A New Strategy for the α-Vinylation of Ketones Applications to Terpene Synthesis

A Thesis Submitted for the Degree of
Doctor of Philosophy

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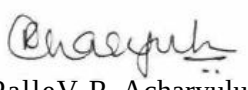
Statement

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, under the supervision of Professor Goverdhan Mehta.

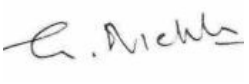
In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of the other investigators.



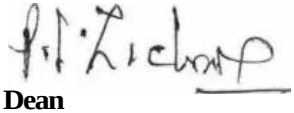
PalleV.R. Acharyulu

Certificate

Certified that the work embodied in this thesis entitled "**A New Strategy for the α-Vinylation of Ketones: Applications to Terpene Synthesis**" has been carried out by Mr. Palle V. R. Acharyulu under my supervision and the same has not been submitted elsewhere for a degree.



GoverdhanMehta
(Thesis Supervisor)



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Acknowledgements

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- All the non-leaching staff for their co-operation
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Words would be insufficient to express my feeling for my friends for all their support and association,

I am indebted to my parents and others at home for their love, affection and encouragement.

Abbreviations

Ac	Acetyl
DCM	Dichloromethane
DIBAL-H	Diisobutyl aluminium hydride
DME	Dimethoxyethane
DMF	Dimethyl fonnamide
Et	Ethyl
hv	Photo irradiation
KHMDS	Potassium hexamethyldisilazide
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilazide
Me	Methyl
MsCl	Methanesuifonyl chloride
NOESY	Nuclear Overhauser and Exchange Spectroscopy
PTS	p-Toluenesulfonic acid
Py	Pyridine
R.T.	Room temperature
TMSC1	Trimeihylsilyl chloride
TMSI	Trimethylsilyl iodide
TPAP	Tetra-n-propyl ammonium perruthenate
THF	Tetrahydrofuran
Δ	Thermolysis

Preface

Sesquitrpeoids are an important class of natural products, whose members include a variety of pheromones, antibiotics, cycloioxins and antitumor agents. The potential biological activity and complex skeletal build-up, in terms of unusual carbocyclic framework and stereochemical control, has projected these molecules as challenging targets for organic chemists. As a solution to the synthesis of complex skeleta, many methodologies have been devised, culminating in the total syntheses of these natural products.

α-Vinylketones, as an important functional moiety, is present in many natural products *viz,,* terpenes, alkaloids, etc. The present study describes our efforts in this direction, aimed at the development of a new and general methodology for the stereoselective construction of a-vinylketones and its elaboration to a variety of chiral sesquiterpene skeleta.

The thesis entitled ***"A New Strategy for the α–Vinylation of Ketones: Applications to the Synthesis of Sesquiterpenes"*** is an account of synthetic manoeuvres involving a new methodology for the α-vinylation of ketones and its efficacy in the synthesis of several sesquiterpene skeleta. The thesis has been organised under six main sections I. Background and objective, II. Synthetic studies, III, Summary, IV. Experimental, V. Spectra and VI. References, An appendix to the thesis entitled "Chiral dialkyl

cycloheptanones from R-(+)-citronellaI" describes our efforts during the formative years of this research project

In the "Background and objective" section a brief overview, with schematic representations, of some of the reported procedures directed towards the synthesis of α-vinyl ketones and the objective of the present study is presented

In the "Synthetic studies" section, we describe our efforts towards a new and general methodology to access the α-vinyl ketone moiety from an alkene functionality. The generality of the aforementioned methodology has been demonstrated by applying it to the enamioselective synthesis of (+)-α-elemene. The synthesis of a germacrane skeleton, a diquinane synthon and efforts towards the taxol AB ring frame-work have also been described in detail. The cleavage of cyclopropane bond in the "push-pull" cyclopropyl ester and its application in the formal synthesis of "copa" sesquiterpenoids and an eudesmane derivative is also described.

The sections III, IV, V and VI provide a brief summary of the work presented, detailed experimental procedures, spectra of some of the important compounds and appropriate literature citations, respectively.

The appendix of the thesis describes a short and diastereoselective synthesis of cycloheptanones bearing a methyl and isopropyl groups in a well

defined 1.4-relationship from R-(+)-cilroncllal, Results of the brief attempts of cydopentannulation on the cycloheplanone to access hydroazulenic skeleta have also been described.

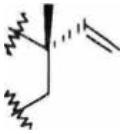
Background and Objective

The creativity of Nature in devising varied molecular architecture is revealed through the isolation of a wide range of molecular structures with remarkable skeletal build-up and multifarious functionalities. The number and complexity of these molecular entities, isolated from plant, marine, microbial and other sources, has taken a quantum leap in recent years as the methods of isolation (HPLC and CCDC etc-) and tools of structure determination (high field 2D NMR, FAB-MS, X-ray) have attained high degrees of sophistication. The unravelling of such a vast range of natural products, embellished with extensive functionalisation and a multitude of stereogenic centres has attracted the attention of synthetic chemists, both as a curiosity and a necessity- Curiosity, because assembling a complex architecture with stereochemical intricacies, dense functionalisation and in enantiomerically pure form poses an intellectual challenge that most synthetic chemists find irresistible. On the other hand, synthesis is a necessity as most of the natural products available are only in minute amounts but are needed in quantity for biological evaluation and application. In addition synthesis offers the opportunity to get access to analogues of the biologically potent natural products.

Natural products to a large extent are responsible for spearheading the enormous strides that synthetic organic chemistry has made in the last four decades, both in terms of new synthetic methodologies and in the attainment of specific target molecules. Indeed, the present scenario in synthetic chemistry is such that, even formidable natural products like taxol.[1]

brevetoxin,[2] phorbol,[3] dynemicin,[4] etc. do not look awesome and have succumbed to organic chemists conquests. Does that mean the end of the road for synthetic chemists interested in Natural products? Far from it; there will always be need, excitement and challenge in devising newer simpler, better and practical strategies and reagents for complex synthesis. Organic synthesis involves art and creativity and, as long as human ingenuity persists, this branch of science will continue to flourish.

Among natural products, terpenes occupy a special position on account of their widespread occurrence and the bewildering array of carbocyclic skeleta that they embody. They exhibit biological responses and activities ranging from flavours for drinks, fragrances in perfumes, sex-aitractants, insecticides and as anti-cancer compounds. Terpenes are also notable for certain structural motifs that are invariably present in them, as a consequence of the biosynthetic pathway through which they are derived. For example, *gem*-dimethyl group, quaternary carbon centres with angular methyl group(s), spiro-fused carbon centres, trisubstituted olefinic bonds and vinyl group at a quaternary carbon centre are extensively present among terpenes- Thus, besides carbocyclic ring construction, appropriate placement of some of these structural motifs along with requisite functionalities is an intrinsic part of terpene synthesis, It is not surprising, therefore, that considerable effort has been directed towards developing protocols for generating structural motifs characteristic of terpenes.



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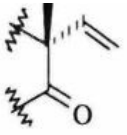
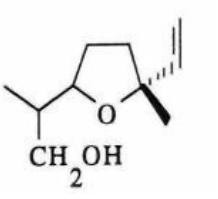


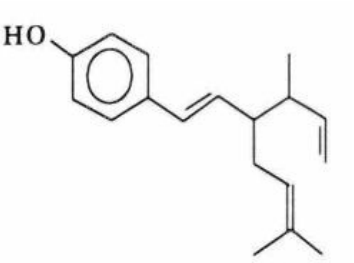
2

As pan of an ongoing research programme in the area of terpene synthesis, our attention and interest was drawn to the extensive occurrence of the structural moiety 1 among many terpenes. In chart I^{5a-h} are displayed selected examples from mono-, niero-, sesqui-, di- and triterpenes, as well as terpenic alkaloids wherein, the moiety 1 is present. While the quaternary carbon centre bearing moiety 1 is important in its own right, we further recognised that a more embellished sub-structure 2 containing an $\alpha-$vinyl ketone moiety would be even better, as this functionality could be elaborated and modified through well known reactions/transformations into a variety of structural fragments present in terpenic natural products, scheme 1, Thus, the presence of sub-structure 1 in many natural products and the various possibilities of elaborating 2 into diverse terpene skeleta became the twin motivating factors for us to consider the development of *de novo* methodology for rapidly and efficiently accessing these two moieties.

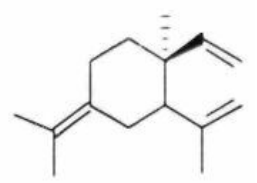
Chart 1



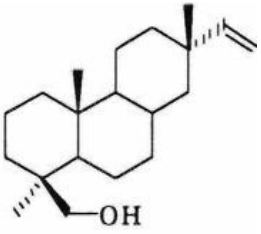
Lilac alcohol A 3[5a]



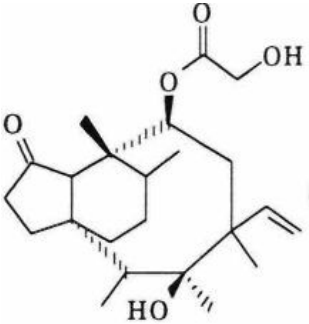
Bakuchiol 4[5b]



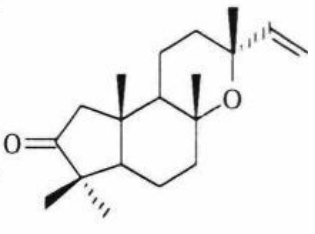
γ–Elemene 5[5c]



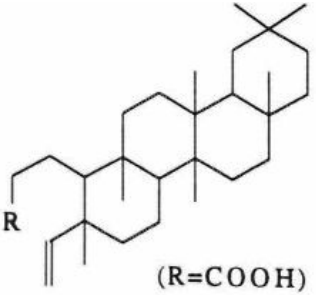
sandaracopimara -dien-19-o16[5d]



Pleuromutilin 7[5e]

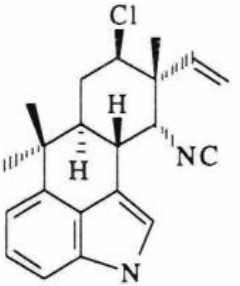


Colensenone 8[5f]



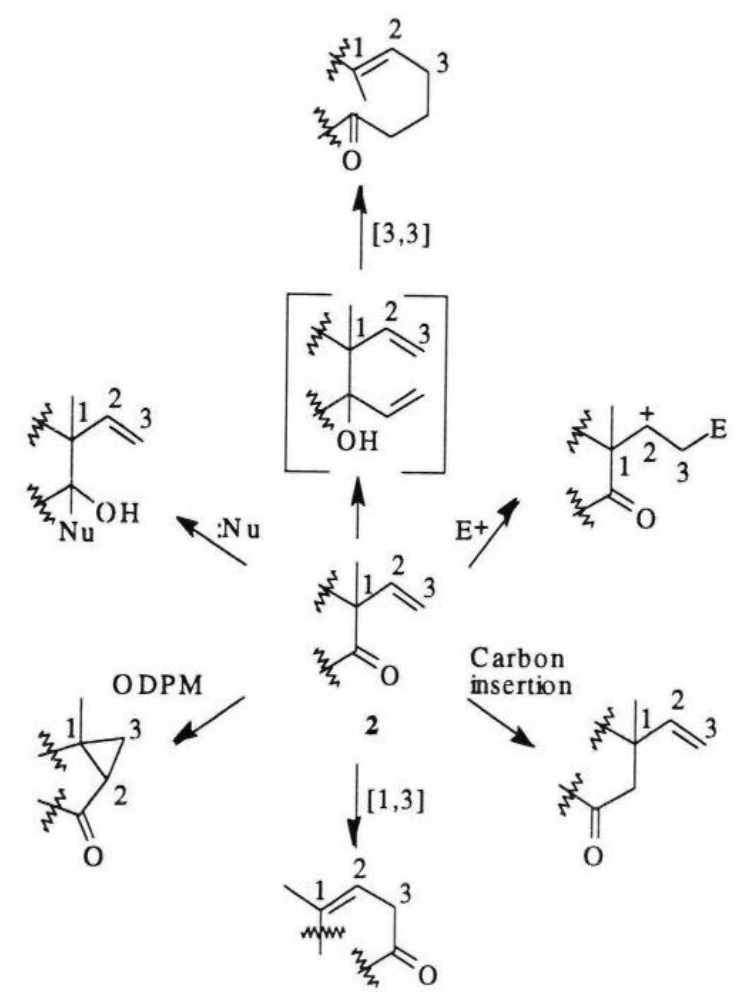
Putranjivic acid 9[5g]

Oxindole **10[5h]**



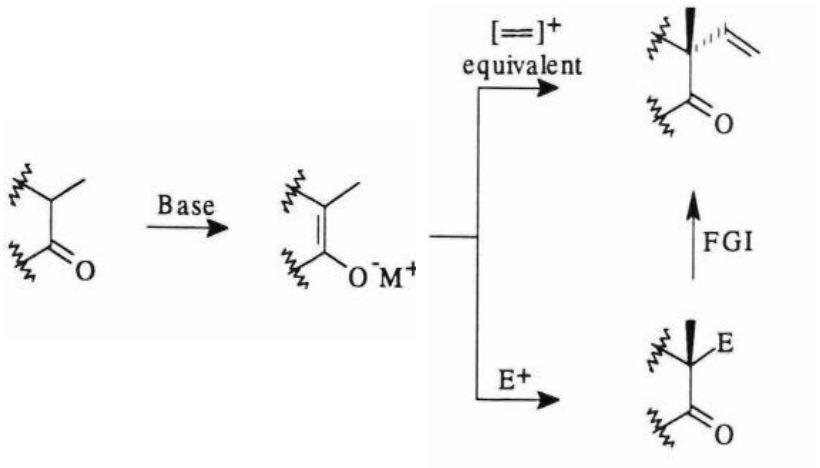
Hapalindole G 11[5h]

Scheme 1



Despite the widespread occurrence of the structural moieties 1 & 2 among natural products, methodologies available in the literature for their generation are rather limited. Particularly, the generation of α-vinyl ketone moiety 2 from a carbonyl precursor via α-vinylalion presents considerable difficulties. While vinyl anion species are well documented, α-vinylation of ketones requires access to a vinyl cation equivalent. Scheme 2. Efforts in recent years have been directed towards generating vinyl cation synthons with some degree of success. Alternately, classical methods of α-suhstitution with vinyl group surrogate and further functional group modifications have also been explored

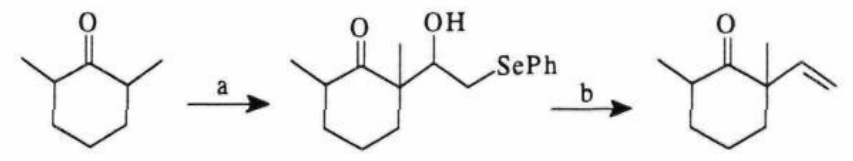
Scheme 2



Before unfolding our strategy for the construction of α-vinyl ketone moiety 2, it would be appropriate to scan through the reported procedures in the literature, for their practical applicability in synthesis. The following is a brief overview, with schematic representations, of some of the efforts directed towards the synthesis of α-vinyl ketones, as general methodologies or as a key step in multi-step syntheses.

Clive and Russel[6] have reported a flew general method for the preparation of α-vinyl ketones from cyclic ketones using phenylselenoacetaldehyde. The key step involved in their methodology was the condensation of zinc enolates derived from ketones **12** with phenylselenoacetaldehyde, to afford the hydroxy-phenylsclenides **13.** Methanesulfonyl chloride mediated elimination afforded the α-vinyl ketones **14.** An example is shown in scheme 3,

Scheme3



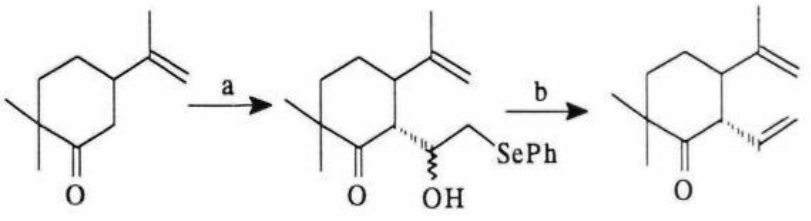
12 **13** 14

Reagents and conditions: (a) LDA, Et_2G, $ZnCl_2$; $PhSeCH_2CHO$. b. MsCI, Et_3N.

Introduction of a vinyl group at a primary or secondary centre, adjacent to a relatively hindered ketone system, has been carried out by Kowalski and Dung,[7] in their efforts to effect Cope-Claisen rearrangements *via* vinyl alcohols, as delineated in Scheme 4,

The aldol condensation of the lithium enolate derived from the corresponding ketone **15** with phenylselenoacetaldehyde resulted in the

Scheme 4



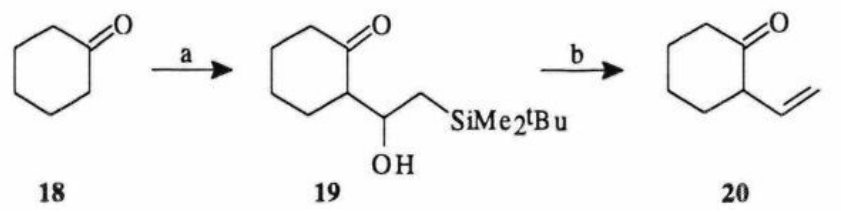
16

Reagents and conditions: (a) LDA, THF, $PhSeCH_2CHO$, (b) MsCl, Et3N, DCM.

intermediate β-hydroxy sclenide 16, The selenide **16,** thus obtained, was subjected to elimination reaction to furnish the α-vinyl ketone **17,**

In a related prolocol Hudrlik *et al.*[8] have demonstrated the use of α–tert-butyldimethylsilyl aldehydes as a stereoselective vinyl cation equivalent.

Scheme 5

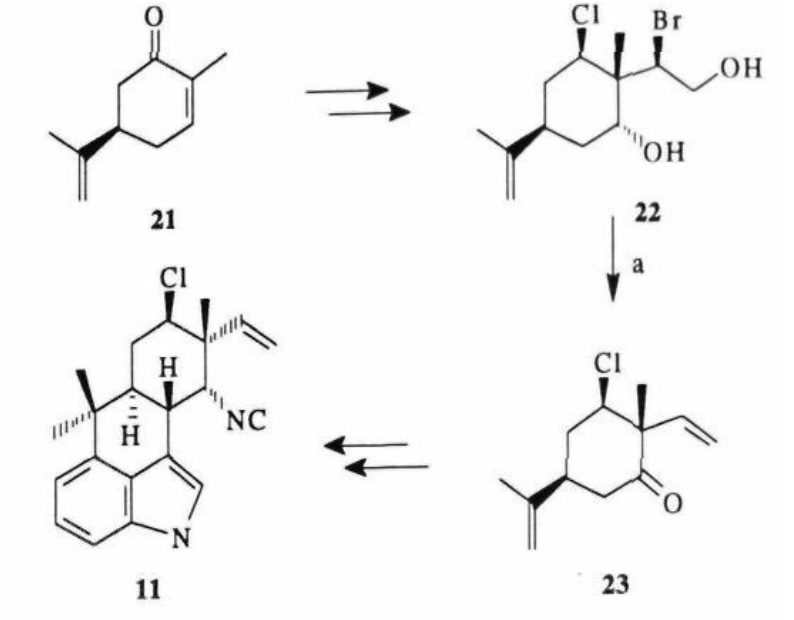


Reagents and conditions; (a) LDA, THF, -78°C, 1 h; t-$BuMe_2SiCH_2CHQ$, -78°C, 30 min. (b) $BF_3.Et_2O$, DCM, 0°C, 10 min.

Scheme 5, The lithium enolates of the ketones 18 were reacted with α-tert-butyldimelhylsilyl aldehydes to give the β-hydroxysilanes 19. The intermediate hydroxysilane **19** on exposure to BF_3-etherate furnished the required α-vinyl ketone 20, The methodology is of general applicability.

Fukuyama & Chen[9] during their enantioselectivc synthesis of (-)-hapalindole-G II from (-)-carvone **21** employed zinc mediated elimination in a bromohydrin 22 followed by Jone's oxidation as key steps to generate the requisite α-vinyl ketone intermediate 23, Scheme 6,

Scheme 6



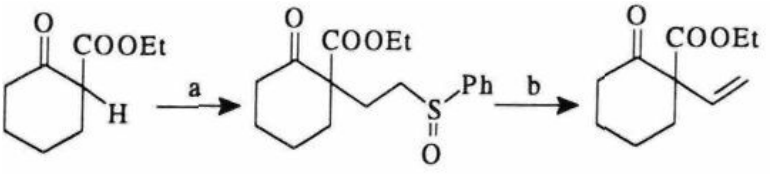
Reagents and conditions: (a) Zn-Cu, EtOH, reflux; Jone's reagent, acetone, 23°C.

Koppel and Kinnick[10] have projected a new vinyl carbonium equivalent (phenyl vinyl sulphoxide), in their approach towards the preparation of α-vinyl ketone as shown in the Scheme 7.

The ketone 24 was treated with phenyl vinyl sulphoxide in the presence of a base to furnish the desired sulphoxide 25. Pyrolysis of the

sulphoxide 25 in toluene under reflux delivered the required α-vinyl ketone 26

Scheme 7

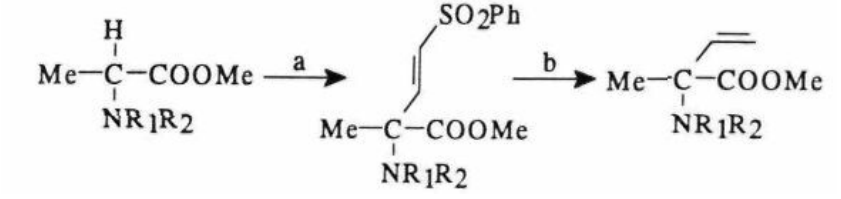


24 **25** **26**

Reagents and conditions: (a) NaH, $PhSQCH{=}CH_2$, THF, Δ (b) Toluene, D, 72 h,

metacalf and Bonilavri[11] have developed a new vinyl ration synthon, plienyl *trans*-2-chloro vinyl sulphone for the α-vinylation of amino acid

Scheme 8



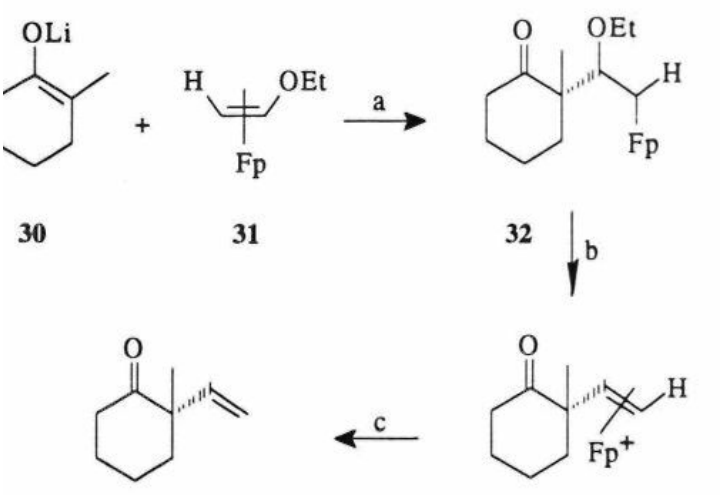
27 **28** **29**

Reagents and conditions; (a) LDA, $ClCH{=}CHSO_2Ph$, -78°C (b) dil.HCL

derivatives. The vinyl cation synthon was added to the enolate of the ester 27, to furnish the sulphone 28. which on further exposure to acid, yielded the α-vinyl a-amino acid derivative 29, Scheme 8.

Rosenblum *et al.*[12] have reported the use of Fp(alkyl vinyl ether), [Fp=C_5H5 $Fe(CO)_2$] complexes as vinyl cation equivalents for the regio- and

Scheme 9

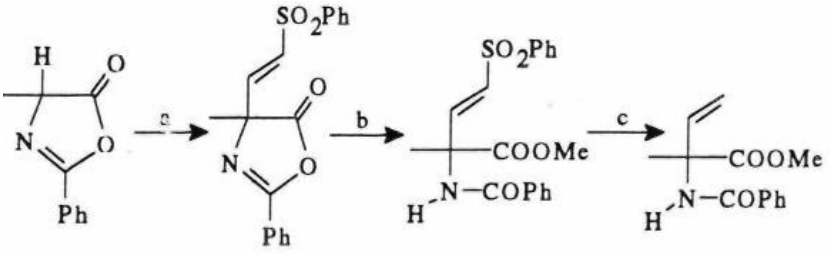


Reagents and conditions: (a) THF, -78°C, 1 h (b) HBF_6, Et_2O-78°C, 30 min. (c) Nal, acetone, 25°C, 15 min.

stereospecific vinylalion of enolates under mild conditions. The enolate 30, reacts smoothly with the metal complex 31, to give the adduct 32 as a mixture of diastereomers. Protonation of this product 32, followed by treatment of the resulting sail 33 with sodium iodide, gave the free enone 34, Scheme 9.

Steglich and Wegmann[13] have employed the use of phenyl ethynyl sulphoxides in the preparation of α–vinyl ketones through Michael addition

Scheme 10



36 37 **38**

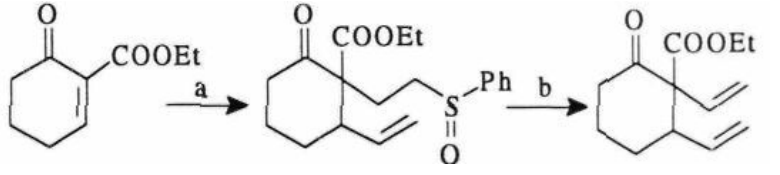
Reagents and conditions: (a) Et3N, DCM, Ethynyl phenyl sulphoxide, -20°C (h) Et_3N, MeOH (c) Al-Hg, H_2O, THF, NaOH, H_2O.

reaction, Scheme 10. Ethynyl phenyl sulphoxide was added to 5-oxo-4,5-dihydro-l,3-oxazole **35** in the presence of triethylamine to give the corresponding sulphoxide 36, which on methanolysis furnished the methyl

ester 37. Treatment of the ester 37 with aluminium-mercury amalgam and hydrolysis furnished the desired α-vinyl amino acid 38.

As an extension of this strategy, Heimgartner *et al.* [14] have described a vinylation procedure for unsaturated β-keto esters, *en route* to the synthesis of large carbocyclic rings, Scheme 11.

Scheme 11



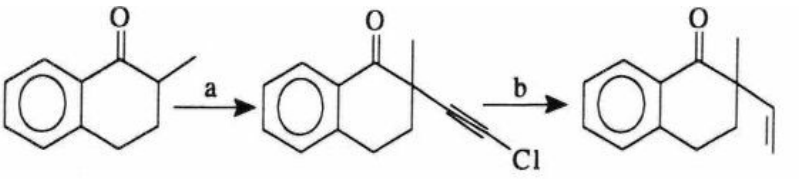
39 **40** **41**

Reagents and conditions; (a) i. CH_2=CHMgCl, THF, CuI, 0°C ii. NaH, PhSOCH=CH_2 (b) 210-250°C/10^{-3} torr.

Vinylation of the β-keto ester 39, through 1,4 addition, followed by treatment with phenyl vinyl sulphoxide in the presence of a base yielded the sulphoxide 40. Pyrolysis of the sulphoxide 40, delivered the required divinyl ketone 41. The introduction of vinyl group through the vinyl sulphides and sulphoxides was also studied extensively by several other groups along similar lines.

A simple approach to α-vinyl ketone *via* partial hydrogenation and reductive dechlorination of chloroettiynyl adduct has been described by Kende[15], Scheme 12.

Scheme 12



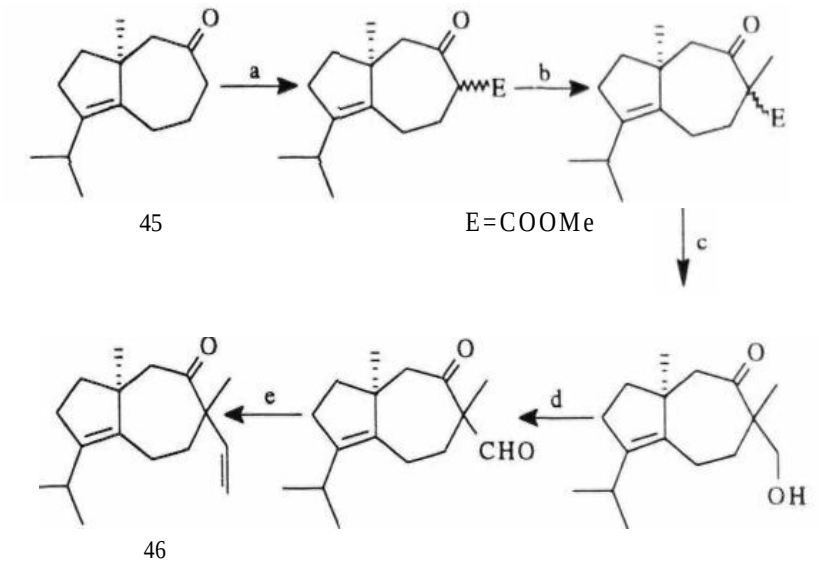
42 **43** **44**

Reagents and conditions: (a) i. Ethereal ClC=CCl to the enolate, -78°C-> R.T (or), enolate to C1C=CC1 at -2G°C->R.T. (b) H_2 (1 atm.), Lindlar cat., 10:1 EtOAc:Et_3N.

Lithium tertiary enolate of tetralone 42 on reaction with dichloroacetylene gave the corresponding chloroethynyl adduct 43 in good to excellent yield. The adduct 43 on semihydrogenation over Lindlar catalyst delivered the corresponding α-vinyl ketone 44 in high yield. However, this method of a-vinylation is restricted to the tertiary enolates.

Mehta *et al.*[16] have described a classical five-step sequence to access the α-vinyl ketone 46, with a quaternary carbon centre, from the corresponding ketone 45, as depicted in Scheme 13,

Scheme 13

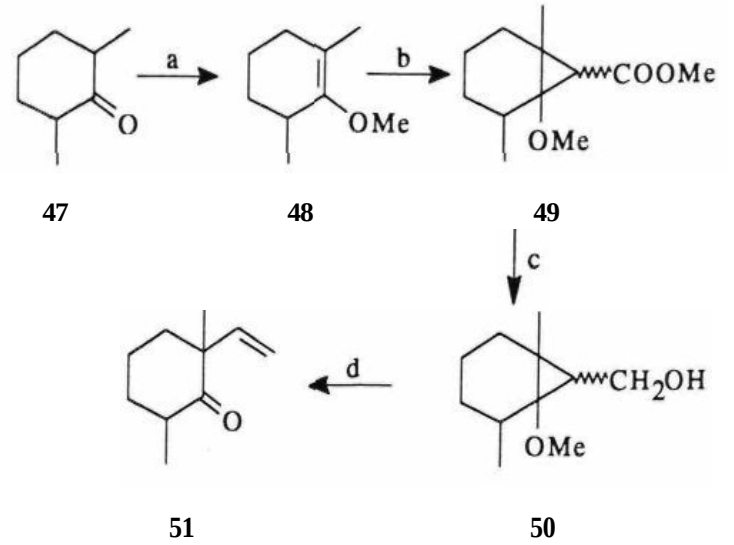


46

Reagents and conditions: (a) **NaH,** $(CH_3O)_2CO$, Δ, 6 h (b) K_2CO_3-Acetone, **Mel** Δ, 24 **h** (c) **LAH, Et_2O,** R.T, **1** h (d) **PCC, DCM,** 4A° molecular sieves, **R.T.** (e) **$Ph_3P^+CH_3Br^-$,** Na-t-amyloxide, R.T., 10 **min.**

Wenkert *et al.*[17] have reported the design of terpene synthesis based on the acid-Induced transformation of β-methoxy cyclopropyl carbinols into quaternary α-mcthyl α-vinyl carbonyl compounds, Scheme 14.

Scheme 14



47 **48** **49**

51 **50**

Reagents and conditions; (a) ref. 12 (b) Ethyl diazoacetate, copper-bronze, methyl cyclohexane, reflux, 1 h (c) LAH, Et_2O, R.T., 12 h (d) *20%* HC1 in MeOH, 50°C, 45 min.

Addition of ethyl diazoacetate to the enol ether 48, obtained from the ketone 47, in the presence of copper-bronze, afforded a stereoisomeric mixture of ester 49. Reduction of the ester moiety with lithium aluminium hydride to carbinols 50, followed by treatment with acid, yielded the desired α-vinyl ketone 51.

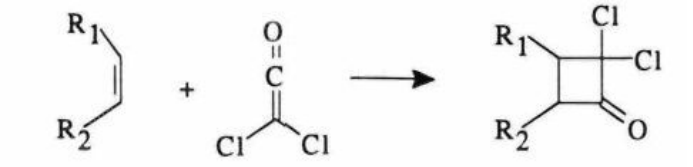
The various strategics described above for generating the α-vinyl ketone moiety have their own disadvantages in terms of regio- and stereochemical intricacies. In many cases, the reagents employed for the purpose are either very expensive or have to be made in tedious, multi-step sequence. The success achieved so far in the stereoselective introduction of the vinyl group on a quaternary carbon is limited. Thus, the generation of a quaternary centre, with methyl and vinyl groups adjacent to carbonyl group with regio- and stereochemical control continue to be a demanding chemical manoeuvre and there is need for simpler and practical solutions.

The wide ranging applications of functional moieties 1 & 2, particularly the later, required that these be accessed in short, reliable, regio- and stereoselective sequences from readily available starting materials. Most of the earlier routes to 2 have emanated from a carbonyl precursor with manoeuvring at the a-pro nucleophilic centre. However, it is well recognised that in such operations, regiochemical control invariably presents some problems. To circumvent this, we felt that employing an olefinic precursor to generate the moiety 2 could be a better preposition. In this context, our attention was drawn to some reports of interesting transformations of the [2+2]-cycloadducts of dichloroketene and olefins.

The addition of α,α-dichloroketene, generated from either trichloroacetyl chloride and activated zinc or from dichloroacetyl chloride and base, to olefins is a fairly general and efficient reaction leading to [2+2]-

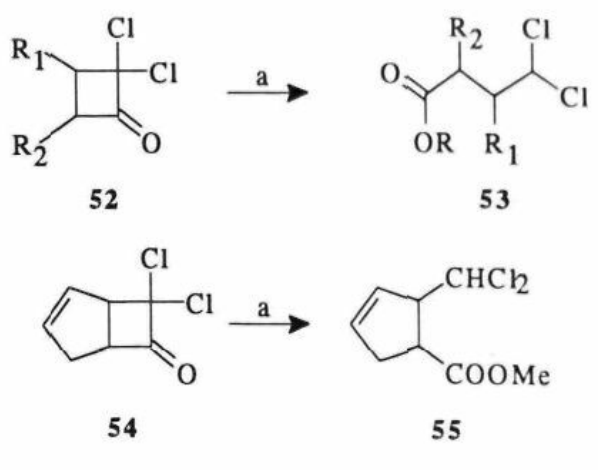
cycloadducts. Scheme 15, Several modifications in experimental conditions, e.g. use of off-the-shelf zinc in the presence of ultrasound irradiation have made this reaction quite simple to perform.[18]

Scheme 15



Both cyclic and acyclic olefins react well to furnish α,α-dichlorocyclobuianones. An intramolecular version of this reaction has also found applications, The regio- and stereochemical aspects of this cycloaddition have also been investigated and clarified.[19] The ready availability of these α,α–dichlorocyclobutanones in a single step from olefins, make them useful synthons for a variety of transformations.[20] Indeed, the chemistry of dichloroketene-olefin adducts have been extensively studied in recent years.

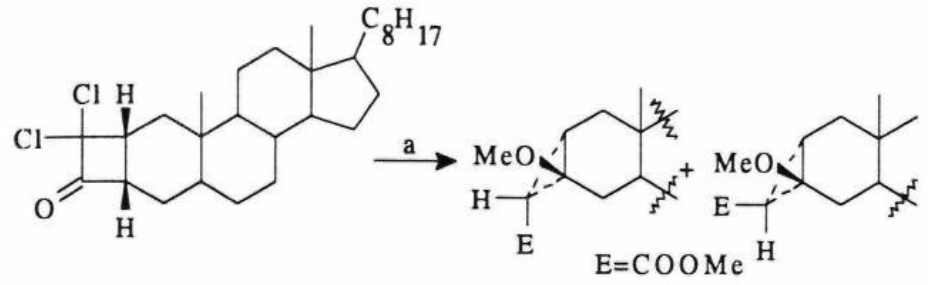
Scheme 16



Reagents and condition; (a) NaOMe, MeOH, R,T,

It has been reported in the literature that α,α-dichlorocyclobutanones e.g. 52 & 54 on exposure to base, undergo Haller-Bauer type of ring cleavage[21] to furnish the esters 53 & 55, respectively, Scheme 16. While many such cleavage reactions have been recorded, Hassner *et. al.*[22] in 1971 reported an interesting deviation from this trend. They found that the dichloroketene adduct 56 of 2-cholestene, on treatment with excess of sodium methoxide in methanol, afforded a mixture of cyclopropyl methyl esters 57a and 57b, in almost quantitative yield. Scheme 17.

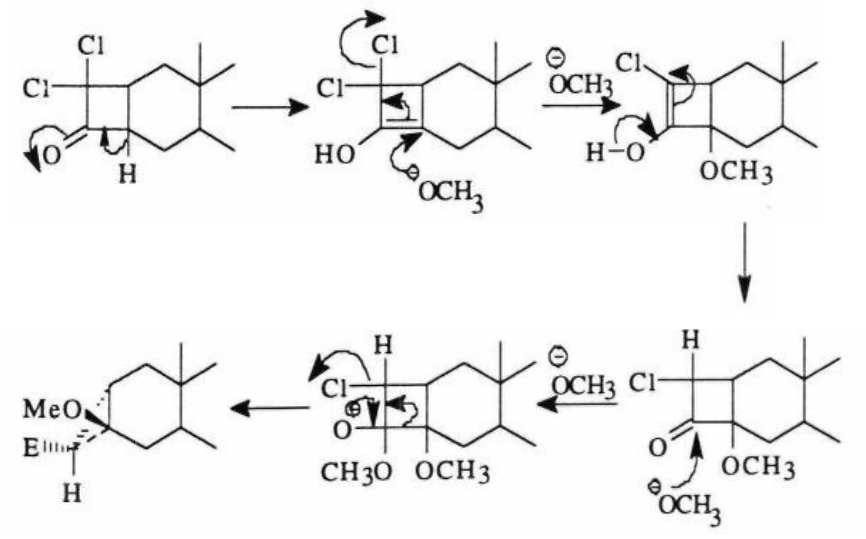
Scheme 17



56 **57a** **57b**

Reagents and condition: (a) NaOMe, MeOH, Δ, quant.

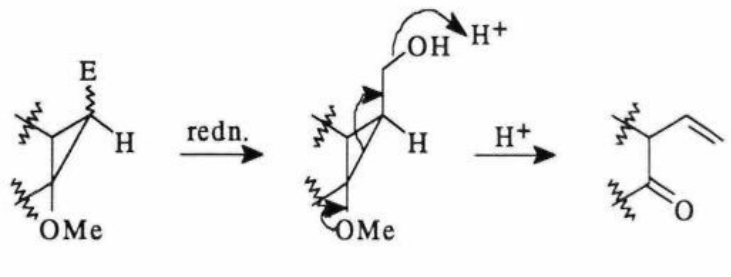
Scheme 18



A few additional examples of this Favorskil-like ring contraction process were also reported.[23] A likely mechanism[22] for the formation of cyclopropyl esters is displayed in Scheme 18, No further work on this interesting rearrangement has been reported since then.

We were greatly attracted by the Hassner observation, through which functionalised cyclopropyl esters with "push-pull" type of substitution pattern could be readily obtained. We recognised that the ester group in these "push-pull" cyclopropanes could be elaborated to a carbinol group, which on activation should readily fragment to furnish the α-vinyl ketone moiety as shown in the Scheme 19. Through this logic, outline of a strategy for the

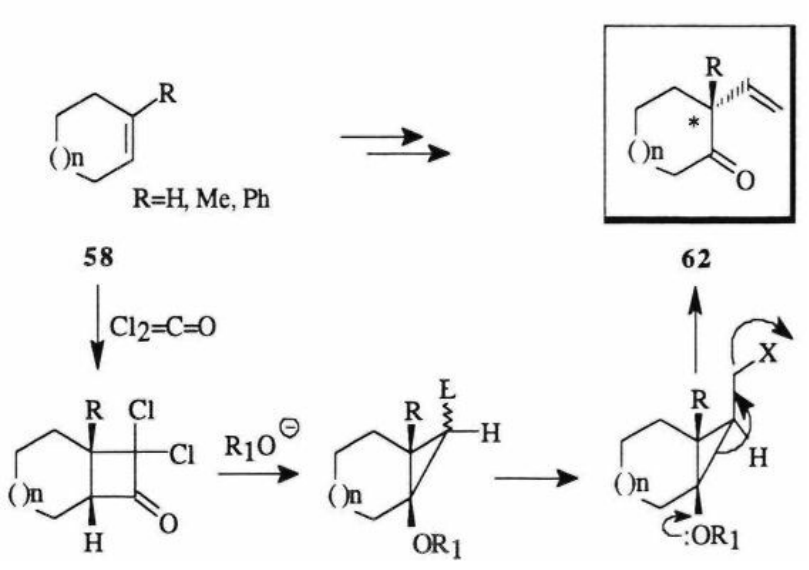
Scheme 19



generation of α-vinyl ketone moiety, with or without a quaternary carbon centre, from an olefin emerged. This is shown in Scheme 20. The steps involved would be (i) olefin-dichloroketene 58 -> 59 [2+2]-cycloaddition, (ii) methoxide mediated ring contraction to a cyclopropane ester 59 -> 60, (iii)

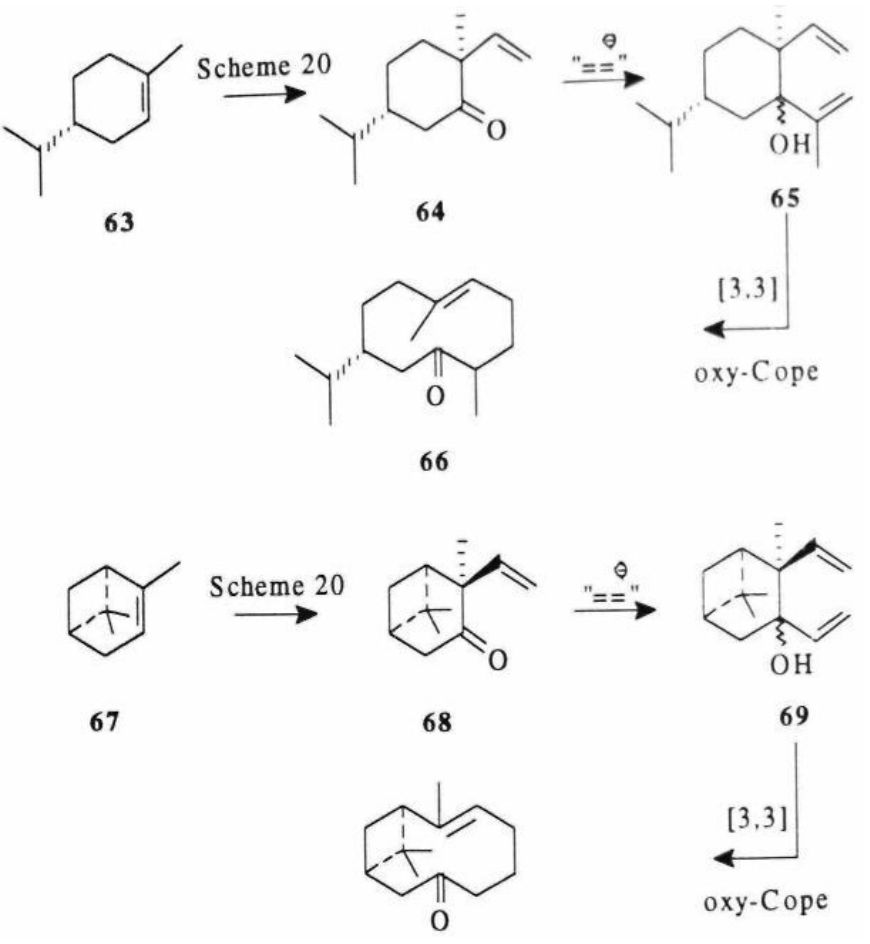
reduction of the ester functionality to a cyclopropyl carbinol moiety 60 -> 61 and (iv) activation of the carbinol hydroxyl group and cyclopropyl fragmentation to generate the α-vinyl ketone moiety 62, Scheme 20. Thus,

Scheme 20



exploring the feasibility of the Scheme 20 to gain entry into α-vinyl ketone moiety from olefinic precursors bacame our initial objective. We also sought to demonstrate the generality of this theme by carrying out the sequence with typical olefinic substrates.

Scheme 21



70

At this stage, we have reasoned that implementation of the Scheme 20, in actuality means homologation of an olefin by two carbon atoms in the form of a vinyl group with concomitant generation of a carbonyl

functionality. Thus, if C_{10}-monoterpene hydrocarbons were to be employed as precursors, homologated C_{12}-entities bearing a- vinylketone functionality would result, following the protocols of Scheme 21. The functionality present in these C_{12}-homo monoterpenes has the potential for further manipulation with amplification of carbon content as indicated earlier in Scheme 1. Thus, monoterpenes can be employed for the synthesis of higher terpenes, particularly sesquiterpenes. While this aspect is going to be discussed in detail later in this segment, it will suffice here to present two intriguing possibilities, employing dihydrolimonene 63 and α-pinene 67 as starting materials. Utilising the α-vinylketone functionality, it is possible to set up an oxy-Cope rearrangement in a straight forward manner. Thus, α-vinylketones 64 & 68, derived from dihydrolimonene 63 and α-pinene 67, respectively, can be elaborated to oxy-Cope precursors 65 & 69, respectively. Successful oxy-Cope rearrangement in 65 & 69 would then provide entry into the germacrane-type sesquiterpene skeleton 66 and a precursor 70 for elaboration into the taxoid diterpenoid frame-work, Scheme 21. The advantage of this kind of approach in terms of brevity and access to enantiomerically pure products is quite obvious.

