TOTAL SYNTHESIS OF (+)-LONGIFOLENE BY AN INTRAMOLECULAR DIELS - ALDER STRATEGY

BO LEI, B.Sc.

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By

© *Bo Lei, B.Sc.*

A thesis submitted to the School of Graduate
Studies in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy

Department of Chemistry
Memorial University of Newfoundland
December 1989

St. John's Newfoundland

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TO MY WIFE AND PARENTS

ABSTRACT

The total synthesis of the sesquiterpene (+)-longifolene by an intramolecular Diels-Alder cycloaddition strategy is described. The route utilized an addition initiated ring closure involving methyllithium and epoxyfulvene **80**. The cyclopentadienyl anion **81** that resulted cyclized in an exo-tet manner to generate a substituted spiro[2.4]hepta-4,6-diene **82** in which the cyclopropane ring blocked the 1,5-sigmatropic rearrangement and acted as a latent methylene group. Oxidation with active MnO_2 afforded cyclopropyl aldehyde **83**, which was condensed with the anion derived from methyl 3,3-dimethylacrylate **97** in the presence of cadmium chloride. These conditions resulted in selective γ substitution and were a consequence of isomerization to the thermodynamically most favored product. This procedure was shown to be general for related systems.

The resulting alcohol-protected triene **100** was cyclized directly to tetracyclic adduct **103** under thermal conditions in a microwave oven. Modification of the functional groups gave cyclopropyl ketone **118**, which opened to the longifolene ring system by lithium/ammonia reduction.

The route to optically active material followed a different pathway which involved the Lewis acid catalyzed addition of methanol to the optically active spirocyclopropane-cyclopentadiene **134**. The product **137** was capable of rapid sigmatropic rearrangement, which in principle could give rise to several different Diels-Alder adducts. In practice, because of the constrained nature of the cyclic dienophile, the lowest energy path led to the adduct **138** with the tricyclic nucleus required for (+)-longifolene. This was the only product isolated and represented the first successful synthesis of a cycloheptane directly from a cyclopentadiene in a

carbocyclic precursor. In order to complete the synthesis the lactone **138** was reduced and the primary alcohol converted selectively to its acetate **144.** Sequential removal of the secondary hydroxyl functions was accomplished under free radical conditions. Pyrolysis of the acetate **146** at 525°C provided (+)-longifolene.

ACKNOWLEDGMENTS

So many people have supported me throughout my graduate career, it is impossible to mention them all by name.

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LIST OF ABBREVIATIONS

Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
APT	attached proton test
bp	boiling point
n-Bu	n-butyl
t-Bu	*tert*-butyl
ca.	about, approximately
cf.	compare
cm	centimeter
m-CPBA	m-chloroperoxybenzoic acid
Cy	cyclohexyl
d	doublet
DEPT	distortionless enhanced polarization transfer
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
dec.	decomposition
DIBAL	diisobutylaluminum hydride
DIPT	diisopropyl tartrate
DMAP	N,N-dimethylaminopyridine
DME	1,2-dimethoxyethane (glyme)
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
Et	ethyl
EtOAc	ethyl acetate

GC	gas chromatography
h	hours
HMPA	hexamethylphosphoramide
Hz	Hertz
IR	infrared
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
M^+	parent molecular ion
m	multiplet
Me	methyl
min	minutes
mmol	millimole
mp	melting point
MS	mass spectrum
nmr (NMR)	nuclear magnetic resonace
Nu	nucleophile or nucleophilic
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
psi	pounds per square inch
py	pyridine
q	quartet
RT (R.T.)	room temperature (about 22°C)
s	singlet
t	triplet
TBAF	tetra-n-butylammonium fluoride

TBDMS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	N,N,N,N,-tetramethylethylenediamine
TMS	tetramethylsilane
TMS	trimethylsilyl
Ts	p-toluenesulfonyl

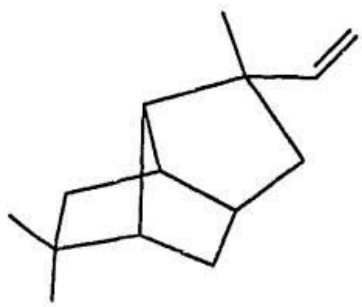
PART I
INTRODUCTION

CHAPTER 1 BACKGROUND

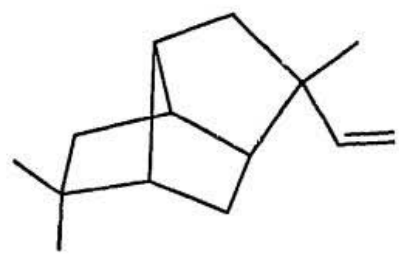
1.1 Structure Elucidation

In 1920 Simonsen demonstrated that the tricyclic sesquiterpene, (+)-longifolene, occurred in the essential oil of *Pinus longifolia.*[1,2] The (+)-enantiomer is known to occur in higher plants, mainly Gymnospermae,[3] while its antipode has been found in liverworts.[4]

The structure of longifolene was first elucidated in 1923 by Simonsen *et al.*[5] At that time their identification was limited to the tricyclic ring system, vinyl group, tertiary methyl group and geminal dimethyl groups established chemically by degradation. Structures **1** and **2** (**Scheme 1**) were suggested for longifolene according to its molecular formula, $C_{15}H_{24}$, the isoprene rule and the results of these chemical investigations.



1

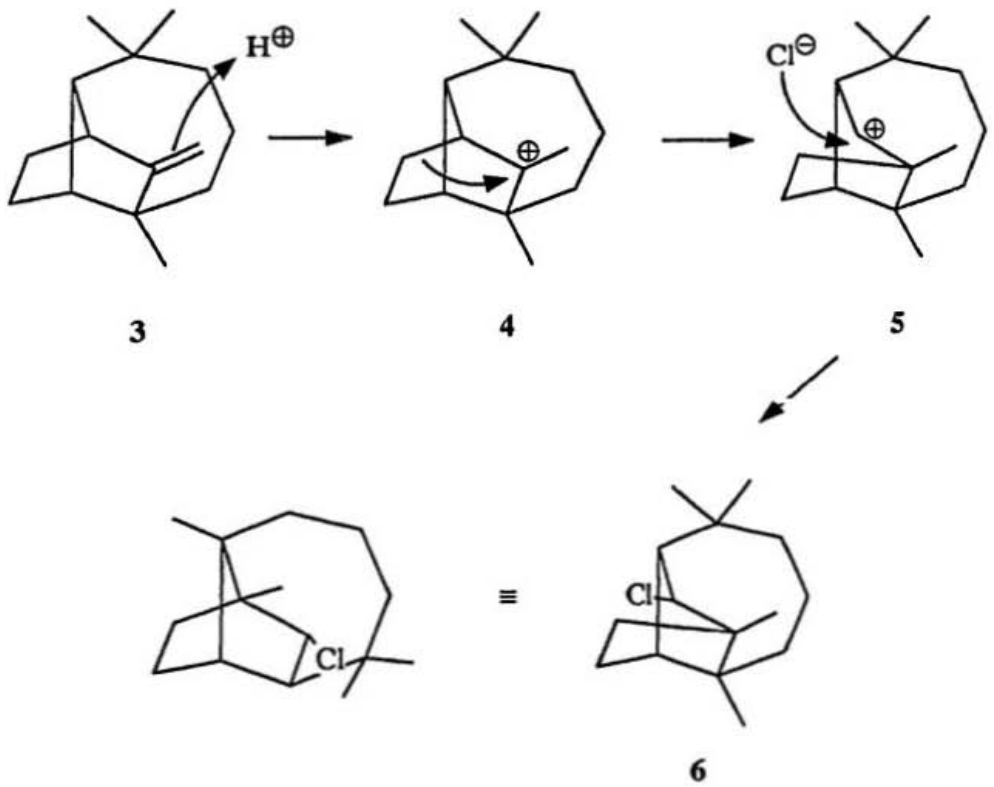


2

Scheme 1

The correct structure of longifolene, long an unsolved and complicated chemical problem, was revealed in 1953 by Ourisson and Naffa[6] on the basis of an X-ray crystallographic study of longifolene hydrochloride **6** by Moffet and

Rogers,[7] and the chemical evidence that upon treatment with hydrogen chloride, longifolene **3** undergoes a Wagner-Meerwein rearrangement to longifolene hydrochloride **6** (**Scheme 2**).



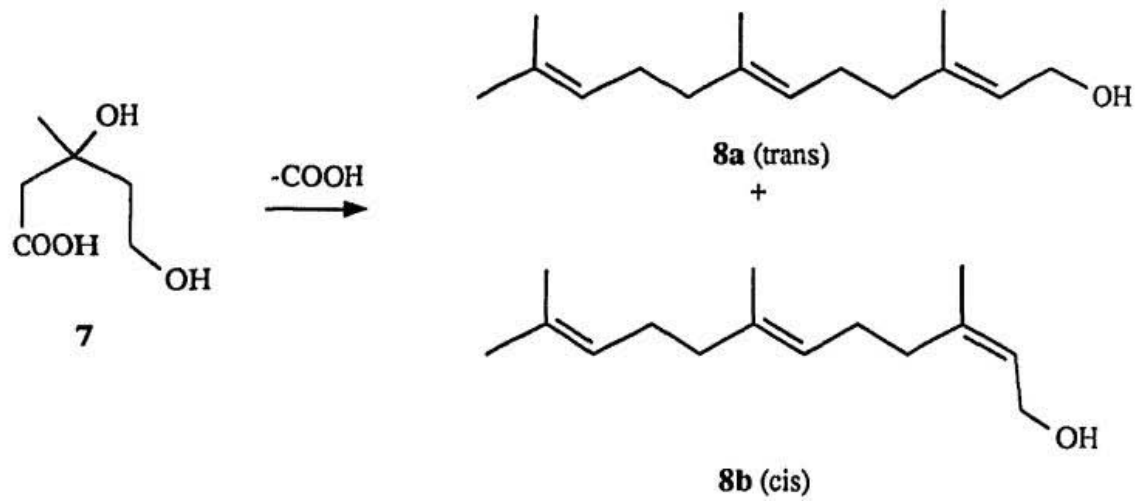
3 **4** **5** **6**

Scheme 2

Further studies on the molecular rotation of derivatives of longifolene suggested that the proposed structure **3** also represented the absolute configuration of (+)-longifolene.[8] This has since been confirmed by several total syntheses.

1.2 Biosynthesis

It has been established that the actual isoprene unit utilized in the terpene biosynthesis is mevalonic acid **7** (or an appropriately activated simple derivative),[9,10,11] three of these self-condense with decarboxylation to farnesol **8a** and **8b**, the simplest acyclic sesquiterpene (**Scheme 3**).

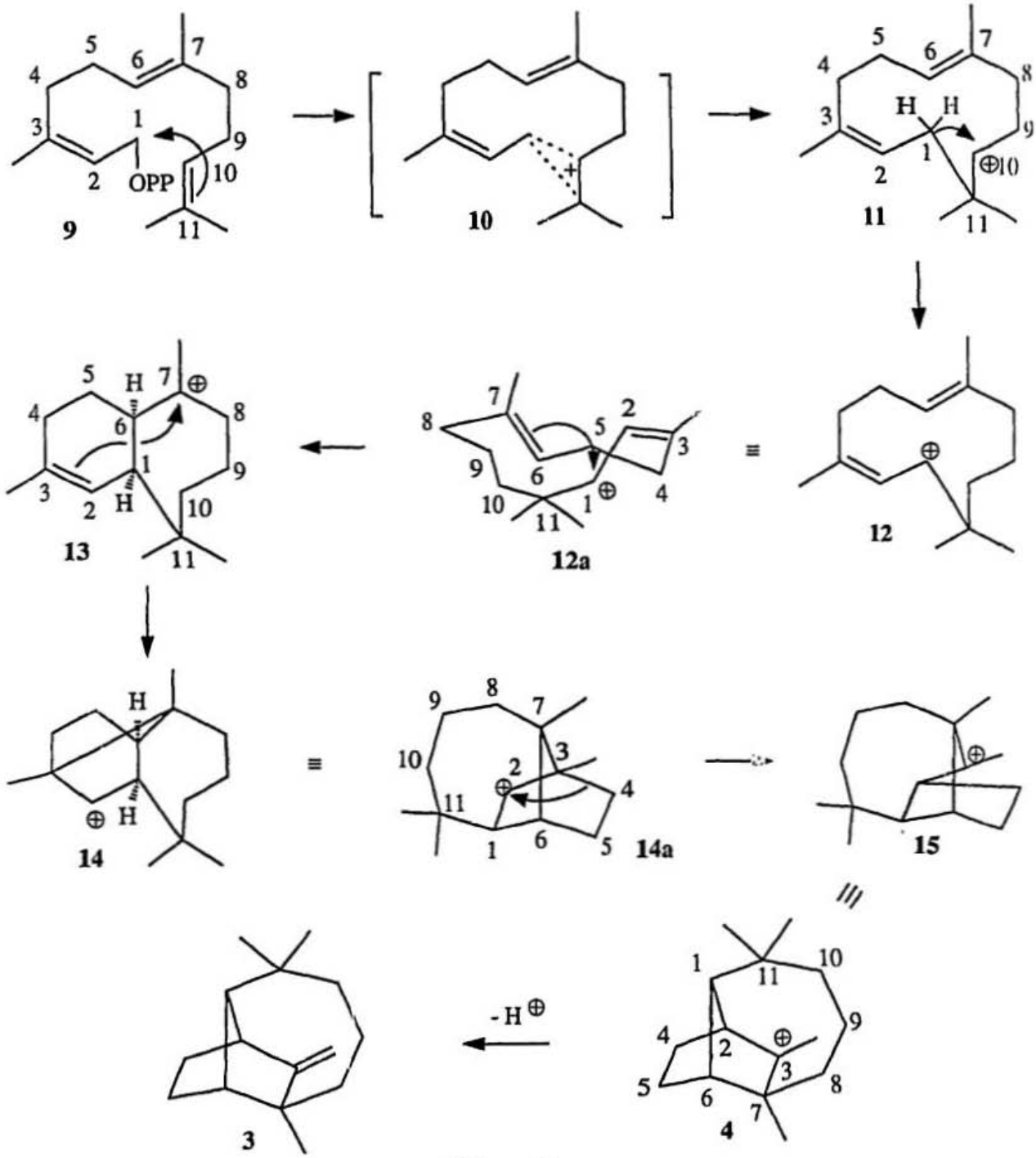


7

Scheme 3

It is now clear that cis-farnesol or trans-farnesol are the precursors for the cyclization to all the cyclic sesquiterpenes.

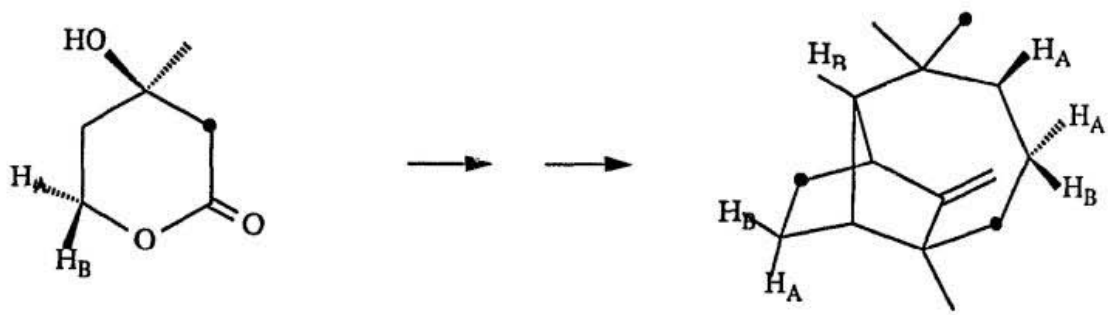
The biosynthesis of longifolene[12,13] (**Scheme 4**) starts with the cyclization of cis-farnesol pyrophosphate **9** to give an eleven-membered ring carbocation **11** *via*



Scheme 4

species **10**. The "inside" hydrogen at C-1 of **11** undergoes a 1,3-hydride shift. The conformation of **12**, as shown **12a**, provides considerable overlap of the π-electrons at C-6 with those of the allylic ion at C-1, so that facile collapse gives rise to the cis-fused bicyclic ion **13**. The geometry of **13** ensures the close proximity of C-7 to the double bond at C2-C3 and the formation of a C3-C7 bond to give tricyclic carbocation **14**, equivalent to **14a**. This carbocation undergoes a 1, 2-carbon migration to give **15**, which affords longifolene **3** by deprotonation.

It should be noted that the mechanism and the intermediates shown in **Scheme 4** do not necessarily represent the actual enzymatic processes, but they do provide a useful framework for the rationalization of the biosynthesis process.



16 **17**

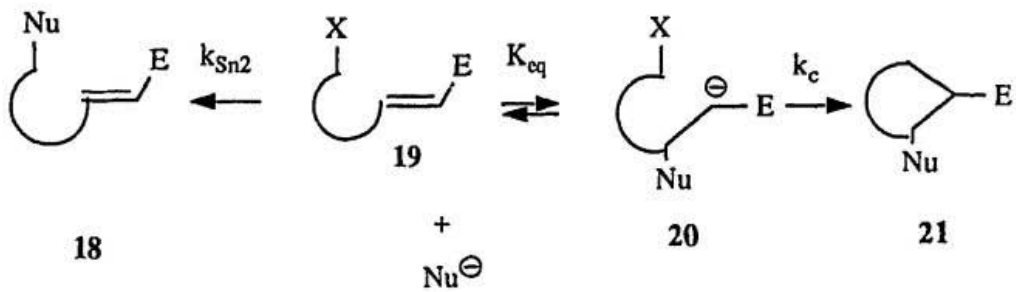
Scheme 5

Arigoni and his co-workers have experimentally investigated the biosynthesis of two antipodal forms of longifolene and developed stereochemical models based on their results.[14] Reasonable incorporation of activity (0.1-0.2 %) from radiolabelled mevalonates into (+)-longifolene were achieved using cuttings of the

Pinus ponderosa tree (**Scheme 5**, also *cf.* **Scheme 4**). A 1, 2 carbon migration was observed and a labelled hydrogen moved from C-1 to C-10 by 1, 3 shift. The mevalonoid (5-*pro-R*)-hydrogen and the (5-*pro-S*)-hydrogen migrate in the biosynthesis of (+)-longifolene and (-)-longifolene respectively.[15]

1.3 Addition Initiated Ring Closure

Conjugated addition (Michael) initiated ring closure is an important synthetic strategy although few fulvene examples are known. It includes the nucleophilic addition to an α, β-unsaturated carbonyl compound to produce an enolate anion which subsequently undergoes an intramolecular ring closure[16, 17]. This type of reaction was termed MIRC (Michael Initiated Ring Closure) by Little,[18] who showed that three, five, six and seven membered rings could be formed by this method. However, the cyclizations were usually accompanied by some direct S_N2 displacement. This is illustrated in **Scheme 6.**



E = CO_2R

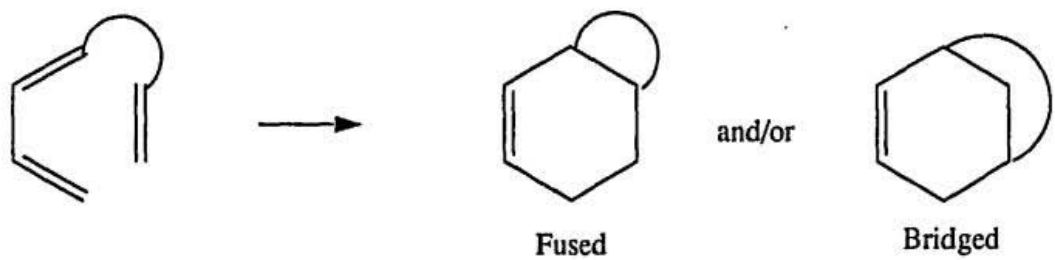
Scheme 6

The ratio of the MIRC reaction product formed is clearly dependent upon the concentration of the enolate as well as the rate constant for ring closure, k_c. The concentration of the enolate depends on K_{eq} which is related to the relative stabilities of the conjugate acid of the nucleophile and the enolate. Therefore, if $K_{eq} < 1$, a MIRC reaction should occur only when k_c is sufficiently large to compensate for the low enolate concentration. The rate of ring closure to three is faster than closure to five or six membered rings. Thus, it is not too surprising that the MIRC reaction has been used more often to construct the cyclopropane ring. Nevertheless, even when considering closure to a cyclopropane, the MIRC and S_N2 reactions are competitive. It has been shown[19] that both the solvent and the nature of the intermediate generated from different nucleophiles exert a remarkable effect on the course of the reaction.

1.4 Diels - Alder Reaction

The Diels-Alder reaction has become one of the most useful methods available to the synthetic organic chemist since its discovery more than 60 years ago.[20] The ability to generate simultaneously up to four chiral centers in a highly stereoselective and largely predictable fashion has resulted in its application to numerous synthetic targets.[21, 22] The intramolecular version has become popular more recently and has also been employed in the construction a variety of polycyclic ring systems in the past fifteen years.[23] **Scheme 7** shows a simple example of the intramolecular Diels-Alder reaction. Of the two possible modes of addition, the fused mode usually predominates except with long chain lengths. If the reacting molecules are themselves cyclic, and / or have ring substituents, complex multicyclic compounds are formed in a single step. The Diels-Alder reaction provides a powerful tool for natural product synthesis because these

multicyclic structures are contained in drugs and natural products and the construction of these molecules are often more difficult and lengthy by other routes.



Scheme 7

The Diels-Alder reaction proceeds through a highly ordered transition state.[24] In the intramolecular Diels-Alder reaction some of the ordering has been achieved by joining the reacting functionalities in the same molecule. This leads to increased reaction rates under mild conditions and successful reactions that would fail even under forcing conditions in the intermolecular version. The constraints on the diene and dienophile imposed by the connecting chain generally facilitate the prediction of regio- and stereoselectivity. Side reactions such as dimerization or polymerization can generally be efficiently avoided by using high dilution. All of these advantages account for the great interest in the study and applications of the intramolecular Diels-Alder reaction and suggest that this reaction should be first considered for any synthesis of a molecule containing a six-membered ring fused

to other rings.[25, 26]

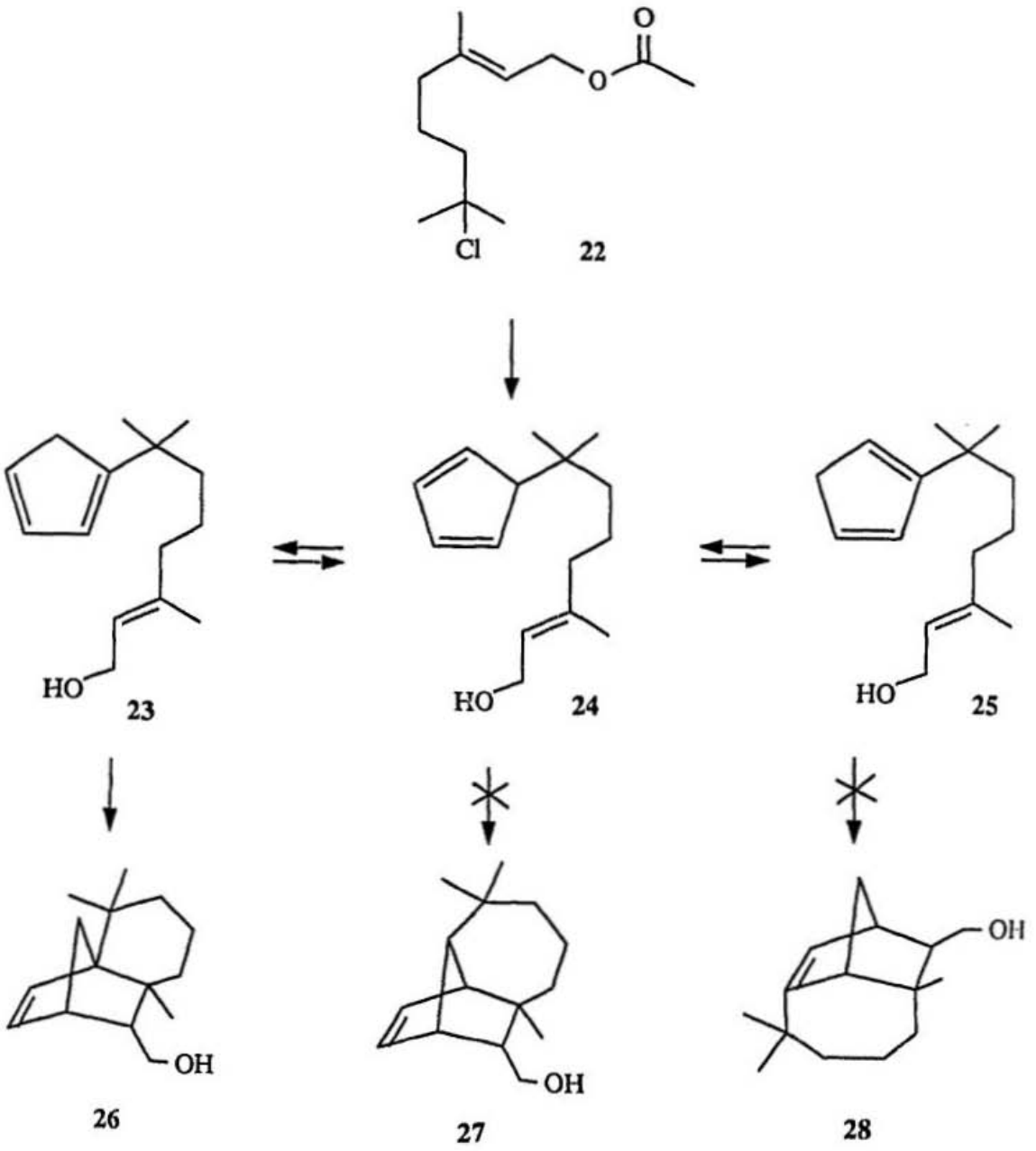
A number of Lewis-acid catalyzed Diels-Alder reactions have also been reported.[27] The main problem with Lewis-acid catalysts is that they may also cause side reactions. Diels-Alder reactions have large negative activation volumes and in general can be accelerated under high pressure. Some Diels-Alder reactions have also been carried out in the gas phase, under either static or flow conditions.[28] However, it is not possible to compare their advantages because the corresponding solution reactions are lacking.

The Diels-Alder reaction has been reviewed frequently.[21, 23-26, 29-37] This indicates the worldwide interest. However, some facets are still imperfectly understood and as our knowledge increases, this cycloaddition will be even more widely employed for synthetic design and methodology.

1.5 Brieger's Work

In principle the complex carbon skeleton of longifolene could be built by an intramolecular Diels-Alder reaction between a cyclopentadiene and an appropriate side-chain. As early as 1963, Brieger attempted to utilize this strategy to synthesize longifolene.[38] In his investigation, chloride **22**, obtained from the addition of hydrochloric acid to geranyl acetate, was treated with excess cyclopentadienyl magnesium bromide. The resulting product, actually a mixture of cyclopentadiene isomers **23** - **25**, was heated in refluxing pseudocumene (bp 176°C) **(Scheme 8)**.

He hoped that thermal equilibration of these isomers would cause the 5-substituted cyclopentadiene **24** to undergo an intramolecular Diels-Alder cycloaddition to give the desired alcohol **27**. However, the reaction gave a nearly quantitative yield of alcohol **26**, which corresponded to the cyclization *via* the



Scheme 8

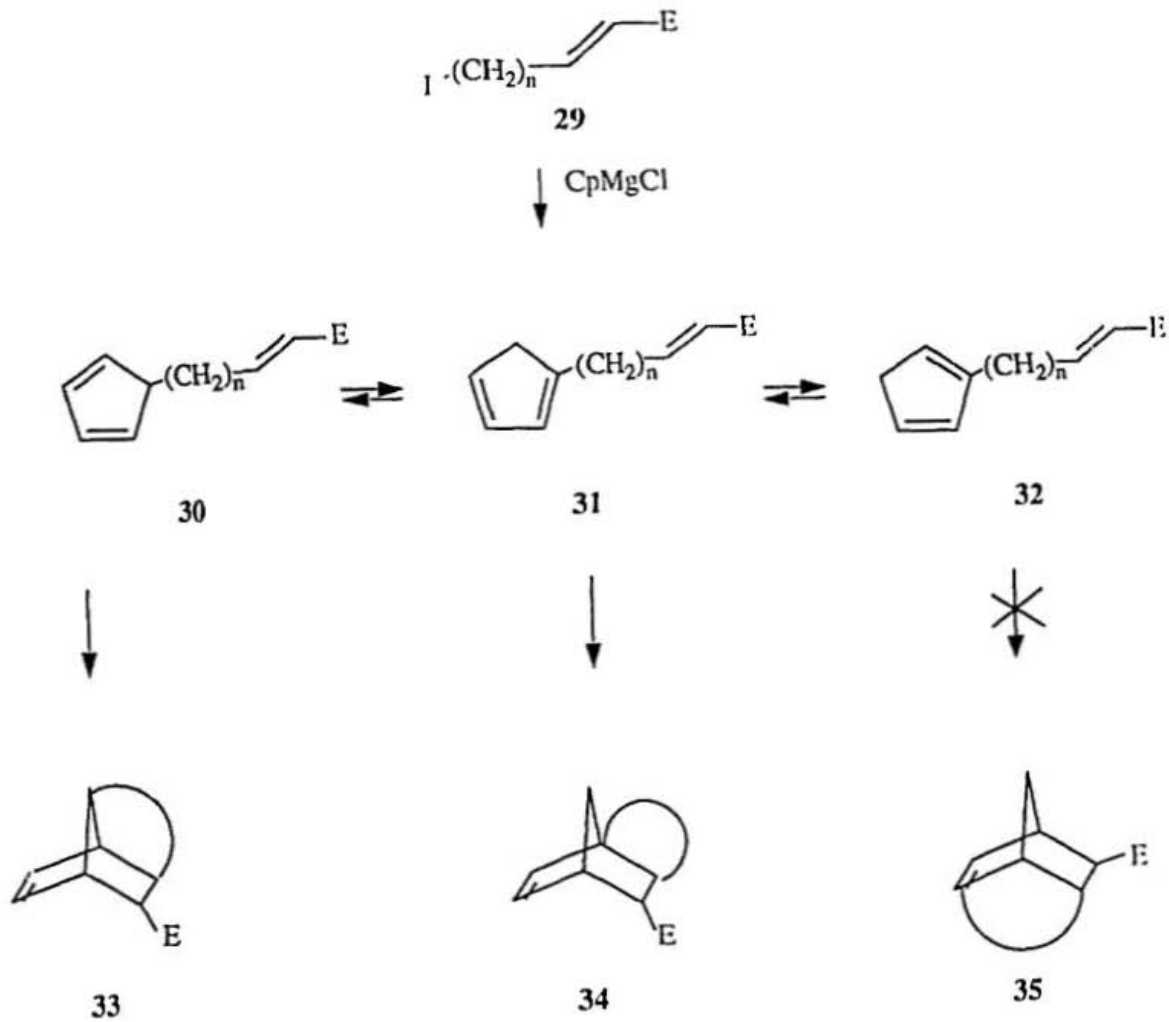
1-substituted cyclopentadiene **23**.

This result showed that the substituted cyclopentadiene underwent a facile 1,5-sigmatropic rearrangement and the intramolecular Diels-Alder adduct of the 1-substituted isomer **23** was thermodynamically stable. In addition, it was clear that cycloaddition to yield a cyclohexane from a C-1 substituted cyclopentadiene was preferred to the competing pathway to a cycloheptane. Subsequent studies have confirmed this behavior and C-5 products arise only when the side-chain is shortened to two linking atoms, as other transition states are extremely strained (*cf.* Grubbs' work discussed below).

In spite of the lack of success of Brieger's synthesis of longifolene, the synthetic plan was concise, and it was possible that the target molecule could be realized with some modifications in the approach.

1.6 Cyclization of Substituted Cyclopentadienes

Cyclopentadiene is useful for the formation of bicyclo[2.2.1]heptane compounds for natural product syntheses.[25] Considerable research work has been done to study the rearrangement of substituted cyclopentadienes [39-41] and corresponding competitive Diels-Alder cycloadditions.[42,43] It has been established, as mentioned above, that the 1, 5-sigmatropic rearrangement occurs under very mild conditions and a mixture of isomers was usually observed even when the pure C-5 isomer was used initially. The composition of the isomeric mixture depends in part on the nature of the substituent and not on the method of the synthesis.[41] The intramolecular Diels-Alder reaction of substituted cyclopentadienes has been carefully examined by Grubbs and Still.[44] They employed cyclopentadiene compounds tethered to an α, β-unsaturated ester functionality as the Diels-Alder reaction precursors. Several functionalized cyclopentadienes were prepared with



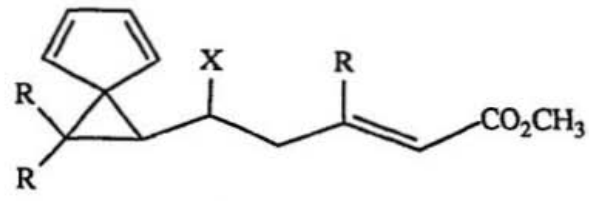
Scheme 9

different tether lengths. These substrates readily underwent intramolecular Diels-Alder reaction at mild temperatures (**Scheme 9**). They showed that the cycloaddition proceeded favorably from a transition state in which the tether formed five- or six-membered rings, but products of type **35** were energetically disfavored.

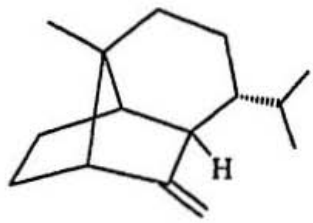
1.7 Fallis' Work

It is apparent that a successful intramolecular Diels-Alder approach to a tricyclic skeleton from a 5-substituted cyclopentadiene requires either blocking the 1,5-sigmatropic rearrangement or arranging for the cycloaddition to compete efficiently with the rearrangement Unfortunately, it has been found that even chlorine does not block the sigmatropic rearrangement and it migrates before the cyclization.[43] This means the "blocking" is not necessarily straightforward. Based on this realization a successful approach has been developed in our research group, as shown in **Scheme 10**. It employs a suitable spiro[2.4]heptadiene of type **A** to form the desired Diels-Alder adduct of type **B.** The cyclopropane unit blocks the 1, 5-sigmatropic rearrangement and, after the selective cyclopropane ring opening, also serves as latent functionality to provide several types of natural products.

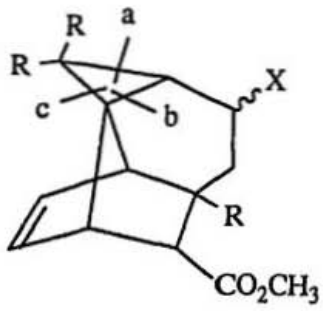
This strategy has been successfully applied to the total synthesis of sinularene.[45] Related studies revealed an oxygen substituent (X group) in the sidechain at the carbon adjacent to the cyclopropyl ring was essential for a successful cyclization.[46]



A



Sinularene



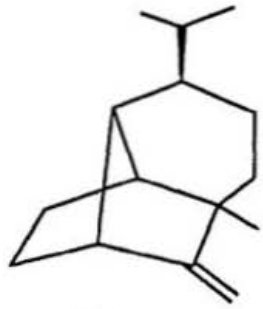
B

"a"

"b"

"c"

Longifolene



Sativene

R = H or CH_3

Scheme 10

CHAPTER 2

LONGIFOLENE: PREVIOUS SYNTHESES

The intricate molecular construction of longifolene has attracted a good deal of attention in the past three decades and served as a challenging test for synthetic principles and methods, especially with respect to the construction of ring systems and carbon networks. To date there have been six published total syntheses of longifolene and at least nine unsuccessful attempts.

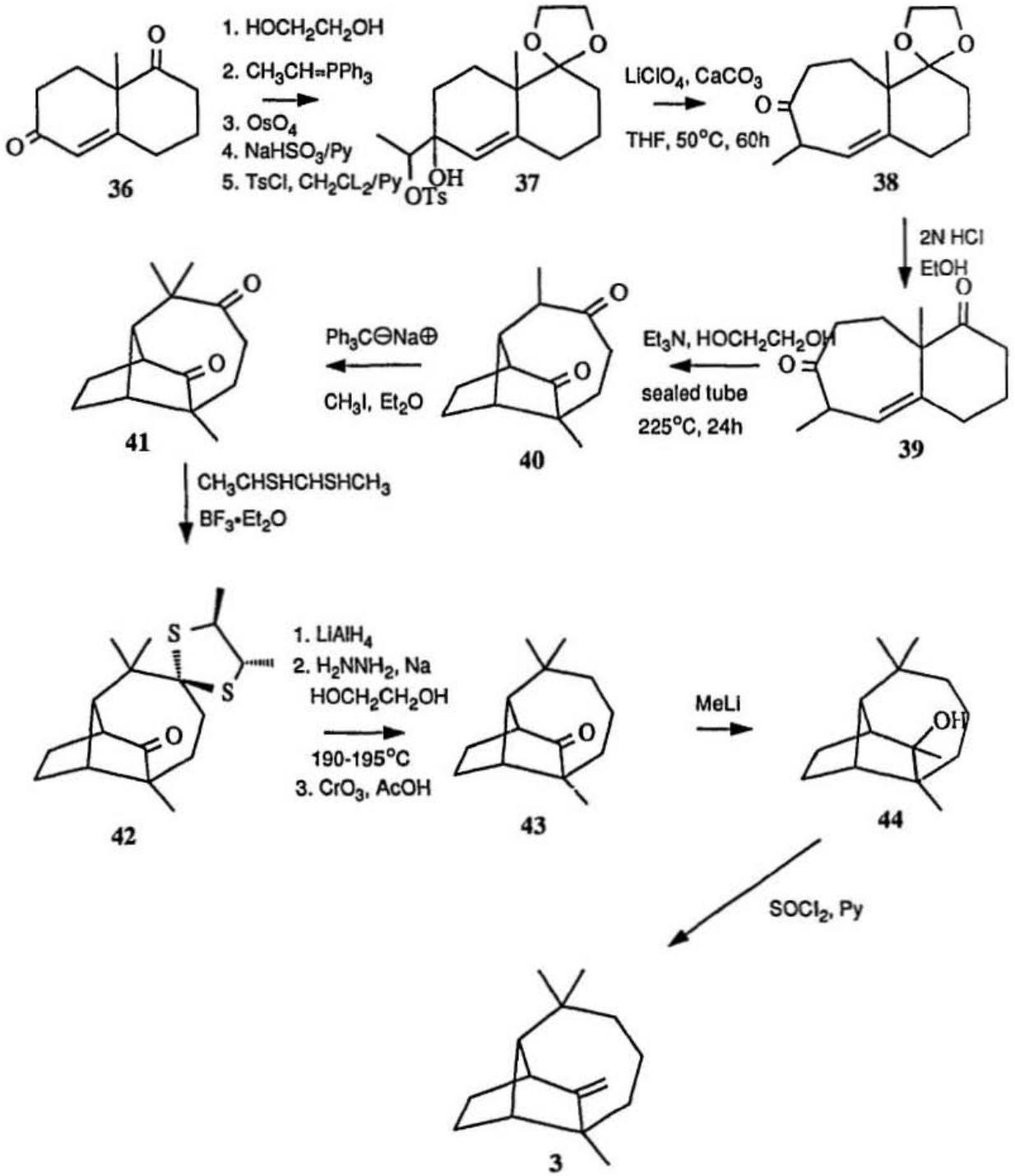
A brief survey of the reported syntheses of longifolene reveals that each approach employed different strategies and methods for the construction of the tricycloundecane carbon skeleton.

2.1 Corey's Synthesis

The first, well-known, total synthesis of longifolene was reported in 1964 by Corey *et al.*[47] The bridged ring system was constructed by an intramolecular Michael cyclization of a homodecalin derivative **39**, as shown in **Scheme 11.**

The Wieland-Miescher ketone **36** was employed as a starting material and converted *via* tosylate **37** and a pinacol rearrangement, resulting in a ring expansion, to the required homodecalin **39** (41-48%).

Precedent for intramolecular Michael reaction of this type existed in the base-catalyzed cyclization of santonin to santonic acid. Although the transformation of santonin to santonic acid was smooth, the corresponding cyclization of homodecalin **39** to the tricyclodiketone **40** proved to be much less facile and yields of only 10-20% were obtained.


1. HOCH2CH2OH
2. CH3CH=PPh3
3. OsO4
4. NaHSO3/Py
5. TsCl, CH2CL2/Py
LiClO4, CaCO3
THF, 50°C, 60h
2N HCl
EtOH
Et3N, HOCH2CH2OH
sealed tube
225°C, 24h
Ph3C⊖Na⊕
CH3I, Et2O
CH3CHSHCHSHCH3
BF3•Et2O
1. LiAlH4
2. H2NNH2, Na
HOCH2CH2OH
190-195°C
3. CrO3, AcOH
MeLi
SOCl2, Py
36
37
38
39
40
41
42
43
44
3

Scheme 11

After the construction of the diketone **40**, the α-methylation of the enolate derived from **40** afforded the diketone **41**. The cycloheptane carbonyl was reduced by the combination of hydride reduction and Wolff-Kishner reaction of the thio-ketal **42**, followed by chromic acid oxidation to give longicamphenylone **43**. Addition of methyllithium to **43** followed by dehydration of the resulting tertiary alcohol **44** gave racemic longifolene.

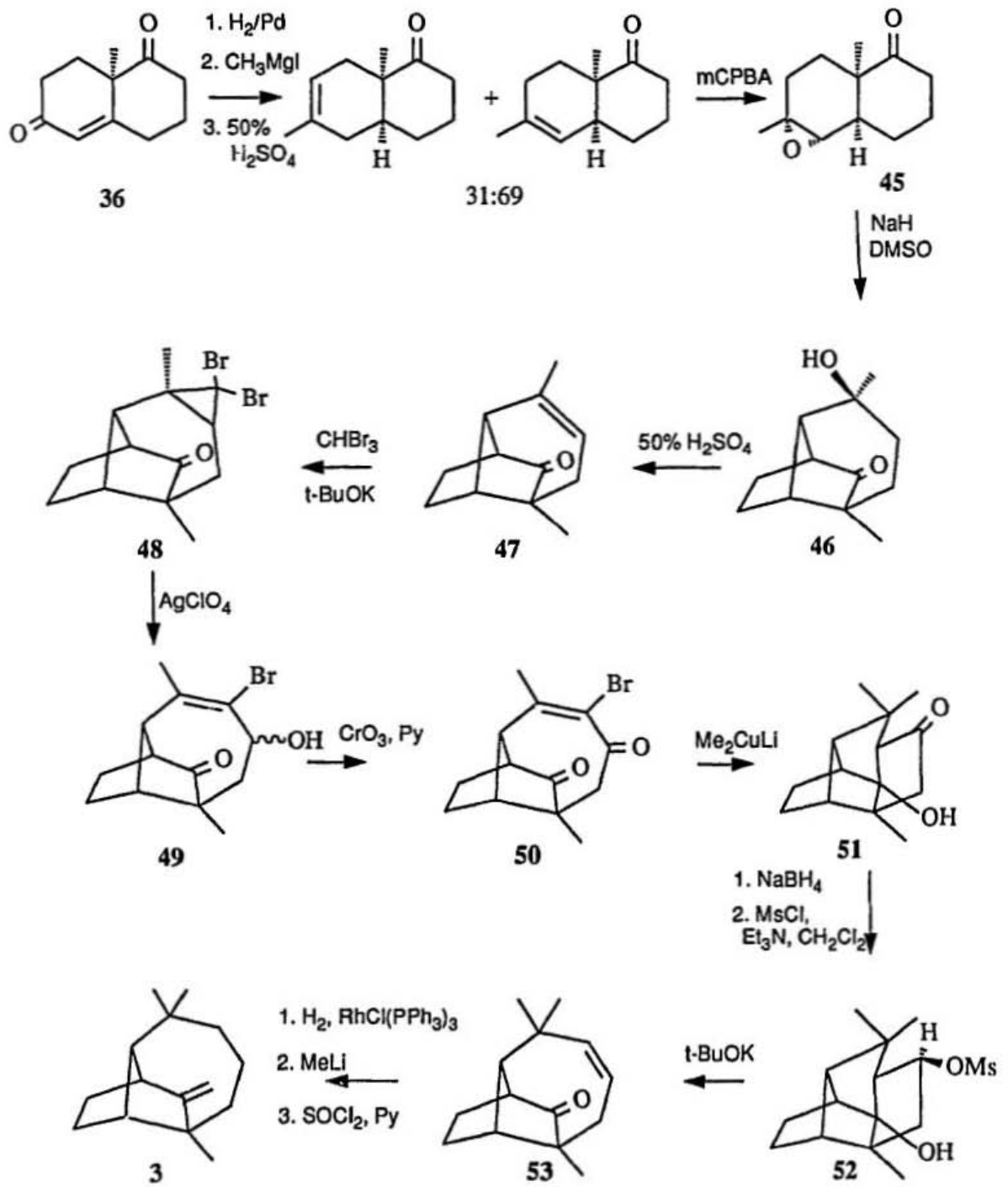
To prepare the optically active product, intermediate **41** was treated with L-(+)-2,3-butanedithiol and the formed diastereomers were resolved. The optically active thiol **42** was then converted to optically active (+)-longifolene **3**.

2.2 McMurry's Synthesis

The second synthesis of longifolene was reported in 1972 by McMurry and Isser.[48] They utilized the same starting material as Corey, but their approach was to form the tricyclic carbon skeleton of longifolene *via* intramolecular alkylation of a bicyclic keto epoxide as outlined in **Scheme 12.**

The Wieland-Miescher ketone **36** was converted to the keto epoxide **45**, whose enolate underwent an intramolecular epoxide opening to provide the tricyclic keto alcohol **46** in high yield (93%).

Completion of the synthesis required addition of a further methyl group after ring expansion to form the dimethycycloheptane ring of the natural product. Therefore, the alcohol **46** was dehydrated to give the endocyclic olefin **47** which was then treated with bromoform and potassium *tert*-butoxide, and the dibromo cyclopropane adduct **48** was obtained as the only isomer. Ring expansion was accomplished by solvolysis of **48** with silver perchlorate to yield allylic alcohol **49** quantitatively and **49** was immediately oxidized to give the enedione **50**. Introduction of the methyl group by conjugate addition of lithium dimethylcuprate to


1. H_2/Pd
2. CH_3MgI
3. 50% H_2SO_4
mCPBA
36
31:69
45
NaH
DMSO
$CHBr_3$
t-BuOK
50% H_2SO_4
48
47
46
$AgClO_4$
CrO_3, Py
49
50
Me_2CuLi
51
1. $NaBH_4$
2. MsCl,
Et_3N, CH_2Cl_2
1. H_2, $RhCl(PPh_3)_3$
2. MeLi
3. $SOCl_2$, Py
t-BuOK
3
53
52

Scheme 12

enedione **50** resulted in tetracyclic ketone **51**, presumably by intramolecular attack of the enolate generated after conjugate addition. The tricyclic system was regenerated by base catalyzed rearrangement of mesylate **52** to give enone **53** which was easily converted to longifolene.

2.3 Johnson's Synthesis

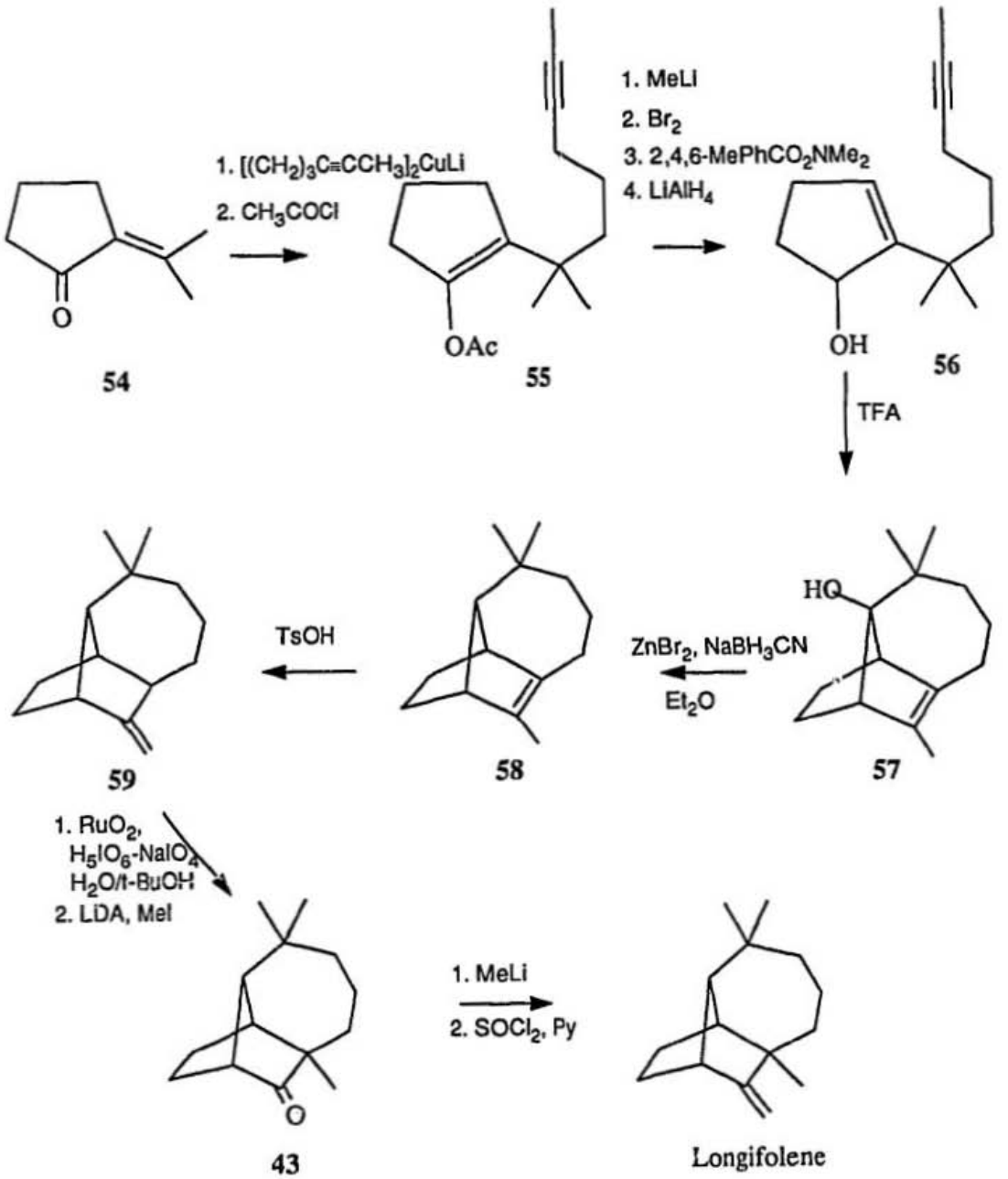
The third synthesis of longifolene, reported in 1975 by Johnson *et al*,[49] utilized the acid-catalyzed rearrangement of an acetylene cyclopentenol to construct the tricyclic ring system of longifolene.

