A SYNTHETIC STUDY OF SOME TRIQUINANE NATURAL PRODUCTS AND MICROBIAL REDUCTION OF PROCHIRAL SPIRODIKETONES

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by

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Shanghai, People's Republic of China, 1986

A thesis submitted to the School of Graduate
Studies in partial fulfillment of the
requirements for the degree of
Master of Science

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March 1993

ISBN 0-315-86635-7

Canada

ABSTRACT

The first half of this thesis describes an approach to the synthesis of a group of triquinane sesquiterpenes, with (±) deoxypentalenic acid as the particular target. The synthesis started from readily available isophorone. The central quaternary center of the natural product was established in an early step by a double acylation reaction on a cyclohexene derivative. Cleavage of the double bond was followed by reclosure to a five-membered ring. The relative stereochemistry at a stereogenic methine was controlled by catalytic hydrogenation. An intramolecular aldol reaction was used to cyclize the third ring of the triquinane moiety. The remaining steps to (±)-deoxypentalenic acid were modeled in reactions leading to β-keto esters and in reductions of the ketone moiety of a β-keto ester.

The second part of the thesis provides the results of chiral reductions of 1,3-cyclopentanedione derivatives using baker's yeast. The series of diketones that was examined included 7,9,9-trimethylspiro[4.5]dec-7-ene-1,4-dione. The yeast reduction of this compound to (4*S*,5*R*)-4-hydroxy-7,9,9-trimethylspiro[4.5]dec-7-en-1-one (**123**) proceeded with high facial selectivity and enantioselectivity, as determined by an analysis of the corresponding Mosher's ester [(+)-α-methoxy-α-trifluoromethylphenylacetate derivative]. The facial selectivity was compared with that of the chemical reduction using sodium borohydride. The absolute stereochemistry was established from CD spectra and an X-ray structure. The transformation of compound **123** into (4*R*,5*S*)-4-hydroxy-4,7,9,9-tetramethylspiro[4.5]dec-7-en-1-one, an optically active form of an intermediate in the triquinane synthesis, required four steps.

ACKNOWLEDGEMENTS

The author wishes to thank:

Professor D.J. Burnell, my supervisor, for his guidance, encouragement and help through the course of my studies;

Professor C.R. Jablonski, Professor B. Gregory, Professor A.R. Stein, Professor J.N. Bridson and the technical staff of the Chemistry Department, Miss M. Baggs and Ms. N. Brunet, for the provision of the spectral data, and Mr. Zhongxin Zhou for help with CD spectra;

Dr. Y.T. Ma, my husband, for his great influence and interest in my work;

Professor J.N. Bridson and Professor R. Helleur, my supervisory committee, for their valuable comments;

all members of Professor Burnell's group for their kind help and fun;

Memorial University of Newfoundland and Professor D.J. Burnell for financial support.

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Glossary of Abbreviations

APT	Attached proton test
CD	Circular dichroism
COSY	^{1}H-^{1}H Correlation spectrum
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIBAL	Diisobutylaluminum hydride
GCMS	Gas chromatography-mass spectrometry
HMPA	Hexamethylphosphoramide
IR	Infrared (spectroscopy)
LDA	Lithium diisopropylamide
Me	Methyl
mp	Melting point
MS	Mass spectrometry
NBS	N-Bromosuccinimide
NMR	Nuclear magnetic resonance (spectroscopy)
nOe	Nuclear Overhauser effect
Nu	Nucleophile
PCC	Pyridinium chlorochromate
*p*TSA	*para*-Toluenesulphonic acid
TBDMSCl	*tert*-Butylchlorodimethylsilane
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMSCl	Chlorotrimethylsilane
UV	Ultraviolet (spectroscopy)

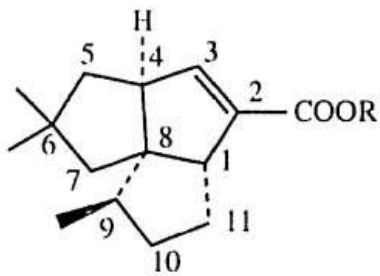
To my dear parents

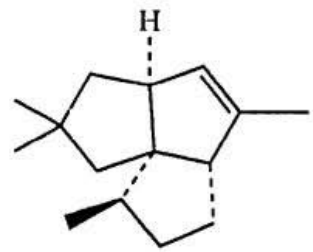
Chapter 1

A SYNTHETIC STUDY OF SOME TRIQUINANE NATURAL PRODUCTS

I. Introduction

Our ultimate goal was the synthesis of deoxypentalenic acid (**1b**), which is a member of a large class of metabolites containing the tricyclo[6.3.0.$0^{4,8}$]undecane skeleton, closely related molecules are deoxypentalenic acid glucuron (**1a**),[1] pentalenene (**2**),[2, 3] and pentalenic acid (**3**).[4, 5]





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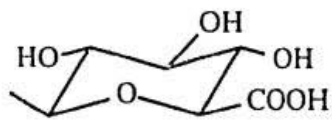
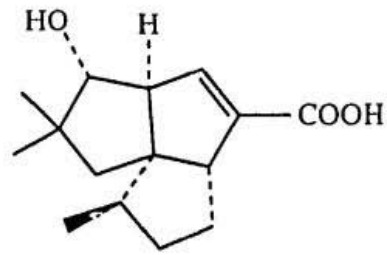
1a **R =**



1b **R = H**



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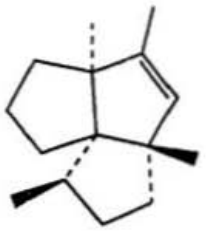
This group of angularly fused triquinanes also includes isocomene (**4**),[6, 7] silphinene (**5**),[8, 9] 5-oxosilphiperfolene (**6**),[10, 11] subergorgic acid (**7**),[12, 13] the unique diterpene laurenene (**8**)[14, 15] (the only known



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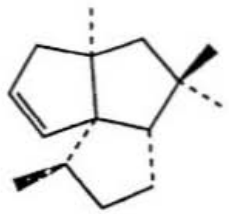

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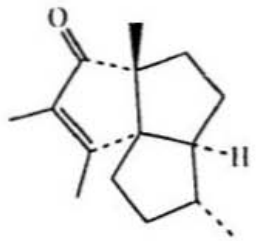

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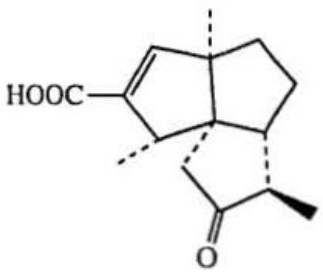

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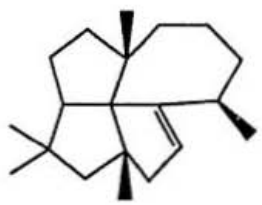

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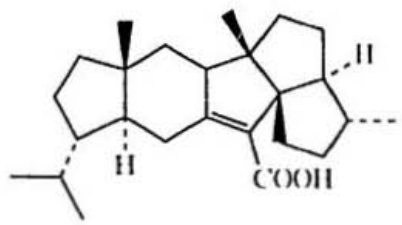

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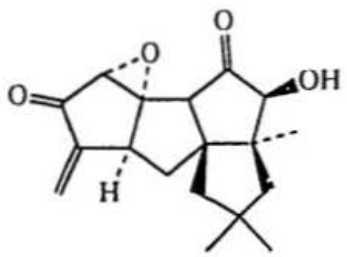

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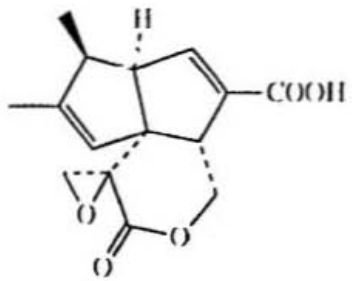


11

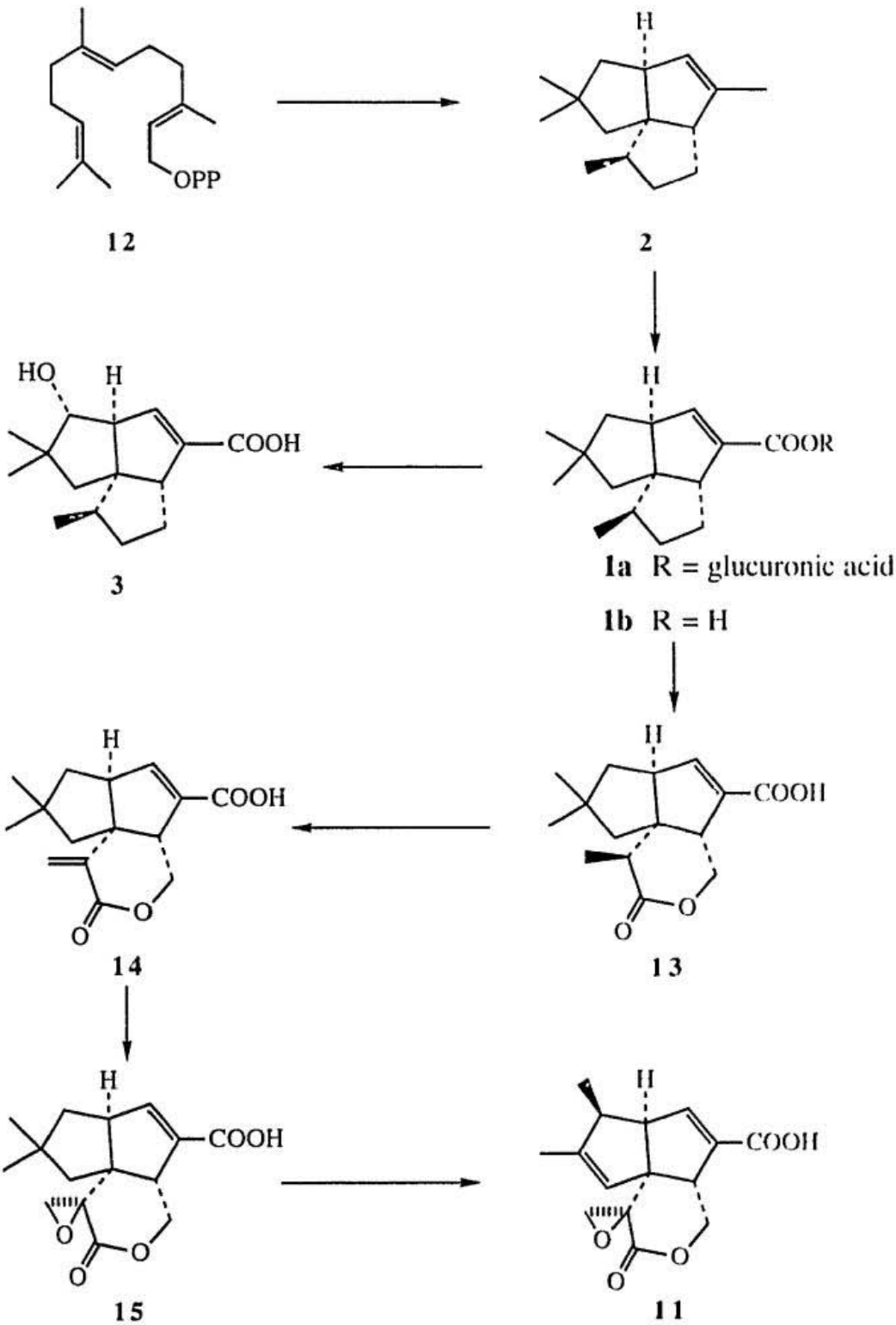
naturally occurring fenestrane), the unusual sesterterpene retigeranic acid (**9**),[16, 17] and crinipellin (**10**).[18, 19] Intensive research on pentalenene (**2**), pentalenic acid (**3**), deoxypentalenic acid (**1b**), and deoxypentalenic

acid glucuron (**1a**) has resulted from their demonstrated role in the biosynthesis of the sesquiterpene antibiotic pentalenolactone (**11**).[20, 21] Seto *et al.*[2, 4] isolated pentalenic acid (**3**) from *Streptomyces chromofuscus* and pentalenene (**2**) from *S. griseochromogenes*. Takahashi *et al.*[1] obtained deoxypentalenic acid glucuron (**1a**) from *S. omiyaensis, S. albofaciens, and S. viridifaciens*. Deoxypentalenic acid glucuron (**1a**) displayed antitumor activity against Sarcoma 180 in mice. Pentalenolactone (**11**) was isolated from several species of *Streptomyces*[20] such as *S. chromofuscus*, *S. griseochromogenes*, *S. baarnensis*, *S. arenae* and *S. roseogriseus*. These are rare examples of cyclic terpenoid antibiotics produced by prokaryotic organisms. Pentalenolactone (**11**) was reported to exhibit potent and specific antiviral activity.[22] Studies in Cane's[23] laboratory have shown that pentalenolactone (**11**) is a time-dependent, irreversible inactivator of glyceraldehyde-3-phosphate dehydrogenase, whose inhibitory action is due to a specific reaction with all four active-site cysteines of the tetrameric enzyme. They also carried out extensive studies on the biosynthesis of **2**, **3**, **1a**, **1b** and **11** as shown in Scheme **1**.[24] Farnesyl diphosphate (**12**) was enzymatically cyclized to pentalenene (**2**), the parent sesquiterpene. Several oxidative steps from pentalenene (**2**) led to deoxypentalenic acid glucuron (**1a**), deoxypentalenic acid (**1b**) and pentalenolactone (**11**).

Additional interest has recently been directed toward the synthesis of these structurally intriguing molecules.

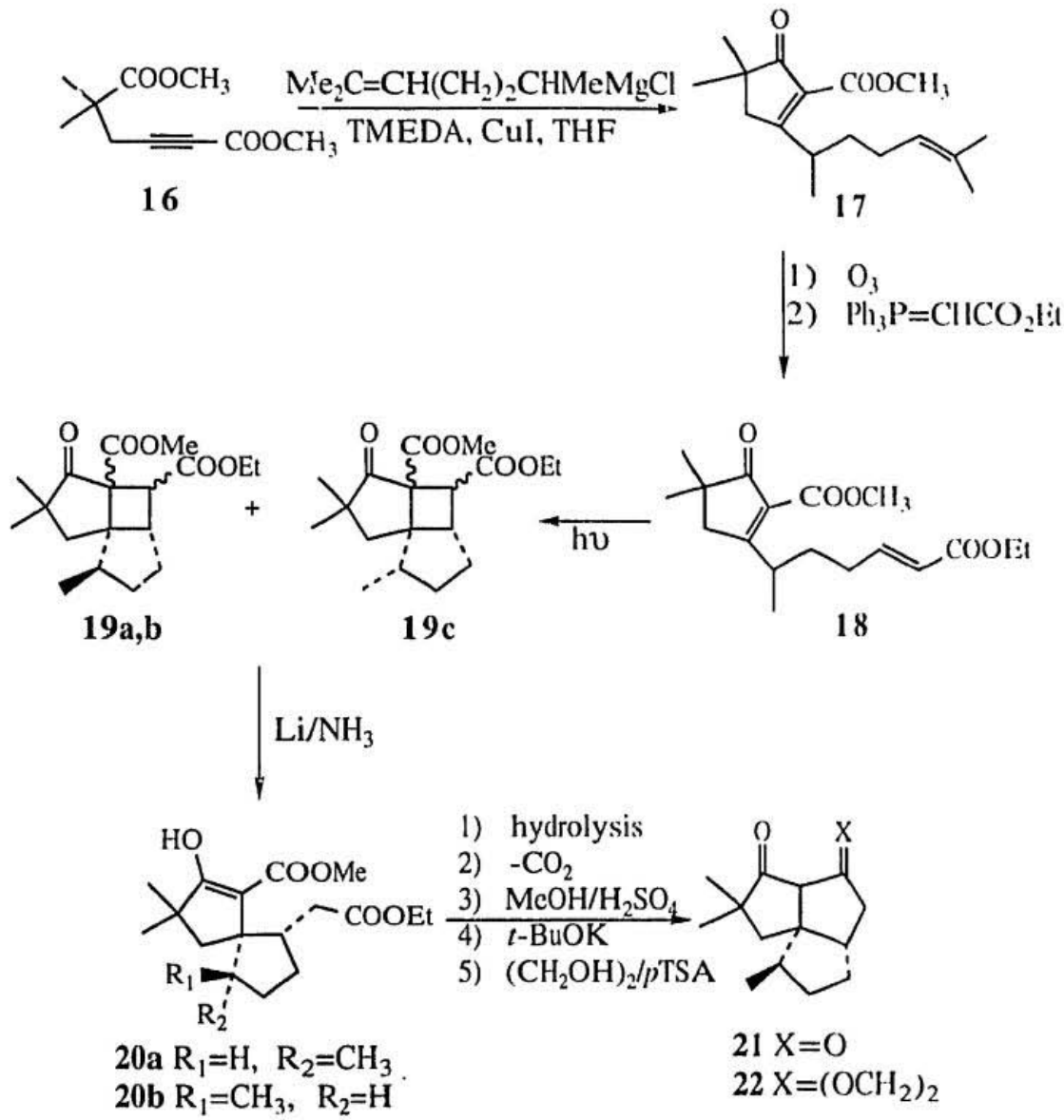
In 1986, Crimmins and coworkers[3f] reported the total synthesis of (±)-deoxypentalenic acid (**1b**) (Scheme **2**) together with (±)-pentalenene **2**), and (±)-pentalenic acid (**3**). A key step in the (±)-deoxypentalenic acid

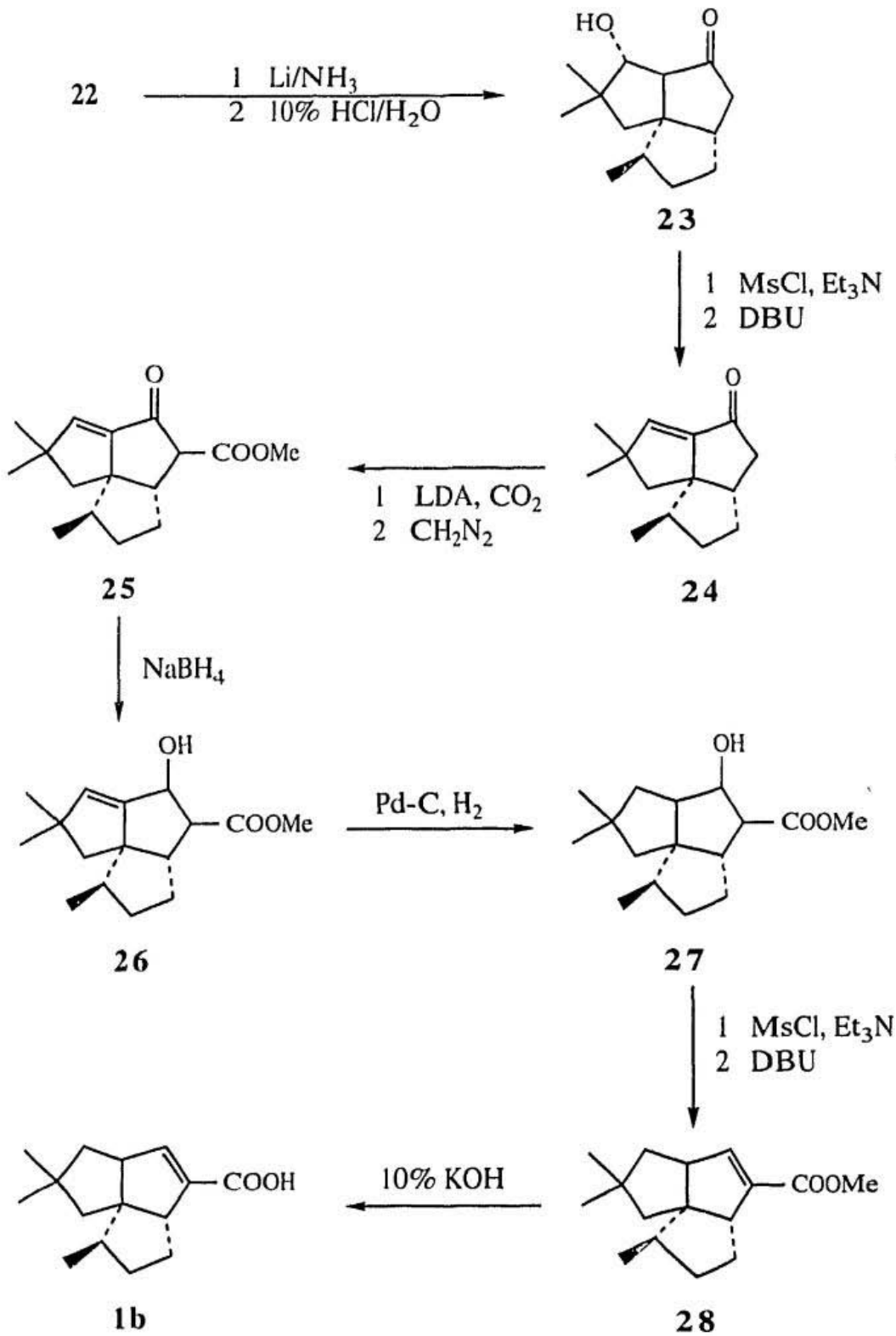
Scheme1 Biosynthesis of pentalenene derivatives



(**1b**) synthesis was a novel conjugate addition-cycloacylation sequence on an acetylenic diester **16**. Treatment of **16** with the appropriate Grignard reagent in the presence of tetramethylethylenediamine (TMEDA) and copper(I) iodide led to diene **17**. Conversion of **17** to diene diester **18** was readily accomplished by selective ozonolysis of the electron-rich trisubstituted double bond to yield an aldehyde, which was immediately condensed with (carbethoxy-methylene)-triphenylphosphorane to provide **18**. Irradiation of diene **18** with UV light resulted in smooth cycloaddition to produce **19** as a 10:3:1 (**19a:19b:19c**) mixture. Reductive cleavage of the cyclobutane ring of **19** was accomplished by treatment with lithium in liquid ammonia to produce β-keto esters **20a** and **20b** in a ratio of 13:1. Following hydrolysis-decarboxylation of β-keto ester **20b**, esterification and cyclization in base generated the triquinane skeleton **21**. Selective ketalization of **21** gave compound **22.** After reducing the carbonyl function of **22** with lithium in ammonia, hydrolysis of the ketal provided keto alcohol **23**. Mesylation of this compound **23** ketone followed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) produced enone **24**. Enone **24** was treated with excess LDA and CO_2 followed by esterification with diazomethane (CH_2N_2) to give keto ester **25**. Sodium borohydride reduction of **25** proceeded to give allylic alcohol **26,** which was catalytically hydrogenated to alcohol **27**. Mesylation of the alcohol and elimination with DBU yielded methyl deoxypentalenate **28**. The total synthesis of deoxypentalenic acid (**1b**) was achieved by hydrolysis of **28** in aqueous potassium hydroxide. Crimmins' synthesis was accomplished in a total of twenty steps.

Scheme **2** Crimmins' synthesis of (±)-deoxypentalenic acid (**1b**)

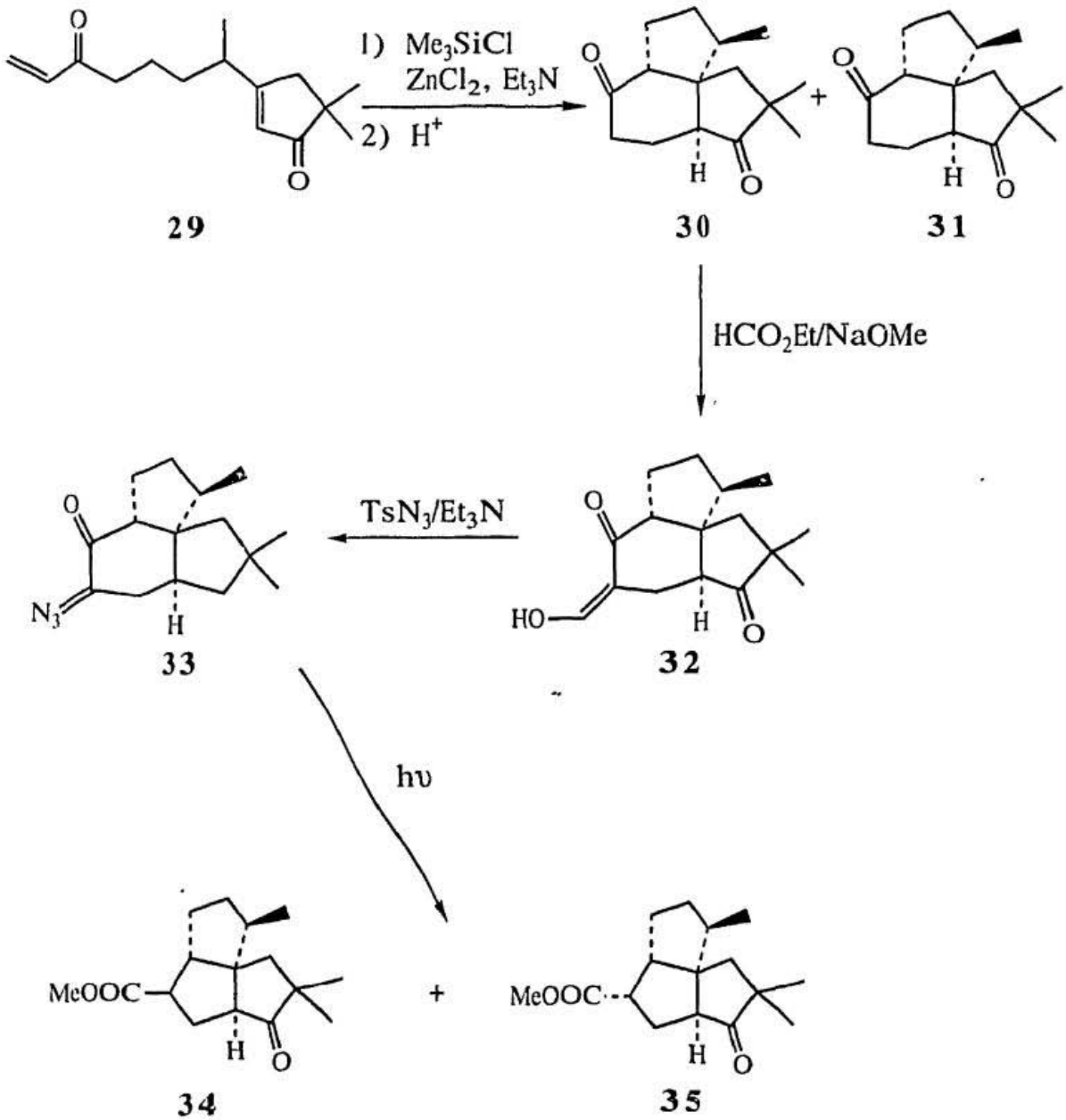


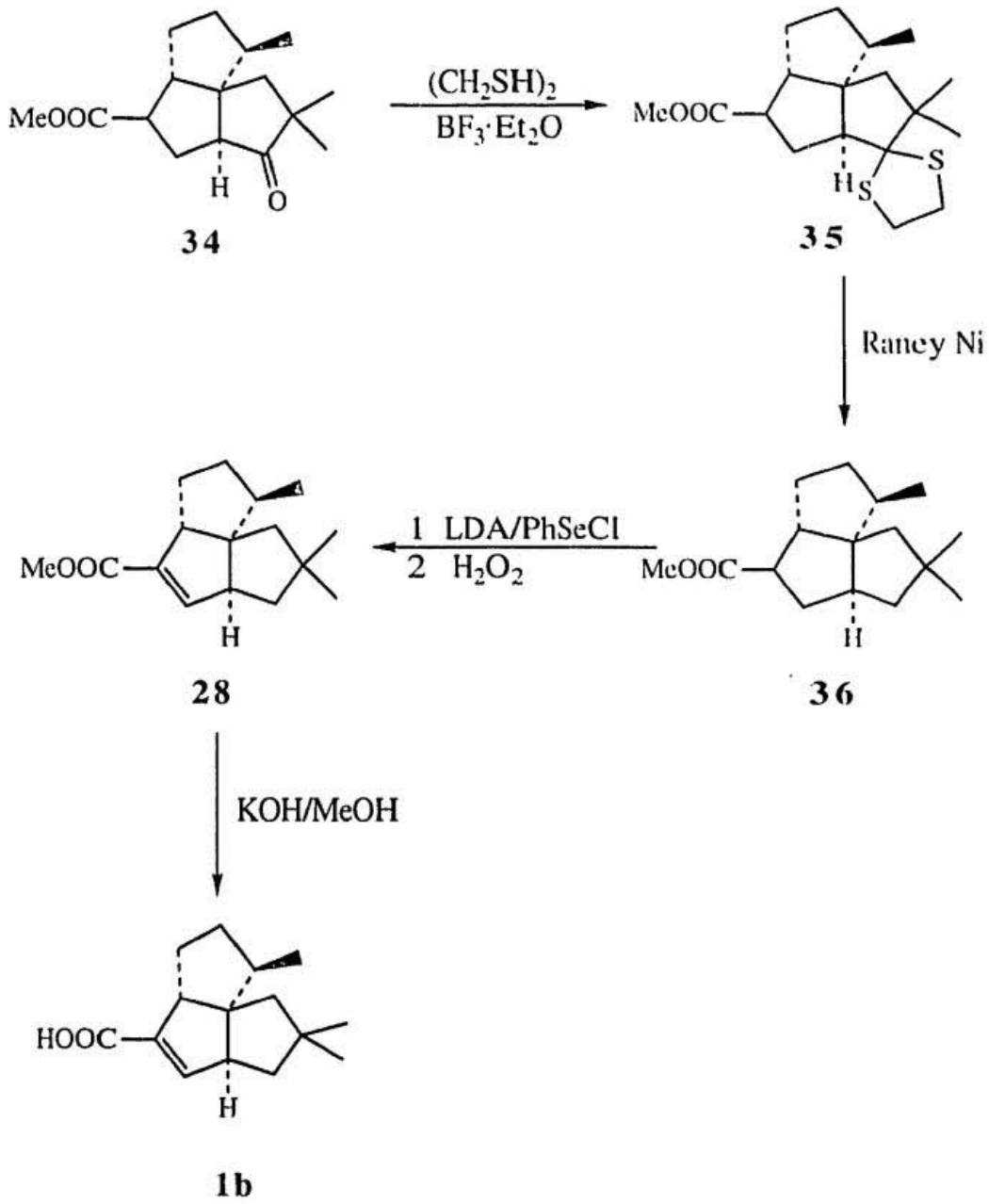

22
1 Li/NH3
2 10% HCl/H2O
HO
O
23
1 MsCl, Et3N
2 DBU
O
24
1 LDA, CO2
2 CH2N2
O
COOMe
25
NaBH4
OH
COOMe
26
Pd-C, H2
OH
COOMe
27
1 MsCl, Et3N
2 DBU
10% KOH
COOH
1b
COOMe
28

In 1988 Fukumoto and coworkers[31] reported the total synthesis of (±)-deoxypentalenic acid (**1b**), using a different approach (Scheme 3). The key step in this synthesis was an intramolecular double Michael reaction. Thus, treatment of bis-enone **29** with chlorotrimethylsilane, triethylamine, and zinc chloride gave two separable diastereomers **30** and **31**. Both the yield and the ratio of those two isomers depended on the reaction temperature and the solvent. Compound **30** was transformed into compound **32** with ethyl formate in the presence of sodium methoxide. Diazo-exchange using *p*-toluene sulphonyl azide and triethylamine gave diazo-ketone **33**. Irradiation of **33** in methanol produced a mixture of the two separable keto esters **34** and **35** in a ratio of 3.6:1. Reduction of the ketone group of **34** to a methylene was achieved by dithioacetal formation and desulfurization with Raney nickel. Selenenylation of **36** followed by oxidative elimination furnished methyl deoxypentalenate (**28**). Hydrolysis of the methyl ester completed the synthesis of deoxypentalenic acid (**1b**). This synthesis was finished in a total of fifteen steps including six steps to **29**. During the synthesis, two steps each produced diastereomeric mixtures of compounds.

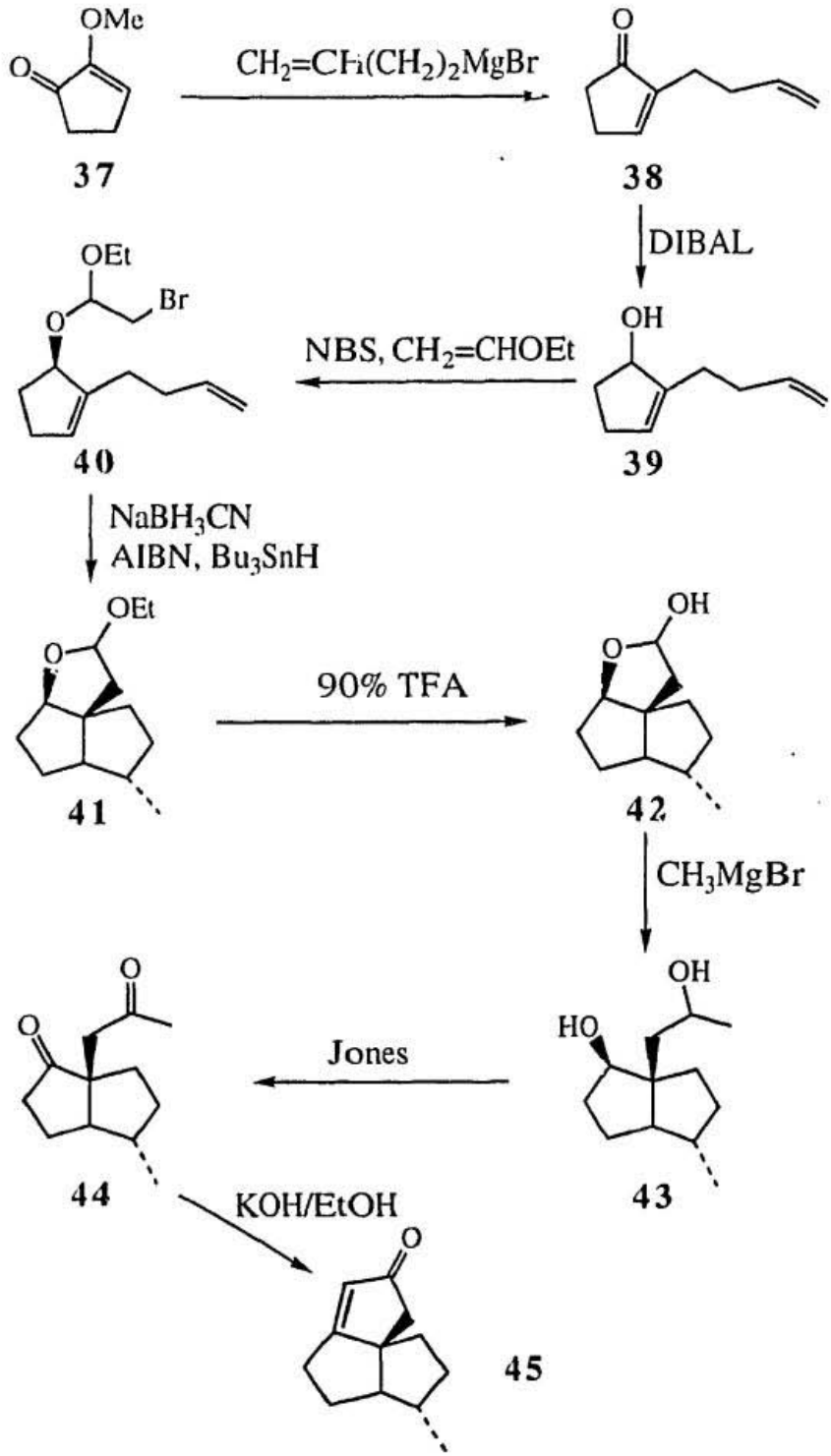
The challenges in the synthesis of this group of natural products are to establish the angular triquinane skeleton itself and to obtain the correct relative sterechemistry at C-9. There are a number of approaches to the synthesis of angular triquinane skeleton. Recently, a radical-mediated approach was reported by Yadav and coworkers[25] (Scheme 4). The required bromoacetal **40** was prepared from 2-methoxycyclopent-2-en-1-one (**37**). A Grignard reagent, prepared from butenyl bromide, was added

Scheme 3 Fukumoto's synthesis of (±)-deoxypentalenic acid (1b)




MeOOC
H
O
34
$(CH_2SH)_2$
$BF_3 \cdot Et_2O$
MeOOC
S
H
S
35
Raney Ni
MeOOC
H
36
1 LDA/PhSeCl
2 H_2O_2
MeOOC
H
28
KOH/MeOH
HOOC
H
1b

Scheme **4** Yadav's synthesis of an angular triquinane

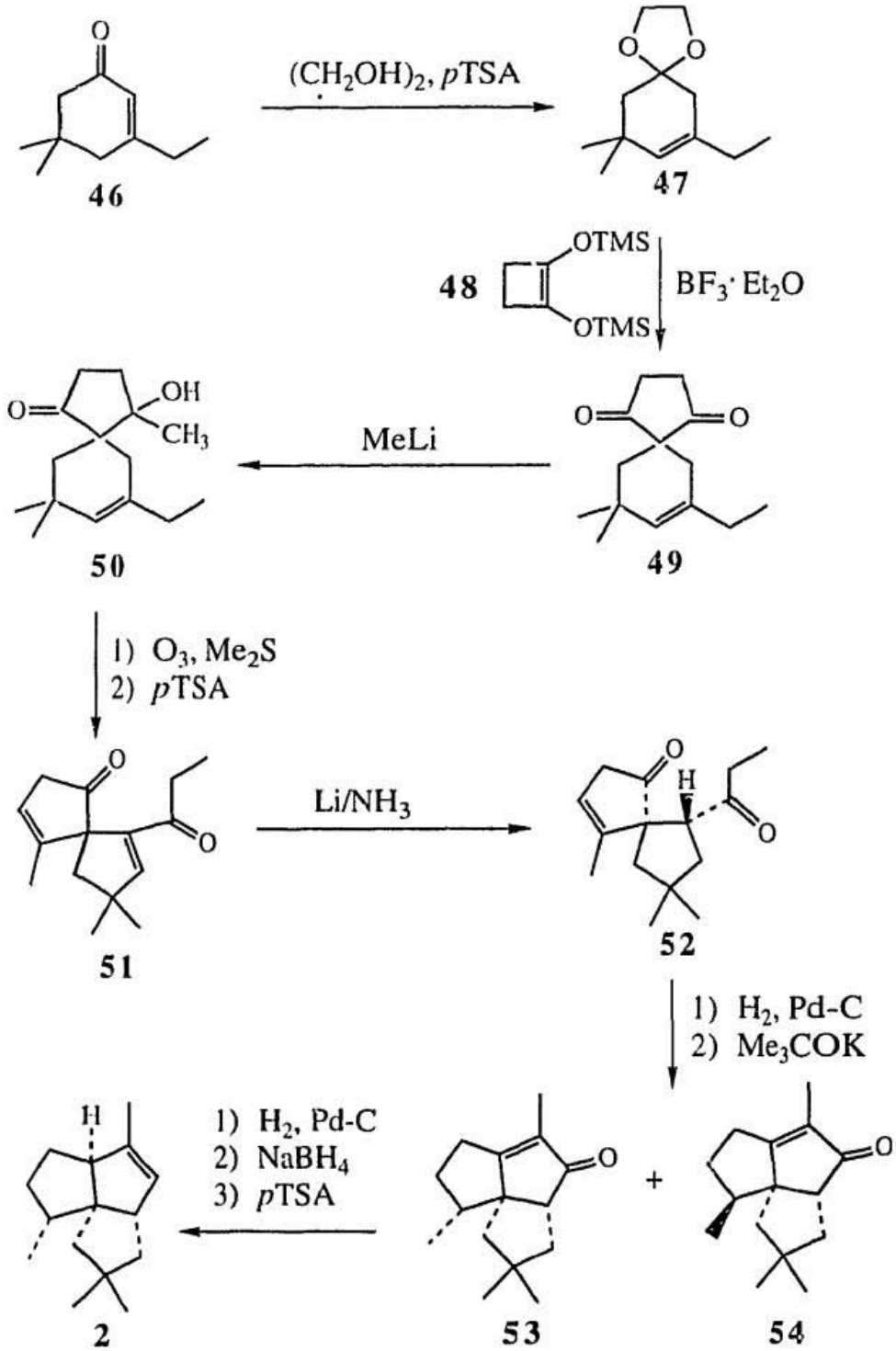


to **37** to give 2-(4-butenyl)cyclopent-2-en-1-one (**38**). Reduction of **38** with DIBAL produced dienol **39**, which was further converted to the desired bromoacetal **40** using NBS and ethyl vinyl ether. Treatment of **40** with sodium cyanoborohydride in the presence of a catalytic amount of tributyltin hydride led to the expected mixed cyclic acetal **41**. Hemiacetal **42** was obtained by hydrolysis of ethyl acetal **41** with 90% trifluoroacetic acid. Reaction of **42** with methyl magnesium bromide produced diol **43**, which was converted to diketone **44** by Jones oxidation. The desired 9-methyl- tricyclo[6.3.0.0^{1,5}]undec-4-en-3-one (**45**) was obtained by treatment of **44** with 20% potassium hydroxide in ethanol.

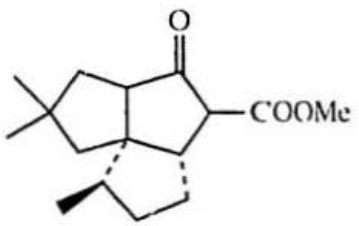
Our synthetic approach to the triquinane skeleton was based on the successful synthesis of the (±)-pentalenene (**2**) by Wu and Burnell[30] (Scheme **5**). Ketalisation of 3-ethyl-5,5-dimethylcyclohex-2-en-1-one (**46**) with ethylene glycol provided ketal **47**. Treatment ketal **47** with 1,2-bis(trimethylsilyloxy)cyclobutene (**48**)[26] and boron trifluoride etherate afforded the spiro-diketone **49**. The mono- alcohol **50** was obtained by addition of methyllithium to **49**. Ozonolysis of **50**, then cyclization with *p*TSA as the catalyst provided **51**. The conjugated double bond was reduced using Birch conditions. Hydrogenation and aldol condensation gave a mixture of the tricyclic products **53** and **54**, which were separated. Starting with **53**, catalytic hydrogenation, sodium borohydride reduction and acid catalysed dehydration resulted in product **2**.

Even though our approach to deoxypentalenic acid (**1b**) was designed to parallel the route to pentalenene (**2**), it could also lead to pentalenene (**2**) itself by a slight modification of the last steps. We

Scheme 5 Burnell's synthesis of (±)-pentalenene (2)



concentrated on the synthesis of compound **55**, which would be only a few steps from the natural product. The results of our work toward the total synthesis of deoxypentalenic acid (**1b**), including some model studies for the final steps, are presented in this chapter of the thesis.



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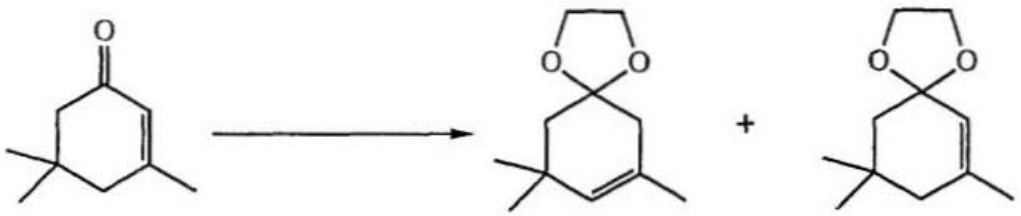
II. Results and Discussion

Scheme **6** Formation of **57** from **56**



56 **57** **58**

The synthesis started from the readily available starting material isophorone (**56**). Ketalisation was carried out with ethylene glycol in the presence of *p*-toluenesulphonic acid (*p*TSA) (Scheme **6**). The reaction produced a mixture of two poorly separable ketals **57** and **58**. The desired isomer **57** was the major component as determined by gas chromatography-mass spectrometry (GCMS). Some starting material always remained no matter how long the reaction was run, and some oligomeric material was formed when the reaction time was increased. We finally opted to run the reaction for 12-14 hours. The solvent was evaporated and the products were distilled under vacuum to remove the yellow color. The crude colorless oil was then flash chromatographed. The ketal **57** was always a major isomer, but the ratio of the two isomers varied with the reaction time. GCMS analysis indicated that the some of the ketal product was hydrolysed back to the starting material **56**, and some of the ketal **57** isomerized to ketal **58** during chromatography. The isomeric

ketals could be clearly distinguished by their mass spectra (Figures **1** and **2**).

