ENANTIOSELECTIVE SYNTHESIS OF TERPENES

A THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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Dedicated To
My Parents

CONTENTS

STATEMENT

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, Hyderabad - 500 134, under the supervision of Professor GOVERDHAN MEHTA.

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

K. Srinivasa Rao

K. SRINIVASA RAO

CERTIFICATE

Certified that the work contained in this thesis entitled: "ENANTIOSELECTIVE SYNTHESIS OF TERPENES", has been carried out by Mr. K. SRINIVASA RAO under my supervision and the same has not been submitted elsewhere for a Degree.

G. Mehta

GOVERDHAN MEHTA

(THESIS SUPERVISOR)

DEAN

SCHOOL OF CHEMISTRY

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ABBREVIATIONS

Ac	:	acetyl
Ac_2O	:	acetic anhydride
aq.	:	aqueous
AIBN	:	azobisisobutyronitrile
Bu	:	butyl
DBU	:	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	:	dichloromethane
DMSO	:	dimethylsulfoxide
Et	:	ethyl
HMPA	:	hexamethylphosphoramide
LAH	:	lithium aluminum hydride
LHMDS	:	lithium hexmethyldisilazide
mCPBA	:	meta-chloroperbenzoic acid
Me	:	methyl
MeOH	:	methanol
Ms	:	methanesulphonyl
PCC	:	pyridinium chlorochromate
PDC	:	pyridinium dichromate
py	:	pyridine
THF	:	tetrahydrofuran
TMSCl	:	trimethylsilylchloride
TPAP	:	tetra-n-propylammonium perruthenate

PREFACE

Terpenoids are among Nature's more versatile and exciting creations. In a remarkable display of synthetic ingenuity and creativity, Nature has endowed terpenes with a bewildering array of carbocyclic frameworks with unusual assemblage of rings and functionality. Because of this phenomenal structural diversity, this class of natural products hold special appeal to the synthetic chemist and provide a fertile ground for developing and testing new synthetic strategies, particularly those directed towards carbocyclic ring construction. As a result, synthetic activity in this area continues to flourish despite the fact that much attention has been lavished on it during the past few decades. In recent years, more emphasis has been on the enantioselective construction of terpenes and many tactics including the 'chiron' approach have been utilised for this purpose. The research described in the present thesis is concerned with the enantioselective construction of diverse terpene skeleta employing some novel monoterpene derived 'chirons'.

The thesis entitled **"Enantioselective Synthesis of Terpenes"** is an account of synthetic manoeuvres involving two bifunctional chirons (-)-(2S,5S)-5-Isopropyl-2-methyl-2(2-oxoethyl)methylene-cyclopentane and (-)-(2S,5S)-5-Isopropyl-2-methyl-2(carboethoxy-methyl)methylenecyclopentane of well defined stereochemistry, readily attainable from R-(+)-limonene, into higher terpene natural products. For clarity, these research results are presented in three chapters:

1) Synthesis of C_{12}-chirons from (R)-(+)-limonene: Construction of the 5,5-, 5,6-, 5,7- and 5,8-fused bicyclic systems. 2) A new cyclopentenone annulation protocol: Total synthesis of novel triquinane sesquiterpene (-)-ceratopicanol. 3) Synthetic studies towards virgane diterpenes.

The first chapter describes the synthesis of two C_{12}-chirons, (-)-(2S,5S)-5-Isopropyl-2-methyl-2(2-oxoethyl)methylene-cyclopentane and (-)-(2S,5S)-5-Isopropyl-2-methyl-2(carboethoxy-methyl)methylenecyclopentane, from restructured R-(+)-limonene employing a highly diastereoselective [3s.3s]-rearrangement, and their further elaboration into 5,5-, 5,6-, 5,7- and 5,8-fused bicyclic chiral building blocks through new, short and practical ring annulation protocols. The two chirons are well disposed towards ring annulation and the two functionalities present in them serve as a convenient handle.

The 5,5-fused bicyclic system has been constructed from (-)-(2S,5S)-5-Isopropyl-2-methyl-2(carboethoxymethyl)methyl-enecyclopentane employing an intramolecular diazo ketone-olefin cyclisation as the key operation. The 5,6-fused bicyclic system has also been constructed from (-)-(2S,5S)-5-Isopropyl-2-methyl-2(carboethoxymethyl)methylenecyclopentane employing the diazo ketone-olefin cyclisation methodology. In an alternative route to the 5,6 fused system, (-)-(2S,5S)-5-Isopropyl-2-methyl-2-(2-oxoethyl)methylenecyclopentane has been homologated to set up an intramolecular ene reaction. The 5,7-fused bicyclic hydro-azulenone (-)-(1S)-8-Isopropyl-1-methyl-bicyclo[5.3.0]dec-7(8)-en-3-one has been assembled in three convenient steps from

(-)-(2S,5S)-5-Isopropyl-2-methyl- 2 (2-oxoethyl) methylenecyclopentane in which the acid catalysed enone-olefin cyclisation is **the pivotal step. The 5,7-fused bicyclic enone has been further elaborated to 5-8 fused bicyclic system through Dowd's one carbon ring expansion methodology.**

The second chapter describes an expedient and simple cyclopentenone annulation protocol which directly generates the 5,5-dimethyl cyclopentenone moiety from a carbonyl precursor . This annulation procedure basically consists of three steps: a) Barbier-type addition of 3-lithio-2,2-dimethylpropyl tert-butyldimethylsilyl ether to the alkanone and deprotection of the TBDMS group b) Clean and efficient oxidation of the resulting diol with the Griffith-Ley's reagent (tetra-n-propylammonium perruthenate, TPAP), to the γ-lactone and c) the rearrangement of the γ-lactone to the gem-dimethyl cyclopentenone moiety in P_2O_5-$MeSO_3H$ milieu. Several examples demonstrate the generality of this methodology. The annulation protocol served as the key operation in the first total synthesis of the enantiomer of the triquinane sesquiterpene (+)-ceratopicanol recently isolated from the fungus Ceratocystis piceae Ha 4/82. The synthesis also establishes the absolute stereochemistry of the natural product. A notable feature of this enantioselective synthesis is that the isopropenyl group of R-(+)-limonene serves as an internal chiral auxiliary and is disposed-off at an appropriate juncture.

The third chapter gives an account of the synthetic studies towards the total synthesis of a 5,7,5-fused, cembrane derived, tricyclic diterpene, 18-oxo-3-virgene recently isolated from

Nicotina tabacum flowers. At the outset, a model study towards the fabrication of a suitably functionalised tricarbocyclic system has been carried out. For this purpose, the enantiomerically pure bicyclic hydroazulenone has been restructured to (+)-(1S)-8-Isopropyl-1-methyl-bicyclo[5.3.0]dec-7-ene-2,6-dione via catalytic ruthenium oxidation followed by base catalysed aldol cyclisation-dehydration. The ene-dione has amplified and redistributed functionalities at the desired position and the enone moiety present was more amenable to reductive manoeuvres for generating the requisite stereochemistry of the natural product. The ene-dione was elaborated to the tricyclic bis-enone (+)-(5R,10R)-13-Isopropyl-10-methyl-tricyclo[8.3.0.$0^{5,9}$]tridec-1(13),8-diene-2,7-dione in a three step sequence.

Chapter 1

Synthesis of C_{12}-Chirons from R-(+)-Limonene: Construction of the 5,5-, 5,6-, 5,7- and 5,8-Fused Bicyclic Systems

I.1. ABSTRACT

A synthesis of two novel and versatile C_{12}-chirons (-)-**14** and (-)-**15** from R-(+)-limonene **16** and their further elaboration into 5,5-, 5,6-, 5,7- and 5,8-fused bicyclic chiral building blocks through new, short and practical ring annulation protocols has been developed. R-(+)-Limonene **16** can be readily and efficiently restructured into a C_{10}-α,β-unsaturated aldehyde (-)-**17** through an unexceptional 5 step sequence. Employing a highly diastereoselective [3s.3s]-rearrangement, (-)-**17** has been elaborated in two steps into two C_{12}-chirons (-)-**14** and (-)-**15** in excellent yield. The two chirons are well disposed towards ring annulation and the two functionalities present in them served as a convenient handle.

The 5,5-fused bicyclic system (-)-**39a** was constructed from (-)-**15** employing an intramolecular diazo ketone-olefin cyclisation as the key operation. Oxidative disposal of the isopropylidine group in (-)-**39a** through catalytic ruthenium oxidation furnished the diquinane dione (-)-**42** which is a potentially serviceable building block for the elaboration to diverse terpenes which embody a diquinane structural moiety.

The 5,6-fused bicyclic system (+)- **57** was also constructed from (-)-**15** employing the diazo ketone-olefin cyclisation methodology. The enone (+)-**57** could be further restructured in two steps into an ene-dione (+)-**60**, which has amplified and redistributed functionality. In an alternative route to the 5,6-fused system, the aldehyde (-)-**14** was

homologated and subjected to an intramolecular ene reaction (**62** ⟶ **63a,b**). PCC oxidation of (-)-**63a,b** led to an oxidative rearrangement and furnished the γ-hydroxy-α,β-unsaturated ketones **64a,b** bearing characteristic functionality present in many terpenes.

The 5,7-fused bicyclic system (-)-**69** was assembled in three convenient steps from (-)-**14** via the α,β-unsaturated enone (-)-**77** in which the acid catalysed enone-olefin cyclisation ((-)-**77** ⟶ (-)-**69**) was the pivotal step. The hydroazulenone (-)-**69** was elaborated to the 5,8-fused bicyclic system (+)-**86** through Dowd's one carbon ring expansion methodology.

I.2. OBJECTIVE

Nature, with meticulous stereochemical precision and efficiency, enantioselectively synthesises a vast array of novel molecular structures, employing relatively few fundamental reactions. Many of these natural products exhibit diverse and notable biological activity. In several cases, only one enantiomer of the natural product is active towards microorganisms. As a result, synthesis of natural products in an enantioselective manner has been receiving increasing attention from synthetic chemists in recent years.

In general, optically pure natural products are synthesised by resolution at some stage during the synthesis or through asymmetric synthesis or by utilising an abundantly available, naturally occurring chiral starting material. While the classical resolution methods continue to be used in some cases, greater emphasis is now on methods based on catalytic asymmetric synthesis and use of biological media (enzymes, abzymes etc.,) for gaining access to enantiomerically pure compounds. Concurrently, several chiral sources such as amino acids[1], carbohydrates[2], terpenes[3], α-hydroxy acids[4] continue to be exploited as chiral templates for the enantiospecific synthesis of natural products.

Among the chiral pool, carbohydrates have received disproportionate attention during the past decade, so much so that even hydrocarbons are being synthesised from sugars regardless of the complications involved. One of the limitations

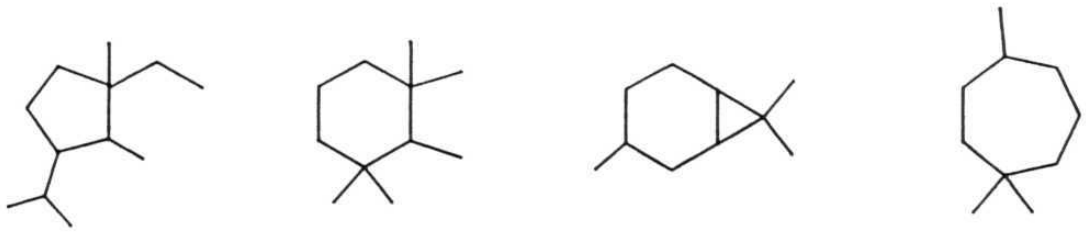
in using carbohydrates in synthesis is the presence of excessive functionality and many asymmetric centres. As a result, destruction of asymmetric centres in order to preserve a few required centres becomes necessary. Also, the laborious task of protection and deprotection of functional groups, which alarmingly increase the number of steps in a synthesis, becomes unavoidable. For example, the triquinane based sesquiterpene hydrocarbon (-)-Silphiperfolene has been synthesised from D-mannose in 30 steps[5a], whereas its synthesis from (+)-pulegone was reported in 18 steps[5b]. Similarly, the irridoid monoterpene (-)-Sarracenin has been synthesised from D-glucose in 16 steps[6a], but from L-(+)-ethyl lactate in only 7 steps[6b]. Also, some carbohydrates are more expensive or more inaccessible than the optically active final product and several enantiomeric forms of sugars (eg. L-sugars) are not readily available.

Such overwhelming accent on carbohydrates as chirons has marginalised the importance of terpenes in an enantioselective synthesis, despite their high potential. Several terpenes are cheap, readily accessible and are available in both the enantiomeric forms. They are generally endowed with only one or two chiral centres with modest functionalisation and thus do not require recourse to wasteful manoeuvres to dispense with the excess functionality. More importantly, terpenes can be readily restructured by employing simple methodologies into cyclic and acyclic fragments with amplified asymmetric centres, that can be directly incorporated into the carbocyclic frameworks of complex target structures. Many terpenes, like camphor[3,7],

citronellol[3,8], pulegone[3,9], limonene[3,9a,10], and carvone[3,11] among others have been used successfully, as chiral templates for the synthesis of highly complex molecules.

Nature assembles its vast repertoire of terpenic skeleta[12] (mono-, sesqui-, di-, sester- and triterpenes) from very few biogenetic precursors like geranyl pyrophosphate (GPP), farnesyl pyrophosphate (FPP), geranylgeranyl pyrophosphate (GGPP), geranylfarnesol and squalene epoxide[13]. There are several closely related modes of cyclisations available to these acyclic terpene precursors and as a result one finds many common structural moieties present in C_{10}-mono-, C_{15}-sesqui-, C_{20}-di-, C_{25}-sester-, C_{30}-triterpenes. A few of such structural moieties are shown in Chart I.1 and can be structurally traced to an abundant and readily recognisable monoterpene. Therefore, an

Chart I.1

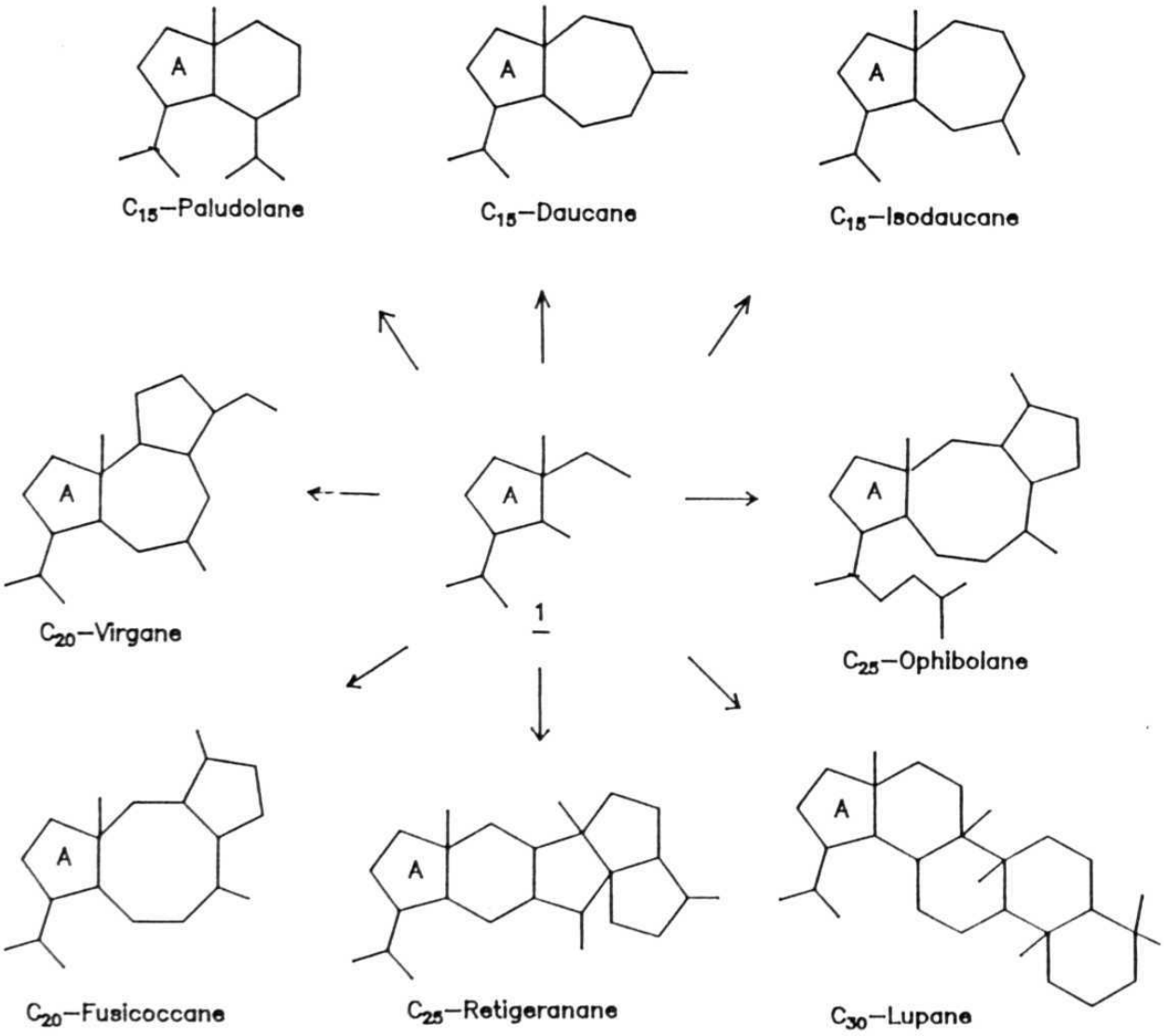


operationally versatile strategy emerges in which such structural moieties extracted from a single, lower terpene chiron, e.g., a C_{10}-monoterpene can be evolved into sesqui-, di-, sester- and triterpenes bearing complex structures. Exploration of this strategy and pursuit of 'Terpene to Terpenes' theme for chiral synthesis is the objective of the present study.

In chart I.2 are displayed a few representative examples of C_{15}-sesqui-, C_{20}-di-, C_{25}-sester- and C_{30}-triterpene skeleta, all

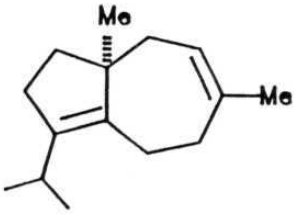
of which share a common structural core 1 (ring A). These are among over two dozen skeletal-types and several hundred natural terpenes, embellished with different stereochemical and functionalisation patterns, which embody this cyclopentane 1

Chart I.2

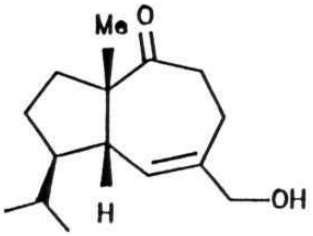


fragment. A few examples of such natural products are shown in Chart I. 3[14-17]. We reasoned that a chiral bifunctional derivative 12, with well defined stereochemistry, could serve as a

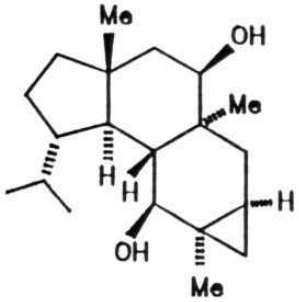
Chart I.3



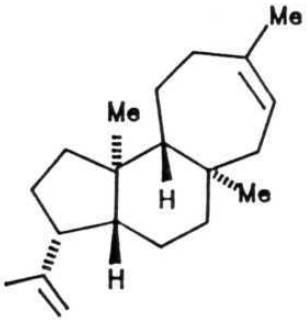
(−)−Daucene 2[14a]



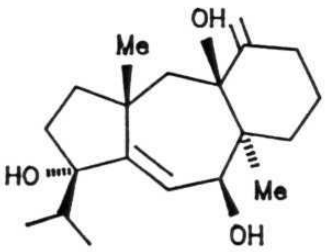
Aphanamol−I 3[14b]



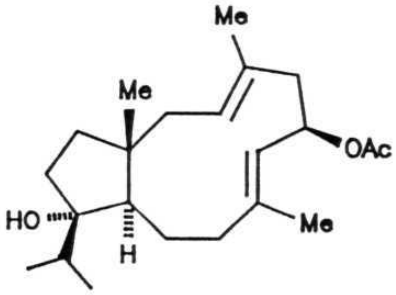
2,8−Dihyroxy verrucosane 4[15a]



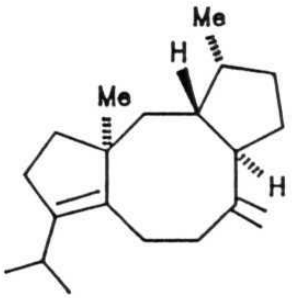
Valparene 5[15b]



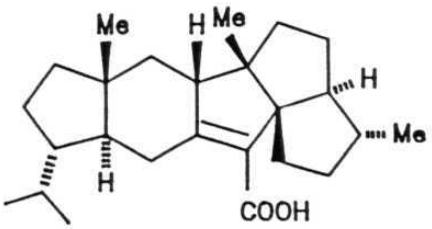
Dolatriol 6[15c]



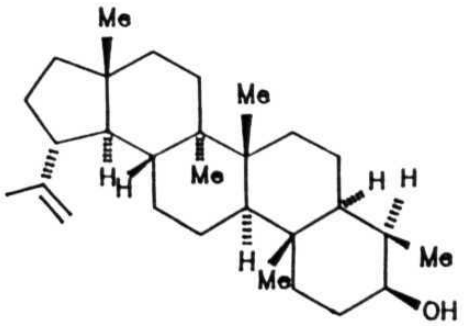
6−Acetoxydolabella−3,7−diene 7[15d]



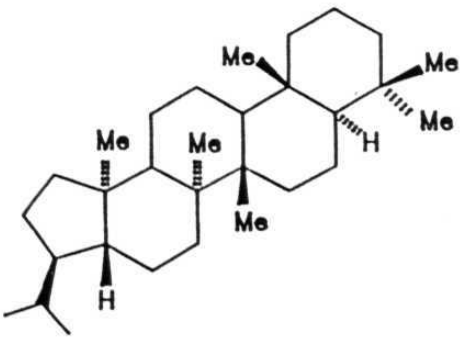
Cycloaraneosene 8[15e]



Retigeranic Acid 9[16a−d]



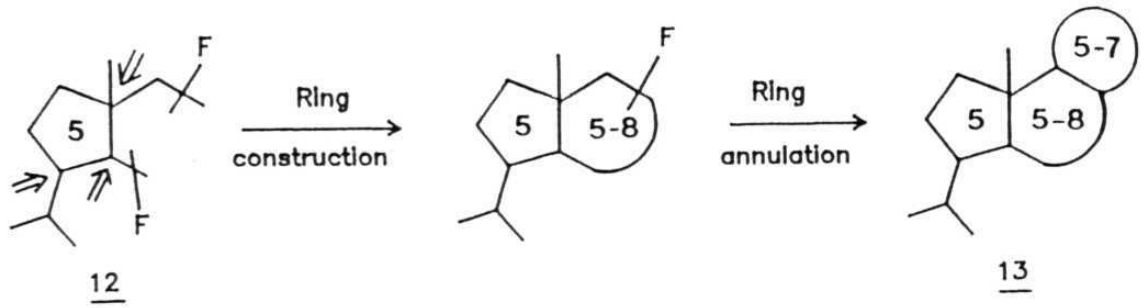
Lupeol 10[17a,b]



Hopane 11[17c]

versatile 'chiron' for the synthesis of diverse terpenes displayed in **Chart I.3** and many others. The two functionalised side arms in 12 could be so created as to be amenable to the annulation of 5, 6, 7 and 8 membered rings and further elaboration to the framework eg., 13 of the target structure as shown in Chart **I.4**. For this purpose, unsaturated aldehyde (-)-**14** and

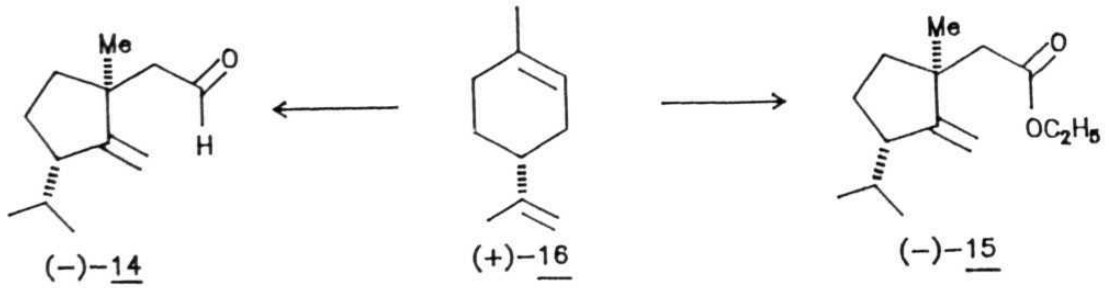
Chart I.4



12 13

unsaturated ester (-)-15 of firmly secured stereochemistry and related to 12 appeared to be eminently serviceable[18], Scheme I.1.

Scheme I.1

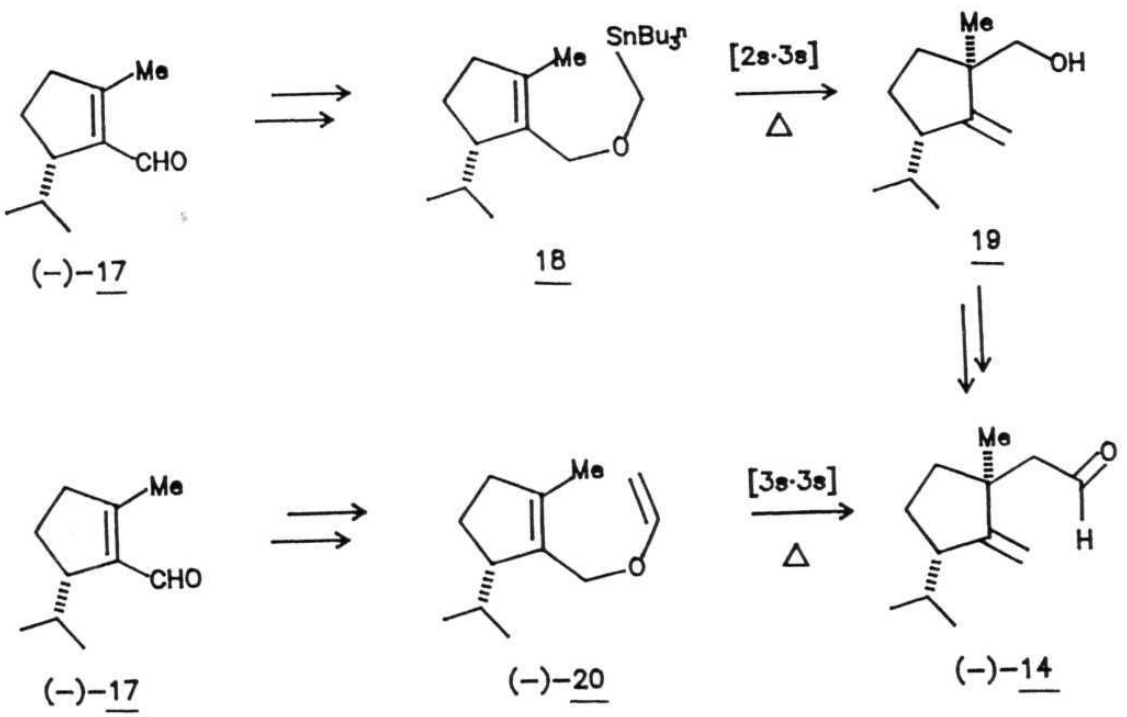


(-)-14 (+)-16 (-)-15

To gain ready access to the C_{12}-chirons (-)-**14** and (-)-**15**, the cheap and abundantly available R-(+)-limonene **16** (with an annual production of 50,000 tonnes[3d]) was chosen as the chiral resource, particularly as it can be readily and efficiently restructured into C_{10}-cyclopentene carboxaldehyde **17**[19] in a five step sequence (vide-infra).

Elaboration of the (-)-C_{10}-aldehyde 17 to the C_{12}-chirons (-)-**14** and (-)-**15** required setting-up the quaternary centre in a diastereoselective manner as well as appendage of a two carbon side arm with desirable functionalities. For this purpose, we considered symmetry allowed sigmatropic processes to be most suited and hoped with considerable optimism that the isopropyl group in (-)-17 would be an effective diastereoselective control element. Two protocols for this purpose were considered feasible and are shown in Scheme I.2. In the first

Scheme I.2

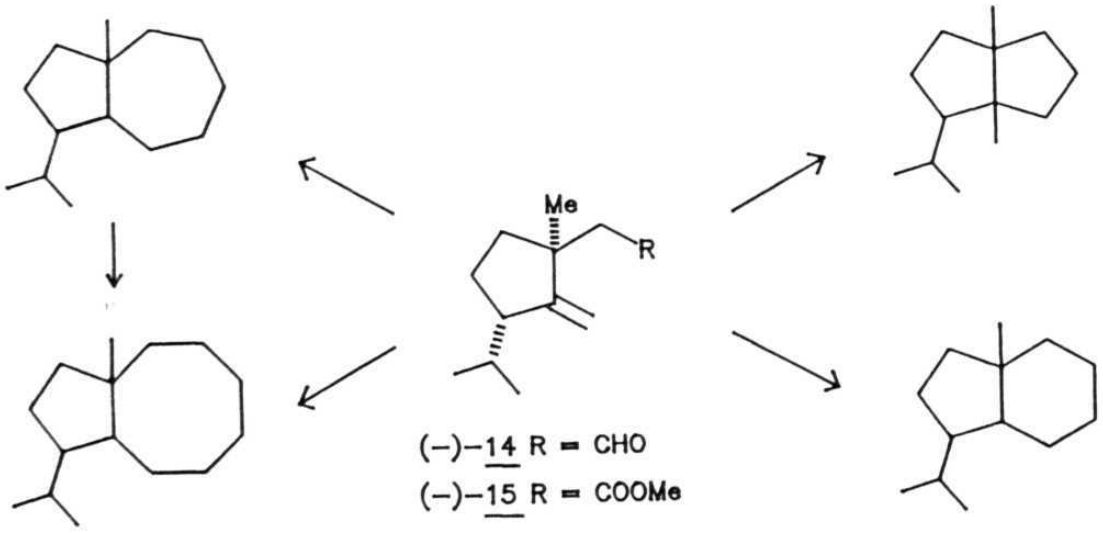


approach an anionic [2s.3s] sigmatropic rearrangement[20] in **18** to **19** followed by one carbon homologation was to lead to (-)-**14**. The second route envisaged a [3s.3s] sigmatropic process directly leading to (-)-**14**. For access to the ester (-)-15 the [3s.3s]

sigmatropic process could be suitably modified and well established protocols exist in the literature for this purpose. While the [2s.3s] sigmatropic process for (-)-**14** appeared tempting, from a practical point of view, particularly from scale-up considerations, the [3s.3s] sigmatropic process (Claisen rearrangement[21]) was preferred and implemented successfully.

With a strategy to (-)-**14** and (-)-15 identified, our next concern was to devise annulation processes for elaborating these chirons into 5,5-, 5,6-, 5,7-, and 5,8-fused bicyclic systems, **Scheme I.3**, enroute to some of the natural products enumerated in **Chart I.3**. All these annulations have been accomplished employ-

Scheme I.3

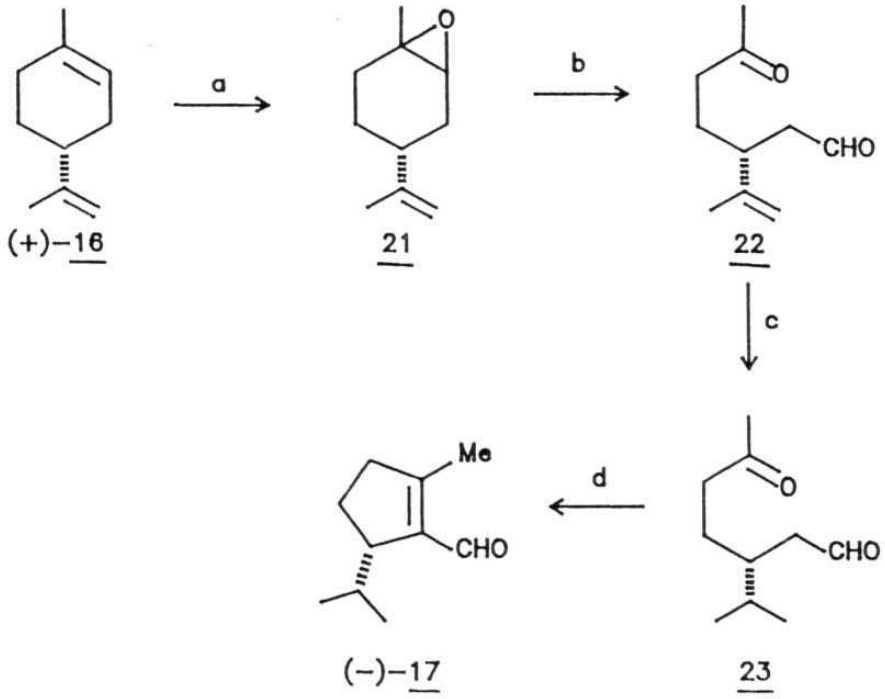


ing the cation-olefin cyclisation as the strategy and forms the subject matter of this chapter.

I.3. SYNTHETIC STUDIES:

As indicated above, the α,β-unsaturated cyclopentene aldehyde (-)-17 was chosen as the building block whose synthesis has been reported[19] previously from R-(+)-limonene **16**. Some tactical experimental modifications were made to obtain large quantities of (-)-17 and full details of its preparation from (+)-16 are provided in the experimental section, **Scheme I.4.**

Scheme I.4

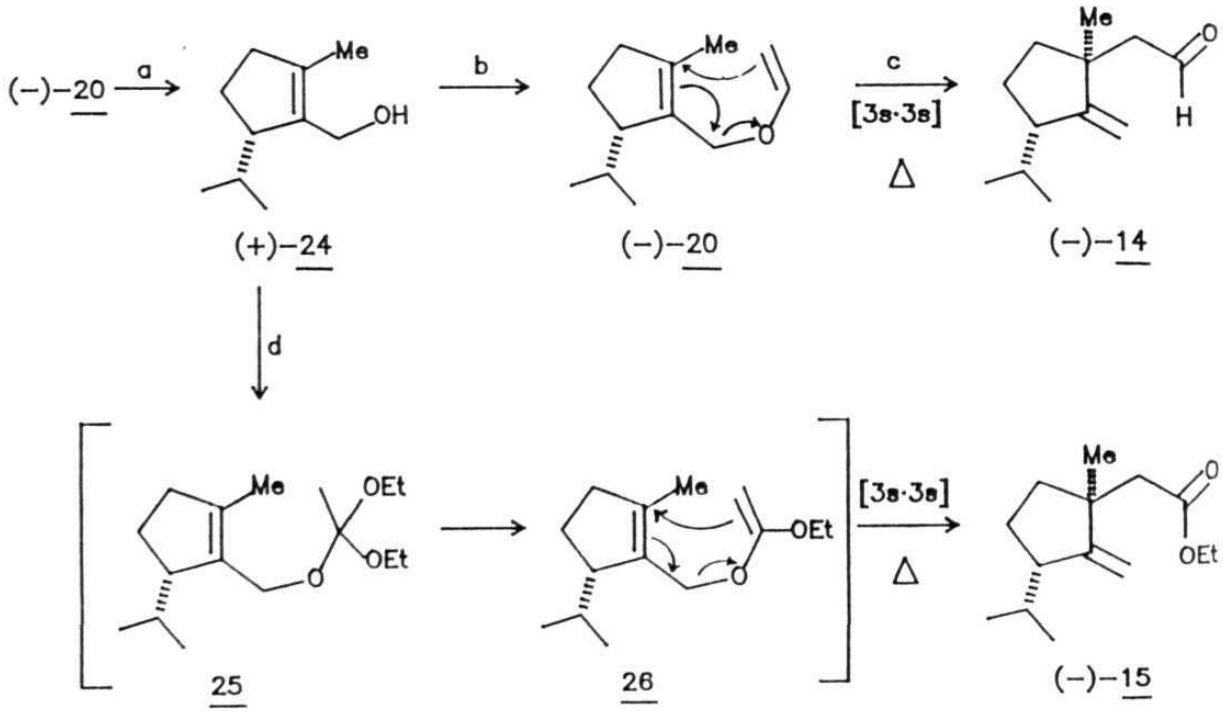


Reagents and yields: (a) m-CPBA, $CHCl_3$, 0°C, 10 h, 80%; (b) (i) 1% H_2SO_4, THF, RT, 1 h; (ii) $NaIO_4$, THF, H_2O, RT, 3 h, 75% from 21. (c) H_2-PtO_2, EtOAc, 20 psi, 1 h; (d) piperidine, AcOH, Benzene, △ , 1 h, 70%.

To setup the Claisen rearrangement outlined in **Scheme I.2**, the α,β-unsaturated aldehyde (-)-17 was chemoselectively reduced

with $NaBH_4 - CeCl_3$ reagent[22] to furnish the allylic alcohol (+)-**24** in quantitative yield and was further transformed to the vinyl ether (-)-**20** on Hg^{+2}-catalysed transetherification[23]. Thermal activation of (-)-**20** at 200°C in a sealed tube, following the common Claisen rearrangement regimen[21b], led to the exclusive formation of unsaturated aldehyde (-)-**14** in 90% yield, **Scheme I.5**. The structure of (-)-**14** rests secured on its spectral data, particularly the methyl singlet at δ 1.09 in the ^1H NMR spectrum (**Fig. I.1**) and the quaternary sp^3 carbon signal at

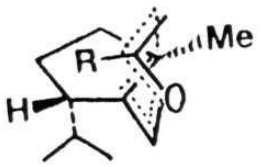
Scheme I.5

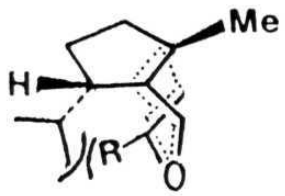


Reagents and yields: (a) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0°C, 0.5 h, quant.; (b) $CH_2{=}CHOCH_2CH_3$, $Hg(OAc)_2$, 30°C, 20 h, 80%; (c) Sealed tube, 200°C,1 h, 90%; (d) $CH_3CH(OC_2H_5)_3$, $Hg(OAc)_2$,C_2H_5-COOH, sealed tube, 200°C, 6 h, 80%

δ 44.0 in the ^{13}C NMR spectrum (Fig. I.2). Similarly, on subjecting (+)-24 to ortho-ester Claisen rearrangement[21d], by heating a mixture of (+)-24, mercuric acetate and triethyl ortho-acetate at 200°C in a sealed tube in the presence of propionic acid, the unsaturated ester (-)-15 was also obtained as a single diastereomer in 80% yield, Scheme I.5. The ortho-ester Claisen rearrangement involves the formation of a mixed ortho-ester 25, followed by acid promoted elimination of ethanol to form ketene acetal 26, which undergoes the [3s.3s]-shift to give the olefinic ester (-)-15. The presence of a methyl singlet at δ 1.08 in the ^{1}H NMR spectrum (Fig. I.3) and a 13 line ^{13}C NMR spectrum (Fig. I.4) with olefinic carbons at δ 161.9, 103.4 secured the structure of (-)-15 and also indicated the exclusive formation of a single diastereomer in the Claisen rearrangement. The diastereofacial selectivity in the Claisen rearrangement with the reaction exclusively taking place on the face opposite to the isopropyl group, was a desirable outcome as conceived earlier. The observed stereochemistry can be rationalised in terms of preference for the Claisen transition state 27 over 28, where unfavourable steric interactions between the group R and isopropyl group are minimised Chart I.5. Having acquired a short access to the enantiomerically pure (-)-14 and (-)-15 with well defined stereochemistry at the quaternary centre from (+)-16 through intramolecular chirality transfer, attention was turned towards the annulation processes. The two functionalities present in (-)-14 and (-)-15 are well disposed for the annulation of 5, 6, 7 and 8 membered rings.

Chart I.5





27a. R = CHO 28a. R = CHO

27b. R = COOEt 28b. R = COOEt

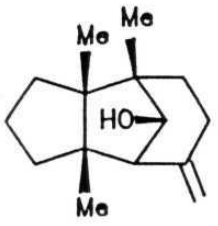
I.3.1. Construction of 5,5-Fused Bicyclic System:

Many terpenes containing two contiguous bridgehead quaternary methyl groups and extensive functionalisation have been isolated from different natural sources in recent years, Chart I.6[24]. Among them gymnomitrol 29[24a,b], ptychanolide 30[24c], (+)-ceratopicanol 31[24d] bear a polyquinane moiety in which a ring junction is substituted with two adjacent quaternary methyl groups.

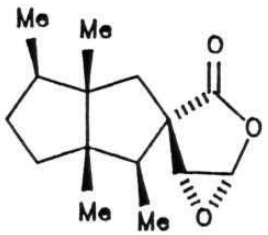
These molecules constitute attractive targets for synthesis because of their unusual carbocyclic framework and interesting biogenesis. Synthetic strategy to these natural products would require rapid assembly of a 5,5-fused bicyclic system possessing two contiguous quaternary carbon centres with the cis-methyl groups. Approaches towards the syntheses of gymnomitrol 29[25], and ptychanolide 30[26] by different research groups have generally adopted this strategy. We therefore considered the possibility of elaborating (-)-14 or (-)-15 into a bicyclo[3.3.0]octane system, which could serve as an effective advanced intermediate for the synthesis of some of the terpenes

depicted in Chart I.6. To achieve the above objective, our choice fell on the acid catalysed intramolecular diazo ketone-olefin cyclisation as the key step to construct a five membered

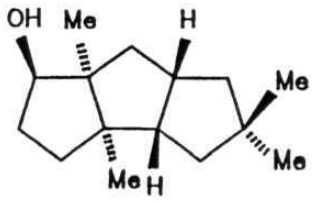
Chart I.6



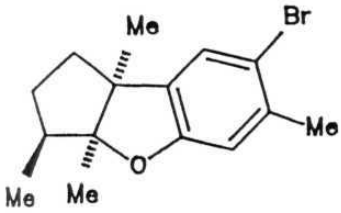
Gymnomitrol 29[24a,b]



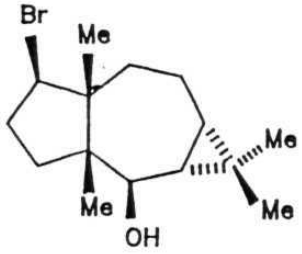
Ptychanolide 30[24c]



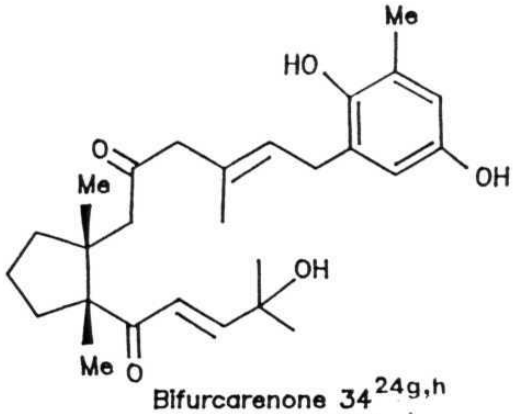
(+)-Ceratopicanol 31[24d]



Apylsin 32[24e]



Neomeranol 33[24f]

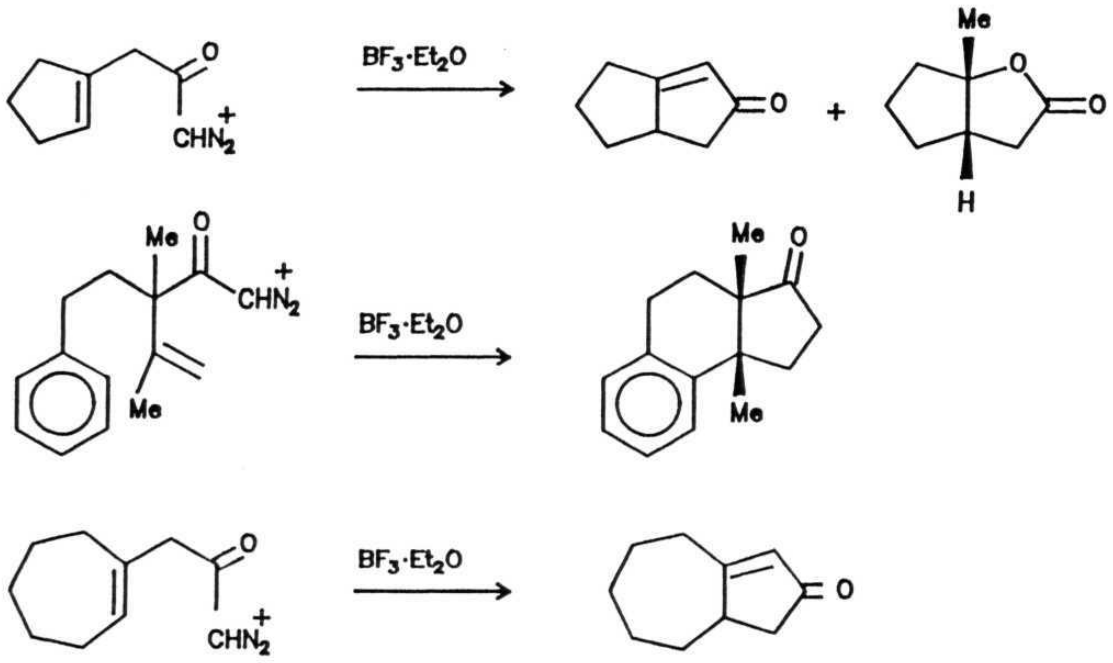


Bifurcarenone 34[24g,h]

ring and install the two vicinal bridgehead carbon centres. It is known through the pioneering studies of Mander[27], Smith[28] and Ghatak[29] that unsaturated diazomethyl ketones undergo facile cyclisation in the presence of protic acids and Lewis acids to furnish fused carbocyclic systems. Some typical examples are

given in Scheme I.6. The reaction thus appeared well suited for the 5 membered ring annulation on (-)-15.

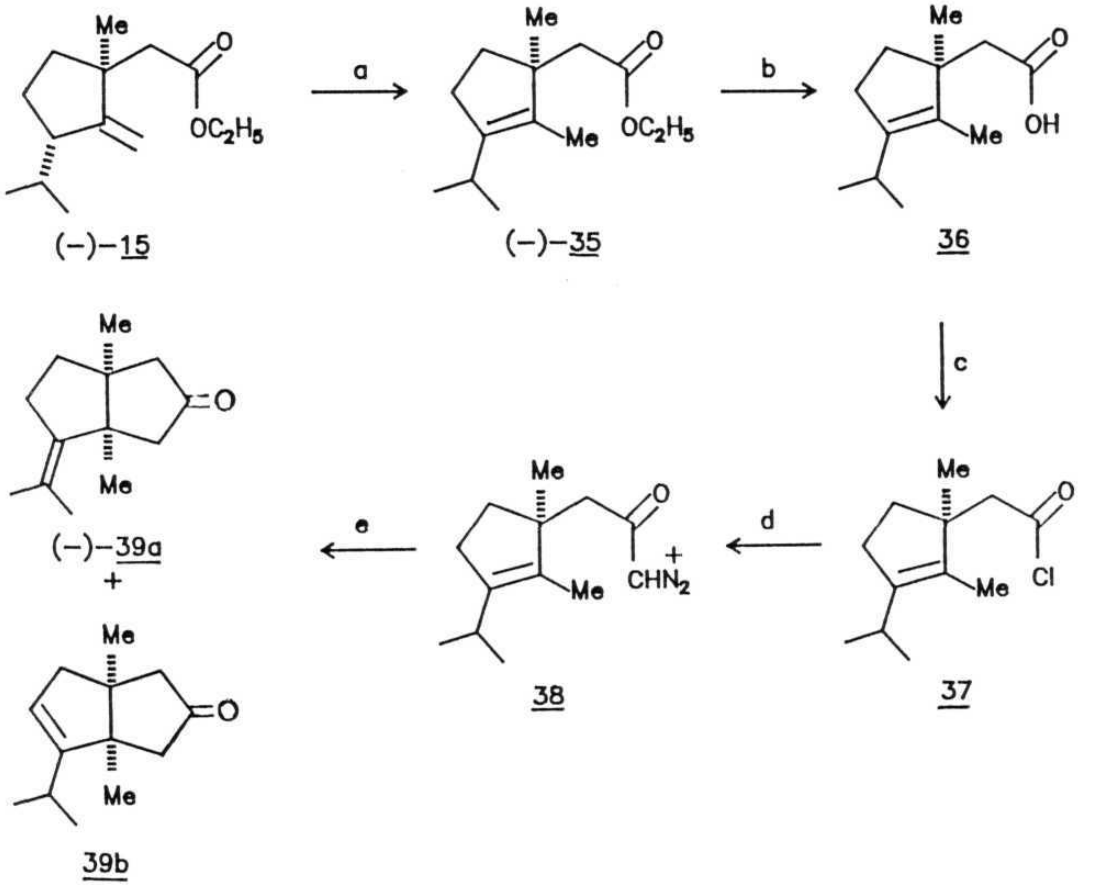
Scheme I.6



To realise the diazo ketone-olefin cyclisation in practice, the exocyclic double bond in (-)-15 was isomerised with $BF_3.Et_2O$ to the tetrasubstituted position to furnish (-)-35. The isomerised ester (-)-35 was hydrolysed with 5% aq. NaOH-MeOH and the crude acid 36 was transformed into the acid chloride 37, Scheme I.7. The presence of 37 was indicated by a strong band at 1800 cm^{-1} in the IR spectrum. The crude acid chloride 37 was treated with diazomethane in ether at 5°C to furnish the α-diazo ketone 38 (IR: 2217 cm^{-1} for N=N stretching, 1660 cm^{-1} for carbonyl group). Brief exposure of 38 to $BF_3.Et_2O$[28c] in dichloromethane at 0°C furnished the expected cyclised products (-)-39

and **39b** (9:1) as a regioisomeric mixture of olefins in 73% yield. The major regioisomer (-)-39a could be isolated for characterisation purposes through careful chromatographic separation. However, for further elaboration and utilisation of (-)-39a, separation at this stage was not considered essential. The IR spectrum of the major cyclised product (-)-39a exhibited a

Scheme I.7

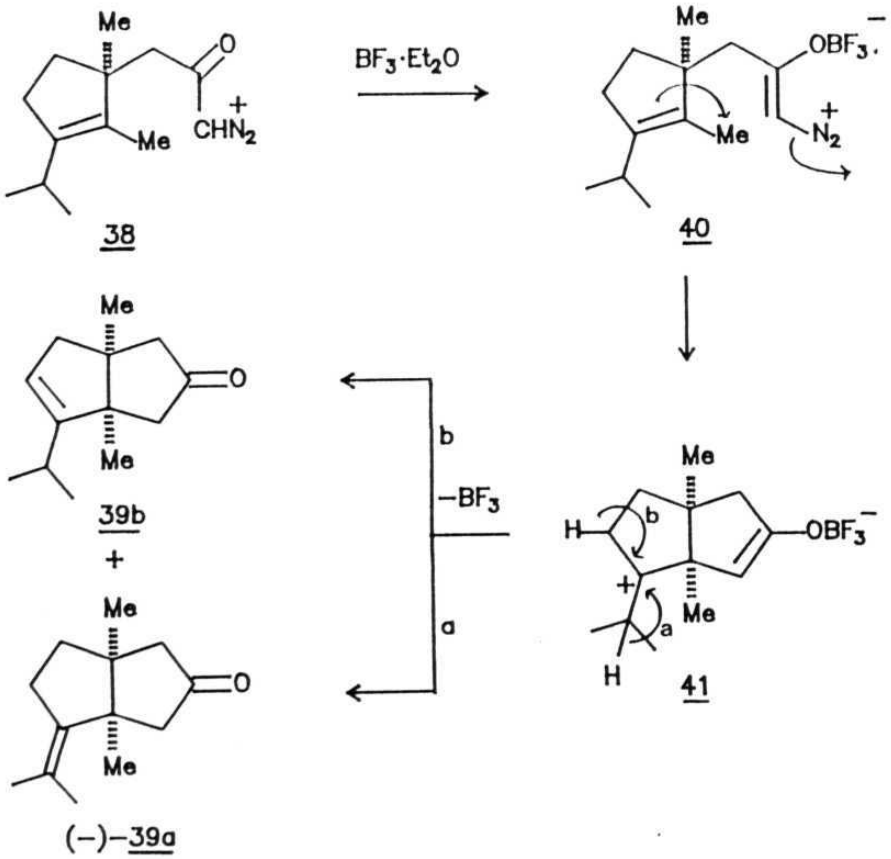


Reagents and yields: (a) $BF_3.Et_2O$, DCM, RT, 16 h, 82%;(b) 5% aq. NaOH-MeOH, 80°C, 3 h; (c) $(COCl)_2$-py, DCM, RT, 5 h; (d)CH_2N_2, ether, 5°C, 16 h, (68% from ester 35); (e) $BF_3.Et_2O$, DCM, RT, 5 min, 73%.

strong carbonyl absorption at 1740 cm^{-1} corresponding to the cyclopentanone moiety. The presence of two sp^3 quaternary methyls at δ 1.1 and 1.0 and two vinylic methyl groups at δ 1.71 and 1.60 in the ^1H NMR spectrum (Fig. I.5) confirmed the formulation (-)-**39a** for this diquinane product. Cyclisation of α-diazo ketone **38** was also attempted using different acid catalysts, particularly trifluoroacetic acid, which has been effectively used by Mander[27]. However, $BF_3.Et_2O$ proved to be the better catalyst in our case.

The mechanism of the diazo ketone-olefin cyclisation involves an intermediate **40** obtained by complexation of BF_3 with the oxygen of the carbonyl group and subsequent loss of N_2 followed by cyclisation to give the stabilised tertiary carbonium ion **41**[28c], Scheme I.8. Elimination of a proton in **41** on

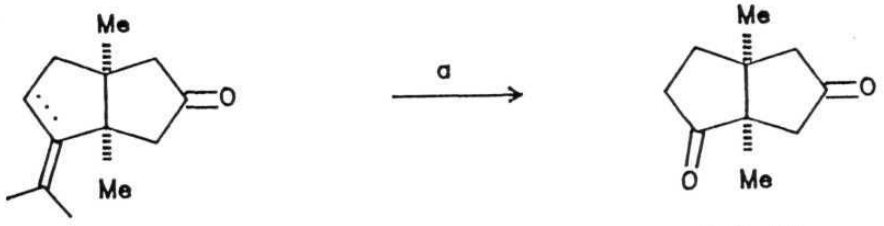
Scheme I.8



either side led to the formation of tetrasubstituted olefin 39a as the major product and the trisubstituted olefin 39b as the minor product.

At this stage, oxidative disposal of the isopropylidine group in (-)-39a, which had served as an internal chiral director, was accomplished through catalytic ruthenium oxidation[30] to furnish the diquinane dione (-)-42 in 66% yield Scheme I.9. For this oxidation, mixture of regioisomeric olefins 39a,b obtained from cyclisation could be directly employed. The carboxylic acid product obtained from the isomer 39b was easily removed during the work-up procedure.

Scheme I.9



39a,b (-)-42

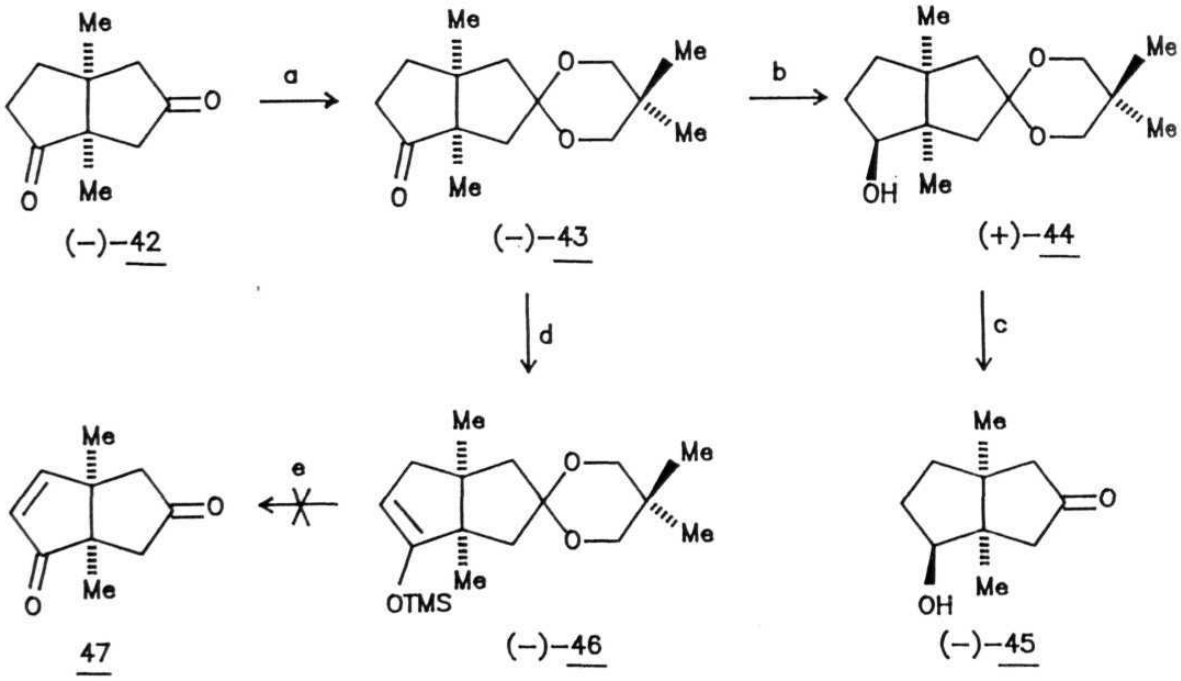
Reagents and yields: (a) $RuCl_3$-$NaIO_4$, CH_3CN-CCl_4-H_2O, RT, 1h, 66%.

The structure of diquinane dione (-)-42 rests secured on its ^1H and ^{13}C NMR spectral data. Thus, the ^1H NMR spectrum (Fig. I.6) exhibited two quaternary methyl groups at δ 1.08 and 0.99. A 10 line ^{13}C NMR spectrum (Fig. I.7) with diagnostic signals due to the two carbonyl groups and two quaternary sp^3 carbon atoms at δ 220.7, 215.2, 55.4 and 45.9 was fully consonant with the structure of the dione (-)-42. The cis-stereochemistry of two quaternary methyl groups is assigned on the well established

premise that cis-fused bicyclo[3.3.0]octanones are more stable than the trans-fused isomer. In the case of (-)-42 strain energy calculations (MMX programme) showed that cis-dione (ΔSE= 16.91 kcal/mole) is substantially more stable than trans-dione (ΔSE= 29.71 kcal/mole) by ~12 kcal. A versatile building block for assembling several sesquiterpenoids was thus available in gram quantities in a short sequence.

The dione (-)-42 can serve as a useful advanced building block for several terpenes indicated in **Chart I.6** and one application leading to the total synthesis of (-)-ceratopicanol is detailed in the next chapter. In order to enhance the utility of (-)-42, it was necessary to chemo-differentiate the two carbonyl groups. This could be readily achieved as shown in **Scheme I.10**.

Scheme I.10



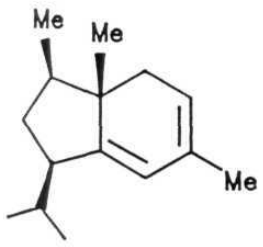
Reagents and yields: (a) 2,2-Dimethyl propan-1,3-diol, PPTS, Benzene, 80°C, 16 h, 61%; (b) $NaBH_4$, MeOH, 0°C, 0.5 h, 88%; (c) 5% HCl, RT, 1 h, 78%; (d) Bu^nLi, HMDS, THF, TMSCl, -78°C, 3 h, 88%. (e) $Pd(OAc)_2$-CH_3CN.

The dione (-)-**42** could be monoprotected as the dimethyl-1,3-dioxalane derivative (-)-**43** and the unprotected carbonyl group was reduced to (+)-**44**. Deprotection in (+)-**44** gave the hydroxy-ketone (-)-**45** with differentiated functionalities. Also, the monoprotected (-)-**43** could be transformed into an unusually stable TMS-enol ether (-)-**46**, which however resisted all attempts towards oxidative dehydrosilylation to the enone **47**[31].

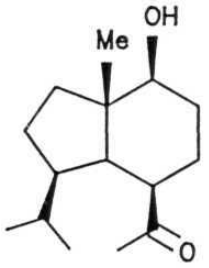
I.3.2. Construction of 5,6-Fused Bicyclic System :

The presence of 5,6-fused hydrindanone skeleton with ring A core (see **Chart I.2**) in many complex natural products, **Chart I.7**[32], stimulated our interest in the enantioselective construction of a versatile precursor for these systems. There-

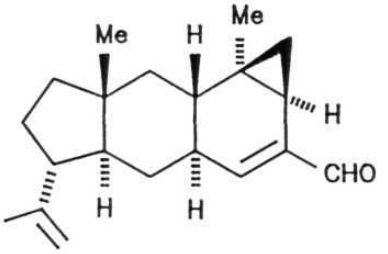
Chart I.7



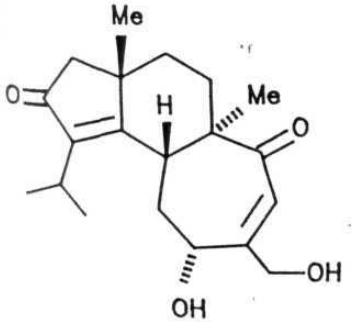
Cascarilladiene 48[32a]



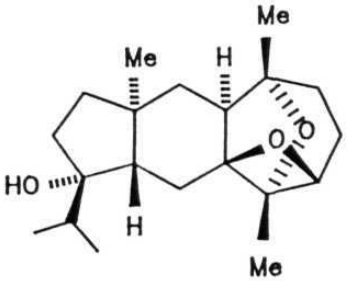
Paludolone 49[32b]



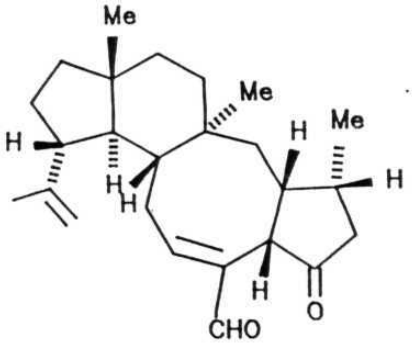
Fasciola-1,18-dien-17-al 50[32c]



Cyafrin B_4 51[32d]



Dictyoxetane 52[32e]

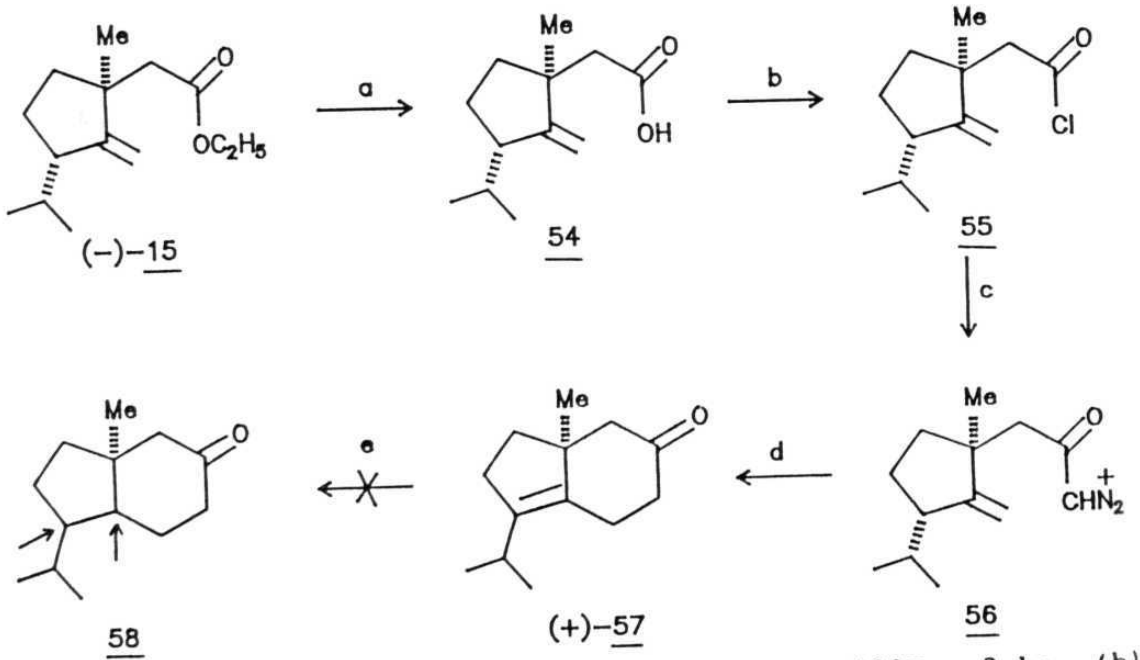


Variecolin 53[32f]

fore, Several hydrindanones with variation in degree and location of functionalisation and of relevance to higher terpene syntheses were conveniently assembled from (-)-14 and (-)-15.

The 5,6-fused system was once again constructed by employing the acid catalysed intramolecular α-diazo ketone-olefin cyclisation methodology from synthon (-)-15. The acid 54, obtained by saponification of the ester (-)-15, was sequentially treated with oxalyl chloride to furnish the acid chloride 55 and then with ethereal diazomethane to furnish the α-diazo ketone 56 (IR: 2110 cm^{-1} for N=N stretching, 1640 cm^{-1} for carbonyl group). On subjecting 56 to cyclisation with $BF_3.Et_2O$ in dichloromethane, the desired hydrindanone (+)-57 was realised in 76% yield, Scheme I.11. The structure of (+)-57 was in full agreement with its ^1H

Scheme I.11

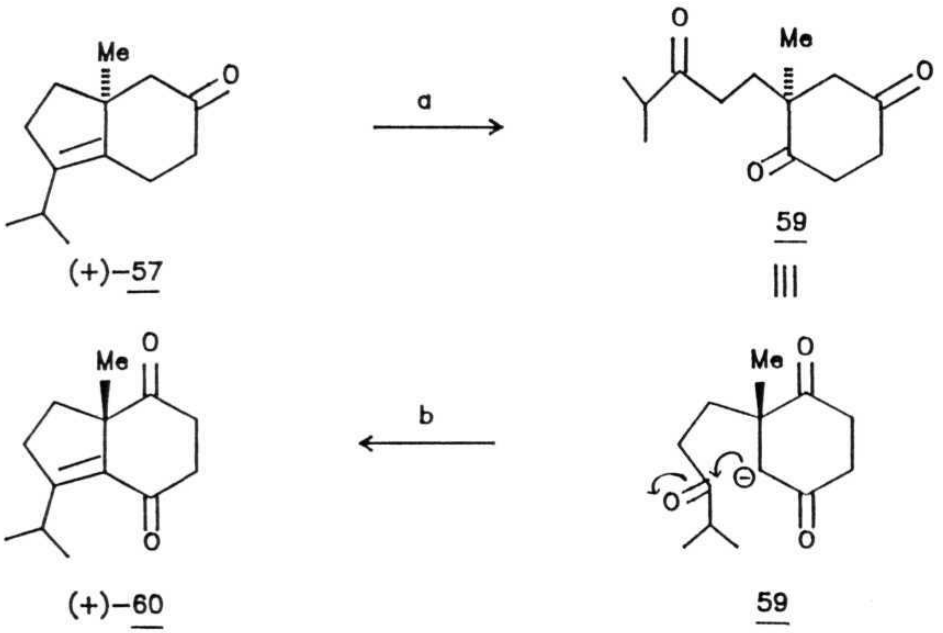


Reagents and yields: (a) 5% aq. NaOH-MeOH, 80°C, 3 h; (b) $(COCl)_2$-py, 30°C, 2 h; (c) CH_2N_2, ether, 5°C, 12 h, (66% from acid 54); (d) BF_3-Et_2O, CH_2Cl_2, 0°C, 3 min, 76%; (e) H_2-PtO_2, EtOAc, 30 psi.

and ^{13}C NMR spectral data. In the ^{1}H NMR spectrum (Fig. I.8) the exocyclic olefinic protons were absent and the ^{13}C NMR spectrum (Fig. I.9) showed diagnostic signals at δ 211.7, 140.4, 134.4 and 41.1 due to the carbonyl group, tetrasubstituted olefin and quaternary sp^3 carbon, respectively.