The enol acetate **55** was obtained from conjugate addition of the cuprate derived from 1-iodo-4-hexyne to enone **54** followed by trapping the resulting enolate with acetyl chloride. Further manipulation of this acetate yielded alcohol **56**. Treatment of alcohol **56** with trifluoroacetic acid gave the rearranged tricyclic alcohol **57** which constituted a rapid entry to the longifolene framework.

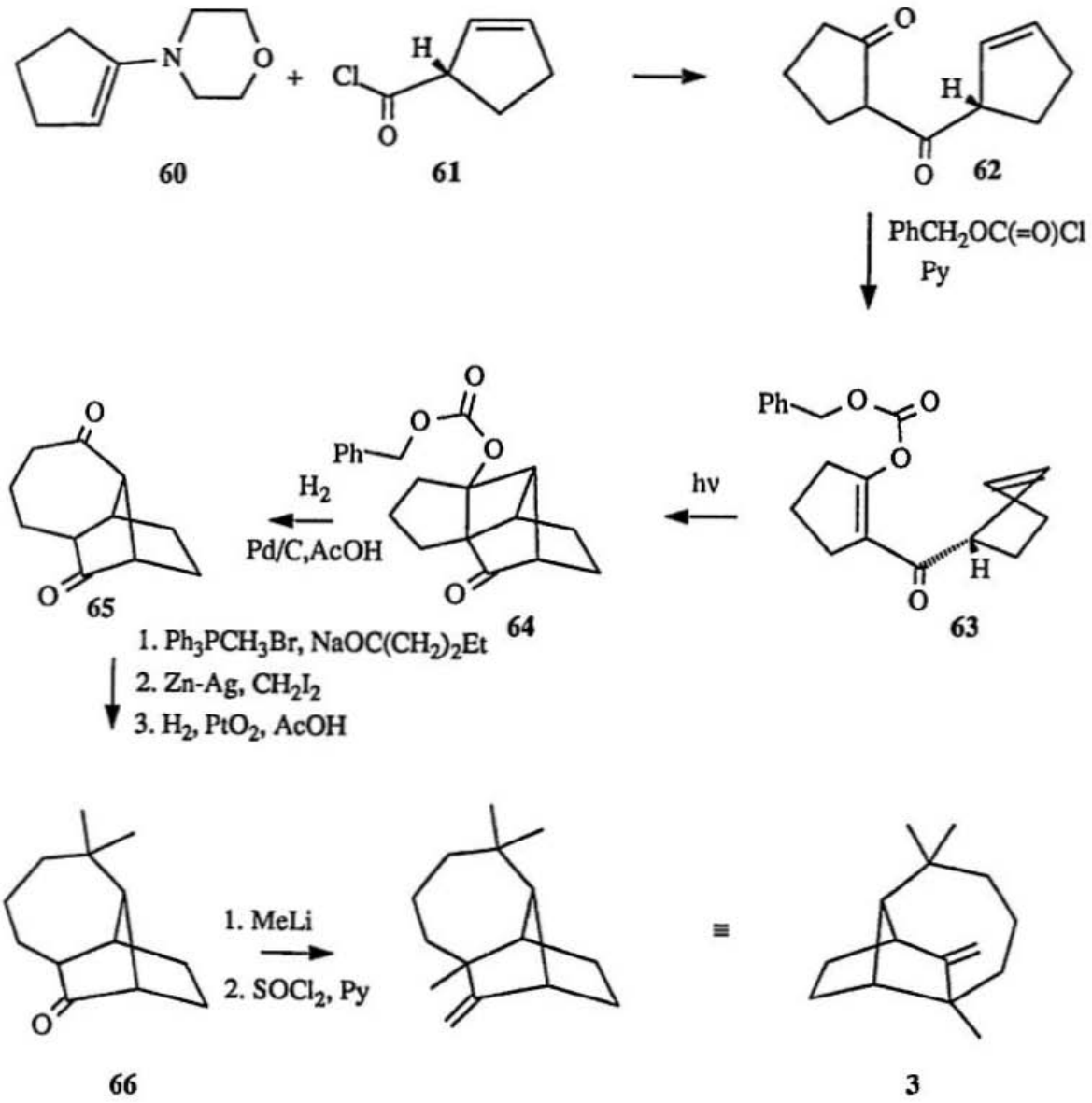
In the presence of acid, the olefin **58** readily isomerized to the exocyclic olefin **59**. The ketone **43**, an intermediate in both Corey's and McMurry's syntheses, was obtained by oxidation and methylation of **59**. Methyllithium addition and dehydration of **43** provide racemic longifolene in eleven steps from **54**, as shown in **Scheme 13**.

2.4 Oppolzer's Synthesis

The fourth synthesis of longifolene was reported in 1977 by Oppolzer and Godel.[50,51] In this synthesis an intramolecular [2 + 2] photoaddition-retroaldol reaction sequence (deMayo reaction) was used to construct the complex longifolene skeleton, as shown in **Scheme 14.**


1. [(CH2)3C≡CCH3]2CuLi
2. CH3COCl
1. MeLi
2. Br2
3. 2,4,6-MePhCO2NMe2
4. LiAlH4
TFA
ZnBr2, NaBH3CN
Et2O
TsOH
1. RuO2,
H5IO6-NaIO4
H2O/t-BuOH
2. LDA, MeI
1. MeLi
2. SOCl2, Py
OAc
OH
HO
O
54
55
56
57
58
59
43
Longifolene

Scheme 13


60
61
62
PhCH2OC(=O)Cl
Py
hν
63
H2
Pd/C,AcOH
64
65
1. Ph3PCH3Br, NaOC(CH2)2Et
2. Zn-Ag, CH2I2
3. H2, PtO2, AcOH
1. MeLi
2. SOCl2, Py
66
3

Scheme 14

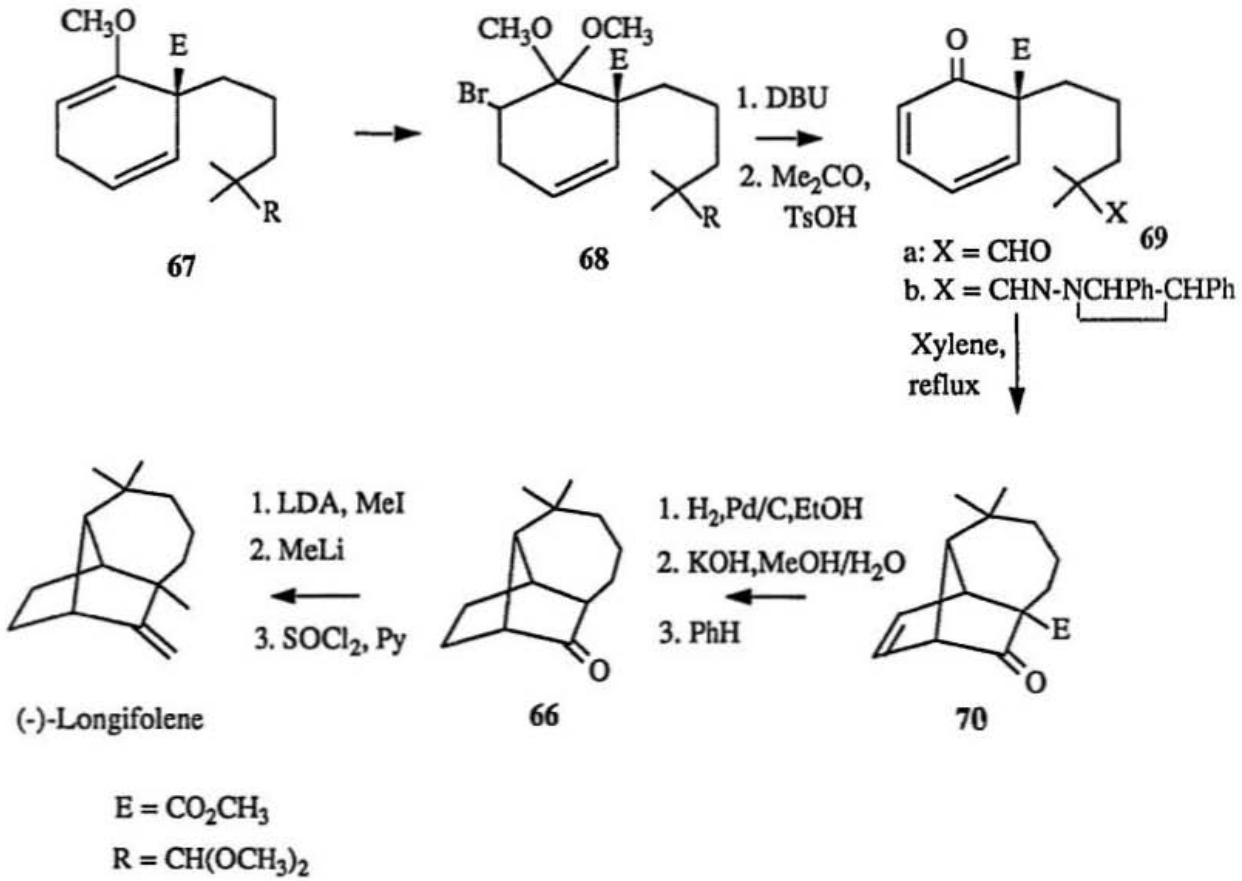
The key intermediate, enol acetate **63**, was obtained from condensation of 1-morpholino-1-cyclopentene **60** with an optically active acid chloride **61** followed by acylation of the resulting diketone **62**. Irradiation of **63** gave the cyclobutane **64** which upon hydrogenolysis of the protecting group underwent a spontaneous retroaldol reaction to afford diketone **65**. This procedure incorporated the required stereochemistry without disturbance of the chiral center.

Crystallization gave the diketone **65** in 100 % optically purity. Introduction of the gem-dimethyl group was accomplished *via* Wittig olefination of the more reactive cycloheptanone carbonyl, Simmons-Smith cyclopropanation and hydrogenolysis to yield ketone **66**, the same intermediate as in the previous syntheses, which was then converted to (+)-longifolene by the literature procedure. The overall yield was 24 % from the chiral acid chloride **61**.

2.5 Schultz's Synthesis

The fifth synthesis of longifolene was reported in 1985 by Schultz and Puig.[52] They used an intramolecular diene-carbene cycloaddition, the synthetic equivalent of an intramolecular Diels-Alder reaction between a diene and a carbene, as the key step for construction of the longifolene seven-membered ring, as shown in **Scheme 15**.

Cyclohexadiene **67** was prepared by Birch reduction–alkylation of methyl 2-methoxybenzoate and alkylated with the dimethyl acetal of 2,2-dimethyl-5-iodopentanal. Conversion of **67** to the key intermediate **69a** was accomplished by (1) Treatment of **67** with N-bromoacetamide in methanol to give a diastereomeric mixture of bromoketals **68**, (2) dehydrobromination followed ketal hydrolysis during silica gel chromatography, and (3) acetal exchange. The aziridinyl imide **69b** generated by reaction of **69a** with 1-amino-trans-2,3-diphenylaziridine,



E = CO_2CH_3

R = $CH(OCH_3)_2$

Scheme 15

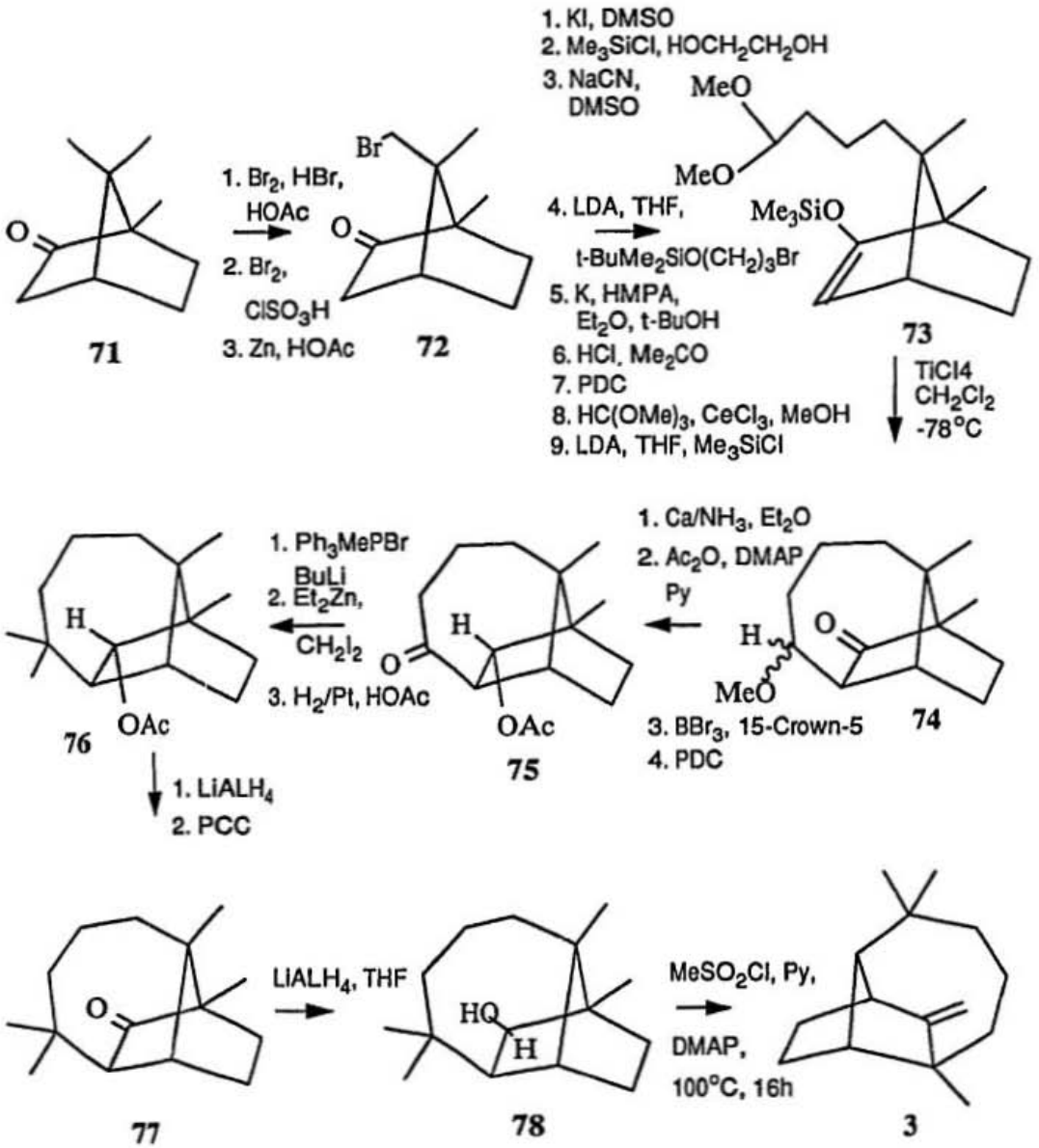
on thermolysis gave tricyclic keto-ester **70**. The tricyclic compound **70** was converted to **66**, an intermediate in Oppolzer's synthesis, by olefin hydrogenation and decarboxylation. Transformation of **66** to racemic longifolene followed the literature procedure.

An enantiospecific synthesis of (–)-longifolene was also achieved, *via* Birch reduction-akylation of a chiral benzoic acid derivative to give the chiral cyclohexadiene **67**.

2.6 Money's Synthesis

The sixth and the most recent synthesis of longifolene was reported in 1986 by Money and Kuo.[53] In their synthesis, (+)-camphor was employed as the chiral starting material and a titanium tetrachloride promoted cyclization provided the tricyclic intermediate **74** which served as the synthetic precursor of (+)-longifolene.

This enantioselective synthesis began with the conversion of (+)-camphor **71** to (+)-8-bromocamphor **72**. The bicyclic trimethylsilyl ether **73**, derived from **72** after nine experimental steps, underwent facile intramolecular cyclization when treated with titanium tetrachloride to give a mixture of diastereomeric methoxyketones **74a** and **74b**. Subsequent reactions provided the ketone **75** and the acetate **76** with the required geminal dimethyl group. Reductive removal of the acetate and oxidation gave (+)-longicamphor **77**, which was converted into isolongiborneol **78** by lithium aluminum hydride reduction. Dehydration of **78** yielded (+)-longifolene **3** *via* a Wagner-Meerwein rearrangement to complete the synthesis.


1. KI, DMSO
2. Me3SiCl, HOCH2CH2OH
3. NaCN, DMSO
MeO
MeO
1. Br2, HBr, HOAc
2. Br2, ClSO3H
3. Zn, HOAc
Br
O
71
72
4. LDA, THF,
t-BuMe2SiO(CH2)3Br
5. K, HMPA, Et2O, t-BuOH
6. HCl, Me2CO
7. PDC
8. HC(OMe)3, CeCl3, MeOH
9. LDA, THF, Me3SiCl
Me3SiO
73
TiCl4
CH2Cl2
-78°C
1. Ca/NH3, Et2O
2. Ac2O, DMAP
Py
3. BBr3, 15-Crown-5
4. PDC
74
1. Ph3MePBr
BuLi
2. Et2Zn,
CH2I2
3. H2/Pt, HOAc
H
OAc
75
76
1. LiALH4
2. PCC
LiALH4, THF
HO
77
78
MeSO2Cl, Py,
DMAP,
100°C, 16h
3

Scheme 16

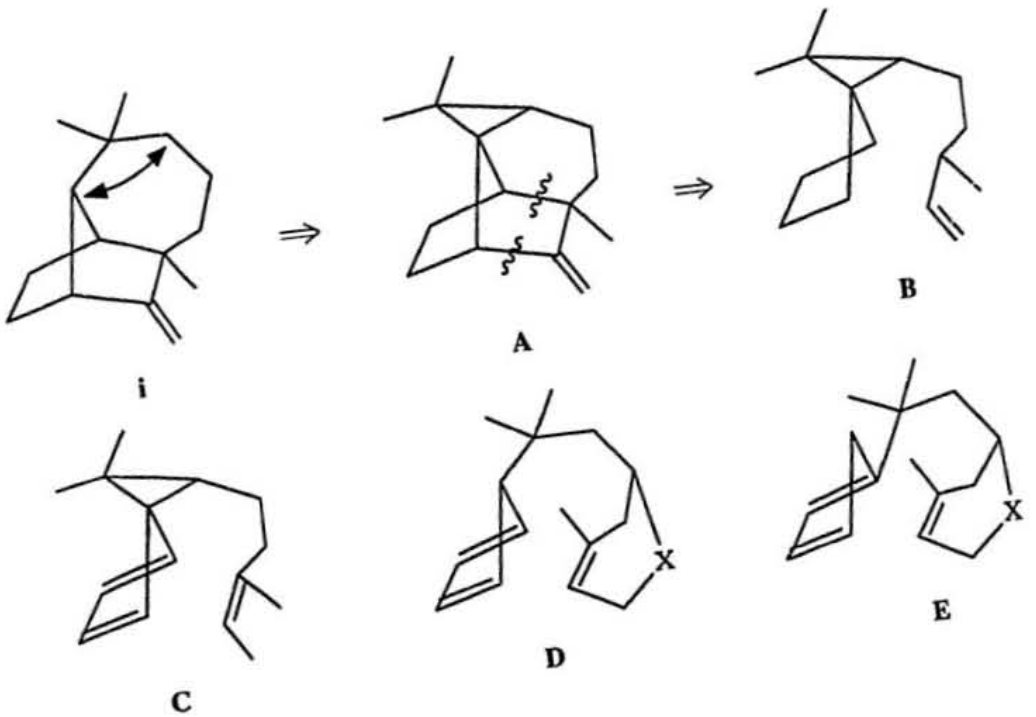
CHAPTER 3

SYNTHETIC PLAN

It is fashionable to analyze a target structure by retrosynthetic bond breaking sequences. However, the direct simplistic application of this idea often leads to long, unimaginative synthetic sequences. As described above the direct double disconnection is not suitable, as Brieger discovered due to the dominance of the 1,5-sigmatropic rearrangement and the preferred cyclization to **26** (see **Scheme 8**).[38] Frequently creating a new bond in a target structure allows one to generate a new species which is more amenable to direct synthesis. Longifolene represents such a case. Creation of a new bond (arrow) in **i** (**Scheme 17**) leads to a new tetracyclic species **A**. A double disconnection of this synthon leads to the part structure **B** which can be transformed into a triene **C** which contains the required functionality for the reverse of the retrosynthetic step *via* a Diels-Alder cyclization.

To reduce these ideas based on the cyclopropyl concept[45] to practice the strategy outlined in **Scheme 18** was envisaged which possesses several interesting synthetic features.

(1) The cyclopropane ring present in the spiro[2.4]heptatriene **iii** will block the generally dominant 1,5-sigmatropic rearrangement of cyclopentadienes under Diels-Alder reaction conditions. This cyclopropyl unit represents a latent methylene group and subsequently undergoes a selective cleavage of the interior cyclopropane bond to provide the tricyclo[5.4.$0^{1,7}$.$0^{6,10}$]undecane ring system possessed by longifolene.



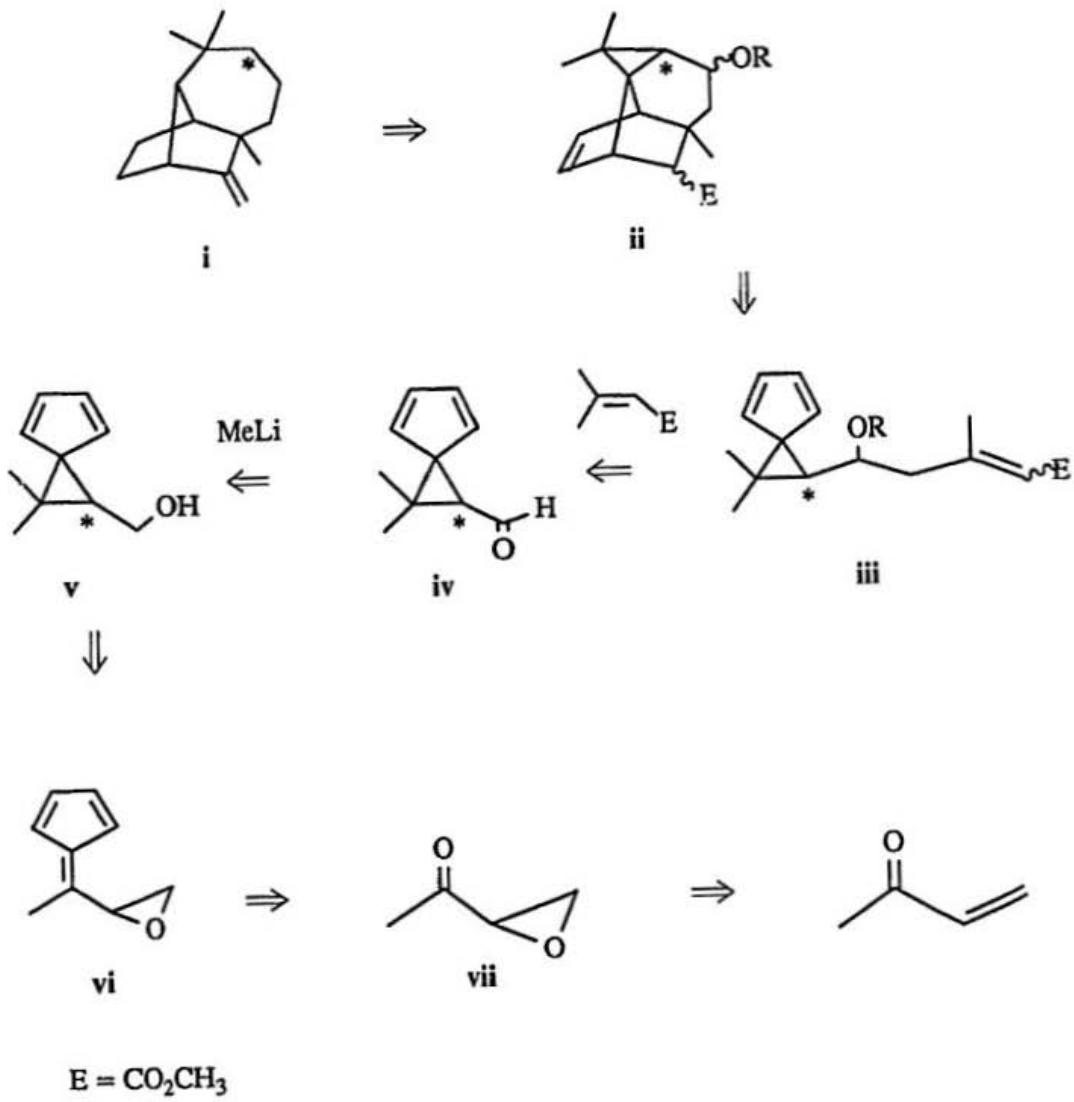
Scheme 17

(2) The Diels-Alder adduct **ii** possesses all of the fifteen carbon atoms required and suitable functionality to allow the introduction of the exocyclic double bond of longifolene.

(3) Based on the experience gained from the sinularene synthesis, a bulky C-5 oxygen substituent is essential to ensure that the desired intramolecular cycloaddition will proceed as required.[46] In a retrosynthetic sense, the preparation of structure **iii** (δ-hydroxy α,β-unsaturated ester) could arise from a selective γ-condensation of the spiro-aldehyde **iv** with an anion derived from methyl 3,3-dimethylacrylate.

(4) The spiro-aldehyde **iv** may be generated by oxidation of the spiro-alcohol **v**. The latter can be obtained from an addition initiated ring closure involving methyllithium and an epoxyfulvene **vi**, which in turn may be synthesized from commercially available materials by known methods.[16]

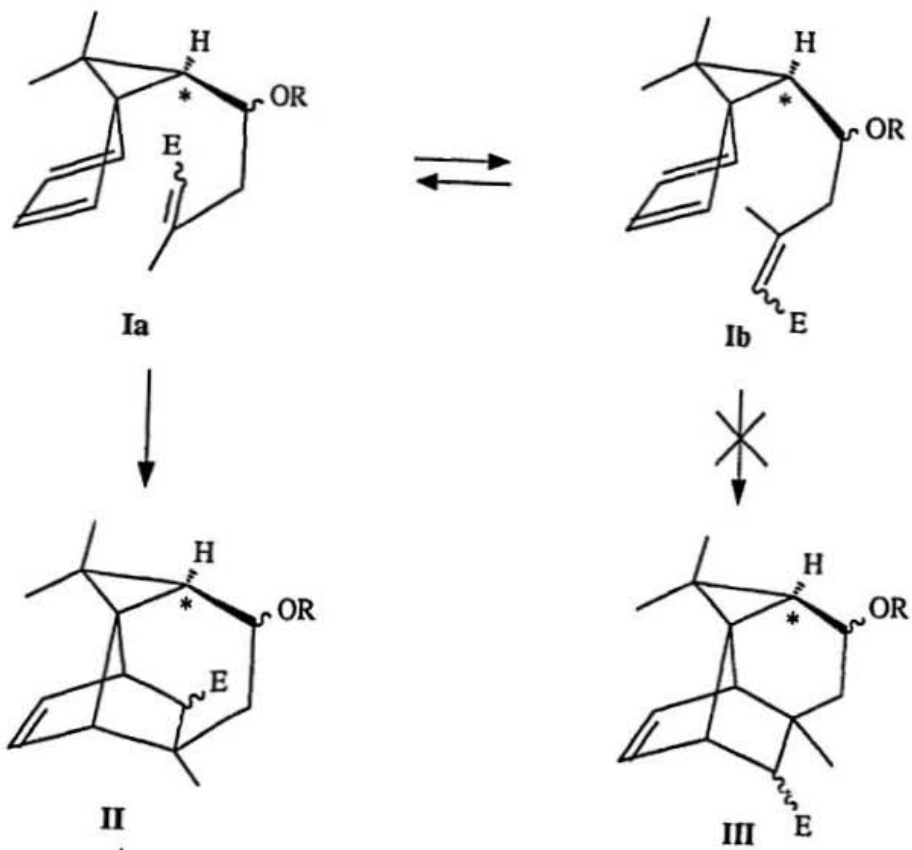
A further potential feature of this strategy arises from the geometric constraints imposed by the Diels-Alder transition state. From **Scheme 19**, it is apparent that only conformation **Ia** will permit the cyclization, while conformation **Ib** will not undergo adduct formation because the dienophile is not aligned with the diene as required for the cycloaddition. Therefore, if the cyclopropyl unit is chiral, the stereochemistry of the asterisk carbon will control the cyclization to lead to an optically active adduct, from which the chiral longifolene may be synthesized. Interestingly, the chirality of this asterisk carbon will disappear after reductive cyclopropane ring opening. To achieve the chiral heptatriene **I**, a single enantiomer of spiro-alcohol **v** (**Scheme 18**) is necessary, which may be obtained either from a chiral starting material or by resolution (*cf.* **Scheme 29** in **Chapter 6**).



i ii iii iv v vi vii

E = CO_2CH_3

Scheme 18



Scheme 19

In spite of the failure of the Brieger's approach it might succeed without resorting to a blocking group if direct cyclization from a C-5 substituted cyclopentadiene was the most favorable pathway. In theory this might be accomplished by confining the dienophile to a cyclic system in which the adducts from the C-1 and C-2 substituted cyclopentadienes are excessively strained. This will be discussed in more detail below but structure **D** (**Scheme 17**) represents this approach in which **X** is a functionality that will allow subsequent ring cleavage after cycloaddition. Molecular models reveal that cyclization of **D** should be preferred over **E** due to the strain inherent in the cyclohexane adduct. It should however be emphasized that no carbocyclic example of direct cycloheptane formation is known.

PART II

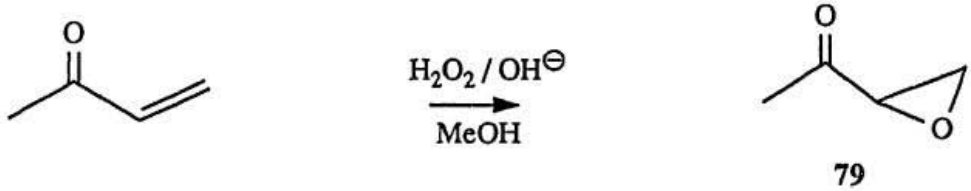
RESULTS AND DISCUSSION

CHAPTER 4

INTRAMOLECULAR DIELS - ALDER REACTION

4.1 Epoxyfulvene Preparation

The epoxidation of methyl vinyl ketone under the basic condition in methanol gave the racemic epoxide **79** (**Equation 1**) in reasonable yield (60 %). The epoxide **79** is quite stable and can be stored in a refrigerator for several months.



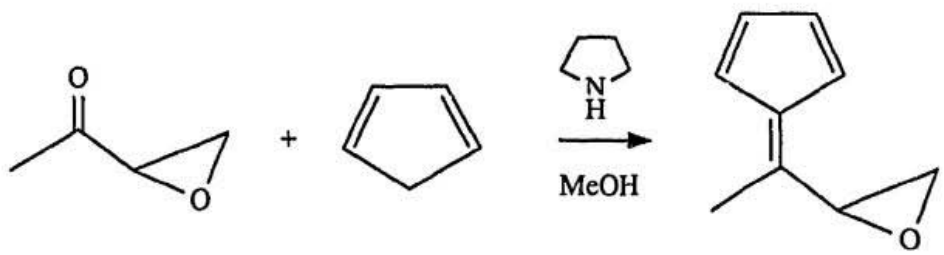
79

Equation 1

The condensation of epoxide **79** with freshly prepared cyclopentadiene was conducted in the presence of a catalytic amount of pyrrolidine to give epoxyfulvene **80** (**Equation 2**) in a highly efficient manner. Other bases resulted in lower yields and extensive decomposition.[16, 54] The ^{1}H nmr spectrum of **80** displayed a characteristic four proton multiplet at δ 6.35 for the vinyl protons, a vinyl methyl singlet at 1.91, a multiplet at 2.82 for the methylene hydrogens, and a doublet of doublets (J = 1.5, 1 Hz) at 3.90 due to the methine hydrogen. These features support the assigned structure.

This bright brown compound is very unstable at room temperature and therefore was used for the next synthetic step as soon as possible. (It may be kept below -20°C for up to 48 hours) In one case, a small explosion and production

of a noxious smoke was observed when a large amount (ca. 20g) of frozen epoxyfulvene **80** was allowed to warm to room temperature. The compound became a black mass of polymer-like material. However, it is safe to use this compound immediately after preparation.



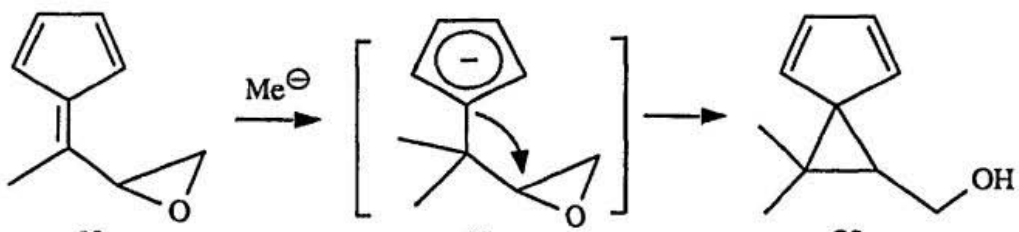
79 **80**

Equation 2

4.2 Epoxyfulvene Cyclization

It is well established that the exocyclic double bound in fulvene is polarized and of reactivity similar to a carbonyl group.[55] This means, in principle, that nucleophilic attack may occur at the exocyclic fulvene double bond or at either end of epoxide in **80**. Thus the nucleophilic attack could generate several different products. However, the treatment of epoxyfulvene **80** with methyllithium at -78°C resulted in the formation of spiro-alcohol **82** as the sole product (55%) and the recovery of starting material **80** (35 %) after work-up and chromatography. The ^{1}H nmr spectrum of the product displayed two methyl singlets at δ 1.40 and 1.42, the

cyclopropyl hydrogen as a triplet (J = 7.5 Hz) at 2.39, the methylene protons as a doublet (J = 7.5 Hz) at 3.78, and the four cyclopentadienyl protons as three overlapping multiplets at 6.30, 6.45 and 6.57, all of which were consistent with the assigned structure. In this case the methyl anion preferentially attacked the C-6 fulvene centre to generate the cyclopentadienyl anion intermediate **81** which cyclized to form the cyclopropane ring by *exo-tet* cleavage of the epoxide ring **(Equation 3)**.



80 **81** **82**

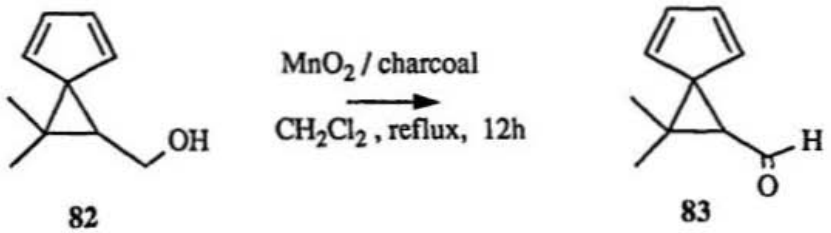
Equation 3

A mixture of product and starting material was always obtained even using a large excess of methyllithium and longer reaction times.

4.3 Cyclopropyl Alcohol Oxidation

The cyclopropyl alcohol **82** was sensitive to chromium based oxidizing reagents. The cyclopropyl aldehyde **83** was prepared with active manganese dioxide oxidation in good yield (86 %) (**Equation 4**). The ^{1}H nmr of **83** showed the aldehyde proton as a doublet (J = 6 Hz) at δ 9.56, the disappearance of the methylene protons at 3.78 and the change of the cyclopropyl hydrogen at 2.78

from a triplet to a doublet ($J = 6$ Hz).



82 **83**

Equation 4

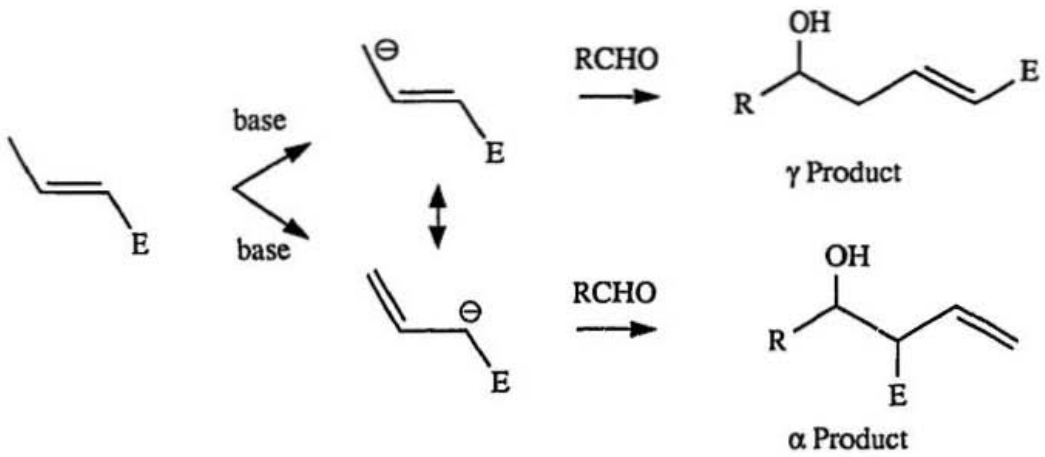
The method of preparation of the active manganese dioxide significantly influenced the oxidation.[56] The most effective manganese dioxide for our case was obtained from the reduction of potassium permanganate by charcoal.[57] In practice, a large excess of charcoal was used to prepared the manganese dioxide and the unreacted charcoal remained in the product mixture as a part of the reagent. It was discovered that charcoal from different companies had different levels of effectiveness. The charcoal from the J. T. Baker Company was the best one in our work.

An alternative preparation of aldehyde **83** from alcohol **82**, in excellent yield (94 %), employed Swern oxidation using oxalyl chloride and highly dried dimethyl sulfoxide. However, with larger scale reactions (ca. 0.02 mole), the manganese dioxide/charcoal oxidation was preferred due to the convenience of the work-up and product separation.

4.4 α *vs* γ Condensation

To prepare a Diels - Alder precursor, such as structure **iii** (**Scheme 18**), we required a reliable procedure to introduce directly a conjugated allyl unit to the

spiro-aldehyde **83**. This necessitates a regioselectively controlled condensation of an allyl anion with an aldehyde (**Scheme 20**).



Scheme 20

Literature methods are available to generate the α-product in a controlled manner but only a few reports describe the regioselective preparation of the γ-product. The control of α *vs* γ substitution in heteroatom-stabilized allylic anions and resonance-stabilized enolates depends upon the complex interplay between the nature of the atoms, charge delocalization, steric effects, solvation, the type of electrophile, and the counter ion. These difficulties are compounded by the observation that halides and carbonyl systems often exhibit opposite regioselectivities.[58]

Hudlicky and his co-workers found the regioselectivity in the Reformatsky reaction of ethyl 4-bromocrotonate with carbonyl substrates depended on the polarity of solvents and the hardness of metal catalysts.[81] We tested his modified Reformatsky conditions using dry zinc and tetrahydrofuran. It worked well when

either methyl 4-bromocrotonate or methyl 3-bromomethyl-2-butenoate (**Table 1**, entry 1, p 41) were reacted with benzaldehyde and gave the γ-product exclusively. Unfortunately the reactions (**Table 1**, entries 5 and 6) with the spiro-aldehyde **83** gave 60 : 40 and 40 : 60 α / γ mixtures (**Scheme 21**), presumably a consequence of the hindered environment of the carbonyl group. Modification of the reaction conditions using an ultrasonic bath or dimethoxyethane (DME) as the solvent provided no significant improvement in the α / γ ratio.

Various lithium anion-salt combinations derived from 2-ethylidene-1,3-dithane were examined (**Scheme 22**). Ziegler and Tam demonstrated earlier that allylation of the lithium anion derived from 2-ethylidene-1,3-dithiane afforded the α-product preferentially, while the corresponding copper derivative gave the γ-product exclusively.[59] However, in the case of the cuprate derivative with spiro-aldehyde **83** a significant quantity of the α-product was obtained (**Table 1**, entry 9), although the γ-product dominated. Added zinc salts did not influence the regioselectivity and the α-product dominated in the presence of zinc chloride (**Table 1**, entry 8).

Except for the reaction of organocadmium reagents with acid chloride, organocadmium species have received relatively little attention.[60] Pure, salt free alkyl cadmiums do not react with carbonyl compounds but this reactivity can be altered markedly by the addition of magnesium or lithium salts,[61, 62] which means that *in situ* cadmium reagents prepared from organolithium compounds or Grignard reagents can be efficiently used to react with carbonyl compounds. Thus the addition of cadmium chloride powder to the lithium anion at -78°C was examined (**Scheme 23**). The appropriate carbonyl compound was added to this reagent and the reaction was allowed to warm to 0°C followed by quenching with saturated aqueous ammonium chloride. As summarized in **Table 1** all reactions of the lithium anions with added cadmium chloride resulted in γ condensation products

predominantly with excellent yields (**Table 1**, entries 2, 4, 10 and 11).

Further studies showed that if the reaction was quenched at -78°C with an acetic acid solution in tetrahydrofuran, the α substituted material was the only product. Equilibration at 0°C for enough time (monitored by TLC) to allow rearrangement to the γ-product was required. Treatment of α-product with lithium diisopropylamide and cadmium chloride at 0°C for one hour resulted in almost same α/γ ratio (**88 : 86** = 10 : 90, **Scheme 24**). This proved that the γ substitution observed was a consequence of isomerization to the thermodynamically more stable product. It should be mentioned that a lactone resulting from the γ-product was also found, similar to the case of the chiral materials employed and discussed in **Chapter 6.**

Lithium amides add in a conjugative manner to methyl crotonate unless hexamethylphosphoramide (HMPA) is present.[61] Thus addition of HMPA was required for complexation and deprotonation of methyl crotonate (**Table 1**, entry 3). This reduced the influence of the cadmium reagent. The γ selectivity also diminished in the presence of more soluble salts such as cadmium iodide. These results suggest that the solvation effects are of prime importance in establishing the regioselectivity.

Relatively few investigations into the composition and structure of organocadmium reagents have been carried out. " Purified " cadmium reagents, isolated by distillation, have the dialkyl structure, for example, di-n-butylcadmium.[62] However, the structure of *in situ* alkylcadmiums are complicated and may be markedly different. We found that yields were less and the reactions were incomplete if the ratio of the lithium to cadmium species was not 2 : 1 molar equivalents. Further work will be required to determine the exact nature of the reactive cadmium reagent.

TABLE 1 α VS γ CONDENSATIONS

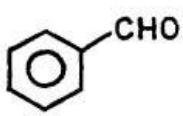
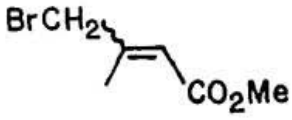
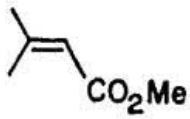
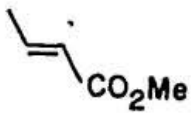
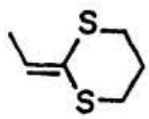
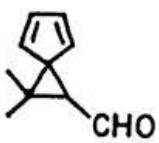
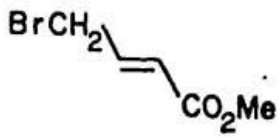
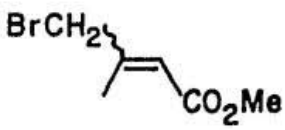
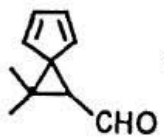
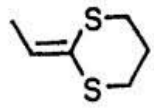
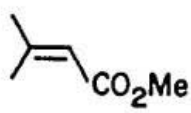
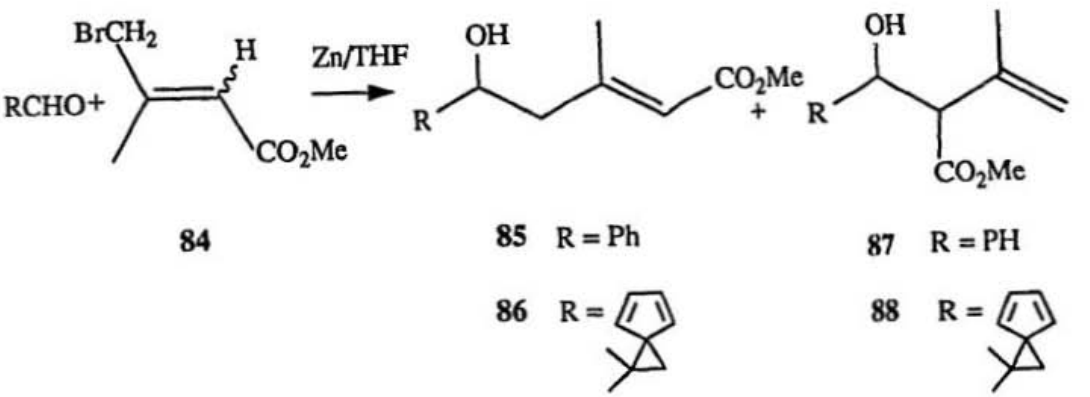
Entry	Aldehyde	Substrate	Metal/Salt	α : γ	Isolated Yield
1			Zn(THF)	0:100	85%
2	"		$LDA/CdCl_2$	15:85	75%
3	"		$LiNCy_2/CdCl_2$ HMPA	50:50	90%
4	"		$LDA/CdCl_2$	10:90	95%
5			Zn(THF)	60:40	60%
6	"		Zn(THF)	40:60	63%

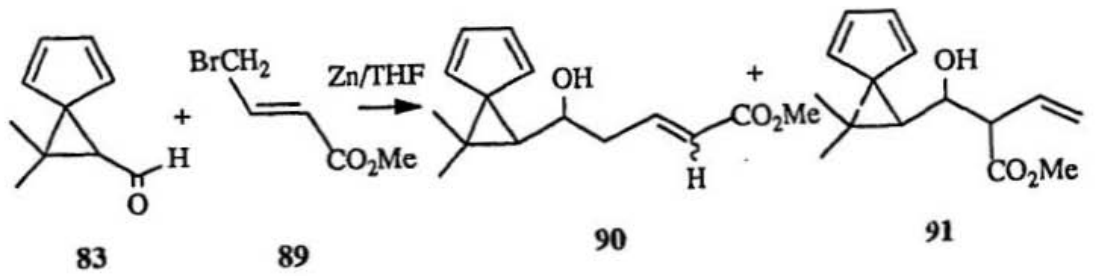
TABLE 1 α VS γ CONDENSATIONS (Continued)

Entry	Aldehyde	Substrate	Metal/Salt	α : γ	Isolated Yield
7			LDA	90:10	96%
8	"	"	$LDA/ZnCl_2$	60:40	70%
9	"	"	$LDA/_3$ CuI.P(OMe)	35:65	61%
10	"	"	$LDA/CdCl_2$	10:90	90%
11	"		$LDA/CdCl_2$	15:85	90%



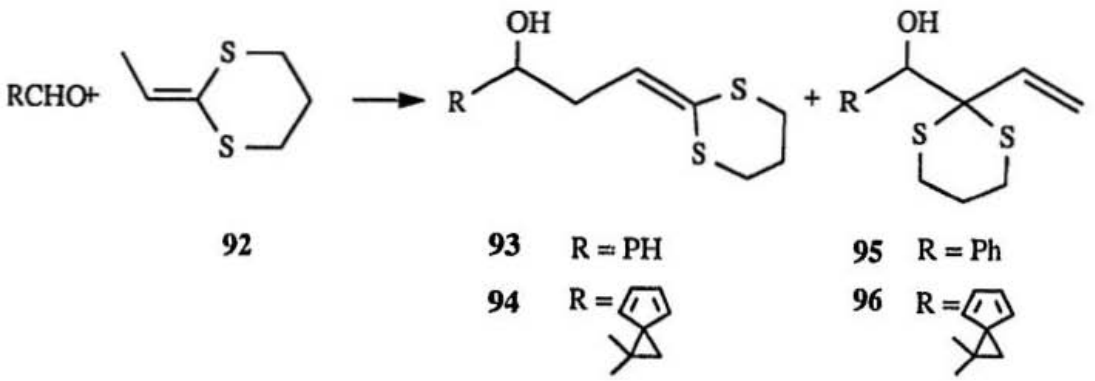
84 **85** R = Ph **87** R = PH

86 R = **88** R =



83 **89** **90** **91**

Scheme 21



92

93 R = PH

94 R =

95 R = Ph

96 R =

Reaction Condition :

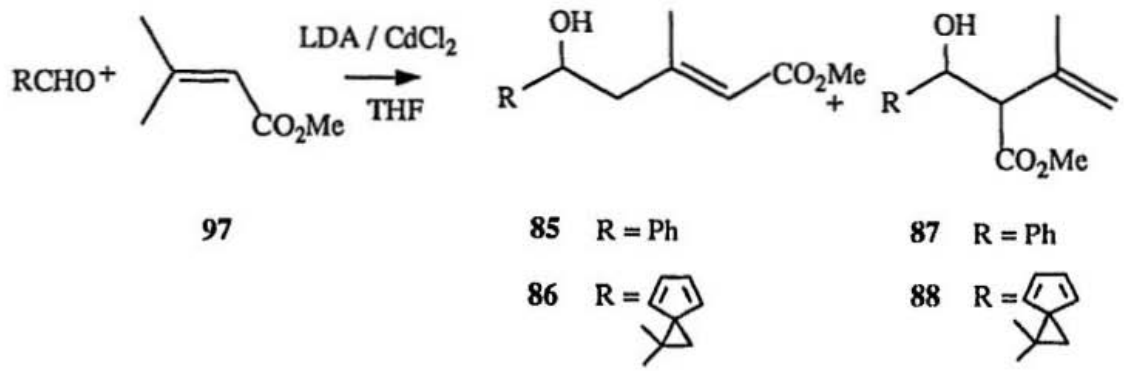
A : LDA / THF

B : LDA / $ZnCl_2$

C : LDA / $CuI.P(OMe)_3$

D : LDA / $CdCl_2$

Scheme 22



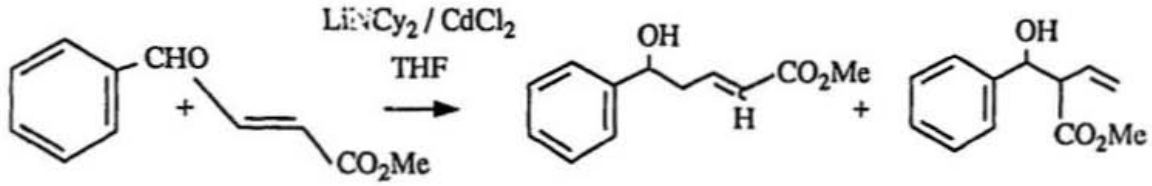
97

85 R = Ph

86 R =

87 R = Ph

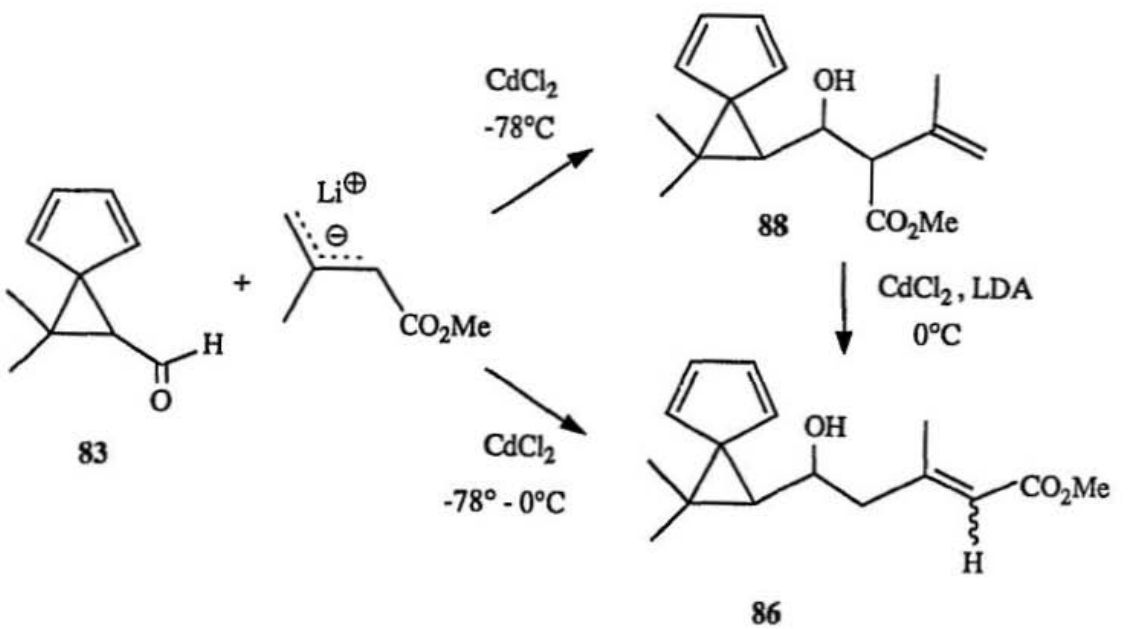
88 R =



98

99

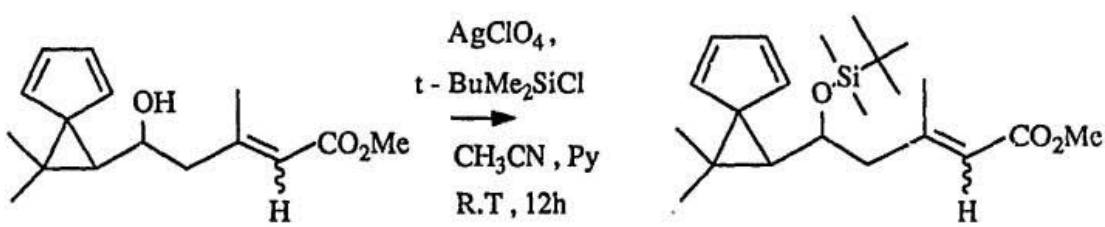
Scheme 23


CdCl2
-78°C
OH
88
CO2Me
Li⊕
⊖
CO2Me
CdCl2, LDA
0°C
H
O
83
CdCl2
-78° - 0°C
OH
CO2Me
H
86

Scheme 24

4.5 Protection of Hydroxy Ester

The direct use of the hydroxy ester **86** for the Diels-Alder reaction was unsuccessful, since even in refluxing benzene the hydroxy ester **86** slowly decomposed. Meanwhile, it was found that a bulky substituent attached to the hydroxyl would encourage this triene precursor to exist in an appropriate conformation for cycloaddition. Therefore, the *tert*-butyldimethylsilyl group was employed as a suitable protecting group. Surprisingly, the normal methods to convert alcohols to silyl ethers failed in this case, possibly due to the sterically hindered environment of the hydroxyl group. A modified condition for hindered alcohols[63] was employed in which *tert*-butyldimethylsilyl perchlorate was prepared *in situ* from alkylsilyl chloride and silver perchlorate. This silyl reagent reacted in acetonitrile with excess pyridine to afford **100** in 93% yield (**Equation 5**).



