


11

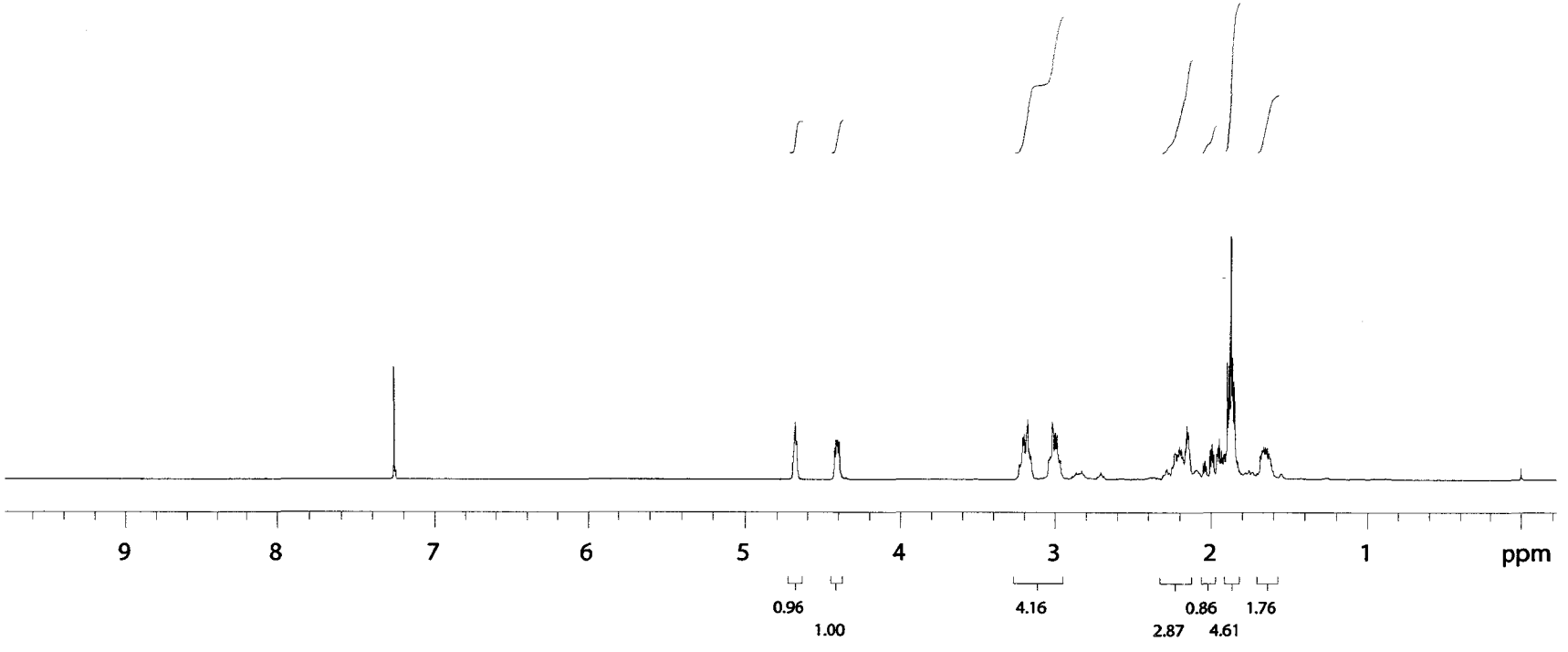


300 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.24 ppm), temp 27.5 C -> actual temp = 27.0 C, id probe
1-(6-chloro-cyclohex-1-enyl)-pyrrolidine