Though the hydrindanone (+)-57 is a good building block for several natural products, Chart I.7, the saturated hydrindanone 58 with well defined stereochemistry at the isopropyl and neighbouring bridgehead centres (see arrows) could be an even better substrate. But, all our attempts to hydrogenate the considerably hindered tetrasubstituted double bond in (+)-57 at moderate pressure were unsuccessful. Therefore, a synthetic stratagem was adapted which allowed considerable amplification and relocation of functionality in (+)-57. This manoeuvre was also expected to prepare the tetrasubstituted double bond for reduction with dissolving metal reducing agents. The tetrasubstituted double bond in (+)-57 was cleaved employing the Sharpless catalytic ruthenium oxidation procedure[30] to furnish the trione 59 in 90% yield, Scheme I.12. The structure of trione 59 rests secured on its spectral data, in particular, the ^{13}C NMR spectrum which showed the presence of 3 carbonyl groups at δ 213.4, 211.9, 208.1. The trione 59 was further transformed into the ene-dione (+)-60 *via* a base catalysed aldol cyclisation-dehydration sequence. The ^{1}H NMR spectrum of (+)-60 (Fig. I.10) showed a considerably deshielded quaternary methyl group at δ 1.30 and its ^{13}C NMR spectrum (Fig. I.11) exhibited diagnostic signals at δ 213.9, 197.4, 168.2, 133.5 due to saturated

Scheme I.12

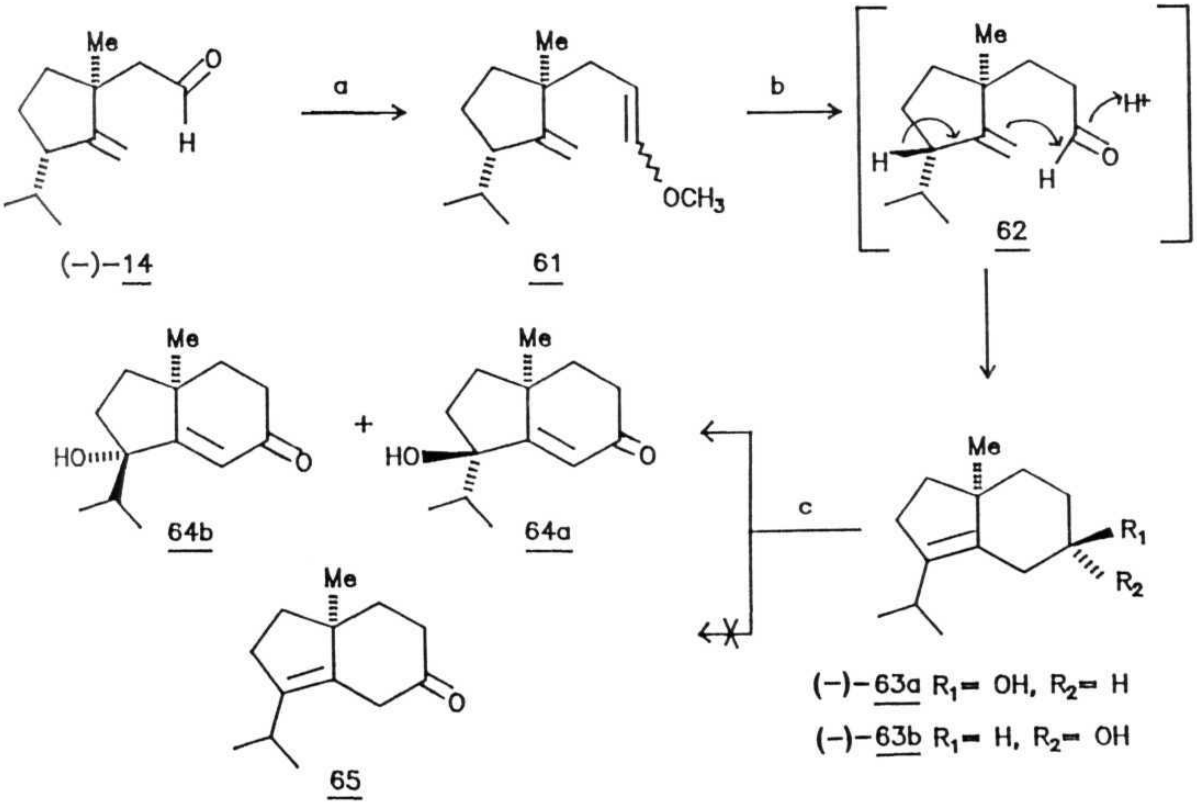


Reagents and yields: (a) $RuCl_3$-$NaIO_4$, CH_3CN-CCl_4-H_2O, 30°C, 1h, 90%; (b) KOH, MeOH, △ , 1 h, 36%.

carbonyl, enone carbonyl and tetrasubstituted olefinic carbons, respectively. The ene-dione (+)-**60**, not only had amplified and redistributed functionality but also belongs to an enantiomeric series with respect to the precursor enone (+)-**57**. Thus, hydrindanones of both enantiomeric series are available from the same chiron (-)-**15**. The presence of enone double bond in (+)-60 makes it amenable to the generation of the desired stereochemistry at the ring junction and isopropyl bearing carbon centre as it could be more conveniently reduced employing metal-liq. NH_3 or catalytic hydrogenation. Moreover, the two carbonyl groups are now chemo-differentiated and could be used for the appendage of a third ring.

In an alternative route to the 5,6-fused system with altered location of the functionality on the six membered ring, one carbon homologation of aldehyde (-)-**14** followed by intramolecular ene reaction was contemplated. Consequently, the aldehyde (-)-**14** was subjected to Wittig olefination with the ylide derived from (methoxymethyl)triphenylphosphonium chloride, to give E:Z mixture of enol ethers **61** in 90% yield, **Scheme I.13**. Mild hydrolysis of the enol ethers **61** with 35% aq. $HClO_4$ furnished the labile, homologated C_{13}-aldehyde **62**, which concomitantly cyclised to a readily separable mixture (3:1)

Scheme I.13



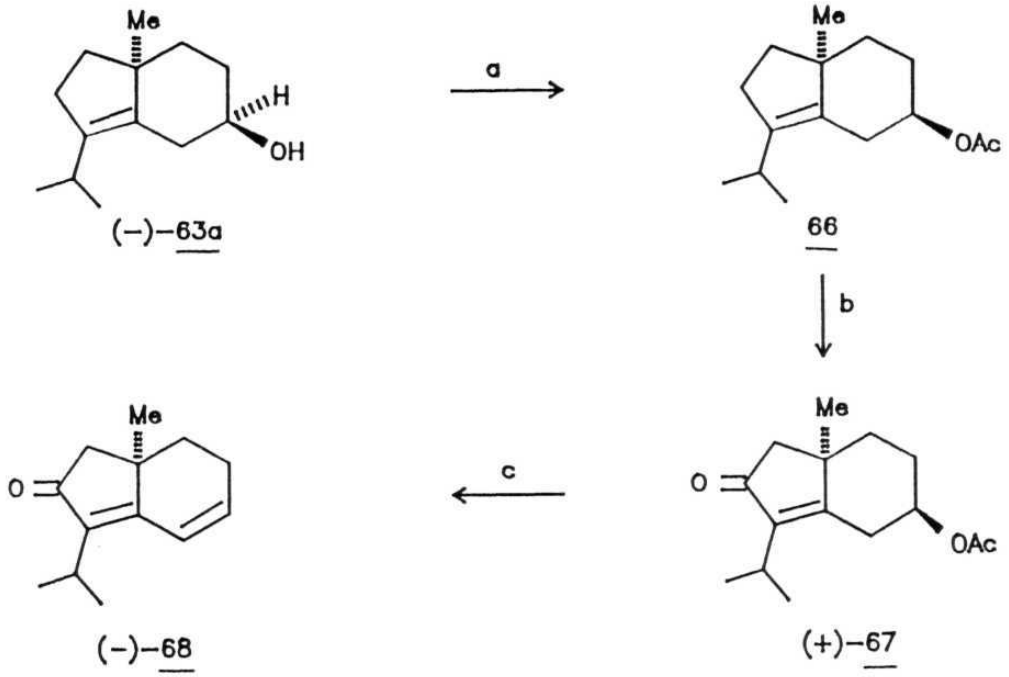
Reagents and yields: (a) $Ph_3P^+CH_2OCH_3Cl^-$-$Na^+C_5H_{11}O^-$, ether, 30°C, 30 min, 90%; (b) 35% $HClO_4$-ether, 0-30°C, 3 h, 73%; (c) PCC, molecular sieves 4 Å, CH_2Cl_2, 3 h, 45%.

of homoallylic alcohols (-)-63a and (-)-63b. The diastereomeric nature of the two alcohols was revealed through their spectral data. Both (-)-63a and (-)-63b showed the absence of olefinic protons in the ^{1}H NMR spectra (Fig. I.12 & Fig. I.14) and exhibited signals at δ 67.0 and 71.9, respectively in the ^{13}C NMR spectra (Fig.I.13 & Fig. I.15) due to the carbons attached to a secondary hydroxyl group. The ^{1}H and ^{13}C NMR spectral data also enabled distinction between the diastereomeric pair. Deshielding of the hydroxy attached proton by 0.66 ppm in the ^{1}H NMR spectrum and shielding of the carbon attached to hydroxy group in the ^{13}C NMR spectrum of (-)-63a (δ 67.0 ppm) compared to that of (-)-63b (δ 71.9 ppm) indicated that the hydroxy group in (-)-63a is in axial orientation. Attempts to oxidise the alcohols (-)-63a and (-)-63b to the corresponding ketone proved to be unexpectedly complicated. Several reagents (PCC, PDC, Swern, TPAP) were unsuccessfully tried for the oxidation. However, when the oxidation of either alcohol (-)-63a or (-)-63b was attempted with PCC for longer periods, an inseparable mixture of Y-hydroxy-α,β-unsaturated enones 64a,b was obtained through an oxidative rearrangement, Scheme I.13, instead of the normal oxidation product 65. Though the result of this oxidation was unexpected, it was not an entirely undesirable observation as the enones 64a,b could also be useful as the characteristic hydroxy-isopropyl is present in many terpenes.

We also sought alternate avenues for preparing some related 5,6-fused bicyclic enones that could be useful building blocks in

terpene synthesis. To accomplish this, the bicyclic alcohol in (-)-63a was converted to the acetate 66, **Scheme I.14.** Allylic oxidation of the acetate 66 with CrO_3-3,5-dimethyl pyrazole

Scheme I.14



Reagents and yields: (a) $(CH_3CO)_2O$-Py, 30°C, 12 h, 95%; (b) CrO_3-3,5-dimethylpyrazole, 30°C, 30 h, 73% (c) KOH, MeOH, 30°C, 3 h, 75%.

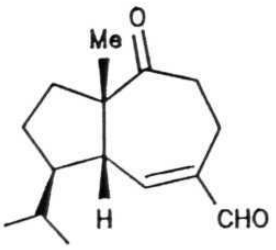
complex[33] furnished the enone acetate (+)-67 in 73% yield. The ^1H and ^{13}C NMR spectral data of enone-acetate (+)-67 was fully consonant with its formulation. When the enone-acetate (+)-67 was treated with methanolic KOH to deprotect the hydroxy group, the hydrolysis was accompanied by <u>in situ</u> elimination of the hydroxy group to produce the dienone (-)-68 in 75% yield. The olefinic signals at δ 6.60, 6.14 in the ^1H NMR spectrum (**Fig.**

I.16) and a 13 line ^{13}C NMR spectrum (Fig. I.17) with characteristic signals at δ 202.9, 168.8, 139.7, 137.2, 121.5 and 51.4 supported the structure of dienone (-)-68. Thus, a hydrindanone with oxygen functionalisation in the A ring became available for further manipulations.

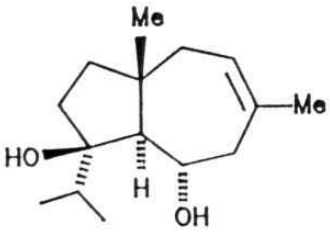
I.3.3. Construction of 5,7-Fused Bicyclic System:

In recent years, terpene natural products embracing 5,7-fused bicyclic hydroazulene skeleton with subtle stereochemical patterns and extensive functionalisation have been proliferating in Nature, Chart I.8[34]. Some of these natural products also possess interesting biological activities towards microorganisms. Therefore, the synthesis of these molecules is an attractive

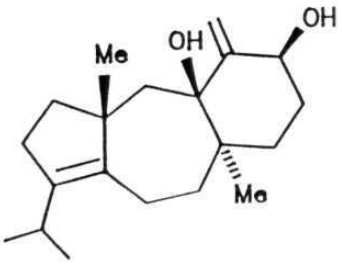
Chart I.8



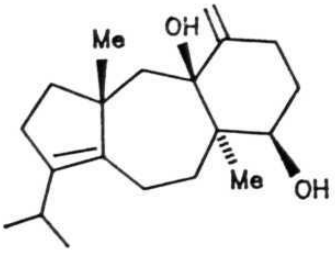
2-Oxo-isodauc-5-en-12-al 70[34a]



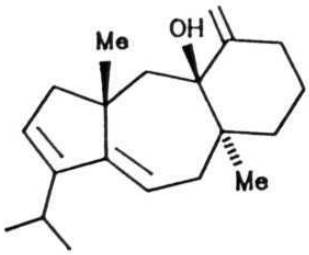
Jaeschkeanadiol 71[34b]



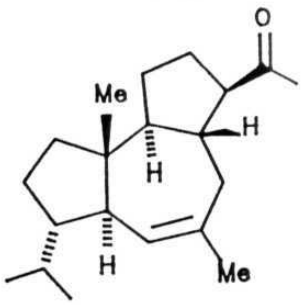
(-)-Isoamijiol 72[34c]



(-)-Amijiol 73[34c]



Dolasta-1(15),7,9-trien-14-ol 74[34d]

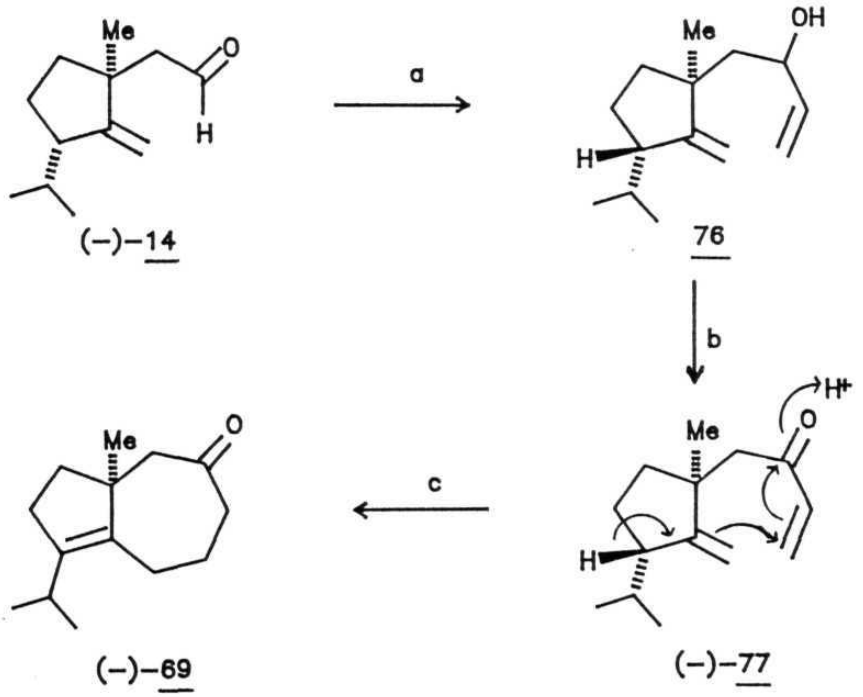


18-Oxo-3-virgene 75[34e]

proposition. In this context, we recognised hydroazulenone (-)-69 as a conveniently utilisable advanced precursor for further elaboration to novel sesqui- and diterpenes. Consequently, synthetic protocol for its construction from the chiron (-)-14 was developed employing acid catalysed enone-olefin cyclisation as the key step.

To elaborate (-)-14 to hydroazulenic system, a two carbon homologation of the aldehyde group was sought and was conveniently accomplished by the addition of vinyl Grignard reagent[35] to (-)-14 to produce the allylic alcohol 76 as a mixture of diastereomers in 75% yield, Scheme I.15. The allylic

Scheme I.15



Reagents and yields: (a) CH_2=CHBr, Mg, THF, 30°C, 30 min, 75%; (b) PCC, CH_2Cl_2, molecular sieves 4 Å, 30°C, 1h, 65%; (c) Cat. $HClO_4$-$(CH_3CO)_2O$, EtOAc, 30°C, 25 min, 65%.

alcohol **76** was directly subjected to PCC oxidation to afford the α,β-unsaturated enone (-)-**77** as a single isomer in 65% yield. The enone structure (-)-**77** was in full agreement with its ^{1}H and ^{13}C NMR spectral data. The ^{13}C NMR spectrum showed the presence of 5 sp^2 carbon resonances at δ 188.6, 162.5, 137.7, 127.4, 107.8. Treatment of (-)-**77** with catalytic amount of 70% $HClO_4$ in ethyl acetate - acetic anhydride[36] afforded the bicyclic enone (-)-**69**. Absence of olefinic proton resonance in the ^{1}H NMR spectrum (Fig. I.18) and the presence of three sp^2 carbon signals at δ 213.0, 141.9, 138.7 in the ^{13}C NMR spectrum (Fig. I.19) were in full consonance with its structure. Synthesis of the hydroazulenic enone (-)-**69** in racemic form employing deMayo reaction as the key step has been recently reported by Pattenden et al[37].

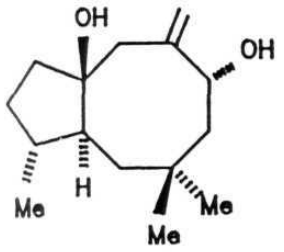
Thus, the 5,7-fused bicyclic hydroazulenone (-)-**69** was assembled in just three convenient steps from (-)-**14** *via* the α,β-unsaturated enone (-)-**77** in multi - gram quantities. Recently, we have successfully elaborated this 5,7-fused bicyclic system to daucane and isodaucane sesquiterpenes, (-)-daucene **2** [18a,d], (+)-aphanamol-I **3** [18b,d] and dolastane diterpenes (+)-isoamijiol **72**[18c,d] and (+)-dolasta-1(15),7,9-trien-14-ol **74**[18c,d], demonstrating the utility of the chiron (-)-**14** for the synthesis of higher terpenes. Further utilisation of (-)-**69** towards the synthesis of virgane diterpenes will be described in the third chapter of this thesis.

I.3.4. Construction of 5,8-Fused Bicyclic System:

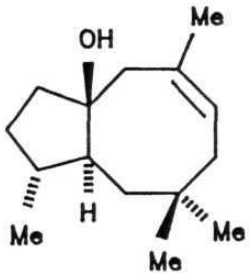
Terpenoid natural products bearing 5,8-fused bicyclic skeleton are widely distributed in Nature and have been isolated from plant, marine and animal sources, Chart I.9[38]. These

Chart I.9

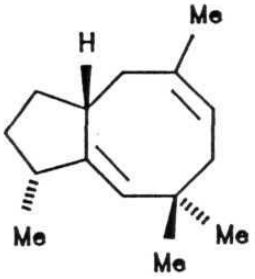
Chart I·8



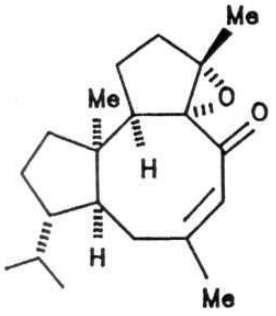
Poitediol 78[38a]



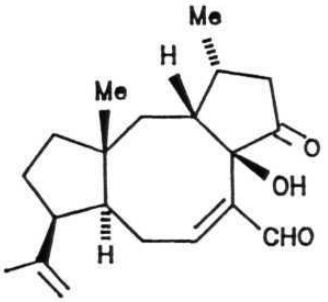
Dictyiol 79[38b]



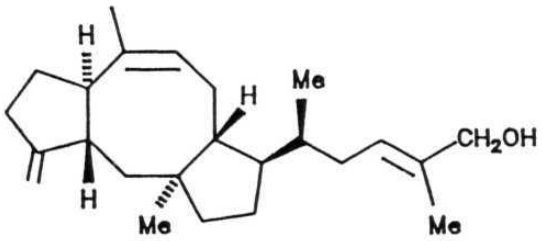
Precapnelladiene 80[38c]



7,8–Epoxy–
4–basmen–6–one 81[38d]



Traversianal 82[38e]



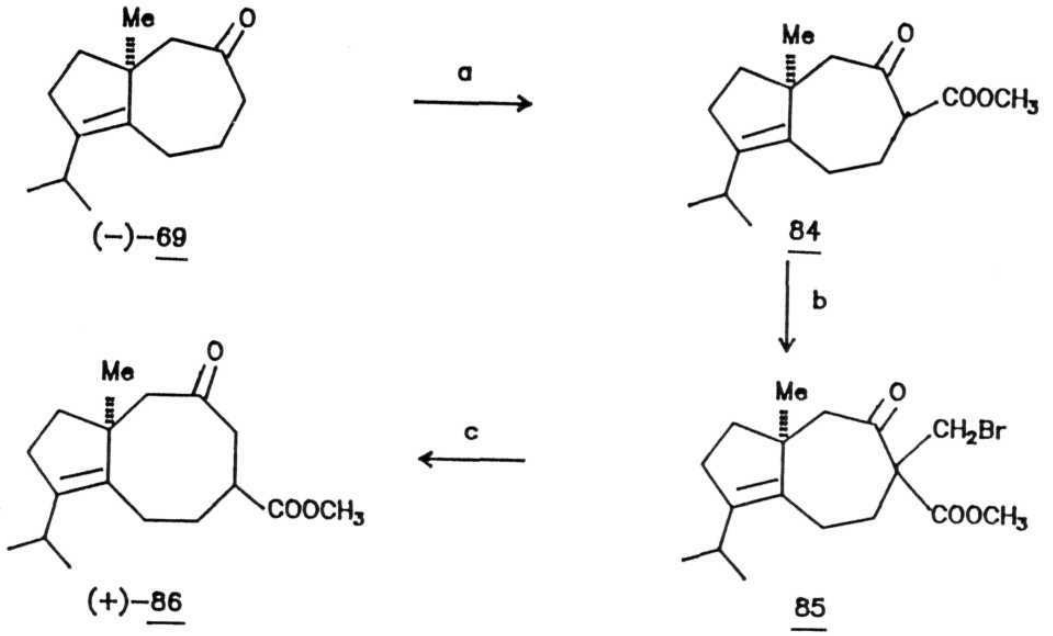
Ceroplastol 83[38f,g]

natural products are derived through interesting biogenetic pathways and many of them exhibit wide ranging biological activities. The 5,8-fused system is found among sesqui-, di- and sesterterpenes. These natural products are attractive targets

for synthesis and interest in the construction of 5,8-fused system has increased enormously in recent years. In fact, very few natural products with this structural feature have been synthesised so far[39]. Therefore, we sought to construct a chiral 5,8-fused bicyclic system which would serve as an advanced building block for the higher terpenes of this class.

For the construction of this ring system, annulation of 8-membered ring to an appropriately substituted 5-membered ring is not a convenient approach as the cylooctane ring is notoriously prone to transannular cyclisations. Instead, one carbon ring expansion of the readily available and optically active hydroazulenone (-)-69 appeared to be an advantageous protocol. After unsuccessful efforts with more conventional protocols for one carbon ring expansion, we were able to effect the desired ring expansion employing the recently developed Dowd methodology.[40] Regioselective enolate generated from (-)-69 with NaH was quenched with dimethyl carbonate to furnish β-keto-ester 84, Scheme I.16. Alkylation of the β-keto-ester **84** with methylene bromide by generating the enolate with sodium hydride-HMPA gave a mixture of uncharacterisable products. However, when **84** was treated with a less stronger base K_2CO_3, the alkylation occurred smoothly. Thus, treatment of **84** with methylene bromide in the presence of K_2CO_3 in acetone led to **85** in 81% yield. Reaction of **85** with tri-n-butylstannane in refluxing benzene in the presence of AIBN led to the contemplated radical induced ring expansion and bicyclic cyclooctanone ester (+)-**86** was realised in 50% yield. A 17 line ^{13}C NMR spectrum (**Fig. I.21**) with

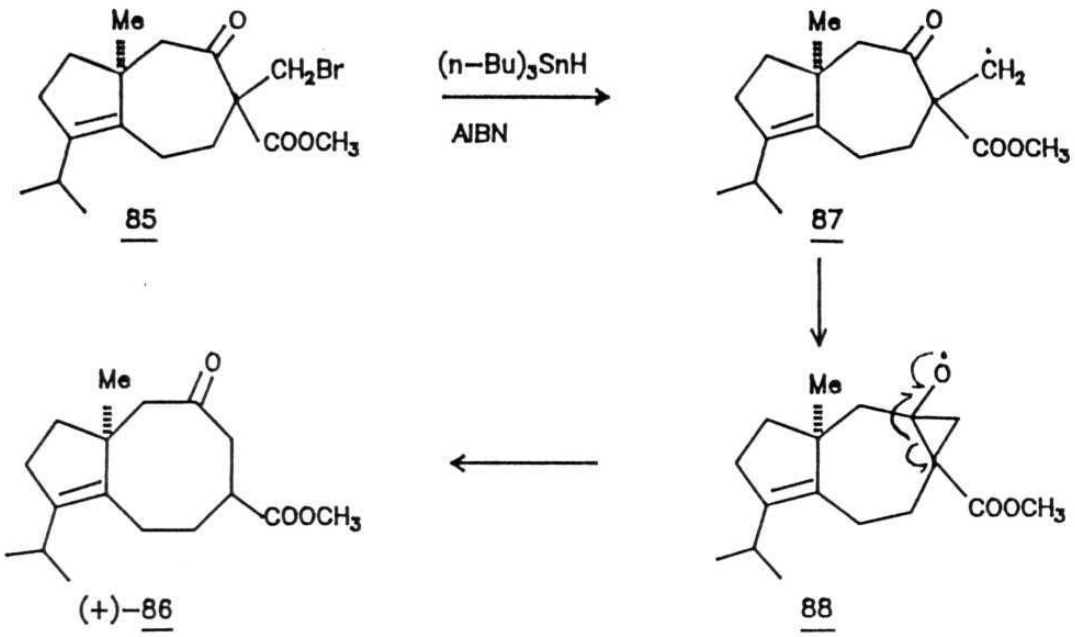
Scheme I.16



Reagents and yields: (a) $(CH_3O)_2C=O$, NaH, △ , 6 h, 78%; (b) K_2CO_3-CH_2Br_2, $(CH_3)_2CO$, △ , 16 h, 81%; (c) $(n\text{-}Bu)_3SnH$, AIBN, C_6H_6, 16 h, 50%.

diagnostic resonances at δ 210.9, 178.5, 144.6 and 135.9 secured the structure of (+)-86, which has the complete carbocyclic content corresponding to two of the rings of 5,8,5-fused diterpenes, e.g., 81 and 82. The radical induced ring expansion reaction in the present case occurs by the attack of the first formed primary radical 87 on the carbonyl carbon to form an oxy radical 88, Scheme I.17. The oxy radical 88 then forces ,the central cyclopropane bond to cleave in a fragmentation reaction to give the product (+)-86.

Scheme I.17



I.4. SUMMARY:

We have outlined practical and enantioselective approaches to 5,5- 5,6-, 5,7- and 5,8-fused bicyclic systems from restructured R-(+)-limonene **16** *via* key synthons (-)-**14** and (-)-**15** These bicyclic systems available in quantities and in enantiomerically pure form are potentially serviceable for the synthesis of diverse higher terpenes. As a demonstration of their utility, we have described the first enantioselective synthesis of triquinane sesquiterpene (-)-ceratopicanol in Chapter II and construction of a 5,7,5-fused tricyclic skeleton related to virgane diterpenoids in Chapter III of this thesis.

1.5 EXPERIMENTAL:

Melting points: All melting points were recorded on a Buchi SMP-20 apparatus and are uncorrected.

Boiling points : Bulb-to-bulb distillations were carried out using oil bath for all liquid samples and boiling points refer to the oil bath temperatures.

Ultraviolet spectra : Ultraviolet spectra were recorded on a Perkin-Elmer Lambda 3B spectrophotometer

Infrared spectra : Infrared spectra were recorded on Perkin-Elmer Model 1310 or 297 spectrophotometer. Spectra were calibrated against the polystyrene absorption at 1601 cm^{-1}. Solid samples were recorded as KBr wafers and liquid samples as thin films between NaCl plates.

Nuclear magentic resonance spectra : Proton magnetic resonance spectra (100 MHz) and carbon-13 NMR spectra (25.0 MHz) were recorded on JEOL FX-100 spectrometer. ^{1}H and ^{13}C samples were made in chloroform-d solvent and chemical shifts are reported on δ scale using tetramethylsilane (Me_4Si) as the internal

standard. The standard abbreviations s, d, t, q and m refer to singlet, doublet, triplet, quartet and multiplet, respectively. Coupling constants (J), wherever discernible have been given in Hz.

Mass spectra : Mass measurements were carried out on Jeol JMSDX 300 Mass spectrometer at the Indian Institute of Science, Bangalore. We thank the authorities for their kind help.

Elemental analysis : Elemental analyses were performed by Mr. V. Bhaskar Rao on a Perkin-Elmer 240 C elemental analyser.

Optical rotation : Optical rotations were measured on AUTOPOL II ^{TM} polalrimeter and JASCO DIP 3 Digital Polarimeter

Chromatography : Analytical thin-layer chromatographies (tlc) were performed on (10 x 5 cm) glas plates coated with Acme's silica gel G or GF-254 (250 μm, containing 13% of calcium sulfate as binder). Visualisation of the spots on tlc plates was achieved either by exposure to iodine or UV light or by spraying sulfuric acid and heating the plates at 120°C. Column chromatography was performed using Acme's silica gel

(100-200 mesh) and the column was usually eluted with ethyl acetate-hexane or petroleum ether mixtures, unless otherwise mentioned.

General : All reactions were monitored by employing tlc technique using appropriate solvent systems for development. Moisture sensitive reactions were carried out by using standard syringe-septum techniques under nitrogen atmosphere. Petroleum ether refers to the fraction boiling between 60-80°C. Dichloromethane and chloroform were distilled over P_2O_5. Dry ether, dry THF and dry benzene and were prepared by distilling them over sodium-benzophenone ketyl.

Hydrogenations were carried out on a Parr hydrogenation apparatus in 1 l and 250 mL pressure bottles. All solvent extracts were washed with with water, brine, dried over anhydrous Na_2SO_4 and concentrated at reduced pressure on a Buchi-EL rotary evaporator. Yields reported are isolated yields of material judged homogenous by tlc and NMR spectroscopy.

Starting materials : All the starting materials were either acquired commercially or prepared according to standard literature procedures. R-(+)-limonene **16** ($[\alpha]_D$: +112) and (+)-**21** ($[\alpha]_D$: +69), tetra-n-propylammonium perruthenate were purchased from Aldrich chemical company, Inc. All the commercial chemicals were distilled prior to use.

Epoxidation of R-(+)-limonene 16 :

R-(+)-limonene 16 (100 g, 0.7 mol) in dry chloroform (500 mL) was placed in a 1 l RB flask. To this was added m-chloroperbenzoic acid (130 g, 0.75 mol) in small portions over a period of 1 h. After addition was complete the reaction mixture was left at room temperature for 10 h with stirring. The reaction mixture was quenched by addition of saturated Na_2CO_3 solution and the organic layer separated. The aqueous layer was extracted with chloroform (250 mL x 3). The combined organic extract was washed and dried. The crude product obtained after removal of the solvent was distilled at reduced pressure to furnish limonene oxide 21 (83 g) in 80% yield as diastereomeric mixture.

IR : 3070, 2960, 1640, 890 cm^{-1}

^1H NMR : δ 4.73 (m, 4H, -C=C$\underline{H}_2$), 3.02 (m, 2H), 2.0-1.4 (m, 20H), 1.31 and 1.22 (s, 6H, -C-C$\underline{H}_3$)

(-)-5S-5-Isopropyl-2-methylcyclopent-1-ene-1-carboxaldehyde (17):

To a solution of limonene oxide 21 (150 g) in 50% aq. THF (500 mL) was added 1% H_2SO_4 slowly at 0°C and the reaction mixture was stirred at room temperature for 1 h. Then the reaction mixture was extracted with ether (500 mL x 3) and the ethereal layer was washed with saturated $NaHCO_3$ solution, water and dried. The crude product obtained after removal of the solvent was used as such for the next step.

The crude diol (100 g, 0.58 mol) in 50% aq. THF (500 mL) was

placed in a 1 l RB and cooled in an ice-bath. To this, sodium metaperiodate (130 g, 0.61 mol) was added in small portions and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was extracted with ether (500 mL x 3) and the ethereal extract was washed and dried. The crude product was distilled under reduced pressure to furnish the keto-aldehyde 22 (70 g) in 75% yield.

A solution of the above keto-aldehyde 22 (5.0 g, 30 mmol) in dry ethyl acetate (20 mL) was hydrogenated (30 psi) over PtO_2 (30 mg) for 1 h. The catalyst was filtered-off and the solvent was removed and distilled at 110°C at 0.1 mm to furnish the saturated keto-aldehyde 23 (4.5 g) in 90% yield.

Into a 500 mL RB flask fitted with a Dean-Stark separator and reflux condenser, the saturated keto-aldehyde 23 (25 g, 150 mmol) was placed in dry benzene (300 mL). To this reaction mixture glacial acetic acid (3 mL) and piperidine (3 mL) were added and the contents refluxed for 1 h. The reaction mixture was diluted with water (100 mL) and the benzene layer was separated. The aqueous layer was extracted with ether (100 mL x 3). The combined organic layer was washed and dried. The crude product obtained after removal of the solvent was distilled at reduced pressure to furnish the aldehyde (-)-17 (17 g) in 70% yield.

$[\alpha]_D$: -7.9 (c, 1.0; $CHCl_3$) (lit. -7.9)

bp : 65°C/4.0 mm

IR : 2720,1670 cm^{-1}

^1H NMR : δ 9.99 (s, 1H, O=C<u>H</u>), 2.6-1.6 (m, 9H), 0.88 (d, J = 7 Hz, 3H, -CH-C<u>H</u>$_3$), 0.65 (d, J = 7 Hz, 3H, -CH-C<u>H</u>$_3$)

(+)-3S-Isopropyl-1-methyl-2-hydroxymethyl-cyclopent-1-ene (24) :

The aldehyde (-)-17 (50.0 g, 0.33 mol) obtained from R-(+)-limonene 16 was dissolved in dry methanol (300 mL) and $CeCl_3.7H_2O$ (2.5 g) was added. The reaction mixture was cooled to 0°C and sodium borohydride (13.3 g, 0.35 mol) was added in small portions. After stirring for 0.5 h, methanol was removed and the residue was diluted with water (50 mL) and extracted with ether (150 mL x 3). The ethereal extract was washed with dilute HCl, saturated $NaHCO_3$ and dried. Distillation furnished the allylic alcohol (+)-24 (48.6 g, 96%), in near quantitative yield.

$[\alpha]_D$: +43.0 (c, 1.0; $CHCl_3$)

bp : 75°C/1.3 mm

IR : 3400, 2950, 1460, 1380, 1000 cm^{-1}

^1H NMR : δ 4.0 (m, 2H, -C<u>H</u>$_2$-OH), 3.0-1.6 (m, 7H), 1.65 (br s, 3H, -C=C-C<u>H</u>$_3$), 0.9 (d, J = 7 Hz, 3H, -CH-C<u>H</u>$_3$), 0.65 (d, J = 7 Hz, 3H, -CH-C<u>H</u>$_3$)

(-)-3S-Isopropyl-1-methyl-2-vinyloxymethyl-cyclopent-1-ene (20) :

To a mixture of allylic alcohol (+)-24 (20.0 g, 0.12 mol) and freshly distilled ethyl vinyl ether (500 mL) was added mercuric acetate (3.0 g) and the reaction mixture was stirred at -30°C for 20 h. The excess ethyl vinyl ether was recovered by

distillation and the residue was filtered through a basic alumina (100 g) column using pet ether to yield the pure vinyl ether (-)-**20** (18.9 g) in 80% yield.

$[\alpha]_D$: -53.0 (c, 1.0; $CHCl_3$)

bp : 100°C/0.5 mm

IR : 3050, 2950, 1630, 1600, 1190, 800 cm^{-1}

^1H NMR : δ 6.6-6.2 (m, 1H, -O-C<u>H</u>=CH_2), 4.4-3.8 (m, 4H, -$C\underline{H}_2$-O-CH=$C\underline{H}_2$), 3.0-1.8 (series of m, 6H), 1.7 (br s, 3H, -C=C-$C\underline{H}_3$), 0.9 (d, J = 7 Hz, 3H, -CH-$C\underline{H}_3$), 0.7 (d, J = 7 Hz, 3H, -CH-$C\underline{H}_3$)

^{13}C NMR : δ 151.8, 138.0, 132.7, 86.3, 63.1, 53.1, 38.0, 28.7, 21.9, 21.4, 16.0, 15.1

Analysis : $C_{12}H_{20}O$ Calcd.: C, 79.94; H, 11.18.
Found : C, 80.01; H, 11.15.

(-)-(2S,5S)-5-Isopropyl-2-methyl-2-(2-oxoethyl)-methylene cyclopentane (14) :

Vinyl ether (-)-**20** (5.0 g, 27.8 mmol) was sealed in a Corning glass tube under N_2 and heated at 200°C for 1 h. After cooling to ~30°C, the crude product was charged on a silica gel (50 g) column. Elution with 5% ethyl acetate-petroleum ether furnished the aldehyde (-)-**14** (4.5 g) in 90% yield.

$[\alpha]_D$: -70.0 (c, 1.0; $CHCl_3$)

bp : 100°C/0.5 mm

IR : 3050, 2950, 2750, 1720, 1640, 890 cm^{-1}

^1H NMR (Fig. I.1) : δ 9.7 (t, J = 4 Hz, 1H, O=C-<u>H</u>), 4.85 (d,

J = 4 Hz, 2H, -C=C$\underline{H}_2$), 2.44 (m, 2H, -C$\underline{H}_2$-CHO), 2.25-1.3 (m, 6H), 1.09 (s, 3H, -C-C$\underline{H}_3$), 0.97 (d, J = 7 Hz, 3H, -CH-C$\underline{H}_3$), 0.79 (d, J = 7 Hz, 3H, -CH-C$\underline{H}_3$)

^{13}C NMR (Fig. I.2) : δ 202.9, 161.0, 104.9, 54.4, 50.7, 44.0, 37.3, 28.8, 27.6, 26.0, 21.7, 16.4

Analysis : $C_{12}H_{20}O$ Calcd.: C, 79.94; H, 11.18.
Found : C, 79.83; H, 11.14.

(-)-(2S,5S)-5-Isopropyl-2-methyl-2-(carboethoxymethyl)-methylene-cyclopentane (15) :

A mixture of allylic alcohol (+)-24 (5 g, 32.5 mmol), triethyl orthoacetate (25 mL), propionic acid (500 mg) and mercuric acetate (750 mg) was sealed under N_2 in a Corning glass tube and heated at 200°C for 6 h. After cooling to ~30°C, the crude product was charged on a silica gel (100 g) column. Elution with 3% ethyl acetate-pet ether furnished the ester (-)-15 (5.5 g) in 80% yield.

$[\alpha]_D$: -53.7 (c, 5.1; $CHCl_3$)

IR : 3070, 2975, 1755, 880 cm^{-1}

^1H NMR (Fig. I.3) : δ 4.88-4.72 (m, 2H, -C=C$\underline{H}_2$), 4.10 (q, J_1 = 14 Hz, J_2 = 7 Hz, 2H, -OC$\underline{H}_2$-CH_3), 2.6-1.44 (m, 8H), 1.24 (t, J = 7 Hz, 3H, -OCH_2-C$\underline{H}_3$), 1.08 (s, 3H,-C-C$\underline{H}_3$), 0.98 (d, J = 7 Hz, 3H, -CH-C$\underline{H}_3$), 0.78 (d, J =7 Hz, 3H,-CH-C$\underline{H}_3$)

^{13}C NMR (Fig. I.4) : δ 171.9, 161.9, 103.4, 59.6, 50.5, 45.9, 44.4,

37.1, 28.7, 26.8, 22.9, 21.6, 16.2, 14.1.

Analysis : $C_{14}H_{24}O_2$ Calcd.: C, 74.95; H, 10.78.

Found : C, 74.77; H, 10.71.

(-)-5S-1,5-Dimethyl-2-isopropyl-5-(carboethoxy methyl)-cyclopent-1-ene (35) :

To a solution of the Claisen ester (-)-15 (9 g, 40 mmol) in 250 mL of freshly distilled dichloromethane at 0°C was added 1.2 equivalents of $BF_3.Et_2O$ under N_2. The reaction mixture was stirred at room temperature for 16 h and then quenched with saturated $NaHCO_3$ solution. The organic layer was separated, washed with water, brine and dried. Removal of the solvent afforded the crude product which was purified on a silica gel (45 g) column by eluting with 10% ethyl acetate - petroleum ether to yield (-)-35 (7.38 g) in 82% yield.

$[\alpha]_D$: -24.4 (c, 4.5; $CHCl_3$)

bp : 110°C/0.4 mm

IR : 1735, 1035 cm^{-1}

^1H NMR : δ 4.07 (q, J_1 = 14 Hz, J_2 = 7 Hz, 2H, $-OC\underline{H}_2-CH_3$), 2.58 (m, 1H, $-C\underline{H}-(CH_3)_2$), 2.32-1.36 (m, 6H), 1.52 (m, 3H, $-C=C-C\underline{H}_3$), 1.24 (t, J = 7 Hz, 3H, $-OCH_2-C\underline{H}_3$), 1.08 (s, 3H, $-C-C\underline{H}_3$), 0.95 (d, J = 7 Hz, 3H, $-CH-C\underline{H}_3$), 0.94 (d, J = 7 Hz, 3H, $-CH-C\underline{H}_3$)

^{13}C NMR : δ 172.4, 141.0, 134.4, 59.7, 49.7, 43.6, 35.2, 27.7, 26.9, 25.0, 20.9 (2C), 14.1, 9.1

Analysis : $C_{14}H_{24}O_2$ Calcd.: C,74.95; H, 10.78.
Found : C,74.80; H, 10.86.

(-)-(1S,5R)-1,5-Dimethyl-6-isopropylidine bicyclo[3.3.0]octan-3-one (39a) :

To a solution of the ester (-)-15 (7 g, 31.2 mmol) in 75 mL of MeOH was added 50 mL of 5% (w/v) aq. NaOH and the mixture was refluxed for 3 h under N_2 atmosphere. The reaction mixture was cooled, poured into water and extracted with hexane to remove the less polar impurities. The aqueous phase was acidified with dil. HCl (P_H 3-4) and extracted with ethyl acetate (75 mL x 3). The combined ethyl acetate was washed with water (25 mL), brine and dried. Removal of the solvent under reduced pressure yielded a crude product 36 (IR: 3300-2900 (br),1710, 860 cm^{-1}) which was directly used for the acid chloride preparation.

A solution of carboxylic acid 36 and oxalyl chloride (9.2 mL, 3 equivalents) in dry dichloromethane (150 mL) cooled to 5°C, was treated dropwise with pyridine (3.1 mL, 1 equivalent) and then stirred under N_2 atmosphere. After 4 h a small aliquot was removed and evaporated to dryness. The residue was extracted with benzene, and the IR spectrum of the benzene extract was recorded. The appearance of a strong band at 1800 cm^{-1} indicated the completion of the reaction. At this stage, the main reaction was worked up with benzene and filtered through a small Celite pad. The filtrate was concentrated to give 37 (IR: 2975, 1800, 990 cm^{-1}) and used as such for the diazo

ketone preparation.

To a solution of the crude acid chloride 37 in 50 mL of anhydrous ether was added, dropwise with ocassional stirring, chilled ethereal solution of diazomethane (5-6 equivalents). After the addition was over, the resulting solution was allowed to stand overnight at 0°C. The excess diazomethane was destroyed by the addition of acetic acid and the ethereal solution was dried and concentrated in vacuo to yield the crude diazoketone. The crude product was chromatographed on a silica gel (35 g) column by eluting with 20% ethyl acetate-petroleum ether to furnish 4.57 g of pure diazo ketone 38 (IR: 3080, 2975, 2170, 1620, 1350 cm^{-1}) in 68% yield.

To a solution of the diazo ketone 38 (4.57 g, 20.7 mmol) in 450 mL of freshly distilled dichloromethane was added at 0°C 1.2 equivalents of $BF_3.Et_2O$ under N_2 blanket. The reaction mixture was stirred for 5 min and quenched with saturated $NaHCO_3$ solution. The organic layer was separated, washed with brine and dried. The crude product obtained after concentration of the solvent was purified on passing through a silica gel (30 g) column. Elution with 10% ethyl acetate-petroleum ether furnished the enones 39a and 39b (2.921 g, 73%) as regioisomeric mixture (9:1).

A small portion of 39a,b was charged on a long silica gel (15 g) column (61 cm x 1.2 cm). Elution with 5% ethyl acetate-petroleum ether gave pure 39a for characterisation purposes.

$[\alpha]_D$: -5.2 (c, 0.7; $CHCl_3$)

bp : 102°C/0.3 mm

IR : 2970, 1740, 1080 cm^{1}

^{1}H NMR (Fig. I.5) : δ 2.92-1.32 (m, 8H), 1.71 (br s, 3H, -C=C-C$\underline{H}_3$), 1.60 (br s, 3H, -C=C-C$\underline{H}_3$), 1.16 (s, 3H, -C-C$\underline{H}_3$), 1.05 (s, 3H, -C-C$\underline{H}_3$)

Analysis : $C_{13}H_{20}O$ Calcd.: C, 81.20; H, 10.48.
Found : C, 80.42; H, 10.43.

(-)-(1S,5R)-1,5-Dimethyl-bicyclo[3.3.0]octan-3,6-dione (42) :

The mixture of bicyclic enones 39a,b (1.2 g, 6.25 mmol) was dissolved in a (1 : 1 : 1) mixture (60 mL) of carbon-tetrachloride, acetonitrile and water. Ruthenium trichloride (25 mg) was then added followed by sodium metaperiodate (2.0 g, 9.38 mmol). After stirring for 1 h, the reaction mixture was diluted with dichloromethane (100 mL) and filtered through a Celite pad. The organic layer was separated and the aq. layer was reextracted with dichloromethane (50 mL x 3). The combined organic phase was washed and dried. The crude product was passed through a silica gel (30 g) column and eluted with 30% ethyl acetate-petroleum ether to furnish dione (-)-42 (617 mg) in 60% yield.

$[\alpha]_D$: -30.9 (c, 3.75; $CHCl_3$)

IR : 2970, 1738, 1400, 1075, 755 cm^{-1}

^{1}H NMR (Fig. I.6) : δ 2.64-1.56 (m, 8H), 1.08 (s, 3H, -C-C$\underline{H}_3$), 0.99 (s, 3H, -C-C$\underline{H}_3$)

^{13}C NMR (Fig. I.7) : δ 220.7, 215.2, 55.4, 50.4, 46.4, 45.9, 34.2, 30.6, 21.4, 16.5.

Analysis : $C_{10}H_{14}O_2$ Calcd.: C, 72.26; H, 8.49.

Found : C, 72.15; H, 8.45.

(-)-(1R,5S)-1,5-Dimethyl-7(2,2-dimethyl trimethylene ketal)-bicyclo[3.3.0]octan-2-one (43) :

Into a 50 mL RB flask fitted with Dean-Stark water separator and reflux condenser, the dione (-)-**42** (145 mg, 0.87 mmol), 2,2-dimethyl-1,3-propanediol (125 mg, 1.2 mmol) and PPTS (25 mg) in dry benzene (20 mL) were placed and the contents were refluxed for 16 h. The reaction mixture was diluted with benzene (50 mL), washed with saturated $NaHCO_3$, water and then dried. The crude product obtained after removal of solvent was charged on a silica gel (10 g) column. Elution with 30% ethyl acetate-petroleum ether afforded the monoketal (-)-**43** (135 mg) in 61% yield.

$[\alpha]_D$: -46.9 (c, 2.75; $CHCl_3$)

IR : 2950, 1740, 1340, 1105, 1010 cm^{-1};

^1H NMR : δ 3.54-3.14 (m, 4H,-OCH_2-$C(CH_3)_2$-CH_2O-), 2.74-1.20 (m, 8H), 1.12 (s, 3H, -C-CH_3), 1.02 (s, 3H, -C-CH_3), 0.94 (s, 3H, -C-CH_3), 0.82 (s, 3H, -C-CH_3).

^{13}C NMR : δ 223.7, 106.7, 73.5, 71.2, 56.4, 51.4, 46.3, 43.4, 35.3, 32.9, 29.7, 24.4, 22.6, 22.2, 17.1

Analysis : $C_{15}H_{24}O_3$ Calcd.: C, 71.39; H, 9.59.

Found : C, 71.68; H, 9.55.

(+)-(1R,2S,5S)-1,5-Dimethyl-2-hydroxy-7(2,2-dimethyl trimethylene ketal)-bicyclo[3.3.0]octane (44) :

To the monoketal (-)-**43** (135 mg, 0.53 mmol) in dry methanol (5 mL) was added sodium borohydride (25 mg, 0.67 mmol) at 0°C under N_2. The reaction mixture was stirred at room temperature for 30 min. Then methanol was evaporated under reduced pressure and the residue was diluted with water (5 mL) and extracted with ethyl acetate (20 mL x 3). The combined extract was washed and dried. The crude product obtained after removal of the solvent was charged on a silica gel (10 g) column. Elution with 40% ethyl acetate-petroleum ether furnished the hydroxy-ketal (+)-**44** (120 mg) in 88% yield.

$[\alpha]_D$: +5.7 (c, 6.0; $CHCl_3$)

IR : 3430, 2950, 1460, 1100 cm^{-1};

^1H NMR : δ 3.56 (m, 1H), 3.36 (m, 4H,-$OC\underline{H}_2$-$C(CH_3)_2$-$C\underline{H}_2O$-), 2.28-1.04 (m, 9H), 0.94 (s, 3H, -C-$C\underline{H}_3$), 0.92 (s, 3H, -C-$C\underline{H}_3$), 0.88 (s, 3H, -C-$C\underline{H}_3$),0.84 (s, 3H, -C-$C\underline{H}_3$)

^{13}C NMR : δ 107.5, 82.0, 71.8, 71.6, 51.2, 49.0, 47.8, 43.3, 36.9, 31.3, 29.8, 25.2, 23.1, 22.3,(2C)

(-)-(1S,5R,6S)-1,5- Dimethyl -6- hydroxy- bicyclo[3.3.0] octan-3-one (45):

To a solution of hydroxy-ketal (+)-**44** (120 mg, 0.47 mmol) in THF (3 mL) was added few drops of 5% aq. HCl and the mixture was stirred at room temperature for 1 h. The reaction mixture was

quenched with saturated $NaHCO_3$ solution, diluted with ether (50 mL), washed with brine and dried. Removal of solvent and purification of the crude product on silica gel (10 g) column by eluting with 40% ethyl acetate-petroleum ether furnished the hydroxy-ketone (-)-45 (62 mg) in 78% yield.

$[\alpha]_D$: -16.6 (c 3.0, $CHCl_3$)

IR : 3430, 2970, 1730 cm^{-1};

^1H NMR : δ 3.92 (m, 1H, -C<u>H</u>OH), 3.04-1.40 (m, 9H), 1.00 (s, 6H, -C-C<u>H</u>$_3$)

^{13}C NMR : δ 219.3, 79.9, 52.3, 51.6, 46.7, 46.0, 35.8, 30.9, 23.3, 20.2

Analysis : $C_{10}H_{16}O_2$ Calcd.: C, 71.39; H, 9.59.
Found : C, 71.11; H, 9.68.

(-)-(1R,5S)-1,5-Dimethyl-7(2,2 dimethyl trimethylene ketal)-2(trimethylsilyloxy)-bicyclo[3.3.0]oct-2-ene (46) :

To a solution of n-butyl lithium (0.5 mL, 0.5 mmol, 1.0M in hexane) cooled to -78°C was added hexamethyldisilazane (0.5 mL, 1.2 mmol) under N_2. After stirring for 30 min, dry THF (1 mL) was added, followed by (-)-43 (40 mg, 0.16 mmol) in THF (1 mL) and the reaction mixture was stirred for 45 min at -78°C. The resulting enolate was quenched by freshly distilled chlorotrimethylsilane (35 mg, 0.32 mmol) in 1 mL of THF. After stirring for an additional hour, the reaction was quenched with brine and extracted with ether (20 mL x 3). The combined organic phase was washed, dried and concentrated. Purification of the oily residue on silica gel (10 g) column by eluting with 1%

ethyl acetate-pet ether afforded the enol ether (-)-**46** (52 mg) in 90% yield.

$[\alpha]_D$: -4.9 (c, 2.85; $CHCl_3$)

IR : 2955, 1630, 1090 cm^{-1}

^1H NMR : δ 4.28 (t, J = 2 Hz, 1H, C<u>H</u>=C-OTMS), 3.42 (d, J = 4 Hz, 4H, -OC<u>H</u>$_2$-C(CH_3)$_2$-C<u>H</u>$_2$O-), 2.38 (1/2 AB q, J = 14 Hz, 1H, -C=C-C<u>H</u>$_2$), 2.04 (m, 4H), 1.64 (1/2 AB q, J = 14 Hz, 1H, -C=C-C<u>H</u>$_2$), 1.06 (s, 3H, -C-C<u>H</u>$_3$), 0.98 (s, 3H, -C-C<u>H</u>$_3$), 0.96 (s, 3H, -C-C<u>H</u>$_3$), 0.92 (s, 3H, -C-C<u>H</u>$_3$), 0.22 (s, 3H, -OSi($C\underline{H}_3$)$_3$), 0.20 (s, 6H, -OSi($C\underline{H}_3$)$_3$).

^{13}C NMR : 159.6, 108.0, 96.4, 72.2, 71.8, 54.1, 51.0, 46.4, 43.8, 41.9, 29.9, 23.4, 22.5 (2C), 20.8, 0.00 (2C), -5.4

HRMS : $C_{18}H_{32}O_3Si$ Calcd. (M^+): 324.2121
Found : 324.2111

(+)-1S-7-Isopropyl-1-methyl-bicyclo[4.3.0]non-6-en-3-one (57) :

A mixture of ester (-)-**15** (1 g, 4.5 mmol) in 15 mL of MeOH ans 10 mL of 5% (w/v) aq.NaOH was refluxed for 2 h under N_2. The reaction mixture was cooled, diluted with water and acidified with dil.HCl. Extraction with ethyl acetate (50 mL x 3), washing and drying gave the crude acid **54** (950 mg) and was directly used for the acid chloride preparation employing oxalyl chloride (1.2 mL, 3 equiv.) and pyridine (0.5 mL, 1 equiv.) in dichloromethane (50 mL). Filtration through a Celite pad gave the crude acid chloride **55** (680 mg) (IR: 3060, 1800, 890 cm^{-1}). The above

acid chloride 55 was dissolved in ether (10 mL) and ethereal diazomethane was added (0-5°C) until a yellow colour persisted. The contents were left overnight at 5°C and concentrated. The residue was filtered through a silica gel (15 g) column to furnish diazoketone 56 (450 mg, 66%); (IR: 3075, 2110, 1640, 1355, 885 cm^{-1})

To a solution of 56 (300 mg, 1.36 mmol) in dichloromethane (150 mL) was added 1.2 equivalents of $BF_3.Et_2O$ under N_2 at 0°C. The reaction mixture was quenched after 3 min with saturated $NaHCO_3$ solution, washed and dried. The crude product was charged on a silica gel (15 g) column and eluted with 10% ethyl acetate-petroleum ether to furnish the bicyclic enone (+)-57 (200 mg) in 76% yield.

$[\alpha]_D$	: +19.2 (c, 2.5; $CHCl_3$)
bp	: 115°C /0.4 mm
IR	: 2955, 1710 cm^{-1}
^1H NMR (Fig. I.8)	: δ 2.78-1.34 (m, 11H), 0.94 (d, J = 7 Hz, 3H, -CH-$C\underline{H}_3$), 0.88 (s, 3H, -C-$C\underline{H}_3$), 0.87 (d, J = 7 Hz, 3H, -CH-$C\underline{H}_3$)
^{13}C NMR (Fig. I.9)	: δ 211.7, 140.4, 134.4, 56.0, 50.9, 41.1, 37.9, 29.1, 26.6, 24.4, 21.5, 21.3, 21.1.
Analysis	:$C_{13}H_{20}O$ Calcd.: C, 81.20; H, 10.48. Found : C, 81.42; H, 10.42.

2S-Methyl-2-(4-methyl-3-oxo-pentyl)-cyclohexan-1,4-dione (59) :

To the bicyclic enone (+)-57 (175 mg, 0.91 mmol) dissolved

in a mixture of (1 : 1 : 1) carbontetrachloride, acetonitrile and water (15 mL), ruthenium trichloride (5 mg) followed by sodium metaperiodate (295 mg, 1.4 mmol) were added.[18] After stirring for 1 h, the reaction mixture was diluted with dichloromethane (50 mL) and filtered through a Celite pad. The phases were separated and the aq. layer was reextracted with dichloromethane (20 mL x 2). The combined organic phase was washed and dried. The crude product was passed through a silica gel (10 g) column with 30% ethyl acetate-petroleum ether to furnish trione 59 (180 mg, 90%).

mp : 66°C,

IR : 2990, 1720, 1010 cm^{-1}

^{1}H NMR : δ 2.68-1.4 (m, 11H), 0.96 (s, 3H, -C-C$\underline{H}_3$), 0.92 (d, J = 7 Hz, 6H, -CH-C$\underline{H}_3$)

^{13}C NMR : δ 213.4, 211.9, 208.1, 50.2, 46.4, 40.6, 36.2, 36.1, 34.3, 31.5, 23.8, 17.9(2C)

Analysis : $C_{13}H_{20}O_3$ Calcd.: C, 69.91; H, 8.99.
Found : C, 69.76; H, 8.91.

(+)-(1S)-7-Isopropyl-methyl-bicyclo[4.3.0]non-6-ene-2,5-dione (60):

A mixture of triketone 59 (100 mg, 0.45 mmol) and 5% methanolic KOH (5 mL) was refluxed for 1 h. Methanol was removed and the residue was diluted with water (10 mL). Extraction with ether (25 mL x 3), washing and drying gave a crude product which was filtered through a small silica gel (10 g) column. Elution with 15% ethyl acetate-petroleum ether furnished the enedione (+)-60 (35 mg) in 36% yield.

$[\alpha]_D$: +234.2°C (c, 1.4; $CHCl_3$)

IR : 2975, 1720, 1680, 1610 cm^{-1}

^1H NMR (Fig. I.10) : δ 3.88-3.56 (m, 1H, -C<u>H</u>-$(CH_3)_2$), 2.80-1.70 (m, 8H), 1.30 (s, 3H, -C-C<u>H</u>$_3$), 1.06 (d, J = 7 Hz 3H, -CH-C<u>H</u>$_3$), 1.0 (d, J = 7 Hz, 3H,-CH-C<u>H</u>$_3$)

^{13}C NMR (Fig. I.11) : δ 213.9, 197.4, 168.2, 133.5, 59.2, 37.6, 35.8, 33.3, 29.2, 27.6, 24.3, 20.9, 20.6.

Analysis: : $C_{13}H_{18}O_2$: Calcd.: C, 75.69; H, 8.80.

Found : C, 75.56; H, 8.85.

(-)-(1S,4R)-7-Isopropyl-1-methyl-bicyclo[4.3.0]non-6-en-4-ol (63a) and (-)-(1S,4S)-7-Isopropyl-1-methyl-bicyclo[4.3.0]non-6-en-4-ol (63b) :

To a suspension of (methoxymethyl)triphenylphosphonium chloride (5.65 g, 16.5 mmol) in 25 mL of ether, freshly sublimed sodium t-amyloxide (910 mg, 8.25 mmol) in 5 mL of ether was added. The resulting dark red reaction mixture was stirred for 15 min at 30°C and aldehyde (-)-14 (1 g, 5.5 mmol) in 5 mL of ether was introduced . The reactants were stirred for 30 min and then quenched with water and extracted with ether (50 mL x 4). The crude product was filtered through basic alumina column to afford E : Z-enol ethers 61 (1.0 g, 90%).

IR : 3080, 3040, 1660, 880 cm^{-1}

^1H NMR : δ 6.24 (br d, J = 12 Hz, 1H, -CH=C<u>H</u>OCH$_3$), 5.9 (d,J = 6 Hz, 1H, -CH=C<u>H</u>OCH$_3$), 4.76 (m, 4H,-C=C<u>H</u>$_2$) 4.68-4.22 (m, 2H), 3.56 (s, 3H, -CH=CHOC<u>H</u>$_3$), 3.50 (s, 3H, -CH=CHOC<u>H</u>$_3$), 2.56-1.0 (m, 16H),

1.06-0.80 (complex doublets and singlets, 18H).

To a solution of enol ethers 61 (500 mg, 2.4 mmol) in 25 mL of ether 35% perchloric acid (2 mL) was added at 0°C. The reaction mixture was allowed to warm to ~30°C and stirred for 3 h. The reaction was quenched with saturated $NaHCO_3$ solution and the ethereal layer was washed and dried. Removal of the solvent and chromatographic separation on a silica gel (15 g) column by eluting with 10% ethyl acetate-petroleum ether furnished the major alcohol (-)-63a (255 mg) in 55% yield.

$[\alpha]_D$: -7.0 (c, 5.0; $CHCl_3$)

mp : 60°C,

IR : 3295, 2920, 1460, 1020, 985 cm^{-1}

^1H NMR (Fig. I.12) : δ 4.04 (br s, 1H, -CHOH), 2.84-1.40 (m, 12H), 1.04 (s, 3H, -C-CH_3), 1.03 (d, J = 7 Hz, 3H, -CH-CH_3), 0.97 (d, J = 7 Hz, 3H, -CH-CH_3).

^{13}C NMR (Fig. I.13) : δ 142.6, 133.4, 67.0, 46.6, 39.2, 35.0, 31.0, 29.4, 28.0, 26.2 22.2, 22.0, 21.1.

Analysis : $C_{13}H_{22}O$ Calcd.: C, 80.35; H, 11.41.
Found : C, 80.54; H, 11.50.

Further elution of the column with 10% ethyl acetate-petroleum ether furnished the minor alcohol (-)-63b (85 mg) in 18% yield.

$[\alpha]_D$: -6.4 (c, 5.0; $CHCl_3$)

mp : 40°C

^{1}H NMR (Fig. I.14) : δ 3.60-3.16 (m, 1H, -CHOH), 2.80-1.04 (m, 12H), 1.00 (s, 3H, -C-CH_3), 0.96 (d, J = 7 Hz, 3H, -CH-CH_3), 0.92 (d, J = 7 Hz, 3H, -CH-CH_3)

^{13}C NMR (Fig. I.15) : δ 139.5, 136.0, 71.9, 46.1, 38.8, 38.6, 33.1, 32.5, 28.8, 26.4, 22.6, 21.8, 21.1.

Analysis : $C_{13}H_{22}O$ Calcd.: C, 80.35; H, 11.41.
Found : C, 80.53; H, 11.34.

Oxidation of (-)-(1S,4R)-7-Isopropyl-1-methyl-bicyclo[4.3.0]-non-6-en-4-ol 63a :

To a suspension of pyridinium chlorochromate (361 mg, 1.0 mmol), molecular sieves 4Å in dichloromethane (5 mL) was added the alcohol (-)-63a (100 mg, 0.5 mmol) in dichloromethane (5 mL) at 0°C. The reaction mixture was stirred for 1h at ~30°C. Passage through a Florisil pad gave a product which was charged on a silica gel (5 g) column. Elution with 50% ethyl acetate-petroleum ether afforded the enones 64a,b (48 mg) in 45% yield.

mp : 61°C

IR : 3350, 2980, 1650 cm^{-1}

^{1}H NMR : δ 5.98 (s, 1H, -C=CH-C=O), 5.96 (s, 1H, -C=CH-C=O), 2.6-1.48 (m, 20H), 1.36 (s, 3H, -C-CH_3), 1.20 (s, 3H, -C-CH_3), 1.08-0.96 (series of doublets, 12H)

^{13}C NMR : δ 201.3, 177.4, 174.4, 123.0, 122.7, 95.8, 94.9, 43.0, 42.8, 38.5, 37.0, 36.3, 33.9(2C), 30.6,

29.4, 29.1, 28.2, 23.5, 23.2, 18.3, 17.7, 17.8, 16.8, 16.3

HRMS : $C_{13}H_{20}O_2$ Calcd. (M^+): 208.1463.
Found : 208.1466.

(1S,4R)-4- Acetoxy-7-isopropyl-1-methyl- bicyclo[4.3.0]non-6-ene (66) :

To a mixture of the alcohol (-)-63a (500 mg, 2.57 mmol) in dry DCM (50 mL) and dry pyridine (2 mL) was added acetic anhydride (0.5 mL) at 0°C. The reaction mixture was stirred for 16 h. Then the reaction was quenched with water and extracted with ether (25 mL x 3). The combined ethereal extract was washed, dried and concentrated to a crude product which was filtered through a small silica gel (15 g) column. Elution with 10% ethyl acetate-pet ether furnished the acetate 66 (550 mg) in 90% yield.

IR : 2970, 1735, 1240 cm^{-1}

^1H NMR : δ 5.04 (br s, 1H, -CHOAc), 2.72-1.40 (m,11H), 2.04 (s, 3H, $-COCH_3$), 1.00 (s, 3H, $-C-CH_3$), 0.96 (d, J = 7 Hz, 3H, $-CH-CH_3$), 0.91 (d, J = 7 Hz, 3H, $-CH-CH_3$)

(+)-(1R,4R)-4- Acetoxy-7-isopropyl-1-methyl- bicyclo[4.3.0]non-6-en-8-one (67) :

3,5-Dimethyl pyrazole (562 mg, 5.85 mmol) was added to a suspension of chromium trioxide (584 mg, 5.84 mmol) in

dichloromethane (15 mL) to give a deep red solution. To this the acetate 66 (230 mg, 0.97 mmol) in dichloromethane (2 mL) was added. The reaction mixture was stirred for 30 h at 30°C. The reaction mixture was diluted with ether (30 mL x 4) and filtered through a small Celite pad. The residue was purified on a silica gel (10 g) column. Elution with 40% ethyl acetate-petroleum ether mixture gave (+)-67 (175 mg) in 73% yield.