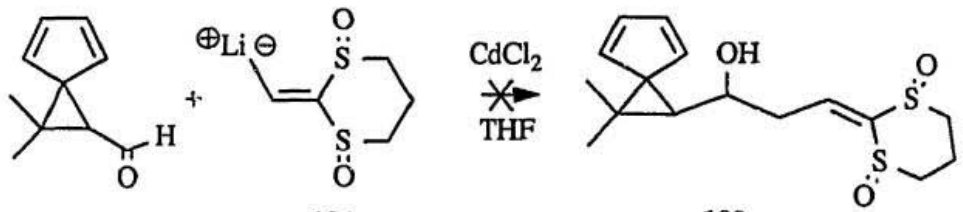
86 **100**

Equation 5

4.6 Attempted Hydroxy Dithiane Dioxide (102) Preparation

The hydroxy dithiane dioxide was proposed as an alternate Diels-Alder reaction precursor because of the known power of the sulfoxide substituent as the dienophile group. Compound **102** could be obtained from the condensation of

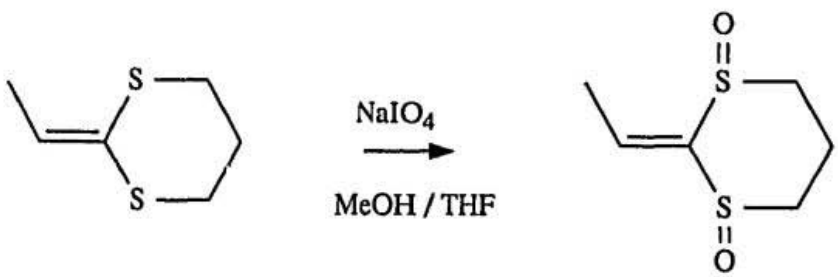
spiro-aldehyde **83** with lithium anion of 2-ethylidene-1,3-dithiane 1,3-dioxide **101** in the presence of cadmium chloride (**Equation 5**).



83 **101** **102**

Equation 6

The dithiane dioxide **101** was synthesized from the corresponding dithiane by sodium periodate oxidation[64] (**Equation 6**). However, this white crystalline compound was largely insoluble in most organic solvents except in dichloromethane and created difficulties in the subsequent synthetic step. A phase-transfer reaction was tried in a mixture of dichloromethane and aqueous sodium hydroxide solution in the presence of benzyltrimethylammonium hydroxide as a phase - transfer catalyst. Unfortunately, the reaction gave a complicated mixture of products.



92 **101**

Equation 7

4.7 Intramolecular Diels - Alder Reaction

In spite of the attention the intramolecular Diels-Alder reaction has received some facets are still imperfectly understood. Thus cyclizations that look promising sometimes fail. A series of unsuccessful thermal Diels-Alder reactions related to this work are listed in **Table 2** (p 52). The triene **100**, a promising precursor, was unstable in refluxing dichlorobenzene (**Table 2,** entry 3) and barely cyclized at lower temperature even when heated for a long time (**Table 2,** entry 1). The reaction in refluxing toluene (**Table 2,** entry 2) was not complete after 24 hours and gave a low yield of adduct accompanied by decomposition. This lead to the conclusion that for a successful Diels-Alder reaction of the triene **100** a reaction temperature higher than 110°C was necessary but the reaction time should be as short as possible. Therefore, a highly efficient thermal source was required.

Until recently microwave ovens have not received much attention as controlled thermal sources for conducting routine chemical reactions. However, recent studies indicated that microwave ovens could be safely used to increase dramatically reaction rates.[65] While our work has been in progress reports of the use of microwave ovens for Diels-Alder reactions have appeared.[66, 67] We were interested in the rapid heating capability of the microwave oven and utilized it in our Diels-Alder reaction.

The reaction was carried out in a screw - cap pressure tube (Pyrex vessel) in a commercial Toshiba Model ERS-6630C (720 Watt) or Magnasonic Model MMW3000 (500 Watt) microwave oven. The power setting at 500 watts was used throughout. The pressure tube was placed in the microwave oven through a hole drilled through the top of oven and encased in Teflon. The diameter of the hole should not be larger than 3 cm otherwise serious microwave leakage may occur. The pressure tube was insulated with damp vermiculite to encourage heat transfer

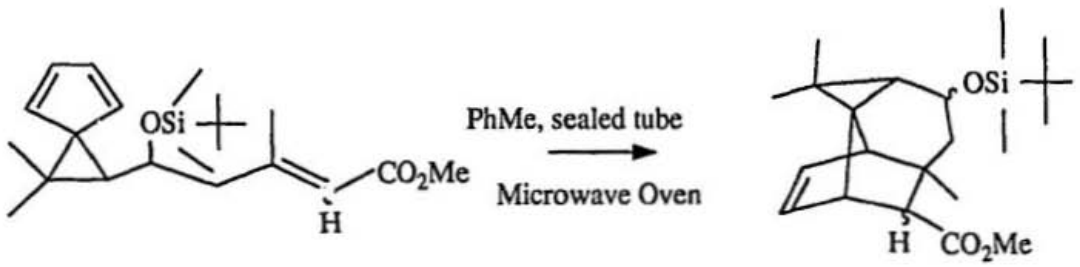
since the magnetron was tuned to the water frequency (2450 MHz). In addition, all microwave oven experiments were conducted in a fumehood (see **Fig. 1**, p 53).

The solvents for microwave reactions must have a certain magnitude of dipolar moment otherwise the solvent cannot effectively absorb the microwave energy. However, solvents such as acetone, ethanol, dimehtylformamide (DMF) etc. with large dipolar moments explode easily in the pressure tube under microwave oven thermal conditions.[66] Reagent solubilities in the solvents available sometimes create difficulties. From our experience, toluene was found to be the best solvent. We have never experienced any difficulty or explosions performing Diels-Alder reactions in toluene but a pressure tube exploded during a Wittig reaction in DMF. In spite of some literature examples DMF should not be employed in microwave experiments.

Thus, the triene **100** was prepared as an approximately 0.05 M solution in toluene and 1 % molar equivalent of hydroquinone added to prevent radical polymerization. The time taken for reactions depended on the reaction scale, generally from 0.5 h to 2 h. The adduct **103** was obtained in an excellent yield (92 %) (**Equation 8**). The hydroxy ester triene **86** was examined in the Diels-Alder reaction under the same conditions but no cyclization was achieved (**Table 2,** entry 6). Clearly, the bulky *tert*-butyldimethylsilyl ether substituent in the side chain assisted the cycloaddition and minimized decomposition. The stereochemistry of the Diels-Alder adduct will be discussed in **Chapter 6.**

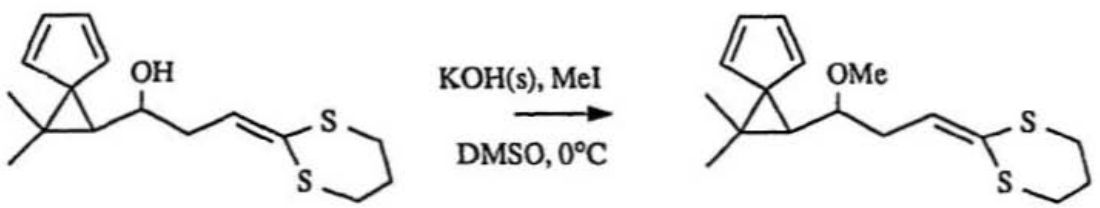
The dithiane triene **104** was prepared as an alternative Diels-Alder reaction precursor. The acylation of the hydroxy group failed and methylation was employed as an alternative protecting method. Again a modified procedure[87] was used for this highly sterically hindered hydroxy group (**Equation 9**). Unfortunately, the Diels-Alder reactions of triene **104**, thermally or in the microwave oven, were

unsuccessful (**Table 2**, entries 7 and 8). We did not investigate the Diels-Alder reaction in the *tert*-butyldimethylsilyl ether dithiane trienes.



100 **103**

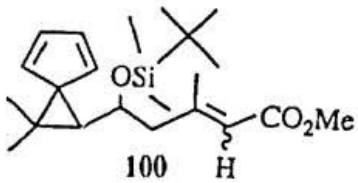
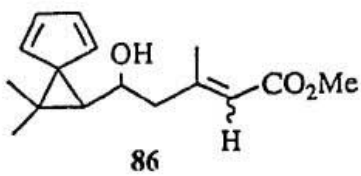
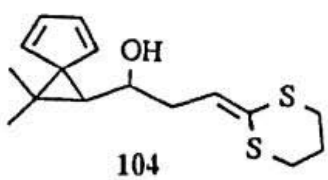
Equation 8



94 **104**

Equation 9

Table 2 Diels-Alder Reactions

Entry	Precursor	Reaction Condition	Result
1	 **100**	benzene, reflux 3 days	N.R.
2	"	toluene, reflux 24 h	10% **103**
3	"	o-dichlorobenzene reflux, 12 h	decomposition
4	 **86**	benzene, reflux 24 h	partial decomposition
5	"	toluene, reflux 24 h	decomposition
6	"	toluene, sealed tube microwave oven	N.R.
7	 **104**	benzene, reflux 48 h	N.R.
8	"	o-xylene, sealed tube microwave oven, 30 min	N.R.

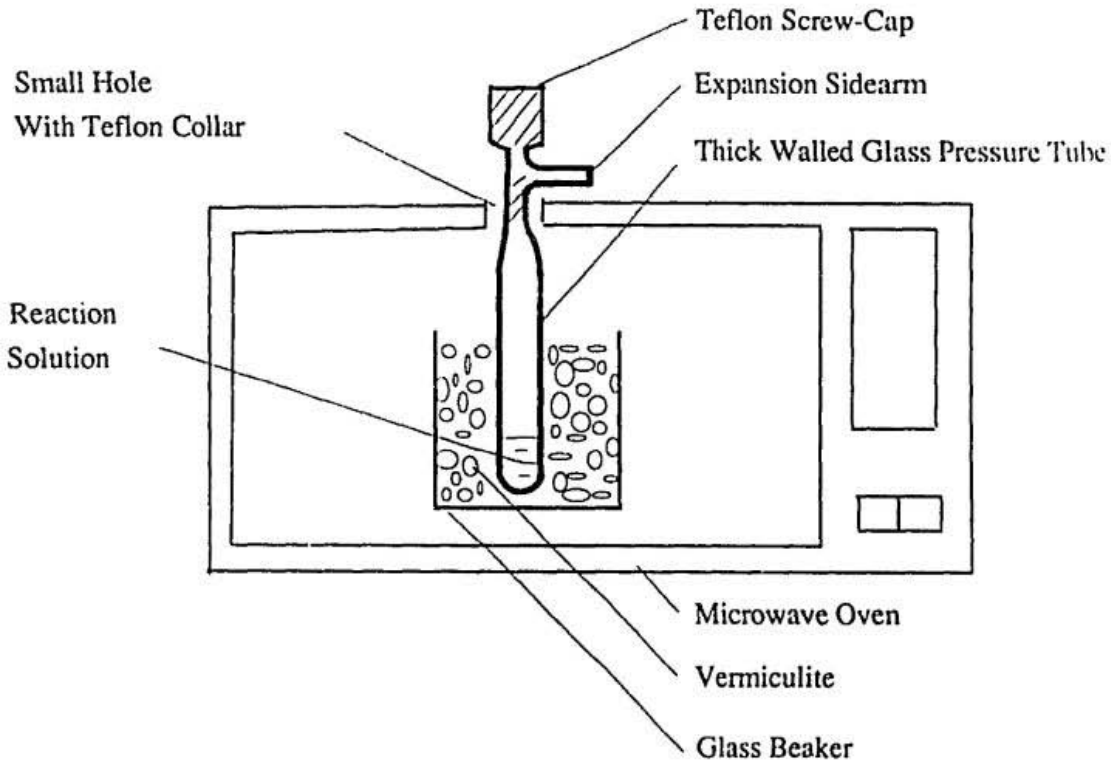
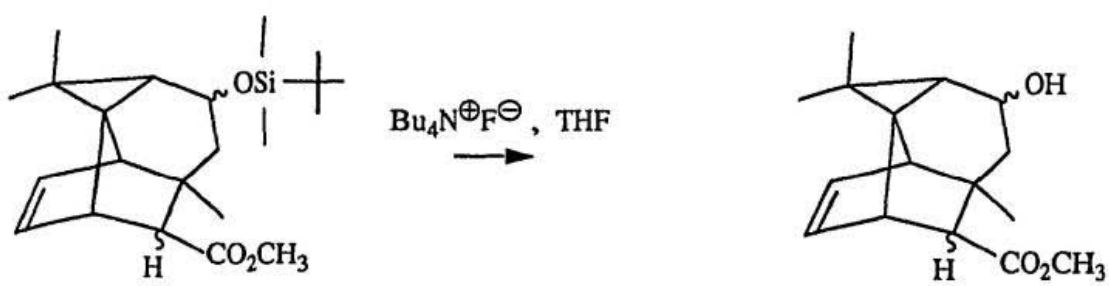


Figure 1 Microwave Oven Reaction Apparatus

CHAPTER 5

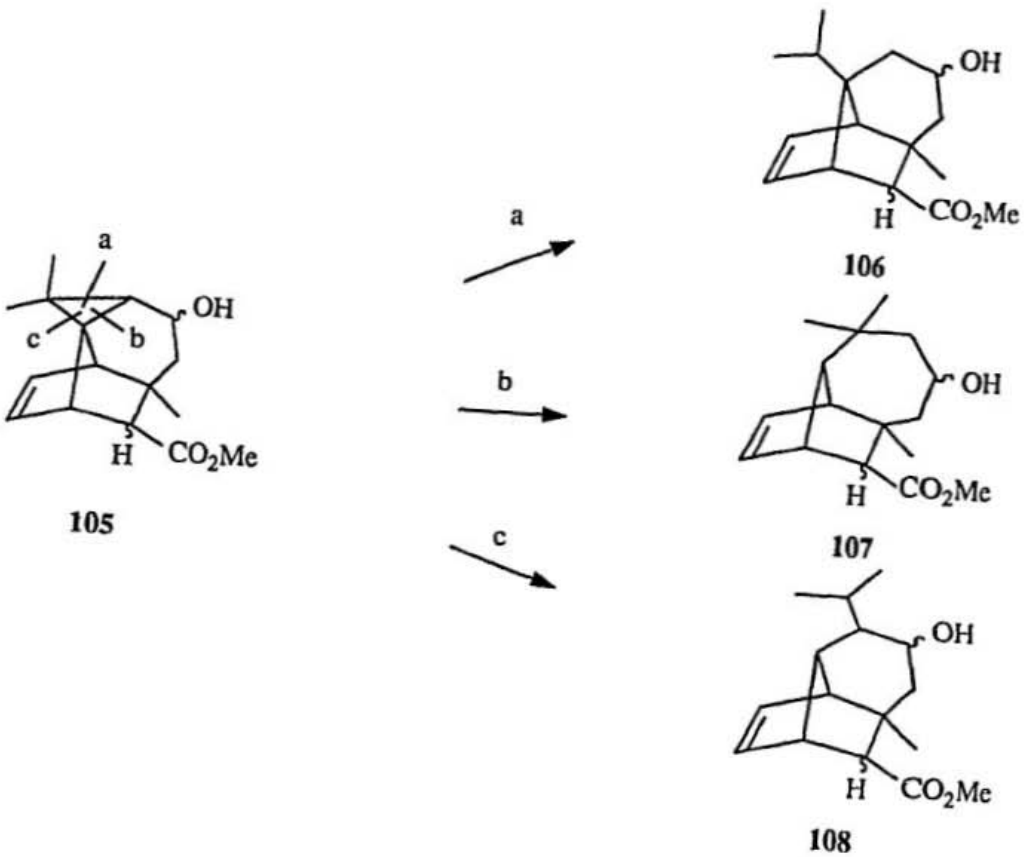
SELECTIVE CYCLOPROPANE RING OPENING

Desilylation of Diels-Alder adduct **103** afforded the required tetracyclic alcohol **105** (**Equation 10**). A selective cyclopropane bond cleavage was now required to afford the desired longifolene tricyclic ring system. As illustrated in **Scheme 25,** there are three possible bond cleavages (a, b, or c) to give different types of products. In general, the cleavage of bond c is least favorable unless activating substituents are present. The following discussion will focus on the series of attempted cyclopropane ring opening approaches summarized in **Table 3** (p56).



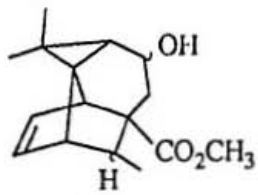
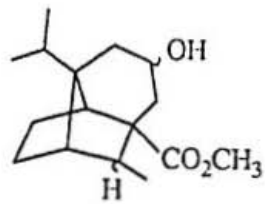
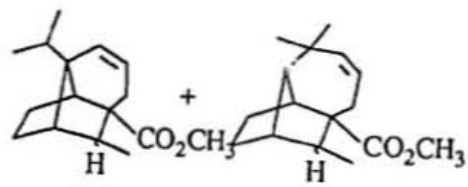
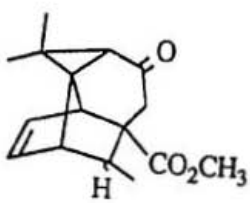
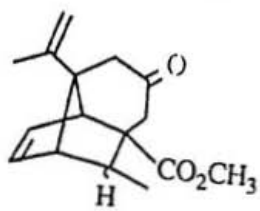
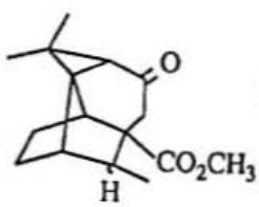
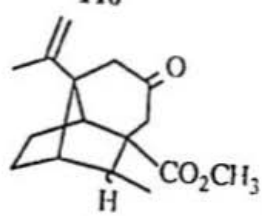
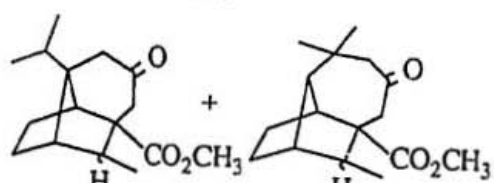
103 **105**

Equation 10


a
b
c
OH
H
CO2Me
105
a
b
c
OH
H
CO2Me
106
OH
H
CO2Me
107
OH
H
CO2Me
108

Scheme 25

TABLE 3 SELECTIVE CYCLOPROPANE RING OPENING

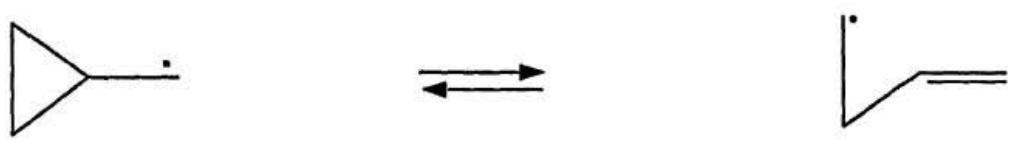
Entry	Reactant	Condition	Ring Opened Product
1	 **105**	H_2, PtO_2, EtOAc	 **109**
2	"	1. H_2, Pd/C, EtOAc 2. PhOC(=S)Cl, Py 3. Bu_3SnH, AIBN	 **111** + **112**
3	 **115**	$Cr_2(SO_4)_3$, Zn, DMF	 **116**
4	 **118**	Zn, MeOH/AcOH, reflux	 **119**
5	"	Li/NH_3, Et_2O	 **123** + **124**

5.1 Hydrogenolysis

It is well established that cyclopropanes can be cleaved at the least substituted bond by catalytic hydrogenolysis. Bond "a" and "b" in tetracyclic alcohol **105** are not very different from the viewpoint of substitution, but bond "a" seems less hindered than bond "b". Hydrogenation of tetracyclic alcohol **105** afforded the bond "a" cleavage product cyclohexane alcohol **109** exclusively (**Table 3**, entry 1). Unexpectedly, under the same reaction conditions (H_2, 60psi, PtO_2, EtOAc / AcOH, 24 h) the *tert*-butyldimethylsilyl ether **103** did not undergo any ring opening. Apparently the hydroxy group assisted the reaction process through coordination with the catalyst.

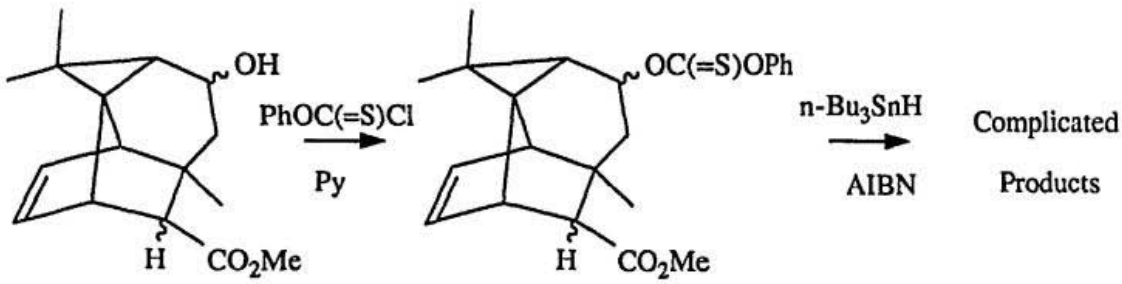
5.2 Radical Ring Opening

The physical organic chemistry of radical ring opening reactions has received considerable study, but their synthetic applications are just beginning to be developed. In principle, the reaction shown in **Equation 11** could be used for the cyclopropane ring opening of our tetracyclic alcohol **105** although the direction of the ring cleavage is unclear.[68] It was hoped that radical ring opening would give a preference for the desired product.



Equation 11

The generation of the initial radical was accomplished stepwise: replacement of the hydroxy group by a radical reaction precursor and then treatment with a stannane.[69] We found the double bond in the tetracyclic alcohol **105** increased the complexity of the products due to the tendency of the radicals to attack the double bond (**Scheme 26**). Therefore, the tetracyclic alcohol **105** was first hydrogenated and then converted into a phenoxythiocarbonate, a radical precursor as described by Robins.[70]



105 **110**

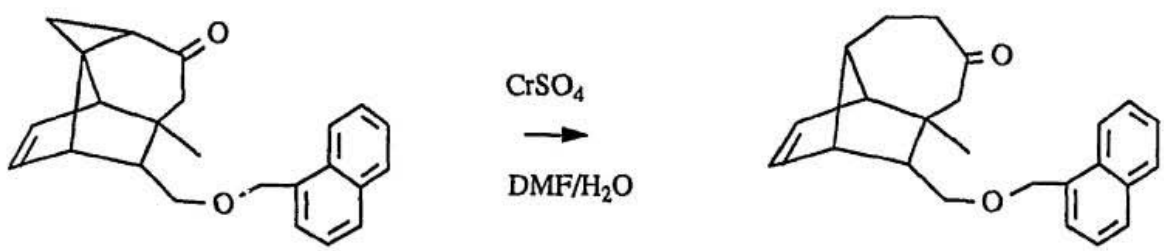
Scheme 26

The radical ring opening reaction was carried out on a dilute solution of phenoxy thiocarbonate compound (ca. 0.02 M) in refluxing toluene with slow addition of tributyltin hydride and radical initiator azobis(isobutyronitrile) (AIBN). A (9 : 1) mixture of cyclopropane ring opened products **111** and **112** was obtained (**Table 3**, entry 2). Different solvents and reaction times did not significantly influence the composition of the product mixture.

5.3 Reductive Ring Opening

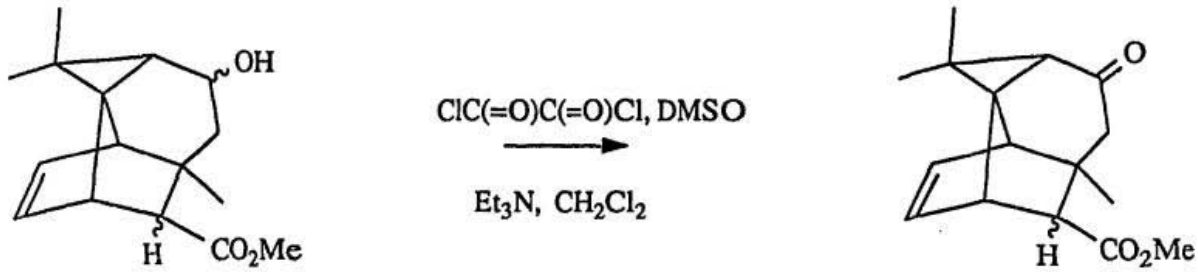
It was established during research on sinularene that chromium (II) salts reduced cyclopropane ketone **113** in DMF / H_2O to give the longifolene type ketone **114** selectively when the double bond was present (**Equation 12**).[71]

The same method was examined. The cyclopropane ketone **115** was generated by Swern oxidation of cyclopropane alcohol **105** (**Equation 13**). A chromium (II) solution was prepared by zinc reduction of chromium (III) sulfate in DMF / H_2O and used immediately. However, the treatment of cyclopropane ketone **115** with the chromium (II) sulfate solution for 36 h at room temperature did not give any ring opened product. Upon heating the reaction solution or in the case of chromium (II) sulfate prepared *in situ* (an exothermic reaction), the cyclopropane isomerization product **116** was obtained as a sole product (**Table 3**, entry 3). This was consistent with the observation that the isomerization of the cyclopropane in this strained tetracyclic system was quite facile. In fact, during recrystallization (EtOAc / hexane) of the hydrogenated product from the tetracyclic alcohol **105**, isomerization occurred when the solution was warmed (see **Experimental**).



113 **114**

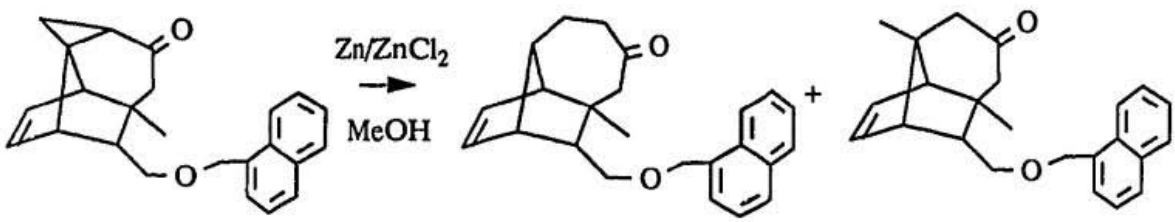
Equation 12



105 **115**

Equation 13

The previous work[71] also found that the reduction of cyclopropane ketone **113** with zinc / zinc chloride in methanol afforded 75% of the bridged cycloheptanone **114** (longifolene type) and 25% of the bridged cyclohexanone **117** (sinularene type). **(Equation 14)**

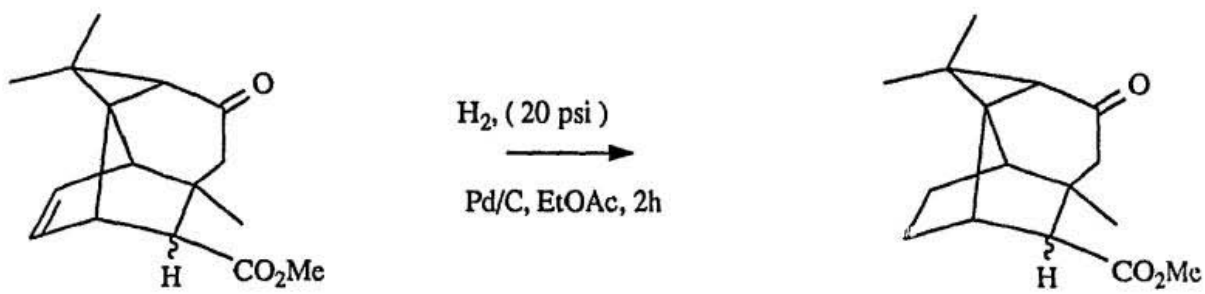


113 **114** **117**

Equation 14

The application of this method to cyclopropane ketone **115** did not result in a ring opening reaction, but it induced acid catalyzed isomerization of the ester substituent. A modified zinc reduction (Zn, MeOH/AcOH, reflux) of the cyclopropane ketone **118**, obtained from hydrogenation of the alkene ketone **115** (**Equation 15**), resulted in the isomerization of the substituted cyclopropane ring to the isopropyl substituted cyclohexanone **119** (**Table 3**, entry 4). Hydrogenation was conducted prior to the zinc reduction because the reaction gave a complicated mixture of products when the double bond was present.

Dissolving metal reductions have been applied to the cyclopropane bond cleavage of conjugated cyclopropyl ketones.[72] They are subject to a variety of influences. Lithium/ammonia reduction of cyclopropyl ketone **120** afforded a mixture of **121** and **122**, in which the longifolene type product **122** was the minor constituent. To facilitate the analysis resulting diols hydrogenated (**Scheme 27**).[71]



115 **118**

Equation 15

120 **121** **122**

70 : 30

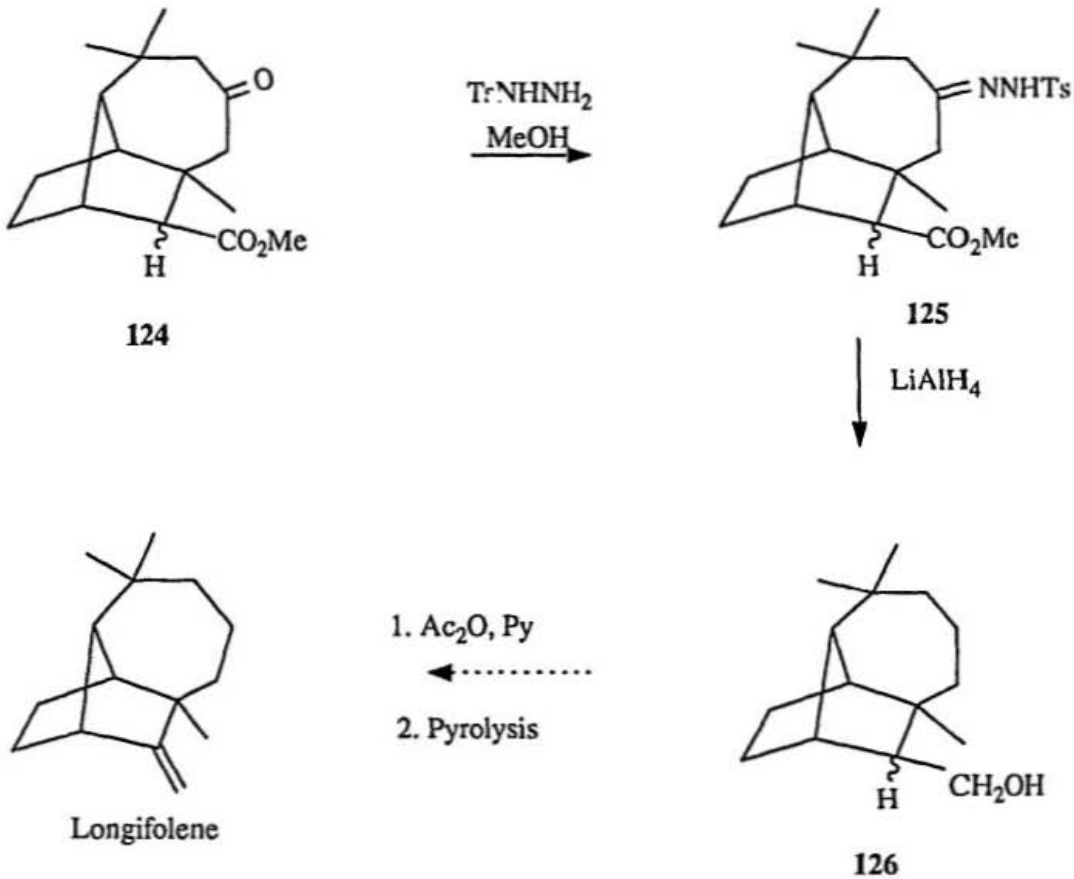
Scheme 27

Lithium / ammonia reduction of cyclopropyl ketone **118** in ether solution at -78°C afforded a 1 : 1 mixture of bond "a" opened product **123** and bond "b" opened product **124** (**Table 3**, entry 5). Here also the double bond must first be saturated to avoid rearrangement products. The amount of lithium and the reaction time were controlled to prevent the further reduction of the carbonyl groups.

This was the best result obtained for the cyclopropane ring opening, although the 1 : 1 mixture was disappointing. The products could not be separated so the mixture was used directly for further synthesis.

5.4 Attempted Ketone Reduction

The remaining steps are illustrated in **Scheme 28.** It was anticipated that the unwanted isomer could be successfully separated at one of the synthetic stages before the acetate pyrolysis required to generate the exocyclic double bond.



124 **125** **126**

Longifolene

Scheme 28

The formation of tosylhydrazone **125** proceeded without any difficulty but the separation of products still remained a problem. Treatment of this mixture with lithium aluminum hydride provided a complicated mixture of reduced products. From the spectroscopic analysis (IR, NMR), this new mixture contained products at different stages of reduction. This was not satisfactory so the synthesis of racemic longifolene was stopped at this step (*cf.* **Experimental**).

CHAPTER 6

ENANTIOSELECTIVE SYNTHETIC APPROACHES

6.1 Initial Approach

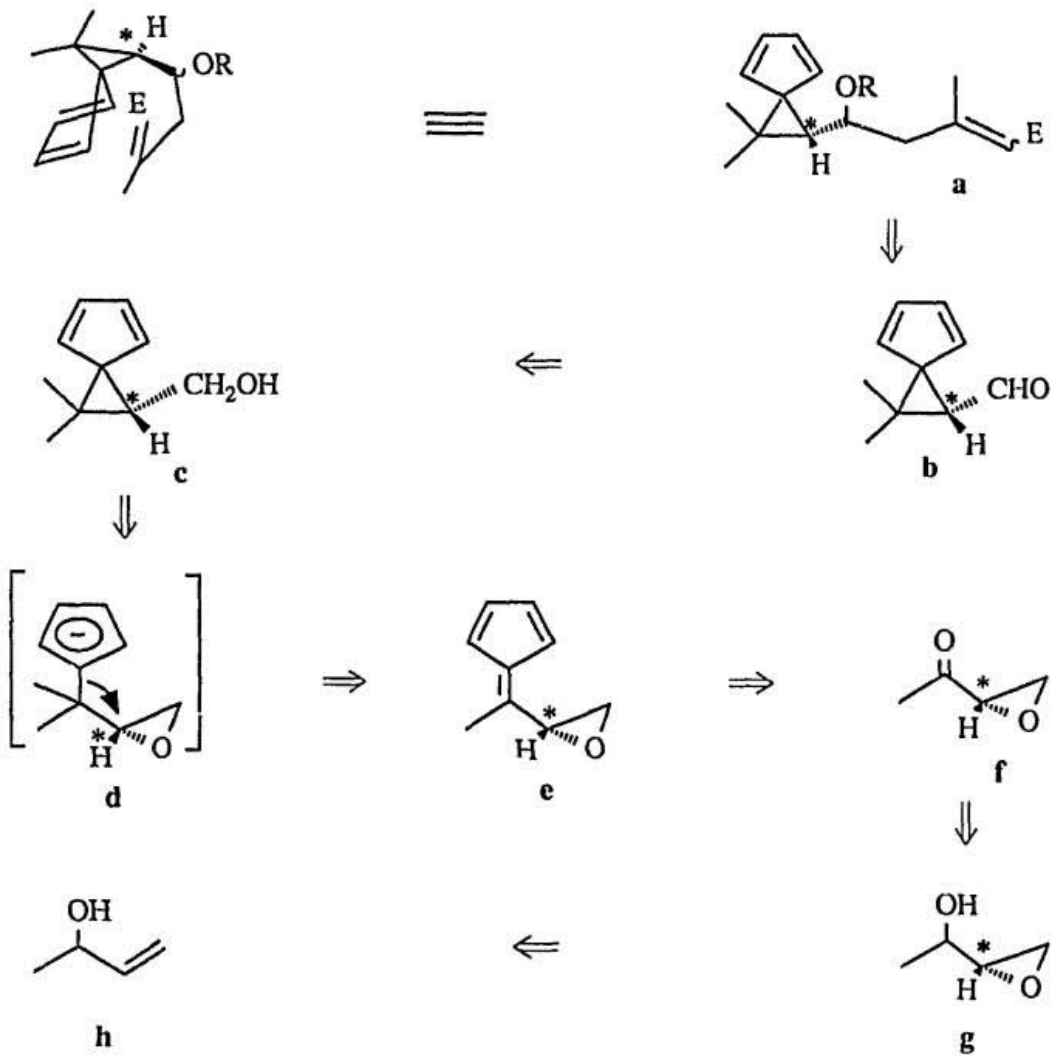
As previously discussed in **Chapter 3**, stereochemical control of the Diels–Alder cyclization should be possible using an optically active spiro-cyclopropane-cyclopentadiene as the precursor (see **Scheme 19**). Our initial approach to optically active material is shown in **Scheme 29**.

The cyclopentadienyl anion **d** cyclizes in an *exo–tet* manner to generate the (1R)-spiro[2.4]hepta-4,6-diene alcohol **c**. Therefore, once the stereochemistry of the asterisk carbon is constructed in the epoxybutanol **g**, its chirality will be carried through the whole synthetic sequence and control the stereochemistry of the Diels-Alder reaction. In principle, the optically active epoxide **g** could be prepared by Sharpless epoxidation of 3-buten-2-ol **h**.

6.2 Attempted Sharpless Epoxidation

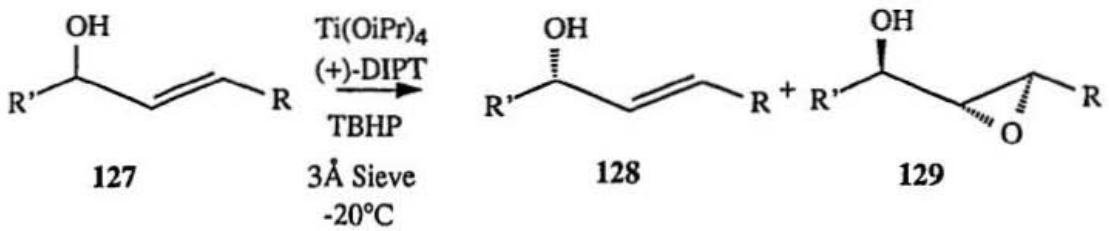
Sharpless and his co-workers reported that the kinetic resolution of secondary allylic alcohols could be achieved by epoxidation with *tert*–butyl hydroperoxide (TBHP) involving a catalytic amount of the titanium tartrate complex in the presence of molecular sieves (**Scheme 30**).[73] In the case illustrated, the epoxy alcohol product is the type of compound we desired for the enantioselective synthesis.

We followed the same procedure in an attempt to prepare the (2S, 3R) 1,2–epoxy–3–butanol **g**, the key intermediate, from the racemic 3-buten-2-ol and examined the stoichiometric method as well.[93] Unfortunately, all attempts failed to



Scheme 29

give the desired product in a significant yield. This low molecular weight allylic alcohol seemed unstable under the Sharpless epoxidation conditions.



127 128 129

Scheme 30

6.3 Resolution of the Spiro Alcohol (82)

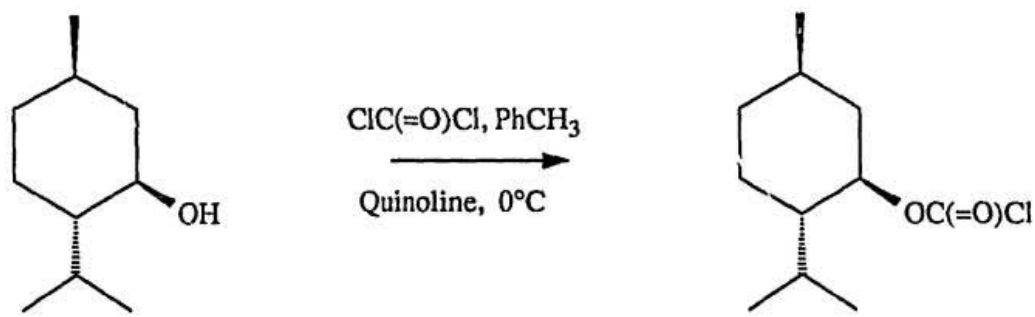
In view of the difficulty experienced preparing optically active epoxy alcohol **g**, the possibility of resolving the racemic spiro alcohol **82** was examined since the compound was relatively easy to prepare and fairly stable in storage.

Today it is possible to carry out resolutions of organic compounds with a high probability of success, although resolutions are often still tedious. In general, racemic alcohols are resolved by forming diastereomeric esters, but these methods require acid-catalyzed esterification conditions. Earlier experiments established that spiro-alcohol **82** was unstable in acidic environments and, therefore, a resolution method under basic conditions was required.

(*l*)-Menthyl chloroformate has been used to make carbonates and cabamates for the analytical resolution of alcohols and amines several years ago,[74] although its preparative application was reported only recently for the resolution of racemic

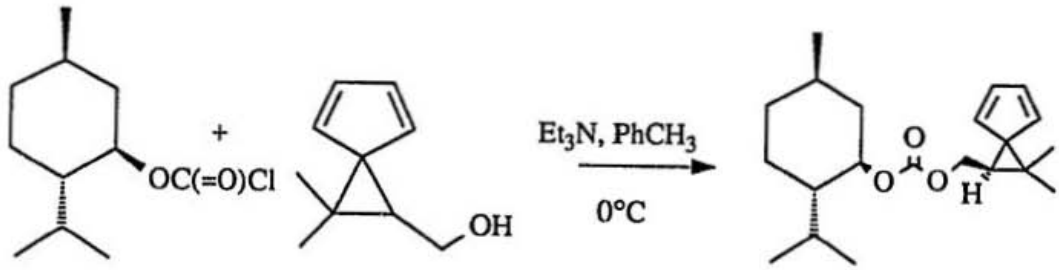
warfarin.[75] The formation of menthyl carbonates proceeds under basic conditions and thus the stability of the acid sensitive spiro-alcohol **82** will not be influenced.

(-)-Menthyl chloroformate **130** was prepared from (-)-menthol and phosgene solution in toluene at 0°C in the presence of quinoline (**Equation 16**).[74] Treatment of the racemic spiro-alcohol **82** with this (-)-menthyl chloroformate solution (ca. 1 mmol/mL) in the presence of triethylamine gave a mixture of products. Careful separation by flash chromatography afforded a component **131** (**Equation 17**). The cyclopropyl hydrogen appeared as a triplet at δ 2.43 (J = 7.2 Hz) in the ^{1}H nmr spectrum. A series of experiments with increasing concentration of a chiral shift reagent (tris [3- (trifluoromethylhydroxymethylene) - (+) -camphorato],europium (III) derivative) caused neither line broadening nor the appearance of a new signal, confirming the presence of a single enantiomer. The other components, including the diastereomer of **131**, were difficult to purify by flash chromatography.



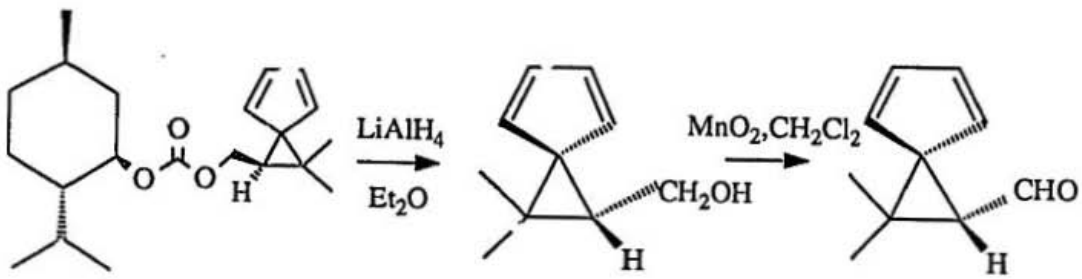
130

Equation 16



130 **82** **131**

Equation 17



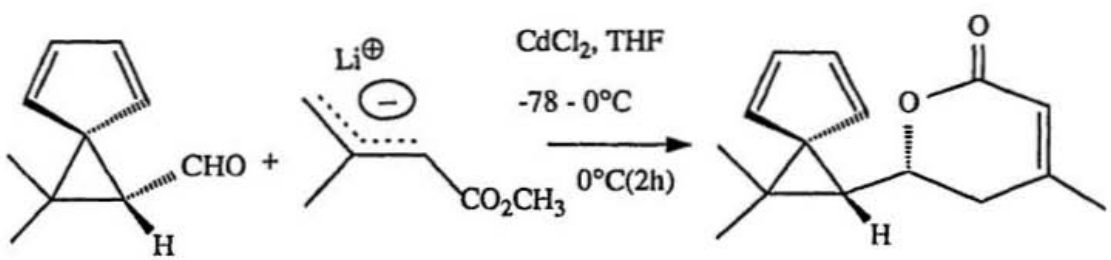
131 **132** **133**

Scheme 31

Lithium aluminum hydride reduction of (-)–menthylcarbonate **131** in ether solution provided the (+)–R–spiro–alcohol **132** (34% yield from racemic alcohol **82**, i.e. 68% of available enantiomer). The stereochemistry of (+)–R–spiro–alcohol **132** was confirmed on the basis of the chemistry of the final product, (+)–longifolene. The manganese dioxide oxidation converted the (+)–R–spiro–alcohol **132** into (+)-R-spiro-aldehyde **133** in the same manner used for the racemic case (**Scheme 31**).

6.4 γ - Condensation

The condensation of (+)–R–spiro–aldehyde **133** with methyl 3,3–dimethylacrylate anion in the presence of cadmium chloride was carried out under the conditions described previously. Surprisingly, after stirring at 0°C for 2 hours, the δ-hydroxy ester intermediate had cyclized to the (+)–lactone **134** in a yield of 73% (**Equation 18**).



