ENANTIOSELECTIVE SYNTHESIS OF IRIDOID MONOTERPENE LACTONES

A Thesis Submitted for the Degree of
Doctor of Philosophy

By
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To

My Parents

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DECLARATION

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, India under the supervision of Dr. Ashwini Nangia.

In keeping with the general practice of reporting scientific observations due acknowledgements have been made wherever the work described is based on the findings of other investigators.

Hyderabad

November 1995

G. Prasuna

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CERTIFICATE

Certified that the work described in the thesis entitled "**Enantioselective Synthesis of Iridoid Monoterpene Lactones**" has been carried out by Ms. G. Prasuna under my supervision and the same has not been submitted elsewhere for any degree.

Dr. Ashwini Nangia

Thesis supervisor

Dean 22/XI/95

School of Chemistry

ACKNOWLEDGEMENTS

I wish to express my deep sense of gratitude to Dr. Ashwini Nangia for his excellent guidance through out the course of this work. His inspiring discussions helped me in cultivating knowledge and his philosophical approach motivated my scientific temper. He has taken a lot of care and interest in all aspects of my career. I have learnt many things from him in addition to Chemistry, and I consider my association with him a rewarding experience.

My due respects to Prof. P.S. Zacharias, Dean, School of Chemistry and all other faculty members of this school for their valuable suggestions and expert comments on various occasions.

It is Dr. P. Bheema Rao who encouraged and helped me in various ways as a senior and husband. I am very thankful to him.

I would like to express my sincere thanks to my labmates Ms. P.S. Chandrakala, Mr. A. Anthony, Ms. N.N.L. Madhavi and K. Sreenivasan for their co-operation and help during my research period.

My family has given me constant support and encouragement all these years, and I am grateful to them.

I wish to thank Prabhavathi and Padmaja who created a homely atmosphere during my stay in the hostel. I am thankful to all my senior research scholars for their help and encourangement. My stay on this campus was pleasant with the association of Manjula, Sudha, Sreelatha, Aparna, Madhavi, Suguna, Srinivas, Raghu, Thakhi,

Murali, Brahmananda, Rangamadhavan, Anuradha, Vijjulatha, Aneetha, Soujanya, Anita, Sindhu, Ramalakshmi and Saroja.

Thanks are also due to all the technical and non-technical staff of School of Chemistry, especially to Mr. Sathyanarayana, Mr. Bhaskar Rao, Mrs. Vijayalakshmi, Mr. Ramana, Mr. Shetty and Mr. Prasad for their assistance during my research period.

I thank University authorities for providing infrastructure facilities. Financial support from University Grants Commission in the form of research fellowship is gratefully acknowledged.

G. Prasuna

ABBREVIATIONS

Ac	acetyl
acac	acetyl acetone
AIBN	azobisisobutyronitrile
aq	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
bp	boiling point
Bu	butyl
C	centigrade
cm	centi metre
CMR	carbon magnetic resonance
conc	concentration
COSY	correlated spectroscopy
d	doublet
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DIBAL-H	diisobutylaluminium hydride
DHP	3,4-dihydro-2H-pyran
DMAP	4-dimethylaminopyridine
DMP	dimethylpyrazole
DMF	dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
epi	epimer

Et	ethyl
ether	diethyl ether
equi	equivalents
h	hour
HRMS	high resolution mass spectroscopy
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HWE	Horner-Wadsworth-Emmons
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrscopy
m	multiplet
M	molar
m-CPBA	*m*-chloroperbenzoic acid
Me	methyl
mg	milli gram
min	minutes
mL	milli litres
mmol	milli moles
mp	melting point
Ms	methanesulfonyl
NBS	N-bromosuccinimide
NOESY	nuclear overhauser and exchange spectroscopy
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PMR	proton magnetic resonance

PPTS	pyridinium *p*-toluenesulfonate
ppm	parts per million
PPA	polyphosphoric acid
Pr	propyl
p-TsOH	*p*-toluenesulfonic acid
Py	pyridine
q	quartet
ref	reference
rt	room temperature
s	singlet
sat	saturated
SGC	silica gel chromatography
SG	silica gel
SM	starting material
t	triplet
TBDMS	*tert*-butyldimethylsilyl
TBAF	tetrabutylammonium flouride
TBHP	*tert*-butylhydroperoxide
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl

ABSTRACT

The thesis has been organised under five main chapters. 1) Iridoid lactones: Introduction and literature survey. 2) Synthetic transformations from *R*-pulegone. 3) Synthesis of iridoid type-I cyclopentapyranone skeleton. 4) Synthesis of type-II lactones: Mitsugashiwalactone and 4-*epi*-mitsugashiwalactone. 5) Synthesis of anhydromevalonolactone and its thiolactone. The experimental details and spectra follow the discussion in each chapter.

1). IRIDOID LACTONES: INTRODUCTION AND LITERATURE SURVEY:

Over the past three decades the class of naturally occurring iridoid cyclopentapyranones has gained increased recognition because of their diverse biological activity. They play a role in the biosynthesis of indole alkaloids and are also used as chiral synthons for the synthesis of different prostaglandins. The iridoids represent a class of highly oxygenated monoterpenoids characterised by a *cis*-linked partially hydrogenated cyclopenta[*c*]pyran skeleton. Basically two isomeric structural types of cyclopentanoid monoterpene lactones are known. They are structural type-I which bear a carbonyl group at C3, and type-II in which the carbonyl group is at C1.

Some of the natural products which belong to structural type-I are iridomyrmecin **10**, isoiridomyrmecin **11** and teucriumlactone **15**. Mitsugashiwalactone **17**, onikulactone **18**, dihydronepetalactone **20** and isodihydronepetalactone **21** belong to iridoid lactones of structural type-II.

Published routes to iridoid lactones are discussed in the first chapter. The literature is surveyed to cover synthetic approaches to chiral and racemic lactone products.

2). SYNTHETIC TRANSFORMATIONS FROM *R*-PULEGONE:

Most of the published syntheses lead to racemic products or unnatural isomers, very few of them lead to the natural isomers. We focused our interest on the synthesis of natural analogs which have the methyl group at C7 in *S*-configuration. *S*-Pulegone **91** was chosen as starting chiron for the synthesis of lactones **10**, **11** and **15**. Since, at present, there are no commercial suppliers for *S*-pulegone, conversion of *R*-pulegone to *S*-pulegone was investigated *via* a 1,3-carbonyl transposition.

R-Pulegone was converted to ketosulfoxide **120**, which upon thermal elimination of phenylsulfinic acid provided *R*-5-methylcyclohex-2-en-1-one **131**. The *R*-enone **118** was inverted to its *S*-enantiomer in three steps. Regioselective introduction of *iso*-propylidene group *via* a Mukaiyama-type aldol reaction between the reductively generated silylenolether **123** and acetone was unsuccessful.

At this juncture we perused the literature for possible utilisation of our key intermediate, enone **118** and felt that *R*- and *S*-3,5-dimethylcyclohex-2-en-1-ones **131** are interesting targets. They also serve as starting chirons in natural product synthesis.

1,2-Addition of MeLi to enone **118** afforded alcohol **137**, which upon PCC oxidation provided transposed enone, *S*-(+)-**131** in 26% yield from ketosulfoxide **120** ($[\alpha]_D^{25}$ +132.2°, 96% optical purity).

Pummerer rearrangement of ketosulfoxide **120** and periodate oxidation gave enone sulfoxide **139**. Conjugate addition of dimethyl cuprate to **139** and thermal elimination provided enone *R*-(-)-**131** in 53% yield from **120** ($[\alpha]_D^{25}$ -132.8°, 96% optical purity).

Thus, *R*-and *S*-3,5-dimethylcyclohex-2-en-1-ones **131** are easily prepared in excellent optical purity from *R*-pulegone. The synthesis of *S*-pulegone from its natural *R*-isomer could not be achieved.

3). SYNTHESIS OF IRIDOID TYPE-I CYCLOPENTAPYRANONE SKELETON:

The synthesis of 7*R*-pyranone **59** which is the common precursor for the three lactones (**10**, **11** and **15**) was initiated to establish the viability of the proposed route. This will, however, lead to iridoids with the unnatural *R*-configuration at C7.

R-Pulegone **91** was converted to *anti*-ketoalcohol **106** and esterified to phosphonate **105** with diethylphosphonoacetic acid. Exposure of **105** to intramolecular Horner-Wadsworth-Emmons (HWE) reaction with DBU/LiCl in CH_3CN provided unsaturated lactone **104**. Stereoselective *exo*-face hydrogenation gave 7*R*-(-)-pyranone **59**.

For the synthesis of natural analog (+)-pyranone **59**, *S*-pulegone **91** was synthesised from *S*-β-citronellol **107** in 66% yield ($[\alpha]_D^{25}$ -15.3°, neat, 66% optical purity). Employing the conditions optmised earlier, *S*-pulegone was converted to 7*S*-(+)-pyranone **59**. The optical purity of (+)-**59** was lower ($[\alpha]_D^{25}$ +71.9°) compared to (-)-**59** ($[\alpha]_D^{25}$ -92.0°) because of lower ee of the starting material.

4). SYNTHESIS OF TYPE-II LACTONES: MITSUGASHIWALACTONE AND 4-*EPI*-MITSUGASHIWALACTONE:

A limitation with the reported procedures for type-II lactones is that all of them, except one, lead to racemic products. Our aim was to synthesise these lactones in enantiomerically pure form.

syn/anti-Alkenealcohol **159,160**, available from our earlier work, was transformed to *syn/anti*-ketoacetal **177**. HWE reaction of ketone **177** with diethyl phosphonoacetate **178** was successful with NaH base and afforded *Z* and *E* unsaturated esters **184,185** in 40:60 ratio. The *Z/E* isomers were characterised by combination of chemical and spectral evidence. The esters were reduced to allylic alcohols **186,187**, but their deprotection-cum-cyclisation to the lactone was unsuccessful. Pd catalysed hydrogenation of alcohols **186,187** gave acetalalcohol **190** as a single diastereomer and again direct cyclisation was problematic. Hence, **190** was converted to lactone in three steps: 1) oxidation of acetal CH to ester **198**, 2) base hydrolysis to hydroxy acid **199**, and 3) acid catalysed cyclisation. The lactone obtained by this route was identified as 4-*epi*-mitsugashiwalactone **200**, a result of hydrogenation occurring *cis* to C7a acetal group.

Pt catalysed hydrogenation of unsaturated esters **186,187** provided a mixture of *cis/trans* acetalester **201,202** in 30:70 ratio. LAH reduction and oxidation gave hydroxyester **198,204**. When ester **198,204** was subjected to base hydrolysis and acidified, the minor *cis*-isomer **204** cyclised and the *trans*-hydroxy acid **199** remained unreacted. Chromatographic purification afforded mitsugashiwalactone **17** in higher optical purity ($[\alpha]_D^{25}$ -3.0°) compared to the reported value ($[\alpha]_D^{25}$ -1.9°).

5). SYNTHESIS OF ANHYDROMEVALONOLACTONE AND ITS THIOLACTONE:

The work described in this chapter is part of an approach towards the total synthesis of subergorgic acid. This project was, however, subsequently abandoned because of numerous problems along the way. A few positive off shoot results are discussed. To investigate the stereo- and regiochemical outcome of intramolecular Diels-Alder reaction for the synthesis of subergorgic acid **206** we needed bromodiene

219. Anhydromevalonolactone **220** was chosen as starting material, which was prepared in the following manner.

The acid catalysed dimerisation of ethyl acetoacetate **227** afforded pyrone **228**. Base hydrolysis of **228** gave a mixture of *trans*- and *cis*-3-methylglutaconic acids **229**,**230** which were converged to the desired *cis* geometry by cyclisation to anhydride **231**. LAH reduction of **231** to diol **232**, followed by selective oxidation of allylic alcohol furnished lactone **220** in 30% overall yield from pyrone **228**.

Lactone **220** was transformed to hydroxyester **235**, and it was immediately converted to bromoester **236**. LAH reduction to alcohol **237** and oxidation with PDC provided a *Z*/*E* mixture of aldehydes **238**,**239** in 85:15 ratio. Wittig olefination of **238**,**239** provided bromodienes **219**,**240** in 30% yield. Because of competing isomerisation, low yields, and other problems the project was prematurely aborted at this stage.

Some of these results were easily adapted for the conversion of α,β-unsaturated lactone **220** to the corresponding thiolactone **253**, a transformation for which no mild conditions are reported. Thus, bromoester **236** was treated with thiolate anion to afford thioester **257**. Saponification of **257** to mercapto acid **258** and acid catalysed cyclisation provided thiolactone **253** in 50% yield from lactone **220**.

In conclusion we have investigated a variety of reaction conditions for the intramolecular HWE reaction on enolisable ketones. The successful application of HWE approach on cyclopentanones derived from *R*-pulegone leads to the stereo- and enantioselective synthesis of iridoid monoterpene lactones.

Parts of the work described in this thesis have been published/communicated.

1. Facile synthesis of anhydromevalonolactone from ethyl acetoacetate

   A. Nangia, B. Madhusudan Rao and **G. Prasuna**

   Synth. Commun. **1992** 22 593-602

2. Enantiodivergent syntheses of (R)- and (S)-3,5-dimethylcyclohex-2-en-1-ones from (R)-pulegone

   A. Nangia and **G. Prasuna**

   Synth. Commun. **1994** 24 1989-1998

3. Intramolecular Horner-Wadsworth-Emmons reaction in base sensitive substrates: enantiospecfic synthesis of iridoid monoterpene lactones

   A. Nangia, **G. Prasuna** and P. Bheema Rao

   Tetrahedron Lett. **1994** 35 3755-3758

4. A mild protocol for lactone to thiolactone transform

   A. Nangia, A. Anthony and **G. Prasuna**

   Ind. J. Chem. (in press)

5. Studies on Horner-Wadsworth-Emmons reaction in base sensitive ketones: synthesis of (-)-mitsugashiwalactone and formal synthesis of (+)-iridomyrmecin, (-)-isoiridomyrmecin and (+)-teucriumlactone

   A. Nangia and **G. Prasuna**

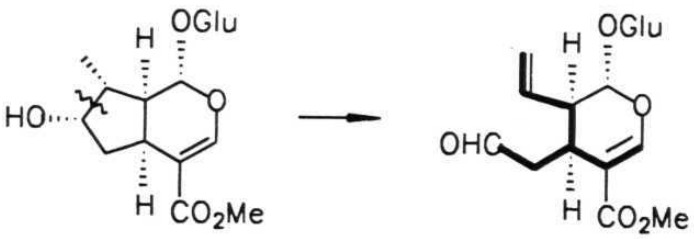
   (Communicated)

CHAPTER-1

IRIDOID LACTONES: INTRODUCTION AND LITERATURE SURVEY

1.1. INTRODUCTION:

Over the past three decades the class of naturally occurring cyclopentanoid monoterpenes, also known as iridoids, has gained increased recognition because of their diverse biological activity [1]. They play a role in the biosynthesis of indole alkaloids [2]. The biogenetic key compound secologanin **1** is derived from the iridoid glycoside loganin **2** by cleavage of the cyclopentane ring. More than a thousand alkaloids are formed from secologanin **1** *in vivo*. Two prominent examples are the indole alkaloid yohimbine **3**, which is used as an aphrodisiac in veterinary medicine [3], and the cinchona alkaloid quinine **4**, which is the oldest known antimalarial agent. Quinine has now regained importance for dealing with pathogenic agents which are resistant to synthetic pharmaceuticals [4]. Other alkaloids derived from **1** are the ipecacuanha alkaloid emetine **5**, which is effective in the treatment of amoebic dysentry [5] and the dimeric indole alkaloids leurocristine **6a** and vincaleukoblastine **6b**. They are used with great success to treat acute leukemia and Hodgkin's disease [6].



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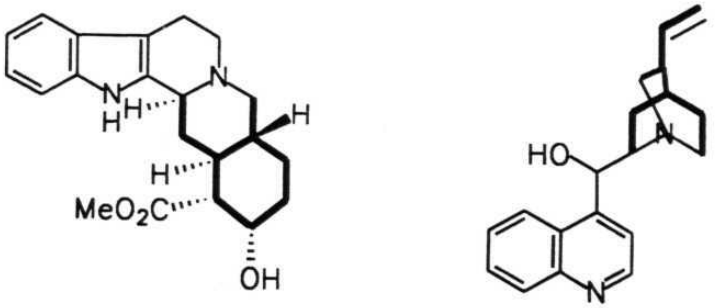

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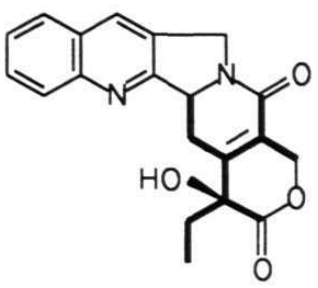

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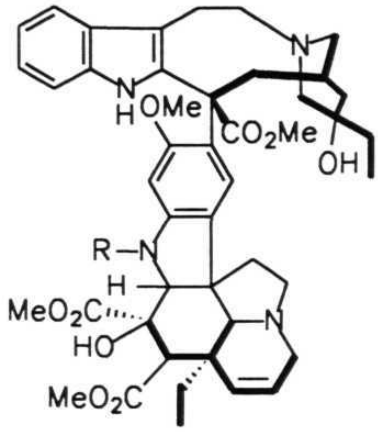
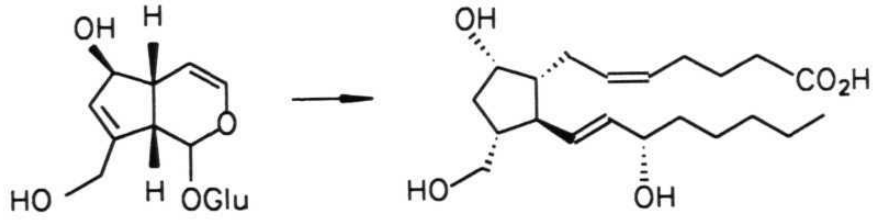


6a: R=CHO
6b: R=Me

Some iridoids have been used as chiral synthons for the synthesis of different prostaglandins [7]. For example, optically active prostaglandin analog, (+)-11-deoxy-11α-hydroxymethyl $PGF_{2\alpha}$ **7** is synthesised from the iridoid glycoside aucubin **8**.



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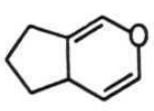
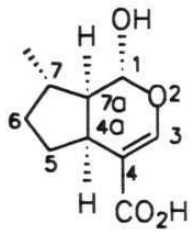
The iridoids represent a class of highly oxygenated monoterpenes, characterised by the presence of a *cis* linked partially hydrogenated cyclopenta[*c*]pyran skeleton.



The iridoid skeleton is named and numbered according to the nomenclature used for heterocycle **9**. Considerable simplification can be achieved by introducing the name "iridene" for (1*R*,4a*S*,7*S*,7a*R*)-1-hydroxy-7-methyl-1,4a,5,6,7,7a-hexahydrocyclopenta[*c*]pyran-4-carboxylic acid. Saturated system "iridane" or *cis*-2-oxabicyclo[4.3.0]nonane is usually adopted for the iridoid natural products. Most of the glycoiridoids are linked to *D*-glucose at C1 *via* a glycosidic bond.



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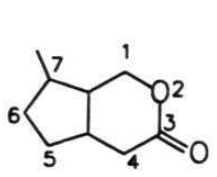
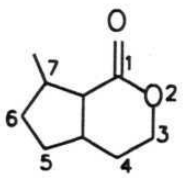
In most of the known cyclopentapyranone natural products the lactone is *cis*-fused to a cyclopentane ring. Basically, two isomeric structural types of cyclopentanoid monoterpene lactones are known. They are the structural type-I which bear a carbonyl group at C3, and type-II in which the carbonyl group is at C1.

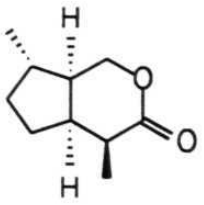


TYPE–I



TYPE–II

Some of the natural products which fall in structural type-I are iridomyrmecin **10**, isoiridomyrmecin **11**, isoepiiridomyrmecin **12**, dehydroiridomyrmecin **13**, isodehydroiridomyrmecin **14**, teucriumlactone **15** and boschnialactone **16**.



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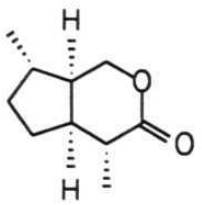

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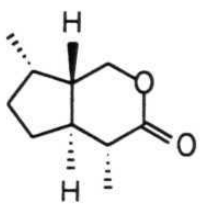

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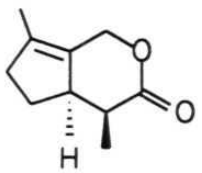

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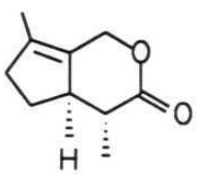

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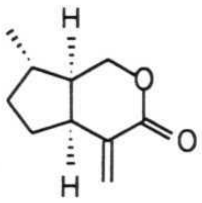

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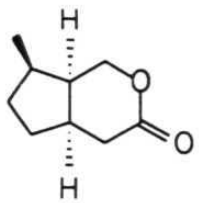

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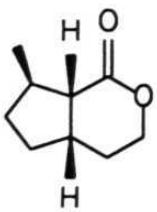
Mitsugashiwalactone **17**, onikulactone **18**, nepetalactone **19**, dihydronepetalactone **20**, isodihydronepetalactone **21**, neonepetalactone **22**, isoneonepetalactone **23**, dihydroepinepetalactone **24**, isodihydroepinepetalactone **25** and booniene **26** belong to iridoid lactones of structural type-II.



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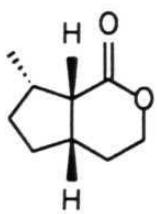

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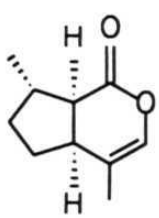

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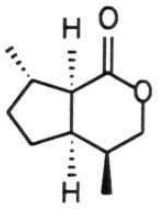

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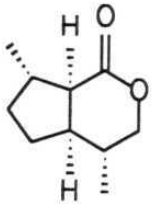

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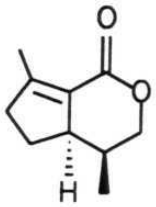

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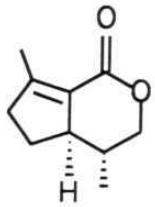

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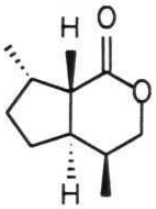

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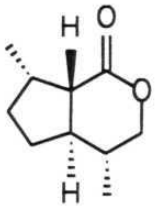

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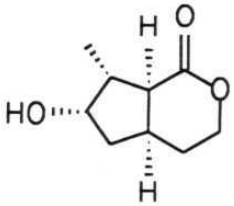

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Iridomyrmecin **10** and isoiridomyrmecin **11** were isolated from *iridomyrmex humilis* Mayr by Pavan *et al.* in 1949 [8] and *iridomyrmex nitidus* Mayr by Locksley *et al.* in 1956 [9], respectively. These lactones are also found in plant kingdom and are minor components of metatabilactone [10], a cat attracting oil isolated from *Actinidia polygama*. These epimeric lactones have attracted considerable attention because of their use by ants as agents of defence against preying insects and as possible means of communication [11]. In addition to these intriguing properties Pavan has claimed that iridomyrmecin **10** is a potent insecticide [12] and exhibits antibiotic action [13].

McConnell and co-workers [14] reported that the difference in biological activity of iridomyrmecin **10** and isoiridomyrmecin **11** is not due to their epimeric relationship but is closely related to the overall shape of the molecules. From X-ray

analysis the actual conformation is the preferential location of C4 methyl group in the equatorial position, irrespective of the orientation of lactone moiety. In isoiridomyrmecin **11**, the cyclopentanoid ring is *exo* to the six membered ring whereas in iridomyrmecin **10** it is *endo*. Thus, isoiridomyrmecin **11** is a relatively flat molecule which has considerable cat-nip activity compared to iridomyrmecin **10**.

10 11

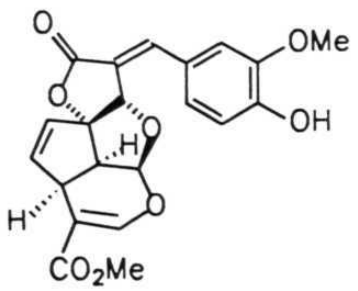
Teucriumlactone **15** was isolated by Pagnoni and co-workers [15] from a wild plant *Teucrium marum* and belongs to the Labiatae family, which grows in the Mediterranean area. Lactone **15** was referred to allodolicholactone in earlier literature and recently renamed as teucriumlactone. In 1967 Sakan *et al.* [16] isolated boschnialactone **16** from *Boschniakai rossica* Hult collected during the flowering season on mount Fuji. This lactone too has a marked physiological activity on cats.

Cyclopentanoid lactones with nine carbons belonging to structural type-II are mitsugashiwalactone **17** and onikulactone **18.** They were isolated by Sakan *et al.* [17] in 1969 as the biologically active principles of *Boschniakai rossica* Hult and *Menyanthes trifoliata* Longifolia. They have highly attractive physiological action on the Filidae and Chrysopidae animals. By the same authors in 1965 [18] dihydronepetalactone **20**, isodihydronepetalacone **21** and neonepetalactone **22** were isolated from the leaves and galls of *Actinidia polygama* and they also were found to be quite attractive to cats. The monoterpene lactone boonein **26** was isolated by Marini-

Bettolo and co-workers [19] from the bark of *Alstonia boonie* De Wild, a Nigerian tree of medicinal value.

The new lactones isoepiiridomyrmecin **12**, dehydroiridomyrmecin **13**, isodehydroiridomyrmecin **14**, neonepetalactone **22**, isoneonepetalactone **23**, dihydroepinepetalactone **24** and isodihydroepinepetalactone **25**, were isolated by Sakai and co-workers [20] in 1980 from the volatile oil of the fresh fruits of lacewing attracting plant *Actinidia polygama* Miq.

In most of the naturally occurring metabolites the configuration at C7 is *S* as in iridomyrmecin **10** and dihydronepetalactone **20**, whereas in others the configuration is *R* as in boschnialactone **16** and mitsugashiwalactone **17**. Although most of the natural products have the terpenoid ten-carbon core (**10** and **20**), some of the natural products are known with nine-carbon core which are devoid of substitution at C4, such as **16** and **17**. Natural products are also known with nineteen (oruwacin **27**), fourteen (plumericin **28**) thirteen (fulvoplumierin **29**) and eight carbon atoms (unedoside **30**).



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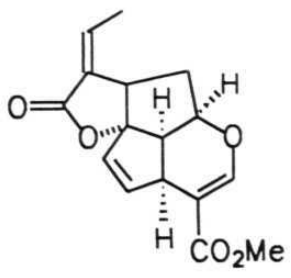

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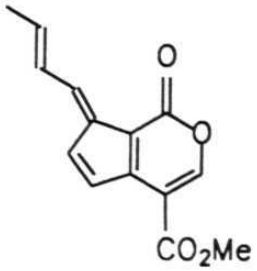

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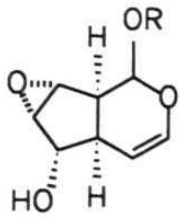

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In this large and interesting class of cyclopentanoid monoterpene lactones we focused our interest on the synthesis of iridomyrmecin **10**, isoiridomyrmecin **11** and teucriumlactone **15** belonging to structural type-I category. The synthetic target was the nine-carbon cyclopentapyranone skeleton from which these three natural products can be synthesised. In structural type-II, mitsugashiwalactone **17** with its nine-carbon core and monoterpene dihydronepetalactone **20** were also targeted.

1.2. LITERATURE SURVEY:

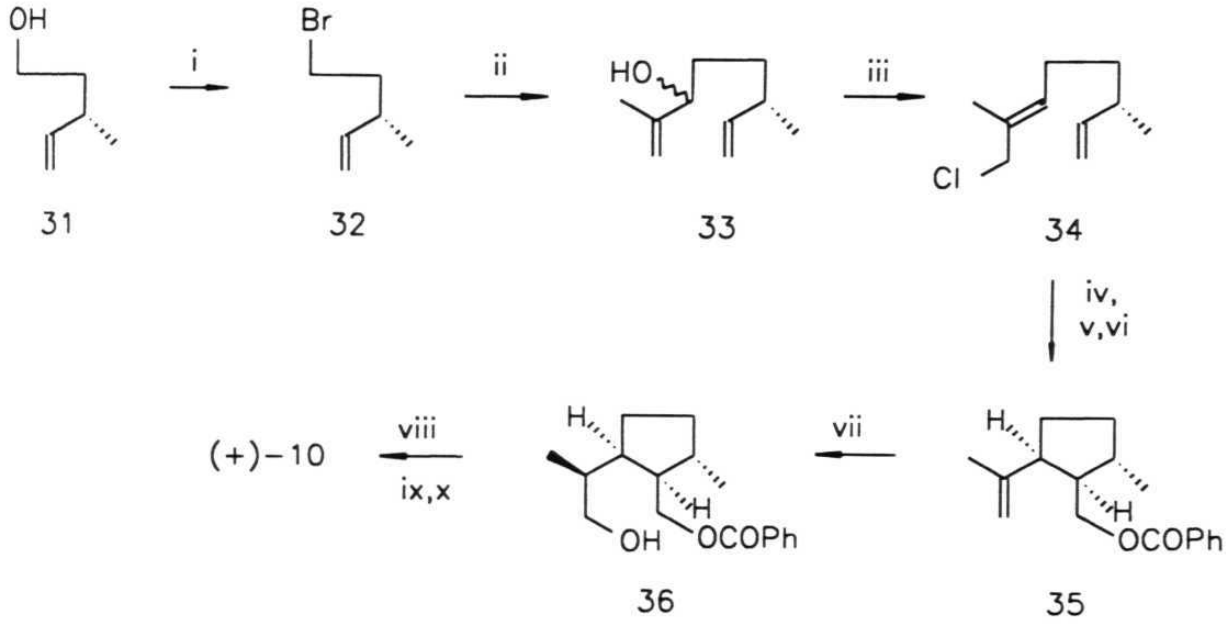
1.2.1. TYPE-I LACTONES:

Synthetic approaches to iridomyrmecin **10**, isoiridomyrmecin **11** and teucriumlactone **15** belonging to structural type-I are detailed in the following pages.

(+)-Iridomyrmecin **10** was synthesised by Oppolzer and co-workers [21] using magnesium-ene reaction as the key step. Alcohol **31**, which is easily accessible in high enantiomeric purity *via* an asymmetric vinyl-copper enolate 1,4-addition, was converted to bromide **32**. Addition of the resulting Grignard reagent to methacrolein afforded dienol **33**. Heating **33** with thionyl chloride gave chloride **34**. Magnesium-

ene reaction of **34**, oxidative traping with MoOPh, and benzoylation of the resulting alcohol gave **35**. Hydroboration gave alcohol **36**, which was converted to (+)-**10** by sequential oxidation, saponification and lactonisation steps.

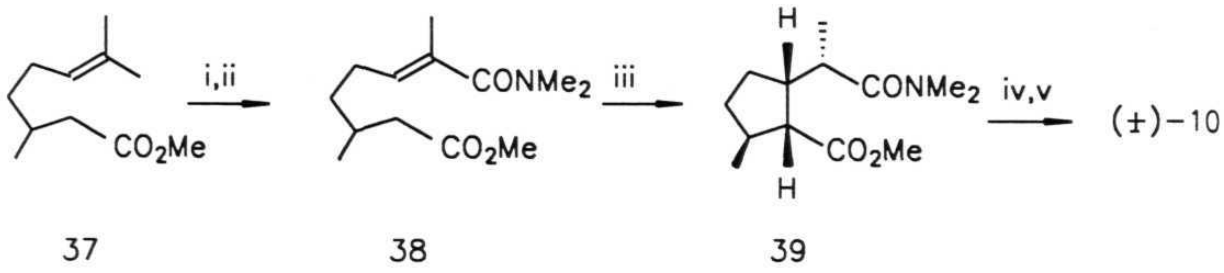
Scheme-1



Reagents: *i) Mscl, LiBr, acetone; ii) Mg, ether, methacrolein; iii) $SOCl_2$, ether; iv), Mg, 40 °C; v) MoOPh; vi) ClCOPh,; vii) 9-BBN, THF, H_2O_2, NaOH; viii) CrO_3-H_2SO_4, aq. acetone; ix) KOH; x) aq. HCl.*

Yokoyama *et al.* [22] reported the synthesis of (±)-iridomyrmecin **10** *via* a diastereoselective intramolecular conjugate addition controlled by allylic 1,3-strain. LDA treatment of amide **38** gave intramolecular Michael adduct **39**. $LiBH_4$ reduction of **39** and cyclisation with Amberlyst afforded (±)-**10**.

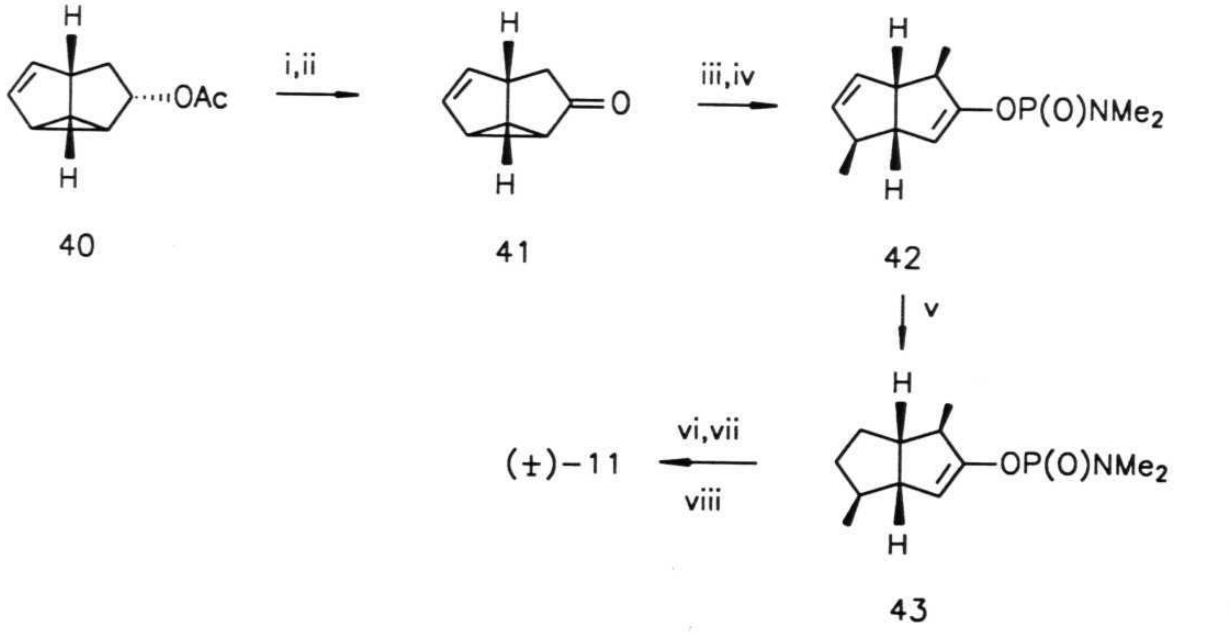
Scheme-2



37 38 39

Reagents: *i) SeO_2, EtOH; ii) MnO_2, Me_2NH, NaCN, i-PrOH; iii) LDA, THF; iv) $LiBH_4$, THF; v) Amberlyst-15, acetone.*

Scheme-3

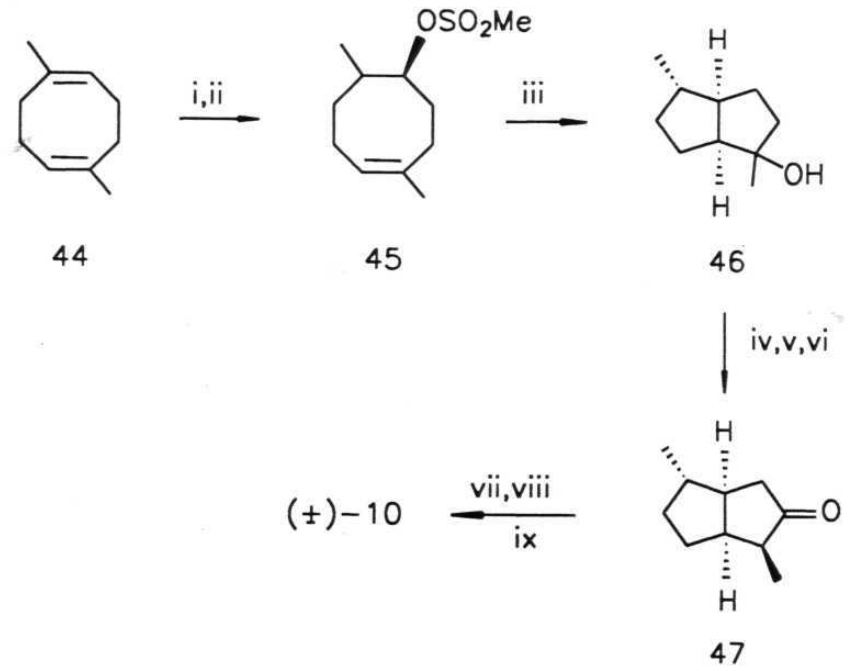


Reagents: *i) $LiAlH_4$; ii) MnO_2; iii) LDA, MeI; iv) Me_2CuLi, $ClP(O)(NMe_2)_2$; v) H_2, Pt_2O, EtOAc; vi) O_3, MeOH, CH_2Cl_2, $NaBH_4$; vii) $NaCNBH_4$, aq. THF; viii) aq. H_2SO_4*

Wender *et al.* [23] synthesised (±)-isoiridomyrmecin **11** using arene-olefin cycloaddition reaction. Photolysis of benzene and vinylacetate produced the tricyclic adduct **40**, which upon deprotection and oxidation gave ketone **41**. Methylation of **41** under kinetic conditions and dimethyl cuprate addition followed by traping of the enolate gave 1,5 addition product **42**. Ozonolysis followed by $NaBH_4$ work-up, $NaCNBH_4$ reduction and acidification provided (±)-**11**.

A highly stereoselective method of cyclopentanoid ring formation by transannular cyclisation of cyclooctane system is reported for the synthesis of (±)-iridomyrmecin **10** by Whitesell and co-workers [24]. Selective monohydroboration,

Scheme-4

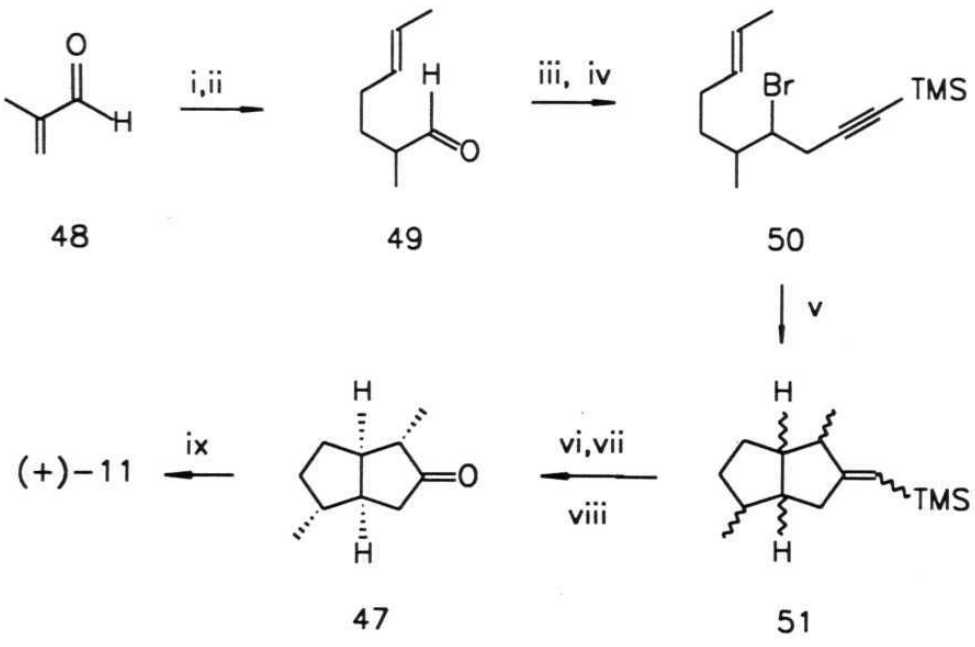


Reagents: *i) 9-BBN, H_2O_2, NaOH; ii) $MeSO_2Cl$, Et_3N, CH_2Cl_2; iii) aq. dioxane, Na_2CO_3; iv) p-TsOH.H_2O, pentane; v) B_2H_6, H_2O_2, NaOH; vi) CrO_3-H_2SO_4, aq. acetone; vii) LDA, THF, TMS-Cl; viii) O_3, MeOH, CH_2Cl_2, $NaBH_4$; ix) aq. HCl.*

oxidation, and then mesylation of diene **44** gave sulfonate ester **45**. Solvolysis of ester **45** afforded the transannular cyclisation product **46**. Acid catalysed dehydration, followed by hydroboration-oxidation and oxidation of resulting alcohol afforded bicyclic ketone **47**. Ketone **47** was transformed to (±)-**10** in three steps: i) transformation of ketone to silyl enolether, ii) oxidative cleavage of olefin with reductive work-up, and iii) acid catalysed lactonisation.

Kilburn [25] reported a tandem radical cyclisation of bromide **50** to bicyclic ketone **47**, an intermediate in the synthesis of (±)-isoiridomyrmecin **11**. Aldehyde **49**, which is prepared from methacrolen **48** in four steps *via* an oxy-Cope rearrangement,

Scheme-5

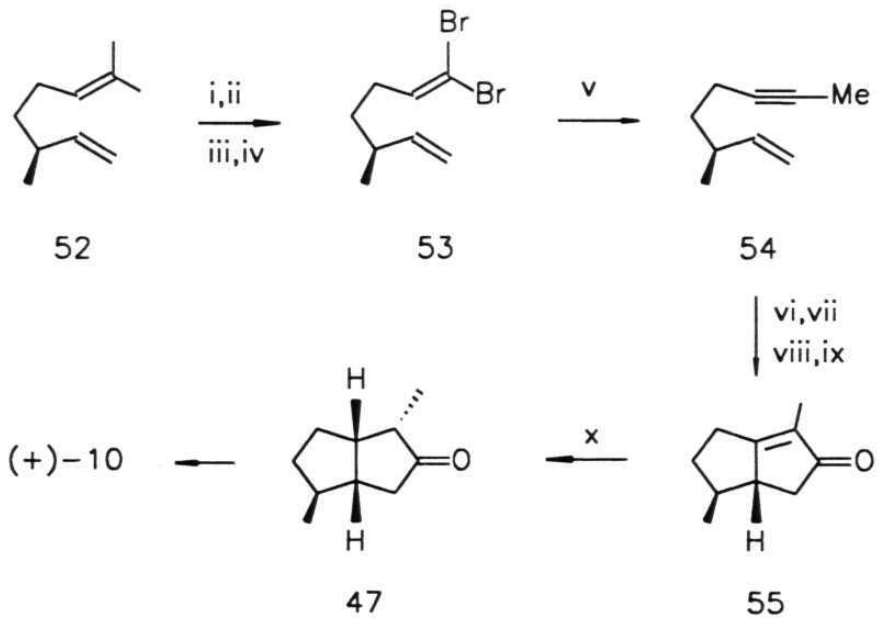


Reagents: *i) $CH_3CH{=}CHCH_2MgBr$; ii) KH, THF; iii) $LiCH_2C{\equiv}CSiMe_3$; iv) CBr_4, PPh_3; v) Bu_3SnH, AIBN; vi) $PhSO_2H$, aq. CH_3CN; vii) O_3, PPh_3; viii) NaOMe, MeOH.*

was converted to bromide **50**. Reductive cyclisation of **50** with *n*-Bu_3SnH-AIBN gave bicyclic product **51**. Protodesilylation of **51**, then ozonolysis of exocyclic olefin, and equilibration with NaOMe gave thermodynamically stable bicyclic ketone **47**. This was converted to (±)-**11** according to published procedures [24].

Negishi *et al.* [26] employed $ZrCp_2$ promoted cyclopentenone annulation procedure towards the synthesis of (+)-iridomyrmecin **10**. (+)-Citronellene **52** was converted to dibromodiene **53** *via* regioselective epoxidation of trisubstituted alkene with *m*-CPBA, oxidation with $Pb(OAc)_4$, and homologation with CBr_4/PPh_3. Treatment of **53** with *n*-BuLi and MeI provided 1,6-heptenyne **54**. $ZrCp_2$ catalysed cyclisation of **54** afforded zircona bicyclic product, which was subjected to

Scheme-6

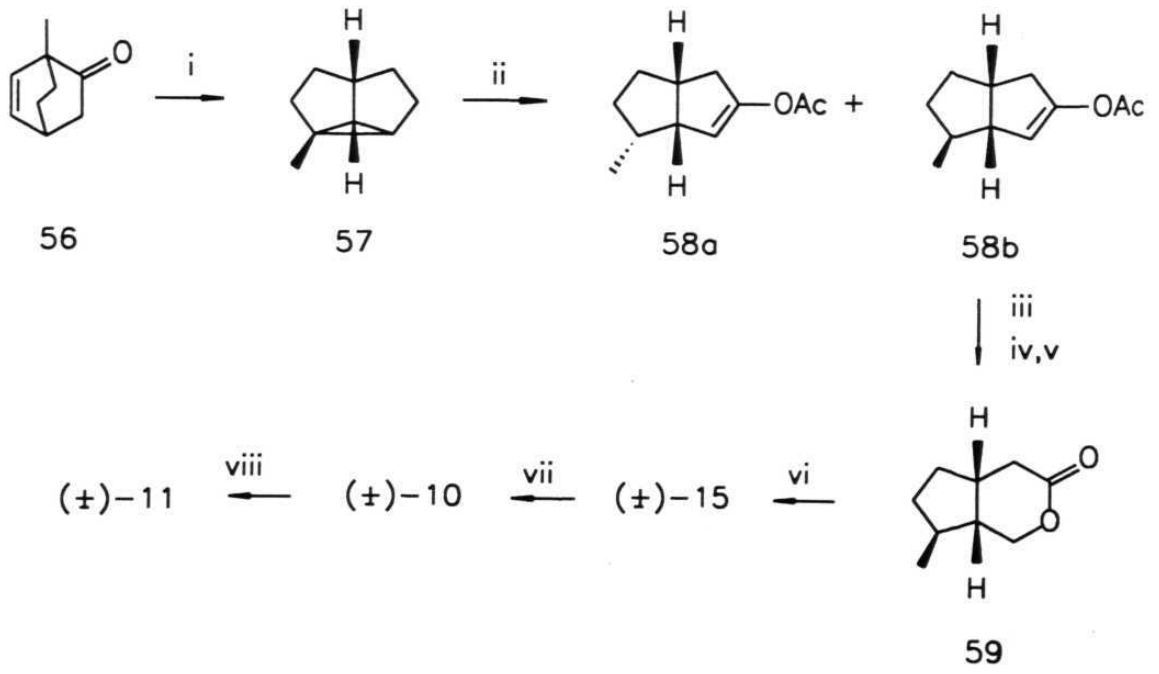


Reagents: *i) m-CPBA; ii) $HClO_4$; iii) $Pb(OAc)_4$; iv) CBr_4, PPh_3; v) n-BuLi, MeI; vi) $ZrCp_2$; vii) 3N HCl; viii) I_2, THF; ix) CO, I_2; x) H_2, Pt_2O, MeOH.*

protonolysis, iodination and carbonylation to provide unsaturated ketone **55**. Catalytic hydrogenation gave bicyclic ketone **47**, which was transformed to (+)-**10** analogous to earlier procedure [24, 25].

Demuth and co-workers [27] developed a methodology for bicyclic systems using photochemical stratagy. Oxa-di-π-methane rearrangement of bicyclo[2.2.2]octenone **56** provided tricyclic ketone **57**. Reductive cyclopropane opening by Birch reduction followed by quenching of the enolate with acetic anhydride gave a seperable 1:1 mixture of epimeric enol-acetates **58a** and **58b**. Osmylation of **58b**, borohydride reduction, and acid treatment gave bicyclic lactone **59** .

Scheme-7

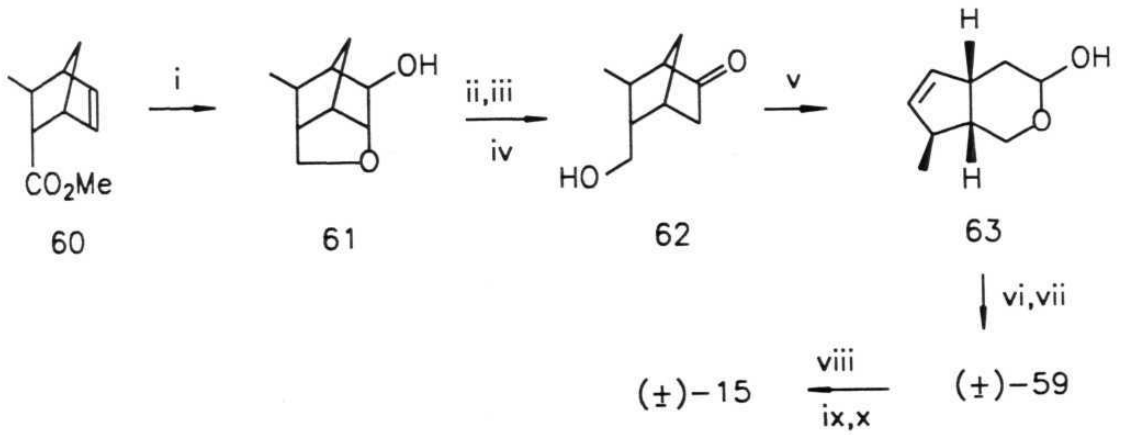


Reagents: *1) hν; ii) Na, NH_3, t-BuOK, Ac_2O; iii) OsO_4, $NaIO_4$; iv) $NaBH_4$; v) H_3O^+; vi) LDA, $CH_2=N^+Me_2I^-$, DBN, benzene; vii) H_2, Pd-C; viii) KOMe.*

Introduction of α-methylene group (LDA, $CH_2=N^+Me_2I^-$, DBN) provided the first synthetic sample of (±)-teucriumlactone **15** in 16% overall yield. Catalytic hydrogenation of **15** afforded (±)-iridomyrmecin **10**, which was epimerised to thermodynamically stable (±)-isoiridomyrmecin **11**.

The synthesis of functionalised cyclopentanoid lactone was reported by Vandewalle and co-workers [28]. Diels-Alder reaction of cyclopentadiene and methyl crotonate gave norbornene **60**, which on LAH reduction gave the alcohol **61**. Treatment of **61** with *m*-CPBA, Swern oxidation, and reductive cleavage of ether bond yielded norbornanone **62**. Norrish-I type reaction afforded bicyclic lactol **63**, which upon oxidation and hydrogenation gave bicyclic lactone **59**. α-Methylenation according to Grieco's method [29] gave (±)-teucriumlactone **15**.

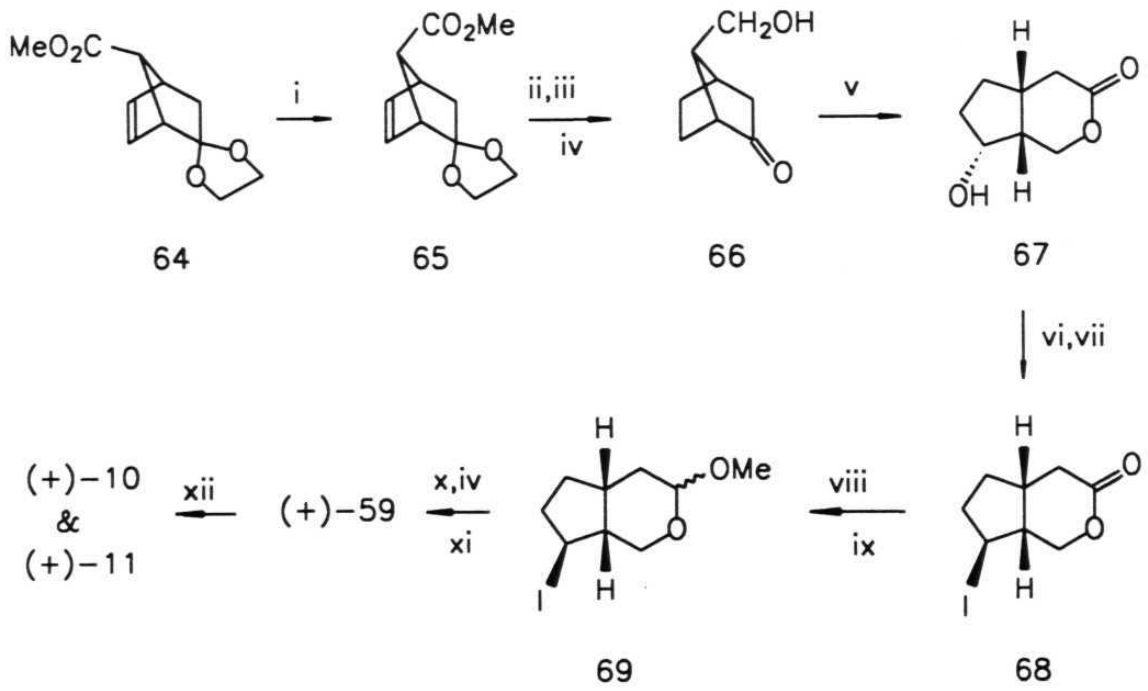
Scheme-8



Reagents: *i) LAH; ii) m-CPBA, CH_2Cl_2; iii) DMSO, ClC(O)C(O)Cl, Et_3N; iv) Al-Hg, THF, EtOH; v) hν, 254 nm, CH_3CN; vi) PCC, CH_2Cl_2; vii) Pd-C, EtOH; viii) LDA, HCHO; ix) MsCl; x) DBU.*

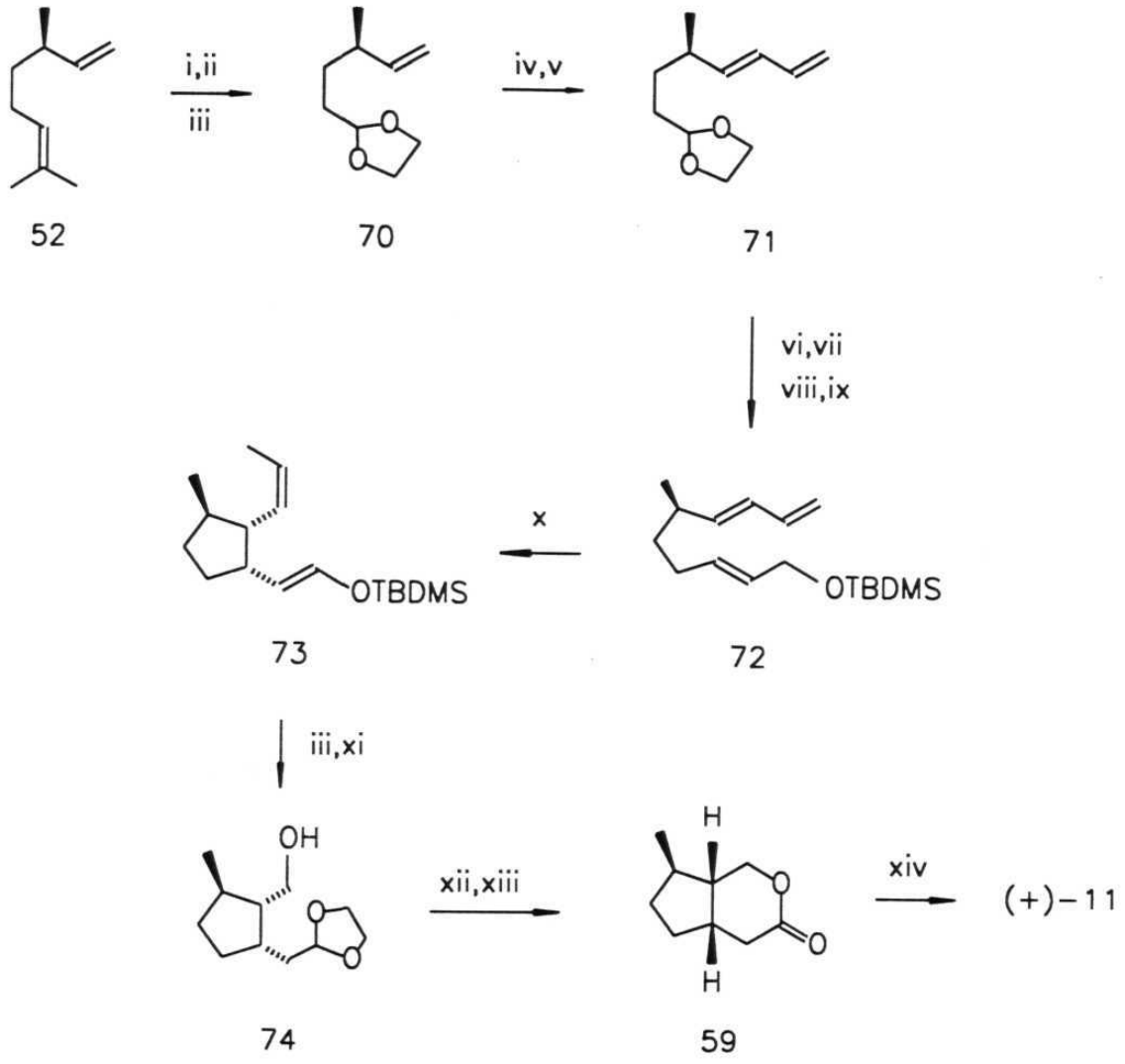
Baeyer-Villiger rearrangement of bicyclo[2.2.1]heptanone for the synthesis of cyclopentapyranone is reported by Wang and co-workers [30]. Ketalester **64**, prepared from 2,5-norbornadiene in 6 steps, was epimerised with LDA to isomeric ketalester **65**. Catalytic hydrogenation, followed by LAH reduction, and ketal hydrolysis afforded ketoalcohol **66**. Sequential Baeyer-Villiger rearrangement and intramolecular transesterification furnished hydroxylactone **67**. Iodolactone **68** was coupled with methylcuprate after protection of lactone group as its acetal. Hydrolysis of methyl

Scheme-9



Reagents: *i) LDA, THF, AcOH; ii) 10% Pd-C, H_2, EtOAc; iii) $LiAlH_4$, ether; iv) p-TsOH.H_2O, aq. acetone; v) m-CPBA, $NaHCO_3$, CH_2Cl_2; vi) $PhSO_2Cl$, pyridine; vii) NaI, acetone; viii) DIBAL-H, THF; ix) PPTS, MeOH; x) MeLi, CuBr-DMS, ether; xi) PDC, CH_2Cl_2; xii) LDA, MeI.*

Scheme-10



Reagents: *i) m-CPBA, CH_2Cl_2; ii) H_5IO_6, ether; iii) $(CH_2OH)_2$, p-TsOH.H_2O, ether; iv) O_3, CH_2Cl_2, Ph_3P; v) Li[CH_2=CHCHP(O)Ph_2], THF, HMPA; vi) p-TsOH.H_2O, aq. acetone; vii) $(EtO)_2P(O)CH_2CO_2Et$, LiCl, DBU, CH_3CN; viii) DIBAL-H, THF; ix) TBDMS-Cl, imidazole, DMF; x) [Fe(acac)$_3$/2,2-bipyridine], Et_3Al; xi) O_3, CH_2Cl_2, $NaBH_4$; xii) 2% HCl, aq. acetone; xiii) PCC, CH_2Cl_2; xiv) LDA, THF, MeI.*

lactol **69** and oxidation provided (±)-**59**. α-Methylation of lactone under kinetic conditions (LDA) gave (±)-**10** and (±)-**11** after silica gel purification.

Recently an enantioselective synthesis of cyclopentanoid lactone **59** was reported by Takacs and co-workers [31] *via* catalytic organoiron complex ene-carbocyclisation reaction. Chemoselective epoxidation of (-)-citronellene **52** followed by treatment with periodic acid and acetalisation of aldehyde afforded acetal **70**. Ozonolysis and dienylation with allyldiphenylphosphine oxide gave diene **71**. Acetal deprotection, Horner-Emmons reaction, DIBAL-H reduction and silylation afforded triene **72**. Highly enantioselective iron catalysed cyclisation of **72** gave *cis*-substituted cyclopentane **73**. Acetalisation of **73** followed by ozonolysis and reductive work-up afforded alcohol **74**. Acid catalysed hydrolysis gave lactol which underwent smooth oxidation to bicyclic lactone **59**. Standard C2 methylation afforded 9:1 mixture of (+)-**10** and (+)-**11**.

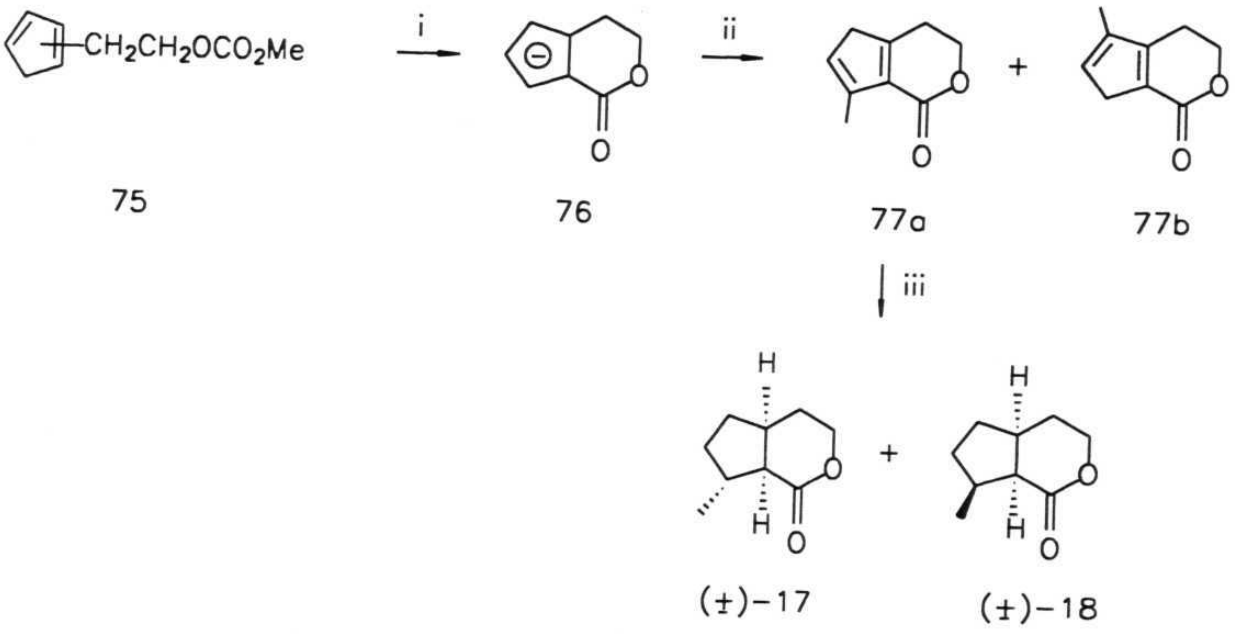
1.2.2. TYPE-II LACTONES:

Synthetic approaches to mitsugashiwalactone **17**, onikulactone **18**, dihydronepetalactone **20** and isodihydronepetalactone **21** belonging to structural type-II are detailed in the following pages.

Fujisawa and co-workers [32] accomplished a total synthesis of nine-carbon cyclopentanoid lactones by a route involving regiospecific lactone annulation of cyclopentadiene. Treatment of cyclopentadienyl methylcarbonate **75** with NaH gave the corresponding cyclopentadienyl anion, which in turn cyclised *via* intramolecular acylation of carbonate to afford the anion **76**. Methylation of **76** with methyl trifluromethane sulfonate gave a mixture of **77a** (50%) and **77b** (17%). Pt catalysed

hydrogenation of **77a** resulted in the formation of (±)-mitsugashiwalactone **17** and (±)-onikulactone **18** in a ratio of 1.8:1.