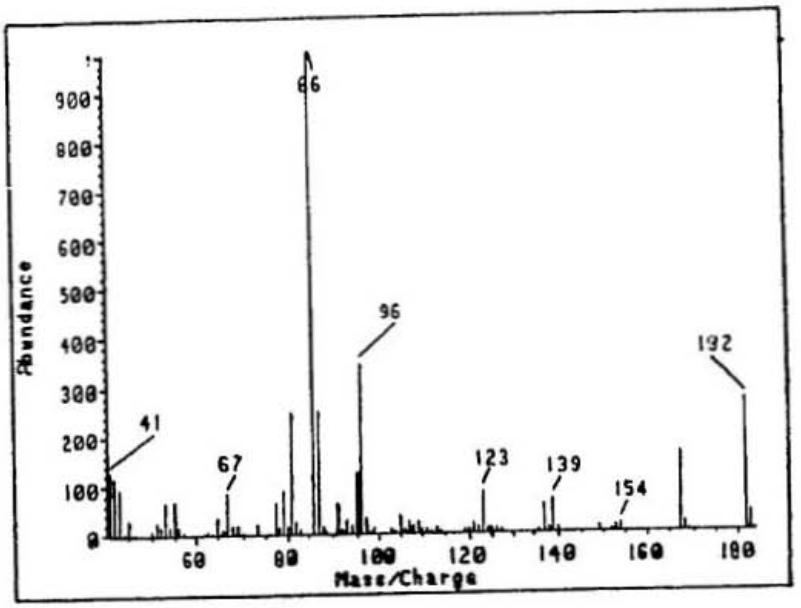


Figure **1** MS of compound **57**

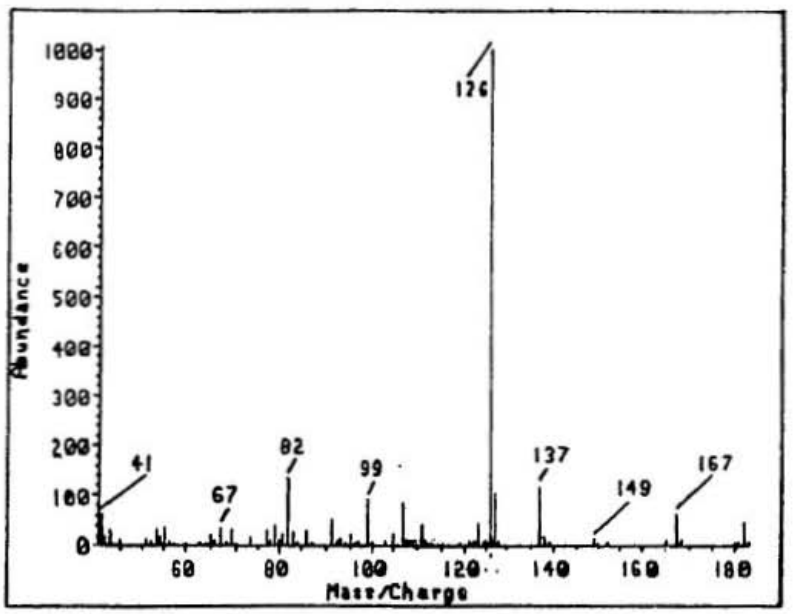
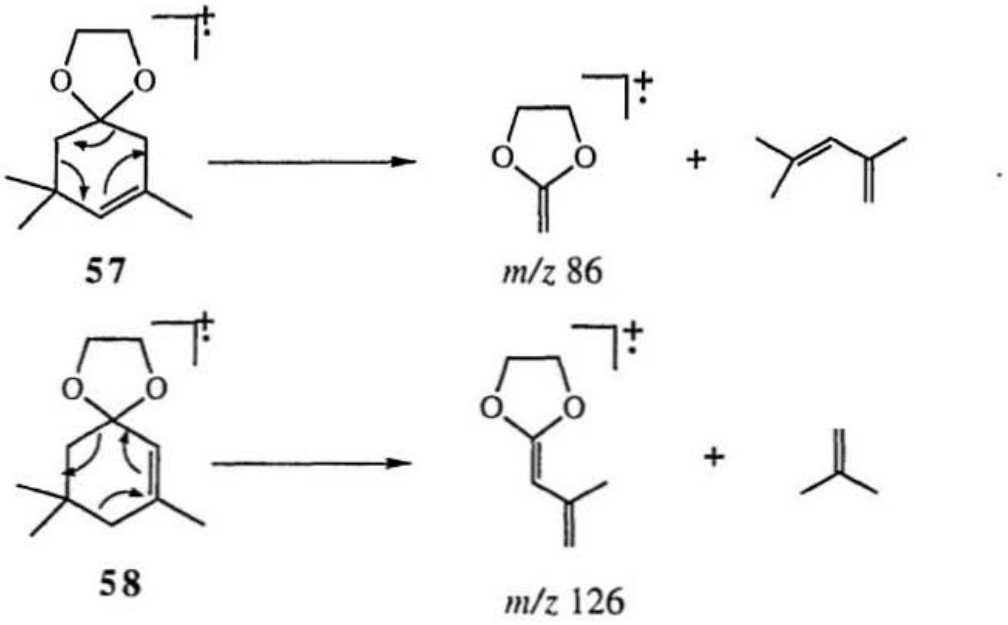


Figure **2** MS of compound **58**

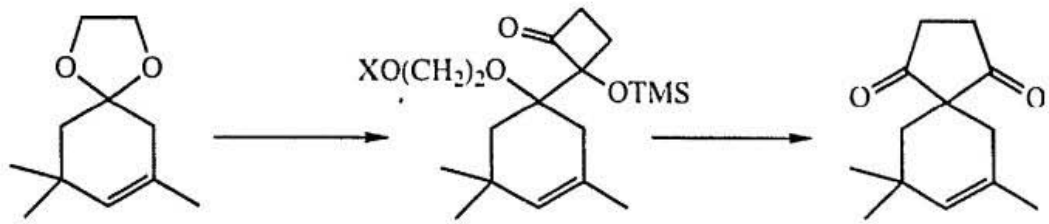
The ketal **57** had its base peak at *m/z* 86 ($C_4H_6O_2^{\cdot+}$), which arose *via* the homolytic retro-Diels-Alder reaction of **57**. Likewise, the base peak at *m/z* 126 in the mass spectrum of **58** could be assigned to a fragment with the formula $C_7H_{10}O_2^{\cdot+}$ (Scheme 7). In the ^1H NMR spectra, the vinyl proton (H-8) of the ketal **57** resonated at δ 5.17, while the vinyl proton (H-6) of the ketal **58** was at δ 5.34.

Scheme 7 MS fragmentation of **57** and **58**



Treatment of this mixture of ketals with three equivalents of 1,2-bis(trimethylsilyloxy)cyclobutene **48** and a large excess of boron trifluoride etherate proceeded, via an intermediate cyclobutanone **59**, to afford in a single operation the rearranged, spiro-annulated diketone **60** (Scheme 8).

Scheme **8** Formation of **60** from **57**



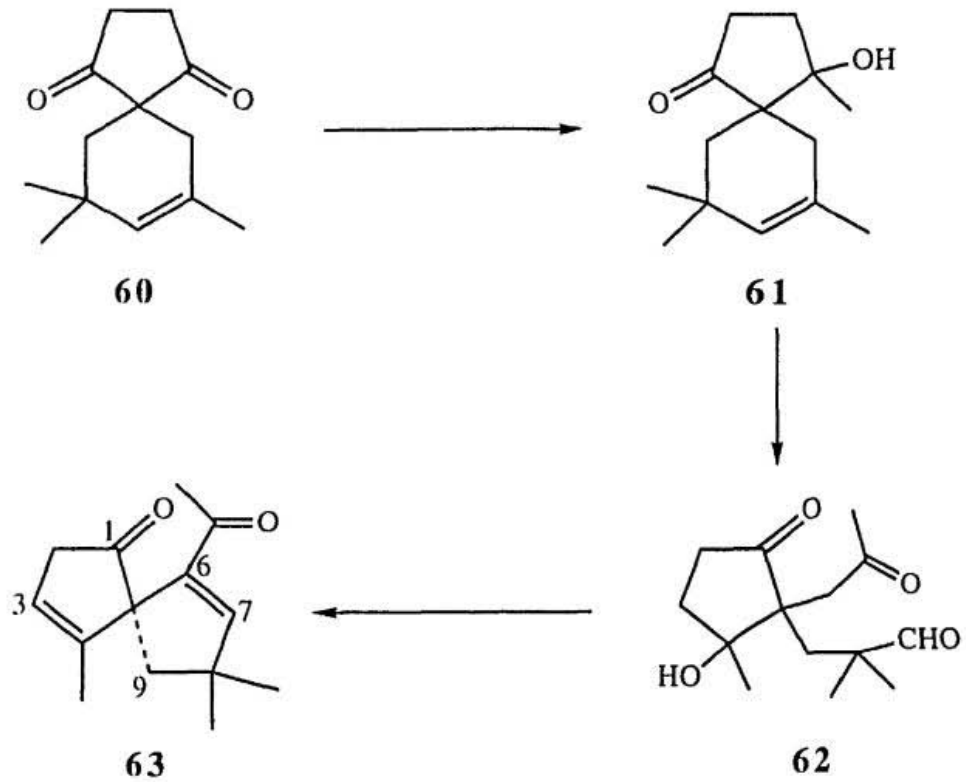
57 **59** **60**

This reaction has now been extensively studied in our laboratory. However, Kuwajima and co-workers[27] first reported this reaction. They demonstrated that under Lewis acid catalysis a ketal reacts with 1,2-bis(trimethylsilyloxy)cyclobutene (**48**) to provide the cyclobutanone, which can be rearranged in the presence of trifluoroacetic acid (TFA) to yield a spirodiketone. Our method employs a single step and leads to a superior yield by prolonging treatment of the ketal with **48** and by using a large excess of boron trifluoride etherate.[28-30]

With the diketone **60** in hand, we introduced the final methyl group. At -78°C addition of methyllithium to the spiro diketone **60** produced monoalcohol **61** as the major product (Scheme **9**). From previous studies in our laboratory,[31] we knew that methyllithium would attack only one ketone, no matter how many equivalents of methyllithium were used. The ^{13}C NMR spectrum of the product showed only one carbonyl signal at δ 220.5, and there was a resonance for a quaternary carbon bearing an hydroxy at δ 77.7.

Ozonolysis of **61** cleaved the double bond, and reduction of the ozonide with dimethylsulfide yielded the aldehyde **62**. Because compound

Scheme **9** Formation of **63** from **60**

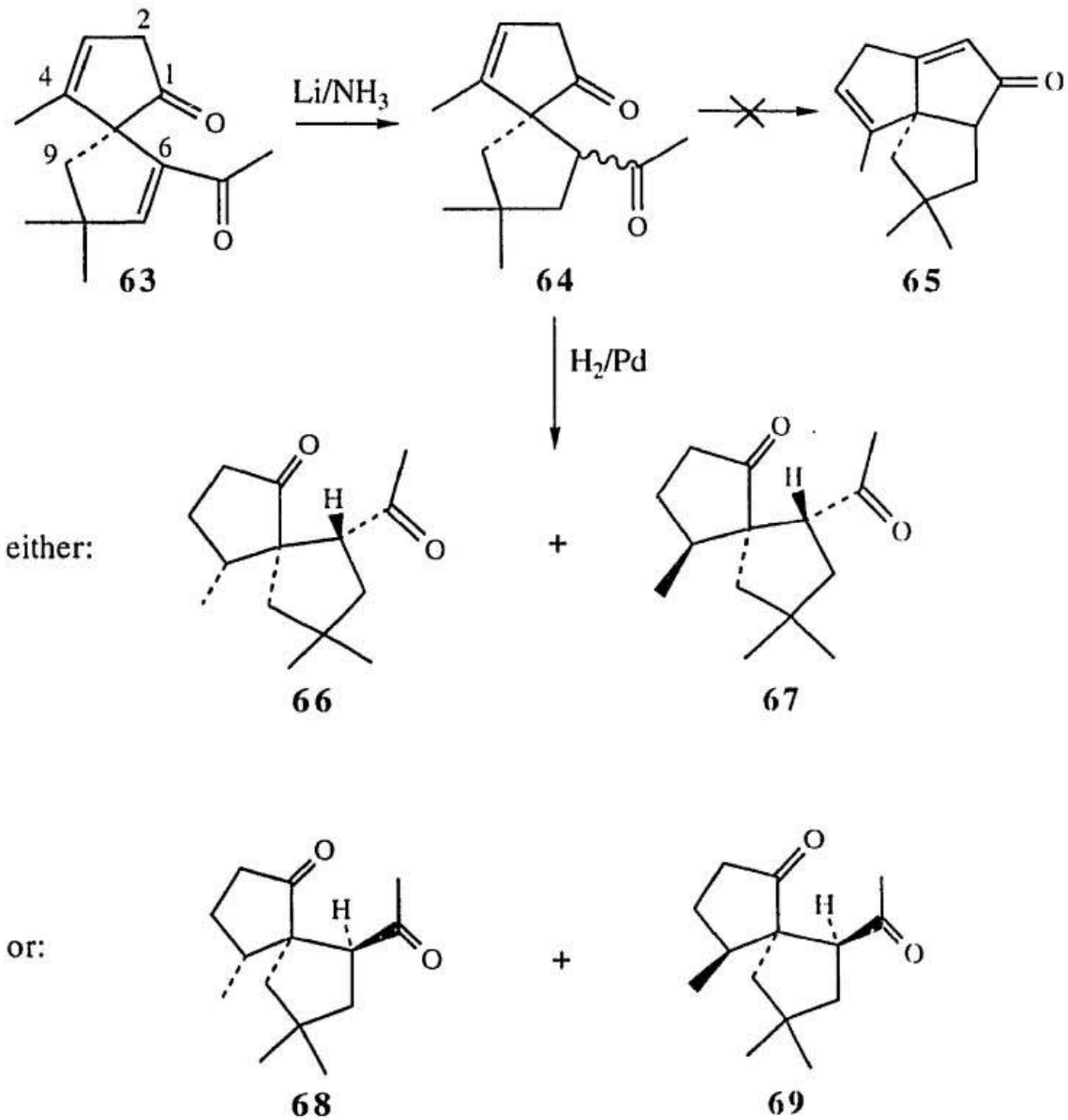


60 **61** **62** **63**

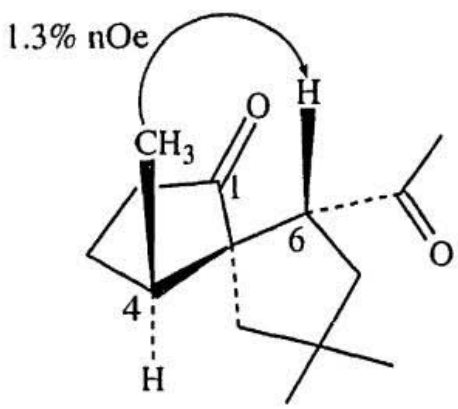
62 was not very stable, without any purification *p*-TSA was added to induce smooth cyclization and concomitant dehydration giving the diketone **63**. The double bond that resulted from dehydration did not move into conjugation with the ring ketone. The ^{1}H NMR spectrum of **63** showed two alkenic resonances: one for an unconjugated double bond proton at δ 5.76 (1H, dd, H-3) and the other for a conjugated double bond proton at δ 6.69 (1H, s, H-7). The H-3 signal was coupled to two H-2 signals (J = 3.3 Hz) and to 4-CH_3 (J = 1.8 Hz). The fact that one double bond in **63** remained unconjugated was probably for two reasons. In this arrangement

the double bond is more substituted, and this shape involves less steric compression, since C-4 is sp^2 the 4-CH_3 does not eclipse either C-6 or C-9.

Scheme **10** Formation of **66** and **67** from **63**



The conjugated double bond of **63** was reduced using Birch conditions to furnish an exclusive product, the enedione **64** (Scheme **10**). In this reaction, a stereogenic center at C-6 was produced. Nuclear Overhauser effect (nOe) measurements were not successful in indicating the relative stereochemistry, because in its ^{1}H NMR spectrum the chemical shifts of 4-CH_3, H-9 and H-7 were very similar. Different solvents, such as C_6D_6 and C_5D_5N, were tested, but they all failed to separate these signals. However, the relative stereochemistry of **64** was determined after the next step. Ketone **64** could not be cyclized to **65** in either acid or base due to the acidity of the C-2 hydrogens. Thus, the unconjugated double bond was also reduced by catalytic hydrogenation, and in the process another stereogenic center at C-4 was generated. We obtained two products, which could have been the pair **66** and **67**, or the pair **68** and **69**. These two products were separated by careful chromatography.



67

Only the minor product showed a significant nOe on H-6 on saturation of the 4-CH_3 signal. Thus, this minor product could only have

been **67**. As the two products were epimeric only at C-4, therefore the major product was **66**.

In the ^{1}H NMR spectrum of this major product **66** (Figure **3**), the 4-CH_3 signal lay between the two 8-CH_3 singlets, so it was difficult to saturate only 4-CH_3. Also, the chemical shift of the 4-CH_3 for **66** was δ 1.04 (d, J = 6.4 Hz), and in compound **67** (Figure **4**) it was at δ 0.76 (d, J = 7.2 Hz) suggesting that in **67** the 4-CH_3 was in both the carbonyl and the acetyl groups' shielding regions, consistent with 4-CH_3 on the *syn* face. Noted from the ^{13}C NMR spectral data, the chemical shifts of 4-CH_3 (δ 14.8) and C-9 (δ 42.6) in **66** were at higher field than the 4-CH_3 (δ 17.4) and C-9 (δ 51.2) in compound **67**, because the 4-CH_3 in **67** was γ-anti to C-9, but in **66**, it eclipsed C-9.

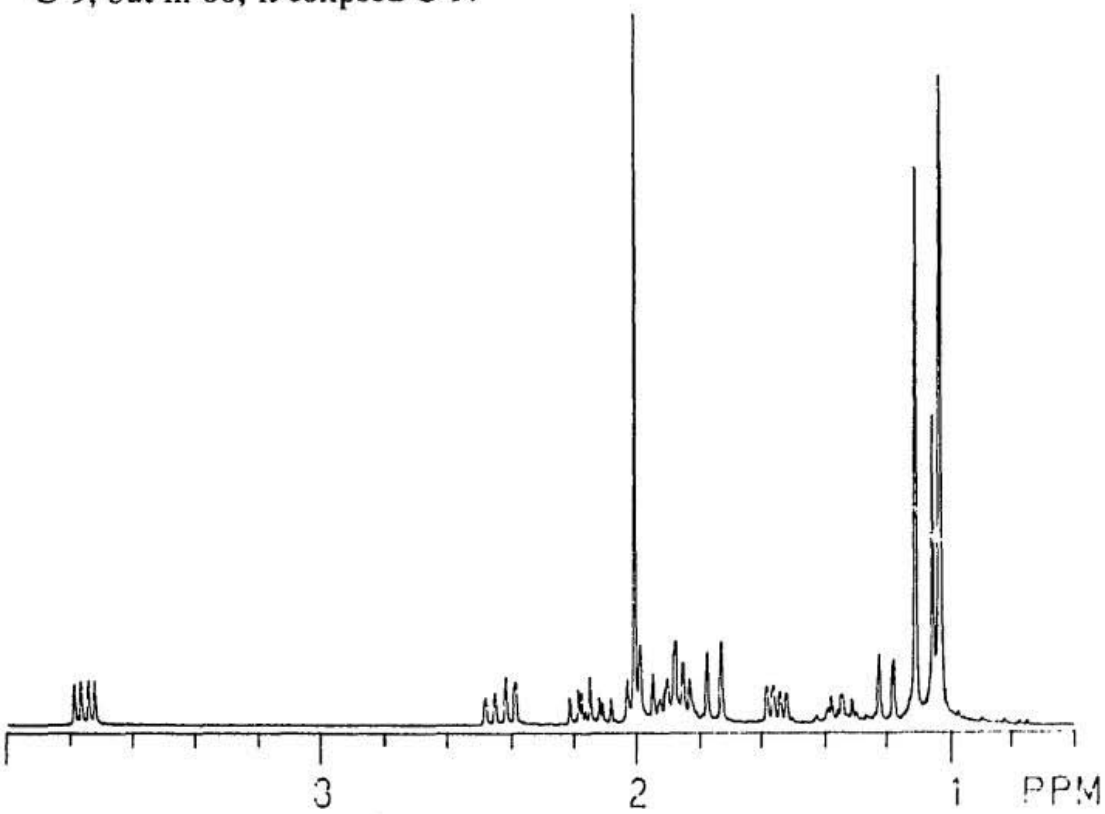


Figure **3** ^{1}H NMR spectrum of compound **66**

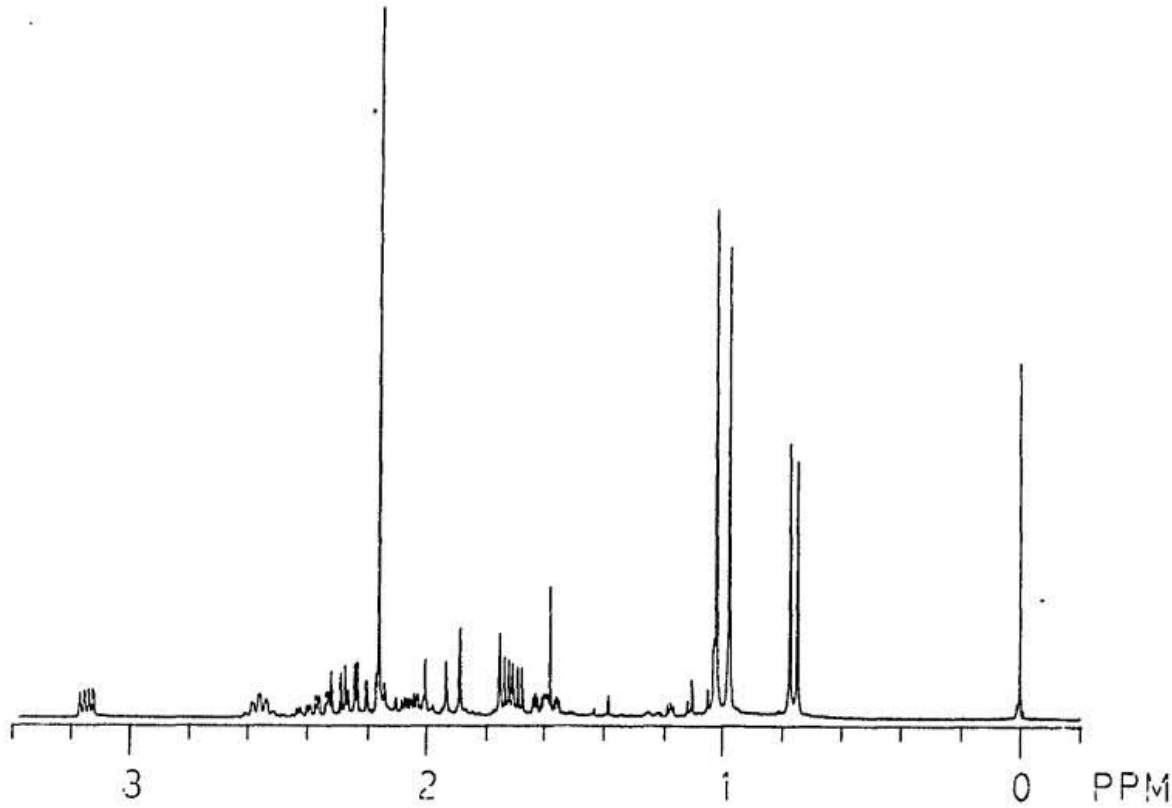
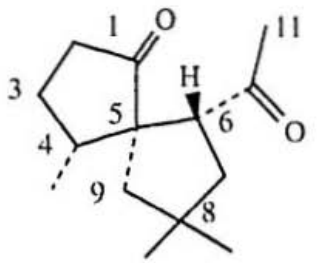


Figure **4** ^{1}H NMR spectrum of compound **67**

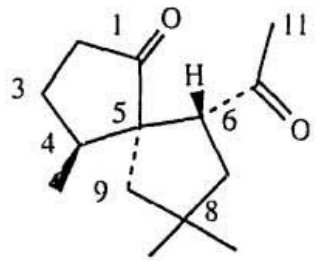
Most important, the major reduction product **66** had the correct relative stereochemistry at C-4 for the target sesquiterpenes. The ratio of compound **66** to **67** was 2:1. The spectral data of both **66** and **67** were assigned in detail based on nOe difference spectra, attached proton test (APT), ^{1}H-^{1}H, and, ^{1}H-^{13}C two dimensional (2D) NMR spectra. The assignments are listed in Tables **1**, **2** and **3**.

Table 1 ^{1}H NMR data for *rel*-(4*R*,5*R*,6*R*)-6-acetyl-4,8,8-trimethylspiro[4.4]nonan-1-one (**66**)



position	chemical shift
H-2	2.45 (1H, ddd, *J* = 1.2, 9, 19.2 Hz)
	2.15 (1H, m)
H-3	1.35 (1H, m)
	1.89 (1H, m)
H-4	1.87 (1H, m)
H-6	3.75 (1H, dd, *J* = 6.2, 13.6 Hz)
H-7	1.55 (1H, dd, *J* = 6, 12.3 Hz)
	1.99 (1H, m)
H-9	1.20 (1H, d, *J* = 13.8 Hz)
	1.75 (1H, d, *J* = 13.8 Hz)
H-11	2.00 (3H, s)
4-CH_3	1.04 (3H, d, *J* = 6.4 Hz)
8-CH_3	1.03 (3H, s)
8-CH_3	1.10 (3H, s)

Table **2** ^{1}H NMR data for *rel*-(4*R*,5*S*,6*S*)-6-acetyl-4,8,8-trimethylspiro[4.4]nonan-1-one (**67**)



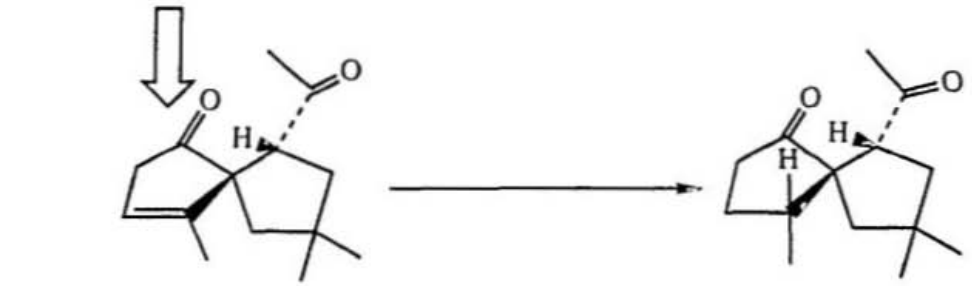
position	chemical shift
H-2	2.20-2.42 (2H, m)
H-3	1.60 (1H. m)
	2.07 (1H, m)
H-4	2.56 (1H, ddq, J = 1.5, 7.2, 14.4 Hz)
H-6	3.15 (1H, dd, J = 4.5, 9.1 Hz)
H-7	1.71 (1H, dd, J = 4.5, 13.5 Hz)
	2.24 (1H, m)
H-9	1.74 (1H, d, J = 13.5 Hz)
	1.91 (1H, d, J =13.5 Hz)
H-11	2.16 (3H, s)
4-CH_3	0.76 (3H, d, J = 7.2 Hz)
8-CH_3	0.98 (3H, s)
8-CH_3	1.02 (3H, s)

Table 3 ^{13}C NMR data for *rel*-(4*R*,5*R*,6*R*)-6-acetyl-4,8,8-trimethylspiro[4.4]nonan-1-one (**66**) and *rel*-(4*R*,5*S*,6*S*)-6-acetyl-4,8,8-trimethylspiro[4.4]nonan-1-one (**67**)

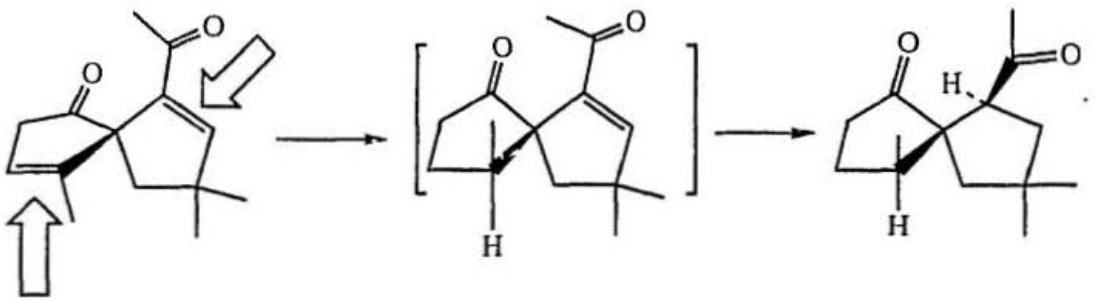
position*	**66**	**67**
C-1(0)	220.4	221.3
C-2 (2)	35.9	32.9
C-3 (2)	27.1	26.4
C-4 (1)	38.2	39.2
C-5 (0)	61.9	65.0
C-6 (1)	55.5	55.1
C-7 (2)	43.1	44.0
C-8 (0)	37.4	37.9
C-9 (2)	42.6	51.2
C-10 (0)	208.7	210.8
C-11 (3)	31.1	30.1
8-CH_3 (3)	29.4 29.2	31.9
4-CH_3 (3)	14.8	17.4

* Number of attached protons in parentheses

Scheme **11** Facial selectivity on hydrogenation of **63** and **64**



64 **66 major**

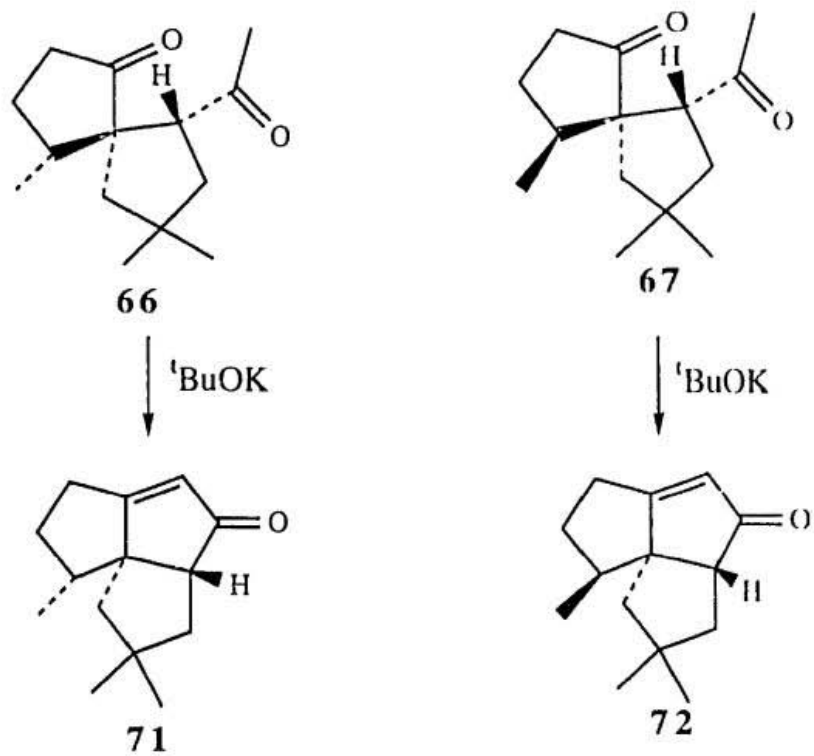


63 **70** **69 major**

Catalytic hydrogenation of **64** appeared to take place with moderate facial selectivity. Since its acetyl group was at some distance from the double bond, hydrogenation could proceed mainly from the direction shown in Scheme **11**. Previously, Wu[31] obtained isomer **69**, a C-4 and C-6 epimer of **66**, by direct hydrogenation of compound **63**. In this case the unconjugated double bond was reduced first. In the intermediate compound **70** one face of the enone was blocked by 4-CH_3, so reduction of the conjugated double bond was mainly from the opposite face. But this method compound **69** was the major isomer, and compound **68**, which had the desired relative stereochemistry at C-4 , was the minor isomer. Hence,

the reduction of the enone*via* the Birch conditions gave the better facial selectivity and provided the desired compound **66** as the major isomer.

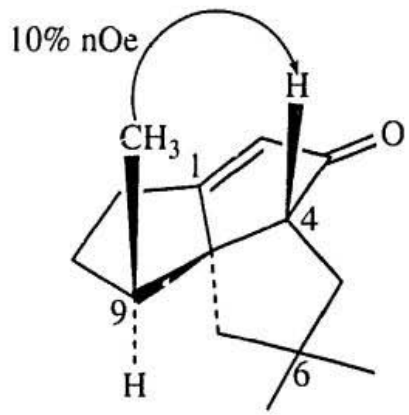
Scheme **12** Formation of **71** from **66** and **72** from **67**



Conversions of **66** to **71** and **67** to **72** were carried out in an intramolecular aldol ring-closure fashion using potassium *tert*-butoxide as the base (Scheme **12**). When the reaction was kept at room temperature, no cyclization product was detected from both TLC and GCMS. However, when this reaction was carried out at reflux, The TLC revealed a new spot that was very clearly visible under UV. The reaction was complete in 10-20 minutes. Careful TLC monitoring was required. The MS showed a strong peak at *m/z* 43 for the acetyl group in the starting materials. This

fragment was not present in the products, and a molecular ion at *m/z* 204 implied cyclization to **71** and **72.**

Both the major isomer **71** and minor isomer **72** could be distinguished from their ^{1}H and ^{13}C NMR spectra data. In the ^{1}H NMR spectra, the chemical shift of 9-CH_3 in **72** (Figure **5**) was at δ 0.76, whereas in **71** (Figure **6**) it was at δ 1.26. Also noted from the ^{13}C NMR spectral data, the chemical shifts of 9-CH_3 (δ 14.6) and C-7 (δ 39.4) in **71** were at higher field than 9-CH_3 (δ 16.6) and C-7 (δ 51.0) in compound **72**. This was due to 9-CH_3 being γ-anti to C-7 in **72**, and γ-eclipsed with C-7 in **71.** The nOe data confirmed the relative stereochemistry of compound **72** with H-4 *syn* to 9-CH_3. When 9-CH_3 was saturated, H-4 had a 10% nOe.



72

The nOe difference experiments failed on compound **71,** because in its ^{1}H NMR spectrum the 9-CH_3 signal was between the two 6-CH_3 signals. It was difficult to saturate 9-CH_3. In C_6D_6 (Figure 7) the 9-CH_3 signal did separate from the two 6-CH_3 peaks, but H-4 was then overlapped with

other proton signals. Thus, it was confirmed that compound **71** had the correct stereochemistry at C-9.

The complete assignments of ^{1}H and ^{13}C NMR data of **71** and **72** based on ^{1}H-^{1}H and ^{1}H-^{13}C 2D NMR spectra are compiled in Tables **4**, **5** and **6**.

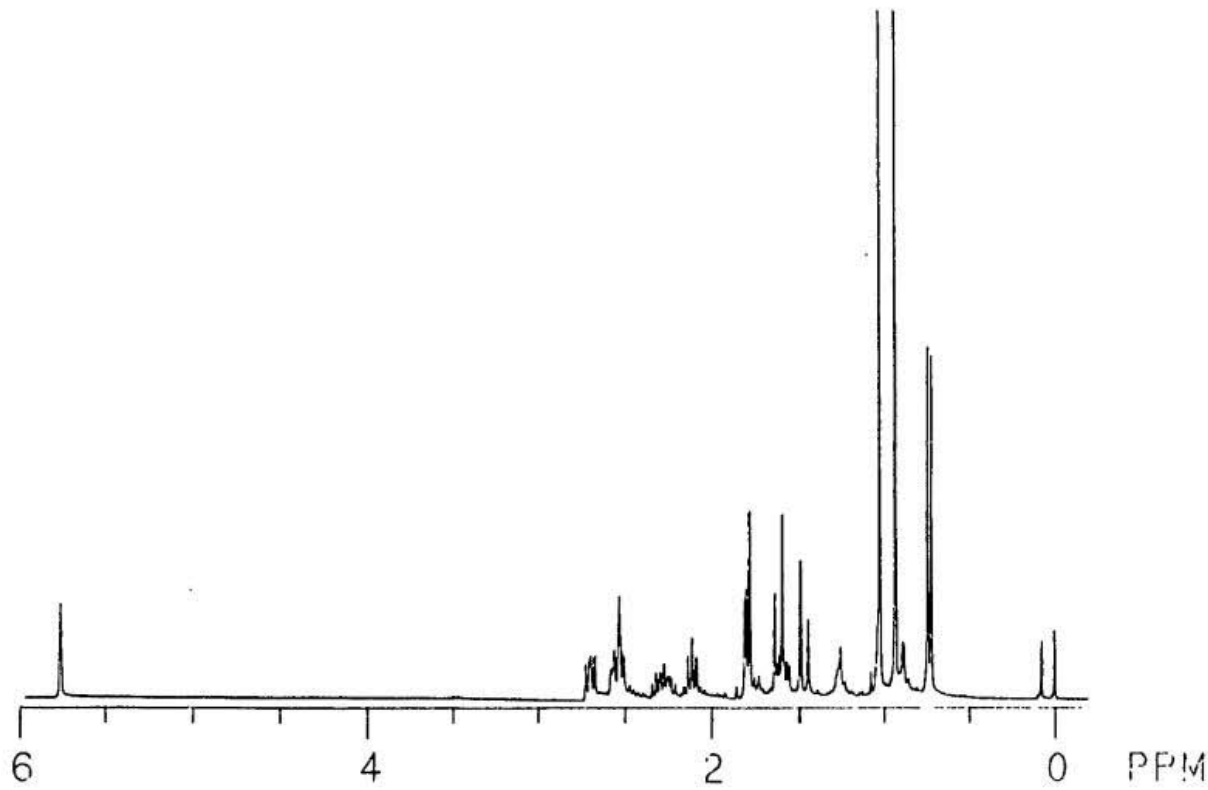


Figure **5** ^{1}H NMR spectrum of compound **72**

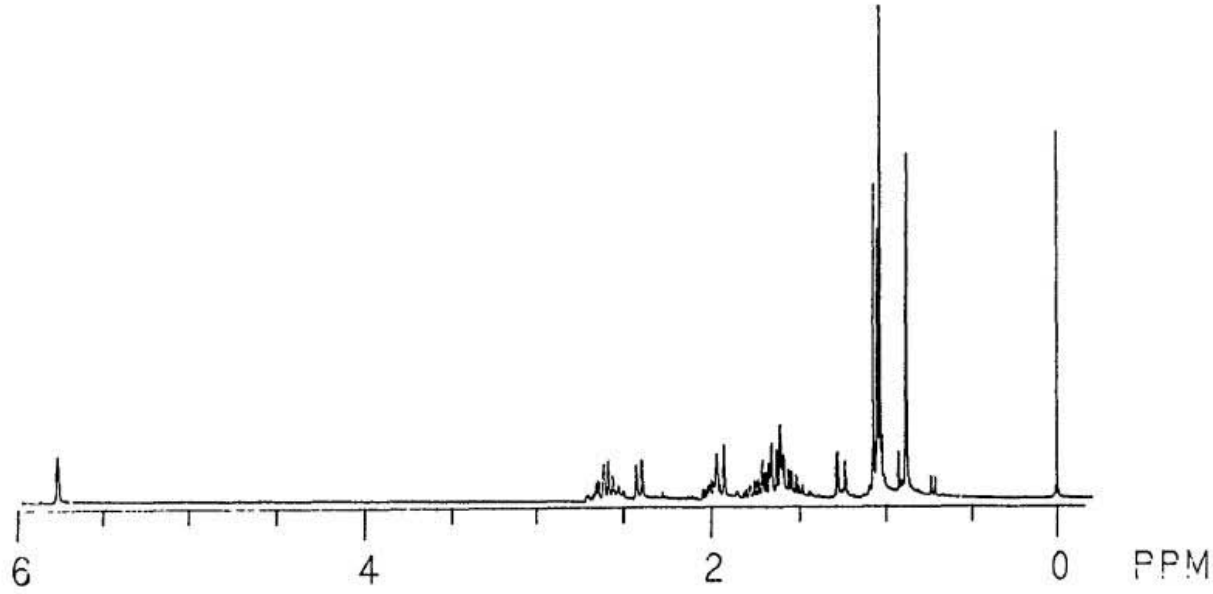


Figure 6 ^1H NMR spectrum of compound 71

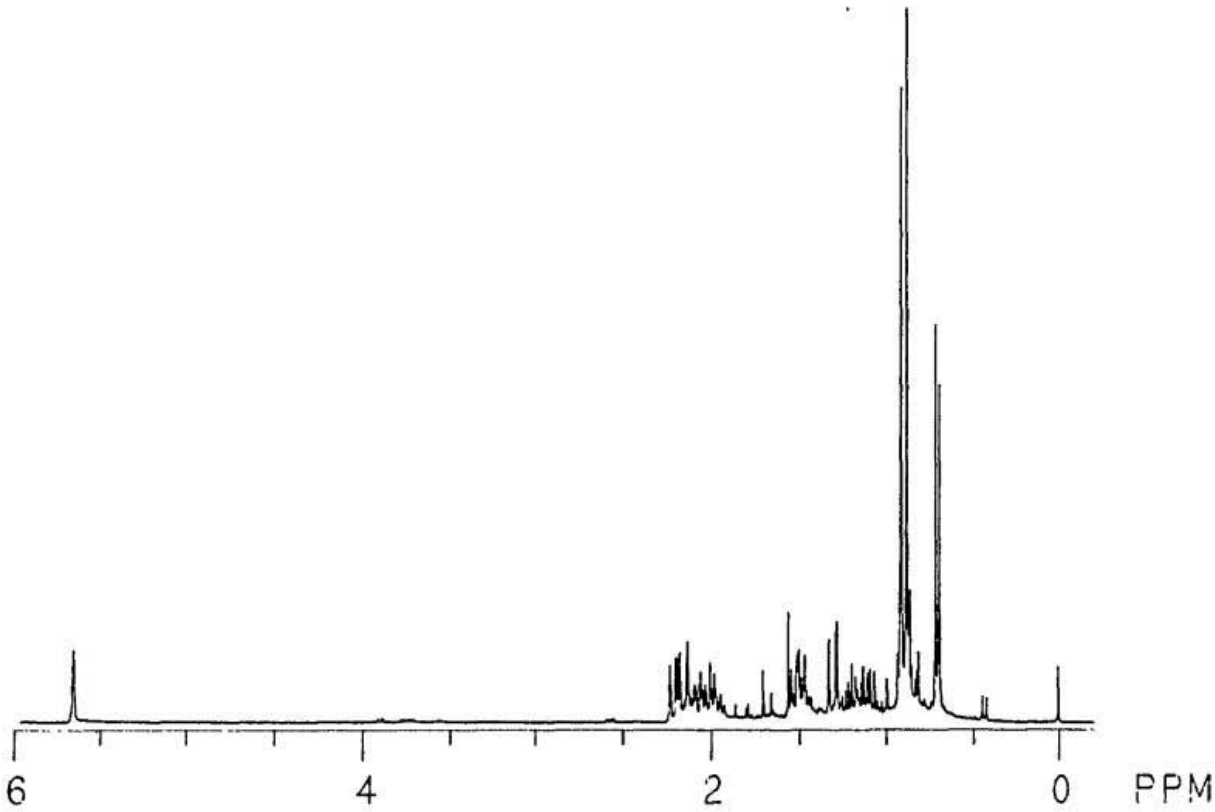
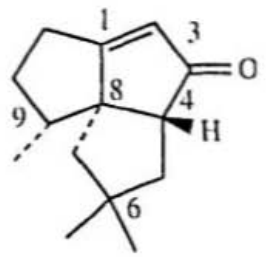


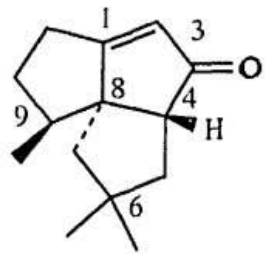
Figure 7 ^1H NMR spectrum of compound 71 (C_6D_6)

Table **4** ^{1}H NMR data for *rel*-(4*R*,8*R*,9*R*)-6,6,9-trimethyltricyclo[6.3.0.0^{4,8}]undec-1-en-3-one (**71**)



position	chemical shift
H-2	5.77 (1H, s)
H-4	2.40 (1H, d, J = 9.6 Hz)
H-5	1.71 (1H, m)
	1.94 (1H, m)
H-7	1.26 (1H, d, J = 13.5 Hz)
	1.63 (1H, d, J = 13.5 Hz)
H-9	1.75 (1H, m)
H-10	1.56 (1H, m)
	2.03 (1H, m)
H-11	2.56-2.65 (2H, m)
6-CH_3	0.89 (3H, s)
	1.03 (3H, s)
9-CH_3	1.06 (3H, d, J = 13.5 Hz)