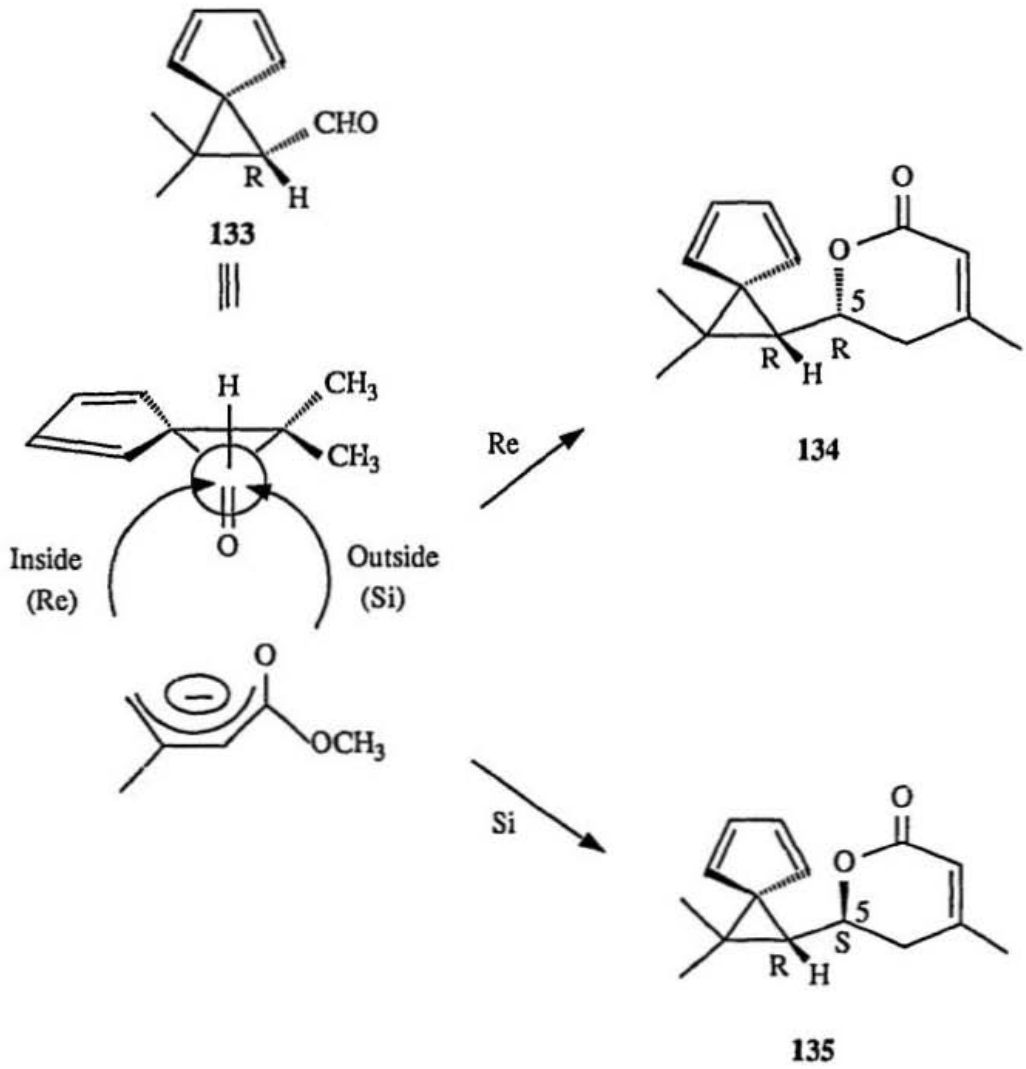
133 **134**

Equation 18

The ^{1}H nmr spectrum of **134** (**Figure 2**, p72) displayed two aliphatic methyl singlets at δ 1.39 and 1.43, a vinyl methyl singlet at 1.87, the cyclopropyl hydrogen as a doublet (J = 4.2 Hz) at 2.31, the methylene protons as multiplets 1.93 to 2.09, a methine proton as double - doublet (J = 4.2 and 10.5 Hz) at 4.48, a vinyl hydrogen as a singlet at 5.76, and the four cyclopentadienyl protons as four mutiplets at 6.17, 6.28, 6.49, and 6.58. The COSY spectrum showed that the cyclopropyl hydrogen is adjacent to the methine hydrogen and the latter is adjacent to the methylene protons (**Figure 3**, p73). The ^{13}C and DEPT (Distortionless Enhancement by Polarization Transfer) spectra contained a carbonyl at δ 164.6, a quaternary vinyl carbon at 156.0, five CH vinyl carbons at 136.4, 132.3, 131.6, 129.7 and 116.8, two CH carbons at 76.6 and 42.1, a CH_2 carbon at 35.6, three CH_3 carbons at 27.2, 23.0 and 20.4, and two quaternary carbons at 51.1 and 31.9 (**Figure 4**, p74). The high resolution mass spectrum had a molecular ion at m/z 230.1303 (Calculated 230.1302). These features support the assigned gross structure.

This condensation can generate two diastereomers (**Scheme 32**). In principle, the organocadmium compound can approach the carbonyl group from either the "inside" (Re) face or "outside" (Si) face. However, the delocalized π system of the organocadmium compound should align itself preferentially with the π system of the diene, resulting in attack from the "inside" (Re) face to generate the C-5(R)-lactone as the predominant product. This anion approach also avoids the nonbonded interaction with the adjacent geminal dimethyl group. The "outside" (Si) approach gave the C-5(S) diastereomer as a minor product in 12% isolated yield. Only the Z-olefin can form this six-membered lactone and the E-olefin hydroxy ester was not detected among the products. This is consistent with the thermodynamic features of this reaction discussed earlier: therefore isomerization

occurs until the requisite intermediates are trapped by lactonization.



Scheme 32

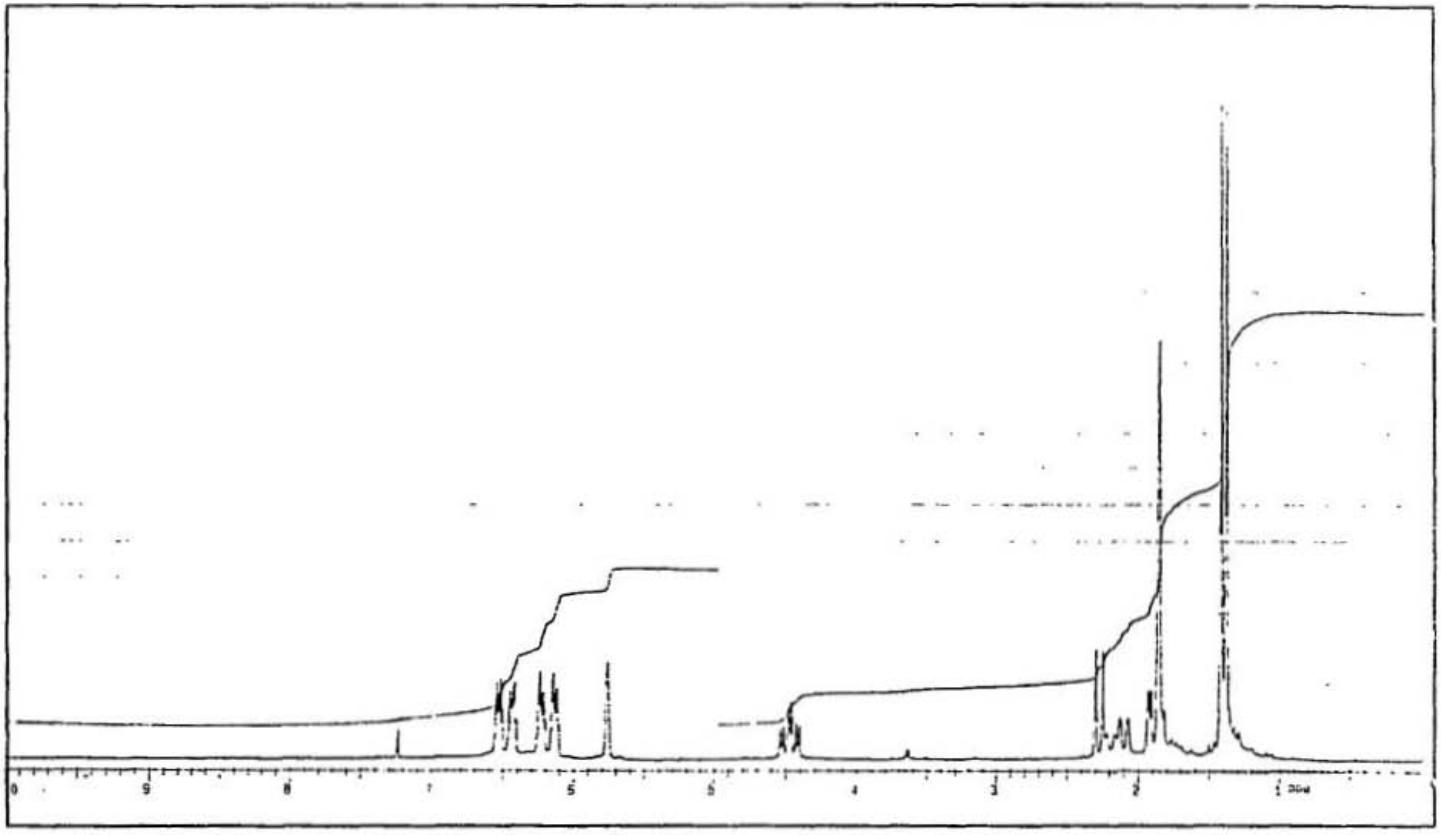


Figure 2 ^{1}H nmr spectrum of (134)

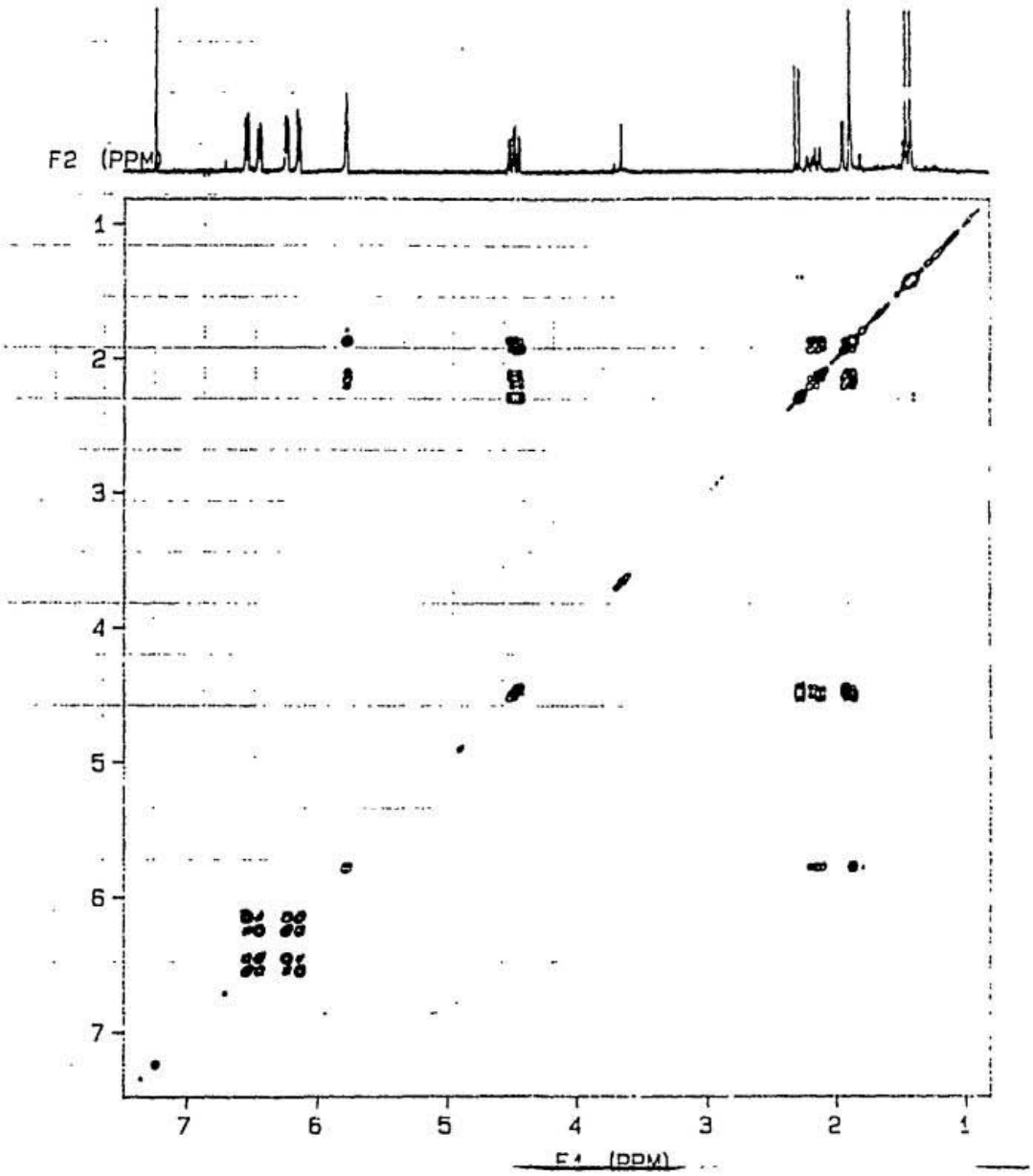
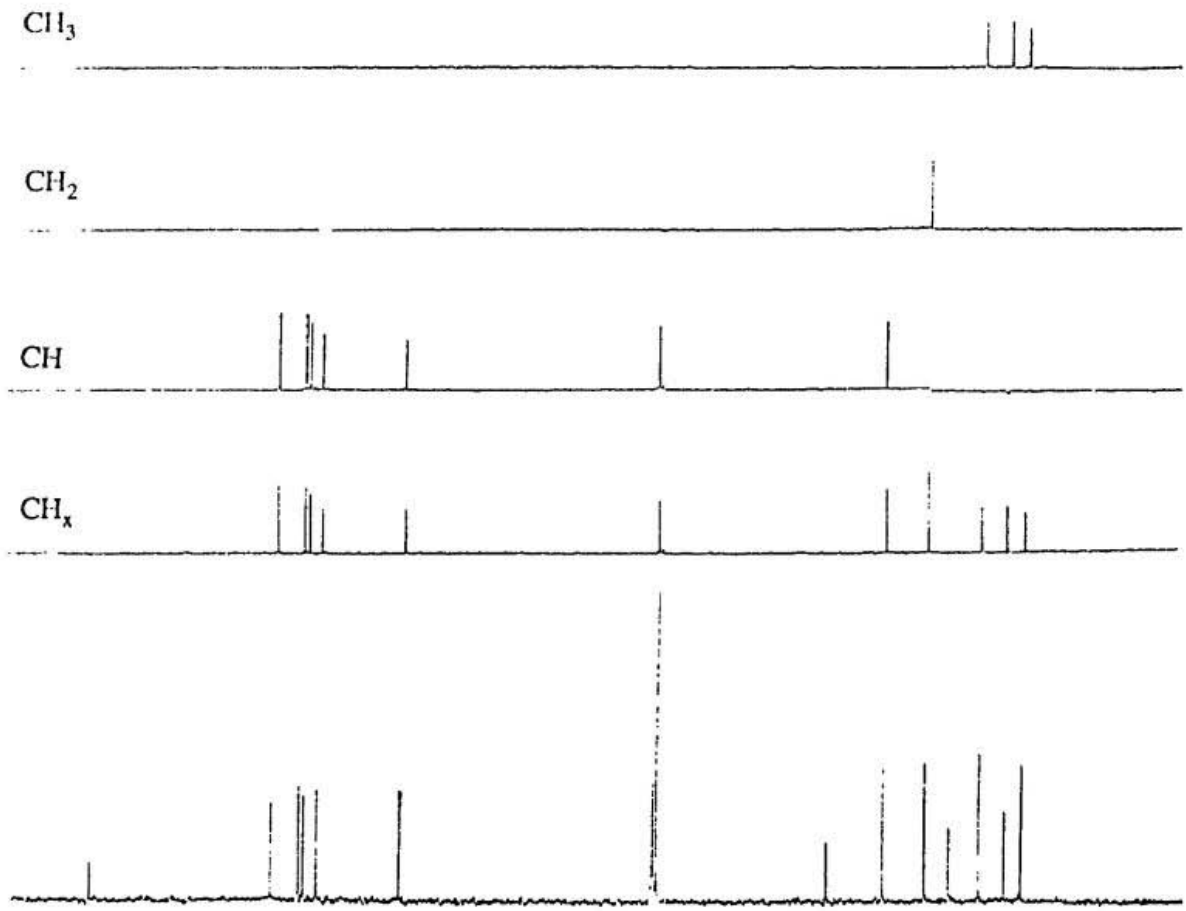


Figure 3 COSY spectrum of (134)



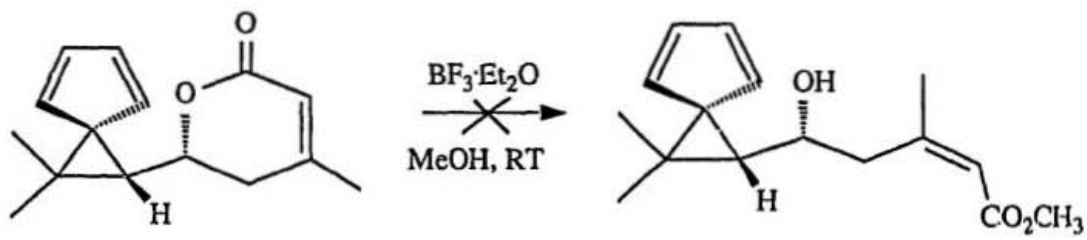
VARIAN XL-300
SPECTRAL LINES FOR THx 10 10
RFL= 5178.2 RFP= 5808.0

INDEX	FREQ	PPM	INTENSITY
01	12413.9	154.574	17 664
02	11765.1	135.976	20 455
03	10291.9	136.443	38 821
04	9978.9	130.295	42 935
05	9926.7	131.603	38 958
06	9752.7	129.694	41 583
07	8811.3	116.812	42 212
08	8617.4	114.765	32 456
09	5840.3	77.428	115 684
10	5819.9	77.156	44 266
11	5808.4	77.005	118 243
12	5775.5	76.582	115 794
13	3850.9	51.053	23 708
14	3174.8	42.090	50 534
15	2686.9	35.648	52 742
16	2410.8	31.961	27 687
17	2249.3	29.168	54 278
18	1736.8	23.026	33 357
19	1137.0	22.377	52 055

Figure 4 ^{13}C and DEPT nmr spectra of (134)

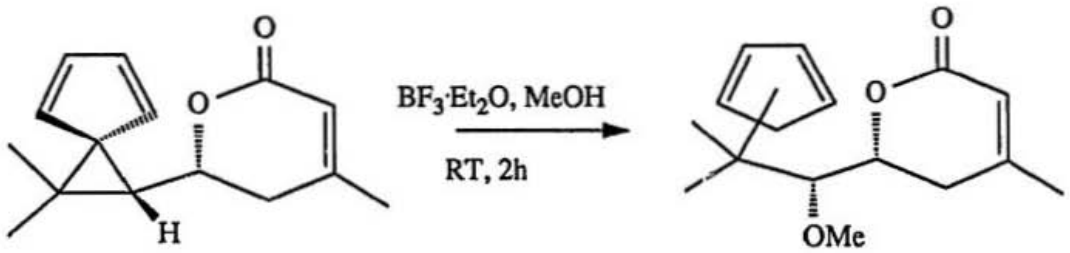
6.5 Preparation of Triene (137)

The treatment of lactone **134** with boron trifluoride etherate in methanol was expected to convert the lactone into the methyl ester **136** (**Equation 19**). However, the sole product, isolated in 83% yield, was not the expected compound. Its IR and ^{1}H nmr spectra (**Figure 5,** p77) did not support the presence of hydroxyl group, but the ^{1}H nmr spectrum contained a signal at δ 3.19 representing 3 hydrogens consistent with a methoxy group. The lactone portion remained and the mass spectrum revealed the molecular weight had increased by 32 mass units. These features were consistent with the addition of methanol. In addition, the signal due to the geminal methyl groups shifted from δ 1.39 and 1.43 to δ 1.02 an 1.38, and the cyclopentadienyl portion also changed both position (from δ 6.17 - 6.58 to δ 6.21 - 6.65) and pattern (*cf.* **Figure 2**). It appeared that the cyclopropane bond had opened to give the isomeric mixture **137** as illustrated in **Equation 20,** a consequence of the stretched, polarized nature of the cyclopropane bonds in this spiro system. The methanol was added to the least hindered centre as a result of backside attack to generate the C-1'(R) ether.



134 **136**

Equation 19



134 **137**

Equation 20

The cyclopentadiene product **137** could be considered a dead end as the desired reaction product **136** had not been obtained. However, we had long suspected that direct cyclization to a cycloheptane should be possible if the dienophile were constrained so that the desired cyclization was the lowest energy pathway. The triene lactone **137** could thus be utilized to test this strategy experimentally.

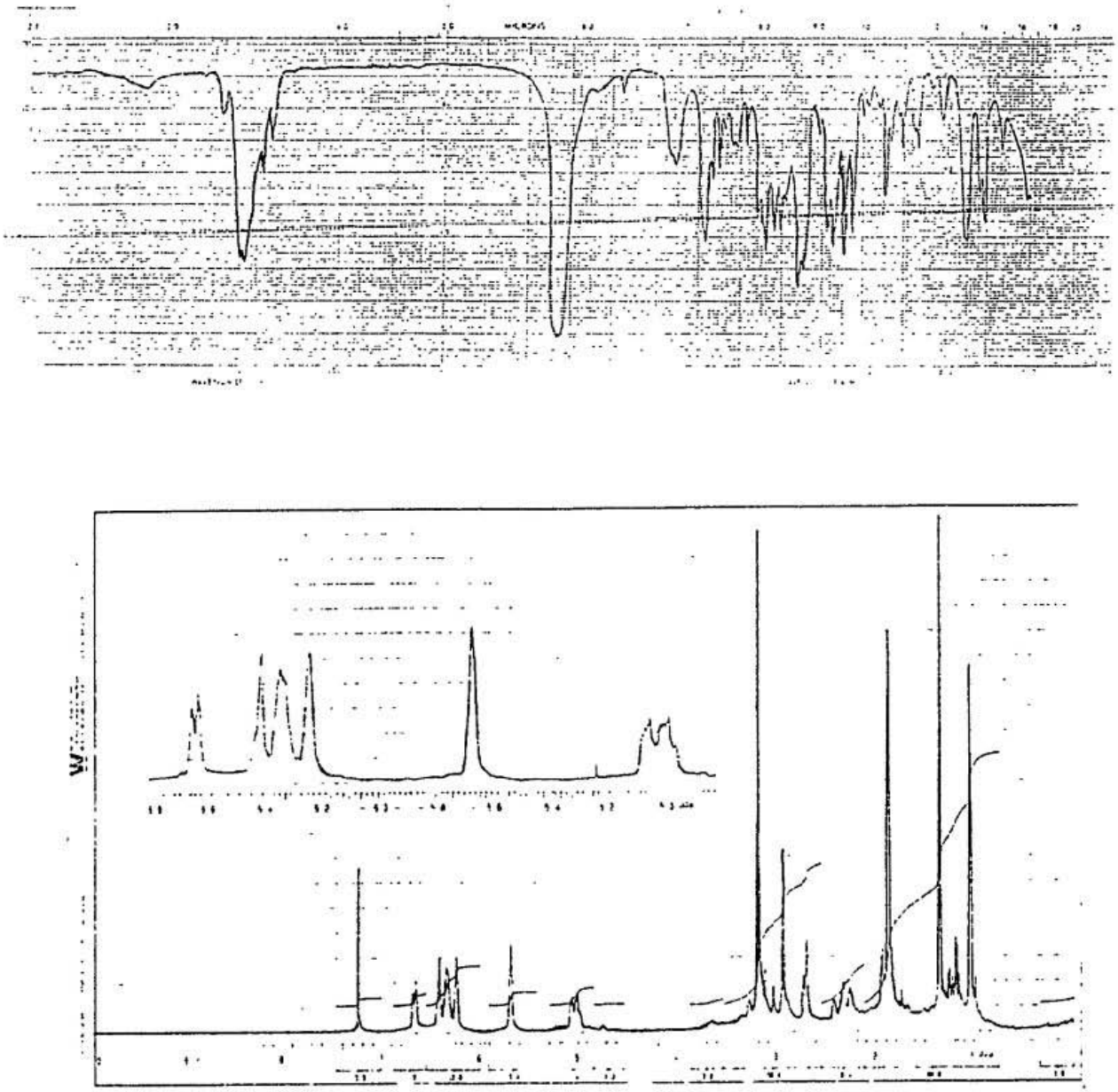
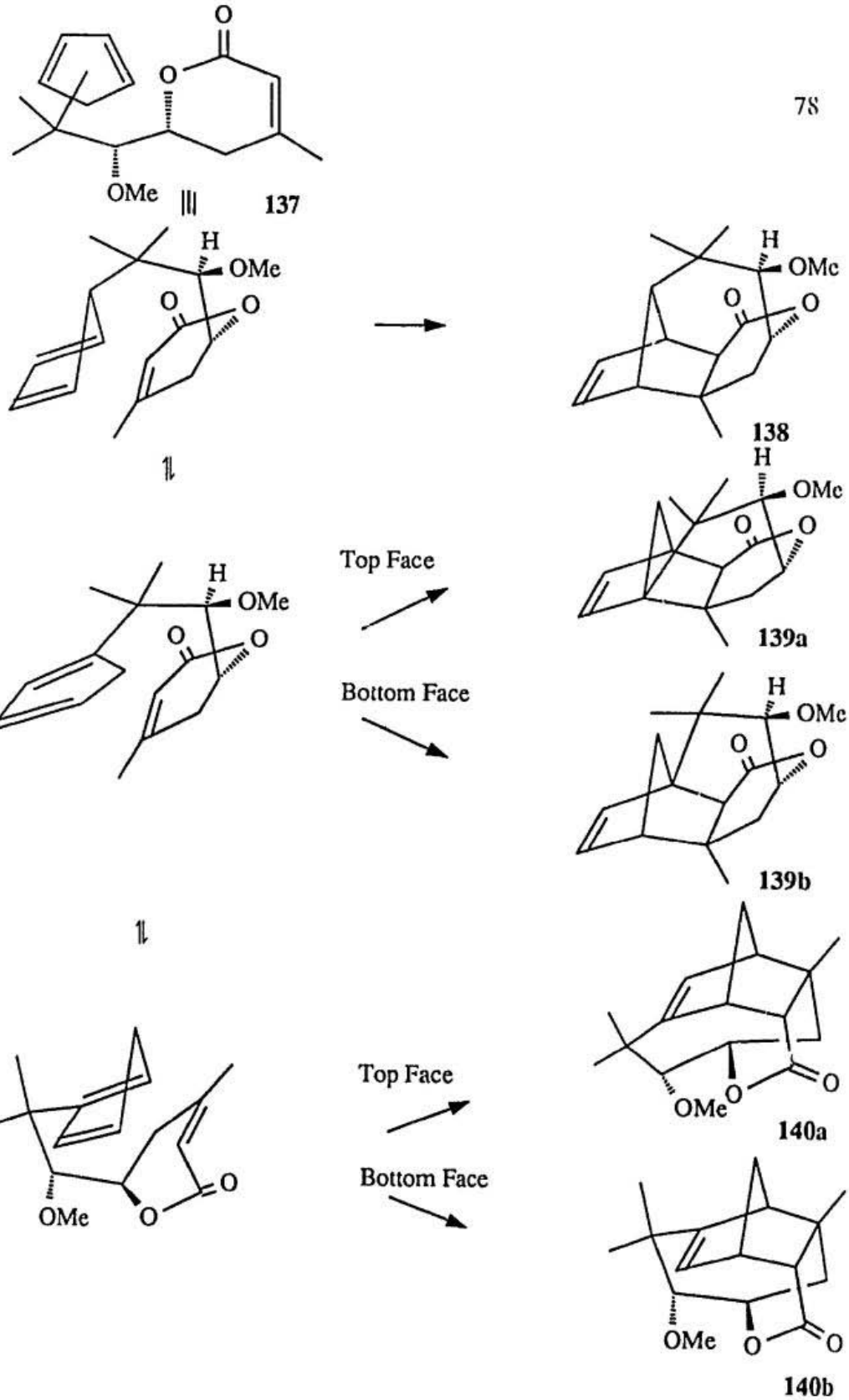


Figure 5 ^1H nmr and IR spectra of (137)



Scheme 33

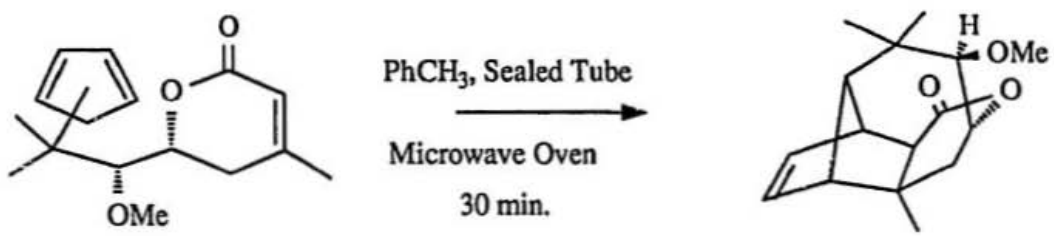
6.6 Diels - Alder Reaction

The C-5(R)C-1'(R)-methoxy triene lactone **137**, similar to Brieger's precursor but with an activated, geometrically restricted dienophile, was capable of rapid sigmatropic rearrangement. The ^{1}H nmr spectrum of **137** (**Figure 5**) showed it was a mixture of rearrangement products although on TLC it appeared as one spot. This mixture could, in principle, give rise to several different Diels-Alder adducts (**Scheme 33**). The isomers **139a**, **139b** and **140a**, **140b** may arise due to cycloaddition to the opposite face of the cyclopentadiene from the C-1 and C-2 substituted series.

Generally, cycloadditions of substituted cyclopentadienes favor incorporation of the tether linkage into a five- or six-membered ring if allowed by the steric constraints. As mentioned the triene **137** contained a constrained cyclic dienophile and molecular models indicated that of the five possible tetracyclic adducts, compound **138** was least constrained tether and the requisite transition state geometry was the most readily achieved. The cycloaddition of triene **137** was conducted in a microwave oven, as described in **Chapter 4**, and afforded only one product after chromatography. The intramolecular Diels-Alder reaction of **137** was expected to afford preferentially the adduct **138** (**Equation 21**). **Table 4** (p 81) lists the ^{13}C nmr spectral characteristics for the possible products. The ^{1}H nmr of the product (**Figure 6**, p 82) contained two olefinic protons at δ 6.24 and 6.32, excluding the possibility of adducts **140a** and **140b**, and the DEPT and ^{13}C nmr spectra (**Figure 7**, p 83) contained one CH_2 carbon at δ 41.5, eight CH carbons at 138.7, 136.5, 76.3, 74.2, 58.5, 52.9, 51.0 and 49.9, and two quaternary carbons at 56.3 and 40.4, excluding the possibility of adducts **139a** and **139b**. Therefore, the Diels-Alder adduct must be the tetracyclic lactone **138**. This compound possessed the tricyclic carbon skeleton required for (+)-longifolene and represented the first

successful synthesis of a cycloheptane directly from the cycloaddition of a substituted cyclopentadiene.

AS the spectrum on page 82 indicates the C-5 proton falls at δ 4.62 but the related proton on the methoxyl bearing carbon is hidden. This is a consequence of its orientation with respect to the carbonyl group. It is shielded and shifted upfield due to the anisotropic effect of the carbonyl falling coincidently under the methoxyl signal at δ 3.11. (Unfortunately the integration is not very reliable since the strongest signals were run well off the page.) Consistent with analysis once the lactone is reduced this signal falls as part of a multiplet at δ 3.95 (*cf* **Figure 32,** p169).



137 **138**

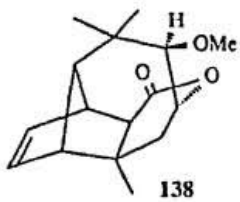
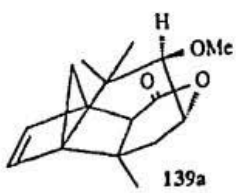
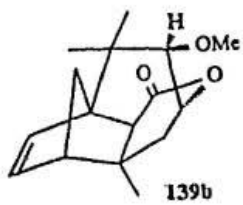
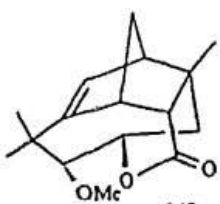
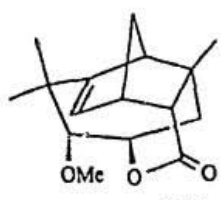
Equation 21

In accord with the experimental result, theoretical calculations by an Alchemy II molecular Model Program gave the following relative energies: 1 : 4.7 : 7.4 : 3.6 : 4.1 for **138** : **139a** : **139b** : **140a** : **140b**. These numbers reflect in part the relative difficulties of their formation and the relative strain of the different transition states. They indicate that the adduct **138** is the least strained.

The enantioselectivity of this Diels-Alder cycloaddition was controlled by the stereochemistry of C-5 of the triene **137**. The restricted geometry of the

dienophile allowed only the C_5-7-exo adduct **138**, which leads to (+)-longifolene. The epimeric adduct **142** which would lead to (-)-longifolene, would have to arise from the (4S)-triene **141** (**Scheme 34**, p 84).

Table 4 Proton and Carbon Types of Possible Diels-Alder Adducts

	Olefinic H	CH_2	CH_2	CH	Quat. C
 **138**	2	4	1	8	2
 **139a**  **139b**	2	4	2	6	3
 **140a**  **140b**	1	4	2	6	3

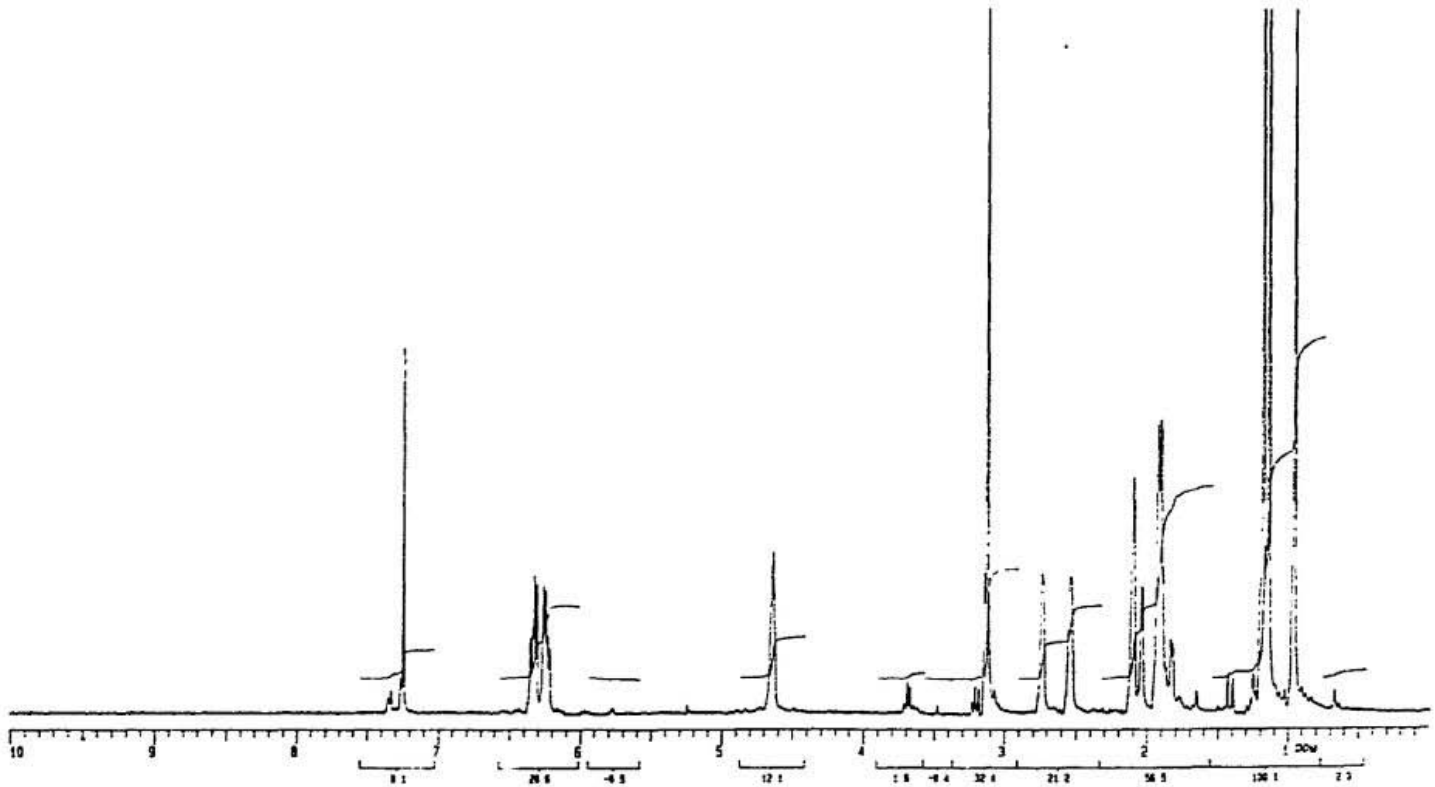


Figure 6 ^{1}H nmr spectrum of (138)

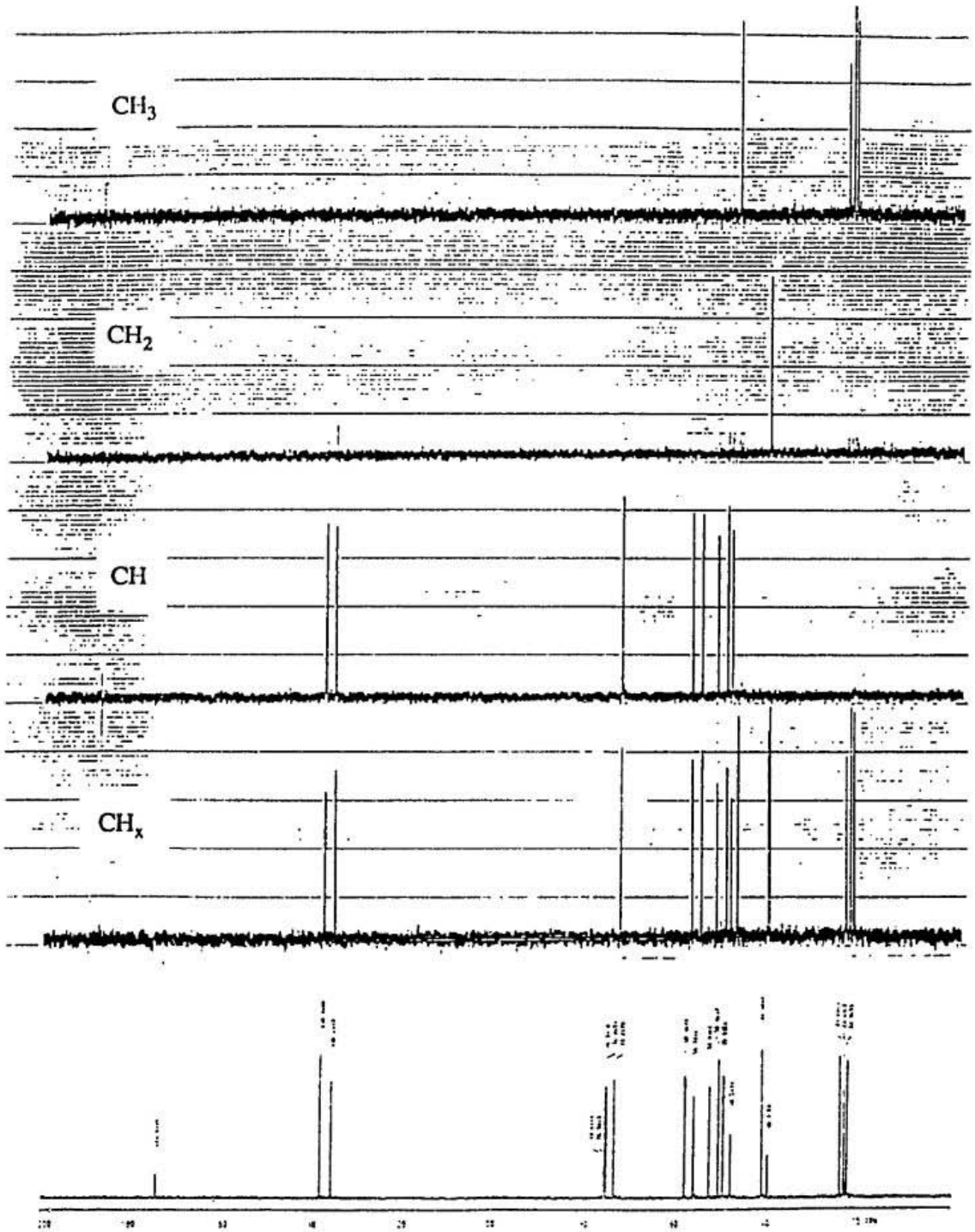
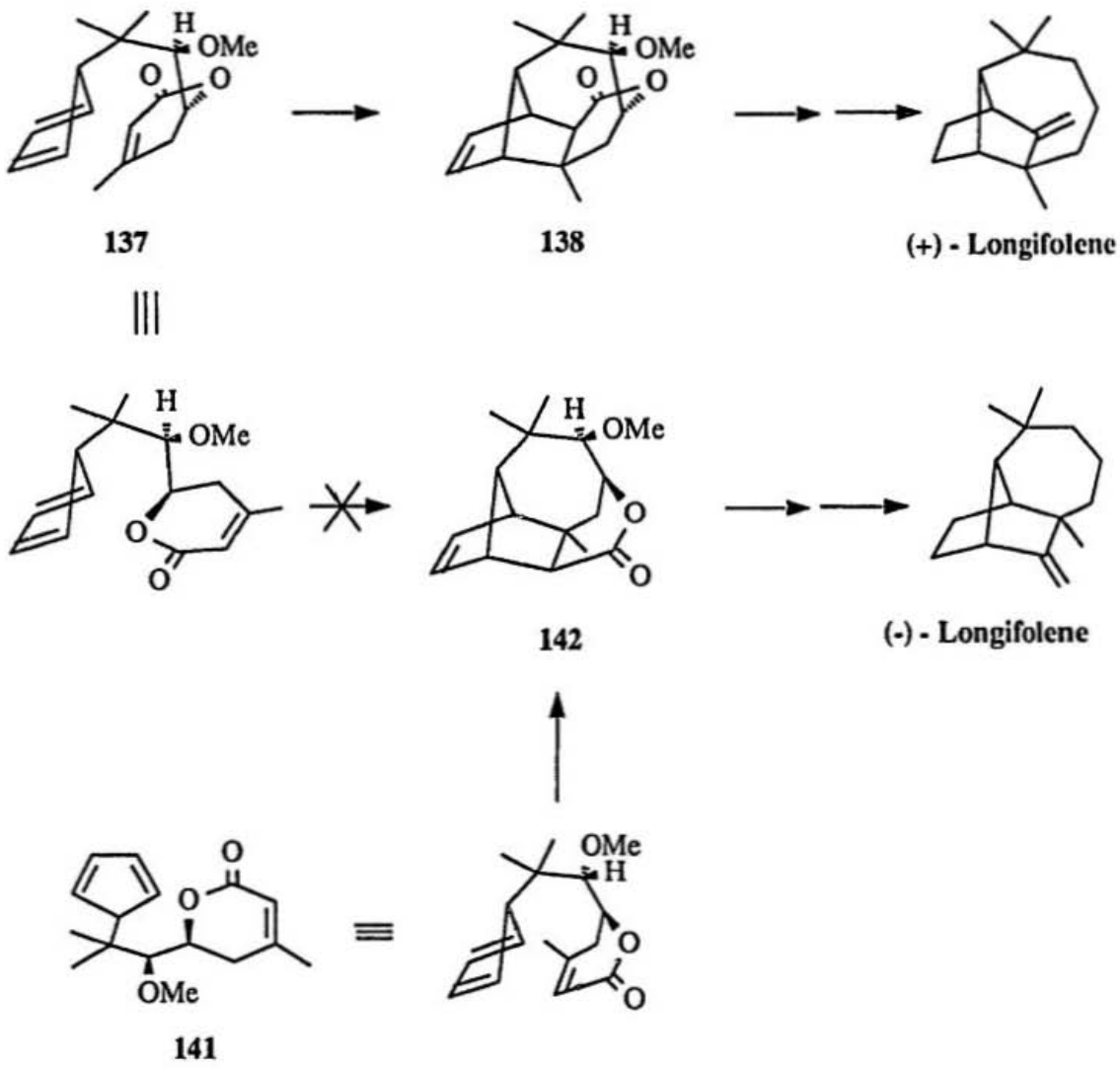


Figure 7 ^{13}C and DEPT nmr spectra of (138)



Scheme 34

6.7 Conversion of Lactone 151 into (+)-Longifolene

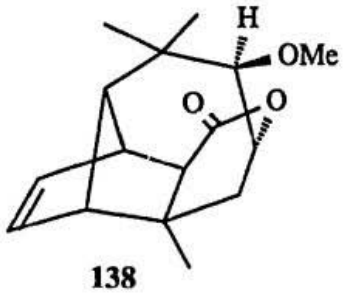
The remaining steps to convert the Diels-Alder adduct **138** into (+)-longifolene are shown in **Scheme 35.**

To remove any likelihood of a retro Diels-Alder reaction, the tetracyclic lactone **138** was hydrogenated under mild conditions (10 psi, EtOAc, 5 % Pd / C, 22°C). Attempts to convert the methyl ether to a secondary hydroxyl group using trimethylsilyl iodide[76,77] failed. Thus, the lactone ring was opened by lithium aluminum hydride reduction to give the methoxy diol **143.**

In general a primary hydroxy is more active than a secondary one in esterifications. Therefore, the treatment of the diol **143** with acetic anhydride in the presence of pyridine under carefully controlled conditions at 0°C selectively produced the desired acetate **144** in 74% yield. This was accompanied by the diacetate (15 % yield) as a by–product which could be reduced to diol **143** and recycled.

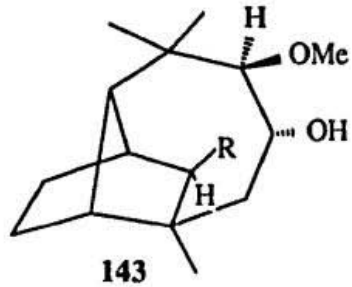
A free radical deoxygenation *via* the Robins procedure[70] removed the secondary hydroxy group. Next the methoxy group was converted into a secondary hydroxyl by treatment with sodium iodide and trimethylsilyl chloride in the presence of triethylamine. This is a modification of the standard procedure[78] and was developed to avoid acetate hydrolysis. The new hydroxyl function was also removed under free radical conditions to afford the acetate **146.**

Pyrolysis of the acetate **146** at 525°C provided (+)-longifolene in 55 % yield. The pyrolysis apparatus is illustrated in **Figure 8** (p 88). The yield is somewhat lower than for sinularene (76 %), probably a result of the scale (30 mg), but the hydrocarbon was generated cleanly. The synthetic conditions of the pyrolysis were examined at 500 °C and 550 °C. The former resulted in the mostly recovered starting material whereas the latter gave additional decomposition.



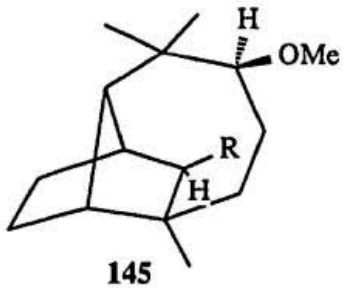
138

1. H_2(10psi), Pd/C
2. $LiAlH_4$, Et_2O



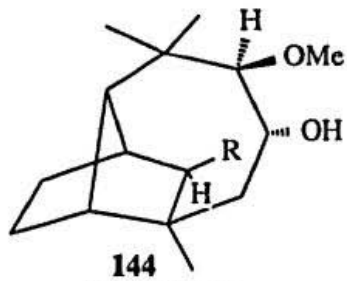
143
R = CH_2OH

$(AcO)_2O$, Py
0°C



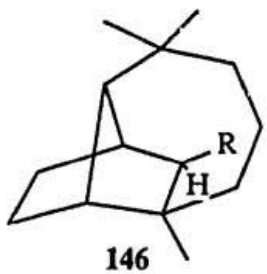
145
R = CH_2OAc

1. PhOC(=S)Cl, Py
2. Bu_3SnH, AIBN



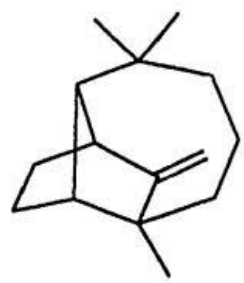
144
R = CH_2OAc

1. NaI, Me_3SiCl, Et_3N
2. PhOC(=S)Cl, Py
3. Bu_3SnH, AIBN



146
R = CH_2OAc

Pyrolysis
525°C



3

Scheme 35

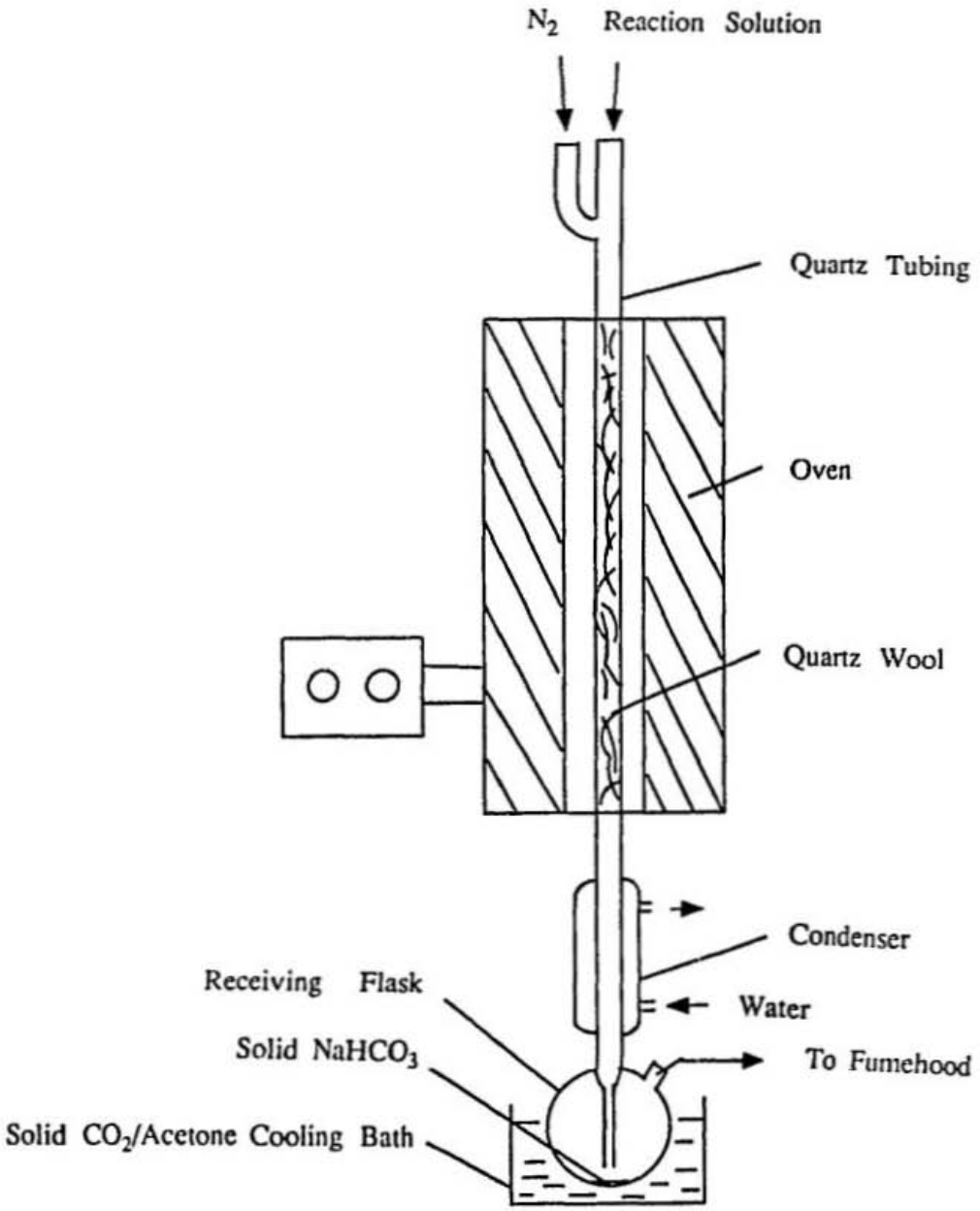
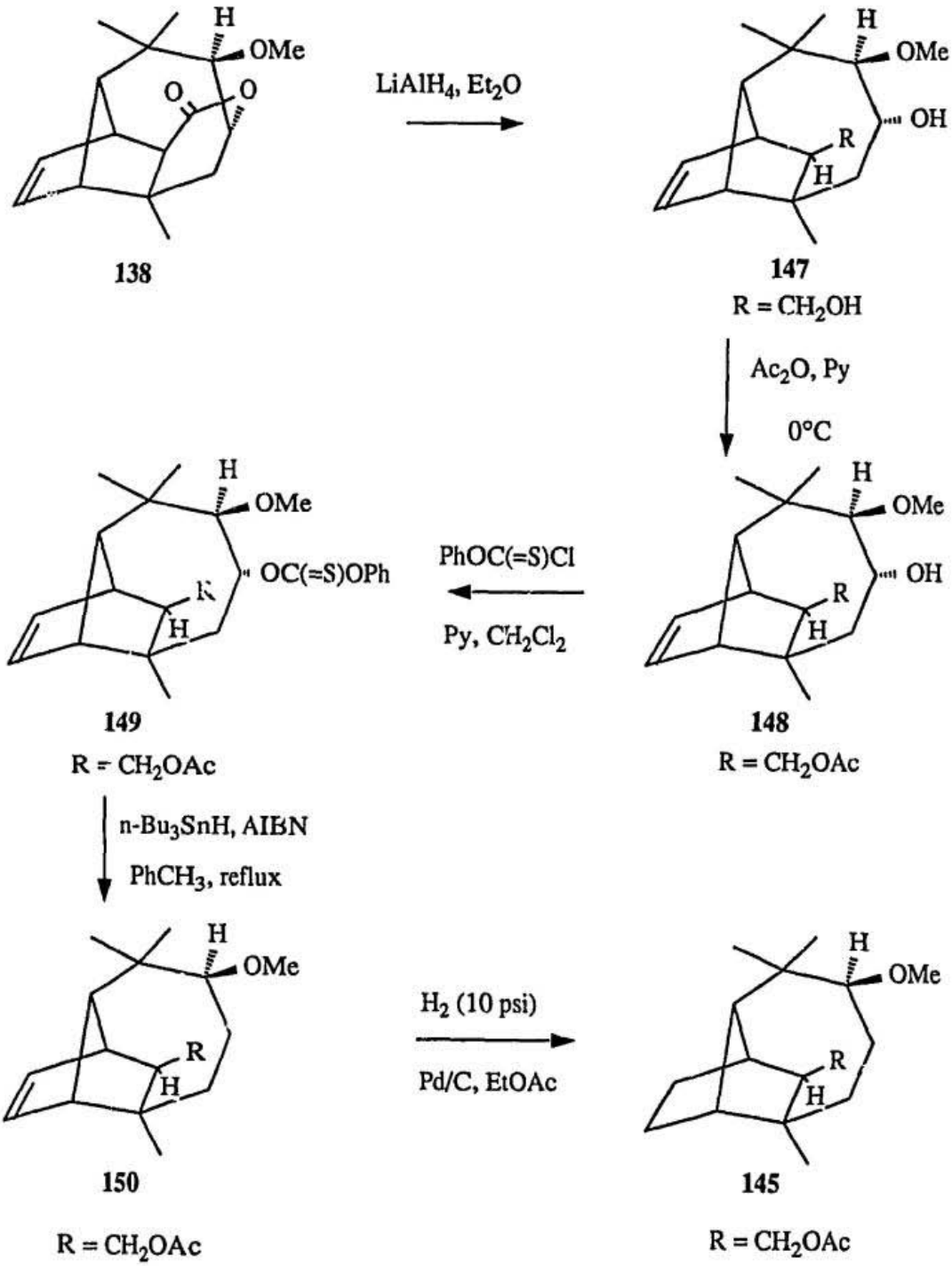


Figure 8 Pyrolysis Apparatus

The purified sesquiterpene was compared by spectroscopy and optical rotation with an authentic sample. This confirmed the structure and the successful completion of the synthesis from the chiral spiro-alcohol **133** *via* eleven steps in 11.2 % overall yield to give (+)-longifolene, $[\alpha]^{22} = +47.04°$ (c 1.7, $CHCl_3$): authentic sample from Aldrich, $[\alpha]^{22} = +51.2°$ (c 1.9, $CHCl_3$); lit[1,2] $[\alpha]^{22} = +45.71°$ (neat). The ^1H, ^{13}C, IR and MS spectra of the synthetic longifolene are displayed in **Figure 9** (p90), **Figure 10** (p91), **Figure 11** (p92), and **Figure 12** (p93) respectively. The ^1H and ^{13}C nmr spectra of the authentic longifolene are displayed in **Figure 13** (p94) and **Figure 14** (p95).