$[\alpha]_D$: +86.8 (c, 2.2; $CHCl_3$)

mp : 55°C

IR : 2965, 1730, 1690, 1640, 1240 cm^{-1}

^1H NMR : δ 5.24 (m, 1H, -C<u>H</u>OAc), 3.20-1.60 (m, 9H), 2.00 (s, 3H, -COC<u>H</u>$_3$), 1.26 (s, 3H, -C-C<u>H</u>$_3$), 1.16 (d, J = 7 Hz, 3H, -CH-C<u>H</u>$_3$), 1.14 (d, J = 7 Hz, 3H, -CH-C<u>H</u>$_3$)

^{13}C NMR : δ 207.1, 173.2, 170.4, 144.3, 70.4, 51.6, 40.2, 34.8, 29.3, 26.0, 24.3, 24.1, 21.1, 20.8, 20.5.

Analysis : $C_{15}H_{22}O_3$ Calcd.: C, 71.97; H, 8.86.
Found : C, 71.85; H, 8.73.

(-)-1R-7-Isopropyl-1-methyl-bicyclo[4.3.0]nona-4,6-dien-8-one (68

To a solution of (+)-67 (24 mg, 0.096 mmol) in methanol (2 mL) was added a few drops of 20% methanolic KOH and the mixture stirred for 3 h at 30°C. The reaction mixture was diluted with water and extracted with ethyl acetate (20 mL x 2). The oily residue was chromatographed on a silica gel (1 g) column to furnish (-)-68 (15 mg) in 75% yield.

$[\alpha]_D$	: -274.2 (c, 0.75; $CHCl_3$)
bp	: 105°C /0.3 mm
IR	: 2940, 1685, 1625, 1100, 730 cm^{-1}
^1H NMR (Fig. I.16)	: δ 6.60 (br d, J = 8Hz, 1H), 6.24-5.96 (m, 1H), 2.92-1.28 (m, 7H), 1.09 (d, J = 7 Hz, 6H, -CH-$C\underline{H}_3$), 1.06 (s, 3H, -C-$C\underline{H}_3$)
^{13}C NMR (Fig. I.17)	: δ 202.9, 168.8, 139.7, 137.2, 121.5, 51.4, 37.9, 33.8, 25.4, 24.2, 24.1, 21.1, 20.5.
Analysis	: $C_{13}H_{18}O$ Calcd.: C, 82.06; H, 9.54. Found : C, 82.20; H, 9.56.

Preparation of vinyl bromide gas:

Into a 100 mL three necked RB flask fitted with a pressure equalizing addition funnel, septum and a tube connecting another three necked 50 mL RB flask containing dry THF (30 mL) and kept at -40°C, were placed ethylene glycol (20 mL), water (16 mL) and potassium hydroxide (20 g). To this mixture 1,2-dibromoethane (15 mL) was added dropwise while heating the reaction mixture at 80-85°C. The vinyl bromide gas thus generated was passed through calcium chloride guard tube and bubbled into dry THF at -40°C. After bubbling for 2 h, the resulting vinyl bromide-THF solution was used for the preparation of the Grignard reaction.

(-)-(2S,5S)-5-Isopropyl-2-methyl-2-(2-oxo-3-butenyl)-1-methylene-cyclopentane (77) :

To an ice-cooled solution of vinylmagnesium bromide (30 mmol), aldehyde (-)-**14** (5.0 g, 27.8 mmol) in THF (10 mL) was

slowly added. The reaction mixture was warmed to ~30°C, stirred for 1 h and then quenched with ice water. The resulting aqueous layer was extracted with ether (100 mL x 3). The combined ethereal extract was washed, dried and concentrated to an oil which was chromatographed on a silica gel (50 g) column. Elution with 10% ethyl acetate-petroleum ether furnished the allylic alcohol 76 (4.3 g) in 75% yield as mixture of diastereomers.

bp : 120°C/0.1 mm

IR : 3400, 3050, 2950, 1640, 1000, 910, 890 cm^{-1}

^1H NMR : δ 6.0-5.6 (m, 2H, -C<u>H</u>=CH_2), 5.3-4.7 (m, 8H, C=C<u>H</u>$_2$), 4.4-4.0 (m, 2H, -C<u>H</u>OH), 2.6-1.3 (series of m, 18H), 1.06 and 1.01 (s, 6H, -C-C<u>H</u>$_3$), 0.98 (d, J = 7 Hz, 6H, -CH-C<u>H</u>$_3$), 0.77 and 0.75 (d, J = 7 Hz, 6H, -CH-C<u>H</u>$_3$)

Analysis : $C_{14}H_{24}O$ Calcd.: C, 80.71; H, 11.61.
Found : C, 80.76; H, 11.58.

To a suspension of pyridinium chlorochromate (6.5 g, 30 mmol) in dry dichloromethane (50 mL) containing 5.0 g of activated molecular sieves (4 Å) was added the above allylic alcohol 76 (4.0 g, 22.5 mmol) in dry dichloromethane (10 mL) at 0°C. The reaction mixture was stirred for 1 h, diluted with dry ether (50 mL) and filtered through a florisil (10 g) column. Removal of solvent gave an oily residue which was charged on a silica gel (40 g) column. Elution with 5% ethyl acetate-petroleum ether furnished the pure enone (-)-77 2.6 g in 65% yield.

$[\alpha]_D$: -62.2 (c, 2.0; $CHCl_3$)

bp. : 120°C/0.1 mm,

IR : 3050, 2950, 1680, 1610, 1400, 890 cm^{-1}

^1H NMR : δ 6.5-6.0 (m, 2H, -CH=C<u>H</u>$_2$), 5.7 (dd, J_1 = 9 Hz, J_2 = 3 Hz, 1H, -C<u>H</u>=CH$_2$), 4.78 (d, J = 4 Hz, 1H, -C=C<u>H</u>$_2$), 4.72 (d, J = 4 Hz, 1H, -C=C<u>H</u>$_2$), 2.7-1.2 (series of m, 8H), 1.08 (s, 3H, -C-C<u>H</u>$_3$), 0.97 (d, J = 7 Hz, 3H,-CH-C<u>H</u>$_3$), 0.77 (d, J = 7 Hz, 3H, -CH-C<u>H</u>$_3$)

^{13}C NMR : δ 188.6, 162.5, 137.7, 127.4, 104.8, 50.8, 50.5, 37.1, 28.6, 27.2, 23.0, 21.7, 21.2, 16.3.

Analysis : $C_{14}H_{22}O$ Calcd.: C, 81.50; H, 10.75.
Found : C, 81.72; H, 10.73.

(-)-1S-8-Isopropyl-1-methyl-bicyclo[5.3.0]dec-7-en-3-one (69) :

To a solution of enone (-)-77 (2.5 g, 12.1 mmol) in dry ethyl acetate (150 mL) was added acetic anhydride (4 mL) and 70% perchloric acid (0.1 mL). The reactants were stirred at room temperature for 25 min. and then quenched with saturated $NaHCO_3$ solution. The organic phase was washed, dried and concentrated to give an oil which was chromatographed on a silica gel (25 g) column. Elution with 10% ethyl acetate-petroleum ether furnished the cyclised enone (-)-69 (1.6 g) 65% yield.

$[\alpha]_D$: -13 (c, 1.0; $CHCl_3$)

bp : 120°C/0.1 mm

IR : 2950, 1695, 1460 cm^{-1}

^1H NMR (Fig. I.18) : δ 2.8-2.5 (series of m, 13H), 1.0 (s, 3H, -C-C<u>H</u>$_3$), 0.97 (d, J = 7 Hz, 3H, -CH-C<u>H</u>$_3$), 0.94 (d,

J = 7 Hz, 3H, -CH-C$\underline{H}_3$);

^{13}C NMR (Fig. I.19) : δ 213.0, 141.9, 138.7, 54.8, 47.59, 43.7, 38.0, 27.2, 26.5, 24.7, 24.1, 23.8, 21.3, 20.9.

Analysis : $C_{14}H_{22}O$ Calcd.: C, 81.50; H, 10.75.

Found : C, 81.91; H, 10.91.

1S-4-Carbomethoxy-8-isopropyl-1-methyl-bicyclo[5.3.0]dec-7-en-3-one (84) :

To a suspension of sodium hydride (360 mg, 5.0 mmol) in dry dimethyl carbonate (15 mL) was added enone (-)-**69** (1.5 g, 4.85 mmol) in dry dimethyl carbonate (10 mL) and the contents were stirred at 30°C for 6 h. The reaction mixture was diluted with ether (100 mL) and washed with water, dried and chromatographed on a silica gel (25 g) column. Elution with 5% ethyl acetate-pet ether furnished the keto-ester **84** (1.5 g, 78%

bp : 160°C/0.1 mm

IR : 2950, 1730, 1700, 1640, 1440, 1240, 1020 cm^{-1}

^{1}H NMR : δ 3.78 (s, 3H, -OC$\underline{H}_3$), 3.7 (s, 3H, -OC$\underline{H}_3$), 2.8-2.5 (series of m, 24H), 1.05-0.85 (series of s and d, 18H).

Analysis : $C_{16}H_{24}O_3$ Calcd.: C, 72.69; H, 9.15.

Found : C, 72.97; H, 9.35.

(+)-(1S,5R)-9-Isopropyl-1-methyl-5-carbomethoxy-bicyclo[6.3.0]undec-8-en-3-one (86) :

A mixture of keto-ester **84** (100 mg, 0.4 mmol), dry aceton

(10 mL) and potassium carbonate (225 mg, 1.6 mmol) was refluxed for 1 h. Methylene bromide (210 mg, 1.2 mmol) was added and the mixture refluxed for 12 h. Acetone was removed and the residue was diluted with water (15 mL) and extracted with ether (25 mL x 3). The ethereal extract was washed, dried and chromatographed on a silica gel (5 g) column to furnish the ester 85 (110 mg, 81%) as a diastereomeric mixture.

IR : 2975, 1735, 1705, 1160 cm^{-1}

^1H NMR : δ 4.26-3.24 (m, 4H), 3.78 (s, 3H, $-OC\underline{H}_3$), 3.72 (s, 3H, $-OC\underline{H}_3$), 2.92-1.12 (m, 22H), 1.04-0.88 (series singlets and doublets, 18H).

Analysis : $C_{17}H_{25}O_3Br$ Calcd.: C, 57.14; H, 7.05.
Found : C, 56.92; H, 7.01.

A solution of ester 85 (100 mg, 0.28 mmol), tri-n-butyltin hydride (85 mg, 0.29 mmol), and AIBN (20 mg) in 350 mL of dry benzene was refluxed for 16 h. The reaction mixture was repeatedly washed with 10% potassium flouride solution followed by water and brine. The crude product was purified on a silica gel (10 g) column to give (+)-86 (40 mg, 50%).

$[\alpha]_D$: + 41.5 (c, 1.3; $CHCl_3$)

bp : 115°C /0.5 mm

IR : 2940, 1745, 1705, 1450 cm^{-1}

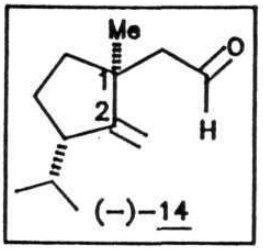
^1H NMR (Fig. I.20) : δ 3.68 (s, 3H, $-OC\underline{H}_3$), 3.08-1.44 (m, 14H), 1.04 (s, 3H, $-C-C\underline{H}_3$), 1.03 (d, J = 7 7Hz, 3H, $-CH-C\underline{H}_3$), 0.95 (d, J = 7 Hz, 3H, $-CH-C\underline{H}_3$)

^{13}C NMR (Fig. I.21) : δ 210.9, 175.5, 144.6, 135.9, 52.4, 52.1, 51.5, 47.4, 38.8(2C), 31.1, 27.2, 27.0, 25.3, 21.3, 20.9(2C).

Analysis : $C_{17}H_{26}O_3$ Calcd.: C, 73.34; H, 9.41.

Found : C, 73.45; H, 9.45.

I.6. **SPECTRA:**



(−)−**14**

Fig. I.1

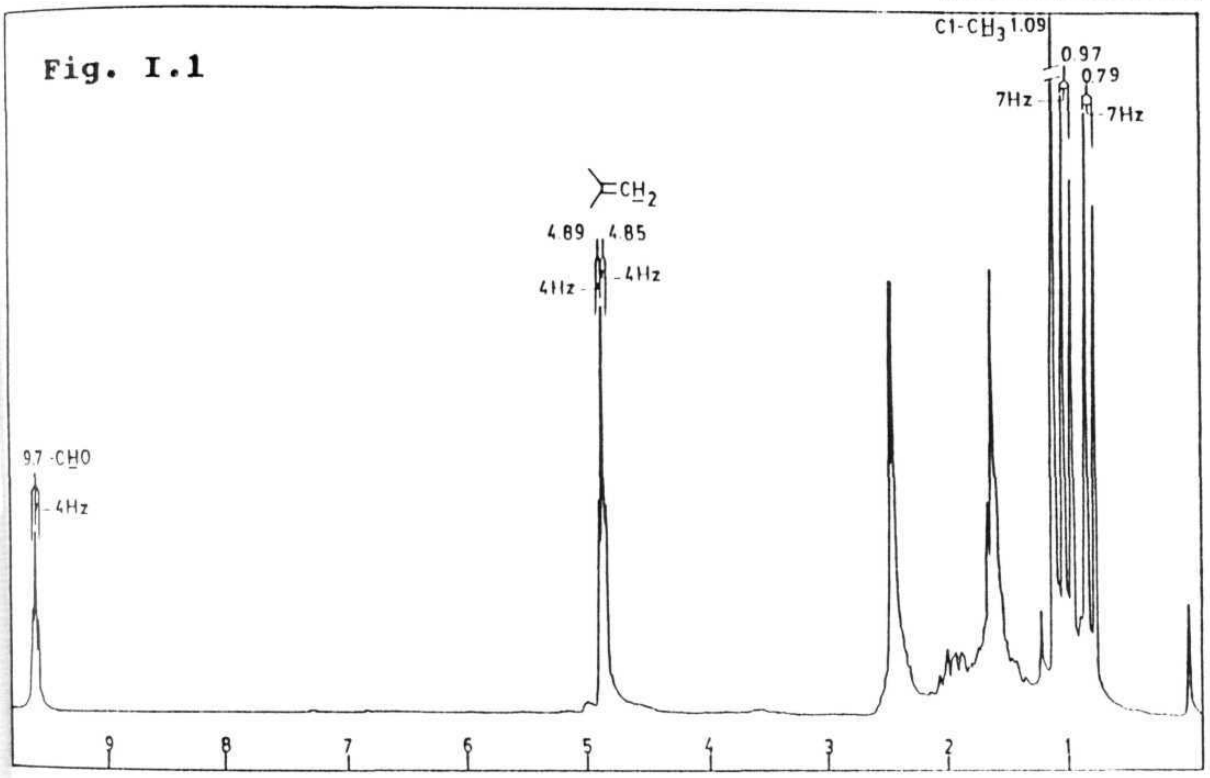
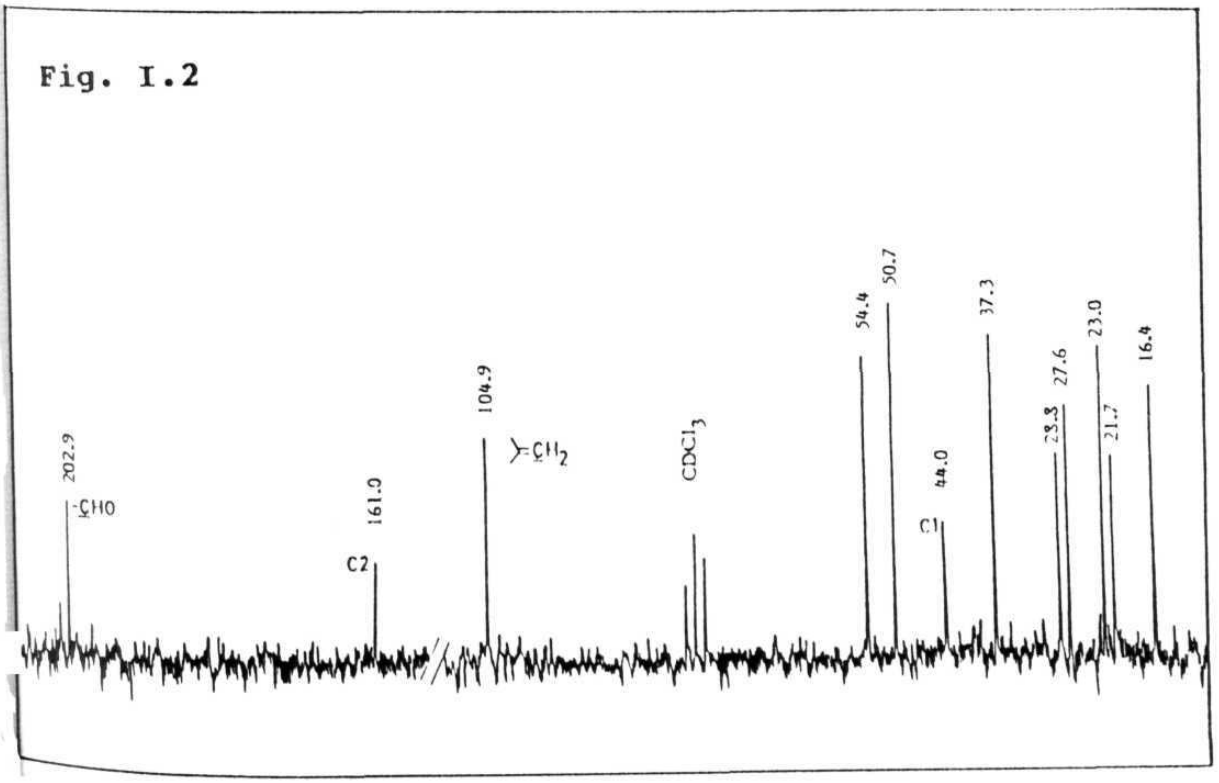
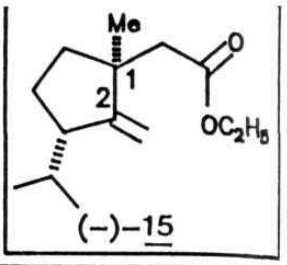


Fig. I.2





(−)−15

Fig. I.3

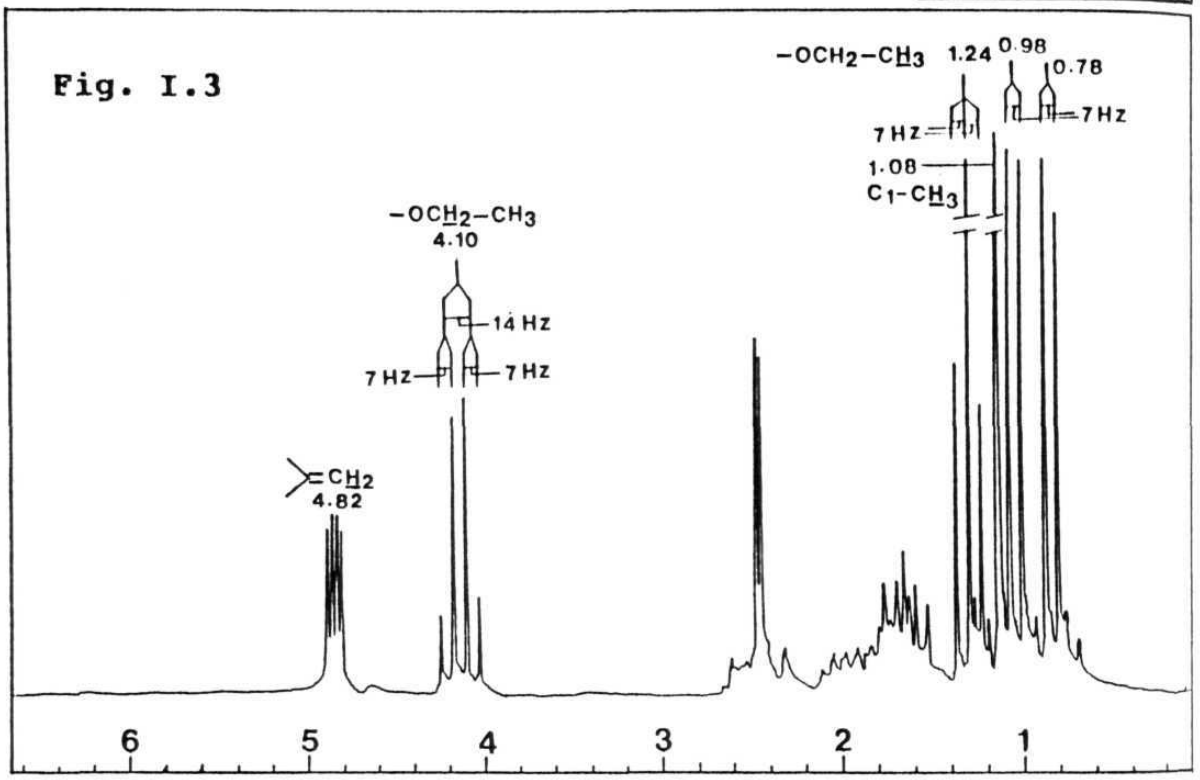
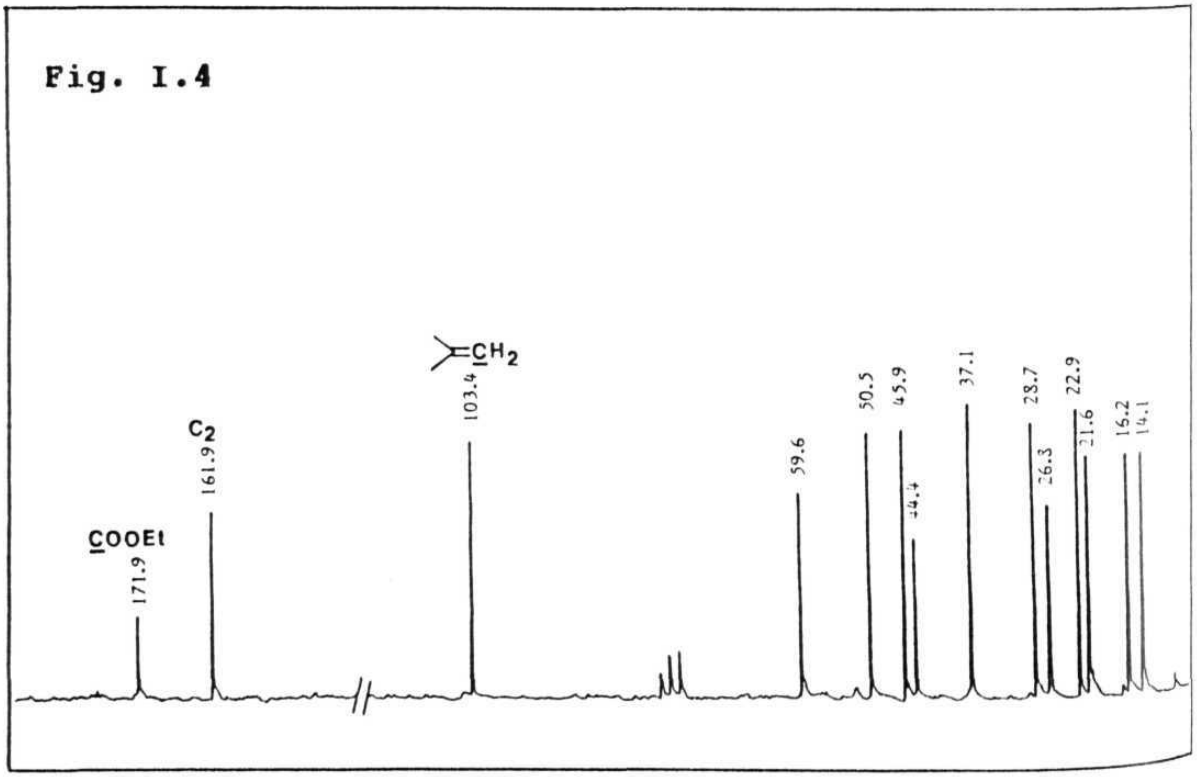
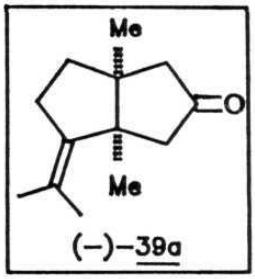


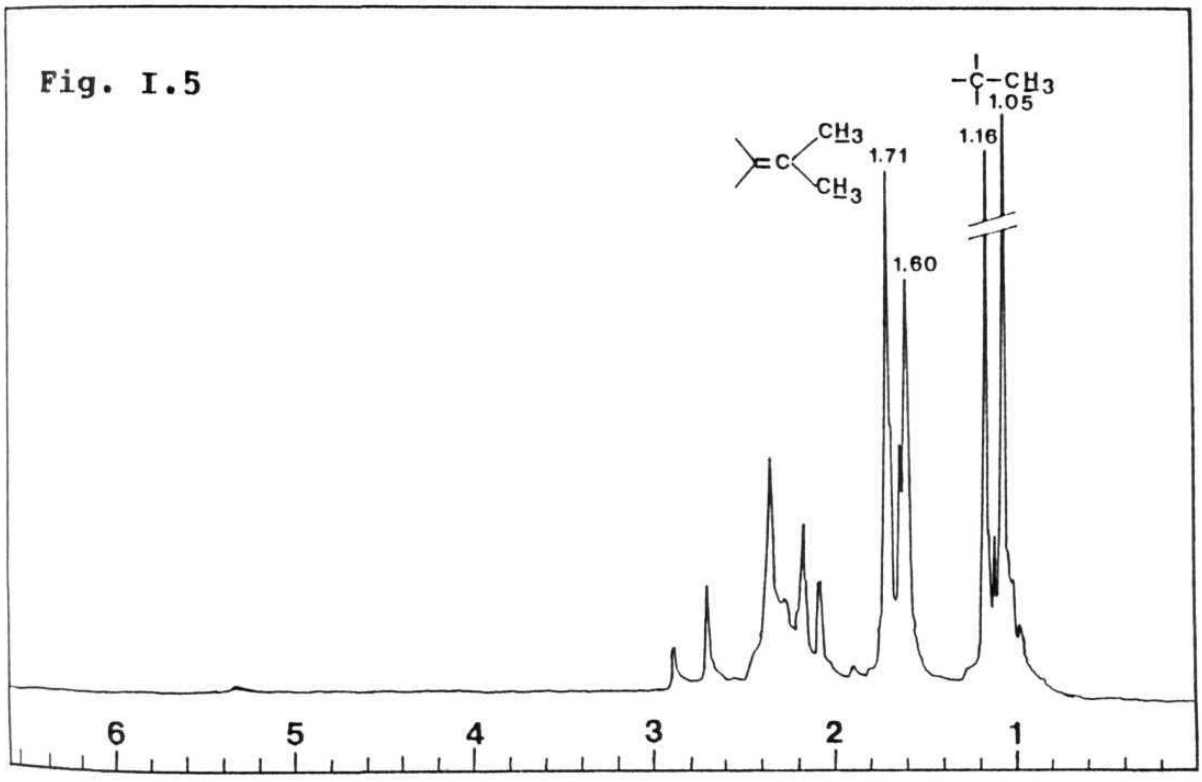
Fig. I.4

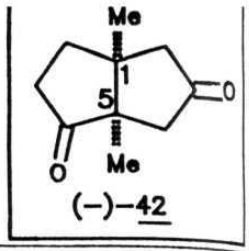




(−)−39a

Fig. I.5





(−)−42

Fig. I.6

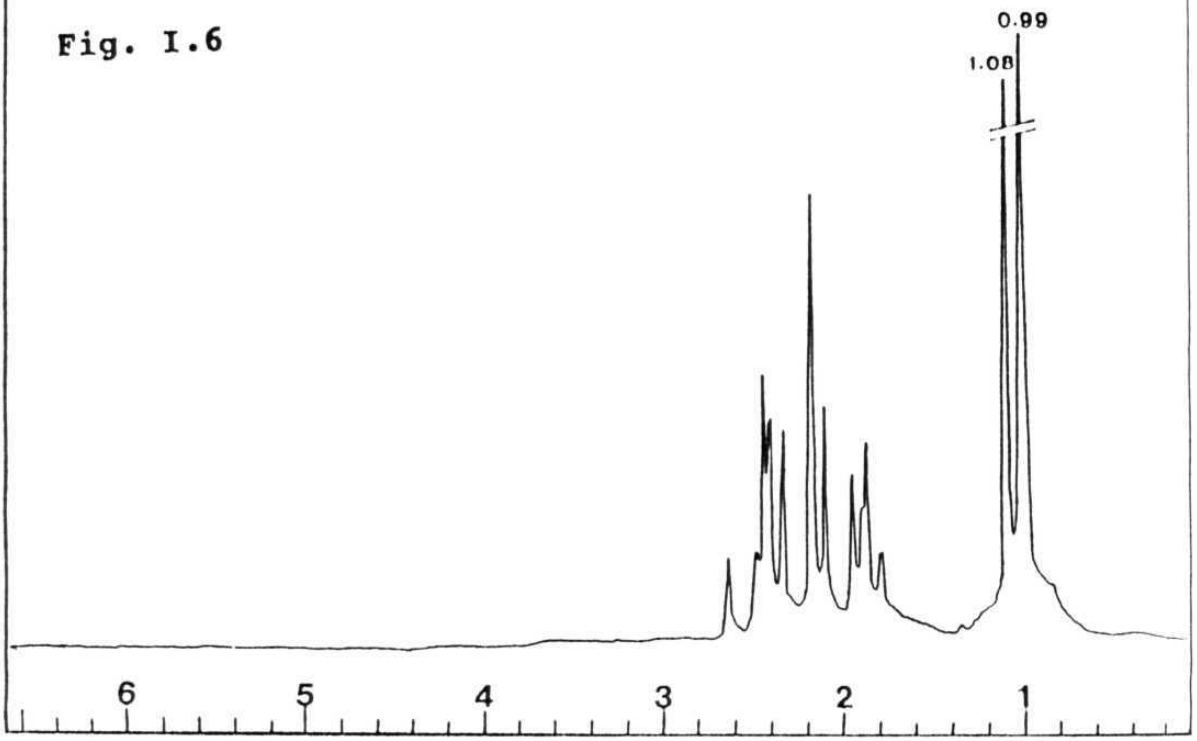
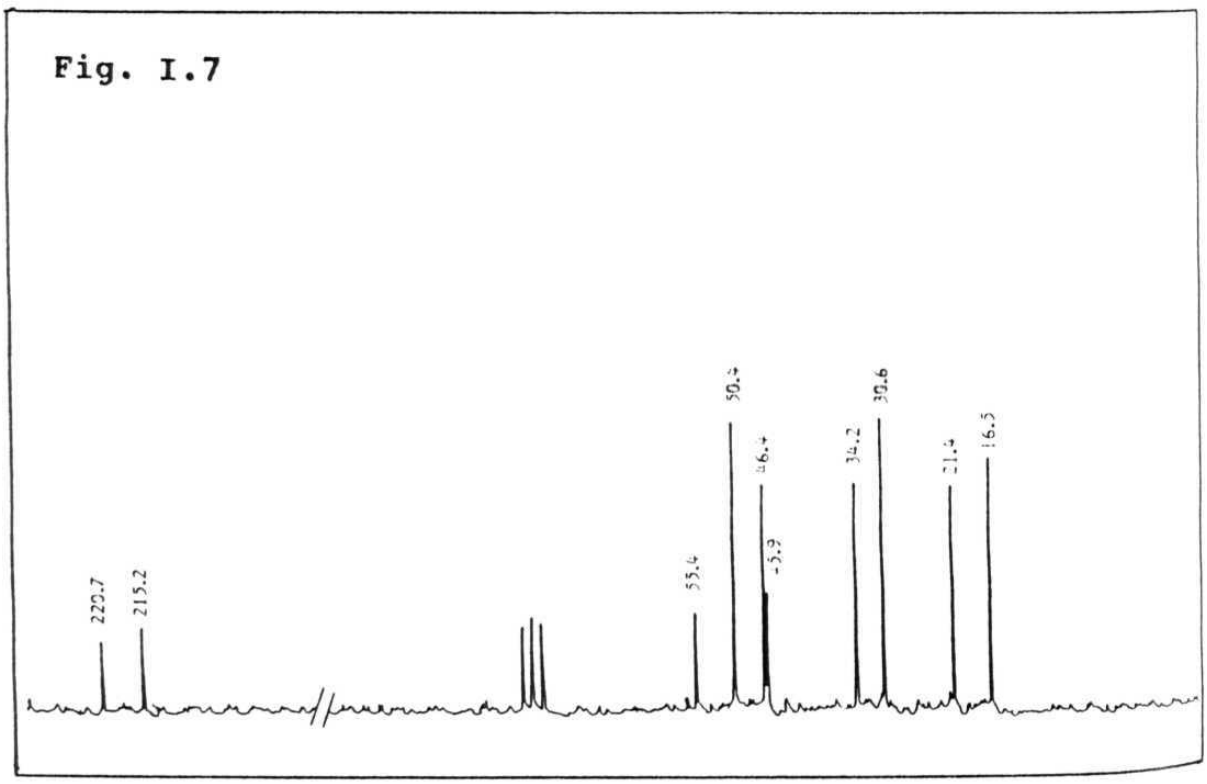
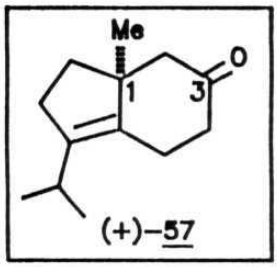


Fig. I.7





(+)-57

Fig. I.8

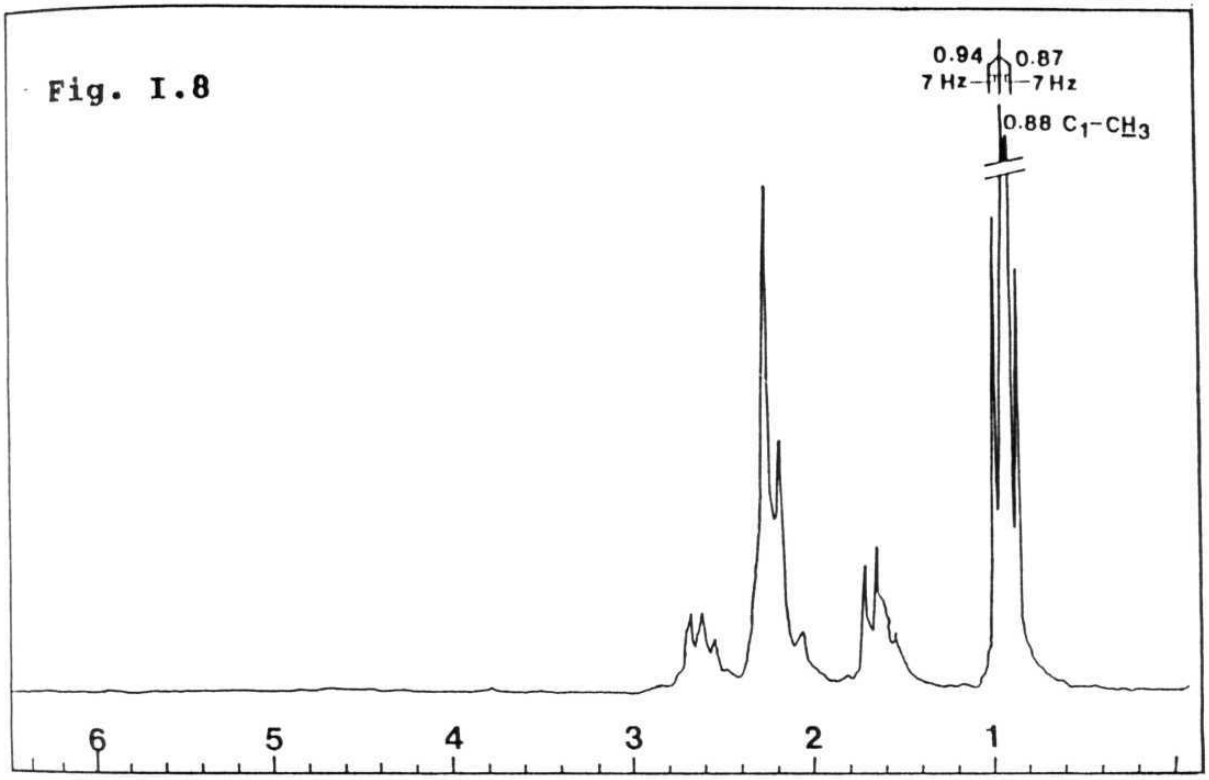
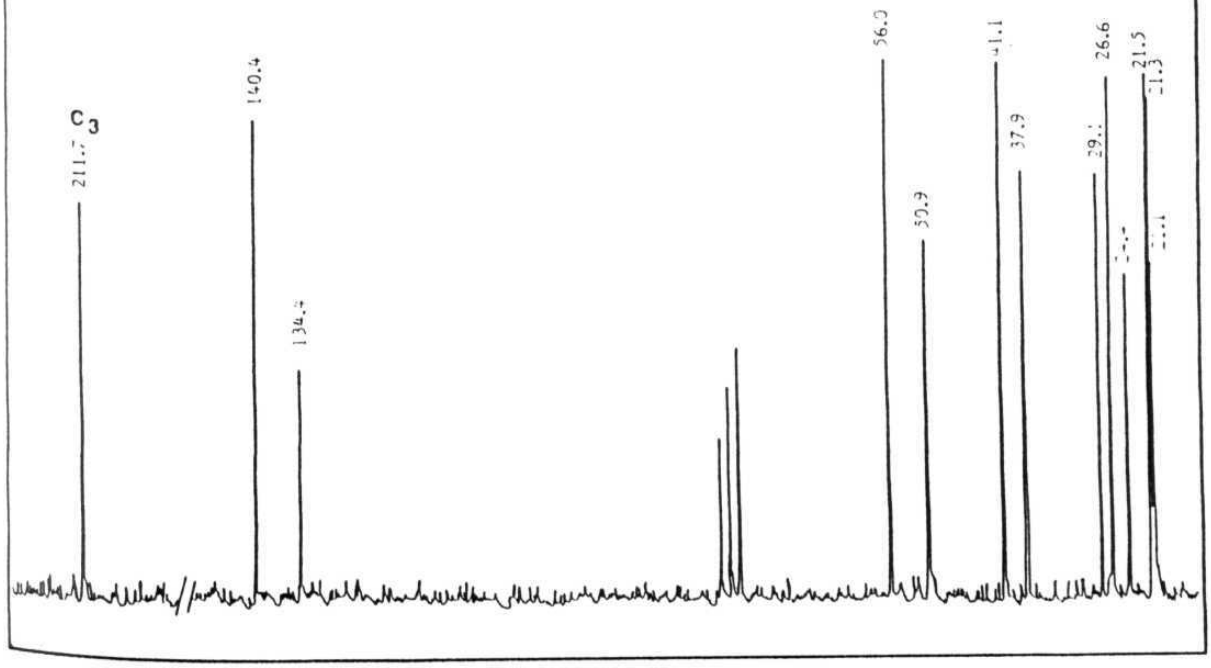
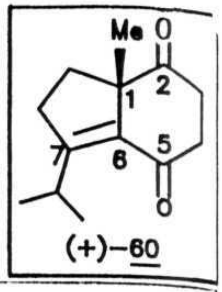


Fig. I.9





(+)–60

Fig. I.10

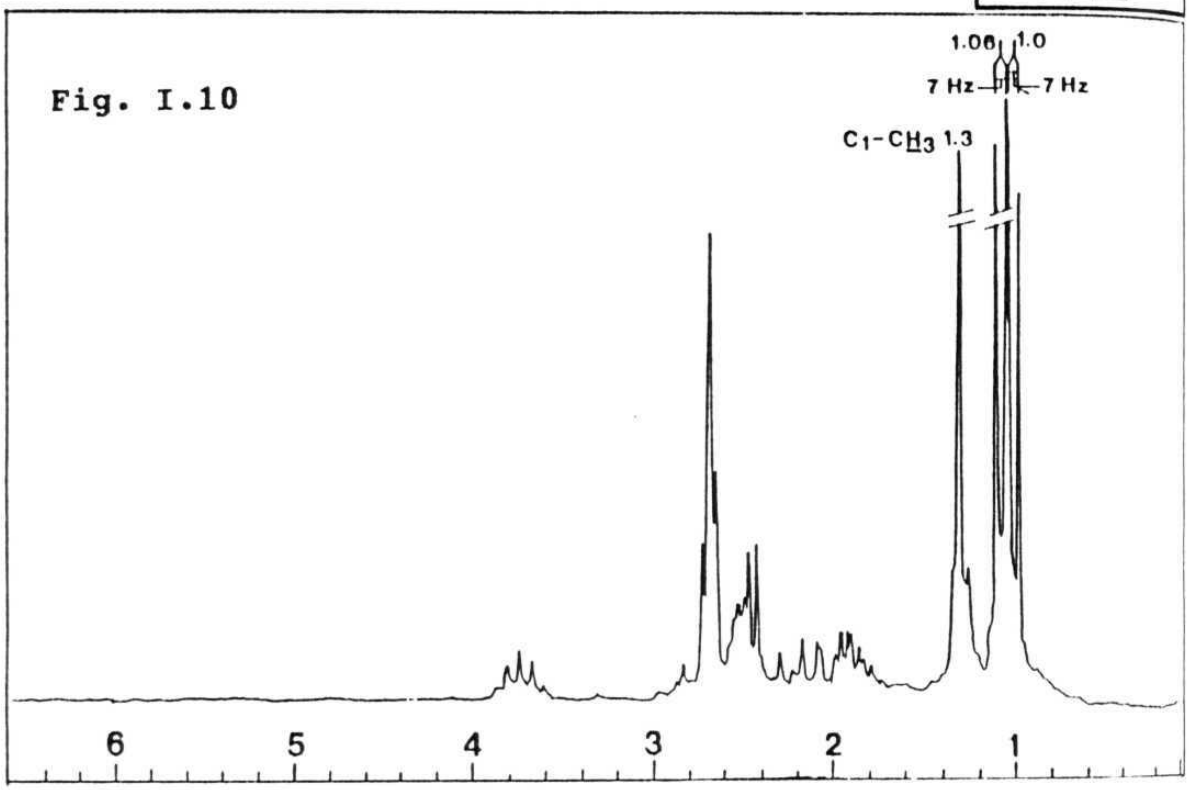
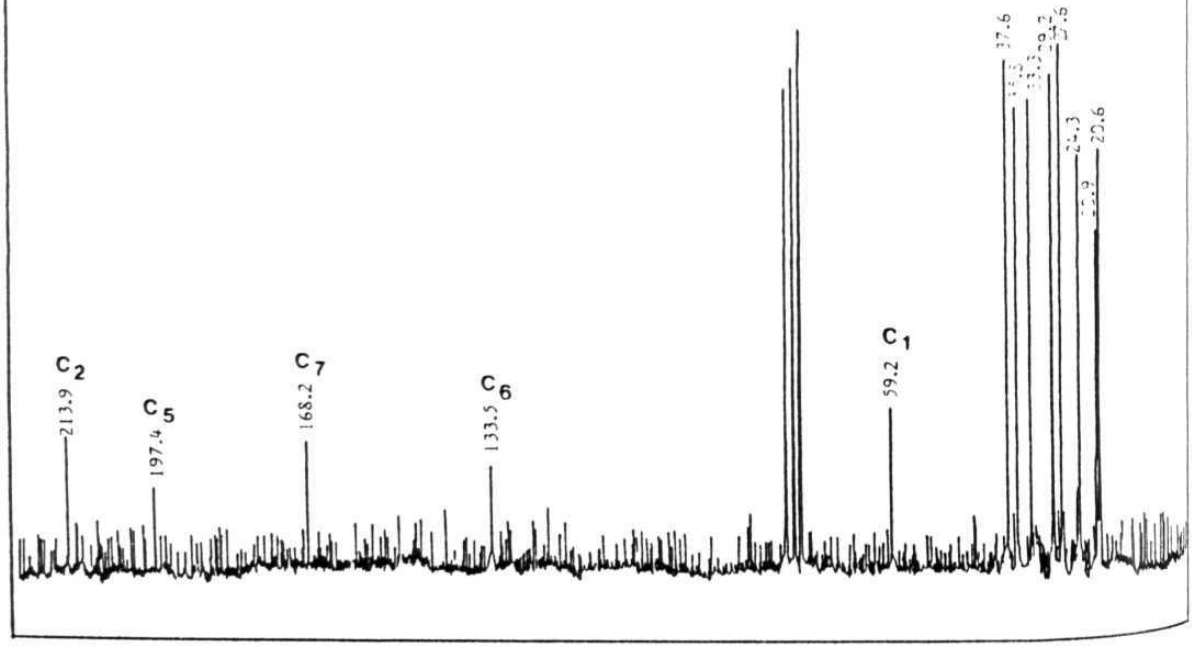
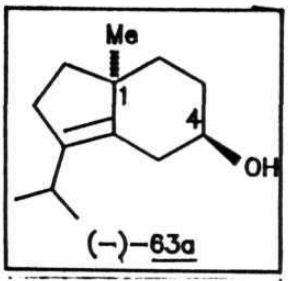


Fig. I.11





(−)−63a

Fig. I.12

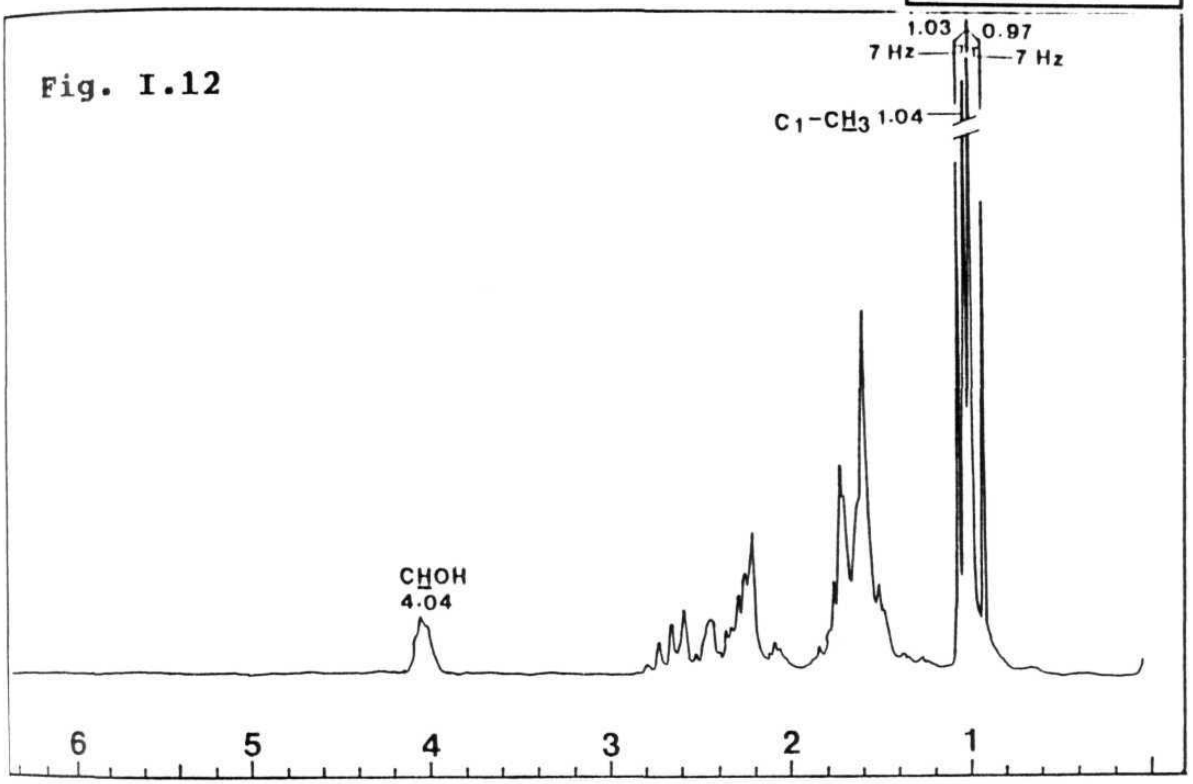
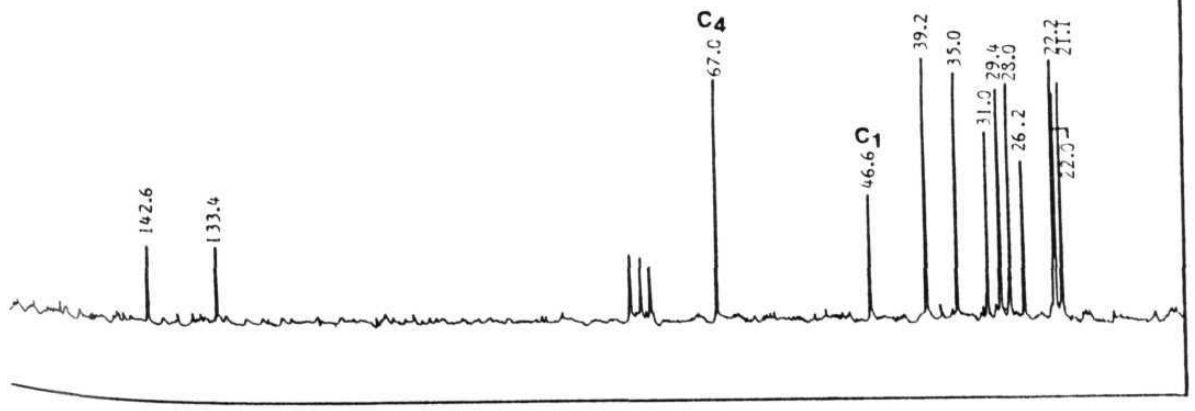


Fig. I.13



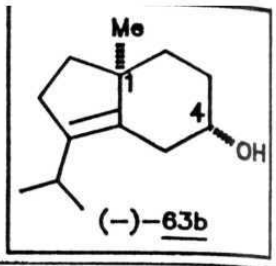


Fig. I.14

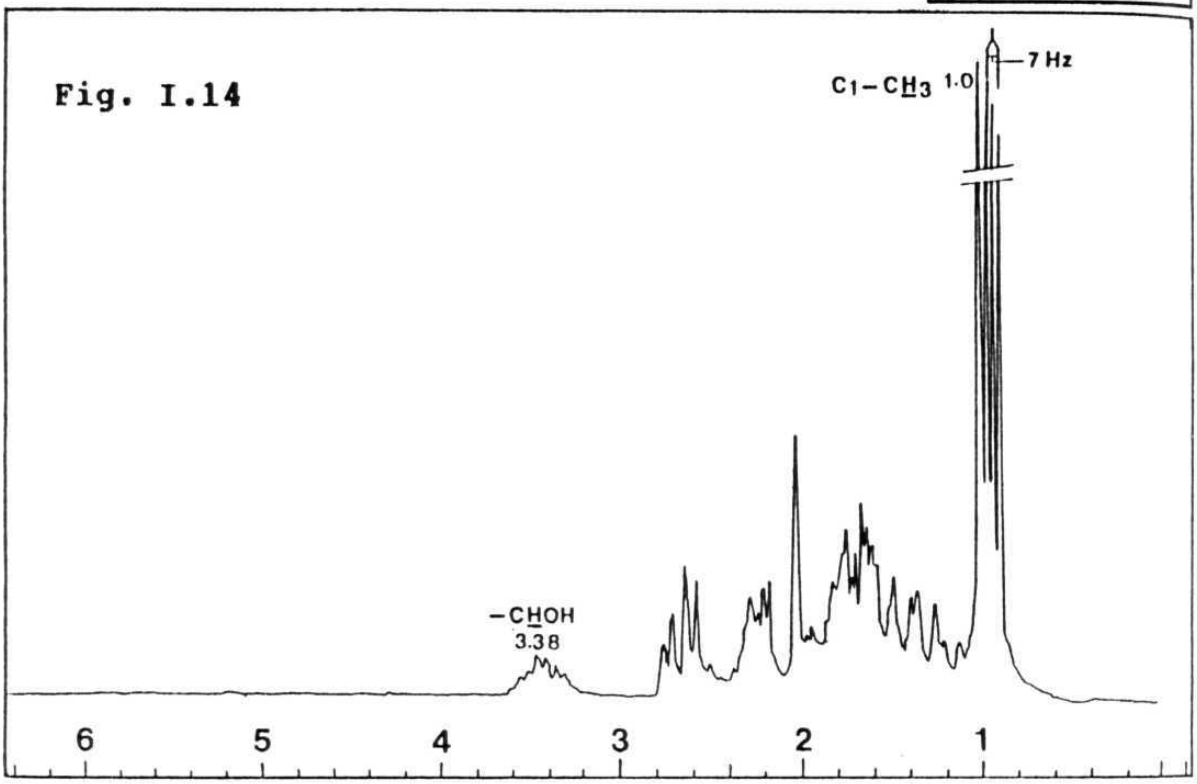
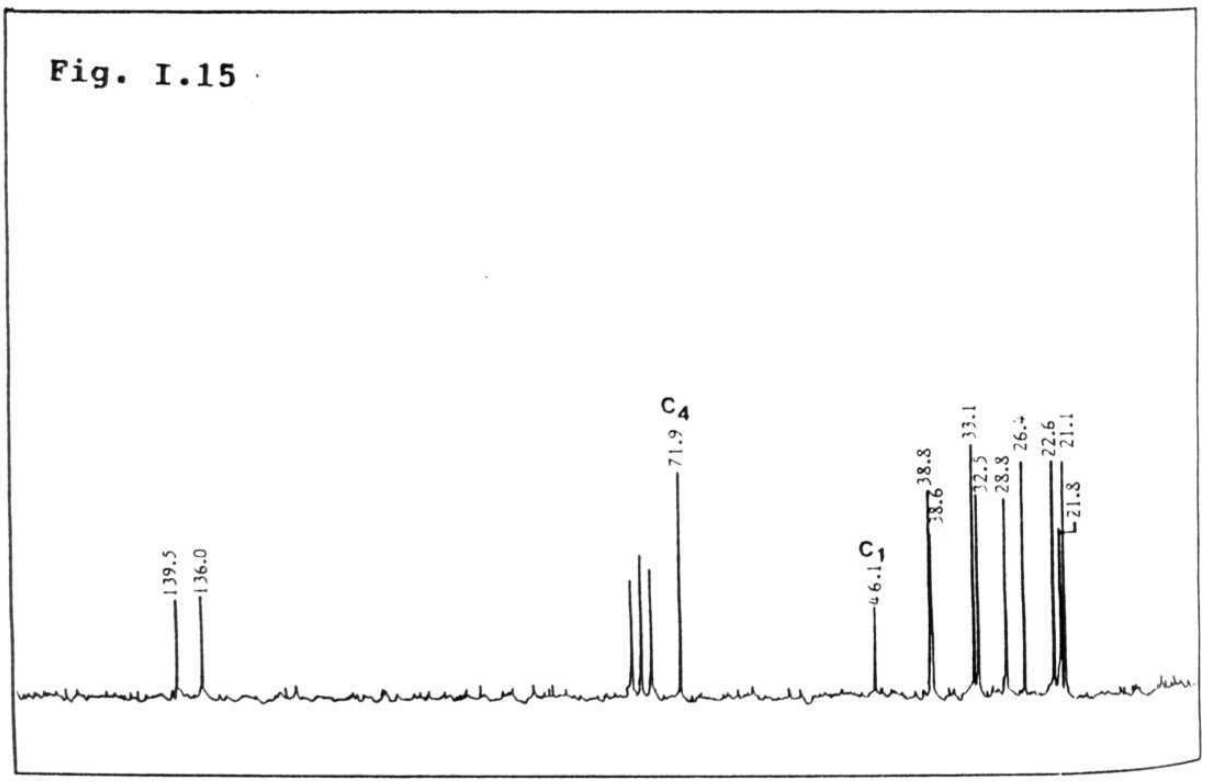


Fig. I.15



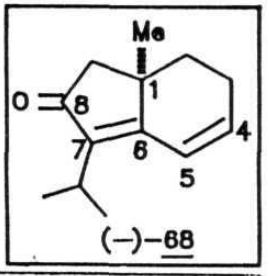


Fig. I.16

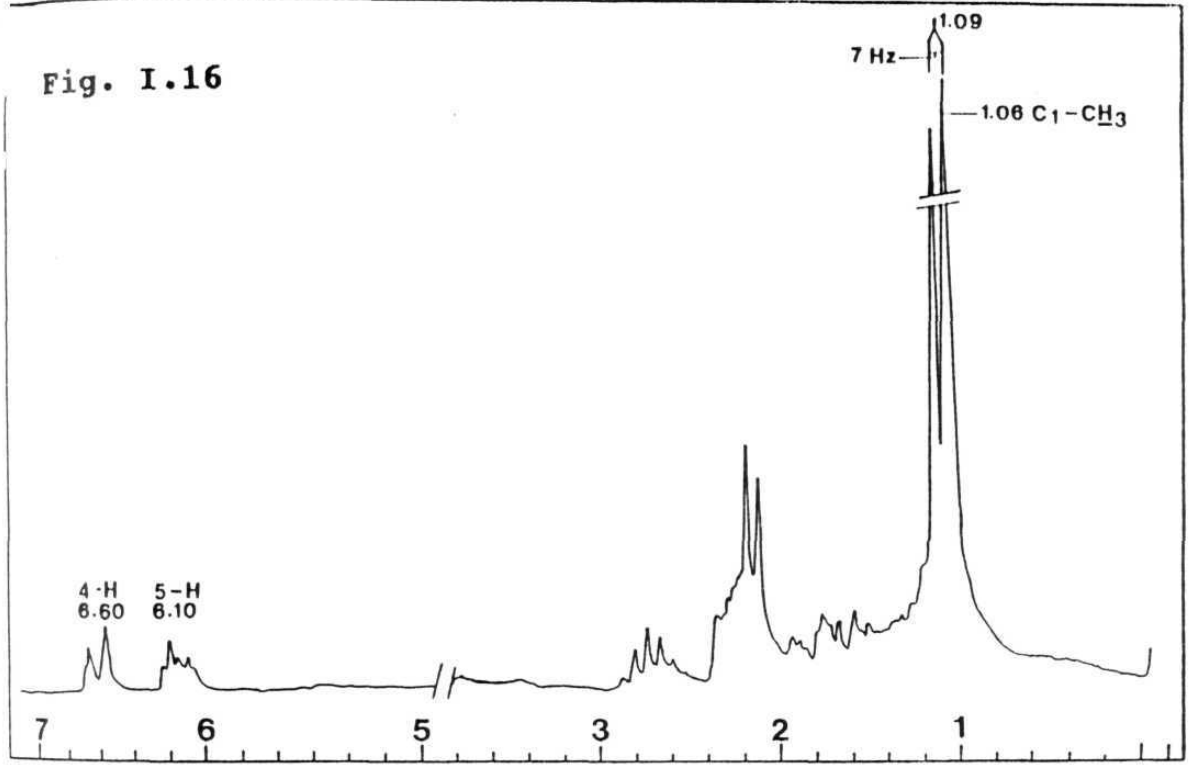
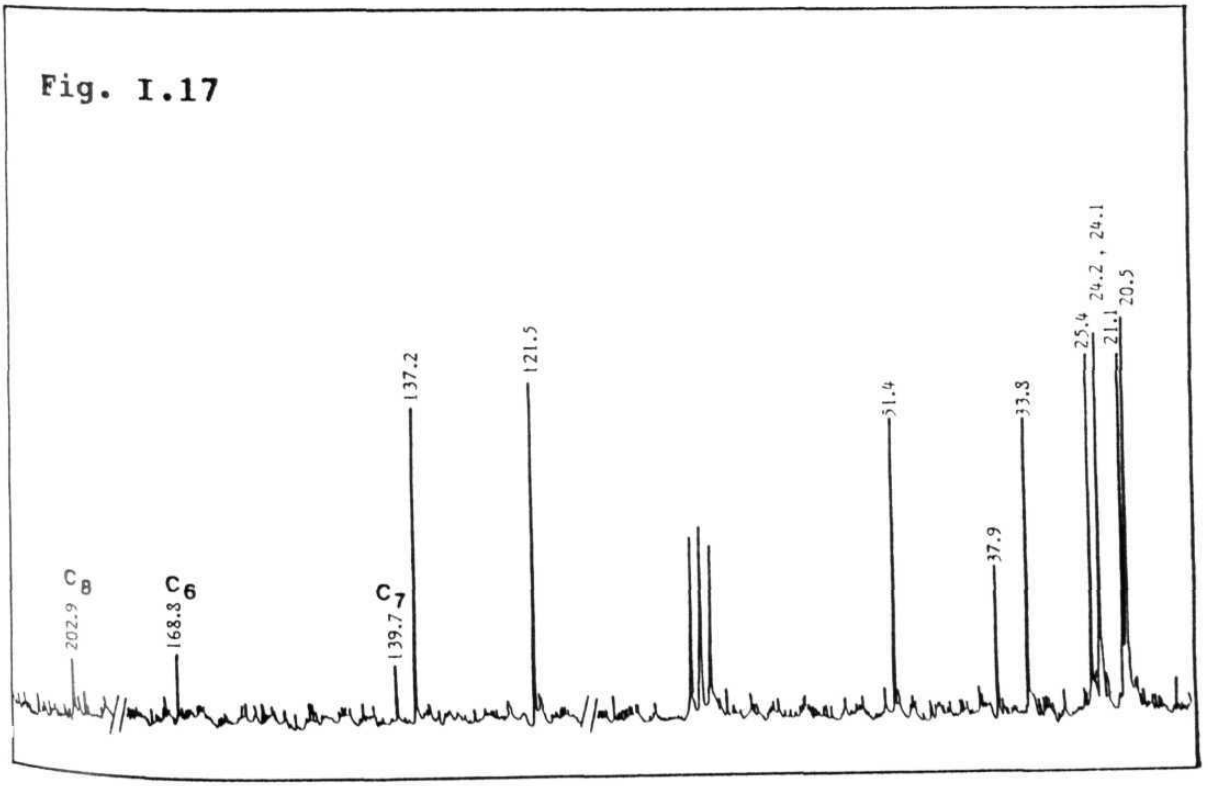


Fig. I.17



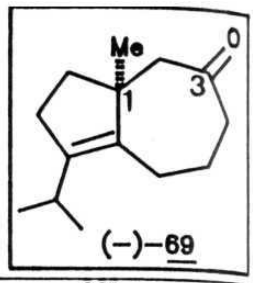


Fig. I.18

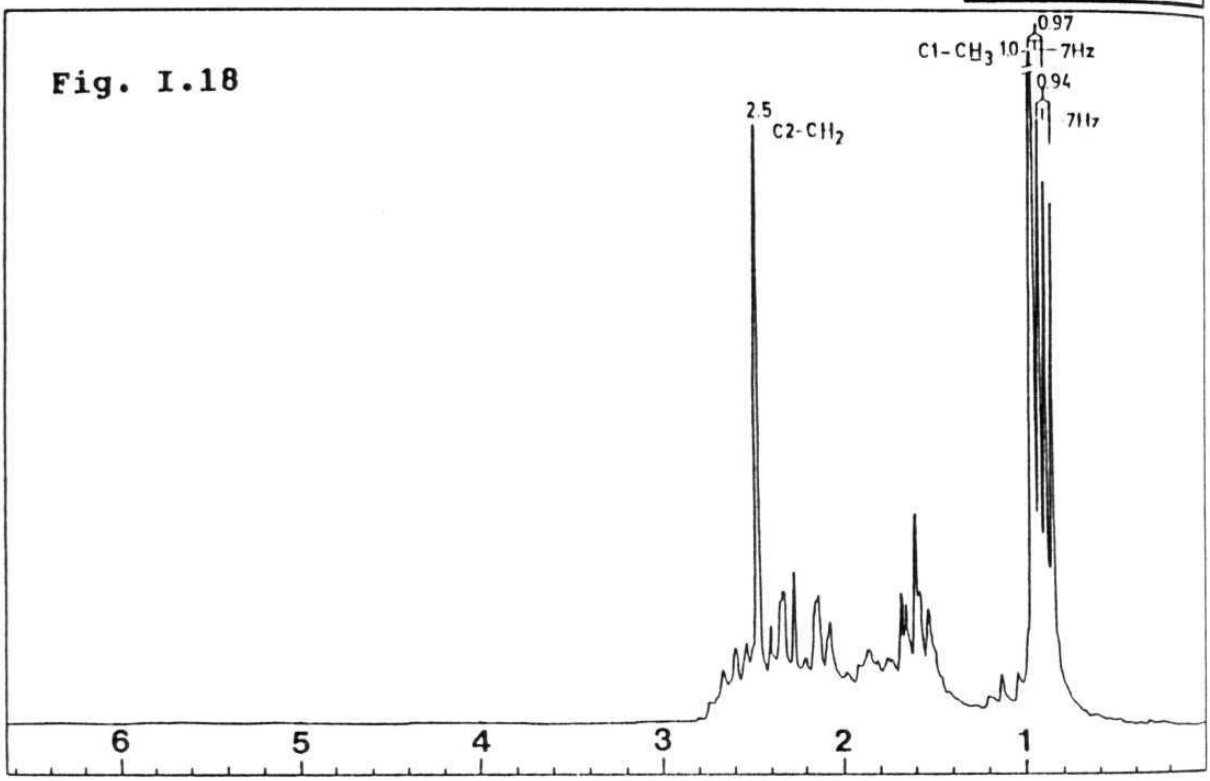
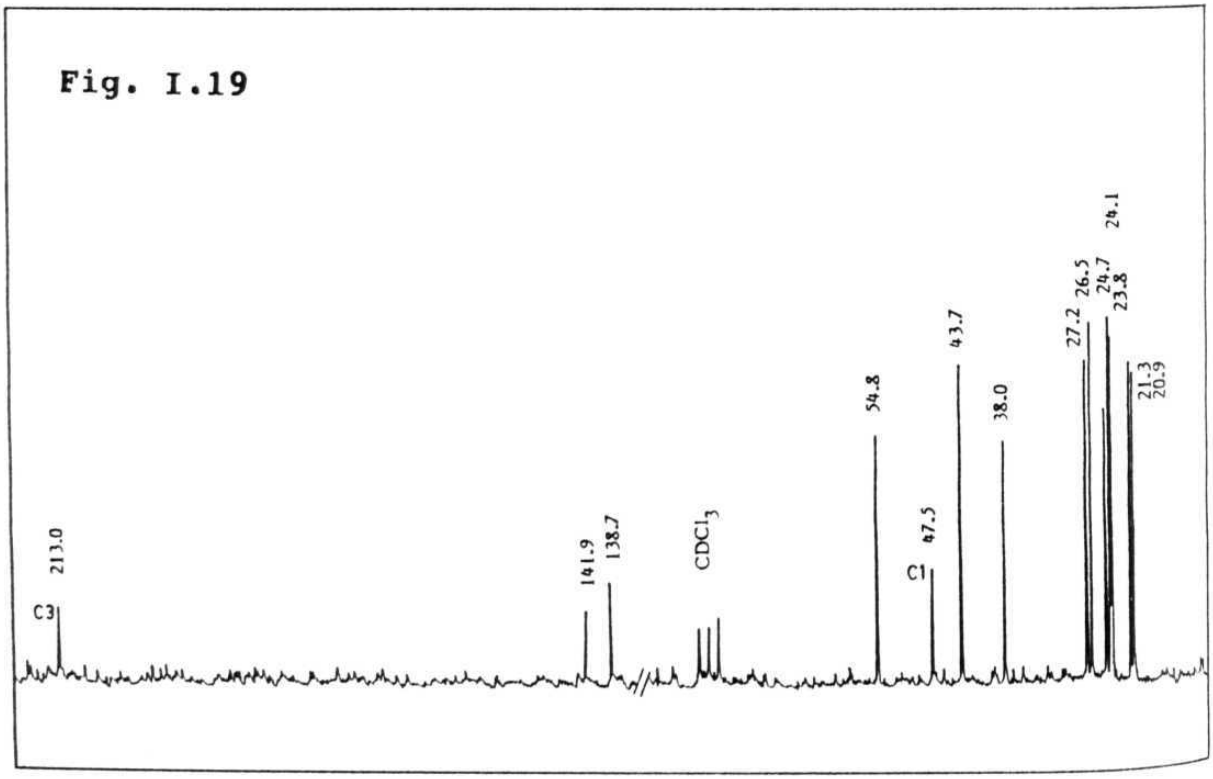
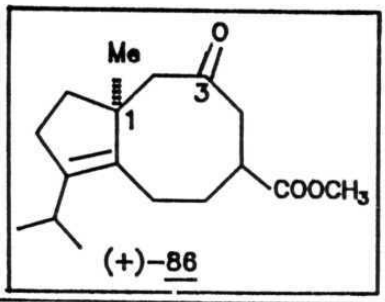


Fig. I.19





(+)-86

Fig. I.20

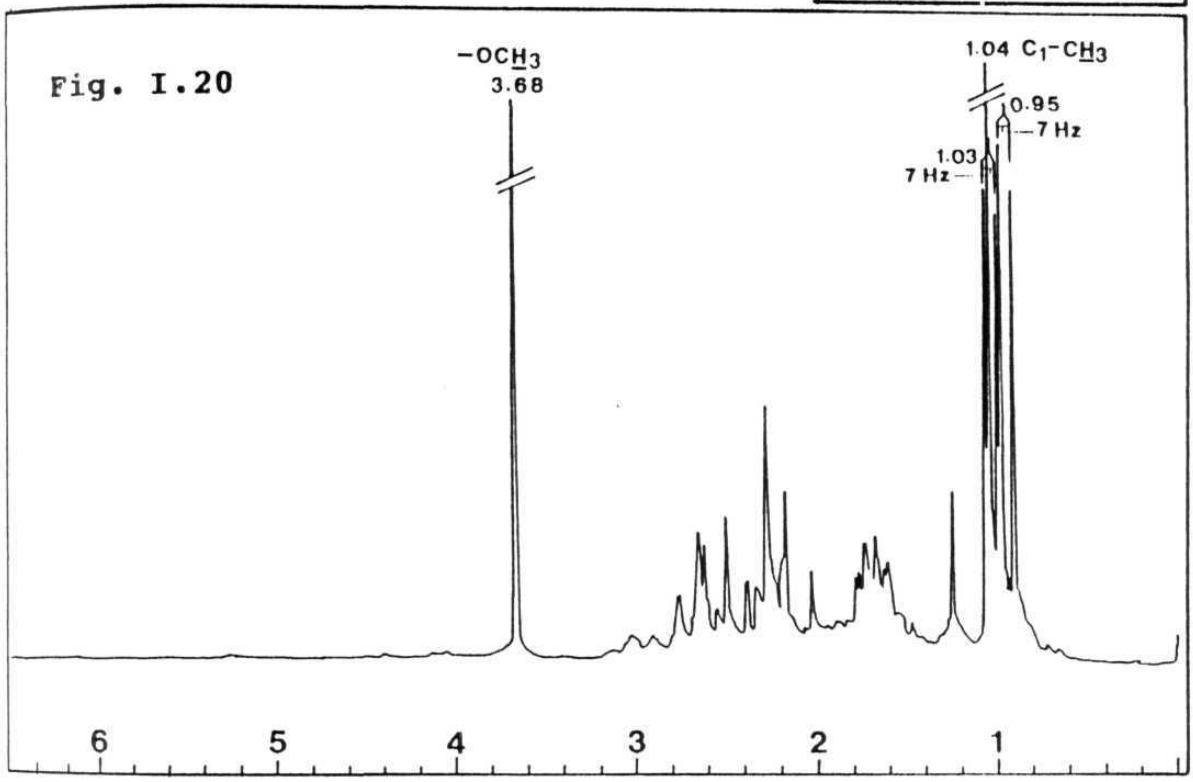
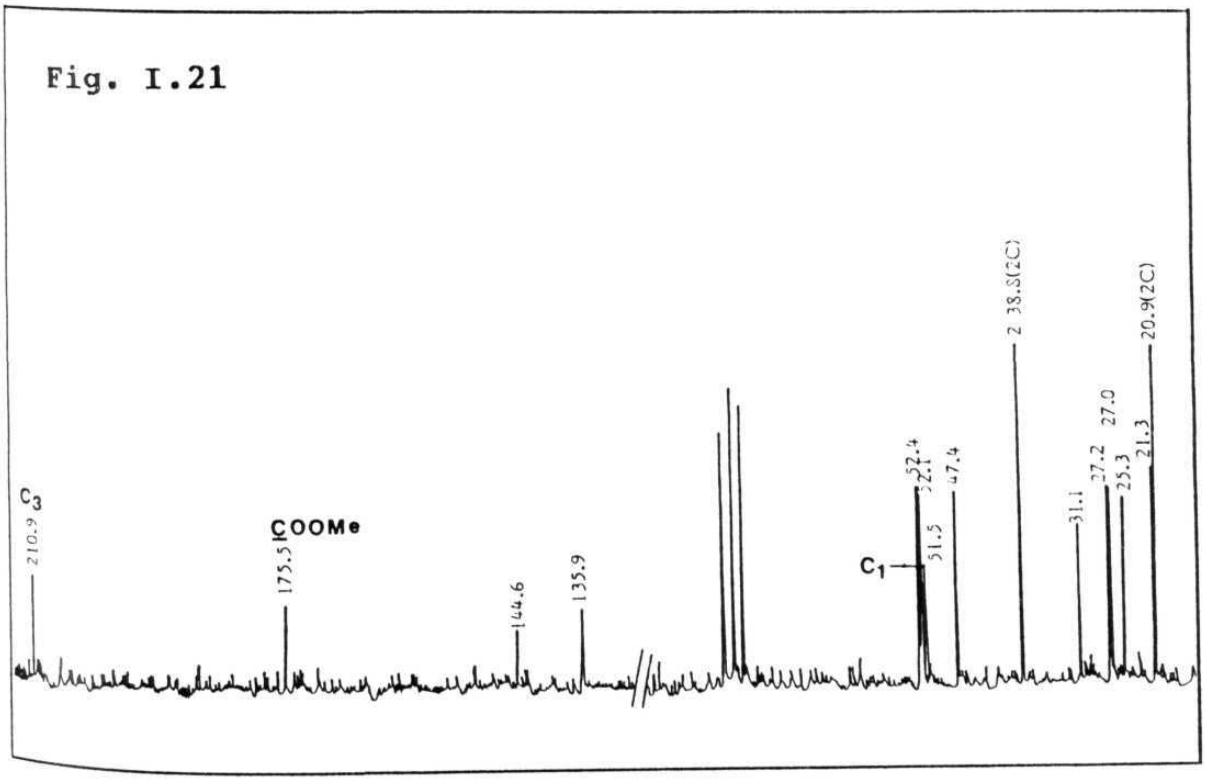


Fig. I.21



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Chapter 2

A New Cyclopentenone Annulation Protocol: Total Synthesis of Novel Triquinane Sesquiterpene (-)-Ceratopicanol

II.1. **ABSTRACT:**

The first enantioselective total synthesis of the novel triquinane sesquiterpene (-)-Ceratopicanol **4** from R-(+)-limonene has been achieved and the absolute configuration of the natural product (+)-ceratopicanol **4** established. The two key steps involved in the construction of the novel linear triquinane skeleton from R-(+)-limonene were a) the stereoselective restructuring of (+)-limonene into the chiral synthon (-)-**19** and its further elaboration into diquinane (-)-**20a**, utilising the isopropenyl group of limonene as an internal, disposable chiral director and b) annulation of 5,5-dimethyl cyclopentane moiety on to the diquinane (-)-**20a** via an acid catalysed rearrangement of spirolactones (-)-**42a** and (-)-**42b**. In practical terms, the monocyclic ester synthon (-)-**19** from R-(+)-limonene was elaborated to the α-diazo ketone **29**, which upon brief exposure to $BF_3.Et_2O$, furnished the diquinane derivative (-)-**20a** in which the two vicinal quaternary centres were correctly installed in cis-fashion.