Table 5 ^{1}H NMR data for *rel*-(4*R*,8*R*,9*S*)-6,6,9-trimethyltricyclo[6.3.0.0^{4,8}]undec-1-en-3-one (**72**)



position	chemical shift
H-2	5.77 (1H, br s)
H-4	2.69 (1H, dd, J = 5.7, 8.4 Hz)
H-5	1.77-1.80 (2H, m)
H-7	1.47 (1H, d, J = 12.9 Hz)
	1.61 (1H, d, J = 12.9 Hz)
H-9	2.11 (1H, dq, J = 7.2, 14.1 Hz)
H-10	1.60 (1H, m)
	2.27 (1H, m)
H-11	2.54 (2H, m)
6-CH_3	0.93 (3H, s)
	1.02 (3H, s)
9-CH_3	0.76 (3H, d, J = 7.2 Hz)

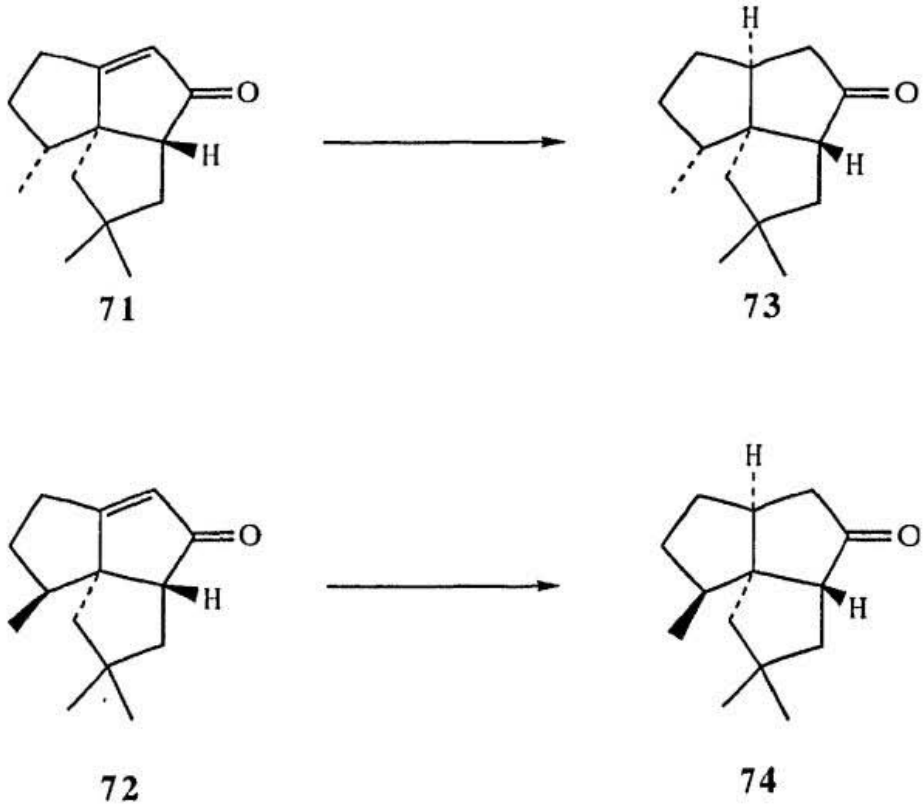
Table **6** ^{13}C NMR data for *rel*-(4*R*,8*R*,9*R*)-6,6,9-trimethyltricyclo[6.3.0.0^{4,8}]undec-1-en-3-one (**71**) and *rel*-(4*R*,8*R*,9*S*)-6,6,9-trimethyltricyclo[6.3.0.0^{4,8}]undec-1-en-3-one (**72**)

position*	**71**	**72**
C-1(0)	194.4	192.2
C-2 (1)	123.9	123.8
C-3 (0)	214.7	215.2
C-4 (1)	57.8	53.9
C-5 (2)	42.9	42.6
C-6 (0)	41.0	42.5
C-7 (2)	39.4	51.0
C-8 (0)	64.9	66.7
C-9 (1)	41.3	40.1
C-10 (2)	32.6	32.3
C-11 (2)	23.5	23.7
6-CH_3 (3)	31.5	30.1
6-CH_3 (3)	29.2	28.9
9-CH_3 (3)	14.6	16.6

* Number of attached protons in parentheses

Catalytic hydrogenation reduced the double bonds in **71** and **72** (Scheme **13**). Both products, **73** and **74**, showed carbonyl absorption at 1736 cm^{-1} for a carbonyl group in their IR spectra. Both the ^{1}H and the ^{13}C NMR spectra showed no olefinic resonances. Detailed ^{13}C NMR assignments are reported in Table **7.**

Scheme **13**



71 **73**

72 **74**

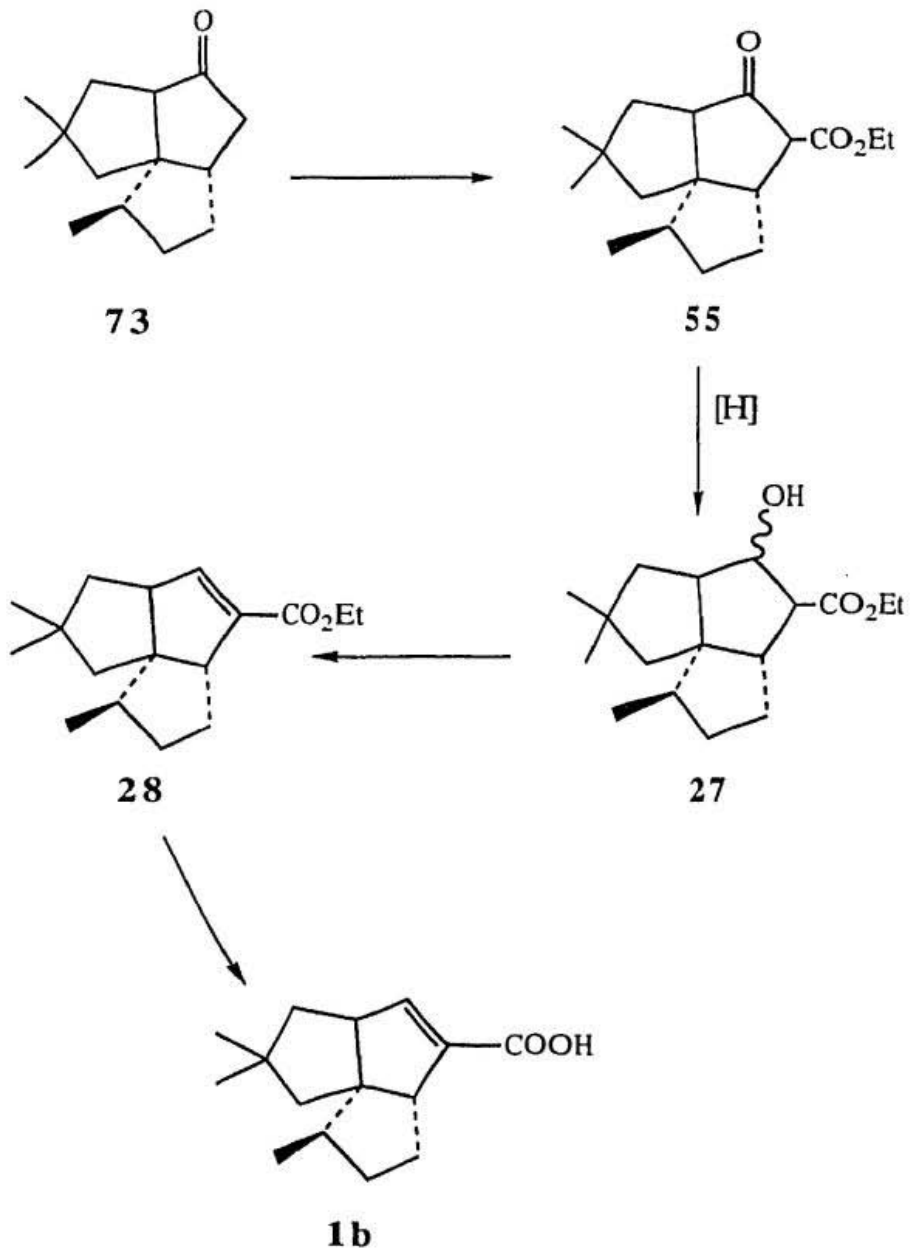
Table 7 ^{13}C NMR data of *rel*-(1*R*,4*S*,8*R*,9*R*)-6,6,9-trimethyltricyclo[6.3.0.0^{4,8}]undecan-3-one (**74**) and *rel*-(1*R*,4*S*,8*R*,9*S*)-6,6,9-trimethyltricyclo[6.3.0.0^{4,8}] undecan-3-one (**73**)

position*	**73**	**74**
1 (1)	45.7	46.0
2 (2)	46.8	47.0
3 (0)	223.0	224.8
4 (1)	59.4	53.6
5 (2)	31.3	32.7
6 (0)	41.3	39.6
7 (2)	47.9	56.3
8 (0)	62.7	60.9
9 (1)	42.9	45.4
10 (2)	34.5	33.2
11 (2)	44.6	45.8
6-CH_3	29.5, 29.2	29.7, 28.1
9-CH_3	15.5	14.0

* Number of attached protons in parentheses

At this point, the triquinane skeleton had been efficiently established. The next four planned steps to deoxypentalenic acid (**1b**) are shown in Scheme **14**.

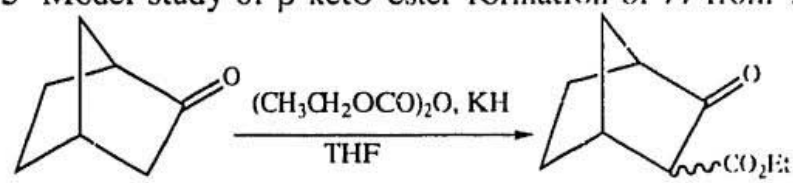
Scheme **14** Formation **1b** from **73**



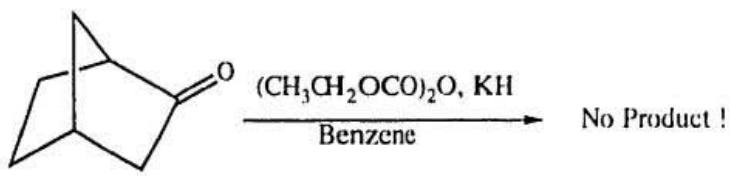
The last two steps to compounds **28** and **1b** are the same as in Crimmins' synthesis. Two steps, to compounds **55** and **27**, remained to be studied.

The first reaction was designed to furnish the β-keto ester **55**. A couple of methods were studied. Fallis[32] reported some acylation success (61%) on cyclopentanone, when it reacted with diethyl dicarbonate with potassium hydride in benzene to afford a β-keto ester product. Mander[33,34] used methyl cyanoformate with LDA as the base at -78°C, and the β-keto ester product was obtained in 71% yield. In this reaction there was a competition between *O*-acylation and *C*-acylation, especially for more sterically hindered ketones. However, in a more recent study Mander[35] discovered that *O*-acylation may be almost completely suppressed by the use of diethyl ether in the place of tetrahydrofuran as solvent, and this resulted in predominant formation of only the β-keto ester. We examined these methods in model studies. Fallis' method was tested with norcamphor (Scheme **15**).

Scheme **15** Model study of β-keto ester formation of **77** from **76**



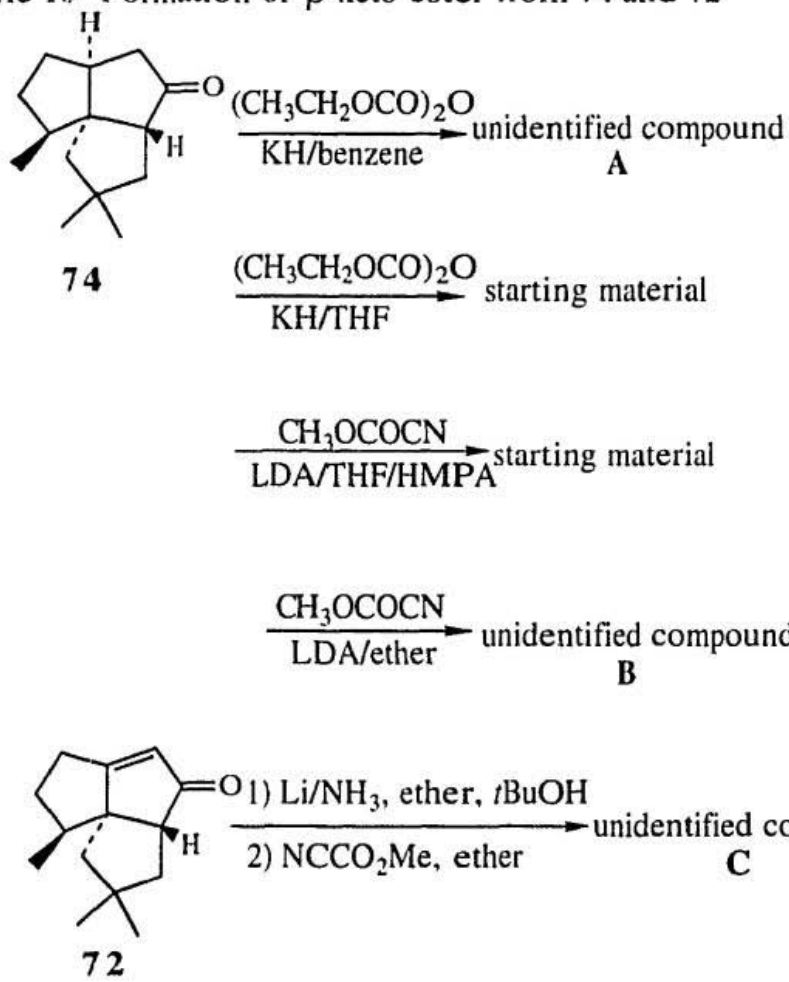
76 **77**



76

We found that the reaction proceeded properly in THF to yield the β-keto ester. In contrast, in benzene the reaction did not work. The product **77** was a mixture of stereoisomers in a ratio of 8:5. IR absorption maxima at 1760 and 1724 cm^{-1} were assigned to two carbonyls. No hydroxyl absorption was found. Also there was no double bond resonance in the ^{13}C NMR spectrum. Therefore compound **77** was in the keto form only, and no enol compound exist. Both Fallis' and Mander's methods were applied to compound **74,** and the results are shown in Scheme **16.**

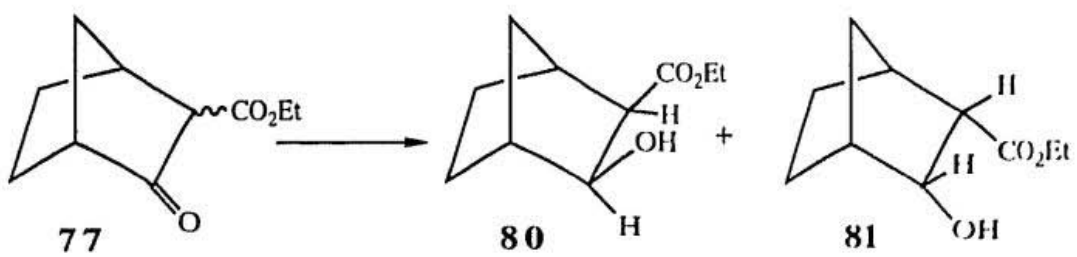
Scheme **16** Formation of β-keto ester from **74** and **72**



The unidentified compounds, which were obtained in some of these reactions, were not very stable under chromatographic conditions. For all these compounds ^{1}H NMR revealed the presence of major skeletal pieces, such as an ester group, 9-CH_3 and gem-dimethyl group at C-6. However, no clear H-1, H-2, or H-4 resonances. These products were present as mixtures, but it was not understood whether or not the mixtures were the enol and keto forms, or *O*-acylation products. It is worth mentioning that the unidentified compound **A** had a similar ^{1}H NMR spectrum to that of unidentified compound **C** except for a different ester group. However the IR results were not consistent. Compound **A** had absorption maxima only at 1766 and 1712 cm^{-1}. Compound **C** had absorption maxima at 3475, 1747, 1660, and 1621 cm^{-1}, and compound **B** at 3432, 1735, 1662, and 1660 cm^{-1}.

Scheme **17** β-keto ester reduction studies on **77** and **78**

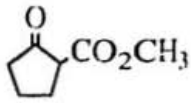
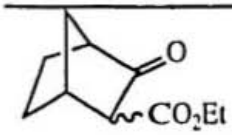
78 **79**



77 **80** **81**

In a further study involving reduction of β-keto esters, it was revealed that none of these unidentified compounds could be reduced by $NaBH_4$. Nevertheless, the reduction of simpler β-keto ester derivatives was well studied with model compounds **77** and **78** (Scheme **17**). The ratio of the two isomeric products was found to change upon the addition of metal chlorides (MCl_2) (Table **8**).

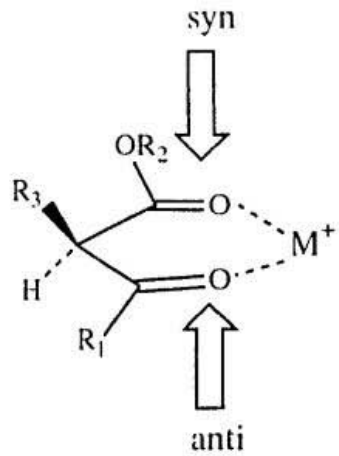
Table **8** Reduction of β-ketoesters by $NaBH_4/MCl_2$

Substrate	Time min	$NaBH_4/MCl_2$ molar equivalents	Yield[a]	Ratio[b]
 **78**	30	$NaBH_4$ (1.0)	98	1:2
	15	$NaBH_4$ (1.3)/ $CaCl_2$ (2.0)	100	2:1
	10	$NaBH_4$ (1.0)/ $CaCl_2$ (2.0)	74	2:1
	10	$NaBH_4$ (1.3)/ $MnCl_2$ (2.0)	70	5:1
	5	$NaBH_4$ (1.0)/ $MnCl_2$ (2.0)	39	5:1
 **77**	30	$NaBH_4$ (1.0)	90	7:1

[a] yield of reduced products as a mixture of stereoisomers.

[b] as determined by ^1H NMR.

Some of these reductions were fairly stereoselective. For compound **78**, $NaBH_4$ gave a 1:2 ratio of hydroxy esters, but with $MnCl_2$ a 5:1 ratio was obtained. A mechanism has been proposed[36,37] that involves a metal complex with two carbonyls, and $NaBH_4$ choosing the *syn* or *anti* face:



The reaction conditions were varied with respect to the nature of metal chloride and the reaction time. Addition of $MnCl_2 \cdot 4H_2O$ led to the best facial selectivity. Changing the reaction time did not affect the product ratio, but it was important in determining the yield.

The final reactions that will furnish the ester group in good yield will require further study. Nevertheless, our approach to the triquinane skeleton, which was presented here, was short (8 steps) and with high yields in each step. Furthermore, the correct stereochemistry at C-9 was obtained. Indeed, while the final stages of the synthesis of (±)-deoxypentalenic acid (**1b**) have yet to be realized, Wu[31] has converted ketone **73** into (±)-pentalenene (**2**) in three straightforward steps. Both the

work described here towards (±)-deoxypentalenic acid (**1b**) and Wu's synthesis of (±)-pentalenene (**2**) demonstrate the utility of the geminal acylation reaction in the total synthesis of triquinane natural products.

III. EXPERIMENTAL

General

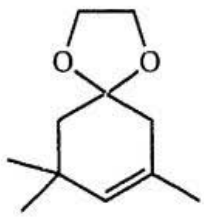
Both high and low resolution electron impact mass spectra (HRMS, and LRMS) were recorded on a V.G. Micromass 7070HS mass spectrometer. Data are reported as *m/z* (relative intensity). Gas chromatography-mass spectrometry (GCMS) data were recorded on a Hewlett-Packard 5890 gas chromatograph coupled to a model 5970 mass selective detector, which was equipped with a 12.5 m fused-silica capillary column with cross-linked dimethylsilicone as the liquid phase. Fourier transform infrared (IR) spectra were recorded on a Mattson FT instrument. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were measured (in $CDCl_3$ unless otherwise noted) on a GE 300-NB (300 MHz for ^{1}H and 75 MHz for ^{13}C) spectrometer. Chemical shifts (δ) are reported in parts per million from tetramethylsilane (TMS). Chloroform (unless otherwise noted) was used as the internal standard, ^{1}H: δ 7.27; ^{13}C: δ 77.0 relative to TMS. TMS was used as the internal stardard when the solvent shift spectra were recorded. Coupling constants, *J*, are expressed in Hertz (Hz) and are reported to within $\pm$ 0.2 Hz. The following abbreviations are used: m=multiplet, s=singlet, d=doublet, t=triplet, q=quartet, br=broad. The ^{13}C NMR shift are followed by the number of attached protons, as determined by Attached Proton Test (APT) and heteronuclear 2D experiments. Nuclear Overhauser effect (nOe) difference experiments were done on degassed solutions on the GE 300-NB spectrometer.

Flash chromatography was carried out with E. Merck silica gel 60 (230-400 mesh) according to the method described by Still.[38] Thin layer chromatograms (TLC) were examined under ultraviolet light (254 nm). The TLC plates were visualized with iodine vapor, or sprayed with a solution of phosphomolybdic acid (10 g of $MoO_3 \cdot H_3PO_4$, 1.25 g of $Ce(SO_4)_2$, 12 mL concentrated H_2SO_4, diluted to 250 mL with H_2O), then the TLC plate was heated on a hot plate.

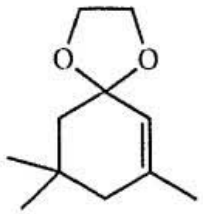
Reagent grade solvents were distilled prior to use. Analytical grade diethyl ether (ether) and benzene (ACS) were used without further purification. Dry dichloromethane and toluene were distilled from calcium hydride. Dry tetrahydrofuran (THF) was distilled from sodium benzophenone.

Most reactions were carried out under a positive pressure of nitrogen gas. Reactions which required anhydrous conditions were performed in oven-dried glassware, which was assembled and allowed to cool while being purged with an inert gas. All reactions were monitored by analytical thin-layer chromatography (TLC). All compounds reported gave a single spot on TLC and were judged to be >95% pure on the basis of both ^1H NMR and GCMS.

7,9,9-Trimethyl-1,4-dioxaspiro[4.5]dec-7-ene (57) and
7,9,9-Trimethyl-1,4-dioxaspiro[4.5]dec-6-ene (58)



57

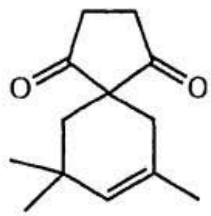


58

A mixture of isophorone (5.0 g, 36 mmol), ethylene glycol (8.5 mL, 155 mmol), and *p*TSA (0.9 g) in benzene was heated at reflux overnight. As the water was formed, it was removed by a Barrett water-separator. Solid then saturated aqueous sodium bicarbonate were added. The aqueous layer was extracted with ether four times. The combined organic layers were washed with brine, dried over anhydrous potassium carbonate, filtered, and concentrated. The residue was distilled under vacuum to give a colorless liquid (4.7g). Further purification was carried out using flash chromatography (12-16% ethyl acetate in hexane) to give a colorless oil composed of a mixture of 7,9,9-trimethyl-1,4-dioxaspiro[4.5]dec-7-ene (**57**) and 7,9,9-trimethyl-1,4-dioxaspiro[4.5]dec-6-ene (**58**) in a ratio of 10:1 (1.52 g, in 30% yield, but 64% based on the consumed starting material). For **57**: ^{1}H NMR: δ 1.04 (6H, s, 9-CH_3), 1.60 (2H, s, H-10), 1.67 (3H, s, 7-CH_3), 2.14 (2H, s, H-6), 3.95 (4H, s, H-2 and H-3), 5.17 (1H, s, H-8); ^{13}C NMR: δ 131.2 (1), 128.((0), 109.2 (0), 64.0 (2, 2C), 43.5 (2), 39.8 (2), 31.6 (0), 30.3 (3, 2C), 23.4 (3); MS from GCMS *m/z* (%): 182 (27, M^+), 167 (16, M^+-CH_3), 154 (1), 139 (7), 123 (8), 96 (34), 86 (100), 67 (8), 41 (13). The ^{1}H NMR of the 6-ene isomer (**58**) is different from that of **57** at H-8 (δ 2.14,

2H, s) and H-6 (δ 5.34, 1H, s); MS of **58** from GCMS *m/z* (%): 182 (4, M^+), 167 (6, M^+-CH_3), 149 (1), 137 (12), 126 (100), 99 (9), 82 (13), 67 (3), 41 (6).

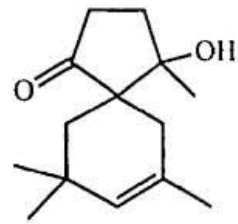
7,9,9-Trimethylspiro[4.5]dec-7-ene-1,4-dione (60)



Boron trifluoride etherate (7.0 mL, 57 mmol) and 1,2-bis(trimethylsilyloxy)cyclobutene (3.0 mL, 11 mmol) in 10 mL of dichloromethane were added to a solution of 7,9,9-trimethyl-1,4-dioxaspiro[4.5]dec-7-ene (622 mg, 3.42 mmol) in dichloromethane (60 mL). The mixture was stirred at -78°C under nitrogen overnight during which time the mixture was allowed to attain room temperature, and then it was poured into an ice-cold saturated sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane three times. The combined organic layers were washed with saturated sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was separated by flash chromatography (10%-16% ethyl acetate in hexane) to give the title compound as a colorless oil (601 mg, 85%): ^{1}H NMR: δ 0.94 (6H, s, 9-CH_3), 1.66 (2H, s, H-10), 1.76 (3H, s, 7-CH_3), 2.03 (2H, s, H-6), 2.59-2.68 (2H, m, H-2 or H-3), 3.02-3.11 (2H, m, H-2 or H-3), 5.20 (1H, s, H-8); ^{13}C NMR: δ 214.2 (0, 2C), 129.6 (1), 128.7 (0), 59.0 (0), 43.3 (2), 34.7 (2, 2C), 32.8 (0), 30.1 (3, 2C), 29.1 (2), 23.6 (3); MS from GCMS *m/z* (%): 206

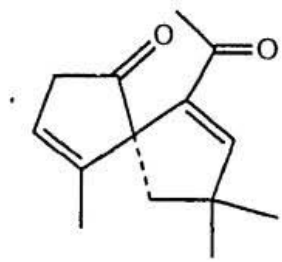
(100, M^+), 191 (38, M^+-CH_3), 178 (13), 163 (73), 145 (59), 107 (35), 91 (37), 77 (19), 41 (21).

rel-(4_R_,5_S_)-4-Hydroxy-4,7,9,9-tetramethylspiro[4.5]dec-7-en-1-one (61)



To a solution of 7,9,9-trimethylspiro[4.5]dec-7-ene-1,4-dione (897 mg, 4.35 mmol) in 30 mL of dry ether at -78°C under nitrogen was added 1.4 M methyllithium in ether (16 mL, 22 mmol). The solution became cloudy. After stirring for 2 hours, the solution was slowly poured into ice-cold brine. The aqueous layer was extracted with ether three times. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was separated by flash chromatography (12%-20% ethyl acetate in hexane) to give the title compound as a colorless oil (803 mg, 83%): ^1H NMR: δ 0.90 (3H, s, 9-CH_3), 1.00 (3H, s, 9-CH_3), 1.15 (3H, s, 4-CH_3), 1.71 (2H, d, J = 4.5 Hz, H-10), 1.74 (3H, s, 7-CH_3), 1.79 (2H, s, H-6), 1.96 (1H, m), 2.21 (2H, m), 2.56 (1H, m), 5.19 (1H, s, H-8); ^{13}C NMR: δ 220.5(0), 130.4 (1), 128.7 (0), 77.7 (0), 55.9 (0), 37.9 (2), 34.0 (2), 33.3 (2), 32.7 (3), 32.0 (0), 30.2 (2), 28.4 (3), 24.1 (3), 23.7 (3); MS from GCMS *m/z* (%): 222 (2, M^+), 189 (1), 164 (4), 149 (7), 123 (13), 99 (32), 83 (13), 43 (100).

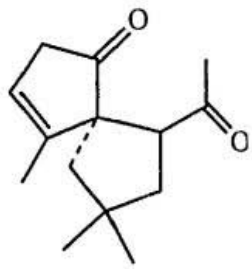
6-Acetyl-4,8,8-trimethylspiro[4.4]nona-3,6-dien-1-one (63)



rel-(4*R*,5*S*)-4-Hydroxy-4,7,9,9-tetramethylspiro[4.5]dec-7-en-1-one (321 mg, 1.45 mmol) in 20 mL of dichloromethane was cooled to -78°C. Ozone was passed through the solution until the solution turned blue. Excess ozone was removed by bubbling the solution with oxygen. Dimethyl sulfide (*ca.* 6 mL) was added, and the mixture was stirred under nitrogen overnight. The dichloromethane was evaporated. The residue was redissolved in benzene (20 mL) and a catalytic amount of *p*TSA (*ca.* 100 mg) was added. The mixture was heated at reflux for 2 hours. The water formed was removed by a Barrett water-separator. After the solution had cooled, saturated sodium bicarbonate was added. The aqueous layer was extracted with ether three times. The combined organic layers were washed with saturated sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was separated by flash chromatography (2% acetone in hexane) to provide **63** as a yellow oil (214 mg, 71%): ^{1}H NMR: δ 1.26 (3H, s, 8-CH3), 1.30 (3H, s, 8-CH3), 1.63 (3H, dd, *J* = 1.8, 2.4 Hz, 4-CH3), 1.71 (1H, d, *J* = 13.9 Hz, H-9), 1.91 (1H, d, *J* = 13.9 Hz, H-9), 2.25 (3H, s, acetyl), 2.88 (1H, ddq, *J* = 2.4, 3.3, 22.6 Hz, H-2), 3.18 (1H, ddq, *J* = 2.4, 3.3, 22.6 Hz, H-2), 5.76 (1H, dd, *J* = 1.8, 3.3 Hz, H-3), 6.69 (1H, s, H-7); ^{13}C NMR: δ 219.2 (0), 195.2 (0), 157.1 (1), 142.6

(0), 141.6 (0), 121.4 (1), 68.3 (0), 46.5 (2), 45.5 (0), 41.9 (2), 29.6 (3), 29.0 (3), 26.5 (3), 14.6 (3); MS from GCMS *m/z* (%): 218 (37, M^+), 203 (10, M^+-CH_3), 175 (96, M^+-$COCH_3$), 161 (23), 147 (44), 133 (43), 119 (18), 105 (22), 91 (25), 77 (16), 43 (100).

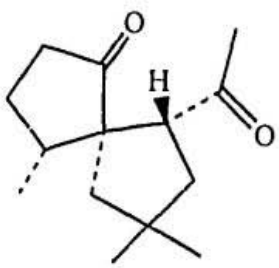
rel-(5*R*, 9*R*)-6-Acetyl-4,8,8-trimethylspiro[4.4]non-3-en-1-one (64)



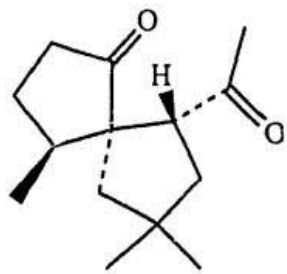
Lithium (*ca.* 60 mg) was added to liquid ammonia (*ca.* 50 mL) at -78°C. 6-Acetyl-4,8,8-trimethylspiro[4.4]nona-3,6-dien-1-one (205 mg, 0.939 mmol) in THF (15 mL) was added when the bath temperature reached -35°C. The mixture was stirred for 35 minutes and then it was quenched by addition of solid ammonium chloride until the blue color disappeared. The ammonia was allowed to evaporate at room temperature. The residue was partitioned between ether and water. The aqueous layer was extracted with ether three times. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was dissolved in dichloromethane (40 mL) and pyridinium chlorochromate (PCC, *ca.* 500 mg, 2.3 mmol) was added. The mixture was stirred at room temperature overnight. Ether was added and the mixture was filtered through a pad of silica gel. Separation of the residue by flash chromatography (2% acetone in hexane) provided the title compound as a

yellow oil (139 mg, 67%): ^{1}H NMR: δ 1.14 (3H, s, 8-CH3), 1.15 (3H, s, 8-CH3), 1.58 (1H, d, AB, *J* = 14.1 Hz, H-9), 1.66-1.71 (5H, m, 4-CH3, H-7, H-9), 1.93 (3H, s, acetyl), 2.04 (1H, t, *J* = 13.1 Hz, H-7), 2.85 (1H, ddq, *J* = 2.4, 4.8, 23.4 Hz, H-2), 2.98 (1H, ddq, *J* = 2.4, 5.1, 23.4 Hz, H-2), 3.51 (1H, dd, *J* = 6.3, 13.5 Hz, H-6), 5.70 (1H, br s, H-3); ^{1}H NMR (C_6D_6): δ 0.94 (3H, s, 8-CH3), 1.10 (3H, s, 8-CH3), 1.30 (1H, d, AB, *J* = 14.1 Hz, H-9), 1.48-1.55 (5H, m, 4-CH3, H-7, H-9), 1.59 (3H, s, H-11), 2.02 (1H, t, *J* = 13.0 Hz, H-7), 2.52 (2H, dq, *J* = 2.1, 4.5 Hz, H-2), 3.43 (1H, dd, *J* = 6.3, 13.5 Hz, H-6), 5.19 (1H, br s, H-3); ^{1}H NMR (C_5D_5N): δ 1.02 (3H, s, 8-CH3), 1.10 (3H, s, 8-CH3), 1.47 (1H, d, AB, *J* = 14.1 Hz, H-9), 1.60-1.65 (5H, m, 4-CH3, H-7, H-9), 1.90 (3H, s, H-11), 2.06 (1H, t, *J* = 12.9 Hz, H-7), 2.90 (2H, dq, *J* = 2.4, 4.8 Hz, H-2), 3.57 (1H, dd, *J* = 6.3, 13.5 Hz), 5.59 (1H, br s, H-3); ^{13}C NMR: δ 220.9 (0), 207.7 (0), 144.2 (0), 121.0 (1), 64.0 (0), 60.1 (1), 49.4 (2), 43.5 (2), 41.5 (2), 37.8 (0), 29.7 (3), 29.2 (3), 28.7 (3), 15.4 (3); MS from GCMS *m/z* (%): 220 (11, M^+), 177 (41, M^+-$COCH_3$), 159 (9), 149 (13), 121 (23), 107 (61), 77 (31), 43 (100).

rel-(4*R*,5*R*,6*R*)-6-Acetyl-4,8,8-trimethylspiro[4.4]nonan-1-one (66) and _rel_-(4*R*,5*S*,6*S*)-6-Acetyl-4,8,8-trimethylspiro[4.4]nonan-1-one (67)



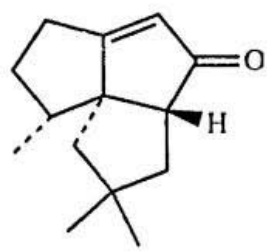
66



67

rel-(5*R*,6*R*)-6-Acetyl-4,8,8-trimethylspiro[4.4]non-3-en-1-one (98 mg, 0.45 mmol) was dissolved in dry methanol (30 mL) and 5% palladium on carbon (*ca.* 250 mg) was added. The mixture was shaken under 50 psi pressure of hydrogen for 1.5 hours and then filtered through a pad of silica gel. The residue was separated on a silica gel column with 4% acetone in hexane providing as a colorless oil *rel*-(4*R*,5*S*,6*S*)-6-acetyl-4,8,8-trimethylspiro[4.4]-nonan-1-one (**67**) (36 mg, 36%) and *rel*-(4*R*,5*R*,6*R*)-6-acetyl-4,8,8-trimethylspiro[4.4]-nonan-1-one (**66**) (63 mg, 64%). For the minor epimer (**67**): IR (film) υ_{max}: 1733, 1707 cm^{-1}; ^{1}H and ^{13}C NMR see Table **2** and **3**; MS from GCMS *m/z* (%): 222 (8, M^+), 207 (7, M^+-CH_3), 179 (19, M^+-$COCH_3$), 161 (33), 152 (60), 137 (30), 123 (35), 110 (17), 109 (23), 95 (36), 81 (27), 55 (31), 43 (100). For the major epimer (**66**): IR (film) υ_{max}: 1735, 1708 cm^{-1}; ^{1}H and ^{13}C NMR see Tables **1** and **3**; MS from GCMS *m/z* (%): 222 (3, M^+), 207 (5, M^+-CH_3), 179 (4, M^+-$COCH_3$), 161 (13), 152 (99), 137 (56), 123 (21), 110 (64), 109 (25), 95 (22), 81 (24), 55 (29), 43 (100).

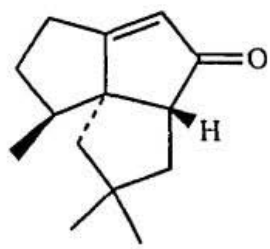
rel-(4*R*,8*R*,9*R*)-6,6,9-Trimethyltricyclo[6.3.0.0^{4,8}]undec-1-en-3-one (71)



Potassium *tert*-butoxide (76 mg, 0.67 mmol) was added to a solution of *rel*-(4*R*,5*R*,6*R*)-6-acetyl-4,8,8-trimethylspiro[4.4]nonan-1-one (70 mg,

0.32 mmol) in 10 mL of benzene. The mixture was heated at reflux for 20 minutes. It had a red color. When the solution had cooled, 10% HCl in water was added. The aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with saturated sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was separated by flash chromatography (2% acetone in hexane) to provide the title compound as a colorless oil (45 mg, 70%): IR (film) υ_{max}: 1704, 1630 cm^{-1}; ^{1}H and ^{13}C NMR see Tables **4** and **6**; MS from GCMS *m/z* (%): 204 (61, M^+), 189 (19, M^+-CH_3), 176 (9, M^+-CO), 148 (100), 133 (58), 107 (94), 91 (78), 77 (49), 41 (60).

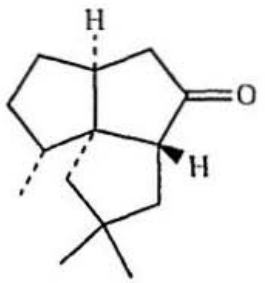
rel-(4*R*,8*R*,9*S*)-6,6,9-Trimethyltricyclo[6.3.0.0^{4,8}]undec-1-en-3-one (72)



Potassium *tert*-butoxide (121 mg, 1.07 mmol) was added to a solution of *rel*-(4*R*,5*S*,6*S*)-6-acetyl-4,8,8-trimethylspiro[4.4]nonan-1-one (110 mg, 0.500 mmol) in 10 mL of benzene. The mixture was heated at reflux for 15 minutes. It had a red color. When the solution had cooled, 10% HCl in water was added. The aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with saturated sodium bicarbonate and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was separated by flash chromatography (2%

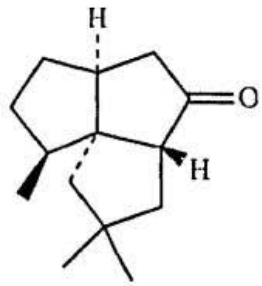
acetone in hexane) to provide the title compound as a colorless oil (64 mg, 63%): IR (film) υ_{max}: 1703, 1630 cm^{-1}; ^{1}H and ^{13}C NMR see Tables **5** and **6**; MS from GCMS *m/z* (%): 204 (7, M^+), 189 (2, M^+-CH_3), 176 (1, M^+-CO), 148 (32), 133 (28), 107 (69), 91 (68), 77 (58), 41 (100).

rel-(1*R*,4*S*,8*R*,9*S*)-6,6,9-Trimethyltricyclo[6.3.0.0^{4,8}]undecan-3-one (73)



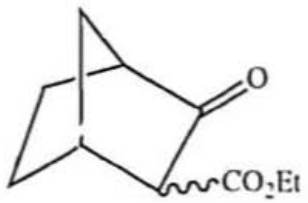
To a solution of *rel*-(4*R*,8*R*,9*R*)-6,6,9-trimethyltricyclo[6.3.0.0^{4,8}]-undec-1-en-3-one (43 mg, 0.21 mmol) in dry methanol (25 mL) was added 5% palladium on carbon (*ca.* 200 mg), and this was shaken under 50 psi pressure of hydrogen for 1 hour. The mixture was filtered through a pad of silica gel, and the filtrate was evaporated. The residue was purified on a silica gel column with 4% acetone in hexane providing the title compound as a colorless oil (43 mg, 98%): IR (film) υ_{max}: 1736 cm^{-1}; ^{1}H NMR: δ 0.97 (3H, d, J = 6.7 Hz, 9-CH_3), 0.985 (3H, s, 6-CH_3),1.01 (3H, s, 6-CH_3), 1.32-1.37 (3H, m), 1.59-1.92 (5H, m), 2.05-2.14 (2H, m), 2.41-2.46 (2H, m), 2.78 (1H, dd, J = 9.2, 18.5 Hz); ^{13}C NMR: δ 223.0 (0), 62.7 (0), 59.4 (1), 47.9 (2), 46.8 (2), 45.7 (1), 44.6 (2), 42.9 (1), 41.3 (0), 34.5 (2), 31.3 (2), 29.5 (3), 29.2 (3), 15.5 (3); MS from GCMS *m/z* (%): 206 (44, M^+), 191 (37, M^+-CH_3), 173 (6), 163 (44, M^+-$COCH_3$), 135 (30), 107 (62), 95 (71), 79 (49), 55 (52), 41 (100).

rel-(1_R_,4_S_,8_R_,9_R_)-6,6,9-Trimethyltricyclo[6.3.0.0^{4,8}]undecan-3-one (74)



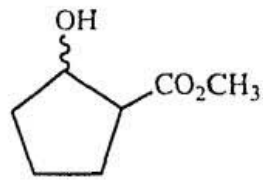
To a solution of _rel_-(4_R_,8_R_,9_S_)-6,6,9-trimethyltricyclo[6.3.0.0^{4,8}]-undec-1-en-3-one (40 mg, 0.19 mmol) in dry methanol (25 mL) was added 5% palladium on carbon (_ca._ 200 mg), and this was shaken under 50 psi pressure of hydrogen for 1 hour. The mixture was filtered through a pad of silica gel and the filtrate was evaporated. The residue was purified on a silica gel column with 4% acetone in hexane providing the title compound as a colorless oil (39 mg, 98%): IR (film) υ_{max}: 1736 cm^{-1}; ^{1}H NMR: δ 0.79 (3H, s, 6-CH3), 0.98 (3H, d, J = 6.6 Hz, 9-CH3), 1.03 (3H, s, 6-CH3), 1.17 (1H, dd, J = 6.1, 12.1 Hz), 1.43-1.65 (4H, m), 1.70-1.94 (4H, m), 2.05 (1H, ddd, J = 1.9, 7.3, 19.1 Hz, H-2), 2.43-2.50 (2H, m), 2.74 (1H, dd, J = 11.6, 19.1 Hz, H-2); ^{13}C NMR: δ 224.1 (0), 60.9 (0), 56.3(2), 53.6 (1), 47.0 (2), 46.0 (1), 45.8 (2), 45.4 (1), 39.6 (0), 33.2 (2), 32.7 (2), 29.7 (3), 28.1 (3), 14.0 (3); MS from GCMS _m/z_ (%): 206 (24, M^{+}), 191 (16, M^{+}-CH3), 163 (39, M^{+}-COCH3), 150 (51), 124 (23), 107 (62), 95 (53), 81 (48), 41 (100).

3-Carboxyethylbicyclo[2.2.1]heptan-2-one (77)



A solution of norcamphor (126 mg, 1.14 mmol) and diethyl dicarbonate (0.34 mL, 2.3 mmol) in 4.0 mL of THF was added to a stirred mixture of potassium hydride (500 mg, 4.36 mmol, 35% oil dispersion). After reflux for 1.5 hours, 10% HCl in water was added at 0°C. The aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with saturated sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (5% acetone in hexane) to give the title compound as a yellow oil (153 mg, 74%): IR (film) υ_{max}: 1760, 1724 cm^{-1}; ^1H NMR (8:5 mixture): δ 1.28 (3H, t, J = 7.2 Hz), 1.45-1.95 (12H, m), 2.19 (1H, t, J = 1.8 Hz), 2.23 (1H, t, J = 1.8 Hz), 2.65 (1H, m), 2.70 (1H, m), 2.84 (1H, d, J = 3.6 Hz), 2.91 (1H, m), 2.96 (1H, m), 3.05 (1H, dd, J = 0.6, 4.5 Hz), 4.17 (2H, q, J = 7.2 Hz); ^{13}C NMR (8:5 mixture): δ 209.7(0), 168.5 (0), 167.5 (0), 61.1 (2), 60.8 (2), 59.1 (1), 57.7 (1), 50.0 (1), 48.6 (1), 39.2 (1), 39.3 (1), 36.4(t), 35.7 (2), 27.0 (2), 24.1 (2), 23.7 (2), 22.9 (2), 14.0 (3); GC-MS *m/z* (%): 182 (9, M^+), 154 (74, M^+-CO), 137 (50, M^+-OCH_2CH_3), 126 (92), 108 (57), 81 (10), 67 (49), 41 (56); HRMS calcd. for $C_{10}H_{14}O_3$: 182.0942; found: 182.0929.