6.8 An Alternative Route To (145) From (138)

We mentioned earlier that the Diels-Alder adduct **138** was hydrogenated first to remove any likelihood of retro Diels-Alder reaction. However, it was later discovered that this adduct was quite stable, so an alternative synthetic sequence from adduct **138** to the methoxy acetate **145** was examined (**Scheme 36**). The double bond of the acetate was hydrogenated before the conversion of the methoxy group to a secondary alcohol because the double bond interfered with this reaction to give a complicated product mixture. Thus both routes are adequate but it is easier to handle the compounds in the saturated series.


H
OMe
O
O
LiAlH4, Et2O
OH
R
H
138
147
R = CH2OH
Ac2O, Py
0°C
OC(=S)OPh
PhOC(=S)Cl
Py, CH2Cl2
149
R = CH2OAc
148
R = CH2OAc
n-Bu3SnH, AIBN
PhCH3, reflux
H2 (10 psi)
Pd/C, EtOAc
150
R = CH2OAc
145
R = CH2OAc

Scheme 36

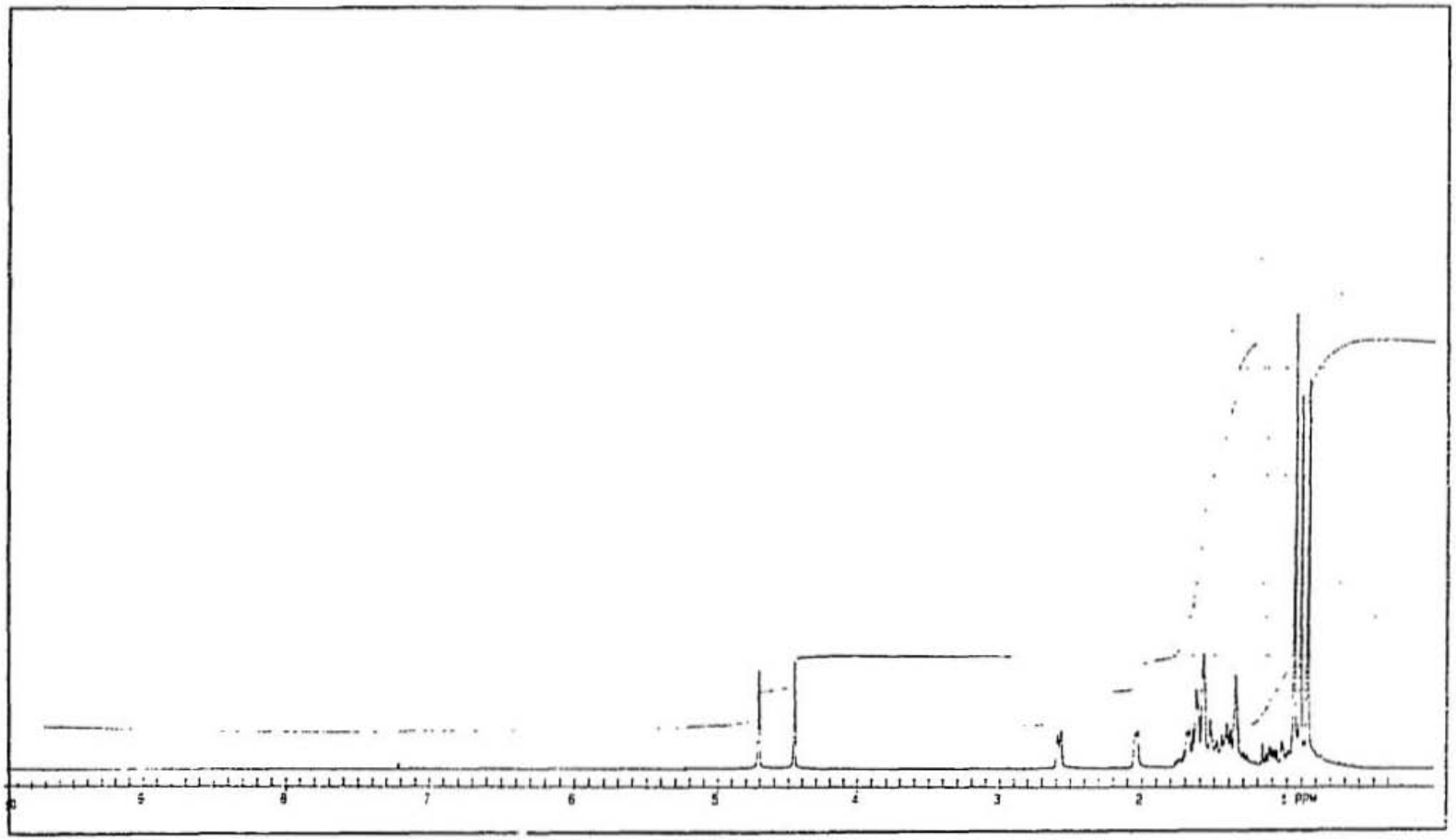


Figure 9 ^{1}H nmr spectrum of (3)

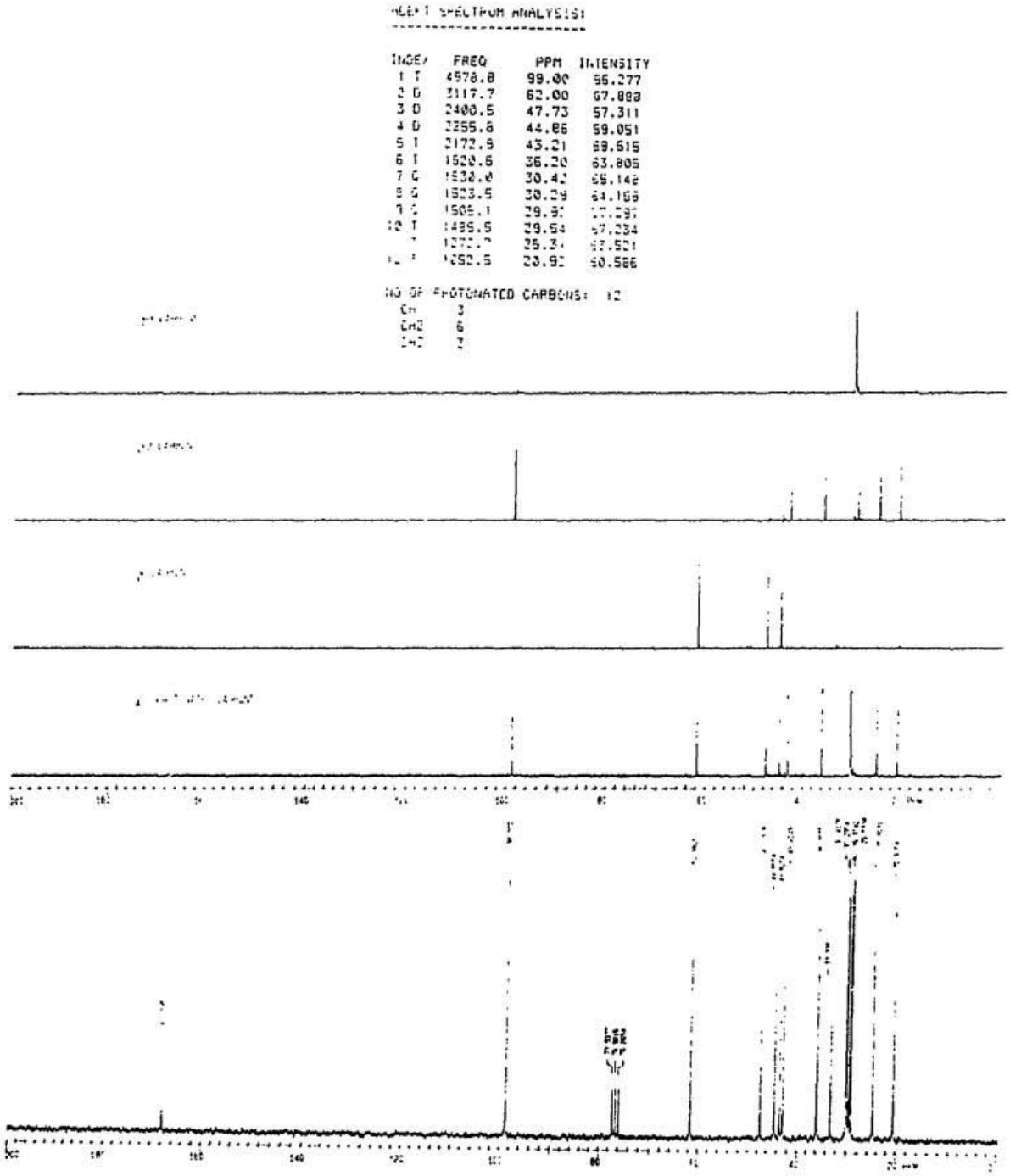


Figure 10 ^{13}C and DEPT nmr spectra of (3)

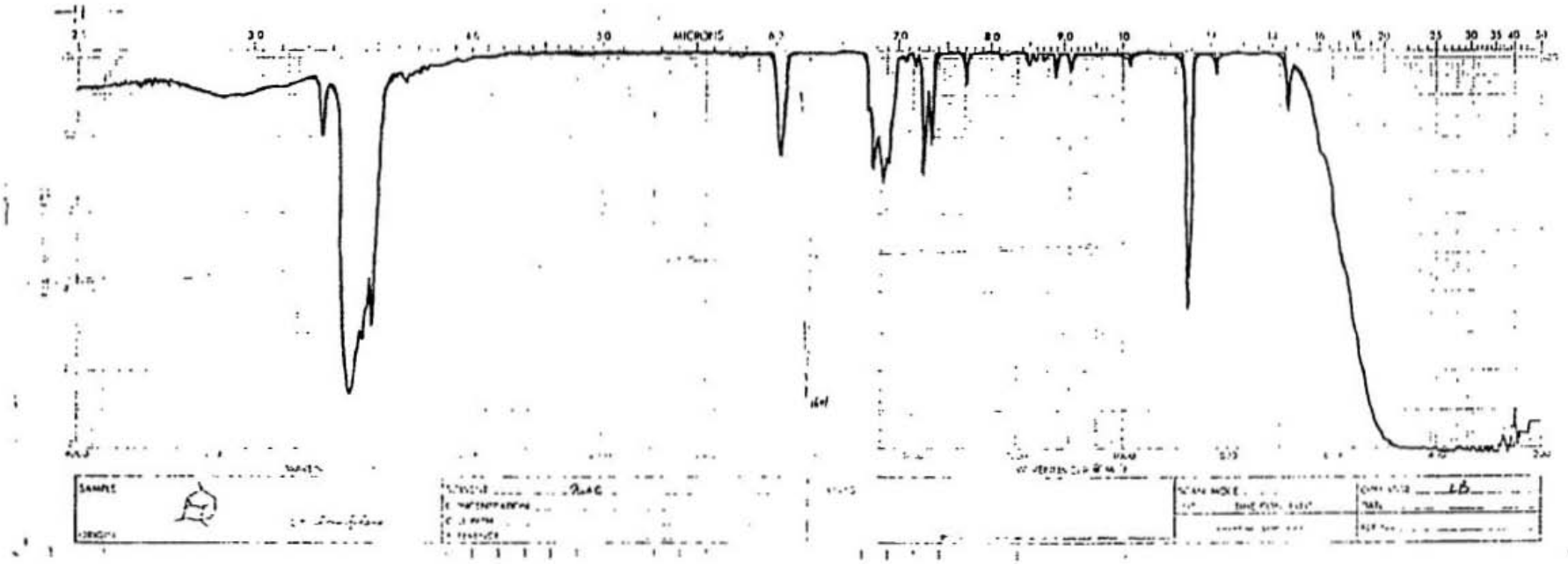


Figure 11 IR spectrum of (3)

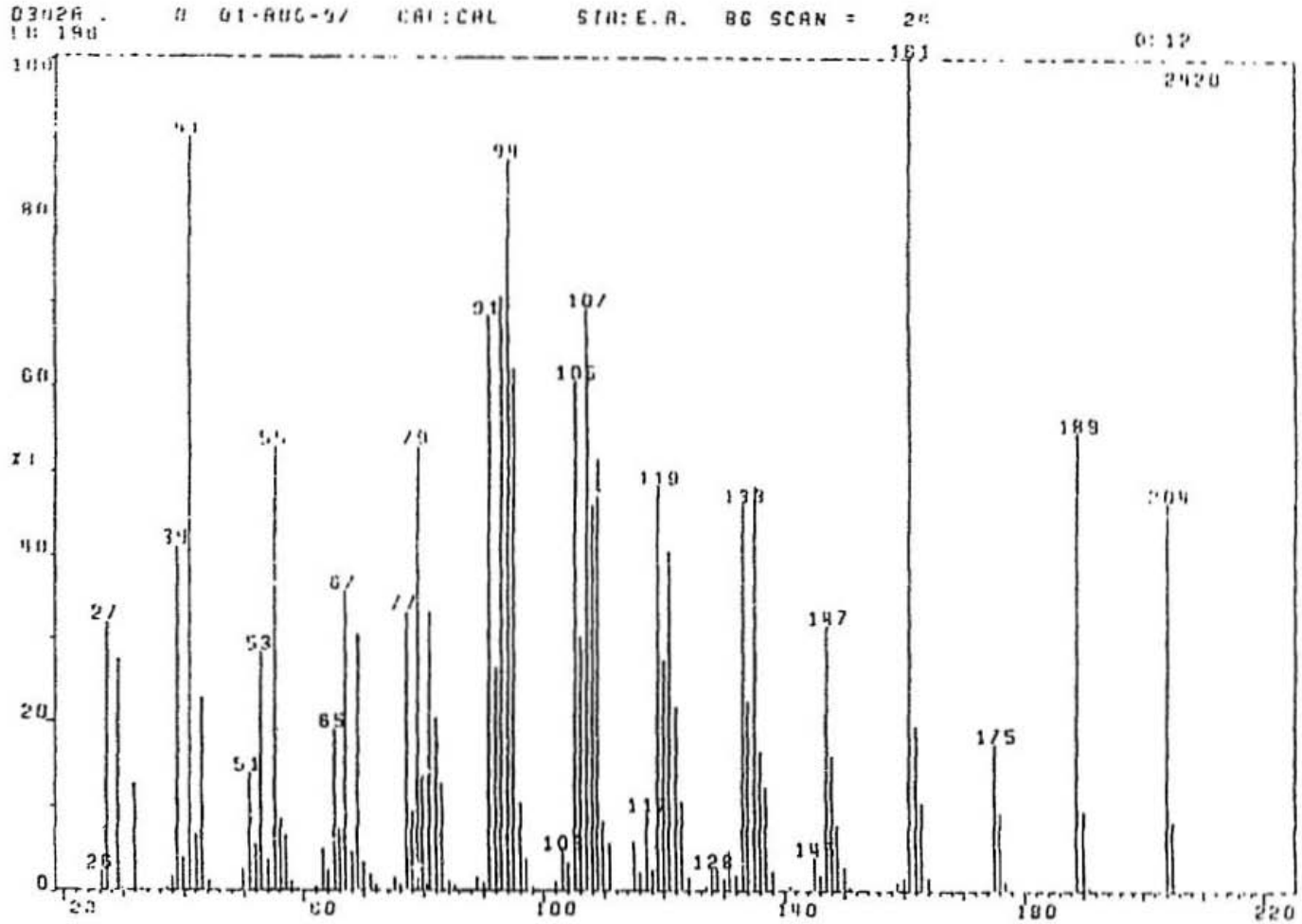


Figure 12 Mass spectrum of (3)

VARIAN XL-300
SPECTRAL LINES FOR FH= 15 18
RFL= 2528 6 RFP= 2171 6

INDEX	FREQ		PPM	INTENSITY
01	2171	55	7 240	59 926
02	1417	62	4 726	96 429
03	1343	10	4 478	105 401
04	782	95	2 610	32 695
05	778	12	2 594	33 983
06	620	45	2 069	30 755
07	616	55	2 056	32 933
08	517	12	1 724	26 155
09	513	95	1 711	27 136
10	512	24	1 708	20 928
11	509	06	1 697	30 175
12	504	67	1 683	49 690
13	502	17	1 675	17 476
14	498	75	1 663	32 311
15	495	45	1 652	38 271
16	492	03	1 640	54 848
17	485	92	1 620	59 576
18	482	75	1 609	39 993
19	481	04	1 604	29 072
20	478	73	1 596	74 369
21	473	99	1 580	29 430
22	466	77	1 556	20 596
23	465	58	1 552	32 196
24	454	49	1 515	23 619
25	447	86	1 493	16 922
26	446	56	1 492	19 575
27	436	34	1 455	20 497
28	433	62	1 446	17 941
29	433	45	1 445	17 079
30	431	59	1 439	21 005
31	430	17	1 434	29 271
32	429	04	1 430	22 182
33	427	95	1 427	19 636
34	424	91	1 417	18 362
35	423	64	1 412	28 455
36	421	41	1 405	26 031
37	417	48	1 392	27 923
38	415	36	1 385	54 227
39	413	41	1 378	63 601
40	351	54	1 172	22 696
41	342	55	1 142	23 138
42	339	92	1 131	21 224
43	336	93	1 123	19 198
44	334	25	1 114	19 144
45	331	05	1 103	19 832
46	324	70	1 081	17 594
47	311	51	1 038	21 549
48	306	79	1 021	43 314
49	303	72	1 011	16 441
50	299	39	997	17 170
51	298	34	0 995	23 487
52	292	98	0 977	576 041
53	290	04	0 967	20 509
54	240	05	0 933	124 410
55	241	91	0 861	441 431

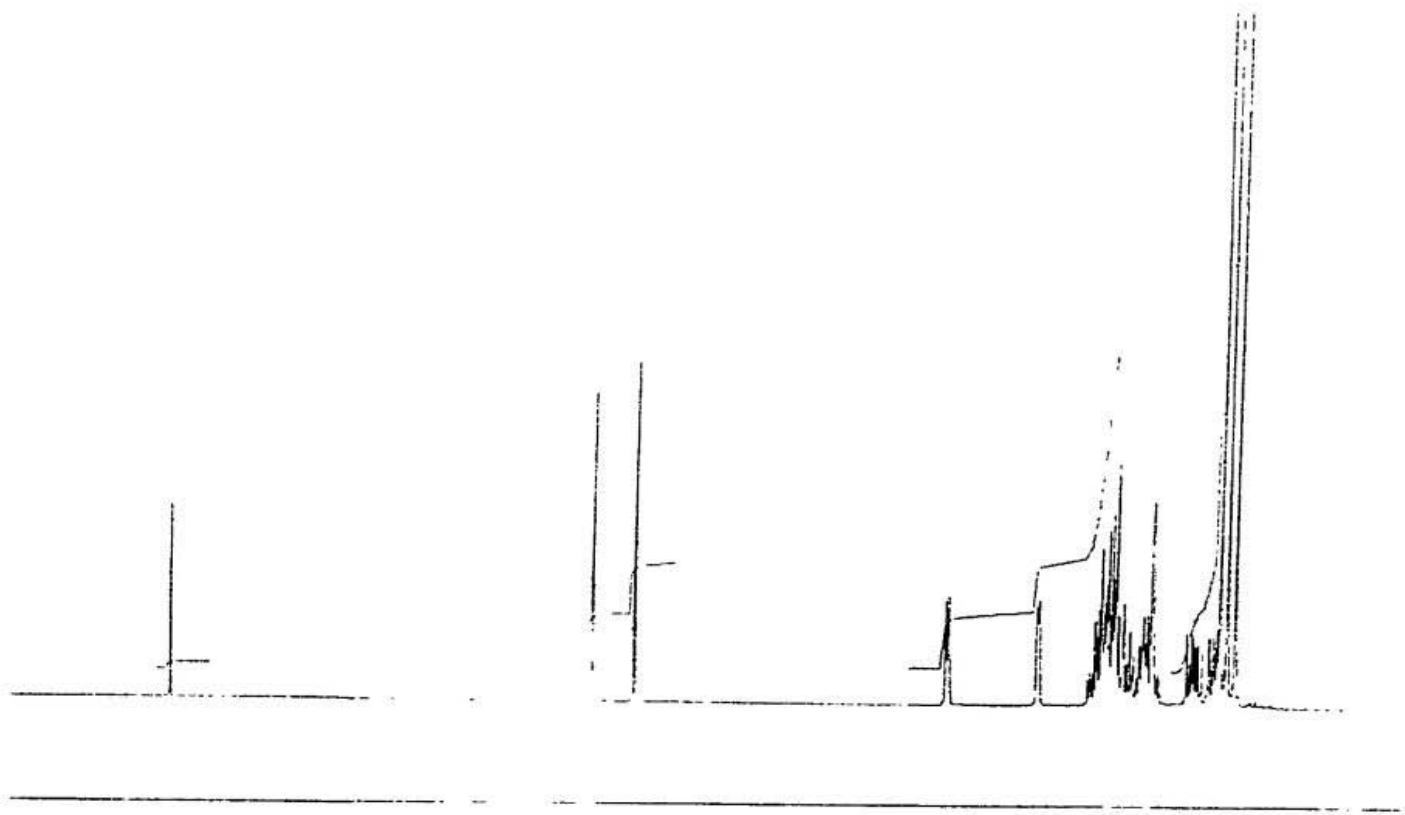


Figure 13 ^{1}H nmr spectrum of Authentic Longifolene (Aldrich)

VARIAN XL-300
SPECTRAL LINES FOR TH= 11 41
RFL= 6154 4 RFP= 5838 0

INDEX	FREQ	PPM	INTENSITY
01	12643 0	167 615	49 820
02	7477 1	99 127	67 544
03	5840 5	77 431	15 414
04	5808 6	77 008	16 145
05	5774 7	76 585	17 123
06	4698 0	62 230	89 569
07	3622 4	48 023	66 408
08	3408 0	45 182	65 083
09	3324 3	44 072	53 784
10	3281 0	43 498	87 522
11	2756 8	36 548	95 170
12	2541 5	33 694	80 038
13	2316 7	30 714	103 519
14	2310 4	30 630	93 018
15	2279 6	30 222	94 210
16	2252 6	29 864	90 [illegible]
17	1935 1	25 655	91 309
18	1407 0	21 304	82 [illegible]

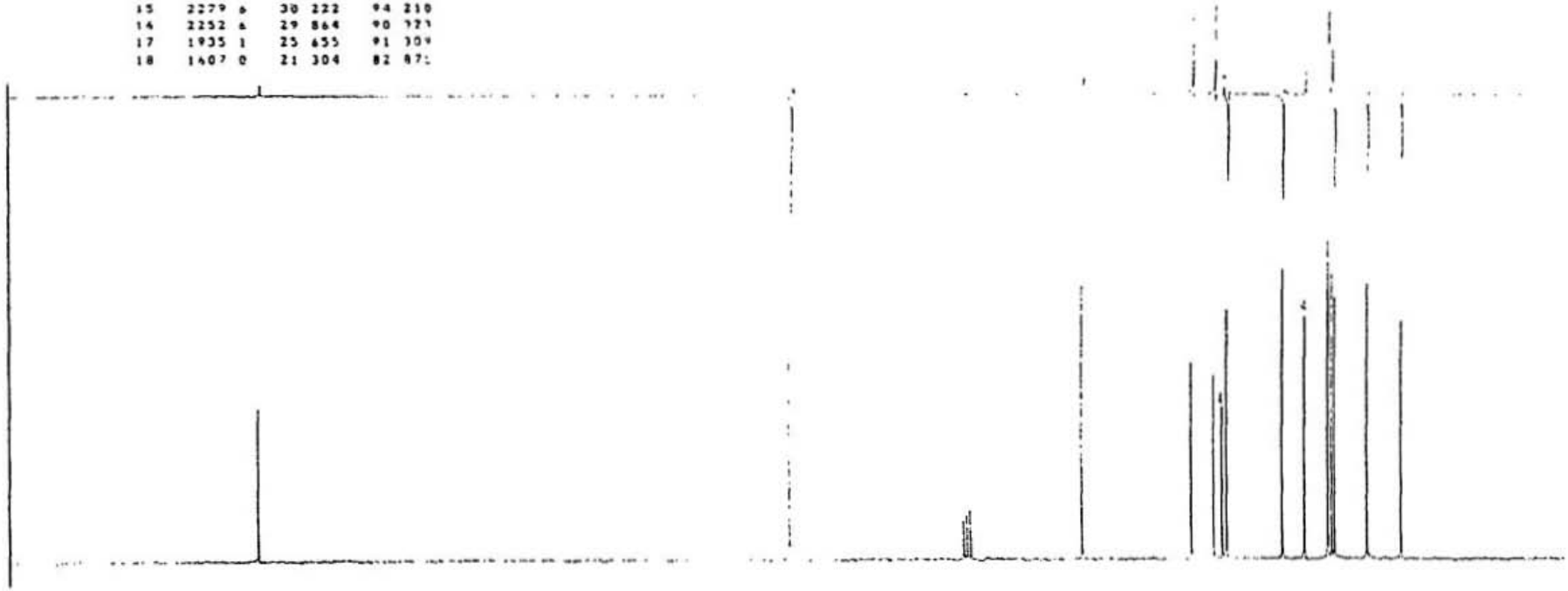


Figure 14 ^{13}C nmr spectrum of Authentic Longifolene (Aldrich)

PART III

EXPERIMENTAL

General:

Infrared (IR) spectra were recorded on a Perkin-Elmer 1320 or 783 grating spectrophotometer, and were calibrated with the 1601 cm^{-1} band of polystyrene film. Proton magnetic resonance (^1H NMR) spectra were measured at 60 MHz with a Varian EM 360 spectrometer or at 80 MHz with a Bruker WP80 spectrometer or at 200 MHz with a Varian Gemini spectrometer or at 300 MHz with a General Electric GN 300 or a Varian XL 300 spectrometer. Carbon magnetic resonance (^{13}C NMR) spectra were measured at 50 MHz with a Varian Gemini spectrometer or at 75 MHz with a General Electric GN 300 or a Varian ZL 300 spectrometer. The residual solvent signal was used as an internal standard $CDCl_3$; ^1H: δ 7.262, ^{13}C: δ 77.00 and signal positions are reported in ppm downfield from tetramethylsilane (δ scale) as an internal standard, the numbers of protons, multiplicities, coupling constants, and proton assignments are indicated in parentheses. Mass spectra were determined on a V.G. Micromass 7070 HS instrument using an ionization energy of 70 eV, or on a Hewlett-Packard 5890A gas chromatograph 5970B mass selective detector equipped with a 12.5 m capillary column (0.2 mm ID) coated with crosslinked dimethyl silicone (0.33 µm). Optical rotations were measured using a Perkin-Elmer 241 polarimeter (sodium light, cell length = 10 cm, c = g / 100 mL).

Gas-liquid chromatographic analyses were conducted on a Hewlett Packard 402B gas chromatograph equipped with a column (3 m × 6 mm i.d.) containing 1.5 % OV-17 supported on Gas Chrome Q using helium as the carrier gas. Analytical thin layer chromatography (TLC) was carried out on commercial precoated silica gel plates with fluorescent indicator (Eastman Kodak silica gel 13181) or on aluminum sheets precoated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck). Flash

column chromatography using E. Merck silica 60 (230-400 mesh) was employed for all column chromatography.

Petroleum ether refers to a fraction with boiling range 30-60°C. Anhydrous diethyl ether (ether), tetrahydrofuran (THF), dimethoxyethane (DME), and dioxane were obtained by distillation from $LiAlH_4$ or potassium / benzophenone. Methanol and absolute ethanol were dried by distillation from magnesium. Dry hexamethylphosphoramide (HMPA), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and diisopropylamine were prepared by distillation from calcium hydride. Solutions in organic solvents were dried over anhydrous magnesium sulfate and stripped of solvent with a Büchi rotary evaporator connected to a water aspirator. Unless otherwise indicated, all reactions were conducted under an atmosphere of dry nitrogen.

1,2 - Epoxy - 3 - butanone (79)

3-Buten-2-one (56 g, 0.8 mol, Aldrich) was dissolved in methanol (400 mL) containing 30 % hydrogen peroxide (230 ml) and the solution cooled to 0 °C with an external ice bath. Aqueous sodium hydroxide (2M, 200 ml) was added dropwise to the stirred solution (**caution:** initially the reaction is very exothermic) maintaining the temperature below 20°C. Stirring was continued for further 8 h at 22°C after the addition was completed. The reaction was extracted with dichloromethane (5 x 100 mL), the extracts dried, filtered, concentrated, and the product was purified by distillation to give the epoxy-ketone **79** (42 g, 60 %, the yield was 71 % on a small scale); bp 45-46°C / 12 Torr; IR (film) : 1715 (C=O), 1260, 865 (C-O) cm^{-1}; ^1H NMR (80 MHz, CCl_4) δ: 1.99 (s, 3H, CH_3), 2.92 (m, 2H, CH_2-O), 3.28 (dd, 1H, J = 1.5, 1 Hz, O=C-CH-O). *Exact mass* calcd. for $C_4H_6O_2$: 86.0368; found: 86.0352.

6 - Methyl - 6 - oxiranylfulvene (80)

A stirred absolute methanol solution (12 mL) of cyclopentadiene (3.30 g, 0.05 mol, freshly distilled) and 1,2-epoxy-3-butanone (4.30 g, 0.05 mol) was cooled to 0°C and pyrrolidine (0.25 mL) was added. The yellow color due to the fulvene was immediately observed and stirring was continued for 2 h at 0°C, then 2 h at 22°C. The reaction was poured into ice water and extracted with petroleum ether (2 x 20 mL). The combined organic layers were washed with 5 % aqueous HCl, 5 % aqueous sodium bicarbonate, followed by brine, dried, filtered and concentrated to give the epoxy fulvene **80** (5.8 g, 86 %). The epoxy fulvene **80** was sufficiently pure for direct use. Upon storage at -20°C it formed yellow crystals and it was kept anhydrous by addition and evaporation of anhydrous benzene; IR (film): 3060 (H-C=), 1635 (s, C=) cm^{-1}; ^1H NMR (80 MHz, CCl_4) δ: 1.91 (s, 3H, CH_3), 2.82 (m, 2H, CH_2-O), 3.90 (dd, 1H, J = 1.5, 1 Hz, CH-O), 6.35 (m, 4H, H-C=C). *Exact mass* calcd. for $C_{10}H_{10}O$: 134.0732; found: 134.0708.

2 , 2 - Dimethyl - 1 - hydroxymethylspiro [2. 4] hepta - 4 , 6 - diene (82)

Methyl lithium (1.5 M in ether, 10.5 mL, 16 mmol, Aldrich) was added dropwise to a stirred anhydrous THF solution (50 mL) containing the epoxy fulvene **80** (2.01 g, 15 mmol) maintained at -78°C by an external solid CO_2 / acetone bath. After stirring for 30 min at -78°C, the reaction mixture was allowed to warm to 0°C and quenched with aqueous ammonium chloride. The mixture was extracted with ether (2 x 20 mL). The combined ether extracts were dried, filtered and concentrated. The crude product was purified by flash chromatography (20 % ethyl acetate / petroleum ether) to give the spiro-alcohol **82** (1.24 g, 55 %); IR

(film): 3350 (br, OH), 3090, 3060 (H-C=), 1650 (s, C=C) cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ: 1.40 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.71 (br s, 1H, OH), 2.39 (t, 1H, J = 7.5 Hz, cyclopropyl H), 3.78 (m, 1H, CH_2-O), 3.94 (m, 1H, CH_2-O), 6.30 (m, 2H, H-C=C), 6.45 (m, 1H, H-C=C), 6.57 (m, 1H, H-C=C); ^{13}C NMR ($CDCl_3$) δ: 138.4, 133.0, 131.8, 129.2, 62.0, 52.3, 43.4, 35.3, 27.5, 20.4. *Exact mass* calcd. for $C_{10}H_{14}O$: 150.1044; found: 150.1025.

(2' , 2' - Dimethylspiro [2. 4] hepta - 4', 6' - diene - 1' - yl) carboxaldehyde (83)

Active MnO_2 Oxidation :

The spiro alcohol **82** (3.0 g, 0.02 mmol) in 25 mL of dichloromethane was added dropwise to a stirred and refluxed suspension of active MnO_2* (30 g, or 40 g as a mixture with charcoal) in 250 mL of dichloromethane. The mixture was stirred under reflux for 12 h, cooled to room temperature and filtered through a band of Celite and anhydrous $MgSO_4$. The solid was washed thoroughly with dichloromethane (200 mL) and the combined filtrate was concentrated. The crude product was purified by flash chromatography (5 % ethyl acetate / petroleum ether) to afford the spiro-aldehyde **83** (2.5 g, 84 %) as a pale yellow liquid; IR (film): 2825 (H-CO), 2720 (H-CO), 1704 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.42 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.78 (d, 1H, J = 6 Hz, cyclopropyl H), 6.17 (m, 1H, cyclopentadienyl H), 6.53 (m, 2H, cyclopentadienyl H), 6.60 (m, 1H, cyclopentadienyl H), 9.56 (d, 1H, J = 6 Hz, H-C=O); ^{13}C nmr ($CDCl_3$) δ: 198.0, 135.5, 132.4, 131.6, 131.4, 56.8, 49.4, 37.1, 26.8, 20.7. *Exact mass* calcd. for $C_{10}H_{12}O$: 148.0888; found: 148.0888.

****Preparation of Active Manganese Dioxide***

1. A solution of manganese sulfate (111 g) in water (150 mL) and a solution

of sodium hydroxide (40 %, 117 mL) were added simultaneously to a hot solution of potassium permanganate (96 g) in water (600 mL) over a period of 1 h. Manganese dioxide was precipitated as a fine brown solid. After stirring for 1 h, the solid was collected by filtration and washed thoroughly with water until the washings were colorless. The solid was dried in an oven at 100 - 120 °C and ground to a fine powder (85 g) for use. (Based on the literature method of reference 56)

2 A mixture of potassium permanganate (40 g) and charcoal (20 g, J. T. Baker) in 500 mL of water was stirred under heating (70-80°C) until the purple color discharged. After cooling to room temperature, the solid was collected by filtration, washed thoroughly with water, and dried in an oven at 100-120 °C. The final product was a mixture of manganese dioxide and charcoal as fine powder. (After considerable experimentation we found this material was best provided Baker charcoal was used. This procedure is based on reference 57.)

Swern Oxidation : [79, 80]

Dimethylsulfoxide (DMSO) (1.76 mL, 25 mmol, dried over CaH_2) in anhydrous dichloromethane (5 mL) was added dropwise to a stirring solution of oxalyl chloride (1.13 mL, 13 mmol, Aldrich) in anhydrous dichloromethane (25 mL) at -78°C with solid CO_2 / acetone cooling bath. After 10 minutes, this was followed by the addition of spiro–alcohol **82** (1.6508 g, 11 mmol) in anhydrous dichloromethane (10 mL) over a period of 5 min. A foamy white precipitate developed. The suspension was stirred for further 15 minutes and triethylamine (8.35 mL, 60 mmol) was added slowly. After the precipitate disappeared, the external cooling bath was removed, the reaction was allowed to gradually warm to

room temperature, cold water (30 mL) was added, and the mixture was stirred for another 15 minutes. The resulting mixture was separated and the aqueous layer was extracted with dichloromethane (30 mL). The organic layers were combined, washed with 5 % HCl, 5 % $NaHCO_3$ and brine (20 mL each time). The washed organic solution was dried, filtered and evaporated to remove solvent. Flash chromatography (5 % ethyl acetate / petroleum ether) of the crude product afforded afforded the spiro-aldehyde **82** (1.50 g, 92 %) as a pale yellow liquid.

Methyl 4 - bromo - 3 - methyl - 2 - butenonate (84)

Methyl 3,3-dimethylacrylate **97** (5.4 g, 47 mmol) was dissolved in a carbon tetrachloride solution (50 mL) containing N-bromosuccinimide (NBS) (8.7 g, 49 mmol, Aldrich) and AIBN (0.078 g). The mixture was stirred under reflux for 8 h, cooled and filtered to remove the precipitate. The filtrate was concentrated and purified by distillation under reduced pressure to afford the bromo-ester **84** (6.9 g, 68 %) as a mixture of Z, E-isomers, b.p range: 45-70 °C / 0.6 Torr. ^{1}H nmr (80 MHz, $CDCl_3$) shows two sets of peaks, A: δ: 1.99 (d, J = 2 Hz, 3H, CH_3-C=C), 3.65 (s, 3H, OCH_3), 4.47 (m, 2H, CH_2Br), 5.68 (d, J = 2 Hz, 1H, H-C=C); B: δ: 2.21 (d, J = 2 Hz, 3H, CH_3-C=C), 3.65 (s, 3H, OCH_3), 3.86 (d, J = 1 Hz, 2H, CH_2Br), 5.87 (m, 1 H, H-C=C). The integration of the two sets of peaks was almost 1 : 1.

Methyl 3,3 - dimethylacrylate (97)

A solution of 3, 3–dimethylacrylic acid (11.0 g, 0.11 mol, Aldrich) and boron trifluoride etherate (14.3 g, 0.10 mol, Aldrich) in 40 mL of absolute methanol was stirred under reflux for 12 h, cooled to 0 °C, and quenched with 5 % aqueous sodium carbonate solution. The mixture was extracted with ether (2 × 30 mL)

and the combined extracts were dried, filtered, and concentrated. Fractional distillation under reduced pressure gave the methyl ester **97** (6.6 g, 54 %) as a colorless liquid; b.p: 30 °C / 0.6 Torr; ^{1}H nmr (200 MHz, $CDCl_3$) δ: 1.88 (d, 3H, J = 1.2 Hz, CH_3), 2.16 (d, 3H, J = 1.5 Hz, CH_3), 3.67 (s, 3H, OCH_3), 5.67 (m, 1H, H-C=C); *Exact mass* calcd. for $C_6H_{10}O_2$: 114.0680; found: 114.0687.

General Procedure for Reformatsky Reaction:

Active zinc powder* (five molar equivalent) suspended in anhydrous THF (2 mL) was placed in a three necked flask equipped with a condenser and a dropping funnel. The reactant aldehyde (benzaldehyde or **83**, ca. 2 mmol) and bromoeters (**84** or **89**, 1.5 molar equivalent) in anhydrous THF (10 mL) were placed in the dropping funnel. A few drops of THF solution containing the starting materials were added to the stirred suspension. Next a small crystal of iodine was added and the reaction was heated. After the reaction began refluxing and the iodine color discharged, the rest of the THF solution was added dropwise to the reaction while stirring under reflux. After the addition was complete, the reaction was continued for another 1 hour, cooled to room temperature, quenched with saturated aqueous ammonium chloride, and filtered to remove zinc solid. The filtrate was extracted with ether (2 × 10 mL) and the combined extracts were washed with brine, dried, filtered and concentrated. The crude product was purified by flash chromatography (20 % ethyl acetate / petroleum ether). This is related to the method of Hudlicky.[81, 82]

**** Preparation of Active Zinc Powder*** [81]

The commercially available zinc dust (Aldrich) was quickly washed with 50 % acetic acid and filtered (done in fumehood). The washed zinc dust was rinsed

thoroughly with water and DME, and dried under vacuum at 110 °C for 12 h. The treated zinc powder can be stored under N_2 but should be re-dried for at least 2 h before use.

Methyl 5 - hydroxy - 3 - methyl - 5 - phenyl - 2 - butenoate (85)

IR (film): 3450 (OH), 1725 (C=O), 1640, 1600 (C=C) cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$) δ: 1.57 (s, 3H, CH_3), 3.02 (d, 1H, J = 4.4 Hz, CH_2), 3.40 (d, 1H, J = 8.8 Hz, CH_2), 3.74 (s, 3H, OCH_3), 4.83 (s, 1H, H-C=C), 4.85 (s, 1H, OH), 5.05 (dd, 1H, J = 4.4, 8.8 Hz, H-C-OH), 7.33 (s, 5H, phenyl H). Low resolution mass spectrum found 220 ($C_{13}H_{16}O_3$, M^+).

Methyl 5 - hydroxy - 5 - (2', 2' - dimethylspiro [2 . 4] hepta - 4', 6' - dien - 1' - yl) - 2 - pentenoate (90)

IR (film): 3450 (OH), 1720 (C=O), 1650 (C=C) cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$) δ: 2.05 (d, J = 3.5 Hz, 1 H, cyclopropyl H), 2.25 (br. s, 1 H, OH), 2.30 - 2.60 (m, 2 H, CH_2), 3.72 (s, 3 H, OCH_3), 4.55 (m, 1 H, H-C-OH), 5.76 (d, J = 6 Hz, 1 H, C=CH-CO_2Me), 6.18 (m, 2 H, cyclopentadienyl H), 6.43 (m, 2 H, cyclopentadienyl H), 6.88 (m, 1 H, H-C=C-CO_2Me). Low resolution mass spectrum found 248 ($C_{15}H_{20}O_3$, M^+).

Methyl 2 - vinyl - 3 - hydroxy - 3 - (2', 2' - dimethylspiro [2 . 4] hepta - 4', 6' - dien - 1' - yl) propanoate (91)

IR (film): 3490 (OH), 1730 (C=O), 1640 (C=C) cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$) δ: 2.80 (d, J = 3 Hz, 1 H, OH), 3.25 (dd, J = 6, 12 Hz, 1H, H-C-CO_2Me), 3.65 (s, 3 H, OCH_3), 4.52 (m, 1 H, H-C-OH), 5.25 (m, 2 H, CH_2=C), 5.60 - 5.90 (m, 1 H, HC=CH_2), 6.22 (m, 1 H, cyclopentadienyl H), 6.45 (m, 1 H,

cyclopentadienyl H). Low resolution mass spectrum found 248 ($C_{15}H_{20}O_3$, M^+).

2 - Ethylidene - 1, 3 - dithiane (92)

Preparation of Propanethioic acid: The Grignard reagent was prepared from bromoethane (21.8 g, 0.20 mmol, Aldrich) and magnesium turnings (6.0g, 0.25 mmol, J. T. Baker) in anhydrous THF (200 mL). A solution of carbon disulfide (15.2 g, 0.20 mmol, Aldrich) in anhydrous THF (20 mL) was added dropwise to the reagent decanted from the remaining magnesium and maintained at -10 °C. The brown solution that formed was allowed to warm to room temperature overnight and then quenched with 10 % hydrochloric acid at -10 °C. The mixture was extracted with ether (2 × 100 mL) and the combined ether layers were washed with brine, dried, filtered, and concentrated at 0 °C. Distillation under reduced pressure gave 13.9 g (65.5 %) of the thioic acid as a brown liquid with a very nasty smell; bp 38 °C / 0.2 Torr; ^{1}H nmr (80 MHz, $CDCl_3$) δ: 1.37 (t, 3H, J = 7.4 Hz, CH_3), 2.63 (s, 1H, SH), 3.06 (q, 2H, J = 7.4 Hz, CH_2-C=S). This is a modification of the literature method.[83]

Preparation of Dithiane (92): A LDA solution was prepared from diisopropylamine (13 g, 128 mmol) and *n*-butyllithium (2.5 M in hexane, 44 mL, 110 mmol, Aldrich) in anhydrous THF (250 mL) at 0 °C. HMPA (27.0 mL, 150 mmol) was added to the solution at 0 °C, followed by a solution of propanethioic acid (5.3 g, 50 mmol) in anhyddrous THF (5 mL) over a period of 10 min. After stirring the golden yellow solution at room temperature for 2 h, it was cooled to -78 °C, followed by the dropwise addition of a anhydrous THF solution (5 mL) of 1-bromo-3-chloropropane (7.9 g, 50 mmol, Aldrich). The solution was allowed to warm to room temperature over night. The reaction mixture was poured into

hexane (100 mL) and washed with 5 % sodium bicarbonate (50 mL) and water (2 × 50 mL), and the combined aqueous layers were backwashed with hexane (50 mL). The combined hexane extracts were washed with brine, dried, filtered and concentrated. The residue was distilled to yield 3.81 g (52 %) of dithiane **92** as a pale yellow liquid with an unpleasant smell; bp 61 - 62 °C / 0.3 Torr (lit.[84] bp 43 - 44 °C / 0.1 Torr); ^{1}H nmr (80 MHz, $CDCl_3$) δ: 1.76 (d, 3H, J = 7 Hz, CH_3), 2.18 (m, 2H, CH_2), 2.87 (m, 4H, SCH_2), 6.00 (q, 1H, J = 7 Hz, H-C=C). Low resolution mass spectrum found 146 ($C_6H_{10}S_2$, M^+).

General Procedure for Condensation of Aldehydes and Dithiane (92) :

A: LDA

A LDA solution was prepared from diisopropylamine (0.232 g, 2.3 mmol, Aldrich) and n-butyllithium (2.5 M in hexane, 0.9 mL, 2.2 mmol, Aldrich) in anhydrous THF (5 mL) at -25°C. Dithiane **92** (0.321 g, 2.2 mmol) in anhydrous THF (2 mL) was added to the solution, forming a yellow solution. After stirring at -25°C for 30 minutes, the solution was cooled to -78°C, followed by dropwise addition of spiro-aldehyde **83** (0.220 g, 1.5 mmol) in anhydrous THF (10 mL). The resulting solution was stirred at -78°C for further 30 minutes, warmed to 0°C, and quenched with saturated aqueous ammonium chloride. The mixture was extracted with ether (2 × 20 mL) and the combined ether extracts were washed with brine, dried, filtered, and concentrated. The crude product was purified by flash chromatography (20 % ethyl acetate / petroleum ether) to give 0.349 g (86 %) of α-hydroxy dithiane **94** and 0.051 g (10 %) of γ-hydroxy dithiane **96**, α : γ = 90 : 10, total yield 96 %.

B: LDA / $ZnCl_2$

2–Ethylidene–1,3–dithiane **92** (0.2044 g, 1.4 mmol) in anhydrous THF (2 mL) was added dropwise to a LDA solution prepared from diisopropylamine (0.152 g, 1.5 mmol) and n-butyllithium (2.5 M in hexane, 0.6 mL, 1.5 mmol, Aldrich) in anhydrous THF (5 mL) at -40°C. The yellow solution was stirred at -40°C for 40 minutes and zinc chloride (0.2031 g, 1.5 mmol, Aldrich) was added. After stirring at -40°C for additional 30 minutes, the reaction solution was cooled to -78°C, followed by dropwise addition of spiro-aldehyde **83** (0.1924 g, 1.3 mmol) in anhydrous THF (10 mL). The reaction was continued for a further hour at -78°C, warmed to 0°C, and quenched with saturated aqueous NH_4Cl. The mixture was extracted with ether (2 × 20 mL) and the combined ether extracts were washed with brine, dried, filtered, concentrated, and purified by flash chromatography (15 % ethyl acetate / petroleum ether) to give 0.1626 g (43 %) of triene **96** (α-product) and 0.1037 g (27 %) of triene **94** (γ-product), $\alpha : \gamma = 60 : 40$, total yield 70 %.