Pulse Sequence: s2pul

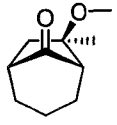


18

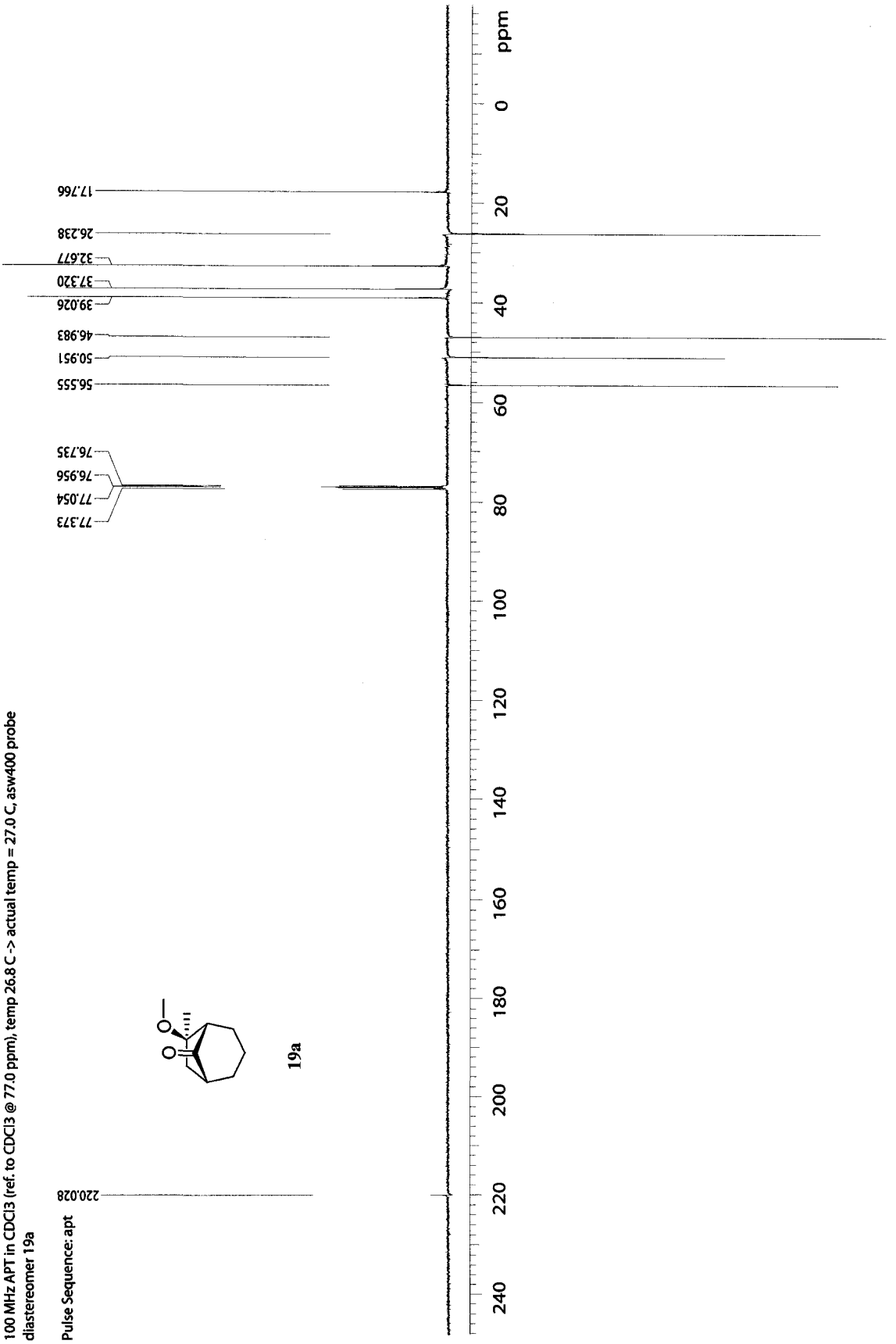


400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe
diastereomer 19a

Pulse Sequence: s2pul

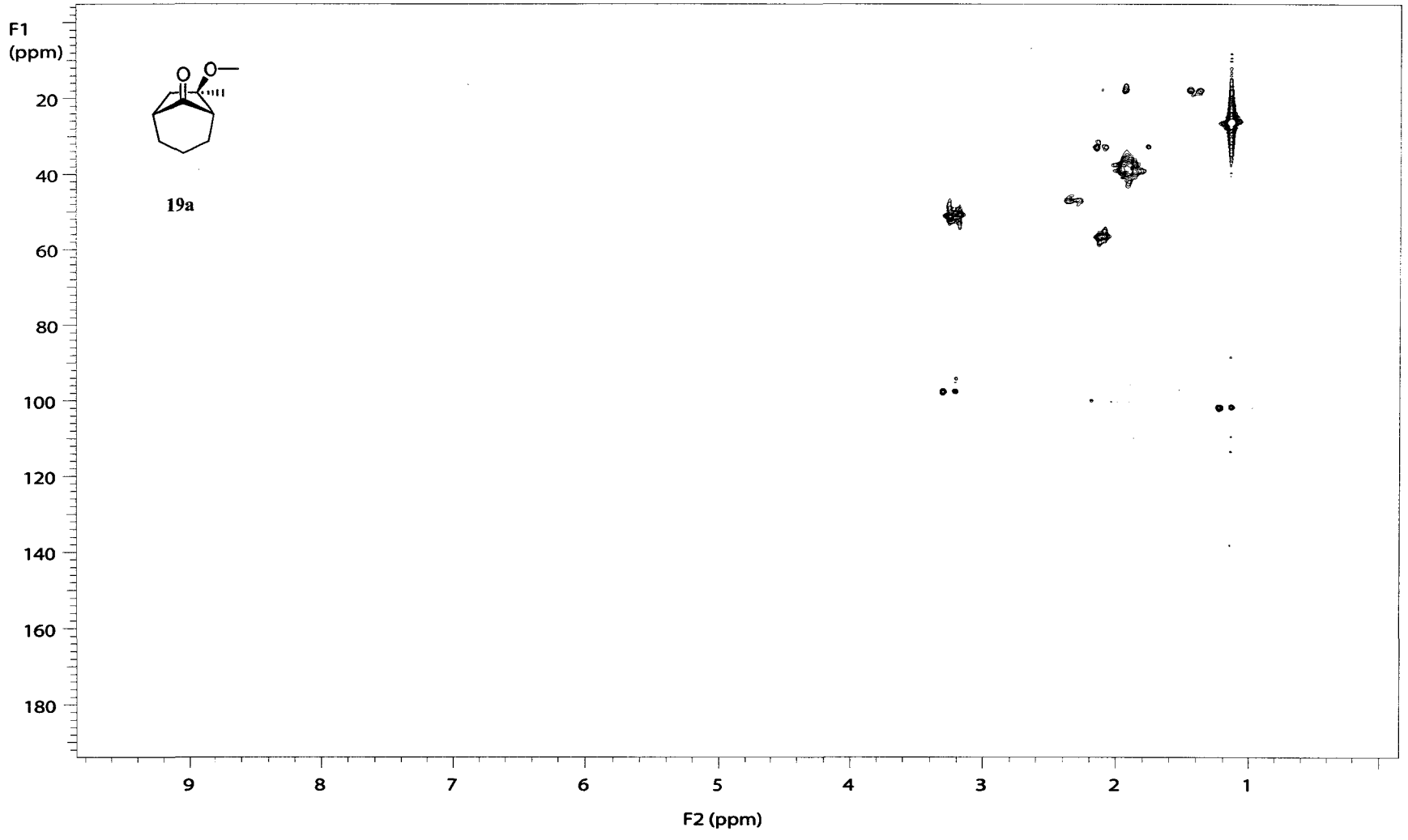


19a


100 MHz APT in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe
diastereomer 19a
Pulse Sequence: apt
19a
220.028
77.373
77.054
76.956
76.735
56.555
50.951
46.983
39.026
37.320
32.677
26.238
17.766
ppm
0
20
40
60
80
100
120
140
160
180
200
220
240

400 MHz ghmqc in CDCl3 (ref. to CDCl3 @ 7.26/77.0 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe
diastereomer 19a