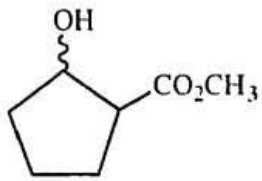
Reduction of 78 with $NaBH_4$ in the presence of calcium chloride



Anhydrous calcium chloride (228 mg, 2.05 mmol) was added to a solution of methyl 2-oxocyclopentanecarboxylate (**78**) (140 mg, 0.99 mmol) in methanol (10 mL). The mixture was stirred at room temperature for 30 minutes, then cooled to 0°C. Sodium borohydride (50 mg, 1.3 mmol) was added. Vigorous gas evolution occurred. After stirring for 15 minutes, the mixture was poured into 1M HCl (10 mL). The aqueous layer was extracted with ethyl acetate five times. The combined organic layers were washed with saturated sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (15-21% ethyl acetate in hexane) providing a minor isomer (41 mg, 29%) and a major isomer (101 mg, 71%) in the ratio 1:2.4. For the minor isomer: IR (film) υ_{max}: 3461, 1736, 1437 cm^{-1}; ^1H NMR: δ 1.60-1.69 (1H, m), 1.76-1.82 (2H, m), 1.91-2.05 (3H, m), 2.70 (1H, dt, J = 4.2, 9.9 Hz, H-1), 3.03 (1H, d, J = 3 Hz, OH), 3.73 (3H, s, COOMe), 4.45 (1H, dq, J = 3.3, 6.9 Hz, H-2); ^{13}C NMR: δ 175.3 (0), 73.7 (1), 51.8 (3), 49.4 (1), 33.9 (2), 26.3 (2), 22.0 (2); MS *m/z* (%): 144 (2, M^+), 127 (3, M^+-OH), 116 (29), 95 (18), 87 (100), 67 (50), 55 (96), 41 (6). For the major isomer: IR (film) υ_{max}: 3430, 1733, 1436 cm^{-1}; ^1H NMR: δ 1.61-1.85 (4H, m), 1.95-2.09 (2H, m), 2.47 (1H, s, OH), 2.67 (1H, m, H-2), 3.71 (3H, s, COOMe), 4.38 (1H, q, J = 6.6 Hz, H-2); ^{13}C NMR: δ 175.5 (0), 76.3 (1), 54.4 (3), 51.8 (1), 34.1 (2), 27.1 (2),

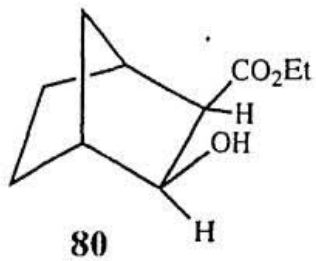
22.0 (2); MS *m/z* (%): 145 (1, M^++1), 126 (3, M^+-H_2O), 116 (20), 113 (26), 95 (8), 87 (98), 67 (56), 55 (100), 41 (6).

Reduction of 78 with $NaBH_4$ in the presence of manganese(II) chloride

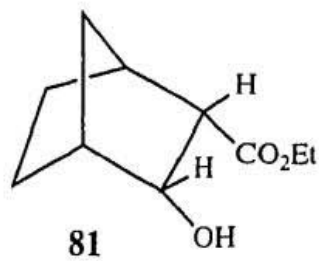


$MnCl_2 \cdot 4H_2O$ (525 mg, 2.65 mmol) was added to a solution of methyl 2-oxocyclopentanecarboxylate (189 mg, 1.33 mmol) in methanol (10 mL). The mixture was stirred at room temperature for 30 minutes, then it was cooled to 0°C. Sodium borohydride (64 mg, 1.7 mmol) was added. Vigorous gas evolution occurred. After stirring for 10 minutes, the mixture was poured into 1M HCl (10 mL). The aqueous layer was extracted with ethyl acetate five times. The combined organic layers were washed with saturated sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (15-21% ethyl acetate in hexane) providing a colorless oil composed of a 5:1 mixture of two products (133 mg, 70%): IR (film) υ_{max}: 3461, 1736 cm^{-1}. For the minor isomer: ^1H NMR: δ 2.67 (1H, m, H-1), 3.15 (1H, br s, OH), 3.73 (3H, s, OCH_3), 4.45 (1H, m, H-2). For the major isomer: ^1H NMR: δ 2.28 (1H, br s, OH), 2.67 (1H, m, H-1), 3.71 (3H, s, OCH_3), 4.38 (1H, m, H-2). Other signals were evident at: δ 1.61-2.08 (6H, m); ^{13}C NMR: δ 175.4 (0), 175.3 (0), 76.3 (1), 73.7 (1), 52.5 (3), 51.8 (1), 49.4 (1), 34.1 (2), 33.9 (2), 27.1 (2), 26.3 (2), 22.0 (2).

2α-Hydroxy-3α-carboxyethylbicyclo[2.2.1]heptane (80) and
2β-Hydroxy-3β-carboxyethylbicyclo[2.2.1]heptane (81)



80



81

$NaBH_4$ (21 mg, 0.56 mmol) was added to a solution of 3-carboxyethylbicyclo[2.2.1]heptan-2-one in methanol (10 mL). The mixture was stirred for 30 minutes at room temperature. Then the mixture was poured into 1M HCl (10 mL). The aqueous layer was extracted with ethyl acetate five times. The combined organic layers were washed with saturated sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (10-15% ethyl acetate in hexane) providing a yellow oil composed of a 7:1 mixture of two products (89 mg, 90%): IR (film) υ_{max}: 3462, 1731, 1704 cm^{-1}. For the minor isomer (**80**): ^1H NMR: δ 1.28 (3H, t, J = 7.2 Hz), 1.37 (2H, m), 1.40-1.50 (2H, m), 1.82-2.00 (2H, m), 2.39 (1H, m), 2.51 (1H, br s), 2.74 (1H, dd, J = 4.8, 9.9 Hz), 4.17 (2H, q, J = 7.2 Hz), 4.74 (1H, d, J = 6.3 Hz); ^{13}C NMR: δ 174.8 (0), 71.5 (1), 60.6 (2), 45.5 (1), 42.9 (1), 41.0 (1), 35.8 (2), 24.5 (2), 19.5 (2), 14.2 (3). For the major isomer (**81**): ^1H NMR: δ 1.27 (3H, t, J = 7.2 Hz), 1.39 (1H, m), 1.59 (3H, m), 1.88 (1H, m), 1.77 (1H, d, J = 3.0 Hz), 1.99 (1H, dd, J = 2.7, 3.9 Hz), 2.33 (1H, m), 2.46 (1H, m), 4.14 (2H, q, J = 7.2 Hz), 4.43 (1H, dd, J = 3.9, 8.1 Hz); ^{13}C NMR: δ 174.9 (0), 75.8 (1), 60.5 (2), 55.7 (1), 42.0 (1), 41.3 (1), 35.7 (2), 29.7 (2), 19.3 (2), 14.2 (3); MS *m/z*

(%): 156 (45, M^+-CO). 139 (18), 128 (16), 110 (23), 101 (55), 88 (28), 81 (37), 67 (100), 43 (77), 41 (92); HRMS calcd. for $C_9H_{16}O_2$ (M^+-CO): 156.1149; found: 156.1151.

Chapter 2

MICROBIAL REDUCTION OF PROCHIRAL SPIRODIKETONES

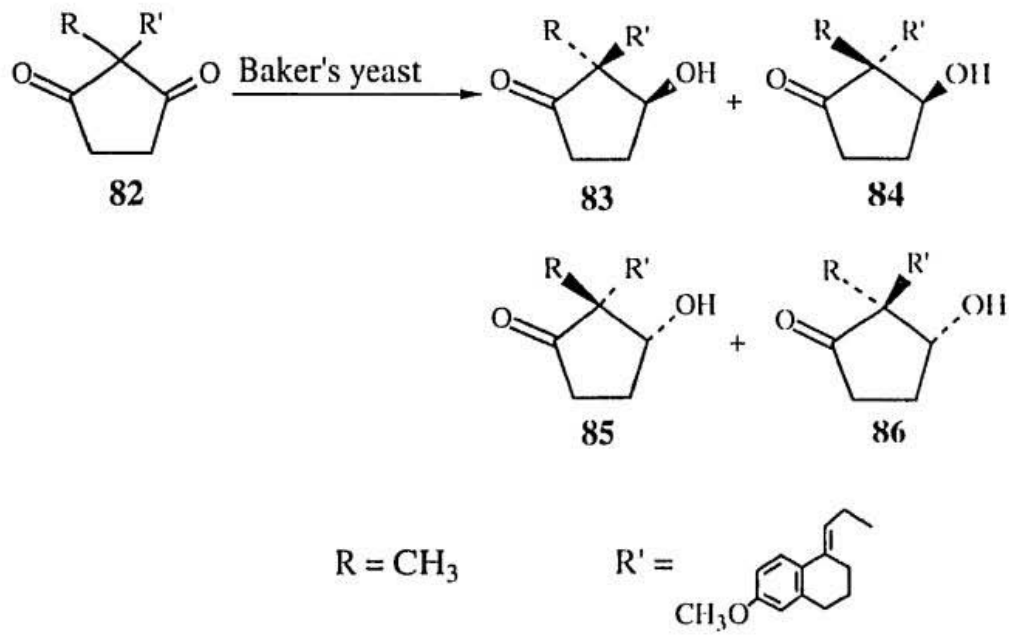
I. Introduction

Enzymes acting as specific and chiral catalysts have been recognized for many years.[39-43] Biochemical procedures that utilize enzymes are becoming accepted as routine procedures in organic synthesis. Recently the application of enzyme-mediated reactions has increased in both academic and industrial laboratories, particularly in the pharmaceutical area, to meet the requirements for enantio- and diastereodifferentiation. This is because enzymatic reactions give products of higher optical purity than do the corresponding chemical reactions. Enzymatic reactions also produce less chemical waste and are therefore environmentally safer.

Baker's yeast is one of the most efficient reagents for the enantioselective reduction of many prochiral ketones. The yeast is easy to use, since it requires only tap water together with the substrate; the yeast itself contains enough nutrients to support its dehydrogenase enzyme. Yeast reduction of 1,3-cyclopentanediones, which have two prochiral carbonyls, has interesting synthetic potential. Kosmol *et al.*[44] first investigated this enzymatic reduction of 2,2-dialkyl-substituted 1,3-cyclopentanedione (**82**) (Scheme **18**), and they applied the reaction as the chirality-introducing step in an industrial total synthesis of estradiol. With the appropriate choice of the microbiological system, the reduction could be carried out with nearly

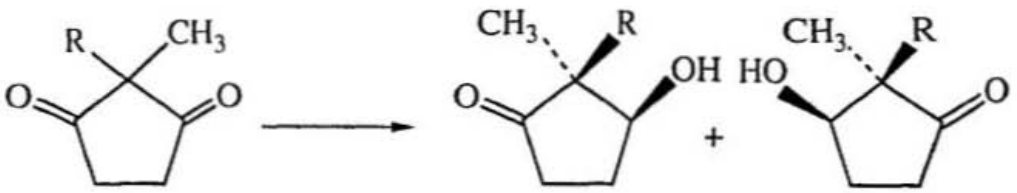
complete stereoselectivity. Only one (**83**) of the four possible stereoisomers (**83-86**) was obtained.

Scheme **18** Yeast reducton of 2,2-dialkyl 1,3-cyclopentanedione by Kosmol



Many enzymes are able to make prochiral distinctions. Their selectivity is based on the formation of a preferred enzyme-substrate complex, which leads to a favored catalytic reaction of only one of the two enantiotopic reaction sites. Microbial reductions of several 2,2-disubstituted 1,3-diones have been reported with a variety of microorganisms to provide chiral products.[45, 46] In more recent work, Brooks *et al.*[47, 48] carried out an investigation with baker's yeast designed to establish the relationship between stereoselectivity and the differences in size between the two substituents attached at C-2 of the 1,3-cyclopentanedione (Scheme **19**).

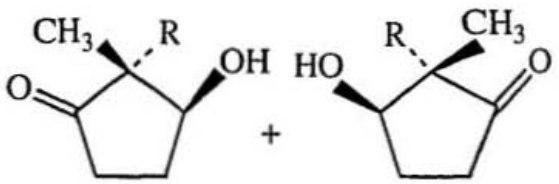
Scheme **19** Yeast reducton of 2,2-disubstituted 1,3-cyclopentanedione by Brooks



87 R=$CH_2CH_2CH_3$ **90a** **90b**

88 R=$CH_2CH{=}CH_2$ **92a** **92b**

89 R=$CH_2C{\equiv}CH$ **94a** **94b**



91a **91b**

93a **93b**

95a **95b**

In Table **9** the results of the yeast reduction are compared with the monoreduction products formed by reduction with $NaBH_4$. It is important to point out that only the 2*S*,3*S* (**90a**, **92a**, **94a**) and 2*R*,3*S* (**91a**, **93a**, **95a**) diastereoisomers were formed by yeast reduction. The enantiomeric purity of each chiral ketoalcohol was over 98% ee, as determined by the ^1H NMR spectrum of the corresponding Mosher's ester of the product.[49]

Table 9. Reduction of prochiral 2,2-disubstituted 1,3-cyclopentanediones by baker's yeast and by $NaBH_4$

dione	Baker's yeast	$NaBH_4$
87	**90a** (100%)	**90a,b** (85%)
		91a,b (15%)
88	**92a** (90%)	**92a,b** (75%)
	93a (10%)	**93a,b** (25%)
89	**94a** (67%)	**94a,b** (67%)
	95a (33%)	**95 a,b** (33%)

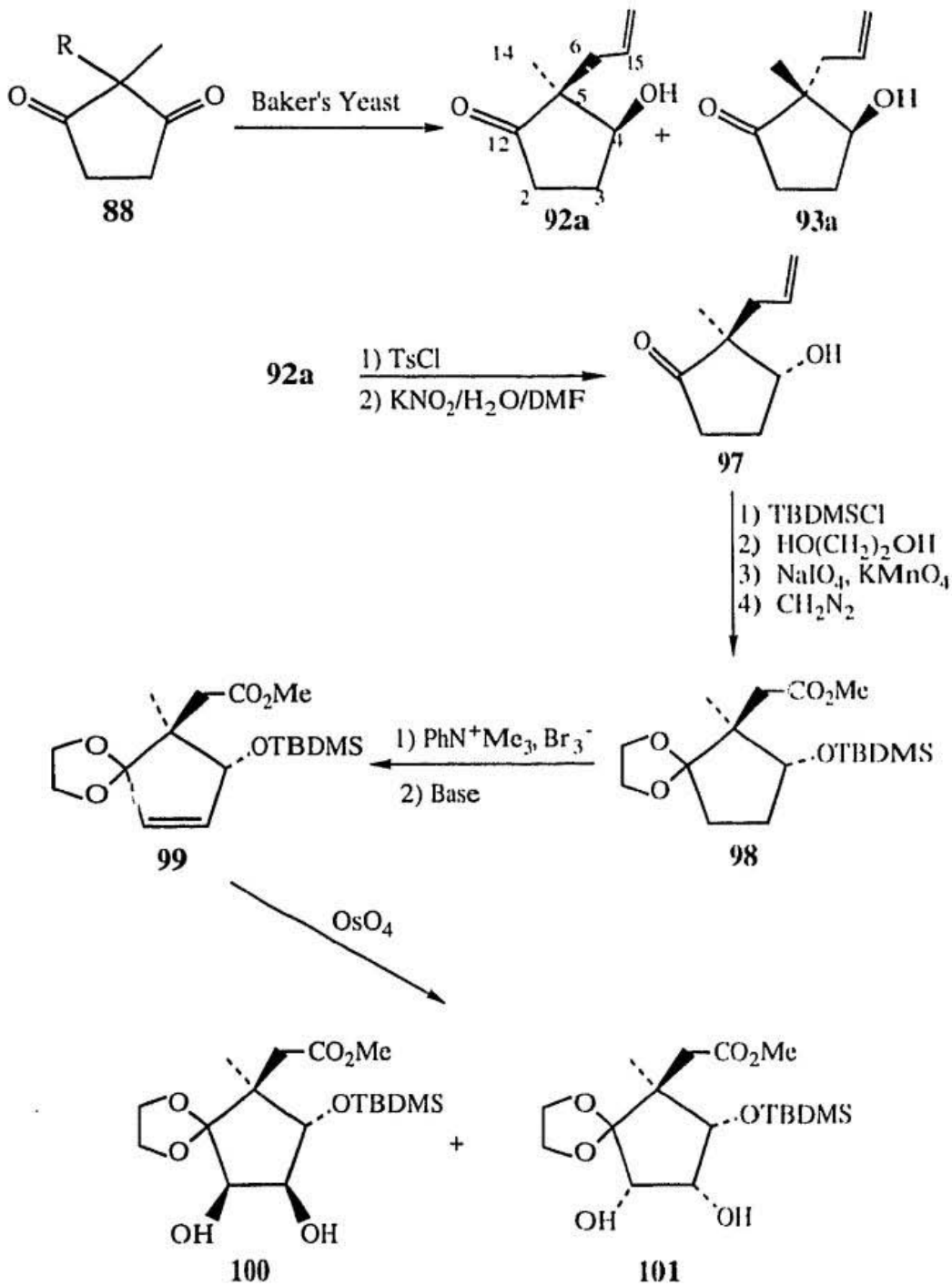
The baker's yeast reduction was more stereoselective than $NaBH_4$, and, like $NaBH_4$ reduction, the microbial system was very sensitive to changes in the substituent changes. Both the microbial and $NaBH_4$ reductions had the same trend of decreasing stereoselectivity: propyl> allyl> propynyl.

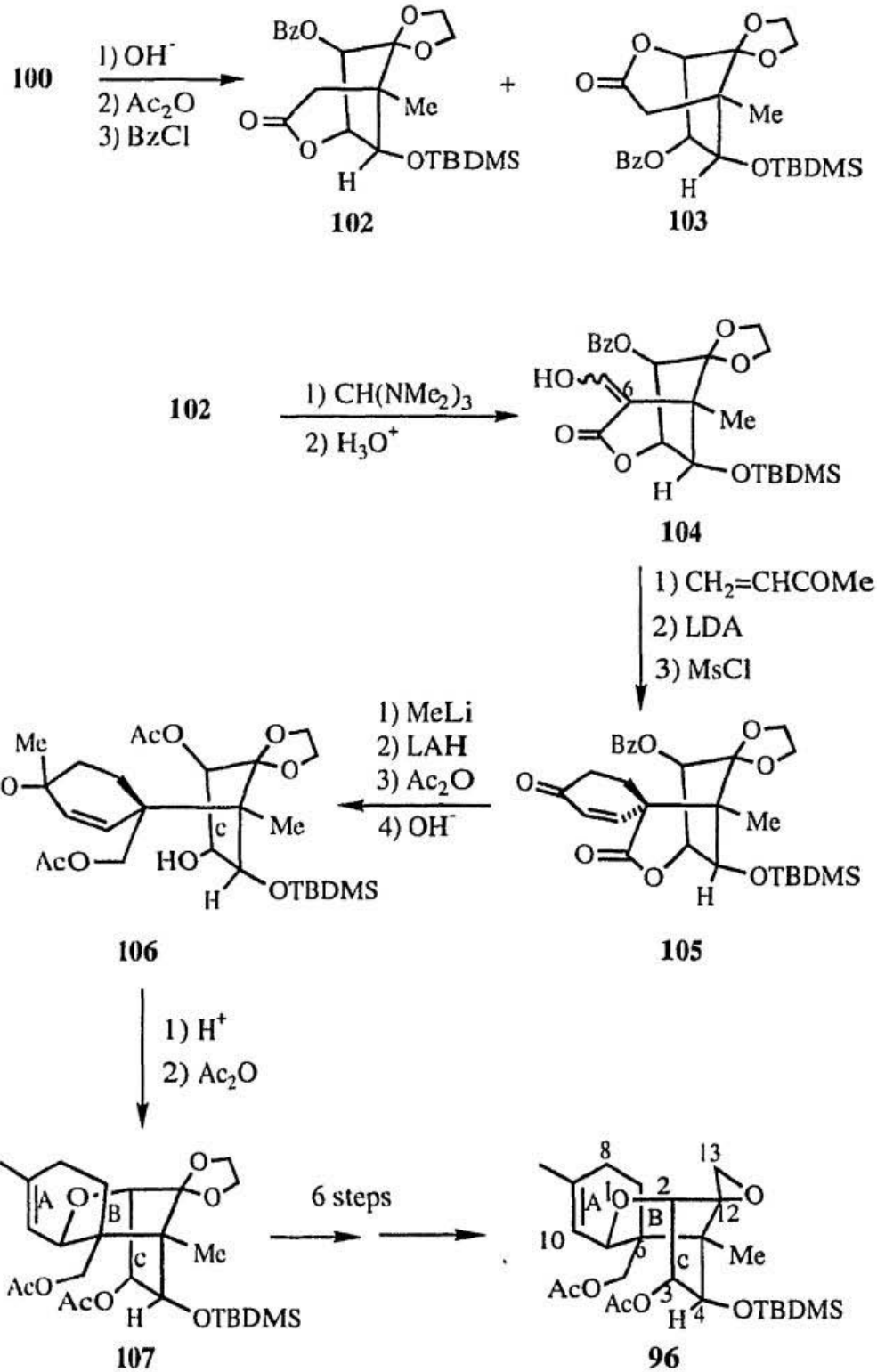
In conjunction with the stereoselectivity studies, Brooks and coworkers[50, 51] used actively fermenting baker's yeast in a key step to synthesize optically pure trichothecene derivatives like anguidine (**96**) (Scheme **20**). Baker's yeast reduced one of the two enantiotopic carbonyl groups of 2-allyl-2-methyl-1,3-cyclopentanedione (**88**), providing the keto-alcohols **92a** (2*S*,3*S*) and **93a** (2*R*,3*S*) in a ratio of 9:1 (Table **9**). Examination of the C-ring of the anguidine (**96**) reveals that keto-alcohol **92a** has the correct absolute configuration at the quaternary carbon C5, but the configuration of the hydroxy group in **92a** is opposite to that required at C4. Therefore all the other chiral centers must be elaborated in the course of

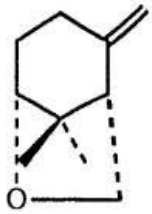
the synthesis. Inversion of the 4-OH group in **92a** was effected in two steps. Compound **92a** was reacted with *p*-toluenesulphonyl chloride in pyridine, and the corresponding tosylate was transformed to (2*R*,3*R*)-keto-alcohol **97** with potassium nitrite. After protection of the hydroxy group and the ketone, oxidative cleavage of the double bond provided the carboxylic acid, which was converted to the corresponding methyl ester **98** with diazomethane. Bromination of **98** with trimethylphenylammonium tribromide followed by treatment with DBU gave compound **99**. Osmium tetroxide oxidation gave a separable mixture (5:1) of two isomeric *cis*-vicinal diols **100** and **101**. Lactonization of **100** by treatment of the carboxylate salt with excess acetic anhydride, and protection of the remaining hydroxy group gave a 3:1 mixture of bicyclic lactones, which could be separated as the benzoates **102** and **103**. The synthesis of ring A was completed by introducing a hydroxymethylene group on C6 to provide compound **104**. Compound **104** was converted into **105** by stereocontrolled Robinson spiroannulation. Reaction of **105** with methyllithium provided an allylic alcohol. The lactone was opened reductively with $LiAlH_4$ followed by triacetylation. Selective deacetylation gave **106**. The 2-hydroxy function was then used for closure of ring B via an acid-induced S_N2'-reaction. Finally, **107** was converted into **96** via six routine steps.

Mori and coworkers used baker's yeast reduction of 2,2-dimethyl-cyclohexane-1,3-dione (**108**) as the key steps to synthesize (1*S*,5*R*)-karahana ether (**109**),[52] (1*S*,5*R*)-karahana lactone (**110**),[52] and both enantiomers of ancistrofuran (**111a**) and (**111b**).[53]

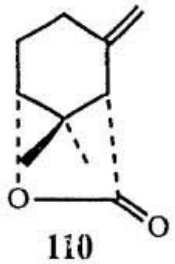
Scheme **20** Brooks' synthesis of anguidine (**96**)



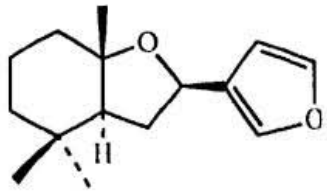

100
1) OH⁻
2) Ac2O
3) BzCl
BzO
Me
OTBDMS
H
102
+
103
102
1) CH(NMe2)3
2) H3O+
HO
104
1) CH2=CHCOMe
2) LDA
3) MsCl
105
1) MeLi
2) LAH
3) Ac2O
4) OH⁻
AcO
106
1) H+
2) Ac2O
A
B
c
107
6 steps
96



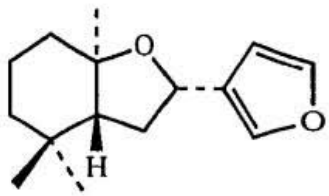
109



110



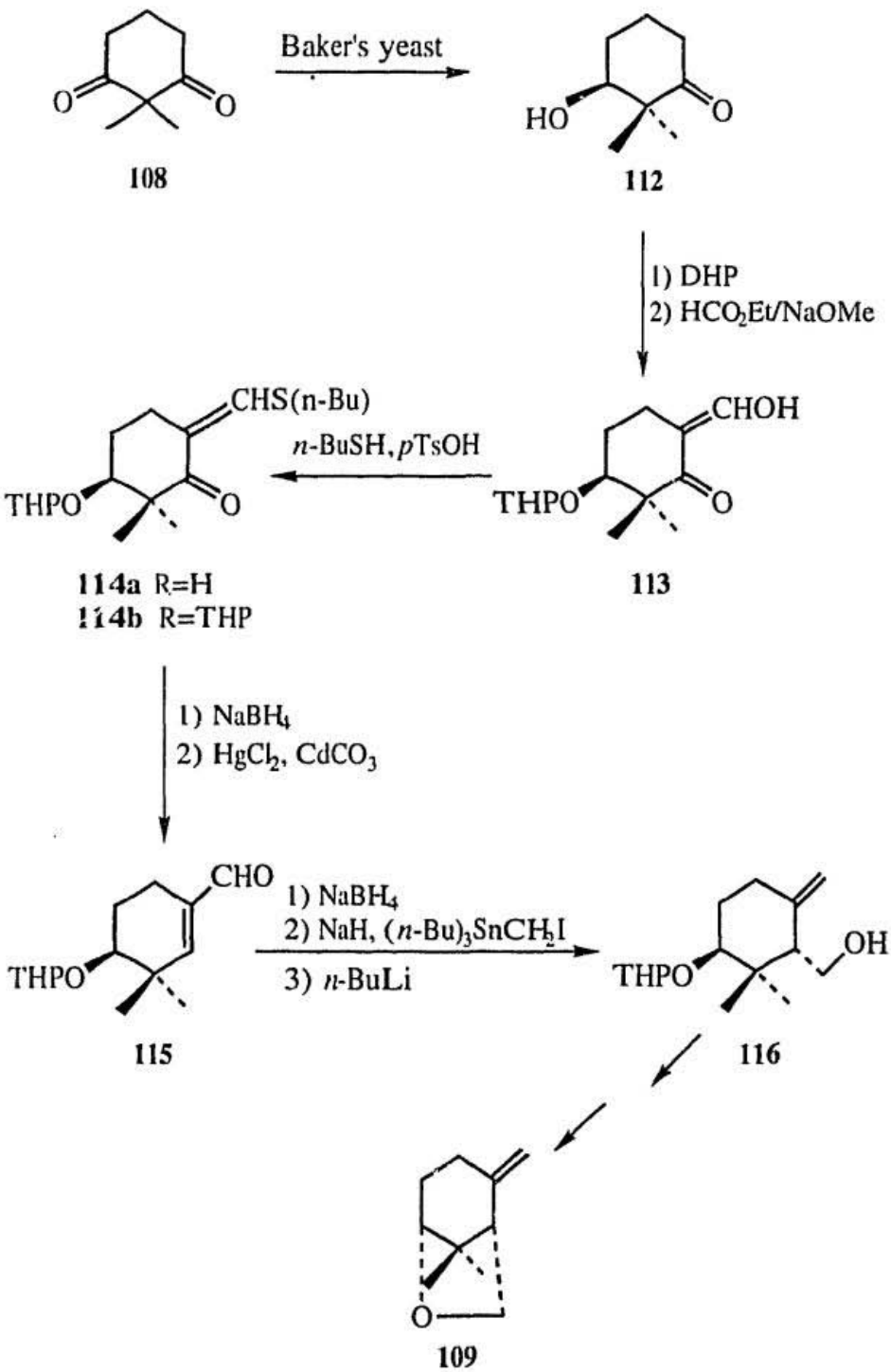
111a



111b

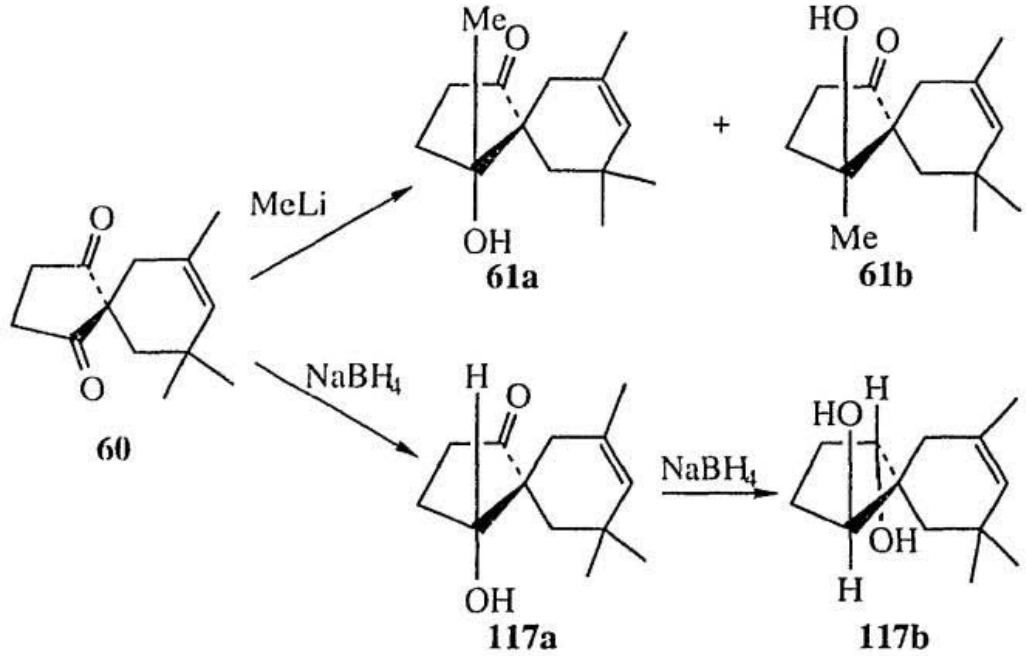
Scheme **21** shows the route to (1*S*,5*R*)-karahana ether (**109**). Baker's yeast reduction of the prochiral diketone **108** gave (3*S*)-keto-alcohol **112** in 99% ee. Compound **112** was treated with HCO_2Et and NaOMe to give **113**. Reaction of **113** with *n*-BuSH, and *p*TSA yielded **114b** along with a considerable amount of **114a** (**114a**:**114b**=1:2). Reprotection of **114a** with dihydropyran and *p*TSA smoothly regenerated **114b**. Reduction of **114b** with $NaBH_4$ and removal of the sulfur with $HgCl_2$ and $CdCO_3$ furnished **115**. Compound **116** was obtained by reducing the aldehyde with $NaBH_4$, followed by alkylation with $(n\text{-}Bu)_3SnCH_2I$, and a [2,3]- sigmatropic rearrangement. (1*S*,5*R*)-Karahana ether (**109**) was reached after a further four steps from **116**.

Scheme 21 Mori's synthesis of (1*S*,5*R*)-karahana ether (**109**)

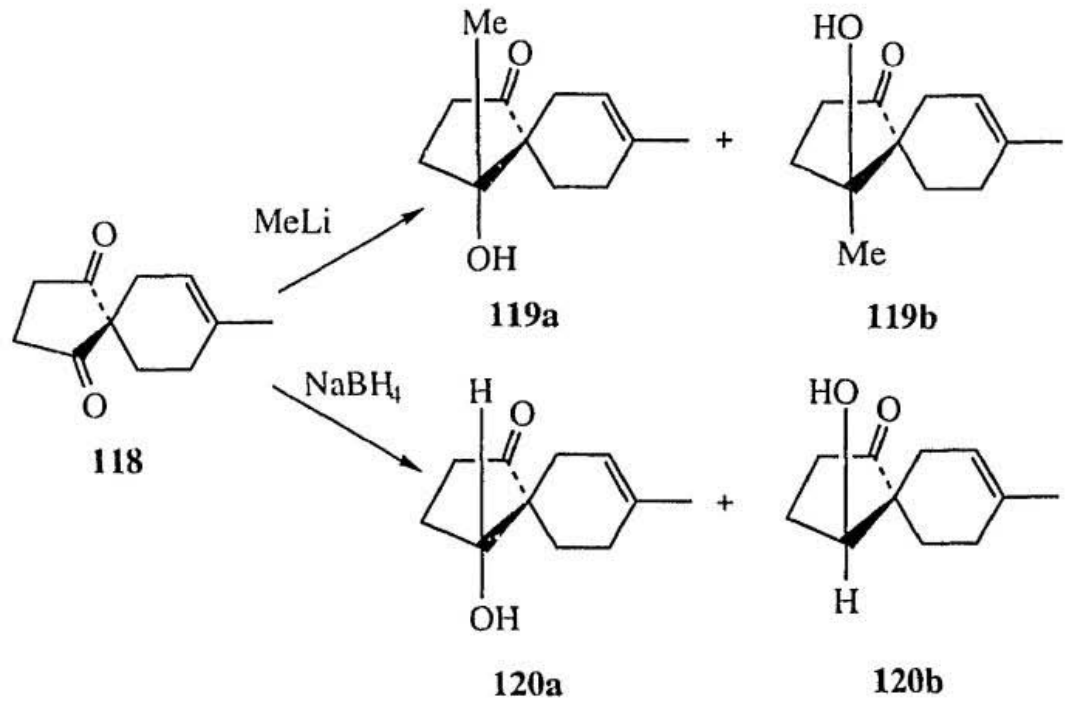


We were interested in the chiral reduction of our spirodiketone systems. During the total synthesis of (±)-pentalenene (**2**), Wu[31] found remarkable facial selectivity in the $NaBH_4$ reduction of the spirodiketone **60.** This gave a single (racemic) product **117a**, and further reduction gave *trans* diol **117b**. Reaction of methyllithium with **60** produced a 63:1 mixture of **61a** and **61b**, respectively (Scheme **22**). Also, in a synthesis of prezizaene, Liu[54] reported that $NaBH_4$ reduction of spirodiketone **118** gave **120a** and **120b** in a 2.5:1 ratio, and addition of methyllithium to **118** gave **119a** and **119b** in a 4:1 ratio, respectively (Scheme **23**). It was clear that there was dramatically less facial selectivity of the purely chemical reactions with spirodiketone **118**. Baker's yeast reductions on these spirodiketones and others of synthetic interest were to be studied, and the facial selectivities were to be compared with those by $NaBH_4$ reduction. The enzymatic reduction was expected to proceed not only with facial selectivity, but also enantiospecifically.[48, 55, 56] Thus, the baker's yeast reduction was to provide an entry to the synthesis of optically pure triquinanes, and this will also be reported in this chapter.

Scheme 22 Methyllithium addition and $NaBH_4$ reduction of **60**



Scheme 23 Methyllithium addition and $NaBH_4$ reduction of **118**



I. Results and Discussion

Scheme **24** Baker's yeast reduction of **121**

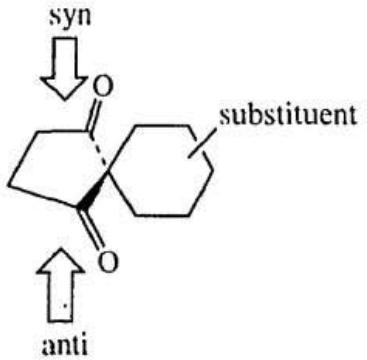
121 **122**

We first applied baker's yeast reduction to the simple spirodiketone **121** (Scheme **24**). The typical procedure was developed, based largely on the procedure of Mori,[52] that involved initial fermentation of some sucrose in water at 31°C by the yeast, then spirodiketone **121** in 0.2% Triton X-100 and 95% ethanol was added, and the fermentation was continued for 48 hours. Reduction of compound **121** required only a small amount of yeast. The starting material **121** appeared to be completely transformed into a keto-alcohol **122**. The mass spectrum of the product showed a molecular ion at *m/z* 168. Absorption maxima in the IR for the ring carbonyl and the hydroxyl were found at 1722 and 3425 cm^{-1}, respectively. The ^{1}H NMR spectrum of **122** was more complicated than that of **121**, since **122** was no longer symmetrical. A one-proton signal at δ 4.27 indicated a proton attached to the carbon bearing the hydroxy group, confirming that only one carbonyl was reduced. The ^{13}C NMR spectrum showed a carbonyl resonance at δ 222.1 and another signal for the carbon bearing the hydroxy

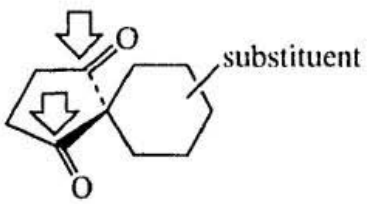
group at δ 75.0 (C-4). The specific rotation of **122** ([α]ᴅ = +80°) verified that enantioselective reduction of a prochiral ketone in compound **121** had occurred. Both the ^{1}H and the ^{19}F NMR spectra of the Mosher's ester [(+)-α-methoxy-α-trifluoromethylphenylacetate] of **122** demonstrated that the optical purity of **122** was over 98% ee.

Compound **121** was a simple symmetrical compound with no substituent on the cyclohexane ring. A series of spirodiketones with different substituents on the six-membered ring was then examined. Reduction could be to either face of the five-membered ring, which would lead to diastereomers (Scheme **25**). Reduction at one carbonyl or the other, on the same face of the five-membered ring, would lead to two enantiomers.

Scheme **25** Principle of yeast reduction: facial selectivity and enantioselectivity



Facial Selectivity---Diastereomers

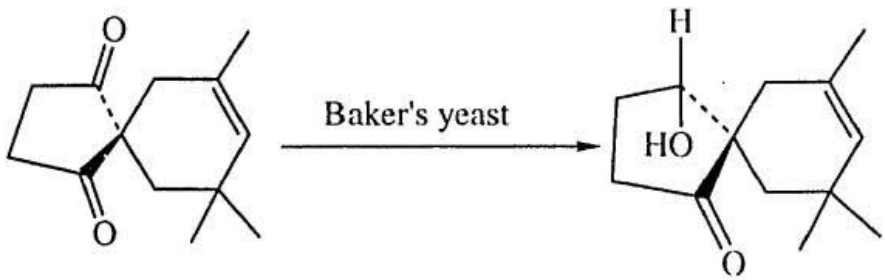


Enantioselectivity---Enantiomers

Whereas diastereoselectivity might be expected in a purely chemical (achiral) process, the yeast reductase is a chiral reducing agent so both diastereoselectivity and enantioselectivity could result.

The spirodiketone **60** was an important intermediate in the synthesis of (±)-pentalenene (**2**) and in our route to (±)-deoxypentalenic acid (**1b**). Unlike in **121**, the spirocenter (C-5) of compound **60** is prochiral. Nevertheless, yeast reduction of **60** produced only one product (**123**), but some starting material **60** was also recovered (Scheme **26**).

Scheme **26** Baker's yeast reduction of **60**



60 **123**

The reduction required roughly four times more baker's yeast than did the reduction of **121.** A larger excess of yeast did not improve yields and some diol was also formed. A small amount of starting material was always recovered. The gross structure and the relative stereochemistry of **123** were evident from the ^{1}H NMR and ^{13}C NMR data. The chemical shift of H-4 was δ 4.24, and that of C-4 was δ 74.7. The remaining carbonyl carbon was at δ 221.7. The reduction of **60** had very high facial selectivity, since only one product was obtained. The ^{1}H NMR and ^{13}C NMR spectra of

compound **123** were the same as those of compound **117a** (racemic), which was obtained by reduction with $NaBH_4$. The stereochemistry of **117a** was established by nOe difference spectra. The addition of hydride was clearly from the face of the five-membered ring *syn* to the double bond. Therefore, the yeast reduction was also from the *syn* face.

The specific rotation of **123** was $[\alpha]_D = +45°$. Initially we used a chiral shift reagent Eu(hfc)$_3$ {tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato] europium (III)} to determine the enantioselectivity by ^1H NMR (Figure **8**). The racemic compound **117a** led to unequal shifts for the enantiomeric carbinol resonances such that two peaks separated, in a ratio of 1:1. Compound **123** gave only a single peak,for the carbinol hydrogen at a very similar concentration of the shift reagent, therefore the optical purity of **123** was over 95% ee. However, ^1H and ^{19}F NMR spectra of the Mosher's ester of **123** more unequivocally determined the optical purity of **123** to be at least 98% ee (Figure **9**). For this ester, the H-4 was shifted to δ 5.41 and the vinyl proton was at δ 5.20.

With the high facial selectivity and the high enantioselectivity, the yeast reduction of compound **60** to **123** might be exploited as a key step to synthesize triquinanes such as (+)-pentalenene[3h] in an optically pure form. A detailed discussion of this synthesis is presented later.

Spirodiketone **118** was used in a route to prezizaene. Yeast reduction of **118** produced two isomers with a diastereoselectivity of 2.5:1, which was no better than in the $NaBH_4$ reduction (2.5:1) (Scheme **27**).