For the construction of the third cyclopentane ring on the diquinane (-)-**20a**, a new annulation protocol of general utility was developed. This involved Barbier-type addition of 3-lithio-2,2-dimethylpropyl tert-butyldimethylsilyl ether to the diquinane 20a,b to furnish **36**. Deprotection of the TBDMS group and cleavage of the isopropylidine group in **36** employing ozonolysis gave keto-diols (-)-**25a,b**. Oxidation of (-)-**25a,b**, with tetra-n-propylammonium perruthenate (TPAP) led to the spiro-lactones

(-)-**42a,b**, respectively. On exposure to P_2O_5-methanesulphonic acid milieu, spiro-lactones (-)-**42a,b** rearranged to the regioisomeric linear triquinane ene-diones (-)-**43a,b** in fair yield. The generality of this short dimethylcyclopentane annulation methodology has been demonstrated through the preparation of bicyclic enones **63a**, **63b**, and **63c** from cyclopentanone, cyclohexanone and cyclooctanone, respectively. Tricyclic ketone **60d** was similarly annulated to the tetracyclic enone **63d**, **Table II.1.**

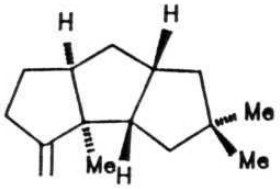
Chemo- and stereoselective reduction of C_9-carbonyl group in the triquinane regioisomer (-)-**43a** with $NaBH_4$ obtained above led to the endo-hydroxy enone (-)-**64**. Li-liq.NH_3 reduction of the enone moiety in (-)-**64** led to the desired cis-anti-cis triquinane diol (+)-**65**. The diacetate (+)-**66** of diol (+)-65 underwent preferential reductive deacetoxylation of the sterically more accessible C_3-exo-acetoxy group in Na-HMPA-t-BuOH milieu to furnish (-)-Ceratopicanol **4** which was found identical (400 MHz ^1H NMR) with the natural product. Our synthesis of (-)-**4** established absolute stereochemistry of natural ceratopicanol as (+)-**4**.

II.2. OBJECTIVE:

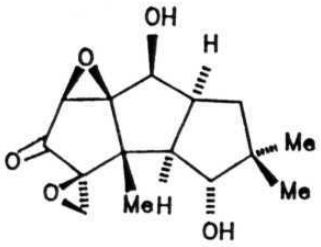
The abundance of terpenoid natural products in Nature with great diversity in their molecular architecture has made terpene research an exciting field of study. Sesquiterpenes , biogenetically derived from farnesyl pyrophosphate, are assembled in monocyclic, bicyclic, tricyclic and even tetracyclic structures containing small, medium and large rings with wide range of functionalities. Among these diverse carbocyclic assemblies, those containing fused five membered rings, generally referred to as polyquinanes, have received a great deal of attention in the 1980-90 period. Some of the polyquinane natural products that have been isolated and synthesised in the recent past are indicated in **Chart II.1**[1-13]. The extent of synthetic activity in this area can be gauged from the appearance of a number of reviews[14] and a monograph[15] on the subject during the past decade.

In our research group, we have a long-standing and on-going research interest in the synthesis of polyquinane natural products. These endeavours have culminated in the synthesis of (±)-hirsutene **1**[16a,b], (±)-coriolin **2**[16b,c], (±)-capnellene **3**[16b,d] and the framework of diterpene crinipellin-A **12**[16e,f] employing a photo-thermal metathesis methodology[17]. Concurrent efforts have also led to the synthesis of (±)-modhephene **9**[18a] and descarboxyquadrone[18b], a biologically active derivative of quadrone **10**, employing an oxa-di-π-methane rearrangement protocol. In addition, transannular cyclisation based strategies have been evolved for the synthesis of angular triquinane sesqui-

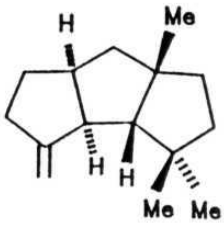
Chart II.1



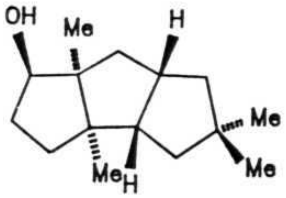
Hirsutene 1[1,16a,b]



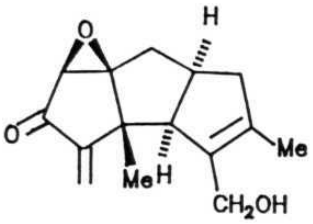
Coriolin 2[2,16b,c]



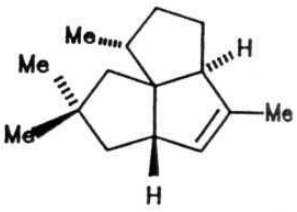
Capnellene 3[3,16b,d]



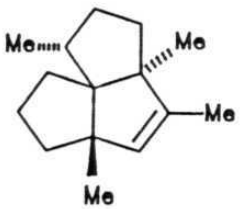
(+)–Ceratopicanol 4[4,22]



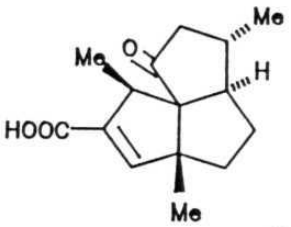
Pleurotellol 5[5]



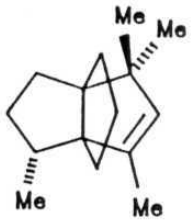
Pentalenene 6[6,19a,b]



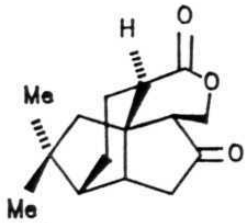
Isocomene 7[7]



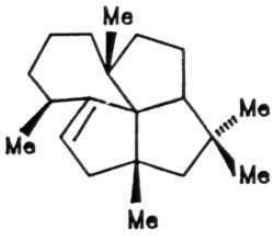
Subergorgic acid 8[8]



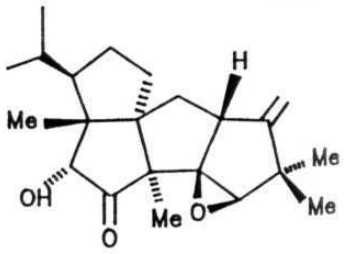
Modhephene 9[9,18a]



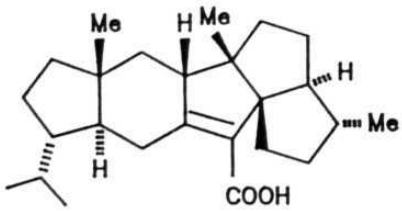
Quadrone 10[10]



Laurenene 11[11]



Crinipellin–A 12[12,16e,f]



Retigeranic acid 13[13]

terpene (±)-pentalenene **6**[19a,b] and the skeleton of diterpene laurenene **11**[19c].

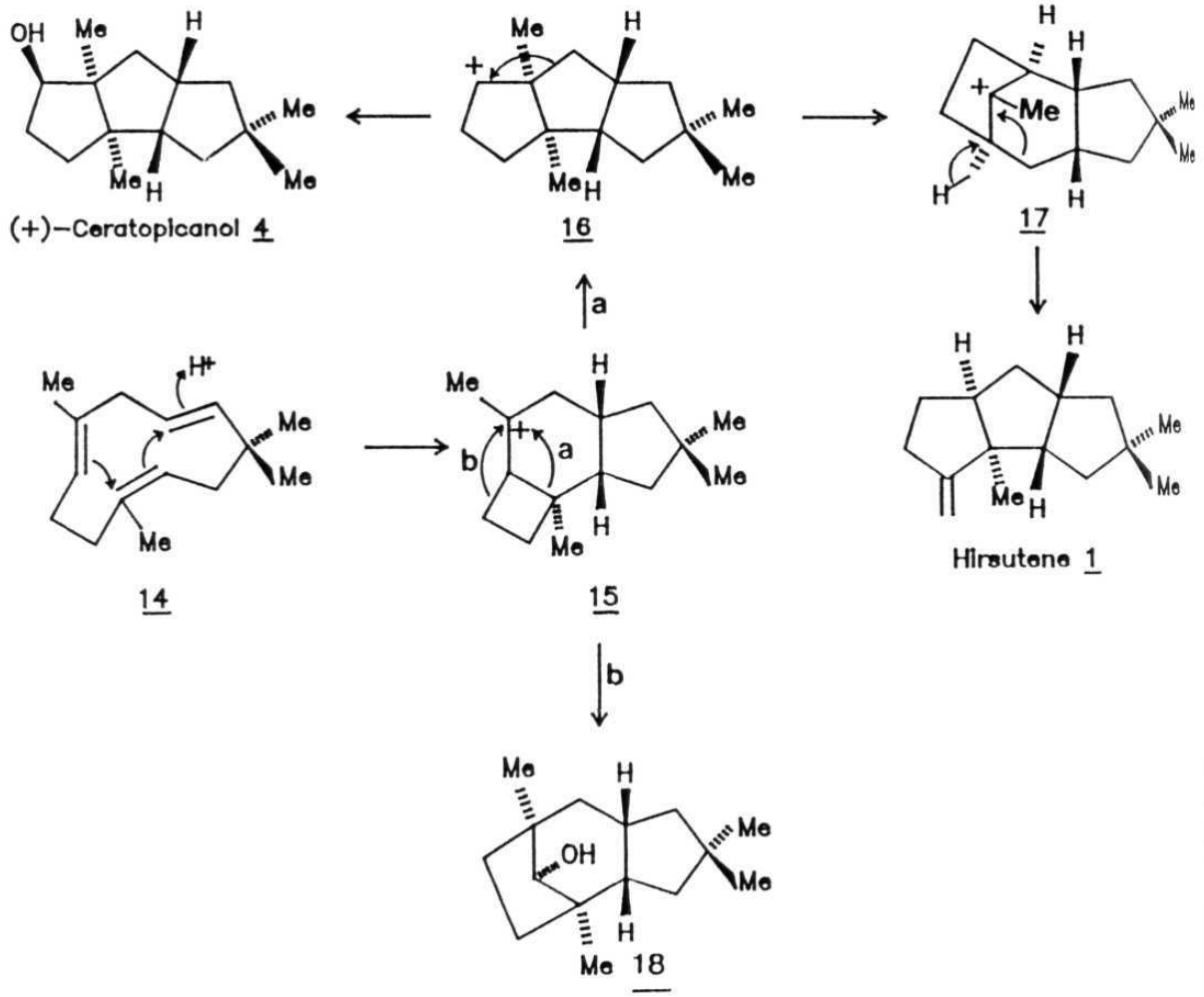
All these and related synthetic efforts, however, only led to racemic compounds and we were on a look-out for an opportunity to develop chiral syntheses of polyquinane natural products. The appearance of a report on the isolation of a novel $C_{15}H_{26}O$ sesquiterpene (+)-ceratopicanol **4** from the agar cultures of the ascomycete Ceratocystis piceae Ha 4/82 in 1988 by Hanssen and Abraham[4] provided new impetus for synthetic efforts in this area. (+)-Ceratopicanol **4** besides possessing the cis-anti-cis fused linear triquinane framework, has two adjacent bridgehead quaternary centres bearing methyl groups. The new carbocyclic skeleton of (+)-**4** has in all five stereogenic centres C_1, C_2, C_6, C_8 and C_9, all of them contiguous and the lone hydroxyl functionality has the less stable and hindered endo- stereochemistry.

The stereostructure of (+)-**4** was deduced largely on the basis of 2D NMR studies, biogenetic considerations (a closely related compound **18** co-occurs with it) and intuition. The study was carried out with only 1.6 mg of the natural product! It appeared to us to be one of the cases, where the natural product structure needed to be further confirmed by total synthesis. In addition, the issue of absolute stereochemistry of the natural product had to be resolved.

An interesting feature of (+)-**4** is its biogenesis. Its formation through the capture of intermediate ceratopicanyl cation **16** completes the biosynthetic cycle from humulene **14** to

hirsutene 1, Scheme II.1. Earlier, Comer and co-workers[20] had postulated the intermediacy of the ceratopicanyl cation 16 in the biosynthesis of the hirsutene based sesquiterpenoids. Feline

Scheme II.1



and Mellow[21] confirmed this proposal by means of ^{13}C labeling pattern in hirsutic acid C. Thus, cyclisation of humulene furnishes the protoilludyl cation 15, which further rearranges to 16, the precursor of ceratopicanol. Alternately, 16 can further rearrange to 17 enroute to hirsutene 1.

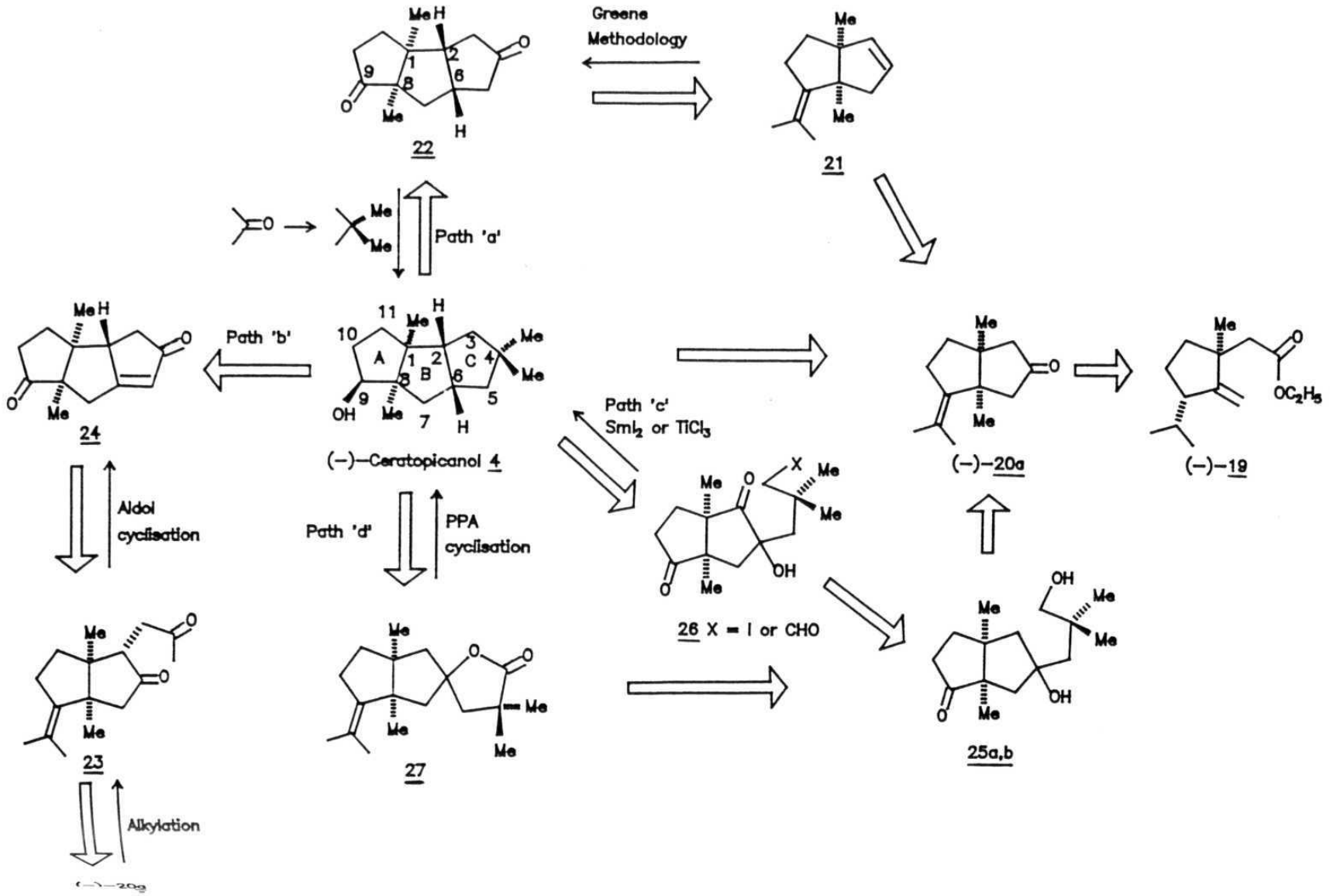
Based on the above considerations, (+)-**4** held substantial attraction and challenge as an objective for synthetic efforts. In this chapter of the thesis, we describe the first synthesis of (-)-ceratopicanol **4**[22], the enantiomer of the natural product (+)-ceratopicanol, from R-(+)-limonene *via* the C_{12}-chiron (-)-**19**. Synthesis of (-)-**19** has been detailed in the first chapter.

II.3. SYNTHETIC STUDIES:

To chart-out a strategy for the synthesis of ceratopicanol **4**, it was considered useful to carry out a retrosynthetic analysis that would enable identification of serviceable advanced precursors, **Scheme II.2**. In the present context, an advanced precursor having diquinane moiety with pre-installed vicinal quaternary centres and readily accessible from R-(+)-limonene derived C_{12} chiron (-)-**19** would be most appropriate. In the previous chapter, we have already outlined the synthesis of a functionalised diquinane (-)-**20a** from (-)-**19** in a short sequence (Scheme **I.7**). This diquinane (-)-**20a** appeared to be eminently suited as it had a carbonyl group in ring B, strategically positioned for the annulation of the third five membered ring. In addition, ring **A** in (-)-**20a** had an isopropylidine moiety as a masked carbonyl equivalent , which could be eventually operated upon to generate the hydroxyl group of ceratopicanol **4**.

In the retrosynthetic theme depicted in **Scheme II.2** are shown various pathways through which ceratopicanol can be reduced to the diquinane (-)-**20a**. Also shown are the steps through which

Scheme II.2


Greene
Methodology
22
21
Path 'a'
Path 'b'
Path 'c'
SmI2 or TiCl3
Path 'd'
PPA
cyclisation
Aldol
cyclisation
Alkylation
24
(−)−Ceratopicanol 4
23
27
26 X = I or CHO
25a,b
(−)−20a
(−)−19

the precursors can be reconstituted to the triquinane framework of the natural product. Thus, through path 'a' ring C can be annulated on the olefin **21** through Greene methodology[23] to furnish **22**. gem-Dimethylation of the carbonyl group in **22** can deliver the desired C_{15}-framework. Alternately, the annulation can be performed via aldol cyclisation **23** ⟶ **24** followed by carbonyl group to gem-dimethyl transformation, path 'b'. In another approach (path 'c'), cyclopentannulation could be accomplished through addition to the carbonyl group to give **26** which could be cyclised via SmI_2[24] or $TiCl_3$ (McMurry coupling)[25] to deliver ring C. The last pathway 'd' that we considered relies on γ-lactone **27** which could be cyclised with polyphosphoric acid[26] to generate the C ring. The advantage of the approaches via **26** and **27** is that the gem-dimethyl group is already in position, **Scheme II.2.**

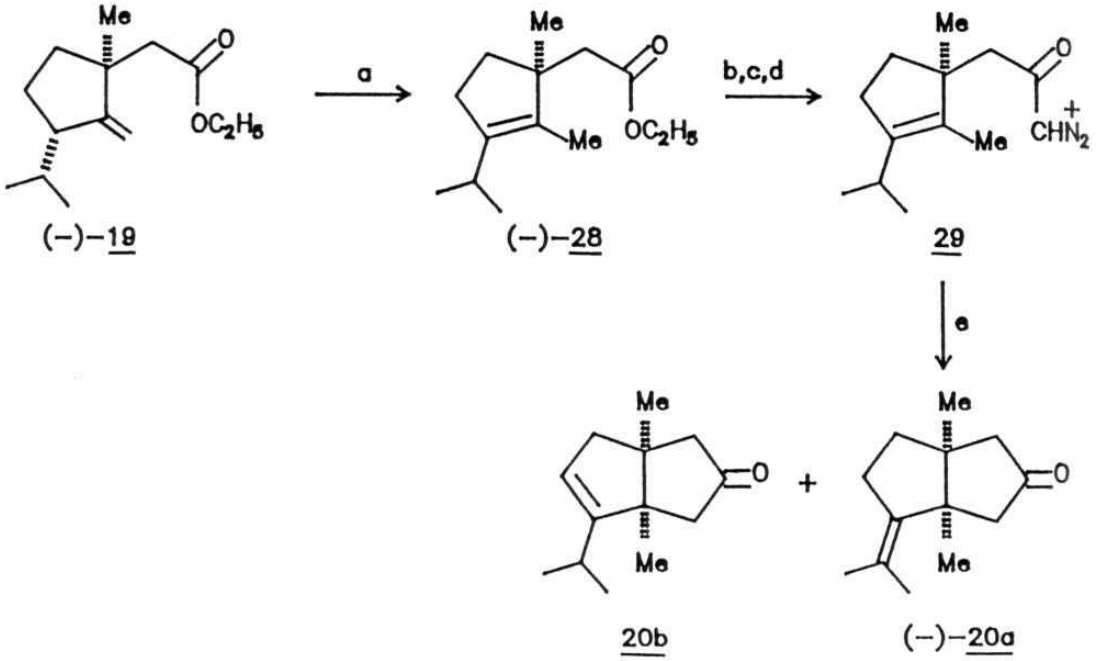
Among the options considered above, we preferred pathways 'a' and 'd' as they appeared shorter and more practical. The first task in this context was to have plentiful access to the diquinane **(-)-20a.**

II.3.1. Assembly of Diquinane System and Cyclopentannulation Studies:

In the previous chapter, elaboration of the C_{12}-chiron to a diquinane has been outlined. To briefly recapitulate, the ester **(-)-19** was isomerised to **(-)-28** and transformed to the α-diazo methyl ketone **29.** Lewis acid catalysed diazo ketone-olefin cyclisation[27] led to the diquinanes **20a,b** (9:1) in 73% yield,

Scheme II.3. Assured of the supply of (-)-20a, we turned our attention to the annulation processes.

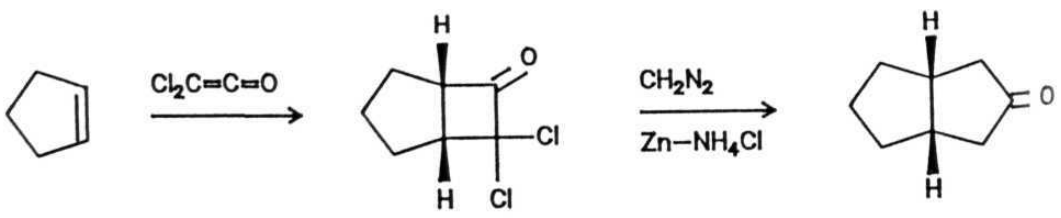
Scheme II.3



Reagents and yields: (a) $BF_3.Et_2O$, DCM, RT, 16 h, 82%;(b) 5% aq. NaOH-MeOH, 80°C, 3 h; (c) $(COCl)_2$-py, DCM, RT, 5 h; (d)CH_2N_2, ether, 5°C, 16 h, (68% from 28) (e) $BF_3.Et_2O$, DCM, RT, 5 min, 73%;

To begin with, the path'a' was explored and therefore attempts were made to prepare the olefin 21 or equivalent to setup the Greene cyclopentannulation methodology[23] as shown in Scheme II.4.

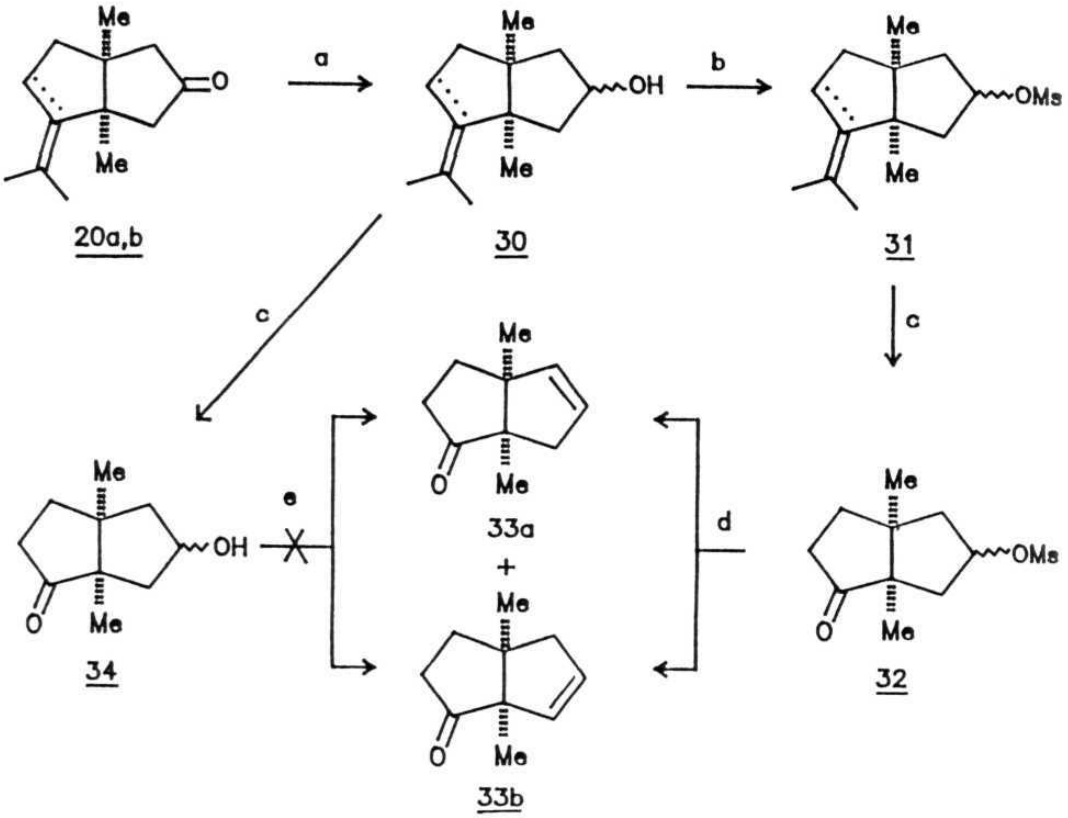
Scheme II.4



According to this protocol, the triquinane **22** could be synthesised *via* dichloroketene addition to the appropriate cyclopentene precursor like **21** followed by regioselective ring expansion with diazomethane and reductive dehalogenation. To reckon with the stereochemical problems at C_2 and C_6 carbon centres, it was predicted that the dichloroketene would attack the folded diquinane olefin from the less hindered convex face in *cis*-fashion to furnish the requisite *cis*-*anti*-*cis* stereochemistry. Functional group adjustment and the transformation of carbonyl group into *gem*-dimethyl group would produce the natural product.

The synthetic plan was put to practice by reducing the carbonyl group in **20a,b** with $NaBH_4$ to furnish a diastereomeric mixture of alcohols **30** in 96% yield. The alcohol mixture **30** was converted to the corresponding mesylates **31** on treatment with methanesulphonyl chloride in pyridine. The isopropylidine group in **31** was now removed *via* ozonolysis to furnish the keto-mesylates **32** in 56% yield, **Scheme II.5**. The IR spectrum of **32** showed a strong absorption at 1740 cm^{-1} due to a cyclopentanone carbonyl group. The diastereomeric nature of the product **32** became apparent from the appearance of four singlets at δ 1.20, 1.08, 1.04, and 0.96, corresponding to the quaternary methyl groups. There was a lone resonance at δ 5.00 due to the proton attached to the mesylate group. The almost equal intensity of the methyl signals in **32** indicated that the *exo*- and *endo*-epimers were present in approximately 1:1 ratio. This mixture was not amenable to chromatographic separation and therefore used as such for further studies. Attempts to directly eliminate the mesylate

Scheme II.5



Reagents and yields: (a) $NaBH_4$, MeOH, 0°C, 0.5 h, 96%; (b) Py-MsCl, DCM, RT, 30 min, 93% (c) O_3, MeOH, Me_2S, -78°C, 56%; (d) HMPA-NaI, 110°C, 2 h, 26%. (e) Burgess salt, Benzene, Δ.

group in 32 were unsuccessful despite considerable variation in the reaction conditions and bases (K^{+}-t-BuO, DBU etc.). Recourse was therefore taken to the NaI-HMPA combination [28], which had been successfully employed in our group[29] for a one pot displacement-elimination sequence on mesylates. Thus, exposure of 32 to NaI in HMPA at 100°C furnished 33 a,b as a mixture of regioisomers in 26% yield. The regioisomeric nature of enone mixture 33a,b was revealed by its ^{1}H NMR spectrum which exhibited olefinic proton multiplet between δ 5.76-5.28 and four

quaternary methyls at δ 1.12, 1.08, 1.02, 1.00. All attempts to either separate the double bond isomers or improve the yield of the mesylate elimination reaction failed. Therefore, an alternate sequence was explored. The diastereomeric mixture of the alcohol **34**, obtained *via* ozonolysis of **30** was subjected to dehydration. However, neither the use of conventional dehydrating reagents ($SOCl_2$, p-TSA etc) nor the Burgess salt[30] proved effective in the elimination of the hydroxy group. In the case of Burgess salt, only the starting material was recovered. Since all our endeavours to procure the enone **33a** in quantities were unfruitful, this cyclopentannulation protocol was aborted.

At this stage, an attempt was also made to execute the path 'b'. This strategy involved regioselective alkylation at the α-position in (-)-**20a** with allyl bromide followed by Wacker-type oxidation[31] and subsequent intramolecular aldol condensation to afford the triquinane intermediate **24**. Further functional group manipulations were expected to lead to the target structure. It was also expected that the alkylation of (-)-**20a** would proceed preferentially from the less hindered *exo*-face and deliver the correct *cis*-*anti*-*cis* stereochemistry. However, it must be added that regiochemical difficulties were anticipated but we hoped to resolve them through separation at an appropriate stage.

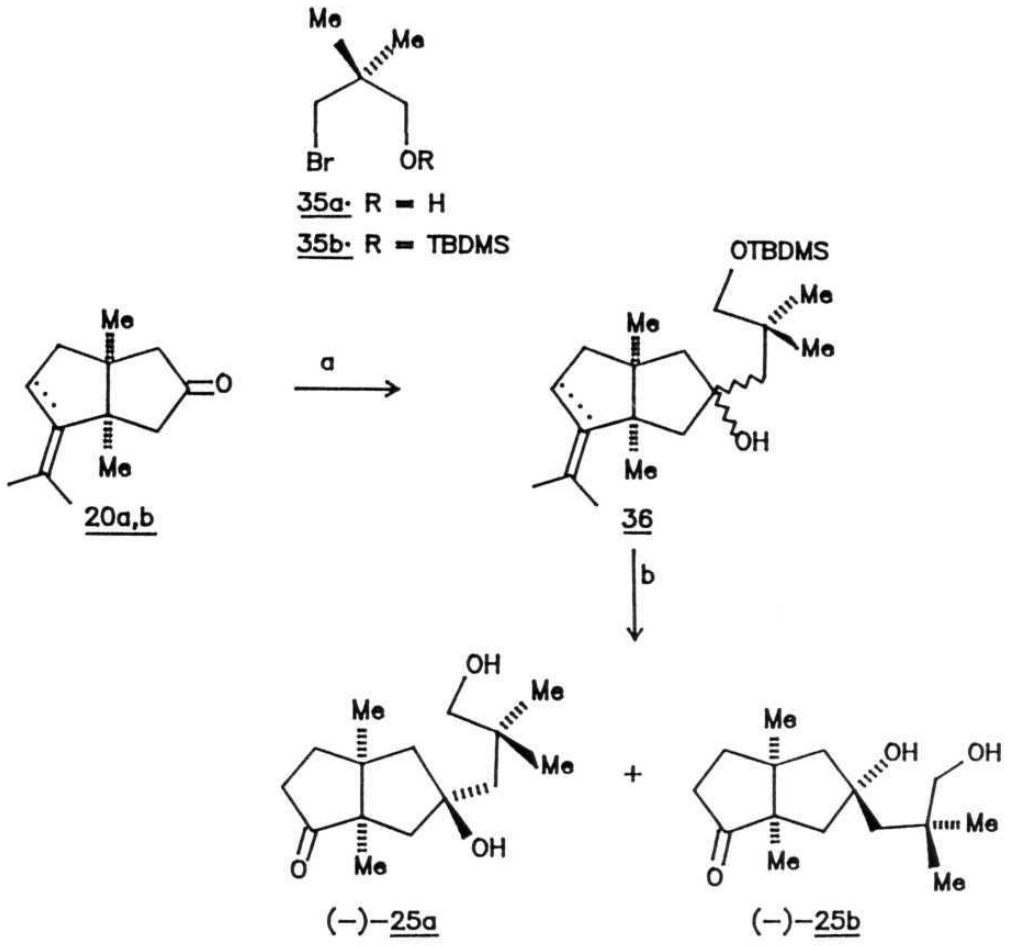
But this strategy also could not be pursued as the first key step itself, i.e., allylation of **20a,b** was not successful. The attempted allylation of **20a,b** under a variety of conditions gave intractable mixture of alkylated products in very poor yield. Both kinetic enolate (Li-hexamethyldisilazide,

-78°C, HMPA-THF and LDA, HMPA-THF, -78°C) as well as thermodynamic enolate (KH, NaH) generation and allyl bromide quenching were attempted. This failure to obtain the allylated product compelled us to abandon this approach also.

Consequently, we considered another possibility to assemble the cyclopentane ring with built-in gem-dimethyl group employing radical induced coupling (path 'c', **Scheme II.2**). This would require an intermediate **26** (x = I, -CHO etc.,) which could be obtained from enone (-)-**20a** employing a Barbier-type addition reaction with a proper alkyl side chain and functional group adjustments. This protocol is superior to other strategies in the sense that the gem-dimethyl group is already present in correct position. However, the disadvantage in this strategy is that functional group readjustment could pose considerable difficulties.

To implement the pathway 'c', 3-bromo-2,2-dimethyl-1-propanol **35a**[32] was chosen as the desired three carbon chain in which the gem-dimethyl group is disposed at correct position and which would eventually become the C_4-carbon centre of the natural product. Thus, Barbier type addition of 3-lithio-2,2-dimethylpropyl tert-butyldimethylsilyl ether[33] (generated from 3-bromo-2,2-dimethylpropyl tert-butyldimethylsilyl ether **35b** and lithium) to **20a,b** led to a 4:1 diastereomeric mixture of **36**, **Scheme II.6**. It was not considered necessary to separate the diastereomers at this stage. The isopropylidine moiety in **36** was disposed-off at this stage through ozonolysis and the TBDMS group in the product was deprotected with tetra-n-butylammonium

Scheme II.6



Reagents and yields: (a) Li, 3-Bromo-2,2-dimethylpropyl tert-butyldimethylsilyl ether, 15°C, 15 min, 57%; (b) O_3, MeOH, Me_2S, -78°C and $(n\text{-}Bu)_4N^+F^-$, 73%;

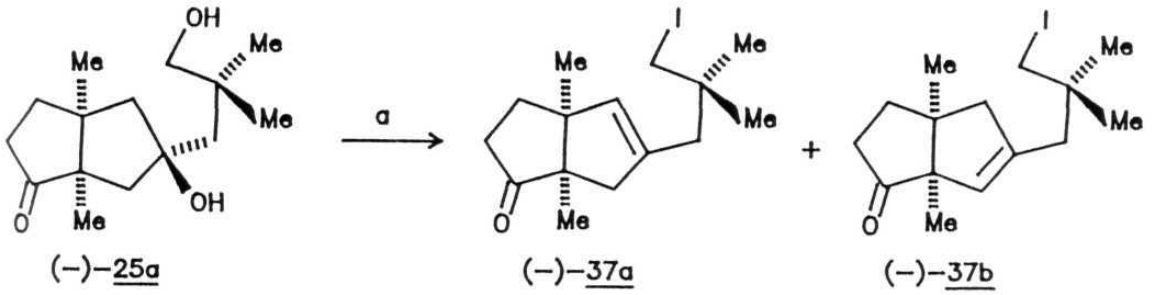
fluoride to yield the keto-diols (-)-25a and (-)-25b in 73% yield. The keto-diols (-)-25a,b were amenable to ready chromatographic separation and were fully characterised on the basis of their IR, ^1H and ^{13}C NMR spectral data. The IR spectrum of both (-)-25a and (-)-25b showed the presence of a hydroxyl group and a keto group. The ^1H NMR spectrum of (-)-25a (Fig. II.1)

exhibited the presence of a methylene group attached to a primary hydroxyl at δ 3.40 and three singlets corresponding to the four quaternary methyls at δ 1.24 (3H), 1.04 (3H), 0.96 (6H). The ^{13}C NMR spectrum (Fig. II.2) showed characteristic signals at δ 81.6, 71.6 due to two carbons attached to a tertiary and a primary hydroxyl groups and at δ 225.2 due to the cyclopentanone carbonyl group. The ^{1}H and ^{13}C NMR spectra of (-)-**25b** also displayed similar features. For example, the ^{1}H NMR spectrum (Fig. II. 3) showed characteristic signals at δ 3.30 (2H), 1.04 (3H), 0.92 (6H) and 0.84 (3H). The ^{13}C NMR spectrum (Fig. II.4) has signals at δ 227.1, 79.7 and 71.2. The assignment of stereochemistry to diols (-)-**25a,b** at the hydroxy-bearing centre is based on the reasonable assumption that the bulky neopentyl-like chain would undergo preferential exo-attack on the diquinane moiety **20a,b**. There is enough literature precedence for this assumption[34]. However, the stereochemistry at this centre is not really critical as it would be destroyed in the ensuing step to form a double bond.

Elaboration of (-)-**25a,b** to (-)-**26** for the coupling reaction envisaged in **path c**, required functional group adjustments. The tertiary hydroxyl group had to be eliminated and the resulting olefin refunctionalised to a carbonyl group. Similarly, the primary hydroxyl group needed to be transformed to the iodo or aldehyde functionality as in **26**. Keeping in mind, these projected transformations, the major diastereomeric keto-diol (-)-**25a** was reacted with in situ generated iodotrimethylsilane (TMSI, sodium iodide and chlorotrimethylsilane in acetonitrile). Two readily

separable regioisomeric iodo-olefins (-)-37a and (-)-37b (3:1) were obtained in 73% yield, **Scheme II.7.** The structures of iodo-olefins **(-)-37a,b** were assigned based on the ^{1}H and ^{13}C NMR spectral data. The ^{1}H NMR spectra of both (-)-37a (**Fig. II.5**) and (-)-37b (**Fig. II.7**) showed olefinic protons at δ 5.24 and 5.14, respectively. The ^{13}C NMR spectra (**Fig. II.6** and **Fig. II.8**) exhibited characteristic peaks at δ 226.2, 140.7, 137.7 and at

Scheme II.7

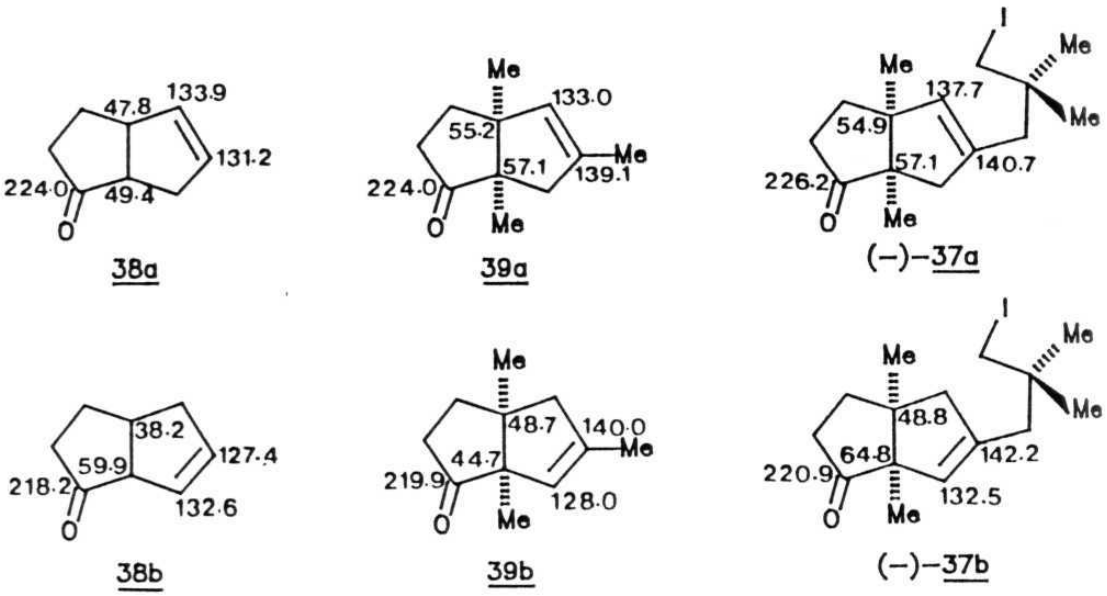


(-)-25a (-)-37a (-)-37b

Reagents and yields: (a) TMSCl-NaI, CH_3CN, 80°C, 2 h, 70%;

δ 220.9, 142.2, 132.5, respectively. The position of the double bond in **(-)-37a,b** was assigned based on the correlation of ^{13}C NMR spectral data with related known compounds, **Chart II.2.** The key evidence being the substantial shielding (~5-6 ppm) of the carbonyl resonance in the ^{13}C NMR spectrum when the double bond is proximal (i.e., β,γ-position). Thus, (-)-37b had its carbonyl resonance at δ 220.9 compared to 226.2 in (-)-37a. Also, the quaternary carbon centre which is both allylic and α to the carbonyl is strongly deshielded δ 64.8 in (-)-37b compared to δ 57.1 in (-)-37a, **Chart II.2.** Smaller but subtle changes in the olefinic ^{13}C resonances in (-)-37a,b also fully confirm this formulation.

Chart II.2

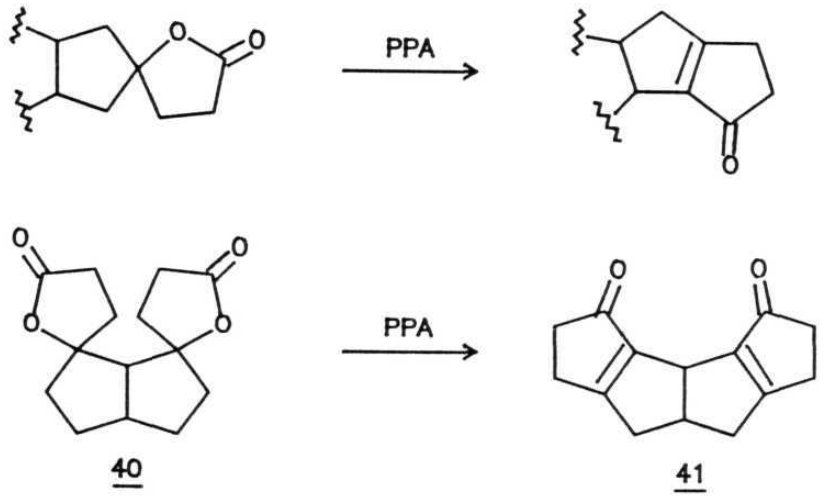


With the availability of (-)-37a,b, attention was turned towards the anti-Markownikoff-type functionalisation of the double bond in the desired isomer (-)-37a. Towards this end, hydroboration of (-)-37a, under different regimen, both with and without the protection of the carbonyl group was attempted. However, the results were disappointing and only small amount of hydroxyl bearing product was detected. Alternately, epoxidation of (-)-37a was also attempted in the hope that further Lewis acid catalysed rearrangement will deliver 26 (x= I). However, the epoxidation-Lewis acid catalysed rearrangement sequence could not be implemented in the desired fashion despite many attempts.

II.3.2. A New Cyclopentenone Annulation Protocol:

Attention was therefore turned to the last option, path 'd' of the **Scheme II.2.** There is ample precedence in the literature that γ-lactones can be readily rearranged to cyclopentenones on polyphosphoric acid treatment, **Scheme II.8**[25a]. More recently,

Scheme II.8



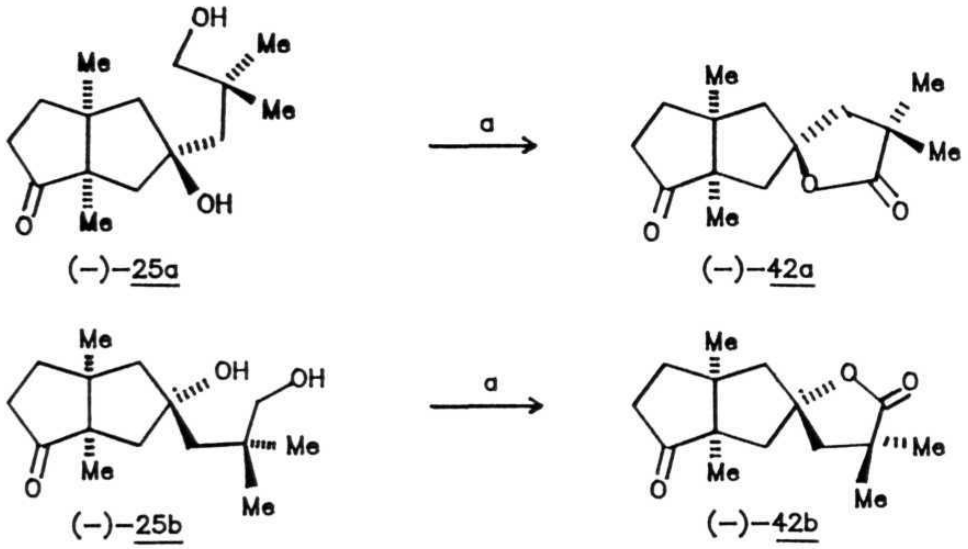
40 41

the use of P_2O_5-$MeSO_3H$ combination has been introduced as an efficacious combination for effecting this rearrangement[35]. In this context, the availability of keto-diols (-)25a and (-)-25b was very promising as each one of them could be oxidised to the corresponding spiro-lactone and subjected to rearrangement to a cyclopentenone moiety.

Consequently, keto-diol (-)-25a was subjected to oxidation with PCC and PDC in dichloromethane in the presence of molecular sieves. Formation of the desired spiro-lactone (-)-42a was observed but the reaction was far from clean. Recourse was

therefore taken to tetra-n-propylammonium perruthenate (TPAP), a recently introduced mild-oxidising agent for hydroxy compounds[36]. When the major keto-diol (-)-25a was oxidised with TPAP in the presence of NMMO, spiro-lactone (-)-42a was obtained in excellent (>90%) yield, **Scheme II.9**. The formulation of the spiro-

Scheme II.9



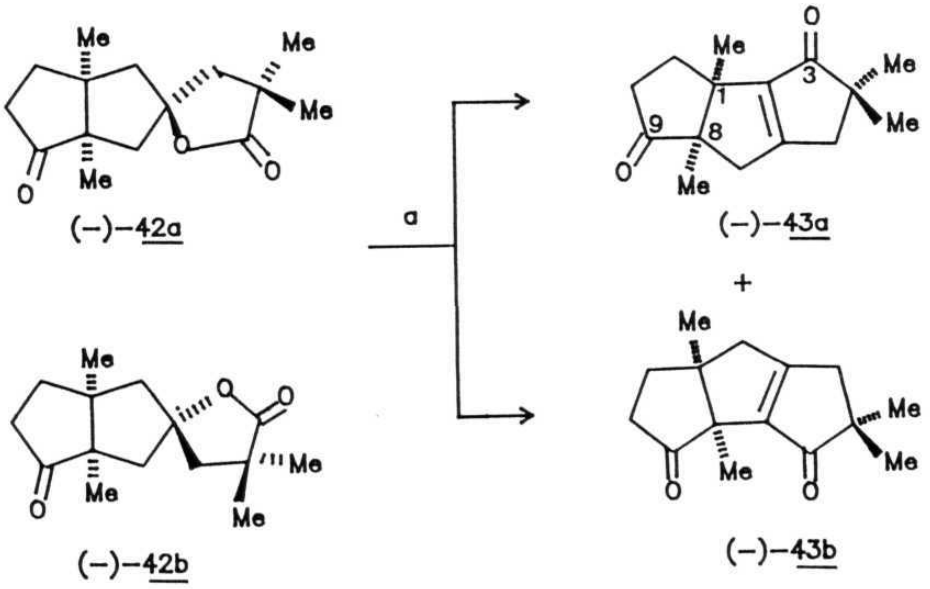
Reagents and yields: (a) TPAP-NMMO, 10%CH_3CN-DCM, RT, 40 min, 91%;

lactone (-)-42a was fully consonant with its IR, ^1H and ^{13}C NMR spectral data. The IR spectrum showed γ-lactone absorption at 1760 cm^{-1} and the ^1H NMR spectrum (Fig. II.9) exhibited the presence of four singlets at δ 1.24, 1.21, 1.18, 0.96 corresponding to four quaternary methyls. In particular, the ^{13}C NMR spectrum (Fig. II.10) had signals at δ 223.5, 181.7, 89.0 due to the cyclopentanone carbonyl, lactone carbonyl and the spiro quaternary carbon, respectively. Similarly, the minor

keto-diol (-)-25b on TPAP oxidation led to (-)-42b, whose ^{1}H and ^{13}C NMR spectral data (Fig. II.11 and Fig. II.12) were fully in agreement with the proposed structure.

Encouraged by the excellent yield obtained in the oxidation of (-)-25a,b, the key transformation of spiro-lactones (-)-42a,b to the corresponding triquinanes (-)-43a,b was attempted. For this purpose, the P_2O_5-$MeSO_3H$ reagent developed by Eaton et al[35] was preferred to the classical PPA cyclisation because of the experimental simplicity associated with the former. To our delight, the spiro-lactone (-)-42a underwent smooth rearrangement with P_2O_5-methanesulphonic acid reagent to furnish the C_{15}-triquinane regioisomers (-)-43a and (-)- 43b (2:1) in 70% yield, Scheme II.10. The major isomer (-)-43a had a strong absorption at 1695 cm^{-1} due to enone carbonyl group and at 1640 cm^{-1} due to

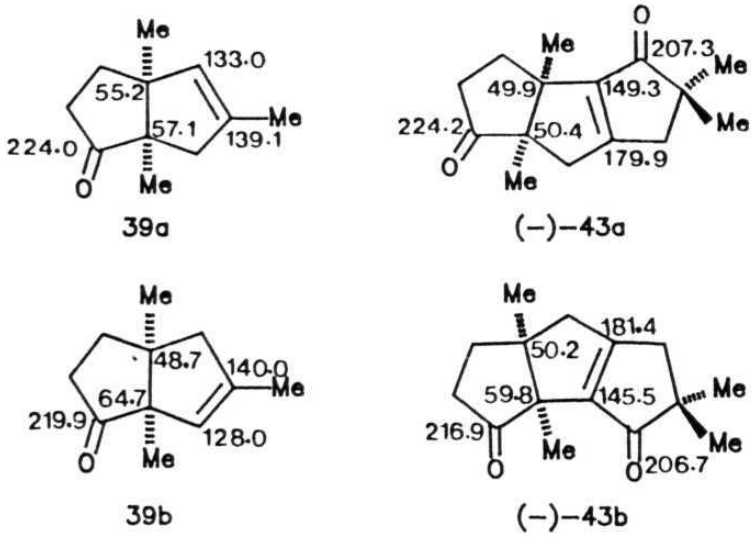
Scheme II.10



Reagents and yields: (a) $MeSO_3H$-P_2O_5, 80°C, 65 min, 70%;

tetra substituted double bond. The ^{13}C NMR spectrum (Fig. II.14) displayed signals at δ 224.2, 207.3, 179.9, and 149.3 due to cyclopentanone, cyclopentenone and tetrasubstituted olefinic carbons, respectively. The formulation of the other regioisomer (-)-43b is also consonant with its IR, ^{1}H NMR (Fig. II.15) and ^{13}C NMR (Fig. II.16) spectral data. The key evidence for differentiation between the regioisomers (-)-43a and (-)-43b was extracted from the ^{13}C NMR spectral data. Once again, the ^{13}C NMR resonance of carbonyl group in enone (-)-43b with proximal double bond showed considerable shielding (~δ 7 ppm) compared to (-)-43a with the distal double bond, see Chart II.3. Predictable

Chart II.3



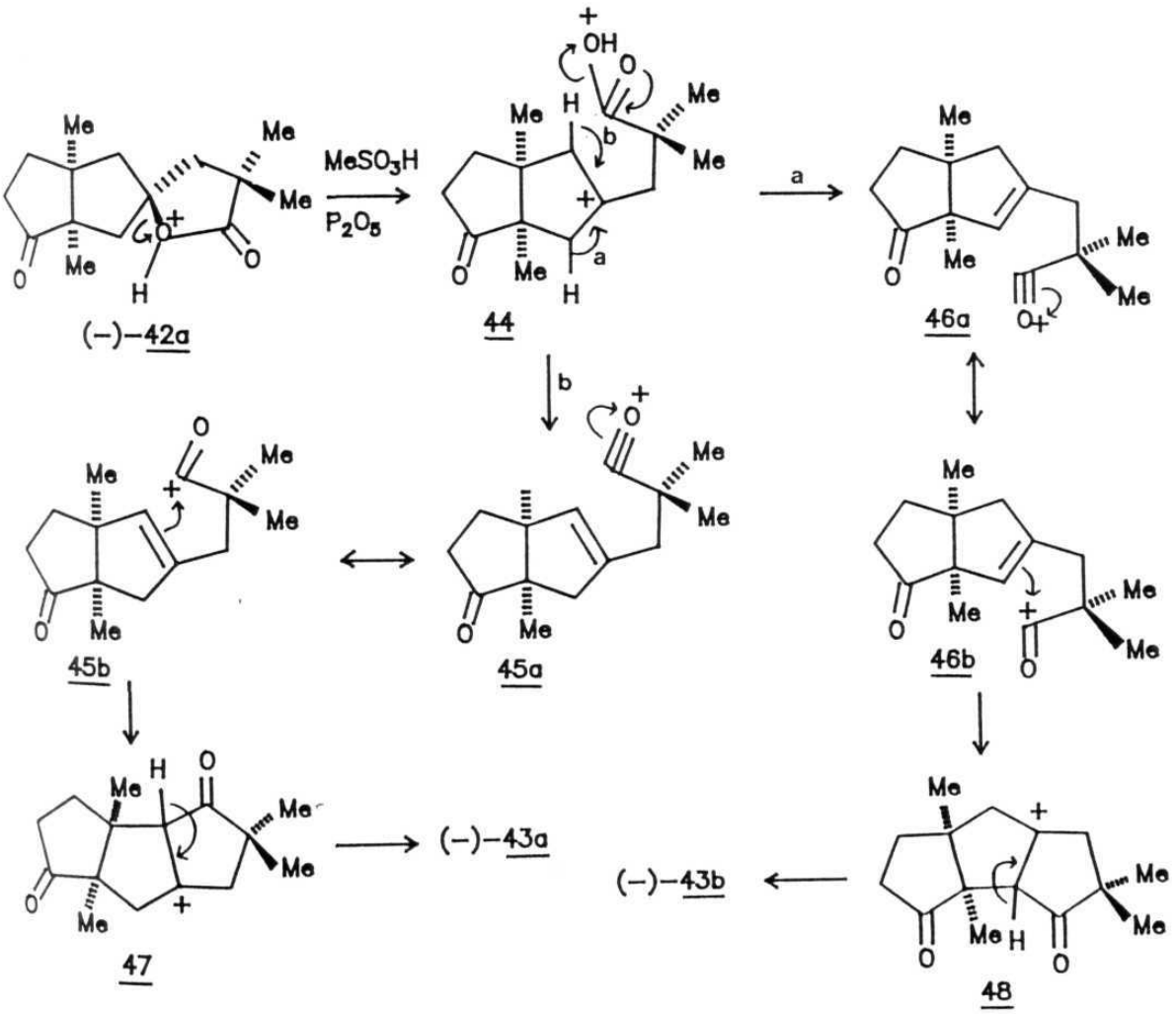
trend in the ^{13}C NMR resonances for the olefinic and quaternary carbons in 39a and 39b also supported the formulation of (-)-43a and (-)-43b.

Similarly, treatment of the minor, diastereomeric spiro-lactone (-)-42b with P_2O_5-methanesulphonic acid furnished the

same triquinane regioisomers (-)-43a and (-)-43b (2:1) in 70% yield. The separation and identification of the regioisomers was readily accomplished as in the case of (-)-42a.

The mechanism through which the γ-lactones rearrange to cyclopentenones is well understood and presented in Scheme II.11. Acid promoted opening of the spiro-lactone (-)-42a leads to the intermediate tertiary carbonium ion 44 which can lose proton from

Scheme II.11



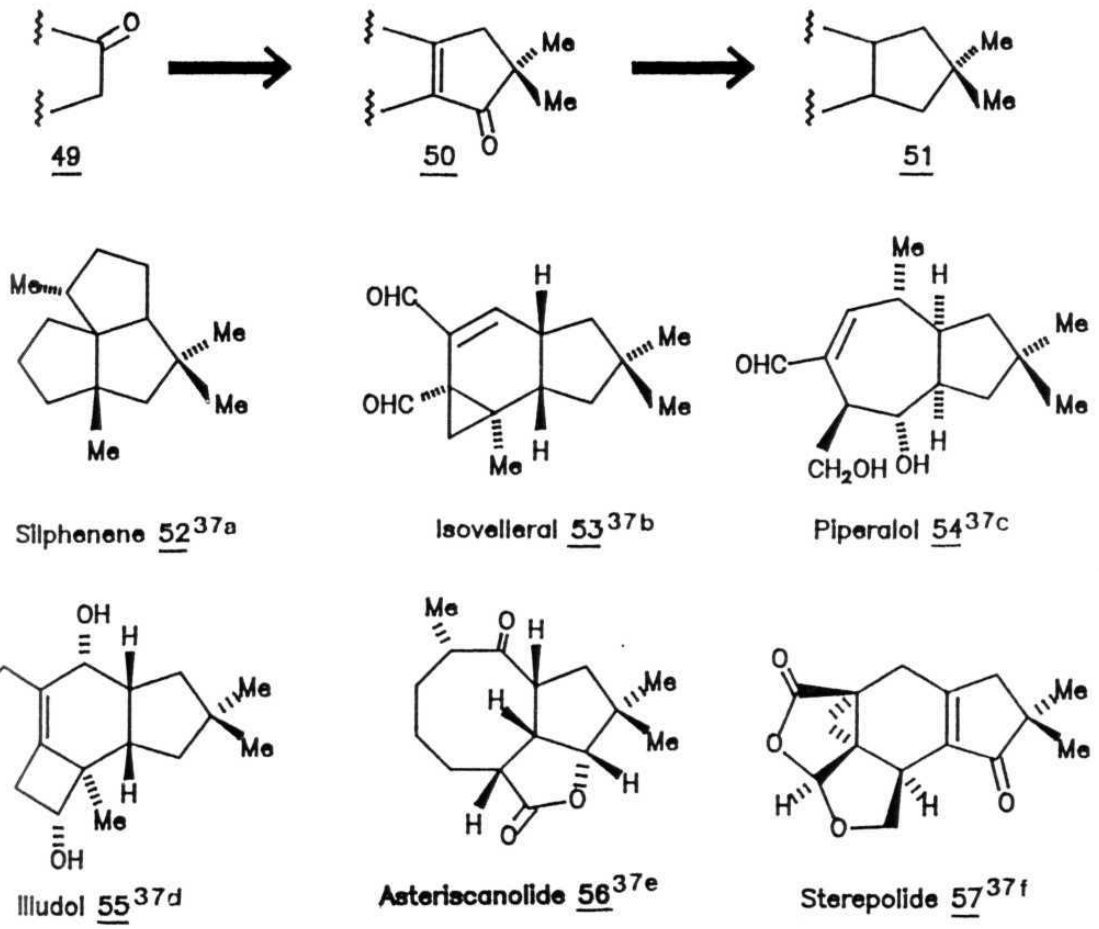
the two available positions to give **45a** and **46a**. The derived acylium ions **45b** and **46b** in turn cyclise to the triquinane carbonium ions **47** and **48**, respectively. Loss of proton from **47** and **48** leads to enones (-)-**43a** and (-)-**43b**, respectively. It is not immediately apparent to us why the olefin (-)-**45b** predominates leading to the desired regioisomeric enone (-)-**43a**. However, the outcome was fortuitous as the desired product was the major one.