C: LDA / CuI • P(MeO)$_3$

A LDA solution was prepared from diisopropylamine (0.36 mL, 2.6 mmol) and n-butyllithium (2.7 M in hexane, 0.96 mL, 2.6 mmol, Aldrich) in anhydrous THF at -25°C. Dithiane **92** (0.3650 g, 2.5 mmol) in anhydrous THF (1 mL) was added to the solution. The reaction solution was stirred at -25°C for 30 minutes, cooled to -78°C, followed by addition of trimethylphosphite cuprous iodide complex * (0.9058 g, 2.8 mmol) in anhydrous THF (2 mL). A yellow precipitate gradually formed during one hour of stirring. The spiro-aldehyde **83** (0.3703 g, 2.5 mmol) in anhydrous THF (10 mL) was added dropwise to the yellow suspension over a period of 30 minutes, resulting in a greenish solution. The solution was stirred at -78°C for an hour, warmed to 0°C, stirred at 0°C for 30 min, and quenched with saturated aqueous NH_4Cl. A minimum amount of water was added to just

dissolve the white precipitate and the mixture was stirred at 0°C for 10 min and extracted with ether (3 × 15 mL). The combined ether extracts were washed with brine, dried, filtered, and concentrated. Flash chromatography (20 % ethyl acetate / petroleum ether) gave 0.1591 g (22 %) of **96** (α-product) and 0.2892 g (39 %) of **94** (γ-product), α : γ = 35 : 65, total yield 61 %. This procedure is related to the method of Ziegler.[59]

**** Preparation of CuI·(MeO)$_3$P Complex :*** [59]

A mixture of trimethyl phosphite (1.61 g, 13 mmol, Aldrich) and cuprous iodide (2.5 g, 13 mmol, Aldrich) in anhydrous benzene (20 mL) was refluxed for 8 hours with stirring. The hot suspension was filtered from the remaining insoluble materials and the filtrate was concentrated to give a white solid. Recrystallization from ether / chloroform mixture afforded 1.94 g (47.5 %) of trimethylphosphite-cuprous iodide complex as white needles, which were kept in freezer until required.

D: LDA / $CdCl_2$

The dithiane **92** (2.2 mmol) in anhydrous THF (5 mL) was added dropwise to a LDA solution prepared from diisopropylamine (2.3 mmol) and n-butyllithium (2.5 M in hexane, 2.3 mmol) in anhydrous THF (10 mL) at -40°C. After stirring at -40°C for 30 min, the reaction was cooled to -78°C and cadmium chloride powder (1.5 mmol, Aldrich, gold label, ground and dried in vacuum at 110°C) was added in one portion. The white suspension was stirred at -78°C for 30 minutes and a anhydrous THF solution (10 mL) containing aldehyde (benzaldehyde or spiro-aldehyde **83**, 1.0 mmol) was added over a period of 30 minutes. After the addition was complete, the reaction was conducted at -78°C for a further hour,

warmed to 0°C, stirred at 0°C for 0.5 hour, and quenched with saturated aqueous NH_4Cl. The mixture was filtered through Celite and the filtrate was extracted with ether (2 × 15 mL). The combined ether layers were washed with brine, dried, filtered, and concentrated. The oily residue was purified by flash chromatography (15 % ethyl acetate / petroleum ether) to give α-product (**95** or **96**) and γ-product (**93** or **94**) in total yield of 90 - 95 %, γ-product dominated (*cf.* **Table 1**).

2 - (3 - Hydroxy - 3 - phenylpropylidene) - 1, 3 - dithiane (93)

IR (film): 3410 (br, OH), 1605, 1585 (C=C), 705 (s, C-S) cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$) δ: 2.01 - 2.27 (m, 3H,), 2.60 - 2.93 (m, 6H), 4.74 (t, 1H, J = 6.4 Hz, HC-O), 5.97 (t, 1H, J = 7.4 Hz, H-C=C), 7.37 (m, 5H, phenyl H). *Exact mass* calcd. for $C_{13}H_{16}OS_2$: 252.0642; found: 252.0647.

2 - [3 - Hydroxy - 3 - (2', 2' - dimethylspiro [2. 4] hepta - 4', 6' - dien - 1' - yl) propylidene] - 1, 3 - dithiane (94)

IR (film): 3410 (OH), 1600 (C=C) cm^{-1}, ^1H nmr (300 MHz, $CDCl_3$) δ: 1.39 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.03 (d, 1H, J = 9.6 Hz, cyclopropyl H), 2.18 (m, 2H, -SCH_2-$C\underline{H}_2$-SCH_2-), 2.58 (dd, 2H, J = 5.7, 7.5 Hz, CH_2-C=C), 2.88 (t, 4H, J = 6.0 Hz, SCH_2), 2.97 (s, 1H, OH), 3.41 (m, 1H, $\underline{H}$-C-OH), 6.07 (t, 1H, J = 7.5 Hz, H-C=C), 6.37 (m, 1H, cyclopentadienyl H), 6.44 (m, 1H, cyclopentadienyl H), 6.49 (m, 2H, cyclopentadienyl H). *Exact mass* calcd. for $C_{16}H_{22}OS_2$: 294.1111; found: 294.1119.

2 - Vinyl - 2 - (1 - hydroxy - 1 - phenyl) - 1, 3 - dithiane (95)

IR (film): 3450 (br, OH), 3080, 3060, 3025 (phenyl H), 1625 (C=C) cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$) δ: 1.94 (m, 2H, CH_2), 2.80 (m, 4H, SCH_2), 2.94 (d,

1H, J = 3.2 Hz, OH), 4.90 (d, 1H, J = 3.2 Hz, H-C-O), 5.35 - 6.00 (m, 3H, H-C=C), 7.26 - 7.48 (m, 5H, phenyl H). *Exact mass* calcd. for $C_{13}H_{16}OS_2$: 252.0642; found: 252.0657.

2 - Vinyl - 2 - [1 - hydroxy - 1 - (2', 2' - dimethylspiro [2. 4] hepta - 4', 6' - dien - 1' - yl)] - 1, 3 - dithiane (96)

^{1}H nmr (80 MHz, $CDCl_3$) δ: 1.39 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.89 (m, 2H, $-SCH_2-C\underline{H}_2-SCH_2$), 2.35 (d, 1H, J = 9.9 Hz, OH), 2.53 (d, 1H, J = 4.5 Hz, cyclopropyl H), 2.83 (m, 4H, SH_2), 3.89 (dd, 1H, J = 4.5, 9.9 Hz, $\underline{H}$-C-OH), 5.11 - 5.59 (m, 3H, H-C=C), 6.15 - 6.50 (m, 4H, cyclopentadienyl H). *Exact mass* calcd. for $C_{16}H_{22}OS_2$: 294; found: 294 (low resolution).

General Procedure of LDA/$CdCl_2$ Reaction with methyl 3,3-dimethylacrylate (97)

A LDA (2.1 equiv) solution was prepared from diisopropylamine and n-butyllithium in anhydrous THF at -78°C. A THF solution of methyl ester **97** (2.0 equiv.) was added dropwise to the solution , yielding a pale yellow solution. After stirring for 30 minutes at -78°C, cadmium powder (Aldrich, gold label, ground and dried under vacuum at 110°C overnight) was added in one portion and the resulting suspension was stirred for further 30 minutes, followed by addition of aldehyde (benzaldehyde or spiro-aldehyde **83**) in THF with a syringe pump (0.1 mL / min). After the addition was complete, the reaction was continued for an additional hour, then allowed to warm to 0°C, stirred for 30 minutes at 0°C, and quenched by saturated aqueous NH_4Cl. The mixture was filtered through Celite and the filtrate was extracted with ether (2 × 20 mL). The combined ether extracts were washed with brine, dried, filtered, and concentrated. Flash chromatography (20 % ethyl acetate / petroleum ether) afforded the hydroxyester **85** or **86**

(γ-product) and the hydroxyester **87** or **88** (α-product), α / γ ratios and yields see **Table 1** in **Chapter 4.**

Methyl 5 - hydroxy - 3 - methyl - 5 - (2', 2' - dimethylspiro [2. 4] hepta - 4', 6' - dien - 1' - yl) - 2 - pentenoate (86)

IR (film): 3480 (OH), 3060 (H-C=C), 1720 (C=O), 1635 (C=C) cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ: 1.38 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 1.71 (s, 3 H, CH_3), 1.95 (d, 2 H, J = 6.5 Hz, CH_2-C=C), 2.15 (d, 1 H, J = 10.6 Hz, cyclopropyl H), 3.35 (br. s, 1 H, OH), 3.62 (s, 3 H, OCH_3), 4.22 (m, 1 H, CH-O), 5.15 (s, 1 H, H-C=C), 6.15 (m, 2 H, cyclopentadienyl H), 6.38 (m, 2 H, cyclopentadienyl H), 6.50 (m, 2 H, cyclopentadienyl H); ^{13}C nmr ($CDCl_3$) δ: 164.4, 138.7, 137.8, 132.5, 131.3, 128.9, 127.7, 70.5, 56.3, 52.1, 51.2, 42.9, 34.5, 27.1, 22.5, 19.9. Low resolution mass spectrum found 262 ($C_{16}H_{22}O_3$, M^+), 244 ($C_{16}H_{20}O_2$, M^+- H_2O).

Methyl 2 - isopropylidenyl - 3 - hydroxy - 3 - (2', 2' - dimethylspiro [2. 4] hepta - 4', 6' - dien - 1' - yl) propanoate (88)

IR ($CHCl_3$): 3660 (OH), 1730 (C=O), 1650 (C=C) cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ: 1.41 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3-C=C), 2.28 d, 1 H, J = 10.5 Hz, cyclopropyl H), 2.82 (br s, 1 H, OH), 3.47 d, 1 H, J = 7.5 Hz, CH-CO_2Me), 3.69 (s, 3 H, OCH_3), 4.02 (m, 1 H, CH-O), 4.76 (s, 1 H, H-C=C), 4.83 (s, 1 H, H-C=C), 6.18 (m, 2 H, cyclopentadienyl H), 6.41 (m, 1 H, cyclopentadienyl H), 6.50 (m, 1 H, cyclopentadienyl H); ^{13}C nmr ($CDCl_3$) δ: 172.9, 139.1, 137.9, 132.5, 132.2, 129.0, 115.6, 71.0, 59.8, 51.9, 51.5, 46.8, 35.7, 26.4, 22.0, 21.0. Low resolution mass spectrum found 262 ($C_{16}H_{22}O_3$, M^+), 244 ($C_{16}H_{20}O_2$, M^+- H_2O).

LDA / CdI_2 Reaction of Benzaldehyde with methyl 3,3 - dimethylacrylate (97)

An anhydrous THF solution (5 mL) of methyl 3,3-dimethylacrylate **97** (1.026 g, 9 mmol) was added dropwise to a LDA solution prepared from diisopropylamine (1.3 mL, 9 mmol) and n-butyllithium (2.6 M in hexane, 3.5 mL, 9 mmol, Aldrich) in anhydrous THF (30 mL) at -78°C. The solution was stirred for 30 min after the addition was complete, followed by addition of cadmium iodide (1.649 g, 4.5 mmol, Aldrich, gold label, dried under vacuum for 2 h at 110°C) in one portion. Cadmium iodide slowly dissolved and formed a light yellow solution.

Benzaldehyde (0.424 g, 4 mmol, Aldrich, re-distilled) in anhydrous THF (5 mL) was added dropwise to this solution. The resulting solution was stirred for an hour at -78°C, for 30 min at 0°C, and quenched with saturated aqueous NH_4Cl. The mixture was extracted with ether (2 × 20 mL) and the organic layers combined, washed with brine, dried, filtered, and concentrated. Flash chromatography (20 % ethyl acetate / petroleum ether) gave hydroxy-ester **85** (γ-product, 0.519 g, 59 %) and hydroxy-ester **87** (α-product, 0.051 g, 6%), α : γ = 10 : 90, 65 % total yield.

Thermodynamic Study of LDA / $CdCl_2$ Reaction :

1. Methyl 3,3-dimethylacrylate **97** (0.114 g, 1.0 mmol) in anhydrous THF (5 mL) was added dropwise into a LDA solution prepared form diisopropylamine (0.15 mL, 1.1 mmol) and n-butyllithium (2.5 M in hexane, 0.44 mL, 1.1 mmol) in anhydrous THF (5 mL) at -78°C. After stirring for 30 min, cadmium chloride powder (0.0916 g, 0.5 mmol, Aldrich, gold label, ground and dried under vacuum at 110°C overnight) was added in one portion. The suspension was stirred for 30 min at -78°C and a anhydrous THF solution (10 mL) containing the spiro-aldehyde **83** (0.074 g, 0.5 mmol) was added dropwise over a period of 45 min. The reaction

was stirred for an hour at -78°C and then quenched by slowly adding acetic acid (1 mL) in anhydrous THF (2 mL). The mixture was filtered with the help of Celite and the filtrate was extracted with ether (2 × 20 mL). The combined ether layers were washed with brine, dried, filtered, and concentrated. Flash chromatography (20 % ethyl acetate / petroleum ether) yielded hydroxy-ester **88** (0.1034 g, 79 %) as the dominant product.

2. An LDA (0.8 mmol) solution was prepared in anhydrous THF (5 mL) at -78°C and a THF solution (2 mL) of methyl 3,3-dimethylacrylate (0.0456 g, 0.4 mmol) was added dropwise. After stirring for 30 min, cadmium chloride powder (0.0732 g, 0.4 mmol, Aldrich, treated as described above) was added in one portion, followed by a solution of hydroxy-ester **88** (0.1034 g, 0.39 mmol) in anhydrous THF (10 mL). The suspension was stirred for an hour at -78°C, warmed to 0°C, stirred for an hour at 0°C, and then quenched with saturated aqueous NH_4Cl. The mixture was filtered and the filtrate was extracted with ether (2 × 20 mL). The ether extracts were combined, washed with brine, dried, filtered, and concentrated. Flash column chromatography (15 % ethyl acetate / petroleum ether) gave hydroxy-ester **86** (0.0755 g, 73 %) and recovered starting material **88** (0.0139 g, 13.4 %), $\alpha : \gamma = 16 : 84$.

$LiNCy_2$ / $CdCl_2$ Reaction of Benzaldehyde with Methyl crotonate

A THF (2 mL) solution of HMPA (1.79 g, 10 mmol) was added to a lithium dicyclohexylamide ($LiNCy_2$) solution prepared from dicyclohexylamine (1.63 g, 9 mmol) and n-butyllithium (2.6 M in hexane, 3.5 mL, 9 mmol) in anhydrous THF (20 mL) at 0°C. The solution was stirred for 30 min at 0°C, then cooled to -78°C, followed by the addition of methyl crotonate (0.905 g, 9 mmol, Aldrich) in

anhydrous THF (5 mL). After stirring for 30 min at -78°C, cadmium powder (0.825 g, 4.5 mmol, Aldrich, gold label, ground and dried under vacuum at 110°C overnight) was added in one portion. The resulting suspension was stirred for 30 min at -78°C and a solution of benzaldehyde (0.424 g, 4 mmol, Aldrich, re-distilled) in anhydrous THF (5 mL) was added dropwise into the suspension. The reaction was continued at -78°C for an hour, at 0°C for 30 min, and quenched with saturated aqueous NH_4Cl. The mixture was filtered through Celite, and the filtrate was extracted with ether (2 × 20 mL). The combined organic layers were washed with brine, dried, filtered, concentrated, and purified by flash chromatography (20 % ethyl acetate / petroleum ether) to give **98** (γ-product, 0.338 g, 41%) and **99** (α-product, 0.328 g, 40 %), α : γ = 50 : 50, 81 % total yield.

Methyl 5 - hydroxy - 5 - phenyl - 2 - pentenoate (98)

IR (film): 3490 (OH), 3080, 3060, 3030 (phenyl C-H), 1715 (C=O), 1600 (C=C) cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$) δ: 2.13 (m, 2 H, CH_2), 2.80 - 3.15 (m, 2 H, H-C-O, OH), 3.69 (s, 1 H, OCH_3), 5.81 (m, 1 H, C=CH-CO_2Me), 6.85 (m, 1 H, H-C=C-CO_2Me), 7.25 (m, 5 H, phenyl H). Low resolution mass spectrum found 206 ($C_{12}H_{14}O_3$, M^+).

Methyl 2 - vinyl - 3 - hydroxy - 3 - phenylpropanoate (99)

IR (film): 3490 (OH), 1725 (C=O), 1460 (C=C) cm^{-1}; ^1H nmr (80 MHz, $CDCl_3$) δ: 2.89 (d, J = 2.6 Hz, 1 H, OH), 3.35 (dd, J = 2.6, 5.8 Hz, 1 H, H-C-CO_2Me, 3.61 (s, 3 H, OCH_3), 5.05 (m, 1 H, H-C-OH), 5.32 (m, 2 H, C=CH_2), 5.96 (m, 1 H, H-C=CH_2), 7.32 (m, 5 H, phenyl H). *Exact mass* calcd. for $C_{12}H_{14}O_3$: 206.0942; found: 206.0968.

2 - Ethylidene - 1, 3 - dithiane 1, 3 - dioxide (101) [64]

Sodium periodate (5.39 g, 25.2 mmol) in water (40 mL) was added dropwise with stirring to 2-ethylidene-1,3-dithiane **92** (1.22 g, 8.4 mmol) in THF (30 mL). A white precipitate was formed in a mildly exothermic reaction. The suspension was stirred for 12 h. The reaction mixture was extracted with dichloromethane (5 × 25 mL), the combined extracts were dried, filtered, and concentrated under vacuum to give a yellow, oily solid. The latter was washed with THF and recrystallized from a mixture of THF and dichloromethane to give the dioxide **101** (0.98g, 65 %), mp 164 - 165.6 °C, ^{1}H nmr (80 MHz, $CDCl_3$) δ: 2.16 (d, 3H, J = 3.5 Hz, CH_3-C=C), 2.2 - 2.9 (m, 4H), 3.06 (m, 1H, H-CHS=O), 3.13 (m, 1H, H-CHS=O), 6.76 (q, 1H, J = 3.5 Hz, H-C=C). *Exact mass* calcd. for $C_6H_{10}O_2S_2$: 178.0122; found: 178.0121. This structure was confirmed by X-ray crystallography.

Procedure of Phase - Transfer Catalyst Reaction : [85]

The spiro-aldehyde **83** (0.1314 g, 0.9 mmol) in dichloromethane (3 mL) was added dropwise at 22 °C to a vigorously stirring mixture of dithiane dioxide **101** (0.14466 g, 0.8 mmol) and benzyltriethylammonium chloride (0.0192 g, 0.08 mmol) in dichloromethane (10 mL) and 10 % aqueous NaOH (2 mL) at room temperature. After stirring for 10 min, the reaction solution was diluted with ice-cold water and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl, dried, filtered, and concentrated to give a brown liquid. TLC (3 % MeOH / $CHCl_3$) and ^{1}H nmr indicated it was a mixture of products.

3 - [Methoxy - 3 - (2', 2' - dimethylspiro [2. 4] hepta - 4', 6' - dien - 1' - yl) -

propylidene] - 1, 3 - dithiane (104) [86]

Commercially available potassium hydroxide was placed in a round bottomed flask and heated under vacuum with Bunsen burner to remove water. The resulting potassium hydroxide was ground quickly and re-dried under vacuum at 110°C to obtain a fine white powder.

An anhydrous THF / DMSO solution (20 mL, 1 : 2 v/v) of the cyclopentadiene-dithiane **94** (0.729 g, 2.4 mmol) was added dropwise to a suspension of dried KOH powder (1.120 g, 20 mmol) in anhydrous THF / DMSO (50 mL, 1 : 2 v/v) maintained at 0°C, followed by iodomethane (1.14 g, 8.0 mmol, Aldrich). After the addition was complete, the reaction was slowly warmed to room temperature and stirred overnight. The resulting solution was quenched with ice-cold water and the mixture was extracted with ether (3 × 10 mL). The combined ether extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. The black residue was purified by flash chromatography (5% ethyl acetate / petroleum ether) to afford the methyl ether dithiane **104** (0.569 g, 77 %) as an oily liquid; ^{1}H nmr (300 MHz, $CDCl_3$) δ: 1.36 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 2.03 (d, 1 H, J = 9.6 Hz, cyclopropyl H), 2.18 (m, 2 H, CH_2), 2.58 (dd, 2 H, J = 5.7, 7.5 Hz, CH_2-C=C), 2.89 (t, 4 H, J = 6 Hz, SCH_2), 2.97 (s, 3 H, OCH_3), 3.41 (m, 1 H, CH-O), 6.07 (t, 1 H, J = 7.5 Hz, H-C=C), 6.22 (m, 1 H, cyclopentadienyl H), 6.35 (m, 1 H, cyclopentadienyl H), 6.46 (m, 1 H, cyclopentadienyl H), 6.50 (m, 1 H, cyclopentadienyl H).

Methyl 5 - tert - butyldimethylsiloxyl - 3 - methyl - 5 - (2', 2' - dimethylspiro [2. 4] hepta - 4', 6' - dien - 1' - yl) - 2 - pentenoate (100) [87, 88]

tert-Butyldimethylsilyl chloride (1.2995 g, 8.6 mmol, Aldrich) was added to a

stirring suspension of silver perchlorate (1.7433 g, 8.5 mmol) in anhydrous acetonitrile (25 mL) at room temperature. The white suspension formed (silver chloride and *tert*-butyldimethylsilyl perchlorate) was stirred for 30 min and pyridine (2 mL, excess) was added, followed by a solution of hydroxy-ester **80** (1.100 g, 4.2 mmol) in anhydrous acetonitrile (5 mL). The resultant mixture was stirred overnight, diluted with ether (30 mL), and then filtered. The filtrate was washed with 5 % aqueous $NaHCO_3$ and brine, dried, filtered, and concentrated. Flash chromatography (5 % ethyl acetate / petroleum ether) afforded the silyl ether product **100** (1.429 g, 91 %) as a colorless liquid. GC-MS analysis indicated it was a mixture of two major components with M^+/z 376, IR spectroscopy indicated the hydroxyl group had disappeared, and ^1H nmr confirmed the existence of *tert*-butyldimethylsilyl group. Therefore, the product was used directly for Diels-Alder reaction without further purification.

5 - tert - Butyldimethylsiloxyl - 3, 3, 7, - trimethyl - 8 - methoxycarbonyltetracyclo [5. 4. $0^{2,4}$. $0^{2,9}$.] undecane (103)

An anhydrous toluene solution (25 mL) containing silyl ether triene **100** (0.6185 g, 1.6 mmol) and hydroquinone (2 mg, Aldrich) was placed in a thick - walled glass pressure tube (Pyrex), flushed with nitrogen, and then sealed. The pressure tube was placed in a microwave oven and surrounded with damp vermiculite. The reaction was conducted for 2 h, the pressure tube was completely cooled, and the solution transferred to a round bottomed flask and concentrated. The residue was purified by flash chromatography (5 % ethyl acetate / petroleum ether) to yield the Diels-Alder adduct **103** (0.5535 g, 92 %) as a colorless liquid; IR (film): 1715 (C=O), 1565 (C=C) cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ: -0.23 (S, 3 H, $SiCH_3$), 0.15 (S, 3 H, $SiCH_3$), 0.21 (d, J = 8.4 Hz, 1 H, cyclopropyl H), 0.83

(S, 3 H, CH_3), 0.84 (S, 9 H, t-butyl H), 1.09 (S, 3 H, CH_3-cyclopropane), 1.16 (S, 3 H, CH_3-cyclopropane), 1.95 (dd, J = 4.2, 11.4 Hz, 1 H, CH_2, another H hidden in CH_3 peak), 2.42 (m, 2 H, bridgehead CH), 2.90 (d, J = 8.7 Hz, H-C-CO_2Me), 3.66 (S, 3 H, OCH_3), 3.94 (m, 1 H, H-C-OTBDMSi), 5.89 (m, 1 H, H-C=C), 6.17 (m, 1 H, H-C=C); ^{13}C nmr ($CDCl_3$) δ: 175.5 (C=O), 136.6 (C=C), 131.5 (C=C), 71.5 (CH), 65.5 (CH), 56.4 (quaternary C), 51.1 (CH_3), 49.0 (CH_2), 46.2 (CH), 43.8 (CH), 43.4 (quaternary C), 32.4 (CH), 25.6 (3 C, CH_3), 25.0 (quaternary C), 23.7 (CH_3), 22.7 (CH_3), 17.9 (quaternary C), 17.2 (CH_3), -4.6 (CH_3), -5.2 (CH_3). *Exact mass* calcd. for $C_{18}H_{27}O_3Si$ (M^+- t-butyl): 319.1728; found: 319.1726.

5 - Hydroxy - 3, 3, 7 - trimethyl - 8 - methoxycarbonyltetracyclo [5. 4. 0 ^{1,7}. 0 ^{2,4}. 0 ^{2,9}] - 10 - undecene (105) [87]

Tetra-n-butylammonium fluoride (1.0 M in THF, 2.5 mL, 2.5 mmol, Aldrich) was added to a stirred solution of the silyl ether ester **103** (0.4718 g, 1.25 mmol) in anhydrous THF (5 mL) at room temperature. The reaction solution was stirred for a further 2 h and then evaporated to remove the solvent. The black residue was dissolved in ether (15 mL) and washed with water (20 mL). The aqueous layer was extracted with ether (10 mL) and the organic layers were combined, washed with saturated aqueous NH_4Cl, dried, filtered, and concentrated. The crude product was purified by flash chromatography (20 % ethyl acetate / petroleum ether) to give 0.2448 g (75 %) of tetracyclic alcohol **105** as a pale yellow oil; IR (film): 3440 (OH), 1720 (C=O), 1570 (C=C) cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$) δ: 0.23 (d, 1 H, J = 8.8 Hz, cyclopropyl H), 0.83 (s, 3 H, CH_3), 1.11 (s, 3 H, CH_3), 1.14 (d, 1 H, J = 11.5 Hz, C<u>H</u>$_2$-CH-O), 1.17 (s, 3 H, CH_3), 1.95 (dd, 1 H, J = 4.1, 11.5 Hz, C<u>H</u>$_2$-CH-O), 2.03 (br. s, 1H, OH), 2.42 (m, 2 H, CH_2-C=C), 2.89 (d, 1

H, *J* = 9 Hz, CH-CO_2Me), 3.72 (s, 3 H, OCH_3), 4.03 (dd, 1 H, J = 8.8, 9 Hz, CH-O), 5.88 (m, 1 H, H-C=C), 6.16 (m, 1 H, H-C=C); ^{13}C nmr ($CDCl_3$) δ: 175.5, 136.6, 131.8, 70.9, 67.3, 64.7, 56.8, 51.5, 49.0, 46.3, 43.8, 32.0, 25.4, 23.4, 22.6, 17.1; DEPT ($CDCl_3$) δ: 136.6 (CH), 131.8 (CH), 70.9 (CH), 64.7 (CH), 51.5 (CH_3), 49.0 (CH_2), 46.3 (CH), 43.8 (CH), 32.0 (CH), 23.4 (CH_3), 22.6 (CH_3), 17.1 (CH_3). *Exact mass* calcd. for $C_{16}H_{20}O_2$ (M^+- H_2O): 244.1458; found: 244.1462. Low resolution mass spectrum found 262 ($C_{16}H_{22}O_3$, M^+).

4 - Hydroxy - 2 - isopropyl - 6 - methyl - 7 - methoxycarbonyltricyclo [5. 3. 0 ^{1,6}. 0 ^{2,8}] - decane (109)

Tetracyclic alcohol **105** (0.057 g, 0.2 mmol) was dissolved in ethyl acetate (15 mL) and a catalytic amount of PtO_2 (ca. 10 mg, Alfa Products) was suspended in the solution. The reaction was carried out in a Parr apparatus under hydrogen (60 psi) for 24 h. The resulting mixture was filtered and the filtrate was concentrated to give a yellow solid. Recrystallization (ethyl acetate / hexane) of the crude product yielded the tricyclic alcohol **109** (0.049 g, 86 %) as a white solid; IR ($CHCl_3$): 3610, 3450 (OH), 1725 (C=O) cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$) δ: 0.81 (d, 3 H, *J* = 6.8 Hz, isopropyl CH_3), 0.90 (d, 3 H, J = 6.8 Hz, isopropyl CH_3), 0.96 (s, 3 H, CH_3), 1.00 - 1.93 (overlaped 9 H), 2.01 (br. s, 1 H, CH), 2.10 (br. s, 1 H, OH), 2.22 (d, 1 H, J = 9.0 Hz, CH-CO_2Me), 3.69 (s, 3 H, OCH_3), 4.16 (m, 1 H, CH-O); ^{13}C nmr ($CDCl_3$) δ: 175.6, 70.5, 63.9, 55.0, 51.4, 49.6, 43.7, 41.9, 41.8, 31.3, 27.8, 27.0, 22.6, 20.7, 18.0, 17.4; DEPT ($CDCl_3$) δ: 70.5 (CH), 63.9 (CH), 51.4 (CH_3), 49.6 (CH_2), 43.7 (CH), 41.8 (CH), 31.3 (CH_2), 27.8 (CH), 27.0 (CH_2), 22.6 (CH_3), 20.7 (CH_2), 18.0 (CH_3), 17.4 (CH_3). *Exact mass* calcd. for $C_{16}H_{24}O_2$ (M^+- H_2O) 248.1770; found 248.1722. Low resolution mass spectrum found 266 ($C_{16}H_{26}O_3$, M^+).

5 - Phenoxythiocarbonyloxy - 3, 3, 7 - trimethyl - 8 - methoxycarbonyltetracyclo [5. 4. 0 ^{1,7}. 0 ^{2,4}. 0 ^{2,9}] - 10 - undecene (110) [70, 89]

Pyridine (160 μL, 2.0 mmol, Aldrich, dried with 4 Å molecular sieves) was added to a stirred solution of tetracyclic alcohol **105** (0.1968 g, 0.75 mmol) in anhydrous dichloromethane (5 mL) maintained at room temperature, followed by phenyl chlorothioformate (118 μL, 0.85 mmol, Aldrich), The resulting yellow solution was stirred for 1 h at room temperature, concentrated, and the residue was dissolved in 20 mL of ether. The ether solution was washed with 5 % aqueous HCl (5 mL), 5 % aqueous $NaHCO_3$ (5 mL), and brine (10 mL), dried, filtered, concentrated, and purified by Chromatotron (2 % ethyl acetate / petroleum ether) to give the thiocarbonate product **110** (0.1662 g, 56 %) as a yellow solid; ^{1}H nmr (300 MHz, $CDCl_3$) δ: 0.42 (d, 1 H, J = 8.4 Hz, cyclopropyl H), 0.88 (s, 1 H, CH_3), 1.19 (d, 1 H, J = 11.6 Hz), 1.22 (s, 3 H, CH_3), 2.00 (dd, 1 H, J = 4.2, 11.6 Hz, CH_2), 2.49 (br. s, 1 H, CH-C=C), 2.54 (m, 1 H, CH-C=C), 3.26 (d, 1 H, J = 9 Hz, CH-CO_2Me), 3.72 (s, 3 H, CH_3), 5.44 (t, 1 H, J = 8.7 Hz, CH-O), 5.94 (m, 1 H, H-C=C), 6.21 (dd, 1 H, J = 2.7, 5.7 Hz, H-C=C), 7.09 (d, 2 H, J = 8.2 Hz, phenyl H), 7.27 (m, 1 H, phenyl H), 7.40 (m, 2 H, phenyl H); ^{13}C nmr ($CDCl_3$) δ: 193.5, 173.7, 153.4, 136.5, 131.2, 129.4 (2 C), 126.4, 121.9 (2 C), 83.0, 61.3, 56.5, 51.6, 48.5, 46.3, 43.9, 43.8, 29.4, 26.2, 23.4, 22.6, 17.9; APT ($CDCl_3$), (CH_2, C=O, quaternary C) δ: 193.5, 173.7, 153.4, 56.5, 48.5, 43.9, 26.2; (CH_3, CH) δ: 136.5, 131.2, 129.4, 126.4, 121.9, 83.0, 61.3, 51.6, 46.3, 43.8, 29.4, 23.4, 22.6, 17.9. Low resolution mass spectrum found 398 ($C_{23}H_{26}O_4S$, M^+), 366 (M^+- S), 338 (M^+- AcOH), 244 (M^+- PhO(C=S)OH).

2 - Isopropyl - 6 - methyl - 7 - methoxycarbonyltricyclo [5. 3. 0^{1,6}. 0^{2,8}] - 3 - decene (111)

1. Tetracyclic alcohol **105** (0.0583 g, 0.22 mmol) was dissolved in ethyl acetate (20 mL) and a catalytic amount (ca. 10 mg) of 10 % Pd / activated carbon (Alfa Products) was suspended in the solution. The reaction was carried out in Parr apparatus under hydrogen (10 psi) for 10 h. The reaction mixture was then filtered and the filtrate was concentrated to give the hydrogenated tetracyclic alcohol (0.0564 g, 96 %) as a pale yellow liquid. This product was used directly for the next synthetic step*.

2. The hydrogenation product was dissolved in anhydrous dichloromethane (5 mL) and pyridine (65 μL, 0.8 mmol, Aldrich, dried over 3 Å molecular sieves) was added at room temperature, followed by phenyl chlorothioformate (53 μL, 0.6 mmol, Aldrich). The yellow solution was stirred for 1 h at room temperature and concentrated to remove the solvent. The residue was dissolved in ether (20 mL) and the ether solution was washed with 5 % aqueous HCl (5 mL), 5 % aqueous $NaHCO_3$ (5 mL), and brine (10 mL). The washed organic solution was dried, filtered, and concentrated to give a dark-brown oily material. The crude product passed through a short silica gel column (eluted with 2 % ethyl acetate / petroleum ether) to afford thiocarbonate product (0.0522 g, 61 %), which was used directly for the radical reaction without further purification.

3. A solution of tributyltin hydride (81 μL, 0.3 mmol, Aldrich) and AIBN (5 mg, recrystallized, from Aldrich) in anhydrous toluene (5 mL) was added with a syringe pump (0.25 mL / h) to a stirred solution of thiocarbonate compound (0.0522 g, 0.13 mmol) in refluxing anhydrous toluene (10 mL). After the addition was complete, the reaction mixture was stirred and refluxed for a further 4 h, cooled to room temperature, and concentrated to remove the solvent. The residue was applied

overnight to the top of a silica gel column (saturated with petroleum ether), eluted first with petroleum ether to wash out the tin compound (nasty odor), and then eluted with 2 % ethyl acetate / petroleum ether to yield 0.0255 g (70.4 %) of a colorless liquid. GC - MS analysis indicated it was a mixture of cyclopropane ring opened products **111** and **112** (approximately 9 : 1). Isopropyl tricyclic alkene **111**; ^{1}H nmr (300 MHz, $CDCl_3$) δ: 0.86 (d, 3 H, J = 6.9 Hz, isopropyl CH_3), 0.92 (d, 3 H, J = 6.9 Hz, isopropyl CH_3), 1.09 (s, 3 H, CH_3), 1.26 (m, 2 H, CH_2), 1.58 - 1.76 (overlaped 4 H, CH_2), 1.89 (sextet, 1 H, J = 6.9 Hz, isopropyl H), 2.04 (m, 1 H, CH), 2.23 (m, 1 H, CH), 2.65 (d, 1 H, J = 4.5 Hz, CH-CO_2Me), 3.65 (s, 3 H, OCH_3), 5.56 (dd, 1 H, J = 4.5, 9.8 Hz, H-C=C), 5.90 (d, 1 H, J = 9.8 Hz, H-C=C); ^{13}C nmr ($CDCl_3$) δ: 173.3, 133.2, 123.6, 57.5, 56.8, 51.3, 46.0, 45.8, 44.0, 41.3, 28.8, 26.5, 22.8, 20.3, 19.0, 17.4.

* A attempt to purify the hydrogenation product by recrystallization (ethyl acetate / hexane) caused an isomerization of the cyclopropane ring to yield a sinularene-type product: 4-hydroxy-2-isopropenyl-6- methyl - 7 - methoxycarbonyltricyclo [5. 3. 0 ^{1,6}. 0 ^{2,8}]-decane; IR (film): 3605 (OH), 1725 (C=O), 1640 (C=C) cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$) δ: 0.97 (s, 3 H, CH_3), 1.15 (m, 1 H), 1.48 (m, 2 H, CH_2), 1.53 (br. s, 2 H, CH_2), 1.73 (s, 3 H, CH_3-C=C), 1.66 - 1.87 (overlap 3 H), 2.01 (br. s, 1 H, CH), 2.22 (d, 1 H, J = 8.7 Hz, CH-CO_2Me), 2.23 (br. s, 1 H, OH), 3.69 (s, 3 H, OCH_3), 4.32 (m, 1 H, CH-O), 4.71 (m, 2 H, CH_2=C); ^{13}C nmr ($CDCl_3$) δ: 175.5, 148.4, 109.6, 69.5, 63.5, 56.9, 51.5, 48.7, 43.9, 42.0, 41.7, 38.1, 27.5, 22.5, 21.1, 19.8; DEPT ($CDCl_3$) δ: 109.2 (CH_2), 69.5 (CH), 63.5 (CH), 48.7 (CH_2), 43.9 (CH), 42.0 (CH), 38.1 (CH_2), 27.5 (CH_2), 22.5 (CH_3), 21.1 (CH_2), 19.8 (CH_3). Low resolution mass spectrum found 264 ($C_{16}H_{24}O_3$, M^+), 246 (M^+- H_2O).

3, 3, 7 - Trimethyl - 8 - methoxcarbonyltetracyclo [5. 4. 0 ^{1,7}. 0 ^{2,4}. 0 ^{2,9}] - 10 - undecen - 5 - one (115) [79, 80]

1. A solution of dimethyl sulfoxide (210 µL, 3.0 mmol, dried over CaH_2) in anhydrous CH_2Cl_2 (2 mL) was added dropwise to a solution of oxalyl chloride (130 µL, 1.5 mmol, Aldrich) in anhydrous CH_2Cl_2 (5 mL) maintained at -78°C with an external solid CO_2 / acetone bath. After stirring for 10 min, alcohol **105** (0.3369 g, 1.3 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise, forming a white precipitate. The suspension was stirred for 15 min at -78°C and triethylamine (0.8 mL, excess) in anhydrous CH_2Cl_2 (2 mL) was added dropwise to form a clear yellow solution. The solution was allowed to warm to 0°C with external ice / water bath, cold water (15 mL) was added, and the mixture was stirred for 10 min at 0°C. The resulting mixture was separated and the aqueous layer was re-extracted with CH_2Cl_2 (10 mL). The combined organic layers were washed with 5 % hydrochloric acid (5 mL), 5 % aqueous $NaHCO_3$ (5 mL), and brine, dried, filtered, and concentrated to afford crude ketone product **115** as a yellow solid (0.3118 g, 93 %). This product was further purified by recrystallization (ethyl acetate / hexane) to give white crystals (0.2527 g, 75.4 %); mp 37-38.5°C; ^{1}H nmr (300 MHz, $CDCl_3$) δ: 0.87 (s, 1 H, cyclopropyl H), 0.90 (s, 3 H, CH_3), 1.12 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 1.30 (d, 1 H, J = 12 Hz, H-CH-C=O), 2.13 (dd, 1 H, J = 4, 12 Hz, H-CH-C=O), 2.68 (m, 1 H, CH-C=C), 2.70 (m, 1 H, CH-C=C), 3.58 (s, 1 H, CH-C=O), 3.72 (s, 3 H, OCH_3), 6.06 (m, 1 H, H-C=C), 6.27 (m, 1 H, H-C=C); ^{13}C nmr ($CDCl_3$) δ: 205.0, 170.7, 136.9, 131.9, 69.9, 57.9, 51.6, 48.3, 47.4, 44.7, 44.6, 35.4, 30.9, 23.1, 22.9, 19.5. *Exact mass* calcd. for $C_{16}H_{20}O_3$ 260.1407; found 260.1420.

2.[88] Trifluoroacetic anhydride (0.56 mL, 4.0 mmol, Aldrich) was added to a solution of dimethylsulfoxide (0.32 mL, 4.5 mmol, dried over CaH_2) in anhydrous CH_2Cl_2 (5 mL) maintained at -78°C with an external solid CO_2 / acetone bath, to form a white precipitate. After stirring for 15 min, a solution of alcohol **105** (0.2018 g, 0.77 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise over a period of 10 min; 30 min later, a solution of triethylamine (1.4 mL, excess) in anhydrous CH_2Cl_2 (2 mL) was added dropwise to give a clear yellow solution. The solution was allowed to warm slowly to 0°C, stirred for 30 min at 0°C, diluted with CH_2Cl_2 (20 mL), and quenched with cold water. The mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layers were washed with an equal volume of water, 5 % hydrochloric acid, 5 % aqueous $NaHCO_3$ and saturated aqueous NH_4Cl, dried, filtered, and concentrated. Flash chromatography (10 % ethyl acetate / petroleum ether) afforded the ketone ester **115** (0.1714 g, 86 %) as a pale yellow oil. The ^1H nmr spectrum of this product was consistent with the product obtained by the method described above. However isomerization of the methyl ester group had occurred at C-8. The most obvious evidence was the presence of a minor OCH_3 peak (δ 3.71) and a major one (δ 3.72) with a combined total integration of three protons.

Unsuccessful Jones' Oxidation to Prepare (115) [89]

Jones' reagent was prepared according to the literature method from CrO_3 (7 g) and concentrated H_2SO_4 (6 mL) in water (50 mL). A stirred solution of alcohol **105** (48 mg) in 10 mL of acetone / THF (10 : 1) at room temperature was treated with the Jones' reagent. The resulting mixture was concentrated and the residue was extracted in a separatory funnel with a mixture of 1 : 1 ether / water

(30 mL). The ether layer was dried, filtered, and concentrated to give a yellow liquid. The ^{1}H nmr spectrum indicated it was a mixture of complicated products.

2 - Isopropenyl - 6 - methyl- 7 - methoxycarbonyltricyclo [5. 3. 0 ^{1,6}. 0 ^{2,8}] dec - 9 - en - 4 - one (116)

1. Crystalline $Cr_2(SO_4)_2.15H_2O$ (2.35 g, Aldrich) and zinc powder (1.6 g, Aldrich) were added in portions to a stirred solution of tetracyclic ketone **115** (0.1735 g, 0.67 mmol) in a 2 : 1 mixture ot DMF / H_2O (50 mL) at room temperature. The reaction was exothermic and formed a deep blue solution with zinc powder suspended in it. The mixture was stirred for 1 h at R.T., diluted with ether (20 mL), and filtered. The filtrate was separated and the aqueous layer was extracted with ether (15 mL). The combined organic layers were washed with water (20 mL), dried, and concentrated. Flash chromatography (10 % ethyl acetate / petroleum ether) yielded cyclopropane ring isomerization product **116** (0.1045 g, 60 %) as a pale yellow liquid; IR (film): 1730 (C=O), 1710 (C=O), 1645 (C=C), 1560 (C=C) cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$) δ: 1.04 (s, 3 H, CH_3), 1.13 (m, 1 H, CH_2), 1.62 (m, 1 H, CH_2), 1.65 (s, 3 H, CH_3-C=C), 2.47 (m, 1 H, CH-C=C), 2.81 (m, 2 H, CH_2-C=O), 3.02 (m, 1 H, CH-C=C), 3.40 (d, 1 H, J = 1.1 Hz, CH-CO_2Me), 3.72 (s, 3 H, OCH_3), 4.69 (m, 1 H, terminal CH_2=C), 4.77 (m, 1 H, terminal CH_2=C), 5.97 (m, 1 H, H-C=C), 6.17 (m, 1 H, H-C=C); ^{13}C nmr ($CDCl_3$) δ: 205.7, 169.2, 148.0, 137.5, 131.0, 111.8, 68.1, 66.7, 52.1, 50.9, 50.1, 47.4, 41.9, 40.3, 24.4, 21.9; DEPT ($CDCl_3$) δ: 137.5 (CH), 131.0 (CH), 111.8 (CH_2), 66.1 (CH), 52.1 (CH_3), 50.9 (CH), 50.1 (CH), 47.4 (CH_2), 40.3 (CH_2), 24.4 (CH_3), 21.9 (CH_3). *Exact mass* calcd. for $C_{16}H_{20}O_3$: 260.1407; found: 260.1411.

2. A Cr(II) solution was prepared as follows:[90] crystalline $Cr_2(SO_4)_3.15H_2O$ (5 g) and zinc powder (1.3 g) were mixed in distilled water (30 mL) and the mixture was stirred overnight at room temperature under nitrogen. Decanted from the precipitates, a clear blue solution of $Cr(II)SO_4$ (ca. 0.5 M) was obtained. This prepared Cr(II) solution (2 mL) and zinc powder (0.1 g) were added to a solution of cyclopropane ketone **115** (8 mg, 0.03 mmol) in DMF (6 mL). The reaction was stirred for 36 h at room temperature and no reaction was observed (GC-MS monitoring). Then the reaction mixture was refluxed for 12 h. After cooling to room temperature, the resulting mixture was filtered and the filtrate was extracted with ether (2 × 15 mL). The combined ether extracts were washed with brine, dried, filtered, and concentrated. Flash chromatography (5 % ethyl acetate / petroleum ether) yielded a single product (7 mg), whose ^1H nmr spectrum was consistent with that of cyclopropane ring isomerization product **116**.

3, 3, 7 - Trimethyl - 8 - methyoxycarbonyltetracyclo [5. 4. 0 ^{1,7}. 0 ^{2,4}. 0 ^{2,9}] undecan - 5 - one (118)

Alkene ketone **115** (0.2210 g, 0.85 mmol) was dissolved in ethyl acetate (10 mL) and a catalytic amount of 10 % Pd / activated carbon (ca. 20 mg, Alfa Product) was suspended in the solution. The hydrogenation was carried out in a Parr apparatus under hydrogen (15 psi) for 12 h. The resulting mixture was filtered through a band of Celite and the filtrate was concentrated to give a yellow solid. Recrystallization (ethyl acetate / hexane) gave the ketone ester **118** (0.2071 g, 93 %) as a white crystal; IR ($CHCl_3$): 1732 (C=O), 1715 (C=O) cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ: 0.94 (s, 1 H, cyclopropyl H), 1.03 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.36 (d, 1 H, J = 12 Hz, H-CH-C=O), 1.75 - 1.80 (overlaped m, 3 H), 1.95 - 2.15 (overlaped m, 4 H), 3.24 (s, 1 H, CH-C=O), 3.71

(OCH_3); ^{13}C nmr ($CDCl_3$) δ: 205.4, 170.1, 72.6, 51.5, 50.6, 47.5, 43.0, 39.9, 33.3, 30.9, 29.0, 22.9, 22.6, 21.4, 19.3. *Exact mass* calcd. for $C_{16}H_{22}O_3$: 262.1563; found: 262.1544.

2 - Isopropenyl - 6 - methyl - 7 - methoxycarbonyltricyclo [5. 3. 0 ^{1,6}. 0 ^{2,8}] decan - 4 - one (119)

A methanol (1 mL) solution of cyclopropane ketone **118** (6 mg, 0.02 mmol) was added to a stirred mixture of zinc powder (0.5 g) and zinc chloride (0.5 g) in methanol (5 mL) at room temperature. A few drops of glacial acetic acid were added and the mixture was refluxed with stirring overnight. After cooling to room temperature, the mixture was filtered and the filtrate was extracted with ether (2 × 10 mL). The combined ether layers were washed with 5 % aqueous $NaHCO_3$ (5 mL) and brine (15 mL), dried, filtered, and concentrated. Flash chromatography (10 % ethyl acetate / petroleum ether) afforded the cyclopropane ring isomerization product **119** (5 mg, 83 %) as a colorless liquid; ^1H nmr (300 MHz, $CDCl_3$) δ: 1.11 (s, 3 H, CH_3), 1.07 - 1.22 (overlap 3 H), 1.72 (s, 3 H, CH_3-C=C), 1.58 - 1.89 (overlap 3 H), 2,16 (m, 2 H, CH_2), 2.34 (m, 1 H, CH), 2,49 (m, 1 H, CH), 3.10 (br. s, 1 H, CH-CO_2Me), 3.71 (s, 3 H, OCH_3), 4.73 (m, 1 H, H-C=C), 4.84 (m, 1 H, H-C=C). Low resolution mass spectrum found 262 ($C_{16}H_{22}O_3$, M^+).

Li / NH_3 Reductive Cyclopropane Ring Opening [71, 91]

Ammonia gas from a cylinder was condensed into a flask through a solid CO_2 / acetone cooling condenser and the flask was also maintained at -78°C with an external solid CO_2 / acetone bath. After the liquid ammonia volume was ca. 3 mL, a small piece of lithium metal (ca. 8 mg) was added and a blue solution

formed. A solution of cyclopropane ketone **118** (0.2091 g, 0.79 mmol) and *tert*-butanol (0.0805 g, 1.1 mmol) in anhydrous ether (10 mL) was added dropwise to the Li / NH_3 solution. After the addition was complete, stirring was continued for 10 min at -78°C. The reaction was quenched with ammonium chloride, and the solid CO_2 / acetone bath was removed. The reaction mixture was allowed to warm to 0°C with an external ice / water bath and the ammonia was allowed to evaporate under a stream of N_2. Water (10 mL) was added, the resulting mixture was separated, and the aqueous layer was extracted with ether (2 × 10 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (20 mL), dried, filtered, and concentrated. Flash chromatography (5 % ethyl acetate / petroleum ether) afforded a pale yellow oil (0.2019 g, 97 %). GC-MS established it was a mixture of two components with M^+/z 264, and the ratio was almost 1 : 1.

This mixture and p-toluenesulfonohydrazide (0.1843 g, 1.0 mmol, Aldrich) were mixed in absolute methanol (5 mL), and the solution was refluxed and stirred for 1 h [92]. After cooling to room temperature, CH_2Cl_2 (10 mL) was added and the mixture was washed with water (10 mL), dried, filtered, and concentrated to give a yellow solid. Recrystallization (ethanol / water) gave a pale yellow solid, which was a mixture of two tosylhydrazone products. Efforts to separate the mixture by flash chromatography were unsuccessful.

The mixture of tosylhydrazone products were dissolved in anhydrous THF (5 mL) and $LiAlH_4$ (0.1 g) was added in portions at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. After work-up by adding ice-cold water, the mixture was filtered, and the filtrate was extracted with CH_2Cl_2 (2 × 15 mL). The combined CH_2Cl_2 extracts were washed with brine (30 mL), dried, flittered, and concentrated to give an oily liquid. Flash chromatography (25 % ethyl acetate / petroleum ether) afforded a colorless liquid (0.091 g), which

still was a mixture of reduction products. This mixture was kept in freezer for further purification.