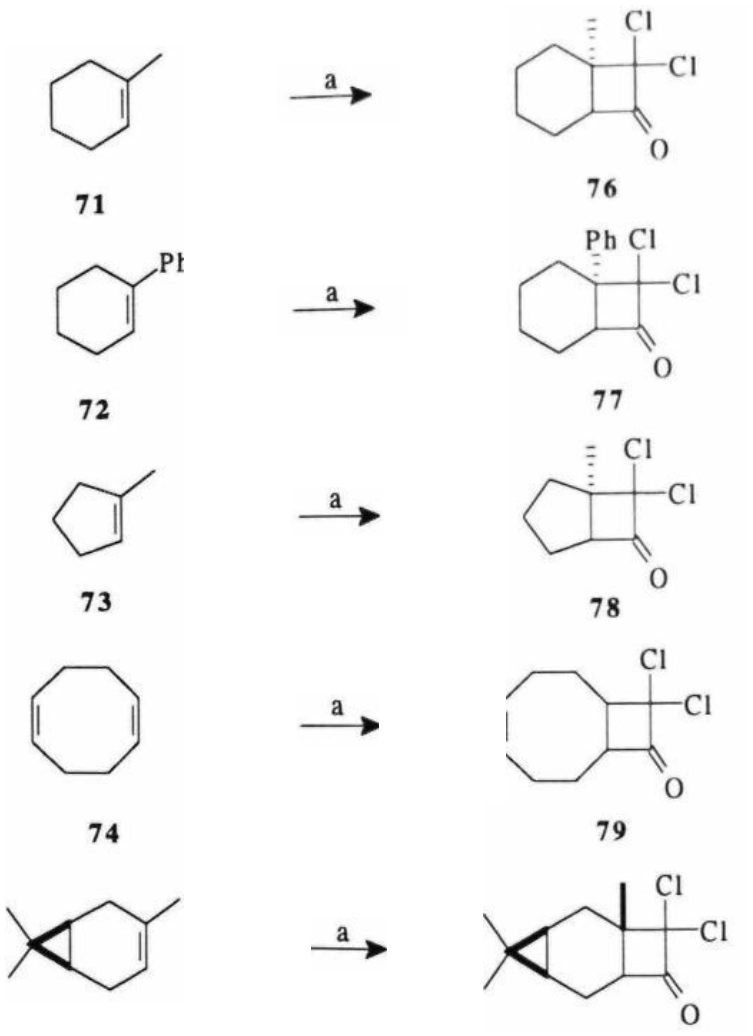
With the thoughts and reasoning enumerated above in mind, it was time to give practical shape to the strategy for two carbon homologation of olefins, Scheme 20, and apply it for the construction of the carbocyclic skeleta of some natural products. The outcome of these studies is described in the next section.

Synthetic Studies

To implement the theme depicted in Scheme 20 and to demonstrate its generality, we selected l-methylcyclohexene, 1-phenylcyclohexene, 1-methyl cyclopentene, 1,5-cyclooctadiene and (+)-Δ^3-carene as the precursor olefins.[24] All the five olefins 71-75 were routinely transformed into their α,α-dichloroketene adducts 76-80 Scheme *22*. The method of choice for this purpose involved trichloroacetyl chloride and off-the-shelf zinc dust in the presence of ultrasound irradiation. Under these conditions, cleaner products were realised and reaction times were considerably shortened. All the ketene adducts 76-80 were duly characterised on the basis of their spectral characteristics.

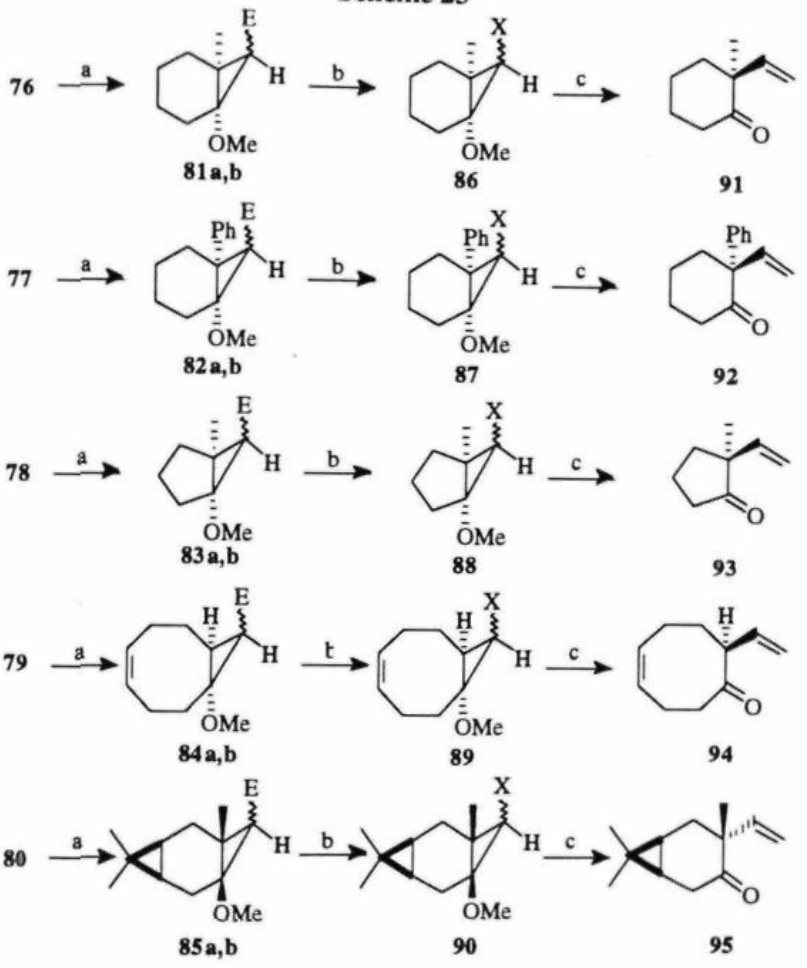
The ketene adducts 76-80, thus obtained, were subjected to the ring-contraction-rearrangement reaction. Treatment of the adducts 76-80 with excess of sodium methoxide in methanol under reflux, furnished the corresponding cyclopropyl esters 81a,b-85a,b as diastereomeric mixtures in good yields (60-80%). This was a pleasing outcome and set the stage for the next key step. Although the mixture of the esters 81a,b-85a,b was separated for the sake of characterization, the stereo structures to the individual compounds could not be assigned unambiguously based on the spectral data. The chemical shift changes were too small for a clear cut distinction. However, for the contemplated sequence, it was not considered necessary to separate the diastereomers. Therefore, the mixture of diastereomeric cyclopropyl ester was carried as such for the next step.

Scheme 22



Reagents and conditions: (a) $CC1_3$ **COC1, Zn,** Et_2O**,** sonication.

Scheme 23

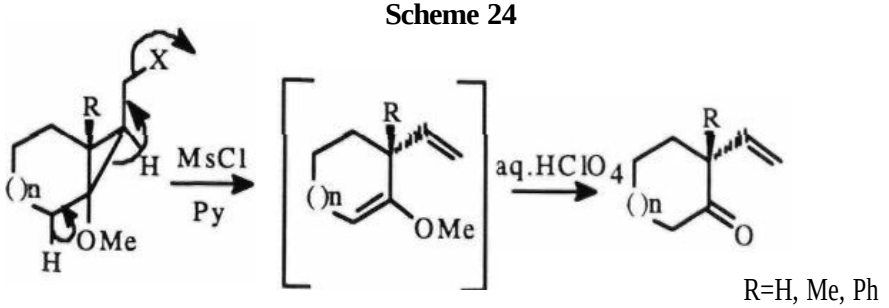


Reagents, conditions and yields; (a) NaOMe 5eq., MeOH, Δ, 10-30 min. (b) DIBAL-H 2 eq., DCM, -78°C, 20-60 min. (c) MsCl 1.2 eq., Py. 0°C-R.T., 15min.; 35% $HC1O_4$, Et_2O, 0°C, 30 min,(E=COOMe and X=CH_2OH)

The next key operation in this sequence was in set up the cyclopropylcarbinyl-homoallylic rearrangement in the activated "push-pull" cyclopropyl carbinol derivatives. For this purpose, the ester moiety in 81a,b-85a,b was reduced using Dibal-H at low temperatures, to furnish the corresponding cyclopropyl carbinols 86-90, respectively, as diastereomeric mixtures. The spectral data of the mixtures enabled their gross characterization.

Having obtained the required cyclopropyl carbinols **86-90 t**he objective now was to carry-out a fragmentation sequence to access the desired a-vinyl ketones by activating the hydroxyl group. To execute this protocol, the carbinols **86-90** were reacted with methanesulphonyl chloride in pyridine, to obtain the corresponding "push-pull" mesylates. Not surprisingly, the mesylates were not isolated but instead we directly obtained the α-vinyl ketones **91-95.** However, the α-vinyl ketones 62 were found to be contami-

Scheme 24



nated with the enol ethers 96 formed concomitantly during the reaction of carbinols 61 with methanesulfonyl chloride in pyridine, Scheme 24. Therefore, the reaction product obtained from methanesulfonyl chloride-pyridine reaction was briefly exposed to aq. perchloric acid (to hydrolyse the enol ether) and α-vinyl ketones 91-95 were isolated in good (40-75%) yield, All the α-vinyl ketones (Fig. 1-10) obtained in this sequence were duly characterised (IR, ^{1}H and ^{13}C NMR) and the data is presented in the experimental section.

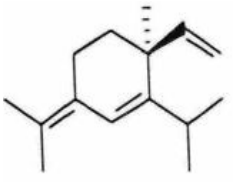
This simple and short protocol for the synthesis of α-vinyl ketones 62, from olefins 58 prompted us to seek further applications in the synthesis of terpenes, particularly those bearing a quaternary carbon centre, The high regio- and stereoselectivities in the addition of the dichloroketene was expected to influence the stereochemical outcome of the α-vinyl ketones, leading to the formation of a single diastereomer and paving the way for the enantioselective synthesis of (+)-α–elemene and other useful carbocyclic skeleta starting from the monoterpene chiral pool.

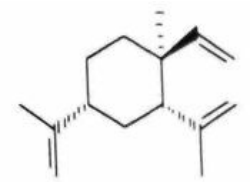
First Enatioselective Synthesis of (+)-α-Elemene

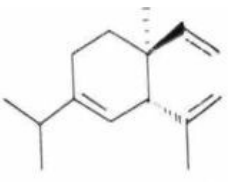
Elated by the success in the development of a new protocol for the generation of α-vinyl ketones, from the corresponding olefin equivalents, it was considered essential to demonstrate its practical utility to the synthesis of some structurally related natural product skeleta. In this pursuit, the elemene group of sesquiterpenes (Chan 2)[25a-f] with the vinyl and the methyl groups

strategically placed at the quaternary centre, attracted our immediate attention. In this section is reported the first enantioselective synthesis of (+)-α-elemcne 97 using the aforementioned protocol, from readily available R-(+)-limonene,

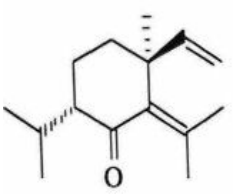
Chart 2

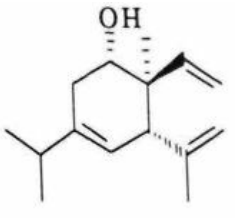


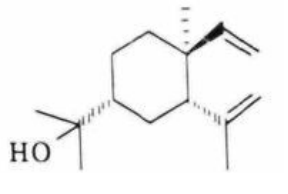




a-Elemene 97[25a] b- **Elemene 98[25b]** d- **Elemenc 99[25c]**







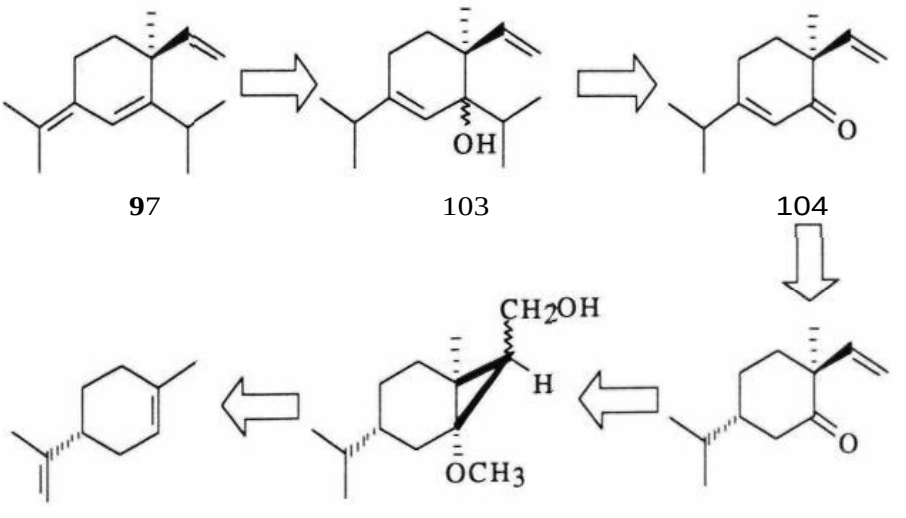
Isoshyobunone 100[25d] **d-Etemen-9-ol 101[25e]** b- **Elemol 102[25f]**

(+)-α- Elemene 97, a sesquiterpene hydrocarbon, was first isolated by Ivanov *et al.,* in 1955 from the oil of *Bulgarian zdravets.*[26] The structural evidence of (+)-a-elemene 97, the main product obtained in the dehydration of elemol, was provided by Paknikar *et at.,*[27] on the basis of degradative and NMR studies. In 1977, Vig and his co-workers[28] have reported the synthesis

of racemic α-elemene. However, the enamioselective synthesis of (+)-α-Elemene 97 has not been reported in the literature.

Terpenes, among the "chiral pool", continue to attract attention in the enantioselective synthesis of complex natural products. They can be conveveniently homologated, annulated and restructured into useful natural product skeleta through simple chemical transformations.[29] The readily available chiral monoterpene R-(+)-limonene 106 with pre-installed isopropyl and

Scheme 25



97 103 104

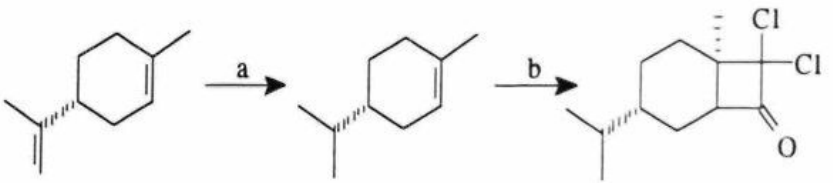
106 105 64

methyl groups in 1,4-reIalionship, as present in the elemene group of sesquiterpenes and our target molecule 97, led us in select it as the starting material. Through the recognition of structural patterns present in limonene and the target structure 97, and keeping in mind our two carbon methodlogy for generating the α-vinyl ketone moiety, a retrmynthetic strategy could be formulated as shown in Scheme 25,

The α-vinyl ketone 64 and the enone 104 were identified as the advanced intermediates for the synthesis of (+)-α-elemene

To execute the synthetic plan revealed through the retrosynthetic analysis, R-(+)-limonene 106 was regioselectively hydrogenated over

Scheme 26



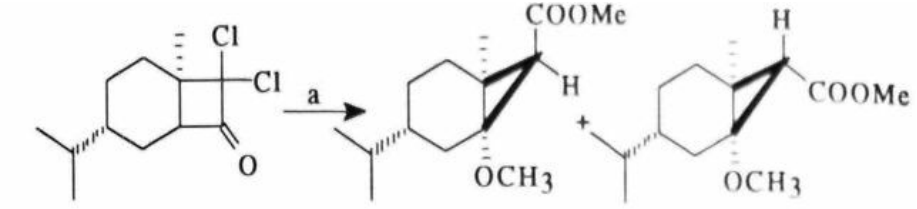
106 63 107

Reagents, conditions and yields: (a) H_2/PtO_2, EtOH, 90% (b) $CC1_3$ COC1, Zn, Et2O, sonication, 65%.

platinum oxide to furnish the desired R-(+)-dihydrolimonene **63** in 90% yield.[30] The olefin **63** on reaction with α,α-dichloroketene, generated from trichlaroacetyl chloride and zinc dust in the presence of ultrasound irradiation furnished the expected [2+2]-adduct 107 stereoselectively, in 65% yield, Scheme 26. The spectral data of the adduct 107 was in full agreement with its formulation, The IR spectrum showed a strong absorption at 1800 cm^{-1} due to the presence of the carbonyl moiety and the ^{1}H NMR spectrum exhibited a characteristic proton resonance at δ 3.70-3.50 (m, 1H) corresponding to me ring junction proton. A 12 line ^{13}C NMR spectrum with carbon absorptions at δ 195.3 and 92,1 characteristic of the carbonyl carbon and the carbon attached to the chlorine atoms, further confirmed the formulation of the ketene adduct 107, The formation of a single diastereomer was an expected and satisfying outcome. We had reasoned on the basis of previous precedences that the ketene addition to the visubstituted double bond will occur from the face opposite to the isopropyl group. Having acquired the ketene adduct 107 in good quantities, our next objective was to carry-out the ring contraction-rearrangement protocol to get the cyclopropyl esters 108a,b. Exposure of the ketene adduct 107, to the sodium methoxide-methanol milieu yielded a diastereomeric mixture of "push-pull" cyclopropyl esters 108a,b in 75%, Scheme 27.

The IR spectrum of the mixture 108a,b with a strong absorption at 1720 cm^{-1}, and sharp singlets in ^{1}H NMR spectrum at δ 3.64 and 3.63 due to carbomethoxy functionality provides strong evidence of its formation. At this

Scheme 27



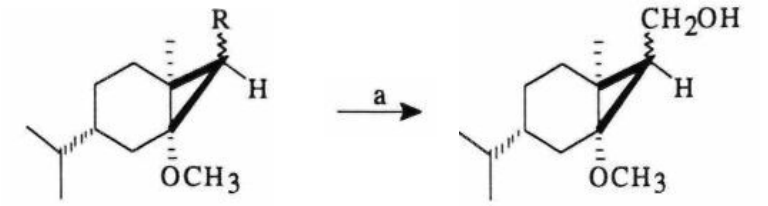
107 **108a** 108b

Reagents, conditions and yields: (a) NaOMe-MeOH. Δ, 75%

stage, the mixture was not required to be separated and the same was carried over to the reduction-step. However, the mixture was separated for characterization purpose, and each diastereomer was found to be in agreement with its gross formulation.

The mixture of the esters 108a,b on reduction with Dibal-H, furnished a diastereomeric mixture of bicyclic cyclopropyl carbinols 105 in 80% yield. Scheme 28. A strong absorption at 3350 cm^{-1} in the IR spectrum established the presence of the hydroxy group. However, reduction of the ester mixture 108a,b with LAH was found to be more efficient, especially for large scale preparation.

Scheme 28

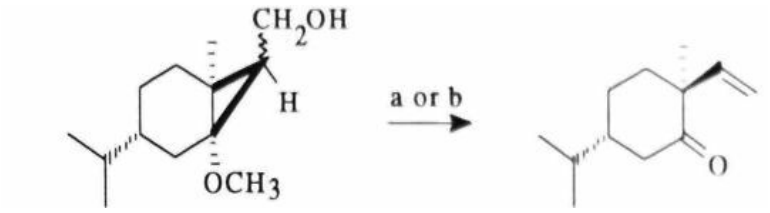


108a,b R=COOMe 105

Reagents, conditions and yields: (a)Dibal-H, DCM, -40°C, 80% (b) LAH, Et_2O,RX75%

The crude carbinol mixture 105 obtained, was directly subjected to the key ring-opening reaction to generate the α-vinyl ketone moiety. Brief reaction of the alcohol mixture 105 to methanesulfonyl chloride and pyridine followed by exposure to aq. $HClO_4$, resulted in the facile ring opening *via* the cyclopropylcarbinyl-homoallylic rearrangement to furnish a single diastereomer, the α-vinyl ketone 64, Scheme 29, in 78% yield. A strong carbonyl absorption at 1705 cm^{-1} in the IR spectrum and the presence of the typical vinyl moiety resonances, between δ 6.2-6.0 and 5.2-4.9, in the ^1H NMR spectrum (Fig, 11), and the signals at δ 214.0, 142.8 and 112,8 characteristic of the carbonyl and the olefinic carbons, respectively, in the ^{13}C NMR spectrum (fig 12) confirmed the identity[1] of its formulation. Later, we found that the 105—>64 transformation involving cyclopropyl cleavage can be carried out more efficiently (90% yield) on exposure to *in situ* generated

Scheme 29



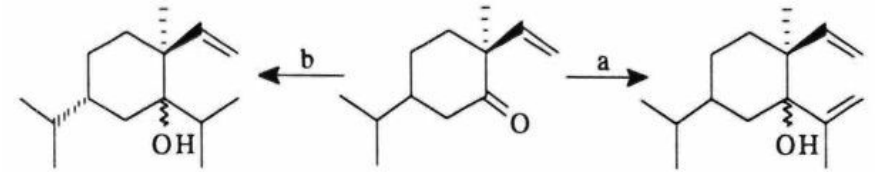
105 **64**

Reagents, conditions and yields: (a) MsCl, Py, 0°C. **R.T., 15 min**.; 35% aq. **HC1O4,** ether, 0°C, 30min,, 78% (b) Me_3SiI, **MeCN. R.T., 90%**

trimethylsilyl iodide[31] (TMSI), In this way, further treatment with aq. perchloric acid was not required as the intermediate enol ether of the type 96, if formed was also cleaved by TMSL

For elaboration to the elemane skeleton, a C_3-unit had to be added to the carbonyl group of C_{12}-ketone 64. For this purpose, addition of isopropenyllithium and isopropyllithium to 64 was attempted. However, the ketone **64** was found to be unreactive, with a portion of it getting convened to either the alcohol 65 or 109 under the reaction conditions and the major portion remaining intact, despite long reaction times. The separation of the alcohols 65 and 109, which were themselves mixtures of diastereomers from the precursor ketone 64 was found to be a tedius exercise and alternative methods to avert this situation were sought.

Scheme 30



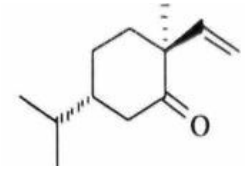
109 **64** **65**

Reagents, Conditions and Yields: (a) Isopropenyllithium, THF, R.T., sonication, 80% (b) Isopropyllithium THF, R.T., sonication, 80% (both yields based on recovery of starting material)

The sluggish reactivity of the ketone 64 was attributed to the steric hindrance by the isopropyl group and the quaternary carbon bearing the vinyl group on roth the faces of the carbonyl group. To circumvent this problem and to continue with our approach, it was decided to transform the ketone 64 into the enone 104, The carbonyl group of the enone 104 was expected to project outward with the introduction of the unsaturation in the ring system and thus partially relieve the steric hindrance caused by the neighbouring isopropyl substituent.

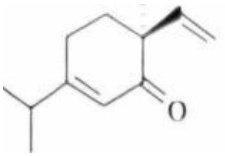
After considerable trial and error, it was found that, dehydrogenation of the α-vinyl ketone 64 with selenium dioxide in ten.-butanol delivered the required enone **104** in 45% **yield** (based on the recovery of the starting material) Scheme 31, The formation of the enone 104 was fully consonant

Scheme 31



64

a



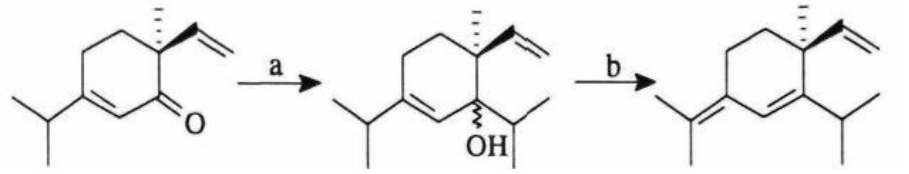
104

Reagents, conditions and yields; (a) SeO_2, Bu^tOH, Δ. 45%

with its UV, IR, ^1H and ^{13}C NMR spectral data. The IR spectrum showed the presence of the enone carbonyl moiety at 1670cm-^{1} and the ^1H NMR spectrum (fig 13) exhibited the presence of the α-proton of the enone and characteristic vinylic protons at δ 5.85 (s, 1H), 5.84 (dd, 1H) and 5.20-4,90 (m, 2H), respectively. In particular, the ^{13}C NMR spectrum (fig 14) had signals at δ 202.1, 170.0, 140.9, 122,7, 114.0 corresponding to the carbonyl and four olefinic carbons.

Having acquired the enone 104, our next objective was to implement a 1,2-nuleophilic addition on the carbonyl group of the enone 104, with suitable alkyl lithium reagent. Thus, treatment of the enone **104** with isopropyl lithium in THF, under ultrasound irradiation, furnished a diastereomeric mixture of the carbinols 103.

Scheme 32



104 **103** **97**

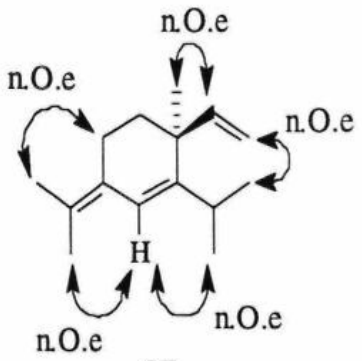
Reagents, conditions and yields; (a) 2-propyllithium, THF, ultrasound (b) p-TsCl, $CHC1_3$, R.T., 42% from 104.

In 103, with all its carbon atoms placed in requisite positions, functional group fine-tuning was sought to accomplish the total synthesis of (+)-α-elemene 97. A dehydration reaction was, therefore, executed on the alcohol mixture 103 and was found to be very facile. Indeed, traces of dehydration product were noticed even in the ^{1}H NMR sample prepared in chloroform-d. However, exposure of the carbinol mixture 103, to p-toluenesulphonyl chloride in chloroform and filtration through a column delivered (+)-α-elemene 97, in 42% yield, Scheme 32.[32] The spectral data UV. IR, ^{1}H & ^{13}C NMR of 97 were found to be in full agreement with its formulation. The ^{1}H NMR spectrum (Fig. 15) clearly exhibited the presence of the α-proton of the diene moiety at δ 6,37 (s, 1H) and the typical vinylic proton resonances at δ 5.78 (dd, 1H) 5.10-4,90 (m, 2H). A 15 line ^{13}C NMR spectrum(fig 16) with the carbon resonances at δ 149.7, 146.3, 128.1, 124.5,

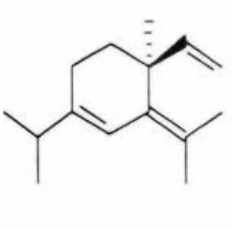
119.7 and 112.4 due In there olefinic moieties, established the structural identity of the natural product.[#]

The specific rotation of the synthetic sample trained by us ($[\alpha]_D$ = + 112.5) matches with that of the natural product ($|\alpha|_D$ = + 116) supports the

While elucidating the structure of a- elemene 97, Paknikar *et. al.*[27] found it difficult to differentiate between the two possible isomeric structures 97 & 110 for this hydrocarbon. Their degradative studies leading to structure 97 for α-elemene, though correct, was not based on unambiguous deductions. Our NOESY spectrum (Fig, 17) settles the structure of 97 unambiguously.



97

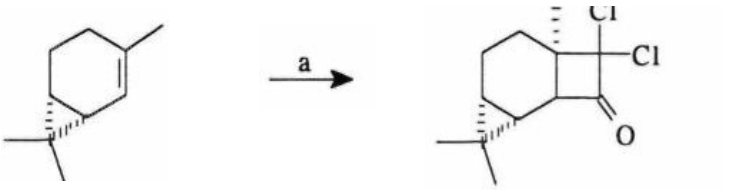


110

absolute configuration assigned earlier to (+)-α-elemene **97.** Thus, the first enantioselective synthesis of (+)-α- eIemene 97 was accomplished.

Although the synthesis of (+)-97 was achieved from R-(+)- limonene, the unsatisfactory yield and the difficult chromatographic separation impeded easy access of the enone 104. To circumvent this problem, it was considered appropriate to use an alkene equivalent that can directly furnish the enone 104, during the cyclopropyl ring opening process. In this context, we realised the importance of (+)-2-carene[33] as the chiral synthon for our projected synthesis of (+}-α-elemene 97.

Scheme 33



111 **112**

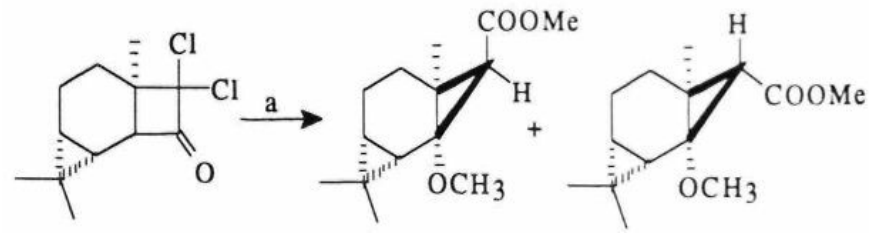
Reagents, conditions and yields: (a) CC13 COC1, Zn, Et_2O, ultrasound, 95%.

The commercially available (+)-2-carene was subjected to the four-step transformation as described earlier for the generation of α-vinyl ketone

moiety. Treatment of (+)-2-carene 111 with α,α- dichloroketene under sonication conditions furnished the required ketene adduct (+)-112, stereoselectively in 95% yield. Scheme 33. and the IR spectrum of the product showed a strong absorption at 1803cm-[1] characteristic of α,α-dichlorocyclobutanone. The ^{1}H NMR spectrum, and in particular, the ^{13}C NMR spectrum resonance at 8 196,6 corresponding to the carbonyl carbon atom established the identity of the ketene adduct 112.

Encouraged by the high yield in the dichloroketene adduct formation we turned our attention towards the ring contraction- rearrangement protocol.

Scheme 34



112 113a **113b**

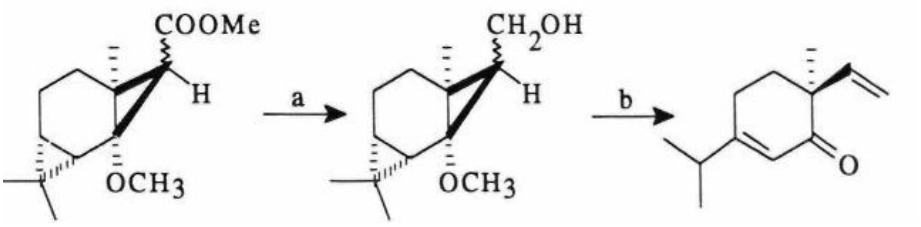
Reagents, conditions and yields; (a) NaOMe-MeOH, heat, 63%.

Treatment of the ketene adduct (+)-112, with sodium methoxide in methanol under reflux, gave a diastereomeric mixture of cyclopropyl esters 113a,b in 63% yield. Scheme 34, The IR spectrum showing strong carbonyl absorption

at 1730 cm-^{1} and the sharp singlets in the ^{1}H NMR spectrum at δ 3.65 due to **c**arbomethoxy group confirmed the formulation of 113a,b. For the sake of characterization, 113a and 113b were separated and the spectral data is gathered in the experimental section. However, separation of the mixture, was not required at this stage and it was carried over to the next step.

Reduction of the ester moiety in 113a,b with LAH in ether furnished the corresponding diastereomeric mixture of alcohol 114, in 92% yield. A strong infrared absorption at 3372 cm-^{1} confirmed the formation of the

Scheme 35



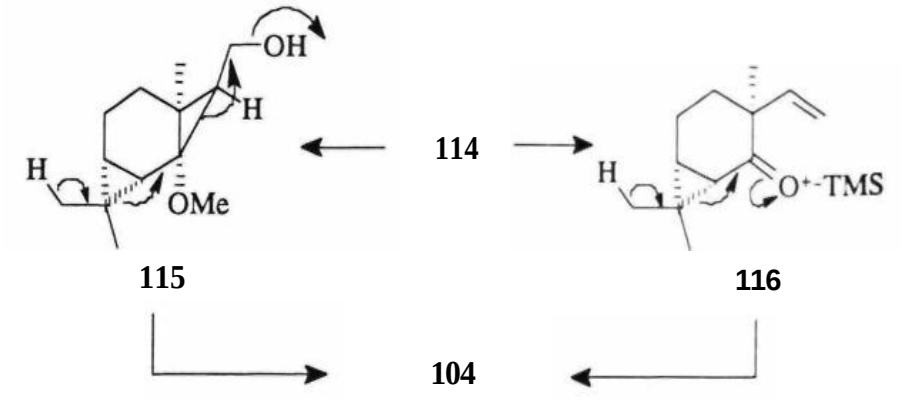
113a,b **114** **104**

Reagents, conditions and yields; (a) LAH, Et_2O, R.T., 92% (b) TMSI, MeCN,R.T., 85%.

cyclopropyl carbinol moiety. Brief exposure of the crude alcohol mixture **114** to **TMSI,** resulted in a facile fragmentation ***via*** cyclopropylcarbinyl-

homoallylic rearrangement to deliver the enone (-)-104 in 85% yield, as a single stereoisomer, Scheme 35. Formation of 104 from 114 is quite interesting as two cyclopropane rings arc cleaved regioselectively in a single pot reaction. Whether this cleavage lakes place in a concerted manner 115 (higher order fragmentation?) or in a step-wise manner 116 is not clear at this point, Scheme 36.[34]

Scheme 36

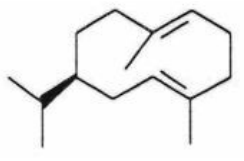


As this enone was identical with the enone 104 obtained from R-(+)-limonene, on the basis of both spectral and optical rotation data, it should be possible to transform this into (+)-α-elemene 97.

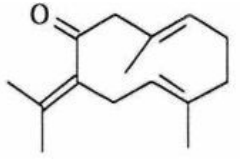
Germacrenes

As a logical continuation to our new protocol, we ventured to pursue the synthesis of medium ring carbocycles. Among the medium ring carbocycles, the germacrane group (Chan 3[35a-f]) comprising of a 10-membcrcd ring occupies a prominent position because of their wide

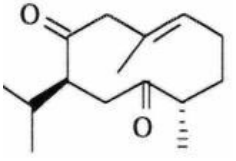
Chart3



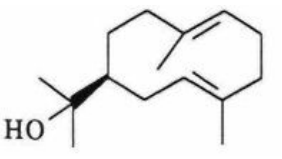
Germacrene A **117**[35a]



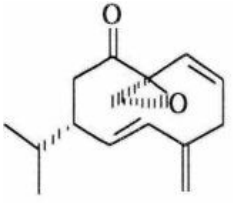
Germacrone **118**[35b]



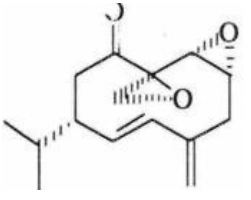
Curdione 119[35c]



Germacradiene-11-o1 **120**[35d]



Periplanone A 121[35e]



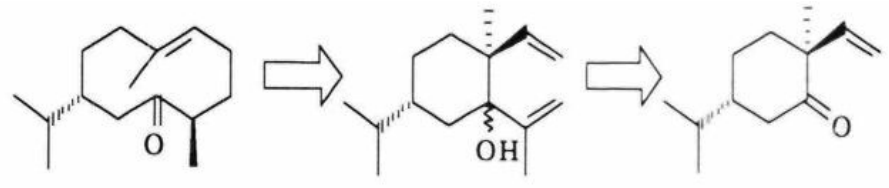
Periplanone B 12**2**[35f]

occurrence, biological activity of some of the compounds, e.g.. periplanone-A&B and their role as biogenetic precursors of many polycyclic sesquiterpenes, e.g., guaianes and eudesmanes. It is worth noting that germacranes are biogenetic precursors of many structural types that are

present among pheromones, antibiotics, cytotoxins and antitumor agents. Consequently, there has been a great deal of interest in the synthesis of germacrane-based sesquiterpene natural products and many new and ingenuous methodologies have been developed. [36]

The ready availability and the strategic disposition of both the isopropyl and methyl groups in the α-vinyl ketone 64. turned our attention towards the synthesis of deoxycurdione 66, a germacrane type sesquiterpenoid. Our approach towards the synthesis of germacrane ring system through an oxy-Cope pathway is delineated through the retrosynthetic route shown in Scheme 37.

Scheme 37

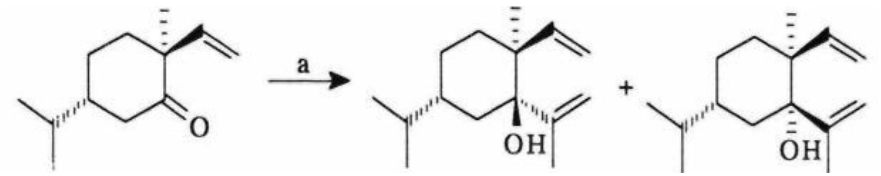


66 **65a,b** **64**

As per this protocol, nucleophilic addition of isopropenyl lithium to the ketone (+)-64, was expected to deliver the 1,2-divinylcyclohexanol 65a,b, An oxy-Cope rearrangement was expected to lead the germacrane skeleton.

The synthetic plan was put into practice by the addition of isopropenyllithium to the α-vinyl ketone (+)-64, under sonication conditions to give a diastereomeric mixture of 1,2-divinylcyclohexanols 65a,b in 80% yield (based on the recovery of the starting material), Scheme 38. The IR

Scheme 38



64 **65a** **65b**

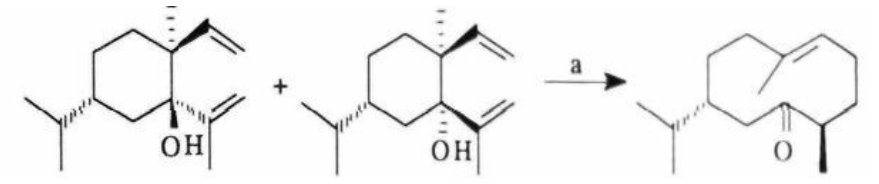
Reagents, Conditions and Yields; (a) isopropenyl lithium, THF, R.T., sonication, 80%.

spectrum of the mixture of alcohols 65a,b showed a strong absorption at 3475 cm^{-1} corresponding to the alcohol moiety. At this stage, separation of the alcohol mixture 65a,b was not attempted and the same was carried over to the next step.

The mixture of alcohols 65a,b, thus obtained, was first subjected to a thermal oxy-Cope rearrangement- However, thermal activation up to ~250°C only led to mixtures of dehydration products and no characterizable material could be isolated. Recourse was, therefore, taken to the anionic version of the

oxy-Cope rearrangement. Treatment of the mixture of alcohols 65a,b with KHMDS in the presence of 18-crown-6, furnished the desired ring expanded product 66 $[\alpha]_D$ -34,6 (lit.[37] $[al]_D$ -50.28) In 60% yield. Scheme 39. The spectral data of the ketone 66 was fully consonant with its formulation, with

Scheme 39



65a 65b 66

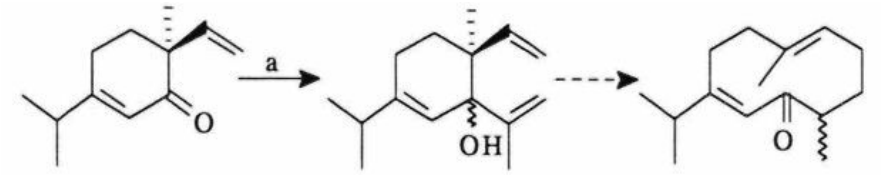
Reagents, Conditions and Yields: (a) KHMDS, 18-crown-6, THF. Δ, 60%

the ^{1}H NMR spectrum (Fig, 18) showing an olefinic proton at 6 4,80-5,00 (m, 1H) and the ^{13}C NMR spectrum (Fig. 19) exhibiting the presence of carbonyl resonance at δ 215.9, establishing the formation of deoxycurdione (-)-66. The spectral data for (-)-66 were found to be identical with that reported for this compound in the literature.[37] The oxy-Cope process was highly diastereoselective, in the sense that only one diastereomer was produced.

The possibility of constructing a germacrane derivative with additional functionality in the 10-membered ring was also been attempted following a similar synthetic plan, starting from the chiral C_{12}-enone (-)-104

and involving oxy-Cope process as the pivotal step, Scheme 40. Addition of isopropenyllithium to the enone (-)-104, under sonication conditions smoothly

Scheme 40



104 123 124

Reagents, Conditions and Yields: (a) isopropenyllithium, THF, ultrasound, R.T., 61%.

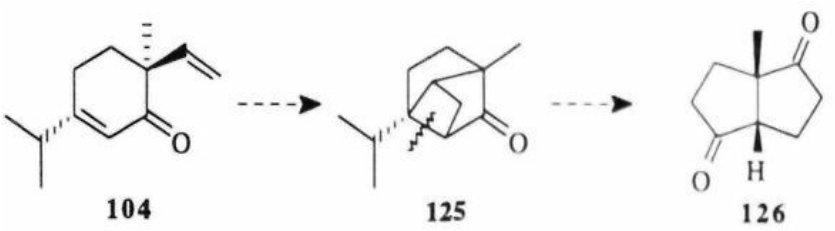
furnished a diastereomeric mixture of allylic alcohols 123, The IR spectrum of the- mixture 123 showed a strong alcohol absorption at 3428 cm^{-1}, along with other relevant features. However, efforts to transform the alcohol mixture 123 into the desired 10-membered ring compound 124 under a variety of anionic and thermal reaction conditions were unsuccessful.

Synthesis of a *cis*-Diquinane Synthon

As a part of our ongoing project on the synthetic applications of the alkene to α-vinyl ketone transformation protocol, a new approach for the synthesis of *cis*-diquinane 126 was considered. The ready availability of the enone 104, both from R-(+)-limonene 106 and (+)-2-carene 111, prompted us

to convert it to a diquinane derivative like **126** through an intramolecular [2+2]-photocycloaddition-fragmented on strategy. **Scheme 41**

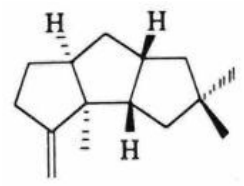
Scheme 41



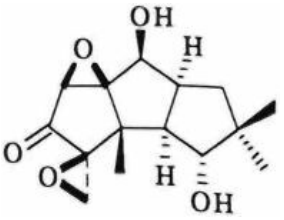
The *cis*-diquinane frame-work, with a quaternary carbon centre, is an important structural moiety present in a variety of polyquinane based natural product skeleta. Some representative examples of the natural products containing this structural moiety are delineated in Chan 4.[38a-h] These molecules constitute challenging targets for the synthesis because of the dense functionalisation and unusual carbocyclic frame-work.

Synthetic strategies towards these molecules require a simple and rapid assembly of the *cis*-diquinane moiety endowed with a quaternary carbon centre. Although several strategies for the construction of these moieties were reported in the literature, the enantioselective approaches are limited. The following is an account of a novel enantioselective approach for the easy and rapid access of the *cis*-diquinane moiety from readily available chirors R-(-+-)-limonene **106** and (+)-2-carene **111.**

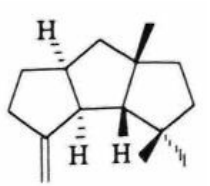
Chart 4



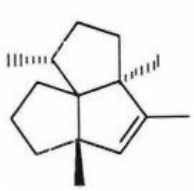
Hirsutene **127**[38a]



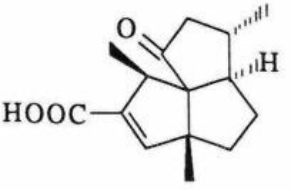
Coriolin128[38b]



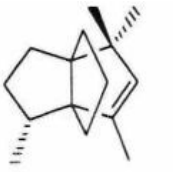
Capnellene **129**[38c]



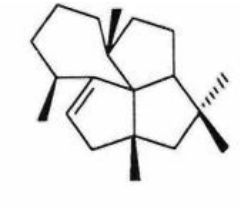
Isocomene130[38d]



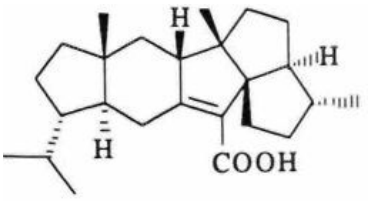
Subergoric acid 131[38e]



Modhephene 132[38f]



Laurcnene 133[38g]

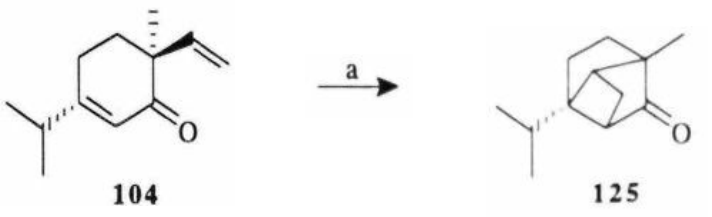


Retigeranic acid 134[38h]

intramolecular [2+2]-Photocycloaddition in the enone 154, effected through irradiation from a 450W Hanovia medium pressure lamp through a pyrex filter, afforded the tricyclic ketone **125** in 87% **yield,** Scheme 42. The IR spectrum of the product **125** exhibited a strong absorption at 1759 cm^{-1}

due to a cyclopentanone moiety. The ^{1}H NMR spectrum (Fig. 20) signals for the quaternary methyl and isopropyl groups at δ 1.20 (s 3H), 0.95 (d, 3H) and 0.88 (d,3H) respectively, confirmed the formation of the cycloaddition product. In particular, a 12 line ^{13}C NMR spectrum (Fig. 21) with diagnostic

Scheme 42



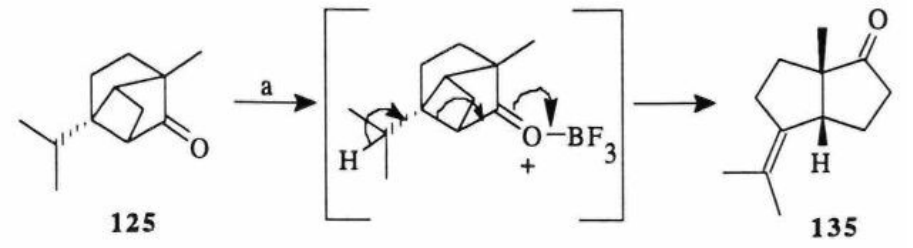
104 125

Reagents, Conditions and Yields: (a) *hv* (450 W Hg lamp), pyrex, EtOAc, 15min.,87%,

carbon resonance at δ218.4 due to carbonyl carbon established the formulation of the ketone 125. Expectedly, both the ^{1}H & ^{13}C NMR spectra were transparent in the olefinic proton and sp^2-carbon regions.

The formation of the tricyclic photoproduct 125. in high yield, encouraged us to administer a regiospecific fragmentation reaction. Exposure of the photoadduct 125 to BF_3-etherate resulted in a facile fragmentation to give the desired *cis*-diquinane 135 in 50% yield, Scheme 43, with the spectral data of the product 135 in full agreement with its formulation. The ^{1}H NMR

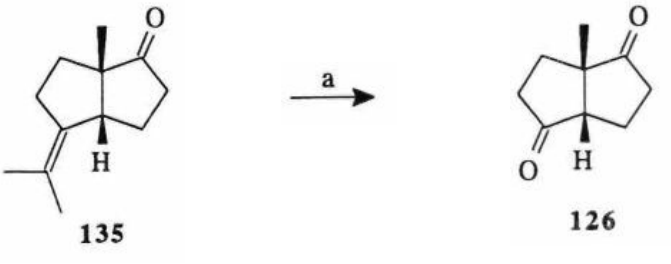
Scheme 43



Reagents, Conditions and Yields: (a) BF_3-Et_2O, DCM, R.T., 50%.