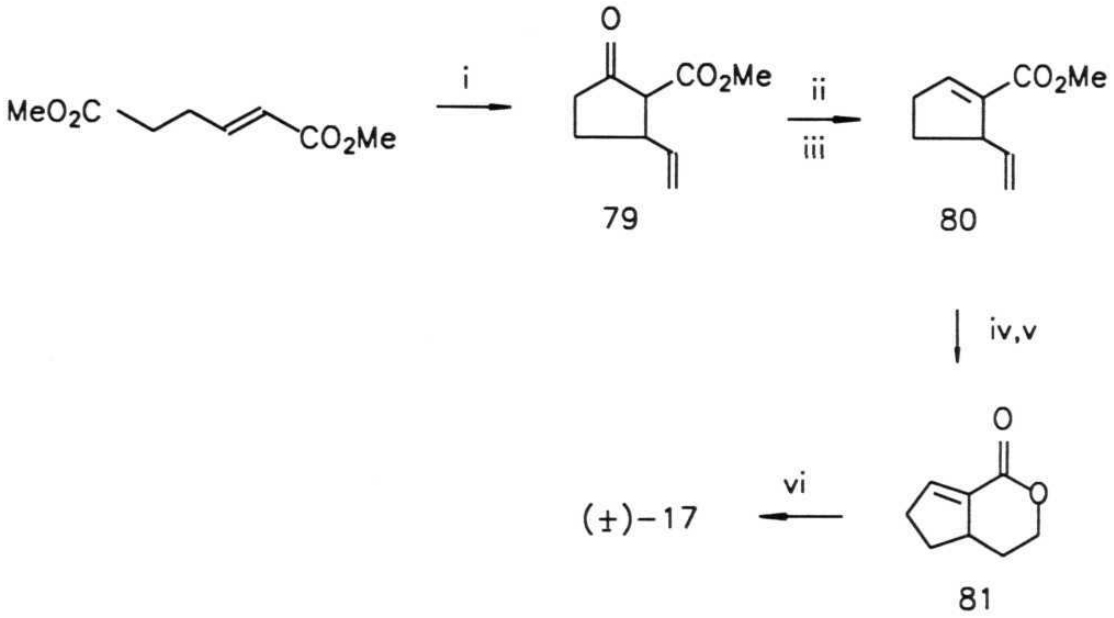
Scheme-11



Reagents: *i) NaH, DME; ii) $CF_3SO_3CH_3$; iii) Pt_2O, H_2, EtOH.*

A short synthesis of (±)-mitsugashiwalactone **17** from alkyl substituted cyclopentanone was reported by Nugent *et al.* [33]. Tandem conjugate addition-cyclisation of dimethyl-*E*-2-hexenedioate **78** using Gillman reagent afforded cyclopentanone **79**. Borohydride reduction and base induced elimination provided α,β-unsaturated ester **80**. Regioselective hydroboration-oxidation in $NaHCO_3$ solution provided lactone **81**. Conjugate addition with Me_2CuLi provided (±)-**17**.

Scheme-12

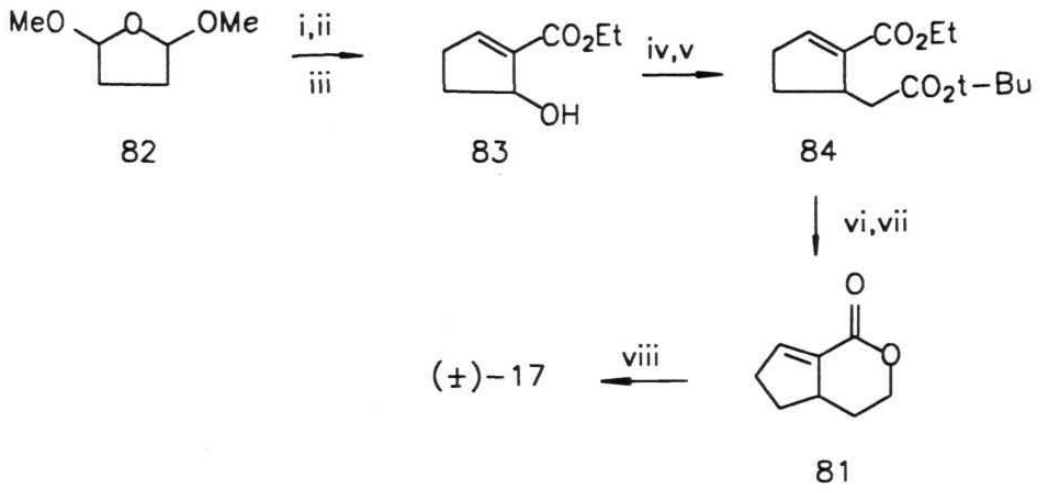


Reagents: *i)* $(CH_2=CH)_2CuLi$*, ether; ii)* $NaBH_4$*; iii) MsCl, DBU; iv) 9-BBN,* H_2O_2*; v) p-TsOH.*H_2O*; vi)* Me_2CuLi*.*

Amri and co-workers [34] reported an efficient synthesis of (±)-**17** from 2,5-dimethoxytetrahydrofuran **82**. The reaction of triethylphosphonoacetate with succinaldehyde (generated by the hydrolysis of 2,5-dimethoxytetrahydrofuran **82**) was carried out in aq. K_2CO_3 solution to produce unsaturated ester **83**. Conversion of **83** to the corresponding acetate followed by the addition of lithium *tert*-butyl acetate gave diester **84**. Reduction of **84** afforded diol, which was converted to the lactone **81** by selective allylic oxidation with MnO_2. Finally, *exo*-face selective dimethyl cuprate addition afforded (±)-**17**.

A Lewis acid catalysed ene-cyclisation to control four contiguous stereogenic centers for the synthesis of (±)-**17** was reported by Mikami *et al.* [35]. DIBAL-H reduction of methyl-δ-velarolactone **85** and Wittig olefination gave selectively *Z*-

Scheme-13

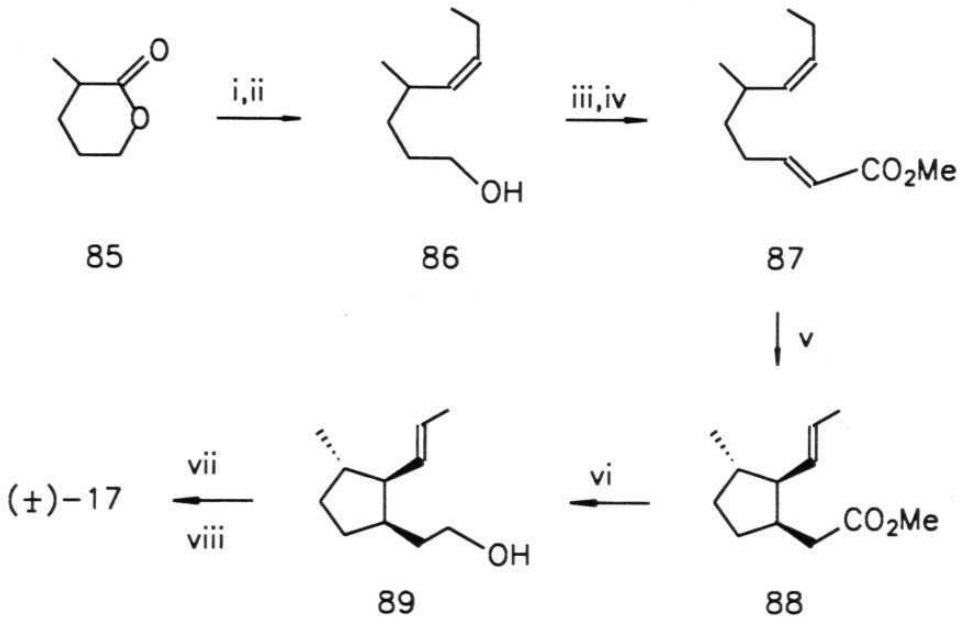


Reagents: *i) H_3O^+; ii) $(EtO)_2P(O)CH_2CO_2Et$; iii) aq. K_2CO_3; iv) MeCOCl, pyridine CH_2Cl_2; v) $LiCH_2CO_2t$-Bu, THF; vi) $LiAlH_4$, ether; vii) MnO_2, $CHCl_3$; viii) Me_2CuLi, ether.*

alcohol **86**. PCC oxidation of **86** and again Wittig olefination afforded *E,Z*-dienoate **87**. Thermal ene-cyclisation of α,ω-diene at 235 °C gave stereoselectively *cis*-fused cyclised product **88**, which was reduced with LAH to afford alcohol **89**. Oxidative cleavage of olefin and Jones oxidation gave (±)-**17**.

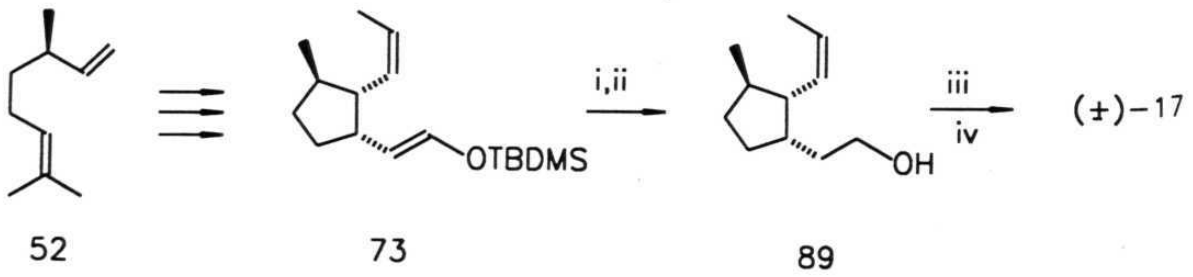
Takacs and co-workers [31] reported the first enantioselective synthesis of (-)-mitsugashiwalactone **17** using an iron catalysed carbocyclisation reaction. (-)-Citronellene **52** was converted to silyl enolether **73** as described earlier for the synthesis of (+)-iridomyrmecin **10** (Scheme-10). Deprotection of **73** with aq. acid and borohydride reduction gave alcohol **89**. Ozonolysis of **89** and PCC oxidation of lactol afforded (-)-**17**.

Scheme-14



Reagents: *i) DIBAL-H, ether; ii) n-Pr(PPh3)Br, BuLi, THF; iii) PCC, CH2Cl2; iv) Ph3P=CHCO2Me, benzene; v) 235 °C, heptane; vi) LiAlH4, ether; vii) O3, MeOH, PPh3; viii) CrO3-H2SO4, aq. acetone.*

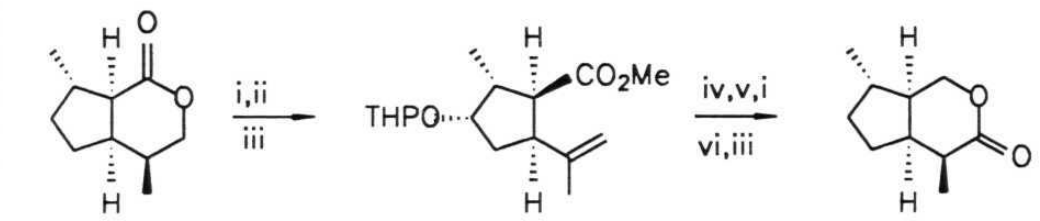
Scheme-15



Reagents: *i) 2% HCl, aq. acetone; ii) NaBH4, MeOH; iii) O3, CH2Cl2, PPh3; iv) PCC, CH2Cl2.*

Recently (1994), Lee and coworkers [36] reported enantioselective synthesis of (+)-iridomyrmecine **10** and (+)-dihydronepetalactone **20** from the stereoselective Favorskii rearrangement product **90** of (+)-carvone chlorohydrin.

Scheme-16



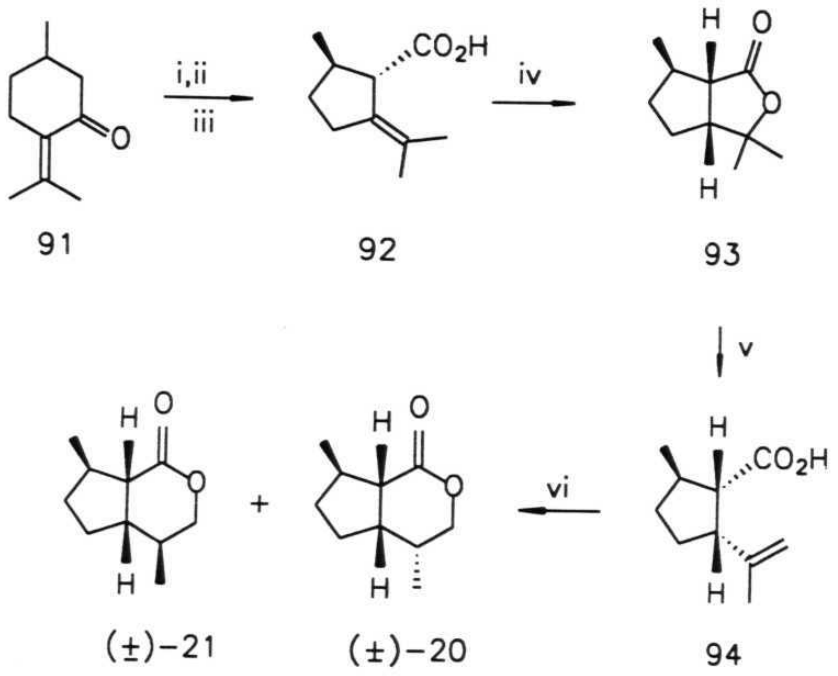
20 90 10

Reagents: *i) Disiamylborane, THF; ii) KOH, aq. MeOH, HCl; iii) NaH, CS_2, MeI, Bu_3SnH, AIBN, benzene; iv) $LiAlH_4$, ether; v) Ac_2O, DMAP, pyridine; vi) p-TsOH.H_2O, MeOH.*

Wolinsky *et al.* [37] reported the synthesis of (±)-dihydronepetalactone **20** and (±)-isodihydronepetalactone **21** using pulegone **91** as starting material. *R*-Pulegone **91** was converted to *trans*-pulegenic acid **92** [38], which on acid treatment gave puleganolide **93**. Treatment of **93** with potasium *tert*-butoxide afforded carboxylic acid **94**. Hydroboration and lactonisation furnished a mixture of (±)-**20** and (±)-**21** in a 7:1 ratio, respectively.

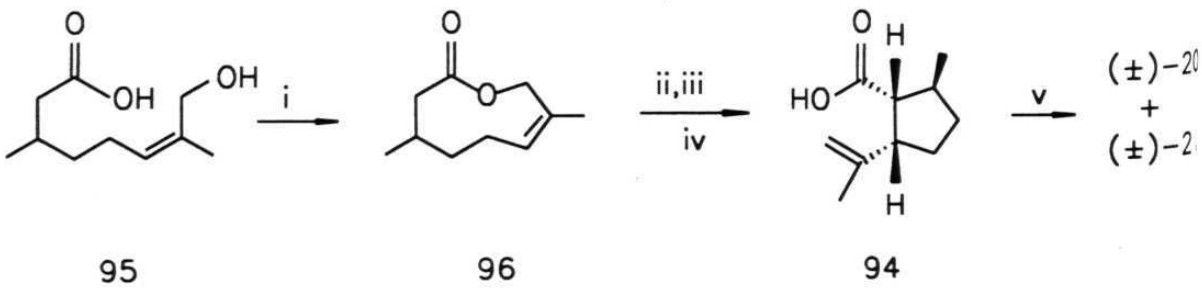
Ring contractive carbocyclic synthesis of large macrocyclic lactones *via* alicyclic Claisen rearrangement was reported by Funk and co-workers [39] for the synthesis of (±)-**20** and (±)-**21**. Lactonisation of ω-hydroxy acid **95** with Mukaiyama reagent gave large macrocyclic lactone **96**. Transformation of lactone **96** to its silyl enolether, and then Claisen rearrangement afforded *cis*-fused cyclopentane carboxylic

Scheme-17



Reagents: *i) Br_2, $NaHCO_3$, ether; ii) NaOEt, EtOH; iii) aq. KOH; iv) H_3O^+; v) t-BuOK, DMF; vi) 9-BBN, H_2O_2, NaOH.*

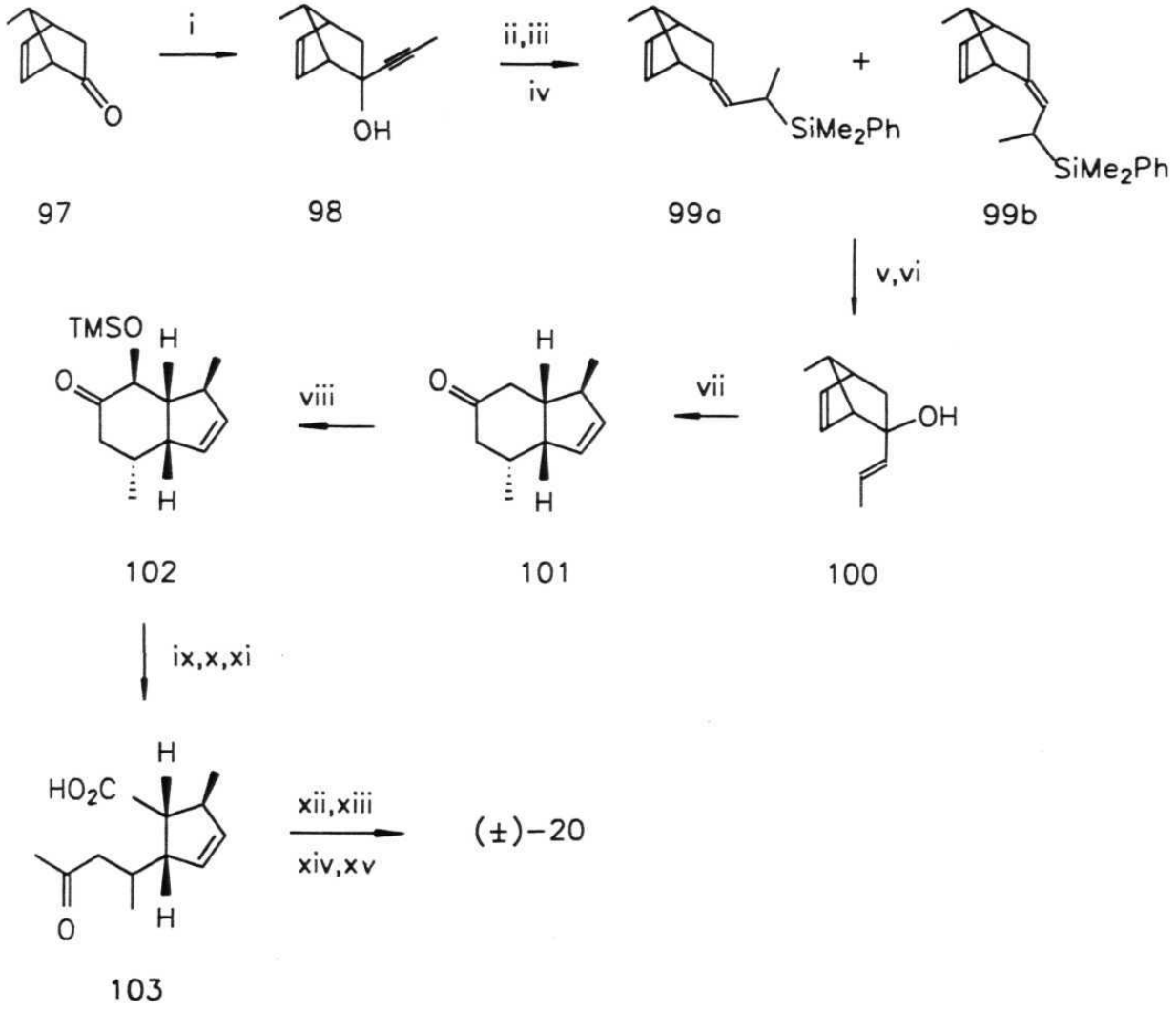
Scheme-18



Reagents: *i) 2-chloro-1-methylpyridinium iodide; ii) LDA, TMS-Cl; iii) toluene, reflux; iv) HF, CH_3CN; v) $(C_6H_{11})_2BH$, H_2O_2, NaOH.*

acid **94** in racemic form. Hydroboration and lactonisation provided (±)-**20** and (±)-**21** in 93:7 ratio, respectively.

Scheme-19



Reagents: *i) $BrMg\text{-}C{\equiv}C\text{-}Me$; ii) H_2, Pd-C, $Ba(OH)_2$; iii) Ac_2O; iv) $(PhMe_2Si)_2CuLi$; v) m-CPBA; vi) TBAF; vii) KH; viii) Et_3N, TMS-Cl; ix) MeLi; x) HIO_4; xi) PDC; xii) H_2, Pt_2O; xiii) CF_3CO_2H; xiv) NaOH; xv) HCl.*

Fleming and co-workers [40] reported the synthesis of (±)-dihydronepetalactone **20** using an oxy-Cope rearrangement reaction. *exo*-Selective addition of propynyl Grignard reagent to norbornenone **97** gave propargylic alcohol **98**. Lindlar reduction of triple bond to a *cis*-alkene, acetate formation and addition of silylcuprate reagent afforded allylsilanes **99a** and **99b**. Epoxidation of the mixture and desilylation gave the *endo-trans*-propenyl norbornenol **100**. Anionic oxy-Cope rearrangement of **100** gave *cis*-fused bicyclic ketone **101**, which upon regioselective Rubottom oxidation gave hydroxy ketone **102**. Addition of MeLi to ketone **102** and periodate oxidation afforded acid **103**. Reduction of double bond and lactonisation furnished (±)-**20**.

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CHAPTER-2

SYNTHETIC TRANSFORMATIONS FROM *R*-PULEGONE

2.1. INTRODUCTION:

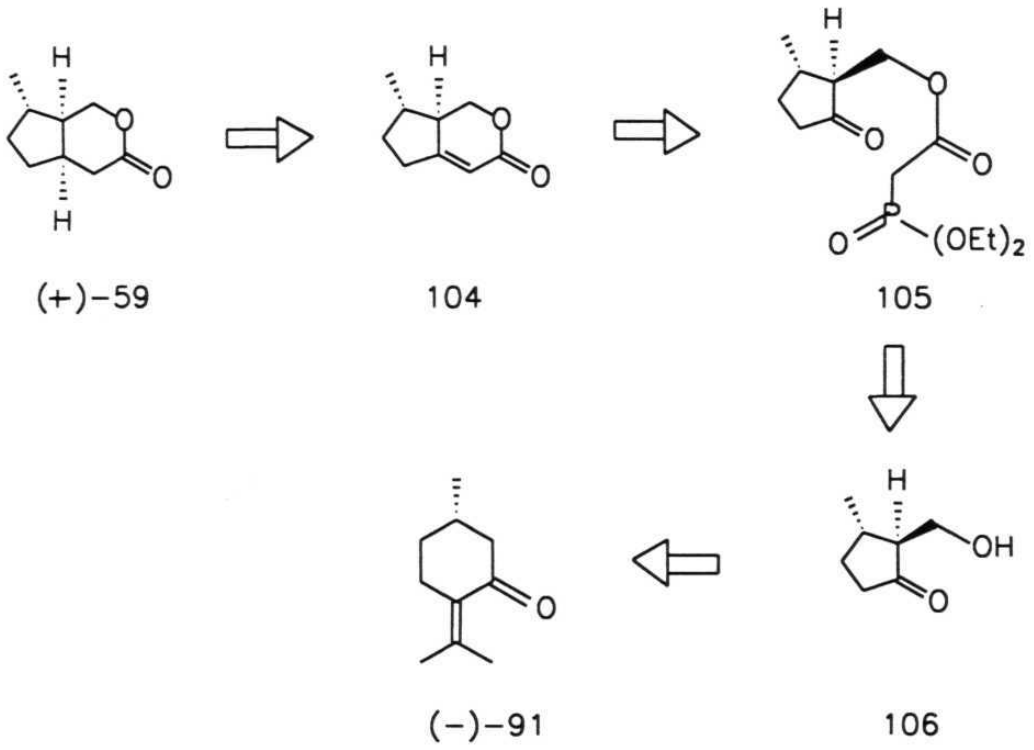
The different approaches for the synthesis of iridoid lactones of structural type-I iridomyrmecin **10**, isoiridomyrmecin **11** and teucriumlactone **15** were documented in the previous section. A close examination of published procedures reveals that most of the syntheses lead to racemic products or unnatural isomers. Some of them suffer from lengthy procedures and produce a mixture of stereo- or regioisomers at a late stage in the sequence. There are very few routes leading to natural (+)-iridomyrmecin **10** and (-)-isoiridomyrmecin **11**. In fact, there is no synthetic approach to naturally occurring (+)-teucriumlactone **15**; only racemic synthesis is reported. Most of the approaches proceed *via* the bicyclic ketone **47** or bicyclic lactone **59**. We focused our interest on the synthesis of natural analogs which have the methyl group in *S*-configuration at C7. The synthetic target was the bicyclic lactone **59**, which is a common precursor for the three natural products, **10**, **11** and **15**.

A retrosynthetic analysis of bicyclic lactone **59** was carried out as delineated in Scheme-1. We reasoned that the *cis* stereochemistry at ring junction (C4a-C7a) can be achieved by a stereoselective *exo*-face hydrogenation of unsaturated lactone **104**. The precursor lactone should arise through an intramolecular Horner-Wadsworth-Emmons (HWE) reaction of ketophosphonate **105**, which can be obtained from ketoalcohol **106**. Ketoalcohol **106** can be prepared in good optical purity and chemical yield from *S*-pulegone **91**. The same transformation in the enantiomeric series from naturally abundant *R*-pulegone **91** is already reported [1].

Thus, the proposed route will afford the target bicyclic lactone **59** for further elaboration to natural iridoids. A drawback of this approach is that commercially available *R*-pulegone **91** leads to unnatural enantiomer **59** having *R*-configuration at C7.

Crucial to the success of this strategy was a ready and convenient source of *S*-pulegone **91**.

Scheme-1



S-Pulegone is isolated from the volatile oils of several plants [2]. At present, there are no commercial suppliers of *S*-pulegone, whereas *R*-pulegone is readily accessible from the "chiral pool" [3].

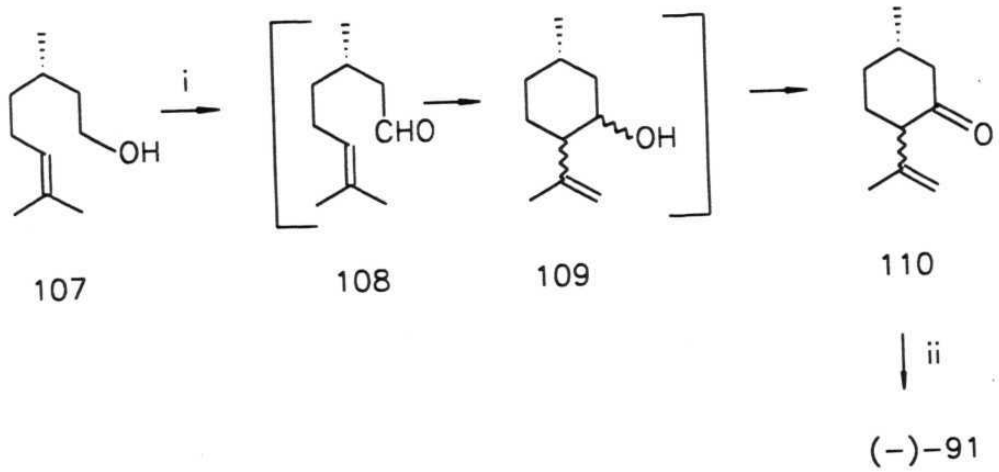
At this juncture we found it expedient to initiate work on the project from inexpensive and commercially available *R*-pulegone **91**. Although, this will produce unnatural lactone **59**, the synthesis will ascertain the viability of this new route. Simultaneously, we also started exploring methods to prepare *S*-pulegone **91** from known procedure or *via* a new route. For the sake of clarity and continuity, work on

the attempted conversion of *R*- to *S*-pulegone is described in this chapter and the work on the enantioselective synthesis of unnatural and natural (-)-**59** and (+)-**59**, respectively, is detailed in the next chapter.

2.2. CONVERSION OF *R*-(+)-PULEGONE TO *S*-(-)-PULEGONE:

Corey *et al.* [4] prepared *S*-(-)-pulegone **91** by an ene cyclisation of (-)-citronellol **107** under oxidative conditions. Thus, treatment of *S*-citronellol **107** with 2.5 equi. of PCC in dry CH_2Cl_2 gave *iso*-pulegone **110** in one step *via* the intermediates citronellal **108** and *iso*-pulegol **109**. Treatment of **110** with ethanolic NaOH provides *S*-(-)-pulegone **91** in 70% overall yield.

Scheme-2

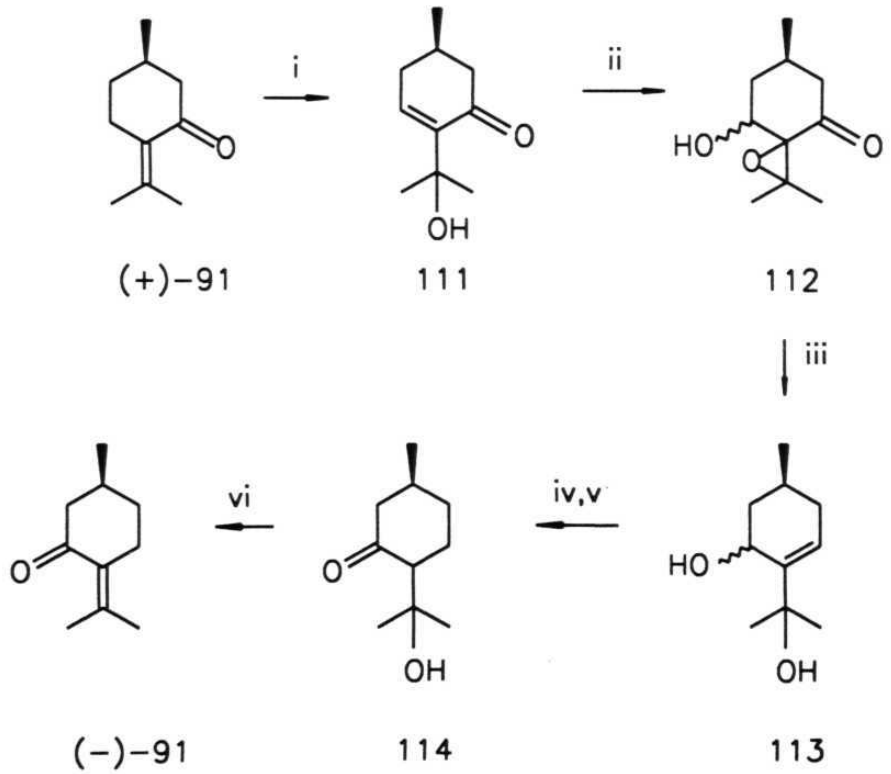


Reagents: *i) PCC, CH_2Cl_2; ii) EtOH, NaOH*

The same method was reported by Scharf and co-workers [5], but the ene cyclisation of citronellal **108** to *iso*-pulegol **109** was achieved by using catalytic $ZnCl_2$.

Conversion of *R*-(+)-pulegone to *S*-(-)-pulegone through a 1,3-carbonyl transposition was reported by Ensley and co-workers [6]. (+)-Pulegone **91** was photochemically irradiated in the presence of 5% photox to produce allylic hydroperoxide, which was reduced with excess of $SnCl_2$ to afford alcohol **111**. Treatment of **111** with alkaline H_2O_2 gave epoxide **112** *via* the base catalysed Payne rearrangement of initially formed epoxide. Treatment of **112** with hydrazine afforded diol **113** in 83% yield. Hydrogenation of **113** with Pt_2O and oxidation with Collins reagent gave β-hydroxy ketone **114**. Iodine catalysed elimination of **114** afforded *S*-(-)-pulegone **91** in 81% yield. The global yield from *R*- to *S*-pulegone is about 40%.

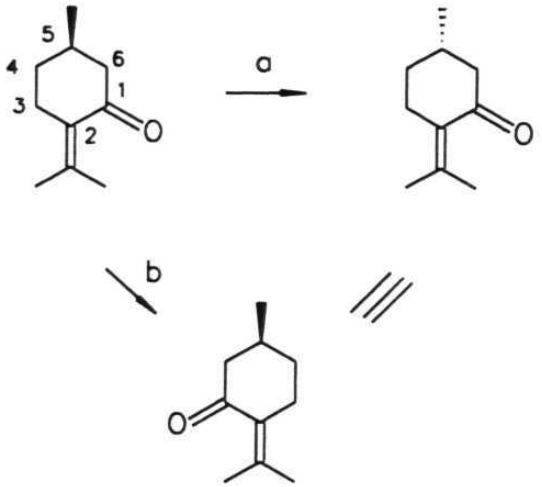
Scheme-3



Reagents: *i) hν, $SnCl_2$, CH_2Cl_2; ii) H_2O_2, NaOH, MeOH; iii) $NH_2NH_2.H_2O$, MeOH, CH_3CO_2H; iv) Pt_2O, EtOH, CH_3CO_2H; v) $CrO_3.2Py$; vi) I_2.*

Since, *R*-pulegone **91** is commercially available, its conversion to *S*-pulegone **91** was also investigated by an independent route. The interconversion of pulegone enantiomers can be visualised in two ways (Scheme-4): a) direct conversion *via* an inversion of stereochemistry at C5, and b) conversion *via* a transposition of carbonyl group from C1 to C3.

Scheme-4

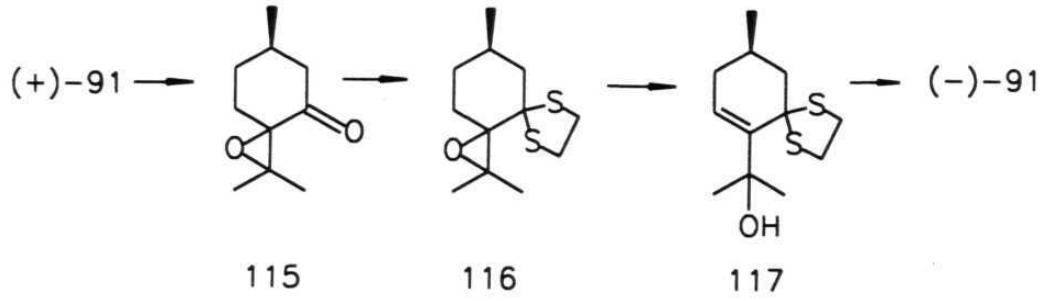


The chemical methods available for executing path-a are limited. However, path-b can be carried out by the introduction of carbonyl group at C3 and its removal from C1. This transposition will, in effect, invert the stereochemistry at C5 from *R* to *S*. The method attempted for the introduction of functionality at C3 is *via* the 1,3-carbonyl transposition precursor *tert*-alcohol **117**. This should arise from *R*-pulegone **91** by epoxidation and thioketal formation.

Epoxidation [7] of *R*-pulegone **91** with alkaline hydrogen peroxide in methanol afforded pulegone epoxide **115** in 90% yield as a mixture of diastereomers. Attempted thioketalisation with ethanedithiol under a variety of reaction conditions, such as

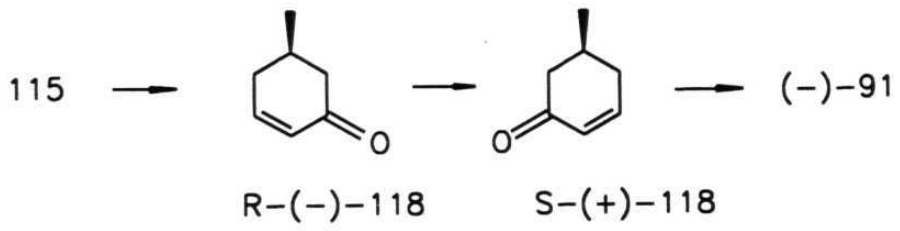
catalytic $BF_3.Et_2O$ in CH_2Cl_2 [8] and acetic acid [9], and catalytic *p*-TsOH.H_2O in benzene [10] using Dean-Stark was unsuccessful.

Scheme-5



With the epoxide **115** in hand the attention was turned to carry out the transformation through a 1,3-enone inversion, for which there is ample precedence [11] in cyclohexenones. Transformation of pulegone **91** to enone **118**, then enone-inversion and introduction of *iso*-propylidene group was expected to lead to *S*-pulegone **91**.

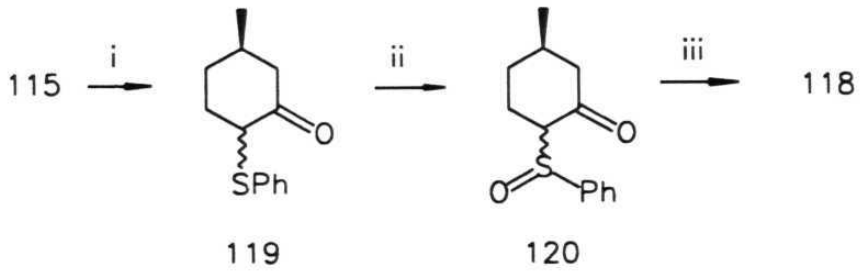
Scheme-6



Regiospecific opening of epoxide **115** with thiophenoxide [12] gave a diastereomeric mixture of ketosulfide **119**, with concomitant retro-aldol expulsion of acetone. The product was identified as a diastereomeric mixture because in PMR

spectrum the **SCH** proton is at δ 3.88 (dd) and δ 3.78-3.60 (m). Oxidation of ketosulfide **119** to ketosulfoxide **120** with *m*-CPBA [13] was unsuccessful, but oxidation proceeded smoothly with $NaIO_4$ in methanol [14] and afforded ketosulfoxide **120** in 65% overall yield from pulegone **91**. The mixture of four possible isomers (C2 and sulfur are stereogenic centres) of sulfoxide **120** was of little consequence because the adjacent carbon is eventually converted to an sp^2-carbon. The thermal elimination of phenylsulfinic acid [15] from sulfoxide **120** using catalytic amount of $CaCO_3$ in CCl_4 provided optically and isomerically pure 5-methylcyclohex-2-en-1-one **118**. The vinylic protons in **118** resonate at the expected δ 6-7 ppm in PMR spectrum.

Scheme-7

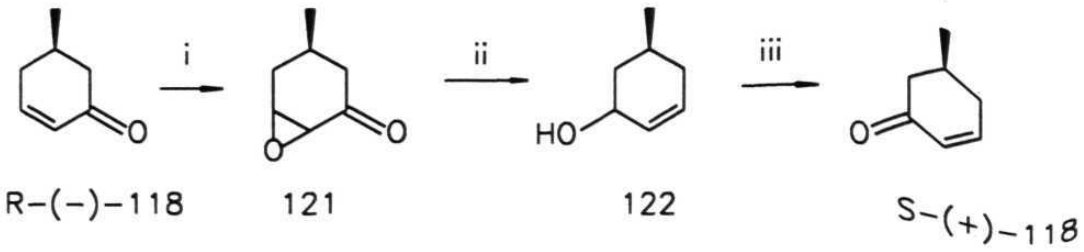


119 120

Reagents: i) NaH, PhSH, THF, reflux, 24 h; ii) $NaIO_4$, aq. MeOH, 0 °C to rt, 10 h; iii) $CaCO_3$, CCl_4, 70 °C, 15 h.

Enone *R*-**118** was inverted to its enantiomer *S*-**118** in three steps according to Burke's procedure [11c]. Epoxidation of *R*-enone with alkaline hydrogen peroxide gave epoxide **121**. Treatment of **121** with hydrazine hydrate in acetic acid afforded allylic alcohol **122**. PCC oxidation [16] of **122** furnished inverted enone *S*-**118**.

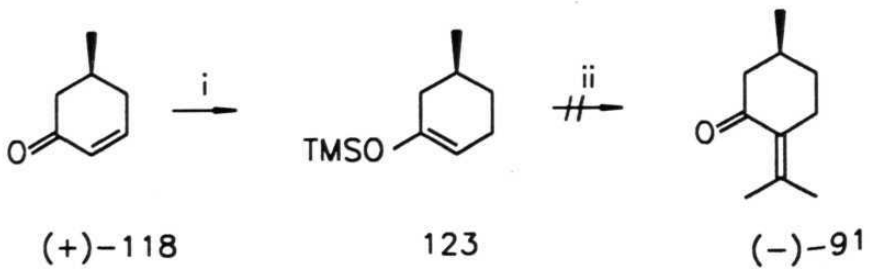
Scheme-8



Reagents: *H_2O_2, NaOH, MeOH, 0 °C to rt, 4 h; ii) $NH_2NH_2.H_2O$, $CH_3CO_2^H$, reflux, 2 h; iii) PCC, CH_2Cl_2, rt, 1h.*

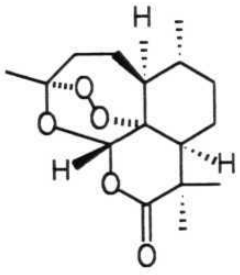
In order to introduce *iso*-propylidene group regioselectively at C2, reduction of enone **118** with lithium metal in liquid NH_3 [17] and trapping of the enolate as its silyl enolether **123** was attempted. The objective was to carryout a Mukaiyama type aldol [18] between silylenolether **123** and acetone to obtain *S*-pulegone **91**. However reductive generation of silyl enolether **123** from enone **118** was unsuccessful.

Scheme-9



Reagents: *i) Li, NH_3, TMS-Cl, -78 °C; ii) acetone*

At this juncture we perused the literature for possible utilisation of our key intermediate enone **118**, synthesised from *R*-pulegone **91**. *R*-(+)-Pulegone **91** has been extensively used as a chiral template for the synthesis of optically active intermediates and natural products. Some recent examples of natural products are (+)-artemisinin **124** [12], (+)-jatrophone **125** [19] and (+)-1233A **126** [20]. Among other possible synthetic transformations (+)-**91** has been converted in to (+)-menthofuran **127** [21], (+)-3-methylcyclohexanone **128** [13], (-)-5-methylcyclohex-2-en-1-one **118** [15], (-)-2-allyl-5-methylcyclohex-2-en-1-one **129** [15], (-)-2,5-dimethylcyclohex-2-en-1-one **130**



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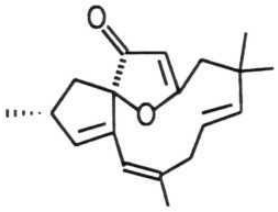

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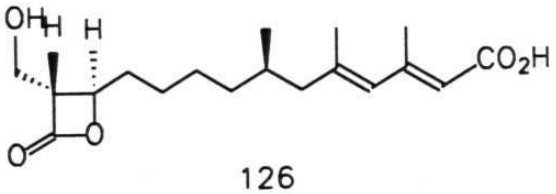

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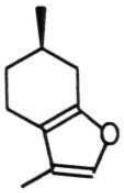

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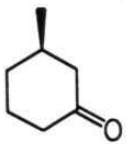

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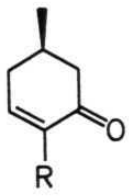
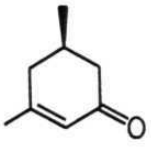


118: R=H

129: R=allyl

130: R=Me



131

[15], and (-)-3,5-dimethylcyclohex-2-en-1-one **131** [22]. (+)-Pulegone **91** is also used in various biogenetic transformations by microorganisms [23].

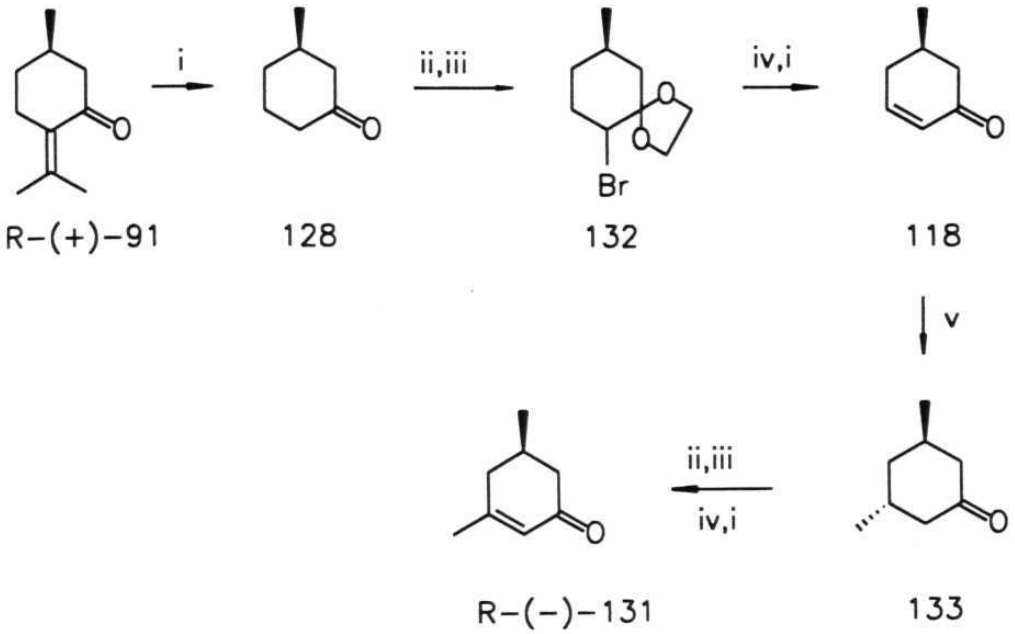
After examining the structures of intermediates and reactions from *R*-pulegone **91**, we felt that both enantiomers of 3,5-dimethylcyclohex-2-en-1-ones **131** should be interesting targets.

2.3. SYNTHESES OF *R*-(-)- AND *S*-(+)-3,5-DIMETHYLCYCLOHEX-2-EN-1-ONES:

R-(-)-3,5-Dimethylcyclohex-2-en-1-one **131** was synthesised from *R*-pulegone 91 by Allinger and co-workers [22]. *R*-Pulegone **91** was converted to *R*-3-methylcyclohexanone **128** by acid catalysed retro-aldolisation. Bromination of **128** and ketal formation with ethanediol afforded bromoketal **132**. Dehydrobromination of **132** followed by acid catalysed hydrolysis afforded *R*-5-methylcyclohex-2-en-1-one **118**. Addition of methyl Grignard to **118** gave 3*R*,5*R*-dimethylcyclohexanone **133**. Again sequential bromination, ketal formation, dehydrobromination and hydrolysis afforded *R*-(-)-**131** in good optical purity ($[\alpha]_D^{25}$ -138.4°, c 0.8, $CHCl_3$), but the overall yield is only 1% over 10 steps.

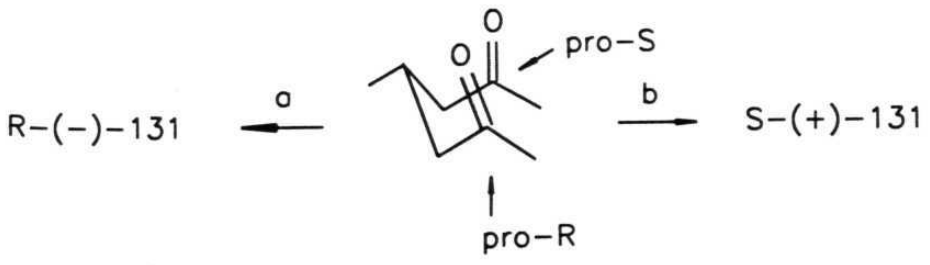
S-Proline catalysed asymmetric annulation of racemic diketones was reported by Agami and co-workers [24]. Treatment of 4-methylheptane-2,6-dione **134** with *S*-proline produces *R*-(-)-**131** ($[\alpha]_D^{25}$ -59.0°, c 2, $CHCl_3$, optical purity 43%) by a nucleophilic attack on to the *Si*-face of the *pro-S*-carbonyl group (path-a) and *S*-(+)-131 by *Re*-face attack on the *pro-R*-carbonyl group (path-b).

Scheme-10



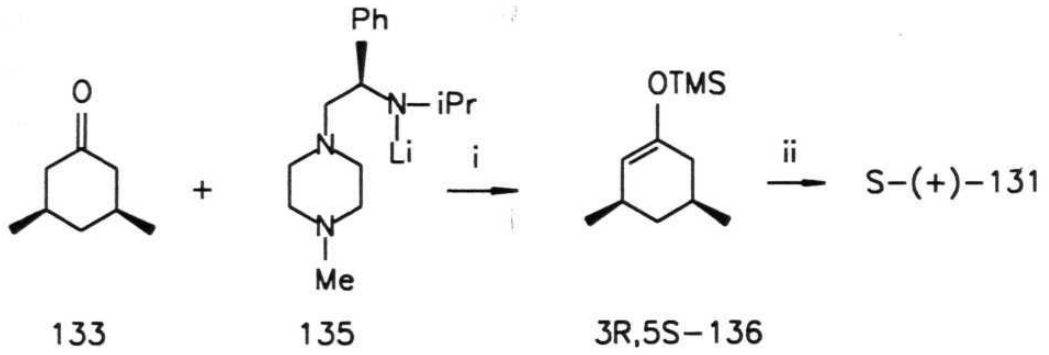
Reagents: *i) H_3O^+; ii) Br_2, H_2O; iii) $(CH_2OH)_2$, p-TsOH.H_2O, benzene; iv) NaOH, MeOH; v) MeMgI, CuCl, ether.*

Scheme-11



Koga *et al.* [25] synthesised *S*-(+)-3,5-dimethylcyclohex-2-en-1-one **131** by kinetic deprotonation of *meso*-dimethyl cyclohexanones with chiral lithium amides. Enantioselective deprotonation of *meso*-3,5-dimethylcyclohexanone **133** by chiral lithium amide **135** in the presence of excess TMS-Cl gave the corresponding 3*R*,5*S*-silylenolether **136**. Treatment of **136** with $Pd(OAc)_2$ gave *S*-(+)-**131** with 58% optical purity ($[\alpha]_D^{25}$ +82.4°, $CHCl_3$).

Scheme-12

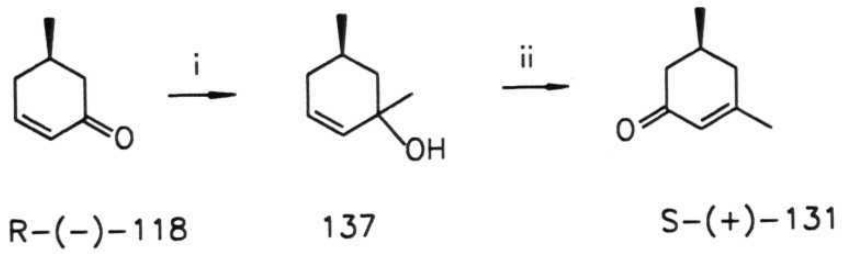


Reagents: *i) TMS-Cl, THF; ii)* $Pd(OAc)_2$.

Racemic 3,5-dimethylcyclohex-2-en-1-one **131** has been used as a starting material in a number of synthetic transformations [26]. The use of *R*-(+) **131** or *S*-(-)-**131** is infrequent presumably due to the unavailability of a convenient method for their preparation.

Since, 5*R*-methylcyclohex-2-en-1-one **118** was already prepared, the attention was turned to transform it to R-(-)- and S-(+)-**131**. S-(+)-**131** was synthesised through an alkylative carbonyl transposition according to the conditions developed earlier by Dauben *et al.* [27].

Scheme-13

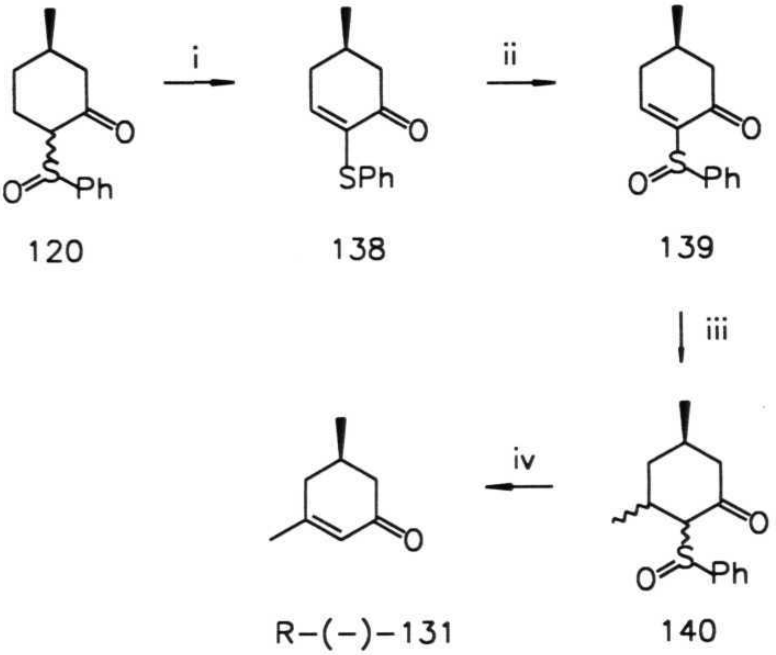


Reagents: *i) MeLi, ether, -78 °C to rt, 3 h; ii) PCC, CH_2Cl_2, rt, 1 h.*

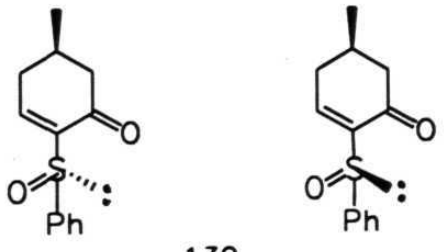
1,2-Addition of MeLi to enone **118** in ether at -78 °C provided somewhat unstable allylic alcohol **137** in quantitative yield as a mixture of diastereomers. Attempted purification on silica gel led to extensive decomposition. Treatment of crude alcohol **137** with PCC in CH_2Cl_2 at ambient temperature for 1 h furnished transposed enone *S*-(+)-**131** in 54% yield from *R*-(-)-**118** with 96% optical purity ($[\alpha]_D^{25}$ +132.2 °, c 0.75, $CHCl_3$).

R-(-)-3,5-dimethylcyclohex-2-en-1-one **131** was prepared from ketosulfoxide **120** as delineated below. Pummerer rearrangement [28] of diastereomeric ketosulfoxide **120** with acetic anhydride in CH_2Cl_2 using catalytic amount of methanesulfonic acid for 15 h at ambient temperature provided enonesulfide **138** in 90% yield after silica gel purification. The product was identified by the appearance of vinyl proton at δ 6.46 (dd, J=6,4 Hz). Sodium periodate oxidation [14] of enonesulfide **138** gave enonesulfoxide **139**. From CMR data it was confirmed that the product is a mixture of diastereomers, because of the lone pair on sulfur atom [29].

Scheme-14



Reagents: *i) Ac_2O, MsOH, CH_2Cl_2, 0 °C to rt, 15 h; ii) $NaIO_4$, aq. MeOH, 0 °C to rt, 6 h; iii) Me_2CuLi, ether-THF, -78 °C to 0 °C; iv) $CaCO_3$, CCl_4, 70 °C, 24 h.*



139

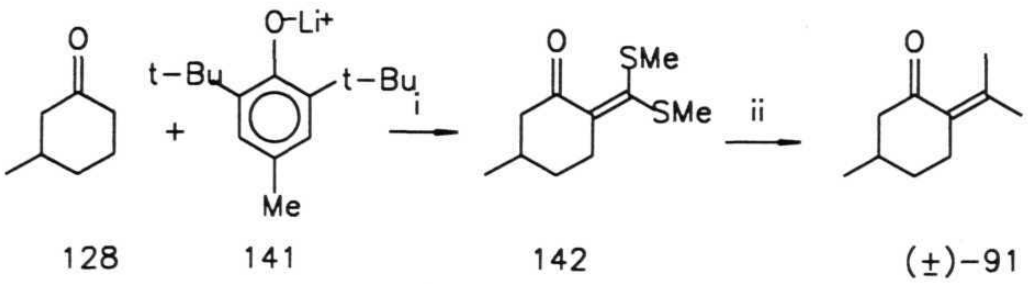
Conjugate addition of dimethylcuprate to **139** in ether-THF mixture at -78 °C provided ketosulfoxide **140** as a mixture of stereoisomers in 96% yield. Without any purification the crude sulfoxide **140** was subjected for thermal elimination of phenylsulfinic acid under conditions optimised earlier to provide 78% of *R*-(-)-**131** in 96% optical purity ($[\alpha]_D^{25}$ -132.8°, c 1.25, $CHCl_3$). The alternative sequence of subjecting enonesulfide **138** to conjugate addition with Me_2CuLi, followed by oxidation with $NaIO_4$ and thermal elimination did not produce satisfactory results. Clearly, the doubly activated ketosulfoxide **140** is a superior Michael acceptor compared to enonesulfide **130**. Thus, *R*-(-)- and *S*-(+)-3,5-dimethylcyclohex-2-en-1-ones **131** were synthesised starting from the common precursor ketosulfoxide **120**. The optical purities are far superior to those reported in the literature.

After developing a convenient method for the preparation of enantiomerically pure *R*-(-)- and *S*-(+)-3,5-dimethylcyclohex-2-en-1-ones **131**, we turned our attention to the unfinished task of introducing an *iso*-propylidene group in *R*-5-methylcyclohex-2-en-1-one **118**.

2.4. INTRODUCTION OF *ISO*-PROPYLIDENE GROUP IN CYCLOHEXENONE:

The synthesis of (±)-pulegone **91** by the introduction of *iso*-propylidene group to 3-methylcyclohexanone **128** is reported by Corey *et al.* [30]. The α-dithiomethylene derivative **142** undergoes successive cuprate additions to provide the requisite *iso*-propylidene group. A minor inconvenience with this method is the lack of regiocontrol in dithiomethylenation of substituted ketones. We felt that the enone group in **118** should be exploited as the functional handle to control the regiochemistry of alkylation.

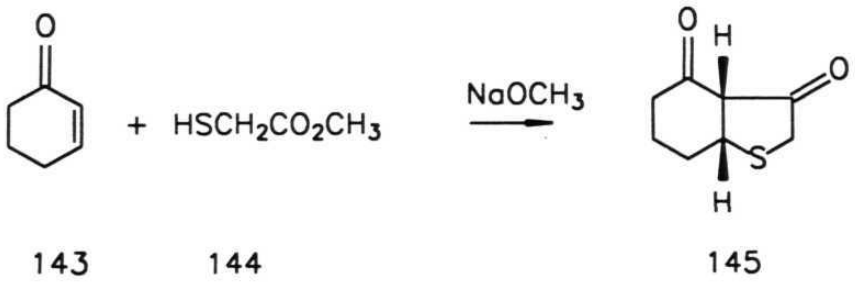
Scheme-15



Reagents: *i) CS_2, MeI; ii) Me_2CuLi, ether-THF.*

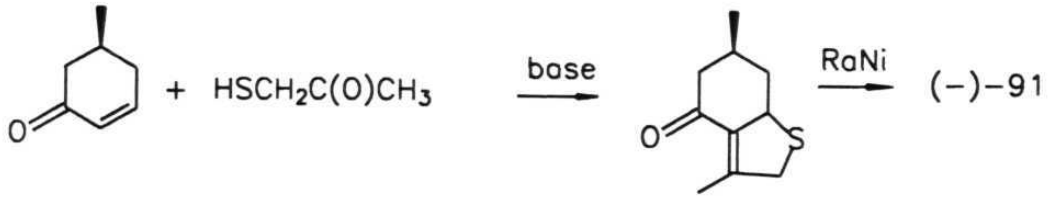
The stratagy attempted to achieve this objective is discussed here. Confalone *et al.* [31] reported in 1981 that base catalysed Michael addition of methyl mercaptoacetate **144** to cyclohexenone **143** afforded bicyclic diketone **145**.

Scheme-16



We felt that conjugate reaction of enone **118** with mercapto acetone **146** and *in situ* aldol condensation should give bicyclic compound **147**, which upon chemoselective desulfurisation will lead to (-)-pulegone **91**.

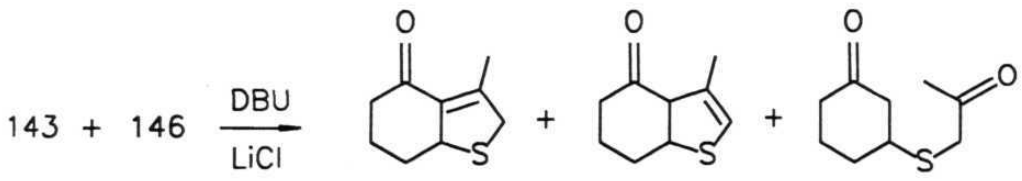
Scheme-17



118 146 147

To study the transformation, cyclohexenone **143** was chosen as model compound. Mercapto acetone **146** was prepared according to Hormatka's procedure [32]. Treatment of chloroacetone with H_2S in NaOH solution gave mercapto acetone **146** in 65% yield. Base (DBU) catalysed Michael addition of mercapto acetone **146** with cyclohexenone **143** gave incipient enolate anion, which underwent spontaneous intramolecular aldol condensation with concomitant elimination of H_2O to afford isomeric bicyclic ketones **147** and **148**; minor amount of intermediate 1,4-addition product **149** was also isolated.

Scheme-18



147 148 149

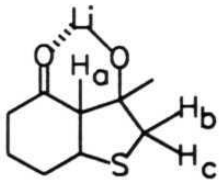
It was observed that depending on the base used and the reaction conditions employed, the ratio of the three products (**147**, **148** and **149**) varied. The reaction

conditions employed and the results obtained are listed in Table-1. Bicyclic hydrindenes **147** and **148** were easily separated from Michael-adduct **149** by column chromatography.

Table-1

Conditions	**Result**	**147:148**
NaH/MeOH, rt, 12 h	**147**, **148** & **149**	1:2
NaH/THF, rt, 3 h	**147**, **148** & **149**	1:2
K_2CO_3/MeOH, rt, 4 h	**147**, **148** & **149**	1:4
K_2CO_3/THF, rt, 10 h	**147**, **148** & **149**	1:1
NaH/MeOH, -20 °C to 0 °C, 4h	**143** & **149**	-
$NaHCO_3$, MeOH, rt, 10 h	**149**	-
Et_3N/LiCl/CH_3CN, rt, 4 h	**149**	-
DBU/LiCl/CH_3CN, rt, 4 h	**147**, **148** & **149**	4:1

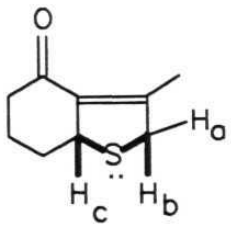
We were somewhat surprised to find that prolonged reaction times and strong base did not favour formation of conjugated enone **147**. However, we were able to divert the elimination in favour of conjugated isomer **147** by judicious choice of base/salt conditions. When the tandem Michael addition-aldol condensation was carried out in the presence of DBU and LiCl, a 4:1 mixture of **147** and **148** was



150

isolated. This is attributed to the chelated structure **149**, which selectively enhances the pKa of H_a over H_b and H_c. Deprotonation of H_a with DBU and elimination of H_2O yields conjugated ketone **147** as the preponderant isomer.

