THE UNIVERSITY OF CALGARY

The Total Synthesis of (±)-Bakkenolide-A

by

Joseph E. Payne

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE

DEGREE OF MASTER OF SCIENCE

DEPARTMENT OF CHEMISTRY

CALGARY, ALBERTA

JUNE, 1999

Abstract

The bakkenolides are a small family of biologically active natural products with an unusual tricyclic skeleton containing a β-methylene spiro γ-lactone ring. This thesis describes a concise intramolecular Diels-Alder approach towards the total synthesis of (±)-bakkenolide-A, the first discovered member of this class, in an overall yield of 13% from ethyl 4-benzyloxyacetoacetate.

The preparation of the pre-Diels-Alder intermediates ethyl 4-benzyloxy-2-[2-methyl-2(Z)-butenyl]-2-[2(Z),4-pentadienyl]acetoacetate and ethyl 4-benzyloxy-2-[2-methyl-2(E)-butenyl]-2-[2(E),4-pentadienyl]acetoacetate, which differ from each other with respect to the stereochemistry of the diene, was achieved by alkylation of ethyl 4-benzyloxyacetoacetate with the corresponding allyl and dienyl bromides. It was observed that the *cis*-triene was more stereoselective than the *trans*-diene at establishing the desired *cis*-fused A- and B-rings of bakkenolide-A. Two novel stereoisomers of (±)-bakkenolide-A, (±)-10-epibakkenolide-A and (±)-7,10-diepibakkenolide-A were also isolated and characterized, along with the previously reported (±)-7-epi derivative.

Acknowledgments

First and foremost, I would like to thank my supervisor, Dr. T. G. Back for his assistance during my project.

I would also like to express my appreciation to Ms. D. Fox, Ms. Q. Wu and Dr. R. Yamdagni for their technical support.

I wish to thank Dr. Richard Bethell, Denise Andersen, Christoph Taeschler, Dr. Kazimierz Minksztym, Susan Nan, Katsu and Suanne Nakajima, Gabriel Sung, Jerry Taylor and Ziad Moussa for their assistance in the lab and for their friendship.

I would like to thank my Mom and Dad for their support and encouragement.

Finally, I would like to acknowledge the University of Calgary for financial support.

for Erin

Table of Contents

List of Figures

List of Tables

List of Abbreviations

Ac	acetyl
AIBN	azobis(isobutyronitrile)
Anal.	Elemental Analysis
Ar	Aryl
aq	aqueous
BHT	2,6-di-*tert*-butyl-4-methylphenol
bp	boiling point
br	broad
BuLi	butyllithium
°C	degrees Celsius
calcd	calculated
cat.	Catalytic
cm^{-1}	reciprocal centimeters-wavenumbers
^{13}C-NMR	carbon-13 nuclear magnetic resonance
d	doublet
δ	chemical shift in ppm
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dd	doublet of doublets
ddd	doublet of doublet of doublets
dddd	doublet of doublet of doublet of doublets
dt	doublet of triplets

E	energy
EAP	2-(ethylamino)pyridine
eq	equivalent
Et	ethyl
EtOAc	ethyl acetate
g	grams
h	hours
^{1}H-NMR	proton nuclear magnetic resonance
HRMS	high resolution mass spectrum
Hz	Hertz
IR	infrared
J	coupling constant
kcal	kilocalories
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
lit.	literature
M	molar
m	multiplet or metre
mm	millimetre
M^+	molecular ion
m/z	mass to charge ratio
Me	methyl
mg	milligrams

MHz	megahertz
min	minutes
mL	millilitres
mmol	millimoles
mol	moles
mp	melting point
MS	mass spectrometry
n-	normal (straight chain)
NME	(-)-N-methylephedrine
NOE	Nuclear Overhauser Effect
NOSEY	Nuclear Overhauser and Exchange Spectroscopy
Nu	nucleophile
[O]	oxidation
p.	page
PCC	pyridinium chlorochromate
Ph	phenyl
pp.	pages
ppm	parts per million
q	quartet
quant.	quantitative
R	generalized alkyl group or substituent
rt	room temperature
s	singlet

t	**triplet**
tert-	**tertiary**
THF	**tetrahydrofuran**
TLC	**thin layer chromatography**
Ts	**p-toluenesulfonyl or tosyl**
UV	**ultraviolet**

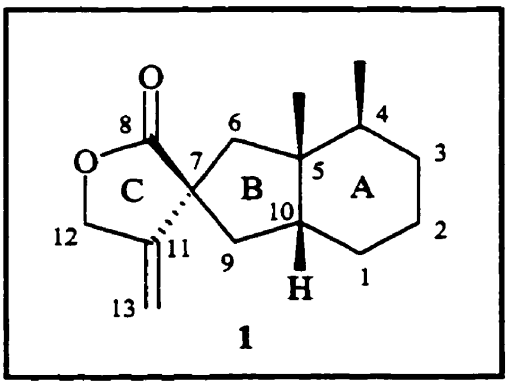
Chapter One

Introduction

1.1 Bakkenolide-A

1.1.1 Structure and Background

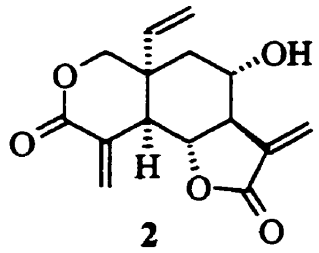
Bakkenolide-A (**1**) is a tricyclic hydrindane natural product where the A and B rings are fused in a *cis* fashion. It also contains a spiro lactone moiety (C ring) with an exocyclic methylene group in the β position. There are four chiral centers at C-4, C-5, C-7 (the spiro center), and C-10, which make the architecture not only interesting, but also more challenging for the synthetic chemist.



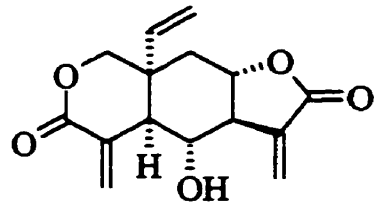
1

Bakkenolide-A (**1**) is a member of a large group of natural products called sesquiterpene butyrolactones.[1] Sesquiterpenes are derived from three isoprene units. Thus, sesquiterpene butyrolactones contain fifteen carbon atoms, including a five-membered lactone moiety.

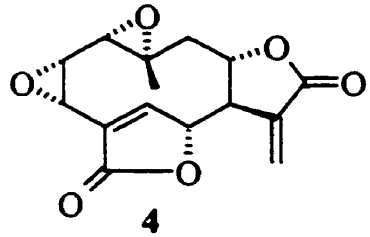
The scientific community has been intrigued by sesquiterpene butyrolactones for decades. This interest stems from the varying biological activities exhibited by this large family of natural products. Many of these compounds, classic examples being vernolepin[2] (2) and vernomenin[3] (3), have been reported to be active anti-tumor agents. Some possess anti-bacterial and/or anti-fungal activity. Mikanolide[4] (4), for example, inhibits the growth of *Staphylococcus aureus* and of the yeast *Candida albicans*.



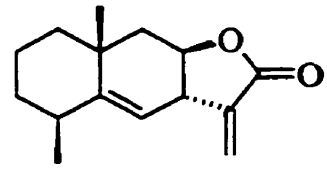
2



3



4

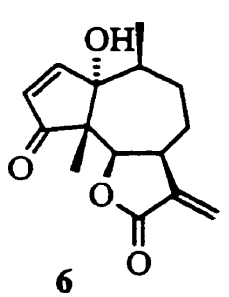


5

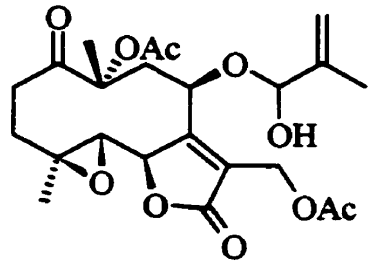
A number of sesquiterpene lactones are plant growth inhibitors. Alantolactone[5] (5), for example, inhibits seed germination and seedling growth, possibly by inhibiting the enzymes responsible for the degradation of starch and protein.

Others are considered allergens responsible for allergic reactions towards particular plants, and plant products such as perfumes. One such example is parthenin[6] (6), the major allergen in the weed *Parthenium hysterophorus*, which was unintentionally brought into India from America in 1956.

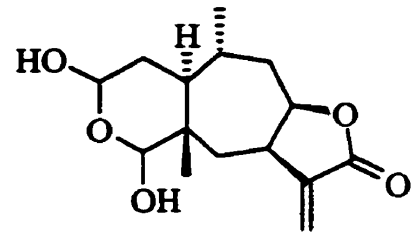
Finally, the insect antifeedant glaucolide-A[7] (**7**) and the bitterweed toxin, hymenovin[8] (**8**), are two more examples of biologically active sesquiterpene butyrolactones.



6



7



8

1.1.2 The Bakkenolide Family

As can be seen from the previous examples (**2-6** and **8**), many sesquiterpene butyrolactones have an exocyclic double bond at the α position of the lactone moiety. A small number of these compounds have this methylene group in the β position instead of the α position, where the α-carbon is a quaternary center. This latter class of naturally occurring β-methylene sesquiterpene butyrolactones are known as the bakkenolides[1] (see Figure 1).

The first bakkenolide to be discovered was bakkenolide-A[9] (**1**). Other members of the β-methylene sesquiterpene butyrolactone family include bakkenolides B through E[9] (**9-12**), homogynolides A[10] (**13**) and B[11] (**14**), and the related epoxide, palmosalide-C[12] (**15**). The novel carbon skeleton they share is named bakkane[9] (**16**).

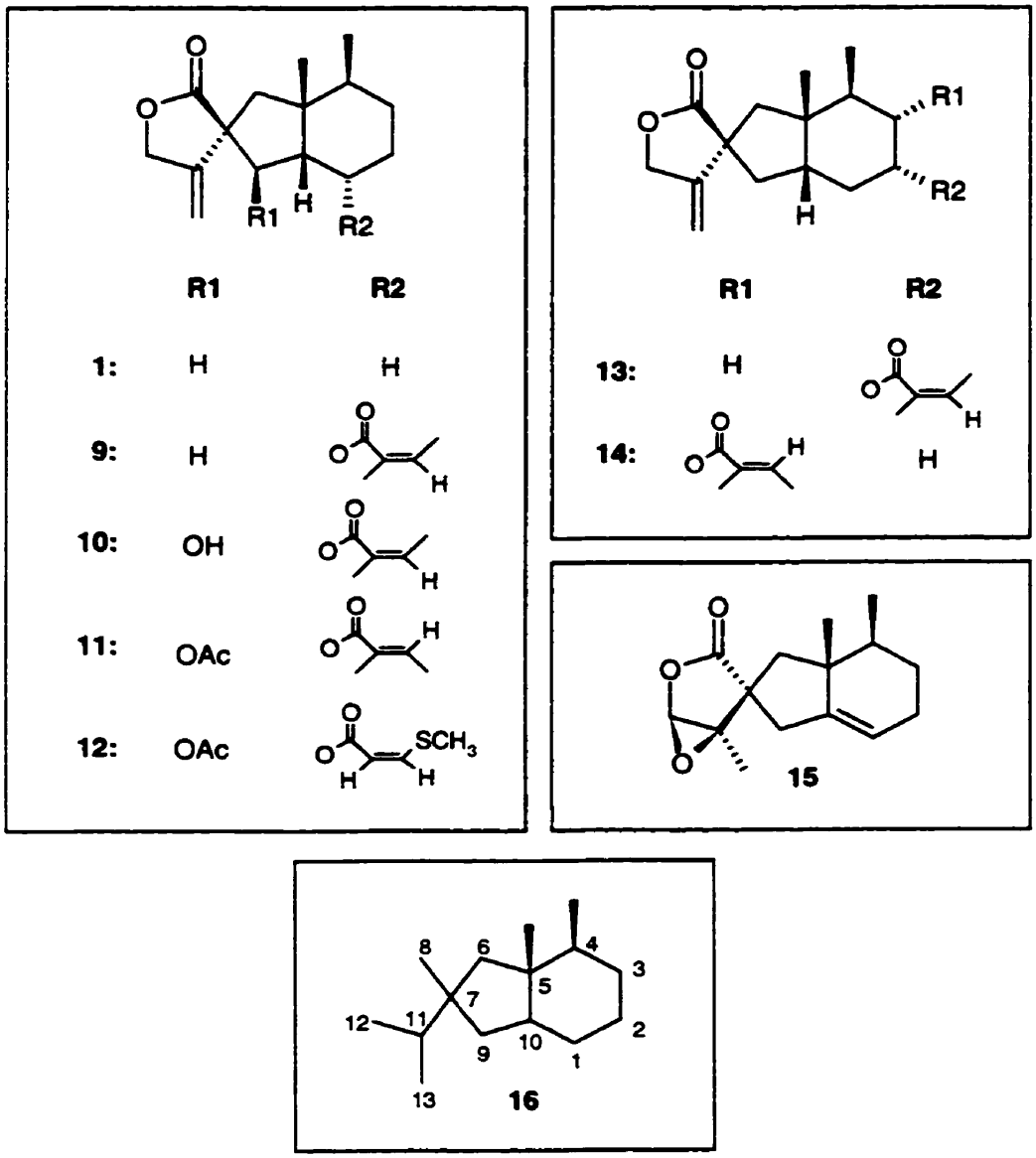


Figure 1. The Bakkenolide Family

1.1.3 Discovery and Structure Elucidation

In 1968, Kitahara and coworkers[9] were investigating the bitter properties of wild butterburs taken from the *Petasites japonicus* subspecies *giganteus* Maxim, a plant that is indigenous to the northern parts of Japan. Several novel hydrindane spirolactone sesquiterpenes were isolated from these buds, the first of which to be elucidated was named bakkenolide-A, after the local name (*Bakke*) of the species.[13] Interestingly, at the same time, Hayashi *et al.*[14] also reported the isolation of some bakkenolides from another natural source and named them as fukinanes.

Proton NMR, IR, and mass spectroscopy, as well as structural degradation, and X-ray crystallography were used to elucidate the structure of bakkenolide-A.[14-17] Since its discovery, **1** has been isolated from several genera of the *Senecioneae* tribe (Compositae) in a variety of areas, including Algeria[18] and, most recently, in China.[19] Not all of the bakkenolides have been isolated from the Compositae, however. The epoxy bakkane palmosalide-C (**15**), for example, was isolated from a rare gorgonian-like soft coral found in the Indian Ocean.[20]

1.1.4 Biological Activity

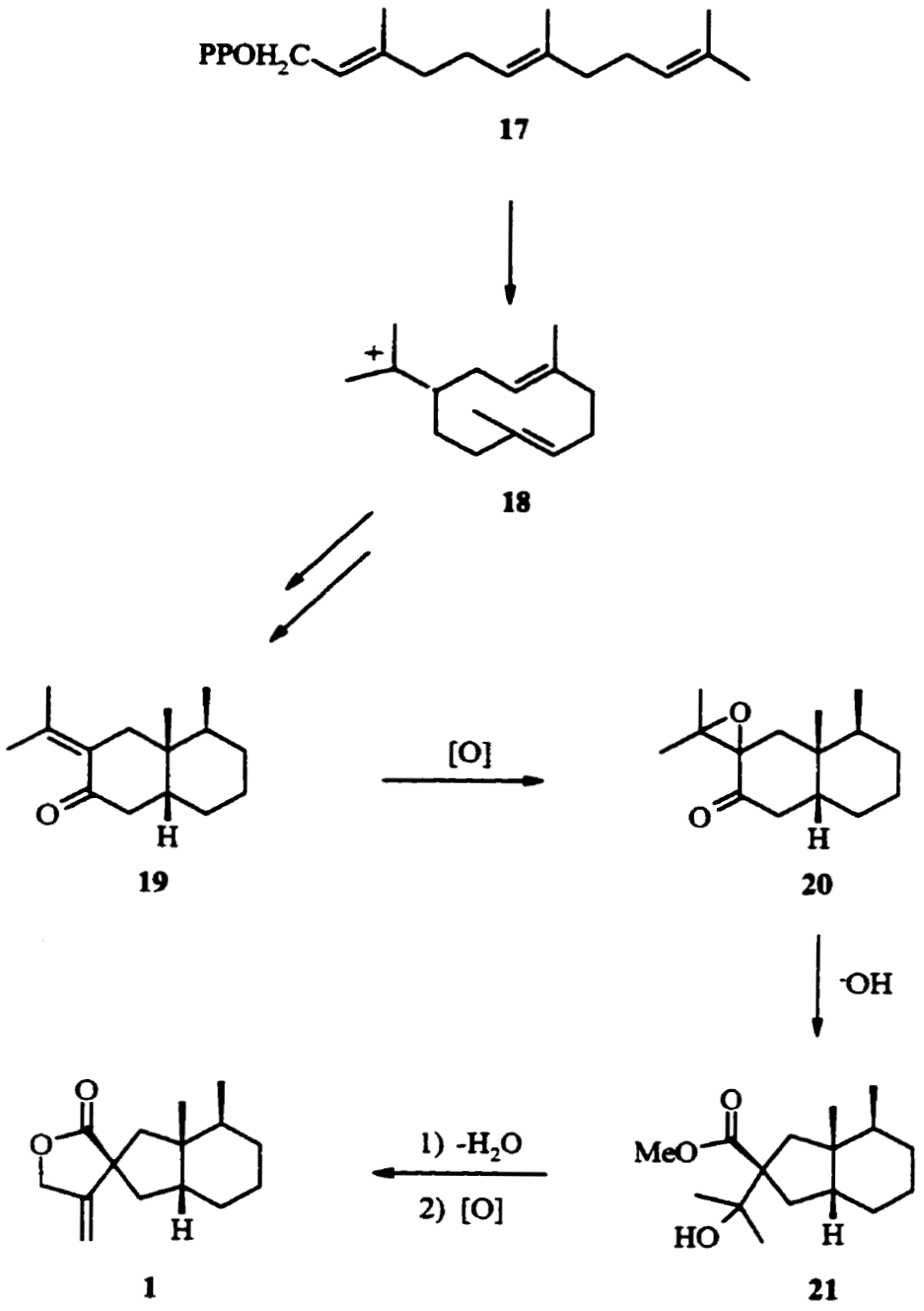
Experiments have shown bakkenolide-A (**1**) to exhibit selective cytotoxic activity towards cell lines derived from human carcinomas (H.Ep.2 and HeLa vs. HeLu).[21] Data also indicate cytotoxicity of bakkenolide-A against Ehrlich carcinoma.[22]

The biological activity of bakkenolide-A against a variety of agricultural pests is impressive. Firstly, it has been reported[23a-f] to have moderate to excellent protectant activity against adult beetles (*Sitophilus granarius, Tribolium confusum*) and larvae (*Trogoderma granarium, Tribolium confusum*). Secondly, **1** exhibits strong insect antifeedant activity against the subterranean termite, *Coptotermes formosanus.*[23i] Finally, bakkenolide-A has shown high biological activity, as an antifeedant and as a larval growth inhibitor, towards the variegated cutworm, *Peridroma saucia.*[23g,h] This polyphagous lepidopteran is a sporadic, but occasionally serious, economic pest of numerous food crops and ornamental plants.[23g]

1.1.5 Biosynthesis

Bakkenolide-A (**1**) is reported[24] to be biogenetically related to the eremophilanes on the basis of their frequent co-occurrence in nature and the successful "biomimetic" conversion[25] of fukinone (**19**) to bakkenolide-A.

The biosynthesis of bakkenolide-A is generally accepted to proceed as illustrated in Scheme 1. Nature's starting material *trans,trans*-farnesyl pyrophosphate (**17**) goes through the cyclic cation intermediate **18**, which undergoes oxidation and skeletal rearrangement to afford the eremophilane, fukinone (**19**). It has been proposed[25] that **19** is likely oxidized to the fukinone epoxide **20** and subsequently undergoes a Favorskii skeletal rearrangement to provide **21**. Dehydration and further oxidation furnishes the lactone, completing the biosynthesis of bakkenolide-A.



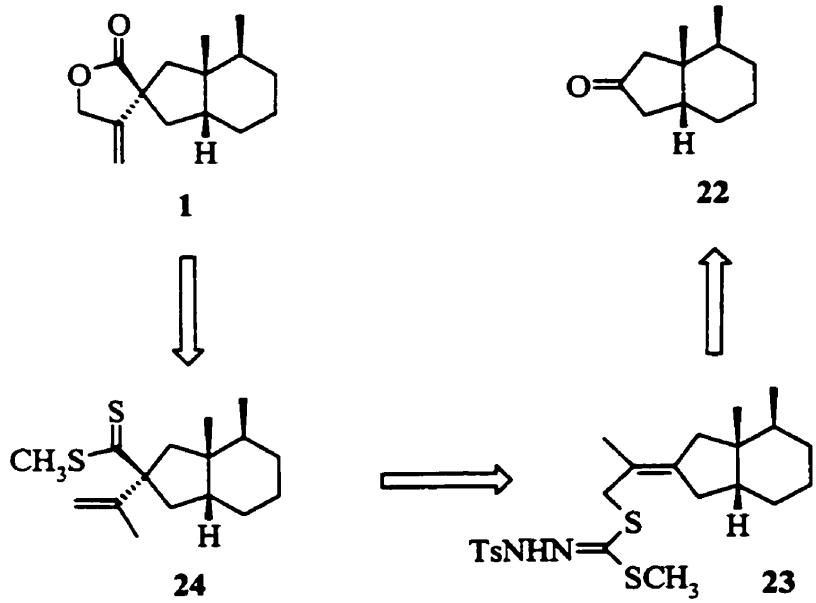
Scheme 1. Biosynthesis of Bakkenolide-A

1.2 Previous Syntheses of Bakkenolide-A

Despite its unusual architecture and biological activity, only three laboratories in the thirty-one years since its discovery have successfully completed a total synthesis of bakkenolide-A: (1) a group from Harvard headed by Evans,[26] (2) a laboratory in France led by Greene,[27] and (3) from the Indian Institute of Science, a group led by Srikrishna.[28] This section outlines each of their approaches.

1.2.1 Evans' Synthesis

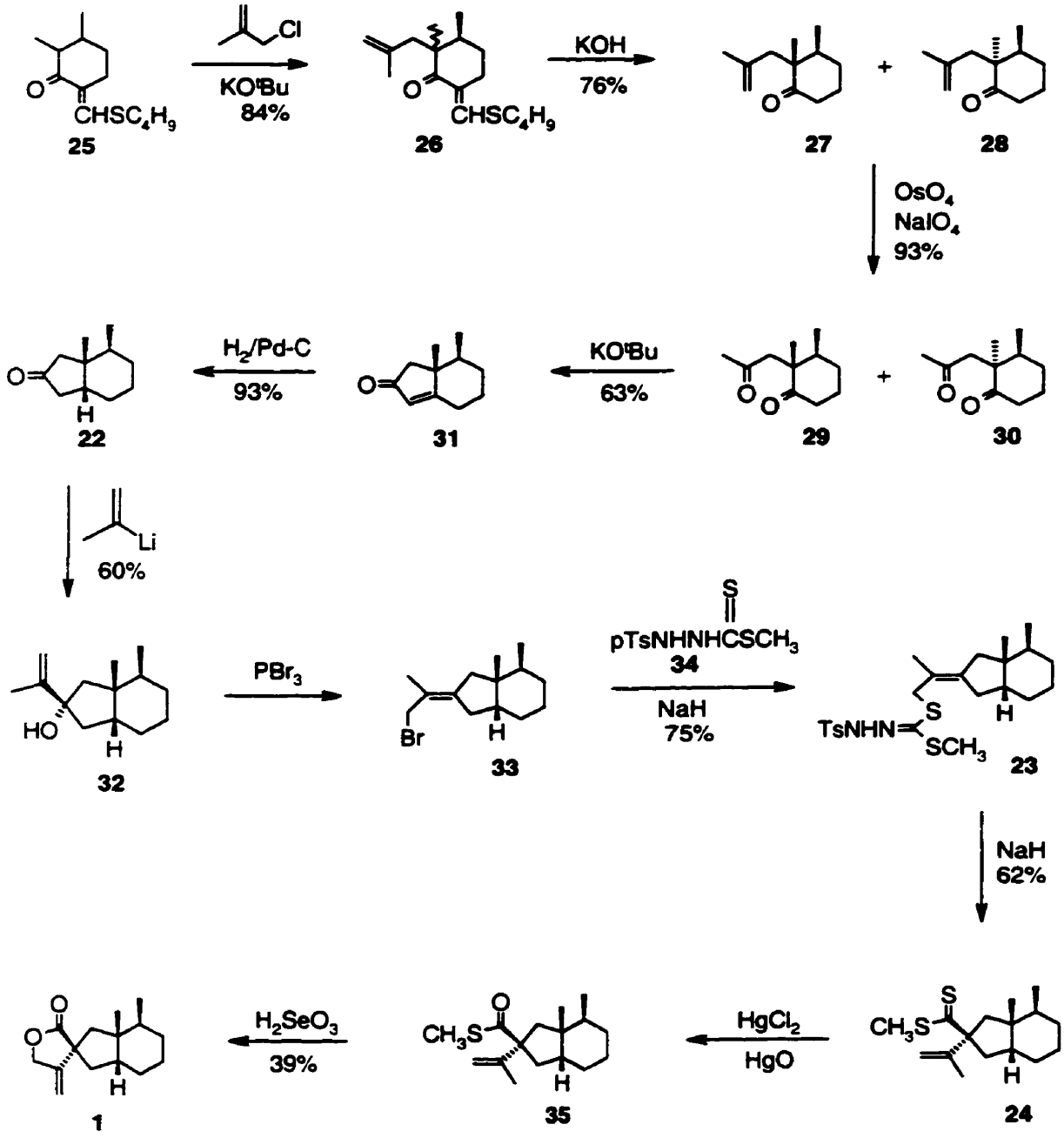
The first total synthesis of bakkenolide-A was completed by Evans and coworkers in 1973.[26a] Their general approach, as outlined in Scheme 2, required the construction of



Scheme 2. Evans' General Approach

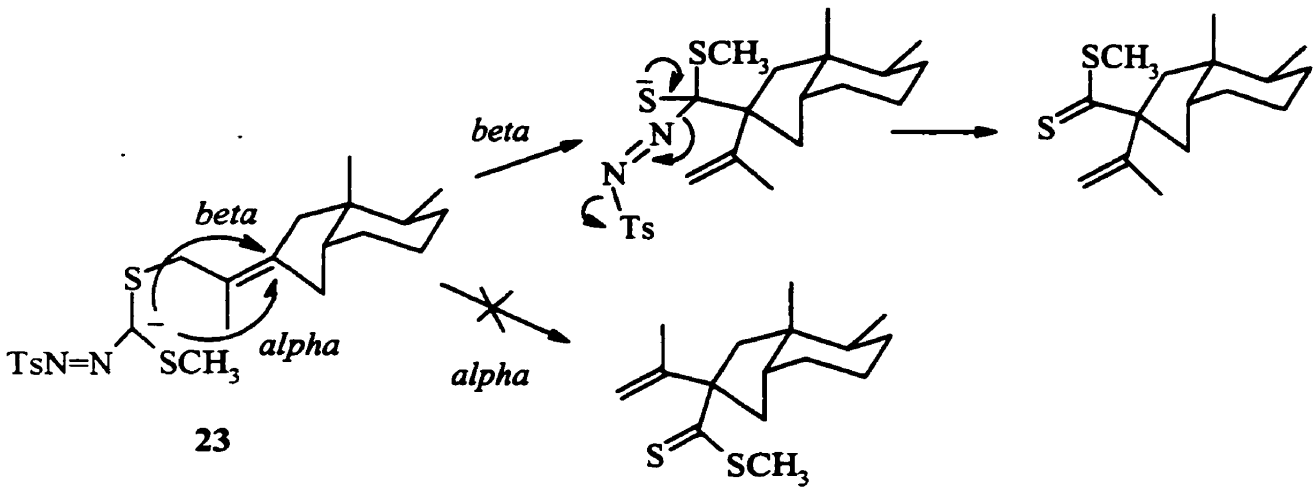
hydrindanone **22** followed by stereospecific elaboration of the spiro lactone ring. The synthesis centered upon the creation of the quaternary pre-spiro center in **24** via a highly stereoselective [2,3]-sigmatropic rearrangement of the anion derived from **23**.