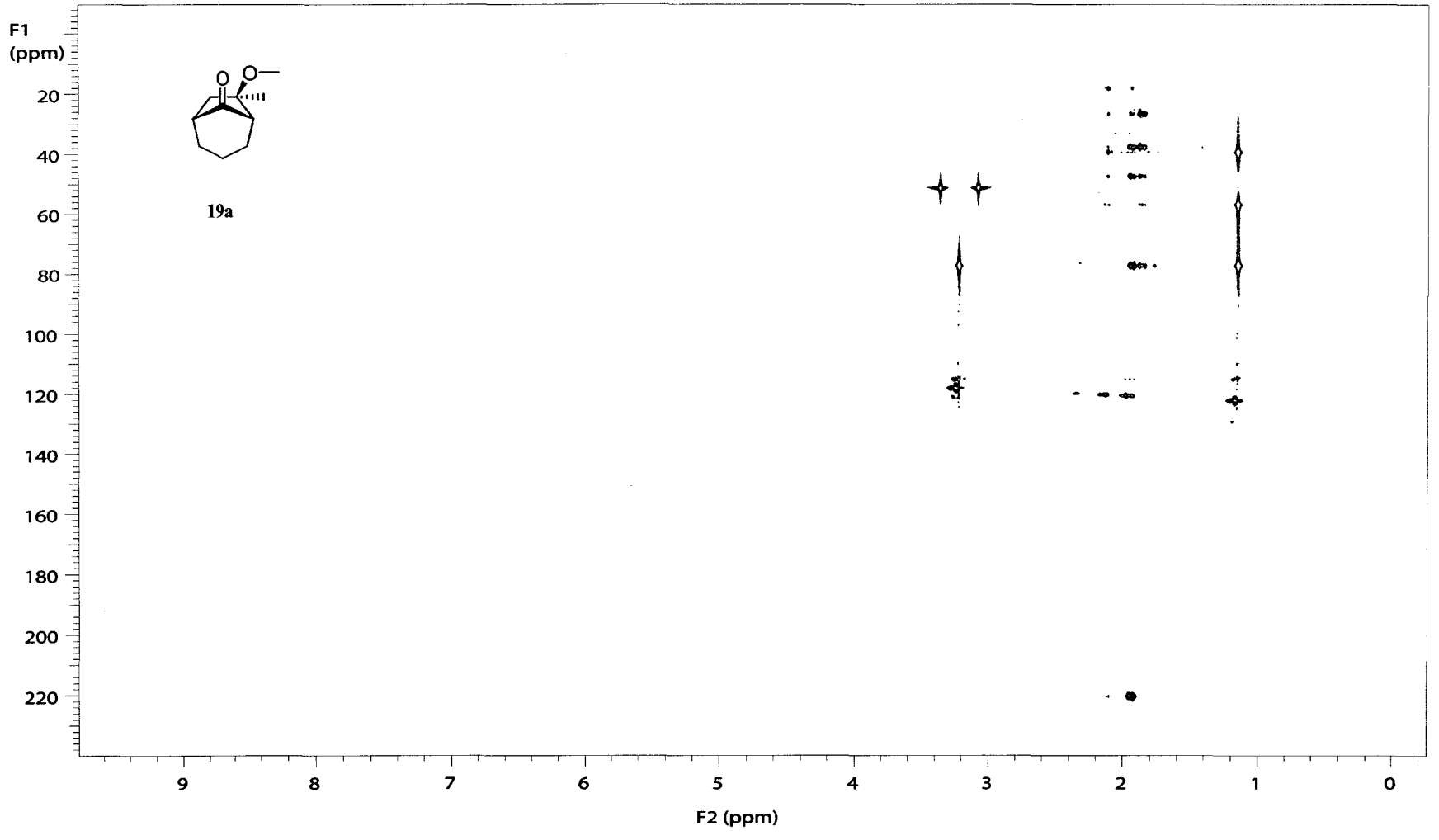
Pulse Sequence: ghmqc



19a

500 MHz GHMBC in CDCl3 (ref. to CDCl3 @ 7.26/77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
diastereomer 19a

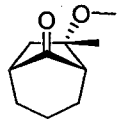
Pulse Sequence: ghmqc



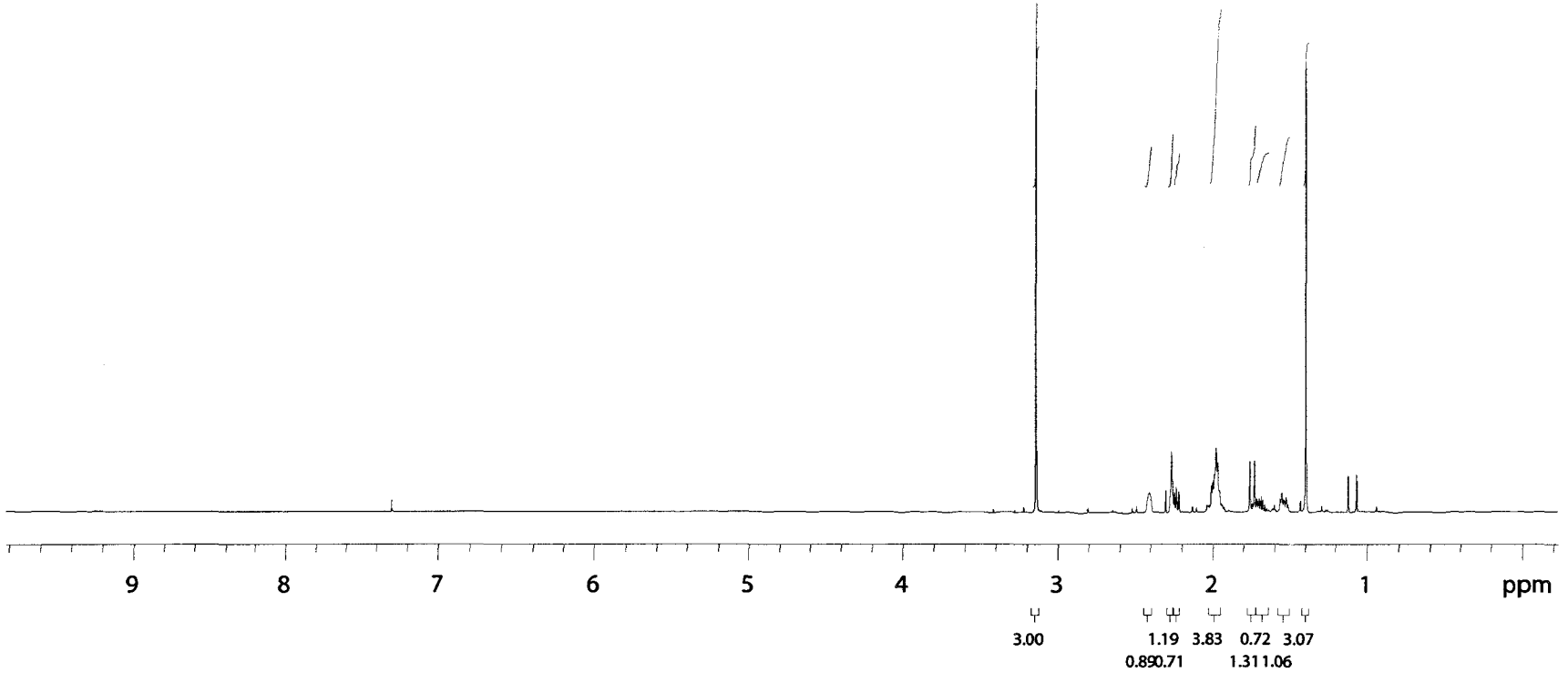
19a

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe
diastereomer 19b

Pulse Sequence: s2pul

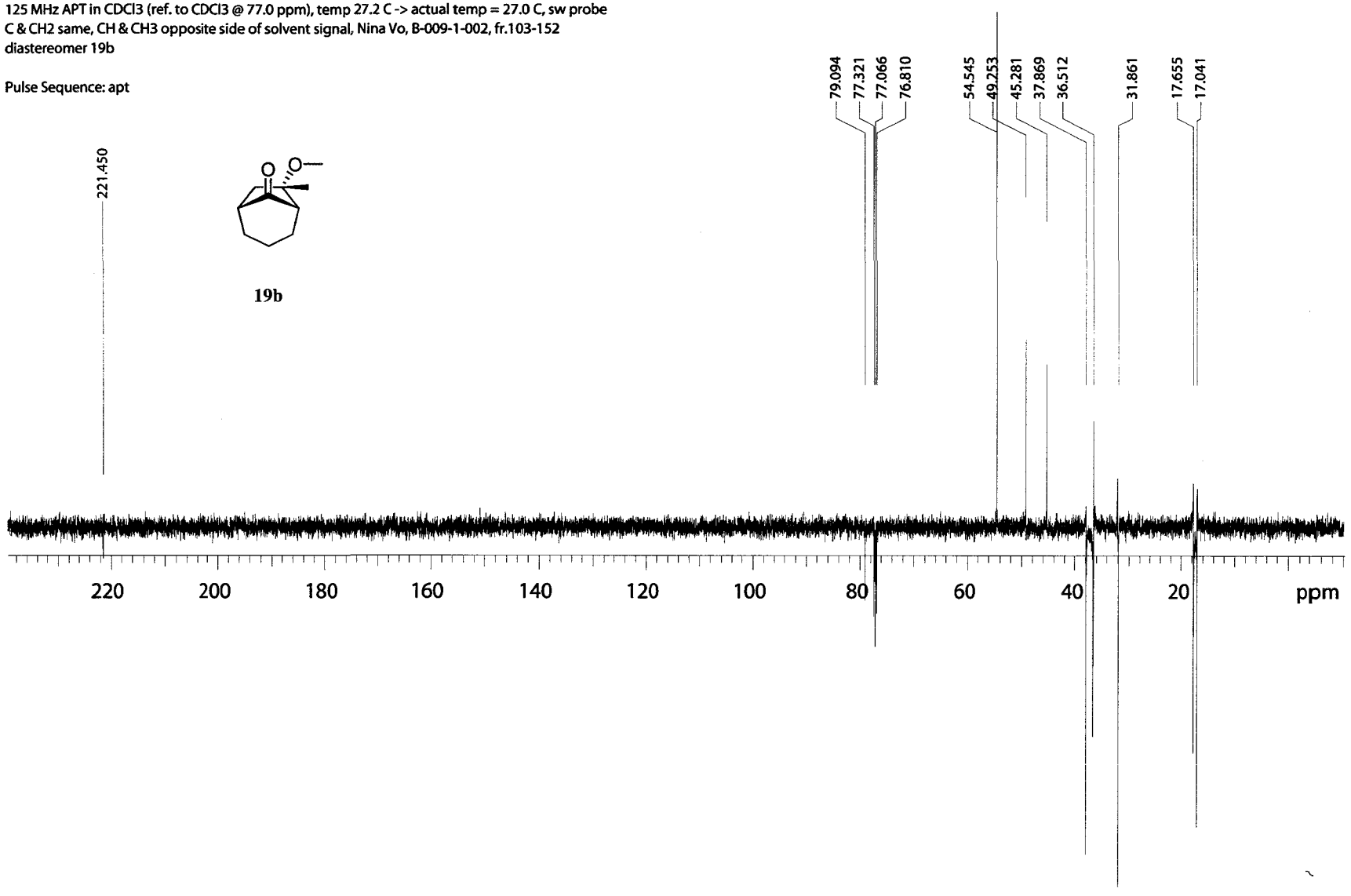


19b



125 MHz APT in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe C & CH2 same, CH & CH3 opposite side of solvent signal, Nina Vo, B-009-1-002, fr.103-152 diastereomer 19b