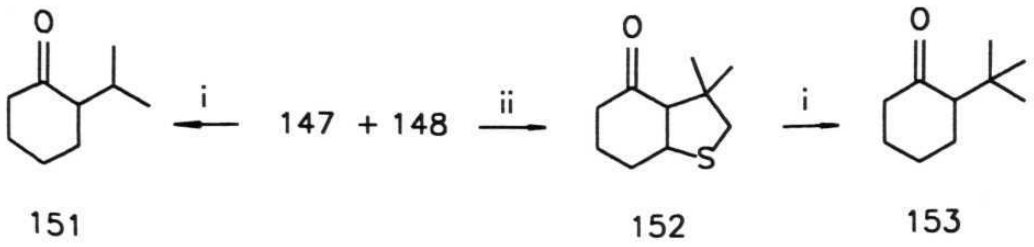
The products **147** and **148** (inseperable) were seperated from **149** by column chromatography and the ratio of **147** and **148** was confirmed by PMR data. Bicyclic ketone **147** was identified by the appearance of AB SCH_2 protons in PMR as a doublet of doublets at δ 3.84 (J=15,3 Hz) and 3.62 (J=15,5 Hz). The larger J coupling is due to geminal proton. The smaller splitting is attributed to long-rang W-coupling with the ring junction **CH** adjacent to sulfur atom. This was confirmed by a NMR decoupling experiment. Irradiation of broad signal at δ 4.36 corresponding to H_c simplified the AB CH_2S pattern into two geminal doublets. The isomeric bicyclic ketone **148** was identified by the appearance of vinylic proton at δ 6.8 as a singlet in PMR spectrum.



147

Attempted desulfurisation of the mixture of compounds (**147** and **148**) with W-2 RaNi [33] and "NiBo" [34] using different reaction conditions did not lead to the required product. Reduction with W-2 RaNi in EtOH (reflux, 1 h) afforded 2-*iso*-propylcyclohexanone **151** because of desulfurisation and concomitant alkene reduction. Dimethylcuprate addition to **147** in ether at -78 °C using catalytic amount of $BF_3.Et_2O$ gave dimethyl ketone **152** which on reduction with W-2 RaNi will give 2-*tert*-butylcyclohexanone **153**.

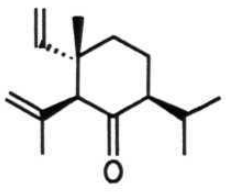
Scheme-19



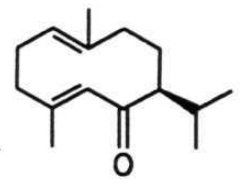
151 152 153

Reagents: *i) RaNi, EtOH, reflux, 1h; ii) Me_2CuLi, $BF_3.Et_2O$, ether, -78 °C, 2 h.*

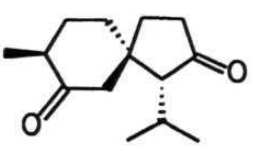
Thus, the transformations lead to the introduction of *iso*-propyl or *tert*-butyl groups adjacent to a ketone function. This structural subunit occurs in a number of important natural products. For example, shyobunone **154** [34], acoragemacrone **155** [35], acorone **156** [36] and acolamone **157** [37] have *iso*-propyl group adjacent to a ketone. The intriguing terpenoids from Ginkgo species have a *tert*-butyl substituted cyclopentane sub-structure [38].



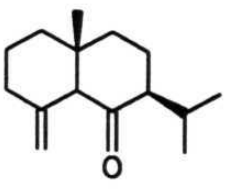
154



155



156



157

Recently, Collins *et al.* [39] reported non-reductive desulfurisation using aged W-7 RaNi. This method appears suitable for the desulfurisaton of bicyclic hydrindenes **147** and **148** .

The optimisation of reaction conditions and generalisation of protocol for the enone-directed α-functionalisation of ketones remains to be fully explored.

2.5. EXPERIMENTAL AND SPECTRA:

Instrumentation:

Melting Points (mp): Melting points were determined on Superfit melting point apparatus and are uncorrected.

Boiling Points (bp): Boiling points refer to bath temperatures (short path distillation) and are uncorrected.

Infrared Spectra (IR): Infrared spectra were recorded on Perkin-Elmer 1310 or 297 and JASCO 5300 spectrophotometers. All spectra were calibrated against a polystyrene absorption at 1601 cm^{-1}. Solid samples were prepared as KBr wafers and liquid samples as film between NaCl plates. All IR samples were recorded as neat liquids unless otherwise stated. Peaks are described as br = broad, w = weak.

Nuclear Magnetic Resonance Spectra (NMR): Proton magnetic resonance (PMR) spectra and carbon-13 magnetic resonance (CMR) spectra were recorded on JEOL FX-100 or Bruker ACF-200 spectrometers. PMR and CMR samples were made in chloroform-D solvent. Samples containing protons attached to heteroatoms, such as alcohols, were exchanged with D_2O for identification. Spectral assignments for PMR are as follows: (1) chemical shift on the δ scale (tetramethylsilane δ = 0.00 ppm); (2) multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of a doublet, dt = doublet of a triplet; (3) coupling constant J in Hertz (Hz);

(4) number of hydrogens integrated for by the signal; (5) assignment of the signal (wherever possible). For CMR spectral data, values are calibrated against $CDCl_3$ δ = 77.0 ppm.

High pressure liquid chromatography (HPLC): Analytical HPLC was performed on Waters liquid chromatograph equipped with model 440 absorbance detector or Shimadzu C-R4A chromatopac equipped with SPD-10A uv-vis detector.

Optical rotation ($[\alpha]_D^{25}$): Optical rotations were measured on Autopol II automatic polarimeter or Jasco DIP 370 polarimeter at the sodium D-line (589 nm) and ambient temperature.

Elemental Analysis: Elemental analysis was performed on Perkin-Elmer 240C CHN analyser.

Mass Spectra: Low resolution mass spectra (LRMS) were recorded on JOEL JMS DX-303 instrument and high resolution mass spectra (HRMS) were recorded on Micromass VG70/70H instruments at IICT, Hyderabad.

Ozonolysis: Ozonolysis was carried out on Welsbach model by purging a steady stream of O_3/O_2 through the solution.

Chromatography: Analytical thin layer chromatography (TLC) was performed on glass plates (2 X 7.5 cm) coated with Acme's silica gel GF 254 containing 13% calcium sulphate as binder. Visualisation of the spots was achieved by exposure to iodine vapour or UV light. Column chromatography (SGC) was effected using Acme's silica gel (100-200 mesh) employing appropriate solvent systems.

General:

All reactions were monitored by TLC using appropriate solvent systems. Moisture sensitive reactions were carried out using standard syringe septum techniques in inert atmosphere (nitrogen) with magnetic stirring unless otherwise stated. All anhydrous solvents were freshly distilled from the appropriate drying agents [40].

Solvent extracts were washed with brine, dried over anhydrous magnesium sulfate or anhydrous sodium sulfate and concentrated on Superfit rotary evaporator at reduced pressure. This is referred to as work-up in experimental procedures. All yields reported are isolated yields of material judged homogeneous by TLC and other spectroscopic techniques and for crystalline solids, material having the indicated melting point.

R-(+)-Pulegone was obtained from Aldrich, tech. 85% with $[\alpha]_D^{20}$ +22° (neat), 96% optical purity.

Pulegone epoxide 115:

A mixture of *R*-pulegone **91** (1.50 g, 10.0 mmol), MeOH (25 mL) and 30% H_2O_2 (6 mL, 15.0 mmol) in a round bottom flask was cooled to 15 °C. A solution of NaOH (1 mL, 2.5 mmol, 2.5 M solution in H_2O) was added dropwise with stirring and continued for 4 h at rt. The reaction mixture was poured into 5 mL of brine and extracted with ether (3x30 mL). Combined organic layers were washed twice with 10% Na_2SO_3 solution and with brine. Work-up afforded a diastereomeric mixture of epoxides **115** which was pure enough to carry out the next reaction.

Yield: 1.53 g, 91%

$[\alpha]_D^{25}$: +7.8° ($CHCl_3$, c 5.0)

IR: cm^{-1} 2900, 1710, 1450, 1380, 1270, 1110, 1020, 880, 820, 700.

PMR: δ 2.68-1.70 (m, 7H); 1.44 (s, 3H, oxirane CH_3); 1.22 (s, 3H, oxirane CH_3); 1.12-1.02 (m, 3H, CH_3).

CMR: δ 206.25, 205.13, 68.95, 62.00, 61.83, 50.18, 48.86, 32.88, 31.27, 29.41, 28.94, 25.18, 20.82, 18.77, 18.41, 18.18, 18.70.

Ketosulfide 119:

A 50% dispersion of NaH in mineral oil (0.90 g, 18.0 mmol) under N_2 atmosphere was washed with dry hexane (3x10 mL) to remove the oil and 17 mL of dry THF was added. A solution of thiophenol (1.90 mL, 2.00 g, 18.0 mmol) in 17 mL of THF was added slowly dropwise and stirring was continued for 30 min at rt. Then the epoxide **115** (1.50 g, 8.9 mmol) in 10 mL of THF was added and the mixture was heated at reflux for 24 h. The reaction mixture was cooled to rt and 15 g of ice was added. After stirring for 15 min, the mixture was extracted with ether (3x20 mL) and the combined organic layers were washed with brine. Work-up afforded 2.32 g of crude sulfide **119** which was purified by SGC (hexane to 5% EtOAc/hexane).

Yield: 1.70 g, 89%

$[\alpha]_D^{25}$: +32.6° ($CHCl_3$, c 5.0)

IR: cm^{-1} 2900, 1710, 1440, 1310, 1140, 1075, 1020, 740, 680.

PMR: δ 7.45-7.10 (m, 5H, aromatic **H**); 3.88 (dd, J=12,6 Hz) and 3.78-3.60 (m, 1H, SC**H**); 2.89-2.62 (m, 1H); 2.40-1.58 (m, 4H); 1.46-1.32 (m, 1H); 1.24-1.10 (m, 1H); 0.98 (overlapping d, J=6 Hz, 3H, CH_3).

CMR: δ 206.66, 205.49, 133.72, 133.59, 132.30, 131.48, 130.95, 130.72, 68.29, 56.36, 53.59, 48.41, 44.83, 36.83, 36.29, 33.88, 32.65, 32.18, 30.83, 28.21, 21.29, 20.88.

Ketosulfoxide 120:

To a solution of ketosulfide **119** (660 mg, 3.0 mmol) in 6 mL of MeOH was added a solution of $NaIO_4$ (640 mg, 3.0 mmol) in 1.5 mL of H_2O at 0 °C. The mixture was stirred at rt for 10 h and the precipitated $NaIO_3$ was removed by filtration. The filtrate was extracted with CH_2Cl_2 (3x20 mL), washed with 10% Na_2SO_3 solution and then brine. Work-up afforded 640 mg of sulfoxide **120** which was purified by SGC (10% to 30% EtOAc/hexane).

Yield: 560 mg, 80%

$[\alpha]_D^{25}$: +49.6° ($CHCl_3$, c 5.0)

IR: cm^{-1} 2900, 1700, 1440, 1380, 1220, 1080, 1040, 740, 680.

PMR: δ 7.74-7.20 (m, 5H, aromatic **H**); 3.75-3.28 (m, 1H, S(O)C**H**); 2.68-2.42 (m, 1H); 2.35-1.78 (m, 5H); 1.48-1.22 (m, 1H); 1.12-0.95 (m, 3H, CH_3).

CMR: δ 205.36, 205.02, 204.83, 131.43, 130.71, 129.30, 129.12, 128.95, 128.83, 127.30, 125.71, 124.41, 74.54, 73.06, 72.43, 50.06, 49.94, 49.53, 33.73, 33.65, 32.88, 31.83, 29.13, 24.88, 22.89, 21.53, 21.18, 20.60.

_R_-5-Methylcyclohex-2-en-1-one 118:

A solution of sulfoxide **120** (236 mg, 1.0 mmol) in 150 mL of dry CCl_4 was heated in the presence of $CaCO_3$ (5 mg, 0.05 mmol) at 70 °C for 20 h. The solution was filtered and solvent evaporated *in vacuo*. Purification by SGC (hexane to 10% ether/hexane) provided optically pure cyclohexenone **118**.

Yield: 59 mg, 52%

$[\alpha]_D^{25}$: -87.1° ($CHCl_3$, c 2.0)

IR: cm^{-1} 3050, 2900, 1670, 1440, 1270, 1030, 880, 740, 700.

PMR: δ 7.04-6.90 (m, 1H, vinyl **H**); 6.08-5.96 (m, 1H, vinyl **H**); 2.58-1.95 (m, 5H); 1.08 (d, J=6 Hz, 3H, CH_3).

CMR: δ 200.25, 150.01, 129.66, 48.18, 33.94, 30.24, 21.06.

_R_-1,5-Dimethylcyclohex-2-en-1-ol 137:

To a stirred solution of enone **118** (33.6 mg, 0.3 mmol) in 2 mL of dry ether at -78 °C was added dropwise an ethereal solution of MeLi (0.24 mL, 0.6 mmol, 2.5 M solution in ether). The resulting solution was allowed to warm to rt over 1 h and stirred at rt for 2 h. The reaction mixture was quenched with 1 mL of saturated NH_4Cl solution and diluted with 2 mL of brine. Extraction with ether (3x10 mL), brine wash

and work-up afforded somewhat unstable allylic alcohol **137** which was transposed as such in the next step.

Yield: 35 mg, 92%

IR: cm^{-1} 3350, 2900, 1450, 1370, 1110, 1060, 1020, 900, 720.

PMR: δ 5.85-5.50 (m, 2H, vinyl **H**); 2.15-1.20 (m, 6H); 1.30 (s, 3H, vinyl CH_3); 0.98 (d, J=6 Hz, 3H, CH_3).

CMR: (for major isomer) δ 134.54, 127.07, 47.53, 33.88, 29.70, 28.30, 28.29, 22.06.

***S*-(+)-3,5-Dimethylcyclohex-2-en-1-one 131:**

To a magnetically stirred slurry of PCC (129 mg, 0.6 mmol) in 1 mL of dry CH_2Cl_2 was added a solution of allylic alcohol **137** (35 mg, 0.3 mmol) in 1 mL of dry CH_2Cl_2 in one portion at rt. The resulting dark red-black mixture was allowed to stir at rt for 1h and then diluted with 5 mL of dry ether. Filtration through celite, work-up and SGC (hexane to 10% ether/hexane) afforded optically pure 3,5-dimethylcyclohex-2-en-1-one **131**.

bp: 100 °C (oil bath)/12 Torr.

Yield: 20 mg, 54%

$[\alpha]_D^{25}$: +132.2° ($CHCl_3$, c 0.75)

IR: cm^{-1} 2900, 1650, 1440, 1370, 1250, 1110, 730, 690.

PMR: δ 5.86 (s, 1H, vinyl **H**); 2.50-1.98 (m, 5H); 1.95 (s, 3H, vinyl CH_3); 1.08 (d, J=6 Hz, 3H, CH_3).

CMR: δ 200.18, 162.06, 126.48, 45.24, 39.41, 30.06, 24.29, 21.06.

LRMS: 124 (M^+).

Enonesulfide 138:

To a solution of sulfoxide **120** (118 mg, 0.5 mmol) in 2 mL of CH_2Cl_2 was added acetic anhydride (95 μL, 102 mg, 1.0 mmol) and methanesulfonic acid (25 μL,

36 mg, 0.375 mmol) at 0 °C. The resulting solution was stirred at the same temperature for 1 h, allowed to warm to rt and stirred for 15 h. 5 mL of H_2O was added and the stirring continued for 30 min. The reaction mixture was extracted with (3x10 mL) of CH_2Cl_2 and the combined organic layers were washed successively with saturated $NaHCO_3$ solution and brine. Work-up afforded 107 mg of crude enonesulfide **138** which was purified by SGC (hexane to 5% EtOAc/hexane)

Yield: 98 mg, 90%

$[\alpha]_D^{25}$: -93.5° ($CHCl_3$, c 2.0)

IR: cm^{-1} 3050, 2900, 1680, 1600, 1480, 1440, 1330, 1260, 1220, 1130, 1070, 1020, 980, 900, 740, 690.

PMR: δ 7.50-7.20 (m, 5H, aromatic **H**); 6.46 (dd, J=6,4 Hz, 1H, vinyl **H**); 2.75-1.98 (m, 5H); 1.05 (d, J=6 Hz, 3H, CH_3).

CMR: δ 195.24, 144.69, 136.96, 133.48, 132.07, 129.30, 128.06, 46.36, 35.06, 30.12, 20.65.

Enonesulfoxide 139:

Enonesulfide **138** (43.6 mg, 0.2 mmol); $NaIO_4$ (42.8 mg, 0.2 mmol).

Yield: 37 mg, 79%

$[\alpha]_D^{25}$: -34.4° ($CHCl_3$, c 5.0)

IR: cm^{-1} 3050, 2900, 1660, 1600, 1440, 1130, 1260,1200, 1120, 1070, 1040, 1010, 920, 740, 680.

PMR: δ 7.82-7.65 (m, 3H, aromatic); 7.50-7.40 (m, 3H, aromatic 2**H** and vinyl **H**); 2.88-1.98 (m, 5H); 1.05 (overlapping d, J=6 Hz, 3H, CH_3).

CMR: δ 195.02, 194.84, 149.83, 148.54, 144.13, 131.24, 129.07, 125.30, 46.53, 46.18, 34.13, 30.35, 29.47, 20.54, 20.35.

Dimethyl ketosulfoxide 140:

An oven dried 10 mL flask with N_2 inlet and rubber septum containing CuI (58 mg, 0.3 mmol) and 2 mL of dry ether was cooled to 0 °C. MeLi (0.6 mL, 0.6 mmol, 1.0 M solution in ether) was added dropwise *via* syringe and stirred for 15 min. The Me_2CuLi reagent was cooled to -78 °C and to it was added a solution of enonesulfoxide **139** (46.8 mg, 0.2 mmol) in 2 mL of dry THF. Stirring was continued at -78 °C for 30 min, followed by warming to 0 °C over 1 h. The reaction mixture was quenched at 0 °C with 2 mL of saturated NH_4Cl solution and diluted with 2 mL of brine. Extraction with ether (3x10 mL), brine wash and work-up afforded epimeric mixture of dimethyl ketosulfoxide **140** which was used in the next step without further purification.

Yield: 48 mg, 96%

$[\alpha]_D^{25}$: +77.5 ($CHCl_3$, c 4.0)

IR: cm^{-1} 2900, 1700, 1440, 1300, 1210, 1140, 1080, 1040, 740, 680, 610.

PMR: δ 7.70-7.40 (m, 5H, aromatic **H**); 3.79-2.94 (m, 1H, S(O)C**H**); 2.70-1.50 (m, 5H); 1.30-1.18 (m, 3H, C**H**$_3$); 1.12-0.95 (m, 3H, C**H**$_3$).

CMR: δ 206.60, 204.25, 203.43, 141.89, 141.79 131.83, 131.59, 131.42, 131.14, 129.24, 128.88, 125.59, 125.07, 124.38, 124.09, 88.06, 79.43, 79.30, 77.30, 76.89, 67.65, 51.36, 50.42, 50.18, 40.13, 35.83, 35.41, 33.77, 32.59, 30.65, 29.88, 29.50, 29.36, 29.06, 28.24, 25.29, 21.94, 21.06, 20.24, 19.06, 13.94.

***R*-(-)-3,5-dimethylcyclohex-2-en-1-one 131:**

Dimethyl ketosulfoxide **140** (50 mg, 0.2 mmol); $CaCO_3$ (1 mg, 0.01 mmol); CCl_4 (30 mL).

Yield: 19.2 mg, 78%

bp: 100 °C (oil bath)/12 Torr.

$[\alpha]_D^{25}$: -132.8° ($CHCl_3$, c 1.25)

IR: cm^{-1} 2900, 1640, 1430, 1370, 1240, 1140, 1010, 880.

PMR: δ 5.88 (s, 1H, vinyl **H**); 2.50-2.00 (m, 5H); 1.95 (s, 3H, vinyl CH_3); 1.08 (d, J=6 HZ, 3H, CH_3).

CMR: δ 200.25, 162.13, 126.48, 45.24, 39.41, 30.06, 24.35, 21.12.

LRMS: 124 (M^+).

Mercaptoacetone 146:

NaOH (2.0 g, 50 mmol) was added to 13 mL of H_2O and cooled to 0 °C. 100 mmol of H_2S gas [generated by slow addition of aq. HCl (67 mL, 200 mmol, 3 N solution) to FeS (9.0 g, 100 mmol)] was passed till the solution becomes black. The reaction mixture was cooled to -5 °C and then chloroacetone (4.0 mL, 4.6 g, 50 mmol) was added slowly and stirred. Initially slow precipitation occurs and at the end of the reaction the precipitation occurs rapidly at once. Filtered the mixture through buchner funnel and washed with cold H_2O, EtOH and then ether. Recrystallisation from benzene afforded mercaptoacetone **146** as a white solid. The compound was somewhat unstable and underwent decomposition after few months despite storing in the refrigerator.

Yield: 2.5 g, 56%

mp: 110-112 °C

PMR: δ 3.36 (d, J=6 Hz, 2H, SCH_2); 2.28 (s, 3H, $C(O)CH_3$); 1.94 (t, J=6 Hz, 1H, SH).

Thiahydrindenes 147, 148 and Michael adduct 149:

Mercaptoacetone **146** (68 mg, 0.75 mmol) was dissolved in 2 mL of CH_3CN, and to it was added LiCl (32 mg, 0.75 mmol), DBU (113 μL, 116 mg, 0.75 mmol) and enone **143** (50 μL, 48 mg, 0.5 mmol) at rt under N_2 atmosphere. The reaction mixture

was stirred for 4 h at ambient temperature and quenched with 2 mL of brine and extracted with ether (3x10 mL). Work-up afforded 87 mg of mixture (**147**, **148** & **149**) which were separated by SGC (hexane to 20% EtOAc/hexane).

Yield: 37 mg, 44% (inseparable mixture of **147** & **148**)

41 mg, 44% (**149**)

IR: cm^{-1} 3398, 3097, 2941, 2868, 1670, 1540, 1404, 1265, 1192, 930, 893, 850, 746.

PMR: (for **147**) δ 4.36 (br s, 1H, SC**H**); 3.84 (dd, J=15,3 Hz, 1H, SC$\mathbf{H_2}$); 3.62 (dd, J=15,5 Hz, 1H, SC$\mathbf{H_2}$); 2.62-2.24 (m, 2H, C(O)C$\mathbf{H_2}$); 2.04 (s, 3H, vinyl C$\mathbf{H_3}$); 1.84-1.62 (m, 4H);

(for **148**) δ 6.62 (s, 1H, vinyl **H**); 3.00 (t, J=6 Hz, 2H, C(O)C**H**C**H**S); 2.54 (t, J=6 Hz, 2H, C(O)C$\mathbf{H_2}$); 2.44 (s, 3H, vinyl C$\mathbf{H_3}$); 2.26-2.08 (m, 4H);

(for **149**) δ 3.54-3.42 (m, 1H, SC**H**); 3.02 (d, J=10 Hz, 1H, SC$\mathbf{H_2}$); 2.84 (d, J=10 Hz, 1H, SC$\mathbf{H_2}$); 2.60-2.04 (m, 4H, C$\mathbf{H_2}$C(O)C$\mathbf{H_2}$); 2.20 (s, 3H, C(O)C$\mathbf{H_3}$); 2.00-1.50 (m, 4H).

CMR: (for **147**) δ 199.53, 156.82, 118.23, 54.68, 42.79, 41.49, 34.61, 23.86, 16.18.

2-*iso*-Propyl cyclohexanone 151:

A mixture of thiahydrindenes **147** and **148** (33 mg, 0.2 mmol) was refluxed in 2 mL of EtOH with excess of W-2 RaNi for 1h, cooled to rt and filtered through celite. Solvent was removed *in vacuo* and the residue dissolved in 2 mL H_2O. Extraction with ether (3x10 mL) and work-up provided crude 2-*iso*-propyl cyclohexanone **151**. The yield is low because of the volatility of product.

Yield: 11 mg, 36%

IR: cm^{-1} 2940, 2864, 1713, 1450, 1423, 1312, 1222, 1118, 908, 750.

PMR: δ 2.54-2.04 (m, 3H, C**H**C(O)C$\mathbf{H_2}$); 1.82-1.54 (m, 6H); 1.30-1.20 (m, 6H, 2xC$\mathbf{H_3}$); 1.96-1.82 (m, 1H).

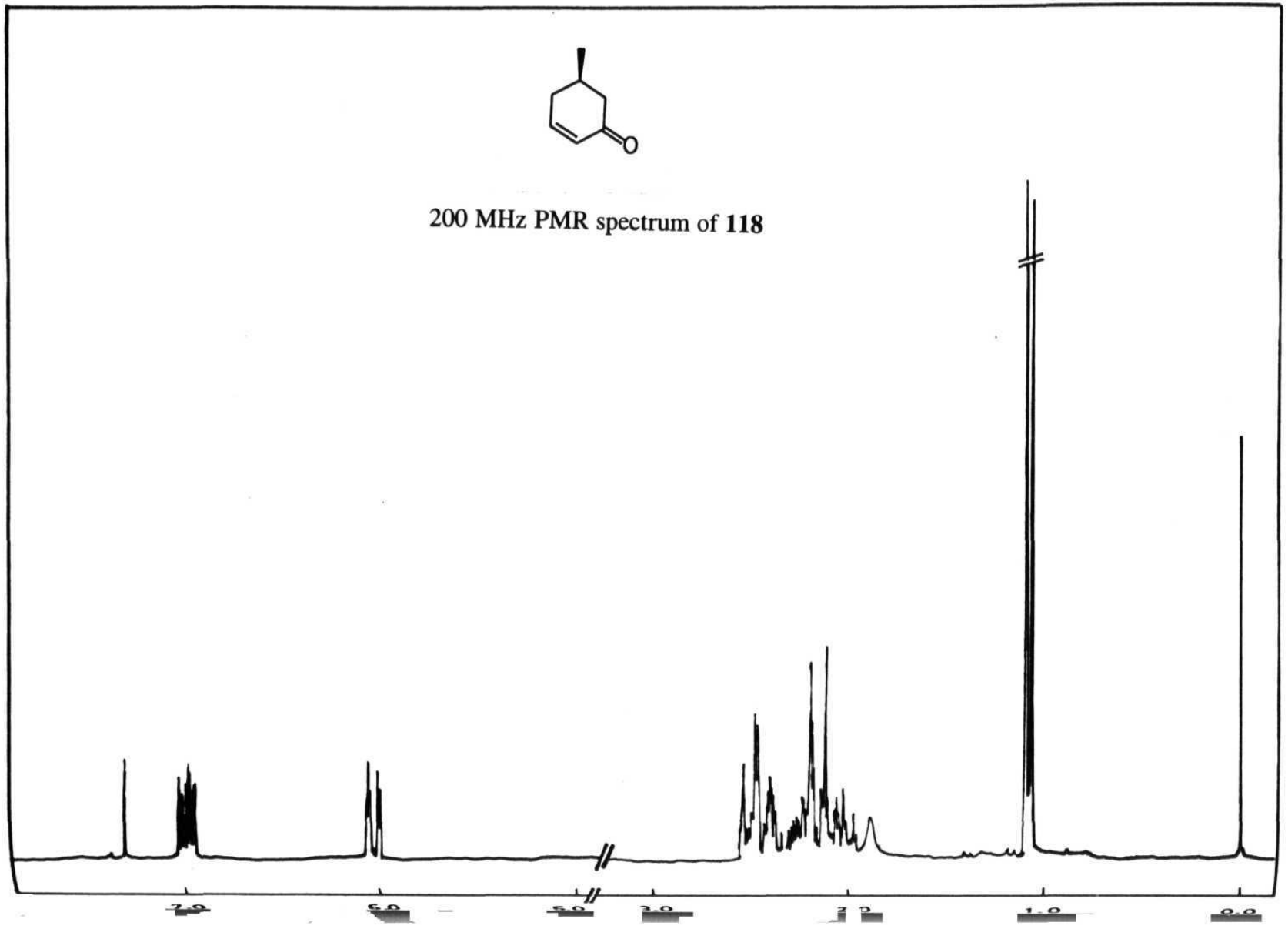
Methyl thiahydrindanes 152:

Bicyclic ketone **147** and **148** (33 mg, 0.2 mmol); CuI (97 mg, 0.5 mmol); MeLi (0.7 mL, 1 mmol, 1.4 M solution in ether); $BF_3.Et_2O$ (61 μL, 71 mg, 0.5 mmol).

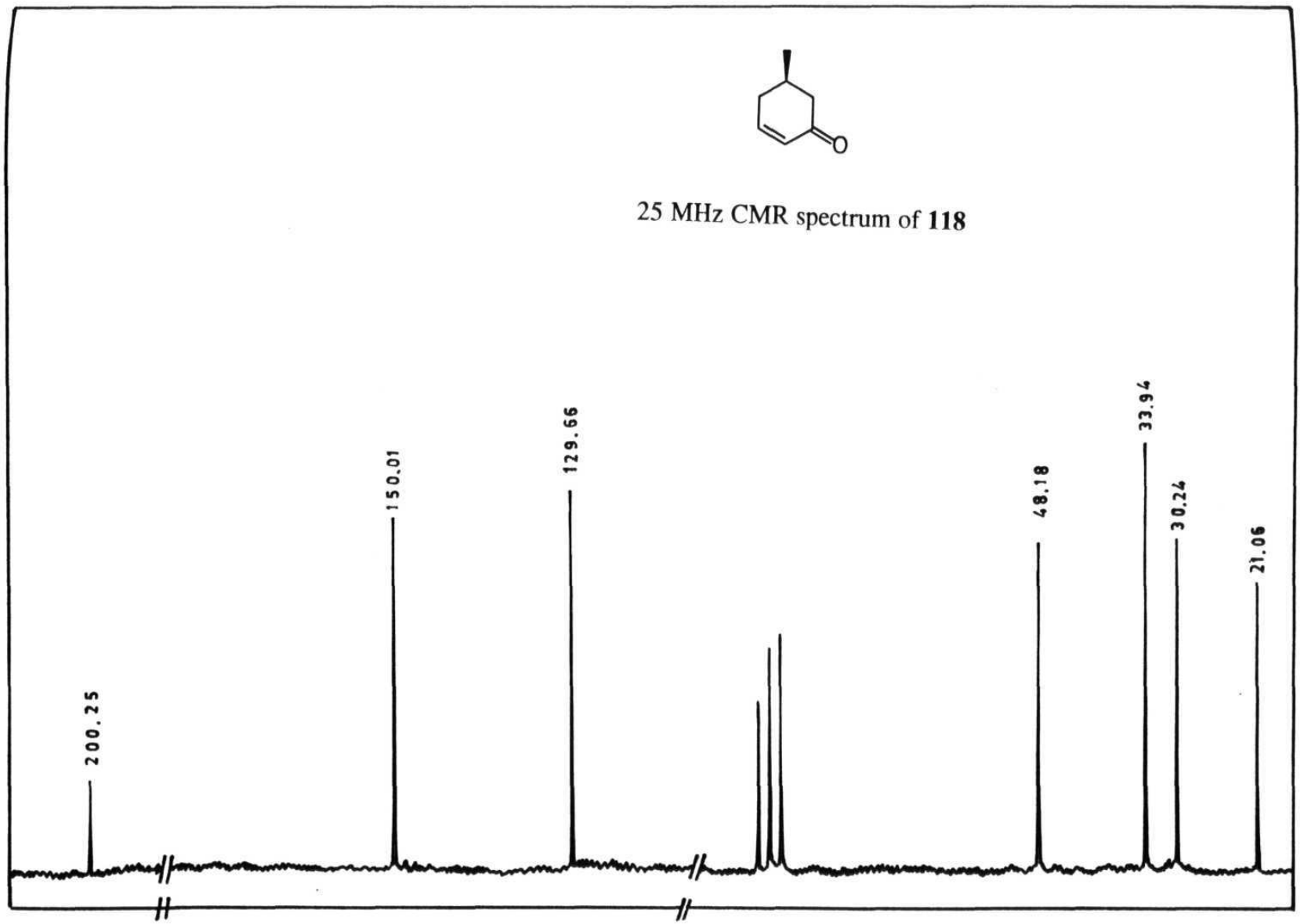
Yield: 8 mg, 23%

IR: cm-1 2930, 1712, 1670, 1439, 1280, 1120, 1028, 720, 700.

PMR: δ 3.54-3.22 (m, 1H, SC**H**); 2.74 (d, J=10 Hz, 1H, SC**H**$_2$); 2.46 (d, J=10 Hz, 1H, SC**H**$_2$); 2.32-2.10 (m, 3H, C**H**C(O)C**H**$_2$); 1.82-1.48 (m, 4H); 1.26 (s, 3H, C**H**$_3$); 1.16 (s, 3H, C**H**$_3$).

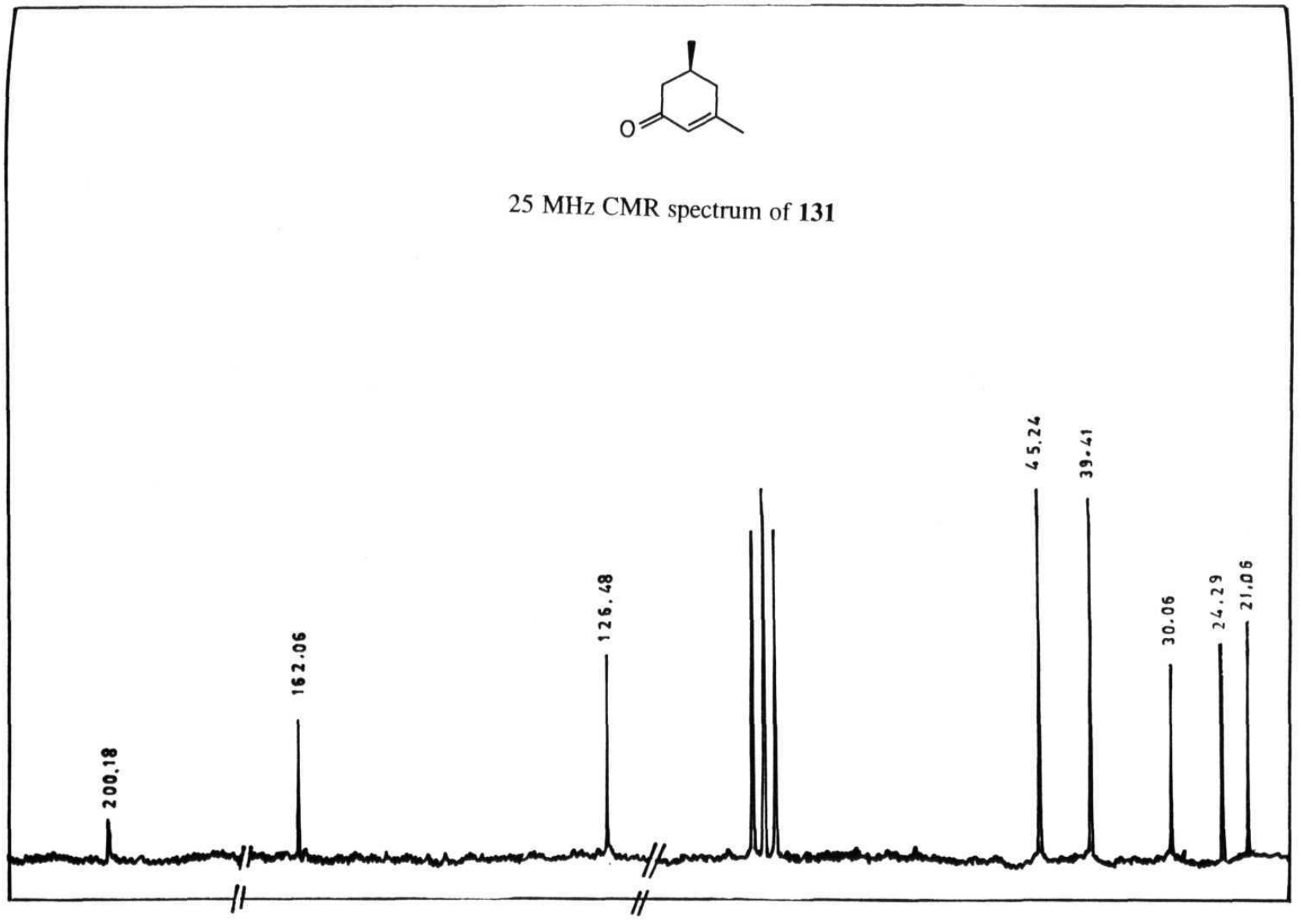


200 MHz PMR spectrum of **118**

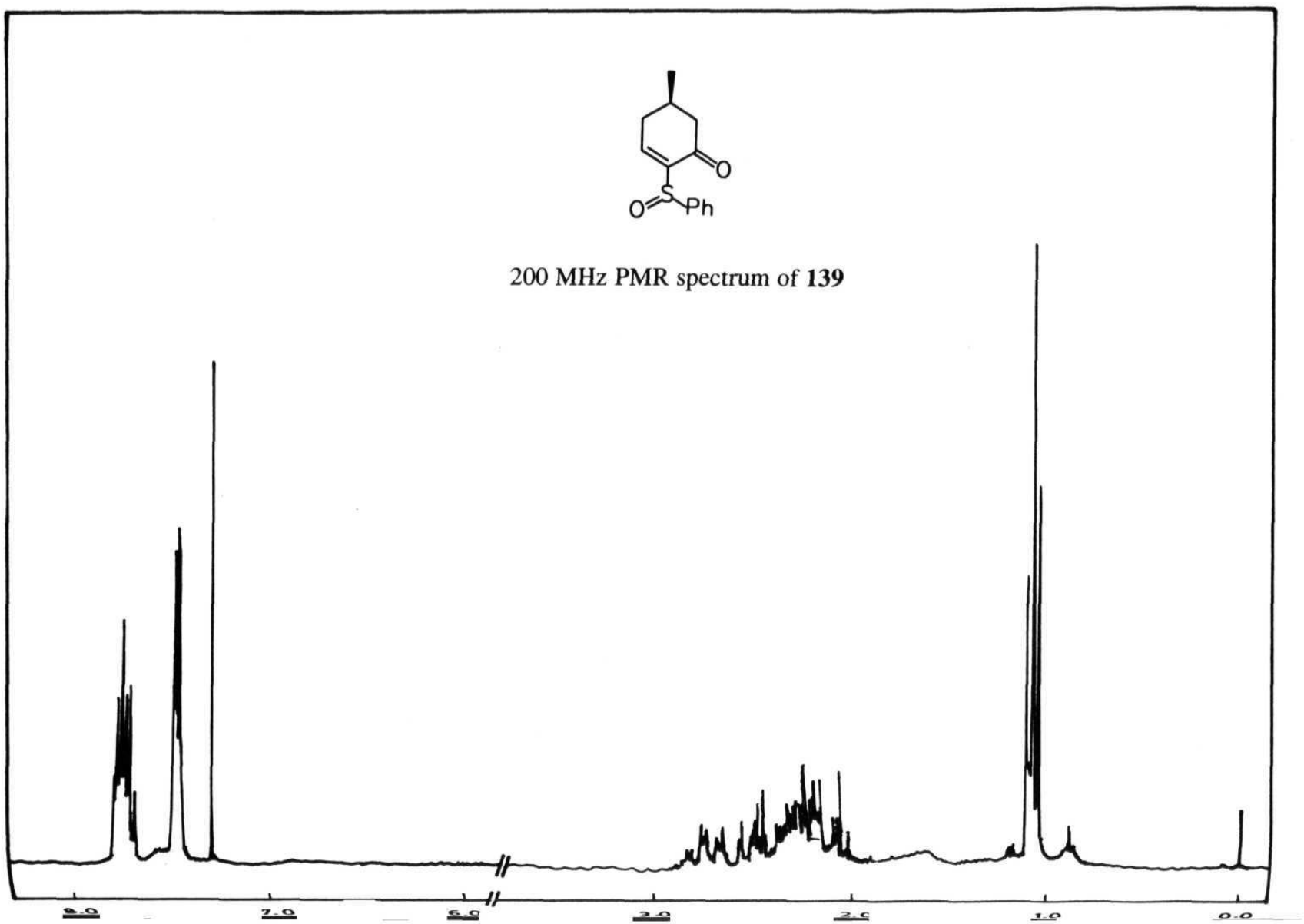


25 MHz CMR spectrum of **118**

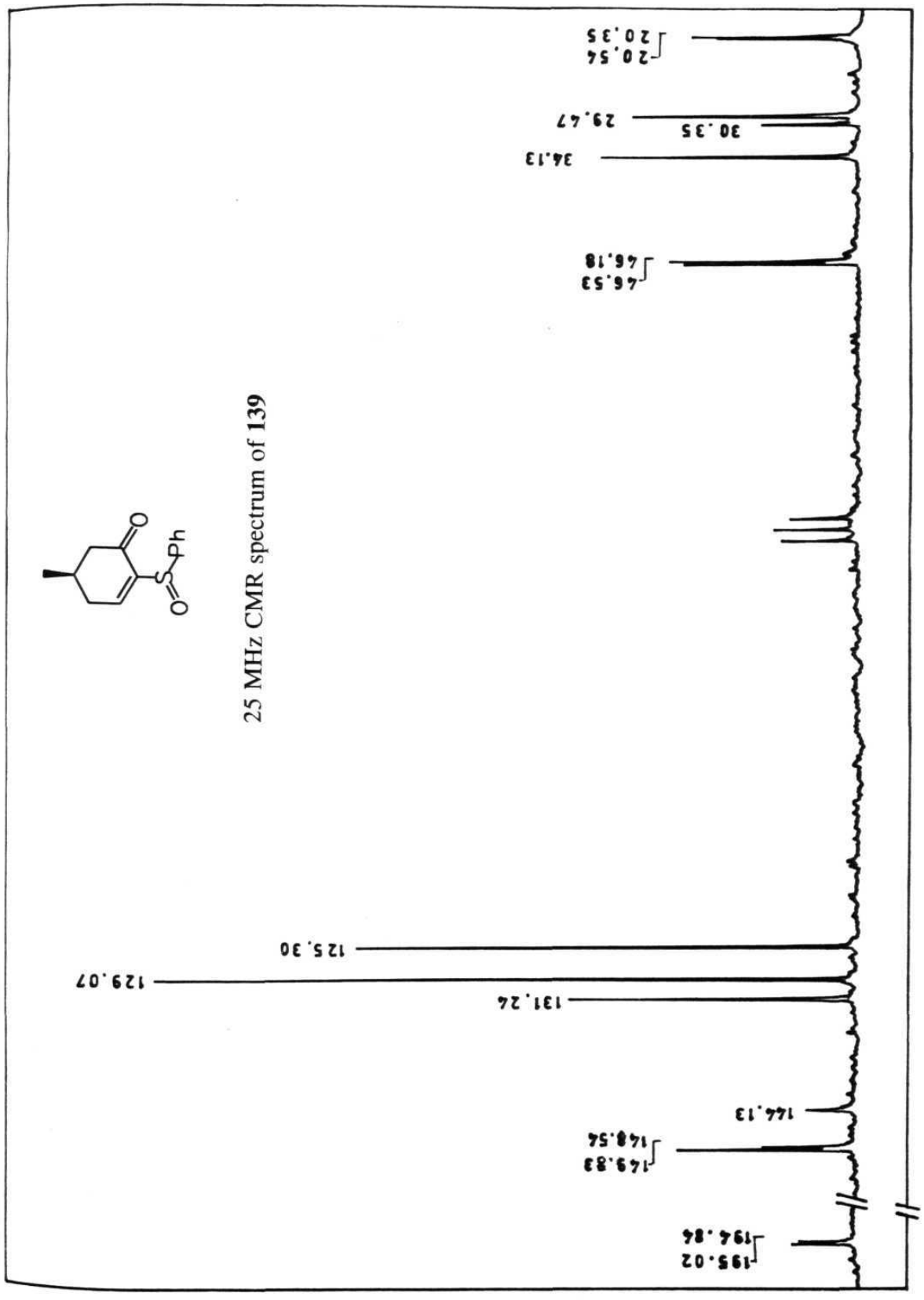
200 MHz PMR spectrum of **131**



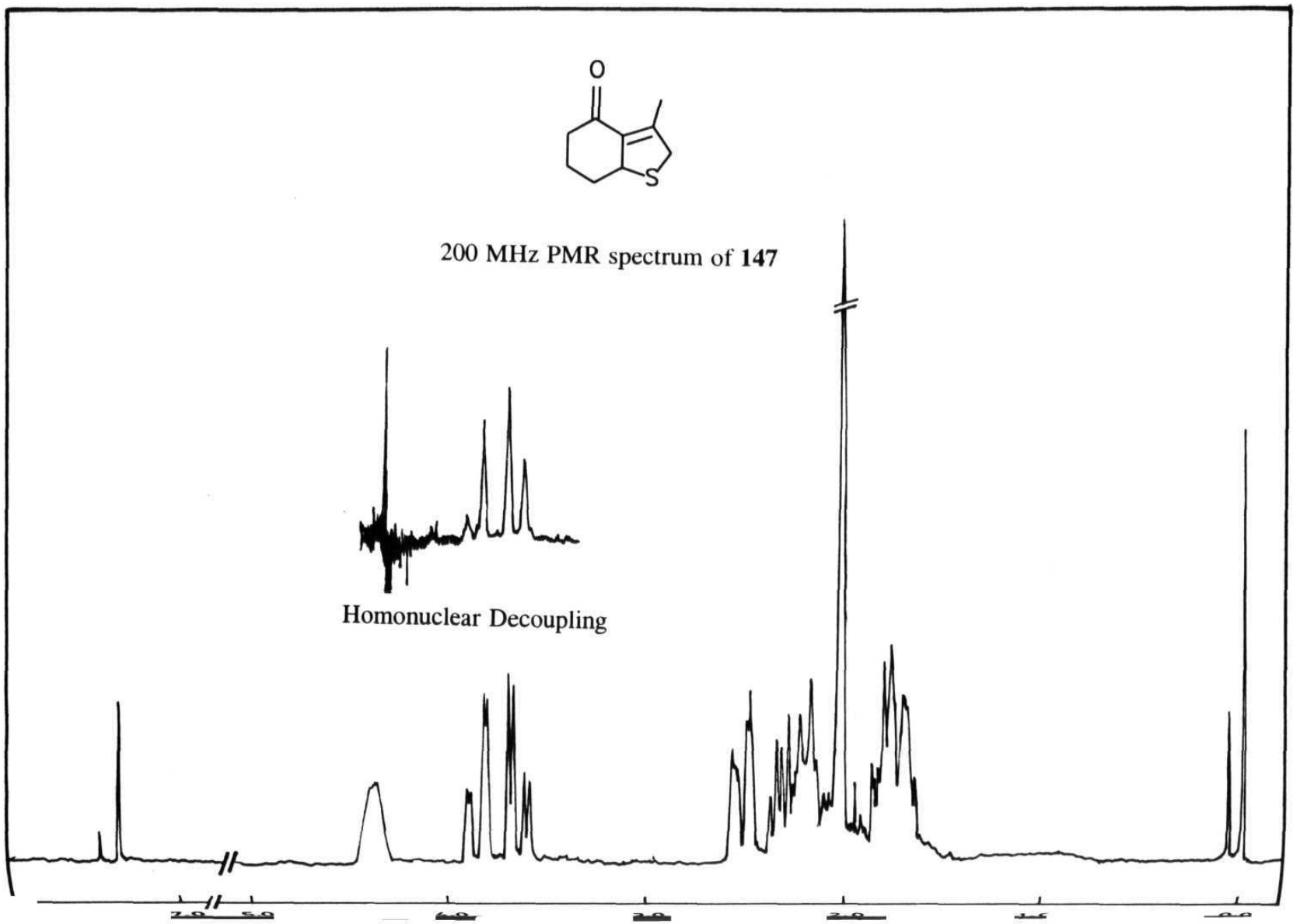
25 MHz CMR spectrum of **131**

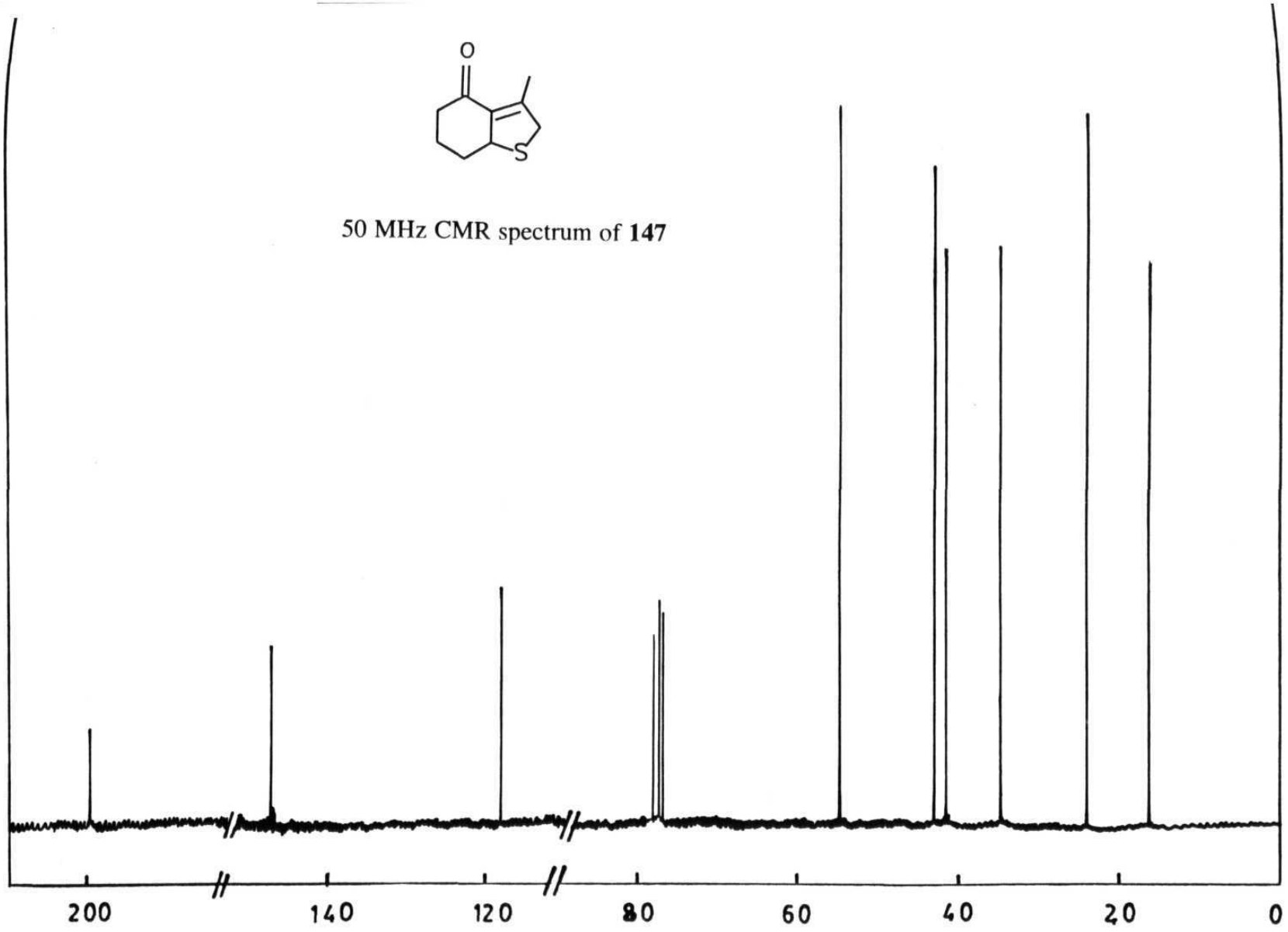


200 MHz PMR spectrum of **139**

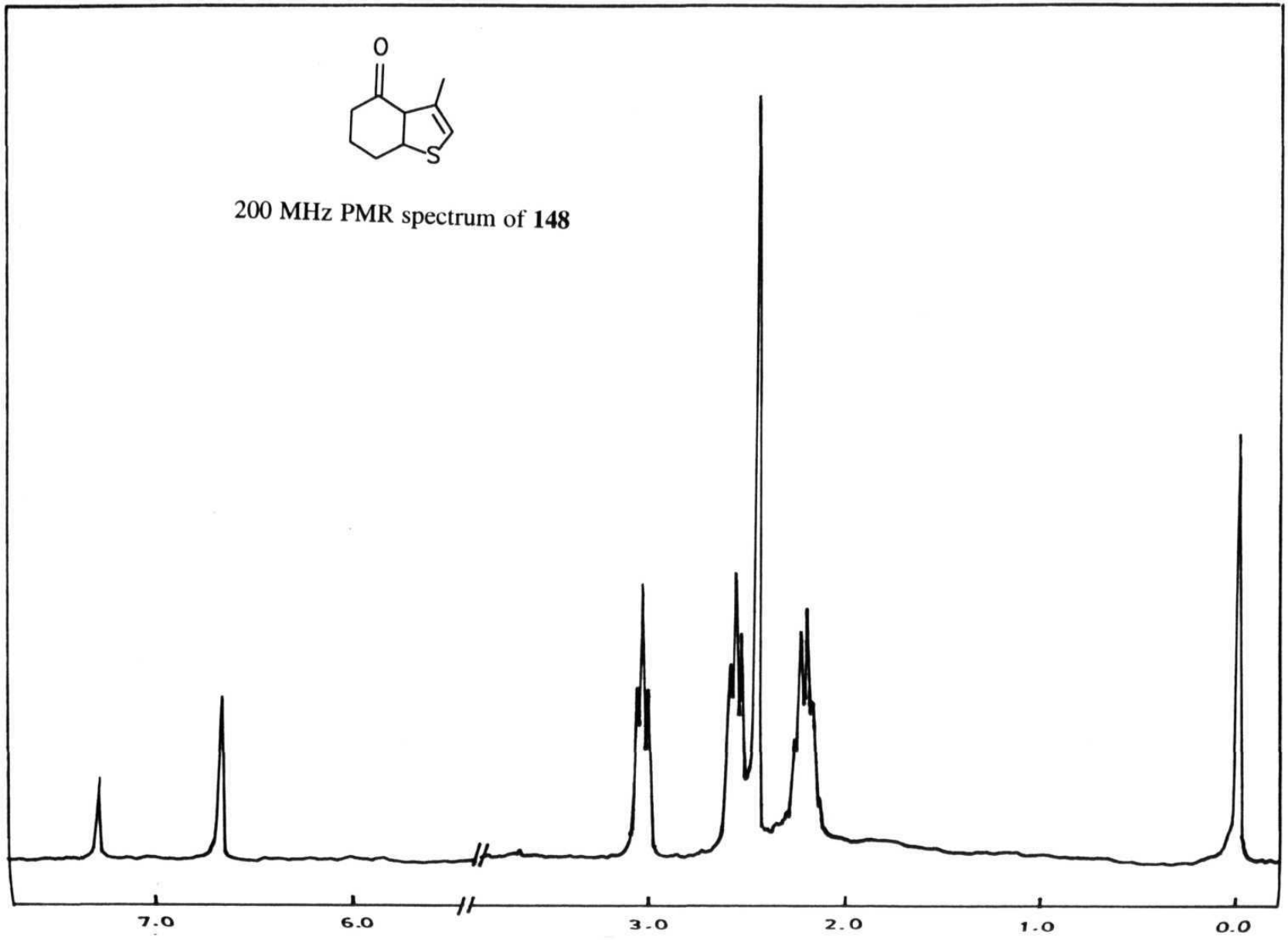


25 MHz CMR spectrum of **139**


O
S
200 MHz PMR spectrum of **147**
Homonuclear Decoupling



50 MHz CMR spectrum of **147**



200 MHz PMR spectrum of **148**

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CHAPTER-3
SYNTHESIS OF IRIDOID TYPE-I CYCLOPENTAPYRANONE SKELETON

3.1. INTRODUCTION:

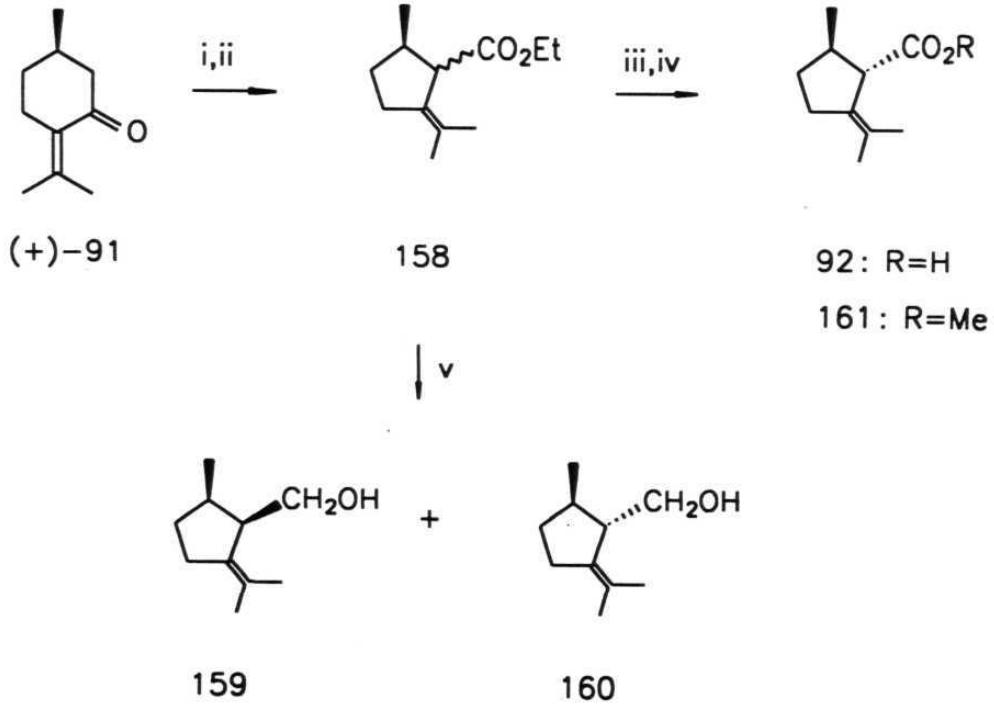
The efforts to synthesise *S*-pulegone were described in the previous chapter. While that work was ongoing the synthesis of 7*R*-cyclopentapyranone **59** which leads to the unnatural iridoid lactones was also being carried out. Based on the retrosynthetic analysis discussed earlier (Chapter-2, Scheme-1) the synthesis of 7*R*-pyranone **59** was initiated to establish the viability of the proposed route.

3.2. SYNTHESIS OF 7*R*-(-)-PYRANONE:

R-Pulegone **91** was converted to ethyl pulegenate **158** according to the procedure of Marx [1]. Addition of Br_2 to *R*-Pulegone at 0 °C for 15 min provided a mixture of dibromide and unreacted starting material. Without isolation the crude mixture was subjected for Favorskii rearrangement. The dibromide was treated with NaOEt in EtOH at reflux for 1 h and then at rt for 12 h to afford ethyl pulegenate **158** as a mixture of *syn* and *anti* isomers. The crude product was contaminated with unreacted *R*-pulegone which was removed by converting it to its water soluble semicarbazone. Attempted separation of *syn*- and *anti*-ethyl pulegenates **158** by silica gel column chromatography was unsuccessful. The PMR spectrum of ethyl pulegenates **158** was in agreement with the data reported for pure *syn* and *anti* isomers [2]. The *syn*/*anti* ratio was determined to be 60:40 by integration of C**H** doublet adjacent to CO_2Et at δ 3.35 (*syn*) and 2.90 (*anti*). The same ratio was confirmed by GC analysis. We were somewhat surprised to find that the *syn* isomer predominates, because *anti*-ethyl pulegenate is reported [1] to be the major isomer formed (75:25) under the equilibrium reaction conditions. The 60:40 ratio was further confirmed by reduction of the ester with $LiAlH_4$ to diastereomeric mixture of alcohols **159** and **160**, which were easily separated by SGC and isolated in pure form.

The *syn/anti* mixture of ethyl pulegenate **158** was converged to the desired and thermodynamically stable *anti*-methyl pulegenate **161** using Vogel's procedure [3]. Ethyl pulegenate **158** was refluxed in ethanolic potassium hydroxide for 4 h and acidified with 10% HCl to afford *anti*-pulegenic acid **92**. Without isolation *anti*-pulegenic acid **92** was treated with an ethereal solution of diazomethane [4] to afford *anti*-methyl pulegenate **161** in 60% yield. PMR spectrum of **161** displayed C**H** doublet adjacent to CO_2Me at δ 2.96 and CO_2CH_3 singlet at δ 3.67.

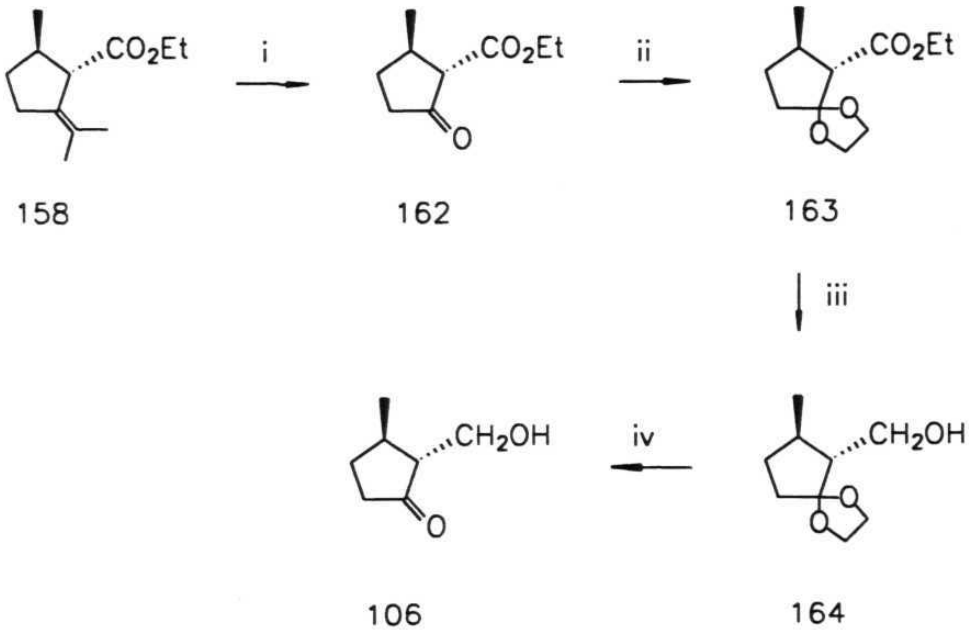
Scheme-1



Reagents: *i) Br_2, ether, 0 °C, 15 min; ii) NaOEt, EtOH, rt, 12 h; iii) KOH, EtOH, then 10% HCl; iv) CH_2N_2, ether; v) $LiAlH_4$, ether, 0 °C, 1 h.*

Marx and Norman [1] prepared ketoalcohol **106** from *anti*-ethyl pulegenate **158** in 4 steps. Ozonolysis of **158** at -96 °C to ketoester **162**, which was protected with ethanediol to corresponding ketalester **163**. $LiAlH_4$ reduction of **163** gave ketalalcohol **164**, which on mild deketalisation furnished ketoalcohol **106**.

Scheme-2

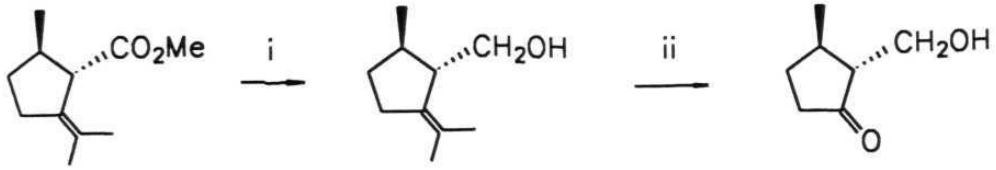


Reagents: i) O_3, EtOAc, -96 °C; ii) $(CH_2OH)_2$, p-TsOH.H_2O, benzene; iii) $LiAlH_4$, ether; iv) H_3O^+.

We found it expedient to prepare ketoalcohol **106** with a modified route in which the protection-deprotection steps were completely avoided. Thus, reduction of *anti*-methyl pulegenate **161** with $LiAlH_4$ in ether at 0 °C for 1 h provided alkenealcohol **160**. The *anti*-alcohol **160** was characterised by the AB CH_2O quartet centred at δ 3.48 (J=10 Hz) and hydroxy band at 3300 cm^{-1}.