The synthesis (Scheme 3) began with the alkylation of butylthiomethylene ketone **25** with 2-methylallyl chloride, producing the diastereomeric ketones **26** in good yield. The two ketones were then treated with aqueous base, removing the thiomethylene group, yielding an epimeric mixture of ketones **27** and **28**. Oxidation of the ketones **27** and **28** with osmium tetroxide - sodium metaperiodate afforded the corresponding diketones **29** and **30**, which were separated by chromatography on silica gel. Successive aldol ring closure of diketone **29** to hydrindenone **31** and stereoselective catalytic hydrogenation to the desired *cis*-fused hydrindanone **22** proceeded in good yield. Treatment of **22** with isopropenyllithum afforded a 60% yield of epimeric alcohols (9:1), of which **32** was the major isomer. Conversion of **32** to the rearranged allylic bromide **33** was readily accomplished with phosphorus tribromide. The unstable allylic bromide was converted to the carbazate **23** upon treatment with the sodium salt of *p*-toluenesulfonyl-*s*-methylcarbazate (**34**). The carbazate **23** then underwent a base-induced [2,3]-sigmatropic rearrangement, providing the dithioester **24**. Hydrolysis of **24** to produce the thioester **35** was followed by oxidation with selenious acid, resulting in the formation of a transient allylic alcohol, which spontaneously cyclized to afford bakkenolide-A (**1**) in 39% yield.



Scheme 3. Evans' Synthesis of (±)-Bakkenolide-A

The [2,3]-sigmatropic rearrangement (Scheme 4) proved to be highly stereoselective and the authors reported no detection of any isomers. The authors suggested that this was due to the topography of the *cis* fused ring system in compound **23**, where the rearrangement occurred via the less hindered convex face of the hydrindane (β attack) as opposed to the more hindered concave face (α attack).



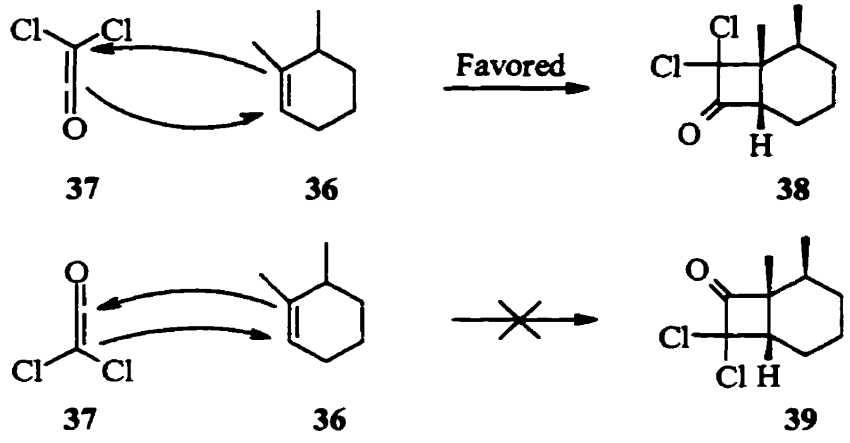
23

Scheme 4. Evans' Key Step

The disadvantages to this approach are that it is lengthy (13 steps), the starting material (**25**) is not readily available, and it gives a low overall yield (1.5 %) of bakkenolide-A. As well, it is not amenable to synthesizing other members of the bakkenolide family, or novel analogues, as this would involve carrying out the entire linear sequence with a modified starting material.

1.2.2 Greene's Synthesis

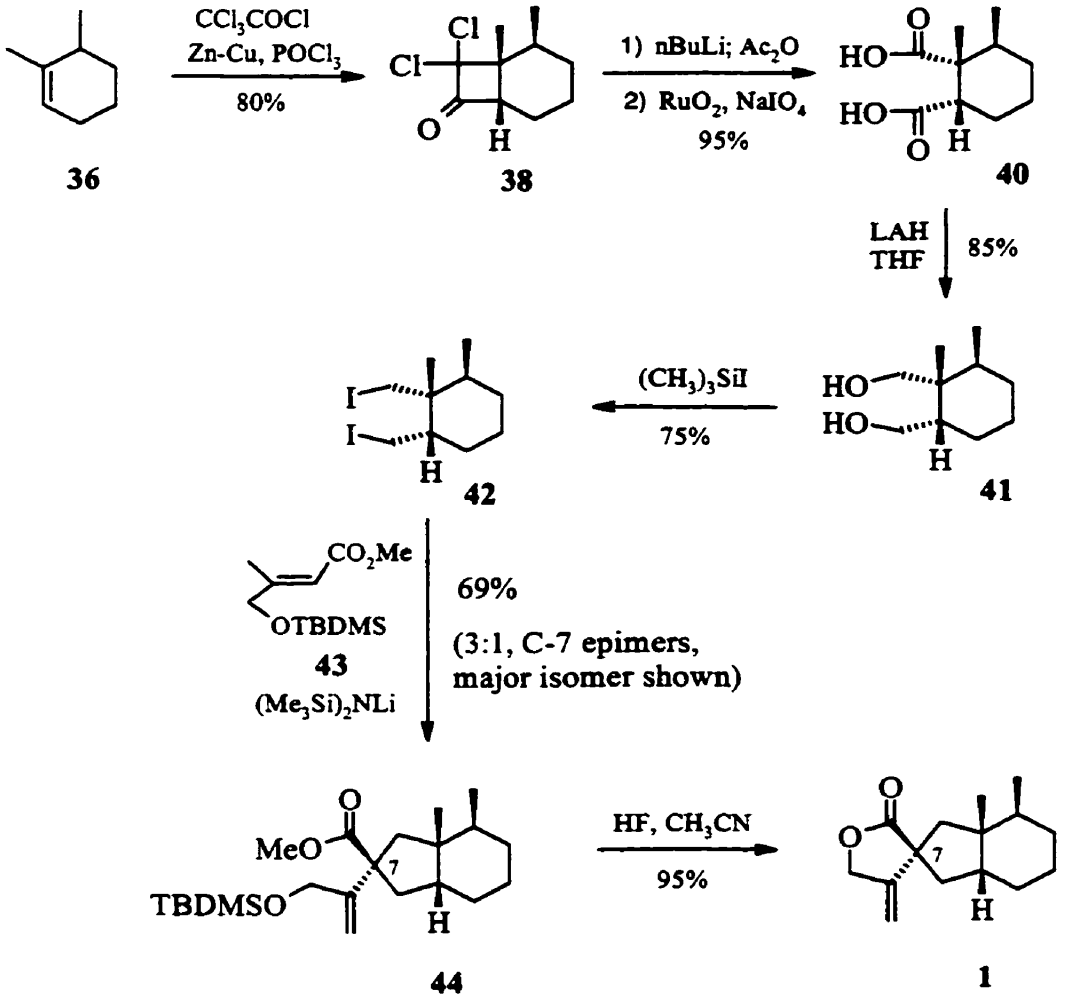
In 1985,[27] Greene and coworkers became the second group to successfully complete a total synthesis of (±)-bakkenolide-A. Their approach began with 1,6-dimethylcyclohexene (**36**), which underwent a [2+2] cycloaddition with dichloroketene (**37**) to selectively afford the desired α,α-dichlorocyclobutanone **38** in 80% yield. The high degree of regioselectivity in this cycloaddition reaction (Scheme 5) reflects the known preference[29] for introduction of the carbonyl group at the less substituted olefinic carbon atom. The authors mentioned that the transition state leading to **39** is stereoelectronically, and/or sterically much less favorable than that which produces **38**.[27]



Scheme 5. Greene's Cycloaddition Step

The one-pot conversion of dichlorocyclobutanone **38** to the succinic acid derivative **40** was accomplished in 95% yield through sequential treatment of **38** with *n*-butyllithium (to afford the α-chloro enolate), acetic anhydride (to form the corresponding enol acetate), and ruthenium(IV) oxide-sodium periodate (Scheme 6). The diacid **40** was

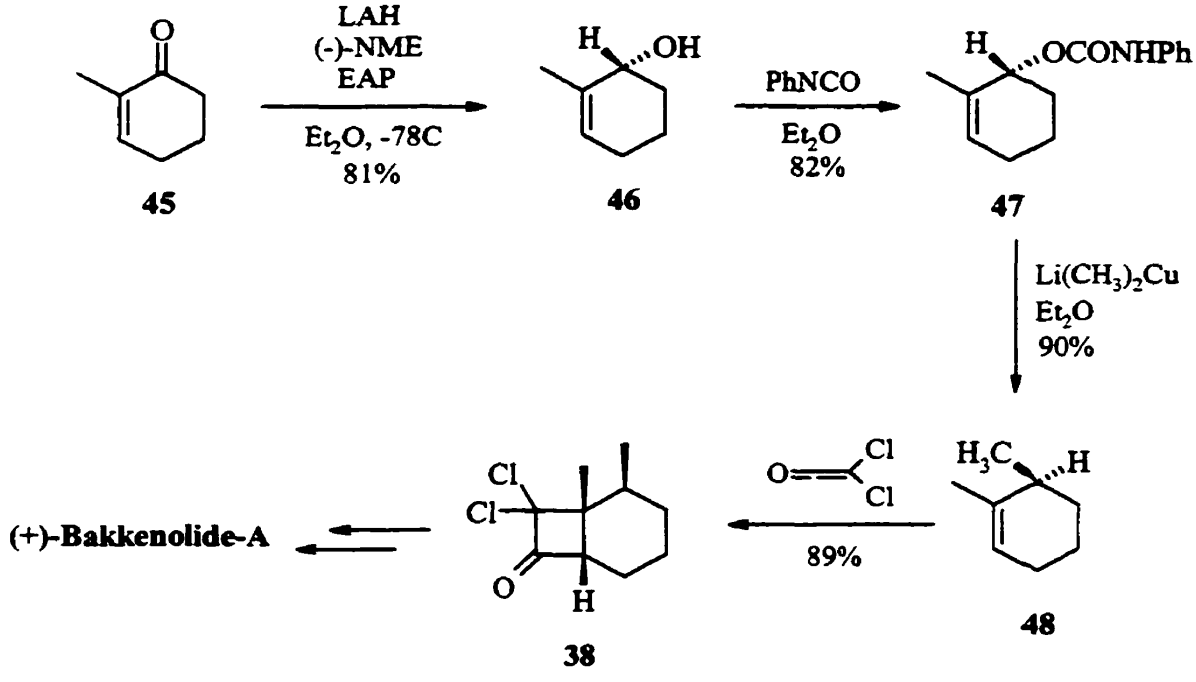
reduced to the diol **41** with lithium aluminum hydride, and then converted to the diiodide **42** through prolonged exposure to trimethylsilyl iodide in chloroform. Reaction of the diiodide with α,β-unsaturated ester **43** in the presence of two equivalents of base stereoselectively (3:1) provided **44**. Deprotection of the t-butyldimethylsilyl ether **44** produced the corresponding alcohol, which spontaneously cyclized to afford bakkenolide-A (**1**).



Scheme 6. Greene's (±)-Bakkenolide-A Synthesis

1.2.2.1 Greene's Enantioselective Modification

Three years later, Greene *et al.* enantioselectively modified[30] their racemic synthesis to provide the natural enantiomer (+)-bakkenolide-A. This was the first enantiocontrolled total synthesis of any of the natural bakkanes (Scheme 7).



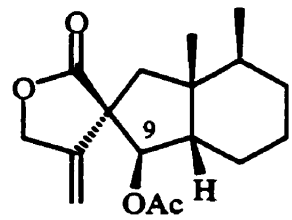
Scheme 7. Greene's Enantioselective Synthesis of (+)-Bakkenolide-A

The starting material, 2-methyl-2-cyclohexene-1-one (**45**), was asymmetrically reduced with lithium aluminum hydride modified with (-)-N-methylephedrine (NME) and 2-(ethylamino)pyridine (EAP, 1:2:2, 4 eq) to give (R)-2-methyl-2-cyclohexen-1-ol (**46**) in 81% yield and 98% ee. The N-phenylcarbamate derivative **47** was exposed to 3 eq of lithium dimethylcuprate to provide (S)-1,6-dimethyl-1-cyclohexene (**48**), with

inversion of configuration. Cycloaddition of **48** with dichloroketene proceeded stereo- and regioselectively. The transformation of the cycloadduct **38** to native bakkenolide-A paralleled Greene's racemic synthetic approach.

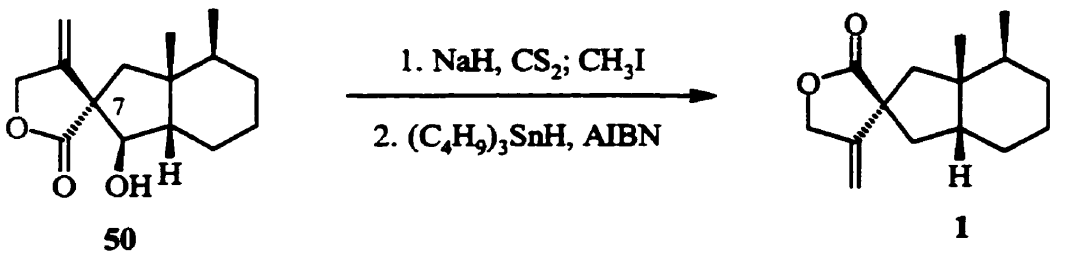
1.2.2.2 Greene's Fortuitous Synthesis

In their recently reported[31] synthesis of 9β-acetoxybakkenolide-A (**49**), Greene and coworkers unintentionally prepared bakkenolide-A while trying to elucidate the stereochemistry at C-9 of 7-epi-9β-hydroxybakkenolide-A (**50**).



49

Since NOSEY experiments proved inconclusive, the C-9 hydroxyl group was removed for the purpose of defining the stereochemistry at C-7 through correlation with bakkenolide-A. In an attempt to remove the hydroxyl group via its xanthate, the stereochemistry of the spirocenter was inverted due to an unforeseen retroaldol-aldol reaction that occurred during xanthate formation, which generated the natural configuration at the C-7 diastereogenic center (Scheme 8).



50 1

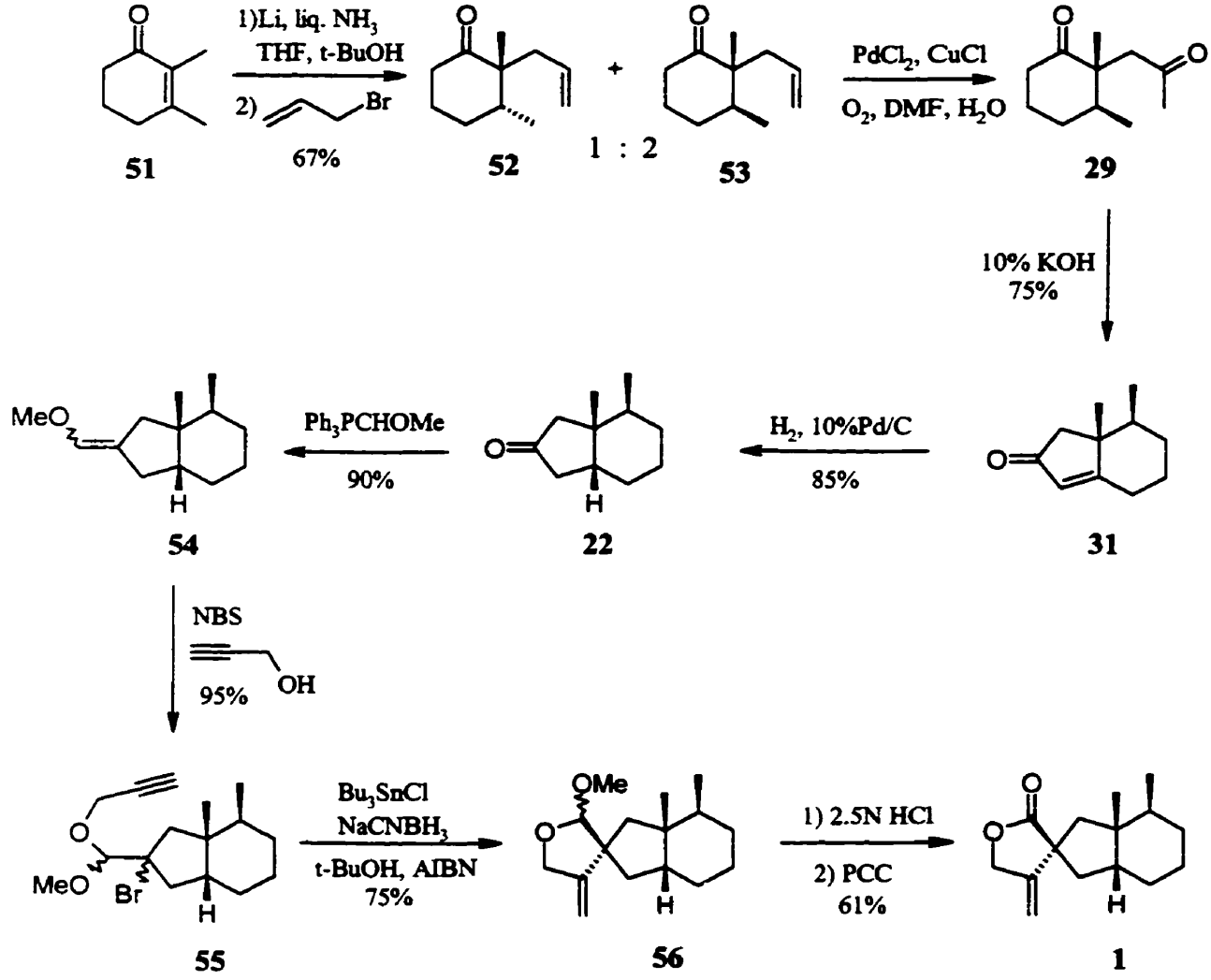
Scheme 8. A Fortuitous Synthesis of Bakkenolide-A

While Greene's approach as shown in Scheme 6 is concise (reported to be 6 steps in 23.8% overall yield) and can be applied to the synthesis of other bakkanes, the silyl ether starting material **43** is not readily available and must also be prepared (in 4 steps, 11% overall yield) from dimethylacrylic acid.

1.2.3 Srikrishna's Synthesis

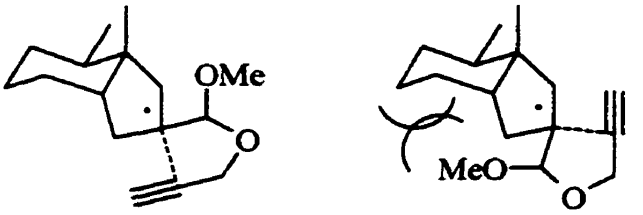
In 1994,[28] the third total synthesis of (±)-bakkenolide-A was reported by Srikrishna and coworkers (Scheme 9). This approach employed a radical cyclization to elaborate the spiro center. The synthesis began with 2,3-dimethyl-2-cyclohexenone (**51**), which was reductively alkylated to give a 1:2 ratio of allylated products **52** and **53**, respectively. After separation by column chromatography, the major product **53** was oxidized under Wacker conditions to furnish the 1,4-diketone **29**. Intramolecular aldol condensation of the dione **29**, followed by catalytic hydrogenation of the resultant cyclopentenone **31**, afforded the desired hydrindanone **22** with the appropriate *cis* ring-fusion and the required *cis* methyl groups. This hydrindanone **22** was the same key intermediate that had been employed in the Evans synthesis. A Wittig reaction produced

enol ether **54**, which was converted into the propargylic bromoacetal **55** by exposure to N-bromosuccinimide and propargyl alcohol. Radical ring-closure of the bromoacetal **55**, using *in situ*-generated catalytic tri-n-butyltin hydride and azobis(isobutyronitrile) (AIBN), furnished the tricyclic product **56** with the correct stereochemistry at the spiro center. The spiro acetal **56** was then hydrolyzed to the corresponding lactol and subsequently oxidized to complete the synthesis of bakkenolide-A (**1**).



Scheme 9. Srikrishna's Synthesis of (±)-Bakkenolide-A

The high degree of stereoselectivity of the radical cyclization was explained by examining the two possible transition states (Figure 2). The cyclization of the less crowded *endo* radical intermediate **57** leads to the desired stereochemistry at the spiro center, while the more crowded *exo* radical intermediate **58** leads to the undesired C-7 epimer.



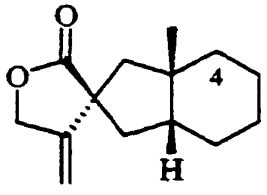
57 **58**

Figure 2. Srikrishna's Radical Cyclization

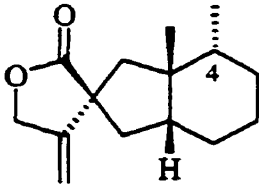
Srikishna's synthesis exhibits a novel stereospecific radical cyclization for its key step and is relatively concise (8 steps, 7.7% overall yield). However, the starting material (**51**) is not readily available and needs to be prepared. Moreover, the synthesis is linear and so to prepare analogues, modified starting materials would have to be used and carried through the entire reaction sequence in each case. Finally, the use of diketone **29** and its conversion into the key hydrindanone intermediate **22** was by the same sequence reported earlier by Evans.

1.3 Synthesis of Other Bakkanes

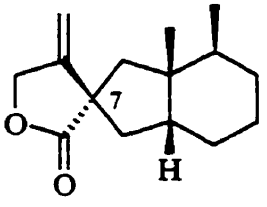
Preparations of homogynolide-A[10] (**13**), homogynolide-B[11] (**14**), palmosalide-C[12] (**15**), and norbakkenolide[32] (**59**) have been reported. Syntheses of 4-epi[33] (**60**), 7-epi[34] (**61**), and 4,7-diepibakkenolide-A[33] (**62**) have also been published.



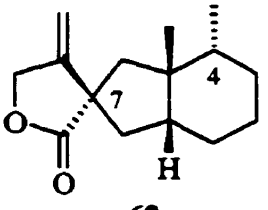
59



60



61



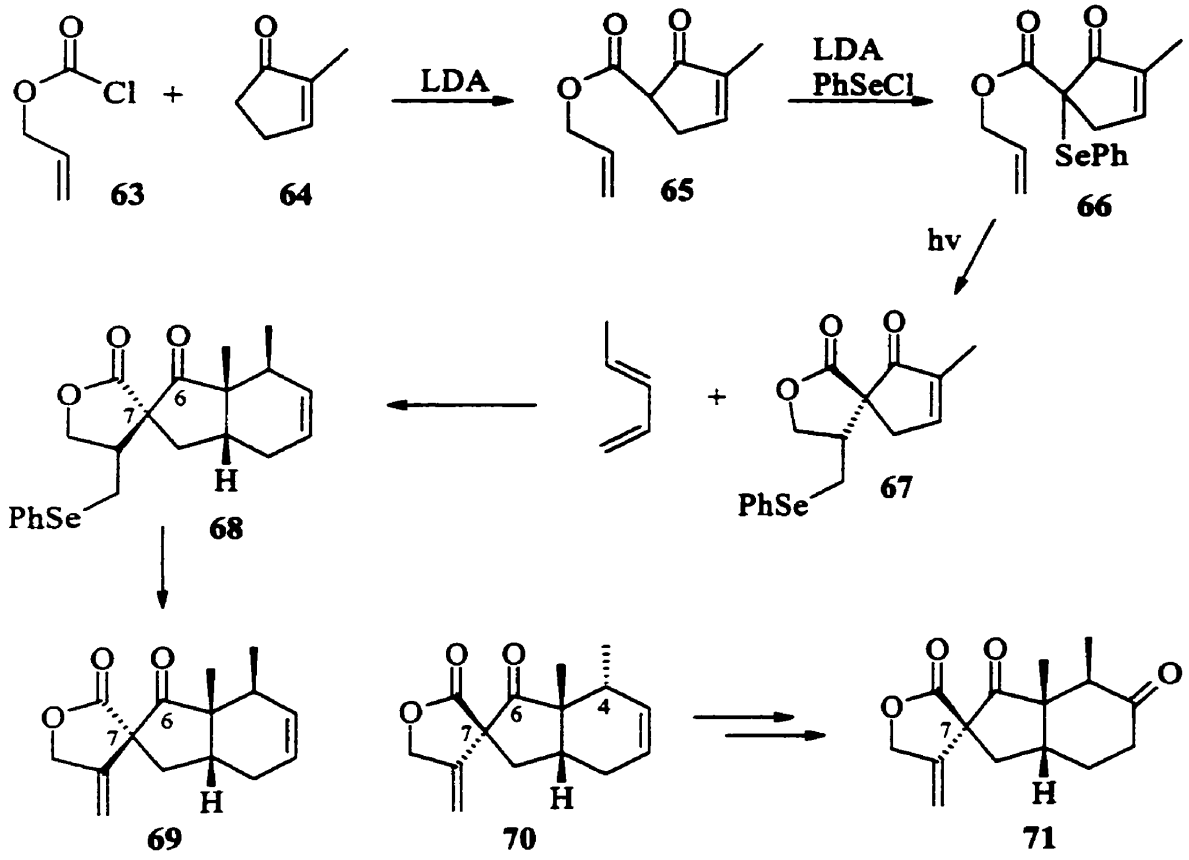
62

1.4 Back and Gladstone's Approach to the Bakkenolides

In 1996, Back and Gladstone reported[35] the synthesis of several novel tricyclic β-methylene spiro lactones related to the bakkenolides. Their approach utilized radical cyclization chemistry to generate the spiro lactone moiety in tandem with high pressure intermolecular Diels-Alder chemistry for annulation of the A ring. Variations of this approach were attempted with the intent of synthesizing bakkenolide-A.[36] One of these approaches is illustrated in Scheme 10.

The kinetic enolate of 2-methylcyclopent-2-enone (**64**) was acylated with allyl chloroformate (**63**) to provide β-ketoester **65** and then selenenylated with benzeneselenenyl chloride to furnish **66**. Photolysis of the phenylseleno β-keto ester **66** gave the spiro lactone **67** by radical cyclization via group transfer of the phenylseleno moiety. Diels-Alder cycloaddition of **67** with piperylene gave cycloadduct **68** as the principal stereoisomer. Selenoxide elimination of **68** produced **69**, a C-6 oxo, C-7 epi, and unsaturated derivative of bakkenolide-A. This approach[36] also afforded **71**, from the minor C-4 epimer **70**, after oxygenation and epimerization of the C-4 methyl group to the equatorial position. Although **71** had the correct relative stereochemistry at all stereocenters, it also contained two extraneous keto groups, one of which could not be removed.