II.3.3. Generalisation of the New Cyclopentenone Annulation Protocol:

The successful and reasonably efficient cyclopentenone annulation of (-)-**42a,b** ⟶ (-)-**43a,b** sequence pointed out its potential as a general protocol for **49** ⟶ **50** type of annulation, particularly as structural fragment **50** and its reduced and deoxygenated form **51** are present among many natural products, Chart II.4[37]. Indeed, dimethylcyclopentenone moiety is rather ubiquitous among sesquiterpenoids. While numerous methodologies for the cyclopentenone annulation of ketones are currently available,[38] we are not aware of any that directly generates the 5,5-dimethyl cyclopentenone moiety **50** from a carbonyl precursor. Therefore, it became expedient to further prove the generality of **49** ⟶ **50** sequence. It needs to be emphasised that the resulting cyclopentenones like **50** can be utilised for a variety of synthetic manoeuvres. For example, the endocyclic tetrasubstituted enone double bond could be utilised as an effective tool for generating the desired stereochemistry at the ring junction.

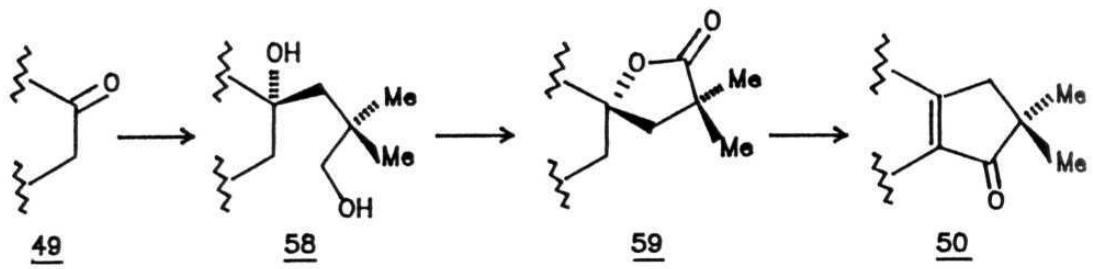
Also, a large variety of appendages could be fastened stereoselectively to the double bond via conjugate addition, and oxidative cleavage of the double bond offers a 3-carbon ring expansion sequence with amplified functionalities.

Chart II.4



Our new annulation procedure basically consists of three steps, **Scheme II.12.** These are the Barbier-type addition of 3-lithio-2,2-dimethylpropyl tert-butyldimethylsilyl ether[33] to the carbonyl compound **49** and deprotection of the TBDMS group; oxidation of the resulting diol **58** with Griffith-Ley's reagent, (TPAP) to the γ-lactone **59**, and rearrangement of the γ-lactone to

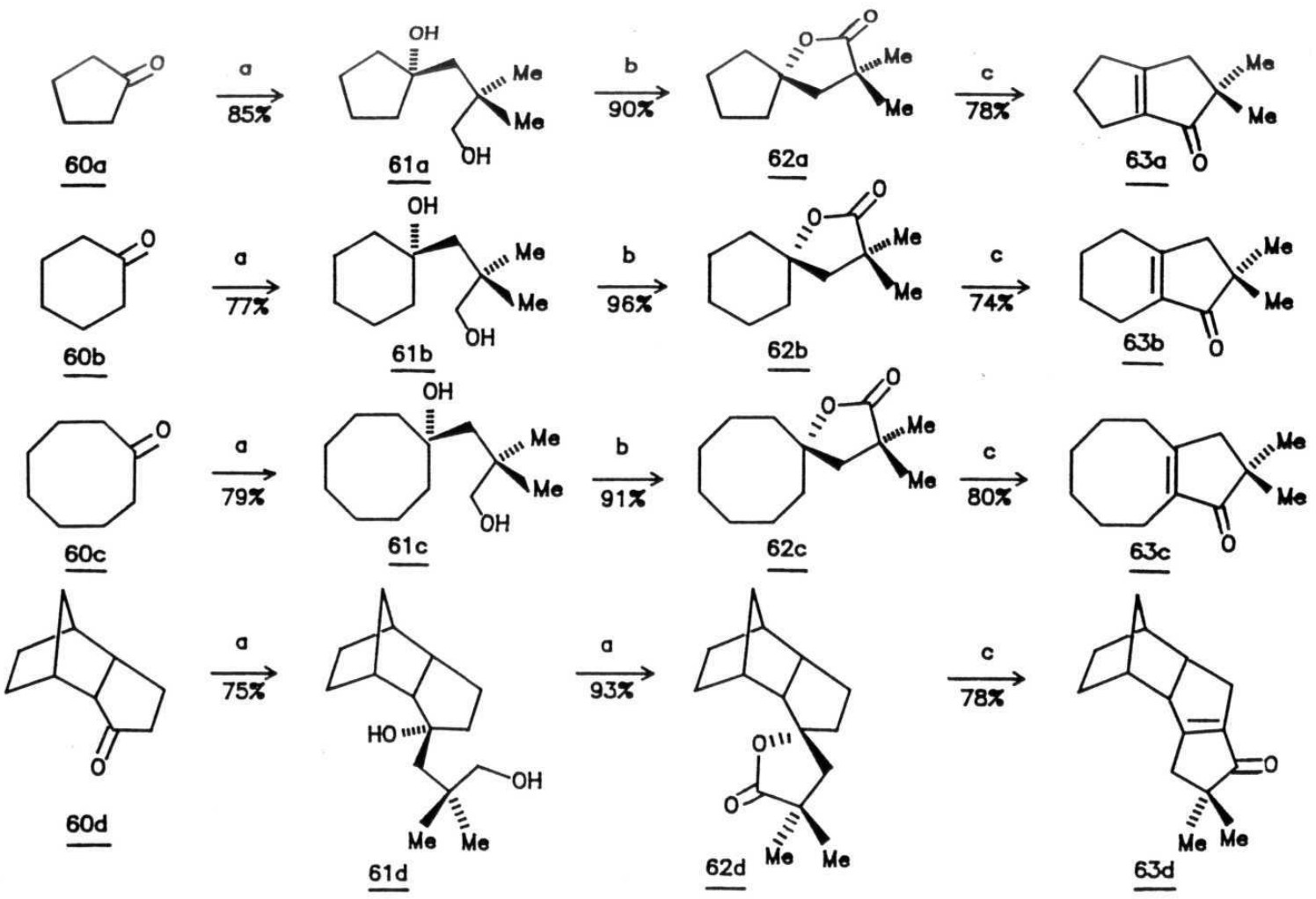
Scheme II.12



49 58 59 50

the gem dimethylcyclopentenone moiety **50** on treatment with P_2O_5-methanesulphonic acid combination. The whole sequence is carried out under mild conditions, with simple experimental and workup procedures and is short enough to be implemented in a long working day. The generality of this methodology[39] has been established by implementing this sequence on cyclopentanone, cyclohexanone, cyclooctanone and the tricyclic ketone **60d**. The results are summarised in **Table II.1**.

In actuality, to an ethereal solution of 3-lithio-2,2-dimethylpropyl tert-butyldimethylsilyl ether (generated from 3-bromo-2,2-dimethylpropyl tert-butyldimethylsilyl ether **35b** and Li) were added the ketones **60a-d** to furnish the TBDMS protected diols which were deprotected with tetra-n-butylammonium fluoride in THF to furnish the diols **61a-d** in yields ranging from 75-85%. Efficient oxidation of the diols **61a-d** with tetra-n-propylammonium perruthenate (TPAP) in the presence of NMMO led to the corresponding spiro-lactones **62a-d** in over 90% yield. The IR, ^1H and ^{13}C NMR spectral data of these compounds were in full agreement with their formulation. All the spiro-lactones **62a-d** underwent smooth rearrangement with P_2O_5-methanesulphonic acid to furnish the corresponding enones **63a-d** in good yields. All



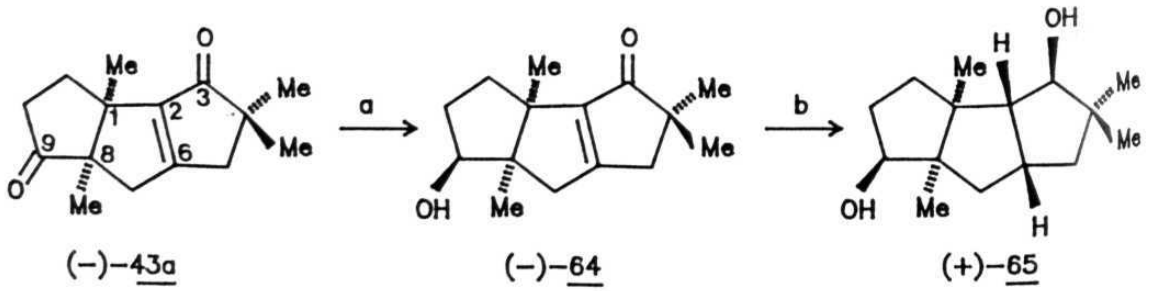
Reagents and conditions: (a) Li, 3-Bromo-2,2-dimethylpropyl tert-butyldimethylsilyl ether, 15°C, 15 min (b) TPAP-NMMO, 10%CH_3CN-DCM, RT. (c) $MeSO_3H$-P_2O_5, 80°C.

the annulated enone products were fully characterised on the basis of their IR, ^{1}H and ^{13}C NMR spectral data, which is duly summarised in the experimental section.

II.3.4. Return to the Ceratopicanol Synthesis - The End Game:

To recall, the C_{15}-triquinane enone (-)-**43a** having the complete framework of ceratopicanol was already in hand and our attention was now drawn towards the installation of the requisite stereochemistry at the C_2-, C_6-ring junction and the C_9-hydroxyl group. The endo-stereochemistry at C_9-position was readily secured through stereo- and chemoselective reduction of the major enedione (-)-**43a** with $NaBH_4$ at -20°C in methanol to furnish (-)-**64** in 87% yield, **Scheme II.13**. The hydroxy-enone (-)-64 exhibited strong absorptions at 3325, 1685 cm^{-1} in the IR spectrum due to the hydroxyl and enone groups, respectively and three singlets representing the four quaternary methyls at δ 1.18, 1.14 (6H) and 1.13 in the ^{1}H NMR spectrum. The endo-

Scheme II.13



(-)-43a (-)-64 (+)-65

Reagents and yields: (a) $NaBH_4$, MeOH, -20°C, 87%; (b) Li-liq. NH_3, t-BuOH, NH_4Cl, 66%.

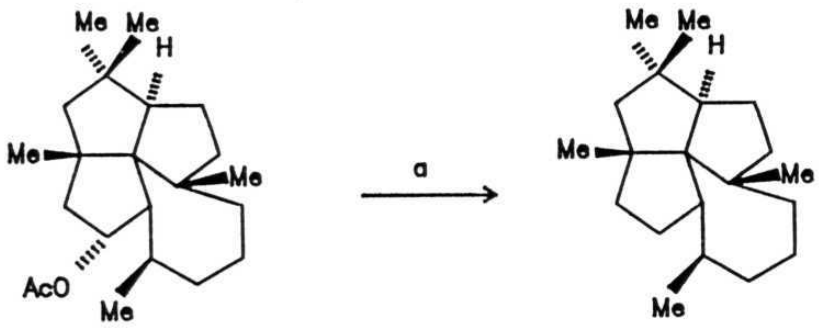
hydroxy stereochemistry in (-)-64 followed from the known propensity of bicyclo[3.3.0]octanones to accept nucleophiles from the exo-face. In addition, the ^{1}H NMR signal due to the hydroxyl attached proton in (-)-64 was very similar to that reported for the natural product[4].

In order to obtain the required stereochemistry at C_2-C_6 ring junction, metal-ammonia reduction of the enone (-)-64 was sought, keeping in view the fact that this reduction occurs under equilibrating conditions and should afford the thermodynamically more stable cis-anti-cis triquinane product. Addition of the hydroxy-enone (-)-64 to the blue coloured Li-liq.NH_3 solution and quenching the reaction with t-butanol gave a single crystalline product (+)-65, Scheme II.13. The IR, ^{1}H NMR (Fig. II.25) and ^{13}C NMR spectra (Fig. II.26) confirmed the gross structure of the diol (+)-65. The IR spectrum showed the absence of enone carbonyl and a 15 line ^{13}C NMR indicated that it was indeed a single isomer with characteristic signals at δ 82.7, 82.5 and 63.2. The stereochemistry of the newly installed C_3-hydroxyl group in the diol (+)-65 was most likely the more stable exo and cis to the neighbouring ring junction hydrogen. Consequently, it was assumed with some degree of certainty that the C_9 and C_3 hydroxyl groups being endo and exo, respectively could be expected to exhibit different reactivities. This was important as the C_3 hydroxyl group in the diol (+)-65 had to be removed to complete the synthesis.

Having secured the correct stereochemistry at all the five carbon centres (C_1, C_2, C_6, C_8 and C_9), the deoxygenation of the

exo-hydroxy group in (+)-65 was now attempted. Among the various deoxygenation protocols that are available[40], we considered the reduction of carboxylic esters in sodium-HMPA milieu[41] as particularly attractive. A recent example[42], Scheme II.14, provided us the confidence in being able to execute this step.

Scheme II.14

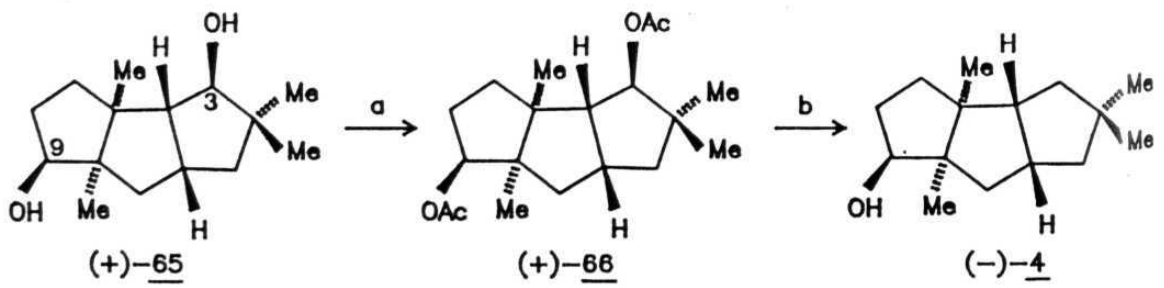


Laurenan-2-yl acetate Laurenane

Reagents and yields: (a) Na-HMPA, t-BuOH-ether, 70%.

Accordingly, the diol (+)-65 was converted into diacetate (+)-66 with DMAP-Ac_2O in high yield, Scheme II.15. The diacetate

Scheme II. 15



(+)-65 (+)-66 (−)-4

Reagents and yields: (a) DMAP-Ac_2O, DCM, RT, 30 min, 90%;(b) Na-HMPA, t-BuOH-ether, 20%.

(+)-66 was exposed to Na-HMPA combination in the presence of t-Butanol and it underwent preferential reductive deacetoxylation of the exo-acetoxy group as well as hydrolysis of the endo-acetoxy group to furnish directly (-)-ceratopicanol 4 $[\alpha]_D$ -5.8 (lit[4] +6.4) in 20% yield. The 100 MHz ^1H NMR spectrum of (-)-Ceratopicanol (Fig. II.27) in $CDCl_3$ exhibited two singlets at δ 1.06 , 0.89 corresponding to the four quaternary methyl groups and a triplet at δ 3.75 representing a proton attached to secondary hydroxy group. In C_6D_6, the ^1H NMR spectrum (Fig. II.28) showed four signals at δ 1.19, 1.11, 1.01, and 0.93 due to four quaternary methyl groups and at δ 3.59 due to the proton attached to secondary hydroxyl group which were identical with those reported in the literature[4]. In particular, a 15 line ^{13}C NMR spectrum (Fig. II.29) which displayed characteristic signals at δ 82.7, 55.0, 51.3, unambiguously confirmed the structure of (-)-Ceratopicanol. The ^{13}C NMR data for the natural product has not been reported in the literature as it was isolated in very small amounts. Finally, the identity of the synthetic compound and the natural product was fully established by comparing the 400 MHz ^1H NMR spectra[#](Fig. II. 30) and (Fig. II.31). The synthetic material (-)-4 obtained by us from R-(+)-limonene had specific rotation opposite in sign to that of the natural product. Therefore, the absolute configuration of the natural product is as shown in (+)-4.

[#] We thank Dr. Abraham for making available to us the 400 MHz spectrum of the natural product.

II.4. SUMMARY:

The first enantioselective total synthesis of the biogenetically important and structurally novel triquinane sesquiterpene (-)-ceratopicanol has been accomplished and its absolute configuration established. A simple and expedient cyclopentannulation methodology which directly generates 5,5-dimethyl cyclopentenone moiety from a carbonyl precursor has been developed. Several examples demonstrate the generality of this methodology. This annulation protocol served as the key operation in the synthesis of (-)-ceratopicanol.

II.5. EXPERIMENTAL

For a general write-up see the experimental section of chapter I.

The diquinane (-)-20a was prepared from R-(+)-limonene as described in the first chapter.

(1R,5S)-1,5-Dimethyl-7-mesyloxy-bicyclo[3.3.0]octan-2-one (32) :

Sodium borohydride (60 mg, 1.62 mmol) was added to a solution of enones (-)-20a,b (225 mg, 1.17 mmol) in dry methanol (10 mL) under N_2 at 0-5°C. The contents were brought to room temperature for 30 min. Most of the methanol was removed under reduced pressure and the residue was diluted with water (5 mL) and extracted with ethyl acetate (30 mL x 3). The combined extract was washed and dried to furnish an oily residue. Filtration through a silica gel (5 g) column with 20% ethyl acetate-petroleum ether furnished 30 in 96% yield as a diastereomeric mixture.

To the above mixture 30 (170 mg, 0.87 mmol) in dry dichloromethane (10 mL) and dry pyridine (1 mL) was added methylsulfonyl chloride (0.3 mL) at 0°C. The reaction mixture was stirred for 1 h and then quenched with water and extracted with ether (25 mL x 3). The combined ethereal extract was washed, dried and concentrated to a crude product which was filtered through a small silica gel (10 g) column. Elution with 20% ethyl acetate-petroleum ether furnished the mesylate 31 (210 mg) in 88% yield.

IR : 2960, 1350, 1175, 890 cm^{-1};

^1H NMR : δ 5.28-4.56 (m, 2H, -C<u>H</u>-OSO_2CH_3), 2.96 (s, 3H, -$OSO_2C\underline{H}_3$), 2.94 (s, 3H,-$OSO_2C\underline{H}_3$), 2.8-1.24 (m, 28H), 1.09 (s, 3H, -C-C<u>H</u>$_3$), 1.07 (s, 3H, -C-C<u>H</u>$_3$), 1.02 (s, 3H, -C-CH_3), 0.94 (s, 3H, -C-CH_3)

The mesylate 31 (180 mg, 0.66 mmol) was dissolved in a mixture of carbontetrachloride, acetonitrile and water (each 5 mL) and sodium metaperiodate (350 mg, 1.63 mmol) and ruthenium trichloride (5 mg) were added. After being stirred for 1 h, the reaction mixture was diluted with dichloromethane (50 mL) and filtered through a celite pad (2 g). The organic layer was separated and the aqueous layer was reextracted with dichloromethane (15 mL x 2). The combined extract was washed and dried and the crude was filtered through a silica gel (10 g) column with 40% ethyl acetate-petroleum ether to furnish keto-mesylate 32 (90 mg) in 55% yield.

IR : 2990, 1740, 1350, 1180, 895 cm^{-1}

^1H NMR : δ 5.24-4.76 (m, 2H, C<u>H</u>-OSO_2CH_3), 2.98 (s, 3H, -$OSO_2C\underline{H}_3$), 2.95 (s, 3H, -$OSO_2C\underline{H}_3$), 2.72-1.04 (m, 16H), 1.20 (s, 3H, -C-C<u>H</u>$_3$), 1.08 (s, 3H, -C-C<u>H</u>$_3$), 1.04 (s, 3H, -C-C<u>H</u>$_3$), 0.96 (s, 3H, -C-C<u>H</u>$_3$)

(1R,5S)-1,5-Dimethyl-bicyclo[3.3.0]oct-6-en-2-one (33a) and (1R,5S) -1,5-Dimethyl-bicyclo[3.3.0]oct-7-en-2-one (33b) :

A mixture of keto-mesylate 32 (47 mg, 0.20 mmol), HMPA (2 mL) and sodium iodide (50 mg, 0.33 mmol) was heated at 110°C

for 2 h. The reaction mixture was cooled and poured into water. The aqueous layer was extracted with ether (30 mL x 3). The ethereal layer was washed with water, brine and dried. Removal of solvent purification of the crude product on a silica gel (5 g) column furnished the keto-olefins **33a,b** (8 mg, 26%) as a regioisomeric mixture.

bp : 107°C/0.5 mm

IR : 3050, 2965, 1040 cm^{-1};

^1H NMR : δ 5.76-5.24 (m, 4H, -C<u>H</u>=C<u>H</u>), 2.76-1.48 (m, 12H), 1.12 (s, 3H, -C-C<u>H</u>$_3$), 1.08 (s, 3H, -C-C<u>H</u>$_3$), 1.02 (s, 3H, -C-C<u>H</u>$_3$), 1.00 (s, 3H, -C-C<u>H</u>$_3$)

Analysis : $C_{10}H_{14}O$ Calcd.: C, 79.95; H, 9.39.
Found : C, 79.64; H, 9.51.

(1R,5S)-1,5-Dimethyl-7-hydroxy-bicyclo[3.3.0]octan-2-one (34) :

Into a solution of alcohol **30** (210 mg, 1.08 mmol) in methanol (15 mL) dry ozone was bubbled at -78°C. Excess of ozone was flushed-out by a continuous stream of N_2. Excess of dimethyl sulfide was added dropwise at -78°C and the reaction mixture was allowed to warm to room temperature. Evaporation of methanol under reduced pressure gave a crude oil which was purified on a silica gel (10 g) column by eluting with 30% ethyl acetate-petroleum ether to furnish 125 mg of keto-alcohol **34** in 68% yield.

bp : 120°C/0.2 mm

IR : 3420, 2970, 1735, 755 cm^{-1}

^1H NMR : 4.36-4.00 (m, 2H, -CHOH), 2.64-1.36 (m, 18H), 1.16 (s, 3H, -C-CH$_3$), 1.04 (s, 3H, -C-CH$_3$), 1.00 (s, 3H, -C-CH$_3$), 0.90 (s, 3H, -C-CH$_3$).

Analysis : $C_{10}H_{16}O_2$ Calcd.: C, 71.39; H, 9.59.
Found : C, 71.62; H, 9.71.

(-)-(1R,5S,7S)-1,5-Dimethyl-7-hydroxy-7(3-hydroxy-2,2-dimethyl propyl)-bicyclo[3.3.0]octan-2-one (25a) and (-)-(1R,5S,7R)-1,5-Dimethyl -7- hydroxy-7 (3-hydroxy-2,2-dimethyl propyl)- bicyclo [3.3.0] octan-2-one (25b) :

Into a 100 mL two necked flask fitted with reflux condenser was suspended freshly cut lithium (850 mg, 121 mg atom) in 30 mL of dry ether under N_2. 3-bromo-2,2-dimethylpropyl tert-butyldimethylsilyl ether 35b (6.5 g, 23 mmol) was injected through a septum. The contents of the flask were stirred for 1 h at room temperature and then cooled to 5-10°C. The enone mixture 20a,b (1.5 g, 7.8 mmol) in 5 mL of ether was slowly introduced. After stirring for 15 min, the reaction mixture was poured into brine and extracted with ether (75 mL x 3). The ethereal layer was dried and concentrated and the product was isolated by passing through a silica gel (35 g) column. Elution with 2% ethyl acetate-petroleum ether furnished the diastereomeric mixture 36 (1.72 g) in an over all yield of 57%.

Dry ozone was bubbled into a solution of 36 (1.72 g) in methanol (50 mL) at -78°C till the blue colour persisted. Excess of ozone was flushed-out by a continuous stream of N_2. Excess of dimethyl sulfide was added dropwise at -78°C and the reaction

mixture was allowed to warm to room temperature. Evaporation of methanol under reduced pressure gave a crude oil which was directly treated with 1.5 equivalents of $(n\text{-}Bu)_4NF$ in THF (50 mL) for 30 min. The reaction mixture was diluted with ethyl acetate (250 mL), washed with water, brine and dried. The solid residue obtained on the removal of solvent was chromatographed on a silica gel (50 g) column. Elution with 40% ethyl acetate-petroleum ether furnished 600 mg of keto-diol (-)-25a in 60% yield as a colourless solid which was recrystallised from petroleum ether.

$[\alpha]_D$: -68.1 (c, 1.1; $CHCl_3$)

mp : 137°C

IR : 3200, 2960, 1735, 1155 cm^{-1};

^1H NMR (Fig. II.1) : δ 3.40 (S, 2H, $-C\underline{H}_2OH$), 2.48-1.44 (m, 12H), 1.24 (s, 3H, $-C-C\underline{H}_3$), 1.04 (s, 3H, $-C-C\underline{H}_3$), 0.96 (s, 6H, $-C-(C\underline{H}_3)_2$)

^{13}C NMR (Fig. II.2) : δ 225.2, 81.6, 71.6, 58.7, 55.1, 54.5, 52.9, 49.7, 36.5, 34.6, 32.3, 27.2, 26.9, 23.2, 17.5

Analysis : $C_{15}H_{26}O_3$ Calcd.: C,70.83; H, 10.30.
Found : C,70.90; H, 10.32.

Further elution of the column with 40% ethyl acetate-petroleum ether furnished the minor keto-diol 25b (136 mg, 13%) as a white solid which was recrystallised from petroleum ether.

$[\alpha]_D$: -43.3 (c, 2.1; $CHCl_3$)

mp : 102-103°C

IR : 3300, 2950, 1735 cm^{-1};

^1H NMR (Fig. II.3) : δ 3.36 (s, 2H, $-C\underline{H}_2OH$), 2.80-1.12 (m, 12H), 1.06 (s, 3H, $-C-C\underline{H}_3$), 0.94 (s, 6H, $-C-(C\underline{H}_3)_2$), 0.86 (s, 3H, $-C-C\underline{H}_3$)

^{13}C NMR (Fig. II.4) : δ 227.1, 79.7, 71.2, 57.6, 57.0, 54.6, 52.8, 47.6, 36.3, 36.1, 34.2, 27.1, 26.8, 26.3, 17.8

Analysis : $C_{15}H_{26}O_3$ Calcd.: C,70.83; H, 10.30.
Found : C,70.75; H, 10.28.

(-)-(1R,5S)-1,5-Dimethyl-7(3-iodo-2,2-dimethyl propyl)-bicyclo-[3.3.0]oct-6-en-2-one (37a) and (-)-(1R,5S)-1,5-Dimethyl-7(3-iodo-2,2-dimethyl propyl)-bicyclo[3.3.0]oct-7-en-2-one (37b) :

Into a 50 mL RB flask fitted with a dry N_2 inlet, septum and mercury seal was placed sodium iodide (300 mg, 2.0 mmol) and keto-diol (-)-25a (90 mg, 0.35 mmol) in 5 mL of dry acetonitrile. Freshly distilled chlorotrimethylsilane (0.5 mL, 4.0 mmol) was added and the mixture refluxed for 1 h. The reaction mixture was diluted with ether (75 mL) and washed successively with aqueous sodium thiosulfate solution and brine. Drying and removal of solvent gave a crude product which was charged on a silica gel (10 g) column. Elution with 5% ethyl acetate-petroleum ether furnished iodo-olefin (-)-37a (62 mg) in 50% yield.

$[\alpha]_D$: -98.6 (c, 3.0; $CHCl_3$)

bp : 125°C/0.4 mm

IR : 2950, 1735, 1465, 1245 cm^{-1};

^1H NMR (Fig. II.5) : δ 5.24 (br s, 1H, $-C=C\underline{H}-$), 3.08 (s, 2H, $-C\underline{H}_2I$), 2.74-1.40 (m, 8H), 1.08 (s, 3H, $-C-C\underline{H}_3$), 1.00

(s, 6H, $-C(CH_3)_2$), 0.96 (s, 3H)

^{13}C NMR (Fig. II.6) : δ 226.2, 140.7, 137.7, 57.1, 54.9, 47.7, 41.5, 36.5, 34.3, 30.9, 27.3, 27.2, 24.3, 21.6, 15.5.

HRMS : $C_{15}H_{23}OI$ Calcd. M^+: 346.0794

Found : 346.0778

Further elution of the column with 5% ethyl acetate-petroleum ether furnished iodo-olefin (-)-37b (23 mg) in 20% yield.

$[\alpha]_D$: -169.5 (c, 1.15; $CHCl_3$)

bp : 115°C/0.4 mm

IR : 2975, 1735, 1290 cm^{-1};

^1H NMR (Fig. II.7) : δ 5.14 (br s, 1H, -C=C<u>H</u>-), 3.14 (s, 2H, $-C\underline{H}_2I$), 2.04-1.16 (m, 8H), 1.09 (s, 3H, $-C-C\underline{H}_3$), 1.04 (s, 6H, $-C(C\underline{H}_3)_2$), 1,00 (s, 3H, $-C-C\underline{H}_3$)

^{13}C NMR (Fig. II.8) : δ 220.9, 142.2, 132.5, 64.8, 52.1, 48.8, 41.8, 36.6, 34.5, 34.1, 27.4 (2C), 24.2, 21.9, 16.8

HRMS : $C_{15}H_{23}OI$ Calcd. M^+ : 346.0794

Found : 346.0794

TPAP oxidation of keto-diol (-)- 25a :

A mixture of keto-diol (-)-25a (450 mg, 1.77 mmol), N-methyl-morpholine N-oxide (NMMO) (420 mg, 3.6 mmol) and powdered molecular sieves (900 mg) in acetonitrile-dichloromethane (1:9, 20 mL) was stirred at room temperature for 10 min under N_2. Tetra-n-propylammonium perruthenate (TPAP) (45 mg) was added in

two portions and the reaction mixture was stirred for 40 min. The black coloured solution was diluted with dichloromethane and filtered through a small silica gel pad. Dichloromethane was evaporated and the residue was passed through a silica gel (10 g) column to furnish the spiro-lactone (-)-**42a** (406 mg) in 91% yield as a colourless solid which was recrystallised from petroleum ether.

$[\alpha]_D$	: -55.5 (c, 1.35; $CHCl_3$)
mp	: 108°C
IR	: 2975, 1760, 1735, 1240 cm^{-1};
^1H NMR (Fig. II.9)	: δ 2.47-1.53 (m, 10H), 1.24 (s, 3H, -C-C$\underline{H}_3$), 1.21 (s, 3H, -C-C$\underline{H}_3$), 1.18, (s, 3H, -C-C$\underline{H}_3$), 0.96 (s,3H, -C-C$\underline{H}_3$)
^{13}C NMR (Fig. II.10)	: δ 223.5, 181.7, 89.0, 59.2, 53.3, 50.3, 49.8, 49.5, 40.5, 34.2, 30.9, 25.7 (2C), 21.9, 16.8
Analysis	: $C_{15}H_{22}O_3$ Calcd. : C, 71.97; H, 8.86. Found : C, 71.95; H, 8.83.

TPAP oxidation of keto-diol (-)-25b :

A mixture of keto-diol (-)-**25b** (75 mg, 0.29 mmol), N-methylmorpholine N-oxide (NMMO) (70 mg, 0.6 mmol) and powdered molecular sieves (140 mg) in acetonitrile-dichloromethane (1:9, 20 mL) was stirred at room temperature for 10 min under N_2. Tetra-n-propylammonium perruthenate (TPAP) (8 mg) was added and the reaction mixture was stirred for 40 min. The black coloured solution was diluted with dichloromethane and filtered through a small silica gel pad. Dichloromethane was evaporated

and the residue was passed through a silica gel (3 g) column to furnish the spiro-lactone (-)-42b (66 mg) in 90% yield as a colourless solid which was recrystallised from petroleum ether.

$[\alpha]_D$: -61.6 (c, 3.15; $CHCl_3$)

mp : 98°C

IR : 2975, 1755, 1735, 1120, 930 cm^{-1};

^1H NMR (Fig. II.11) : δ 2.74-1.34 (m, 10H), 1.18 (s, 6H, -C-CH_3), 1.03 (s, 3H, -C-CH_3), 0.90 (s, 3H, -C-CH_3)

^{13}C NMR (Fig. II.12) : δ 222.6, 180.8, 88.3, 57.9, 55.6, 52.0, 48.6 (2C), 40.4, 35.4, 32.7, 25.8 (2C), 24.3, 17.8

Analysis : $C_{15}H_{22}O_3$ Calcd.: C,71.97; H, 8.86.
Found : C,71.87; H, 8.81.

Rearrangement of spiro-lactone 42a : (-)-(1R,8R)-1,4,4,8-Tetramethyl tricyclo[6.3.0.$0^{2,6}$]undec-2(6)ene-3,9-dione (43a) and (-)-(1S,8S)-1,4,4,8-tetramethyl tricyclo [6.3.0.$0^{2,6}$]undec-2(6)ene-3,11-dione (43b) :

The spiro-lactone (-)-42a (375 mg, 1.5 mmol) in 1 mL of P_2O_5-CH_3SO_3H (1:10, by weight) was heated at 80°C for 65 min under N_2. The reaction mixture was cooled, poured into water (5 mL), and extracted with ethyl acetate (25 mL x 3). The combined ethyl acetate extract was washed with saturated sodium bicarbonate, brine and dried. The residue was charged on a silica gel (10 g) column. Elution with 40% ethyl acetate-petroleum ether afforded tricyclic enedione (-)-43a (165 mg) as the major product in 48% yield.

$[\alpha]_D$: -168.2 (c, 2.55; $CHCl_3$)

bp : 135°C/0.3 mm

IR : 2950, 1735, 1695, 1640 cm^{-1};

^1H NMR (Fig. II.13) : δ 2.92-1.44 (m, 8H), 1.21 (s, 3H, -C-C$\underline{H}_3$), 1.11 (s, 3H, -C-C$\underline{H}_3$), 1.08 (s, 3H, -C-C$\underline{H}_3$), 1.06 (s, 3H, -C-C$\underline{H}_3$)

^{13}C NMR (Fig. II.14) : δ 224.2, 207.3, 179.9, 149.3, 62.0, 50.4, 49.9, 41.8, 41.7, 36.2, 28.1, 25.2, 24.4, 19.9, 15.5

Analysis : $C_{15}H_{20}O_2$ Calcd.: C,77.55; H,8.68.
Found : C,77.27; H,8.60.

Further elution of the column with 50% ethyl acetate-petroleum ether yielded the minor enedione (-)-**43b** (78 mg) in 22% yield as a white solid which was recrystallised from petroleum ether.

$[\alpha]_D$: -170.0 (c, 2.0; $CHCl_3$)

mp : 119-120°C

IR : 2960, 1735, 1695, 1620 cm^{-1};

^1H NMR (Fig. II.15) : δ 2.56-1.68 (m, 8H), 1.16 (s, 6H, -C-C$\underline{H}_3$), 1.09 (s, 3H, -C-C$\underline{H}_3$), 1.07 (s, 3H, -C-C$\underline{H}_3$)

^{13}C NMR (Fig. II.16) : δ 216.9, 206.7, 181.4, 145.5, 59.8, 55.2, 50.2, 45.5, 42.2, 36.2, 33.9, 25.2, 25.1, 22.2, 14.6

Analysis : $C_{15}H_{20}O_2$ Calcd.: C,77.55; H, 8.68.
Found : C,77.45; H, 8.65.

Rearrangement of spiro-lactone (-)-42b :

The minor spiro-lactone (-)-42b (35 mg) was heated with 0.5 mL of P_2O_5-CH_3SO_3H (1:10, by weight) for 70 min at 80°C under N_2. After usual workup as described above furnished a crude product which was purified on a silica gel to give (-)-43a and (-)-43b in a 2:1 ratio, aproximately in 70% yield.

1-Hydroxy-1(3-hydroxy-2,2-dimethylpropyl)cyclopentane (60a) :

Into a 100 mL RB flask fitted with a reflux condenser, was suspended freshly cut lithium (100 mg, 14.2 mg atom) in 5 mL of dry ether under N_2. 3-Bromo-2,2-dimethylpropyl tert-butyldimethylsilyl ether 35b (775 mg, 2.75 mmol) was injected through a septum. The contents of the flask were stirred for 1 h at room temperature and then cooled to 5-10 °C. Cyclopentanone 60a (115 mg, 1.36 mmol) in 1 mL of ether was slowly introduced. After stirring for 15 min, the reaction mixture was diluted with moist ether and the excess lithium was filtered off. The filtrate was washed and dried. Removal of solvent, gave an oil which was passed through a silica gel (10 g) column with 5% ethyl acetate-petroleum ether to afford the TBDMS ether (310 mg).

The above TBDMS ether (310 mg, 1.08 mmol) and tetra-n-butylammonium fluoride (700 mg, 2.22 mmol) in THF (10 mL) was stirred for 30 min. The reaction mixture was diluted with ethyl acetate and washed with brine and dried . Removal of solvent and passage through a silica gel (10 g) column with 40% ethyl acetate-petroleum ether furnished the diol 61a (195 mg) in 83% yield.

IR : 3300, 2975, 1050 cm^{-1}

^1H NMR : δ 3.38 (s, 2H, $-C\underline{H}_2OH$), 1.98-1.38 (m, 12H), 0.94 (s, 6H, $-C-(C\underline{H}_3)_2$)

TPAP oxidation of diol 61a :

A mixture of diol **61a** (105 mg, 0.61 mmol) , N-methylmorpholine N-oxide (NMMO) (180 mg, 1.5 mmol) and powdered molecular sieves (200 mg) in acetonitrile-dichloromethane (1:9, 5 mL) was stirred at room temperature for 10 min under N_2. Tetra-n-propylammonium perruthenate (TPAP) (15 mg, 0.042 mmol) was added and the reaction mixture was stirred for 30 min. The black coloured solution was diluted with dichloromethane and filtered through a small silica gel pad. The solvent was evaporated and the residue was passed through a silica gel (10 g) column with 10% ethyl acetate-petroleum ether to furnish the spiro-lactone **62a** (92 mg) in 90% yield.

mp : 33°C

IR : 2970, 1760, 1030 cm^{-1}

^1H NMR : δ 2.08-1.40 (m, 10H), 1.18 (s, 6H, $-C-(C\underline{H}_3)_2$)

^{13}C NMR : δ 181.9, 90.9, 46.7, 40.6, 40.1 (2C), 25.9 (2C), 23.6 (2C)

Analysis : $C_{10}H_{16}O_2$ Calcd.: C, 71.39; H, 9.59.
Found : C, 71.55; H, 10.68.

3,3-Dimethyl-bicyclo[3.3.0]oct-1(5)en-2-one (63a) :

The spiro-lactone **62a** (58 mg) in 0.5 mL of P_2O_5-CH_3SO_3H (10:1 by weight) was heated at 80°C for 65 min under N_2. The

reaction mixture was cooled, poured into water (5 mL) and extracted with ethyl acetate. The combined extract was washed with saturated sodium bicarbonate, brine and dried. The residue was charged on a silica gel (10 g) column. Elution with 10% ethyl acetate-petroleum ether afforded the bicyclic enone 63a (40 mg) in 78% yield.

bp : 125°C/0.2 mm

IR : 2970, 1695, 1640 cm^{-1}

^{1}H NMR (Fig. II.17) : δ 2.52-2.04 (m, 8H), 1.08(s, 6H, -C-($C\underline{H}_3$)$_2$)

^{13}C NMR (Fig. II.18) : δ 208.6, 183.5, 146.1, 50.6, 42.2, 31.9, 27.2, 25.3 (2C), 24.7.

Analysis : $C_{10}H_{14}O$ Calcd.: C, 79.95; H, 9.39.
Found : C, 80.10; H, 9.47.

1-Hydroxy-1(3-Hydroxy-2,2-dimethylpropyl)cyclohexane (61b) :

Into a 100 mL RB flask fitted with a reflux condenser, was suspended freshly cut lithium (40 mg, 5.7 mg atom) in 5 mL of dry ether under N_2. 3-Bromo-2,2-dimethylpropyl tert-butyldimethylsilyl ether 35b (300 mg, 1.06mmol) was injected through a septum. The contents of the flask were stirred for 1 h at room temperature and then cooled to 5-10 °C. Cyclohexanone 60b (50 mg, 0.51 mmol) in 1 mL of ether was slowly introduced. After stirring for 15 min, the reaction mixture was diluted with moist ether (60 mL) the excess lithium was filtered off. The filtrate was washed and dried. Removal of solvent, gave an oil which was used as such for deprotection of the TBDMS group.

The above TBDMS ether (165 mg) and tetra-n-butylammonium fluoride (325 mg, 1.03 mmol) in THF (10 mL) was stirred for 30 min. The reaction mixture was diluted with ethyl acetate and washed with brine and dried . Removal of solvent and passage through a silica gel (10 g) column with 40% ethyl acetate-petroleum ether furnished the diol **61b** (73 mg) in 77% yield.

mp : 85-86°C

IR : 3175, 2975, 1060 cm^{-1}

^1H NMR : δ 3.42 (br s, 2H, $-C\underline{H}_2OH$), 1.80-1.04 (m, 14H), 0.99 (s, 6H, $-C-(C\underline{H}_3)_2$)

TPAP oxidation of diol 61b :

A mixture of diol **61b** (73 mg, 0.39 mmol) , N-methylmorpholine N-oxide (NMMO) (115 mg, 0.98 mmol) and powdered molecular sieves (100 mg) in acetonitrile-dichloromethane (1:9, 5 mL) was stirred at room temperature for 10 min under N_2. Tetra-n-propylammonium perruthenate (TPAP) (10 mg, 0.028 mmol) was added and the reaction mixture was stirred for 30 min. The black coloured solution was diluted with dichloromethane and filtered through a small silica gel pad. The solvent was evaporated and the residue was passed through a silica gel (10 g) column with 5% ethyl acetate-petroleum ether to furnish the spiro-lactone **62b** (61 mg) in 96% yield as a colourless solid which was recrystallised from petroleum ether.

mp : 110-113°C

IR : 2950, 1760, 1240 cm^{-1}

^{1}H NMR : δ 1.96-1.08 (m, 12H), 1.04 (s, 6H, -C-($C\underline{H}_3$)$_2$)

^{13}C NMR : δ 182.3, 82.5, 47.8, 40.2, 38.8 (2C), 27.7 (2C), 24.7, 22.5 (2C)

Analysis : $C_{11}H_{18}O_2$ Calcd.: C, 72.49; H, 9.96.
Found : C, 72.70; H, 9.90.

8,8-Dimethyl-bicyclo[4.3.0]non-1(6)en-7-one (63b) :

The spiro-lactone **62b** (30 mg) in 0.5 mL of P_2O_5-CH_3SO_3H (10:1 by weight) was heated at 80°C for 5 h under N_2. The reaction mixture was cooled, poured into water (5 mL) and extracted with ethyl acetate. The combined extract was washed with saturated sodium bicarbonate, brine and dried. The residue was charged on a silica gel (10 g) column. Elution with 10% ethyl acetate-petroleum ether afforded the bicyclic enone **63b** (20 mg) in 78% yield.

bp : 120°C/0.3 mm

IR : 2930, 1700, 1650, 1400 cm^{-1}

^{1}H NMR (Fig. II.19) : δ 2.40-1.52 (m, 10H), 1.10 (s, 6H, -C-($C\underline{H}_3$)$_2$)

^{13}C NMR (Fig. II.20) : δ 213.5, 170.4, 136.0, 47.2, 43.1, 28.3, 25.2 (2C), 22.2, 21.7, 20.2

Analysis : $C_{11}H_{16}O$ Calcd.: C, 80.44; H, 9.83.
Found : C, 80.23; H, 9.88.

1-Hydroxy-1(3-Hydroxy-2,2-dimethylpropyl)cyclooctane (61c) :

Into a 100 mL RB flask fitted with a reflux condenser, was suspended freshly cut lithium (75 mg, 10.7 mg atom) dry ether (5 mL) under N_2. 3-Bromo-2,2-dimethylpropyl tert-butyldimethylsilyl ether **35b** (500 mg, 2.12 mmol) was injected through a septum. The contents of the flask were stirred for 1 h at room temperature and then cooled to 5-10 °C. Cyclooctanone **60c** (100 mg, 0.79 mmol) in 1 mL of ether was slowly introduced. After stirring for 15 min, the reaction mixture was diluted with moist ether (75 mL) the excess lithium was filtered off. The filtrate was washed and dried. Removal of solvent, gave an oil which was used as such for deprotection of the TBDMS group.

The above TBDMS ether (240 mg) and tetra-n-butylammonium fluoride (380 mg, 1.45 mmol) in THF (10 mL) was stirred for 30 min. The reaction mixture was diluted with ethyl acetate and washed with brine and dried . Removal of solvent and passage through a silica gel (10 g) column with 40% ethyl acetate-petroleum ether furnished the diol **61c** (IR : 3300, 2950, 1470, 1050 cm^{-1}) (135 mg) 79% yield.

TPAP oxidation of diol 61c :

A mixture of diol **61c** (100 mg, 0.46 mmol) , N-methyl-morpholine N-oxide (NMMO) (140 mg, 1.19 mmol) and powdered molecular sieves (200 mg) in acetonitrile-dichloromethane (1:9, 5 mL) was stirred at room temperature for 10 min under N_2. Tetra-n-propylammonium perruthenate (TPAP) (12 mg, 0.034 mmol) was

added and the reaction mixture was stirred for 45 min. The black coloured solution was diluted with dichloromethane and filtered through a small silica gel pad. The solvent was evaporated and the residue was passed through a silica gel (10 g) column with 10% ethyl acetate-petroleum ether to furnish the spiro-lactone 62c (90 mg) in 91% yield.

mp : 37°C

IR : 2920, 1760, 1455, 1235 cm^{-1}

^{1}H NMR : δ 2.16-1.4 (m, 16H), 1.35 (s, 6H, $-C-(C\underline{H}_3)_2$)

^{13}C NMR : δ 182.2, 86.2, 47.6, 40.3, 37.3 (2C), 27.2 (4C), 24.3, 21.6 (2C)

Analysis : $C_{13}H_{22}O_2$ Calcd.: C, 74.24; H, 10.54

Found : C, 73.96; H, 10.60.

10,10-Dimethyl-bicyclo[6.3.0]undec-1(8)en-9-one (63c) :

The spiro-lactone 62c (75 mg) in 0.75 mL of P_2O_5-CH_3SO_3H (10:1 by weight) was heated at 80°C for 65 min under N_2. The reaction mixture was cooled, poured into water (5 mL) and extracted with ethyl acetate. The combined extract was washed with saturated sodium bicarbonate, brine and dried. The residue was charged on a silica gel (10 g) column. Elution with 10% ethyl acetate-petroleum ether afforded the bicyclic enone 63c (55 mg) in 80% yield.

bp : 135°C/0.4 mm

IR : 2925, 1700, 1645, 1000 cm^{-1}

^{1}H NMR (Fig. II.21) : δ 2.46-1.10 (m, 14H), 1.02 (s, 6H, $-C-(C\underline{H}_3)_2$)

^{13}C NMR (Fig. II.22) : δ 213.3, 171.9, 137.8, 47.1, 43.0, 29.9, 28.5, 27.1, 26.1, 25.6, 25.1 (2C), 21.3

Analysis : $C_{13}H_{20}O$ Calcd.: C, 81.20; H, 10.48

Found : C, 81.45; H, 10.40

3-Hydroxy-3(3-hydroxy-2,2-dimethylpropyl)-tricyclo [5.2.1.$0^{2,6}$] decane (61d) :

Into a 100 mL RB flask fitted with a reflux condenser, was suspended freshly cut lithium (50 mg, 7.1 mg atom) in 5 mL of dry ether under N_2. 3-Bromo-2,2-dimethylpropyl tert-butyldimethylsilyl ether **35b** (375 mg, 1.33 mmol) was injected through a septum. The contents of the flask were stirred for 1 h at room temperature and then cooled to 5-10 °C. The tricyclic ketone **60d** (110 mg, 0.73 mmol) in 1 mL of ether was slowly introduced. After stirring for 15 min, the reaction mixture was diluted with moist ether (75 mL) the excess lithium was filtered off. The filtrate was washed and dried. Removal of solvent, gave an oil which was used as such for deprotection of the TBDMS group.

The above TBDMS ether (270 mg) and tetra-n-butylammonium fluoride (465 mg, 1.47 mmol) in THF (10 mL) was stirred for 30 min. The reaction mixture was diluted with ethyl acetate and washed with brine and dried . Removal of solvent and passage through a silica gel (10 g) column with 40% ethyl acetate-petroleum ether furnished the diol **61d** (131 mg) in 75% yield.

mp : 93-95°C

IR : 3300, 2970, 1475 cm^{-1}

^1H NMR : δ 3.68-3.20 (m, 2H, $-C\underline{H}_2OH$), 2.40-1.16 (m, 18H), 1.04 (s, 3H, $-C-(C\underline{H}_3)_2$), 0.99 (s, 3H, $-C-(C\underline{H}_3)_2$)

TPAP oxidation of diol 61d :

A mixture of diol **61d** (75 mg, 0.31 mmol), N-methylmorpholine N-oxide (NMMO) (100 mg, 0.85 mmol) and powdered molecular sieves (150 mg) in acetonitrile-dichloromethane (1:9, 5 mL) was stirred at room temperature for 10 min under N_2. Tetra-n-propylammonium perruthenate (TPAP) (8 mg, 0.022 mmol) was added and the reaction mixture was stirred for 30 min. The black coloured solution was diluted with dichloromethane and filtered through a small silica gel pad. The solvent was evaporated and the residue was passed through a silica gel (10 g) column with 10% ethyl acetate-petroleum ether to furnish the spiro-lactone **62d** (68 mg) in 93% yield as a colourless solid which was recrystallised from petroleum ether.

mp : 103-104°C

IR : 2950, 1760, 1195 cm^{-1}

^1H NMR : δ 2.36-1.28 (m, 16H), 1.26 (s, 3H, $-C-(C\underline{H}_3)_2$), 1.24 (s, 3H, $-C-(C\underline{H}_3)_2$)

^{13}C NMR : δ 183.6, 89.6, 55.6, 52.4, 42.3, 41.8, 41.6, 40.6, 40.1, 26.8 (2C), 24.3, 22.5, 22.2

Analysis : $C_{15}H_{22}O_2$ Calcd.: C, 76.88; H, 9.46.
Found : C, 76.70; H, 9.41.

5,5-Dimethyl-tetracyclo[8.2.1.$_0$2,9.$_0$3,7]tridec-3(7)en-6-one (63d) :

The spiro-lactone **62d** (55 mg) in 0.5 mL of P_2O_5-CH_3SO_3H (10:1 by weight) was heated at 80°C for 65 min under N_2. The reaction mixture was cooled, poured into water (5 mL) and extracted with ethyl acetate. The combined extract was washed with saturated sodium bicarbonate, brine and dried. The residue was charged on a silica gel (10 g) column. Elution with 20% ethyl acetate-petroleum ether afforded the tetracyclic enone 63d (39 mg) in 78% yield.

IR : 2950, 1690, 1635, 1380 cm^{-1}

^1H NMR (Fig. II.23) : δ 2.96 (br s, 2H), 2.48-2.00 (m, 6H), 1.64-1.18 (m, 6H), 1.14 (s, 3H, -C-($C\underline{H}_3$)$_2$), 1.11 (s, 3H, -C-($C\underline{H}_3$)$_2$)

^{13}C NMR (Fig. II.24) : δ 209.9, 183.8, 146.5, 51.0, 50.3, 48.8, 43.5, 41.5, 41.0, 38.9, 25.9, 25.1 (2C), 24.7, 21.9.

Analysis : $C_{15}H_{20}O$ Calcd.: C, 83.28; H, 9.32.
Found : C, 83.11; H, 9.43

(-)-(1R,8R,9S)-9-Hydroxy-1,4,4,8-tetramethyltricyclo[6.3.0.$_0$2,6] undec-2(6)en-3-one (64) :

To 55 mg of enone (-)-**43a** (0.23 mol) in dry methanol (3 mL) was added 10 mg of sodium borohydride (1.2 mmol) at -20°C . The contents were stirred for 30 min and methanol was removed at reduced pressure and the residue left was diluted with water (5 mL) and extracted with ethyl acetate (20 mL x 3). The combined extract was washed and dried. The crude product

obtained after removal of solvent was charged on a silica gel (5 g) column. Elution with 40% ethyl acetate-petroleum ether furnished the hydroxy-enone (-)-**64** (48 mg) in 87% yield.

$[\alpha]_D$: -29.0 (c, 0.55; $CHCl_3$)

mp : 113-114°C

IR : 3325, 2975, 1685, 1630 cm^{-1};

^1H NMR : δ 3.92-3.58 (m, 1H, -C<u>H</u>OH), 3.14-1.22 (m, 9H) 1.18 (s, 3H, -C-C<u>H</u>$_3$), 1.14 (s, 6H, -C-(C<u>H</u>$_3$)$_2$), 1.13 (s, 3H, -C-C<u>H</u>$_3$)

Analysis : $C_{15}H_{22}O_2$ Calcd.: C, 76.88; H, 9.46.
Found : C, 76.70; H, 9.40

(+)-(1S,2R,3S,6R,8R,9S)-1,4,4,8-Tetramethyl tricyclo[6.3.0.0^{2,6}] undecane-3,9-diol (65) :

Into a two necked 100 mL RB flask fitted with a guard tube and septum was placed freshly distilled liq.NH_3 (40 mL) and freshly cut lithium metal (25 mg, 3.5 mg. atom) was added . The resulting blue solution was stirred for 5 min and the hydroxy-enone (-)-**64** (45 mg, 0.19 mmol) in dry ether (1 mL) and t-butanol (0.5 mL) was slowly introduced. After stirring for 10 min, the reaction mixture was quenched by addition of solid NH_4Cl. Ammonia was allowed to evaporate and the residue was dissolved in water (15 mL) and extracted with ether (25 mL x 3). The combined ethereal extract was washed, dried and concentrated to a crude product which was filtered through a small silica gel (5 g) column. Elution with 50% ethyl acetate-petroleum ether furnished the tricyclic diol (+)-**65** (30 mg) in 66% yield.

$[\alpha]_D$: +13.0 (c, 1.0; $CHCl_3$)

mp : 108-109°C

IR : 3375, 1470, 1090 cm^{-1};

^1H NMR (Fig. II.25) : δ 3.94-3.56 (m, 2H,-CHOH), 2.74-1.12 (m, 12H), 1.06 (s, 3H,-C-CH_3), 1.05 (s, 3H, -C-CH_3), 1.01 (s, 3H, -C-CH_3), 0.85 (s, 3H, -C-CH_3)

^{13}C NMR (Fig. II.26) : δ 82.7, 82.5, 63.2, 55.8, 51.2, 46.5, 43.5, 40.7, 39.3, 36.6, 30.8, 27.2, 22.6, 20.3, 19.6

Analysis : $C_{15}H_{26}O_2$ Calcd.: C, 75.58 ; H, 11.00.
Found : C, 75.70 ; H, 10.94.

(+)-(1S,2R,3S,6R,8R,9S)-1,4,4,8-Tetramethyl-3,9-diacetoxy-tricyclo [6.3.0.$0^{2,6}$] undecane (66) :

To a mixture of diol (+)-65 (30 mg, 0.13 mmol), and DMAP (25 mg, 0.2 mmol) in dichloromethane (10 mL) was added with acetic anhydride (20 mg, 0.19 mmol) at 0°C. The reaction mixture was stirred for 30 min and the dichloromethanewas evaporated. The residue was dissolved in water (10 mL) and extracted with ether (15 mL x 3). The combined ethereal extract was washed, dried and concentrated to a crude product which was filtered through a small silica gel (5 g) column. Elution with 30% ethyl acetate-petroleum ether furnished the diacetate (+)-66 (36 mg) in 90% yield.

$[\alpha]_D$: +14.5 (c, 0.55; $CHCl_3$)

mp : 67-69°C

IR : 2970, 1740, 1240, 1135 cm^{-1};

^1H NMR : δ 5.08 (d, J= 10 Hz, 1H), 4.84-4.64 (m, 1H

2.80-1.12 (m, 10H), 2.04 (s, 3H, -OCO-$C\underline{H}_3$), 2.03 (s, 3H,-OCO-$C\underline{H}_3$)), 1.06 (s, 3H, -C-$C\underline{H}_3$), 0.96 (s, 3H, -C-$C\underline{H}_3$), 0.88 (s, 6H, -C-$(C\underline{H}_3)_2$)

Analysis : $C_{19}H_{30}O_4$ Calcd.: C, 70.77; H, 9.38
Found : C, 70.54; H, 9.30.

(-)-Ceratopicanol (4) :

A solution of the diacetate (+)-66 (40 mg, 0.12 mmol) in dry ether-dry tert-butanol (1:1, 0.5 mL) was added to a blue coloured mielieu containing suspended sodium (100 mg) pieces in dry ether-dry HMPA (1:2, 1.5 mL) at such a rate that the solution never decolourised. When the addition was complete, the reaction mixture was diluted with ether (25 mL) and the ethereal layer was carefully decanted. The ethereal layer was washed with brine and dried. Removal of solvent gave an oily residue which was chromatographed on a silica gel (5 g) column. Elution with 10% ethyl acetate-petroleum ether furnished 5 mg of (-)-ceratopicanol 4 in 20% yield.

$[\alpha]_D$: -5.9 (0.45, $CHCl_3$)

mp : 53-55°C

IR : 3350, 2935, 1060 cm^{-1};

^1H NMR (Fig. II.27) : δ 3.73 (m, 1H), 2.64-1.08 (m, 13H), 1.06 (s, 6H, -C-$C\underline{H}_3$), 0.89 (s, 6H, -C-$(C\underline{H}_3)_2$)

^{13}C NMR (Fig. II.28) : δ 82.7, 58.9, 55.0, 51.3, 48.8, 44.2, 41.9, 41.7, 40.9, 39.6, 31.6, 30.7, 28.6, 23.9, 21.3

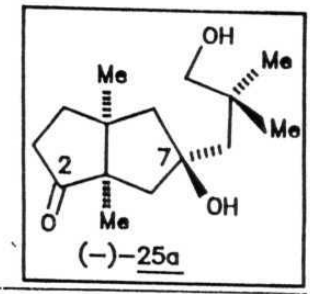
^{1}H NMR (100 MHz, C_6D_6): δ 3.59 (m, 1H), 2.60-1.24 (m, 13H), 1.19 (s, 3H, -C-C$\underline{H}_3$), 1.11 (s, 3H, -C-C$\underline{H}_3$), 1.01 (s, 3H, -C-C$\underline{H}_3$), 0.93 (s, 3H, -C-C$\underline{H}_3$) (Fig. II.29)

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.72 (dd, 1H), 2.50 (ddddd, 1H), 2.36 (ddd, 1H), 2.17 (dd, 1H), 1.91 (m, 1H), 1.69 (ddd, 1H), 1.62-1.52 (m, 3H), 1.42 (m, 1H), 1.39 (dd, 1H) 1.33 (ddd, 1H), 1.25 (dd, 1H), 1.08 (dd, 1H), 1.06 (s, 6H), 0.90 (s, 3H), 0.89 (s, 3H). (Fig. II.30)

The ^{1}H NMR spectrum (Fig. II.30) was found identical with the spectrum (Fig. II.31) provided by Dr. Abraham.

Further elution of the column with 30% ethyl acetate-petroleum ether furnished the diol (+)-65 (7 mg, 24%) due to the hydrolysis of the diacetate (+)-66.