The alcohol **160** was ozonised at -78 °C in CH_2Cl_2 and reductive work-up with DMS afforded somewhat unstable β-hydroxyketone **106** along with the elimination product exocyclic olefin **165**. The appearance of exocyclic methylene doublets at δ 5.26 and 5.98 suggested that elimination of H_2O from β-hydroxyketone **106** was occurring to form enone **165,** presumably due to the acidic nature of O_3. When the ozonolysis was carried out under buffered conditions with $NaHCO_3$ in 1:4 MeOH-CH_2Cl_2 at -78 °C the only product obtained was β-hydroxyketone **106**; no elimination product was observed. The material suffered significant decomposition upon attempted SGC purification.

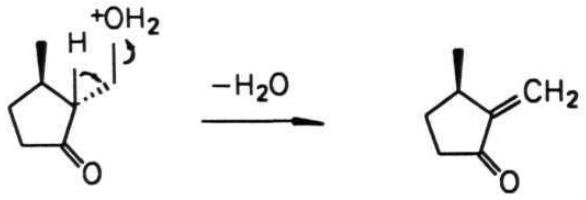
Scheme-3



161 160 106

Reagents: *i) $LiAlH_4$, ether O °C, 1 h; ii) O_3, 1:4 MeOH-CH_2Cl_2, $NaHCO_3$, -78 °C, then DMS, O °C.*

Scheme-4



106 165

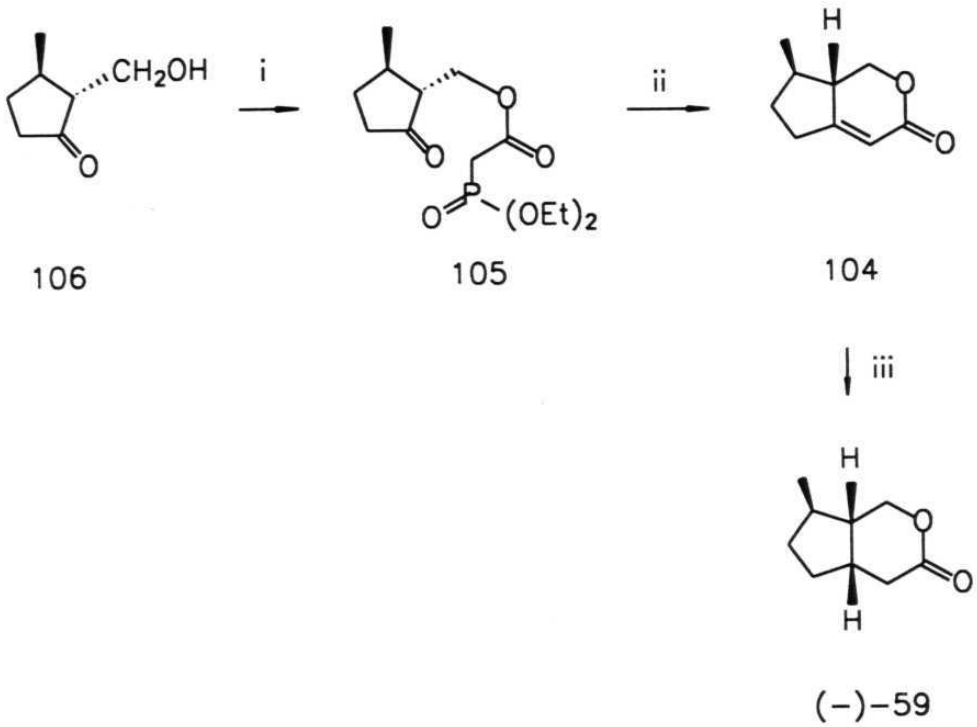
The crude β-hydroxyketone **106** was immediately esterified to ketophosphonate **105** under neutral conditions with dicyclohexylcarbodiimide (DCC) [5] and diethylphosphonoacetic acid [6] in CH_2Cl_2 at 0 °C for 1 h. The characteristic CH_2 doublet adjacent to $P(O)(OEt)_2$ at δ 2.94 with 22 Hz coupling supported the structure of phosphonate **105**.

The intramolecular Horner reaction of ketophosphonate **105** under the conditions developed earlier in our laboratory [7] (DBU, LiCl, CH_3CN, rt, 1 h) provided the unsaturated lactone **104** in 57% yield after column chromatography. The lactone **104** was evidenced from the appearance of vinylic proton at δ 5.76 and IR carbonyl stretch at 1720 cm^{-1}.

Highly stereoselective hydrogenation [8] of unsaturated lactone **104** with 10% Pd-C in ethyl acetate occured to install the third stereogenic centre and afforded bicyclic lactone **59**. The PMR spectrum of **59** showed AB CH_2O pattern at δ 4.26 (dd, J=12,4 Hz) and 4.06 (dd, J=12,6 Hz) in agreement with the reported data [9] for *R*-cyclopentapyranone **59**. The optical rotation of lactone **59** is $[\alpha]_D^{25}$ -92.0° ($CHCl_3$, c 1.0) and -82.0° (CCl_4, c 0.5). The reported [9] value is $[\alpha]_D^{25}$ -72.5° (CCl_4, c 1.7). Thus, pyranone (-)-**59** was obtained in higher ee than so far reported.

The proposed scheme was successfully applied for the enantioselective synthesis of pyranone (-)-**59** from *R*-pulegone. The contiguous stereogenic centres at the *cis* fused ring junction C4a-C7a are installed under complete stereo- and enantiocontrol communicated through the asymmetric C7 methyl group.

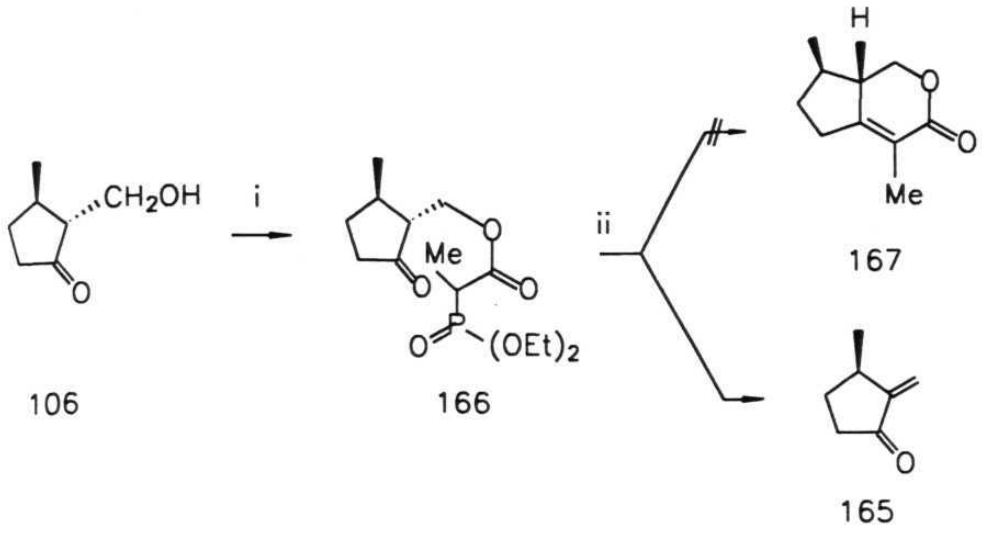
Scheme-5



Reagents: *i) $(EtO)_2P(O)CH_2CO_2H$, DCC, CH_2Cl_2, O °C, 1h; ii) DBU, LiCl, CH_3CN, rt, 1 h; iii) 10% Pd-C, EtOAc, atmospheric pressure, 6 h.*

In an attempt to synthesise iridomyrmecin **10** directly, the ketoalcohol **106** was treated with diethylphosphonopropionic acid [6b, 10] under optimised DCC conditions to afford methyl ketophosphonate **166**. Exposure of phosphonate **166** to intramolecular HWE reaction with DBU/LiCl did not give unsaturated lactone **167**; only starting material was recovered. Use of stronger base (NaH, THF) afforded a mixture of elimination product and starting material. The intramolecular HWE reaction of methyl phosphonate **166** is slower because of steric congestion and formation of tetrasubstituted olefinic product **167** is not observed. Therefore, no HWE reaction occurs and product arising out of competing elimination is isolated.

Scheme-6



Reagents: i) $(EtO)_2P(O)CH(CH_3)CO_2H$, DCC, CH_2Cl_2, O °C, 1 h, ii) base.

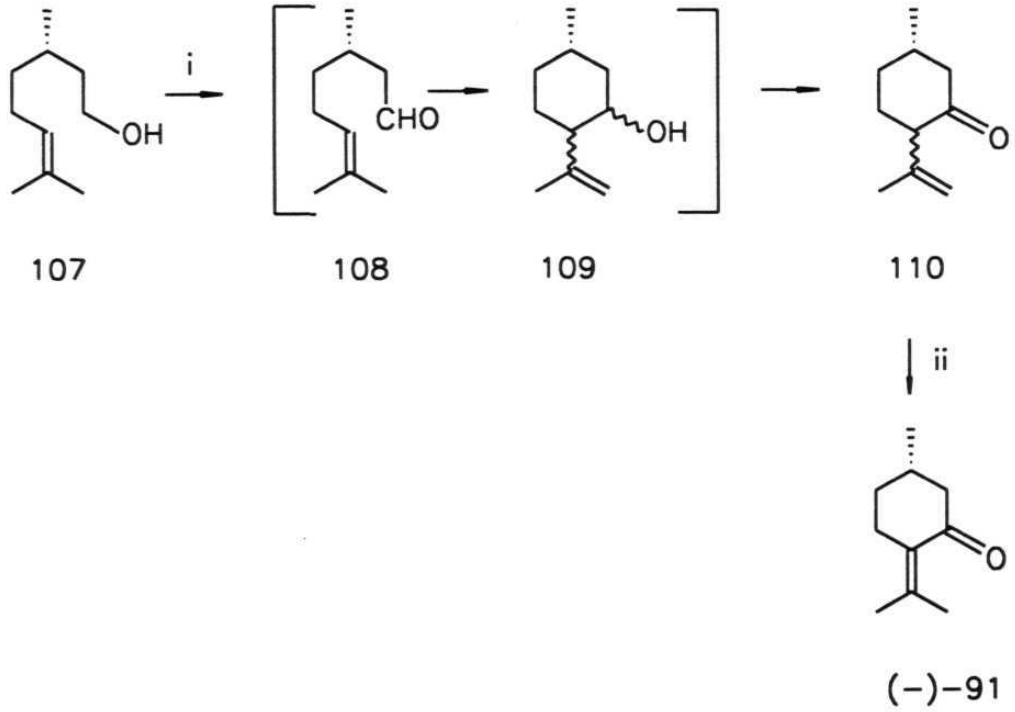
3.3. SYNTHESIS OF 7*S*-(+)-PYRANONE:

We next tutrned to the task of synthesising 7*S*-pyranone **59** which will lead to natural iridoids. Applying the established conditions, the synthesis of cyclopentapyranone (+)-**59** was carried out starting from *S*-pulegone **91**. The best and most convenient method for synthesising *S*-pulegone **91** was chosen from those published in the literature. Corey's procedure [11] appeared to be the most attractive in terms of availability of starting chiron (*S*-β-citronellol), the number of steps (two) and overall yield (70%).

Thus, oxidative cyclisation of *S*-citronellol **107** (Aldrich, $[\alpha]_D^{20}$ -3.5°, neat) with PCC gave *iso*-pulegone **110** by ene cyclisation on citronellal **108**. Isomerisation of *iso*-pulegone **110** to pulegone **91** with ethanolic potassium hydroxide was

unsuccessful; however, acid catalysed conjugation was more fruitful. Refluxing *iso*-pulegone **110** in benzene with catalytic amount of *p*-TsOH.H_2O for 6 h provided *S*-pulegone **91** as evidenced from the disappearance of vinylic CH_2 singlets at δ 4.86 and 4.65.

Scheme-7



107 108 109 110

(−)−91

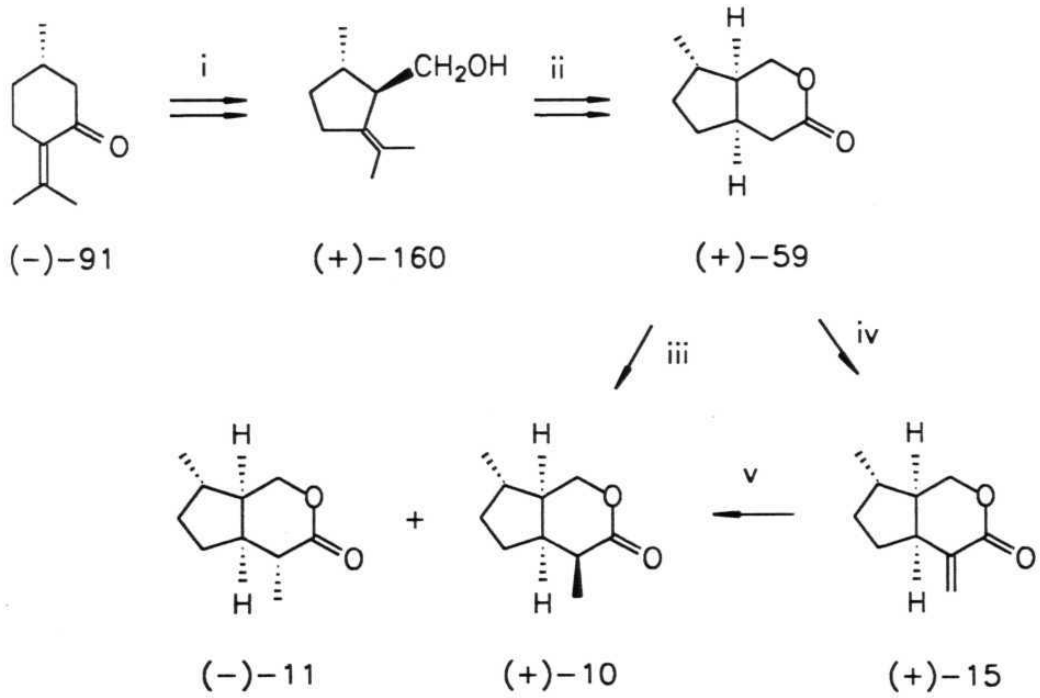
Reagents: *i) PCC, CH_2Cl_2, rt, 24 h; ii) p-TsOH.H_2O, benzene, reflux, 6h.*

The optical purity of *S*-pulegone obtained by this route was 66% ($[\alpha]_D^{25}$ -15.3°, neat) when compared with the optical rotation of *R*-pulegone ($[\alpha]_D^{20}$ +22.0°, neat) used in our study. A value of $[\alpha]_D^{20}$ +23.0° (neat) is reported for high purity *R*-pulegone. The *S*-citronellol ($[\alpha]_D^{20}$ -3.5°, neat) used as the starting chiron had an

optical purity of 86% (pure $[\alpha]_D^{20}$ -4.1°, neat). The ee of *S*-pulegone is lower compared to the *R*-pulegone used for the synthesis of pyranone (-)-**59**.

Employing the conditions optimised earlier, *S*-pulegone **91** was converted to cyclopentapyranone (+)-**59** according to the protocol for *R*-series. All the intermediates displayed satisfactory IR and PMR spectra with somewhat lower optical rotations compared to compounds in the *R*-series. Stereoselective *exo*-face hydrogenation of unsaturated lactone *S*-(+)-**104** furnished pyranone *S*-(+)-**59**. The optical purity of pyranone (+)-**59** was lower ($[\alpha]_D^{25}$ +71.9°, $CHCl_3$, c 0.16, 80%

Scheme-8



Reagents: i) Scheme-1; ii) Scheme-5; iii) ref-9a,12; iv) ref-13; v) ref-14.

ee) compared to pyranone (-)-**59** ($[\alpha]_D^{25}$ -92.0°, $CHCl_3$, c 0.5) because of the lower optical purity of the starting material.

Since, the *cis*-fused pyranone *S*-(+)-**59** is the penultimate precursor for the synthesis of natural iridoids [12-14], a formal synthesis of (+)-iridomyrmecin **10**, (-)-isoiridomyrmecin **11** and (+)-teucriumlactone **15** is accomplished.

3.4. EXPERIMENTAL AND SPECTRA:

S-(-)-β-Cilronellol was purchased from Aldrich, USA with $[\alpha]_D^{20}$ -3.5 °(neat), 86% optical purity.

_R_-Ethyl pulegenate 158:

To a stirred mixture of *R*-pulegone **91** (1.49 g, 10 mmol) and anhydrous $NaHCO_3$ (250 mg, 3.0 mmol) in 10 mL of dry ether at 0 °C under N_2 atmosphere was added bromine (500 μL, 1.6 g, 10 mmol) dropwise and stirring continued for another 15 min at the same temperature. Meanwhile, a solution of sodium ethoxide was prepared by adding sodium (500 mg, 20 mmol) to 20 mL of dry ethanol. The above mixture of dibromide was filtered to this NaOEt solution at 0 °C. The mixture was warmed to rt and refluxed for 1h, stirring continued for another 12 h at rt. The reaction mixture was neutralised with 20 mL of 5% aq. HCl and extracted with ether (3x20 mL). Work-up provided 1.8 g of oily material which contained some unreacted *R*-pulegone **91** and ethyl pulegenate **158**.

To a solution of NaOAc (750 mg, 9.0 mmol) in 6 mL of water was added semicarbazide hydrochloride (750 mg, 6.7 mmol) and heated to make a clear solution. The above crude oil was added to this reaction mixture and 6 mL of boiling EtOH was

added to make the solution homogeneous. The mixture was refluxed for 2 h, then cooled to rt and stirred for 12 h at the same temperature. The reaction mixture was diluted with 10 mL of water and extracted with hexane (3x20 mL). The semicarbazone of pulegone is readily soluble in water and separated from esters during extractive isolation. Usual work-up afforded 1.6 g of crude ester **158**, which was purified by SGC using hexane as eluent.

Yield: 1.2 g, 62%

$[\alpha]_D^{25}$: +35.0° ($CHCl_3$, c 5.0)

IR: cm^{-1} 2900, 1710, 1440, 1360, 1320, 1280, 1220, 1130, 1020, 940.

PMR: δ 4.14 (q, J=6 Hz, 2H, OCH_2); 3.36 (d, J=6 Hz, *syn*) and 2.92 (d, J=6 Hz, *anti*), (1H, $CHCO_2$); 2.54-2.12 (m, 3H); 2.06-1.90 (m, 1H); 1.84-1.72 (m, 1H); 1.64-1.56 (m, 6H, 2xCH_3); 1.28 (t, J=6 Hz, 3H, CH_2CH_3); 1.04 (overlapping d, J=6 Hz, 3H, CH_3).

CMR: δ 175.36, 173.22, 135.01, 134.25, 125.43, 125.39, 59.84, 59.43, 55.53, 52.59, 40.47, 38.71, 33.47, 32.47, 30.18, 29.95, 21.17, 20.93, 20.70, 19.79, 15.39, 14.11, 14.00.

S-Ethyl pulegenate 158:

$[\alpha]_D^{25}$: -18.5° ($CHCl_3$, c 2.0)

***R-anti*-Methyl pulegenate 161:**

To a solution of ethyl esters **158** (980 mg, 5.0 mmol) in 5 mL of dry ethanol was added KOH (560 mg, 10.0 mmol) in 2.5 mL of H_2O. The resulting solution was kept at reflux for 4 h and cooled to rt. After dilution with 10 mL of H_2O the solution was extracted with ether (2x20 mL) to remove the neutral products. The alkaline solution was acidified with 10% HCl (pH 2) and the mixture was extracted with ether (3x20 mL).

10 mL of 50% KOH solution and 20 mL of ether were placed in a conical flask and cooled to -5 °C. N-Nitroso-N-methylurea (1.0 g, 10.0 mmol) was added slowly portionswise with shaking of the flask. The ether layer containing CH_2N_2 turns yellow. The above ether extract was treated with this ethereal diazomethane solution till the yellow colour persists. Excess CH_2N_2 was quenched with acetic acid (0.8 mL, 600 mg, 10.0 mmol) and the reaction mixture was washed with saturated $NaHCO_3$ solution and with brine. Usual work-up and SGC purification using hexane as eluent afforded *anti*-methyl pulegenate **161**.

Yield: 570 mg, 63%

IR: cm^{-1} 2900, 1720, 1450, 1370, 1340, 1295, 1225, 1140, 1030.

$[\alpha]_D^{25}$: +62.8° ($CHCl_3$, c 5.0)

PMR: δ 3.67 (s, 3H, OCH_3); 2.96 (d, J=6 Hz, 1H, $CHCO_2$); 2.42-2.18 (m, 3H); 2.04-1.86 (m, 1H); 1.64 (s, 3H, vinyl CH_3); 1.56 (s, 3H, vinyl CH_3); 1.35-1.18 (m, 1H); 1.04 (d, J=6 Hz, 3H, CH_3).

CMR: δ 176.18, 134.30, 125.89, 55.53, 51.47, 40.70, 33.59, 30.29, 21.35, 20.76, 19.47.

***S-anti*-Methyl pulegenate 161:**

$[\alpha]_D^{25}$: -37.5° ($CHCl_3$, c 2.0)

***R-anti*-Alkenealcohol 160:**

To a suspension of $LiAlH_4$ (152 mg, 4.0 mmol) in 5 mL of dry ether was added a solution of ester **161** (546 mg, 3.0 mmol) in 5 mL of dry ether slowly dropwise at 0 °C under N_2 atmosphere. Stirred it for 1 h and quenched the reaction mixture with 0.16 mL of H_2O, 0.16 mL of 15% NaOH and again with 0.4 ml of H_2O. To this mixture anhydrous $MgSO_4$ was added and filtration through celite gave 412 mg of alkenealcohol **160** which was purified by SGC (hexane to 10% EtOAc/hexane).

Yield: 378 mg, 82%

$[\alpha]_D^{25}$: -23.2° ($CHCl_3$, c 5.0)

IR: cm^{-1} 3300, 2900, 1440, 1370, 1050, 1020.

PMR: δ 3.48 (ABq, J=8,2 Hz, 2H, OCH_2); 2.36 (t, J=6 Hz, 1H, allyl CH); 2.24 (t, J=6 Hz, 1H); 2.22-2.02 (m, 2H); 1.94-1.76 (m, 1H); 1.70 (s, 3H, vinyl CH_3); 1.65 (s, 3H, vinyl CH_3); 1.58 (br s, 1H, OH); 1.38-1.18 (m, 1H); 0.96 (d, J=6 Hz, 3H, CH_3).

CMR: δ 135.47, 125.06, 64.41, 52.71, 36.18, 31.53, 28.77, 21.42, 21.15, 20.47.

Analysis: Calculated for $C_{10}H_{18}O$: C=77.87%, H=11.76%; Found C=77.92%, H=11.80%

S-anti-**Alkenealcohol 160:**

$[\alpha]_D^{25}$: +18.0° ($CHCl_3$, c 1.0)

R-syn-**Alkenealcohol 159:**

$[\alpha]_D^{25}$: +55.9° ($CHCl_3$, c 2.5)

IR: cm^{-1} 3300, 2900, 1450, 1370, 1160, 1020.

PMR: δ 3.70 (dd, J=12,6 Hz, 1H, OCH_2); 3.43 (dd, J=12,8 Hz, 1H, OCH_2); 2.73 (q, J=6 Hz, 1H, allyl CH); 2.38-2.15 (m, 2H, allyl CH and OH); 2.10-1.95 (m, 1H); 1.86-1.72 (m, 1H); 1.75 (s, 3H, vinyl CH_3); 1.64 (s, 3H, vinyl CH_3); 1.54-1.30 (m, 2H); 1.06 (d, J=6 Hz, 3H, CH_3).

CMR: δ 136.95, 125.12, 61.89, 49.06, 37.53, 32.06, 29.36, 21.54, 21.00, 15.35.

R-**Ketoalcohol 106:**

To a solution of alkenealcohol **160** (154 mg, 1.0 mmol) in 15 mL of 1:4 MeOH-CH_2Cl_2 containing $NaHCO_3$ (840 mg, 10 mmol), a stream of ozone was passed at -78 °C until the blue colour persisted. The reaction mixture was flushed with oxygen for 5 min. DMS (300 μL, 200 mg, 4.0 mmol) was added dropwise to the reaction mixture at 0 °C and then stirred for 2 h at 0 °C to 10 °C. Removal of solvent afforded 286 mg of

ketoalcohol **106** which was used in subsequent reaction without further purification. The only impurity in the crude concentrate was DMSO (δ 2.64).

Yield: 286 mg (crude)

IR: cm^{-1} 3400, 2880, 1710, 1390, 1250, 1120, 1020, 940.

PMR: δ 3.90 (dd, J=10,2 Hz, 1H, OCH_2); 3.72 (dd, J=10,6 Hz, 1H, OCH_2); 2.48-2.30 (m, 1H); 2.24-2.00 (m, 3H); 1.94-1.74 (m, 1H); 1.56-1.28 (m, 2H); 1.16 (d, J=6 Hz, 3H, CH_3).

***R*-Ketophosphonate 105:**

To a solution of ketoalcohol **106** (192 mg, 1.5 mmol) in 1 mL of dry CH_2Cl_2 at 0 °C under N_2 atmosphere was added a solution of diethylphosphonoacetic acid (392 mg, 2.0 mmol) in 1 mL of dry CH_2Cl_2. Upon addition of DCC (412 mg, 2.0 mmol) to the reaction mixture, a white precipitate immediately formed. The heterogeneous mixture was stirred for 1 h and filtered through celite and concentrated. The resulting oil, contaminated with a white solid, was taken up in 10 mL of 1:1 ether-hexane and filtered through celite and concentrated to give 651 mg of oily compound which was purified by SGC (20% EtOAc/hexane to 50% EtOAc/hexane).

Yield: 300 mg, 65%

$[\alpha]_D^{25}$: +61.0° ($CHCl_3$, c 5.0)

IR: cm^{-1} 2900, 1730, 1450, 1380, 1260, 1110, 1020, 960, 840.

PMR: δ 4.42 (dd, J=12,4 Hz, 1H, OCH_2); 4.34 (dd, J=12,4 Hz, 1H, OCH_2); 4.22-4.06 (m, 4H, 2xOCH_2); 2.94 (d, J=22 Hz, 2H, P(O)CH_2C(O)); 2.46-2.04 (m, 4H); 1.96-1.82 (m, 1H); 1.52-1.40 (m, 1H); 1.34 (t, J=6 Hz, 6H, 2xCH_3); 1.18 (d, J=6 Hz, 3H, CH_3).

CMR: δ 218.96, 159.60, 62.59, 62.36, 61.42, 55.42, 38.00, 33.82 (d, J=135 Hz, CH_2P(O)); 33.71, 29.13, 18.77, 16.12, 15.88.

***S*-Ketophosphonate 105:**

$[\alpha]_D^{25}$: -45.4° ($CHCl_3$, c 1.5)

***R*-Methyl ketophosphonate 166:**

Ketoacetal **106** (128 mg, 1.0 mmol); DCC (400 mg, 1.5 mmol); diethylphosphonopropionic acid (294 mg, 1.5 mmol).

Yield: 160 mg, 50%

IR: cm^{-1} 2900, 1720, 1390, 1250, 1010, 960, 750.

PMR: δ 4.42 (dd, J=12,4 Hz, 1H, OCH_2); 4.30 (dd, J=12,4 Hz, 1H, OCH_2); 4.22-4.02 (m, 4H, 2xOCH_2); 3.06-2.84 (m, 1H, C(O)C**H**P(O)); 2.42-2.02 (m, 5H); 1.94-1.80 (m, 1H); 1.42 (d, J=6 Hz, 3H, $CHCH_3$); 1.38-1.22 (m, 6H, 2xCH_2CH_3); 1.14 (d, J=6 Hz, 3H, CH_3).

***R*-Unsaturated lactone 104:**

To a stirred solution of ketophosphonate **105** (30.6 mg, 0.1 mmol) in 1 mL of dry CH_3CN containing LiCl (6.36 mg, 0.15 mmol) at rt, under N_2 atmosphere was added DBU (19 μL, 19.03 mg, 0.125 mmol) and stirred for 1h. The reaction mixture was quenched with 0.2 mL of sat. NH_4Cl solution and diluted with 2 mL of brine then extracted with $CHCl_3$ (3x10 mL). Usual work-up provided 28 mg of lactone **104**, which was purified on SGC (hexane to 20% EtOAc/hexane).

Yield: 12.5 mg, 81%

$[\alpha]_D^{25}$: -136.6° ($CHCl_3$, c 1.5)

IR: cm^{-1} 2900, 1720, 1620, 1460, 1390, 1300, 1240, 1200, 1020, 860.

PMR: δ 5.72 (m, 1H, vinyl **H**); 4.54 (dd, J=12,6 Hz, 1H, OCH_2); 3.96 (dd, J=12,10 Hz, 1H, OCH_2); 2.74-2.32 (m, 3H, allyl **H**); 2.14-2.00 (m, 1H); 1.74-1.52 (m, 1H); 1.46 (t, J=11 Hz, 1H); 1.12 (d, J=6 Hz, 3H, CH_3).

CMR: δ 170.28, 164.77, 112.12, 70.86, 46.86, 38.07, 33.39, 29.64, 18.01.

S-Unsaturated lactone 104:

$[\alpha]_D^{25}$: +126.7° ($CHCl_3$, c 0.3)

R-Cyclopentapyranone 59:

To a solution of unsaturated lactone **104** (15.2 mg, 0.1 mmol) in 2 mL of EtOAc was added 10% Pd-C (5 mg), flushed with H_2 and then the mixture was stirred for 3 h under H_2 atmosphere. The reaction mixture was filtered through celite. Work-up afforded pyranone **59** which was purified by SGC (hexane to 20% EtOAc/hexane).

Yield: 12.4 mg, 81%

$[\alpha]_D^{25}$: -92.0° ($CHCl_3$, c 1.0); -82.0° (CCl_4, c 0.5)

IR: cm^{-1} 2925, 1740, 1550, 1480, 1350, 1290, 1250, 1180, 1080, 1050, 980, 860.

PMR: δ 4.26 (dd, J=12,4 Hz, 1H, OCH_2); 4.06 (dd, J=12,6 Hz, 1H, OCH_2); 2.64-2.52 (m, 2H, CO_2CH_2); 2.34 (t, J=8 Hz, 1H); 2.06-1.96 (m, 1H); 1.92-1.72 (m, 3H); 1.32-1.14 (m, 2H); 1.06 (d, J=6 Hz, 3H, CH_3).

CMR: δ 173.73, 69.04, 44.71, 37.59, 34.89 (x2), 34.71, 33.49, 18.79.

Analysis: Calculated for $C_9H_{14}O_2$: C=70.10%, H=9.15%; Found: C=70.22%, H=9.10%

S-Cyclopentapyranone 59:

$[\alpha]_D^{25}$: +71.9° ($CHCl_3$, c 0.16)

S-*iso*-Pulegone 110:

To a suspension of PCC (8.0 g, 37 mmol) in 50 mL of dry CH_2Cl_2 was added *S*-(-)-citronellol **107** (2.0 g, 12.8 mmol). The slurry was mechanically stirred at rt for 36 h. The mixture was filtered through celite and the filtrate washed with 10% HCl, 10% $NaHCO_3$ and brine. The crude oil obtained after work-up was dissolved in ether and filtered through celite. Removal of solvent *in vacuo* furnished *iso*-pulegone 110 which was used in the next step without any purification.

Yield: 1.6 g, 85%

IR: cm^{-1} 2955, 2928, 2872, 1711, 1456, 1377, 1167, 1124, 893.

PMR: δ 4.86 (s, 1H, vinyl **H**); 4.65 (s, 1H, vinyl **H**); 2.88 (dd, J=10,4 Hz, 1H); 2.32 (d, J=6 Hz, 1H); 2.08-1.72 (m, 5H); 1.68 (s, 3H, vinyl CH_3); 1.46-1.12 (m, 1H); 0.98 (d, J=6 Hz, 3H, CH_3).

***S*-Pulegone 91:**

iso-Pulegone **110** (1.6 g, 10.7 mmol) in 16 mL of benzene containing catalytic amount of *p*-TsOH.H_2O (80 mg, 0.4 mmol) were refluxed for 6 h. The reaction mixture was cooled to rt and diluted with 16 mL of ether. Washed with saturated $NaHCO_3$ solution and brine. Work-up afforded 1.4 g of *S*-pulegone **91** which was purified by SGC (hexane to 5% EtOAc/hexane)

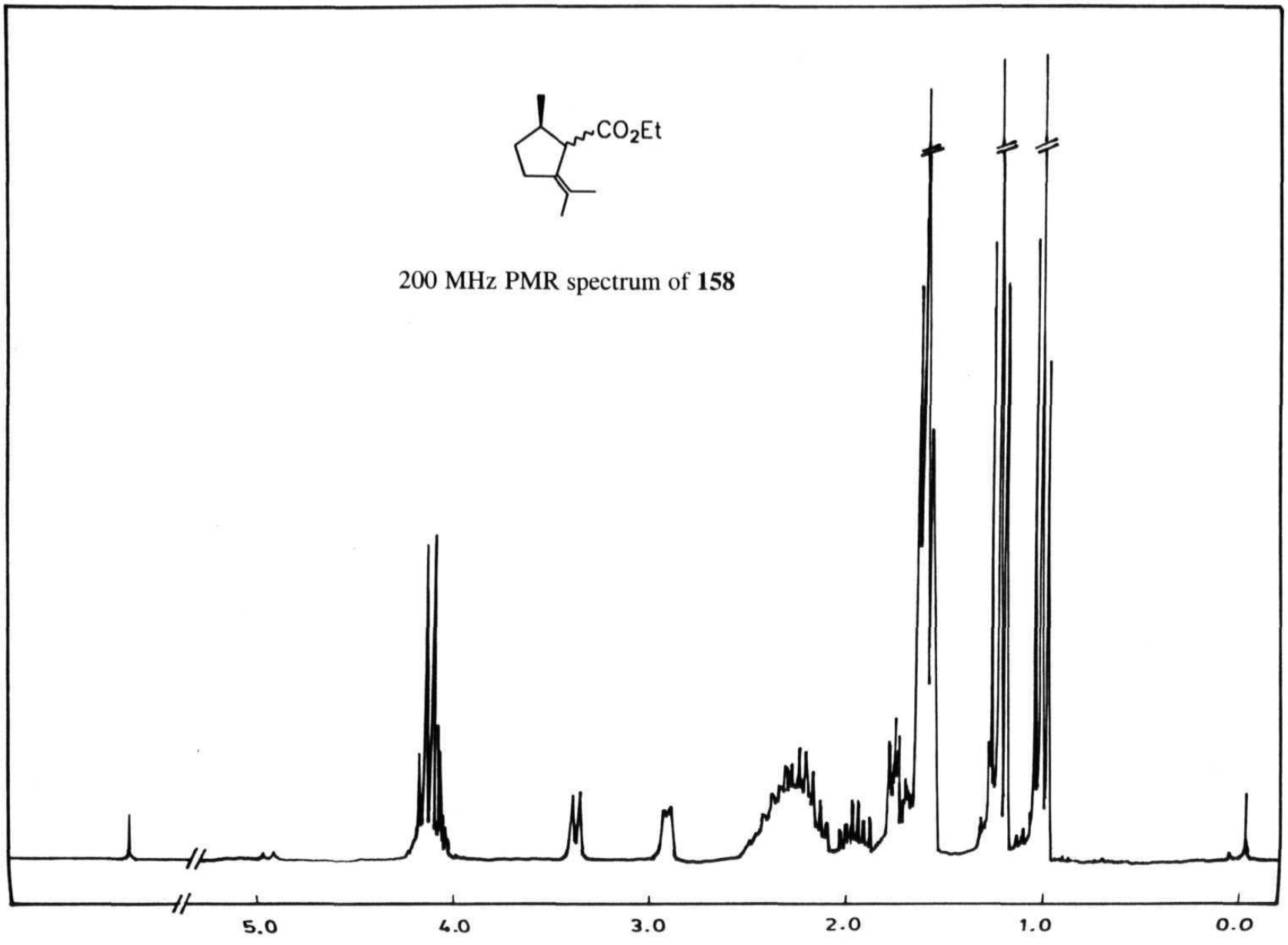
Yield: 1.3 g, 78%

$[\alpha]_D^{25}$: -15.3° (neat, 66% ee); *R*-pulegone +22.0° (neat).

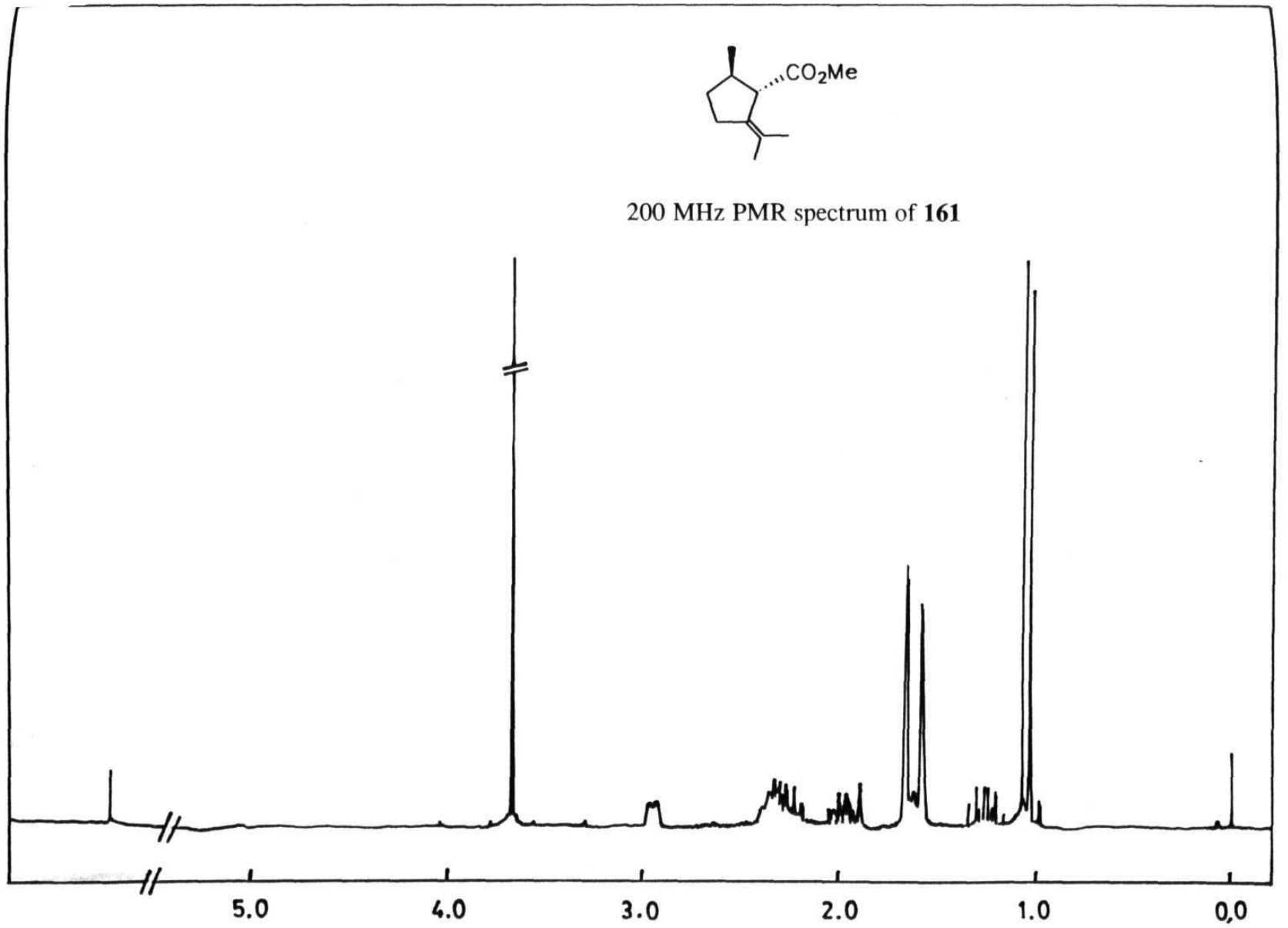
IR: cm^{-1} 2900, 1670, 1595, 1445, 1365, 1280, 1200, 1130, 1080, 1020.

PMR: δ 2.70 (dt, J=15,4 Hz, 1H, $COCH_2$); 2.50 (dd, J=12, 2 Hz, 1H, $COCH_2$); 2.36-2.14 (m, 1H); 2.10-1.56 (m, 3H); 1.98 (s, 3H, vinyl CH_3); 1.78 (s, 3H, vinyl CH_3); 1.46-1.22 (m, 1H); 1.02 (d, J=6 Hz, 3H, CH_3).

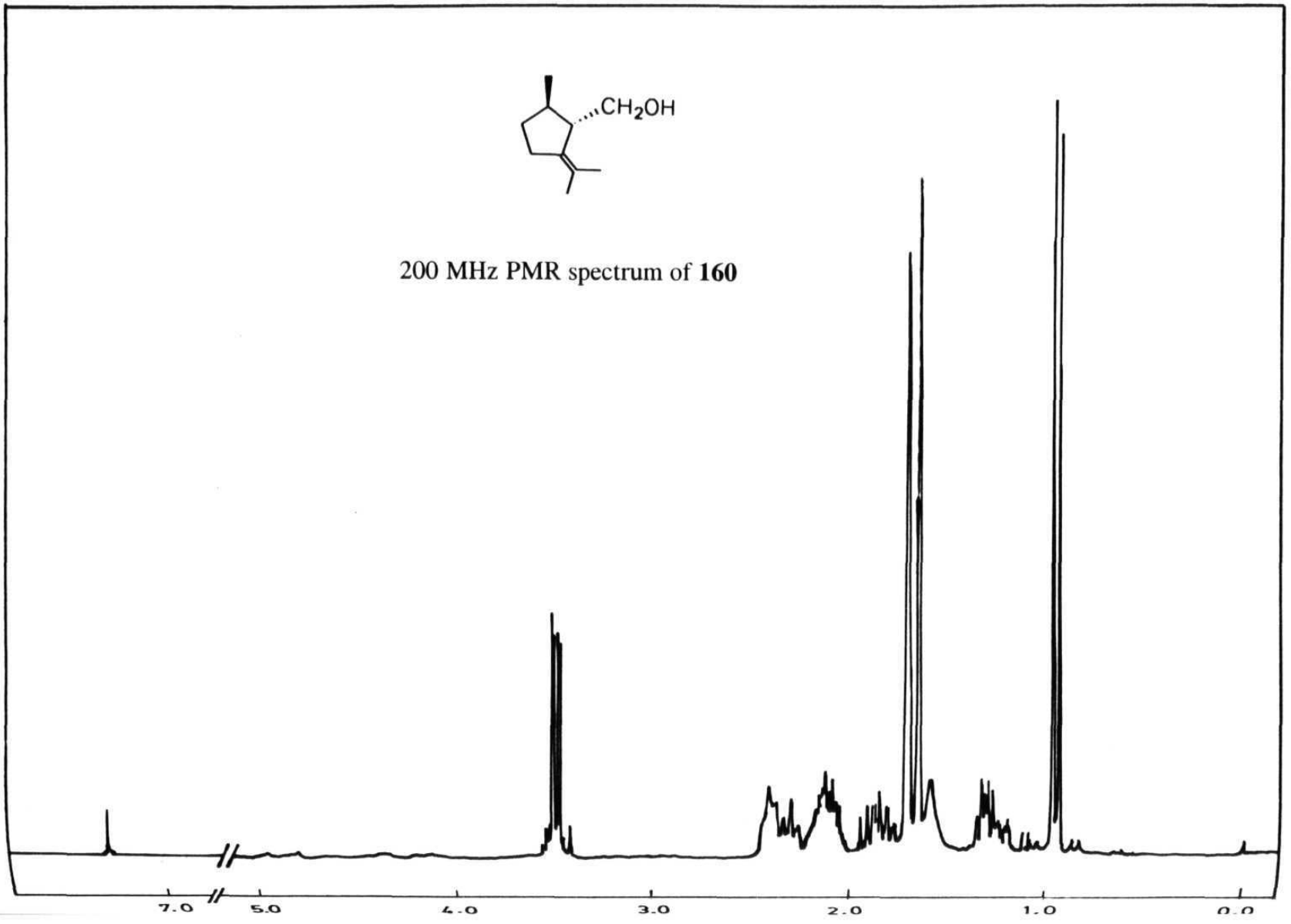
CMR: δ 203.69, 141.54, 131.59, 50.53, 32.47, 31.24, 28.29, 22.65, 21.77, 21.41.