While this approach was novel, it had some major failings as a method to synthesize bakkenolide-A. First of all, the Diels-Alder reaction required extremely high pressures (10000 atm) to coerce the [4+2] cycloaddition to go to completion. Secondly, when the reaction did go to completion, the desired C-7 diastereomer was a relatively minor product. Finally, deoxygenation of the C-6 ketone could not be achieved under a variety of conditions.[36]



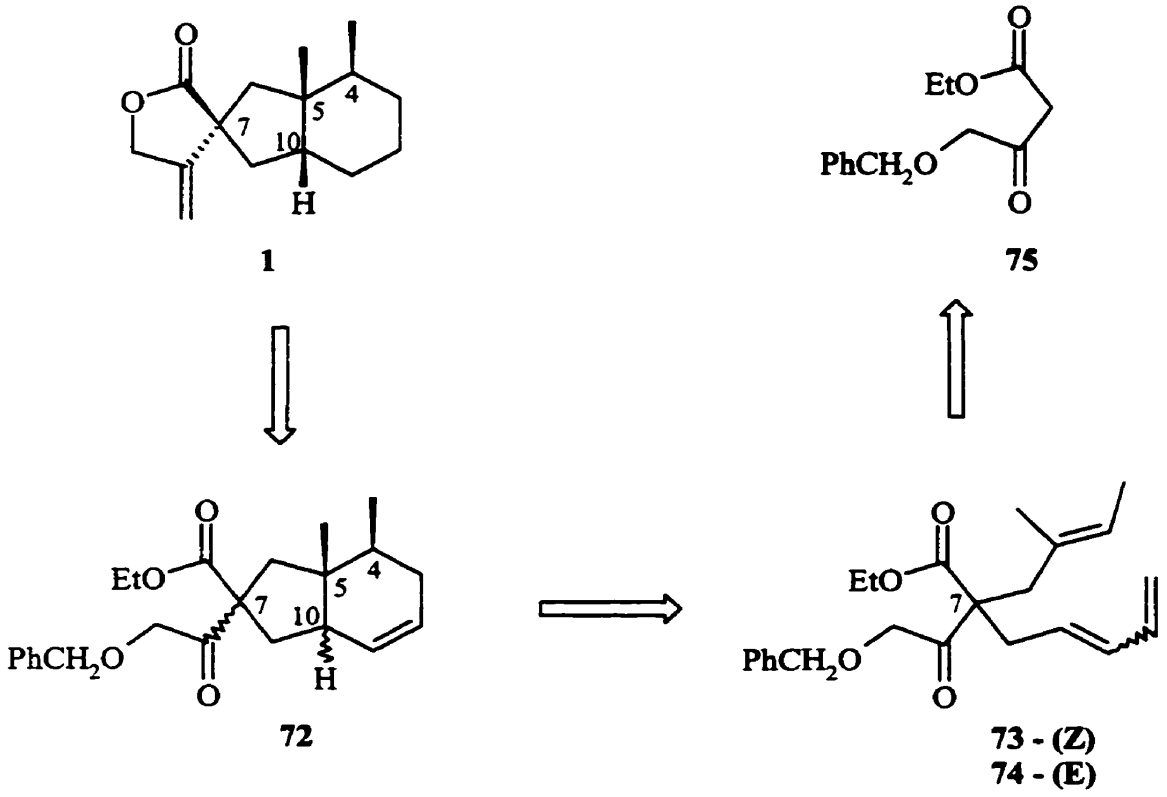
Scheme 10. Back and Gladstone's Approach to the Bakkenolides

1.5 A New Approach to (±)-Bakkenolide-A

The failure of the Back-Gladstone approach prompted the investigation of a different route to **1**, which is the subject of the remainder of this Thesis. Our new approach to bakkenolide-A also employs Diels-Alder chemistry. A [4+2] intramolecular cycloaddition was intended to construct simultaneously the A and B rings and selectively establish the appropriate stereochemistry for all four of its stereocenters. Our concise,

synthetic approach is based on inexpensive and easily prepared starting materials and is illustrated retrosynthetically in Scheme 11.

Our plan was to obtain the target compound **1** from the Diels-Alder adduct **72** by reducing the double bond, removing the benzyl protecting group, inducing lactonization, and then performing a Wittig reaction to convert the ketone to the desired exocyclic double bond. The pre-Diels-Alder triene intermediate, whether *cis* (**73**) or *trans* (**74**), was expected to be easily prepared from the protected keto ester **75** via a pair of alkylations.



Scheme 11. A New Approach to Bakkenolide-A

One related objective of this approach was to determine how the stereochemistry of the triene, whether *cis* (**73**) or *trans* (**74**), affected the relative ratio of diastereomers in the product mixture (**72**). We predicted that the *cis* isomer **73** would be more diastereoselective than its *trans* counterpart **74** in favor of the desired bakkenolide-A framework. In particular, we expected **73** to be more effective than **74** at establishing the desired *cis*-fused topography (see Figure 3).

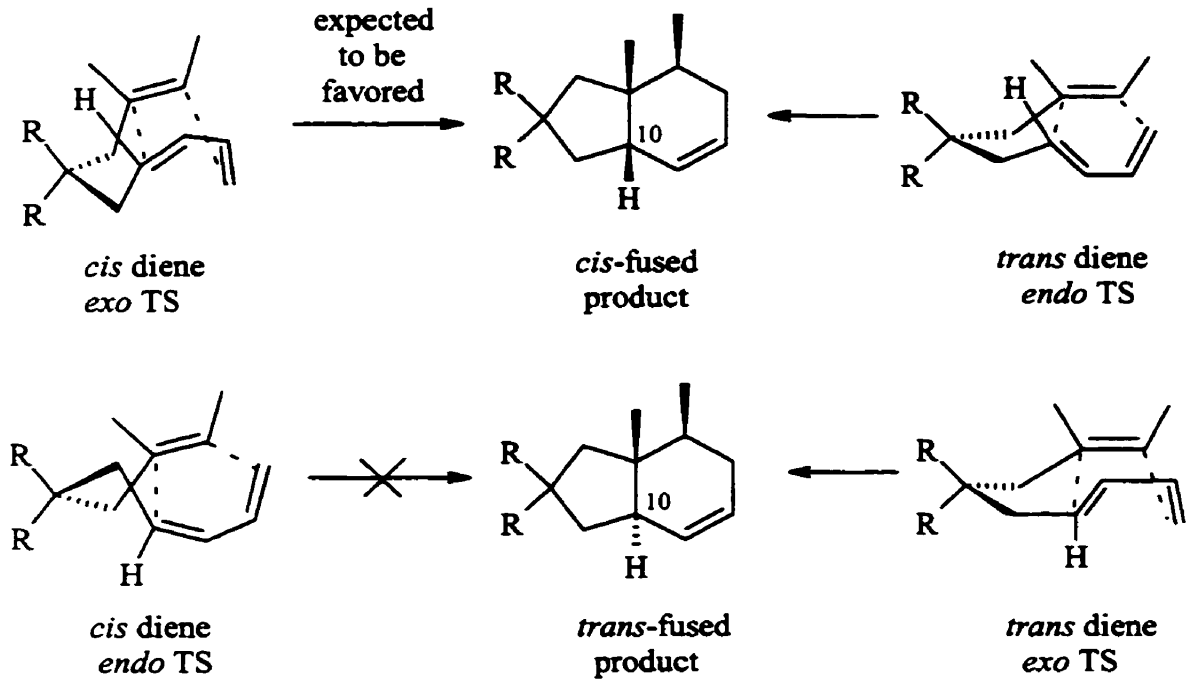


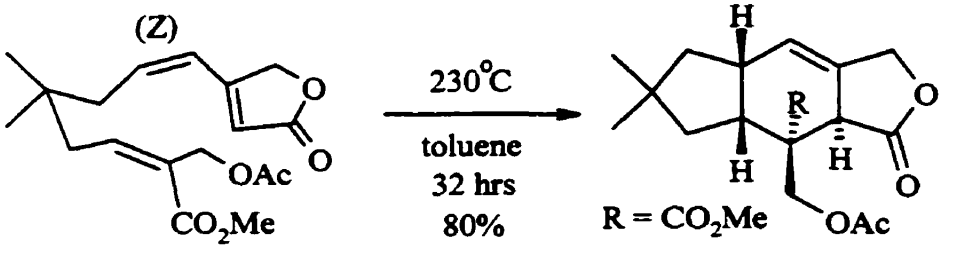
Figure 3. Transition States and the Relative Stereochemistry at C-10.

The terms *endo* and *exo* have been commonly used to describe the orientation of activated diene and dienophile systems with substituents that can enter into secondary orbital interactions. Our system is unactivated and lacks such substituents. Therefore, in order to avoid any confusion surrounding the definitions of *endo* and *exo*, the following

definition is provided. When the interior atoms of the diene and the atom in the tether that is connected to the dienophile are on the opposite sides of the plane defined by the atoms undergoing primary orbital interactions in the transition state, the orientation is called *exo*. Similarly, when they are on the same side of the plane, the orientation is called *endo*.

Generally, *cis* dienes tethered by three carbon atoms to a dienophile tend to cyclize via an *exo* transition state to produce [4.3.0]bicyclo *cis*-fused products. This is because the *endo* transition state, which leads to *trans*-fused products, is too strained.[37,38] *Trans* dienes tethered by three carbon atoms to a dienophile seem to be less predictable in intramolecular Diels-Alder reactions and usually provide a mixture of *cis*- and *trans*-fused products.[37,38]

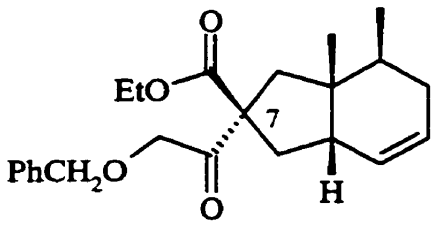
The successful use of (Z)-dienes in intramolecular Diels-Alder reactions to stereoselectively provide *cis*-fused products has been reported.[39] In one example, Boeckman and Alessi[39c] reported that the reaction of *cis* diene **76**, connected by three carbon atoms to its dienophile, provides the *cis*-fused product **77** in 80% yield. In addition to the respectable yield, the *trans*-fused product was not observed (Scheme 12). This and other similar precedents[39] led us to expect that our system would do likewise.



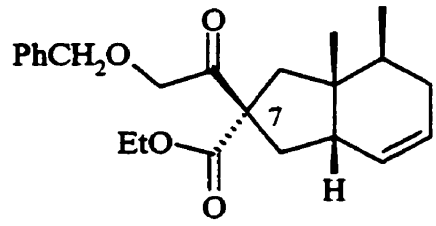
76 **77**

Scheme 12.

The stereospecific nature of the Diels-Alder reaction assured us that the relative stereochemistry of the *cis* methyl groups in the dienophile of **73** and **74** would be preserved at C-4 and C-5 in the mixture of cycloadducts **72**. Discerning what stereoselectivity would likely be observed at the C-7 quaternary center during the Diels-Alder reaction was not as obvious. Therefore, *ab initio* molecular modeling experiments were utilized, as will be discussed in more detail in Chapter Two, to determine whether the Diels-Alder adduct **78** with the appropriate C-7 orientation, would be selected over its epimer **79**.

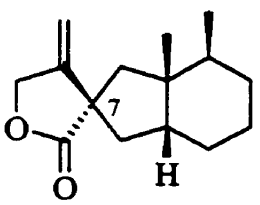


78

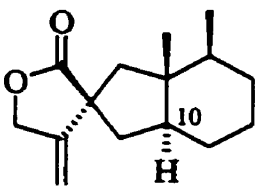


79

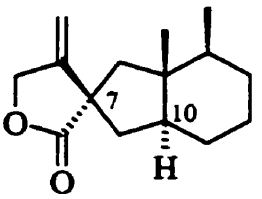
Although the synthesis of bakkenolide-A was the principal objective of the Thesis, it was also considered of interest to isolate and characterize any novel stereoisomers of **1** and to subject them for biological testing. The C-7 spiro epimer (**61**) was reported for the first time while this work was in progress.[34] However, 10-epibakkenolide-A (**80**) and 7,10-diepibakkenolide-A (**81**) would be new additions to the bakkenolide family, with potentially useful biological properties.



61



80



81

Detailed discussion of our synthesis of bakkenolide-A, including the results from our molecular modeling studies and a thorough analysis of the key intramolecular Diels-Alder step will be given in Chapter Two.

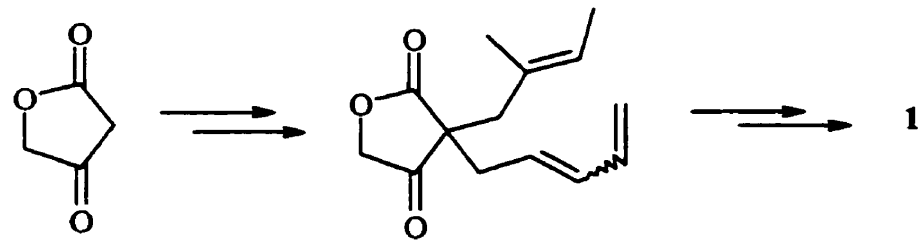
Chapter Two

Synthesis of (±)-Bakkenolide-A

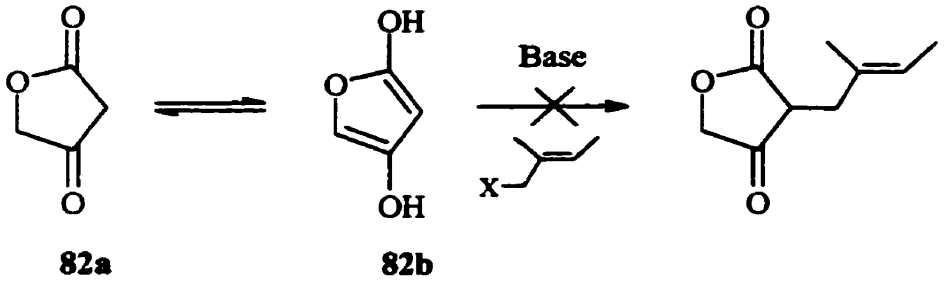
Using the approach outlined in Chapter One, our laboratory became the fourth group to successfully complete a total synthesis of (±)-bakkenolide-A (**1**). This chapter explicates each step employed in this synthesis, including a discussion of how some of these reactions were developed and optimized.

2.1 Attempted Alkylation of Tetronic Acid

Originally, an attempt was made to dialkylate tetronic acid (**82**) and establish the pre-Diels-Alder intermediate **83** with the lactone intact (Scheme 13). However, this idea was short-lived because tetronic acid could not be C-alkylated[40] due to the aromatic stabilization of the tautomer **82b** (Scheme 14). Thus, an alternative starting material for our synthesis was prepared.



Scheme 13.



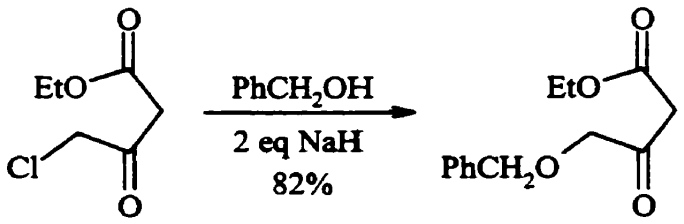
82a **82b**

Scheme 14.

2.2 Preparation of Ethyl 4-Benzyloxyacetoacetate (75)

Rather than alkylate an intact lactone moiety, it was decided to alkylate a lactone synthon, ethyl 4-benzyloxyacetoacetate (**75**), which could be converted to the butyrolactone later in the synthesis.

The β-keto ester **75** was easily synthesized, using a known procedure,[41] from commercially available ethyl 4-chloroacetoacetate (**84**) (Scheme 15). Two equivalents of base were required in this preparation. One equivalent was needed for generation of the enolate, while the second equivalent of base generated the benzyloxy anion that subsequently displaced the chloride from **84**.

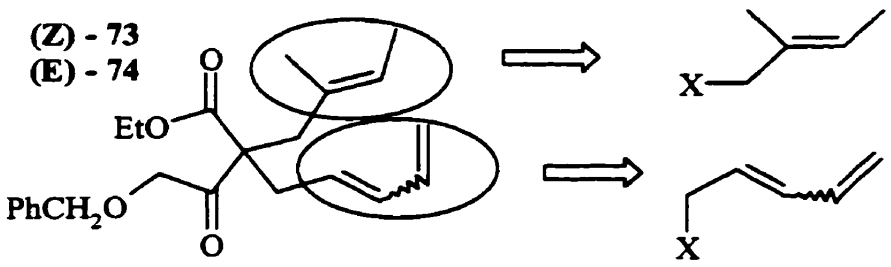


84 **75**

Scheme 15.

2.3 Preparation of Dienyl and Tiglyl Starting Materials

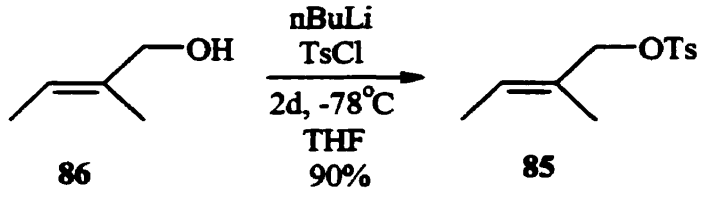
The requisite dienes and dienophiles in the pre-Diels-Alder intermediates **73** and **74** originated from pentadienyl and 2-methyl-2-butenyl (or tiglyl) starting materials (Scheme 16). This section explains how these starting materials were selected and synthesized.



Scheme 16.

2.3.1 Preparation of Tiglyl Tosylate (85)

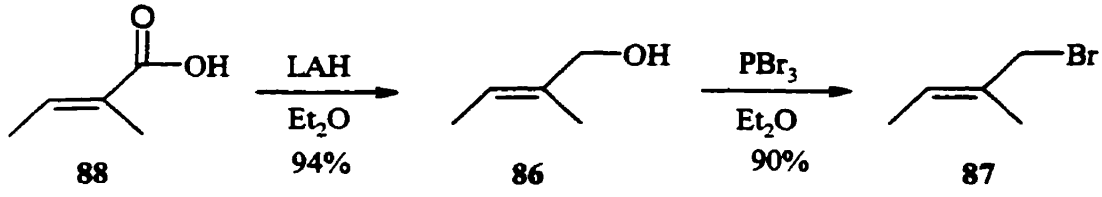
Initially, tiglyl tosylate (**85**) was investigated as a possible reagent for introducing the dienophile component into the keto ester **75**. Tosylate **85** was synthesized using the procedure of Kurth and Decker,[42] where n-butyllithium was employed to generate the alkoxide of tiglyl alcohol (**86**), which was then treated with tosyl chloride (Scheme 17). The allylic tosylate **85** is relatively unstable and decomposes in a few hours at room temperature or after a few days if stored in the freezer. For this reason, tiglyl bromide (**87**) was synthesized and found to be more stable and more practical than **85** for the purpose at hand.



Scheme 17. The Preparation of Tiglyl Tosylate

2.3.2 Preparation of Tiglyl Bromide (87)

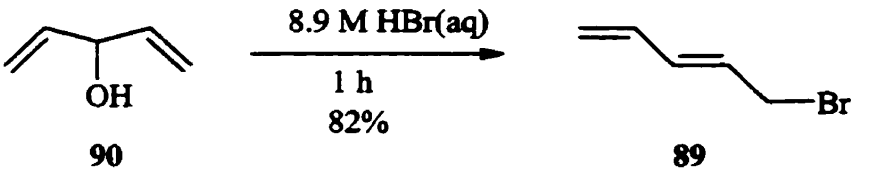
Tiglyl bromide (**87**) was straightforwardly prepared from commercially available tiglic acid (**88**). Reduction of **88** to the alcohol **86**, followed by bromination, provided the desired bromide **87** in 85% overall yield (Scheme 18).



Scheme 18. The Preparation of Tiglyl Bromide (**87**)

The reduction of tiglic acid was accomplished by using lithium aluminum hydride[43] as the reducing agent and provided tiglyl alcohol (**86**) in 94% yield. The alcohol **86** was then converted in 90% yield to tiglyl bromide (**87**) by phosphorus tribromide, using a procedure by Crumrine *et al.*[44] As mentioned earlier, tiglyl bromide (**87**) is considerably more stable than tiglyl tosylate (**85**), and can be stored for several months in the freezer.

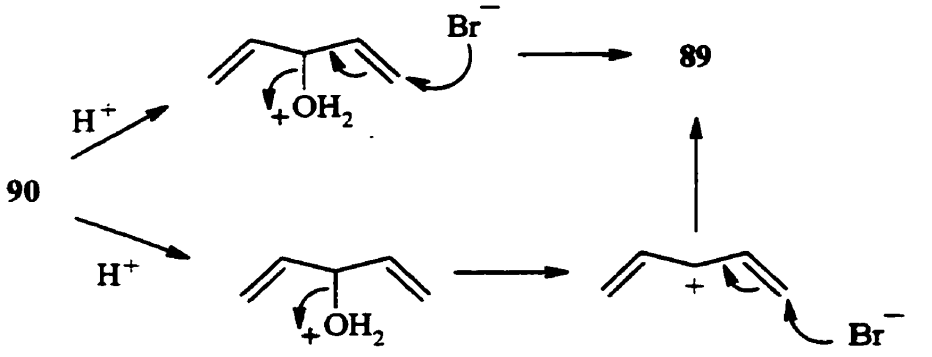
2.3.3 Preparation of (E)-5-Bromo-1,3-pentadiene (89)



90 **89**

Scheme 19.

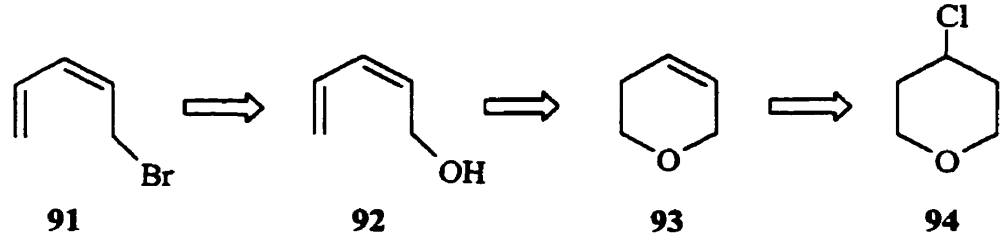
The *trans*-dienyl bromide **89**, which is required for the synthesis of **74**, was prepared using the procedure of Prevost *et al.*[45] Concentrated hydrobromic acid was added to divinyl carbinol (**90**) and the desired bromide **89** was furnished in 82% yield (Scheme 19). The mechanism of this reaction likely involves protonation of alcohol **90**, followed by a nucleophilic attack by the bromide ion toward either of the terminal vinylic carbon atoms via either of the two possible pathways illustrated in Scheme 20.



Scheme 20.

2.3.4 Synthesis of (Z)-5-Bromo-1,3-pentadiene (91)

Unlike the preparations of **87** and **89**, the synthesis of (Z)-5-bromo-1,3-pentadiene (**91**), which is required for the construction of **73**, was far more challenging. It was somewhat of a surprise to discover that there was no practical procedure in the literature for its preparation. The lone reference to **91** described it as the minor product of a 1 to 1.4 mixture with the corresponding (E) isomer **89**.[47] Since it was our desire to efficiently synthesize **91** stereoselectively, we developed the following procedure, shown retrosynthetically in Scheme 21.

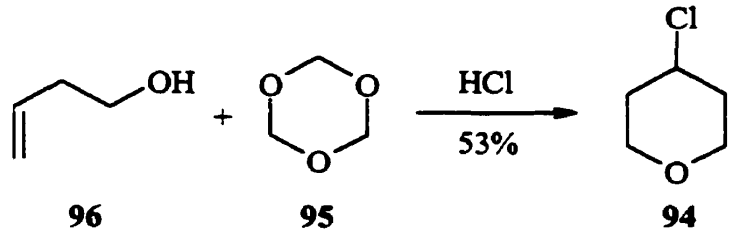


Scheme 21.

The desired *cis*-dienyl bromide **91** was prepared from the *cis*-dienyl alcohol **92** via bromination with phosphorus tribromide. Alcohol **92** was furnished utilizing chemistry developed by Schlosser *et al.*[48] from the cyclic allyl ether **93**, such that the *cis* configuration of the double bond of **93** is retained in the dienyl product **92**. Dihydropyran **93** was, in turn, prepared via dehydrochlorination of 4-chlorotetrahydropyran (**94**).

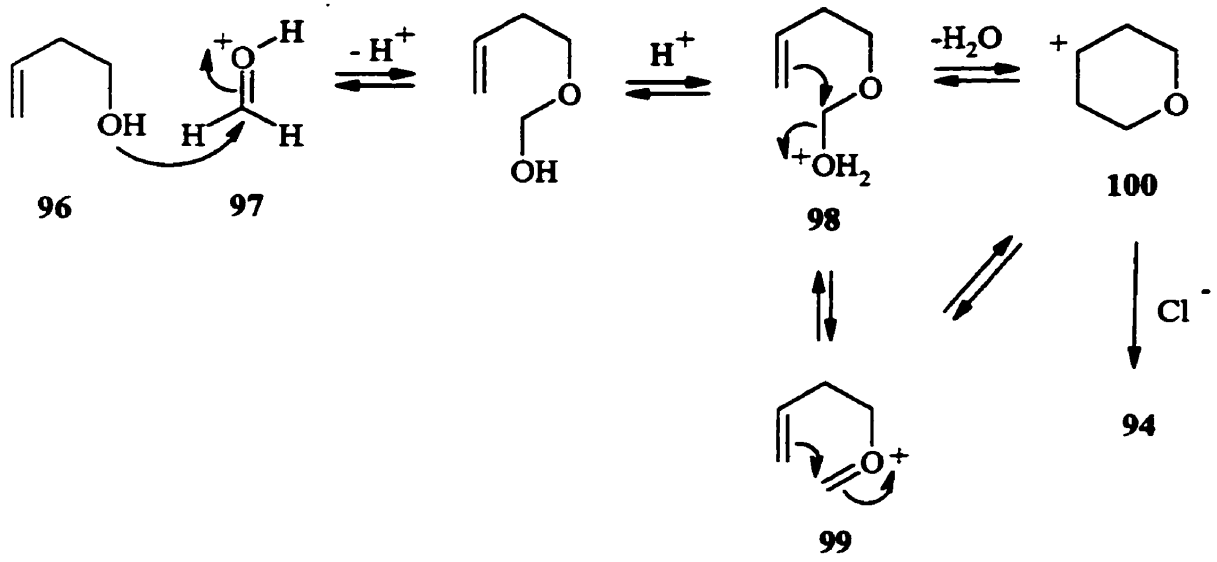
2.3.4.1 Preparation of 4-Chlorotetrahydropyran (94)

The first step in the synthesis of **91** required the preparation of 4-chlorotetrahydropyran (**94**). To do so, a literature procedure by Colonge *et al.* was utilized[49] (Scheme 22). Trioxane **95** was dissolved in 3-buten-1-ol (**96**) and hydrogen chloride was then bubbled through the reaction mixture until 1.3 equivalents of the acid had dissolved. The reaction was allowed to stand at room temperature for 16 hours, and the desired 4-chlorotetrahydropyran (**94**) was then isolated in 53% yield.



Scheme 22. Preparation of 4-Chlorotetrahydropyran (**94**)

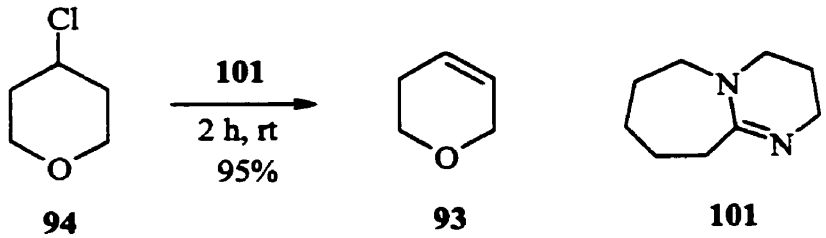
A proposed mechanism for this reaction is illustrated in Scheme 23. With the understanding that trioxane **95** is essentially trimeric formaldehyde, it is possible that the acid protonates formaldehyde in the first step of the mechanism. The nucleophilic hydroxyl group of **96** could then attack the electrophilic carbon atom of **97**, providing a hemiacetal, which upon further protonation would furnish intermediate **98**. A ring closure involving the displacement of water could occur concertedly, or via intermediate **99**, to provide the heterocyclic cation intermediate **100**, which can be quenched by chloride ion to furnish **94**.