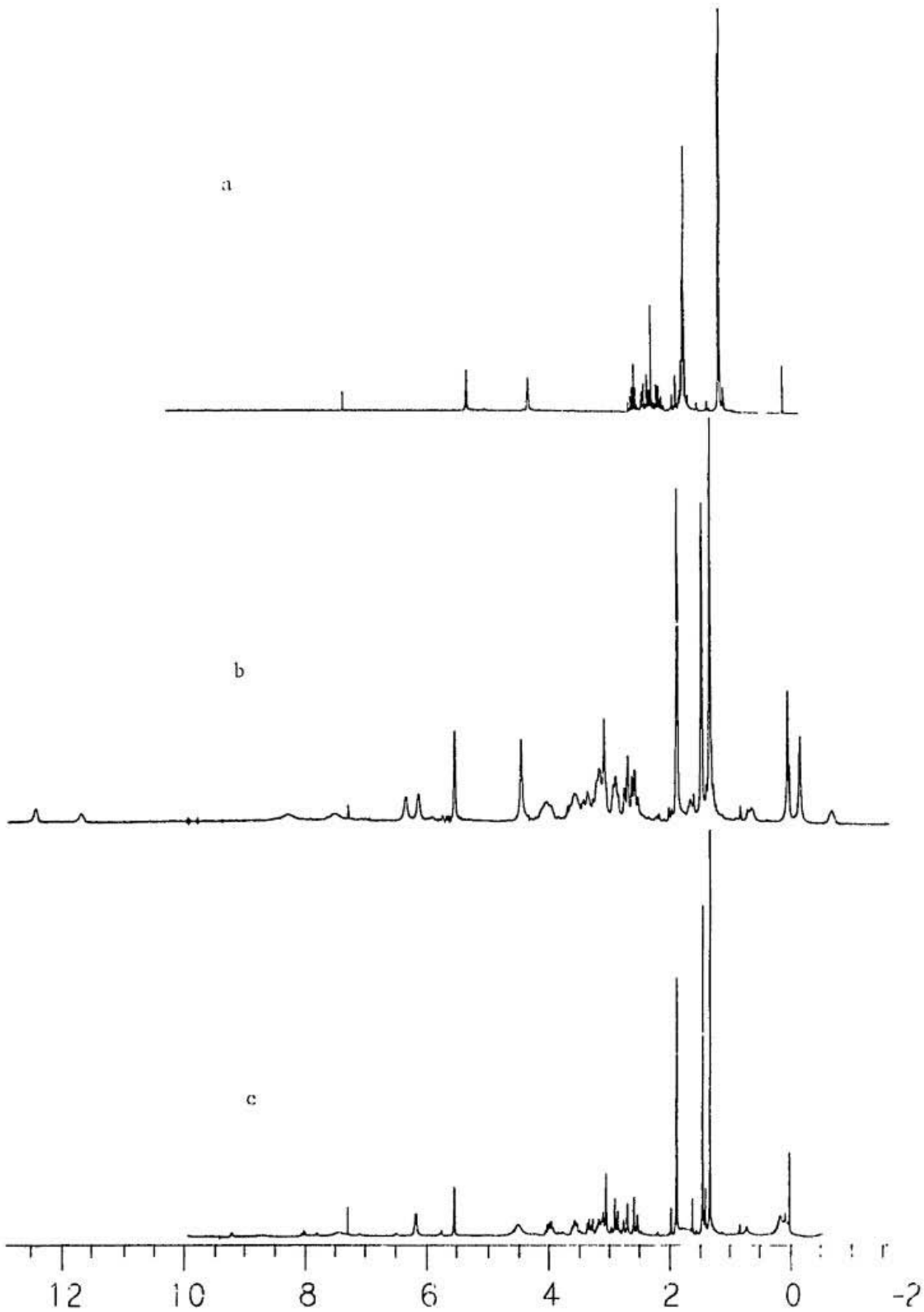


Figure 8 a) ^{1}H NMR spectra of **123** and **117a** b) ^{1}H NMR spectrum of **117a** plus Eu(hfc)$_3$ c) ^{1}H NMR spectrum of **123** plus Eu(hfc)$_3$

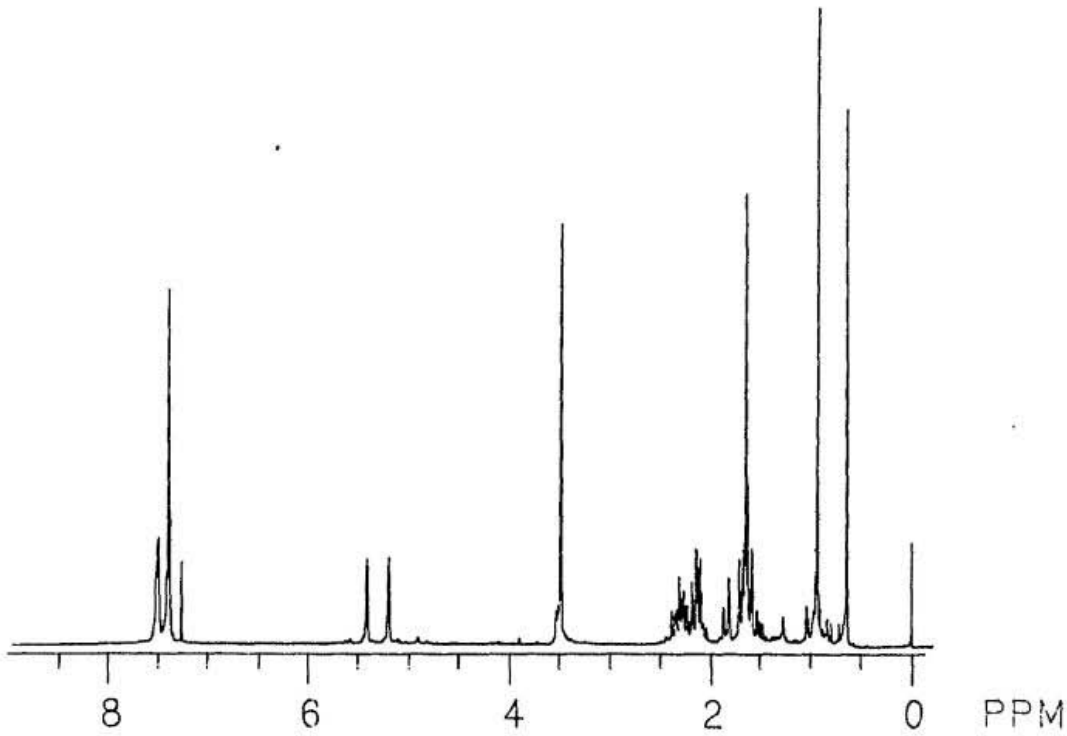
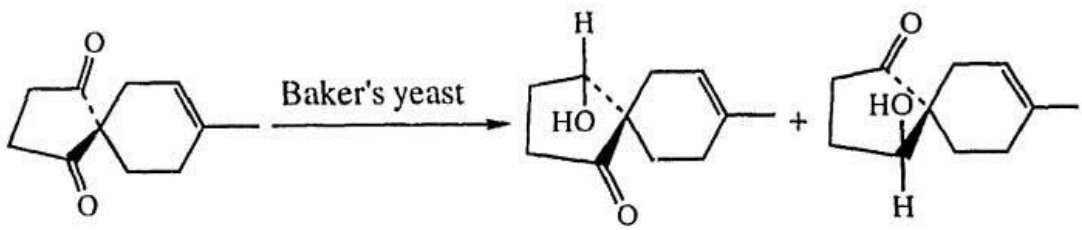


Figure **9** ^{1}H NMR spectrum of **123** Mosher's ester

Scheme **27** Baker's yeast reduction of **118**



118 **124a** **124b**

The reduction used four times more yeast than did the reduction of **121**. No starting material remained and the isolated yield was 74%. The ratio

of the two diastereomers was determined by integration of the ^1H NMR spectrum. The chemical shift of the vinyl proton (H-7) of the major isomer was δ 5.28 and for the minor isomer it was δ 5.44. In the ^{13}C NMR spectrum of the mixture, signals at δ 134.7 and δ 117.2 (C-7) were assigned to the double bond carbons of the major isomer, and signals at δ 145.0 and δ 119.2 (C-7) were attributed to the double bond carbons of the minor isomer. Both the ^1H NMR and the ^{13}C NMR spectra of **124a** and **124b** were the same as those of **120a** and **120b**, which were obtained by $NaBH_4$ reduction of **118.** The mixture of the keto-alcohol epimers **124a** and **124b** proved very difficult to separate, but the mixture showed optical activity ($[\alpha]_D = +89°$). The enantiomeric purity of each diastereomer was over 98% ee, which was determined from the ^1H and ^{19}F NMR spectra of the Mosher's esters of **124a** and **124b** (Figure **10**). The ratio of the two ester isomers was 1.6:1.

The results of the reductions of spirodiketones **60** and **118** showed that the facial selectivity was greatly influenced by substituents on the six-membered ring. To determine how these substituents affected the selectivity, reduction of more spirodiketones **125**, **126**, **127** and **128** with baker's yeast was investigated (Scheme **28**). Yeast reduction of **125** gave an exclusive, optically active product **129**. Its ^1H NMR spectrum showed a carbinol resonance at δ 4.48 (H-4), and in the ^{13}C NMR spectrum the carbinol appeared at δ 79.5 (C-4). The signal at δ 222.0 was due to the remaining carbonyl carbon. The spectra of compound **129** were the same as those of the major isomer obtained by reduction **125** with $NaBH_4$.

Yeast reduction of compound **126** gave one optically active product too. Both the ^1H NMR and the ^{13}C NMR spectra confirmed that the product

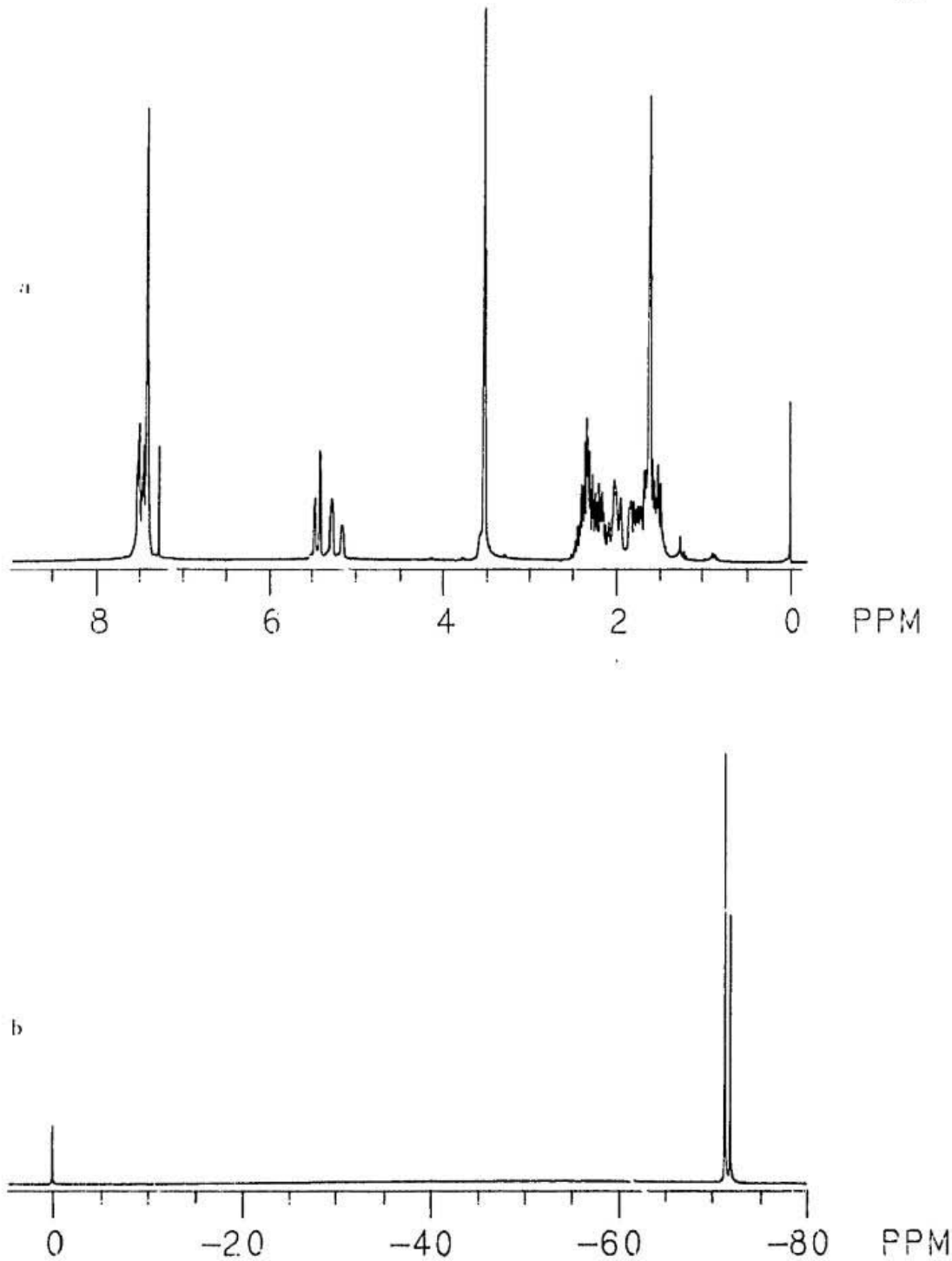
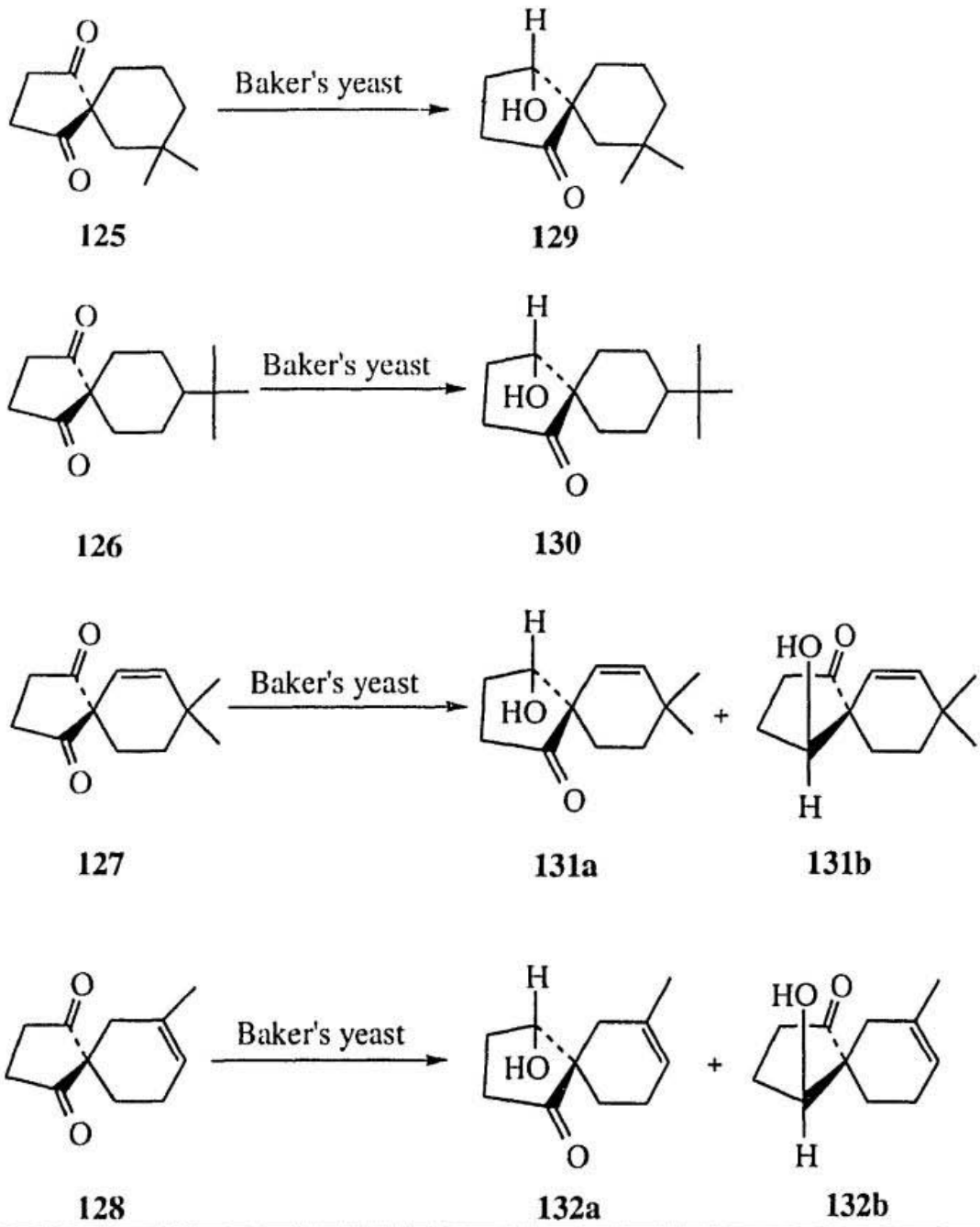


Figure 10 a) ^{1}H NMR spectrum of **124a** and **124b** Mosher's ester

b) ^{19}F NMR spectrum of **124a** and **124b** Mosher's ester

130 was same as the major compound obtained by reduction of **126** with $NaBH_4$. Yeast reduction of compound **127** provided a diastereomeric mixture **131a** and **131b**, in a ratio of 1:1. The two isomers were clearly evident from the ^1H NMR and ^{13}C NMR spectra. Vinyl doublets were found at δ 5.12 (J = 9.9 Hz), δ 5.37 (J =10.2 Hz), δ 5.73 (J = 9.9 Hz), and δ 5.88 (J = 10.2 Hz). The chemical shifts for H-4 were δ 4.11 and δ 4.15 (in a ratio of 1:1). The result was the same for the yeast reduction of **128**, which produced a 1:1 diastereomeric mixture. In the ^1H NMR spectrum of the product, the vinyl signals at δ 5.44 and δ 5.49 were in a ratio of 1:1. In the ^{13}C NMR spectrum of the product, there were two carbonyl resonances, at δ 221.6 and δ 220.7. Nevertheless, the mixture of **131a** and **131b** and the mixture of **132a** and **132b** were both optically active, which showed that in spite of a lack of facial selectivity, the enzyme still exhibited enantio-selectivity in its action. All compounds **125**, **126**, **127** and **128** were efficiently reduced by baker's yeast to keto-alcohols with over 98% ee, which was assessed by ^1H NMR of the corresponding Mosher's esters. The ^{19}F NMR spectrum of the two diastereomeric Mosher's esters of **131a** and **131b** gave a single signal at δ -71.83. Also, there was only one signal at δ -71.55 in the ^{19}F NMR spectrum for the two diastereomeric Mosher's esters of **132a** and **132b**. However, both the ^1H NMR and the ^{13}C NMR spectra of these Mosher's esters showed two, and only two, sets of signals. The methine protons H-4 of the Mosher's esters were at δ 5.64 (1H, d, J = 3.6 Hz) for **129**, δ 5.19 (1H, t, J = 3.9 Hz) for **130**, δ 5.43 (2H, m) for **131a** and **131b**, δ 5.43 (2H, m) for **132a** and **132b.**

Scheme **28** Baker's yeast reduction of **125**, **126**, **127** and **128**



125 **129**

126 **130**

127 **131a** **131b**

128 **132a** **132b**

*These spirodiketones were kindly supplied by P.Y. Liu (compounds **125** and **128**), and T.J. Jenkins (compounds **126** and **127**).

Table **10** summarizes the results of the yeast reduction of spirodiketones **60**, **118**, **125**, **126**, **127** and **128**. Table **11** compares the facial selectivity of the yeast reduction with that of $NaBH_4$ reduction. Liu[54] studied the reduction of several spirodiketones with $NaBH_4$. The donation of electron density by a suitable substituent to C-7 or C-9, or withdrawal of electron density from C-8, would increase the ability of bond *b* to donate electron density relative to bond *a* (Scheme **29**). This correlated directly with the facial selectivity of the $NaBH_4$ reduction of these spirodiketones. Thus, the facial selectivity in the $NaBH_4$ reductions was controlled largely by a stereoelectronic effect. The facial selectivity of yeast reductions was quite different from that of the $NaBH_4$ reductions. In contrast, facial selectivity in the yeast reductions must have depended mainly on the binding of the substrate in the active site of the reductase enzyme. As the plane-nonsymmetric moieties of the substrates are nonpolar, binding was probably controlled by steric factors.

Scheme **29** Principle of chemical reduction: facial selectivity

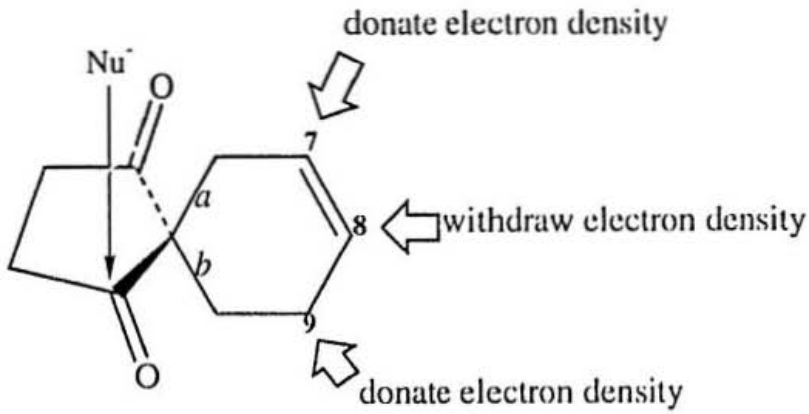


Table **10** Baker's Yeast Reduction

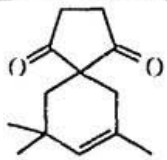
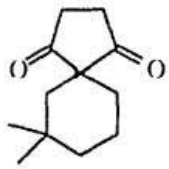
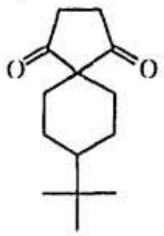
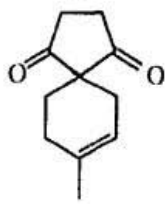
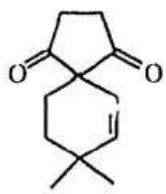
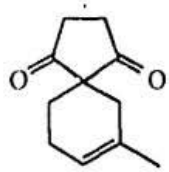
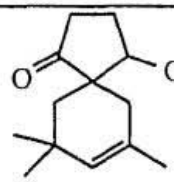
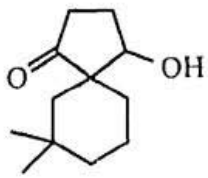
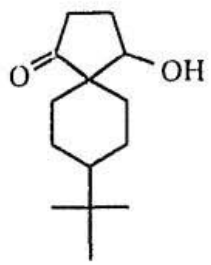
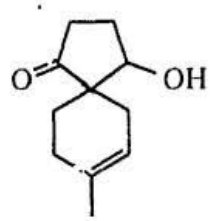
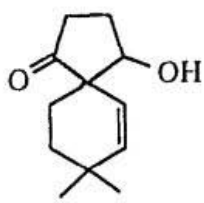
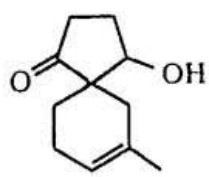
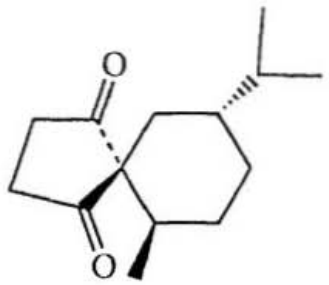
Compound Structure	$[\alpha]_D$	Ratio of the Diastereomers	Isolated Yield (%)	Recovered Starting Material (%)
	$+45^0$ (MeOH)	exclusive	62	23
	$+82^0$ (MeOH)	exclusive	79	11
	$+7^0$ ($CHCl_3$)	exclusive	50	20
	$+89^0$ (MeOH)	2.5:1	74	0
	$+42^0$ ($CHCl_3$)	1:1	52	43
	$+112^0$ (MeOH)	1:1	61	19

Table 11 Comparison of facial selectivities in yeast and chemical reductions (product ratios)

Compound Number	Gross Structure	Baker's Yeast	$NaBH_4$
123		>100:1	>100:1
129		>100:1	6.5:1*
130		>100:1	18:1*
124a/b		2.5:1	2.5:1*
131a/b		1:1	3:1
132a/b		1:1	9:1*

* From the Ph.D. thesis of P-Y. Liu[54]

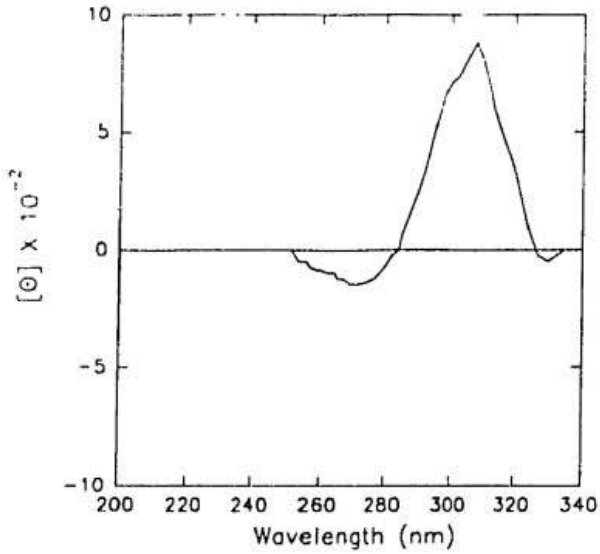
Not all spirodiketones could be reduced by the yeast. Yeast reduction of spirodiketone **133** failed, which suggested that the bulky substituents on the six-membered ring prevented the binding of **133** to the active site of the enzyme.



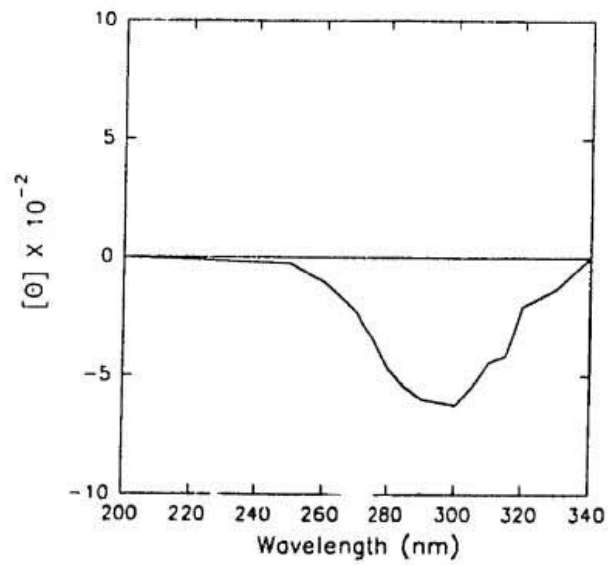
133

Brooks *et al.*[55] studied several 2,2-disubstituted 1,3-diones, and they concluded that reduction by baker's yeast provides only the (*S*) configuration at the carbinol carbon, including in compound **122**. Thus, the absolute configurations of our spirodiketones were established relative to this carbinol's configuration, by comparsion of some circular dichroism (CD) spectra,[57] and this absolute stereochemistry was confirmed by two X-ray structures.

Compounds **122** and **130** both had only one chiral center (C-4). The CD spectra of compound **122** and of **130** (Figure **11**) had opposite Cotton effects. Compound **122** (*S*)-enantiomer displayed a positive Cotton effect at 310 nm, and compound **130** had a negative Cotton effect at 300 nm. (Both compounds showed observable signals in 240-340 nm region.) Compound **130** was different from other diketones in that it had only one significant



a

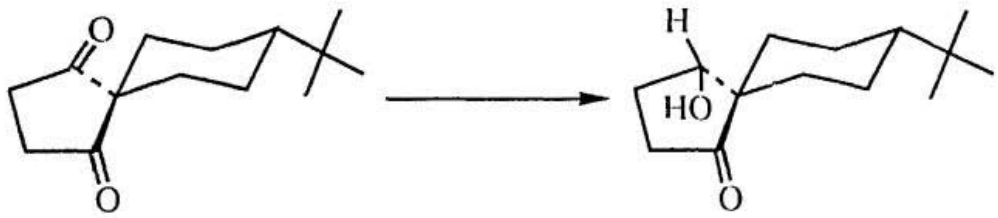


b

Figure 11 a) CD spectrum of compound 122 (MeOH)
b) CD spectrum of compound 130 ($CHCl_3$)

conformational form. From the studies of $NaBH_4$ reduction and methyllithium addition on **126**,[54] it was conformed that the equatorial carbonyl was the more reactive one. An X-ray structure (Figure **12**) of the Mosher's ester of the product of yeast reduction **130** demonstrated conclusively that the yeast also chose to reduce the equatorial carbonyl, and, consistent with reductions on other spirodiketones, the configuration at the new stereogenic center was *S* (Scheme **30**).

Scheme **30** Baker's yeast reduction on **126**



126 **130**

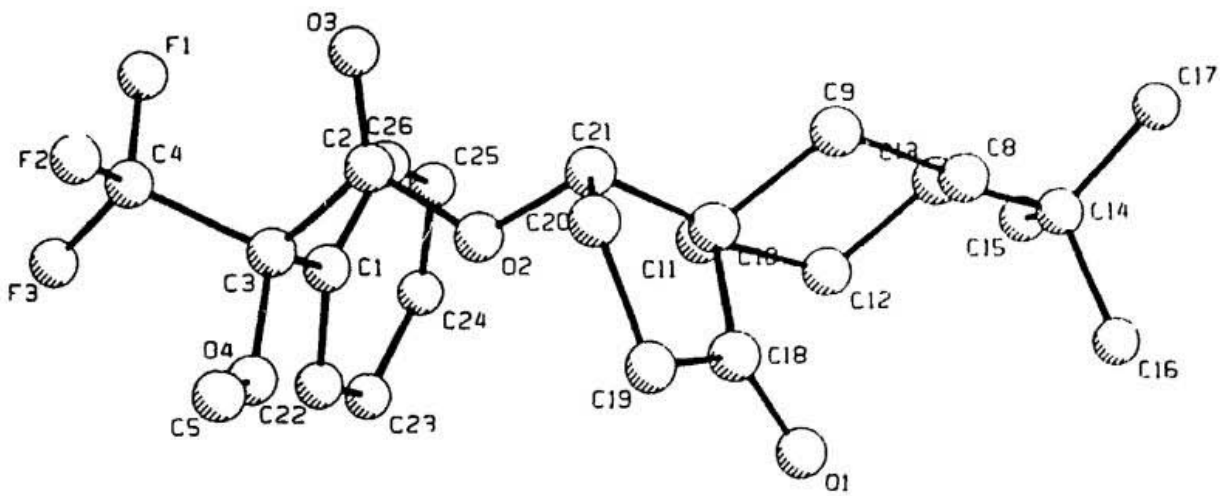


Figure **12** X-Ray structure **130** Mosher's ester

The CD spectrum of compound **129** was consistent with that of compound **122** (Figure **13**), they both showed a positive Cotton effect with maxima at 310 nm. Thus, **129** had the (4*S*,5*S*) configuration. The diastereomeric mixtures of compounds **131a**:**131b**, **132a**:**132b**, and **124a**:**124b** all showed a positive Cotton effect with maxima around 300 nm. The $NaBH_4$ reductions and baker's yeast reductions on spirodiketones both showed a preference for reduction of a ketone on its face *syn* to the double bond. Nevertheless, when the diastereomeric mixtures of yeast reduction products were derivatized to the corresponding mixtures of Mosher's esters the number of sets of signals in the NMR spectra did not double. This is consistent with high enantioselectivity in the reduction to give the *S* configuration at the carbinol, even when the facial selectivity (diastereoselectivity) was low or even nonexistant. Thus, the diastereomeric mixtures were composed only of the (4*S*,5*S*) and (4*S*,5*R*) isomers.

Compound **123** was produced by yeast reduction with very high facial and enantioselectivity. This compound has potential as a key intermediate for the production of optically pure triquinanes via the strategy described in the first chapter of this thesis. In order to produce a compound that would link into the previously described synthetic route we explored the reaction sequence shown in Scheme **31**. The hydroxy group of **123** was protected with chlorotrimethylsilane to give **134**. The X-ray structure of **134** was obtained (Figure **14**) which confirmed its relative stereochemistry. Methyllithium addition to **134** was initially difficult because of competing enolate formation. However, employing several cycles of methyllithium addition-quench in one pot, as Corey[58] had done, overcame this problem

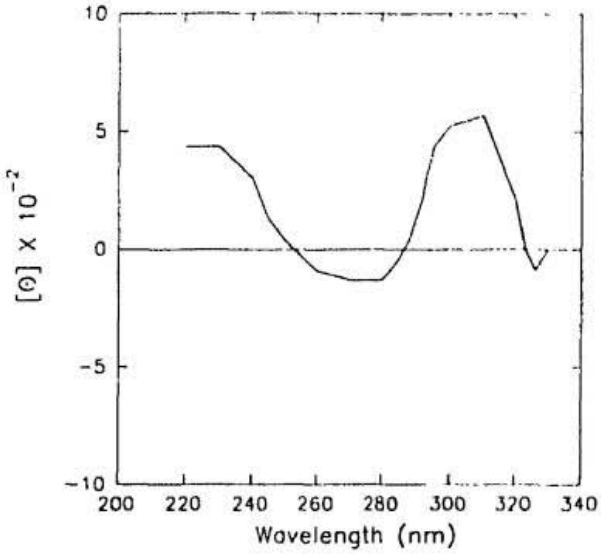


Figure 13 CD spectrum of compound 129 (MeOH)

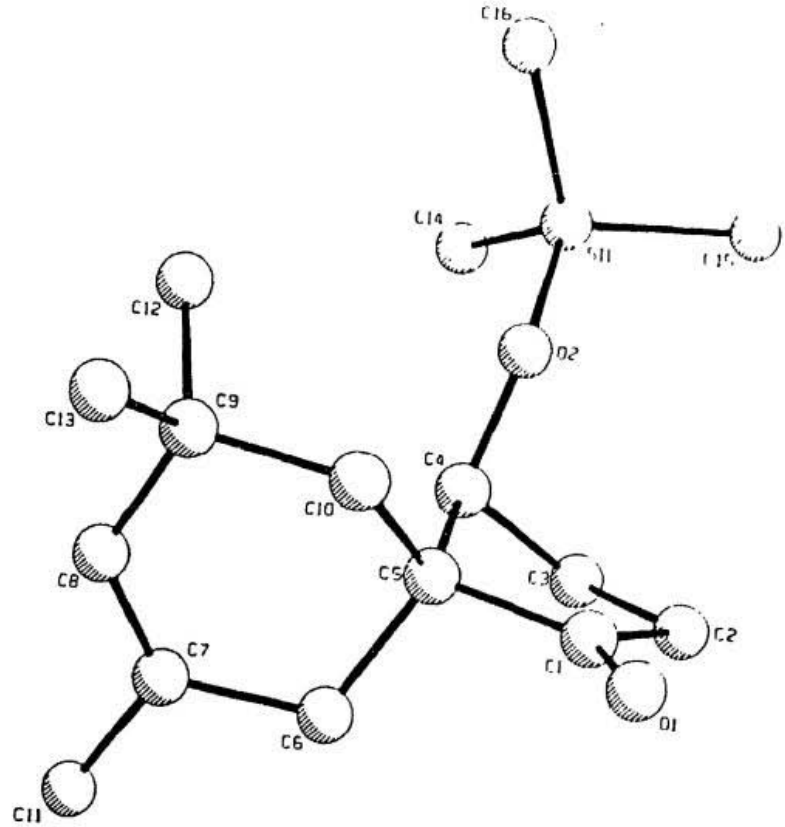
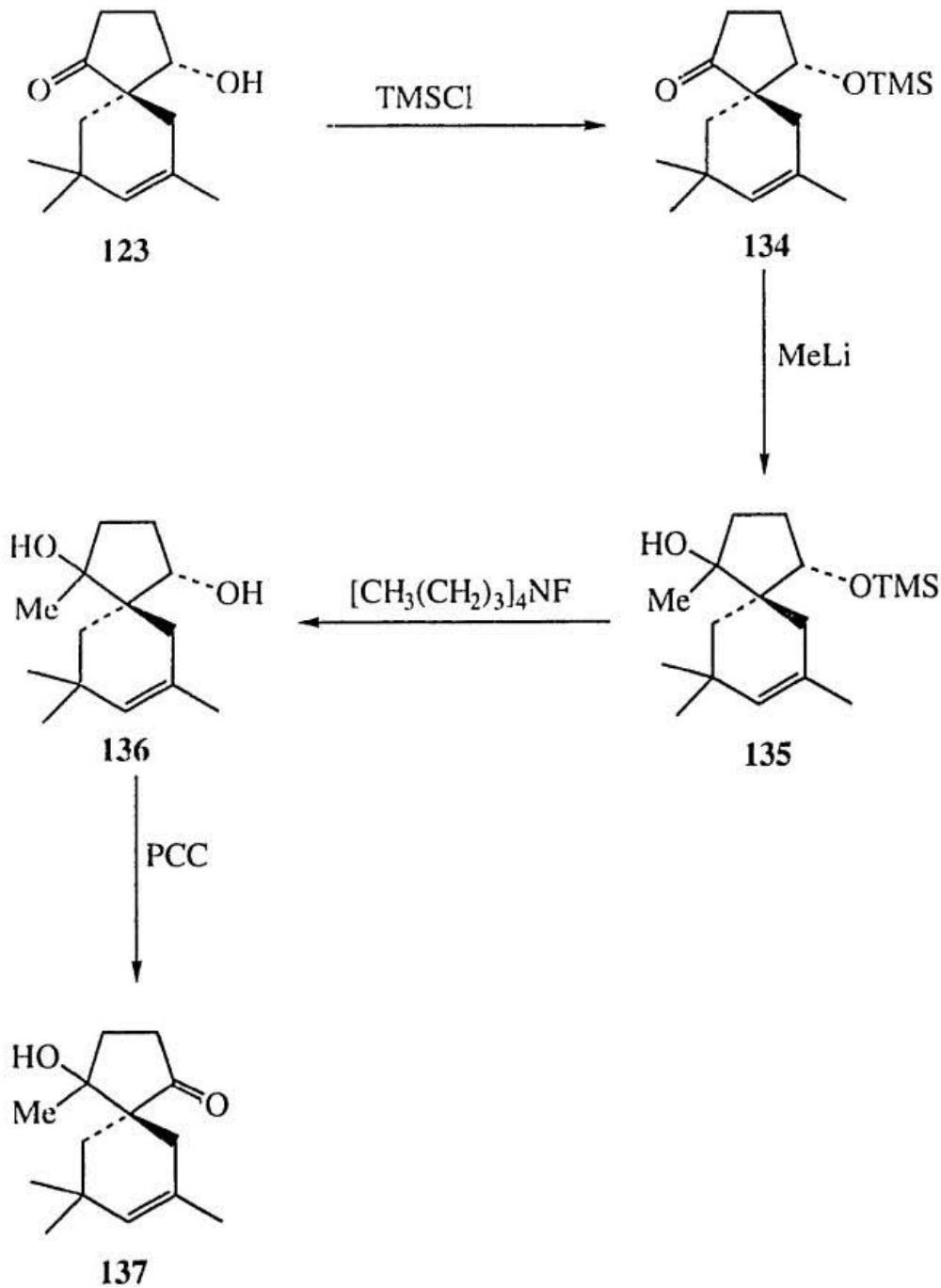


Figure 14 X-ray structure 134

Scheme 31 Formation of 137 from 123



and **135** was obtained in good yield. Since our reaction was conducted at reflux, a minor amount of compound **136**, in which the trimethylsilyl group had been lost, was detected, so without further purification **135** was deprotected with tetrabutylammonium fluoride. A diastereomeric mixture of **136a** and **136b** (7:1, respectively) was obtained, but it should be emphasized that each isomer of **136** had an enantiomeric excess of over 98%, as determined by ^{1}H NMR of the corresponding Mosher's esters. Compound **137** was generated by oxidation of the mixture of **136a** and **136b**. The relative stereochemistry of **137** is shown in the X-ray structure in Figure **15**. The ^{1}H NMR and ^{13}C NMR spectra of compound **137** were identical with those of compound **61** (racemic).

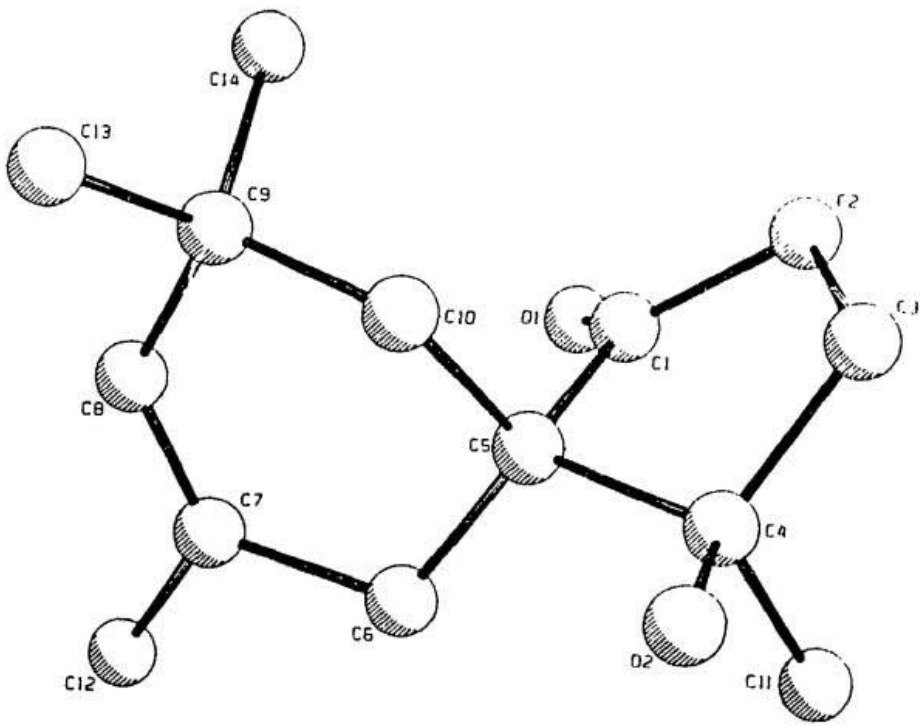


Figure **15** X-ray structure of **137**

It is important to realize that the chirality of the spiro-center (C-5) in **123** is *opposite* to the chirality of the central quaternary center in the triquinane sesquiterpenes that were investigated in Chapter 1.

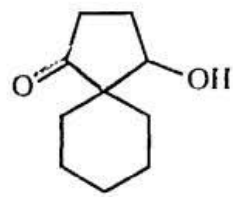
After oxidation, the spiro center (C-5) of **137** was effectively inverted with respect to compound **123**, which was (4*S*,5*R*). Therefore compound **137** was assigned the (4*R*,5*S*) stereo-chemistry, and **137** had the chirality at C-5 that would lead to the "correct" enantiomer of deoxypentalenic acid or pentalenene. Racemic **61** was an intermediate in our approach to (±)-deoxypentalenic acid (**1b**) and in Wu's route to (±)-pentalenene (**2**). Therefore, it is now obvious that the corresponding optically pure compound **137** could be used in the place of **61** to yield optically pure triquinanes with the same absolute stereochemistry as it is found in Nature.

III. EXPERIMENTAL

General

For general information and a detailed description of the instruments, see the Experimental Section of Chapter 1. Baker's yeast reactions were carried out in a water-bath shaker at about 32°C. The yeast was Fleischmann's "Traditional" brand purchased in local grocery stores. All reactions were monitored by analytical thin-layer chromatography (TLC). Optical rotations were recorded on a Perkin Elmer 141 polarimeter. Circular dichroism (CD) measurements were made on a Jasco J40A instrument using a cell of 0.05 cm path length.

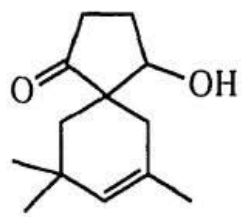
(4*S*)-4-Hydroxyspiro[4.5]decan-1-one (122)



A mixture of dry baker's yeast (2.0 g) and sucrose (4.5 g) in water (30 mL) was stirred at 31°C for 10 minutes. Diketone **121** (197 mg, 1.18 mmol) in 95% ethanol (0.3 mL) and 0.2% Triton X-100 (1.2 mL) was added. The mixture was stirred for 48 hours. Ether (2.4 mL) was added, and the solution was allowed to stand overnight at room temperature. After precipitation of the yeast cells, the mixture was filtered through Celite, and the filter cake was extracted with ethyl acetate. The aqueous layer was re-extracted with

ethyl acetate. and the combined organic solutions were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was separated by flash chromatography (10-16% ethyl acetate in hexane) to provide compound **122** as a colorless oil (134 mg, 68%): $[\alpha]_D = +80°$ (c = 0.0069, MeOH); IR υ_{max}: 3425, 1722 cm^{-1}; ^1H NMR: δ 1.26-1.42 (4H, m), 1.46-1.63 (4H, m), 1.94 (1H, m), 2.09-2.27 (2H, m), 2.34-2.46 (2H, m), 4.27 (1H, br s); ^{13}C NMR: δ 222.1 (0), 75.0 (1), 54.2 (0), 34.1 (2), 30.8 (2), 27.8 (2), 25.6 (2), 25.5 (2), 22.0 (2), 21.9 (2); MS from GCMS *m/z* (%): 168 (44, M^+), 150 (65, M^+-H_2O), 124 (16), 108 (98), 93 (41), 81 (100), 67 (62), 55 (39), 41 (35); HRMS calcd. for $C_{10}H_{16}O_2$: 168.1149; found: 168.1152.