Attempt to Prepare (2S, 3R) 1, 2 - Epoxy - 3 -butanol (g)

1. Activated 3 Å molecular sieves (2 g, 30 % w/w to alcohol, Fisher, ground and dried overnight *in vacuo* at 110°C) were added to a stirred solution of 3-buten-2-ol (7.21 g, 100 mmol, Aldrich) and (+)-diisopropyl tartrate [(+)-DIPT] (3.52 g, 15 mmol, Aldrich) in anhydrous CH_2Cl_2 (400 mL). The suspension was cooled to -20°C and titanium tetraisopropoxide (3 mL, 10 mmol, Aldrich, re-distilled) was added dropwise. After stirring for 30 min at -20°C, a solution of anhydrous *tert*-butyl hydroperoxide* (3.3 M in toluene, 21.2 mL, 70 mmol) was added dropwise and the reaction mixture was stirred for 6 days in a freezer (ca. -20°C). A freshly prepared aqueous solution (100 mL) of ferrous sulfate heptahydrate (33 g) and citric acid monohydrate (11 g) was cooled to 0°C with an external ice / water bath and the reaction mixture was poured into it. The two-phase mixture was stirred for 15 min and filtered. The filtrate was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were treated with an aqueous solution (100 mL) of NaCl (5 g) and NaOH (30 g) by vigorously stirring for 1 h at 0°C. The mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried and then concentrated at 0°C. None of the desired product was found in the residue. (Based on the method of Sharpless.[73])

2. Titanium tetraisoproxide (30 mL, 100 mmol, Aldrich, re-distilled) was added dropwise to a stirred solution of 3-buten-2-ol (7.2 g, 100 mmol, Aldrich) and (+)-diisopropyl tartrate (28.1 g, 120 mmol, Aldrich) in anhydrous CH_2Cl_2 (400 mL)

maintained at -20°C. After stirring for 30 min at -20°C, a solution of anhydrous *tert*-butyl hydroperoxide* (3.3 M in toluene, 18 mL, 60 mmol) was added dropwise and then the reaction mixture was stirred for 3 days in a freezer (ca. -20°C). The resulting mixture was poured into a cooled (-20°C) solution of acetone (300 mL) and water (30 mL). The viscous mixture was stirred while warming to R.T. and then filtered. The filtrate was concentrated to ca. 50 mL and mixed with an aqueous solution (100 mL) of NaCl (5 g) and NaOH (30 g) at 0°C. The two-phase mixture was vigorously stirred for 1 h at 0°C and separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers were washed with brine (100 mL), dried, filtered, and concentrated at 0°C to give a milky liquid, which did not contain the desired product. (Based on the method of reference 94.)

3. 3-Buten-2-ol (3.6 g, 50 mmol, Aldrich), 3 Å molecular sieves (3.5 g, Aldrich, ground and dried overnight *in vacuo* at 110°C) and (+)-diethyl tartrate (2.5 mL, 15 mmol, Aldrich) were mixed in anhydrous CH_2Cl_2 (200 mL). The mixture was stirred and cooled to -10°C with an external ice / salt bath. Titanium tetraisoproxide (2.5 mL, 8 mmol, Aldrich, re-distilled) was added dropwise, followed by anhydrous *tert*-butyl hydroperoxide* (3.3 M in toluene, 20 mL, 60 mmol), and the reaction mixture was stirred for 24 h at -20°C. GC-MS did not indicate any of the desired reaction product. (Based on the method of reference 93.)

* *tert*-Butyl hydroperoxide (70 % in H_2O, 325 mL, Aldrich) and reagent-grade toluene (400 mL) were mixed in a 1 L separatory funnel by swirling (do not shake), and then separated. The organic layer was transferred to a 1 L

round-bottom flask equipped a Dean-Stark trap and a condenser. The solution was refluxed under N_2, about 20 mL of water was collected, and then a further 20 mL of distillate was removed through the side arm to ensure removal of the last trace of water. After cooling to room temperature, the remaining solution (ca. 600 mL) was transferred to a brown glass bottle and stored over 4 Å molecular sieves in a cold-room (ca. 4°C). The concentration of *tert*-butyl hydroperoxide was approximately 3.3 M.

(-) - Menthyl chloroformate (130)

Phosgene gas was bubbled through toluene (100 mL, pre-weighed with container) at 0°C for an hour and the container was weighed to establish the amount of phosgene dissolved in toluene. This work must be done in the fumehood.

A solution of (-)-menthol (15.6 g, 0.1 mol, Fisher) and quinoline (14.2 g, 0.11 mol, Aldrich, re-distilled) was prepared in toluene (100 mL) and cooled to 0°C. A stock toluene solution of phosgene (20 g, 0.2 mol) was added dropwise to the solution and slowly formed a white precipitate. The mixture was stirred at 0°C and monitored by TLC until the reaction was complete. The resulting mixture was filtered to remove the precipitate, and the filtrate was flushed with nitrogen in fumehood at 21°C to remove the excess phosgene. The flushed solution was transferred to an Erlenmeyer flask and a few grams of calcium carbonate were added as the stabilizer. This (-)-menthyl chloroformate **130** solution in approximately 1 mmol / mL concentration was stored in refrigerator before use. (Based on the method of reference 74.)

(1R') (2', 2' - Dimethylspiro [2. 4] - 4', 6' - dien - 1' - yl) methyl (-) menthyl carbonate (131)

The stock solution of (-)-menthyl chloroformate **130** (1.2 equimolar to spiro-alcohol **82**) was concentrated and the residue was re-dissolved in anhydrous benzene to prepare a 0.5 mmol / mL solution. To the solution was added dropwise a solution of racemic spiro-alcohol **91** and triethylamine (equimolar) in anhydrous benzene (1 mmol / mL). The reaction mixture was filtered to remove the precipitate formed, and the filtrate was concentrated to give a thick brown liquid. This mixture was separated by flash chromatography (2 % ethyl acetate / petroleum) to afford the spiro-heptadienyl (-)-menthyl carbonate **131** as a white solid; mp 29-31°C; ^{1}H nmr (300 MHz, $CDCl_3$) δ: 0.79 (d, 3 H, J = 7 Hz, CH_3), 0.91 (t, 6 H, J = 6.5 Hz, isopropyl CH_3), 1.05 (m, 2 H, CH_2), 1.41 (s, 6H, CH_3-cyclopropane), 1.36 - 1.46 (m, 2 H, CH_2), 1.66 (m, 2 H, CH_2), 1.94 (m, 1 H, CH), 2.03 (m, 1 H, CH), 2.43 (t, 1 H, J = 7.2 Hz, cyclopropyl H), 4.38 (d, 2 H, J = 7.2 Hz, CH_2-O), 4.52 (dt, 1 H, J = 4.4, 10.9 Hz, CH-O), 6.25 (m, 2 H, cyclopentadienyl H), 6.45 (m, 1 H, cyclopentadienyl H), 6.53 (m, 1 H, cyclopentadienyl H); ^{13}C nmr ($CDCl_3$) δ: 158.8, 137.4, 132.5, 131.2, 129.3, 78.4, 66.3, 51.2, 47.0, 40.7, 37.8, 34.1, 33.9, 31.4, 26.8, 26.1, 23.3, 21.9, 20.6, 19.8, 16.3.

Chiral shift reagent, tris[3-(trifluoromethyhydroxymethylene)-(+)-camphorato], europium(III) derivative, was added to a $CDCl_3$ solution (0.5 mL) containing the (-)-menthyl carbonate **131** (6.7 mg, 0.02 mmol) in the following molar ratios (1 : 1, 1 : 2, 1 : 3, 1 : 4) and ^{1}H nmr spectra were recorded. No new signals were observed, and there was no line broadening except for the isopropyl methyl resonances (δ 0.91) which were isolated into two doublets.

(+) (1R) 2, 2 - Dimethyl - 1 - hydroxymethylspiro [2. 4] hepta - 4, 6 - diene (132)

Spiroheptadienyl (-)-menthyl carbonate **131** (3.98 g, 12 mmol) was dissolved in anhydrous THF (50 mL) and cooled to 0°C with an external ice - water bath. Lithium aluminum hydride (1.14 g, 30 mmol) was added in several small portions. The reaction suspension was allowed to warm slowly to room temperature, and the suspension was stirred until the reaction was complete by TLC monitoring. The reaction mixture was re-cooled to 0°C and the excess $LiAlH_4$ was destroyed with careful addition of cold water. The resulting mixture was filtered and the filtrate was neutralized with 5 % aqueous hydrochloric acid. This solution was extracted with ether (3 × 25 mL) and the combined ether layers were dried, filtered and concentrated. Flash chromatography (20 % ethyl acetate / petroleum ether) afforded (+)-R-spiro-alcohol **133** (1.762 g, 98 %) as a colorless liquid; $[\alpha]^{22} = +21.4°$ (c 4.6, $CHCl_3$); IR (film): 3350 (br, OH), 3090, 3060 (H-C=C), 1650 (s, C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.41 s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.71 (br s, 1H, OH), 2.41 (dd, 1H, J = 7.5, 8.1 Hz, cyclopropyl H), 3.80 (dd, 1H, J = 8.1, 11.7 Hz, CH_2-O), 3.99 (dd, 1H, J = 7.5, 11.7 Hz, CH_2-O), 6.30 (m, 2H, cyclopentadienyl H), 6.45 (m, 1H, cyclopentadienyl H), 6.57 (m, 1H, cyclopentadienyl H); ^{13}C NMR ($CDCl_3$) δ: 138.4, 133.0, 131.8, 129.2, 62.0, 52.3, 43.4, 35.3, 27.5, 20.4. *Exact mass* calcd. for $C_{10}H_{14}O$: 150.1044; found: 150.1032.

(+) (1'R) (2', 2' - Dimethylspiro [2. 4] hepta - 4', 6'- diene - 1' - yl) carboxaldehyde (133)

The spiro-alcohol **145** (2.25 g, 15 mmol) in dichloromethane (25 mL) was added dropwise to a stirring, refluxing suspension of activated MnO_2 / charcoal (40 g as a prepared mixture) in dichloromethane (250 mL). The mixture was stirred

under reflux for 12 h, cooled to room temperature, filtered through Celite and anhydrous $MgSO_4$, and washed thoroughly with dichloromethane. The combined filtrates were concentrated and the crude product was purified by flash chromatography (5 % ethyl acetate / petroleum ether) to yield the (+)-R-spiro-aldehyde **133** (1.90 g, 86 %) as a pale yellow liquid; $[\alpha]^{22} = +23.0°$ (c 2.9, $CHCl_3$); IR (film): 2825 (H-CO), 2720 (H-CO), 1704 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.42 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.78 (d, 1H, $J = 6$ Hz, cyclopropyl H), 6.17 (m, 1H, cyclopentadienyl H), 6.53 (m, 2H, cyclopentadienyl H), 6.60 (m, 1H, cyclopentadienyl H), 9.56 (d, 1H, $J = 6$ Hz, H-C=O); ^{13}C nmr ($CDCl_3$) δ: 198.0, 135.5, 132.4, 131.6, 131.4, 56.8, 49.4, 37.1, 26.8, 20.7. *Exact mass* calcd. for $C_{10}H_{12}O$: 148.0888; found: 148.0888.

(+) (5R, 1'R) 3 - Methyl - 5 - (2', 2' - dimethylspiro [2 . 4] hepta - 4', 6' - dien - 1' - yl) - 6 - oxa - 2 - cyclohexenone (134)

An LDA solution was prepared from diisopropylamine (0.32 mL, 2.3 mmol) and n-butyllithium (2.5 M, 0.9 mL, 2.3 mmol, Aldrich) in anhydrous THF (5 mL) at -40°C, and a solution of 3,3-dimethylacryate **97** (0.2510 g, 2.2 mmol) in anhydrous THF (2 mL) was added dropwise. After stirring for 20 min, cadmium chloride powder (0.3660 g, 2.0 mmol, Aldrich, gold label, ground and dried overnight under vacuum at 110°C) was added in one portion. The suspension was stirred for 30 min at -40°C, and a solution of (+)-spiro-aldehyde **133** (0.1586 g, 1.1 mmol) in anhydrous THF (5 mL) was added by syringe pump (0.1 mL / min). After the addition was complete, stirring was continued for a further 30 min at -40°C. The reaction was allowed to warm to 0°C, stirred for 2 hours at 0°C, and then quenched with saturated aqueous NH_4Cl. The mixture was filtered through Celite and the filtrate was extracted with ether (2 × 15 mL). The combined organic layers

were dried, filtered and concentrated. Flash chromatography (15 % ethyl acetate / petroleum ether) afforded (+)-triene lactone **134** (0.1846 g, 73 %) as a colorless liquid and α-product **88** (0.0387 g, 15 %). (+)-Triene-lactone **134**; $[\alpha]^{22} = +17.7°$ (c 3.4, $CHCl_3$); IR (film): 1710 (C=O), 1650 (C=C) cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ: 1.39 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 1.87 (s, 3 H, CH_3-C=C), 1.93 - 2.09 (m, 2 H, CH_2-C=C), 2.31 (d, 1 H, $J = 4.2$ Hz, cyclopropyl H), 4.48 (m, 1 H, H-C-O), 5.76 (s, 1 H, H-C=C), 6.17 (m, 1 H, cyclopentadienyl H), 6.28 (m, 1 H, cyclopentadienyl H), 6.49 (m, 1 H, cyclopentadienyl H), 6.58 (m, 1 H, cyclopentadienyl H); ^{13}C nmr and DEPT ($CDCl_3$) δ: 164.6 (C=O), 156.0 (C=C), 136.4 (C=CH), 132.3 (C=CH), 131.6 (C=CH), 129.7 (C=CH), 116.8 (C=CH), 76.6 (CH), 51.1 (quaternary C), 42.1 (CH), 35.6 (CH_2), 31.9 (quaternary C), 27.2 (CH_3), 23.0 (CH_3), 20.4 (CH_3). *Exact mass* calcd. for $C_{15}H_{18}O_2$: 230.1302; found: 230.1303.

(5R, 1'R) 5 - (2' - Cyclopentadienyl - 1' - methoxy - 2', 2' - dimethylethyl) - 3 - methyl - 6 - oxa - 2 - cyclohexenone (137)

Boron trifluoroetherate (92 μL, 0.75 mmol, Aldrich) was added to a solution of spiro-heptadiene lactone **134** (0.1652 g, 0.72 mmol) in absolute methanol (10 mL) at room temperature. The reaction solution was stirred for 4 h and quenched with 5 % aqueous $NaHCO_3$. The mixture was extracted with ether (2 × 25 mL) and the ether extracts were combined, washed with brine, dried, filtered, and concentrated. The crude product was purified by flash chromatography (15 % ethyl acetate / petroleum ether) to give the cyclopropane ring - opened product **137** (0.1573 g, 83 %) as a pale yellow liquid. This product was a mixture of substituted cyclopentadienes from the rapid 1, 5-sigmatropic rearrangement. IR (film): 1730 (C=O), 1575 (C=C) cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ: 1.11, 1.12

(s, total 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.87 (m, 1 H), 1.88 (br s, 3 H, CH_3-C=C), 2.24 - 2.41 (m, 1 H), 2.65 (m, 1 H), 2.87 (m, 1 H), 3.19, 3.20 (s, total 3 H, OCH_3), 5.02 (m, 2 H, CH-O), 5.64 (s, 1 H, H-C=C), 6.22, 6.34, 6.42, 6.64. 6.68 (m, total 4 H, cyclopentadienyl H). Low resolution mass spectrum found 262 ($C_{16}H_{22}O_3$, M^+), 230 ($C_{15}H_{18}O_2$, M^+-MeOH).

(1S, 2R, 5R, 6R, 8R, 9S, 12R) 1, 7, 7 - Trimethyl - 6 - methoxy - 4 - oxatetracyclo [7. 3. 1. $0^{2,9}$. $0^{8,12}$] tridec -10- en - 3 - one (138)

Cyclopentadiene **137** (0.1378 g, 0.6 mmol) and hydroquinone (5 mg) were dissolved in anhydrous toluene (10 mL). The solution was placed in a Pyrex pressure tube and flushed with nitrogen for 2 hours and sealed. The pressure tube was placed in a microwave oven (Toshiba ERS-6630C) and surrounded with damp vermiculite. The power level was set to 500 watts and the reaction was conducted for an hour. After cooling to room temperature, the pressure tube was opened and concentrated. The residue was purified by flash chromatography (10 % ethyl acetate / petroleum ether) to give the Diels-Alder adduct **138** (0.1335 g, 97 %) as a colorless liquid; IR (film): 1725 (C=O), 1575 (C=C) cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ: 0.95 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.82 - 2.19 (m, overlap 4 H), 2.53 (s, 1 H, CH_2-C=C), 2.72 (s, 1 H, bridge head CH_2), 3.11 (s, 4 H, OCH_3, one H-C-O hidden), 4.62 (s, 1 H, H-C-O), 6.44 (m, 1 H, H-C=C), 6.32 (m, 1 H, H-C=C); ^{13}C nmr ($CDCl_3$) δ: 174.9, 138.7, 136.5, 76.3, 74.2, 58.5, 56.3, 52.9, 51.0, 49.9, 48.5, 41.5, 40.4, 24.6, 23.6, 23.0; DEPT ($CDCl_3$) δ: 138.7 (CH), 136.5 (CH), 76.3 (CH), 58.5 (CH), 52.9 (CH), 51.0 (CH), 49.9 (CH), 48.5 (CH_3), 41.5 (CH_2), 24.6 (CH_3), 23.6 (CH_3), 23.0 (CH_3). *Exact mass* calcd. for $C_{15}H_{18}O_2$ (M^+-CH_3OH): 230.1302; found: 230.1321. Low resolution mass spectrum found 262 ($C_{16}H_{22}O_3$, M^+).

(1R, 2R, 4R, 5R, 7S, 8R, 9S) 5 - Hydroxy - 8 - hydroxymethyl - 4 - methoxy - 3, 3, 7 - trimethyltricyclo [5. 4. $0^{1,7}$. $0^{2,9}$] undecane (143)

Tetracyclic lactone **138** (0.0792 g, 0.3 mmol) was dissolved in ethyl acetate (10 mL) and a catalytic amount (ca. 10 mg) of 5 % Pd / activated carbon was suspended in the solution. Hydrogenation was conducted in a Parr apparatus under hydrogen (30 psi) for 4 h at room temperature. The resulting mixture was filtered through a band of Celite and the filtrate was concentrated to give a pale yellow liquid. This crude product was checked by nmr to make sure the double bond was completely hydrogenated, and used directly for the next step.

The hydrogenated lactone was dissolved in anhydrous ether (5 mL) and cooled to 0°C with an external ice / water bath. Lithium aluminum hydride (50 mg, Aldrich) was added to the cold solution and the reaction was allowed to warm to room temperature. After stirring for 4 h at room temperature, the reaction was cooled to 0°C and quenched with cold water. The mixture was filtered and the filtrate was extracted with ether (2 × 10 mL). The combined organic layers were washed with brine, dried, filtered, and concentrated. Flash chromatography (40% ethyl acetate / petroleum ether) yielded 0.0652 g (92% from **138**) of the diol **143** as a colorless liquid; IR (film): 3460 (OH) cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ: 0.94 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3), 1.19 - 1.85 (m, 9 H, CH_2, CH), 2.10 (br. s, 2 H, OH), 3.18 (s, 3 H, OCH_3), 3.73 (m, 2 H, CH_2-O), 3.95 (m, 1 H, CH-O), 4.60 (s, 1 H, CH-O); ^{13}C nmr (200 MHz, $CDCl_3$) δ: 81.3, 66.1, 63.2, 55.6, 49.2, 48.7, 48.1, 45.7, 44.9, 42.3, 39.7, 31.5, 25.8, 22.9, 21.6, 17.6. Low resolution mass spectrum found 236 (M^+-CH_3OH), 218 (236 - H_2O), these peaks were too weak for a high resolution mass spectrum.

(1R, 2R, 4R, 5R, 7S, 8R, 9S) 8 - Acetoxymethyl - 5 - hydroxy - 4 - methoxy - 3, 3, 7 - trimethyltricyclo [5. 4. 0 ^{1,7}. 0 ^{2,9}] undecane (144)

Diol **143** (0.4820 g, 1.8 mmol) was dissolved in anhydrous ether (5 mL) and cooled to 0°C with an external ice-water bath. To the solution was added pyridine (0.3 mL), followed by acetic anhydride (0.2 mL, 2.0 mmol, Aldrich). The reaction solution was stirred for 6 h at 0°C, diluted with ether (20 mL), and then quenched with cold water. The mixture was separated and the aqueous layer was re-extracted with ether (15 mL). The combined organic extracts were washed with 5 % aqueous $NaHCO_3$ and brine, dried, filtered, and concentrated. Flash chromatography (10 % ethyl acetate / petroleum ether) afforded 0.0724 g (15 %) of recovered starting material and 0.4127 g (74 %) of the hydroxy acetate **144** as a oily liquid; IR (film): 3460 (br, OH), 1740 (C=O) cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ: 0.77 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.40 - 2.10 (overlaped m, 9 H), 2.03 (s, 3 H, CH_3-C=O), 2.25 (m, 1 H, C<u>H</u>-CH_2-O), 2.73 (br. s, 1 H, OH), 3.20 (s, 3 H, OCH_3), 4.05 - 4.20 (overlaped m, 3 H, CH_2-O and CH-O), 5.50 (dd, 1 H, J = 7.5, 10 Hz, CH-O).

(1R, 2R, 4R, 7S, 8R, 9S) 8 - Acetoxymethyl - 4 - methoxy - 3, 3, 7 - trimethyltricyclo- [5. 4. 0 ^{1,7}. 0 ^{2,9}] undecane (145)

1. Pyridine (0.16 mL, 2.0 mmol), followed by phenyl chlorothioformate (0.14 mL, 1.0 mmol) were added to a stirred anhydrous dichloromethane solution (5 mL) containing hydroxy acetate **144** (0.2016 g, 0.65 mmol) at room temperature. After the reaction was complete (TLC monitoring), the solvent was evaporated under reduced pressure. The residue was dissolved in ether (30 mL) and the ether solution was washed with 5 % aqueous $NaHCO_3$ and brine. This ether solution was dried, filtered, and concentrated. The residue was passed through a short

silica gel column with 10 % ethyl acetate / petroleum ether as elute. The chromatographed material (0.2395 g) was used directly for the radical reduction. This thiocarbonate radical precursor was stirred and refluxed in anhydrous toluene (5 mL) while a solution of tributyltin hydride (0.22 mL, 0.8 mmol) and a catalytic amount of AIBN (6 mg) in anhydrous toluene (2 mL) was added with a syringe pump at a speed of 0.5 mL / h. After the addition was complete, the reaction solution was stirred and refluxed for further 4 h, cooled to room temperature, and evaporated under reduced pressure to remove the solvent. The crude product was applied (overnight) to the top of a silica gel column (saturated with hexane), eluted first with hexane until the tin compound (with a very nasty odor) was washed out, and then eluted with 5 % ethyl acetate / petroleum ether to afford the methoxy acetate **145** (0.1356 g, 71 %) as a colorless liquid; IR (film): 1715 (C=O) cm^{-1}; ^1H nmr (200 Mhz, $CDCl_3$) δ: 0.83 (s, 3 H, CH_3), 1.05 (s, 3 H, CH_3), 1.11 (s, 3 H, CH_3), 1.10 - 1.40 (m, 8 H, CH_2), 1.56 - 2.15 (m, 4 H, CH), 2.00 (s, 3 H, CH_3C=O), 2.40 (dd, 1 H, J = 8, 10.5 Hz, CH-O), 3.14 (s, 3 H, OCH_3), 3.98 (d, 2 H, J = 8 Hz, CH_2-O); ^{13}C nmr ($CDCl_3$) δ: 171.4, 65.8, 60.0, 49.5, 48.8, 48.4, 47.4, 47.3, 45.9, 37.2, 24.5, 25.6, 24.6, 22.4, 20.8, 17.7. Low resolution mass spectrum found 294 ($C_{18}H_{30}O_3$, M^+), 262 (M^+- MeOH), these peaks were too weak for high resolution Mass spectrum.

2. Alkene acetate **150** (0.0646 g, 0.22 mmol) was dissolved in ethyl acetate (15 mL) and a catalytic amount (ca. 10 mg) of 5 % Pd / activated carbon was suspended in the solution. Hydrogenation was conducted in a Parr apparatus under H_2 (20 psi) for two hours. The resultant mixture was filtered through Celite and concentrated. The residue was purified by flash chromatography (5 % ethyl acetate / petroleum ether) to give methoxy acetate **145** (0.0627 g, 97 %) as a colorless liquid, the

spectral data were identical with those of the compound obtained by the other synthetic route.

(-) (1R, 2R, 7S, 8R, 9S) 8 - Acetoxymethyl - 3, 3, 7 - trimethyltricyclo [5. 4. 0 ^{1,7}. 0 ^{2,9}] undecane (146)

Methoxy acetate **145** (0.0650 g, 0.22 mmol) and sodium iodide (0.045 g, 0.30 mmol) were mixed in anhydrous dichloromethane (5 mL). Triethylamine (56 µL, 0.40 mmol) was added to this solution , followed by chlorotrimethysilane (38 µL, 0.30 mmol, Aldrich), forming a yellow solution. After stirring for an hour, the reaction was stopped by adding saturated aqueous NH_4Cl. The mixture was extracted with dichloromethane (2 × 20 mL) and the extracts were combined, washed with 10 % aqueous sodium thiosulfate (to remove iodine) and brine, dried, and concentrated to give a pale yellow liquid.

The resulting crude alcohol product was dissolved in anhydrous dichloromethane (2 mL) and pyridine (32 µL, 0.40 mL, Aldrich, re-distilled) was added, followed by phenyl chlorothioformate (42 µL, 0.30 mmol) in anhydrous dichloromethane (1 mL). The reaction mixture was stirred for 3 h at room temperature and then concentrated to remove solvent. The residue was dissolved in ether (20 mL) and the ether solution was washed with water (2 × 20 mL), dried, filtered, and concentrated. The residue was passed through a short silica column to give the crude thiocarbonate product for direct use in the radical reaction.

To a stirring, refluxing solution of thiocarbonate in anhydrous toluene (2 mL) was added a solution of tributyltin hydride (54 µL, 0.2 mmol) and AIBN (5 mg) in anhydrous toluene (2 mL) by syringe pump at a speed of 0.5 mL / h. After the addition was complete, the reaction solution was stirred and refluxed for

a further five hours, cooled to room temperature, and concentrated. The crude product was applied (overnight) to the top of a silica gel column (saturated with hexane), eluted first with hexane until the tin compounds (nasty odor) were washed out, and then eluted with 5 % ethyl acetate / petroleum ether to afford the acetate **146** (0.0291 g, 50 % from **145**) as a colorless liquid; $[\alpha]^{22} = -11.8°$ (c 3.7, $CHCl_3$); IR (film): 1745 (C=O), 1240 (C-O) cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ: 0.88 (s, 3 H, CH_3), 0.94 (s, 3 H, CH_3), 1.00 - 1.65 (m, 13 H, CH_2 and CH), 1.95 (m, 1 H, C<u>H</u>-CH_2-O), 2.00 (s, 3 H, CH_3C=O), 4.19 (d, 2 H, J = 7.9 Hz, CH_2-O); ^{13}C nmr ($CDCl_3$) δ: 171.1, 66.2, 64.3, 54.8, 44.9, 44.5, 41.3, 38.9, 36.6, 33.5, 32.7, 32.1, 31.7, 30.8, 24.6, 20.9, 20.8. *Exact mass* calcd. for $C_{15}H_{24}$ (M^+-AcOH): 204.1872; found: 204.1884. Low resolution mass spectrum found 264 (M^+).

(+) Longifolene (3)

A pyrolysis apparatus was assembled as shown in **Figure 8**. The quartz tubing filled with quartz-wool was preheated to 525°C under a flow of nitrogen. A solution of acetate **146** (0.0261 g, 0.0984 mmol) in anhydrous benzene (2 mL) was added dropwise in order to pass through the hot quartz tubing at a rate that permitted the hot vapor to condense completely in the cold (-78°C) receiving flask. To prevent the acetic acid formed in pyrolysis from interfering with the product a small amount of solid $NaHCO_3$ was placed in the receiving flask. After the reaction solution was pyrolyzed, additional anhydrous benzene (3 mL) was added in the same manner to wash the quartz-wool. The apparatus was cooled to room temperature under nitrogen. Then the cold receiving flask was removed from the apparatus and warmed to room temperature. Ether (15 mL) was added and the ether solution was transferred to a separatory funnel by filtration. Th ether

solution was washed with saturated aqueous NH_4Cl (15 mL), dried, filtered, and concentrated. The yellow residue was purified by flash chromatography (petroleum ether) to yield 0.0110 g (55 %) of (+)-longifolene as a colorless liquid; $[\alpha]^{22}$= + 47.0° (c 1.7, $CHCl_3$), (authentic commercial sample $[\alpha]^{22}$= + 51.2°, c 1.9, $CHCl_3$); IR (film): 1658 (C=C) cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ: 0.88 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3), 1.10 (m, 1 H), 1.35 - 1.70 (m, 10 H), 2.04 (d, 1 H, J = 4 Hz), 2.58 (d, 1 H, J = 5 Hz, CH-C=C), 4.45 (s, 1 H, H-C=C), 4.71 (s, 1 H, H-C=C ; ^{13}C nmr (300 MHz, $CDCl_3$) δ: 168.0, 99.0, 62.0, 47.7, 44.9, 43.8, 43.2, 36.2, 33.4, 30.4, 30.3, 29.9, 29.5, 25.3, 20.9; DEPT (300 MHz, $CDCl_3$) δ: 99.0 (CH_2), 62.0 (CH), 47.7 (CH), 44.9 (CH), 43.2 (CH_2), 36.2 (CH_2), 30.4 (CH_3), 30.3 (CH_3), 29.9 (CH_3), 29.5 (CH_2), 25.2 (CH_2), 20.9 (CH_2). *Exact mass* calcd. for $C_{15}H_{24}$: 204.1872; found: 204.1870.

(1R, 2R, 4R, 5R, 7S, 8R, 9S) 5 - Hydroxy - 8 - hydroxymethyl - 4 - methoxy - 3, 3, 7 - trimethyltricyclo [5. 4. $0^{1,7}$. $0^{2,9}$) - 10 - undecene (147)

Tetracyclic lactone **138** (0.1574 g, 0.6 mmol) was dissolved in anhydrous ether (5 mL) and cooled to 0°C with an external ice-water bath. $LiAlH_4$ (100 mg, excess) was added in several small portions and the resulting suspension was allowed to warm slowly to room temperature. The suspension was stirred with monitoring by TLC until the reaction was complete. The reaction mixture was then cooled to 0°C, diluted with ether (15 mL), and quenched with cold water to destroy the excess $LiAlH_4$. The resulting mixture was filtered, and the filtrate was separated. The aqueous layer was re-extracted with ether (2 × 15 mL), the organic phases were combined, washed with saturated aqueous NH_4Cl, dried, filtered, and concentrated to give a very pure diol **147**, which was used directly for further synthetic work. IR (film): 3410 (br, OH), 3060 (H-C=C), 1585 (C=C), cm^{-1};

^{1}H nmr (200 MHz, $CDCl_3$) δ: 0.94 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3), 1.28 (t, 1 H, J = 8 Hz, CH), 1.43 (br s, 1 H, OH), 1.66 - 1.73 (m, 2 H, CH_2), 1.89 (br s, 1 H, OH), 1.96 (d, 1 H, J = 9.5 Hz, CH), 2.29 (br s, 1 H, CH-C=C), 2.39 (br. s, 1 H, CH-C=C), 3.19 (s, 3 H, OCH_3), 3.77 - 4.10 (overlap m, 3 H, CH_2-O and CH-O), 4.56 (s, 1 H, H-C-O), 5.93 (m, 1 H, H-C=C), 6.31 (m, 1 H, H-C=C); ^{13}C nmr ($CDCl_3$) δ: 140.6, 132.8, 66.9, 62.3, 58.4, 53.2, 50.8, 50.4, 49.5, 48.6, 40.0, 38.5, 37.0, 28.4, 22.8, 17.4. Low resolution mass spectrum found 248 ($C_{16}H_{24}O_2$, M^+- H_2O).

(1R, 2R, 4R, 5R, 7S, 8R, 9S) 8 - Acetoxymethyl - 5 - hydroxy - 4 - methoxy - 3, 3, 7 - trimethytricyclo [5. 4. 0 ^{1,7}. 0 ^{2,9}] - 10 - undecene (148)

Diol **147** (0.3052 g, 1.15 mmol) was dissolved in anhydrous ether (5 mL) and cooled to 0°C with an external ice / water bath. Pyridine (0.2 mL) was added to this solution, followed by acetic anhydride (0.2 mL, 2.0 mmol, Aldrich). The reaction solution was stirred overnight at 0°C, diluted with ether (20 mL), and then quenched with cold water. The mixture was separated and the aqueous layer was extracted with ether (15 mL). The combined organic extracts were washed with 5 % aqueous $NaHCO_3$ and brine, dried, filtered, and concentrated. The crude product was purified by flash chromatography (10 % ethyl acetate / petroleum ether) to afford 0.2610 g (74 %) of acetate **161** and 0.0772 g (15 %) of the diacetate. Subsequently, the latter material was treated with $LiALH_4$ to recover the starting material. Acetate **148**; IR (film): 3460 (OH), 1740 (C=O), 1560 (C=C) cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$) δ: 0.72 (s, 3 H, CH_3), 1.05 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 1.48 (m, 1 H, CH), 1.60 - 2.10 (overlaped m, 3 H), 2.05 (s, 3 H, CH_3-C=O), 2.25 (m, 1 H, CH-C=C), 2.72 (m, 1 H, CH-C=C), 3.08 (br s, 1 H, OH), 3.25 (s, 3 H, OCH_3), 3.35 (d, 1 H, J = 7.5 Hz, CH-O), 4.25 (overlape d, 2

H, CH_2-O), 5.52 (m, 1 H, C<u>H</u>-OH), 5.88 (m, 1 H, H-C=C), 6.42 (d, J = 6 Hz, H-C=C).

(1R, 2R, 4R, 5R, 7S, 8K, 9S) 8 - Acetoxymethyl - 4 - methoxy - 5 - phenoxythiocarbonyloxy - 3, 3, 7 - trimethyltricyclo [5. 4. 0 ^{1,7}. 0 ^{2,9}] - 10 - undecene (149)

Pyridine (0.16 mL, 2 mmol), followed by phenyl chlorothioformate (0.14 mL, 1 mmol, Aldrich), was added to a stirred solution of alcohol **148** (0.2016 g, 0.65 mmol) in anhydrous CH_2Cl_2 (5 mL) at room temperature. The reaction was stirred for 3 h at room temperature and then concentrated to remove the solvent. The residue was extracted with ether (30 mL), and the ether solution was washed with 5 % aqueous $NaHCO_3$ and brine, dried, filtered, and concentrated. Flash chromatography (5 % ethyl acetate / petroleum ether) gave recovered starting material (0.0413 g, 20.5 %) and the thiocarbonate **149** (0.1936 g, 67 %); IR (film): 1745 (C=O), 1595 (C=C), 1490 (phenyl) cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$) δ: 0.77 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.54 (m, 2 H, CH_2), 1.70 - 2.00 (overlaped m, 4 H), 2.04 (s, 3 H, CH_3-C=O), 2.33 (d, 1 H, J = 7.5 Hz, CH-C=C), 2.54 (m, 1 H, CH-C=C), 2.79 (br s, 1 H, CH-O), 3.20 (s, 3 H, OCH_3), 4.28 (dd, 2 H, J = 3.6, 7.1 Hz, CH_2-O), 5.94 (dd, 1 H, J = 2.3, 5.5 Hz, H-C=C), 6.07 (dd, 1 H, J = 7.5, 10.1 Hz, CH-OC(=S)OPh), 6.35 (d, 1 H, J = 5.9 Hz, H-C=C), 7.03 (m, 1 H, phenyl H), 7.06 (m, 1 H, phenyl H), 7.25 (m, 1 H, phenyl H), 7.35 (m, 2 H, phenyl H); ^{13}C nmr ($CDCl_3$) δ: 194.1, 172.0, 153.5, 138.2, 133.1, 129.5 (2 C), 126.5, 121.9 (2 C), 90.6, 74.9, 64.3, 63.6, 58.4, 55.6, 52.3, 48.9, 48.8, 43.7, 41.1, 23.3, 22.6, 20.9, 20.1. Low resolution mass spectrum found 291 ($C_{18}H_{27}O_3$, M^+- PhOC(=S)O), 259 ($C_{17}H_{23}O_2$, M^+ - PhOC(=S)O - MeOH). These peaks were too weak for a high resolution mass spectrum.

(1R, 2R, 4R, 7S, 8R, 9S) 8 - Acetoxymethyl - 4 - methoxy- 3, 3, 7 - trimethyltricyclo [5. 4. 0 ^{1,7}. 0 ^{2,9}] - 10 - undecene (150)

A solution of tributyltin hydride (0.22 mL, 0.8 mmol, Aldrich) and AIBN (16 mg) in anhydrous toluene (2 mL) was added to a stirred, refluxing solution of phenoxythiocarbonate **149** (0.1396 g, 0.31 mmol) in anhydrous toluene (5 mL) at a rate of 0.5 mL / h with a syringe pump. After the addition was complete, the reaction solution was stirred and refluxed for a further 6 h. It was cooled to room temperature, and concentrated to remove the solvent. The residue was applied (overnight) to the top of a silica gel column (saturated with hexane), eluted first with hexane to wash out the tin compounds, and then eluted with 5 % ethyl acetate / petroleum ether to afford methoxy acetate (0.0806 g, 89 %) as a colorless liquid; IR (film): 3060 (H-C=C), 1735 (C=O), 1574 (C=C) cm^{-1}; ^{1}H nmr (200 MHz, $CDCl_3$) δ: 0.66 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 1.31 (m, 2 H, CH_2), 1.56 - 2.17 (overlaped m, 5 H), 2.00 (s, 3 H, CH_3-C=O), 2.52 (m, 1 H, CH-C=C), 2.70 (br s, 1 H, CH-C=C), 3.15 (s, 3 H, OCH_3), 4.04 (d, 2 H, J = 7.3 Hz, CH_2-O), 5.91 (dd, 1 H, J = 3, 5.7 Hz, H-C=C), 6.35 (d, 1 H, J = 5.7 Hz, H-C=C); ^{13}C nmr ($CDCl_3$) δ: 171.2, 138.9, 133.0, 75.6, 66.5, 66.4, 58.1, 50.8, 49.4, 48.7, 46.4, 43.7, 41.1, 33.7, 23.3, 23.0, 20.7, 18.9. Low resolution mass spectrum found 292 ($C_{18}H_{28}O_3$, M^+), 260 ($C_{17}H_{24}O_2$, M^+ - MeOH).

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SPECTRA

^{1}H nmr, ^{13}C nmr, IR and / or MS spectra of some key intermediates are listed here.

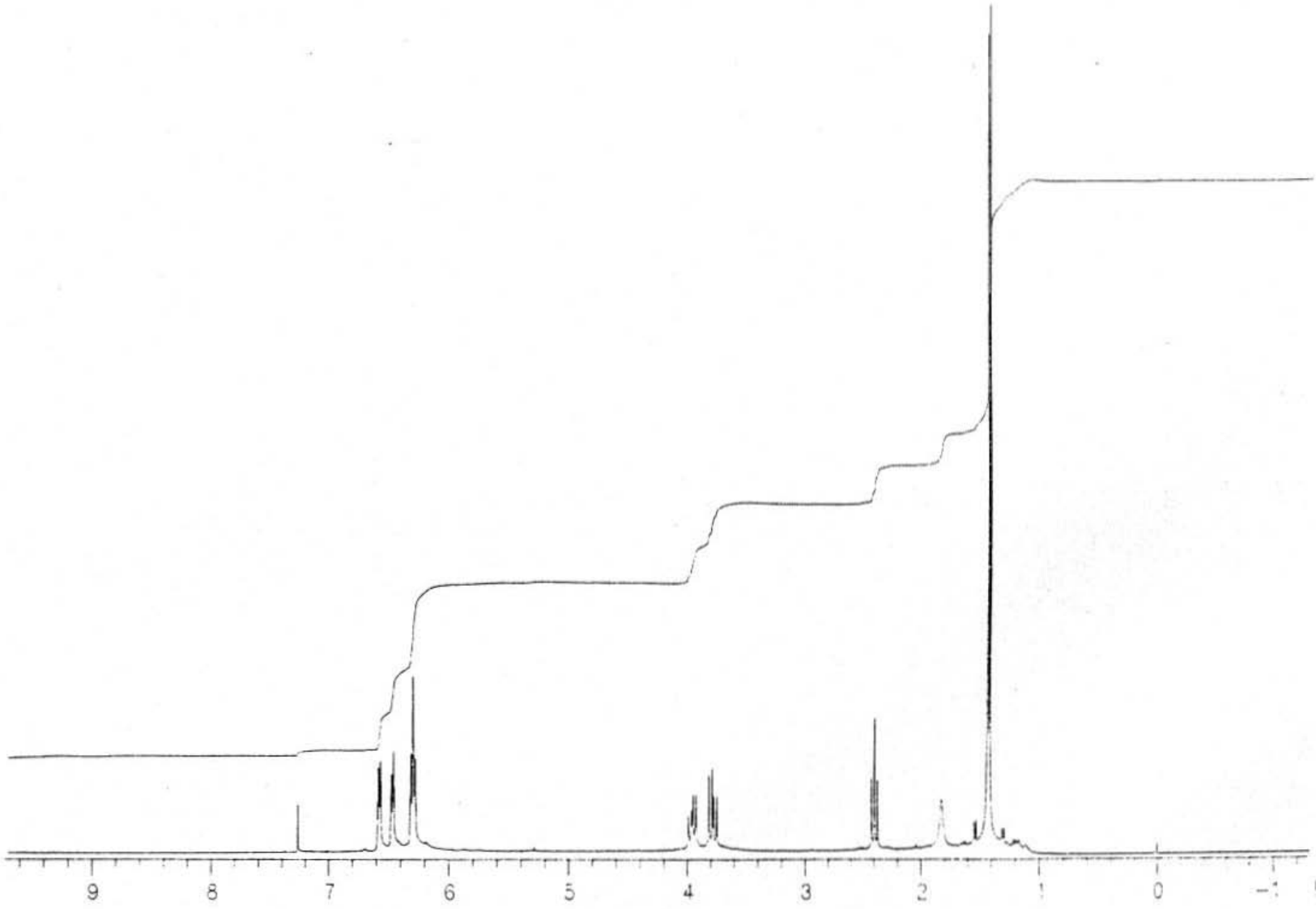

Figure 15 ^{1}H **nmr spectrum of (132)**

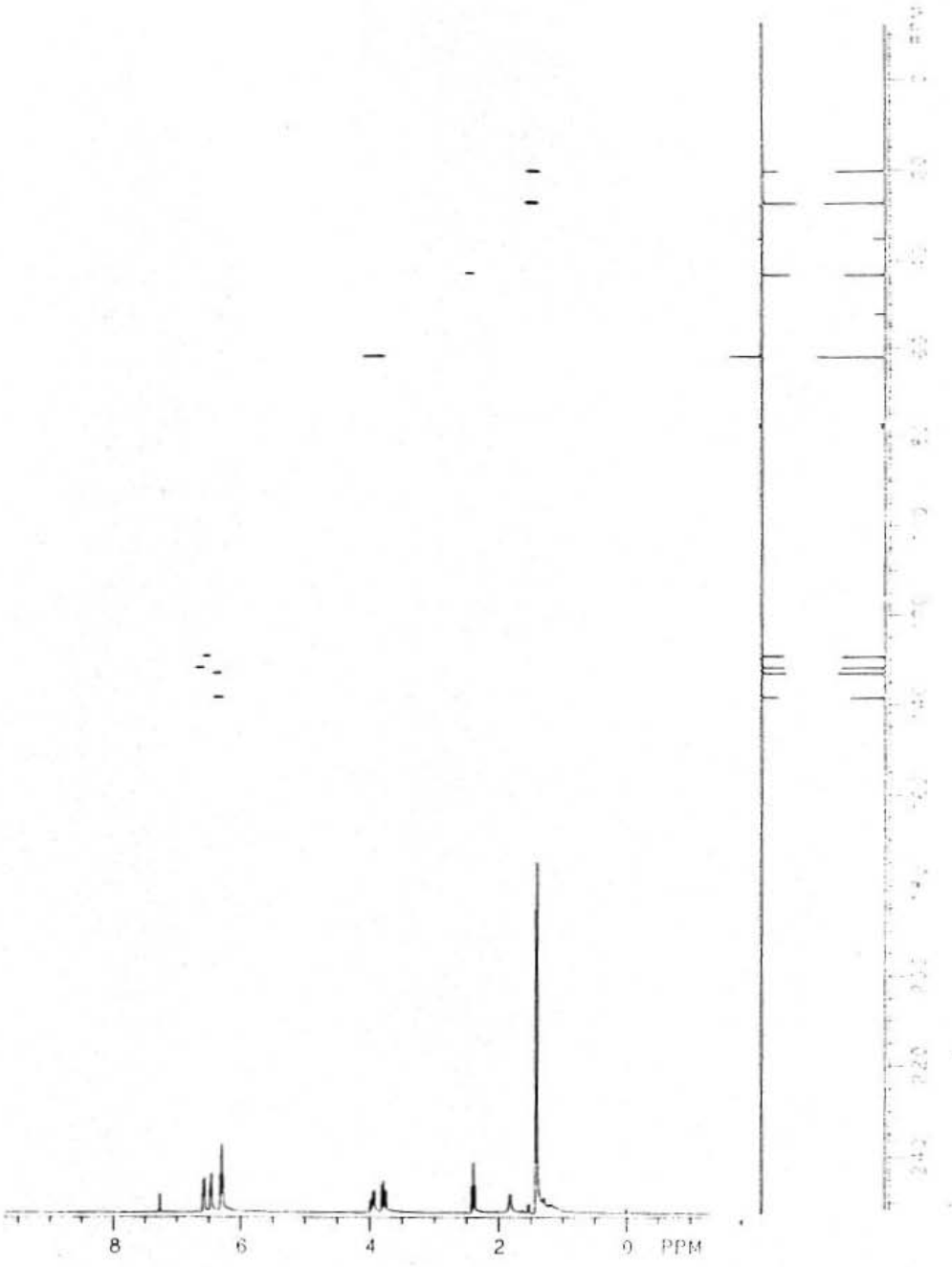

Figure 16 $^{13}C-{}^{1}H$ correlation spectrum of (132)

SPECTRAL LINES FOR TH= 10.33
RFL= 450.3 RFP= 0

INDEX	FREQ	PPM	INTENSITY
01	1915.22	9.577	25.671
02	1908.83	9.545	23.662
03	1323.57	6.619	11.779
04	1321.90	6.610	12.321
05	1320.80	6.605	11.321
06	1318.93	6.595	21.908
07	1316.69	6.584	14.087
08	1309.53	6.548	20.564
09	1307.21	6.537	23.689
10	1304.24	6.522	25.325
11	1301.84	6.510	17.927
12	1299.72	6.499	15.721
13	1238.59	6.194	10.495
14	1237.21	6.187	15.270
15	1234.36	6.173	12.089
16	1232.81	6.165	12.265
17	559.93	2.800	21.452
18	553.34	2.767	21.063
19	311.30	1.557	133.136
20	281.92	1.410	128.541

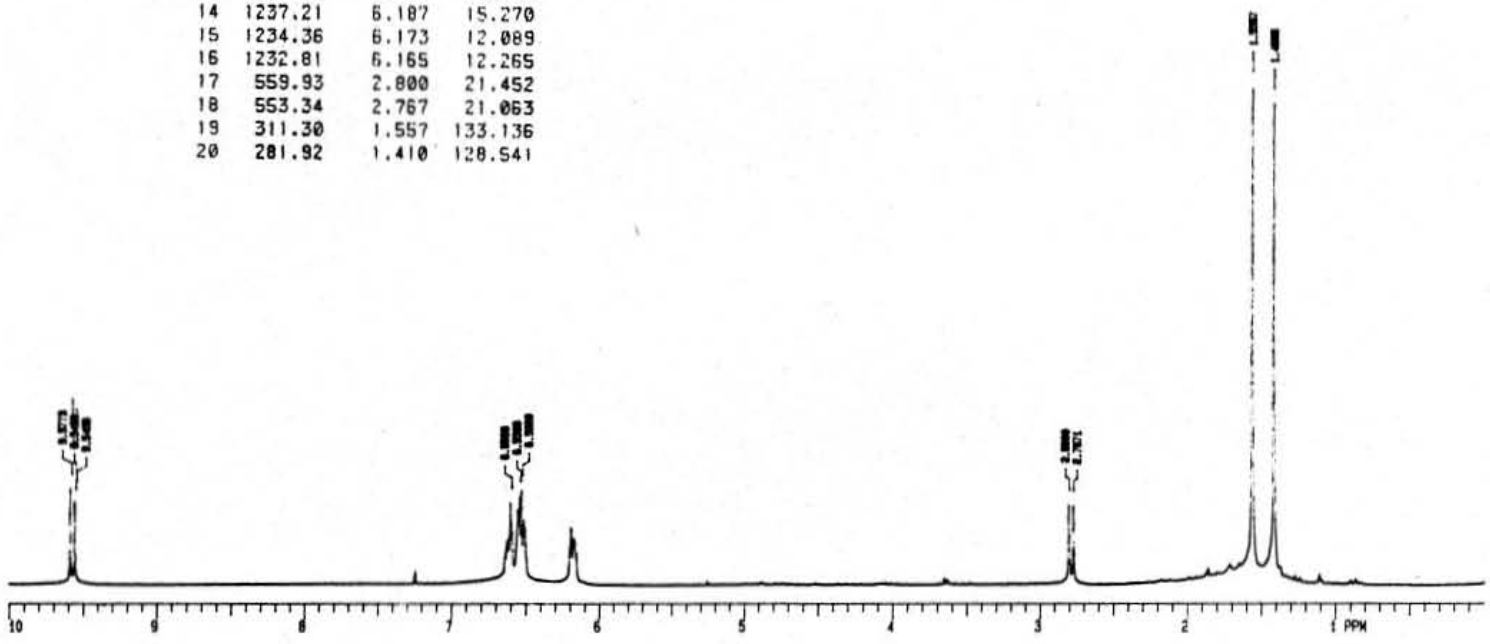

Figure 17 ^{1}H nmr spectrum of (133)