Scheme 23. Suggested Mechanism for the Preparation of **94**

2.3.4.2 Preparation of 3,6-dihydro-2*H*-pyran (93)

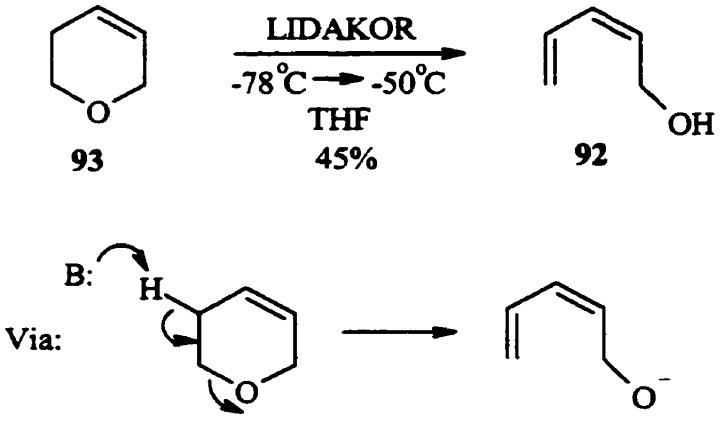
The second step in the synthesis of **91** required the dehydrochlorination of **94** to produce 3,6-2*H*-dihydropyran (**93**). This was accomplished by adding **94** to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (**101**), which acted as the solvent and as the base. The resulting volatile product **93** was distilled directly from the reaction mixture and collected in a receiving flask in 95% yield (Scheme 24).



Scheme 24. The Preparation of **93**

2.3.4.3 Preparation of (Z)-2,4-pentadien-1-ol (92)

The third step towards the synthesis of **91** was the base-induced opening of **93** to the *cis*-dienyl alcohol **92** (Scheme 25). A procedure for this reaction was provided in the literature by Schlosser *et al.*[48] By using a mixture of potassium *t*-butoxide and lithium diisopropylamine (LIDAKOR), cyclic allyl ether **93** was converted to the desired *cis*-dienyl alcohol **92** via a proposed 1,2 elimination, as shown in Scheme 25.

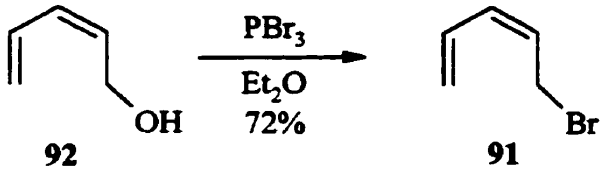


Scheme 25. Preparation of *cis*-Dienyl Alcohol **92**

2.3.4.4 Conversion of 92 to (Z)-5-Bromo-1,3-pentadiene (91)

The final step in the synthesis of (Z)-5-bromo-1,3-pentadiene required the conversion of alcohol **92** to the desired bromide **91**. This was accomplished in 72% yield following a procedure similar to that used by Katzenellenbogen and Crumrine[44] for the preparation of tiglyl bromide (Scheme 26). The product contained less than 5% of the corresponding E-isomer **89**.

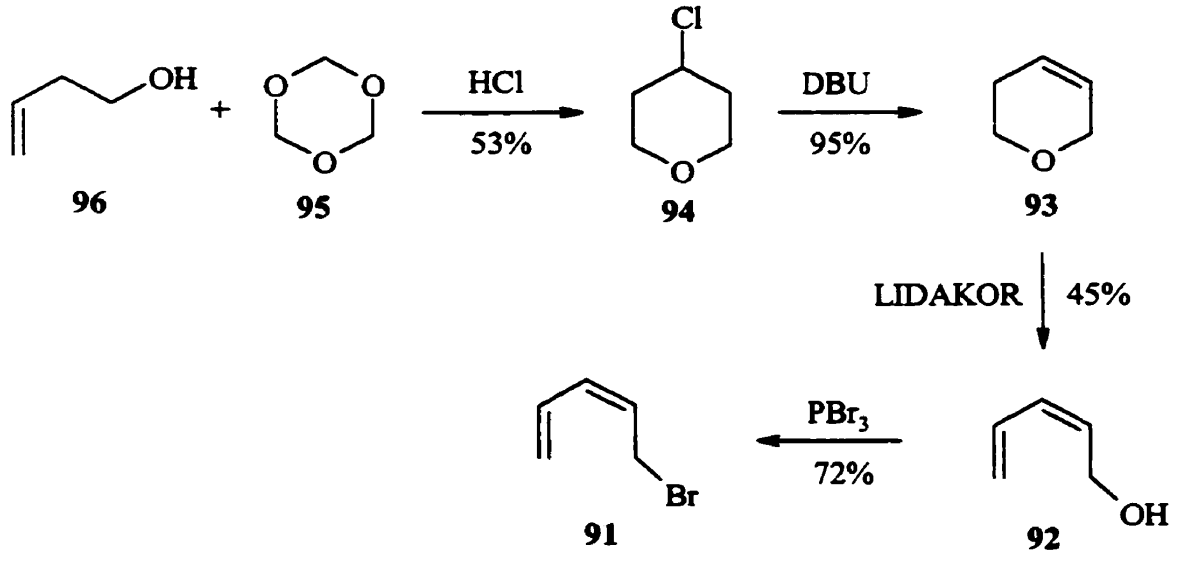
The ^{1}H-NMR spectrum of our synthetic sample agreed with ^{1}H-NMR data of the minor component **91** in the E,Z-mixture of **91** and **89** provided in the literature.[47]



Scheme 26. Bromination of **92**

2.3.4.5 Summary of the Synthesis of (Z)-5-Bromo-1,3-pentadiene (91)

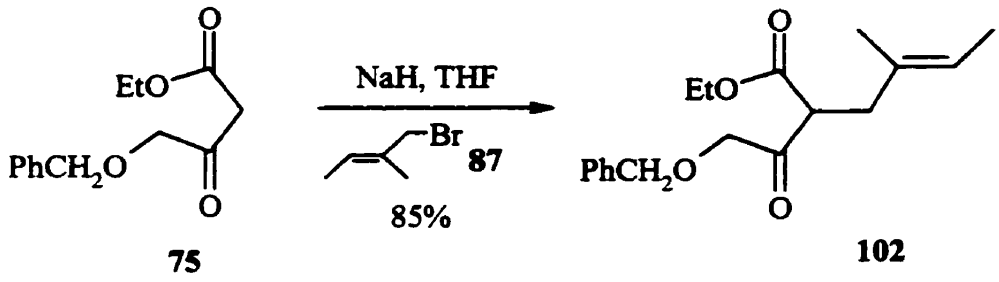
Thus, the synthesis of (Z)-5-Bromo-1,3-pentadiene was efficiently completed in four steps with an overall yield of 17%. The complete synthesis of **91** is illustrated below in Scheme 27.



Scheme 27. Summary of the Synthesis of **91**

2.4 Preparation of the Pre-Diels-Alder Intermediates 73 and 74

A pair of alkylations was utilized to affix the necessary diene and dienophile moieties needed in the construction of the *cis* and *trans* pre-Diels-Alder intermediates (**73** and **74**, respectively). These alkylations were successfully completed using sodium ethoxide as the base in absolute ethanol as the solvent; however the yields for these reactions were later improved using sodium hydride in THF.

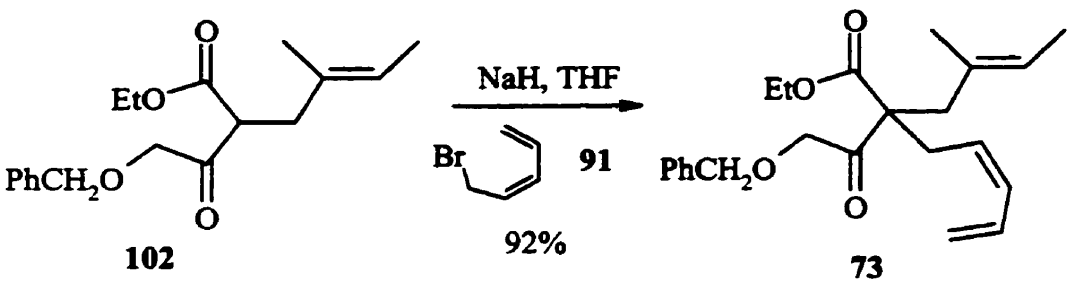


75 **102**

Scheme 28.

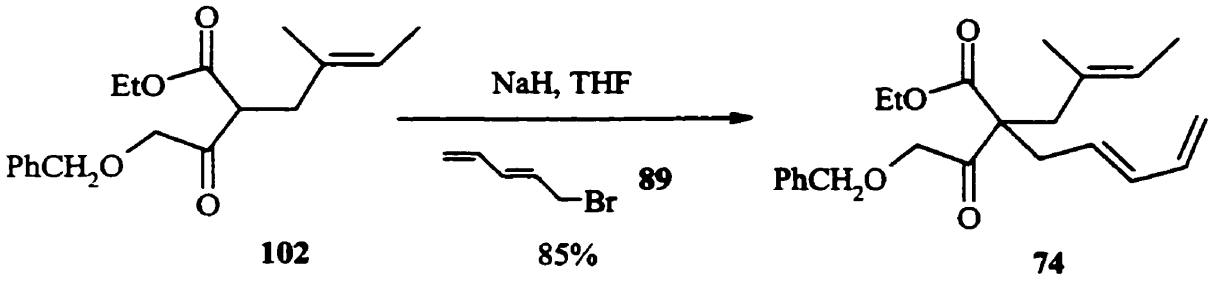
In the first alkylation (Scheme 28) sodium hydride was employed to generate the enolate of **75**, which subsequently attacked bromide **87**, providing the desired mono C-alkylated product **102** in 85% yield. Dialkylation was minimized by diluting **87** in THF prior to its dropwise addition to the reaction mixture.

The *cis*-pre-Diels-Alder intermediate **73** was prepared by following an analogous alkylation procedure that furnished **102**. Sodium hydride was again employed to generate the enolate of **102**, which then displaced bromide ion from **91**, furnishing the dialkylated product **73** in 92% yield (Scheme 29).



Scheme 29.

The *trans*-pre-Diels-Alder intermediate **74** was synthesized by following the same alkylation procedure that furnished **73**. This time, however, the *trans*-dienyl bromide **89**, rather than the *cis* bromide **91**, was added to the enolate of **102**, providing the dialkylated product **74** in 85% yield (Scheme 30).

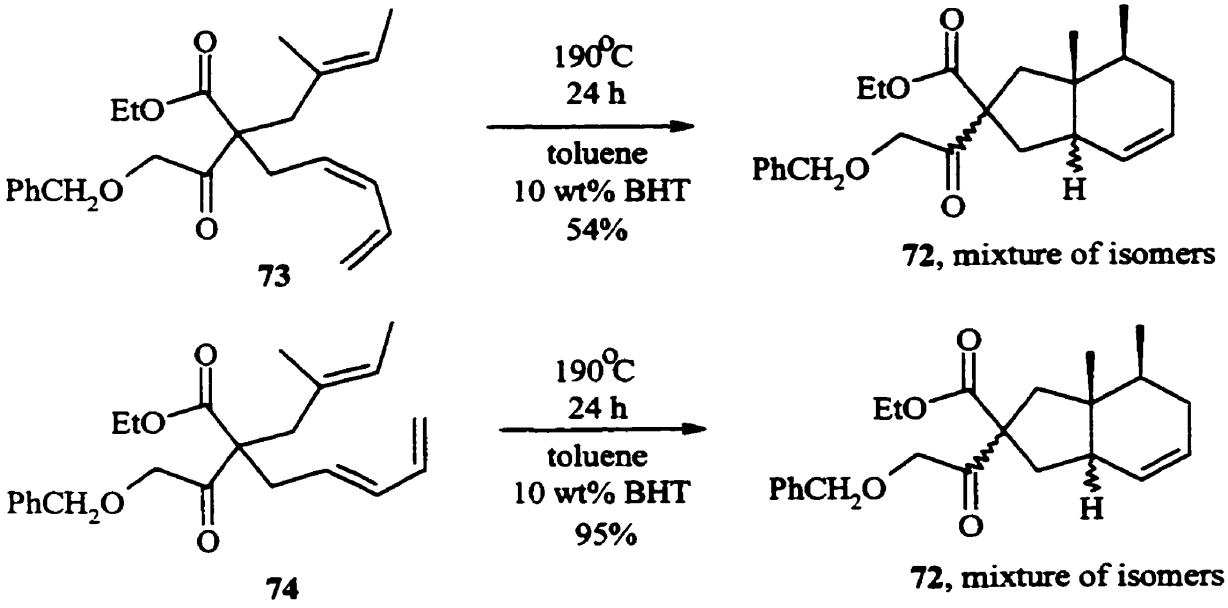


Scheme 30.

The decision to alkylate **75** with tiglyl bromide (**87**) first, and subsequently with *trans*- or *cis*-dienyl bromide (**89** and **91**, respectively) to furnish the pre-Diels-Alder intermediates was made in order to require only one common monoalkylated intermediate. Attempts to reverse this alkylation order were never attempted because of the success with the original approach.

2.5 The Intramolecular Diels-Alder Reaction

Intermediates **73** and **74** were now in hand for the key intramolecular Diels-Alder step. Optimum reaction conditions were determined for the conversion of these intermediates to the desired mixture of cycloadducts **72**, and are summarized in Scheme 31. The yields of the cycloadducts (obtained as a mixture of isomers) were optimized to an excellent 95% when starting with the *trans* intermediate **74**, and a respectable 54% when starting with the *cis* intermediate **73**.



Scheme 31. The Key Intramolecular Diels-Alder Step

2.5.1 Optimization of the Diels-Alder Reaction of *trans*-Diene 74

The results of the optimization efforts for the conversion of the *trans*-diene **74** to **72** are given in Table 1.

Table 1. Optimization of the Diels-Alder Reaction of *trans*-Diene **74**

Entry[a]	Time	Solvent	Temp. (°C)	Yield **72** (%)
1	45 min	None	100	0[b]
2	28 h	Toluene	110	0[c]
3	5.5 h	o-xylene	140	0[c]
4	20 h	Diglyme	162	0[c]
5	24 h	Toluene	260	0[d]
6	24 h	o-xylene	205	38
7	24 h	Toluene	190	70
8	24 h	Toluene	190	95[e]

a - Entries 5-8 were performed in a sealed Parr apparatus b - a clear polymer was formed
c - no reaction d - a black tarry polymer was formed e - 10 wt% BHT was added

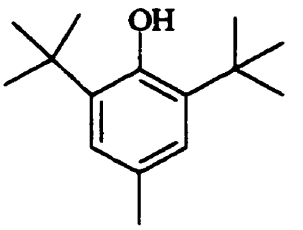
It was observed that the intramolecular Diels-Alder reaction of **74** was highly temperature-dependent (see Table 1, Entries 2-7). Heating **74** in the absence of solvent (Entry 1) produced a clear, glutinous polymer and none of the desired cycloadduct mixture **72**. ^{1}H-NMR spectroscopy of the clear polymer product showed broadened overlapping signals throughout much of the spectrum.

To prevent polymerization from occurring, **74** was diluted in toluene (bp 110°C) prior to heating. The reaction mixture was then refluxed for 28 hours (Entry 2). While these conditions succeeded in preventing polymerization, none of the desired conversion of **74** to **72** was observed. Therefore, higher boiling solvents (o-xylene and diglyme) were employed to increase the reaction temperatures to 140°C and 162°C, respectively (Entries 3 and 4). Again, these increases in temperature did not provide any of the desired cycloadducts **72**.

In order to increase the temperature further, the Diels-Alder reaction was performed within a sealed Parr apparatus, which permitted reaction temperatures to exceed the boiling point of the solvent being used. Under these conditions, it was possible to increase the reaction temperature to 260°C (Entry 5). These vigorous conditions converted **74** into a black tar and none of the desired **72** was produced. When the reaction temperature was lowered to 205°C, the cylcoadducts **72** were finally observed in 38% yield (Entry 6). A considerable amount of black polymer was still formed, however, even after the yield for this reaction was improved to 70% by further lowering the temperature to 190°C (Entry 7).

The observed polymerization was possibly the result of free radicals generated from peroxides produced by autoxidation[50] of the unsaturated starting material. Since the removal of all traces of peroxides from the starting material could not be guaranteed, a radical inhibitor was added to the reaction mixture.

Thus, a small amount of 2,6-di-*tert*-butyl-4-methylphenol (**103**) (more commonly known as butylated hydroxytoluene or BHT) was added to the reaction mixture to act as a radical scavenger.[51] The addition of BHT to the reaction mixture proved to be successful by significantly increasing the yield from 70 to 95 % (compare Entries 7 and 8).



103

2.5.2 Optimization of the Diels-Alder Reaction of *cis*-Diene 73

The results of the optimization efforts for the conversion of the *cis*-diene **73** to **72** are given in Table 2.

Table 2. Optimization of the Diels-Alder Reaction of *cis*-Diene **73**

Entry[a]	Temp. (°C)	Yield **72** (%)
1	163	28
2	173	33
3	190	54
4	201	5

a) All entries (1-4) were performed over 24 h in a sealed Parr apparatus with toluene as the solvent and with 10% BHT added to the reaction mixture.

It was observed that the intramolecular Diels-Alder reaction of **73** was also highly temperature-dependent (Table 2). Interestingly, the optimum temperature was determined to be 190°C, which was the same temperature determined for the Diels-Alder reaction of *trans*-diene **74**. However, the yield for the intramolecular Diels-Alder reaction of the *cis* intermediate **73** was only 54% (unlike the 95% yield attained when starting with **74**). This drop in yield was primarily due to an increased tendency towards polymerization by **73** compared to **74**. However, some non-polymer by-products were also produced during the conversion of **73** to **72**. While these by-products were not isolated, one can speculate that some of the starting material **73** underwent a 1,5 hydrogen shift within its *cis* diene substituent. These 1,5 sigmatropic rearrangements are well known to occur during intramolecular Diels-Alder reactions involving *cis* dienes at higher temperatures.[37,38]

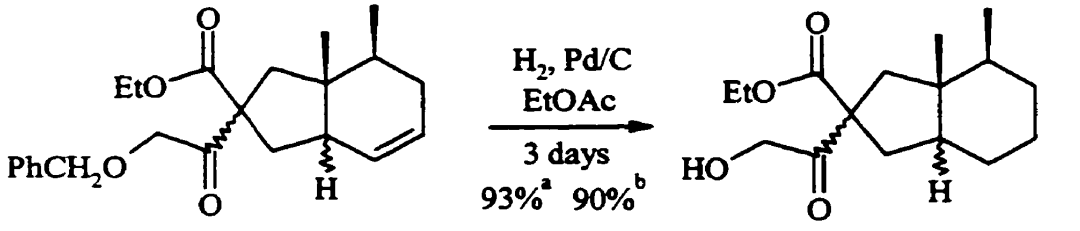
The conclusion that the Diels-Alder reaction had succeeded for both **73** and **74** was based on ^{1}H-NMR spectra of the products. The array of multiplets corresponding to the six vinylic hydrogens observed in the ^{1}H-NMR spectra of each of **73** and **74** was reduced to a single multiplet at δ 5.6 ppm integrating for two hydrogens in the ^{1}H-NMR spectrum of the mixture of isomers **72**. This evidence, in conjunction with the M^+ at m/z 370 in the mass spectrum, strongly suggested that an intramolecular Diels-Alder reaction had occurred in both cases.

As explained in Chapter One, it was predicted that the *cis* isomer **73** would be more selective than its *trans* counterpart **74** at furnishing the desired bakkenolide-A stereochemistry. However, any stereoselectivity that had taken place during the Diels-Alder reactions could not be confirmed until later in the synthesis because the mixture of

isomers generated by the reaction could not be separated by flash chromatography. Thus, it was decided to carry the unseparated mixture of isomers **72** through subsequent steps with the hope of being able to separate them at a later stage. As it turned out, separation proved most facile at the end of the synthesis and so all intervening steps were performed on the mixtures of stereoisomers. Products derived from *cis*-diene **73** and *trans*-diene **74** were carried through the synthesis separately, but under the same conditions.

2.6 Hydrogenation and Deprotection of 72

Reduction of the cyclohexene double bond and simultaneous removal of the benzyl protecting group in **72** was accomplished by catalytic hydrogenation (Scheme 32). A balloon filled with hydrogen provided a continuous positive pressure of hydrogen. Palladium-activated charcoal was employed as the catalyst and the reaction mixture was stirred for three days in ethyl acetate as the solvent. Under these conditions, mixture **72** was converted in high yields (see entries 2 and 4 of Table 3) to the mixture of hydroxy esters **104**.



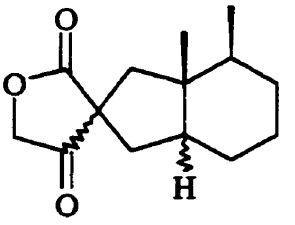
72, mixture of isomers

104, mixture of isomers

a - Starting material **72** was obtained from *cis* **73**
b - Starting material **72** was obtained from *trans* **74**

Scheme 32.

When the catalytic hydrogenation was allowed to proceed for only one day, 65% of the starting material **72** did not react (see entry 1 of Table 3). Entries 3 and 5 show that when the reaction proceeded beyond three days, the yield of **104** was lowered by the spontaneous lactonization of the mixture of isomers **104** to the corresponding lactones **105**, which could be separated by flash chromatography from **104**.



105, mixture of isomers

Table 3. Hydrogenation and Deprotection of **72**

Entry	Time	Yield **104** (%)	Yield **105** (%)
1	1 day	30[a,c]	0
2	3 days	93[b]	0
3	4 days	68[a]	21[a]
4	3 days	90[a]	0
5	4 days	78[b]	15[b]

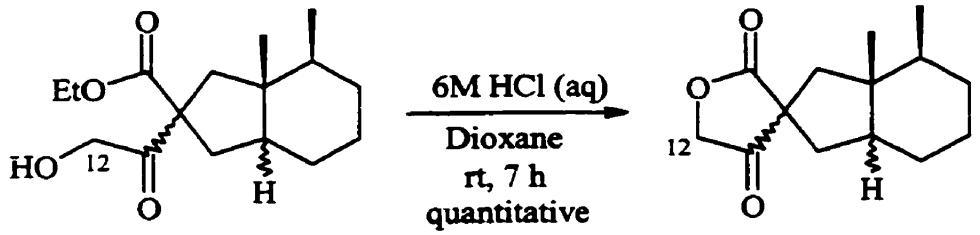
a - the starting material **72** was obtained from *cis* **73**
b - the starting material **72** was obtained from *trans* **74**
c - 65% of **72** was recovered

An analysis of the ^{1}H-NMR and mass spectra of the unseparated mixture of isomers of **104** provided evidence that this reaction was indeed successful. Signals corresponding to the aromatic and olefinic hydrogens of **72** were not present in the ^{1}H-NMR spectrum of **104**. Moreover, a broadened triplet at δ 2.95 ppm, which

corresponded to the unprotected alcohol proton of **104**, was observed. The mass spectrum of the mixture of isomers **104** showed the M^+ at m/z 282, while the characteristic $PhCH_2^+$ ion at m/z 91 (which was observed in the mass spectrum of the mixture of isomers **72**) was not seen. Product **105** was identified by comparison with an authentic sample (*vide infa*).

2.7 Lactonization of 104

Although the mixture of hydroxy ester isomers **104** tended to lactonize spontaneously, the rate was too slow to be useful. Thus, a simple lactonization procedure was developed to expedite the process (Scheme 33). The mixtures of isomers **104** were stirred for 7 h in a mixture of dioxane and 6M HCl (3:1), resulting in a quantitative yield of the mixture of lactone stereoisomers **105**. This procedure worked equally effectively when the mixture of isomers **104** was derived from the *cis*-diene **73** and from the *trans*-diene intermediate **74**.



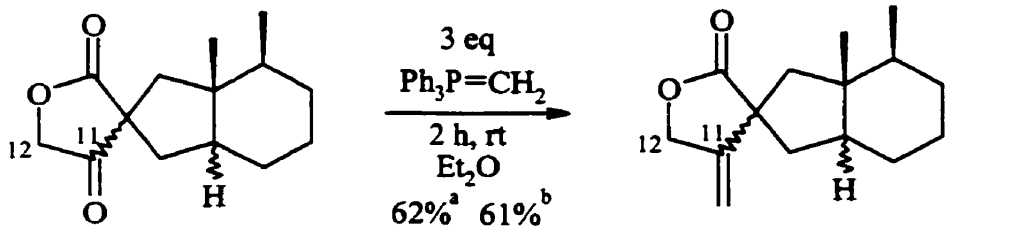
104, mixture of isomers **105**, mixture of isomers

Scheme 33. Lactonization

Analysis of ^{1}H-NMR and mass spectra of the unseparated mixture of isomers **105** provided evidence that the lactonization was successful. Product **105** showed the disappearance of ^{1}H-NMR signals from the ethyl group and the alcohol proton. Moreover, the C-12 protons of **104**, which appeared as a multiplet between δ 4.10 and 4.40 ppm, were visible further downfield in the ^{1}H-NMR spectrum of **105**, appearing between δ 4.56 and 4.72 ppm. The mass spectrum of the mixture of lactones **105** showed the correct M^+ at m/z 236.

2.8 The Final Step -- The Wittig Reaction

To complete our synthesis of bakkenolide-A, the mixture of unseparated isomers **105** was converted to the mixture of bakkenolide stereoisomers **106** by converting the C-11 ketone to the required exocyclic methylene group via a Wittig reaction[52] (Scheme 34).

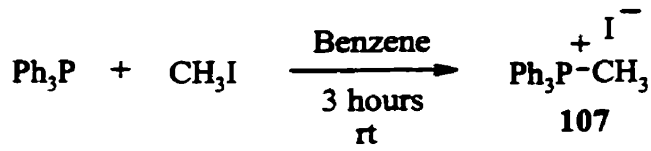


105, a mixture of isomers **106**, a mixture of isomers

a - Starting material **105** was obtained from *cis* **73**
b - Starting material **105** was obtained from *trans* **74**

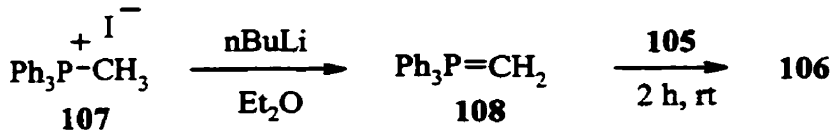
Scheme 34. The Wittig Reaction

Prior to performing this reaction, methyl triphenylphosphonium iodide (**107**) was prepared by mixing triphenylphoshine and methyl iodide in benzene at room temperature for three hours (Scheme 35).[52]



Scheme 35.

The phoshonium salt **107** was converted to the methylene ylide **108** immediately prior to the addition of **105**. This was done via deprotonation by *n*-butyllithium[52] in diethyl ether (Scheme 36).



Scheme 36.

Three equivalents of the *in situ*-generated ylide **108** were required to provide optimum yields of the bakkenolide mixture **106** (see entries 3 and 4 of Table 4). When only one equivalent of ylide was employed, the yields for this reaction (see entries 1 and 2) were slightly lower. The >60% yield attained was somewhat fortunate considering that ketones adjacent to spirocenters are often sterically hindered and, therefore, not easily reacted with **108**.[53]

Table 4. Optimization of the Wittig Reaction

Entry[a]	Eqs. of **108**	Yield **106** (%)
1	1 eq	50[b]
2	1 eq	50[c]
3	3 eq	62[b]
4	3 eq	61[c]

a - all entries (1-4) were performed in diethyl ether for 2 h at rt
b - the starting material **105** was obtained from *cis* **73**
c - the starting material **105** was obtained from *trans* **74**

The ^{1}H-NMR spectrum of the bakkenolide mixture **106** showed new signals between δ 4.95 and 5.20 ppm, which correspond to the geminal methylene hydrogens of the exocyclic double bond. The lactone methylene protons at C-12, which showed up as a multiplet between δ 4.56 and 4.72 ppm in the ^{1}H-NMR spectrum of **105**, appeared slightly more downfield (δ 4.70-4.90 ppm) in the ^{1}H-NMR spectrum of **106**. Furthermore, the expected M^+ at m/z 234 was observed in the mass spectrum for the unseparated mixture of bakkenolides **106**.