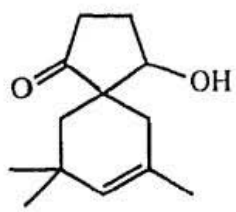
(4*S*,5*R*)-4-Hydroxy-7,9,9-trimethylspiro[4.5]dec-7-en-1-one (123)



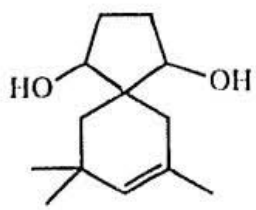
A mixture of dry baker's yeast (8.0 g) and sucrose (18.0 g) in water (100 mL) was shaken in a 32°C water bath for 10 minutes. After brisk fermentation had started, a solution of diketone **60** (158 mg, 0.780 mmol) in 95% ethanol (3.0 mL) and 0.2% Triton X-100 (12 mL) was added. The mixture was shaken for 48 hours. Ether (15 mL) was added, and the solution was allowed to stand overnight at room temperature. After precipitation of the yeast cells, the mixture was filtered through Celite, and the filter cake was extracted with ethyl acetate. The aqueous layer was re-extracted with ethyl acetate, and the combined organic solutions were washed with brine,

dried over magnesium sulfate, filtered, and concentrated. The residue was separated by flash chromatography (12-18% ethyl acetate in hexane) to provide compound **123** as a colorless oil (100 mg, 62%), and 36 mg (23%) of the starting material was recovered. For **123**: $[\alpha]_D = +45°$ (c = 0.0063, MeOH); IR υ_{max}: 3447, 1729 cm^{-1}; ^1H NMR: δ 1.03 (3H, s), 1.05 (3H, s), 1.64 (3H, s), 1.66-1.73 (2H, m), 1.81 (1H, d, J = 17.2 Hz), 2.05 (1H, m), 2.17-2.25 (2H, m), 2.32 (1H, dd, J = 2.4, 9.0 Hz), 2.50 (1H, m), 4.24 (1H, br s, H-4), 5.24 (1H, br s, H-8); ^{13}C NMR: δ 221.7 (0), 131.8 (1), 127.4 (0), 74.7 (1), 54.5 (0), 35.1 (2), 35.0 (2), 33.3 (2), 32.1 (3), 31.3 (0), 30.3 (3), 28.0 (2), 23.8 (3); MS *m/z* (%): 208 (32, M^+), 175 (95), 149 (100), 133 (46), 121 (61), 119 (40), 91 (40), 79 (25), 41 (41); HRMS calcd. for $C_{13}H_{20}O_2$: 208.1462; found: 208.1460.

rel-(4*R*,5*S*)-4-Hydroxy-7,9,9-trimethylspiro[4.5]dec-7-en-1-one (117a) and _trans_-7,9,9-trimethylspiro[4.5]dec-7-ene-1,4-diol (117b)



117a

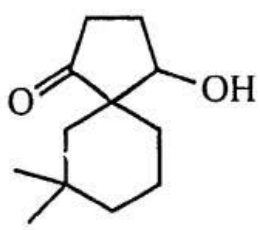


117b

7,9,9-Trimethylspiro[4.5]dec-7-ene-1,4-dione (85 mg, 0.40 mmol) was dissolved in methanol (10 mL), and $NaBH_4$ (*ca.* 7.0 mg, 0.19 mmol) was added to the solution in several small portions. The mixture was stirred at room temperature for 1 hour. Water was added. The aqueous layer was extracted with ether four times, and the combined organic solutions were

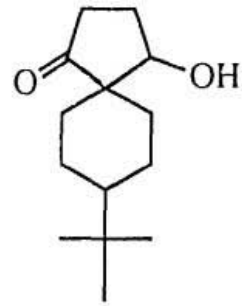
washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was separated by flash chromatography (5% acetone in hexane) to give **117a** (60 mg, 70%), and **117b** (22 mg, 26%). For **117a**: IR υ_{max}: 3447, 1729 cm^{-1}; ^1H NMR: δ 1.03 (3H, s), 1.05 (3H, s), 1.64 (3H, s), 1.66-1.73 (2H, m), 1.81 (1H, d, *J* = 17.2 Hz, AB), 2.05 (1H, m), 2.17-2.25 (2H, m), 2.32 (1H, dd, *J* = 2.4, 9.0 Hz), 2.50 (1H, m), 4.24 (1H, br s, H-4), 5.23 (1H, s, H-8); ^{13}C NMR: δ 221.8 (0), 131.8 (1), 127.4 (0), 74.7 (1), 54.4 (0), 35.0 (2), 34.9 (2), 33.3 (2), 32.1 (3), 31.2 (0), 30.3 (3), 28.0 (2), 23.8 (3); MS *m/z* (%): 208 (13, M^+), 175 (46), 149 (52), 133 (60), 131 (22), 123 (15), 121 (34), 119 (35), 107 (35), 105 (28), 91 (45), 81 (24), 77 (31), 65 (22), 57 (26), 55 (49), 43 (79), 41 (100); HRMS calcd. for $C_{13}H_{20}O_2$: 208.1462; found: 208.1462. For **117b**: IR υ_{max}: 3340 cm^{-1}; ^1H NMR: δ 1.03 (3H, s), 1.06 (3H, s), 1.38-1.63 (5H, m), 1.67 (3H, s), 2.11-2.19 (4H, m), 3.97 (1H, m), 4.10 (1H, t, *J* = 7.9 Hz), 5.19 (1H, s, H-8); ^{13}C NMR: δ 131.4 (1), 129.4 (0), 77.1 (1), 76.8 (1), 48.5 (0), 38.6 (2), 2.1 (2C, 0 and 3), 31.1 (2C, 2 and 3), 29.7 (2), 29.0 (2), 24.1 (3); MS *m/z* (%): 210 (6, M^+), 195 (26, M^+-Me), 177 (36), 159 (70), 149 (21), 148 (20), 136 (29), 135 (32), 133 (100), 123 (35), 121 (25), 119 (33), 109 (20), 107 (38), 105 (39), 93 (27), 91 (38), 81 (29), 79 (23), 77 (20), 55 (32), 43 (64), 43 (64), 41 (70); HRMS calcd. for $C_{12}H_{19}O_2$ (M^+-Me): 195.1384; found: 195.1379.

(4*S*,5*S*)-4-Hydroxy-7,7-dimethylspiro[4.5]decan-1-one (129)



A mixture of dry baker's yeast (6.0 g) and sucrose (16.0 g) in water (50 mL) was shaken in a 32°C water bath for 10 minutes. After brisk fermentation started, a solution of diketone **125** (47 mg, 0.24 mmol) in 95% ethanol (2.0 mL) and 0.2% Triton X-100 (8.0 mL) was added, and another 50 mL of water was added. The mixture was shaken for 48 hours. Ether (10 mL) was added, and the solution was allowed to stand overnight at room temperature to precipitate the yeast cells. The mixture was filtered through Celite, and the filter cake was extracted with ethyl acetate. The aqueous layer was re-extracted with ethyl acetate, and the combined organic solutions were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was separated by flash chromatography (16-20% ethyl acetate in hexane) to provide **129** as colorless crystals (37 mg, 79%), and some starting material (5 mg, 11%) was recovered. For **129**: $[\alpha]_D$ = +82° (c = 0.0045, MeOH); mp 82-85°C; IR υ_{max}: 3456, 1736 cm^{-1}; ^1H NMR: δ 0.98 (3H, s), 1.00 (3H, s), 1.24 (1H, m), 1.44-1.56 (7H, m), 2.00-2.46 (4H, m), 4.48 (1H, br s, H-4); ^{13}C NMR: δ 222.0 (0), 74.9 (1), 55.1 (0), 38.7 (2), 37.0 (2), 33.4 (3), 33.1 (2), 31.0 (2), 29.6 (0), 27.9 (2), 26.7 (3), 19.2 (2); MS *m/z* (%): 196 (11, M^+), 181 (66), 149 (14), 127 (13), 121 (27), 109 (84), 95 (24), 81 (37), 69 (100), 57 (24), 41 (64); HRMS calcd. for $C_{12}H_{20}O_2$: 196.1462; found: 196.1462.

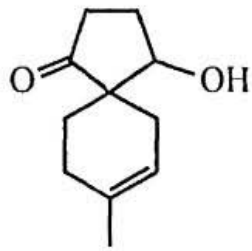
(4*S*)-8-*tert*-Butyl-4-hydroxyspiro[4,5]decan-1-one (130)



A mixture of dry baker's yeast (1.0 g) and sucrose (2.5 g) in water (75 mL) was shaken in a 32°C water bath for 10 minutes. After brisk fermentation started, a solution of diketone **126** (51 mg, 0.23 mmol) in 95% ethanol (0.40 mL) and 0.2% Triton X-100 (1.2 mL) was added. The mixture was shaken for 48 hours. Ether (0.5 mL) was added, and the solution was allowed to stand overnight at room temperature to precipitate the yeast cells. The mixture was filtered through Celite, and the filter cake was extracted with ethyl acetate. The aqueous layer was re-extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was separated by flash chromatography (14-20% ethyl acetate in hexane) to provide **130** as colorless crystals (26 mg, 50%), and some starting material (10 mg, 26%) was recovered. For **130**: $[\alpha]_D = +7°$ (c = 0.0086, $CHCl_3$); mp 135-137°C; IR υ_{max}: 3408, 1729 cm^{-1}; ^1H NMR: δ 0.86 (9H, s), 1.26-1.45 (3H, m), 1.56-1.71 (5H, m), 1.81-1.92 (2H, m), 2.19-2.28 (2H, m), 2.42 (1H, m), 3.88 (1H, t, *J* = 4.8 Hz); ^{13}C NMR: δ 219.8 (0), 79.5 (1), 51.9 (0), 47.7 (1), 34.6 (2), 32.5 (0), 31.5 (2), 27.6 (3, 3C), 27.1 (2), 26.3 (2), 22.5 (2), 22.1 (2); MS

m/z (%): 224 (8, M^+), 206 (9), 167 (32), 150 (29), 126 (13), 107 (34), 81 (32), 67 (24), 57 (100), 41 (58); HRMS calcd. for $C_{14}H_{24}O_2$: 224.1775; found: 224.1777.

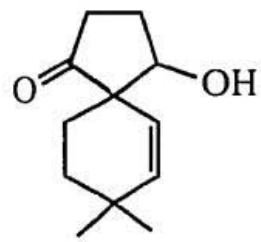
(4*S*,5*R*) and (4*S*,5*S*)-4-Hydroxy-8-methylspiro[4.5]dec-7-en-1-one (2.5:1 mixture) (124a and124b)



A mixture of dry baker's yeast (8.0 g) and sucrose (18.0 g) in water (100 mL) was shaken in a 31°C water bath for 10 minutes. After brisk fermentation started, a solution of diketone **118** (119 mg, 0.67 mmol) in 95% ethanol (3.0 mL) and 0.2% Triton X-100 (12 mL) was added, and another 100 mL of water was added. The mixture was stirred at 32°C for 48 hours. Ether (15 mL) was added and the solution was allowed to stand overnight at room temperature to precipitate the yeast cells. The mixture was filtered through Celite, and the filter cake was extracted with ethyl acetate. The aqueous layer was re-extracted with ethyl acetate, and the combined organic solutions were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The flash chromatography of the residue (12-20% ethyl acetate in hexane) provided a mixture of **124a** and **124b** (89 mg, 74%) as a colorless oil: $[\alpha]_D = +89°$ (c = 0.0033, MeOH); IR υ_{max}: 3443, 1727 cm^{-1}; ^1H NMR for the major product: δ 1.65 (3H, s), 1.77 (1H, m), 1.80-

2.40 (8H, m), 2.48 (1H, m), 5.28 (1H, s); for the minor one: δ 1.65 (3H, s), 1.80-2.40 (9H, m), 2.48 (1H, m), 4.25 (1H, m), 5.44 (1H, br s); ^{13}C NMR for the major product: δ 222.0 (0), 134.7 (0), 117.2 (1), 75.1 (1), 52.6 (0), 34.3 (2), 31.1 (2), 28.4 (2), 27.1 (2), 23.3 (3), 22.7 (2); for the minor one: δ 222.0 (0), 145.0 (0), 119.2 (1), 75.2 (1), 52.6 (0), 34.1 (2), 27.9 (2), 27.8 (2), 26.8 (2), 25.5 (2), 23.3 (3); MS of the mixture *m/z* (%): 180 (54, M^+), 147 (17), 136 (100), 120 (49), 93 (54), 91 (45), 79 (43), 43 (40); HRMS calcd. for $C_{11}H_{16}O_2$: 180.1149; found: 180.1147.

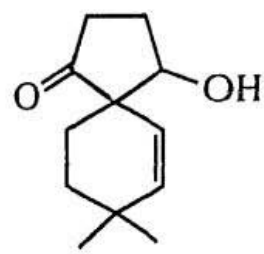
(4*S*,5*R*) and (4*S*,5*S*)-4-Hydroxy-8,8-dimethylspiro[4.5]dec-6-en-1-one (1:1 mixture) (131a and 131b)



A mixture of dry baker's yeast (10.0 g) and sucrose (22.0 g) in water (100 mL) was shaken in a 31°C water bath for 10 minutes. After brisk fermentation started, this system was poured into the solution of diketone **127** (187 mg, 0.97 mmol) in 95% ethanol (4.0 mL) and 0.2% Triton X-100 (16 mL). Another 100 mL of water was added. The suspension was shaken at 32°C for 48 hours. Ether (15 mL) was added, and the solution was allowed to stand overnight at room temperature to precipitate the yeast cells. The mixture was filtered through Celite, and the filter cake was extracted with ethyl acetate. The combined organic solutions were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The flash

chromatography of the residue (12-20% ethyl acetate in hexane) provided an inseparable mixture of **131a** and **131b** as a colorless oil (97 mg, 52%), and some starting material (81 mg, 43%) was recovered. For **131a** and **131b**: $[\alpha]_D = +42°$ (c = 0.0048, $CHCl_3$); IR υ_{max}: 3472, 1723 cm^{-1}; ^1H NMR of the mixture: δ 0.99 (3H, s), 1.00 (3H, s), 1.03 (3H, s), 1.03 (3H, s), 1.42-1.69 (8H, m), 1.84 (1H, m), 1.97-2.10 (3H, m), 2.23-2.35 (4H, m), 2.45-2.53 (2H, m), 4.11-4.15 (2H, m, H-4), 5.12 (1H, d, J = 9.9 Hz), 5.37 (1H, d, J = 10.2 Hz), 5.73 (1H, d, J = 9.9 Hz), 5.88 (1H, d, J = 10.2 Hz); ^{13}C NMR of the mixture: δ 219.5 (0), 218.2 (0), 143.8 (1), 142.5 (1), 122.6 (1), 119.6 (1), 78.2 (1), 77.0(1), 56.3 (0), 55.8 (0), 34.3 (2), 34.0 (2), 33.0 (2), 32.8 (2), 31.4 (0, 2C), 29.3 (3, 2C), 29.0 (3), 28.9 (3), 27.8(2), 27.0 (2), 26.0 (2), 19.8 (2); MS of the mixture *m/z* (%): 194 (39, M^+), 161 (32), 135 (100), 107 (80), 105 (42), 93 (44), 91 (36), 41 (47); HRMS calcd. for $C_{12}H_{18}O_2$: 194.1306; found: 194.1308.

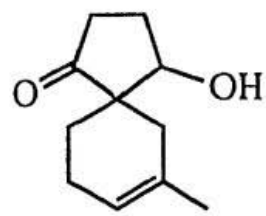
rel-(4*R*,5*S*) and _rel_ -(4*R*,5*R*)-4-Hydroxy-8,8-dimethylspiro[4.5]dec-6-en-1-one (3 :1 mixture) (131a' and 131b')



8,8-Dimethylspiro[4.5]dec-6-ene-1,4-dione (**127**) (78 mg, 0.40 mmol) was dissolved in 10 mL of methanol, and $NaBH_4$ (4.0 mg, 0.10 mmol) was added to the solution in several small portions. The mixture was stirred at

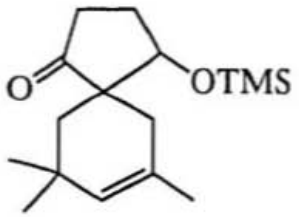
room temperature for 1 hour. Water was added. The aqueous layer was extracted with ether four times, and the combined organic layers were washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was separated by flash chromatography (10%-16% ethyl acetate in hexane) to give the keto-alcohol mixture (78 mg, 98%): IR υ_{max}: 3472, 1723 cm^{-1}; ^1H NMR of the mixture: δ 1.00 (3H, s), 1.01 (3H, s), 1.04 (6H, s), 1.44-1.48 (2H, m), 1.62-1.72 (4H, m), 1.82-2.05 (4H, m), 2.20-2.33 (4H, m), 2.45-2.57 (2H, m), 4.11-4.15 (2H, m, H-4), 5.12 (1H, d, J = 9.9 Hz, H-6), 5.36 (1H, d, J = 10.2 Hz), 5.74 (1H, d, J = 9.9 Hz, H-7), 5.90 (1H, d, J = 10.2 Hz); nOe data for **131a'**: irradiate δ 5.12 (H-6), 1.5% nOe at δ 4.15 (H-4); irradiate δ 4.15 (H-4), 1.9% nOe at δ 5.12 (H-6); ^{13}C NMR for the major product: δ 217.8 (0), 142.7 (1), 122.6 (1), 77.2 (1), 56.3 (0), 34.3 (2), 32.9 (2), 31.5 (0), 29.4 (3), 29.1 (3), 27.0 (2), 19.9 (2); for the minor product: δ 219.3 (0), 144.2 (1), 119.5 (1), 78.3 (1), 55.9 (0), 34.1 (2), 33.1 (2), 31.5 (0), 29.4 (3), 28.9 (3), 27.9 (2), 26.1 (2); MS of the mixture *m/z* (%): 194 (60, M^+), 179 (17, M^+-CH_3), 161 (32), 135 (100), 121 (27), 119 (30), 107 (78), 105 (33), 93 (35), 85 (21), 79 (22), 55 (19), 43 (28); HRMS calcd. for $C_{12}H_{18}O_2$: 194.1306; found: 194.1320.

(4*S*,5*R*) and (4*S*,5*S*)-4-Hydroxy-7-methylspiro[4.5]dec-7-en-1-one (1:1 mixture) (132a and 132b)



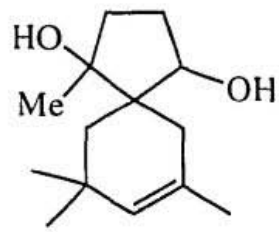
A mixture of dry baker's yeast (8.0 g) and sucrose (18.0 g) in water (100 mL) was stirred at a 31°C water bath for 10 minutes. After brisk fermentation started, a solution of diketone **128** (140 mg, 0.79 mmol) in 95% ethanol (3.0 mL) and 0.2% Triton X-100 (12 mL) was addded, and another 100 mL of water was added. The mixture was stirred at 32°C for 48 hours. Ether (15 mL) was added, and the solution was allowed to stand overnight at room temperature to precipitate the yeast cells. The mixture was filtered through Celite, and the filter cake was extracted with ethyl acetate. The aqueous layer was re-extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was separated by flash chromatography (14-20% ethyl acetate in hexane) to provide a mixture of **132a** and **132b** as a colorless oil (87 mg, 61%), and some starting material (27 mg, 19%) was recovered. For **132a** and **132b**: $[\alpha]_D = +112°$ (c = 0.0072, MeOH); IR υ_{max}: 3450, 1729 cm^{-1}; ^1H NMR of the mixture: δ 1.65 (6H, s), 1.71 (2H, s), 1.95-2.60 (18H, m), 4.19-4.25 (2H, m), 5.44 (1H, s), 5.49 (1H, s); ^{13}C NMR of the mixture: δ 221.6 (0), 220.7 (0), 133.0 (0), 130.4 (0), 121.4 (1), 119.9 (1), 75.6 (1), 75.3 (1), 53.3 (0), 53.1 (0), 35.3 (2), 34.3 (2), 34.1 (2), 29.9 (2), 28.3 (2), 27.9 (2), 27.4 (2), 23.7 (3, 2C), 22.3 (2), 22.1 (2), 22.0 (2); MS of the mixture *m/z* (%): 180 (55, M^+), 147 (15), 124 (20), 121 (100), 105 (36), 93 (74), 91 (50), 79 (46), 77 (38), 43 (31); HRMS calcd. for $C_{11}H_{16}O_2$: 180.1150; found: 180.1152.

(4*S*,5*R*)-7,9,9-Trimethyl-4-trimethylsilyloxyspiro[4.5]dec-7-en-1-one (134)



(4*S*,5*R*)-4-Hydroxy-7,9,9-trimethylspiro[4.5]dec-7-en-1-one (**123**) (82 mg, 0.39 mmol) was dissolved in pyridine (2.0 mL). Chlorotrimethylsilane (0.15 mL, 1.2 mmol) was added to the solution of keto-alcohol at 0°C under nitrogen. Then the ice bath was removed, and the mixture was stirred at room temperature for 1 hour. Carbon tetrachloride was added, and the mixture was filtered, and concentrated. The crude sample was separated by flash chromatography (1% ethyl acetate in hexane) to provide **134** as a colorless solid (106 mg, 97%): $[\alpha]_D$ = +39° (c = 0.0064, MeOH); mp 75-77°C; IR υ_{max}: 1742 cm^{-1}; ^1H NMR: δ 0.13 (9H, s), 0.96 (6H, s), 1.54 (1H, d, *J* = 14.1 Hz, AB), 1.65 (3H, s), 1.69-1.76 (3H, m), 2.01-2.17 (2H, m), 2.24 (1H, dd, *J* = 4.1, 8.3 Hz), 2.40 (1H, m), 4.12 (1H, t, *J* = 3.7 Hz), 5.20 (1H, s); ^{13}C NMR: δ 221.6 (0), 132.1 (1), 127.5 (0), 75.9 (1), 54.6 (0), 34.9 (2), 34.1 (2), 33.3 (2), 31.5 (0), 31.3 (3), 31.1 (3), 27.9 (2), 23.8 (3), 0.45 (3, 3C); MS *m/z* (%): 280 (90, M^+), 175 (58), 164 (19), 149 (23), 133 (24), 129 (29), 107(16), 91 (18), 75 (28), 73 (100), 41 (19); HRMS calcd. for $C_{16}H_{28}O_2Si$: 280.1857; found: 280.1858.

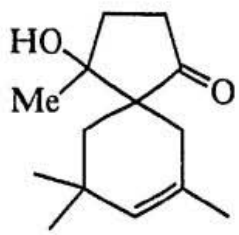
(1*S*,4*S*,5*R*) and (1*R*,4*S*,5*R*)-1,7,9,9-Tetramethylspiro[4.5]dec-7-ene-1,4-diol (7:1 mixture) (136a and 136b)



(4*S*,5*R*)-7,9,9-Trimethyl-4-trimethylsilyloxyspiro[4.5]dec-7-en-1-one (**134**) (348 mg, 1.24 mmol) was dissolved in hexane-ether (1:1, 30 mL). The solution was heated under nitrogen, and 1.4 M methyllithium (2.70 mL, 3.78 mmol) was added. After 10 min, 0.15 mL of methanol was added. Then 1.4 M methyllithium (2.70 mL, 3.78 mmol) was added again. After 10 min, methanol (0.15 mL) was added. The methyllithium addition continued in this way for a total of six cycles. After the mixture was cooled, water was added. The aqueous layer was extracted with ether four times, and the combined organic solutions were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was redissolved in dichloromethane (5.0 mL), and 1.0 M tetrabutylammonium fluoride (2.0 mL, 2.0 mmol) was added. The mixture was stirred at room temperature for 3 hours. The water was added. The aqueous layer was extracted with dichloromethane four times, and the combined organic solutions were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was separated by flash chromatography (14%-18% ethyl acetate in hexane) to provide a colorless product that was a 7:1 epimeric mixture (221 mg, 80%). For the major isomer **136a**: $[\alpha]_D = +98°$ (c = 0.022, $CHCl_3$); IR υ_{max}: 3361 cm^{-1}; ^1H NMR: δ 1.03 (3H, s), 1.10 (3H,

s), 1.19 (3H, s), 1.56 (2H, s), 1.62 (3H, s), 1.66-1.99 (5H, m), 2.19 (1H, m), 2.58 (1H, d, J = 6.3 Hz, OH), 2.88 (1H, s, OH), 4.04 (1H, t, J = 6.3 Hz, H-4), 5.21 (1H, s, H-8); ^{13}C NMR: δ 131.6 (1), 128.1 (0), 84.7 (0), 78.0 (1), 51.4 (0), 37.7 (2), 35.4 (2), 33.9 (2), 33.3 (3), 31.9 (0), 31.1 (2), 30.3 (3), 24.1 (3), 21.5 (3); MS *m/z* (%): 206 (56, M^+-H_2O), 191 (51), 188 (3, M^+-2 H_2O), 173 (49), 163 (12), 149 (48), 148 (39), 147 (20), 133 (51), 121 (44), 107 (38), 105 (16), 85 (63), 67 (13), 43 (100); HRMS calcd. for $C_{14}H_{21}O$ (M^+-H_2O): 206.1670; found: 206.1675. For the minor isomer **136b**: $[\alpha]_D$ = +36° (c = 0.029, $CHCl_3$); IR υ_{max}: 3354, 1736 cm^{-1}; ^{1}H NMR: δ 0.95 (3H, s), 0.96 (3H, s), 1.11 (3H, s), 1.79 (3H, s), 1.63-1.70 (4H, m), 1.85-1.94 (2H, m), 2.21-2.32 (2H, m), 2.85 (1H, d, J = 6.9 Hz, OH), 2.92 (1H, s, OH), 4.19 (1H, t, J = 6.6 Hz, H-4), 5.64 (1H, s, H-8); ^{13}C NMR: δ 138.1 (0), 117.3 (1), 85.9 (0), 79.3 (1), 53.5 (0), 44.1 (2), 40.8 (2), 37.4 (2), 32.5 (3), 31.4 (2), 30.8 (0), 27.2 (3), 25.0 (3), 21.7 (3); MS *m/z* (%): 206 (56, M^+-H_2O), 191 (32), 173 (29), 163 (24), 149 (100), 133 (30), 121 (56), 107 (51), 93 (30), 85 (38), 69 (23), 55 (34), 43 (98); HRMS calcd. for $C_{14}H_{21}O$ (M^+-H_2O): 206.1670; found: 206.1649.

(4*R*,5*S*)-4-Hydroxy-4,7,9,9-tetramethylspiro[4.5]dec-7-en-1-one (137)



The mixture of (1*S*,4*S*,5*R*) and (1*R*,4*S*,5*R*)-1,7,9,9-tetramethyl-spiro[4.5]dec-7-ene-1,4-diol (**136**) (221 mg, 0.99 mmol) was dissolved in

dichloromethane (20 mL). PCC (250 mg, 1.16 mmol) was added. The mixture was stirred for six hours at room temperature. The mixture was filtered through a pad of silica gel, which was extracted with ether. The combined organic solutions were concentrated. The residue was separated by flash chromatography (12%-20% ethyl acetate in hexane) to provide the title compound as a yellow oil (107 mg, 49%), and some spirodiketone **60** (40.8 mg, 19%) was recovered. For compound **137**: $[\alpha]_D = +12°$ (c = 0.099, $CHCl_3$); IR υ_{max}: 3426, 1730 cm^{-1}; ^1H NMR: δ 0.90 (3H, s, 9-CH_3), 1.00 (3H, s, 9-CH_3), 1.15 (3H, s, 4-CH_3), 1.71 (2H, d, J = 3.9 Hz, H-10), 1.74 (3H, s, 7-CH_3), 1.79 (2H, s), 1.96 (1H, m), 2.21 (2H, m), 2.56 (1H, m), 5.19 (1H, s, H-8); ^{13}C NMR: δ 219.9 (0), 130.6 (1), 128.9 (0), 78.1 (0), 55.9 (0), 38.0 (2), 34.1 (2), 33.6 (2), 32.8 (3), 32.0 (0), 30.5 (2), 28.6 (3), 24.4 (3), 23.9 (3); MS *m/z* (%): 222 (43, M^+), 189 (14), 164 (20), 149 (19), 123 (26), 99 (50), 84 (17), 55 (16), 43 (100); HRMS calcd. for $C_{14}H_{22}O_2$: 222.1619; found: 222.1612.

Preparation of (*R*)-(+)-MTPA Derivatives (Mosher's esters)

The reaction was carried out in a dried vial fitted with a rubber septum. The reagents were injected into the vial, to which was added about 0.1 mmol of the keto-alcohol, in the following order: dry pyridine (300 μL), (+)-MTPA-chloride (52 μL), and dry CCl_4 (300 μL). The mixture was allowed to stand at room temperature for 3 days with occasional stirring. After the reaction was complete by TLC, 3-dimethylamino-1-propylamine (*ca.* 50 μL) was added, and the mixture became a yellow color. After 5 minutes, the mixture was diluted with ether, then it was washed with ice

cold 10% aqueous HCl, cold saturated Na_2CO_3, and cold brine. It was dried over anhydrous magnesium sulfate, filtered, and concentrated. Carbon tetrachloride was added to the residue, and the solution was reconcentrated. This was repeated several times in order to remove the traces of ether. Each sample was analysed by ^1H NMR and, in many cases, by ^{19}F NMR, also.

For the Mosher's ester of **122:** ^1H NMR: δ 1.26-1.54 (10H, m), 2.10-2.39 (4H, m), 3.53-3.54 (3H, m, OCH_3), 5.63 (1H, m), 7.41-7.55 (5H, m); ^{19}F NMR: δ -71.68.

For the Mosher's ester of **123**: ^1H NMR: δ 0.64 (3H, s, CH_3), 0.93 (3H, s, CH_3), 1.59 (1H, m), 1.63 (3H, s, CH_3), 1.67 (1H, m), 1.81 (1H, m), 2.11-2.31 (5H, m), 3.49 (3H, m, OCH_3), 5.21 (1H, s), 5.41 (1H, m), 7.40-7.53 (5H, m); ^{19}F NMR: δ -70.73.

For the Mosher's ester of **124**: ^1H NMR (1.6:1): δ 1.42-1.60 (2H, m), 1.61 (3H, s, CH_3), 1.62 (3H, s, CH_3), 1.65-2.10 (4H, m), 2.18-2.50 (4H, m), 3.51-3.53 (3H, m, OCH_3), 5.14 (1H, br s), 5.26 (1H, br s), 5.39 (1H, d, J = 3.6 Hz), 5.46 (1H, d, J = 3.6 Hz), 7.41-7.50 (5H, m); ^{19}F NMR: δ -71.92 (minor isomer), -71.40 (major isomer).

For the Mosher's ester of **129**: ^1H NMR: δ 0.61 (3H, s, CH_3), 0.84 (3H, s, CH_3), 1.02-1.56 (8H, m), 2.08-2.39 (4H, m), 3.51 (3H, d, J = 1.2 Hz, OCH_3), 5.65 (1H, d, J = 3.6 Hz), 7.41-7.55 (5H, m).

For the Mosher's ester of **130**: ^{1}H NMR: δ 0.83 (9H, s), 1.15-1.35 (4H, m), 1.51-1.75 (5H, m), 2.03 (1H, m), 2.34-2.40 (3H, m), 3.53 (3H, d, J = 1.2 Hz, OCH_3), 5.19 (1H, m), 7.41-7.55 (5H, m).

For the Mosher's ester of **131**: ^{1}H NMR (1:1): δ 0.90 (3H, s, CH_3), 0.95 (3H, s, CH_3), 0.99 (3H, s, CH_3), 1.00 (3H, s, CH_3), 1.22-1.62 (4H, m), 2.02-2.41 (4H, m), 3.52-3.54 (3H, m, OCH_3), 4.98 (1H, d, J = 10.2 Hz), 5.11 (1H, d, J = 10.2 Hz), 5.40-5.44 (2H, m), 5.64 (1H, d, J = 10.2 Hz), 5.70 (1H, d, J = 10.2 Hz), 7.41-7.50 (5H, m); ^{19}F NMR: δ -71.83.

For the Mosher's ester of **132**: ^{1}H NMR (1:1): δ 1.45 (3H, s, CH_3), 1.64 (3H, s, CH_3), 1.51-1.70 (3H, m), 1.90-2.48 (7H, m), 3.51-3.53 (3H, m, OCH_3), 5.29 (1H, br s), 5.42-5.43 (2H, br s), 7.41-7.50 (5H, m); ^{19}F NMR: δ -71.55.

For the Mosher's ester of **136a**: ^{1}H NMR: δ 0.61 (3H, s, CH_3), 0.92 (3H, s, CH_3), 1.19 (3H, s, CH_3), 1.24-1.28 (2H, m), 1.62 (3H, s, CH_3), 1.75-1.93 (6H, m), 2.22 (1H, m), 2.67 (1H, s, OH), 3.52 (3H, s, OCH_3), 5.15 (1H, s), 5.22 (1H, d, J = 5.4 Hz), 7.41-7.56 (5H, m).

For the Mosher's ester of **136b**: ^{1}H NMR: δ 0.96 (6H, s), 1.10 (3H, s, CH_3), 1.55 (2H, s), 1.61 (3H, s, CH_3), 1.62-1.99 (5H, m), 2.40 (1H, m), 3.56 (3H, d, J = 1.2 Hz, OCH_3), 5.19 (1H, br s), 5.47 (1H, dd, J = 2.1, 7.8 Hz), 7.41-7.56 (5H, m); ^{19}F NMR: δ -71.76.

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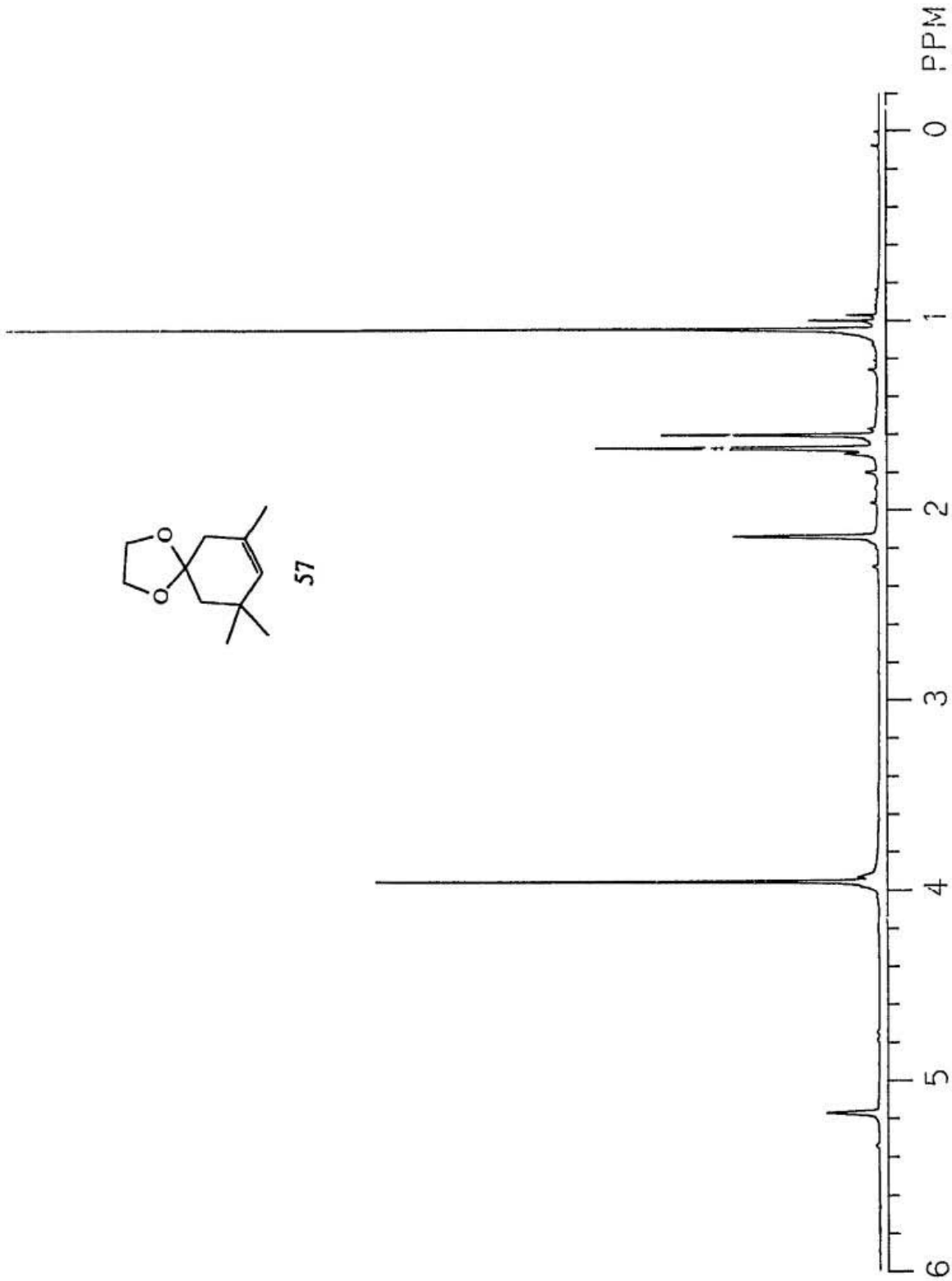
APPENDIX

The selected ^{1}H NMR spectra are arranged according to the order in which they appear in the text.



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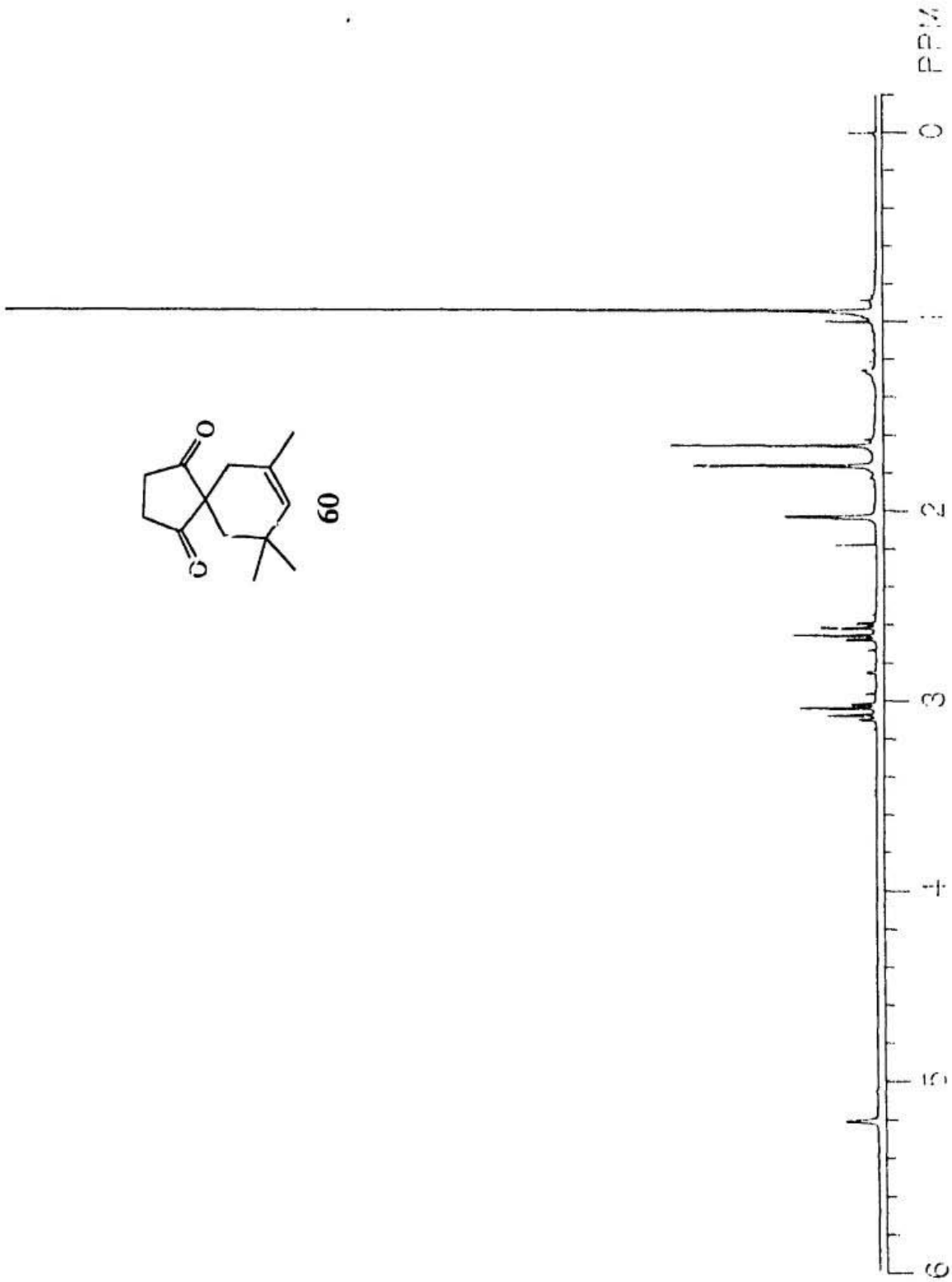
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PPM
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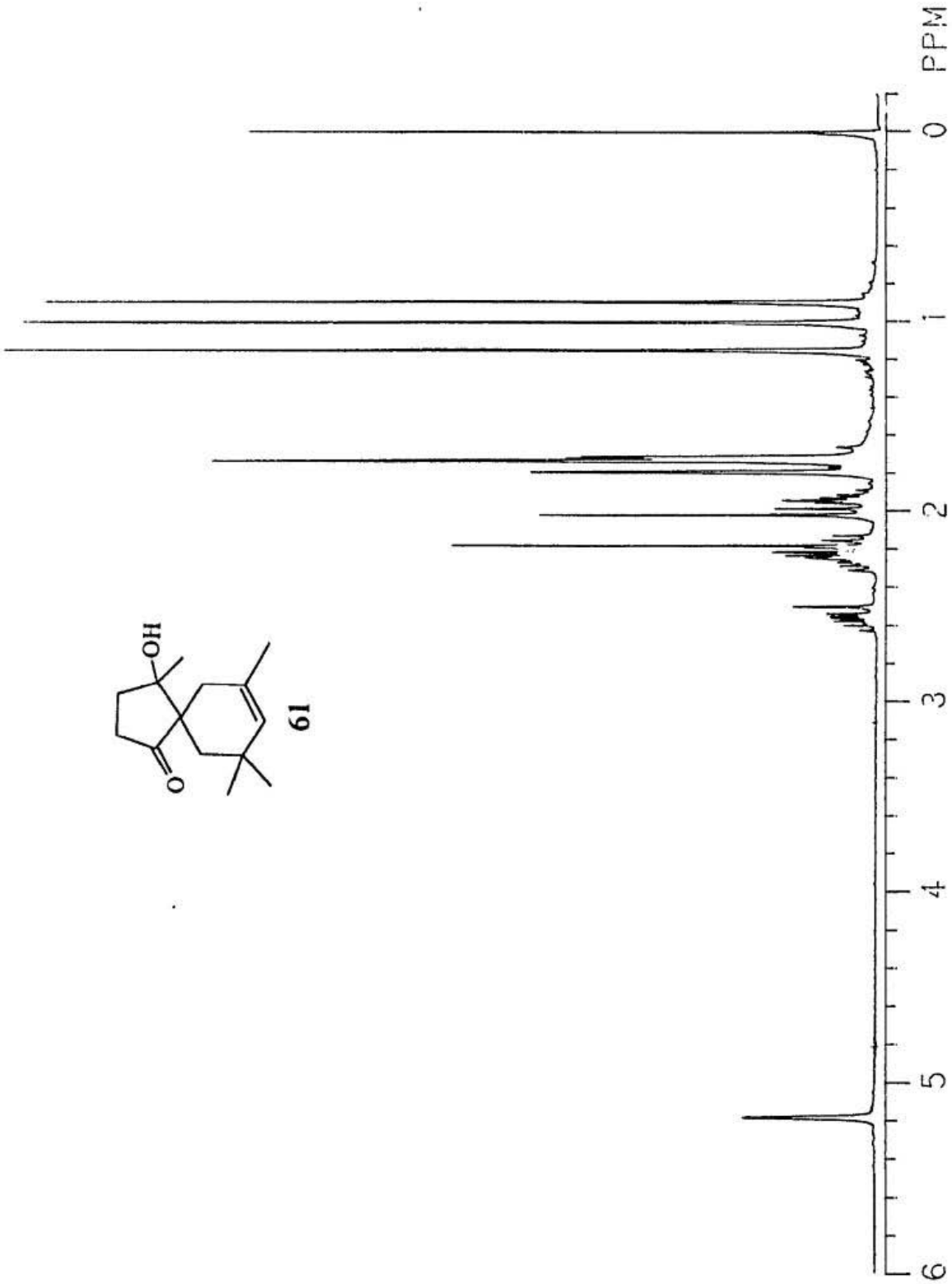
3
4
5
6