(Fig. 22) signals at δ 1,70 (s,3H), L63 (s,3H) and 1.08 (s, 3H) due to the isopropylidene and quaternary methyl groups and a 12 line ^{13}C NMR spectrum (Fig. 23) with characteristic signals at 6 223.5, 138.6 and 123.7 due to carbonyl and olefinic carbons, established the identity of the compound **135,**

Scheme 44



Reagents, Conditions and Yields: (a) O_3. DCM, -78°C. 87% or $RuCl_3$, MeCN-CCl4-H_2O, $NaIO_4$. 76%

Having obtained the required *cis*-diquinane 135 moiety, it was considered necessary to oxidatively cleave the isopropylidene group by either cat.ruthenium oxidation or ozonolysis, to give the bifunctional cis-diquinane dione 126, Ozonolysis of the *cis*-diquinane 135 proceeded smoothly to give the bifunctional (+)-*cis*-diquinane dione 126, $[\alpha]_D$ +289.45, wilh an angular methyl group, in 87% yield Scheme 44. Catalytic ruthenium oxidation of the *cis*-diquinane 135 also afforded the *cis*-diquinane dione in 76% yield. The spectral (Fig. 24 & 25) and analytical data of the dione 126 were in agreement with its formulation. The 9 line ^{13}C NMR spectrum with two carbonyl signals at δ 221.4 and 220.0 established the presence of two cyclopentanone rings. The chiral dione 126 with its secured stereochemistry and strategic placement of the functionality in the two rings is a promising starting point for further polyquinane synthesis.

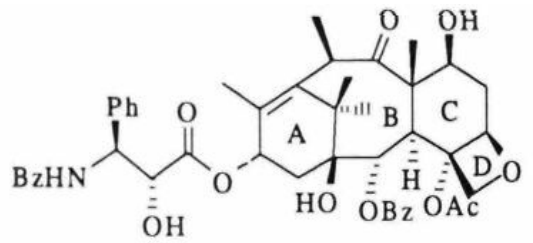
Towards the Synthesis of AB Rings of Taxol 136 (Paclitaxel®)

Having successfully applied the olefin 58 -> α-vinylketone 62 methodology to the enantioselective synthesis of (+)-α–elemene, germacrane and diquinane skeleta, we considered further opportunities in the synthesis of more complex molecules tike taxol 136.

Taxol 136 is a densely functionalized, tetracyclic diterpenoid isolated from the Western Yew *(Taxus brevifolia)* by Wall, Wane and co-workers in 1971.[39] Its proven efficacy as an anti-cancer drug, has elicited a great deal of biochemical attention from both clinical perspective and medicinal chemistry

point of view Despite its clinical activity against ovarian, breast and several other cancer cell lines, the sources of its supply remains limited,

Structure



136

The paucity of the material being a major impediment for its successful usage in clinical trials, the demand for its supply can only be achieved by a semi- or total synthesis.[40] So far, only three successful total syntheses of taxol have been reported in literature[1] as a result of massive efforts and their accomplishment is regarded as major milestone in contemporary organic synthesis. The semi-synthesis of taxol has been projected as an attractive alternative, as the lengthy total syntheses have received little interest from commercial considerations. Various research groups have since been engaged in the investigation of a pro-drug version of taxol for their successful application in clinical usage.[41] Presently, the focus of attention is directed towards the development of improved analogue of the drug.

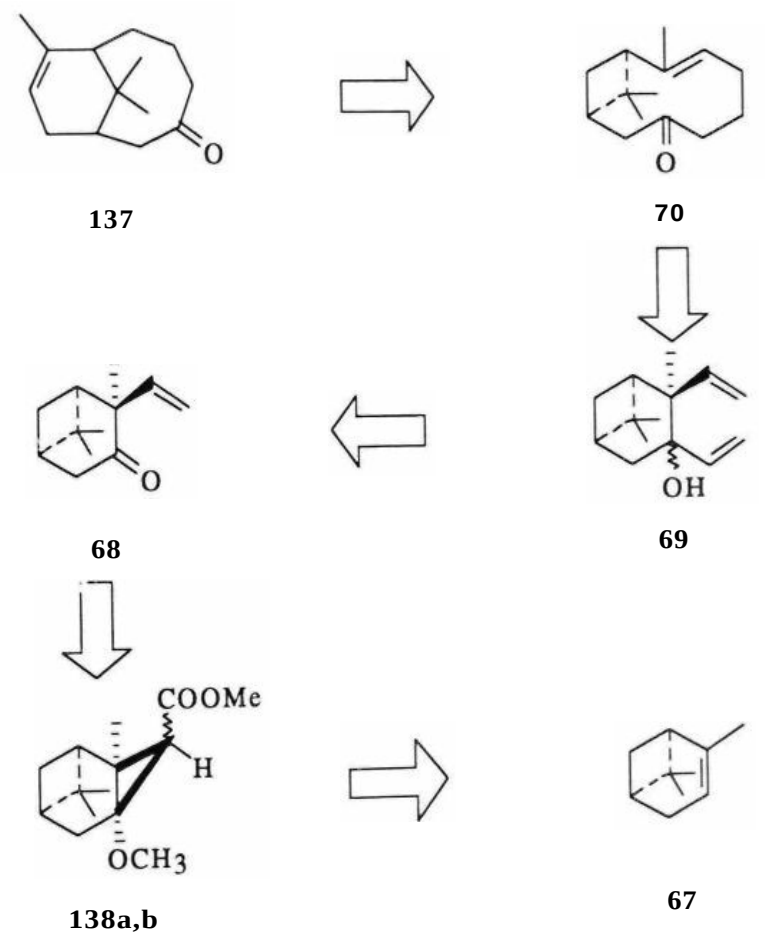
While the successful syntheses of taxol have been few, the number of methodologies and strategies evolved for the construction of various ring fragments and substitution patterns is very large and impressive and reflect the ongoing world-wide interest in this molecule.[40]

We recognised the importance of our newly developed protocol in the context of taxol, and began a model study on the construction of AB ring portion 137 of its tetracyclic framework- A retrosynthetic approach invoking the aforementioned methodology is represented in the Scheme 45.

As indicated in the retrosynthetic analysis, the α-vinyl ketone 68, was identified as an advanced precursor in the construction of AB rings of taxol The α-vinyl ketone 68 can be readily accessed from (-)-pinene 67 *via* the protocol evolved during the present study through the formation of the "push-pull" bicyclic β-methoxy cyclopropylester 138a,b. When treated with a suitable nucleophile the ketone 68, with a strategically positioned olefin, can be used to generate an oxy-Cope system 69. The oxy-Cope transformation on the alcohol 69 can be expected to lead to the formation of the ketone 70 which can be further transformed into the AB rings of taxol 137 through a light irradiated [1.3] sigmatropic alkyl shift.

As a first step towards the synthesis of the frame-work 137, the synthesis of the α-vinyl ketone 68 was attempted. For this purpose, the cheap

Scheme 45

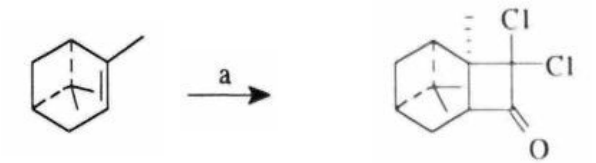


137 **70** **68** **69** **138a,b** **67**

and commercially available monoterpene (-)-α-pinene was chosen as the starting material to prepare optically active α-vinyl ketone 68,

Addition of α,α–dichloroketene, generated *in situ* from trichloroacetyl chloride and zinc, to (-)-α-pinene, under ultrasound initiation, preceded in

Scheme 46



67 **139**

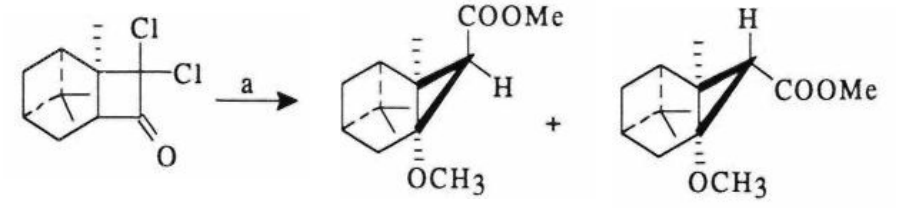
Reagents, Conditions and Yields; (a) CCI_3COCl, Zn, Ether. ultrasound, 30 **min.,** 40%.

modest yield to give the ketene [2+2]-adduct (+)-139 in 40% yield. Scheme 46. The spectral data of the ketene adduct was in full agreement with the reported values. The steric hindrance of the olefin in the rigid tricyclic system was found to be the main reason for the low yield in the kstene addition reaction. However, the ready availability of the (-)-α-pinene allowed us to prepare ketene adduct (+)-139 on multigram scale. The stereochemistry of the ketene addition follows from the expected addition from the *endo-face* opposite to the *gem*-dimethyl bearing methano-bridge.

Having accessed the ketene adduct (+)-139 in good quantities, our next objective was to effect the ring contraction-rearrangement step. The

ketene adduct (+)-139 was subjected to sodium methoxide mediated rearrangement in methanol to deliver a diastereomeric mixture of cyclopropyl esters 138a,b in 73% yield, Scheme 47. The IR spectrum of the mixture of isomers exhibited a strong carbonyl absorption at 1750 cm^{-1}. The sharp resonances at δ 3.67 and 3,66 in the ^1H NMR spectrum due to carbomethoxy functionality in 138a,b confirmed their formulation.

Scheme 47

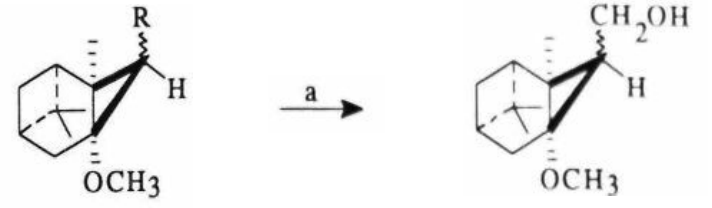


139 **138a** **I38b**

Reagents, conditions and yield: (a) NaOMe (5 eq.), MeOH, Δ, 30 min., 73%.

However, separation of the diastereomer mixture was not required and the same was carried over to the reduction step. Reduction of the ester moiety present in 138a,b, with DIBAL-H, furnished the required cyclopropyl carbinol 140, again as a mixture of diastereomers, Scheme 48. A strong absorption at 3376 cm^{-1} in the IR spectrum due to the presence of hydroxy group established the identity of the carbinol 140.

Scheme 48



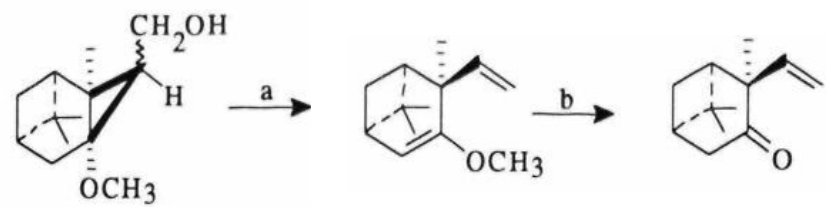
138a,b R=COOMe 140

Reagents, conditions and yields: (a) DIBAL-H, DCM. -78°C 30 min., 72%.

Satisfied by the high yields in the ring contraction-rearrangement and the subsequent reduction steps, the cyclopropylcarbinyl-homoallylic rearrangement was now attempted. The crude carbinol mixture 140 on treatment with methanesulphonylchloride in pyridine, yielded the enol ether 141, Scheme 49, The spectra IR, ^{1}H & ^{13}C NMR of the enol ether were in agreement with its formulation. The resonances at δ 5.77(dd, 1H), 5.04(d, 1H), 4.99 (d, 1H) and 4.86(d, 1H) in the ^{1}H NMR spectrum established the presence of the vinyl protons and the proton on The enol ether functionality.

The enol ether 141 was hydrolysed with aq. 35% perchloric acid at $0^{o}C$ to furnish the desired (-)-α-vinyl ketone 68 in 65% yield as a single stereoisomer. The IR spectrum showed the presence of the carbonyl moiety at 1720 cm^{-1} and the characteristic vinylic proton pattern was observed in the

Scheme 49



140 14! 68

Reagents, conditions and yields: (a) Py, MsCl, 0°C, 30 min. 89% (b) 35% $HC10_4$(aq.), Ether, 0°C, 65%.

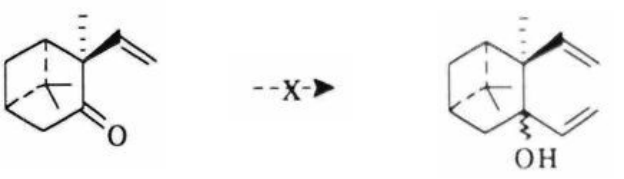
^{1}H NMR spectrum (Fig. 26) at δ 5.63 (dd, 1H), 5.03(d, 1H) and 4.84(d, 1H) confirming the formation of the (-)-α-vinyl ketone 68. A 12 line ^{13}C NMR spectrum (Fig, 27) with carbonyl and olefinic carbon resorances at d 214.8, 143,3 and 113.4 further supported the formulation of (-)-68,

Our next goal was to convert the a-vinyl ketone (-)-68 into a 1,2-divinyl carbinol 69 to carry out the oxy-Cope rearrangement as outlined in the retrosynthetic analysis, Scheme 45. To transform the (-)-α-vinyl ketone 68 to the 1,2-divinyl carbinol 69, a simple vinyl Grignard/alkyl lithium reagent addition to (-)-68 was sought.

Addition of vinyl lithium or vinyl magnesium bromide to the ketone (-)-68 did not give the required 1,2-addition product 69 but resulted either in

the recovery of starting material or some complex and uncharacteristic reaction mixture. Scheme 50.

Scheme 50



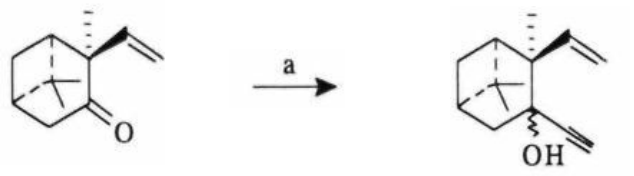
68 69

Attempts to carry out the nucleophilic addition to the ketone (-)-68, under different reaction conditions and with varied reagents, proved to be unsuccessful. Efforts to activate the carbonyl functionality in (-)-68 with reagents like cerium chloride[42] and lithiumperchlorate[43] were also unsuccessful. The reason for this was attributed to the steric hindrance experienced by the carbonyl group due to the presence of *gem*-dimethyl bearing methano-bridge and the flanking quaternary centre with a methyl and vinyl groups.

Alternate methods to overcome this problem were therefore sought to prepare the 1,2-divinyl carbinol 69. At this stage the use of a sterically less demanding nucleophile, like lithium acetylide, which can probably approach the hindered carbonyl group easily to effect the required nucleophilic addition was considered. This possibility was put into practice and the lithium

acetylide-elhylenediaminc complex was allowed to react with the (-)-α-vinyl ketone 68, Scheme 51. Reaction of lithium acetylide ethylenediamine complex

Scheme51



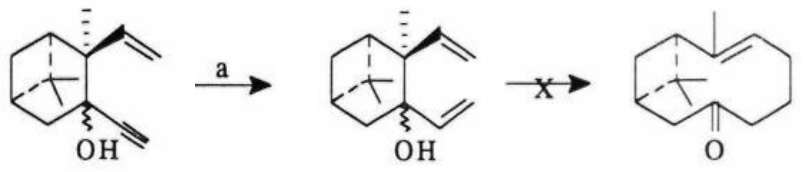
68 **142**

Reagents, conditions and yields: (a) Lithium acetylide-EDA, THF Acetylene, 3-4 h, 27%.

with the ketone (-)-68 resulted in the formation of a diastereomeric mixture of ethynyl vinyl carbinol 142 in 27% yield, A strong absorption at 3400 and 3306 cm^{-1} in the IR spectrum revealed the presence of the hydroxy and alkyne functionality, respectively. The ^{1}H NMR spectrum with characteristic vinylic proton pattern at d 6.30-4.80 (m, 3H) and the alkyne proton at δ 2.59 (s, 1H) established the identity of the product 142. The low yield obtained during the lithium acetylide addition further substantiates our earlier finding that the high steric hindrance at the carbonyl site makes the approach of the nucleophile difficult.

The success in getting the ethynyl vinyl carbinol 142, although in poor yields, allowed us to reduce it into the required 1,2-divinly carbinol 69, through partial hydrogenation of the alkyne functionality, Scheme 52. The carbinol mixture **142,** was subjected to semi hydrogenation in the presence of Lindlar catalyst at atmospheric pressure to give the 1,2-divinyl carhinol in 85% yield, again as a diastereomeric mixture. The IR and ^{1}H NMR spectra of 69 were in full agreement with its formulation. A strong absorption at 3383 cm-^{1} in the IR spectrum and the resonances at δ 6.20-4,70 (m, 6H) in ^{1}H NMR spectra clearly established the formation of 69.

Scheme 52



142 69 70

Reagents, conditions and yields: (a) Lindlar cat., EtOAc, 1 h, 85%.

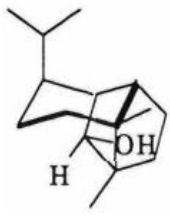
However, conversion of the carbinol mixture 69 to the corresponding oxy-Cope rearrangement product 70 under a variety of thermal as well as anionic conditions were unsuccessful. Exposure of the 69 to a variety of reagents resulted either in the recovery of the starting material or formation of complex reaction mixture. Efforts to overcome this obstacle and carryout

the rearrangement, using new reagents and micro-wave reaction conditions were also of no avail. It is quite likely that due to the rigidity inherent in the bicyclo[3.l.1]heptane system and the steric congestion present, the required cope transition state (chair or boat) for a [3.3]-sigmatropic rearrangement is difficult to attain. This is probably the reason for our inability to effect the key oxy-Copc rearrangement in **69.**

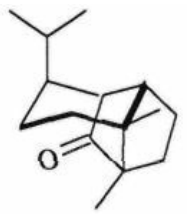
Formal synthesis of "Copa" Sesquiterpenes

The ready access to 108a,b *via* the ring contraction-rearrangement of [2+2]-ketene adduct 107, in good quantities, encouraged us to consider further restructuring it into a 1,4-dicarbonyl functionality through a ring opening approach. It was realised that 108a,b is a "push-pull" cyclopropane derivative[44] in which the cleavage of the cyclopropane bond should genera a

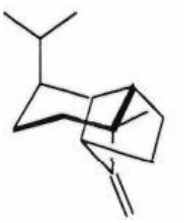
Chart 5



copaborneol 143[45a]



copacamphor 144[45b]

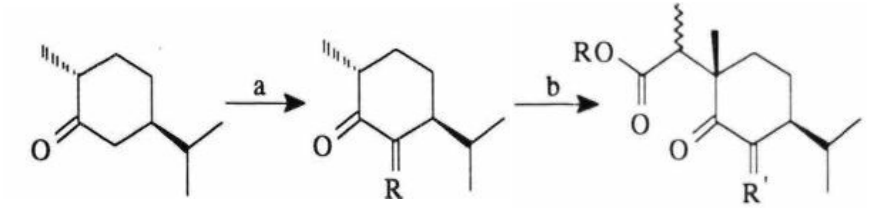


copacamphene 145[45c]

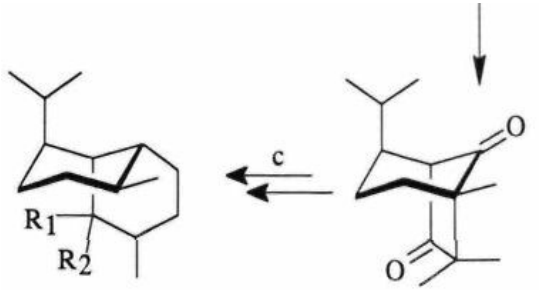
1,4-dicarbonyl derivative. Such 1,4-dicarbonyl derivatives emanating from 108a,b appeared to be useful for the synthesis of tricyclic "copa"

sesquiterpenoid frameworks. Some member of this family of natural products are shown in Chan 5[45a-c], Among them (+)-copaborneol **143** and copacamphor 144 have been isolated from the wood of *Pinus Silvestris* and *Espeletiopsis guacharaca,* respectively. The hydrocarbon copacamphene **145** has been made by chemical transformation from (+)-copaborneol 143, Several synthesis of "copa" sesquiterpenes have been reported in the literature.[46]

Scheme 53



146



R_1 =H, R_2=OH
R_1-R_2=O
R_1=OH, R_2=H

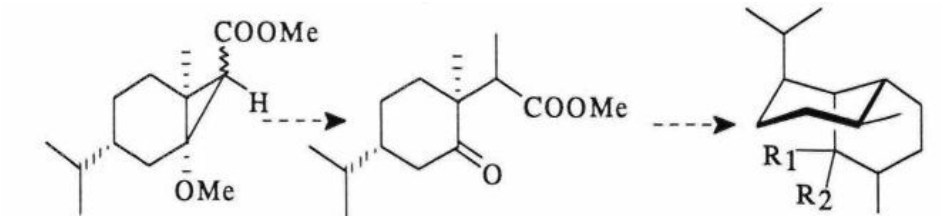
147

Reagents, conditions and yields: (a) ref. 46a (b) 2-iodopropionate, Pu^{t}OK, BuOH, 73%; KOH, aq. diethylene glycol; CH_2N_2-Et_2O, 85%

However, the synthesis of these sesquiterpenes by Piers and coworkers.[46a] Scheme 53, caught our attention as we saw the opportunity to prepare the advanced intermediate employed by them in a short, efficient sequence from readily available chirons. In our scheme of things, the α-mcihyl γ–oxo ester 148 could he prepared from the cyclopropane ester as shown in Scheme 54. Further base catalysed cyclisation in 148 was expected to deliver the tricyclic intermediate, Scheme 54.

Our strategy for the construction of "copa" sesquiterpenoid intermediate 148 involved a ring opening in the substituted donor-acceptor cyclopropyl ester 108a,b as delineated in Scheme 54.

Scheme 54



108a,b **148** **R_1=H, R_2=OH**

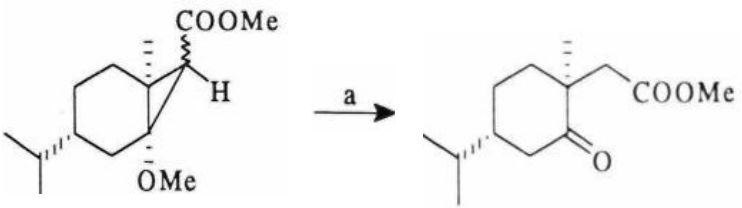
R_1, R_2=O

R_1=OH, R_2=H

To demonstrate the above sequence, the ring opening reaction was attempted on the cyclopropyl ester 108a,b. Thus, treatment of the ester

108a,b with trimethylsilyl iodide at ice temperature readily furnished the γ-oxo ester 149 in 64% yield. Scheme 55, The IR. ^{1}H and ^{13}C NMR spectral data were in harmony with its formulation. The proton resonances at δ 3.66 (s,3H), 1.23 (s,3H) and 0.91 (d, 3H) due to the carbomethoxy, quaternary methyl and the isopropyl groups, in the ^{1}H NMR spectrum (Fig. 28) clearly

Scheme 55



108a,b 149

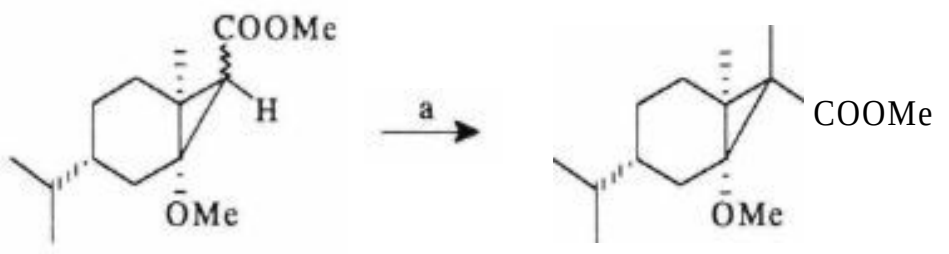
Reagents, conditions and yields;(a) Me_3SiI, CH_3CN, 0°C, 30min., 64%.

established its identity. A 13 line ^{13}C NMR spectrum (Fig. 29) with characteristic carbon resonances at δ 214.0 and 172.3 due 10 the ester and ketone carbonyl moieties further confirmed the formation of 149.

Spurred on by the success in the above transformation, a recourse was taken to study the ring opening in the α-substituted cyclopropyl esters, Deprotonation of the ester 108a,b with LDA at low temperature and quenching the anion with methyl iodide furnished the required α-methyl-β-

methoxy cyclopropyl ester 150 in 70% yield, Scheme 56. The IR and ^1H NMR spectra were in agreement with its formulation. It is interesting to note that only one diastereomer is formed in >90% yield.

Scheme 56

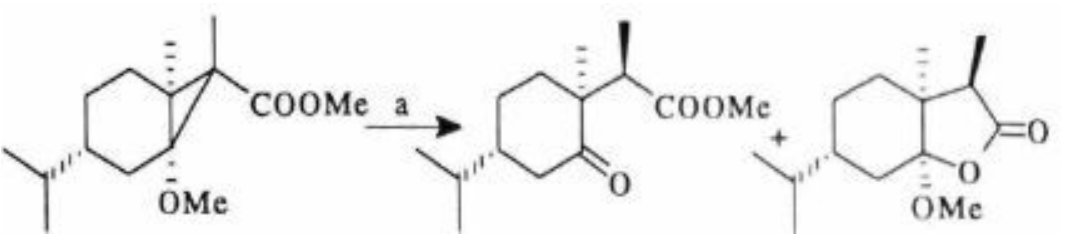


108a,b 150

Reagents, conditions and yields: (a) LDA, THF, -78°C, MeI, 30 min., 70%.

Having obtained the required α-methyl-β-methoxy cyclopropyl ester 150, the stage was now set for the ring opening strategy to deliver the required α-methyl γ-oxo ester. Trimethylsilyl iodide mediated ring opening of the α-methyl cyclopropyl ester 150 in acetonitrile, smoothly furnished the required α-methyl γ-oxo ester 148 (60%) along with the side product, methoxy lactone 151 (20%), Scheme 57. The spectral data of these compounds are in full agreement with their formulations. Strong absorptions at 1740 and 1707 cm^{-1} due to the ketone and the ester moieties in IR spectrum and the proton resonances at δ 3.65 (s, 3H) and 1,15 (d, 3H) corresponding to the carbomethoxy and the secondary methyl groups

Scheme 57



150 **148** **1S1**

Reagents, conditions and yields: (a) TMSI, R.T., MeCN, 0°C. 30min., 60%.

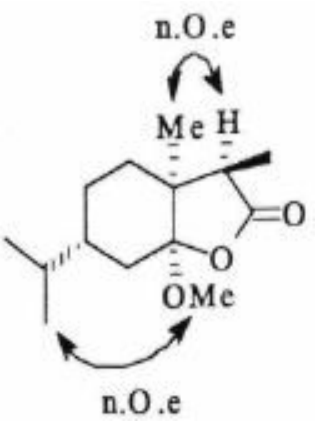
in the ^{1}H NMR spectrum (Fig. 30) support the identity of the γ-oxo ester 148, A 14 line ^{13}C NMR spectrum (Fig. 31) with peaks at 8 215.3 and 176.2 characteristic of the ketone and ester carbonyl carbons further confirm its formulation. The α-methyl γ-oxo ester 148 obtained in this sequence was predominantly a single diastereomer.

The formation of the methoxy lactone 151 in this sequence was evident from its spectral and analytical data. The IR, ^{1}H and ^{13}C NMR spectra of the metnoxy lactone **151** were consonant with its structure. The strong absorption at 1784 cm^{-1} in the IR spectrum showed the presence of a γ-lactone moiety. The proton resonances at δ 3.31 (s, 3H) and 1.02 (d, 3H) in the ^{1}H NMR spectrum (Fig. 32) exhibited the presence of a methoxy group and a secondary methyl group. The carbon resonances at δ 179.3 and 109.4

in the ^{13}C NMR spectrum (Fig 33) due to the lactone carbonyl and an acetal carbon further confirmed the structure of **151.**

The stereochemistry of the secondary methyl group with respect to the quaternary methyl and the methoxy group in 148 and 151 was deduced from the correlations in the 2-D NOESY experiment in 151 (fig. 34).#

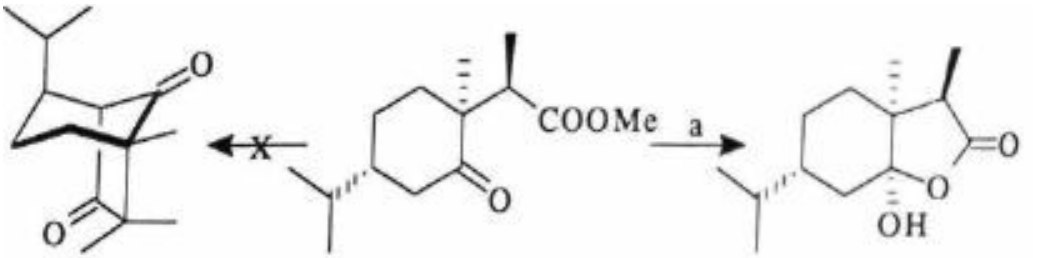
Treatment of the γ-oxo ester 148 with sodium hexamethyldisilazide (generated from sodamidc and hexamethyldisilazane) delivered the hydroxy lactone 152. The expected tricyclic product was not observed probably due to



151

the preferential hydrolysis of the ester over the condensation under the basic conditions, Scheme 58.

Scheme 58

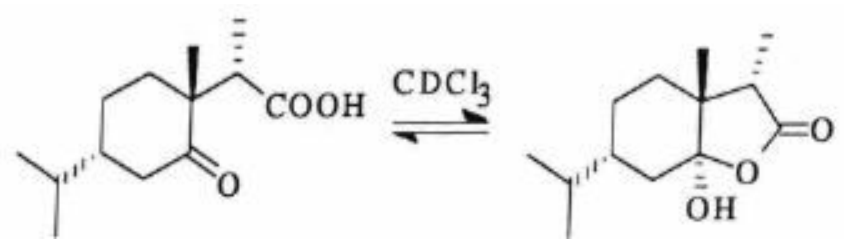


147 **148** **152**

Reagents, conditions and yields, (a) $NaNH_2$, HMDS, DME, D, 1h, 92%.

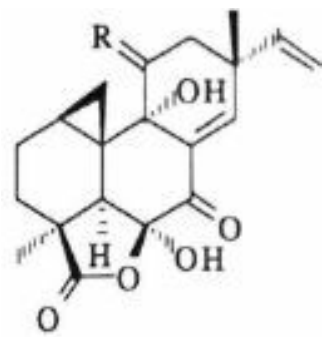
The formation of the hydroxy lactone in this type of transformation has a precedence in the literature and expected to be in equilibrium with the corresponding acid,[47] Scheme 59.

Scheme 59

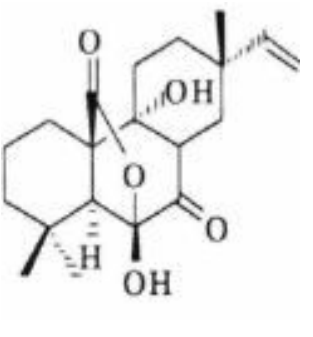


The hydroxy lactone fragment 152 is an important functional moiety present in a number of biologically active diterpenes e.g. myrocene C 153

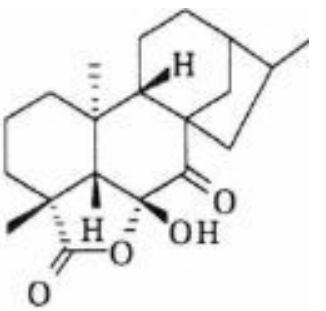
Chart 6



Myrocin C (R=H,H)153[48a]
Myrocin B (R=O)154



LL-S491 β 155[48b]



Gibberellin precursor 156

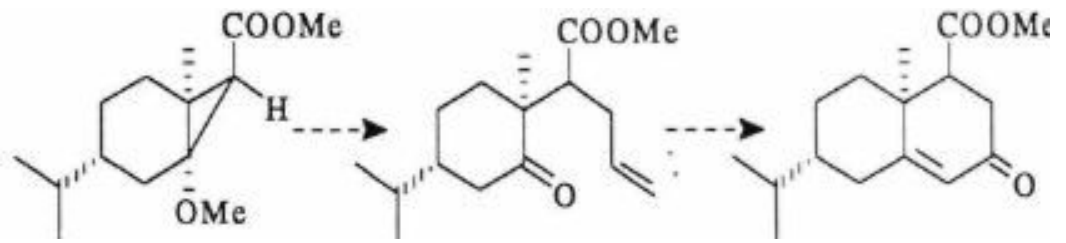
and its 11-oxo derivative **154.** These molecules have interesting biological activity against gram-positive bacteria and show *in vivo* inhibitory activity against Ehrlich ascites carcinoma. The same moiety is also present in gibberellin precursor 156. A structurally related form of myrocin, LL-S491β 155 which was obtained by fermentation of the fungus *Aspergillus chenalieri* also exhibits significant antibacterial activity, Chart 6.

The γ-oxo ester 148 was a single diastereomer, whereas the advanced intermediate in the Piers synthesis of "Copa" sesquiterpenes (Scheme 53) was a mixture of diastereomers. Our preparation of 148 in a sense constitutes a formal enantioselective synthesis of "Copa" sesquiterpenes.

Towards the synthesis of eudesmane sesquiterpenes

The methylation of β-methoxy cydopropyl ester **157** and its subsequent ring opening protocol resulting in the formation of γ-oxo-**a**-methyl ester, *en route* to the formal synthesis of "copa" sesquiterpenoids has been illustrated in the earlier section. A more general version of this sequence *i.e* allylation of the ester 108a,b. followed by ring opening and further fine tuning of the resulting α-allyl-γ-oxo-ester 157 can be exploited for the synthesis of fused bicyclic systems. In Scheme 60 is illustrated the possible realisation

Scheme 60



108a,b **157** **158**

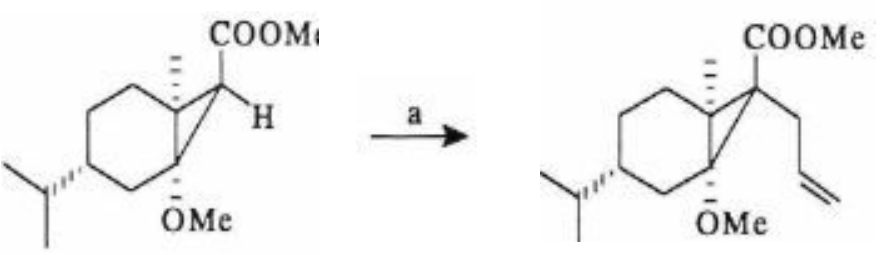
of this theme leading to the synthesis of eudesmane framework. Some of the sesquiterpenes belonging to the eudesmane-type are depicted in Chart 7.[49a-c] The formation of the α-allyl-γ–oxo-cyclopropylester 157 could easily be envisaged from the routine alkylation-ring opening sequence of the β-methoxy cyclopropyl ester 108a,b. Oxidation of the olefinic moiety in the ester 157, followed by aldol type cyclisation was expected to deliver the desired eudesmane frame-work. Scheme 60.

Chart 7

β-Selinene 159[49a] α-Eudesmol **160**[49b] α-Cyperone **161**[49c]

In practice, deprotonation of the β-methoxy cyclopropyl ester 108a,b with LHMDS and subsequent quenching of the anion with allyl bromide furnished the desired α-allyl-β-methoxy cyclopropyl ester 162 in 90% yield.

Scheme 61



10Sa,b **162**

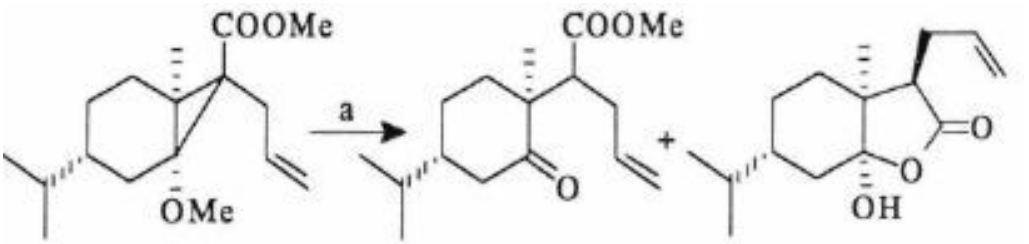
Reagents, Conditions and Yields: (a) LHMDS, THF, -78°C, allyl bromide, 1h, 90%.

The IR, ^{1}H & ^{13}C NMR spectra of the allylated product 162 were in agreement with its formulation with strong absorptions in the IR spectrum at

3076 and 1730 cm-^{1} exhibiting the presence of olefinic and carbonyl moieties and the proton resonances at δ 6.00-5.60 (m, 1H), 5.20-4.90 (m. 2H), 3.64 (s,3H) and 3.35 (s,3H) in the ^{1}H NMR spectrum (Fig. 35) indicated the presence of olefinic, carbomethoxy and methoxy group protons of the allyl ester 162. A 17 line ^{13}C NMR spectrum (Fig. 36) with characteristic carbon resonances at δ 171.6, 136.1 and 116.3 due to the ester carbonyl and olefinic carbons establish the identity of the allylated product 162. Once again during the conditions of kinetic alkylation, only one diastereomer was predominantly formed.

Having obtained the desired allylated ester 162, in good quantities, the next objective was to administer a cyclopropyl ring opening sequence.

Scheme 62

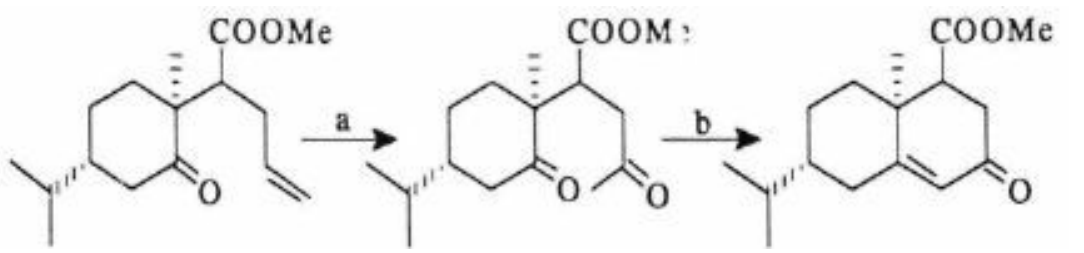


162 157 163

Reagents and conditions: (a) TMS1, MeCN, 0°C, 30 min.

Trimethylsilyl iodide mediated ring opening of the α-allyl-β-methoxy cyclopropyl ester **162** furnished the α-alkyl-γ-cyclopropylester **157** and the corresponding hydroxy lactone 163 in 63% and 22% yields respectively, Scheme 62. Both the products obtained were characterised analytically and spectroscopically and the data was found to be in good agreement with their formulations, While the ester 157 (Fig. 37 & 38) shows a 16 line ^{I3}C NMR spectrum with carbonyl carbon resonances at δ 214.9 and 175.4 corresponding to the ketone and ester groups, the hydroxy lactone 163 (Fig. 39 & 40) exhibited the lactone carbonyl and the acetal attached carbon at δ 178.5 and 107.1, respectively, confirming the assigned structure,

Scheme 63



157 164 158

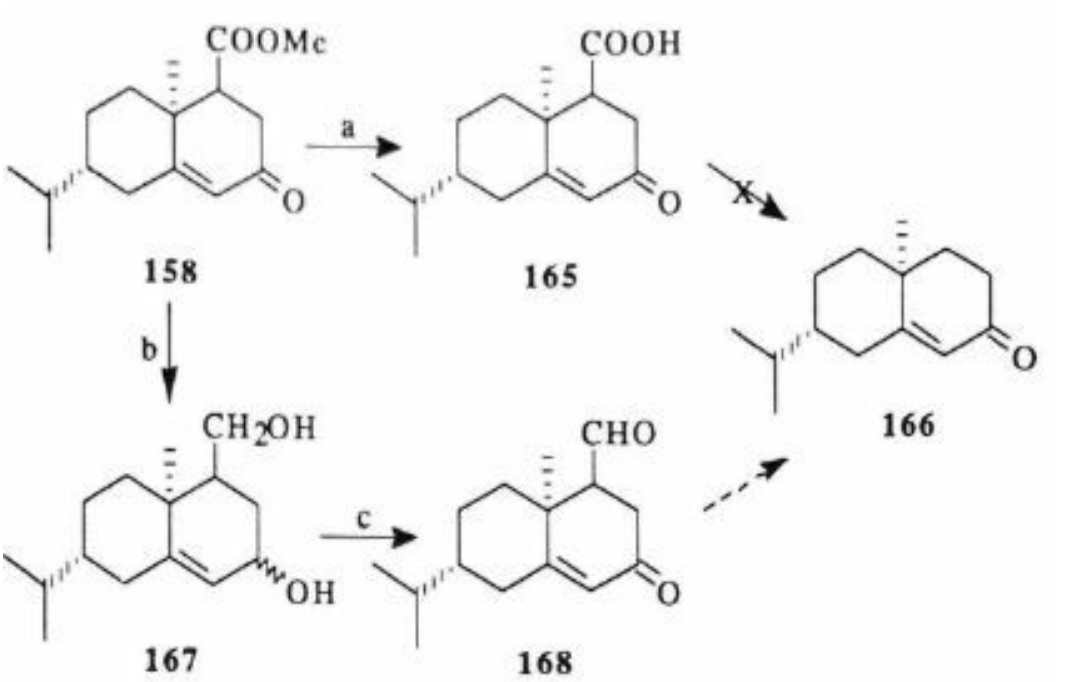
Reagents, conditions and yields: (a) O_2, $PdCl_2$, CuCl, DMF, H_2O, R.T., 6 h, 70% (b) FTS, C_6H_6, Δ, 2 h, 45%.

As could be envisaged from the Scheme 60 the α-allyl-γ-oxo-ester 157, was subjected to Wacker-type oxidation following the Tsuji conditions to

set up the aldol condensation reaction for the construction of eudesmane skeleton. Thus, the α-allyl-γ-oxo-ester 157 was subjected to Pd^{+2} oxidation to yield the diketo ester 164 in 70% yield. The IR spectrum of the diketo ester 164, with a broad ketone absorption at 1722cm-^{1} indicated the presence of the additional carbonyl functionality. At this stage, the aldol ring closure of the diketoester 164 was expected to complete the cudesmane frame-work synthesis and the cyclisation attempted was under different basic conditions, but all such efforts proved to be unsuccessful. However, treatment of the diketoester 164 with p-toluenesulphonic acid using Dean-Stark water separator delivered the desired bicyclic [4.4.0] framework present in eudesmane sesquiterpenes. The spectral data of the ester 158 was in full agreement with its formulation. A strong absorption at 1667cm-^{1} in the IR spectrum and the olefinic proton resonance at δ 5.80 (s, 1H) due to α-proton of the enone functionality, in the ^{1}H NMR spectrum (Fig. 41) clearly established the identity of the enone 158. D 16 line ^{13}C NMR spectrum (Fig 42) with characteristic resonances at 5 i97.4 and 172.5 further confirmed the identity of the structure 158.

Having obtained the bicyclo [4.4.0] system 158, efforts were made to refine the framework by decarboxylating the unrequired ester moiety, Scheme 64. Hydrolysis of the ester moiety in 158 with methanolic sodium hydroxide solution furnished the corresponding carboxylic acid 165 almost in quantitative yield Unfortunately, attempts at the reductive decarboxylation under different radical reaction conditions to give the enone 166 were in vain.

Scheme 64



Regents, conditions and yields: (a) 20% **NaOH, MeOH,** 4h, quant.(b) LAH, Et_2O, 2h, quant, (c) **TPAP-NMMO,** 10% **$CHC1_3$-DCM, R.T., 30 min.**

Similar attempts at oxidative decarboxylation to furnish the cross conjugated dienone were also unsuccessful. A recourse was taken to reduce the ester functionality in 158 to the diol **167** and further oxidise it to give the keto aldehyde 168 for reductive decarbonylation with Rhodium complexes. However, this too proved unsuccessful. In this sequence the keto aldehyde 168 formed was found to be unstable and gave a complex reaction mixture on work-up. Further efforts at the synthesis of eudesmane sesquiterpenes were not pursued.

Conclusions

In summary, a new simple and preparalively useful protocol for the construction of α-vinyl ketones, particularly (hose bearing a quaternary carbon centre from the corresponding alkenes has been developed during the course of this study. The generality of this methodology has been demonstrated with a few representative alkenes. The versatility of the methodology has been established by applying it to the enantioselective synthesis of sesquiterpene (+)-α-elemene (starting from R-(+)-limonene and (+)-2-carene). The efficacy of this methodology has been explored to construct an useful diquinane synthon and the framework of germacrane sesquiterpene. Our attempts to synthesise the taxol AB skeleton using this protocol, though looked promising, ultimately proved to be unsuccessful.

The intermediate, β-methoxy cyclopropyl ester in our newly developed sequence, have been elaborated towards the formal synthesis of *copa* series of sesquiterpenes. A chiral eudesmane derivative has also been synthesised through the alkylation-ring opening strategy.

Experimental

Melting points	Melting points were recorded on a Buchi SMP-20 apparatus and are uncorrected.
Boiling points	Bulb-to-bulb distillalions were carried out using oil bath for all liquid samples and boiling point refers to oil bath temperature.
Infrared spectra	Infrared spectra were recorded on JASCO FT-IR 5300 or Perkin-Elmer Model 1310. 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 magnetic resonance spectra	Proton magnetic resonance spectra (^{1}H NMR were generally recorded on Bruker AC 200 (200 M Hz) or JEOL FX-100 (100 M Hz) spectrophotometer. Carbon-13 magnetic resonance (^{13}C NMR} spectra were recorded on Bruker AC 200 (50 M Hz) or JEOL FX-100 (25.0 M Hz). ^{1}H NMR and ^{13}C NMR samples were made in chloroform-D solvent and chemical shifts are reported in δ scale using tetramethylsilane (Me4Si) as the internal standard. The standard abbreviations s, d, t, q, m and dd refer to singlet, doublet, triplet, quartet, multiplet and double doublet respectively.