2.9 Separation by High Pressure Liquid Chromatography (HPLC)

The mixture of bakkenolides **106** could not be separated by flash chromatography. Therefore, HPLC was employed to separate the isomers. The optimum HPLC parameters used for the separation are summarized in Table 5. A more detailed procedure for this HPLC separation is provided in Chapter Three.

Table 5. HPLC Parameters Required to Separate Bakkenolide Mixture **106**.

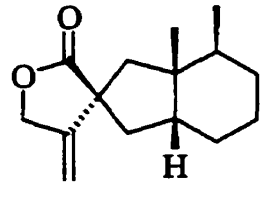
Analytical Column (Reverse Phase)	**Preparatory Column (Reverse Phase)**
UV Detector: 212 nm	UV Detector: 225 nm
Flow Rate: 0.85 ml/min	Flow Rate: 7.0 ml/min
Elution Time: 10-12 min.	Elution Time: 22-26 min.
Solvent System: 30% H_2O / 70% MeOH	Solvent System: 30% H_2O / 70% MeOH

The UV detector was initially set at 212 nm because this is the wavelength corresponding to λ_{max} for bakkenolide-A.[54] After switching from the analytical to the preparatory column, the UV detector was reset to 225 nm in order to reduce the very strong absorbance caused by the increased concentration of **106**.

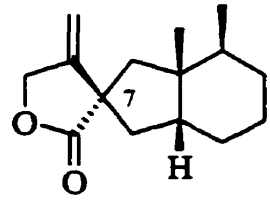
The solvent system had to be chosen carefully such that it would not mask the lactone chromophore of **106**. Therefore, water and methanol were selected because their UV cutoffs were below 205 nm. Optimum separation of the bakkenolide isomers was possible when the solvent ratio was 30% water and 70% methanol. Moreover, the flow

rates were adjusted to provide optimum separation. The analytical HPLC traces for each of the mixtures **106** derived from intermediates **73** and **74** are shown in Figures 4 and 5, respectively.

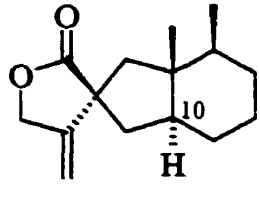
At the conclusion of the HPLC separation procedure, it was determined that the first isomer to elute from the column, corresponding to the first peak in the HPLC traces (Figures 4 and 5), was the target compound bakkenolide-A (**1**). The other three isomers, corresponding to the second, third, and fourth peaks in the HPLC traces, were determined to be 7-epibakkenolide-A (**61**), 7,10-diepibakkenolide-A (**81**), and 10-epibakkenolide-A (**80**), respectively. By repeated preparative HPLC of the initial mixture **106**, small samples of each stereoisomer were obtained in a high state of purity, with the exception of **61**, which was obtained as a 4:1 mixture with bakkenolide-A (**1**). A discussion of how these bakkenolide stereoisomers were identified is provided later in this chapter.



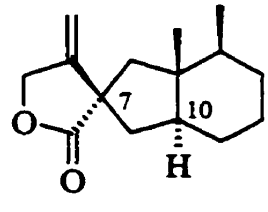
1



61



80



81

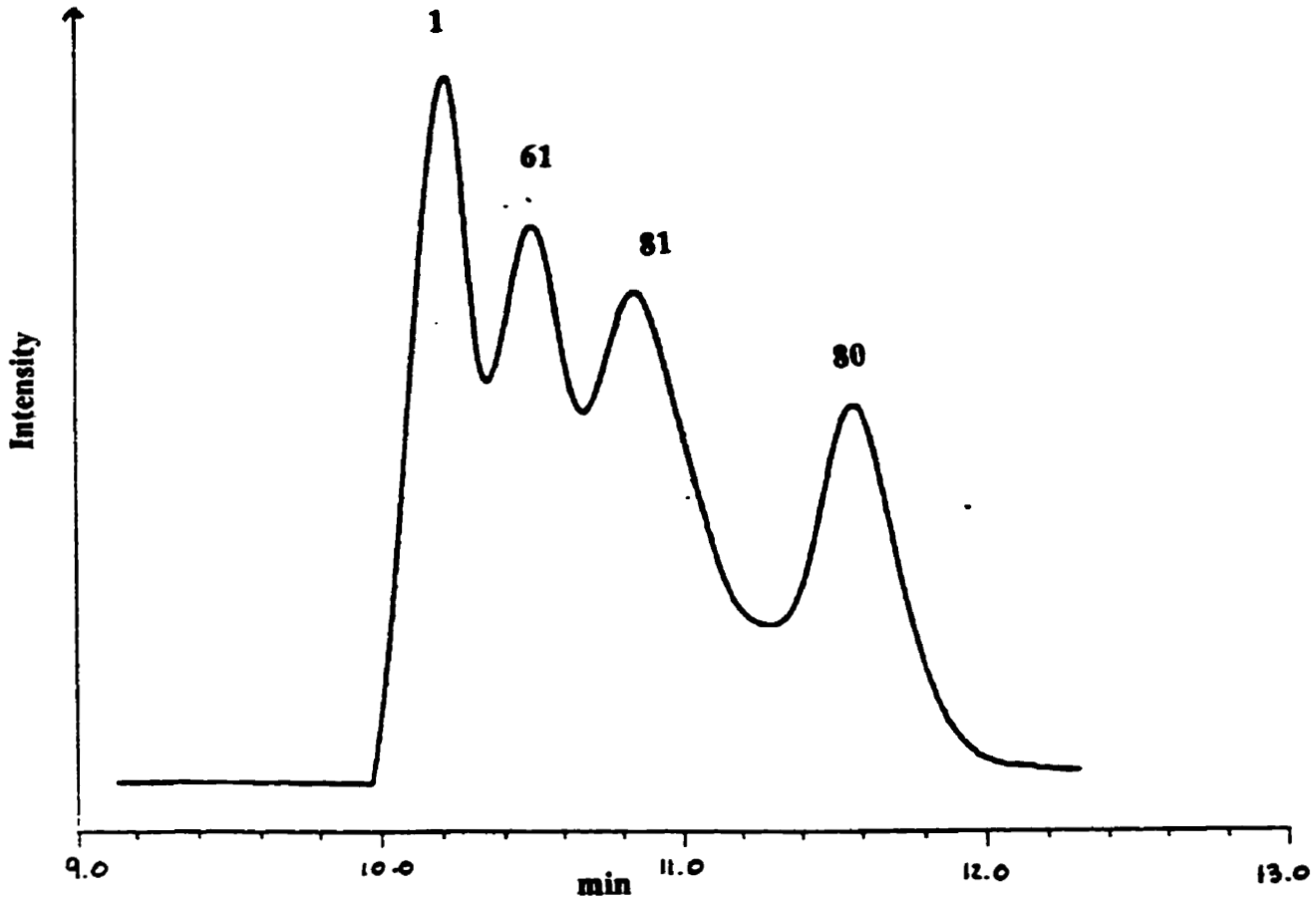


Figure 4. HPLC Trace of Mixture **106** derived from *cis*-Diene **73**

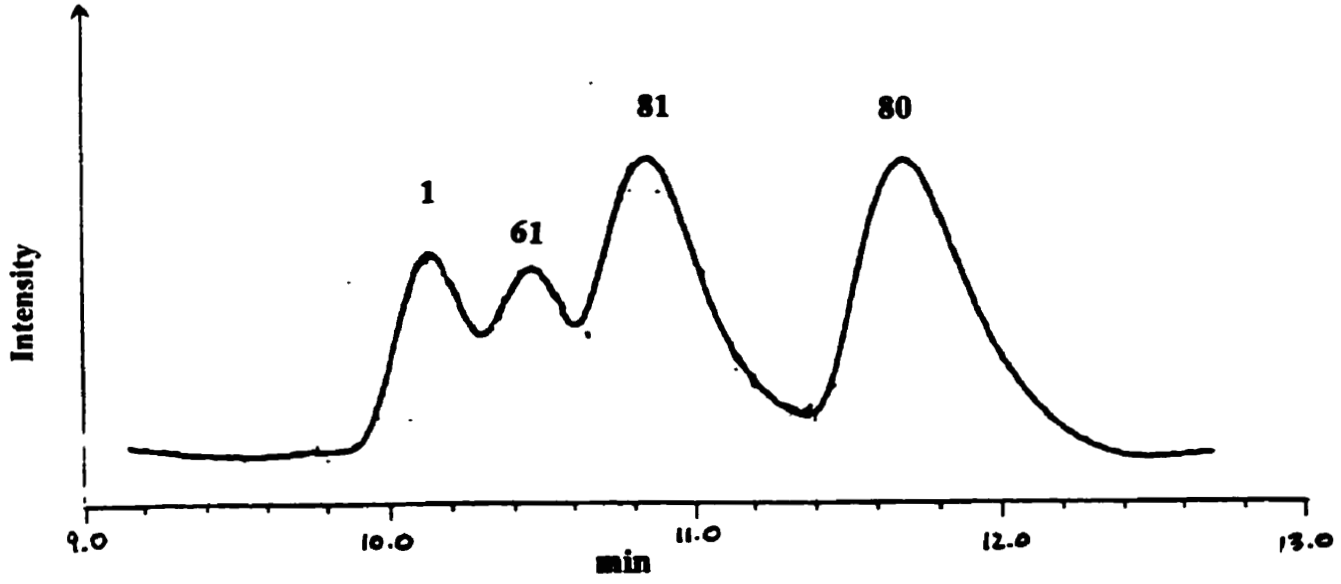


Figure 5. HPLC Trace of Mixture **106** derived from *trans*-Diene **74**

2.10 The Relative Yields of Bakkenolides derived from 73 and 74

Since even minor changes in structure can cause significant changes in extinction coefficients, the original mixtures of bakkenolides were also analyzed by GC in order to more accurately determine their relative amounts. The relative yields of bakkenolides **1**, **61**, **80**, and **81** were thus determined for both product mixtures derived from *cis* and *trans* pre-Diels-Alder intermediates **73** and **74**, respectively, and are listed in Table 6. The GC chromatograms themselves are shown in Figures 6 and 7. These percentages agreed reasonably well with the analytical HPLC analyses described earlier.

Table 6. Relative Yields of Bakkenolides **1**, **61**, **80**, **81**

	1	**61**	**80**	**81**
From *cis* **73**	54%	19%	16%	11%
From *trans* **74**	24%	10%	34%	32%

It is unlikely that catalytic hydrogenation, the lactonization procedure, or the Wittig reaction caused any epimerization to occur at C-7 or C-10. Therefore, it is assumed that the relative percentages of each of the four isomers in the post-Diels-Alder reaction mixture **72** remained unchanged as the mixture was carried through to the end of the synthesis. It is therefore also assumed that the ratio of bakkenolides in the final product mixture **106** indicates the degree of stereoselectivity exhibited by the intramolecular Diels-Alder reaction.

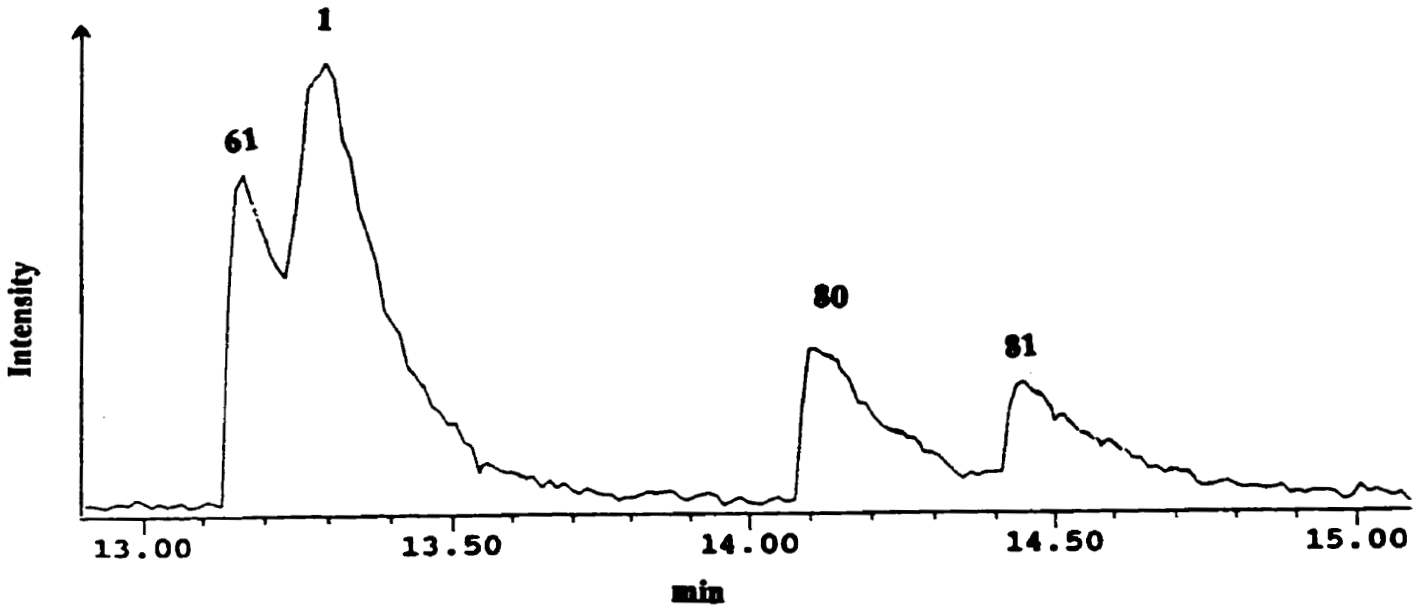


Figure 6. GC Chromatogram of Mixture **106** derived from *cis*-Diene **73**

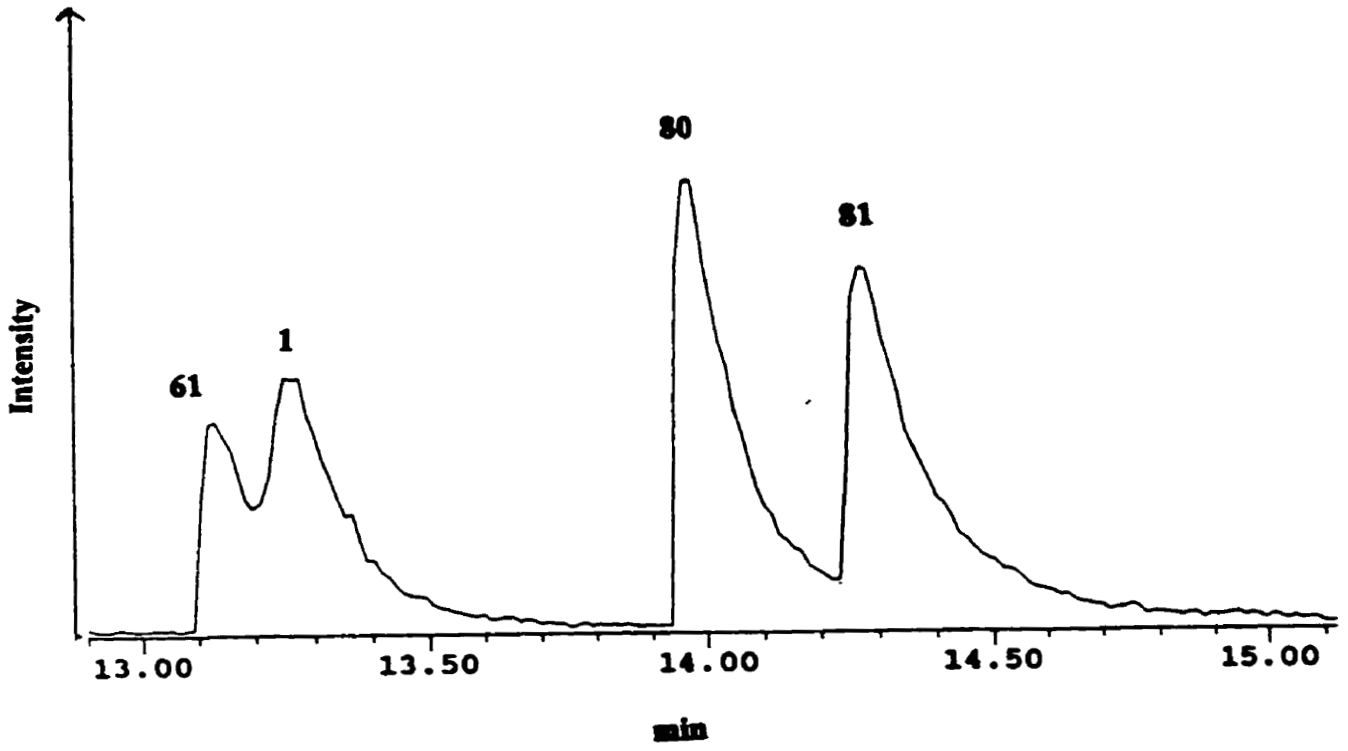


Figure 7. GC Chromatogram of Mixture **106** derived from *trans*-Diene **74**

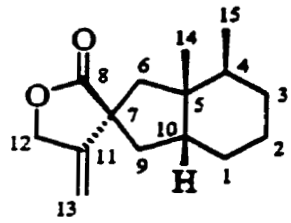
2.11 Structure Elucidation of the Four Bakkenolides 1, 61, 80, 81

As mentioned earlier, the mixture of isomers **106** consisted of four bakkenolides (**1**, **61**, **80** and **81**). This section explicates how each of these stereoisomers was identified.

A pure sample of authentic (+)-bakkenolide-A (**1**) was kindly provided by Professor Harmatha of the Czech Republic. Thus, it was possible to compare spectra of our synthetic samples to those of the natural sample of bakkenolide-A. The ^{1}H- and ^{13}C-NMR spectra matched unequivocally, confirming that the synthesis described in this Thesis successfully constructed the target compound **1** (Figures 8 and 9). The structure was further confirmed by GC-MS, which showed the same retention time, as well as the expected M^{+} at m/z 234 and fragmentation pattern as obtained with the authentic sample.

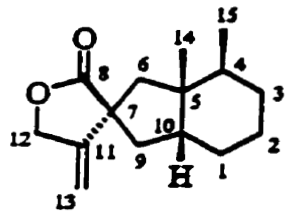
The 400MHz ^{1}H-NMR spectrum of **1** showed signals for its vinylic protons at δ 5.04 and 5.12 ppm. The lactone methylene hydrogens at C-12 appeared as a multiplet at δ 4.75 ppm. A singlet was seen at δ 1.00 ppm corresponding to the protons of the angular methyl group C-14 and a doublet (J = 6.7 Hz) was observed at δ 0.86 ppm for the protons of the adjacent *cis* methyl group C-15.

The 100MHz ^{13}C-NMR spectrum of synthetic **1** showed all of the carbons with the exception of the relatively weak C-8 carbonyl signal (reported to be at δ 182.8 ppm), which was not detected because of the relatively low concentration of **1** in the NMR sample (1.2 mg in 0.5 ml $CDCl_3$).



1

Figure 8. ^{1}H-NMR Spectra of Authentic (Top) and Synthetic (Bottom) Bakkenolide-A



1

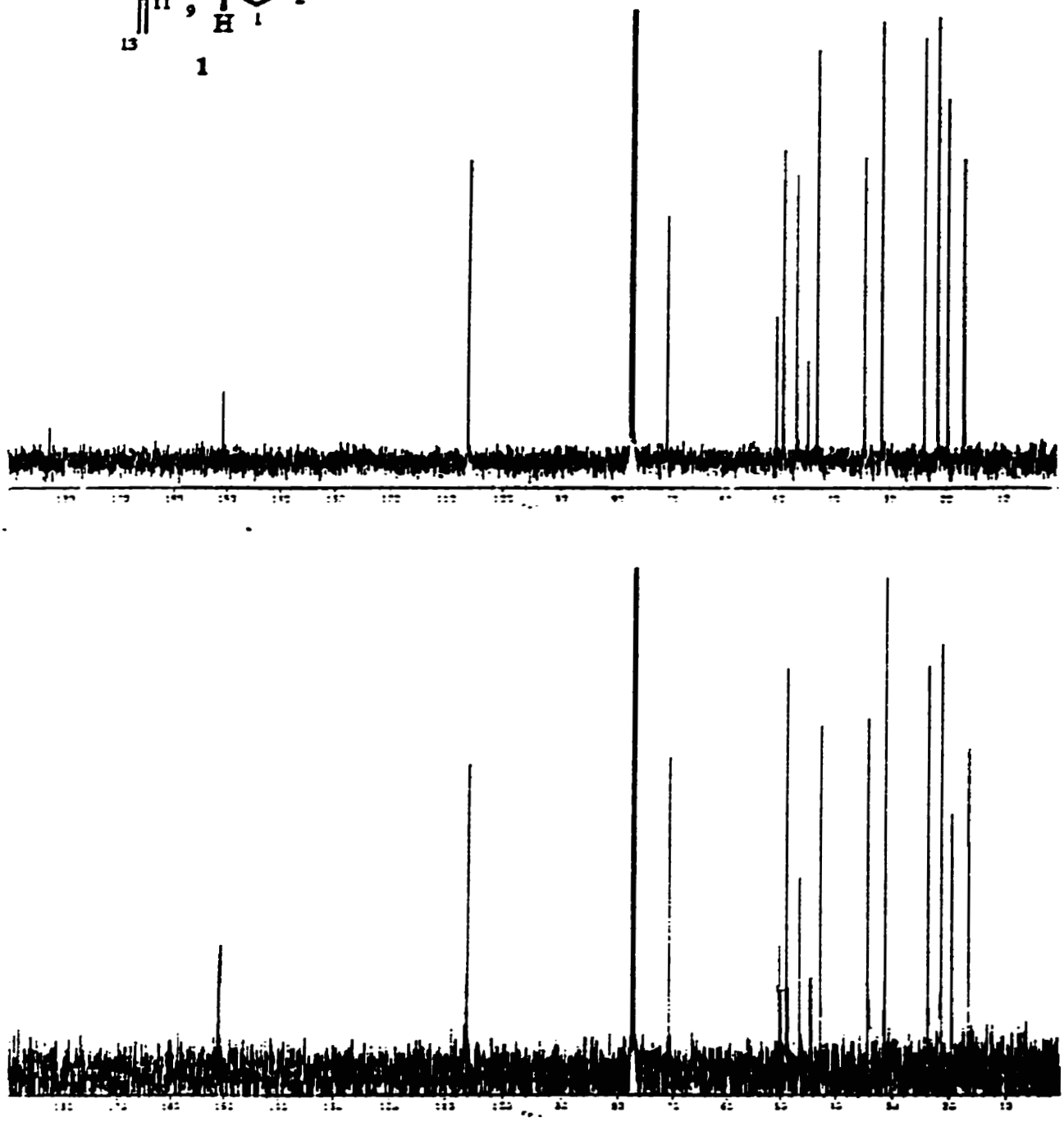
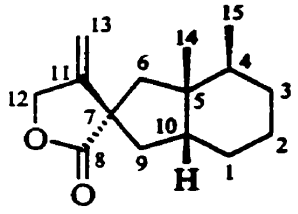


Figure 9. ^{13}C-NMR Spectra of Authentic (Top) and Synthetic (Bottom) Bakkenolide-A

7-Epibakkenolide-A (**61**) was synthesized for the first time by Srikrishna *et al.*[34] while this work was in progress. Spectral data provided by them in the literature matched the ^{1}H-NMR data for the product comprising the second peak eluted from the HPLC column shown in Figures 4 and 5. Mass spectrometry further revealed the expected M^+ at m/z 234 and a fragmentation pattern similar to that of bakkenolide-A (**1**). The 400MHz ^{1}H-NMR spectrum of **61** is shown in Figure 10. As mentioned in section 2.9, **61** was obtained as a 4:1 mixture with bakkenolide-A (**1**).



61

Figure 10. ^{1}H-NMR Spectrum of the 4:1 Mixture of **61** and **1**

The ^{1}H-NMR spectrum of **61** showed signals for its vinylic protons at δ 4.99 and 5.07 ppm. The C-12 methylene hydrogens appeared as a multiplet at δ 4.75 ppm. A singlet was seen at δ 0.97 ppm corresponding to the protons of the angular methyl group C-14 and a doublet (J = 6.6 Hz) was observed at δ 0.82 ppm for the protons of the adjacent *cis* methyl group C-15.

10-Epibakkenolide-A (**80**) was a new compound that needed to be fully characterized. To do so, ^{1}H- and ^{13}C-NMR spectra were acquired as well as GC-MS data for **80**. The 400MHz ^{1}H-NMR spectrum of **80** (Figure 11) showed signals for the vinylic protons at δ 4.97 and 5.08 ppm and also a multiplet at δ 4.79 ppm corresponding to the pair of hydrogens at C-12. The hydrogens of the angular methyl group C-14 appeared as a fine doublet (J = 0.8 Hz) at δ 0.91 ppm in the ^{1}H-NMR spectrum of **80**. This long range "W" coupling[55] of 0.8 Hz, which was not observed in the *cis*-fused systems of **1** and **61**, occurred between the time-averaged hydrogens of the angular methyl group at C-5 and the hydrogen at C-10, confirming that **80** has *trans*-fused A and B rings (Figure 12). A doublet (J = 6.5 Hz) was also observed at δ 0.86 ppm for the hydrogens of the adjacent *cis* methyl group C-15.

Mass spectral data confirmed that **80** had the desired M^{+} at m/z 234 and a fragmentation pattern similar to the other bakkenolides **1** and **61**. The 100MHz ^{13}C-NMR spectrum of **80** showed all of the carbon atoms with the exception of the relatively weak C-8 signal, which was not detected because of the relatively low concentration of **80** in the NMR sample (0.5 mg in 0.5 ml $CDCl_3$). An accurate exact mass measurement of the parent ion was also achieved.