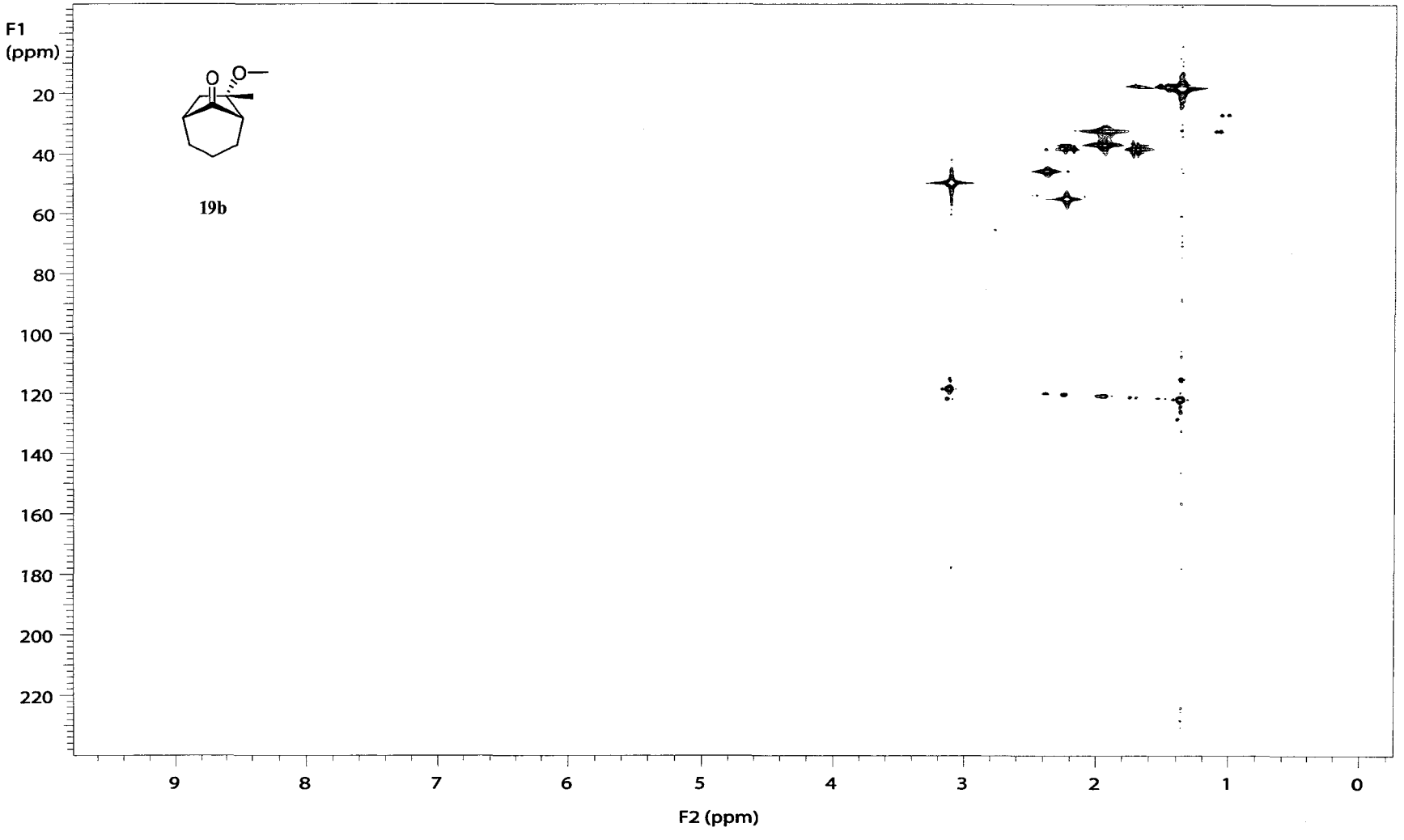
Pulse Sequence: apt



19b

500 MHz GHMQC in CDCl3 (ref. to CDCl3 @ 7.26/77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
diastereomer 19b

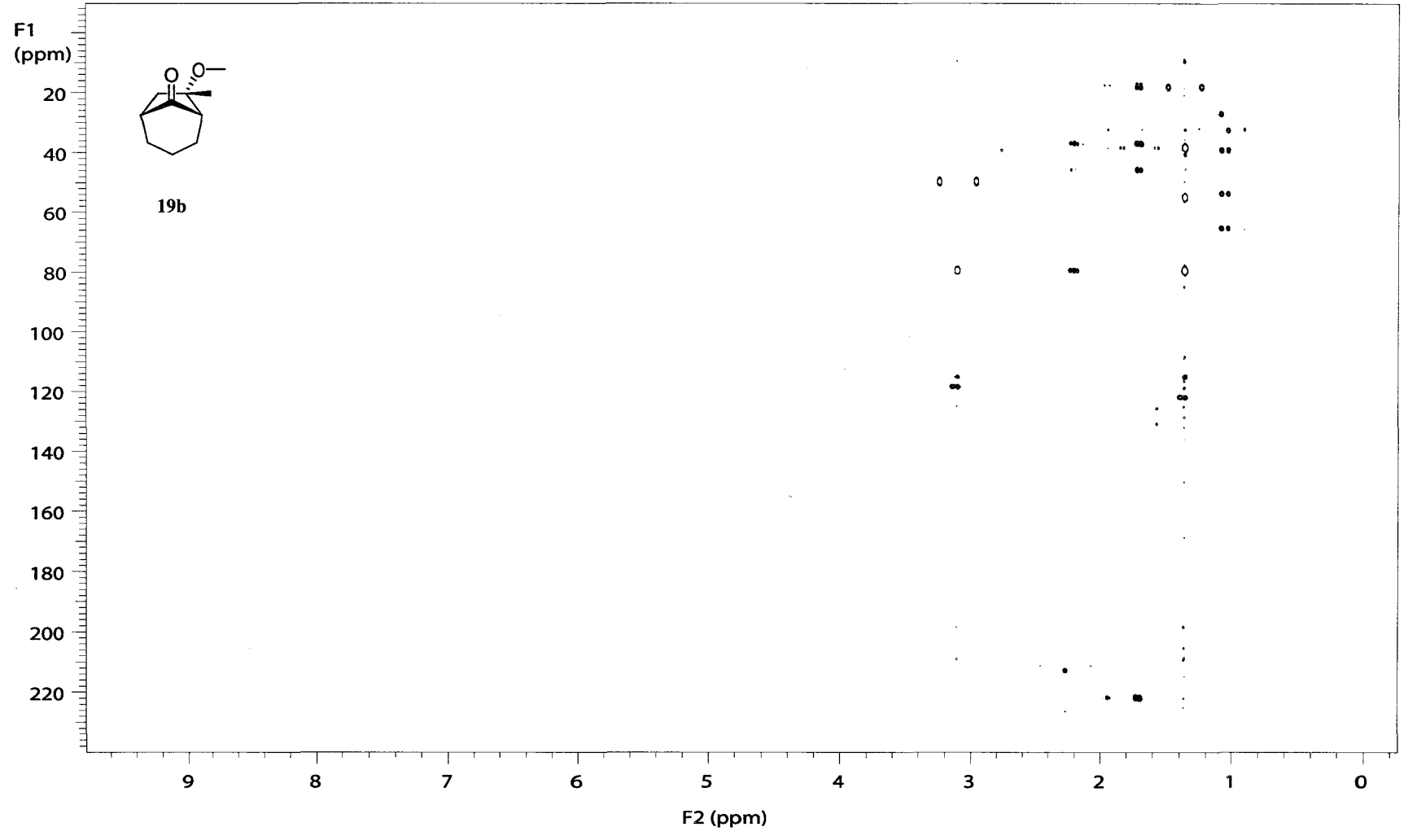
Pulse Sequence: ghmqc



19b

500 MHz GHMBC in CDCl3 (ref. to CDCl3 @ 7.26/77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
diastereomer 19b

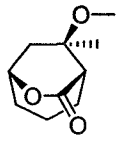
Pulse Sequence: ghmqc



19b

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.24 ppm), temp 29.4 C -> actual temp = 27.0 C, sw500u probe
9-methoxy-9-methyl-6-oxa-bicyclo[3.2.2]nonan-7-one

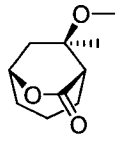
Pulse Sequence: s2pul



27

125 MHz APT in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
C & CH2 same, CH & CH3 opposite side of solvent signal
9-methoxy-9-methyl-6-oxa-bicyclo[3.2.2]nonan-7-one

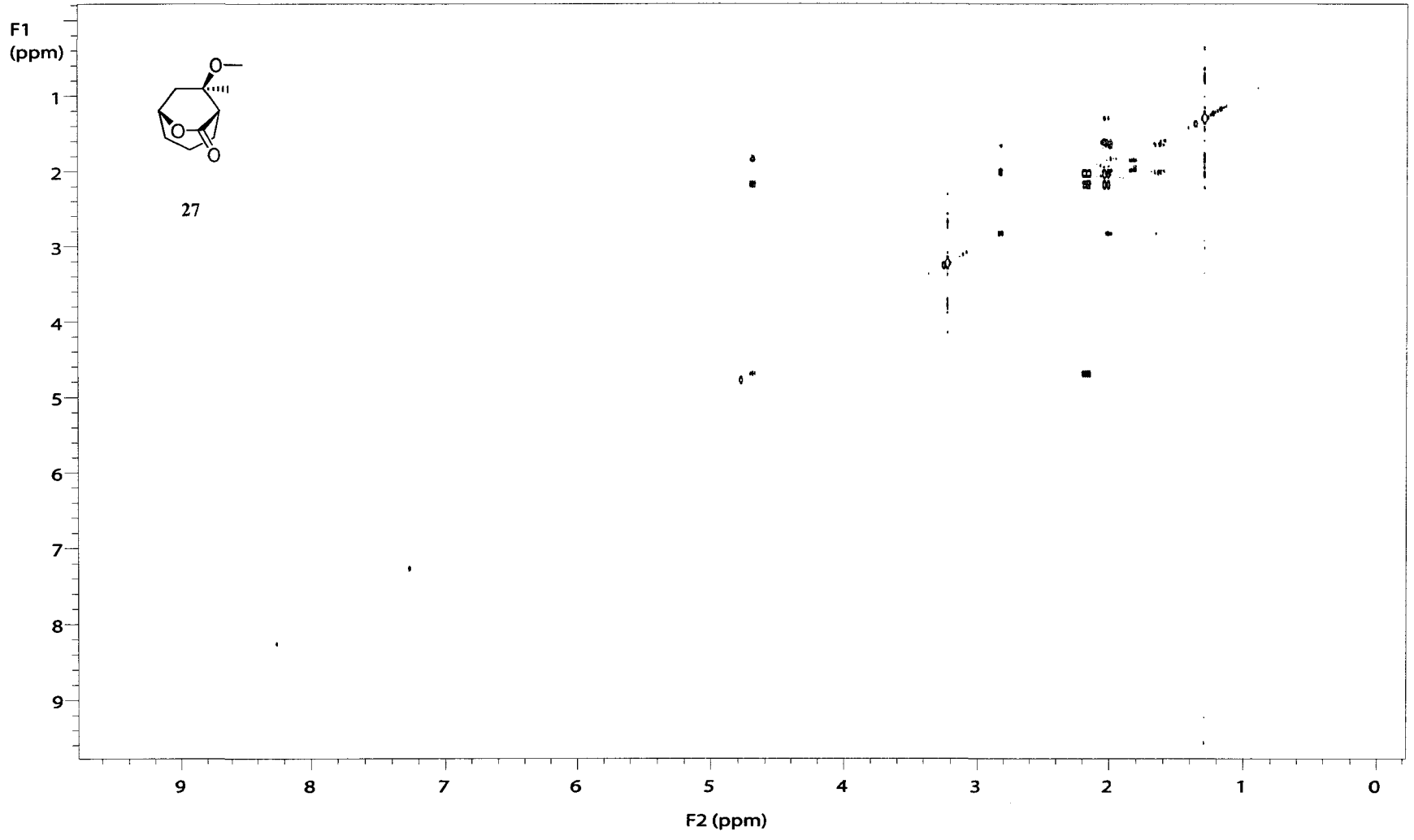
Pulse Sequence: apt



27

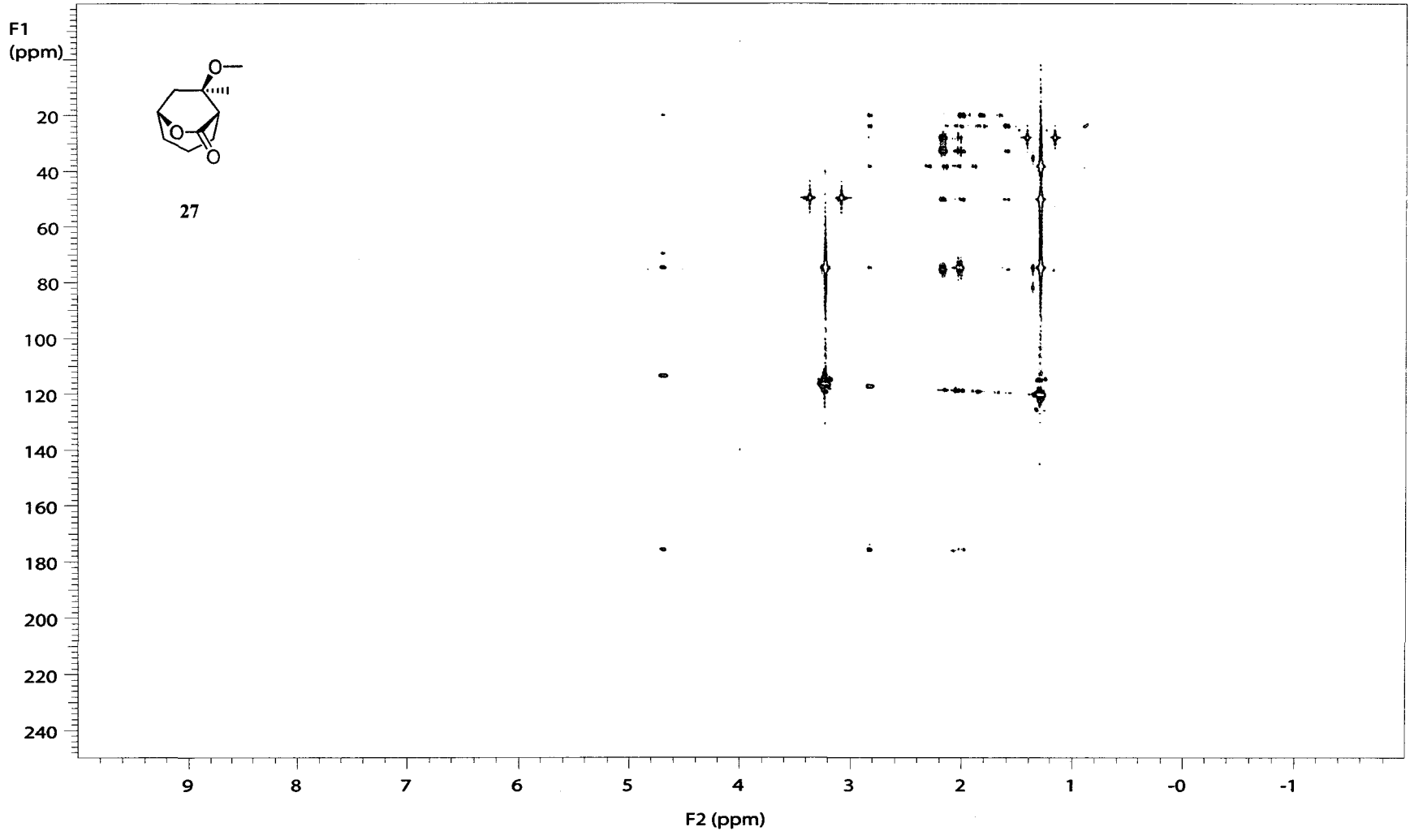
500 MHz GCOSY in CDCl3 (ref. to CDCl3 @ 7.24 ppm), temp 29.4 C -> actual temp = 27.0 C, sw500u probe
9-methoxy-9-methyl-6-oxa-bicyclo[3.2.2]nonan-7-one