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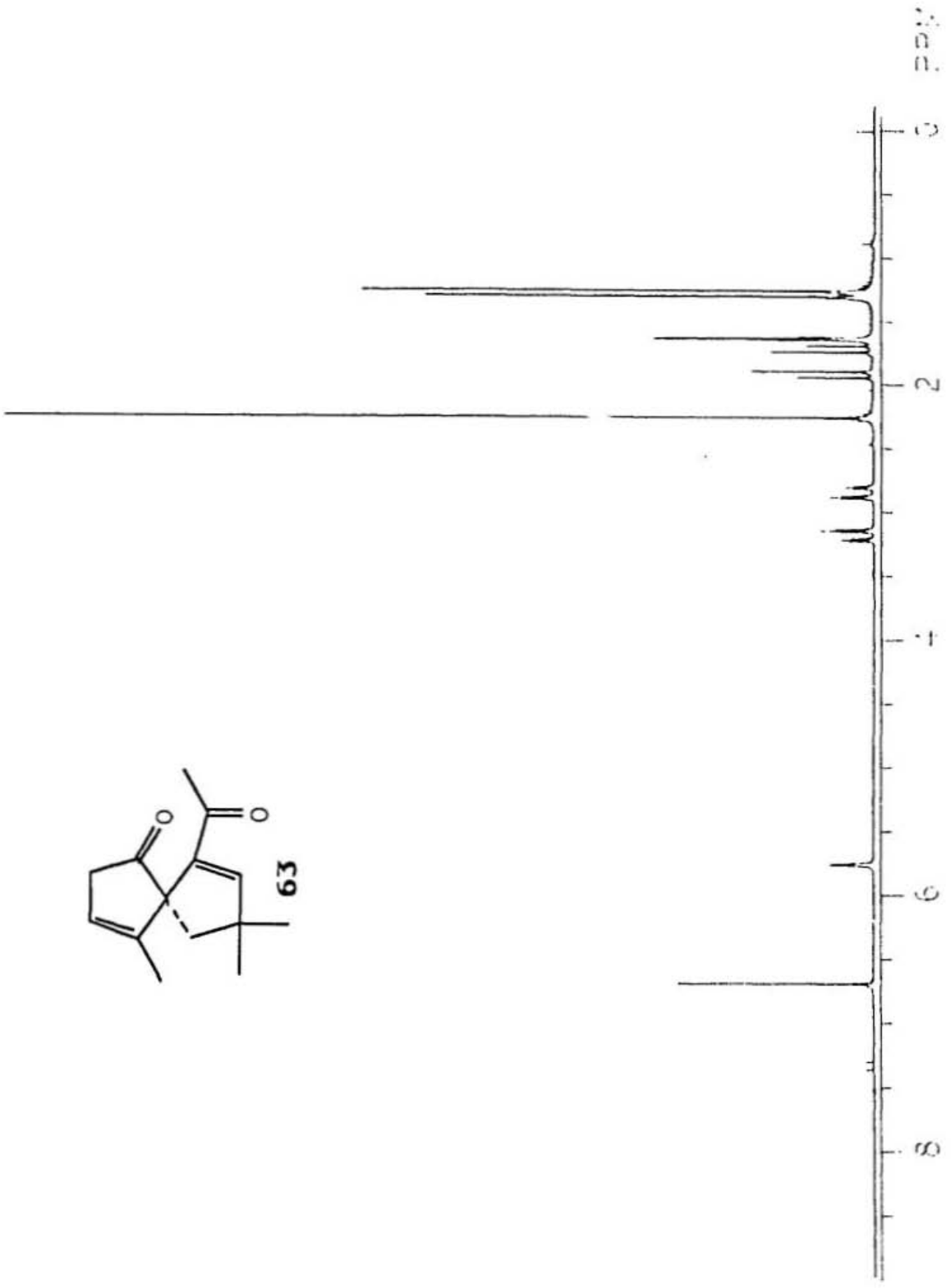

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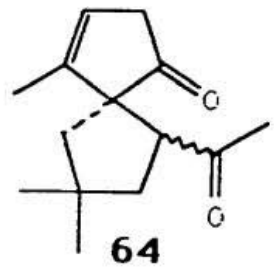

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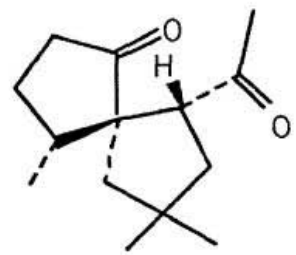

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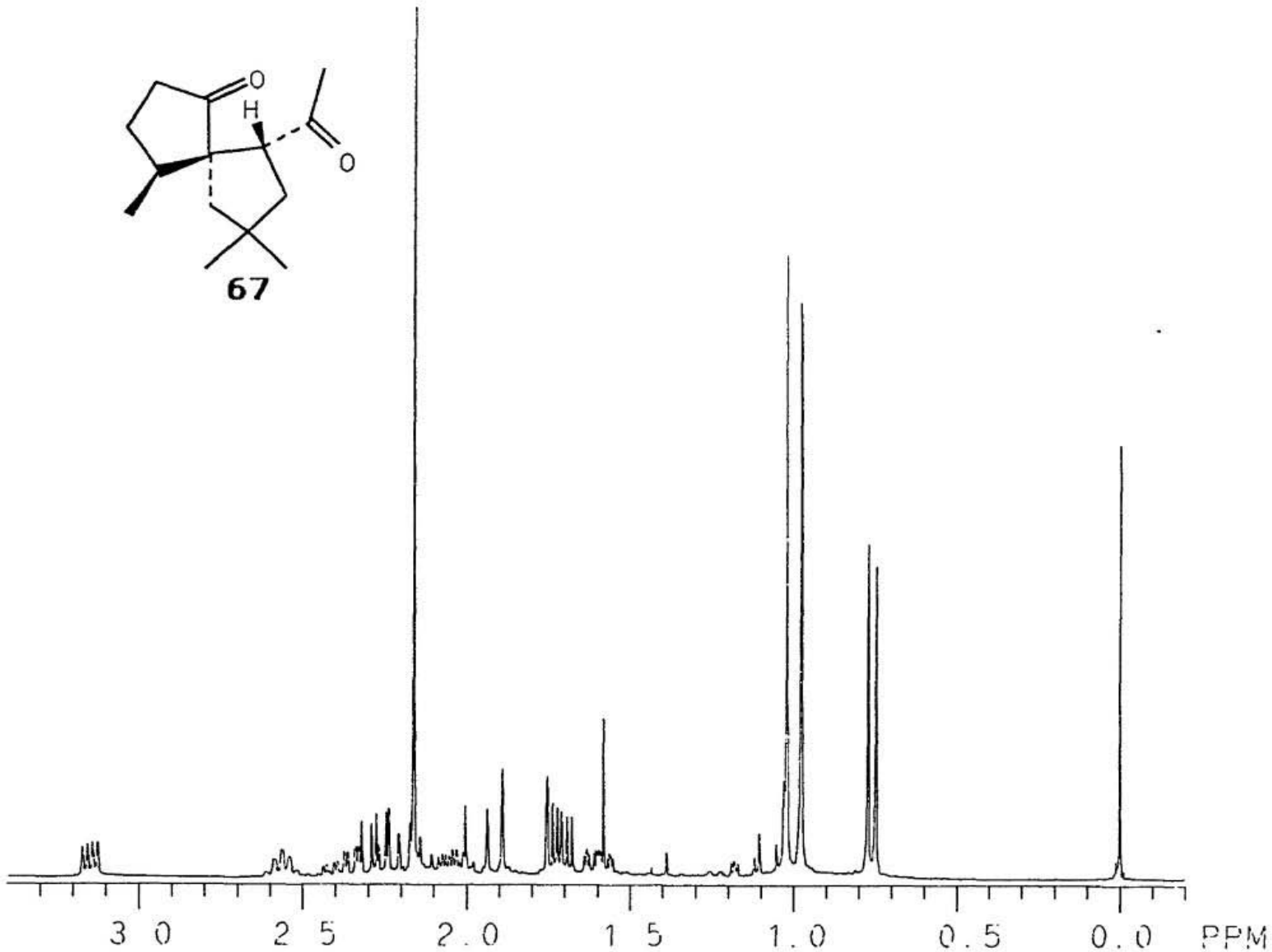
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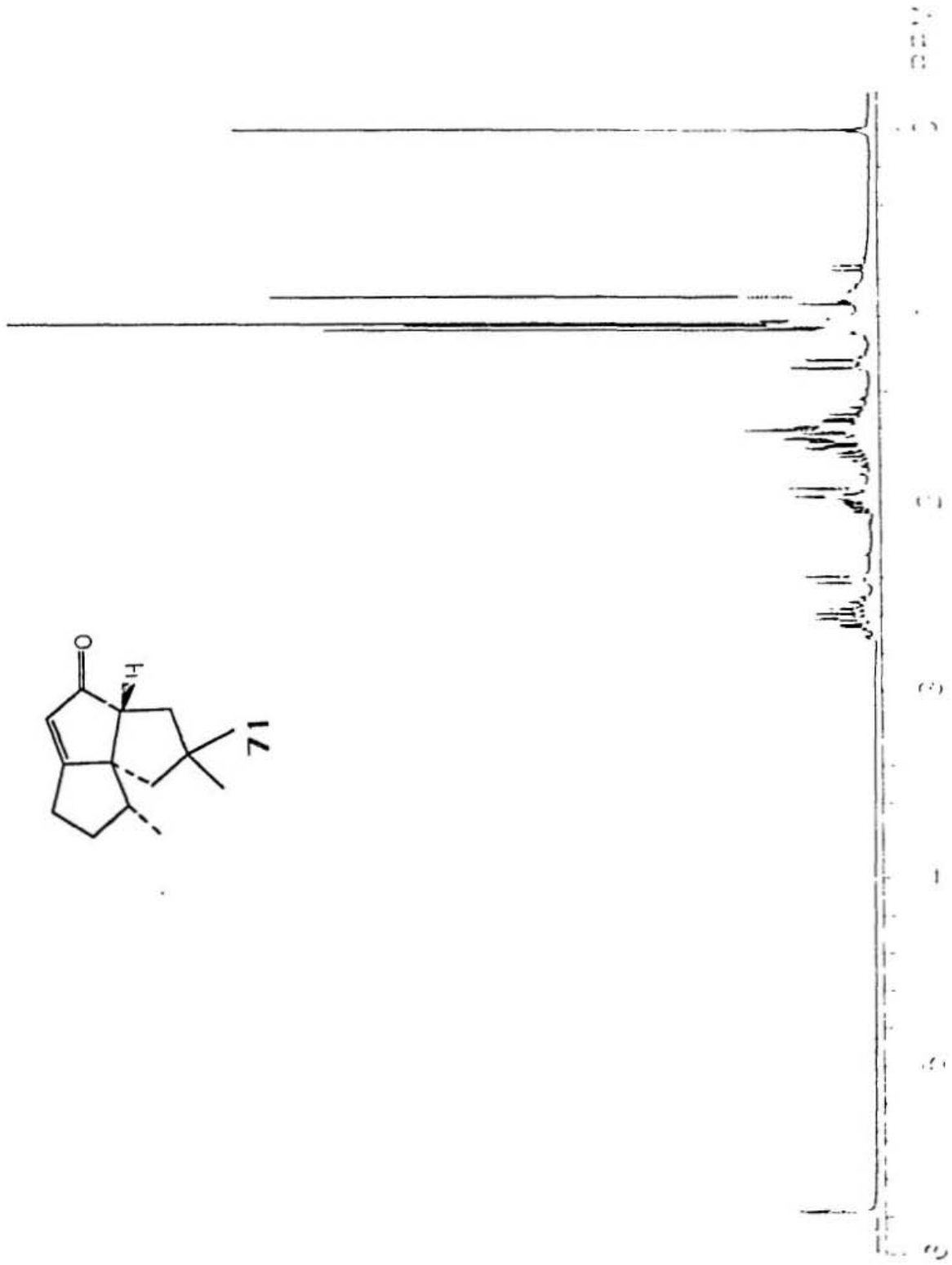
H
O
67
3.0
2.5
2.0
1.5
1.0
0.5
0.0
PPM



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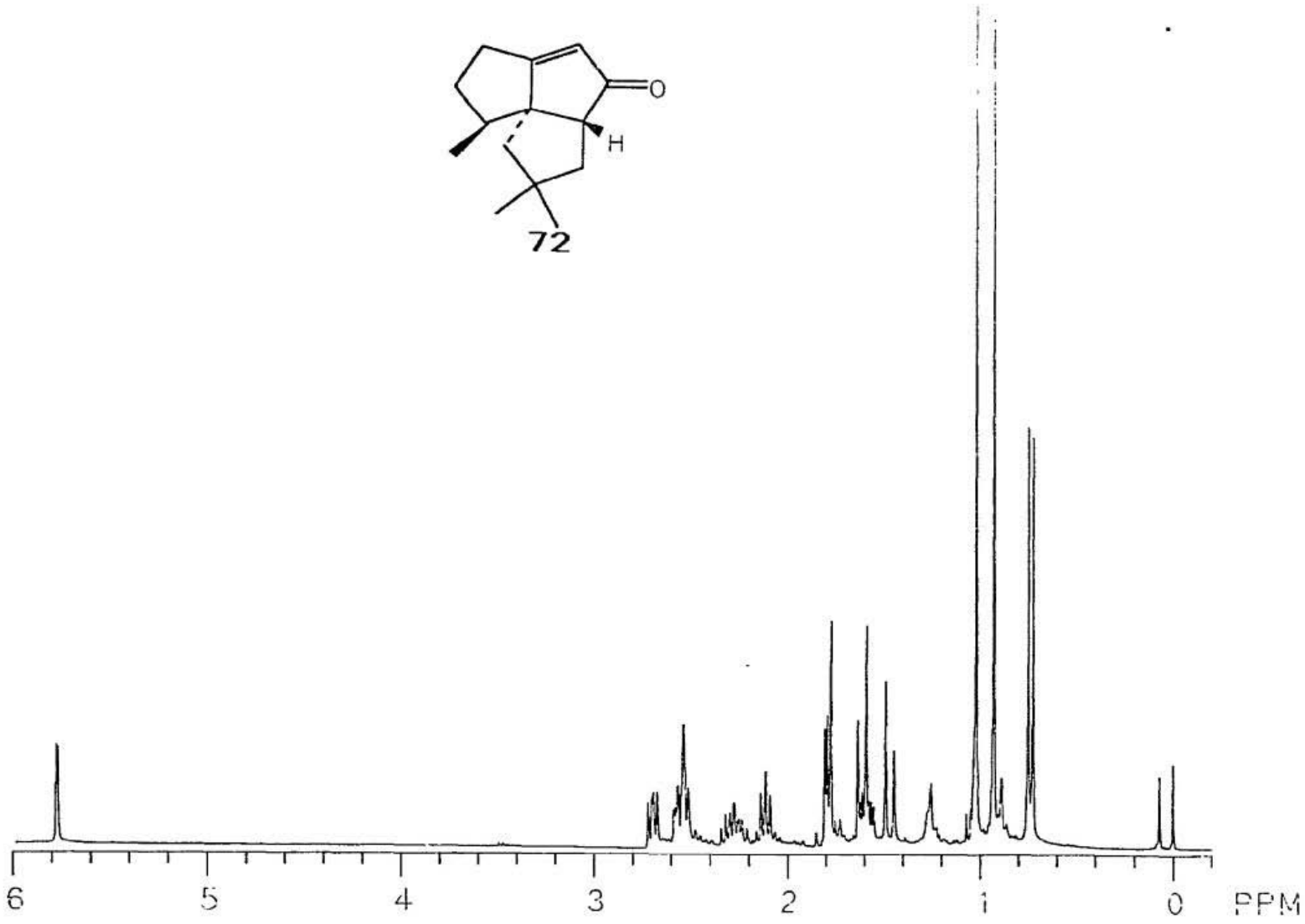
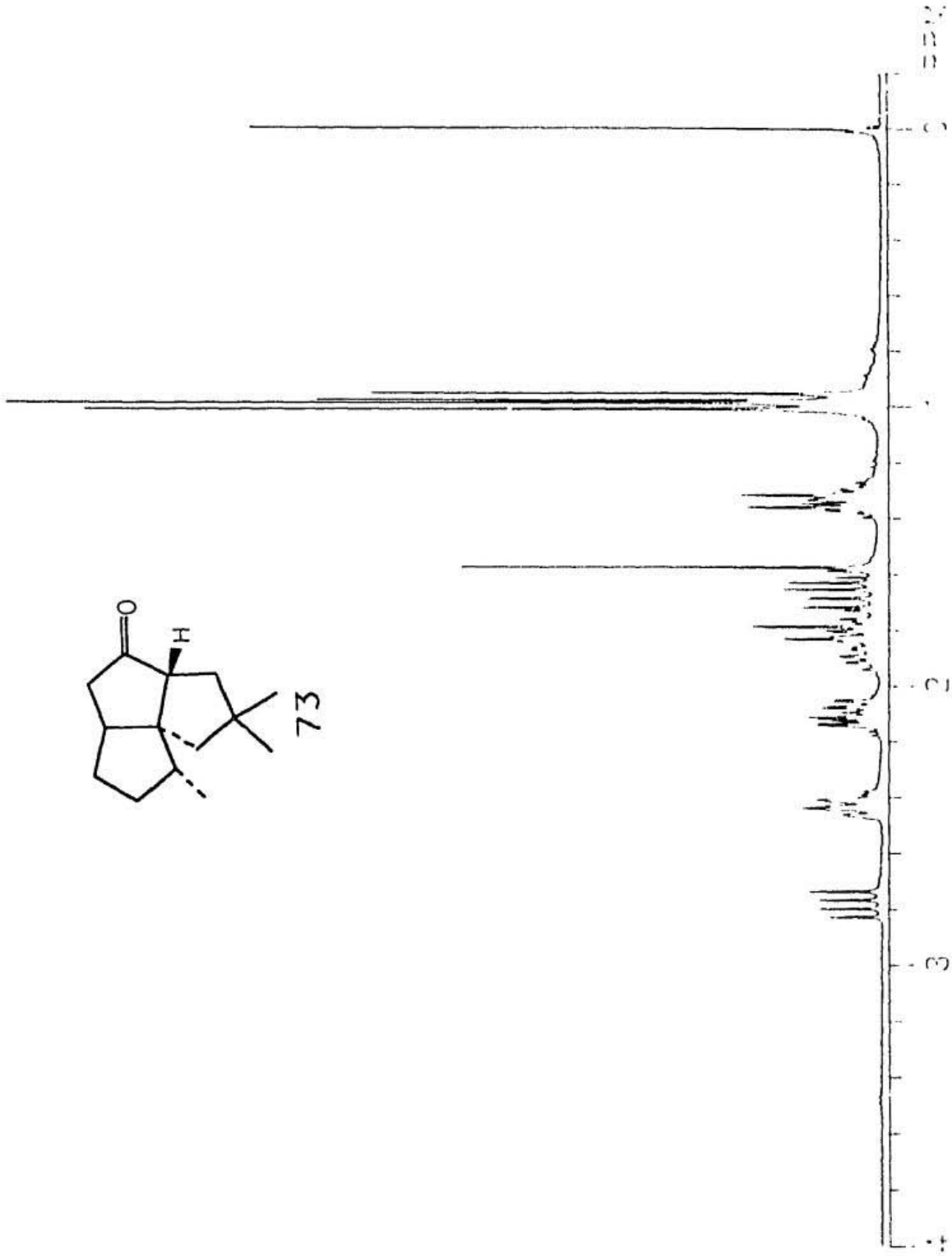
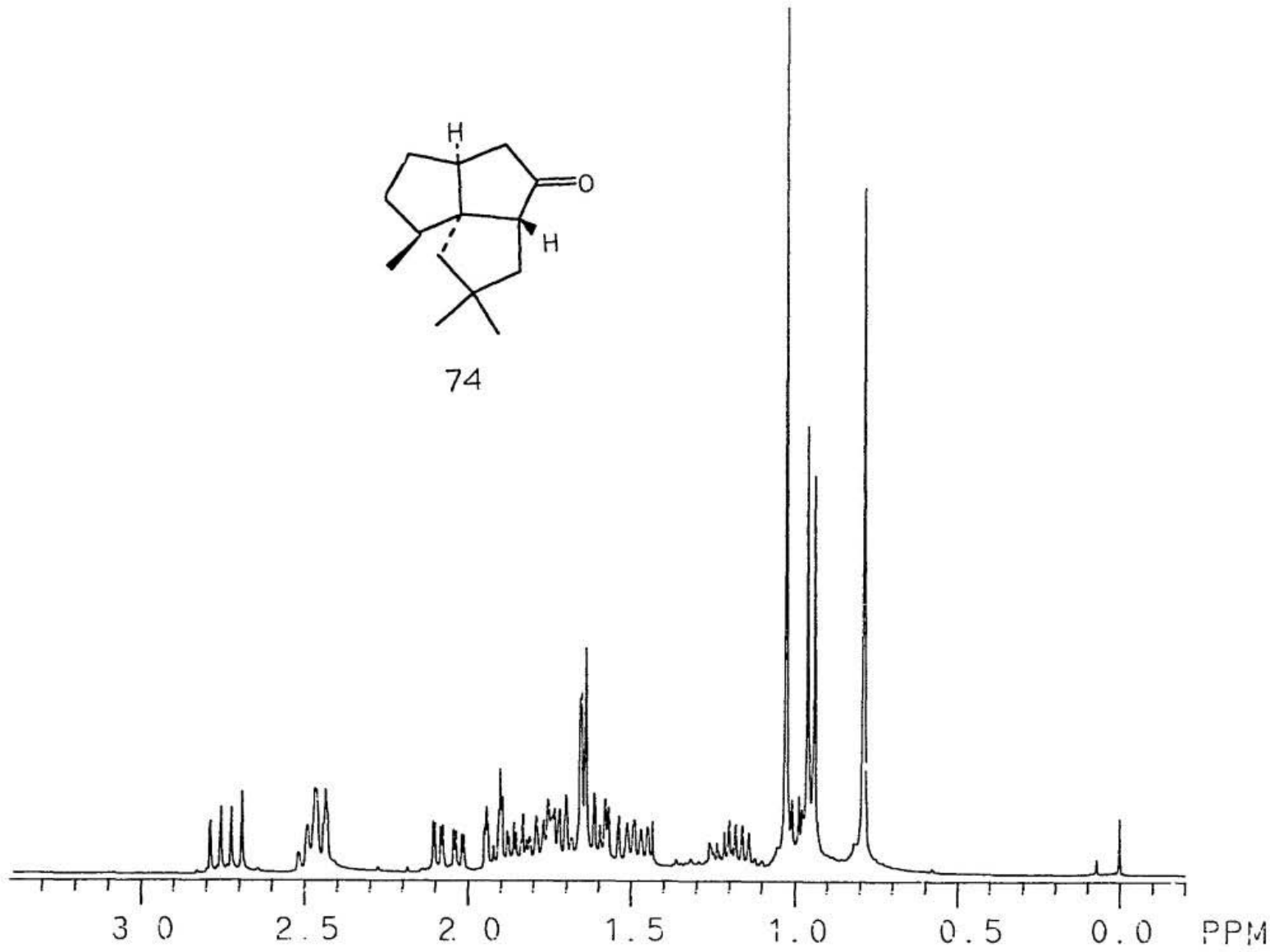
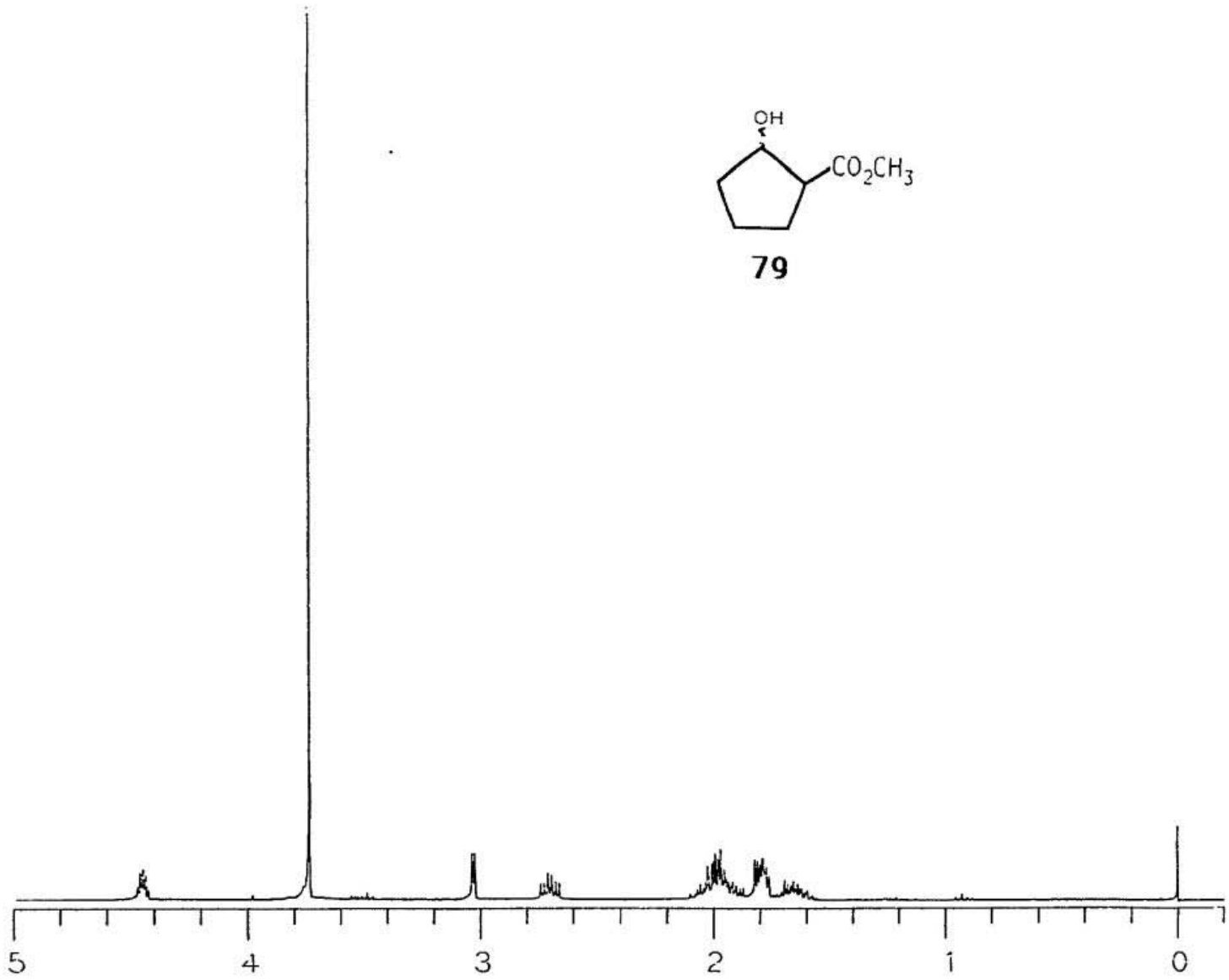

O
H
72
6
5
4
3
2
1
0
PPM


O
H
73

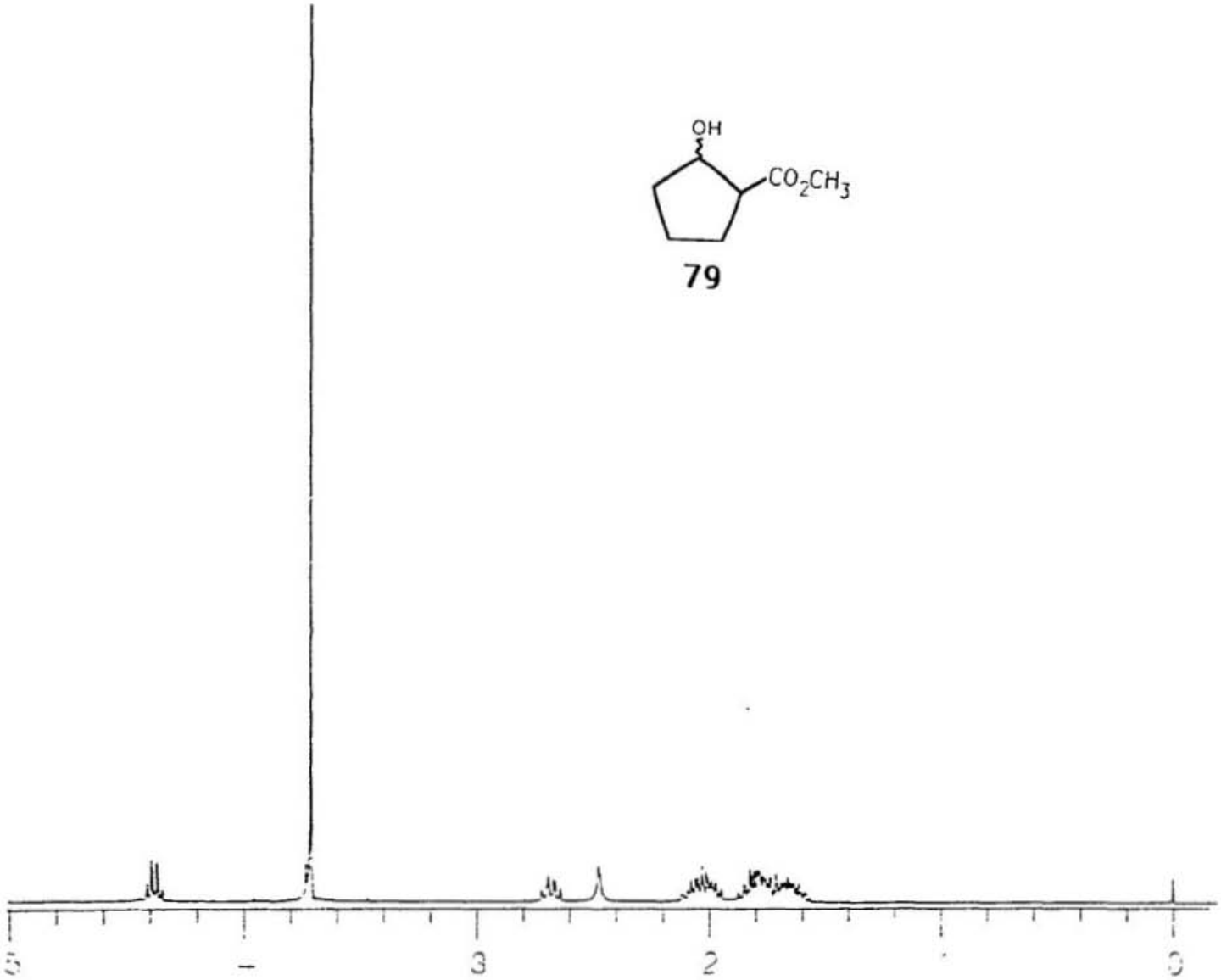


74

CO2Et
O
77
0
1
2
3
4
5
PPM



79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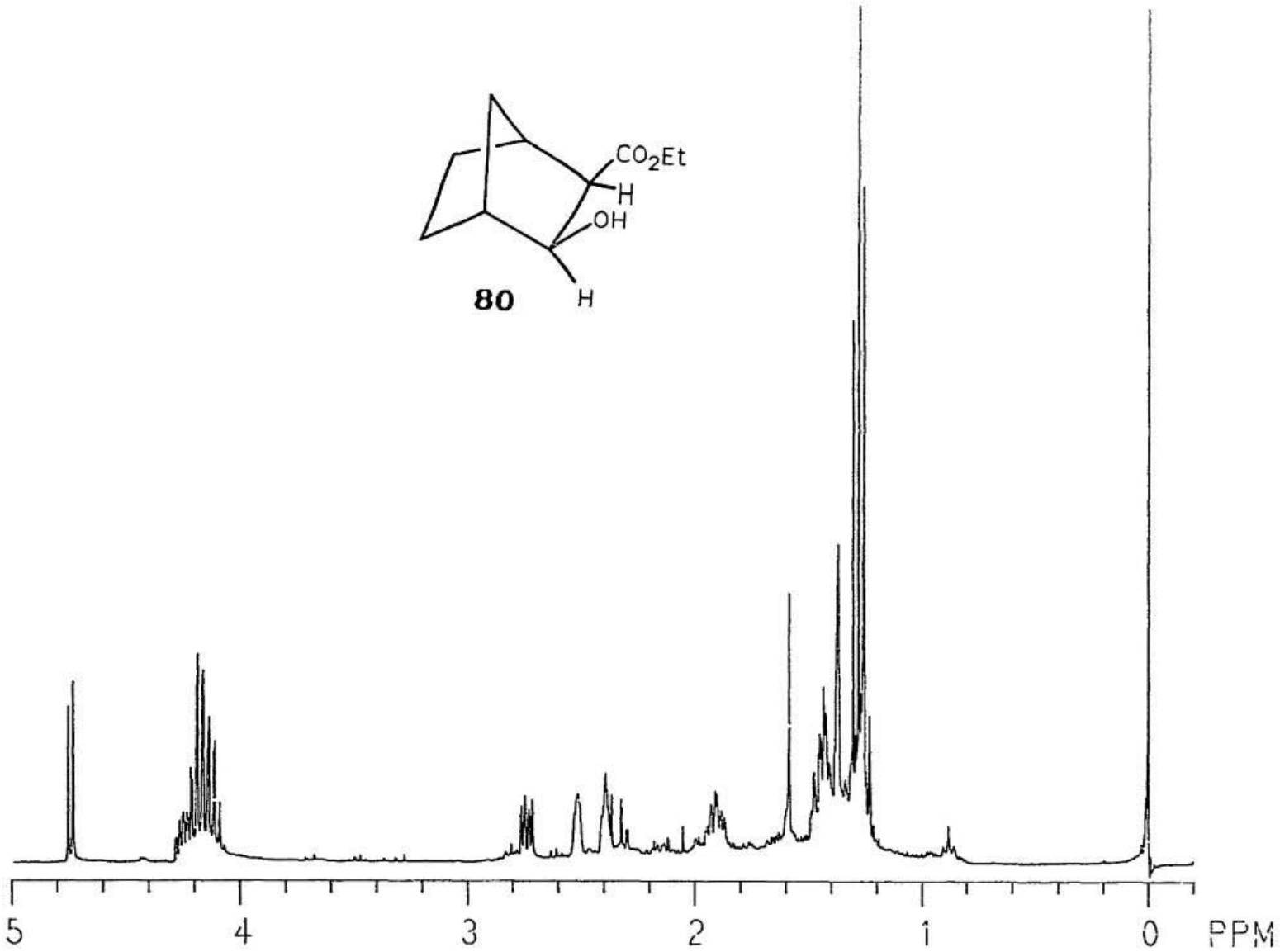
CO2CH3
79
3
2
PPM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H
OH
H
80
5
4
3
2
1
0
PPM

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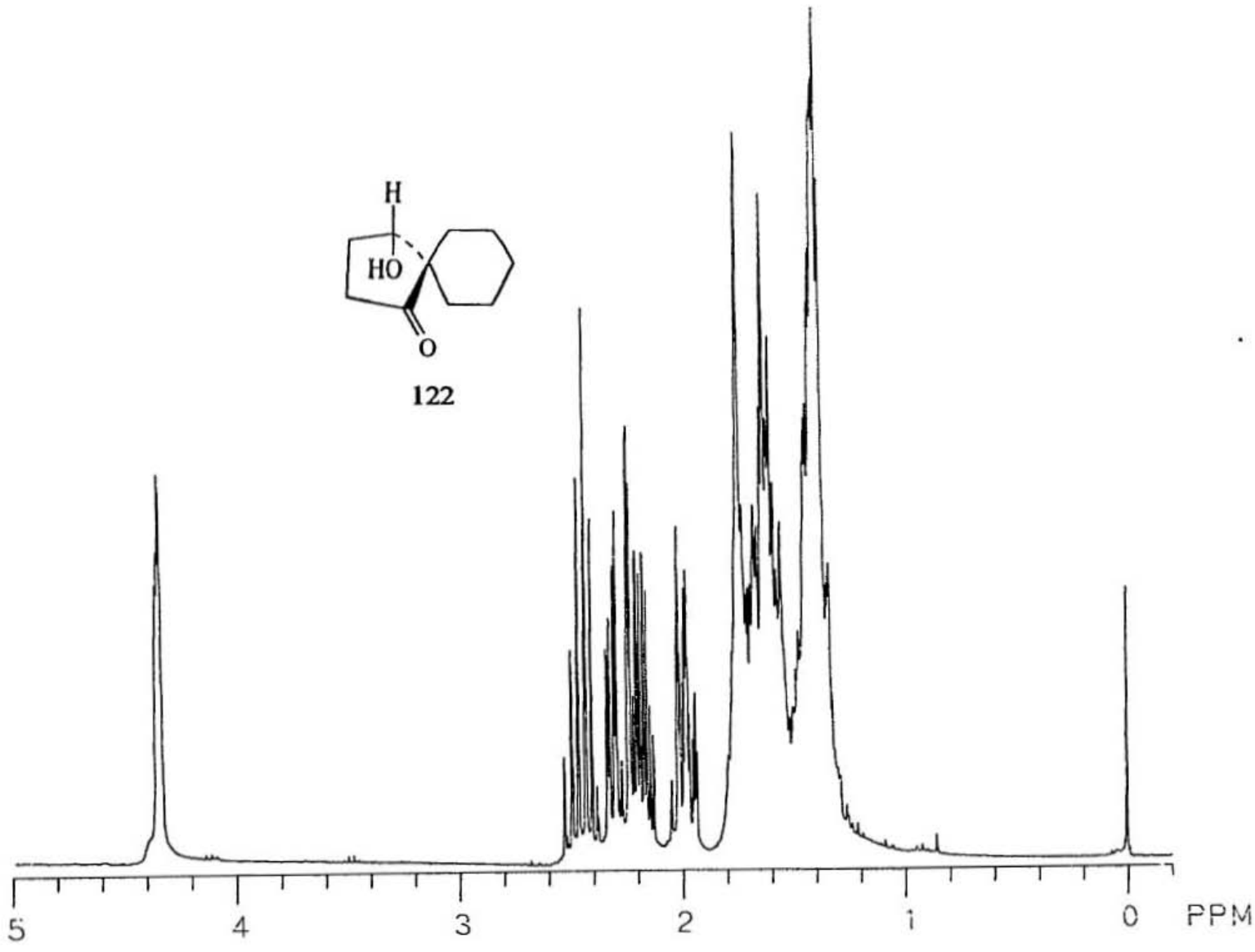
H
80
+
H
CO2Et
H
OH
81
PPM
0
1
2
3
4
5



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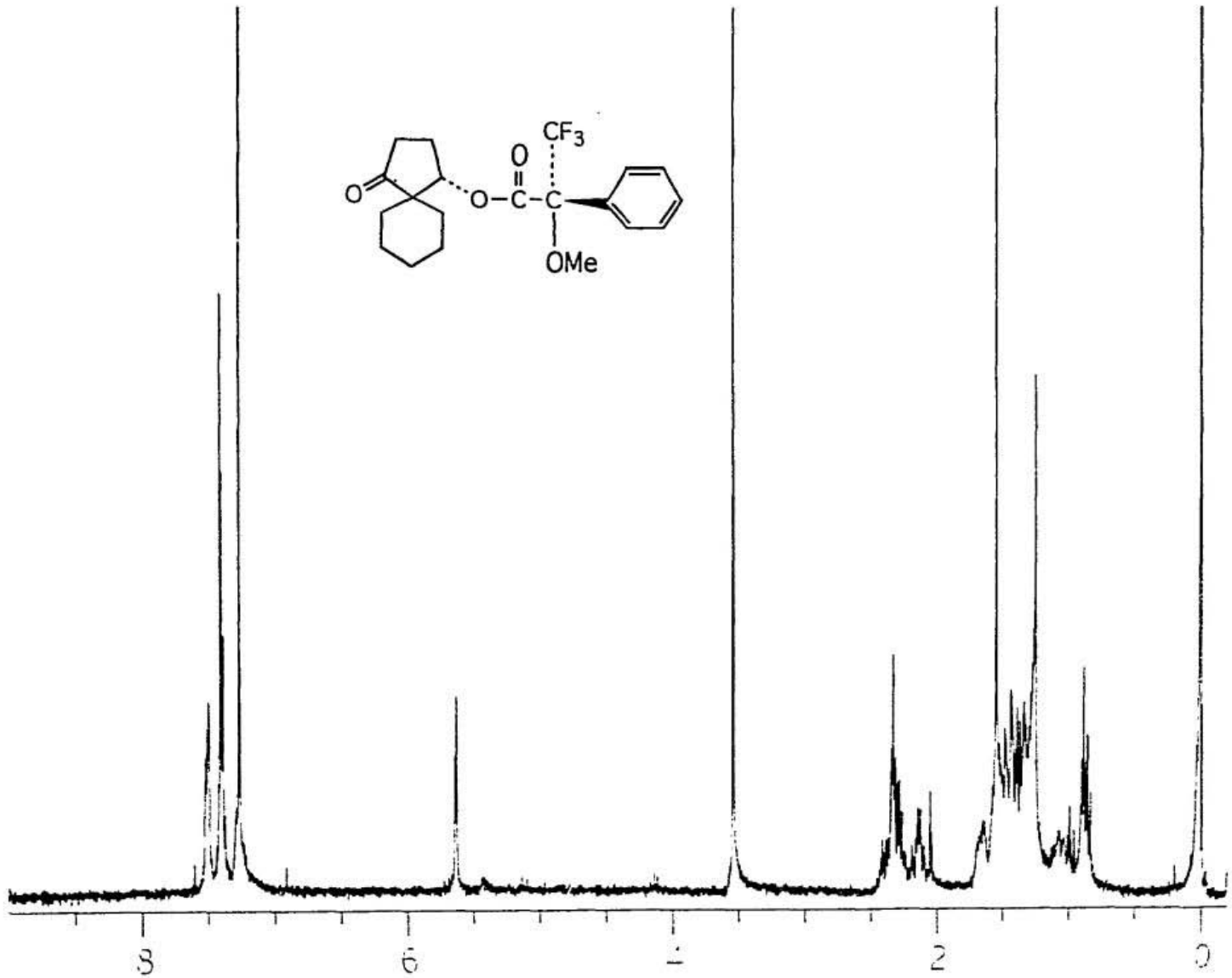
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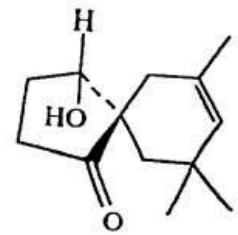
O
O–C–C
OMe
8
6
4
2
0
PPM