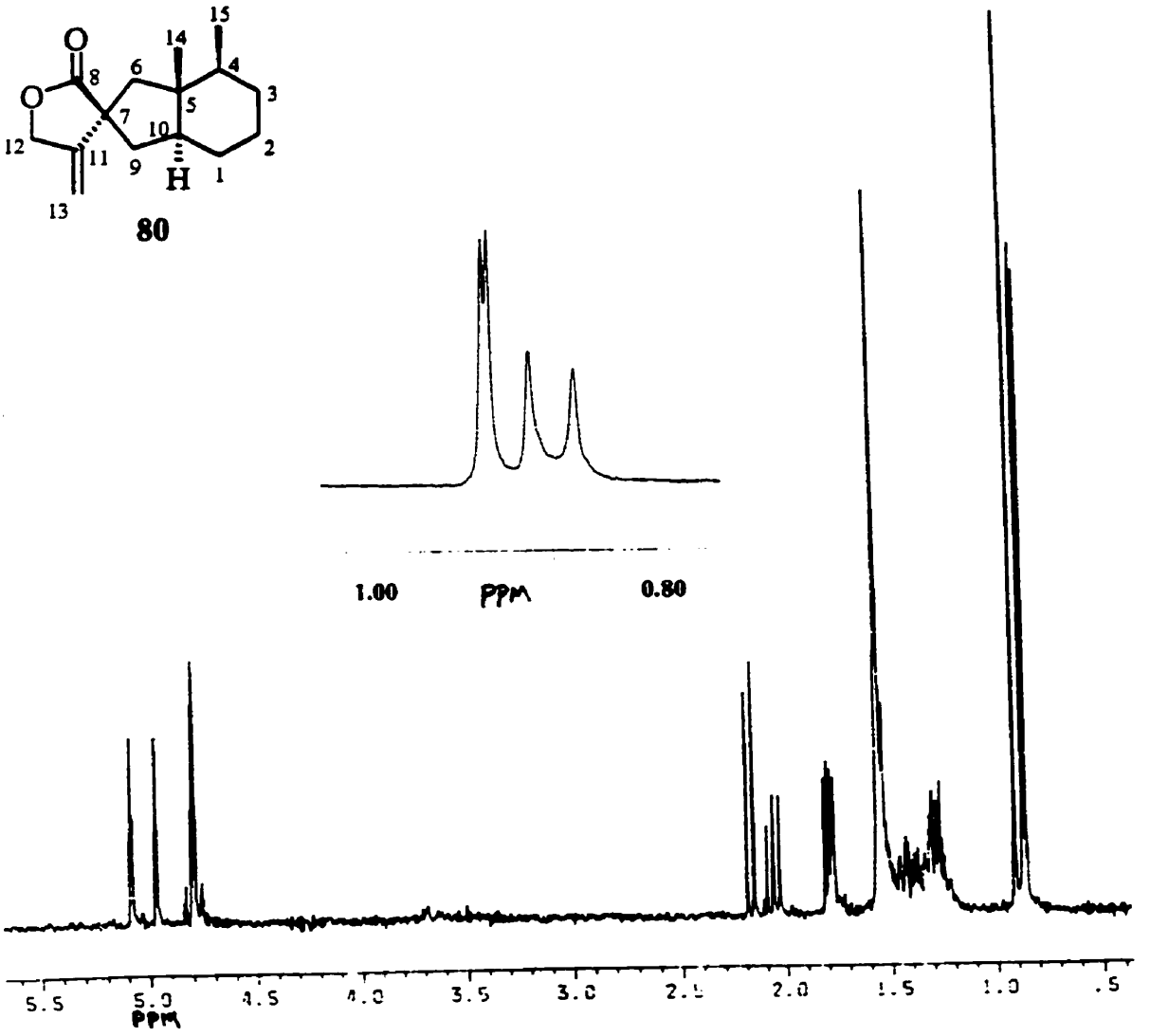


Figure 11. ^{1}H-NMR Spectrum of **80**

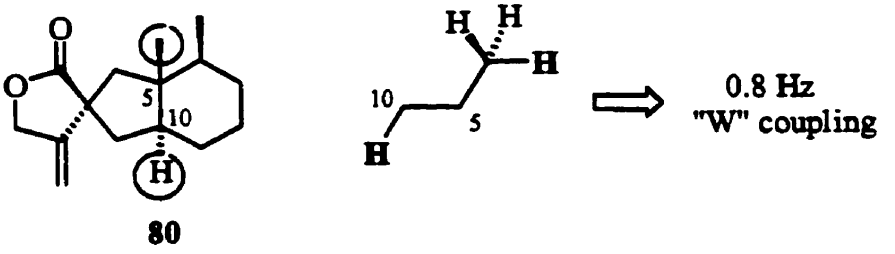
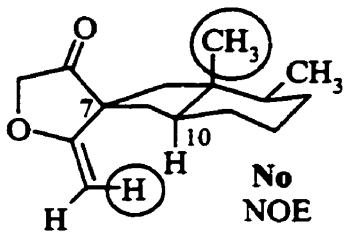


Figure 12. Long Range "W" Coupling Observed in the ^{1}H-NMR Spectrum of **80**

The stereochemistry at the spiro center of **80** was consistent with the absence of an NOE between the vinylic proton signals and the angular methyl group (Figure 13).



80

Figure 13. NOE Difference Experiment for **80**

7,10-Diepibakkenolide-A (**81**) was also a new compound that needed to be fully characterized. ^{1}H- and ^{13}C-NMR spectra were acquired as well as GC-MS data for **81**. The 400MHz ^{1}H-NMR spectrum (Figure 14) showed signals for the vinylic protons at δ 5.03 and 5.17 ppm. The lactone methylene hydrogens at C-12 appeared as a multiplet at δ 4.77 ppm.

The hydrogens of the angular methyl group C-14 again appeared as a fine doublet (J = 0.8 Hz) at δ 0.80 ppm in the H-NMR spectrum of **81**. This long range "W" coupling[55] of 0.8 Hz, which was also observed in the *trans*-fused product **80**, occurred between the time-averaged hydrogens of the angular methyl group at C-5 and the proton at C-10, confirming that **81** has *trans*-fused A- and B-rings (Figure 15). A doublet (J = 6.7 Hz) was observed at δ 0.85 ppm for the protons of the adjacent *cis* methyl group C-15.

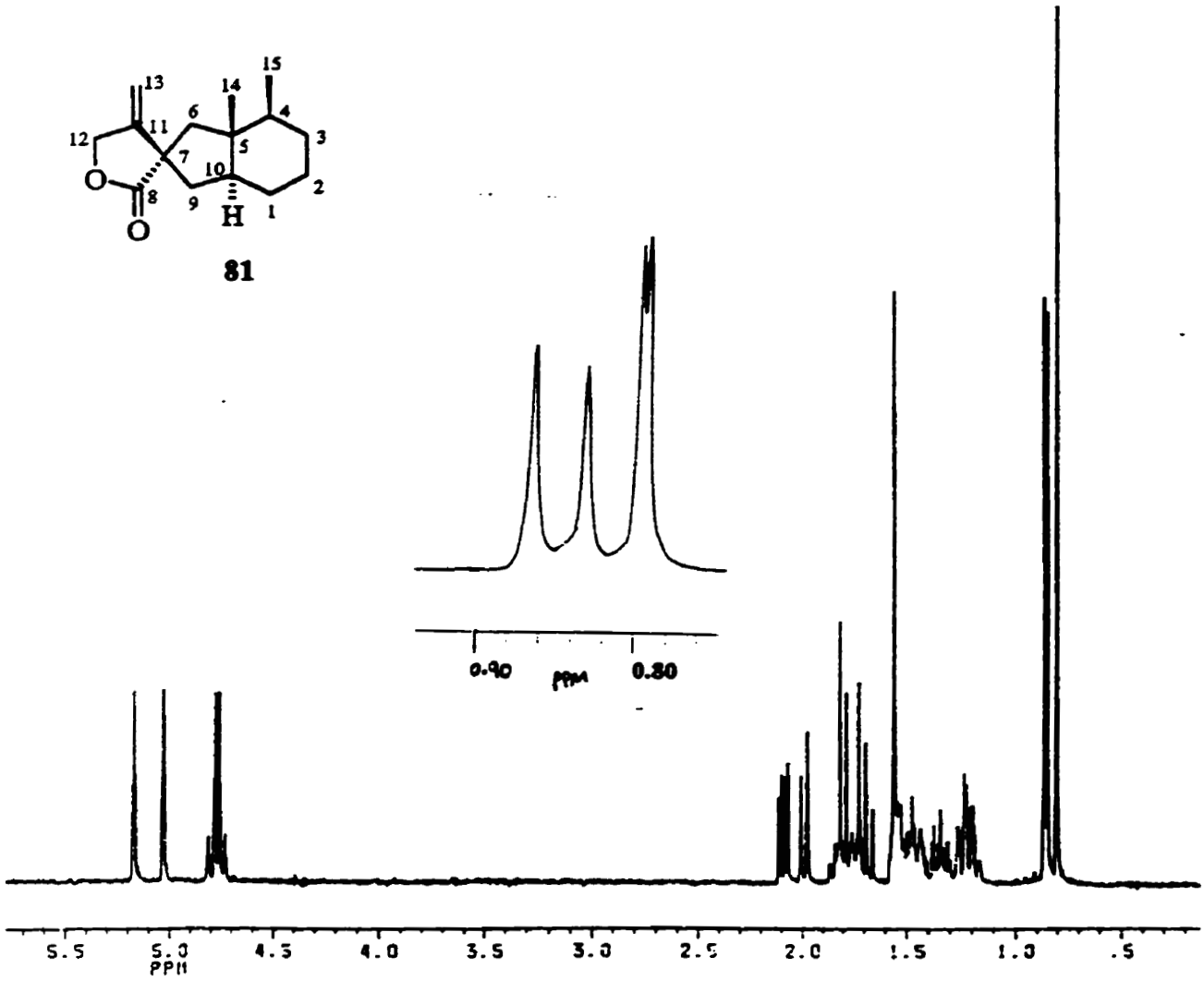


Figure 14. ^{1}H-NMR Spectrum of **81**

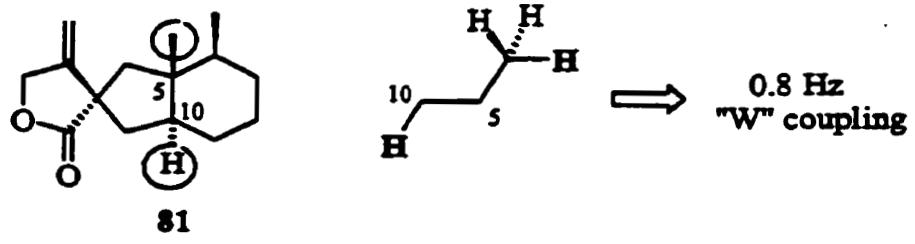
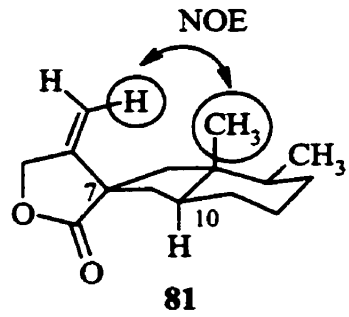


Figure 15. Long Range "W" Coupling Observed in the ^{1}H-NMR Spectrum of **81**

Mass spectrometry of **81** showed the expected M^+ at m/z 234 and a fragmentation pattern similar to that of **1**, **61**, and **80**. The 100MHz ^{13}C-NMR spectrum of **81** showed all of the carbon atoms, again with the exception of the relatively weak C-8 signal in the dilute sample (0.8 mg in 0.5 ml $CDCl_3$). An accurate exact mass measurement of the parent ion was also achieved.

The stereochemistry at the C-7 spiro center of **81** was confirmed by an NOE difference experiment (Figure 16), which showed a 2% enhancement of the vinylic proton signal at δ 5.17 ppm upon irradiation of the angular methyl group. Irradiation of the vinylic proton at δ 5.17 ppm was inconclusive, since the angular methyl group showed only a very small enhancement.



81

Figure 16. NOE Difference Experiment for **81**

2.12 Thermodynamic vs. Kinetic Control

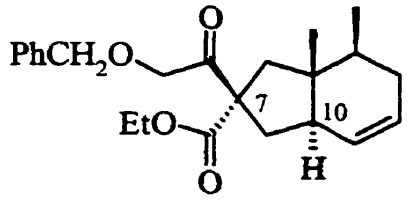
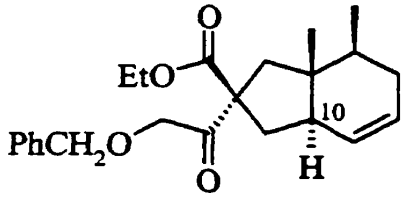
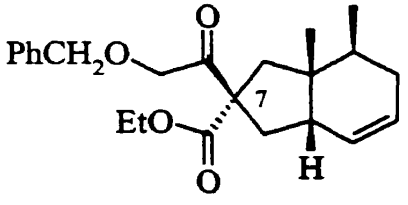
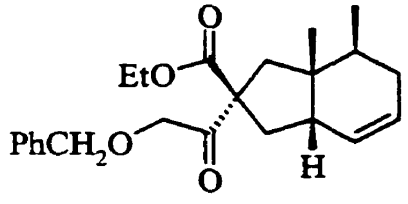
To help explain the observed stereoselectivities exhibited by the intramolecular Diels-Alder reaction, it was essential to first determine whether this reaction was under thermodynamic or kinetic control. To do so, *ab initio* molecular modeling experiments were utilized, so that the calculated stabilities of the four stereoisomers could be compared with the observed product distribution as given in Table 6.

SPARTAN[C] was used to calculate the minimum energies of the four Diels-Alder cycloadducts (**78**, **79**, **109**, **110**) (Figure 17). These energies were calculated by submitting each of the structures for a semi-empirical PM3 geometry optimization followed by an *ab initio* STO-3G single point energy calculation. The energies were then converted from Hartrees to kilocalories and **78**, which had the lowest of the four energies, was set to zero. From the relative minimum energies an estimated product distribution was calculated, assuming that the Diels-Alder reaction was under thermodynamic control. The reader is reminded that cycloadducts **78**, **79**, **109** and **110** correspond respectively to the final products **1**, **61**, **80** and **81** respectively.

The results of the molecular modeling experiment suggested that the *cis*-fused cylcoadducts **78** and **79** would be thermodynamically favored over the *trans*-fused products **109** and **110**. Furthermore, it was predicted that the cycloadducts **78** and **109** would be thermodynamically favored over the respective C-7 epimers **79** and **110**.

The actual product distributions from the *cis* and *trans* pre-Diels-Alder intermediates (**73** and **74**, respectively) were not the same, however. For example, intermediate **74** favored the *trans*-fused products **109** and **110**, while **73** favored the cis-fused products **78** and **79**. The lack of correlation between the product distributions from

73 and 74, and with their calculated relative energies, suggests that the Diels-Alder reaction did not proceed under thermodynamic control, but rather, under kinetic control.

	Relative Energy	Predicted Product Distribution[a]	Actual Product Distribution[b]	
			From 73	From 74
 **110**	5.67 kcal/mol	0.1 %	11 %	32 %
 **109**	3.75 kcal/mol	0.9 %	16 %	34 %
 **79**	0.26 kcal/mol	43 %	19 %	10 %
 **78**	0 kcal/mol	56 %	54 %	24 %

a - Assuming the reaction is under thermodynamic control
b - Based on GC analysis of the final bakkenolide mixture (Table 6)

Figure 17. Determining if the Diels-Alder Reaction is under Thermodynamic Control

2.13 Explanation of Observed Stereoselectivity at C-10 and C-7

With the assumption that the intramolecular Diels-Alder reaction proceeded under kinetic control, we can more accurately speculate about the origin of the observed stereoselectivity at C-10 and C-7.

As discussed in Chapter One, it was anticipated that the *cis* pre-Diels-Alder intermediate **73** would be more stereoselective than its *trans* counterpart **74** in favor of the desired bakkenolide-A stereochemistry at C-10. The results observed (Table 7) are in accord with this prediction in that **73** was found to be more than twice as effective as **74** at establishing the desired *cis*-fused ring junction as found in isomers **1** and **61**.

Table 7. Observed Selectivity of *cis*-Fused **1** and **61** vs. *trans*-Fused **80** and **81**

	Relative Combined Yields of *cis*-Fused **1** and **61**[a]	Relative Combined Yields of *trans*-Fused **80** and **81**[b]
From *cis* **73**	73%	27%
From *trans* **74**	34%	66%

a - **1** and **61** differ from each other with respect to the relative configuration at the spiro center
b - **80** and **81** differ from each other with respect to the relative configuration at the spiro center

The *cis* diene and the dienophile in **73** prefer to cyclize via the *exo* transition states **73a** and **73b**, which provide *cis*-fused products (**78** and **79**, respectively) because the *endo* transition states **73c** and **73d**, which lead to *trans*-fused products (**109** and **110**, respectively) are relatively more strained (Figure 18). This strain has been attributed to the relatively short three-carbon tether between the *cis* diene and the dienophile, which limits the flexibility required for the *endo* transition states **73c** and **73d**.[37,38,39]

It is more difficult to explain the stereoselectivity observed at C-7 during the Diels-Alder reaction of *cis* **73**. Perhaps the bulkier benzyloxy methyl ketone side chain plays a significant role in destabilizing the transition states **73b** and **73d** through steric interactions with the angular methyl group, in at least some of the conformers that are possible from rotation about the single bonds in this substituent. This side chain may also interact with the hydrogen atom at C-10 in **73b**, which provides a very tentative explanation for the stereoselectivity observed at C-7.

The *trans* diene and the dienophile in **74** prefer to cyclize via the *exo* transition states **74c** and **74d**, which furnish *trans*-fused products **109** and **110**, because the *endo* transition states **74a** and **74b**, which lead to the *cis*-fused products **78** and **79**, are energetically less favorable (Figure 19). This is perhaps due to the relatively strained tether between the *trans* diene and the tiglyl dienophile in the *endo* transition states **74a** and **74b**.

Again, it is more difficult to explain the stereoselectivity observed at C-7 during the Diels-Alder reaction of *trans* **74**. As shown before in Figure 18, the greater bulkiness of the ketone side chain may destabilize the transition states **74b** and **74d** through a steric interaction with the indicated methyl groups, as well as with the hydrogen atom at C-10 in **74b**.

Finally, it must be pointed out that each of the pre-Diels-Alder trienes **73** and **74** contains a chiral center. Since these compounds were employed as racemates, the final products were similarly obtained in racemic form. The transition states in Figures 18 and 19 are arbitrarily shown as single enantiomers (**73a**, **73b**, **73c**, **73d** are R, S, R, S, respectively, while **74a**, **74b**, **74c**, **74d** are R, S, R, S, respectively) in which the diene

substituent is shown in front of the dienophile in each structure to facilitate comparisons. The antipodes of structures **73a-d** and **74a-d** are not shown, but would lead to the enantiomers of the indicated products **78, 79, 109, 110,** and ultimately to those of the final products **1, 61, 80** and **81**, respectively.

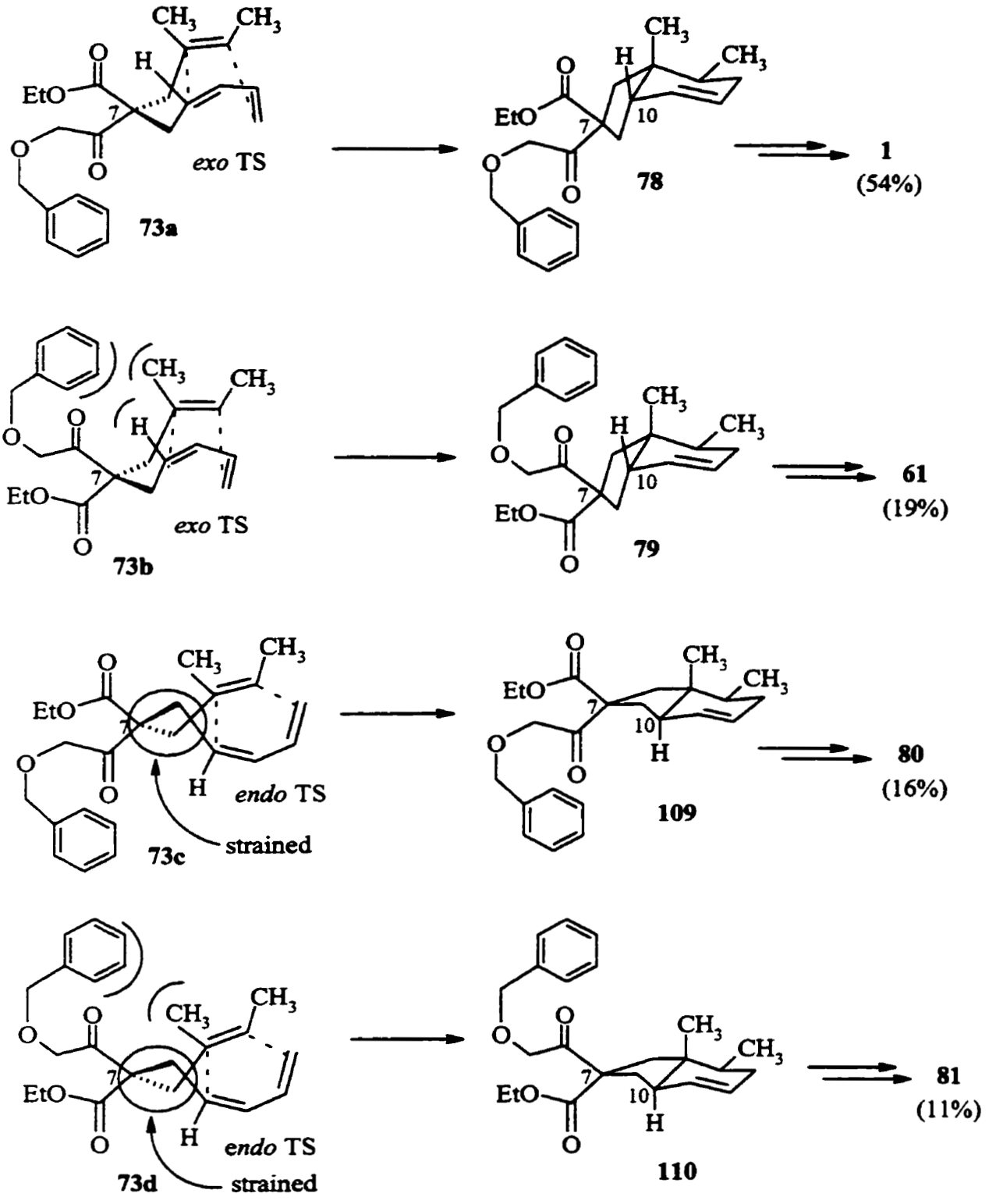


Figure 18. Four Possible Transition States of *cis* **73**

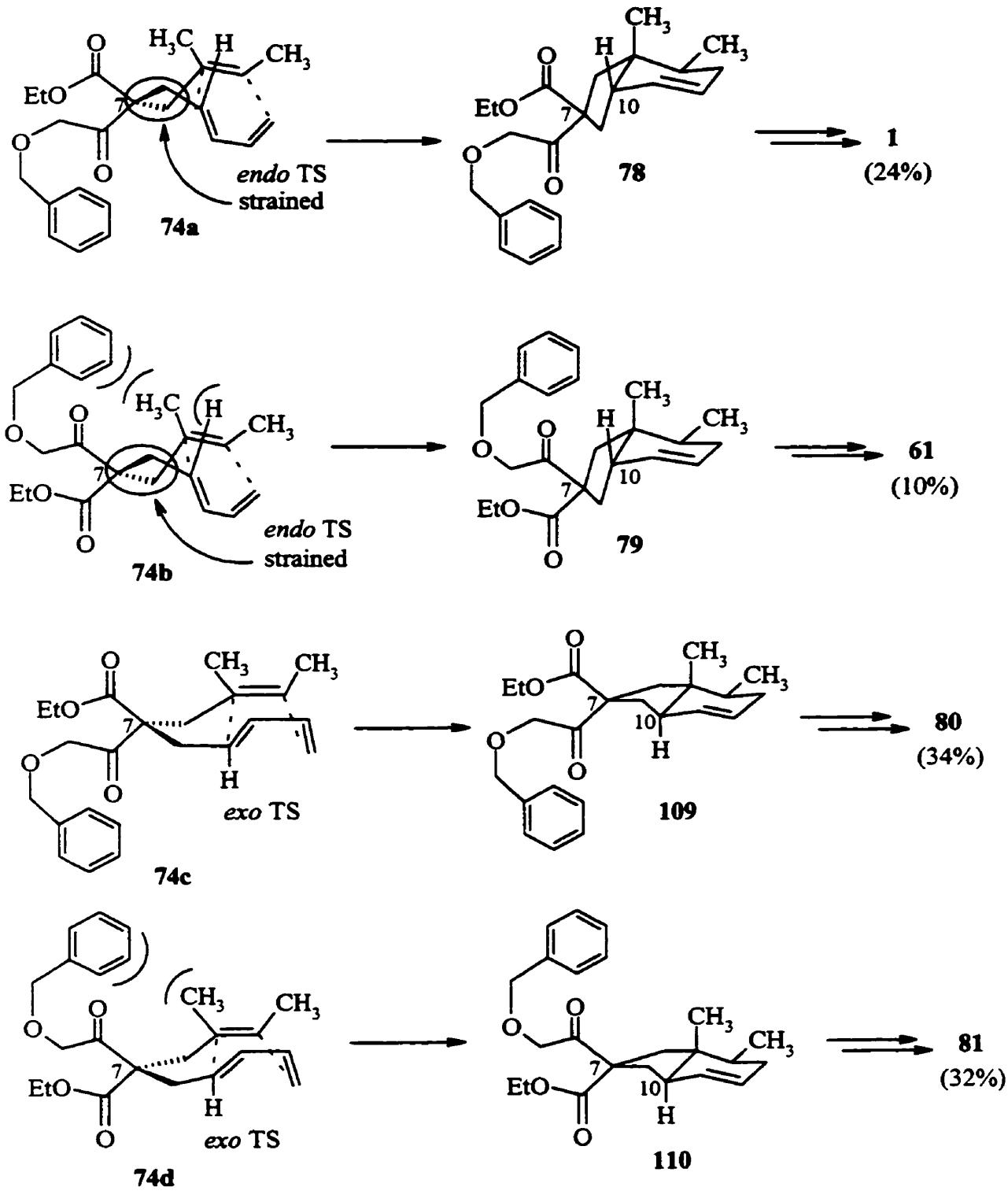
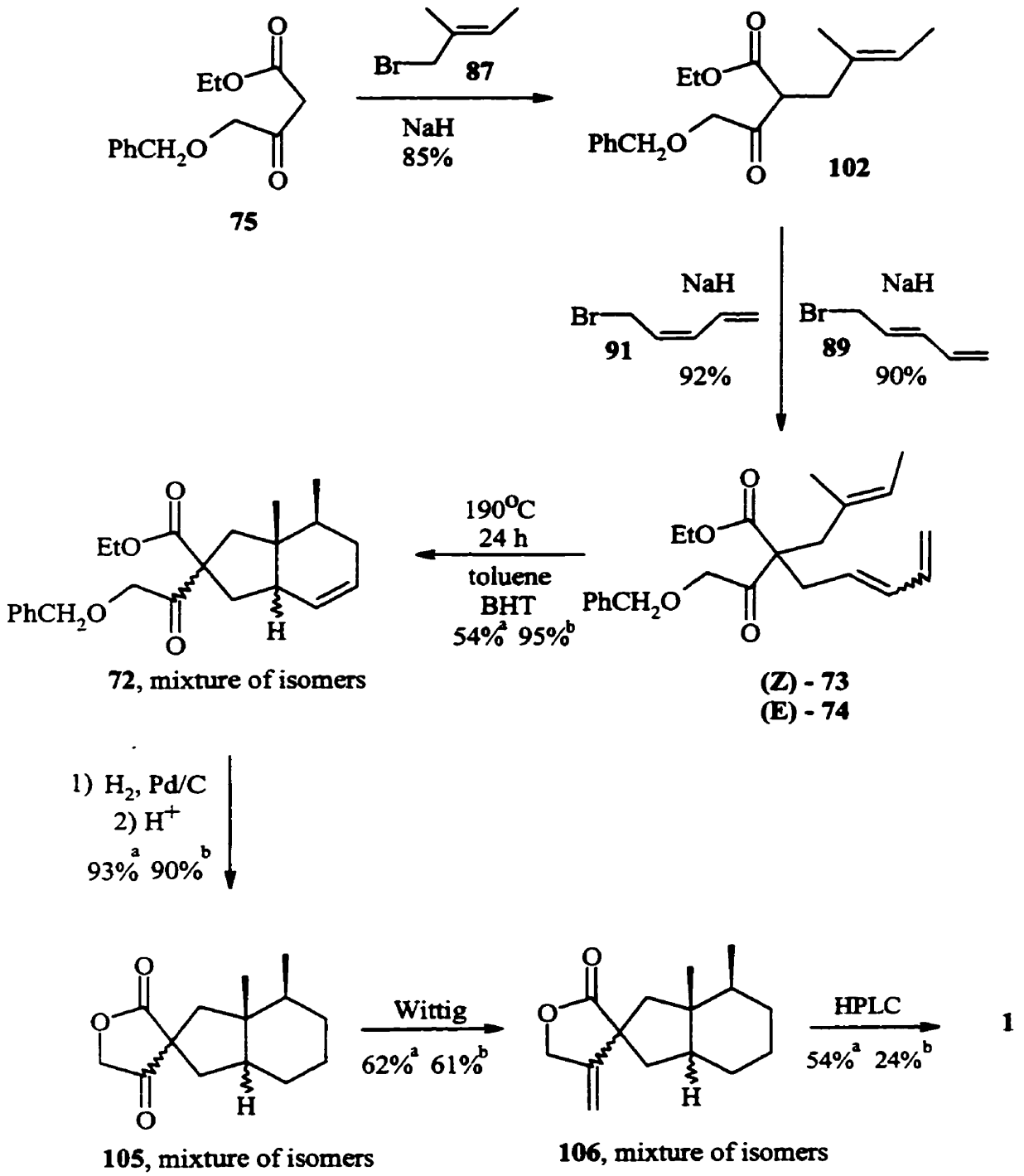


Figure 19. Four Possible Transition States of *trans* **74**

2.14 Summary of Strengths and Weaknesses of This Synthesis

Our successful synthesis of (±)-bakkenolide-A (**1**) is summarized in Scheme 37. The protected β-keto ester starting material **75** underwent a mono C-alkylation with tiglyl bromide (**87**) to provide **102** in 85% yield. A second alkylation with *cis*- and *trans*-dienyl bromides **91** and **89** provided the (Z) and (E) pre-Diels-Alder intermediates **73** and **74**, respectively, in high yields. The third and key step of our synthesis utilized intramolecular Diels-Alder chemistry to convert **73** or **74** into **72** (obtained as mixture of cylcoadduct isomers) in 54% and 95% yield, respectively. Catalytic hydrogenation, followed by acid-catalyzed lactonization reduced the double bond, cleaved the benzylic protecting group and closed the lactone to furnish **105** in 93% an d 90% overall yield, respectively. The unseparated mixture of isomers **105** underwent a Wittig reaction in the final step of the synthesis to provide the mixture of bakkenolides **106** in 62% and 61% yield, respectively. The mixture of four bakkenolide isomers **106** was then separated via HPLC to provide the target compound **1** in 54% or 24% yield, respectively. The other three bakkenolide-A stereoisomers were also isolated and identified as **61**, **80** and **81**.