	^{13}C NMR assignment differing by only 2-3 ppm can, in some cases, be interchanged,
Elemental analysis	Elemental analyses were performed on a Perkin-Elmer 240C-CHN analyzer.
Optical rotation	Optical rotations were measured on AUTOPOL II™ polarimeter and JASCO DIP 370 digital polarimeter.
Chromatography	Analytical thin-layer chromatographies (tlc) were performed on (10 x 5 cm) glass plates coated (250 mu.) with Acme's Silica gel G or GF_{254} (containing 13% of calcium sulphate as binder). Visualization of the spots on tlc plates was achieved either by exposure to iodine vapour 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 amount of silica gel used is approximately in the ratio of 1:25 and the column was usually eluted with ethyl acetate-hexane, unless mentioned otherwise.
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 Petroleum ether refers to the fraction boiling between 60-80°C Dictiloromethane was distilled ova P_2O_5. Benzene was distilled over sodium and stored over pressed sodium wire. Ethyl acetate was distilled over potassium carbonate. Absolute ethanol and methanol were prepared by distilling them over freshly ignited calcium oxide, followed by distillation over magnesium metal. Dry ether, dry dioxane, dry dimethoxy ethane and dry THF were made by distilling them from sodium-benzophenone ketyl. Hydrogeoations were carried out on a Parr-hydrogenation apparatus in 250 mL pressure bottles or in hydrogen balloons. All solvent extracts were washed 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 homogeneous by tlc and NMR spectroscopy.

General procedure for dichloroketene addition reactions

A dry nitrogen filled 100 mL three necked RB flask lilted with a nitrogen inlet and pressure equalising addition funnel was charged with olefin (5 mmol), zinc dust (10 mmol) and 50 mL of anhydrous ether. The flask was then partially submerged in the sonicator water hath in a place that produced maximum agitation to the suspension and freshly distilled trichloroacetyl chloride (7.5 mmol) in 25 mL anhydrous ether was added during 30 min. period. Sonication was continued at 15-20°C and the reaction was usually complete within 1h. After quenching with wet ether, the reaction mixture was filtered through celite and the filtrate was washed with water (2 x 20 mL), saturated sodium bicarbonate (2 x 20 mL) and brine solution (20 mL). The ethereal solution was dried over anhydrous sodium sulphate and the solvent was evaporated. Purification of the crude product was effected by chromatography over a short column of silica gel and vacuum distillation.

8,8-Dichloro-1-methylbicyclo[4.2.0]octan-7-one(76)[50]

Reaction of 1-methylcyclohexene (1.9 g, 20.0 mmol), zinc dust (2.6 g, 40.0 mmol) and trichloroacetyl chloride (3.4 mL, 30.0 mmol) afforded the dichloroketene adduct 76 (3.3 g, 80%) after bulb to bulb distillation.

b.p. 60°C/0.14mm

IR (neat) 2900, 2840,1790, 1440 cm^{-1}

^1H NMR (200MHz) δ 3.60-3.50 (m, 1H, O=C-C<u>H</u>), 2.20-1.00 (m, 8H), 1.49(s,3H,-C-C<u>H_3</u>)

8,8-Dichtoro-1-phenylblcyclo[4.2.0]octon-7-one(77)[51]

Reaction of 1-phenylcyclohcxene (3.2g, 20.0 mmol), zinc dust (2.6 g, 40.0 mmol) and trichloroacetyl chloride (3.4 mL, 30.0 mmol) afforded the dichloroketene adduct 77 (3.2 g, 60%).

b.p.	150°C/0.1 mm
IR(neat)	3061, 3030, 1805, 1603, 1497, 1449cm-^{1}
^{1}H NMR (200MHz)	δ 7.50-7.20 (m, 5H, aromatic protons), 4.20-4.10 (m, 1H, O=C-CH), 2.40-2.10 (m, 2H), 2.00-0.80 (m. 6H)

7,7-Dichloro-1-methylbicyclo[3.2.0]heptan-6-one(78)[50]

Reaction of 1-methylcyclopentene (2.0 g, 24.0 mmol), zinc dust (3.2 g, 48.0 mmol) and trichloroacetyl chloride (4 mL, 36 mmol) afford, d the dichloroketene adduct 78 (3.29 g, 70%) after bulb to bulb distillation..

b.p.	100°C/0.2mm
IR (neat)	2950, 2850, 1790, 800 cm-^{1}

10,10-Dichlorobicyclo[6.2.0]dec-4-ene-9-one(79)[18]

Reaction of 1,5-cyclooctadiene (500 mg, 4.62 mmol), zinc dust (600 mg, 9.17mmol) and trichloroacetyl chloride (0.78 mL, 7.0 mmol)

afforded the dichloroketene adduct 79 (1.16 g. 70%) after bulb-to-bulb distillation.

b.p.	110°C/0.1mm
IR(neat)	1805cm-^{1}
^{1}H NMR (200 MHz)	δ 5.64 (br s, 2H. -C<u>H</u>=C<u>H</u>-), 3.88-3.52 (m. 1H, Cl_2C-C<u>H</u>-), 3.20-2.80 (m, 1H, O=C-C<u>H</u>-), 2.60-1.80(m. 8H)
^{13}C NMR (25.0 MHz)	δ 196.7, 130.3, 129.9, 88.0, 58.6, 49.7, 24.2, 25.1, 24.1

(-)-(lS,3S,5R,7R)-9,9-Dichloro-l,4,4-trimethyltricyclo[5.2.0.0^{3,5}]nonan-8-one(80)

Reaction of (+)-D^{3}-carene (2.0g, 14.7 mmol), zinc dust (1.9g, 29.4 mmol) and trichloroacetyl chloride (2.5 mL, 22.0 mmol) afforded the dichloroketene adduct 80 (2.4 g, 68%) after bulb-to-bulb distillation.

b.p.	120°C/0.2mm
$[\alpha]_D$	-80.43° (c, 5.59 ;CHC1$_3$)
IR (neat)	2900, 2850, 1790, 1455, 870 cm-^{1}
^{1}H NMR (200MHz)	δ 3.36 (t, J = 4.0 Hz, 1H, O=C-C<u>H</u>), 2.50-2.20 (m, 2H). 1.42 (s, 3H, -C-CH_3), 1.20-0.50 (m, 4H), 1.01 (s, 3H, -C-C<u>H</u>$_3$), 0.95 (s, 3H, -C-C<u>H</u>$_3$).

General procedure for dichloroketene adduct rearrangement

A three-necked 100 mL RB flask fitted with a reflux condenser, mercury seal and nitrogen inlet was charged with dichloroketene adduct (10 rnmol) in 10 mL of dry melhanol. To this was added freshly prepared sodium methoxide (5 equiv.) solution in methanol through a septum under reflux, The reaction mixture was refluxed for ~30 min. After the complete consumption of the starting material, methanol was removed at reduced pressure and the residue obtained was diluted with water and extracted with ether (2 x 100 mL). The combined ethereal extract was washed, dried and the crude oily product thus obtained was charged on a silica gel column.

1-Methoxy-6-methylbicyclo[4.1.0]hept-7-carboxylic acid methyl ester (81a,b)

Reaction of the ketene adduct 76 (290 mg, 0.71 mmol) in 5 mL of methanol with sodium methoxide (5 equiv.) solution in methanol afforded the diastereomers mixture of cyclopropyl esters 81a,b (202 mg, 73%). Elution of the column with *2%* ethyl acetate-hexane afforded the less polar diastereomeric isomer.

IR(neat) 2915, 1735, 1440, 1210, 1160 cm^{-1}

^1H NMR(200MHz) δ 3.66 (s, 3H, -COOC$\underline{H}_3$), 3.30 (s, 3H, -OC$\underline{H}_3$), 2.30-1.10 (series of m, 8H), 1.46 (s, 1H, -C$\underline{H}$-COOCH$_3$), 1.29 (s, 3H, -C-C$\underline{H}_3$)

^{13}C NMR (25.0 MHz) δ 171.0. 69.7. 54.0. 50.9. 35.1. 31.5. 27,2. 23.8, 22.1, 21.6, 21.1

Further elution of the column with same eluent gave the more polar diastereomeric isomer.

IR (neat) 2925, 1730, 1440. 1190, 1160, 1020 cm-^{1}

^{1}H NMR(200MHz) δ 3.65 (s, 3H, -COOC<u>H</u>$_3$). 3.27 (s, 3H. -OC<u>H</u>$_3$), 2.10-2.00 (m. 2H). 1.80-1.60 (m, 2H), 1.50-1.00 (m, 4H). 1.45 (s. 1H), 1.42 (s. 3H, -C-C<u>H</u>$_3$)

13c NMR (25.0 MHz) δ 170.2, 70.1, 54.1. 50.9, 33.5, 32.1, 31.6, 28,0, 21.9, 20.6. 15.3

l-Methoxy-6-phenylbicyclo[4.1.0]hept-7-carboxylic acid methyl ester (82a,b)

Reaction of 77 (300 mg, 1.1 mmol) with 5 equiv. of sodium methoxide solution in methanol afforded the diastereomeric mixture of cyclopropyl esters 82a,b (214 mg, 74%). Elution with *2%* ethyl acetate-hexane afforded the less polar diastereomeric isomer.

IR(neat) 2910, 1725, 1440, 1220, 1180, 1150 cm-^{1}

^{1}H NMR (200 MHz) δ 7.40-7.10 (m, 5H, aromatic protons), 3.75 (s, 3H, -COOC<u>H</u>$_3$), 3.20 (s, 3H, -OC<u>H</u>$_3$), 2.40-1.40 (m, 8H), 1.54 (s. 1H, -C<u>H</u>-COOCH$_3$)

^{13}C NMR (25.0 MHz) δ 170.5, 144.4, 128.6(2C), 128.1(2C), 126.1, 68.3, 57.8, 51.1, 40.1, 34.0. 29.9, 24.3, 21.4(2C)

Further elution of the column with the same eluent gave the more polar diastereomeric isomer

IR(neat) 2900, 2850, 1740, 1700, 1440, 1160 cm-^{1}

^{1}H NMR (200 MHz) δ 7.40-7.10 (m, 5H, aromatic protons), 3.55 (s, 3H, -$COOCH_3$), 3.21 (s, 3H, -OCH_3), 2.30-1.10 (series of m, 9H)

^{13}C NMR (25.0 MHz) δ 169.2, 140.8, 129.4(2C), 128.0(2C), 127.2, 69.9, 54.1, 51.2, 40.8, 36.6, 32.1, 28.9, 21.7, 20.8

l-Methoxy-5-methylbicyclo[3.1.0]hexane-6-carboxylic acid methyl ester (83a,b)

Reaction of 78 (430 mg, 2.23 mmol) with 5 equiv. of sodium methoxide solution in methanol afforded the diastereomeric mixture of cyclopropyl esters 83a,b (360 mg, 88%).

IR(neat) 2900, 2850, 1725, 1460, 1440, 1320, 1210, 1170, 1140, 1080, 1040 cm-^{1}

1-Methoxybicyclo[6.1.0]non-4-en-9-carbniylic acid methyl ester (84a,b)

Reaction of 79 (250 mg, 1.l4 mmol) with 5 equiv. of sodium methoxide solution in methanol afforded the cyclopropyl ester 84a,b (120 mg, 50%). Elution of the reaction mixture with 2% ethyl acetate-hexane afforded the ester 84a,b.

IR(neat) 2900, 1730, 1440, 1360, 1270, 1200cm^{-1}

^{1}H NMR(200MHz) δ 5.80-5.60 (m, 2H, -CH=CH-) 3.69 (s. 3H, -COOCH$_3$), 3.19 (s, 3H. -OCH$_3$), 2.70-2.50 (m, 1H), 2.50-1.90 (m. 6H), 1.70-1.10 (m, 3H)

^{13}C NMR (25.0 MHz) δ 170.1, 129.9, 129.6, 72.2, 53.9, 51.4, 33.8, 32.7, 30.8,28.2,25.8,23.1

(lR,3R,5R,7S)-3-Methoxy-5,8,8-trimethyl-tricyclo[5.1.0.0^{3,5}]octane-4-carboxylic acid methyl ester (85a,b)

Reaction of 80 (200 mg, 0.81 mmol) with 5 equiv. of sodium methoxide solution in methanol afforded the diastereomeric mixture of cyclopropyl esters 85a,b (133 mg, 70%). Elution with 2% ethyl acetate-hexane afforded the less polar diastereomeric isomer.

IR(neat) 2905. 1725. 1440,1120.1055, 1020cm^{-1}

^{1}H NMR(200MHz) δ 3.65 (s, 3H, -COOCH$_3$), 3.32 (s, 3H, -OCH$_3$), 2.57 (dd, J_1=14.54 Hz, J_2=8.8 Hz, 1H), 2.23 (dd. J_1=15.2 Hz, J_2=8.6 Hz, 1H), 1.80-1.30 (m, 3H),

1.18 (s, 3H. -C-C$\underline{H}_3$), 0.97 (s, 3H, -C-C$\underline{H}_3$), 0.80 (s, 3H, C-C$\underline{H}_3$). 0.60-0.20 (m, 2H)

^{13}C NMR(25.0MHz) δ 170.6, 67.1, 54.3, 51.3, 32.7, 28.0, 27.7, 23.7, 20.8, 19.0, 18.2, 17.2, 16.8, 14.7

Further elution of the column with same eluent gave the more polar diastereomeric isomer.

IR (neat) 2925. 1730, 1440,1360, 1325 cm^{-1}

^{1}H NMR (200 MHz) δ 3.66 (s, 3H, -COOC$\underline{H}_3$), 3.28 (s, 3H. -OC$\underline{H}_3$), 2.60-2.40 (m, 1H), 2.20-1.90 (m, 1H), 1.74 (s, IH, -C$\underline{H}$-COOCH$_3$), 1.50-1.20 (m, 2H), 1.33 (s, 3H, -C-C$\underline{H}_3$), 1.01 (s, 3H, -C-C$\underline{H}_3$), 0.82 (s, 3H, -C-C$\underline{H}_3$). 0.70-0.30(m, 2H)

^{13}C NMR (25.0 MHz) δ 170.9, 69.3, 54.5, 51.1, 29.0, 27.8(2C), 27.4, 26.2, 20.3, 18.0, 15.9, 15.1, 13.8

General procedure for DIBAL-H reduction

To a solution of cyclopropyl esters (1 mmol) in dry dichloromethane (5 mL) cooled to -78°C, DIBAL-H (2mL of 1.2 M solution in toluene, 2.4 mmol) was added under nitrogen. After the complete consumption of the Starting material the reaction mixture was quenched with saturated ammonium chloride solution and diluted with dichloromethane, washed and dried. Removal of solvent furnished a mixture of cyclopropyl carbinols.

(l-Methoxy-6-methylbicyclo[4.1.0]hepl-7.yl)rnethanol(86)

Reaction of the cyclopropyl esters 81 (500 mg. 2 50 mmol) with DIBAL-H afforded the diastereomeric mixture of cyclopropyl carbinols 86 (340 mg) in 80% yield.

IR (neat) 3350, 2900, 1450, 1090, 1020 cm^{-1}

(l-Metfioxy-6-phenylbicyclo[4.1.0]hept-7-y1)methanol(87)

Reaction of the cyclopropyl esters 82 (116mg, 0.45 mmol) with DIBAL-H afforded the diastereomeric mixture of cyclopropyl carbinols 87 (88mg) in 85% yield

IR (neat) 3350, 2900, 2850, 1600, 1440, 1020cm^{-1}

(l-Methoxy-5-methylbicyclo[3.1.0]hex-6-yl)methanol(88)

Reaction of the cyclopropyl esters 83 (350 mg, 1.90 mmol) with DIBAL-H afforded the diastereomeric mixture of cyclopropyl carbinols 88 (230 mg) in 77% yield.

IR(neat) 3350, 2900, 2850,1450, 1380, 1080, 1020 cm^{-1}

(l-Methoxy-6-bicyclo[6.1.0]non-4-en-9-yl)methanol(89)

Reaction of the cyclopropyl esters 84 (200 mg, 0.95 mmol) with DIBAL-H afforded the diastereomeric mixture of cyclopropyl carbinols 89 (150 mg) in 86% yield.

IR(neat) 3350, 2900, 1460, 1250, 1070, 1020 cm^{-1}

(IR,3R,5R, 7S)-(3-Methoxy-5,8,8-trimethyltricyclo[51.0.$0^{3,5}$]octa-4-yl)methanol (90)

Reaction of the cyclopropyl esters 85 (200 mg, 0.84 mmol) with DIBAL-H afforded the diastereomeric mixture of cyclopropyl carbinols 90 (123 mg) in 70% yield

IR(neat) 3350, 2900, 2850, 1440, 1120, 1100cm^{-1}

General procedure for α-vinyl ketone preparation

To a mixture of cyclopropyl carbinols (1 mmol) in dry pyridine (5 mL) was added methanesulphonyl chloride (1.2 equiv.) at 0°C. The reaction mixture was stirred for 30 min., quenched with water and acidified with dilute hydrochloric acid. The reaction mixture was extracted with ether (50 mL x 3) and the combined ethereal extract was washed and dried over anhydrous sodium sulphate. After the removal of the solvent, the crude reaction mixture was again dissolved in ether (50 mL) and treated with a few drops of aq.35% perchloric acid at 0°C. The reaction mixture was allowed to

warm to room temperature and stirring continual for 30 min. The reaction mixture was quenched and the ethereal layer was washed and dried. Removal of the solvent and chromatographic separation on a silica gel column by elution with 2% ethyl acetate-hexane furnished the α-vinyl ketone.

2-Methyl-2-vinylcyclohexanone (91)

Reaction of the carbinols 86 (325 mg. 1.91 mmol) with methanesulfonyl chloride (1.2 equiv.) and treatment of the crude reaction mixture with a few drops of 35% aq. perchloric acid afforded the a-vinyl ketone 91 (180 mg) in 68% yield

b.p.	120°C/1 mm of Hg
IR(neat)	2915, 1710, 1440, 1080 cm^{-1}
^{1}H NMR (200 MHz) (Fig. 1)	δ 5.93 (dd, J_1=17.7 Hz. J_2= 10.6 Hz, 1H, • $CH=CH_2$), 5.08 (d, J=10.8 Hz, 1H, -CH=CH2), 4.93 (d, J=17.6 Hz, 1H, $-CH=CH_2$). 2.60-1.40 (series of m, 8H). 1.11 (s, 3H.-C-CH_3)
^{13}C NMR (50.0 MHz) (Fig. 2)	δ 213.1, 142.7, 114.7, 52.1. 39.8, 39.2. 27.6. 23.9, 21.7
Analysis($C_9H_{14}O$)	Calcd. :C, 78.21; H, 10.21 Found :C, 78.15; H, 10.18

2-Phenyl-2-vlnylcyclohexanone (92)

Reaction of the carbinols 87 (116mg, 0.50 mmol) with methanesulfonyl chloride (1.2 equiv.) and treatment of the crude reaction mixture with a few drops of 35% aq. perchloric acid afforded the α-vinyl ketone 92 (67 mg) in 65% yield.

b.p. 120°C/0.1 mm of Hg

IR (neat) 2900, 2850, 1700, 1440, 1120 cm-[1]

^{1}H NMR (200 MHz) δ 7.50-7.10 (m, 5H aromatic Hs), 6.25 (dd,

(Fig. 3) J_1=17.4 Hz, J_2=10.6 Hz, 1H, -CH=CH_2), 5.10 (d,

J=10.6 Hz, 1H, , -CH=CH_2), 4.56 (d, J=17.0 **Hz,**

1H,, -CH=CH_2), 2.80-2.50 (m, 1H), 2.50-2.20 (m,

2H), 2.10-1.60 (m,5H)

^{13}C NMR (25.0 MHz) δ 212.4, 143.4, 137.8, 129.0(2C), 127.6(2C),

(Fig. 4) 127.0, 114.8, 61.0, 40.0. 36.2, 28.0, 21.5

Analysis ($C_{14}H_{16}O$) Calcd.: C, 83.96; H, 8.05

Found : C, 83.75; H. 8.00

2-Methyl-2.vinykyclopentanone (93)

Reaction of the carbinols 88 (220 mg, 1.41 mmol) with methanesulfonyl chloride (1.2 equiv.) and treatment of the crude reaction mixture with a few drops of 35% aq. perchloric acid afforded the volatile product, α-vinyl ketone 93 (70 mg) in 40% yield.

IR(neat) 2900, 2850, 1740, 1450, 920 cm^{-1}

^1H NMR(200MHz) (Fig.5) δ 5.78 (dd, J_1= I7.4 Hz, J_2=I0.8 Hz, 1H. -$CH=CH_2$), 5.10 (d, J=10.0 Hz, 1H, -$CH=CH_2$), 5.05 (d, J=18.0 Hz, 1H, -$CH=CH_2$). 2.40-1.70 (m, 6H), 1.14(s,3H,-C-CH_3)

^{13}C NMR (50.0 MHz) (Fig. 6) δ 219.7, 140.5, 113.9, 51.8, 36.9, 36.2, 22.2, 18.5

8-Vinylcyclooct-4-enone (94)

Reaction of the carbinols 89 (108 mg, 0.6 mmol) with methanesulfonyl chloride (1.2 equiv.) and treatment of the crude reaction mixture with a few drops of 35% aq. perchloric acid afforded the α-vinyl ketone 94 (70 mg) in 72% yield.

b.p. 140°C/0.1 mm of Hg

IR (neat) 3010, 1710, 920. 740cm^{-1}

^1H NMR (200 MHz) **(Fig.** 7) δ 6.00-5.60 (m, 3H), 5.10-4.90 (m, 2H, •$CH=CH_2$), 3 50-3.30 (m, 1H), 2.70-2.50 (m, 2H), 2.40-2.00 (m, 4H), 1.70-1.40 (m, 2H)

^{13}C NMR (25.0 MHz) (Fig. 8) δ 214.4. 138.2, 130.7, 129.9. 115.3. 55.1. 46.5, 31.2, 25.3, 21.9

Analysis ($C_{10}H_{14}O$) Calcd.: C, 79.95; H. 9.39
Found : C, 80.05; H, 9.27

(+)-(lR,4R,6S).4,7.7-Trimethyl-4-vinylbicyclo[4.1.0]hept-3-one(95)

Reaction of the carbinols 90 (270mg, 1.30 mmol) with metnanesulfonyl chloride (1.2 equiv.) and treatment of the crude reaction mixture with a few drops of 35% aq. perchloric acid afforded the α-vinyl ketone 95(156 mg) in 68% yield.

b.p. 130-135°C/1.0 mm of Hg

$[\alpha]_D$ +31° (c, 3.78;$CHC1_3$)

IR(neat) 2875, 1695, 1445, 905 cm^{-1}

^1H NMR (200 MHz) δ 6.14 (dd, J_1=17.4 Hz, J_2=10.8 Hz, 1H, -CH=CH_2), 5.16 (d, J=10.6 Hz, 1H, -CH=CH_2), 5.09 (d, J=17.6 Hz, 1H, , -CH=CH_2). 2.80-2.60 (m, IP), 2.30-2.10 (m, 2H), 1.50-1.30 (m, 1H), 1.00-0.90 (m, 2H), 1.05 (s, 6H, -$C(CH_3)_2$), 0.87 (s, 3H, -C-CH_3)

(Fig. 9)

^{13}C NMR (25.0 MHz) δ 215.4, 141.1, 115.1, 49.3, 34.5, 33.9, 27.8, 22.2, 19.2, 18.3, 14.9

(Fig. 10)

Analysis ($C_{12}H_{18}O$) Calcd.: C. 80.85; H, 10.18

Found :C, 80.70; H, 10.14

(+)-(4R)-Isopropyl-l-methylcyclohexene oxide (63)[30]

A mixture of R-(-+-)-limonene 106 (63.5 g, 0.46 mmol) and 160 mg of platinum oxide in 200 mL of 95% ethanol was stirred at room temperature

under 1 atm. of hydrogen. The reaction was monitored by GC and after the total consumption of the starting material, the solution was filleted and dried over sodium sulphate. The solvent was removed in vacuo and the residue was distilled to give **63** (55.2 g, 90%).

b.p.	55-60°C/20 mm
$[\alpha]_D$	+107.9° (c, 2.20 ; $CHC1_3$)
IR{neat)	1450,1380. 1360, 1090.1055,798cm-[1]
^{1}H NMR(200 Hz}	δ 5.47.5.18 (m, 1H, -C=C<u>H</u>), 2.30-1.00 (m, 8H), 1.60 (s, 3H, -C-C<u>H</u>$_3$), 0.85 (d, J=6 Hz, 6H, -CH-C<u>H</u>$_3$)

(+)-(lS3R,6R)-8,8-Dichloro-3-isopropyl-6-methylbieyclo[4.2.0]octan-7-one(107)

This experiment was performed as described in the general procedure for dichloroketcee addition reaction.

Reaction of (+)-R-dihydrolimonene 63 (4.6 g, 40 mmol) with zinc dust (4 g, 60 mmol) and triehloroacetyl chloride (6.7 mL, 50 mmol) afforded the dichloroketene adduct 107 (4.8 g) in 65% yield,

b,p.	140-145°C/1 mm
$[\alpha]_D$	+26.55° (c, 3.05 ;$CHC1_3$)
IR(neat)	2900,2850, 1800cm^{-1}

^{1}H NMR (200 MHz) δ 370-3.50 (m. 1H, OC-C<u>H</u>-), 2.20-0.70 (series or m. 8H). 1 48 (s, 3H, -C-C<u>H</u>$_3$), 0.87 (d, J=6.66 Hz,6H.-CH-C<u>H</u>$_3$)

^{13}C NMR (50.0 MHz) δ 195.3, 92.1, 58.8, 43.8, 40.3. 34.4. 32.4. 24.8. 23.8, 199, 19.4, 19.3

(lS,3R,6S)-3-Isopropyl-1-metthoxy-6-methylbicyelo[4.1.0]lieptan-7-carboxylic acid methyl ester (108a.b)

This experiment was performed as described in the general procedure for dichloroketene adduct rearrangement.

Reaction of the ketene adduct 107 (3.25 g. 13 mmol) in 10 mL of methanol with sodium methoxide (5 equiv.) solution in methanol afforded the diastereomcric mixture of cyclopropyl esters 108a,b (2.34g. *75%).* Elution with 2% ethyl acetate-hexane afforded the less polar diastereomeric isomer.

$[\alpha]_D$ +15.41° (c, 5.27 ;CHC1$_3$)

IR(neat) 2900, 2850, 1720, 1460, 1440, 1330, 1200, 1160, 1020,740cm^{-1}

^{1}H NMR (200 MHz) δ 5 3.64 (s, 3H, -CO-OCH$_3$), 3.32 (s, 3H, -OCH$_3$), 2.60-1.20 (series of m, 9H), 1.28 (s, 3H, -C-CH$_3$). 1.00-0.80 (m, 6H.-CH-CH$_3$)

^{13}C NMR (25.0 MHz) δ 171.2, 71.0, 54.3, 51.1, 39.2, 35.6, 32.8, 32.7, 28.6,27.2,25.4,22.1. 19.3(2C)

Further elution of the column afforded the more polar diastereomeric isomer of the cyclopropyl ester (520 mg) in 17% yield.

$[\alpha]_D$	+50.86° (c, 1.687 ; $CHC1_3$}
IR(neat)	2900,2850, 1730, 1440,1360.1040, 1020cm^{-1}
^{1}H NMR(200MHz)	δ 3.64 (s, 3H, -COOC$\underline{H}_3$), 3.28 (s, 3H, -OC$\underline{H}_3$), 2.40-1.20 (series of m,9H), 1.39 (s, 3H, -C-CH_3), 1.00-0.70 (m, 6H, -CH-(C$\underline{H}_3)_2$)
^{13}C NMR (50.0 MHz)	δ 170.1, 71.5, 54.5, 51.0, 39.3, 35.0, 32.9, 32.2(2C), 30.7, 25.7,19.7, 19.5, 15.7

(lS,3R,6S)-(3-Isopropyl-l-methoxy-6-methylbicyclo[4.1.0]hept-7-yl)melhanol (105)

Reduction of 108a,b using DIBAL-H:

This experiment was performed as described in the general procedure for DIBAL-H reduction.

Reaction of the cyclopropyl esters 108a,b (200 mg, 0.94 mmol) with DIBAL-H afforded the diastereomeric mixture of cyclopropyl carbinols 105 (136 mg) in 80% yield.

Reduction of 108a,b using LAH

To a suspension of lithium aluminium hydride (133 mg, 3,5 mmol) in dry ether (50 mL) cooled in an ice-bam, the ester **108a,b** (1,65 g, 6.9 mmol) in ether (10 mL) was added under nitrogen. The reaction mixture was stirred for 2 h till the starting ester was fully consumed. The reaction mixture was then quenched with a saturated solution of sodium sulphate and extracted with ether (3 x 100 mL). The ethereal layer was dried over sodium sulphate and concentrated to get a crude diastereomeric mixture of alcohols **105** (1.09 g) in 80% yield

IR (neat) 3350, 2900, 2850,1460,1105,1020, 725 cm^{-1}

(+)-(2S ,5R)-S-Isop; opyl-2-methyl-2-vinylcyclohexanone (64)

Using Py/MsCI Method

This experiment was performed as described in the general procedure for a-vinyl ketone preparation.

Reaction of the carbinols **105** (800 mg. 4 mmol) with methanesulfonyl chloride (1.2equiv.) and treatment of the crude reaction mixture with a few drops of 35% aq. perchloric acid afforded the α-vinyl ketone 64 (567 mg) in 78% yield.

Using TMSI method

Into a 50 mL RB flask fitted with a dry nitrogen inlet, septum and mercury seal, was placed sodium iodide (1.5 g, 10 mmol) in 10 mL of dry acetonitrile. The cyclopropyl alcohol 105 (1 g. 4.7 mmol) in 5 ml. of acetonitrile was then added to the mixture at 0°C and the same was stirred for 30 min. at room temperature. The reaction mixture was diluted with ether (200 mL) and washed successively with sodiumthiosulphate solution and brine. Drying and removal of solvent gave a crude product which was charged on a silica gel column. Elution with 2% ethyl acetate-hexane furnished vinyl ketone 64 in 90% yield

b.p.	95-100°C/l mm
$[\alpha]_D$	+60° (c, 0.35 ; $CHC1_3$)
IR(neat)	2950,1705, 1465,1365, 1180,910cm-[1]
^{1}H NMR (200 MHz) (Fig. 11)	δ 6,20-6.00 (m, 1H, -C<u>H</u>=CH_2), 5.20-4.90 (m, 2H, -CH=CH_2), 2.34 (d, 1=5.32 Hz, 2H, -C<u>H</u>$_2$-CO-), 1,90-1.40 (m, 6H), 1,23 (s, 3H, -C-C<u>H</u>$_3$). 0.89 (d, J=5.97 Hz, 6H, -CH-(C<u>H</u>$_3$)$_2$)
^{13}C NMR (50.0 MHz) (Fig. 12)	δ 8214.0, 142.8. 112.8,50,5.45,2,41.9, 36.7,31.9, 24.3,22,5,19.7, 19.6
Analysis ($C_{12}H_{20}O$)	Calcd.: C, 79.94; H, 11.18
	Found :C, 80,12; H, 11.28

(2S,5R)-l-1sopropthyl-5-isopropyl-2-melhyl-2-vlnyl cyclohexanol (65)

Into a 100 mL. two-neceked flask fitted with reflux condenser was suspended freshly cut lithium (10 mg. 2.7mmol) in 5ml of dry tetrahydrofuran under nitrogen. 2-Bromopropene was injected through a septum. The contents of the flask were sonicated for 10 min. for activation. The vinyl ketone 64 (100 mg, 0.54 mmol) in 2 mL of dry tetrahydrofuran was introduced into OK flask and the sonication continued for 1 h. The THF solvent was removed at low pressure and the residue was diluted with 5 mL of water. The reaction mixture was extracted with ether (3 x 50 mL), The ethereal layer was washed with water, brine and dried over Na_2SO_4. After evaporation of the solvent, the crude reaction mixture was charged on a silica gel column. Elution with 2% ethyl acetate-hexane afforded a diastereomeric mixture of allylic alcohols 65 (50 mg) in 80% yield, based on recovery of

IR (neat) 3475, 3100, 2950. 2870.1640,1020,910cm^{-1}

(2S,5R)-l-Isopropyl-5-isopropyl-2.methyl-2-vinyl cyclohexanol (109)

Into a 100 mL, two-necked flask fined with reflux condenser was suspended freshly cut lithium (60 mg, 8.0 mmol) in 5 ml of dry tetrahydrofuran under nitrogen. 2-Bromopropane was injected through a septum. The contents of the flask were sonicated for 10 min. for activation. The vinyl ketone 64 (300 mg, 1.62 mmol) in 2 mL of dry tetrahydrofuran was introduced into the flask and the sonication continued for 1 h. The THF

solvent was removed at low pressure and the residue was diluted with 5 mL of water. The reaction mixture was extracted with ether (3 x 50 mL). The ethereal layer was washed with water, brine and dried over Na_2SO_4. After evaporation of the solvent, the crude reaction mixture was charged on a silica gel column. Elution with 2% ethyl acetate-hexane afforded a diastereomeric mixture of allylic alcohols 109 (50 mg) in 80% yield based on recovery of starting material.

IR(neat) 3400,2950,1460,1380,900cm-'

(-)-(6S)-3-Isopropyl-6-methyl-6-vinylcyclohex-2-enone(104)

To a solution of vinyl ketone 64 (l.0 g, 5.55 mmol) in 10 mL of anhydrous tert.butanol in a 50 mL three-necked RB flask fitted with a reflux condenser, mercury seal, was added selenium dioxide (1.1 g, 10 mmol) in 10 mL of tert.butanol. The reaction mixture was refluxed for 6 h and cooled to room temperature. Excess tert.butanol was removed at reduced pressure. The residue was charged on a silica gel column. Elution with 2% ethyl acetate-hexane afforded the enone 104 in 45% yield based on recovered starting material.

b.p. 110°C/2mm

$[\alpha]_D$ -76.08° (c, 0.74 ; $CHC1_3$)

UV λ(max) 237.0 nm, $\log_t$=4.1196

IR(neat) 2965, 2428, 2868, 1670, 1630, 1020, 916, 875, 800cm^{-1}

^{1}H NMR (200 MHz) δ 5.84 (dd, J_1=17.49 H, J_2=10.74 Hz. 1H. -

(Fig. 13) CH=CH_2), δ 5.85 (s, 1H, -C=CH-CO-). 5.20-4.90 (m, 2H, -CH=CH_2). 2.50-2.10 (m. 3H), 2,10-1.70 (m, 2H). 1.19(s, 3H.-C-CH_3), 1.09 (d, J=6.91 Hz, 6H, -CH-CH_3)

^{13}C NMR(50.0MHz) δ 202.1, 170.0, 140.9, 122.7, 114.0, 47.5, 35.4,

(Fig. 14) 35.0, 25.0, 22.9, 20.8, 20.6

Analysis ($C_{12}H_{18}O$) Calcd.: C, 80.85; H. 10.18

Found :C, 81.00; H, 10.23

(+)-a-elemene [(+)-(6S)-l-lsopropyl-3-isopropylidene-6-methyl-6-vinyl-cyclohexene (97)]

Into a 25 mL two-necked flask fitted with reflux condenser was suspended freshly cut lithium (5 mg, 0.7 mmol) in 5 mL of dry tetrahydrofurn under nitrogen. 2-Bromopropane (0.5 mL) was injected through a septum. The contents of the flask were sonicated for 10 min, for activation. The enone 104 (25 mg, 0.14 mmol) in 2 mL of dry tetrahydrofuran was slowly introduced into the flask and the sonication continued for 15 min. The reaction mixture was poured into brine and extracted with ether (2 x 20 mL). The ethereal layer was dried and concentrated to furnish the crude product 103.

To a mixture of the above crude product 103 in dry chloroform (10 mL) was added p-toluenesulfonyl chlorite (cat,) at 0°C. The reaction mixture was stirred for 30 min., quenched with water and extracted with dichloromethane (2 x 20 mL). The combined organic solvent was washed, dried and concentrated to a crude product which was filtered through a small silica gel column. Elution with 1% ethyl acetate-hexane furnished 97 (12 mg) in 42% yield based on enone.

b.p,	120-130°C/7mrn
$[\alpha]_D$	+111.5° (c, 0.65 ;$CHC1_3$)
IR(neat)	3082, 2959, 2924, 2870, 1634. 1460, 1120. 1001, 910,876,806 cm^{-1}
UVλ(max)	251 nm, logt=4.998
H NMR (200 MHz) (Fig. 15)	δ 6.37 (s, 1H, -C=C-C-C<u>H</u>=C-), 5.78 (dd, J_1=17.24 Hz, J_2=10.73 Hz, 1H, -C<u>H</u>.=CH_2). 5.10-4.90 (m, 2H, -CH=C<u>H_2</u>), 2.40-2.20 (m, 3H), 1.81 (s, 3H, -C=C-CH_3), 1.73(s, 3H, -C=C-C<u>H_3</u>), 1.70-1.40 (m, 2H), 1.18 (s, 3H, -C-C<u>H_3</u>), 1-06 (d, J=6.85 Hz, 3H, -CH-CH_3), 1.45 (d, J=6.01 Hz, 3H, -CH-C<u>H_3</u>)
^{13}C NMR (50.0 MHz) (Fig. 16)	δ 149.7, 146.2, 128.1, 124.5, 119.7, 112.4, 42.2, 37.8, 29.4, 25,3, 24.7, 23.8, 23.1, 20.7. 19.7

(+)-(1S,2R,4R.7R)-8-8-Dichloro-3,3,7-trimethyltriclo[5.2.0.$0^{2,4}$]nonan-9-one(112)

for dichloroketene addition reaction.

Reaction of R-(+)-2-carene 111 (5.4g, 40 mmol), zinc dust (4g, 60 mmol) and trichloroacetyl chloride (6.8 mL, 60 mmol) afforded the dichloroketene adduct 112 (8.4 g) in 95% yield.

b,p. 150°C/l.0 mm

$[\alpha]_D$ +128.3° (C, l.54;$CHC1_3$)

IR(neat) 2945, 1803,1454, 1246,1126,933,883cm-^{1}

^{1}H NMR (200 MHz) δ 3.36 (s, 1H, OC-C<u>H</u>-), 2.20-1.00 (m, 1H), 1.70-0.80 (series of m, 5H), 1.37 (s, 3H, -C-C<u>H</u>$_3$), 1-04 (s, 3H, -C-C<u>H</u>$_3$), 0.83 (s, 3H, -C-C<u>H</u>$_3$)

^{13}C NMR (50.0 MHz) δ 196.6, 93.2, 56.8. 44,2, 31.1, 27.8. 21.4, 19.7, 17.8,15.9(2C)

(lS,2S,4S,7R)-2-Methoxy-4,8,8-trimelhyltricyclo[5.1.0.$0^{2,4}$]octane-3-carboxytic acid methyl ester (113a,b)

This experiment was performed as described in the general procedure for dichloro ketene adduct rearrangement.

Reaction of the ketene adduci 112 (2.22 g, 10 mmol) in 10 mL of methanol with sodium methoxide (5 equiv.) solution in methanol afforded the diastereomeric mixture of cyclopropyl esters 113**a,b** (1.48 g) in 62.6% yield. Elution with 2% ethyl acetate-hexane afforded the less polar diastereomeric

$[\alpha]_D$	-30.88°(c, 0.62 ;$CHC1_3$)
1R (neat)	2992, 2822,1730, 1454,1171, 1140cm^{-1}
^{1}H NMR(200MHz)	δ 3.65 (s, 3H, -COOC$\underline{H}_3$), 3.37 (s, 3H, -OC$\underline{H}_3$), 2.00-0.80 (series of m, 7H), 1.22 (s, 3H, -C-C$\underline{H}_3$), 1.13 (s, 3H, -C-C$\underline{H}_3$), 1.03 (s, 3H, -C-C$\underline{H}_3$)
^{13}C NMR (50.0 MHz)	δ 170.9, 69.4, 54.2, 50.8, 36.4, 33.9. 28.1, 26.1, 26.0,22.2, 19.7, 18.8, 17.4, 17.1

Further elution of the column with the same eluent afforded the more polar diastereomeric isomer of the cyclopropyl ester.

$[\alpha]_D$	+53.75° (c, 0.62 ;$CHC1_3$)
IR (neat)	2990, 2944, 2868,1736,1437,1140 cm^{-1}
^{1}H NMR(200MHz)	δ 3.66 (s, 3H, -COOC$\underline{H}_3$), 3.35 {s, 3H. -OC$\underline{H}_3$). 1.80-0.70 (series of m, 7H), 1.34 (s, 3H, -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 (50.0 MHz)	δ 169.9, 69.1, 54.3, 50.9, 32.7, 32.2(2C), 28.7 24.3, 22.9, 21.3,17.2,16.5,13.9

(lS,2S,4S,7R).2-Melhoxy-4,8,8-trimethylricyclo[5.1.0.$0^{2,4}$] octa-3-yl)methanol(114)

To a suspension of lithium aluminium hydride (90 mg. 2.3 mmol) in dry ether (50 mL) cooled in an ice bath was added the ester 113a,b (1.1 g, 4.62 minol) in ether (10 mL) under nitrogen. The reaction mixture was stirred for 6 h. till the starling cyclopropyl ester was fully consumed. The reaction mixture was then quenched with saturated solution of sodium sulphate and extracted with ether (2 x 100 mL). The ethereal layer was dried over sodium sulphate and concentrated to gel crude diastereomeric mixture of alcohols 114 (900 mg) in 92% yield

IR(neat) 3372. 2992, 2940, 1134,1117,1018cm^{-1}

(-)-(6S)-3-lsoproply-6-methyl-6ovinlcyclohex-2 (104)

Into a 50 mL RB flask fitted with a dry nitrogen inlet, septum and mercury seal was placed sodium iodide (1.5g, 10 mmol) and freshly distilled chlorotrimethylsilae (1.3 mL, 10 mmol) in 10 mL of dry acetonitrile. The cyclopropyl alcohol 114 (1.06 g, 5 mmol) in 5 mL of acetonitrile was added to the mixture at 0°C and the mixture was stirred for 30 min at the same temperature. The reaction mixture was diluted with ether (100 mL) and washed successively with aq. sodium thiosulphate solution and brine. Drying and removal of solvent gave a crude product which was charged

on a silica gel column. Elution with 5% ethyl acetate-hexane furnished enone 104 (720 mg) in 85% yield.

(2R,9R)-9-Isopropyl-2,6-dimelhylcyclodec-5-enone(66)

Potassium hydride (20 mg, 0.5 mmol) in a mineral oil suspension was washed with dry hexane (3 x 2 mL) and suspended in THF (2 mL). To this suspension at 0°C was added HMDS (0.1 mL, 0.5 mmol) and the resulting suspension was stirred for 15 min. at the same temperature. 18-Crown-6 (132 mg, 0.5 mmol) and divinylcarbinol **65** (100 mg, 0.45 rnmol) dissolved in THF (2 rnL) were added in a single portion and the reaction mixture was refluxed for 30 min. The contents were then cooled to -78°C and quenched with absolute ethanol (1 mL) *via* rapid injection. The resulting slurry was immediately poured into a mixture of ether solvent and sat. ammonium chloride (5 mL). The organic layer was washed with brine (5 mL) dried over sodium sulphate and filtered. After removal of the solvent under reduced pressure the crude reaction mixture was passed through a silica gel column and elution with 2% ethyl acetate-hexane afforded the pure ketone **66** (48 mg) in 60% yield

m.p.		45°C
$[\alpha]_D$	-34.6°	(c, 0.50 ; $CHC1_3$)
IR (neat)		2957, 2928, 2872, 1707, 1458,1371 cm^{-1}
^1H NMR (200 MHz) (Fig. 18)		δ 5.00-4.80 (m, 1H. -C=CH-CH_2-) 2.50-0.80 (series of m, 13H), 1.69 (s, 3H, -C-CH_3), 0.85 (d,

J=6.6 Hz, 3H, CH-C$\underline{H}_3$). 0 81 (d. J=6 Hz. 6H. -CH-C$\underline{H}_3$)

^{13}C NMR(50.0 MHz) δ 215.9. 134 1, 129.8. 47 4. 46.2. 40.7. 39 7. 37.2. (Fig.19) 34.7.29.9, 27.6, 19.2. 19.1, 18.7, 15. 6

(6S)-l-lsopropenyl-3-lsopropyl-6-melhyl-6-vinyl cyclohex-2-enol (123)

Into a 100 mL, two-necked flask fitted with reflux condenser was suspended freshly cut lithium (10 mg, 1.35 mmol) in 5 ml of dry tetrahydrofuran under nitrogen. 2-Bromopropene (0.1-0.2 mL) was injected through a septum. The contents of the flask were sonicated for 10 min. for activation. The enone 104 (50 mg. 0 27 mmol) in 2 mL of dry tetrahydrofuran was introduced into the flask and the sonication continued for 1 h. The THF solvent was removed at low pressure and the residue was diluted with 5 mL of water. The reaction mixture was extracted will ether (3 x 50 mL). The ethereal layer was washed with water, brine and dried over Na_2SO_4. After evaporation of the solvent the crude reaction mixture was charged on a silica gel column. Elution with *2%* ethyl acetate-hixane afforded a diastercomeric mixture of allylic alcohols 123 (37 mg) in 61% yield, based on recovery of starting material.

IR (neat) 3428, 3082,1636,1460, 904 cm^{-1}

(+)-(2R,5S)-2-Isopropyl-5-methyltricyclo[3.3.0.$0^{2,7}$]octan-6-one(125)

A solution of the enone 104 (150 mg, 0.84 mmol) in 125 mL of ethyl acetate was irradiated with a 450 W Hg lamp using pyrex filter for 30 min. After the removal of the solvent, the residue was charged on a silica gel column. Elution of the column with 2% ethyl acetate-petroleum ether furnished the desired product 125 (130 mg) in 87% yield.