II.6. SPECTRA



(−)−25a

Fig. II.1

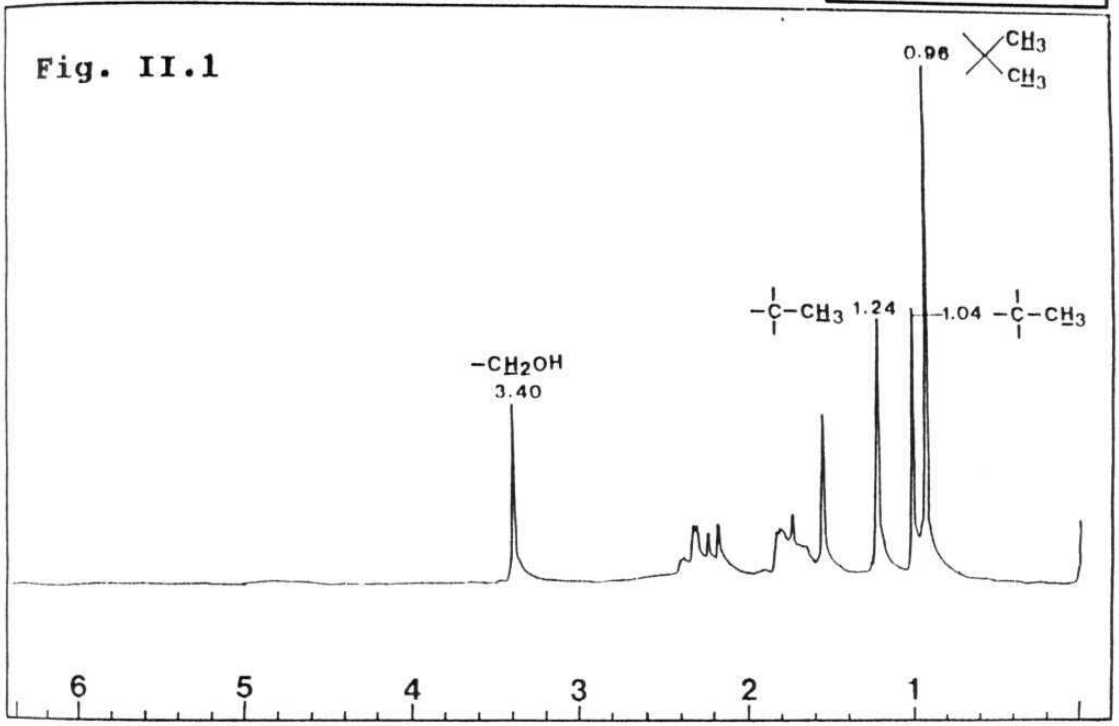
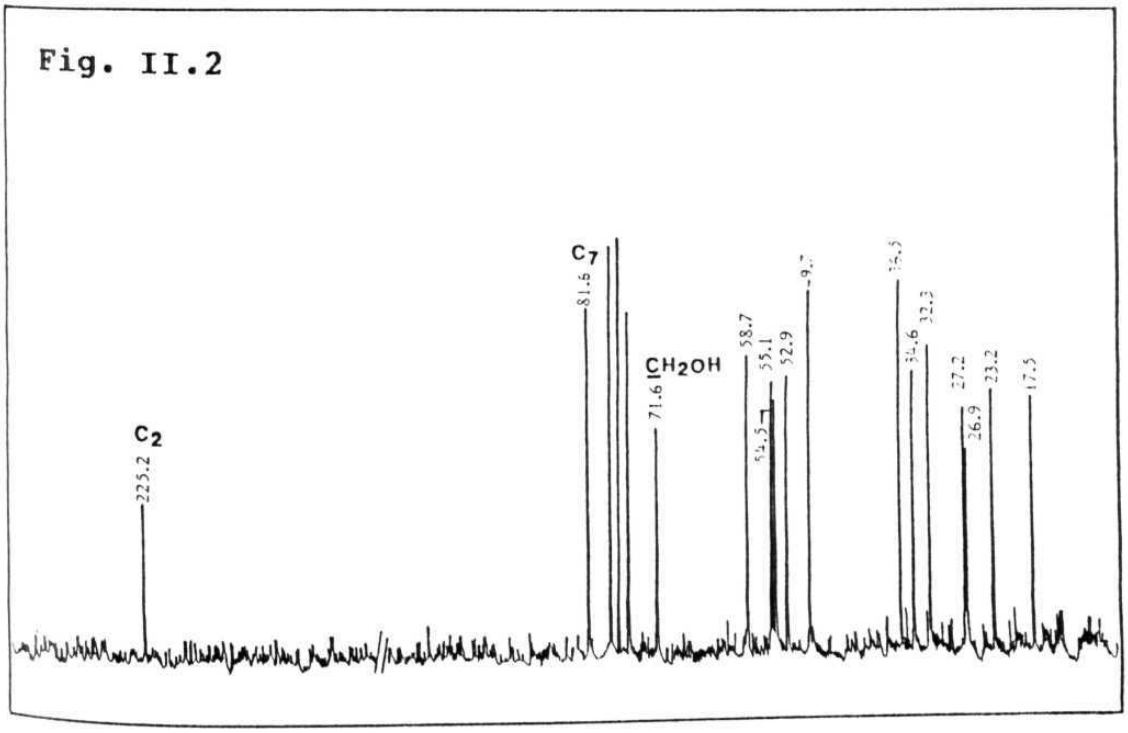
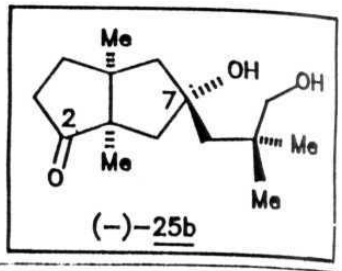


Fig. II.2





(−)−25b

Fig. II.3

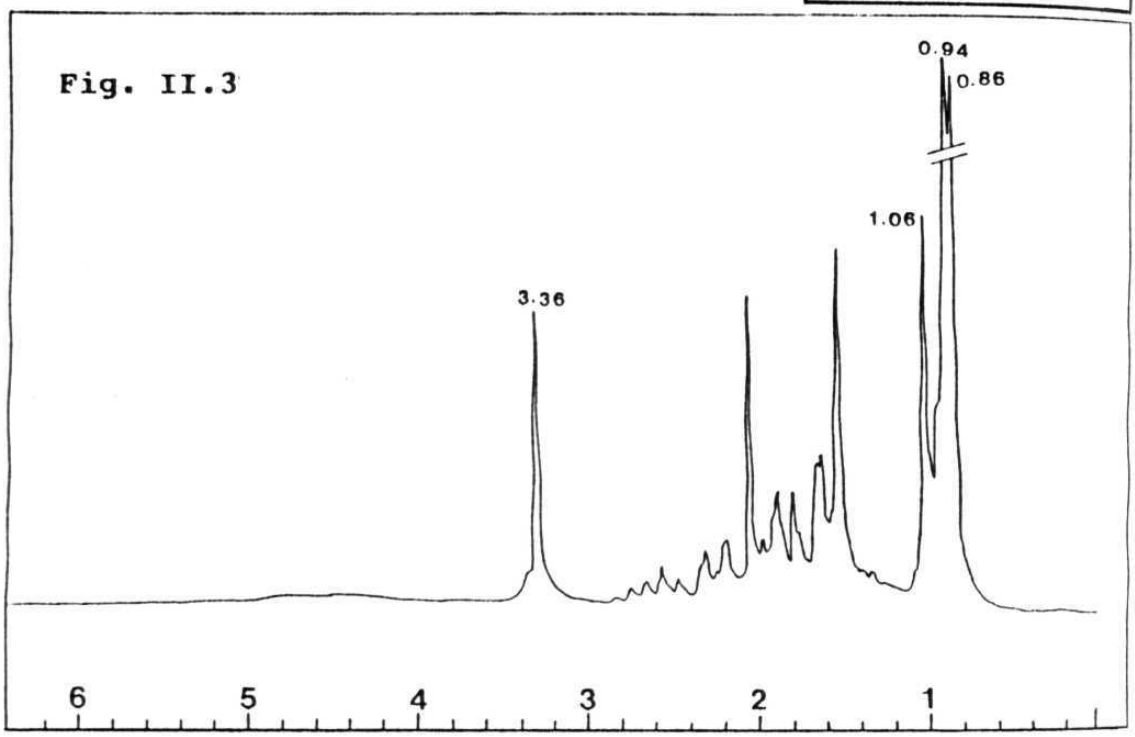
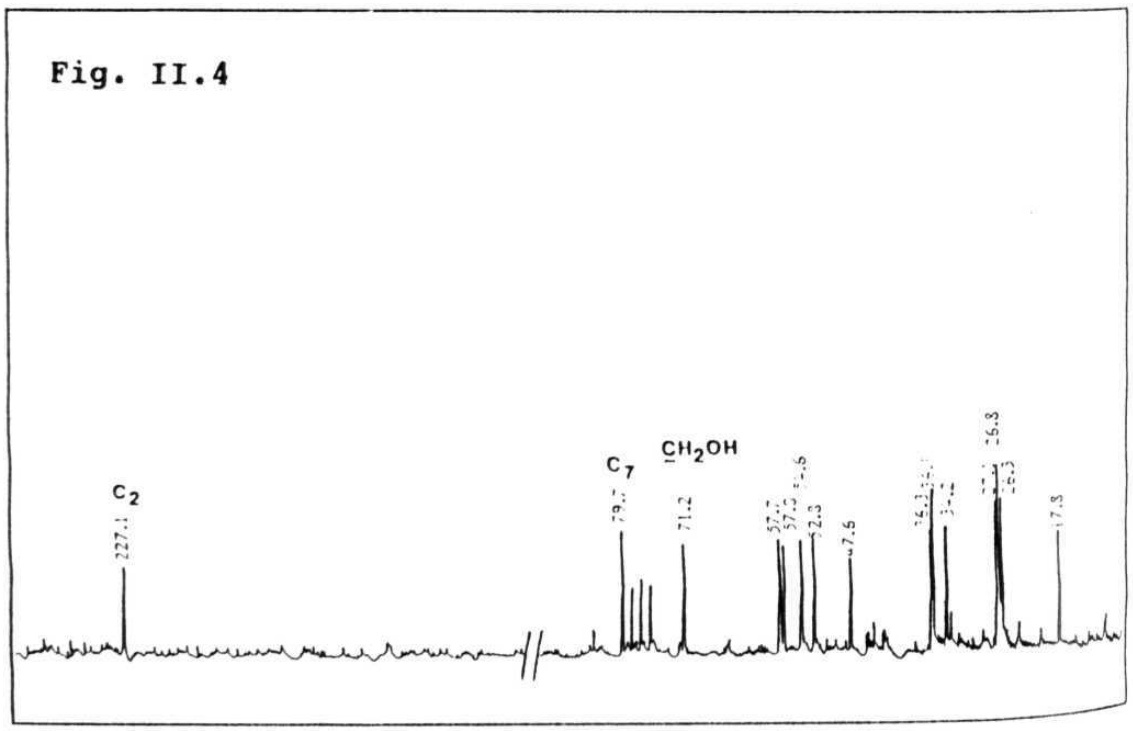
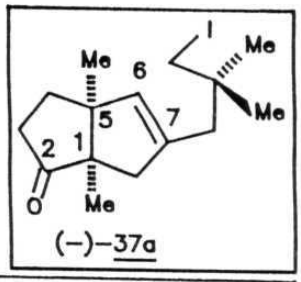


Fig. II.4





(−)−37a

Fig. II.5

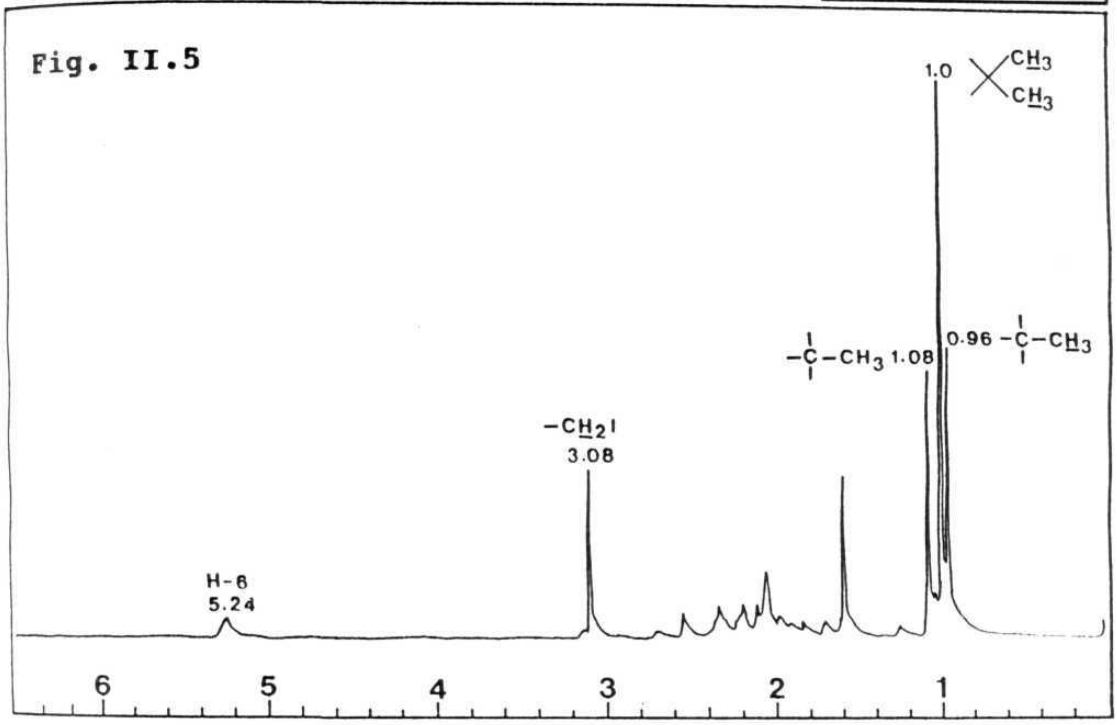
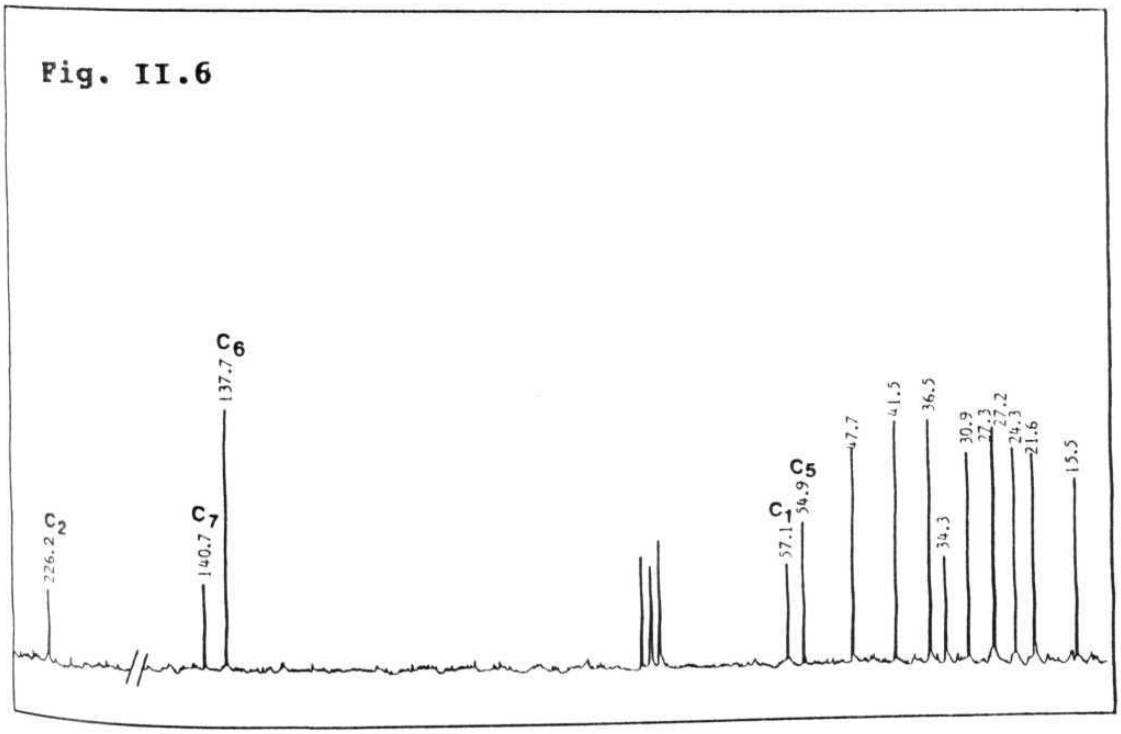


Fig. II.6



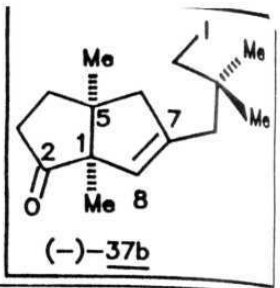


Fig. II.7

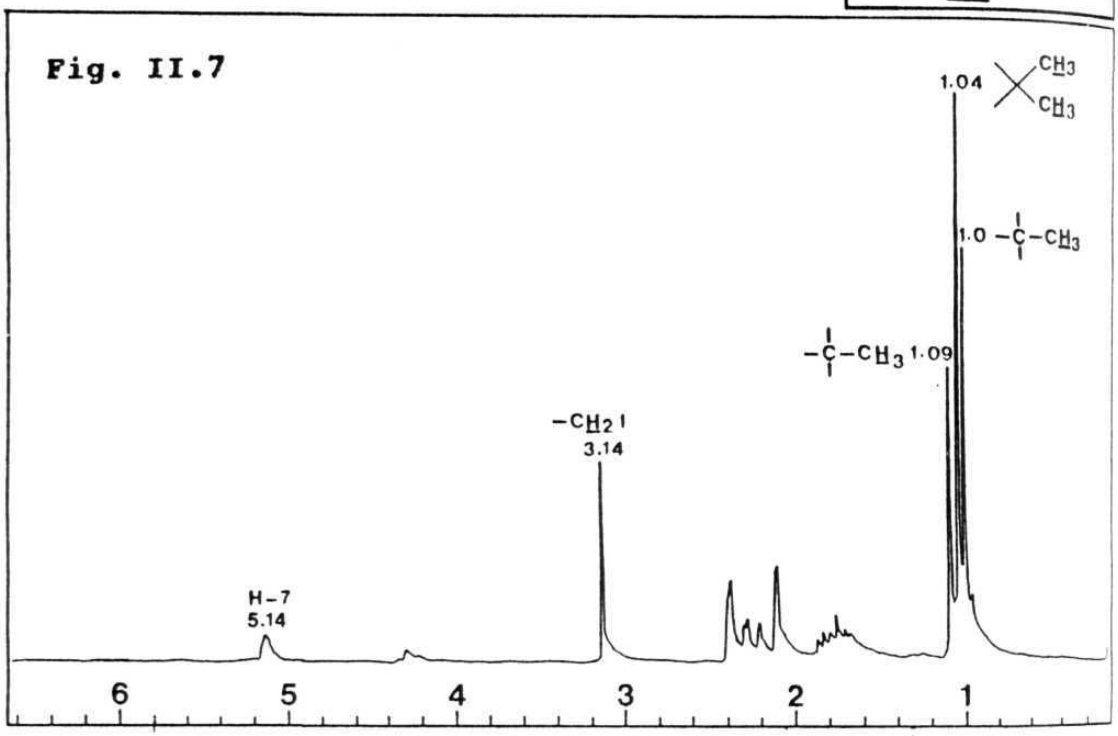
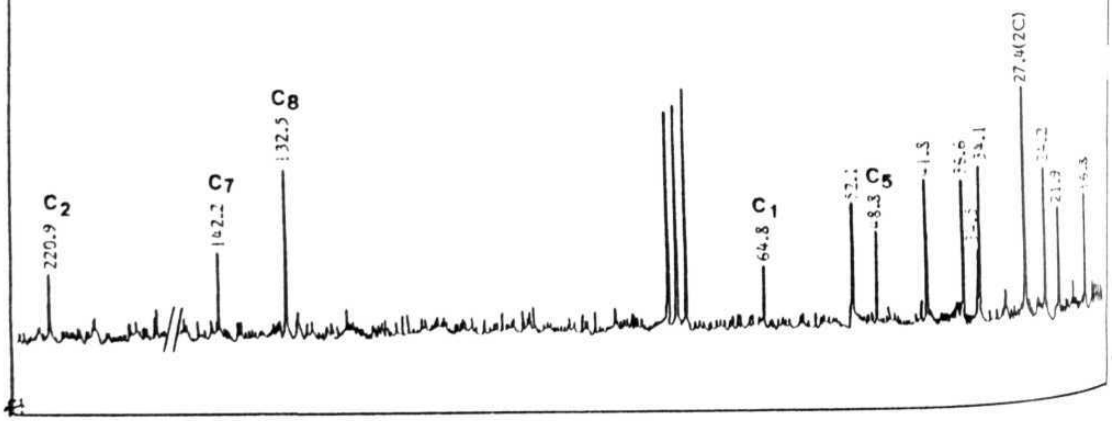
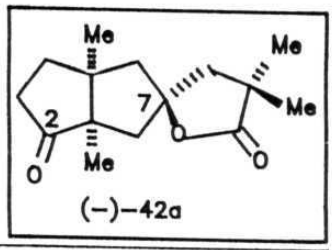


Fig. II.8





(−)−42a

Fig. II.9

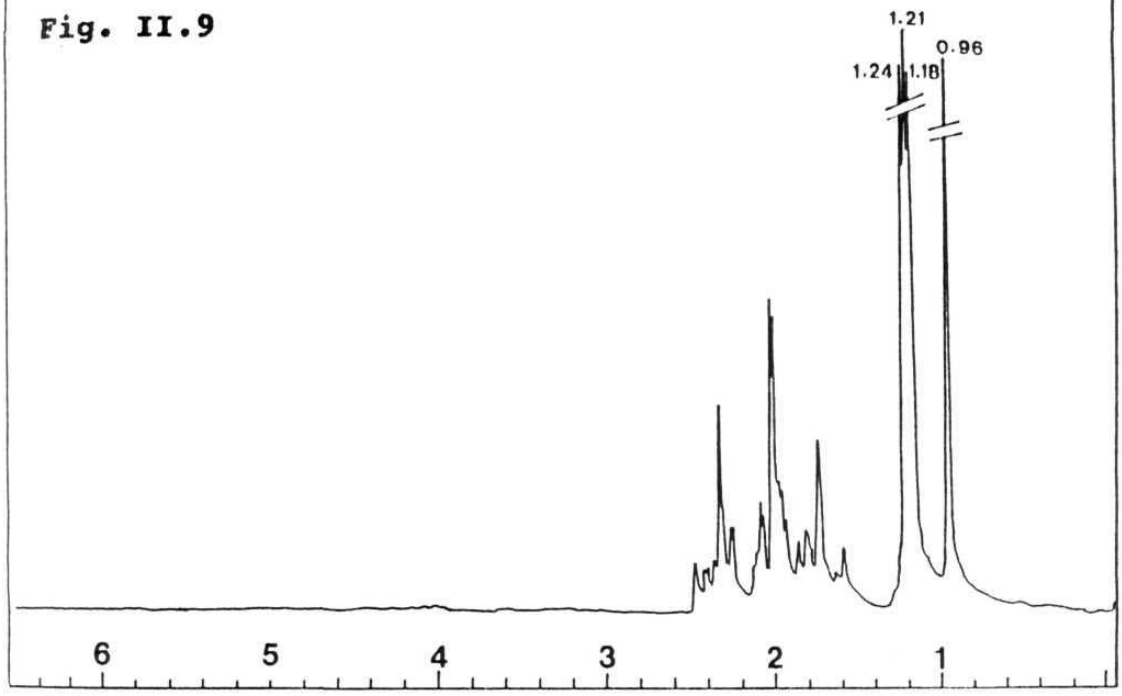
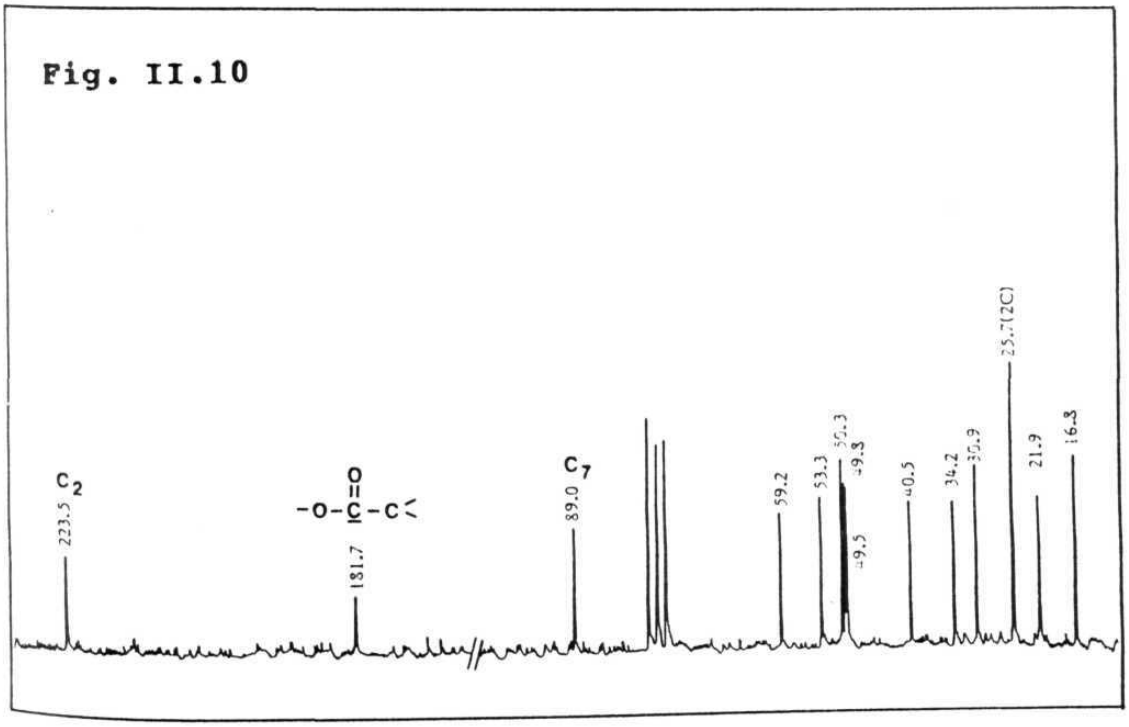


Fig. II.10



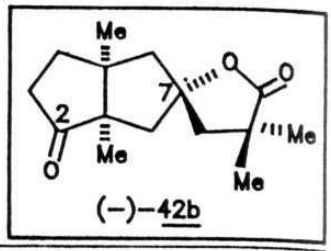


Fig. II.11

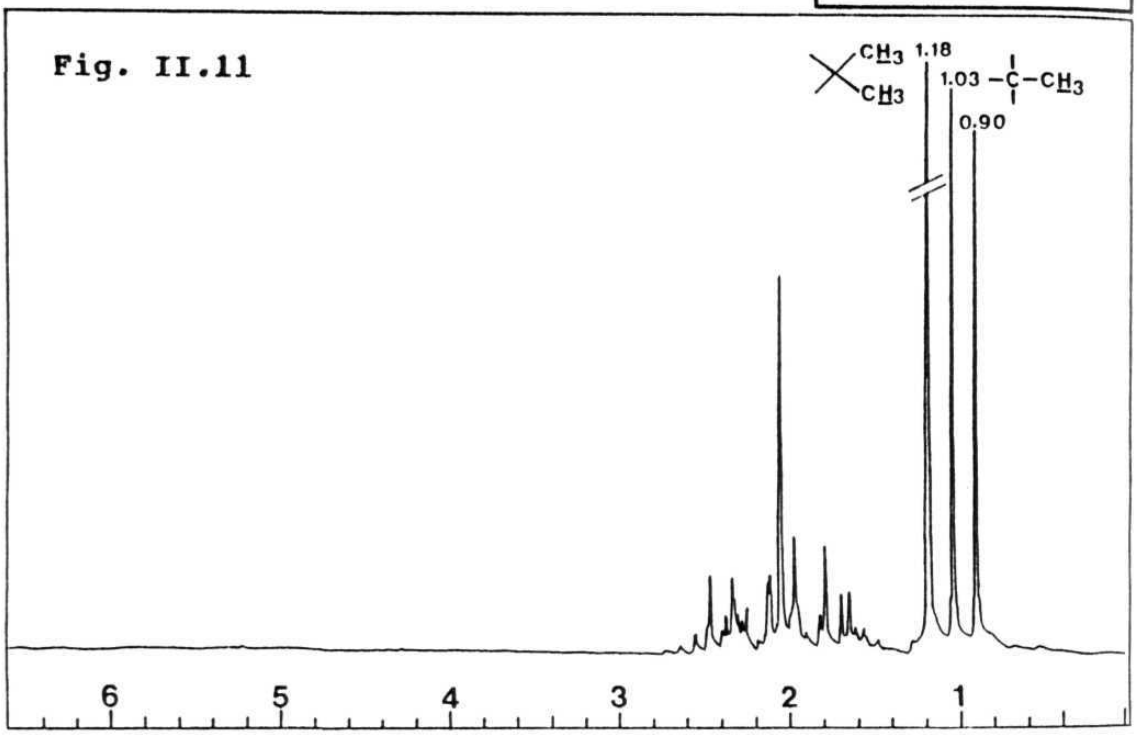
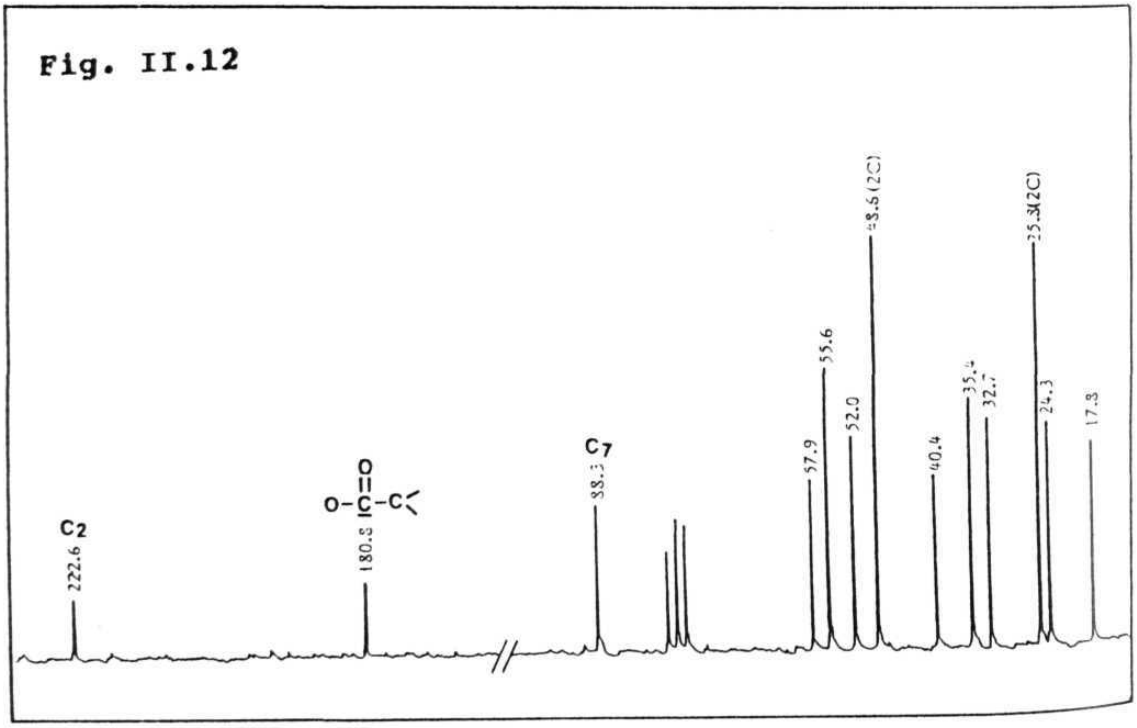
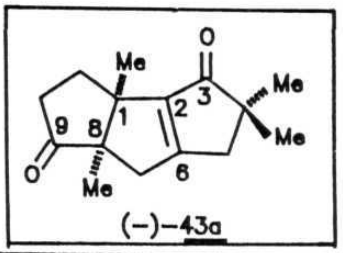


Fig. II.12





(−)−43a

Fig. II.13

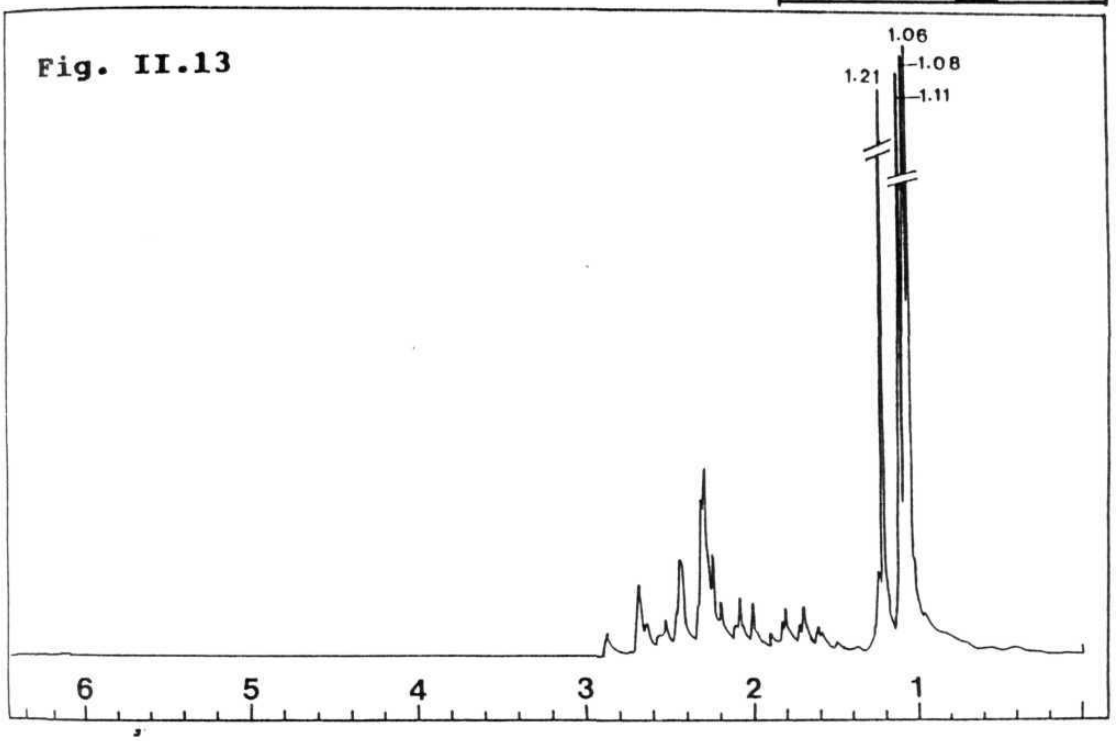
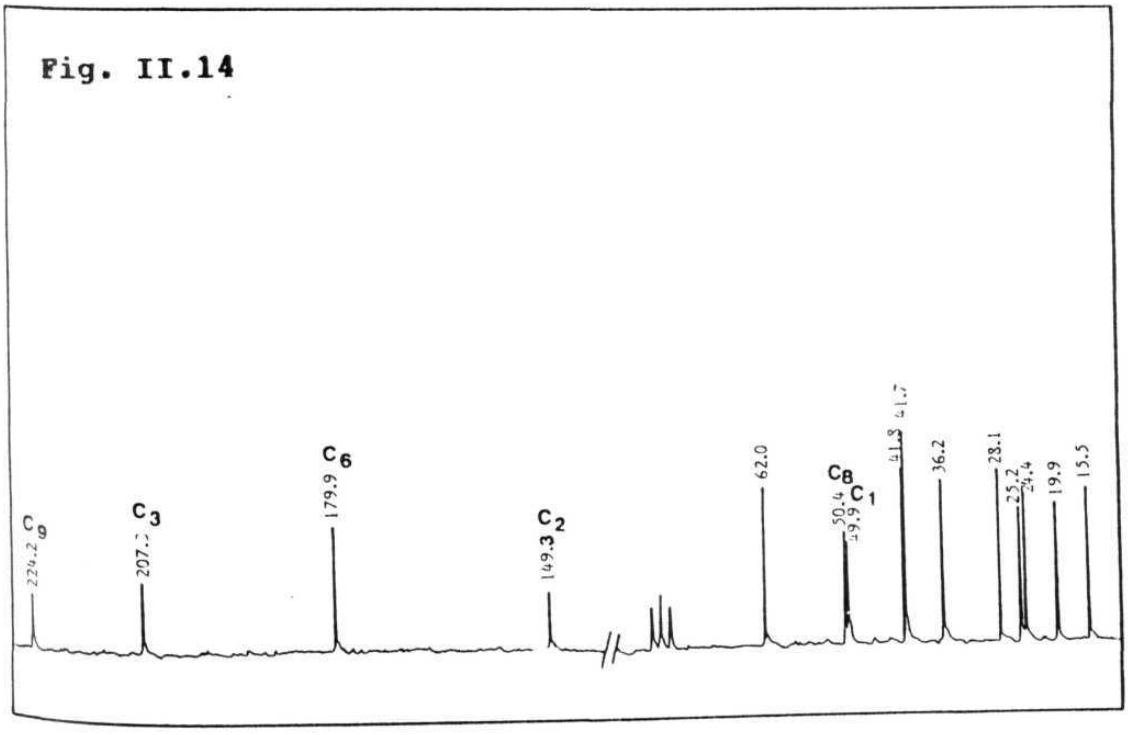
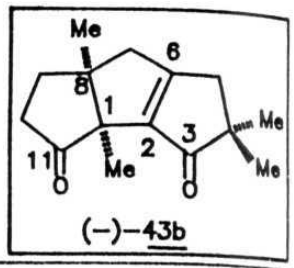


Fig. II.14





(−)−43b

Fig. II.15

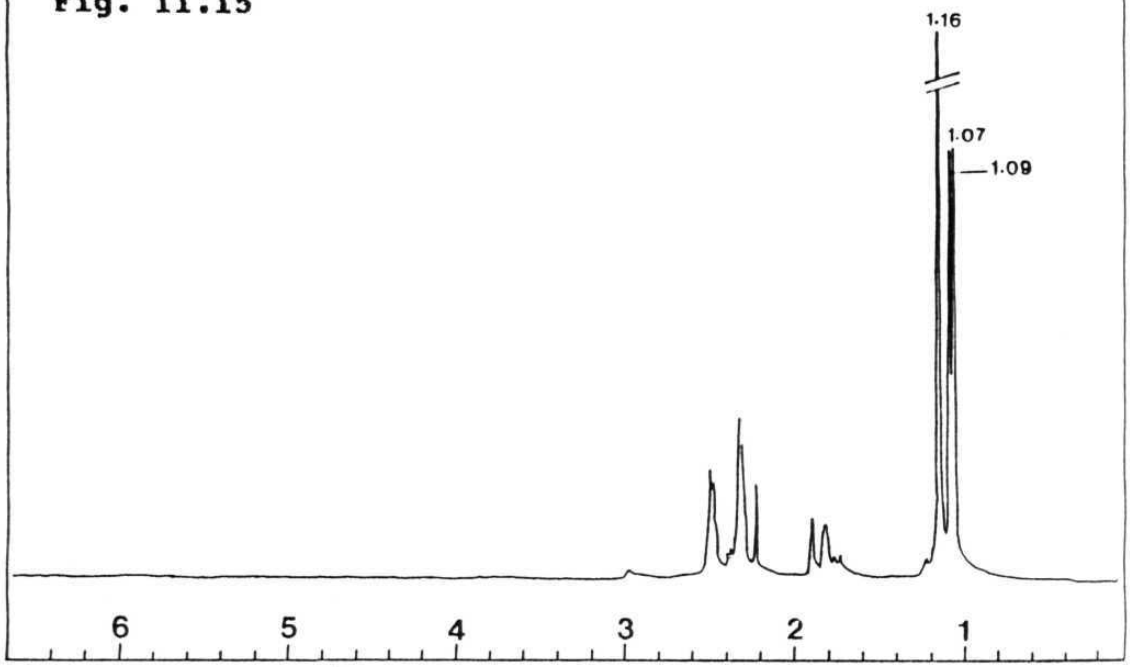
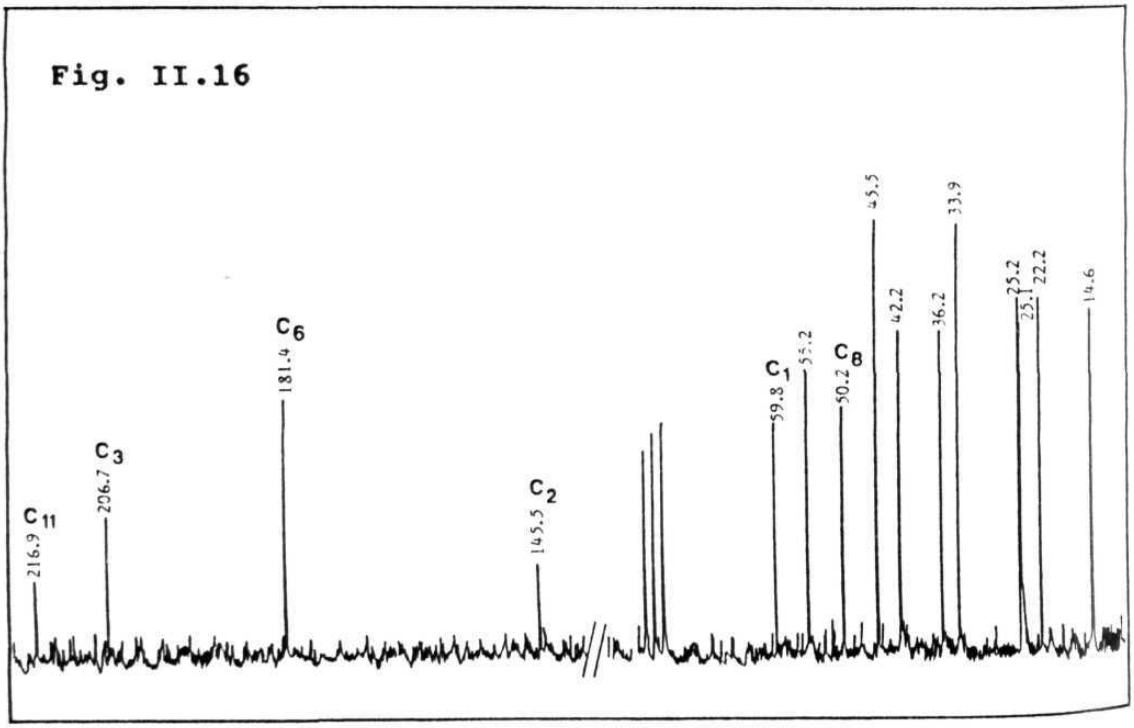
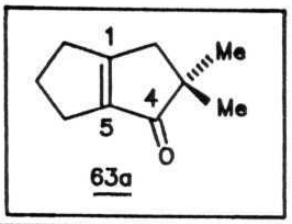


Fig. II.16





63a

Fig. II.17

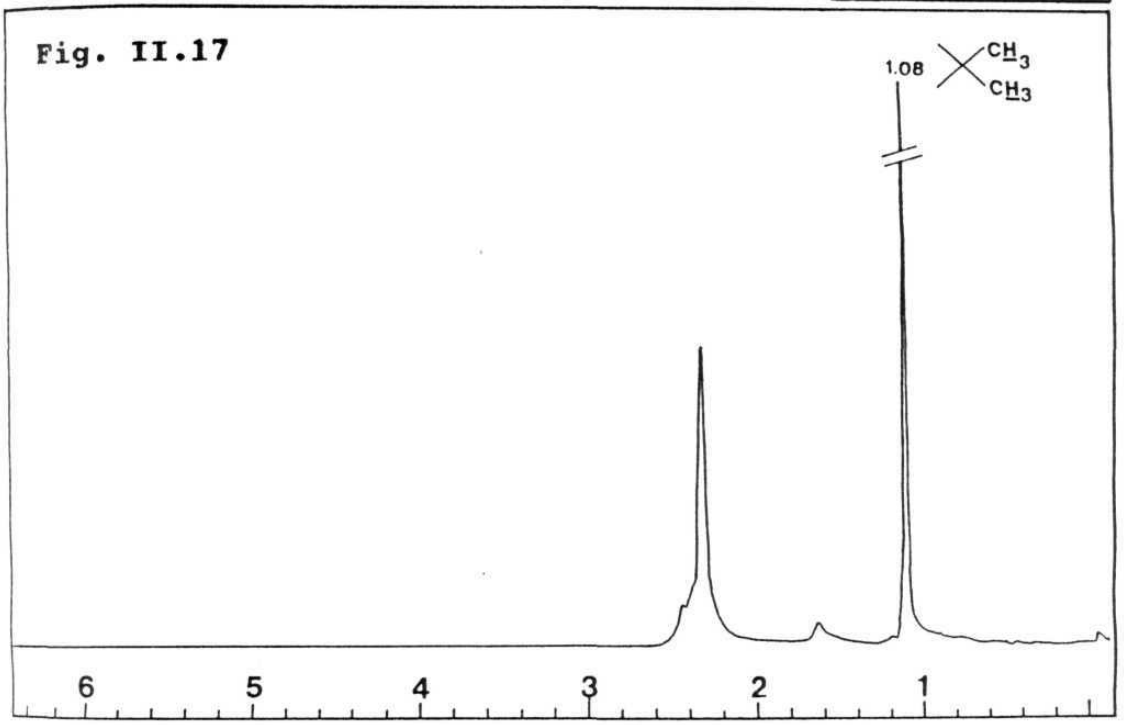
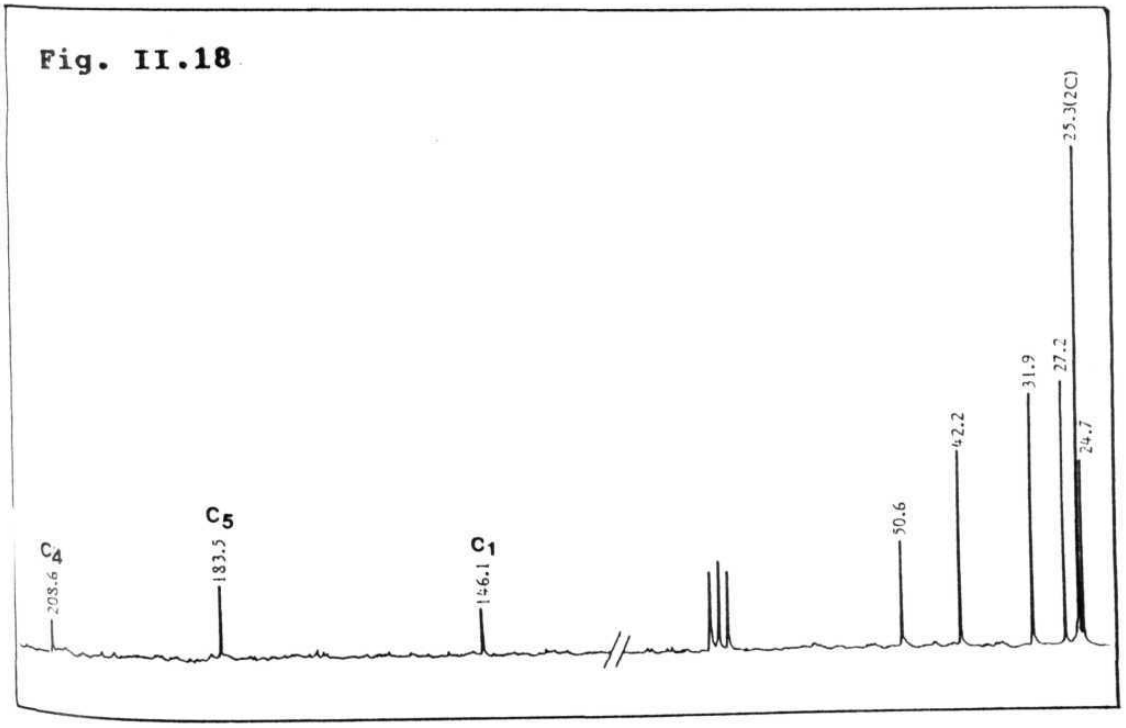
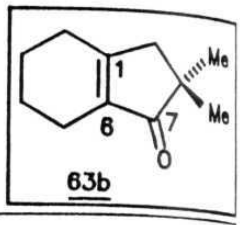


Fig. II.18





63b

Fig. II.19

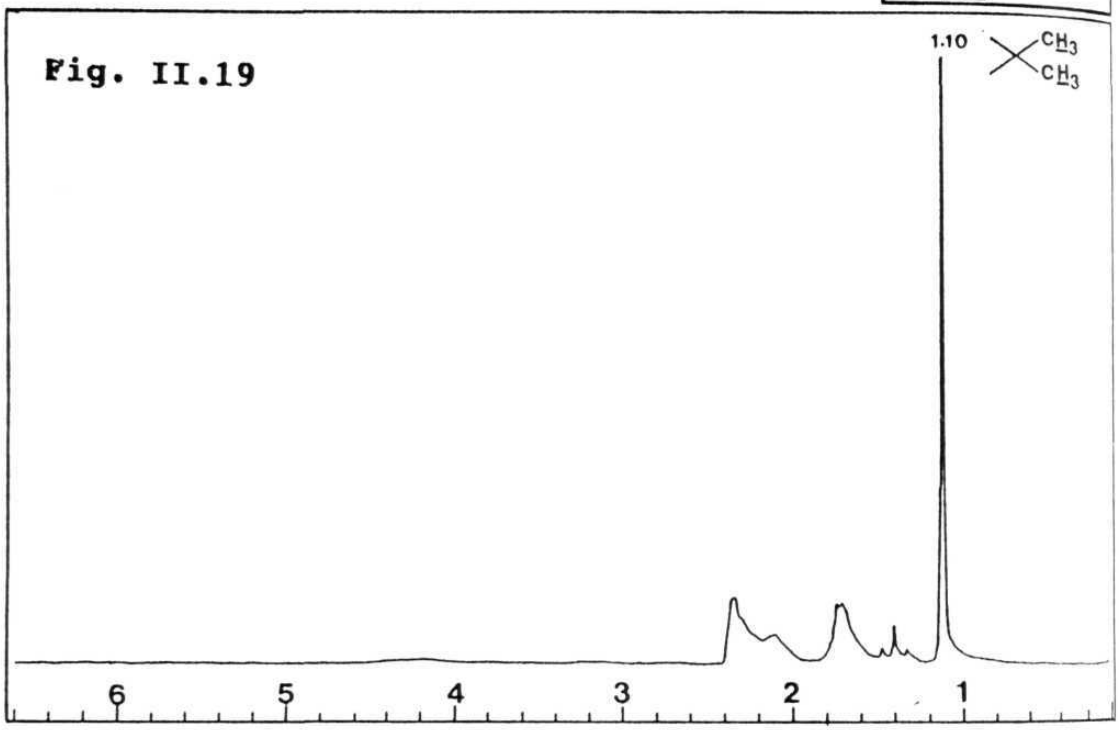
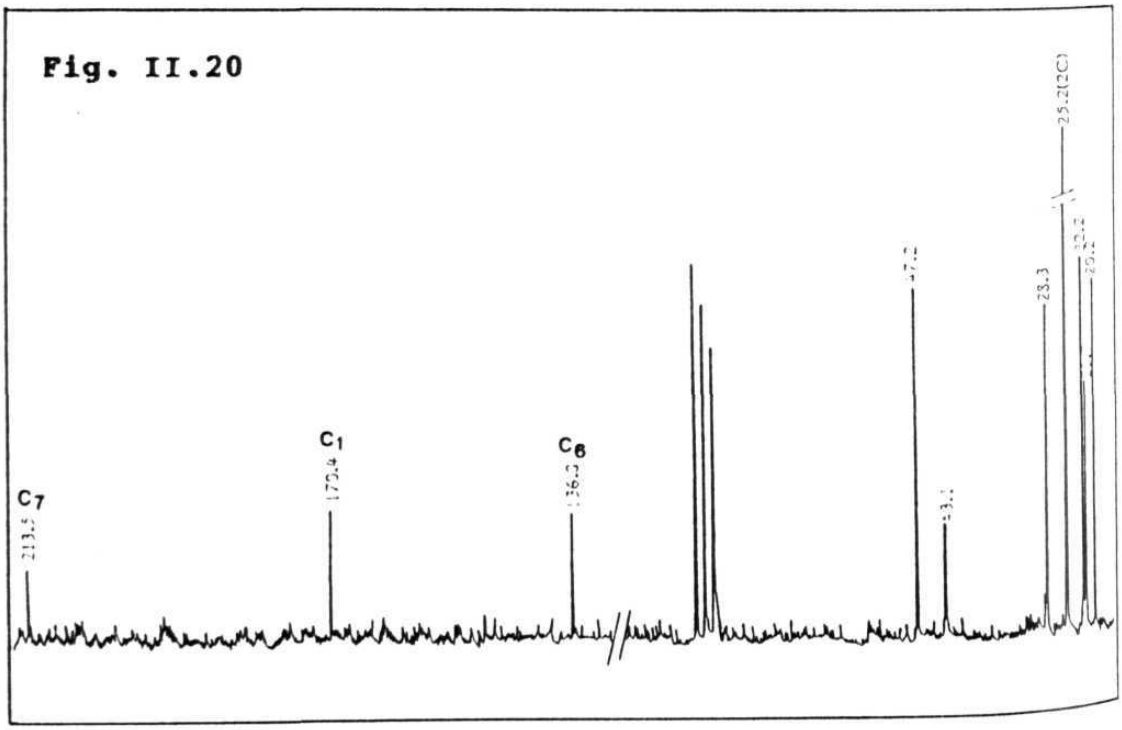
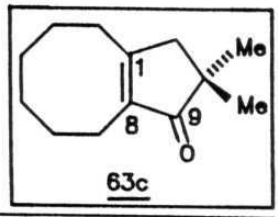


Fig. II.20





63c

Fig. II.21

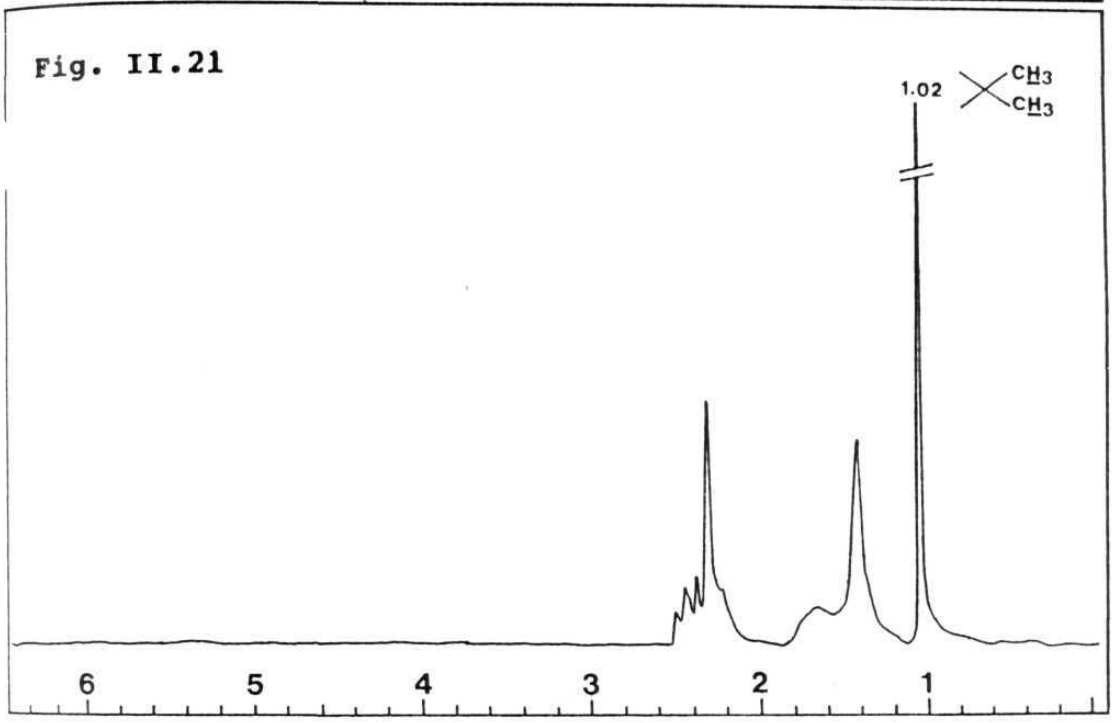
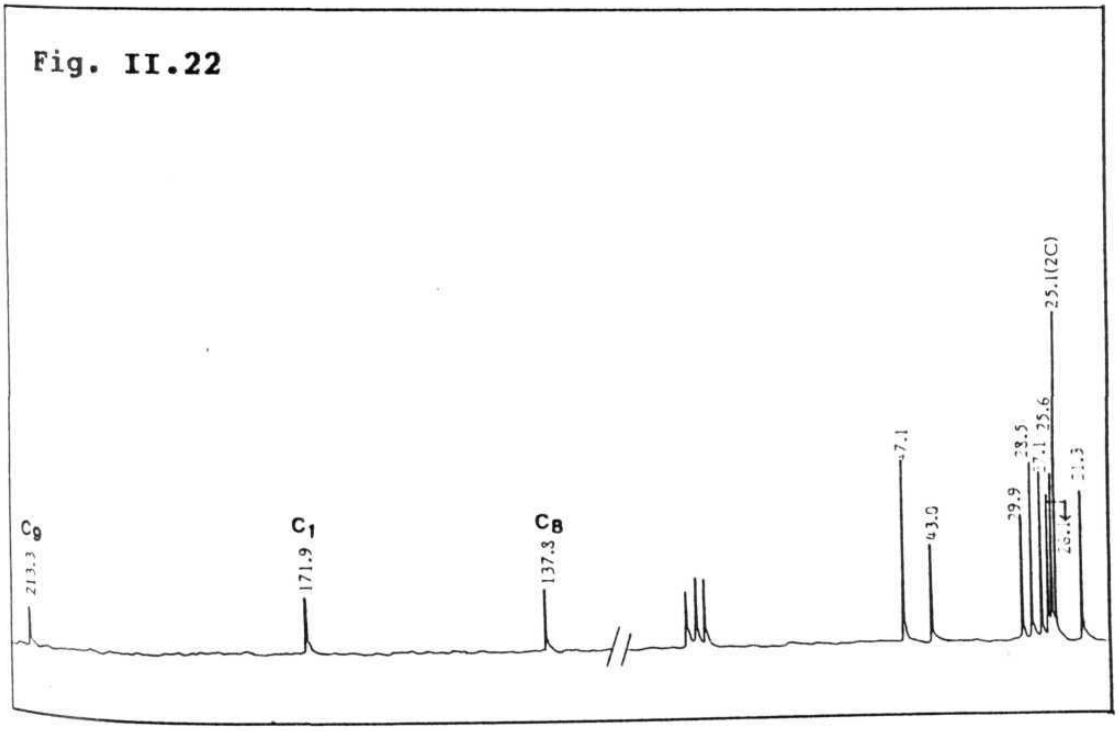
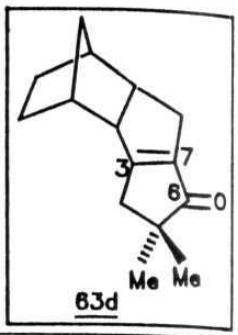


Fig. II.22





63d

Fig. II.23

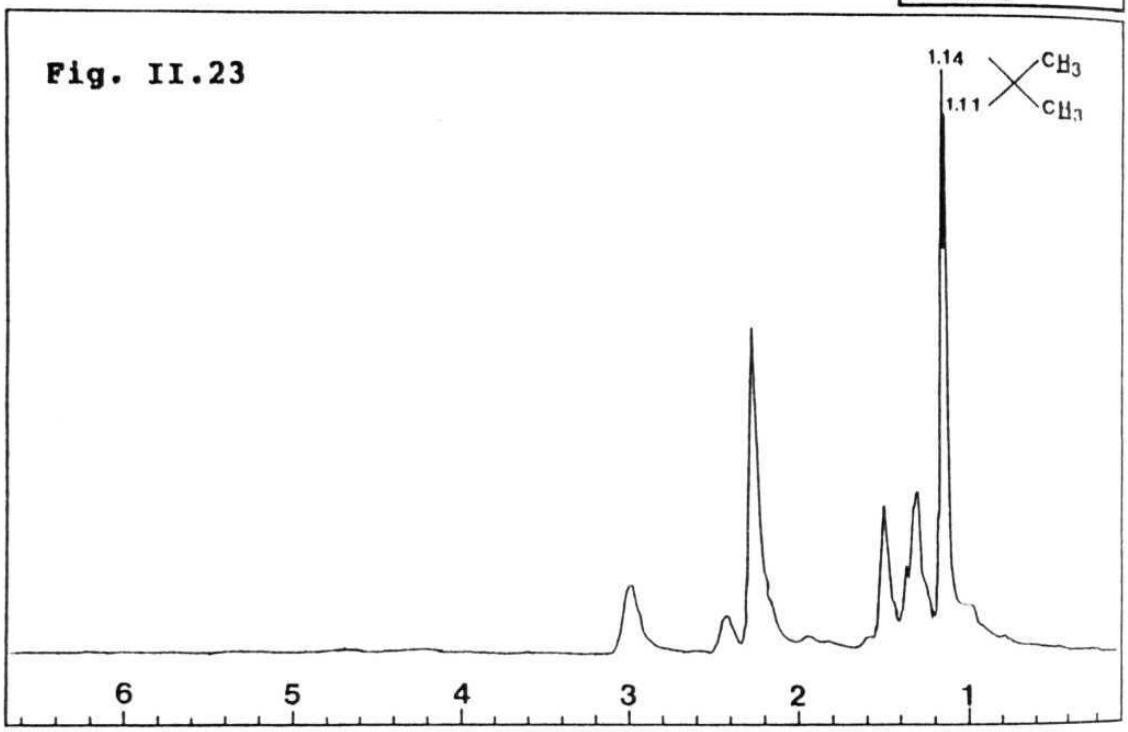
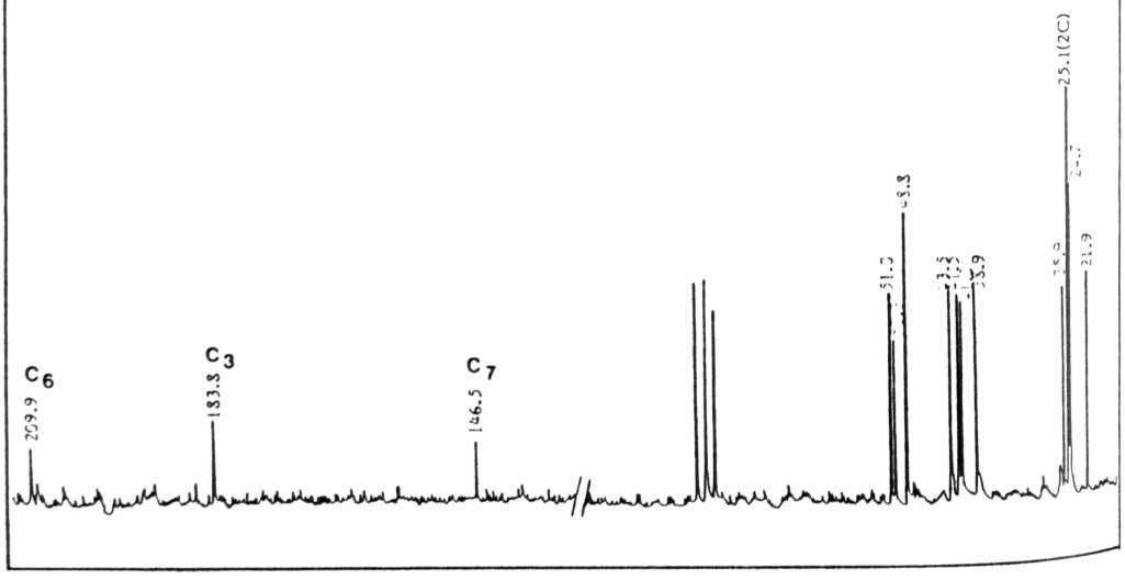
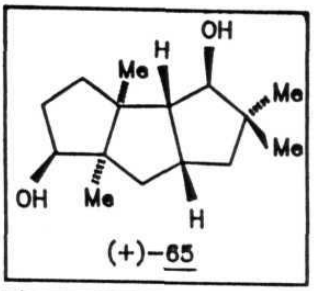


Fig. II.24





(+)-65

Fig. II.25

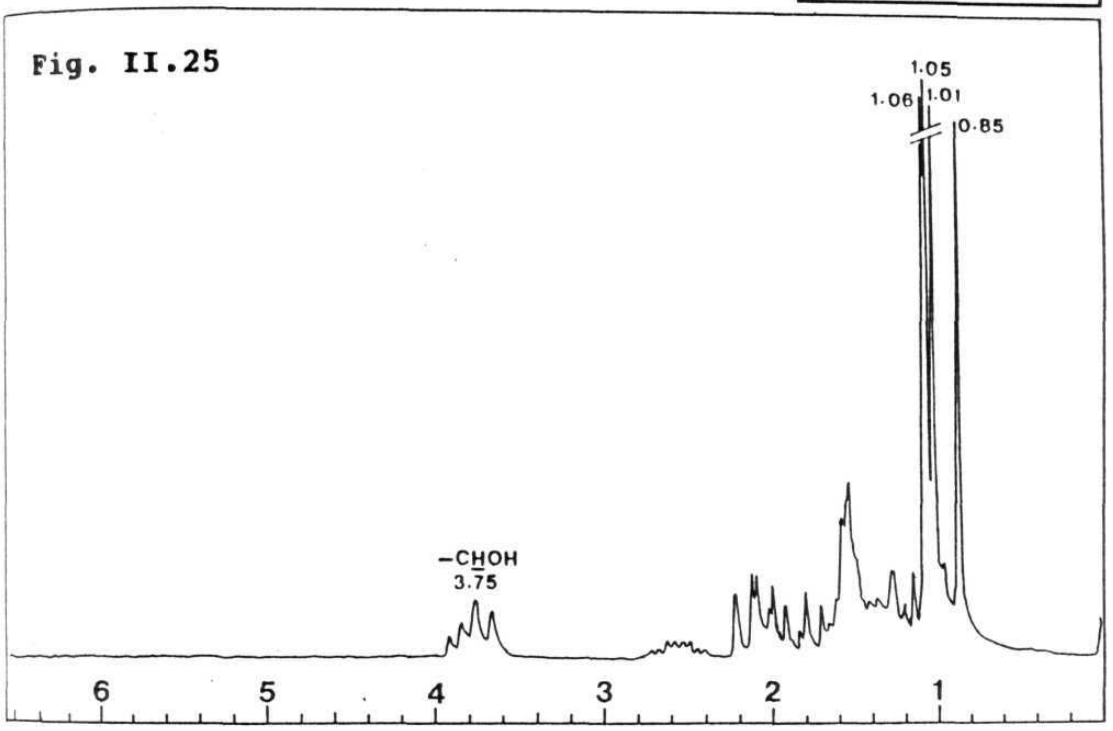
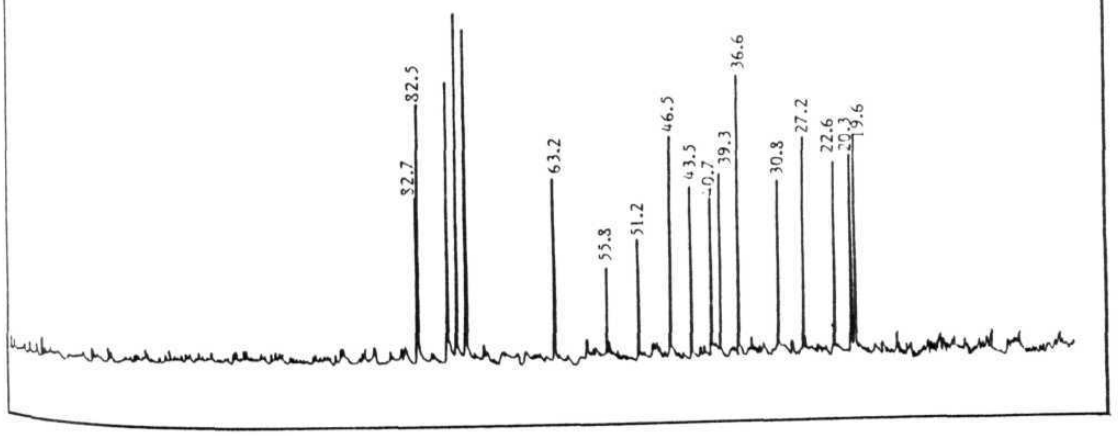
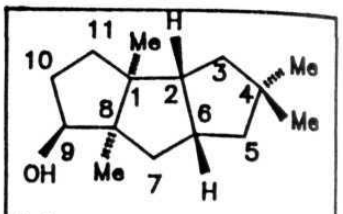


Fig. II.26





(−)−Ceratopicanol 4

Fig. II.27

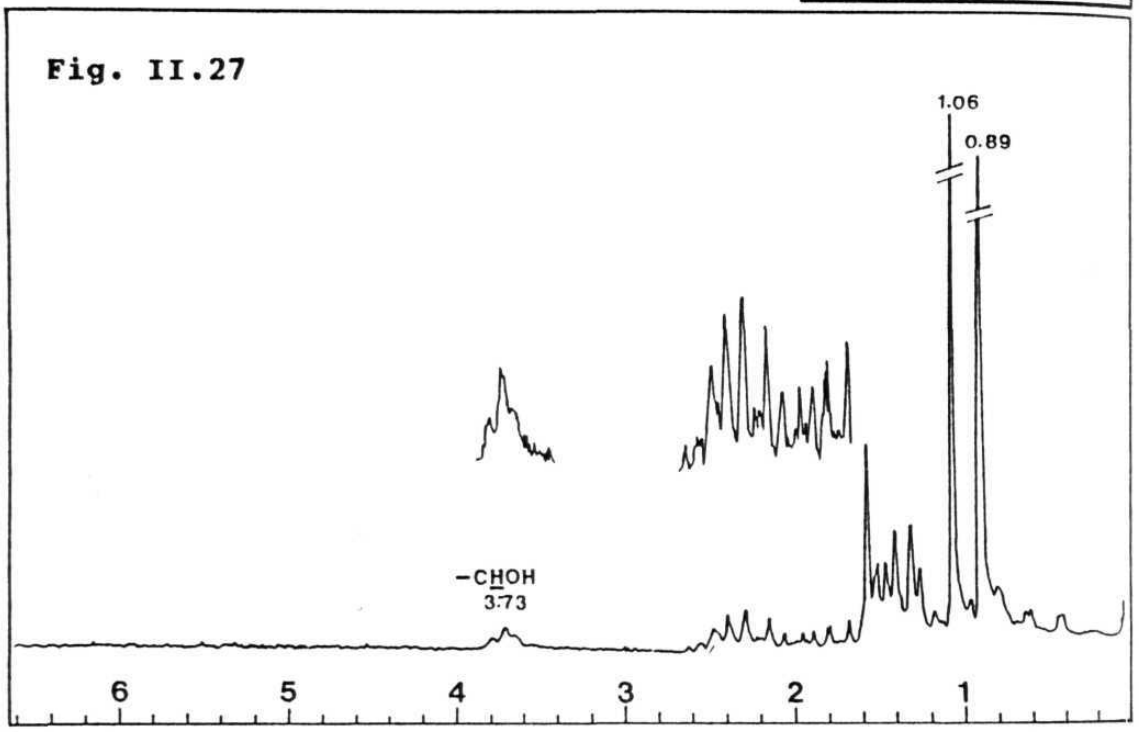
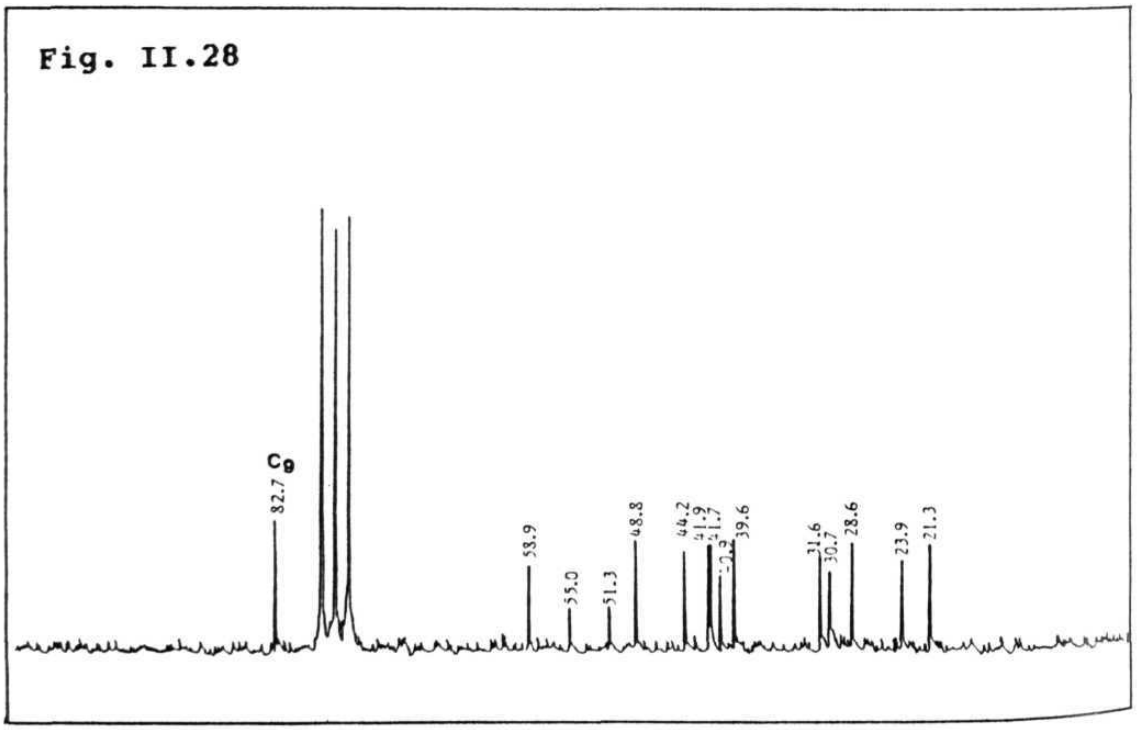
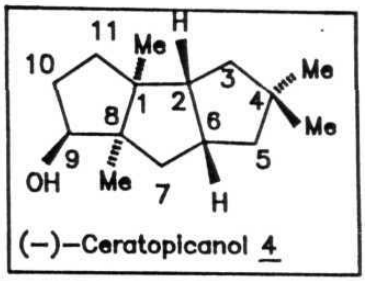