Compared with the three previous approaches to bakkenolide-A, our synthesis is arguably the most concise (only 5 steps from the known β-keto ester starting material **75**). The overall yield of bakkenolide-A from **75** is 13%, which is higher than in the previous syntheses, except for that of Greene (24% overall yield via Scheme 6). While it must be conceded that the required *cis*-dienyl bromide **91** is not readily available (overall yield is 17% from 3-buten-1-ol as shown in Scheme 27), the same is true for the silyl ether intermediate **43** employed by Greene, which was synthesized in only 11% overall yield from dimethylacrylic acid.



a - The starting material was derived from **(Z)-73**
b - The starting material was derived from **(E)-74**

Scheme 37. The Back/Payne Total Synthesis of (±)-Bakkenolide-A (**1**).

Another strength of this approach is its amenability toward the synthesis of other bakkenolides. By varying the substituents in the allylic bromide reagents **87**, **89** and **91**, a variety of A and B ring-functionalized bakkenolides could likely be synthesized using our approach. Our synthesis also introduced two previously unknown bakkenolides (**80** and **81**) and the first stereoselective preparation of (Z)-5-bromo-1,3-pentadiene (**91**).

Our synthesis of bakkenolide-A requires the use of HPLC, however, and therefore is not applicable towards the large-scale preparation of **1** in its present form. Furthermore, the diastereoselectivity of the key step is relatively low (54%) and, to date, only the racemic product has been produced.

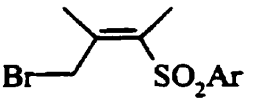
2.15 Future Work

2.15.1 Improving the Yield and Diastereoselectivity of the Diels-Alder Reaction

As mentioned earlier, the yield for the intramolecular Diels-Alder reaction of the *cis* intermediate **73** was only 54% due to undesired polymerization and possibly competing 1,5 hydrogen shifts in the *cis* diene substituent at the elevated temperatures that were employed. Lowering the requisite reaction temperature should thus markedly improve the yield of the Diels-Alder reaction. This might be possible by using appropriate activating groups in the cycloaddition.

Furthermore, improving the diastereoselectivity of the intramolecular Diels-Alder reaction would not only increase the efficiency of the synthesis by raising the overall yield, but it would also facilitate the separation of the desired product from its stereoisomers and might obviate the need for HPLC.

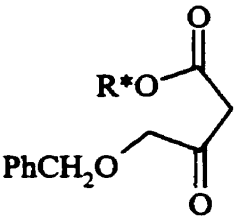
It may be possible to perform the Diels-Alder reaction under milder conditions and with improved diastereoselectivity by activating the dienophile of the pre-Diels-Alder intermediates with a disposable electron-withdrawing group such as a sulfone that can subsequently be removed by reduction. Thus, a future approach could investigate the use of a modified dienophile moiety introduced via the bromide **111**.



111

2.15.2 An Enantioselective Modification

An enantioselective modification of our approach to bakkenolide-A might be possible by starting the synthesis with a chiral β-keto ester **112**. Appropriate chiral auxiliaries (denoted by R*) such as menthol could be used to control the absolute configuration of the chiral center created by the double alkylation protocol.



112

Chapter Three

Experimental Section

3.1 General Comments

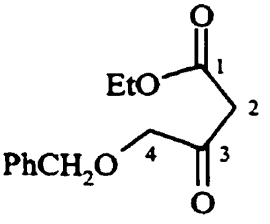
Melting points were determined using an A.H. Thomas hot-stage apparatus and are uncorrected. IR spectra were recorded on a Mattson 4030 spectrometer. ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50MHz) spectra were acquired on a Bruker ACE 200 spectrometer, with deuteriochloroform as the solvent, and either chloroform or tetramethylsilane as the internal standard, unless otherwise indicated. Other ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were obtained on a Bruker AM 400. Low and high resolution mass spectra were obtained on a Kratos MS80 or a VG 7070 mass spectrometer by Dr. Q. Wu and Ms. D. Fox at the University of Calgary. Elemental analyses were determined by Ms. D. Fox. The GC-MS instrument used was a Hewlett Packard 5890 Series II with a Hewlett Packard OV-101, low polarity, 12 m x 0.2 mm column, employed in conjunction with a Hewlett Packard Mass Selective Detector 5971A. The GC-MS temperature program used began at 180°C and increased by 2°C/min over 40 min. Analytical TLC was carried out with aluminum sheets coated with Merck silica gel 60 F-254, and the spots were visualized with UV light, or by spraying with a 2% ceric sulfate solution in 12% aqueous sulfuric acid, followed by heating for several seconds. Preparative TLC was carried out on Analtech 20 X 20 cm glass plates coated with 1 mm of silica gel GF. Chromatography refers to flash chromatography[56] and was performed on Merck silica gel, 60-200 or 230-400 mesh. HPLC was performed

using a Waters 600 Controller, 600 Pump, and 486 Tunable Absorbance Detector. A 3.5 mm x 10.5 mm Waters Nova-Pak, C18, 6 μm reverse-phase column was used for analytical HPLC. Preparatory HPLC was performed on a similar but larger 25 mm x 105 mm column. High temperature reactions were performed in a 600 mL Parr apparatus.

The concentration of n-butyllithium solutions was determined by titration with 2,5-dimethoxybenzyl alcohol.[57] Dry diisopropylamine was obtained by distillation from calcium hydride. All other reagents were obtained from commercial sources and used without further purification, unless otherwise noted. Solvents were reagent grade. Anhydrous THF and diethyl ether were obtained by distillation from lithium aluminum hydride. Anhydrous benzene was obtained by distillation from calcium hydride.

Structures in Chapter Three are numbered for convenience in making spectroscopic assignments. The numbering schemes do not necessarily follow IUPAC conventions.

3.2 Preparation of Ethyl 4-Benzyloxyacetoacetate (75)

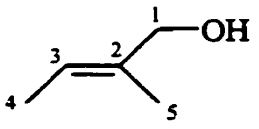


75

Compound **75** was prepared using the procedure of Tenud *et al.*[41] THF (100 mL) was placed in a flame-dried 500 mL round-bottomed flask equipped with a magnetic stirring bar under nitrogen. NaH (60% suspension, 6.29 g, 157 mmol) was added,

followed by benzyl alcohol (8.50 g, 78.6 mmol). The solution was warmed to 40°C and allowed to stir for 1 h until the bubbling subsided. Ethyl 4-chloroacetoacetate (**84**) (12.9 g, 78.4 mmol) in 50 ml THF was added slowly over 5 min. The reaction mixture was stirred for 15 h. Aqueous 10% HCl was then added until the solution turned litmus paper red. The solvent was removed under reduced pressure and water (50 mL) was added. The mixture was extracted with diethyl ether (4 x 50 mL) and the combined extracts were concentrated. The product **75** was isolated via distillation, bp 132-135°C/0.5 mmHg (lit.[41] bp 136-140°C/1.0 mmHg) and then purified further via chromatography with 4:1 hexanes/EtOAc (12" x 2" column of silica gel) to afford 15.2 g (82%) of a light yellow oil; ^{1}H-NMR δ 7.42-7.28 (m, 5 H, Ar), 4.59 (s, 2 H, Ph**CH$_2$**O), 4.18 (q, J = 7.2 Hz, 2 H, CH$_3$**CH$_2$**O), 4.15 (s, 2 H, H-4), 3.54 (s, 2 H, H-2), 1.25 (t, J = 7.2 Hz, 3 H, CH$_3$). The spectrum is in accord with that reported in the literature.[41]

3.3 Preparation of (E)-2-Buten-1-ol (86)

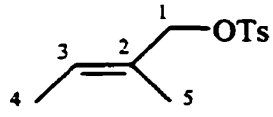


86

Tiglyl alcohol (**86**) was prepared using the general procedure of Nystrom and Brown.[43] Lithium aluminum hydride (16.0 g, 0.422 mol) and 600 mL of diethyl ether were placed in a 2 L three-necked round-bottomed flask equipped with a septum, condenser, addition funnel and a magnetic stirring bar under nitrogen. The mixture was stirred and a solution of tiglic acid (**88**) (19.0 g, 0.190 mol) in 200 mL of diethyl ether

was added over 2 h using the addition funnel. The resulting reaction mixture was stirred for an additional 24 h. Ice water (19 mL) was then added dropwise over 1 h, followed by the addition of 15% NaOH solution (19 mL) and more ice water (57 mL). The mixture was filtered and the filtered salts were thoroughly washed with diethyl ether (3 x 200 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 150 mL). The organic layers were combined, dried ($MgSO_4$) and filtered. The diethyl ether was removed under reduced pressure and the resulting colourless oil was distilled, bp 64-67°C (lit.[59] 65-70°C/760 mmHg), to afford 15.4 g (94%) of **86**; ^{1}H-NMR δ 5.42 (m, 1 H, H-3), 3.91 (s, 2 H, H-1), 2.24 (br s, 1 H, OH), 1.60 (s, 3 H, H-5), 1.57 (d, J = 6.9 Hz, 3 H, H-4). The spectrum is in accord with that reported in the literature.[60]

3.4 Preparation of Tiglyl Tosylate (85)

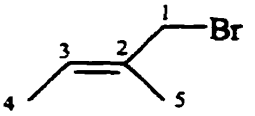


85

Tiglyl tosylate (**85**) was prepared using the procedure of Kurth and Decker.[42] Tiglyl alcohol (**86**) (200 mg, 2.32 mmol) and 5 mg of 1,10-phenanthroline were placed in a 25 mL flame-dried round-bottomed flask equipped with a magnetic stirring bar under nitrogen. THF (12 mL) was added and the reaction mixture was cooled to -78°C. *n*-Butyllithium (2.3 M in hexanes) was added to the reaction mixture until the end point was reached (mixture turns brown), at which time tosyl chloride (443 mg, 2.32 mmol) was added in one portion. The mixture was stirred for 20 h at -78°C, then diluted with an

equal volume of cold petroleum ether, washed with 50% NaCl solution, followed by saturated NaCl solution, and dried (K_2CO_3). The organic solution was decanted and concentrated under reduced pressure. The residual oil was taken up in diethyl ether and dried over fresh K_2CO_3 for 2 min, filtered, and concentrated to give 475 mg (86%) of **85** as a bright orange oil, which was not purified further; ^{1}H-NMR δ 7.79 (d, J = 8.4 Hz, 2 H, Ar), 7.34 (d, J = 8.3 Hz, 2 H, Ar), 5.52 (q, J = 7 Hz, 1 H, H-3), 4.42 (s, 2 H, H-1), 2.45 (s, 3 H, Ar**CH$_3$**), 1.60-1.50 (m, 6 H, H-4 and H-5). The spectrum is in accord with that reported in the literature.[42] The product decomposed after two days at room temperature.

3.5 Preparation of (E)-1-Bromo-2-methyl-2-butene (87)

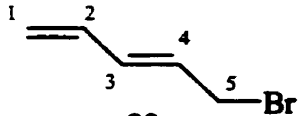


87

Tiglyl bromide (**87**) was prepared using the bromination procedure of Crumrine *et al.*[44] (E)-2-buten-1-ol (**86**) (1.30 g, 15.1 mmol) and 20 mL of diethyl ether were added to a flame-dried 50 mL round-bottomed flask equipped with a septum and a magnetic stirring bar under nitrogen. The solution was stirred for two min. The flask was wrapped in aluminum foil and cooled to 0°C, at which time PBr_3 (0.57 mL, 6.0 mmol) was added. The reaction mixture was stirred for an additional 2 h and ice water (15 mL) was added to quench the reaction. The mixture was extracted with diethyl ether (5 x 15 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and the solvent was carefully removed under reduced pressure at room temperature. Distillation, bp 44-46°C/45

mmHg (lit.[61] 43-47°C/44 mmHg) afforded 2.08 g (90%) of **87** as a colourless liquid; ^{1}H-NMR δ 5.69 (br q, J = 6.8 Hz, 1 H, H-3), 3.98 (d, J = 0.7 Hz, 2 H, H-1), 1.75 (br t, J = 1.1 Hz, 3 H, H-5), 1.63 (br d, J = 6.8 Hz, 3 H, H-4). The spectrum is in accord with those reported in the literature.[62,63]

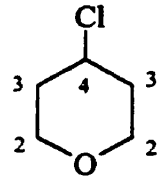
3.6 Preparation of (E)-5-Bromo-1,3-pentadiene (89)



89

Bromide **89** was prepared following the procedure of Prevost.[45] Aqueous HBr (8.9 N, 3.15 mL) was placed in a 25 mL round-bottomed flask and cooled to 0°C. Divinyl carbinol (**90**) (2.27 g, 27.0 mmol) was then added dropwise over 5 min. The reaction mixture was stirred for 1 h at room temperature, at which time 15 mL of diethyl ether was added. The organic layer was separated from the aqueous layer and washed with ice water (4 x 10 mL), dried ($MgSO_4$) and filtered. The solvent was carefully removed under reduced pressure at room temperature and the resulting colourless liquid was distilled, bp 56-57°C/38 mmHg (lit.[45] 54-55°C/34 mmHg), to afford 3.25 g (82%) of **89**; ^{1}H-NMR δ 6.45-6.20 (m, 2 H), 6.00-5.80 (m, 1 H), 5.42-5.06 (m, 2 H), 4.03 (d, J = 8.0 Hz, 2 H, H-5). The spectrum is in accord with those reported in the literature.[47,64]

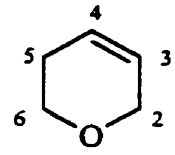
3.7 Preparation of 4-Chlorotetrahydropyran (94)



94

4-Chlorotetrahydropyran (**94**) was prepared following the procedure of Colonge.[49] Trioxane (**95**) (1.69 g, 18.8 mmol) was placed in a flame-dried 25 mL round-bottomed flask equipped with a septum and a magnetic stirring bar under nitrogen. 3-Buten-1-ol (**96**) (4.2 g, 58 mmol) was then added, dissolving most of the trioxane (**95**). The mixture was cooled to 0°C, at which time the flask and its contents were weighed. HCl gas was then bubbled through the stirred mixture at 0°C until 2.8 g (77 mmol) had been absorbed. After the addition of the HCl was complete, the reaction mixture was allowed to warm to room temperature and was stirred for an additional 16 h. The light brown reaction mixture was transferred to a 250 mL separatory funnel and diethyl ether (100 mL) was added. After agitation of the separatory funnel the mixture was allowed to separate into two layers. The lower dark layer was discarded. The colourless upper layer was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The resulting colourless oil was distilled, bp 53-54°C/25 mmHg (lit.[65] 45°C/12 mmHg), to afford 3.70 g (53%) of **94**; ^{1}H-NMR δ 4.19 (m, 1 H, H-4), 3.95 (m, 2 H, H-2), 3.51 (m, 2 H, H-2), 2.09 (m, 2 H, H-3), 1.86 (m, 2 H, H-3).

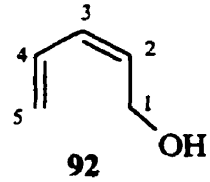
3.8 Preparation of 3,6-Dihydro-2*H*-pyran (93)



93

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (**101**) (10 mL) was added to a flame-dried 25 mL round-bottomed flask equipped with a septum and a magnetic stirring bar under nitrogen. 4-Chlorotetrahydropyran (**94**) (2.70 g, 22.4 mmol) was added dropwise over 5 min. The reaction mixture was then allowed to stir at room temperature for 2 h, at which time the mixture was heated and the resulting colourless liquid was distilled from the reaction mixture, bp 91-93°C (lit.[66] 93-94°C/760 mmHg), to afford 1.79 g (95%) of **93**; ^{1}H-NMR δ 5.78 (m, 2 H, H-3 and H-4), 4.13 (m, 2 H, H-2), 3.80 (t, J = 5.5 Hz, 2 H, H-6), 2.13 (m, 2 H, H-5). The spectrum is in accord with that reported in the literature.[66]

3.9 Preparation of (Z)-2,4-Pentadien-1-ol (92)

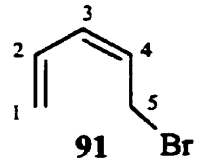


92

Alcohol **92** was prepared following the procedure of Schlosser.[48] Under reduced pressure, the solvent was stripped off from a solution of 2.3 M n-butyllithium (21.7 mL, 50 mmol in hexane). Diisopropylamine (7.1 mL, 5.1 g, 50 mmol), potassium *t*-butoxide

(0.6 g, 5 mmol) and 3,6-dihydro-2*H*-pyran (**93**) (4.2 g, 50 mmol) were added at -78°C. After 2 h at -50°C, the solvent was removed under reduced pressure. Water (150 mL) was added to the residue, which was then extracted with hexanes (3 x 50 mL). The combined organic layers were concentrated and the resulting colourless liquid was distilled, bp 81-83°C/19 mmHg (lit.[48] 76-79°C/12 mmHg), to afford 1.89 g (45%) of **92**; ^{1}H-NMR δ 6.63 (dddd, J = 16.9, 11.1, 10.2, 1.0 Hz, 1 H, H-4), 6.10 (crude t, J = 11.1 Hz, 1 H, H-3), 5.64 (dt, J = 10.5, 7.0 Hz, 1 H, H-2), 5.28 (dd, J = 17.0, 1.5 Hz, 1 H, H-5), 5.19 (d, J = 10.2 Hz, 1 H, H-5), 4.32 (dd, J = 7.0, 1.2 Hz, 2 H, H-1), 1.95 (br s, 1 H, OH). The spectrum is in accord with that reported in the literature.[48]

3.10 Preparation of (Z)-5-Bromo-1,3-pentadiene (91)

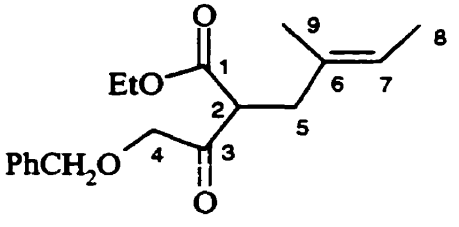


91

Bromide **91** was prepared following a procedure similar to that used by Crumrine *et al.*[44] for the preparation of tiglyl bromide (**87**). (Z)-2,4-Pentadien-1-ol (**92**) (0.900 g, 10.7 mmol) and diethyl ether (10 mL) were added to a flame-dried 25 mL round-bottomed flask equipped with a septum and a magnetic stirring bar under nitrogen. The solution was stirred for two min. The flask was wrapped in aluminum foil and cooled to 0°C, at which time PBr_3 (0.42 mL, 4.4 mmol) was added. The reaction mixture was stirred for an additional 2 h and ice water (10 mL) was added to quench the reaction. The mixture was extracted with diethyl ether (5 x 10 mL). The organic layers were

combined, dried ($MgSO_4$), filtered, and the solvent was carefully removed under reduced pressure at room temperature. The product, which is a strong lachrymator, was distilled, bp 42-43°C/25 mmHg, to afford 1.15 g (72%) of **91** as a colourless liquid; ^{1}H-NMR δ 6.69 (dt, J = 16.8, 10.7 Hz, 1 H, H-2), 6.14 (t, J = 10.8 Hz, 1 H, H-3), 5.73 (m, 1 H, H-4), 5.43-5.26 (m, 2 H, H-1), 4.13 (d, J = 8.5 Hz, 2 H, H-5). The spectrum is in accord with that reported in the literature.[47]

3.11 Preparation of Ethyl 4-Benzyloxy-2-[2-methyl-2(E)-butenyl]acetoacetate (102)

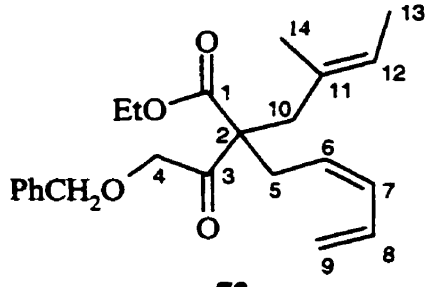


102

THF (100 mL) and NaH (60% suspension, 1.74 g, 43.5 mmol) were placed inside a flame-dried 500 mL round-bottomed flask equipped with a septum and a magnetic stirring bar under nitrogen. A solution of β-keto ester **75** (10.3 g, 43.5 mmol) in 75 mL of THF was added over 10 min. The reaction mixture was stirred for 30 min until the bubbling subsided, then a solution of tiglyl bromide (**87**) (6.48 g, 43.5 mmol) in 100 mL of THF was added dropwise over 15 min. The reaction mixture was stirred for 18 h. It was then filtered to remove salts that had formed during the reaction and the THF was removed under reduced pressure (some cloudiness was still evident). Water (150 mL) was added and the mixture was extracted with diethyl ether (3 x 100 mL). The extracts were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure.

Chromatography with 5:1 hexanes/EtOAc (12" x 2.5" column of silica gel) afforded 11.2 g (85%) of **102** as a colourless oil; IR(neat) 1750 (ester C=O), 1733 (ketone C=O), 741, 699 cm^{-1}; ^{1}H-NMR δ 7.35 (m, 5 H, Ar), 5.24 (m, 1 H, H-7), 4.58 (s, 2 H, Ph**CH$_2$**O), 4.18-4.05 (m, 4 H, H-4 and CH_3**CH_2**O), 3.82 (t, J = 7.6 Hz, 1 H, H-2), 2.55 (m, 2 H, H-5), 1.60 (t, J = 1.1 Hz, 3 H, H-9), 1.53 (crude d, J = 6.7 Hz, 3 H, H-8), 1.20 (t, J = 7.1 Hz, 3 H, **CH_3**CH_2O); mass spectrum, m/z (relative intensity, %) 258 (4), 207 (16), 167 (38), 91 (100), 41 (17). Anal. calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.60; H, 8.20.

3.12 Preparation of Ethyl 4-Benzyloxy-2-[2-methyl-2(E)-butenyl]-2-[2(Z),4-pentadienyl]acetoacetate (73)

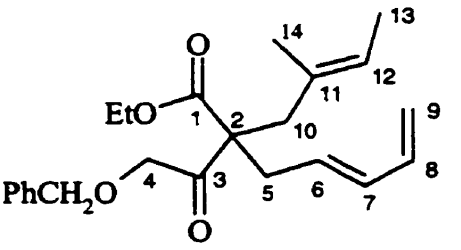


73

THF (10 mL) and NaH (60% suspension, 0.171 g, 4.28 mmol) were placed inside a flame-dried 50 mL round-bottomed flask equipped with a condenser, septum and magnetic stirring bar under nitrogen. A solution of compound **102** (1.30 g, 4.27 mmol) in 5 mL of THF was added. The reaction mixture was stirred for 30 min until bubbling subsided, then a solution of (Z)-bromide **91** (0.636 g, 4.27 mmol) in 5 mL of THF was added. The reaction mixture was refluxed for 2 h and allowed to cool to room temperature. The mixture was then filtered to remove salts that had formed during the

reaction and the THF was removed under reduced pressure (some cloudiness was still evident). Water (30 mL) was added and the mixture was extracted with diethyl ether (3 x 20 mL). The extracts were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography with 7:1 hexanes/EtOAc (12" x 1.5" column of silica gel) afforded 1.45 g (92%) of **73** as a colourless oil; ^{1}H-NMR δ 7.34 (m, 5 H, Ar), 6.58 (dt, J = 16.8, 10.6 Hz, 1 H, H-8), 6.08 (t, J = 11.1 Hz, 1 H, H-7), 5.35-5.06 (m, 4 H, H-6, H-9 and H-12), 4.54 (s, 2 H, $PhCH_2O$), 4.18 (s, 2 H, H-4), 4.12 (q, J = 7.2 Hz, 2 H, CH_3CH_2O), 3.00-2.60 (m, 2 H, H-5), 2.69 (br s, 2 H, H-10), 1.57 (d, J = 4.4 Hz, 3 H, H-14), 1.50 (t, J = 1.2 Hz, H-13), 1.18 (t, J = 7.2 Hz, 3 H, CH_3CH_2O); mass spectrum, m/z (relative intensity, %) 281 (23), 207 (100), 91 (88), 40 (58). Anal. calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.52; H, 8.50.