$[\alpha]_D$	+55.66°	(c, 0.785 ; $CHCI_3$)
IR(neat)	2959,2870,1759cm-^{1}	
^{1}H NMR (200 MHz) (Fig. 20)	δ 2.68 (dd, J_1=14.81 Hz, J_2=2.93 Hz, IH), 2.43 (m,1H)2.40-2.10 (m, 2H), 1.80-1.40 (m, 4H). 1.40-1.10 (m, 1H), 1.20 (s. 3H, -C-C$\underline{H}_3$). 095 (d J=6.86 Hz, 3H. -CH-C$\underline{H}_3$), 0.88 (d, J=6.83 Hz. 3H, -CH-CH_3)	
^{13}C NMR (50.0 MHz) (Fig. 21)	δ 218.4, 70.3. 62.5. 57.8, 49.4, 36.5, 30.4, 26.2, 24.3, 19.1, 17.7, 13.7	

(+)-(lS,5R)-Methyl-6-isopropylidene bicyclo[3-3.0]octan-3-one (135)

To a solution of cyclic ketone 125 (100 mg, 0.56 mmol) in dichloromethane (50 mL) was added few drops of $BF_3.Et_2O$ solution under nitrogen at 0°C. The reaction mixture was quenched after 3 h with saturated $NaHCO_3$ solution, washed with brine and dried. The crude product was charged on a silica gel column and eluted with 3% ethyl acetate-hexane to furnish the bicyclic enone (+)-135 (50 mg) in 50% yield.

$[\alpha]_D$	+171.5°(c. 0.45 ;$CHC1_3$)
IR(neat)	2957, 2926, 2864,1738. cm^{-1}
^{1}H NMR (200 MHz) (Fig. 22)	δ 3.0-2 8 (m, 1H), 2.5-1,0 (scries of m, 8H), 1.70 (s. 3H.-C=C-CH_3), 1.63 (s,3H,-C=C-$\underline{C}H_3$),1.08 (s, 3H,-C-C$\underline{H}_3$)
^{13}C NMR (50.0 MHz) (Fig. 23)	δ 223.5. 138.6, 123.7, 36.6. 52.5, 37.8, 34.9, 29.8, 25.5,21.2,21.0,20.4

(+)-(lS,5S)-Meltiylbicyclo[3.3.0]octan-2,6-dione(126)

Cat ruthenium chloride oxidation of (135)

To the enone 135 (12 mg, 0.07 mmol) in a mixture (1:1:1) of carbometrachloride, acetonitrile and water (3 mL), ruthenium trichloride (5 mg) followed *by* sodium metaperiodate (21 mg, 0.1 mmol) were added. After stirring for 1h, the reaction mixture was diluted with dichloromethane (10 mL) and filtered through a celite pad. The phases were separated and the aq. layer was reextracted with dichloromethane (2 x 10 mL). The combined organic phase was washed with brine and dried. The crude product was passed through a silica gel column with 25% ethyl acetate-hexane to furnish ttedionel26(7mg,76%).

Ozonolysis of(135)

Dry ozone was bubbled into a solution of 135 (42 mg) in dichloromethane (20 mL) at -78°C till the blue colour persisted. Excess of ozone was flushed out by a continuous stream of nitrogen. Dimethyl sulfide (2 mL) was added dropwise at -78°C and the reaction mixture was allowed to warm to room temperature. The crude oily product obtained after the removal of the solvent was charged on a silica gel column. Elution with 25% ethyl acetate-hexane furnished the diketone 126 (28 mg) in 87% yield

b.p.	100°C/1	mm of Hg
$[\alpha]_D$	$+289.45^o$	(c. 1.1; $CHCI_3$)
IR (neat)	2963,2874, 1736 cm^{-1}	
^1H NMR (200 MHz} (Fig. 24)	δ 2.60-2.00 (series of m, 8H), 1.90-1.00 (m, 1H), 1.24(s,3H,-C-C$\underline{H}_3$)	
^{13}C NMR (50.0 MHz) (Fig. 25)	δ 221.4, 220.0, 57.0. 53.8, 37.9, 36.9, 30.6, 21.4(2C)	
Analysis ($C_9H_{12}O_2$)	Calcd.: C, 71.02; H, 7.95	
	Found :C, 70.88; H, 7.90	

(+)-(lR,2R,5S,7R)-,3,3-Dicriloro-2,8,8-trimethyltricyclo[5.1.1.$0^{2,5}$]nonan 4-one (139)[52]

This experiment was performed as described in the general procedure for dichloroketene addition reaction

Reaction of (-)-α-pinene 67 (5.0 g. 30 mmol), zinc dust (4 g. 60 mmol) and trichloroacetyl chloride (5.2 mL. 45 mmol) afforded me (dichloroketene adduct 139 (3.6 g) in 40% yield.

b.p.	150°C/0.5 mm of Hg
$[\alpha]_D$	$+30.1^o$(c,10.0;$CHCl_3$)
IR (neat)	2925. 2875,1800,1460 cm^{-1}
^{1}H NMR (200 MHz)	δ 3.37 (d. J=9.5 Hz, 1H), 2.50-2.00 (m, 4H), 2.00-1.80 (m, 1H), 1.54 (s, 3H, -C-CH_3). 1.34 *(s*, 3H, -C-CH_3). 1.343 (d, J=12.5 Hz, 1H), 1.00 (s, 3H, -C-CH_3)
^{13}C NMR (50.0 MHz)	δ 200.9, 93.1, 55.0, 49.6, 49.3, 39.5, 38.8, 27.9, 27.3,27.1,24.0,21.6

(lR,2S,4S,6R)-4-Methoxy-2,7,7-trimethyltrieyclo[4.1.1.$0^{2,4}$]octane-3-earboxylic acid methyl ester (138a,b)

This experiment was performed as described in the general procedure for dichloroketene adduct rearrangement.

Reaction of the ketene adduct 139 (3.0 g, 12.1 mmol) in 10 mL of methanol with sodium methoxide (5 equiv.) solution in methanol afforded the diastereomeric mixture of cycloprapyl esters 13Sa,b (2.0 g, 73%). Elution with 2% ethyl acetate-hexanc afforded the less polar diastereomeric isomer.

IR(neat) 2900.1718, 1420cm-^{1}

^{1}H NMR (200 MHz) δ 3.67 (s, 3H, -COOCH$_3$), 3.37 (s. 3H, -OCH$_3$). 2.70 (dd, J_1=13.74 Hz, J_2=2.48 Hz., 1H), 2.20-1.50 (m. 5H), 1.42 (s. 1H), 1.24 {s, 3H, -C-CH$_3$), 1.23 (s, 3H, -C-CH$_3$). 1.01 (s, 3H, -C-CH$_3$)

Further elution of the column with the same eluent afforded the more polar diastereotneric isomer of the cyclopropyl ester.

IR(neat) 2900, 1715,1420cm-^{1}

^{1}H NMR(200MHz) δ 3.66 (s, 3H, -COOCH$_3$), 3.29 (s, 3H, -OCH$_3$), 2.20-1.70 (m, 5H), 1.60 (s, 1H), 1.34 (s, 3H, -C-CH$_3$), 1.27 {s, 3H, -C-CH$_3$), 0.99 (s. 3H, -C-CH$_3$), 0.99(d,J-10.98 Hz. 1H)

^{13}C NMR (25.0 MHz) δ 171.9, 63.4, 56.6, 51.6, 45.3, 41.7, 39.8, 37.5, 35.9, 29.9, 26.4, 26.3, 20.2

(lR,2S,4S,6R)-(4-Methoxy-2,7,7-trimethyltricyclo[4.1.1.0^{2,4}]oct-3-yDmethanol (140)

The experiment was performed as described in the general procedure for DIBAL-H reduction.

Reaction of the cydopmpyl ester 138a,b (1.5g, 6.0 mmol) with DIBAL-H afforded the diastcreomeric mixture of cyclopropyl carbinols 140 (900 mg) in 72% yield.

IR(neat) 3375.2922, 1460, 1232, 1141, 1049cm^{-1}

(lR,2R,5R)-3-Methoxy-4,6,6-trimethyl-4-vinyl-bicyclo[3.1.1]hept-2-ene (141)

To the mixture of cyclopropyl carbinols 140 (210 mg, 1 mmol) in dry pyridine (10 mL) was added methanesulphonyl chloride (1.2 equiv.) at 0°C. The reaction mixture was stirred for 30 min., quenched with water and acidified with dilute hydrochloric acid. The reaction mixture was extracted with ether (50 mL x 3) and the combined ethereal extract was washed and dried over anhydrous : sodium sulphate. After the removal of the solvent, the crude reaction mixture was filtered through a small pad of silica gel to give the end-ether 141 (813 mg) in 89 % yield.

IR(neat) 2975, 2900,1640,1250,920. 780 cm^{-1}

^{1}H NMR (200 MHz) δ 5.77 (dd, J_1=12.5 Hz, J_2=10.7 Hz, 1H, -CH=C$\underline{H}_2$), 5.04 (d, J=7.33 Hz. 1H, -CH-C$\underline{H}$=C-OCH$_3$), 4.99 (dd. J_1=10.7 Hz. J_2=1.65 Hz, 1H, -CH=C$\underline{H}_2$). 4.86 (dd, J_1=17.50 Hz, J_2=1.58 Hz, 1H, -CH=C$\underline{H}_2$), 3.55 (s, 3H, -OC$\underline{H}_3$), 2.30-2.18 (m, 1H), 2.15-2.00 (m, 1H), 1.87(t,J=6.1 Hz, 1H),

1.32 (s. 3H, -C-C$\underline{H}_3$), 1.22 (s, 3H, -C-C$\underline{H}_3$), 1.05 (s, 3H, -C-C$\underline{H}_3$)

^{I3}C NMR (25.0 MHz) δ 157.3, 146.3. 113.1. 100.8. 54.5, 51.7. 48.1, 42.4,40.0.32.4,27.7.24.5,21.9

(-)-(1R,2R,5R)-2,6,6-Trimethyl-2-vinylbicyclo[3.1.1]hept-3-oiie(68)

To the enol-ether 141 (813 mg, 4.23 mmol) dissolved in ether (50 mL) was added a few drops of aq.35% perchloric acid at 0°C. The reaction mixture was allowed to warm to room temperature and stirring continued for 30 min. The reaction mixture was then quenched with brine and the ethereal layer was washed and dried Removal of the solvent and chromatograhic separation on a silica gel column by eluting with 2% ethyl acetate-hexane furnished the a-vinyl ketone 68 (490 mg) in 65% yield

b.p. 100°C/1.0 mm of Hg

$[\alpha]_D$ -120.7° (c, 0.81 ;$CHC1_3$)

IR (neat) 2900, 1720,1640,1060,1000, 920 cm^{-1}

^{1}H NMR(200MHz) {Fig. 26) δ 5.63 (dd, J_1=17.5 Hz, J_2=10.7 Hz, 1H, -$\underline{C}$H=CH_2),5.03 (d, J=9.95 Hz, 1H, -CH=C$\underline{H}_2$), 4.84 (d. J=18.24 Hz, 1H. -CH=C$\underline{H}_2$), 2.80-2.30 (m, 3H), 2.20-1.90 (m, 2H), 1.60-1.40 (m, 1H), 1.36 (s, 3H, -C-C$\underline{H}_3$), 1.26 (s. 3H, -C-C$\underline{H}_3$),0.95 (s,3H,-C-C$\underline{H}_3$)

^{I3}C NMR(25.0 MHz) δ 214.8, 143.3, 113.4, 56.8, 48.7. 44.8, 39.5, 38.7, (Fig.27) 31.0.27.4, 25.5, 23.0

Analysis ($C_{12}H_{18}O$) Calcd.: C, 80.85; H, 10.18

Found :C, 80.51; H, 10.22

(lR,2R,5R)-3-Ethynyl-2,6,6-trimethyl-2-vinylbicylo[3.1.l]heptan-3-ol (142)

To a 10 mL of anhydrous dioxane saturated with acetylene, was added with stirring 1 g of lithium acetylide-ethylenediamine complex, Mowed by α-vinyl ketone 68 (900 mg, 5 mmol) in anhydrous dioxane (10 mL) over a period of 30min. The bubbling of acetylene gas was continued for another 30 min. The reaction mixture was stirred for 24 h under nitrogen atmosphere and quenched with saturated solution of ammonium chloride. The layers were separated and the aqueous layer was extracted several times with ether. The organic phases were dried over sodium sulphite and concentrated under vacuum. The crude reaction mixture, thus obtained, was chronlatographed over silica gel with 2% ethyl acetate and hexane as eluent to give the ethynyl carbinol 142 (280 mg) in 27% yield.

IR (neat) 3400, 3306, 3084, 2922,922, 738 cm^{-1}

^{1}H NMR(200MHz) δ 6.304.80 (series of m, 3H), 4.40 (s, 1H), 2.60-1.00 (m, 6H), 2.59 (s, 1H, -C=C<u>H</u>), 1.37 (s, 3H, -C-CH_3), 1.32 (s, 3H, -C-C<u>H_3</u>), 1.11 (s, 3H, -C-C<u>H_3</u>)

(lR,2R,5R)-2,6,6-Trimelhyl-2,3-divinylbiclo[3.1.1]heptan.3.ol(69)

To a mixture of alcohols 142 (70 mg, 0.03 mmol) was added 5 mg of Lindlar catalyst in 5 rnL of dry ethyl acetate and stirred at room temperature under 1 atm. of hydrogen. After UK complete consumption of the starting material, UK solution was filtered and dried over sodium sulphate. The solvent was removed in vaeuo and the residue was passed through a small column of silica gel to give the pure 1,2-divinyl alcohol 69 (60 mg. *85%k).*

1R (neat) 3383, 2926, 2856,1049,922, 758 cm^{-1}

^1H NMR (200 MHz) δ 6.02 (dd, J_1=l6.7 Hz, J_2=10.5 Hz, 1H), 5.94 (dd, Jpl7.4 Hz. J_2=11.0 Hz. 1H). 5.37 (dd. JpI6.9 Hz, J_2=1.7 Hz, 1H), 5.17 (dd, J_1=10.51, J_2=1.7 Hz, 1H), 5.02 (dd, J_1=l 1,02 Hz, J_2=1.27 Hz, 1H), 4.87 (dd. J_1=17.77 Hz, J_2=1.17 Hz, 1H) [olefinic protons], 2.96 (s, 1H, -OH), 2.30-1.80 (m, 3H), 1.80-1.00 (m, 3H), 1.32 (s, 3H, -*C-CH*$_3$), 1.13 (s, 3H, -C-C$\underline{H}_3$), 1.08 (s, 3H, -C-C$\underline{H}_3$)

(+)-(lS,4R)-(4-Isopropy]-l-methyl-2-oxocyclohexyl)acetic acid methyl ester (149)

Into a 50 mL RB flask, fined with a dry nitrogen inlet, septum and mercury seal was placed sodium iodide (150 g, 1.0 mmol) and freshly distilled chlorotrimethylsilane (0.12 rnL, 1.0 mmol) in 5 mL of dry acetonitrile. The

cyclopropyl ester mixture 108a,b (100 mg. 0.41 mmol) in acetonitrile (3 mL) was added to UK mixture at 0°C and stirred for 30min. at the same temperature. The reaction mixture was diluted with ether (50 mL) and washed successively with aq. sodium thiosulphate solution and brine. Drying and removal of solvent gave a crude product which was charged on a silica gel column. Elution with 3% ethyl acelate-hexane furnished the keto ester 149 (60 mg) in 64% yield

b.p.	120-126°C/0.2mm
$[\alpha]_D$	+80.5° (c, 0.86 ; $CHC1_3$)
IR (neat)	2957, 2872, 1740, 1707, 1273, 1197, 1130, 1016
^{1}H NMR(200 MHz) (Fig. 28)	δ 3.66 (s, 3H, -COOC$\underline{H}_3$), 2.80-1.30 (series of m, 10H), 1.23 (s, 3H, -C-C$\underline{H}_3$). 0.91 (d, 1=6.54 Hz, 6H, -CH-C$\underline{H}_3$)
^{13}C NMR (50.0 MHz) (Fig. 29)	δ 214.1, 172.3, 51.2, 46.3, 44.8, 42.2, 41.7, 36.6, 32.5, 24.5, 23.6, 19.4, 19.2

(lR,4R,6S}-3-Isopropyl-l-niethoxy-6,7-dimethylJbicyclo[4.l.0]heptane-7-earboxylic acid methyl ester (150)

To a solution of n-butyl lithium (6 mL in hexane, 9 mmol), cooled to -78°C was added diisopropyl amine (0.7 mL, 5.28 mmol) under nitrogen. After stirring for 30min. dry tetrahydrofuran (10 mL) followed by cyclopropylesters 108a,b (1 g, 4.4 mmol) in tetrahydrofuran (5mL) were

added The reaction mixture was stirred for 30 mm. at the same temperature and then methyl iodide (2 mL) was introduced into the flask. Reaction was quenched by adding brine and extraction was done with ether (3 x 50 mL). The combined organic phase was washed dried and concentrated to yield an oily residue, Column chromatrography on silica gel column and elution with 2% ethyl acetate-hexane afforded the methylated product 150 (720 mg) in 70% yield.

IR (neat) 2968, 2874. 1709 cm^{-1}

^1H NMR (200 MHz) δ 3.66 (s, 3H, $-COOH_3$), 3.32 (s. 3H. $-OCH_3$), 2.50-1.00 (m. 8H). 1.29 (s, 3H. $-C-CH_3$), 0.884 (s, 3H, $-C-CH_3$), 0.882 (d, J=10.0 Hz, 6H, $-CH-CH_3$)

(+)-2R-(4R-Isopropyl-lS-methyl-2-oxocyclohexyl)propionic acid methyl ester (148)

Into a 50 mL RB flask, fitted with a dry nitrogen inlet, septum and mercury sea! was placed sodium iodide (750 mg, 5.0 mmol) and freshly distilled chlorotrimethylsilane (0.6 mL, 5.0 mmol) in 5 mL of dry acetonitrile. The cyclopropyl ester 150 (600 mg, 2.36 mmol) in 3 mL of acetonitrile was added to the mixture at 0^oC and stirred for 30 min. at the same temperature. The reaction mixture was diluted with ether (100 mL), washed successively with aq. sodium thiosulphate solution and brine. Drying and removal of solvent gave a crude product which was charged on a silica gel column.

Elution with 3% ethyl scetate-hexane furnished the keto ester 148 (340 mg) in 60% yield.

b.p.	120-126°C/0.2mm
$[\alpha]_D$	+62.8° (c, 2.27 ;$CHCI_3$)
IR(neat)	2957, 2874, 1736, 1705, 1462,1209cm^{-1}
^{1}H NMR (200 MHz) (Fig. 30)	δ 3.65 (s, 3H), 3.10-2.90 (m, 1H), 2.50-1.30 (m, 9H),1.15 (d, J=7.54 Hz. 3H, -CH-C$\underline{H}_3$), 1-13 (s, 3H, -C-CH_3), 0.91 (d, J=6.80 Hz, 3H, -CH($C\underline{H}_3)_2$), 0.90 (d, J=6.6 Hz, 3H, -CH-C$\underline{H}_3$)
^{13}C NMR (50.0 MHz) (Fig, 31)	δ 215.3, 176.2, 51.3, 48.7, 44.7, 43.6, 42.0, 32.6, 32.4, 24.6, 21.9, 19.4, 19.3, 11.6

(+)-(3R,3a,S,6R,7aS)-6-Isopropyl-7a-methoxy-3,3a-dimethylhexahydrobenzofuran-2-one (151)

Further elusion of the column with 10% ethyl acetate-hexane afforded the methoxy lactone 151 (120 mg) in 21% yield as aside product.

b.p.	140°C/0.2 mm
$[\alpha]_D$	+39.7° (c, 2.34 ; $CHC1_3$)
IR (neat)	2940, 2870,1784,1464,1196,1123 cm^{-1}
^{1}H NMR (200 MHz) (Fig.32)	δ 3.31 (s, 3H, -OC$\underline{H}_3$), 3.00-2.80 (m, 1H), 2.40-2.20 (m, 1H), 1.70-0,70 (m, 7H), 1.06 (s, 3H, -C-C$\underline{H}_3$), 1.02 (d, J=7.42 Hz, 3H, -CH-C$\underline{H}_3$), 0.88 (d,

J=6.75 *Hz*, 3H, -CH-C$\underline{H}_3$). 0.87 (d. J=6.75 Hz, 3H. -CH-C$\underline{H}_3$)

^{13}C NMR (50.0 MHz) (Fig. 33) δ 179.3. 109.4, 49.4, 45.3, 45.0, 396, 32.2, 32.1, 30.3,23.8, 19.6, 19.4, 16.7, 7.0

Analysis ($C_{14}H_{24}O_3$) Calcd.: C. 69.96; H, 10.12
Found :C, 69.85; H, 10.07

(+)-(3R,3aS,6R,7aS)-7a-Hydroxy-6-isopropyl-3,3a-dimetlhezahydro-benzofuran-2-one (152)

To a solution of sodium bis(trimethylsilyl)amide (generated from sodamide and hexamethyldisilazane) (0.18 mmol) in 2 mL of dry dimethoxyethane was added a solution (16 mg, 0.06 mmol) of the keto ester 148 in 2 mL of dry dimethoxyethane and refluxed under an atmosphere of dry nitrogen for 1 h. The reaction mixture was cooled and pouted into a solution of glacial acetic acid in 10 mL ice water. The resultant mixture was thoroughly extracted with ether. The ethereal extracts were combined and washed with water, 10% sodium bicarbonate solution, brine and dried over sodium sulphate. Removal of the solvent afforded a product 152 (14 mg) in 92% yield, whose spectral data was inagreement with the formation of the hydroxy lactone 152.

$[\alpha]_D$ +19.05° (c, 0.58 ; $CHC1_3$)

IR(neat) 3420, 2959, 2874,1755,1466, 1373 1337, 1219 cm^{-1}

^{1}H NMR (200 MHz) δ 3.00-2.80 (m, 2H), 2.20-2.00 (m, IH), l.80-1.00 (m, 7H). 1.14 (s, 3H, -C-C$\underline{H}_3$). 1.07 (d. J=7.63 Hz, 3H. -CH-C$\underline{H}_3$), 0.88 (d, J=6.77 Hz, 6H, -CH-C$\underline{H}_3$)

^{13}C NMR (50.0 MHz) δ 179.3, 107.2,45.4.44.4.40.0, 36.2. 32.0. 31.9, 2.1, 19.5(2C). 16.7,6.9

(lR3R,6S)-7-Allyl-3-isopropyl-l-methoxy-6-methylbicyclo[4.1.0]heptane-7-carboxylic acid methyl ester (162)

To a solution of n-butyl lithium (6 mL in hexane, 9 mmol), cooled to -7S°C was added hexarnethyldisilzane (1.9 mL, 9 mmol) under nitrogen. After stirring for 30 min. dry THF (10 mL) followed by cyclopropylester mixture 108a,b (1.8 g, 7.5 mmol) in tetrahydrofuran (5 mL) were added. The reaction mixture was stirred for 30 min. at the same temperature and then allyl bromide (1.3 mL, 15 mmol) was introduced into the flask. Reaction was quenched by adding brine and extraction was done with ether (3 x 100 mL). The combined organic phase was washed, dried and concentrated to yield an oily residue. Column chromatography of the crude reaction mixture on silica gel column afforded the alkylated product 162 (1.9 g) in 90% yield.

n.p. 140°C/0.5mm of Hg

IR(neat) 3076, 2951, 2876, 1730, 1639. 1466, 1203, 1099, 997,914 cm^{-1}

^{1}H NMR (200 MHz) δ 6.00-5.60 (m, 1H, -CH=C$\underline{H}_2$), 5.20-4.90 (m, 2H. (Fig. 35) -C$\underline{H}$=CH$_2$), 3.64 (s, 3H, -COOC$\underline{H}_3$), 3.35 (s, 3H,

OCH_3), 2.70-2.30 (m, 3H). 2.10-0.50 (m, 7H). 1.1S (*s*. 3H, -C-C$\underline{H}_3$). 0.85 (d. J=6.73 Hz, 3H, -CH-C$\underline{H}_3$), 0.84 (d, J=6.6 Hz, 3H, -CH-C$\underline{H}_3$)

^{13}C NMR (50.0 MHz) (Fig. 36) δ 171.6, 136.1, 116.3,66.9, 54.5. 51.2. 39.9. 39.4, 32.8(2C), 30.3, 28.8, 28.3, 25.8, 99.9, 19.6, 17.3

Analysis ($C_{17}H_{28}O_{3)}$ Calcd.: C, 72.82; H, 10.06
Found : C, 72.88; H, 10.10

(+)-2-(4(R)-Isopropyl-l(S)-methyl-2-oxocyclohexyl)pent-4-enoic acid methyl ester (157)

Into a 50 mL RB flask fitted with a dry nitrogen inlet, septum and mercury seal was placed sodium iodide (450 mg, 3.0 mmol) and freshly distilled chlorotrimethylsilane (0.38 mL, 3.0 mmol) in 5 mL of dry acetonitrile. The cyclopropyl ester 162 (380 mg, 1.35 mmol) in 5 mL of acetonitrile was added to the mixture at 0°C and stirred for 30 min. at the same temperature. The reaction mixture was diluted with ether (50 mL) and washed successively with aq. sodium thiosulphate solution and brine. Drying and removal of solvent gave a crude product which was charged on a silica gel column. Elution with 3% ethyl acetate-hexane furnished the keto ester 157 (228 mg) in 63% yield

b.p. 130°C/0.5 mm of Hg

$[\alpha]_D$ $+47.2^o$(c,0.58 ; $CHC1_3$)

IR(neat) 3079, 2926, 2854, 1734, 1707, 1641, 1462, 1435, 1194, 1172, 993, 914cm^{-1}

^{1}H NMR (200 MHz) (Fig. 37) δ 6.10-5.70 (m, IH, -CH=C$\underline{H}_2$), 5.20-4.90 (m, 2H, -CH=C$\underline{H}_2$). 3.63 (s. 3H, -COOC$\underline{H}_3$), 3.00-1.00 (m. 11H), 1.25 (s, 3H, -C-C$\underline{H}_3$), 0.89 (d, J=6.70 *Hz*, 6H, -CH-C$\underline{H}_3$)

^{13}C NMR (50.0 MHz) (Fig, 38) δ 214.9. 175.4, 136.3, 116.3, 51.1, 50.6, 49.6, 45.*2*,41.9, 34.6, 32.5. 32,3, 24.4, 20.1, 19.8, 19.5

Analysis ($C_{16}H_{26}O_3$) Calcd.: C, 72.14; H, 9.84
Found :C, 72.25; H, 9.89

Further elution of the column with 15% ethyl acetate-hexane afforded the hydroxy lactone 163 (76 mg) in 22% yield as a side product.

b.p. 160°C/0.5mm of Hg

$[a]_d$ +19.05°(c,1.17;CHCl3)

IR(neat) 3424, 3081, 2959, 2878, 1755, 1641. 1123, 924

^{1}H NMR (200 MHz) (Fig. 39) δ 6.10-5.80 (m, 1H, -CH=C$\underline{H}_2$), 5.20-5.00 (m, 2H, -CH=CH_2), 3.00-2.90 (m, 1H), 2.60-2.40 (m, 1H), 2.30-1.90 (m, 3H), 1.80-1.00(m, 7H), 1.19 (s, 3H, -C-C$\underline{H}_3$), 0.89 (d, J=6.74 Hz, 6H, -CH-C$\underline{H}_3$)

^{13}C NMR (50.0 MHz) (Fig. 40) δ 6 214.8, 178.5, 136.3, 116.4, 107.1, 50.2, 44.9, 40.0, 35.8,32.2, 31.9, 28.6, 23.9,19.5(2C)

Analysis ($C_{15}H_{24}O_3$) Caled.: C. 71 39; H, 9 59

Found: C, 71.52; H, 9.68

2-(4(R)-Isopropyl-l(S)-methyl-2-oxocyclohexyl)-4-oxopentanoic add methyl ester (164)

To a stirred mixture of palladium chloride (15 mg), cuprous chloride (150 mg) in dimethyl formamide (2 mL) and water (2 mL) under oxygen atmosphere was added the aliylated ester 157 (80 mg, 0.3 mmol). After stirring for 4h, the reaction mixture was poured into water (10 mL) and extracted with ether (3 x 25 mL). The combined ethereal extract was washed, dried and concentrated. The crude oily product was charged on silica gel column. Elution with 5% ethyl acetate-hexane mixture furnished the product 164 (60 mg) as a diastereomeric mixture in 70% yield.

IR(neat) 2957,2874, 1722(br), 1183,1041 cm^{-1}

(+)-(8aS,6R)-6-Isopropyl-8a-methyl-3-oxo-l,2,3,5,6,7,8,8a-octahydro-naphthalene-1-carboxylic acid methyl ester (158)

Into a 50 mL RB flask, fitted with Dean-Stark water separator and reflux condenser, the dione 164 (200 mg, 0.71 mmol) and p-tolucnesulfonic acid (1.2 equiv.) in dry benzene (25 mL) were placed and the contents were refluxed for 6h. The reaction mixture was diluted with benzene (50 mL) washed with saturated sodium bicarbonate, water and dried. The crude product obtained after removal of solvent was charged on a silica gel column.

Elution with 20% ethyl acetate-hexane afforded the enone 158 (84 mg) in 45% yield.

b.p.	165-170°C/0.5 mm of Hg
$[\alpha]_D$	+118.66° (c, 0.60 ; $CHCI_3$)
IR(neat)	2959, 2870, 1732, 1667, 1614, 1207cm^{-1}
^1H NMR(200MHz) (Fig. 41)	δ 5.80 (s, 1H, -C=C<u>H</u>-CO-), 3.72 (s, 3H, -<u>C</u>OOC<u>H</u>$_3$), 3.00-2.70(m, 2H),2.60-1.10(m, 9H), 1.20 (s, 3H, -C-C<u>H</u>$_3$), 0.92 (d, J=5.95, 6H, -CH-C<u>H</u>$_3$)
^{13}C NMR (50.0 MHz) (Fig. 41)	δ 197.4, 172.5, 169.4, 124.5, 51.8, 51.4, 44.9, *39.7,38.6,*36.7 (2C),32.7, 24.9,19.7,19.5,18.3
Analysis ($C_{16}H_{24}O_3$)	Calcd.: C, 72.69; H, 9.15 Found:C,72.81;H,9.19

(6R,8aS)-6-lsopropyl-8a-methyl-3-oxo-l,2,3,5,6,7,8,8a-oclahydro-naphthale-1-carboxylic acid (165)

To a solution of the ester 158 (20 mg, 0.075 mmol) in 2 mL of methanol was added 5 mL of 5% aq. sodium hydroxide and the mixture was stirred for 3h. The reaction mixture was poured into water and extracted with hexane to remove the less polar impurities. The aq. phase was acidified with dil. hydrochloric acid (pH 3-4) and extracted with ethyl acetate (2 x 25 mL). UK combined ethyl acetate layer was washed with water (25 mL). brine and

dried. Removal of the solvent under reduced pressure yielded crude acid 165 (18 mg) in 95% yield.

IR(neat) 3200(br), 2971, 1712, 1393, 1283cm^{-1}

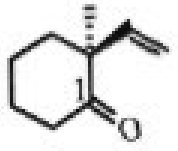
(4s,7R)-4-Hydroxymethyl-7-isopropyl-2,3,4,4a,5,6,7,8-octahydro-naphthalen-2-ol (167)

To a suspension of excess of lithium aluminium hydride (10 rag) in dry ether (10 mL) cooled to 0°C, was added the enone 158 (25 g, 0,094 mmol) in ether (5 mL) under nitrogen atmosphere. The reaction mixture was stirred for 1 h till the starting ester was fully consumed. The reaction mixture was then quenched with a saturated solution of sodium sulphate and extracted with ether (2 x 25 mL). The ethereal layer was dried over sodium sulphate and concentrated to give a mixture of alcohols 167 (21 mg) in 95% yield.

IR (neat) 3337, 2937, 1057,1003 cm^{-1}

Spectra

Fig.1


1
O

1.11
-CH3
17.7 Hz
5.93
10.6 Hz
7.0
6.0
5.0
4.0
3.0
2.0
1.0

Fig.2

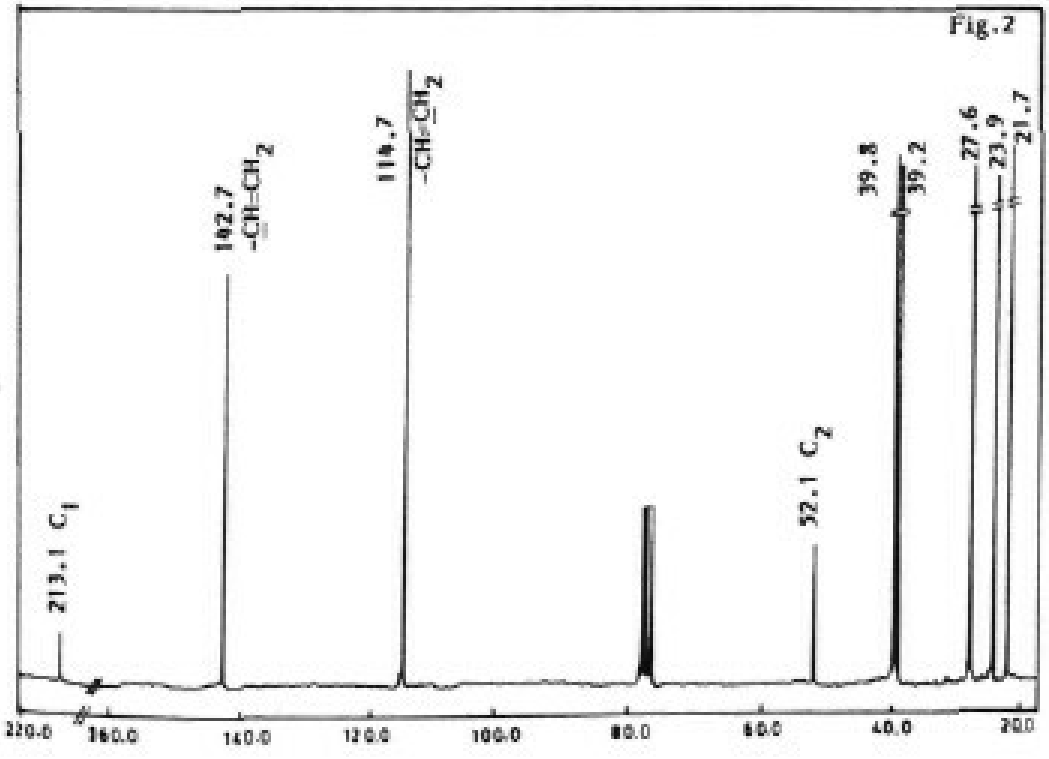

213.1 C1
142.7
-CH=CH2
114.7
-CH=CH2
32.1 C2
39.8
39.2
27.6
23.9
21.7
220.0
180.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0

Fig.3

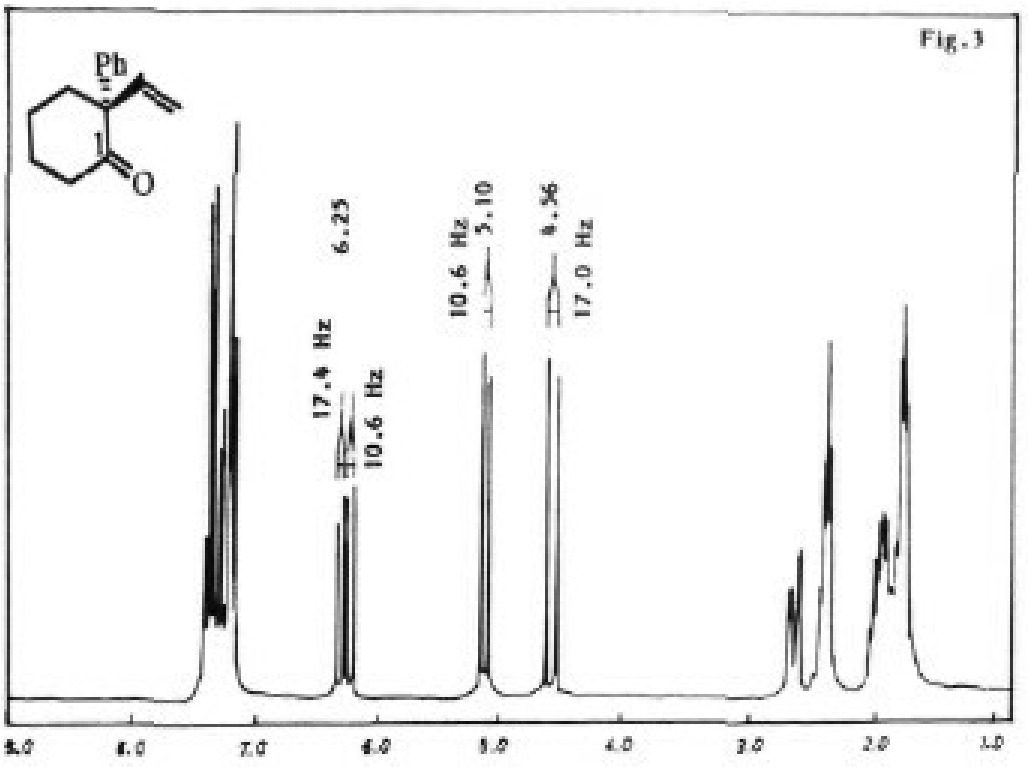

Ph
O
6.25
17.4 Hz
10.6 Hz
10.6 Hz
5.10
4.36
17.0 Hz
8.0
6.0
7.0
4.0
5.0
4.0
3.0
2.0
1.0

Fig.4

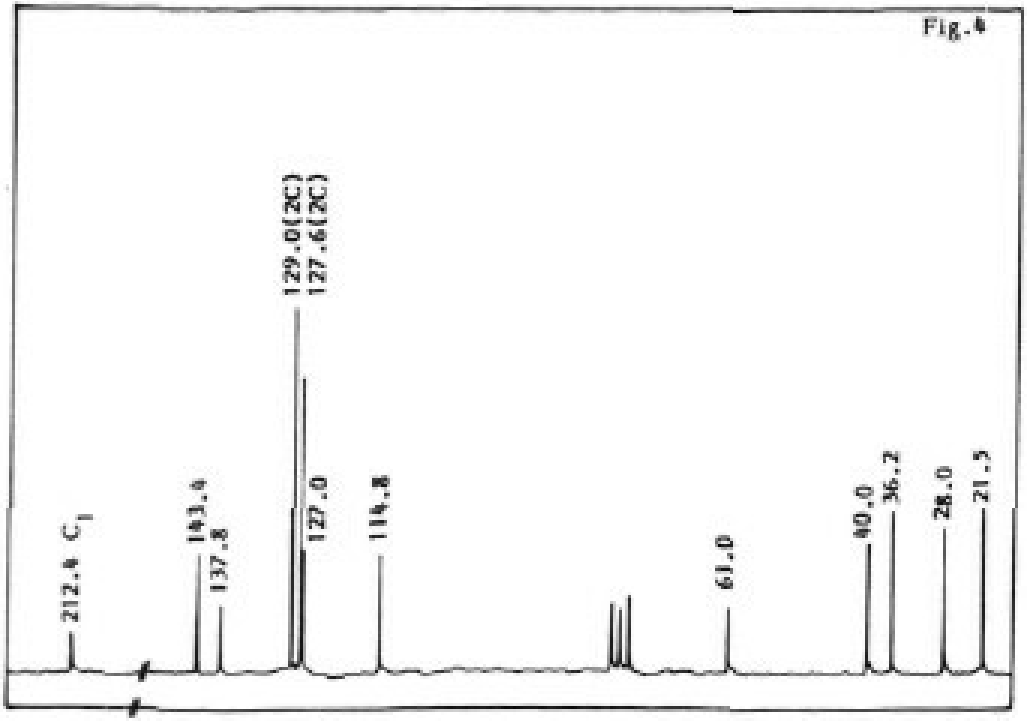

212.4 C1
143.4
137.8
129.0(2C)
127.6(2C)
127.0
114.8
61.0
40.0
36.2
28.0
21.5

Fig. 5

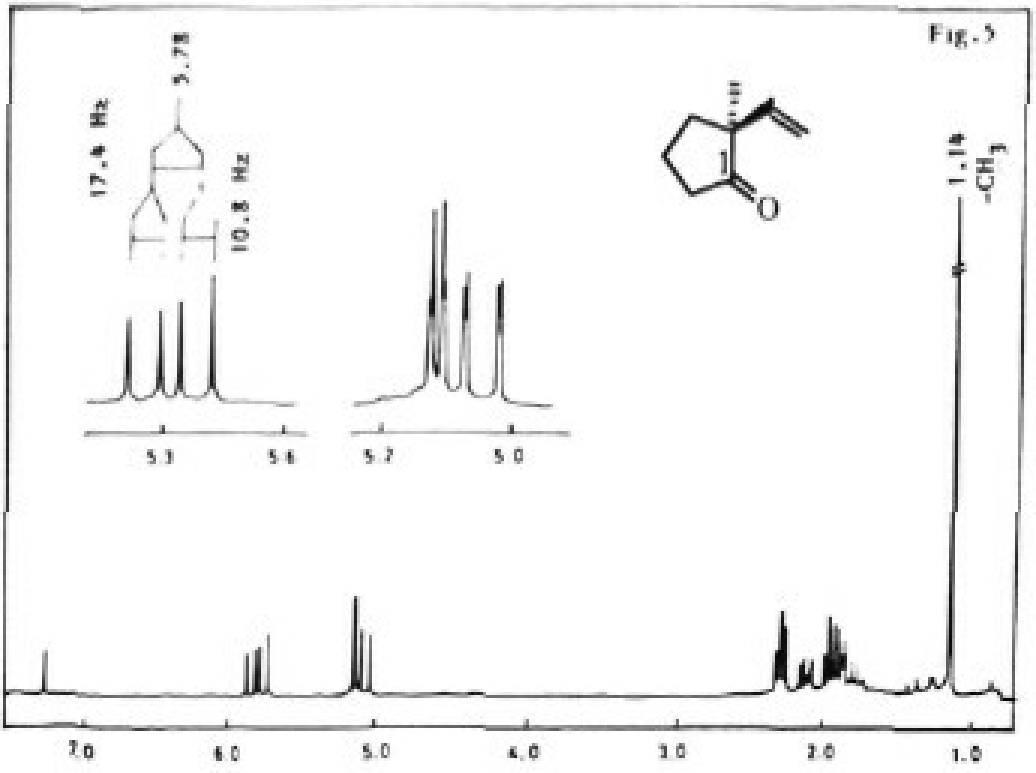

17.4 Hz
5.78
10.8 Hz
5.3
5.6
5.2
5.0
1.14
-CH3
O
7.0
6.0
5.0
4.0
3.0
2.0
1.0

Fig. 6

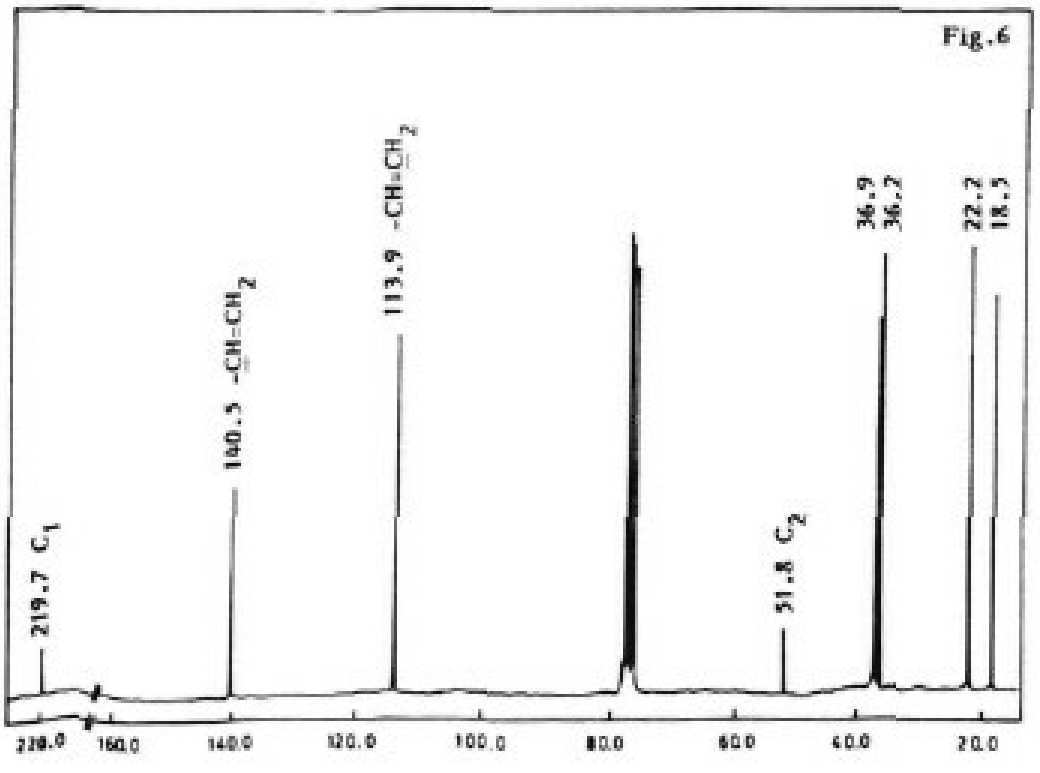
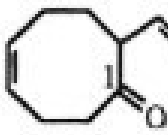

219.7 C1
160.3 -CH=CH2
113.9 -CH=CH2
31.8 C2
36.9
36.2
22.2
18.3
220.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0