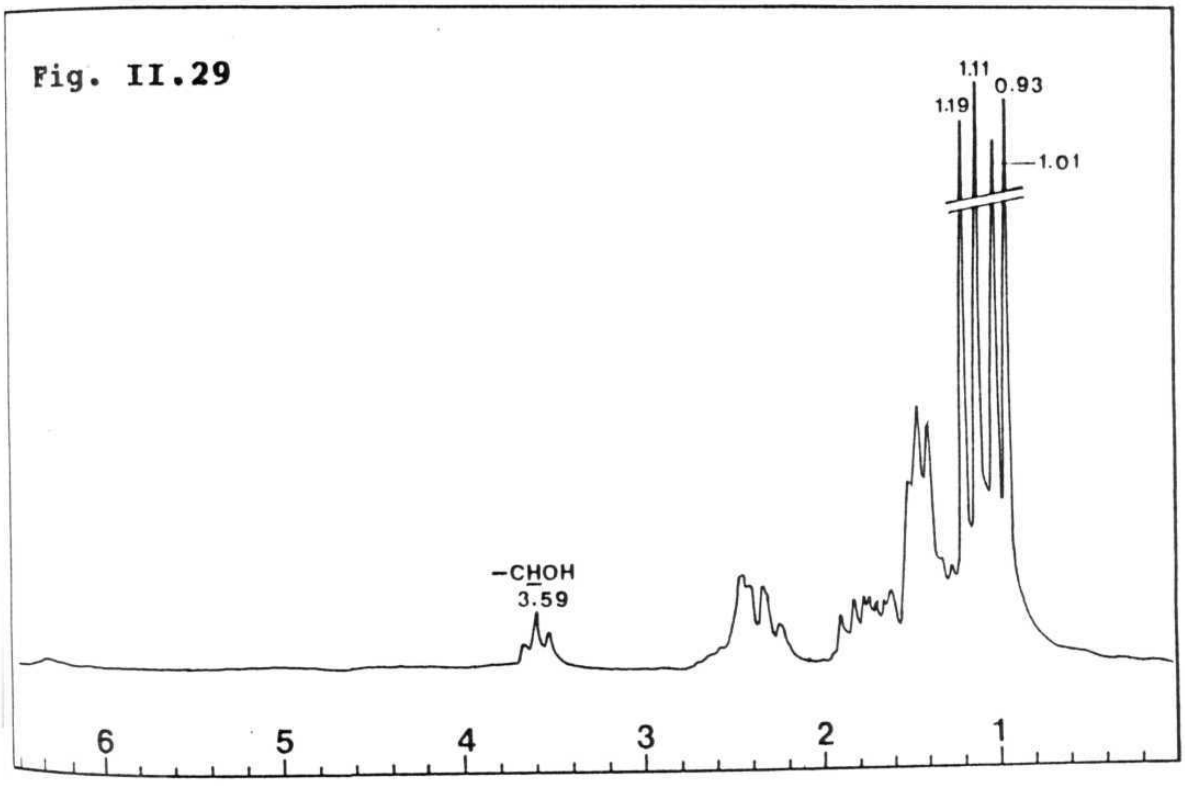
Fig. II.28





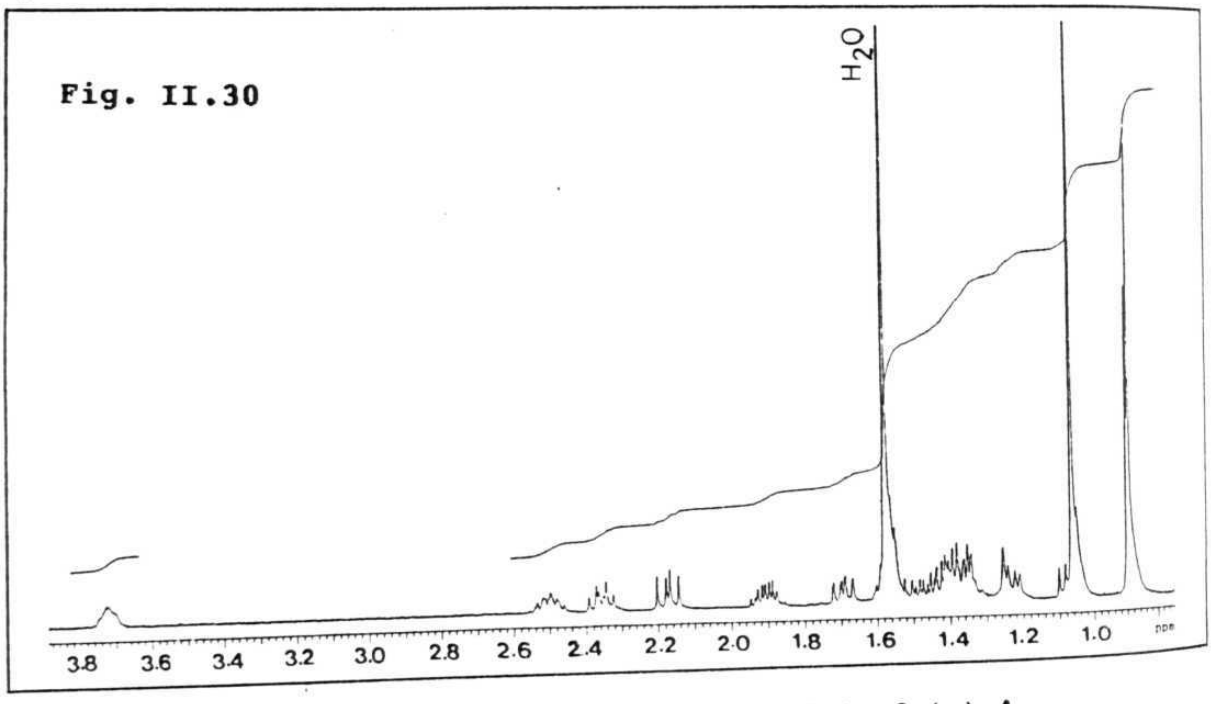
(−)−Ceratopicanol 4

Fig. II.29

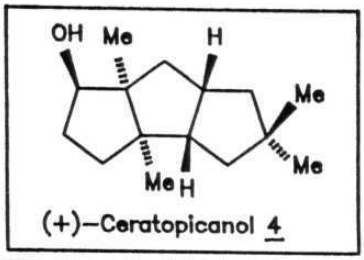


^{1}H NMR spectrum (100 MHz, C_6D_6) of (−)-4

Fig. II.30

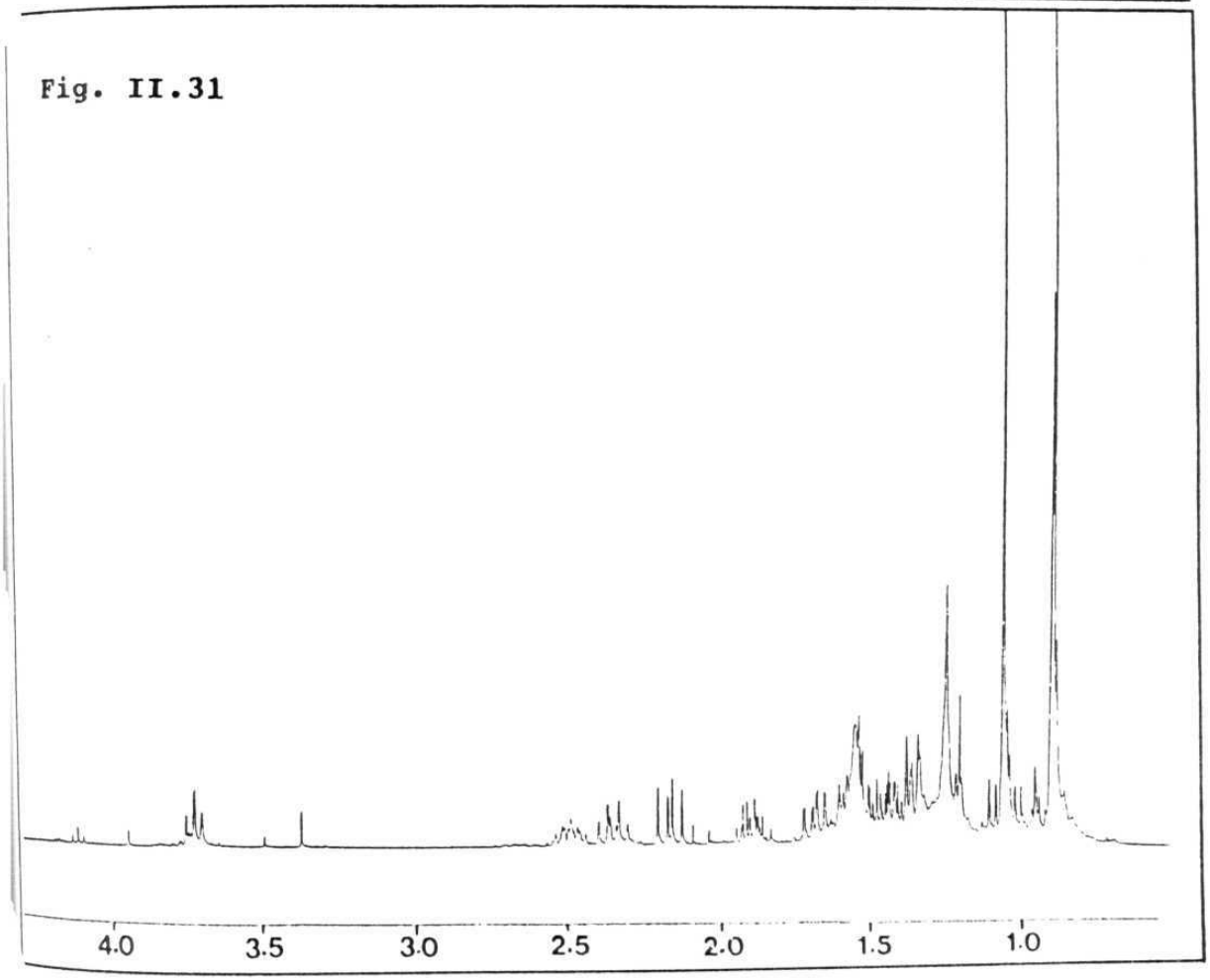


^{1}H NMR spectrum (400 MHz, $CDCl_3$) of (-)-**4**



(+)–Ceratopicanol 4

Fig. II.31



^{1}H NMR spectrum (400 MHz, $CDCl_3$) of (+)-4

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Chapter 3

Synthetic Studies Towards Virgane Diterpenes

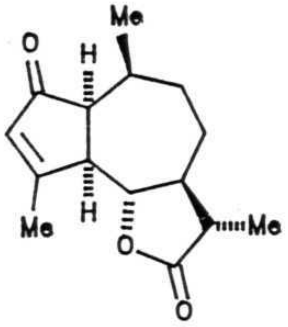
III.1. ABSTRACT:

An enantioselective synthesis of 5,7,5-fused tricyclic ring system present in the novel virgane diterpenes has been synthesised from R(+)-limonene. Our synthetic pursuit of the natural product 18-oxo-3-virgene **16** emanated from the bicyclic enone (-)-**19**, readily available from the route described earlier in this thesis. The enantiomerically pure enone (-)-**19** was restructured to (+)-**31** in a two step sequence involving oxidation to the trione (+)-**41** and aldol cyclisation-dehydration. Kinetic deprotonation of (+)-**31** with Li-HMDS and quenching of the enolate with allyl bromide furnished a 1:2 mixture of allylated products **42** and **43**. The allyl side chain in **42** and **43** was subjected to Pd^{+2} mediated Wacker-type oxidation to furnish (+)-**32** and **46**, respectively. The resulting tricarbonyl compounds (+)-**32** and **46** were cyclised with sodium hydride to furnish the corresponding tricyclic bis-enones (+)-**33** and **47**. To generate the requisite AB ring junction stereochemistry, reduction of the restructured ene-dione (+)-**31** with metal-ammonia and through catalytic hydrogenation was carried out. Through these reductions, in conjunction with equilibration studies, it was possible to prepare all the diastereomers **48-51** of the 5,7-fused perhydroazulenic system. Attempts to further elaborate (-)-**51** towards the virgane diterpene skeleton are also described.

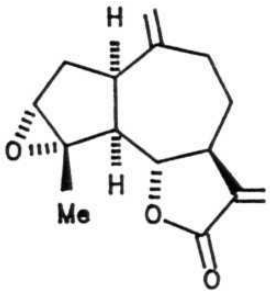
III.2. OBJECTIVE:

Many natural products embodying the hydroazulenic frame work have been encountered in Nature among sesqui- and diterpenes. These hydroazulenic natural products contain a range of diverse functionalities and many of them exhibit a broad spectrum of biological activity. Consequently, hydroazulenoids have aroused considerable interest among synthetic chemists. For example, guaianolides and pseudoguaianolides like 1-8 (Chart III.1) have

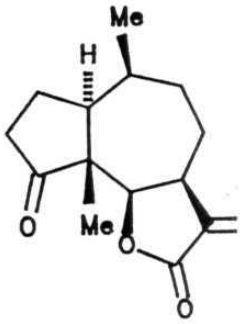
Chart III.1



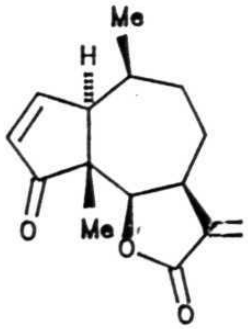
Dihydroarbigiovin 1



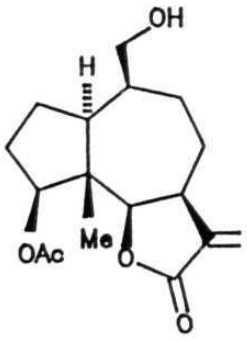
Estafiatin 2



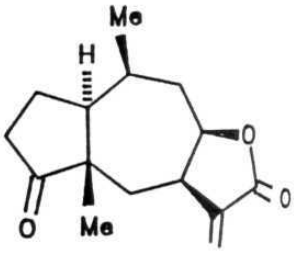
Damsin 3



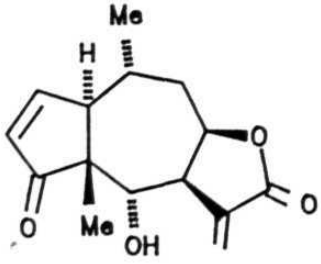
Ambrosin 4



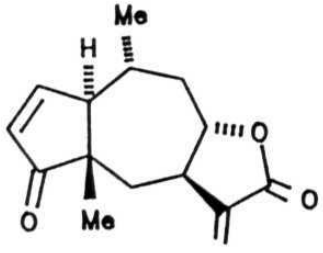
Hysterin 5



Confertin 6



Helenalin 7

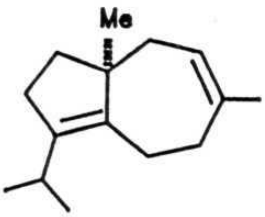


Aromaticin 8

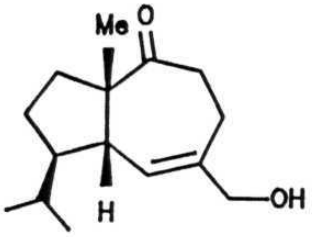
attracted a great deal of attention during the past 20 years.[1] In general, strategies involving, a) annulation of cycloheptane ring on to the cyclopentane ring, b) cyclopentannulation on to the cycloheptane ring and c) skeletal rearrangements of other carbocyclic systems have been developed for the construction of the hydroazulenic system[2-4].

Besides guaianolides and pseudoguaianolides, there are many other sesqui- and diterpene skeleta which contain a hydroazulenic moiety as part of their carbocyclic framework, see Chart III. 2[5]. However, synthetic efforts towards these compounds have been rather limited. One of the challenges in the synthesis of these compounds is the stereochemical problems associated with the conformationally labile 5,7-bicyclic system. Also, very few methods have been developed to gain access to the hydroazulenic system in enantiomerically pure form. In the first chapter of this thesis, we have described the synthesis of a chiral 5,7-fused hydroazulenic building block (-)-19 from R-(+)-limonene, which could be used as an advanced precursor for enantioselective synthesis of higher terpenes. Indeed, we have already demonstrated the utility of (-)-19 in the total synthesis of daucane and isodaucane sesquiterpenes, (-)-daucene 9[6a], (+)-aphanamol-I 10[6b,d] and dolastane diterpenes (+)-isoamijiol 15[6c,d] and (+)-dolasta-1(15),7,9-trien-14-ol 20[6c,d], Scheme III.1. More recently, we have also reported the restructuring of the abundantly available sesquiterpene (+)-longifolene 21 to a hydroazulene (+)-22[6e]. The framework of (+)-22 is present in many marine diterpenes of the spongian class [5h,i,j]. As an

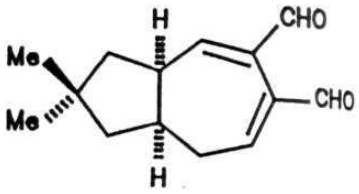
Chart III.2



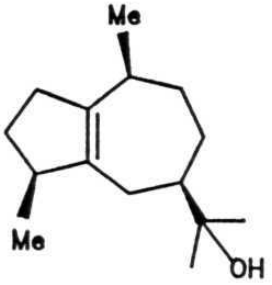
Daucene 9[5a]



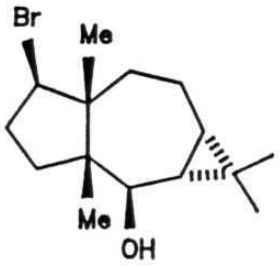
Aphanamol 10[5b]



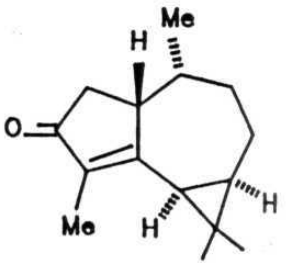
Velleral 11[5c]



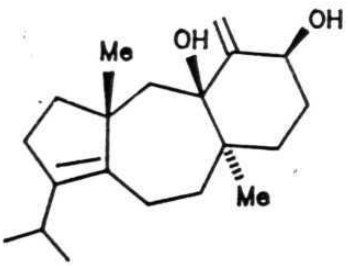
Guaiol 12[5d]



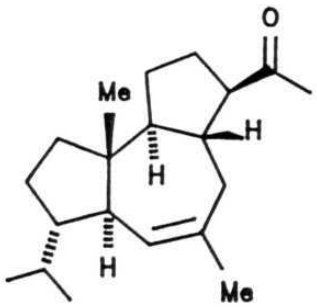
Neomeranol 13[5e]



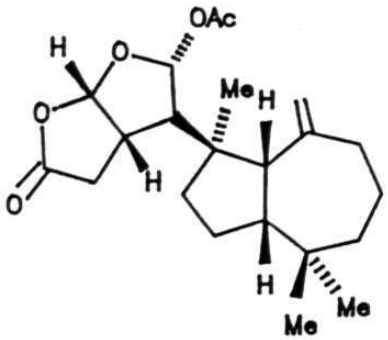
Cyclocolorenone 14[5f]



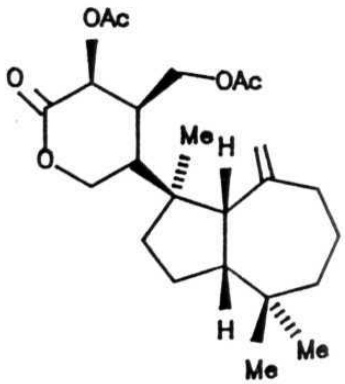
(−)−Isoamijiol 15[5g]



18−Oxo−3−virgene 16[7]



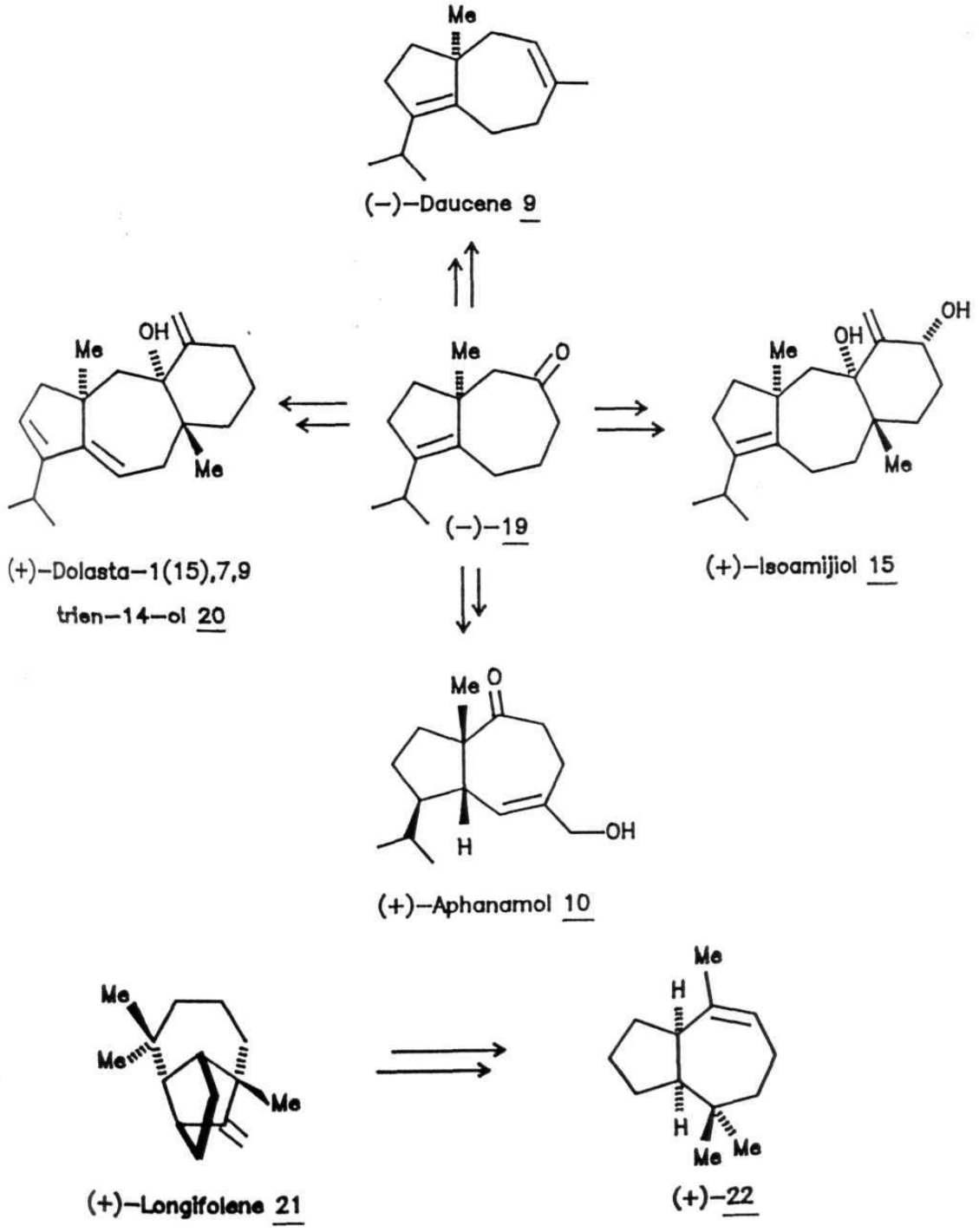
Dendrillolide A 17[5h,i,j]



Shahamin D 18[5h,i,j]

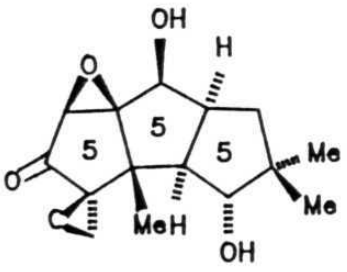
extension of our interest in the synthesis of 5,7-fused hydroazulenic terpene natural products and to demonstrate further the utility of the building block (-)-19, we chose the novel, tri-

Scheme III.1

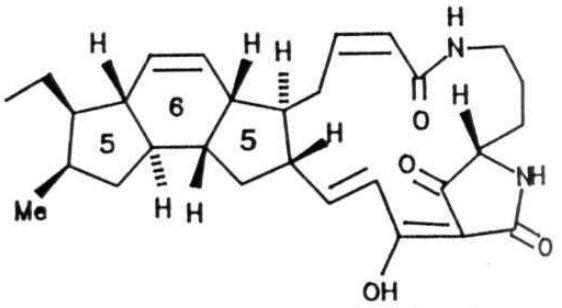


cyclic diterpene 18-oxo-3-virgene **16** as a synthetic objective. Recently, isolation of the diterpene **16** from the waxy, surface resin of flowers of tobacco Nicotina tabacum cv Virginia 115 has been reported[7]. Structure of **16** was deduced on the basis of extensive spectral studies and confirmed by X-ray crystallography. Isolation of a natural product with 5,7,5-fused tricyclic skeleton was an interesting outcome as this completed the occurrence of the 5,n,5-fused (n=5,6,7,8,9) tricyclic series in Nature. Examples of important natural products bearing the 5,5,5-, 5,6,5-, 5,7,5-, 5,8,5-, 5,9,5-fused tricyclic skeleta are shown in the chart III.3[8].

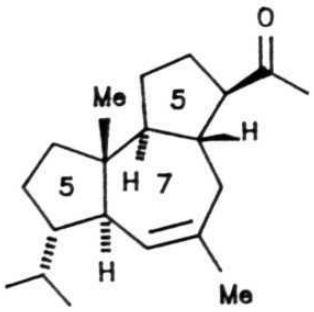
Chart III.3



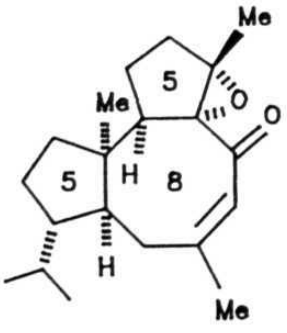
Coriolin **23**[8a]



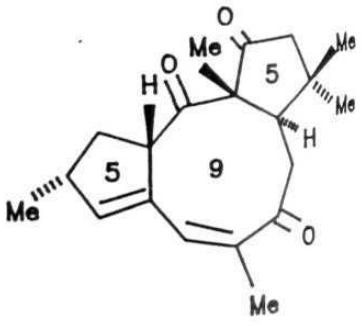
Ikarugamycin **24**[8b,c,d]



18-Oxo-3-virgene **16**[7]



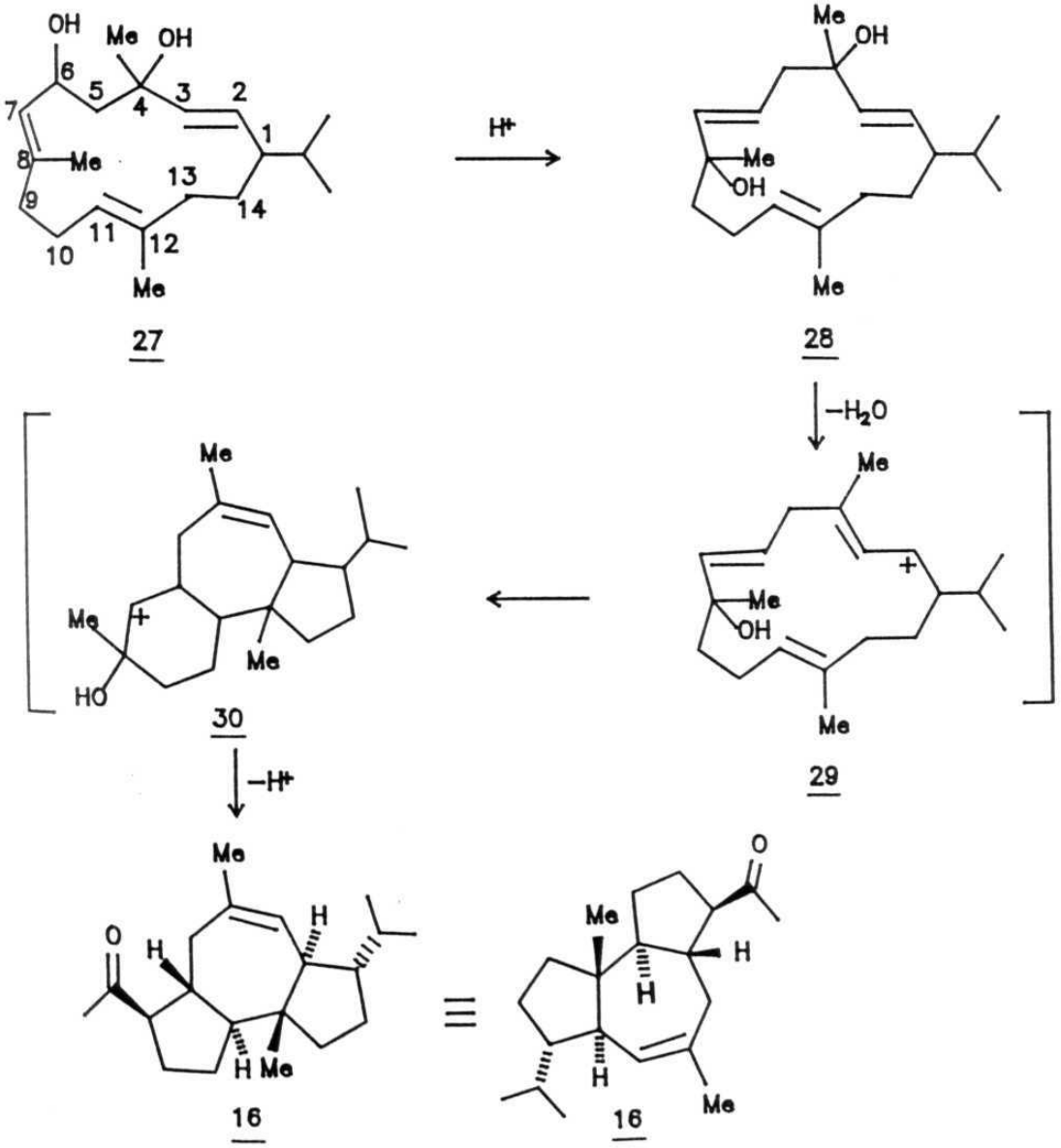
7,8-Epoxy-4-basmen-6-one **25**[8e]



Jatrophatrione **26**[8f]

From a biogenetic point of view the origin of the 18-oxo-3-virgene **16** is very interesting. It is well known that various tobacco species are a complex and rich source of labdanoid and cembranoid diterpenes[9a]. For example, over 50 cembranoids have been isolated from tobacco[9b]. It is therefore reasonable to speculate that **16** can be derived from <u>in vivo</u> cyclisation of an appropriate cembrane precursor, Scheme III.2. The 4,8-diol 28

Scheme III.2



can be formed from a tricyclic cembranoid **27** by an allylic rearrangement, which can further undergo dehydration to furnish **29**. Transannular cationic cyclisation in **29** would lead to **30**. A pinacol-type rearrangement in **30** would lead to the natural product 18-oxo-3-virgene **16**[#].

The tricyclic diterpene **16** with a novel tricyclic framework constitutes an interesting and formidable synthetic objective. Besides, its unique 5,7,5-fused framework, it has six contiguous stereogenic centres arranged in cis, anti, anti, anti, cis-fashion. In particular, setting the isopropyl and the angular methyl and the acetyl group and the flanking hydrogen relative stereochemistry could be a challenging proposition. So far, no synthetic studies directed towards **16** have appeared in the literature. In this chapter of the thesis, we describe our synthetic efforts aimed at 18-oxo-3-virgene **16**.

III.3. SYNTHETIC STUDIES:

In the pursuit of **16**, our first objective was to construct the 5,7,5-fused tricyclic core present in the natural product. An

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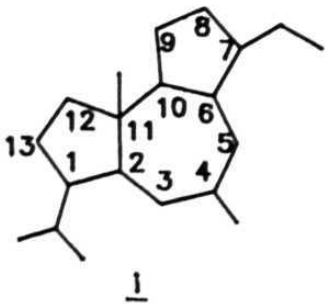
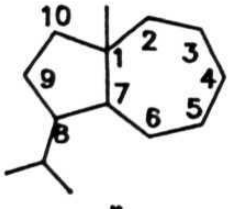
[#] The virgane **i** and hydroazulene **ii** systems have been numbered as follows:



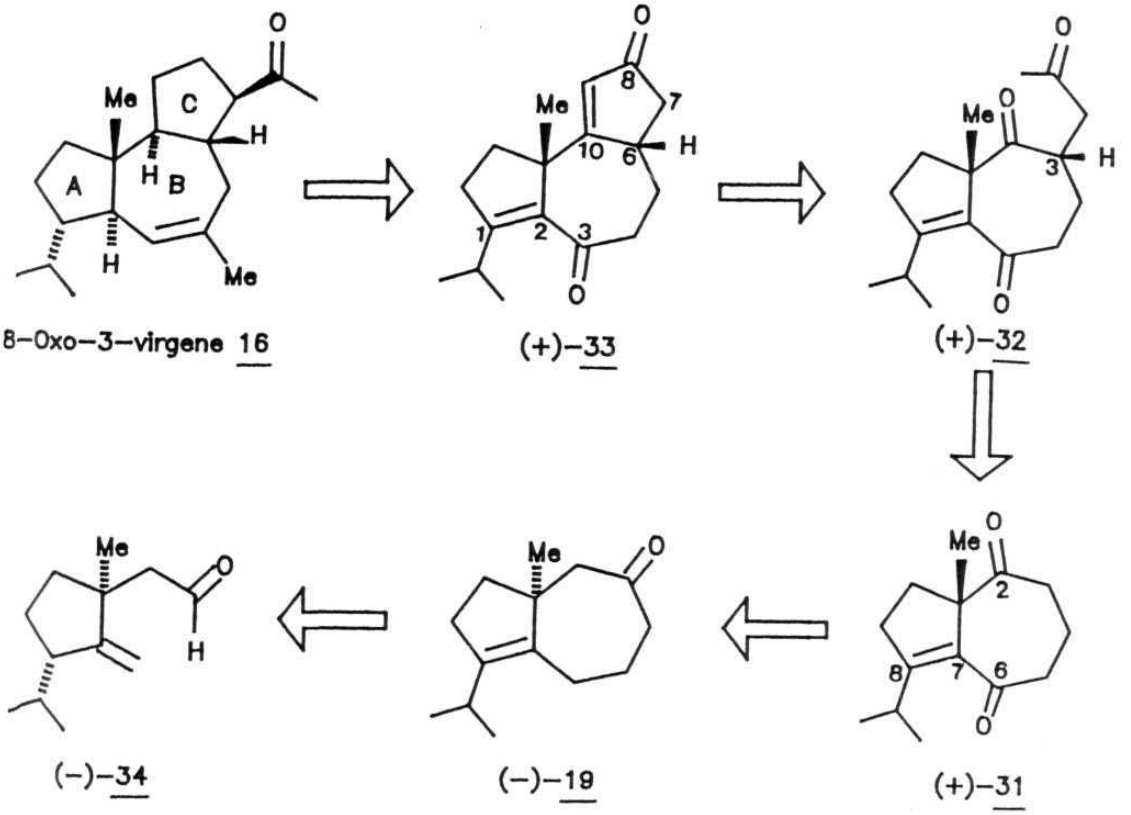
I



II

approach to this system was revealed through the retrosynthetic plan depicted in **Scheme III.3.** We readily recognised the bicyclic enone (-)-19, which we had earlier synthesised

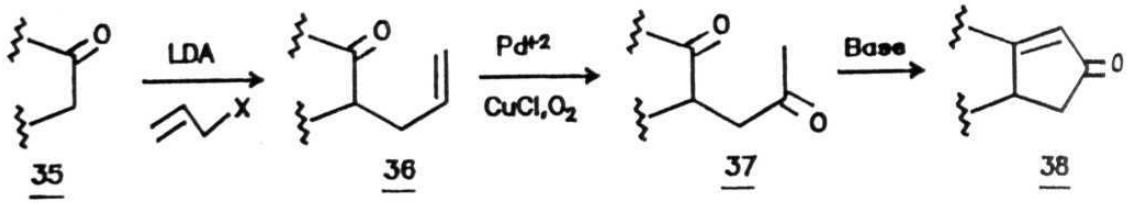
Scheme III.3



from R-(+)-limonene (**Chapter I**) as an advanced precursor. A key feature of this retrosynthetic protocol was to have access to the bicyclic ene-dione (+)-31 from (-)-19 through a restructuring process. This was considered essential for two reasons. Firstly, the functionality in the seven membered ring in (-)-19 had to be amplified and relocated for the purpose of annulating the five membered ring and for installing the trisubstituted double bond. Secondly, in order to secure the AB-ring junction stereochemistry, the hindered tetrasubstituted double bond in

(-)-19 needed to be activated. This could be achieved by providing appropriate conjugation. The ene-dione (+)-31 eminently fulfills the requirement of contemplated synthetic steps. Thus, the presence of enone double bond in (+)-31 could effectively control the stereochemistry at C_7-, C_8-positions. The C_2-carbonyl group could be utilised for the appendage of a cyclopentenone ring and C_6-carbonyl could be used to generate the methyl substituted double bond in the seven membered ring. The elaboration of the five membered ring on the ene-dione (+)-31 was sought to be achieved through a three step annulation sequence indicated in Scheme III.4. This envisaged regio- and stereoselective allylation at C_3-position in (+)-31 and Wacker-type oxidation[10] to generate an acetonyl side chain as in

Scheme III.4



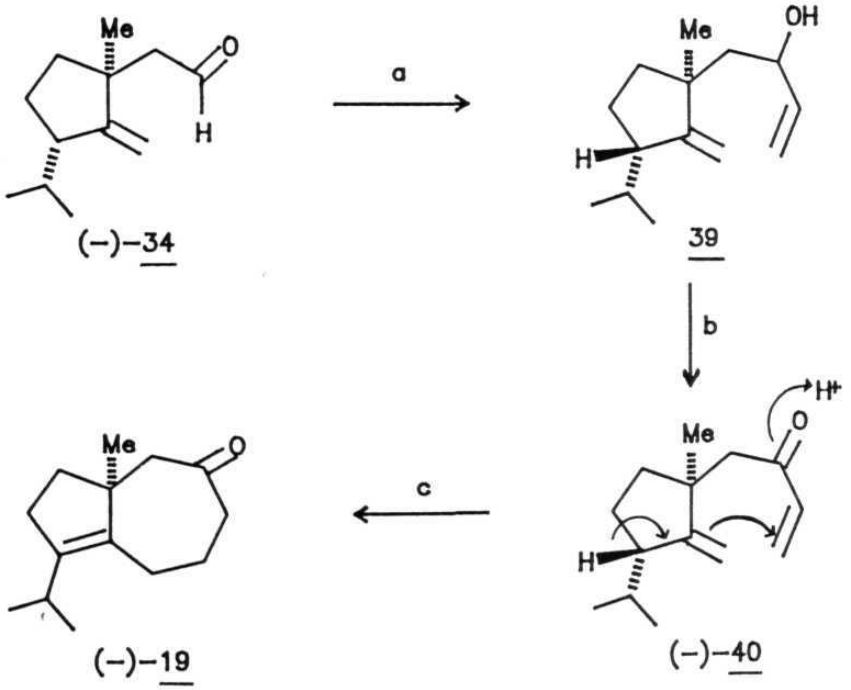
(+)-32. Base catalysed aldol condensation-dehydration sequence was expected to generate the tricyclic bis-enone (+)-33. It was surmised that the two enone moieties in (+)-33 will enable effective stereocontrol at C_1-, C_2-and C_{10}-positions. Finally, the C_8 carbonyl could be exploited to install the C_7 acetyl side chain. With these thoughts, we ventured to give practical shape to our synthetic plan.

To begin with, the enantiomerically pure and readily accessible chiral aldehyde (-)-34 was elaborated to the bicyclic

hydroazulenic enone (-)-19, as described in the first chapter of this thesis. Grignard reaction on (-)-34 with vinyl bromide followed by oxidation of the resulting allylic alcohol mixture 39 afforded the α,β-unsaturated enone (-)-40. Acid catalysed enone-olefin cyclisation in (-)-40 was the pivotal step and proceeded smoothly to furnish the bicyclic enone (-)-19, Scheme III.5.

With the ready access to the 5,7-fused bicyclic enone (-)-19, we turned our attention towards establishing a restructuring protocol for it. In this connection, we wished to exploit the 1,4-relationship of the carbonyl group and the exocyclic double bond in the seven membered ring. Consequently, the

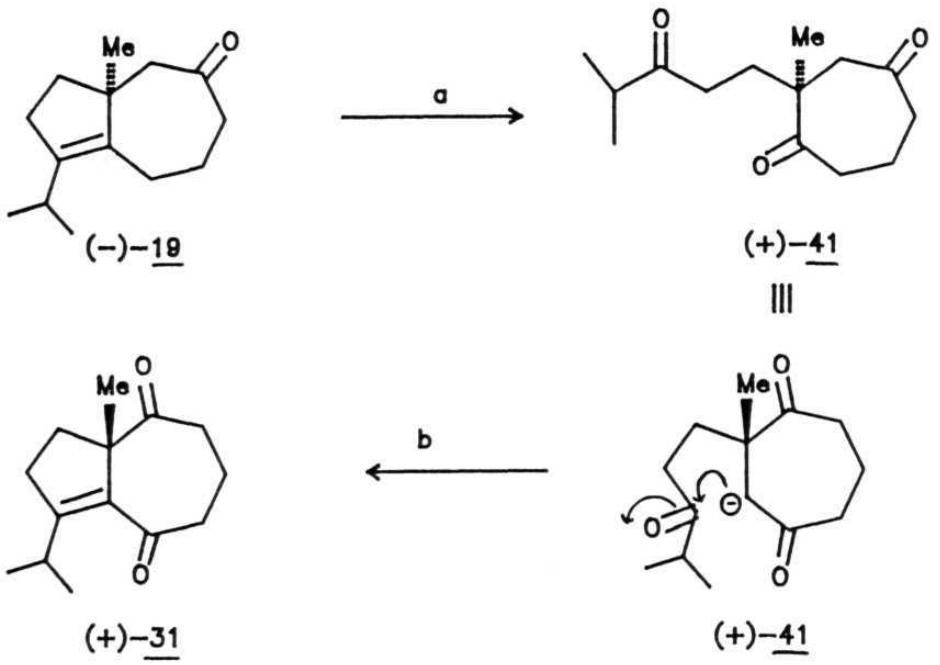
Scheme III.5



Reagents and yields: (a) CH_2=CHBr, Mg, THF, 30°C, 30 min, 75%; (b) PCC, CH_2Cl_2, molecular sieves 4 Å, 30°C, 1 h, 65%; (c) Cat. $HClO_4$-$(CH_3CO)_2O$, EtOAc, 30°C, 25 min, 65%.

tetrasubstituted double bond of bicyclic hydroazulenone (-)-19 was smoothly cleaved employing the Sharpless catalytic Ru(IV) oxidation procedure[11] to furnish the trione (+)-41 in near quantitative yield, Scheme III.6. The presence of three carbonyl resonances in the ^{13}C NMR at δ213.4, 213.2 and 209.6 besides,

Scheme III.6



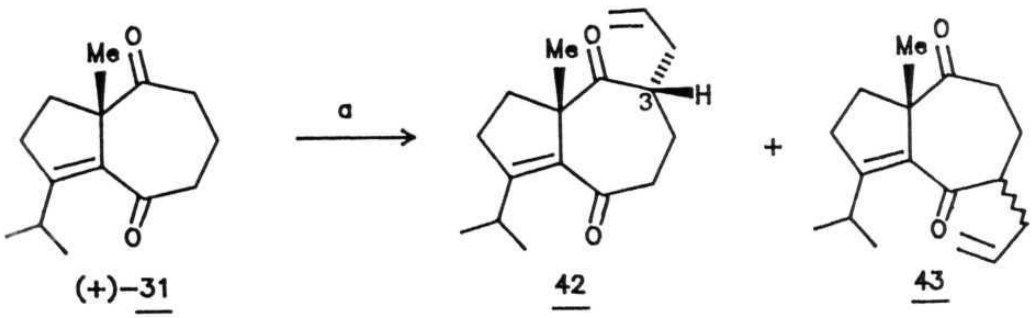
Reagents and yields: (a) RuO_2-$NaIO_4$, CH_3CN-CCl_4-H_2O, 30°C, 1 h, quant.; (b) 5% KOH-CH_3OH, △ , 30 min, 60%;

complimentary ^1H NMR data confirmed the monocyclic structure of (+)-41. The trione (+)-41 was readily induced to undergo intramolecular aldol cyclisation in the presence of 5%KOH-MeOH to furnish the bicyclic ene-dione (+)-31 in 60% yield. The ene-dione formulation was fully consonant with the spectral data. The IR spectrum showed two carbonyl absorptions at 1700 and 1670 cm^{-1}, representing the enone and saturated carbonyl group

respectively. The ^{13}C NMR spectrum (Fig. III.2) in particular exhibited four characteristic sp^2 carbon resonances at δ 213.7, 199.8, 167.3 and 136.8 due to a conjugated enone moiety and a saturated carbonyl group. Thus, in a two-step synthetic stratagem, (-)-19 was restructured with amplification and relocation of functionality. It is of interest to note that the restructured (+)-31 belongs to an enantiomeric series with respect to its precursor (-)-19.

The next key step involving alkylation of (+)-31 was executed under kinetically controlled conditions, but the expected regioselectivity was not observed. Kinetic deprotonation of the ene-dione (+)-31 with Li-HMDS at -78°C and quenching of the enolate with allyl bromide furnished a 1:2 mixture of 42 and 43, Scheme III.7. Though the separation of the isomers at

Scheme III.7



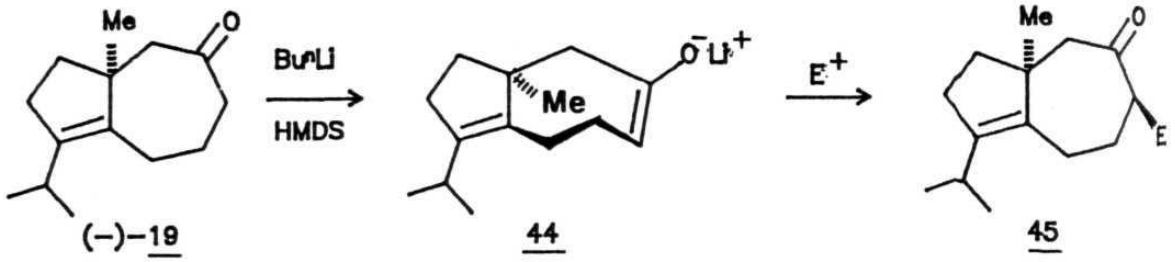
(+)-31 42 43

Reagents and yields: (a) Bu^nLi, HMDS, THF, allyl bromide, -78°-0°C.

this stage was not successful, the olefinic signals at δ 5.56 and 4.86 characteristic of an allyl group in the ^1H NMR spectrum of 42 and 43 were most informative in assigning the gross structure. The stereochemistry of the allyl group at C_3-position in 42 was

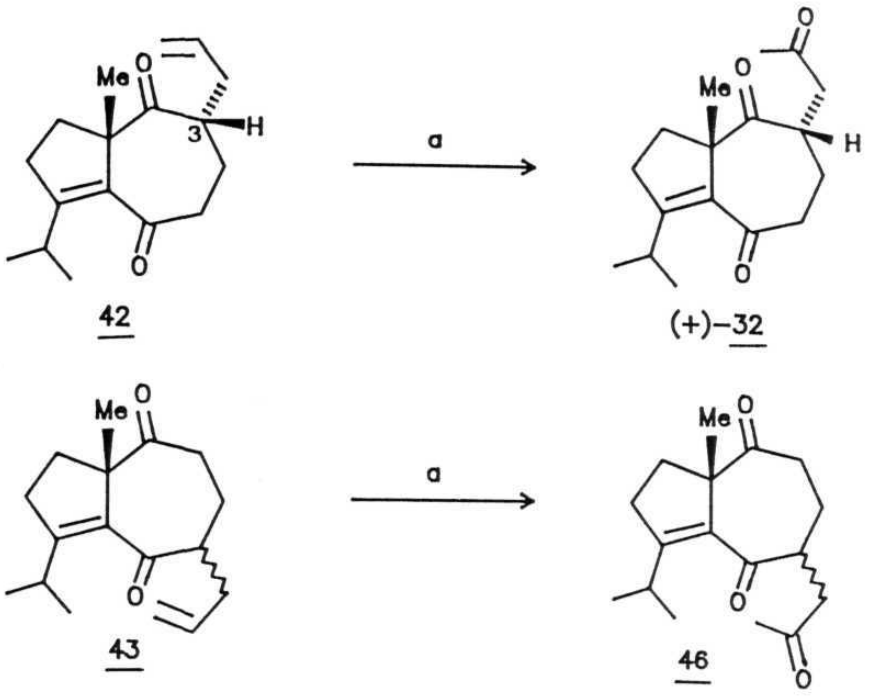
assigned as opposite to the angular methyl group, based on our earlier observation, wherein the enolate **44** derived from (-)-19 accepts electrophiles from β-face opposite to the angular methyl group to give **45**, **Scheme III.8.** However, it was not possible to make any assignment in the case of **43.** The allyl group in **42** and

Scheme III.8



43 was oxidised to the acetonyl group via Wacker-type oxidation employing Tsuji's Pd^{+2} methodology [10]. Thus, the mixture of **42** and **43** was treated with $PdCl_2$-CuCl-O_2 system in DMF to furnish readily separable regioisomers (+)-**32** and **46** in 75% yield, **Scheme III.9.** The gross structures of the tricarbonyl compounds (+)-**32** and **46** could be arrived on the basis of the ^1H and ^{13}C NMR spectral data. Thus, the ^1H NMR spectrum (**Fig. III.3**) of (+)-**32** showed a methyl resonance at δ 2.16 due to acetonyl group and the ^{13}C NMR spectrum (**Fig. III.4**) exhibited three signals at δ 210.6, 207.2, and 202.7 due to the three carbonyl groups. Similarly, the major isomer present in the diastereomeric mixture **46**, displayed methyl group resonances at δ 2.18 in the ^1H NMR spectrum and three carbonyl resonances at δ 215.0, 206.7 and 198.5 in the ^{13}C NMR spectrum. There were also present resonances in the same region due to the minor diastereomer.

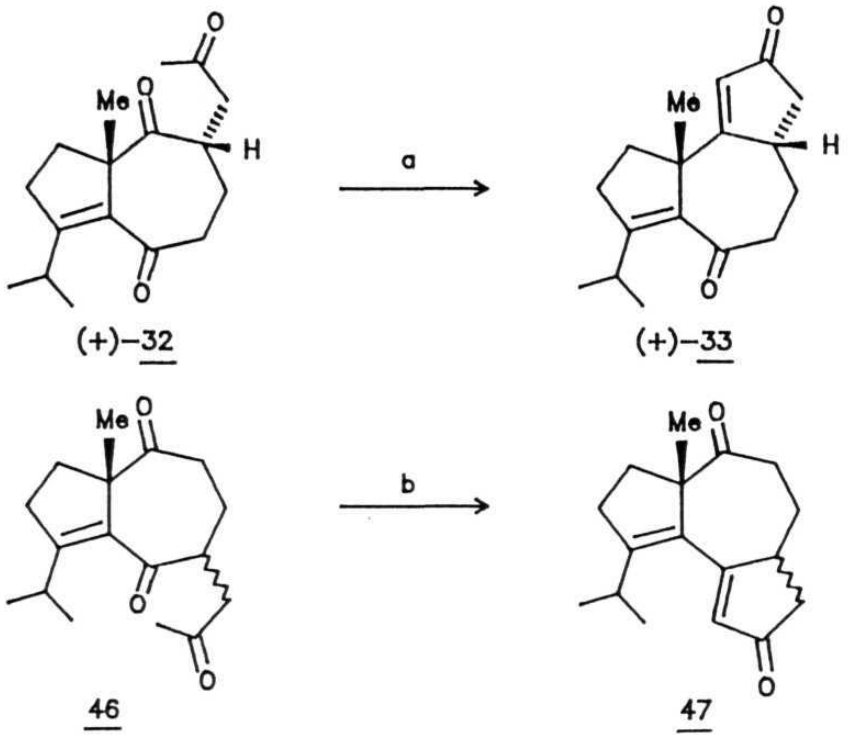
Scheme III.9



Reagents and yields: (a) $PdCl_2$-CuCl, O_2, DMF-H_2O, 75%;

Having obtained the precursor (+)-32 for cyclopentannulation, the key cyclisation step was attempted. Exposure of (+)-32 to sodium hydride in THF resulted in smooth cyclisation and furnished the required tricyclic bis-enone (+)-33 in 30% yield, **Scheme III.10**. The spectral data of (+)-33 was fully consonant with its formulation. The ^1H NMR spectrum (Fig. III.5) showed olefinic proton at δ 6.0 and the UV spectrum exhibited absorption peaks at λ_{max} 231 and 256 nm. These are compatible with the two chromophores present in (+)-33. The calculated values for the two chromophores present in (+)-33 are 231 and 254 nm.

Scheme III.10



Reagents and yields: (a) NaH, THF, 2 h, 30%. (b) NaH, THF, 10min, 80°C, 35%.

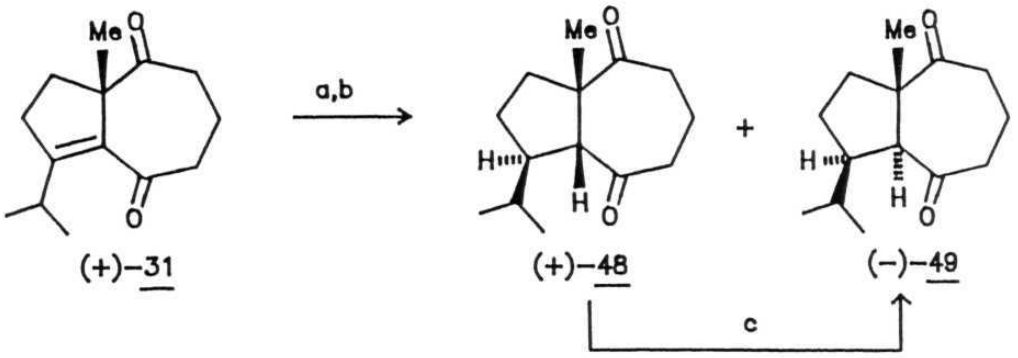
In a similar fashion, the diastereomeric mixture **46** also cyclised with NaH to furnish the tricyclic dienone **47** as an epimeric mixture in 35% yield, **Scheme II.10.** The gross structure of **47** was quite apparent from its spectral data. The ^{1}H NMR spectrum exhibited two olefinic protons at δ 6.14 and 6.02 indicating the diastereomeric nature of **47.** The UV spectrum exhibited strong absorption at λ_{max} 308 nm indicating the presence of extended conjugation which is compatible with the dienone **47** formulation.

Successful construction of the 5,7,5-fused tricyclic system

proved the viability of our basic strategy and encouraged us to attempt the total synthesis of the natural product **16**. Therefore, we turned our attention to generate the requisite stereochemistry at the ring junctions (C_1-,C_2-, and C_{11}-positions) enroute to **16**.

Reduction of the enone moiety in (+)-**31** with Li-liq. NH_3 and PCC oxidation of the resulting reduction products led to the saturated diones (+)-**48** and (-)-**49** (9:1) in 70% yield, **Scheme III.11**. While the ^1H and ^{13}C NMR spectra of the major isomer

Scheme III.11



Reagents and yields: a) Li-liq.NH_3, THF-MeOH; (b) PCC, CH_2Cl_2, Molecular sieves 4 Å, 70%; (c) NaOMe-CH_3OH, 12 h, 30°C, quant.;

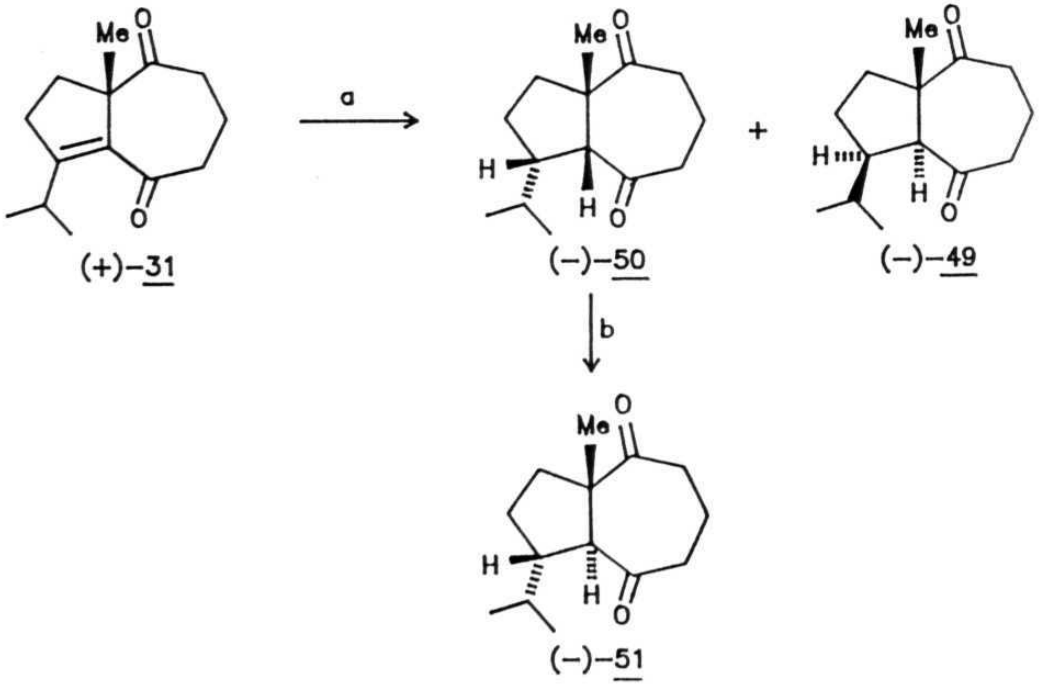
(+)-**48** (**Fig. III.6** and **Fig. III.7**) and minor isomer (-)-**49** (**Fig. III.8** and **Fig. III.9**) were fully supportive of their gross structures, they were not incisive enough for making firm stereochemical assignments. However, firm stereochemical assignments could be made on the basis of the following observations.

It was observed that the major isomer (+)-**48** on exposure to base (NaOMe-MeOH) completely equilibrated to the minor isomer

(-)-49 having more stable trans- ring junction stereochemistry, Scheme III.11. In the light of this observation, it is possible that the minor isomer (-)-49 is a product of equilibrium taking place during the isolation procedures rather than a true product of Li-liq. NH_3 reaction. Predominant formation of cis-48 during Li-liq. NH_3 reduction, though not entirely predictable, is in keeping with the recent observations on the metal-ammonia reductions of several hydrindanones which mainly furnish cis-fused products.[12] In the reduction of (+)-31, two successive kinetic protonations result in the observed stereochemistry of (+)-48.

Catalytic hydrogenation of (+)-31 over Pd/C catalyst proceeded smoothly and produced readily separable isomers (-)-49 and (-)-50 (5:4) in over 90% yield, Scheme III.12. The ^1H

Scheme III.12

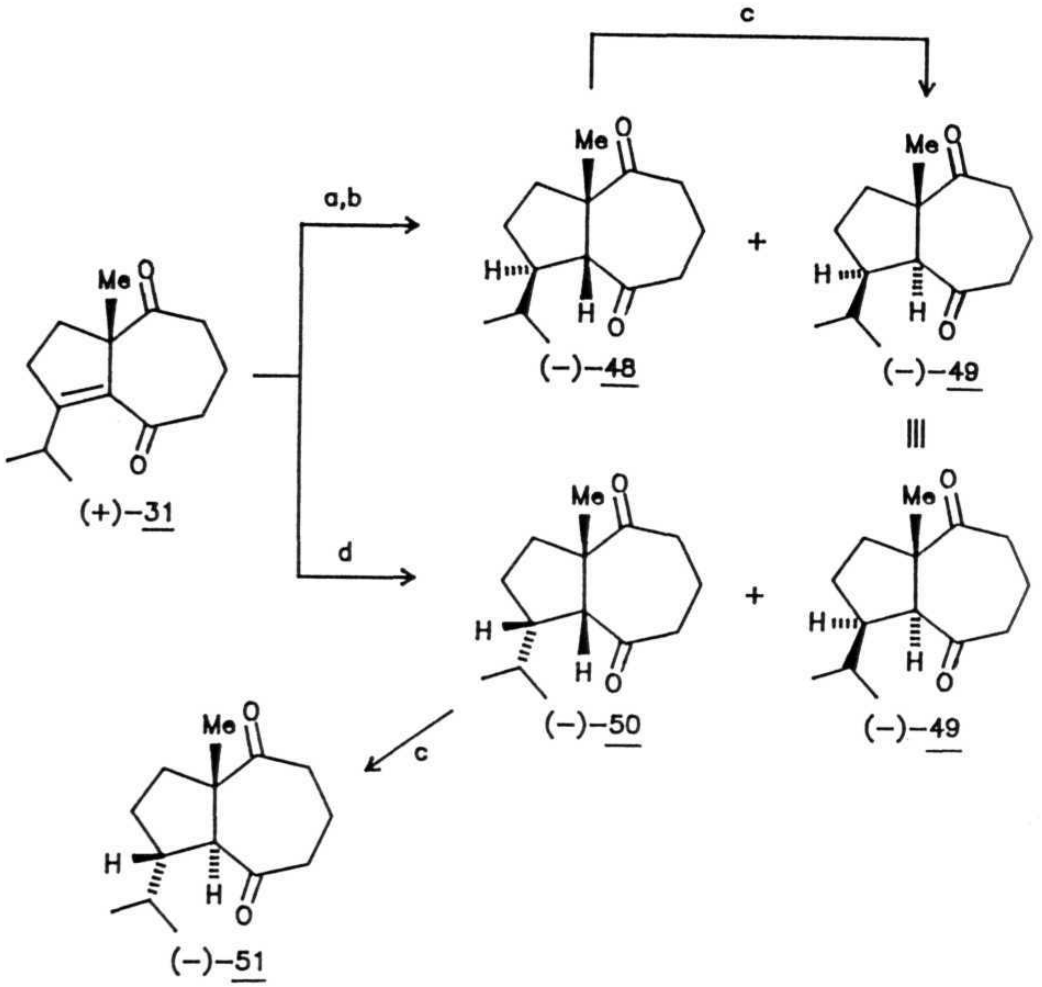


Reagents and Yields: (a) H_2, Pd/C. 20 psi, 1 h, 90%. (b) NaOMe-CH_3OH, 12h, quantitative

and ^{13}C NMR spectra of (-)-49 and (-)-50 fully supported their gross structure, particularly the latter exhibited the presence of two saturated carbonyl groups in each of them. The ^{1}H and ^{13}C NMR spectra of (-)-50 are displayed in Fig. III.10 and Fig. III.11, respectively. The marginally more abundant isomer (-)-49 was found to be identical with the minor trans- fused product from the Li-NH_3 (liq.) reduction.

Keeping in mind the favoured cis-addition of hydrogen to the double bond, the two isomers obtained from (+)-31 should be (-)-50 and (-)-49 having cis- and trans-ring junction stereochemistry, respectively. Since, the latter isomer was found to be identical with the minor product of Li-liq. NH_3 reduction (also the product of epimerisation of (+)-48), its identity was established. Expectedly, on exposure to NaOMe-MeOH, the trans-isomer (-)-49 remained unchanged. However, the cis-ring junction isomer (-)-50 from hydrogenation on exposure to NaOMe-MeOH epimerised completely into a new diastereomer (-)-51 having trans-stereochemistry. This stereoisomer was different (^{1}H and ^{13}C NMR, Fig. III.12 and Fig. III.13) from the three other stereoisomers (+)-48, (-)-49 and (-)-50, described earlier. Thus, it was possible to synthesise all the four possible stereoisomers 48-51 and their stereochemistry was rigorously secured on the basis of internally consistent correlation, Scheme III.13. To our knowledge, this is the first time that these bicyclic hydroazulenoids of well defined stereochemistry have become available and that too in enantiomerically pure form. Among the four diastereomers that we have prepared success-

Scheme III.13



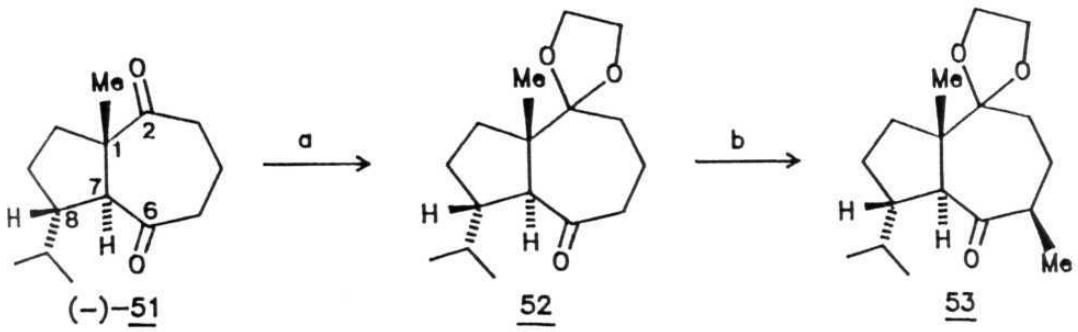
Reagents and yields: a) Li-liq.NH_3, THF-MeOH; (b) PCC, CH_2Cl_2, Molecular sieves 4 Å, 70%; (b) NaOMe-CH_3OH, 12 h, quantitative (c) NaOMe-CH_3OH, 12 h, 30°C, quant.; (d) H_2, Pd/C. 20 psi, 1 h, 90%.

fully for the first time, the dione (-)-51 has the requisite stereochemistry at the ring junction and isopropyl bearing carbon for elaboration to 18-oxo-3-virgene 16.