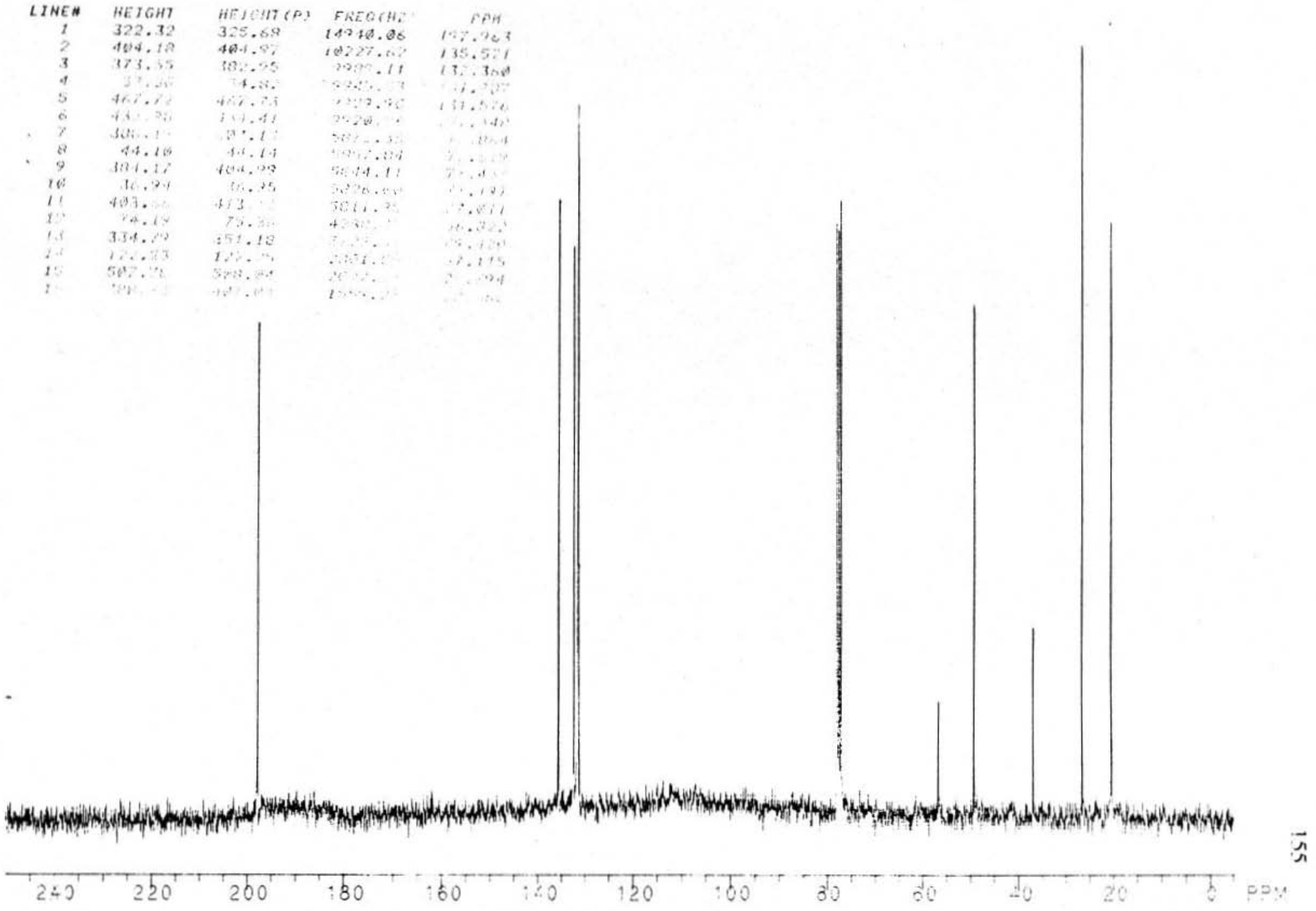

Figure 18 ^{13}C nmr spectrum of (133)

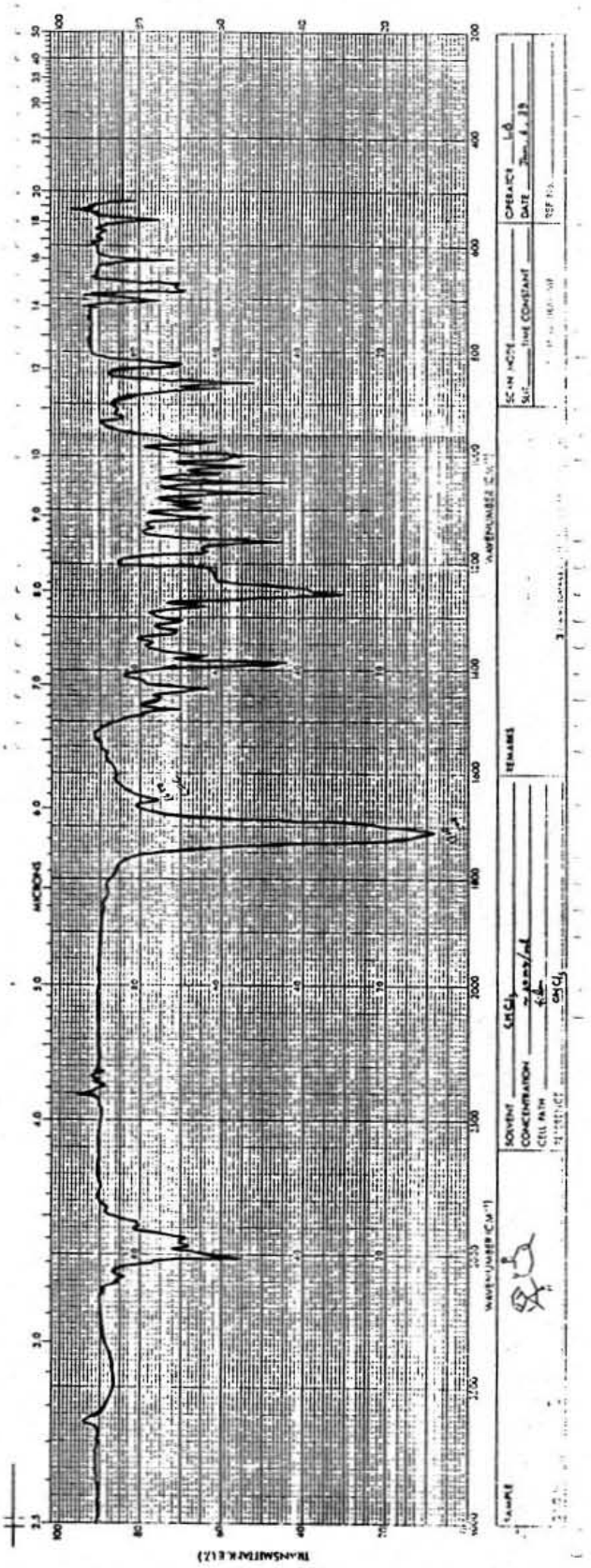

Figure 19 IR spectrum of (134)

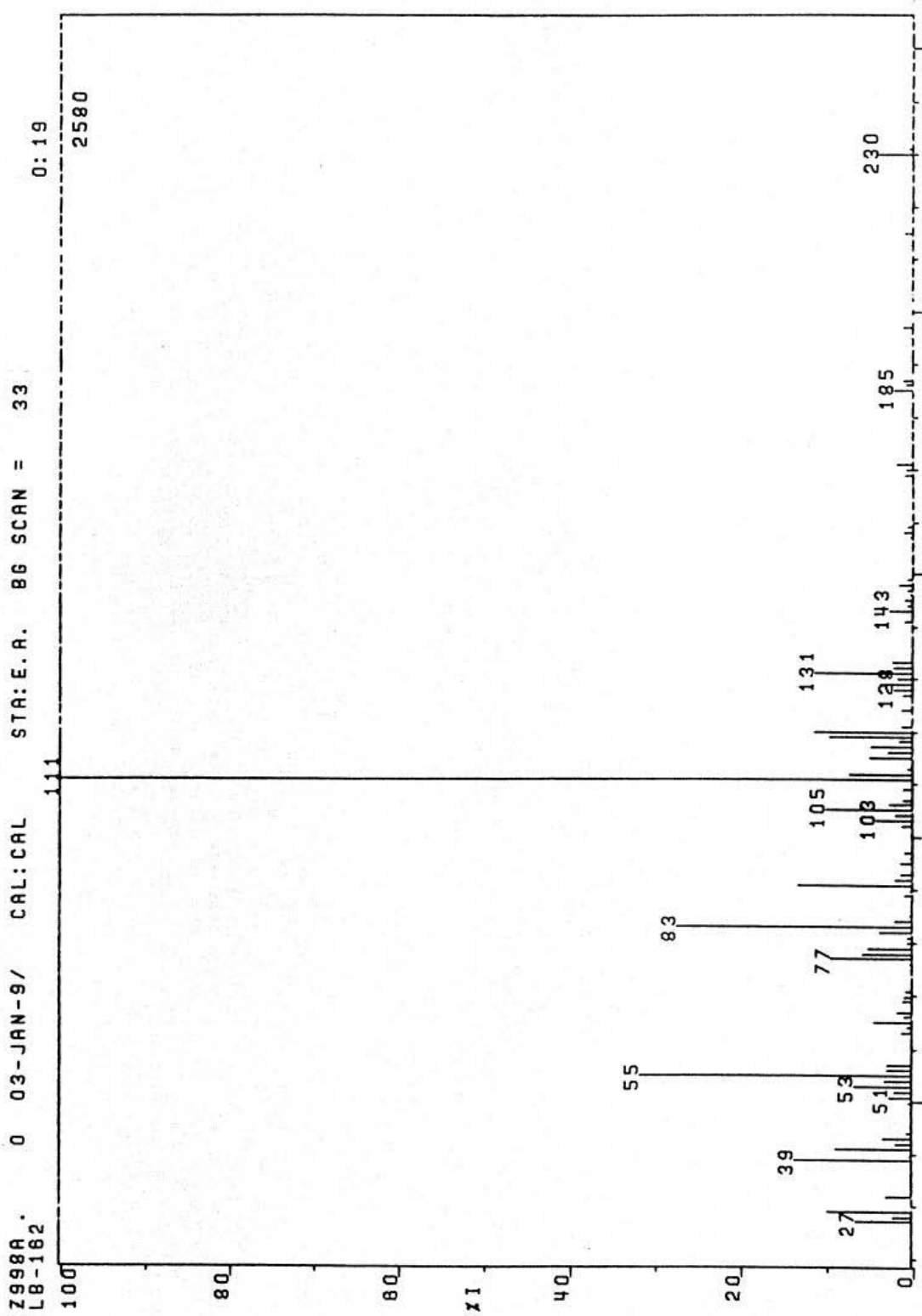

Figure 20 Mass spectrum of (**134**)

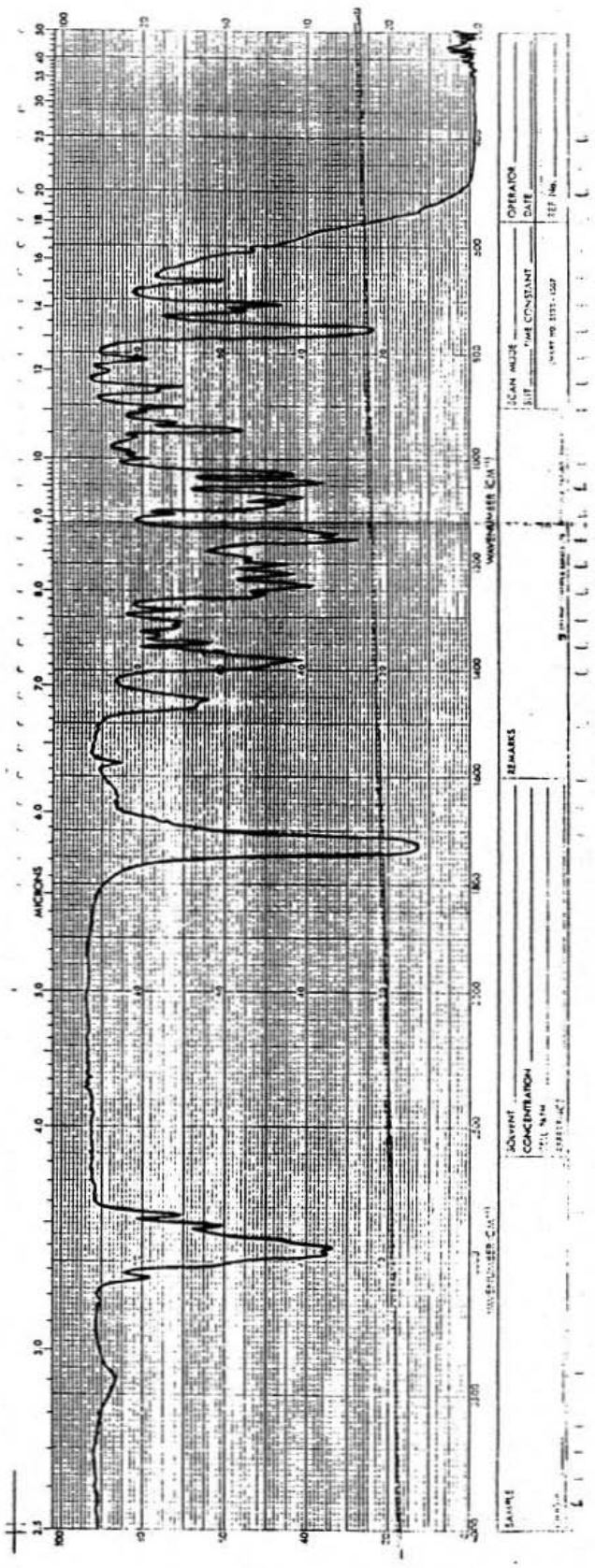

Figure 21 IR spectrum of (138)

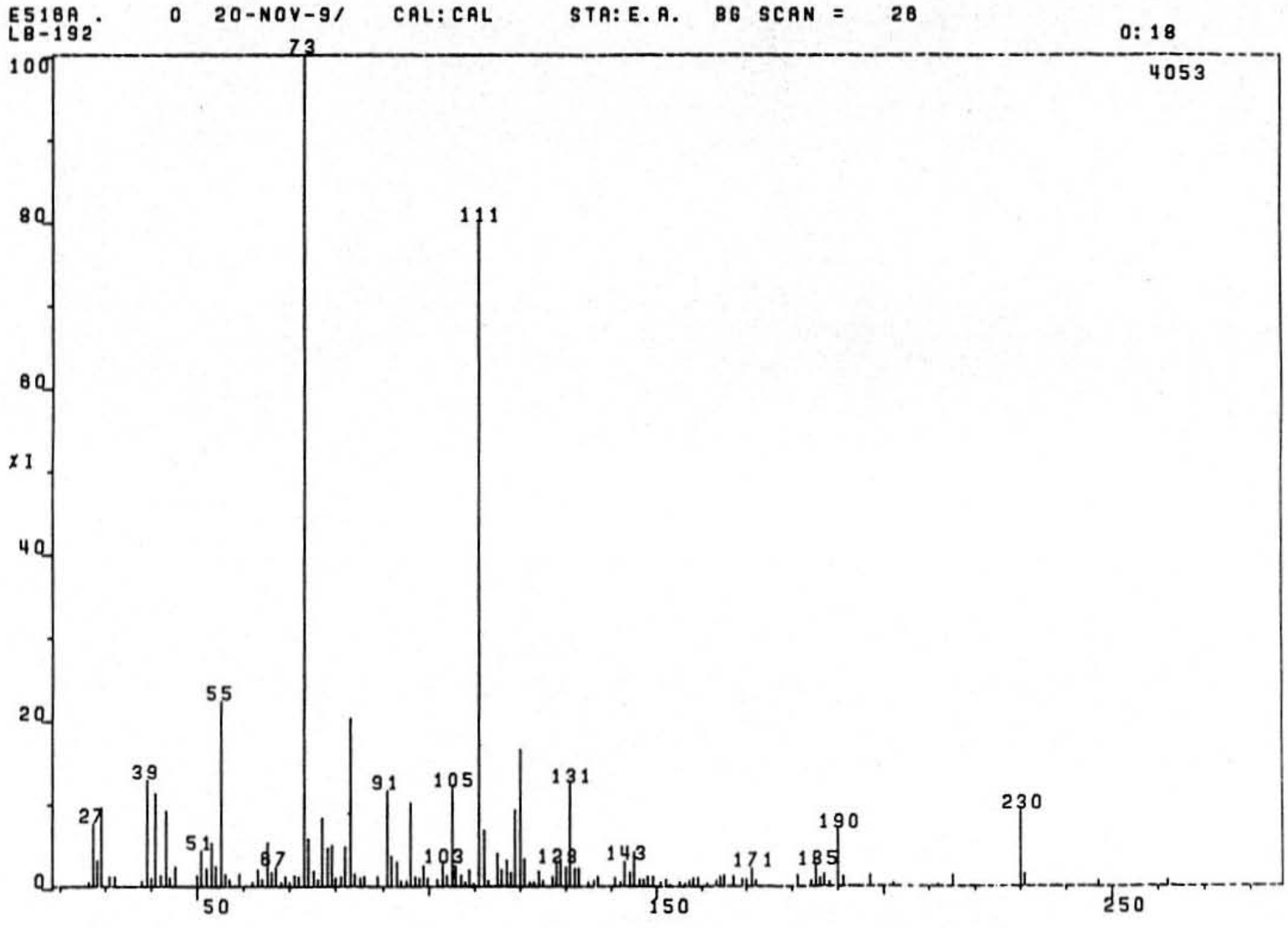

Figure 22 Mass spectrum of (138)

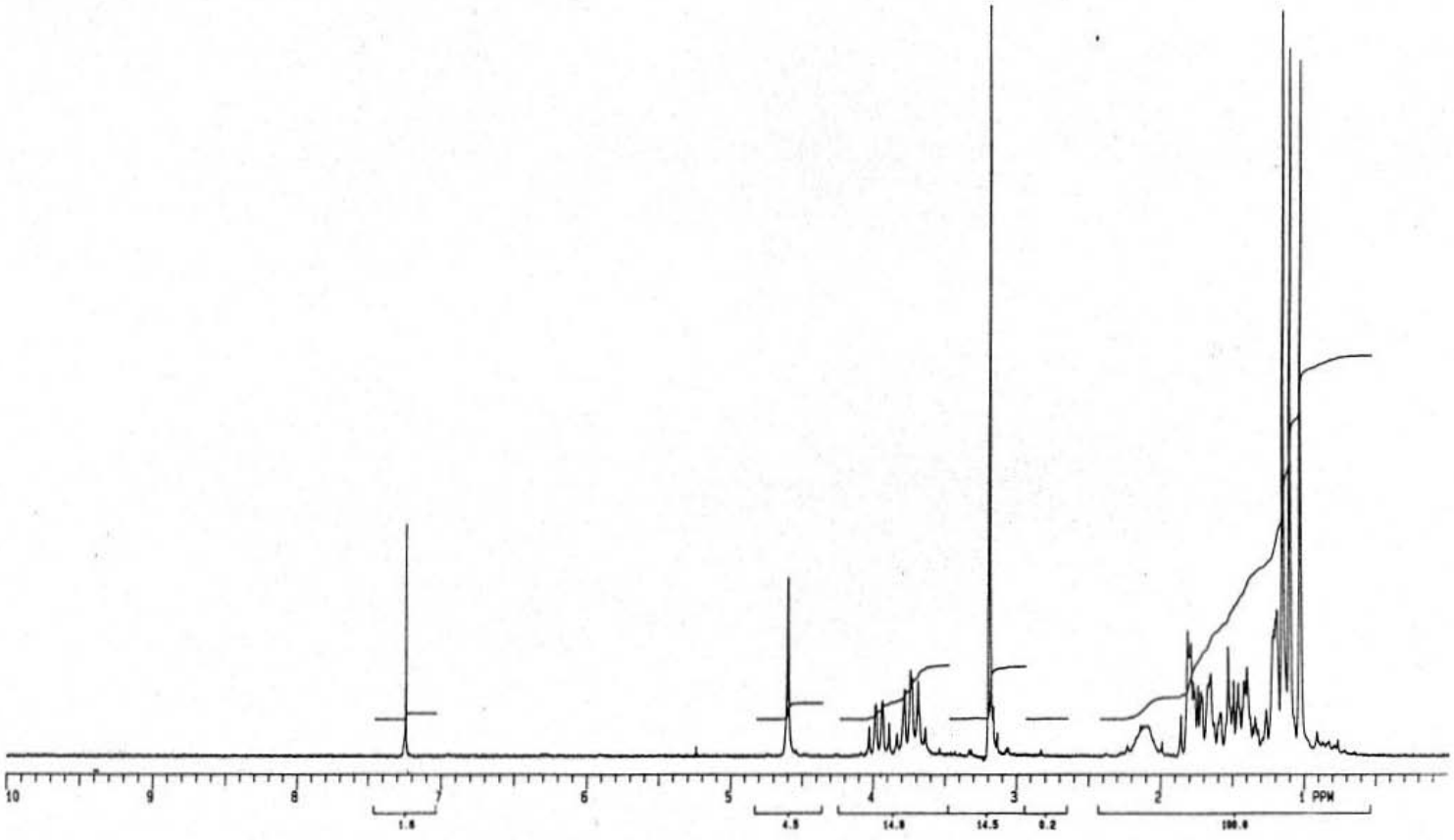

Figure 23 ^{1}H nmr spectrum of (143)

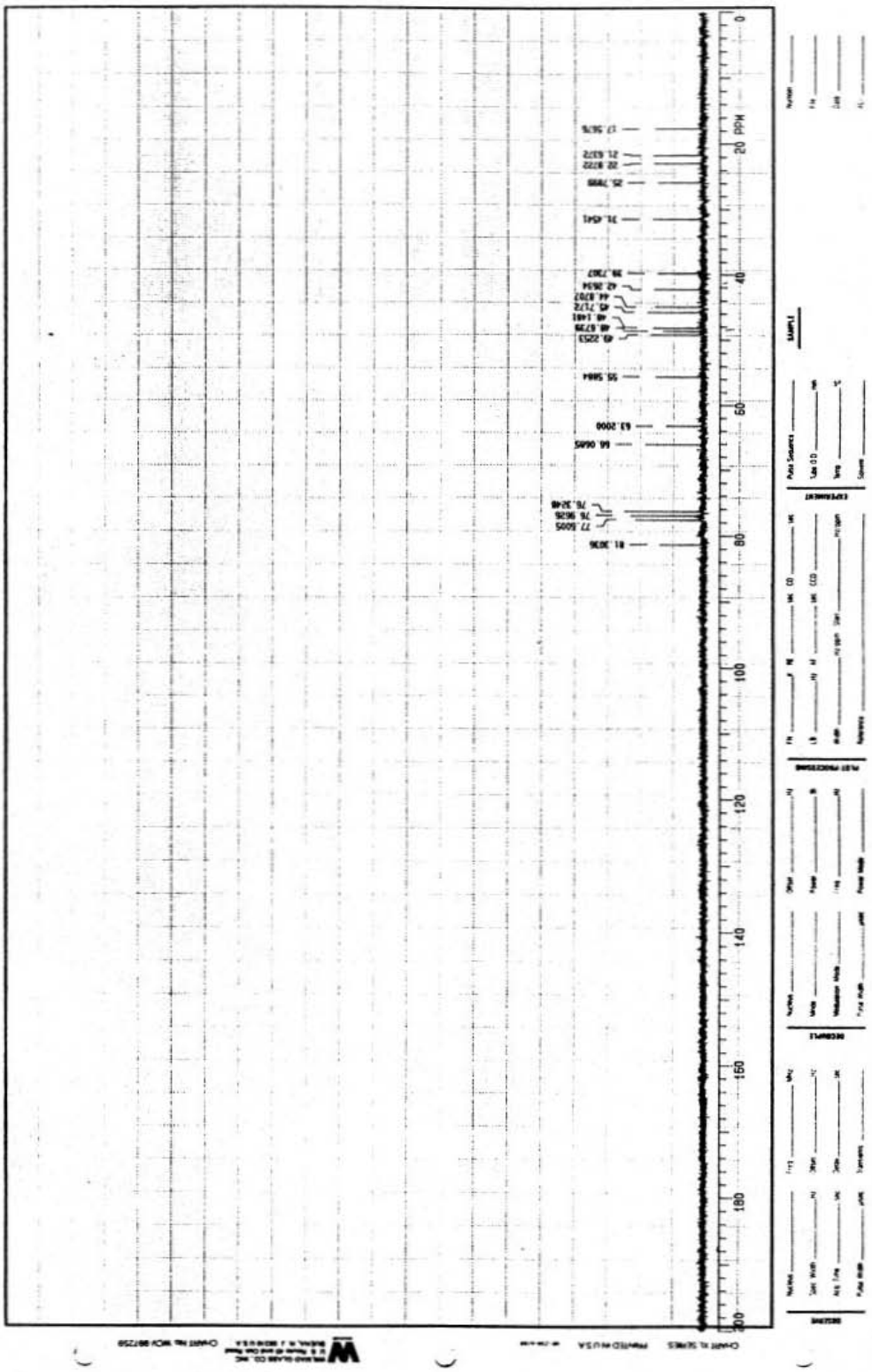

Figure 24 ^{13}C nmr spectrum of (143)

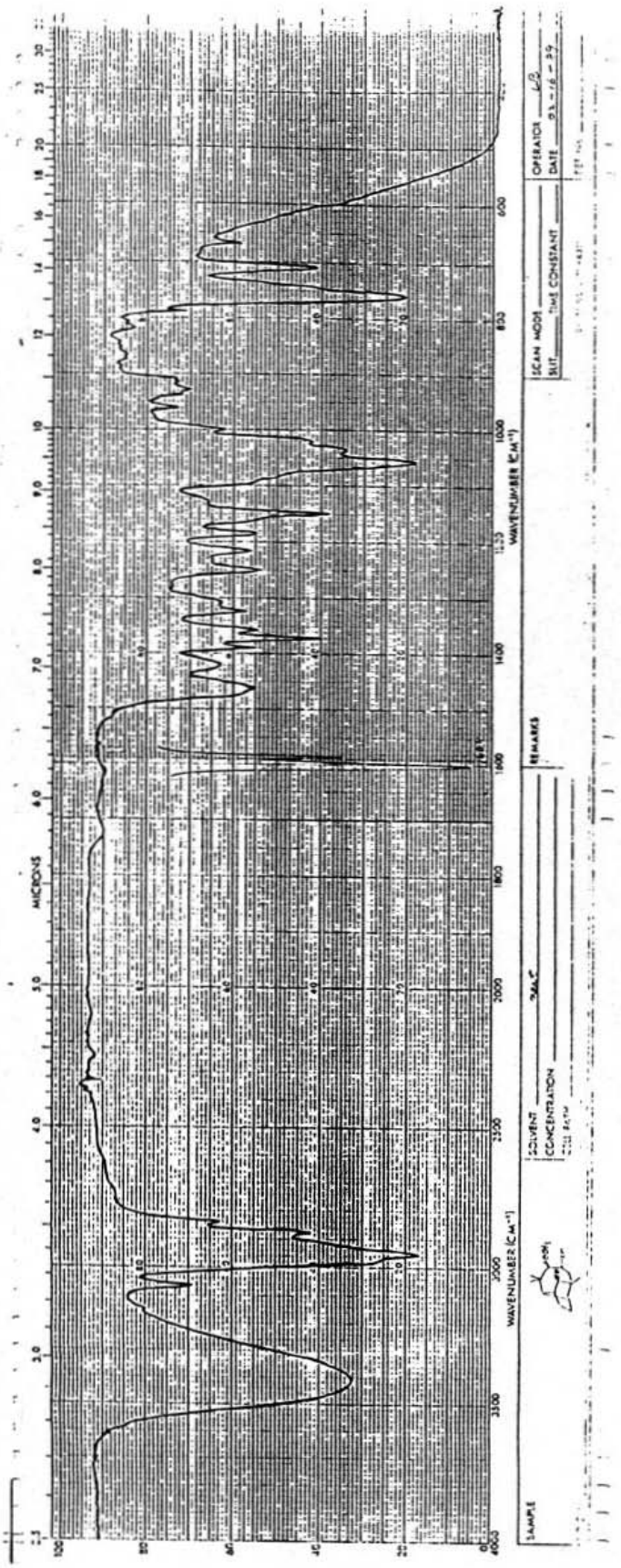

Figure 25 IR spectrum of (143)

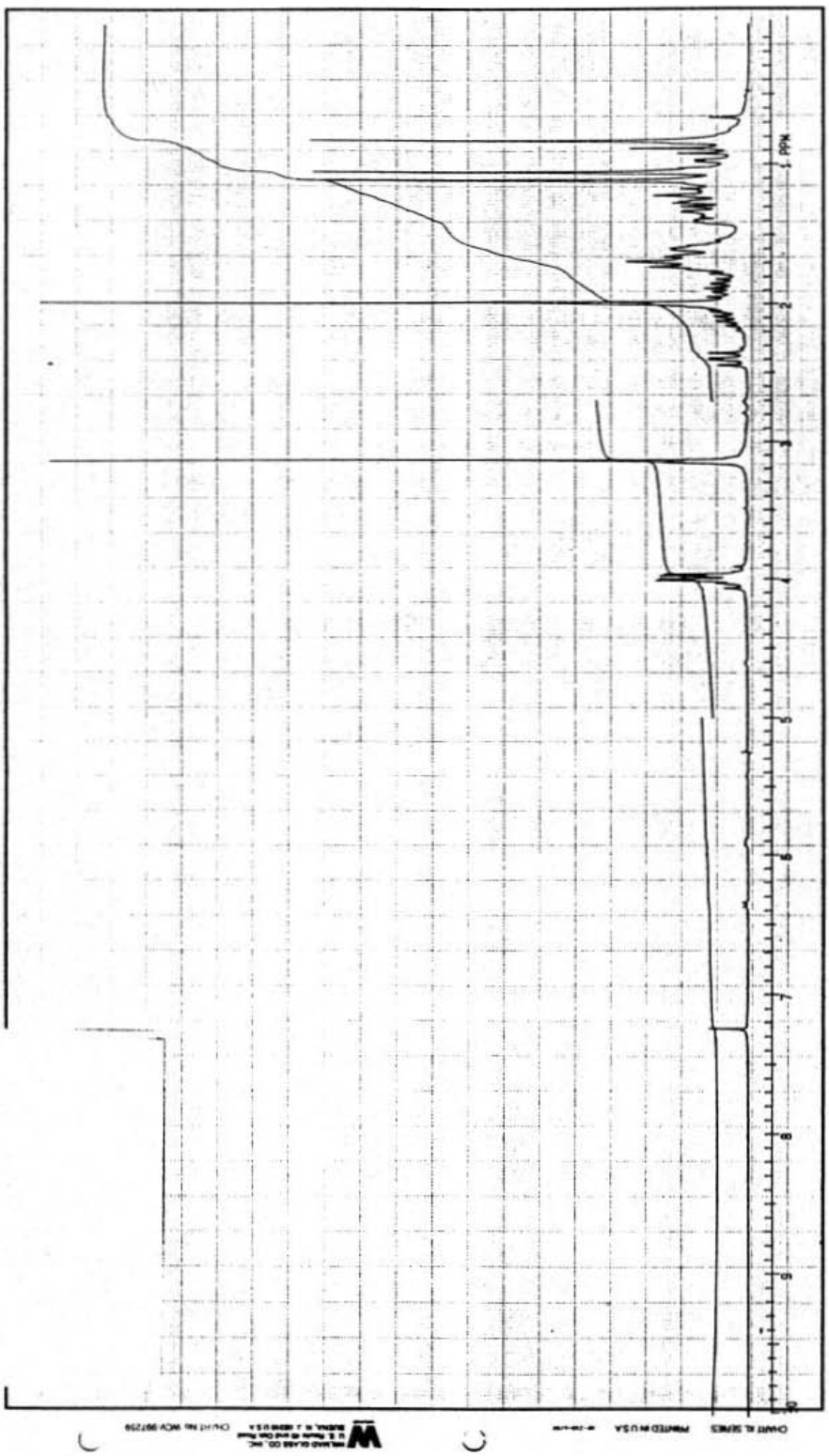

Figure 26 ^{1}H nmr spectrum of (145)

VARIAN XL-300
SPECTRAL LINES FOR TH= 13.39
RFL= 6158.2 RFP= 5808.0

INDEX	FREQ	PPM	INTENSITY
01	12899.1	171.009	26.500
02	5838.4	77.403	112.215
03	5834.3	77.348	49.551
04	5806.6	76.981	116.302
05	5774.7	76.559	120.552
06	4972.9	65.928	60.552
07	4542.0	60.215	41.186
08	3748.5	49.696	53.515
09	3699.5	49.046	46.710
10	3666.6	48.610	34.305
11	3594.3	47.651	109.174
12	3480.7	46.145	83.897
13	2826.5	37.472	83.113
14	2622.4	34.766	84.021
15	2190.0	29.033	94.732
16	1950.8	25.863	76.685
17	1877.7	24.894	72.139
18	1714.6	22.732	59.278
19	1588.6	21.061	31.162
20	1357.9	18.002	87.103

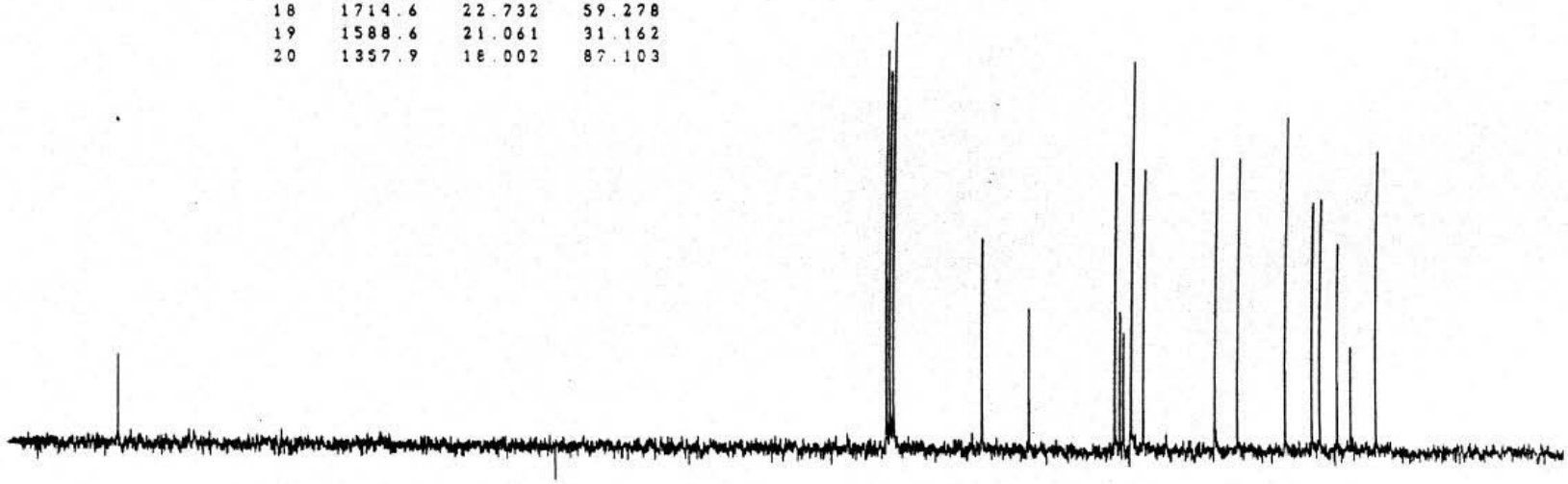

Figure 27 ^{13}C nmr spectrum of (145)

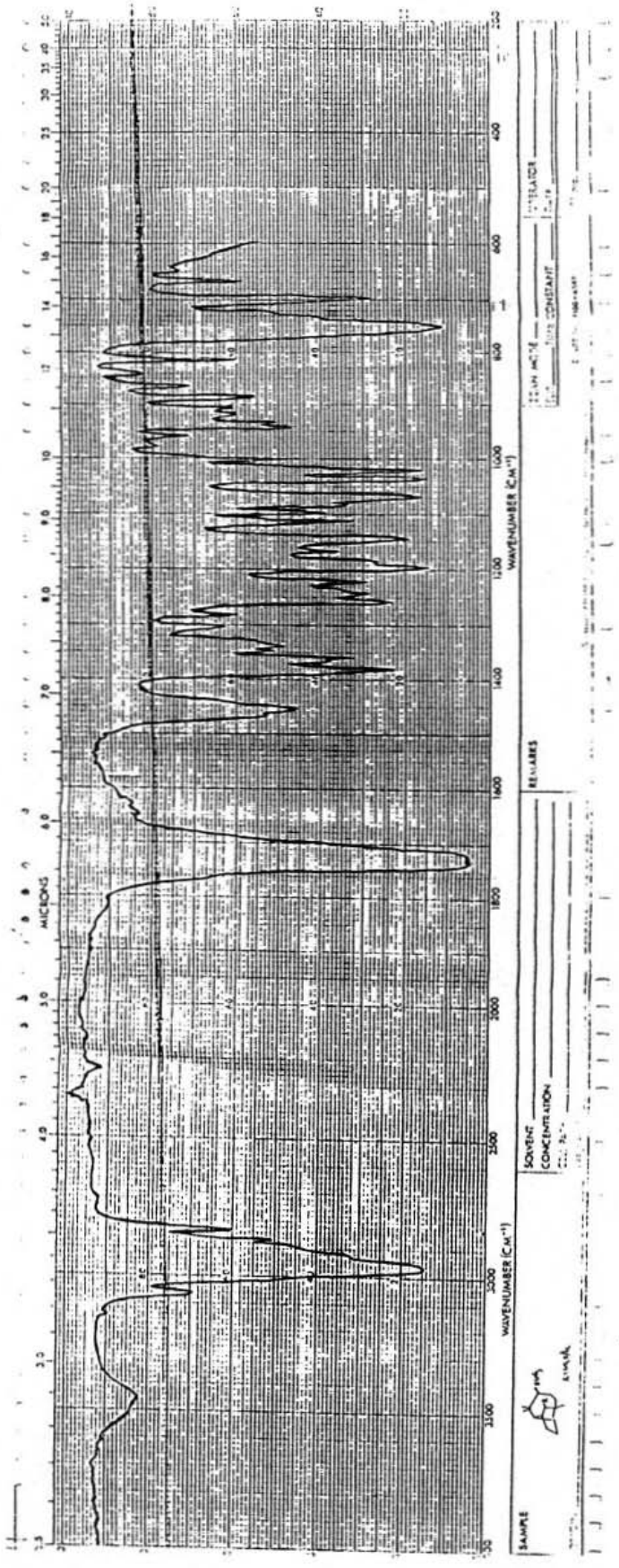

Figure 28 IR spectrum of (145)

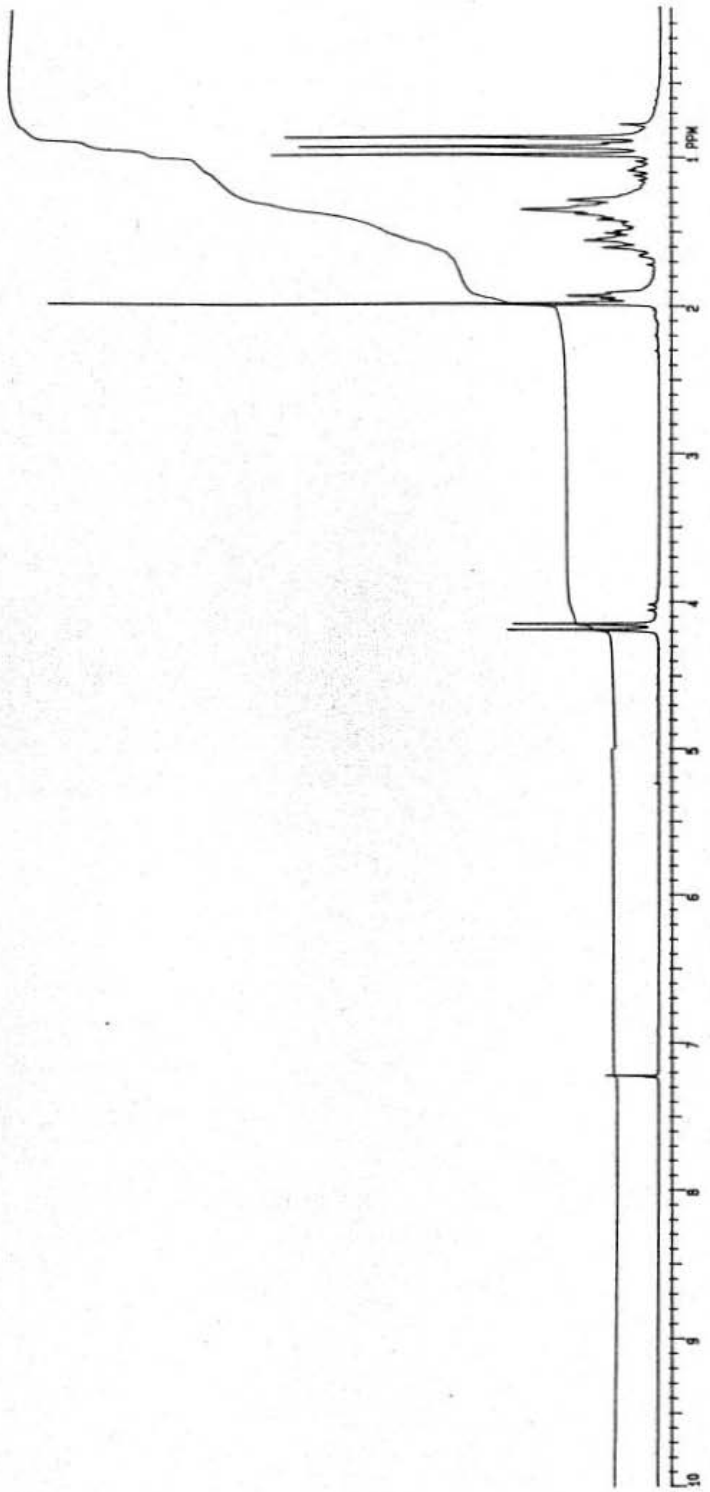

Figure 29 ^{1}H nmr spectrum of (146)

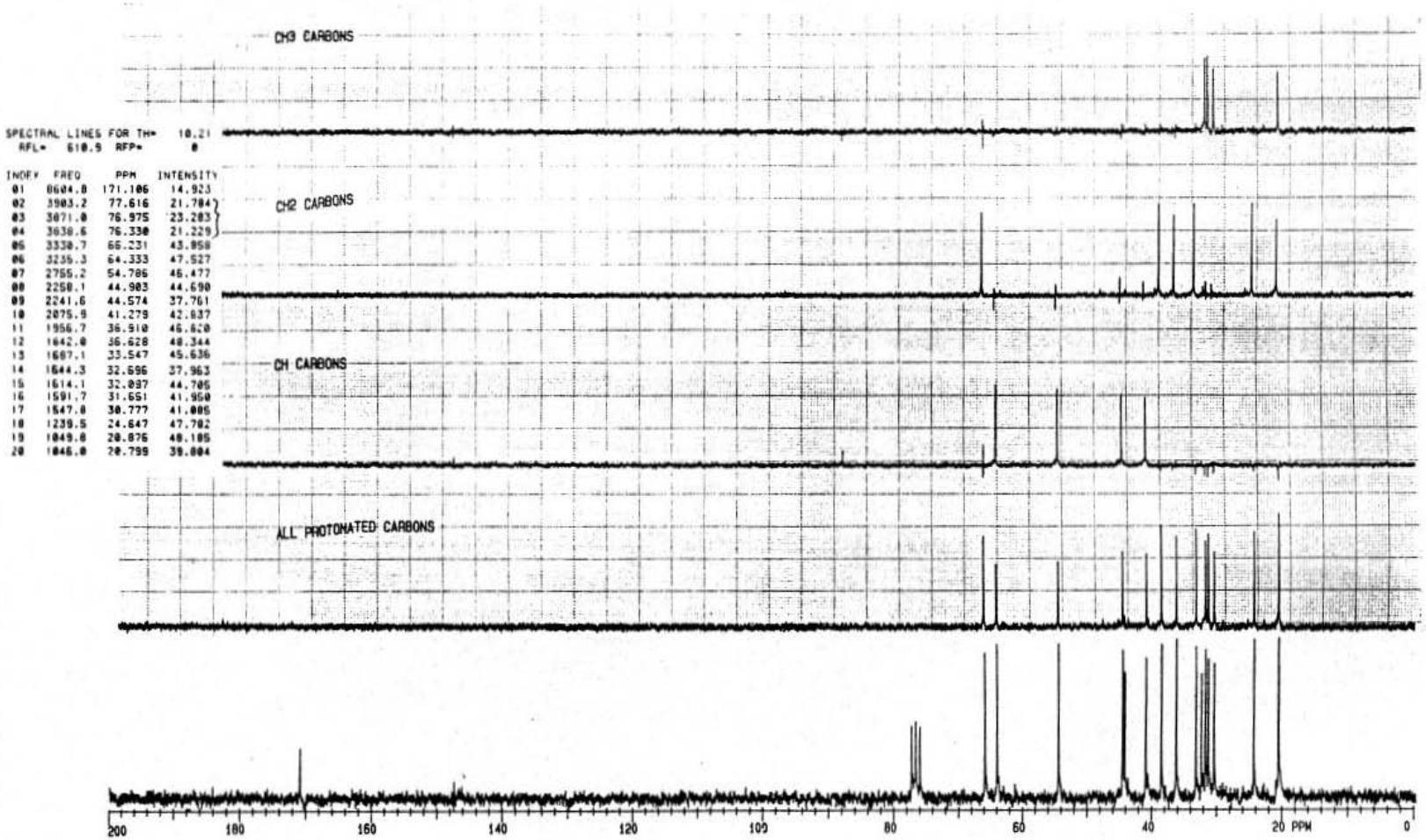

Figure 30 ^{13}C and DEPT nmr spectra of (146)

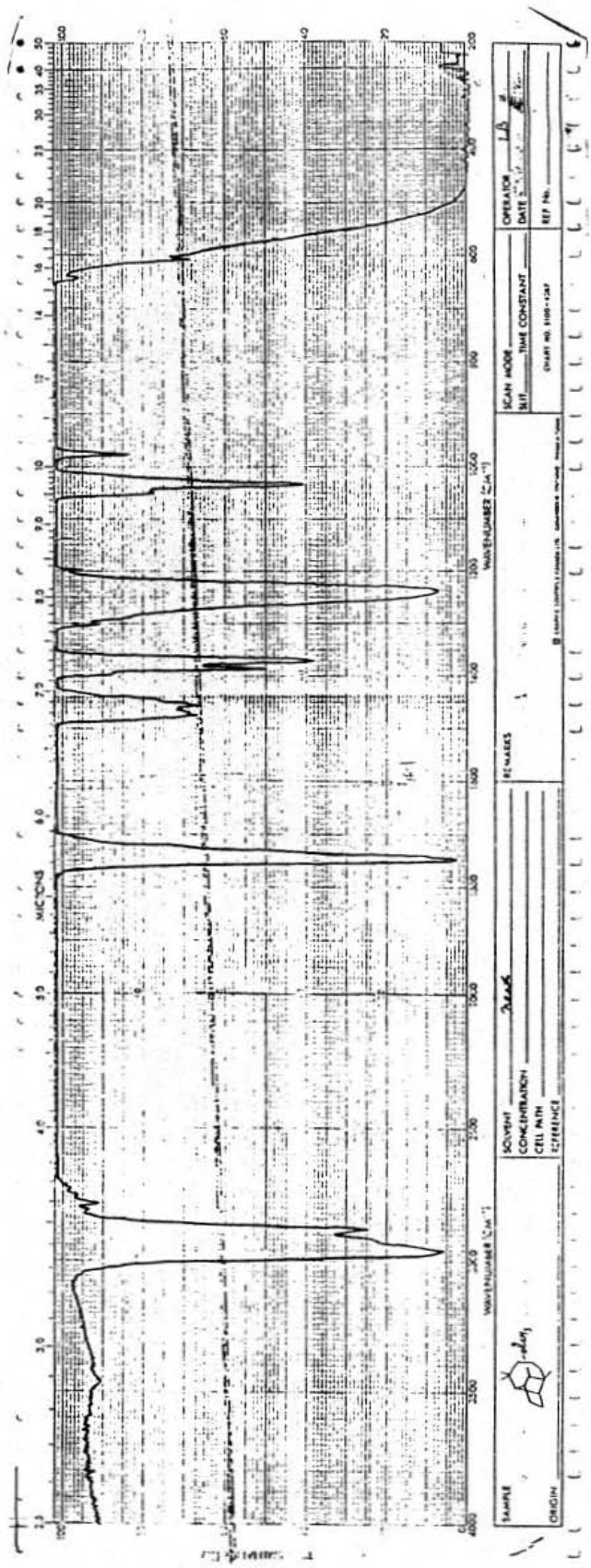

Figure 31 IR spectrum of (146)

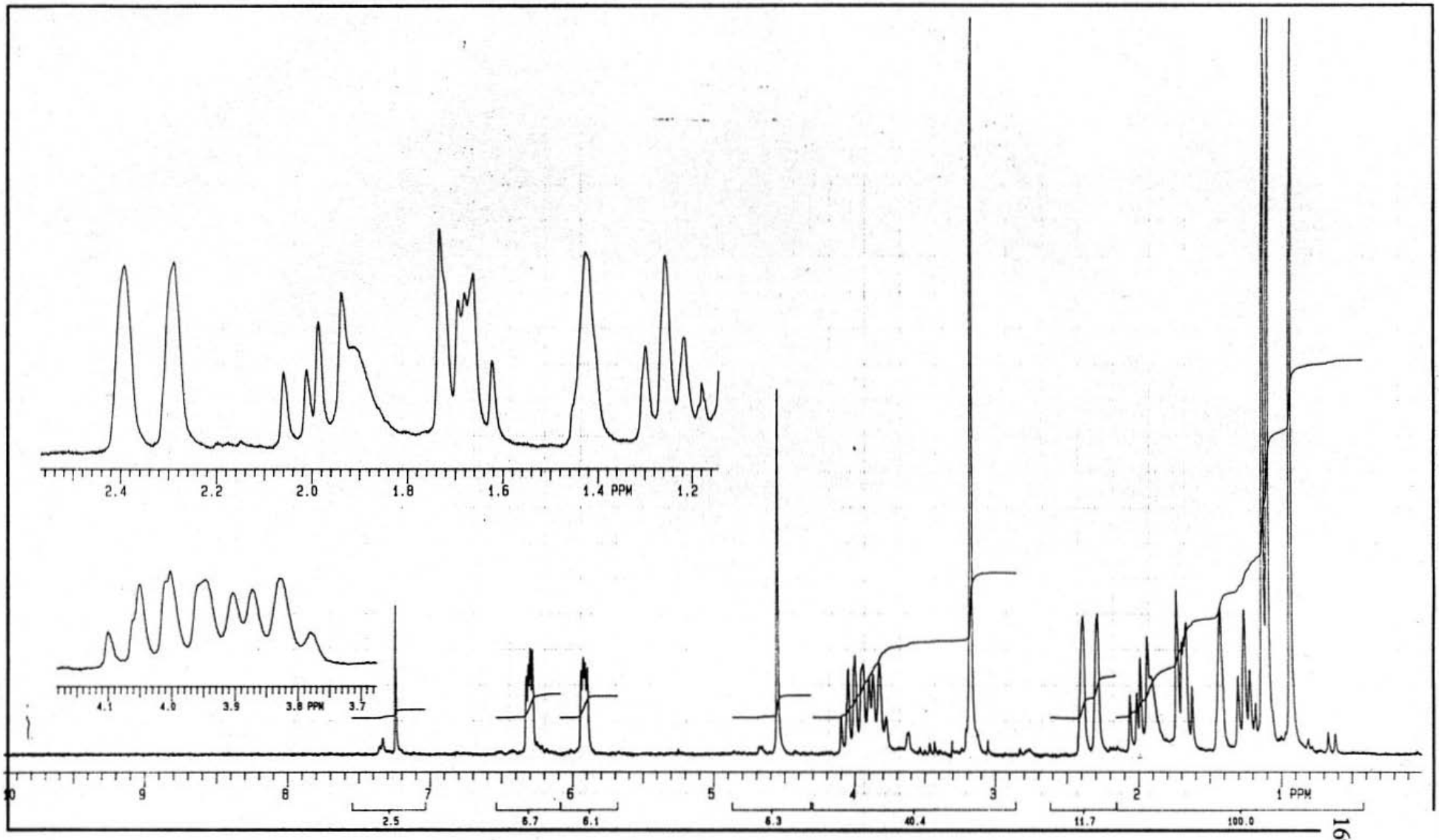

Figure 32 ^{1}H **nmr spectrum of (147)**