Pulse Sequence: aogcosy



500 MHz GHMBC in CDCl3 (ref. to CDCl3 @ 7.26/77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
9-methoxy-9-methyl-6-oxa-bicyclo[3.2.2]nonan-7-one

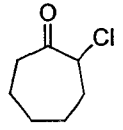
Pulse Sequence: ghmqc



27

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 29.4 C -> actual temp = 27.0 C, sw500u probe
2-chlorocycloheptanone

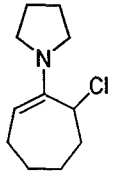
Pulse Sequence: s2pul



43

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe
1-(7-chloro-cyclohept-1-enyl)-pyrrolidine

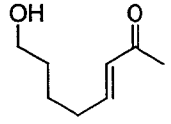
Pulse Sequence: s2pul



5

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe
8-hydroxy-oct-3-en-2-one

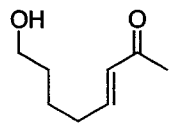
Pulse Sequence: s2pul



59

125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 29.4 C -> actual temp = 27.0 C, sw500u probe
8-hydroxy-oct-3-en-2-one

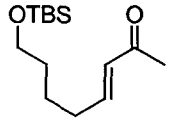
Pulse Sequence: s2pul



59

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe
8-(tert-butyl-dimethyl-silanyloxy)-oct-3-en-2-one

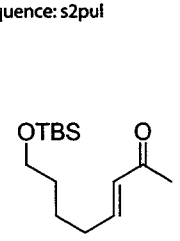
Pulse Sequence: s2pul



60

125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
8-(tert-butyl-dimethyl-silanyloxy)-oct-3-en-one

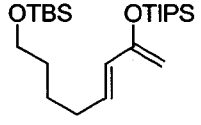
Pulse Sequence: s2pul



60

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
8-(tert-butyl-dimethyl-silanyloxy)-2-triisopropylsilanyloxy-1,3-diene

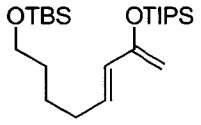
Pulse Sequence: s2pul



61

125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
8-(tert-butyl-dimethyl-silanyloxy)-2-triisopropylsilanyloxy-octa-1,3-diene

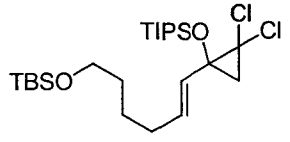
Pulse Sequence: s2pul



61

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe
1-[6-(tert-butyl-dimethyl-silanyloxy)-hex-1-enyl]-2,2-dichloro-1-triisopropylsilanyloxy-cyclopropane

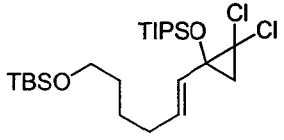
Pulse Sequence: s2pul



62

125 MHz APT in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
C & CH2 same, CH & CH3 opposite side of solvent signal
1-[6-(tert-butyl-dimethyl-silanyloxy)-hex-1-enyl]-2,2-dichloro-1-triisopropylsilanyloxy-cyclopropane

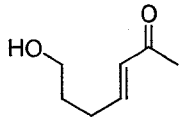
Pulse Sequence: apt



62

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe
7-hydroxy-hept-3-en-2-one

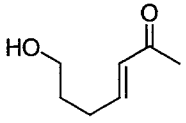
Pulse Sequence: s2pul



71

125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
7-hydroxy-hept-3-en-2-one

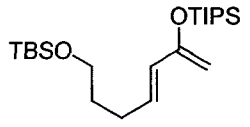
Pulse Sequence: s2pul



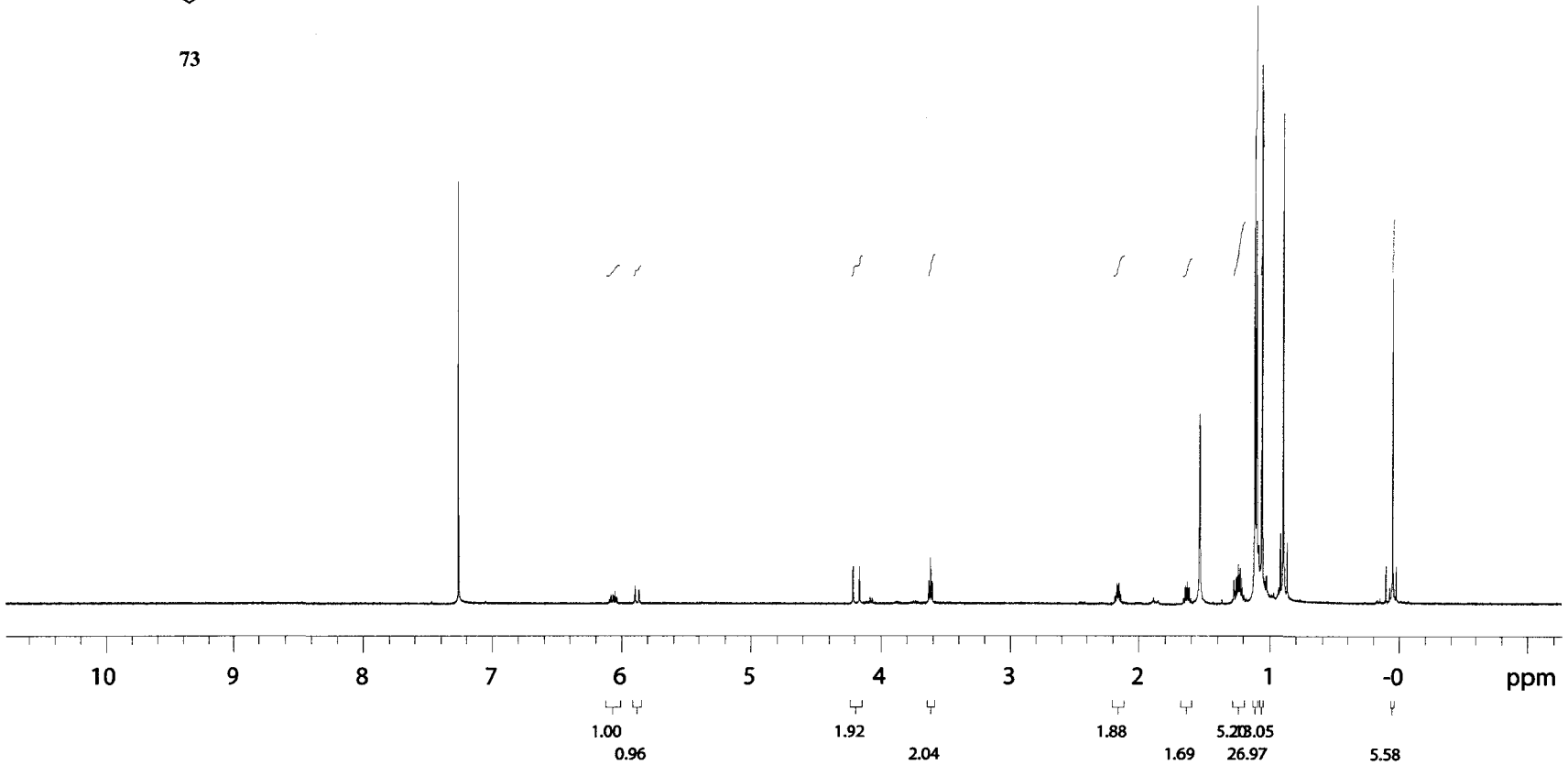
71

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe
7-(tert-butyl-dimethyl-silanyloxy)-2-triisopropylsilanyloxy-hepta-1,3-diene

Pulse Sequence: s2pul

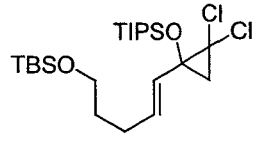


73



500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe
1-[5-(tert-butyl-dimethyl-silanyloxy)-pent-1-enyl]-2,2-dichloro-1-triisopropylsilanyloxy-cyclopropane