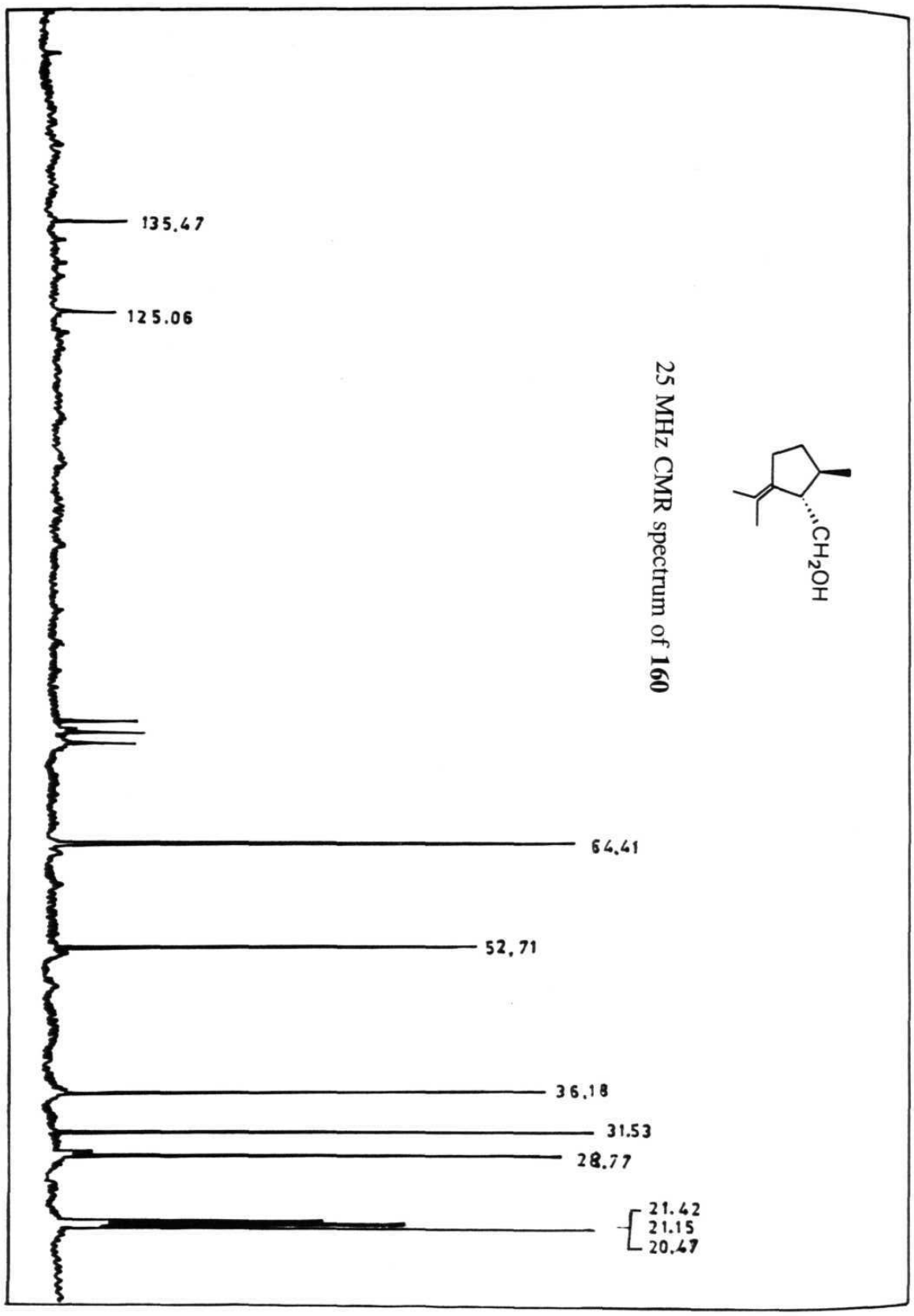
200 MHz PMR spectrum of **158**



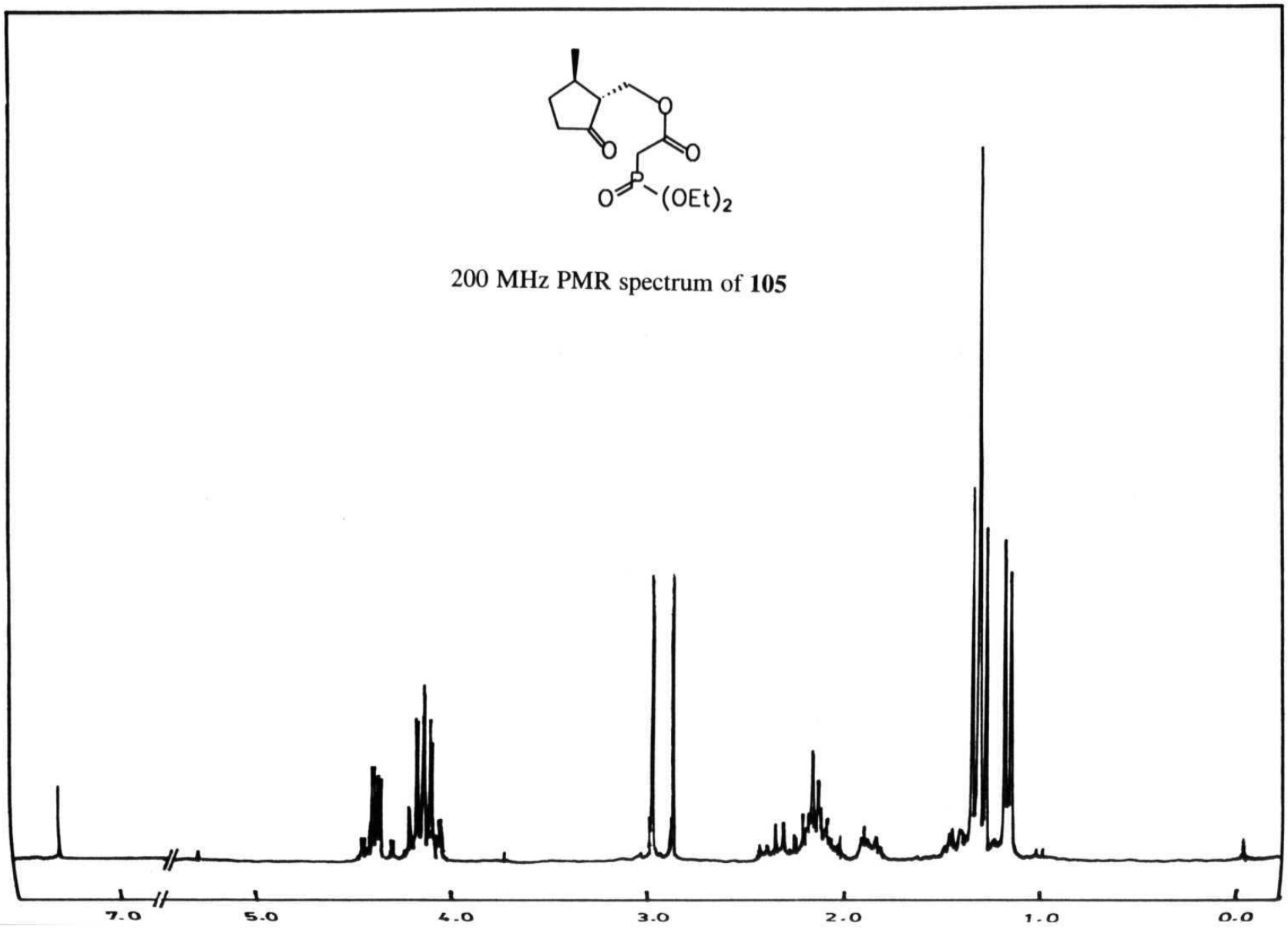
200 MHz PMR spectrum of **161**



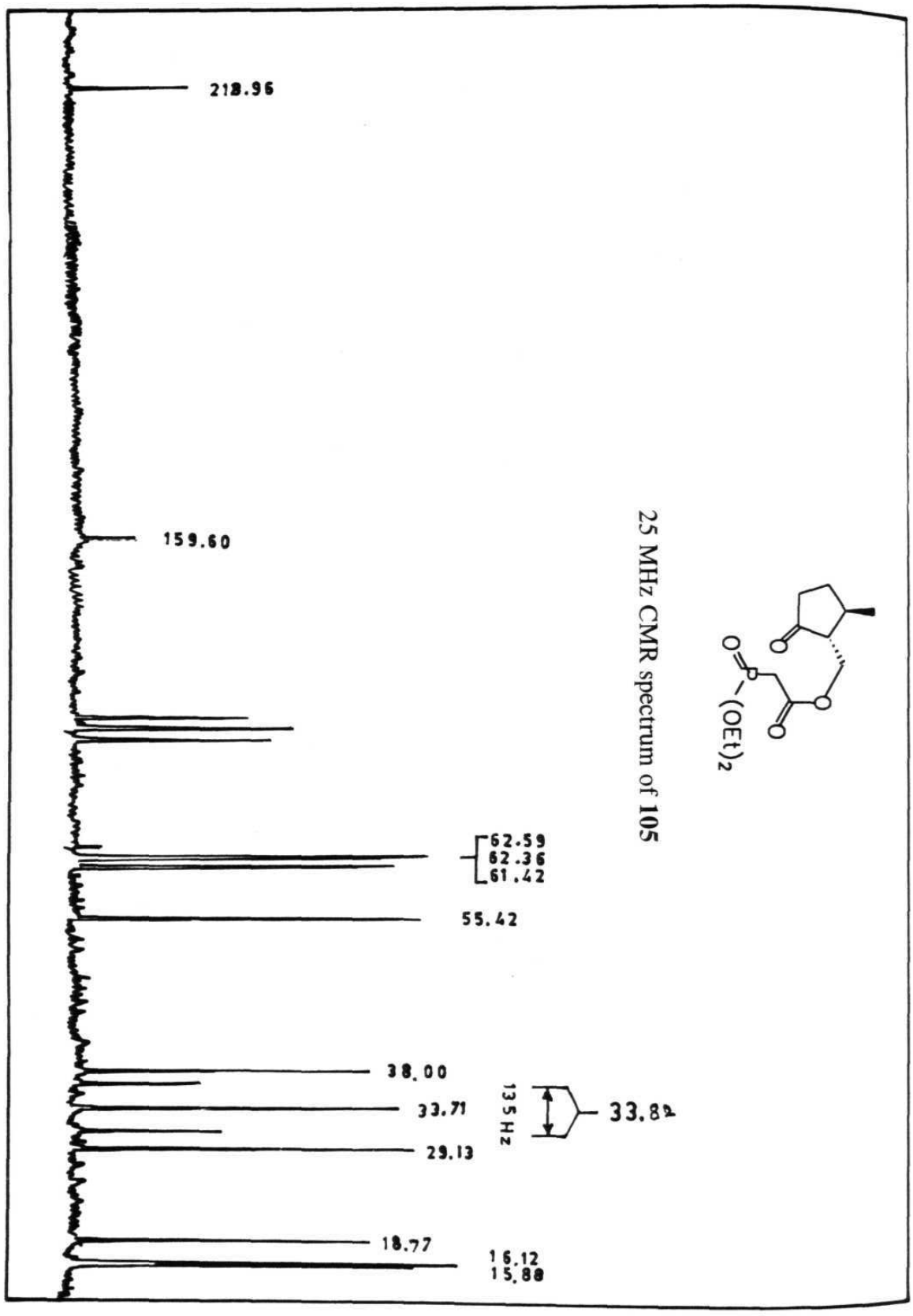
200 MHz PMR spectrum of **160**



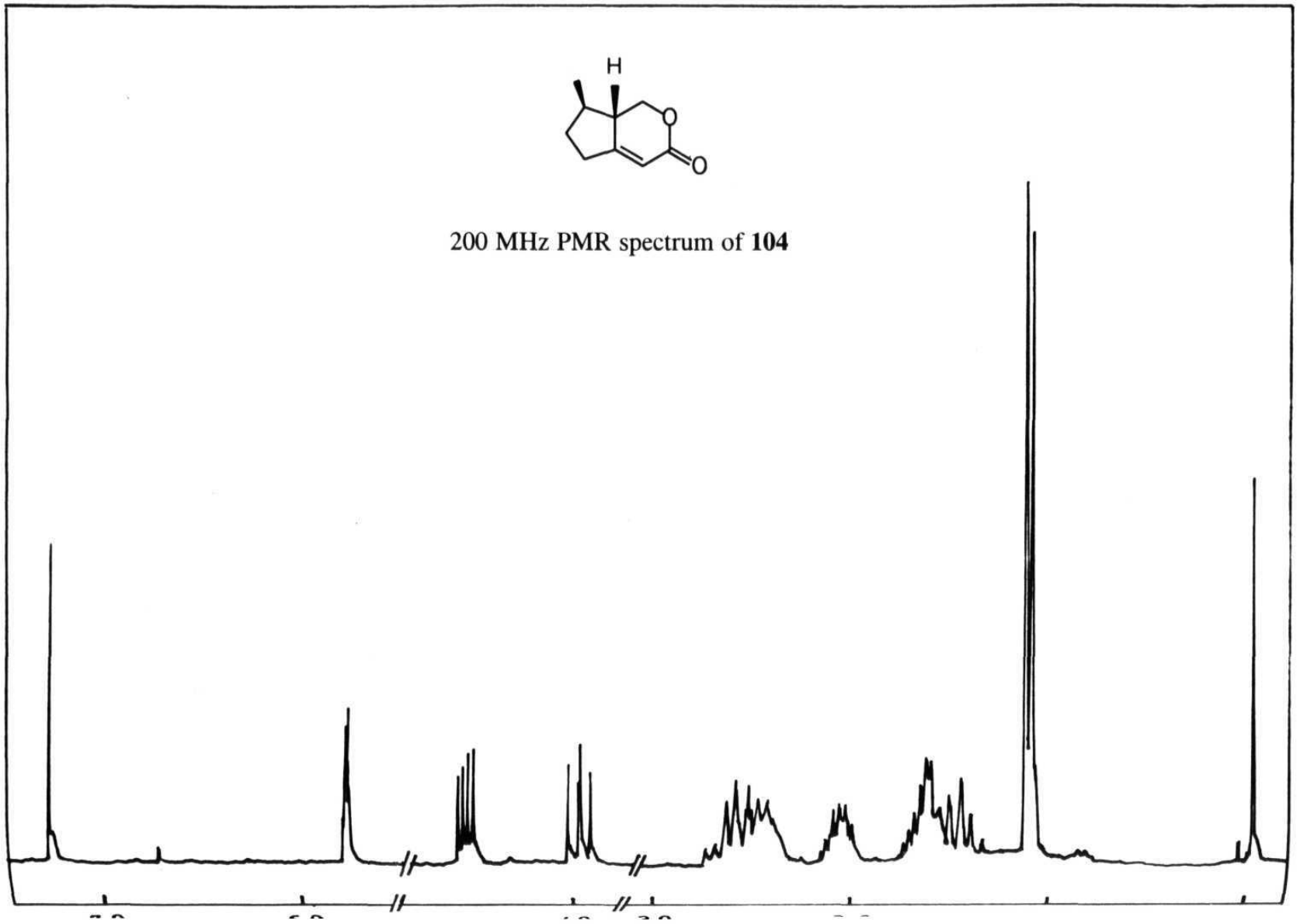
25 MHz CMR spectrum of **160**



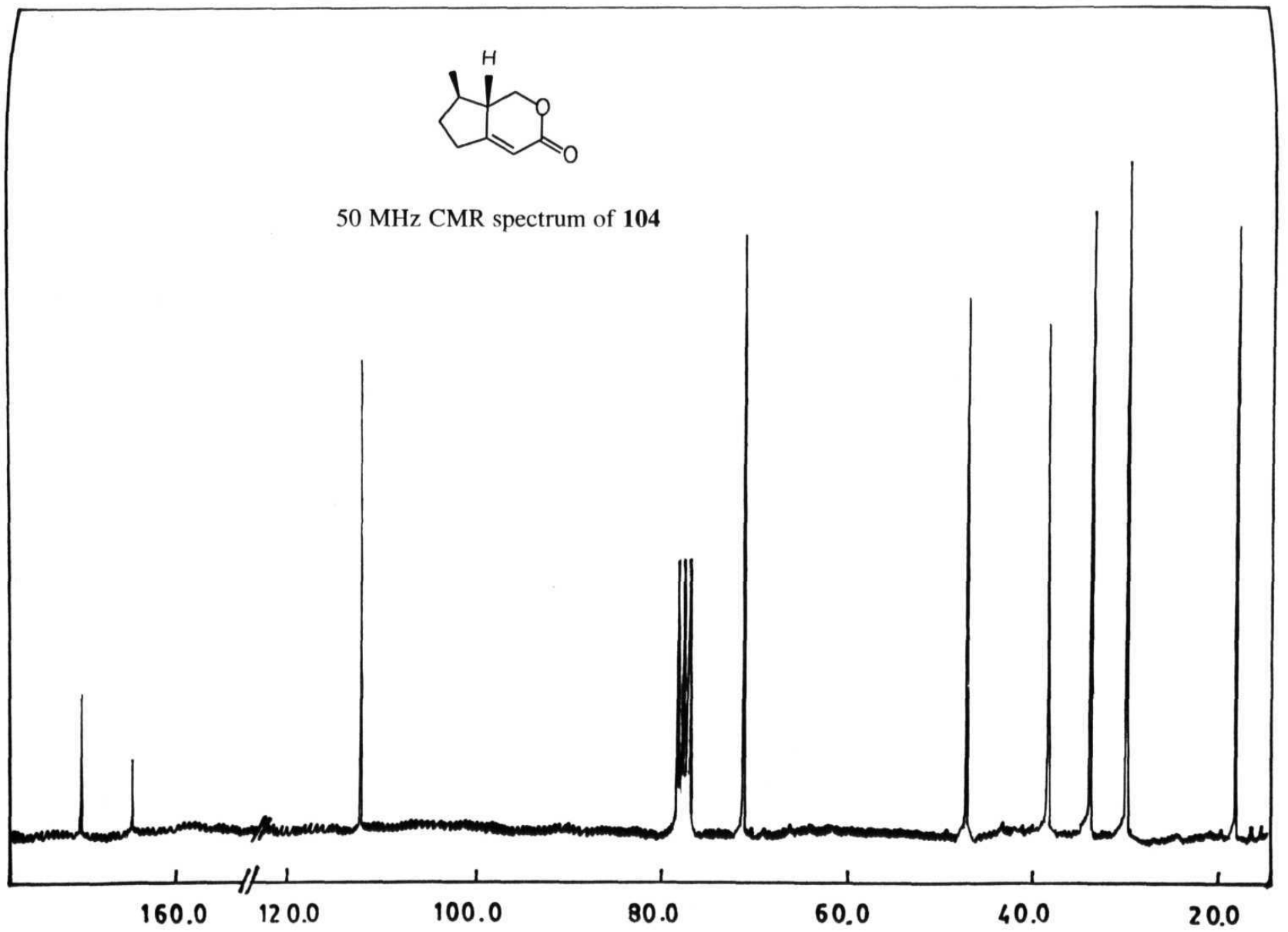
200 MHz PMR spectrum of **105**



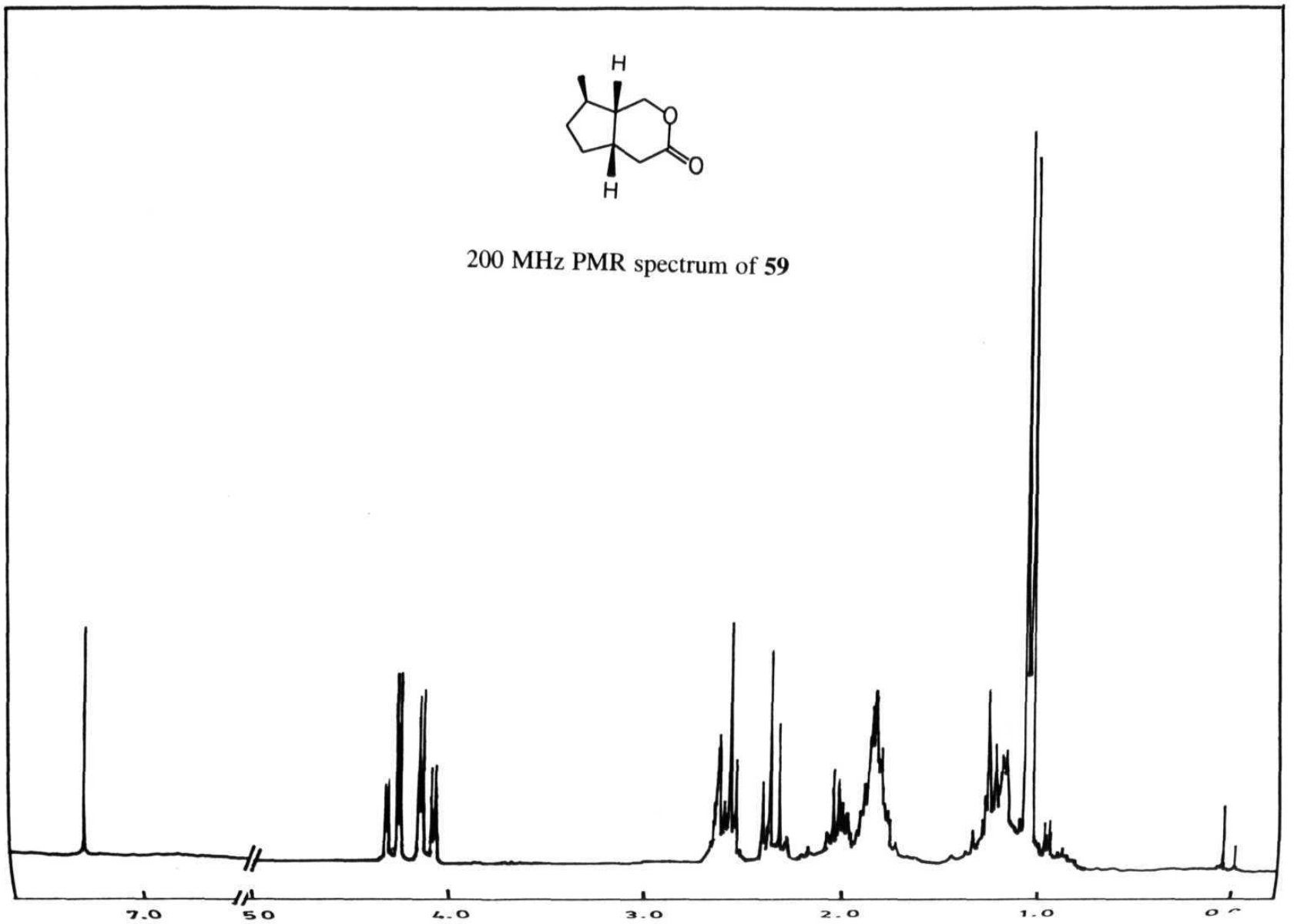
25 MHz CMR spectrum of **105**



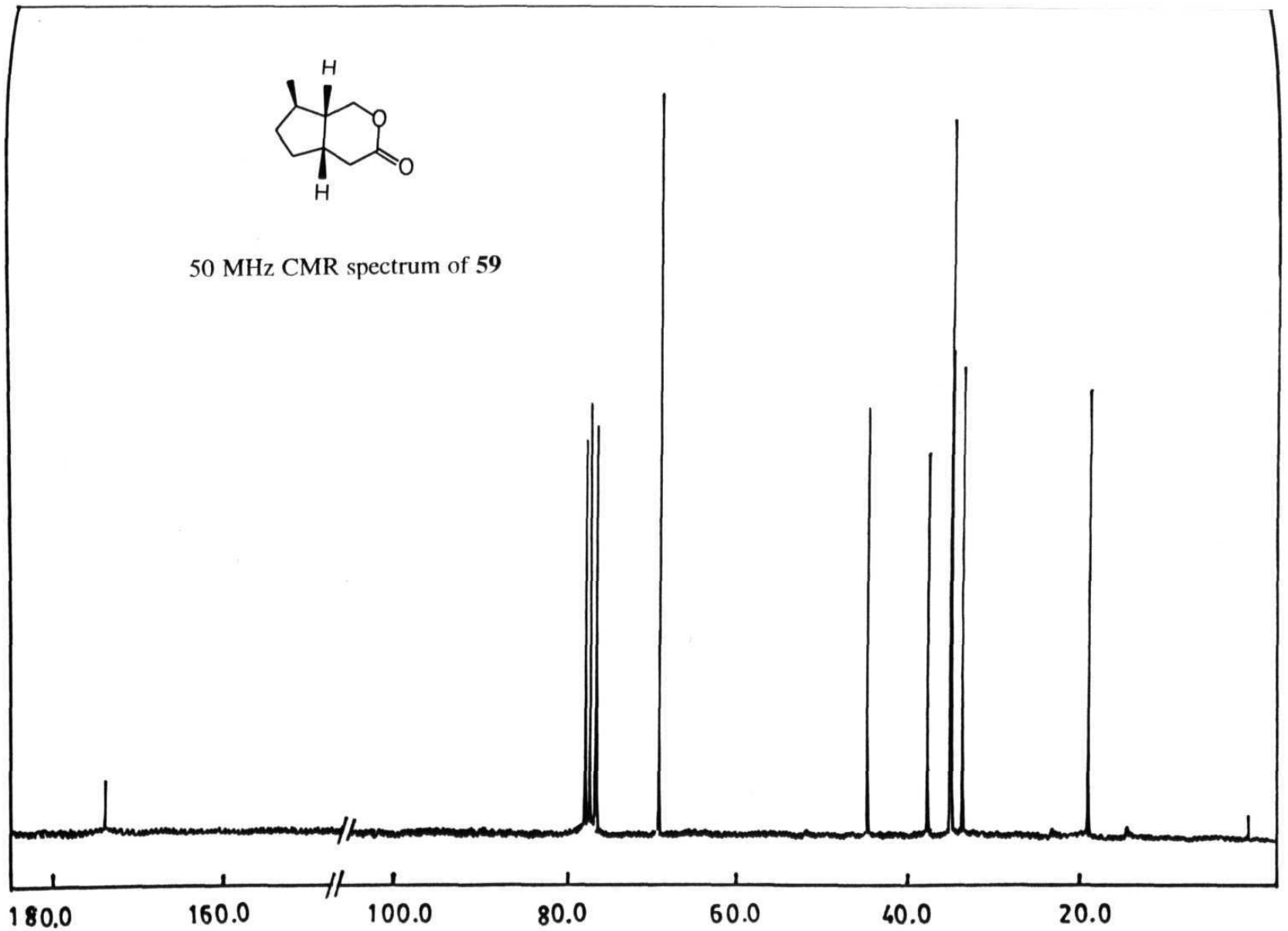
200 MHz PMR spectrum of **104**



50 MHz CMR spectrum of **104**

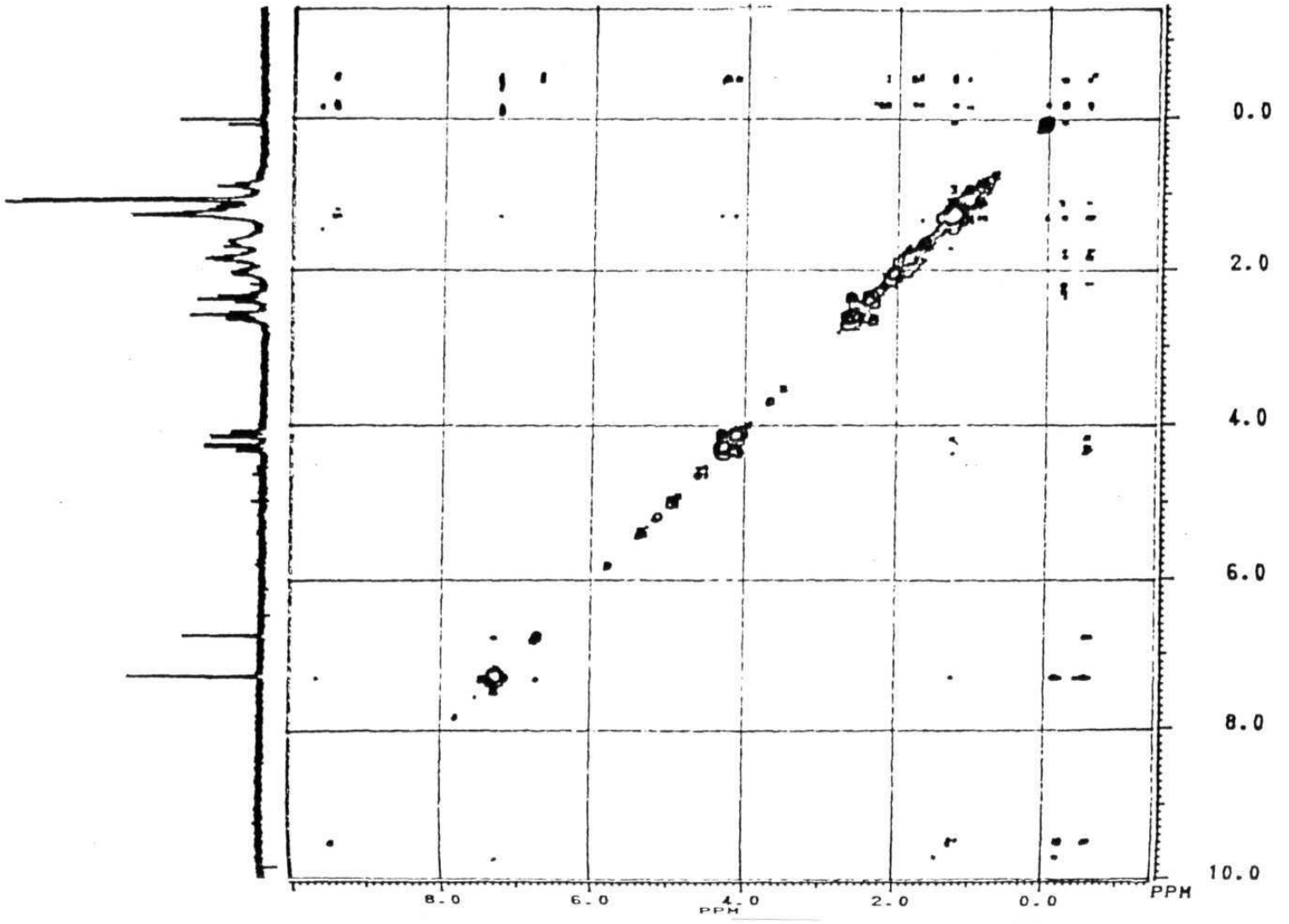


200 MHz PMR spectrum of **59**



50 MHz CMR spectrum of **59**

2D NOESY spectrum of **59**



3.5. REFERENCES AND NOTES:

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CHAPTER-4
SYNTHESIS OF TYPE-II LACTONES: 4-*EPI*-MITSUGASHIWALACTONE AND MITSUGASHIWALACTONE

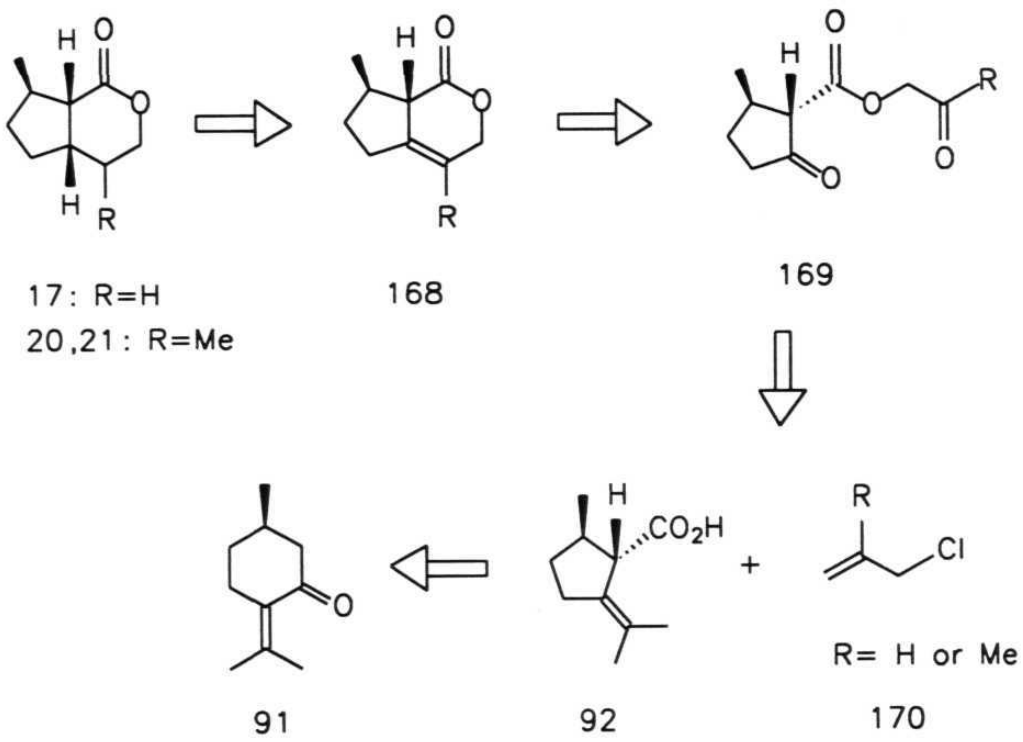
4.1. INTRODUCTION:

After completing the formal synthesis of (+)-iridomyrmecin **10**, (-)-isoiridomyrmecin **11** and (+)-teucriumlactone **15** belonging to type-I iridoid lactones, we turned our attention towards the synthesis of type-II lactones. Both types of bicyclic lactones are *cis*-fused at C4a-C7a, the only difference is that the carbonyl group is at C3 in type-I lactones whereas it is at C1 in type-II lactones. The different methods for the synthesis of mitsugashiwalactone **17**, onikulactone **18**, dihydronepetalactone **20** and isodihydronepetalactone **21** belonging to structural type-II were documented in Chapter-1. A limitation of the reported methods is that all of them, except one, lead to racemic products. So far, only one enantioselective synthesis for (-)-mitsugashiwalactone **18** has been reported by Takacs and Myoung [1]. Our aim was to investigate an enantioselective route towards lactones **17**,**18**,**20** and **21** employing the HWE protocol.

4.2. SYNTHETIC APPROACH TO DIHYDRONEPETALACTONE AND ISODIHYDRONEPETALACTONE:

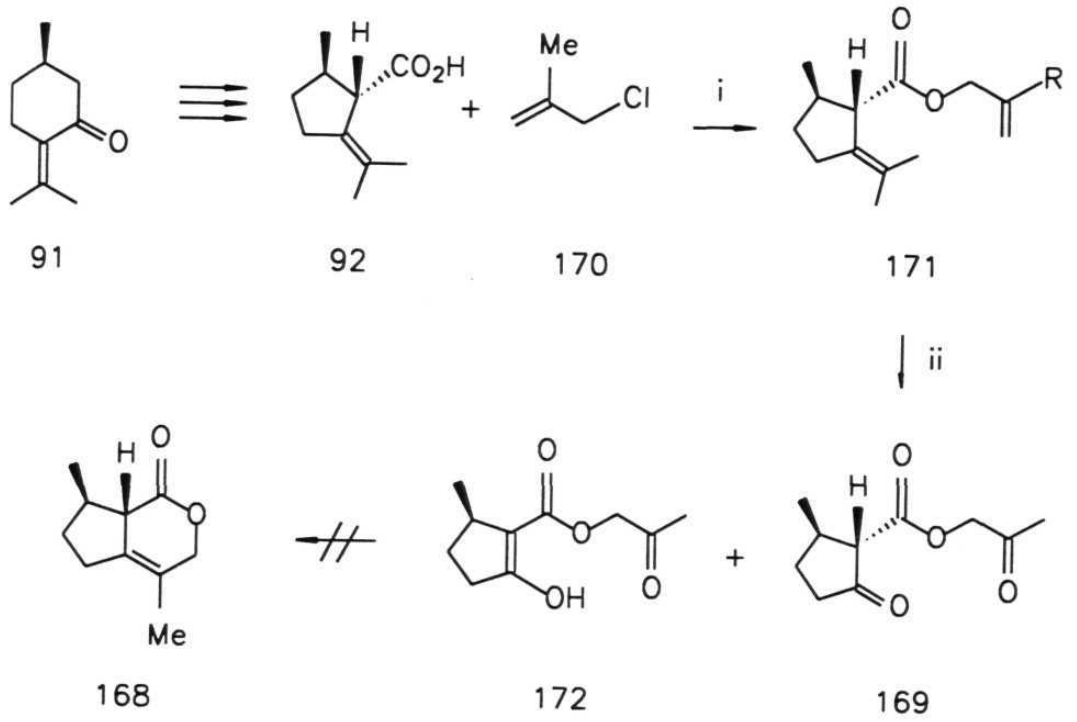
From our earlier work on type-I lactones (Chapter-3) we were aware that the stereoselective *exo*-face hydrogenation of unsaturated lactone **104** gives the *cis*-fused lactone **59**. Hence, the unsaturated lactone **168** was retro analysed as arising from a McMurry coupling of the diketone **169**, which can be prepared from *anti*-pulegenic acid **92**. The acid **92** was chosen as starting material because, it has the required *anti* stereochemistry at C7 and C7a, and also because it is easily prepared from *R*-pulegone **91**.

Scheme-1



Thus, *anti*-pulegenic acid **92** was converted to the corresponding carboxylate anion with K_2CO_3 and alkylated with methallyl chloride **170** in acetone to provide ester **171**. The exocyclic methylene protons in ester **171** appeared at δ 4.98 and 4.90 as singlets in PMR spectrum. Ozonolysis of ester **171** in 1:4 MeOH-CH_2Cl_2 at -78 °C followed by quenching with DMS afforded triketone as a mixture of keto **169** and enol **172** forms. The hydroxy band at 3450 cm^{-1} in IR spectrum suggested equilibrium with enol form **172** of triketone **169**. Attempted cyclisation under McMurry coupling conditions [2] of $TiCl_4$ did not provide the desired unsaturated lactone **168**. The failure of the reaction may be due to the 1,3-dicarbonyl moiety in the molecule, which exists predominantly in the enol form **172**.

Scheme-2

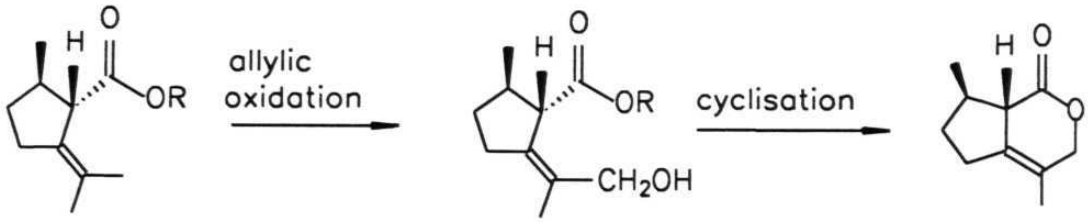


Reagents: i) K_2CO_3, NaI, acetone, rt, 12 h; ii) O_3, $NaHCO_3$, 1:4 MeOH-CH_2Cl_2, -78 °C, then DMS.

A closer inspection of dihydronepetalactone **20**, suggested that all the required carbons for the target skeleton are present in *anti*-pulegenic acid **92** or its methyl ester **161**. Therefore, the synthesis of lactone **168** was planned through a tandem allylic oxidation and cyclisation reaction.

The acid **92** and the ester **161** were subjected to allylic oxidation with various oxidising agents such as SeO_2 [3], SeO_2/TBHP [4], SeO_2.SG/TBHP [5], CrO_3.2Py [6] and CrO_3.DMP [7]. None of these reagents gave the required product. The crude

Scheme-3



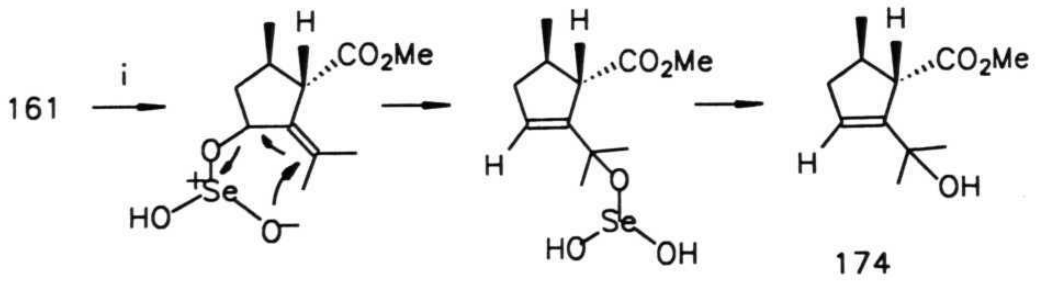
92: R=H
161: R=Me

173

168

PMR spectrum showed either unreacted starting material (CrO_3.2Py, CrO_3.DMP) or a complex unidentified pattern (SeO_2/TBHP, SeO_2.SG/TBHP). Oxidation with SeO_2 in aq. dioxane did not afford the desired allylic alcohol **173**. Instead, the intermediate secondary selenyl ester underwent further rearrangement to the tertiary ester, which upon hydrolysis afforded the isolated product. This was tentatively characterised as *tert*-alcohol **174** based on its PMR spectrum which displayed the olefin proton at δ 5.72 and also a hydroxy band at 3350 cm^{-1} in IR spectrum.

Scheme-4



174

Reagents: *SeO_2, aq. dioxane, reflux, 1 h.*

The problems encountered with approaches outlined in Schemes 1 and 3 was a temporary setback. Both the planned routes were elegant and efficient in carbon economy and number of steps. At this juncture we sought recourse to more familiar HWE chemistry.

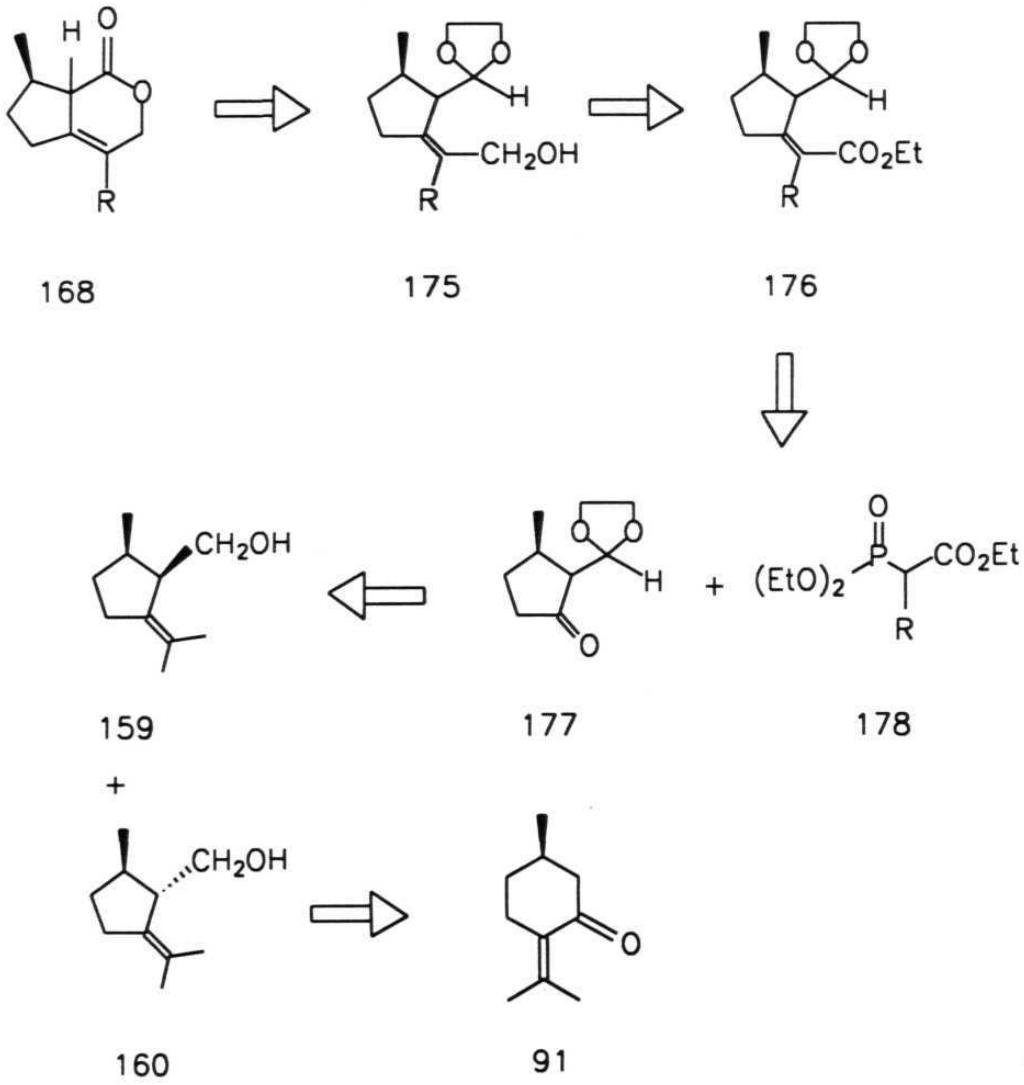
4.3. SYNTHESIS OF (-)-4-*EPI*-MITSUGASHIWALACTONE:

Since, the carbonyl at C1 was causing enolisation thereby preventing cyclisation, it appeared that the C1 carbonyl function should be protected. A retrosynthetic analysis is delineated in Scheme-5 which leads to the four lactones (**17**,**18**,**20** and **21**) and is also related to our earlier HWE approach. The lactone **168** should arise from hydroxy acetal **175** which can be obtained from the corresponding α, β-unsaturated ester **176**. Ester **176** can be prepared by HWE reaction between ketoacetal **177** and phosphonate **178**. Depending on the choice of phosphonate reagent 178 (R=H or Me), lactones **17**,**18** or **20**,**21** can be synthesised. The homoallylic alcohols **159**,**160** which are easily available from *R*-pulegone **91** were the precursors for ketoacetal **177**.

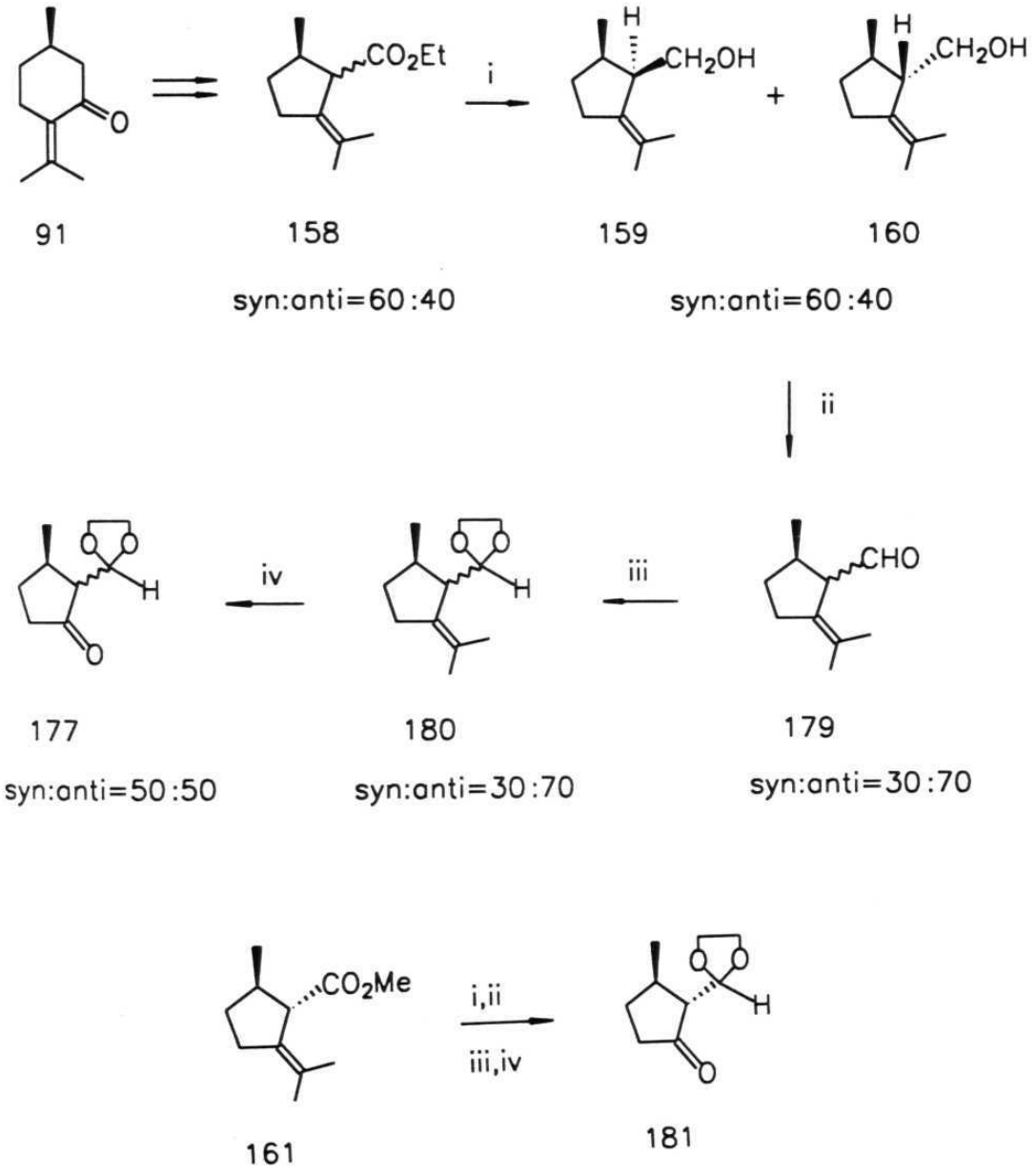
Thus, *R*-pulegone **91** was converted to a 60:40 mixture of *syn*- and *anti*-alkene alcohol **159**,**160** as described in previous chapter. PCC oxidation [8] of **159**,**160** in CH_2Cl_2 at rt for 1 h provided a mixture of *syn*- and *anti*-aldehyde **179**. The integration of aldehydic **CH** doublets at δ 9.34 (*syn*) and at δ 9.22 (*anti*) suggested that the ratio is 30:70, respectively. Acetalisation [9] of aldehyde **179** with ethanediol and triethyl orthoformate using catalytic amount of *p*-TsOH.H_2O in benzene at rt provided a 30:70 mixture of *syn*- and *anti*-acetal **180**. Again, the ratio was determined by the integration of acetal **CH** doublet at δ 4.94 (*syn*) and 4.86 (*anti*) in PMR spectrum. Ozonolysis of exocyclic olefin **180** under buffered conditions ($NaHCO_3$) at -78 °C in

1:4 MeOH-CH_2Cl_2 provided ketone **177** which was contaminated with acetal cleavage products. Oxidation of **180** with $RuCl_3/NaIO_4$ [10] was clean and gave the somewhat unstable *syn*- and *anti*-ketoacetal **177** as a 50:50 mixture in 55% yield.

Scheme-5



Scheme-6



Reagents: i) $LiAlH_4$, ether, O °C, 1 h; ii) PCC, CH_2Cl_2, rt, 1 h; iii) $(CH_2OH)_2$, $(EtO)_3CH$, p-TsOH.H_2O, benzene, rt, 4 h; iv) $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O, rt, 4 h.

In addition to carrying out this sequence with the mixture of isomers, the *anti*-ketoacetal **181** was also prepared in isomerically pure form, without contamination with its *syn*-isomer, by starting from *anti*-methyl pulegenate **161**. The PMR spectrum of **181** showed acetal **CH** doublet at δ 5.16 (J=2 Hz) and $\mathbf{CH_3}$ doublet at δ 1.14 (J=6 Hz). The spectral data on products in isomerically pure series facilitated the characterisation of mixtures and assignment of diastereomeric ratios.

The HWE reaction of a 50:50 mixture of *syn/anti*-ketoacetal with triethylphosphonopropionate (R=Me) **178** [11] was attempted under different reaction conditions [12] which are listed in Table-1.

Table-1

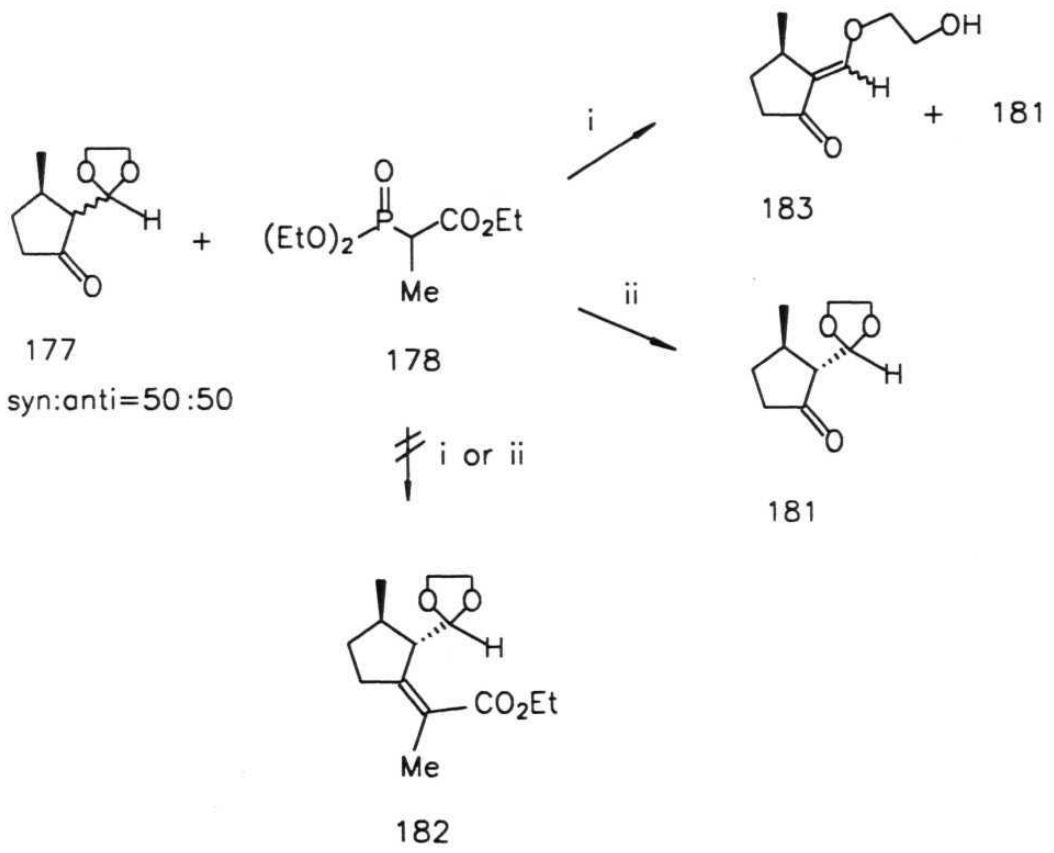
Conditions	**Result**
t-BuOK/THF, rt, 20 h	E2 + epi
NaH/THF, rt, 6 h	epi
NaH/HMPA/THF, rt, 20 h	E2 + epi
NaH/THF, -20 °C to 15 °C, 20 h	epi
$LiOH.H_2O$/ether, rt, 48 h	E2 + epi
$CsCO_3$/*t*-BuOH, rt, 24 h	epi
DBU/LiCl/CH_3CN, rt, 10 h	E2 + epi
HMDS/NaH/THF, 0 °C to rt 6 h	epi

E2= elimination; epi= epimerisation.

The coupling between ketone **177** and phosphonate **178** was extremely sluggish and unreacted ketone **181** was recovered. Under forcing conditions the only product isolated was the opened dioxolane as a result of β-elimination, which was evidenced

from the appearance of vinyl hydrogen signal at δ 6-7 in PMR spectrum. None of the reaction conditions gave the required product, α,β-unsaturated ester **182**, either with the dioxolane group intact or opened up. Spectral analysis of recovered ketoacetal **181** provided information about the relative rates of C=C bond formation *vs* epimerisation and elimination.

Scheme-7



Reagents: *i) Strong bases: NaH, $LiOH.H_2O$, DBU/LiCl, $CsCO_3$; ii) Weak bases: t-BuOK, NaHMDS.*

Although the reaction was carried out on a mixture of *syn/anti* diastereomers, the recovered ketoacetal was exclusively the *anti*-isomer **181**. This suggested that α-epimerisation and β-elimination are faster process than the desired C=C forming HWE reaction. Since, the basic HWE reaction conditions converge the *syn/anti* mixture 177 to *anti*-ketoacetal **181**, the subsequent studies were carried out with the mixture 177 which was synthetically easier to obtain.

The HWE reaction with triethylphosphonopropionate **178** (R=Me) is sluggish, because it leads to the formation of tetrasubstituted olefin **182**. In order to accelerate the Horner reaction, diethylphosphonoacetate **178** (R=H) [13] was used which is devoid of a methyl group.

Thus, HWE reaction of ketoacetal **177** with diethylphosphonoacetate **178** [13] under the conditions listed in Table-2 provided a mixture of unsaturated esters **184,185** along with elimination (E2) **183** and epimerisation (epi) **181** products.

Table-2

Conditions	**Result**
HMDS/NaH/THF, -20 °C, 6 h	HWE + epi
HMDS/NaH/HMPA/THF, 0 °C to rt 20 h	HWE + E2 + epi
DBU/LiCl/CH_3CN, rt, 10 h	E2 + epi
NaH/THF, rt, 10 h	HWE + epi
NaH/THF, rt, 3 days	HWE

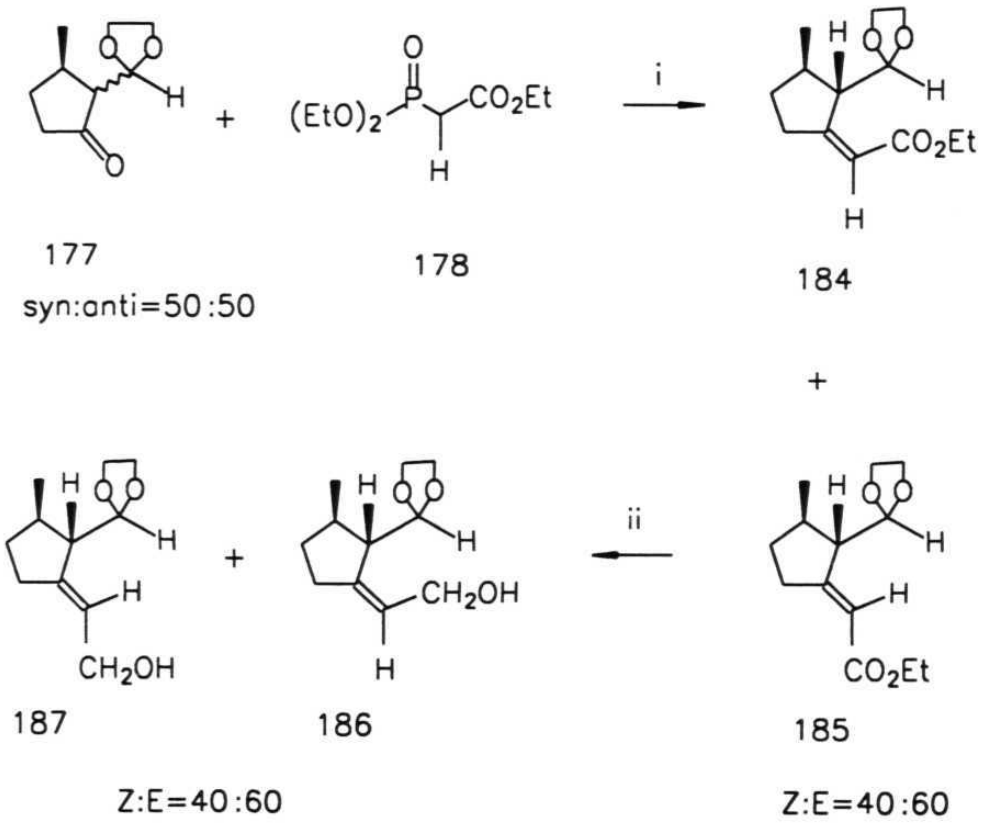
HWE= unsaturated ester product **184,185**; E2= elimination **183**; epi= epimerisation **181**.

After experimenting with a number of bases, solvents and reaction temperatures, the following conditions were found to be optimal: addition of ketone 177 to excess phosphonate anion **178** (5 equi, NaH base) in THF and stirring at ambient temperature for 3 days provided a mixture of unsaturated esters **184** and **185** in 60% yield; no elimination product **183** or unreacted ketone **181** was detected in the crude concentrate (TLC, PMR). The esters **184,185** were obtained reproducibly in 40:60 ratio as concluded from PMR integration of vinyl and acetal **CH** signals corresponding to the major isomer at δ 5.98, 4.92 and the minor isomer at δ 5.84 and 5.24, respectively. Attempted seperation of isomeric esters by column chromatography was unsuccessful. The esters **184,185** were reduced to the corresponding allylic alcohols **186,187** with $LiAlH_4$ in ether at 0 °C. The ratio of the two isomers was again 40:60 as substantiated from its PMR spectrum. The alcohols **186,187** were seperated by column chromatography and the isolated yields of the purified alcohols **186** and **187** further confirmed the 40:60 ratio.

At this stage the nature of isomers, as to whether they are diastereomers at carbon adjacent to acetal group (C7a, *syn/anti*) or geometrical isomers at the newly formed olefin (C4-C4a, *Z/E*), or both, was deduced in the following manner. (i) The unreacted β-ketoacetal recovered after incomplete reaction was exclusively the *anti*-acetal **181** and, hence, it is this diastereomer which participates in the Horner-Wadsworth reaction. (ii) The acetal **CH** doublet of *Z*-ester **184** was expected to be downfield compared to that of *E*-ester **185** because of its proximity to the carbonyl group [14]. (iii) Comparison of vinyl and acetal **CH** shifts in PMR spectrum of allylic alcohols **186** and **187** with those reported for *Z*- and *E*-3-methyl-2-pentene-1,5-diol **188** and **189**, respectively, [14,15] facilitated in the assignment of isomers as *Z*-**186** and *E*-**187**. (iv) Palladium catalysed hydrogenation of allylic alcohols **186,187** produced a single diastereomer **190** as concluded from PMR and CMR spectra. (v) Treatment of

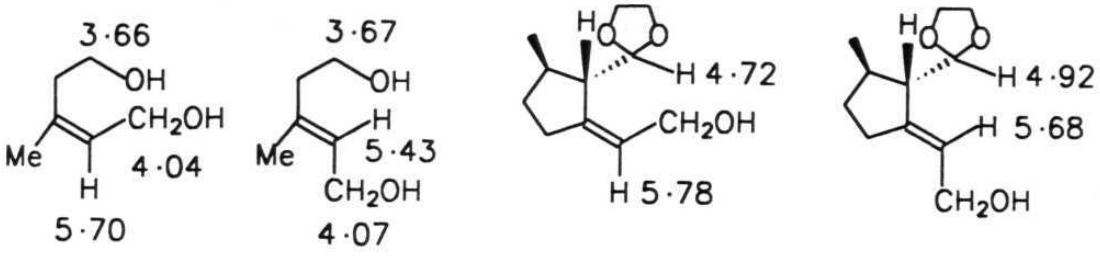
allylic alcohols **186,187** with $BF_3.Et_2O$ at -78 °C afforded a mixture of lactol **191** and unreacted *E*-alcohol **187**.

Scheme-8



Reagents: *i) NaH, THF, rt, 3 days; ii) $LiAlH_4$, ether, 0 °C, 1 h.*

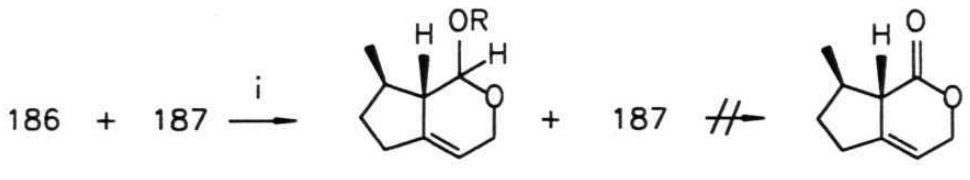
Based on the above evidence it was concluded that the 40:60 mixture of *Z*- and *E*-unsaturated esters **184,185** and alcohols **186,187**, are isomeric at the olefinic group and not at the stereogenic allylic centre.



188 189 186 187

Attempted deprotection-cum-cyclisation of the mixture of allylic alcohols **186,187** with *p*-TsOH.H_2O, PPTS or 2% HCl did not provide the unsaturated lactone **168**. The PMR spectrum showed a complicated pattern which did not reveal any signals arising from aldehyde or lactol **191** protons. The substrate presumably decomposes because of the sensitivity of allylic alcohol portion of molecule to such acidic conditions. Cyclisation of alcohol was successful with $BF_3.Et_2O$ in CH_2Cl_2 at -78 °C, but the product was difficult to purify and contaminated with unreacted *E*-isomer **187**. Moreover, the cyclised product was a mixture of lactol **191** (R=H) and cyclic acetal **192** ($R=CH_2CH_2OH$) because cleavage of the dioxolane group did not proceed to completion. Therefore, the reaction was not synthetically useful but served a crucial role in identification of *Z*- and *E*-allylic alcohols **186,187**.

Scheme-9

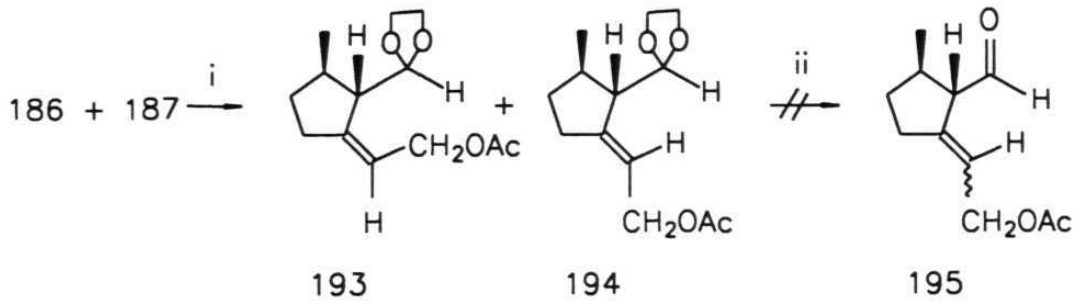


191 : R=H
192 : $R=CH_2CH_2OH$ 168

Reagents: *i)* $BF_3.Et_2O$, CH_2Cl_2, -78 °C, 1 h.

In an attempt to perform the hydrolysis of acetal and cyclisation to lactol in a stepwise manner, the alcohols **186,187** were protected as acetates **193,194** and subjected to acetal hydrolysis. Exposure of hydroxy acetates **193,194** to PPTS and *p*-TsOH.H_2O in aq. acetone produced only unreacted starting material; no aldehyde 195 signals were observed in δ 9-10 region.

Scheme-10



193 194 195

Reagents: *i) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 2 h; ii) H_3O^+.*

At this juncture we decided to continue the synthesis with the saturated hydroxy acetal **190**. Hydrogenation of allylic alcohols **186,187** with 10% Pd-C in EtOAc at atmospheric pressure provided hydroxy acetal **190** as a single diastereomer. The compound displayed non overlapping acetal C**H** and CH_3 doublets at δ 4.76 (J=6 Hz) and 4.06 (J=6 Hz) in PMR spectrum and a 11 line (two dioxolane carbons) CMR spectrum. The facial selectivity in the hydrogenation is a consequence of the interplay of steric (*syn* to hydrogen) and polar (*syn* to acetal) effects [16]. A rigorous and complete stereochemical assignment of hydroxy acetal **190** was postponed to after cyclisation to lactone.

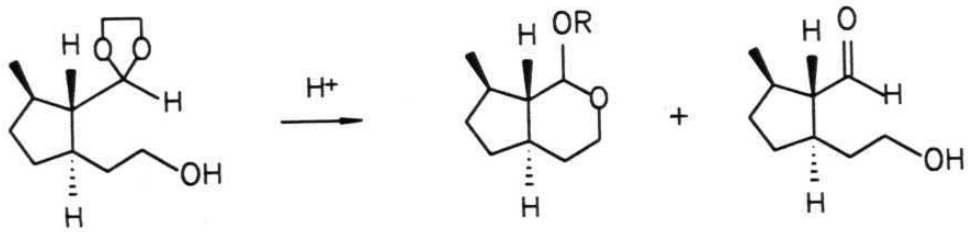
Hydroxy acetal **190** was subjected to a variety of deprotection-cum-cyclisation conditions [17] which are listed in Table-3.

Table-3

Conditions	Result
10% HCl, aq. acetone, rt, 10 h	UP
2% HCl, aq. acetone, rt, 6 h	UP
PPTS, aq. acetone, rt, 8 h	SM
p-TsOH.H_2O, aq. acetone, rt, 10 h	SM
3% $HClO_4$, THF, 0 °C to rt, 4 h	UP
10% $(COOH)_2$/SG, CH_2Cl_2, rt, 4 h	SM
15% H_2SO_4/SG, rt, 10 h	UP
3N HCl, CH_3CO_2H, rt, 5 h	**197** + SM
3N HCl, CH_3CO_2H, rt, 15 h	**197** + SM + UP
$BF_3.Et_2O$, CH_2Cl_2, -78 °C, 1 h	**196**

UP= Unidentified Products; SM= Starting Material.

Scheme-11



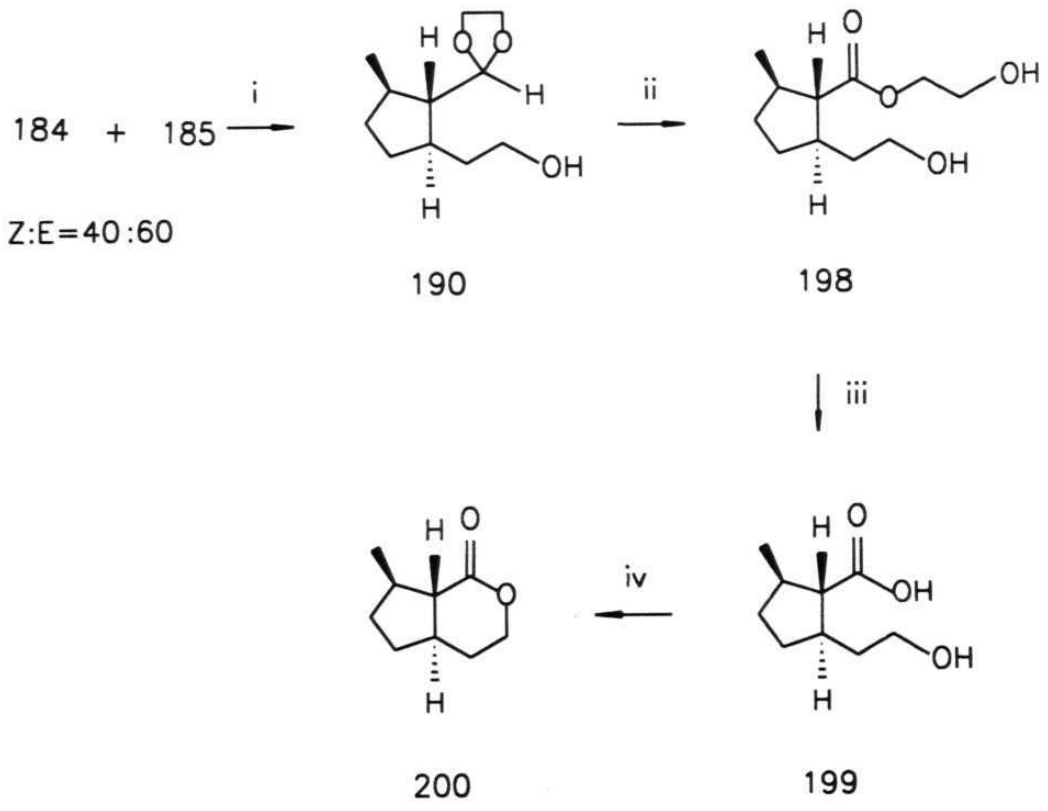
190 196 197

R= H or CH_2CH_2OH

The PMR spectrum showed either unreacted starting material or unidentified products; once again no cyclisation product was observed. Some faint aldehyde signals were detected but optimisation of AcOH/HCl conditions was not fruitful.

Since efforts towards deprotection-cum-cyclisation were unsuccessful, the hydroxy acetal **190** was oxidised to the ester **198** under Deslongchamp's conditions [18]. Ozonolysis of acetal **190** in EtOAc at -78 °C furnished hydroxy ester **198** in quantitative yield, which was evidenced from the carbonyl band at 1728 cm^{-1} in IR spectrum. Direct cyclisation of ester **198** to lactone with PPTS, *p*-TsOH.H_2O or HCl was unsuccessful. Base hydrolysis of ester **198** with 1N NaOH and then acidification with 1N HCl provided hydroxy acid **199**.

Scheme-12



Reagents: *i) 10% Pd-C, H_2, EtOAc, atmospheric. pressure, 4 h; ii) O_3, EtOAc, -78 ° C, 10 min; iii) 1N NaOH, then 1N HCl; iv) PPTS, toluene, reflux.*

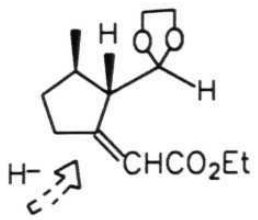
Lactonisation of hydroxy acid **199** with catalytic amount of PPTS in refluxing toluene afforded lactone, but the PMR spectrum of the product was visibly different from that reported for mitsugashiwalactone **17**. Lactone **200** exhibited AB CH_2O multiplet at δ 4.46-4.24 and a CH_3 doublet at δ 1.20. Moreover, the C7a downfield proton which appears in mitsugashiwalactone **17** at δ 2.66-2.45 was moved upfield and appeared as part of the aliphatic multiplet above δ 2.30. The CMR spectrum was also different from that reported for lactone **17**. Since lactone **200** did not correlate with natural lactone **17** we reasoned that the ring fusion C4a-C7a in **200** should be *trans*. We were reasonably certain of the C7-C7a *anti* relationship from the earlier discussion. The stereochemistry at ring junction C4a-C7a is directly dependent on the facial control during the hydrogenation of exocyclic olefin. It is very likely that due to the affinity of polar acetal group and its electronegative oxygen atoms for the palladium surface, the delivery of hydrogen at C4a occurs *cis* to the acetal group at C7a and the ring fusion C4a-C7a is consequently *trans*. Therefore, the Pd catalysed hydrogenation is chelation controlled and occurs from the sterically more congested face to produce *trans*-fused lactone, 4-*epi*-mitsugashiwalactone **200**.

4.4. SYNTHESIS OF (-)-MITSUGASHIWALACTONE:

The natural lactone **17** will be obtained if the hydrogenation occurs under steric control *cis* to the allylic hydrogen atom. Hence, the hydrogenation was attempted with different catalysts to obtain a *cis*-fusion at C4a-C7a.

Conjugate reduction of α,β-unsaturated esters **184,185** with $NaBH_4$/CuCl [19] system also afforded hydroxy acetal **190** with *trans* C4a-C7a relationship. The methyl group on the β-carbon at C7 has a stronger bearing on the conjugate hydride reduction

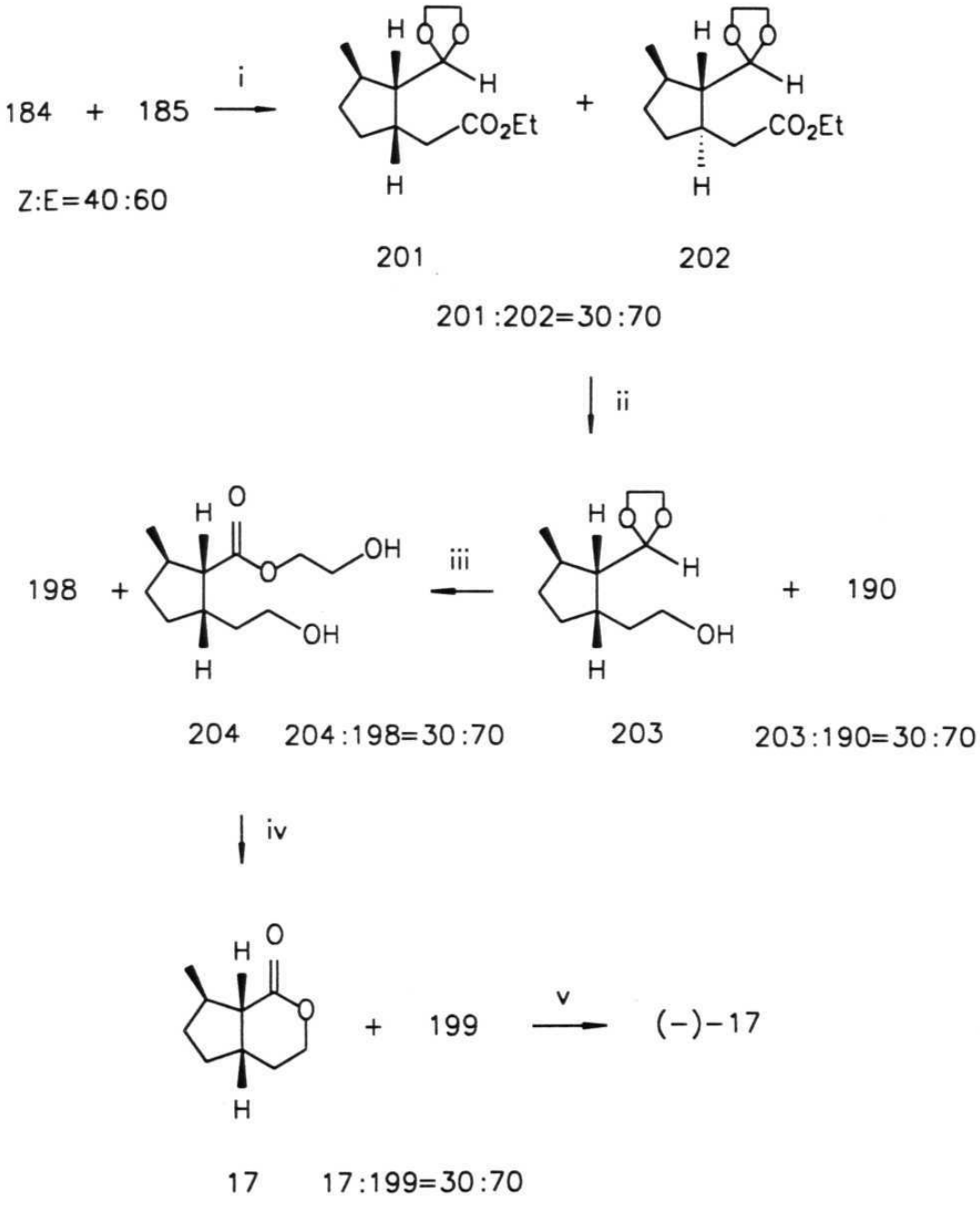
than the acetal group on α-carbon at C7a. Therefore, hydride attack occurs *anti* to C7 methyl group and produces a *trans* fusion at C4a-C7a.



Hydrogenation of esters **184,185** with homogeneous Wilkinson catalyst $RhCl(PPh_3)_3$ [20] was tried in benzene at atmospheric to elevated pressure (60 psi) and under sonication. No reaction occured and only starting esters **184,185** were recovered. When allylic alcohols **186,187** were subjected to the same conditions isomerisation occurred and *E*-isomer was isolated; once again no hydrogenation product was observed.

PtO_2 catalysed hydrogenation of esters **184,185** in EtOAc at atmospheric pressure provided a mixture of acetal esters **201,202**. The integration of acetal CH doublets at δ 4.76 and 4.82 suggested that the two isomers were produced in the ratio of 10:90. When the hydrogenation was performed at elevated pressure (60 psi) the ratio of **201,202** improved to 30:70. Reduction of acetal esters **201,202** with $LiAlH_4$ furnished acetal alcohols **203,190** and again the ratio of two isomers was 30:70. Comparison of the crude PMR spectrum of acetal alcohols **203,190** with that of palladium reduction product indicated that the minor component of the mixture corresponded to the desired stereoisomer having the *cis* relationship at C4a-C7a. The acetal **CH** doublet of the *cis* isomer **203** appeared at δ 4.84, whereas that of the *trans* isomer **190** exhibited the doublet slightly upfield at δ 4.76. Attempted chromatographic separation of the isomers **203,190** was extremely difficult.

Scheme-13

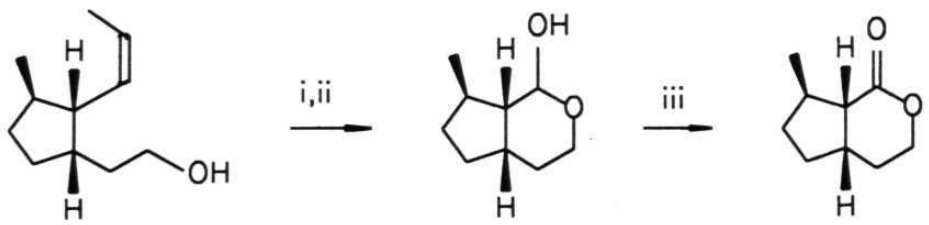


Reagents: i) PtO_2, EtOAc, 60 Psi, 10 min; ii) $LiAlH_4$, ether, 0 °C, 1 h; iii) O_3, EtOAc, -78 °C, 10 min; iv) 1N NaOH, then 1N HCl; v) SGC.

The mixture of acetals **203,190** were oxidised to the corresponding hydroxy esters **204,198** under conditions employed earlier with **198**. When the esters **204,198** were subjected to base hydrolysis the *cis*-isomer **204** cyclised, whereas the *trans*-hydroxy acid **198** remained unreacted. Thus, refluxing **204,198** in 1N NaOH for 30 min. and then acidification to pH 2 with 1N HCl and stirring for 1 h at rt furnished an easily separable mixture of *cis*-lactone **17** and unreacted *trans*-hydroxy acid **198**. The ready cyclisation of *cis*-hydroxy acid **204** to mitsugashiwalactone **17** is in agreement with final stages of Takacs and Myoung synthesis [1].

The crude material accumulated from few batches was combined and purified by SGC to afford mitsugashiwalactone **17**, whose PMR and CMR spectra were identical to the reported data. The AB CH_2O pattern (ddd) of lactone **17** appeared at δ 4.28 and 4.15 and downfield $CHCO_2$ multiplet at δ 2.66-2.45 in PMR spectrum. The lactone exhibited the expected 9 line CMR spectrum and gave a saticifactory HRMS analysis.

Scheme-14



89 205 17

Reagents: *i) O_3, CH_2Cl_2, -78 °C, PPh_3; ii) 2% HCl; iii) PCC, CH_2Cl_2.*

The optical rotation of mitsugashiwalactone **17** obtained from natural sources is not reported in published literature because the value is very low. The recorded optical rotation of $[\alpha]_D^{25}$ -3.0° ($CHCl_3$, c 0.5) is far superior to the value $[\alpha]_D^{25}$ -1.9° ($CHCl_3$, c 1.25) reported by Takacs and Myoung [1], who used (-)-citronellene **52** as the starting chiron. Thus, The synthesis of (-)-mitsugashiwalactone **17** was accomplished from *R*-(+)-pulegone in higher enantiomeric purity then so far reported in the literature.

4.5. EXPERIMENTAL AND SPECTRA:

anti-Pulegenic acid 92:

Ethyl pulegenate **158** (392 mg, 2.0 mmol); KOH (224 mg, 4.0 mmol)

Yield: 238 mg, 71%

IR: cm^{-1} 3250, 2600, 1690, 1410, 1370, 1290, 1210, 940, 700.