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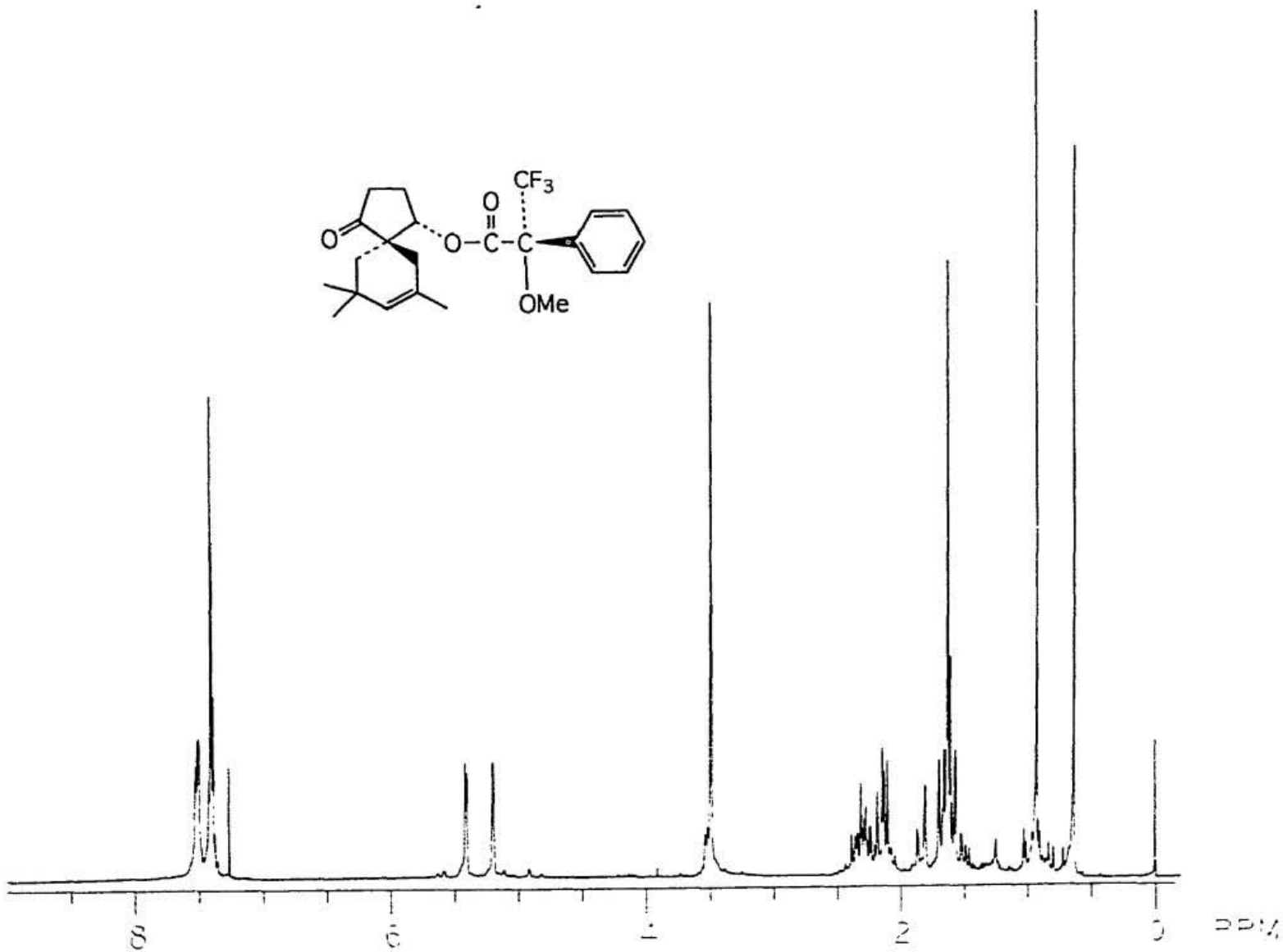
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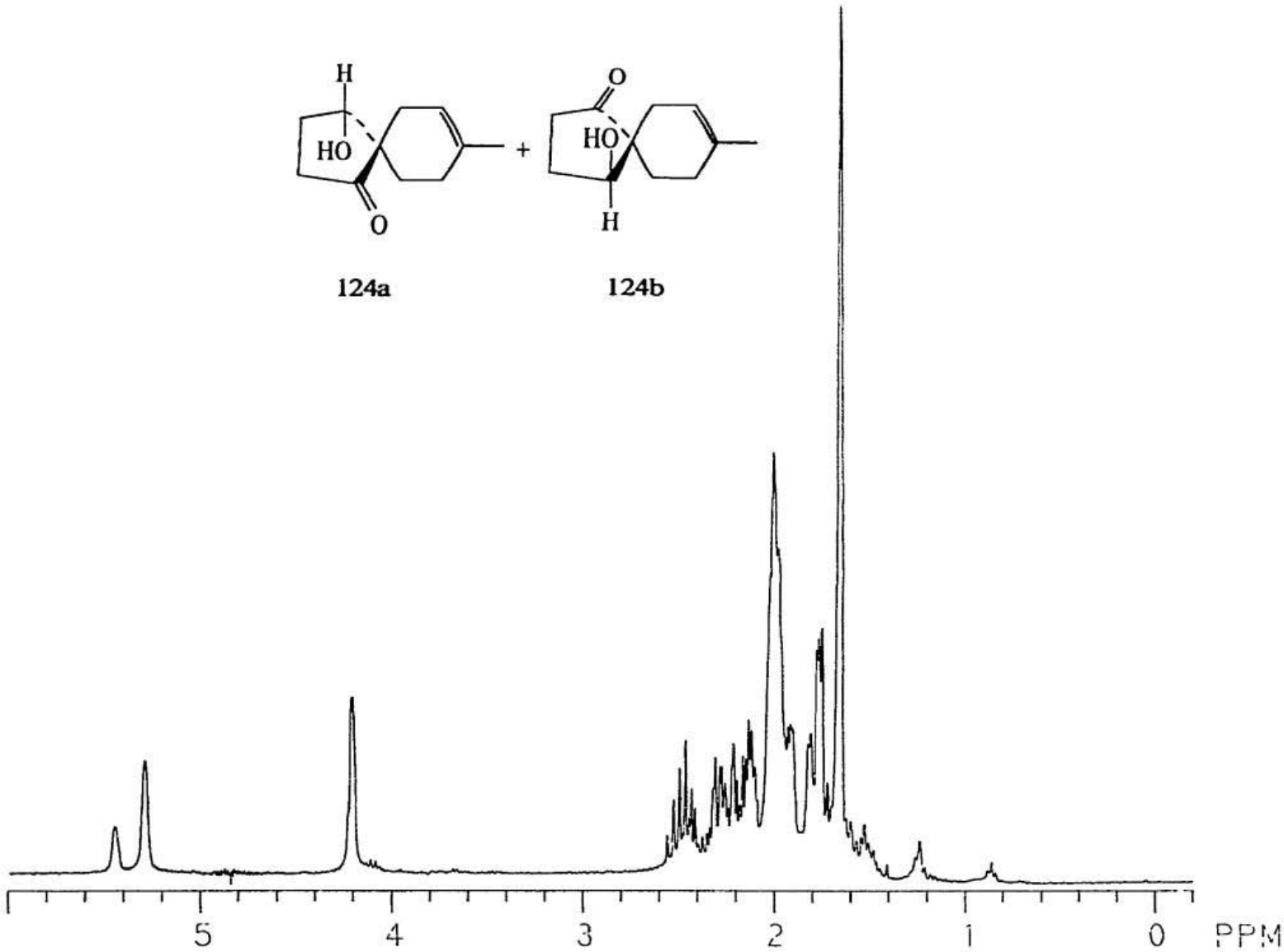
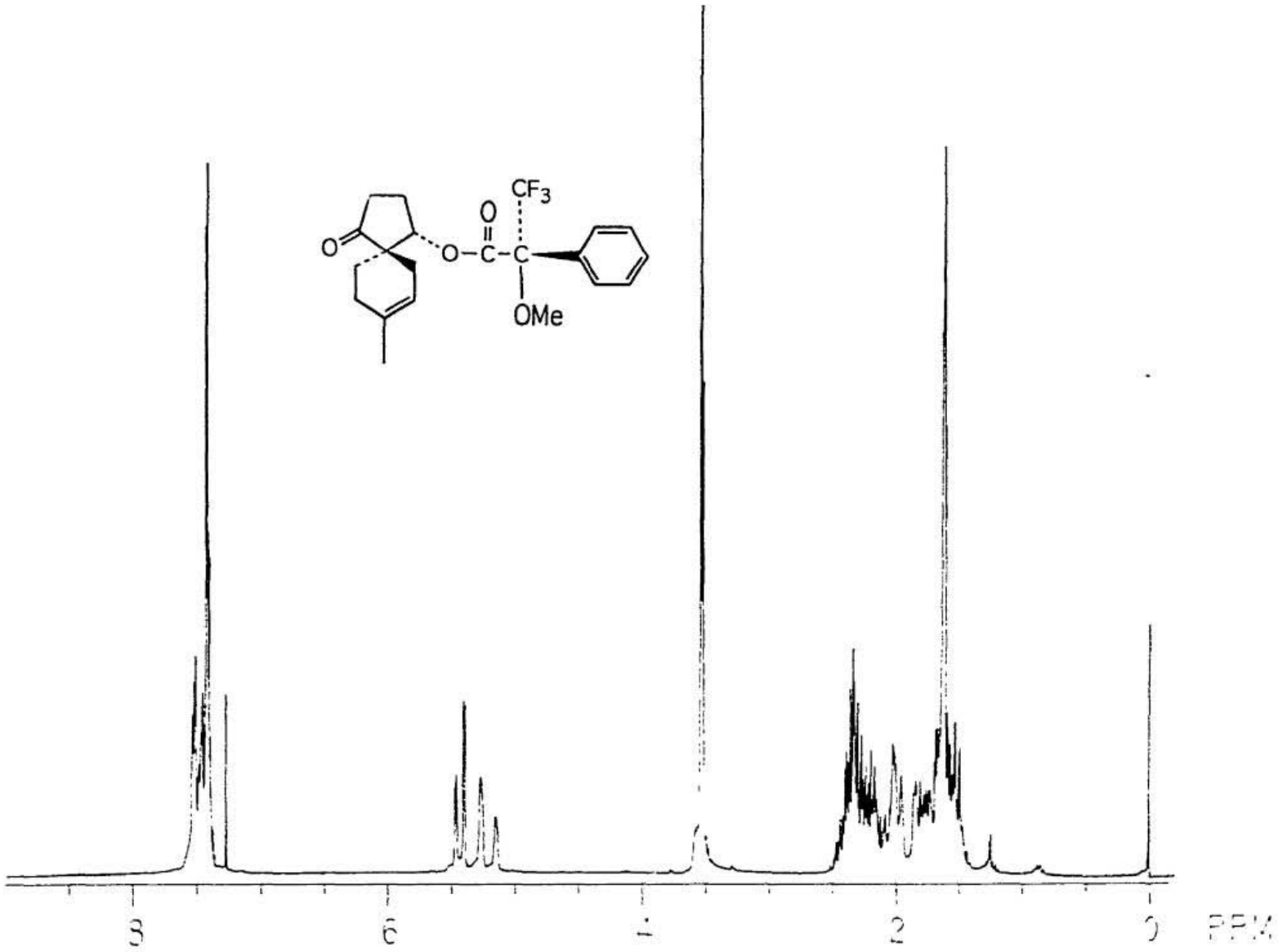
O
C
C
OMe
8
6
4
2
0
PPM



124a **124b**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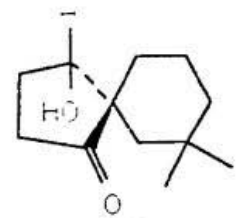
O–C–C
OMe
PPM



129

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O
O
PPM
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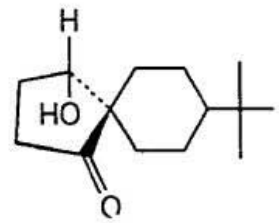
2
4
6
8



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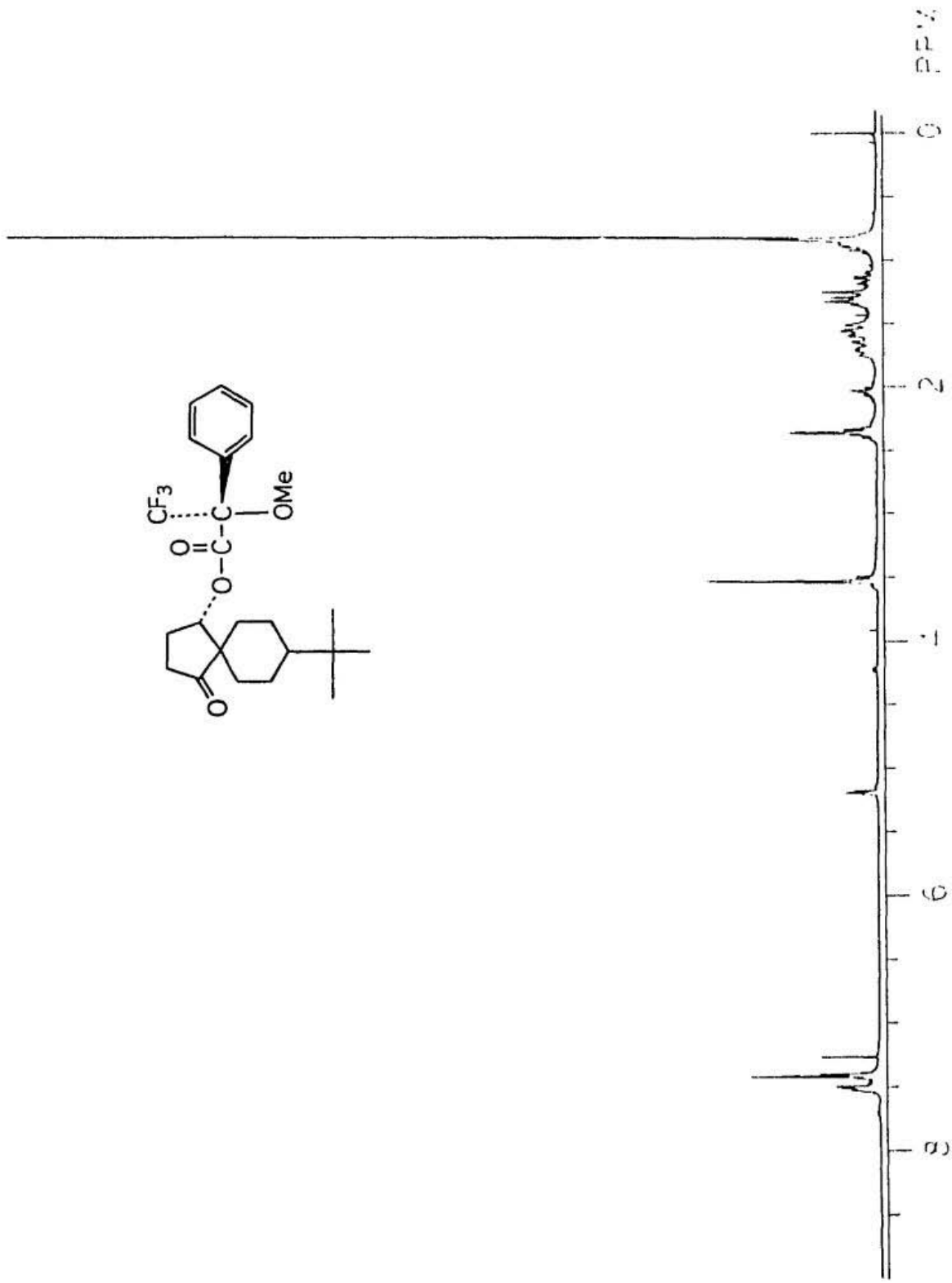
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3
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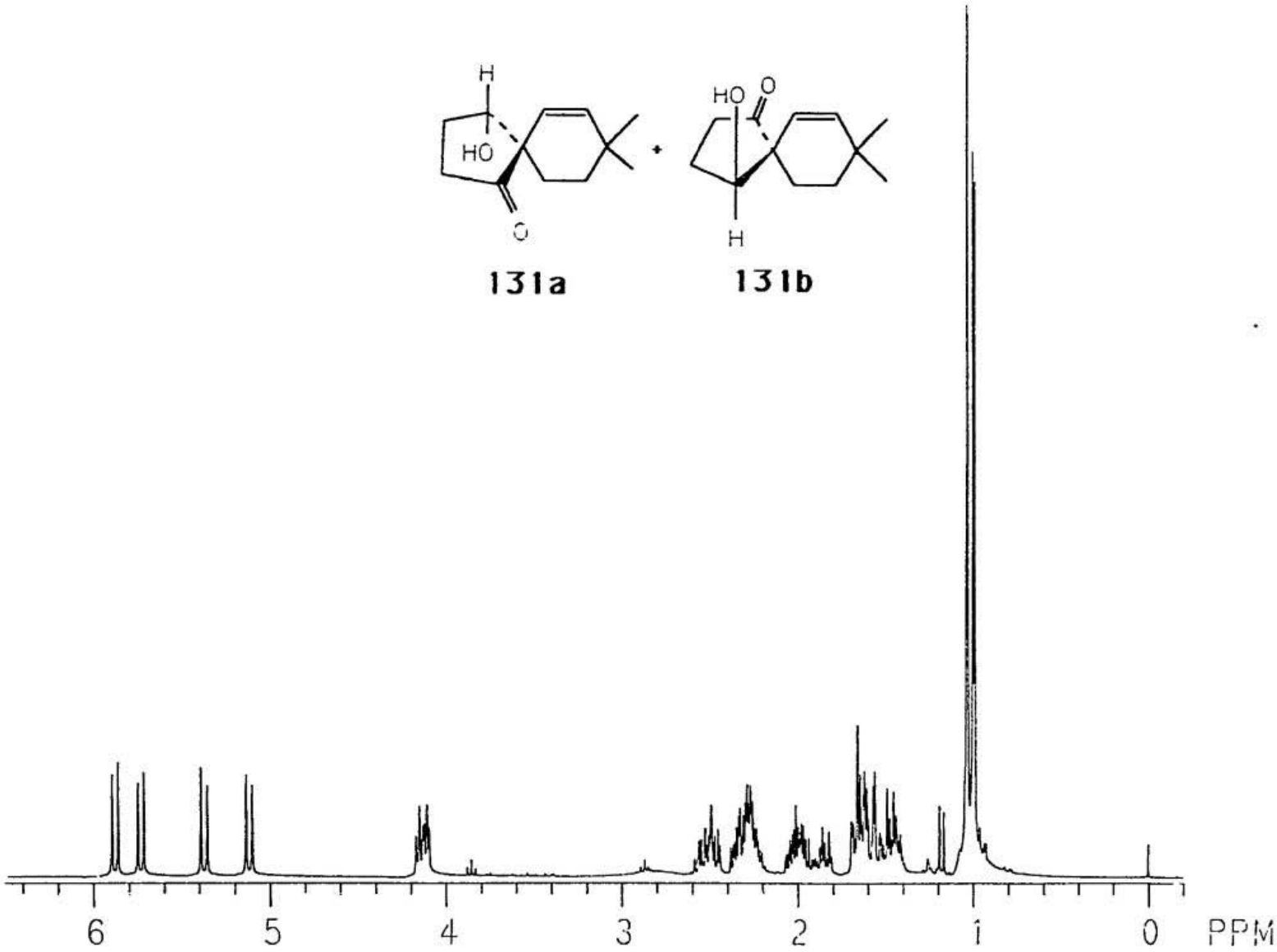
1
0



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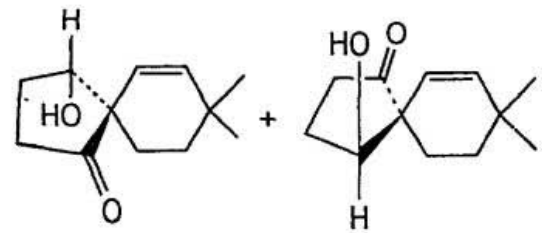

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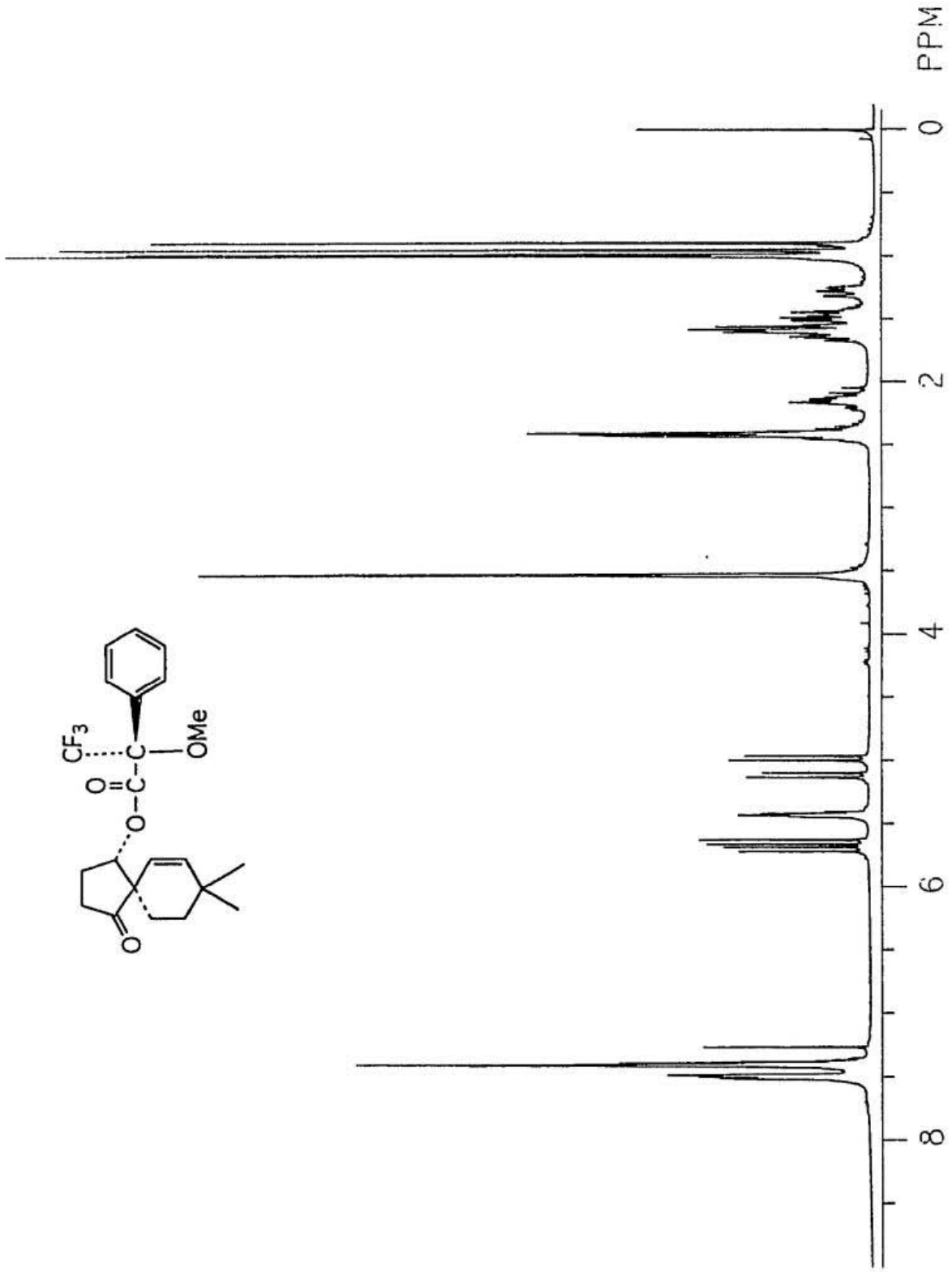
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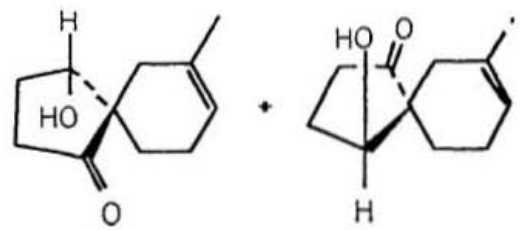
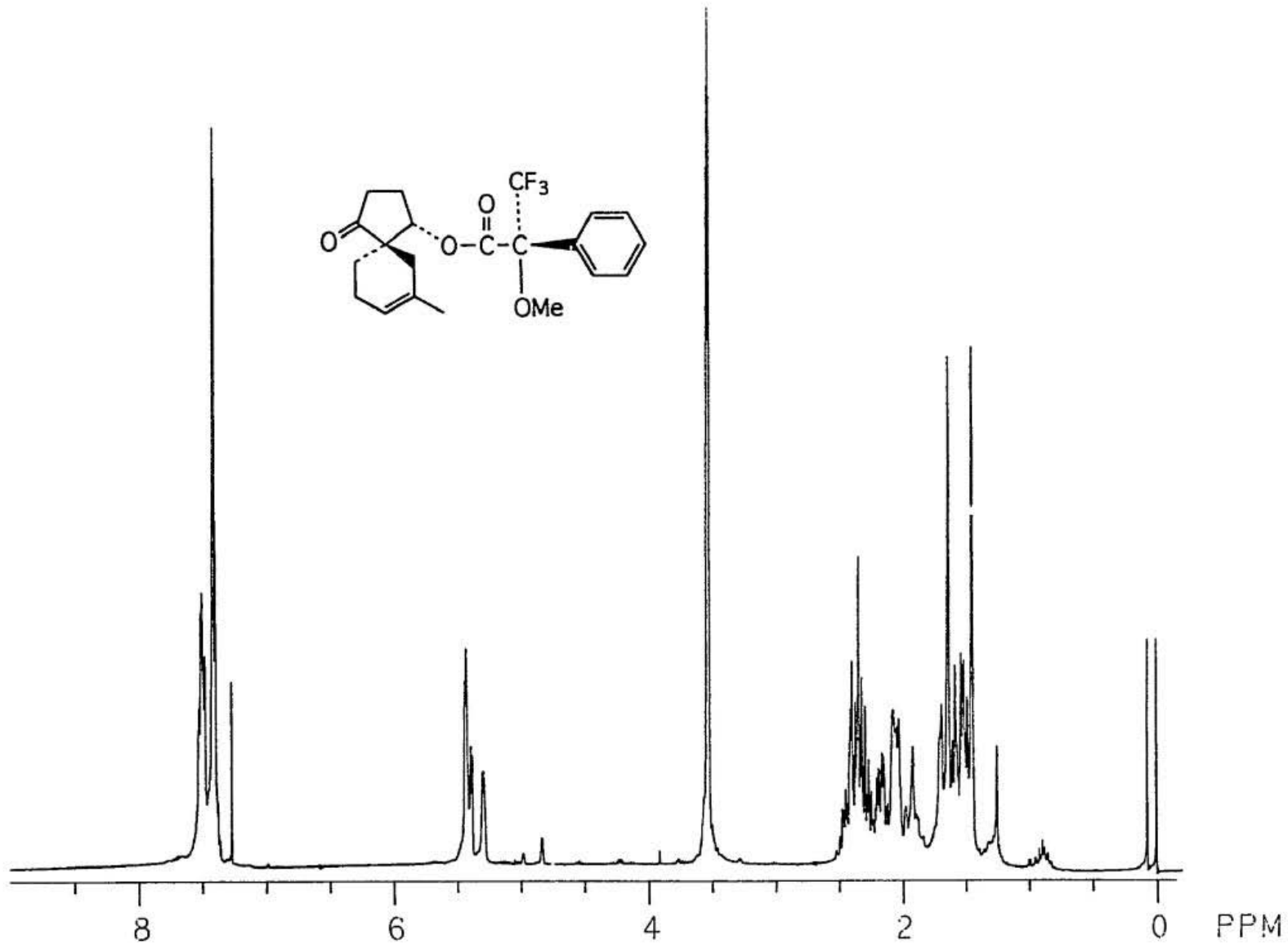
6
8



132a

132b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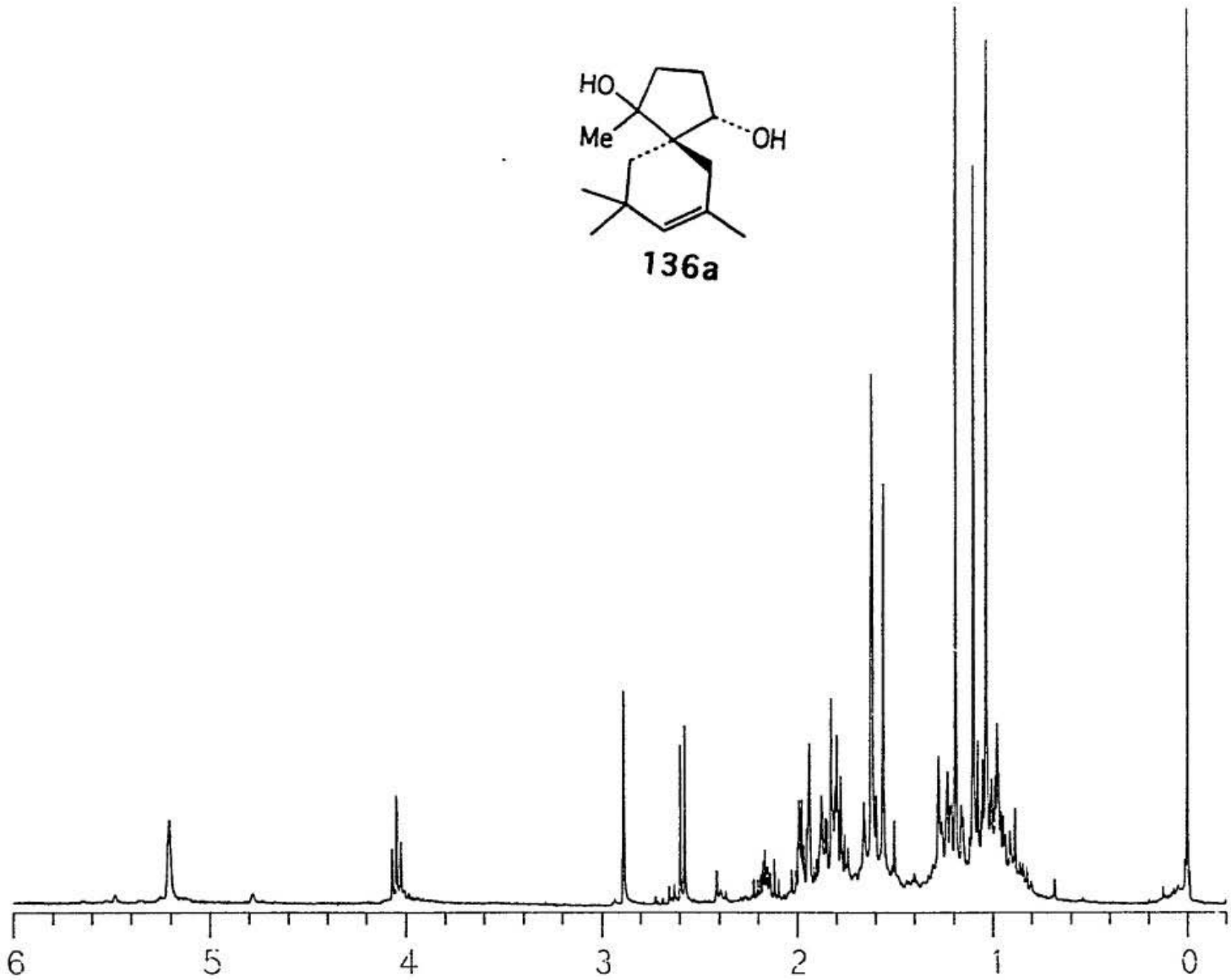
4
2
0
PPM

134



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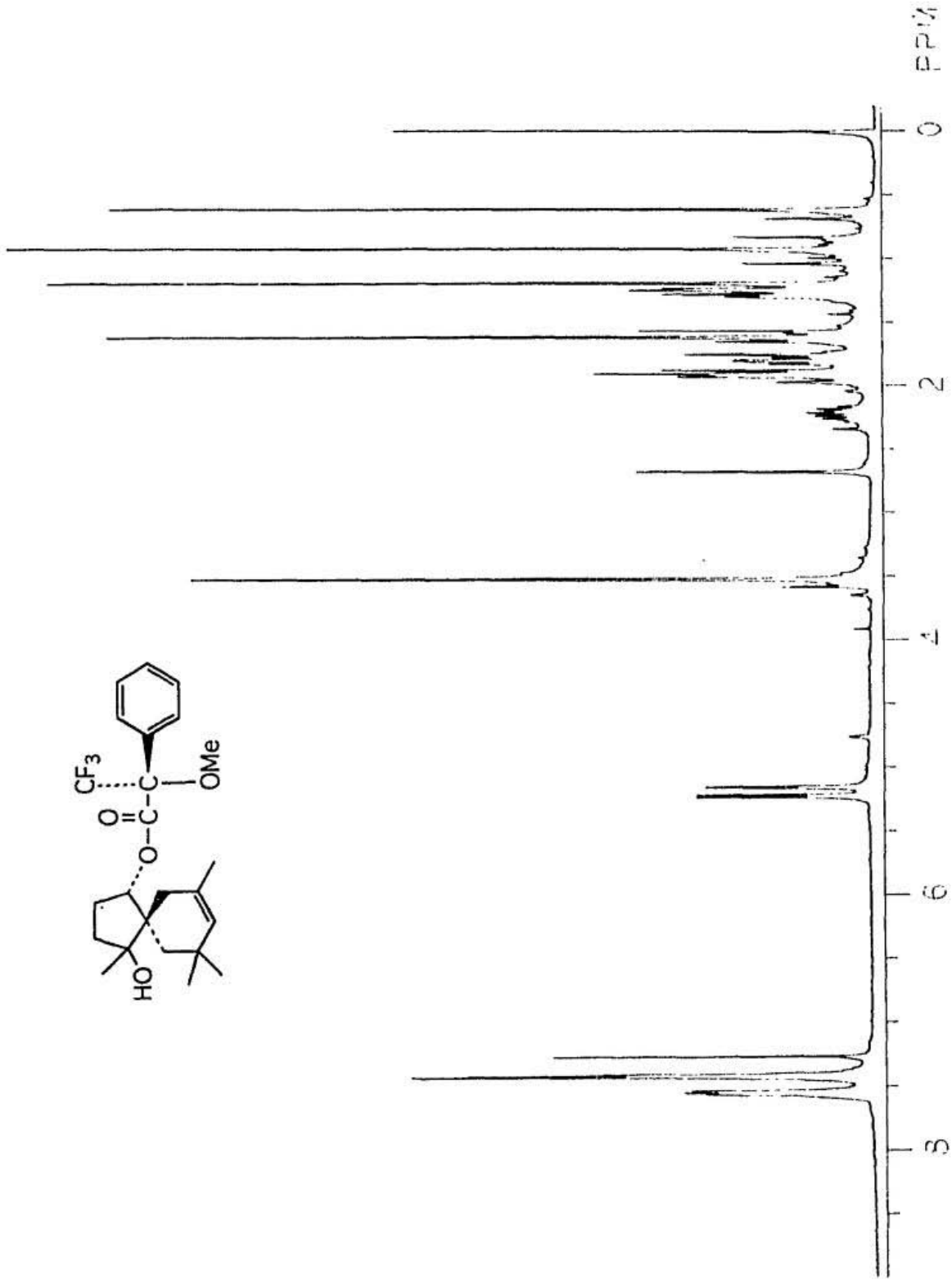
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O
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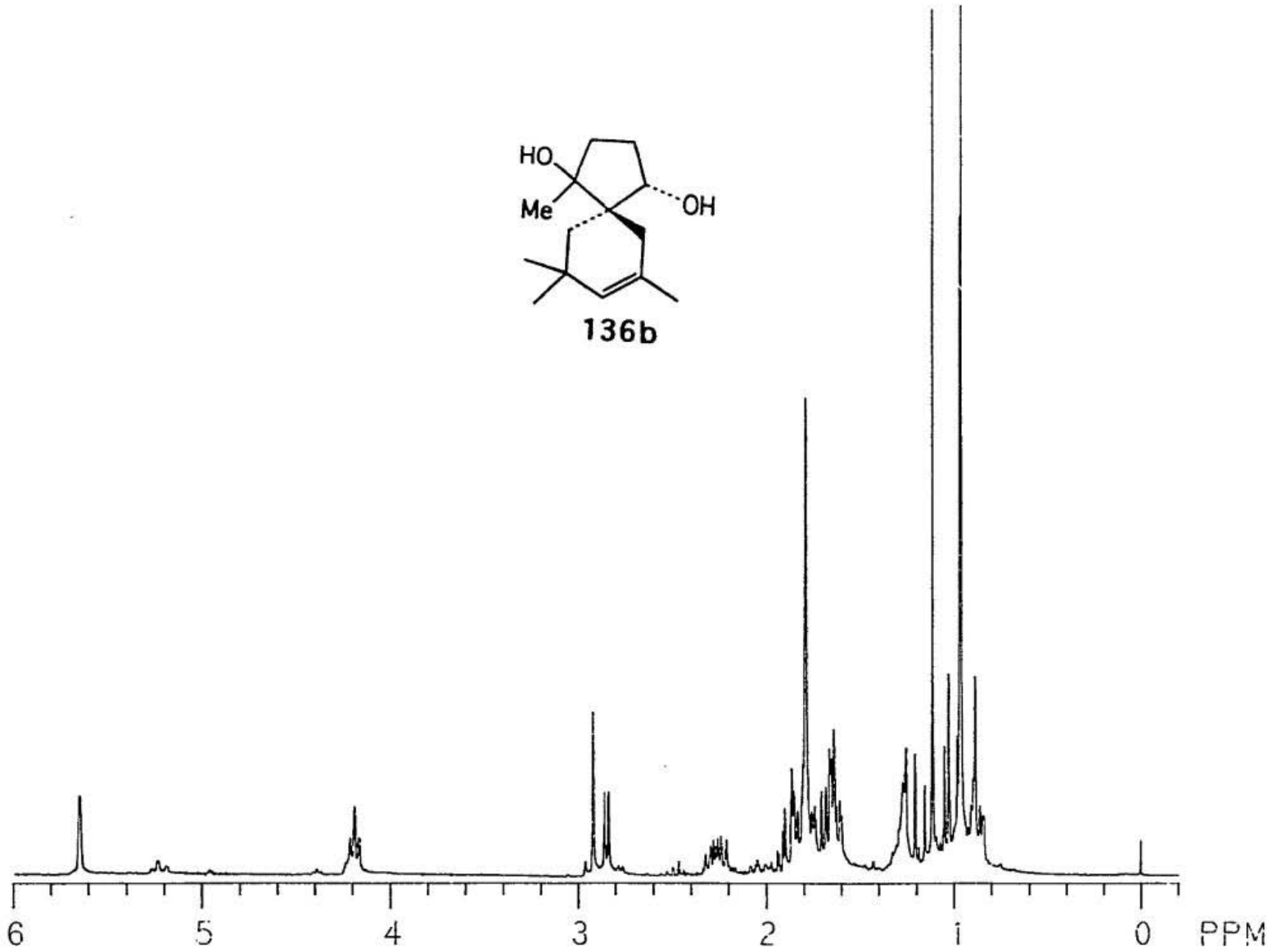
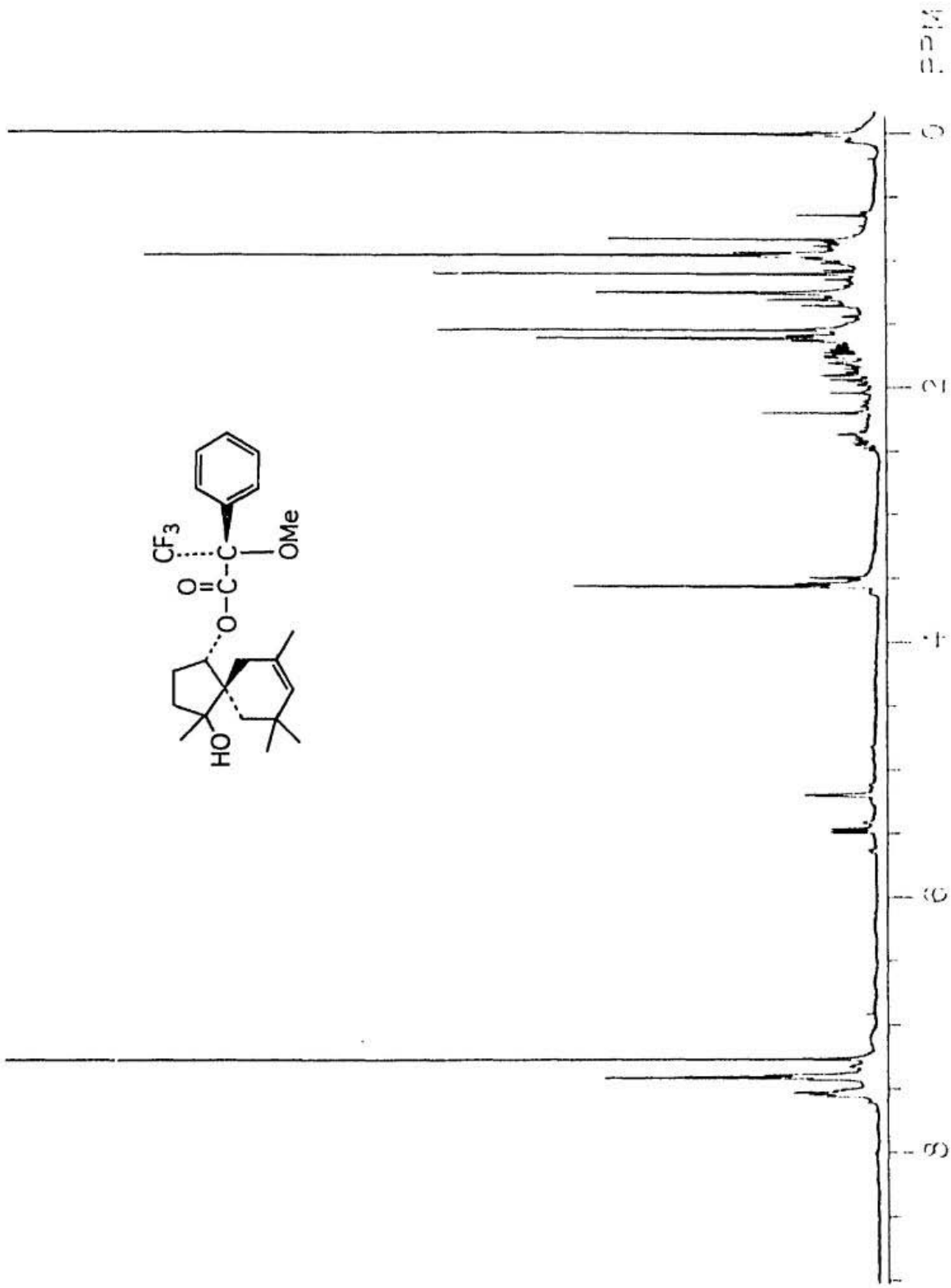


136b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5
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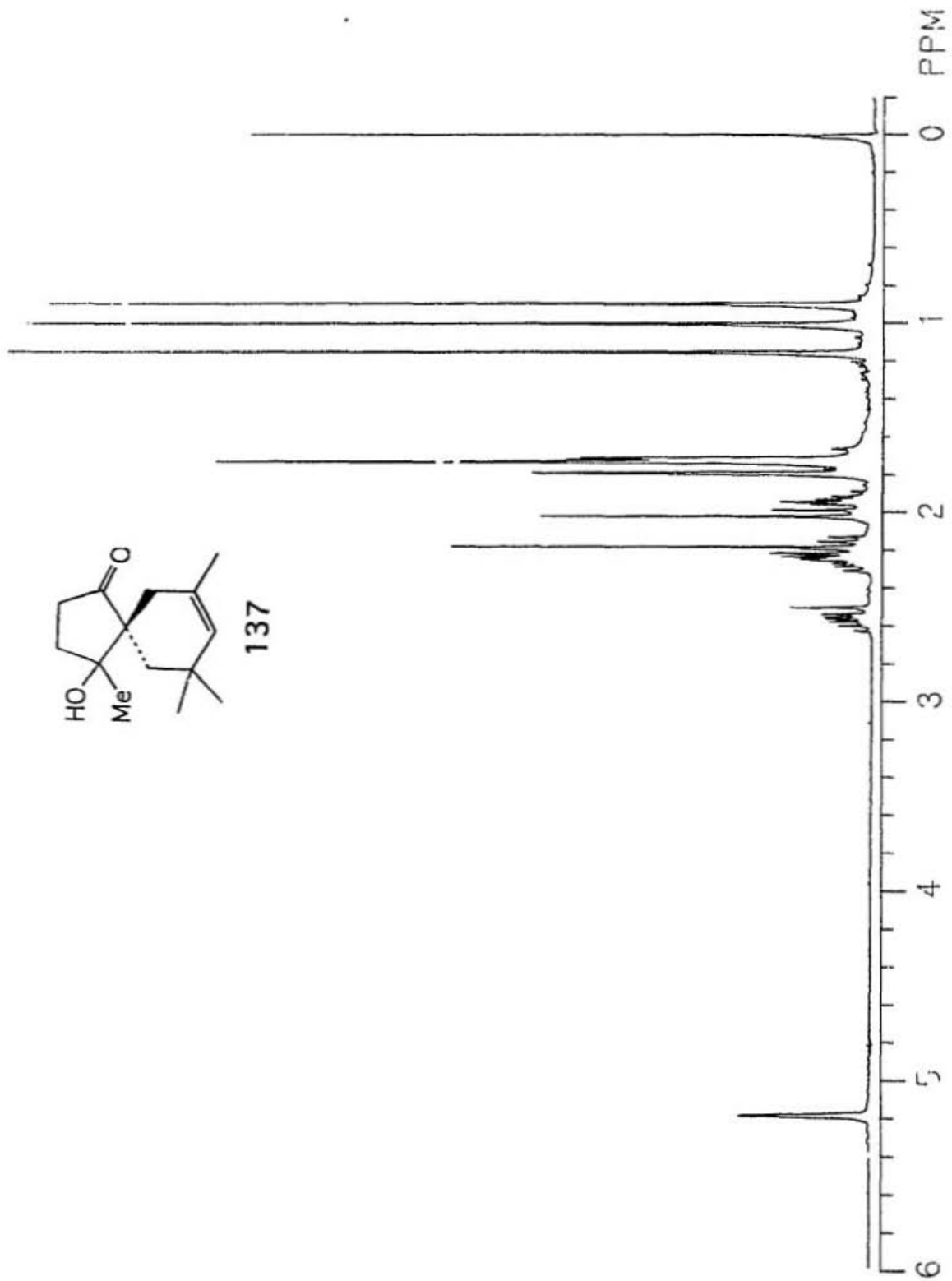
3
2
1
0
CF3
OMe
O
O
HO


O
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137
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