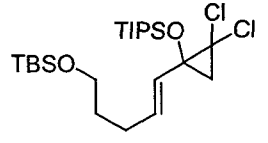
Pulse Sequence: s2pul



68

125 MHz APT in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
C & CH2 same, CH & CH3 opposite side of solvent signal
1-[5-(tert-butyl-dimethyl-silanyloxy)-pent-1-enyl]-2,2-dichloro-1-triisopropylsilanyloxy-cyclopropane

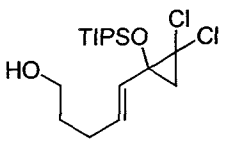
Pulse Sequence: apt



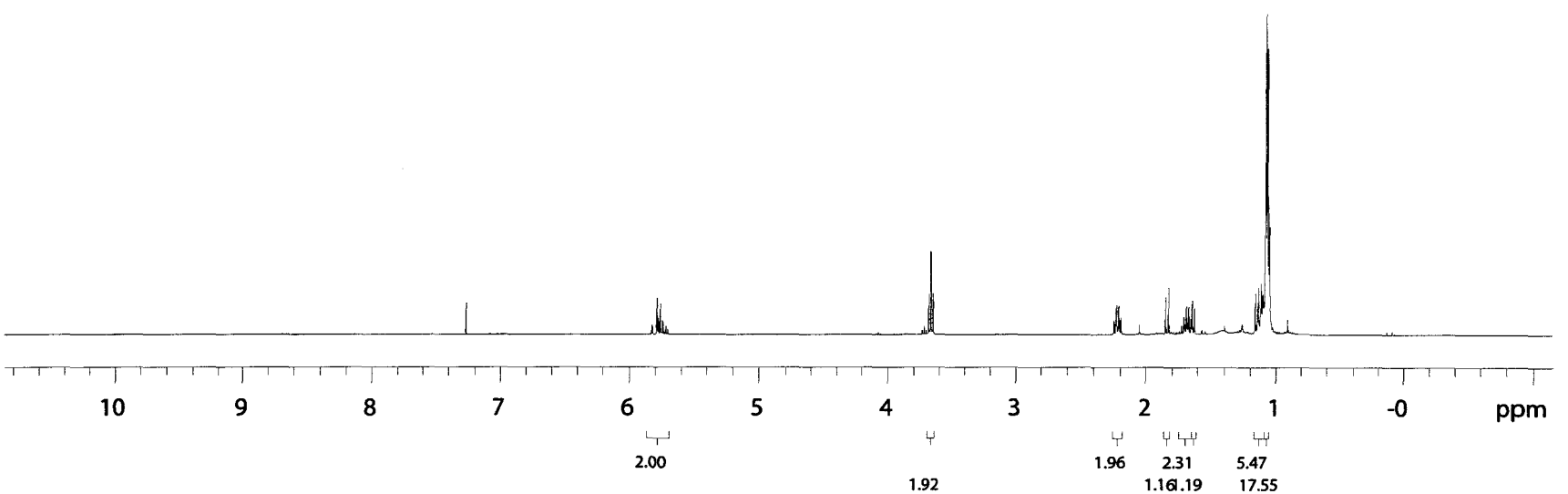
68

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe
5-(2,2-dichloro-1-triisopropylsilanyloxy-cyclopropyl)-pent-4-en-1-ol

Pulse Sequence: s2pul

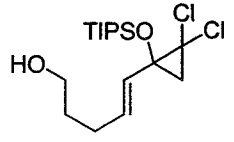


74

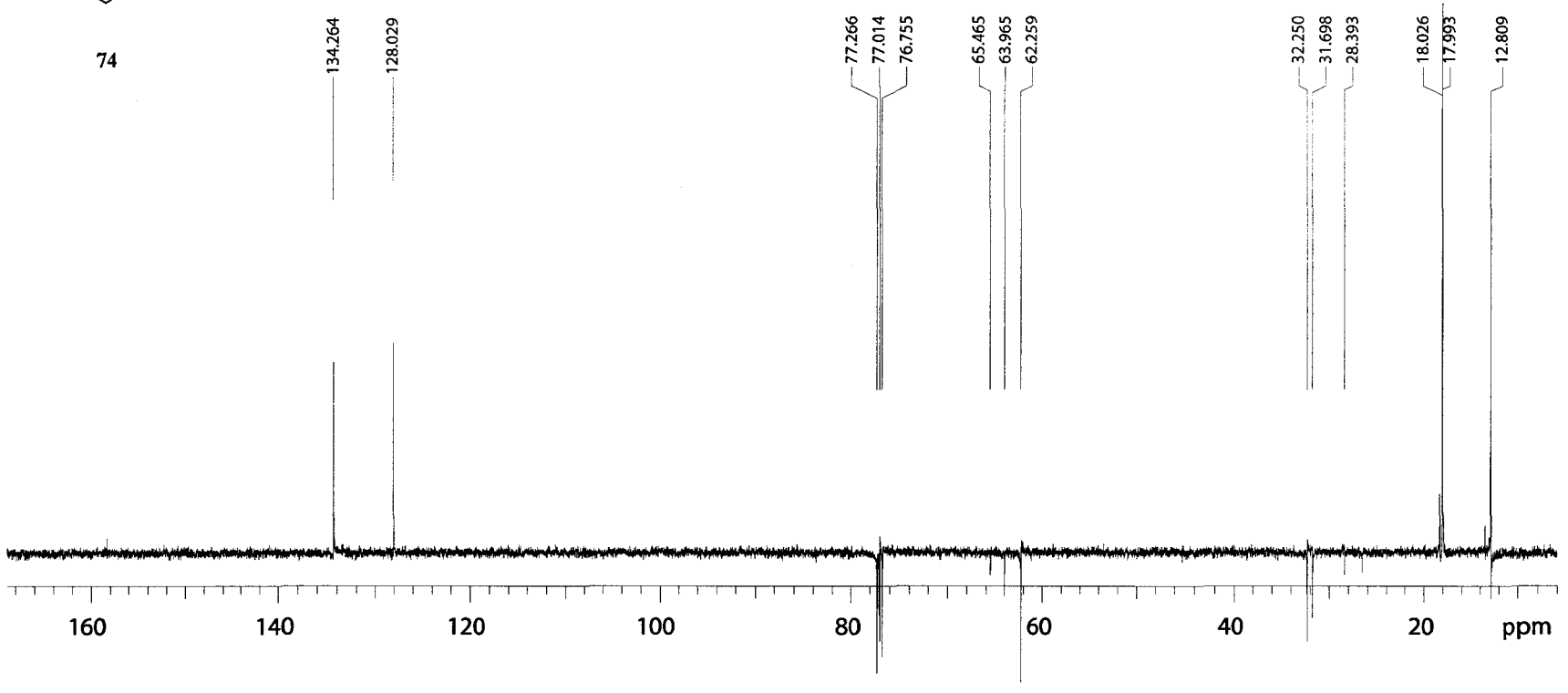


125 MHz APT in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
C & CH2 same, CH & CH3 opposite side of solvent signal
5-(2,2-dichloro-1-triisopropylsilanyloxy-cyclopropyl)-pent-4-en-1-ol