Accordingly, we sought to generate the trisubstituted double bond between C_3-and C_4-positions in the seven membered ring as

present in the natural product **16** . In this context it was essential to chemo-differentiate the C_2 and C_6 carbonyl groups. We were pleased to observe that exposure of (-)-**51** to ethylene glycol in the presence of PPTS led to the formation of monoketal **52** in good yield and with high selelctivity. Kinetically controlled deprotonation and methylation in **52**, using LiHMDS as the base and methyl iodide as the electrophile led to **53** in 72% yield, **Scheme III.14.** The structure of **53** was confirmed on the

Scheme III.14

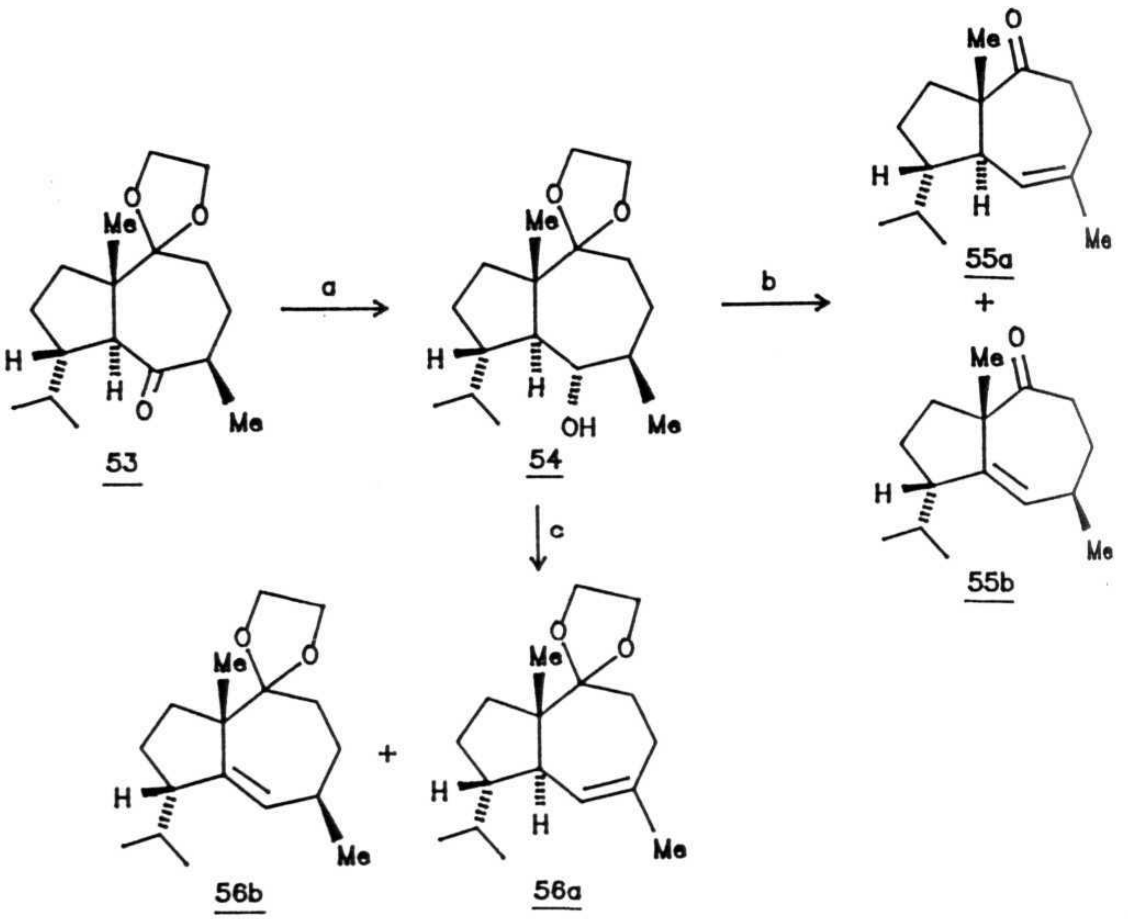


(-)-**51** **52** **53**

Reagents and yields: (a) PPTS, Ethylene glycol, Benzene, reflux, 16 h, 83%; (b) Bu^nLi, HMDS, THF, MeI,-78°C, 72%

basis of ^1H and ^{13}C NMR spectral data. The ^1H NMR exhibited a doublet at δ 1.05 due to the newly added secondary methyl group and the 17 line ^{13}C NMR spectrum with characteristic peaks at δ 216.0, 113.1, 19.4 suggested that **53** was a single isomer. The methylated compound **53** was reduced with LAH to furnish the alcohol **54** in 89% yield. The bicyclic alcohol **54** was subjected to dehydration with $POCl_3$ in pyridine containing traces of DBU, but the required dehydration product **55a** was not obtained. In another attempt at the dehydration, **54** was heated with catalytic amount of p-toluenesulphonic acid, **Scheme III.15.** However, in

Scheme III.15



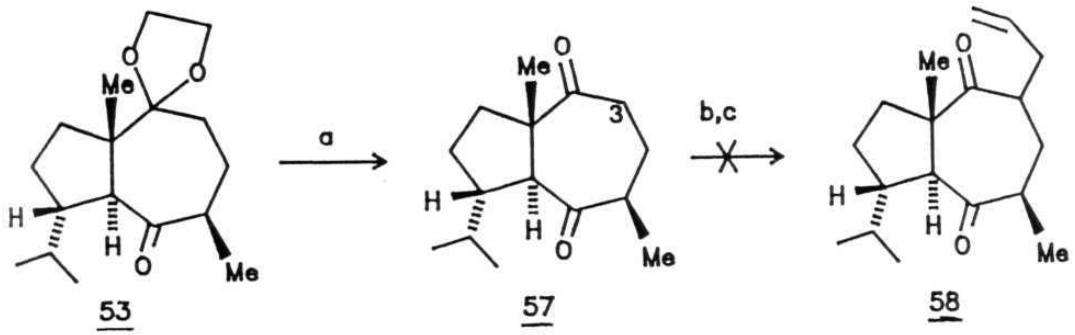
Reagents and yields: (a) LAH, Ether, rt, 15 min, 89% (b) PTS, Benzene, reflux, 30 min, 71% (c) Burgess salt, Benzene, reflux, 2 h, 30%.

this case an inseparable mixture of 55a and 55b through simultaneous deacetalisation was obtained. Attempted dehydration of 54 with Burgess salt[13] also furnished the regioisomeric mixture of olefinic acetals 56a,b.

Since our efforts to obtain the required enone 55a were unsuccessful, we decided to effect the dehydration at a later

stage and decided to address ourselves to the annulation of the five membered ring. Towards this end, the three step annulation sequence **Scheme III.4**, which was successfully employed to construct the tricyclic bis-enone 33 was chosen. The acetal group in 53 was deprotected through transacetalisation in the presence of PPTS to furnish the dione 57 in 75% yield, **Scheme III.16**. The regioselective allylation at C_3-position in 57 under

Scheme III.16



53 57 58

Reagents and yields: (a) PPTS, Acetone, reflux, 1h, 75%; (b) Bu^nLi,HMDS, THF, allyl bromide, -78°C-0°C;(c) LDA,HMPA, -78°C-0°C.

kinetic conditions with LiHMDS as the base was attempted, without success. The alkylation reaction was also tried under thermodynamic conditions (NaH, KH etc.,). In this case also the desired allylated product was not obtained. As a result, we could not proceed further to complete the synthesis of the target molecule and the efforts were abandoned.

III.4. SUMMARY:

We have described the construction of a carbotricyclic bis-enone (+)-33 related to virgane diterpenes. This skeleton was obtained by the elaboration of the chiral 5,7-fused bicyclic enone (-)-19 which was obtained from R-(+)-limonene *via* the key synthon (-)-34. The bicyclic enone (-)-19 was restructured to the ene-dione (+)-31 in a two step protocol. The reduction manoeuvres on (+)-31 gave accessibility to all the four possible diastereomers 48 – 51. These four isomers have the potential for use as the basic building blocks for the synthesis of higher terpenes possessing various stereochemical patterns.

III.5. EXPERIMENTAL:

For a general write-up see the experimental section of chapter I.

Hydroazulenone (-)-19 was prepared from R-(+)-limonene according to the procedure described in the chapter I.

(+)-2S-Methyl-2-(4-methyl-3-oxopentyl)cycloheptan-1,4-dione (41):

Into a 50 mL RB flask ketone (-)-19 (1.5 g, 7.27 mmol) was placed in a (1 : 1 : 1) mixture of of carbontetrachloride-acetonitrile-water (each 5 mL). Ruthenium trichloride (30 mg) and sodium metaperiodate (2.30 g, 10.7 mmol) were then added. After being stirred for 1 h, the reaction was diluted with dichloromethane (150 mL) and the phases were separated. The aq. phase was reextracted with dichloromethane (50 mL x 3). The combined extract was washed, dried and the crude product was filtered through a small silica gel (25 g) column with 10% ethyl acetate-petroleum ether to furnish the triketone (+)-41 (1.66 g, quantitative),

$[\alpha]_D$: +84.2 (c 3.0; $CHCl_3$)

bp : 160°C/0.16 mm

IR : 2950, 1700, 1310, 1170, 920 cm^{-1}

^1H NMR : δ 3.1-2.2 (m, 8H), 2.1-1.5 (m, 5H), 1.12 (s, 3H, -C- $C\underline{H}_3$), 1.05 (d, J = 7 Hz, 6H, -CH-$C\underline{H}_3$)

^{13}C NMR : δ 213.4, 213.2, 209.6, 50.0, 47.3, 43.5, 40.4, 39.6, 34.2, 32.5, 21.4, 20.6, 17.7(2C).

Analysis : $C_{14}H_{22}O_3$ Calcd.: C, 70.55; H, 9.31.
Found : C, 70.87; H, 9.35.

(+)-8-Isopropyl-1S-methyl-bicyclo[5.3.0]dec-7-ene-2,6-dione (31):

Into a 50 mL RB flask with a reflux condenser and mercury seal, triketone (+)-**41** (1.66 g, 6.97 mmol) was placed and 5% methanolic KOH (25 mL) was added to it. The resulting reaction mixture was refluxed for 1 h. Methanol was removed at reduced pressure and the residue was diluted with water (20 mL) and extracted with ether (100 mL x 3). The combined ethereal extract was washed and dried and the crude oily product which was charged on silica gel (50 g) column. Elution with 15% ethyl acetate-petroleum ether furnished the ene-dione (+)-**31** (920 mg) in 60% yield.

$[\alpha]_D$: +177.1 (c, 2.0; $CHCl_3$)

bp : 155°C/0.1 mm

IR : 2950, 1700, 1670, 1590, 930, 860 cm^{-1};

^1H NMR (Fig. III.1) : δ 3.62 (m, 1H), 3.1-1.45 (series of m, 10H), 1.35 (s, 3H, -C-C$\underline{H}_3$), 1.06 (d, J = 7 Hz, 3H, -CH-C$\underline{H}_3$), 1.04 (d, J = 7 Hz, 3H, -CH-C$\underline{H}_3$);

^{13}C NMR (Fig. III.2) : δ 213.7, 199.8, 167.3, 136.8, 61.3, 41.4, 37.2, 35.0, 29.7, 27.7, 20.9, 20.7, 20.5(2C).

Analysis : $C_{14}H_{20}O_2$ Calcd.: C, 76.32; H, 9.31.
Found : C, 76.51; H, 9.32.

8-Isopropyl-1-methyl-3(prop-3-enyl)bicyclo[5.3.0]dec-7(8)ene-2,6-dione (42) and 8-isopropyl-1-methyl-5(prop-3-enyl)bicyclo[5.3.0]-dec-7(8)ene-2,6-dione (43) :

To a solution of n-butyl lithium (1 mmol, 1 mL in hexane) cooled to -78°C was added hexamethyldisilazane (0.5 mL, 1.2 mmol) under N_2 . After stirring for 30 min, dry THF (1 mL) followed by ene-dione (+)-31 (170 mg, 0.77 mmol) in THF (1 mL) were added. The reaction mixture was stirred (-78°C-0°C) for 45 min at 0°C and recooled to -78°C. Allyl bromide (0.5 mL) was then introduced and stirring continued for 15 min. Reaction was quenched by adding brine and extraction was done with ether (20 mL x 3). The combined organic phase was washed, dried and concentrated to yield an oily residue. Column chromatography on a silica gel (15 g) column and elution with 10% ethyl acetate-petroleum ether afforded the allylated products **42** and **43** (45 mg) in 35% yield. Further elution with the same solvent gave the unreacted starting material (60 mg).

8-Isopropyl-1-methyl-5(2-oxo propyl)bicyclo[5.3.0]dec-7(8)ene-2,6-dione (46) and (+)-(1S,3S)-8-Isopropyl-1-methyl-3(2-oxo propyl) bicyclo [5.3.0] dec-7(8)ene-2,6-dione (32) :

To a stirred mixture of palladium chloride (10 mg), cuprous chloride (75 mg) in DMF (1 mL) and water (1 mL) under O_2 atmosphere was added the allylated ketones **42** and **43** (43 mg, 0.17 mmol). After stirring for 4 h, the reaction mixture was poured into water (10 mL) and extracted with ether (25 mL x 3).

The combined ethereal extract was washed, dried and concentrated. The crude oily product was charged on silica gel (10 g) column. Elution with 30% ethyl acetate-petroleum ether mixture furnished the triketone **46** (22 mg) as diastereomeric mixture in 49% yield.

IR : 1695, 1660, 1580, 1350 cm^{-1};

^1H NMR : δ 3.96-1.46 (m, 12H), 2.18 (s, 3H, $-COC\underline{H}_3$), 1.44 (s, 3H, $-C-C\underline{H}_3$), 1.04 (d, J = 7 Hz, 3H, $-CH-C\underline{H}_3$), 1.02 (d, J = 7 Hz, 3H, $-CH-C\underline{H}_3$)

^{13}C NMR : δ 215.0, 206.8, 198.5, 170.0, 136.9, 61.0, 44.1, 36.5, 35.5, 30.1 (2C), 28.1, 27.5, 20.9, 20.7, 20.5 19.6.

Further elution of the column yielded the minor triketone (+)-**32** (11 mg) in 23% yield.

$[\alpha]_d$: +71.8 (c, 0.32; $CHCl_3$)

bp : 135°C/0.3 mm

IR : 1695, 1660, 1170 cm^{-1}

^1H NMR (Fig. III.3) : δ 3.8-1.12 (m, 12H), 2.17 (s, 3H, $-COC\underline{H}_3$) 1.53 (s, 3H, $-C-C\underline{H}_3$), 1.04 (d, J = 7 Hz, 3H, $-CH-C\underline{H}_3$), 0.88 (d, J = 7 Hz, 3H, $-CH-C\underline{H}_3$)

^{13}C NMR (Fig. III.4) : δ 210.6, 207.3, 202.8, 166.1, 135.9, 62.1, 45.4, 44.1, 42.0, 34.3, 30.5, 30.2, 28.4 (2C), 24.4, 21.2, 20.9

Analysis : $C_{17}H_{24}O_3$ Calcd.: C, 73.88; H, 8.75.
Found : C, 73.65; H, 8.84

11-Isopropyl-1-methyl-tricyclo[8.3.0.$_0^{5,9}$]tridec-1(11), 8-diene-2,7-dione (47) :

To a suspension of sodium hydride (25 mg) in THF (3 mL) was added a solution of triketone **46** (10 mg, 0.036 mmol) in THF (1 mL) under N_2. After refluxing the reaction mixture for 15 min, the excess sodium hydride was destroyed by the addition of 5% aq. HCl (2 mL). The reaction mixture was extracted with ether (20 mL x 3) and the organic phase was washed and dried. The solvent was evaporated and the crude product was charged on a silica gel (5 g) column. Elution with 30% ethyl acetate-petroleum ether furnished the tricyclic dienone **47** (3 mg) in 35% yield.

UV : 226, 240, 287, 308 nm

IR : 1700, 1680, 1590 cm^{-1}

^1H NMR : δ 6.14 (br s, 1H, -C=C<u>H</u>-CO), 6.01 (br s, 1H, -C=C<u>H</u>-CO), 3.72-1.52 (m, 24H), 1.45 (s, 3H, -C-C<u>H</u>$_3$), 1.26 (s, 3H, -C-C<u>H</u>$_3$), 1.16-0.88 (series of doublets, 12H)

(+)-(5R,10R)-13-Isopropyl-10-methyl-tricyclo [8.3.0.$_0^{5,9}$] trideca-1(13), 8-diene-2,7-dione (33) :

To a stirred suspension of sodium hydride (25 mg) in THF (3 mL) was added the triketone (6 mg, 0.021 mmol) in THF (1 mL) under N_2 . After stirring for 4 h at room temperature, the excess sodium hydride was destroyed by the addition of 5% aq. HCl and the reaction mixture was extracted with ether (10 mL x 3). The ethereal layer was washed and dried. After removal of

solvent, the residue was purified by column chromatography on silica gel. Elution with 40% ethyl acetate-petroleum ether yielded the cyclised bis-enone (+)-33 (2 mg) in 30% yield.

$[\alpha]_D$: +33.3 (c, 0.12; $CHCl_3$)

UV : 231, 256 nm

IR : 1695, 1675, 1600, 1200 cm^{-1}

^1H NMR (Fig. III.5) : δ 6.0 (br s, 1H, -C=C<u>H</u>-), 3.4-1.6 (m, 12H), 1.48 (s, 3H), 1.12 (d, J = 7 HZ, 3H, -C<u>H</u>-CH_3), 0.96 (d, J = 7 Hz, 3H, -C<u>H</u>-CH_3)

Li-NH_3 reduction of (+)-31 . (+)-(1S,7R,8R)-8-Isopropyl-1-methyl-bicyclo[5.3.0]decan-2,6-dione (48) and (-)-(1S,7S,8R)-8-Isopropyl-1-methyl-bicyclo[5.3.0]decan-2,6-dione (49) :

Into a two necked 100 mL RB flask, fitted with a guard tube and septum, was taken freshly distilled liq.NH_3 (150 mL). To this was added freshly cut lithium metal (150 mg, 21.5 mg atom) The resulting blue solution was stirred for 5-min and ene-dione (+)-31 (500 mg, 2.25 mmol) in dry THF (5 mL) was added slowly. After stirring for 10 min the reaction mixture was quenched by careful addition of dry methanol (1 mL). After all the ammonia had evaporated, the reaction mixture was diluted with water (25 mL) and extracted with ether (75 mL x 3). The combined ethereal extract was washed and dried to a crude oil which was used directly for the next step. To a suspension of pyridinium chlorochromate (500 mg, 2.2 mmol) in dry dichloromethane (50 mL) containing 2.0 g of activated molecular sieves (4 Å) was added

the above diol (400 mg) in dry dichloromethane (5 mL) at 0°C. The reaction mixture was stirred for an additional 1 h and then filtered through a small florosil (10 g) column. Removal of the solvent gave an oily liquid which was charged on a silica gel (25 g) column and elution with 10% ethyl acetate-petroleum ether furnished the cis-dione (+)-48 (317 mg) in 63% yield.

$[\alpha]_D$: +26.2 (c, 1.0; $CHCl_3$)

bp : 148°C/0.1 mm

IR : 2950, 1700 cm^{-1}

^1H NMR (Fig. III.6) : δ 3.5 (d, J = 9 Hz, 1H), 2.8-1.2 (series of m, 12H), 1.0 (s, 3H, -C-CH_3), 0.85 (d, J = 7 Hz, 3H, -CH-CH_3), 0.74 (d, J = 7 Hz, 3H, -CH-CH_3)

^{13}C NMR (Fig. III.7) : δ 212.9, 210.5, 56.5, 51.7, 51.3, 45.1, 40.8, 35.8, 29.7, 28.1, 23.7, 23.0, 21.6, 21.5.

Analysis : $C_{14}H_{22}O_2$ Calcd.: C, 75.63; H, 9.97.
Found : C, 75.11; H, 9.91.

Further elution of the column with 15% ethyl acetate-petroleum ether furnished the trans-dione (-)-49 (37 mg, 7%).

$[\alpha]_D$: -15.0 (c, 1.0; $CHCl_3$)

bp : 145°C/0.1 mm

IR : 2950, 1700 cm^{-1}

^1H NMR (Fig. III.8) : δ 3.0-1.2 (series of m, 13H), 1.4 (s, 3H, -C-CH_3), 0.95 (d, J = 7 Hz, 3H, -CH-CH_3), 0.82 (d, J = 7 Hz, 3H, -CH-CH_3);

^{13}C NMR (Fig. III.9) : δ 213.3, 211.1, 63.0, 59.2, 47.9, 42.6, 39.9, 34.8, 33.5, 27.5, 25.5, 21.5, 20.4, 20.2.

Analysis : $C_{14}H_{22}O_2$ Calcd.: C, 75.63; H, 9.97.
Found : C, 75.33; H, 9.99.

Equilibration of (+)-48 :

Sodium (5 mg, 0.2 mmol) was dissolved in dry methanol under N_2 and the cis-dione (+)-**48** (25 mg, 0.11 mmol) in dry methanol (2 mL) was added. After stirring for 12 h, methanol was removed and the residue was worked-up in the usual manner. The crude product was filtered through a small silica gel column with 5% ethyl acetate-petroleum ether to furnish the trans-dione (-)-49 (25 mg, quantitative) identical in all respects with the sample obtained earlier.

Catalytic hydrogenation of (+)-31 : (-)-(1S,7S,8R)-8-Isopropyl-1-methyl-bicyclo[5.3.0]decan-2,6-dione (49) and (-)-(1S,7R,8S)-8-Isopropyl-1-methyl-7-bicyclo[5.3.0]decan-2,6-dione (50) :

A solution of the ene-dione (+)-31 (500 mg, 2.25 mmol) in dry ethyl acetate (10 mL) was hydrogenated (25 psi. pressure) over 10% Pd/C (100 mg) for 1 h. The catalyst was filtered-off and the solvent was removed to furnish the saturated dione mixture which was chromatographed on a silica gel (25 g) column. Elution with 10% ethyl acetate-petroleum ether furnished the trans-dione (-)-**49** (250 mg, 50%) and found identical with the minor product obtained in the liq.NH_3 reduction of (+)-31. Further elution with 12% ethyl acetate-petroleum ether furnished the cis-dione (-)-**50** (200 mg) in 40% yield.

$[\alpha]_D$: -55 (c, 1.0; $CHCl_3$)

bp : 145°C/1 mm

IR : 2950, 1700 cm^{-1}

^1H NMR (Fig. III.10) : δ 3.25-1.2 (series of m, 13H), 1.35 (s, 13H, -C-$C\underline{H}_3$), 0.92 (d, J = 7 Hz, 3H, -CH-$C\underline{H}_3$), 0.8 (d, J = 7 Hz, 3H, -CH-$C\underline{H}_3$);

^{13}C NMR (Fig. III.11) : δ 214.5, 212.0, 59.4, 58.7, 49.8, 45.4, 40.1, 31.7, 29.0, 28.0, 26.4, 23.8, 22.7, 21.8.

Analysis : $C_{14}H_{22}O_2$ Calcd.: C, 75.63; H, 9.97.

Found : C, 75.49; H, 9.91.

Equilibration of (-)-50 : (-)-(1S,7S,8S)-8-Isopropyl-1-methyl-bicyclo [5.3.0] decan-2,6-dione (51) :

Into a 25 mL three necked RB flask, fitted with a dry N_2 inlet, septum and mercury seal was placed dry methanol (10 mL). To this freshly cut sodium (15 mg) was added and the reaction mixture was stirred until all the sodium had dissolved. Then the cis-dione (-)-50 (200 mg, 0.90 mmol) was added in dry methanol (2 mL) and the contents were stirred at room temperature for 12 h. Usual work-up gave an oily product which was filtered through a silica gel column with 5% ethyl acetate-petroleum ether to furnish the trans-dione (-)-51 (200 mg, quantitative),

$[\alpha]_D$: -43.0 (c, 1.0; $CHCl_3$)

bp : 150°C/0.1 mm,

IR : 2955, 1690, 1370, 1180 cm^{-1}

^1H NMR (Fig. III.12) : δ 3.0-2.4 (m, 5H), 2.1-1.2 (m, 8H), 0.98 (s, 3H, -C-$C\underline{H}_3$), 0.78 (d, J = 7Hz, 3H, -CH-$C\underline{H}_3$), 0.70 (d,

J = 7 Hz, 3H, -CH-C<u>H</u>3);

^{13}C NMR (Fig. III.13) : δ 213.5, 210.3, 58.1, 57.3, 44.1, 43.4, 41.2, 35.6, 32.2, 24.3, 21.0, 20.7, 20.2, 19.7.

Analysis : $C_{14}H_{22}O_2$ Calcd.: C, 75.63; H, 9.97.

Found : C, 75.92; H, 9.95.

(-)-(1S,7S,8S)-2-Ethyleneketal-8-Isopropyl-1-methyl-bicyclo [5.3.0] decan-6-one (52):

Into a 25 mL RB flask fitted with Dean-Stark water separator and reflux condenser, dione (-)-51 (100 mg, 0.45 mmol), ethylene glycol (0.2 mL) and PPTS (25 mg) in dry benzene (15 mL) were placed and the contents were refluxed for 15 h. The reaction mixture was diluted with benzene (50 mL), washed with saturated sodium bicarbonate solution and dried. Elution with 30% ethyl acetate-petroleum ether from a silica gel column (10 g) furnished the monoketal 52 (100 mg, 83%).

IR : 1690, 1200, 1085 cm^{-1}

^{1}H NMR : δ 3.96 (m, 4H, -OC<u>H</u>2-C<u>H</u>2O-), 3.12 (d, J = 9 Hz, 1H), 2.72-1.04 (m, 12H), 0.86 (s, 3H, -C-C<u>H</u>3), 0.80 (d, J = 7 Hz, 3H, -C<u>H</u>-CH3), 0.76 (d, J = 7 Hz)

^{13}C NMR : δ 213.0, 117.2, 65.5, 65.1, 57.7, 53.3, 43.3, 42.8, 34.1, 33.5, 31.9, 24.8, 21.1, 19.8, 19.4, 18.2

(1S, 3R,7S,10S)-6-Ethyleneketal-10-Isopropyl-3,7-dimethyl-bicyclo [5.3.0]decan2-one (53) :

Into a 25 mL three necked RB flask fitted with a dry N_2 inlet, septum and mercury seal was introduced n-butyllithium (0.6 mL, 1.0 mmol in hexane) and cooled to -78°C. Hexamethyldisilazane (0.25 mL, 1.2 mmol) was carefully added and the resulting slurry was stirred for 20 min. Additional THF (1 mL) was added to dissolve the slurry. A solution 52 (50 mg, 0.19 mmol) in dry THF (1 mL) was then slowly added and the resulting solution was stirred for 30 min. The enolate thus obtained was quenched by the addition of excess methyl iodide (0.5 mL) at -78°C. After further stirring for 45 min the reaction mixture was quenched by the addition of water and extracted with ether (20 mL x 3). The ethereal extract was washed, dried and charged on a silica gel column. Elution with 20% ethyl acetate-petroleum ether furnished 53 (37 mg) in 71% yield.

IR : 1690, 1095 cm^{-1}

^1H NMR : δ 3.94 (br s, 4H, $-OC\underline{H}_2-C\underline{H}_2O-$), 2.68-1.12 (m, 11H), 1.05, (d, J = 7 Hz, 3H, $-C\underline{H}-CH_3$), 0.82 (s, 3H, $-C-C\underline{H}_3$), 0.77 (d, J = 7 Hz, 3H, $-C\underline{H}-CH_3$), 0.73 (d, J = 7 Hz, 3H, $-C\underline{H}-CH_3$).

^{13}C NMR : δ 216.0, 113.1, 65.5, 65.0, 55.8, 53.3, 47.9, 43.4, 33.8, 32.5, 31.6, 27.1, 24.8, 21.1, 20.2, 19.41.

(1R,2S,3R,7S,10S)-6-Ethyleneketal-10-isopropyl-3,7-dimethyl-bicyclo[5.3.0]decan-2-ol (54) :

To a solution of **53** (35 mg, 0.12 mmol) in ether (5 mL) was added lithium aluminium hydride (15 mg) at 0°C. The reaction mixture was stirred for 15 min. Then the excess LAH was destroyed by careful addition of ethyl acetate followed saturated Na_2SO_4 solution (1 mL). The reaction mixture was extracted with ethyl acetate (15 mL x 3) and the combined organic extract was washed, dried and concentrated to a crude product which was purified by passing through a silica gel (5 g) column. Elution with 30% ethyl acetate-petroleum ether furnished **54** (31 mg) in 88% yield.

IR : 3230, 2930, 1080 cm^{-1}

^1H NMR : δ 3.94 (br s, 4H, $-OC\underline{H}_2-C\underline{H}_2O-$), 3.30 (m, 1H), 2.32-1.0 (m, 13H), 1.20 (s, 3H, $-C-C\underline{H}_3$), 1.09 (d, J = 7 Hz, 3H, $-C\underline{H}-CH_3$), 0.94 (d, J = 7 Hz, 3H, $-C\underline{H}-CH_3$), 0.82 (d, J = 7Hz, 3H, $-C\underline{H}-CH_3$)

Dehydration of 54 with p-toluenesulphonic acid :

Into a 10 mL RB flask **54** (9 mg, 0.032 mmol) was placed in dry benzene (5 mL) and cat. amount of PTS was added. The reaction mixture was refluxed for 1 h and then quenched by the addition of saturated soium bicarbonate solution. The benzene layer was separated, washed and dried to give an oily residue. Filtration through a small silica gel (5 g) column using 15% ethyl acetate-petroleum ether furnished **55a,b** (5 mg, 71%).

IR : 2920, 1690, cm^{-1}

^1H NMR : δ 5.32 (m, 2H, -C<u>H</u>=C-), 3.04-1.20 (m, 25H), 1.16-0.72 (series of singlets and doublets, 21H)

Dehydration of 54 with Burgess salt:

Burgess salt [methyl(carboxy sulfamoyl)triethyl ammonium hydroxide)][12] (5 mg) was added to a solution of **54** (4 mg, 0.014 mmol) in benzene (5 mL) under N_2. The reaction mixture was refluxed for 1 h and diluted with benzene (20 mL), washed and dried. The solvent was evaporated and the crude product was charged on a silica gel (2 g) column. Elution with 15% ethyl acetate-pet ehter furnished the ketal-olefin mixture **56a,b** (1 mg) in 30%yield.

IR : 2925, 1455 cm^{-1}

^1H NMR : δ 5.2 (br s, 2H, -C<u>H</u>=C-), 3.94 (m, 8H, -OC<u>H</u>$_2$-C<u>H</u>$_2$O-), 2.74-1.12 (m, 25H), 1.08-0.80 (series of singlets and doublets, 21H)

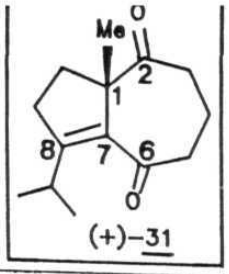
(1S,5R,7S,8S)-8-Isopropyl-1,5-dimethyl-bicyclo[5.3.0]decane-2,6-dione (57) :

To a solution of **53** (12 mg) in acetone (3 mL) was added PPTS (3 mg) and the reaction mixture was refluxed for 30 min. The acetone was evaporated and the residue was dissolved in 5 mL of water. Then it was extracted with ether (10 mL x 3). The combined extract was washed and dried. The solvent was removed and the crude was purified on a silica gel (3 g) column by eluting with 20% ethyl acetate-petroleum ether to furnish **57** (7 mg)

in 70% yield.

IR : 2970, 1690, 1380 cm^{-1}

^1H NMR : δ 2.95 (d, J = 9 Hz, 1H), 2.80-1.08 (m, 11H), 1.19 (d, J = 7 Hz, 3H, -C<u>H</u>-CH_3), 1.00 (s, 3H, -C-$C\underline{H}_3$), 0.82 (d, J = 7 Hz, 3H, -C<u>H</u>-CH_3), 0.78 (d, J = 7 Hz, 3H, -C<u>H</u>-CH_3)



(+)–31

Fig. III.1

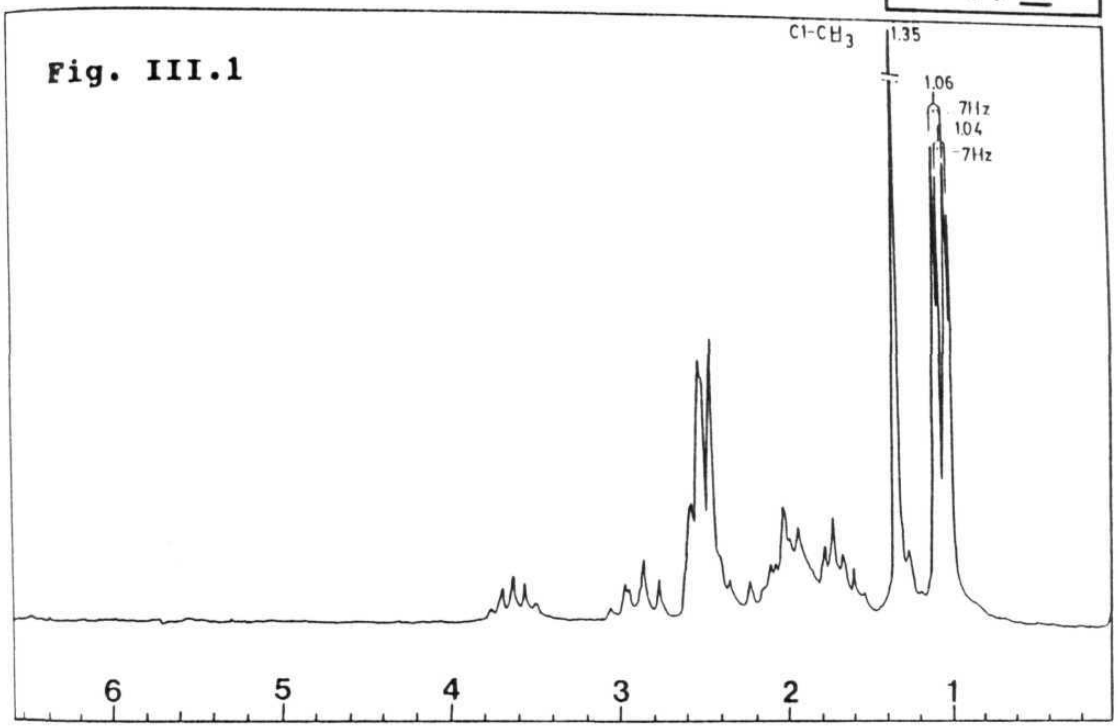
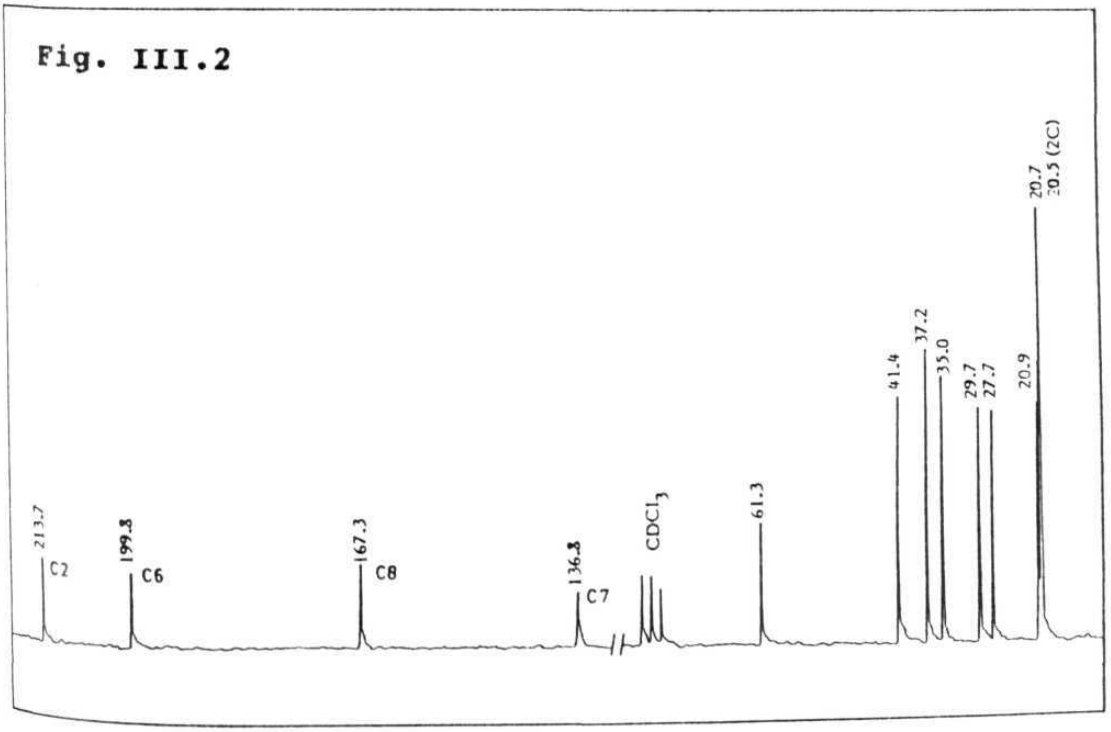
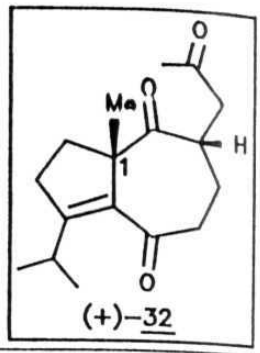


Fig. III.2





(+)-32

Fig. III.3

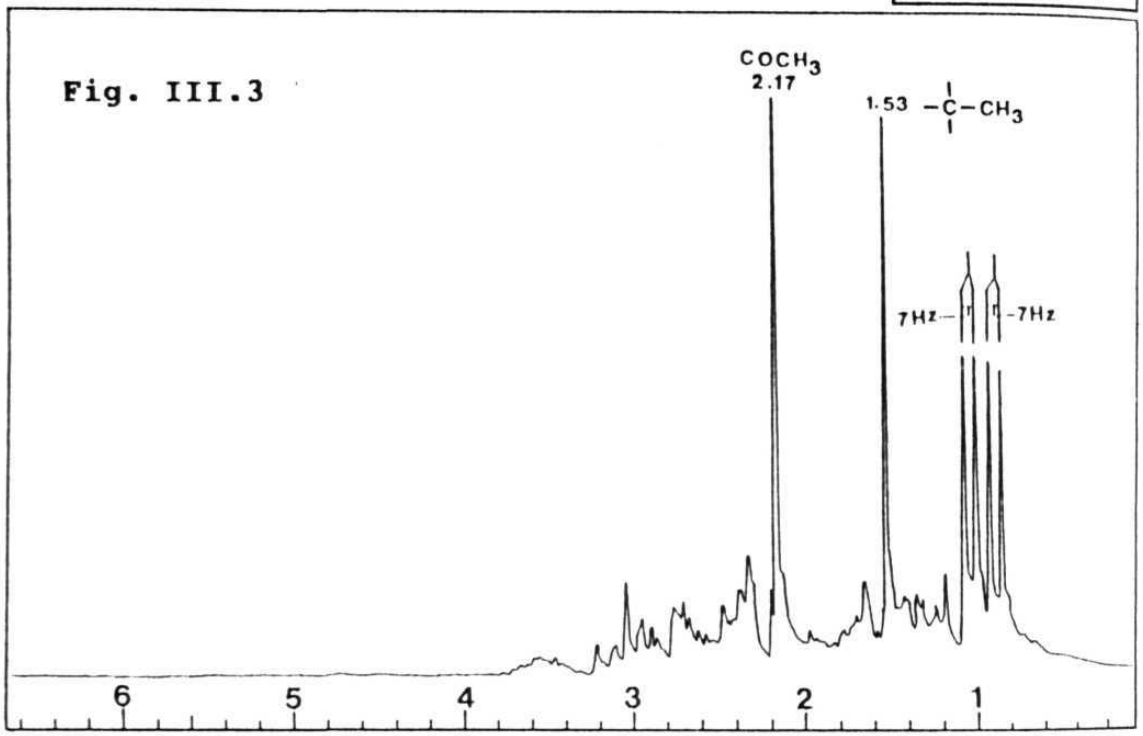
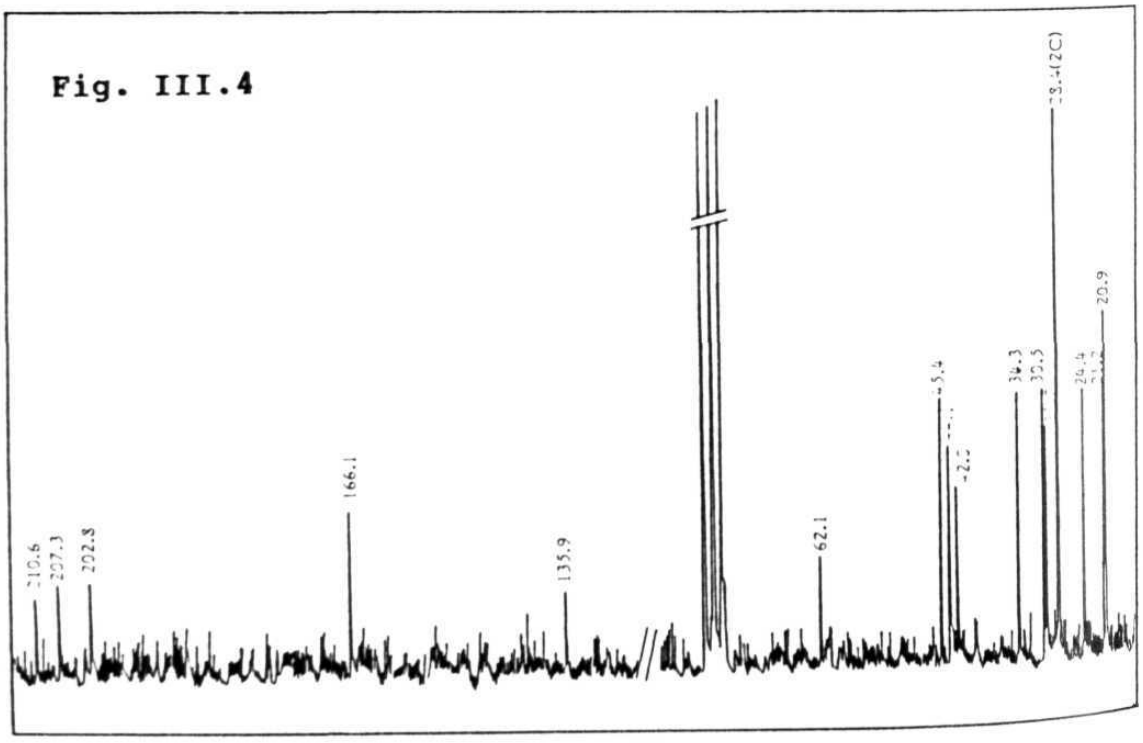


Fig. III.4



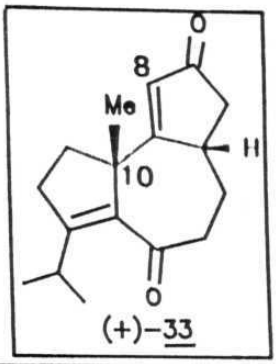
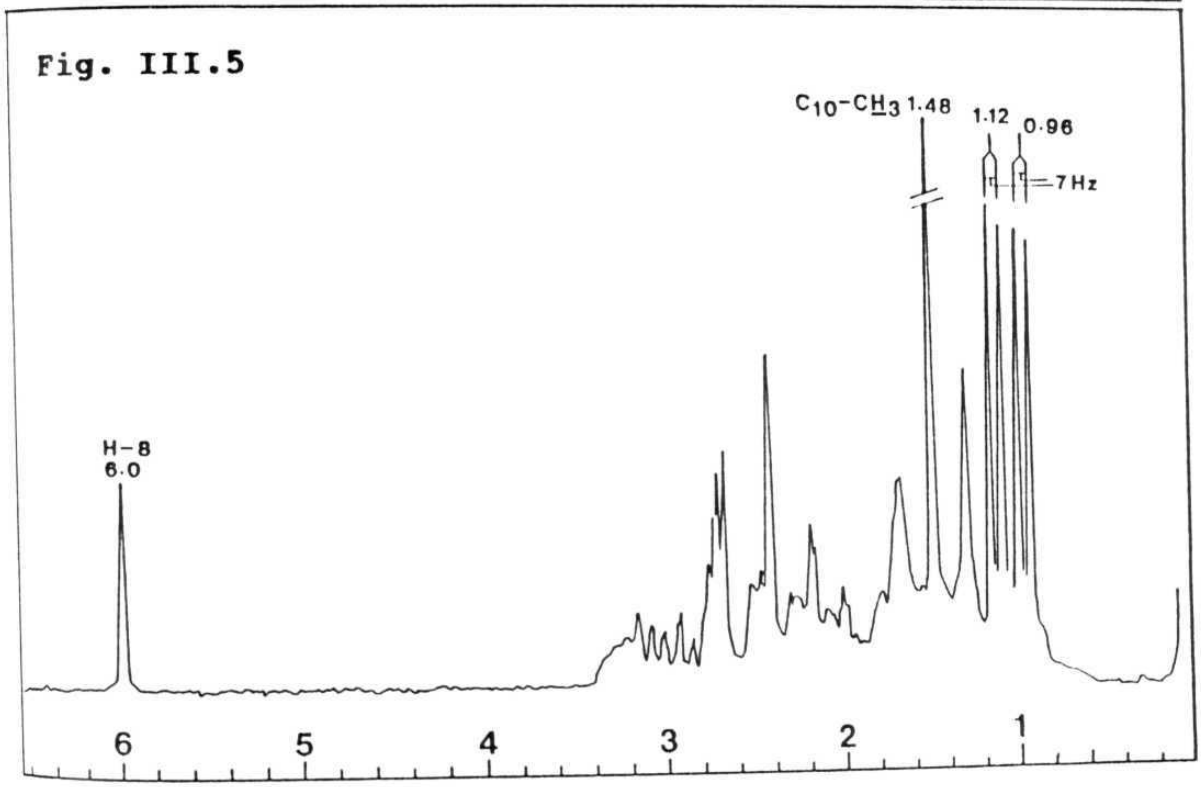


Fig. III.5



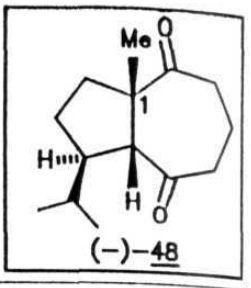


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Fig. III.6

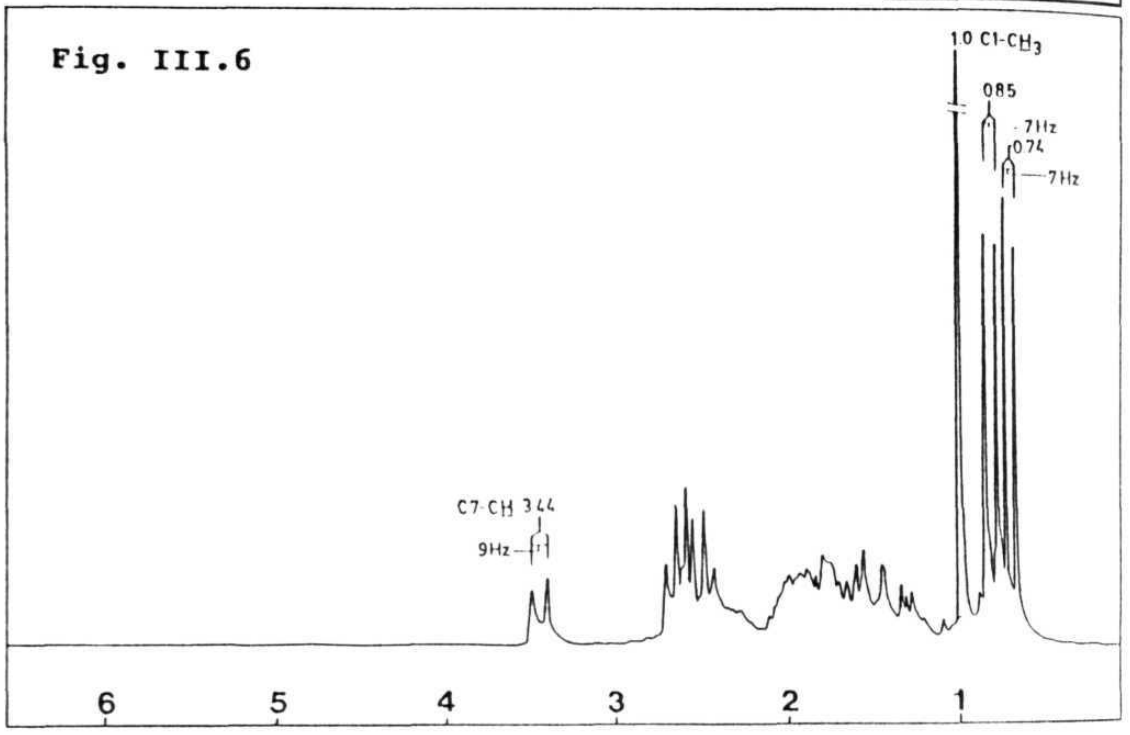
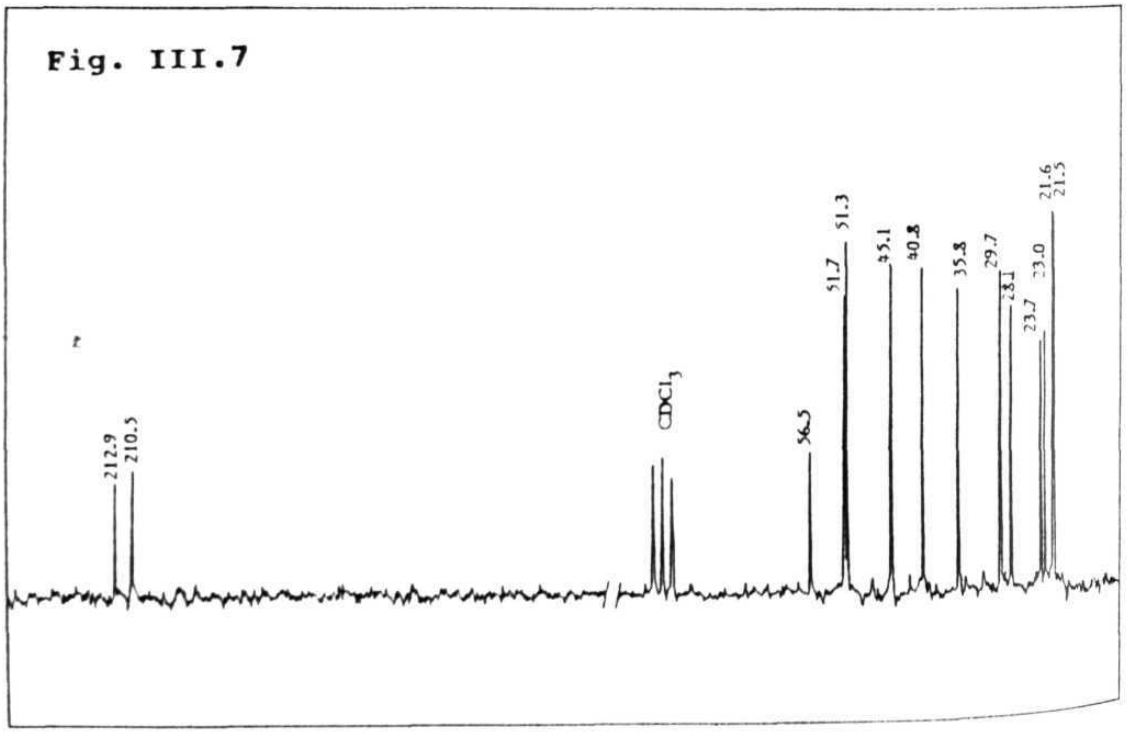
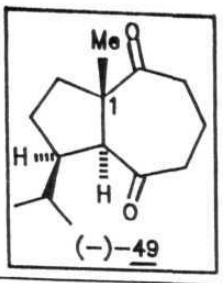


Fig. III.7





(−)−49

Fig. III.8

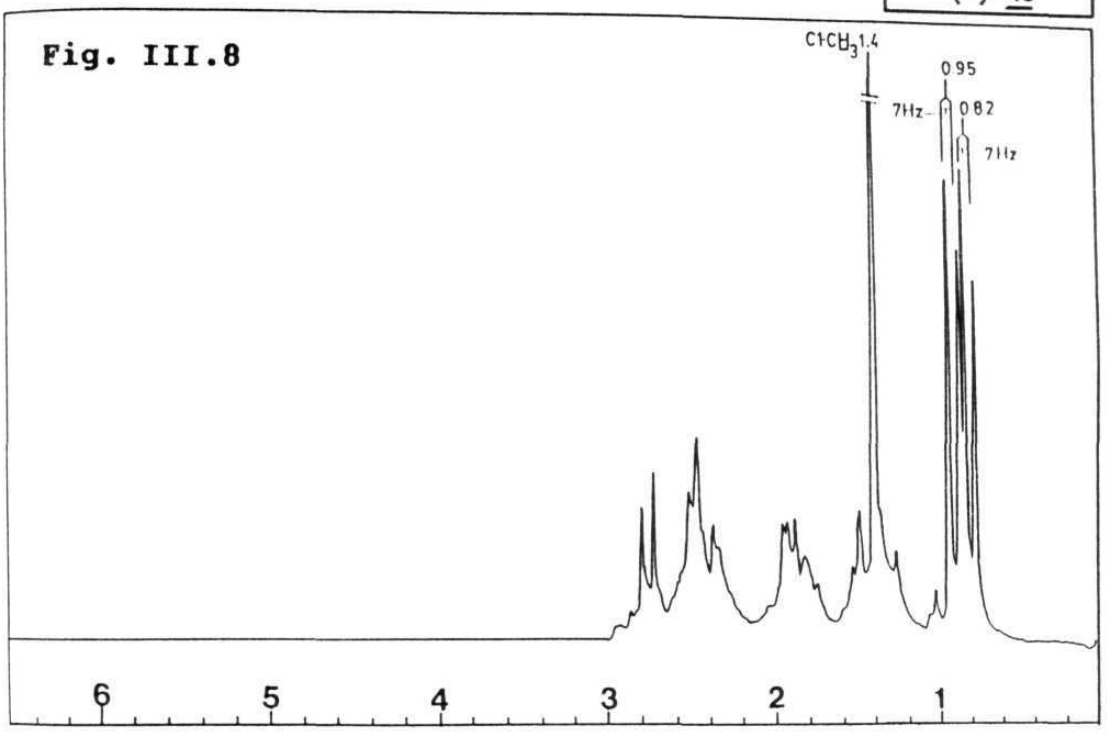
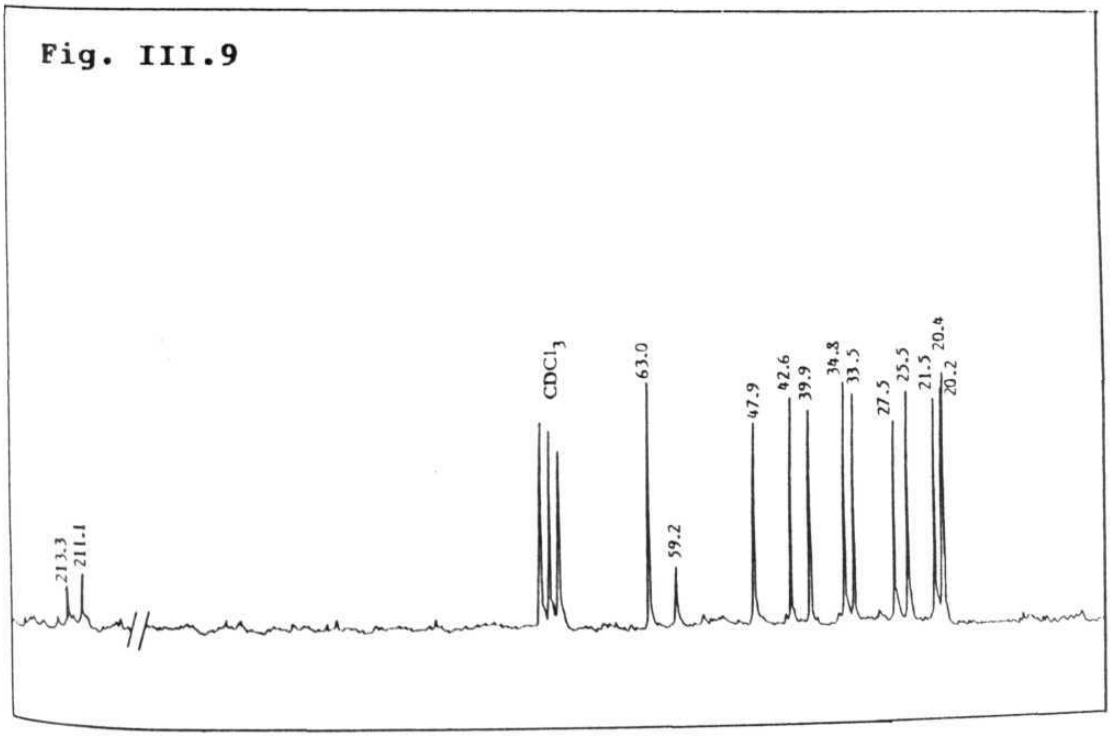


Fig. III.9



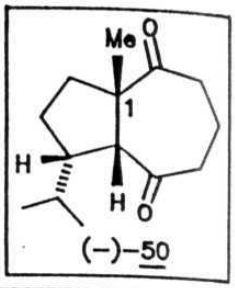


Fig. III.10

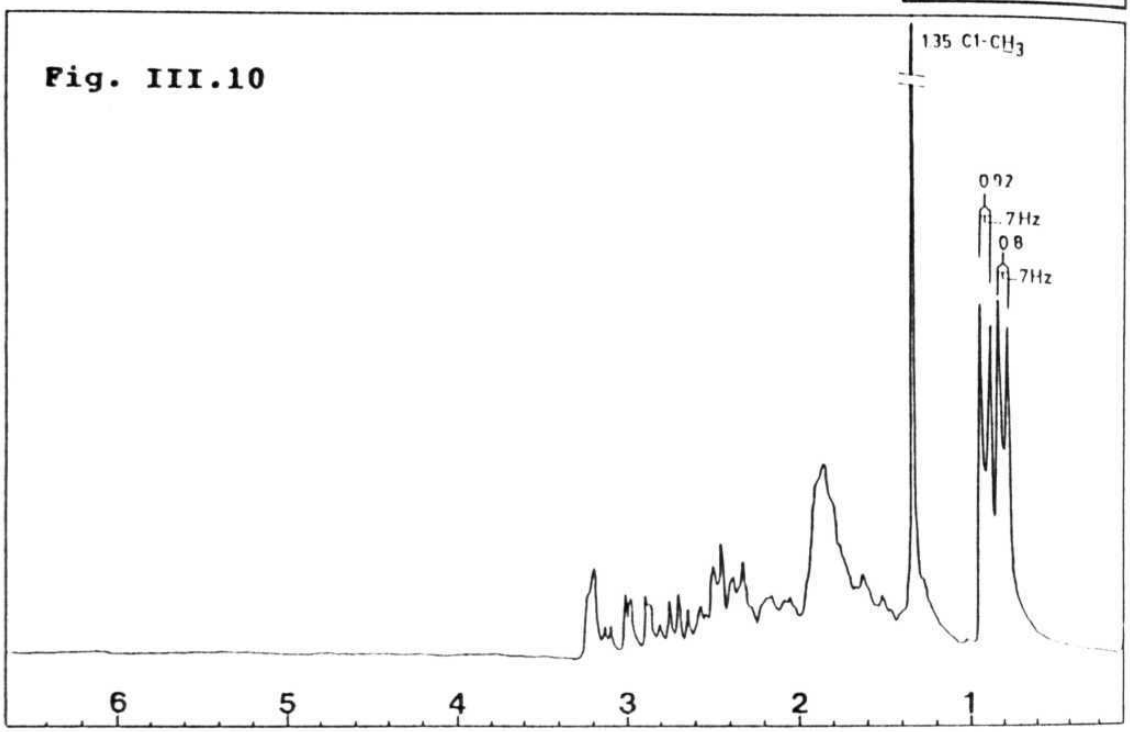
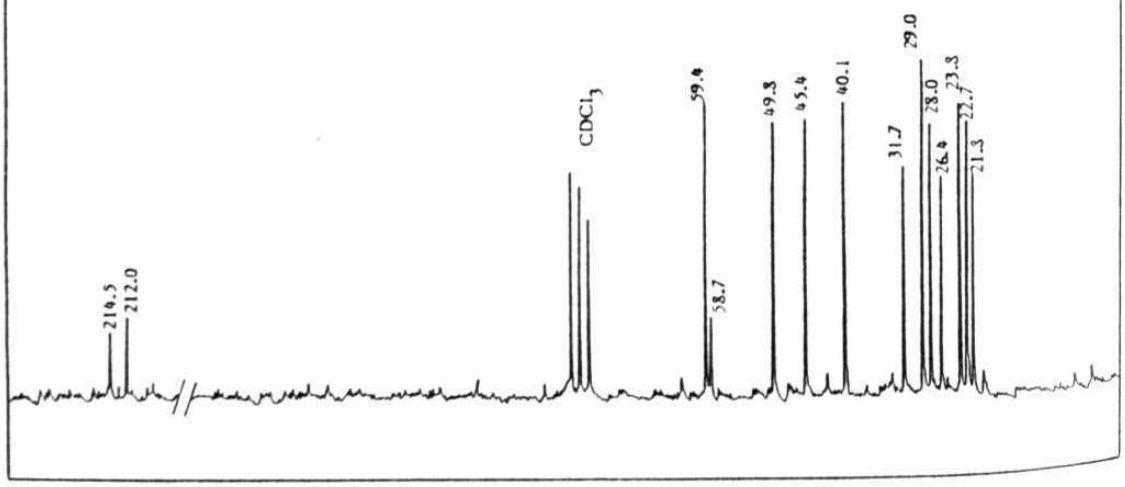
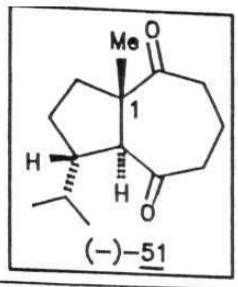


Fig. III.11





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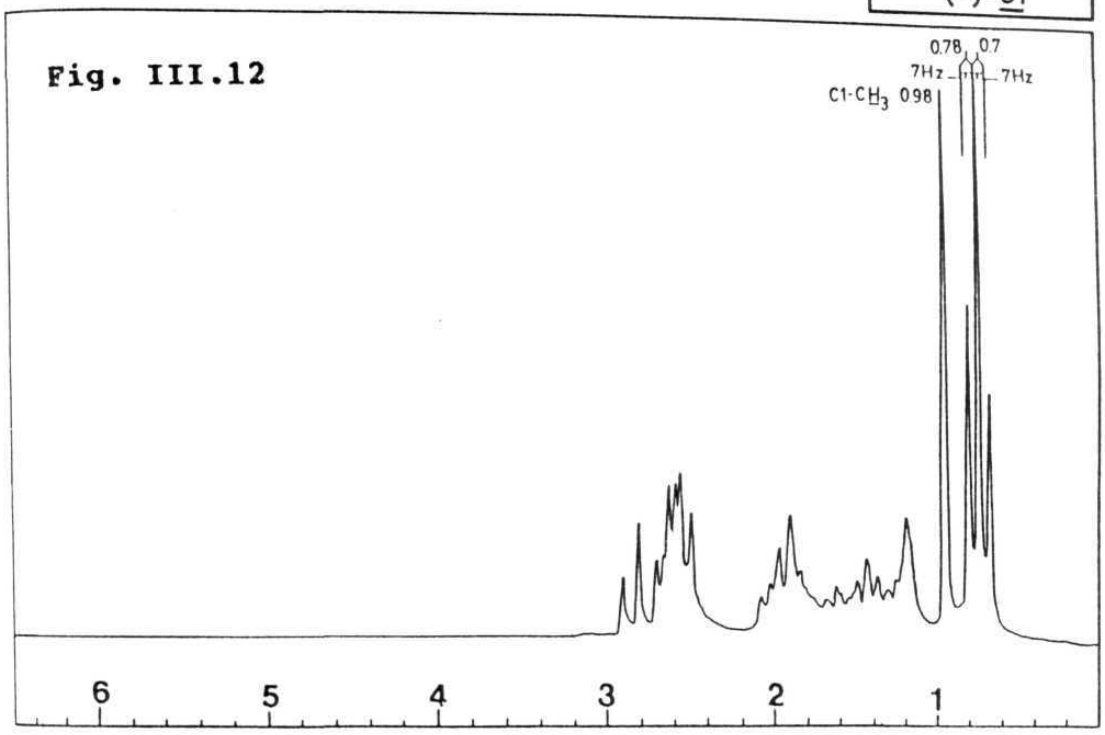
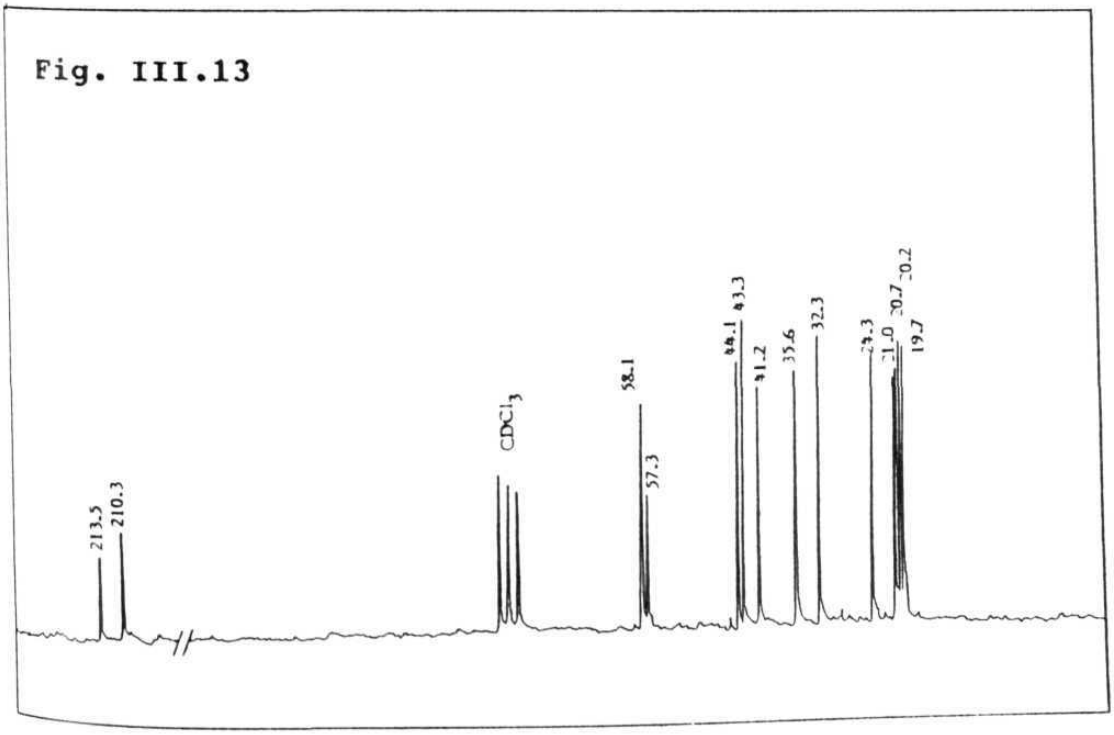


Fig. III.13



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VITAE

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List of Publications:

1. Steady-State and Laser Flash Photolysis Studies of Norbornenobenzoquinones and their Diels-Alder Adducts
   G. Mehta, S. Padma and Srinivasa Rao Karra, K.R. Gopidas, D.R. Cyr, P.K. Das and M.V. George, J. Org. Chem., 54, 1342 (1989).
2. π-Facial Selectivity in Norbornenobenzoquinone-Tropone Cycloaddition
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3. Enantioselective Approach to Isodaucane Sesquiterpenes. Total Synthesis of (+)-Aphanamol and (+)-2-Oxo-isodauc-5-en-12-al
   Goverdhan Mehta, N. Krishnamurthy and Srinvasa Rao Karra, J. Chem. Soc., Chem. Commun., 1299 (1989)
4. Synthetic Approach towards Virgane Diterpenes: Construction of 5,7,5-tricarbocyclic frame
   Goverdhan Mehta and Srinivasa Rao Karra, Indian J. Chem., 28B, 367 (1989)

5. Terpenoids to Terpenoids: Enantioselective Construction of 5,6- 5,7- and 5,8-Fused Bicyclic Systems. Application to the Total Synthesis of Isodaucane Sesquiterpenes and Dolastane Diterpenes
Goverdhan Mehta, N. Krishna Murthy and Srinivasa Rao Karra, J. Am. Chem. Soc., 113, 5765 (1991)

6. An Expedient Cyclopentenone Annulation Protocol
Goverdhan Mehta and Srinivasa Rao Karra, Tetrahedron Lett., 32, 3215, (1991)

7. Polyquinanes form (R)-(+)-Limonene: Enantioselective Total Synthesis of the Novel Tricycli Sesquiterpene (-)-Ceratopicanol
Goverdhan Mehta and Srinivasa Rao Karra, J. Chem. Soc., Chem. Commun., 1367 (1991)