PMR: δ 2.98 (d, J=6 Hz, 1H, $CHCO_2H$); 2.42-2.26 (m, 3H); 2.08-1.90 (m, 1H); 1.68 (s, 3H, vinyl CH_3); 1.64 (s, 3H, vinyl CH_3); 1.36-1.20 (m, 1H); 1.08 (d, J=6 Hz, 3H, CH_3).

CMR: δ 182.18, 138.76, 126.65, 55.48, 40.73, 33.65, 30.25, 21.47, 21.14, 19.73.

anti-Pulegenic ester 171:

To pulegenic acid **92** (84 mg, 0.5 mmol) in 5 mL of acetone was added K_2CO_3 (138 mg, 1.0 mmol) and stirred for 30 min at rt. Methallyl chloride **170** (100 μL, 90 mg, 1.0 mmol) was added followed by the addition of NaI (150 mg, 1.0 mmol) and stirred for 12 h. The reaction mixture was quenched with 12 mL of H_2O and extracted with ether (3x10 mL). Brine wash and work-up afforded 126 mg of ester which was purified by SGC (hexane to 5% EtOAc/hexane).

Yield: 93 mg, 84%

IR: cm^{-1} 2900, 1720, 1640, 1440, 1370, 1290, 1220, 1120, 1000, 9000.

PMR: δ 4.98 (s, 1H, vinyl **H**); 4.90 (s, 1H, vinyl **H**); 4.49 (s, 2H, CO_2CH_2); 3.00 (d, J=6 Hz, 1H, $CHCO_2$); 2.42-2.12 (m, 3H); 2.08-1.90 (m, 1H); 1.74 (s, 3H, vinyl CH_3); 1.64 (s, 3H, vinyl CH_3); 1.60 (s, 3H, vinyl CH_3); 1.38-1.18 (m, 1H); 1.08 (d, J=6 Hz, 3H, CH_3).

CMR: δ 173.56, 140.18, 134.24, 125.87, 112.82, 67.49, 55.69, 40.59, 33.65, 30.28, 21.21, 20.99, 19.75, 19.43.

Triketone 169:

Alkene ester **171** (22 mg, 0.1 mmol); DMS (73 μL, 62 mg, 1.0 mmol).

Yield: 10 mg, 53% (keto **169** and enol **172**)

IR: cm^{-1} 3450, 2850, 1720, 1410, 1370, 1270, 1170, 1040, 730.

PMR: (for enol **172**) δ 4.72 (s, 2H, CO_2CH_2CO); 2.74-2.58 (m, 1H, allyl C**H**); 2.48-2.22 (m, 2H, allyl CH_2); 2.14 (s, 3H, $COCH_3$); 1.62-1.40 (m, 2H); 1.24 (d, J=6 Hz, 3H, CH_3).

***tert*-Alcohol 174:**

Selenium dioxide (22 mg, 0.2 mmol) in 1 mL of moist dioxane (5% H_2O) was added to a solution of methyl pulegenate **161** (36 mg, 0.2 mmol) in 1 mL of dioxane. The reaction mixture was refluxed for 2 h. Cooled to rt and filtered through celite. Work-up afforded 23 mg of alcohol **174** along with some amount of unreacted starting material **161**.

Yield: 13 mg, 34%

IR: cm^{-1} 3400, 2850, 1710, 1430, 1180, 1110, 820.

PMR: δ 5.72 to 5.68 (m, 1H, vinyl **H**); 3.70 (s, 3H, CO_2CH_3); 3.20-3.14 (m, 1H, $CHCO_2$); 2.74-2.32 (m, 2H, allyl CH_2); 1.98-1.84 (m, 1H); 1.64-1.56 (m, 1H); 1.42 (s, 3H, CH_3C-O); 1.26 (s, 3H, CH_3C-O); 1.06 (d, J=6 Hz, 3H, CH_3).

syn/anti-**Alcohols 159,160:**

Ethyl pulegenate **158** (462 mg, 3 mmol); $LiAlH_4$ (152 mg, 4 mmol).

Yield: 370 mg, 82%

$[\alpha]_D^{25}$: +14.4° ($CHCl_3$, c 2.5)

IR: cm^{-1} 3356, 2924, 1452, 1373, 1057, 1024, 890.

PMR: δ 3.70 (dd, J=12,8 Hz, 1H, OCH_2); 3.52-3.38 (m, 1H, OCH_2); 2.75 (q, J=6 Hz) and 2.46-2.36 (m) (1H, $CHCH_2O$); 2.32-2.04 (m, 3H, allyl CH_2 and OH); 2.00-1.78 (m, 1H); 1.74 and 1.70 (s, 3H, vinyl CH_3); 1.73 and 1.63 (s, 3H, vinyl CH_3); 1.54-1.18 (m, 2H); 1.08 and 0.96 (d, J=6 Hz, 3H, CH_3).

CMR: δ 136.79, 135.34, 124.72, 64.19, 61.72, 52.72, 48.04, 37.55, 36.03, 32.04, 31.43, 29.32, 28.67, 21.49, 21.37, 21.02, 20.93, 20.48, 15.36.

Analysis: Calculated for $C_{10}H_{18}O$: C=77.87%, H=11.76%; Found: C=77.92%, H=11.80%.

syn/anti-**Aldehydes 179:**

syn/anti-Alcohols **159,160** (308 mg, 2.0 mmol); PCC (645 mg, 3.0 mmol).

Yield: 232 mg, 76%

$[\alpha]_D^{25}$: +109.6° ($CHCl_3$, c 2.5)

IR: cm^{-1} 2955, 1726, 1633, 1456, 1373, 1145, 815.

PMR: δ 9.34 (d, J=6 Hz) and 9.22 (d, J=4 Hz) (1H, CHO); 3.22 (t) and 2.84 (br s) (1H, CHCHO); 2.60-2.08 (m, 3H); 2.02-1.70 (m, 1H); 1.64 (s, 3H, vinyl CH_3); 1.54 (s, 3H, vinyl CH_3); 1.40-1.18 (m, 1H); 1.06 and 0.98 (d, J=6 Hz, 3H, CH_3).

CMR: δ 199.74, 191.72, 131.30, 131.07, 128.95, 127.79, 63.10, 60.00, 39.78, 38.70, 36.09, 35.15, 33.51, 33.43, 24.43, 24.31, 20.27, 20.24, 18.63, 15.53.

anti-**179:** δ 9.22 (d, J=4 Hz, 1H, CHO); 0.98 (d, J=6 Hz, 3H, CH_3).

***syn/anti*-Acetals 180:**

Aldehydes **179** (228 mg, 1.5 mmol), ethanediol (0.9 mL, 930 mg, 15.0 mmol), triethyl orthoformate (0.5 mL, 444 mg, 3.0 mmol) containing catalytic amount of *p*-TsOH.H_2O (2.8 mg, 0.15 mmol) in 2 mL of dry benzene were stirred for 3h at rt. The reaction mixture was diluted with ether and washed with $NaHCO_3$ solution and brine. Work-up afforded 368 mg of acetal **180** which was purified by SGC (hexane to 5% EtOAc/hexane).

Yield: 275 mg, 87%

$[\alpha]_D^{25}$: +11.6° ($CHCl_3$, c 2.5)

IR: cm^{-1} 2900, 1460, 1280, 1120, 1040, 960.

PMR: δ 4.94 and 4.86 (d, J=6 Hz, 1H, acetal **H**); 4.02-3.66 (m, 4H, $(OCH_2)_2$); 2.78 (t) and 2.52 (br s) (1H, allyl C**H**); 2.46-2.08 (m, 3H); 2.02-1.82 (m, 1H); 1.65 (t, 6H, 2xCH_3); 1.32-1.16 (m, 1H); 1.12 and 0.96 (d, J=6 Hz, 3H, C**H**$_3$).

CMR: δ 139.93, 137.72, 125.27, 124.97, 105.87, 105.23, 65.03, 64.92, 64.68, 64.57, 52.91, 48.62, 37.79, 34.27, 32.63, 32.46, 29.76, 29.47, 22.32, 21.61, 21.21, 16.05.

***anti*-180:** δ 4.86 (d, J=6 Hz, 1H, acetal **H**); 0.96 (d, J=6 Hz, 3H, C**H**$_3$).

***syn/anti*-Ketoacetals 177:**

To a solution of alkeneacetals **180** (212 mg, 1.0 mmol) in 1.5 mL of CCl_4, 1.5 mL of CH_3CN and 2.5 mL of H_2O was added $NaIO_4$ (535 mg, 2.5 mmol) and catalytic amount of $RuCl_3$ (5 mg). The reaction mixture was stirred at rt for 4 h and diluted with 10 mL of CH_2Cl_2. Washed rapidly with H_2O (2x5 mL) and then brine. Work-up afforded 372 mg of ketoacetals **177** which was purified by SGC (hexane to 20% EtOAc/hexane).

Yield: 101 mg, 54%

$[\alpha]_D^{25}$: +57.2° ($CHCl_3$, c 2.5)

IR: cm^{-1} 2900, 1720, 1440, 1360, 1200, 1110, 1050, 950, 810

PMR: δ 5.16 (d, J=2 Hz) and 5.00 (d, J=4 Hz) (1H, acetal **H**); 4.02-3.72 (m, 4H, $(OCH_2)_2$); 2.66-1.74 (m, 5H); 1.52-1.32 (m, 1H); 1.14 and 1.10 (d, J=6 Hz, 3H, CH_3).

CMR: δ 217.40, 217.10, 103.29, 102.36, 65.24 (x2); 64.98, 64.41, 58.33, 55.75, 39.01, 36.66, 34.18, 33.20, 31.91, 29.63, 20.75, 15.45.

***anti*-177=181:** δ 5.16 (d, J=2 Hz, 1H, acetal **H**); 1.14 (d, J=6 Hz, 3H, CH_3).

***Z/E*-Esters 184,185:**

A 50% dispersion of NaH in mineral oil (38 mg, 0.8 mmol) was washed with dry hexane to remove the oil and 1 mL of dry THF was added. To this triethyl phosphonoacetate **178** (R=H) (224 mg, 1.0 mmol) in 1 mL of dry THF was added slowly dropwise at rt and stirred for 30 min. Then ketone **177** (36 mg, 0.2 mmol) in 1 mL of dry THF was added and again stirred for 3 days at ambient temperature. Quenched with 5 mL of H_2O and extracted with $CHCl_3$ (3x10 mL). The organic layer was washed with brine and usual work-up afforded 125 mg of esters **184,185** which was purified by SGC (hexane to 20% EtOAc/hexane).

Yield: 30 mg, 60%

$[\alpha]_D^{25}$: +21.2° ($CHCl_3$, c 2.5)

IR: cm^{-1} 2900, 1710, 1440,1370, 1270, 1120, 1060, 1030, 980, 740.

PMR: δ 5.98 and 5.84 (m, 1H, vinyl **H**); 5.24 (d, J=2 Hz) and 4.92 (d, J=4 Hz) (1H, acetal **H**); 4.12 (q, J=6 Hz, 2H, OCH_2); 4.02-3.78 (m, 4H, $(OCH_2)_2$); 3.20-3.02 (m, 1H); 2.68-2.26 (m, 3H); 2.16-1.90 (m, 2H); 1.28 and 1.22 (d, J=6 Hz, 3H, CH_3); 1.06 (t, J=6 Hz, 3H, CH_2CH_3).

CMR: δ 166.72, 166.25, 114.52, 113.56, 105.58, 104.61, 65.14, 64.99 (x2); 64.92, 59.57, 59.50, 56.27, 52.57, 36.05, 34.82, 33.49, 33.22, 32.38, 32.28, 29.65, 21.64, 20.16, 14.31.

***Z/E*-Alcohols 186,187:**

Unsaturated esters **29,30** (48 mg, 0.2 mmol); $LiAlH_4$ (15 mg, 0.4 mmol).

Yield: 34 mg, 87%

$[\alpha]_D^{25}$: +6.0° ($CHCl_3$, c 1.0)

IR: cm^{-1} 3398, 2953, 2872, 1456, 1394, 1145, 1037.

***Z*-Alcohol 186:**

$[\alpha]_D^{25}$: -31.0° ($CHCl_3$, c 1.0)

PMR: δ 5.78 (t, J=6 Hz, 1H, vinyl **H**); 4.72 (d, J=6 Hz, 1H, acetal **H**); 4.16-3.78 (m, 7H, 3xOCH_2 and O**H**); 2.52 (t, J=6 Hz, 1H, allyl **H**); 2.44-2.14 (m, 2H, allyl CH_2); 2.02-1.82 (m, 1H); 1.42-1.12 (m, 2H); 1.02 (d, J=6 Hz, 3H, CH_3).

CMR: δ 145.82, 123.89, 105.33, 64.88, 64.73, 59.91, 51.42, 35.82, 33.75, 32.27, 21.07.

***E*-Alcohol 187:**

$[\alpha]_D^{25}$: +41.0° ($CHCl_3$, c 1.0)

PMR: δ 5.68 (br s, 1H, vinyl **H**); 4.92 (d, J=4 Hz, 1H, acetal **H**); 4.16 (d, J=6 Hz, 2H, OCH_2); 4.04-3.82 (m, 4H, $(OCH_2)_2$); 2.56-1.82 (m, 6H); 1.44-1.18 (m, 1H); 1.06 (d, J=6 Hz, 3H, CH_3).

CMR: δ 145.56, 122.51, 106.49, 64.90 (x2); 60.66, 54.29, 34.89, 33.61, 28.82, 20.50.

***syn/anti*-Acetal acetates 193,194:**

Pyridine (160 μL, 158 mg, 2.0 mmol), Ac_2O (100 μL, 102 mg, 1.0 mmol) and DMAP (5 mg, 0.04 mmol) were added to alcohol **186**, **187** (20 mg, 0.1 mmol) at 0 °C. The reaction mixture was stirred for 4 h and diluted with ether. Organic layer washed

with aq. $CuSO_4$ solution, saturated $NaHCO_3$ solution and brine. Work-up afforded 29 mg of acetate **193,194** which was purified by SGC (hexane to 20% EtOAc/hexane).

Yield: 22 mg, 91%

IR: cm^{-1} 2926, 2856, 1730, 1462, 1377, 1116, 1062.

PMR: δ 5.70-5.46 (m, 1H, vinyl **H**); 4.90 and 4.82 (d, J=6 Hz, 1H, acetal **H**); 4.74-4.50 (m, 2H, $CH_2OC(O)$); 4.00-3.76 (m, 4H, $(OCH_2)_2$; 2.60-2.42 (m, 1H, allyl C**H**); 2.40-2.22 (m, 2H, allyl CH_2); 2.06 (s, 3H, $COCH_3$); 2.00-1.80 (m, 1H); 1.42-1.18 (m, 2H); 1.04 (overlapping d, J=6 Hz, 3H, CH_3).

***trans*-Hydroxyacetal 190:**

Allylic alcohol **186**, **187** (40 mg, 0.2 mmol); Pd/C (20 mg).

Yield: 30 mg, 75%

$[\alpha]_D^{25}$: -13.6° ($CHCl_3$, c 2.5)

IR: cm^{-1} 3422, 2950, 2870, 1460, 1400, 1110, 1050, 950, 875.

PMR: δ 4.76 (d, J=6 Hz, 1H, acetal **H**); 4.06-3.82 (m, 4H, $(OCH_2)_2$); 3.74-3.60 (m, 2H, OCH_2); 2.64-2.40 (br s, 1H, O**H**); 2.14-1.92 (m, 2H); 1.84-1.56 (m, 3H); 1.52-1.14 (m, 3H); 1.06 (d, J=6 Hz, 3H, CH_3); 1.14-0.86 (m, 1H).

CMR: δ 107.20, 65.01, 64.66, 61.15, 54.54, 39.59, 37.40, 36.82, 34.02, 32.51, 20.86.

Analysis: Calculated for $C_{11}H_{20}O_3$: C=65.97%, H=10.07%; Found C=65.98%, H=9.97%.

***trans*-Hydroxyester 198:**

Hydroxyacetal **190** (10 mg, 0.05 mmol) was dissolved in 1 mL of EtOAc and cooled to -78 °C and ozonised until the blue colour persisted. Excess ozone was removed by flushing with oxygen. The mixture was washed with brine. Work-up gave hydroxyester **198** which was pure enough to carry out the next reaction.

Yield: 11 mg, ~99% (crude)

$[\alpha]_D^{25}$: -13.2° ($CHCl_3$, c 2.5)

IR: cm^{-1} 3420, 2953, 2872, 1728, 1456, 1381, 1263, 1159, 1080, 887, 736.

PMR: δ 4.42-4.12 (m, 2H, OCH_2); 3.80 (t, J=6 Hz, 2H, CO_2CH_2); 3.76-3.54 (m 2H, OCH_2); 3.60-3.40 (br s, 2H, 2xOH); 2.50-2.14 (m, 2H); 2.02-1.76 (m, 2H); 1.72-1.60 (m, 1H); 1.46-1.14 (m, 3H); 1.10-0.84 (m, 1H); 0.98 (d, J=6 Hz, 3H, CH_3).

CMR: δ 176.48, 65.84, 61.03 (x2); 58.59, 40.82, 39.79, 38.71, 33.33, 31.55, 19.71.

***trans*-Hydroxyacid 199:**

Hydroxyester **198** (10.8 mg, 0.05 mmol) and 1N NaOH (1 mL) were refluxed for 30 min and cooled to rt. The reaction mixture was extracted with ether to remove the neutral products. Aqueous layer was acidified with 1N HCl (>1 mL) and saturated with NaCl. Extracted with EtOAc (3x10 mL) and washed with brine. Work-up afforded hydroxyacid **199** which was subjected for cyclisation without any purification.

Yield: 8.5 mg, 98% (crude)

$[\alpha]_D^{25}$: -12.0° ($CHCl_3$, c 1.0)

IR: cm^{-1} 3300, 2953, 1707, 1381, 1100, 950, 845.

PMR: δ 7.24-6.70 (br s, 2H, CO_2H and OH); 3.68 (t, J=6 Hz, 2H, OCH_2); 2.76-2.18 (m, 3H); 2.06-1.86 (m, 2H); 1.74-1.62 (m, 1H); 1.48-1.16 (m, 3H); 1.10 (d, J=6 Hz, 3H, CH_3).

CMR: δ 181.38, 61.45, 58.63, 41.20, 39.86, 38.31, 33.40, 31.35, 19.88.

(-)-4-*epi*-Mitsugashiwalactone 200:

Hydroxyacid **199** (8.6 mg, 0.05 mmol) was dissolved in 20 mL of dry toluene and catalytic amount (~2 mg) of PPTS was added. The solution was heated at 120 °C with slow removal of toluene by short-path distillation. The residue was dissolved in

10 mL of EtOAc and washed with $NaHCO_3$ solution and with brine. Usual work-up afforded 6 mg of lactone which was purified by SGC (hexane to 20% EtOAc/hexane).

Yield: 4.3 mg, 56%

$[\alpha]_D^{25}$: -39.0° ($CHCl_3$, c 0.5)

IR: cm^{-1} 2955, 2870, 1745, 1462, 1398, 1260, 1165, 1138, 1097, 1057, 941.

PMR: δ 4.46-4.24 (m, 2H, OCH_2); 2.30-2.08 (m, 2H); 2.06-1.86 (m, 2H); 1.82-1.60 (m, 2H); 1.46-1.32 (m, 2H); 1.26-1.12 (m, 1H); 1.20 (d, J=6 Hz, 3H, CH_3).

CMR: δ 174.42, 68.31, 53.82, 40.37, 33.51, 31.66, 30.25, 28.42, 20.61.

Analysis: Calculated for $C_9H_{14}O_2$: C=70.10%, H=9.15%; Found: C≈70.21%, H=9.19%.

LRMS: 155 (M+1).

cis/trans-**Acetalesters 201,202:**

Unsaturated ester **186, 187** (12 mg, 0.05 mmol); PtO_2 (5 mg); EtOAc (1 mL); 60 psi; 15 min.

Yield: 11 mg, 90%

$[\alpha]_D^{25}$: +23.0° ($CHCl_3$, c 1.0)

IR: cm^{-1} 2953, 1736, 1462, 1375, 1260, 1160, 1120, 1033, 975, 670.

PMR: δ 4.82 and 4.76 (d, J=4 Hz, 1H, acetal **H**); 4.18-4.06 (m, 2H, CO_2CH_2); 4.00-3.74 (m, 4H, $(OCH_2)_2$); 2.72-2.52 (m, 2H, CH_2CO_2); 2.44-2.10 (m, 2H); 2.00-1.68 (m, 3H); 1.50-1.36 (m, 1H); 1.28-1.18 (m, 3H, CH_2CH_3); 1.06 and 1.04 (d, J=6 Hz, 3H, CH_3); 1.00-0.86 (m, 1H).

CMR: δ 173.48, 173.12, 106.55, 105.46, 65.24, 64.97 (x2); 64.41, 59.94, 58.36, 55.45, 51.05, 40.81, 38.98, 37.73, 36.16, 35.94, 34.33, 33.70, 33.53, 31.85, 31.27, 29.65, 21.77, 20.94, 20.74.

***cis/trans*-Hydroxyacetals 203,190:**

Acetalester **201,202** (25 mg, 0.1 mmol); $LiAlH_4$ (6 mg, 0.15 mmol).

Yield: 16 mg, 80%

$[\alpha]_D^{25}$: -20.0° ($CHCl_3$, c 1.0)

PMR: δ 4.84 (d, J=6 Hz, acetal **H**).

***cis/trans*-Hydroxyesters 204,198:**

Hydroxyacetal **203,190** (10 mg, 0.05 mmol); EtOAc (1 mL); O_3, -78 °C.

Yield: 11 mg, ~99% (crude)

$[\alpha]_D^{25}$: -21.0° ($CHCl_3$, c 1.0).

(-)-Mitsugashiwalactone 17:

1N NaOH (2 mL) was added to hydroxyester **204,198** (21.6 mg, 0.1 mmol) and refluxed for 30 min. Cooled to rt and extracted with ether to remove the neutral products. Aqueous layer was acidified to pH 2 with 1N HCl (5 mL) and stirred for 1 h at rt. Extracted with EtOAc (3x10 mL) and washed with brine. Work-up afforded a mixture of *trans*-hydroxyacid **199** and *cis*-lactone **17** (14 mg) which were seperated by SGC (hexane to 20% EtOAc/hexane, then EtOAc)

Yield: 3 mg, 74%

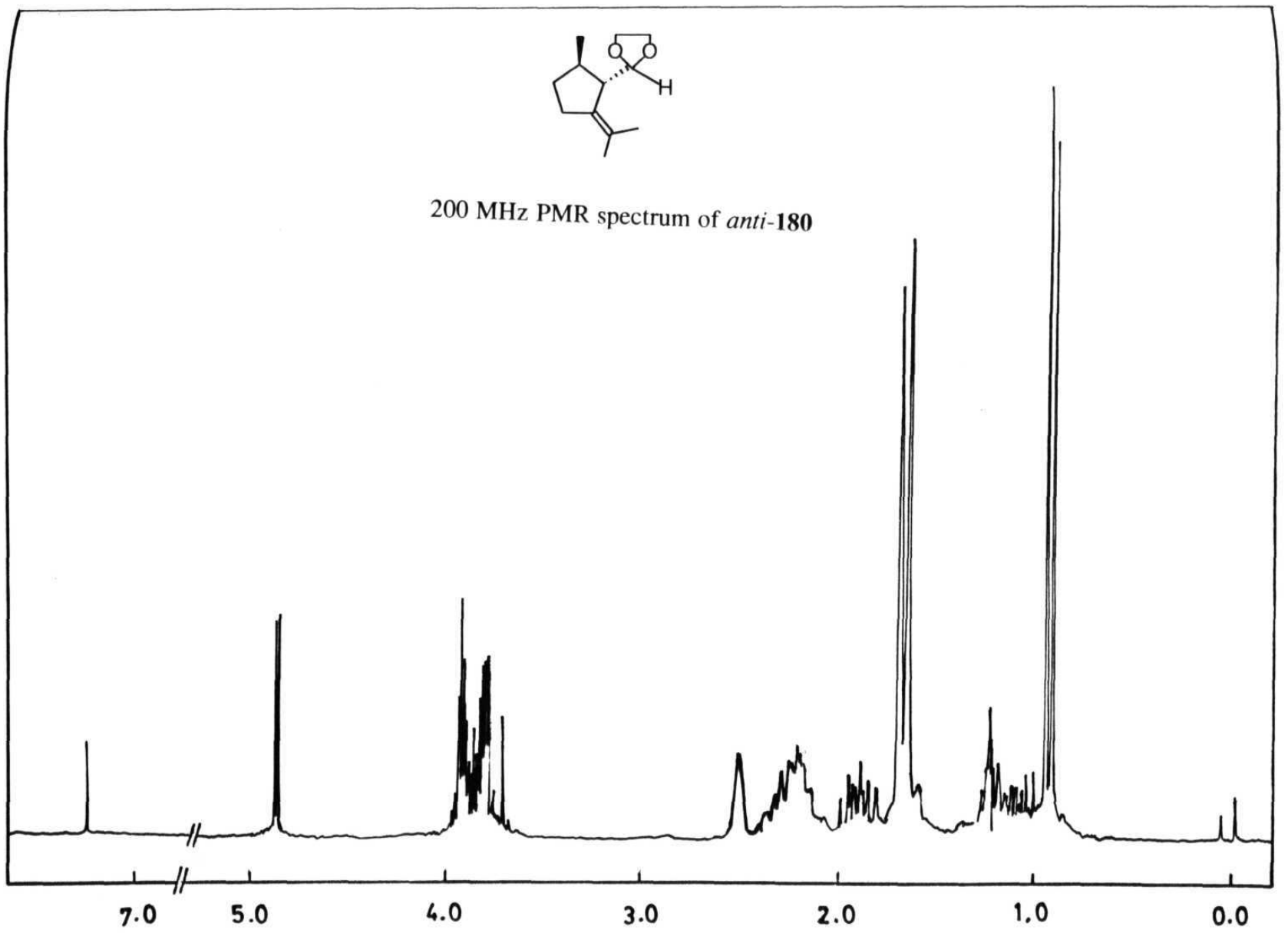
$[\alpha]_D^{25}$: -3.0° ($CHCl_3$, c 0.5)

IR: cm^{-1} 2924, 2852, 1734, 1462, 1392, 1257, 1178, 1074.

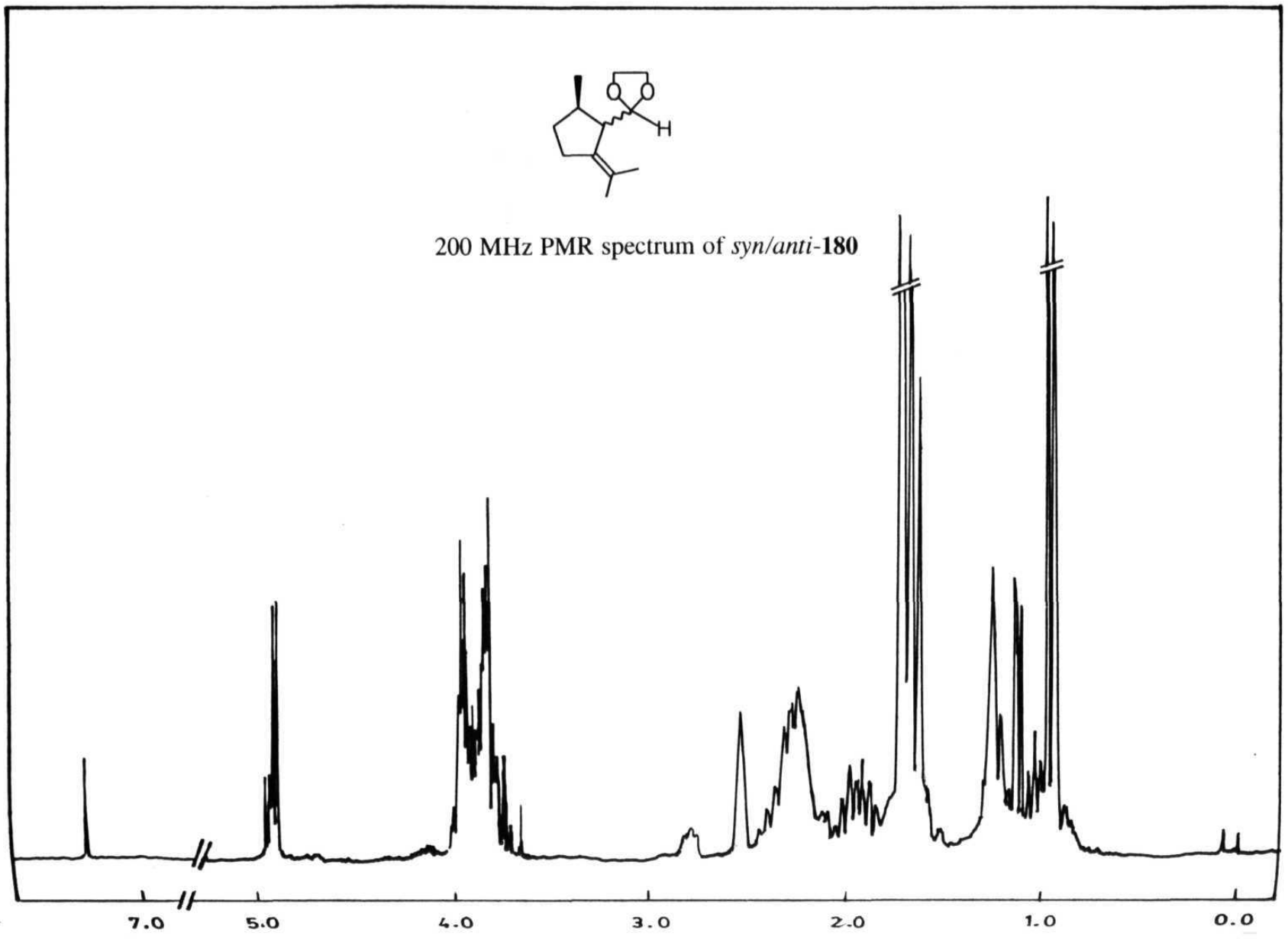
PMR: δ 4.28 (ddd, J=12,6,2 Hz, 1H, OCH_2); 4.15 (ddd, J=12,6,2 Hz, 1H, OCH_2); 2.66-2.45 (m, 1H, $CHCO_2$); 2.34 (t, J=12 Hz, 1H); 2.30-2.16 (m, 1H); 2.08-1.84 (m, 2H); 1.72-1.44 (m, 2H); 1.32-1.15 (m, 2H); 1.16 (d, J=6 Hz, 3H, CH_3).

CMR: δ 174.51, 66.86, 50.22, 39.49, 36.29, 34.62, 32.68, 29.24, 19.90.

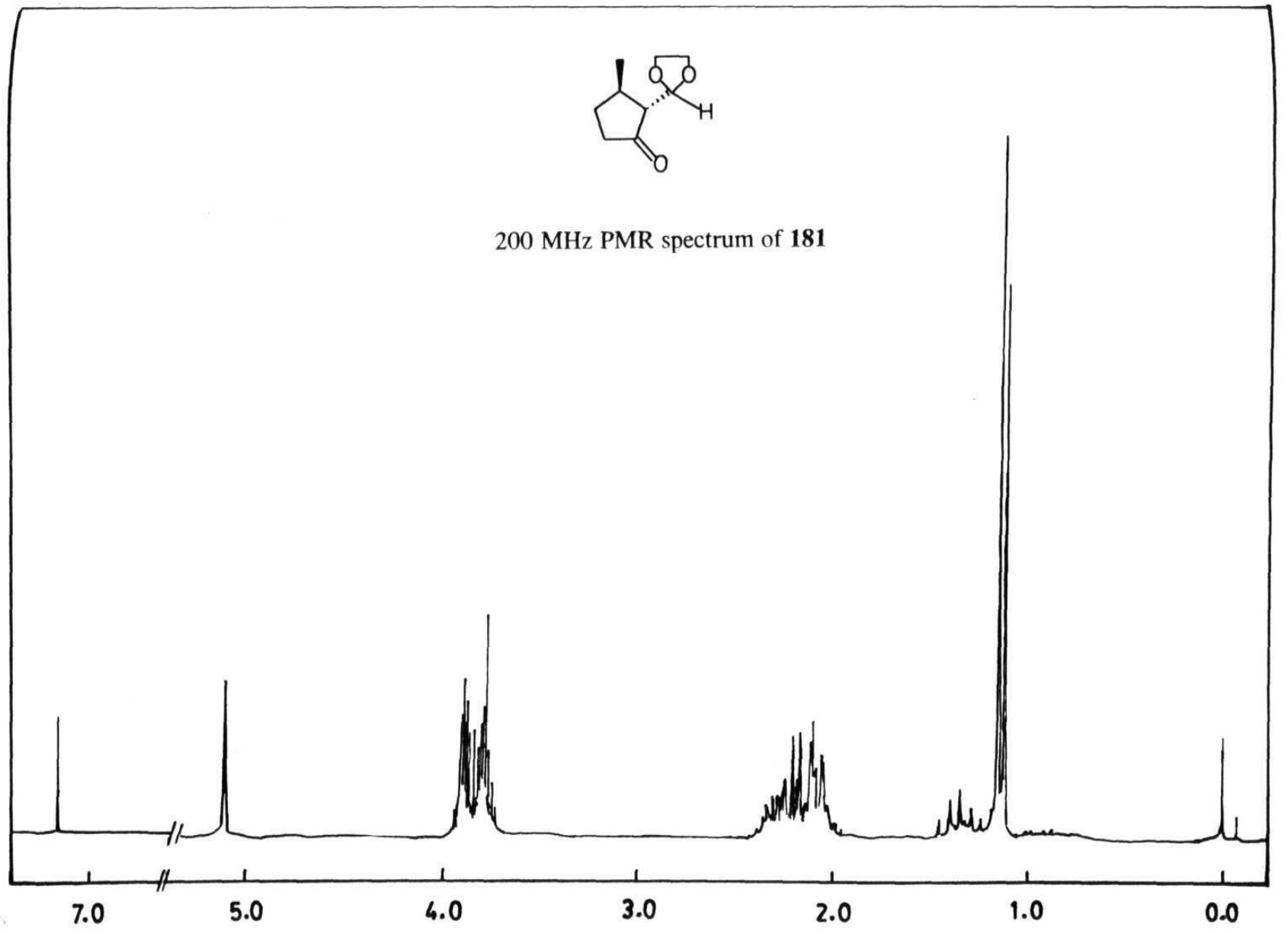
HRMS: Calculated for $C_9H_{14}O_2$: 154.0994; Found 154.0994.



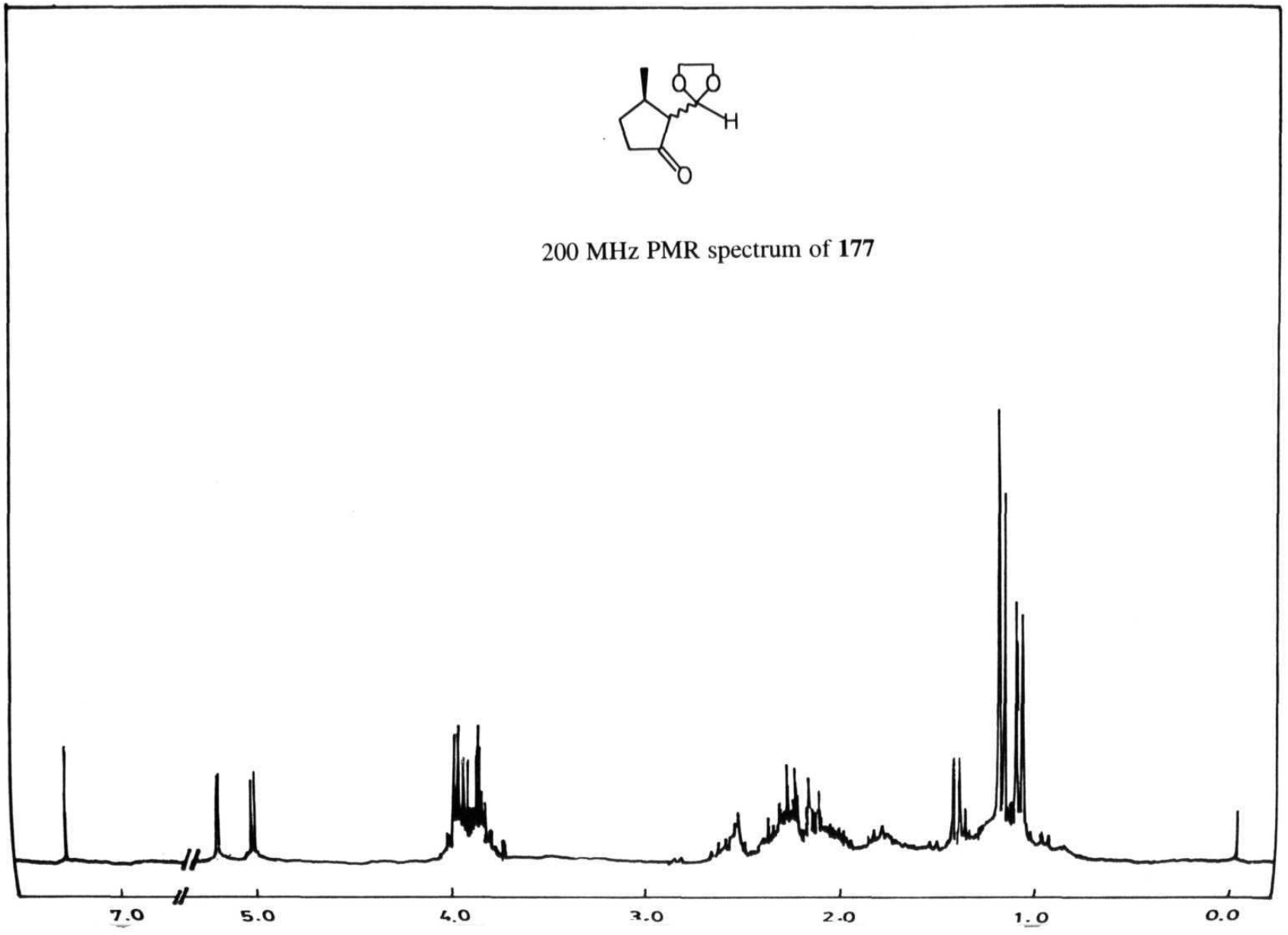
200 MHz PMR spectrum of *anti*-**180**



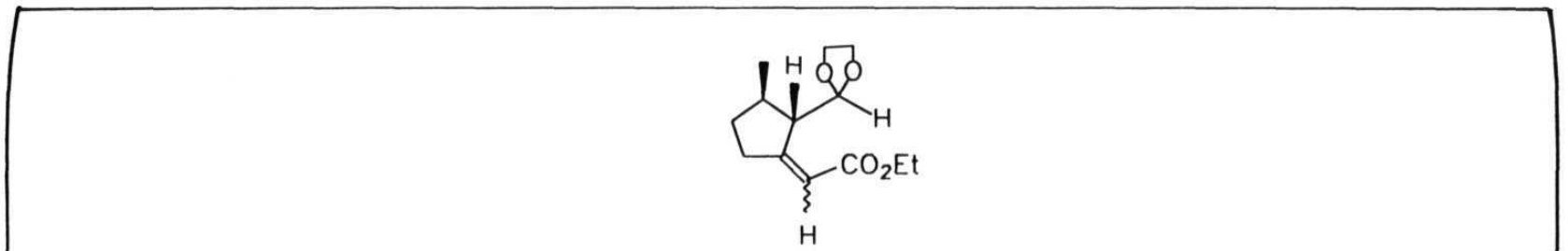
200 MHz PMR spectrum of *syn/anti*-**180**