Fig.7


1
O

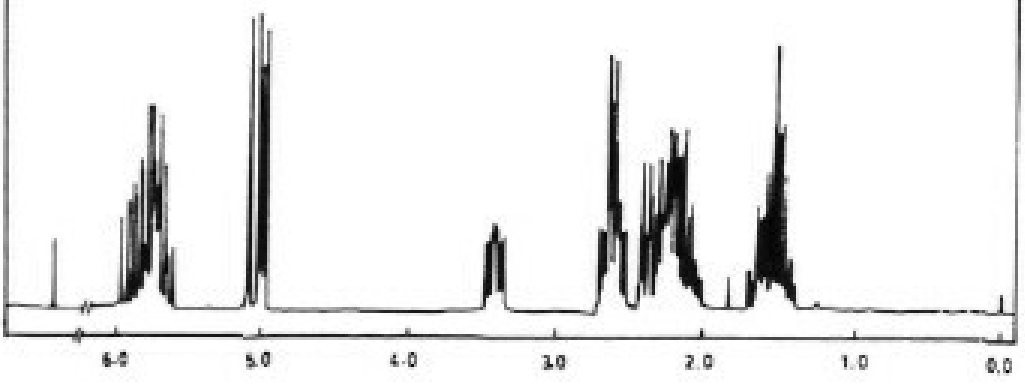
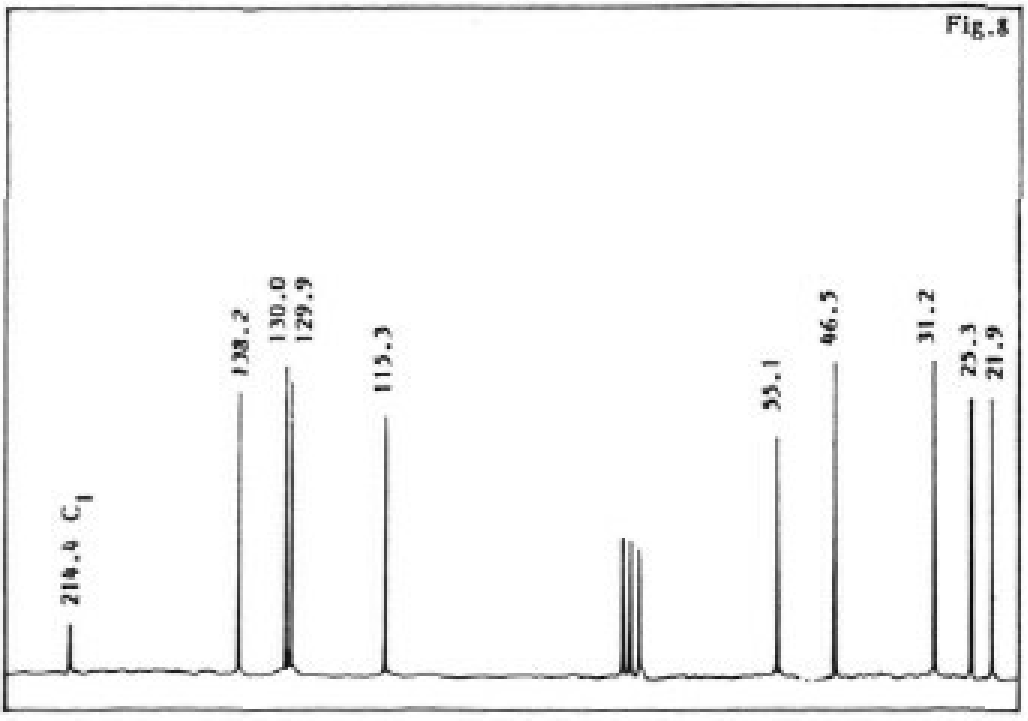

6.0
5.0
4.0
3.0
2.0
1.0
0.0

Fig.8


219.4 C1
138.2
130.0
129.9
115.3
33.1
46.3
31.2
25.3
21.9

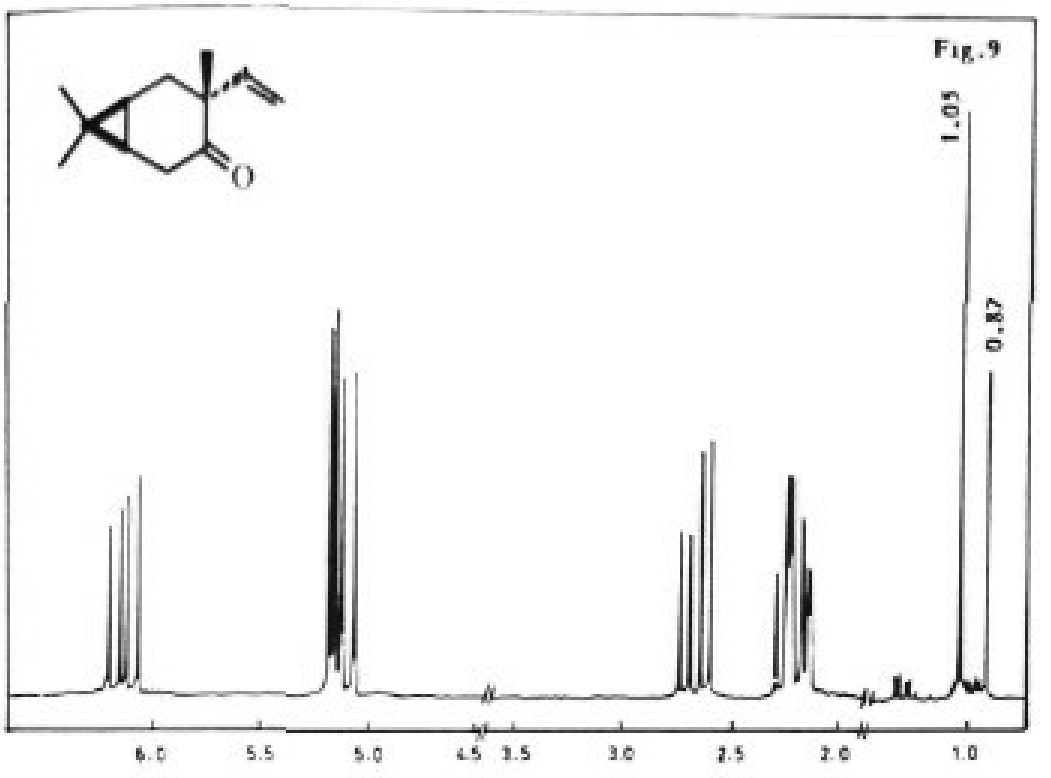


Fig.9
O
1.05
0.87
6.0
5.5
5.0
4.5
3.5
3.0
2.5
2.0
1.0

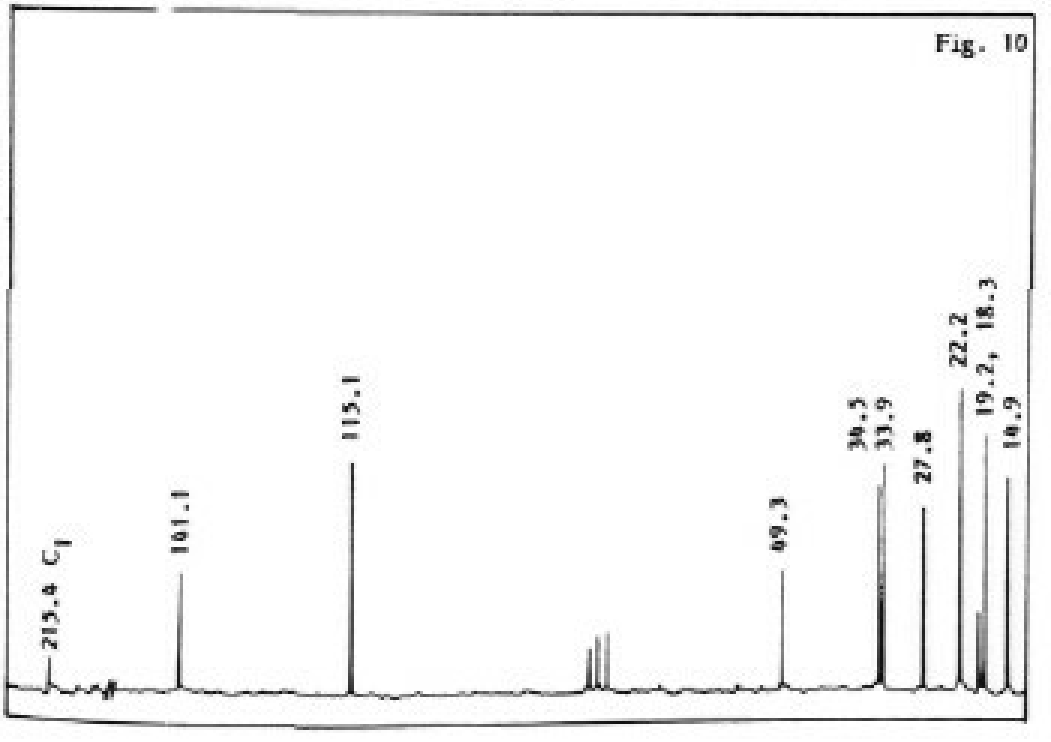


Fig. 10
213.4 C1
101.1
115.1
69.3
36.5
33.9
27.8
22.2
19.2, 18.3
14.9

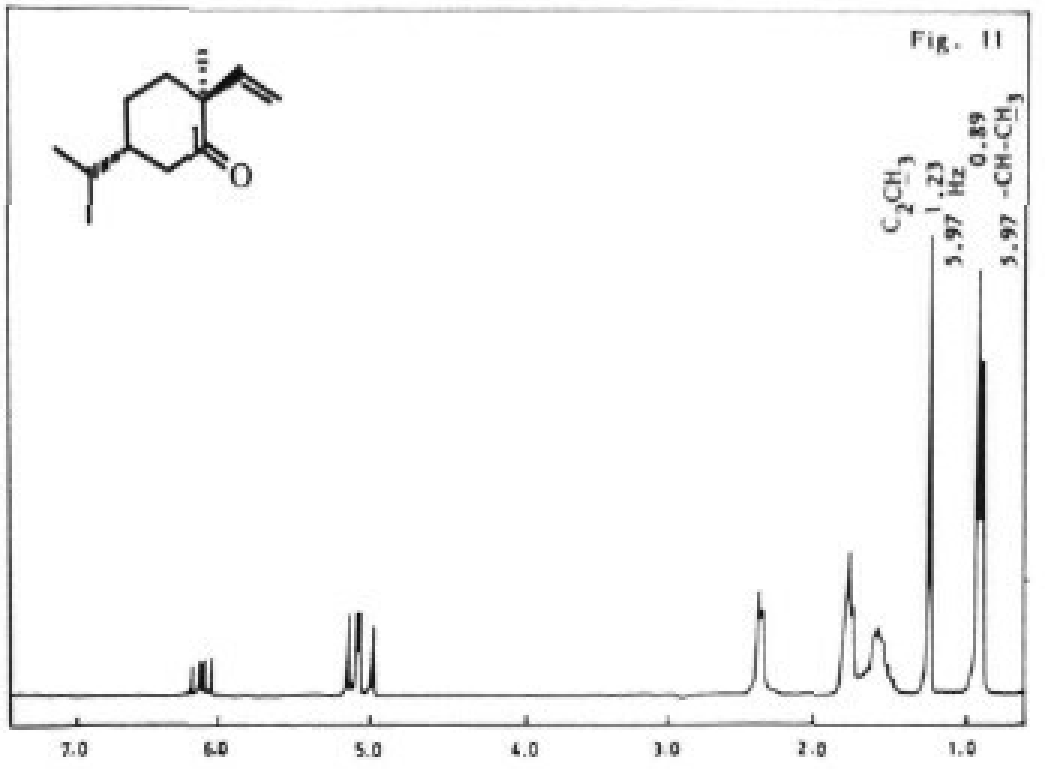


Fig. 11
O
C_2CH_3
1.23
Hz
5.97
0.89
5.97
$-CH-CH_3$
7.0
6.0
5.0
4.0
3.0
2.0
1.0

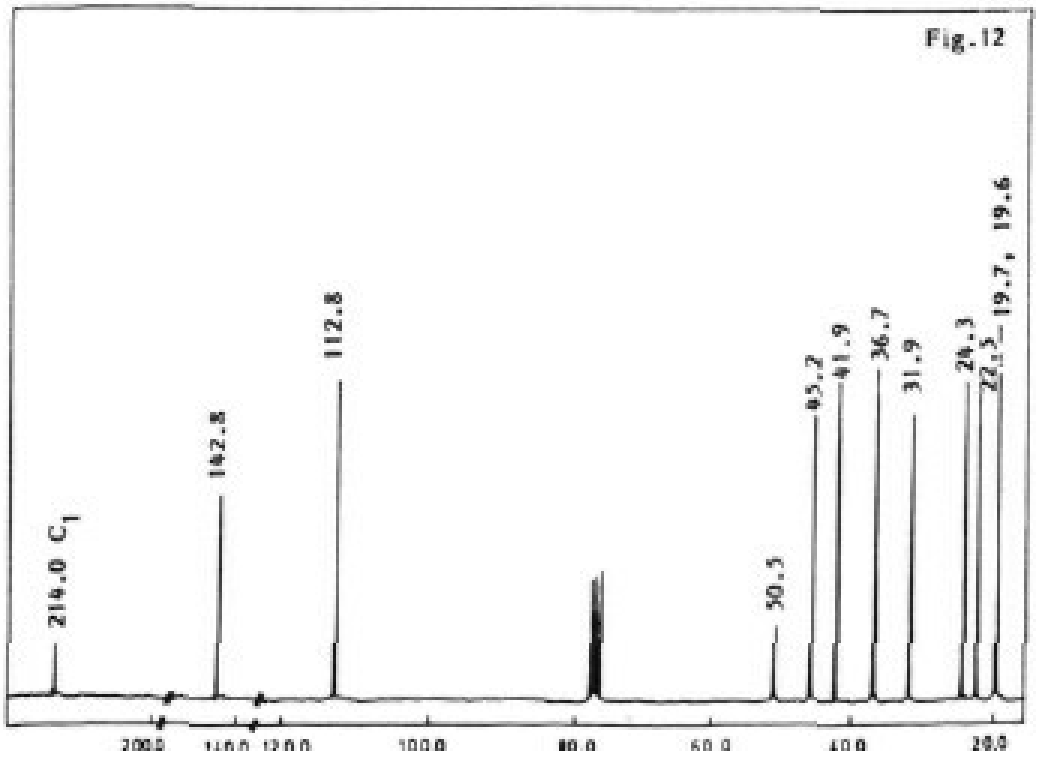


Fig.12
219.0 C_1
142.8
112.8
50.3
45.2
41.9
36.7
31.9
24.3
22.2
19.7, 19.6
200.0
100.0
80.0
60.0
40.0
20.0

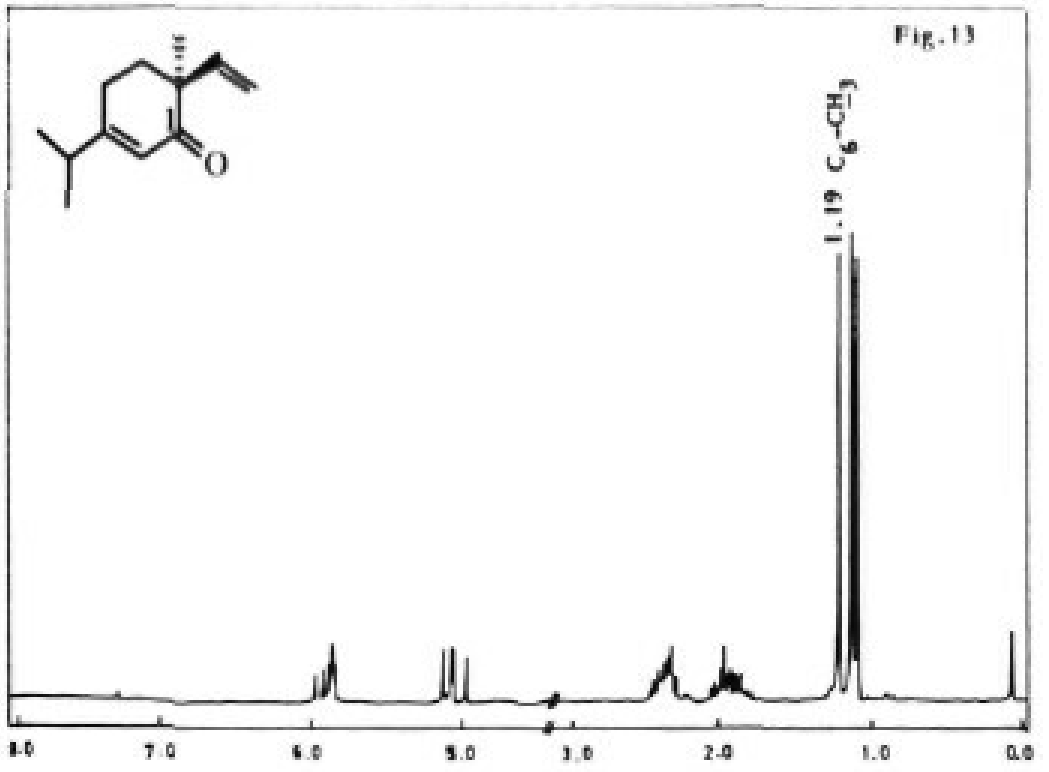


Fig. 13
O
1.19 C_8-CH_3
8.0
7.0
6.0
5.0
3.0
2.0
1.0
0.0

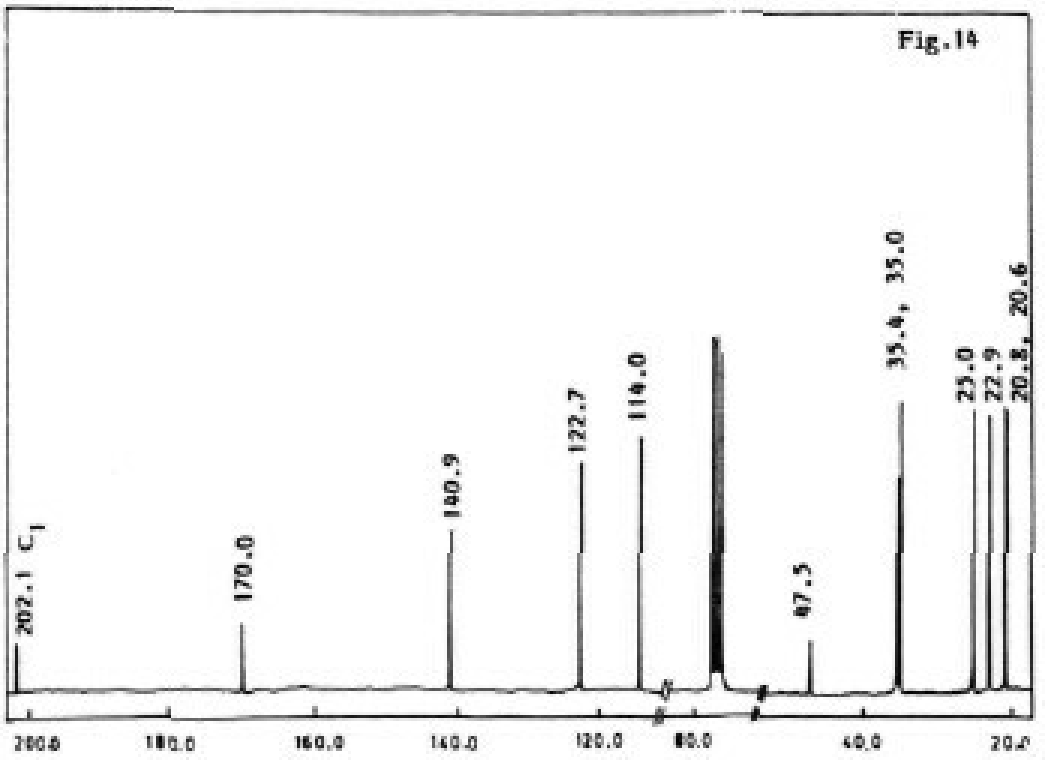


Fig. 14
202.1 C_1
170.0
140.9
122.7
114.0
47.5
35.4, 35.0
23.0
22.9
20.8, 20.6
200.0
180.0
160.0
140.0
120.0
80.0
40.0
20.0

Fig. 15

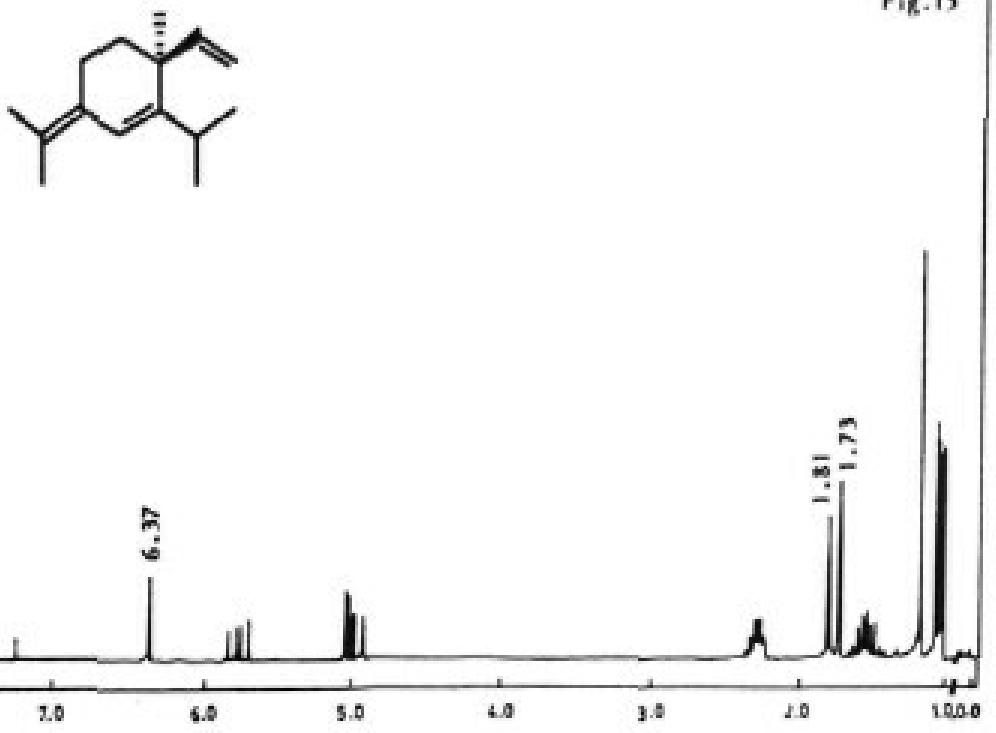
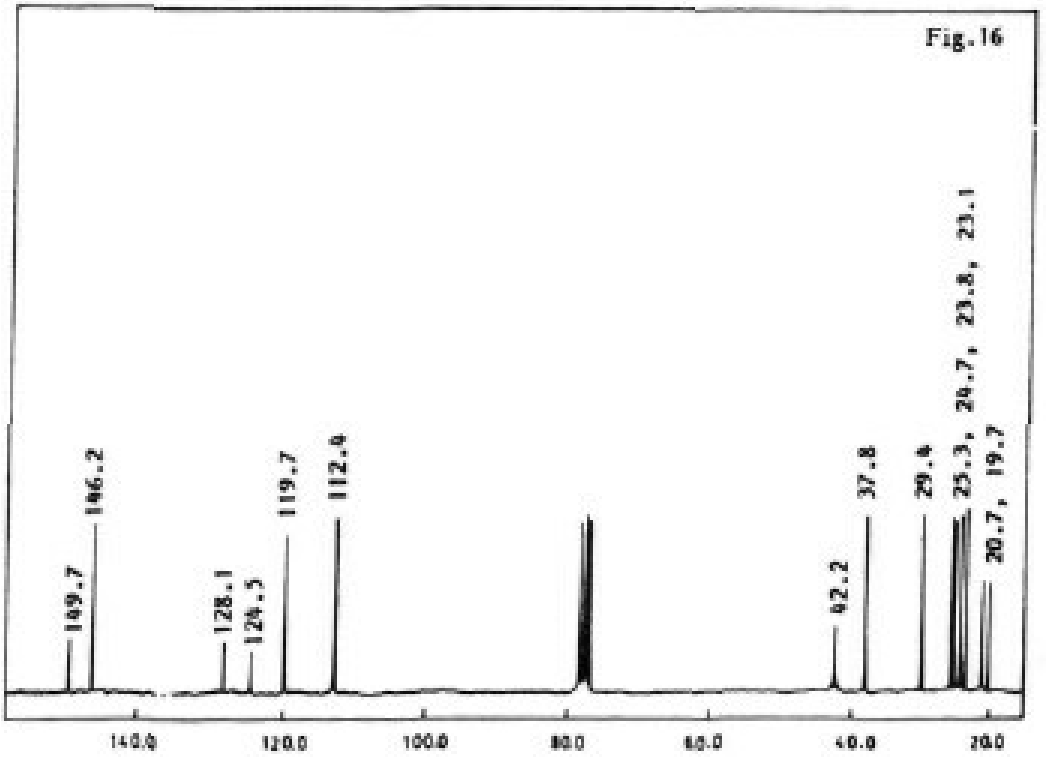

6.37
1.81
1.73
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

Fig. 16


149.7
146.2
128.1
126.3
119.7
112.4
62.2
37.8
29.4
25.3, 24.7, 23.8, 23.1
20.7, 19.7
140.0
120.0
100.0
80.0
60.0
40.0
20.0

(Fig. 17)

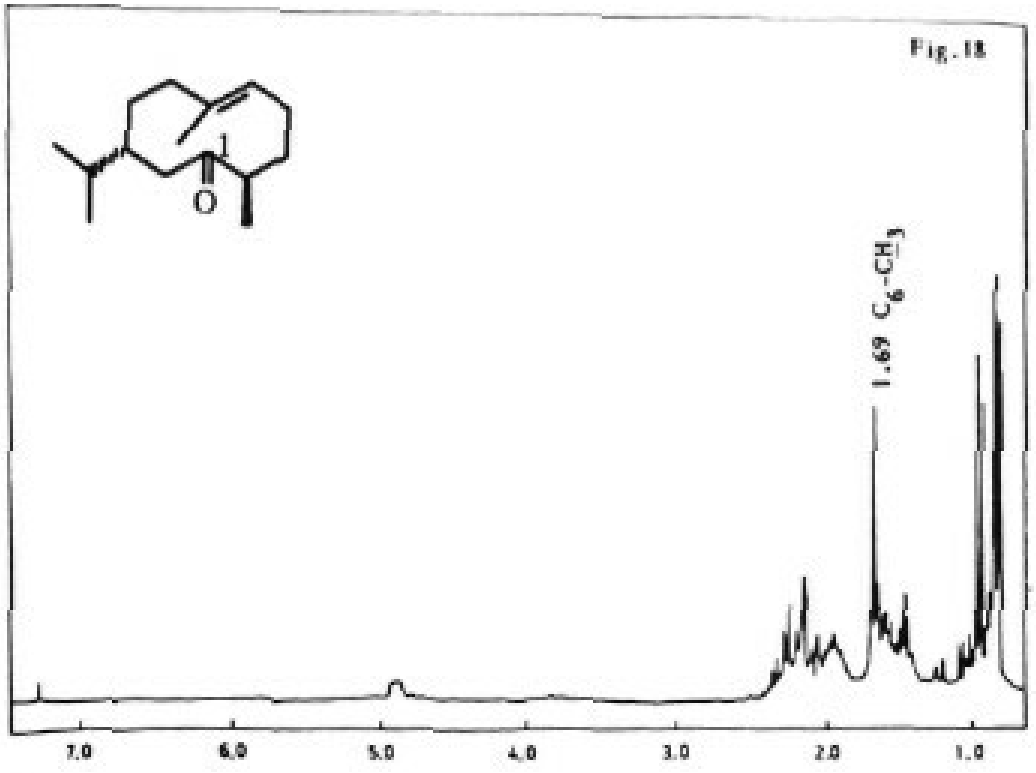


Fig. 18
O
1.69 C_6-CH_3
7.0
6.0
5.0
4.0
3.0
2.0
1.0

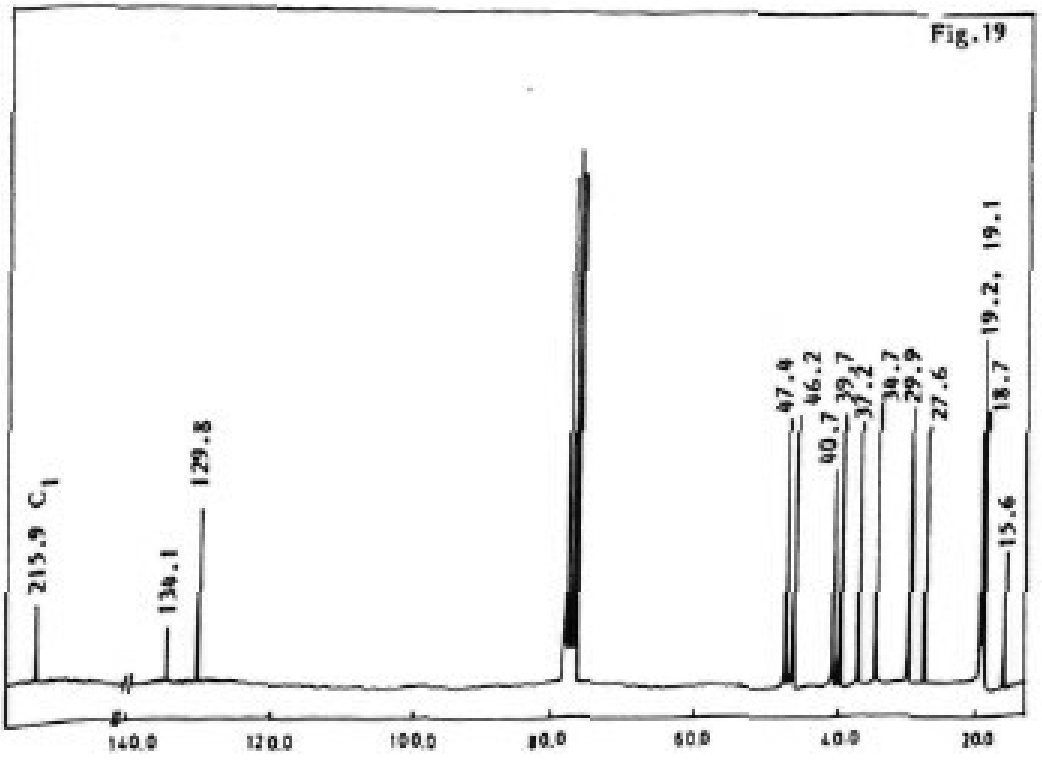


Fig. 19
215.9 C_1
138.1
129.8
47.4
46.2
40.7
39.7
37.2
34.7
29.9
27.6
19.2, 19.1
18.7
15.6
140.0
120.0
100.0
80.0
60.0
40.0
20.0

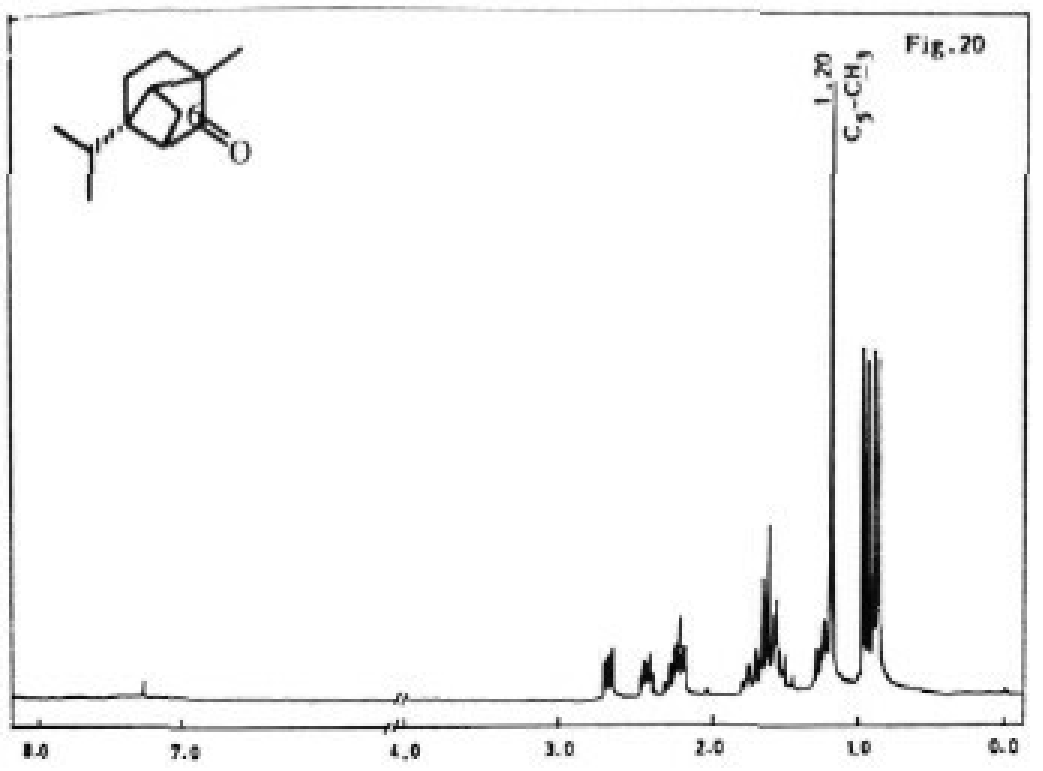


Fig.20
1.20
C_5-CH_3
O
8.0
7.0
4.0
3.0
2.0
1.0
0.0

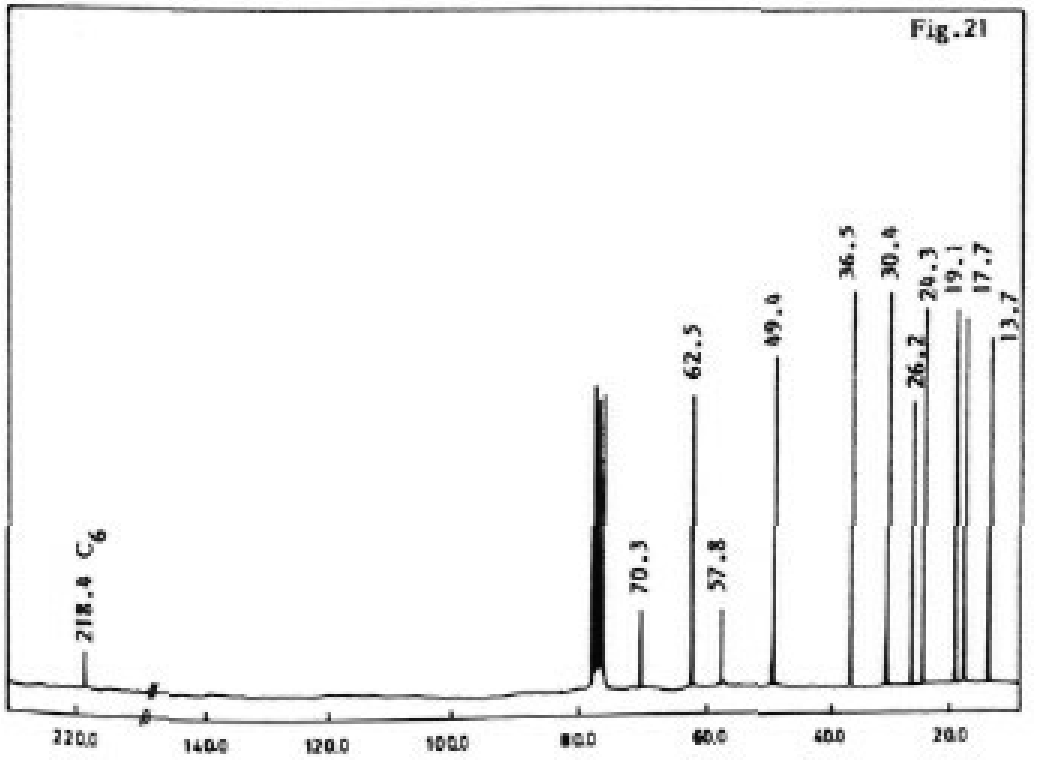


Fig.21
218.4 C_6
70.3
62.5
57.8
49.0
36.5
30.4
26.3
26.2
19.1
17.7
13.7
220.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0

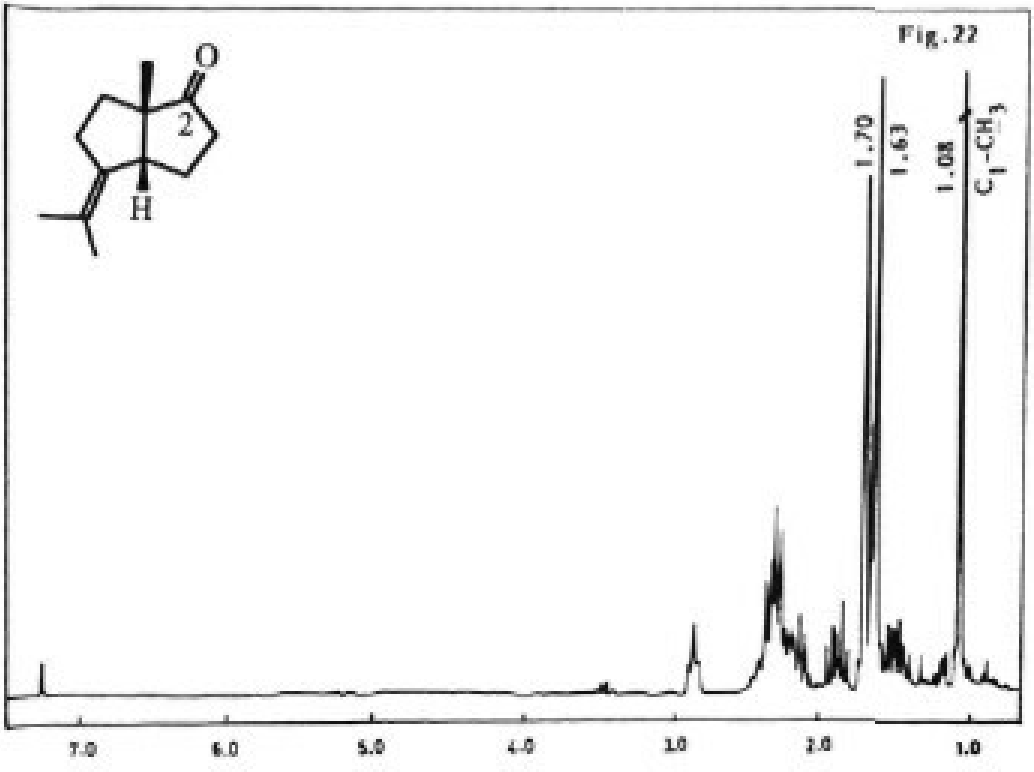


Fig. 22
O
2
H
1.70
1.63
1.08
C_1-CH_3
7.0
6.0
5.0
4.0
3.0
2.0
1.0

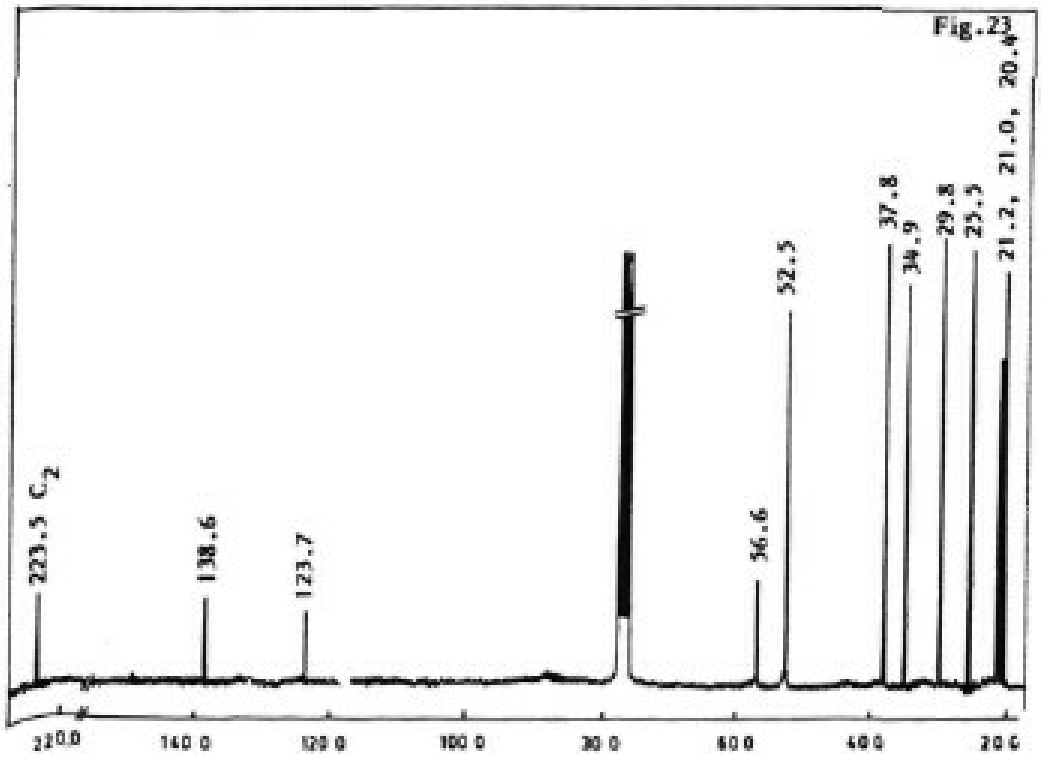
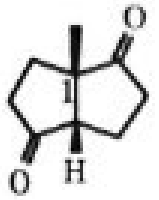


Fig. 23
223.5 C_2
138.6
123.7
36.6
32.5
37.8
34.9
29.8
25.5
21.2, 21.0, 20.4
220.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0

Fig. 24


O
O
H

1.24
C1-CH3
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

Fig. 25

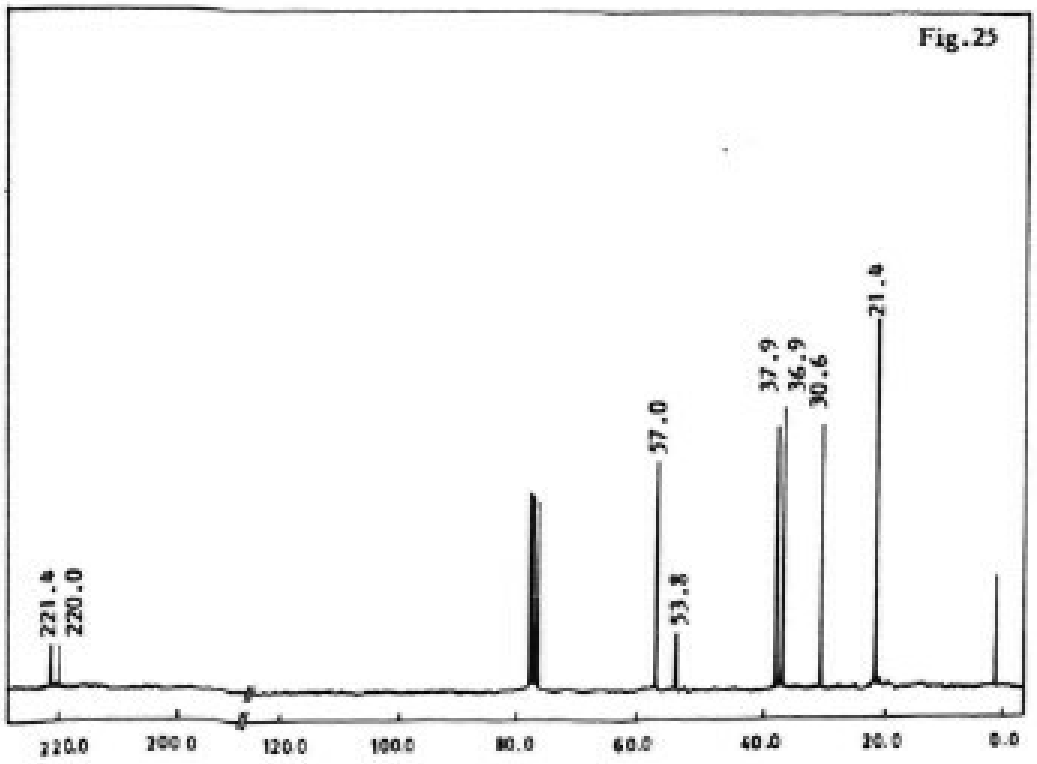
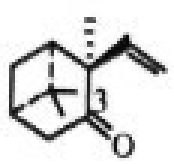

221.4
220.0
57.0
53.8
37.9
36.9
30.6
21.4
220.0
200.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0

Fig. 26


3
O

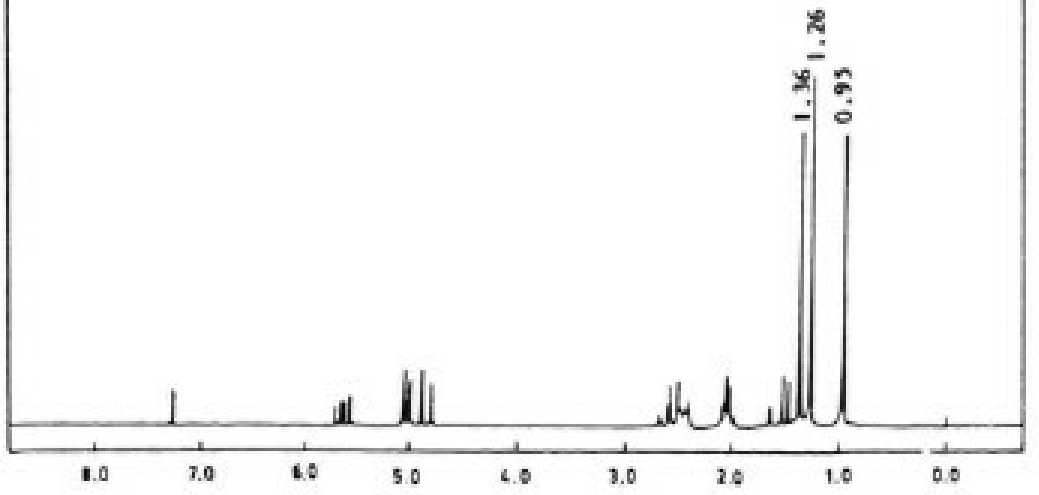
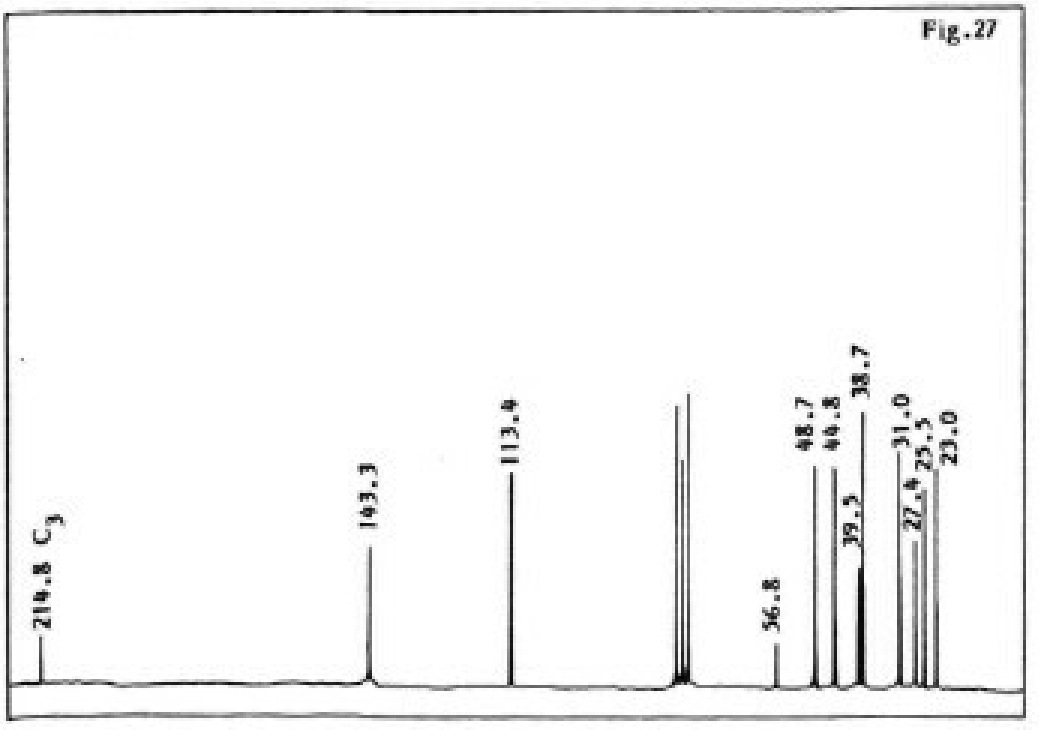
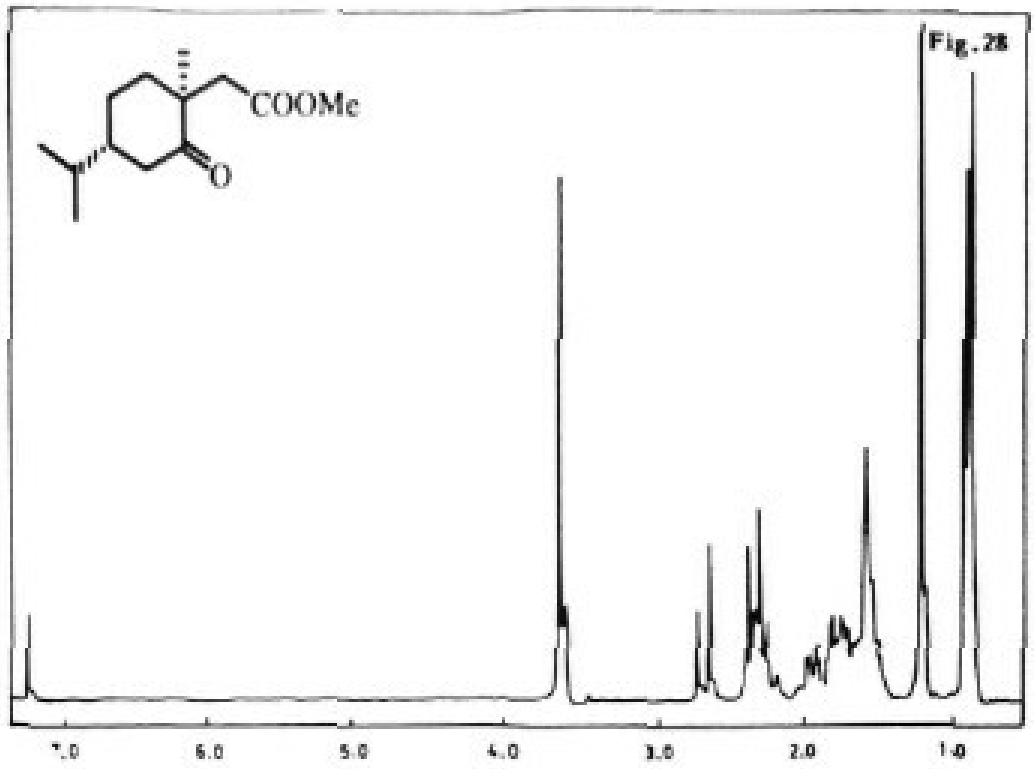