3.13 Preparation of Ethyl 4-Benzyloxy-2-[2-methyl-2(E)-butenyl]-2-[2(E),4-pentadienyl]acetoacetate (74)

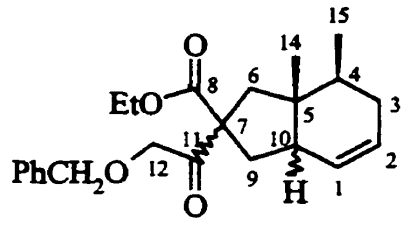


74

THF (25 mL) and NaH (60% suspension, 0.445 g, 11.1 mmol) were placed inside a flame-dried 200 mL round-bottomed flask equipped with a condenser, septum and a magnetic stirring bar under nitrogen. A solution of compound **102** (3.38 g, 11.1 mmol) in 10 mL of THF was added. The reaction mixture was stirred for 30 min until bubbling

subsided, then a solution of bromide **89** (1.65 g, 11.1 mmol) in 10 mL of THF was added. The reaction mixture was refluxed for 2 h and allowed to cool to room temperature. The mixture was filtered to remove salts that had formed during the reaction and the THF was removed under reduced pressure (some cloudiness was still evident). Water (75 mL) was added and the mixture was extracted with diethyl ether (3 x 50 mL). The extracts were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography with 7:1 hexanes/EtOAc (12" x 2.5" column of silica gel) afforded 3.69 g (90%) of **74** as a colourless oil; IR(neat) 1745 (ester C=O), 1718 (ketone C=O), 1609 (C=C), 744, 697 cm^{-1}; ^{1}H-NMR δ 7.34 (m, 5 H, Ar), 6.25 (dt, J = 16.8, 10.2 Hz, 1 H, H-8), 6.10-5.93 (m, 1 H, H-7), 5.50 (dt, J = 14.7, 7.2 Hz, 1 H, H-6), 5.25 (m, 1 H, H-12), 5.14-4.97 (m, 2 H, H-9), 4.54 (s, 2 H, $PhCH_2O$), 4.19 (s, 2 H, H-4), 4.08 (q, J = 7.2 Hz, 2 H, CH_3CH_2O), 2.75-2.60 (m, 4 H, H-5 and H-10), 1.63-1.47 (m, 6 H, H-13 and H-14), 1.19 (t, J = 7.2 Hz, 3 H, CH_3CH_2O); ^{13}C-NMR δ 204.8 (C-3), 171.4 (C-1), 137.0, 136.6, 134.7, 130.6, 128.4, 128.3, 127.9, 127.7, 124.6, 116.3, 74.2, 73.3, 61.4, 61.0, 42.1, 35.5, 16.9, 14.0, 13.5; mass spectrum, m/z (relative intensity, %) 281 (27), 207 (100), 91 (93), 40 (42). Anal. calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 72.93; H, 8.16.

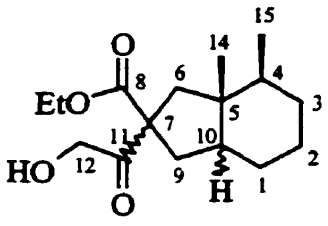
3.14 Preparation of the Mixture of Diels-Alder Products 72



72

Compound **74** (1.05 g) and 400 mL of toluene were placed in a 600 mL Parr apparatus. The reaction mixture was heated at 190°C for 24 h. After cooling to room temperature, the toluene was removed under reduced pressure. Chromatography with 8:1 hexanes/EtOAc (9" x 2" column of silica gel) afforded 1.00 g (95%) of **72** (obtained as a mixture of isomers) as a light yellow oil; IR(neat) 1746 (ester C=O), 1715 (ketone C=O), 750, 698 cm^{-1}; ^{1}H-NMR (400 MHz) δ 7.40-7.25 (m, 5 H, Ar), 5.70-5.55 (m, 2 H, H-1 and H-2), 4.55 (m, 2 H, Ph**CH$_2$**O), 4.25-4.00 (m, 4 H, O**CH$_2$**CH$_3$ and H-12), 2.70-1.40 (m, 8 H), 1.21-1.14 (m, 3 H, OCH$_2$**CH$_3$**), 0.95-0.50 (m, 6 H, H-14 and H-15); mass spectrum, m/z (relative intensity, %) 370 (M^+, 1), 279 (21), 233 (20), 147 (33), 91 (100), 41 (14). Exact mass calcd for $C_{23}H_{30}O_4$: 370.2144. Found 370.2148. The mixture of isomers **72** was also prepared in 54% yield from compound **73** following the same procedure.

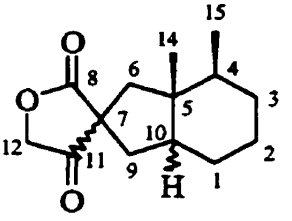
3.15 Preparation of the Mixture of Hydroxy Esters 104



104

Palladium catalyst on activated charcoal (10%Pd-C, 20 mg) and 2 mL of EtOAc were placed into a flame-dried 10 mL round-bottomed flask equipped with a septum and a magnetic stirring bar. A solution of **72** (57 mg, 0.15 mmol) in 2 mL of EtOAc was added, followed by an additional 1 mL of EtOAc to wash down the sides of the flask. The flask was purged with hydrogen and the reaction mixture was stirred under a hydrogen atmosphere (provided by a balloon filled with hydrogen) for 3 days. The catalyst was removed from the reaction mixture by filtration through Celite. The filtrate was concentrated under reduced pressure and chromatography with 5:1 hexanes/EtOAc (12" x 1" column of silica gel) afforded 39 mg (90%) of **104** (obtained as a mixture of isomers) as a colourless oil; ^{1}H-NMR (400 MHz) δ 4.40-4.10 (m, 4 H, CH_3CH_2O and H-12), 2.97-2.93 (m, 1 H, OH), 2.6-1.0 (m, 15 H), 0.95-0.50 (m, 6 H, H-14 and H-15). Because of the facile lactonization of **104**, it was converted into the lactone mixture of isomers **105** without further characterization. The mixture of isomers **104** was also prepared in 93% yield by following the same procedure with starting material **72** that had been obtained from **73**.

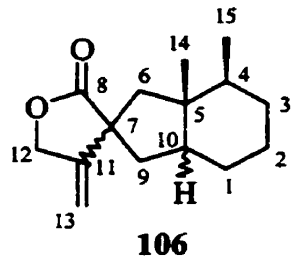
3.16 Preparation of the Mixture of β-Keto Spiro Lactones 105



105

The mixture of isomers **104** (81 mg, 0.30 mmol), 1.5 mL of dioxane, and 0.5 mL of 6M HCl were placed in a 10 mL round-bottomed flask equipped with a septum and a magnetic stirring bar. The reaction mixture was stirred for 7 h. The mixture was then extracted with diethyl ether (3 x 10 mL). The extracts were combined, dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure and chromatography with 3:1 hexane/EtOAc (10" x 1" column of silica gel) afforded 72 mg (quantitative) of **105** as a colourless oil; IR(neat) 1756 (lactone C=O), 1740 (ketone C=O) cm^{-1}; ^{1}H-NMR (400 MHz) δ 4.72-4.56 (m, 2 H, H-12), 2.45-1.05 (m, 12 H), 1.00-0.80 (m, 6 H, H-14 and H-15); mass spectrum, m/z (relative intensity, %) 236 (M^+, 5), 221 (6), 123 (100), 109 (77), 81 (48), 67 (36), 41 (27). The mixture of isomers **105** was also prepared in quantitative yield from **104** that had been obtained from **73**.

3.17 Preparation of the Mixture of Bakkenolides 106

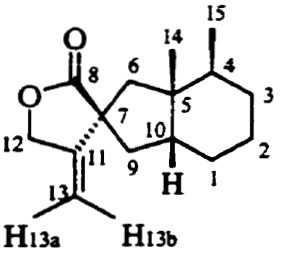


106

Methyl triphenylphosphonium iodide (**107**) (0.24 g, 0.59 mmol) and 4 mL of diethyl ether were placed in a 10 mL flame-dried round-bottomed flask equipped with a septum and a magnetic stirring bar under nitrogen. *n*-Butyllithum (2.17 M, 0.27 mL, 0.59 mmol) was added and the reaction mixture was stirred for 5 min, generating a clear bright yellow solution. A solution of **105** (47.0 mg, 0.199 mmol) in 1 mL of diethyl ether was added and the reaction mixture was stirred for an additional 2 h. The reaction was quenched with an equal volume of ice water. The mixture was extracted with diethyl ether (5 x 10 mL) and the extracts were combined and concentrated under reduced pressure. Chromatography with 5:1 hexanes/EtOAc (10" x 1" column of silica gel) afforded 28.9 mg (62%) of **106** (obtained as a mixture of isomers) as a colourless oil. Mixture **106** consisted of four bakkenolide isomers **1**, **61**, **81** and **80** that were isolated via HPLC. Analytical HPLC: UV detector, 212 nm; solvent system, 30% H_2O - 70% CH_3OH; flow rate, 0.85 mL/min; elution times for **1**, **61**, **81** and **80** were 10.2, 10.5, 10.8, and 11.6 min, respectively. Preparative HPLC: UV detector, 225 nm; solvent system, 30% H_2O - 70% CH_3OH; flow rate, 7.0 mL/min; elution times for **1**, **61**, **81** and **80** were 22.4, 23.0, 23.6, and 25.2 min, respectively. Repeated preparative HPLC afforded 1.2 mg of **1**, 0.5 mg of **80** and 0.8 mg of **81** in greater than 95% purity and 0.5 mg of **61** as a

4:1 mixture with **1**. The mixture of isomers **106** was also prepared in 61% yield by following the same procedure when the starting material **105** was obtained from **74**. The characterization data for **1**, **61**, **80** and **81** is described in sections 3.18-3.21, respectively.

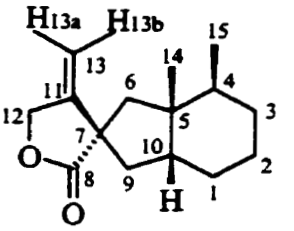
3.18 Spectral Data for (±)-Bakkenolide-A (1)



1

^{1}H-NMR (400 MHz) δ 5.12 (m, 1 H, H-13b), 5.04 (m, 1 H, H-13a), 4.78 (m, 2 H, H-12), 2.26 (m, 1 H, H-10), 2.10 (t, J = 13.1 Hz, 1 H), 1.98 (m, 2 H), 1.70-1.40 (m, 10 H), 1.20 (m, 1 H), 1.00 (s, 3 H, H-14), 0.86 (d, J = 6.8 Hz, 3 H, H-15); ^{13}C-NMR (100 MHz) δ 150.7 (C-11), 106.0 (C-13), 70.6 (C-12), 50.1, 48.8, 46.4, 44.3, 42.6, 34.1, 31.1, 23.6, 21.2, 19.4, 16.6; mass spectrum, m/z (relative intensity, %) 234 (M^+,10%), 219 (8), 123 (45), 124 (100), 111 (71), 41 (12). These spectra were identical to ones obtained from an authentic sample provided by Dr. J. Harmatha. The ^{1}H- and ^{13}C-NMR of the above synthetic sample and the authentic sample are shown in Figures 8 and 9.

3.19 Spectral Data for (±)-7-Epibakkenolide-A (61)

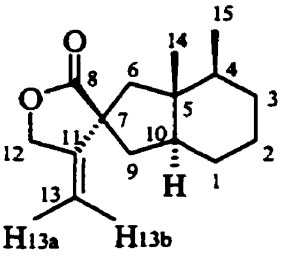


61

^{1}H-NMR δ 5.07 (m, 1 H, H-13b), 4.99 (m, 1 H, H-13b), 4.75 (m, 2 H, H-12), 2.47 (dd, J = 13.5, 12.3 Hz, 1 H), 2.41 (d, J = 14.0 Hz, 2 H), 2.10-1.40 (m, 10 H), 0.97 (s, 3 H, H-14), 0.82 (d, J = 6.6 Hz, 3 H, H-15); these signals were superimposed on those corresponding to **1**; the ratio of integrated intensities of signals of **61** to those of **1** was ca. 4:1; the spectrum is shown in Figure 10; mass spectrum, m/z (relative intensity, %) 234 (M^+, 72%), 219 (30), 123 (82), 124 (78), 111 (100), 41 (40).

7-Epibakkenolide-A (**61**) was synthesized for the first time while this work was in progress. Srikrishna, *et al.* reported[34] the following: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.07 (s, 1 H, H-13b), 4.99 (s, 1 H, H-13a), 4.75 (m, 2 H, H-12), 2.48 (d, J = 13.1 Hz, 1 H), 2.39 (d, J = 14.1 Hz, 1 H), 2.10-1.40 (m, 10 H), 0.97 (s, 3 H, H-14), 0.82 (d, J = 6.6 Hz, 3 H, H-15);

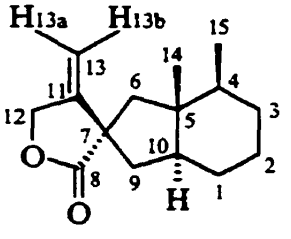
3.20 Spectral Data for (±)-10-Epibakkenolide-A (80)



80

^{1}H-NMR (400 MHz) δ 5.08 (m, 1 H, H-13b), 4.97 (m, 1 H, H-13a), 4.79 (m, 2 H, H-12), 2.17 (d, J = 13.2 Hz, 1 H), 2.06 (dd, J = 13..3, 12.2 Hz, 1 H), 1.80 (m, 2 H), 1.60-1.20 (m, 8 H), 0.91 (d, J = 0.8 Hz, 3 H, H-14), 0.86 (d, J = 6.5 Hz, 3 H, H-15); this spectrum is shown in Figure 11; ^{13}C-NMR (100 MHz) δ 151.9 (C-11), 104.9 (C-13), 70.1 (C-12), 51.8, 50.2, 49.1, 45.4, 43.8, 42.3, 30.0, 26.4, 24.5, 17.2, 11.9; mass spectrum, m/z (relative intensity, %) 234 (M^+, 10%), 219 (7), 123 (100), 124 (67), 111 (80), 41 (22). Exact mass calcd for $C_{15}H_{22}O_2$: 234.1620. Found: 234.1630.

3.21 Spectral Data for (±)-7,10-Diepibakkenolide-A (81)



81

^{1}H-NMR (400 MHz) δ 5.17 (t, J = 2.0 Hz, 1 H, H-13b), 5.03 (t, J = 2.0 Hz, 1 H, H-13a), 4.77 (m, 2 H, H-12), 2.09 (dd, J = 12.2, 5.8 Hz, 1 H), 1.99 (d, J = 12.8 Hz, 1 H),

1.90-1.13 (m, 10 H), 0.85 (d, J = 6.7 Hz, 3 H, H-15), 0.80 (d, J = 0.8 Hz, 3 H, H-14); this spectrum is shown in Figure 14; NOE: double irradiation of the signal at δ 5.17 ppm resulted in an enhancement of 2% of the signal at δ 0.80 ppm; ^{13}C-NMR (100 MHz) δ 149.9 (C-11), 106.1 (C-13), 70.5 (C-12), 50.3, 49.3, 45.0, 43.1, 42.4, 30.0, 26.2, 24.5, 17.1, 13.1; mass spectrum, m/z (relative intensity, %) 234 (M^+, 5%), 219 (4), 123 (56), 124 (100), 111 (81), 41 (14). Exact mass calcd for $C_{15}H_{22}O_2$, 234.1620: Found: 234.1627.

References

1. Fischer, N. H.; Olivier, E. J.; Fischer, H. D. In *Progress in the Chemistry of Organic Natural Products*; Herz, W.; Grisebach, H.; Kirby, G. W., Eds.; Springer-Verlag, New York, 1979; Vol. 38, Chapter 2.
2. Kupchan, S. M.; Hemingway, R. J.; Werner, D.; Karim, A. *J. Am. Chem. Soc.* **1968,** *90*, 3596.
3. Kupchan, S. M.; Hemingway, R. J.; Werner, D.; Karim, A. *J. Am. Chem. Soc.* **1968,** *90*, 3597.
4. Herz, W.; Subramaniam, P. S.; Santhanam, P. S.; Aota, K.; Hall, A. L. *J. Org. Chem.* **1970,** *35*, 1453.
5. Tsuda, K.; Tanabe, K.; Iwai, I.; Funakoshi, K. *J. Am. Chem. Soc.* **1957,** *79*, 5721.
6. Herz, W.; Watanabe, H.; Miyazaki, M.; Kishida, Y. *J. Am. Chem. Soc.* **1962,** *84*, 2601.
7. Abdel-Baset, Z. H.; Southwick, L.; Padolina, W. G.; Yoshioka, H.; Mabry, T. J. *Phytochem.* **1971,** *10*, 2201, and references cited therein.
8. Ivie, G. W.; Witzel, D. A.; Herz, W.; Kannan, R.; Norman, J. O.; Rushing, D. D.; Johnson, J. H.; Rowe, L. D.; Veech, J. A. *J. Agric. Food Chem.* **1975,** *23*, 841.
9. Abe, N.; Onoda, R.; Shirahata, K.; Kato, T.; Woods, M. C.; Kitahara, Y. *Tetrahedron Lett.* **1968,** 369.
10. For the background and synthesis of homogynolide-A, see (a) Hartmann, B.; Kanazawa, A. M.; Depres, J. -P.; Greene, A. E. *Tetrahedron Lett.* **1991,** *32*, 767. (b) Hartmann, B.; Kanazawa, A. M.; Depres, J. -P.; Greene, A. E. *Tetrahedron Lett.*,

1993, *34*, 3875. (c) Mori, K.; Matsushima, Y. *Synthesis* **1995**, 845. (d) Srikrishna, A.; Reddy, T. J. *Indian J. Chem.* **1995**, *34B*, 844.

11. For the background and synthesis of homogynolide-B, see (a) Coelho, F.; Depres, J. -P.; Brocksom, T. J.; Greene, A. E. *Tetrahedron Lett.* **1989**, *30*, 565. (b) Srikrishna, A.; Nagaraju, S.; Venkateswarlu, S. *Tetrahedron Lett.* **1994**, *35*, 429.

12. Hartmann, B.; Depres, J. -P; Greene, A. E.; Freire de Lima, M. E. *Tetrahedron Lett.* **1993**, *34*, 1487.

13. Reddy, T. J.; Srikrishna, A. *Tetrahedron* **1998**, *54*, 11517.

14. (a) Naya, K.; Takagi, I.; Hayashi, M.; Nakamura, S.; Kobayashi, M.; Katsumura, S. *Chem Ind. (London)* **1968**, 318. (b) Naya, K.; Hayashi, M.; Nakamura, M; Kobayashi, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3673.

15. (a) Abe, N.; Onoda, R.; Shirahata, K.; Kato, T.; Woods, M. C.; Kitahara, Y. *Tetrahedron Lett.* **1968**, 369. (b) Abe, N.; Onoda, R.; Shirahata, K.; Kato, T.; Woods, M. C.; Kitahara, Y. *Tetrahedron Lett.* **1968**, 1993. (c) Abe, N.; Shirahata, K.; Kato, T.; Kitahara, Y. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1732.

16. Shirahata, K.; Kato, T.; Kitahara, Y.; Abe, N. *Tetrahedron*, **1969**, *25*, 3179 and 4671.

17. (a) Katayama, C.; Furusaki, A.; Nitta, I.; Hayashi, M.; Naya, K. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1976.

18. Aclinou, P.; Benkouider, A.; Massiot, G.; Le Men-Olivier, L. *Phytochem.* **1991**, *30*, 2083.

19. Chen, H, -M.; Cai, M, -S; Jia, Z, -J. *Phytochem.* **1997**, *45*, 1441.

20. Wiemer, D. F.; Wolfe, L. K.; Fenical, W.; Strobel, S. A.; Clardy, J. *Tetrahedron Lett.* **1990**, *31*, 1973.

21. (a) Jamieson, G. R.; Reid, E. H.; Turner, B. P.; Jamieson, A. T. *Phytochem.* **1976,** *15*, 1713. (b) *Antitumor Compounds of Natural Origin: Chemistry and Biochemistry*; Aszalos, A., Ed., CRC Press: Boca Raton, FL, 1981.

22. Kano, K.; Hayashi, K.; Mitsuhashi, H. *Chem. Pharm. Bull.* **1982,** *30*, 1198.

23. (a) Nawrot, J.; Bloszyk, E.; Harmatha, J.; Novotny, L.; Drozdz, B. *Acta Entomol. Bohemoslov.* **1986,** *83*, 327. (b) *Fourth Int. Conf. Stored-Product Protection.* Tel-Aviv, Israel, Sept. **1986,** Donahaye, E.; Navarro, S, Eds.; pp 591-597. (c) Streibl, M.; Nawrot, J; Herout, V. *Biochem. Syst. Ecol.* **1983,** *11*, 381. (d) Harmatha, J; Nawrot, J. *Biochem. Syst. Ecology.* **1984,** *12*, 95. (e) Nawrot, J.; Harmatha, J; Novotny, L. *Biochem. Syst. Ecology.* **1984,** *12*, 99. (f) Nawrot, J.; Bloszyk, E.; Harmatha, J.; Novotny, L. *Sonderdruck aus Bd.* **1984,** *98*, 394. (g) Isman, M. B.; Brard, N. L.; Nawrot, J.; Harmatha, J. *J. Appl. Entomol.* **1989,** *107*, 524. (h) Nawrot, J.; Koul, O.; Isman, M. B.; Harmatha, J. *J. Appl. Entomol.* **1991,** *112*, 194. (i) Kreckova, J.; Krecek, J.; Harmatha, J. *Endocrinological Frontiers in Physiological Insect Ecology.*; Senhal, F.; Zabza, A; Denlinger, D. L., Eds.; Wroclaw Technical Univesity Press, Wroclaw, 1988, p. 105. (cited in ref. 23g)

24. Nagaraju, S.; Reddy, T. J.; Sattigeri, J. A.; Srikrishna, A. *Tetrahedron Lett.* **1994,** *35*, 7841, and references cited therein.

25. Hayashi, K.; Nakamura, H.; Mitsuhashi, H. *Chem. Pharm. Bull.* **1973,** *21*, 2806.

26. (a) Evans, D. A.; Sims, C. L. *Tetrahedron Lett.* **1973,** *47*, 4691. (b) Evans, D. A.; Sims, C. L.; Andrews, G. C. *J. Am. Chem. Soc.* **1977,** *99*, 5453.

27. Greene, A. E.; Depres, J. -P.; Coelho, F. *J. Org. Chem.* **1985,** *50*, 3943.

28. Nagaraju, S.; Reddy, T. J.; Sattigeri, J. A.; Srikrishna, A. *Tetrahedron Lett.* **1994,** *35*, 7841.

29. Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978,** *43*, 2879 and 3173.

30. Greene, A. E.; Depres, J. -P.; Coelho, F.; Brocksom, T. J. *Tetrahedron Lett.* **1988,** *29*, 5661.

31. Hamelin, O.; Depres, J. -P.; Greene, A. E.; Tinant, B.; Declercq, J. -P. *J. Am. Chem. Soc.* **1996,** *118*, 9992.

32. Srikrishna, A.; Nagaraju, S.; Sharma, G. V. R. *J. Chem. Soc., Chem. Commun.* **1993,** 285.

33. Sattigeri, J. A.; Srikrishna, A.; Viswajanani, R. *J. Chem. Soc., Chem. Commun.* **1995,** 469.

34. Reddy, T. J.; Srikrishna, A. *Tetrahedron* **1998,** *54*, 11517.

35. Back, T. G.; Gladstone, P. L.; Parvez, M. *J. Org. Chem.* **1996,** *61*, 3806.

36. Gladstone, P. *Total Synthesis of Compounds Related to the Bakkenolides*, PhD. Dissertation, University of Calgary, **1995**.

37. Ciganek, E. *Organic Reactions*, **1984**, *32*, 1.

38. (a) Fallis, A. G. *Can J. Chem.* **1984,** *62*, 183. (b) Taber, D. F. *Intramolecular Diels-Alder and Alder Ene Reactions*; Springer Verlag, Berlin, 1984. (c) Craig, D. *Chem Soc. Rev.* **1987,** *16*, 187. (d) Roush, W. R. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press, Greenwich CT, 1990, Volume 2, p. 91. (e) Carruthers, W. *Cycloaddition Reactions is Organic Synthesis*; Baldwin, J. E.; Magnus, P. D., Eds.; Pergamon Press, Oxford, 1990; Volume 8, Chapter 3. (f) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Pergamon Press, Oxford, 1991; Volume 5, Chapter 4.4.

39. (a) House, H. O.; Cronin, T. H. *J. Org. Chem.* **1965**, *30*, 1061. (b) Pyne. S. G.; Hensel, M. J.; Byrn, S. R.; McKenzie, A. T.; Fuchs, P. L. *J. Am. Chem. Soc.* **1980,**

102, 5960. (c) Boeckman, Jr., R. K.; Alessi, T. R. *J. Am. Chem. Soc.* **1982**, *104*, 3216.

40. Prat, M.; Moreno-Manas, M.; Ribas, J. *Tetrahedron* **1988**, *44*, 7205.

41. Meul, T.; Miller, R.; Tenud, L. *Chimia* **1987**, *41*, 73.

42. Kurth, B.; Decker, L. *J. Org. Chem.* **1985**, *50*, 5769.

43. Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc.* **1947**, *69*, 1197.

44. Katzenellenbogen, D.; Crumrine, R. *J. Am. Chem. Soc.* **1976**, *98*, 4925.

45. Prevost, C.; Miginiac, P.; Miginiac-Groizeleau, L. *Bull. Soc. Chim. Fr.* **1965**, 2485.

46. Balint, A. E.; Cserr, R. *J. Am. Chem. Soc.* **1957**, *79*, 1602.

47. Davies, A. G.; Griller, D.; Ingold, K. U.; Lindsay, D. A.; Walton, J. C. *J. Chem. Soc., Perkin Trans. II* **1981**, 633.

48. Margot, C.; Rizzolio, M.; Schlosser, M. *Tetrahedron* **1990**, *46*, 2411.

49. Colonge, J.; Boisde, P. *Bull. Soc. Chim. Fr.* **1956**, 824.

50. For a review on autoxidation, see Sheldon, L. T.; Kochi, Y. *Adv. Catal.* **1976**, *25*, 272.

51. For a review, see Duncan, L. *Chem Soc. Rev.* **1980**, *9*, 1.

52. For a review on the Wittig Reaction, see Maryanoff, J.; Reitz, L; *Chem. Rev.* **1989**, *89*, 863.

53. For examples of lower yields obtained in Wittig reactions with sterically hindered systems, see the following: (a) Smith, A. B.; Jerris, P. J. *J. Org. Chem.* **1982**, *47*, 1845. (b) Olah, G. A.; Wu, A. -H.; Farooq, O. *J. Org. Chem.* **1989**, *54*, 1375. (c) Clawson, L.; Buchwald, S. L.; Grubbs, R. H. *Tetrahedron Lett.* **1984**, *25*, 5733. (d) Pine, S. H.; Shen, G. S.; Hoang, H. *Synthesis* **1991**, 165. (e) Hibino, J.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5579. (f) Stille, J. R.; Grubbs, R.

H. *J. Am. Chem. Soc.* **1986,** *108*, 855. (g) Paquette, L. A.; Stevens, K. E. *Can. J. Chem.* **1984,** *62*, 2415.

54. Novotny, L.; Kotva, K.; Toman, J.; Herout, V. *Phytochem.* **1972,** *11*, 2795.

55. For example, see: Lambert, J. B.; Shurvell, H. F.; Lightner, D. A.; Cooks, R. G. In *Organic Structural Spectroscopy*; Prentice Hall, New Jersey, 1998; Chapter 4.

56. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978,** *43*, 2923.

57. Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87.

58. (a) Kato, T; Sato, M; Kimura, H. *J. Chem. Soc., Perkin Trans I* **1979,** 529. (b) Beck, G.; Jendrella, H.; Kesseler, K. *Synthesis* **1995,** *8*, 1014.

59. Kitamura, M.; Hsiao, Y.; Noyori, R.; Takya, H. *Tetrahedron Lett.* **1987,** *41*, 4829.

60. Iyer, R. S.; Kobierski, M. E.; Salomon, R. G. *J. Org. Chem.* **1994,** *20*, 6038.

61. Edelson, T. *J. Am. Chem. Soc.* **1959,** *81*, 5150.

62. Bury, A.; Corker, S. T.; Johnson, M. D. *J. Chem. Soc., Perkin Trans. I* **1982,** 645.

63. Haynes, R. K.; Katsifis, A. G.; Vonwiller, S. C.; Hambley, T. W. *J. Am. Chem. Soc.* **1988**, *110*, 5423.

64. Mori, K. *Tetrahedron* **1974,** *30*, 3807.

65. Anderson, B.; Geis, L. *Tetrahedron* **1975,** *31*, 1149.

66. Infarnet, Y.; Accary, A.; Huet, J. *Bull. Soc. Chim. Fr.* **1980,** *2*, 261.