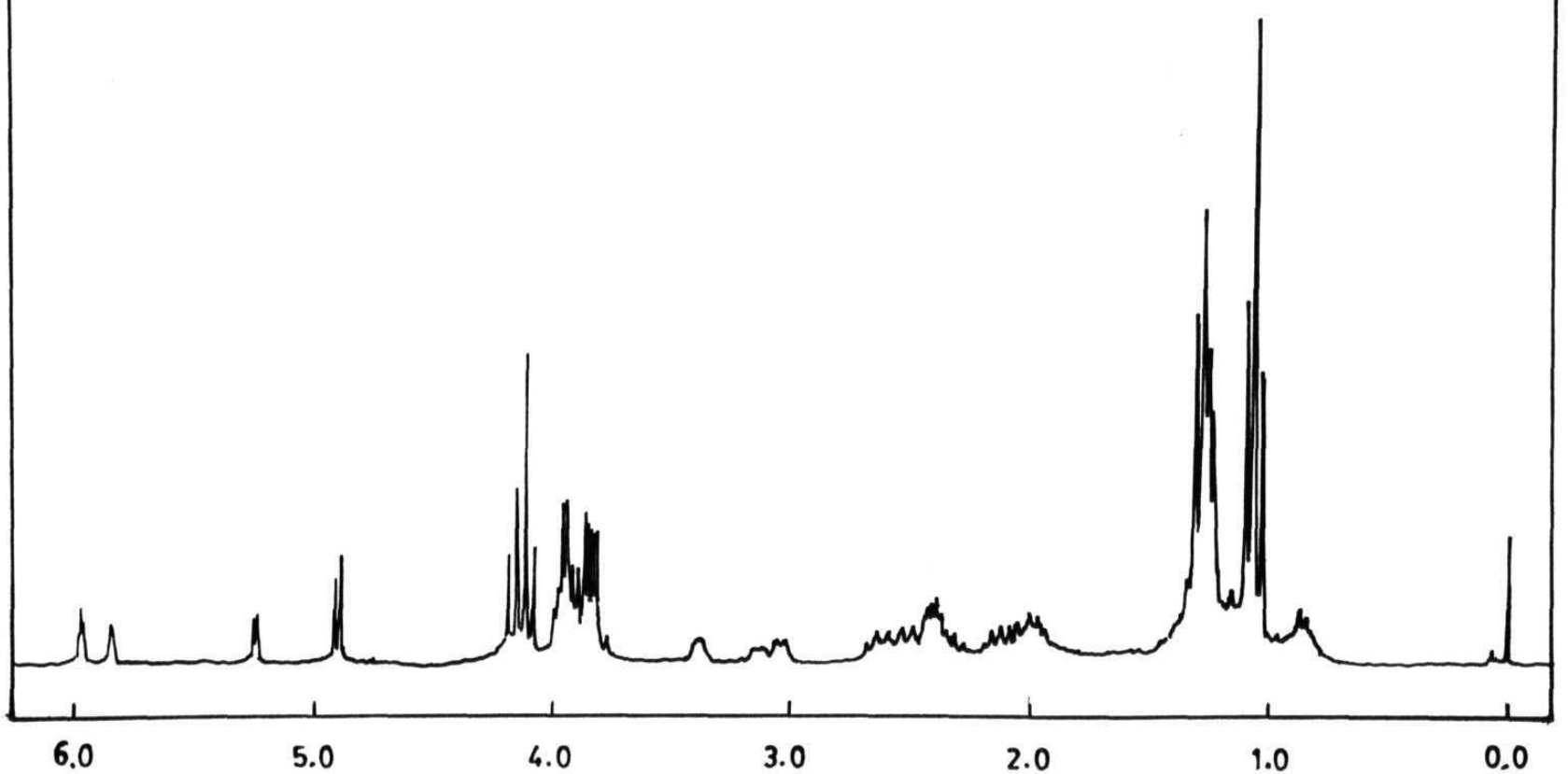
200 MHz PMR spectrum of **181**

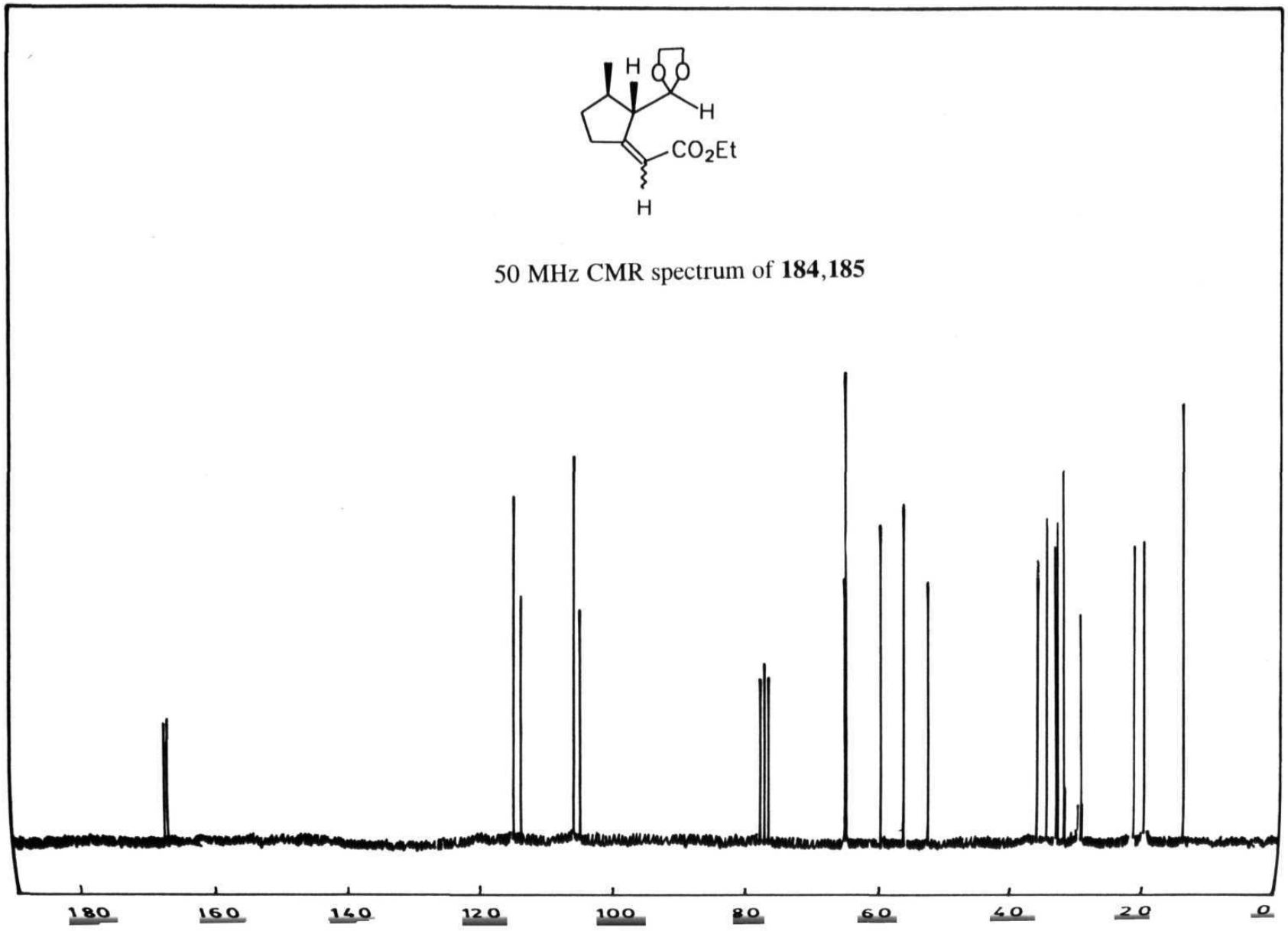


200 MHz PMR spectrum of **177**

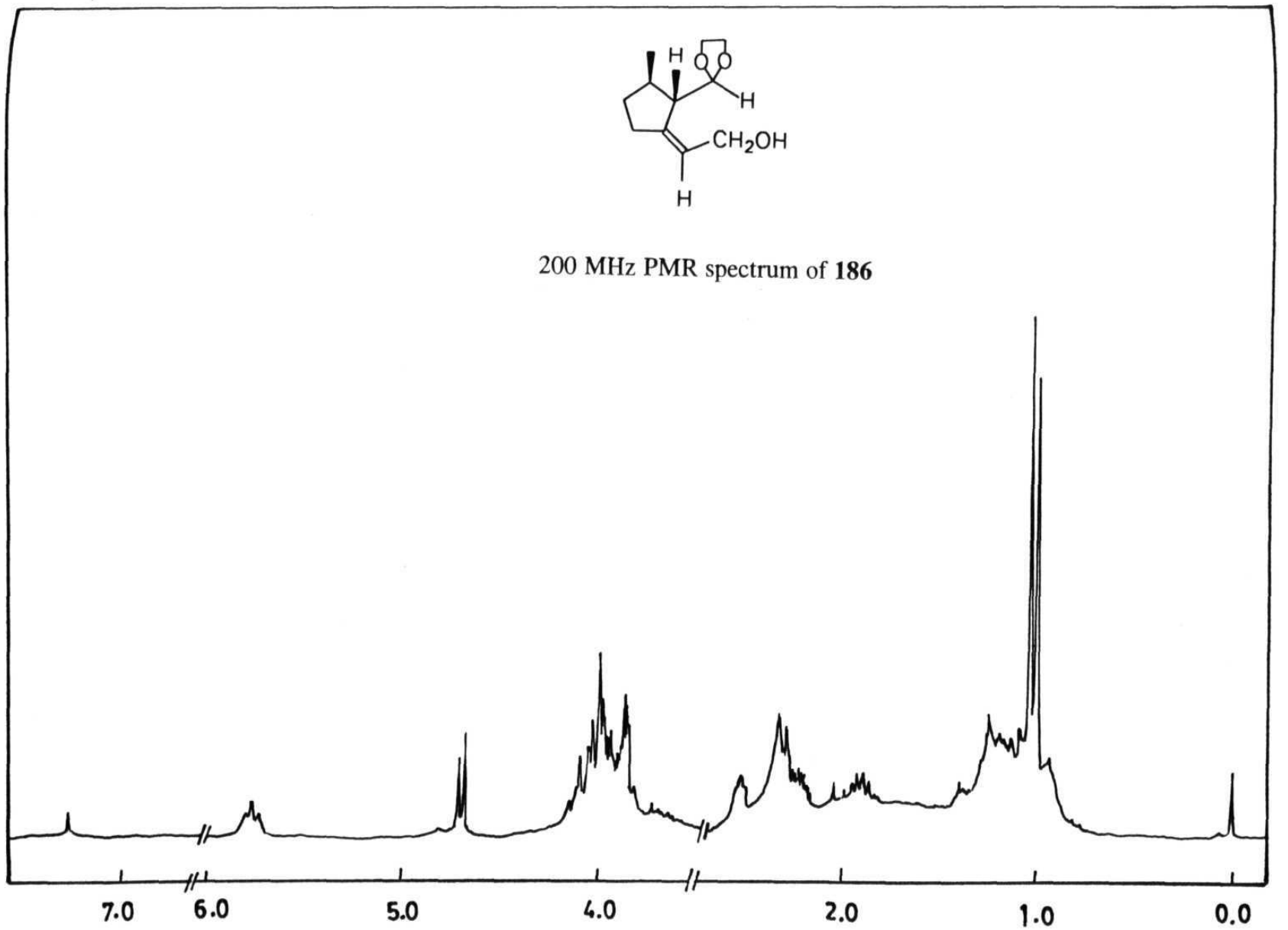


200 MHz PMR spectrum of **184,185**

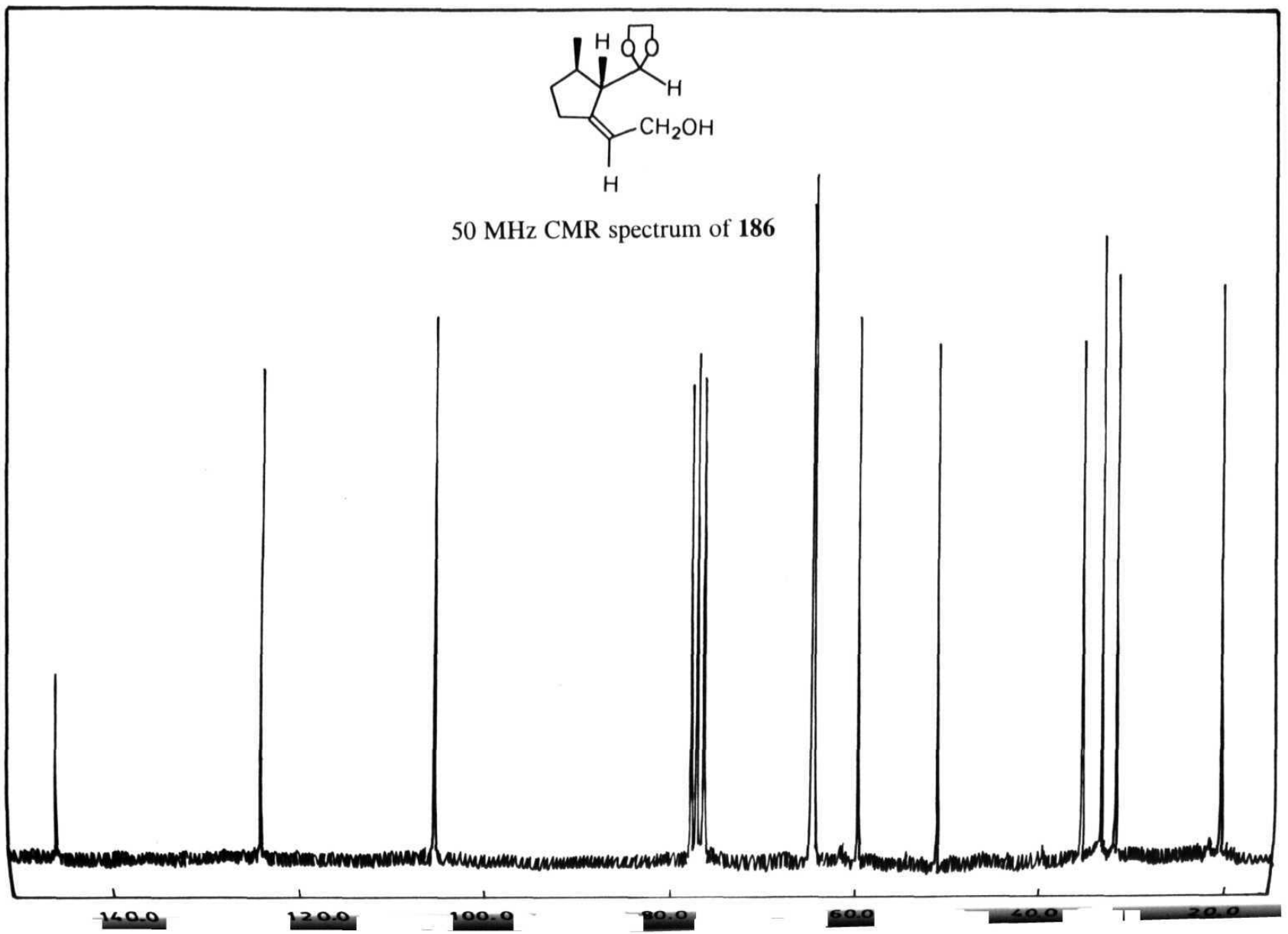




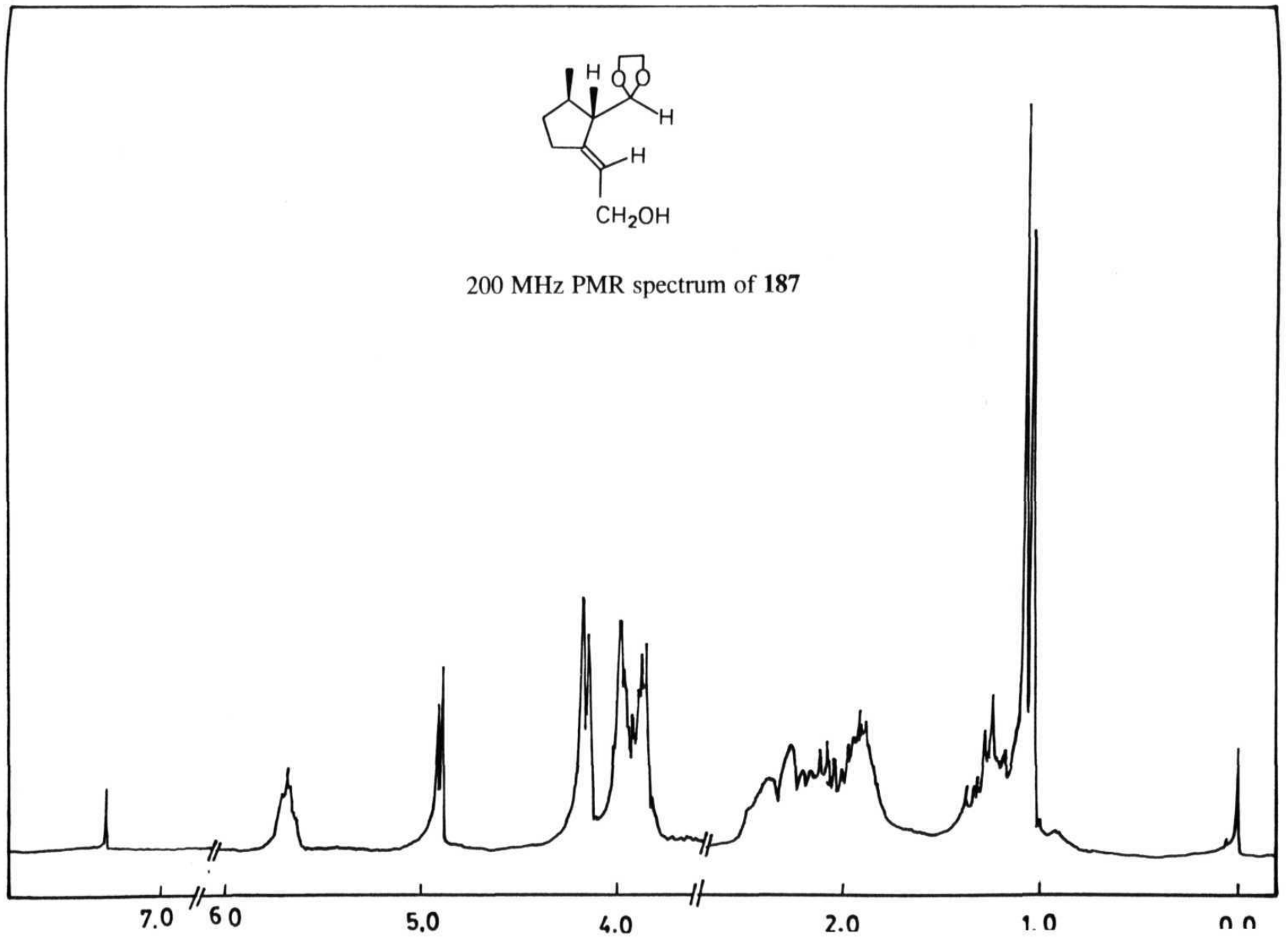
50 MHz CMR spectrum of **184**,**185**



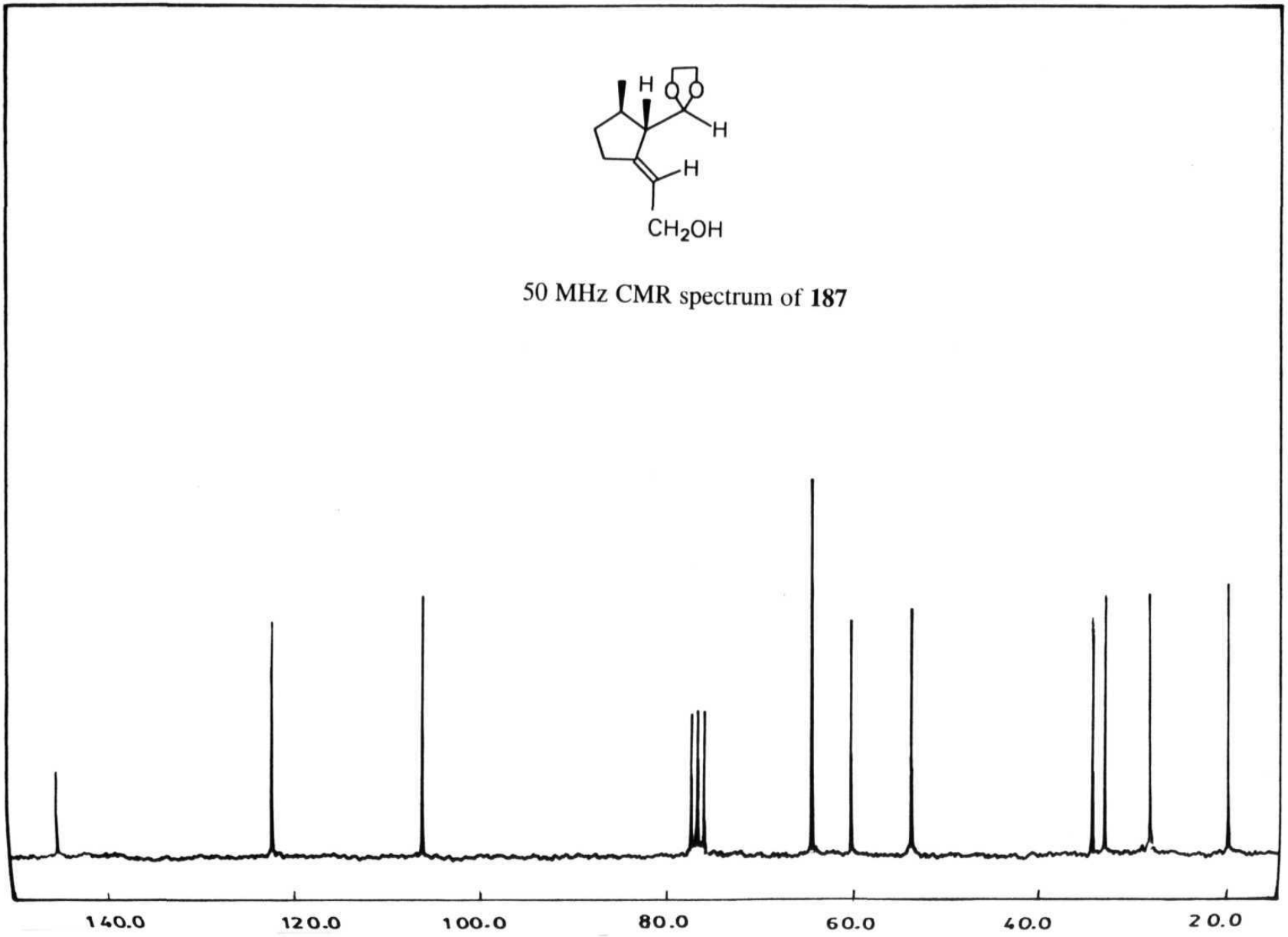
200 MHz PMR spectrum of **186**



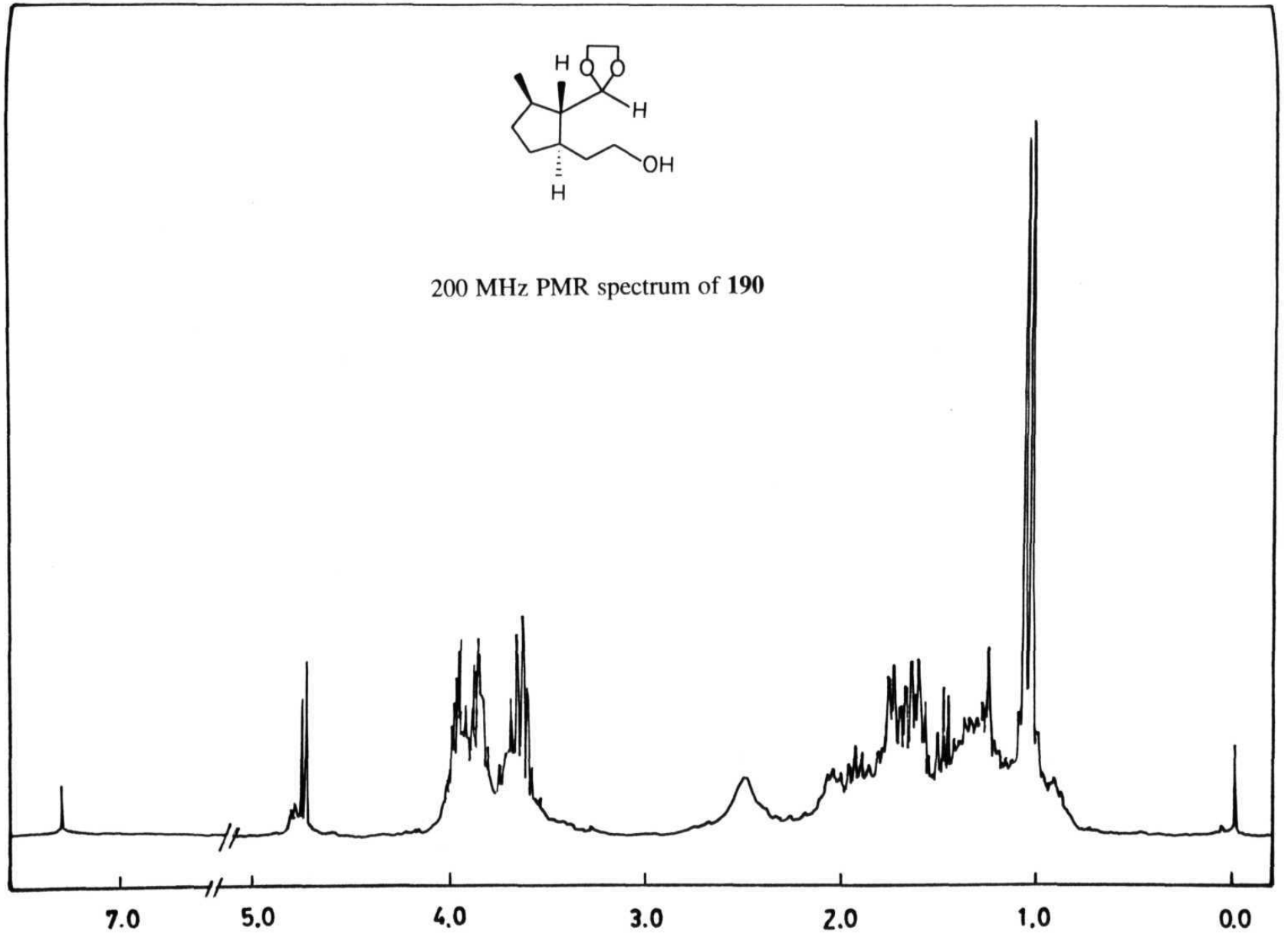
50 MHz CMR spectrum of **186**



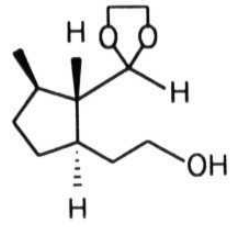
200 MHz PMR spectrum of **187**



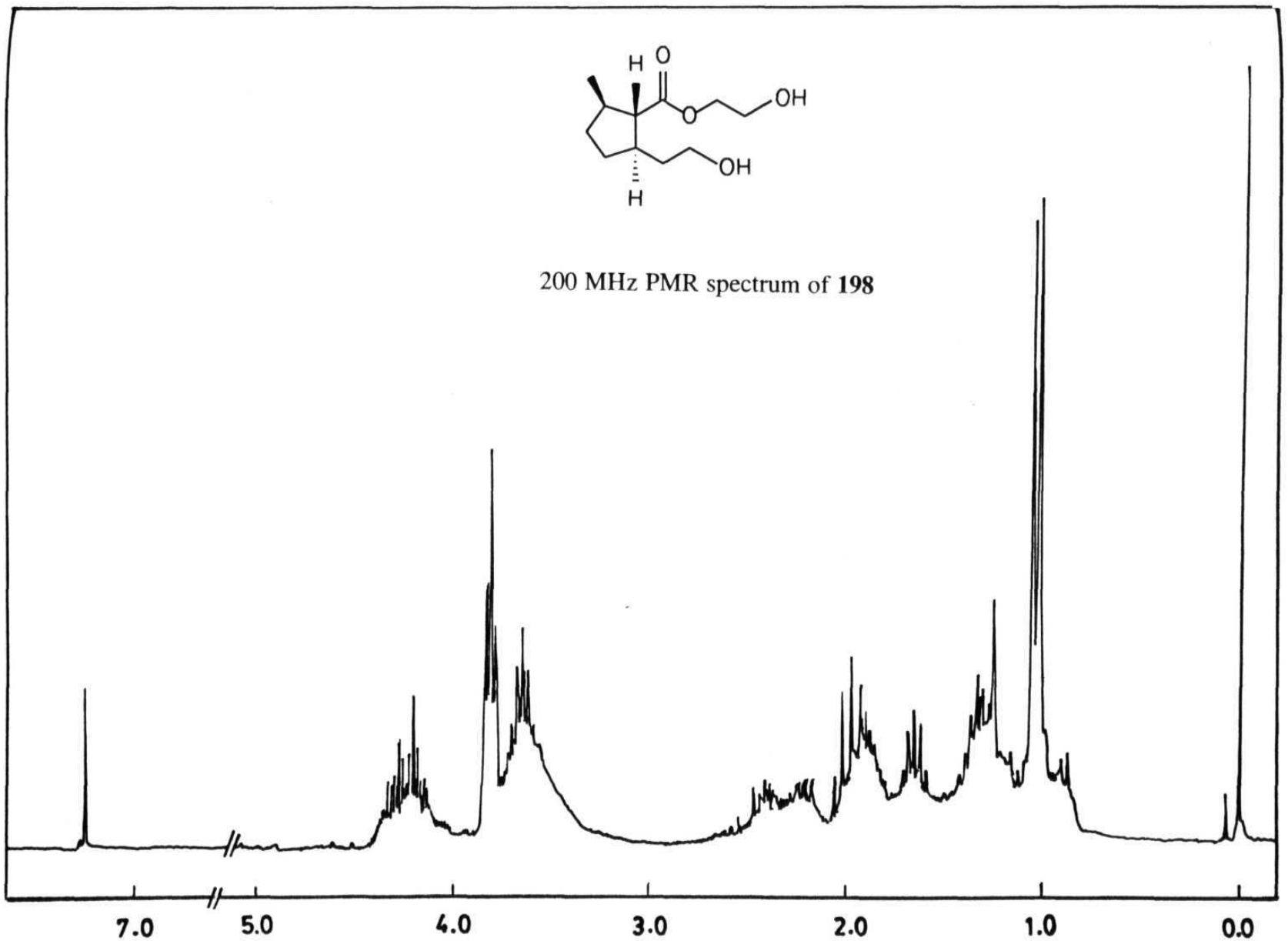
50 MHz CMR spectrum of **187**



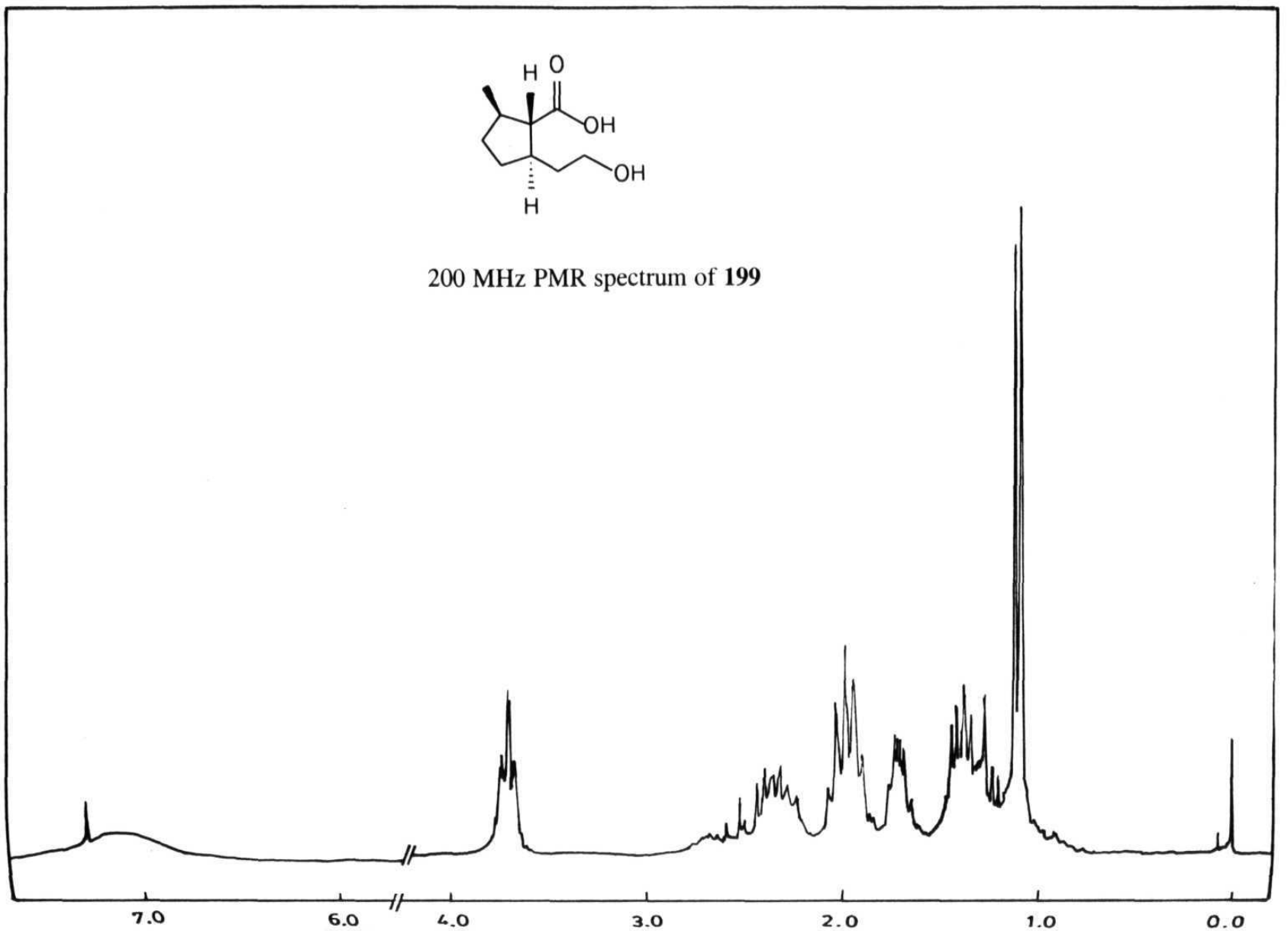
200 MHz PMR spectrum of **190**



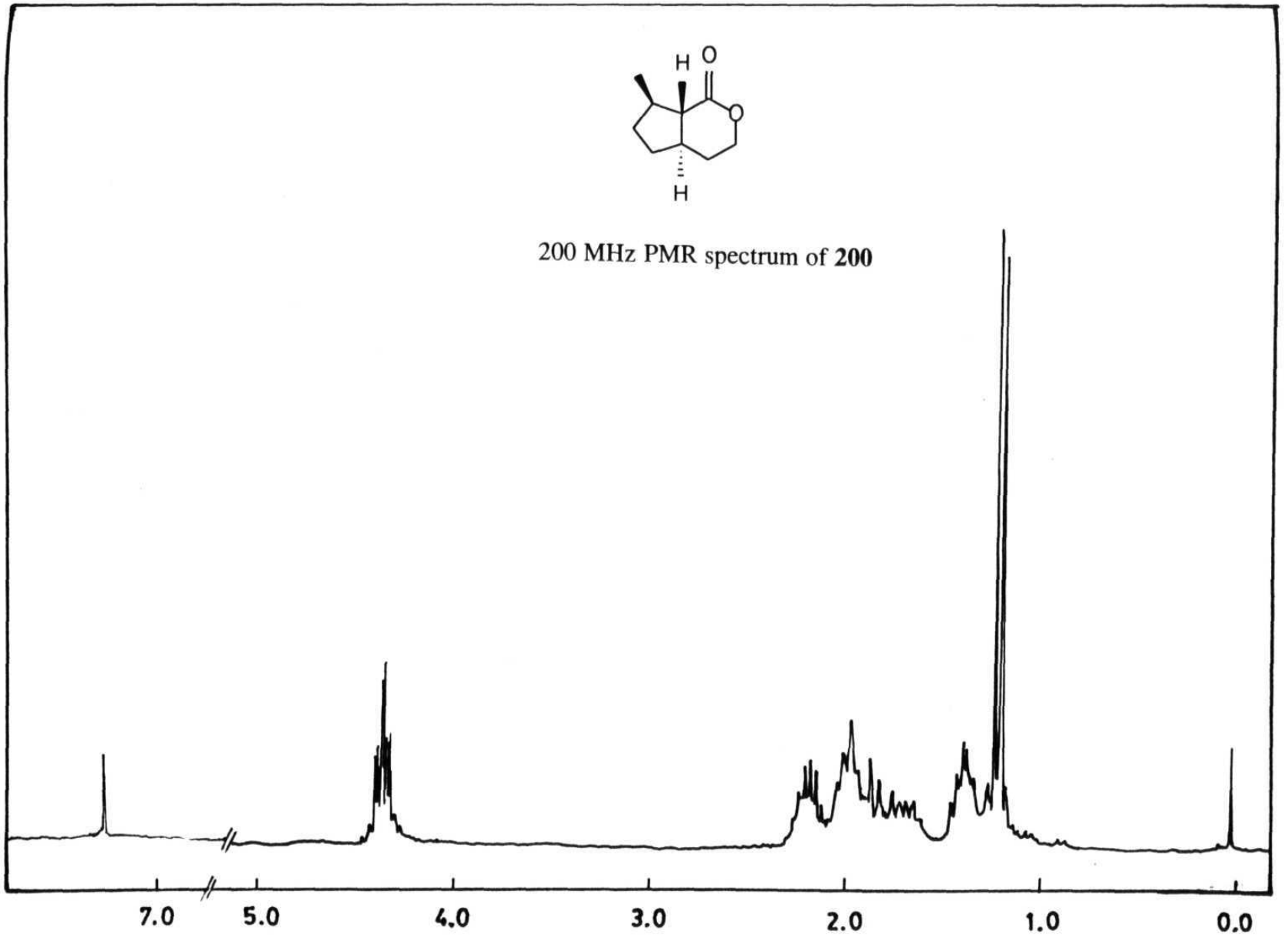
50 MHz CMR spectrum of **190**



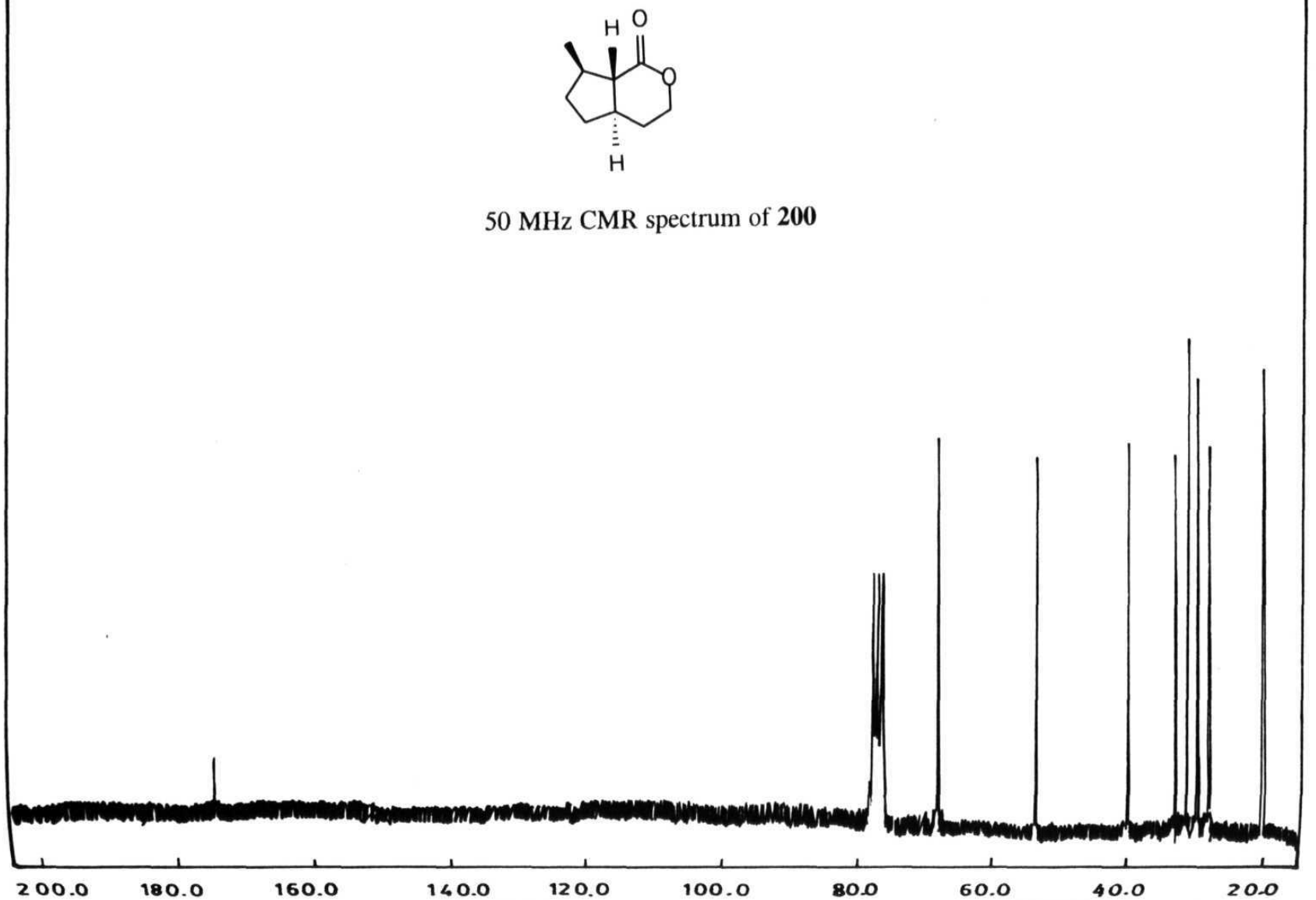
200 MHz PMR spectrum of **198**



200 MHz PMR spectrum of **199**

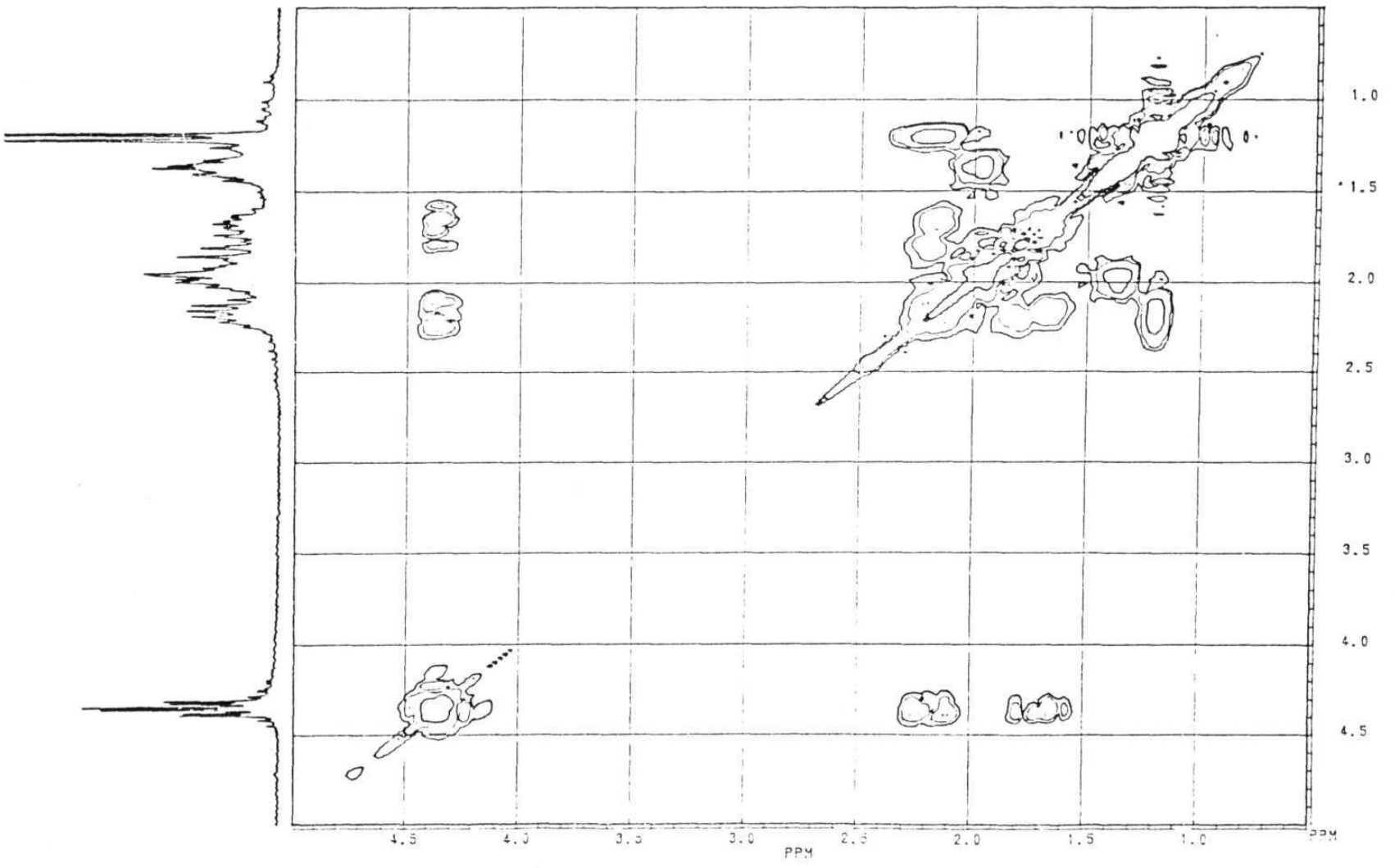


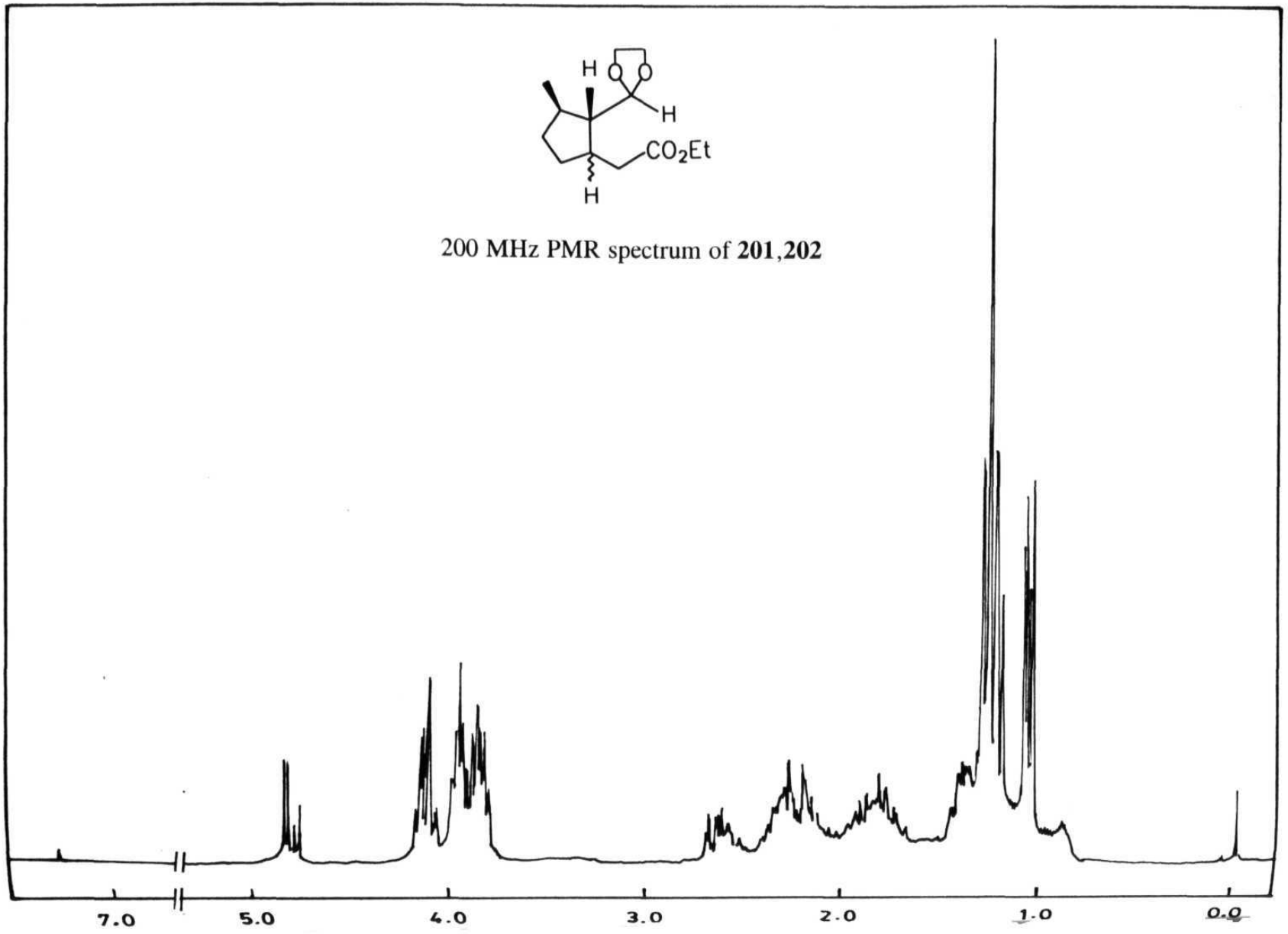
200 MHz PMR spectrum of **200**



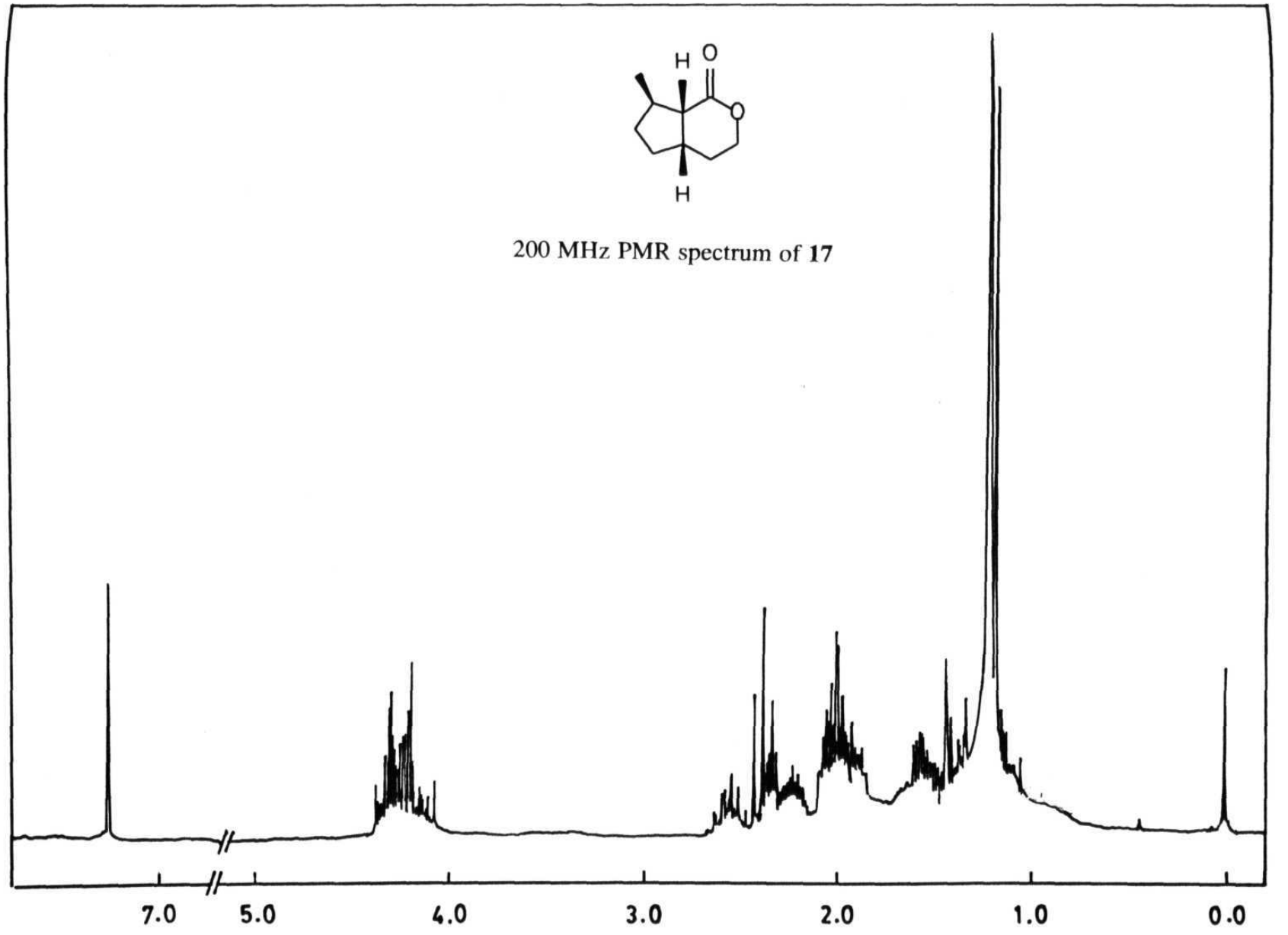
50 MHz CMR spectrum of **200**

2D H-H COSY spectrum of **200**

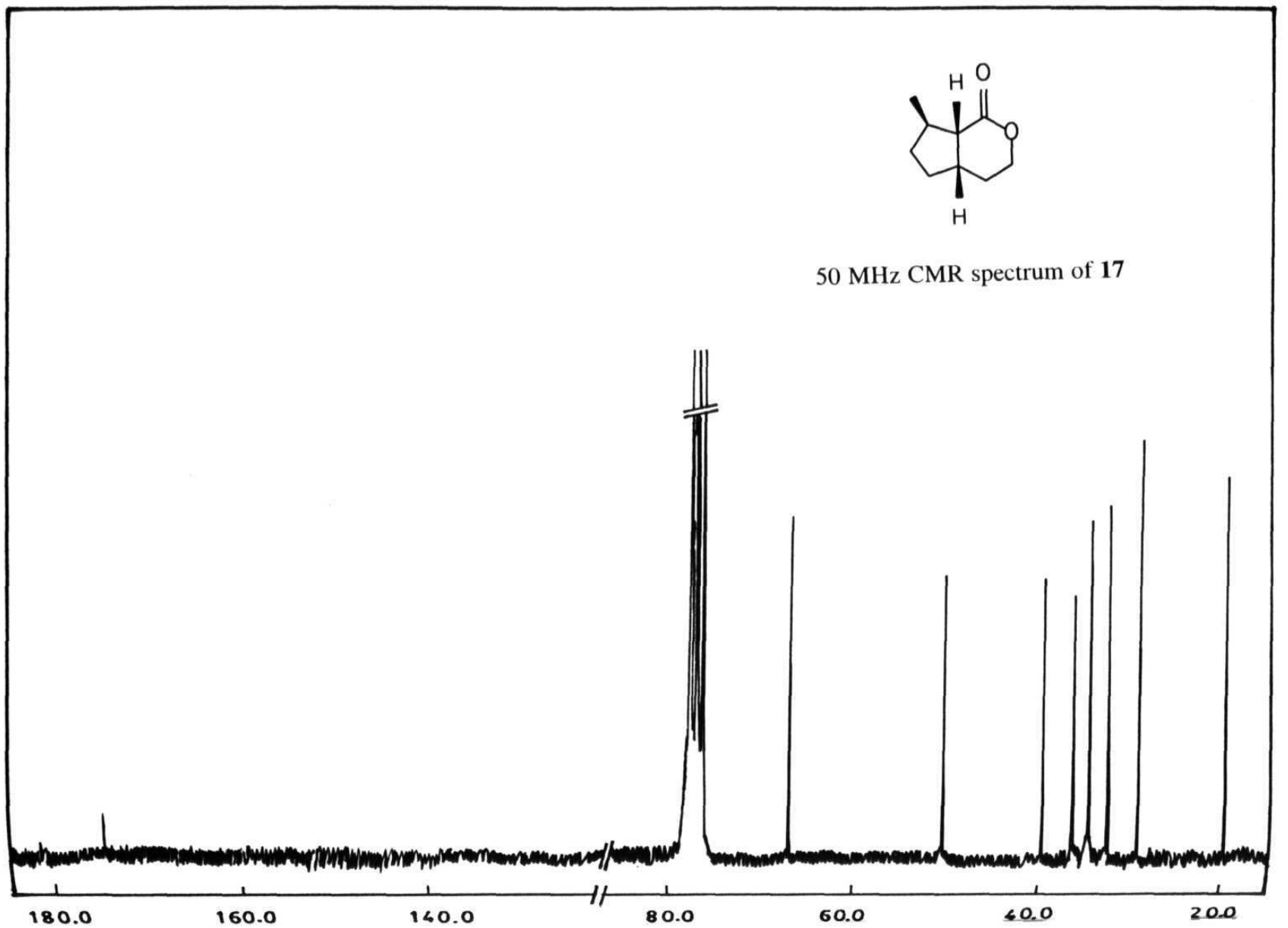




200 MHz PMR spectrum of **201**,**202**



200 MHz PMR spectrum of **17**



50 MHz CMR spectrum of **17**

4.6. REFERENCES AND NOTES:

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CHAPTER-5
SYNTHESIS OF ANHYDROMEVALONOLACTONE AND ITS THIOLACTONE

5.1. INTRODUCTION:

The work described in this chapter is part of an approach towards the total synthesis of tricyclic sesquiterpene, subergorgic acid **206**. This project was, however, subsequently abondoned because of numerous problems along the way. A few off shoot results are discussed here.

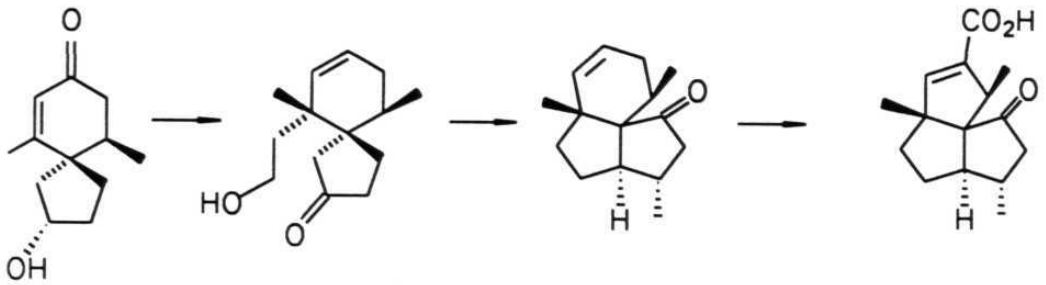
5.2. SYNTHETIC APPROACH TOWARDS SUBERGORGIC ACID:

Subergorgic acid **206** was discovered by Wu, Yiao and Long in 1982 during the course of an investigation of the chemical constituents of gorgonians from the south China sea [1]. It is a powerful cardiotoxic agent having the capacity for inhibiting neuromuscular transmission at levels below 0.20 μg/mL. The distinctive triquinane framework of **206** was initially deduced based on spectroscopic data [1], and subsequently confirmed by X-ray crystallographic analysis [2].

So far, two racemic syntheses and one enantioselective synthesis for subergorgic acid **206** are reported. The first of these, due to Iwata and co-workers [3] is based on intramolecular alkylation within a functionalised spiro[4,5]dec-6-en-8-one **208** and subsequent construction of ring C *via* aldol condensation of a dialdehyde produced by ozonolysis of cyclohexene **209**.

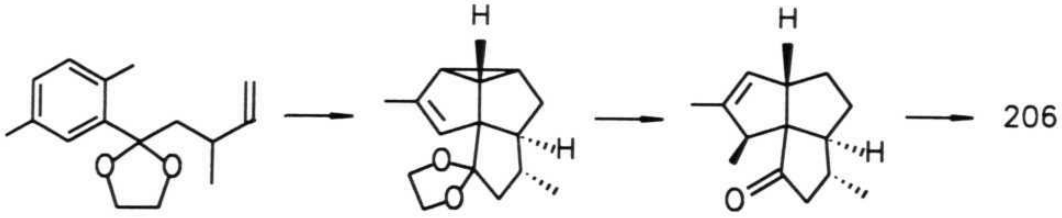
The more expeditious Wender's [4] approach features an arene-olefin cycloaddition of **210** in tandem with a free radical addition step involving a vinylcyclopropane **211**.

Scheme-1



207 208 209 206

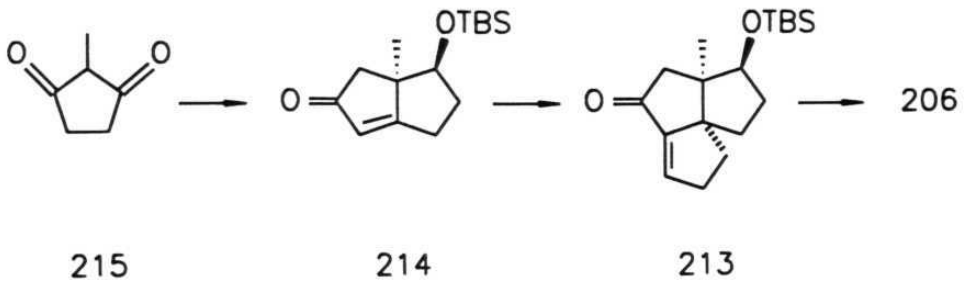
Scheme-2



210 211 212

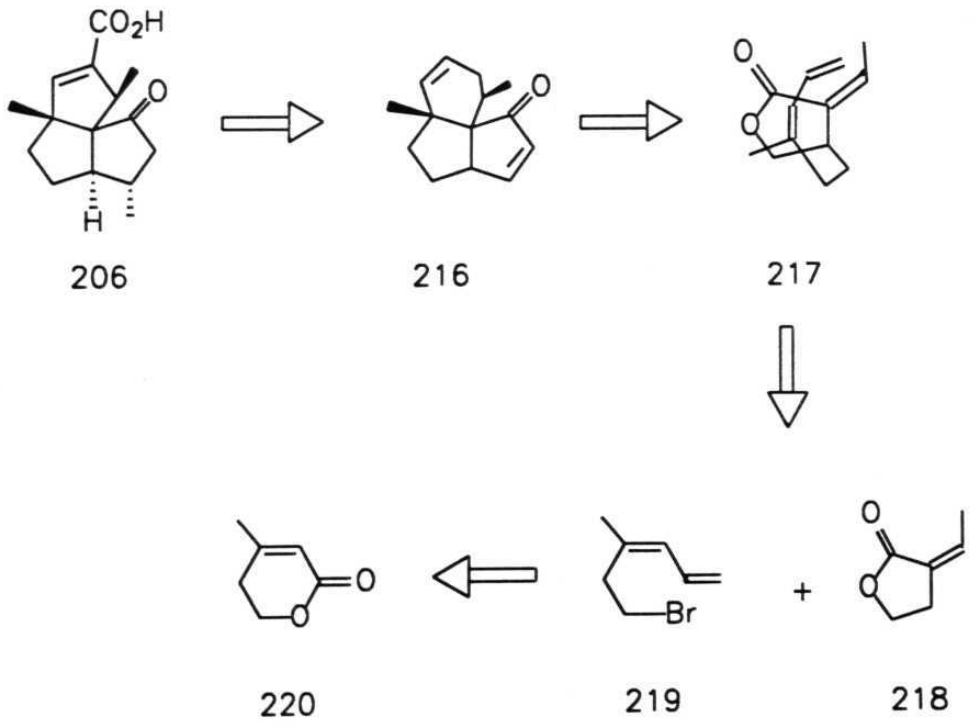
Recently, Paquette and co-workers [5] reported the enantioselective synthesis of subergorgic acid **206**. The tricyclic framework **213** was constructed by a Michael addition followed by a simple aldol condensation on optically pure enone **214** which was obtained from 2-methyl-1,3-cyclopentanedione **215**. Functional group manipulations of **213** and introduction of methyl groups leads to (-)-subergorgic acid **206**.

Scheme-3



Our retrosynthesis of subergorgic acid **206** was planned as arising from the tricyclic skeleton **216** which is the product of intramolecular Diels-Alder reaction of **217.** Triene **217** may be obtained from lactone **218** and bromodiene **219**. The bromodiene **219** should arise from anhydromevalonolactone **220**.

Scheme-4

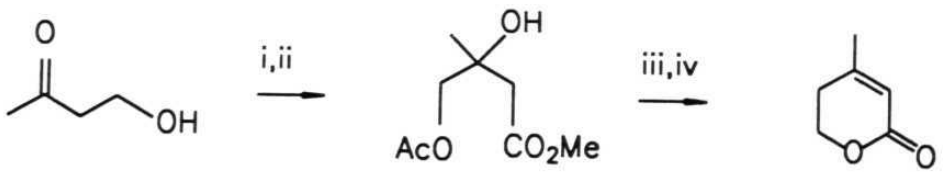


5.3. SYNTHESIS OF ANHYDROMEVALONOLACTONE:

Since we needed lactone **220** in gram quantities for the preparation of bromodiene **219**, the literature was surveyed for the preparation of **220** to find a convenient method.

One of the earliest methods reported by Cornforth *et al.* [6] starts from 4-hydroxy-2-butanone **221**. Protection of hydroxy group in **221** as its acetal and reformatsky reaction with methyl bromoacetate gave ester **222**. Lactonisation with methanolic KOH and dehydration with $KHSO_4$ afforded lactone **220** in 48% overall yield.

Scheme-5

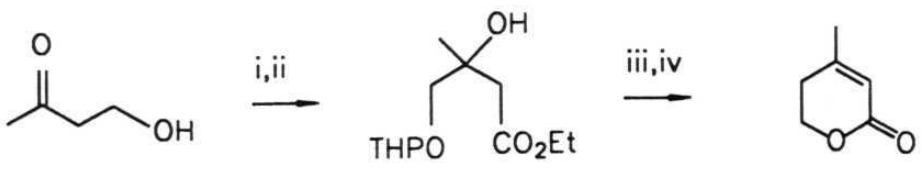


221 222 220

Reagents: *i) Ac_2O, H_2SO_4; ii) $BrCH_2CO_2Me$, Zn; iii) KOH, H^+; iv) $KHSO_4$.*

Subsequently White and co-workers [7] modified the same method by protecting **221** as its tetrahydropyranyl ether and condensation with ethyl acetate to ester **223**. Lactonisation with catalytic acetyl chloride and dehydration with polyphosphoric acid afforded lactone **220** in 68% yield.

Scheme-6



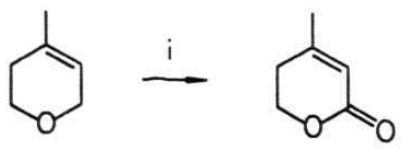
221 223 220

Reagents: *i) DHP, PPTS; ii) LDA, CH_3CO_2Et; iii) AcCl; iv) PPA.*

A disadvantage with the above methods is that the starting material **221** is prepared from the aldol condensation of acetone and paraformaldehyde in 23% yield [8].

Bonadies *et al.* [9] prepared lactone **220** by PCC oxidation of commercially available pyran **224** in 85% yield. This method is unviable because the pyran **224** is no longer commercially available.

Scheme-7

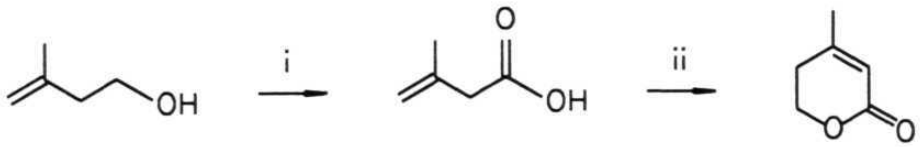


224 220

Reagents: *i) PCC, CH_2Cl_2.*

Peter and co-workers [10] reported that Jones oxidation of 3-methyl-3-butene-1-ol **225** to corresponding acid **226** followed by Prins reaction provided lactone **220** in 15% yield. The disadvantage with this method is that the yield is low and starting material is expensive.

Scheme-8



225 226 220

Reagents: *i) Cro_3-H_2SO_4, acetone; ii) $(HCHO)_n$, H_2SO_4, CH_3CO_2H.*

After examining these literature procedures, we felt that there is a need to develop a convenient method for the preparation of lactone **220**. Therefore, we proposed a five step synthesis for lactone **220** starting from inexpensive and commercially available ethyl acetoacetate **227** *via* the protocol delineated in Scheme-9.

Thus, dimerisation of ethyl acetoacetate **227** with conc. H_2SO_4 at ambient temperature for 3 days provided ethyl isodehydroacetate **228** in 45% yield [11]. Hydrolysis of **228** with 5N NaOH afforded a 2:1 mixture of *trans*- and *cis*-3-methylglutaconic acids **229**,**230** in quantitative yield. The assignment of olefin geometry and ratio of isomers was determined in the following manner. It is known that in trisubstituted olefins bearing an α,β-unsaturated carbonyl group the CH_3 protons *cis* to the vinyl CO_2H will be deshielded [12]. Hence, CH_2 protons in *trans* isomer **229** are deshielded relative to the corresponding signals in the *cis* isomer. The

peaks correspond to CH_2 and CH_3 groups in *trans* isomer **229** appear at δ 3.24 and 2.28, whereas in *cis* isomer **230** they resonate at δ 3.76 and 2.04, respectively. Integration of CH_2 and CH_3 signals furnished a ratio of 2:1 which is in agreement with the PMR data reported by Jackman and Wiley (1958) [13]. A *cis/trans* ratio of 2:1 was incorrectly assigned by Payne (1968) [14] and went unnoticed by Jung (1984) [11].

The crude mixture of diacids **229,230** were converged to the desired *cis* geometry by cyclisation to 3-methylglutaconic anhydride **231** with Ac_2O by heating at 70 °C for 1 h. The PMR spectrum showed peaks corresponding to anhydride **231** [11] along with traces of undistilled Ac_2O and AcOH at δ 2.24 and 2.05, respectively.

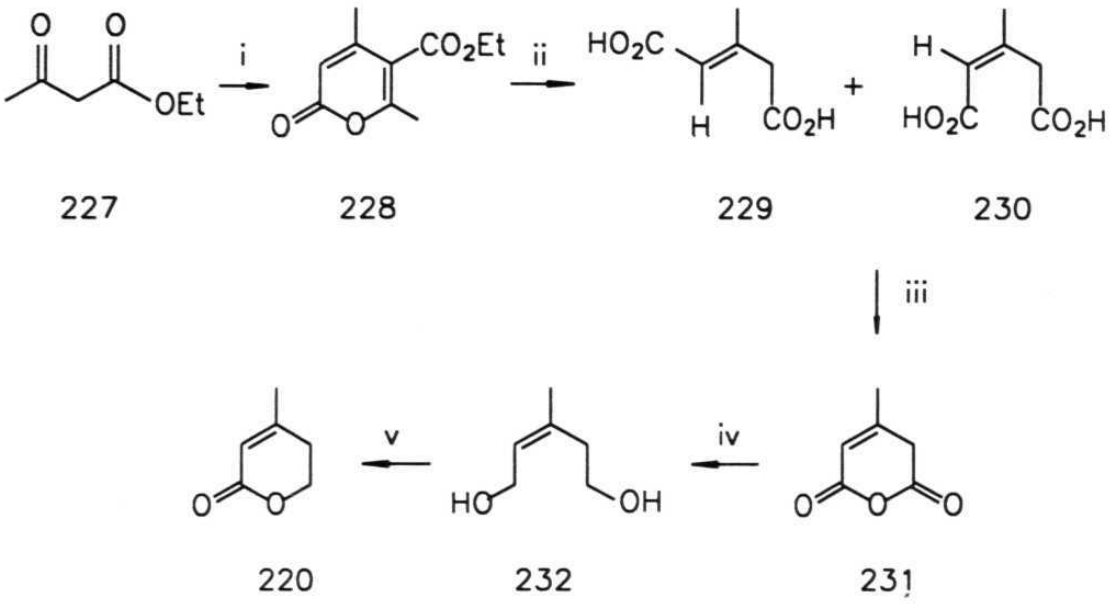
The unsymmetrical anhydride **231** can be transformed to lactone by two methods.

1). Selective and controlled reduction of saturated carbonyl of **231** to lactone **220**. This was attempted with $NaBH_4$/THF [15] but was unsuccessful.

2). Reduction of anhydride **231** to diol **232** and selective oxidation of allylic over homoallylic alcohol to lactone **220**. This reaction was fruitful.

Thus, reduction of anhydride **231** with $LiAlH_4$ in THF [16] at ambient temperature for 1 day provided *Z*-alcohol **232**. The PMR spectrum of **232** showed vinyl **H** at δ 5.70 as a triplet (J=6 Hz) and CH_2O doublet at δ 4.04 (J=6 Hz) and a broad hydroxy band at 3300 cm^{-1} in IR spectrum [17]. Selective oxidation of **232** with PDC in CH_2Cl_2 [18] afforded lactone **220** in low yield (18%). Oxidation with 2 equi. of 8N Jones reagent [19] at 0 °C afforded lactone **220** in 32% yield. If excess of Jones reagent was used, over-oxidation products, such as diacid **229,230** were observed on TLC. The PMR spectrum of **220** was in agreement with the reported data [10]. The vinyl **H** appeared at δ 5.76 and CH_3 singlet at δ 1.96.

Scheme-9



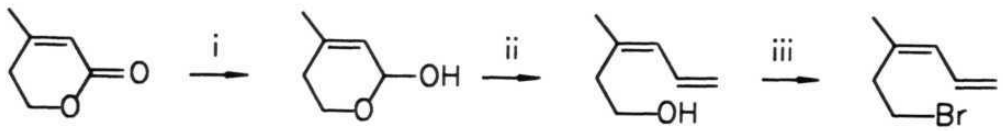
Reagents: *i) H_2SO_4, rt, 3 days; ii) 5N NaOH, 70 °C, 1 h; iii) Ac_2O, 70 °C, 30 min; iv) LAH, THF, rt, 1 day; v) CrO_3-H_2SO_4, acetone, 0 °C.*

Thus, the synthesis of anhydromevalonolactone **220** was successfully completed by using mild reaction conditions, simple reagents, inexpensive and commercially available starting materials in 30% overall yield from pyrone **228.**

5.4. SYNTHESIS OF 3-METHYL-3,5-HEXADIENYL BROMIDE:

To investigate the stereo- and regiochemical outcome of intramolecular Diels-Alder reaction, we required 3-methyl-3,5-hexadienyl bromide **219** as an alkylating agent. It appeared logical to us that bromodiene **219** should arise from anhydromevalonolactone **220** *via* the sequence delineated in Scheme-10. Thus, controlled reduction of lactone **220** to the corresponding lactol **233** with DIBAL-H, Wittig homologation and bromination should provide diene **219**.

Scheme-10



220 233 234 219

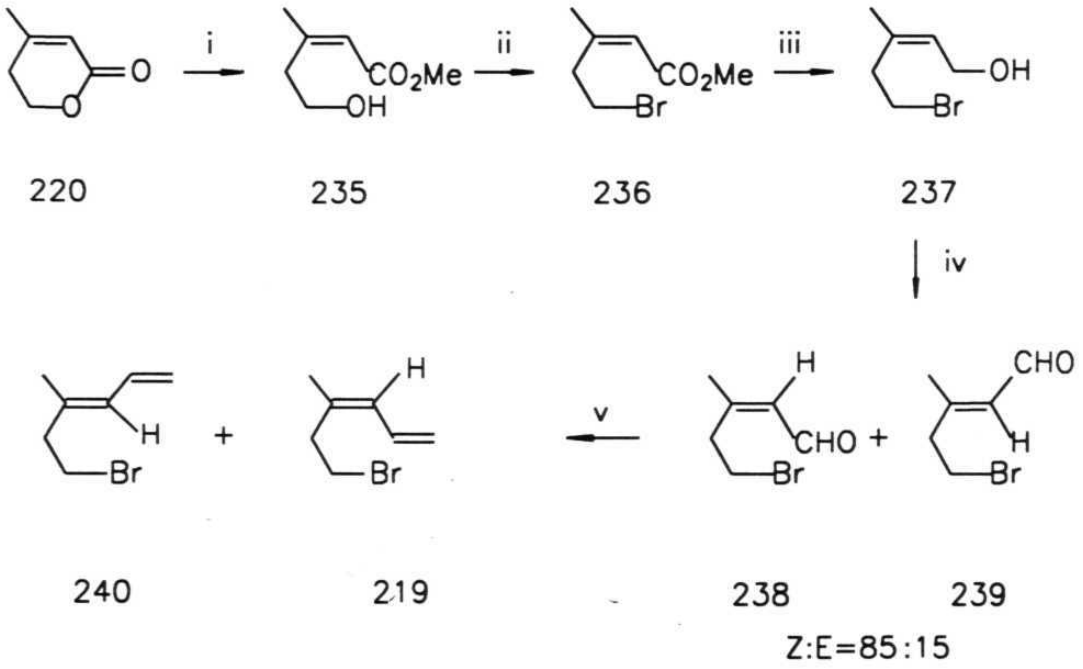
Reagents: i) DIBAL-H, CH_2Cl_2; ii) $Ph_3P{=}CH_2$, THF; iii) CBr_4, Ph_3P, CH_2Cl_2.

The DIBAL-H reduction [20] of lactone **220** to lactol **233** presented several execution problems on large scale because of the reaction mandates low temperatures (-78 °C to -40 °C) and scrupulously anhydrous conditions. In addition to this, the prohibitive cost and capricious quality of the reagent (available locally) made it difficult for us to carry out the reaction in multigram scale. Instead of DIBAL-H, the reaction was attempted with $Li(OEt)_3AlH$ [21] and $Li(O\text{-}t\text{-}Bu)_3AlH$ [22]; unreacted starting material was recovered with both the reagents. Since the conversion of lactone **220** to lactol **223** appeared to be difficult, we developed a surrogate sequence for the synthesis of bromodiene **219** from lactone **220** *via* the protocol delineated in Scheme-11.

Saponification of **220** with 1N NaOH for 20 min and acidic work-up with 1N HCl provided unstable hydroxy acid [7]. Without isolation it was immediatly treated with an ethereal solution of diazomethane [23] to afford hydroxy ester **235**, which was evidenced from the appearance of CO_2CH_3 singlet at δ 3.60 in PMR and hydroxy band at 3400 cm^{-1} in IR spectrum. Bromination of alcohol **235** with CBr_4 and Ph_3P in CH_2Cl_2 [24] at 0 °C for 1 h provided bromoester **236** in 75% yield. LAH reduction of ester **236** in ether at 0 °C for 1 h furnished bromo alcohol **237**. The structure was

concluded from the appearance of vinyl **H** as a triplet at δ 5.52 (J=6 Hz) and CH_2O doublet at δ 4.06 (J=6 Hz) in PMR and a 6 line CMR spectrum.

Scheme-11



Reagents: *i) 1N NaOH, then 1N HCl, CH_2N_2, ether; ii) CBr_4, Ph_3P, CH_2Cl_2, 0 °C, 1 h; iii) $LiAlH_4$, ether, 0 °C, 1 h; iv) PDC, CH_2Cl_2, 0 °C, 1 h; v) CH_3PPh_3Br, n-BuLi, THF, rt, 1 h.*

The oxidation of alcohol **237** to α,β-unsaturated aldehyde **238** proved troublesome because of concomitant isomerisation to the more stable *trans* isomer **239**. Attempted oxidation with PCC [25] provided a mixture of *Z*- and *E*-aldehydes **238**,**239**. The olefin geometry was assigned on the basis of deshielding of allylic protons *cis* to the carboxaldehyde by 0.1-0.2 ppm as discussed earlier for diacids **229**,**230** [12]. Thus, integration of aldehyde doublets (J=6 Hz) at δ 9.94 and 10.04 revealed a 50:50 mixture of *Z*- and *E*-aldehydes **238**,**239**. Oxidation of **237** under Swern conditions [26]

furnished a 60:40 mixture of *Z*- and *E*-aldehydes **238**,**239**. In order to retain the *cis* geometry of the unsaturated aldehydes, oxidation with "activated" MnO_2 in hexane [27] at ambient temperature for 12 h was attempted. Because of the long reaction times required, the unsaturated aldehyde decomposed through deleterious pathways during the course of the reaction. Oxidation of alcohol **237** with PDC [18] in CH_2Cl_2 at 0 °C for 1 h provided *Z*- and *E*-aldehydes **238**,**239** in the ratio of 85:15, respectively.

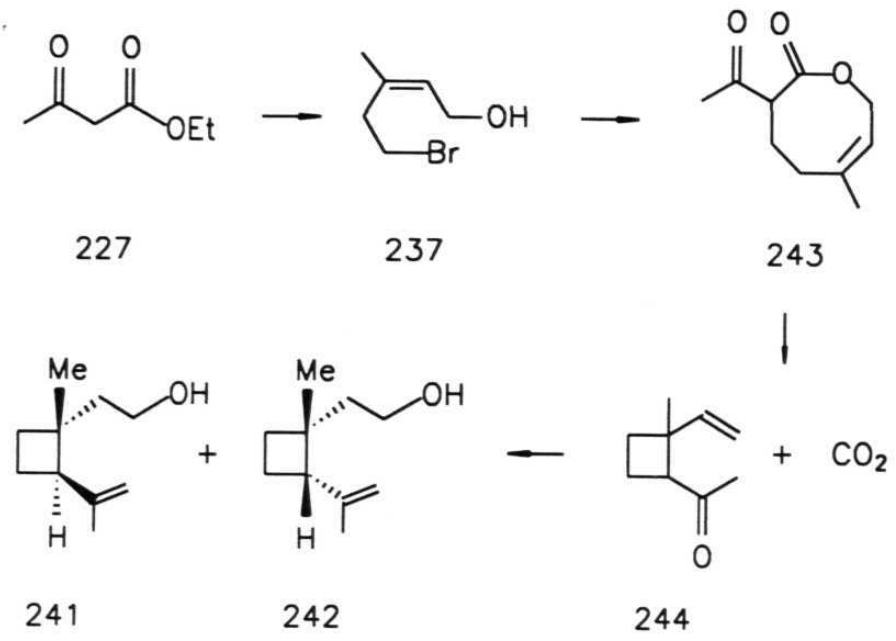
The mixture of aldehydes **238**,**239** was methylenated with $Ph_3P{=}CH_2$ in THF at rt for 1 h to furnish *Z*/*E* mixture of bromodienes **219**,**240**, which were evidenced by the appearance of vinyl protons between 6-7 ppm. Because of the problems arising from isomerisation and low yields, this project was prematurely aborted at this stage. No further work in this direction has since been pursued on this project.

5.5 SYNTHETIC APPROACH TO GRANDISOL AND FRAGRANOL:

Grandisol **241** and fragranol **242** are the pheromones isolated from the male boll Weevils, *Anthonomus grandis* Boheman [28]. These cyclobutane compounds have attracted attention of many synthetic chemists and a number of syntheses are reported. The subject was reviewed in 1976 by Katzenellenbogen [29].

We planned to synthesise grandisol **241** or fragranol **242** using bromo alcohol **237** which we had prepared for the synthesis of bromodiene **219**. The proposed synthesis is shown in Scheme-12. Thus, transesterification and alkylation of ethyl acetoacetate **227** and bromo alcohol **237** should give an eight membered lactone **243** which undergoes [3,3]-sigmatropic rearrangement with concomitant expulsion of CO_2 to provide cyclobutane compound **244**. Routine functional group manipulation of **244** should afford grandisol **241** or fragranol **242**.

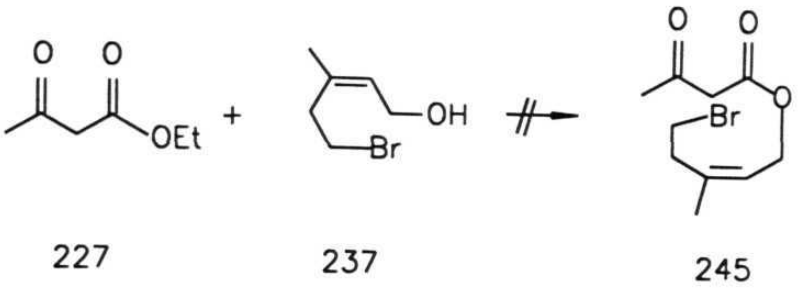
Scheme-12



Transesterification [30] of allylic alcohol **237** and ethyl acetoacetate **227** with DMAP, molecular seives in refluxing benzene or toluene did not gave the required product, allyl acetoacetate **245**. The unstable allylic alcohol **237** decomposed during the course of the reaction and only ethyl acetoacetate **227** was isolated.

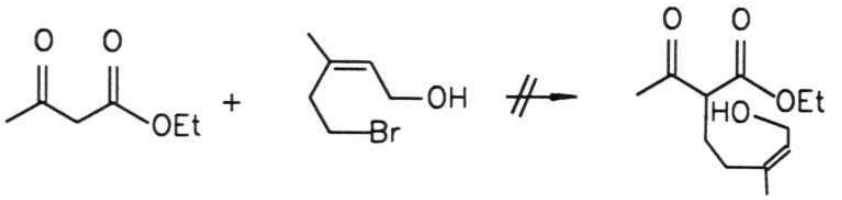
Since transesterification was unsuccessful, ethyl acetoacetate **227** was subjected to alkylation with bromoalcohol **237**. Attempted alkylation of **227** with **237** using different bases such as NaOMe/MeOH, NaOEt/EtOH, *t*-BuOK/BuOH, *t*-BuOK/THF/18-crown-6 at ambient temperatures to reflux conditions did not provide the alkylated β-ketoester **246**. At ambient temperatures starting materials were recovered and at reflux conditions the isolated product was pyran **247**, resulting from an intramolecular O-alkylation of bromoalcohol **237**, along with unreacted ethyl acetoacetate **227**. The structure of pyran **247** was tentatively assigned by PMR data.

Scheme-13

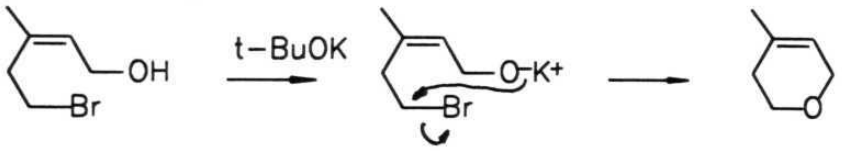


227 237 245

Scheme-14



227 237 246



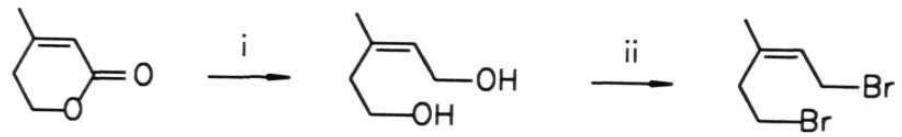
237 247

To avoid the intramolecular O-alkylation, the bromo alcohol **237** was protected as its THP ether and then subjected for alkylation. Even then, the required product could not be obtained.

Since the transesterification and alkylation reactions failed, the synthesis of eight membered lactone was planned by a different route as delineated in Scheme-15. Now, the two starting materials were dibromide **248** and ketal acid **249**. The dibromide **248**

was prepared from anhydromevalonolactone **220**. LAH reduction of lactone **220** provided diol **232** which was evidenced by the appearance of broad hydroxy band at 3360 cm^{-1}. Diol **232** was converted to dibromide **248** with CBr_4, Ph_3P in THF [24] at rt for 3 h in near quantitave yield.