1.36
1.26
0.93
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

Fig. 27


214.8 C3
143.3
113.4
36.8
48.7
44.8
39.3
38.7
31.0
27.4
25.3
23.0


COOMe
O
Fig. 28
7.0
6.0
5.0
4.0
3.0
2.0
1.0

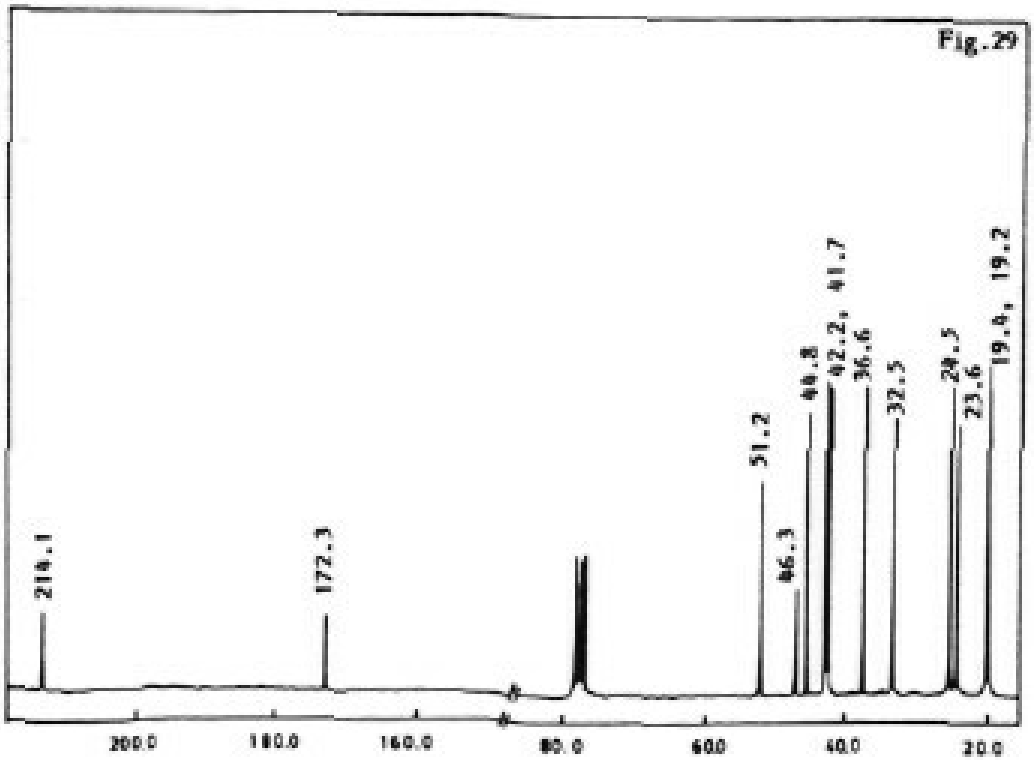
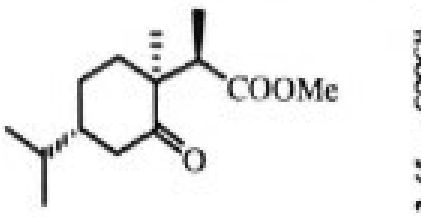


Fig. 29
214.1
172.3
51.2
46.3
40.8
42.2,
41.7
36.6
32.5
29.5
23.6
19.4,
19.2
200.0
180.0
160.0
80.0
60.0
40.0
20.0

Fig. 30


COOMe
O

3.65 -COOCH3
1.13
7.0
5.0
4.0
3.0
2.0
1.0
0.0

Fig. 31

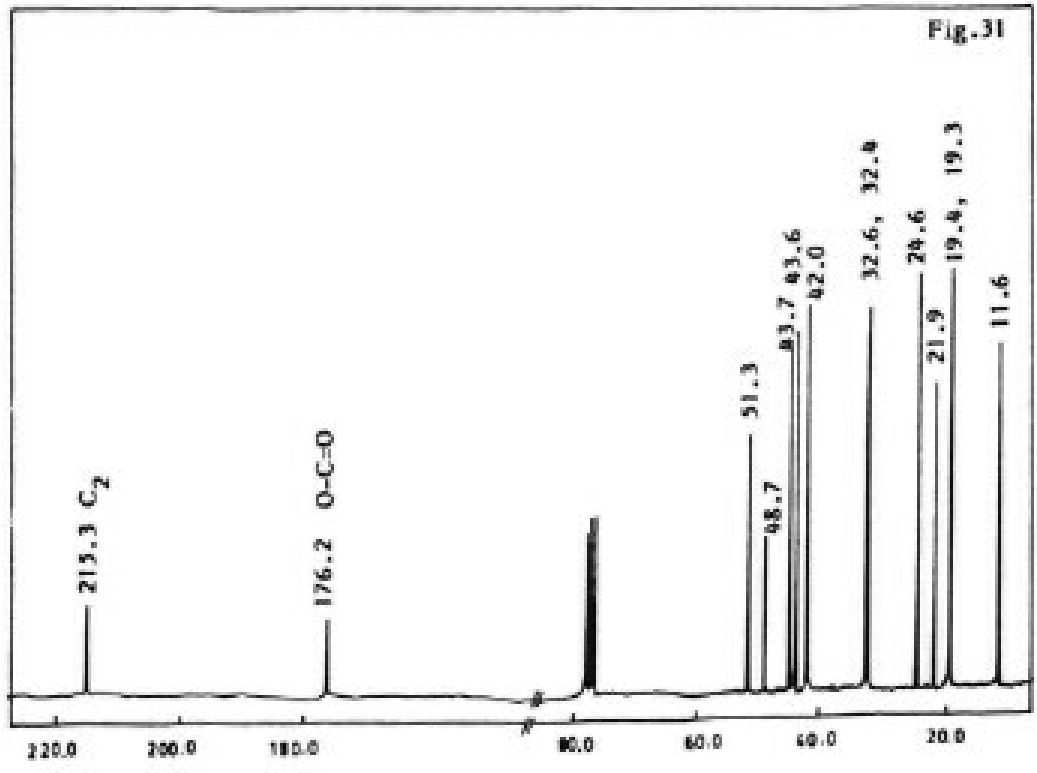

213.3 C2
176.2 O-C=O
51.3
48.7
43.7
43.6
42.0
32.6, 32.4
29.6
21.9
19.4, 19.3
11.6
220.0
200.0
180.0
80.0
60.0
40.0
20.0

Fig. 32

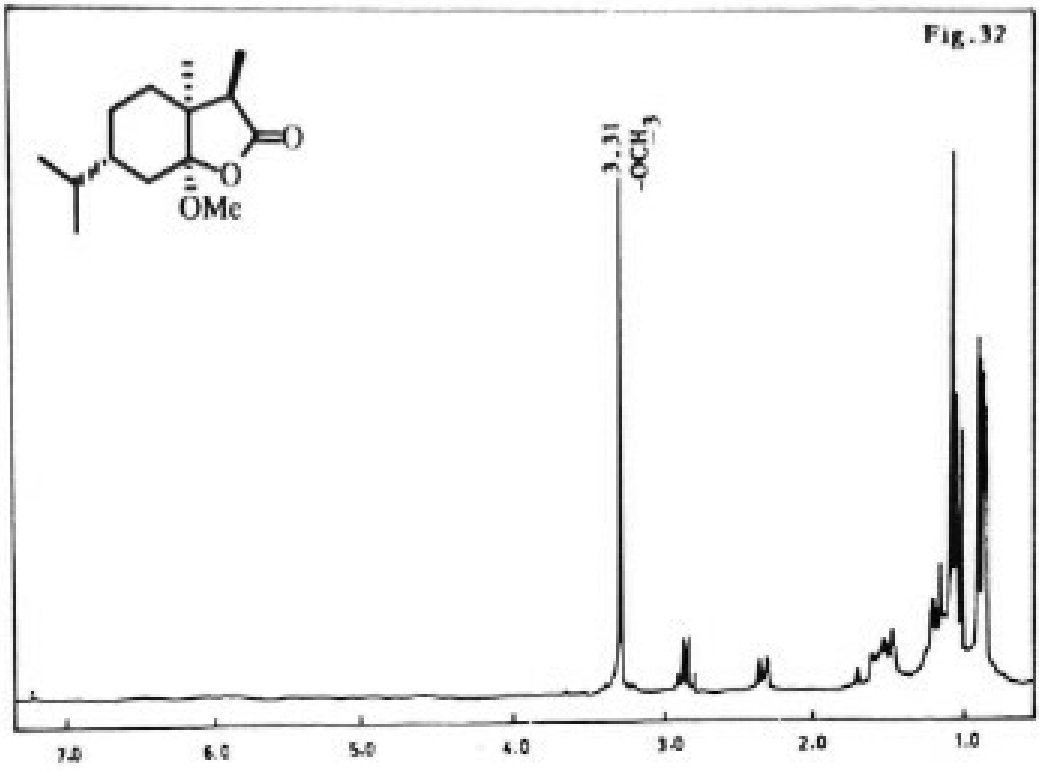
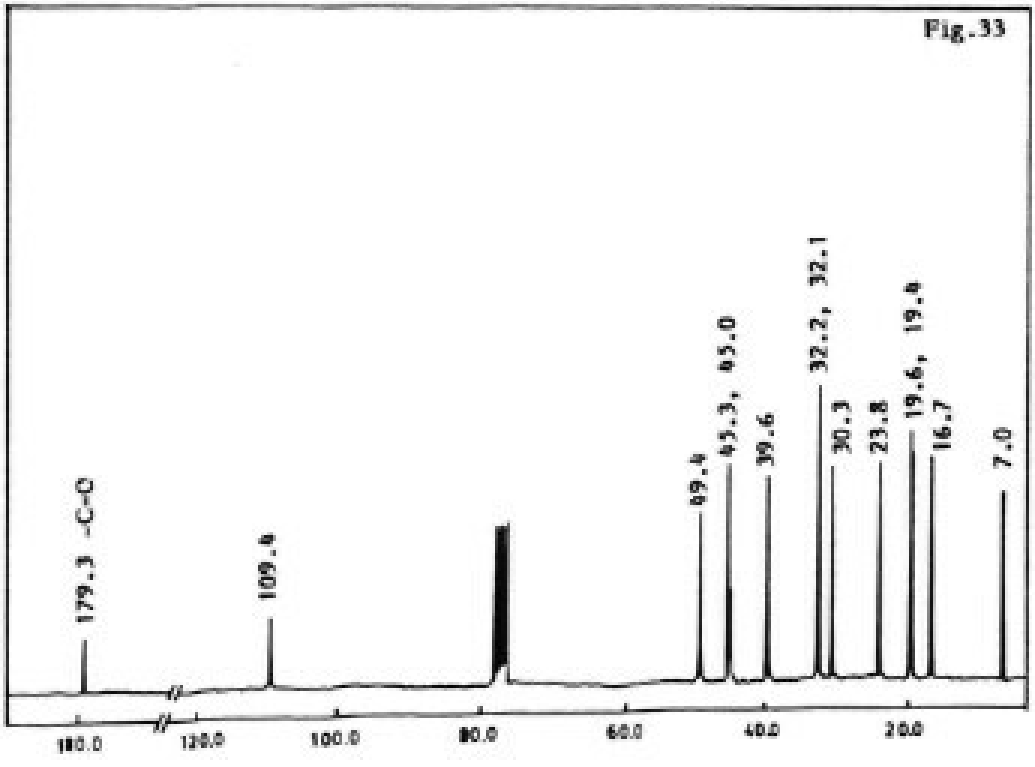
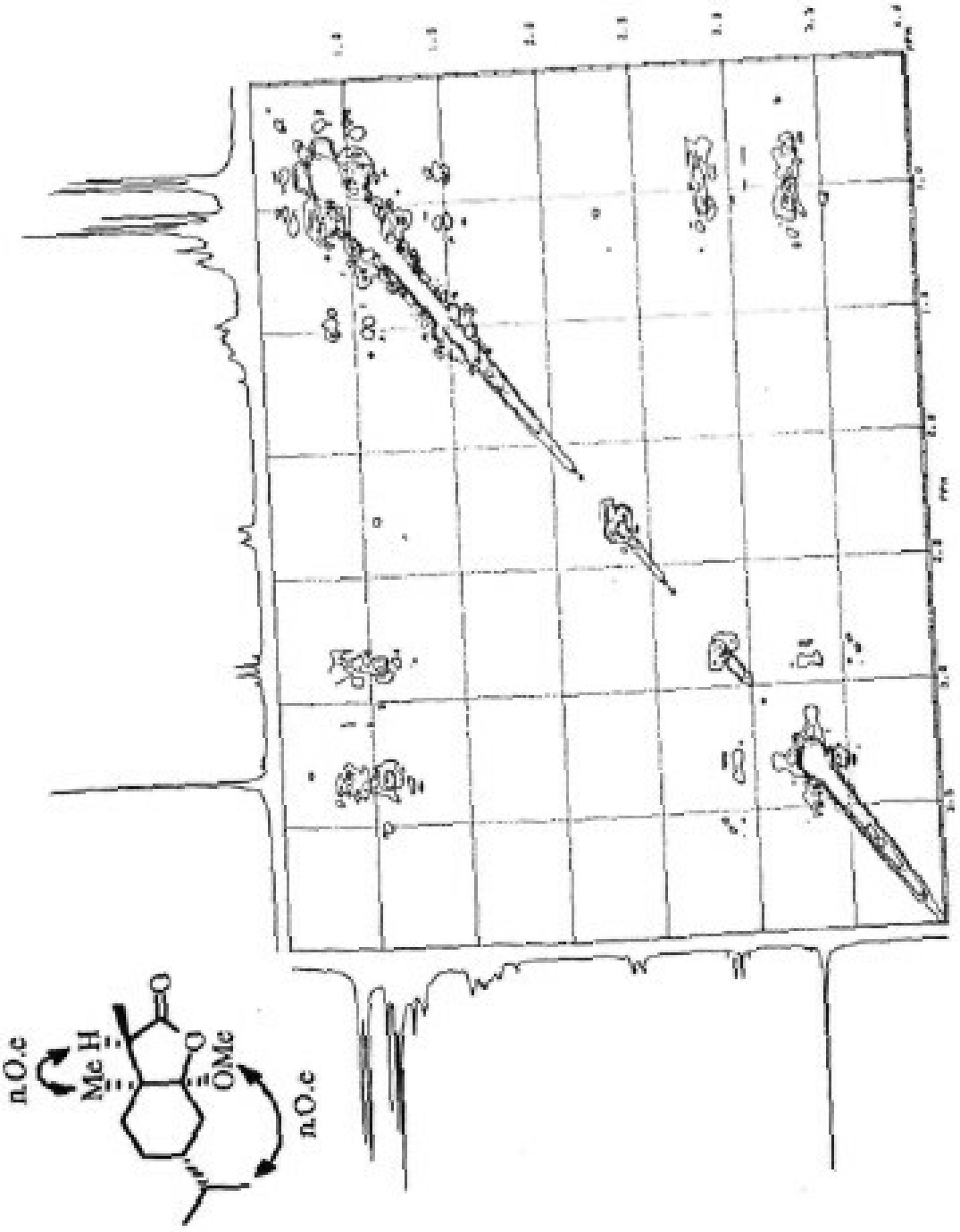

3.31
-OCH3
7.0
6.0
5.0
4.0
3.0
2.0
1.0

Fig. 33


179.3 -C=O
109.4
69.4
65.3, 65.0
39.6
32.2, 32.1
30.3
23.8
19.6, 19.4
16.7
7.0
180.0
120.0
100.0
80.0
60.0
40.0
20.0

(Fig. 34)



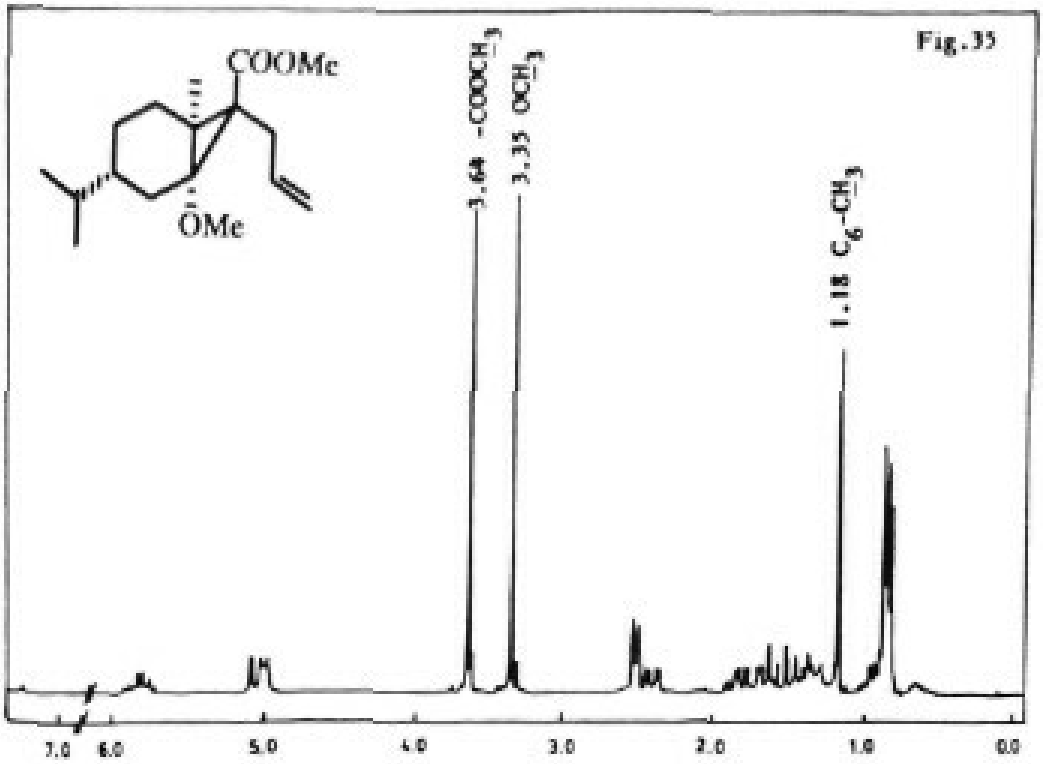

COOMe
OMe
3.64 -COOCH3
3.35 OCH3
1.18 C6-CH3
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

Fig.35

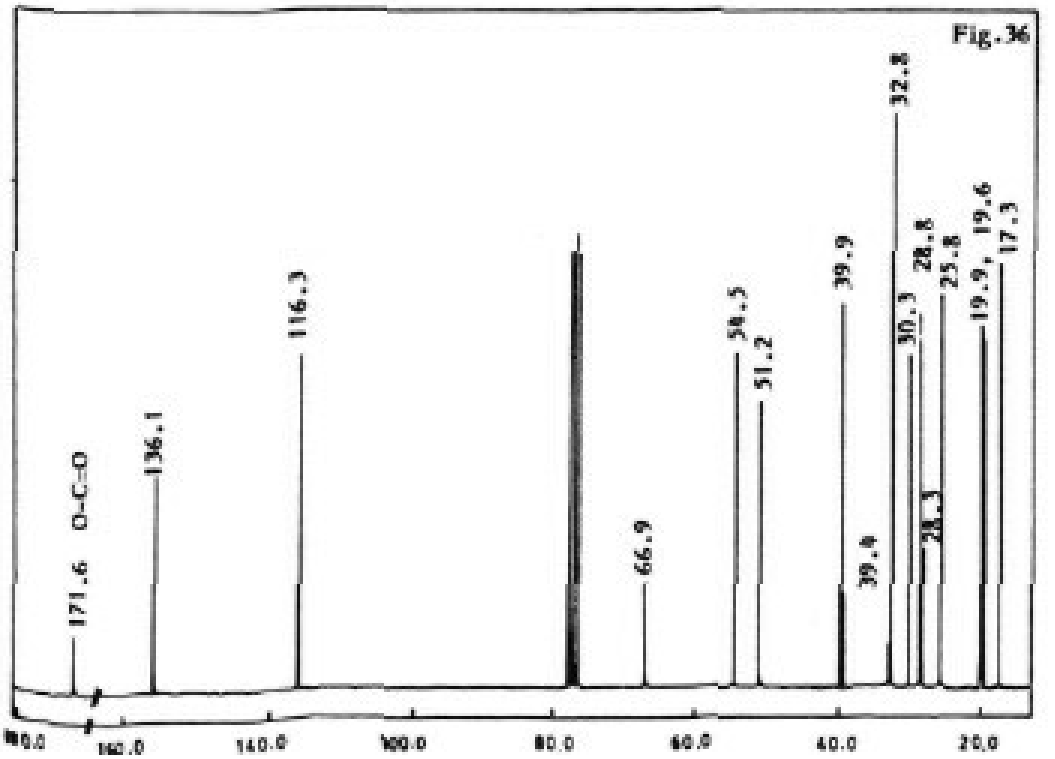
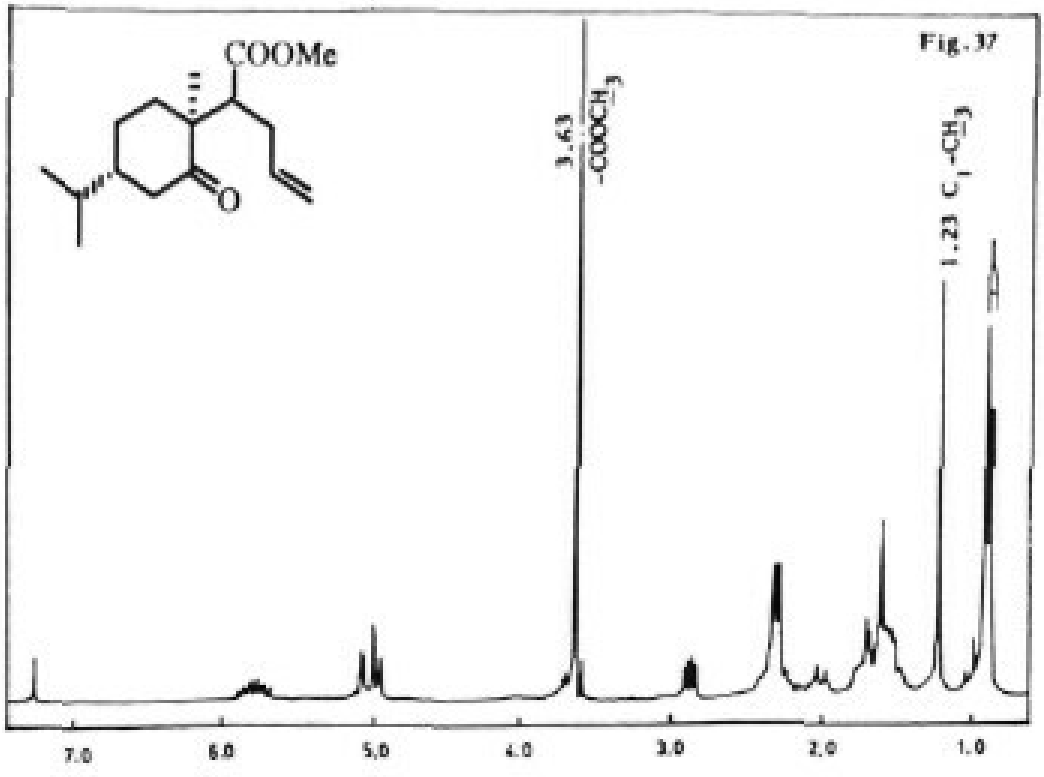

171.6 O-C=O
136.1
116.3
66.9
58.5
51.2
39.9
39.4
32.8
30.3
28.8
28.3
25.8
19.9, 19.6
17.3
160.0
140.0
100.0
80.0
60.0
40.0
20.0

Fig.36


COOMe
O
Fig. 37
3.63
-COOCH3
1.23 C1-CH3
7.0
6.0
5.0
4.0
3.0
2.0
1.0

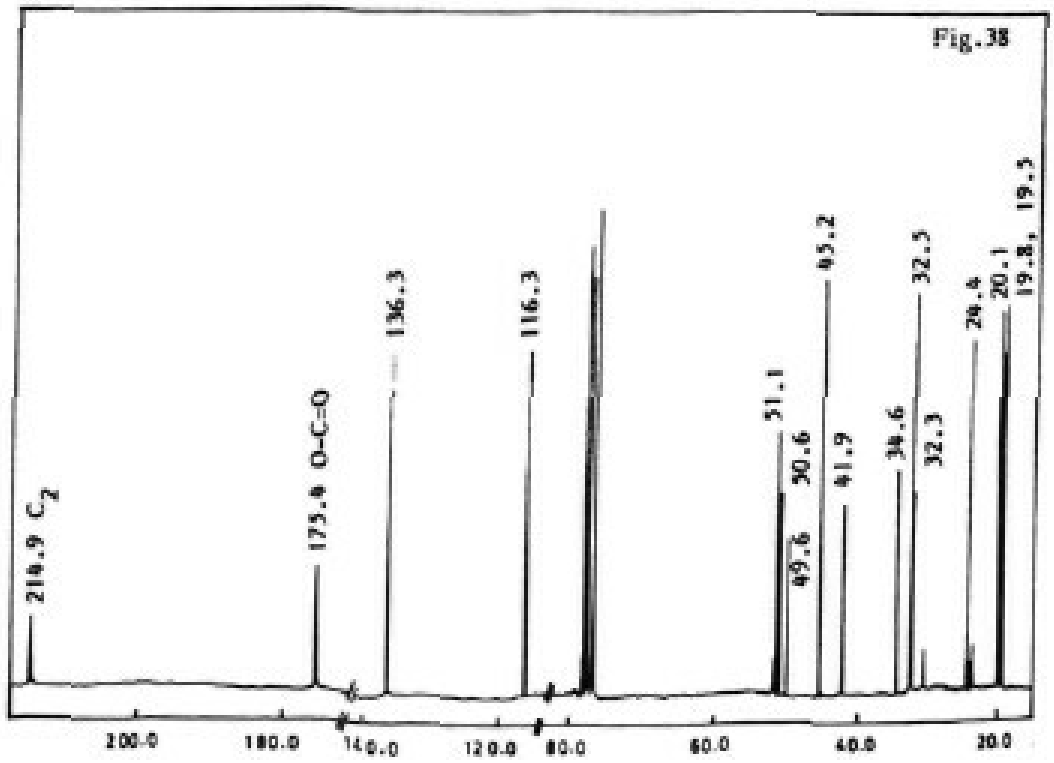


Fig. 38
214.9 C2
175.4 O-C=O
136.3
116.3
51.1
49.6
30.6
45.2
41.9
34.6
32.3
32.3
20.4
20.1
19.8, 19.3
200.0
180.0
140.0
120.0
80.0
60.0
40.0
20.0

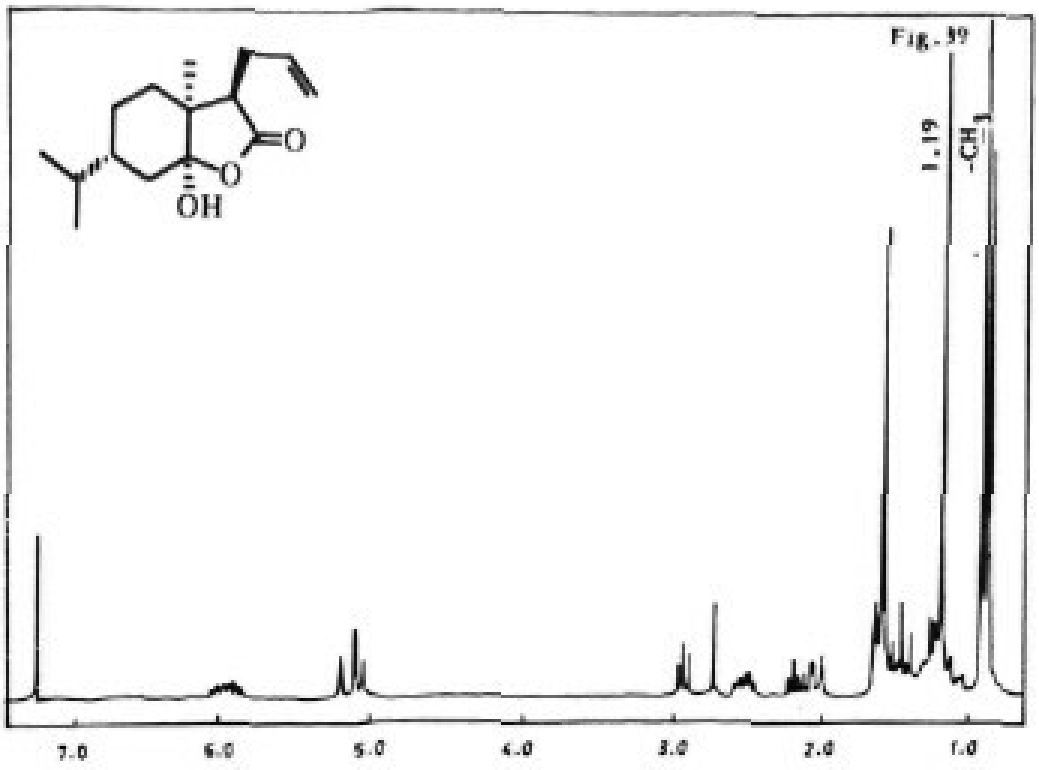


Fig. 39
O
O
OH
1.19
-CH3
7.0
6.0
5.0
4.0
3.0
2.0
1.0

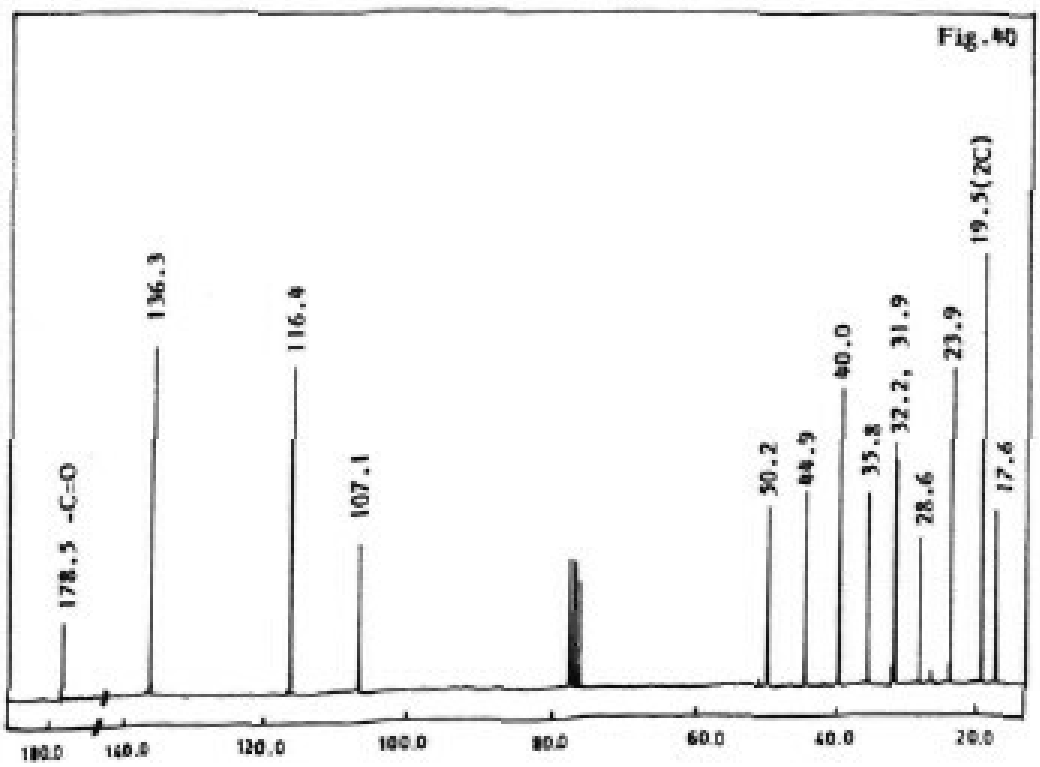
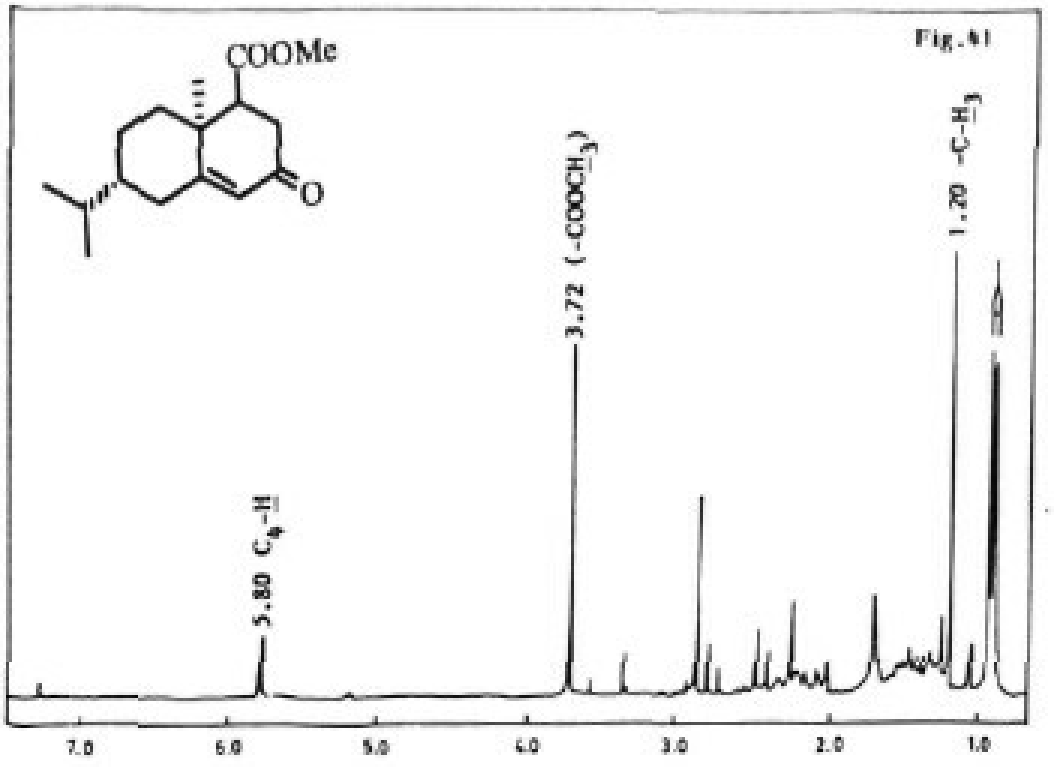


Fig. 40
178.3 -C=O
136.3
116.9
107.1
50.2
44.9
40.0
35.8
32.2, 31.9
28.6
23.9
19.5(2C)
17.6
180.0
160.0
120.0
100.0
80.0
60.0
40.0
20.0


COOMe
O
Fig.41
5.80 C4-H
3.72 (-COOCH3)
1.20 -C-H3
7.0
6.0
5.0
4.0
3.0
2.0
1.0

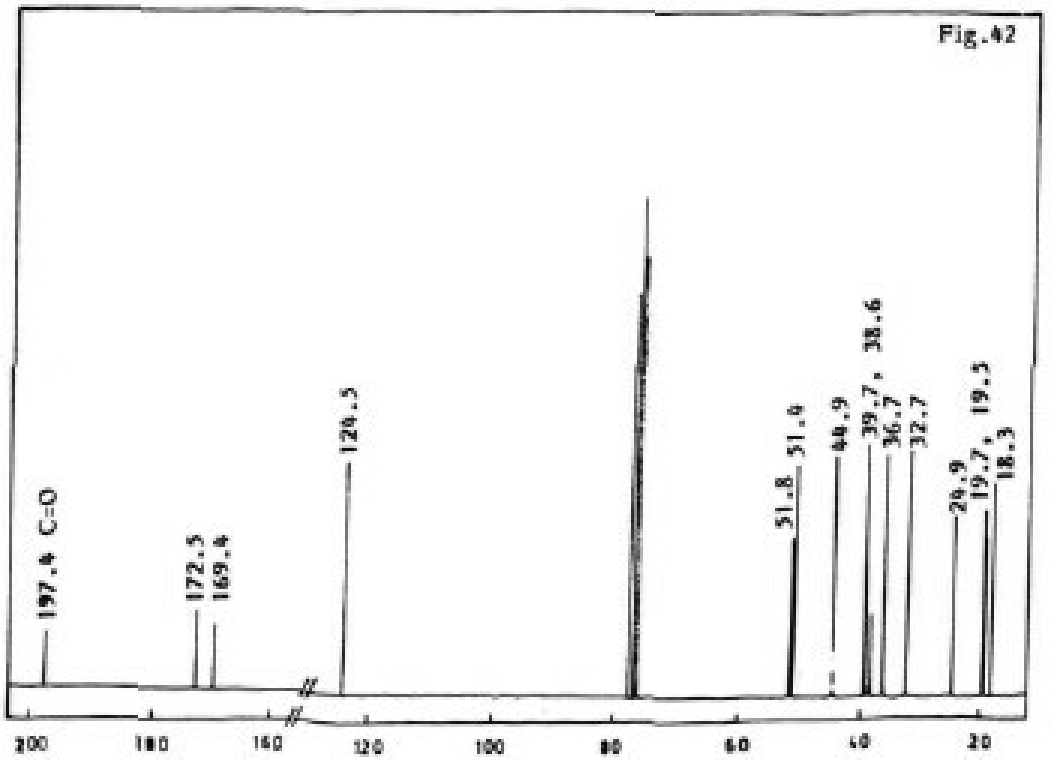


Fig.42
197.4 C=O
172.5
169.4
124.5
51.8
51.9
44.9
39.7
38.6
36.7
32.7
29.9
19.7
19.5
18.3
200
180
160
120
100
80
60
40
20

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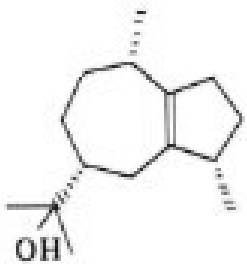
Appendix

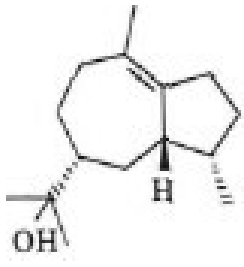
Chiral Dialkyl Cycloheptanones from R-(+)-Citronellal

Several sesquiterpenes possessing a hydroazulenic frame-work, e.g., guainolides and pseudoguainolides, have been isolated from plant sources, Chart 1.[1] These natural products contain a wide range of functionality and some of them exhibit broad spectrum biological activity.

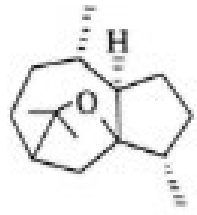
Chart 1



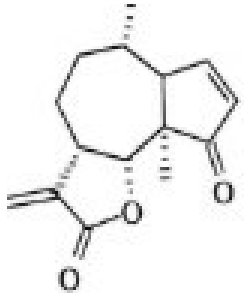
Guaiol 1[la]

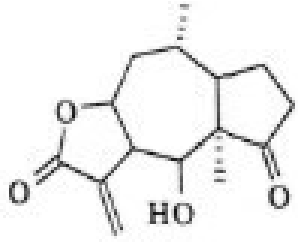


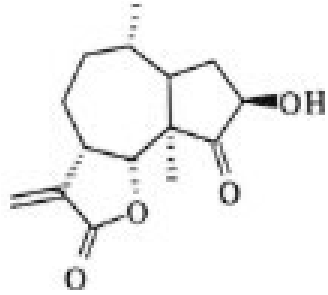
Bulnesol [1b]



guaioside3[le]







The presence of the seven membered ring in various perhydroazulene skeleta, with an isopropyl and a methyl group in a stereochemically well defined 1,4-relationship, has attracted a great deal of attention from synthetic

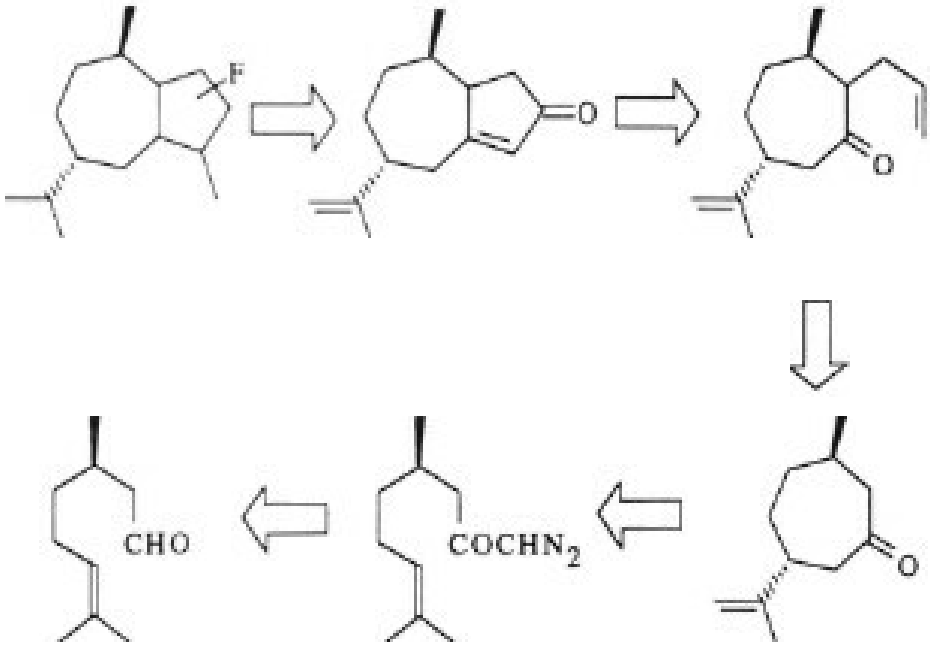
chemists in the recent past. The strategies involved for the synthesis of these natural products include- annulation of cycloheptane ring on to a cyclopentane ring,[2] cyclopentannulation of a cycloheptane ring[3] and skeletal rearrangements of other carbocyclic systems.[4]

The presence of a seven membered ring with an isopropyl and a methyl group in a well defined 1,4-relationship, as a common core, in hydroazulenic natural product skeleta drew our attention. As the access to such skeleta in their chiral form is limited.[5] it was considered appropriate to develop a new strategy for their construction. Therefore, the construction of suitably substituted cycloheptanones 7 from simple starting materials was considered and herein, we describe a simple and preparatively useful protocol for the diasteroselective synthesis of the cycloheptanone moiety employing an olefin-a-diazo ketone cyclisation as the key-step. It has been reported in the literature that unsaturated diazomethyl carbonyl compounds readily undergo cyclisation in the presence of protic acids or Lewis acids.[6] Efforts to elaborate this cyclopentanone moiety to the hydroazulenic frame-work 7 arc also described.