Pulse Sequence: apt

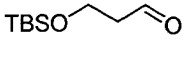


74

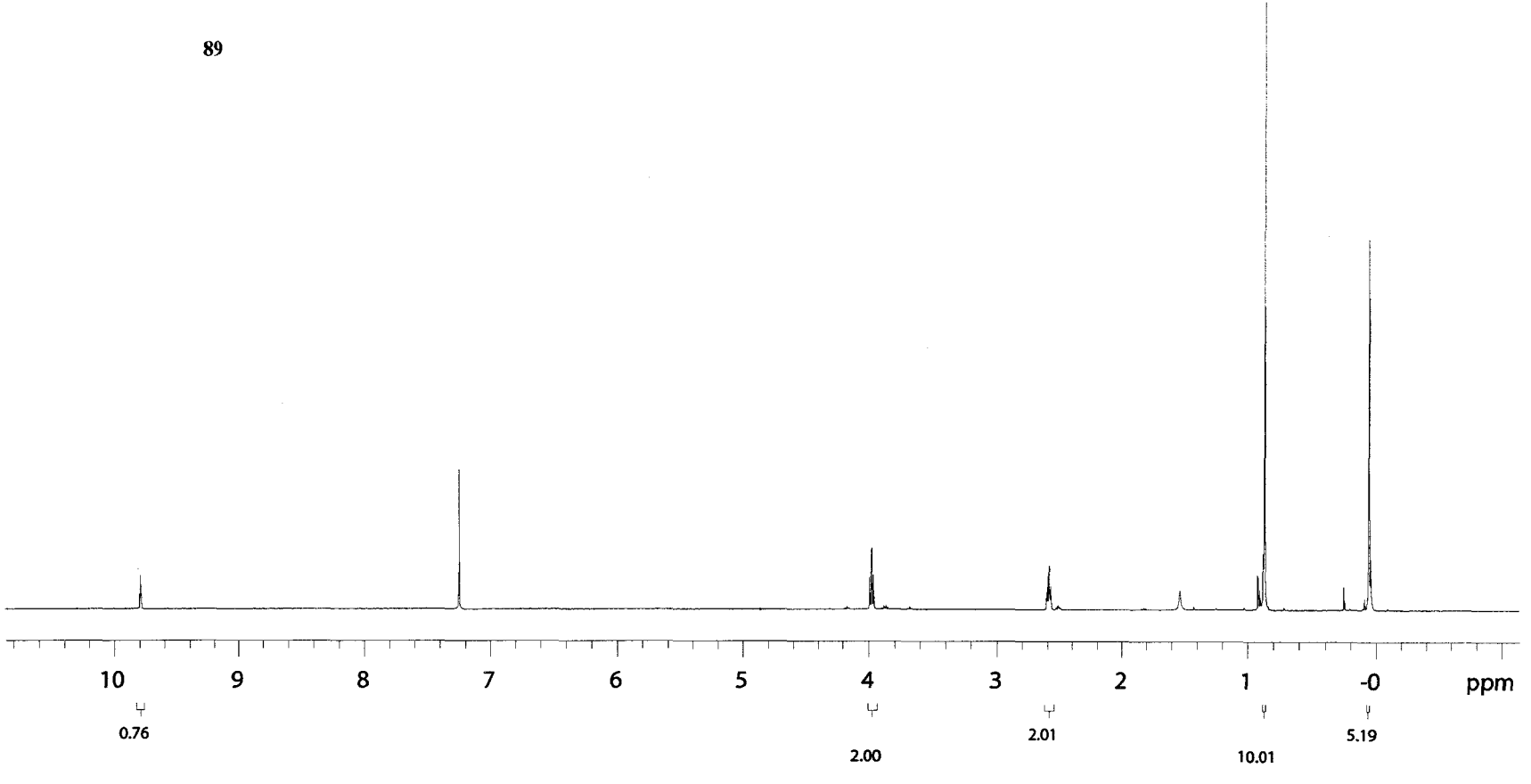


400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe
3-(tert-butyl-dimethyl-silanyloxy)-propionaldehyde

Pulse Sequence: s2pul

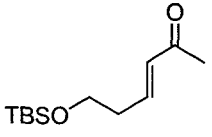


89



400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
6-(tert-butyl-dimethyl-silanyloxy)-hex-3-en-2-one

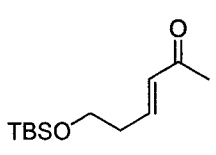
Pulse Sequence: s2pul



90

Nina Vo, D-030 125 MHz APT in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
C & CH2 same, CH & CH3 opposite side of solvent signal
6-(tert-butyl-dimethyl-silanyloxy)-hex-3-en-2-one

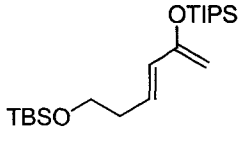
Pulse Sequence: apt



90

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
6-(tert-butyl-dimethyl-silanyloxy)-2-triisopropylsilanyloxy-hexa-1,3-diene

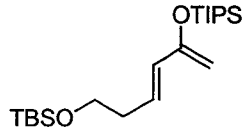
Pulse Sequence: s2pul



91

125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
6-(tert-butyl-dimethyl-silanyloxy)-2-triisopropylsilanyloxy-hexa-1,3-diene

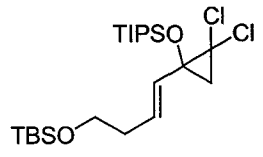
Pulse Sequence: s2pul



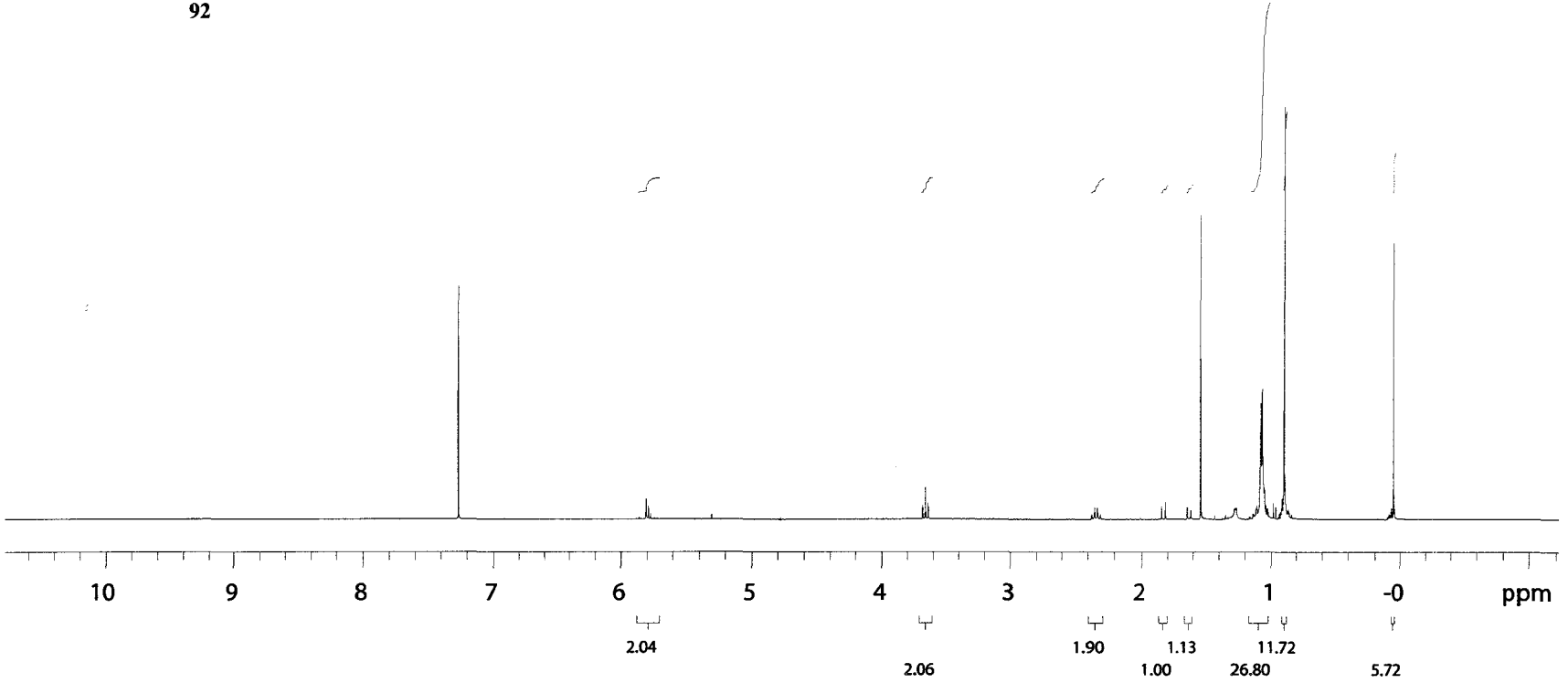
91

300 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.5 C -> actual temp = 27.0 C, id probe
1-[4-(tert-butyl-dimethyl-silanyloxy)-but-1-enyl]-2,2-dichloro-1-triisopropylsilanyloxy-cyclopropane

Pulse Sequence: s2pul

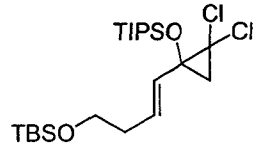


92



125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
1-[4-(tert-butyl-dimethyl-silanyloxy)-but-1-enyl]-2,2-dichloro-1-triisopropylsilanyloxy-cyclopropane

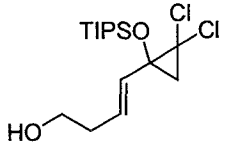
Pulse Sequence: s2pul



92

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.8 C -> actual temp = 27.0 C, asw400 probe
4-(2,2-dichloro1-triisopropylsilanyloxy-cyclopropyl)-but-3-en-1-ol

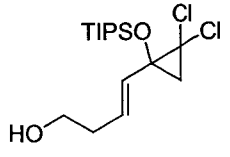
Pulse Sequence: s2pul



80

125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
4-(2,2-dichloro-1-triisopropylsilanyloxy-cyclopropyl)-but-3-en-1-ol

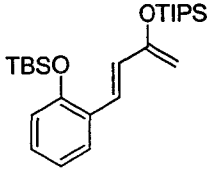
Pulse Sequence: s2pul



80

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
1-(tert-butyl-dimethyl-silanyloxy)-2-(3-triisopropylsilanyloxy-buta-1,3-dienyl)-benzene

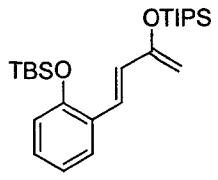
Pulse Sequence: s2pul



99

125 MHz 1D C13 in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
1-(tert-butyl-dimethyl-silanyloxy)-2-(3-triisopropylsilanyloxy-buta-1,3-dienyl)-benzene

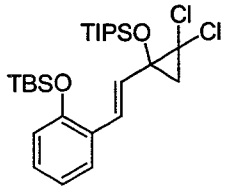
Pulse Sequence: s2pul



99

125 MHz APT in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
C & CH2 same, CH & CH3 opposite side of solvent signal
1-(tert-butyl-dimethyl-silanyloxy)-2-[2-(2,2-dichloro-1-triisopropylsilanyloxy-cyclopropyl)-vinyl]-benzene