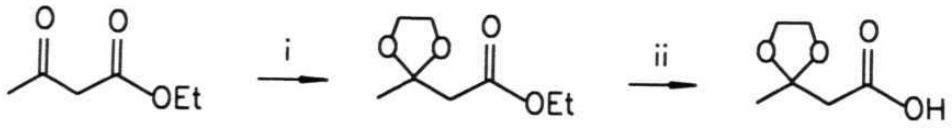
Scheme-15



220 232 248

Reagents: *i) $LiAlH_4$, ether, 0 °C, 1 h; ii) CBr_4, Ph_3P, THF, rt, 3 h.*

Scheme-16



227 250 249

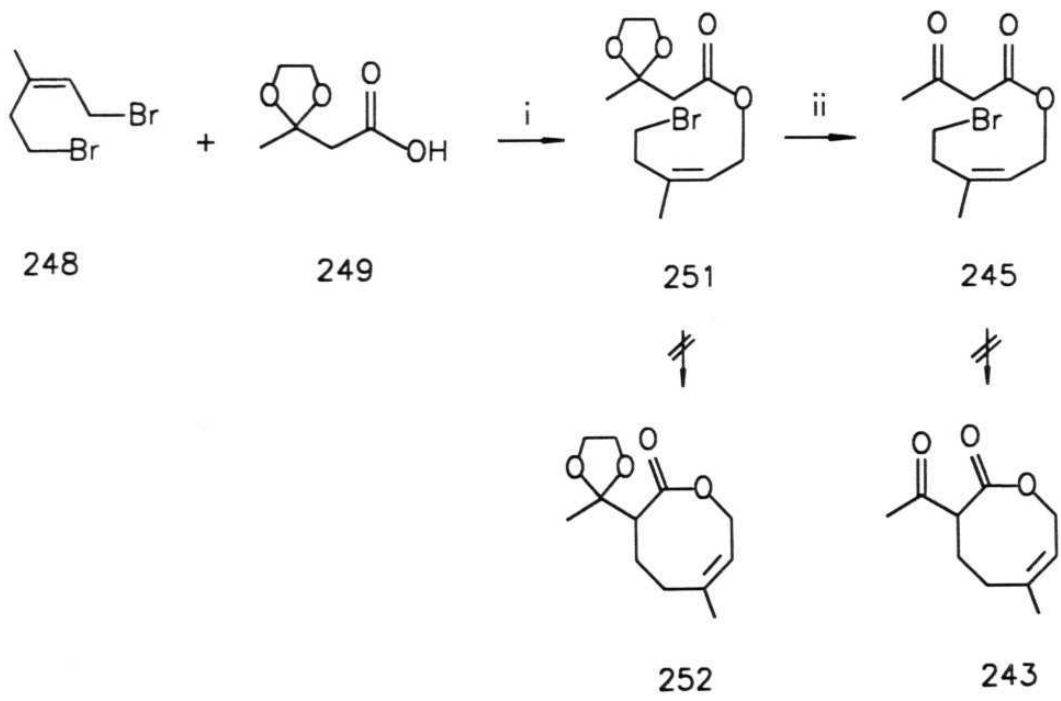
Reagents: *i) $(CH_2OH)_2$, p-TsOH.H_2O, benzene, reflux, 3 h; ii) 10% NaOH, then 10% HCl.*

The other starting material ketal acid **249** was prepared from ethyl acetoacetate **227**. Thus, the keto group in **227** was protected as its ketal with ethanediol, *p*-TsOH.H_2O in benzene using Dean-Stark apparatus [31] to afford ketal ester **250** in

excellent yield. Saponification of ester with NaOH and acidic work-up provided ketal acid **249**.

The ketal acid **249** was transformed to its potassium carboxylate with K_2CO_3 in MeOH and then coupled with dibromide to provide ester **251**. When ester **251** was subjected to cyclisation using the bases NaH and *t*-BuOK to afford 8-membered lactone **252,** the reaction was unsuccessful. The ketal protection in ester **251** was removed with *p*-TsOH.H_2O and again subjected to cyclisation using the same conditions. No characterisable material was isolated, only starting material was recovered. Since, the formation of 8-membered lactone **243** is difficult, the synthesis of grandisol **241** or fragranol **242** was aborted at this stage.

Scheme-17

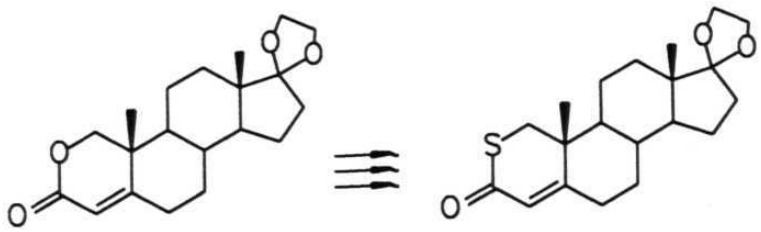


Reagents: *i) K_2CO_3, NaI, acetone, rt, 12 h; ii) p-TsOH.H_2O, aq. acetone.*

5.6. SYNTHESIS OF THIOLACTONE:

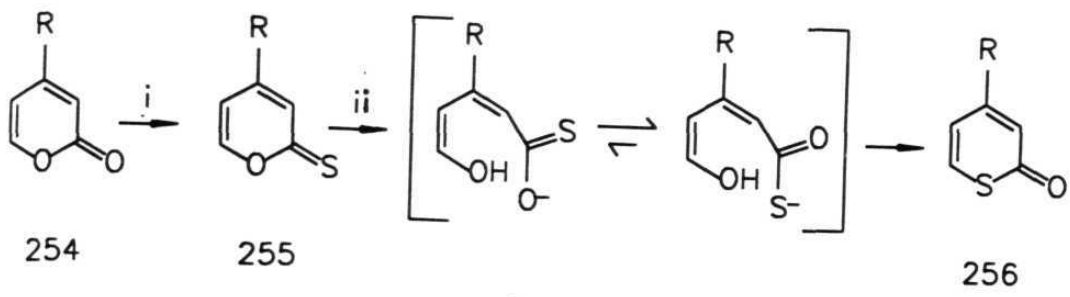
In connection with an ongoing project on the synthesis of steroidal thiolactone as antiandrogens, we required a mild protocol for the transformation of α,β-unsaturated-δ-lactone to the corresponding thiolactone.

Scheme-18



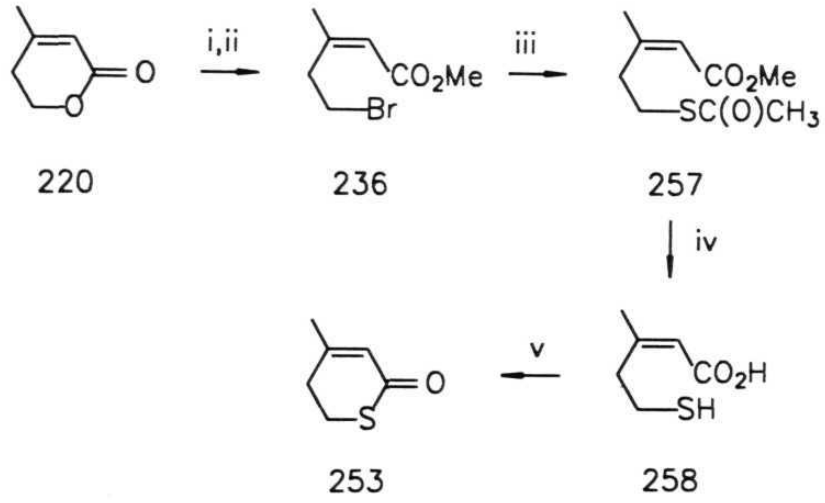
Examination of published procedures to carry out this transformation recommend the use of strongly acidic reagents like HI with thiourea [32], FSO_3H-SbF_5 or Et_3O-BF_4 [33], etc. The thionoesters or lactones are also easily prepared from the corresponding ester or lactone by treatment with P_2S_5 [34, 35]. Many of the papers deal with pyrones **254** as examples in which the conversion of intermediate thionolactone **255** to thiolactone **256** is easily accomplished *via* intramolecular conjugate addition of -C(O)S- and elimination of H_2O. Adaptation of these literature procedures will not be viable because of the absence of extended conjugation in steroidal substrates. Hence, we planned to develop a mild transformation of lactone **220** to thiolactone **253**.

Scheme-19



Reagents: i) P_2S_5, toluene; ii) 10% $NaHCO_3$, MeOH.

Scheme-20



Reagents: i) 1N NaOH, 1N HCl, CH_2N_2, ether; ii) CBr_4, Ph_3P, THF, 0 °C, 1 h; iii) $CH_3C(O)SH$, NaH, 1:1 DMF-THF, 65 °C, 2 h; iv) aq. $NaHCO_3$, then aq. HCl; v) p-$TsOH.H_2O$; benzene, reflux, 1 h.

Thus, anhydromevalonolactone **220** was transformed to its thiolactone **253** *via* bromoester **236** which is available from our earlier synthesis. Treatment of bromoester **236** with thiolate anion in 1:1 DMF-THF provided thioester **257** in 95% yield, which was evidenced by the appearance of $SC(O)CH_3$ singlet at δ 2.24. Saponification of diester **257** with saturated $NaHCO_3$ solution furnished mercapto acid **258** as concluded from the absence of CO_2CH_3 and $SC(O)CH_3$ singlets at δ 3.70 and 2.24, respectively, in PMR spectrum. Without extensive characterisation the crude acid **258** was cyclised to thiolactone **253** with *p*-TsOH.H_2O in benzene by azeotropic distillation of H_2O for 1 h. The PMR spectrum of thiolactone showed SCH_2 protons as triplet at δ 3.18 (J=6 Hz) and a 6 line CMR spectrum. Thus, the conversion of O-lactone **220** to S-lactone **253** was performed in 50% global yield using mild reaction conditions.

5.7. EXPERIMENTAL AND SPECTRA:

Ethyl isodehydroacetate 228:

Ethyl acetoacetate **227** (12.6 mL, 13.0 g, 100 mmol) was added to conc. H_2SO_4 (10.0 mL, 18.4 g, 110 mmol) at 0 °C, slowly dropwise with stirring through an addition funnel over 30 min at such a rate that the temperature was maintained between 10 to 15 °C. The orange solution was stirred at ambient temperature for 3 days. The reaction mixture was poured in to 20 g of ice and extracted with ether (3x30 mL). The organic layer was washed with 10% Na_2CO_3 solution and brine. Work-up and distillation afforded pure pyran **228** as a yellow liquid.

Yield: 8.95 g, 45%

bp: 110-120 °C/2-3 Torr

IR: cm^{-1} 2995, 1730 (br), 1620, 1550, 1440, 1400, 1270, 1150, 1080, 960.

PMR: δ 5.88 (s, 1H, vinyl **H**); 4.20 (q, J=6 Hz, 2H, OCH_2); 2.28 (s, 3H, vinyl CH_3); 2.08 (s, 3H, vinyl CH_3); 1.24 (t, J=6 Hz, 3H, CH_2CH_3).

***E/Z*-3-Methylglutaconic acid 229,230:**

A solution of ethyl isodehydroacetate **228** (6.0 g, 30 mmol) in 5N NaOH (30 mL, 150 mmol) was heated at 70 °C for 1 h. The reaction mixture was cooled to rt and extracted with ether to remove the neutral products. The aqueous layer was cooled to 0 °C and acidified with conc. HCl (14 mL, 160 mmol) to pH 2. The reaction mixture was saturated with solid NaCl and extracted with ether (3x20 mL). The organic extracts were washed with brine and work-up afforded *E/Z* mixture of diacid **229,230** as an off-white solid and it was pure enough to carry out the next reaction.

Yield: 4.33 g, 98% (crude)

mp: 113-115 °C

IR: cm^{-1} 3000 (br), 2800, 1700, 1460, 1390, 1280, 1230, 1180, 980.

PMR: ($CDCl_3$+DMSO-D_6) δ 5.88 (s, 1H, vinyl **H**); 3.76 and 3.24 (s, 2H, allyl CH_2); 2.28 and 2.04 (s, 3H, vinyl CH_3).

3-Methylglutaconic anhydride 231:

A mixture of crude diacid **229,230** (864 mg, 6.0 mmol) and Ac_2O (1.5 mL, 1.63 g, 18.0 mmol) was heated at 70 °C for 30 min. The volatile materials were removed *in vacuo* and anhydride **231** was obtained along with traces of undistilled Ac_2O and AcOH. The anhydride **231** was immediatly used without further purification.

PMR: δ 6.04 (s, 1H vinyl **H**); 3.44 (s, 2H, allyl CH_2); 2.05 (s, 3H, vinyl CH_3).

***Z*-3-Methyl-2-pentene-1,5-diol 232:**

Anhydride **231** (800 mg, 6.0 mmol), $LiAlH_4$ (684 mg, 18.0 mmol), THF (10 mL), 0 °C to rt, 3 days.

Yield: 662 mg, 95% (crude)

IR: cm^{-1} 3300 (br), 2950, 1450, 1390, 1050, 1010, 920, 870.

PMR: δ 5.70 (t, J=6 Hz, 1H, vinyl **H**); 4.04 (d, J=6 Hz, 2H, allyl CH_2O); 3.66 (t, J=6 Hz, 2H, CH_2O); 2.76 (brs, 2H, 2xO**H**); 2.32 (t, J=6 Hz, 2H, allyl CH_2); 1.76 (s, 3H, vinyl CH_3).

Anhydromevalonolactone 220:

To diol **232** (660 mg, 5.7 mmol) in 8 mL of acetone was added 8N Jones reagent (1.5 mL, 12 mmol) slowly dropwise at 0 °C. After completion of the addition *i*-PrOH (3-5 drops) was added to destroy excess of Jones reagent. The reaction mixture was diluted with ether (10 mL) and washed with saturated $NaHCO_3$ solution and brine. Usual work-up afforded 400 mg of lactone **220** which was purified by SGC (hexane to 20% EtOAc/hexane.

Yield: 208 mg, 31%

IR: cm^{-1} 2950, 1710, 1600, 1440, 1400, 1320, 1280, 1140, 1100, 1070, 1000, 860, 800.

PMR: δ 5.76 (s, 1H, vinyl **H**); 4.34 (t, J=6 Hz, 2H, OCH_2); 2.34 (t, J=6 Hz, 2H, allyl CH_2); 1.96 (s, 3H. vinyl CH_3).

Hydroxy ester 235:

A mixture of lactone **220** (1.0 g, 8.9 mmol) and 1N NaOH (10 mL) were refluxed for 20 min. The reaction mixture was cooled to 0 °C and acidified with 1N HCl (10 mL). Saturated with NH_4Cl solution (10 mL) and extracted with ether (3x20 mL). The ether extracts were treated with an ethereal solution of diazomethane [prepared by the addition of 25 mL of 50% KOH in 50 mL of ether to N-nitroso-N-methylurea (2.5 g, 25 mmol) at -5 °C] until the yellow colour persisted. Excess of diazomethane was destroyed with CH_3CO_2H (1.45 mL, 1.5 g, 25 mmol) until the yellow colour disappeared. The reaction mixture was washed with saturated $NaHCO_3$

solution, brine and usual work-up afforded ester **235**. The only impurity was N-nitroso-N-methylurea which was removed by SGC (hexane to 20% EtOAc/hexane).

Yield: 945 mg, 74%

IR: cm^{-1} 3800 (br), 2950, 1710, 1650, 1450, 1390, 1250, 1150, 1060, 870.

PMR: δ 5.76 (s, 1H, vinyl **H**); 3.76 (t, J=6 Hz, 2H, CH_2O); 3.64 (s, 3H, CO_2CH_3); 3.12 (br s, 1H, **OH**); 2.78 (t, J=6 Hz, 2H, allyl CH_2); 1.90 (s, 3H, vinyl CH_3).

Bromoester 236:

To a magnetically stirred solution of alcohol **235** (940 mg, 6.5 mmol) in 10 mL of dry CH_2Cl_2 was added CBr_4 (2.8 g, 8.2 mmol). To this mixture Ph_3P (2.6 g, 9.8 mmol) was added slowly portionwise at 0 °C. Stirred it for 1 h and the solvent was removed *in vacuo*. The residue was washed with hexane and all the washings were combined and concentrated. Purification by SGC afforded bromoester **236**.

Yield: 940 mg, 70%

IR: cm^{-1} 2950, 1720, 1660, 1450, 1390, 1290, 1240, 1170, 1060, 880, 760.

PMR: δ 5.82 (s, 1H, vinyl **H**); 3.64 (s, 3H, CO_2CH_3); 3.48 (t, J=6 Hz, 2H, CH_2Br); 3.10 (t, J=6 Hz, 2H, allyl CH_2); 1.94 (s, 3H, vinyl CH_3).

Bromoalcohol 237:

Bromoester **236** (518 mg, 2.5 mmol); $LiAlH_4$ (115 mg, 3.0 mmol).

Yield: 370 mg, 83%

IR: cm^{-1} 3350 (br), 2950, 1450, 1390, 1280, 1220, 1090, 1000.

PMR: δ 5.52 (t, J=6 Hz, 1H, vinyl **H**); 4.06 (d, J=6 Hz, 2H, CH_2O); 3.38 (t, J=6 Hz, 2H, CH_2Br); 2.60 (t, J=6 Hz, 2H, allyl CH_2); 1.66 (s, 3H, vinyl CH_3).

CMR: δ 134.89, 126.95, 57.82, 34.53, 30.17, 22.11.

***Z/E*-Unsaturated aldehyde 238,239:**

To a slurry of PDC (170 mg, 0.45 mmol) in 0.5 mL of dry CH_2Cl_2 was added a solution of alcohol **237** (54 mg, 0.3 mmol) in 1 mL of CH_2Cl_2 and stirred for 1 h at 0 °C. The reaction mixture was diluted with dry ether and filtered through celite. The residue was washed with dry ether and the filtrate was concentrated to afford a **85:15** *Z/E* mixture of unsaturated aldehyde **238,239** which was immediatly used in the next reaction without purification.

Yield: 40 mg, 74% (crude)

IR: cm^{-1} 2900, 1670, 1440, 1380, 1270, 1210, 950, 840.

PMR: δ 9.90 (overlapping d, J=6 Hz, 1H, aldehyde **H**); 5.94 (overlapping d, J=6 Hz, 1H, vinyl **H**); 3.48 (overlapping t, J=6 Hz, 2H, CH_2Br); 3.12 and 2.74 (t, J=6 Hz, 2H, allyl CH_2); 2.14 and 1.98 (s, 3H, vinyl CH_3).

***Z/E*-Bromodiene 219,240:**

To a solution of methyltriphenylphosphonium bromide (214 mg, 0.6 mmol) in 2 mL of dry THF was added *n*-BuLi (0.75 mL, 0.6 mmol, 0.8 N solution in hexane) slowly dropwise at rt. After the addition the solution turned to yellow colour. To the reaction mixture aldehyde **238,239** (54 mg, 0.3 mmol) was added in 0.5 mL of dry THF. The reaction mixture was stirred for 1 h and quenched with 1 mL of H_2O and extracted with hexane (3x5 mL). Brine wash and work-up afforded bromodiene **219,240** as a mixture of *Z*- and *E*-isomers which was purified by SGC (hexane).

Yield: 28 mg, 54%

IR: cm^{-1} 3075, 2950, 1450, 1200, 1130, 890, 750, 700.

PMR: (for major isomer ***Z*-219**) δ 6.72-6.28 (m, 1H, vinyl **H**); 6.00 (br d, J=10 Hz, 1H, vinyl **H**); 5.20 (d, J=16 Hz, 1H, vinyl **H**); 5.02 (d, J=8 Hz, 1H, vinyl **H**); 3.40 (t, J=8 Hz, 2H, CH_2Br); 2.75 (t, J=8 Hz, 2H, allyl CH_2); 1.80 (s, 3H, vinyl CH_3).

Diol 232:

Anhydromevalonolactone **220** (896 mg, 8.0 mmol); $LiAlH_4$ (418 mg, 11.0 mmol).

Yield: 915 mg, 98%

Dibromide 248:

Diol **232** (348 mg, 3.0 mmol); PPh_3 (2.1 g, 8.0 mmol); CBr_4 (3.3 g, 10.0 mmol); THF (15 mL).

Yield: 690 mg, 95%

IR: cm^{-1} 2968, 2359, 1655, 1440, 1380, 1273, 1200, 1143, 667.

PMR: δ 5.70 (t, J=6 Hz, 1H, vinyl **H**); 4.02 (d, J=6 Hz, 2H, allyl CH_2Br); 3.56 (t, J=6 Hz, 2H, CH_2Br); 2.72 (t, J=6 Hz, 2H, allyl CH_2); 1.80 (s, 3H, vinyl CH_3).

Ketal ester 250:

A mixture of ethyl acetoacetate **227** (6.7 mL, 6.5 g, 50 mmol), ethanediol (5.3 mL, 4.7 g, 75 mmol) and *p*-TsOH.H_2O (475 mg, 2.5 mmol) in 75 mL of benzene was refluxed for 5 h with azeotropic removal of H_2O using Dean-Stark apparatus. The reaction mixture was cooled to rt and diluted with 50 mL of ether. The mixture was washed with saturated $NaHCO_3$ solution and brine. Usual work-up provided ketal ester **250** which was pure enough to carry out next reaction.

Yield: 8.5 g, 98% (crude)

IR: cm^{-1} 2950, 1740, 1460, 1380, 1200, 1120, 1060, 960, 880.

PMR δ 4.12 (q, J=6 Hz, 2H, OCH_2); 3.96 (s, 4H, OCH_2CH_2O); 2.64 (s, 2H, $CH_2C(O)$); 1.50 (s, 3H, $CH_3C(OCH_2)_2$); 1.24 (t, J=6 Hz, 3H, CH_2CH_3).

Ketal acid 249:

Ketal ester **250** (8.5 g, 49 mmol) was added to 50 mL of 10% NaOH solution and refluxed for 1 h. The reaction mixture was cooled to 0 °C and neutralised with 10% HCl and extracted with ether (5x20 mL). Brine wash and work-up afforded ketal acid **249** which was used in the next step without purification.

Yield: 3.5 g, 50% (crude)

IR: cm^{-1} 3422, 2978, 1718, 1381, 1194, 1047, 952, 879.

PMR: δ 4.00 (s, 4H, OCH_2CH_2O); 2.72 (s, 2H, CH_2CO_2H); 1.50 (s, 3H, $CH_3C(OCH_2)_2$).

Ketal bromide 251:

Dibromide **248** (60 mg, 0.25 mmol); ketal acid **249** (45 mg, 0.3 mmol); K_2CO_3 (85 mg, 0.6 mmol); acetone (2 mL).

Yield: 53 mg, 69%

IR: cm^{-1} 2974, 1736, 1444, 1381, 1182, 1047.

PMR: δ 5.52 (t, J=6 Hz, 1H, vinyl **H**); 4.60 (d, J=6 Hz, 2H, CO_2CH_2); 3.98 (s, 4H, OCH_2CH_2O); 3.42 (t, J=6 Hz, 2H, CH_2Br); 2.68 (t, J=6 Hz, 2H, allyl CH_2); 2.66 (s, 2H, CH_2CO_2); 1.78 (s, 3H, vinyl CH_3); 1.48 (s, 3H, $CH_3C(OCH_2)2$).

Keto bromide 245:

Ketal bromide (30.6 mg, 0.1 mmol) was taken in 1 mL of acetone and *p*-TsOH.H_2O (4 mg, 0.02 mmol) was added. The reaction mixture was stirred at rt for 20 h and diluted with 5 mL of ether. The mixture was washed with saturated $NaHCO_3$ solution, brine and Work-up afforded keto bromide **245**.

Yield: 20 mg, 76% (crude)

IR: cm^{-1} 2972, 1739, 1444, 1361, 1151, 1028.

PMR: δ 5.50 (t, J=6 Hz, 1H, vinyl **H**); 4.64 (d, J=6 Hz, 2H, CO_2CH_2); 3.44 (s, 2H, $C(O)CH_2C(O)$); 3.42 (t, J=6 Hz, 2H, CH_2Br); 2.68 (t, J=6 Hz, 2H, allyl CH_2); 2.24 (s, 3H, $CH_3C(O)$); 1.80 (s, 3H, vinyl CH_3).

Thioester 257:

To a suspension of NaH (144 mg, 2.88 mmol, 50% dispersion oil washed with hexane) in 2 mL of 1:1 mixture of DMF-THF was added thiolacetic acid (200 μL, 218 mg, 2.88 mmol) slowly dropwise at rt and stirred for 30 min. To this sodium thiolate anion bromoester **236** (100 mg, 0.48 mmol) in 1 mL of THF was added and then heated at 65 °C for 2 h. The reaction mixture was cooled to rt and diluted with 30 mL of H_2O. The mixture was extracted with ether (3x20 mL), washed with 1N NaOH solution and brine. Usual work-up afforded thioester **257** which was purified by SGC (hexane to 5% EtOAc/hexane).

Yield: 90 mg, 95%

PMR: δ 5.74 (s, 1H, vinyl **H**); 3.70 (s, 3H, CO_2CH_3); 3.04-2.94 (m, 2H, CH_2S); 2.88-2.78 (m, 2H, allyl CH_2); 2.24 (s, 3H, $SC(O)CH_3$); 1.94 (s, 3H, vinyl CH_3).

Mercapto acid 258:

The diester **257** (60 mg, 0.3 mmol) in 3 mL of H_2O containing $NaHCO_3$ (243 mg, 3.0 mmol) was refluxed for 2 h. The reaction mixture was cooled to 0 °C, acidified with 10% HCl and extracted with ether (3x10 mL). Brine wash and work-up afforded mercapto acid **258** which was cyclised immediatly without any purification.

Yield: 42 mg, 91% (crude)

PMR: δ 5.74 (s, 1H, vinyl **H**); 2.96-2.84 (m, 2H, CH_2SH); 2.74-2.62 (m, 2H, allyl CH_2); 1.96 (s, 3H, vinyl CH_3); 1.48 (t, J=6 Hz, 1H, **SH**).

4-Methyl-5,6-dihydro-2(H)-thiopyran-2-one 253:

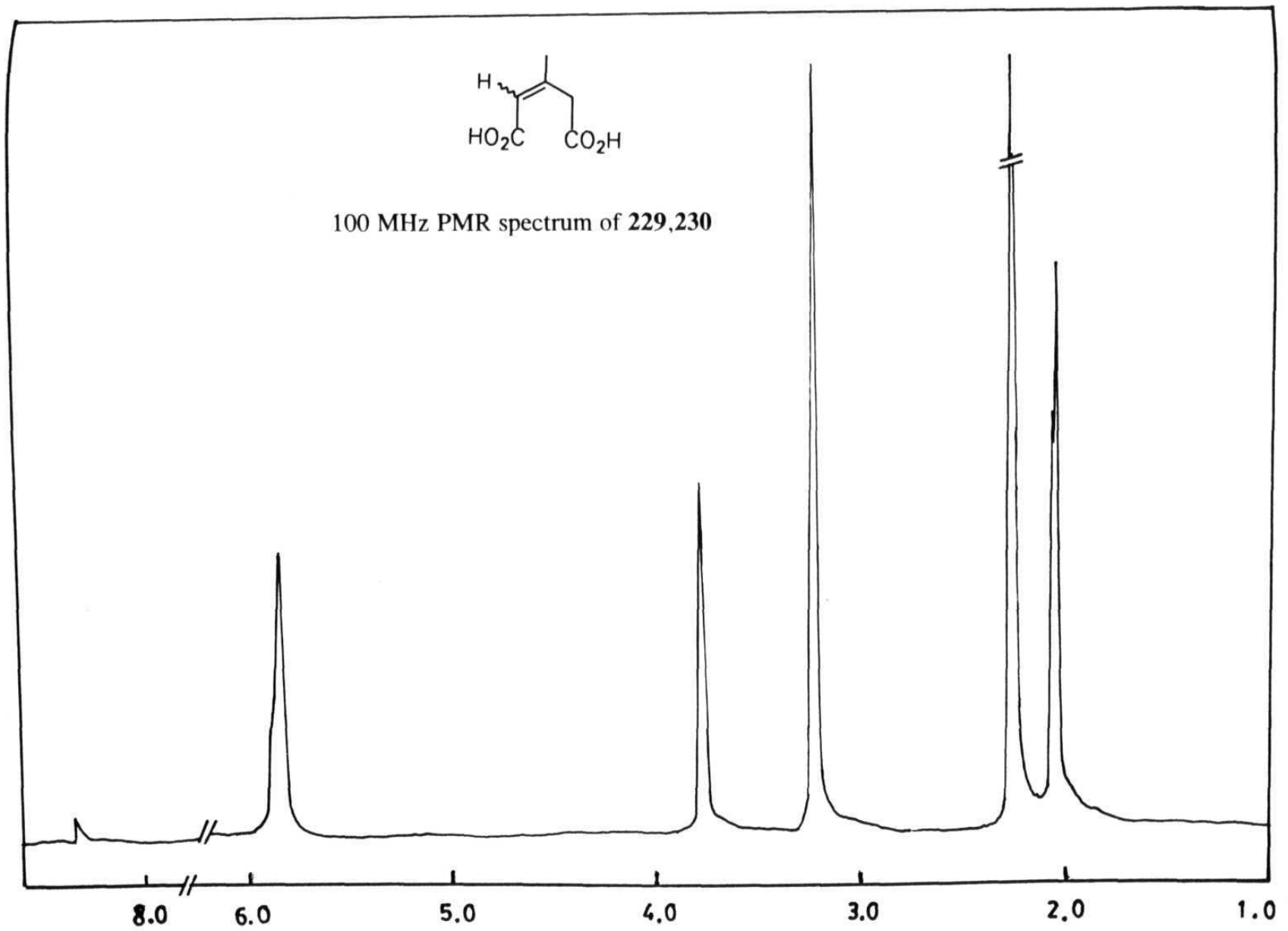
Mercapto acid (42 mg, 0.3 mmol) in 25 mL of benzene containing catalytic amount of *p*-TsOH.H_2O (5 mg) was heated at reflux for 1 h by azeotropic distillation using shot-path condenser. The reaction mixture was cooled to rt and diluted with 10 mL of ether , washed with saturated $NaHCO_3$ solution and brine. Usual work-up provided thiolactone **253** which was purified by SGC (hexane to 30% EtOAc/hexane).

Yield: 26 mg, 70%

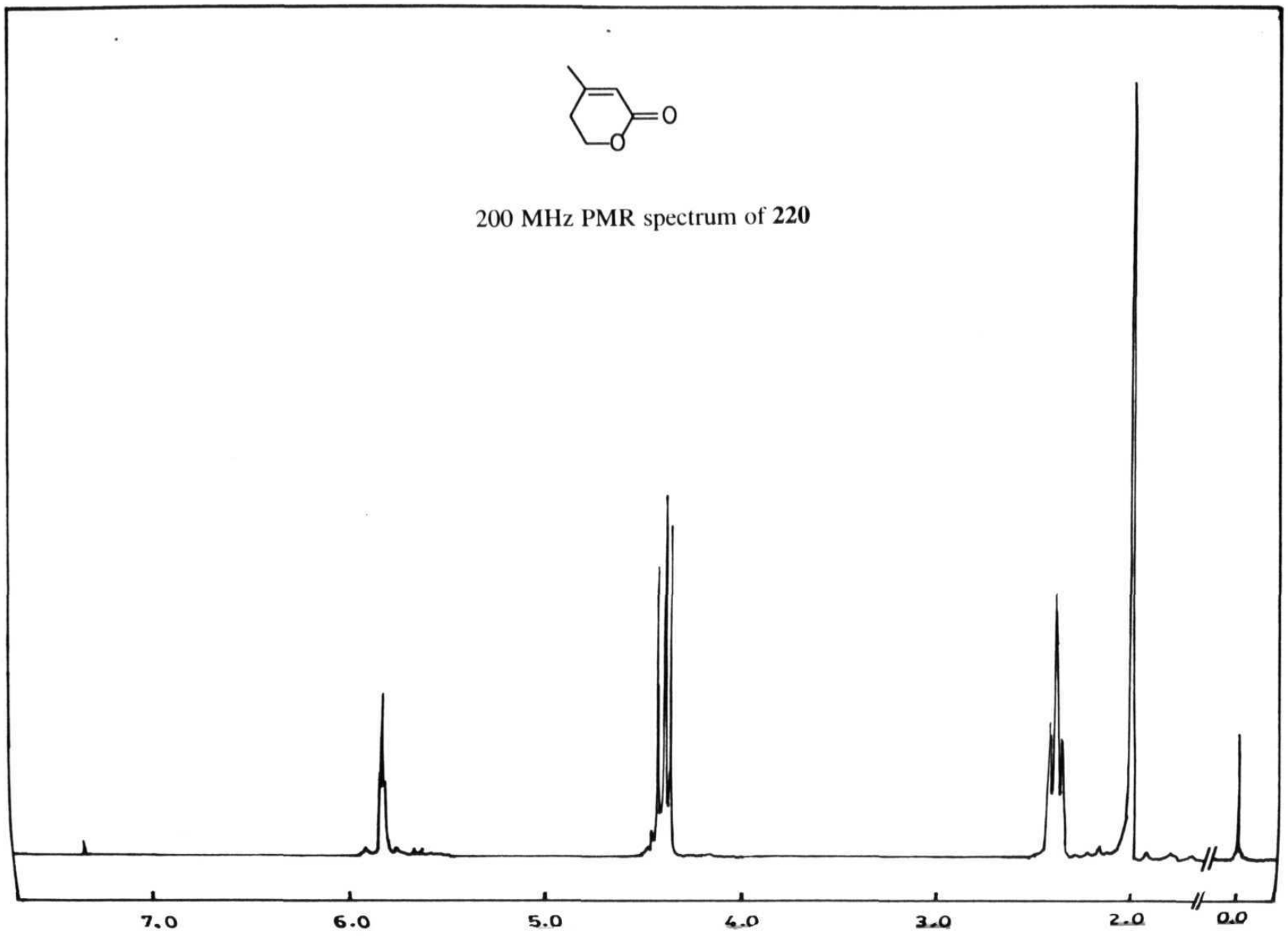
IR: cm^{-1} 2930, 1643, 1626, 1433, 1296, 1178, 1120, 846.

PMR: δ 5.98 (s, 1H, vinyl **H**); 3.18 (t, J=6 Hz, 2H, S**C**H_2); 2.52 (t, J=6 Hz, 2H allyl **C**H_2); 2.02 (s, 3H, vinyl **C**H_3).

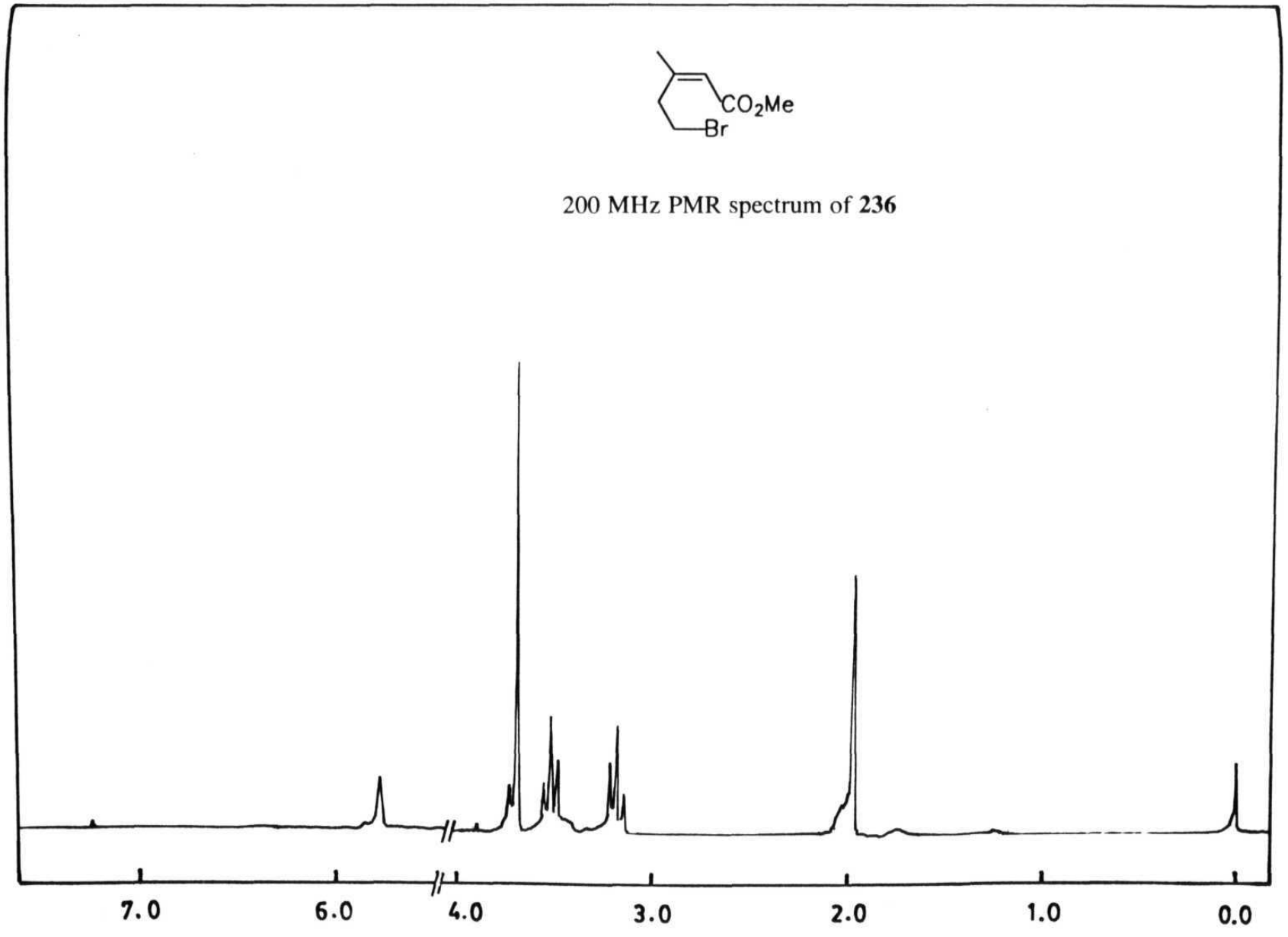
CMR: δ 189.66, 158.70, 125.05, 29.70, 27.66, 25.34.



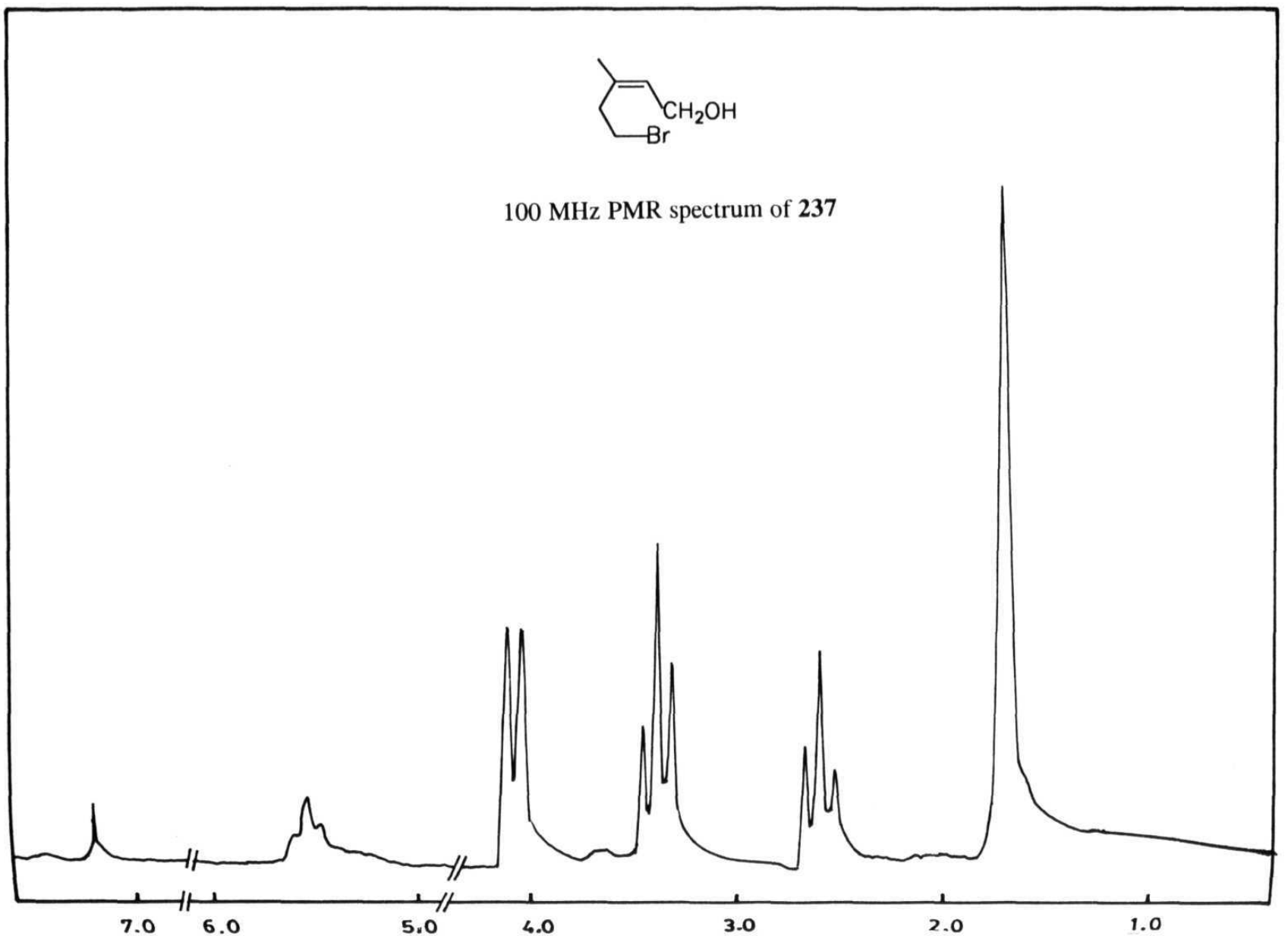
100 MHz PMR spectrum of **229**,**230**



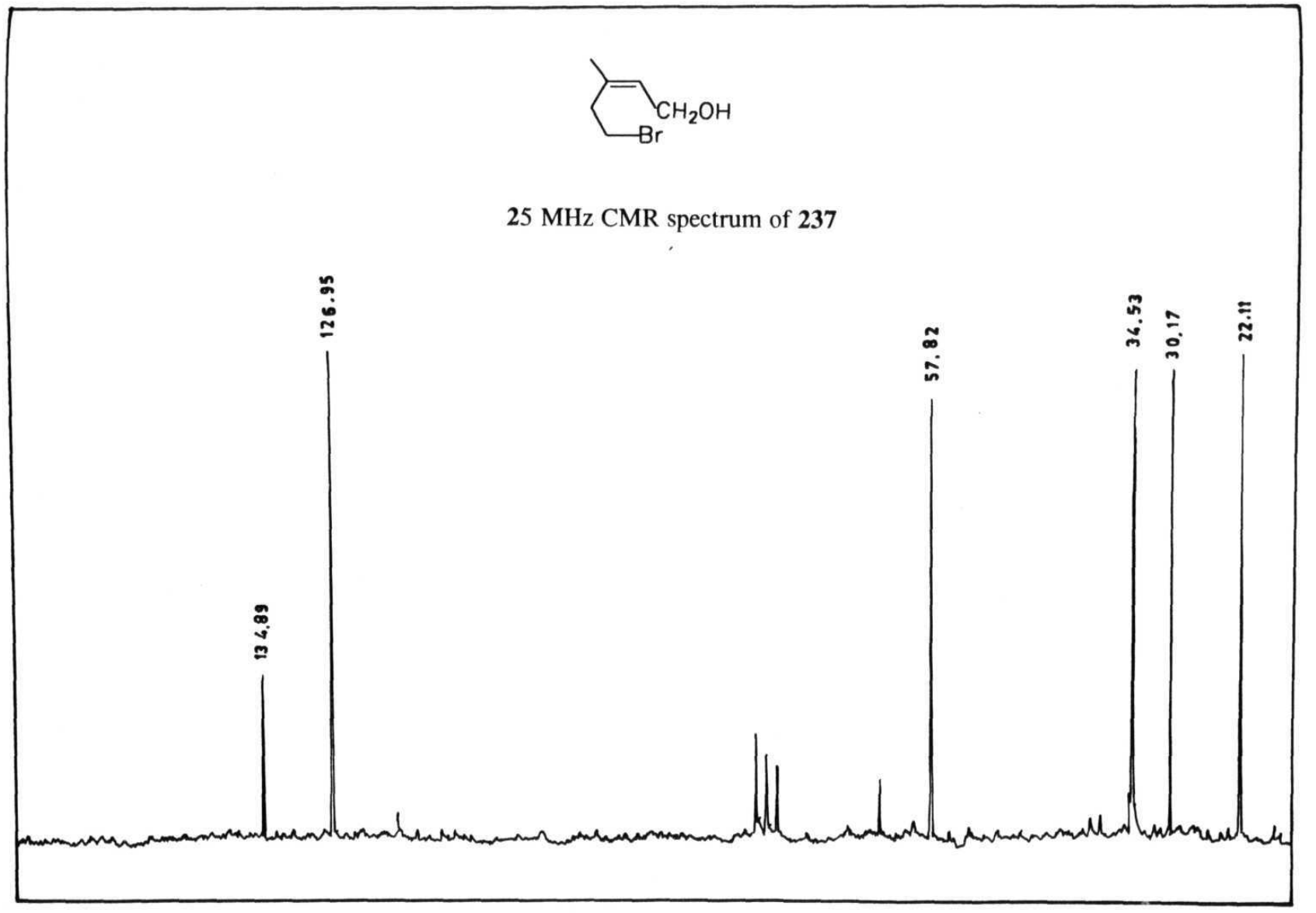
200 MHz PMR spectrum of **220**



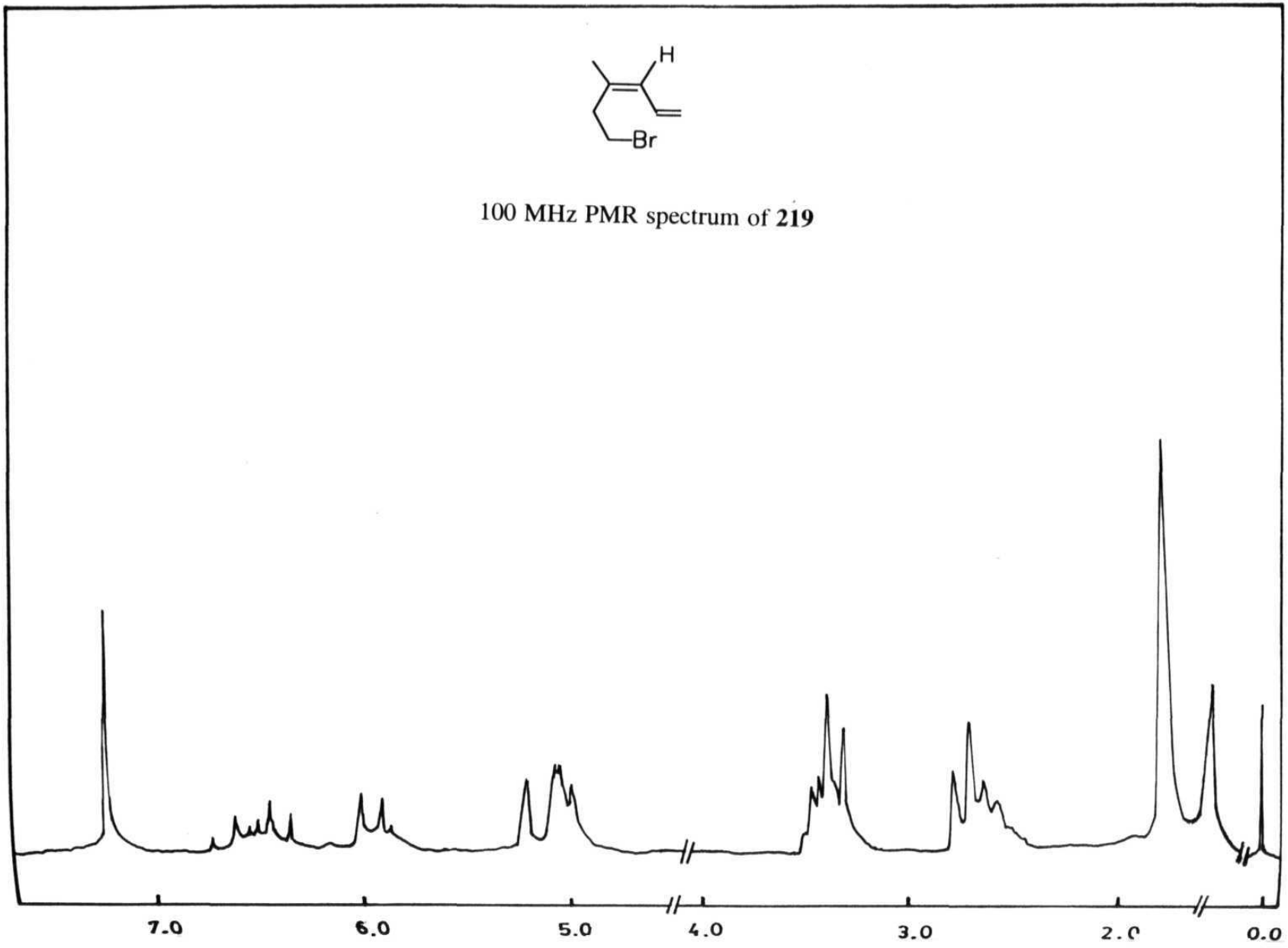
200 MHz PMR spectrum of **236**



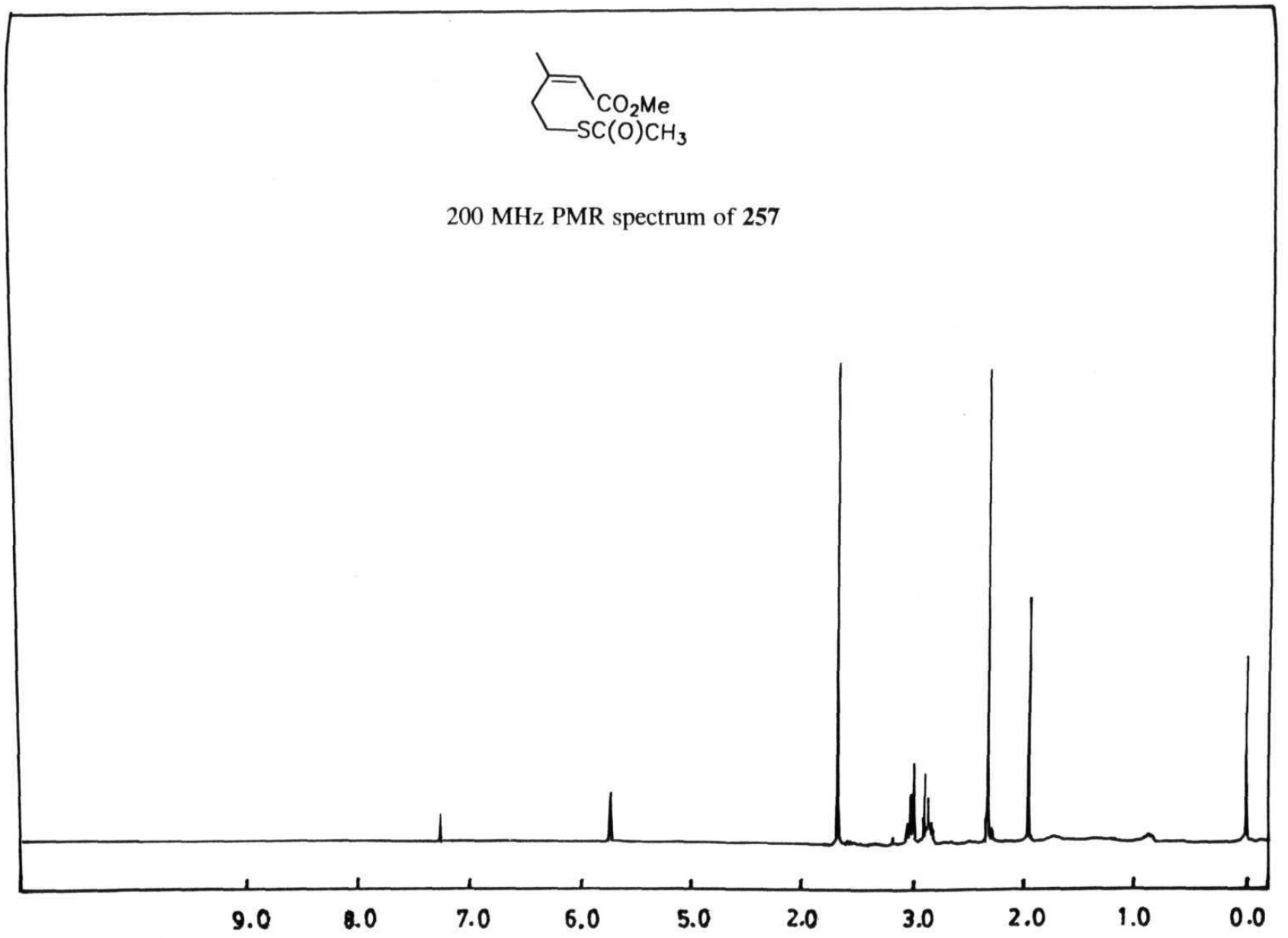
100 MHz PMR spectrum of **237**



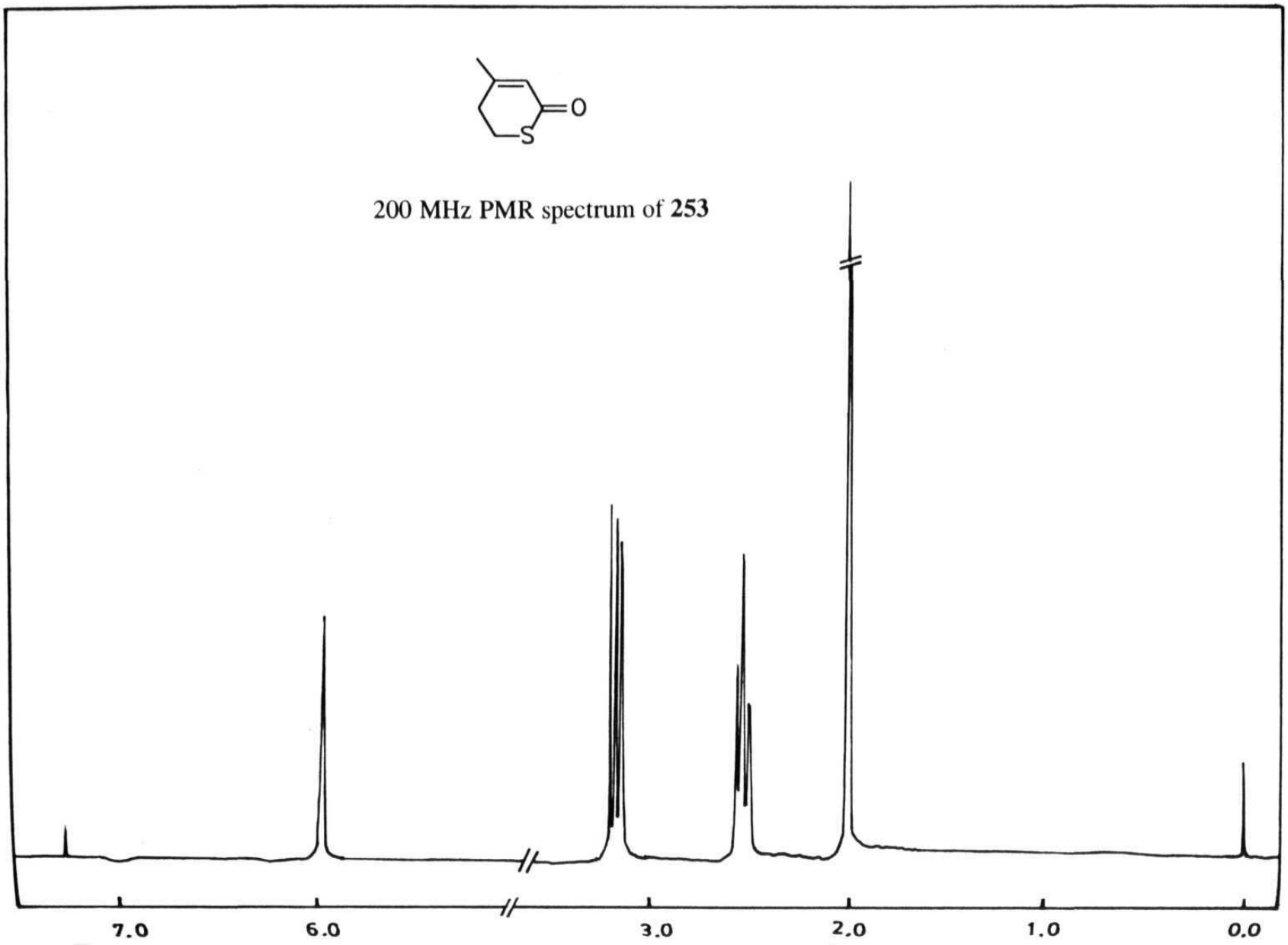
25 MHz CMR spectrum of **237**



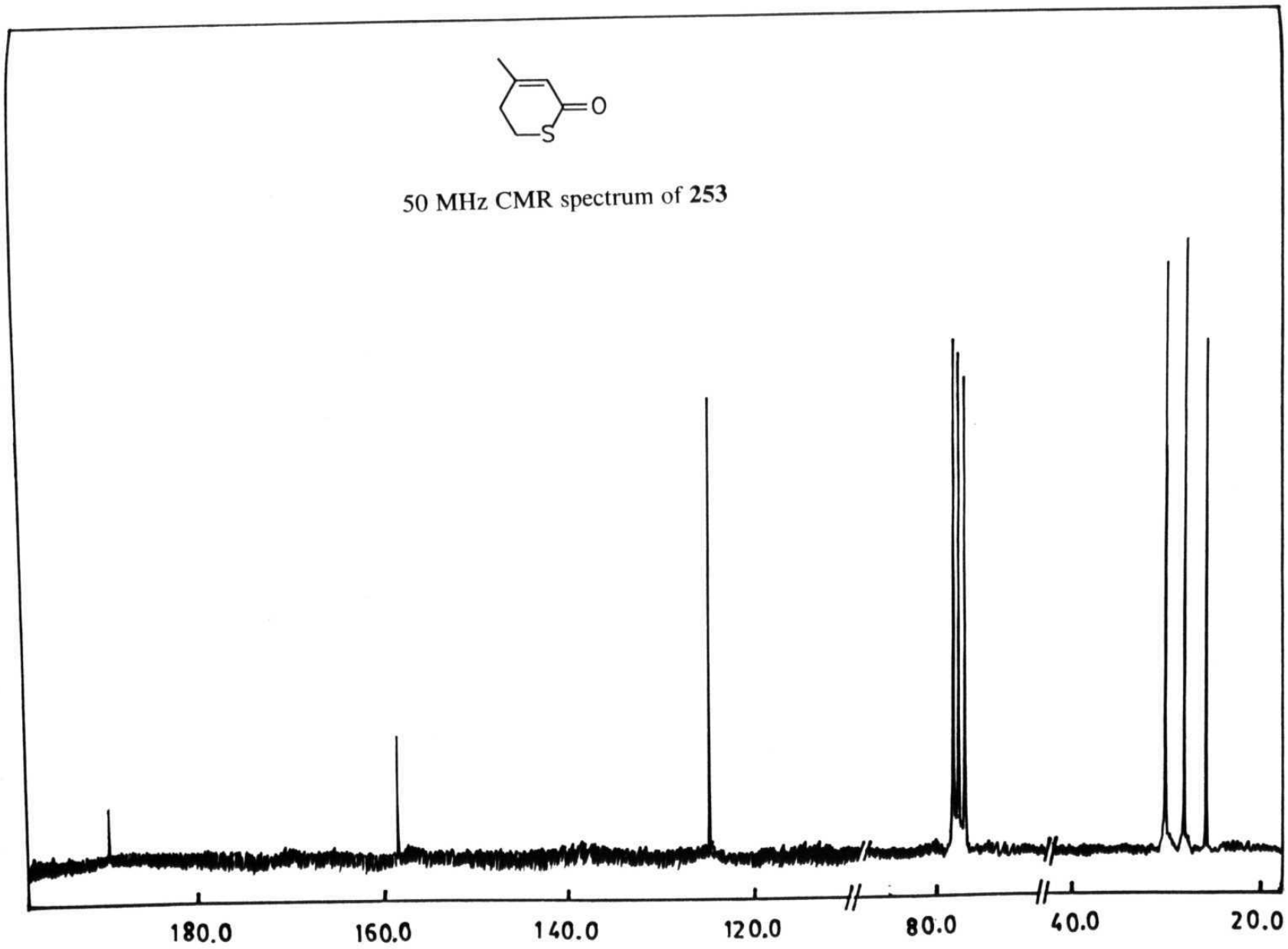
100 MHz PMR spectrum of **219**



200 MHz PMR spectrum of **257**



200 MHz PMR spectrum of **253**



50 MHz CMR spectrum of **253**

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CHAPTER-6
CONCLUSIONS

Introduction to iridoid monoterpene lactones and the various synthetic approaches towards chiral as well as racemic forms are documented in Chapter-1. There are two isomeric structural types of iridoid lactones: type-I, which bear a carbonyl group at C3, and type-II in which the carbonyl group is at C1. Most of the synthetic approaches which target type-I lactones proceed *via* bicyclic ketone **47** or bicyclic lactone **59**.

In Chapter-2, *R*-(+)-pulegone **91** was transformed to *R*-(-)- and *S*-(+)-3,5-dimethylcyclohex-2-en-1-ones **131** *via* the common precursor ketosulfoxide **120**. The optical purities are far superior to those reported in the literature. The conversion of *R*-(+)-pulegone to *S*-(-)-pulegone *via* a 1,3-carbonyl transposition was unsuccessful because the introduction of *iso*-propylidene group proved difficult. However, we have developed a method for the introduction of *iso*-propyl and *tert*-butyl groups adjacent to ketones. This occurs in a number of important natural products. Generalisation of the protocol for the enone direct α-functionalisation of ketones remains to be fully explored.

In Chapter-3 the formal synthesis of naturally occurring type-I lactones, (+)-iridomyrmecin **10**, (-)-isoiridomyrmecin **11** and (+)-teucriumlactone **15** was accomplished. A stereoselective synthesis from *R*-pulegone was developed for 7*R*-(-)-pyranone **59**, which leads to unnatural type-I lactones. Similarly, *S*-pulegone was transformed to 7*S*-(+)-pyranone **59**, which is the penultimate precursor for three natural iridoid lactones.

In Chapter-4 we have synthesised (-)-4-*epi*-mitsugashiwalactone **200** and (-)-mitsugashiwalactone **17** of type-II category using the HWE reaction. The synthesis of dihydronepetalactone was unsuccessful because the HWE reaction of ketone **177** with

phosphonate **178** is sluggish. In the synthesis of 4-*epi*-mitsugashiwalactone **200** the *trans*-stereochemistry at ring junction C4a-C7a arises from the chelation controlled Pd catalysed hydrogenation of exocyclic olefin **186,187**. Pt catalysed hydrogenation produces *cis*-ring junction at C4a-C7a and provided (-)-mitsugashiwalactone **17** in higher enantiomeric purity compared to that reported in the literature.

In Chapter-5 a synthetic approach towards subergorgic acid **206** is discussed. Although the synthesis was discontinued at an early stage, related results found general applications. Anhydromevalonolactone **220**, which is a versatile starting template, was synthesised using simple reaction conditions, inexpensive and commercially available starting materials. We have developed a surrogate sequence for DIBAL-H reduction of lactones for the preparation of bromodiene **219**. The conversion of O-lactone **220** to its S-lactone **253** was carried out employing mild reaction conditions and is applicable for the synthesis of α,β-unsaturated thiolactones.