As a part of our continuing interest in employing monoterpenes as chirons for the synthesis of higher terpenes, cheap and commercially available R-(+)-citronellal 13 was chosen as the starting material. Synthetic strategy towards hydroazulenic sesquiterpenoids required rapid assembly of a suitably

fused system through a cylopentannulationalien protocol, Scheme 1. The seven membered ring moiety 10, with the isopropyl and methyl groups in required positions, could be obtained by employing an olefin-a-diazo ketone cyclisation as shown in the retrosynthetic Scheme 1,

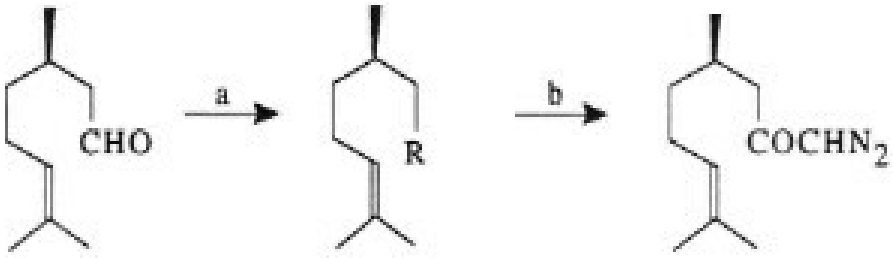
Scheme 1



The α-diazo ketone was sought to be prepared from R-(+)-citronellal

The above synthetic plan was put into practice by oxidation of R-(+)-citronellal with Jone's reagent to furnish the corresponding acid 14 (80% yield). Treatment of the acid **14** with oxalyl chloride in the presence of pyridine delivered the acid chloride 15**.** The formation of the acid chloride was monitored and confirmed by the strong absorption at 1800 cm^{-1} in the IR spectrum. The acid chloride, thus obtained, was treated with diazomethane to deliver the a-diazo ketone **12** in 60% yield, Scheme 2. The characteristic

Scheme 2



14 R=COOH

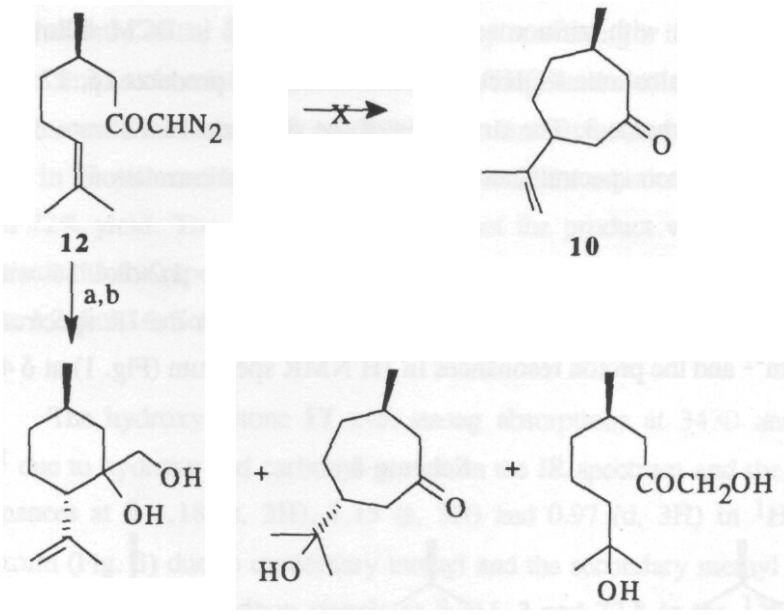
13

15 R=COCI

Reagents, Conditions and Yields: (a) i. Jone's oxidation, 0 ^{o}C, 1 h, 80% ii. $(COCI)_2$, Py, DCM, 0 ^{o}C-R.T., 34 h (b) CH_2N_2, ether, 0-20 °C, over night, 60% from acid **14.**

absorption at 2100 cm^{-1} in the IR spectrum confirmed the formation of the a-diazo ketone **12.**

Scheme 3



16 17 **18**

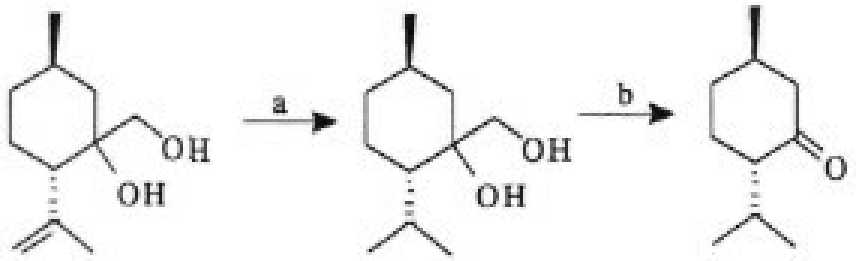
Reagents, Conditions and Yields: (a) CF_3COOH, DCM, -20 °C, 30 min. (D) 10% KOH-MeOH, 70% from **12**

Having obtained the diazo ketone **12,** the stage was now set to carry-out the key olefin-diazo ketone cyclisation reaction to give the cycloheptanone **10.** Unfortunately, treatment of the oc-diazo ketone **12** with a variety of reagents (e.g., $BF_3.Et_2O$ in DCM and CH_3CN, aq. $HC1O_4$, $TiCl_4$, aq. HBF_4

etc.) did not proceed satisfactorily to give the expected cycloheptanone 10 and resulted in the formation of complex mixtures. However, treatment of the diazo ketone 12 with trifluoroacetic acid,[7] at -20°C in DCM followed by hydrolysis with alcoholic KOH furnished a mixture of products 16. 17 and 18 in 70% yield, Scheme 3, The structures of the products 16-18 were deduced on the basis of their spectral data and through chemical correlation.

The spectral and analytical data of the cyclic 1,2-diol 16 was in agreement with its formulation, A strong absorption in the IR spectrum at 3400 cm^{-1} and the proton resonances in ^{1}H NMR spectrum (Fig. 1) at δ 4.79

Scheme 4



16 19 20

Reagents, Conditions and Yields: (a) H_2, PtO_2, 1 h, 40 atm. 66% (b) $NaIO_4$, aq.THF, 72%.

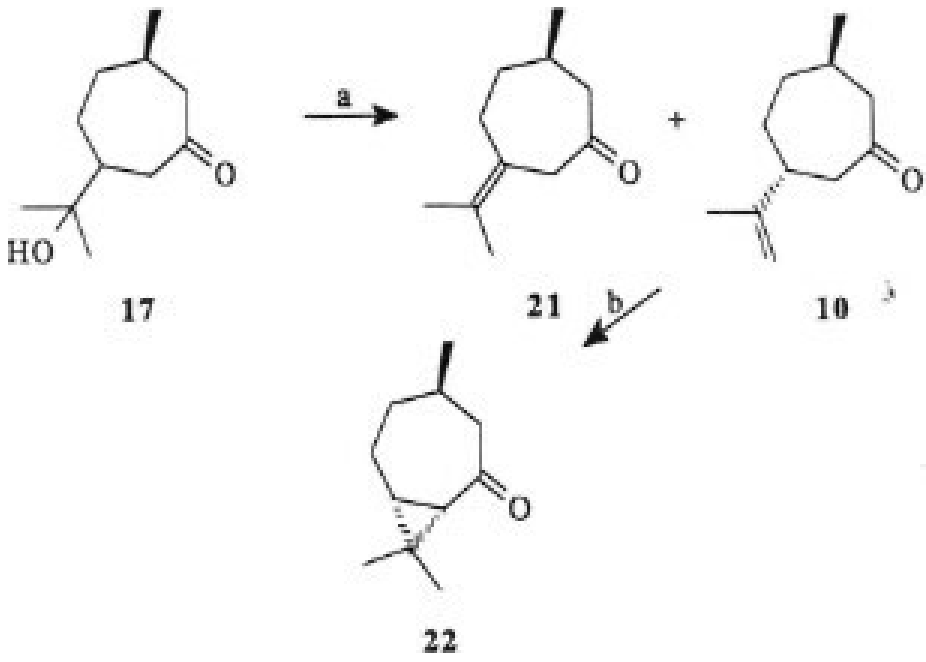
(m, 2H) due to the olefinic protons established the gross identity of the product 16. Particularly, a 11 line ^{13}C NMR spectrum (Fig. 2) with

characteristic peaks at δ 145.0. 112.5, 734 and 70.2 due to olefinic and onygen attached carbons further confirmed its formulation. The stereochemistry[1] of the diol 16 was deduced by convening it into menthone 20 through simple chemical transformation. Hydrogenation of the diol 16 over platinum oxide furnished 19 in 66% yield. Oxidative cleavage of the diol moiety in 19 with sodium metaperiodate delivered the monoterpene, menthone 20 in 72% yield The ^{1}H NMR spectrum of the product was found to be identical with the reported (-)-menthone and established the stereochemistry of cyclic 1,2-diol 16. Scheme 4.

The hydroxy-ketone 17 with strong absorptions at 3430 and 1690 cm^{-1} due 10 hydroxy and carbonyl groups in the IR spectrum and the proton resonances at δ 1.18 (s, 3H), 1.15 (s, 3H) and 0.97 (d, 3H) in ^{1}H NMR spectum (Fig. 3) due to quaternary methyl and the secondary methyl groups and in particular, the carbon signals at δ 211..3 and 72.8 in the ^{13}C NMR spectrum (Fig. 4) due to the carbonyl group and the hydroxy attached carbon atom established the gross formulation of 17. The stereochemistry of the isopropyl with respect to the methyl group in the hydroxy-ketone 17 was assigned through simple chemical correlation with the reported compound. Dehydration of the hydroxy-ketone 17 with methanesulphonyl chloride in the presence of triethylamine and DMAP furnished a mixture of enones 21 and 10 (1:1), in 45% yield, the latter being identical (^{1}H and ^{13}C NMR spectra) to the compound reported in the literature,[5a] Scheme 5. The enone 10 has

already been transformed into the bicyclo[5.1.0]octanone 22. an important sesquiterpene synthon, in two high yielding steps.

Scheme 5



Reagents, Conditions and Yields: (a) CH_3S0_2Cl, TEA, DMAP, DCM, R.T., 3h.45%(b)Ref. 5a.

The acyclic diol 18 with a characteristic absorption at 3350, 1710 am^{-1} in the IR spectrum due to hydroxy and carbonyl functionalities and the proton resonance at δ 4.16 (2H, s) in the ^1H NMR spectrum (Fig. 5) due to methylene protons attached to the primary hydroxy group indicated its

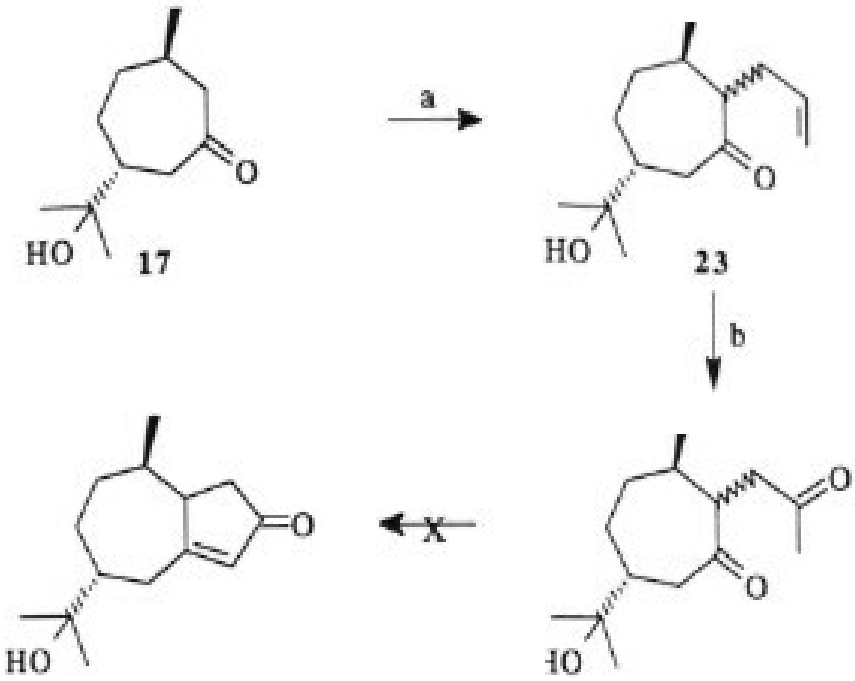
formulation as 1ft In particular, the carbon resonances at δ 209.9, 70.8 and 68.6 in the ^{13}C NMR spectrum (Fig 6) due to the carbonyl group and the cartons attached to hydroxy groups were decisive in arriving at its structure.

It may be noticed that while the acid catalysed olefin-α-diazornethyl ketone cyclisation has found extensive applications for the construction of five- and *six*-membered rings, the present study records one of the few examples of the formation of a seven membered ring.[7c] Earlier attempts to construct 22 directly from 12 through an intramolecular carbenoid [2+1]-cycloaddition to form a seven membered ring have not been successful. Formation of the α-hydroxy-ketones from α-diazo ketones has been observed previous1y[5c] and the formation of the diols 16 and 18 along with the keto-alcohol is unexceptional.

Although the α-diazo ketone cyclisation did not yield the expected cycloheptanone 10 directly, the hydroxy-ketone 17 obtained in this transformation, was considered to be a serviceable substrate to carry-out the further annulation protocol.

Our next objective was to attempt the cyclopentannulation to access the hydroazulenic frame-work as described in the synthetic plan, Scheme 1. Alkylation of the hydrony-ketone 17 with allyl bromide using sodium hydride as base furnished the required allylated product in 31% yield (minor amounts of o-allylated product was also noticed during this transformation). The α-

Scheme *6*



Reagents, Conditions and Yields: (a) NaH, THF, allyl bromide, 30 min. 31% (yield based on the recovery of starting material) (b) $PdCl_2$, CuCl, DMF, H_2O,O_2, R.T., 4 h, 62%

allyl ketone 23 was characterised spectroscopically. A strong absorption at 3400 and 1690 cm^{-1} in the IR spectrum due to hydroxy and the carbonyl groups and the proton resonances at δ 5.80-5.40 (1H, m) and δ 5.20-4.80 (2H, m) in ^{1}**H** NMR spectrum (Fig. 7) due to olefinic protons indicated OK formulation of 23. A 14 line ^{13}C NMR spectrum (Fig. 8} with carbon

absorptions at δ 216.2, 135.6, 116.6 and 72.6 further confirmed the formulation of 23 Efforts to improve the yield of the allylation reaction under different reaction conditions were not satisfactory.

The allyl ketonc 23, thus obtained, was subjected to oxidation to give the ditaone 24. Oxidation of the allyl ketone 23 under Tsuji conditions resulted in the formation of a diastereomeric mixture (~5:1) of the diketone 24 in 62% yield, Scheme 6. The spectral data of the diketone was in full agreement with its formulation. The absorptions at 3450 and 1700 cm^{-1} in the IR spectrum and the proton resonance at δ 2,16 (3H, s) due to acetyl group in the ^{1}H NMR spectrum established the identity of the diketone 24. In particular, the carbon resonances at 215.2, 208.2 and 72.8 in ^{13}C NMR spectrum due to carbonyl carbon and oxygen attached carbon absorptions established the structure of the diketone 24. However, no attempt was made to separate this mixture.

With the availability of the diketone 24, the cyclisation step to construct the hydroazulenic frame-work was attempted. But aldol cyclisation in the diketone under a variety of acidic and basic reaction conditions was unsuccessful and resulted in the formation of complex reaction mixture. Presence of the tertiary hydroxyl group could be a complicating factor in our inability to effect the aldol cyclisation. Further work was not pursued in the light of the failure of this key step.

Summary

In summary, a short and diastereoselective synthesis of cycloheptanones bearing a methyl and isopropyl groups in a well defined 1,4-relalionship, employing an olefin-α-diazo ketone cyclisation as key step, was developed from the cheap, readily available R-(+)-citronellal.

Results of the attempted cyclopentannulation on the cycloheptanone ring using α-allylation, Tsuji oxidation and aldol cyclisation strategy to the construction of the hydroazulenic skeleta, have also been described.

Experimental section

For genera] write-up see the experimental of earlier section, R-(+)-Citroncllai was purchased from Fluka, $[\alpha]_D$ +2.1 ($CHC1_3$) of low optical purity, was used as such for all experiments described in this section.

Acid catalysed cyclisation of (4R)-l-diazo-4,8-dimethyl-non-7-en-2-one (12)

Into a 250 mL RB flask was taken R-(+)-citronellal **13** (9gm, 58 mmol) in 100 mL of acetone and Jone's reagent was added dropwise at 0° C, till the colour persists. The solvent was then removed in vacuo and 50 mL of water was added to dissolve the inorganic salts and extracted with ethyl acetate (3 x 250 ml.) The organic layer was washed with brine (50 ml) and concentrated to give the crude citronellic acid **14** (8 gm) in 80% yield.

IR (neat) 2975, 2950,1710,1260cm-^{1}

The above crude carboxylic acid **14** (8 gm, 47 mmol) and oxalyl chloride (12.3 mL, 0.14 mmol) in dry dichloromethane (200 mL), was treated dropwise with pyridine (2.5 mL, 47 mmol) at 5 °C and stirred under nitrogen 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 competion of the reaction. At this stage, the main reaction was

worked up with benzene and filtered through a small celite pad. The filtrat was concerntrated to furnish the acid chloride 15 (8gm) and was used as such for the diazo ketone preparation.

IR(neat) $1800cm^{-1}$

To a solution of the crude acid chloride 15 (3 gm, 16 mmol) in dry ether (50 mL) was added, dropwise with occasional stirring, chilled ethereal solution of diazomethane (5-6 equiv). 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, the ethereal solution was dried and concentrated in vacuo to yield the crude diazo ketone. The crude product was chromatographed on a silica gel column and elution with *20%* ethyl acetate-petroleum ether furnished 4,57 gm of pure diazo ketone 15(l,8gm, 60%)

IR (neat) $2100,1630,1350\ cm^{-1}$

A solution of the diazo ketone 12 (2gm, 10 mmol) in dichloromethane (5 mL) was added dropwise to a stirred solution of trifluoroacetic acid (4 mL) in dichloromethane in a 50 mL three necked RB flask fitted with a condenser, nitrogen inlet and mercury seal (4 mL) at -20°C after 30 min. the reaftion mizture was diluted with dichloromethane (25 mL) washed with brine and dried. The residue obtained after removal of solvent was dissolved in 10% methanolic KOH and stirred for 30 min. Methanol was

removed under vacuo and the residue dissolved in cthyl acetate (50 mL), washed and dried. Removal of the solvent gave an oily residue (1.4 gm, 70%) which consisted mainly of a 1:2:2 mixture of 16. 17 and 18, respectively. Chromatography on silica gel column and elution with 20% ethyl acetate-hexane furnished (+)-(2RJS)-l-hydroxymethyl-2-isopropenyl-5-methyl cyclohexanol (16).

$[\alpha]_D$	+3.9° (c, 0.19 ;$CHC1_3$)
IR(neat)	3400, 3050,1635, 1450, 1340,1050, 890cm^{-1}
^{1}H NMR (100 MHz) (Fig. 1)	δ 4.79 (m, 2H)), 3.39 (ABq,J=llHz, 2H) 2.20 (brs, 2H), 2.10-0.90 (m, 8H), 1.79 (s, 3H, -C-CH_3), 0.86 (d, J=7Hz, 3H, -CH-CH_3)
^{13}C NMR (25.0 MHz) (Fig. 2)	δ 145.0, 112.5, 73.4, 70.2, 50.7, 43.5, 34.8, 27.4, 2,3, 23.0,22.4
Analysis ($C_{11}H_{20}O_2$)	Calcd.: C, 71.69; H, 10.94 Found: C, 71.58; H, 10.86

Further elution of the column gave the (3R,6R)-3-(l-hydroxy-l-methylethyl)-6-mettiyl-cycloheptanone (17).

$[\alpha]_D$	+4.7° (c, 3.15 ;$CHC1_3$)
IR (neat)	3430, 2925,1690 cm^{-1}

^{1}H NMR(100 MHz) δ 2.80-1.50 (m. 11H), 1.18 (s, 3H. -C-CH_3),
(Fig. 3) 1.15 (s, 3H, -C-CH_3), 0.97 (d, J = 7 Hz. 3H, -CH-CH_3)

^{13}C NMR (25.0 MHz) δ 211.3, 72.8. 51.5, 47,4, 45.8, 38.5, 32.5, 31.5,
(Fig. 4) 26.8,26.1,23.9

Analysis ($C_{11}H_{20}O_2$) Calcd.: C, 71.69; H, 10.94
Found: C, 71.84; H, 10.93

Continued elution with the same solvent gave (IR)-l,8-dihydroxy-4,8-dimethyl-nonan-2-one (18).

IR(neat) 3350,1710cm-^{1}

^{1}H NMR (100 MHz) δ 4,16(s, 2H), 2.70 (br s, 2H), 2.45-0.96 (m, 9H).
(Fig. 5) 1.17 (s, 6H, -C-CH_3), 0.88 (d, J = 7 Hz, 3H, -CH-CH_3)

^{13}C NMR (25.0 MHz) δ 209.9, 70.8, 68.6, 45,6. 43.7, 37.2, 29.4, 29.2,
(Fig.6) 29.1,21.5, 19.8

Analysis($C_{11}H_{20}O_2$) Calcd.: C, 65.31; H, 10.96
Found: C, 65.25; H, 10.93

Convertion of the diol 16 into menthone 20

A solution of the diol 16 (30 mg,0.16 mmol) in dry ethyl acetate (2 mL) was hydrosenated (40psi) overPtO_2 (4mg) for 1 h. The catalyst was

filtered off and the solvent was removed and the crude product 19 (20 mg, 66%) obtained was subjected to sodium metaperiodate reaction.

IR (neat) 3400, 2950,1460

The crude diol 19 (20 mg, 0.11 mmol) in 50% aq. THF (500 mL) was placed in a 25 mL RB and cooled in an ice-bath. To this, sodium metaperiodate (28 mg, 0.13 mmol) was added in small portions and the reaction niixture was stirred at room temperature for 4 h. The reaction mixture was extracted with ether (25 mL x 3) and the ethereal extract was washed and dried. Filtration of the crude product through a small silica gel column gave (-)-menthone 20(12 mg) in 72% yield.

Dehydration of hydroxy-ketone (17)

To a solution of the hydroxy-ketone 17 (90 mg, 0.5 mmol) in dichloromethane (5 mL) containing 4,4-dimethylaminopyridine (61 mg), and triethylamine (2 equiv.) was added methanesulphonyl chloride (1.2 equiv.) at 0°C under nitrogen. After 3 h, the reaction mixture was diluted with water and extracted with dichlorornethane (15 mL). The residue (42 mg, 45%) obtained after the removal of solvent consisted of 1:1 mixture of the isomers 21 and 10 and was charged on a silica gel column. Elution with 3% ethyl acetate-hexane furnished (6R)-3-isopropylidene-6-methyl-cycloheptanone (21)

$[\alpha]_D$	+6.0° (c, 0.30 ;$CHC1_3$)
IR(neat)	2950, 2920,1705 cm^{-1}
^{1}H NMR(100 MHz)	δ 3.13 (ABq. J=16 Hz, 2H) 2.78-1.48 (m, 7H), 1.72 (s, 3H,-C=C-CH_3), 1.68 (s. 3H,-C=C-CH_3), 0.98 (d, J = 7 Hz, 3H, -CH-CH_3)

Further elution gave (3R,6R)-3-isopropeny 1-6-methyl-cycloheptanone (10)

$[\alpha]_D$	+12.4° (c 0.5 ;$CHC1_3$)
IR(neat)	1690,1440,890cm-'
^{1}H NMR(100 MHz)	δ 4.69 (br s, 2H, -C=CH_2) 2.69-2.25 (m, 5H), 2.06-1.17 (m, 5H). 1.73 (s, 3H, -C=C-CH_3). 1.02 (d, J = 7 Hz. 3H. -CH-CH_3)
^{13}C NMR (25.0 MHz)	δ 213.4, 149.7, 109.5.52,1,49.3,43.9, 39.4, 35.3, 31.2,24.1,20.0

(3R,6R)-2-Allyl-6-(l-hydroxy-l-methyiylelhyl)-3-metliyl-cyclohtptanone (23)

To a stirred suspension of sodium hydride (360 mg of 40% NaH) in THF (5 mL) was added hydroxy-ketone 17 (680 mg, 3.8 mmol) in THF (5 mL) under nitrogen atmosphere. After refluxing for 30 min., the reaction mixture was quenched with allyl bromide (0.4mL, 1.2 equiv.) and heatiag was continued After 30 min. the reaction mixture was cooled and the excess

of sodium hydride was destroyed by the addition of 5% aq. HC1 and the reaction mixture was extracted with ether The ethereal layer was washed and dried. After removal of solvent. the residue was purified by column chromalography on silica gel Elution of the column with 10% ethyl acetate-hexane yielded the allyl ketone 23 (130 mg) in 31 % yield.

IR(neat) 3400, 2900,1690,1440,1360,920,760cm-^{1}

^{1}H NMR (100 MHz) δ 5.80-5.40 (m, 1H, -CH=CH_2), 5.20-1.80 (m, 2H, -CH=CH_2), 2.600.80 (m, 12H), 1,24 (s, 3H, -C-CH_3), 1.16 (s, 3H, -C-CH_3), 1.04 (d, J = 7 Hz, 3H, -CH-CH_3)

(Fig. 7)

^{I3}C NMR (25.0 MHz) δ 216.2, 135.6, 116.5,72.6,59.8,48.8, 42.6, 36.1, 35.8, 35,4, 29.9, 27,6, 25.7, 21.1

(Fig 8)

6-(l-Hydroxy--l-methylethyl)-3-methyl-2-(2-oxo-propy1)-cycloheptanone (24)

To a stirred mixture of palladium chloride, (15 mg) cuprous chloride (150 mg) in dirnethylformamide (2mL) and water (2 mL) under oxygen atmosphere was added the allyl ketone 23 (120 mg, 0.53 mmol). After stirring for 4h, the reaction mixture was poured into water (10 mL) and extracted with ether (2 x 50 mL). The combined ethereal extract was washed, dried, concentrated and the crude oily product was charged on silica gel column. Elution of the column with 15% ethyl acetate-hexane mixture furnished the product 24 (80 mg) as a diastereomeric mixture in 62% yield.

IR(neat)	3450, 2950, 1700. 1360, 1180 cm^{-1}
^{1}H NMR(100MHz)	δ 3.40-0.80 (m, 12H). 2.16 (s, 3H, -CO-CH_3), 1,24 (s, 6H, -C-CH_3). 1.00 (3H, d, J = 8 Hz, -CH-CH_3)
^{13}C NMR (25.0 MHz)	δ 215.2, 208.2, 72.8, 50.9, 45.7, 45.5, 44.6, 37.9, 36.1,29.8,27.6,26.9,26.1,20.3
Analysis ($C_{14}H_{24}O_3$)	Calcd.: C, 69.96; H, 10,07
	Found: C, 69.86; H, 9,98

Fig. 1

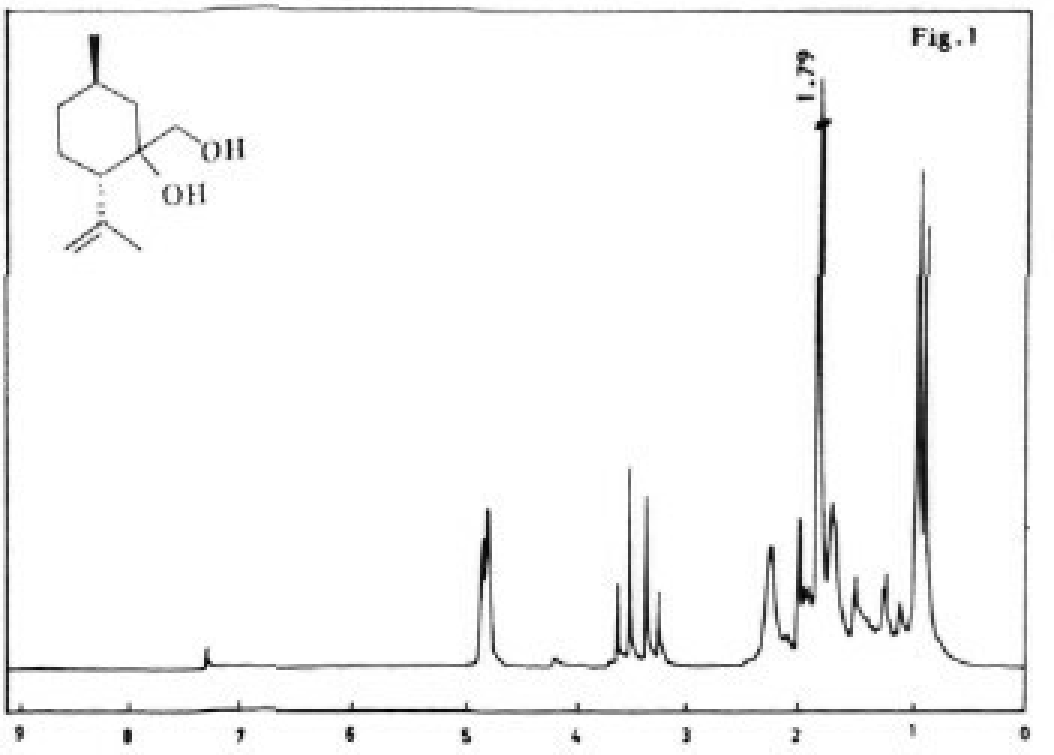
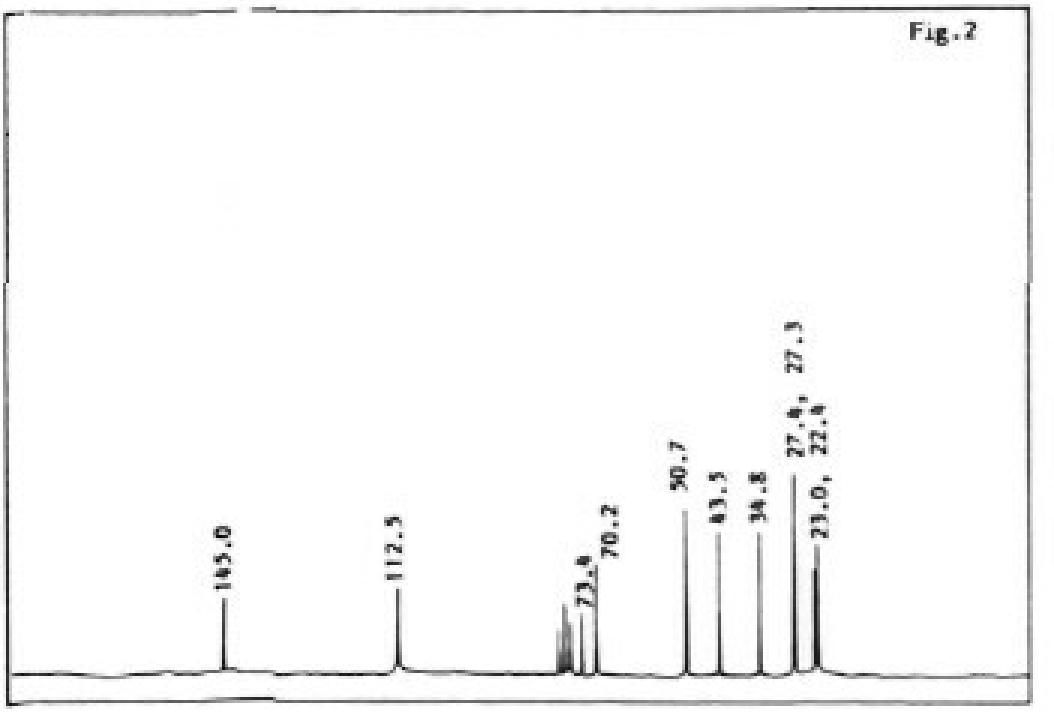

OH
OH
1.79
9
8
7
6
5
4
3
2
1
0

Fig. 2


145.0
112.5
73.9
70.2
50.7
43.5
34.8
27.4,
27.3
22.4
23.0,

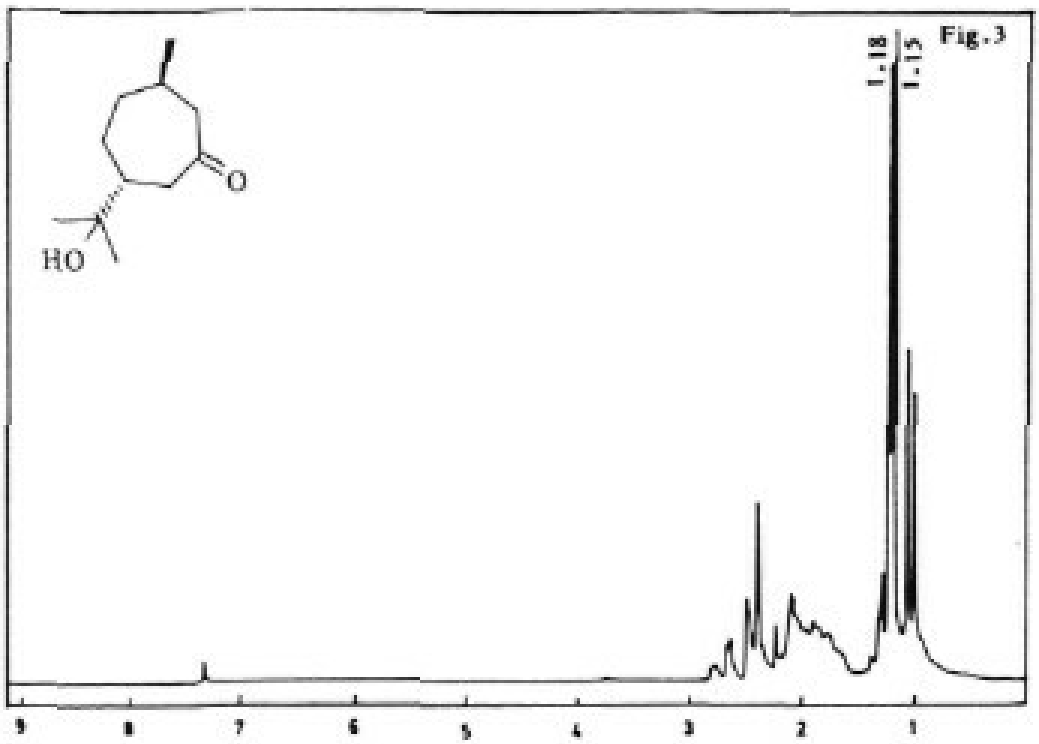


Fig.3
1.18
1.15
O
HO
9
8
7
6
5
4
3
2
1

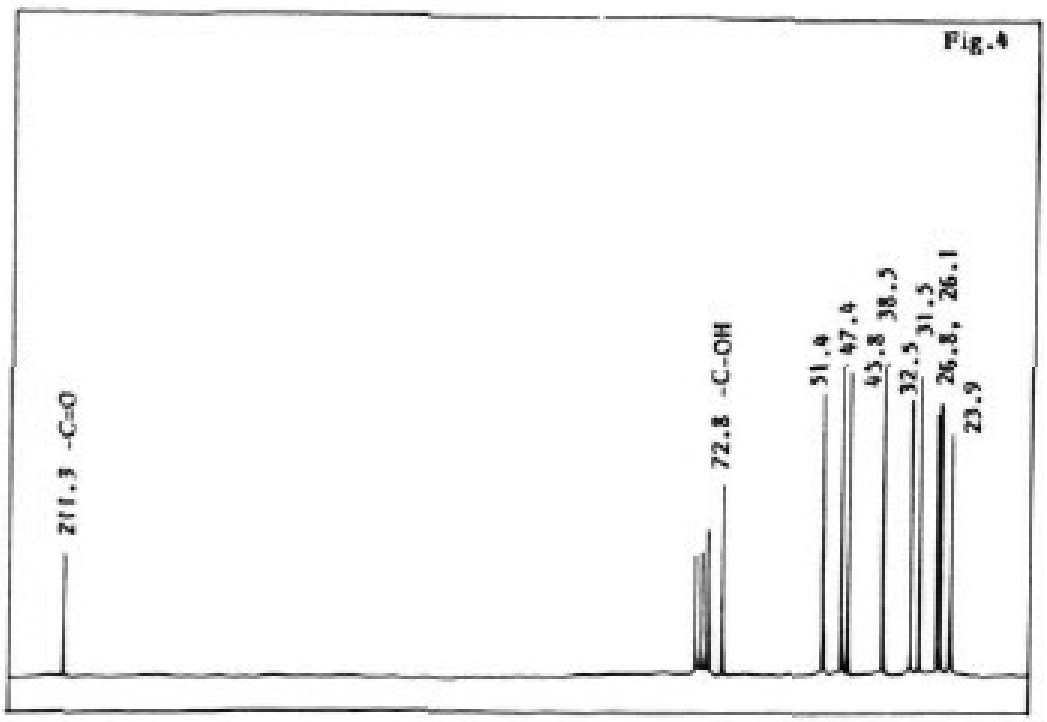


Fig.4
211.3 -C=O
72.8 -C-OH
51.9
47.4
43.8
38.3
32.5
31.3
26.8
26.1
23.9

Fig.3

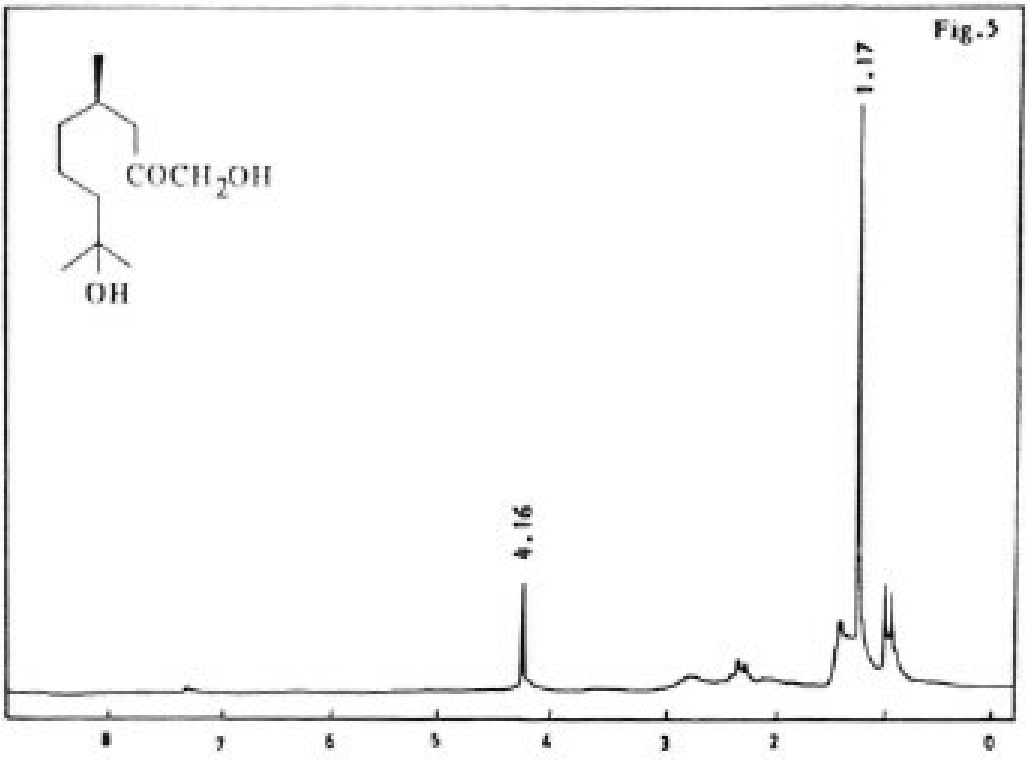

COCH2OH
OH
1.17
4.16
8
7
6
5
4
3
2
0

Fig.4

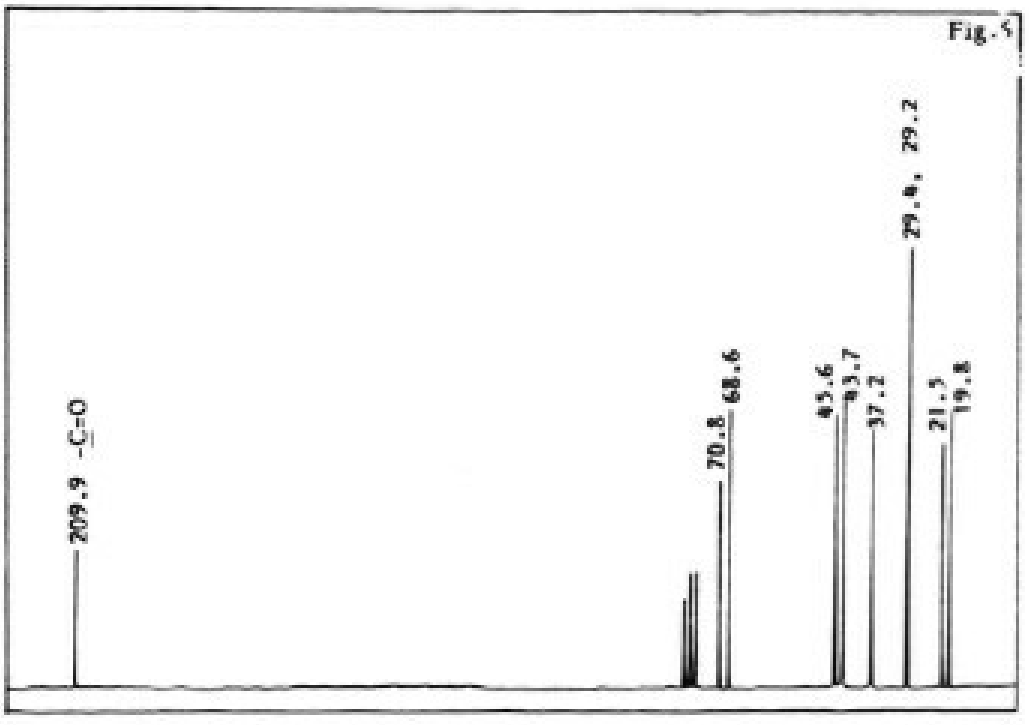

209.9 -C=O
70.8
68.6
45.6
43.7
37.2
29.4, 29.2
21.3
19.8

Fig.7

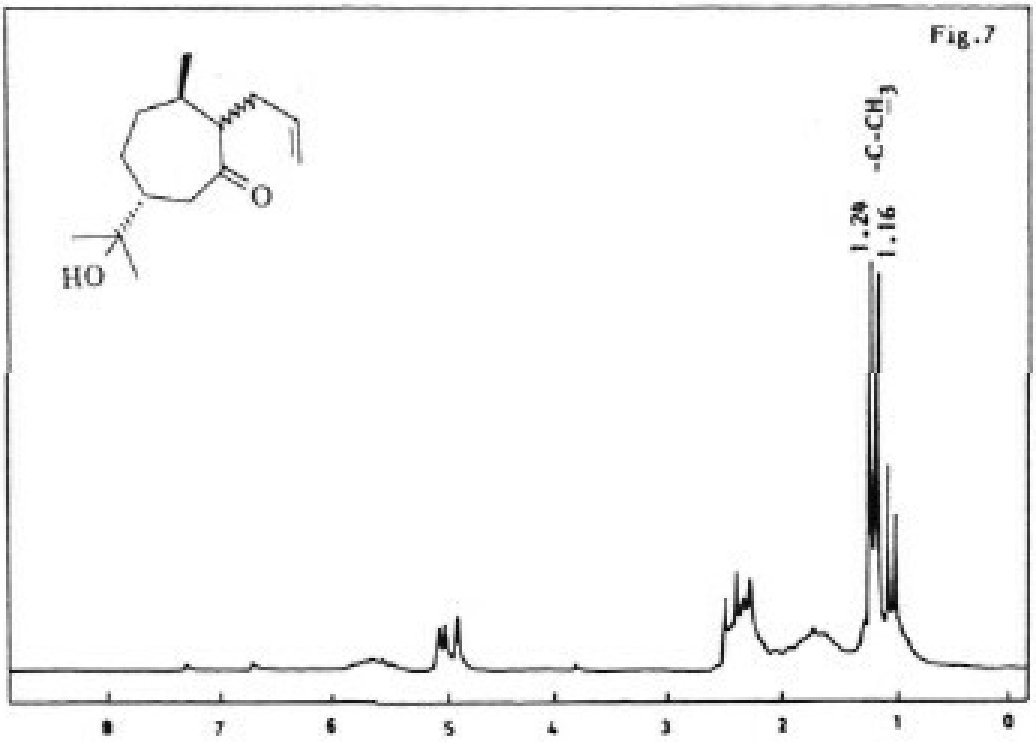
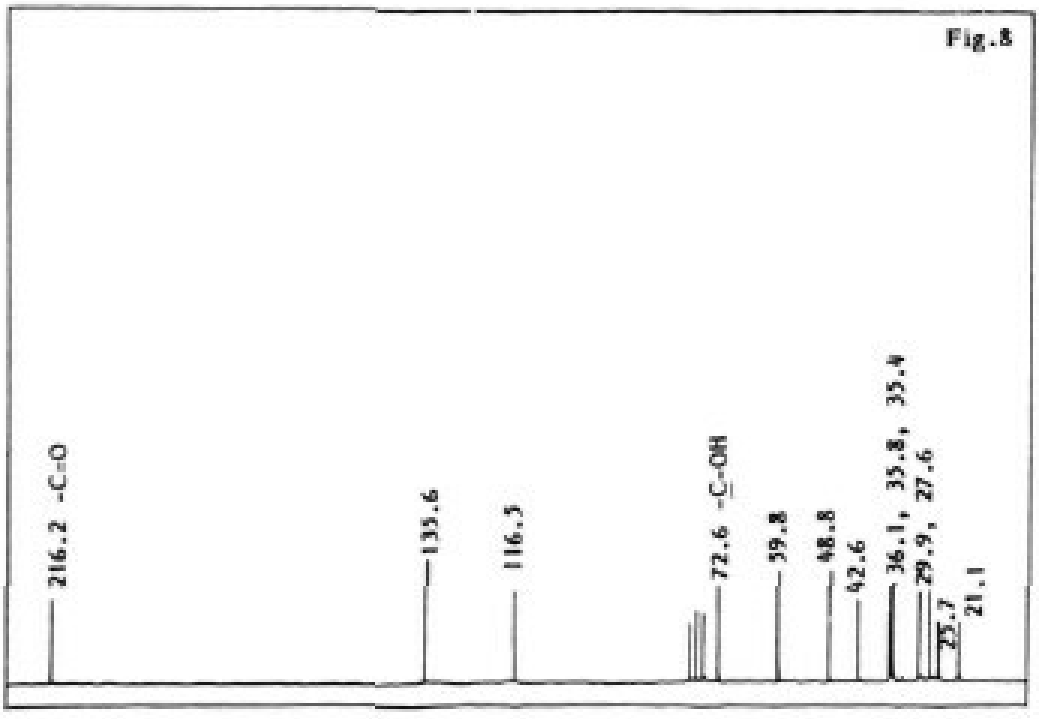

HO
O
1.24
1.16
-C-CH3
8
7
6
5
4
3
2
1
0

Fig.8


216.2 -C=O
135.6
116.3
72.6 -C-OH
39.8
48.8
42.6
36.1, 35.8, 35.4
29.9, 27.6
25.7
21.1

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List of Publications

1. Chiral dialkyl cyclohepunones from R-(+)-citronellal

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2. Dichloroketene-olefin cycloadducts in synthesis. A short, convenient, protocol for olefin --> a-vinylketone transformation

   G. Mehta and Palle **V.R** Acharyulu. *Telrahedron Lett.*, **1993, 3***4*, 8157

3. Terpenes to terpenes. Stereo- and enantio-selective synthesis of (+)-a-elemene and a short route to a versatile diquinane chiron

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