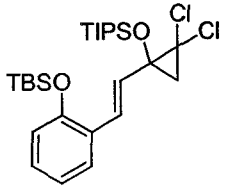
Pulse Sequence: apt



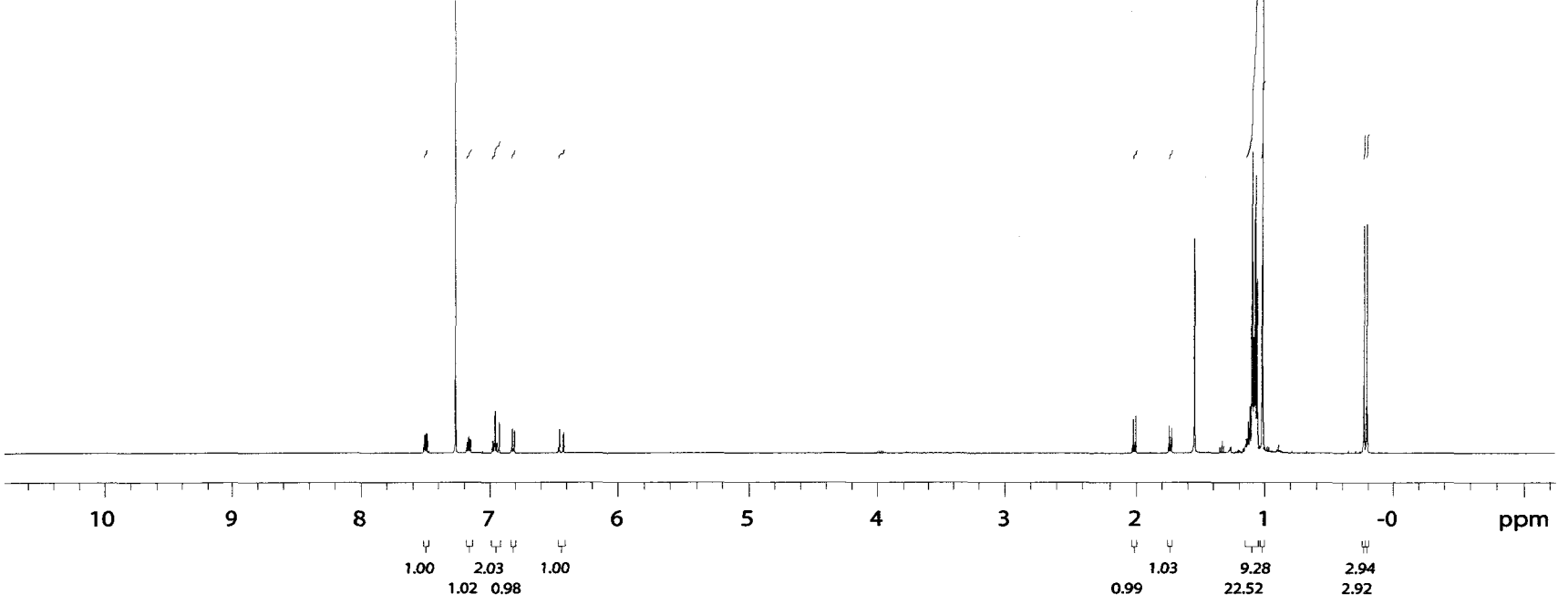
100

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, sw500u probe
1-(tert-butyl-dimethyl-silanyloxy)-2-[2-(2,2-dichloro-1-triisopropylsilanyloxy-cyclopropyl)-vinyl]-benzene

Pulse Sequence: s2pul

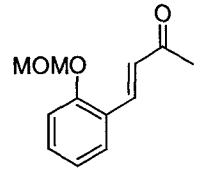


100



500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.2 C -> actual temp = 27.0 C, sw500 probe
4-(2-methoxymethoxy-phenyl)-but-en-2-one

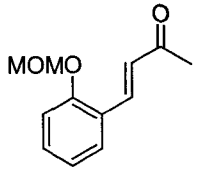
Pulse Sequence: s2pul



108

Nina Vo, D-049 125 MHz APT in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe
C & CH2 same, CH & CH3 opposite side of solvent signal
4-(2-methoxymethoxy-phenyl)-but-3-en-2-one

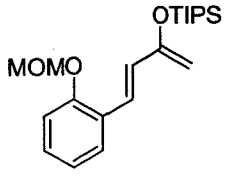
Pulse Sequence: apt



108

400 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 27.0 C -> actual temp = 27.0 C, m400gz probe
triisopropyl-[3-(2-methoxymethoxy-phenyl)-1-methylene-allyloxy]-silane

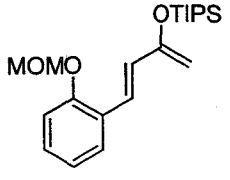
Pulse Sequence: s2pul



109

125 MHz 1D C13 in CD2Cl2 (ref. to CD2Cl2 @ 53.8 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe
triisopropyl-[3-(2-methoxymethoxy-phenyl)-1-methylene-allyloxy]-silane

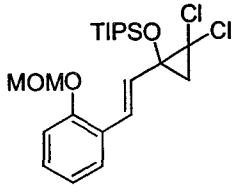
Pulse Sequence: s2pul



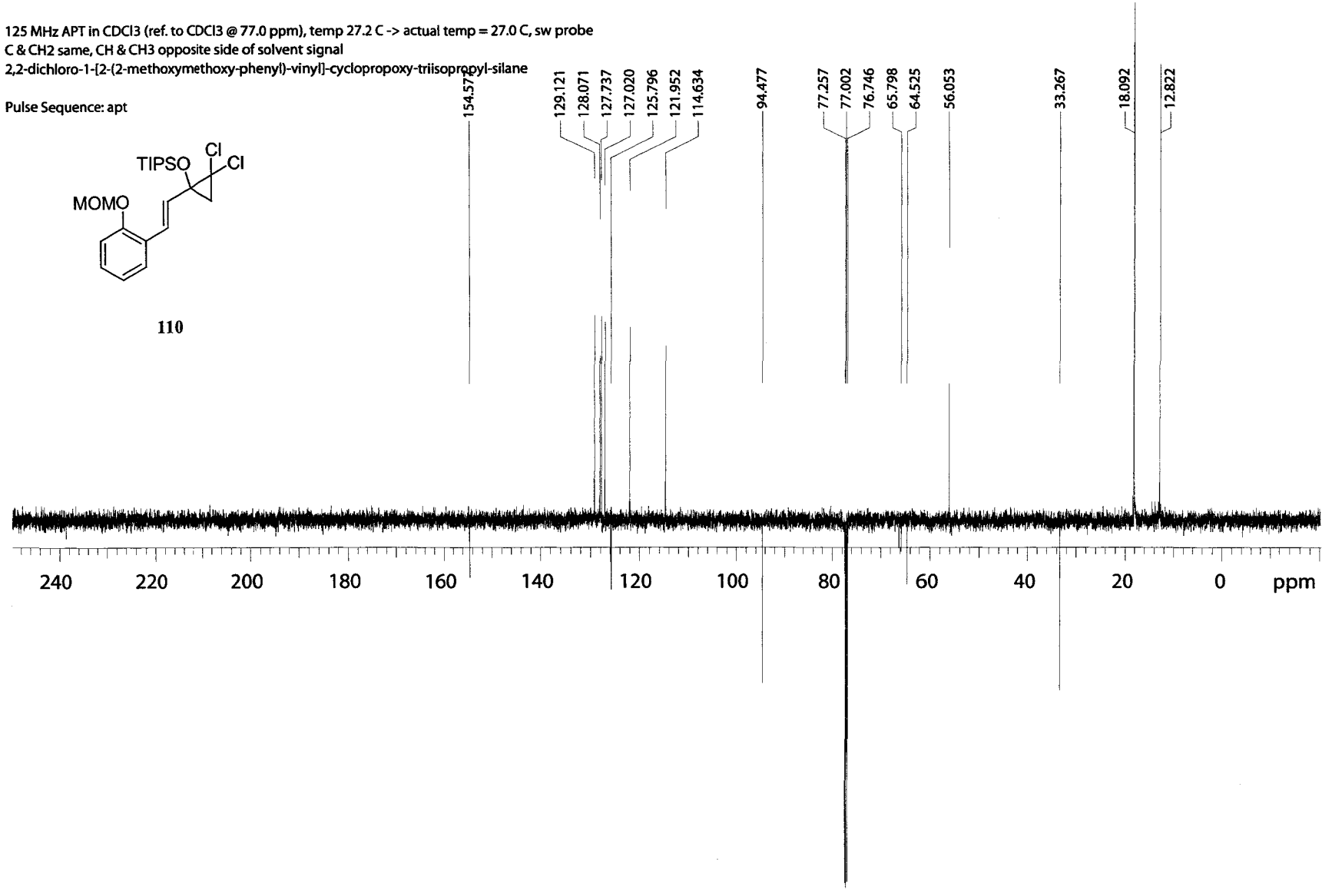
109

500 MHz 1D in CDCl3 (ref. to CDCl3 @ 7.26 ppm), temp 26.1 C -> actual temp = 27.0 C, autoxdb probe
2,2-dichloro-1-[2-(2-methoxymethoxy-phenyl)-vinyl]-cyclopropoxy-triisopropyl-silane

Pulse Sequence: s2pul



110


125 MHz APT in CDCl3 (ref. to CDCl3 @ 77.0 ppm), temp 27.2 C -> actual temp = 27.0 C, sw probe
C & CH2 same, CH & CH3 opposite side of solvent signal
2,2-dichloro-1-[2-(2-methoxymethoxy-phenyl)-vinyl]-cyclopropoxy-triisopropyl-silane
Pulse Sequence: apt
TIPSO
Cl
Cl
MOMO
154.578
129.121
128.071
127.737
127.020
125.796
121.952
114.634
94.477
77.257
77.002
76.746
65.798
64.525
56.053
33.267
18.092
12.822
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

110